35th Pezcoller Seminar – Surgical pathology of the skin: hot topics and slide seminars
Trento, May 9-10, 2024

Cutaneous lymphomas & pseudolymphomas 1

Lorenzo Cerroni

blood

Special Report

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

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REVIEW ARTICLE OPEN

LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

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We herein present an overview of the upcoming 5th edition of the World Health Organization Classification of Haematolymphoid Tumours focusing on lymphoid neoplasms. Myeloid and histiocytic neoplasms will be presented in a separate accompanying article. Besides listing the entities of the classification, we highlight and explain changes from the revised 4th edition. These include reorganization of entities by a hierarchical system as is adopted throughout the 5th edition of the WHO classification of tumours of all organ systems, modification of nomenclature for some entities, revision of diagnostic criteria or subtypes, deletion of certain entities, and introduction of new entities as well as inclusion of tumorlike lesions, mesenchymal lesions specific to lymph node and spleen, and germline predisposition syndromes associated with the lymphoid neoplasms.

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INTRODUCTION

Evidence-based classification of disease is fundamental for the treatment of individual patients, monitoring of global disease incidence, and investigating all aspects of disease causation, prevention and therapy. The World Health Organization (WHO) classification of lymphoid tumours has provided a global reference for the diagnosis of lymphoid neoplasms since its 3rd edition in 2001 [1] which was based on the R.E.A.L Classification developed by the International Lymphoma Study Group (ILSG) in the early 1990s [2]. The definitions laid down in the successive WHO classifications [3, 4] have not only been adopted for use by pathologists, clinicians, and basic and translational research scientists, but they have also been incorporated into the International Classification of Diseases (ICD) codes, and thereby serve as a global reference for epidemiological monitoring across national and international health policy organizations. In this article, we provide the conceptual framework and major developments in lymphoid neoplasms in the upcoming 5th edition of the WHO Classification of Haematolymphoid Tumours (WHO-HAEM5) scheduled to be published in 2022. An overview of myeloid neoplasms will be published separately.

The International Agency for Research on Cancer (IARC) initiated the process culminating in WHO-HAEM5 in 2018 by laying out the governance rules and classification principles for the entire 5th Edition series of the WHO classification of tumours, comprising 14 volumes, each dedicated to neoplasia of specific organ systems and/or clinical contexts (Paediatric Tumours and Genetic Tumour Syndromes). In 2021, expert members of the editorial board and authors were invited to contribute to WHO-HAEM5 based on their records of diagnostic and/or scientific expertise, regional

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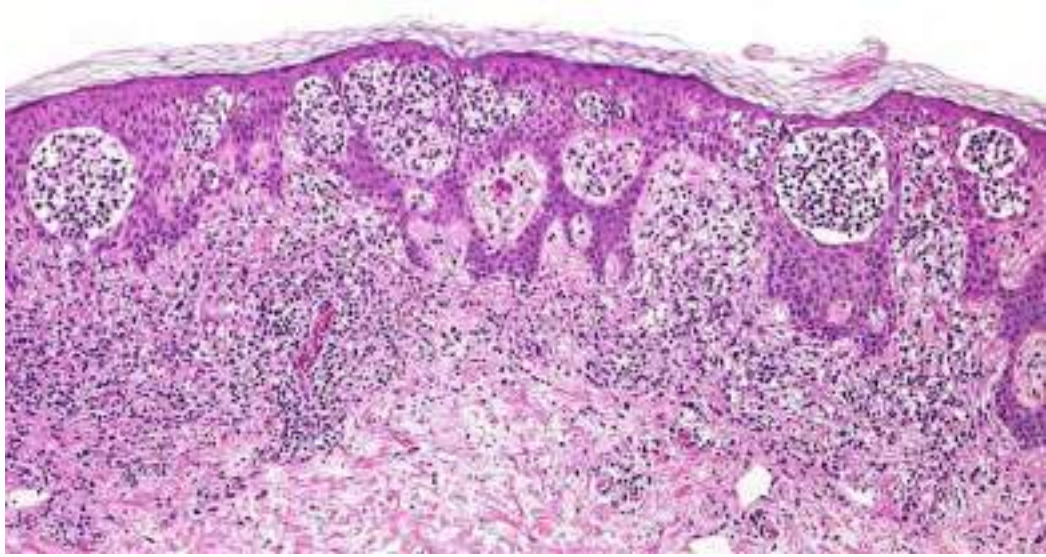
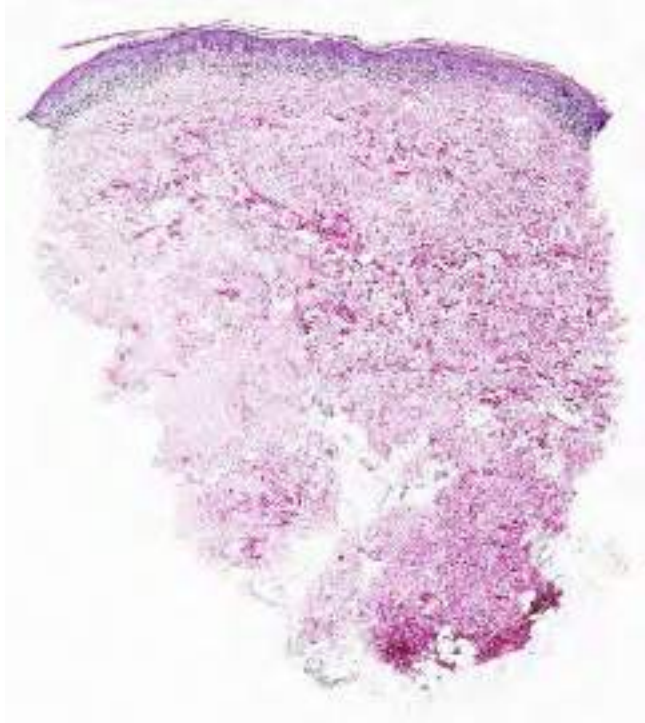
Cutaneous lymphomas

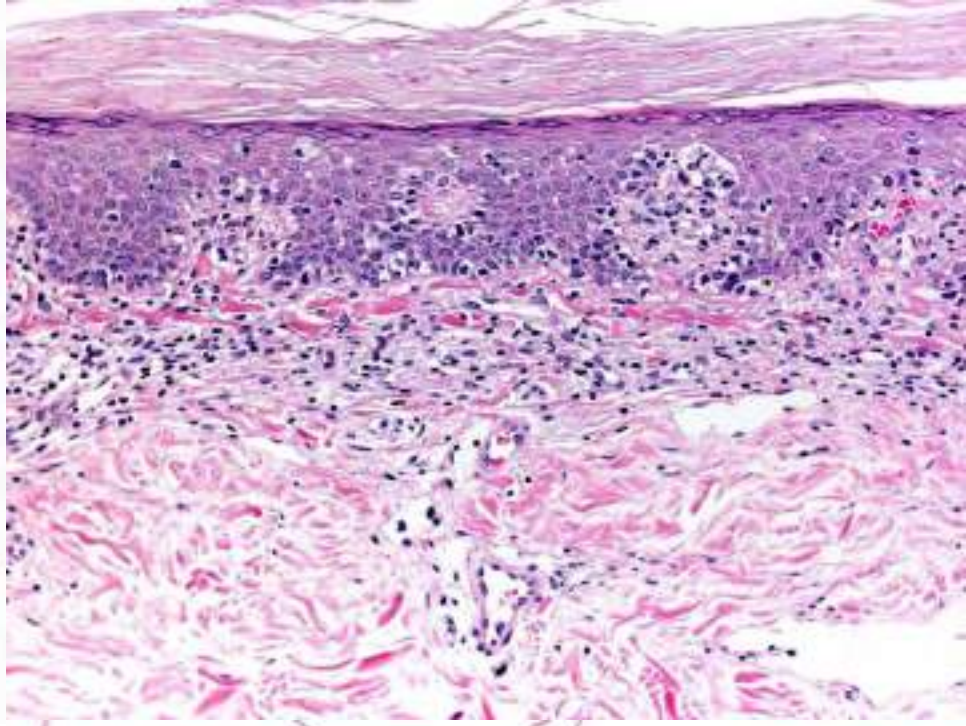
WHO 5ed	***International Consensus Classification 2022***
Mycosis fungoides & variants	Mycosis fungoides & variants
Sézary syndrome	Sézary syndrome
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
Cutaneous CD30+ lymphopr. disorders	Cutaneous CD30+ lymphopr. disorders
Cutaneous anaplastic large cell lymphoma	*Cutaneous anaplastic large cell lymphoma*
Lymphomatoid papulosis	*Lymphomatoid papulosis*
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Cut. extranodal NK/T-lymphoma, nasal-type	Cut. extranodal NK/T-lymphoma, nasal-type
Cutaneous γ/δ T-cell lymphoma	Cutaneous γ/δ T-cell lymphoma
Aggressive epidermotropic CD8+ CTCL	Aggressive epidermotropic CD8+ CTCL
SMPCD4+T-cell lymphoprolif. disorder	SMPCD4+T-cell lymphoprolif. disorder
Acral CD8+ T-cell lymphoproliferative disorder	Acral CD8+ T-cell lymphoproliferative disorder
Systemic chronic active EBV disease	Chronic active EBV infection
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Cutaneous marginal zone lymphoma	Cutaneous marginal zone lymphopr. disorder
Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma
Diffuse large B-cell lymphoma, leg-type	Diffuse large B-cell lymphoma, leg-type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
EBV+ mucocutaneous ulcer	EBV+ mucocutaneous ulcer

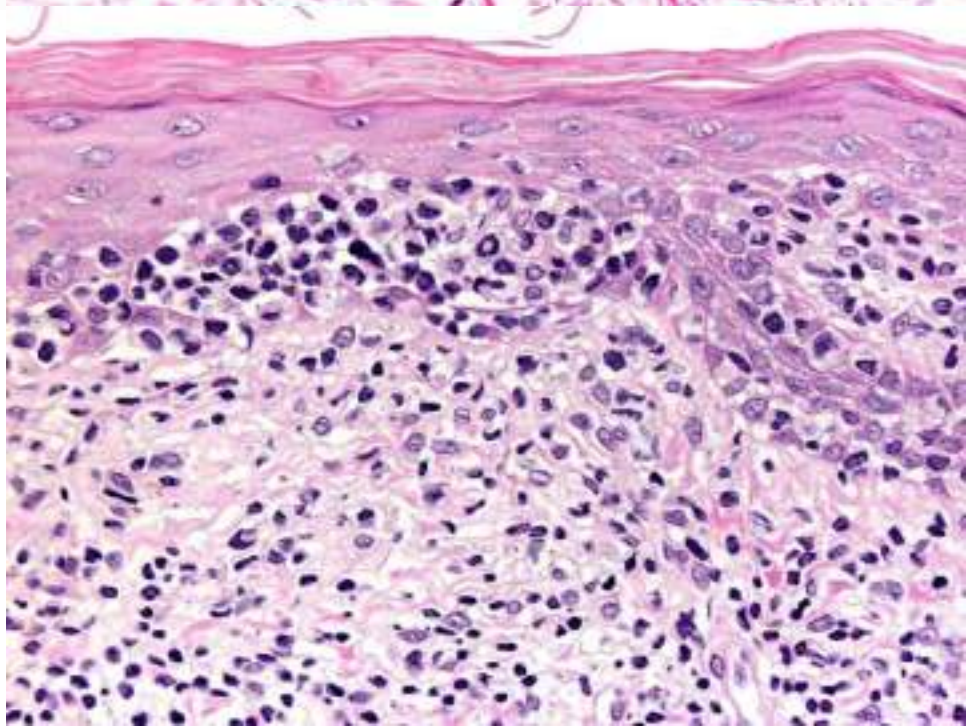


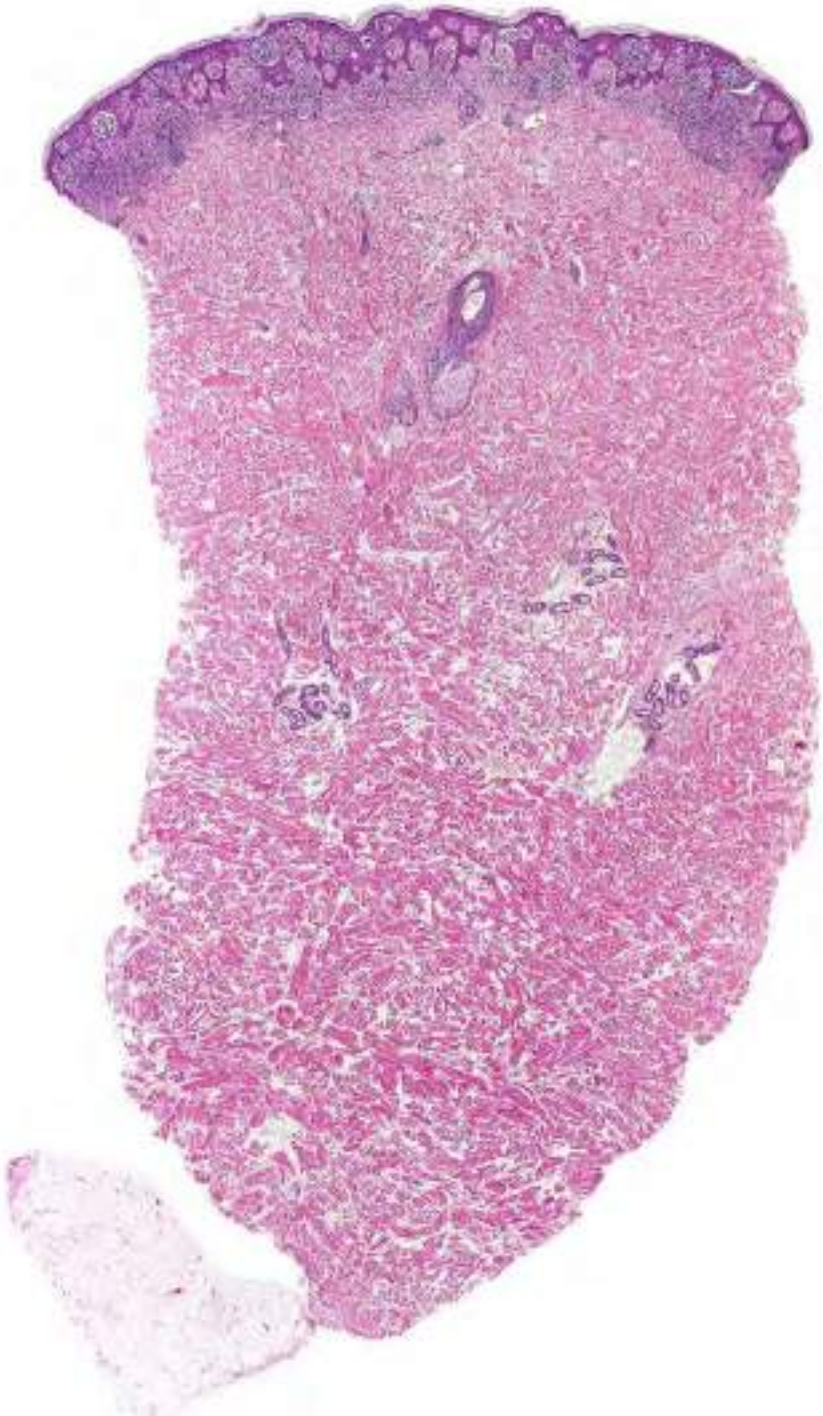
Mycosis fungoides

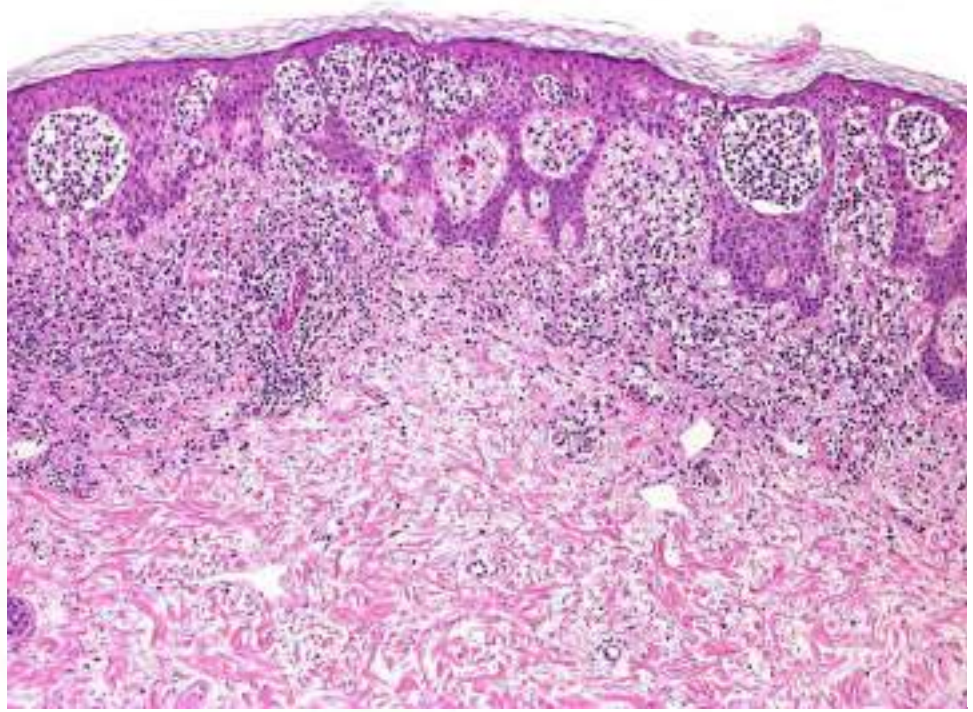
Represents the most common cutaneous T-cell lymphoma and is characterized by a chronic, indolent course. Histology shows in early stages band-like, epidermotropic infiltrates, sometimes with formation of intraepidermal collections of lymphocytes (Darier nests). The phenotype is mostly CD4+ T-helper (may by CD8+ or γ/δ+). In later stages formation of tumors.
Four main clinicopathological variants: 1) "classic"; 2) adnexotropic; 3) pagetoid reticulosis; 4) granulomatous slack skin.

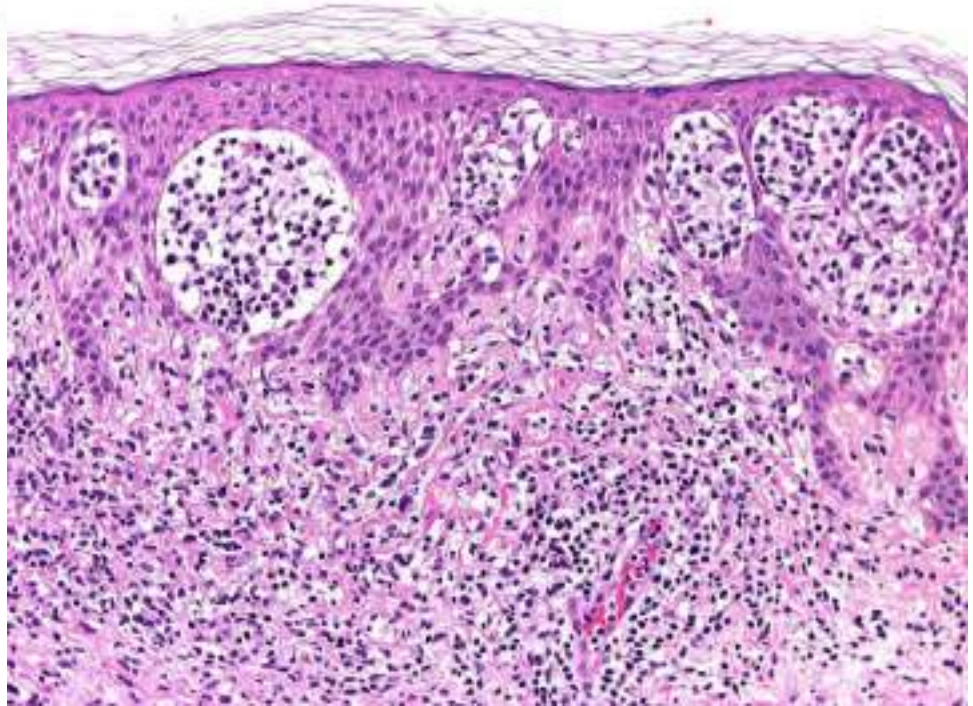












Histopathologic Features of Early (Patch) Lesions of Mycosis Fungoides

A Morphologic Study on 745 Biopsy Specimens From 427 Patients

Cesare Massone, MD,† Rainer Kodama, MD,*‡ Helmut Kerl, MD,* and Lorenzo Cerroni, MD**

Abstract: The histologic diagnosis of early mycosis fungoides (MF) is one of the most serious problems in dermatopathology. We reviewed the histopathologic features of 745 biopsy specimens from 427 patients (male:female = 277:150; median age, 52 years; range, 5–95 years) with early (patch) lesions of MF collected from the lymphoma database of the Department of Dermatology of the Medical University of Graz (Austria). In all patients, the diagnosis was established by clinicopathologic correlation. The most common histopathologic pattern consisted of a bandlike or patchy lichenoid infiltrate associated with coarse bundles of collagen in the superficial dermis. Epidermotropism of lymphocytes was observed in most cases (in one or more forms: single lymphocytic epidermotropism, 33%; bundle lymphocytes, 27%; Pautrier's microabscesses, 19%; "halo cell" lymphocytes, 60%; dyskeratotic cell necrosis, 17%; papillomatosis/acanthosis, 9%). In 4% of cases, spongiosis/exocytosis was completely missing. Atypical lymphocytes were present only in 9% of cases. Features of bandlike dermatitis were observed in 58% of cases. Other associated findings were the presence of eosinophils (25%), melanophages (18%), and vessel-associated erythrocytes (41%). In 24 patients, two or more biopsies taken on the same day at different sites were classified based on pathologic aspects, underlying the positive features of MF, even in a single patient or a given time. Our study supports previous observations on histopathologic features of early lesions of MF. Although sometimes the histopathologic findings are nonspecific, they should be considered consistent with MF, if clinical features are also suggestive for the diagnosis.

Key Words: mycosis fungoides, cutaneous T-cell lymphoma, early diagnosis, histopathologic features

(Am J Surg Pathol 2005;29:1558–1566)

ORIGINAL ARTICLE

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(Am J Surg Pathol 2005;29:1558–1566)

Krol and Kreienbeck[17] and Bonifazi and Santoianni[18] in 1975, the histopathologic features of these lesions were considered to be nonspecific,[1,2,5,6,8,9,11,12,15,16] and their histopathologic study for the diagnosis of MF only in cases characterized by the presence of markedly hyperchromatic, cerebriform lymphocytes in the epidermis forming the so-called Pautrier's microabscesses.[3,4,7,10,13,14] In the last years, several authors attempted to refine the histopathologic criteria for diagnosis of early lesions of MF,[1,2,5,6,8,9,11,12,15,16] but the diagnosis and differential diagnosis of these lesions are still considered one of the most vexing problems in dermatopathology.

We reviewed the histopathologic features of 745 biopsy specimens from 427 patients with early (patch) lesions of MF, to delineate the aspects that may be helpful for histologic diagnosis of early lesions of the disease.

PATIENTS AND METHODS

Data from 427 patients with early lesions of MF were retrieved from the lymphoma database of the Department of Dermatology, Medical University of Graz (Austria). Thirty-six cases were excluded because biopsy specimens were technically inadequate or because of lack of correlation between clinical and histologic data. A total of 745 biopsy specimens from 427 patients (male:female ratio = 1.8:1; mean age, 51.7 years; median age, 52 years; age range, 5–95 years) with early (patch) lesions of MF were available for review. The diagnosis of MF was confirmed in all cases by correlation with the clinical features at the time of observing personally the patient in the outpatient service for cutaneous lymphomas of the Department of Dermatology, Medical University of Graz, Graz, Austria, or reviewing the patient's chart and clinical pictures. Biopsies were taken at least at

TABLE 1. Histologic Features of Early (Patch) Lesions of MF Observed in 745 Biopsy Specimens

Feature	No. (%)
Normal epidermis	330 (48)
Acanthosis/hyperplasia	220 (30)
Irregular hyperplasia	38 (4)
Flat and/or atrophic epidermis	97 (13)
Marked spongiosis	26 (4)
Necrotic keratinocytes	172 (23)
Changes at the dermoepidermal junction	
Basal interface dermatitis	436 (58)
Widespread interface dermatitis	90 (4)
Epidermotropism*	
Single lymphocytic epidermotropism	161 (22)
Bundle lymphocytes	170 (23)
Pautrier's microabscesses	140 (19)
"Halo cell" lymphocytes	510 (68)
Deepithelialization	124 (17)
Papillomatosis/acanthosis	17 (3)
Absence of epidermotropism	42 (6)
Atypical lymphocytes	
Only in the epidermis	77 (9)
Both in epidermis and dermis	58 (8)
Only in the dermis	2 (0.3)
Dermal lymphocytic infiltrate	
Bandlike	372 (50)
Patchy/lichenoid	492 (66)
Superficial perivascular	26 (3)
Dermal changes	
Papillary dermal fibrosis/coarse collagen bundles	725 (97)
Melanophages	56 (8)
Purpura	32 (4)
Edema of the papillary dermis	0

*More than one feature was observed in some cases.

Cutaneous Eruption Limited to Skin Covered by a Swimming Suit

Renato Grilli, MD; Luisa Soriano, MD; Carmen Fariña, MD; Lucia Martin, MD; Luis Requena, MD; Fundación Jiménez Diaz, Madrid, Spain

REPORT OF A CASE

A 72-year-old white woman with a history of hypertension that had been treated in the past with nifedipine presented with an asymptomatic cutaneous eruption that was limited to the skin covered by her swimming suit. The eruption had first appeared 3 years earlier, and she attributed its origin to a new swimming suit that she had worn during the summer when the rash first appeared. The next 2 summers she had worn the same swimming suit, without noting any change in the cutaneous lesions. Her primary care physician attributed the eruption to nifedipine use and changed her medication to verapamil, but the cutaneous lesions remained unchanged. The patient did not use any underwear that covered the same areas as her swimming suit.

Physical examination revealed a cutaneous eruption that was limited to the areas of the skin that had been covered by the swimming suit. The eruption consisted of erythema, scaling, and telangiectases (**Figure 1** and **Figure 2**). Skin folds under the breasts and redundant abdominal wall were less affected. The rest of the physical findings were within normal limits.

The results of patch testing with standard textile resins and dye trays were negative.

A cutaneous biopsy specimen was obtained from the lesions on the abdominal wall (**Figure 3** and **Figure 4**).

What is your diagnosis?

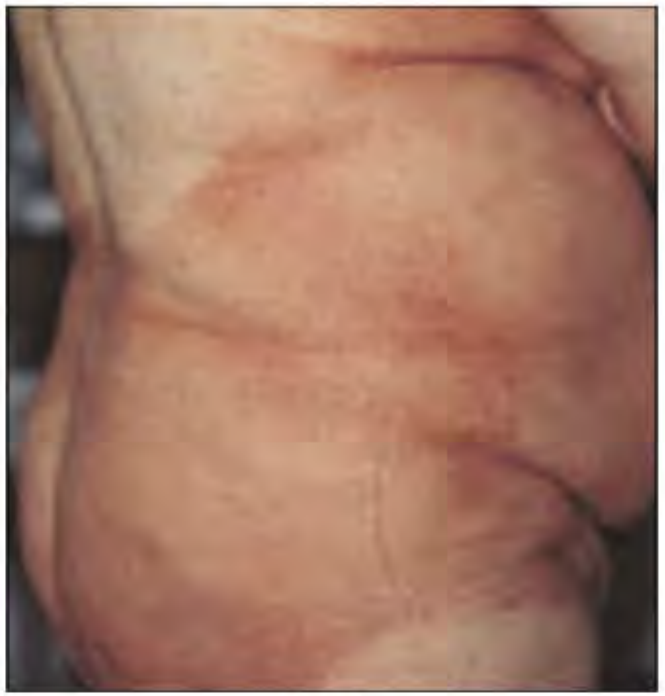
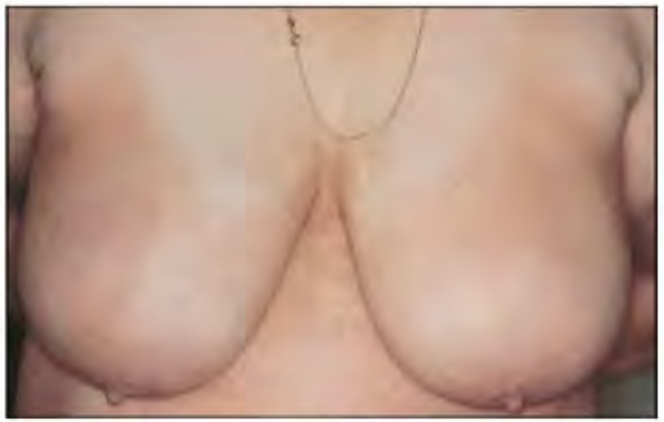


Figure 1.



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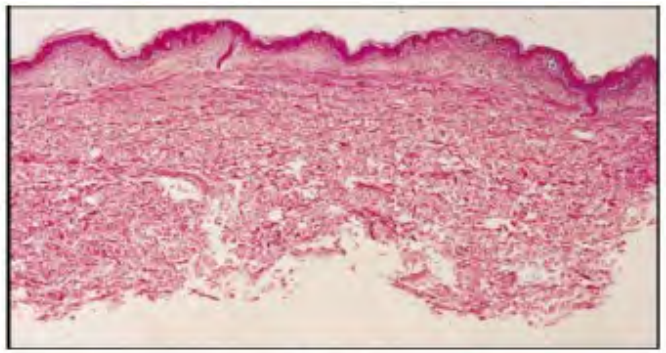


Figure 3.

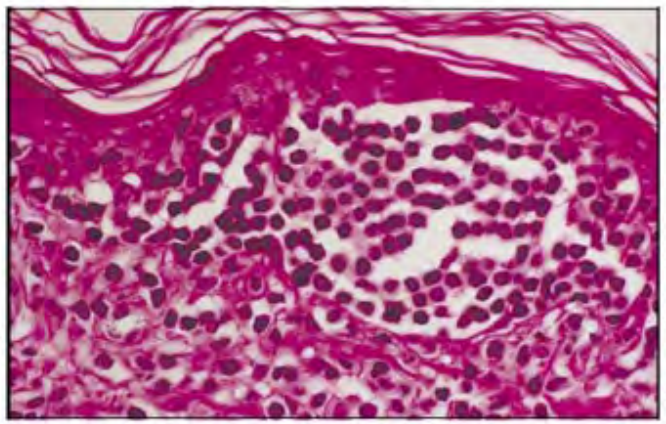
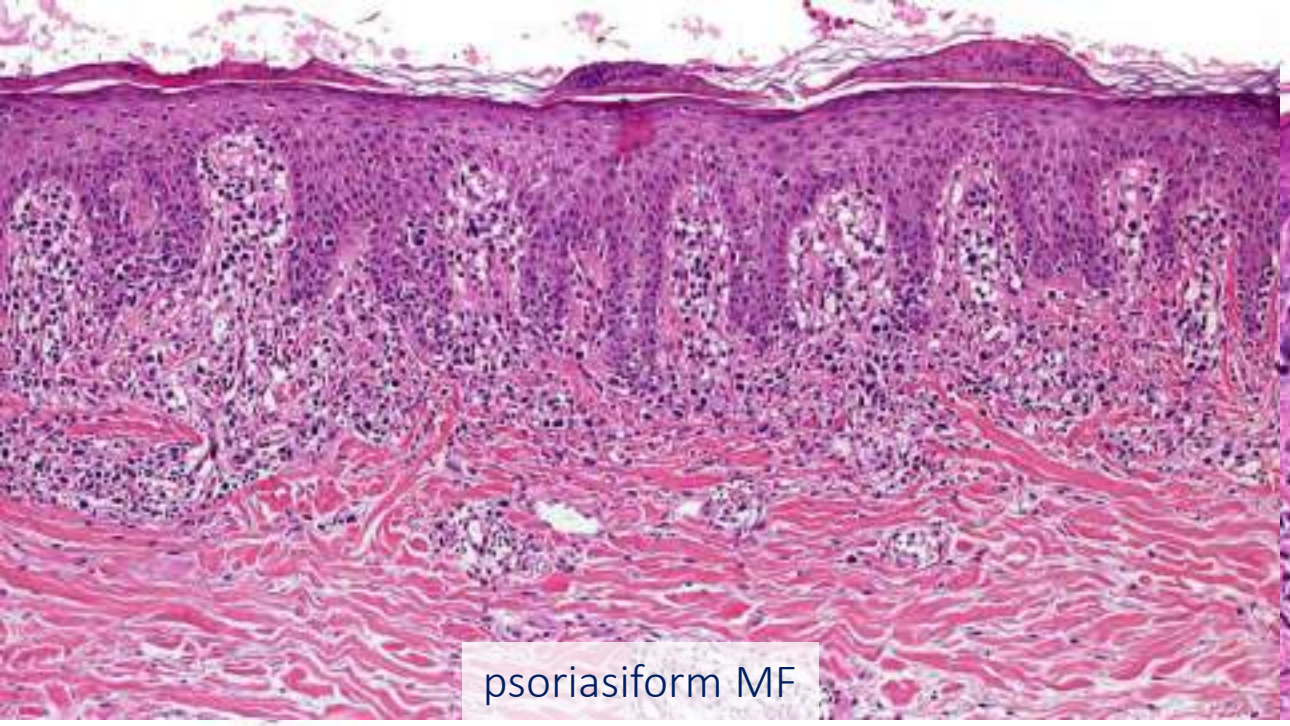
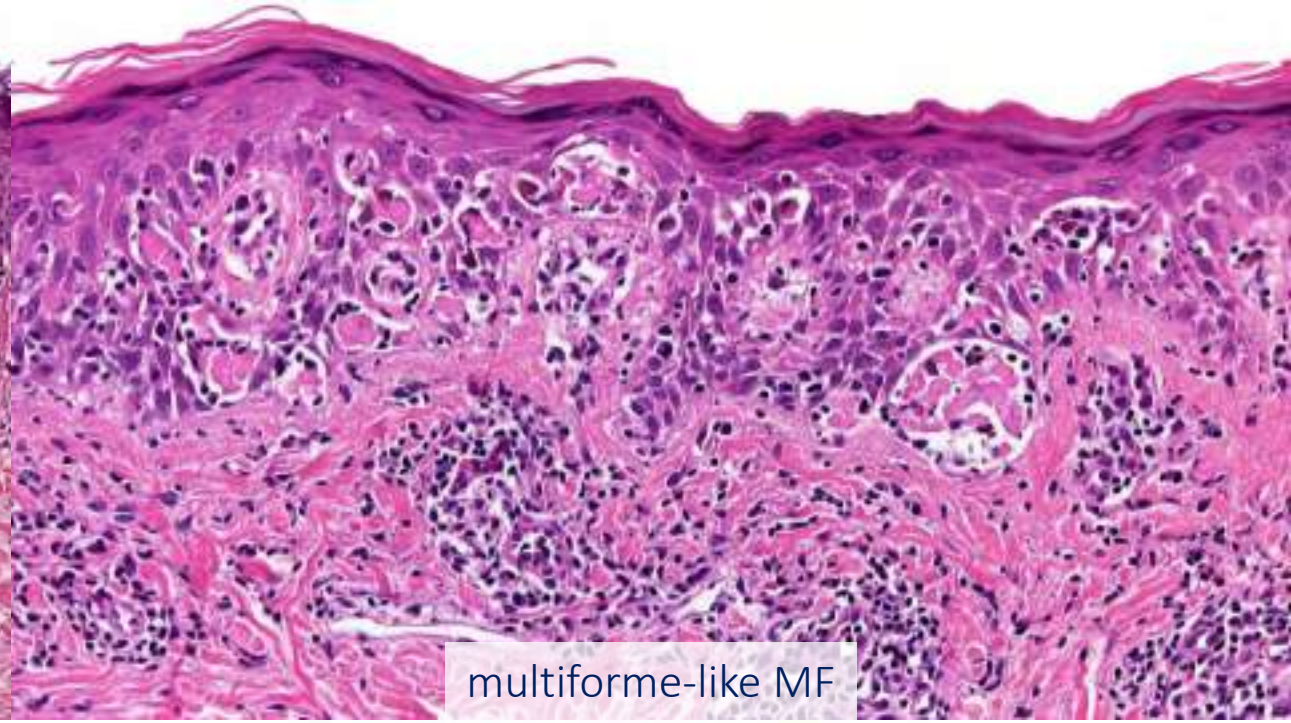
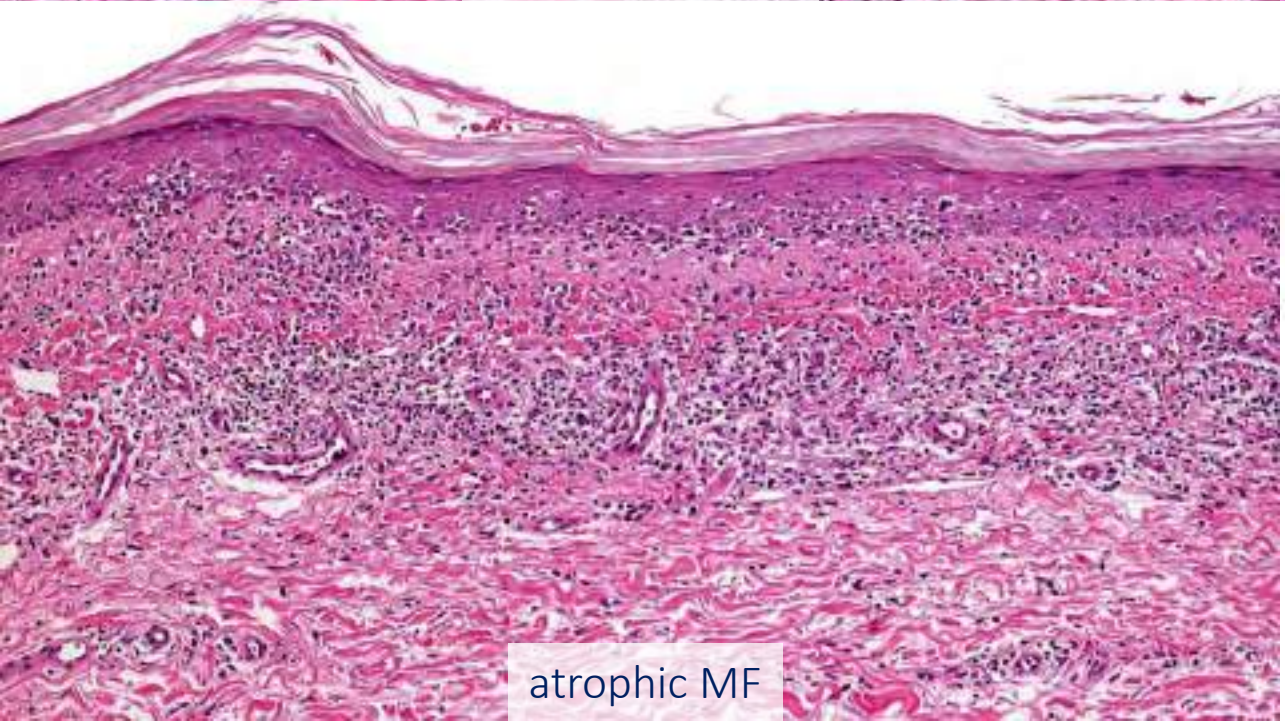


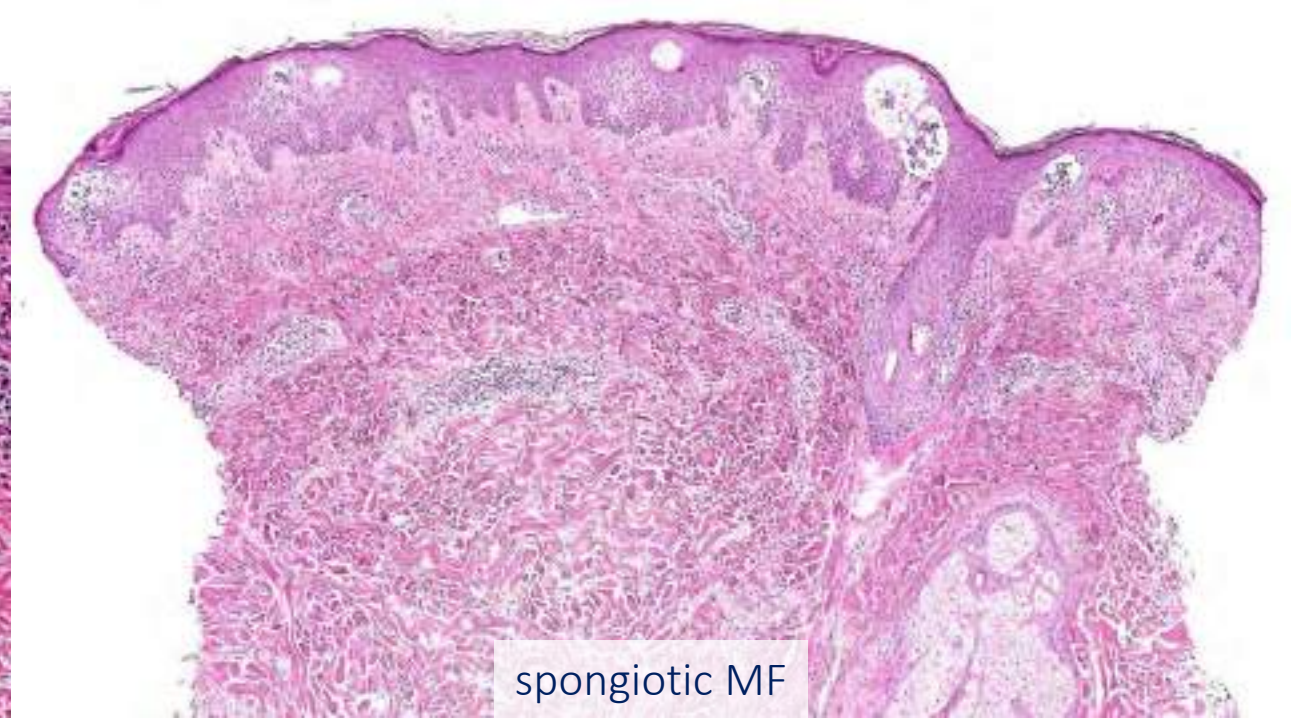
Figure 4.

Arch Dermatol 2002;138:527-532


psoriasiform MF


multiforme-like MF


atrophic MF


spongiotic MF

Histopathologic Features of Early (Patch) Lesions of Mycosis Fungoides

A Morphologic Study on 745 Biopsy Specimens From 427 Patients

Cesare Massone, MD,† Kazuo Kodama, MD,*† Helmut Kerl, MD,* and Lorenzo Cerroni, MD**

Abstract: The histologic diagnosis of early mycosis fungoides (MF) is one of the most vexing problems in dermatopathology. We reviewed the histopathologic features of 745 biopsy specimens from 427 patients (male:female = 237:190; median age, 52 years; range, 3-95 years) with early (patch) lesions of MF collected from the lymphoma database of the Department of Dermatology of the Medical University of Graz (Austria). In all patients, the diagnosis was established by clinicopathologic correlation. The most common histopathologic pattern consisted of a band-like or patchy lichenoid infiltrate admixed with coarse bundles of collagen in the superficial dermis. Epidermotropism of lymphocytes was observed in most cases in one or more forms (single lymphocyte epidermotropism, 22%; basilar lymphocytes, 23%; Pautrier's microabscesses, 13%; "haloed" lymphocytes, 40%; disproportionate exocytosis, 17%; pagetoid epidermotropism, 3%); in 4% of cases, epidermotropism was completely missing. Atypical lymphocytes were present only in 9% of cases. Features of interface dermatitis were observed in 59% of cases. Other unusual findings were the presence of necrotic keratinocytes (23%), melanophages (8%), and extravasated erythrocytes (4%). In 26 patients, two or more biopsies taken on the same day at different body sites showed different histopathologic aspects, underlying the protean features of MF even in a single patient at a given time. Our study expands previous observations on histopathologic features of early lesions of MF. Although sometimes the histopathologic features are not diagnostic, they should be considered consistent with MF and do not rule out the diagnosis.

Key Words: mycosis fungoides, cutaneous T-cell lymphoma, early diagnosis, histopathologic features

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The histologic diagnosis of early (patch) lesions of mycosis fungoides (MF) is often difficult because the histopathologic features may simulate a variety of inflammatory skin disorders. Indeed, before the delineation of precise criteria by Kerl and Knobloch[28] and Sanchez and Ackerman[11] in 1976, the histopathologic features of these lesions were considered to be nonspecific,[4,9,13,15,16,18,21,26,27,30,37] and pathologists made the diagnosis of MF only in cases characterized by the presence of markedly hyperchromatic, cerebriform lymphocytes in the epidermis forming the so-called Pautrier's microabscesses.[23,33] In the last years, several authors attempted to refine the histopathologic criteria for diagnosis of early lesions of MF,[5,20,31,35,38] but the diagnosis and differential diagnosis of these lesions are still considered one of the most vexing problems in dermatopathology.

We reviewed the histopathologic features of 745 biopsy specimens from 427 patients with early (patch) lesions of MF to delineate the aspects that may be helpful for histologic diagnosis of early lesions of the disease.

PATIENTS AND METHODS

Data from 463 patients with early lesions of MF were retrieved from the lymphoma database of the Department of Dermatology, Medical University of Graz (Austria). Thirty-six cases were excluded because biopsy specimens were technically inadequate or because of lack of exact clinical information. A total of 745 biopsy specimens from 427 patients (male:female ratio = 1.8:1; mean age, 57.2 years; median age, 52 years; age range, 3–95 years) with early (patch) lesions of MF were available for the study. The diagnosis of MF was confirmed in all cases by correlation with the clinical features (either observing personally the patient in the outpatient service for cutaneous lymphomas of the Department of Dermatology, Medical University of Graz, Graz, Austria, or reviewing the patient's chart and clinical pictures). Biopsies were taken at onset of disease or from recurrent patches. Biopsies obtained under ongoing treatment were not included.

Cases of Sézary syndrome or epidermotropic cutaneous T-cell lymphomas other than MF were excluded. We also excluded patients with so-called "small plaques parapsoriasis" because of the controversies concerning classification of these cases, and patients with MF associated with follicular mucinosis.

Histology

Biopsy specimens were retrieved from the archive material of the section of Dermatopathology, Department of Dermatology, Medical University of Graz (Graz, Austria).

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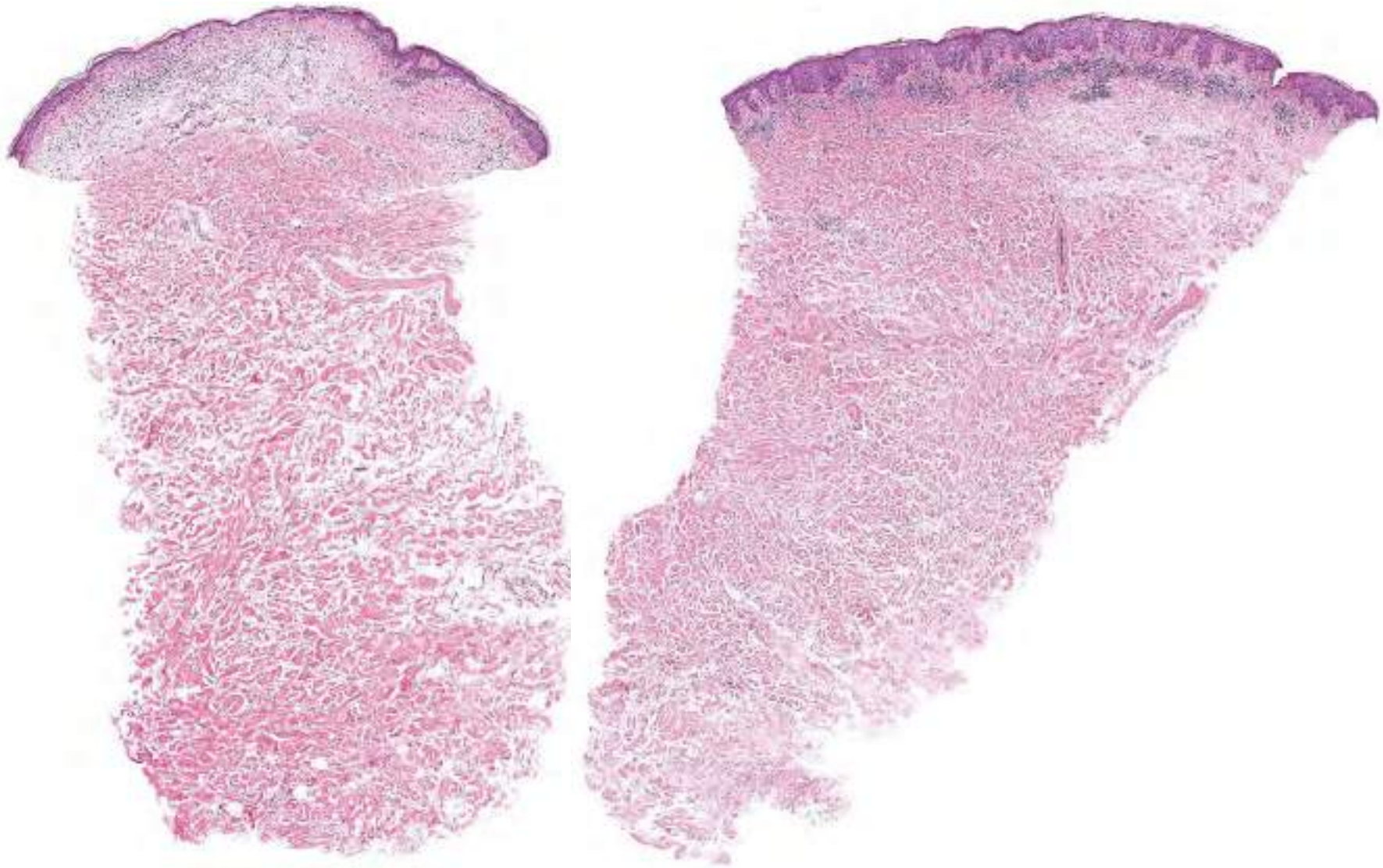
TABLE 1. Histologic Features of Early (Patch) Lesions of MF Observed in 745 Biopsy Specimens

Feature	No. (%)
Normal epidermis	356 (48)
Psoriasiform hyperplasia	258 (35)
Irregular hyperplasia	34 (4)
Flat and/or atrophic epidermis	97 (13)
Marked spongiosis	28 (4)
Necrotic keratinocytes	172 (23)
Changes at the dermoepidermal junction	
Focal interface dermatitis	438 (59)
Widespread interface dermatitis	30 (4)
Epidermotropism*	
Single lymphocyte epidermotropism	161 (22)
Basilar lymphocytes	170 (23)
Pautrier's microabscesses	140 (19)
"Haloed" lymphocytes	298 (40)
Disproportion exocytosis	124 (17)
Pagetoid epidermotropism	17 (3)
Absence of epidermotropism	32 (4)
Atypical lymphocytes	
Only in the epidermis	27 (4)
Both in epidermis and dermis	38 (5)
Only in the dermis	2 (0.3)
Dermal lymphocytic infiltrate	
Band-like	227 (30)
Patchy-lichenoid	492 (66)
Superficial perivascular	26 (3)
Dermal changes	
Papillary dermal fibrosis/coarse collagen bundles	725 (97)
Melanophages	56 (8)
Purpura	32 (4)
Edema of the papillary dermis	0

*More than one feature was observed in some cases.



2 biopsies taken on the same day

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CHAPTER 3

Mycosis fungoides

Mycosis fungoides is the most common type of cutaneous lymphoma, representing almost 50% of all lymphomas arising primarily in the skin [1–4]. It is defined as a tumor composed of small/medium-sized epidermotropic T-helper lymphocytes (but T-cytotoxic variants are not uncommon, and neoplastic cells may be medium/large in advanced stages).

Mycosis fungoides is the oldest entity in the field of cutaneous lymphomas, having been described more than two centuries ago, in 1806, by the French dermatologist Alibert. Traditionally it is divided into three clinical phases: patch, plaque, and tumor stage. The clinical course can be protracted over years or decades. In the 2018 update of the classification of cutaneous lymphomas by the European Organization for Research and Treatment of Cancer (EORTC)/World Health Organization (WHO) [1] and in the WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, the term "mycosis fungoides" is restricted to the classic type of the disease (so-called Alibert–Bazin), characterized by the typical slow evolution and protracted course [1, 3]. It is estimated that over 90% of patients with early mycosis fungoides neither progress to tumor stage nor show extracutaneous manifestations of the disease [5, 6]. Phenotypic and genetic studies showed that entities described in the past as "rapidly progressive" mycosis fungoides (e.g., pagetoid reticulosis, Woringer–Kolopp disease, generalized pagetoid reticulosis – Ketron–Goodman) are better classified among the group of aggressive cutaneous cytotoxic natural killer (NK)/T-cell lymphomas (see Chapter 7).

The incidence of the disease worldwide is probably around [illegible] cases/100, with many regional variations and with a regular increase in recent decades [7, 8]. A stabilization of the incidence has been noted in the United States in the period 1998–2009 [9]. There is a higher incidence in black patients [10], and the average age of onset seems to be younger for black than for white patients [11].

In spite of decades of research, the etiology of mycosis fungoides remains unknown. A genetic predisposition may play a role in some cases. A familial occurrence of the disease has been reported in a few instances including disease onset in identical twins [12–14], but a large study on Danish patients showed that twins of patients affected by mycosis fungoides or Sézary syndrome did not develop the disease after a median period of observation of 20 years (range: 3–40 years) [15]. A study conducted among Israeli Jewish patients showed a significantly greater allele frequency of HLA DQB1*03, suggesting that genetic factors may play a role in the etiology of the disease, at least in selected groups of patients [16]. On the other hand, mycosis fungoides has been rarely observed in unrelated married individuals, pointing to the existence of environmental factors [17]. In this context, a study on Iranian veterans confirmed to have exposure to sulfur mustard during the Iraq–Iran war of the 1980s showed an increased incidence of mycosis fungoides compared with the Iranian general population [18]. Association with long-term exposure to various allergens and association with chronic skin disorders have also been suggested as possible etiologic factors, but no epidemiologic study confirmed these hypotheses beyond doubt. In this context, it has been suggested that bacterial triggers may be involved in disease onset and progression and staphylococcal enterotoxin A stimulates STAT3 activation and IL-17 expression [19, 20]. STAT3 is involved in neoplastic cell survival in mycosis fungoides [21]. In fact, antibiotic treatment induces a reduction of the tumor burden in advanced stages (see section on therapy below in this chapter). A relationship with *Borrelia burgdorferi* infection, human T-lymphotropic virus I (HTLV-I), cytomegalovirus (CMV), human herpesvirus (HHV)-6, HHV-8, Merkel cell polyomavirus (MCPyV), and Epstein–Barr virus (EBV) has also been investigated, but so far a link to infectious agents could not be demonstrated [22, 23]. Interestingly, mycosis fungoides has been observed rarely in patients who received solid organ transplantation, suggesting that immune suppression may contribute to the development of the disease [24, 25]. In one exceptional case, mycosis fungoides has been acquired as a donor-derived malignancy following reduced-intensity hematopoietic stem cell transplantation from a matched unrelated donor [26]. In short, genetic background, environmental factors, chronic antigenic stimulation, and exposure to cancerogenic agents seem to play a role in mycosis fungoides (as in many other human cancers), but the frame keeping all of these factors together is still elusive.

Genetic alterations have been identified mainly in late stages of the disease, and their importance for disease initiation is

Table 3.1 Clinicopathologic and phenotypic variants of mycosis fungoides

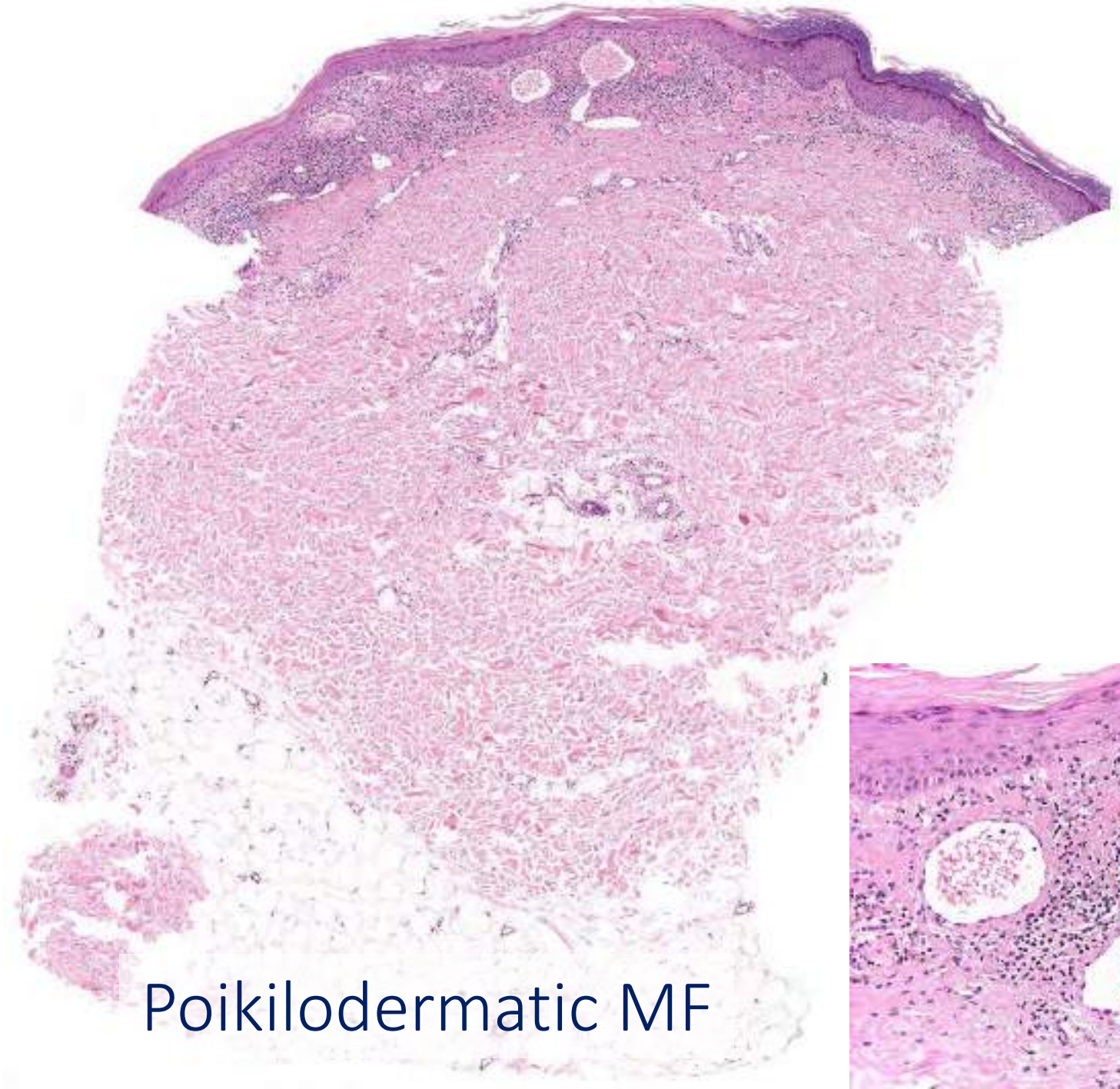
Clinical variants with "conventional" histopathological features
- Acanthosis nigricans-like mycosis fungoides
- Atopic dermatitis-like mycosis fungoides
- Erythrodermic mycosis fungoides
- Hypopigmented mycosis fungoides
- Ichthyosiform mycosis fungoides
- Palmoplantar mycosis fungoides
- Papular mycosis fungoides
- Papuloerythroderma of Ofuji (subset of cases)
- Parapsoriasis ("large patch") (for a discussion on small and large patch parapsoriasis, see Chapter 2)
- Perifollicular dermatitis-like mycosis fungoides
- Pityriasis lichenoides-like mycosis fungoides (clinical variant)
- Psoriasiform mycosis fungoides
- Unilesional (solitary) mycosis fungoides
- Zosteriform mycosis fungoides

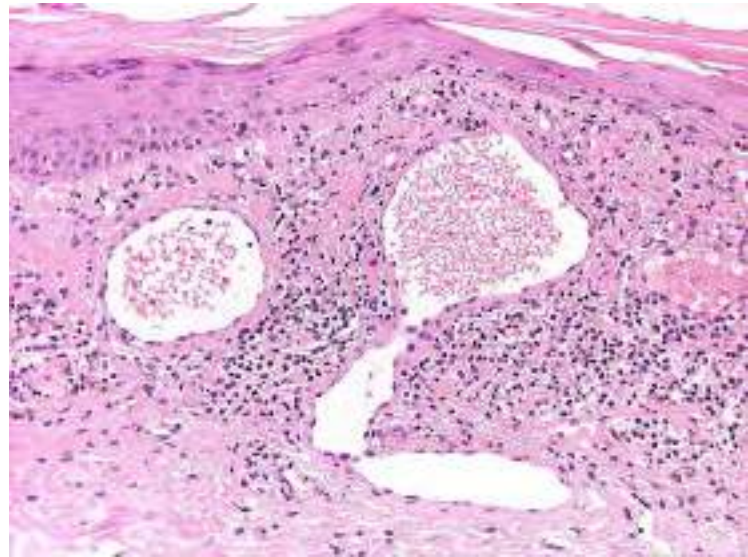
Clinical variants with peculiar histopathological features
- Adnexotropic mycosis fungoides, including pilotropic (folliculotropic) mycosis fungoides (with or without follicular mucinosis), mycosis fungoides with eruptive infundibular cysts and comedones, and syringotropic mycosis fungoides[2]
- Anetodermic mycosis fungoides (mycosis fungoides with secondary anetoderma) (secondary anetoderma may be observed also in generalized follicular mucinosis)
- Bullous (vesiculobullous) mycosis fungoides
- Dyshidrotic mycosis fungoides
- Epidermal mucinosis in mycosis fungoides
- Granulomatous slack skin
- Hypopigmented mycosis fungoides
- "Invisible" mycosis fungoides
- Pagetoid reticulosis (Woringer–Kolopp type)
- Poikilodermatous mycosis fungoides
- Purpuric mycosis fungoides
- Pustular mycosis fungoides
- Verrucous/hyperkeratotic mycosis fungoides

Histopathological variants
- Annular lichenoid dermatitis of youth-like mycosis fungoides
- Granulomatous mycosis fungoides
- Interstitial mycosis fungoides
- Large cell transformation
- Pityriasis lichenoides-like mycosis fungoides (histopathological variant)
- Sclerosing mycosis fungoides (lichen sclerosus-like)

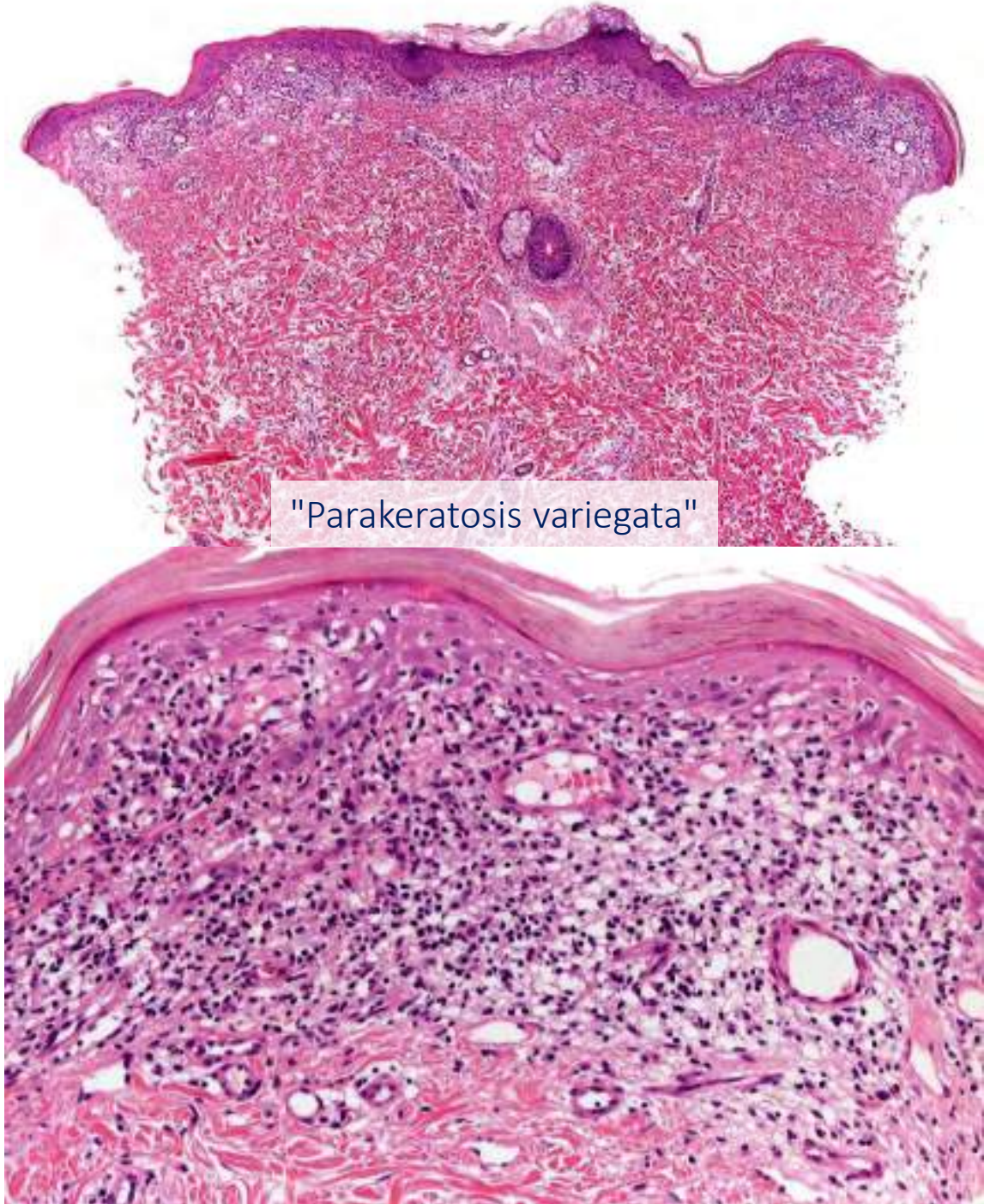
Phenotypic variants[3]
- Cytotoxic mycosis fungoides (CD8+ and/or γ/δ+, rarely CD4+ with expression of cytotoxic proteins)
- Mycosis fungoides with T follicular helper (T_{FH}) phenotype
- Mycosis fungoides with T-regulatory (Treg) phenotype

[1] Histopathologically characterized often by variable spongiotic changes.
[2] Adnexotropic mycosis fungoides and syringotropic mycosis fungoides may be observed independently from one another, but in many instances of syringotropic mycosis fungoides the hair follicles are involved as well. Thus the term adnexotropic mycosis fungoides better reflects the clinicopathological features of this variant of the disease.
[3] A phenotypic switch may occur in sequential biopsies, and sometimes different phenotypic features are present in different biopsies taken on the same day.

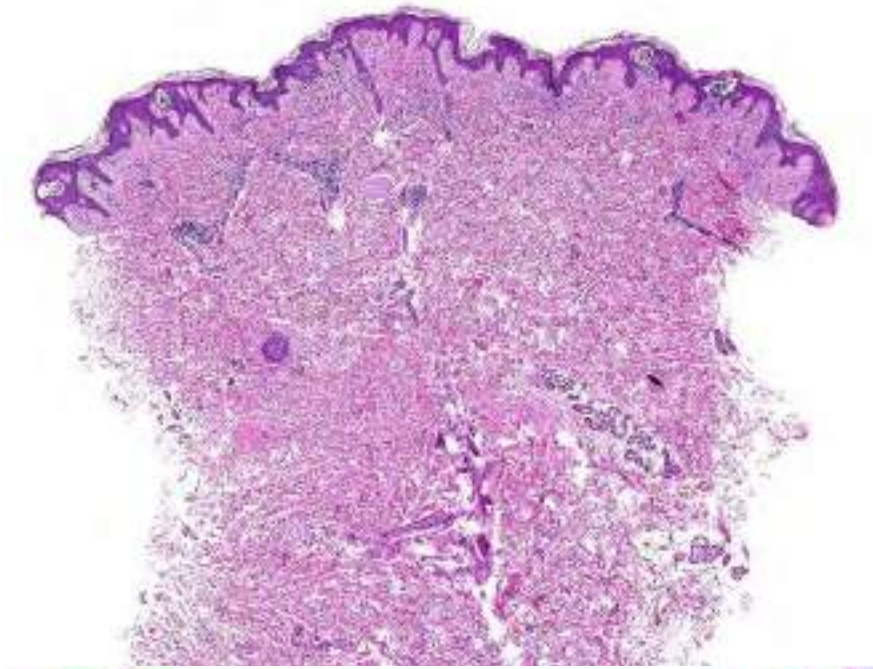


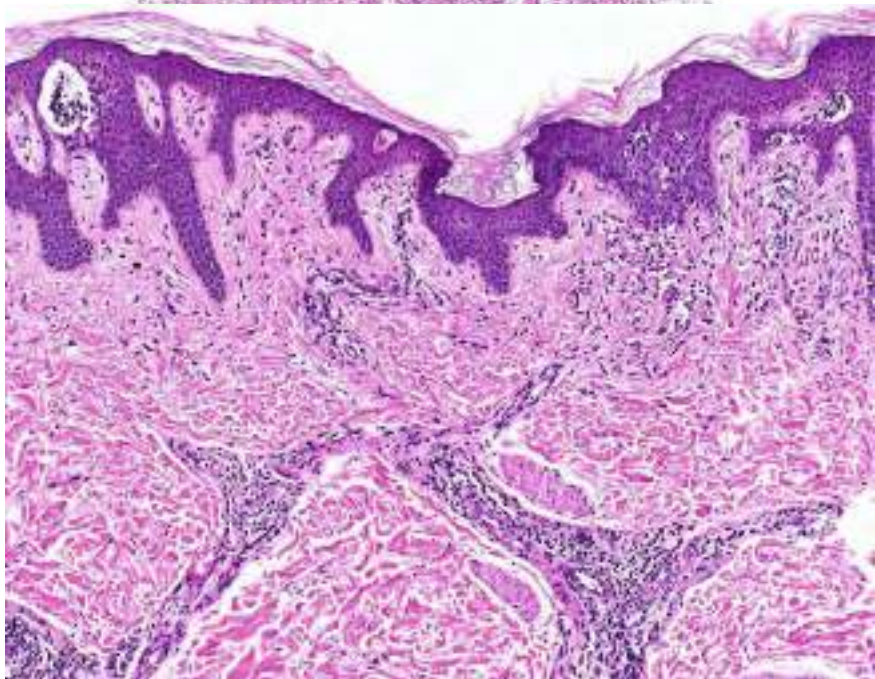


Poikilodermatic MF

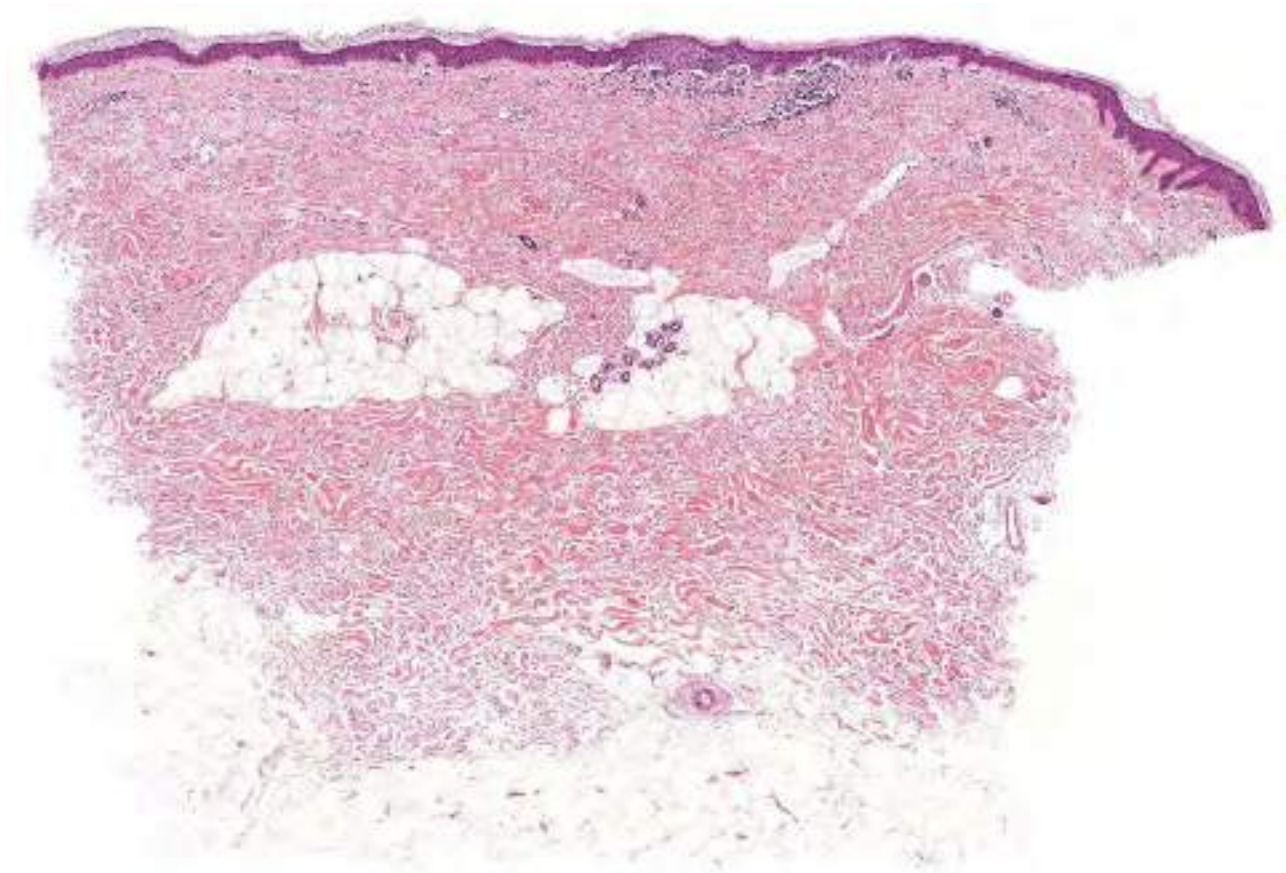

"Parakeratosis variegata"

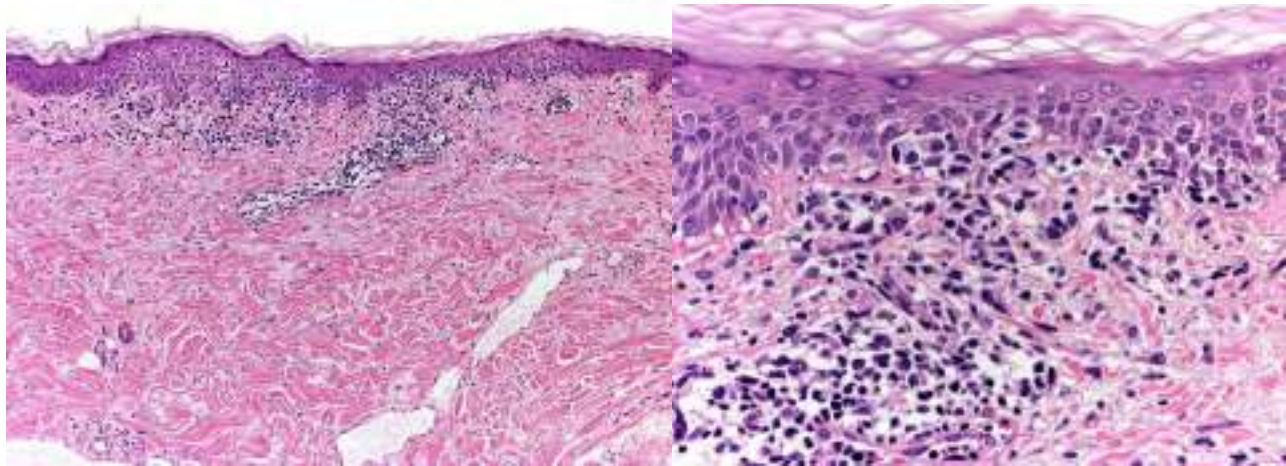
Hypopigmented MF





Papular MF





Papular Mycosis Fungoides Is a Distinctive Variant of Early-stage Mycosis Fungoides

Extended Retrospective Study With Long-term Follow-up

Andrea Saggini, MD,† Regina Fink-Puches, MD,* Carlo Cota, MD,‡ Viviana Lora, MD,‡ Heide Pinzinger, MD,* Cesare Massone, MD,§ and Lorenzo Cerroni, MD**

Abstract: Papular mycosis fungoides (PMF) is a rare variant of mycosis fungoides (MF). The exact nosology and prognosis of PMF are still unclear. We retrospectively identified cases of PMF from the files of the Department of Dermatology of the Medical University of Graz, Austria, and checked the follow-up data. The patients comprised 13 men and 5 women (median age: 57.5 y; range: 13 to 77 y). In 4 patients, an initial clinicopathologic diagnosis of atypical parapsoriasis lichenoides was made; these cases were subsequently reclassified as PMF due to the onset of conventional patches of MF during follow-up. Follow-up data of our cases showed that 2 patients died of disease progression 50 and 199 months after the first presentation, respectively. Two patients are alive with progressive disease after 215 and 300 months, respectively. Ten patients are alive with stable disease (median: 70 mo). Four patients were in complete remission at last follow-up visit (median: 215 mo; 2 of them died of unrelated causes). Our data confirm that PMF represents a clinicopathologic variant of early MF with prognosis similar to conventional presentations of the disease. Familiarity with PMF and distinction from other cutaneous papular lymphoid proliferations is necessary for a precise diagnosis and management of these patients.

Key Words: mycosis fungoides, papular mycosis fungoides, lymphomatoid papulosis, pityriasis lichenoides, cutaneous T-cell lymphoma

(*Am J Surg Pathol* 2019;43:1129–1134)

Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma. In early stages, it is characterized clinically by the presence of irregular erythematous patches (so-called patch-stage of MF).[1] In 2005, our group described a clinical variant of MF characterized at onset by the presence of small papules rather than patches (papular MF—PMF).[2] Following our initial study, a few case reports of PMF with limited follow-up data have been published.[3–11] Some authors have questioned whether PMF exists, suggesting that most cases may be reconciled as a variant of lymphomatoid papulosis (LyP) type B.[12,13]

We present the long-term follow-up of the 6 cases first reported in 2005, describing in addition 12 novel cases of PMF.

METHODS

A total of 18 cases of patients with PMF were retrieved from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria. Six of these cases were included in the original publication.[2] Clinical data were available for all patients. The histopathologic diagnosis of MF was made according to the criteria listed in the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues published in 2017 (fourth revised edition).[1] The study has been approved by the ethical committee of the Medical University of Graz.

RESULTS

Clinical and follow-up data of all patients are summarized in Table 1. The patients comprised 13 men and 5 women. Age at first diagnosis ranged from 13 to 77 years (median: 57.5 y). Clinically, all patients showed, at first presentation, small erythematous, partly scaly papules in the absence of patches or plaques (Figs. 1, 2). The lesions were located on the trunk (including buttocks; 6 patients), trunk and extremities (11 patients), or lower extremities (1 patient). A drug eruption could be excluded in all cases by the absence of pertinent history. In all cases, the diagnosis of PMF was confirmed by one or more biopsies with histopathologic features of MF; large cell transformation was observed in subsequent biopsies in 3 cases. No involvement of hair follicles or eccrine glands was present. Immunohistochemistry revealed a conventional phenotype ($CD4^+/CD8^-$) in 14 cases, while 4 cases displayed a cytotoxic phenotype (2 being $CD4^-/CD8^+$, and 2 double positive for CD4 and CD8 as well as for the cytotoxic protein TIA-1). Staining for CD30 was negative in the first diagnostic biopsy in all of our cases. Molecular analysis of the T-cell

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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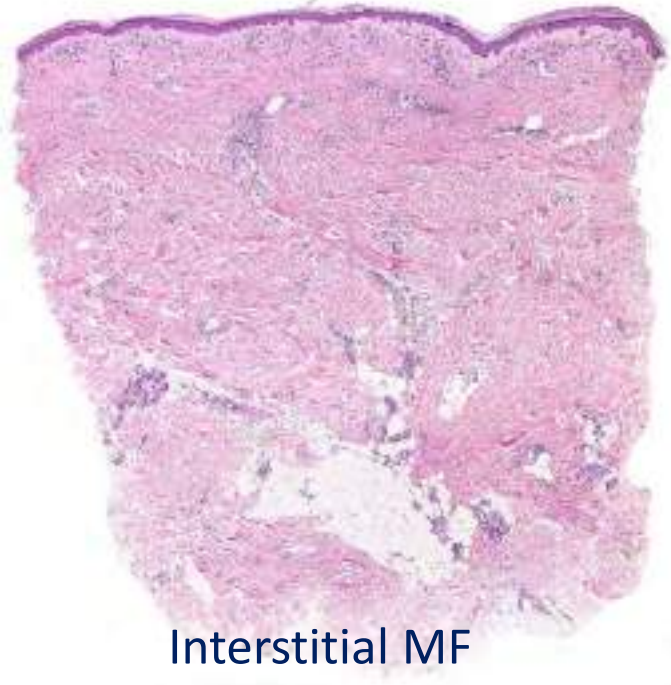
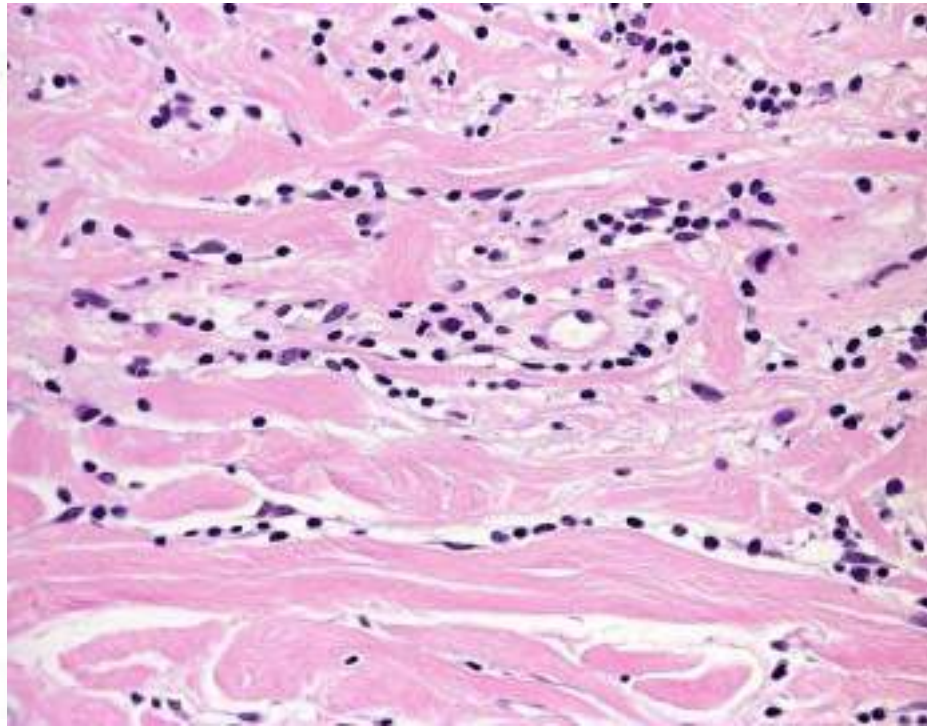
18 patients (M:F = 13:5); Median age: 57,5 (range: 13-77)

M, 57	(1-JAAD)	D- (239)	(bronchial carcinoma)
F, 58	(2-JAAD)	A+ (215)	(progressive disease)
F, 57	(3-JAAD)	D- (194)	(ovarian carcinoma)
M, 41	(4-JAAD)	A+ (300)	(progressive disease)
M, 59	(5-JAAD)	D+ (50)	(death of disease progression)
M, 61	(6-JAAD)	A- (236)	(remission at last follow-up)
M, 77		A- (88)	(remission at last follow-up)
M, 49		D+ (199)	(death of disease progression)
M, 64		A+ (62)	(stable disease)
M, 55		A+ (107)	(stable disease)
F, 67		A+ (6)	(stable disease)
M, 68		A+ (113)	(stable disease)
M, 70		A+ (304)	(stable disease)
M, 76		A- (17)	(remission at last follow-up)
M, 13		A+ (20)	(stable disease)
M, 15		A+ (66)	(stable disease)
F, 43		A+ (46)	(stable disease)
F, 17		A+ (74)	(stable disease)



Interstitial MF



Interstitial Mycosis Fungoides

A Clinicopathologic Study of 21 Patients

Camilla Reggiani, MD,† Cesare Massone, MD,*‡ Regina Fink-Puches, MD,* Carlo Cota, MD,§ and Lorenzo Cerroni, MD**

Abstract: Interstitial mycosis fungoides (IMF) is a rare histopathologic variant of mycosis fungoides (MF) that may mimic other inflammatory dermatoses, mainly interstitial granulomas annulare, inflammatory morphea, and interstitial granulomatous dermatitis. Only small series and sporadic case reports of IMF have been described in the literature. We reviewed 27 specimens from 21 patients with IMF (M:F = 11:10; median age 60) to better characterize clinical, histopathologic, and immunohistochemical features of this disease. Most patients presented clinically with patches and/or plaques. Conventional MF was documented before, concomitant with, or after IMF in 12 patients, whereas only in 2 patients different biopsies showed exclusive features of IMF over a period of 4 and 191 months, respectively. Histology revealed in all cases variably long, linear aggregates of dermal lymphocytes splaying the collagen fibers, involving predominantly the superficial and mid-dermis (6 cases) or the entire dermis (21 cases). Immunohistochemical staining revealed a cytotoxic phenotype in 9/13 tested cases. Variable amounts of histiocytes/macrophages were found interstitially in all tested biopsies but never represented a population larger than that of T lymphocytes. Our study shows that IMF is a peculiar variant of MF with frequent cytotoxic phenotype. This histopathologic variant in most cases represents a transient pattern in otherwise conventional MF. Accurate clinicopathologic correlation and phenotypic studies of atypical dermal interstitial lymphohistiocytic infiltrates allow to make a correct diagnosis.

Key Words: mycosis fungoides, interstitial mycosis fungoides, cutaneous T-cell lymphoma, T-cytotoxic lymphocytes

(*Am J Surg Pathol* 2016;40:1360–1367)

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Mycosis fungoides (MF) is the most common type of cutaneous lymphoma.[1,2] Several clinicopathologic variants have been described (reviewed in Cerroni[2]). Interstitial mycosis fungoides (IMF) is a rare variant of MF mimicking histopathologically inflammatory dermatoses, especially interstitial granuloma annulare, inflammatory morphea, and interstitial granulomatous dermatitis (IGD).[3] Only small series and sporadic case reports of IMF have been published to date. We reviewed 21 cases of IMF to better characterize this rare histopathologic variant of MF.

MATERIALS AND METHODS

Cases of IMF were retrieved from the files of the Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz (Austria). The study has been approved by the ethical committee of the Medical University of Graz.

Clinical appearance of the lesions and history of biopsies of conventional MF (before, concomitant with, or after the biopsy classified as IMF) were evaluated in each case.

Skin biopsies were fixed in 4% buffered formalin and embedded in paraffin. Histologic examination was performed on sections stained with hematoxylin and eosin, assessing the following features: architecture of the infiltrate, epithelitropism, depth of the infiltrate, and cell morphology. Immunohistochemical analyses were performed with a standard immunoperoxidase method using the following panel of antibodies: CD2, CD3, CD4, CD5, CD30 (Novocastra-Leica Mikrosysteme, Vienna, Austria) CD8, CD68, (Dako Austria, Vienna, Austria), and TIA-1 (Immunotech-Beckman Coulter, Vienna, Austria).

RESULTS

A total of 27 biopsies from 21 patients were included in the study (M:F = 11:10; median age, 60 y; mean age, 57.3 y) (Table 1). A clinical diagnosis of MF was made in all patients. Biopsied lesions were located on the trunk (n = 13), upper limbs (n = 3), lower limbs (n = 5), or buttocks (n = 2). According to the staging system proposed by the International Society for Cutaneous Lymphomas and the European Organization for Research and Treatment of Cancer,[4] at the time of diagnosis of IMF most patients were in stage I (IA: 6 cases; IB: 10 cases), and 3 were in stage IIB.

TABLE 1. Clinical, Histopathologic, and Phenotypic Features

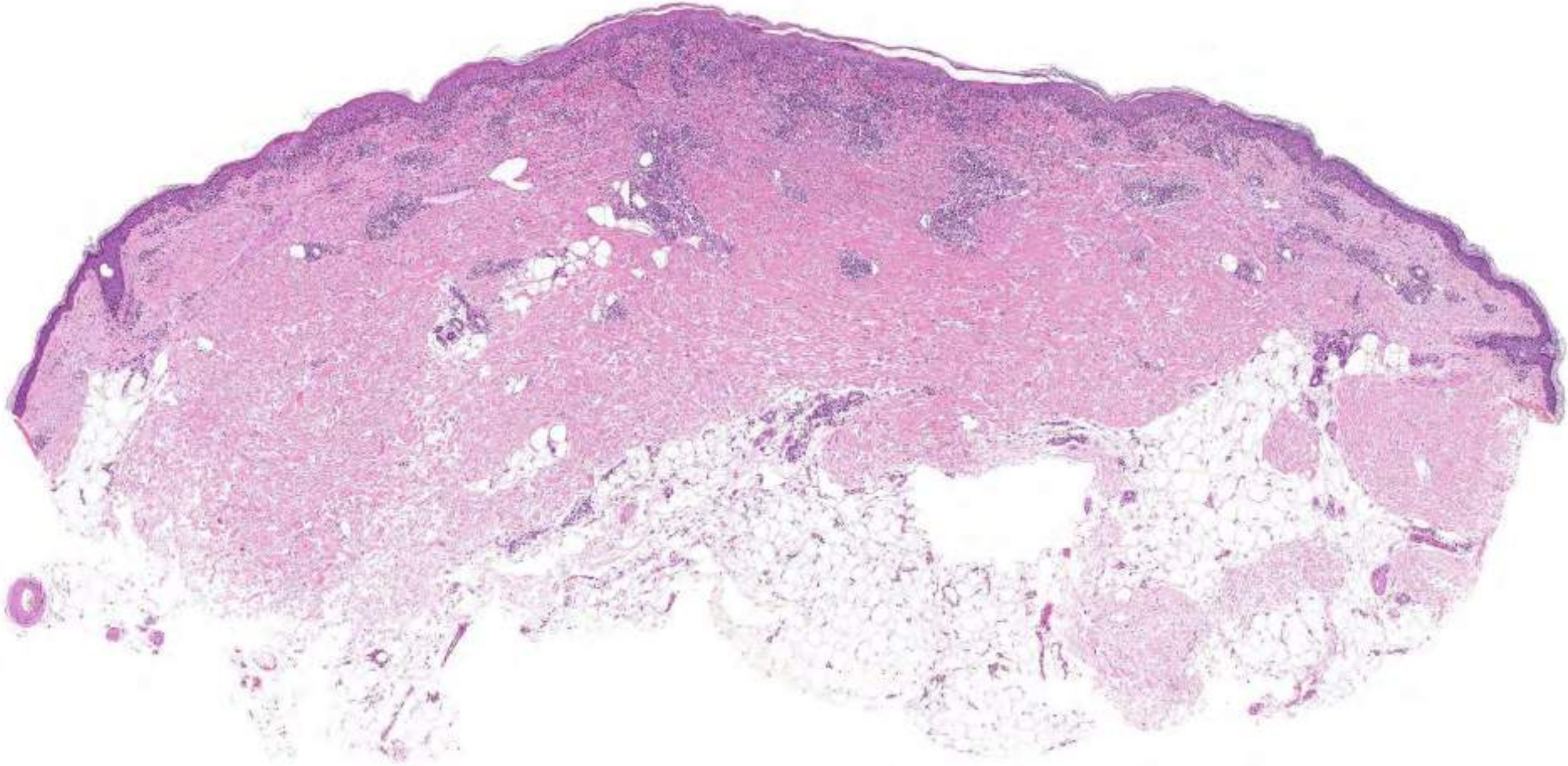
Patient #	Age (y)	Sex	Conventional MF Before (mo) or Concomitant (C) to IMF	Stage at Time of Diagnosis of IMF	Conventional MF After IMF	Follow-up (mo)	Biopsy Site	Clinical Morphology of Biopsied Lesion
1	78	M	Yes (C)	IA		NA	Right arm	Plaque
2	63	F	Yes (19)	IA		NA	Right leg	Patch
3	55	M		IA		A+ (3)	Trunk	Plaque
4	44	M		IB		A+ (2)	Trunk	Plaque
							Trunk	Plaque
5	28	M	Yes (257)	IIB	Yes	DoD (42)	Trunk	Flat tumor
6	41	M	Yes (2)	IB	Yes	A+ (125)	Trunk	Patch
7	59	M		IA		A+ (1)	Right leg	Patch
8	68	F	Yes (26)	IB	Yes	A+ (9)	Trunk	Patch
							Trunk	Patch
9	39	F		IA		NA	Trunk	Plaque
10	58	F		IA		NA	Trunk	Patch
11	67	F		IB		NA	Trunk	Plaque
12	74	M	Yes (C)	IB		A+ (12)	Trunk	Plaque
13	60	F		IB		A+ (191)	Left arm	Patch
							Left arm	Patch
							Right arm	Patch
14	69	F	Yes (C)	IA		NA	Right leg	Plaque
15	51	M		IB	Yes	A+ (54)	Trunk	Patch
16	42	M	Yes (77)	IIB	Yes	DoD (40)	Trunk	Plaque
							Buttock	Plaque
17	70	F		IB		NA	Trunk	Patch
18	62	F		IB		A+ (4)	Right arm	Patch
							Left leg	Patch
19	73	F	Yes (3)	IB	Yes	A+ (110)	Trunk	Patch
20	45	M	Yes (36)	IIB		NA	Left leg	Flat tumor
21	62	M	Yes (C)	IA		A+ (85)	Buttock	Patch

*See text for explanation.

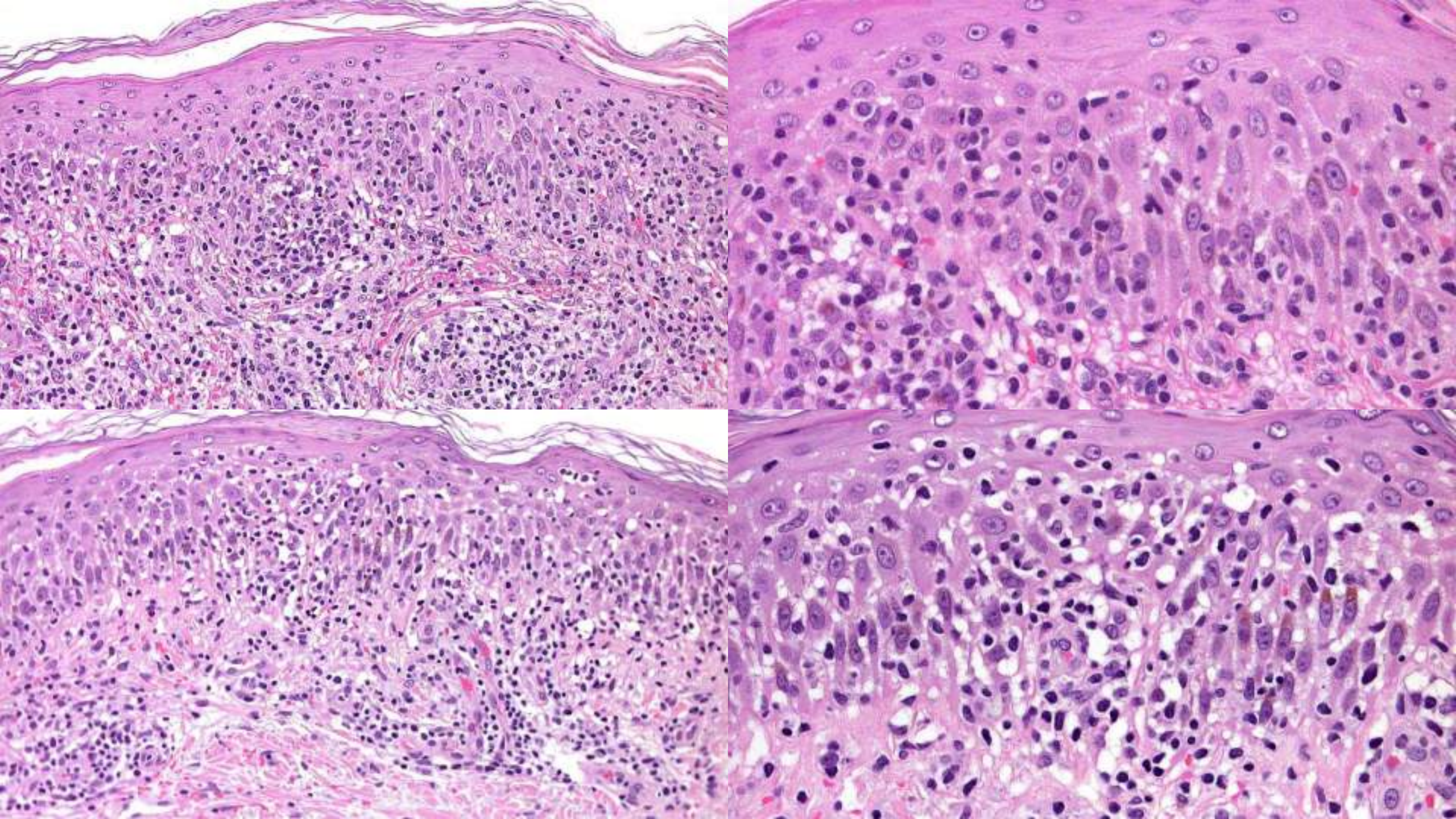
A+ indicates alive with skin disease; DoD, death of disease; F, female; M, male; NA, not available; ND, not done; SD, superficial and deep dermis; SM, superficial and mid-dermis.

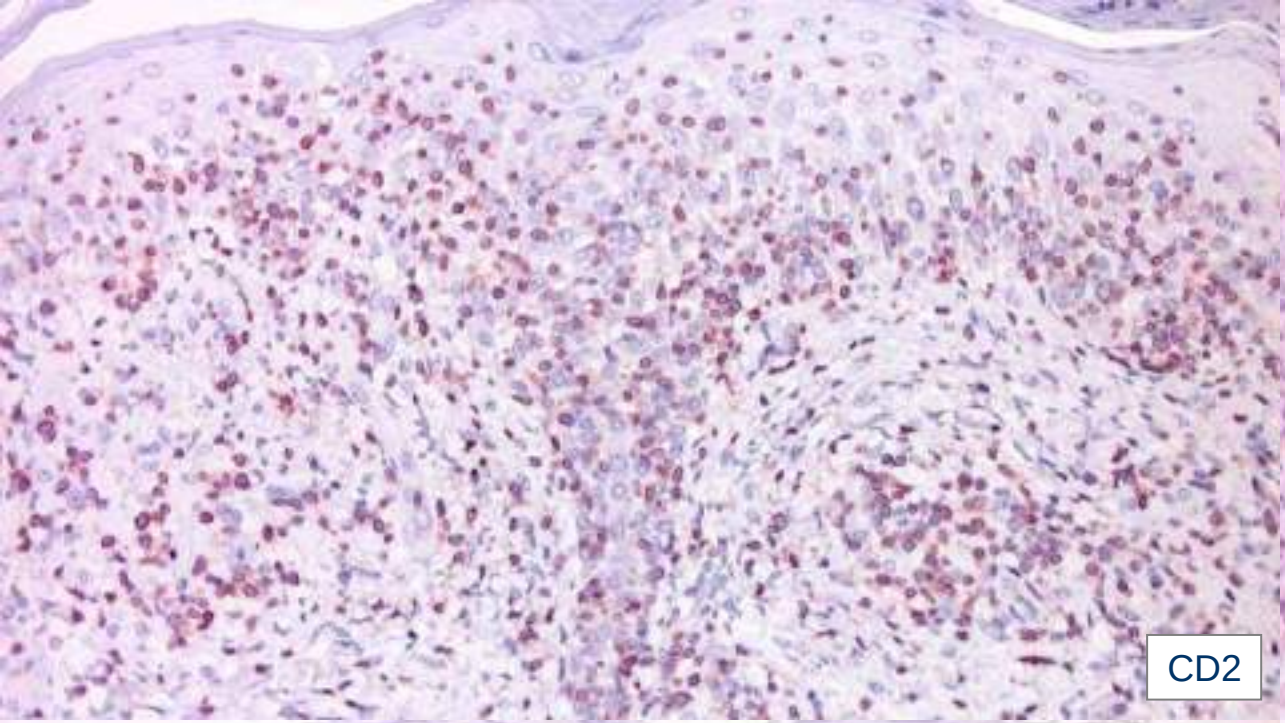
Beware the crucial importance of clinicopathological correlation

F, 70



(Consultation Dr. Mavrot, Maribor)

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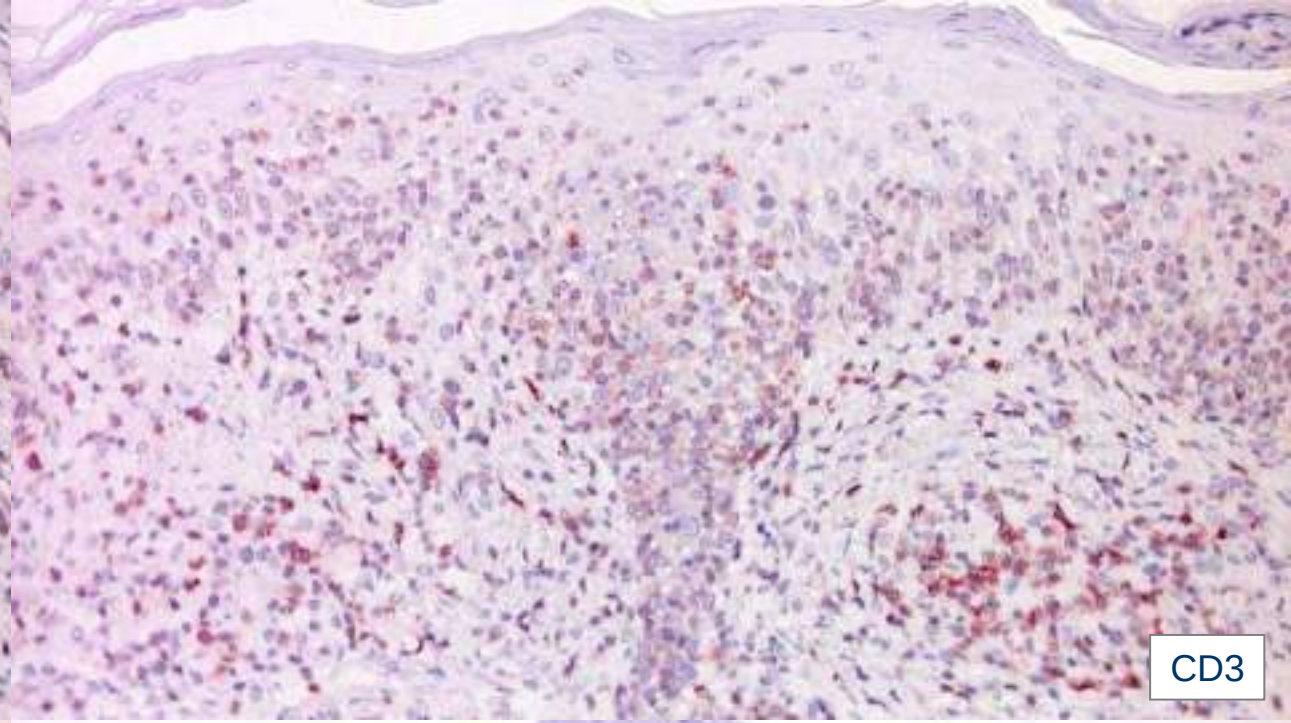
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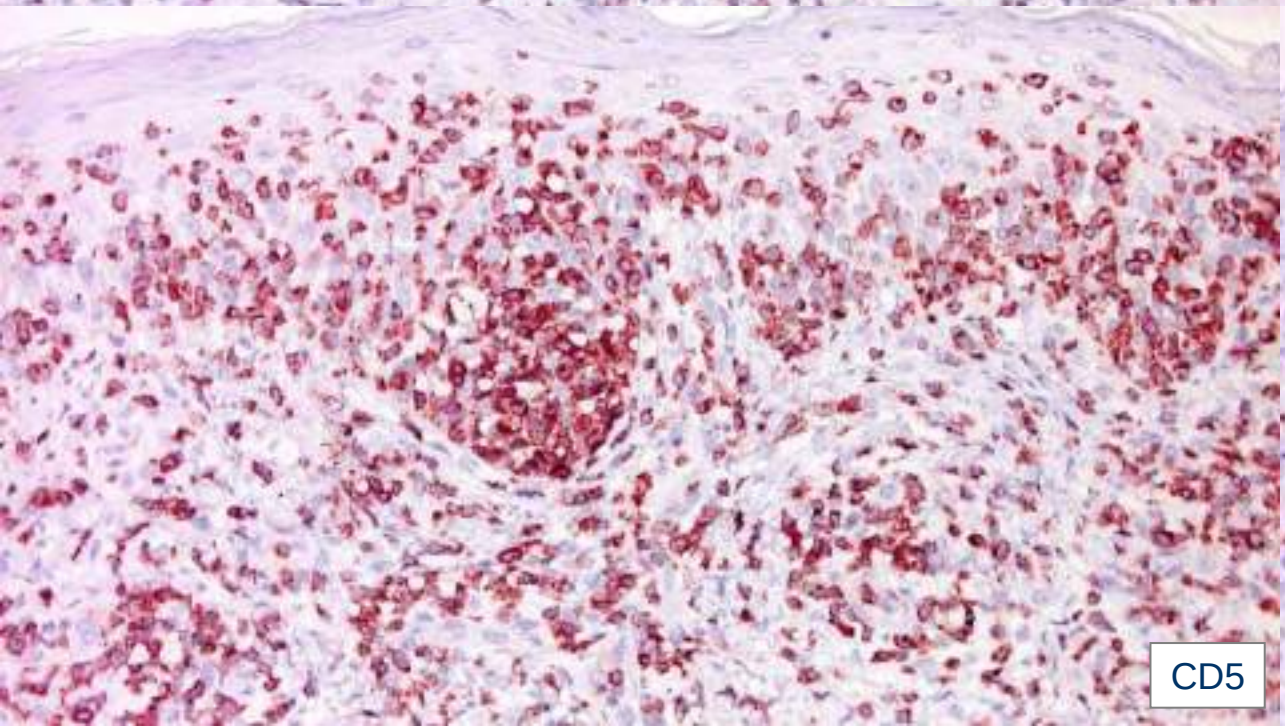
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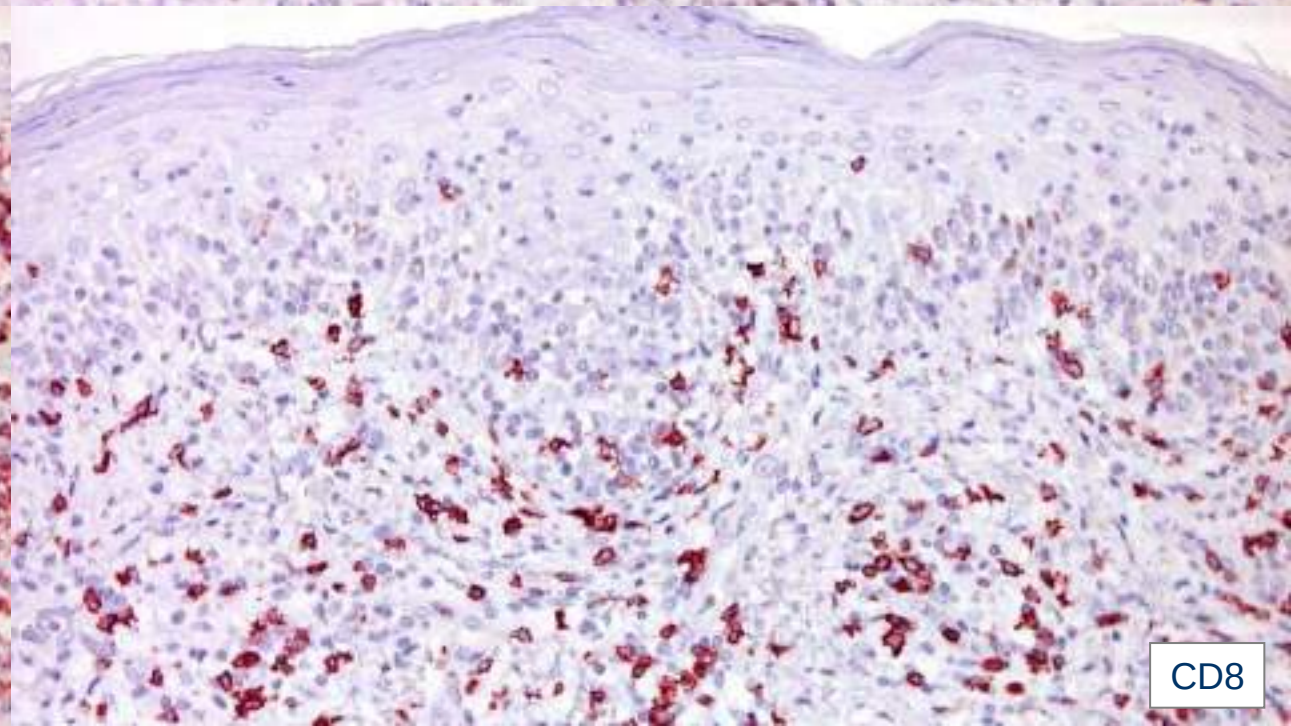
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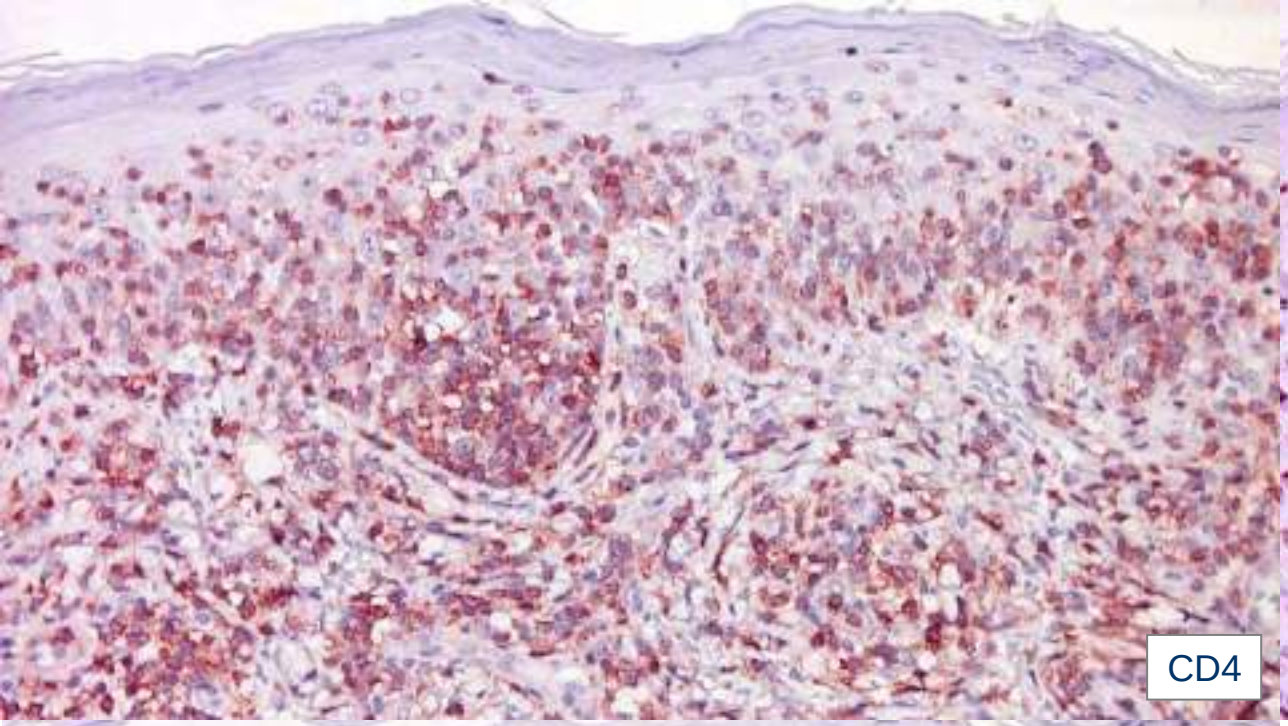
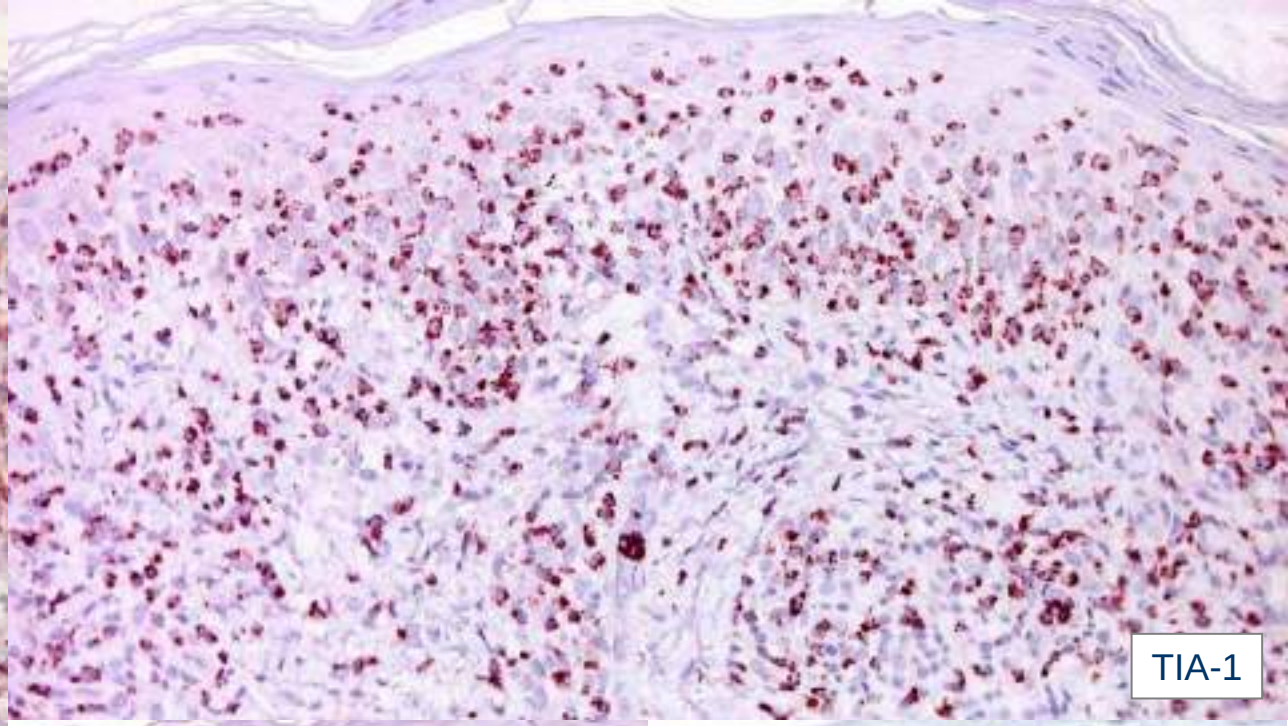

CD4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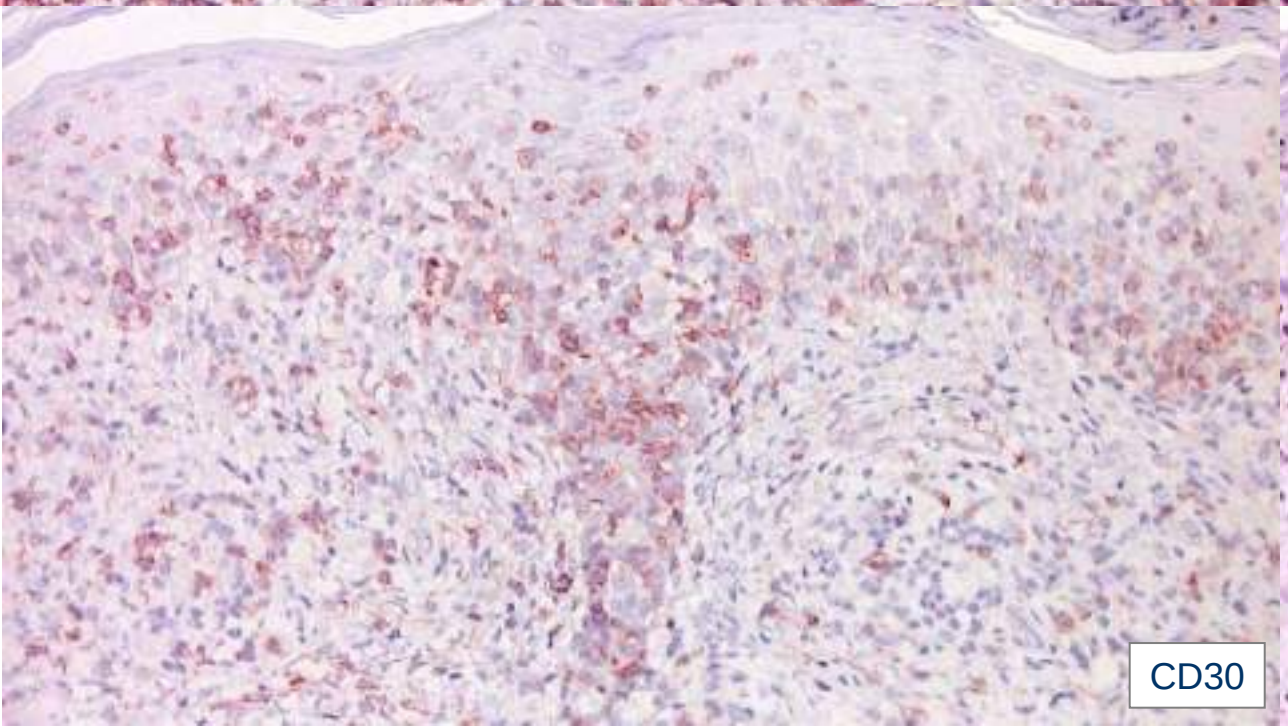
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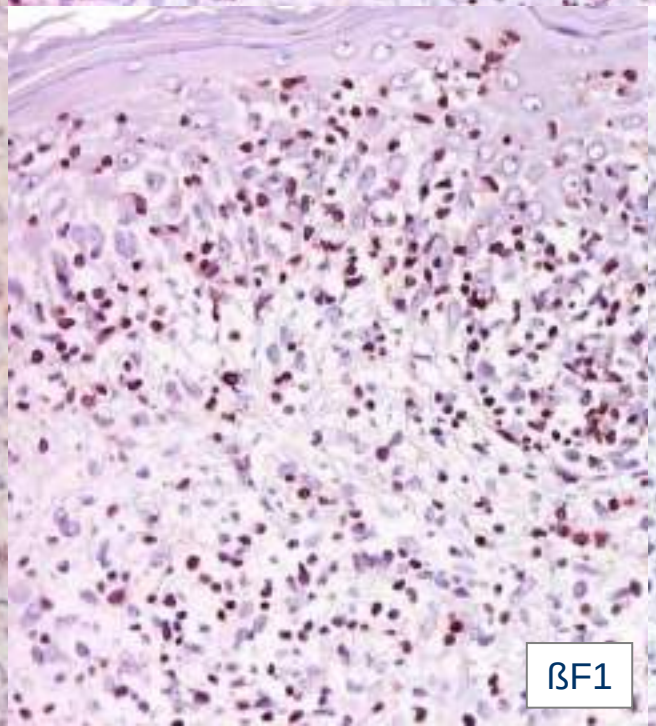
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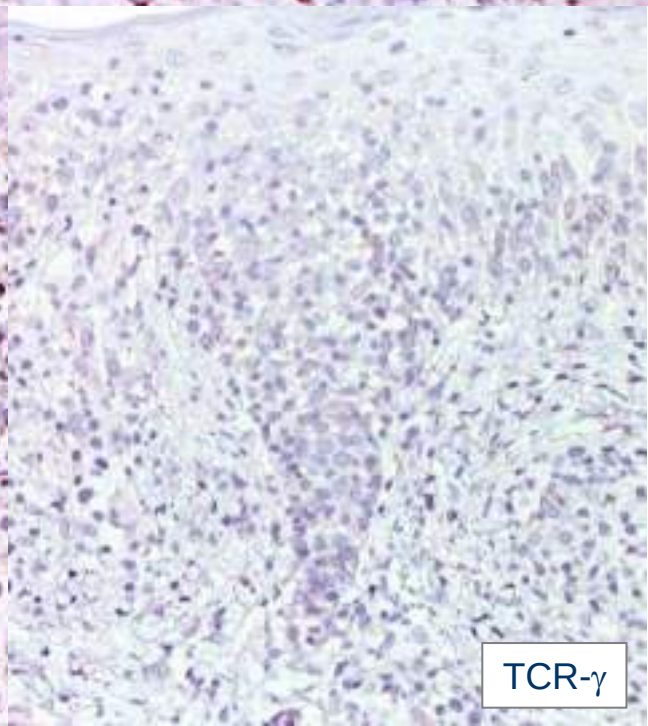
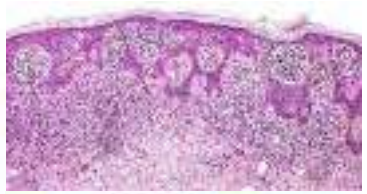
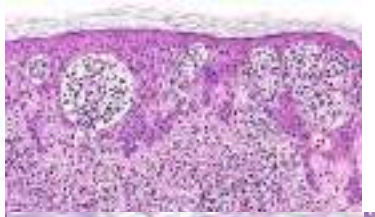

TCR-γ

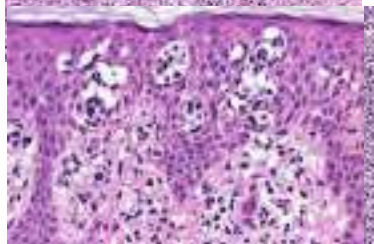
Lymphomatoid papulosis, type B

- Epidermotropic variant of lymphomatoid papulosis mimicking the histopathological features of MF
- Phenotype: CD4+ (distinct from type D, also epidermotropic but CD8+); it may express cytotoxic proteins
- In old reports described as "CD30$^-$ variant": it is always positive with antigen retrieval methods (but the positivity may be weak); repeat staining in case of doubt; a diagnosis of "CD30$^-$ LyP" should be judged critically

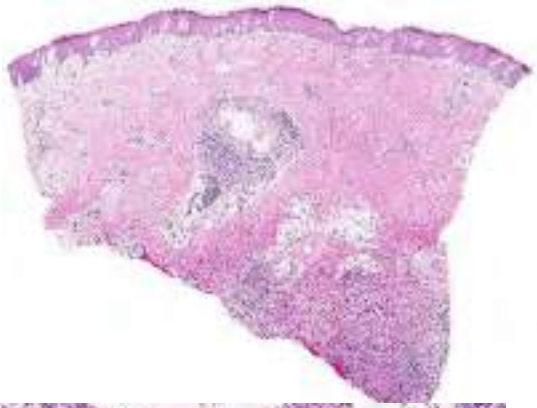
"Classic" MF

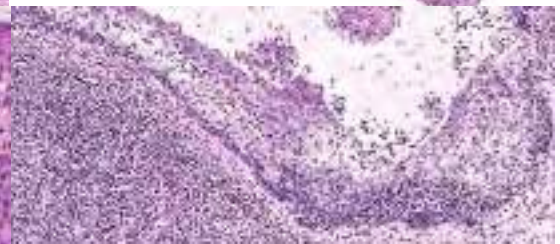




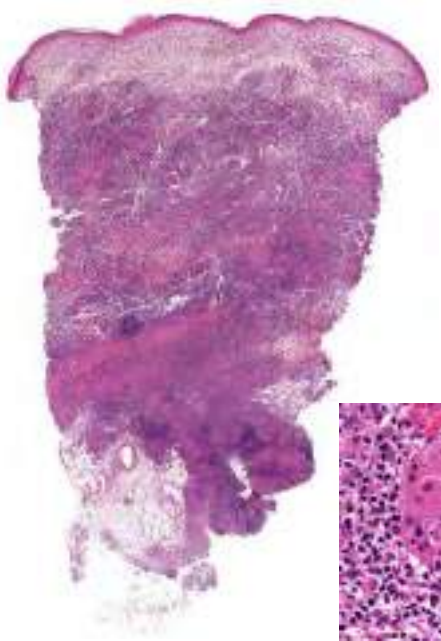


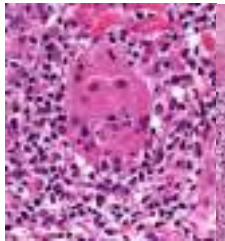
Adnexotropic MF



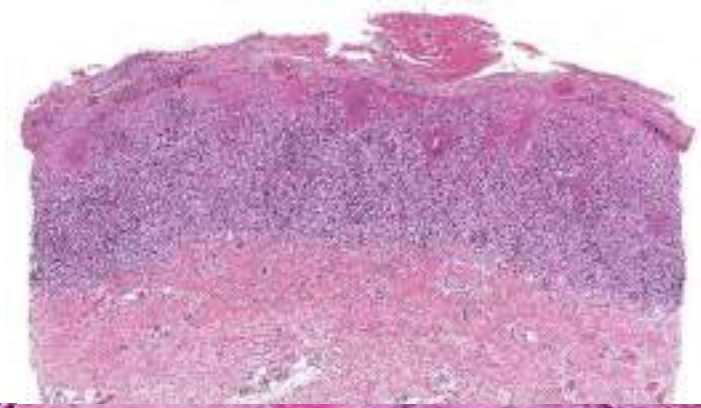


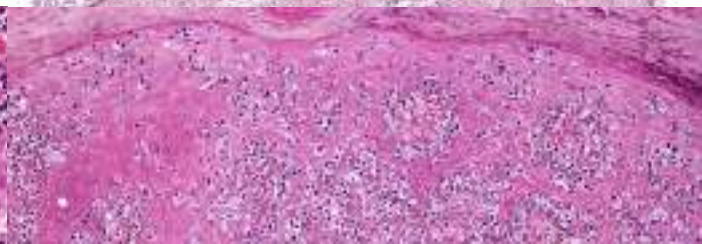
Granulomatous slack skin

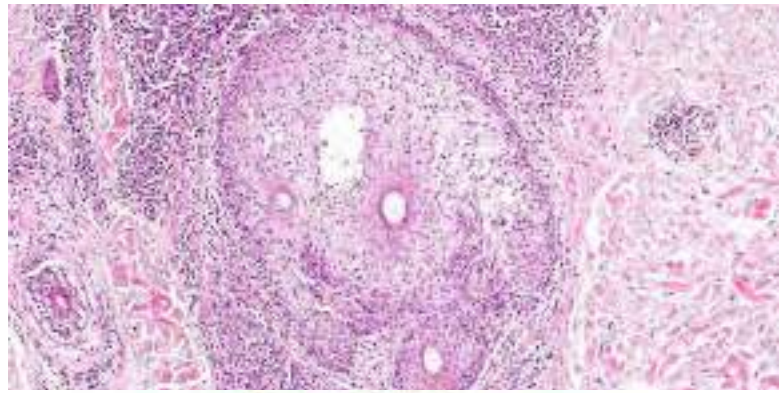


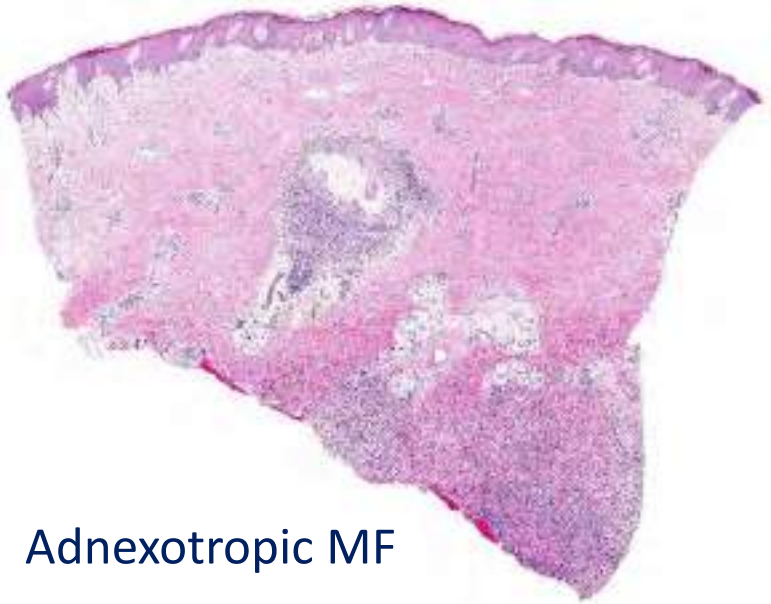


Pagetoid reticulosis



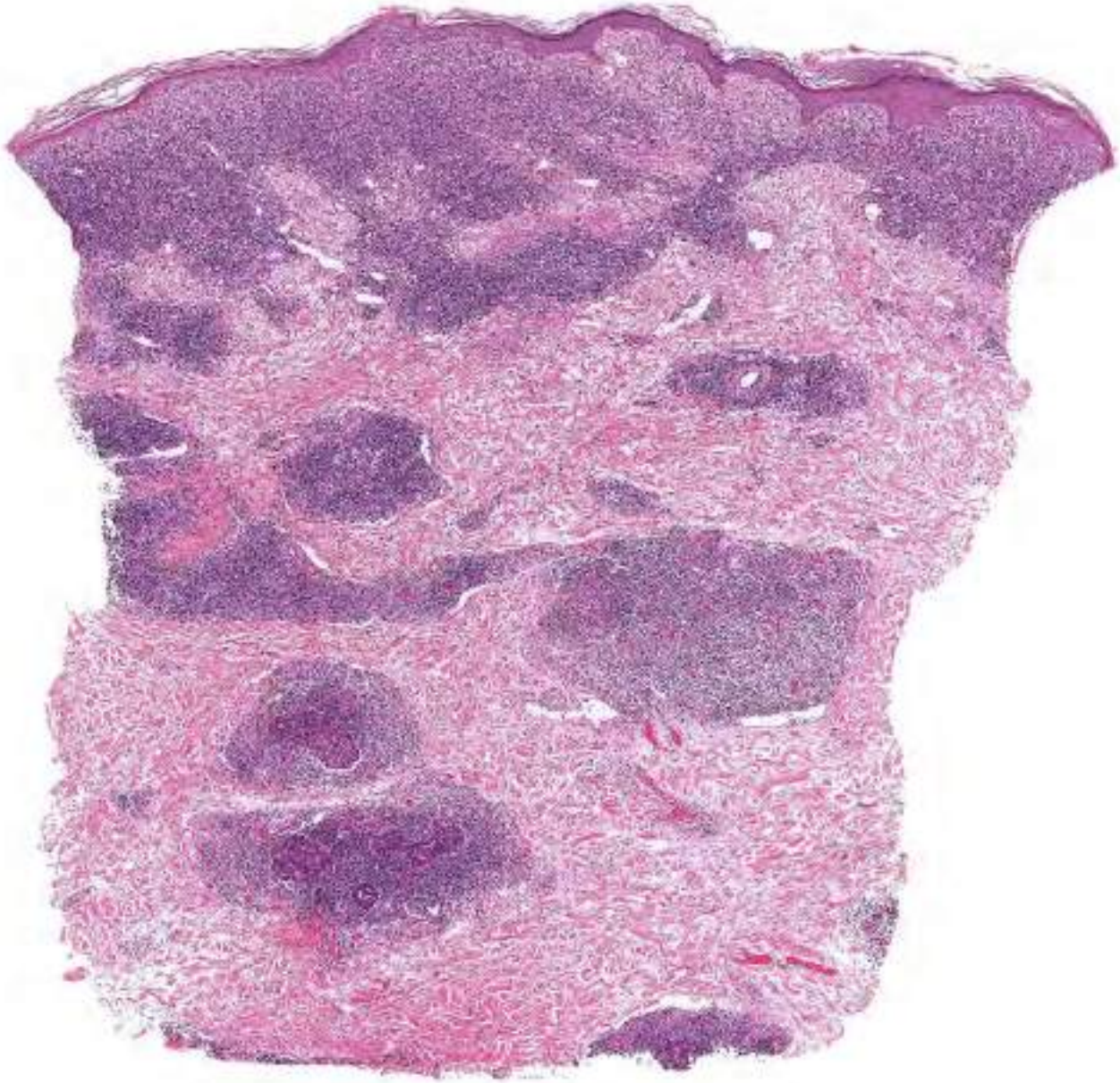


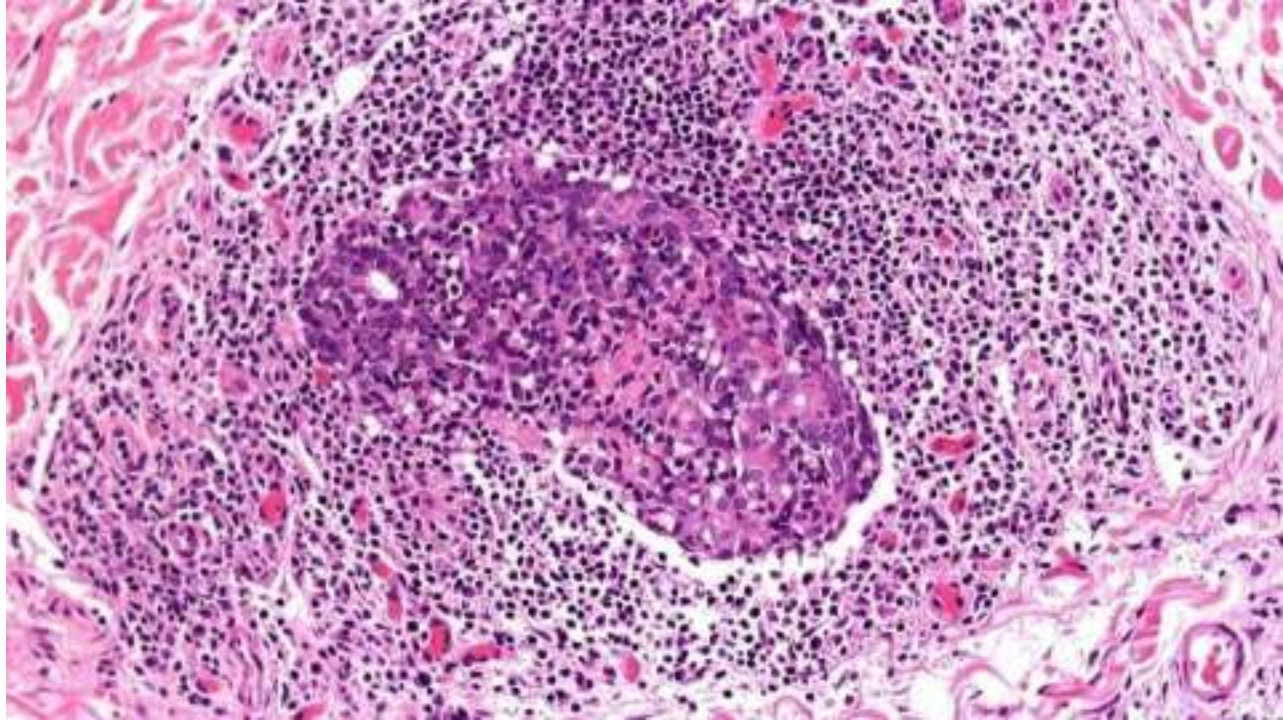




Adnexotropic MF

Adnexotropic MF (syringotropic)





ORIGINAL ARTICLE

Syringotropic Mycosis Fungoides: A Rare Variant of the Disease With Peculiar Clinicopathologic Features

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Abstract: A rare variant of mycosis fungoides (MF) characterized by prominent involvement of the eccrine glands with syringometaplasia has been reported in the past as "syringolymphoid hyperplasia with alopecia," "syringotropic cutaneous T-cell lymphoma," "adnexotropic T-cell lymphoma," or "syringotropic MF." The clinicopathologic features of this variant are not well understood, and only a few case reports or small series have been published to date. We reviewed the clinicopathologic features of 14 patients with syringotropic MF (male:female = 10:4; median age, 59 years; mean age, 57.8; age range, 33 to 83 y). Six patients had variably large, solitary patches or plaques, located on the thigh (n = 3), arm, trunk, or eyebrow (1 each). The other 8 patients had multiple, mostly generalized lesions. A history of MF was known in 4 of these 8 patients. With the exception of 1 biopsy specimen that was too superficial and did include the eccrine secretory coils but not the eccrine glands, all cases showed prominent involvement of the eccrine glands. Variable degrees of syringometaplasia ranging from small to large epithelial complexes were present in all specimens. The eccrine glands and syringometaplastic structures were surrounded by dense lymphoid infiltrates with prominent epidermotropism. Concomitant involvement of the epidermis and of the hair follicles was observed in 12 and 8 biopsies, respectively. This is the largest series of syringotropic MF, showing that this is a rare variant of the disease with peculiar clinicopathologic features. Dermatologists and dermatopathologists should be aware of this rare variant of MF to avoid delayed diagnosis and treatment.

Key Words: mycosis fungoides, syringotropic mycosis fungoides, cutaneous T-cell lymphoma, syringolymphoid hyperplasia with alopecia, pilotropic mycosis fungoides, follicolotropic mycosis fungoides

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Mycosis fungoides (MF) is the most common type of cutaneous lymphoma, accounting for approximately 50% of all cases of primary cutaneous lymphoma.[1–3,5,14] In the World Health Organization classification of hematological malignancies and in the World Health Organization-European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas, besides the conventional type of MF (so-called Alibert-Bazin type), 3 variants of the disease are explicitly mentioned, namely, solitary pagetoid reticulosis (Woringer-Kolopp), folliculotropic MF, and granulomatous slack skin.[14,31] Besides these presentations, many other clinical and/or histopathologic variants of the disease have been described.[1]

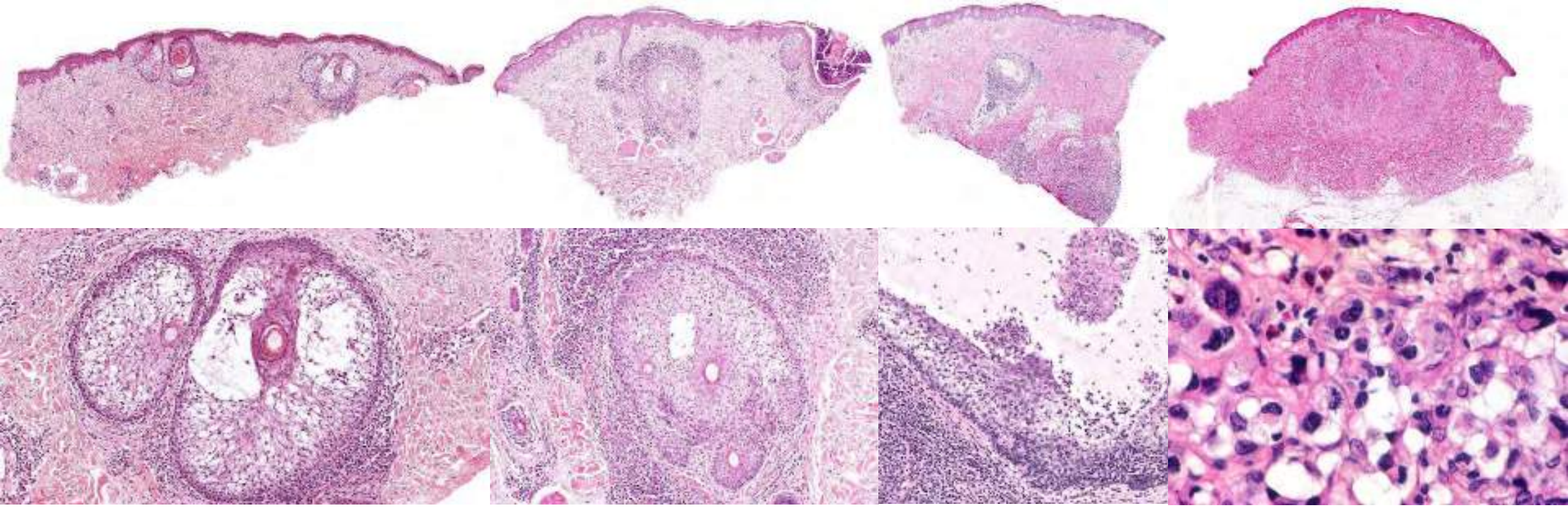
A rare variant of MF characterized by prominent involvement of the eccrine glands with "syringometaplasia," has been reported in the past as "syringolymphoid hyperplasia with alopecia,"[1,3,6,10,23,25,26,29] "syringotropic cutaneous T-cell lymphoma,"[1,2,12,24,30,32,33] "adnexotropic T-cell lymphoma,"[24,3] or "syringotropic MF."[9,30] The clinicopathologic features of this variant are not well understood, and only a few case reports or small series have been published to date.

Herein, we report 14 patients with syringotropic MF with emphasis on the clinical and histopathologic features of this rare variant of the disease.

MATERIALS AND METHODS

We reviewed the lymphoma database of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz for cases of MF that showed prominent involvement of the eccrine glands (defined as dense, nodular lymphoid infiltrates around hyperplastic eccrine structures with syringotropism). Cases of MF showing lymphoid infiltrates surrounding the eccrine coils or glands, but without epithelial hyperplasia and/or syringotropism were not included (see also Fig. 10). All diagnoses were confirmed by histopathologic examination and correlation with the clinical picture and/or detailed clinical data. Thirteen cases matching the inclusion criteria were found. We also included 1 additional case that showed prominent involvement of the eccrine coils. The biopsy of this case was too superficial and did not include the eccrine

- Clinico-pathologic variant of mycosis fungoides; sometimes solitary lesions
- Clinical manifestations oft different from "conventional" MF
- Prominent involvement of the eccrine glands; syringometaplasia
- Oft concomitant involvement of the hair follicles *(syringotropic-pilotropic MF; "syringolymphoid hyperplasia with alopecia")*



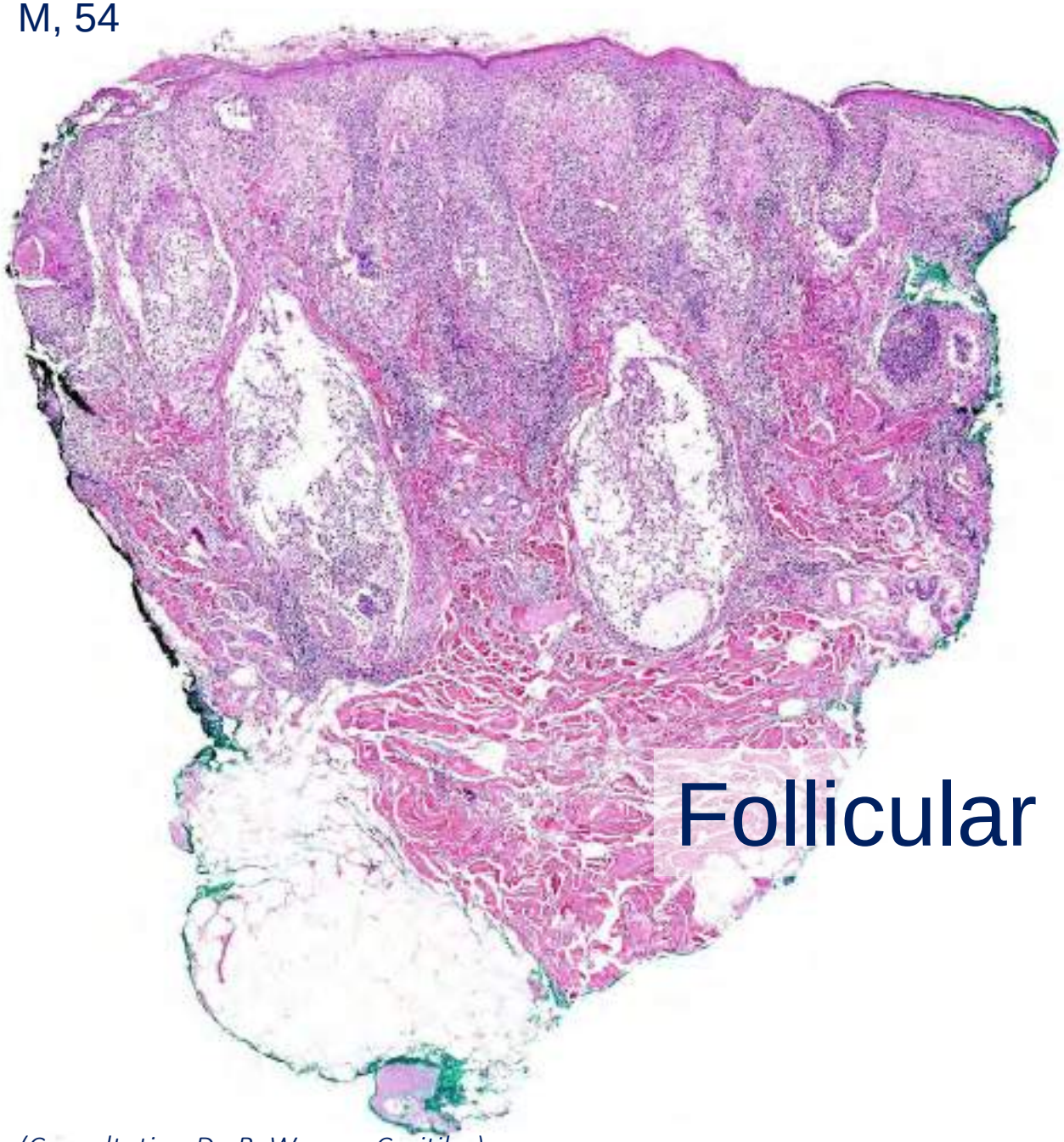
1st diagnosis (4-year history) | 5 years later | 6 more years later

Died of progressive MF, November 1989 (12 years after 1st diagnosis, 16 after onset of disease)

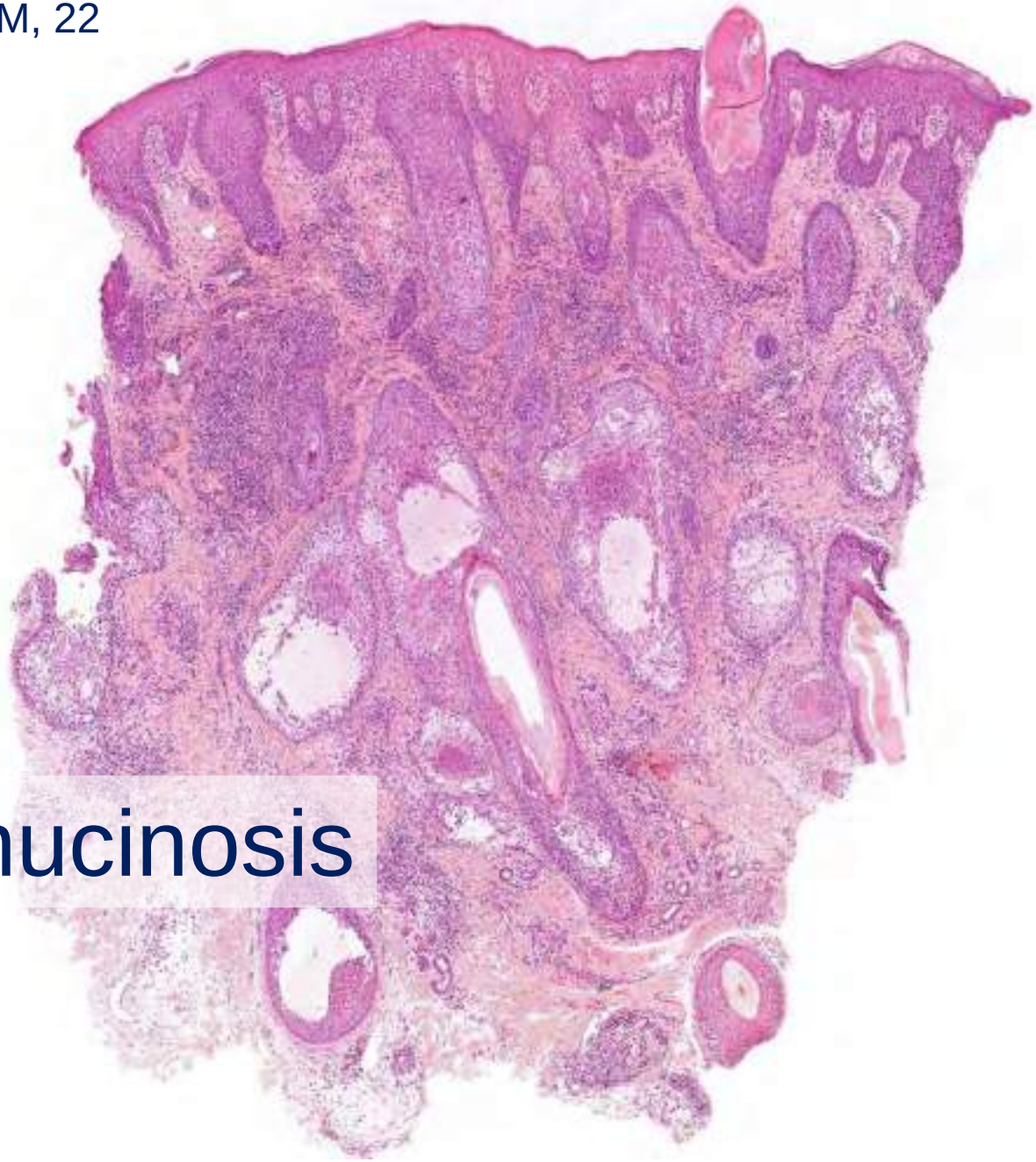
"Idiopathic" generalized follicular mucinosis

- "Idiopathic" generalized follicular mucinosis is a form of early pilotropic MF
- Course and prognosis similar to early "conventional" MF, but response to skin-directed treatment may be less pronounced and/or more delayed
- Avoid aggressive treatment; manage as other cases of early MF, eventually with the association of systemic retinoids to other standard options

M, 54



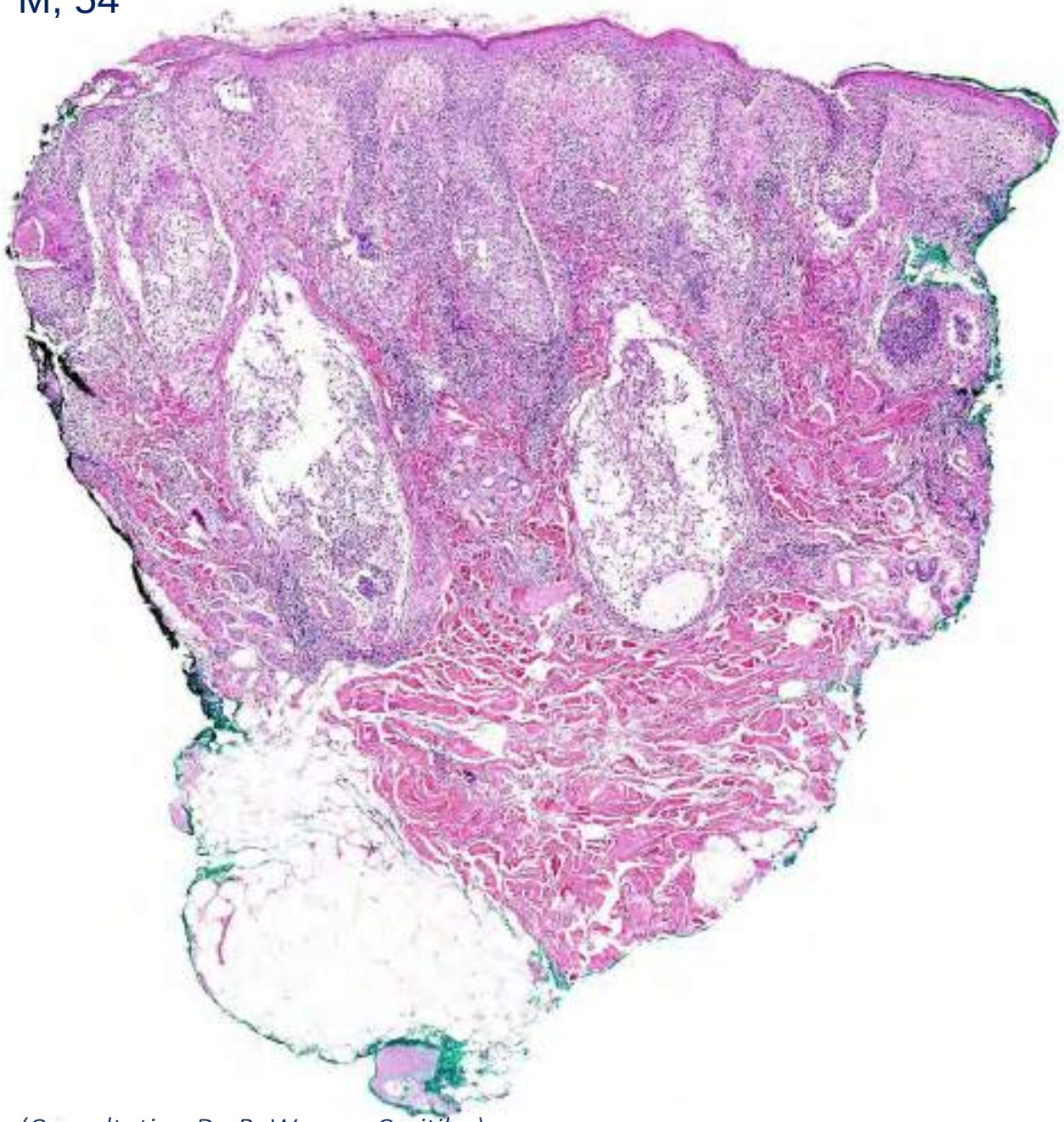
M, 22

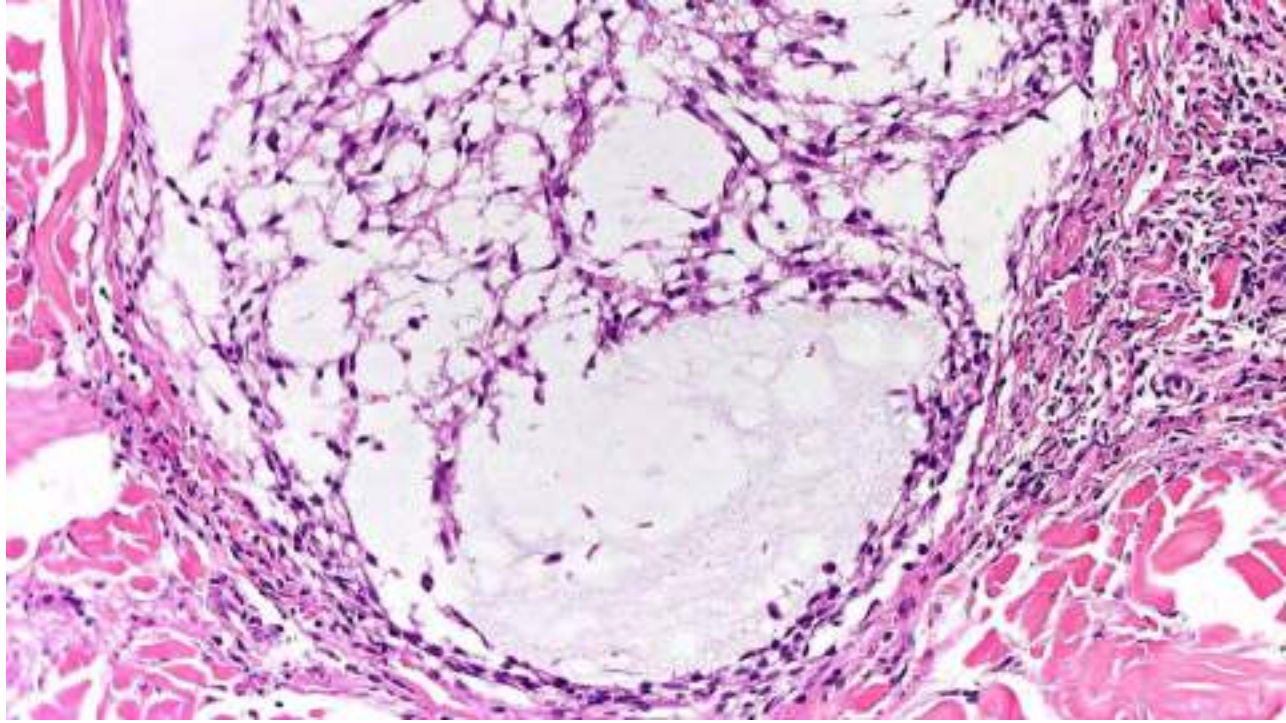


Follicular mucinosis

(Consultation Dr. B. Werner, Curitiba)

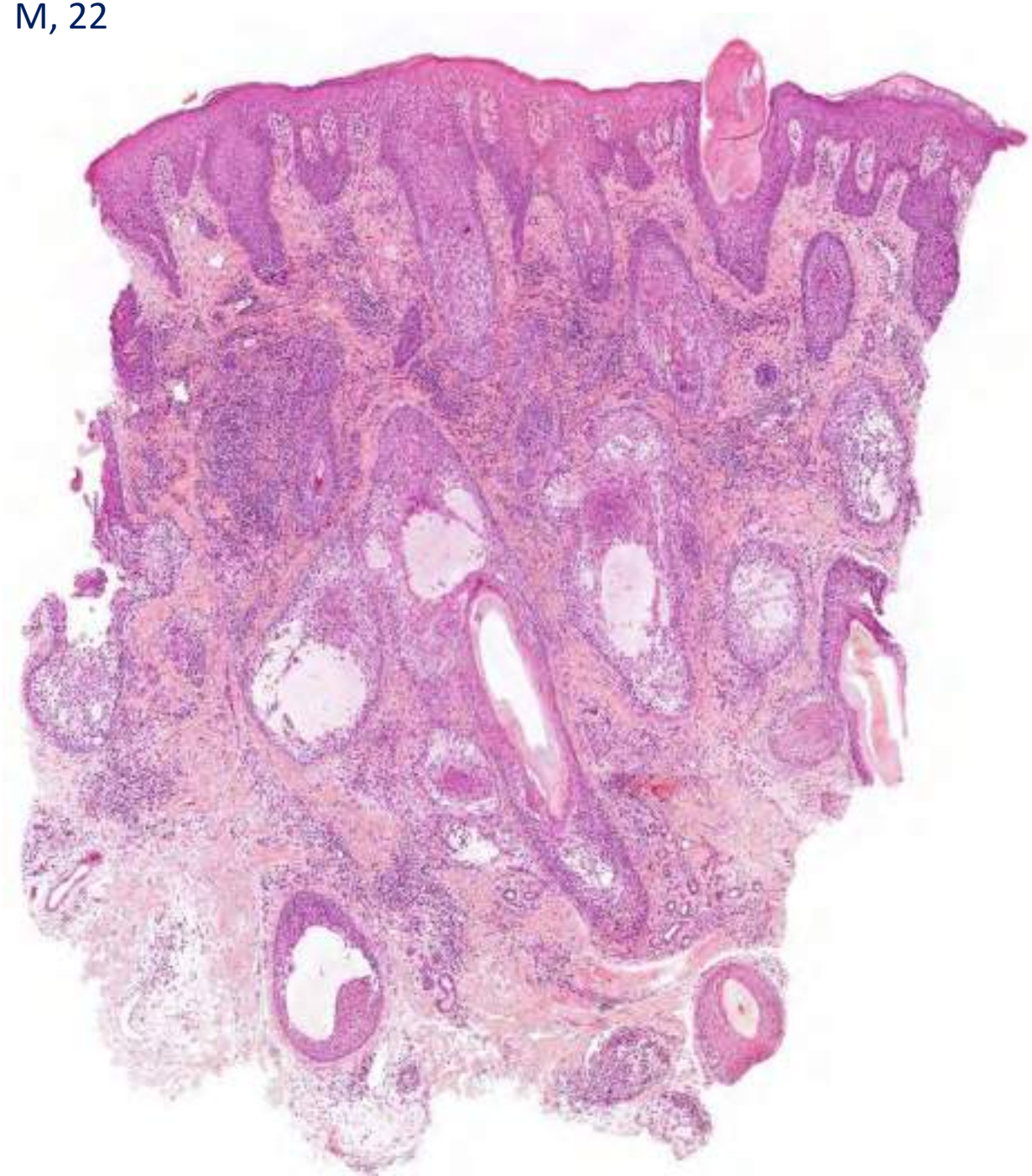
M, 54

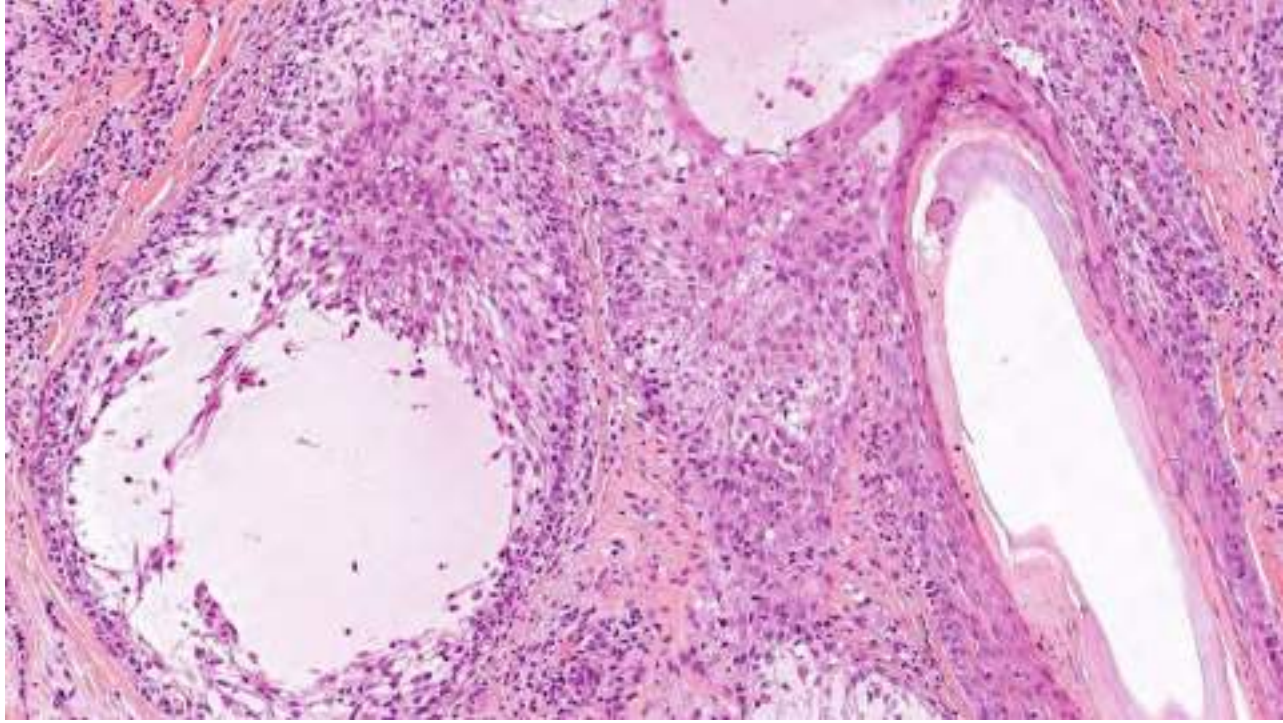




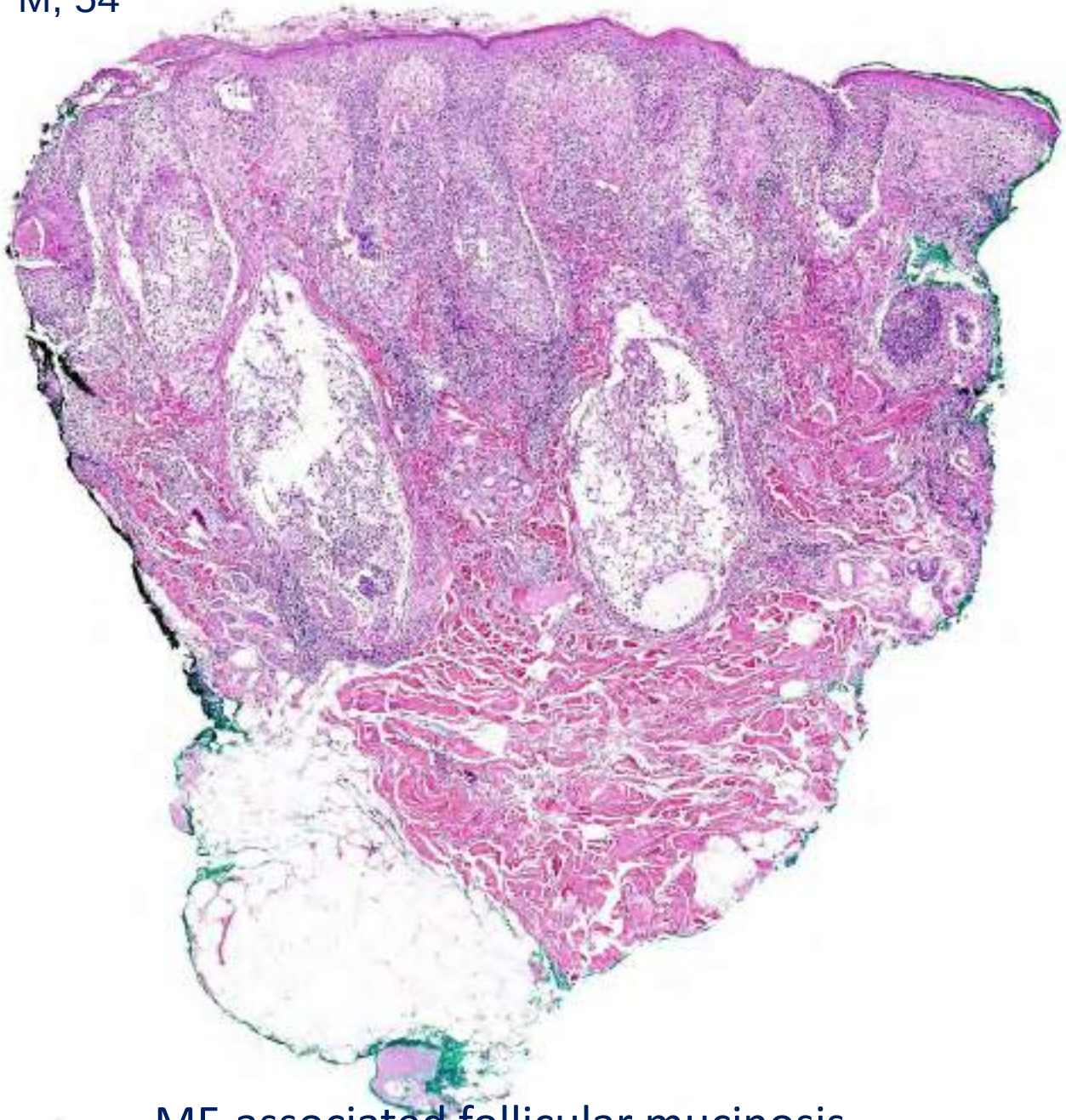
(Consultation Dr. B. Werner, Curitiba)

M, 22



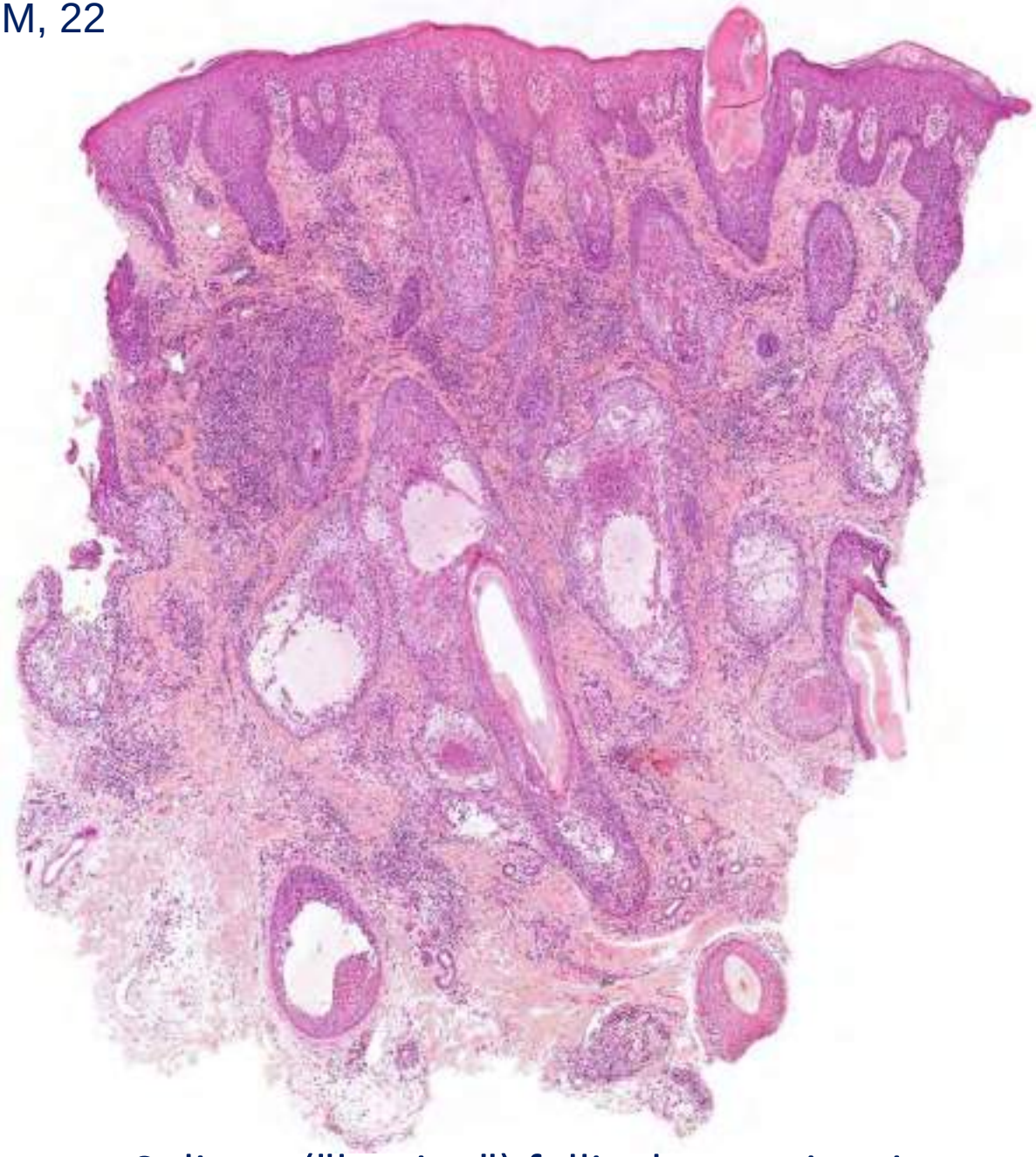


M, 54



MF-associated follicular mucinosis

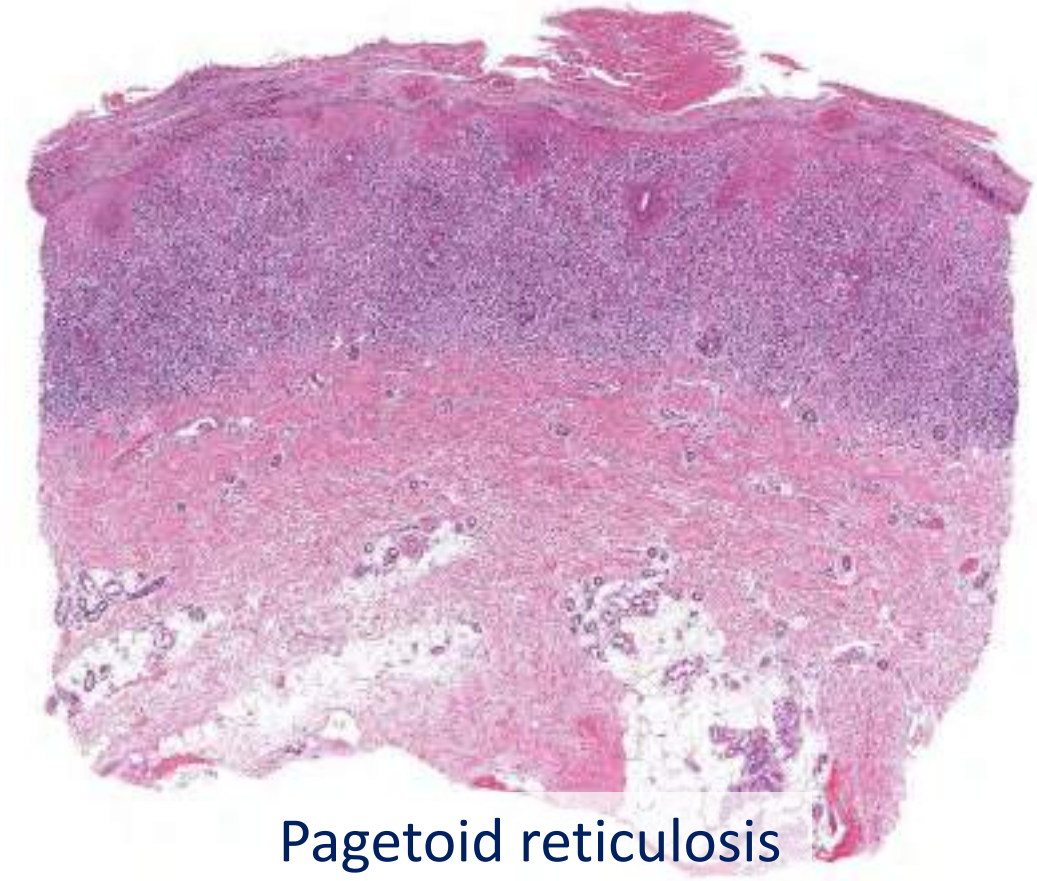
M, 22



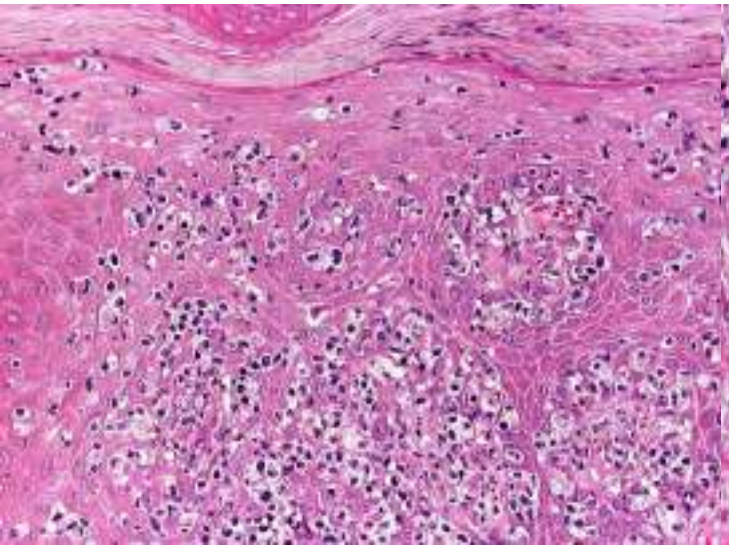
Solitary ("benign") follicular mucinosis

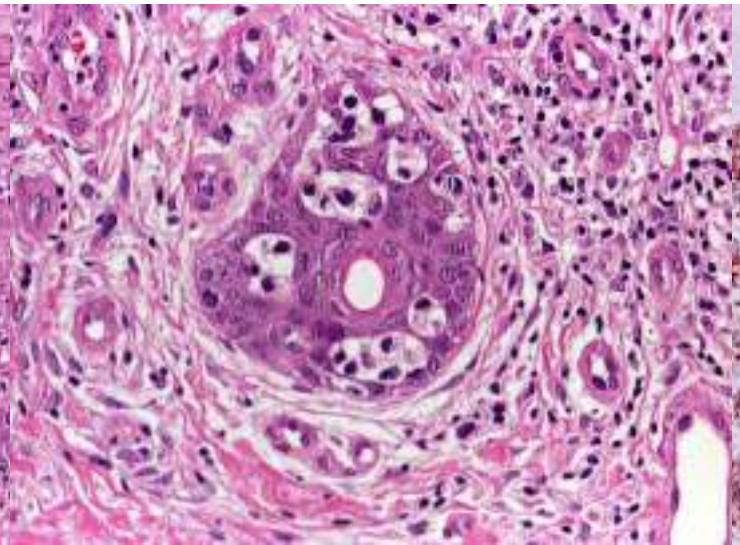
Pilotropic & adnexotropic mycosis fungoides

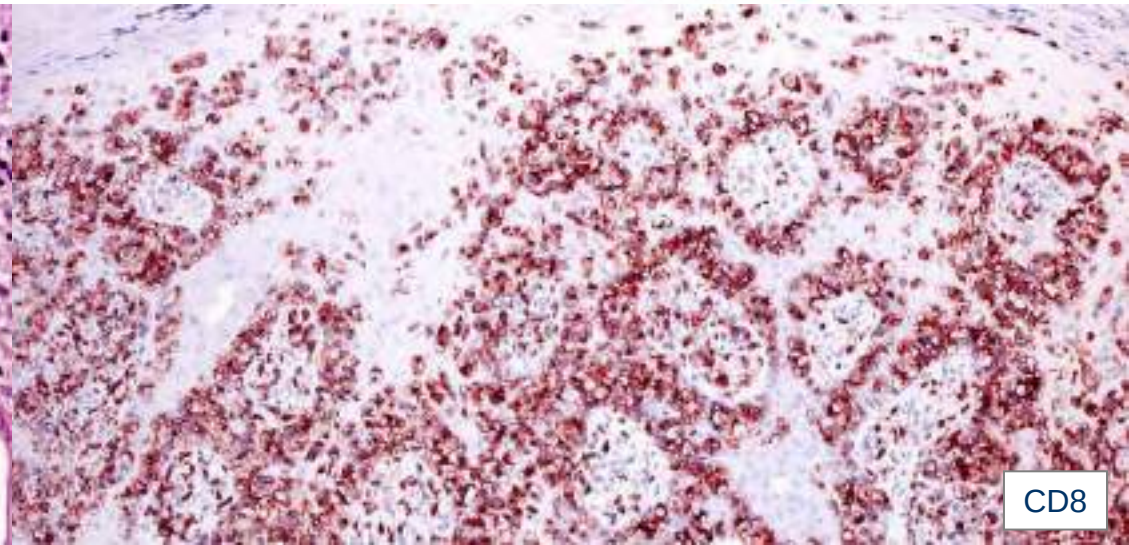
- A variant observed in all ages including children; pilotropic & syringotropic patterns may be present in the same lesion
- Several clinicopathologic presentations; some variants similar to those observed in MF *(e.g., hypopigmented follicular mucinosis)*
- Classification of "benign alopecia mucinosa" yet unclear
- Morphological, phenotypic and molecular features don't allow to separate MF-associated cases from "benign" ones
- Conservative approach; avoid aggressive treatment (but local radiotherapy may be an option)
- *Non-malignant follicular mucinosis may be observed histologically on the background of several inflammatory and neoplastic conditions*



Pagetoid reticulosis







Pagetoid Reticulosis

- Pagetoid reticulosis is considered as a localized (often solitary) variant of MF *(Woringer-Kolopp disease)*
- Mostly on acral skin; may mimic viral warts or inflammatory dermatoses – clinically deceptive ("non-responsive eczema"), histologically clear-cut
- Prognosis usually favourable
- *Similar histopathological features may be observed also in clinically "conventional" MF*

Br. J. Derm. (1970), **82**, 397.

Department of Dermatology, Harvard Medical School

GRANULOMATOUS MYCOSIS FUNGOIDES

A. BERNARD ACKERMAN AND B. ALLEN FLAXMAN*

SUMMARY.—An unusual form of mycosis fungoides was characterized clinically by the spontaneous resolution of ulcerated nodular lesions into poikiloderma and histologically by a granulomatous malignant lymphoma.

An extraordinary form of mycosis fungoides was characterized clinically by extensive ulcerated nodules, many of which healed spontaneously leaving atrophic scars and patches of poikiloderma. Granulomatous malignant lymphoma was found on histological examination.

CASE REPORT

For 18 years, a white factory worker aged 46 had a skin disease consisting of polymorphous lesions. It began as scaling on the thighs and abdomen and was diagnosed as psoriasis. These lesions increased in number and after 13 years involved most of the body. Five years before his admission to the Massachusetts General Hospital, some of the lesions became nodular and ulcerated. These ulcerated nodules showed a pronounced tendency to heal spontaneously, but new lesions continued to appear. The patient did not seek dermatological help because he thought that "psoriasis" was not treatable. Despite the extensive involvement of the skin, he felt well and continued to work.

Physical examination.—The cutaneous lesions were generalized (Fig. 1). There were reddish-purple nodules, many of which were ulcerated and covered with purulent material, on the scalp, buttocks and hands (Fig. 2). Violaceous, indurated scaling plaques with irregular borders, some ulcerated, were distributed over the entire body. There were numerous areas of atrophy at sites of previous lesions. Some of these residual lesions had features of poikiloderma with atrophy, hypo- and hyperpigmentation, and telangiectasia (Fig. 3). There was scarring alopecia of the scalp (Fig. 4) and partial loss of the right eyebrow. The palms and soles were not involved. Except for minimally enlarged inguinal lymph nodes, the remainder of the physical examination was normal.

Histopathology.—Multiple biopsies from nodular lesions showed parakeratosis and elongation of the rete ridges with preservation of the rete-papillae pattern. The interface between the epidermis and dermis was partially obscured by an infiltrate composed of foamy histiocytes, lymphocytes, eosinophils, and large mononuclear cells with atypical pleomorphic nuclei, some of which were in mitosis (Fig. 5). These atypical mononuclear cells were scattered throughout the epidermis and some formed small collections in the region of the granular zone. Large dense aggregates of this polymorphous infiltrate were present throughout the dermis. Within the infiltrates were huge giant

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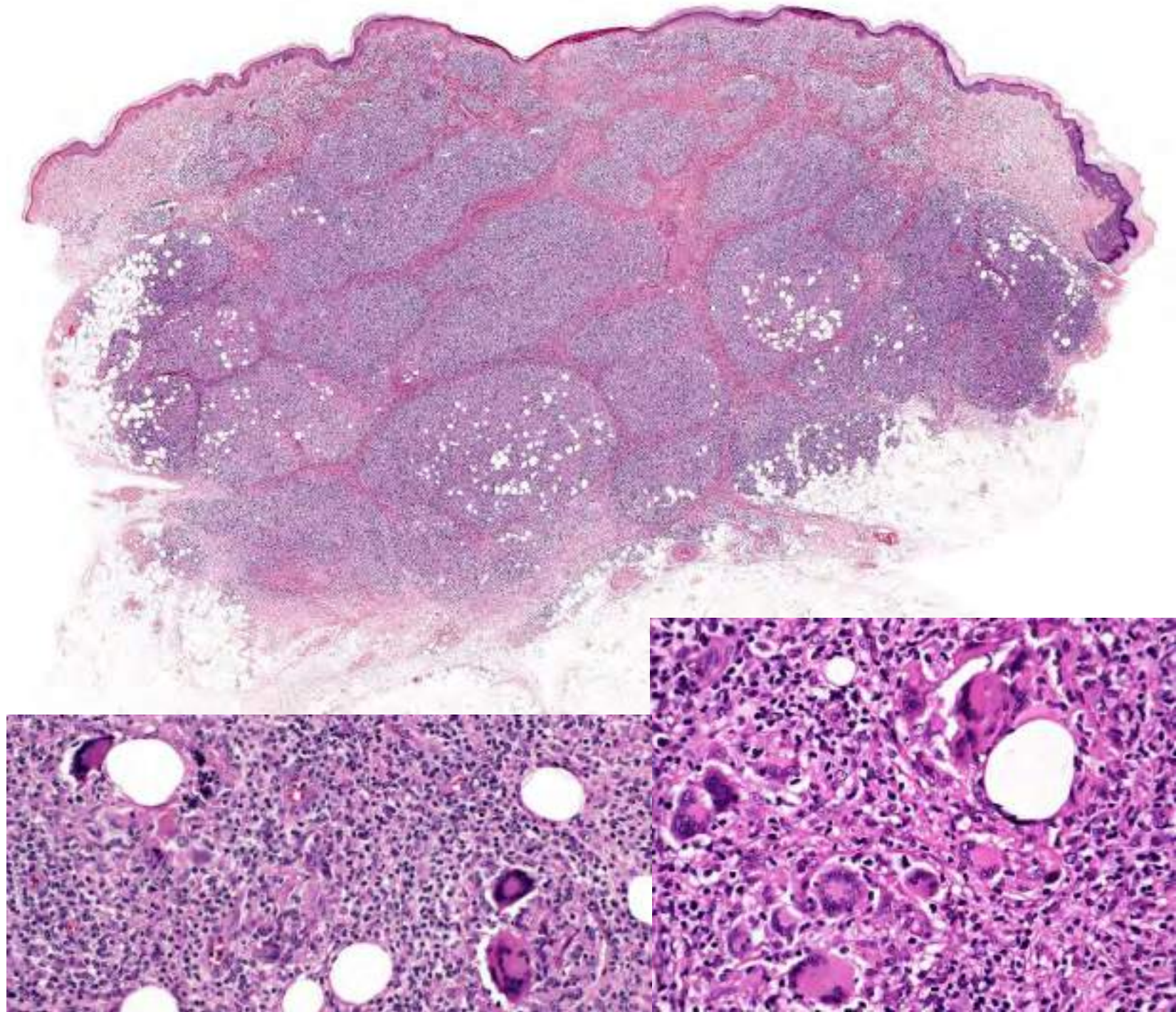
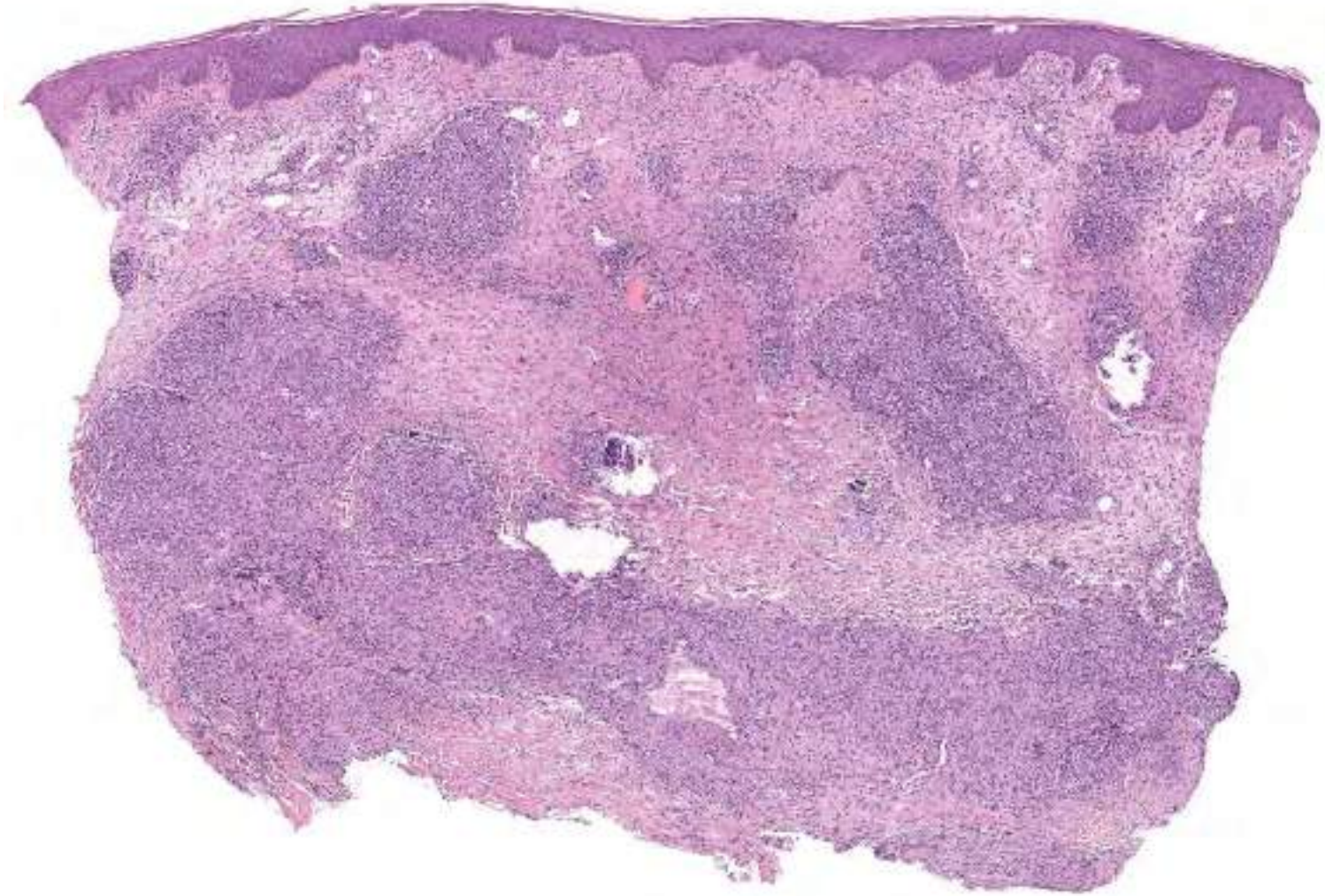
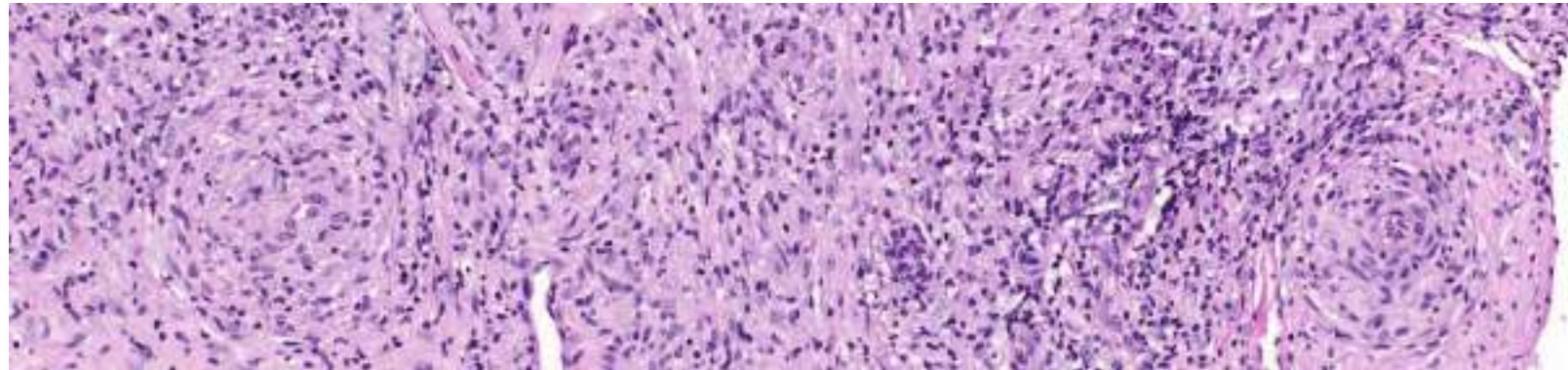
Abstract

A unique form of mycosis fungoides was characterized clinically by the spontaneous resolution of ulcerated nodular lesions into poikiloderma and histologically by a granulomatous malignant lymphoma.







Progressive, Atrophying, Chronic Granulomatous Dermohypodermitis

Autoimmune Disease?

Jacinto Convit, MD; Francisco Kerdel, MD; Mauricio Gochman, MD; Antonio J. Rondón, MD; José M. Soto, MD, Caracas, Venezuela

A chronic, progressive dermatosis is described, characterized by papular lesions forming plaques in various parts of the body, with secondary phenomena of acquired cutis laxa. Histologically, the lesions were typified by a granuloma formed by histiocytes, epithelioid cells and giant cells, lymphocytes, plasmocytes, and lipophagia phenomena.

The disease started after the successive injection of Mitsuda antigen and of BCG vaccine. One of the initial lesions appeared at the site where the Mitsuda antigen had been injected. The disease evolved during a period of more than 20 years.

Oral treatment with corticosteroid produced partial regression. When treatment with this drug was discontinued the clinical manifestations became worse, with fever and arthralgia.

In face of such a special clinical picture we thought of the possibility that it might be an autoimmune disease. When azathioprine was administered, there was regression of the lesions.

The patient died after a period of intense diahrrea. He also had a generalized inflammation of lymph nodes. The postmortem study of one of his lymph nodes rendered a diagnosis of Hodgkin's disease.

Accepted for publication April 4, 1972.

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Reprint requests to Instituto Nacional de Dermatología, Apartado Postal 4042, Caracas 101, Venezuela (Dr. Convit).

Unusual diseases may represent "experiments of nature." Reporting their occurrence may help in understanding mechanisms of general interest—or at least in creating awareness of possible ways in which the body may react.

We now describe a case that has been followed up for more than 20 years. The illness started after the injection of BCG vaccine and lepromin. Clinical features were highly unusual, and did not fit into any previously described entity known to us. The condition improved when corticosteroids or other immunosuppressive agents were given, but finally, the patient died in a rather precipitous final course. Postmortem studies showed Hodgkin's disease.

We feel that a detailed report of the evolution of this case may be of interest, because of its unusual clinical and histopathological features, and of the likelihood of a connection between lymphoid tissue malignancy and manifestations of autoimmune disease.[1,2]

Report of a Case

The patient was 37 years old and dark-skinned. When 15 years old, he consulted a skin specialist about two erythematous, popular plaques, one of which was located on the anterior side of his right forearm and the other in the left deltoid region. These plaques measured about 5 cm in diameter. He had been under control as a contact since his mother suffered from lepromatous leprosy. The lepromin reaction on his right forearm was negative after three weeks. He was consequently given two intradermal BCG vaccinations, both on his back, 0.1 ml of a suspension that contained 1 milligram of bacilli per milliliter. He was tested again with 0.1 ml of standard Mitsuda (10×10^6 acid-fast bacillus/ml) and showed a positive reaction.

He indicated that the plaque on his right forearm appeared at the exact site where he had been given the Mitsuda test, a few weeks after he had been vaccinated with BCG.

The dermatologist whom he consulted took a skin specimen for biopsy from the plaque on his right forearm and diagnosed the case as tuberculoid leprosy on the basis of the histological findings, the clinical aspect of the lesion, and epidemiological reasons.

When he later developed several "tumorations" in his left armpit, they were diagnosed as "suppurative hidroadenitis" and were treated with penicillin.

We first saw the patient in 1960 when he was 26 years old. He showed erythematous infiltrated plaques on his chin, left deltoid region, anterior area of both forearms, and on the back of his right hand. The plaque on the left deltoid region had an atrophic center with a noticeable depression, around which the infiltrated border appeared as a raised ring (Fig 1). On the left armpit, the skin formed a large hanging bag-like fold (Fig 2).

The patient had been receiving dapsone treatment (DDS) since he first saw a der-

Fig 1.—[illegible]

Fig 2.—[illegible]

Fig 3.—[illegible]

Fig 4.—Great hanging bag-like fold on left armpit; fifteen years' evolution.

Fig 5.—Great hanging bag-like fold on left armpit, fifteen years' evolution, under treatment with oral corticosteroids.

Fig 6.—Lesion on left armpit with important atrophy.

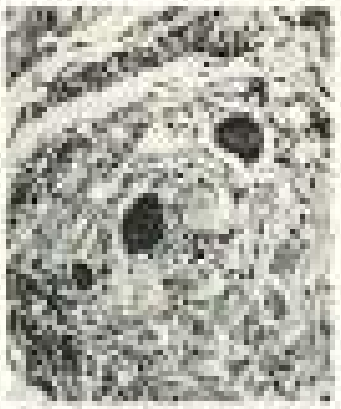


Fig 7.—[illegible]

Fig 8.—[illegible]

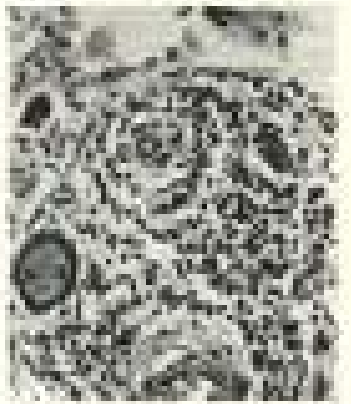
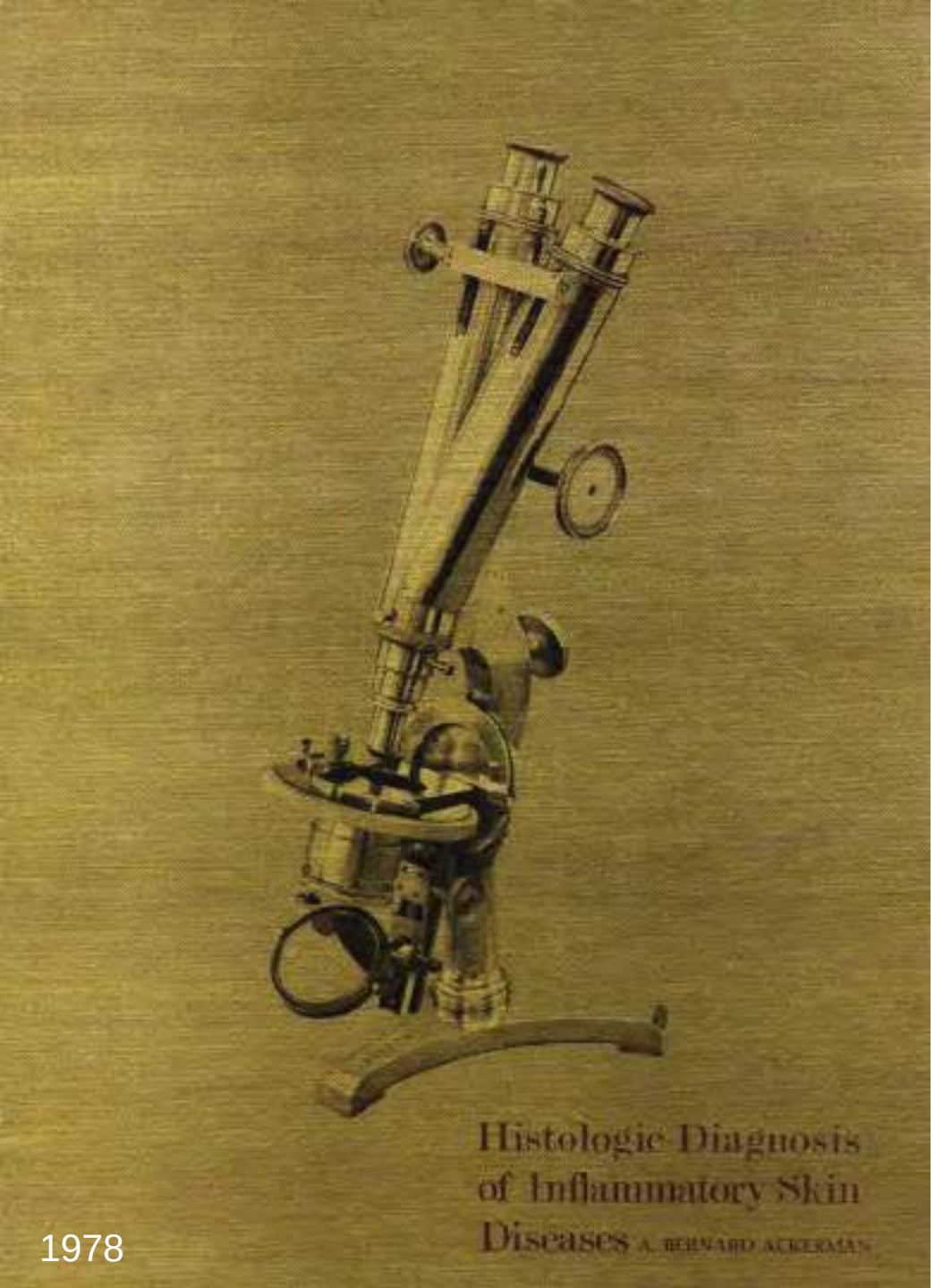


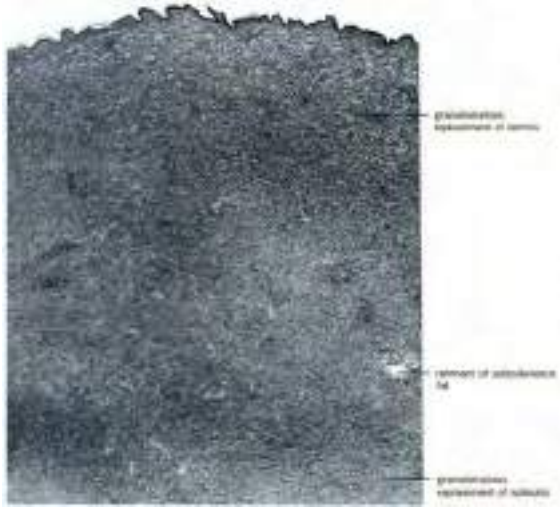
Fig 9.—[illegible]



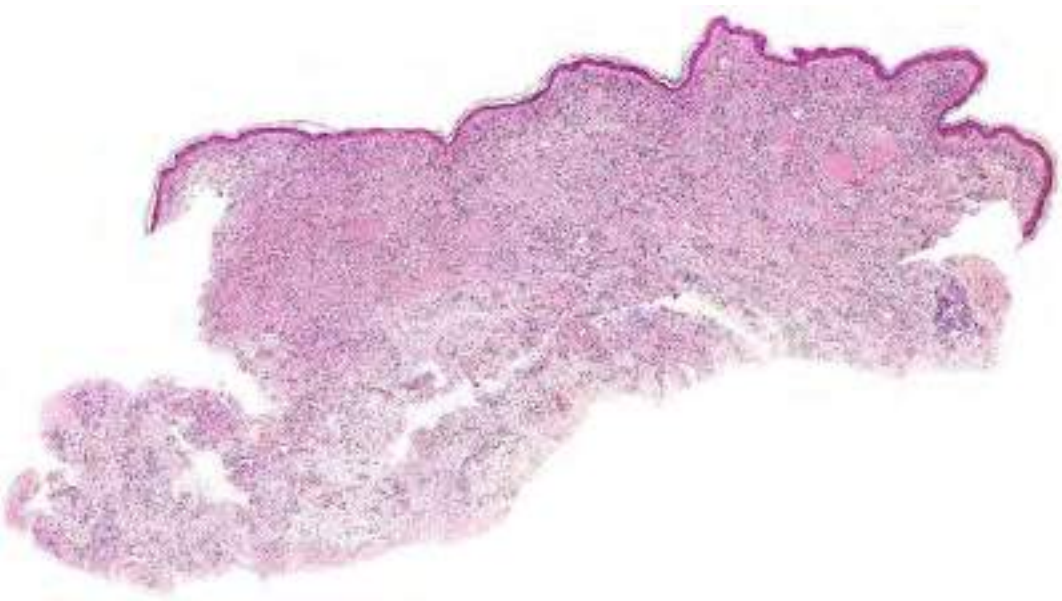
1978

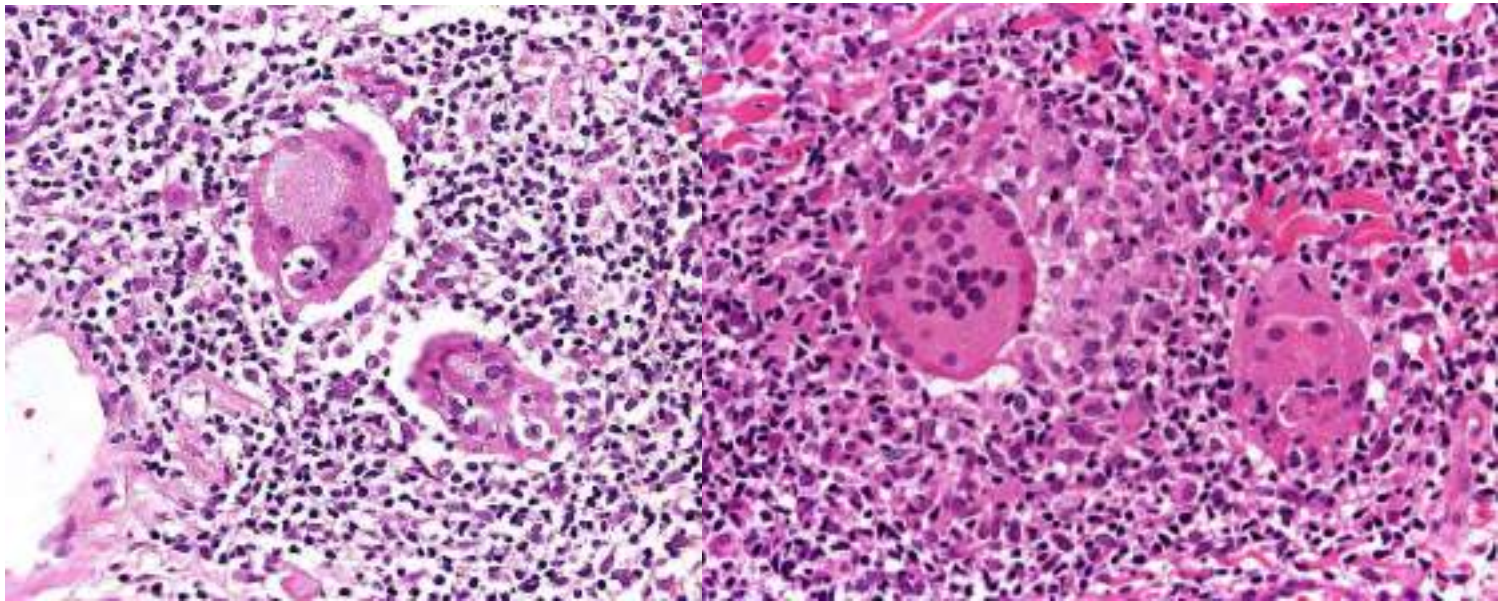
Granulomatous Slack Skin (Fig. 9-79)

—Histiocytes, many multinucleated, scattered throughout the entire dermis and subcutis
—Epithelioid tubercles associated with numerous lymphocytes, plasma cells, and eosinophils throughout the dermis and subcutis
—Calcified bodies of various sizes and shapes within histiocytic giant cells and in a fibrotic stroma; some matter polarizable
—Fibrotic stroma replacing the normal dermis and the subcutaneous fat
—Fibrotic collagen mostly aligned parallel to the skin surface
—Bandlike mixed inflammatory-cell infiltrate in the upper part of the dermis and a few mononuclear cells within the epidermis



This rare condition seems to have a predilection for young adult men who, over several years, progressively develop pendulous skin that droops on the arms near the axillae and on the flanks. The skin is not only slack like that of cutis laxa, but it has surface features of parapsoriasis en plaques. Whether this distinctive condition of granulomatous slack skin inevitably eventuates in malignant lymphoma has yet to be determined.





OBSERVATION

Granulomatous Mycosis Fungoides and Granulomatous Slack Skin

A Multicenter Study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer (EORTC)

Werner Kempf, MD; Sonja Ostheeren-Michaelis, MD; Marco Paredes, MD; Marco Cozzio, MD; Janine Wechsler, MD; Heike Hadrig, MD; Chalid Assaf, MD; Thomas Rüdiger, MD; Reto Willemze, MD; Chris J. L. M. Meijer, MD; Emilio Berti, MD; Lorenzo Cerroni, MD; Marco Santucci, MD; Christian Hallermann, MD; Mark Boersberg, MD; Sergio Chimenti, MD; Alfonso Reboni, MRCS; Mario Menchalho, MD; Dmitry V. Kazakov, MD, PhD; Tony Petrella, MD; Sylvie Fraitag, MD; Agnes Carlotti, MD; Philippe Courville, MD; Hubert Laroy, MD; Robert Knobler, MD; Philippe Golling, MD; Reinhard Dummer, MD; Günter Burg, MD

Background: Granulomatous cutaneous T-cell lymphomas (CTCLs) are rare and represent a diagnostic challenge. Only limited data on the clinicopathological and prognostic features of granulomatous CTCLs are available. We studied 19 patients with granulomatous CTCLs to further characterize the clinicopathological, therapeutic, and prognostic features.

Observations: The group included 15 patients with granulomatous mycosis fungoides (GMF) and 4 with granulomatous slack skin (GSS) defined according to the World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. Patients with GMF and GSS displayed overlapping histologic features and differed only clinically by the development of bulky skin folds in GSS. Histologically, epidermotropism of lymphocytes was not a prominent feature and was absent in 9 of 19 cases (47%). Stable or progressive disease was observed in most patients despite various treatment modalities. Extracutaneous spread occurred in 5 of 18 patients (28%), second lymphoid neoplasms developed in 4 of 19 patients (21%), and 6 of 19 patients (32%) died of their disease. Disease-specific 5-year survival rate in GMF was 66%.

Conclusions: There are clinical differences between GMF and GSS, but they show overlapping histologic findings and therefore cannot be discriminated by histologic examination alone. Development of hanging skin folds is restricted to the intertriginous body regions. Granulomatous CTCL show a therapy-resistant, slowly progressive course. The prognosis of GMF appears worse than that of classic nongranulomatous mycosis fungoides.

Arch Dermatol. 2008;144(12):1609-1617

THE OCCURRENCE OF SARCOID-like granulomas is a well-known phenomenon in malignant lymphoma and is most commonly observed in patients with Hodgkin disease.[1,2] In contrast, granulomatous features are rarely found in primary cutaneous lymphomas (CLs), with approximately 2% of all CLs displaying granulomatous features.[3-5]

Granuloma formation was reported in a broad variety of primary CLs,[6] such as Sézary syndrome,[7] primary cutaneous anaplastic large T-cell lymphoma,[8] subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous B-cell lymphomas.[9] Granulomatous mycosis fungoides (MF) is the most common form of granulomatous cutaneous T-cell lymphoma (CTCL). In contrast, granulomatous slack skin (GSS) is a very rare form of CTCL, and to date only approximately 30 cases have been reported in the literature.[10-12] In the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas, GSS is considered a distinct subtype of MF with characteristic clinical and histologic features.[13,14]

There have been only a limited number of studies on granulomatous CTCLs, particularly granulomatous MF (GMF). The clinicopathological features and the course of granulomatous CTCLs are still poorly characterized. The granulomatous reaction can be very extensive, so that the histologic diagnosis of lymphoma may be delayed, and the findings are often initially misdiagnosed as granulomatous dermatitis.[9] There is controversy over whether the presence of granulomas in CLs correlates with a better prognosis.[5,15] Thus, a multicenter study was conducted to analyze the clinical, histopathological, immunophenotypic, and ge-

Author Affiliations are listed at the end of this article.

Table 2. Histologic, Immunophenotypic, and Genotypic Data From a Series of 19 Patients With Granulomatous Cutaneous T-Cell Lymphomas

Patient No.	Growth Pattern	Epidermotropism	Cell Size	Granulomas	Giant Cells	EI Loss	Elastophagocytosis	Eos	Plasm	Angio	Phenotype	Genotype
Granulomatous Mycosis Fungoides[a]												
1	Diffuse	+	S-M plas	+	+	+	+	+	–	+	CD3+, 4+, 8+, 30+, TIA-1+	TCR+
2	Diffuse		S-M plas	+	+	NA	NA				CD3+, 4+	NA
3	Perivascular	+/– Lining ep	S	+	+ (Few)	NA	NA				CD3+, 4+	TCR+
4	Perivascular		S		+ (Few)	NA	NA				NA	TCR+
5	Perivascular/ periadnexal	+	S-M plas	+ (Few)	+	+		+			CD3+, 4+, 8–, 30+/–, TIA-1+/–	TCR+
6	Perifollicular/ periadnexal	+	S	+	+	+	–	+	–	–	CD3+, 4+, 8–, 30+, TIA-1	TCR+
7	Perivascular/ nodular		S-M-L plas	+		+		+ (Few)	+		CD3+, 4+, 8+, 30+, TIA-1+/–	TCR+
8	Nodular	–	S-M plas	+	–	+	–	+	–	–	CD3+, 4+, 30+, TIA-1+	TCR+
9	Nodular	–/+	S	+	–	+	–	+	–	–	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
10	Nodular		S	+		+		+			CD3+, 4+, 8+	TCR+
11	Diffuse	–	S	–	+	+	–	–	–	+	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
12	Diffuse	+	S-M plas	+	–	+	–	+	–	+	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
13	Diffuse	–/+	S	+	–	+	–	+	–	+	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
14	Nodular	–/+	S	+	–	+	–	+	+	–	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
15	Diffuse	–	S	–	+	+	–	–	–	–	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
Granulomatous Slack Skin												
16	Diffuse	–	S	–	+	+	–	+ (Few)	+	+	CD3+, 4+, 8–, 30+, TIA-1+	TCR+
17	Diffuse	–	S	–	+	+	+	+ (Few)	+	–	CD3+, 4+, 8+, 30+, TIA-1+, granzyme B+	TCR+
18	Diffuse	–	S-M plas	–	+	+	+	+	–	–	CD3+, 4+, 8–	TCR+
19	Diffuse	+	S-M plas	–	+	+	–	+	+	+	CD3+, 4+, 8–	TCR+

Abbreviations: Angio, angiocentric growth; EI loss, loss of elastic fibers on elastica staining; Eos, eosinophilic granulocytes; L, large; M, medium sized; NA, not available; Plasm, plasma cells; plas, pleomorphic; S, small; TIA-1, T-cell intracellular antigen 1; TCR, T-cell receptor rearrangement (+, monoclonal; –, polyclonal); +, present/positive; –, absent/negative; –/+, very few cells positive (<5%); +/–, few positive cells (10%-20%).

[a] All except patient 3 had multiple lesions. Patient 6 had folliculotropic disease.

"There are clinical differences between GMF and GSS, but they show overlapping histologic findings and therefore cannot be discriminated by histologic examination alone."

The American Journal of Surgical Pathology 26(10):1255–1268, 2002

Cutaneous Lymphomas With Prominent Granulomatous Reaction

A Potential Pitfall in the Histopathologic Diagnosis of Cutaneous T- and B-Cell Lymphomas

Alessandra Scarabello, M.D., Bernd Leinweber, M.D., Marco Ardigò, M.D., Arno Rütten, M.D., Alfred C. Feller, M.D., Helmut Kerl, M.D., and Lorenzo Cerroni, M.D.

The presence of a granulomatous reaction in lesions of cutaneous lymphomas has been described in the past in several cases. Especially in mycosis fungoides, a "granulomatous" variant of the disease has been well characterized. We studied the clinicopathologic features of cutaneous lymphomas with prominent granulomatous reaction, including both cutaneous T-cell lymphomas and B-cell lymphomas (primary cutaneous lymphoma 22, secondary cutaneous lymphomas one). Biopsies of 25 patients with histopathologic features of cutaneous T-cell lymphoma or cutaneous B-cell lymphoma with prominent granulomatous reaction were included in this study. A prominent granulomatous reaction was defined as the presence of a granulomatous component exceeding 25% of the dermal infiltrate. There were 14 cases of mycosis fungoides, two of subcutaneous panniculitis-like T-cell lymphoma, four of small/medium pleomorphic T-cell lymphoma, one of follicle center cell lymphoma, one of large B-cell lymphoma, and one of secondary cutaneous peripheral T-cell lymphoma. Altogether, a prominent granulomatous reaction could be observed in 1.8% of all patients with cutaneous lymphoma (primary or secondary) registered in the files of the Department of Dermatology of the University of Graz (Graz, Austria), demonstrating that there is a distinct, albeit small, proportion of cases revealing this peculiar reaction pattern. In seven cases a misdiagnosis of granulomatous dermatitis preceded the correct diagnosis for a period of 1–216 months, suggesting that sequential biopsies and complete phenotypic and molecular genetic analyses should be carried out in cases of "unusual" granulomatous dermatitis.

Key Words: Granulomatous lymphoma—Cutaneous T-cell lymphoma—Cutaneous B-cell lymphoma.

Am J Surg Pathol 26(10):1259–1268, 2002.

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The presence of a granulomatous reaction in lesions of cutaneous lymphomas has been described in the past in several cases. Especially in mycosis fungoides (MF), a "granulomatous" variant of the disease has been well characterized.[1–3,13] Another well-known, albeit rare, entity of granulomatous cutaneous lymphoma is represented by granulomatous slack skin (GSS), which can be associated with either MF or Hodgkin's disease (HD).[4,5] In the literature, however, there is no systematic study on "granulomatous" cutaneous lymphomas, i.e., lymphomas of the skin with a prominent granulomatous reaction.[4–9]

We studied the clinical, histologic, and molecular features of cutaneous lymphomas with prominent granulomatous reaction, including both cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs).

MATERIALS AND METHODS

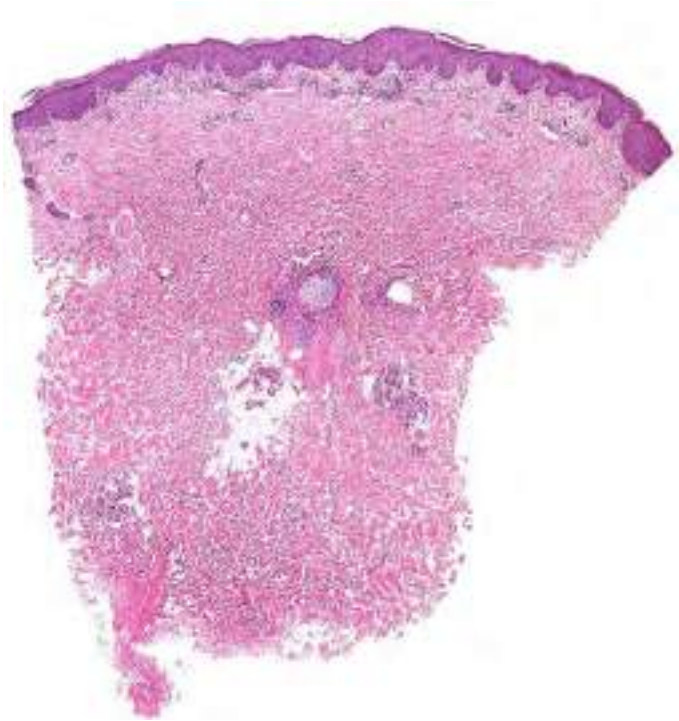
Patients

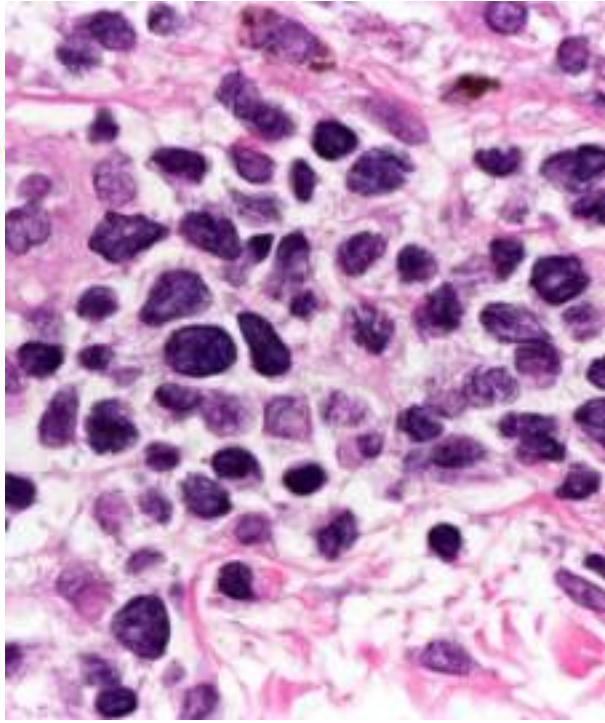
Biopsies of 25 patients with histopathologic features of CTCL or CBCL with prominent granulomatous reaction were included in this study. Biopsies of seven other patients were not included because of lack of sufficient clinical information. Primary cutaneous lymphoma was defined as absence of systemic involvement for a period

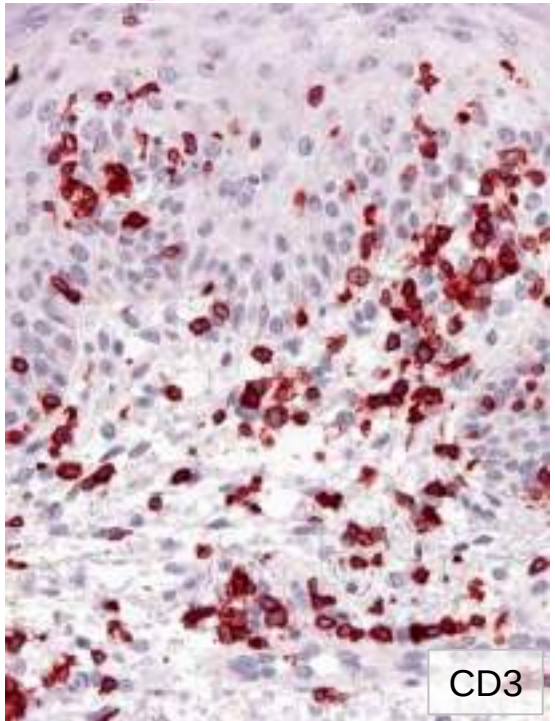
TABLE 1. *Clinicopathologic features of patients with cutaneous granulomatous lymphoma*

Patient no.	Sex age (y)	Lesions	Site	Granulomatous reaction	Misdiagnosis of granulomatous dermatitis (mo)	TCR	IgH	Follow-up (mo)
Mycosis fungoides								
1	M/82	G	5	++		ND		A+ (29)
2	M/39	G	5	++		Monoclonal		A++ (225)
3	M/75	M	2,4	+		Smear		A+ (12)
4	M/51	S	4	+		Monoclonal		A– (16)
5	M/53	G	5	++		Monoclonal		A++ (451)
6	M/73	G	5	+		Monoclonal		A– (18)
7	F/56	G	5	+		Monoclonal		A+ (8)
8	M/75	G	5	++		Monoclonal		A+ (2)
9	M/57	G	5	++		ND		D+ (192)
10	M/53	G	5	++	Yes (60)	Monoclonal		A+ (215)
11	M/80	M	2,4	++		Monoclonal		A+ (11)
12	F/60	S	2	+++	Yes (216)	Monoclonal		A– (240)
Mycosis fungoides-associated granulomatous slack skin								
13	M/29	M	2	+		Monoclonal		A+ (21)
14	M/52	M	2, 3, 4	+		Monoclonal		A+ (130)
Subcutaneous T-cell lymphoma								
15	F/60	M	4	++	Yes (1)	ND		A+ (105)
16	F/50	M	3,4	++	Yes (12)	Monoclonal		A+ (60)
Small/medium pleomorphic T-cell lymphoma								
17	M/80	S	2	+		Monoclonal		A– (13)
18	M/49	S	3	+		Smear		A+ (8)
19	F/64	M	2	+		Smear		A+ (12)
20	F/61	S	4	+++	Yes (20)	Monoclonal		A– (80)
Peripheral T-cell lymphoma								
21	M/73	M	1,2	++	Yes (1)	Monoclonal		A++ (4)
Follicle center cell lymphoma								
22	M/56	M	2	+			Smear	D– (60)
Large B-cell lymphoma								
23	M/75	M	2, 3, 4	+++	Yes (1)		Monoclonal	A+ (8)

S, solitary lesion; M, multiple lesions; G, generalized; 1, head and neck; 2, trunk; 3, upper extremities; 4, lower extremities; 5, generalized; A+, alive with skin disease; A++, alive with skin and systemic disease; A–, alive in complete remission; D–, dead of unrelated causes; D+, dead of disease; ND, not done.

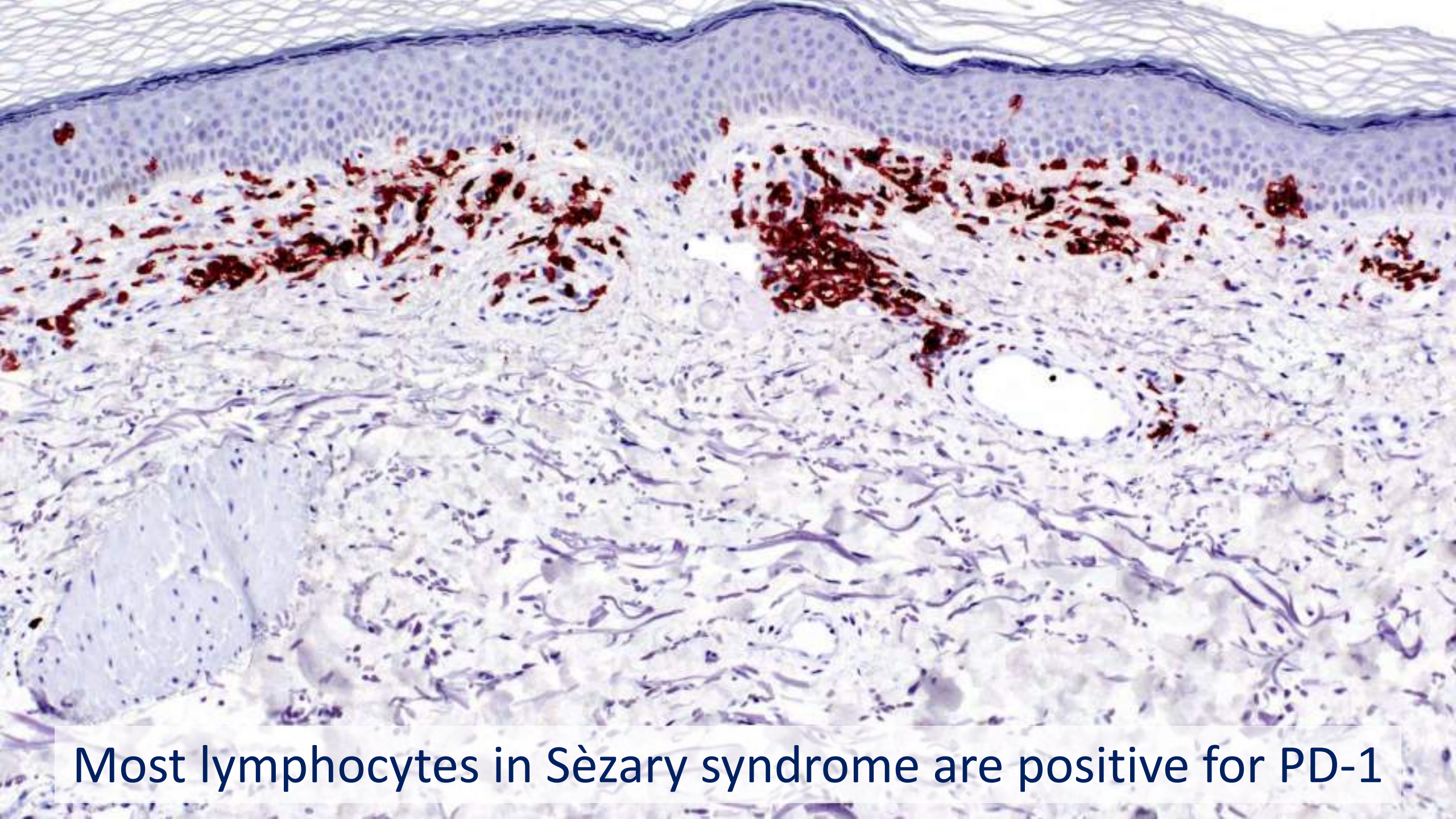






Sezary syndrome

Erythroderma (may be missing in early phases), enlarged lymph nodes, clonal T-cells in skin, lymph nodes and blood. Strong pruritus, irregular or generalized alopecia, ectropion, palmar and/or plantar hyperkeratoses, onychodystrophy. Phenotype always CD4+. Histology often non-specific ("pseudo-dermatitis").



Most lymphocytes in Sèzary syndrome are positive for PD-1

blood
Review Article

Genetic and epigenetic insights into cutaneous T-cell lymphoma

Connie P. Tensen, Koen D. Quint, and Maarten H. Vermeer

Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands

Primary cutaneous T-cell lymphomas (CTCLs) constitute a heterogeneous group of non-Hodgkin T-cell lymphomas that present in the skin. In recent years, significant progress has been made in the understanding of the pathogenesis of CTCLs. Progress in CTCL classifications combined with technical advances, in particular next-generation sequencing, enabled a more detailed analysis of the genetic and epigenetic landscape and transcriptional changes in clearly defined diagnostic entities. These studies not only demonstrated extensive heterogeneity between different CTCL subtypes but also identified recurrent alterations that are highly characteristic for diagnostic subgroups of CTCLs. The identified alterations, in particular, involve epigenetic remodeling, cell cycle regulation, and the constitutive activation of targetable oncogenic pathways. In this respect, aberrant JAK-STAT signaling is a recurrent theme; however, it is not universal for all CTCLs and has seemingly different underlying causes in different entities. A number of the mutated genes identified are potentially actionable targets for the development of novel therapeutic strategies. Moreover, these studies have produced an enormous amount of information that will be critically important for the further development of improved diagnostic and prognostic biomarkers that can assist in the clinical management of patients with CTCL. In the present review, the main findings of these studies in relation to their functional impact on the malignant transformation process are discussed for different subtypes of CTCLs.

Introduction

Primary cutaneous T-cell lymphomas (CTCLs) constitute a heterogeneous group of non-Hodgkin T-cell lymphomas that present in the skin. Clinicopathologic studies combined with long-term follow-up were critically important in defining different types of CTCLs with highly characteristic clinical and histologic features. These studies also demonstrated that CTCL differ in clinical behavior and prognosis compared with morphologically similar nodal lymphomas that may involve the skin secondarily.

As a result of these studies, primary CTCLs were included as distinct entities in current lymphoma classifications. The first classification dedicated to cutaneous lymphomas was the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) consensus classification published in 2005 that was subsequently incorporated in the 2008 WHO classification and its 2016 revision.[1] These advances in lymphoma classification allow clinicians to correctly diagnose and select appropriate treatment in CTCL (see Table 1 for updated classification of CTCLs).

However, until recently, molecular characterization of the pathogenesis and progression of different CTCL subtypes remained largely unknown. Early cytogenetic studies demonstrated widespread genomic instability and complex karyotypes, but recurrent translocations or other recurrent genetic alterations were not found. The heterogeneity in the results of these studies combined with the lack of appropriate mouse models and limited number of informative cell lines severely hampered progress in the field.

Recent technical advances including array-based comparative genomic hybridization (aCGH) and, in particular, next-generation sequencing (NGS) enabled a more detailed analysis of genetic, epigenetic, and transcriptional changes in CTCL tumor cells. These studies confirmed the extensive heterogeneity between and within CTCL subtypes but also identified recurrent molecular alterations affecting oncogenic pathways in different types of CTCLs. In the present review, the main findings of these studies for different subtypes of CTCL are presented.

Genetic alterations in Sézary syndrome: copy number alterations

Early studies on genetic alterations in Sézary syndrome (SS), mainly using arrays and cytogenetics, already identified extensive genetic instability with complex karyotypes.[2-5] A series of genomic studies using aCGH or single nucleotide polymorphism arrays identified small chromosomal regions affected by

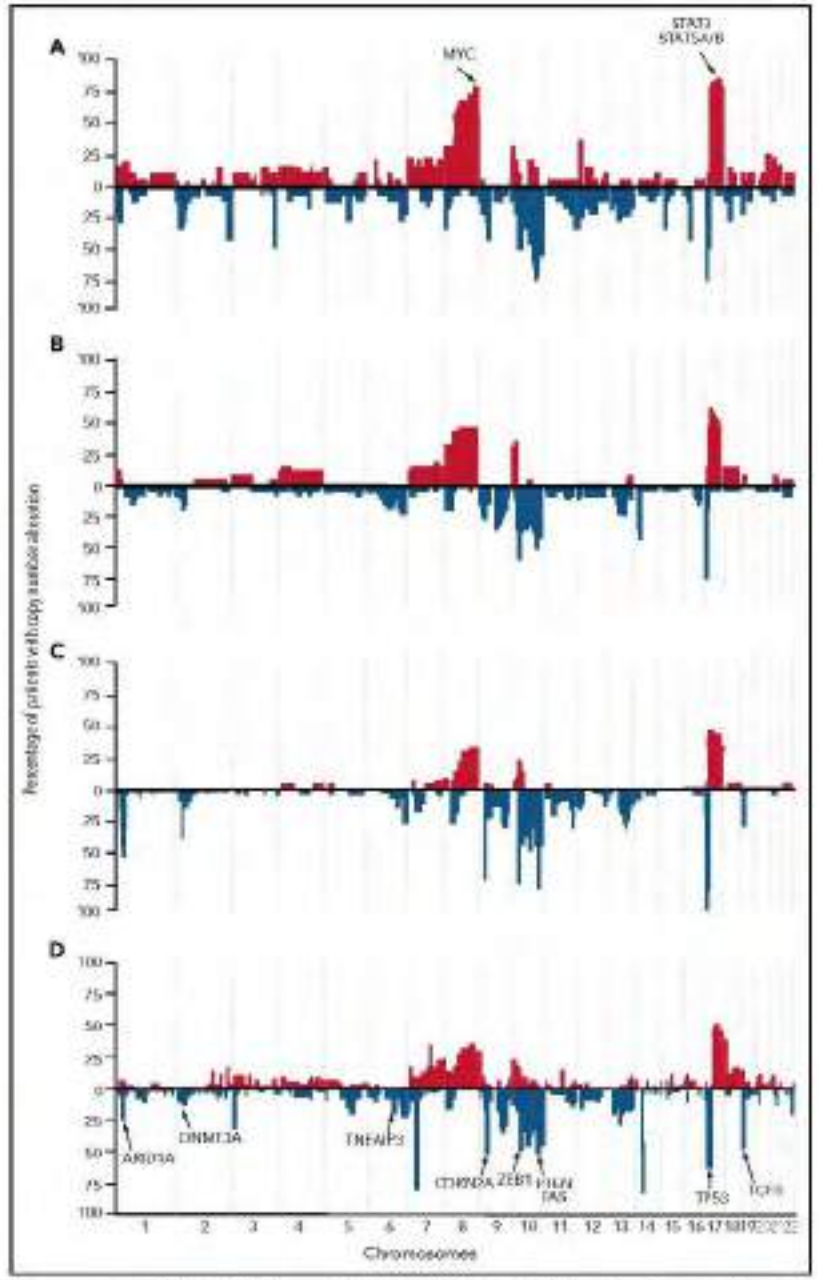


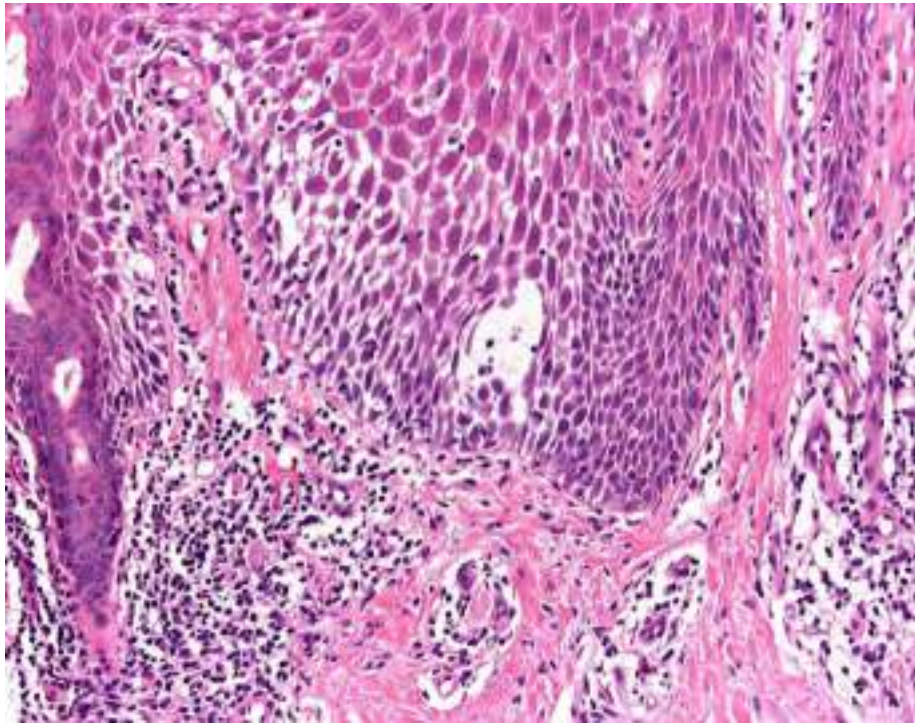
Figure 1. Schematic representation of CNAs in DNA of tumor cells of patients with Sz determined for independent cohorts using different platforms. Gains

Extensive genetic instability with complex karyotypes.
Significant gains in regions with known oncogenes like MYC; common STAT3/5B amplifications and P53 deletions.

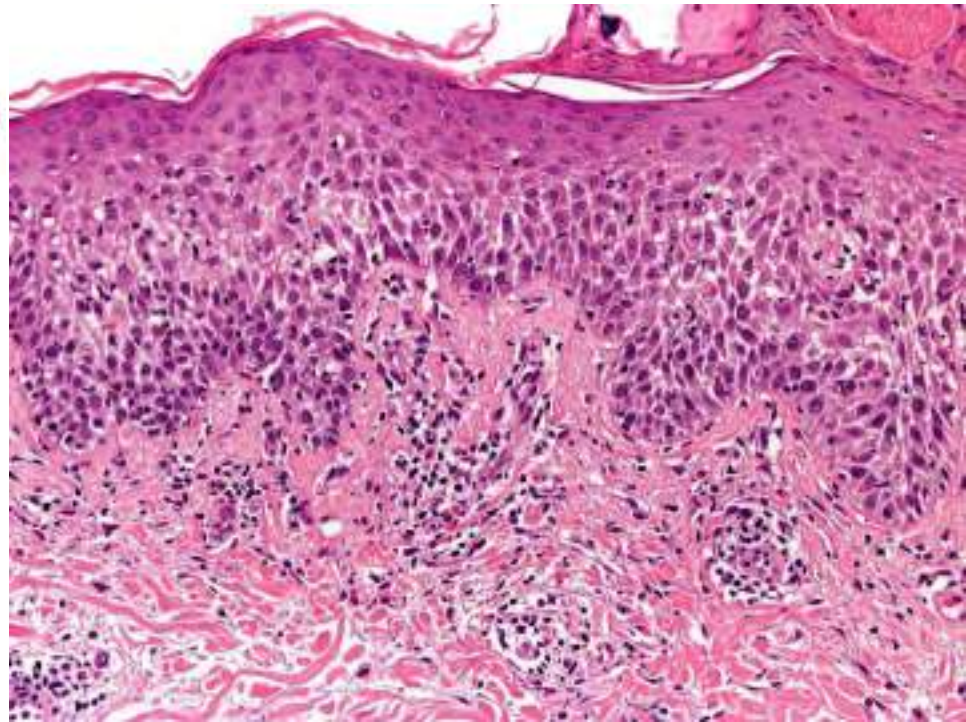
Aberrant JAK-STAT signaling is a hallmark of T-cell lymphoma and appears to be of critical importance in Sèzary syndrome.

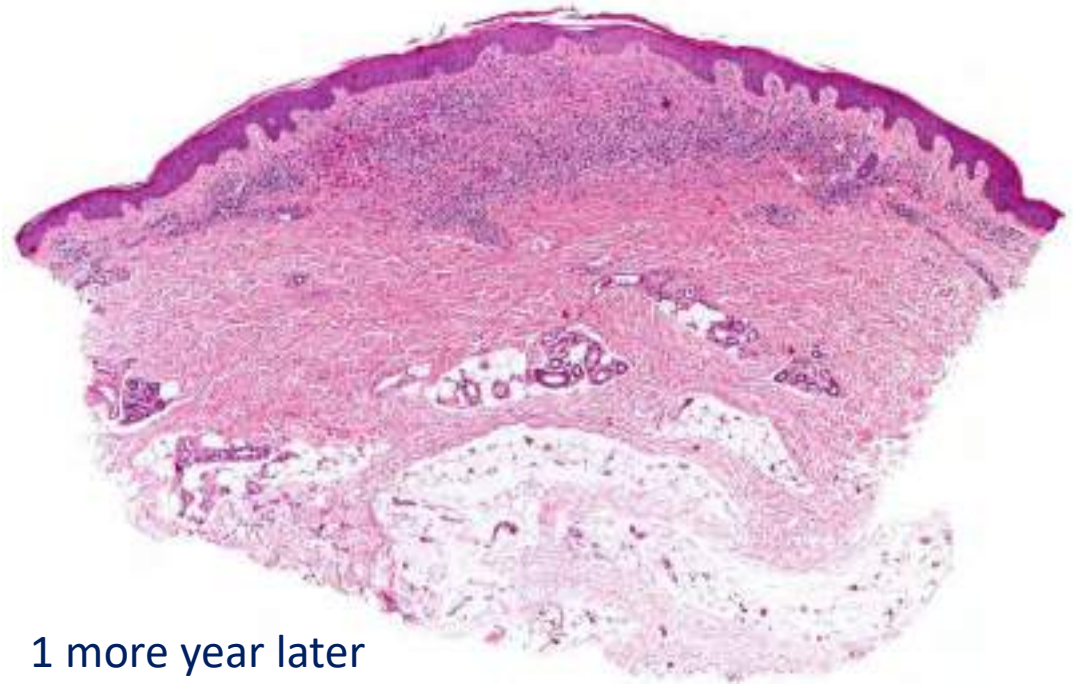
M, 51

According to the patient itchy, "eczematous" lesions for the last 3 years.

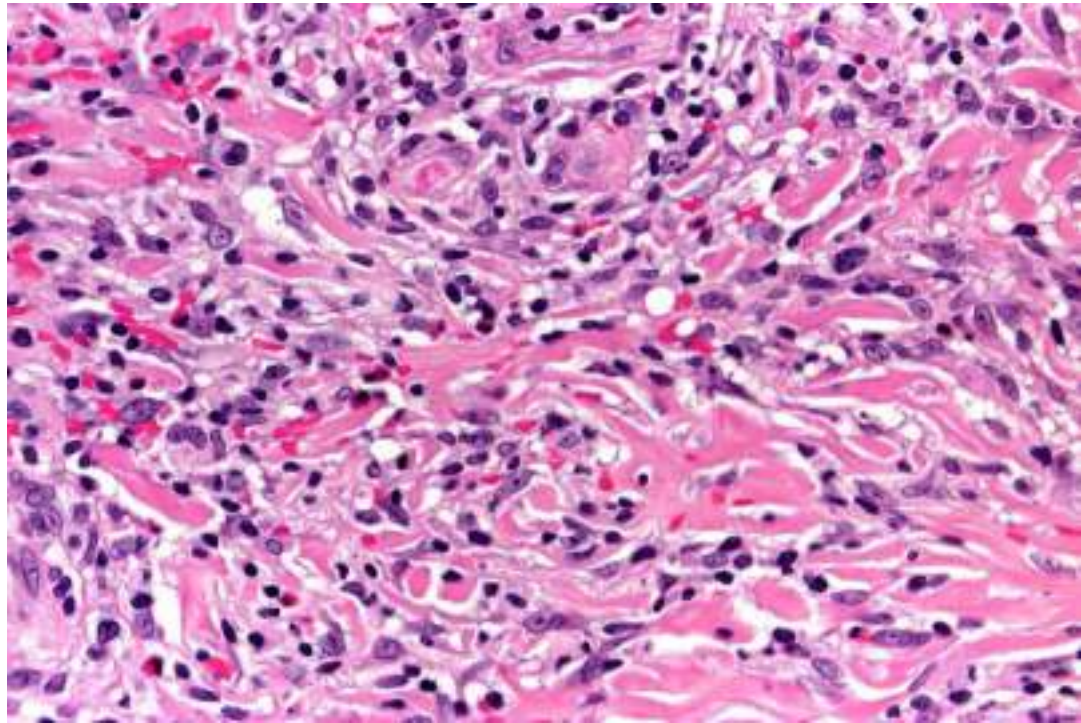


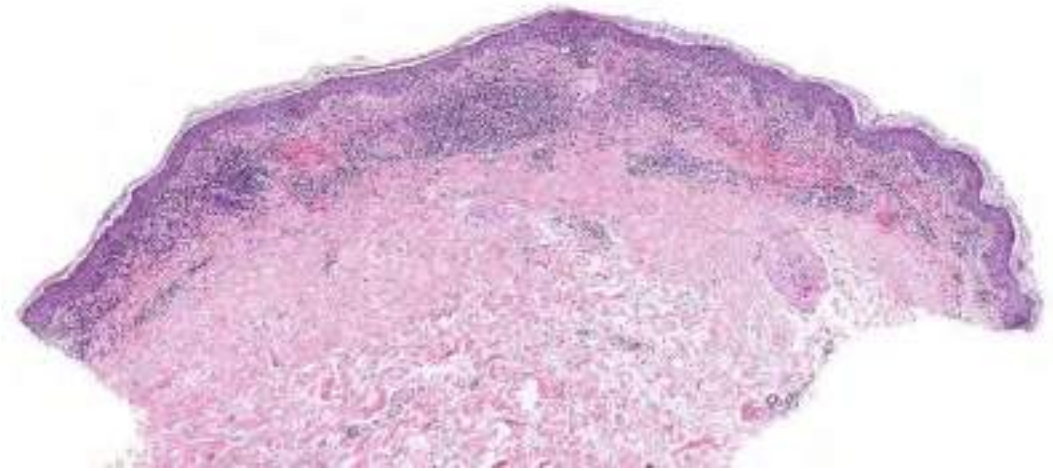
1 year later



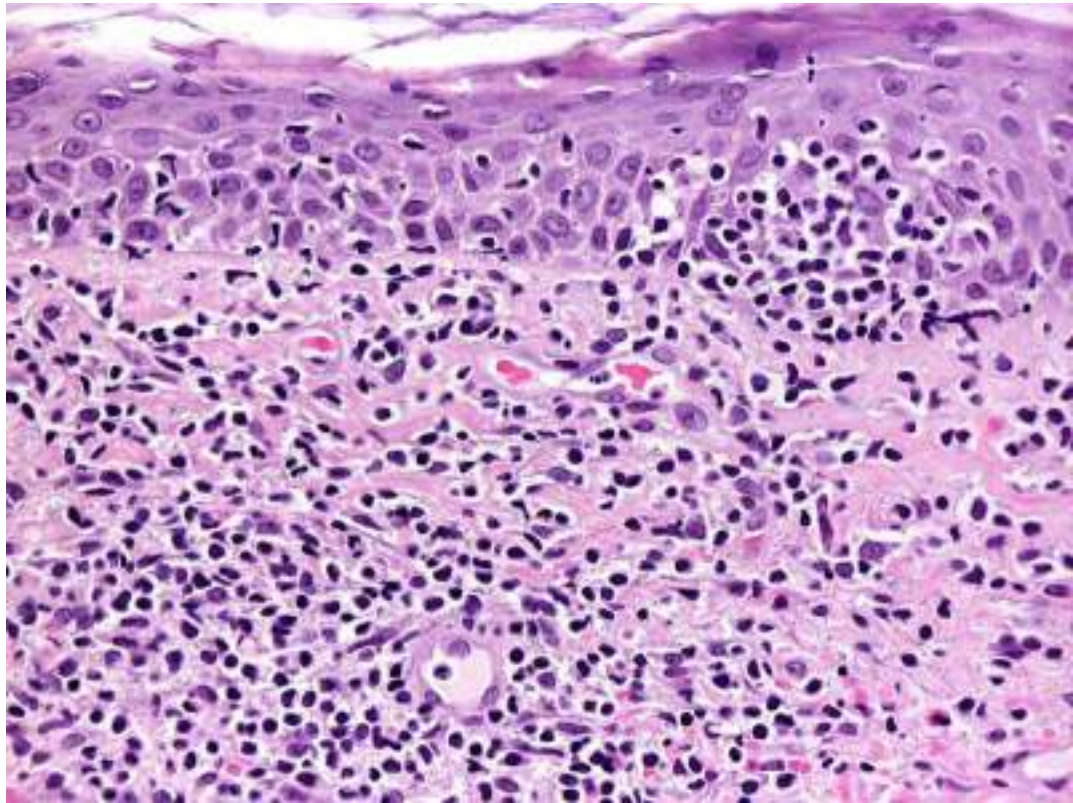


1 more year later



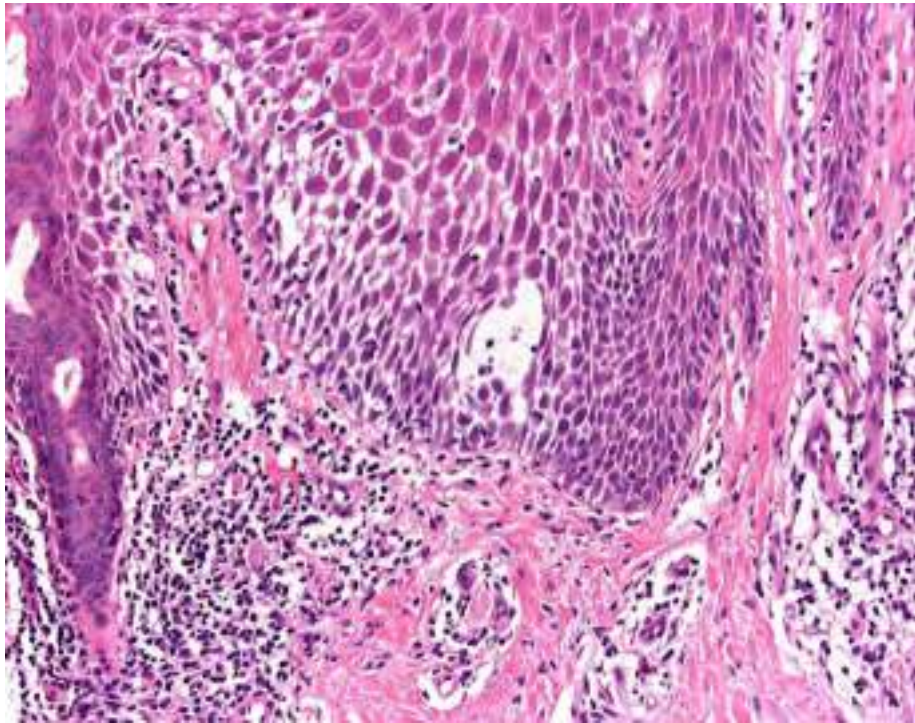


3 more years later
(5 years after first presentation); DoD (8y survival)



Prodromic phases of Sézary syndrome may mimic clinically an inflammatory disease, particularly an eczematous / pruriginous dermatosis *("red man syndrome").*

Histopathological features of overt Sézary syndrome may be non-specific as well, simulating a spongiotic dermatitis *("pseudo-dermatitis");* neoplastic cells may "colonize" an eczematous dermatitis in prodromic, subclinical phases of the disease *("koebnerization")*.



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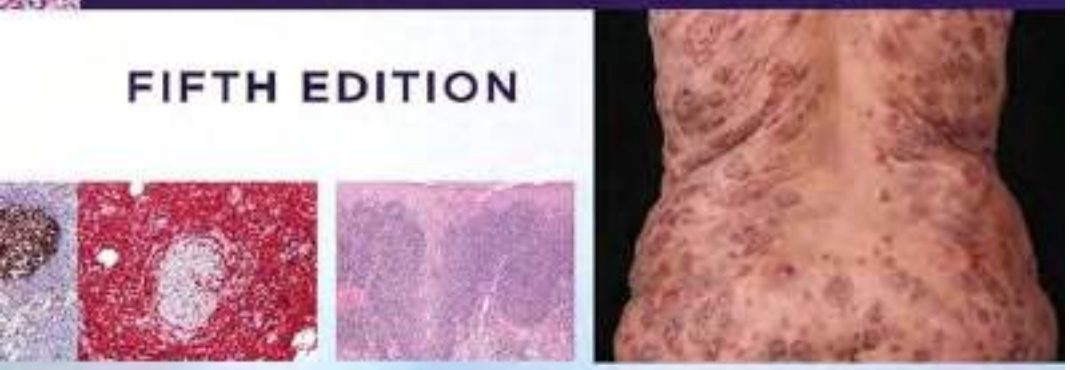

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Table 28.1 Classification of cutaneous pseudolymphomas including "malignant" pseudolymphomas

Clinicopathologic entity	Simulated malignant lymphoma
Chronic actinic dermatitis (actinic reticuloid) Lymphomatoid contact dermatitis Non-mycosis fungoides-associated follicular mucinosis and other benign alopecic infiltrates Lichenoid (lymphomatoid) keratosis (including "solitary idiopathic B/T-cell pseudolymphoma") Lichen sclerosus/lichenoid pigmented purpuric dermatitis Lichen sclerosus Vitiligo (inflammatory stage) Annular lichenoid dermatitis of youth Pseudolymphomatous acrodermatitis chronica atrophicans (superficial type) Pseudolymphomatous atopic dermatitis Nonneoplastic erythroderma in adult patients Superficial CD8+ cutaneous infiltrates in HIV-infected patients or in other immune deficiencies Lymphomatoid drug reaction, lichenoid type Pseudolymphomas in tattoos, lichenoid type Pseudolymphomas after vaccination, lichenoid type Syphilis, secondary (superficial type) Pityriasis lichenoides Lupus erythematosus (superficial variant) Occasional pseudolymphomatous infiltrates in other inflammatory disorders (e.g., lichen planus, psoriasis, bullous pemphigoid, etc.)	Mycosis fungoides/Sézary syndrome
Pseudolymphomas in herpes simplex or herpes zoster infections Pityriasis lichenoides, including the ulceronecrotic variant Lupus erythematosus, angiocentric variant Syphilis, secondary, plasma cell poor	Cytotoxic NK/T-cell lymphomas or lymphomatoid papulosis/cutaneous anaplastic large cell lymphoma
Atypical lymphoid infiltrates (CD30+) associated with orf, Milker's nodule, molluscum contagiosum, and other infectious or noninfectious disorders Persistent arthropod bite reactions (including nodular scabies) Syphilis, primary	Lymphomatoid papulosis/cutaneous anaplastic large cell lymphoma
Lupus panniculitis Lipoatrophic panniculitis of the ankle Lobular panniculitis in children with congenital immune deficiencies	Subcutaneous panniculitis-like T-cell lymphoma
"Acral pseudolymphomatous angiokeratoma in children (APACHE)," "T-cell-rich angiomatoid polypoid pseudolymphoma," "pleomorphic lymphoplasmacytic plaque in children" ("TA-cell angiomatoid pseudolymphoma") Nodular pseudolymphomatous cutaneous infiltrates in congenital immune deficiencies Pseudolymphomas in tattoos (T-cell-rich nodular variant)	Cutaneous CD8+ small/medium T-cell lymphoproliferative disorder or marginal zone lymphoma
Conventional hydroa vacciniforme	Hydroa vacciniforme-like lymphoma
Lymphocytoma cutis (Borrelia associated) Lymphocytoma cutis due to several causes (non-Borrelia associated) Pseudolymphoma after vaccination, B-cell type Lymphomatoid drug reaction, B-cell type	Follicle center lymphoma or diffuse large B-cell lymphoma Follicle center lymphoma
Cutaneous plasma cell granuloma Pseudolymphoma in tattoos, B-cell type Pseudolymphomatous acrodermatitis chronica atrophicans, nodular plasmacytic type Pseudolymphomatous drug eruptions with prominent plasma cell population Syphilis, secondary (plasma cell-rich nodular type) Localized scleroderma/morphea, inflammatory stage Cutaneous and systemic plasmacytosis Cutaneous manifestations of Castleman disease	Marginal zone lymphoma
Lupus tumidus/lymphocytic infiltration of the skin (Jessner–Kanof)	Cutaneous manifestations of B-cell chronic lymphocytic leukemia
Cutaneous extramedullary hematopoiesis Histiocytoid Sweet syndrome*	Cutaneous manifestations of myeloid leukemia
Intralymphatic histiocytosis Benign intravascular proliferation of T-cell lymphoblasts	Intravascular diffuse large cell lymphoma, intravascular anaplastic large cell lymphoma or intravascular lymphomatoid papulosis

* In some cases neoplastic cells of a myeloid leukemia are present within the infiltrate of histiocytoid Sweet syndrome.

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REVIEW

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Cutaneous pseudolymphoma—A review on the spectrum and a proposal for a new classification

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Abstract

Cutaneous pseudolymphomas (PSLs) belong to a group of lymphocytic infiltrates that histopathologically and/or clinically simulate lymphomas. Different causative agents (e.g., Borrelia sp., injected substances, tattoo, arthropod bite) have been described, but in many cases no cause can be identified, hence the term idiopathic PSL. Clinicopathological correlation is important to make the diagnosis. Four main groups of cutaneous PSL can be distinguished based on histopathologic and/or clinical presentation: (a) nodular PSL; (b) pseudo mycosis fungoides (pseudo MF) and simulators of other CTCLs; (c) other PSL (representing distinct clinical entities); and (d) intravascular PSL. This article gives an overview of the histopathologic and clinical characteristics of cutaneous PSLs and proposes a new classification.

KEYWORDS

B-cell lymphoma, Borrelia, clonality, cutaneous pseudolymphoma, infection, T-cell lymphoma, tattoo

1 | INTRODUCTION

1.1 | Definition

Cutaneous pseudolymphoma (PSL) is described in the literature as a reactive lymphoproliferation that histopathologically and/or clinically mimics cutaneous lymphoma.[1-3] Based on this wide definition it is clear that many processes fulfill the criteria of PSL. Not surprisingly, the term PSL defined in this way seems to have been overstretched in the literature. Many infectious and non-infectious diseases are characterized by atypical lymphocytic infiltrates, which can be easily misinterpreted as cutaneous lymphoma based on histopathologic features alone. To limit the usage of the term cutaneous PSL, we suggest a narrower definition. In analogy to cutaneous lymphomas, clinical information is essential in arriving at the diagnosis. By histopathology alone, the diagnosis of cutaneous pseudolymphoma can in many cases, only be suspected. Additional clinical information and further diagnostic work-up are necessary to confirm the suspected diagnosis. Therefore, the term cutaneous PSL should be restricted to cases that histopathologically simulate cutaneous lymphomas and do not fit into any other diagnosis after clinical correlation. Figure 1 illustrates this approach.

1.2 | Etiology

The literature documents a wide range of causes of PSL, broadly divided into infections, drugs, and foreign agents (Table 1). Miguel et al[4] summarized the frequency of different causes of PSL (Figure 2). Despite the wide range of agents, in many PSL cases no trigger can be found; such cases are designated as idiopathic PSL.

1.3 | Classification

The literature describes many approaches to classify cutaneous PSL. These include a separation according to the predominating immunophenotype (T-cell, B-cell, or mixed), the histopathologic growth pattern, the etiology, or distinct clinical features (reviewed in Refs. 1,2,5). None of these approaches allows consideration of overlapping features. Moreover, the phenotype and etiology are not evident at first glance; further diagnostic work-up is essential. The composition of the infiltrate is variable, being influenced by genetic and immunological factors of the host, as reflected in the observation that identical agents (e.g., Borrelia spl) can induce either B-PSL or T-PSL.

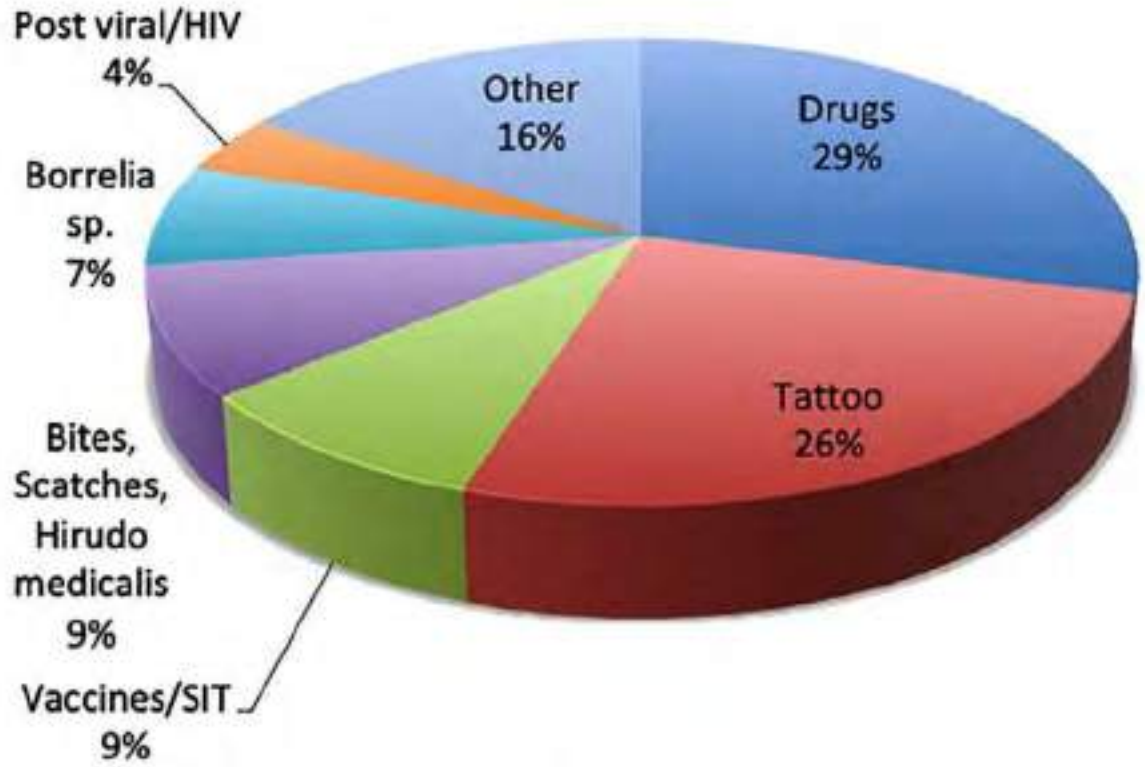
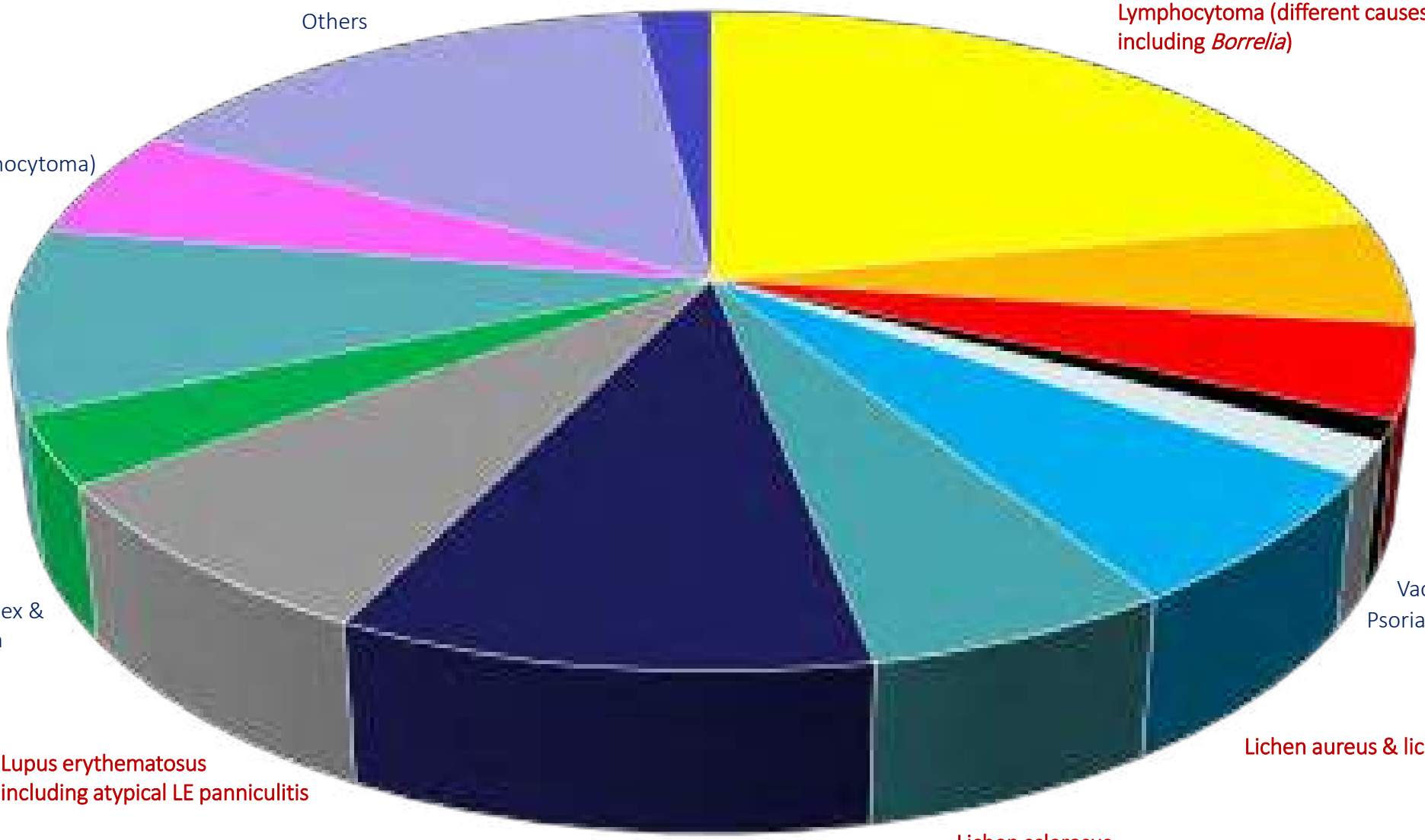


FIGURE 2 Frequency of different causes of cutaneous pseudolymphomas, modified after Miguel et al[4]

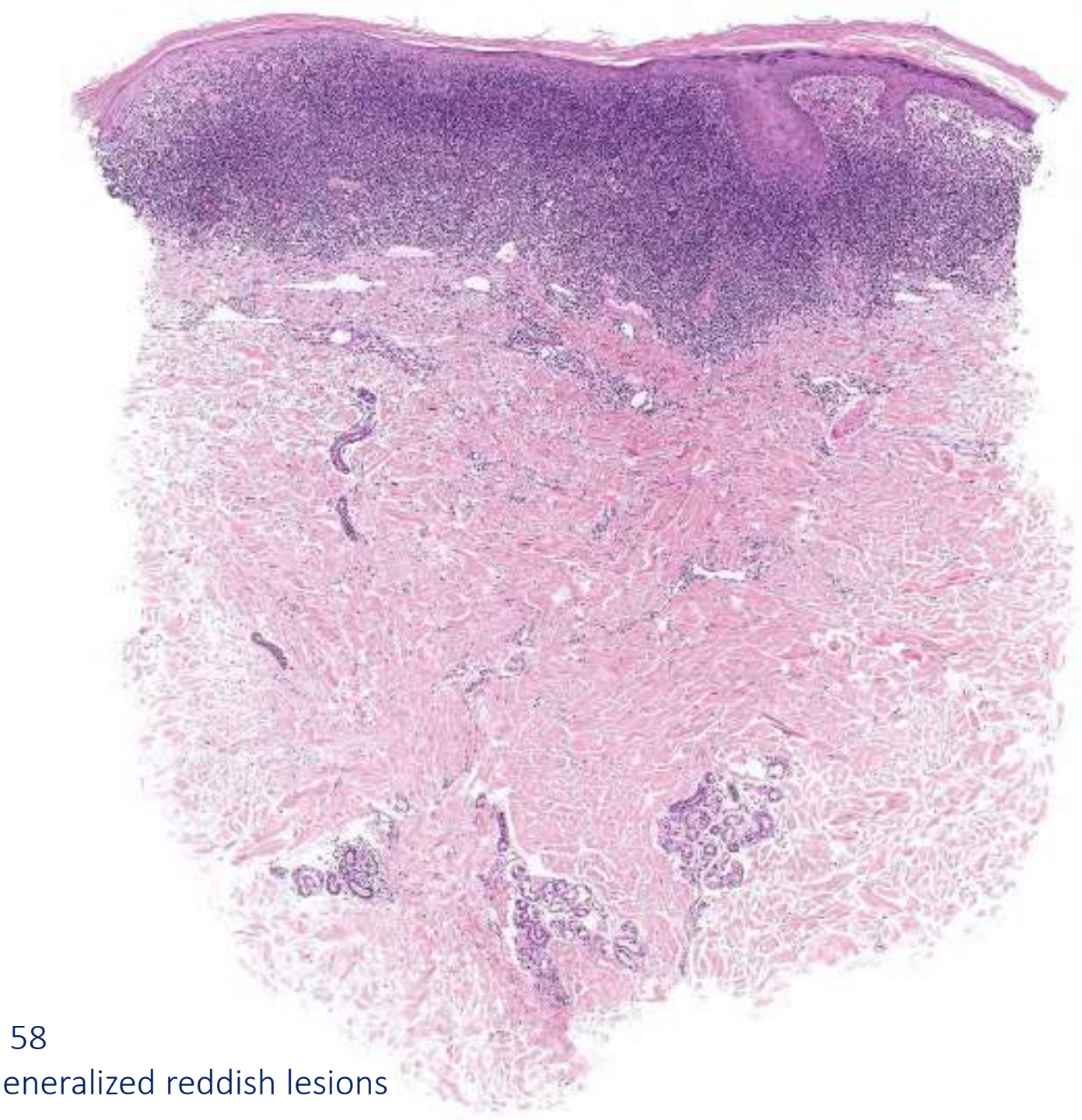
Cutaneous pseudolymphomas (my experience)

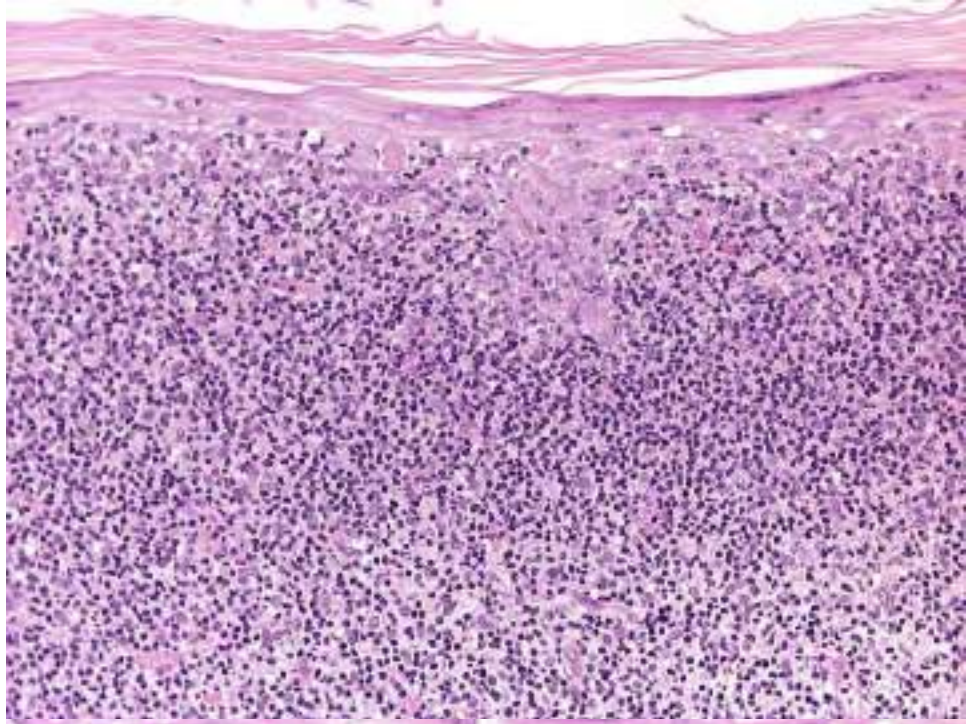


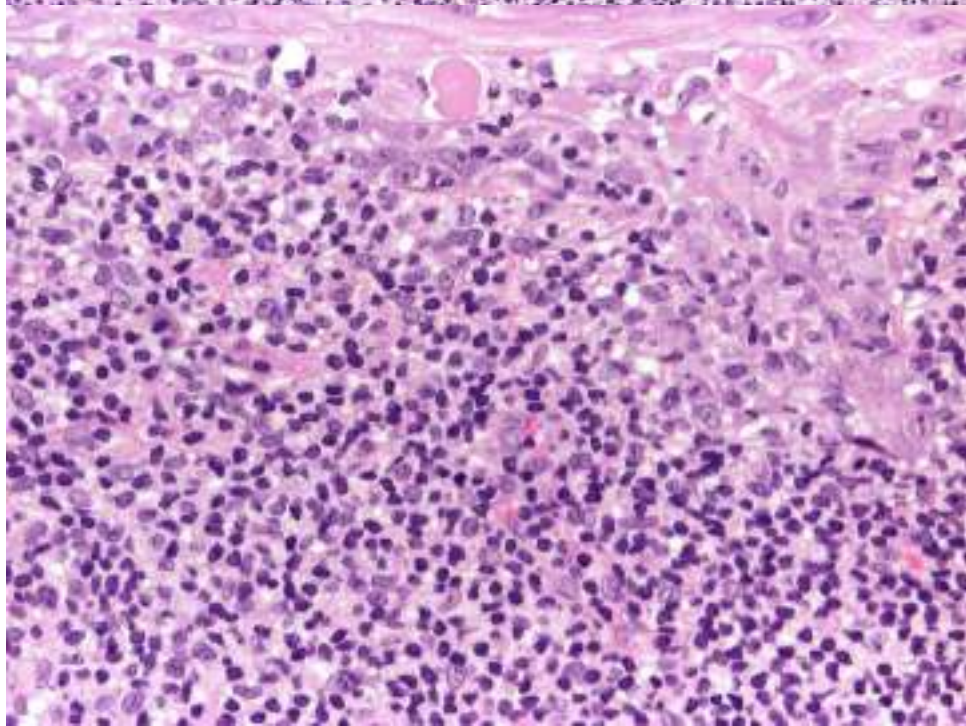
Cutaneous Pseudolymphomas

General Histopathologic Remarks

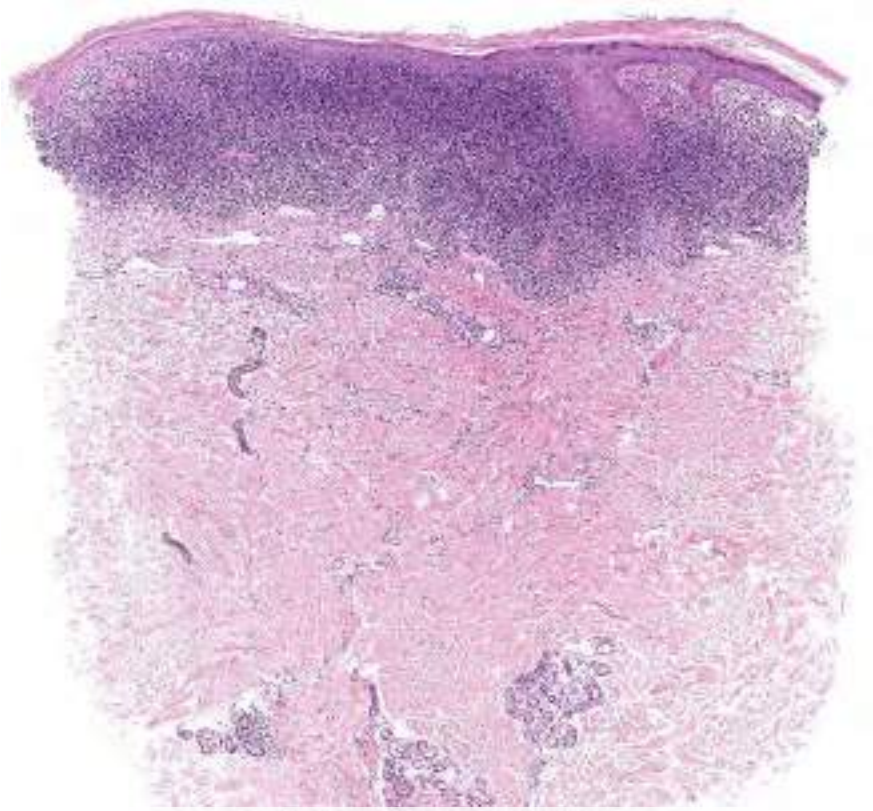
- A band-like T-cell infiltrate with intraepithelial lymphocytes is not restricted to MF or other CTCLs, and is not uncommon in several inflammatory disorders (e.g., lichenoid dermatoses)
- Low-grade malignant cutaneous B-cell lymphomas are usually characterized by a prominent population of reactive lymphocytes that may be the predominant one
- Identification of the neoplastic population crucial for proper diagnosis and classification (phenotype, proliferation pattern)
- kappa/lambda ratio for detection of monoclonality: 10:1; lambda/kappa: 4:1



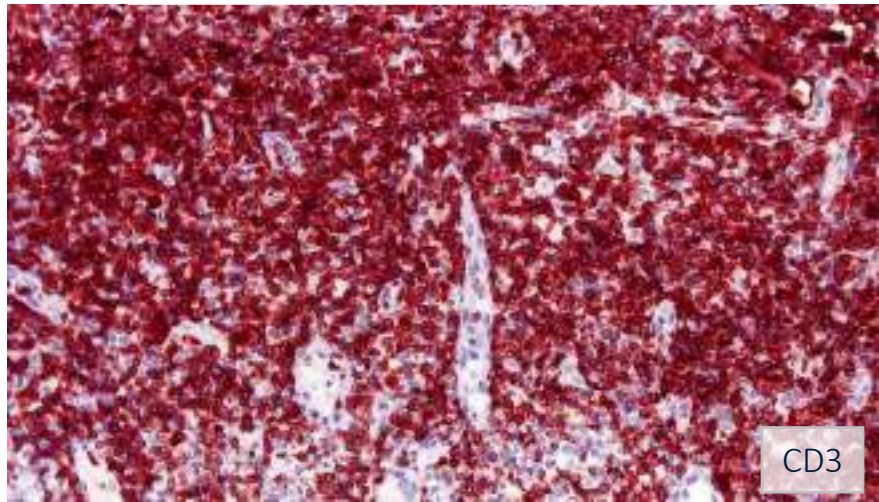


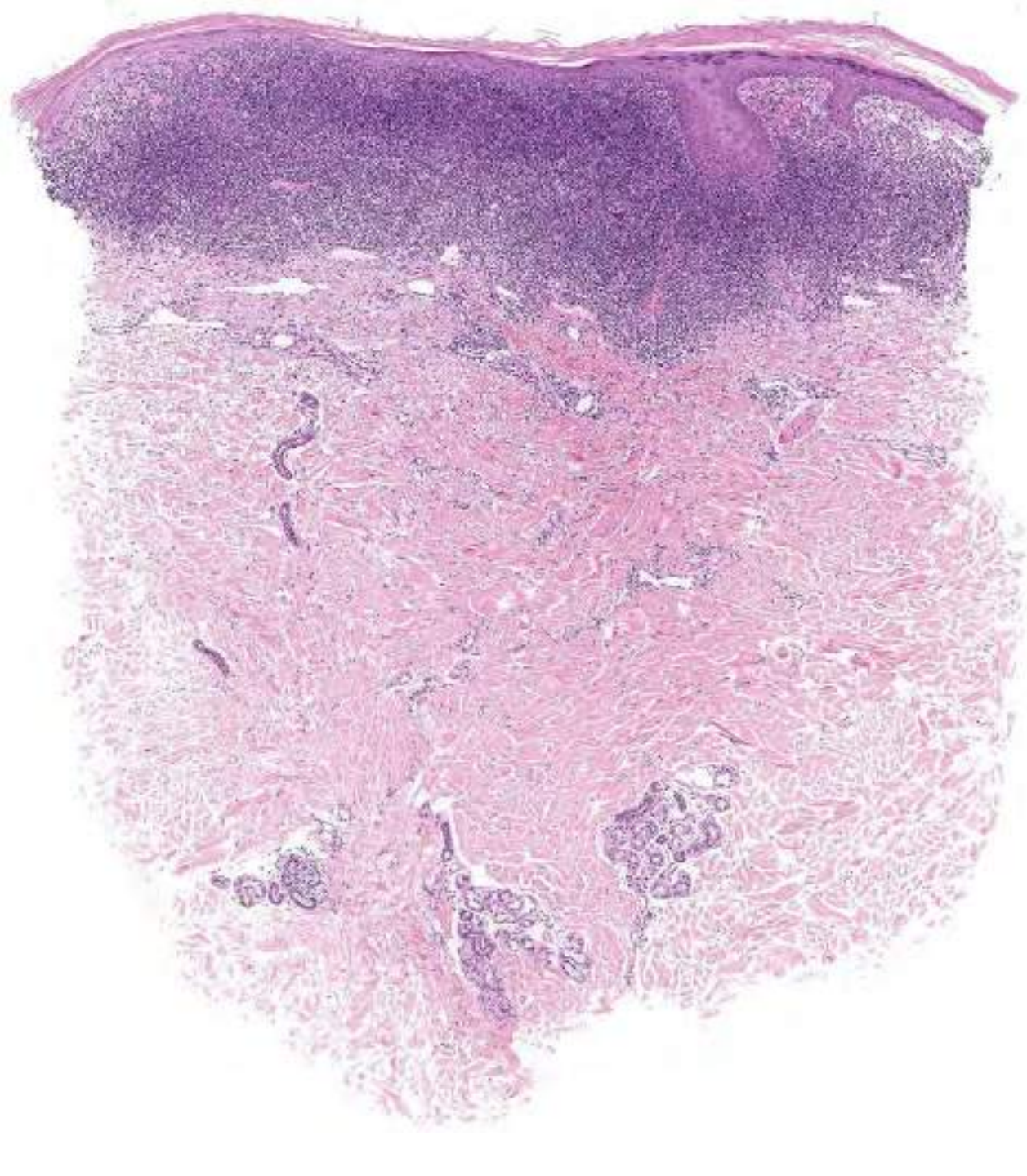


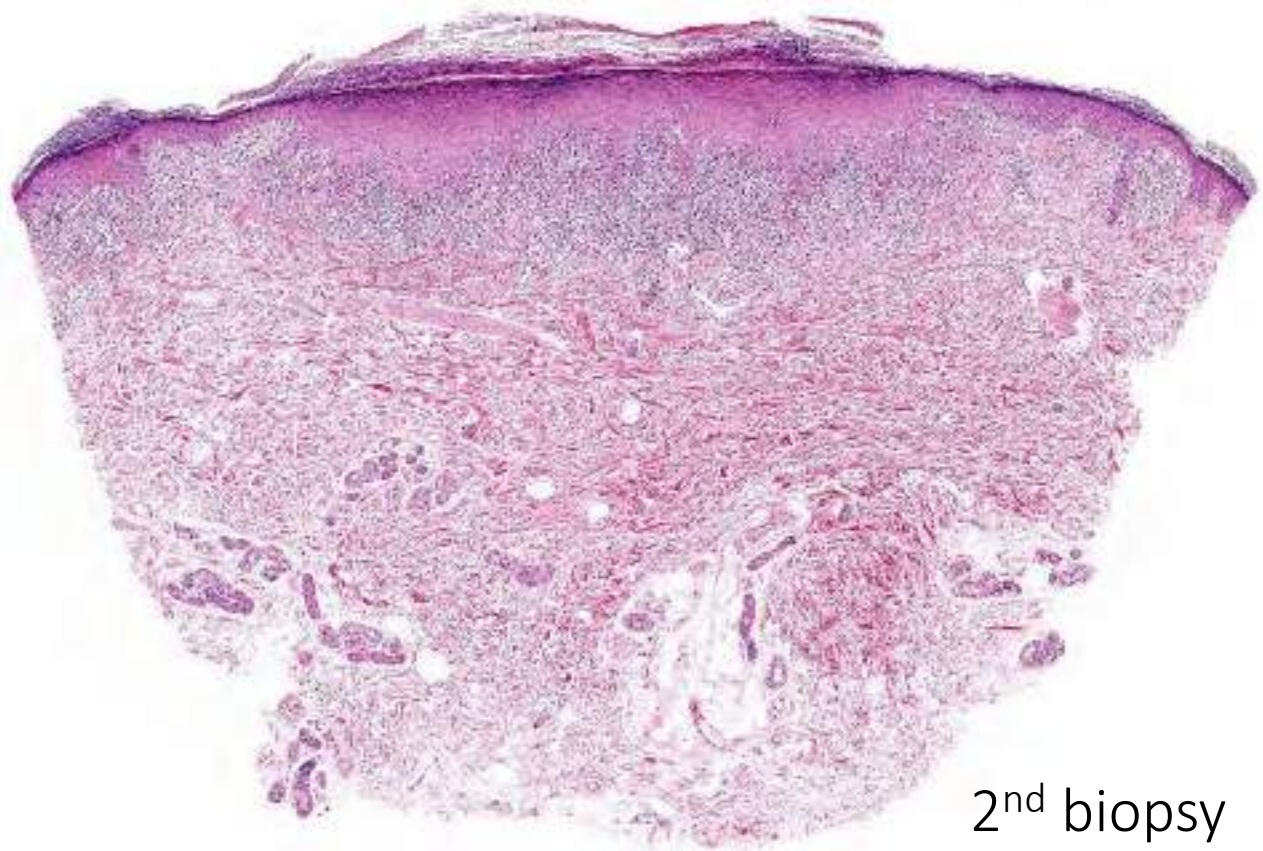
F, 58
Generalized reddish lesions



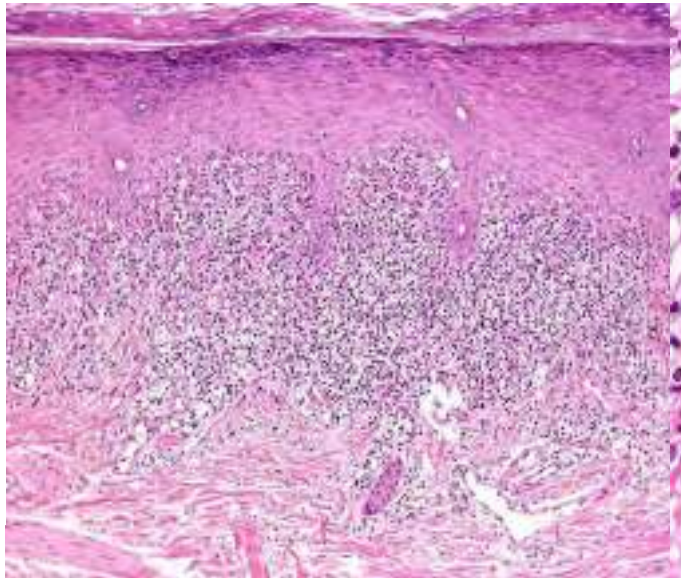
Lichen planus

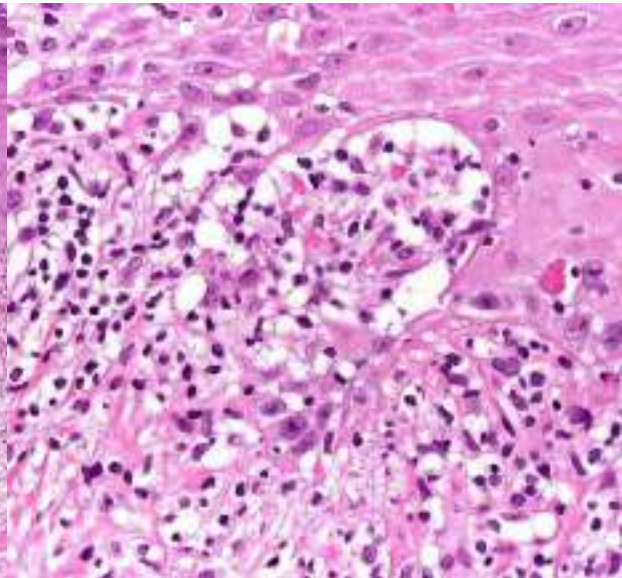






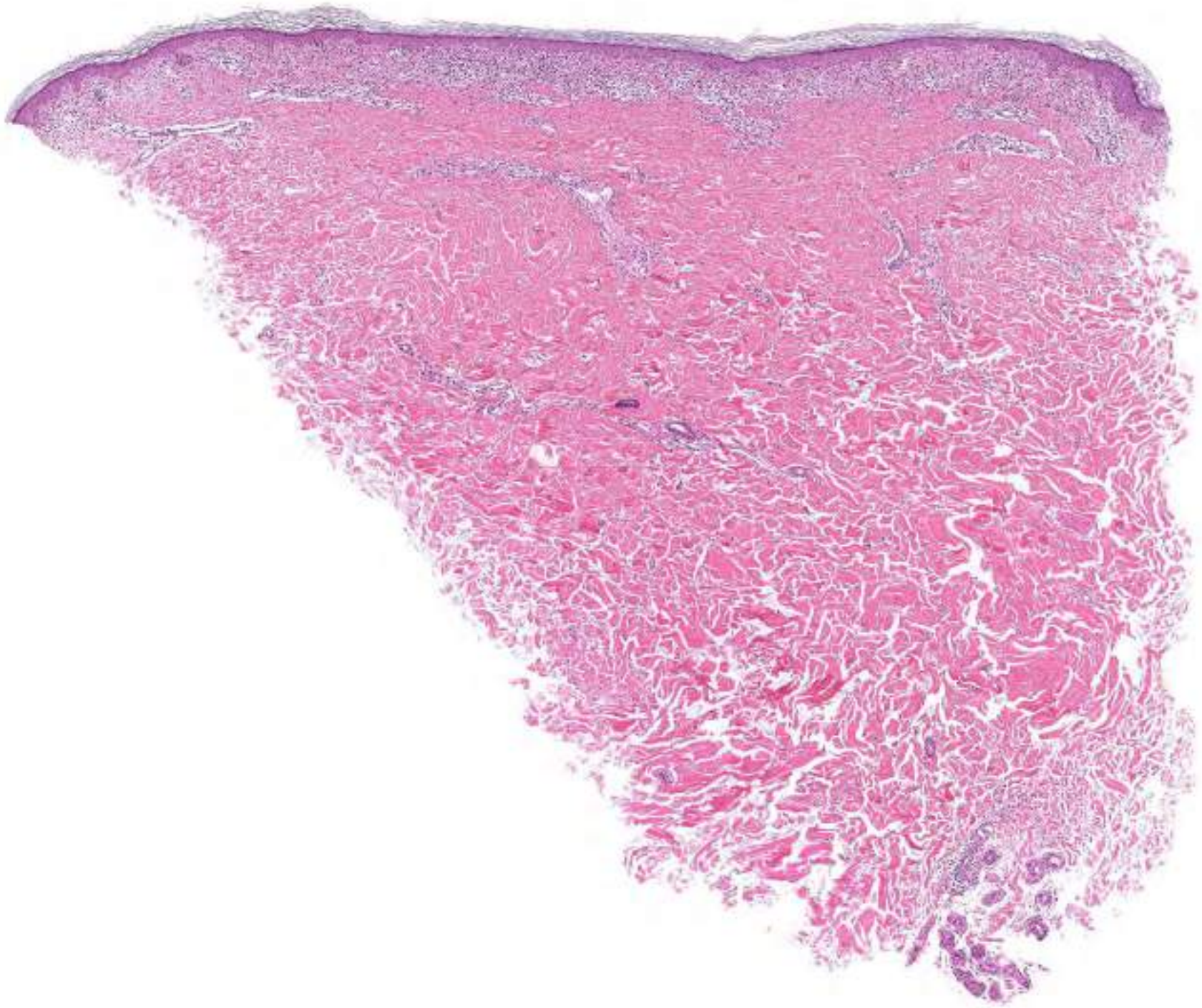
2nd biopsy

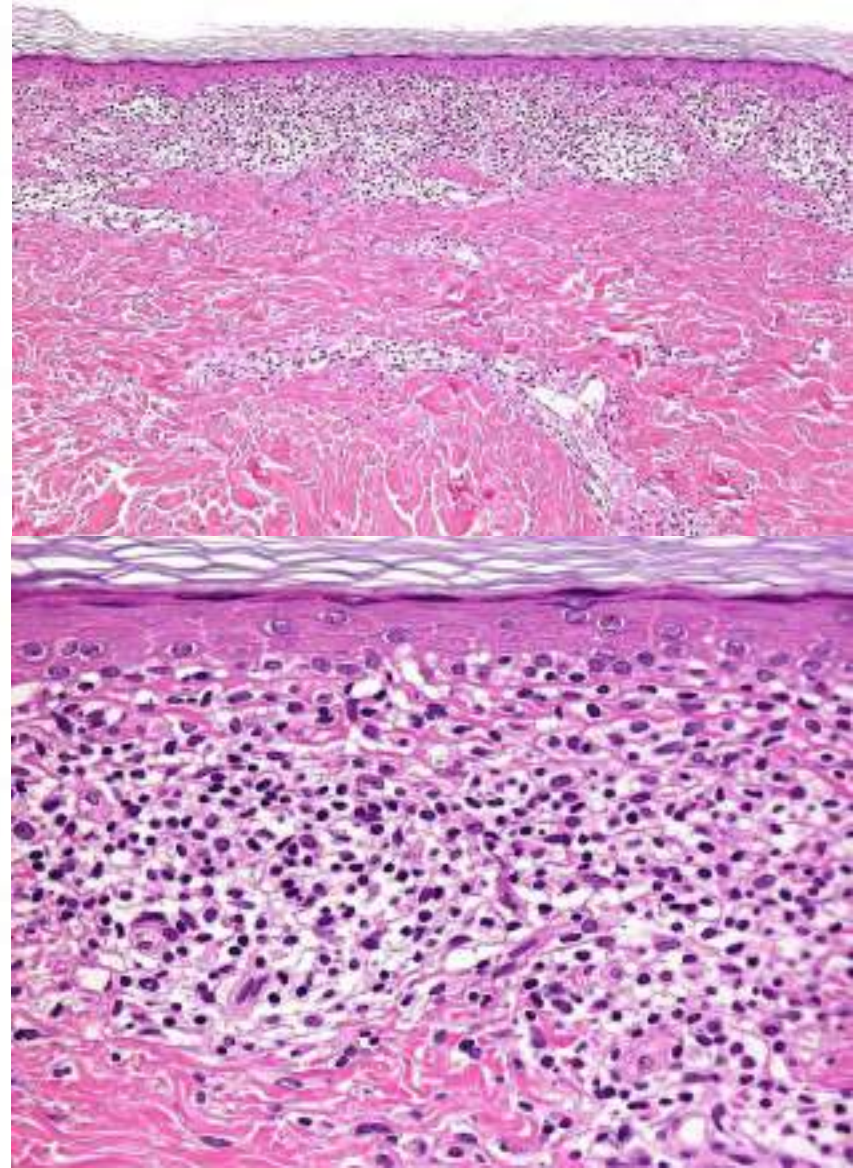


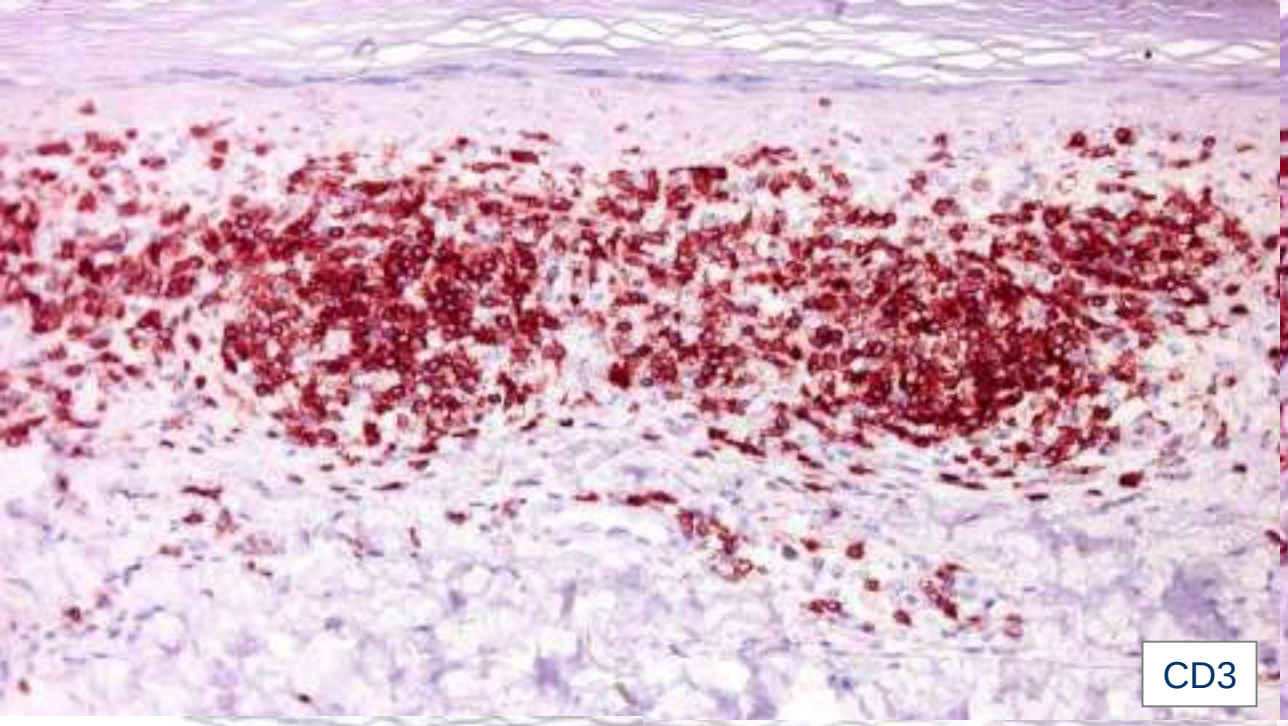


M, 50.

Several, partly hyperpigmented macules on the trunk and flexural regions.



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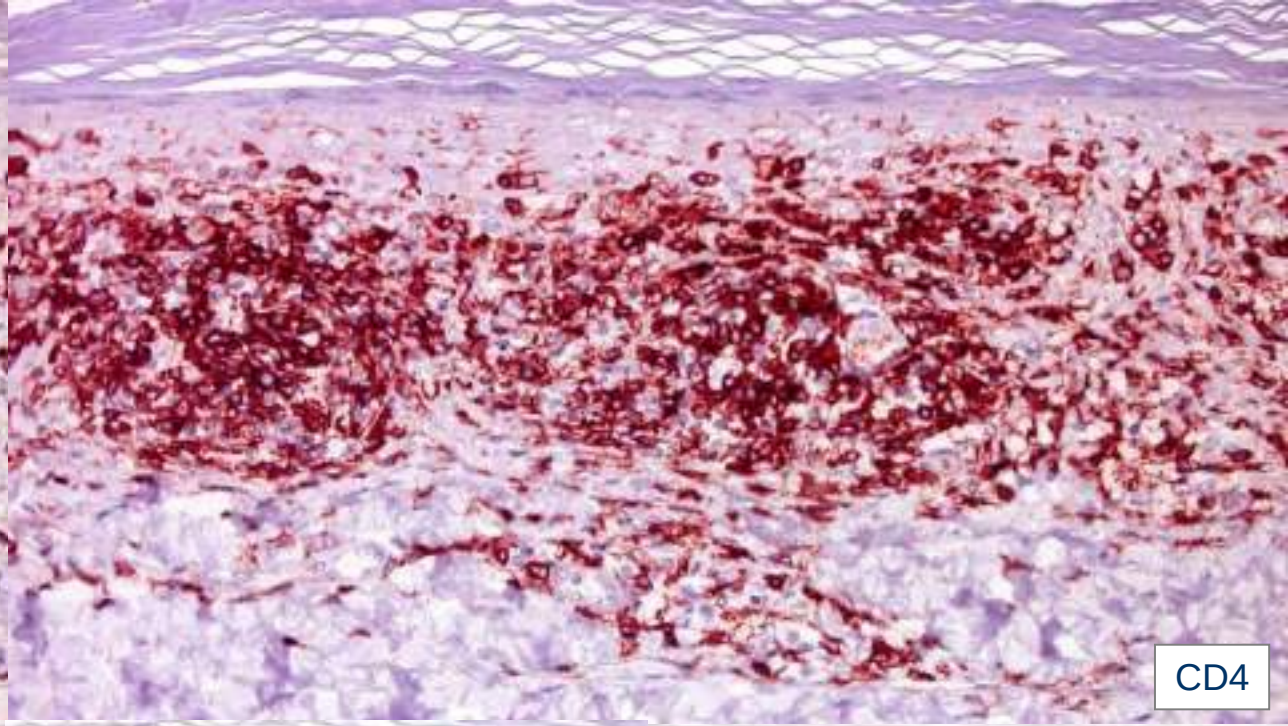
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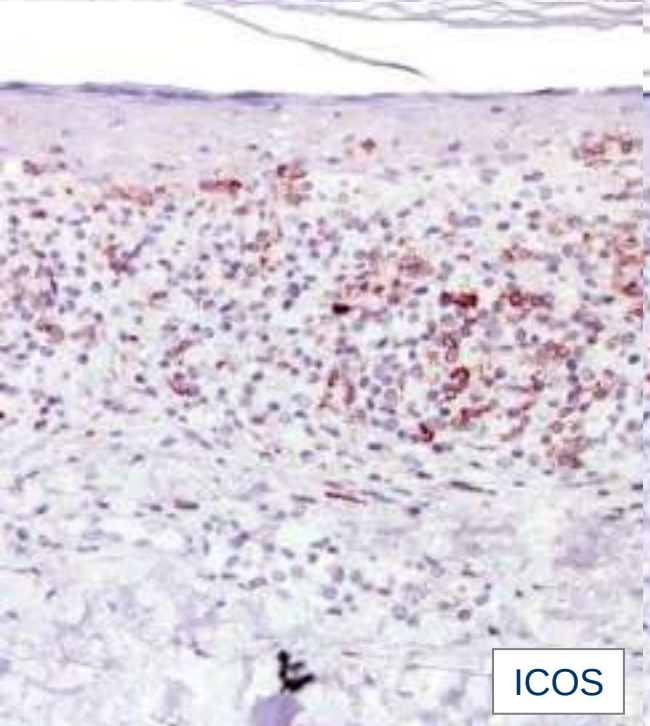
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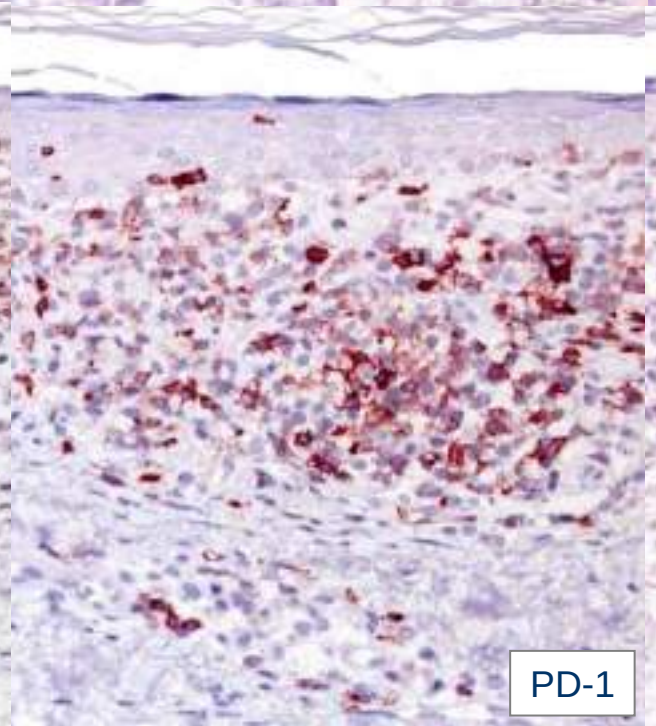
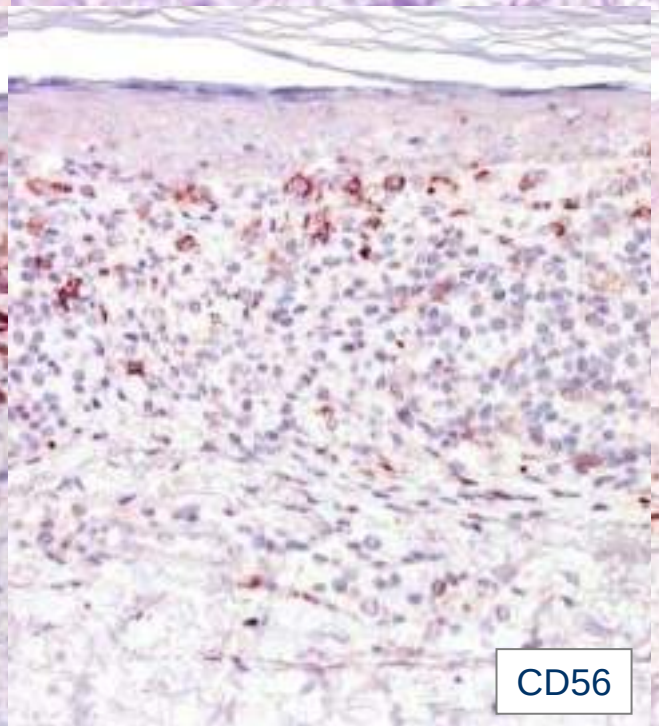

PD-1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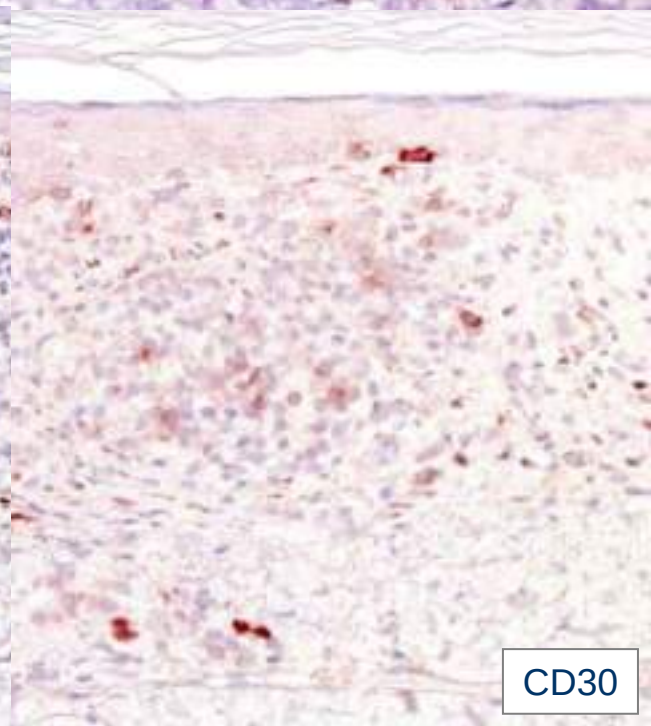
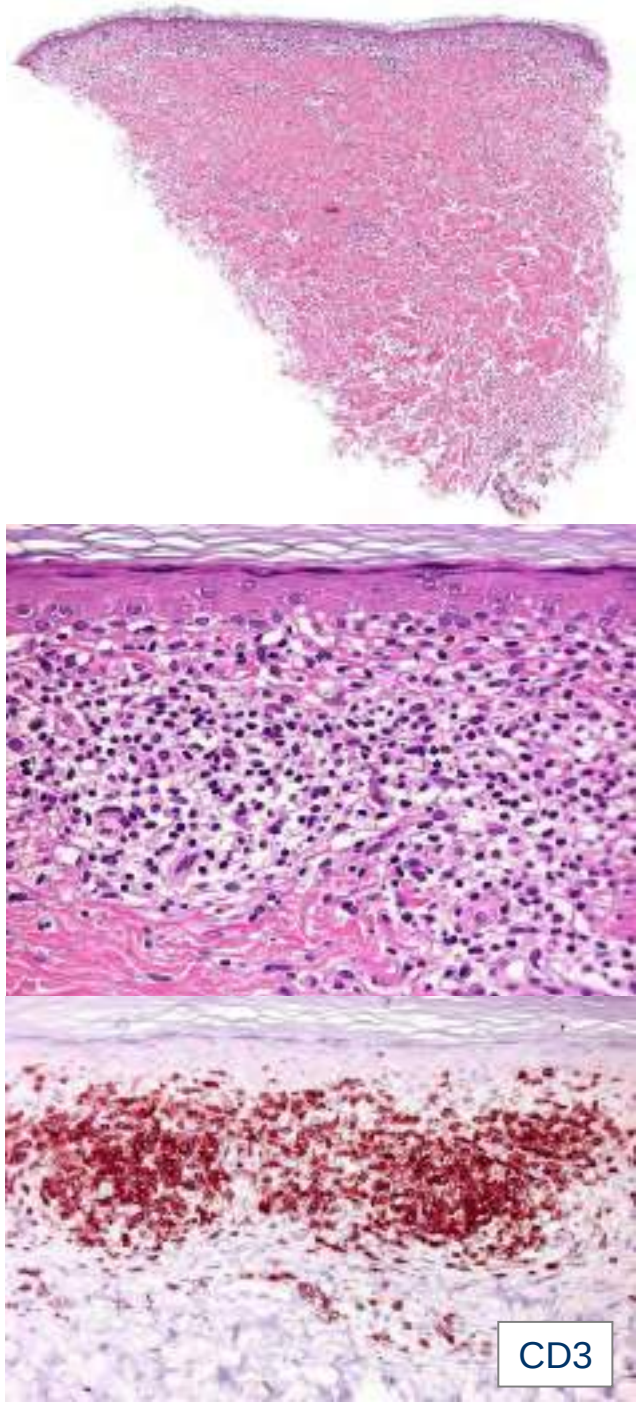
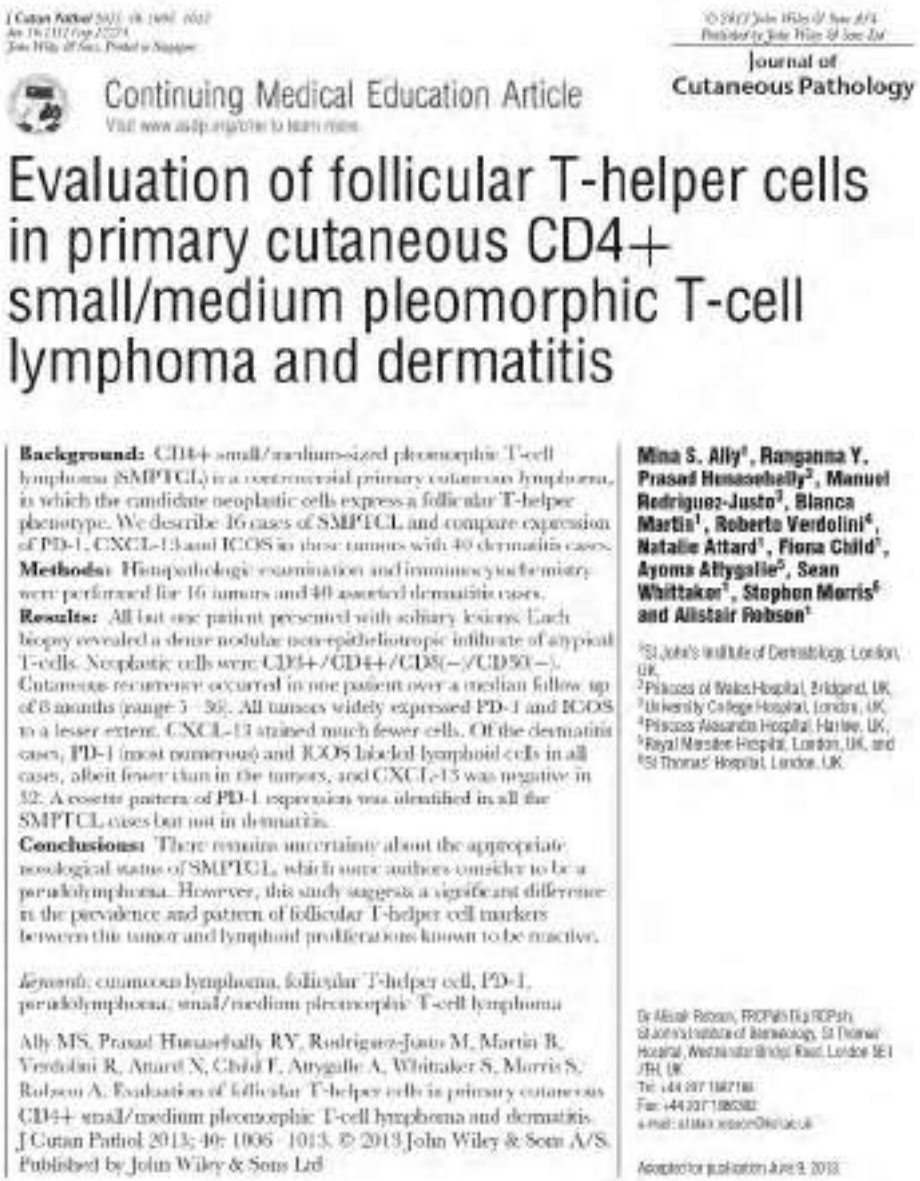

CD30

Atrophic lichen planus



Pseudolymphomatous lichen planus

- The lichenoid infiltrate of lichen planus is easily distinguished from band-like infiltrates of MF in the vast majority of cases
- In some cases lack of other typical histopathological features of lichen planus (e.g., epithelial hyperplasia, hypergranulosis) and presence of epidermotropic lymphocytes may be the reason for concern
- Phenotypic features of these cases do not provide differential diagnostic criteria; correlation with the clinical picture and/or repeat biopsies allow a precise diagnosis



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Evaluation of follicular T-helper cells in primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma and dermatitis

Background: CD4+ small/medium-sized pleomorphic T-cell lymphoma (SMPTCL) is a controversial primary cutaneous lymphoma, in which the candidate neoplastic cells express a follicular T-helper phenotype. We describe 16 cases of SMPTCL and compare expression of PD-1, CXCL-13 and ICOS in these tumors with 40 dermatitis cases.
Methods: Histopathologic examination and immunocytochemistry were performed for 16 tumors and 40 assorted dermatitis cases.
Results: All but one patient presented with solitary lesions. Each biopsy revealed a dense nodular non-epitheliotropic infiltrate of atypical T-cells. Neoplastic cells were CD3+/CD4+/CD8(−)/CD30(−). Cutaneous recurrence occurred in one patient over a median follow up of 8 months (range 5 – 36). All tumors widely expressed PD-1 and ICOS to a lesser extent. CXCL-13 stained much fewer cells. Of the dermatitis cases, PD-1 (most numerous) and ICOS labeled lymphoid cells in all cases, albeit fewer than in the tumors, and CXCL-13 was negative in 32. A rosette pattern of PD-1 expression was identified in all the SMPTCL cases but not in dermatitis.
Conclusions: There remains uncertainty about the appropriate nosological status of SMPTCL, which some authors consider to be a pseudolymphoma. However, this study suggests a significant difference in the prevalence and pattern of follicular T-helper cell markers between this tumor and lymphoid proliferations known to be reactive.

Keywords: cutaneous lymphoma, follicular T-helper cell, PD-1, pseudolymphoma, small/medium pleomorphic T-cell lymphoma

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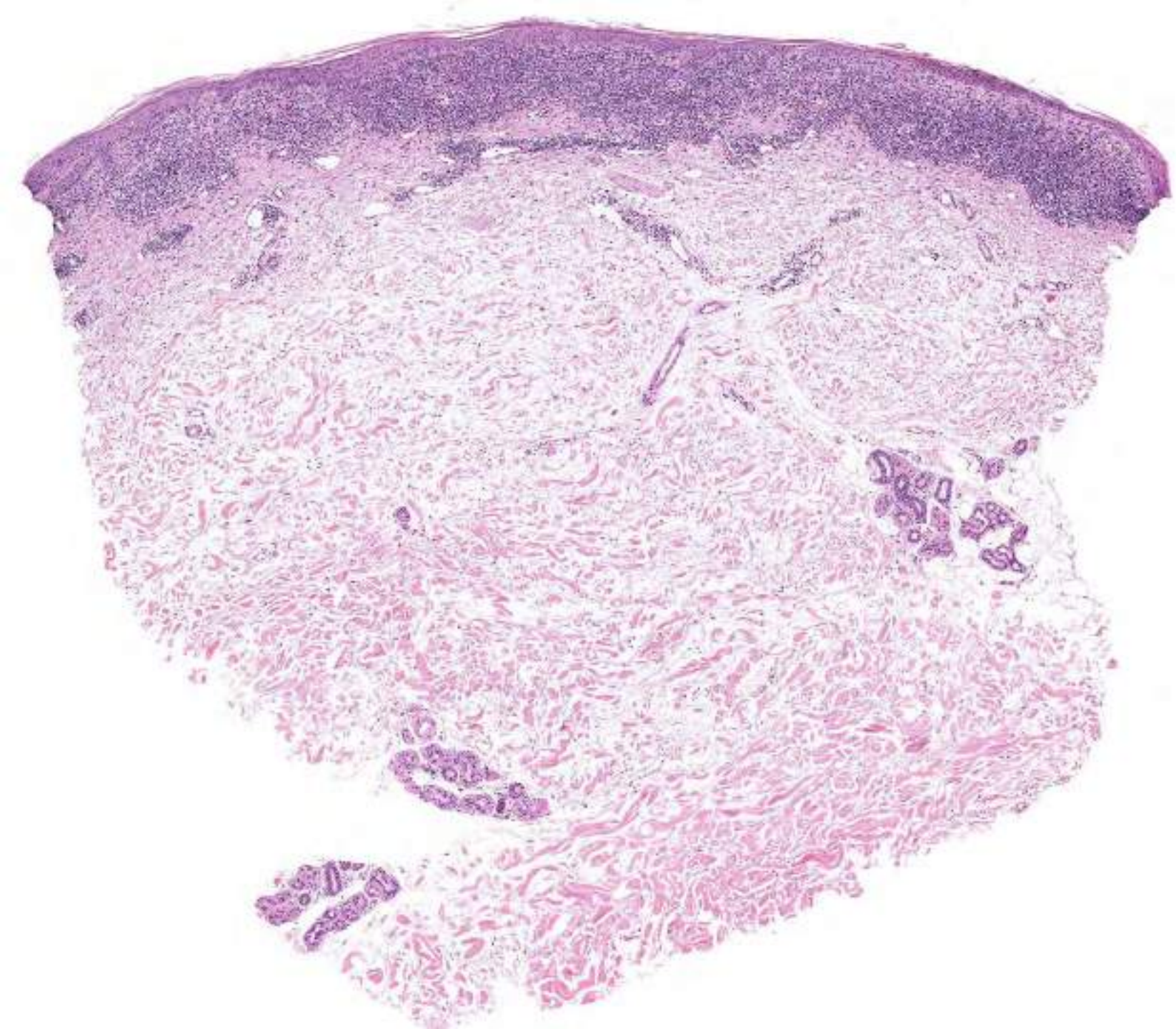
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (SMPTCL) is a provisional entity in the WHO-EORTC classification of cutaneous lymphomas. It represents approximately 3% of all primary cutaneous lymphomas.[1] Clinically, SMPTCL is characterized by a solitary plaque or tumor on the head, neck or extremities. Less frequently it can present

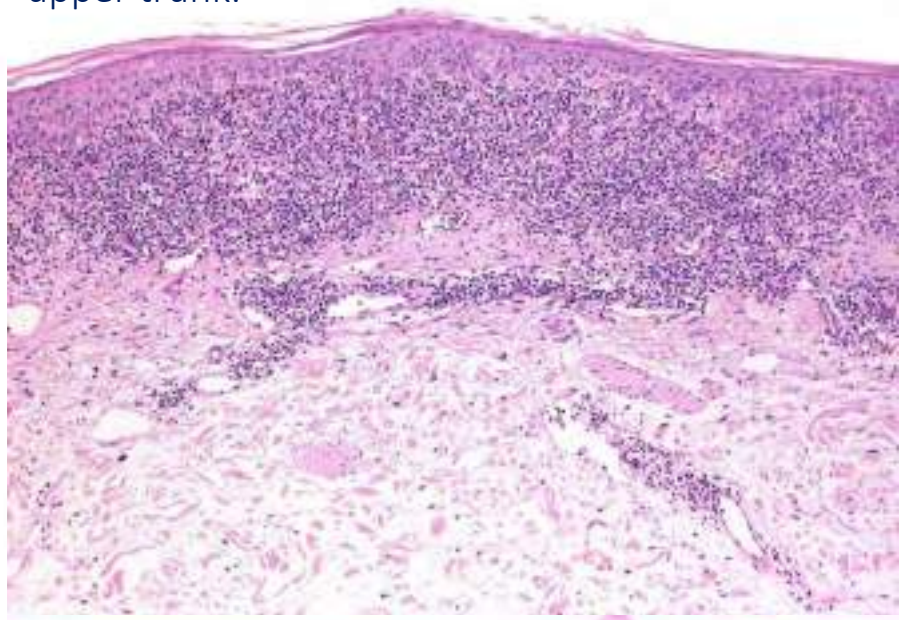
SMPTCL: 16 (15 solitary)
Eczema: 11
Drug reaction: 10
Lupus erythematosus: 5
Psoriasis: 2
Hidradenitis suppurativa: 2
Lichen aureus: 2
Erythema nodosum: 1
Folliculitis: 1
Erythema annulare centrifugum: 1
Viral exanthema: 1
Lichen sclerosus: 1
Lichen planus: 1
Urticaria: 1
AHWE (epithelioid hemangioma): 1

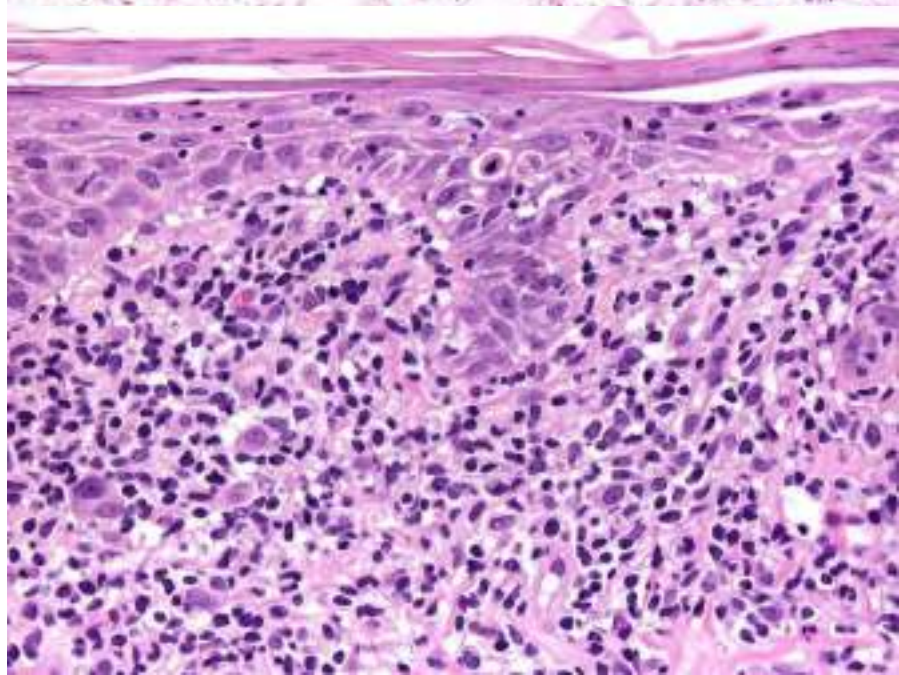
SMPTCL: all cases positive for PD-1 and ICOS (ICOS: lower # of cells); CXCL13 stained "much fewer cells"
Controls: all cases positive for PD-1 and ICOS (ICOS: lower # of cells); CXCL13-

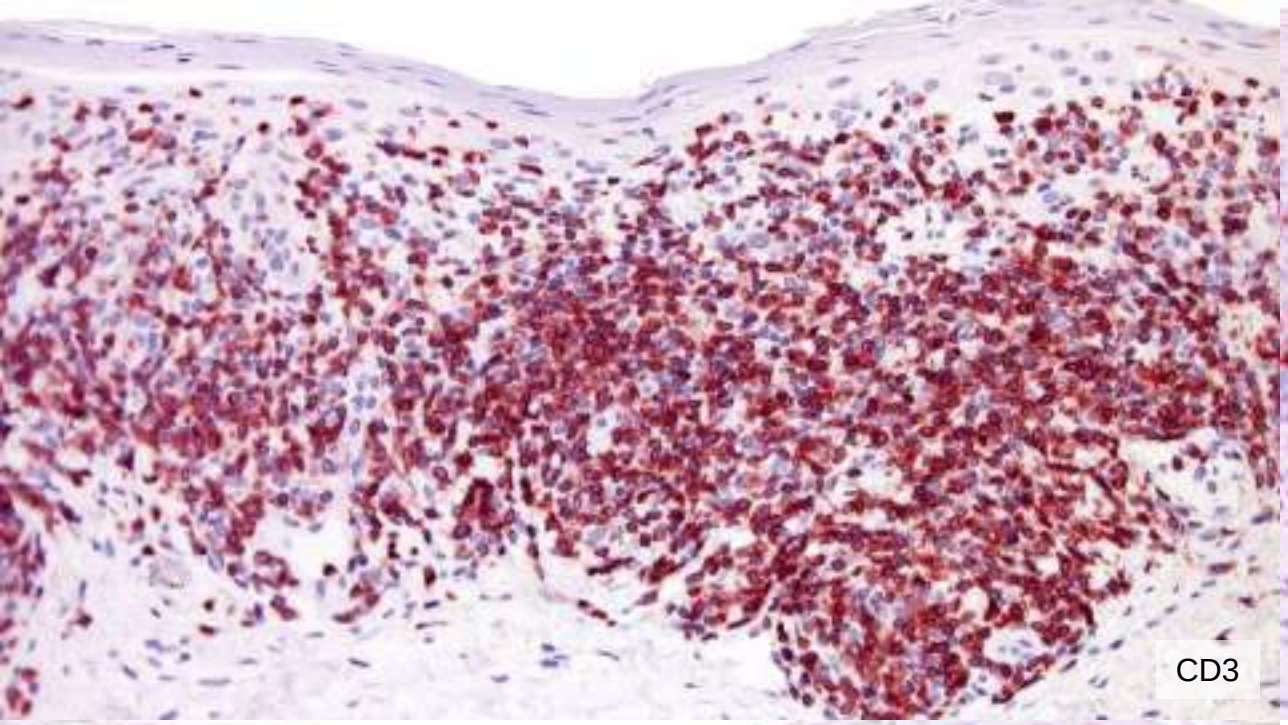
F, 69.

Infiltrated, reddish papules and plaques on the upper trunk.





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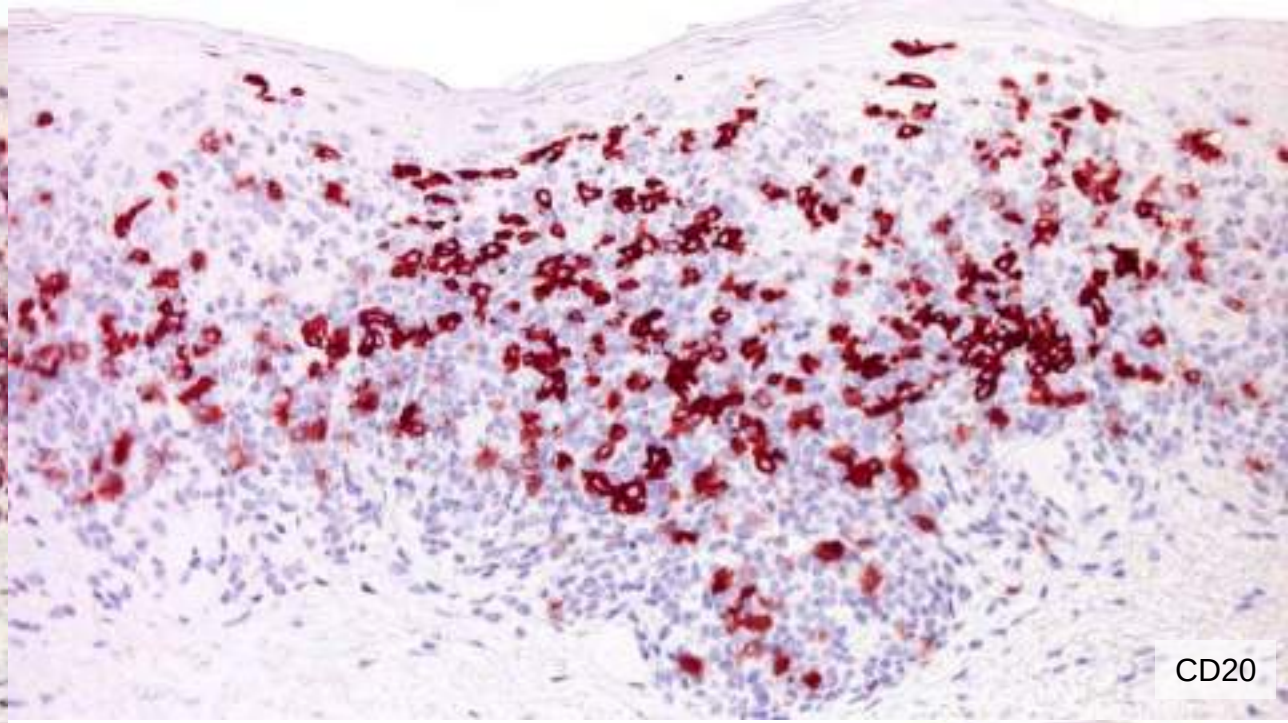
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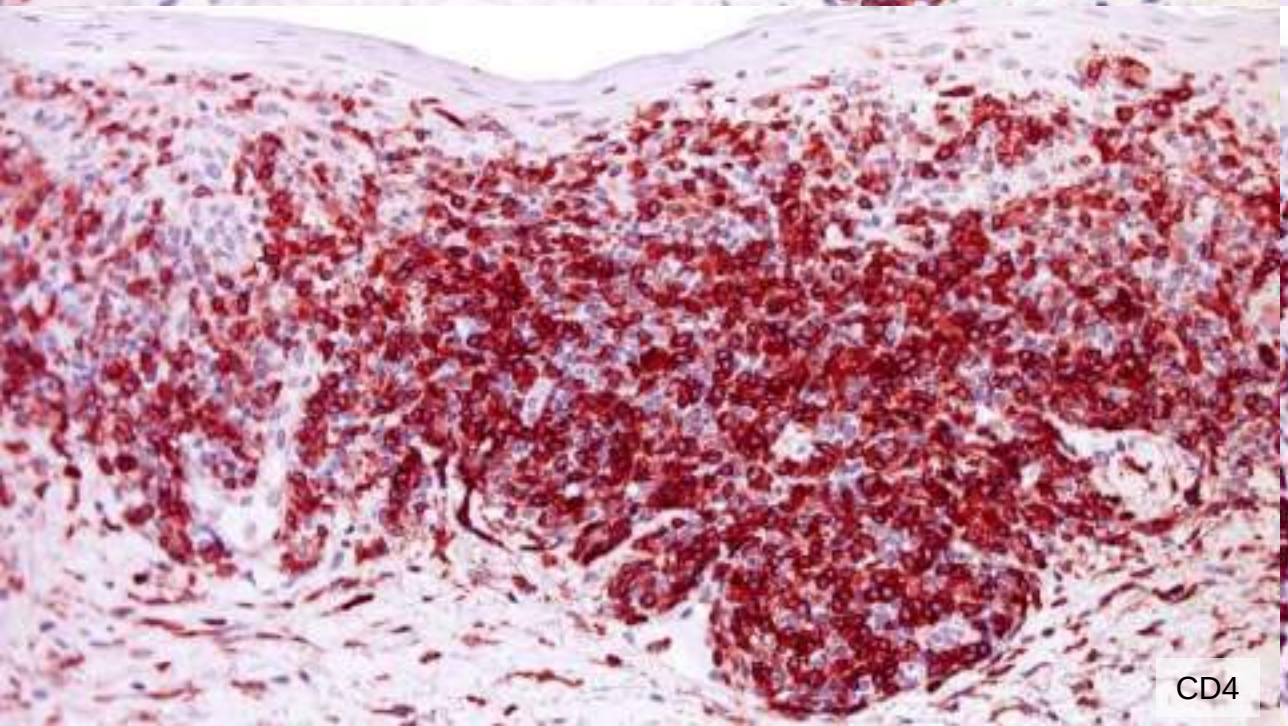
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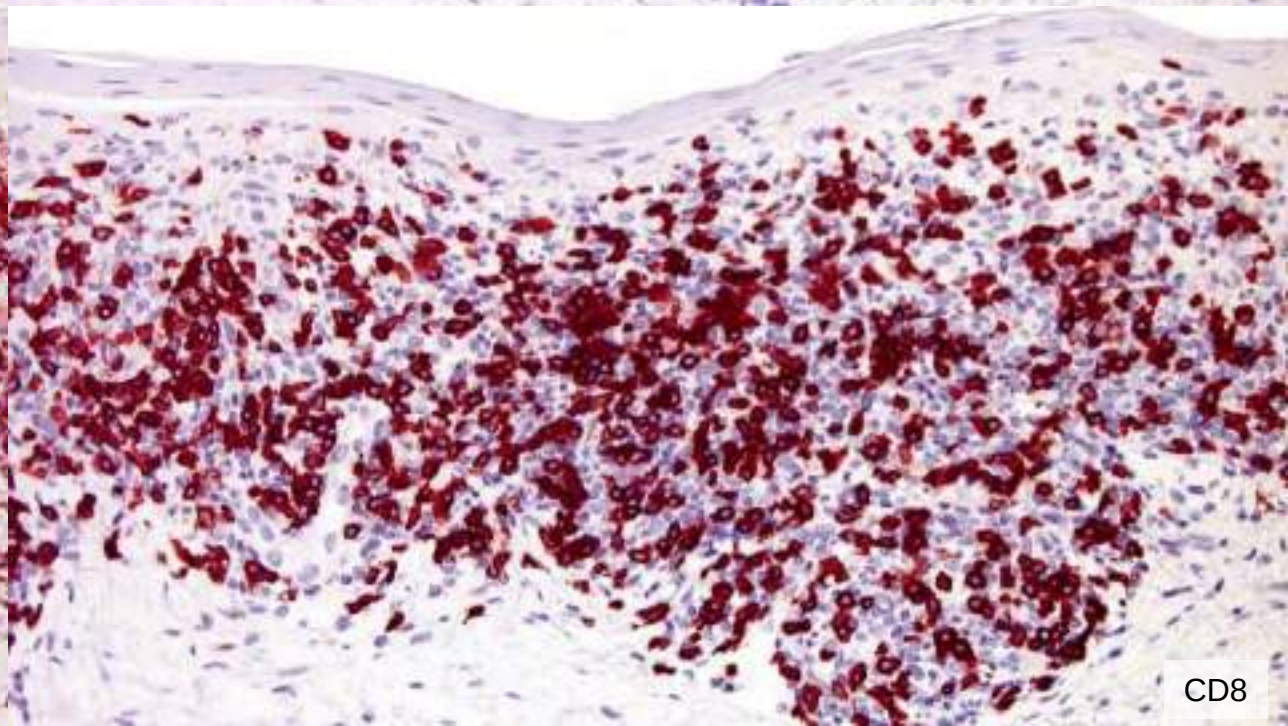
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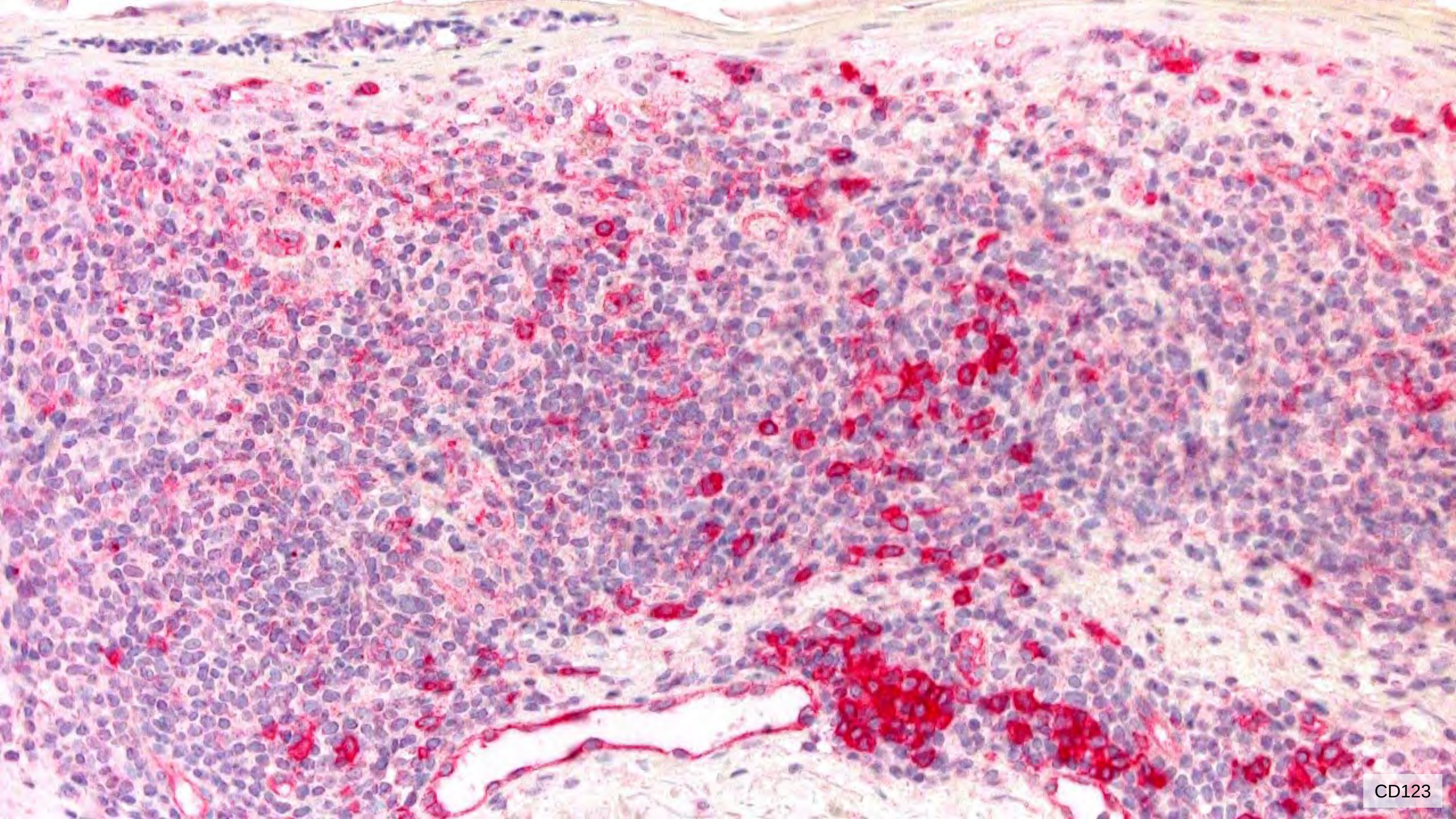
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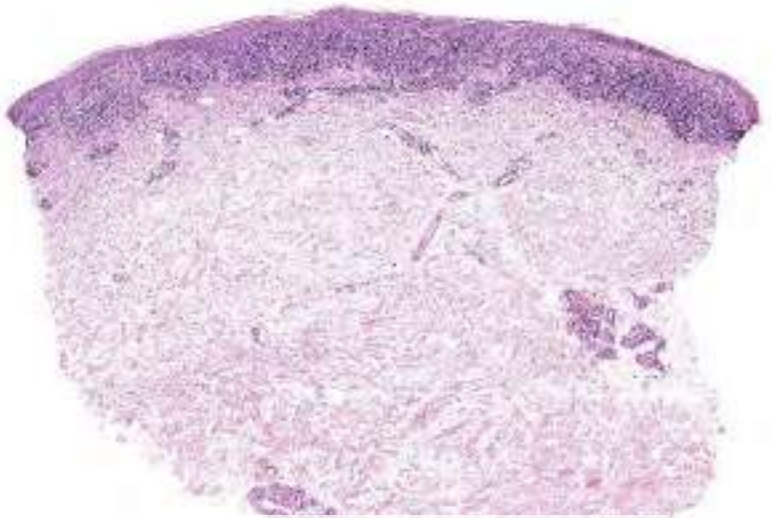


"Pseudolymphomatous" LE

ANA 1:1280

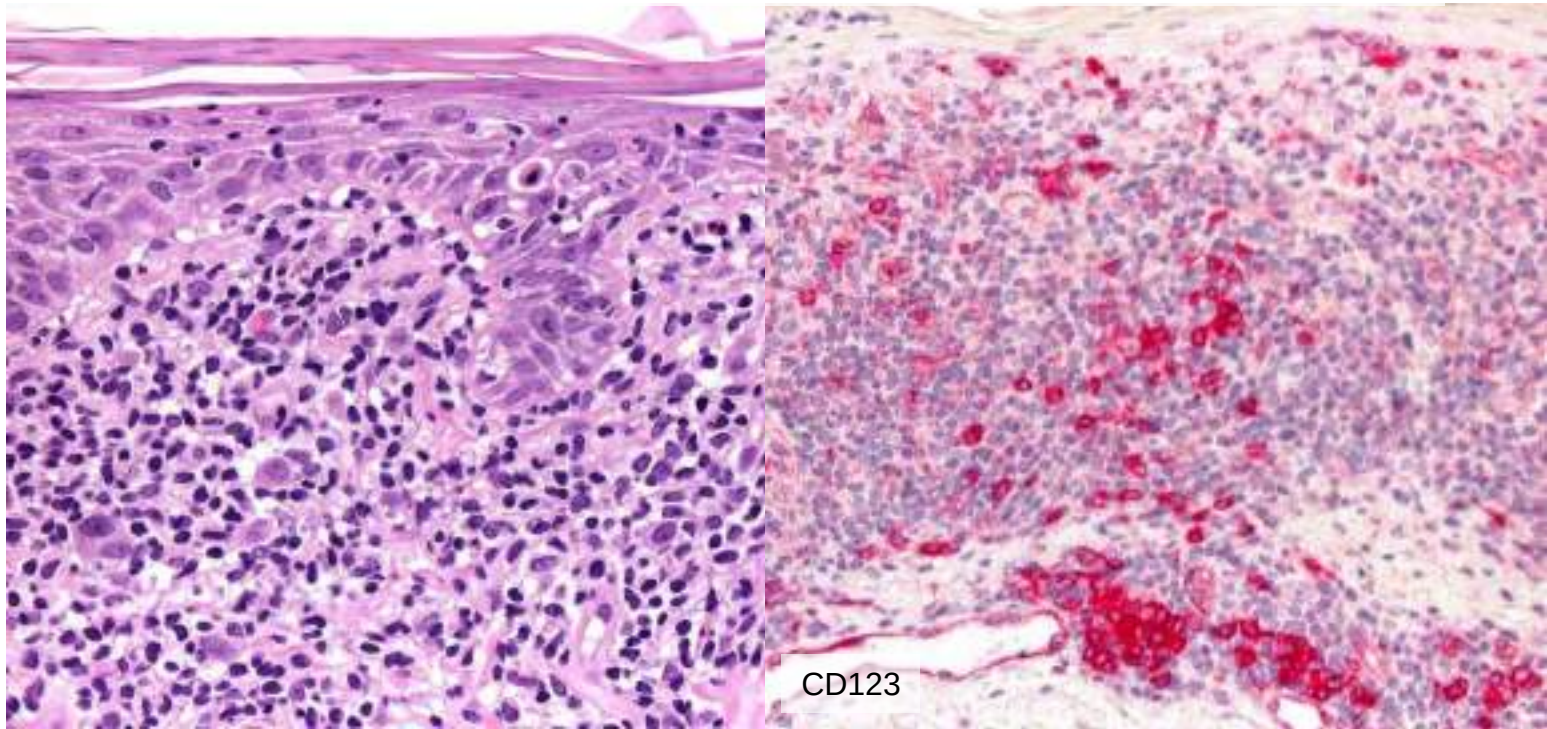
ENA >32.0 U/ml (0 – 1)

Ro-Abs >240.0 U/ml (0 – 10)

Ro 52-Abs >240.0 U/ml (0 – 10)

Ro 60-Abs >282.0 U/ml (0 – 10)

La-Abs 19.0 U/ml (0 – 10)



The Histopathological Spectrum of Pseudolymphomatous Infiltrates in Cutaneous Lupus Erythematosus

Amanda Pereira, MD.† Gerardo Ferrara, MD.*‡ Paola Calomaro, MD.*§ Carlo Cota, MD.¶ Cesare Massone, MD.*‖ Francesca Boggio, MD.*** Lucia Prieto-Torres, MD.*†† and Lorenzo Cerroni, MD**

Abstract: The occurrence of pseudolymphomatous infiltrates in cutaneous lupus erythematosus (cLE) is described mainly in lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin (Jessner Kanof). We collected 15 cases of pseudolymphomatous cLE other than lupus panniculitis and lupus tumidus (M/F = 4/11; age range: 13–79 years; mean age: 50.9 years; median age: 57 years). Of the 15 cases, 9 (60%) were characterized by dense nodular infiltrates. Three cases (20%) showed an angiocentric pattern with cytological atypia of lymphoid cells; 2 cases (13.3%) showed a band-like infiltrate extending beyond folliculis, and 1 case had mixed features of the band-like and angiocentric patterns. Close to the histopathological diagnosis of cLE were presence of interface dermatitis, clusters of plasmacytoid dendritic cells, and dermal mucin deposition. Our study shows that the spectrum of pseudolymphomatous presentations of cLE is broader than previously described, including band-like cases that may be misinterpreted as mycosis fungoides, and angiocentric cases that may be misinterpreted as an aggressive lymphoma. Recognition of such cases is possible only on careful clinicopathologic correlation and requires a high level of histopathological suspicion to allow a correct diagnosis and the proper management of the patients.

Key Words: cutaneous lupus erythematosus, cutaneous pseudolymphoma, interface dermatitis, plasmacytoid dendritic cells, band-like infiltrate, angiocentric infiltrate

(*Am J Dermatopathol* 2018;40:247–255)

INTRODUCTION

Cutaneous lupus erythematosus (cLE) is a chronic autoimmune disease of the skin which may be associated with systemic involvement.[1] Histopathologically several patterns can be observed, depending on the type of cLE and the skin structure(s) involved. The most typical features are the presence of interface dermatitis with vacuolar changes of the basal keratinocytes and necrotic keratinocytes, mucin deposition, and variably dense lymphoid cell infiltrates.[2] The latter usually do not pose differential diagnostic problems with cutaneous lymphomas, with 2 exceptions, namely (1) lupus panniculitis, which may mimic subcutaneous panniculitis-like T-cell lymphoma[3]; and (2) lupus tumidus/lymphocytic infiltration of the skin (Jessner Kanof), which may be misinterpreted morphologically as a cutaneous lymphoproliferative disorder.[3,4] To date, only anecdotal reports have focused on the occurrence of pseudolymphomatous infiltrates in cases of cLE other than lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin.[3,5] However, because of the common absence of systemic symptoms and/or immunological abnormalities, and the possible negative direct immunofluorescence test even on involved skin,[2] a cLE with atypical lymphoid infiltrates may be misinterpreted as a cutaneous lymphoproliferative disorder, particularly in cases in which a careful clinicopathologic correlation is not possible.

We describe the histopathological findings in 15 cases of cLE characterized by pseudolymphomatous infiltrates, with emphasis on the different patterns mimicking various cutaneous lymphoproliferative conditions.

PATIENTS AND METHODS

The cases were retrieved from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Graz, Austria. The study has been approved by the ethical committee of the Medical University of Graz. Cases of lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin were excluded because they were already described as potential diagnostic pitfalls.[3,4] In all cases, the final diagnosis of pseudolymphomatous cLE was based on the synthesis of clinical and histopathological data.

All slides were reviewed for architectural and cytological features of the infiltrate, and for the presence/absence of histopathological features consistent with cLE. In all cases, an appropriate panel of antibodies had been initially applied because of the histopathological suspicion of a cutaneous lymphoproliferative disorder.

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The authors declare no conflicts of interest.

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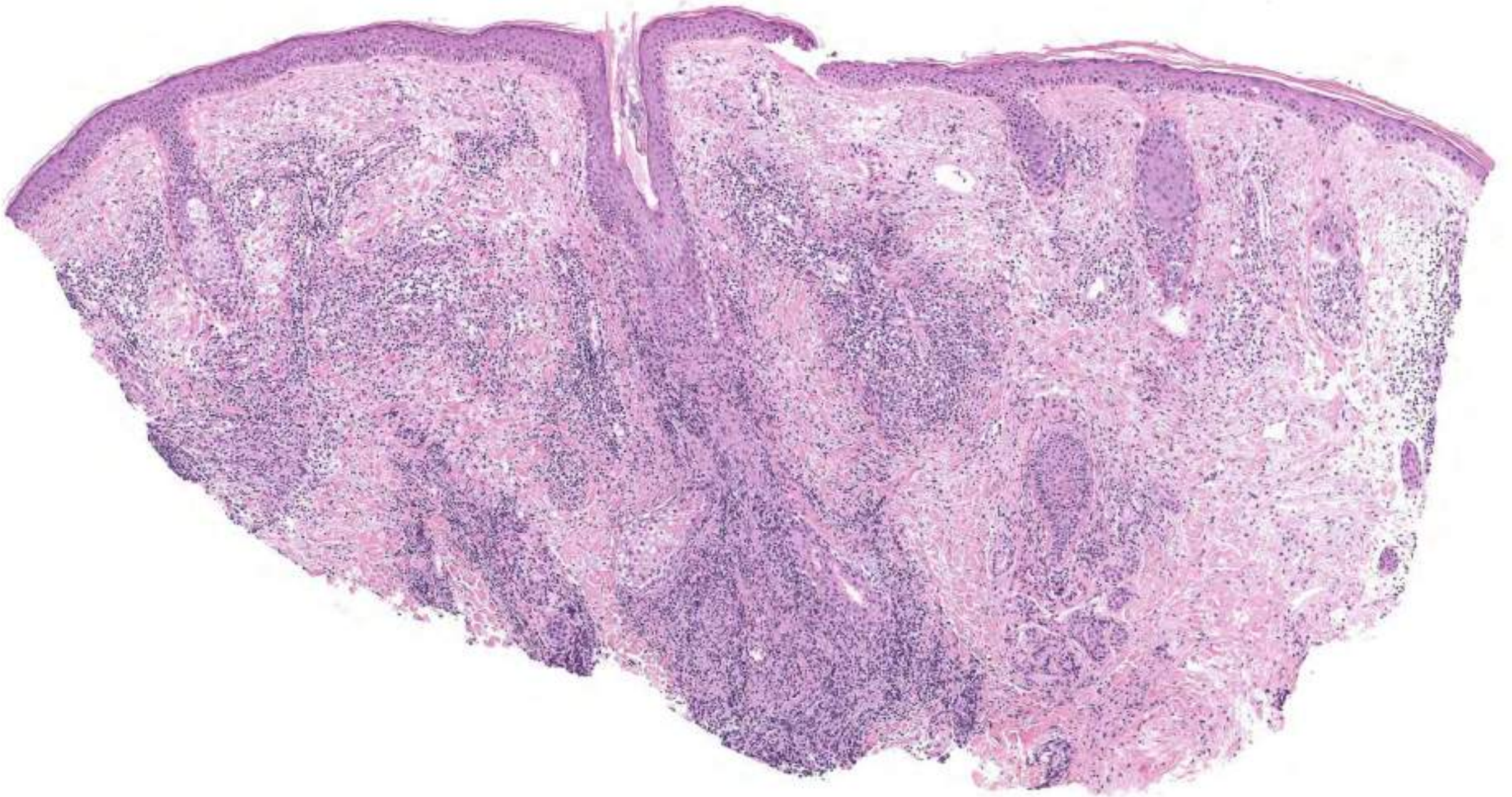
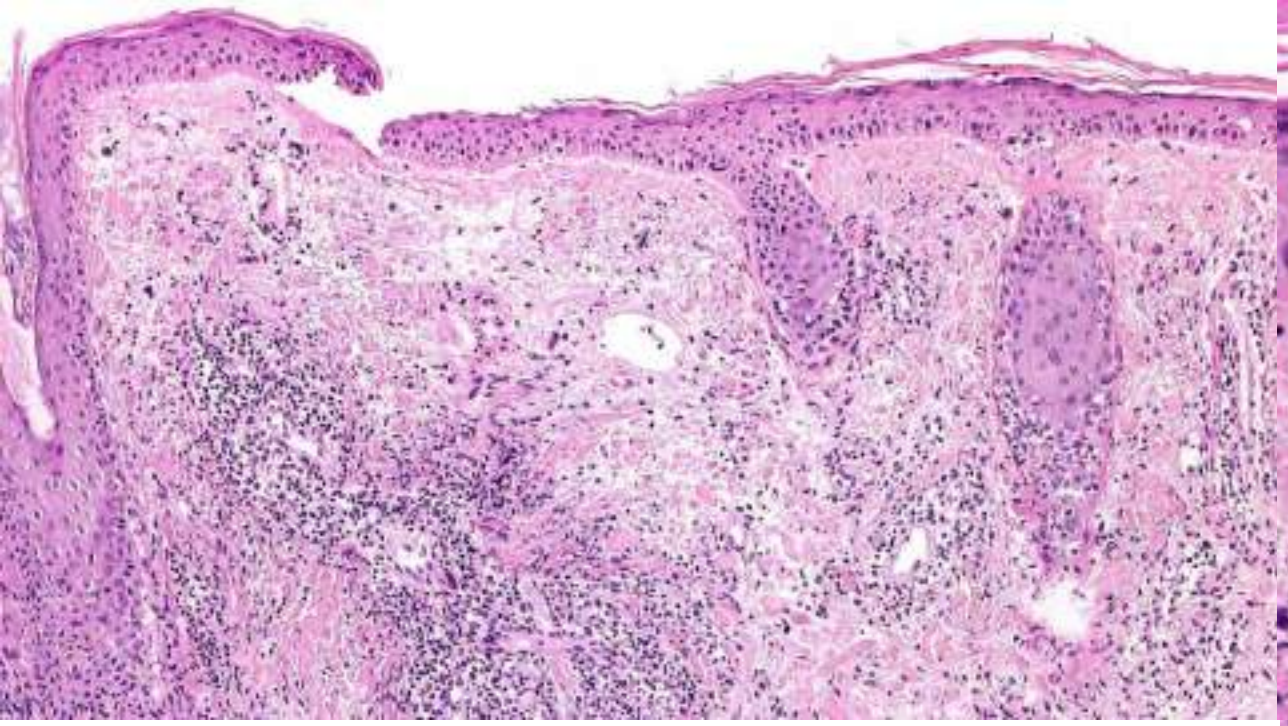
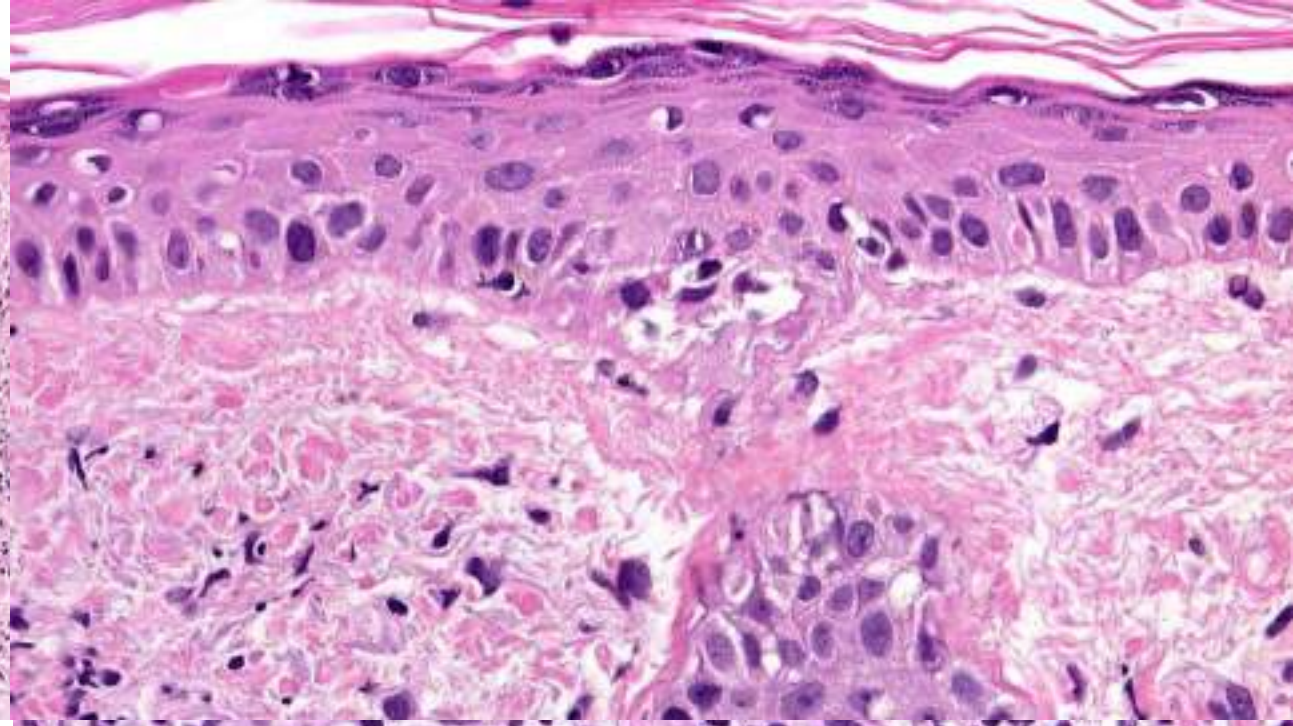
15 cases

9 cases: dense nodular infiltrates
3 cases: angiocentric pattern
2 cases: band-like pattern
1 case: band-like + angiocentric pattern

F, 35, pregnant.







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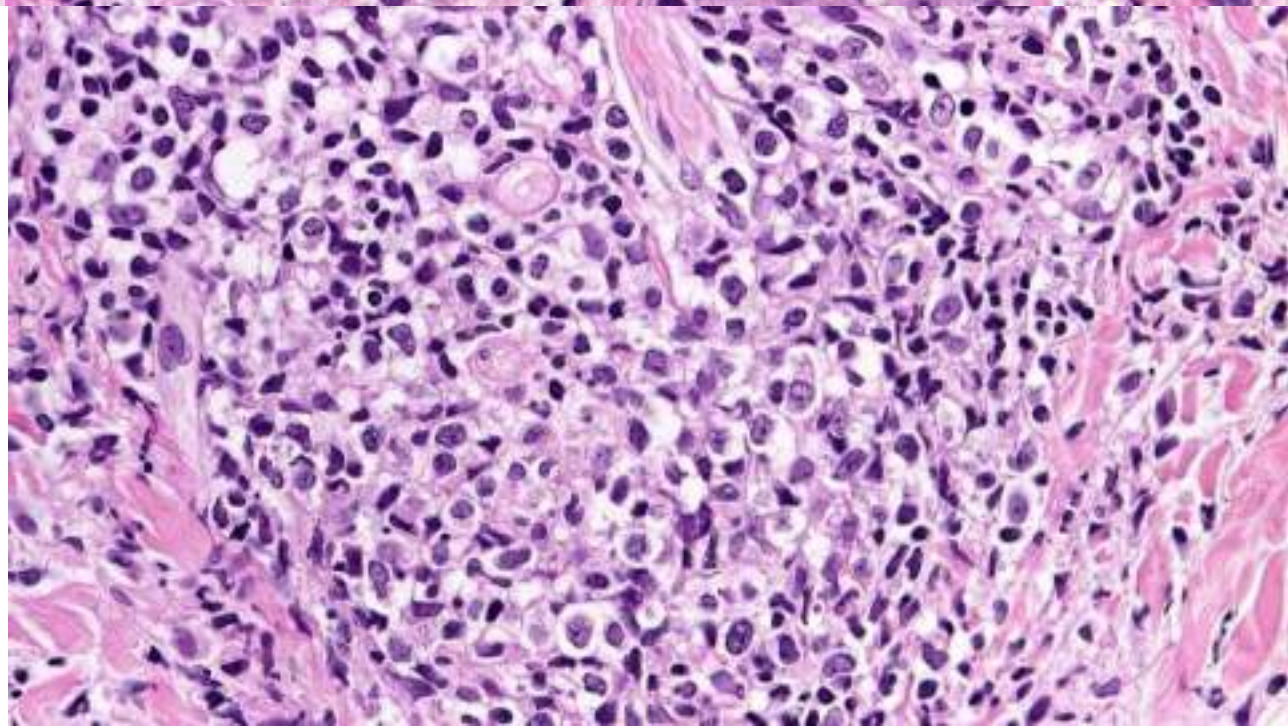
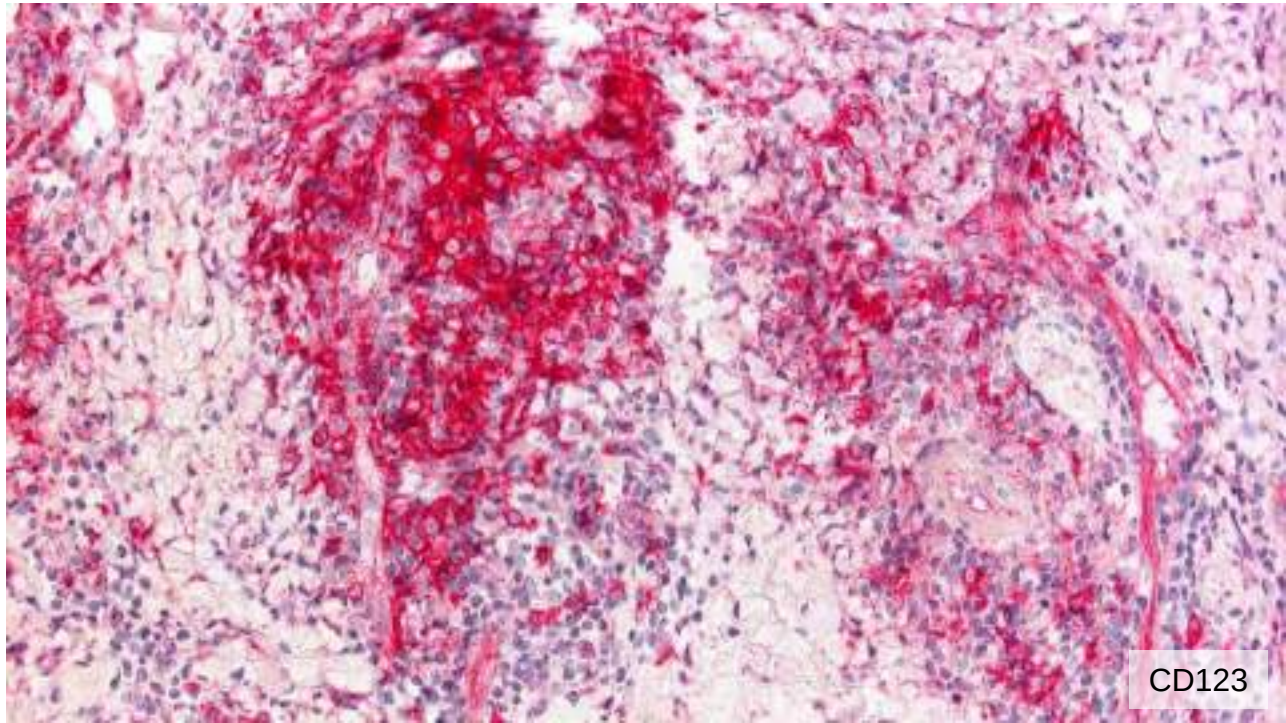
ENA-Screening	>32.0 U/mL (-1.0)
Ro-AK	>240.0 U/mL (-10.0)
Ro52-AK	>240.0 U/mL (-10.0)
Ro60-AK	>282.0 U/mL (-10.0)
La-AK	290.0 U/mL (-10.0)

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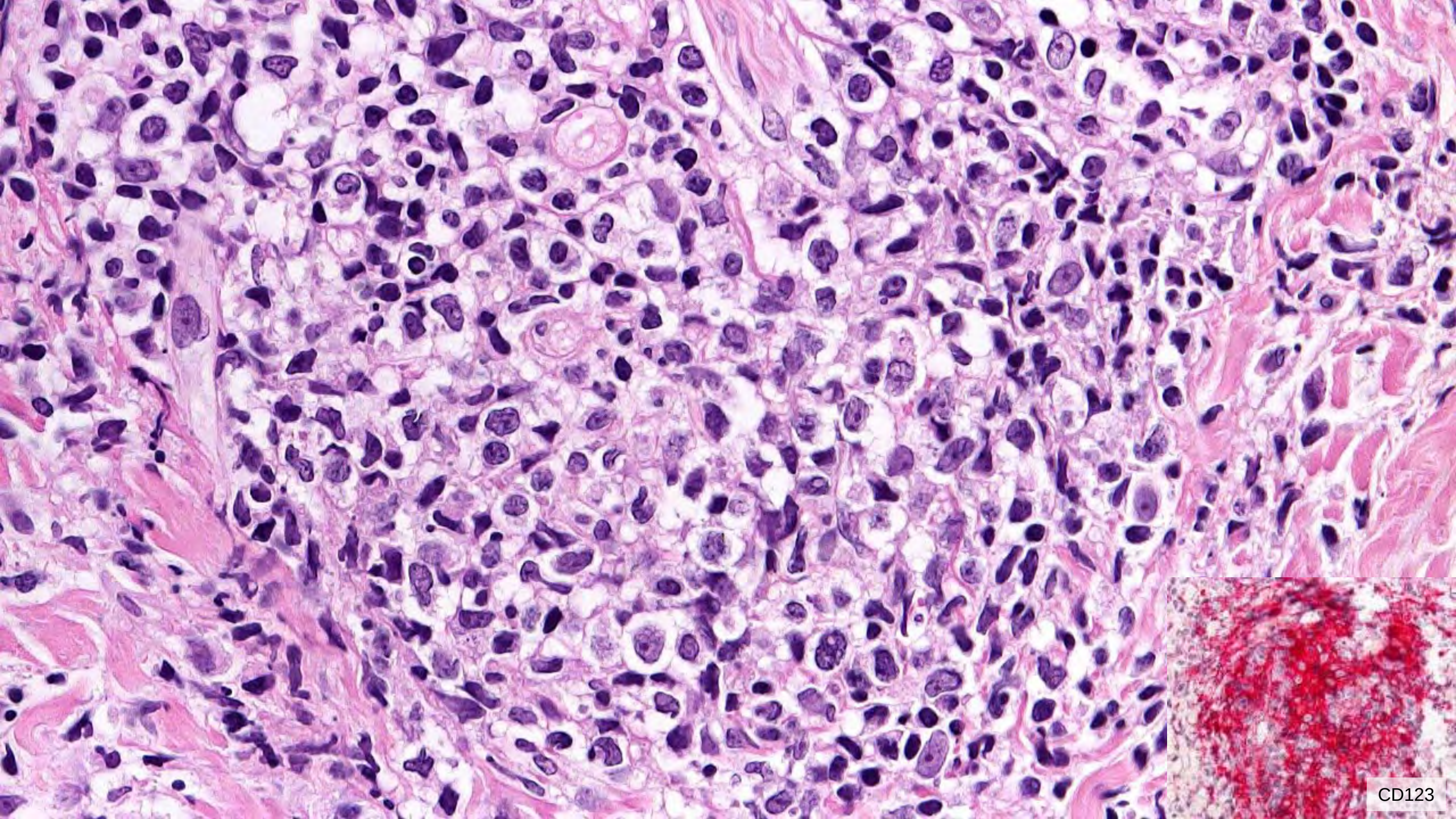
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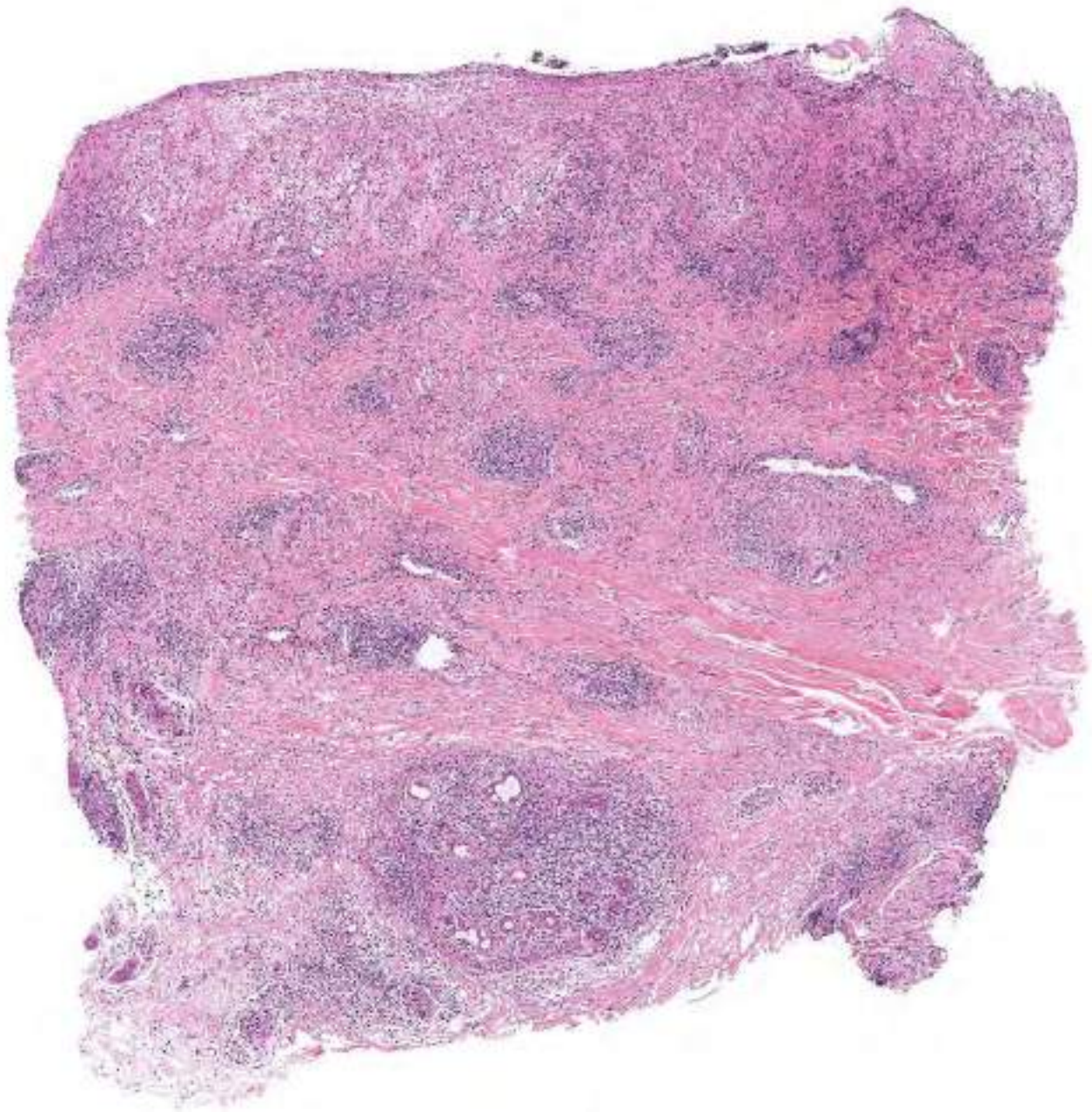
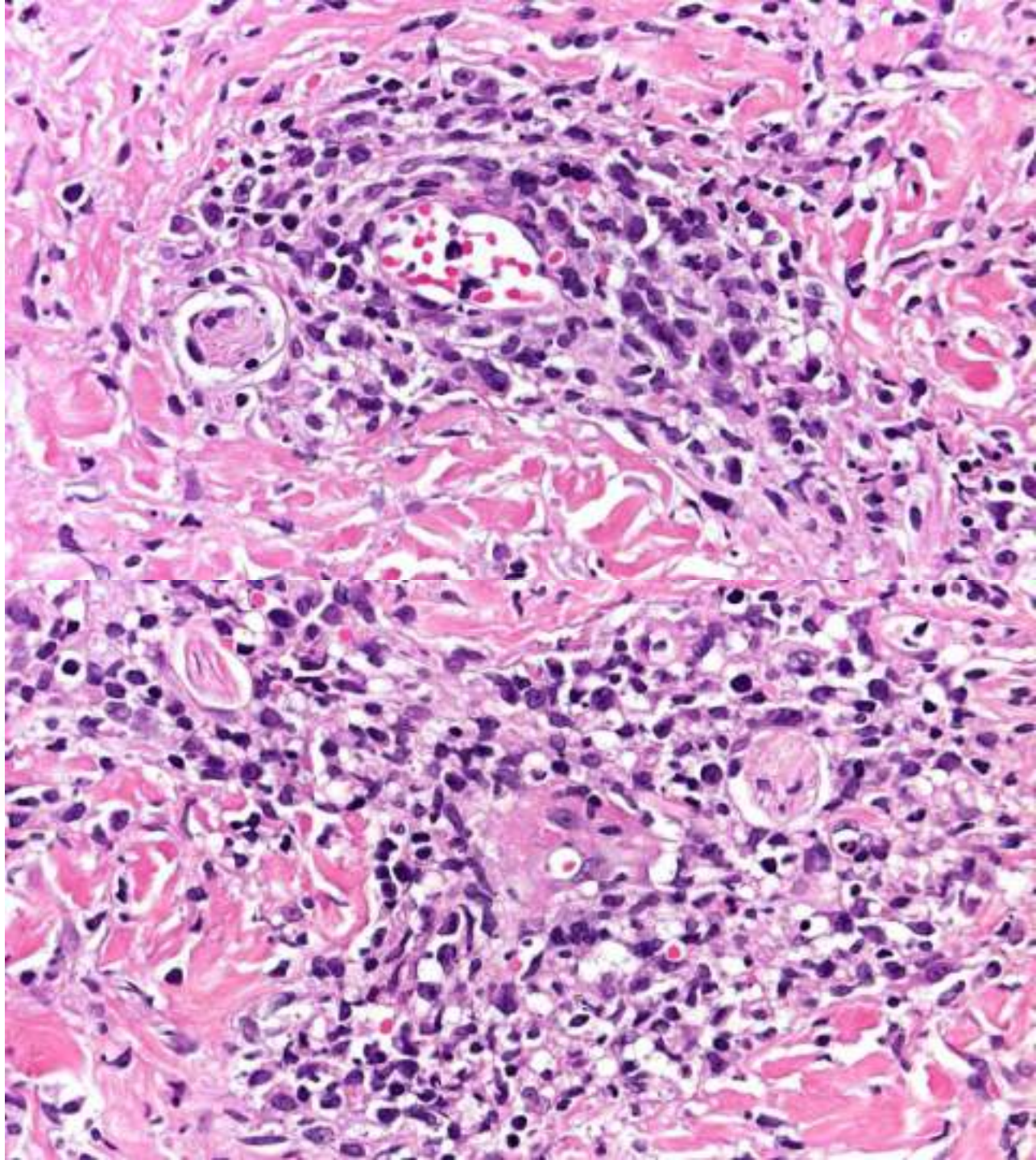
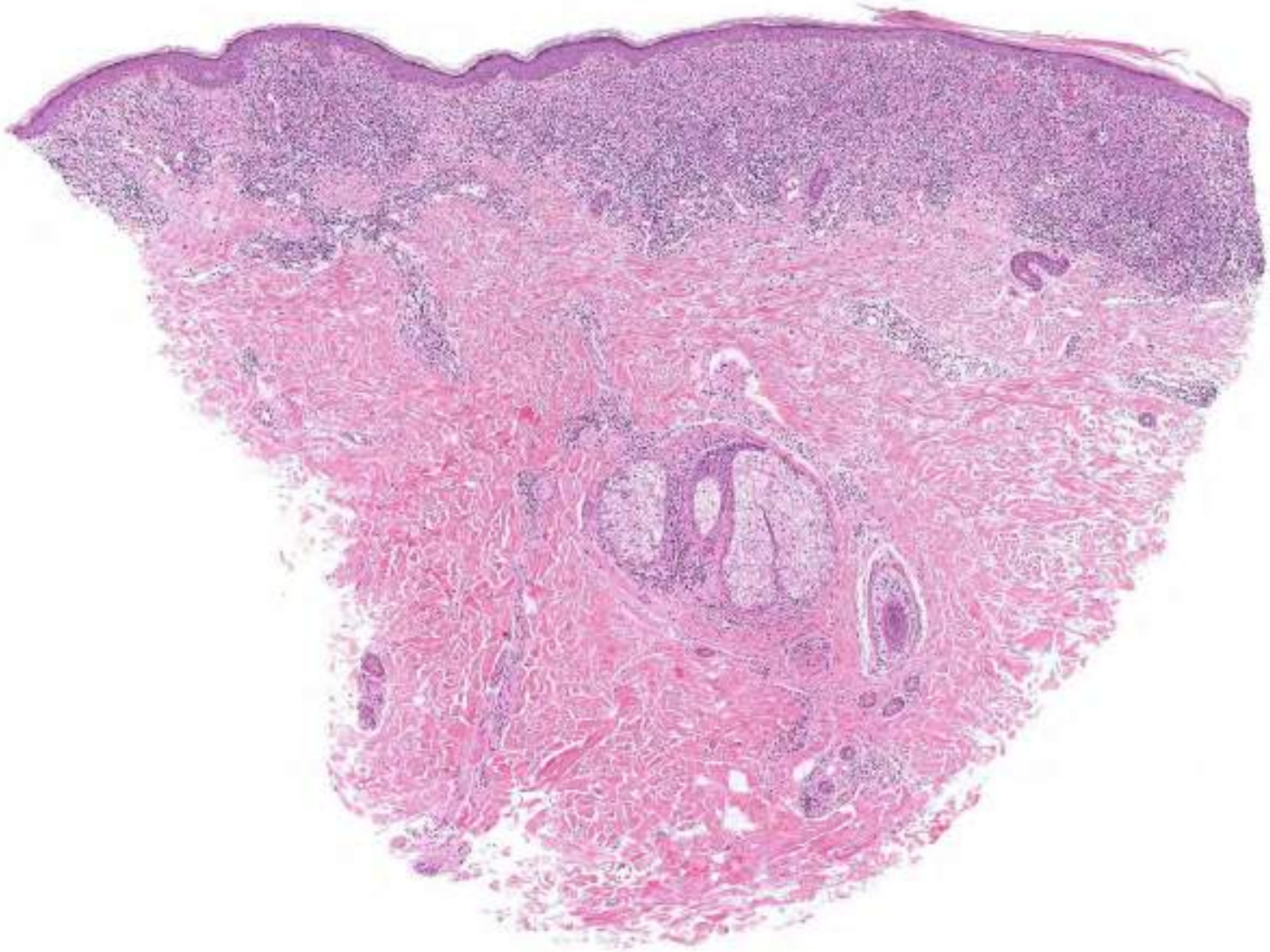
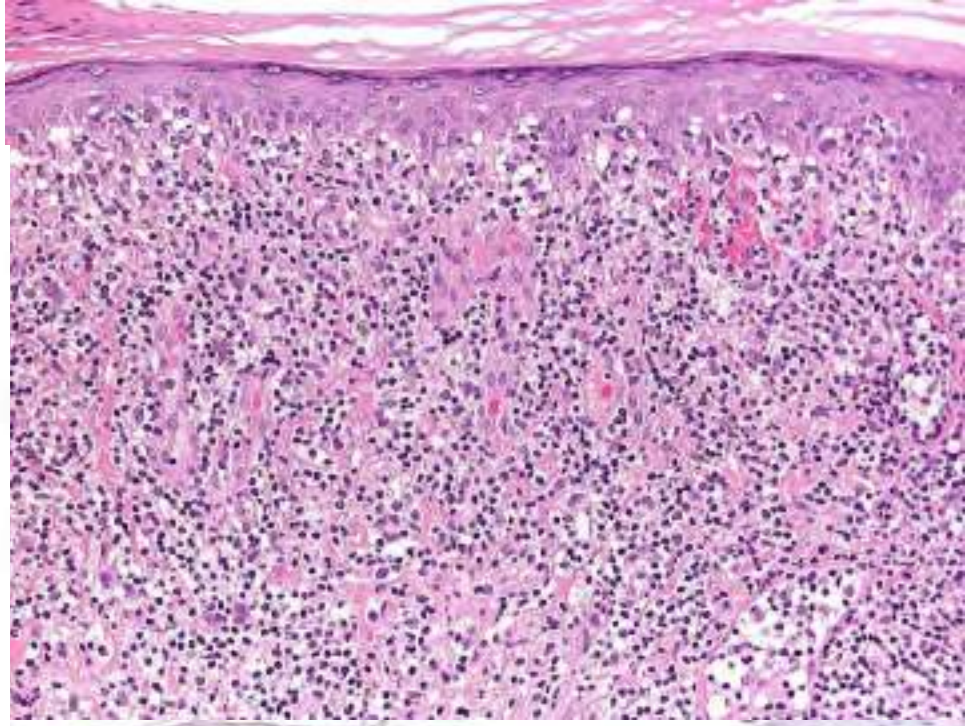
F, 23

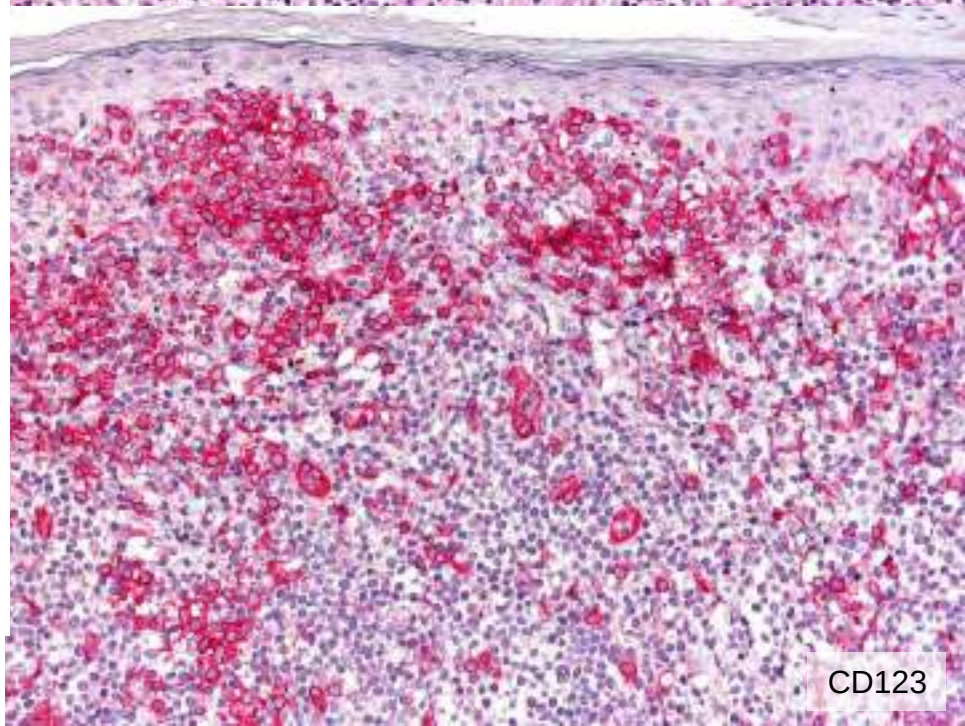




M, 47



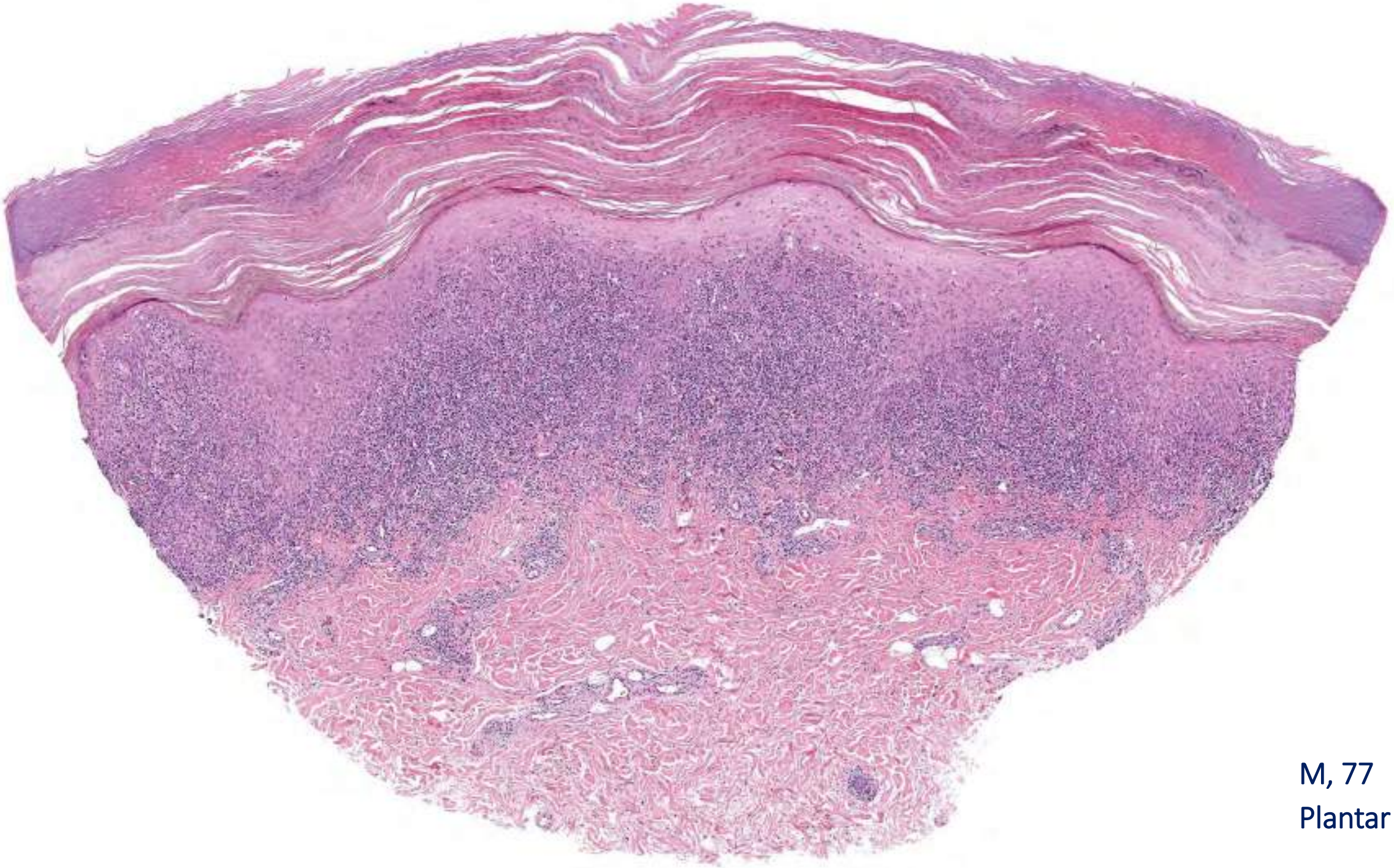




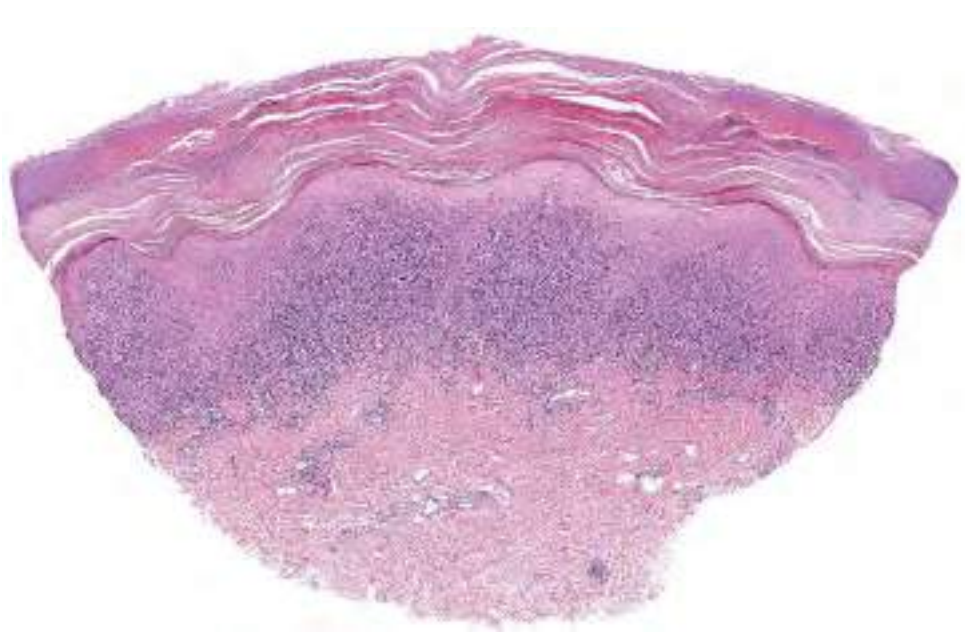
CD123

Variants of lupus erythematosus

- LE tumidus / Jessner-Kanof
- LE profundus (LE panniculitis)
- Neonatal LE
- Chilblain LE
- Multiforme-like LE - Rowell syndrome / Toxic epidermal necrolysis-like eruption of ACLE (acute syndrome of apoptotic pan-epidermolysis - ASAP)
- Bullous LE
- Drug-induced LE
- Paraneoplastic LE
- Linear LE
- Urticarial neutrophilic dermatitis in LE
- Verrucous LE
- Follicular LE
- Acrosyringeal LE
- Alopecia in LE (cicatricial and non-cicatricial)
- Mucosal involvement in LE
- Interstitial granulomatous dermatitis in LE
- Papulonodular LE with diffuse mucin deposition
- SLE / scleroderma overlap syndrome
- LE / lichen planus overlap syndrome
- Pseudolymphomatous LE (several variants)
- Reticular erythematous mucinosis
- ? Degos disease (malignant atrophic papulosis)



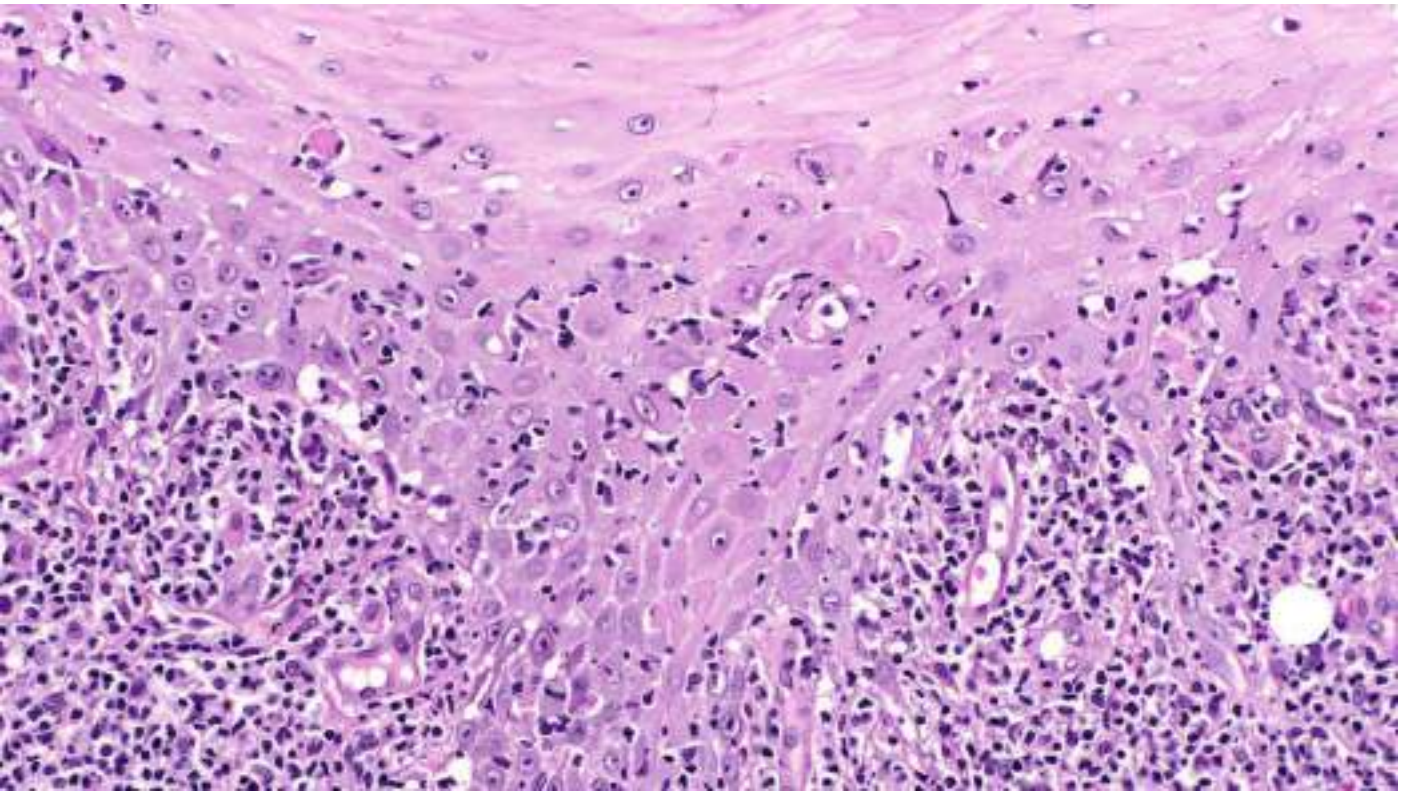
M, 77
Plantar region

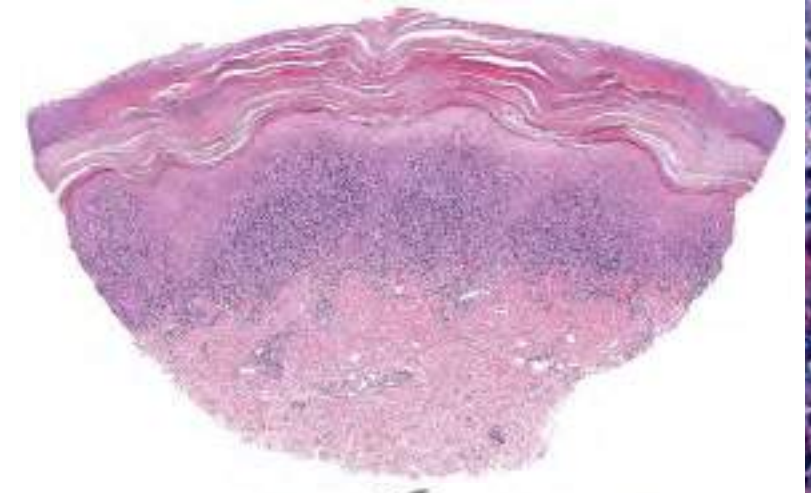


M, 77

According to the patient lesions on the soles for approximately 3 years. Mostly asymptomatic, sometimes mild pruritus.

Last sexual intercourse 12 years previously. Screening for syphilis negative.





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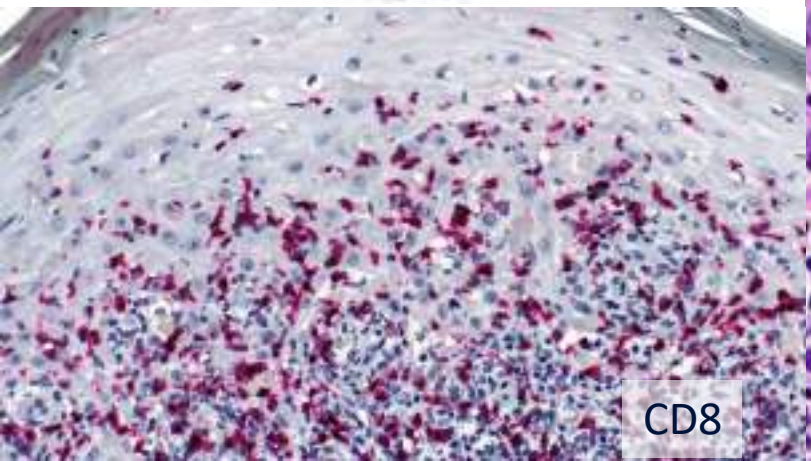

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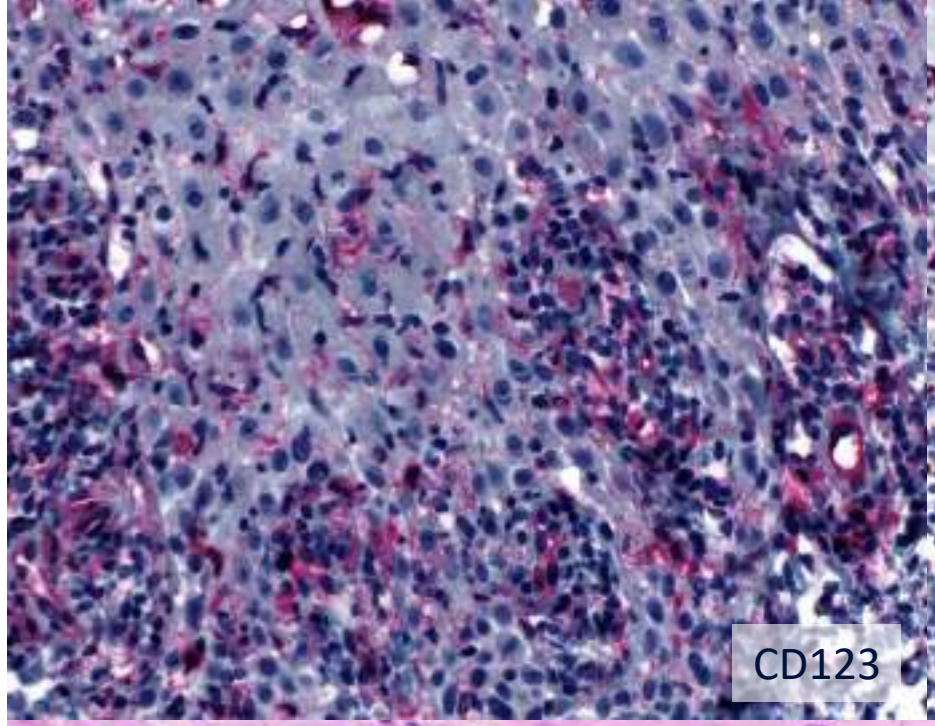
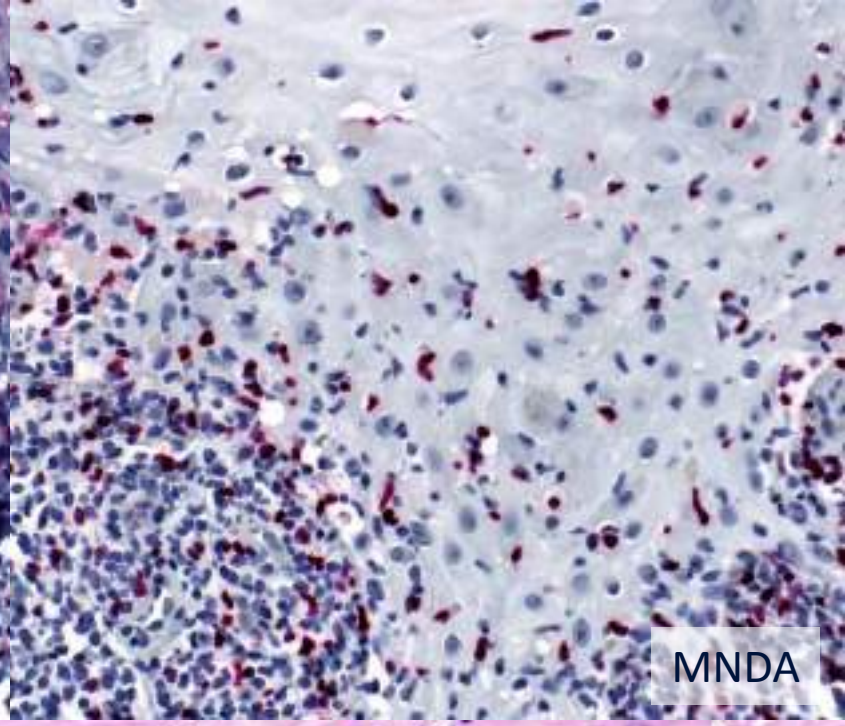
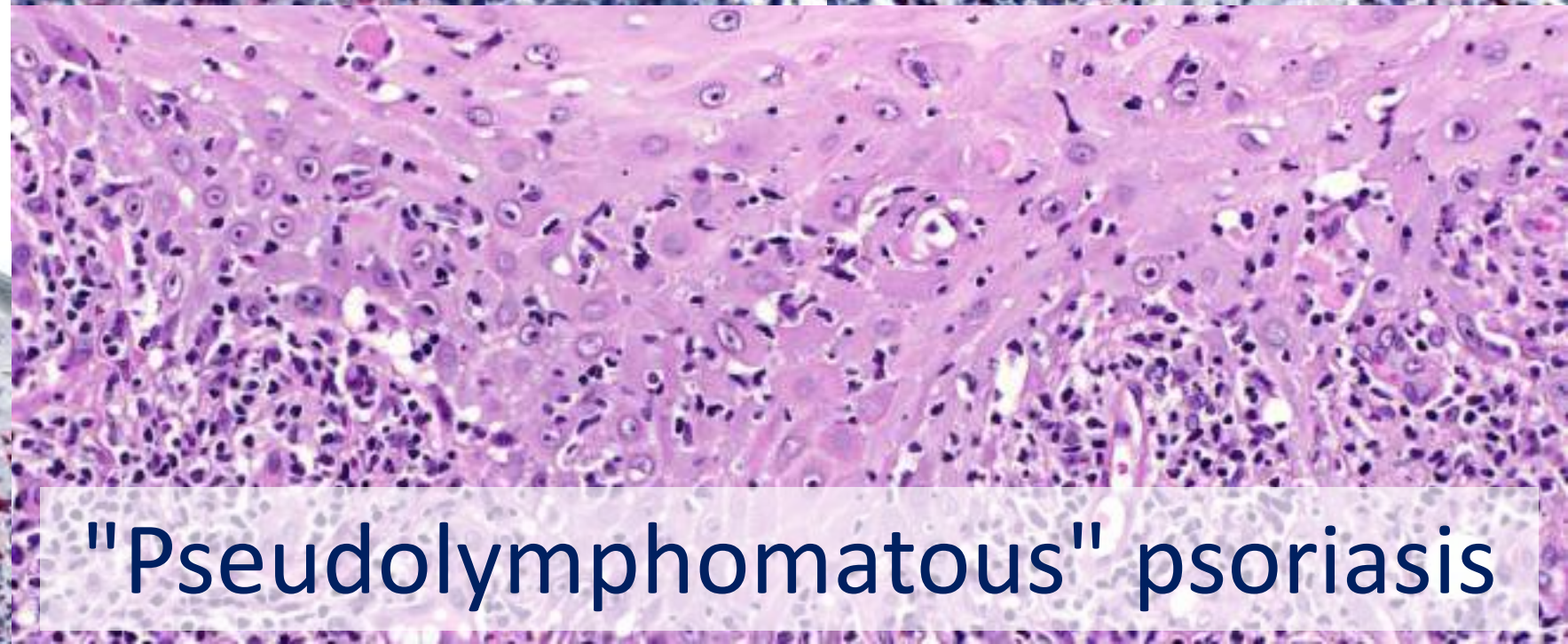


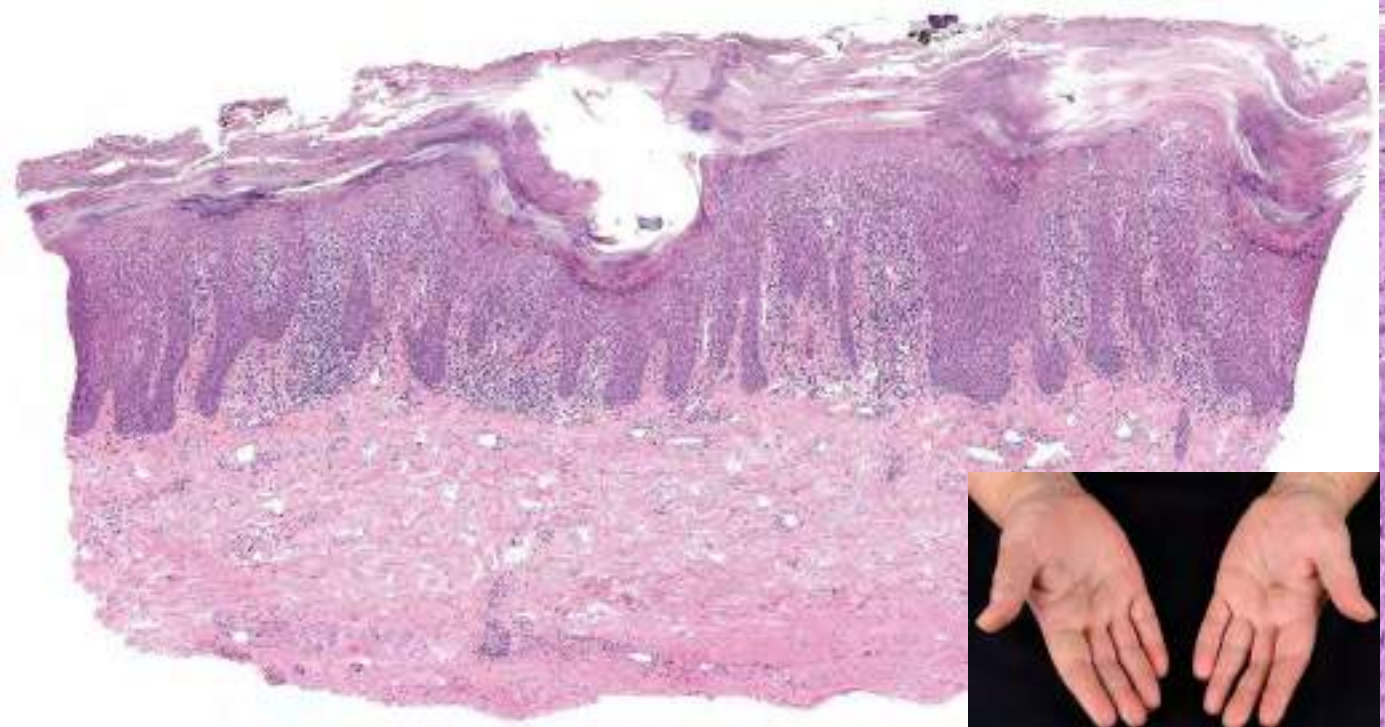
CD123

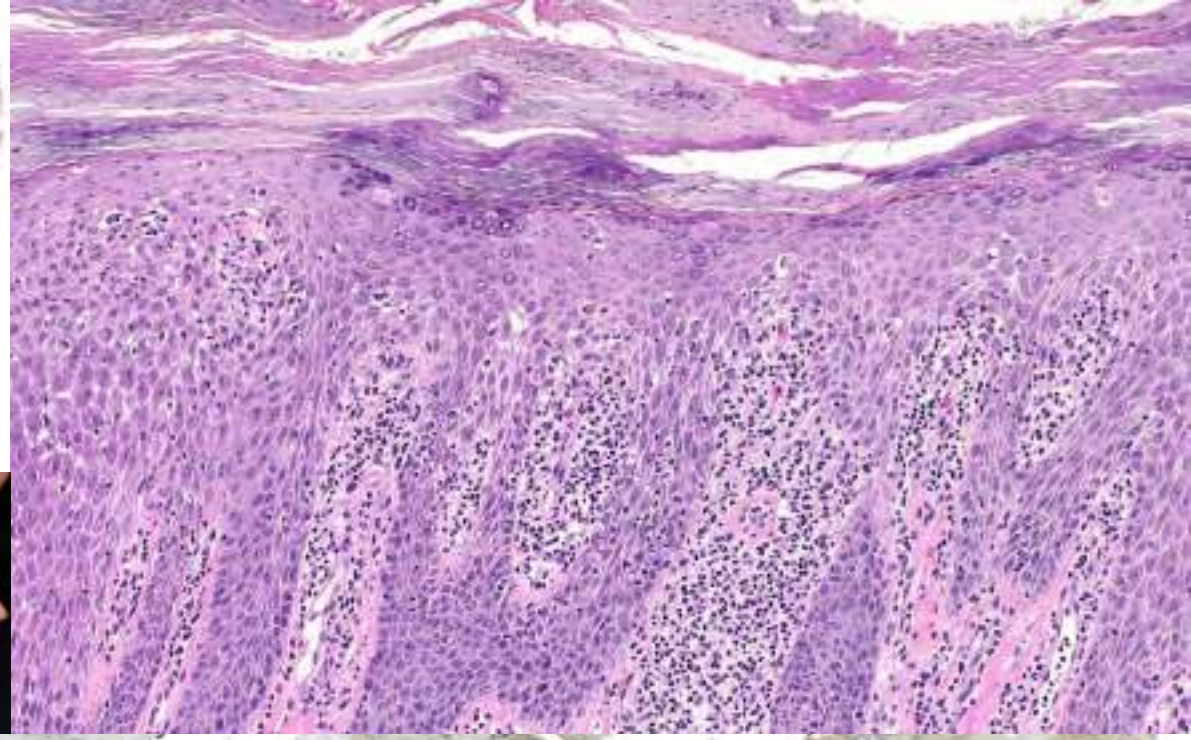


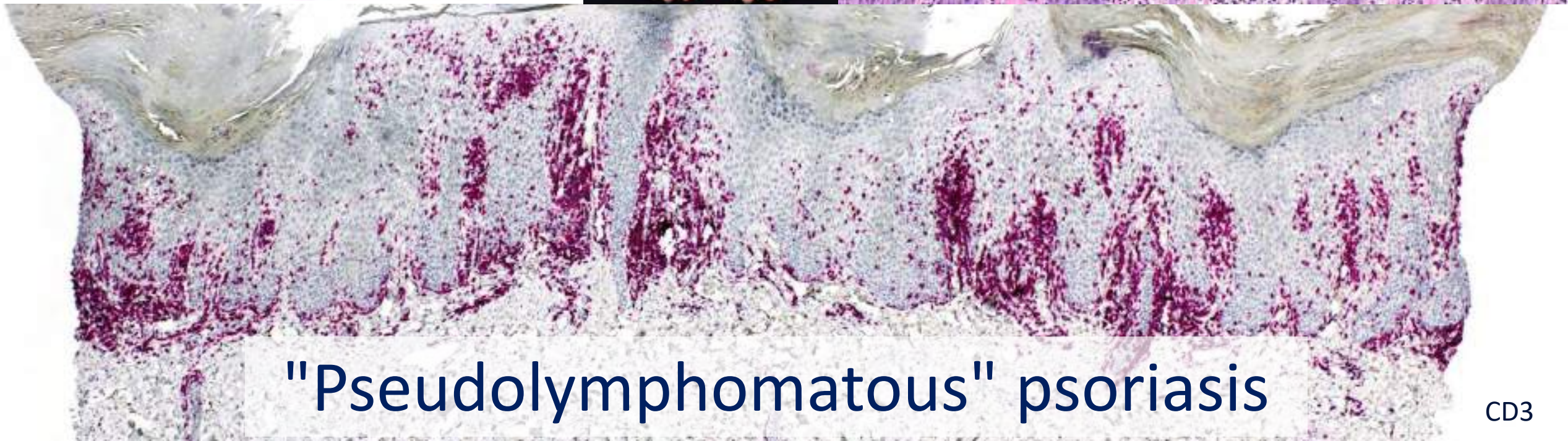
MNDA



"Pseudolymphomatous" psoriasis







"Pseudolymphomatous" psoriasis

CD3

Volume 7
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Gross and microscopic symposium

Hyperkeratotic mycosis fungoides restricted to the palms*

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San Antonio, TX

The case of a 45-year-old Latin American man, who presented to the Dermatology Clinic with a 6-month history of hyperkeratotic lesions confined to the palms and the palmar aspects of the digits of both hands, is discussed. Biopsy of these lesions revealed the classic histologic findings of mycosis fungoides. The clinical and histologic differential diagnosis of mycosis fungoides is considered. (J Am Acad Dermatol 7:792-796, 1982.)

The clinical diagnosis of mycosis fungoides may at times be difficult because of the variability of its clinical presentation and course. The histologic diagnosis can also, at times, be difficult, and several entities have been described which cannot be separated histologically from mycosis fungoides.[1-3] The biologic behavior of the lesions in any given patient is the ultimate confirmation of the correct diagnosis. We present a patient with unusual clinical and histologic findings and discuss the difficulty of prospective analysis of a patient with premycotic stage mycosis fungoides.

CASE REPORT

A 45-year-old Mexican American man presented to the Dermatology Clinic at Audie Murphy Veterans Hospital with a 6-month history of hyperkeratotic lesions confined to the palms and the palmar aspects of the digits of both hands. The patient had previously been treated for several months with various topical steroids without improvement. The patient denied any history of extensive exposure to petrochemicals, frequent contact with irritants, or any history of contact allergy. Medications at the time of presentation included NPH insulin, 40 units each morning, for adult-onset diabetes mellitus present since 1975; amitriptyline, 200 mg four times a day; and isoproterenol sulfate inhaler, 1.3 mg, four times a day, for chronic asthma and chronic obstructive pulmonary disease; and chlordiazepoxide hydrochloride (Librium) for a long-standing anxiety neurosis.

The lesions consisted of small hyperkeratotic pits and small hyperkeratotic plaques. These lesions were predominantly located on the palmar aspect of the digits. Clinically the lesions resembled a hand eczema (Fig. 1).

A biopsy was taken which revealed a psoriasiform epidermis with a dense lichenoid infiltrate of mononuclear cells (Fig. 2). Closer examination showed the infiltrate to contain predominantly lymphocytes, many with large, atypical nuclei. No spongiosis of the epidermis was observed. Large, atypical mononuclear cells could be seen within the epidermis, singly and in groups. In some areas, small, subepidermal abscesses filled with atypical mononuclear cells could be seen (Fig. 3).

Since the patient lived quite a distance from San Antonio, an interval of approximately 2 months elapsed before his next visit. During this period, the patient was treated with keratolytics and high-potency topical steroids. On return his lesions had worsened slightly.

A biopsy was again obtained. Histologic findings were identical to those of the previous sample. A specimen was also submitted for electron microscopy. This examination revealed in the dermis the presence of lymphocytes with large hyperconvoluted nuclei (Fig. 4).

Complete physical examination at this time was unremarkable except for the lesions on the hands. In particular, there was no palpable adenopathy and no palpable increase in liver or spleen size. Patch testing was performed with the standard tray of the North American Patch Test Kit, with negative results. A blind axillary node biopsy was performed, and no tumor was found

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*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

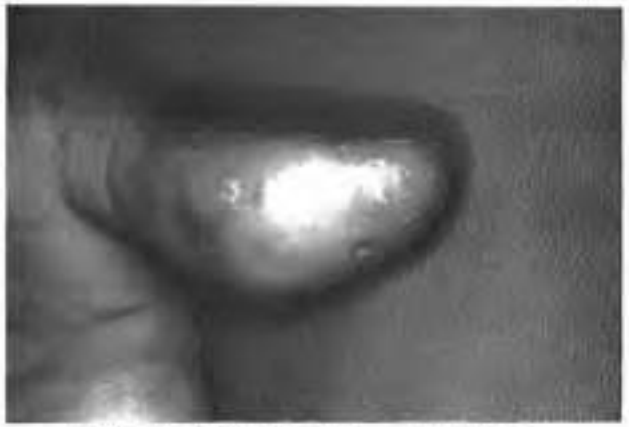

Fig. 1. Small hyperkeratotic pits and plaques confined to the hands.

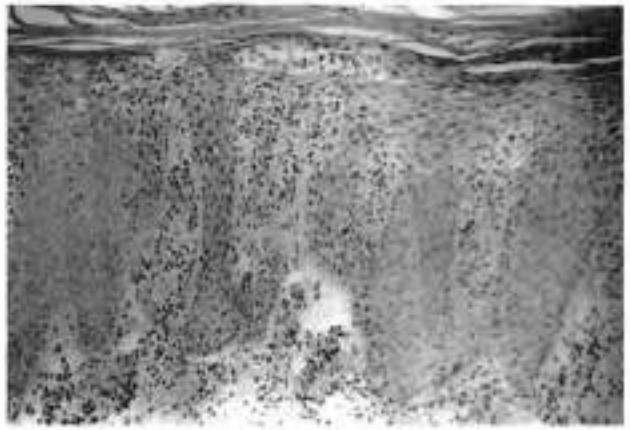

Fig. 2. Psoriasiform epidermis with dense lichenoid infiltrate of mononuclear cells. (Hematoxylin-eosin stain; original magnification, ×100.)

"Our case may be distinguished from psoriasis by the density and bandlike characteristics of the lymphohistiocytic infiltrate and the lack of polymorphonuclear cells in the dermal papillae. The cells seen in the epidermis and in the abscesses are atypical mononuclear cells rather than polymorphonuclear cells."

Clinicopathologic features and T-cell receptor gene rearrangement findings of mycosis fungoides palmaris et plantaris

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Background: Mycosis fungoides palmaris et plantaris (MFPP), characterized by hyperkeratotic patches or plaques confined to the palms and soles, is rare and easy to misdiagnose because of its clinical similarity to psoriasis, cutaneous inflammatory dermatoses, and dermatophytic infections. The literature about MFPP mostly consists of case reports with short-term follow-up.

Objective: Our purpose was to evaluate the clinicopathologic features, T-cell receptor (TCR) gene rearrangement findings, and prognosis of MFPP.

Patients and methods: This retrospective study has been reviewed in the clinicopathologic, TCR γ gene rearrangement findings and follow-up study of 12 patients with MFPP.

Results: The duration of diseases ranged from 9 months to 25 years with a mean duration of 5.3 years. Clinically, hyperkeratotic patches and plaques were observed in all cases, with 6 cases having developed on the palms and soles and 6 cases on the palms only. In TNM classifications, all cases were confined to T1N0M0 (stage IA) showing an early stage of mycosis fungoides (MF). Histopathologic findings revealed marked hyperkeratosis, parakeratosis with plasma, epidermotropism, convoluted lymphocytes, halined lymphocytes, dense infiltrate of lymphocytes in all 12 cases (100%), Pautrier's microabscess in 9 cases (75%), a wiry bundle of collagen in 11 cases (91.7%) and basilar epidermotropism in 3 cases (25%). TCR γ gene rearrangement was performed except for one case and monoclonality was detected in 10 of 11 cases. In the comparison group with cutaneous inflammatory dermatoses, all cases showed polyclonality. Treatment was done with Re-PUVA (acitretin and PUVA), ultraviolet A1, as well as systemic acitretin and mild steroids. Most patients showed a good response. In the follow-up study of 9 cases for a mean period of 47.6 months, only one patient's skin lesions were extended to the trunk and face, but the other patients had no sign of extracutaneous involvement.

Limitations: These results were obtained from patients with MFPP in Korea. A cooperative study with other ethnic groups will be helpful.

Conclusions: If a patient has recalcitrant palmoplantar dermatosis, MFPP should be suspected and histopathologic studies with TCR gene rearrangement should be done for early diagnosis of MFPP. (J Am Acad Dermatol 2006;54:466-71.)

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0190-9622/$32.00

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Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, which has 3 clinical stages of patch, plaque, and tumor. Histopathologic findings of early MF are quite similar to other cutaneous inflammatory dermatoses, unlike the plaque and tumor stage of MF, making the diagnosis difficult. T-cell receptor (TCR) γ gene rearrangement analysis on lesional skin using polymerase chain reaction (PCR) may be helpful as an adjunct to the histopathologic features of early MF. TCR gene rearrangement analysis has been performed using Southern blot technique or PCR

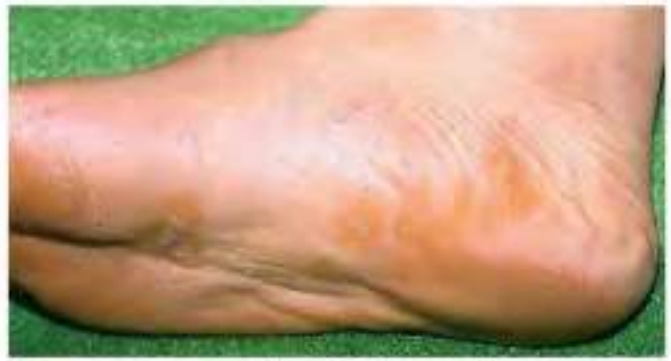


Fig 1. Case 1. Relatively well-demarcated, erythematous to brownish, hyperkeratotic plaques on the foot.

and face. However, to date, the remaining cases showed no further development of the skin lesions and no extracutaneous involvement (Table I).

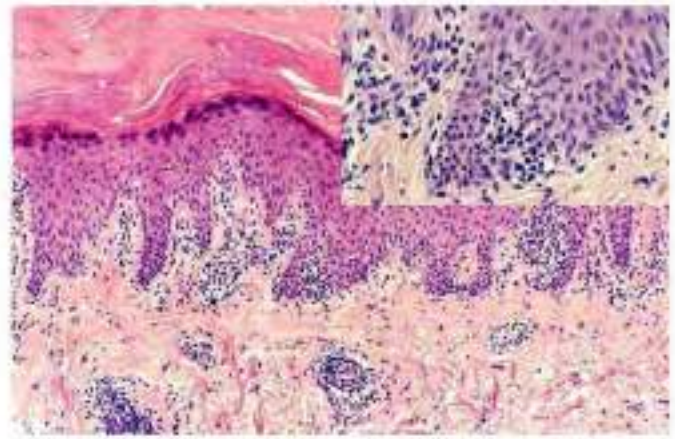
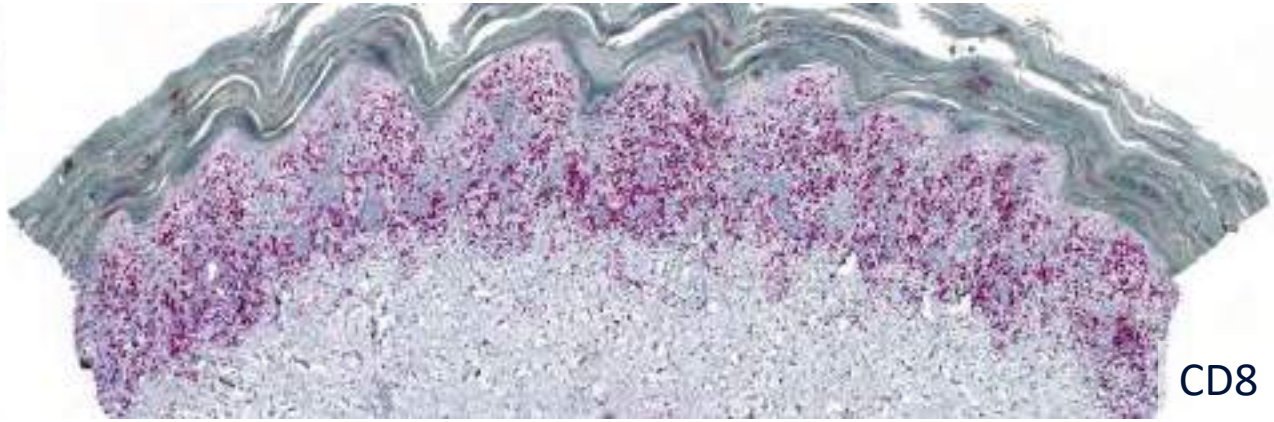


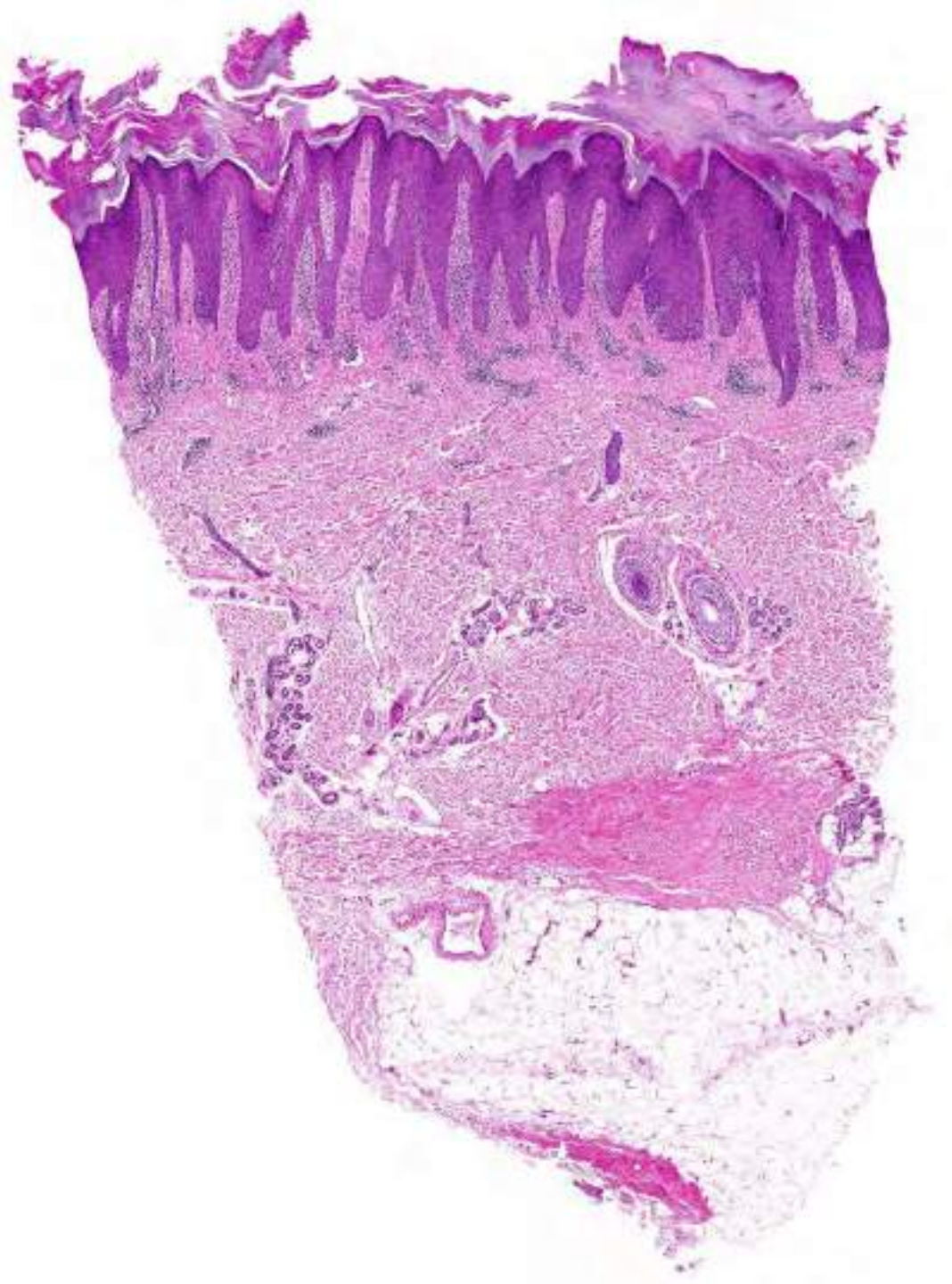
Fig 2. Case 2. Skin biopsy specimen reveals epidermotropism and coarse papillary dermal collagen. Epidermotropism composed of atypical hyperchromatic lymphocytes are seen *(inset)*. (Hematoxylin-eosin stain; original magnification: ×100; *inset*, ×400.)

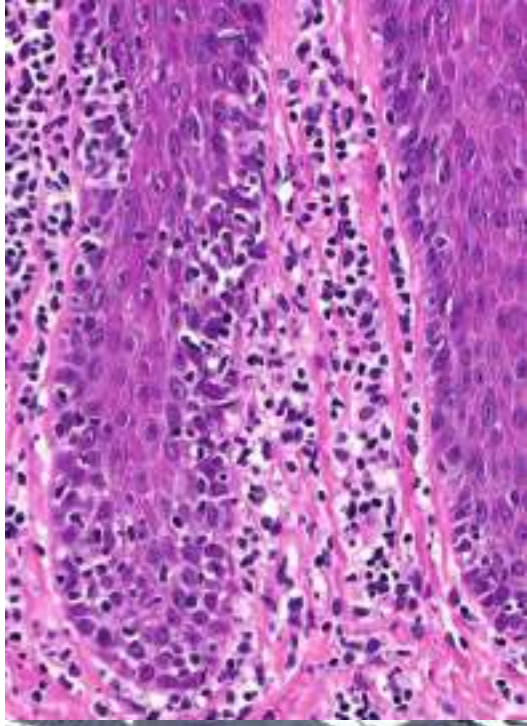
CD3



CD8

Mycosis fungoides may involve the palms and soles, in exceptional cases without lesions at other sites of the body; these cases usually clinically atypical and histopathologically showing infiltrates that involve also the reticular dermis. At least some of the published cases probably do not represent genuine MF. Palmoplantar psoriasis may present with band-like lymphocytic rather than neutrophil-rich infiltrates; a diagnosis of MF in a patient with lesions confined to the palms and/or soles should be made only when features are compelling; positivity of some of the mononuclear cells for MNDA may represent a clue.






CD5

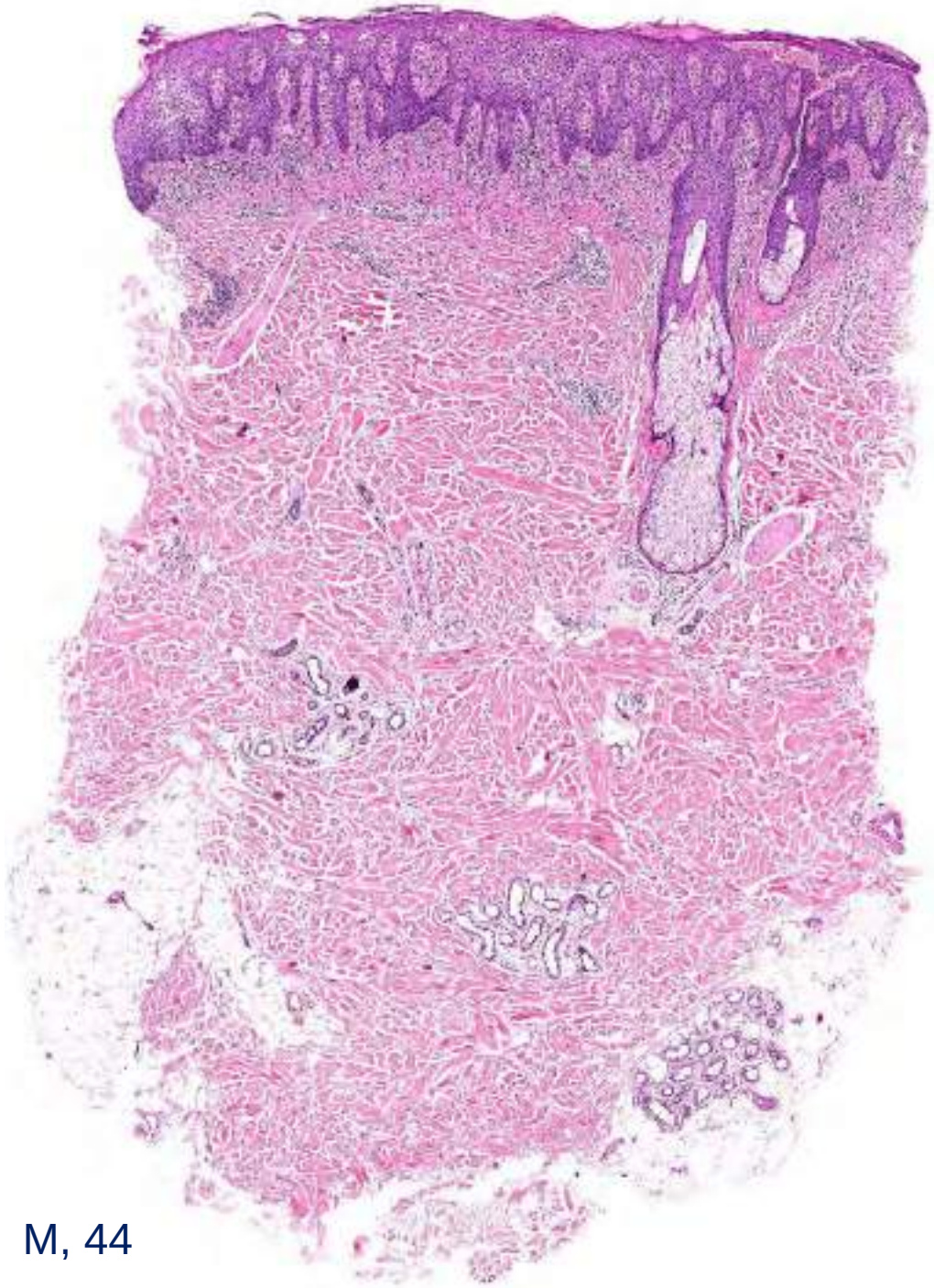
Psoriasis mimicking mycosis fungoides

- A variant of mycosis fungoides restricted to the palms and soles has been described in the literature as "mycosis fungoides palmaris et plantaris"; in my opinion ***this variant does not exist***, and these cases are examples of psoriasis with a band-like infiltrate of lymphocytes and many epidermotropic cells
- Variable numbers of intraepidermal lymphocytes may be observed also in psoriasis at sites other than palms and soles (usually CD8+); these cells are admixed with MNDA+ histiocytoid cells (most likely neutrophilic precursors)

35th Pezcoller Seminar – Surgical pathology of the skin: hot topics and slide seminars
Trento, May 9-10, 2024

Cutaneous lymphomas & pseudolymphomas 2

Lorenzo Cerroni



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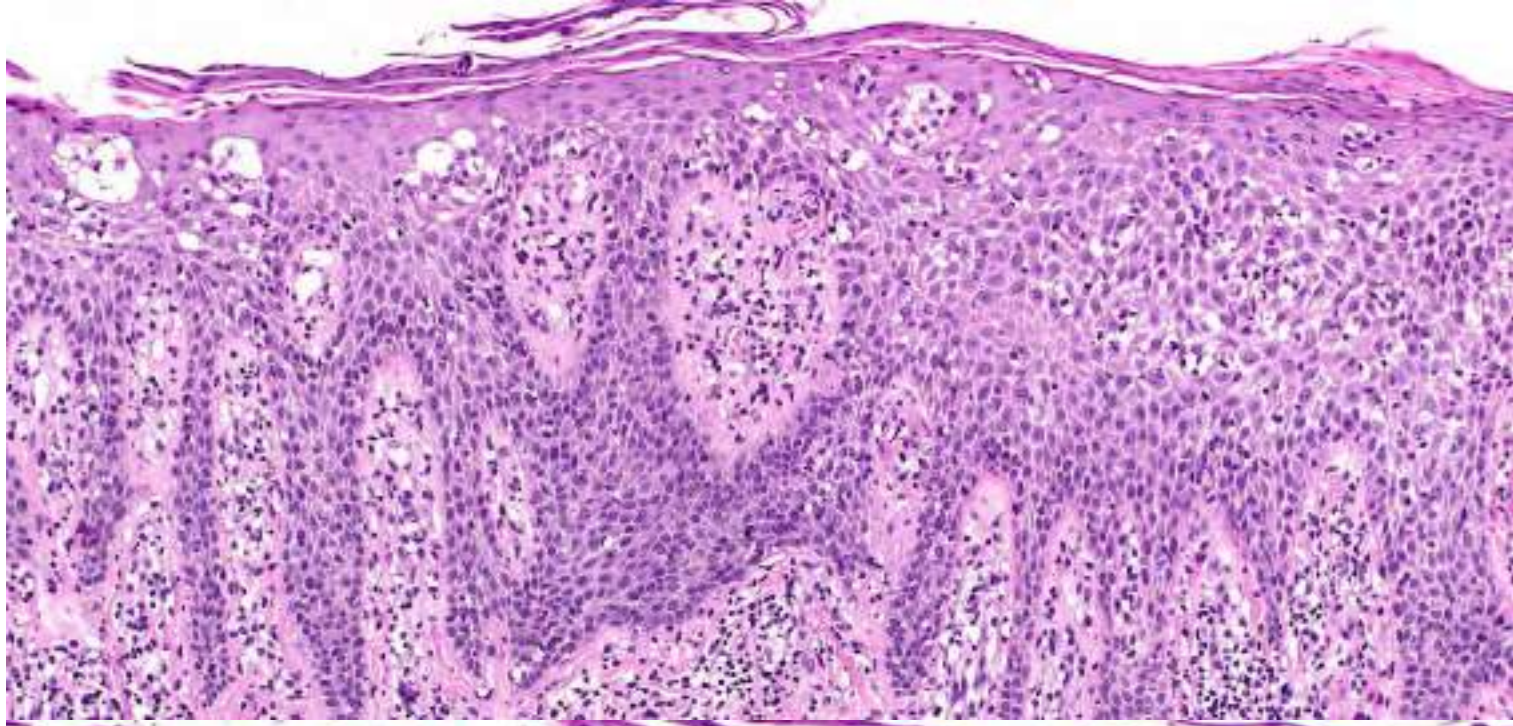
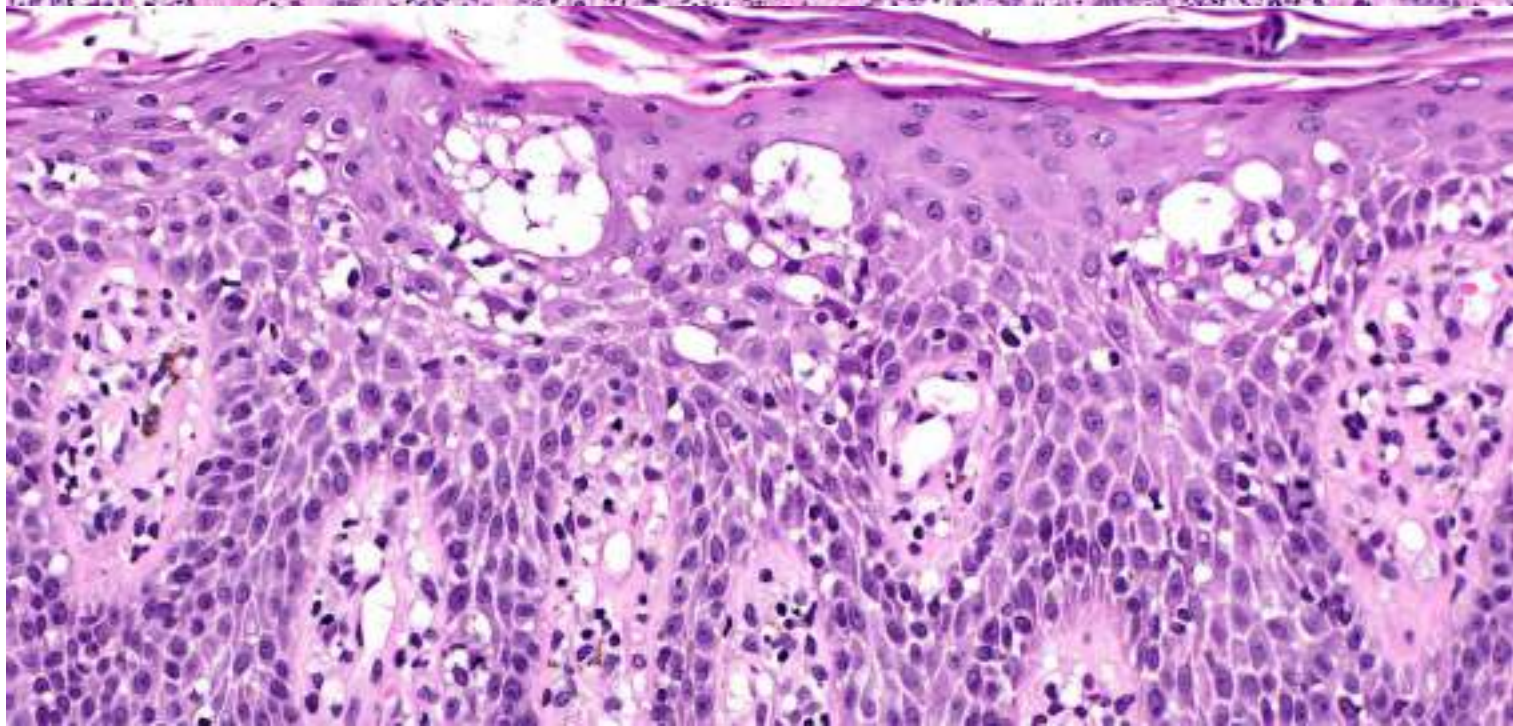
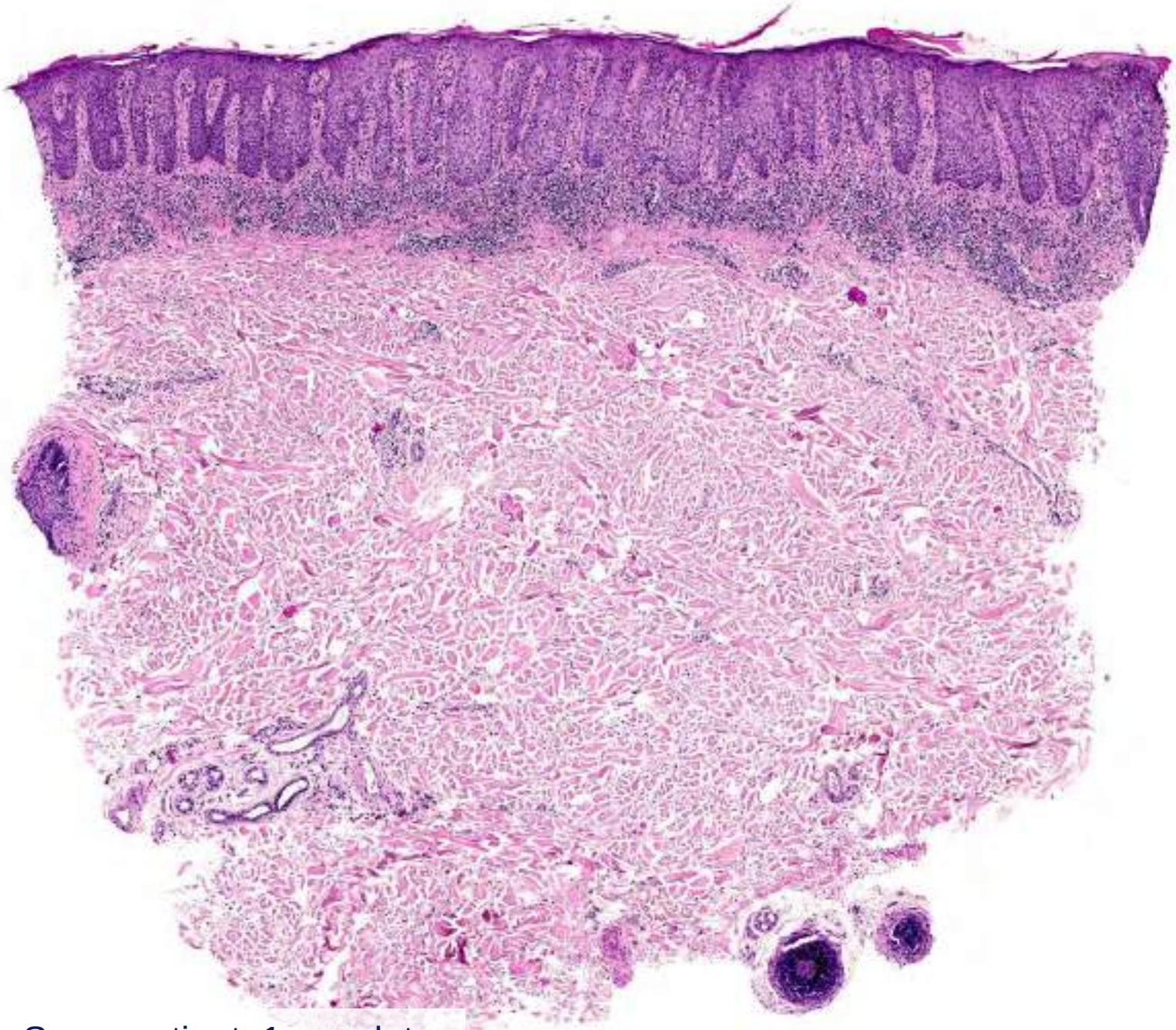
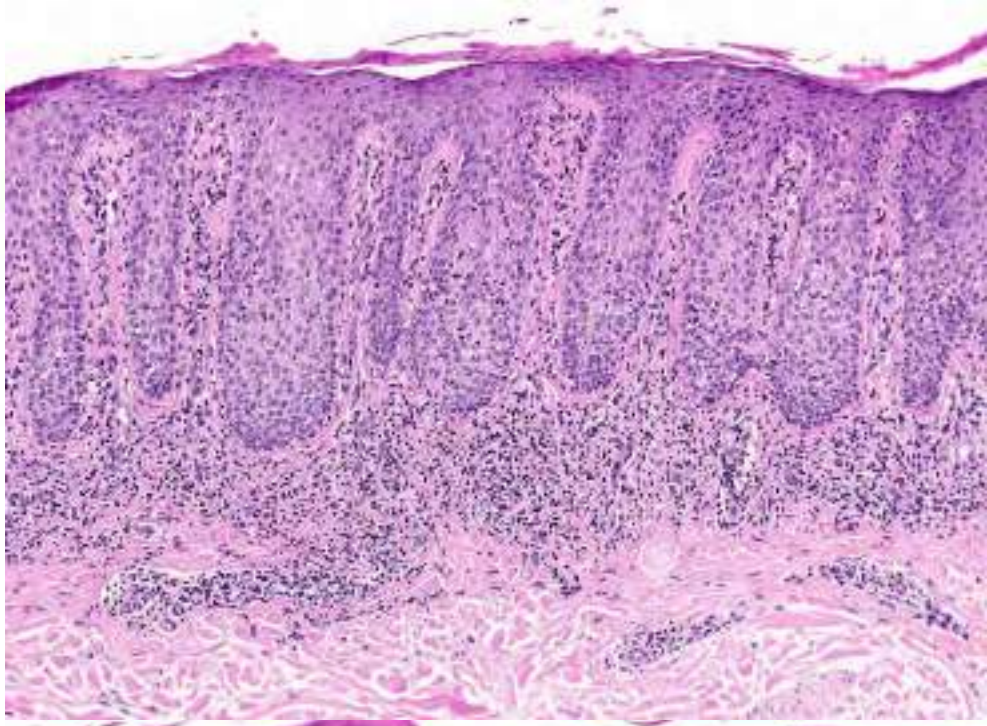
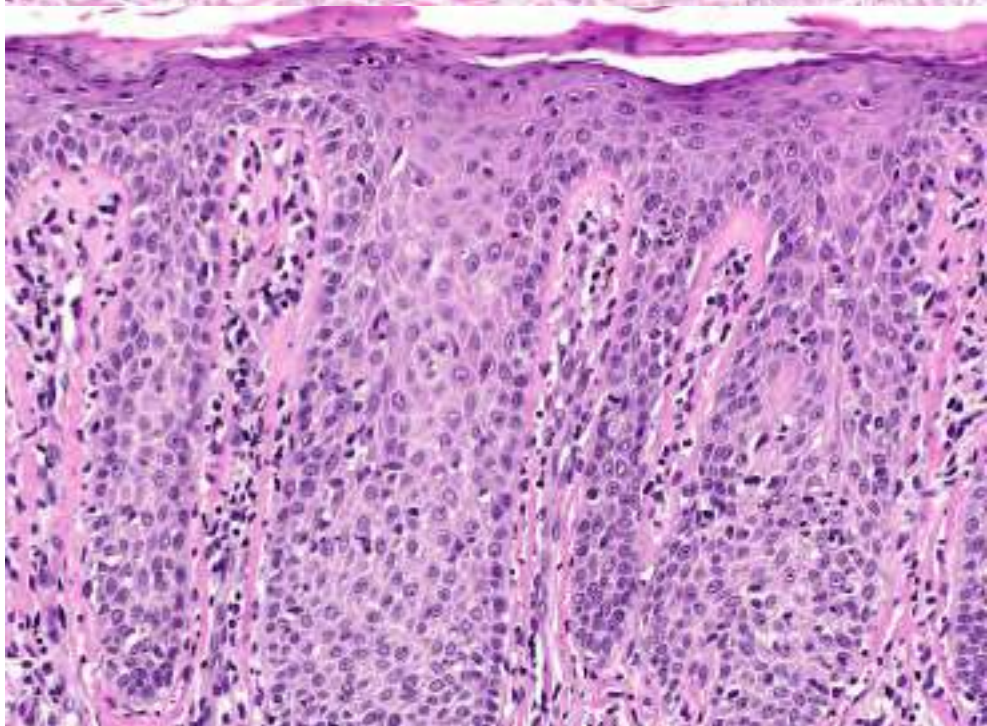


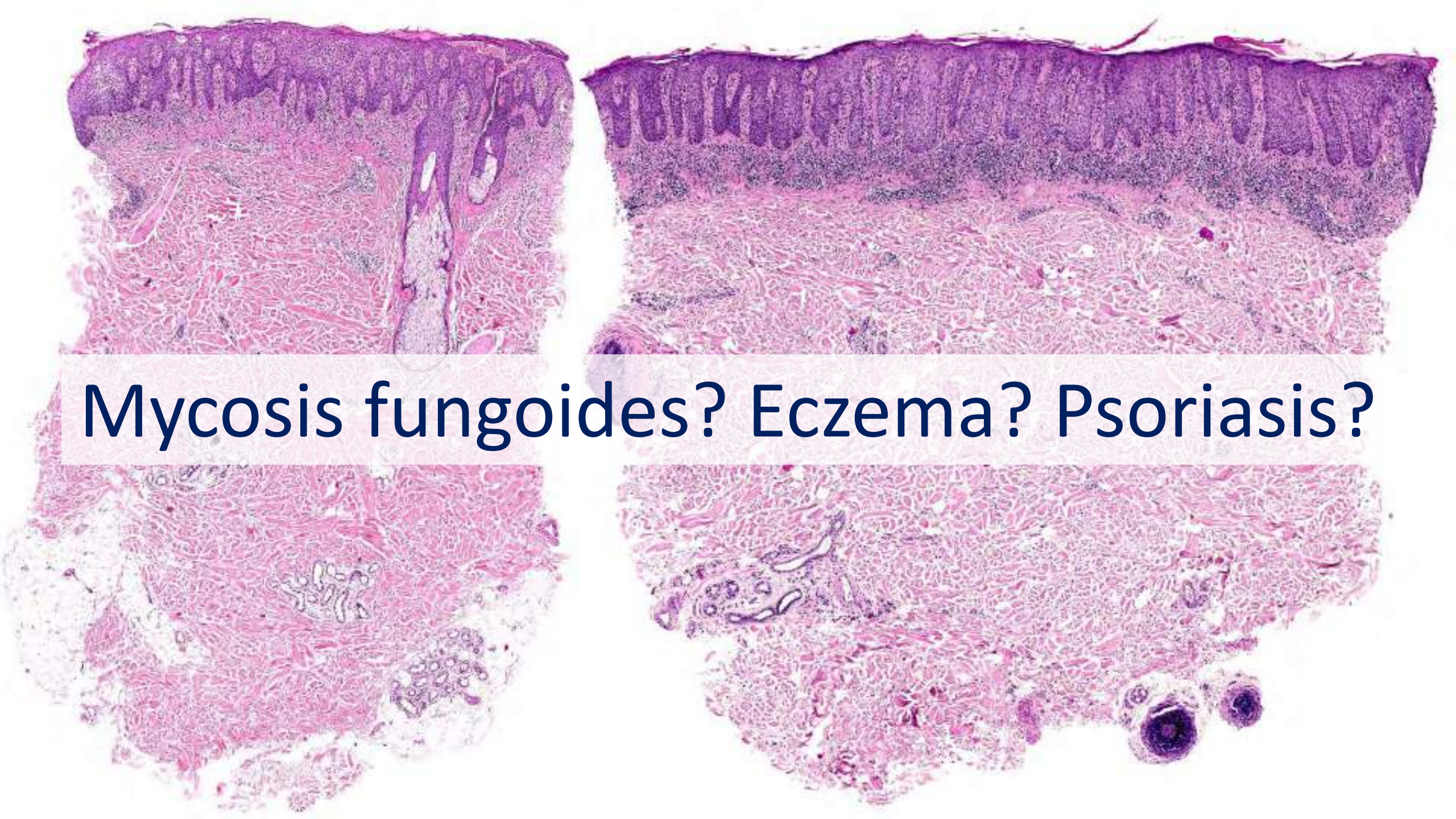




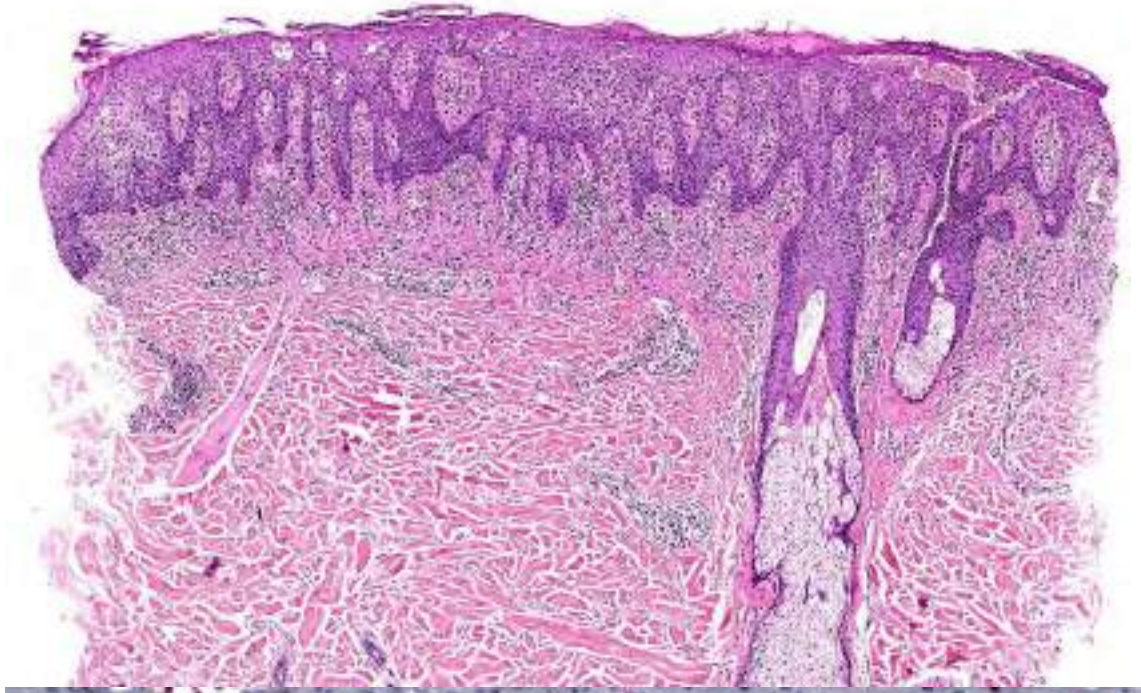


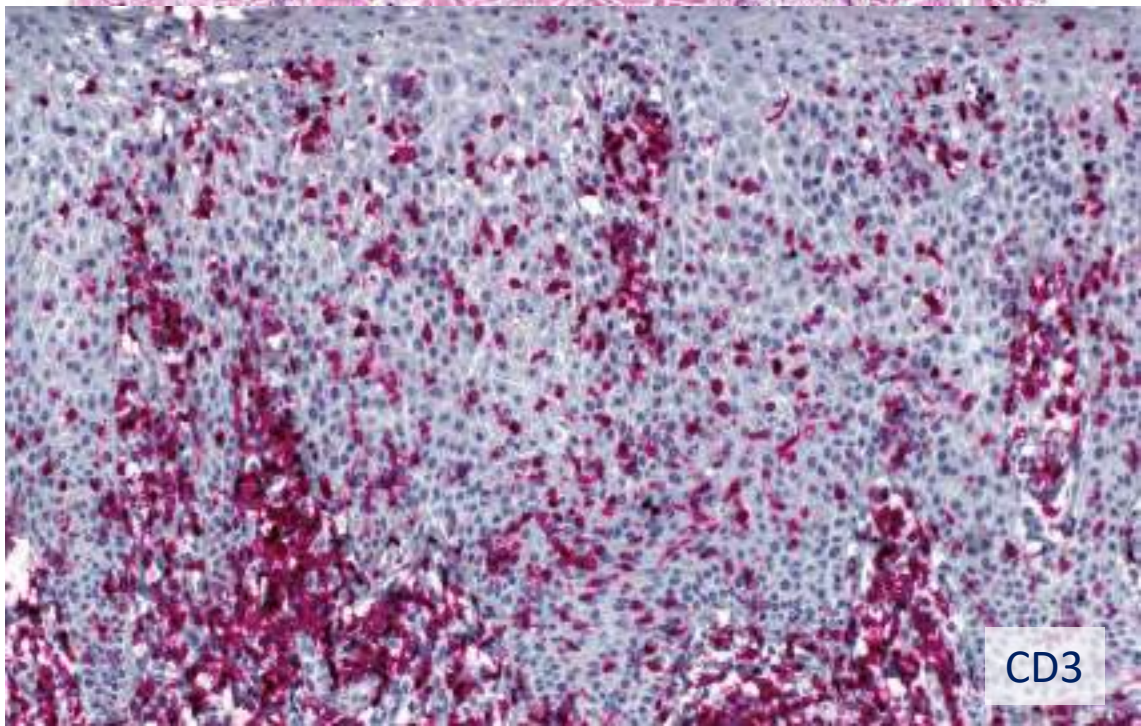


Same patient, 1 year later



Mycosis fungoides? Eczema? Psoriasis?

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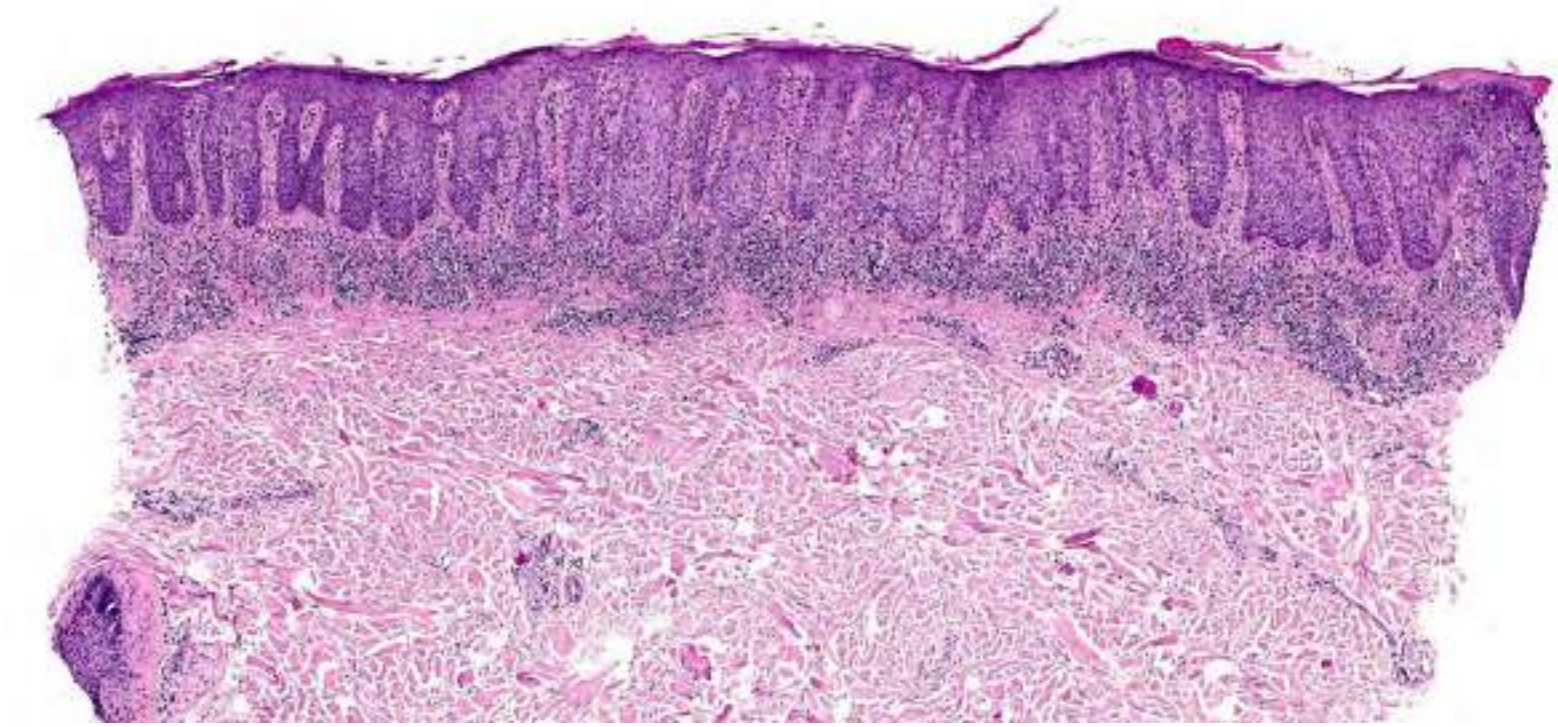

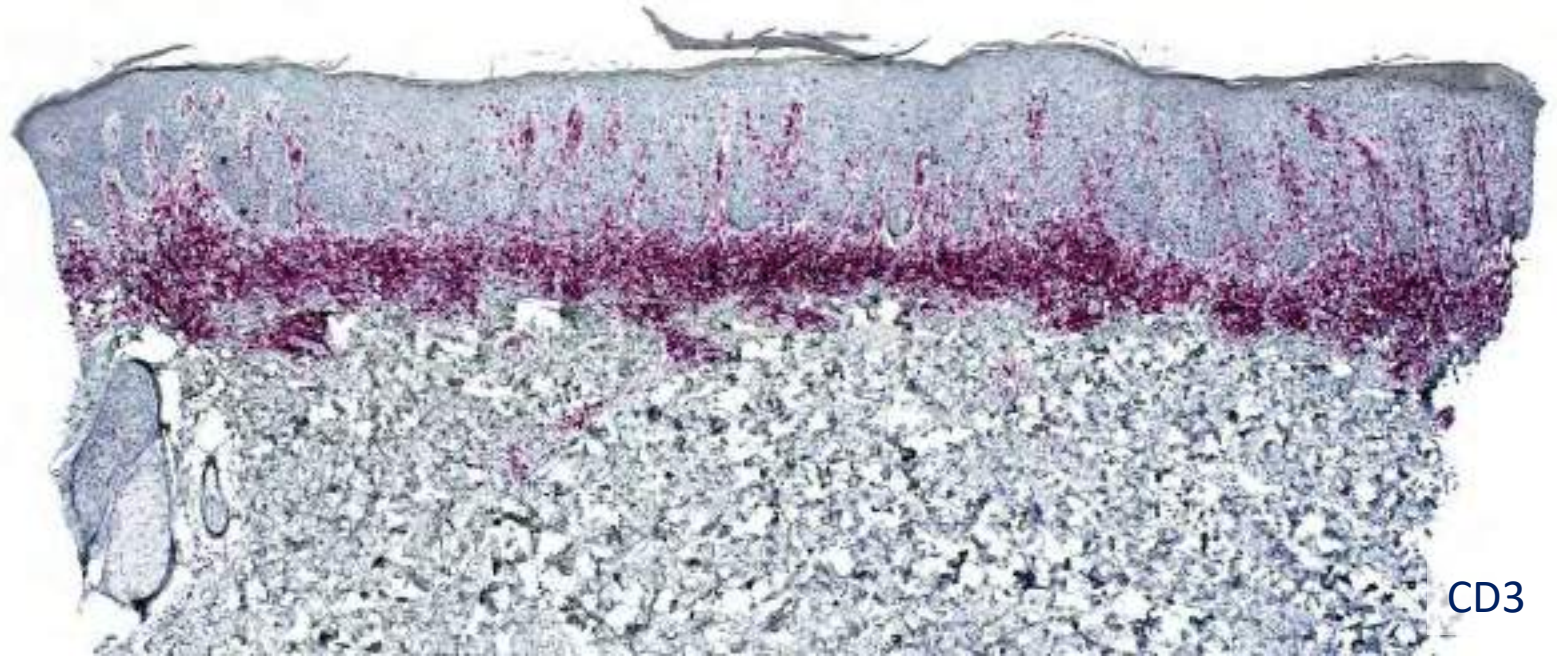

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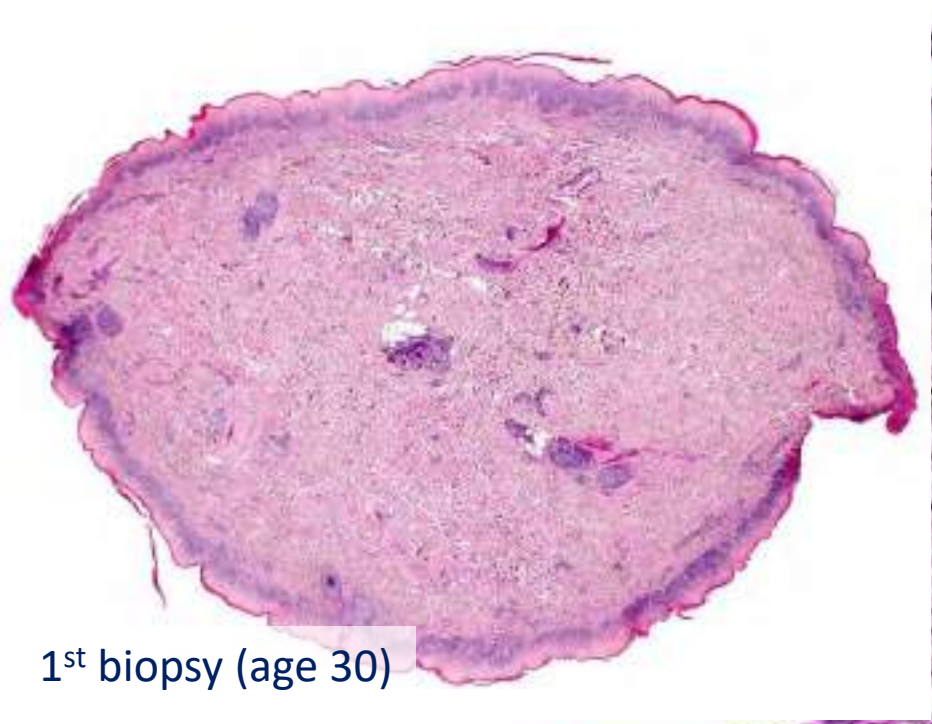

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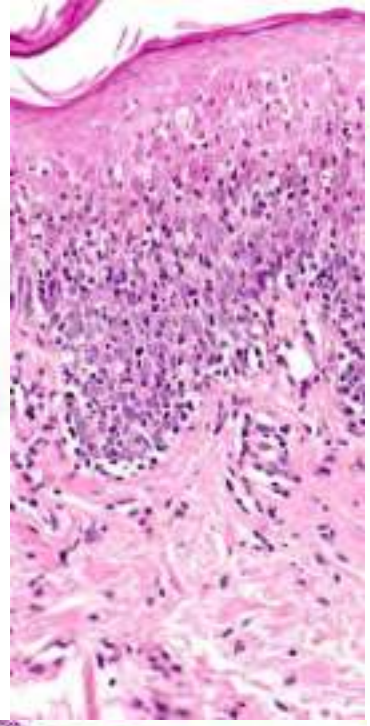
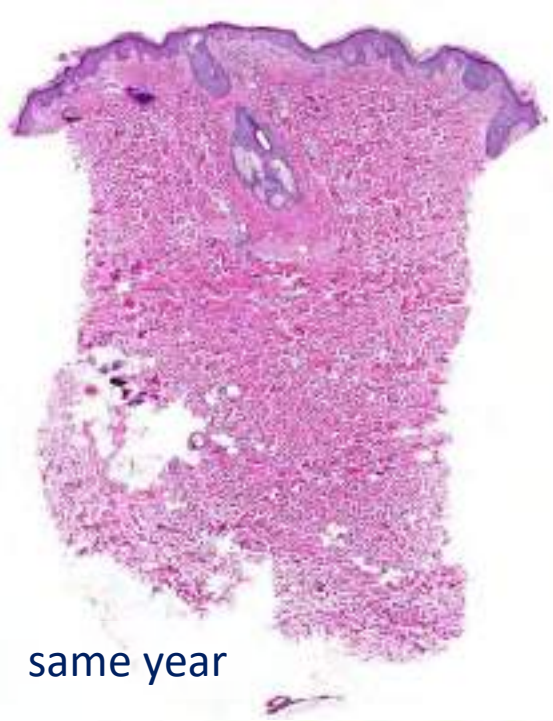
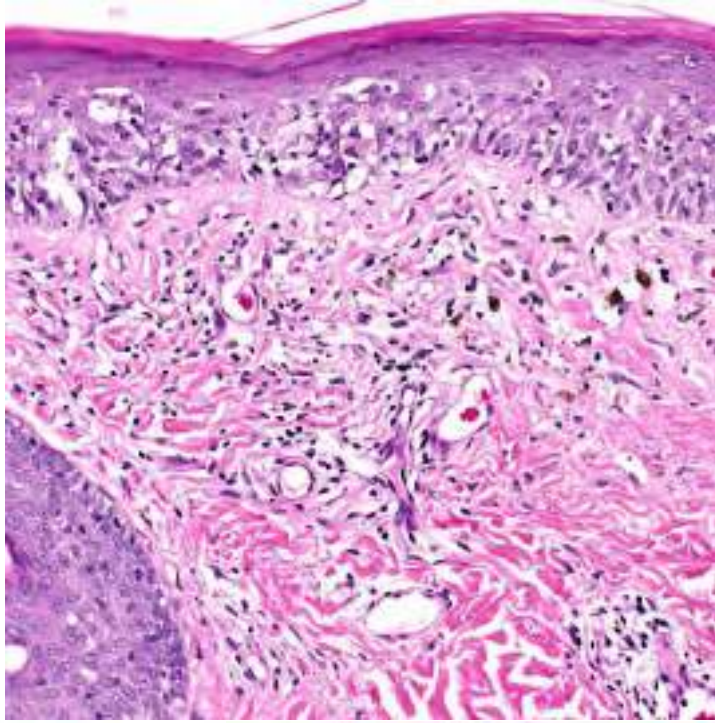
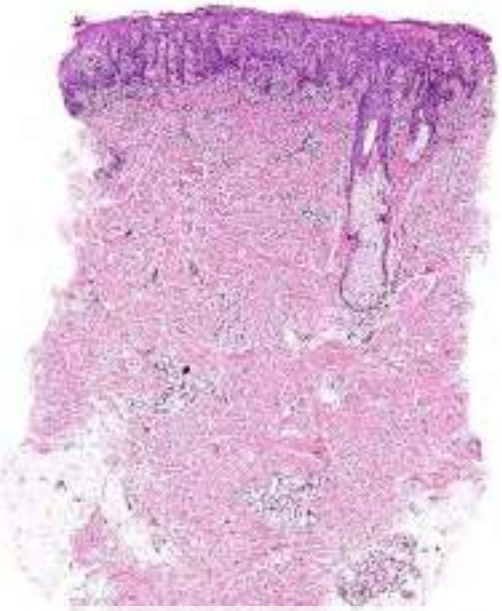


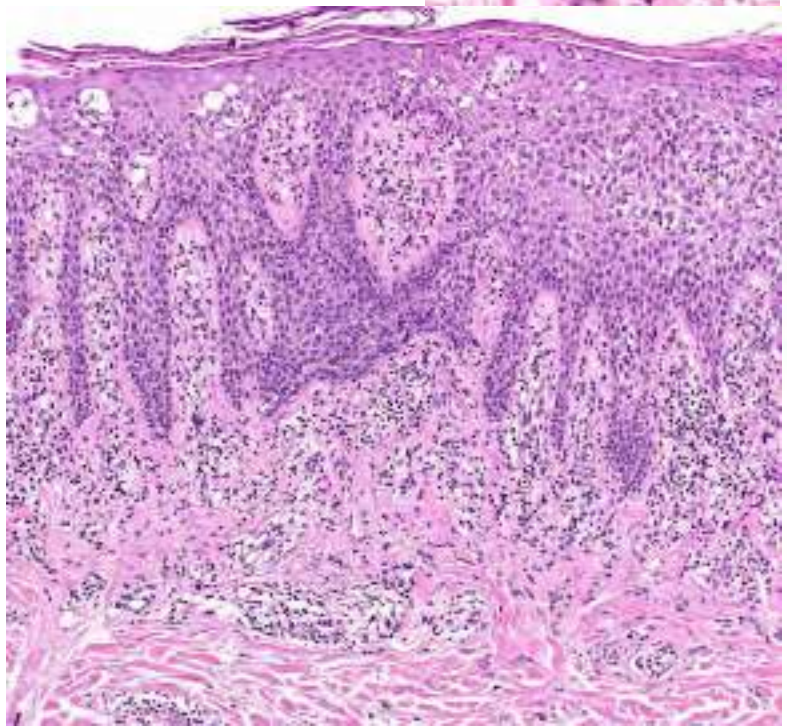


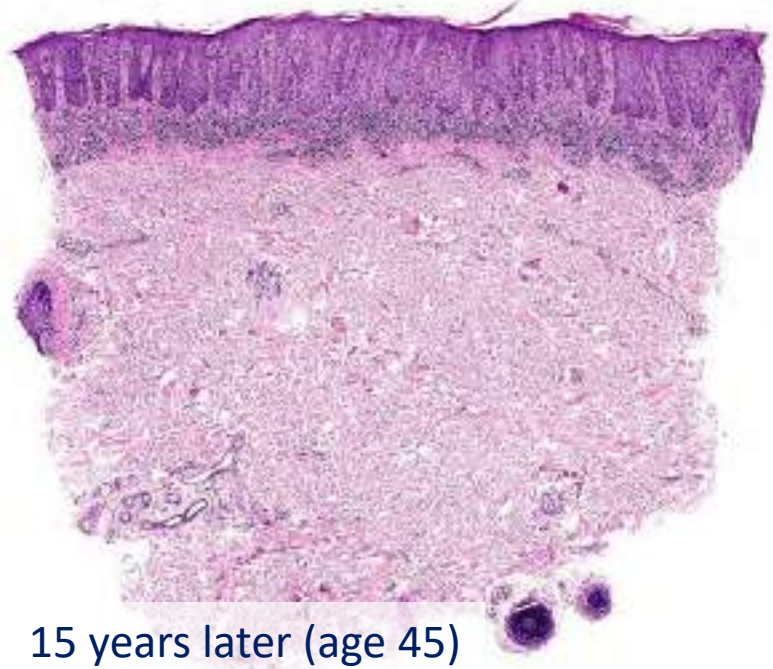
same year





14 years later (age 44)





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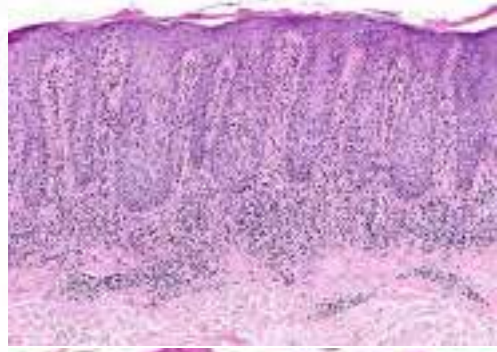
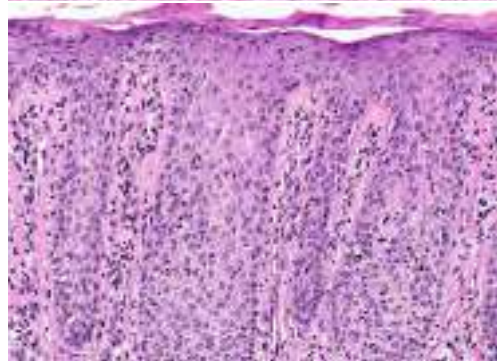
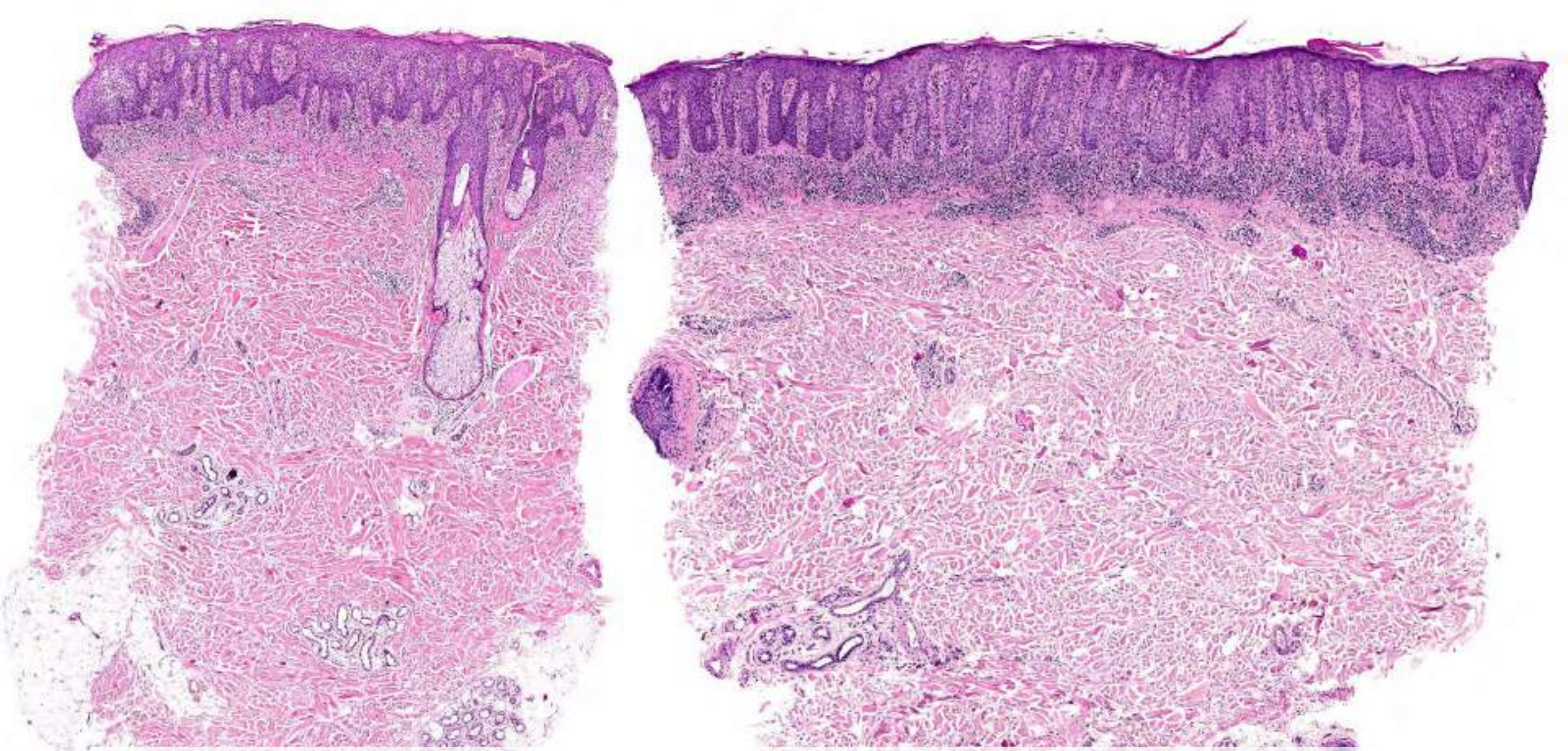






Psoriasiform/spongiotic mycosis fungoides

Histopathologic Features of Early (Patch) Lesions of Mycosis Fungoides

A Morphologic Study on 745 Biopsy Specimens From 427 Patients

Cesare Massone, MD,† Kazuo Kodama, MD,*‡ Helmut Kerl, MD,* and Lorenzo Cerroni, MD**

Abstract: The histologic diagnosis of early mycosis fungoides (MF) is one of the most vexing problems in dermatopathology. We reviewed the histopathologic features of 745 biopsy specimens from 427 patients (male:female = 277:150; median age, 52 years; range, 3–95 years) with early (patch) lesions of MF collected from the lymphoma database of the Department of Dermatology of the Medical University of Graz (Austria). In all patients, the diagnosis was established by clinicopathologic correlation. The most common histopathologic pattern consisted of a band-like or patchy lichenoid infiltrate admixed with coarse bundles of collagen in the superficial dermis. Epidermotropism of lymphocytes was observed in most cases in one or more forms (single lymphocyte epidermotropism, 22%; basilar lymphocytes, 23%; Pautrier's microabscesses, 19%; "haloed" lymphocytes, 40%; disproportionate exocytosis, 17%; pagetoid epidermotropism, 3%). In 4% of cases, epidermotropism was completely missing. Atypical lymphocytes were present only in 9% of cases. Features of interface dermatitis were observed in 59% of cases. Other unusual findings were the presence of necrotic keratinocytes (23%), melanophages (8%), and extravasated erythrocytes (4%). In 28 patients, two or more biopsies taken on the same day at different body sites showed different histopathologic aspects, underlying the protean features of MF even in a single patient at a given time. Our study expands previous observations on histopathologic features of early lesions of MF. Although sometimes the histopathologic features are not diagnostic, they should be considered consistent with MF and do not rule out the diagnosis.

Key Words: mycosis fungoides, cutaneous T-cell lymphoma, early diagnosis, histopathologic features

(*Am J Surg Pathol* 2005;29:550–560)

Kerl and Kreshach[28] and Sanchez and Ackermann[43] in 1979, the histopathologic features of these lesions were considered to be nonspecific,[8–10,17,24,30,34,39,41,42,57] and pathologists made the diagnosis of MF only in cases characterized by the presence of markedly hyperchromatic, cerebriform lymphocytes in the epidermis forming the so-called Pautrier's microabscesses.[13,43] In the last years, several authors attempted to refine the histopathologic criteria for diagnosis of early lesions of MF,[25,29,37,40,48] but the diagnosis and differential diagnosis of these lesions are still considered one of the most vexing problems in dermatopathology.

We reviewed the histopathologic features of 745 biopsy specimens from 427 patients with early (patch) lesions of MF to delineate the aspects that may be helpful for histologic diagnosis of early lesions of the disease.

PATIENTS AND METHODS

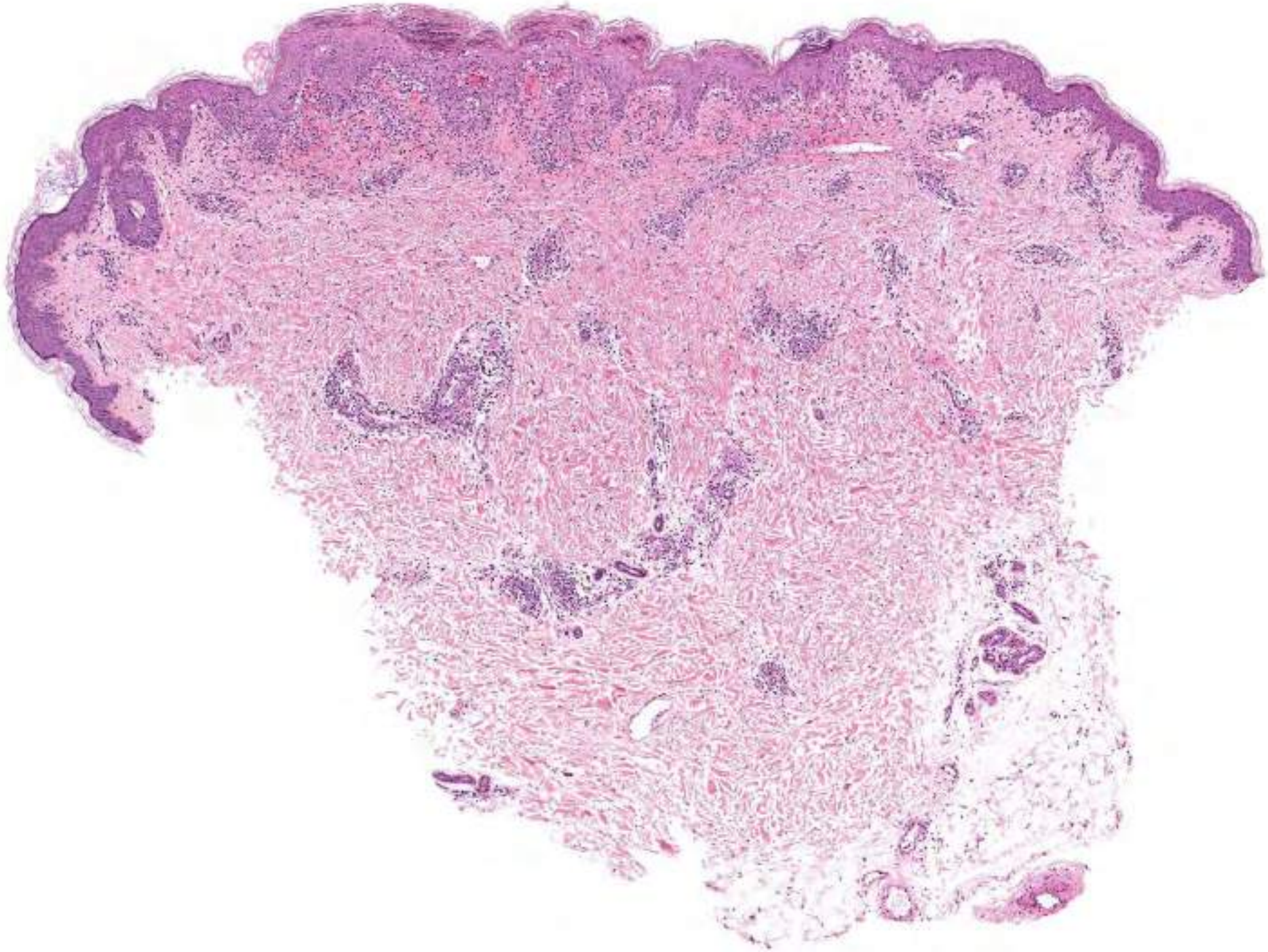
Data from 463 patients with early lesions of MF were retrieved from the lymphoma database of the Department of Dermatology, Medical University of Graz (Austria). Thirty-six cases were excluded because biopsy specimens were technically inadequate or because of lack of exact clinical informations. A total of 745 biopsy specimens from 427 patients (male:female ratio = 1.8:1; mean age, 57.2 years; median age, 52 years; age range, 3–95 years) with early (patch) lesions of MF were available for the study. The diagnosis of MF was confirmed in all cases by correlation with the clinical features (either observing personally the patient in the outpatient service for cutaneous lymphomas of the Department of Dermatology, Medical University of Graz, Graz, Austria, or reviewing the patient's chart and clinical pictures). Biopsies were taken at onset of

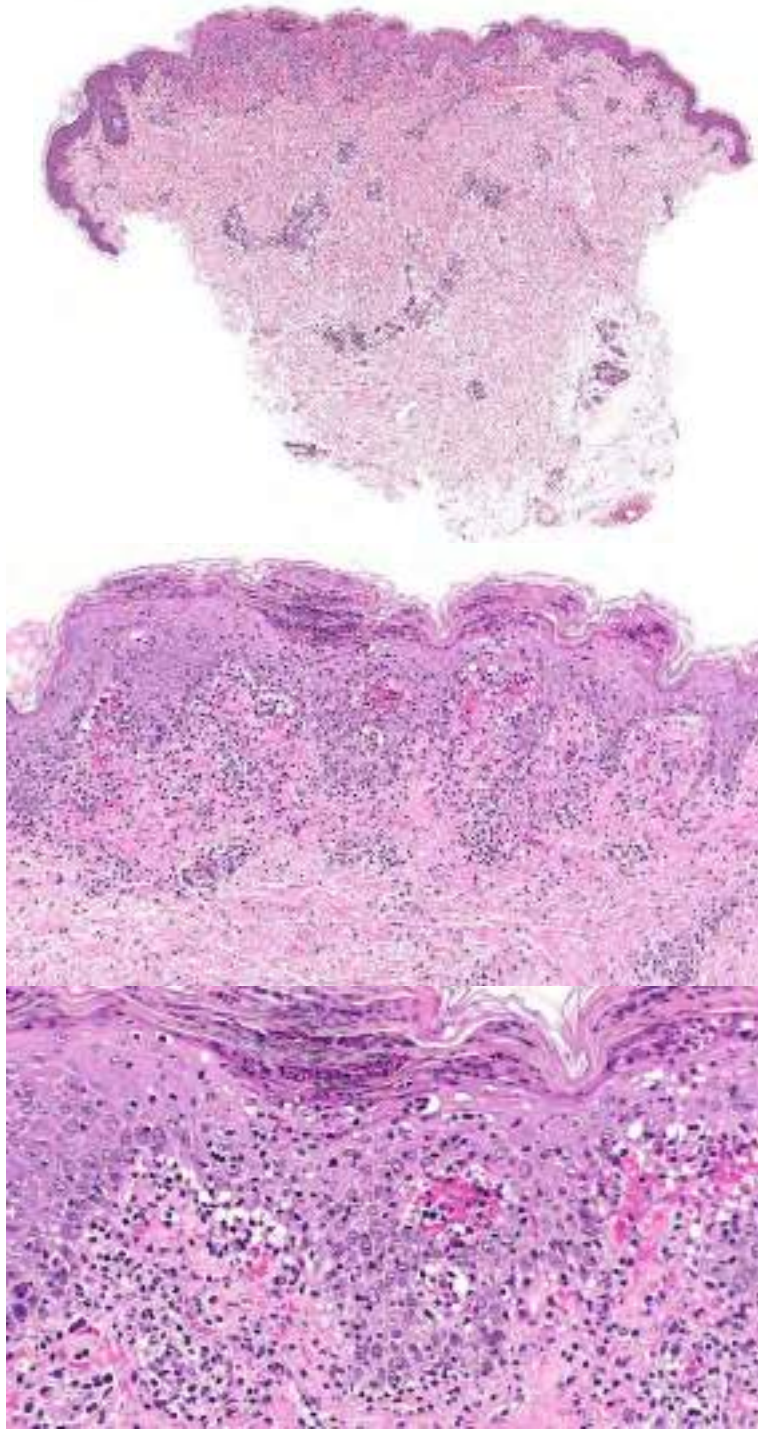
TABLE 1. Histologic Features of Early (Patch) Lesions of MF Observed in 745 Biopsy Specimens

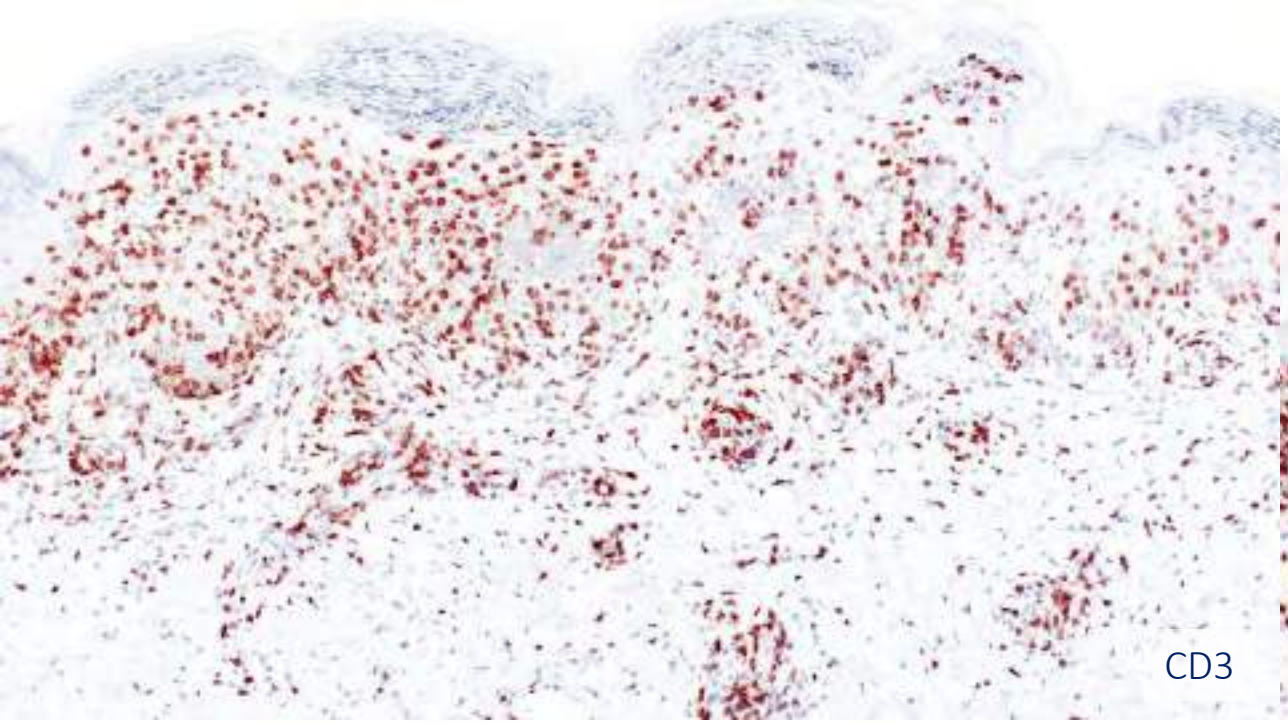
Feature	No. (%)
Normal epidermis	356 (48)
Psoriasiform hyperplasia	258 (35)
Irregular hyperplasia	34 (4)
Flat and/or atrophic epidermis	97 (13)
Marked spongiosis	28 (4)
Necrotic keratinocytes	172 (23)
Changes at the dermoepidermal junction	
Focal interface dermatitis	438 (59)
Widespread interface dermatitis	30 (4)
Epidermotropism*	
Single lymphocyte epidermotropism	161 (22)
Basilar lymphocytes	170 (23)
Pautrier's microabscesses	140 (19)
"Haloed" lymphocytes	298 (40)
Disproportion exocytosis	124 (17)
Pagetoid epidermotropism	17 (3)
Absence of epidermotropism	32 (4)
Atypical lymphocytes	
Only in the epidermis	27 (4)
Both in epidermis and dermis	38 (5)
Only in the dermis	2 (0.3)
Dermal lymphocytic infiltrate	
Band-like	227 (30)
Patchy-lichenoid	492 (66)
Superficial perivascular	26 (3)
Dermal changes	
Papillary dermal fibrosis/coarse collagen bundles	725 (97)
Melanophages	56 (8)
Purpura	32 (4)
Edema of the papillary dermis	0

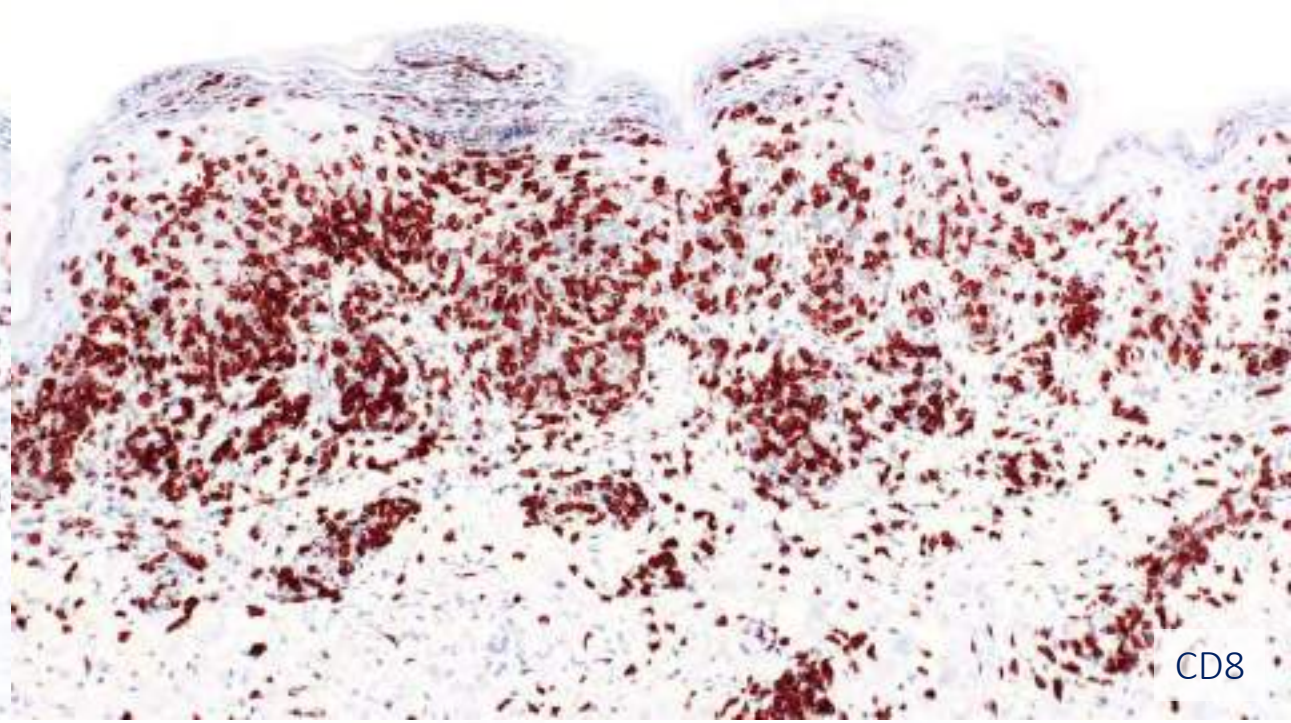
*More than one feature was observed in some cases.

F, 7






CD3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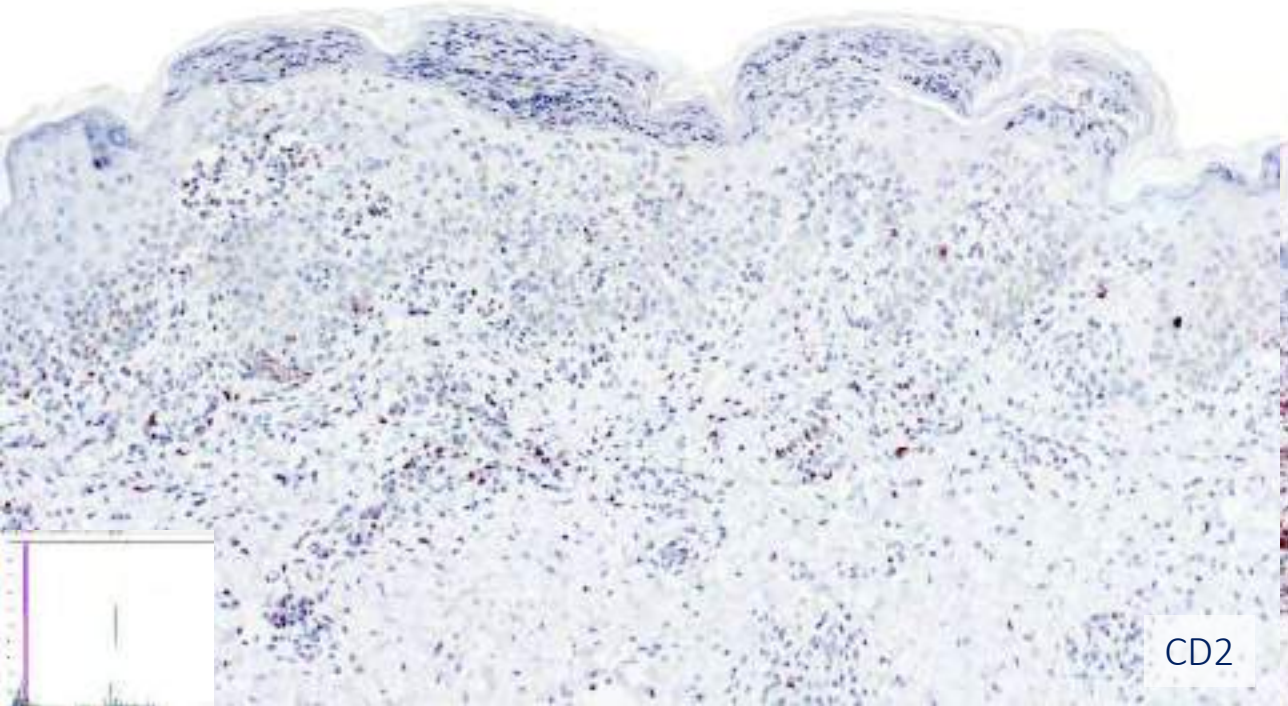
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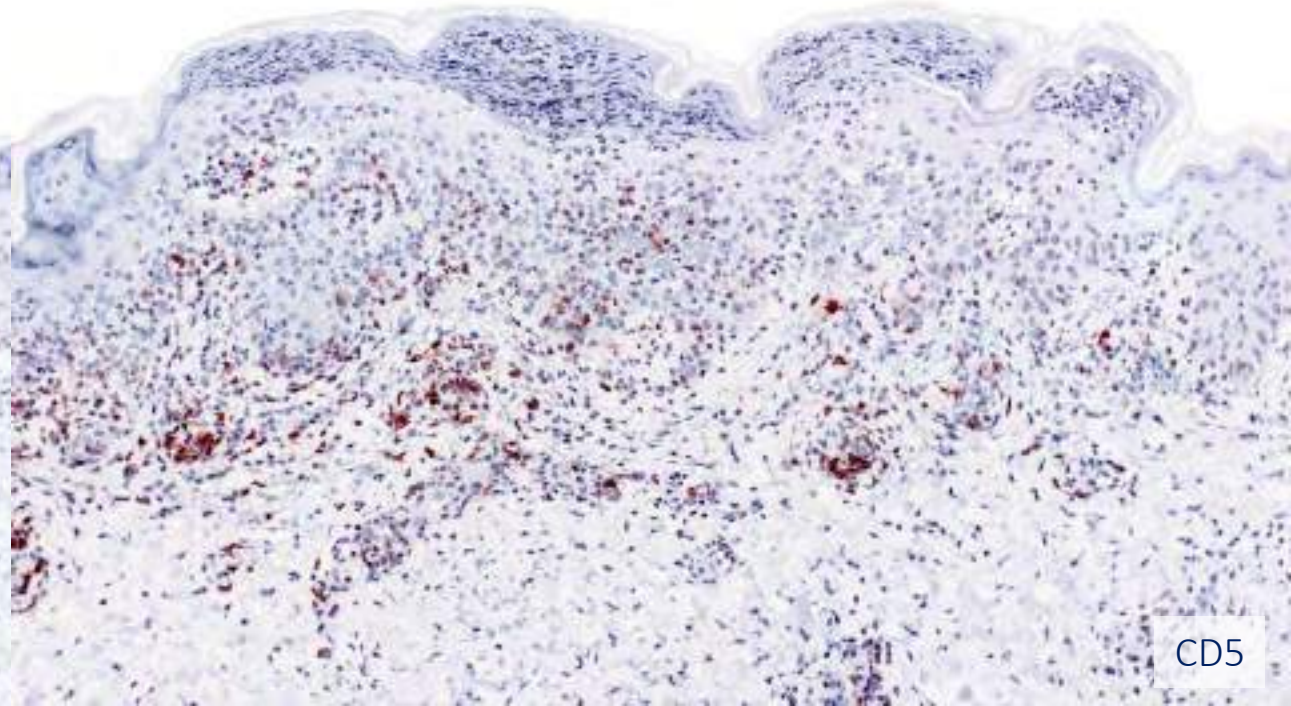
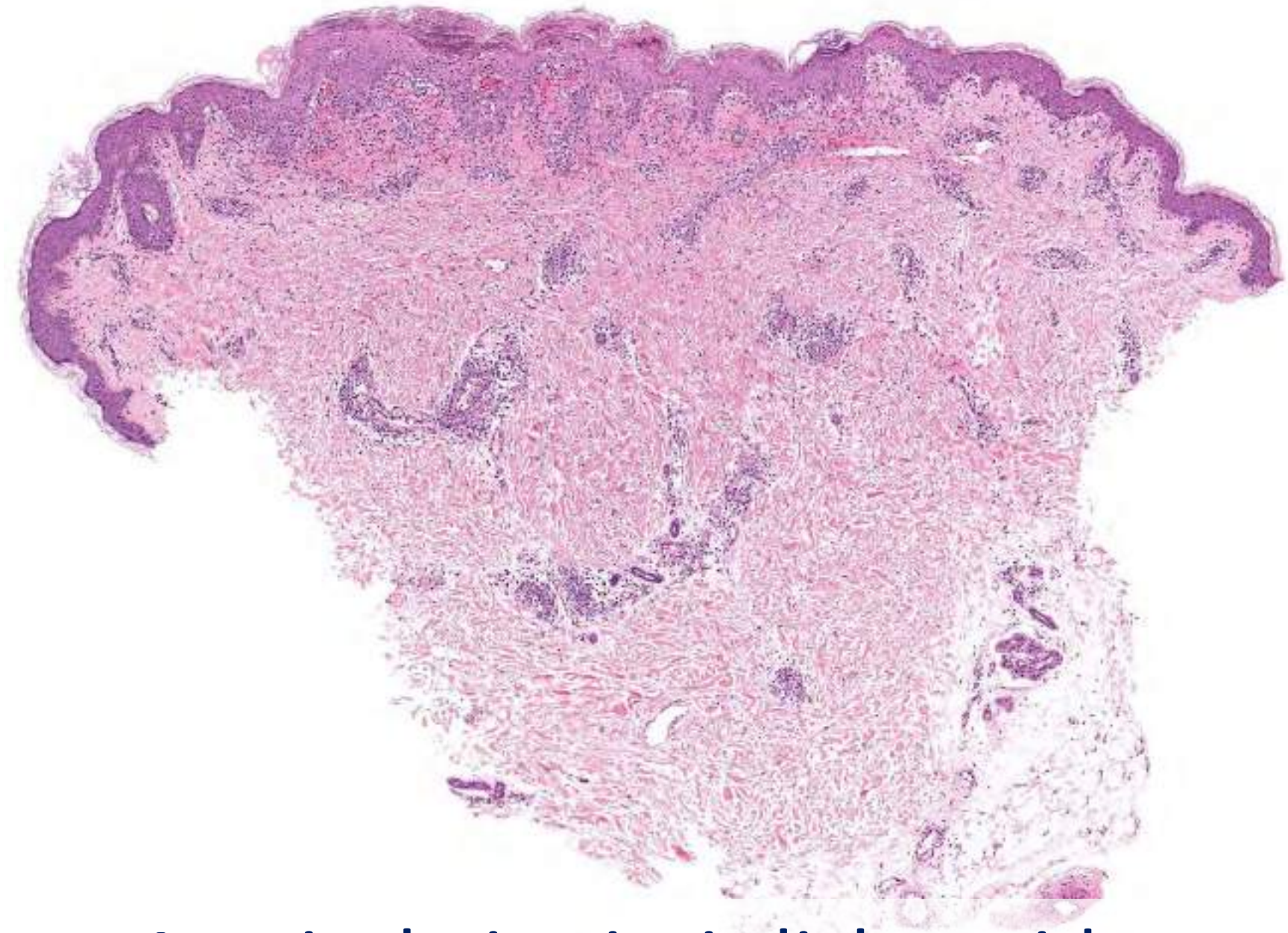
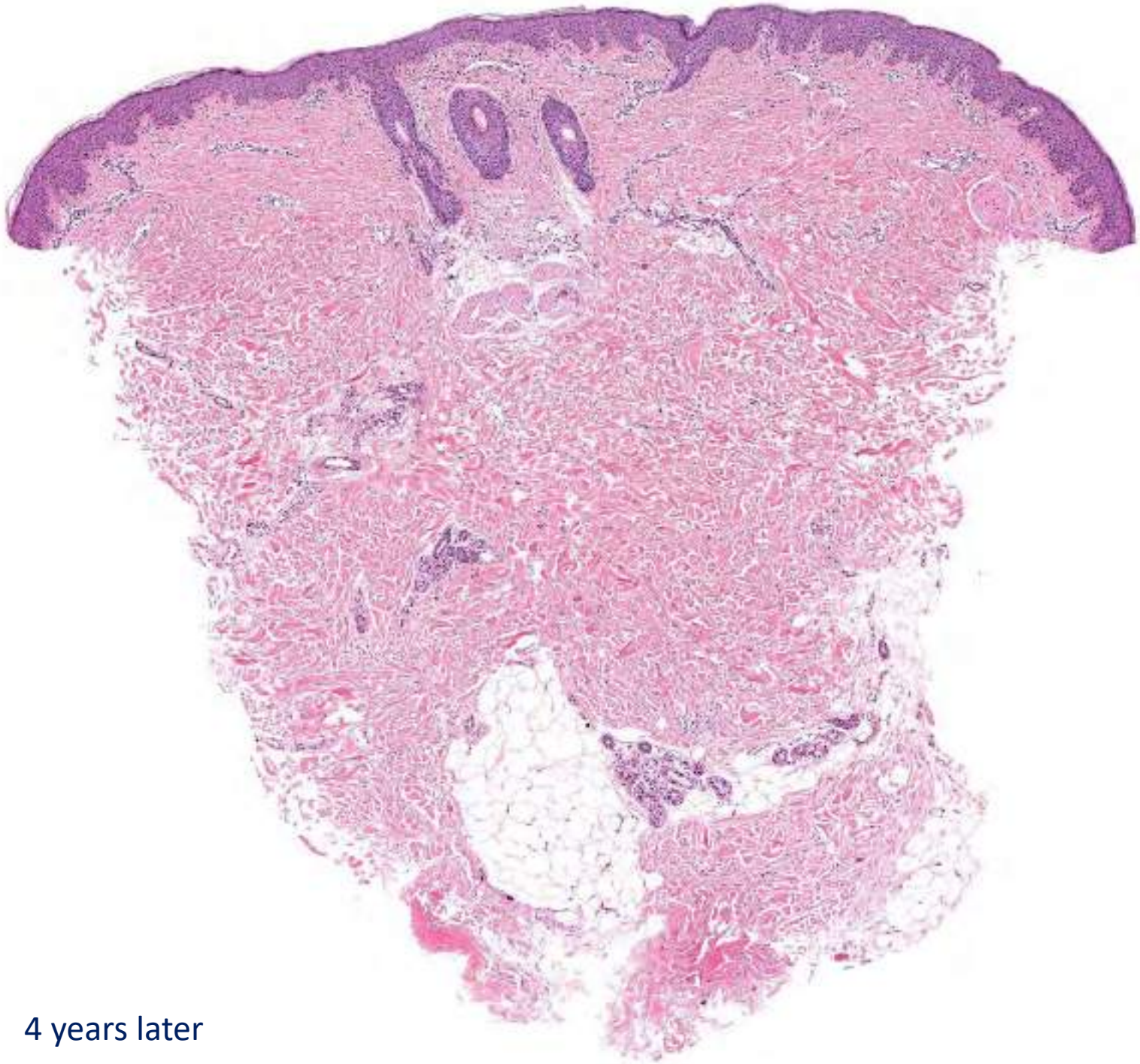
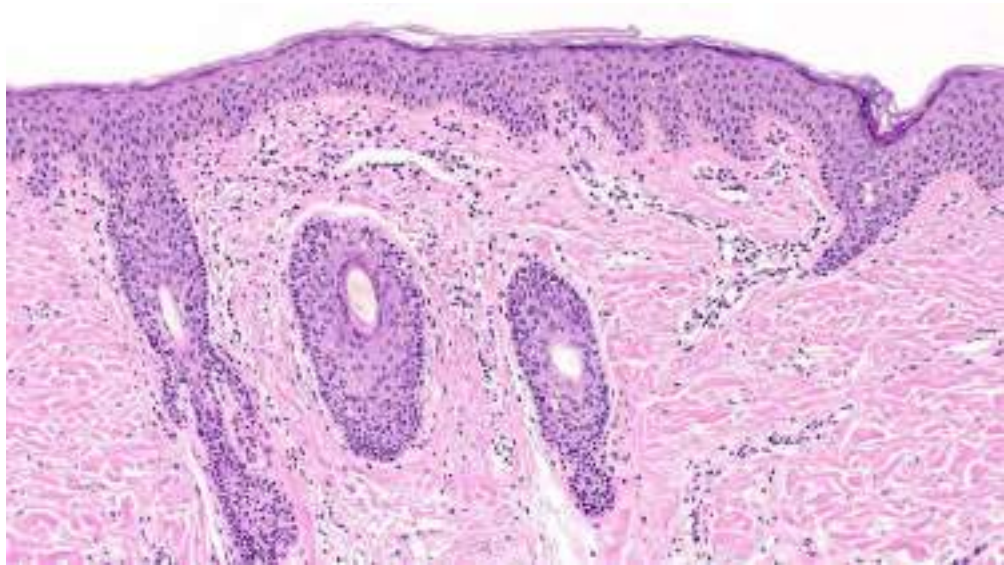

CD5



Atypical pityriasis lichenoides



4 years later



Report

Adult pityriasis lichenoides-like mycosis fungoides: a clinical variant of mycosis fungoides

4 patients (M:F=2:2); Age: 35-70

Pityriasis Lichenoides, Atypical Pityriasis Lichenoides, and Related Conditions

A Study of 66 Cases

Tiziana Bovenzi MD,† Ana Cuerda MD,*‡ Andrea Saggini MD,*§ Regina Fink-Puches MD,* Carlo Cota MD,|| William Fermi MD,† Fabio Facchetti MD,† and Lorenzo Cerroni MD**

Abstract: Pityriasis lichenoides (PL) is an uncommon skin disease of unknown etiology. In recent years, an atypical form of PL has been described, showing overlapping features with mycosis fungoides (MF) and lymphomatoid papulosis. We studied 66 patients with an initial histopathologic diagnosis of PL (M:F = 34:32; median age, 35 y; range, 7 to 85 y). According to clinical and phenotypic features, cases were classified into 4 categories: (1) Conventional PL (characteristic clinical features of PL without phenotypic aberrations) (n = 28; M:F = 8:12; median age, 37 y; range, 8 to 74 y); (2) Atypical form of PL (characteristic clinical features of PL with phenotypic aberrations) (n = 25; M:F = 16:9; median age, 31 y; range, 7 to 72 y). Four of these patients subsequently developed MF; (3) Lymphomatoid papulosis (waxing and waning lesions and positivity for CD30) (n = 10; M:F = 4:6; median age, 41 y; range, 16 to 83 y); (4) MF' (clinical features typical of MF) (n = 11; M:F = 8:3; median age, 17 y; range, 8 to 85 y). Molecular analysis of clonality of the infiltrate did not reveal relevant differences among these 4 groups. Our study suggests that patients with an initial histopathologic diagnosis of PL may belong to different groups, showing that clinicopathologic correlation and complete phenotypic analyses are paramount in order to achieve proper classification. Although the relationship between PL and MF is yet a matter of debate, at the present state of knowledge, patients with a clinicopathologic presentation consistent with PL but with aberrant phenotypic features should be monitored in order to detect a possible evolution into MF.

Key Words: pityriasis lichenoides, pityriasis lichenoides et varioliformis acuta, mycosis fungoides, lymphomatoid papulosis, atypical pityriasis lichenoides, cutaneous T-cell lymphoma

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Pityriasis lichenoides (PL) is an uncommon inflammatory skin disease of unknown etiology, usually classified into an acute (pityriasis lichenoides et varioliformis acuta [PLEVA]) and a chronic (pityriasis lichenoides chronica) variant.[1,2] A considerable overlap exists between these 2 variants, in terms of both clinical and histopathologic presentation.[2,3] In recent years, an atypical form of pityriasis lichenoides (APL) (usually referred to as atypical PLEVA) has been described, characterized mainly by phenotypic aberrations in otherwise conventional PLEVA.[4,5] The exact nosology of PL, including the atypical form, is yet a matter of discussion, and some authors consider it as a type of cutaneous lymphoproliferative disorder showing overlapping features with mycosis fungoides (MF) and lymphomatoid papulosis (LyP).[6] In fact, cases of PLEVA evolving into MF have been reported in the past.[7–9] In addition, some histopathologic features of PLEVA, such as presence of interface dermatitis and of necrotic keratinocytes, are not infrequent in MF,[10] and a histopathologic variant of MF similar to PLEVA has been described, thus further complicating the classification of these cases.[11,12] Finally, a small series and a few case reports described a CD30+ variant of PLEVA, and PL and LyP are considered as being part of a spectrum by some authors.[13–15]

We evaluated 66 patients with an initial histopathologic diagnosis of PLEVA, correlating the histopathologic features with clinical data, immunohistochemical investigations, analysis of the T-cell receptor (TCR) gene rearrangement, and follow-up.

PATIENTS, MATERIALS, AND METHODS

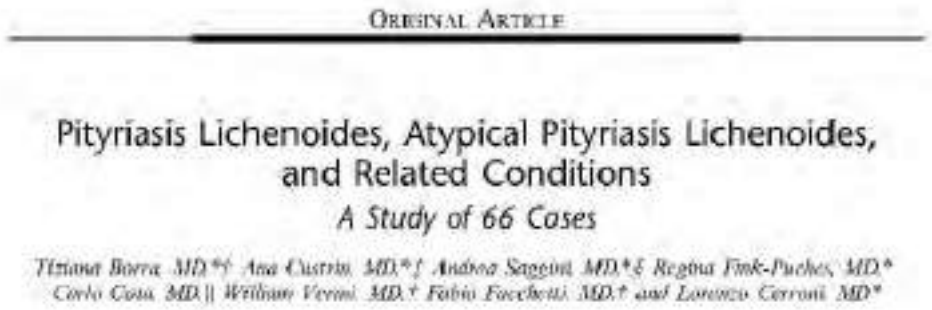
Data of 66 patients with an initial histopathologic diagnosis of PLEVA were retrieved from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria. Only cases with complete clinical information at presentation as well as sufficient phenotypic analysis in at least 1 biopsy have been included. Some of the cases had been sent for second expert opinion to 1 of us (L.C.). The study has been approved by the ethical committee of the Medical University of Graz.

A total of 106 biopsies from the 66 patients was available for study. Upon correlation with clinical and phenotypic features, the cases have been classified into 1 of

TABLE 1. Clinical Features of the Cases

Case #	Sex/Age (y)	Classification	Follow-up (mo)
1	F/12	PL	A+ (1)
2	M/10	PL	A− (96)
3	F/48	PL	A− (103)
4	F/44	PL	A− (68)
5	M/55	PL	A− (4)
6	F/23	PL	A− (74)
7	M/13	PL	A− (60)
8	M/9	PL	A+ (3)
9	F/45	PL	A− (182)
10	M/25	PL	NA
11	F/32	PL	A− (264)
12	F/17	PL	A− (240)
13	F/60	PL	A− (186)
14	M/31	PL	A− (23)
15	M/63	PL	A− (117)
16	F/54	PL	A− (99)
17	F/42	PL	A− (171)
18	M/74	PL	A− (2)
19	F/45	PL	NA
20	F/10	PL	NA
21	M/11	APL	A− (25)
22	M/15	APL	A+ (58)
23	M/24	APL	A− (8)
24	F/21	APL	A+ (3)
25	M/7	APL	A− (181)
26	M/9	APL	A− (170)
27	M/12	APL	A+ (65)
28	F/53	APL	A− (49)
29	M/49	APL	A− (108)
30	M/28	APL	A− (56)
31	M/25	APL	A− (240)
32	F/72	APL	A− (42)
33	M/12	APL	A− (77)
34	F/7	APL	A+ (28)
35	F/43	APL	A+ (46)
36	M/11	APL	NA
37	M/13	APL	A+ (20)
38	F/17	APL	A+ (74)
39	M/15	APL	A− (89)
40	F/28	APL	A− (99)
41	M/7	APL	NA
42	F/25	APL	A− (80)
43	M/22	APL	A+ (1)
44	M/31	APL	NA
45	F/24	APL	NA
46	F/41	LyP	A+ (35)
47	M/30	LyP	A− (22)
48	M/57	LyP	A− (54)
49	M/23	LyP	NA
50	F/83	LyP	A− (76)
51	F/16	LyP	A− (94)
52	F/41	LyP	A+ (74)
53	F/51	LyP	A+ (73)
54	M/50	LyP	A+ (3)
55	F/18	LyP	A+ (86)
56	F/27	MF	A+ (114)
57	F/85	MF	NA
58	M/82	MF	A+ (3)
59	M/8	MF	NA
60	M/9	MF	NA
61	M/11	MF	A+ (2)
62	M/17	MF	A+ (8)
63	F/14	MF	NA
64	F/8	MF	A+ (120)
65	F/27	MF	NA
66	M/56	MF	NA

A− indicates alive without disease, A+, alive with disease; F, female; M, male; NA, not available.



ORIGINAL ARTICLE

Pityriasis Lichenoides, Atypical Pityriasis Lichenoides, and Related Conditions

A Study of 66 Cases

Tiziana Borra, MD,*† Ana Custrin, MD,*‡ Andrea Saggini, MD,*§ Regina Fink-Puches, MD,* Carlo Cota, MD,‖ William Vermi, MD,† Fabio Facchetti, MD,† and Lorenzo Cerroni, MD*

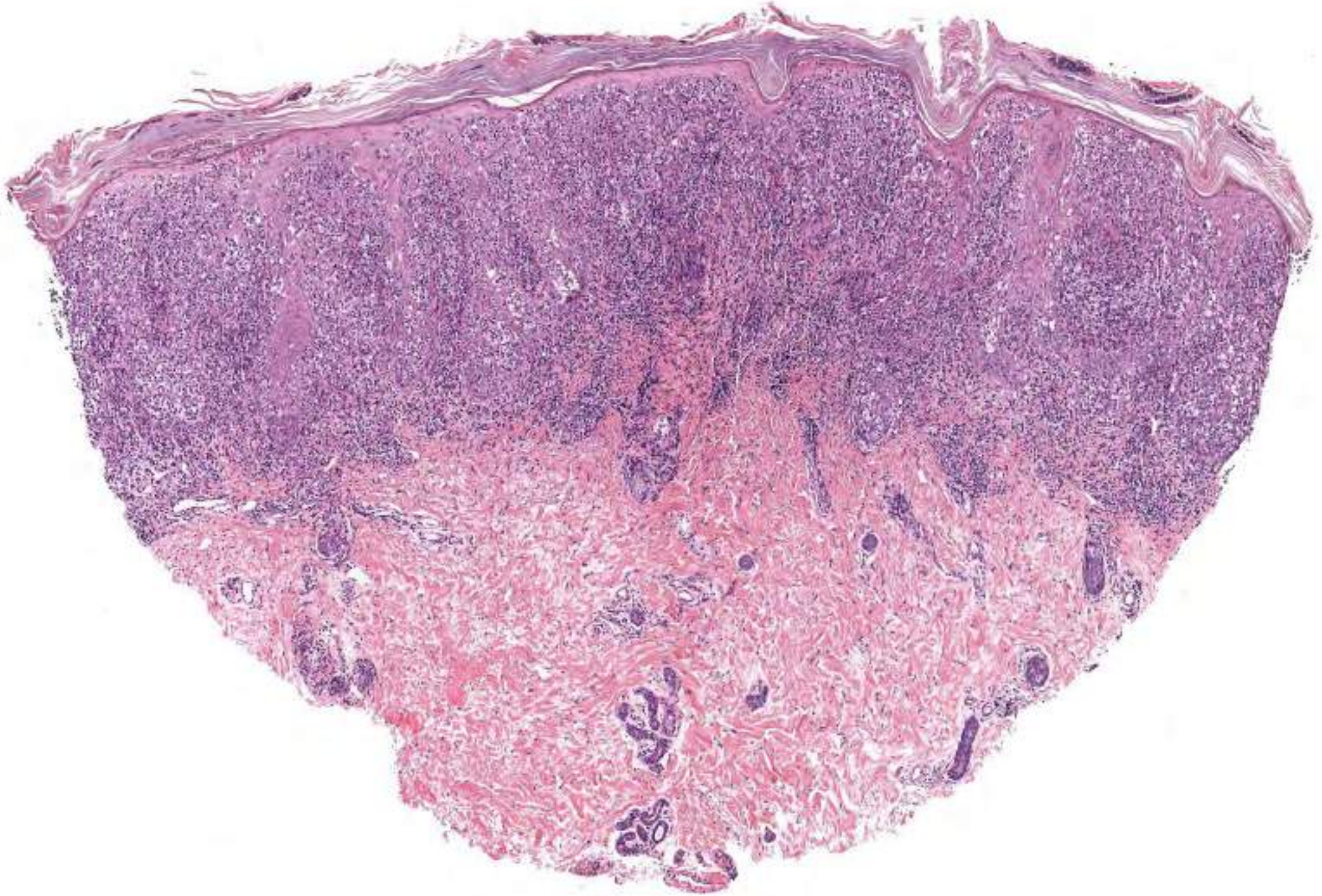
66 cases

Initial histopathological diagnosis of PLEVA

Phenotype, Clinical presentation, Follow-up

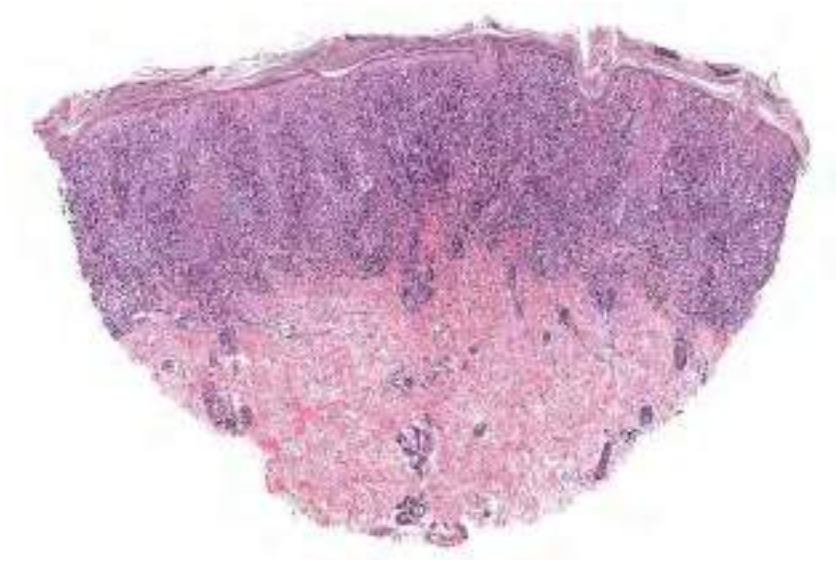
- Conventional PLEVA
  - **Conventional PLEVA n=20**
    - PCR-M/P: 6/7
      - Follow-up (n=17):
        A+ (1-3, 2): n=2
        A- (2-264, 99): n=15
- Clinically typical but aberrant phenotype
  - **Atypical PLEVA n=25**
    - PCR-M/P: 10/9
      - Follow-up (n=21):
        A+ (1-74, 37): n=8*
        A- (8-240, 80): n=13
        *"Progression" to MF: n=4
- CD30+; Recurrent crops
  - **LyP n=10**
    - PCR-M/P: 5/3
      - Follow-up (n=9):
        A+ (3-86, 73): n=5
        A- (22-94, 65): n=4
- Clinical features inconsistent with PLEVA and typical of MF
  - **PLEVA-like MF n=11**
    - PCR-M/P: 3/1
      - Follow-up (n=5):
        A+ (2-120, 8): n=5

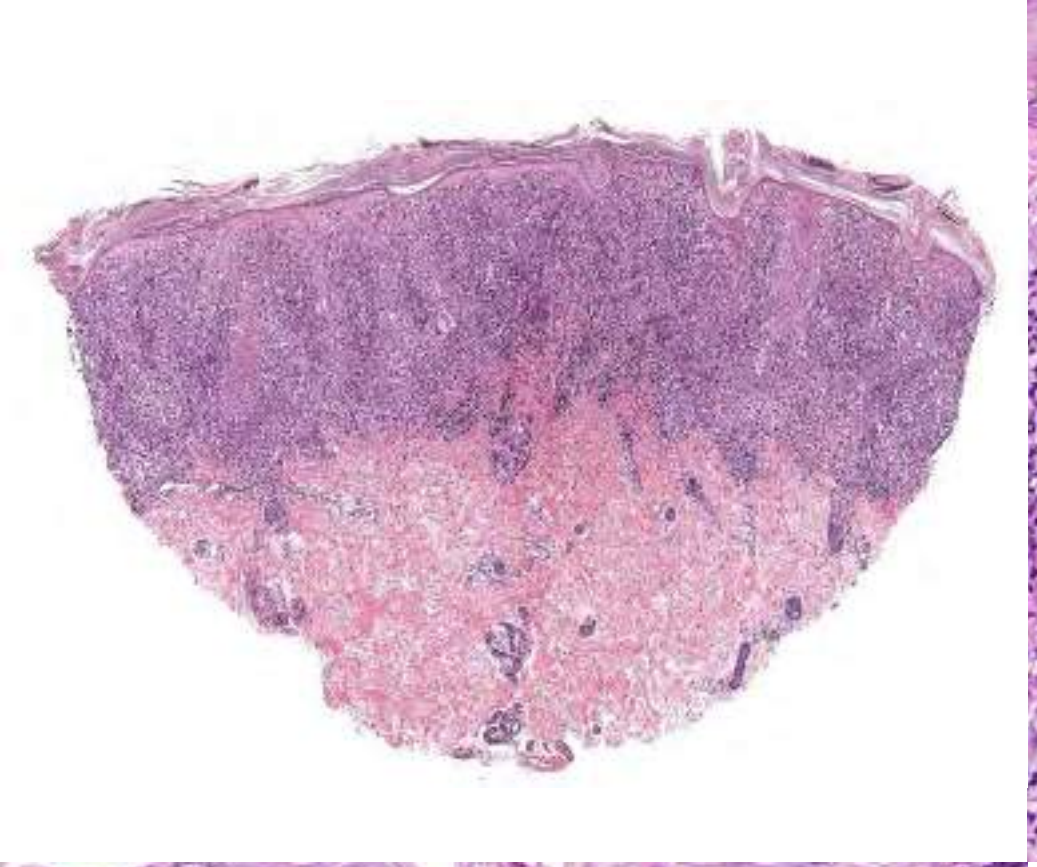
F, 44
Lower arm

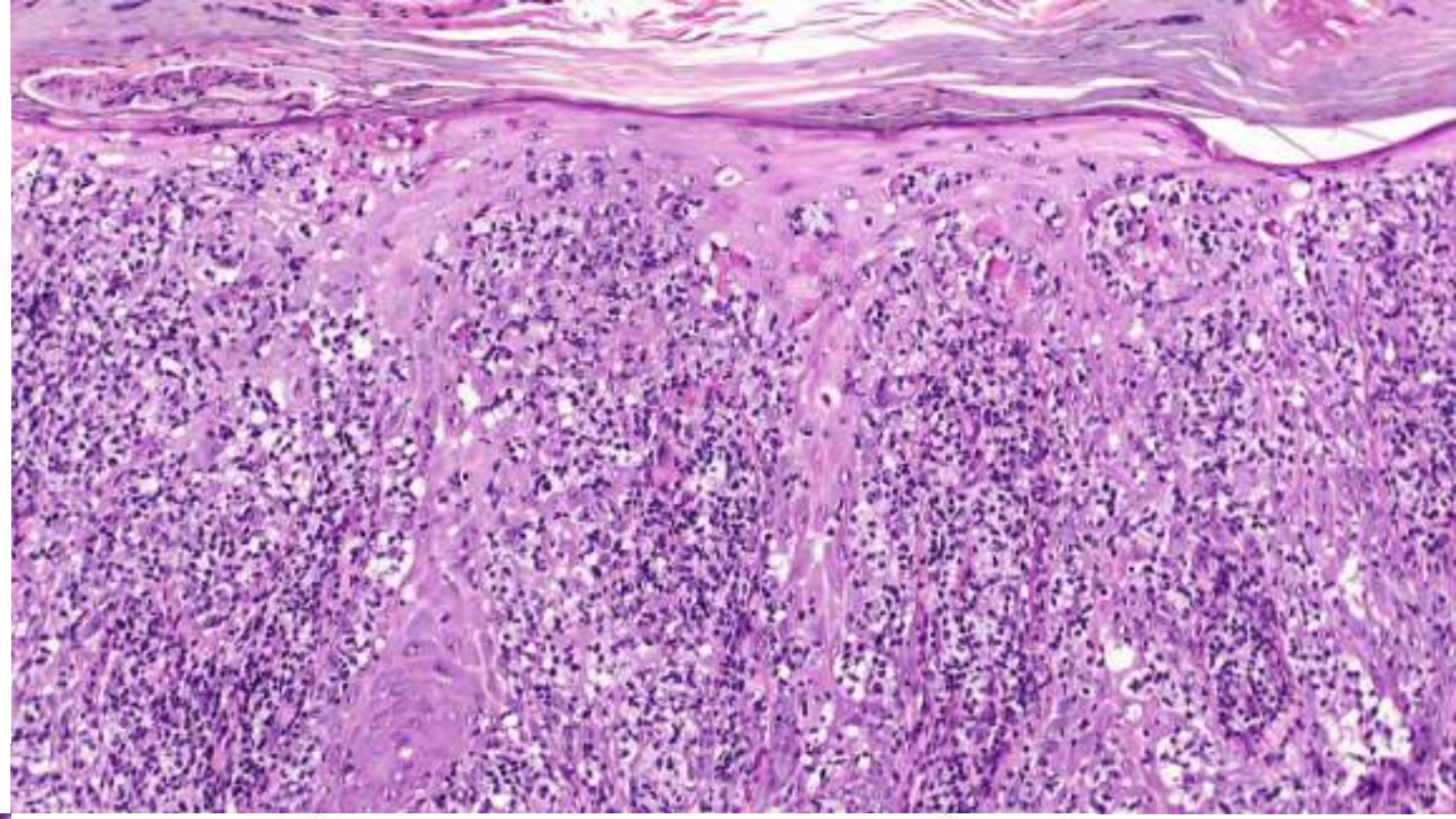


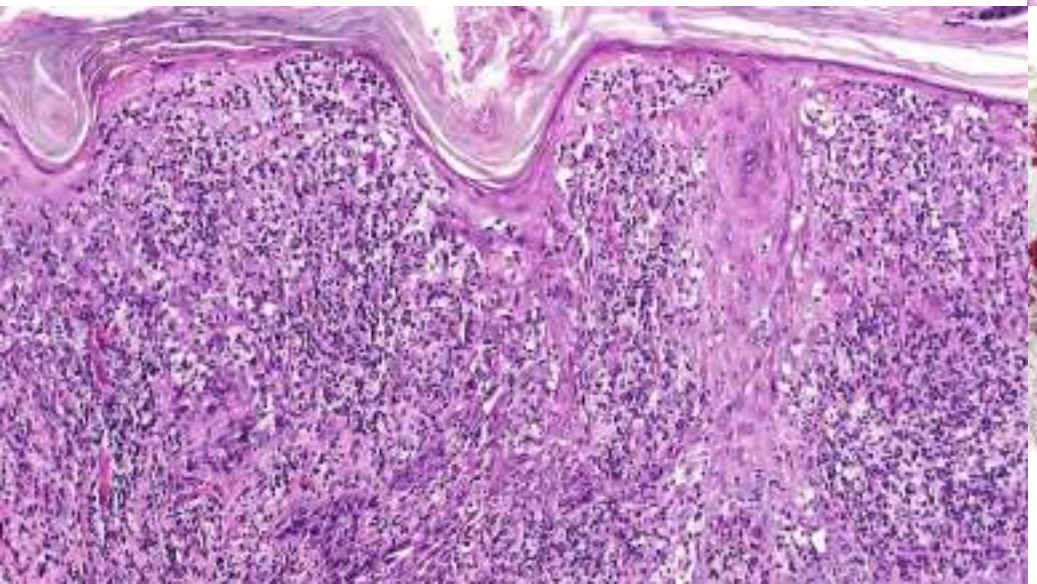
F, 44

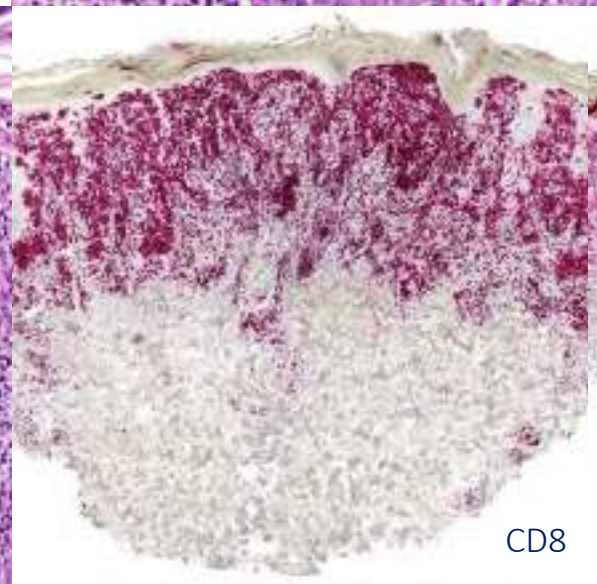
According to the patient asymptomatic skin lesion on the left lower arm for approximately 9 months (picture taken after a punch biopsy).











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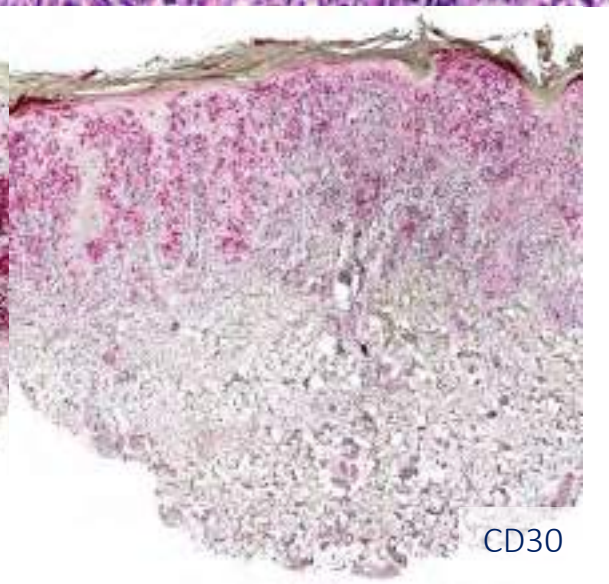
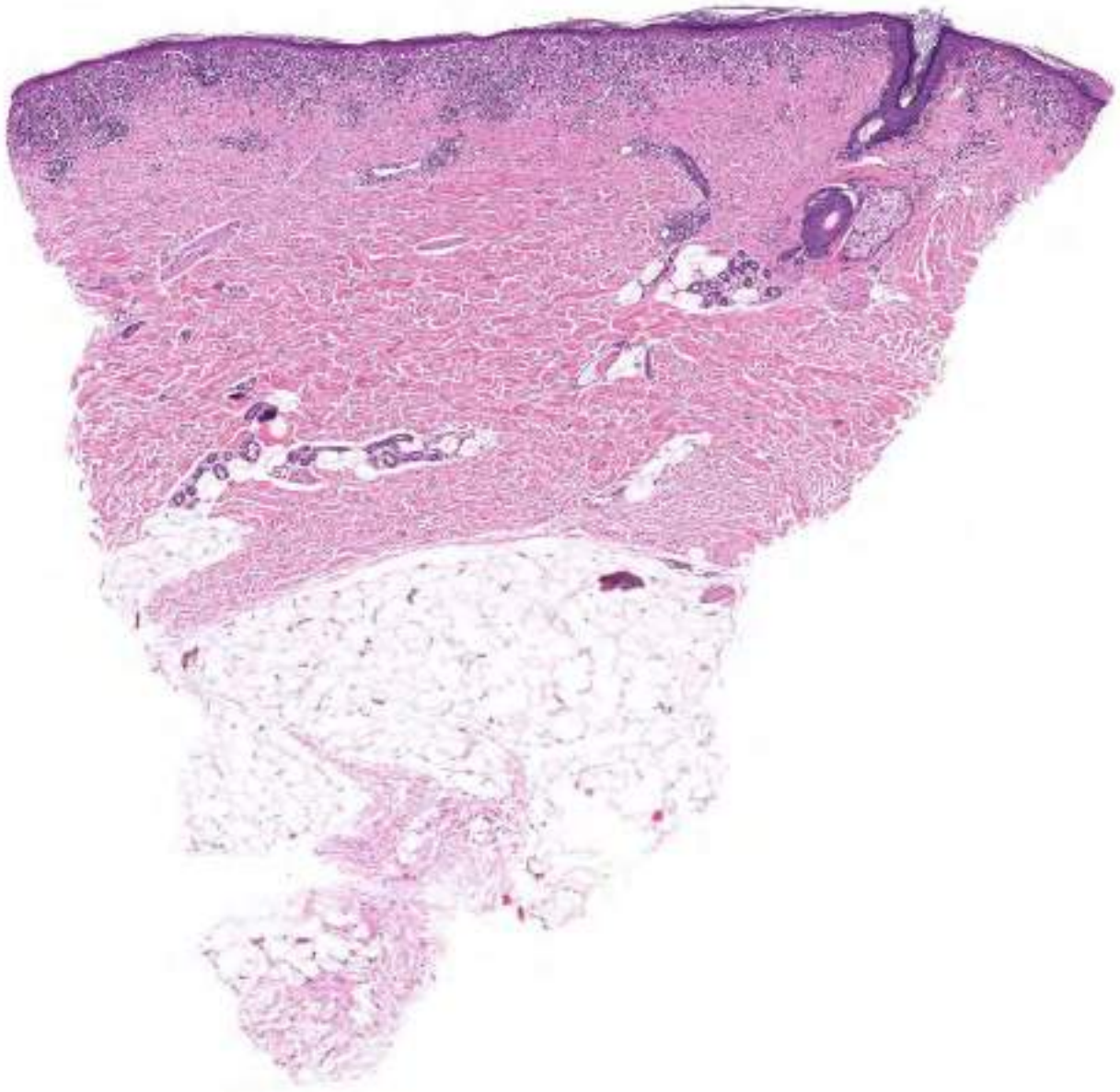
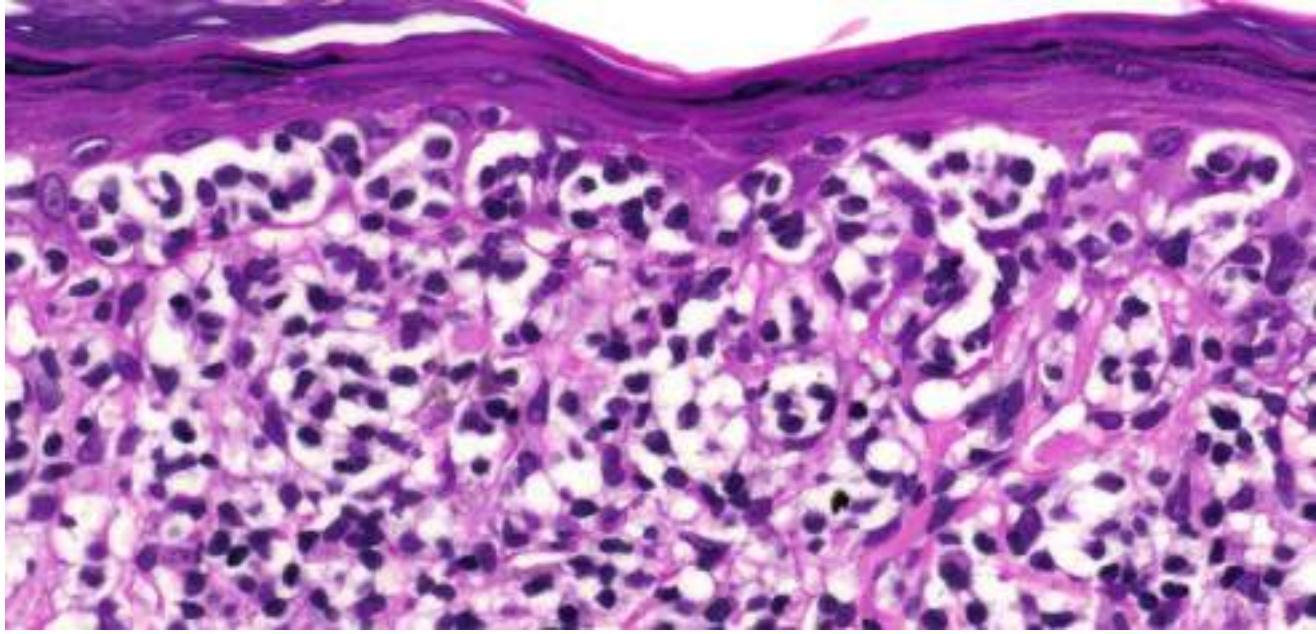
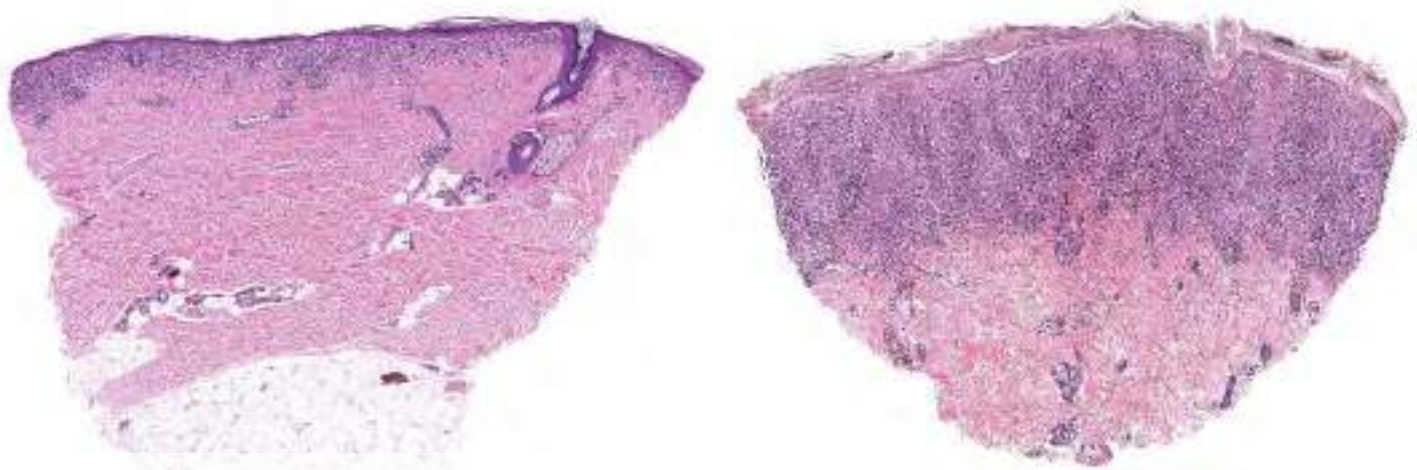


CD30



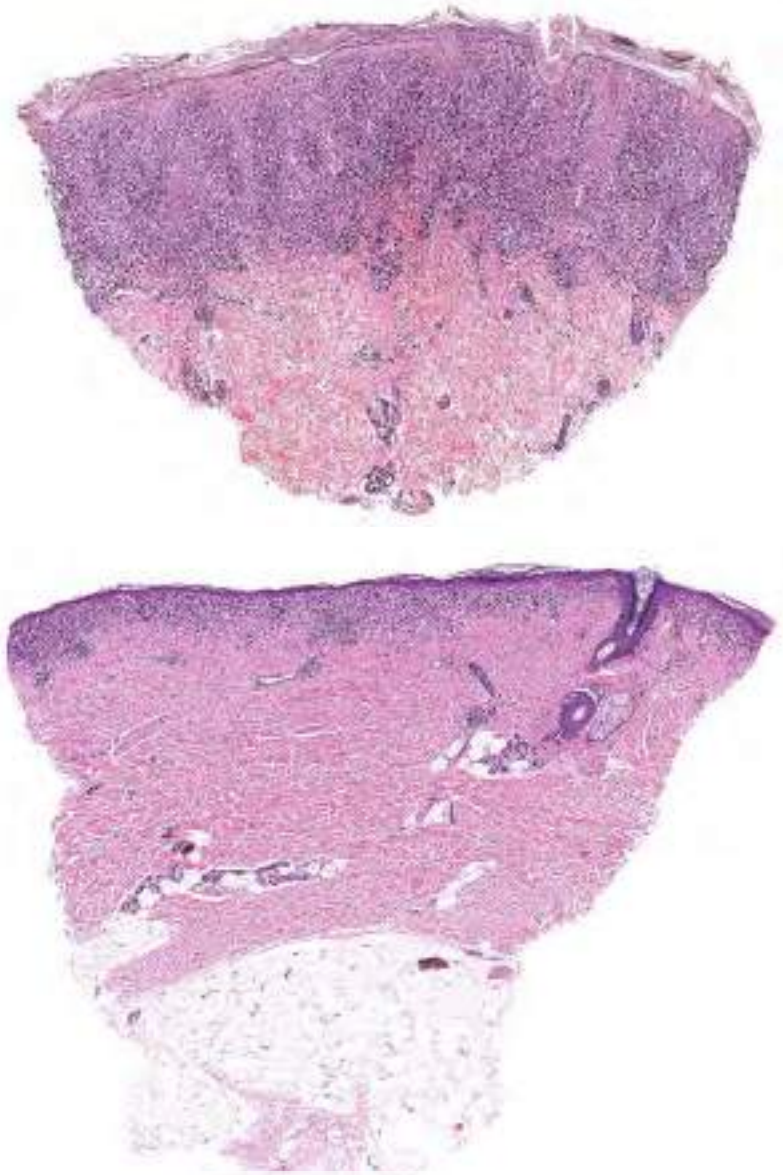


Two further lesions on the lower leg and left arm (biopsy from the arm).



Reported as mycosis fungoides...

(pagetoid reticulosis-like)



... vitiligo

(pagetoid reticulosis-like)

Baby Wet Wipes: An Unusual Culprit of Lymphomatoid Contact Dermatitis Mimicking Mycosis Fungoides

Emily Coleman, MD and Jag Bhawan, MD

Abstract: Lymphomatoid contact dermatitis (LCD) is a rare, benign pseudolymphoma with clinicopathologic features of both allergic contact dermatitis and cutaneous T-cell lymphoma (CTCL). In this article, we report a fascinating case of LCD secondary to chronic baby wet wipe use with clinical features of allergic contact dermatitis and histopathologic changes of mycosis fungoides, a subtype of CTCL. We argue that LCD should be added to the list of mimickers of mycosis fungoides, a subtype of CTCL.

Key Words: lymphomatoid contact dermatitis, mycosis fungoides, cutaneous T cell lymphoma, allergic contact dermatitis, clinicopathologic correlation

(*Am J Dermatopathol* 2022;44:205–206)

BACKGROUND

Lymphomatoid contact dermatitis (LCD) is a rare, benign pseudolymphoma with overlapping clinical and pathologic features of allergic contact dermatitis and cutaneous T-cell lymphoma (CTCL) that often represents a diagnostic challenge.[1] Clinicopathologic correlation is essential in the diagnosis of LCD. In this article, we report a case of baby wet wipes use as the culprit of LCD showing typical histopathologic changes of mycosis fungoides (MF). LCD should be added to the list of mimickers of MF.[2,3]

REPORT OF A CASE

An African American woman in her 50s with well-controlled hypertension presented with a history of discoloration of the inguinal and intergluteal areas. Initially she was seen by a gynecologist who performed a biopsy that was reported as nondiagnostic. Two years later, she presented to dermatology for evaluation of the persistent lesions. Medications and family history were noncontributory. Clinical examination revealed hypopigmented, minimally scaly patches with focal erosion and erythema overlying the suprapubic, intergluteal, and bilateral inguinal areas (Fig. 1). Two 3-mm punch biopsies revealed abundant lymphocytic epidermotropism with occasional Pautrier microabscesses (Fig. 2A), an interstitial proliferation of lymphocytes, and papillary dermal fibrosis (Fig. 2B). There was a predominance of $CD8^+$ and $CD4^-$ lymphocytes in the epidermis (Fig. 3A) and dermis (Fig. 3B), respectively. A mild decrease in epidermal melanocytes was noted on MART-1 staining. T-cell receptor (TCR) gene rearrangement polymerase chain reaction studies demonstrated a clonal T-cell population, supporting a diagnosis of hypopigmented MF. However, given a lack of clinicopathologic correlation for MF, additional probing revealed frequent cleansing with baby wet wipes. Topical corticosteroids and cessation of baby wet wipes led to complete resolution of the lesions without recurrence.

DISCUSSION

Although histologic and polymerase chain reaction findings were consistent with MF, the lack of clinical evidence of MF led to the conclusion that this case represented LCD. Furthermore, given resolution of the lesions with cessation of baby wet wipes, we concluded that these were the etiologic agent of LCD. In addition, we would not expect to see clinical resolution of MF with cessation of baby wet wipes, which further supports the diagnosis of LCD.

First coined in 1976 after 4 patients with CTCL had positive patch tests for phosphorus sesquisulfide secondary to matchbox use, LCD is a pseudolymphoma with clinicopathologic features of both allergic contact dermatitis and CTCL.[4] The distribution of lesions of LCD along the buttocks, pelvis, and upper legs more closely mimics the so-called "bathing trunk" distribution of the lesions MF, which often clouds diagnosis.[1] In addition to the initial report of phosphorous sesquisulfide,[4] other causative allergens identified include dimethyl fumarate, ethylenediamine dihydrochloride, azo dyes, gold sodium thiosulfate, cobalt naphthenate, nickel sulfate, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine, *p*-phenylenediamine, *Tectona grandis*, *para*-tertiyl-butyl phenol, methylchloroisothiazolinone/methylisothiazolinone and parabens, benzalkonium hydrochloride, and methylchloroisothiazolinone quaternium-15.[5] Similar to our case, moist wipes were the causative agent of LCD on the buttock, genitals, or intergluteal cleft in 2 reported cases, with methylchloroisothiazolinone as a common underlying allergen identified by patch testing in both cases.[1,5] Although we did not conduct patch testing, this agent may have been the allergen in our case as well.

Although LCD may have features of MF,[1,4] none of the previously reported cases had the extent and intensity of epidermotropism as seen in our case. Our case is unique in that the histopathological features were indistinguishable from MF. Furthermore, LCD rarely shows TCR gene

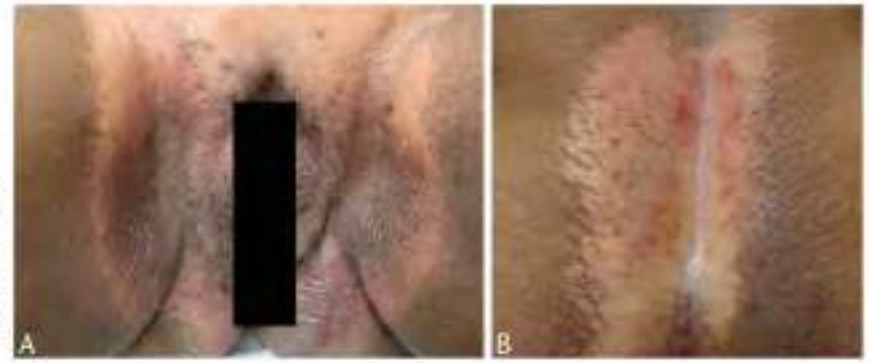


FIGURE 1. A, The inguinal and genital regions demonstrated a hypopigmented, minimally scaly plaque with a mildly erosive plaque posteriorly. B, The intergluteal cleft was notable for a hypopigmented patch with a cluster of 0.1–0.3 mm erythematous macules coalescing into a patch centrally.

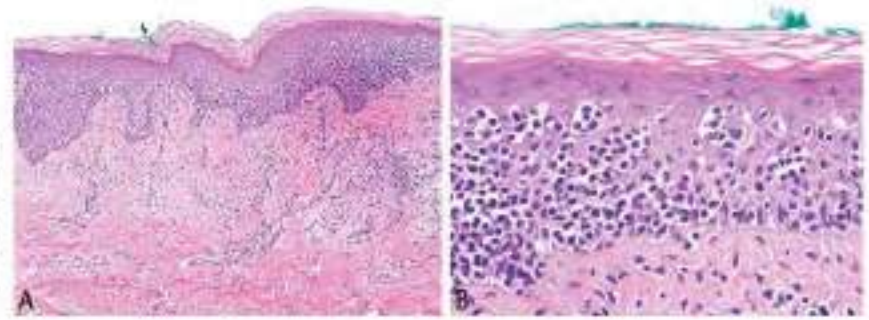


FIGURE 2. A, Hemotoxylin and eosin revealed abundant lymphocytic epidermotropism with occasional Pautrier microabscesses, an interstitial proliferation of lymphocytes, and papillary dermal fibrosis ×10. B, Epidermotropism with Pautrier microabscesses are easily seen in higher magnification ×40.

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The authors declare no conflicts of interest.

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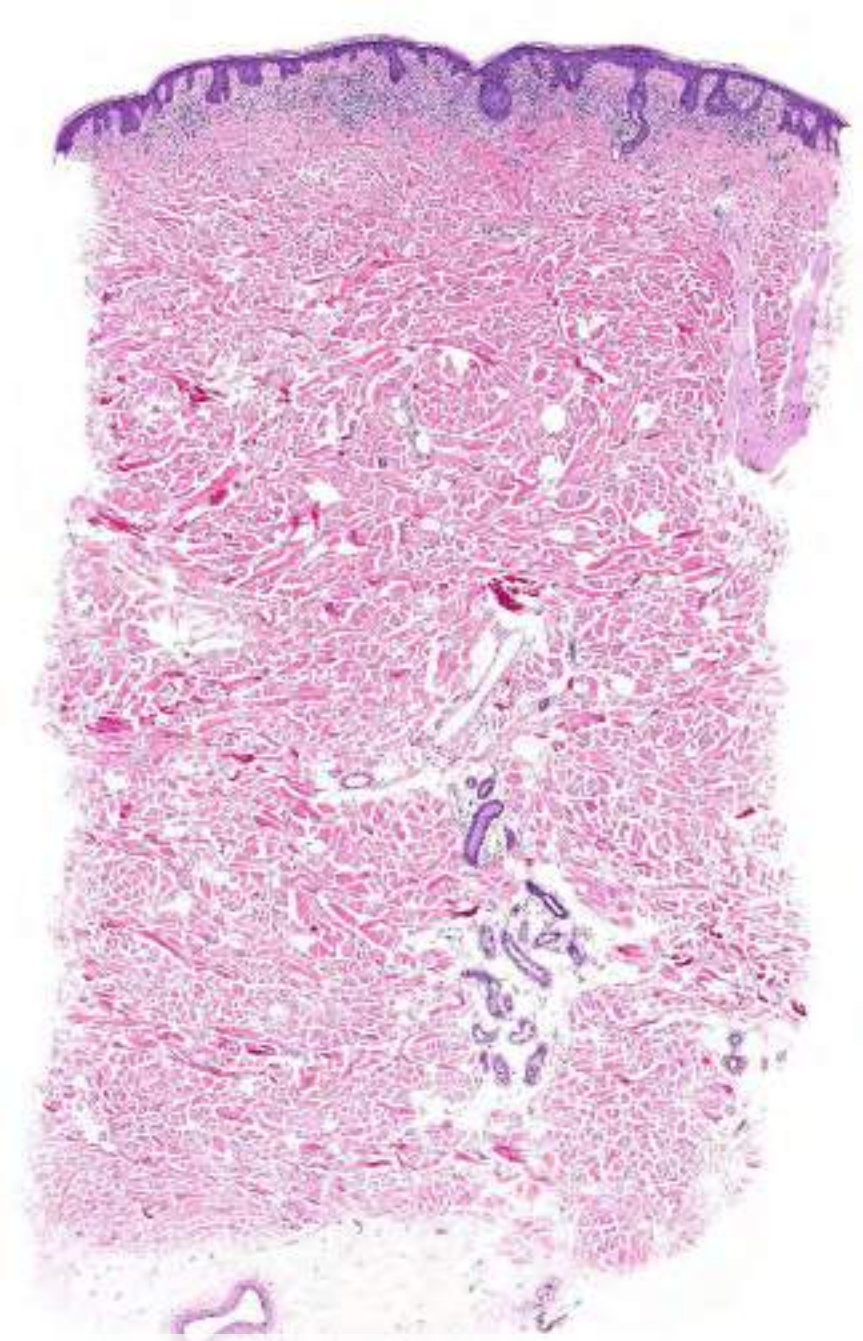
M, 71

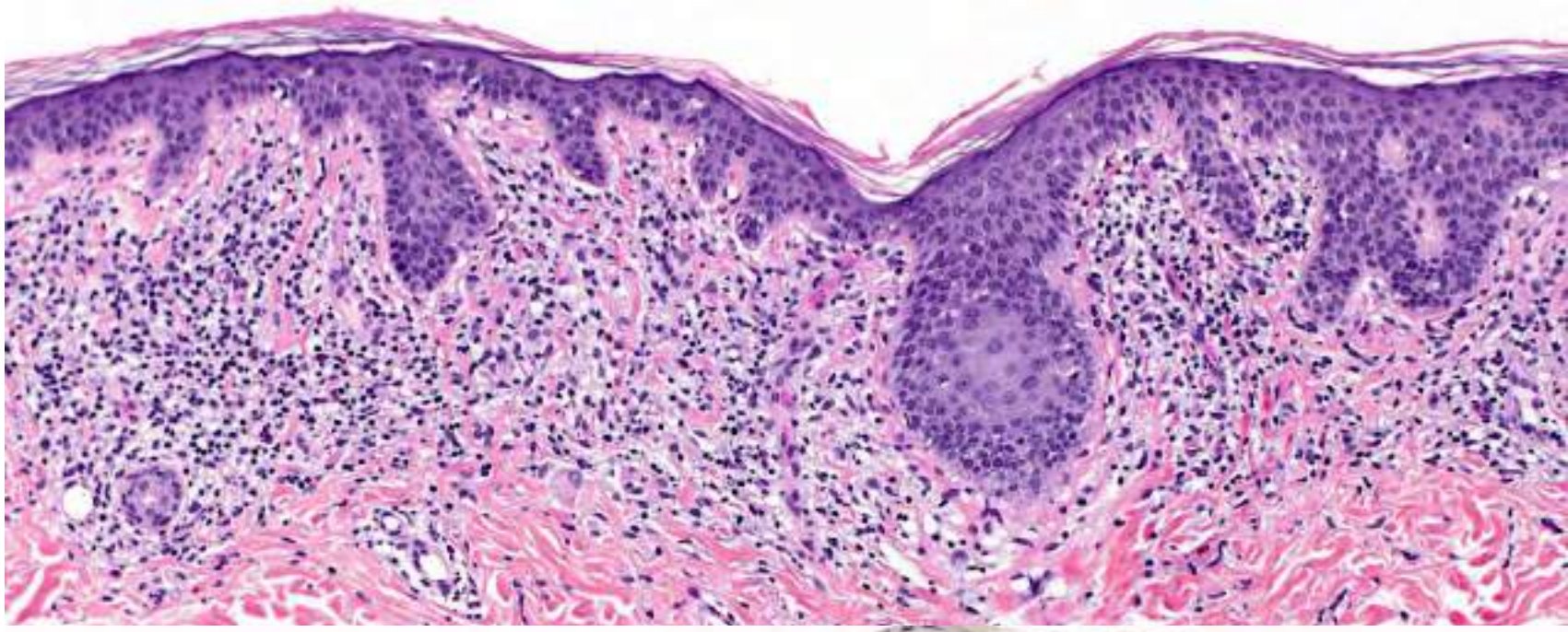
History of cytotoxic MF diagnosed histopathologically 7 years before presentation.

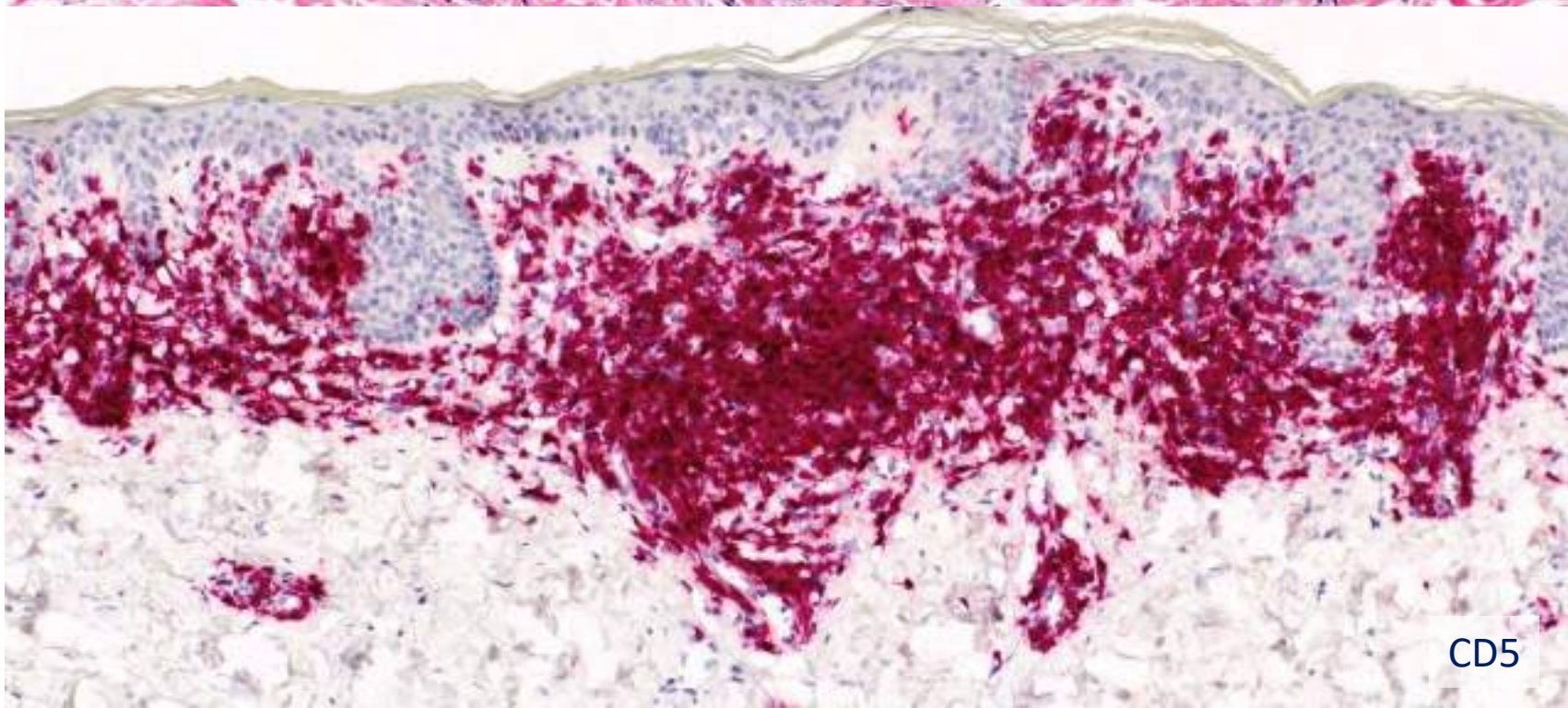
Managed as hypopigmented MF since diagnosis.

Comes for a planned control; a new biopsy is taken (including both the hypopigmented area and the erythematous rim).

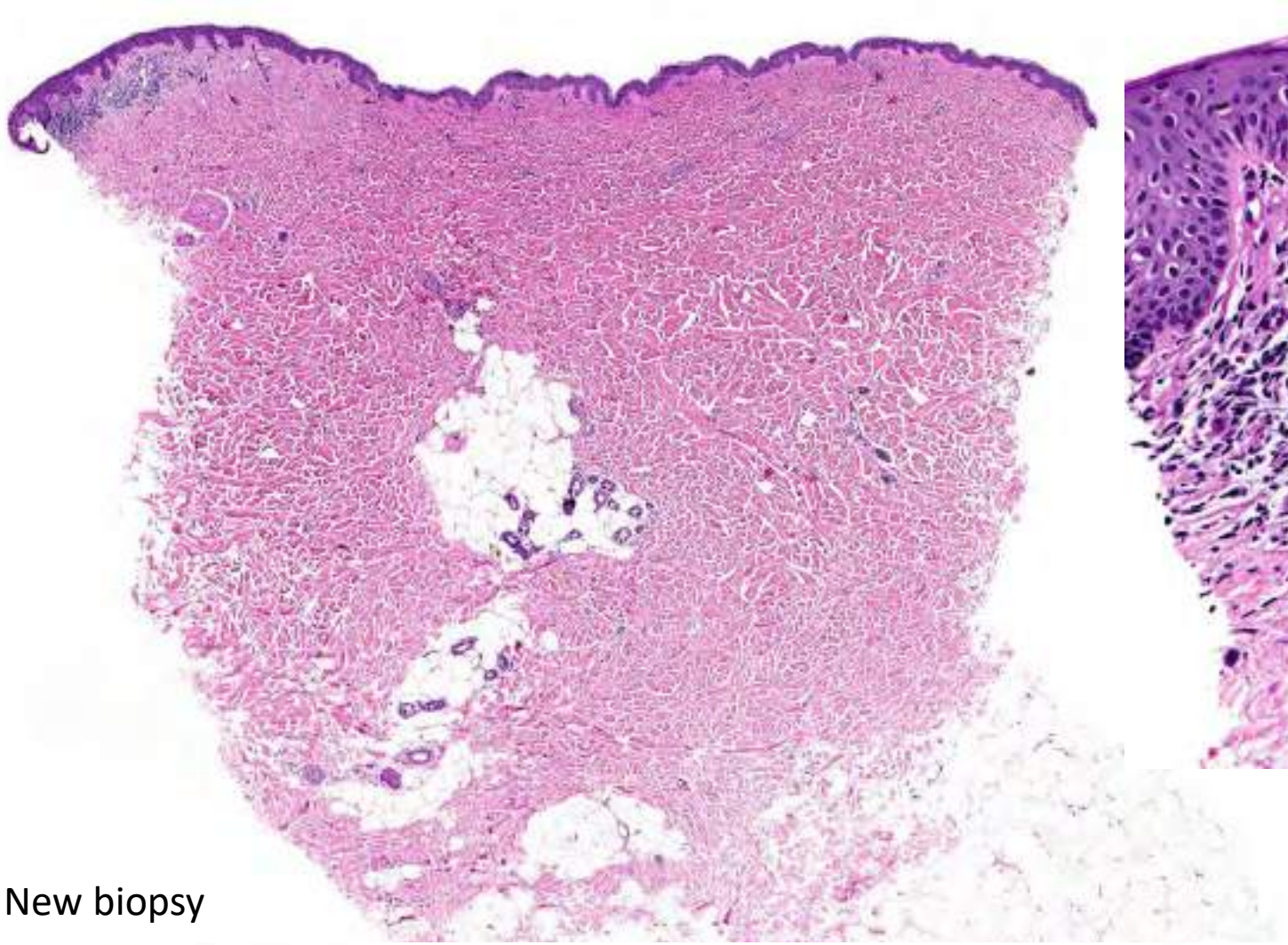


Original biopsy (7 years previously)

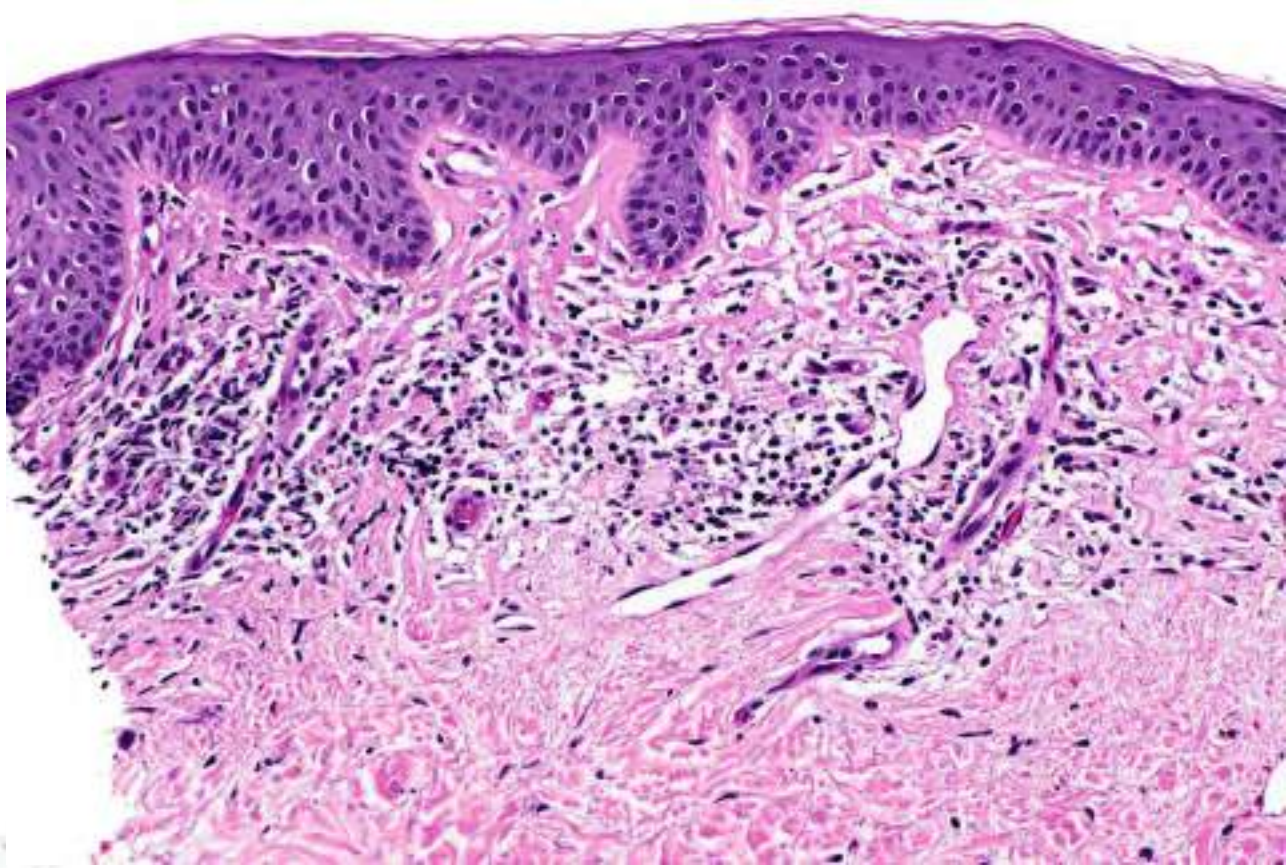




CD5

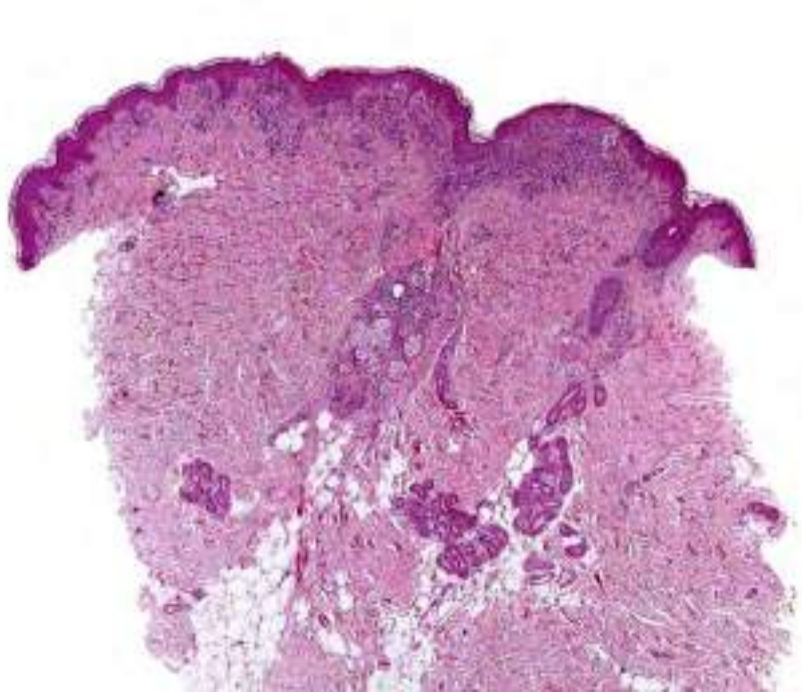


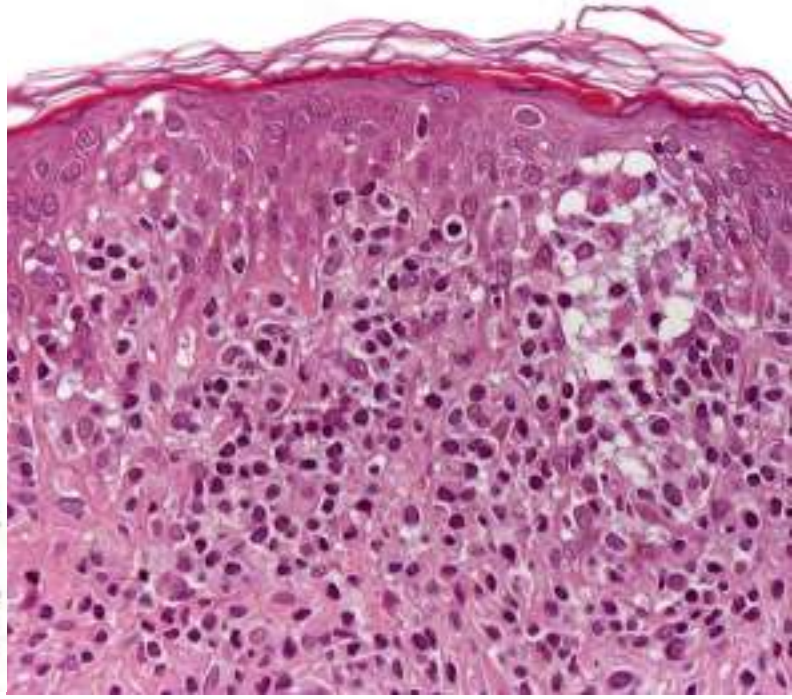
New biopsy



Vitiligo

Same CD8+ phenotype in the original and the new biopsy.
Absence of melanocytes in the hypopigmented area.





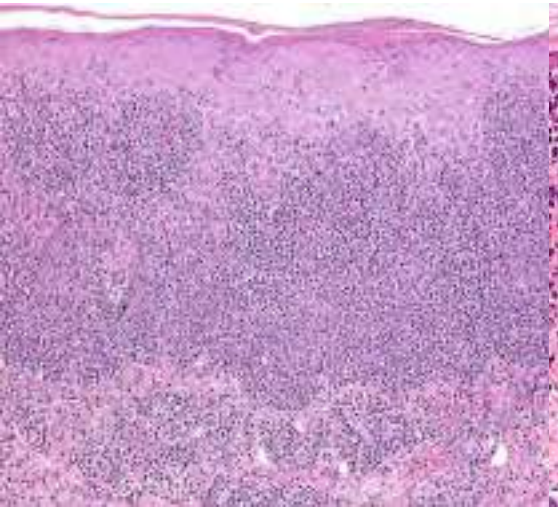
(consultation Dr. Riccioni, Cesena)

Vitiligo – Inflammatory stage

- Erythematous patches with evolving central depigmentation; borders not as sharply demarcated as in later stages; "inflammatory" borders may persist around central depigmentation
- Band-like infiltrate of lymphocytes; several epidermotropic lymphocytes
- Cytotoxic lymphocytes (CD8+) predominate (similar to cases of hypopigmented MF)
- A source of dermatopathological mistakes
  (my humble experience: 3 out of 3 (100%) "MF-like" cases missed...)

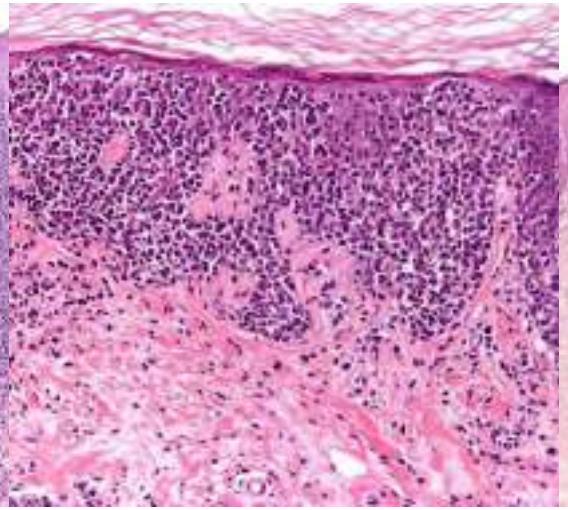
Prominent ("pagetoid") epidermotropism

Aggressive T-cell lymphomas



Aggressive epidermotr. CD8+ cytotoxic T-cell ly

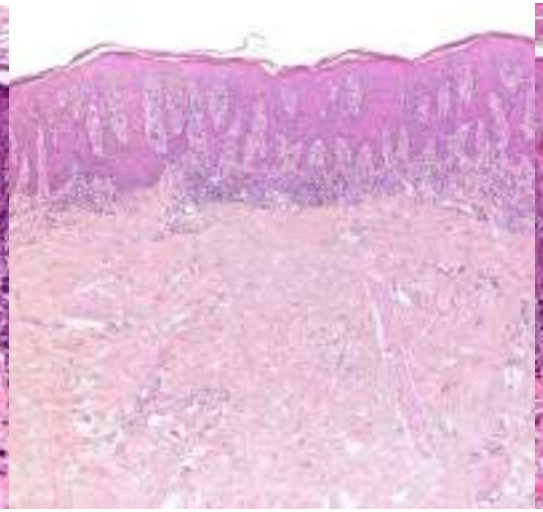
Generalized, partly ulcerated plaques and tumors. CD8+ by definition; CD30 usually negative (Ddx from LyP type D); TCRß+ / TCRγ/δ–.



Cutaneous γ/δ T-cell lymphoma

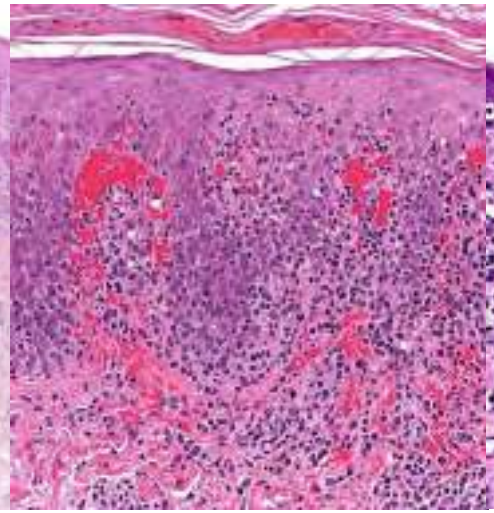
Generalized, partly ulcerated plaques and tumors. TCRγ/δ cytotoxic phenotype pre-requisite for diagnosis; TCRß may be coexpressed. Angiocentricity, concomitant subcutaneous involvement; Haemophagocytosis.

Indolent T-cell lymphomas



Mycosis fungoides

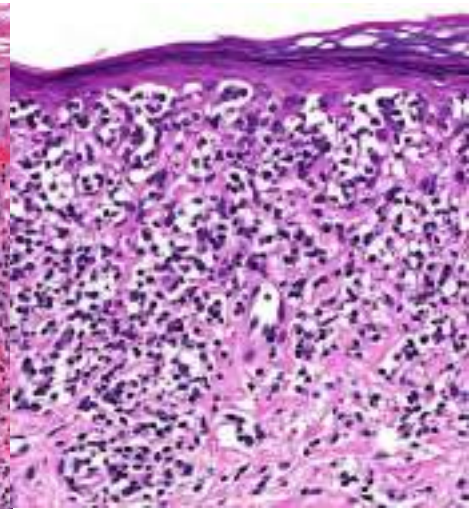
Conventional clinical presentation or features of solitary pagetoid reticulosis. Pagetoid epidermotropism mostly in cases with cytotoxic phenotype.



Lymphomatoid papulosis, type B or D

Waxing and waining papules and small nodules. Positivity for CD30 and CD4 (type B) or CD8 (type D) are a pre-requisite for the diagnosis; may be positive for TCRγ/δ .

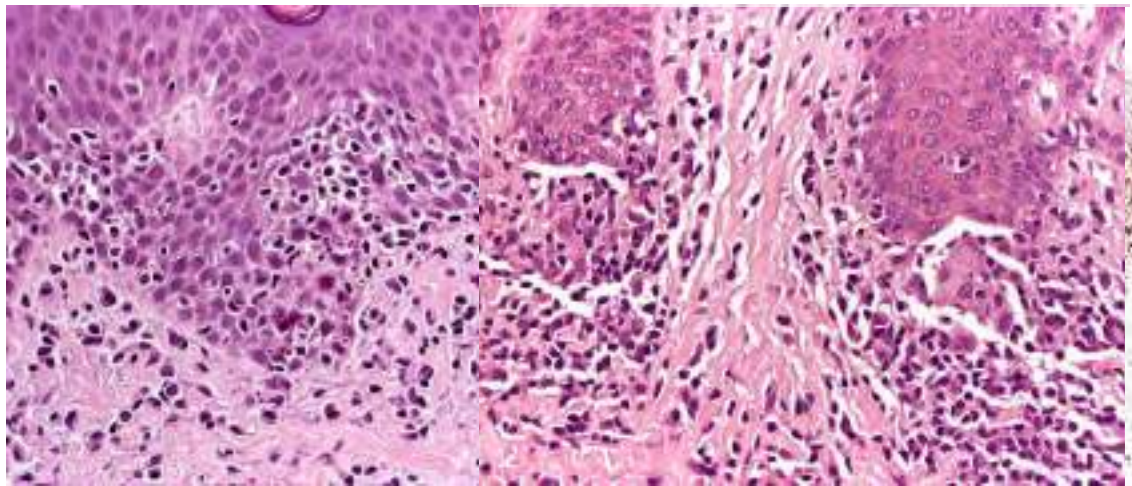
Pseudolymphomas

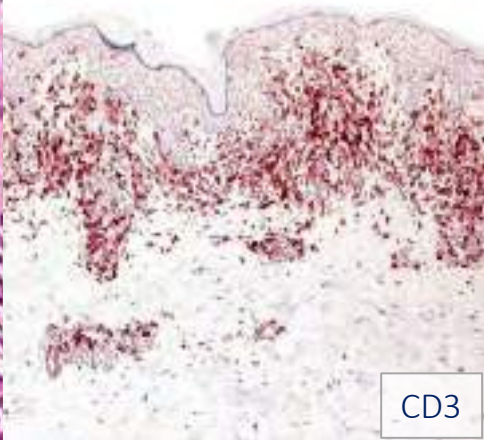


Exceedingly rare

Vitiligo.
Lymphomatoid contact dermatitis.
Lichen sclerosus.
Usually predominance of CD8+ T lymphocytes.

Annular lichenoid dermatitis of youth





Annular lichenoid dermatitis of youth

Giorgio Annessi, MD, Mauro Paradisi, MD, Corrado Angelo, MD,
Marie Perez, PhD, Pietro Puddu, MD, and Giampiero Girolomoni, MD
Rome, Italy

Background: Lichenoid dermatoses are composed of a wide spectrum of disorders with a common histopathologic interface pattern but diverse causes and pathophysiology.

Objective: We describe a series of young patients with a peculiar annular lichenoid dermatitis, the clinical appearance of which initially suggested diagnoses of morphea, mycosis fungoides, or annular erythema.

Results: The study involved 23 patients (median age 10 years; age range 5-22 years). Lesions consisted of persistent asymptomatic erythematous macules and round annular patches with a red-brownish border and central hypopigmentation, mostly distributed on the groin and flanks. Histology revealed a peculiar lichenoid dermatitis with massive necrosis/apoptosis of the keratinocytes limited to the tips of rete ridges, in the absence of dermal sclerosis and epidermotropism of atypical lymphocytes. The infiltrate was composed mainly of memory $CD4^+$ $CD30^-$ T cells with few B cells and macrophages. Analysis of T-cell receptor-γ-chain gene rearrangement in skin biopsy specimens revealed polyclonality in all the 15 cases studied. Topical and systemic corticosteroids or phototherapy were effective in most patients with relapse after treatment withdrawal.

Conclusions: We suggest that this is a distinctive inflammatory condition, and we propose to term it "annular lichenoid dermatitis of youth." (J Am Acad Dermatol 2003;49:1029-36.)

Lichenoid dermatoses are composed of a wide spectrum of disorders characterized histologically by vacuolar alteration and necrotic/apoptotic keratinocytes in the basal layer of the epidermis together with a bandlike lymphohistiocytic infiltrate obscuring the dermoepidermal junction. These histologic changes are associated with disparate clinical lesions, including erythematous macules, flat-topped violaceous papules, papulovesicles, and plaques that can be arranged in linear or, more rarely, annular pattern.[1]

During the last 6 years we have observed a series of young patients with peculiar skin changes consisting of persistent erythematous macules and annular patches mostly localized on the groin and flanks. In all cases the clinical picture was suggestive of inflammatory morphea, patch-/plaque-stage mycosis fungoides, or annular erythema. However, all 3 of these diagnoses were excluded histologically with a distinctive superficial lichenoid dermatitis with massive necrosis/apoptosis of the keratinocytes situated at the tips of rete ridges.

In this study we describe the clinical, histologic, immunohistochemical, and molecular characteristics of this condition, which we have termed "annular lichenoid dermatitis of youth" (ALDY), and discuss the differential diagnosis with morphea, patch-/plaque-stage mycosis fungoides, and annular erythemas.

PATIENTS AND METHODS

Patient selection

We reviewed the history, clinical photographs, and histologic slides of 23 cases of ALDY, which have been seen during the last 6 years at our institution.

Histology and immunohistochemistry

From 23 patients, 32 biopsy specimens were collected for histologic study. In each case 2 hematoxylin and eosin sections were prepared. In all, 2 biopsy specimens from lesions at different stages of evolution were acquired from 6 patients; in another 3 patients, skin samples were obtained from both initial lesions and lesions recurring after 6 to 12

From the Istituto Dermopatico dell'Immacolata, IRCCS.
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Conflicts of interest: None.
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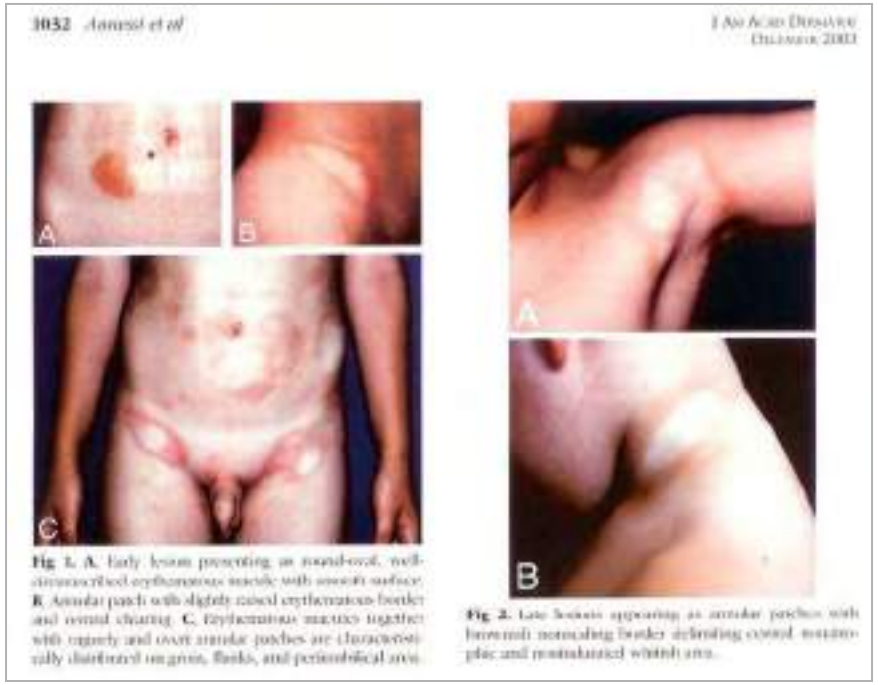
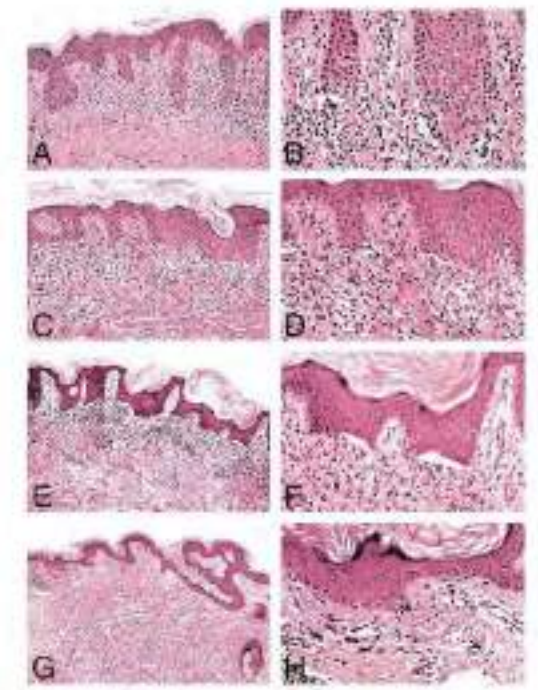
0190-9622/2003/$30.00 + 0
doi:10.1016/S0190-9622(03)02147-9





- Characteristic clinical presentation resembling morphea or MF
- Histopathologic features mimic MF; necrosis of keratinocytes at tip of rete ridges ("squaring" of rete ridges) typical of ALDY
- Polyclonal pattern of TCR genes rearrangement
- Benign behaviour (yet few cases described, relatively short follow-up)
- Long-term follow-up advisable

Annular Lichenoid Dermatitis of Youth ... and Beyond: A Series of 6 Cases

Two young girls
Four adult males

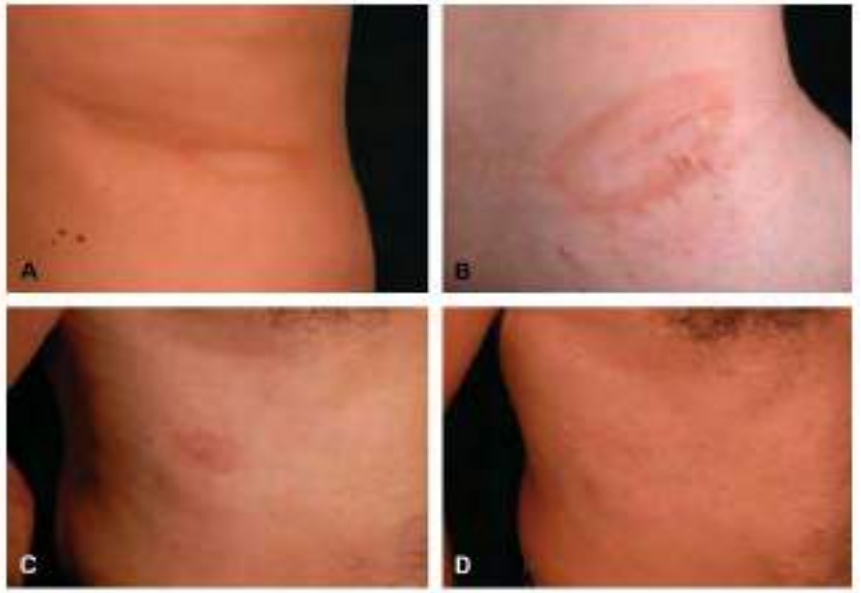


FIGURE 1. Clinical presentation in case 6 (A), case 1 (B), and case 5 (C). D, Complete resolution in patient 5 at the 24-month follow-up.

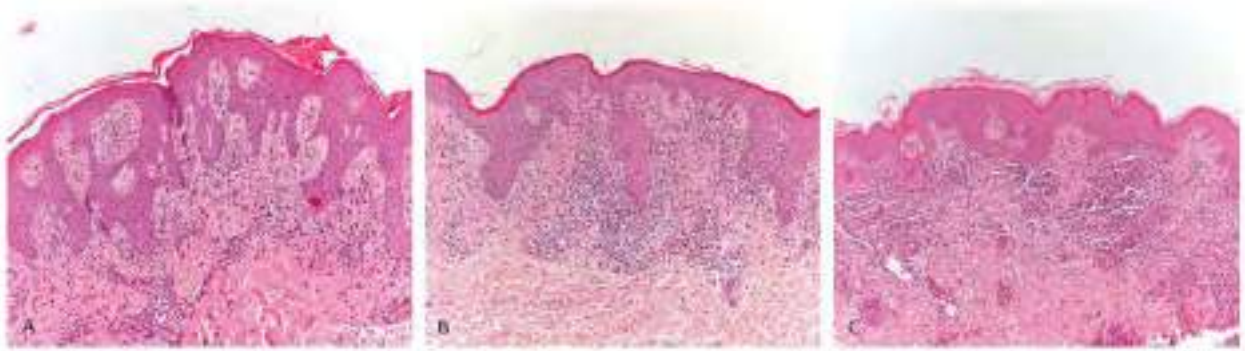
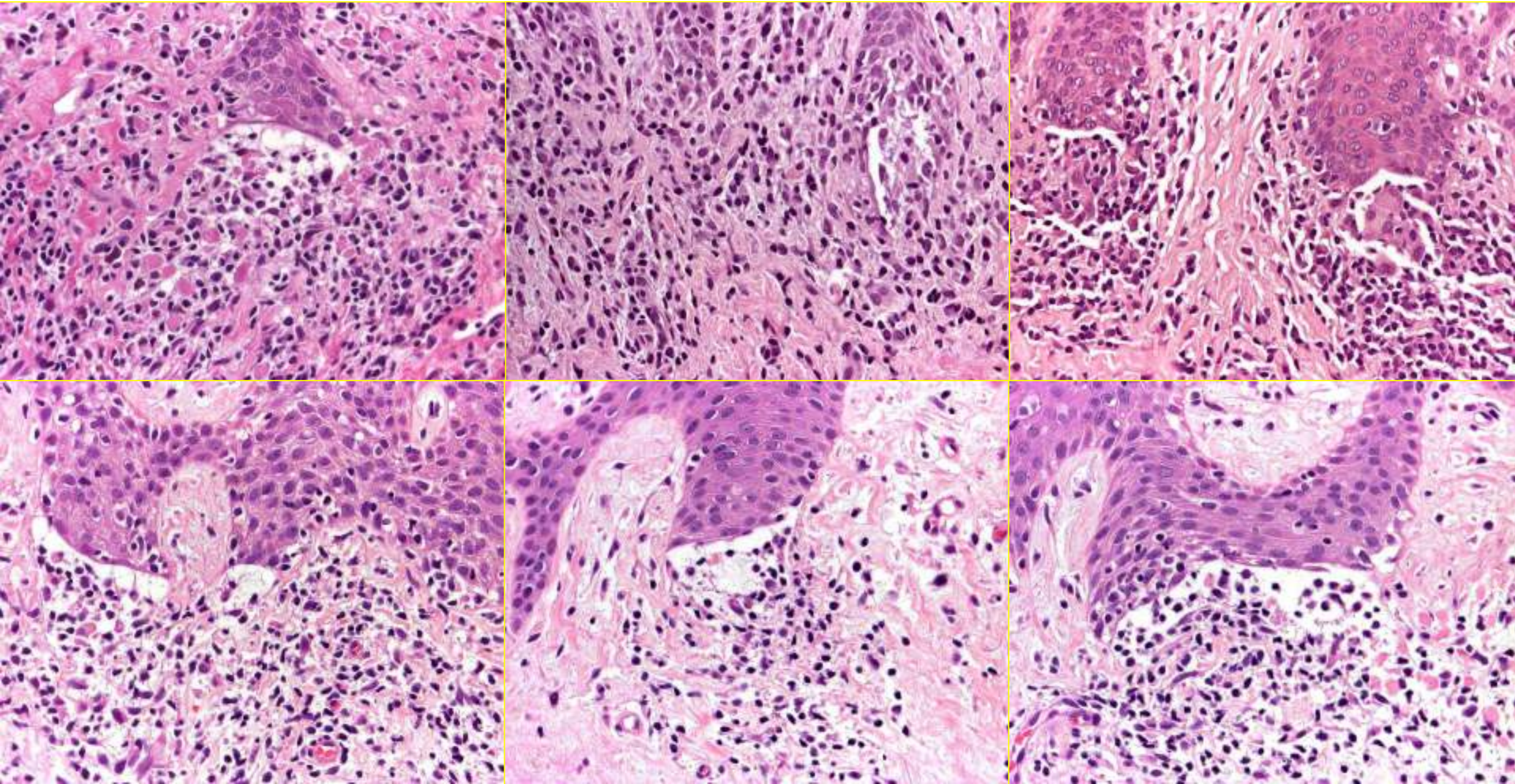


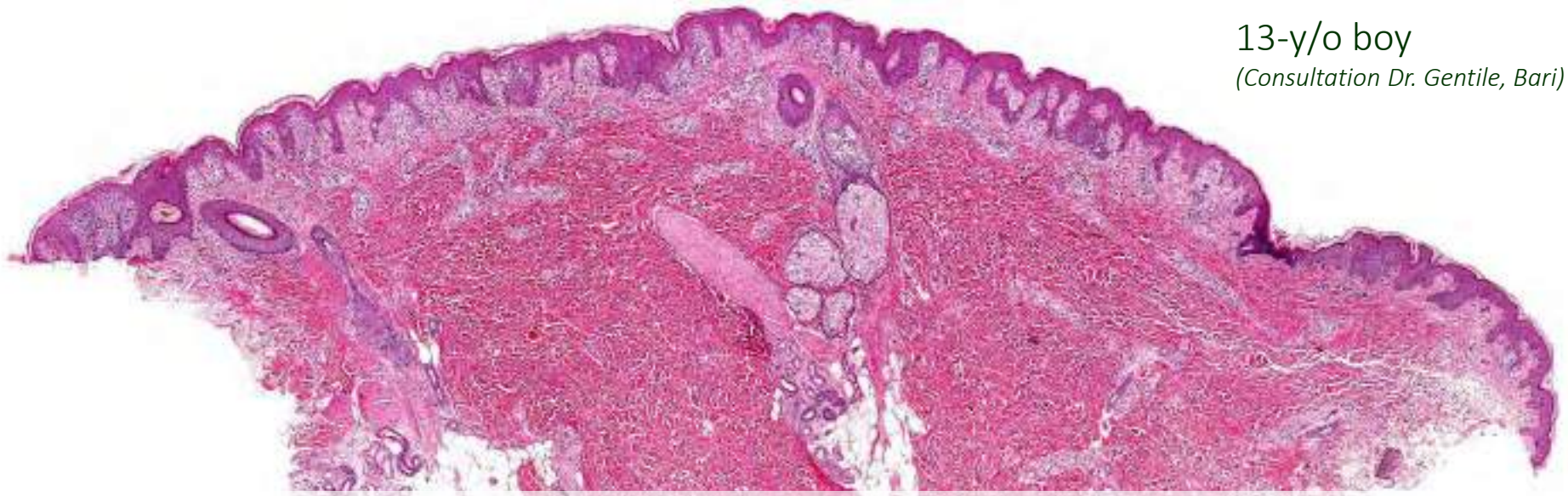
FIGURE 2. Lichenoid lymphocytic infiltrate with basal vacuolization in case 3 (A), case 5 (B), and case 1 (C) (hematoxylin and eosin, ×100).

Clue: "squaring" of tip of rete ridges by lymphoid infiltrate

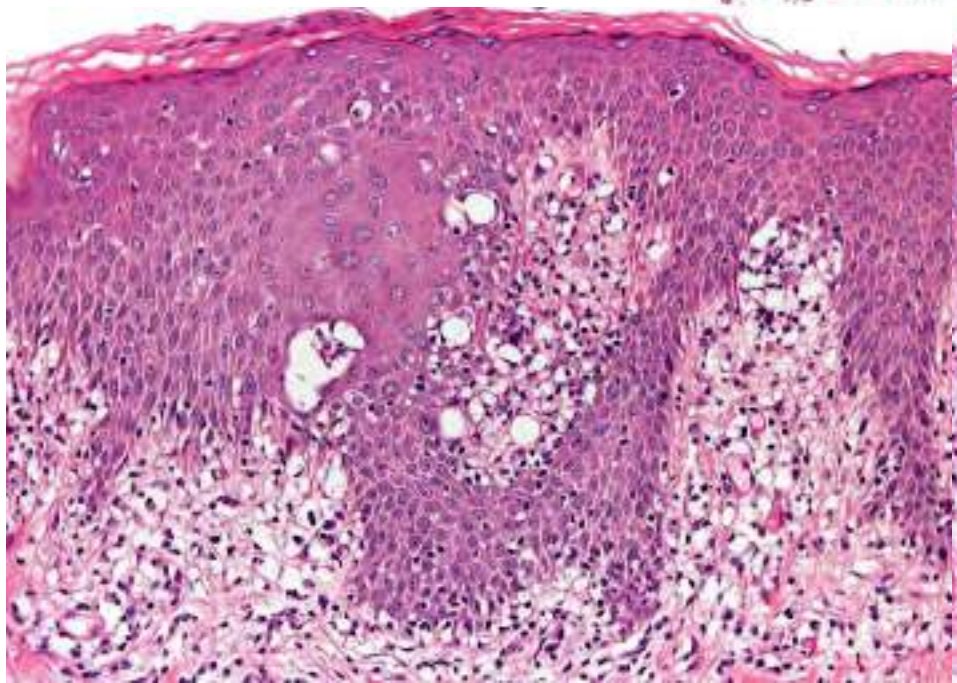


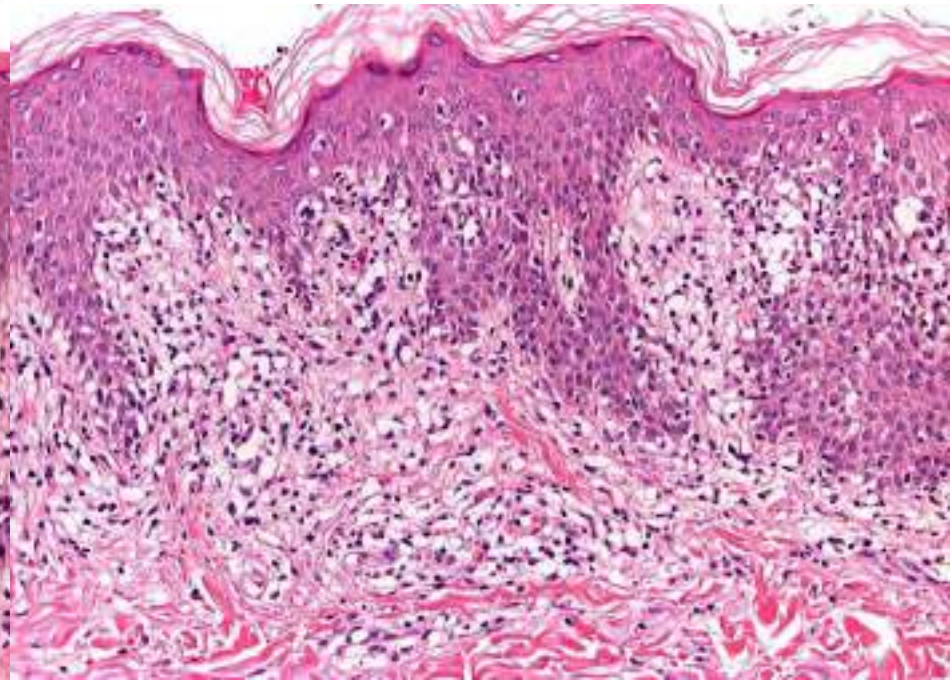
13-y/o boy

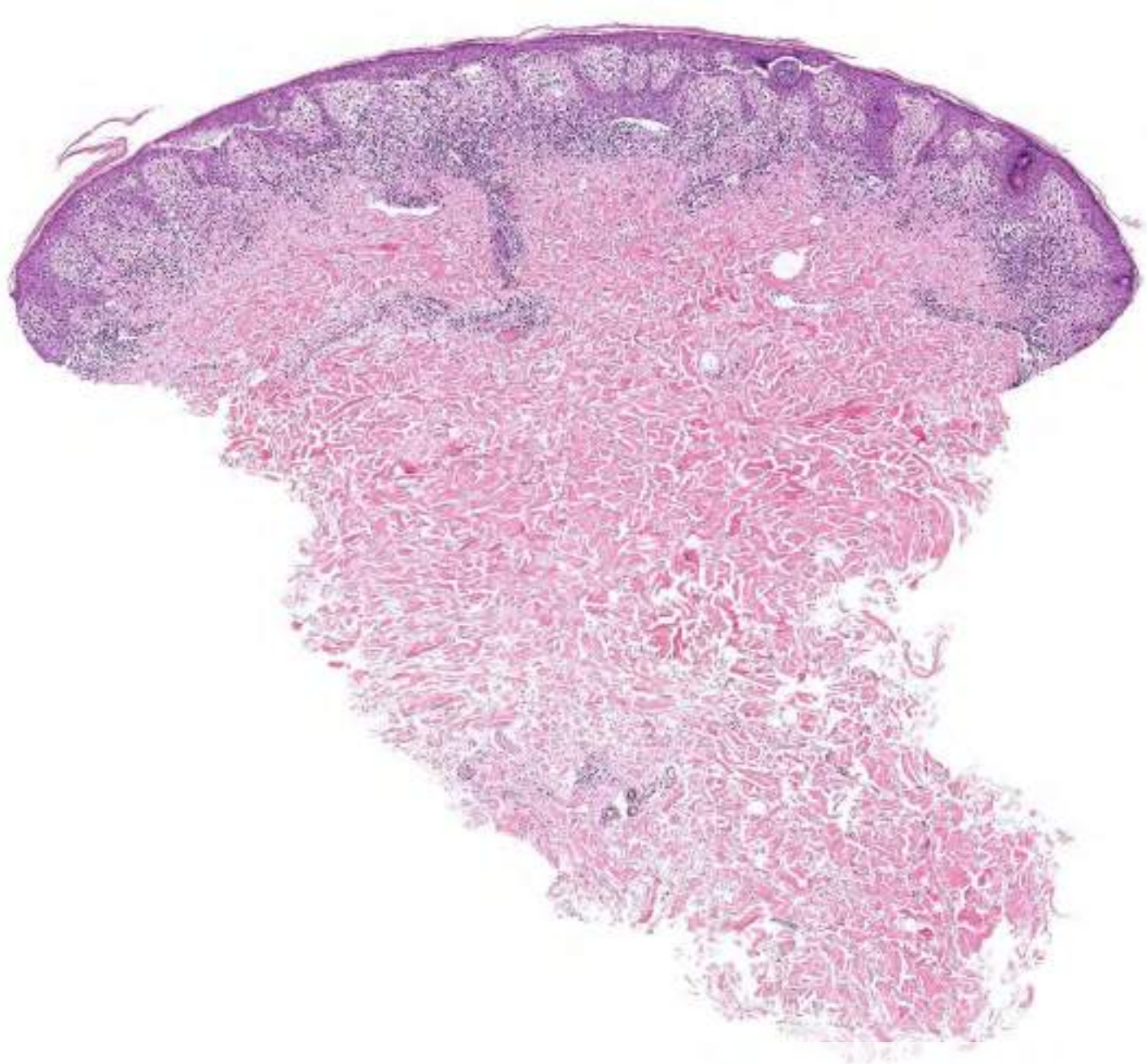
(Consultation Dr. Gentile, Bari)

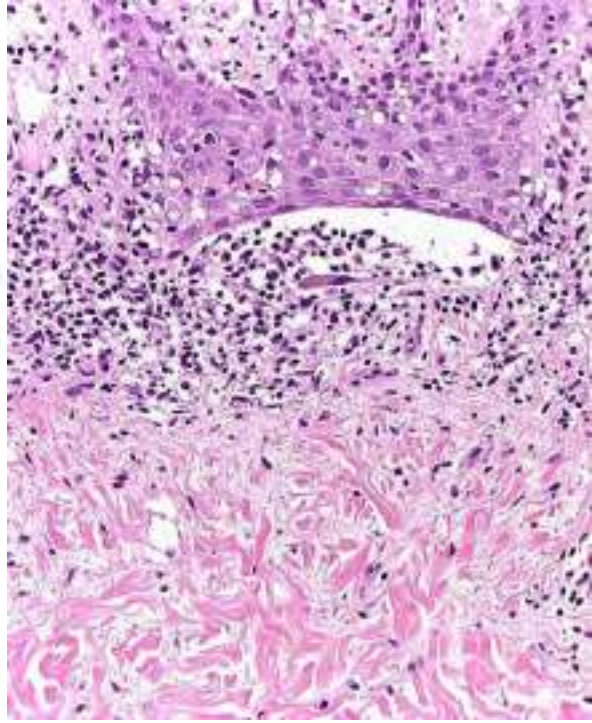


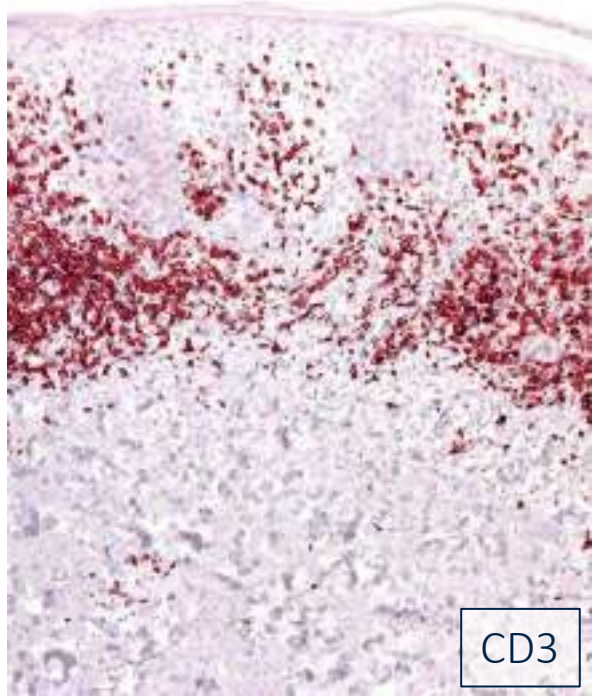
Clinically ALDY-like hypopigmented MF





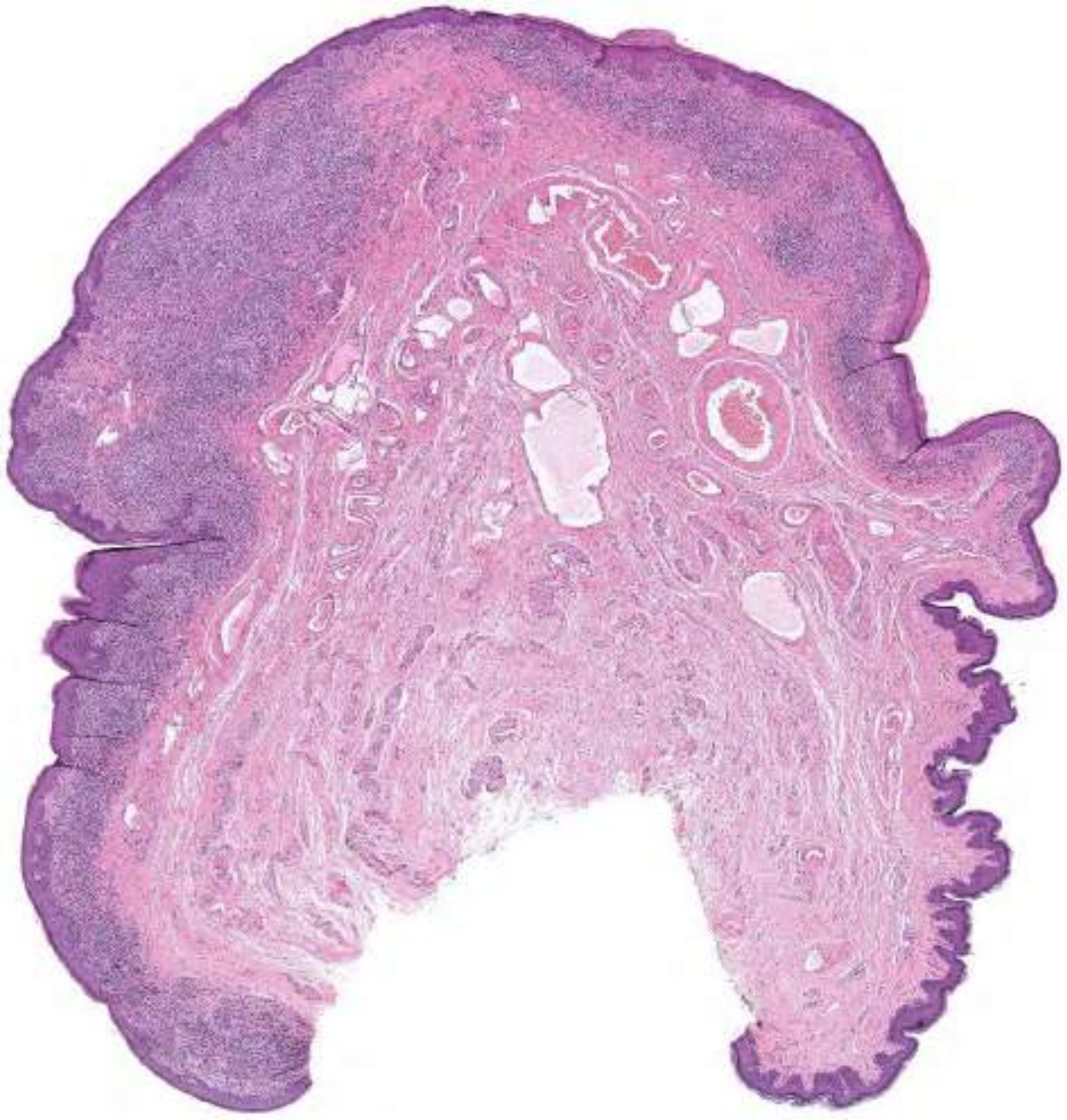


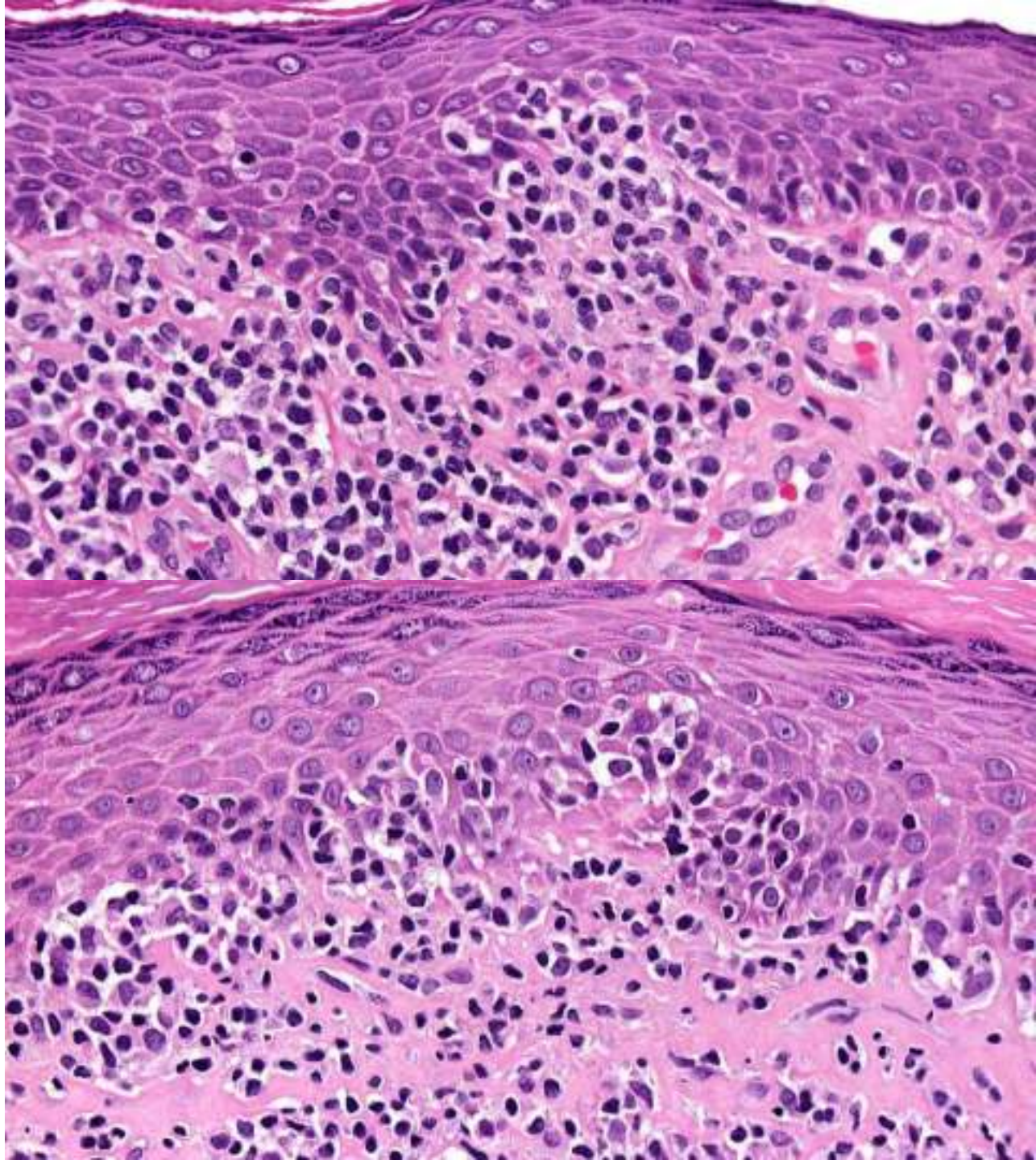


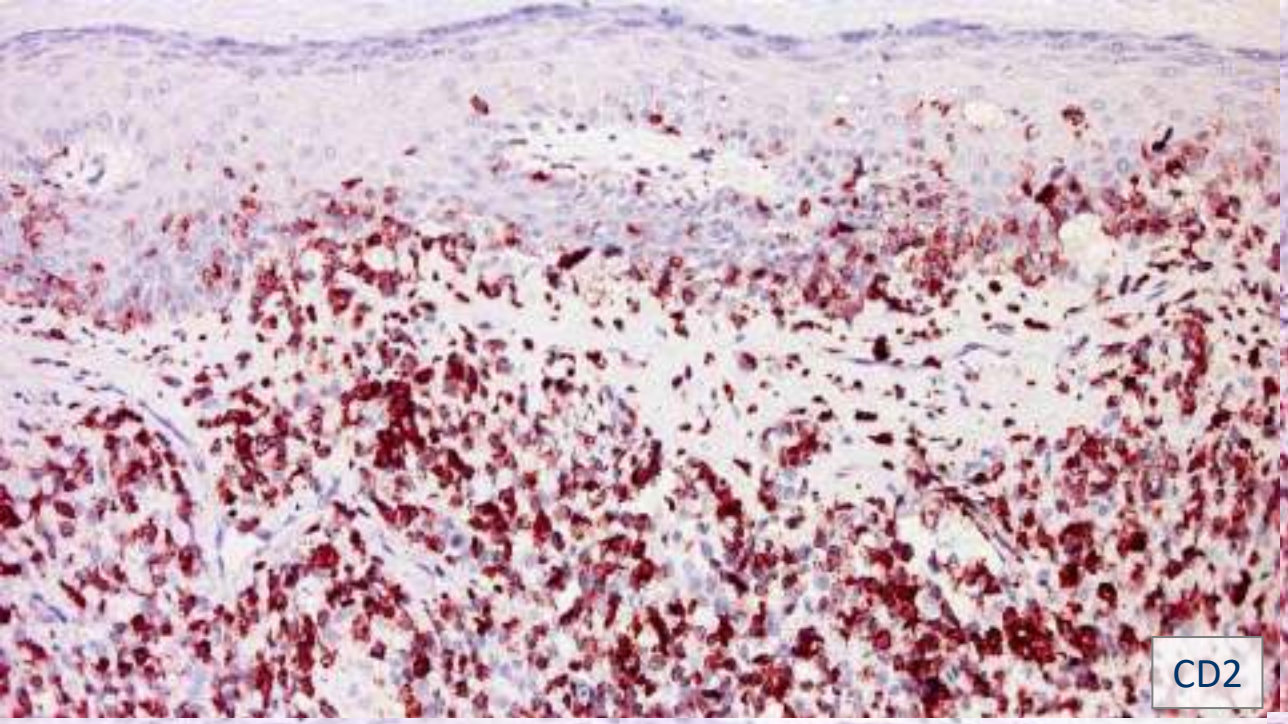


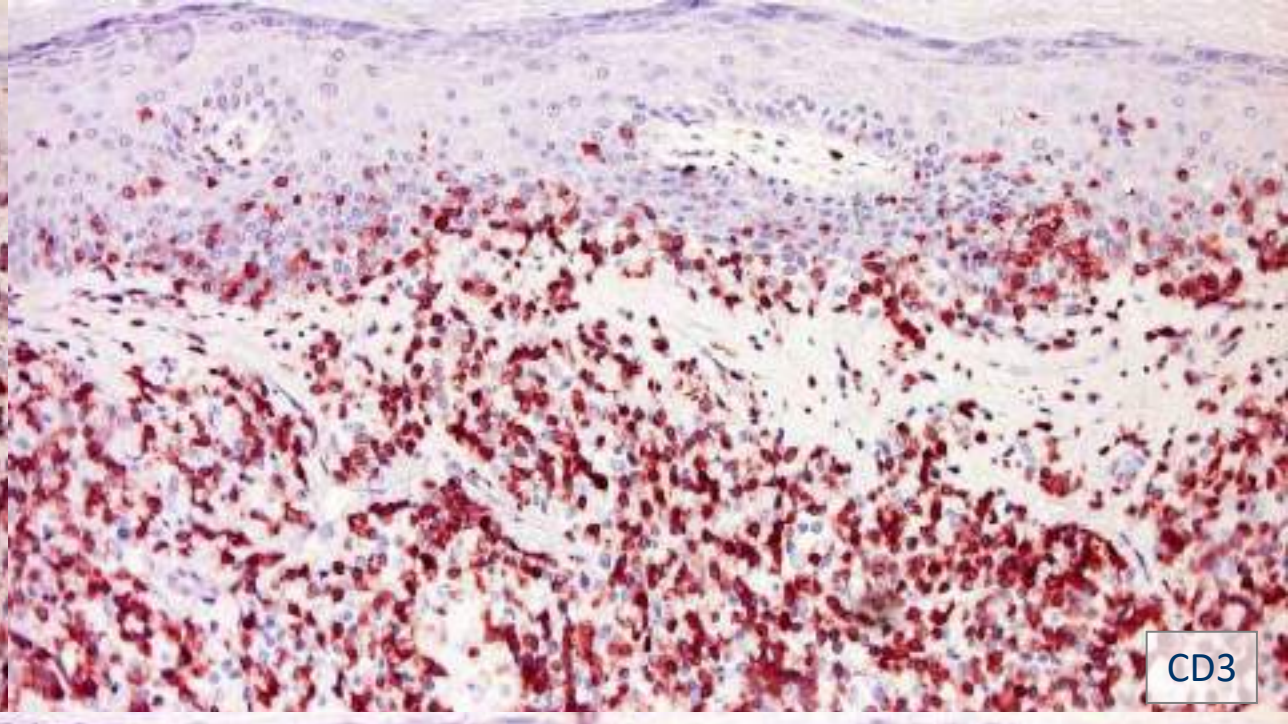
Histopathologically ALDY-like MF

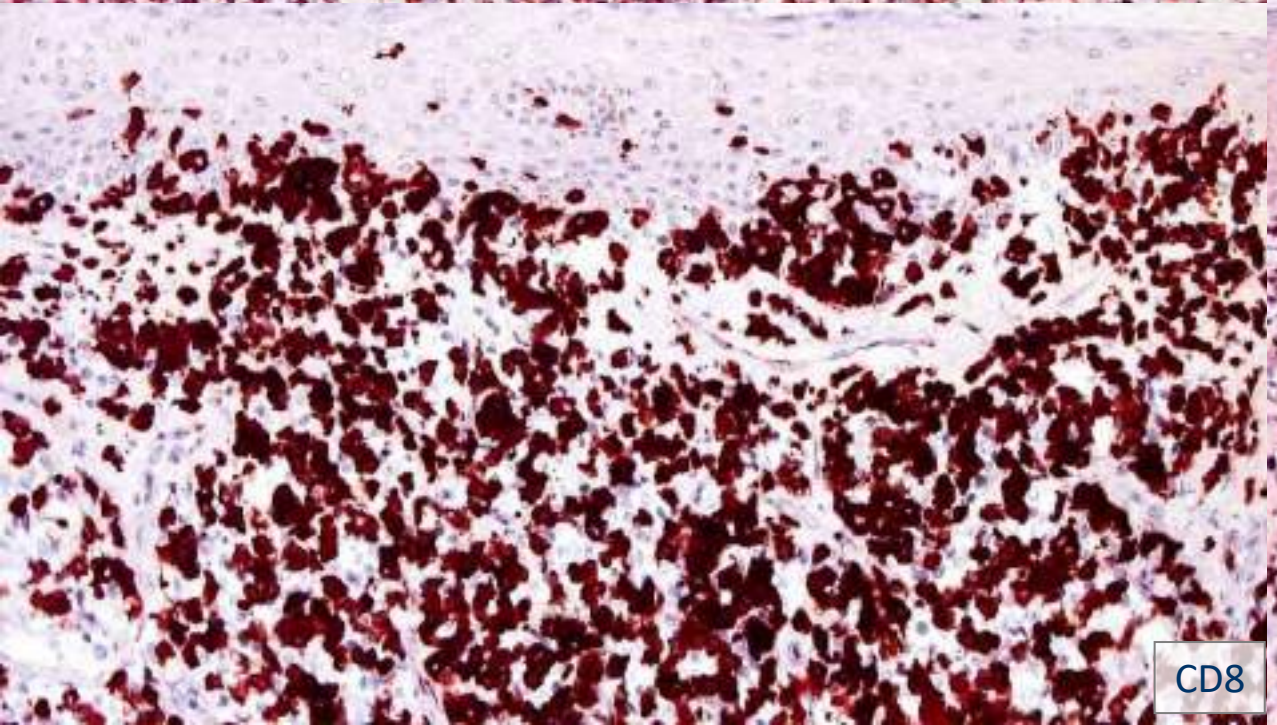
8-year-old boy with phymosis.

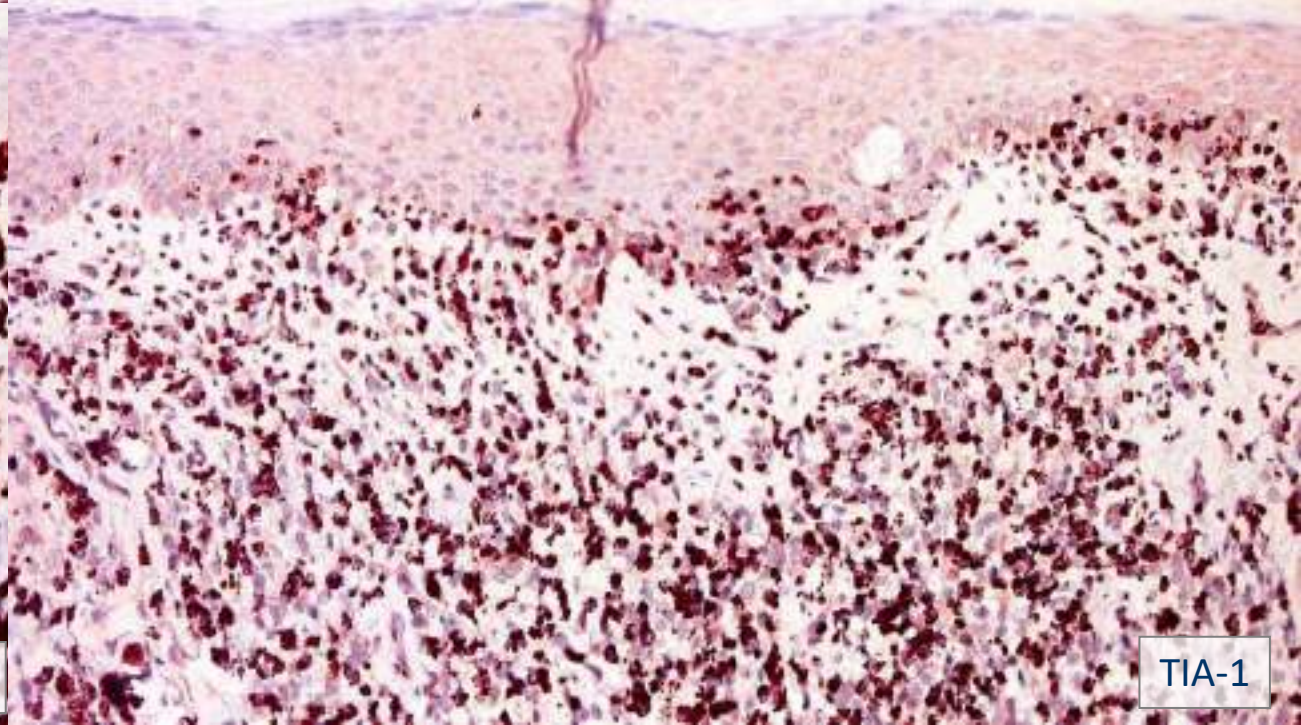





CD2


CD3


CD8


TIA-1

Lichen sclerosus, inflammatory stage

- Pseudolymphomatous features are observed almost exclusively in genital LSA
- Most frequent presentation is phymosis in male children
- Band-like infiltrate of T-lymphocytes with variable numbers of epidermotropic 'haloed' cells; CD8+
- Conventional histopathological features of LSA are often missing or present only focally; clinicopathologic correlation crucial

Lichen Sclerosus with Histopathologic Features Simulating Early Mycosis Fungoides

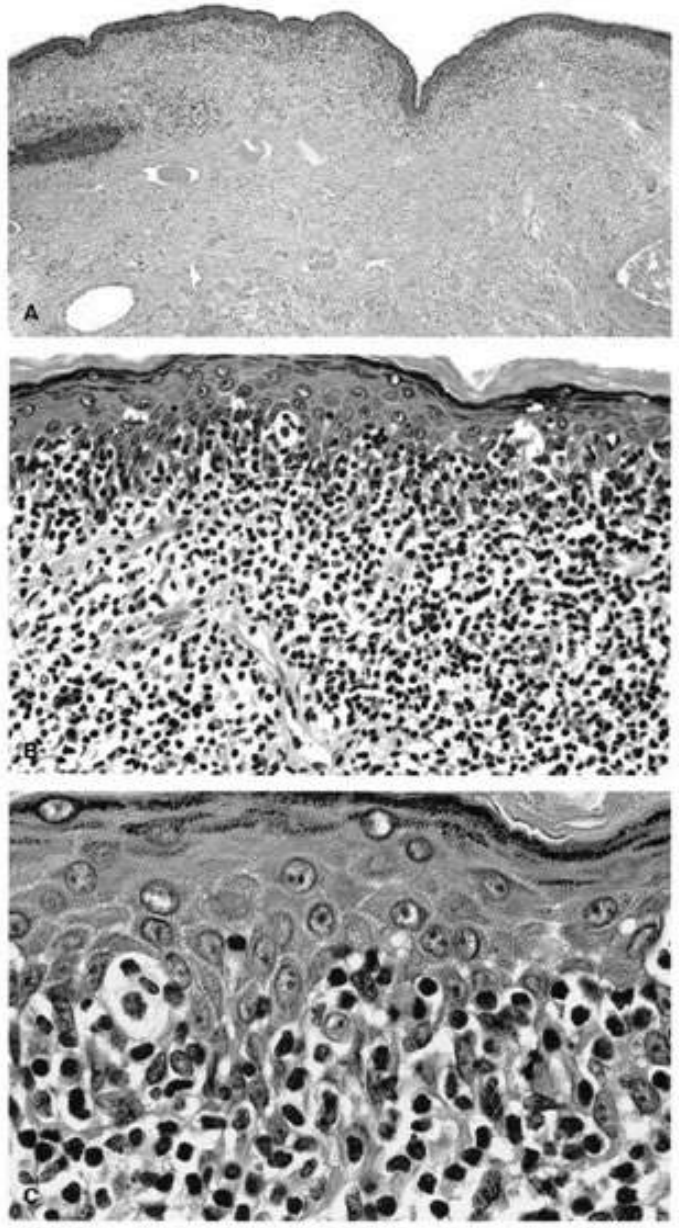


FIGURE 1. A, Dense band-like infiltrate in the superficial dermis. B, The infiltrate obscures the dermo-epidermal junction and involves the epidermis. C, Note intraepidermal lymphocytes with "haloed" nuclei resembling epidermotropic lymphocytes in MF.

ORIGINAL ARTICLE

Lichen Sclerosus et Atrophicus With Histopathologic Features Mimicking Mycosis Fungoides

A Large Series of Cases Comparing Genital With Extragenital Lichen Sclerosus

Eleonora Leoni, MD, Werner Kempf, MD,†‡ and Lorenzo Cerroni, MD§*

Abstract: Lichen sclerosus et atrophicus (LSA) is a chronic inflammatory dermatosis of unknown etiology involving the genital and/or extragenital area, showing histopathologically a characteristic homogenization and sclerosis of the superficial collagen with variably dense lymphoid infiltrates. Intraepidermal lymphocytes may be observed, and in some cases may pose differential diagnostic problem with mycosis fungoides (MF). We studied the histopathologic features of 121 cases of LSA with dense lymphoid infiltrates (genital: 94; male:female: 93:1; age range: 2 to 87 y; median age: 11 y; extragenital: 27; male:female: 0.1:1; age range: 11 to 79 y; median age: 59 y), to better characterize the intraepidermal lymphoid infiltrate and to compare genital with extragenital cases. Epidermotropic lymphocytes mimicking the histopathologic features of MF were present in 93.6% of the genital specimens but none of the extragenital cases. Interestingly, typical features of LSA were missing in 39.4% of genital LSA, and in a further 25.5% were present only focally. Immunohistochemical analyses showed a predominance of $CD8^+$ T-lymphocytes within the epidermis. Molecular studies of the T-cell receptor genes revealed a monoclonal population of T-lymphocytes in nearly half of the cases. Our study shows that MF-like histopathologic features are extremely common in genital LSA but are never encountered in extragenital cases. A diagnosis of MF in the genital area should be made only upon compelling features, keeping in mind the frequent pseudolymphomatous aspects of LSA.

Key Words: lichen sclerosus, mycosis fungoides, cutaneous T-cell pseudolymphoma, cutaneous T-cell lymphoma, cutaneous pseudolymphoma, extragenital lichen sclerosus

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Lichen sclerosus et atrophicus (LSA) is a chronic inflammatory dermatosis of unknown etiology involving the genital mucosa or the extragenital skin. The typical histopathologic findings are characterized by atrophic epidermis with orthohyperkeratosis overlying a papillary dermis showing homogenized, sclerotic collagen, and a variably dense lymphocytic infiltrate. In typical cases, the histopathologic diagnosis of LSA is not problematic; some cases, however, may lack typical features being characterized instead by a dense lymphocytic infiltrate with prominent exocytosis of lymphocytes within the epidermis, thus mimicking mycosis fungoides (MF).[1–3]

We studied the clinicopathologic features of LSA with particular emphasis on histopathologic features mimicking MF, and with comparison of genital with extragenital cases.

PATIENTS AND METHODS

One hundred twenty-one patients (male:female = 3.8:1; age range: 2 to 87 y; mean age: 30.6 y; median age: 15 y) presenting with LSA have been included in our study. Ninety-four cases were from the anogenital area (male:female = 93:1; age range: 2 to 87 y; median age: 11 y), and 27 from the extragenital area (male:female = 0.1:1; age range: 11 to 79 y; median age: 59 y). The cases were collected at the Department of Dermatology of the Medical University of Graz and at the Kempf und Pfaltz Histologische Diagnostik, Zurich, Switzerland. Variably dense lymphoid infiltrates were present in all cases (cases devoid of lymphoid infiltrates were excluded). Partial data on 9 cases had been published previously.[3] The study has been approved by the ethical committee of the Medical University of Graz.

A total of 123 formalin-fixed, paraffin-embedded biopsy specimens were available for histopathologic analysis. Following histopathologic features were evaluated: presence of typical aspects of LSA; presence of epidermotropic lymphocytes (pseudo-MF aspects); presence of pronounced hemorrhage (pseudovascular aspects); presence of associated morphea; presence of granulomatous phlebitis; presence of germinal centers; presence of perineural inflammatory infiltrates.

In 69 cases (27 from the extragenital, 42 from the genital area), immunohistochemical analyses were performed with a standard immunoperoxidase technique using

121 cases of LSA with dense lymphoid infiltrates (genital: 94; M:F: 93:1; age range: 2-87; median age: 11; extragenital: 27; M:F: 0.1:1; age range: 11-79; median age: 59).

Epidermotropic lymphocytes mimicking the histopathological features of MF were present in 93.6% of the genital specimens but none of the extragenital cases.

Interestingly, typical features of LSA were missing in 39.4% of genital LSA, and in a further 25.5% were present only focally.

In genital "pseudo-MF" cases, immunohistochemical analyses showed a predominance of CD8+ T lymphocytes within the epidermis. Molecular studies of the T-cell receptor genes revealed a monoclonal population of T lymphocytes in nearly half of the cases.

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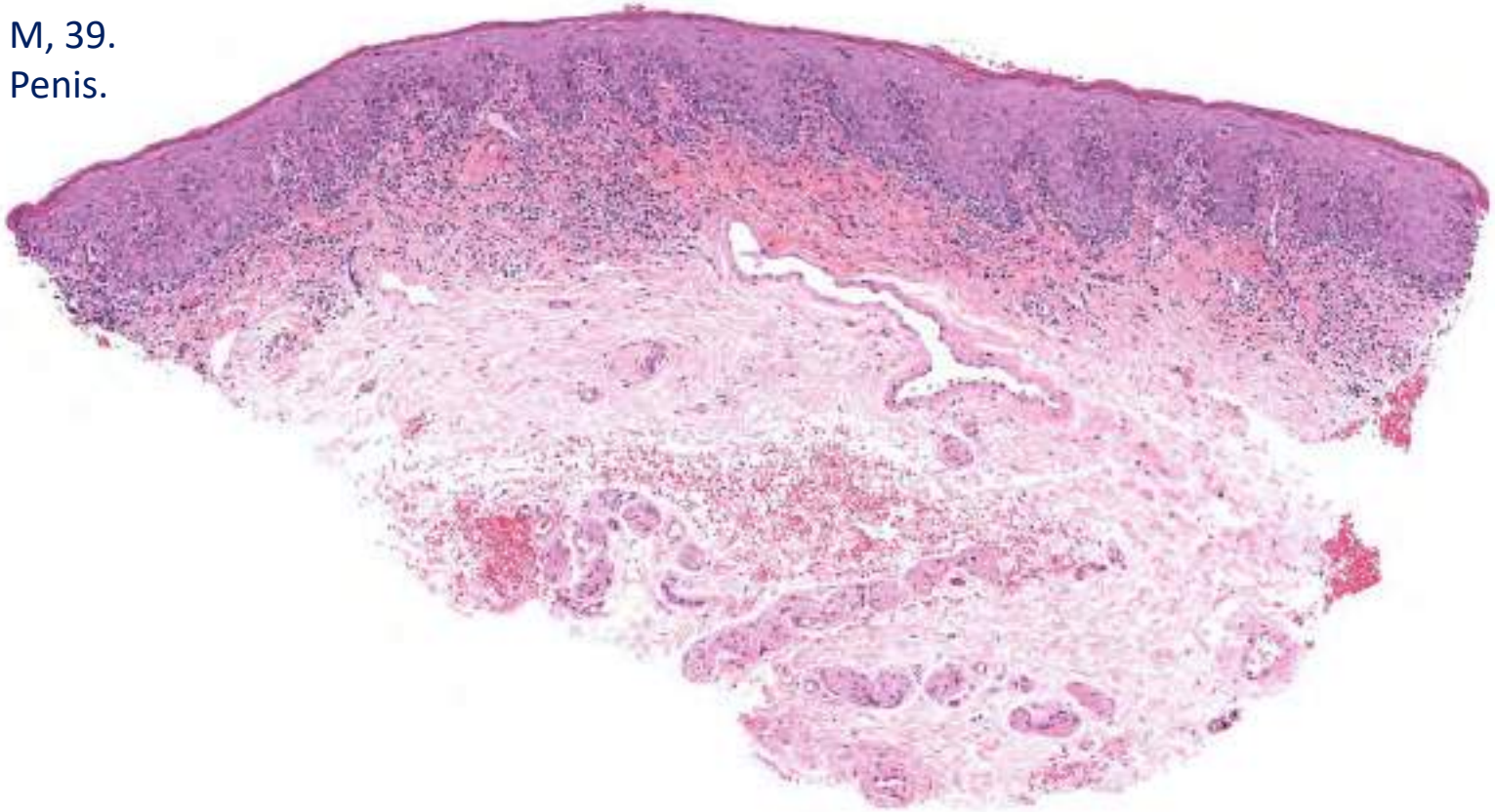
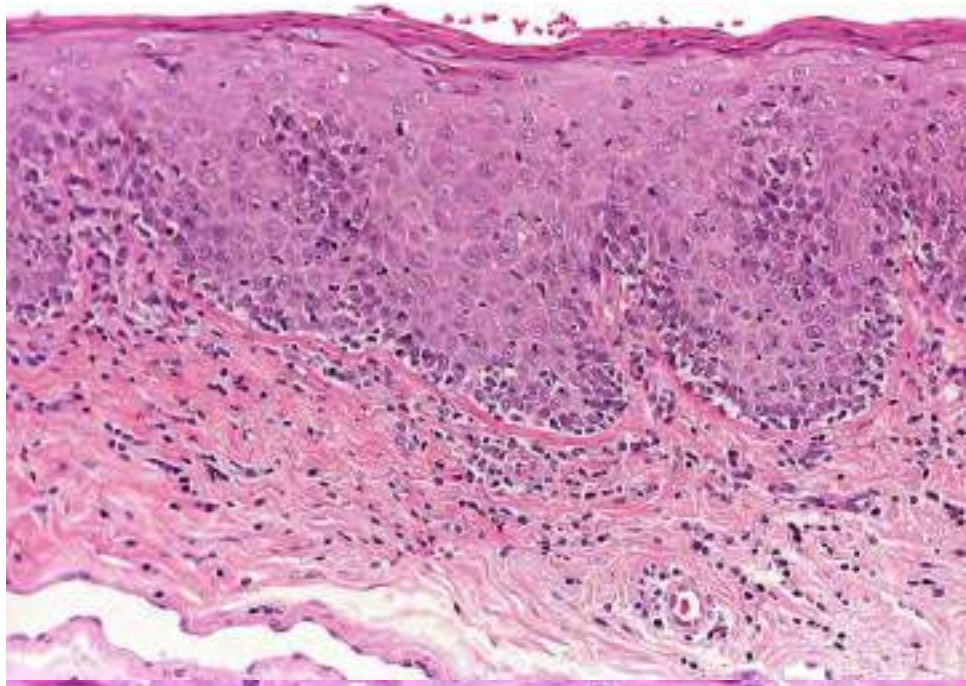
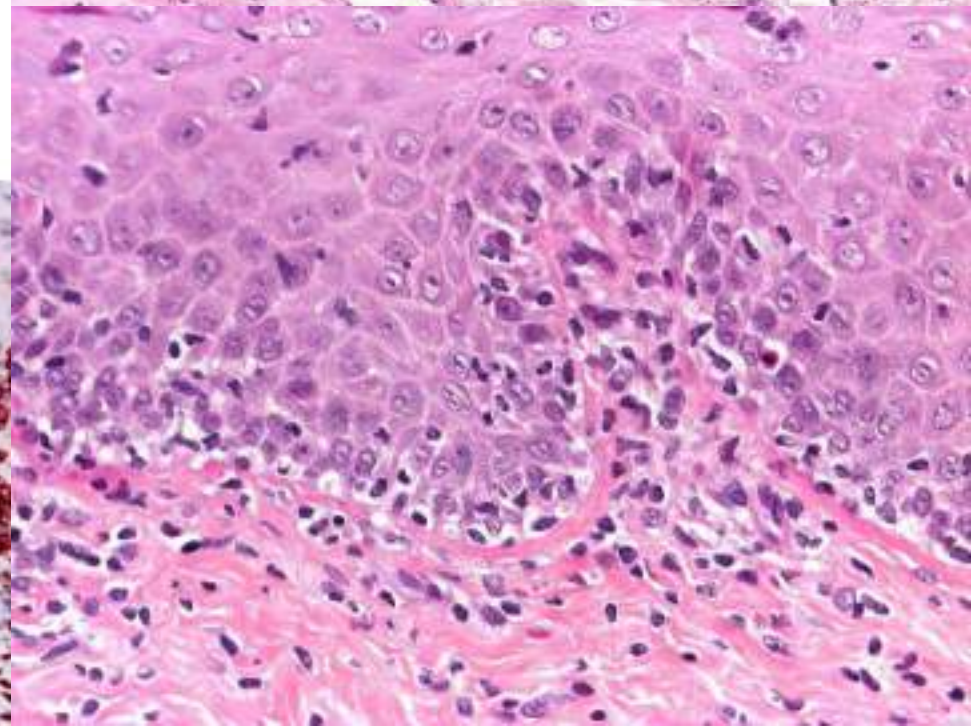
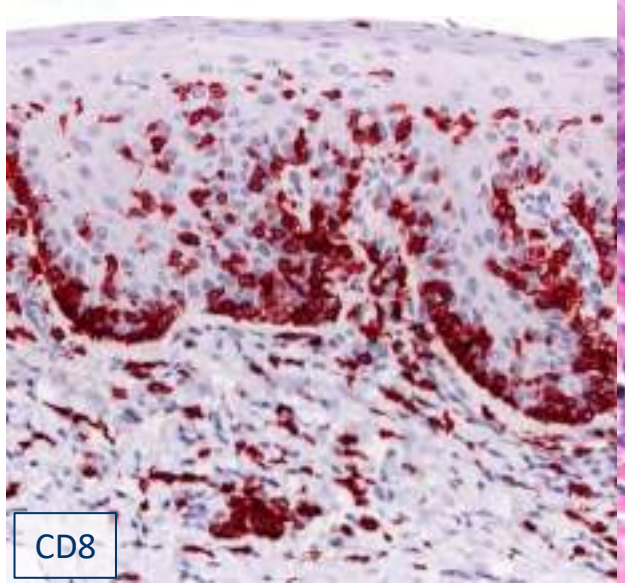


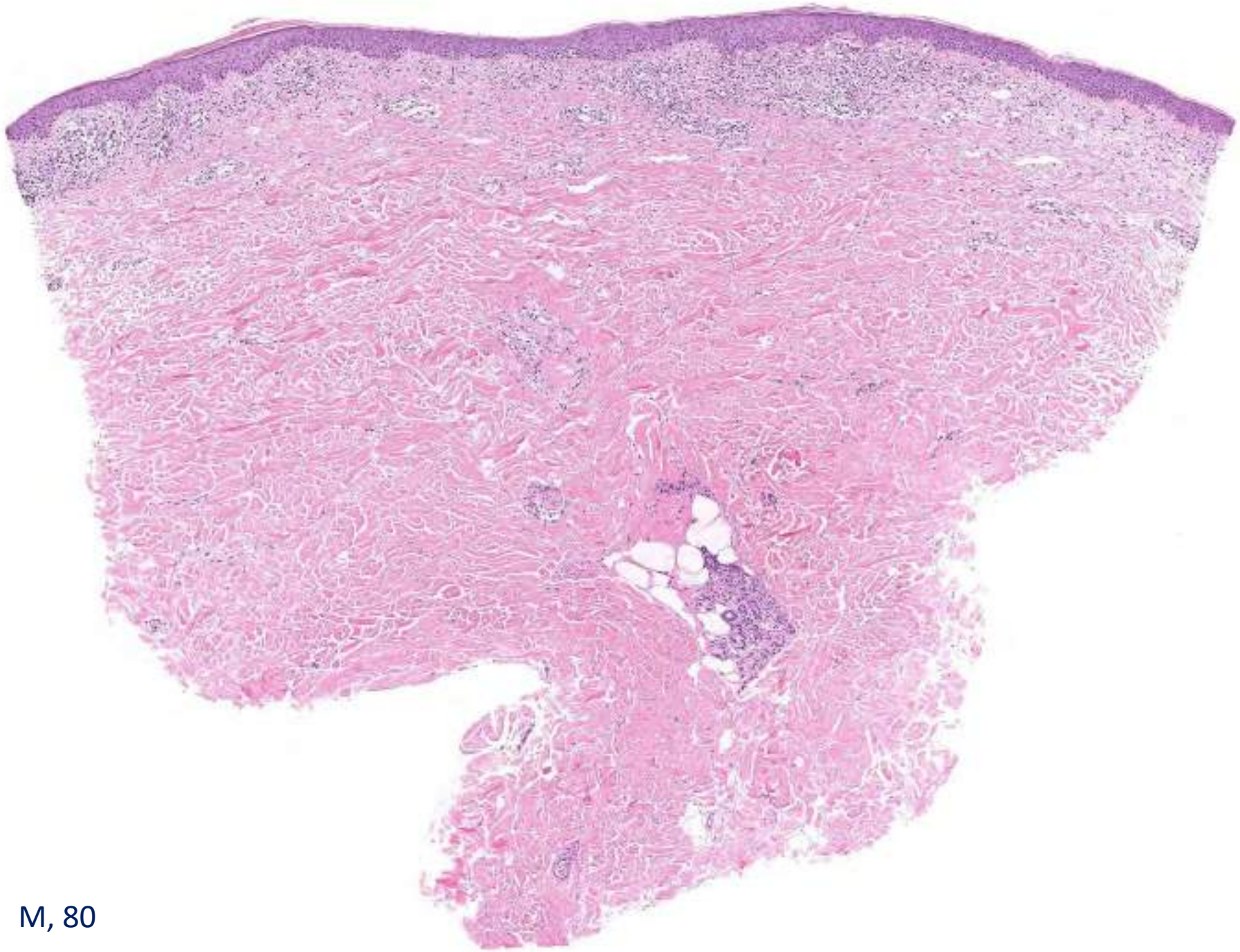






Pseudo-MF features on genital skin

- MF-like histopathological features are very common in genital lichen sclerosus and may be observed rarely also in balanitis / balanoposthitis / vulvitis
- In all such conditions presence of intraepidermal (epidermotropic) lymphocytes, usually with cytotoxic phenotype (CD8+)
- The genital area may be a special site for MF-like cytotoxic T-cell infiltrates
- A diagnosis of MF on genital skin should be made only upon compelling evidence



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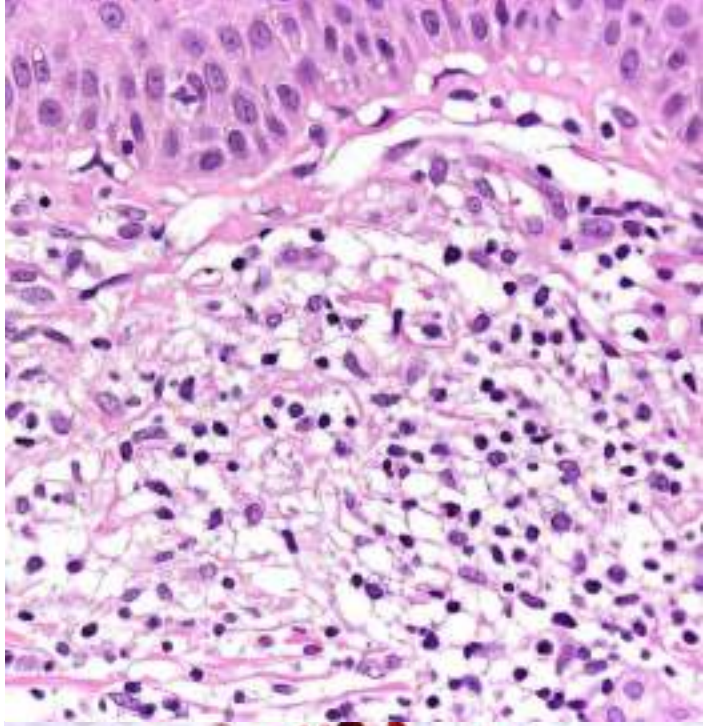

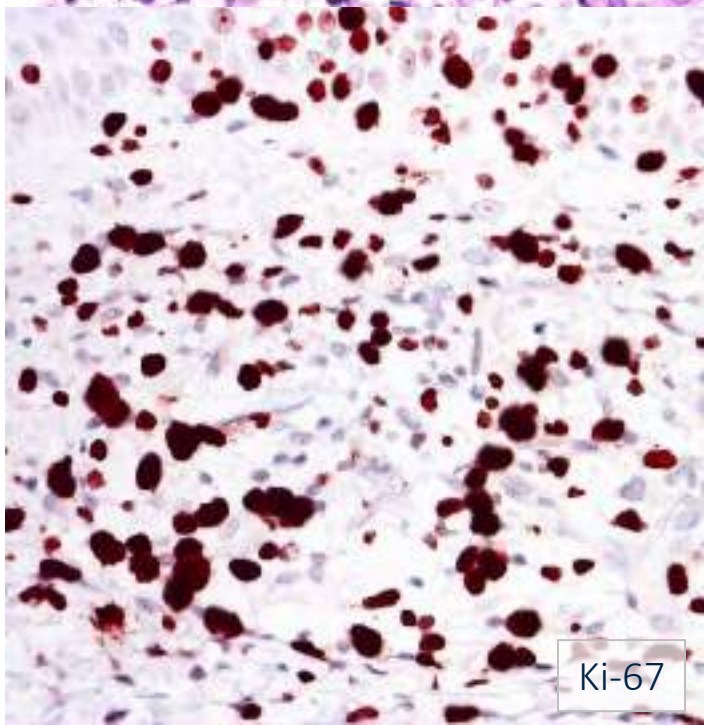

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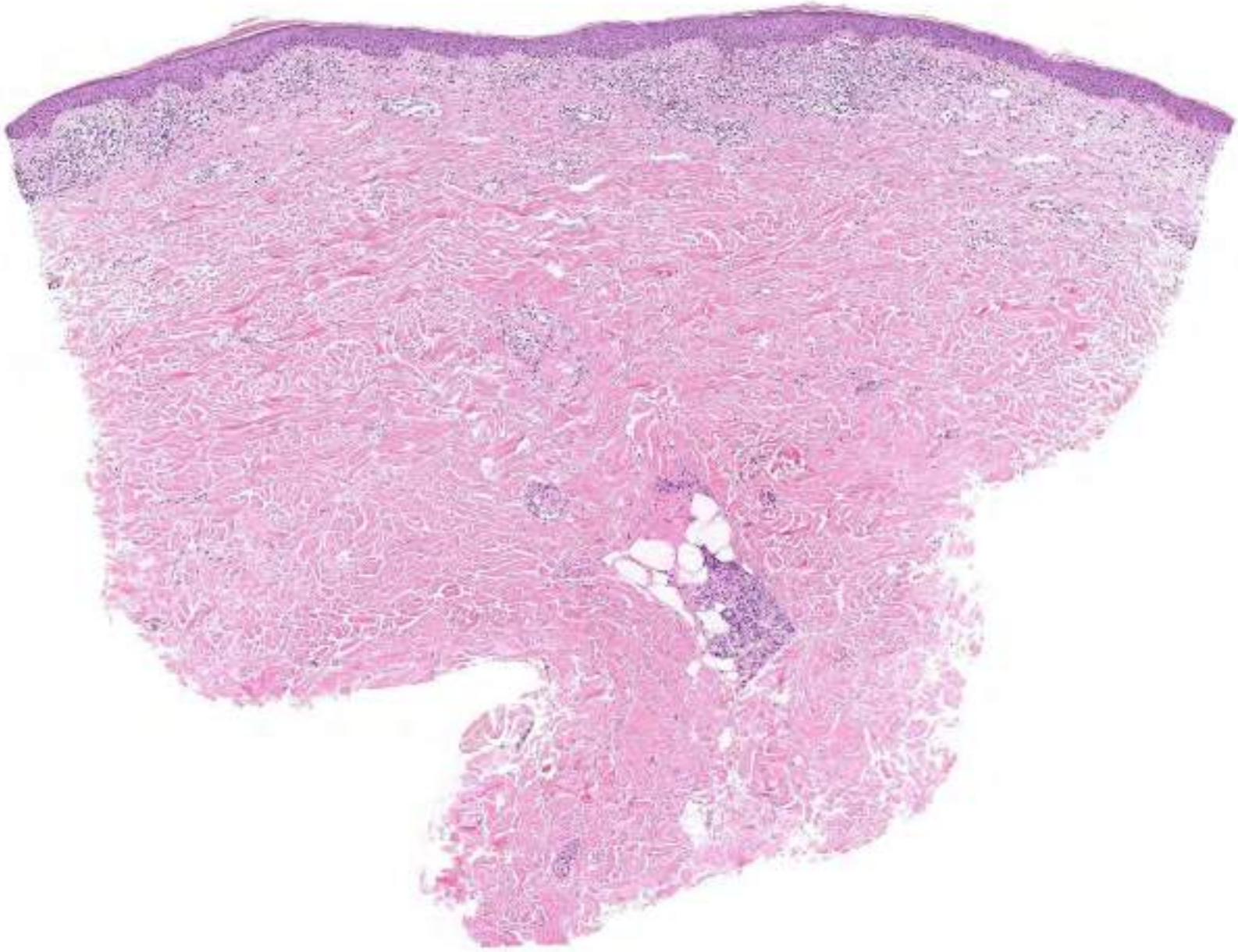
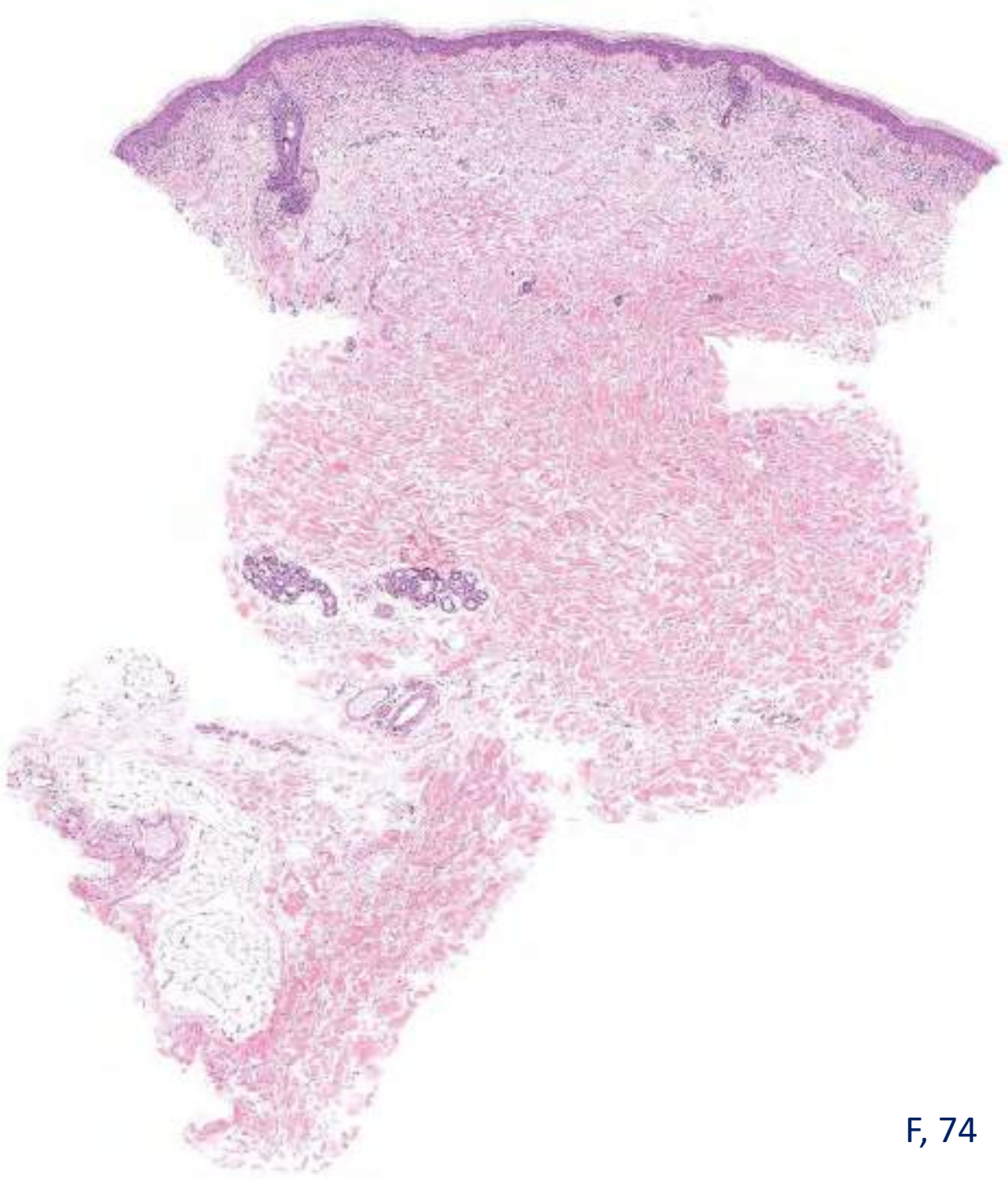


Lymphomatoid drug eruption



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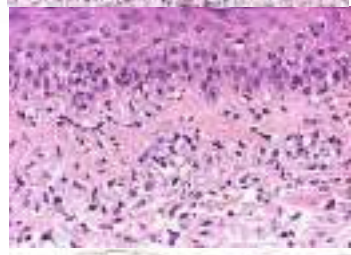

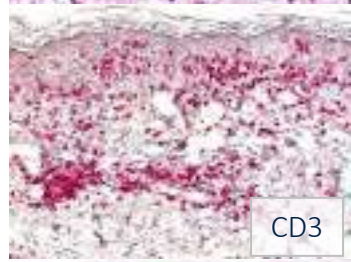

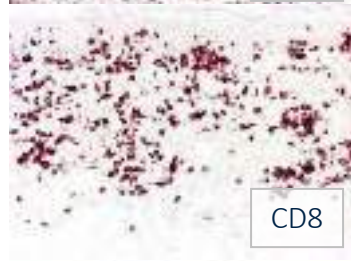

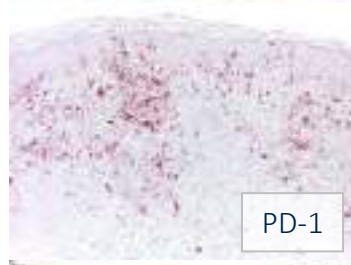

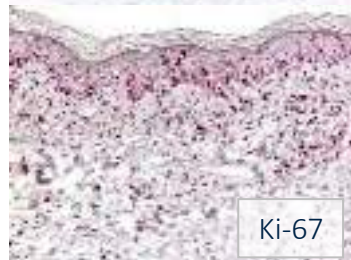

Lymphomatoid drug eruption (T-cell pattern)

- Drug eruptions may occasionally mimic histopathologically a cutaneous T-cell lymphoma (MF-like or lymphomatoid papulosis-like)
- Sudden onset, generalized distribution; Resolution upon discontinuation of the offending drug
- Cases with T-cell pattern show band-like lymphoid infilrates with several activated cells and often with high proliferation (>90%); Epidermotropism usually minimal but atypia may be striking
- Cases with CD30+ activated lymphocytes usually characterized by mostly perivascular rather than interstitial CD30+ cells

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Review article

Drug induced pseudolymphoma

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ABSTRACT

Atypical lymphocytic infiltrates of the skin comprise a broad spectrum of entities ranging from benign infiltrates to those that are malignant. Many of these infiltrates are in fact reactive lymphoproliferative disorders related to drug therapy falling under the general category of drug associated pseudolymphoma. While this histologic pattern can mimic a cutaneous lymphoma, especially true grade T-cell rich cell lymphoma consistent with lymphomatoid papulosis, drug associated reversible T cell dyscrasias exhibit distinct morphologic and phenotypic parallels with cytotoxic lymphocytes and the various pseudolymphomatoid T cell dyscrasias, and angiocentric CD30 positive T cell infiltrates mimicking lymphomatoid papulosis. The implicated drug classes are quite varied and include anti-depressants, antihypertensives, calcium channel blockers, statins, antiretrovirals and various biologic drugs. Latency periods from these various drug classes exert certain effects on lymphocytic function including preventing cytotoxic suppressor function and antigenic stimuli. As the cytotoxic effects on lymphocytic function may be cumulative over years and/or reflect the toxicity of other drugs, a temporal association may not exist between the onset of the infiltrates and the initiation of the drug. In certain lymphomatoid reactions however such as DRESS syndrome the drug may function here as antigen as well as an immunodysregulating agent. It is critical that the pathologist works carefully with the clinician in the evaluation of all atypical cutaneous lymphoid infiltrates where the distinction between pseudolymphoma versus lymphoma can not be reliably made based on pathologic analysis alone.

Introduction

The spectrum of atypical cutaneous lymphocytic infiltrates of the skin is broad especially in regard to the various subtypes of primary cutaneous lymphoma. A common cause of atypical cutaneous lymphoid infiltrates that can resemble B and T cell lymphoma is the drug induced pseudolymphoma. In routine dermatopathology practice, most biopsies showing atypical lymphocytic infiltrates are not neoplastic in nature but instead represent a lymphomatoid state that often reflects underlying iatrogenic and endogenous immune dysregulation.

The intent of this review is to address the clinical and pathologic aspects of drug induced pseudolymphoma by examining the two main categories, namely: lymphocytoma cutis and those atypical T cell lymphocytic infiltrates that resemble varied forms of T cell lymphoproliferative disease, for which we have coined the term drug associated reversible T cell dyscrasia. While lymphocytoma cutis has a uniform clinical and histomorphologic appearance, the drug associated reversible T cell dyscrasias show wide variation in their clinical and histologic presentations.

Examples of drug induced reversible T cell dyscrasias comprise the following entities: the pseudo-mycosis fungoides-like drug reaction including the drug associated reversible granulomatous T cell dyscrasia which can masquerade as interstitial granulomatous mycosis fungoides, the CD30 positive angiocentric lymphomatoid drug reaction as a mimic of lymphomatoid papulosis, drug associated reversible erythrodermic T cell dyscrasia (i.e. pseudo-Sezary syndrome), the pityriasis lichenoides-like drug reaction and drug induced atypical pigmented purpuric dermatoses.[1]

Many of the clinical, histologic and phenotypic features that are encountered in endogenous T cell lymphoproliferative disorders can be observed in drug induced pseudolymphomas. At times the distinction is so difficult that we make treatment recommendations similar to those applied to endogenous T cell dyscrasias, such as light therapy, along with a trial of drug modification. In theory, if the process is truly a reversible state induced by drug therapy, resolution of the rash should occur with the associated interventional therapy and should not recur. Recurrent and/or persistent disease is the hallmark of endogenous T cell lymphoproliferative disease.[2]

In drug induced reversible T cell dyscrasias, the temporal association between the initiation of the drug and the development of the

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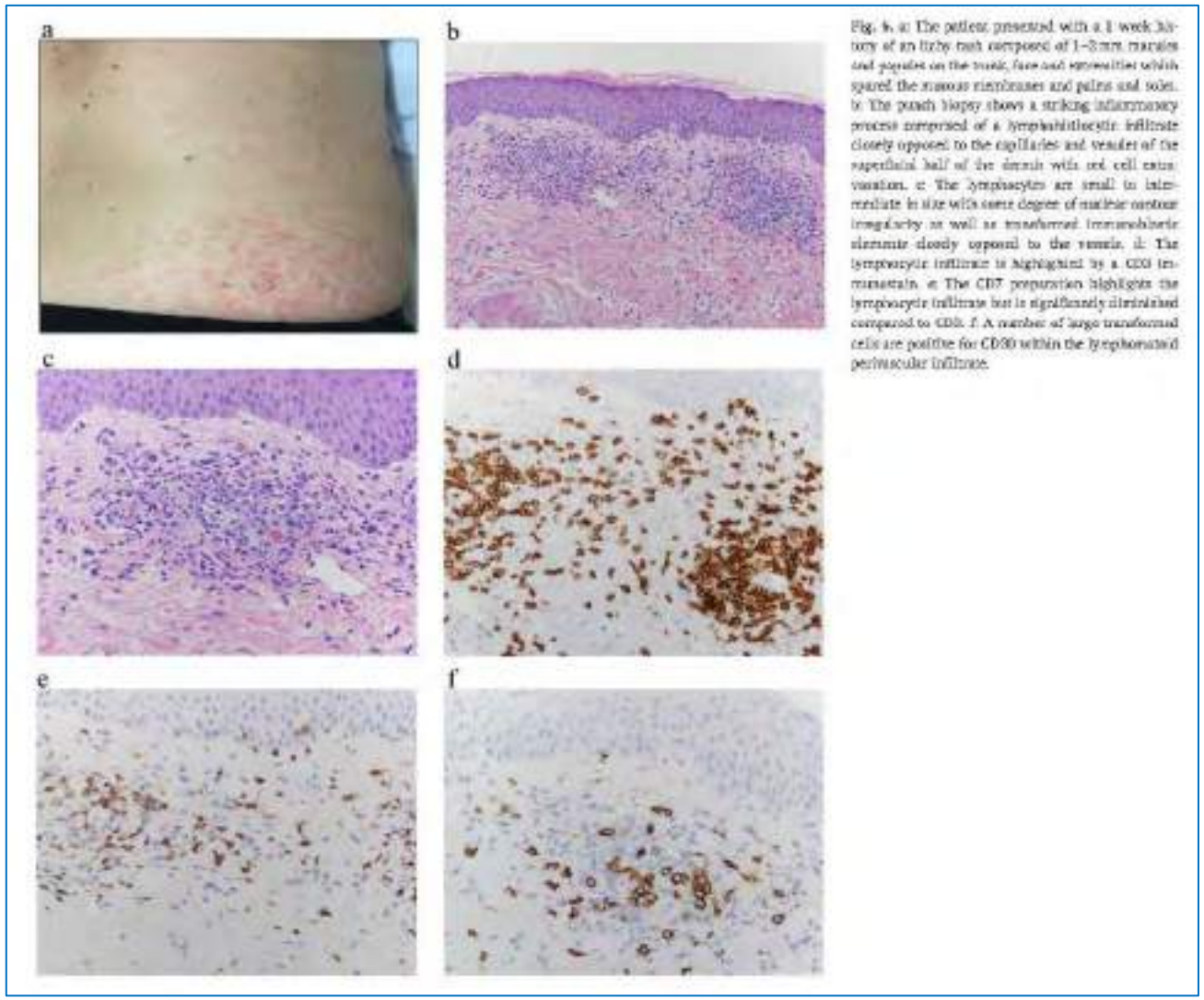

Fig. 6. a: The patient presented with a 1 week history of an itchy rash composed of 1–3 mm macules and papules on the trunk, face and extremities which spared the mucous membranes and palms and soles. b: The punch biopsy shows a striking inflammatory process comprised of a lymphohistiocytic infiltrate closely opposed to the capillaries and venules of the superficial half of the dermis with cell extravasation. c: The lymphocytes are small to intermediate in size with some degree of nuclear contour irregularity as well as transformed immunoblastic elements closely opposed to the vessels. d: The lymphocytic infiltrate is highlighted by a CD3 immunostain. e: The CD7 preparation highlights the lymphocytic infiltrate but is significantly diminished compared to CD3. f: A number of large transformed cells are positive for CD30 within the lymphomatoid perivascular infiltrate.

Drug-Induced Immune Dysregulation As a Cause of Atypical Cutaneous Lymphoid Infiltrates:

A Hypothesis

CYNTHIA M. MAGRO, MD, AND A. NEIL CROWSON, MD

The authors encountered 22 patients in whom a skin biopsy showed atypical lymphoid hyperplasia and in whom a subsequent drug history showed ingestion of one or more agents before lesional onset. In 13 patients, the biopsy had been performed to rule out a diagnosis of malignant lymphoma, whereas in the other nine the clinical impression was that of a drug eruption. Among the most frequently prescribed agents were calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, antidepressants, antihistamines, β-blockers, benzodiazepines and lipid-lowering agents, all of which are either known to perturb lymphocyte function or have been implicated as a cause of pseudolymphomata. Twelve of the patients were on two or more of these drugs. The effect of drug combination on the clinical course was assessed. The clinical presentations were as one or more erythematous plaques or as single infiltrative papules, or as solitary nodules. The patients had been on one or more of the aforementioned drugs from 2 weeks to 2 years before developing the lesions. Resolution of the eruptions occurred in 17 patients within 1 to 52 weeks (mean, 7 weeks) of discontinuing the medication. Five additional patients had complete excision of solitary lesions without recurrence. A history of atopy, autoimmune disease, or previous cutaneous neoplasia was elicited in two patients. All biopsy specimens showed atypical lymphoid infiltrates, which assumed one or more of the following patterns: mycosis fungoides (MF)–like, a lymphomatoid vascular reaction, lymphocytoma cutis, and follicular mucinosis. Based on the histopathology of the biopsied lesions and the clinical course being one of lesional resolution after cessation of drug therapy or excision of a solitary lesion without subsequent recurrence, a diagnosis of drug-associated lymphocytoid hypersensitivity was established in all specimens. A diagnosis of drug-associated pseudolymphoma should be evaluated before a diagnosis of cutaneous lymphoma is rendered, and should be considered if the patient is on a drug known to alter lymphocyte function, particularly in the setting of systemic immune dysregulation or prohibiting therapy where agents may not synergistically or cumulatively to alter lymphoid function. The authors postulate that the drug may promote an aberrant immune response to an antigen that may be the drug itself or some other stimulus. A skin biopsy may be particularly helpful, as the lesions of drug-associated pseudolymphoma have a morphology distinctive from malignant lymphoma. Hum Pathol 27:125–132. Copyright © 1996 by W.B. Saunders Company

Key words: drug-induced lymphoid hyperplasia, immune dysregulation.

Abbreviations: ACE, angiotensin-converting enzyme; MF, mycosis fungoides; LYP, lymphomatoid papulosis; LyVR, lymphomatoid vascular reaction; AIL, angioimmunoregulatory/reactive lesions; DTH, delayed type hypersensitivity.

Cutaneous pseudolymphomata are benign infiltrates that mimic malignant lymphoma and encompass a spectrum of entities including infiltrative reticuloid, Kikuchi's disease, Rosai-Dorfman disease, Jessner's lymphocytic infiltrate of skin, lymphomatoid papulosis (LYP), pseudolymphomatous angiokeratoma of children,[1] and hypersensitivity reactions to antigens such as viruses,[2] *Borrelia burgdorferi*,[3] arthropods,[4] enzymes,[5] or drugs.[6,7] An aberrant immune response to microbial or other antigens may reflect a state of systemic immune dysregulation as is proposed for eosinophilic pustular follicular reactions,[8] diphenylhydantoin (Dilantin)-associated pseudolymphoma,[9] and pseudolymphomata developing in the setting of leukemia.[10] The distinction between pseudolymphoma and malignant lymphoma may be problematic, because a pseudolymphoma can mimic both cutaneous T-cell and B-cell lymphoma.[10] Furthermore, a pseudolymphoma may progress to malignant lymphoma.[11]

The authors describe 22 patients who developed drug-associated atypical cutaneous lymphoid infiltrates consistent with pseudolymphomata. Certain microscopic light microscopic features enabled the distinction of these infiltrates from malignant lymphoma. A role for drug-induced immune dysregulation is proposed as the pathogenetic basis for the evolution of these lesions.

MATERIALS AND METHODS

Twenty-two skin biopsies from 22 patients were selected from 70,000 specimens accessioned over a 10-month period in the dermatopathology laboratories of Pathology Services, Inc. (Cambridge, MA) and Central Medical Laboratories (Winnipeg, Canada), and examined by conventional light microscopy. In 10 of the specimens, the clinician questioned a drug eruption, and in two a specific drug was mentioned. In all specimens, a complete drug history was obtained by the authors before finalizing the biopsy report, revealing drug ingestion before lesional onset. In all specimens, although an atypical lymphoid infiltrate was observed, the authors rendered a final diagnosis of probable drug-associated lymphomatoid hypersensitivity based on specific histological criteria outlined later. In 12 specimens, malignant lymphoma was the most histological differential diagnosis. Cessation of drug therapy was recommended by the authors, and in 20 of 22 specimens, this advice was accepted by the clinician. The clinical courses of all patients were followed for up to 3.5 years after cessation of drug therapy.

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Pattern		
MF-like	69,6%	(n= 16)
Angiocentric	39,1%	(n= 9, 8 with MF-like features)
Folliculotropic	8,7%	(n=2)
Lymphocytoma	17,4%	(n=4)

Histopathologic Characterization of Mogamulizumab-associated Rash

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Abstract: Rash is one of the most common adverse events observed with mogamulizumab, an anti-C-C chemokine receptor 4 monoclonal antibody approved for previously treated mycosis fungoides (MF) and Sézary syndrome (SS). Given the nonspecific clinical presentation of this rash, histopathologic distinction from MF/SS is critical for informing clinical management. We performed a comprehensive characterization of the histopathology of mogamulizumab-associated rash (MAR) with the [illegible] high-throughput sequencing of T-cell receptor (TCR) [illegible] two biopsy specimens from 19 patients were evaluated respectively. Three major histologic reaction patterns were spongiotic/psoriasiform dermatitis (14/52), interface (11/52), and granulomatous dermatitis (8/52). Almost all specimens (51/52) showed at least 2 of these reaction patterns concurrently. Dermal eosinophils were not a consistent finding present in only half (27/52) of specimens and [illegible] only 3. Features mimicking MF/SS, including lymphotropism, Pautrier microabscesses, and adnexal involvement, were rarely seen but tended to be focal and mild. In 38 specimens with available immunohistochemistry, intraepidermal lymphocytes demonstrated a CD4:CD8 ratio ≤1 : 1. Low background [illegible] the patient's previously identified MF/SS-associated [illegible] (s) were demonstrated in 20/46 specimens analyzed by high-throughput sequencing of TCR. We conclude that MAR can demonstrate diverse histologic features. Findings that distinguish MAR from MF/SS include the inversion of the CD4:CD8 ratio within intraepidermal lymphocytes, preservation of absent or underexpressed levels of classical TCR sequences. Correlation with the clinical findings and immunohistochemical and molecular characterization of [illegible]

MF/SS before mogamulizumab, when possible, may facilitate recognition of MAR.

Key Words: mogamulizumab, rash, mycosis fungoides, histopathology, high-throughput sequencing

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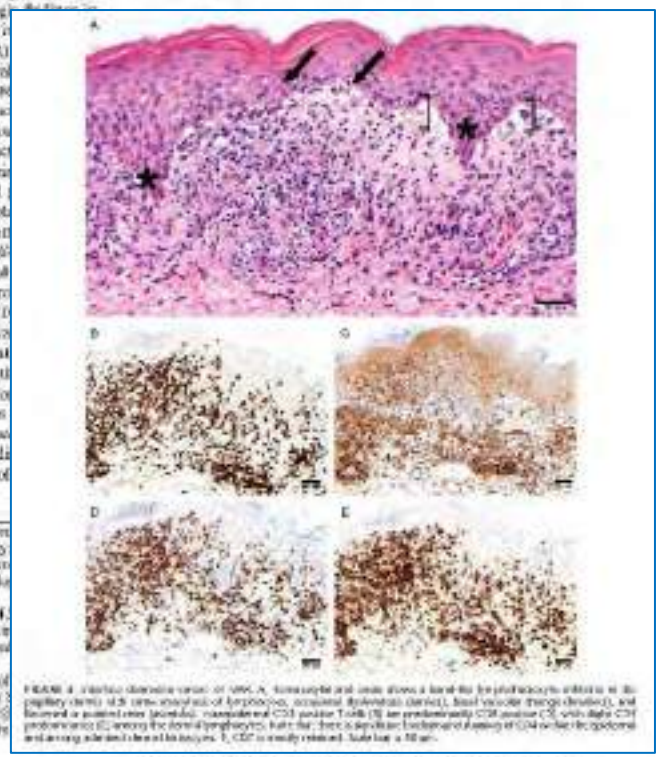

FIGURE 4. Interface dermatitis variant of MAR. A, Scanning optical scan shows a band-like lymphohistiocytic infiltrate at the papillary dermis with dermal-epidermal lymphocytes, occasional dyskeratotic cell(s), basal vacuolar change (interface), and lymphocytic exocytosis (satellitosis). Immunostained CD3 positive T cells (B) are predominantly CD8 positive (C), with slightly CD4 predominance (D), among the dermal lymphocytes. Note that there is also a significant background admixture of CD4 positive T cells in the epidermis and among adnexal structures in the biopsy. E, CD7 is mostly retained. Scale bar: a, 50 μm; b–e, 100 μm.

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Mogamulizumab efficacy is underscored by its associated rash that mimics cutaneous T-cell lymphoma: a retrospective single-centre case series*

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Funding sources
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Conflicts of interest
[illegible]

Summary

Background Mogamulizumab is a humanized antibody against chemokine receptor type 4. It was recently approved by the US Food and Drug Administration for relapsed or refractory mycosis fungoides (MF) and Sézary syndrome (SS). The most commonly reported adverse event in the phase III licensing trial was drug eruption (78%), now termed mogamulizumab-associated rash (MAR). Clinical recommendations about MAR and its treatment differ between the current package insert and postapproval insights reported from two single-centre studies that focused on its characterization, but less so on outcomes and clinicopathological differentiation from cutaneous T cell lymphoma (CTCL).

Objectives To describe our experience in the diagnosis of MAR and treatment of patients with CTCL with mogamulizumab.

Methods This is a single-centre retrospective case series study.

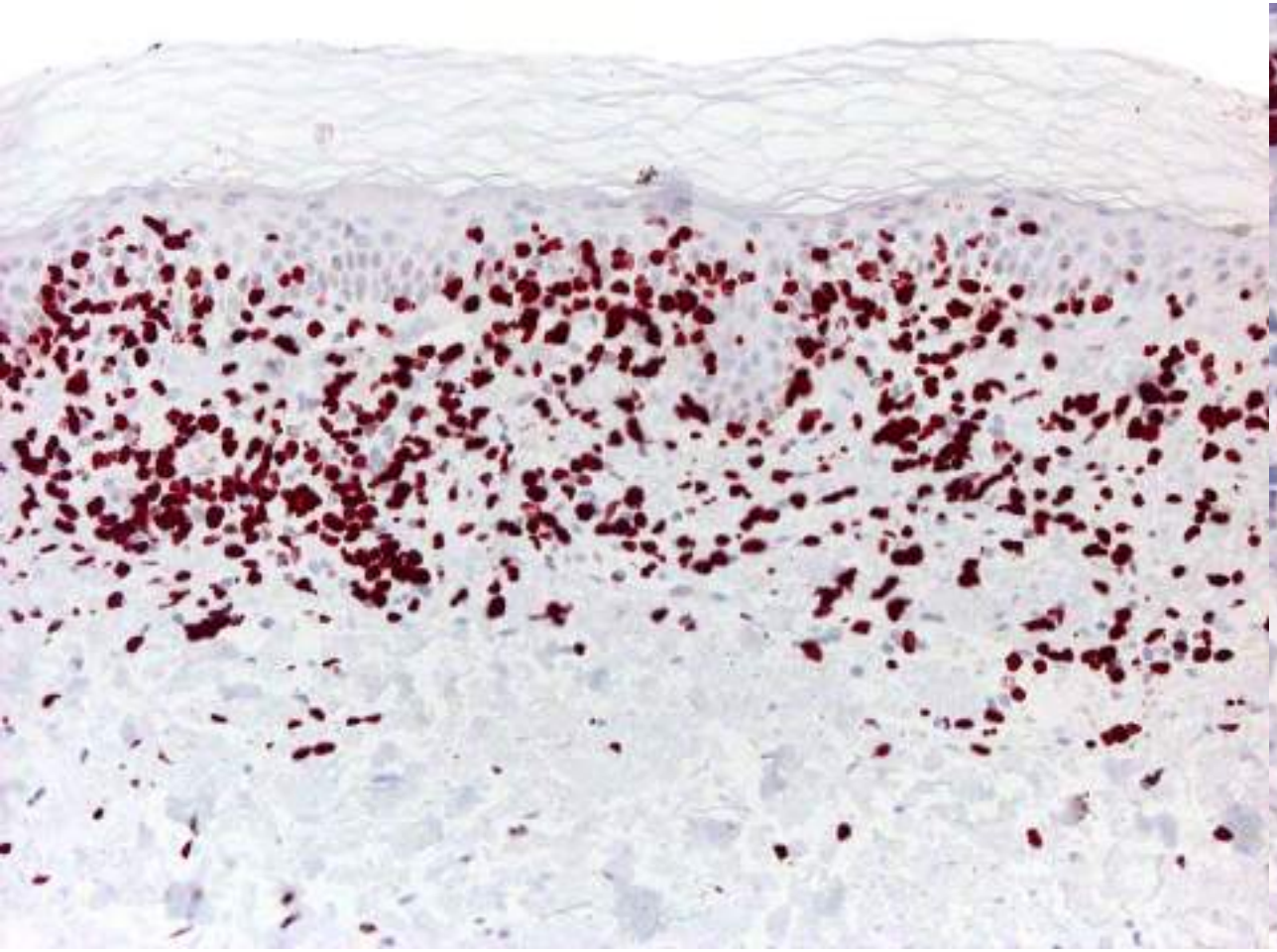
Results We found a higher incidence of MAR in patients with CTCL (17 of 24, 68%) than previously reported. MAR development is associated with complete (11 of 17) or partial (four of 17) responses, with an overall response rate of 88%, compared with 39% (two of seven) in patients without MAR. Diagnosis of MAR may be obscured by its ability to mimic key CTCL features both clinically and histologically, but an absence of T cell receptor clonality and relatively decreased CD4 : CD8 ratio compared with baseline lesions strongly favour MAR over recurrent disease.

Conclusions MAR has the potential to create a significant management problem for patients on mogamulizumab. Misidentification of MAR as recurrent CTCL may detrimentally result in the premature discontinuation of mogamulizumab in patients whose disease is historically hard to treat. Thorough clinicopathological investigation of new lesions during treatment with mogamulizumab is required to inform ideal treatment decision and achieve better outcomes.

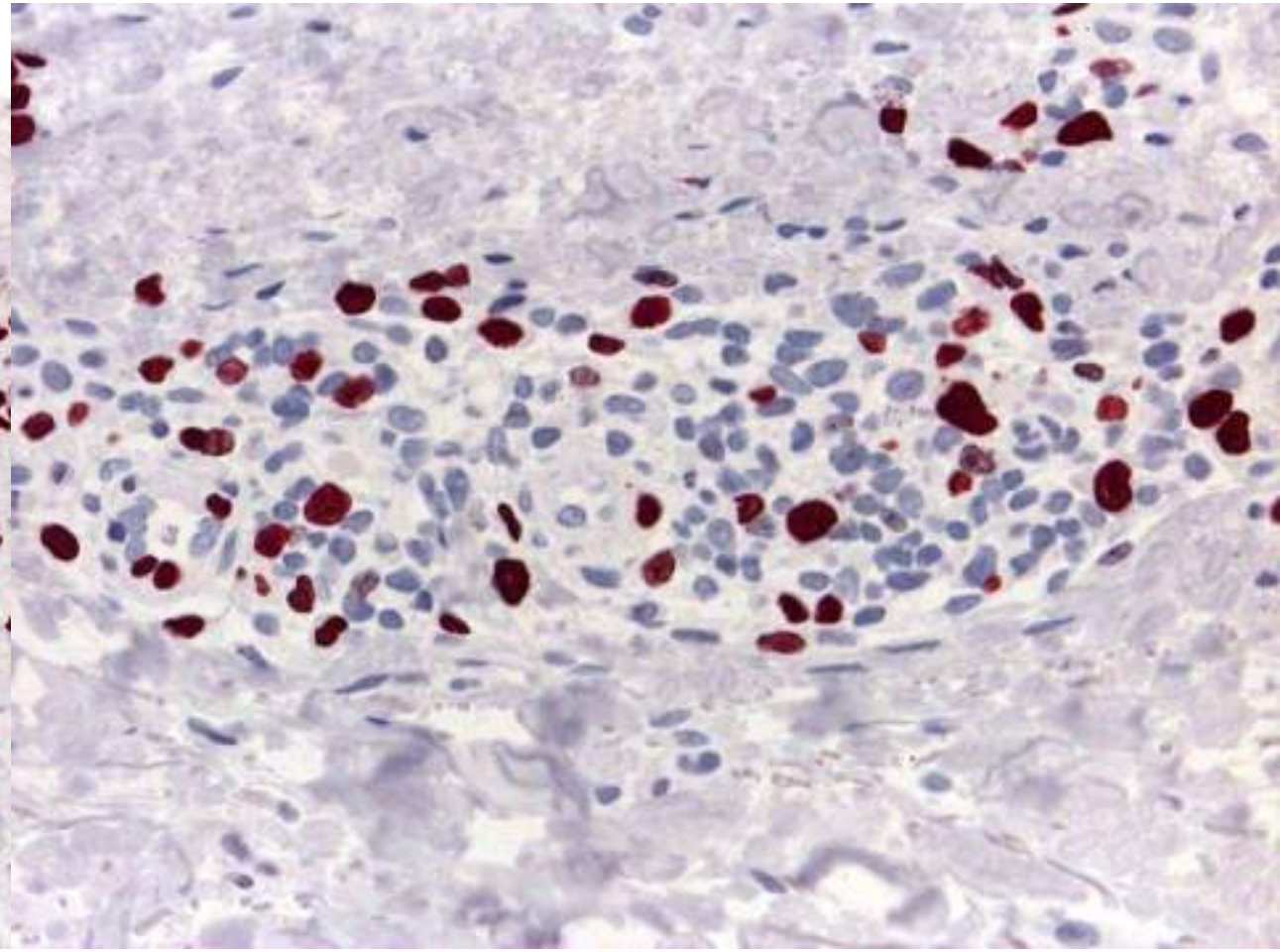
What is already known about this topic?

- Previous descriptions of mogamulizumab-associated rash (MAR) include case reports or series and two subgroup analyses of the mogamulizumab-approving MAVORIC clinical trial.

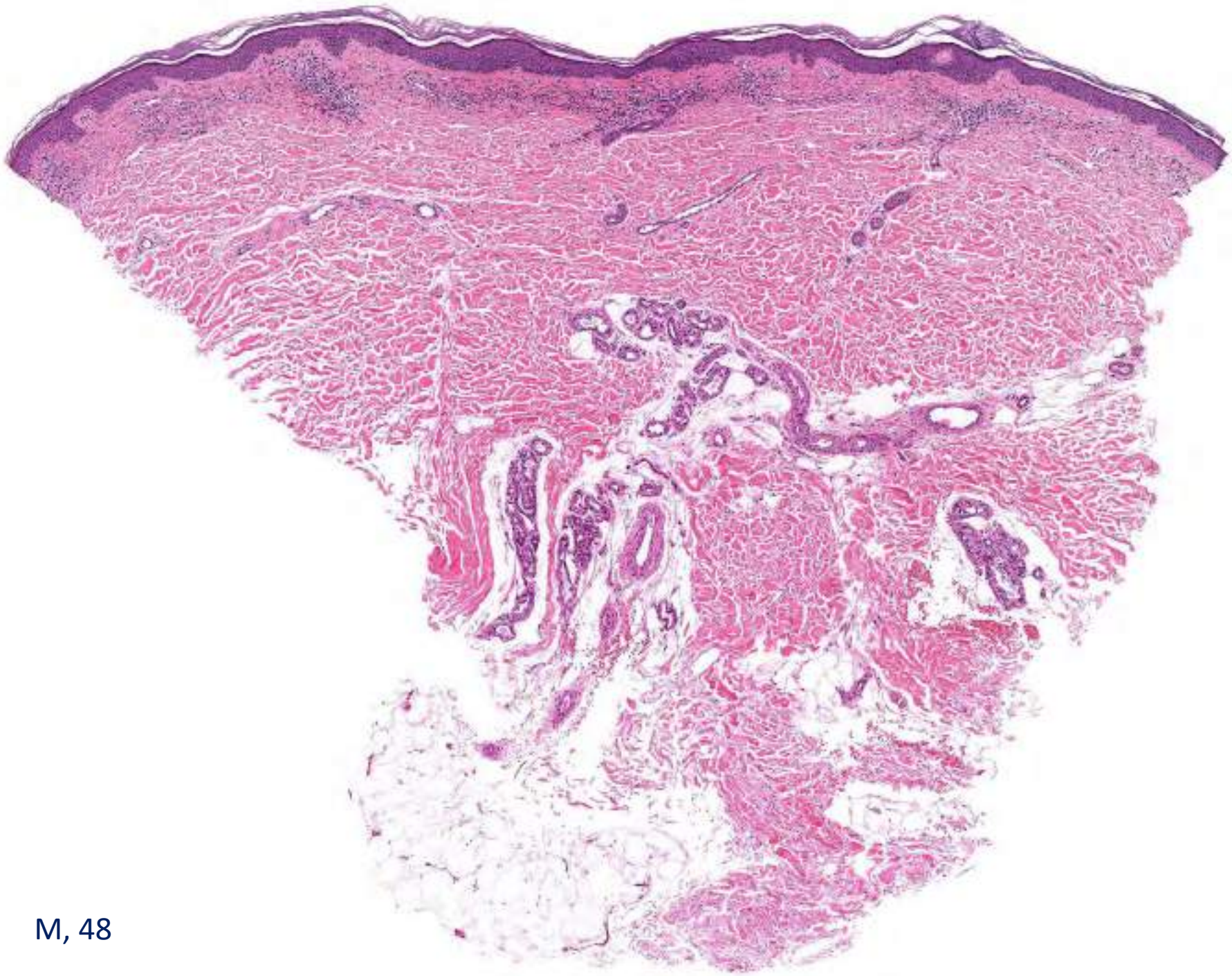
Clue: Proliferation rate (Ki-67) too high for early MF

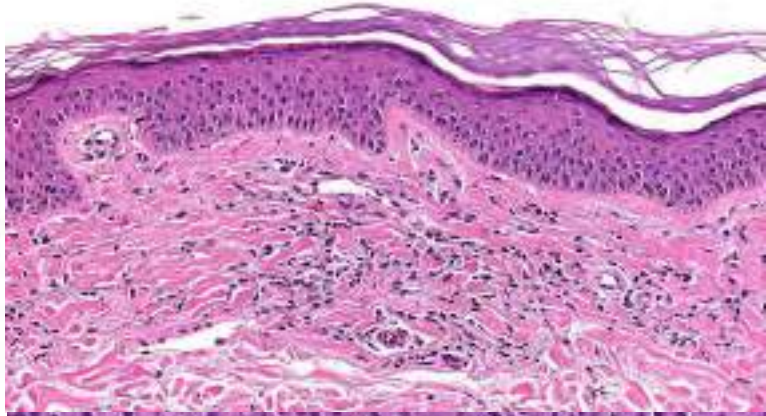


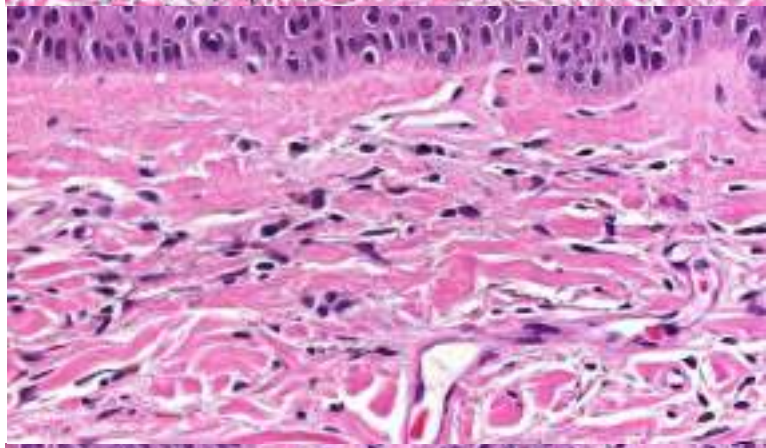
Lymphomatoid drug eruption

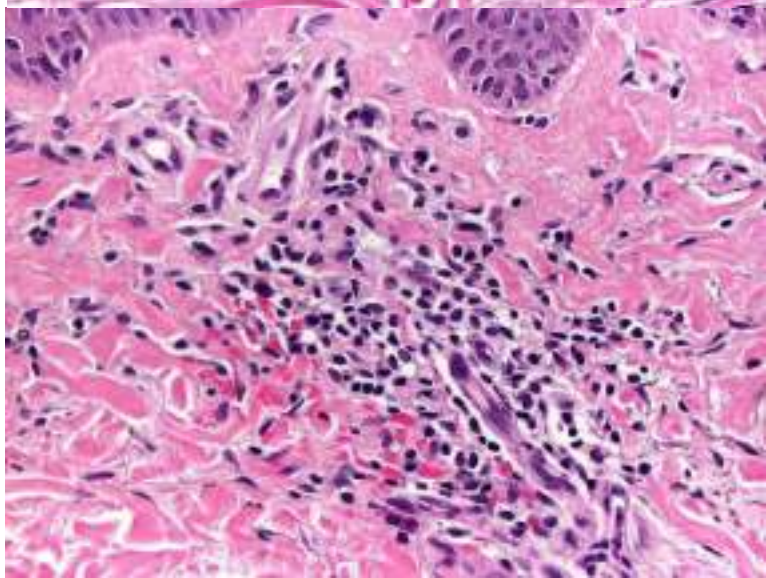


Mycosis fungoides / Sézary

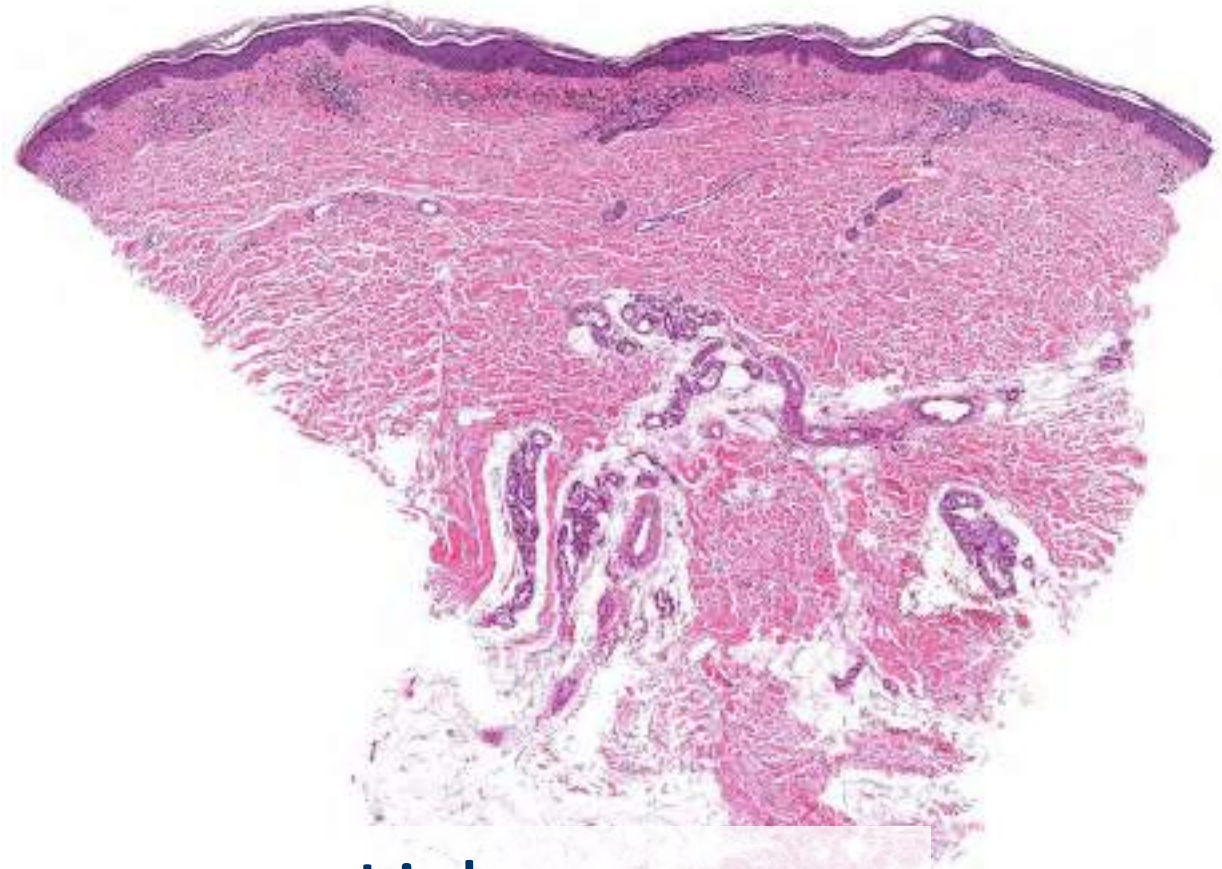




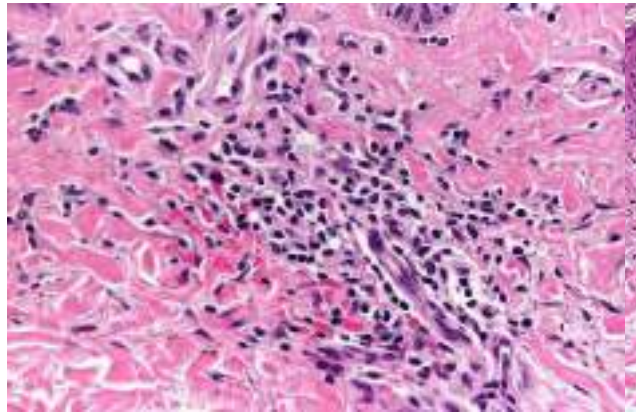


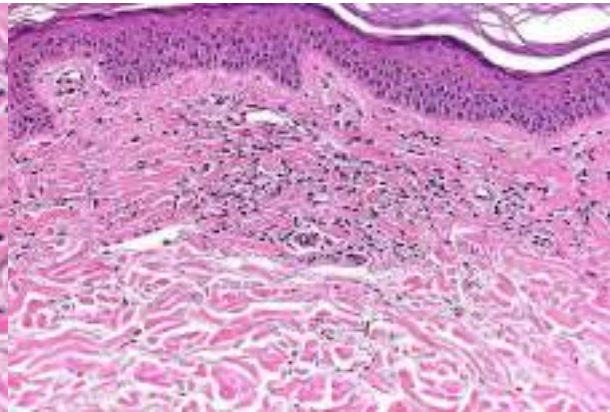


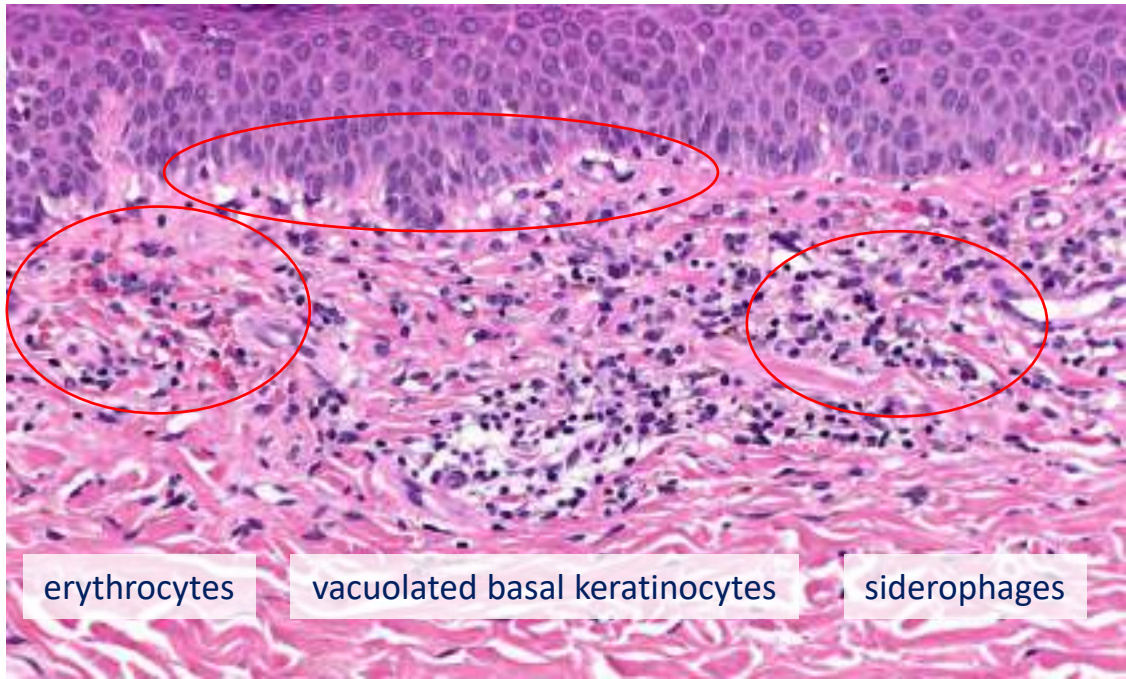
M, 48



Lichen aureus






erythrocytes
vacuolated basal keratinocytes
siderophages

Lichen Aureus

- Persistent, localized form of "pigmented purpuric dermatitis"
- Spontaneous resolution observed in >50% of cases; in some cases lesions persist unchanged for years
- T-cell monoclonality in ~50% of cases
- No relationship between treatment / clonality and outcome
- Probably represents one of so-called "clonal dermatoses" – follow-up advisable

The American Journal of Dermatopathology 19(2):108–118, 1997

Persistent Pigmented Purpuric Dermatitis and Mycosis Fungoides: Simulant, Precursor, or Both?

A Study by Light Microscopy and Molecular Methods

Jorge R. Toro, M.D., Christian A. Sander, M.D., and Philip E. LeBoit, M.D.

Mycosis fungoides (MF) can present with purpuric lesions, and rare patients who seemed to have persistent pigmented purpuric dermatitis (PPPD) have developed MF. We recently encountered two patients referred to our cutaneous lymphoma clinic who had PPPD rather than MF and two others who appeared to have both conditions, leading us to explore the histologic similarities of these diseases. We examined specimens from 56 patients with PPPD to determine the frequency of MF-like histologic configurations, namely, the psoriasiform lichenoid, psoriasiform spongiotic lichenoid, and atrophic lichenoid patterns. We also noted the degree of spongiosis, epidermotropism, papillary dermal fibrosis, lymphocytic atypia, and epidermal hyperplasia, the number of extravasated erythrocytes and siderophages, and the distribution of lymphocytic infiltrate within the epidermis. In 29 of 56 patients, there were patterns typically seen in MF. PPPD can feature lymphocytes aligned along the epidermal side of the dermoepidermal junction, with few necrotic keratinocytes, as can MF. Papillary dermal edema occurred frequently in PPPD but not in MF, while lymphocytes in MF but not PPPD had markedly atypical nuclei and had ascended into the upper spinous layer. Given these similarities, we tested for clonality of the T-cell population using a polymerase chain reaction assay for γ-chain rearrangements. Clonal populations were present in three of three and one of two specimens from patients with both PPPD and MF, but also in 9 of 12 specimens typical of lichenoid patterns of PPPD. These findings raise the possibility that the lichenoid variants of PPPD are biologically related to MF.

Key Words: Mycosis fungoides—Persistent pigmented purpuric dermatitis—T-cell gene rearrangements—Lichenoid purpura—Schamberg's disease—Cutaneous T-cell lymphoma.

The many clinical and histological features of mycosis fungoides (MF) are more than curiosities because MF is one of the most common non-Hodgkin's lymphomas. The profusion of variants may be due to the admixture of non-neoplastic inflammatory cells in many lesions of MF and the skin's large repertoire of reaction patterns (1). Among the variants of MF is one in which purpuric areas develop within lesional skin (2–4).

Several considerations led us to examine the relationship between MF and the group of conditions known as persistent pigmented purpuric dermatitis (PPPD). Purpuric lesions can occur in MF. The first patient reported in the American literature as having lichen aureus (5) later proved to have MF (6). The diagnosis of several patients referred to our cutaneous lymphoma clinic was changed from MF to PPPD following review of sections from their skin biopsies. Last, we have seen two patients with both conditions; in one, PPPD preceded MF. We therefore examined sections from a large group of cases of PPPD to determine how often MF-like patterns of lymphocytic infiltration were present and ascertained the degree to which other features characteristic of MF, such as papillary dermal fibrosis and lymphocytes aligned along the epidermal side of the dermoepidermal junction, were present. Upon determining that MF-like histopathologic features were common in PPPD, we used the polymerase chain reaction (PCR) to test for clonal rearrangement of the T-cell receptor γ-chain gene.

From the Departments of Dermatology (J.R.T., P.E.L.) and Pathology (P.E.L.), University of California, San Francisco, California, U.S.A.; and Department of Dermatology (C.A.S.), Ludwig Maximilians University, Munich, Germany.

Address correspondence and reprint requests to Dr. P.E. LeBoit at Dermatopathology Section–408 HSW, Department of Pathology, University of California School of Medicine, San Francisco, CA 94143-0506, U.S.A.

Dr. Toro was a fellow in the Department of Dermatology at the University of California, San Francisco, California, U.S.A., at the time this study was performed. He is currently a resident in the Division of Dermatology at Southern Illinois State University School of Medicine in Springfield, Illinois, U.S.A.

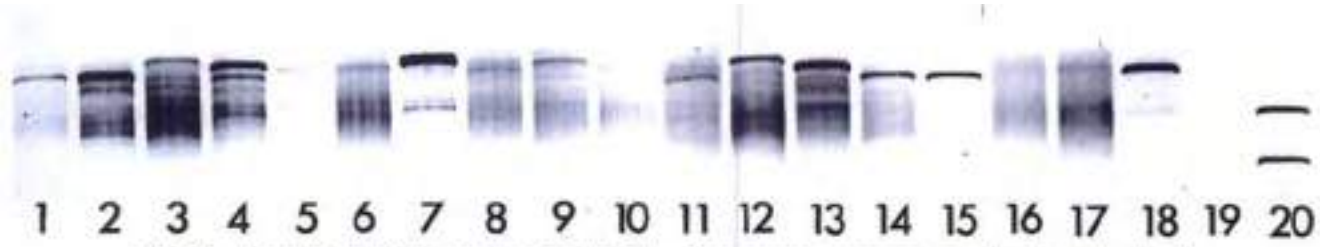
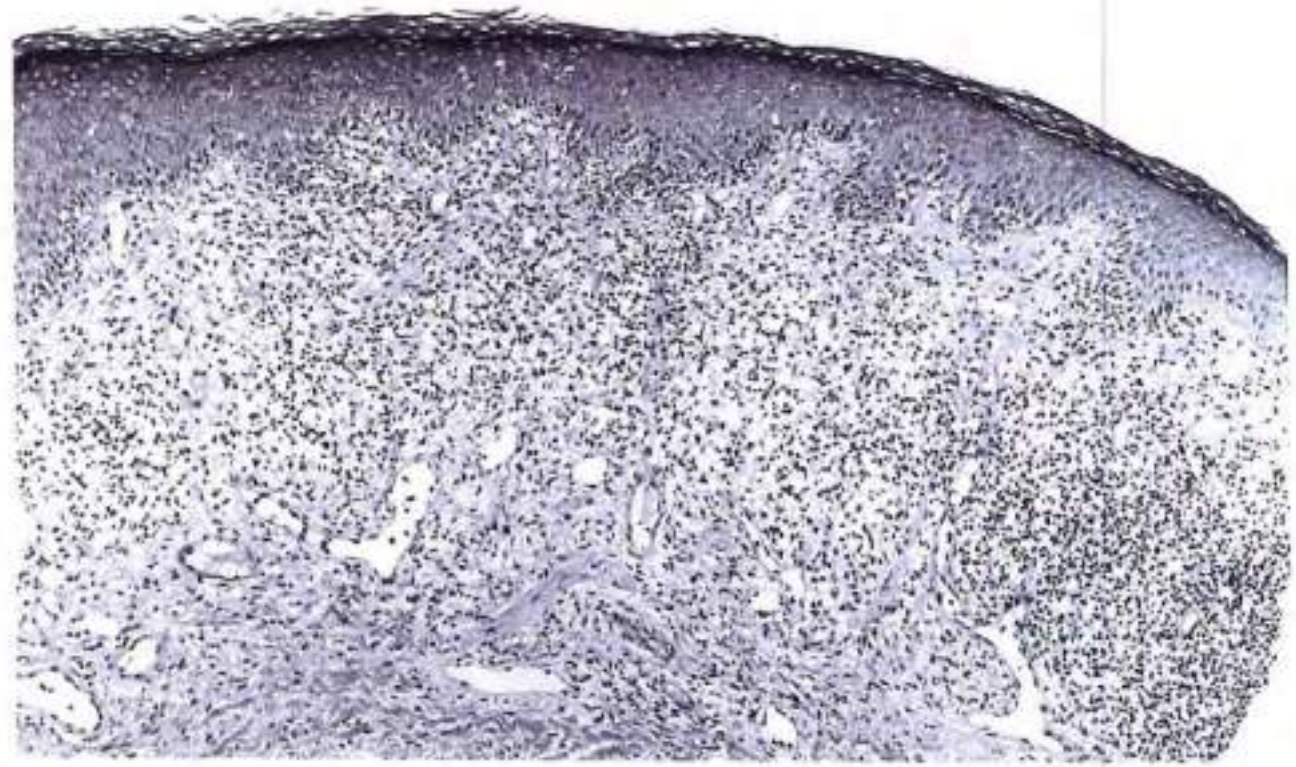


FIG. 6. Results of PCR reaction for T-cell γ-chain gene rearrangement using the Vγ10 probe. Positive control is in lane 18, negative control lane 19, and molecular standards lane 20. Bands signifying rearrangements are present in lanes 1,2,4,7, and 12–15. Smears or faint bands are present in the remaining lanes.



OBSERVATION

Lichen Aureus

Clinicopathologic Features, Natural History, and Relationship to Mycosis Fungoides

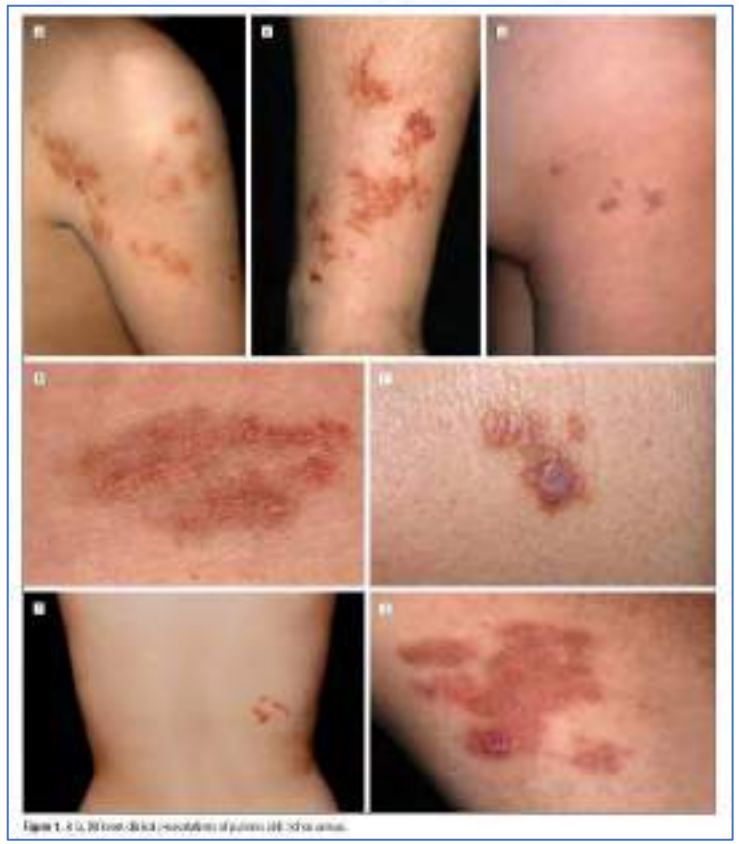
Regina Fink-Puches, MD; Peter Wolf, MD; Helmut Kerl, MD; Lorenzo Cerroni, MD

Background: A possible association between lichen aureus (LA) and mycosis fungoides (MF) has been suggested in the past. We evaluated the clinicopathologic features of LA and its relationship to MF. Data from 23 patients with a clinicopathologic diagnosis of LA were reviewed.

Observations: Lesions were asymmetrically localized on 1 area of the body (mostly 1 extremity) and were characterized histologically by dense, bandlike lymphocytic infiltrates. A monoclonal T-cell population was detected in half of the cases. After a mean follow-up of 102.1 months, 14 patients had no sign of skin disease, 7 patients had unmodified skin lesions, and 2 other patients with unmodified skin lesions had died of unrelated conditions. Treatment modalities did not affect the outcome. There was no relationship between the presence or absence of monoclonality and patient status at follow-up assessments.

Conclusion: Patients with classic lesions of LA do not show progression to MF.

Arch Dermatol. 2008;144(9):1169-1173



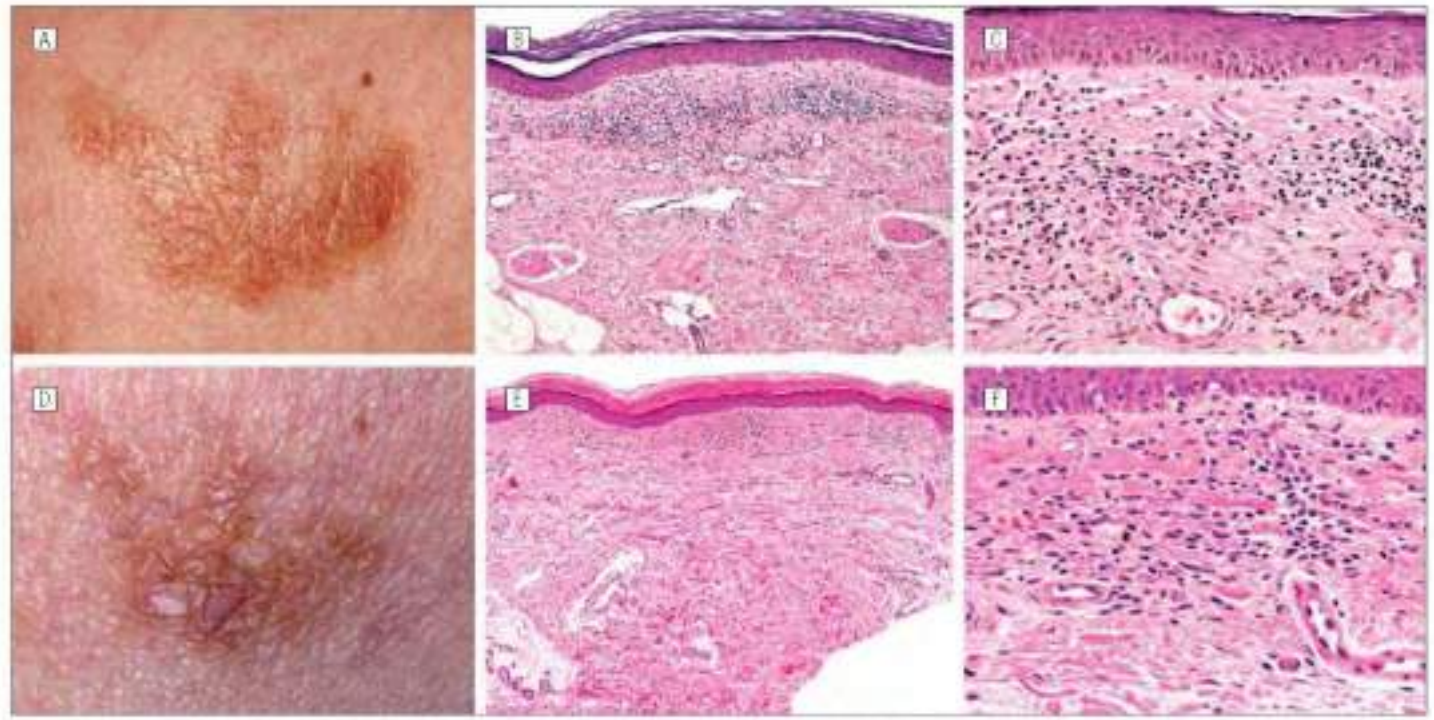
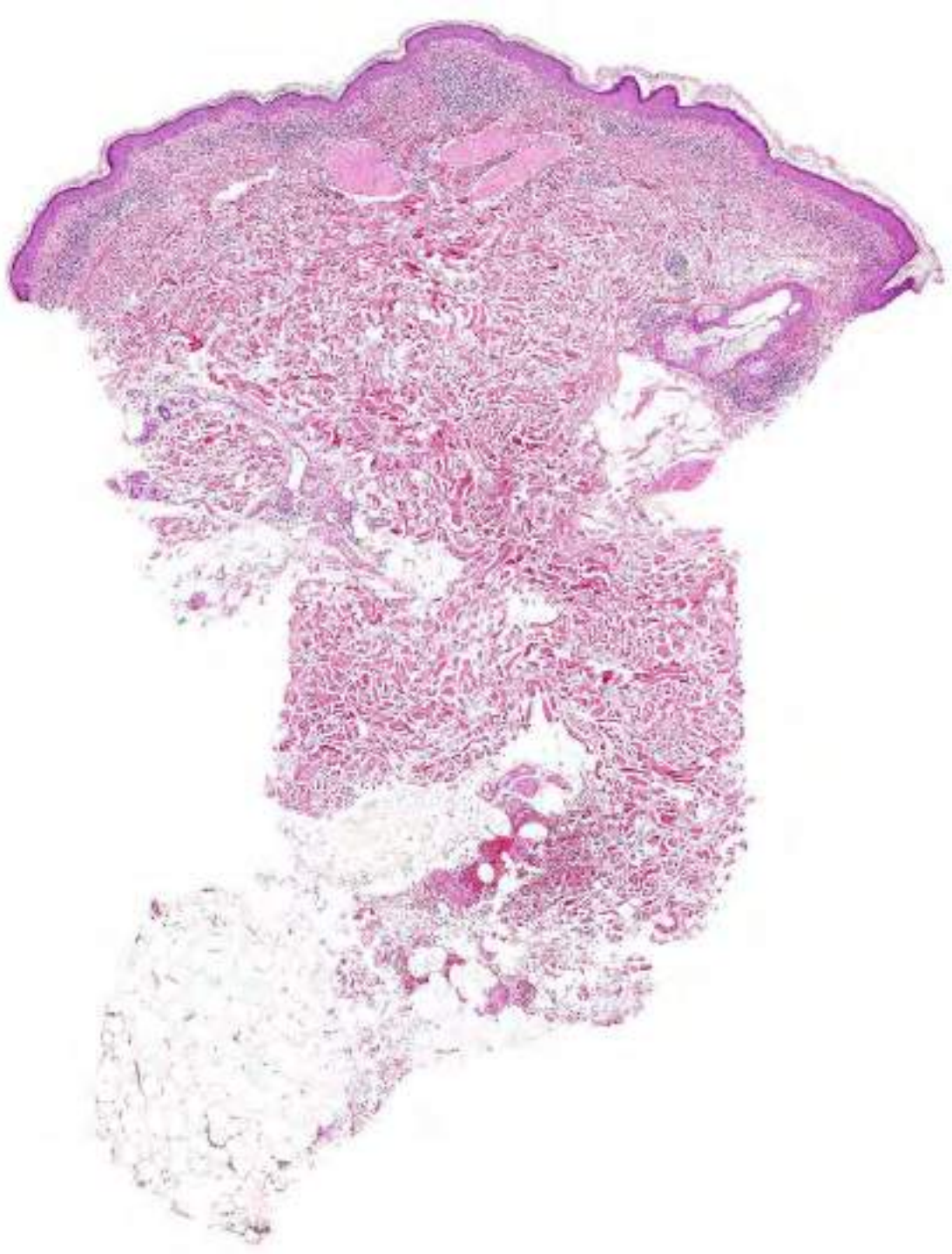
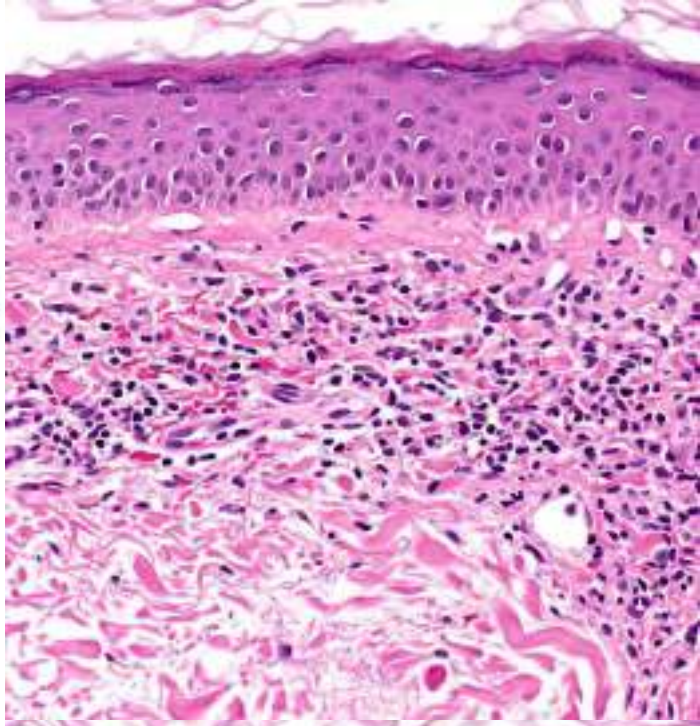
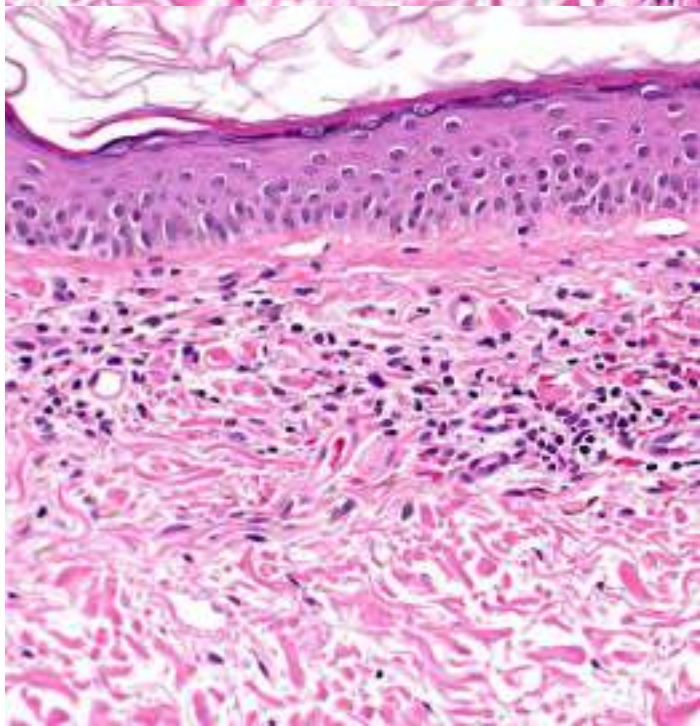
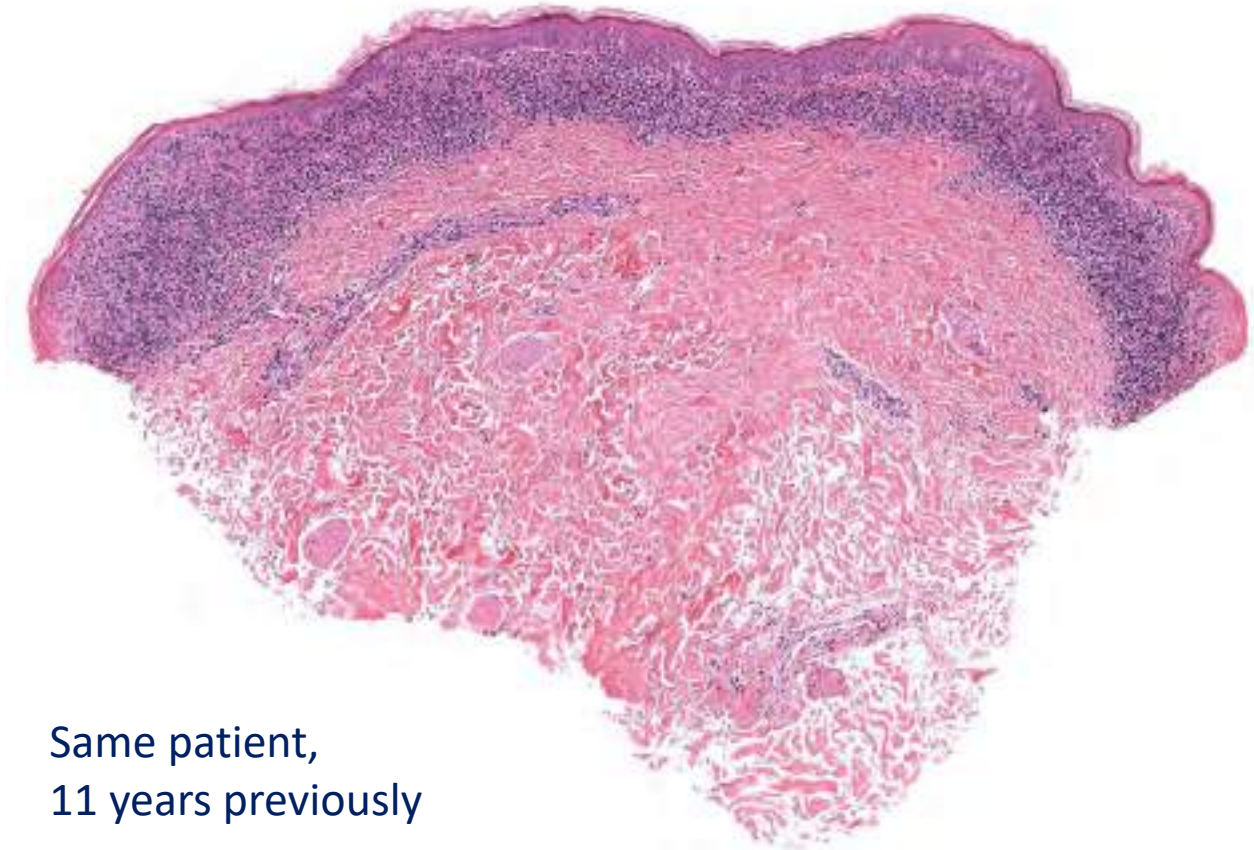


Figure 3. Patient 3 in the Table. A, Appearance of skin lesion in 1990. B, A biopsy specimen obtained in 1990 showed a bandlike infiltrate. C, Note sparse hemorrhage and coarse bundles of collagen in the papillary dermis. D, Appearance of the lesion in 2007. E, A biopsy specimen obtained in 2007 revealed persistence of the lymphocytic infiltrate. F, Note features similar to those of the biopsy specimen obtained in 1990. Hematoxylin-eosin, original magnification ×10 (B), ×20 (C and F), and ×4 (E).

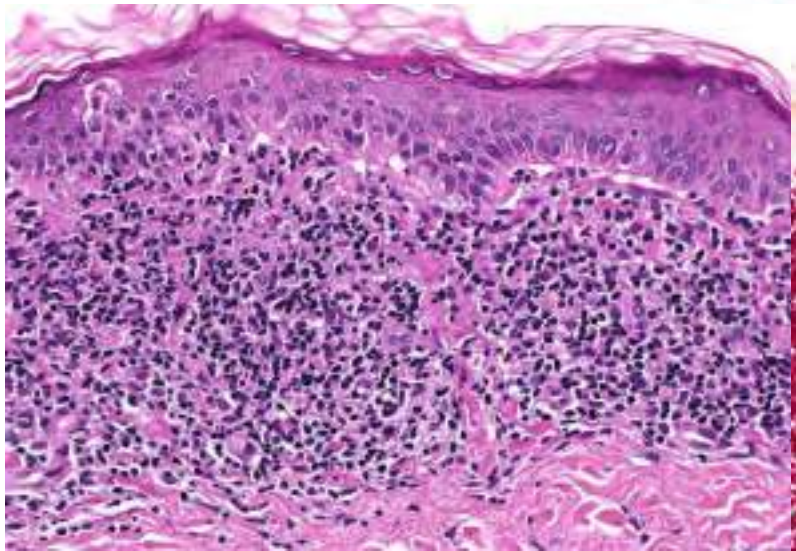


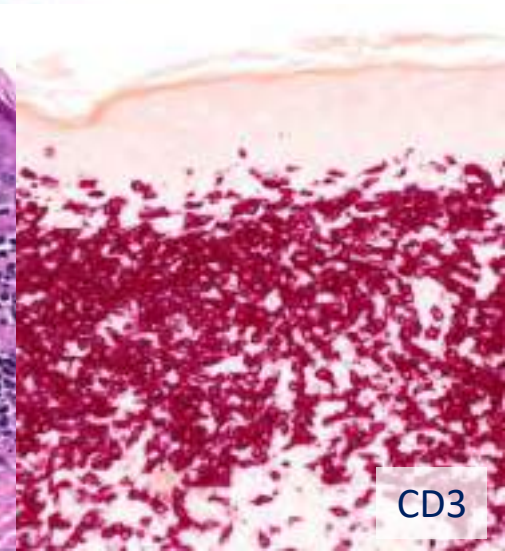






Same patient,
11 years previously





CD3

OBSERVATION

Lichen Aureus

Clinicopathologic Features, Natural History, and Relationship to Mycosis Fungoides

Regina Bisk-Fischer, MD; Peter Wolf, MD; Helmut Kerl, MD; Lorenzo Cerroni, MD

Background: A possible association between lichen aureus (LA) and mycosis fungoides (MF) has been suggested in the past. We evaluated the clinicopathologic features of LA and its relationship to MF. Data from 23 patients with a clinicopathologic diagnosis of LA were reviewed.

Observations: Lesions were asymmetrically localized on 1 area of the body (usually 1 extremity) and were characterized histologically by dense bandlike lymphocytic infiltrates. A monoclonal T-cell population was detected in half of the cases. After a mean follow-up of 102.1 months, 14 patients had no sign of skin disease, 7 patients had unmodified skin lesions, and 2 other patients with unmodified skin lesions had died of unrelated conditions. Treatment modalities did not affect the outcome. There was no relationship between the presence or absence of monoclonality and patient status at follow-up assessments.

Conclusion: Patients with classic lesions of LA do not show progression to MF.

Arch Dermatol. 2003;139:1169-1173

LICHEN AUREUS (LA) IS A chronic, persistent pigmented purpuric dermatitis (PPPD) characterized clinically by infiltrated localized golden brown lesions and histopathologically by a lichenoid lymphocytic infiltrate. The lesions are subtle, are usually symptomless, and may persist for years.[1] Although all body regions may be affected, LA occurs mainly on the legs. Histopathologically, LA differs from other PPPDs in the density of the lichenoid tissue reaction and the marked accumulation of hemosiderin-containing macrophages.[1] In some cases, because of the dense bandlike infiltrates, the histopathologic differential diagnosis relative to mycosis fungoides (MF) may be difficult or impossible. In fact, purpuric lesions resembling LA histopathologically have been described in MF.[2,3]

An association between PPPD and MF has been reported in the context of cases of PPPD progressing to MF[4-6] or the presence of purpura in lesions of MF.[7,8] In a study of many cases of PPPD, Toro and coworkers[9] suggest that this condition may be related to MF.

The aim of our study was to evaluate the clinicopathologic features and natural history of LA in a sample of patients. We also aimed to define its relationship, if any, to MF.

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Department of Dermatology, Medical University of Graz, Graz, Austria.

METHODS

PATIENTS

Data from 23 patients from the files of the Department of Dermatology, Medical University of Graz, were included in the study. In each case, the original histopathologic sections were reviewed by one of us (L.C.). Lichen aureus was diagnosed according to clinicopathologic correlation by reviewing clinical photographs when available or by reviewing medical records. Clinical data analyzed included age, sex, date of first diagnosis, duration of follow-up, and status of disease at the last follow-up assessment.

HISTOLOGIC, IMMUNOHISTOLOGIC, AND MOLECULAR BIOLOGIC EVALUATION

Sections with a maximum thickness of 4 µm and stained with hematoxylin-eosin, tolonium, and periodic acid–Schiff were available for standard histologic evaluation. In all cases in which a paraffin block could be retrieved, analysis of the T-cell receptor was performed using polymerase chain reaction (PCR) techniques and primers as published previously[10-12] with minor modifications.[13] Details about PCR procedures have been published previously.[14]

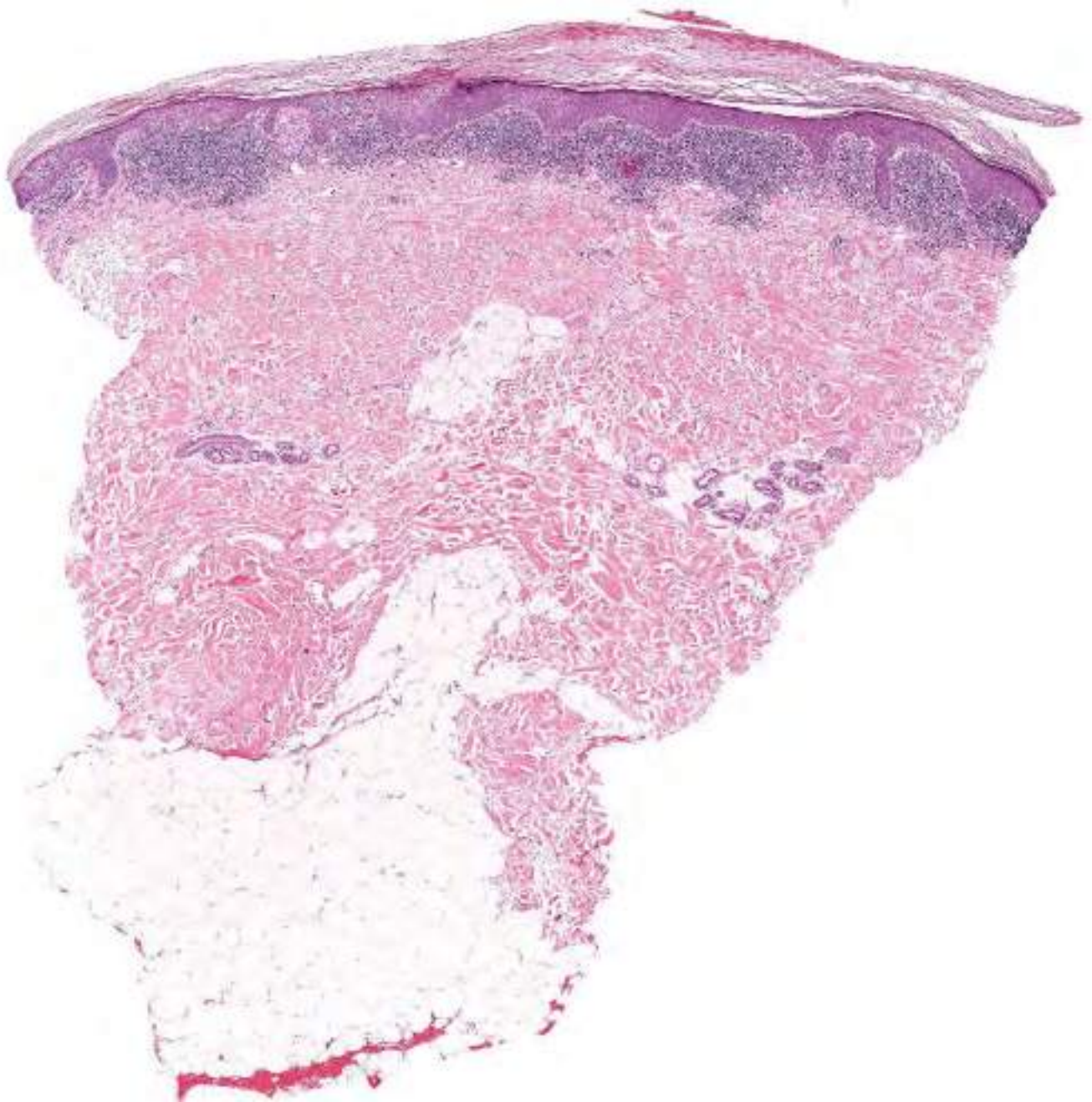
Table. Clinical Data of Patients

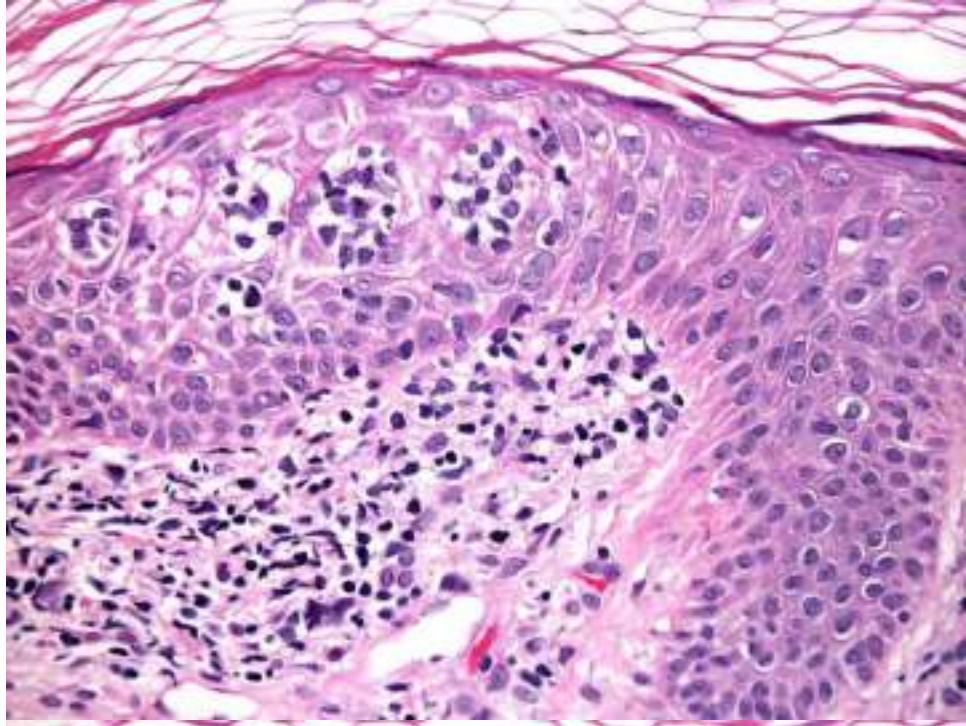
Patient No./ Sex/Age, y	Site	T-Cell Rearrangement	Follow-up, mo	Status
1/M/37	Heel	Polyclonal	11	A–
2/F/69	Thigh	Polyclonal	84	A–
3/F/53	Knee	Monoclonal	204	A+
4/F/53	Buttocks	Monoclonal	89	A–
5/M/77	Thigh	Monoclonal	51	Av
6/F/13	Lower leg	Monoclonal	76	A+
7/M/47	Forearm	Monoclonal	30	D+
8/M/75	Upper arm	Polyclonal	25	D+
9/M/61	Popliteal	Polyclonal	20	A+
10/F/51	Lower leg	Monoclonal	37	A–
11/M/36	Lower leg	Monoclonal	64	A+
12/M/65	Foot	Polyclonal	41	A+
13/F/44	Lower leg	ND	89	A–
14/F/25	Back	Polyclonal	281	A–
15/F/35	Knee	Monoclonal	144	A–
16/M/60	Thigh	Polyclonal	67	A–
17/M/50	Lower leg	ND	39	A+
18/F/49	Lower leg	Polyclonal	103	A+
19/M/7	Shoulder	ND	104	A–
20/F/24	Breast	ND	168	A–
21/F/37	Lower leg	ND	72	A–
22/F/1	Forearm	ND	168	A–
23/M/33	Right trunk	ND	382	A–

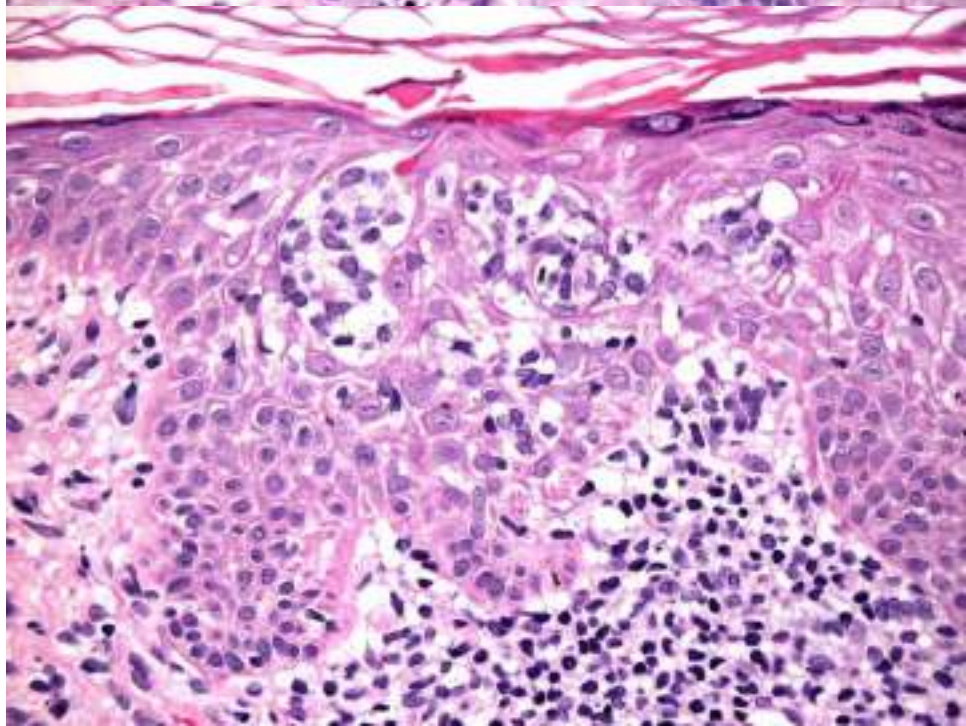
Abbreviations: A–, alive without skin disease; A+, alive with skin disease; D+, dead of unrelated conditions with persistent skin disease; ND, not done.

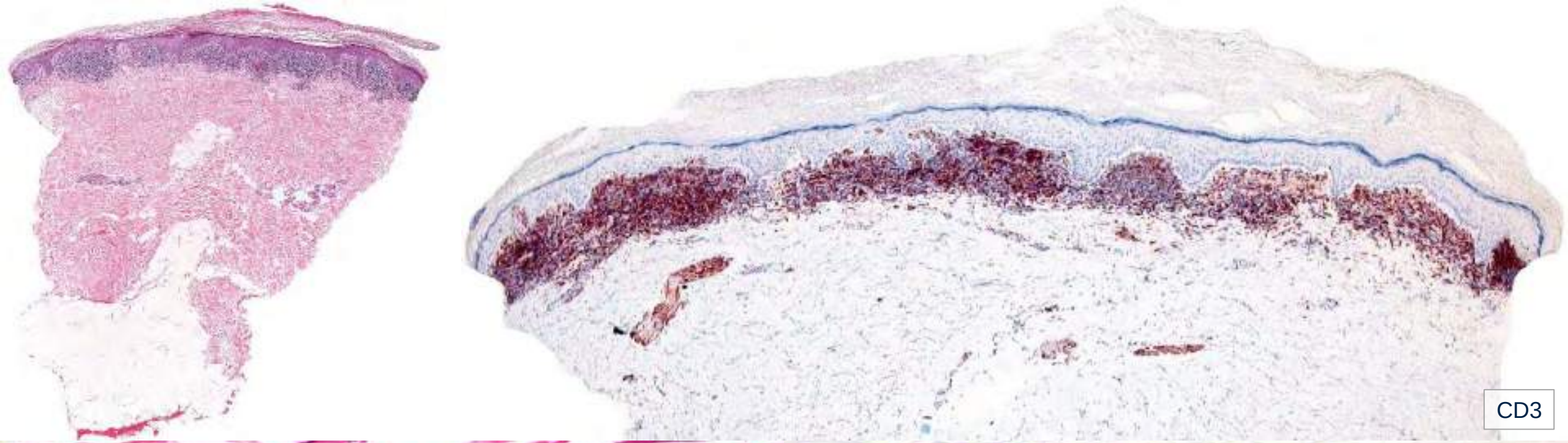
Monoclonal:	8 (50%)
Persistent disease:	9 (39,1%) (20-204)

70-year-old woman with a scaly, solitary lesion on the breast.





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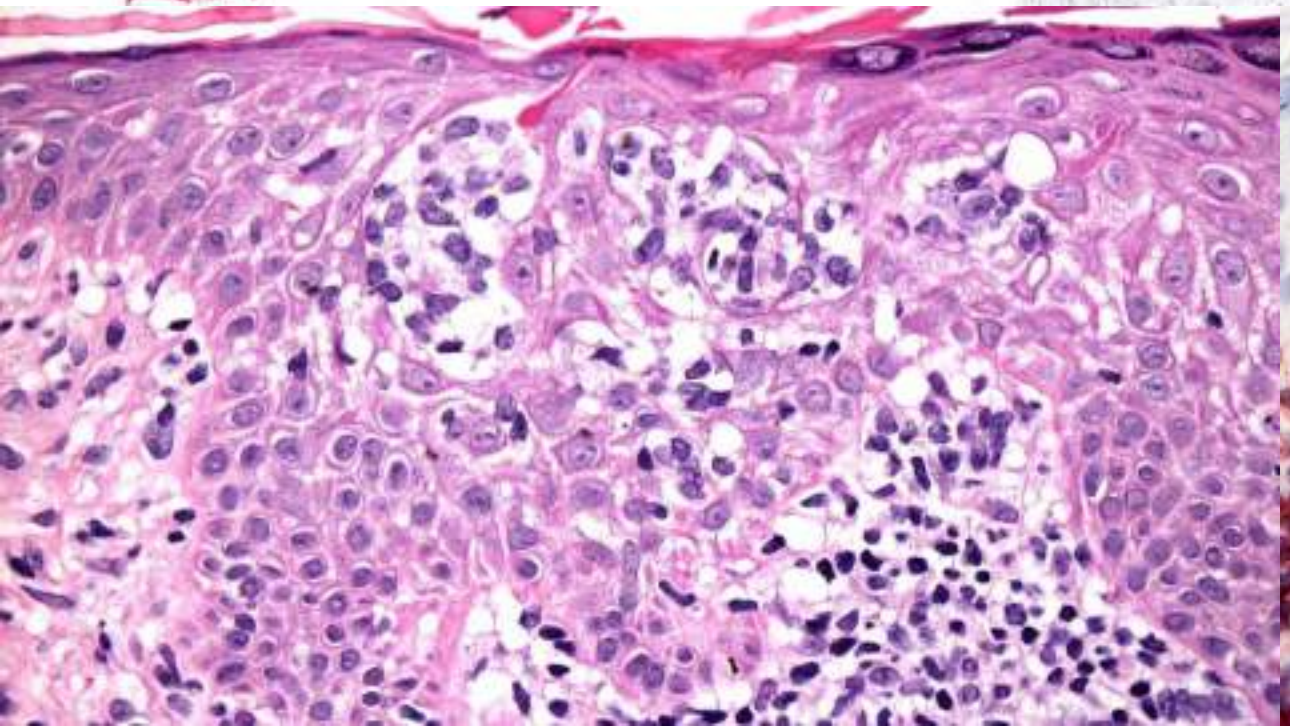

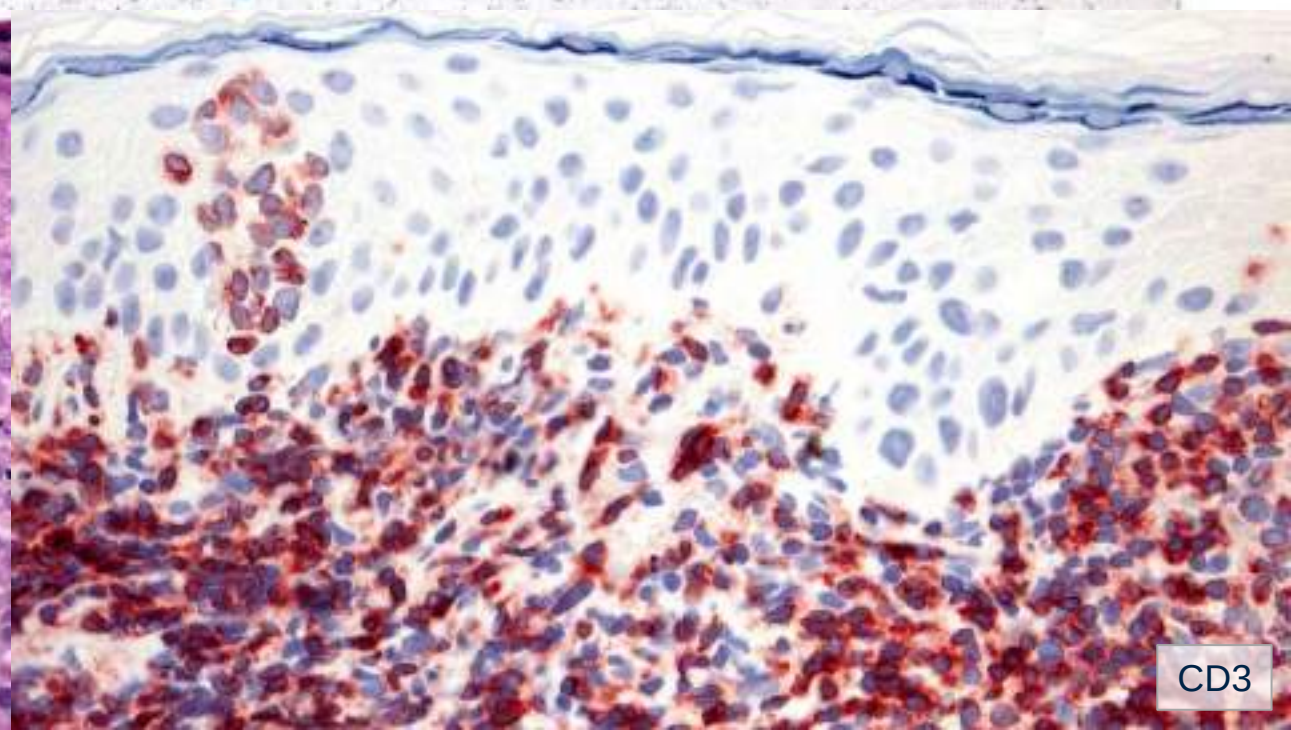
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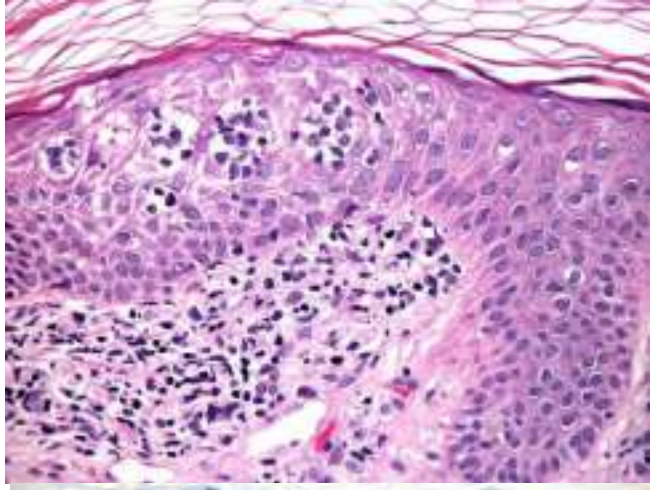

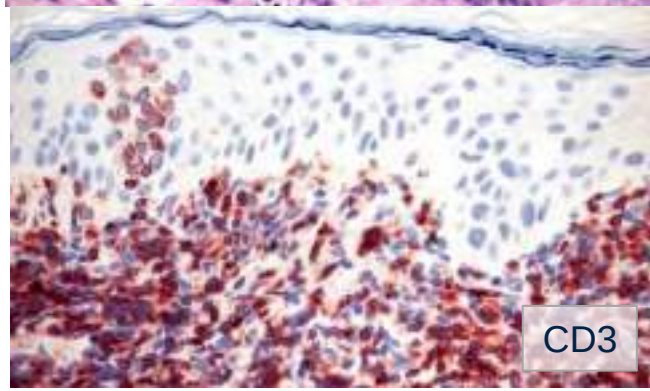
CD3

Lichenoid (lymphomatoid) keratosis

- Dense, band-like infiltrate with sharp lateral circumscription *(not visible on partial biopsies!)*
- Epithelial hyperplasia (variable); sometimes remnants of an epithelial tumor *(e.g., lentigo actinica, seborrheic keratosis)*
- Mixed infiltrate of T-cells (predominant) and B-cells
- Lack or minimal fibrosis of papillary dermis
- Variable numbers of intraepithelial ("epidermotropic") lymphocytes; may be larger than normal
- In the past reported often (and published) as "solitary" MF *(also by me...)*

The American Journal of Dermatopathology 21(6): 519–524, 1999

Solitary Skin Lesions With Histopathologic Features of Early Mycosis Fungoides

Lorenzo Cerroni, M.D., Regina Fink-Puches, M.D., Laila El-Shabrawi-Caelen, M.D., H. Peter Soyer, M.D., Philip E. LeBoit, M.D., and Helmut Kerl, M.D.

Mycosis fungoides (MF) is a cutaneous T-cell ly
usually begins with cutaneous patches that evolve
and tumors. A few recent reports describe a solit
MF distinct from localized pagetoid reticulosis,
which solitary verrucous lesions occur on acral
skin lesions with some of the histopathologic fe
rarely occur during treatment with several drug
antidepressants or antihistamines. We analyzed th
clinic features of 20 patients with solitary skin le
histopathologic features of patch- or early plaq
Eight men and 12 women (mean age 50.6, range 2
49) had solitary, small erythematous patches or pl
on the trunk (16 cases, 6 of them on the breast), u
ties (3 cases), and inguinal region (1 case). Tes
treated with one or more drugs; only two of t
antidepressants or antihistamines. Histopathologic
revealed in all cases a band-like infiltrate in the
frequently with epidermotropism of solitary
Atypical lymphocytes were present in a minority
immunohistology showed a predominance of CD3
cytes, in most cases admixed with clusters of CI
Only a small proportion of the infiltrate was CD8
analysis of the rearrangement of the T-cell recep
performed in 16 cases using the polymerase c
(PCR) technique and revealed a monoclonal band
After surgical excision, 2/14 patients had a recurr
surgical scar. In 18 patients with complete follo
evidence of "classic" MF could be observed afte
follow-up of 31.9 months. Solitary skin lesions w
pathologic features of MF can be considered as a
clinicopathologic entity, probably representing a soli
mycosis fungoides.

Key Words: Solitary mycosis fungoides—Cu
lymphoma—Cutaneous T-cell pseudolympho
lymphomatous drug eruptions.

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TABLE 1. *Clinical data, drug history, and results of PCR analysis of TCR genes*

Patient no.	Sex	Age	Location	Drugs	PCR analysis of TCR genes	Treatment	Follow-up (months)	
1	F	59	back	no	P	TE	A&W (45)	A&W (83)
2	F	53	breast	[illegible]	M	TE	A&W (50)	A&W (176)
3	F	45	breast	Developed new lesions	P	TE	A&W (26)	A&W (194)
4	F	23	breast	no	M	TE	A&W (76)	A&W (258)
5	F	44	inguinal	unknown	nd	TE	LFU	LFU
6	M	63	breast	no	P	TE	A&W (7)	A&W (27)
7	M	71	flank	no	nd	TE	A&W (38)	A&W (196)
8	M	47	arm	unknown	P	TE	LFU	D- (30)
9	M	47	back	no	M	TE	A&W (75)	A&W (239)
10	M	75	flank	Isocorbide 5-mononitrat	M	TE	A&W (48)	A&W (48)
11	M	36	back	Clofibrate; Atenolol, Allopurinol	M	local steroids	A&D (15)	A&W (35)
12	F	51	breast	Developed new lesions & LyP	P	local steroids	A&D (8)	A&W (167)
13	F	58	back	Hydrochlorothiazide Sucralfate; Ranitidine; Famotidine	P	local steroids	A&D (11)	A&W (176)
14	F	58	breast	Levothyroxine	M	local steroids	A&D (57)	A&W (118)
15	F	29	abdomen	Levothyroxine	P	TE	A&W (23)	A&W (184)
16	F	70	arm	Levothyroxine; Isradipine; Allopurinol; Bisoprolol; Terbutaline; Chlordiazepoxide; Amitriptyline; Ketotifene	P	TE	A&W (22)	A&W (207)
17	F	34	back	no	M	TE	recurrence (36)	
18	F	43	back	Fluoxetine	M	local steroids	A&D (18)	
19	M	24	back	no	P	local steroids	A&D (8)	
20	M	82	arm	[illegible] Naproxen; Acetyl Salicylic acid; Acetaminophen	P	TE	recurrence (12)	

PCR, polymerase chain reaction; TCR, T-cell receptor; nd, not done; TE, total excision; recurrence, recurrence within surgical scar; PB, punch biopsy; M, monoclonal band; P, polyclonal smear; A&W, alive and well; A&D, alive with persistent disease; LFU, lost to follow-up.

San Francisco

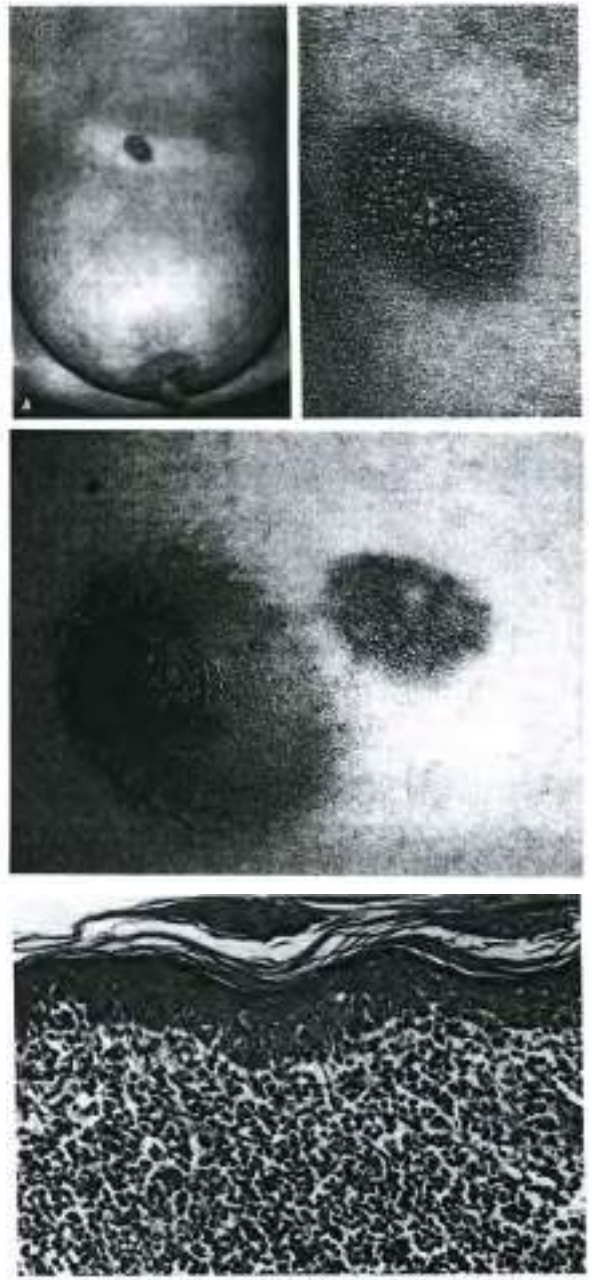
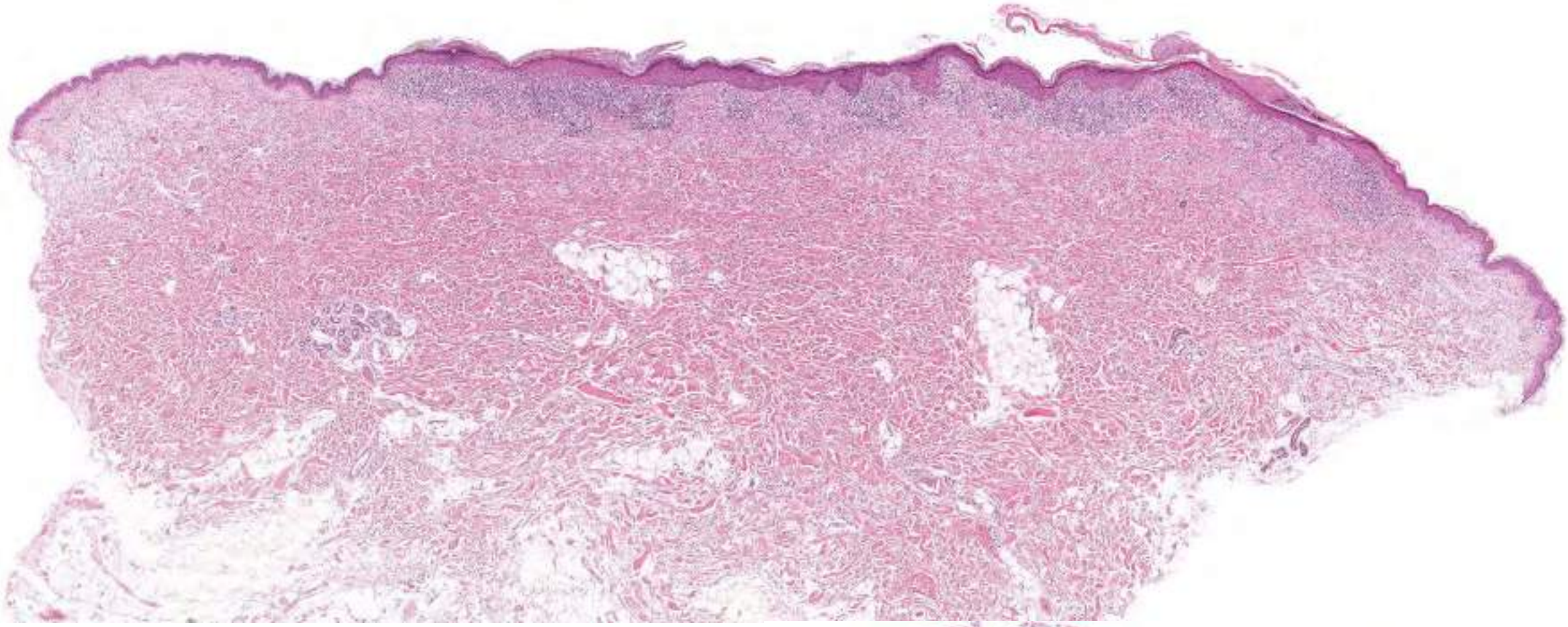
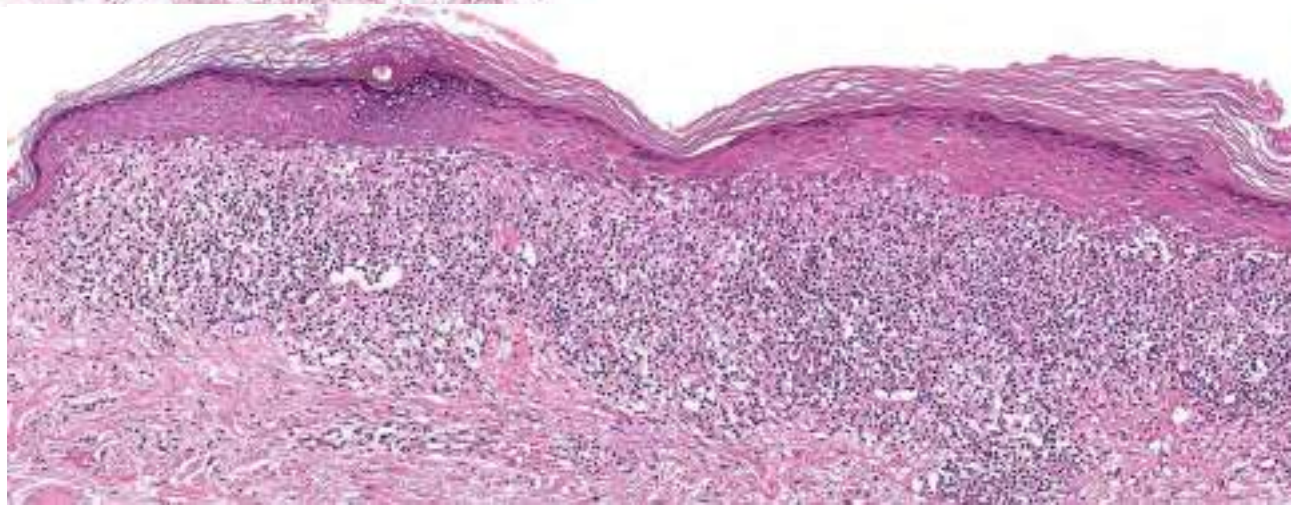
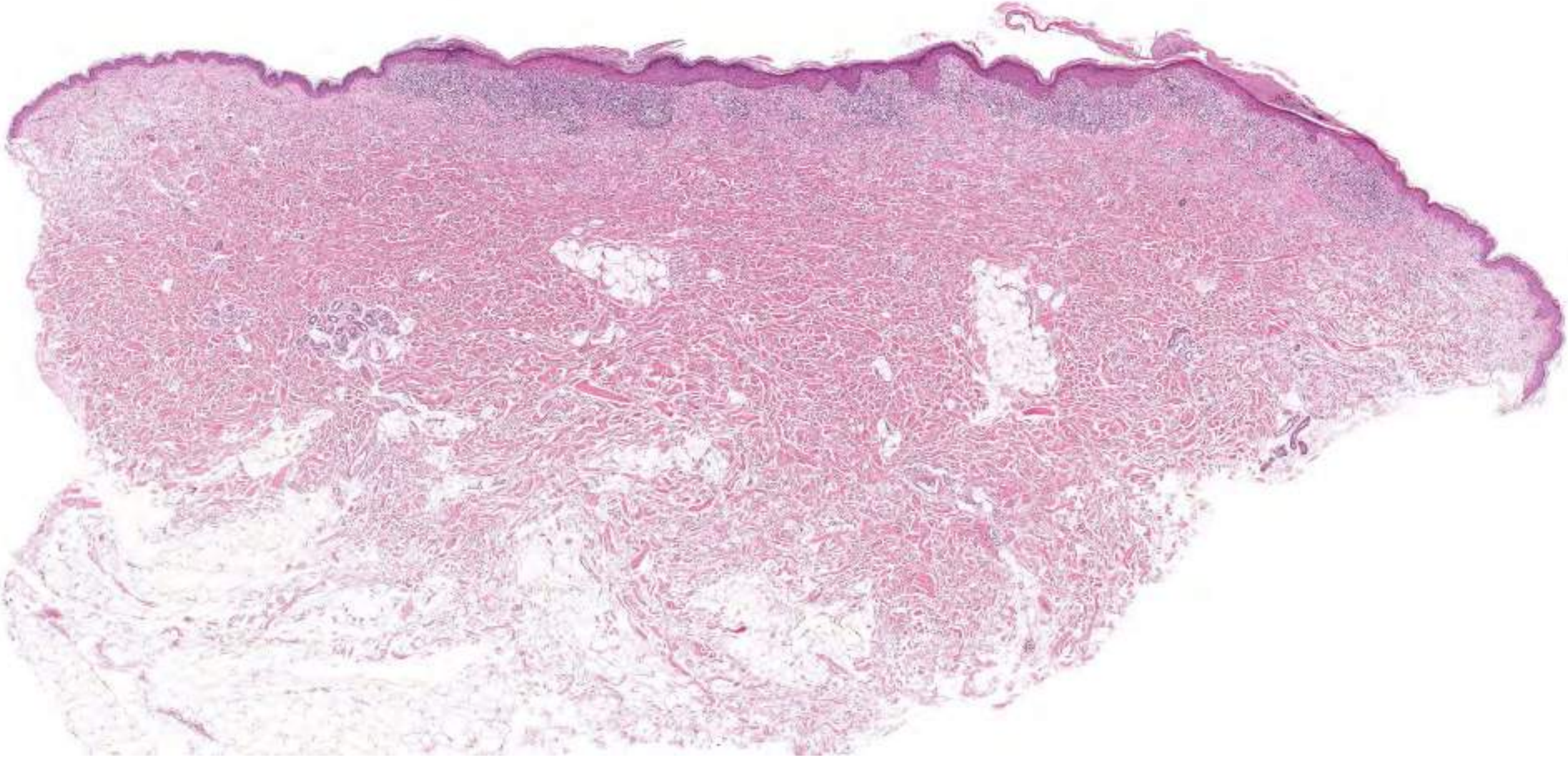


FIG. 5. Small lymphocytes predominate; note small intraepidermal collection of lymphocytes.

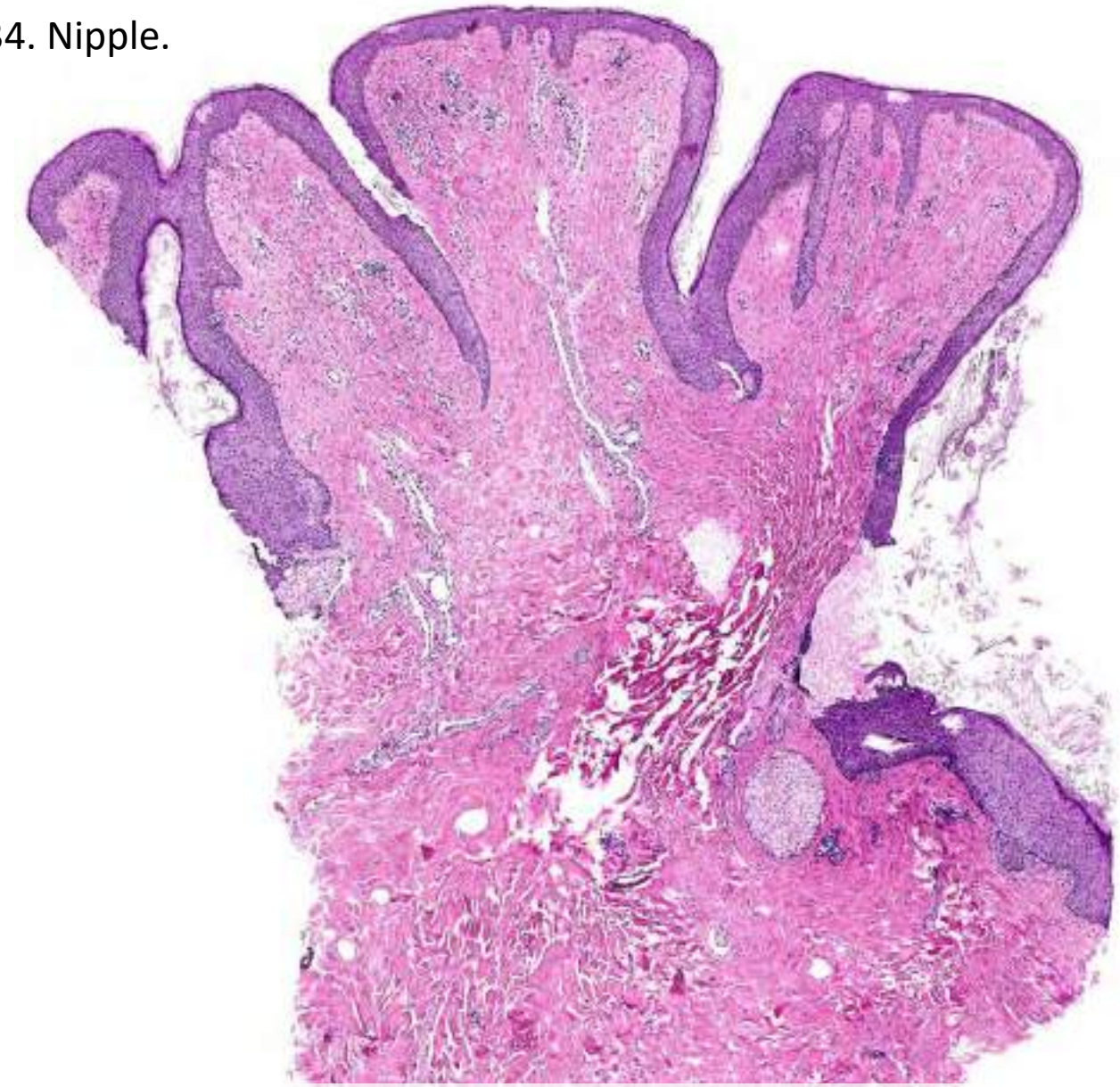


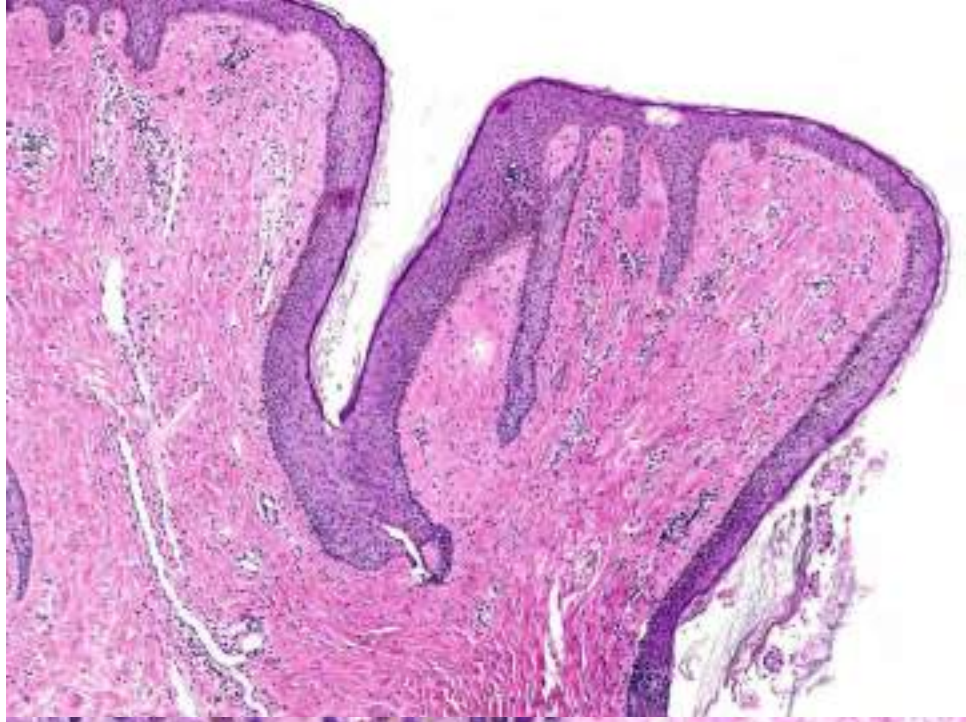


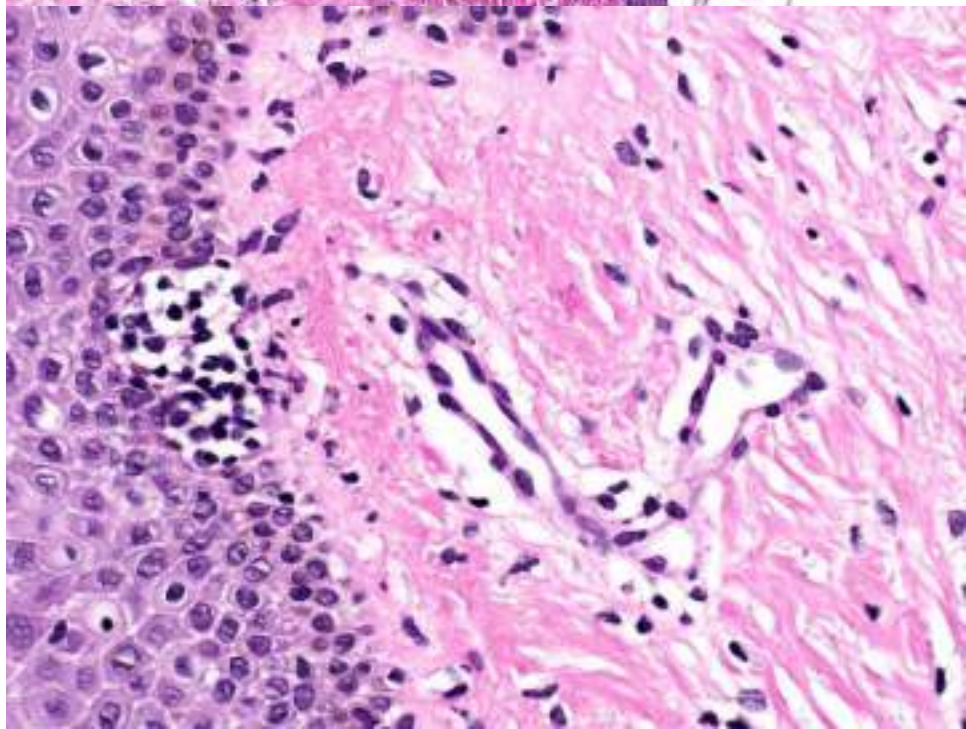
Clue: sharp circumscribed, dense infiltrate; mixed T- and B-lymphocytes; in many cases focal rests of an epithelial tumor, often seborrheic keratosis



F, 34. Nipple.

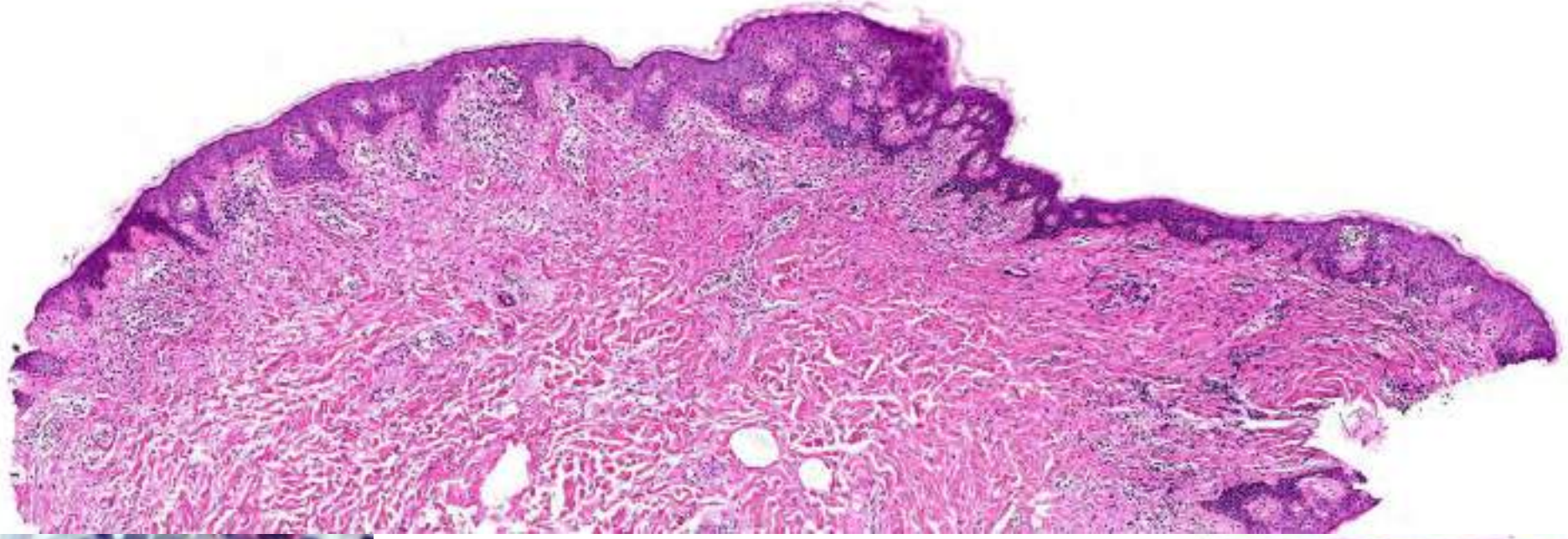


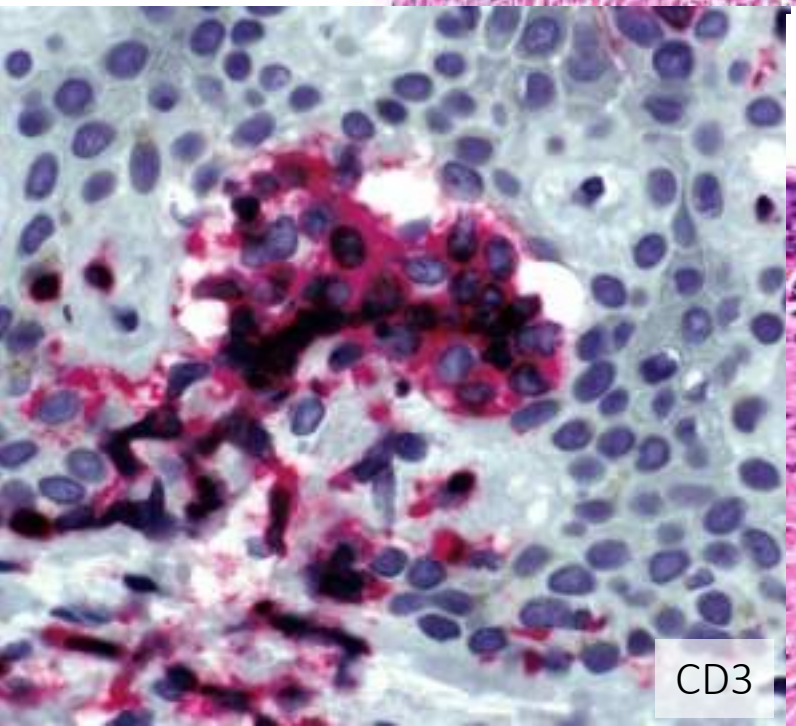


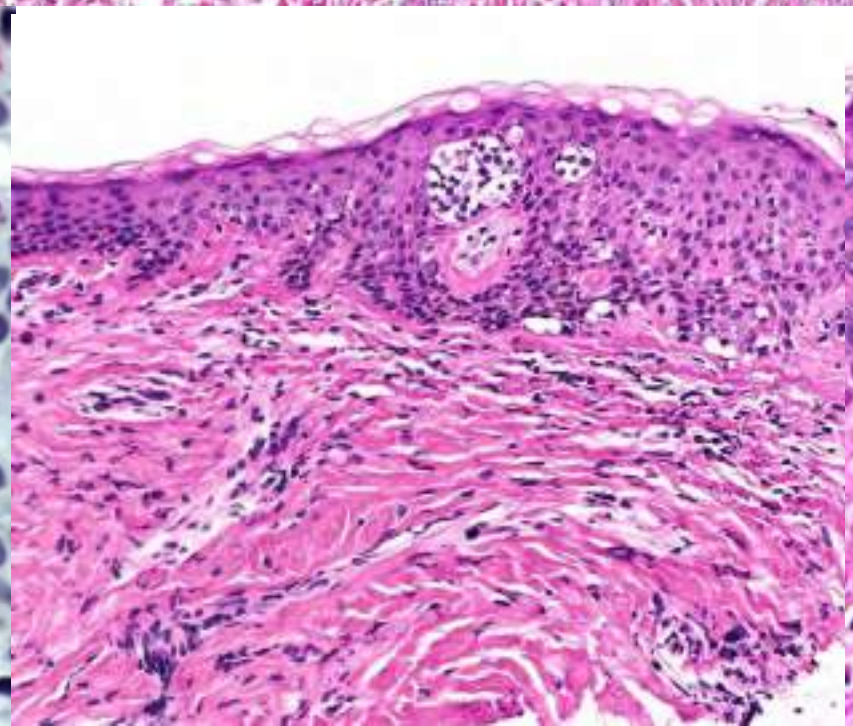


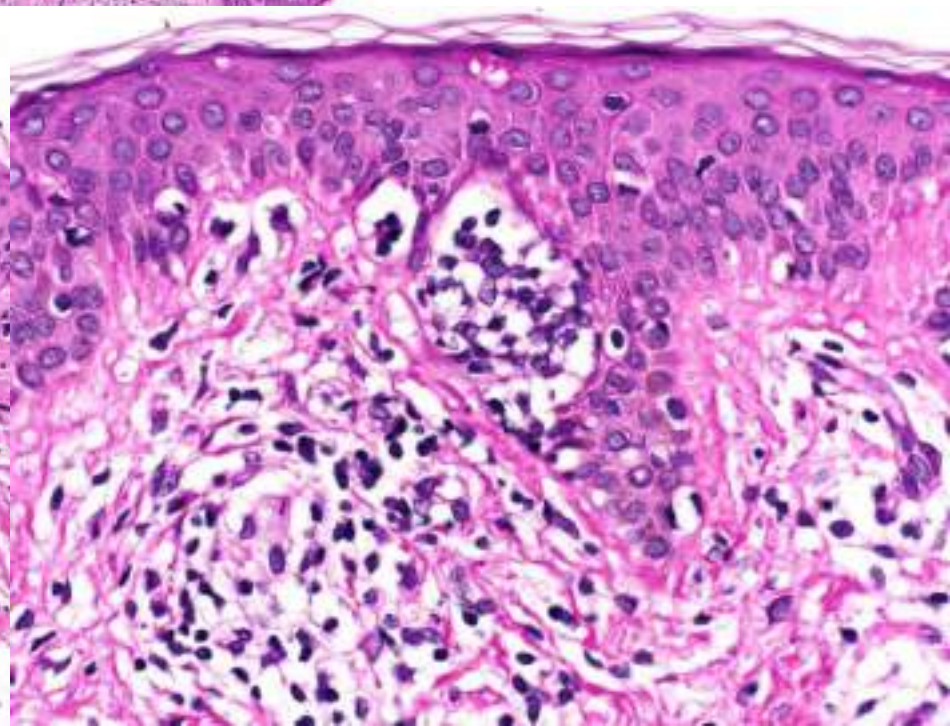
Reported as "suspicion of MF"

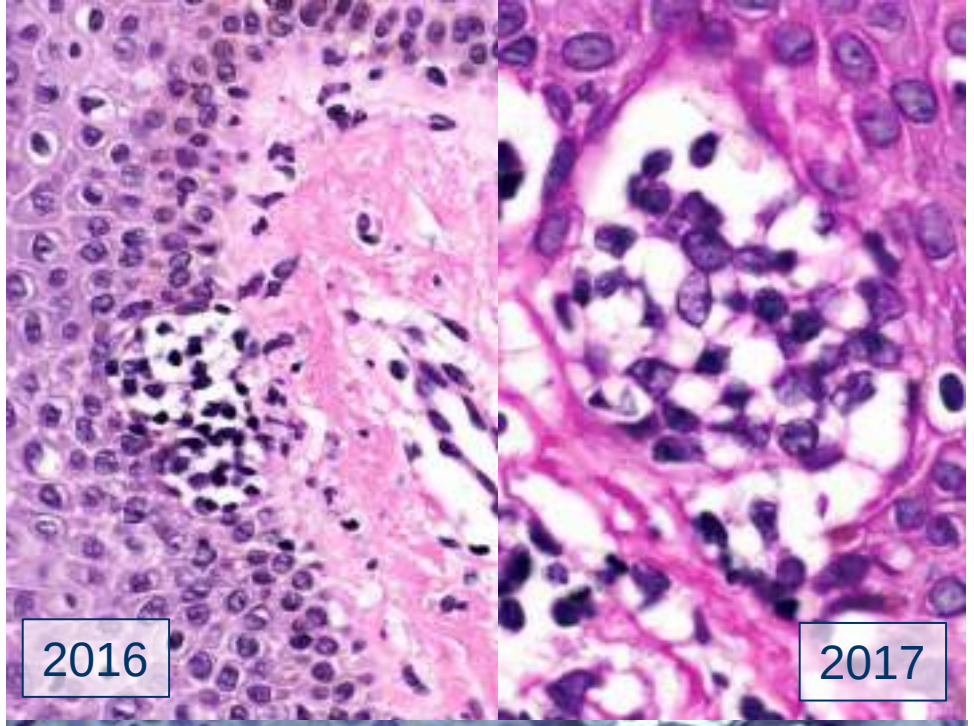
One year later repeat biopsy on same nipple to confirm the "suspicion of MF" made on the previous biopsy.

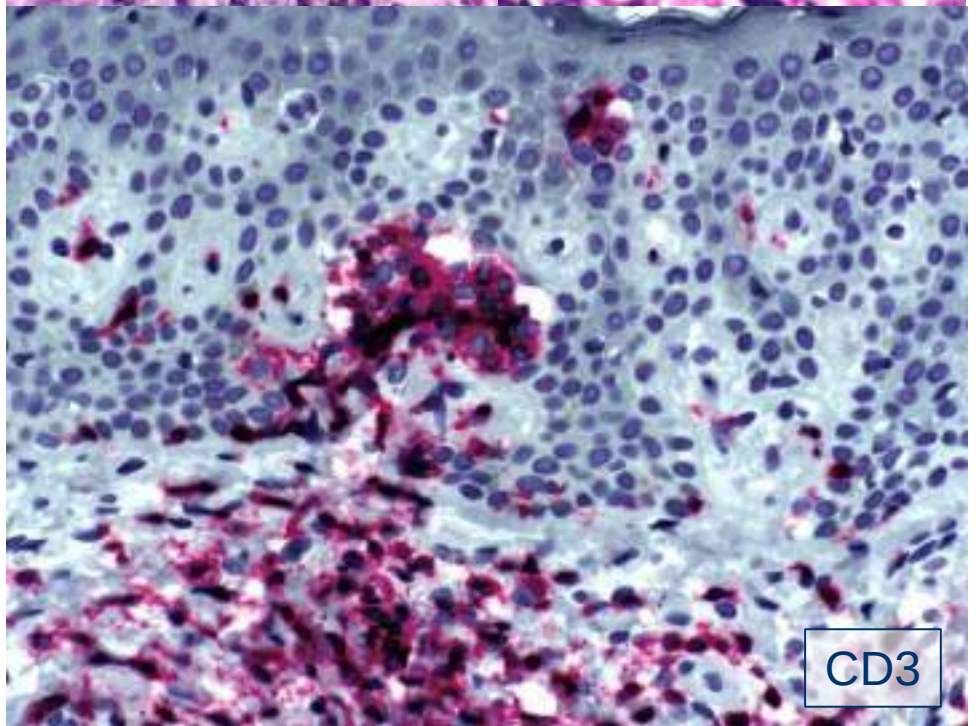












2019

Clinical correlation (available only 2 years after the second biopsy, 3 years after the first one).

Nevoid hyperkeratosis of the nipple

J Cutan Pathol

Journal of
Cutaneous Pathology

Nevoid hyperkeratosis of the areola misinterpreted as mycosis fungoides

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Nevoid hyperkeratosis of the nipple and areola is a benign condition with fewer than 70 cases reported in the literature. We report a case of unilateral nevoid hyperkeratosis of the areola with intraepidermal lymphocytes that resembled Pautrier's microabscesses on histological examination. This is the third report of mycosis fungoides-like changes in nevoid hyperkeratosis of the nipple and areola. In addition, this is the first case to present immunohistochemical and T-cell gene rearrangement studies of the intraepidermal lymphocytes. This case highlights a potential histopathological pitfall in the diagnosis of nevoid hyperkeratosis of the nipple and areola.

Keywords: mycosis fungoides, nevoid hyperkeratosis, pitfall, simulator

Rosman IS, Hepper DM, Lind AC, Anadkat MJ. Nevoid hyperkeratosis of the areola misinterpreted as mycosis fungoides. J Cutan Pathol 2012; 39: 545–548. © 2012 John Wiley & Sons A/S.

Nevoid hyperkeratosis of the nipple and areola is a rare benign condition with fewer than 70 cases reported in the literature. Nevoid hyperkeratosis presents as asymptomatic verrucous plaques on the nipples and/or areolae and is characterized histopathologically by hyperkeratosis, acanthosis, papillomatosis and keratin plugging or hyperkeratosis.

We report a case of unilateral nevoid hyperkeratosis of the areola with intraepidermal lymphocytes that resembled Pautrier's collections on microscopic examination. To our knowledge, this is the third report of mycosis fungoides-like changes in nevoid hyperkeratosis of the nipple and areola. In addition, this case is the first to present immunohistochemical studies of the intraepidermal lymphocytes and the results of T-cell gene rearrangement analysis.

Case report

A 43-year-old Caucasian woman with no significant medical history presented with a 4-year history of thickening of the right areola. She had no history of treatment with oral contraceptives or other hormonal agents. Three years prior, the area had been biopsied and diagnosed as mycosis fungoides by dermatopathologists at an outside institution. The lesion had remained stable over the subsequent years with only occasional pruritus. Intermittent treatment with a topical corticosteroid was employed without benefit. She presented to our clinic for a second opinion prior to undergoing further treatment for mycosis fungoides.

On physical examination, an irregular verrucous plaque was present on the right areola with extension of a velvety tan plaque beyond the margin of the areola (Fig. 1). There was no lymphadenopathy, and no other cutaneous lesions were evident.

Two 4-mm punch biopsies of the right areola were performed during her visit to our institution. The findings from both showed similar features, including hyperkeratosis, papillomatosis and acanthosis (Fig. 2). There were occasional small aggregates of monomuclear cells within the epidermis, and the superficial dermis was sclerotic with stellate-appearing fibroblasts (Figs. 3 and 4). A CD3 immunohistochemical stain highlighted the monomuclear cells, including the epidermal aggregates.

Dermato pathology

Dermatopathology 2015;2:61–66

Case Studies

The Dilemma of Coexisting Nevoid Hyperkeratosis of the Nipple and Areola in Mycosis Fungoides: A Report of Three Cases

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Can Baykal[a]

Departments of [a]Dermatology and Venereology and [b]Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Key Words
Nevoid hyperkeratosis of the nipple and the areola · Mycosis fungoides

Abstract
Nevoid hyperkeratosis of the nipple and areola (NHNA) is a rare clinicopathological entity showing persistent and strictly localized hyperkeratotic lesions of the nipple, areola or both with unknown etiopathogenesis. A similar clinical appearance may also be seen in different diseases with specific histopathological features. There are a few anecdotal reports on the association of NHNA with mycosis fungoides (MF), but they do not describe a uniform condition. In this report, we present 3 patients with hyperkeratotic lesions of the nipple and areola associated with MF but showing different histopathological features. We also review similar cases in the literature and discuss possibilities concerning this association. Two of our cases represent the association between MF and NHNA without histopathological features of MF on the nipple-areola complex. The other case represents hyperkeratosis of the nipple and areola with specific histological and immunohistochemical features of MF. Hence, we would like to hypothesize that MF may involve the nipple and areola and have an appearance similar to NHNA. Intriguingly, however, NHNA may occasionally also be seen in association with MF. However, this peculiar association requires further explanation.

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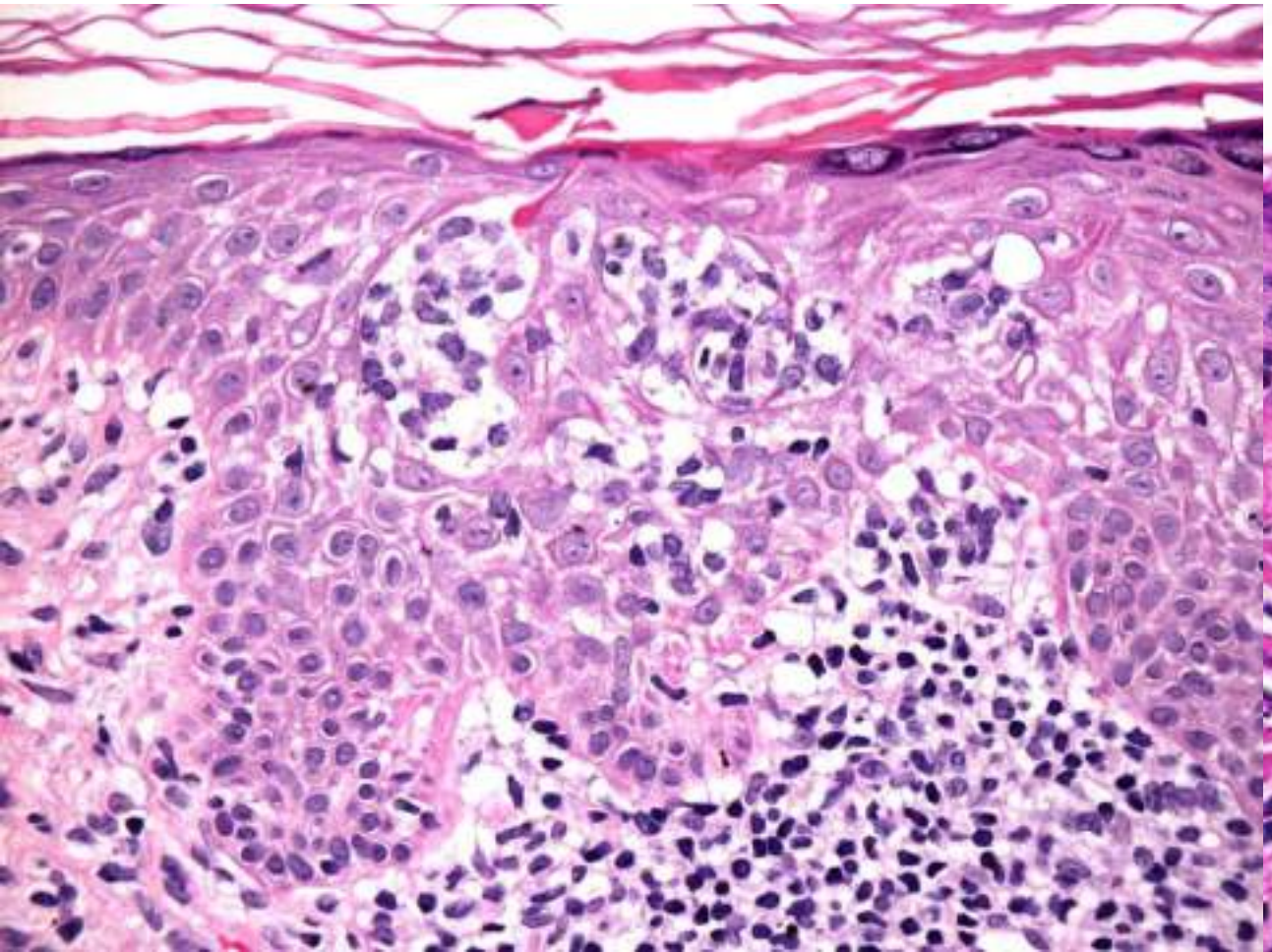
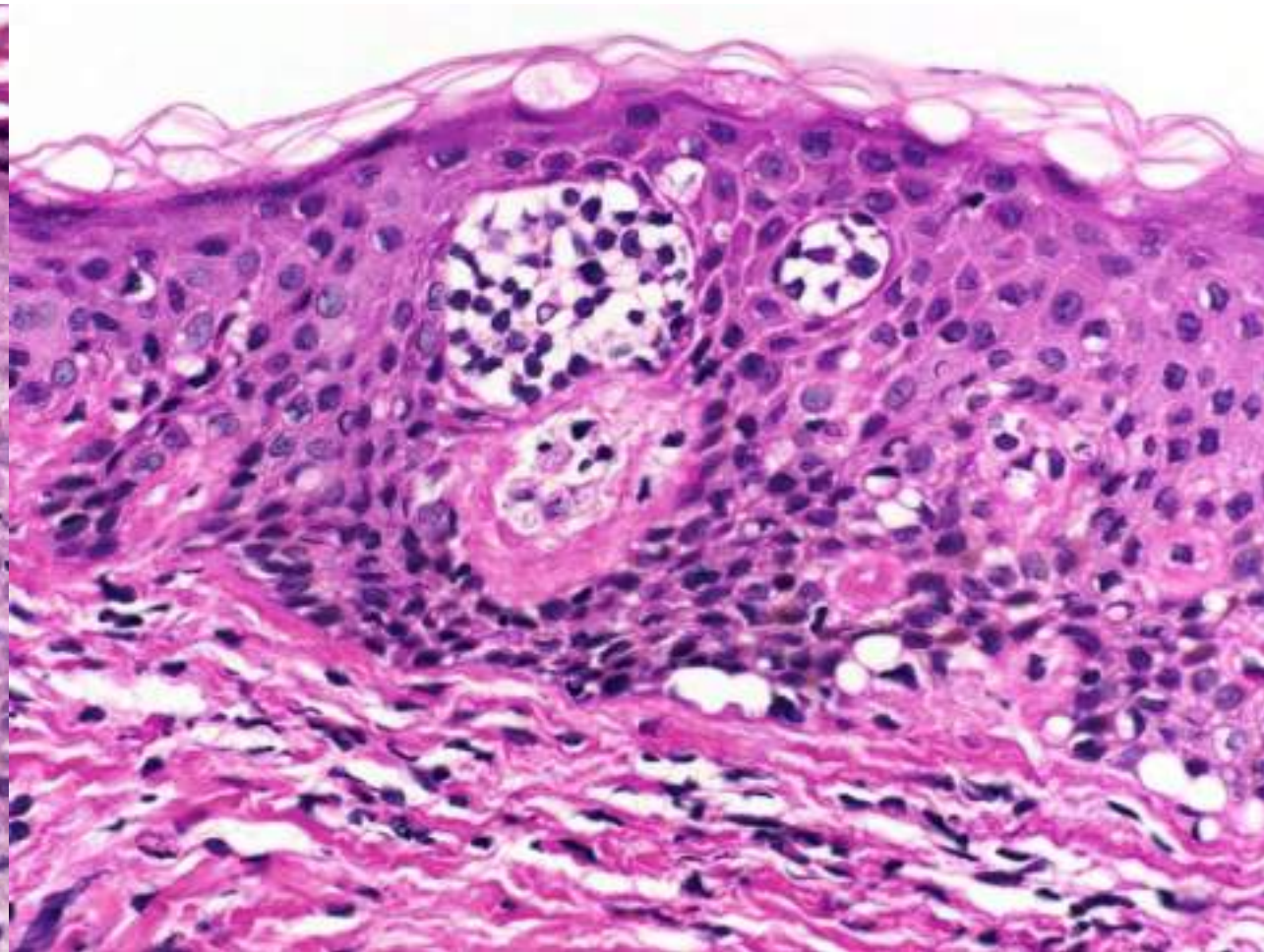
KARGER 129

Benign intraepidermal collections of lymphocytes ("pseudo"-Darier nests / Pautrier microabscesses)

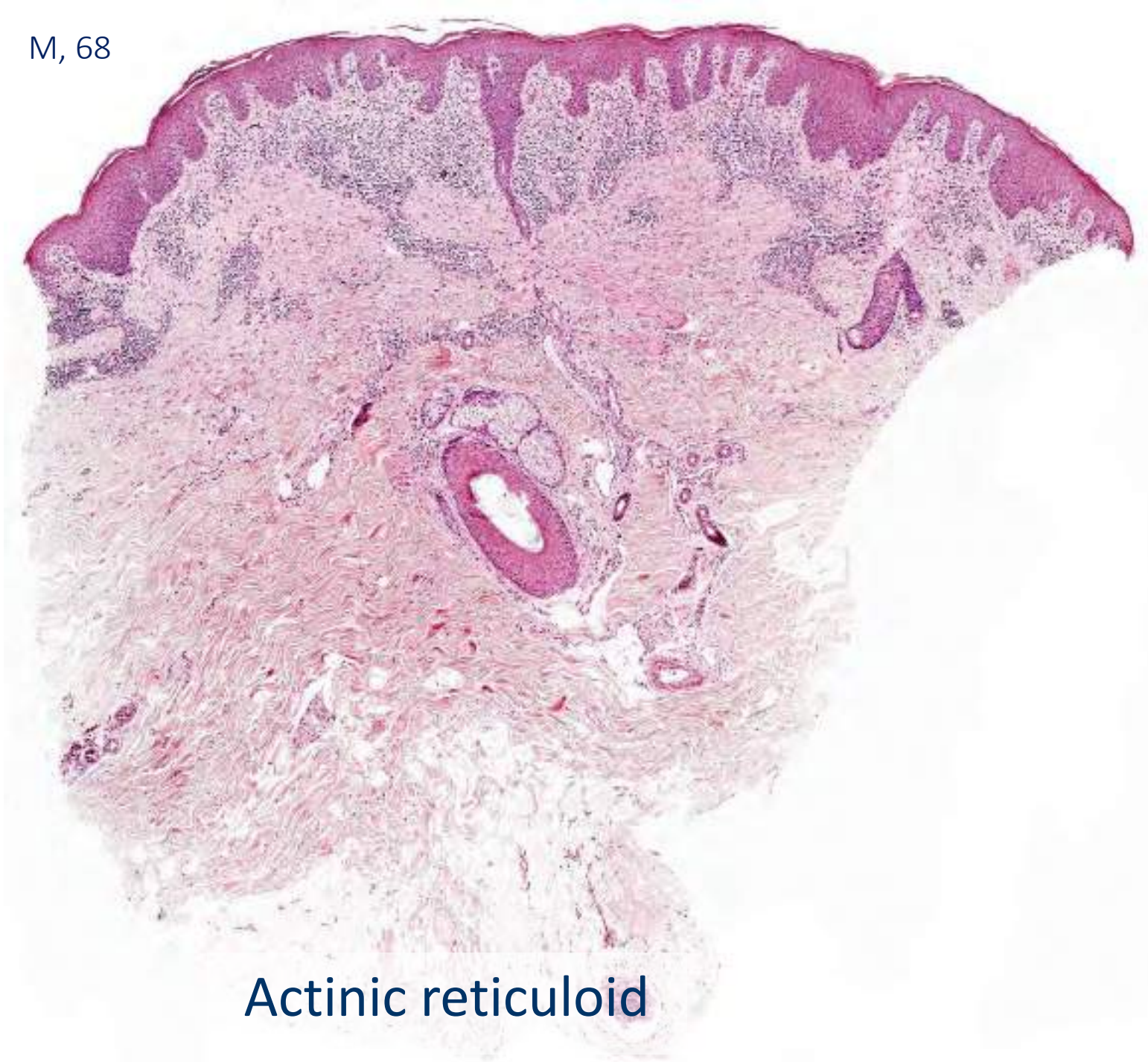
Lichenoid keratosis



Nevoid hyperkeratosis of the nipple

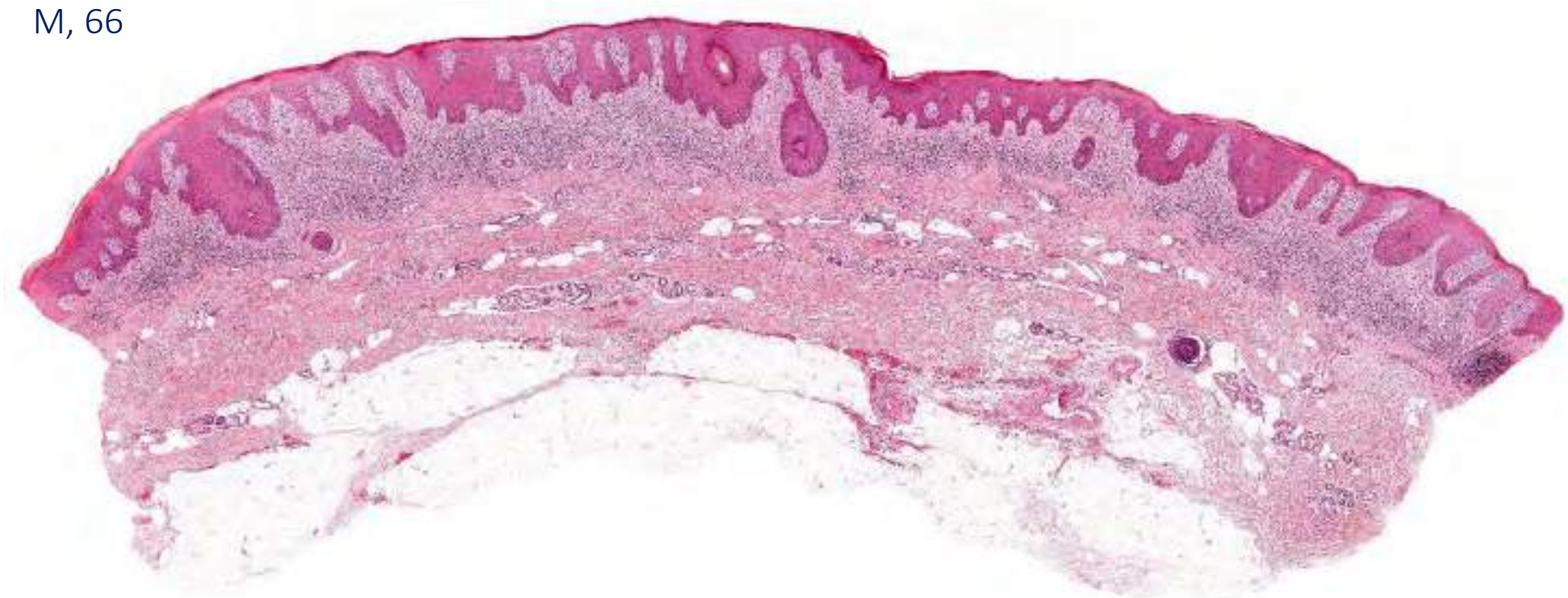


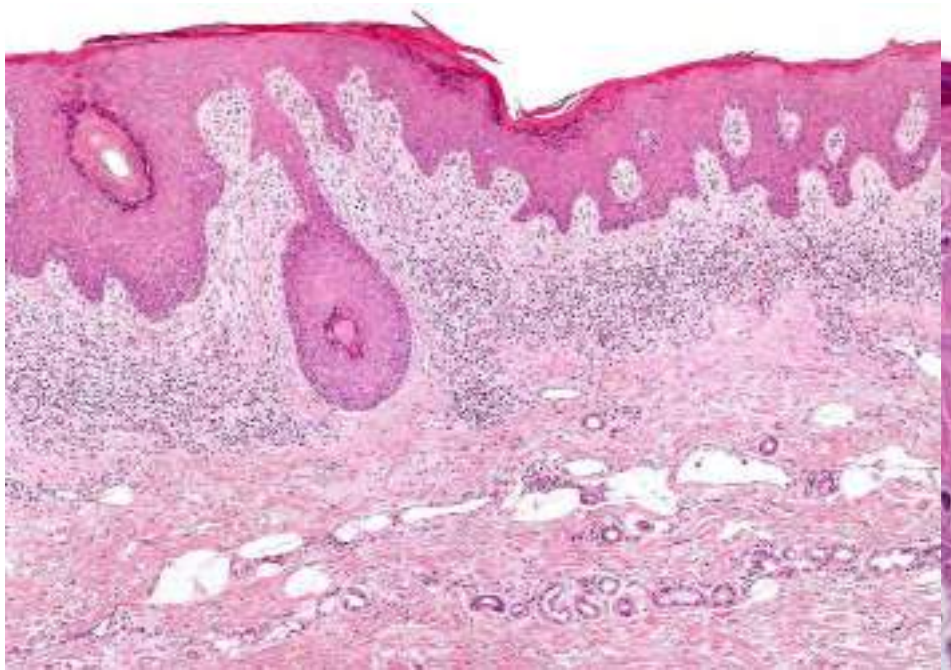
M, 68

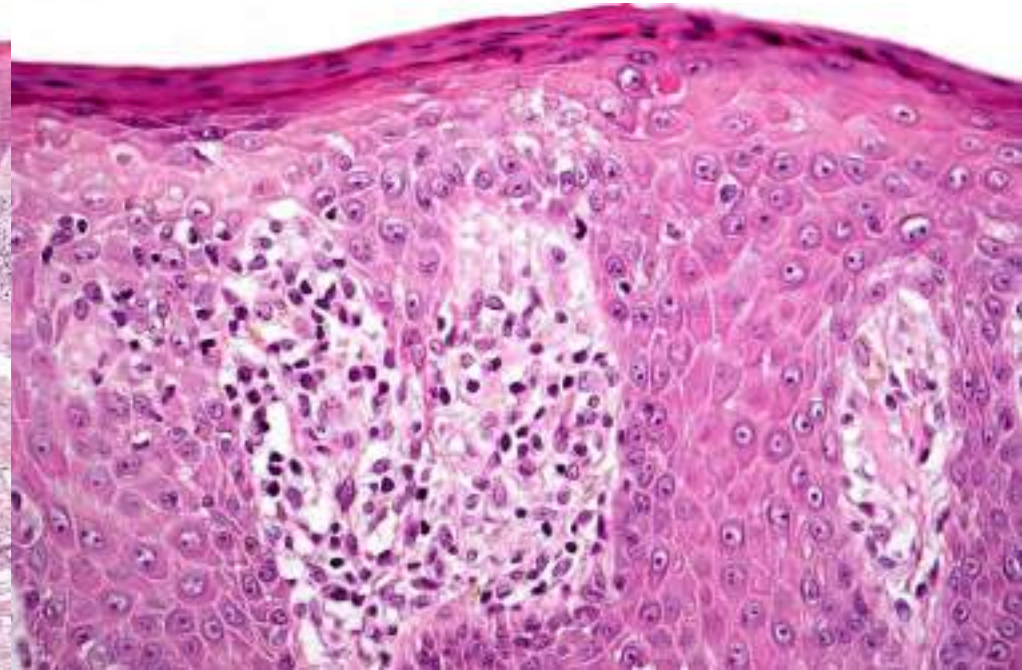


Actinic reticuloid

M, 66







Differentiation between actinic reticuloid and cutaneous T cell lymphoma by T cell receptor γ gene rearrangement analysis and immunophenotyping

V Bakels, J W van Oosterom, A H Pieterman, C J L M Meijer, R Willemze

Abstract

Aims—Differentiation between actinic reticuloid and cutaneous T cell lymphoma can be extremely difficult. Demonstration of clonal T cell receptor (TCR) gene rearrangements has been suggested as a potential diagnostic criterion, but the results obtained thus far have been conflicting. This study investigated whether TCRγ gene rearrangement analysis, using polymerase chain reaction (PCR) in combination with denaturing gradient gel electrophoresis (DGGE) and immunohistochemistry, can serve as a diagnostic criterion.

Methods—PCR/DGGE was performed on skin, peripheral blood mononuclear cells, and/or lymph nodes of seven patients with actinic reticuloid, 11 patients with Sézary syndrome, and 15 patients with a benign form of erythroderma. The results of PCR/DGGE and Southern blot analysis of TCRβ gene rearrangements were compared. In addition, CD4:CD8 ratios in skin and peripheral blood samples were [illegible]

Results—Clonal TCRγ gene rearrangements were detected in all seven cases of actinic reticuloid. Clonal TCRβ gene rearrangements were detected in only five of the 12 samples from patients with actinic reticuloid. Clonal TCRγ gene rearrangements were also found in 10 of 11 patients with Sézary syndrome. Previous studies suggested that clonal TCR gene rearrangements are not found in benign forms of erythroderma. PCR/DGGE and Southern blot analysis of TCR gene rearrangements have been found in almost 100% of patients with unequivocal cutaneous T cell lymphoma, but studies for the presence of clonal T cells in samples with actinic reticuloid have been few and the results have been conflicting.

Conclusions—The results of this study [illegible] analysis, in combination with immunohistochemistry, may be an important adjunct in differentiating between actinic reticuloid and cutaneous T cell lymphoma. In patients suspected of having actinic reticuloid, application of both techniques is recommended.

J Clin Pathol 1998;51:154–158

Keywords: actinic reticuloid; T cell receptor gene rearrangement; cutaneous T cell lymphoma; polymerase chain reaction/denaturing gradient gel electrophoresis

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Accepted for publication 9 December 1997

Actinic reticuloid is a severe, chronic photosensitivity disorder, first described by Dubois.[1] The clinical picture is characterised by an eczematous, pruritic eruption, predominantly present on light exposed areas of skin. Frequently, lesions spread to covered areas, leading to erythroderma. This erythrodermic variant of actinic reticuloid can resemble Sézary syndrome, a type of cutaneous T cell lymphoma. Apart from erythroderma, pruritus, lymphadenopathy, and the presence of atypical lymphocytes in the peripheral blood, patients with the erythrodermic form of actinic reticuloid and patients with Sézary syndrome may also have alopecia, palmoplantar hyperkeratosis, or onychodystrophy.[2 3]

Histologically, actinic reticuloid is characterised by the presence of extensive dermal infiltrates of medium sized lymphoid cells with cerebriform or convoluted nuclei. These cells show epidermotropism and sometimes even form Pautrier-like microabscesses.[2 3] These cellular and histological features are also characteristic for mycosis fungoides, the most common variant of cutaneous T cell lymphoma, and Sézary syndrome. Previous studies suggested that clonal T cell receptor (TCR) gene rearrangements have been found in almost 100% of patients with unequivocal cutaneous T cell lymphoma,[4] but studies for the presence of clonal T cells in samples with actinic reticuloid have been few and the results have been conflicting.[5 6]

Therefore, we investigated the presence of clonal T cell populations in skin, lymph node and/or peripheral blood samples of patients with actinic reticuloid, Sézary syndrome, or a benign form of erythroderma, by means of polymerase chain reaction (PCR) amplification of the TCRγ gene in combination with denaturing gradient gel electrophoresis (DGGE). In addition, immunophenotypic analysis was performed on skin and peripheral blood samples to assess the proportions of $CD4^+$ and $CD8^+$ T cells.

Immunophenotypic analysis demonstrated increased proportions of CD8+ T cells in the skin in seven of seven cases of patients with actinic reticuloid.

Chronic Actinic Dermatitis/Actinic Reticuloid: A Clinicopathologic and Immunohistochemical Analysis of 37 Cases

Michael Salfinopoulos, MD, MSc, Jacynna Dennicke, MD,* M. Estela Martinez-Escala, MD,* Pedram Gerami, MD,*† and Joan Guitart, MD*†*

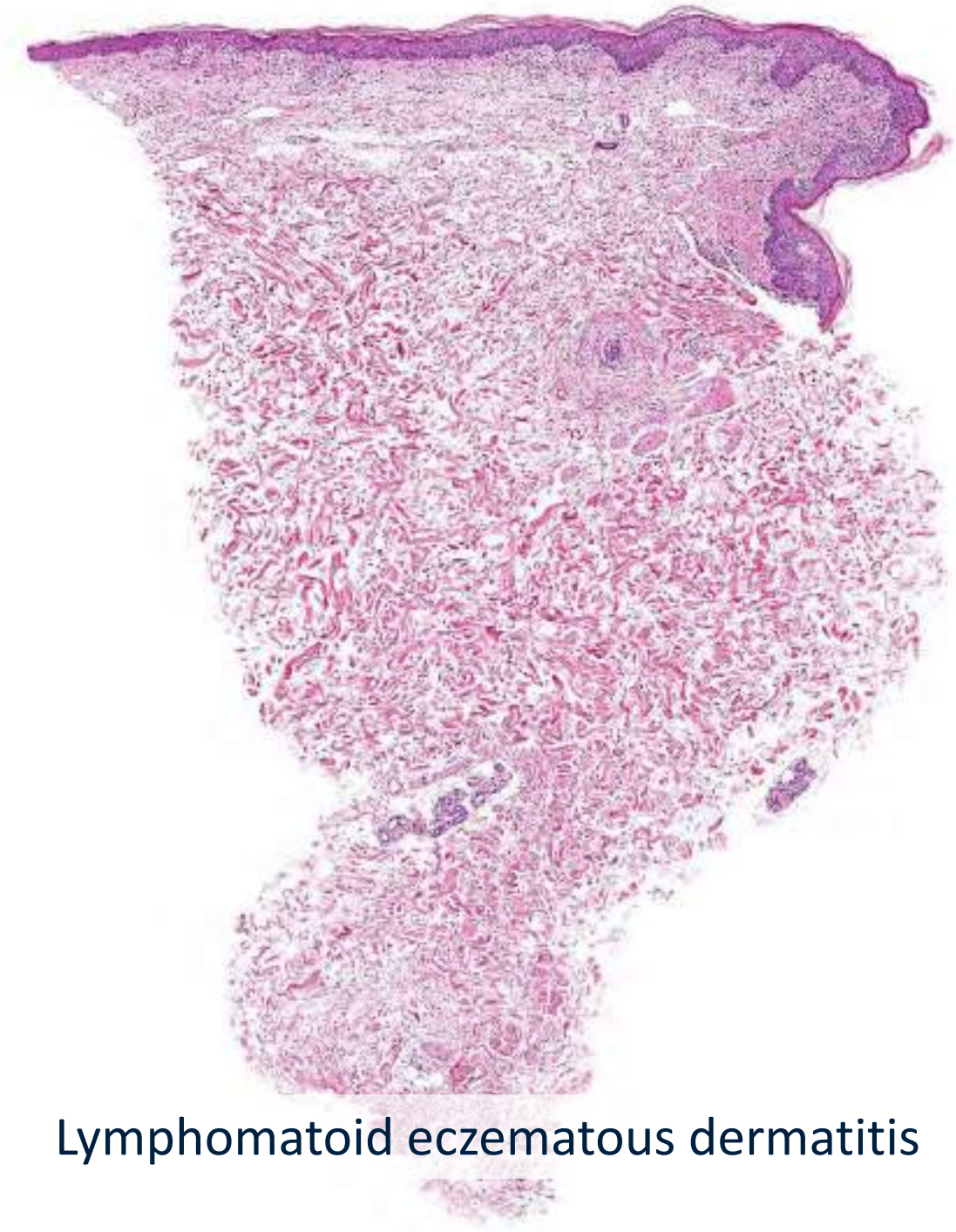
[illegible] which can vary from mild eczematous cases to AR, the [illegible]

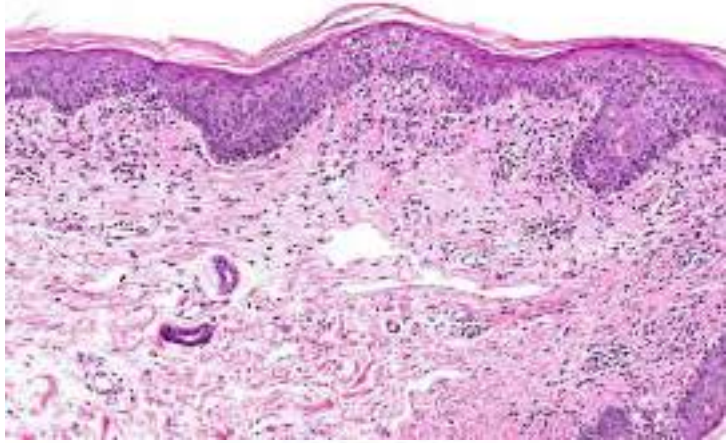
TABLE 2. Summary of Pathologic Data

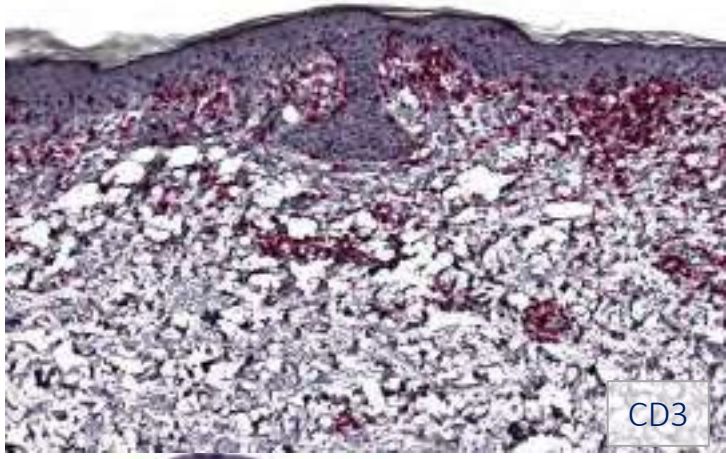
Characteristic	Total Sample (%)
Acanthosis	37/37 (100)
Spongiosis	37/37 (100)
Dermal lymphocytic infiltrate	37/37 (100)
Papillary dermal fibroplasias	37/37 (100)
Melanin-laden macrophages	37/37 (100)
Prominent stellate dermal dendrocytes	37/37 (100)
Multinucleated dendritic cells	35/37 (95)
Plasma cells	33/37 (89)
Eosinophils	33/37 (89)
Parakeratosis	31/37 (84)
Medium-large reactive lymphocytes	25/37 (68)
Follicular infundibulum spongiosis and exocytosis	18/27 (67)
Exocytosis	23/37 (62)
Solar elastosis	23/37 (62)
Superficial serous exudate	18/37 (49)
Pautrier-like microabscesses	13/37 (35)
Epidermal infiltrate	
$CD8^+$	20/25 (80)
$CD4^+$	5/25 (20)
CD4:CD8 ratio	
<1:1	9/25 (36)
1:1	11/25 (44)
>1:1	5/25 (20)

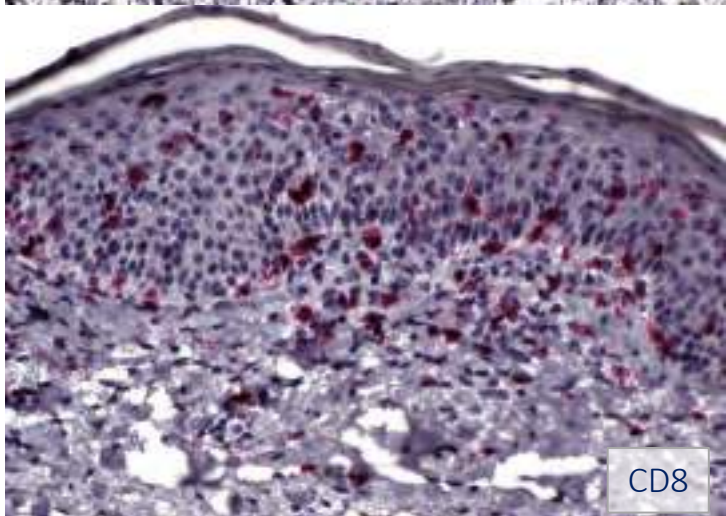
Actinic reticuloid

- Considered as a "prototypic" T-cell pseudolymphoma, yet most cases do not resemble histopathologically mycosis fungoides or other CTCLs (it may be indistinguishable from a chronic eczematous dermatitis)
- Clinically may become erythrodermic
- Hyperplastic epidermis with variable spongiosis, similar to lichen simplex chronicus
- "Bizarre" fibroblasts in the superficial dermis
- UV test necessary to confirm the diagnosis

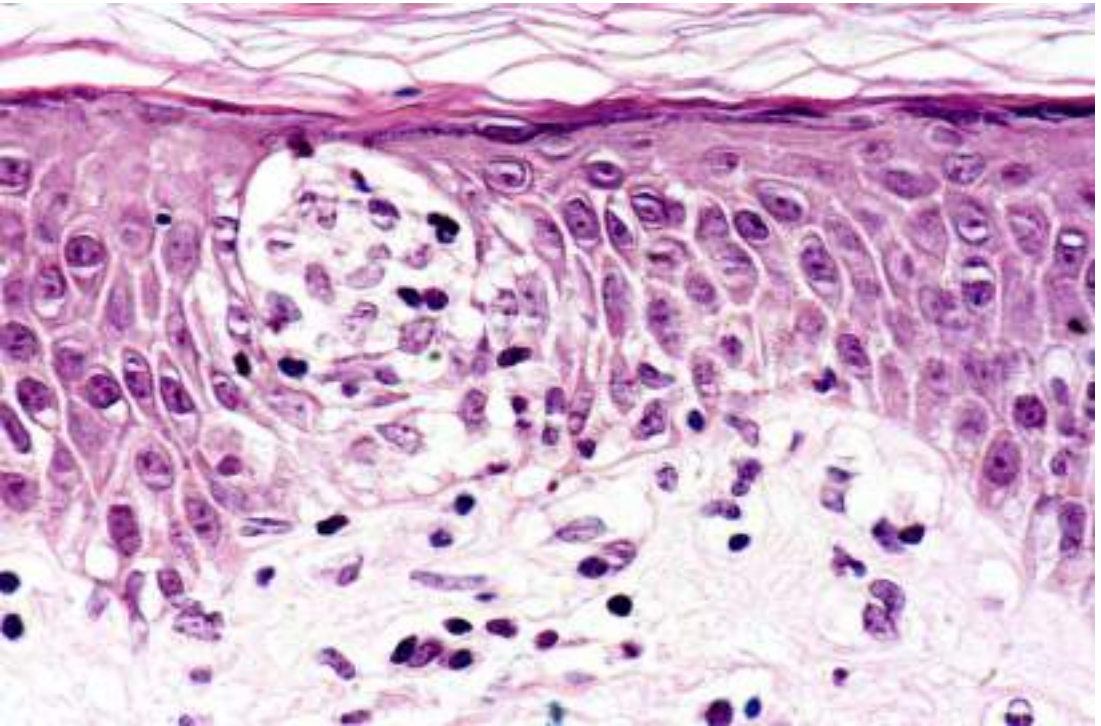


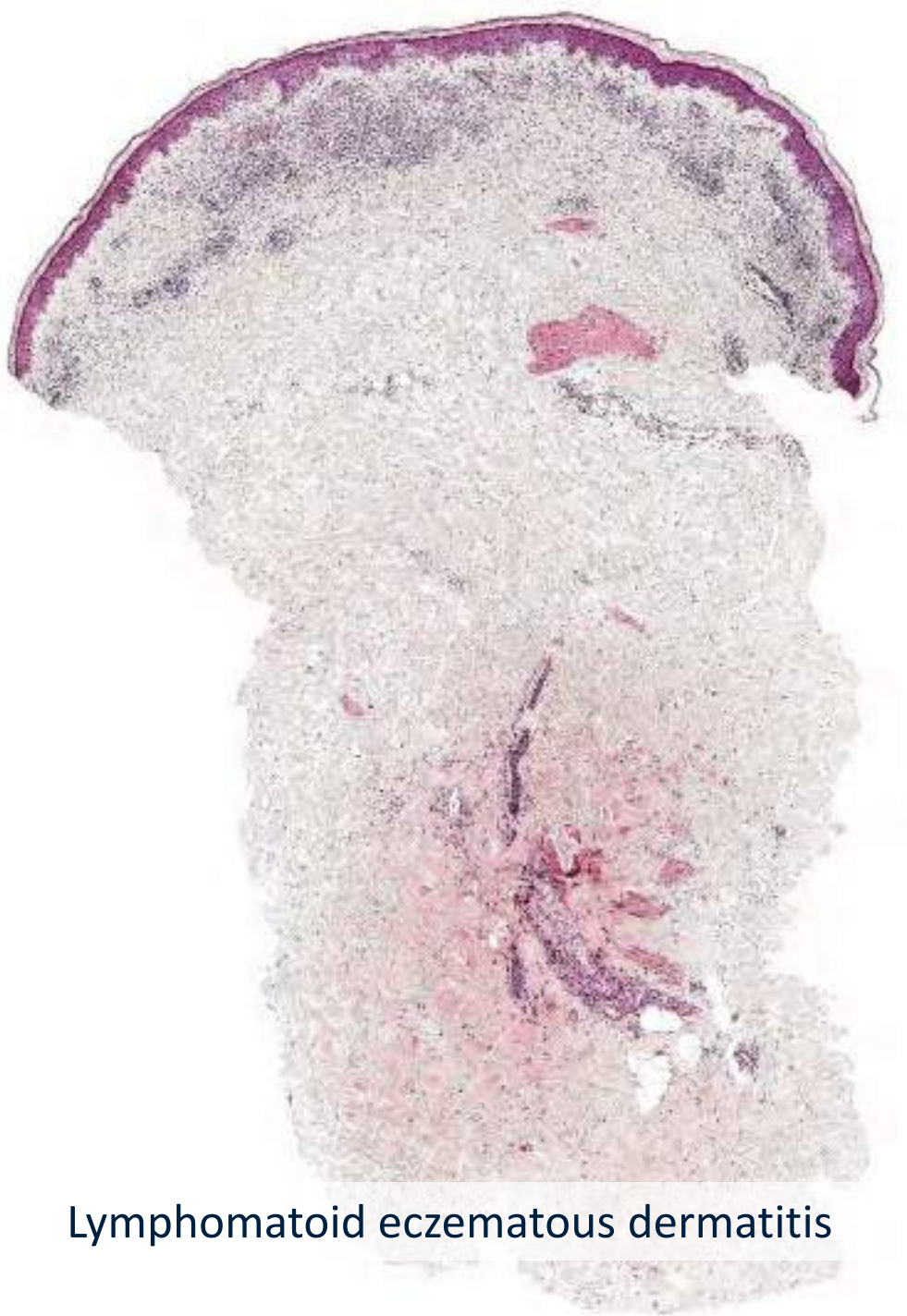




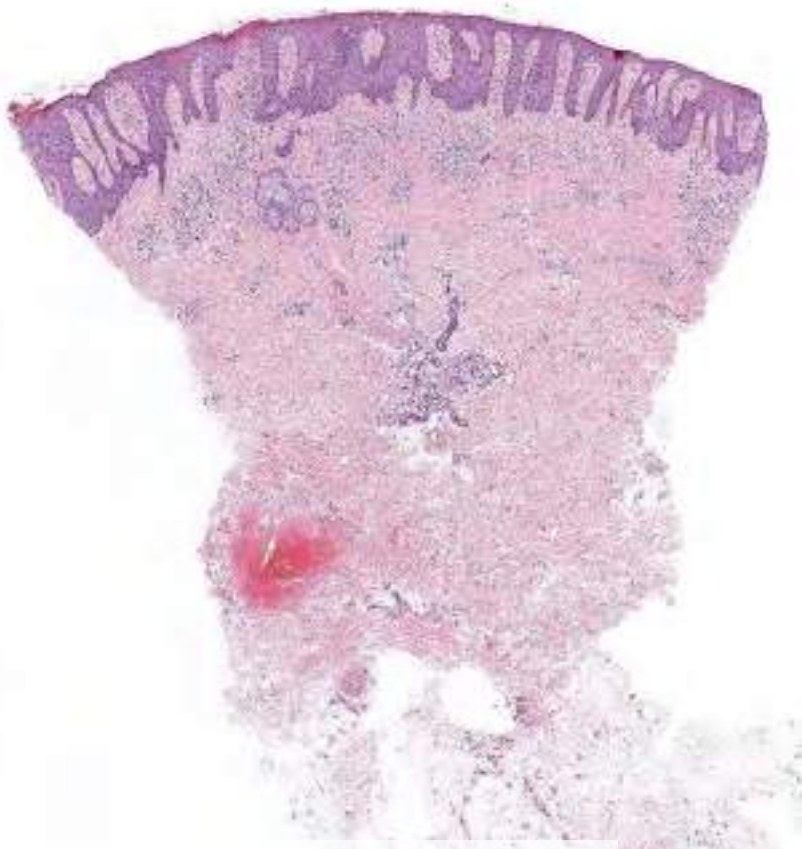


Lymphomatoid eczematous dermatitis

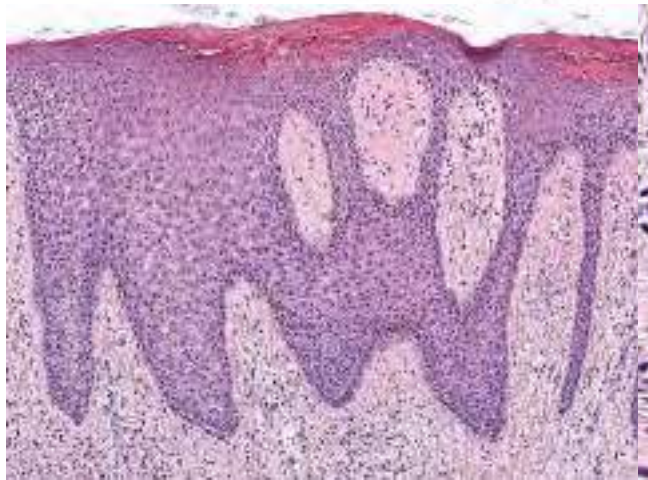


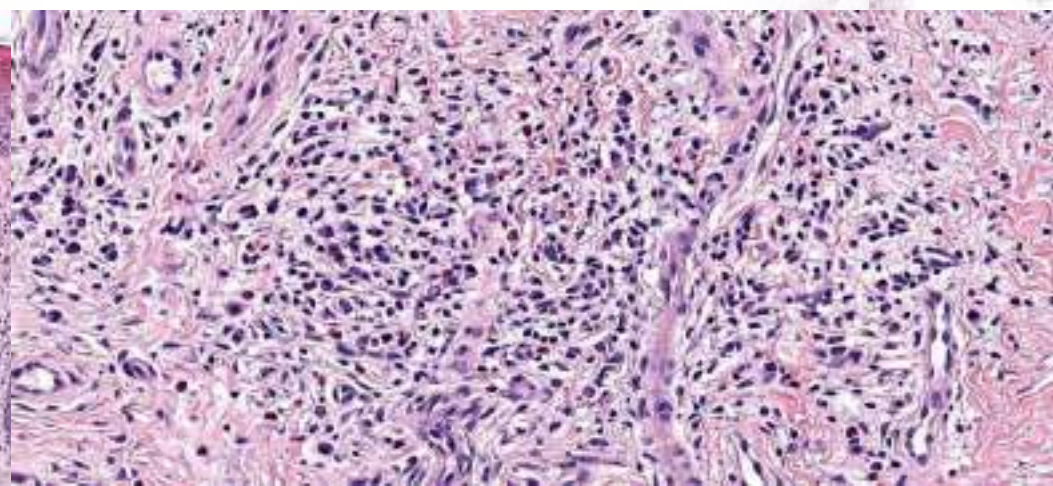


Lymphomatoid eczematous dermatitis



"Pseudotumoral" eczematous dermatitis





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(Consultation Dr. T. Wiesner, Vienna)

Contact Dermatitis 1976: 2: 139–143

Lymphomatoid contact dermatitis

A syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides

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Hospital Clinico de San Carlos, Facultad de Medicina, Madrid 3, Spain

Four cases have been studied which were clinically suggestive of mycosis fungoides because of their infiltrated plaque-like lesions, but in which the suspicion of a topical hypersensitivity arose when a positive patch test was obtained with the striker part of a box of matches.

Key words: contact dermatitis – mycosis fungoides.

Received for publication October 30, 1975

We have had occasion to observe several cases which could be interpreted clinically, from the morphological character and persistence of the lesions, as a form of xanthoerythrodermia perstans or parapsoriasis-en-plaques; with their complaint of intense pruritus they were reminiscent of mycosis fungoides. Several cases were histologically diagnosed as such. We consider it important to report these cases because they are caused by a hypersensitivity reaction.

Case histories

Case 1. A 54-year-old male had noticed a dry, pruritic erythematous plaque about the size of the palm of his hand on his right thigh about four months earlier. The plaque grew progressively in area and in depth. Some time later, a similar lesion appeared on his left thigh. The first lesion appeared in August 1973. During the ensuing months, there arose multiple erythematous, oedematous, ill-defined lesions all over the face, retroauricular areas and the sides of the neck. Their course was one of remissions and exacerbations. Topical treatment with corticosteroids did not produce any improvement. Later, he developed another lesion on the left pectoral area. Examination showed on both thighs two plaque-like lesions, about 10 cm wide, which were erythematous, scaly, intensely infiltrated and with well-defined borders. Violaceous erythematous, scaly infiltrated plaques were also found on the face, behind the ears and on the neck. There was another plaque, the size of the palm of a hand, on the left pectoral region; it had the same features as the others. Multiple biopsies were obtained which showed a dense infiltrate, band-like with histiocytes, lymphocytes and some eosinophils. There was lymphocytic exocytosis, sometimes forming nests and in some areas, limited spongiosis. The histologic picture and its clinical counterpart were like that of infiltrated mycosis fungoides.

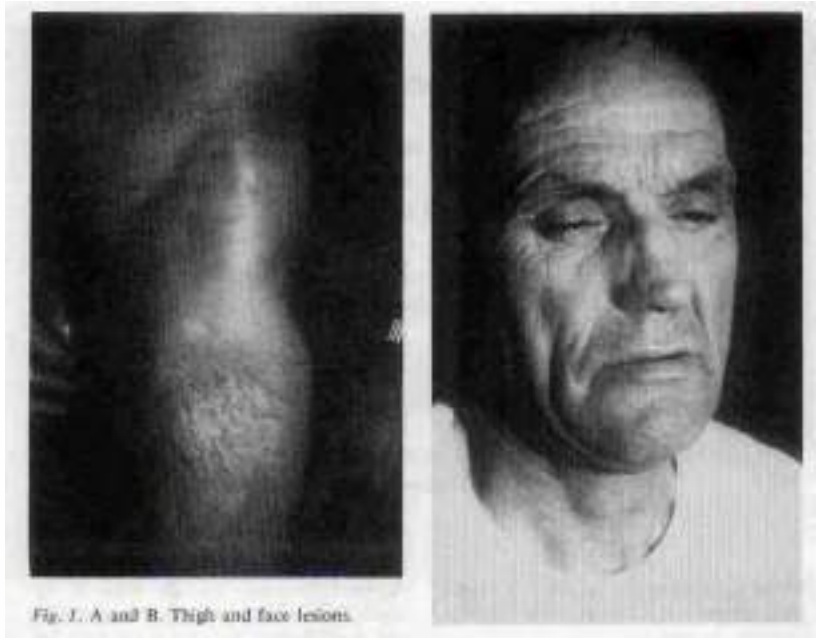

Fig. 1. A and B. Thigh and face lesions.

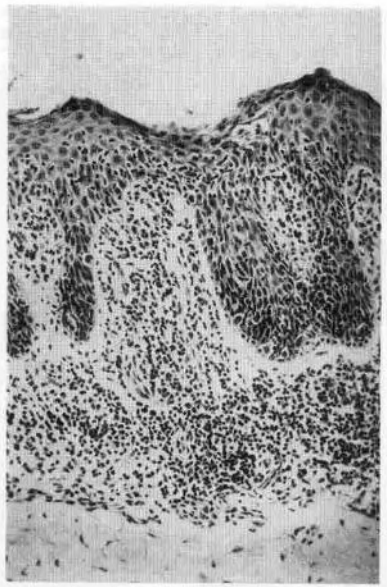

Fig. 2. Acantholytic epidermis. In the dermis there is a dense infiltrate in the form of a superficial band.

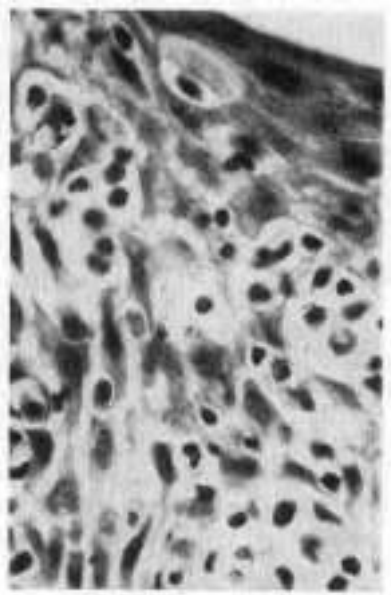

Fig. 3. Lymphocytic exocytosis sometimes forming nests, and limited spongiosis.

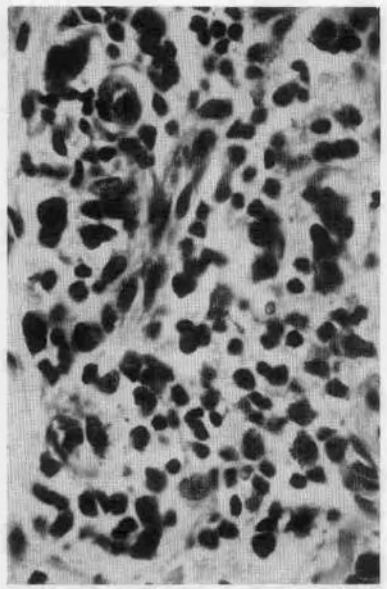

Fig. 4. Dense infiltrate of histiocytes and lymphocytes, some of which are hyperchromatic.

In my experience not restricted to contact dermatitis; may be observed in any "eczematous" dermatitis, including atopic dermatitis, xerosis cutis, and lichen simplex chronicus among others.

Lymphomatoid eczematous dermatitis

- Not restricted to contact dermatitis; can be observed in different types of "eczema" including atopic dermatitis
- Band-like lymphoid infiltrates with some epidermotropic lymphocytes
- Spongiosis variable (minimal in chronic eczematous dermatitis)
- Clinically may present with "pseudotumoral" lesions
- Correlation with the clinical picture allows to classify cases correctly in the vast majority of cases

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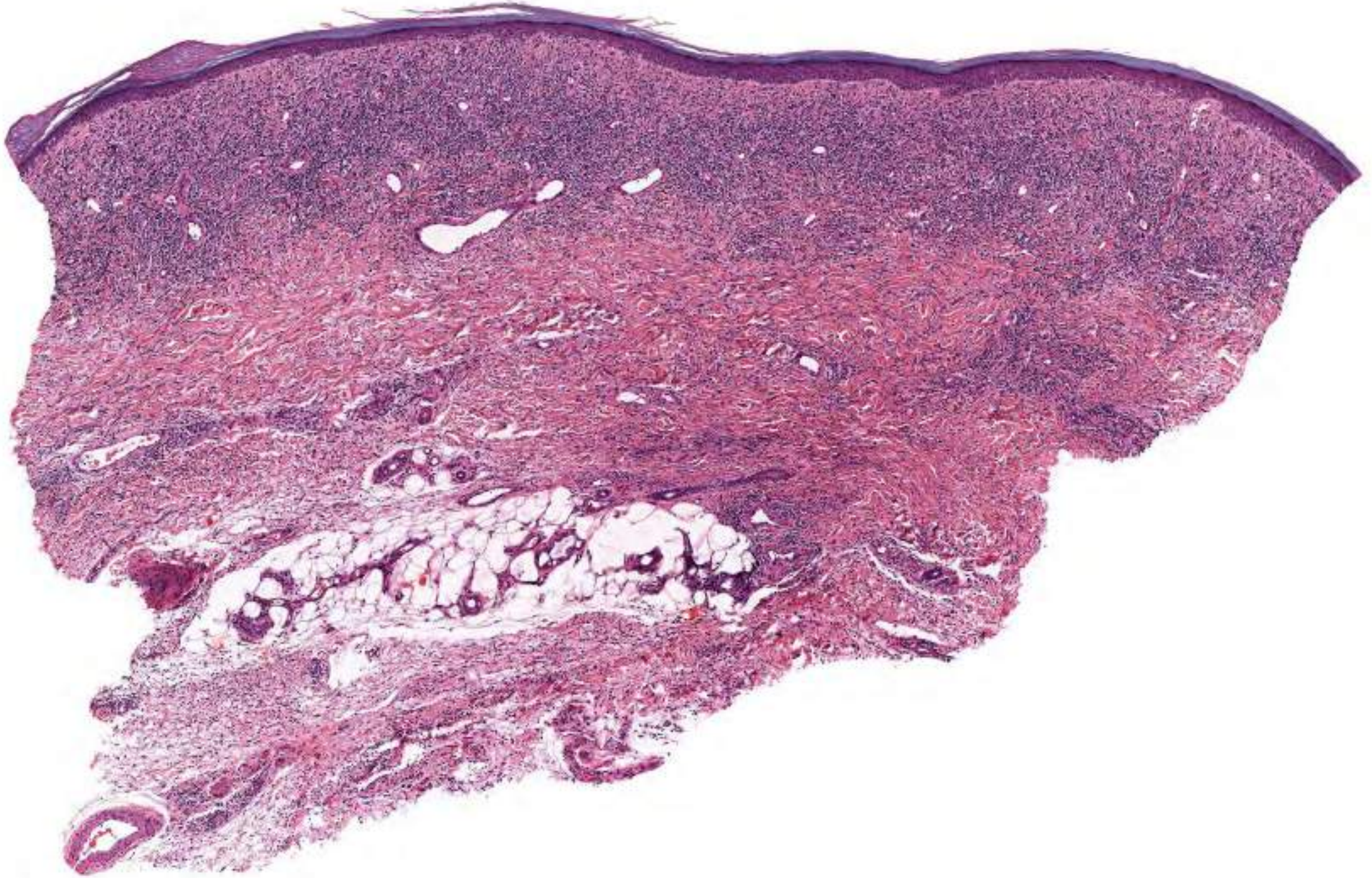
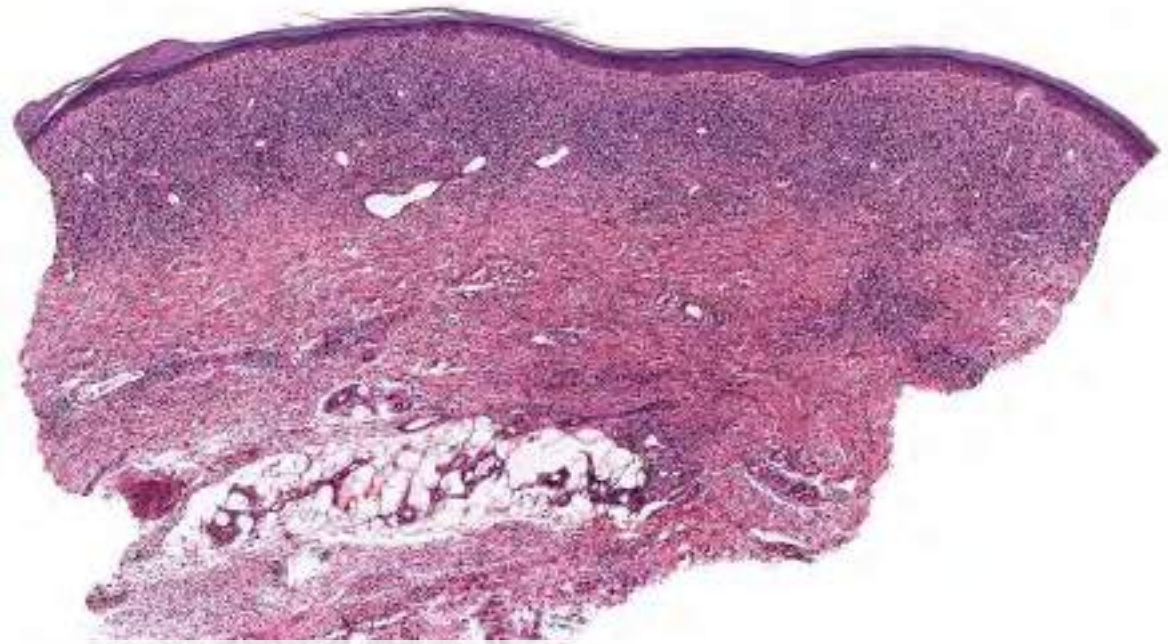
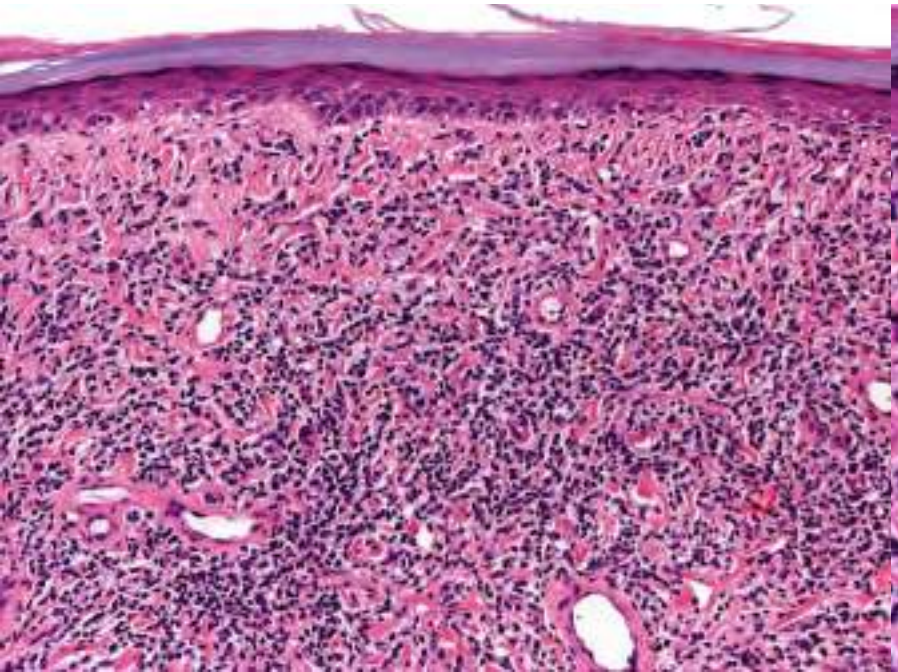
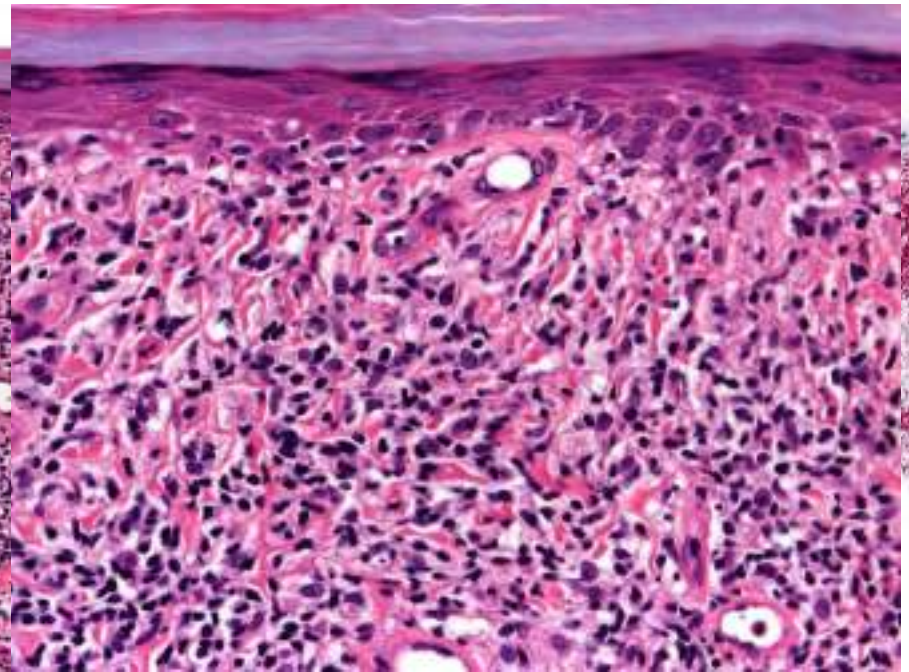
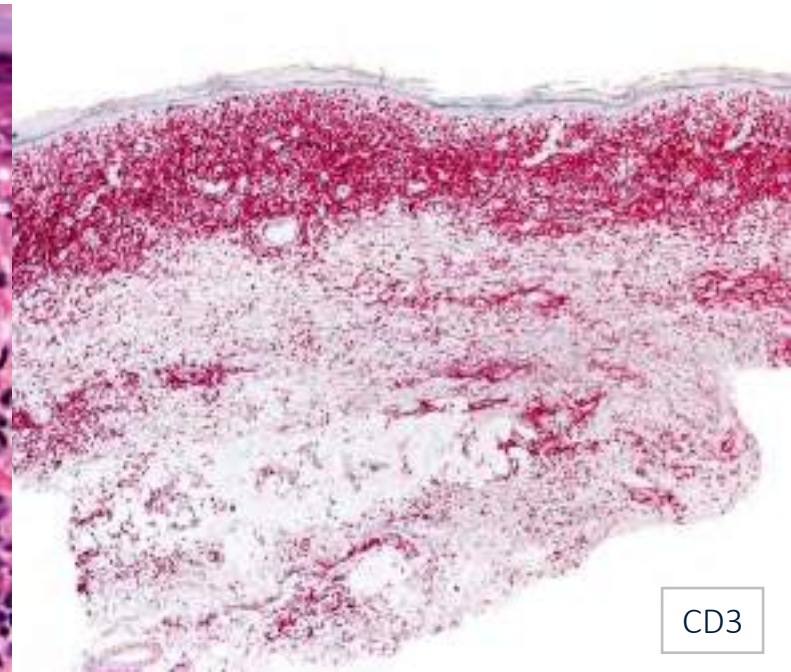




Acrodermatitis chronica atrophicans







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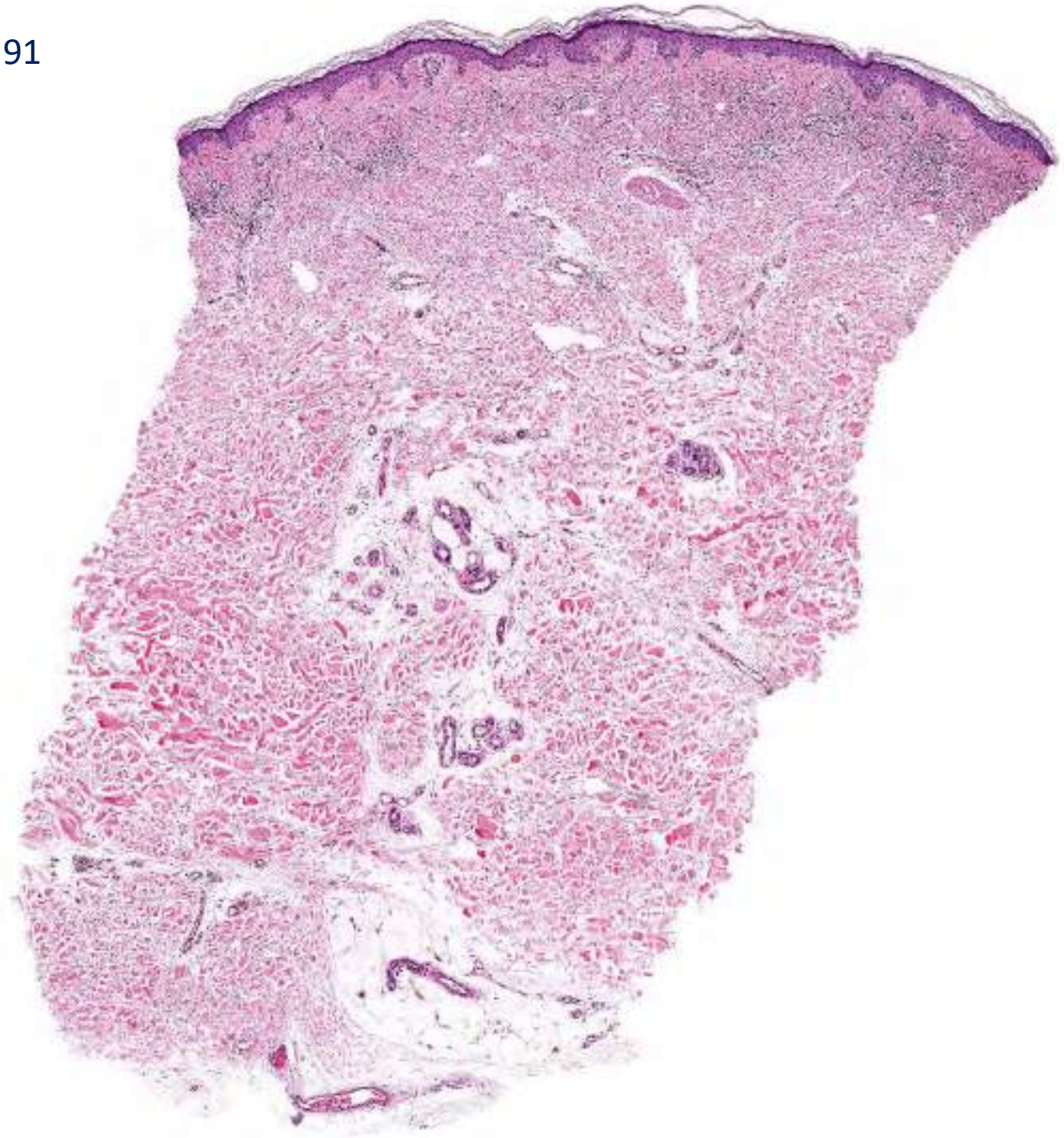

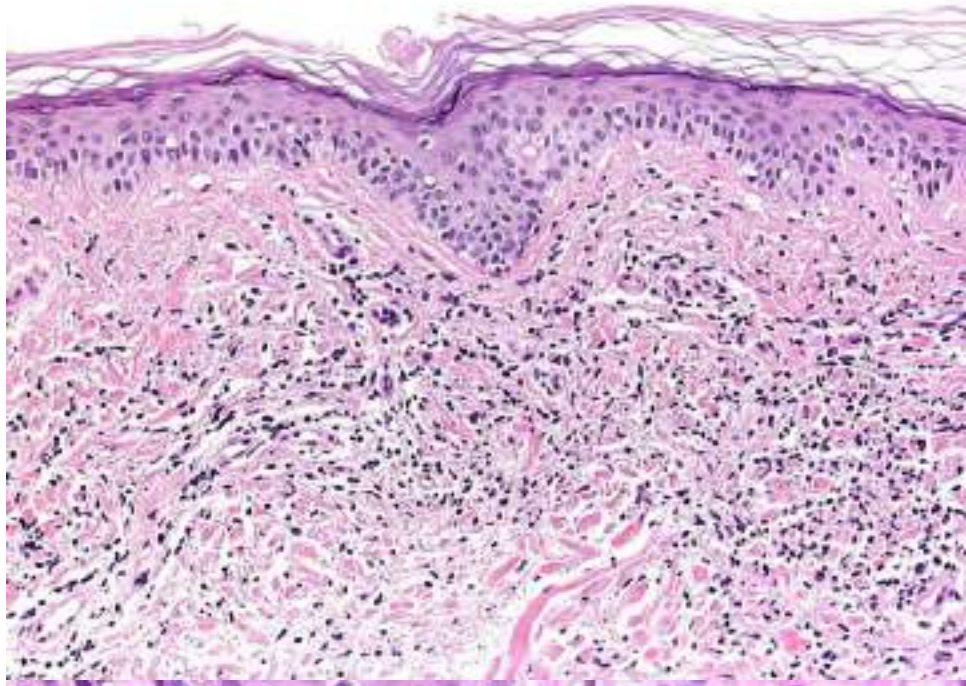

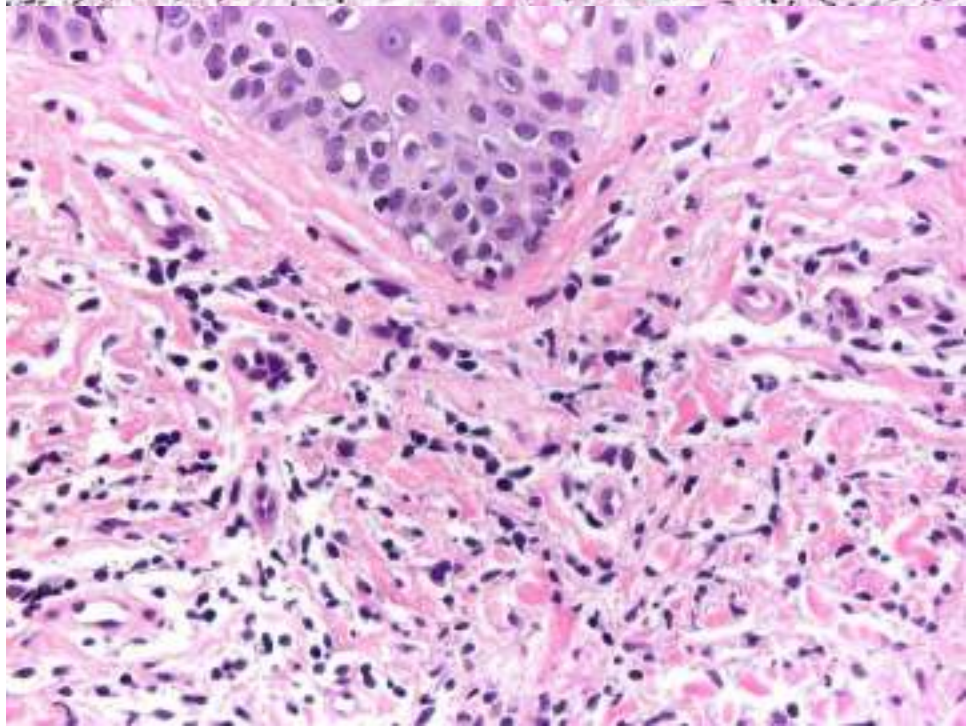

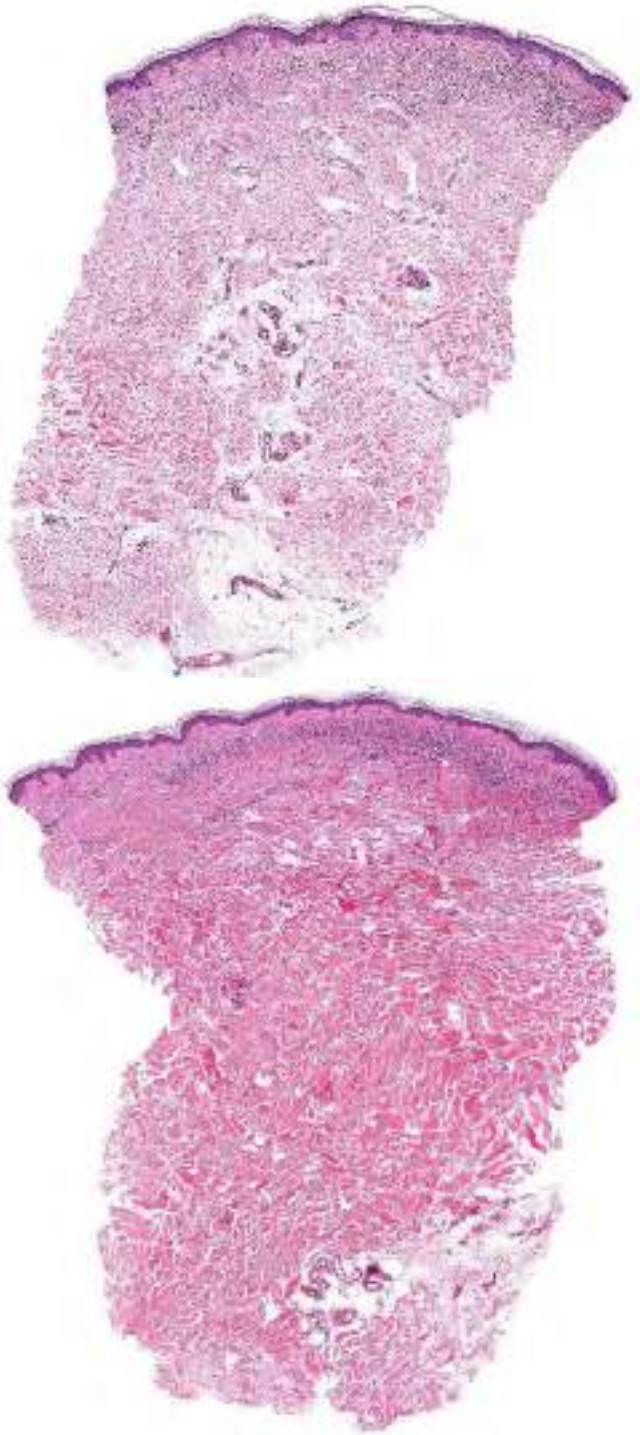

Acrodermatitis chronica atrophicans

Pseudolymphomatous ACA

- Acral sites (particularly leg, foot); usually asymmetrical distribution; may simulate histopathologically either MF or MZL
- Dense inflammatory infiltrates; frequent band-like arrangement
- T lymphocytes predominate in some cases; plasma cells reveal a polyclonal pattern
- Positive *Borrelia* serology; PCR positive for *Borrelia*
- Resolution with antibiotic treatment

Acrodermatitis Chronica Atrophicans With Pseudolymphomatous Infiltrates

Shang-Jan Tee, MRCP,† Marcela Martinez-Escanamé, MD,* Daniel Zuriel, MD,*‡ Isabella Fried, MD,* Ingrid Wolf, MD,* Cesare Massone, MD,* and Lorenzo Cerroni, MD**

Abstract: In this study, we describe the clinicopathologic features of pseudolymphomatous infiltrates found within lesions of acrodermatitis chronica atrophicans (ACA). We studied 11 patients (10 females, 1 male; age range 60–85 years). The diagnosis of ACA in all cases was confirmed by clinicopathologic correlation and positive serology for *Borrelia*. Histopathologic examination revealed prominent pseudolymphomatous inflammatory cell infiltrates in all cases, with 2 distinct patterns. Eight of 11 cases showed a band-like lymphocytic infiltrate, exocytosis of lymphocytes and a fibrotic papillary dermis, similar to features seen in necrosis lingoidea. The other 3 cases showed dense, nodular-diffuse dermal infiltrates with many plasma cells and without germinal centers. The plasma cells expressed both kappa and lambda immunoglobulin light chains with a polyclonal pattern in all 3 cases. In conclusion, ACA may present with pseudolymphomatous infiltrates showing both a B-cell and, less frequently, a B-cell pattern. These lesions need to be distinguished from a cutaneous lymphoma. In the context of the knowledge of *Borrelia*-associated cutaneous lymphoma, follow-up seems advisable in these cases.

Key Words: acrodermatitis chronica atrophicans, pseudolymphoma, *Borrelia*

(*Am J Dermatopathol* 2013;35:338–342)

INTRODUCTION

Acrodermatitis chronic atrophicans (ACA) is a late cutaneous manifestation of infection by *Borrelia afzelii*.[1] It typically affects elderly women, usually involving the dorsal surfaces of acral sites. After an initial inflammatory phase characterized by edematous swelling and bluish-red discolorations, the skin becomes atrophic, dry, and wrinkled with prominent telangiectasias, dermal sclerosis, and loss of appendageal structures. The diagnostic evaluation of suspected cases commonly includes a histopathological examination. Characteristic histopathologic changes of ACA include (1) a superficial and deep, perivascular, and interstitial dermal inflammatory infiltrate composed of lymphocytes, histiocytes and plasma cells, (2) atrophic dermis with reduction in size and number of adnexal structures, (3) thinning of the epidermis with flattened rete ridges, (4) variable dermal edema.[2]

Rarely, prominent dermal lymphoid infiltrates may be present within lesions of ACA, which may mimic a cutaneous lymphoma. In this study, we present the clinicopathologic features of 11 cases of ACA with pseudolymphomatous infiltrates.

PATIENTS AND METHODS

Patients

We reviewed the database of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz for cases of ACA containing dense lymphoid infiltrates. In all cases, the diagnosis of ACA was confirmed clinically and by positive serology for *Borrelia*. We excluded cases in which histopathological specimens were inadequate, or in which complete clinical information was unavailable.

Histopathology

All specimens were fixed in 4% buffered formalin, routinely processed and embedded in paraffin. Sections were subsequently stained with hematoxylin and eosin for routine histopathologic analysis.

Immunohistology

Immunohistology was performed in 4 cases on routinely fixed, paraffin-embedded tissue sections according to a previously described 3-step immunoperoxidase technique.[3] The panel of monoclonal antibodies included the following markers: CD3 (Novocastra, clone PS1, dilution 1:100), CD4 (Novocastra, clone 3I6, dilution 1:30), CD8 (Dako, Dakopatts, clone C8/144b, dilution 1:25), CD20 (Dako, Dakopatts, clone L26, dilution 1:500), kappa and lambda light chains (both Dako, Dakopatts; clones R10/2-15 and N10/2, respectively; dilution 1 drop in 500 μL). Biopsy specimens of tonsil tissue were used as positive controls. Negative controls were obtained by omitting the primary antibody or replacing it with normal human serum. Heat-induced antigen retrieval was performed for all the antibodies.

Molecular Biology

In 3 cases, analysis of *Borrelia* DNA was performed by polymerase chain reaction (PCR) with standard methods.

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Funding sources: none.
Conflict of Interests: None.

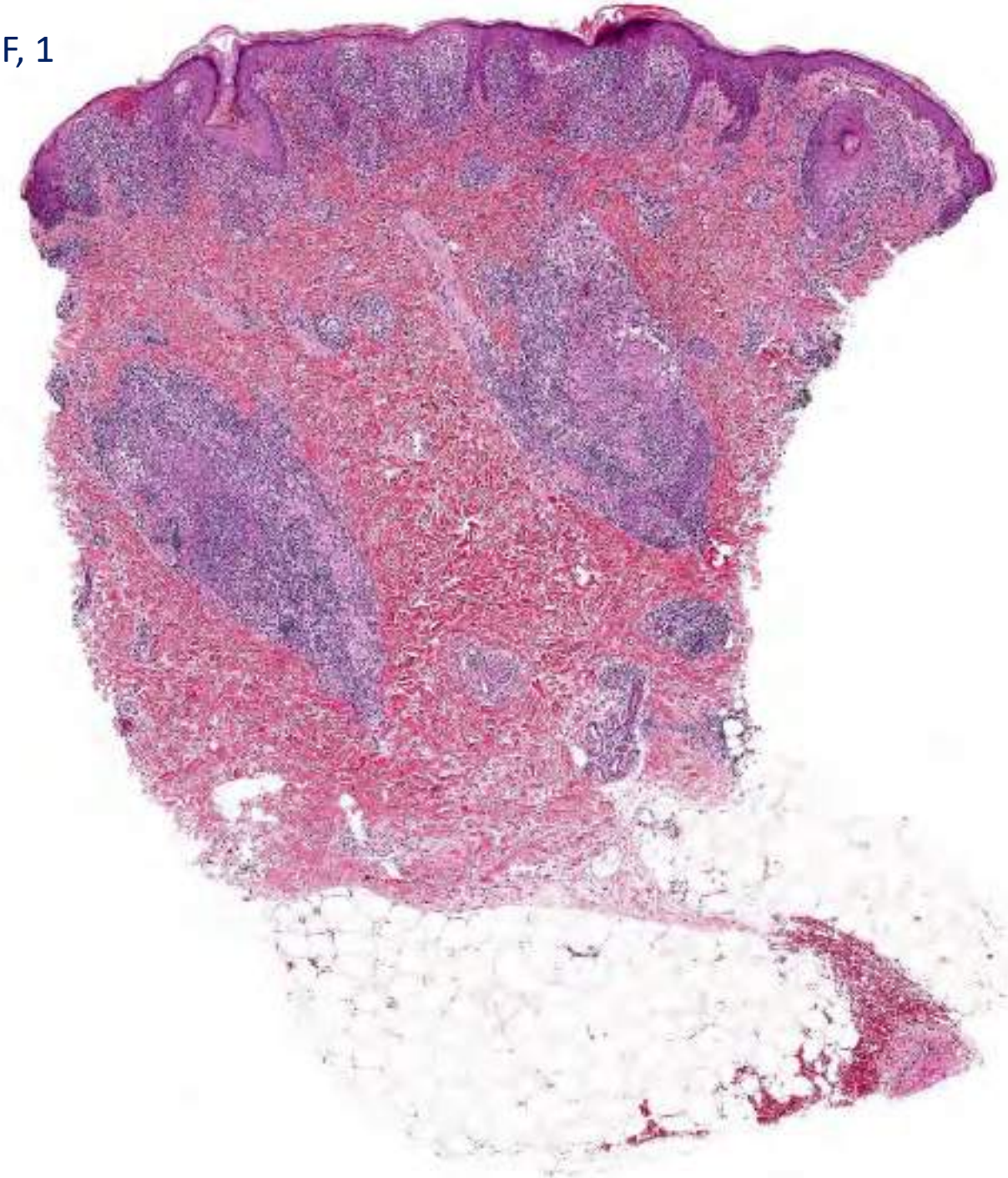
Reprints: Lorenzo Cerroni, MD, Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria (e-mail: lorenzo.cerroni@medunigraz.at).

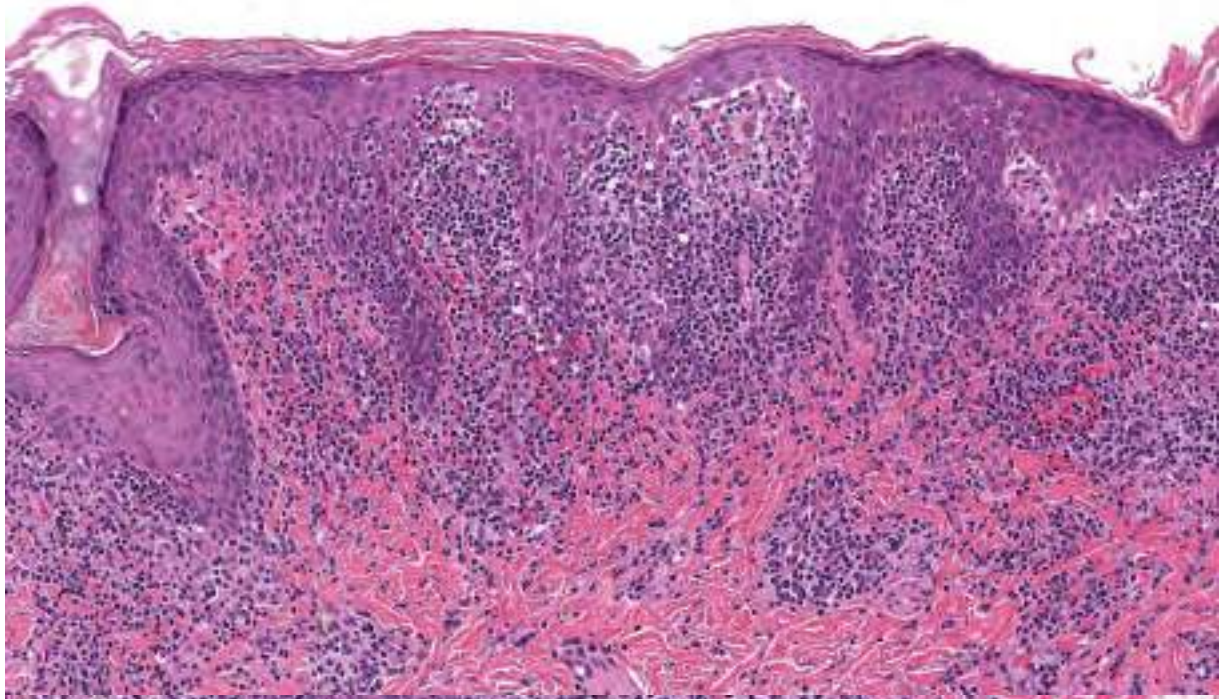
TABLE 1. Clinical Data of the Patients and Histopathologic Pattern

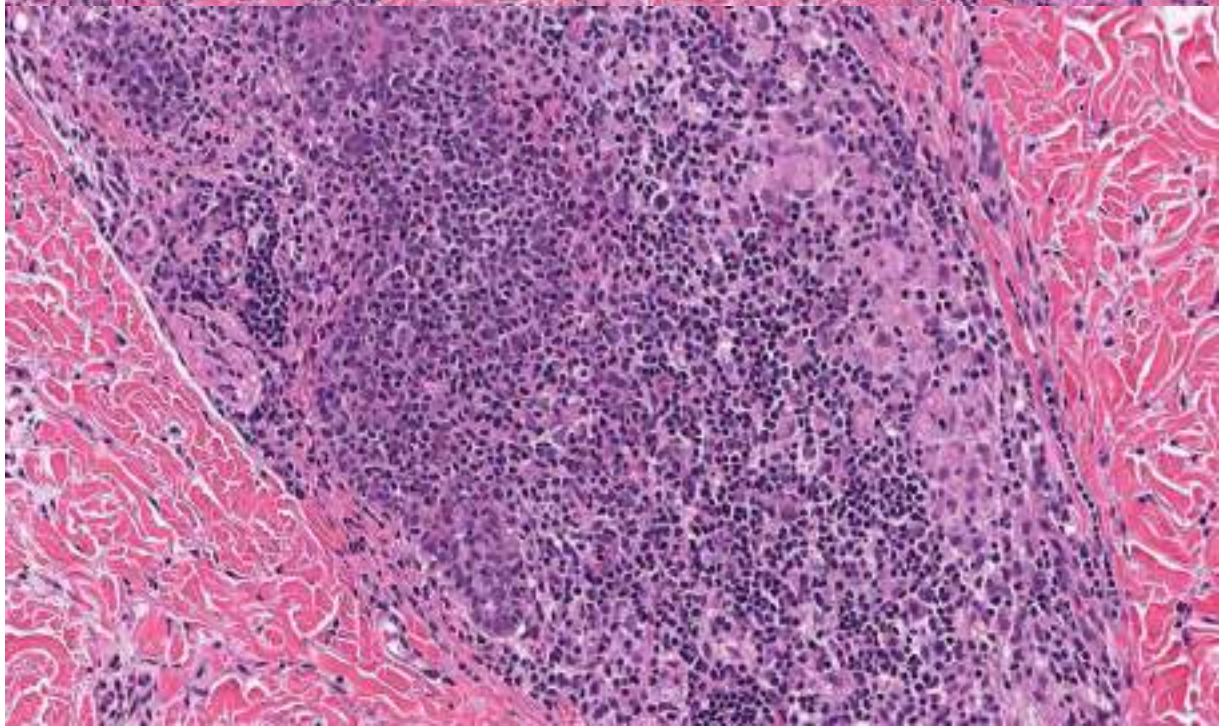
No	Sex, Age (yrs)	Location	Histological Pattern	*Borrelia* PCR	*Borrelia* Serology	Follow-up (Time)
1	F, 70	Foot	Band-like	ND	IgG and IgM	NA
2	F, 68	Foot	Band-like	Positive	IgG and IgM	CR (2 mos)
3	F, 64	Foot	Band-like	ND	IgG and IgM	CR (13 yrs)
4	F, 68	Leg	Band-like	ND	IgG and IgM	CR (8 mos)
5	F, 77	Leg	Superficial and deep, diffuse with plasma cells	Positive	IgG and IgM	CR (8 yrs)
6	F, 60	Leg	Band-like	ND	IgG and IgM	CR (8 yrs)
7	M, 88	Hand	Band-like	ND	IgG and IgM	NA
8	F, 60	Hand	Superficial and deep, diffuse with plasma cells	ND	IgG and IgM	CR (22 yrs)
9	F, 77	Leg	Band-like	Positive	IgG	Almost CR (16 mos)
10	F, 61	Leg	Band-like	ND	IgG and IgM	CR (2 mos)
11	F, 74	Leg	Superficial and deep, diffuse with plasma cells	ND	IgG and IgM	CR (2 mos)

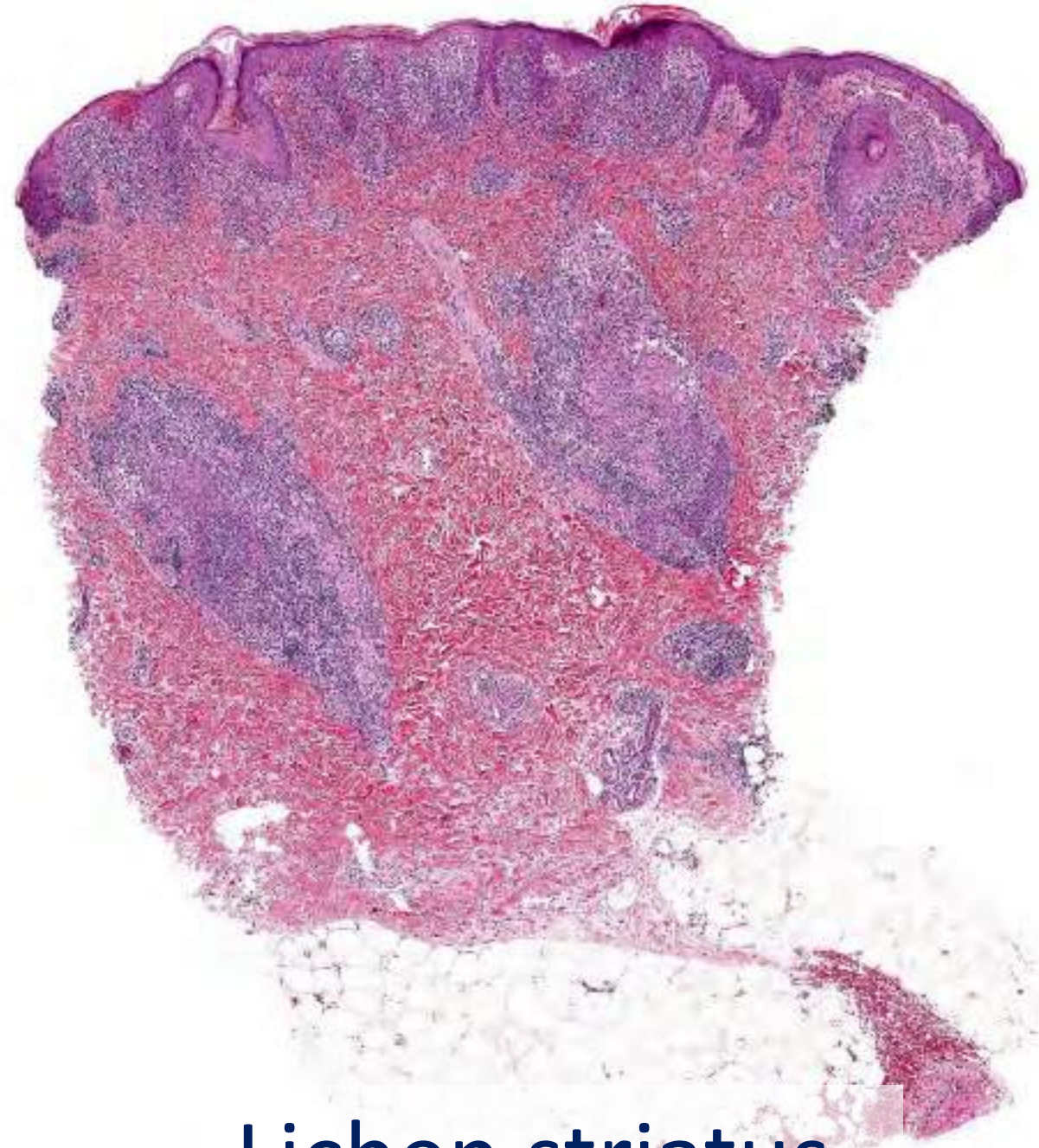
CR, complete remission; F, female; M, male; NA, not available; ND, not done; PR, partial remission.

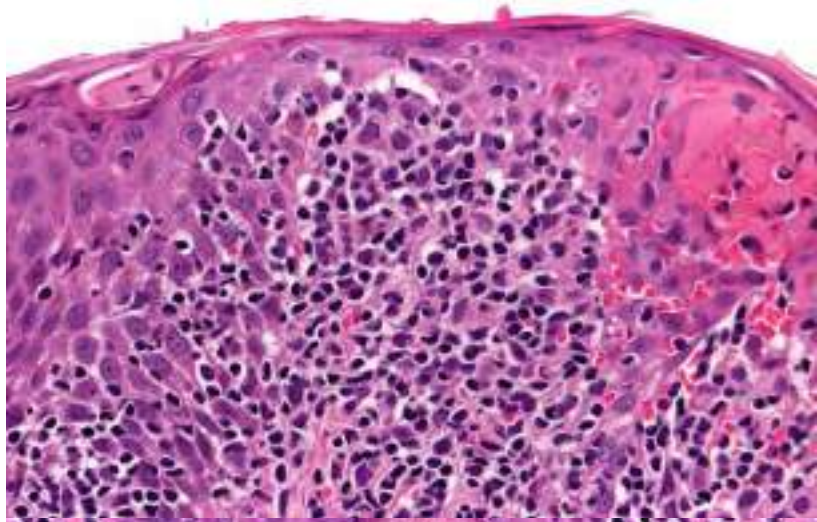
F, 1

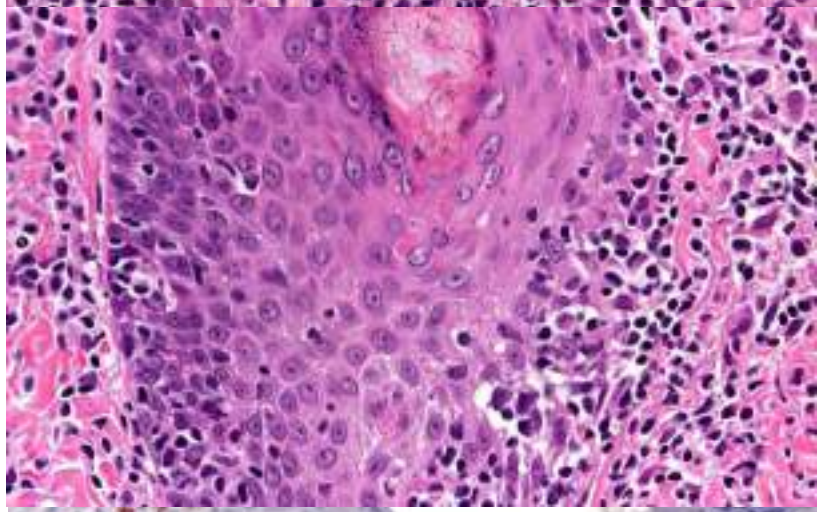


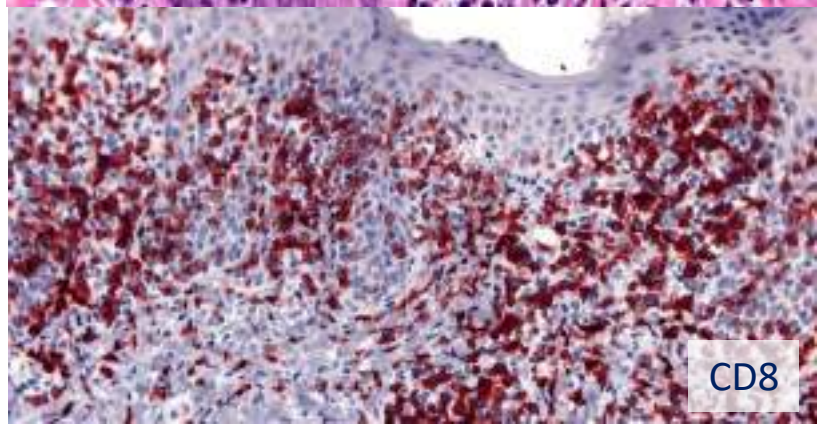












Lichen striatus

Correspondence

Lichen striatus mit histopathologischer Imitation einer Mycosis fungoides

Lichen striatus histopathologically mimicking mycosis fungoides

DOI: 10.1111/ddg.13918
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Sehr geehrte Herausgeber,

wir schicken eine Hautbiopsie vom rechten Arm einer vierjährigen Mädchens mit sehr wenig klinischen Begleitinformationen und ohne weiteres Bildmaterial. Die Biopsie zeigte ein dichtes bandartiges Infiltrat, vorwiegend aus kleinen und mittelgroßen Lymphozyten in einer leicht fibrotischen papillären Dermis. Eine deutliche Exozytose der Lymphozyten war sichtbar, von denen einige entlang der Basalmembran angeordnet waren und die von intraepidermalen Vesikeln begleitet war (Abbildung 1a–e). Das Infiltrat betraf die mittlere und tiefe Dermis und bildete lymphoide Knötchen, die vor allem um die Haarfollikel und ekkrinen Drüsen herum angeordnet waren und sich nur gelegentlich bis in die Subkutis erstreckten. Die Lymphozyten waren CD2, CD3 (Abbildung 1d–f), CD5 und CD7-positiv, mit überwiegend CD8+ zytotoxischen T-Zellen im Vergleich zu CD4+ T-Helferzellen. Ein Verlust der T-Zell-Antigene CD2, CD5, CD7 trat nicht auf; das tiefe noduläre lymphoide Infiltrat zeigte gleiche T-Zell-Profile. Zusätzlich traten fokal CD1a-positive (Abbildung 1g–i und

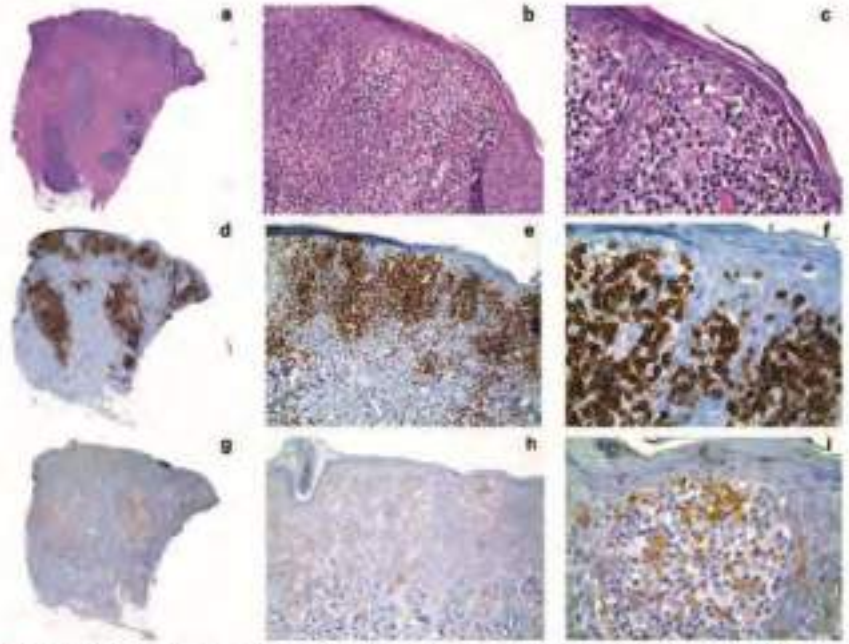


Abbildung 1 Die Biopsie zeigt ein bandförmiges lymphozytäres Infiltrat in der oberen Dermis und ein dichtes perifollikuläres lymphozytäres Infiltrat in der mittleren und tiefen Dermis (HE, ×5) (a); verdickte Epidermis mit deutlicher lymphozytärer Exozytose und Vesikelbildung gekoppelt mit einem bandförmigen lymphozytären Infiltrat in der papillären Dermis (HE, ×10) (b); deutliche Lymphozytäre Exozytose und kleine Vesikel (HE, ×10) (c); Immunfärbung für CD3 zeigt das Überwiegen von T-Zellen (CD3, ×5) (d); bandförmiges subepidermales Infiltrat v.a. aus T-Zellen (CD3, ×10) (e); deutliche Exozytose von T-Zellen (CD3, ×10) (f); Immunfärbung für CD1a zeigt einige Langerhans-Zellen (g: CD1a, ×5; h: CD1a, ×10) (g–h); einige Langerhans-Zellen in epidermalen Vesikeln (CD1a, ×10) (i).

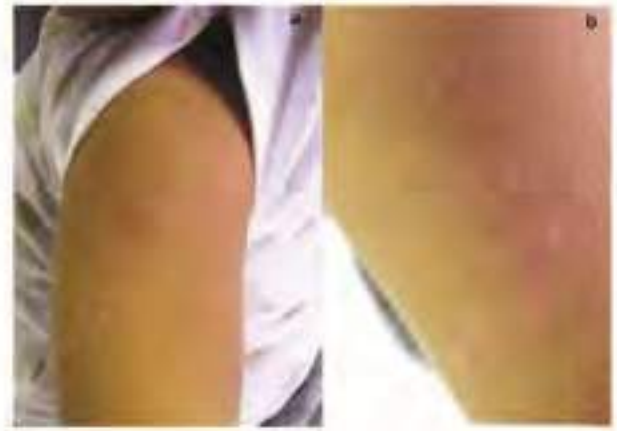


Abbildung 2 Empfangen Mädchen mit erythematösen Papeln in linearer Anordnung (a); Detailansicht der Läsionsareale (b).

CD117-negative Zellen auf. Die vorläufige Diagnose einer atypischen lymphoproliferativen Erkrankung mit Verdacht auf Mycosis fungoides (MF) wurde gestellt, und die Notwendigkeit einer engen Korrelation mit der Anamnese und dem klinischen Erscheinungsbild der Läsionen wurde in histologischen Befundbericht betont.

In der Zwischenzeit wurde der Kind in unsere Klinik überwiesen. Es wies kleine pruritische Papeln von 0,5 bis 1,5 cm Durchmesser auf, die bandförmig am Arm angeordnet waren (Abbildung 2a–b), anamnestisch war der Kind beschwerdefrei. Aufgrund des klinischen Bildes konnte somit die definitive Diagnose einer Lichen striatus (LS) mit ungewöhnlich dichten entzündlichen Infiltraten gestellt werden. Die Diagnose wurde von einem externen Dermatopathologen verifiziert. Eine T-Zell-Rezeptor-Gen Rearrangement-Analyse zeigte ein polyklonales Muster. Unter dreimonatlichen Kontrollen traten nach 14 Monaten erste Zeichen der Abheilung auf.

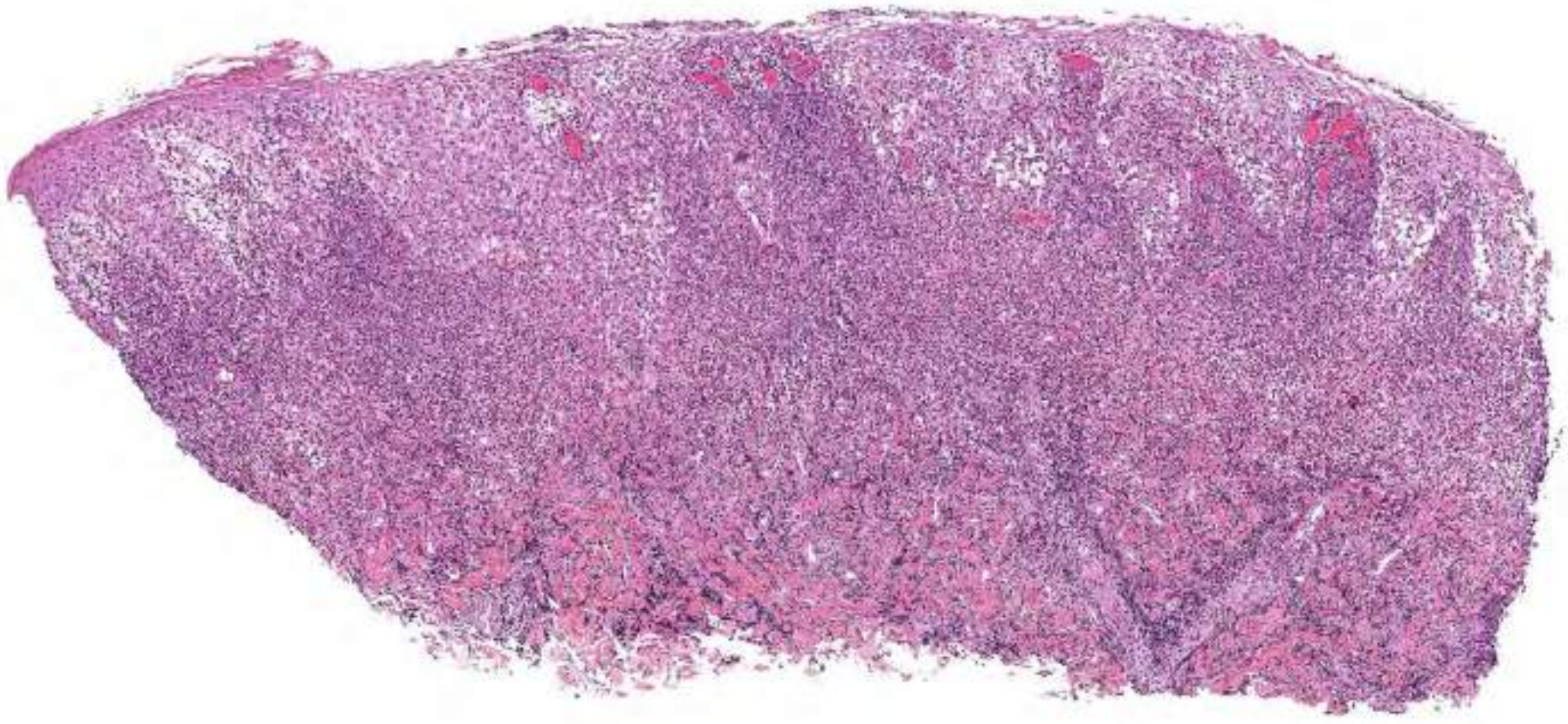
Diskussion

LS ist eine seltene inflammierende entzündliche Erkrankung, vorwiegend der Arme, Beine und Schultern, die vor allem bei Kindern auftritt [1, 2]. Üblicherweise zeigen sich multiple meist asymptomatische Papeln, die linear entlang der Blaschko-Linien angeordnet sind [3]. Die meisten Fälle heilen spontan innerhalb weniger Monate, einige Fälle mit prolongierter Aktivitätsphase persistieren für zwei bis drei Jahre, bevor sie abheilen [4].

Obwohl die Erkrankung sich klinisch deutlich von linearen Nävi oder chronisch-entzündlichen Hautkrankheiten, die den Blaschko-Linien folgen, wie Psoriasis, Lupus erythematosus und Morphea, unterscheiden lassen sollte, beruht die Diagnose in der Regel auf dem klinischen Befund [5]. Trotzdem kann in unklaren Fällen eine Hautbiopsie erforderlich sein. Der histologische Befund ist normalerweise nicht aussagekräftig und zeigt bandförmige entzündliche lympho- und histiozytäre Infiltrate in der papillären Dermis mit epidermaler Akanthose, Parakeratose und lymphozytärer Exozytose [1]. Das Infiltrat ist unter Umständen nicht dicht und um die ekkrinen Drüsen und Gefäße herum verteilt. Kleine intraepidermale Vesikel, die Lymphozyten und Langerhans-Zellen enthalten, können vorhanden sein. Gelegentlich überlappen die histopathologischen Befunde mit denen bei Lichen nitidus, Lichen planus, Lichen simplex, lichenoiden Arzneimittelexanthemen oder MF. Bei Kindern zeigt die MF häufiger hypopigmentierte oder ittyrasis lichenoides-ähnliche Läsionen, kann aber selten auch als lineares Exanthem auftreten [6–8]. MF ist histopathologisch durch ein bandförmiges Infiltrat in der papillären Dermis gekennzeichnet, welches aus monomorphen lymphoiden Zellen unterschiedlichen Atypiegrades besteht. Oftmals dominieren bei früher MF kleine Lymphozyten, und atypische Zellen treten selten auf [6]. Ein Epidermotropismus der Lymphozyten kann in verschiedenen Formen auftreten, auch mit entlang der Basalmembran aufgereihten Lymphozyten und der Bildung von Pautrier-Mikroabszessen [8]. Die neoplastischen Lymphozyten bei MF zeigen normalerweise einen CD3+, CD4+, CD8- Phänotyp [6]. Ein Verlust der pan-T-Zell-Marker-Expression kann manchmal beobachtet werden, ist bei früher MF jedoch sehr selten [6]. Besonders in Kindesalter kommen jedoch häufig CD8+ zytotoxische T-Zellen vor [6, 7]. Bei unserer

Lichen Striatus

- A prototypic example of the "linear dermatoses"
- Psoriasiform epidermal hyperplasia and variably dense lichenoid infiltrate, involving the deep dermis growing along the adnexal structures
- Epitheliotropism may be prominent
- Phenotype not studied in detail; some cases are positive for CD8

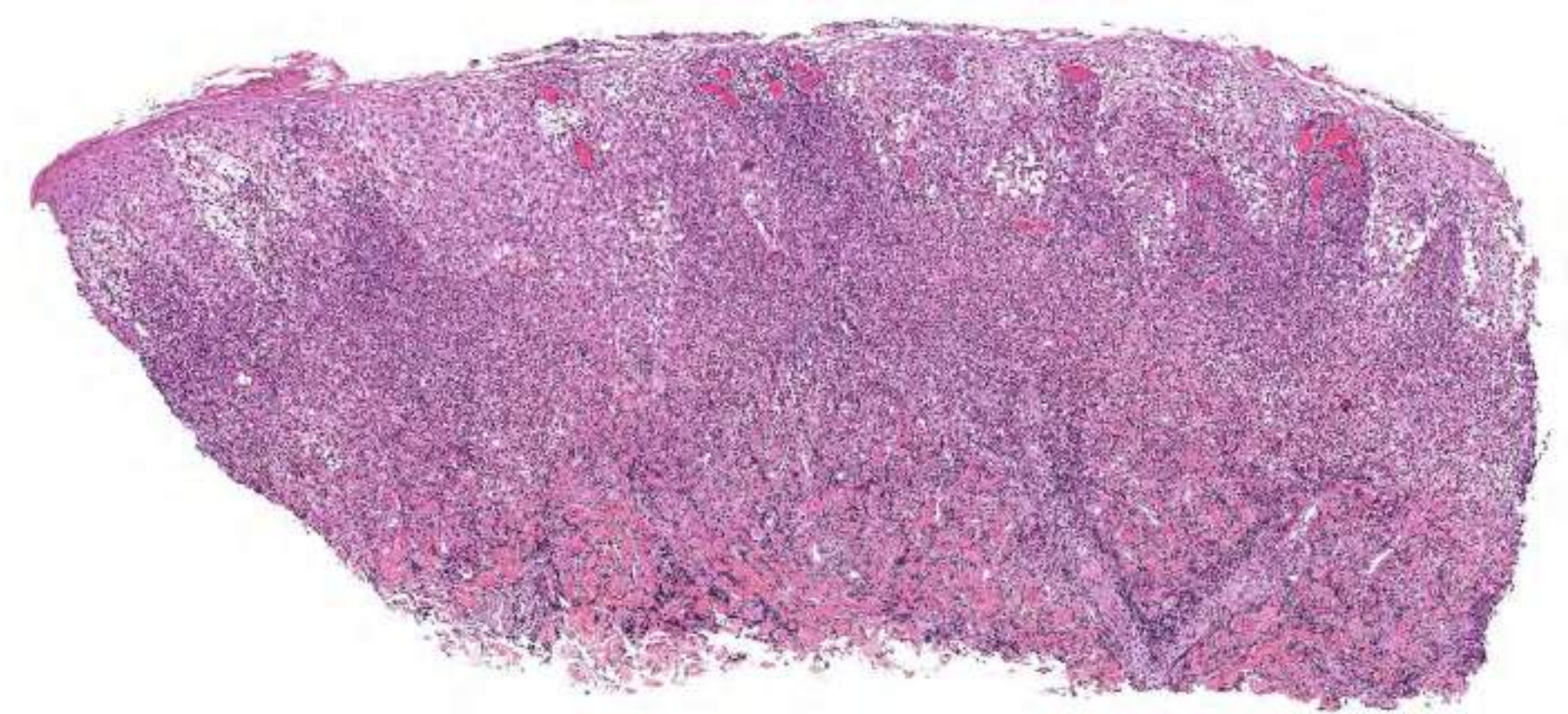


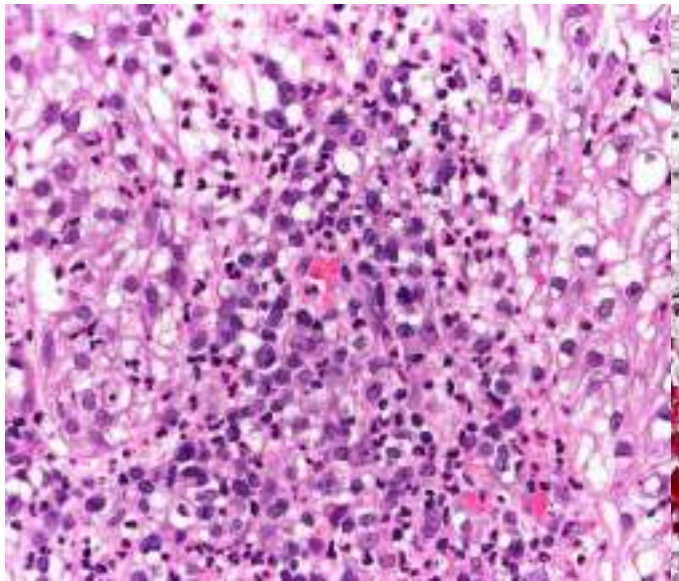
Cutaneous anaplastic large cell lymphoma

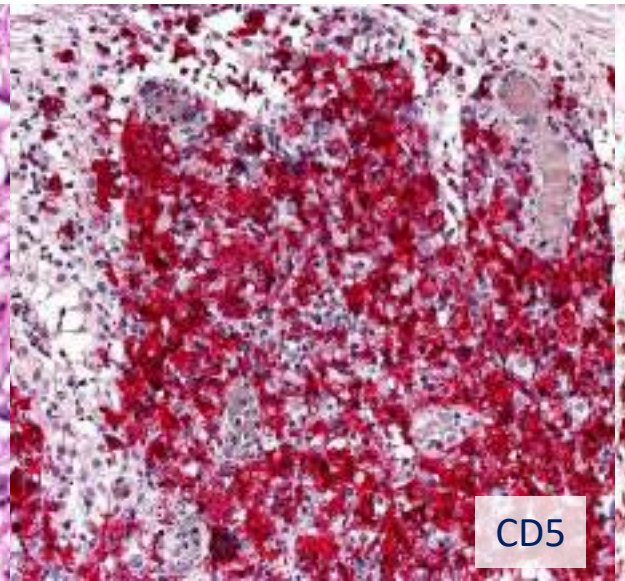
Solitary lesions (rarely grouped), mostly ulcerated. Spontaneous regression (mostly partial) common. A clinical presentation with extensive involvement of one lower extremity has a worse prognosis (extensive limb disease)

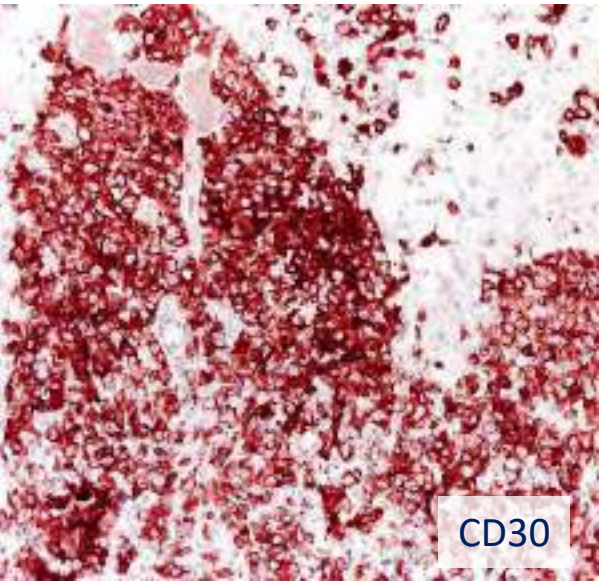
Mixed infiltrate with predominance of CD30+ T-lymphocytes (>70% of the infiltrate). Common intralymphatic complexes of neoplastic cells. Phenotypic aberrations common. Rearrangement of the *DUSP22* locus at 6p25.3 occurs in 20-25% of C-ALCL. The t(2;5) chromosomal translocation is absent in most cutaneous cases.

Indolent behavior, excellent prognosis.



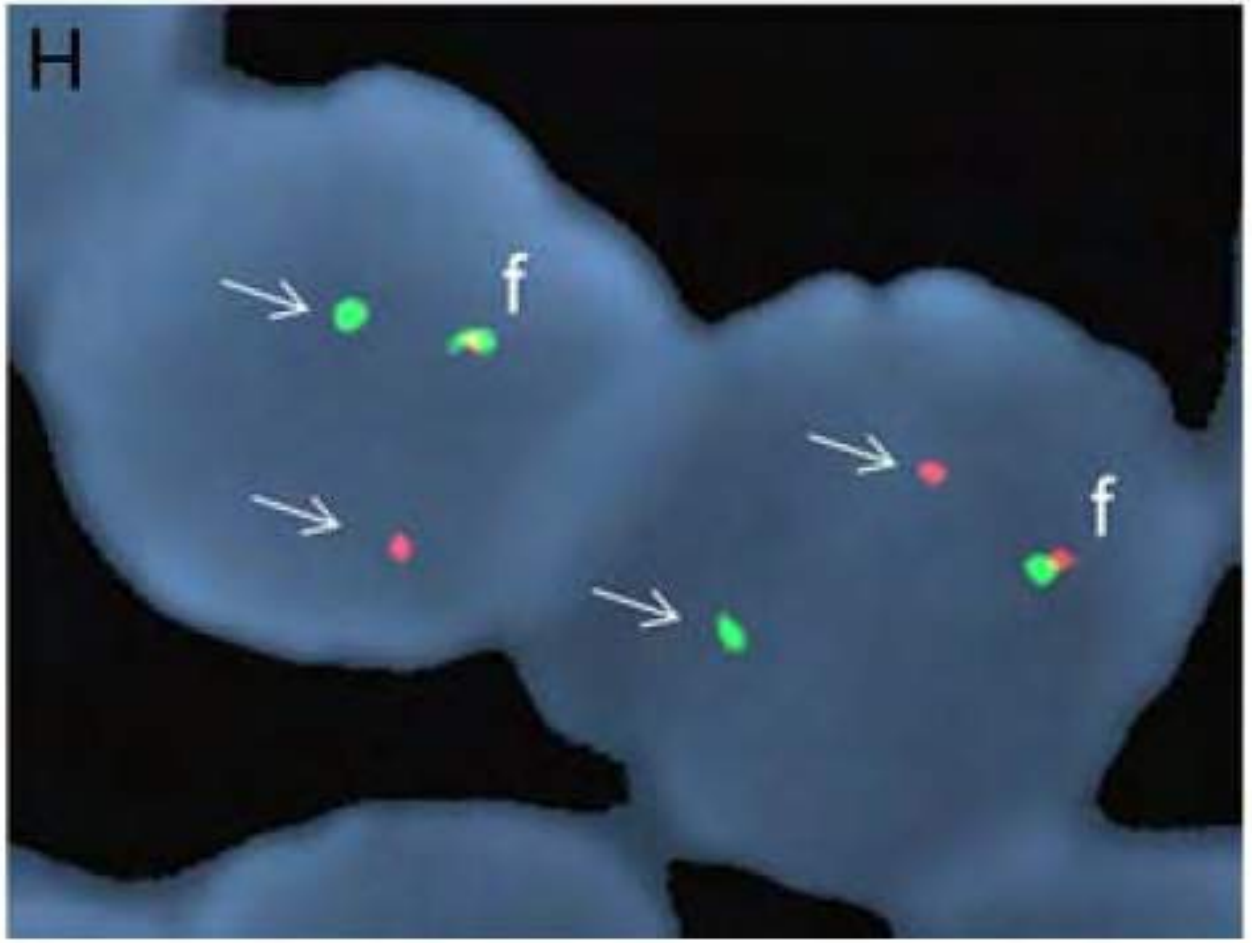



CD5

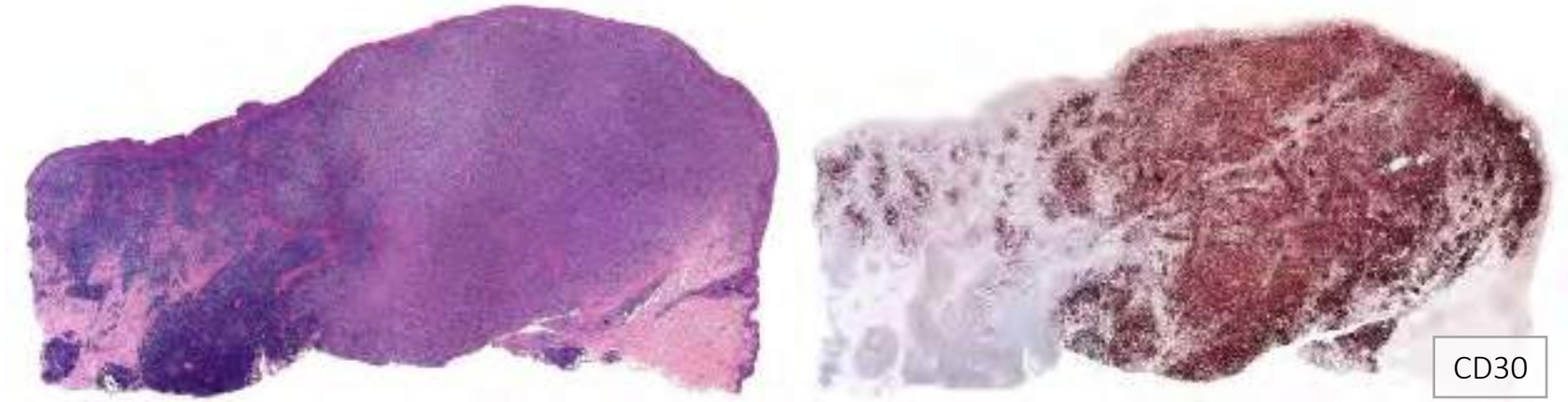

CD30

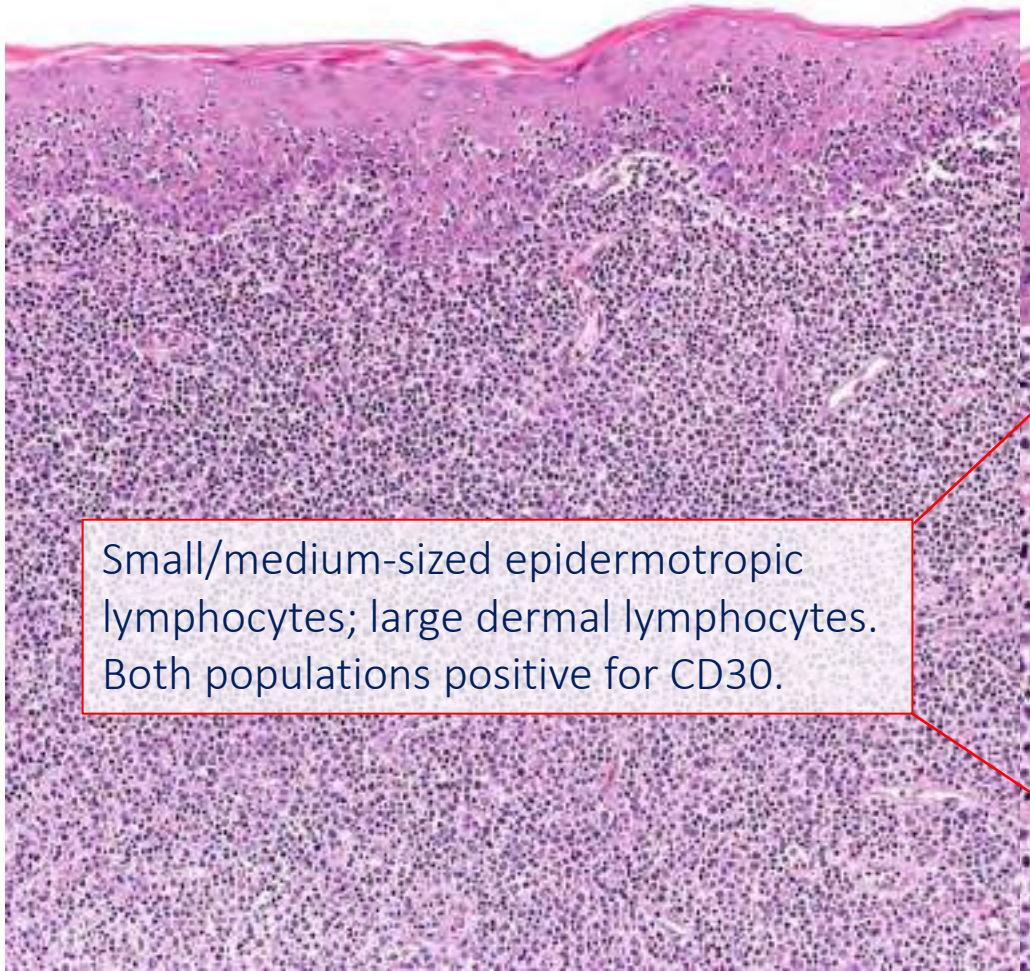
Chromosomal Rearrangements of 6p25.3 Define a New Subtype of Lymphomatoid Papulosis

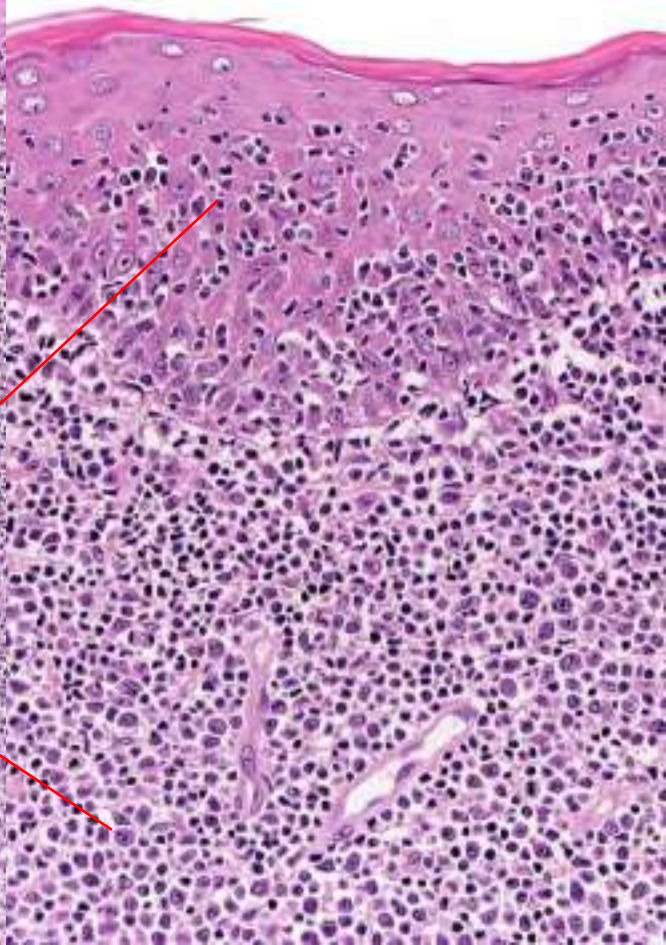
Lucia J. Kim, MD*† Marshall A. Kadin, MD‡ Eric R. Orr, MD§ Aaron C. Shaver, MD‖ Ellen F. Remstein, MD* Ryan A. Knudson, BS* and Andrew L. Feldman, MD*



11 patients (M:F = 9:2; age: 67 to 88 y)

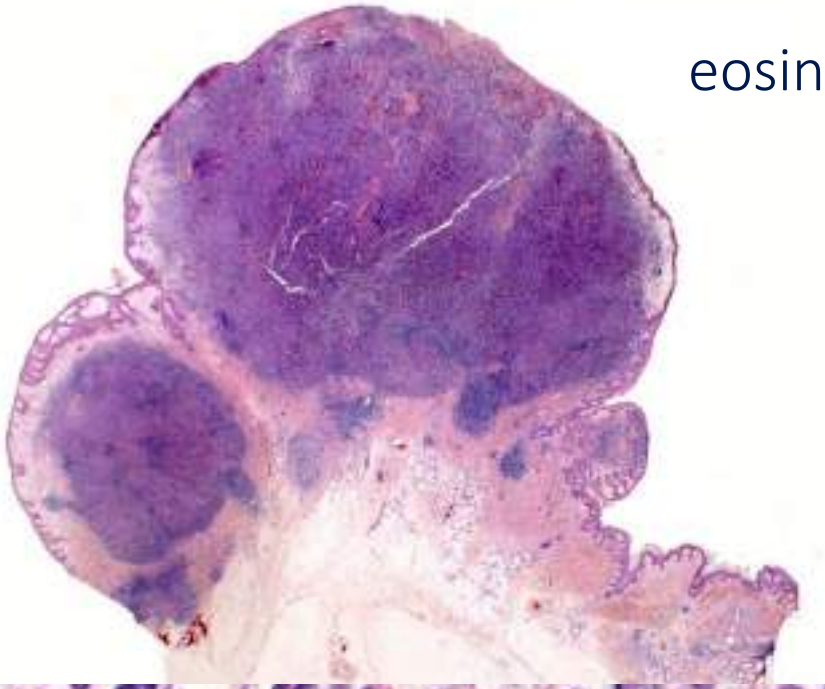


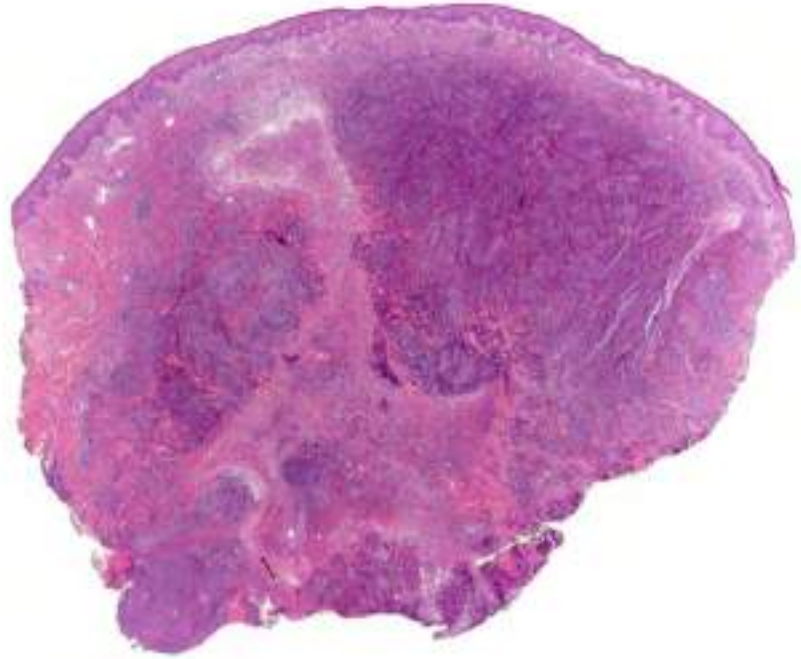


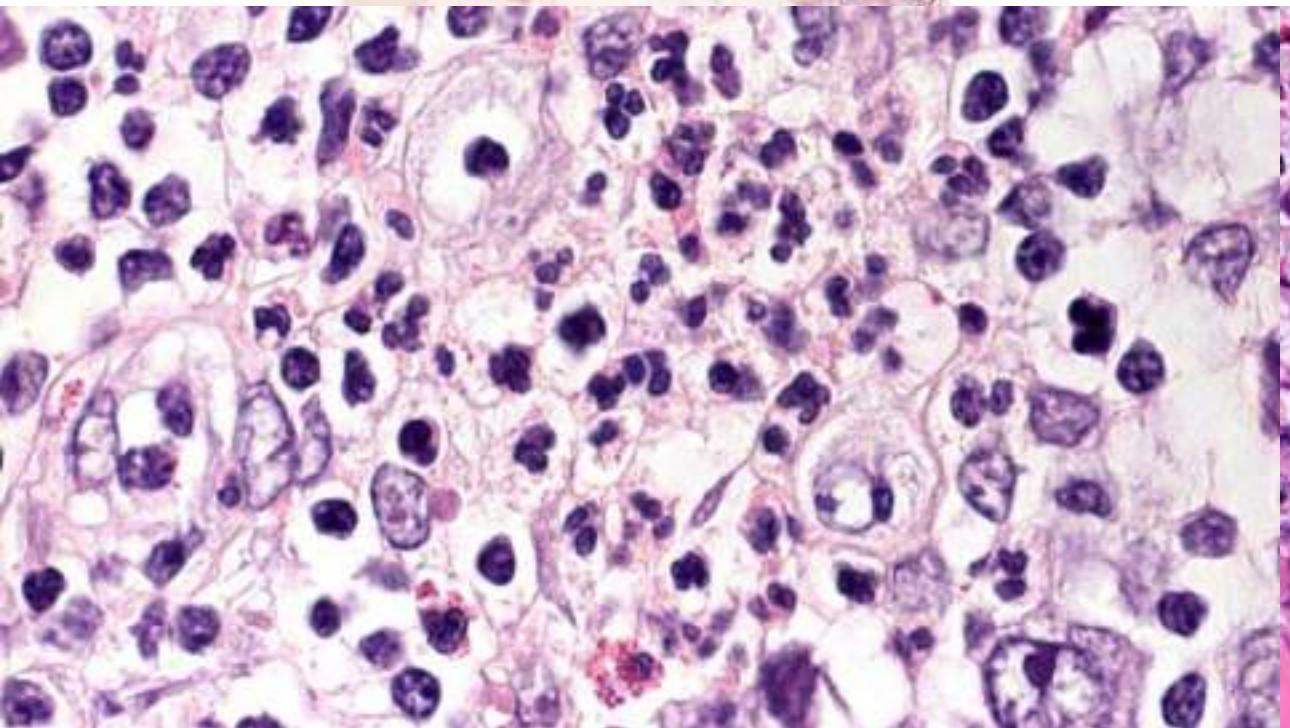


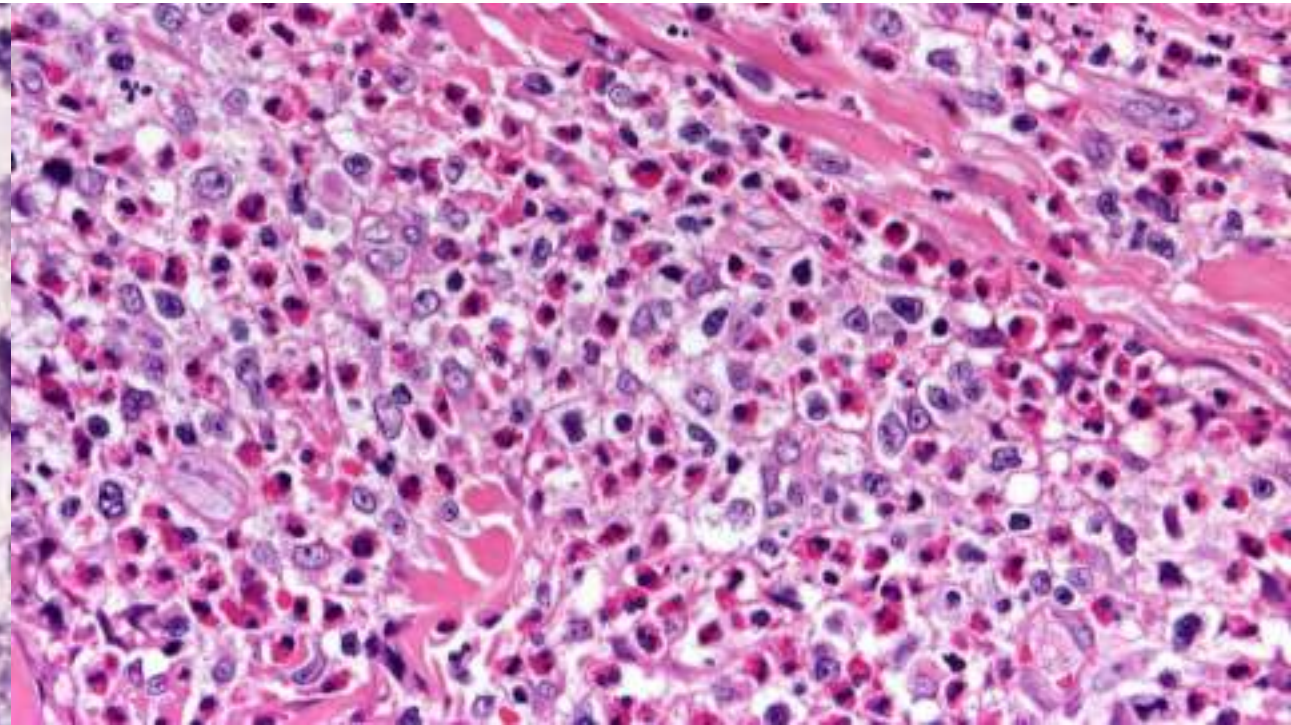
Histological pattern of rearrangement of the *DUSP22* locus at 6p25.3

eosinophils and/or neutrophils
may be prominent

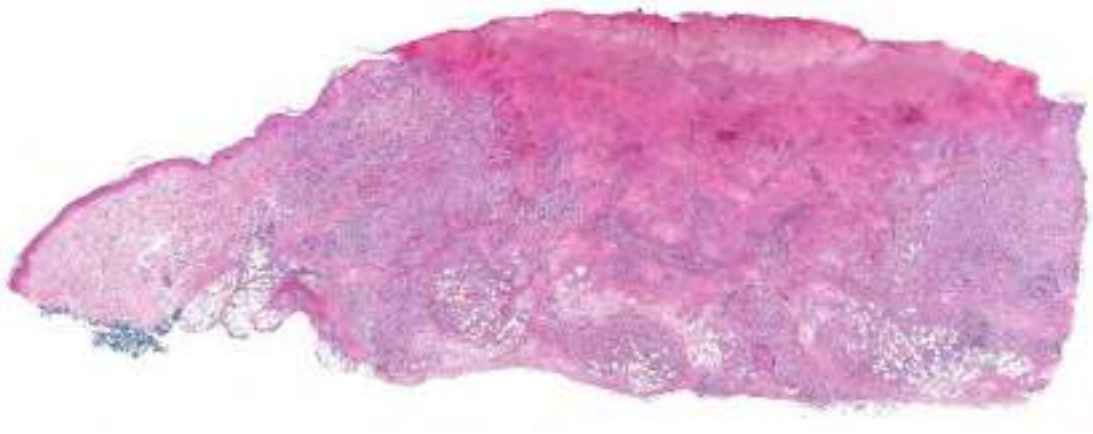




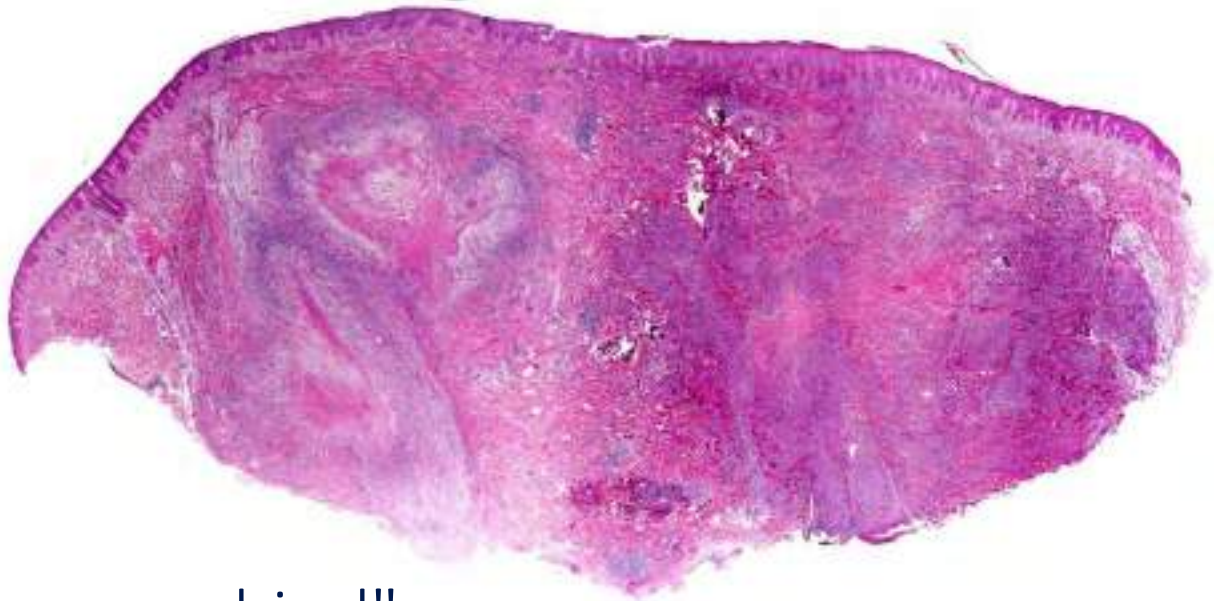




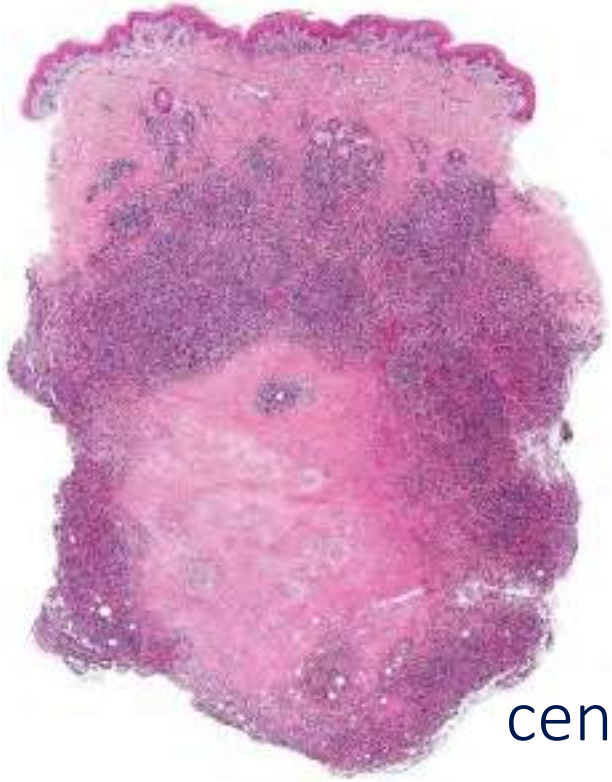
Different patterns of necrosis in cALCL



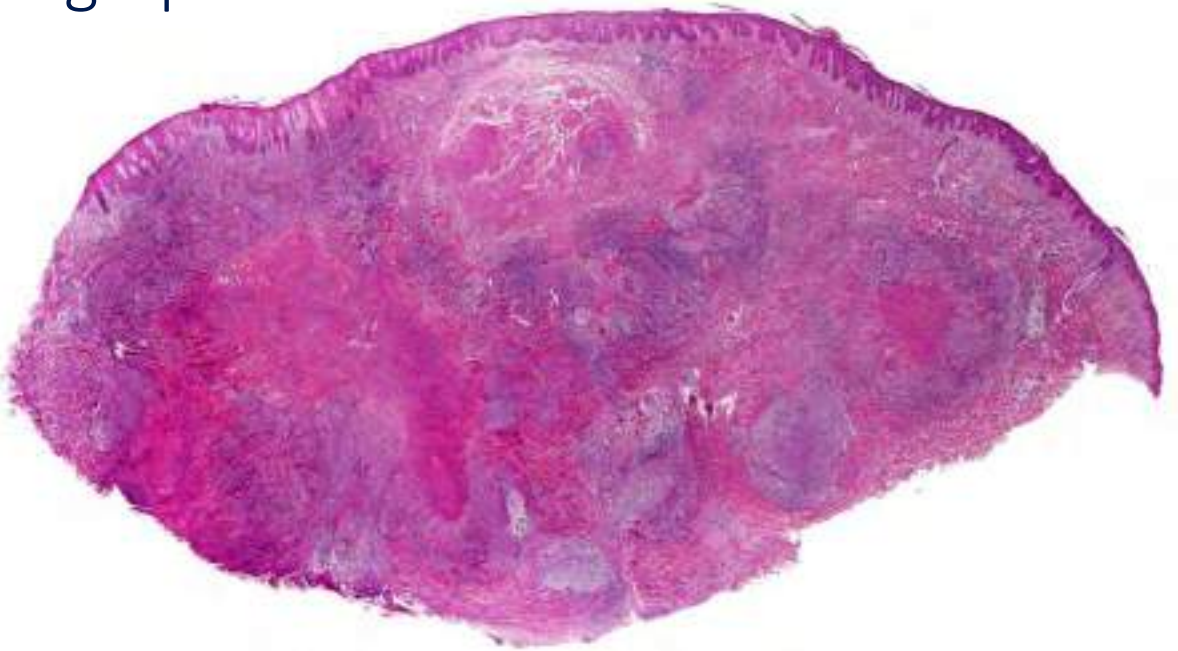
wedge-shaped

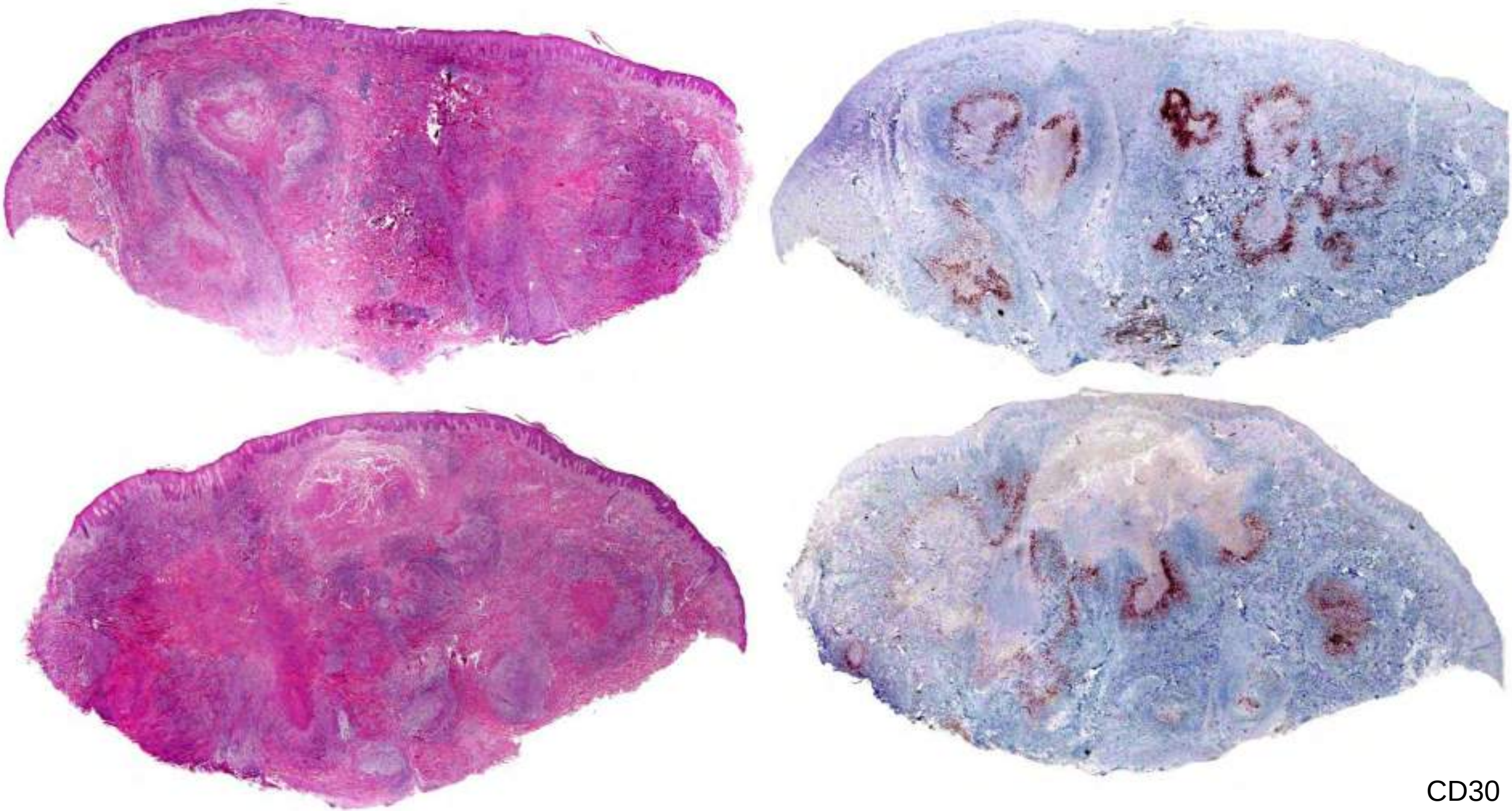


"geographical"

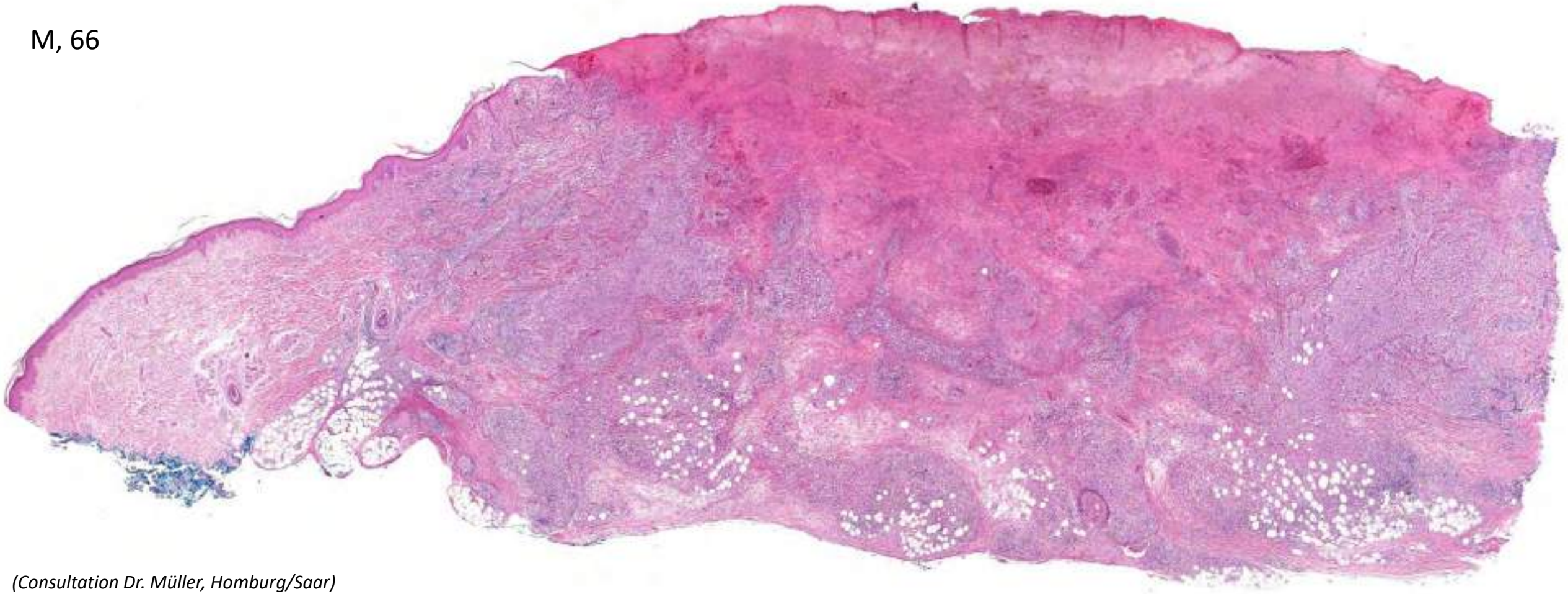


central

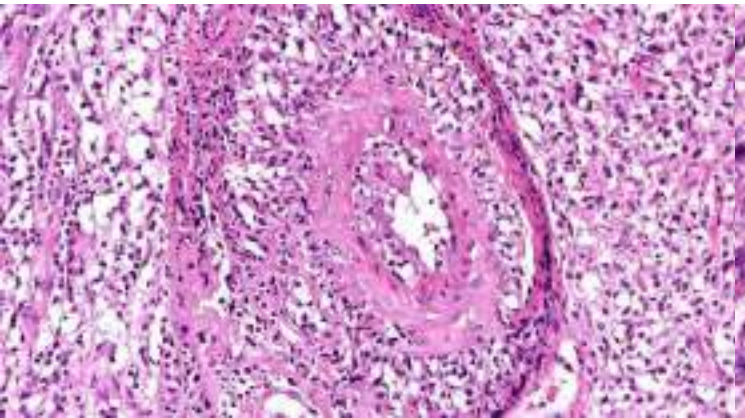


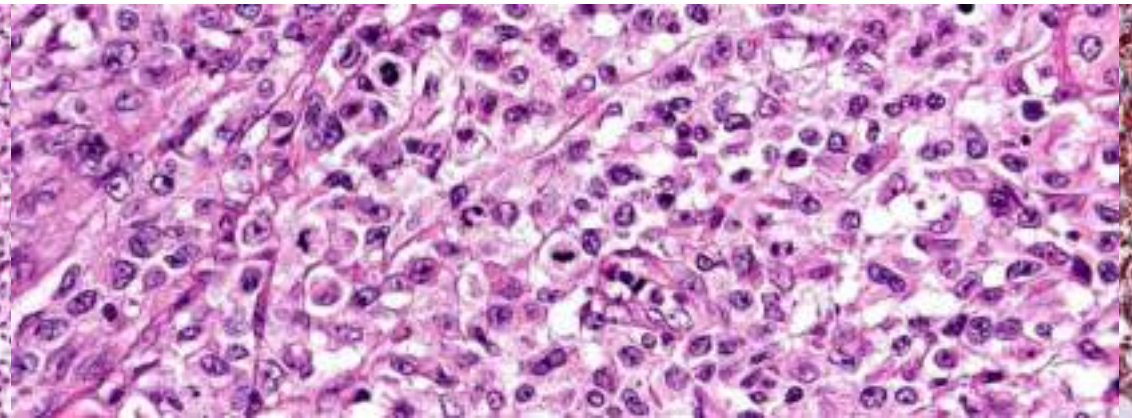

CD30

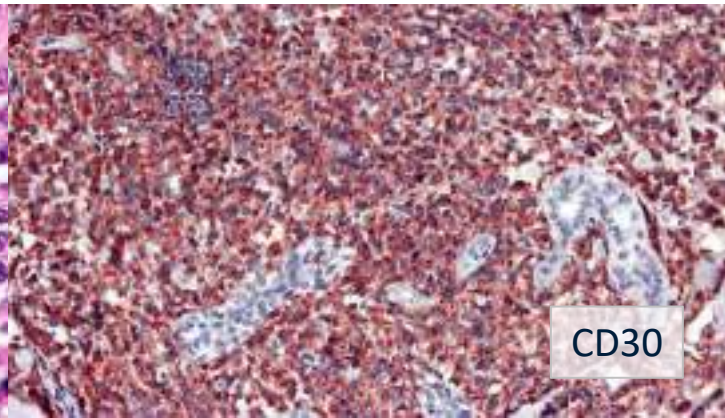
M, 66



(Consultation Dr. Müller, Homburg/Saar)







Journal of
Cutaneous Pathology

The morphologic spectrum of primary cutaneous anaplastic large T-cell lymphoma: a histopathologic study on 66 biopsy specimens from 47 patients with report of rare variants

Cesare Massone, Laila El-Shabrawi-Caelen, Helmut Kerl and Lorenzo Cerroni

Department of Dermatology, Research Unit of Dermatopathology, Medical University of Graz, Graz, Austria

Background: Primary cutaneous anaplastic large T-cell lymphoma (PCALCL) is a well-defined entity with prognostic differences from the nodal counterpart [nodal anaplastic large cell lymphoma (NALCL)]. Several histological variants of NALCL have been characterized (common, lymphohistiocytic and small cell). However, studies on morphological variants of PCALCL are lacking.
Methods: We analyzed retrospectively the clinicopathologic features of 66 biopsies from 47 patients (M : F = 27 : 20; median age: 53 years; mean age: 51.8 years; range: 14–82) with PCALCL, in order to better characterize the spectrum of this unusual neoplasm.
Results: The 'common variant' was the most frequent (40.4%). In contrast to NALCL, in PCALCL marked reactive infiltrates are more commonly present. In fact, 26 cases were classified as 'inflammatory type' (15 cases) and 'lymphohistiocytic' (11 cases). Concerning the predominant cell morphology, large anaplastic cells (33%) were almost as frequent as large pleomorphic (36%) and small to medium-sized cells (26%). We reported for the first time in the skin 2 rare cases with the predominance of large cells with a 'signet-ring'-like appearance. Epidermotropism and presence of eosinophils were found in a proportion of cases in all PCALCL variants.
Conclusions: PCALCL is characterized by variable histopathological presentations and a broad cytomorphologic spectrum.

Massone C, El-Shabrawi-Caelen L, Kerl H, Cerroni L. The morphologic spectrum of primary cutaneous anaplastic large T-cell lymphoma: a histopathologic study on 66 biopsy specimens from 47 patients with report of rare variants.
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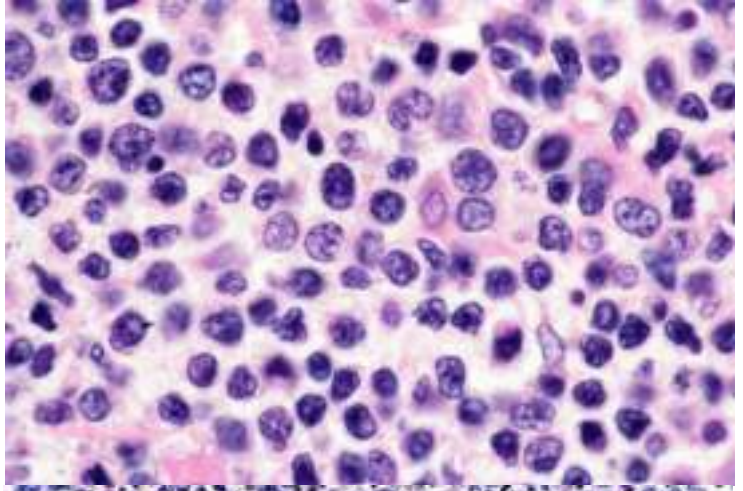
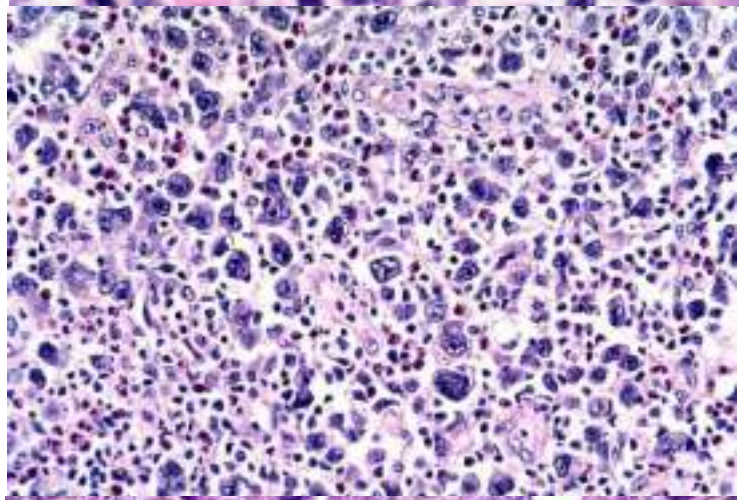
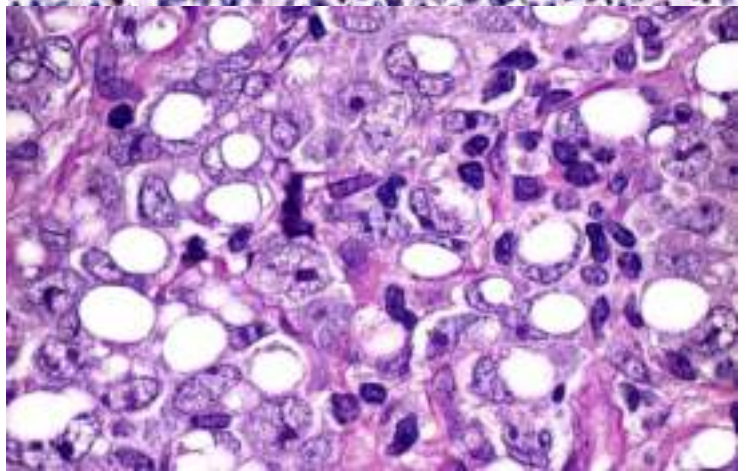
Primary cutaneous anaplastic large T-cell lymphoma (PCALCL) is a well-defined entity with prognostic and biological differences from the nodal counterpart.[1,2] In fact, cases arising in the lymph nodes and the skin are classified into separate groups in the World Health Organization (WHO) classification for hematopoietic neoplasms.[2] In spite of prognostic differences, PCALCL and nodal anaplastic large cell lymphoma (NALCL) are morphologically identical and cannot be distinguished based on



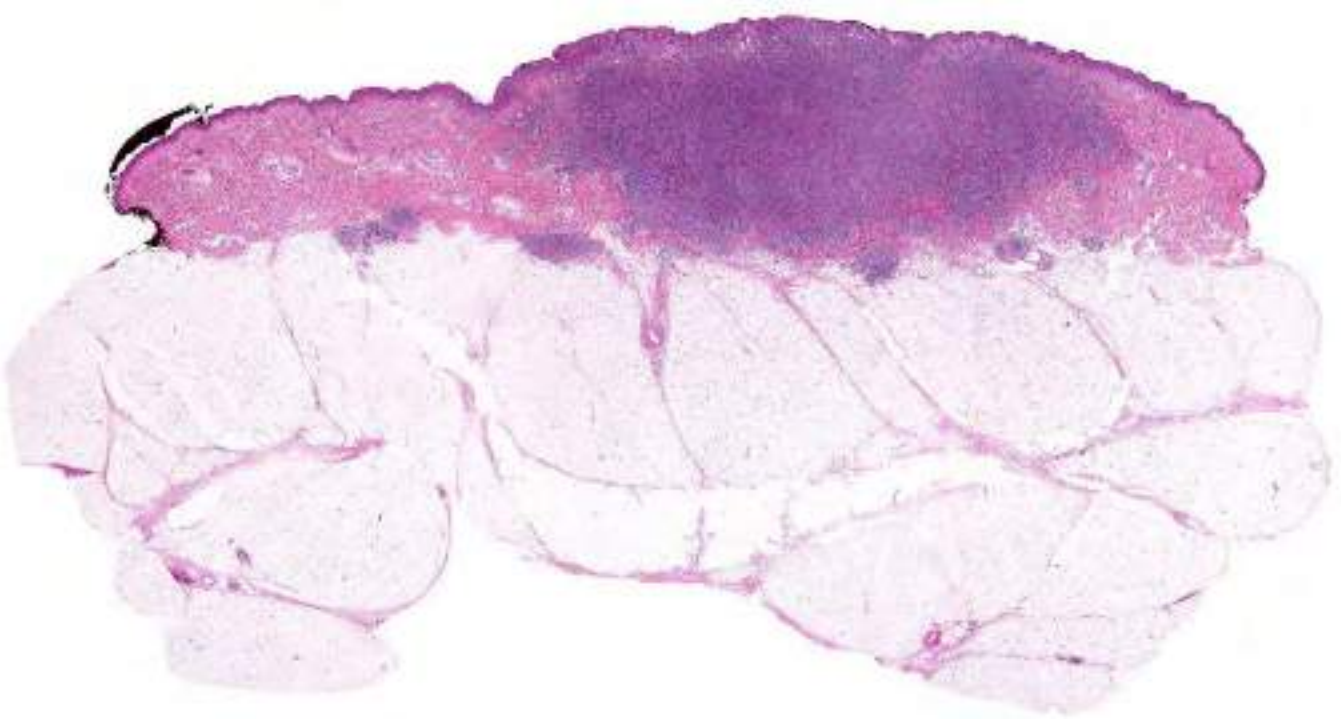
small cell type

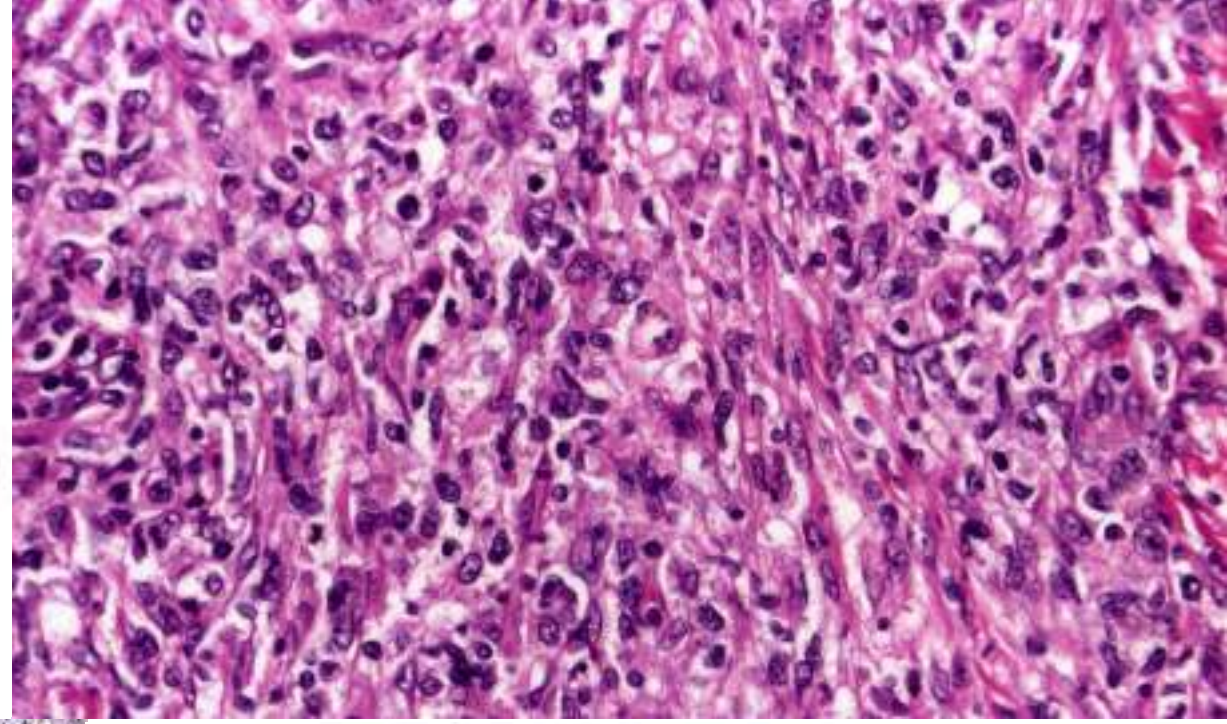


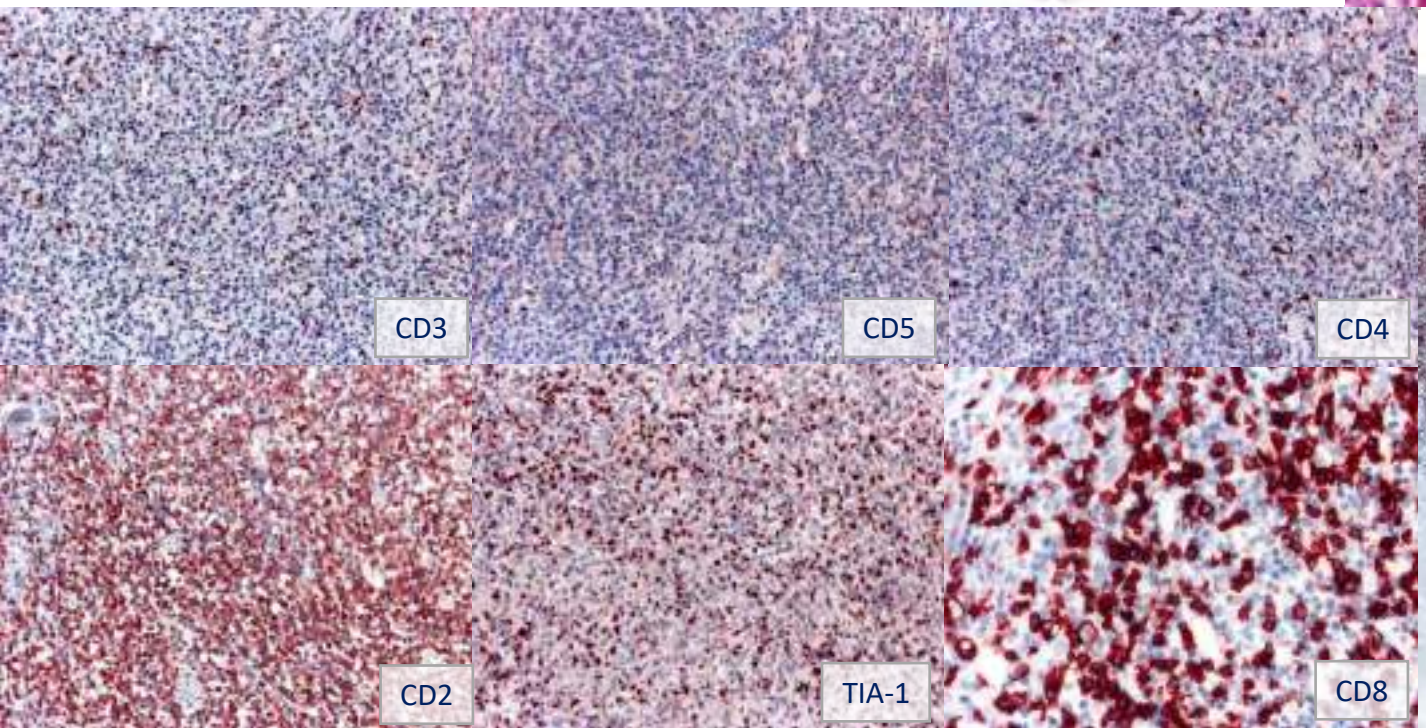
"inflammatory" type

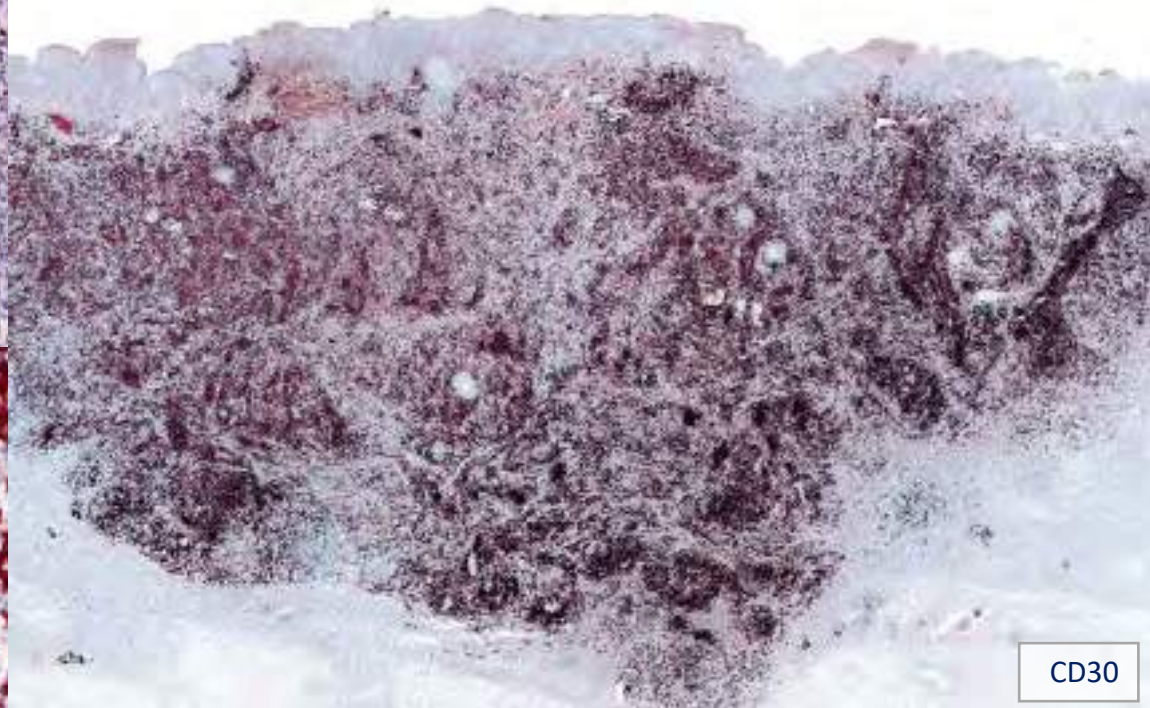


signet ring cell type






CD3
CD5
CD4
CD2
TIA-1
CD8


CD30

Phenotypic Variability in Primary Cutaneous Anaplastic Large T-cell Lymphoma: A Study on 35 Patients

Cesare Massone, MD and Lorenzo Cerroni, MD

Abstract: Primary cutaneous anaplastic large T-cell lymphoma (pcALCL) is a well-defined entity characterized by neoplastic cells expressing CD30, CD2, CD3, CD4, and CD5. Cases with different phenotype have been reported, including variable loss of CD2, CD3, and CD5, and expression of cytotoxic phenotype ($CD8^+$) and/or of cytotoxic proteins. Aberrant phenotypes represent a diagnostic pitfall and may be the cause of misdiagnoses. We reviewed 35 cases of pcALCL (M:F = 19:16; mean age, 50.8 years; range, 14–92 years), to better characterize the immunophenotypic spectrum of the disease. Twelve cases (34%) had a T-helper phenotype ($CD4^+/CD8^-$), and TIA-1 was positive in 5 of 8 stained cases. Six cases (18%) had a T-cytotoxic phenotype ($CD4^-/CD8^+$) and were also positive for TIA-1. Positivity for both CD4 and CD8 was observed in 7 cases (20%), 4 of which were stained for TIA-1 and found to be positive, whereas both CD4 and CD8 were negative in 9 cases (26%), only 1/8 tested cases being TIA-1 positive). CD2 was positive in 21 of 27 tested cases (78%), CD3 in 21 of 34 cases (62%), and CD5 in 15 of 31 cases (48%). Interestingly, 11 cases (31%) showed a profoundly aberrant phenotype lacking simultaneously several T-cell markers. Our data allow a better characterization of pcALCL with aberrant phenotypes, showing the remarkable variability in expression of different markers.

Key Words: primary cutaneous anaplastic large T-cell lymphoma, $CD30^+$ cutaneous lymphoproliferative disorders, cutaneous T-cell lymphoma, immunophenotype

(*Am J Dermatopathol* 2014;36:153–157)

INTRODUCTION

Primary cutaneous anaplastic large T-cell lymphoma (pcALCL) is a well-defined entity with prognostic and biological differences from the nodal counterpart. It is usually characterized by large cells with anaplastic, pleomorphic, or immunoblastic morphology, but several histopathologic variants have been described.[1–3] Neutrophils ("inflammatory-type" pattern), lymphocytes ("lymphohistiocytic" pattern), or even eosinophils can predominate in the infiltrate, and cases with small- to medium-sized cells ("small-cell" pattern) or signet-ring cell morphology have also been reported.[4,5]

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The authors declare no conflicts of interest.

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Neoplastic cells in conventional cases of pcALCL express CD30 and CD2, CD3, CD4, and CD5 (T-helper phenotype) and are negative for CD8, CD56, and cytotoxic proteins.[1–3] Cases with different phenotype have been reported, including variable loss of the T-cell markers CD2, CD3, and CD5, and expression of cytotoxic phenotype ($CD8^+$) and/or of cytotoxic proteins (granzyme B, TIA-1, perforin).[1–3,6–11] Aberrant phenotypes represent a diagnostic pitfall and may be the cause of misdiagnoses. Although pcALCL is traditionally considered as a lymphoma of T-helper lymphocytes, the exact proportion of cases with aberrant phenotype is unknown. In this study, we analyzed the clinicopathologic and immunophenotypic features of 35 patients with pcALCL, to better characterize the immunophenotypic spectrum of this cutaneous lymphoma.

MATERIALS AND METHODS

From a total of 114 cases of pcALCL documented in the lymphoma database of the Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz (Graz, Austria), 35 cases were selected for the study. The other 79 cases were excluded because of lack of complete data or of available material for further stainings. Patients with history of mycosis fungoides (MF) or lymphomatoid papulosis (LyP) and "borderline cases" of $CD30^+$ cutaneous lymphoproliferative disorder (cases in which a definitive distinction between pcALCL and LyP could not be made) and cases of cutaneous Hodgkin disease have been excluded from the study. Diagnosis of pcALCL has been made according to the WHO classification of lymphomas.[1,2] Primary skin involvement was defined as the presence of cutaneous lymphoma without nodal and/or visceral involvement after complete staging procedures.[1,2] Details of some of the cases have been published previously.[4,11]

Histology

Biopsy specimens were fixed in 10% buffered formalin and subsequently embedded in paraffin. Sections were stained with hematoxylin–eosin for routine histopathologic evaluation. All cases and stainings have been reviewed independently by both the authors.

Immunohistology

Detailed immunophenotypic analyses were performed on routinely fixed paraffin-embedded tissue sections according to a previously described 3-step immunoperoxidase method. Microwave enhancement was used for all the antibodies. Second and third antibodies were obtained from Dako (Dakopatts; Glostrup, Denmark). The first antibody were from

Common loss of pan-T-cell antigens:

CD2– 6/27 (22%)

CD3– 13/34 (38%)

CD5– 16/31 (52%)

4/35 cases (11%) lacked all pan-T cell markers

Often cytotoxic phenotype:

CD4+/CD8– in 12 (35%) (TIA-1+ in 62,5%)

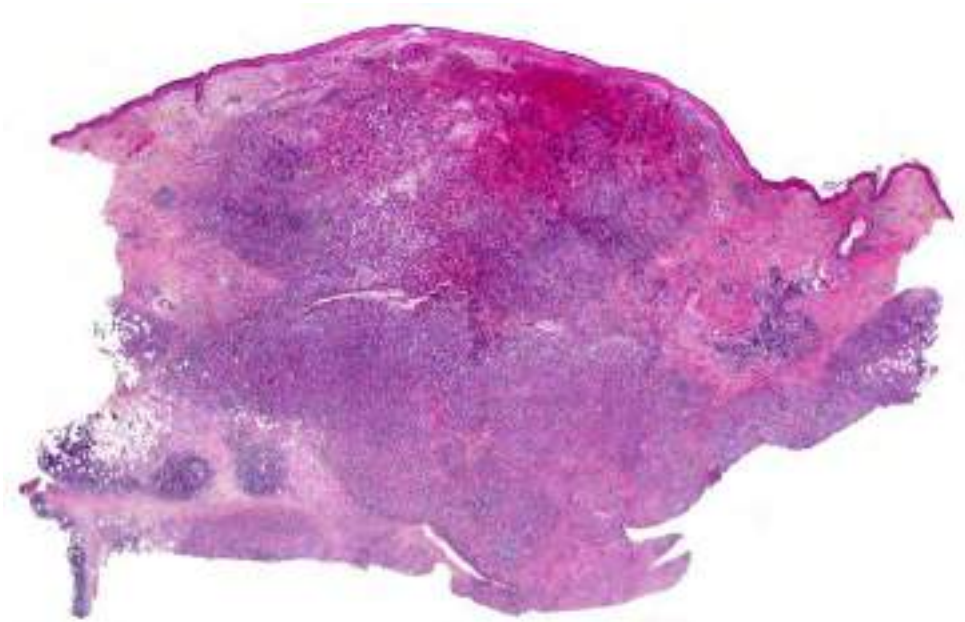
CD4–/CD8+ in 6 (18%) (all TIA-1+)

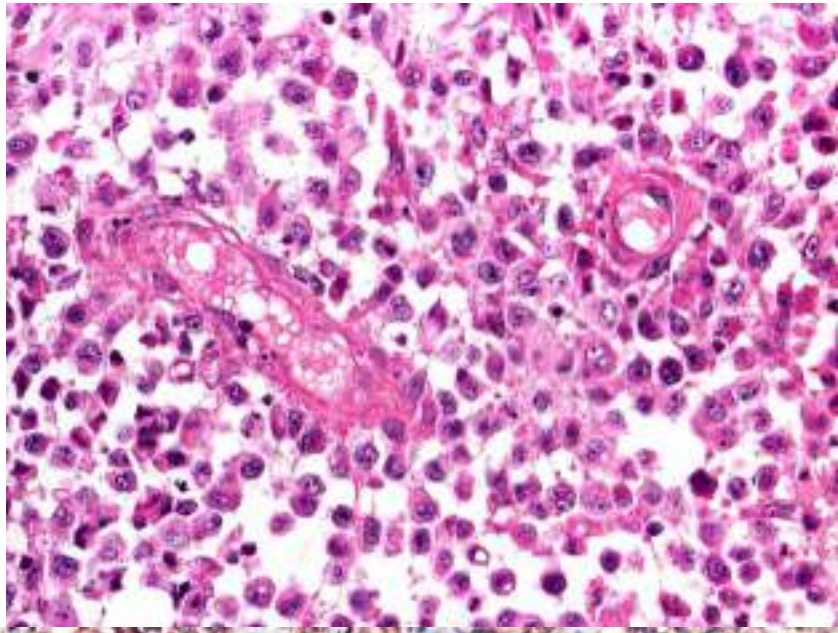
CD4+/CD8+ in 7 (21%) (all TIA-1+)

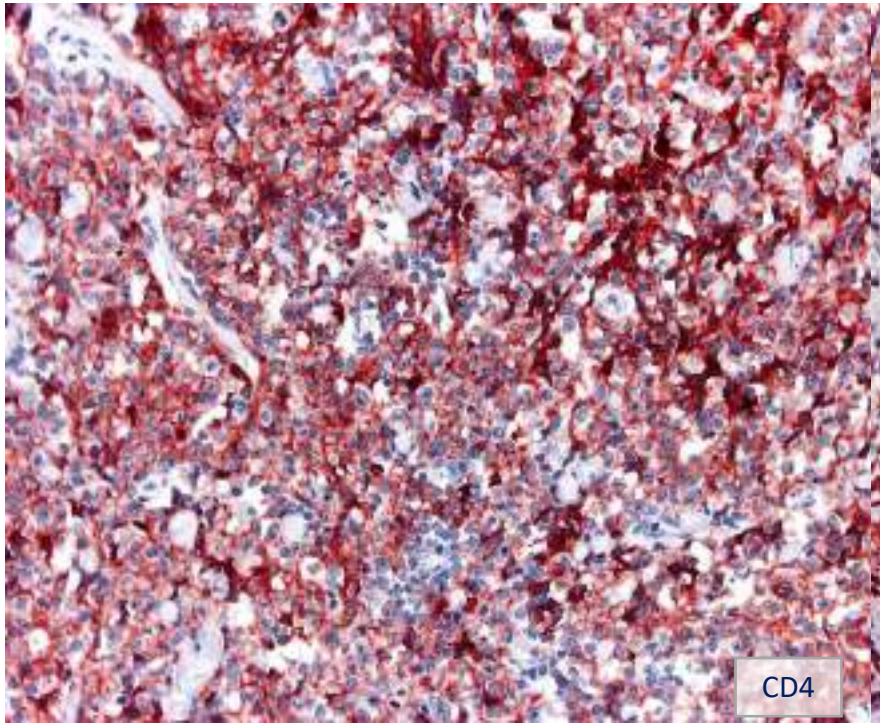
CD4–/CD8– in 9 (26%) (TIA-1+ in 12%)

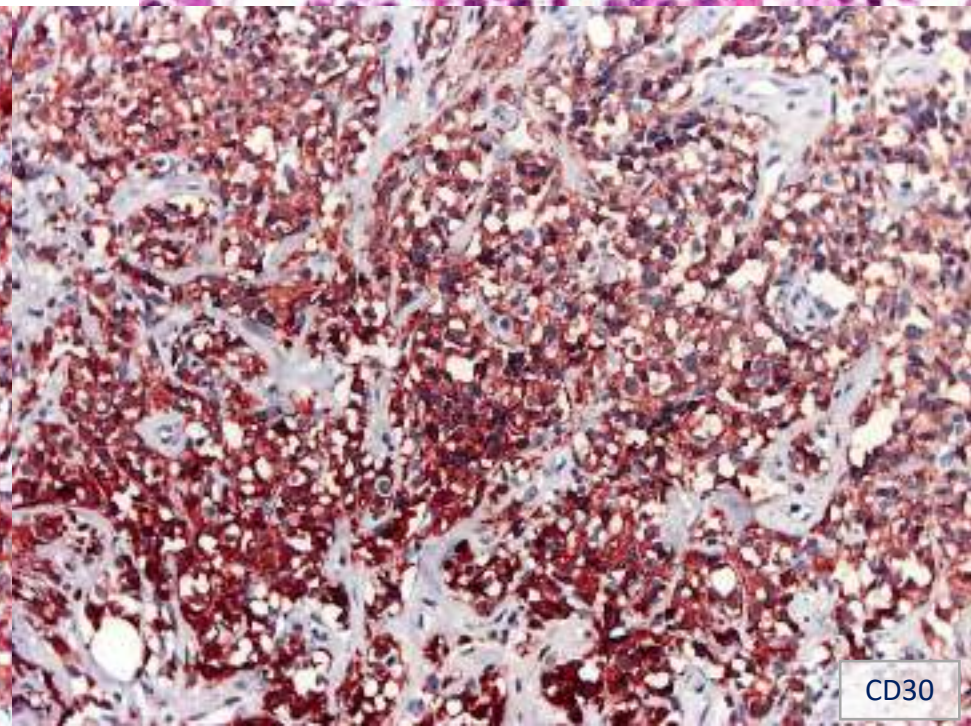
TIA-1+ in 16/26 cases (62%)

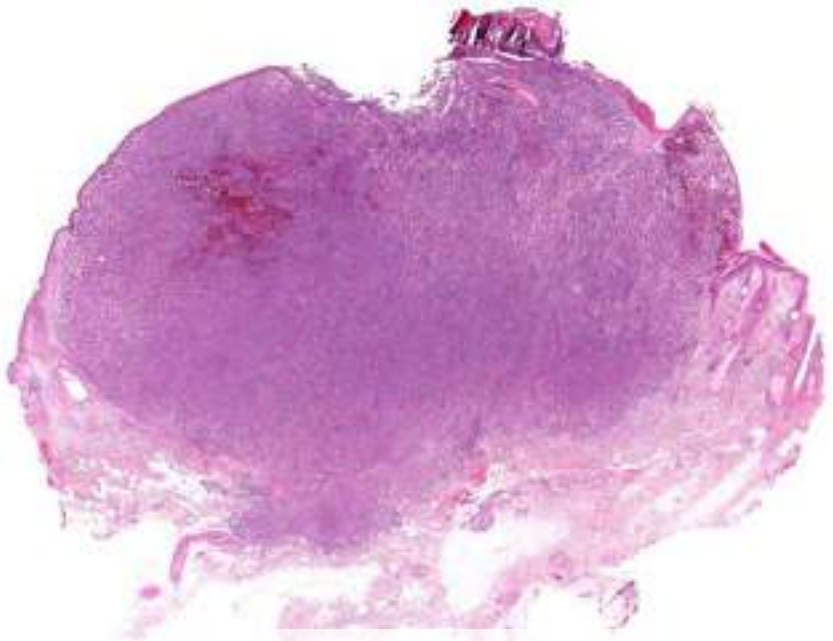
cALCL with extensive limb disease



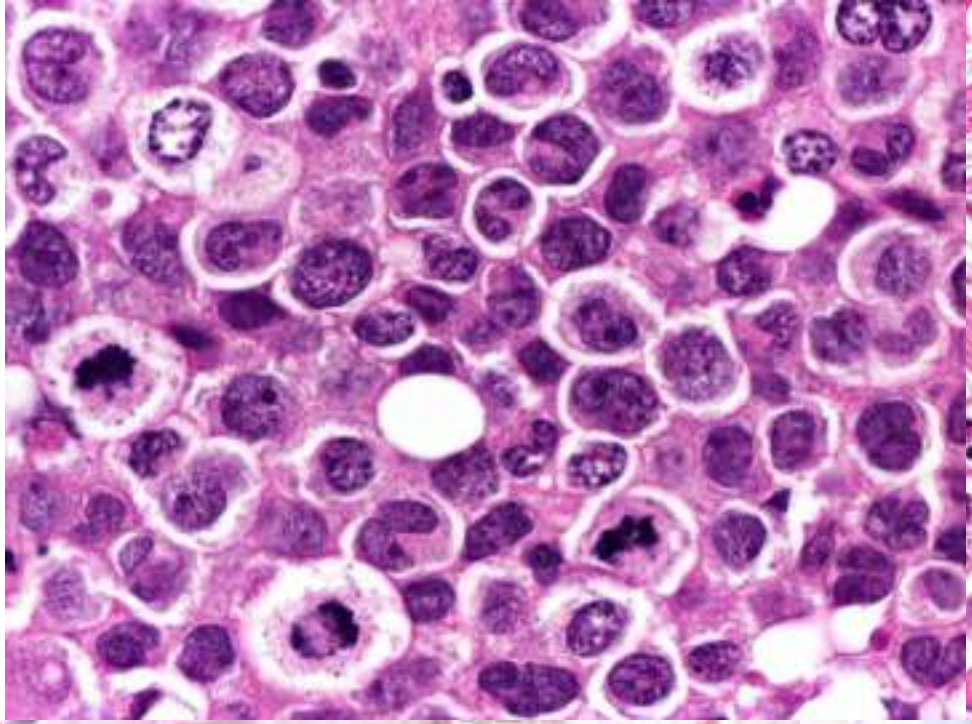


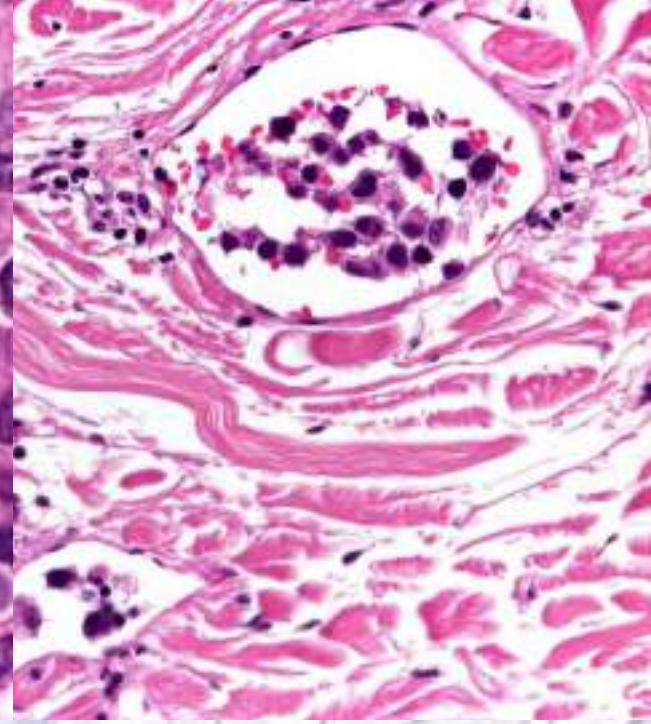


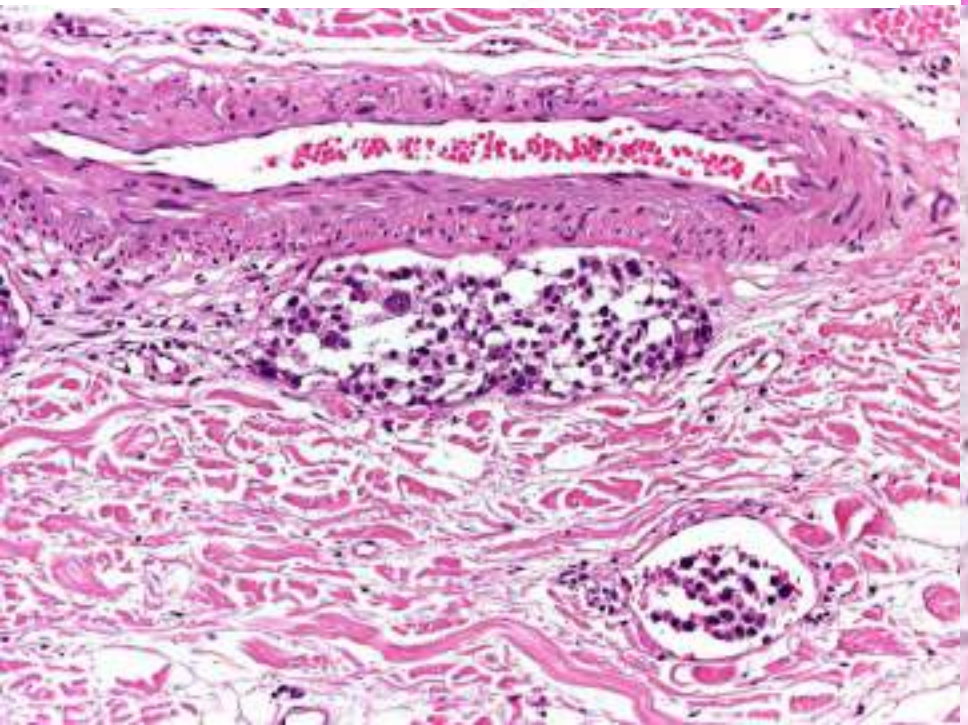


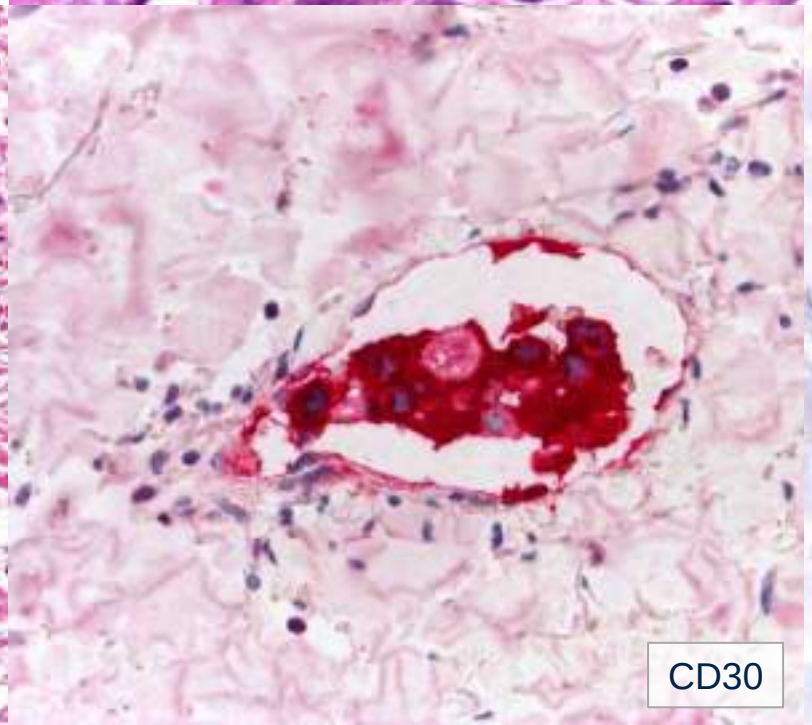


Intralymphatic cALCL









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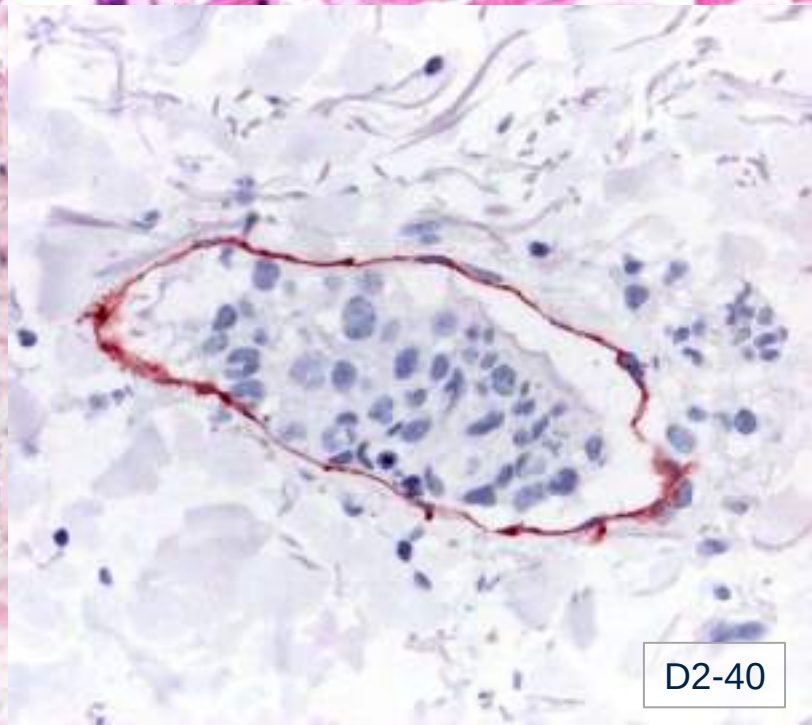

D2-40

Intralymphatic Cutaneous Anaplastic Large Cell Lymphoma/Lymphomatoid Papulosis

Expanding the Spectrum of CD30-positive Lymphoproliferative Disorders

Mark A. Samols, MD, Albert Su, MD,† Seong Ra, MD,†‡ Mark A. Cappel, MD,§ Abner Louissaint, Jr, MD,‖ Ryan A. Knudson, CG(ASCP)CM,¶ Rhett P. Ketterling, MD,¶ Jonathan Said, MD,† Scott Binder, MD,† Nancy Lee Harris, MD,‖ Andrew L. Feldman, MD,¶ Jinah Kim, MD, PhD,* Youn H. Kim, MD,†† and Dita Gratzinger, MD, PhD**

Abstract: Intravascular large B-cell lymphomas and EBV$^+$ NK/T-cell lymphomas commonly follow an aggressive clinical course. We recently reported an entirely intravascular anaplastic large cell lymphoma (ALCL) in the skin with a surprisingly indolent clinical course; interestingly, this lymphoma involved the lymphatic rather than the blood vasculature. We hypothesized that intravascular skin-limited ALCL is distinct from aggressive systemic intravascular lymphomas in its intralymphatic localization and clinical course. We now describe 18 cases of cutaneous intravascular large cell lymphoproliferations from 4 institutions. All 12 intravascular large T-cell lesions were intralymphatic; the majority (9) were CD30$^+$ T-cell lymphoproliferative disorders (TLPDs). 5 further classified as intravascular ALK$^-$ ALCL. One ALK$^-$ ALCL and 2 benign microscopic intravascular T-cell proliferations were also intralymphatic. A single case of otherwise typical cutaneous follicle center lymphoma contained intralymphatic centroblasts. The clinical and pathologic characteristics of the CD30$^+$ TLPDs were similar to those of their extravascular counterparts, including extralymphatic dermal involvement in a subset, *DUSP22-IRF4* translocations in half of tested ALK$^-$ ALCLs, and associated mycosis fungoides in 1; most were skin-limited at baseline and remained so at relapse. All 5 cases of intravascular large B-cell lymphoma involved the blood vasculature and behaved in a clinically aggressive manner; the ALK$^+$ ALCL, although intralymphatic, was systemic and clinically aggressive. We propose that cutaneous ALK$^-$ ALCL and related CD30$^+$ ALK$^-$ TLPDs involving the lymphatics are part of an expanding spectrum of CD30$^+$ TLPDs. The identification of intralymphatic as distinct from blood vascular localization may provide critical prognostic and therapeutic information.

Key Words: anaplastic large cell lymphoma, intravascular, CD30$^+$ cutaneous lymphoproliferative disorder, lymphatic

(*Am J Surg Pathol* 2014;38:1203–1211)

Anaplastic large cell lymphoma (ALCL) comprises 3 morphologically and immunophenotypically similar but clinically distinct entities: 2 systemic lymphomas—ALK$^+$ ALCL[1] and ALK$^-$ ALCL[2]—and primary cutaneous ALCL.[3] Primary cutaneous ALCL is distinguished by its generally indolent clinical course with a propensity to cutaneous but not systemic relapse.[4] Primary cutaneous ALCL can be histologically indistinguishable from lymphomatoid papulosis, particularly type C, whereas the clinical presentation differs (a solitary ulcerating nodule in ALCL vs. multiple papules that regress spontaneously or wax and wane in lymphomatoid papulosis). For this reason, skin biopsies may be diagnosed more generically as CD30$^+$ T-cell lymphoproliferative disorders (TLPDs) pending further clinical follow-up.[5] Recently, there have been several case reports of cutaneous intravascular presentation of CD30$^+$ TLPDs, including ALCL[6–10] and lymphomatoid papulosis type C.[11] These patients typically presented with localized cutaneous disease and an indolent clinical course. Interestingly, the reported cases of intravascular ALCL presenting in the skin[6] appeared to involve lymphatic channels rather than blood vessels.

The only lymphoma classified by the World Health Organization according to its intravascular location is intravascular large B-cell lymphoma (IVLBCL),[12] which presents with extranodal involvement of small vessels,

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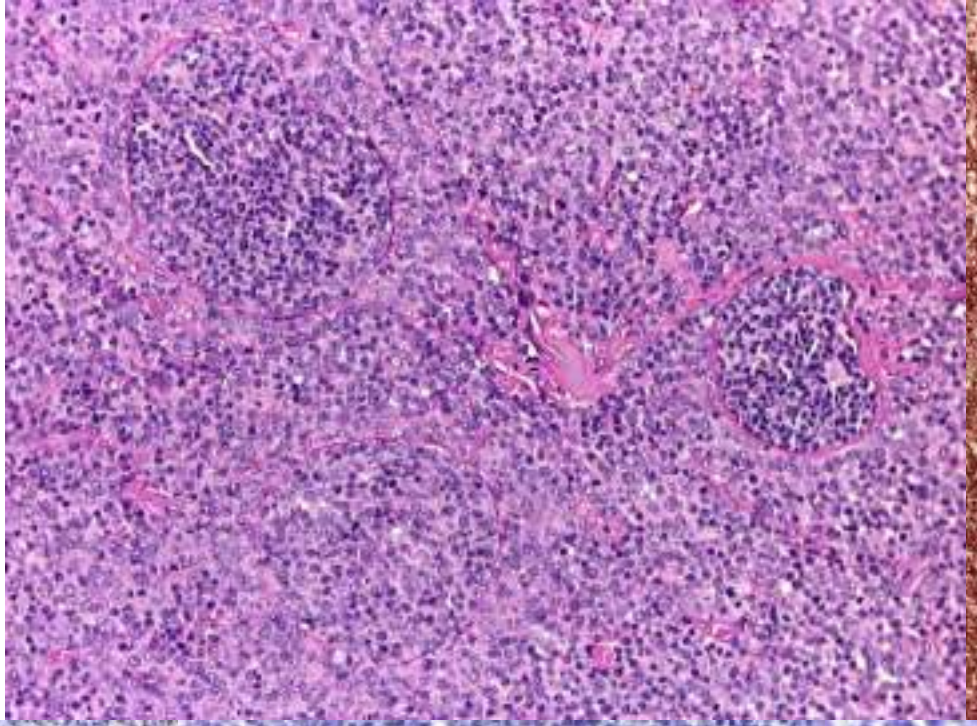
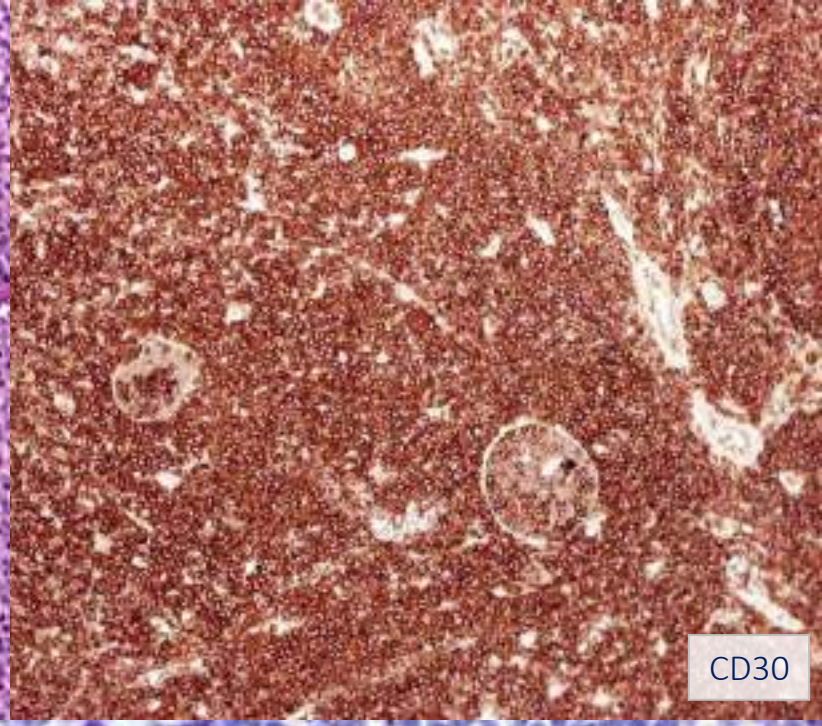
5 ALK$^-$ ALCL
1 ALK$^+$ ALCL
3 "LyP-like"
2 benign intralymphatic proliferations of T-cell lymphoid blasts

Intralymphatic Spread Is a Common Finding in Cutaneous CD30+ Lymphoproliferative Disorders

Lymphatic vessel involvement was found in 36/60 cases (60%) of ALCL (primary cutaneous: 24; concomitant: 3; secondary cutaneous: 4; staging unknown: 5), and in 6 cases (37.5%) of LyP.
Follow-up data, available in 28 patients with ALCL and 11 with LyP, suggested that lymphatic vessel involvement had no negative prognostic implication.

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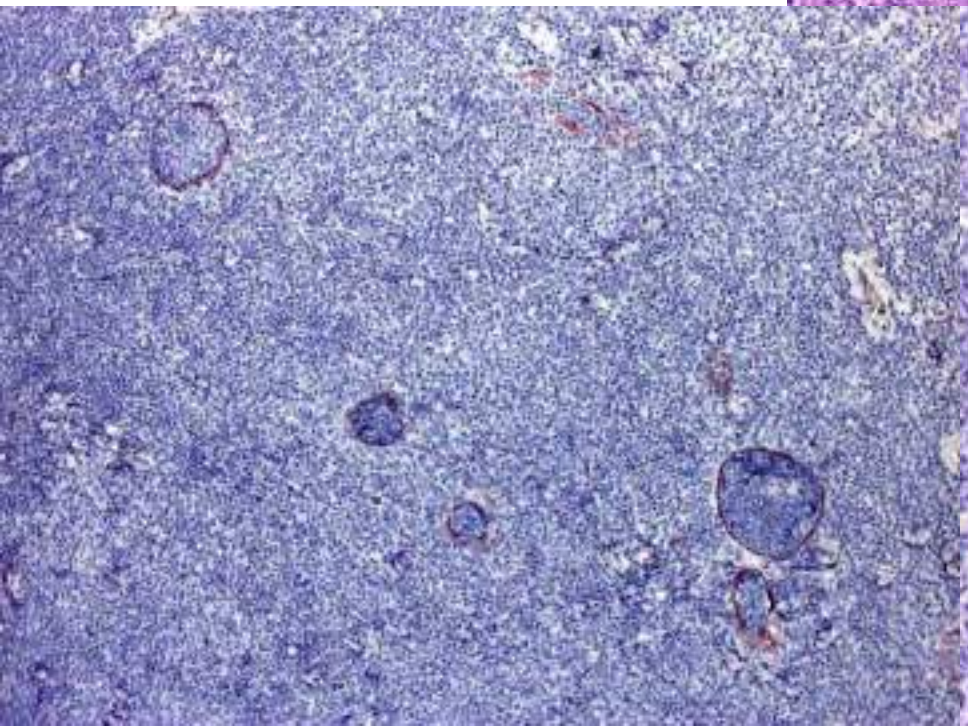

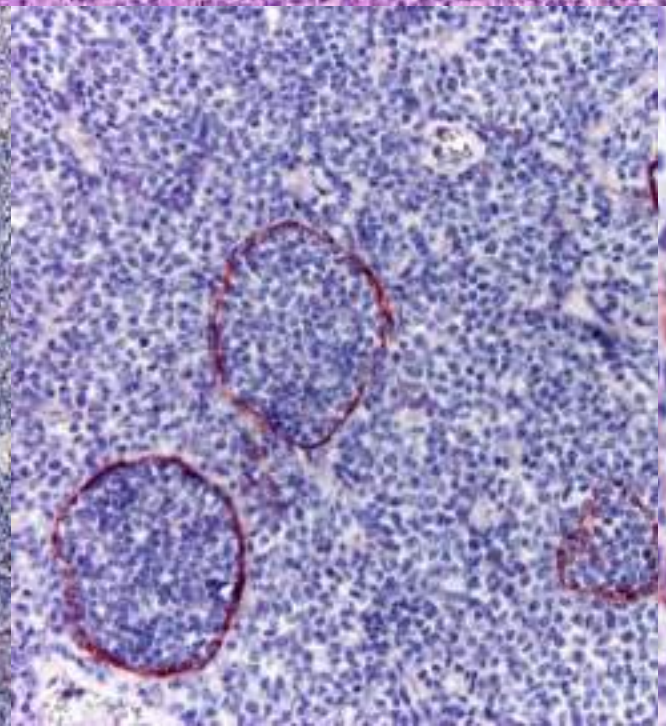

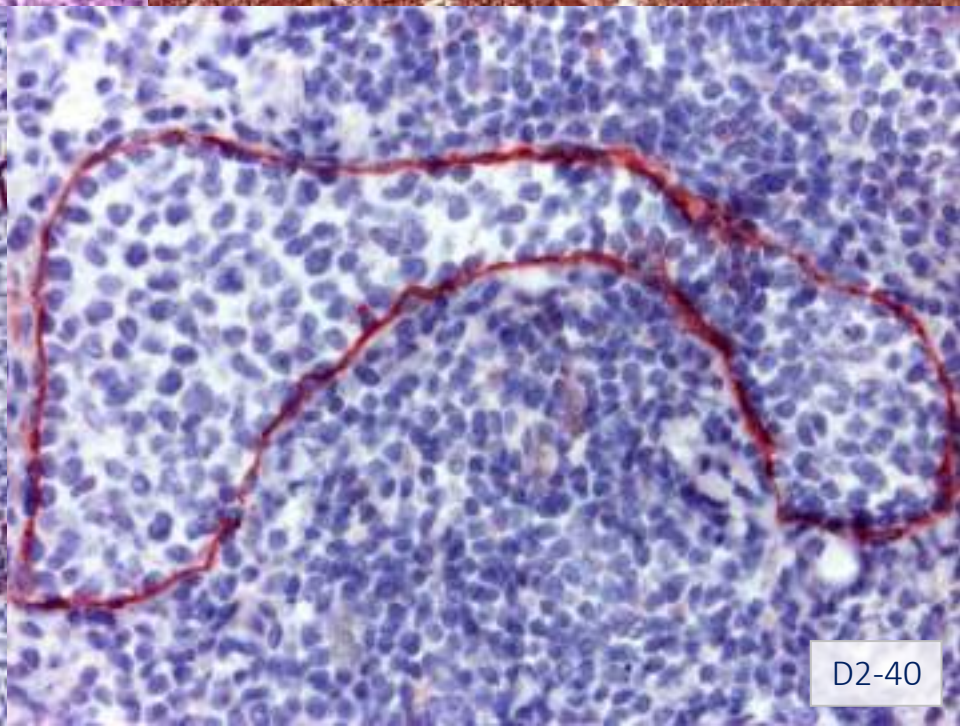
D2-40

35th Pezcoller Seminar – Surgical pathology of the skin: hot topics and slide seminars
Trento, May 9-10, 2024

Cutaneous lymphomas & pseudolymphomas 3

Lorenzo Cerroni

Case Reports

Lymphomatoid Papulosis

A Continuing Self-Healing Eruption, Clinically Benign—Histologically Malignant

Warren L. Macaulay, MD, Fargo, ND

A 41-year-old woman has an asymptomatic eruption of three years' duration. The clinical course is benign and is characterized by a continuing, random, coming and going of papules, some of which undergo necrosis, and all of which involute spontaneously within three to four weeks. Results of repeated physical examinations and laboratory studies are normal. Yet, biopsies of the skin lesions show an alarming infiltrate of anaplastic cells of disputatious origin, suggesting to most reviewers a diagnosis of malignant lymphoma. A number of comparable cases are reviewed, their similarity implying an uncommon entity.

HERE IS A paradox: a 41-year-old woman has a skin eruption of three years' duration which is best described as clinically resembling acute parapsoriasis (pityriasis lichenoides et varioliformis acuta, Mucha-Habermann's disease). Lesions are continually developing and regressing at random. The patient's health is good, results of physical examination and laboratory studies are normal. Yet, repeated biopsies of her skin lesions (an average of four biopsies a year since coming under my observation in August 1964) consistently reveal an alarming infiltrate of large pleomorphic hyperchromatic cells which expert histopathologists and hematologists have variously classified as highest grade malignant lymphoma (a majority opinion), malignant reticulosis, metastatic carcinoma, malignant melanoma, undifferentiated malignant tumor. The details of this case are herewith reported, a number of similar cases noted, and this curious phenomenon discussed.

Accepted for publication June 28, 1967.

From the Department of Dermatology, Fargo Clinic, Fargo, ND.

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Report of a Case

The patient is a 41-year-old woman. She had acute appendicitis and appendectomy in 1950. In 1963, she experienced an episode diagnosed by her local physician as subacute glomerulonephritis. This was associated with a transient elevation of blood pressure and edema of the hands and feet. Erythrocytes and polymorphonuclear leukocytes were present in the urine with only a slight trace of albumin. This ailment cleared uneventfully and without apparent residua. Aside from these two illnesses, the patient has enjoyed good health. Married for 19 years, she has never been pregnant although she has not practiced contraception.

The patient has worked in the business office of a dairy for 22 years. For years, both the office and the contiguous dairy have been routinely sprayed every three months with organic phosphate and/or chlorinated hydrocarbon insecticides. This practice has now been discontinued in the office section.

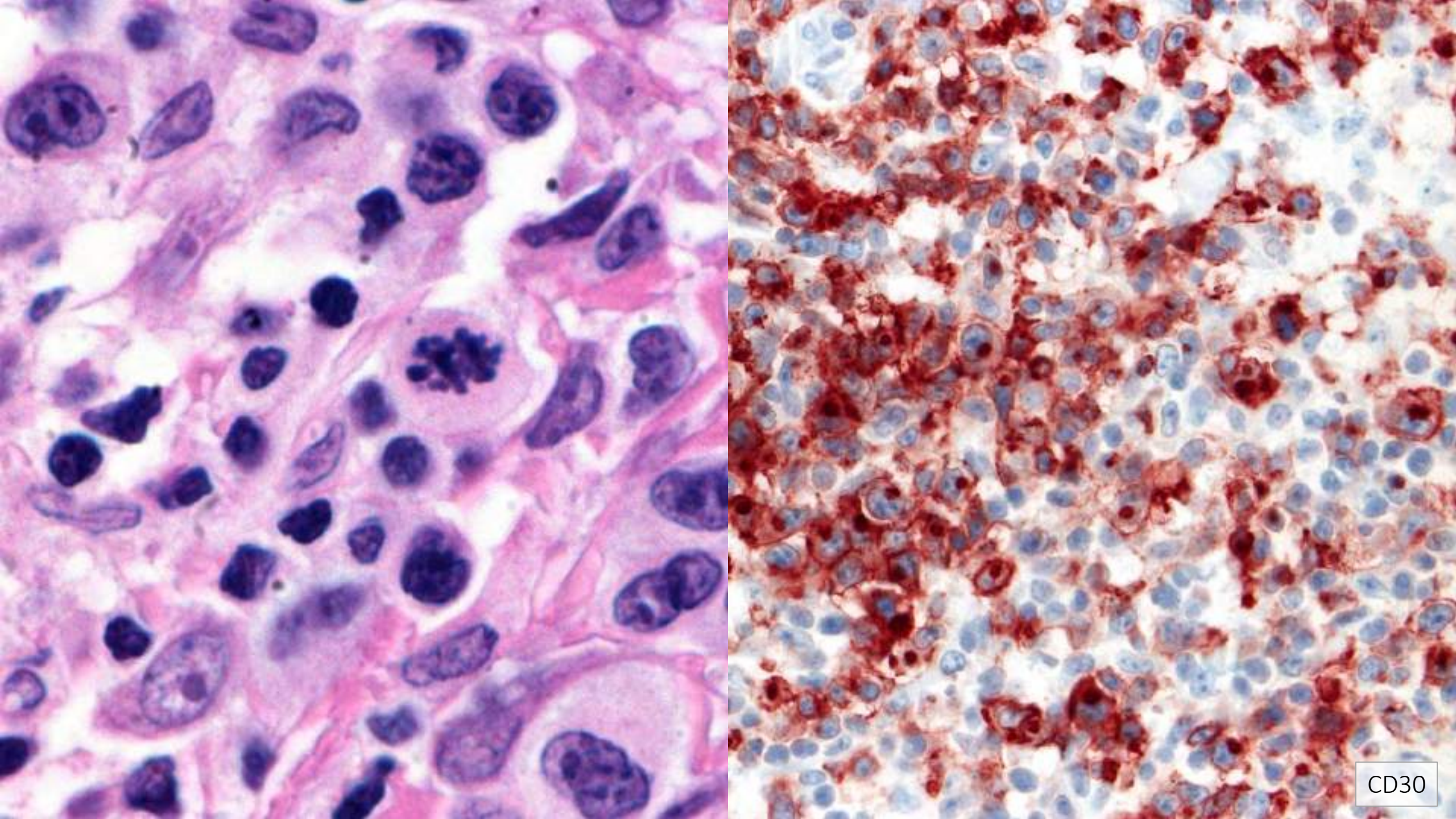
The patient takes aspirin for headache about once a week. Otherwise, there is no drug history.

The Eruption

In the spring of 1964, an eruption first appeared on the buttocks and soon lesions

"Here is a paradox:..."

HERE IS A paradox: a 41-year-old woman has a skin eruption of three years' duration which is best described as clinically resembling acute parapsoriasis (pityriasis lichenoides et varioliformis acuta, Mucha-Habermann's disease). Lesions are continually developing and regressing at random. The patient's health is good, results of physical examination and laboratory studies are normal. Yet, repeated biopsies of her skin lesions (an average of four biopsies a year since coming under my observation in August 1964) consistently reveal an alarming infiltrate of large pleomorphic hyperchromatic cells which expert histopathologists and hematologists have variously classified as highest grade malignant lymphoma (a majority opinion), malignant reticulosis, metastatic carcinoma, malignant melanoma, undifferentiated malignant tumor. The details of this case are herewith reported, a number of similar cases noted, and this curious phenomenon discussed.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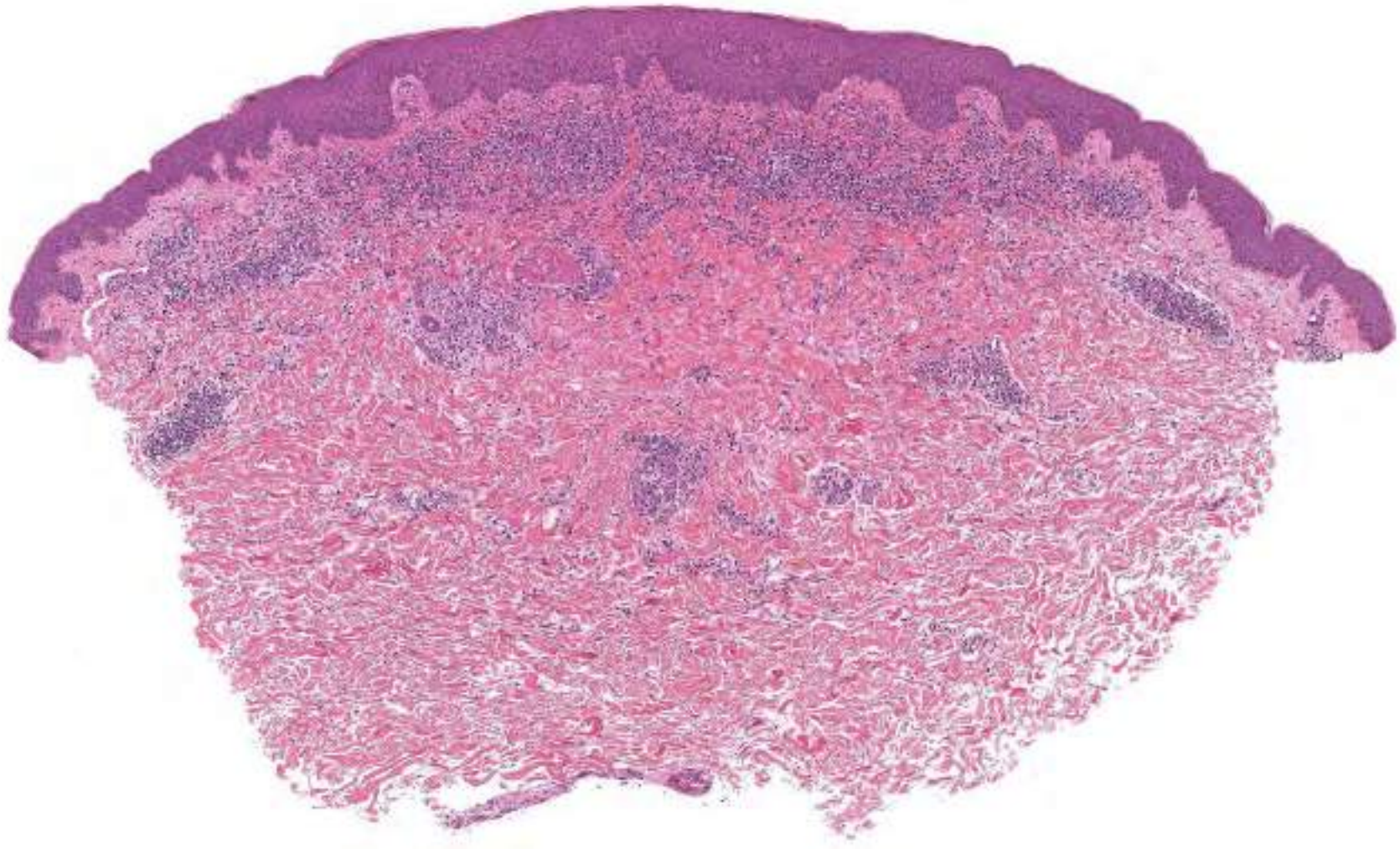
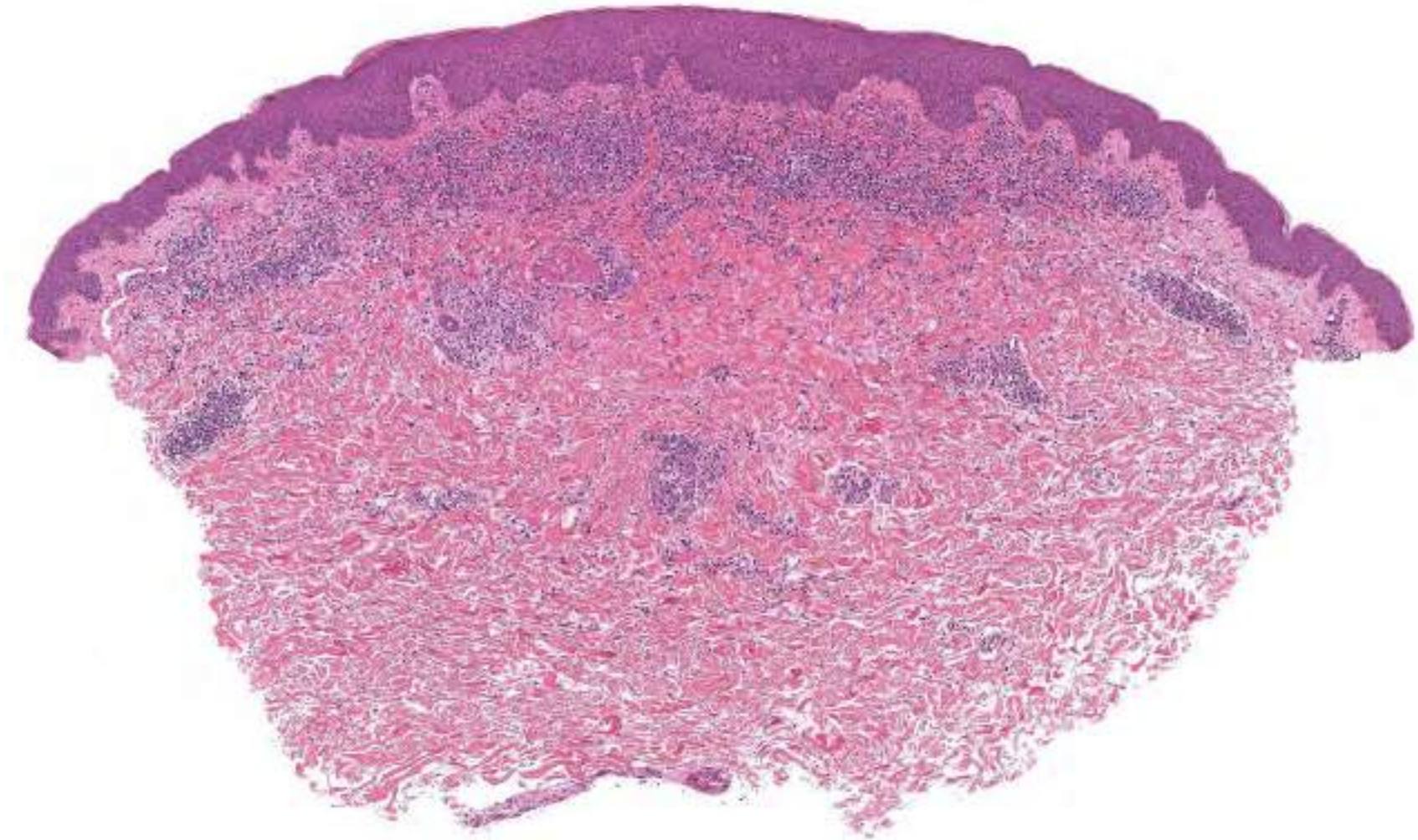
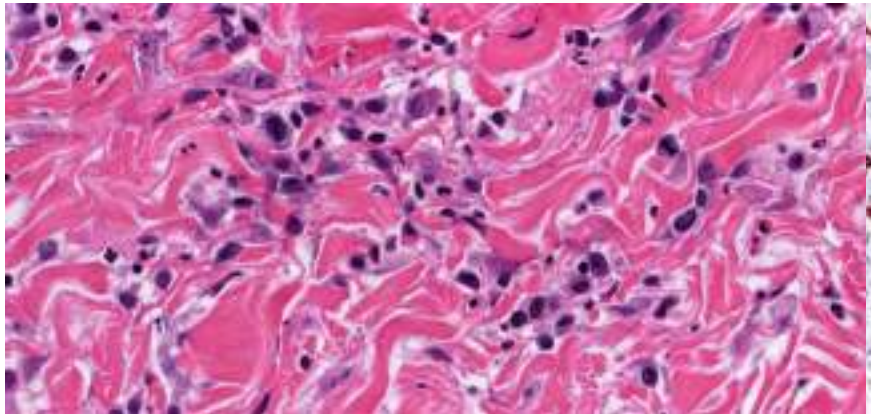
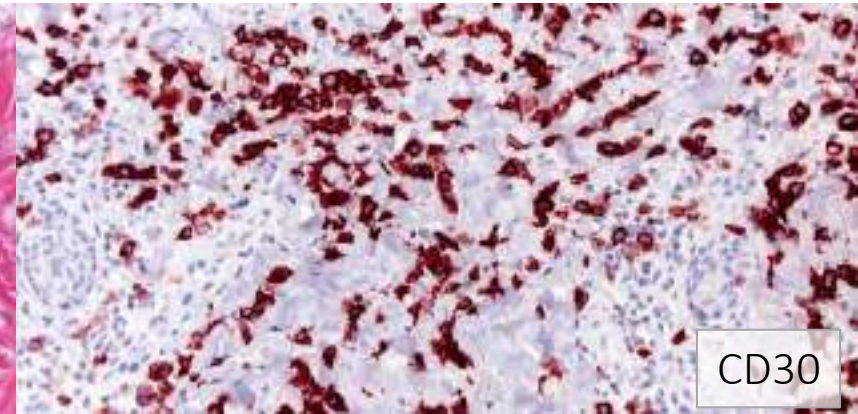


Lymphomatoid papulosis

Recurrent, waxing and waning eruption of papules and small nodules that tend to ulcerate and may resolve with scars. Number of lesions variable from a few to >100. Number of crops variable as well (in some patients continuous presence of lesions, in other only occasional crops). Several types according to clinic-pathological presentation. Benign, but may be associated with other cutaneous lymphomas.



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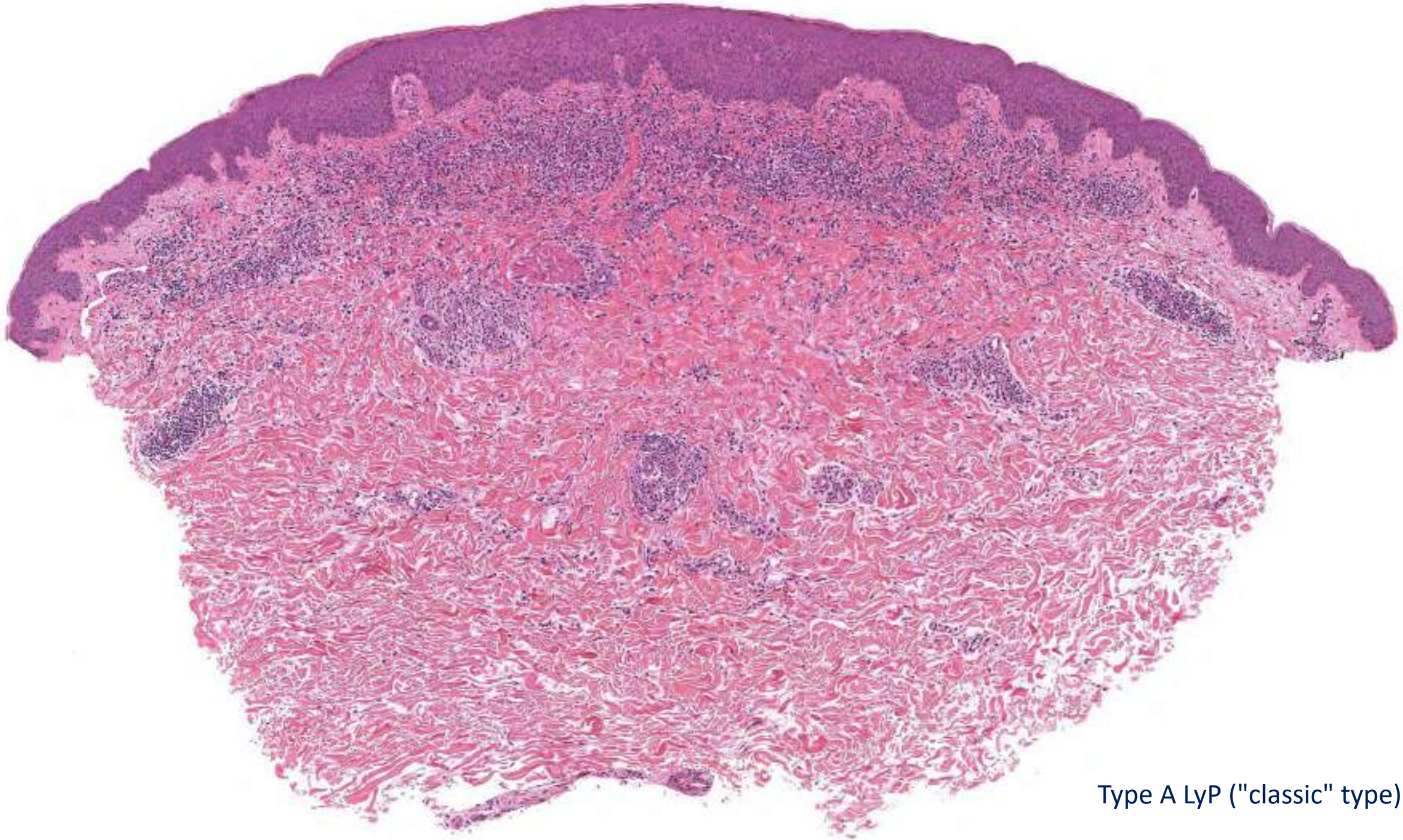
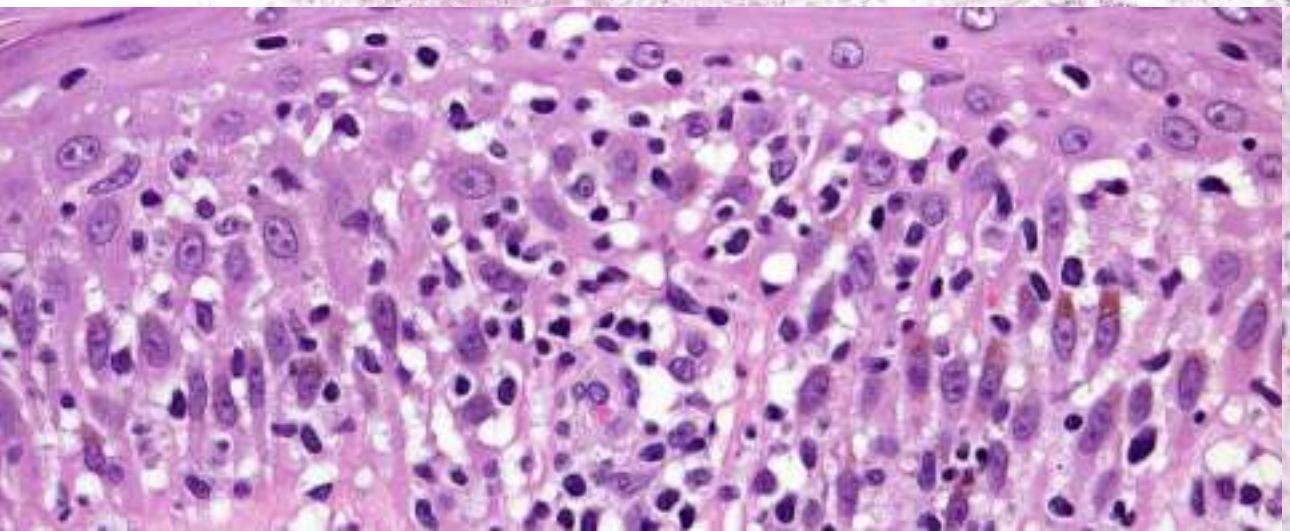
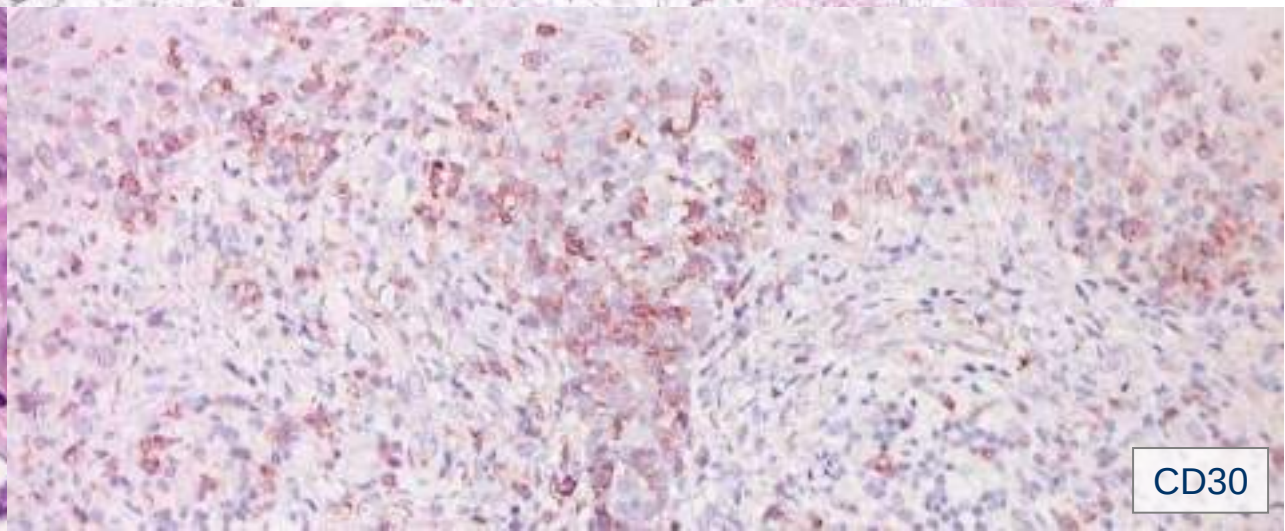


Type A LyP ("classic" type)

Type B LyP (MF-like)





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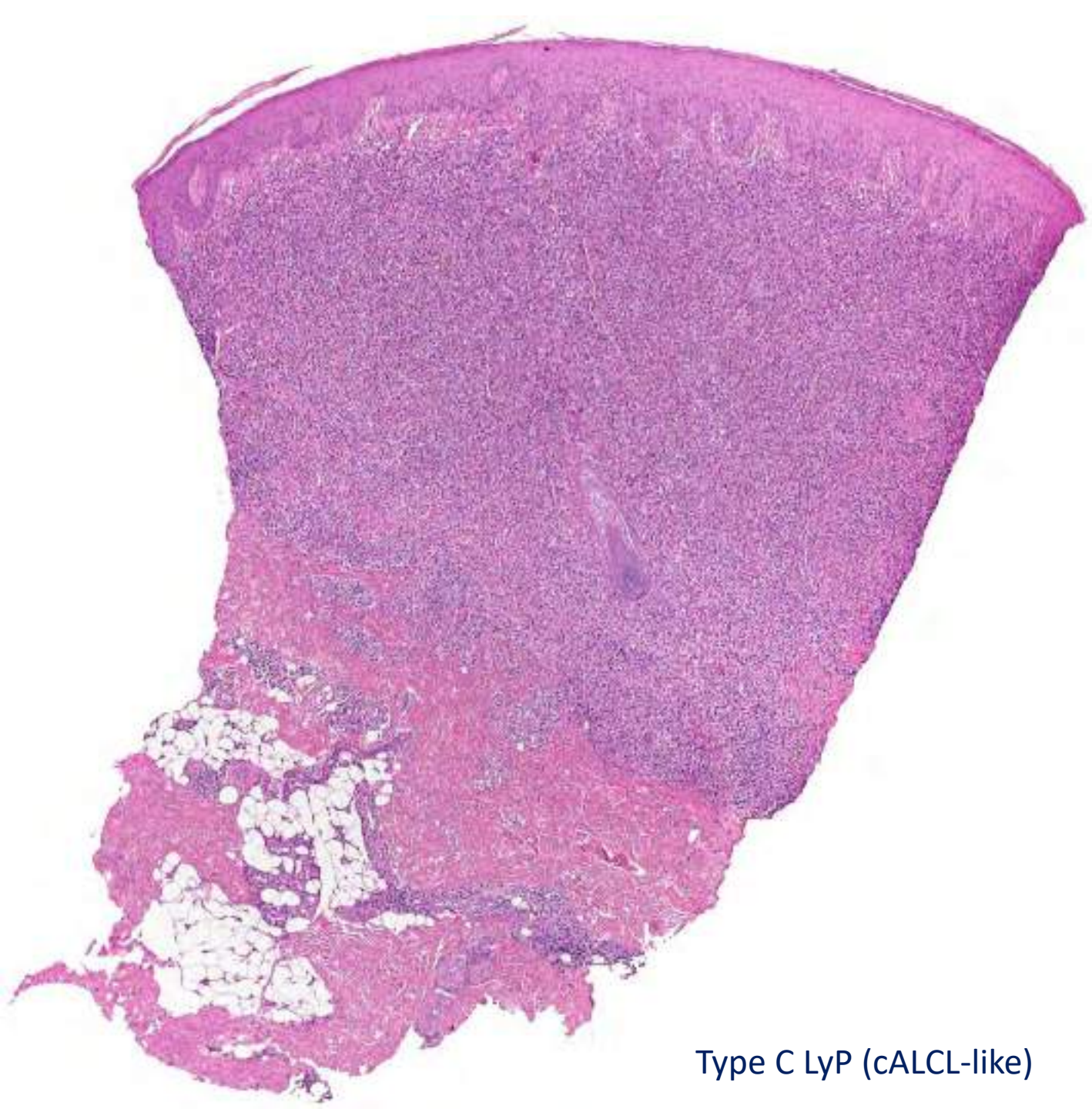
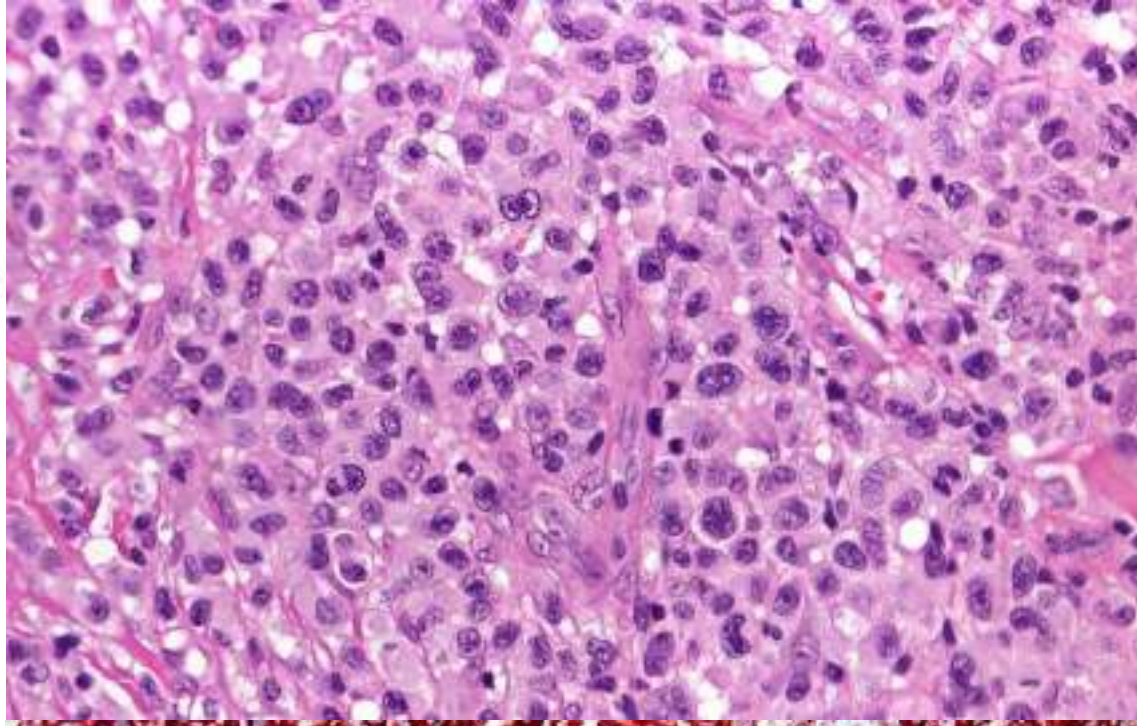
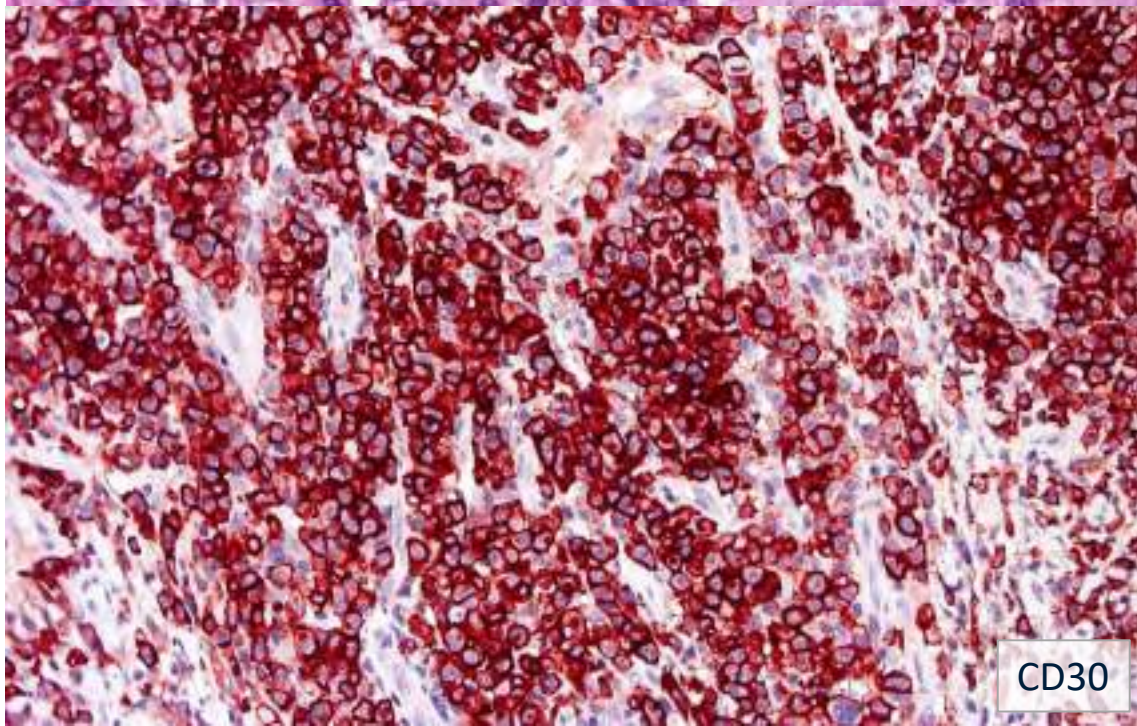


Type C LyP (cALCL-like)





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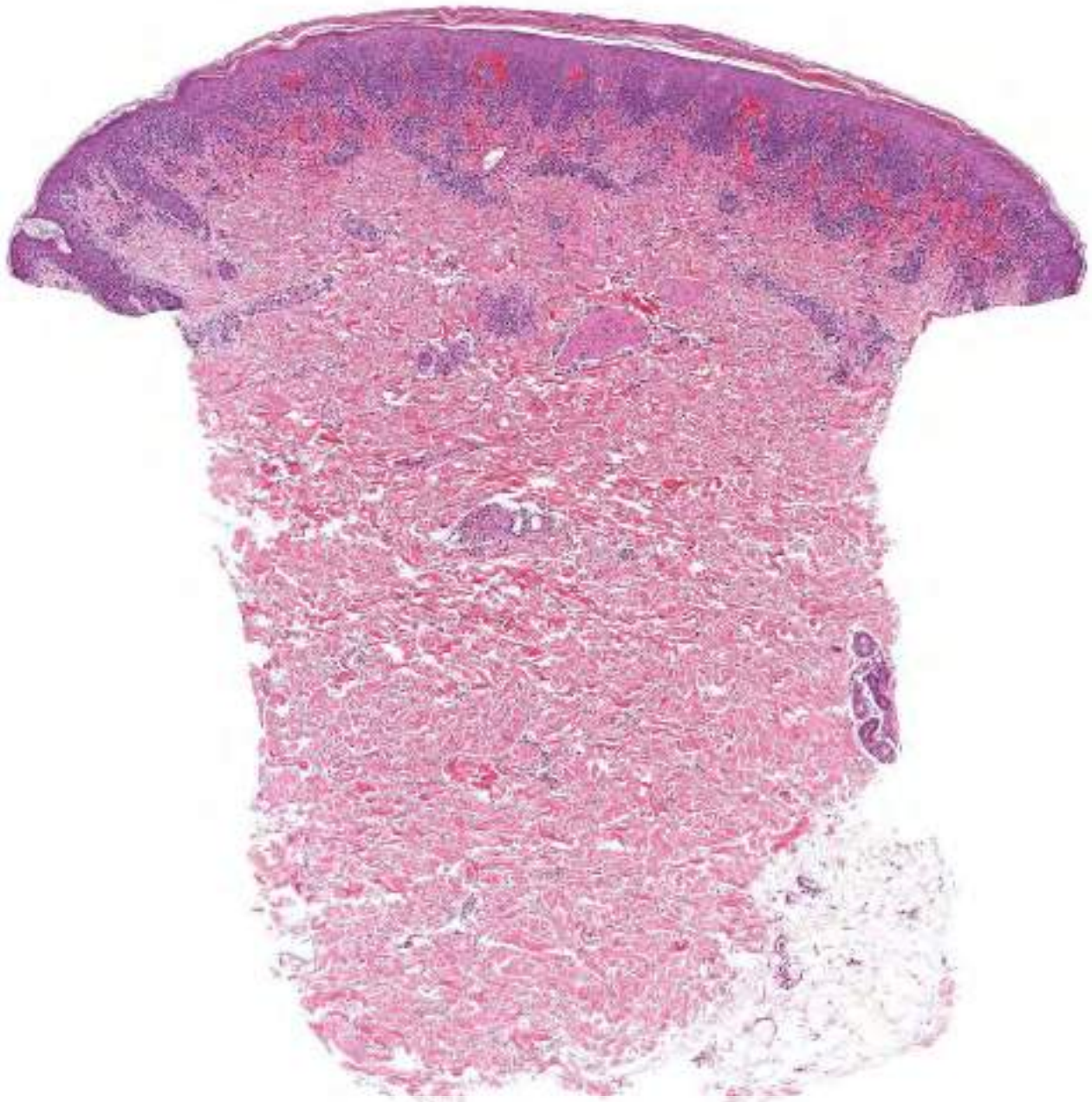

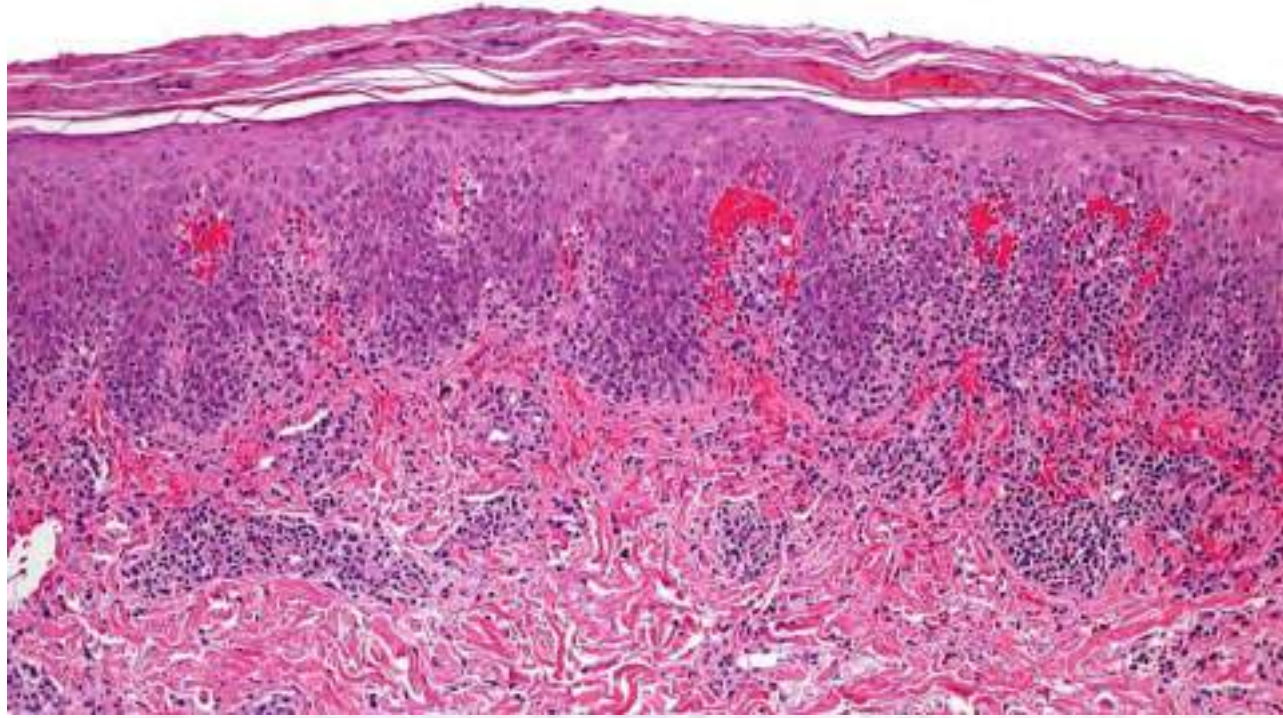

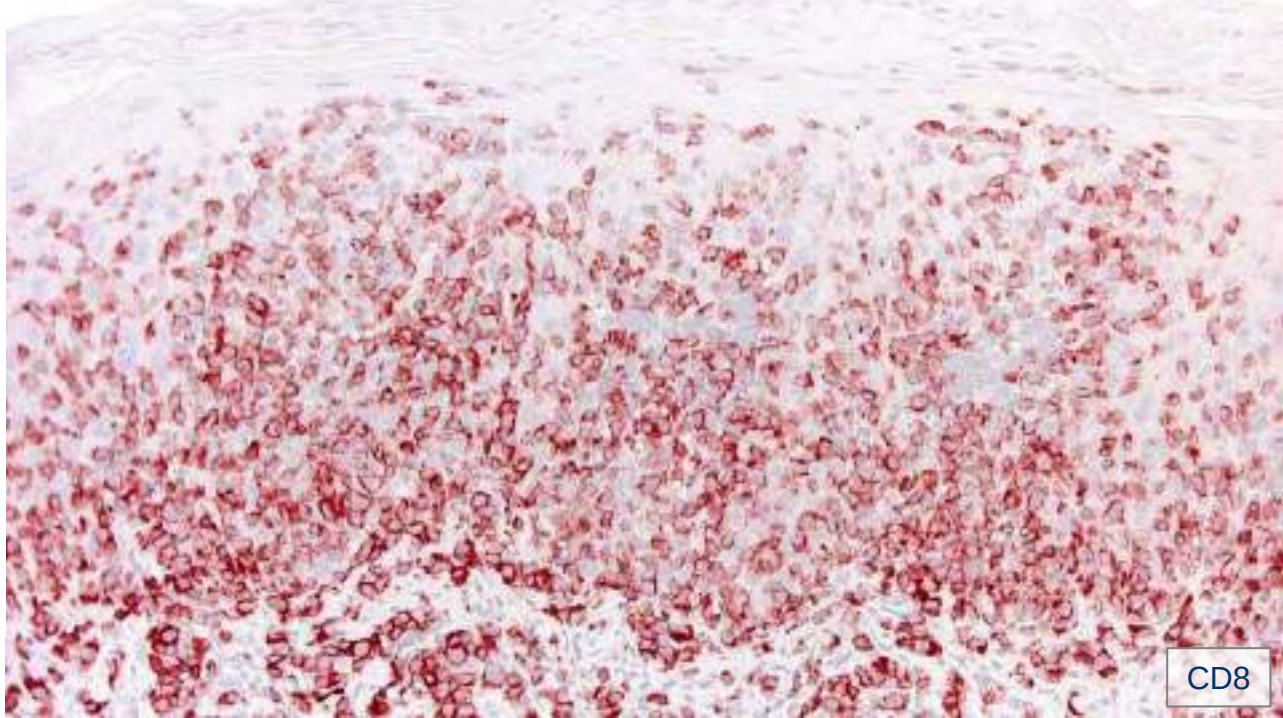

Type D LyP (pagetoid epidermotropism, CD8+)

A Variant of Lymphomatoid Papulosis Simulating Primary Cutaneous Aggressive Epidermotropic CD8+ Cytotoxic T-cell Lymphoma. Description of 9 Cases

Andrea Saggini, MD.† Andrea Gulia, MD.*‡ Zsolt Argenyi, MD.§ Regina Fink-Puches,* Amelia Lissia, MD.‖ Mario Magaña, MD.¶ Luis Requena, MD.# Ingrid Simonitsch, MD.** and Lorenzo Cerroni, MD**

Abstract: Lymphomatoid papulosis (LyP) is a recurrent, self-healing eruption belonging to the spectrum of cutaneous CD30+ lymphoproliferative disorders. Three main histologic subtypes of LyP are recognized: type A (histiocytic), type B (mycosis fungoides—(MF)-like), and type C (anaplastic large cell lymphoma-like). We reviewed 26 biopsies from 9 patients (M:F = 6:3; median age: 29; mean age 27.2; age range 10 to 38) who presented with clinical features typical of LyP but with histopathologic aspects that resembled primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. In all but 1 case atypical lymphoid cells showed expression of CD30, and in 8 of 9 cases a T-cell cytotoxic phenotype could be observed (βF1+, CD3+, CD4−, CD8+). Expression of at least 1 cytotoxic marker (TIA-1, granzyme B) was observed in all cases. Polymerase chain reaction analysis of the T-cell receptor genes revealed a monoclonal rearrangement in 2 of 5 cases tested. Follow-up data available for 8 patients (mean follow-up time: 84 mo; median: 32.5 mo; range: 1 to 303 mo) revealed that none of them developed systemic involvement or signs of other cutaneous lymphomas. This cytotoxic variant of LyP may be histopathologically indistinguishable from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and may be the source of pitfalls in the diagnosis and classification. We propose the term LyP type D for this unusual variant of the disease. Accurate clinicopathologic correlation is required in this setting, with crucial implications regarding prognosis and management of patients.

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Key Words: lymphomatoid papulosis, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, mycosis fungoides, cytotoxic lymphoma, cutaneous T-cell lymphoma

(*Am J Surg Pathol* 2010;34:1168–1175)

Lymphomatoid papulosis (LyP) is defined as a chronic, recurrent, self-healing eruption of papules and small nodules, characterized by a waxing and waning course and by histopathologic features of a cutaneous T-cell lymphoma[1–3]. LyP is currently classified within the spectrum of the primary cutaneous CD30+ lymphoproliferative disorders in both the 2005 WHO-EORTC classification of cutaneous lymphomas and the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues.[21,31] Histopathologically, 3 subtypes are recognized, namely, type A (histiocytic), type B (mycosis fungoides—(MF)-like), and type C (anaplastic large cell lymphoma—(ALCL)-like).[10–12] All 3 types may be seen in 1 and the same patient. Type B LyP, the least common and the most controversial variant, is considered as a histopathologic simulator of MF.[10,13]

We describe 9 patients who presented with typical aspects of LyP clinically but with unusual histopathologic features resembling pagetoid reticulosis, simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. This lymphoma is characterized by an aggressive course with very poor prognosis,[2,13] thus differentiation from LyP is crucial for proper management of the patients.

PATIENTS AND METHODS

In the last few months one of us (LC) received 5 cases in consultation characterized by histopathologic features resembling those of pagetoid reticulosis, but clinical aspects typical of LyP. On the basis of this experience, we reviewed all specimens of LyP type B registered in the database of the Research Unit Dermatopathology, Medical University of Graz and found additional 4 cases with similar clinicopathologic features. Two further similar cases (one sent in consultation and

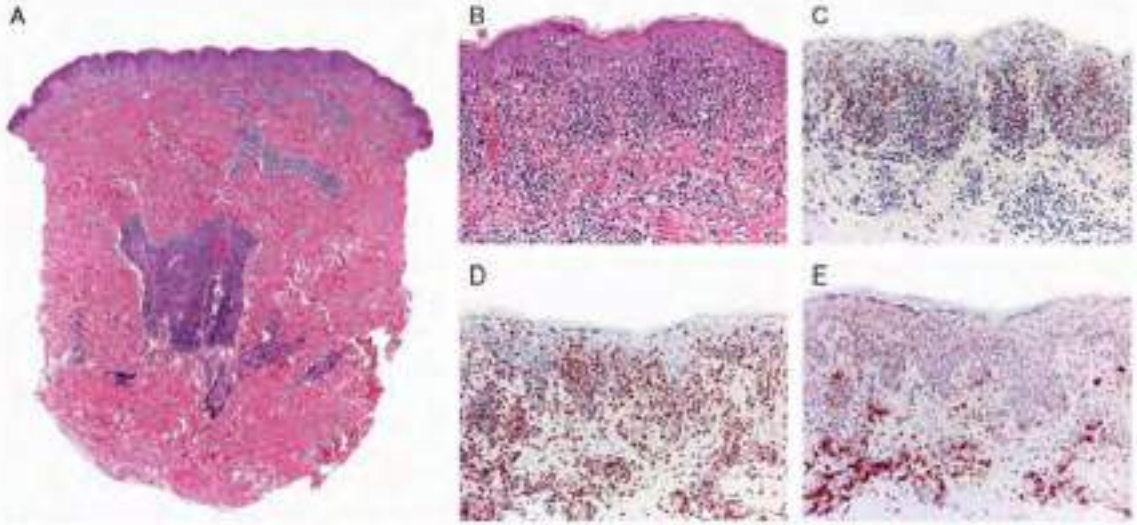
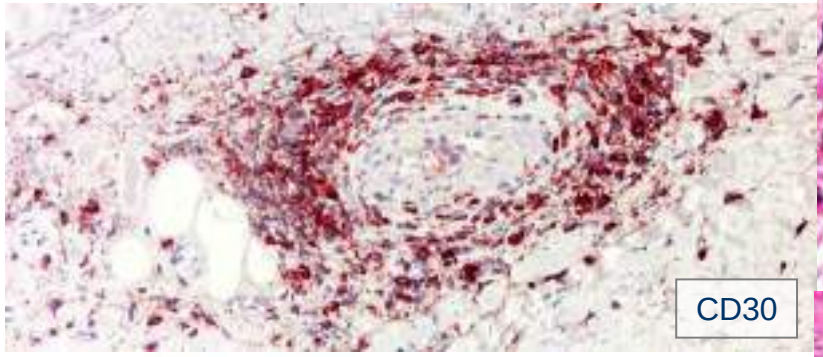
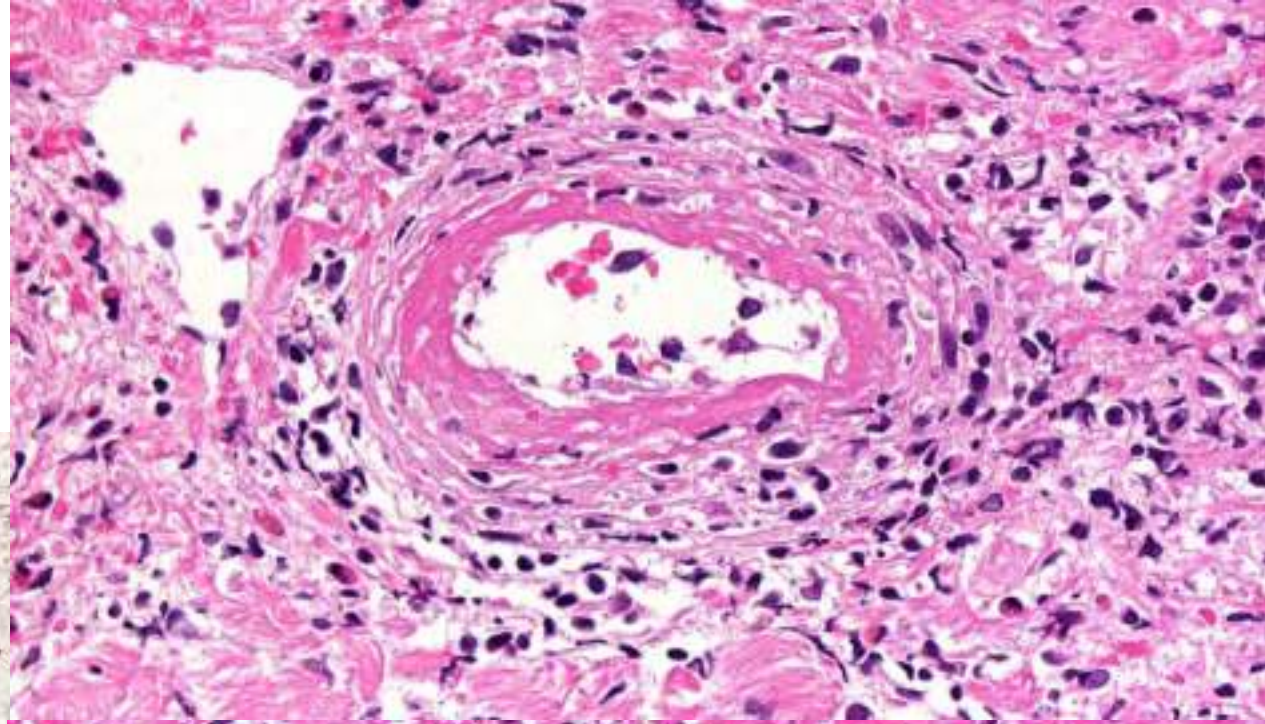


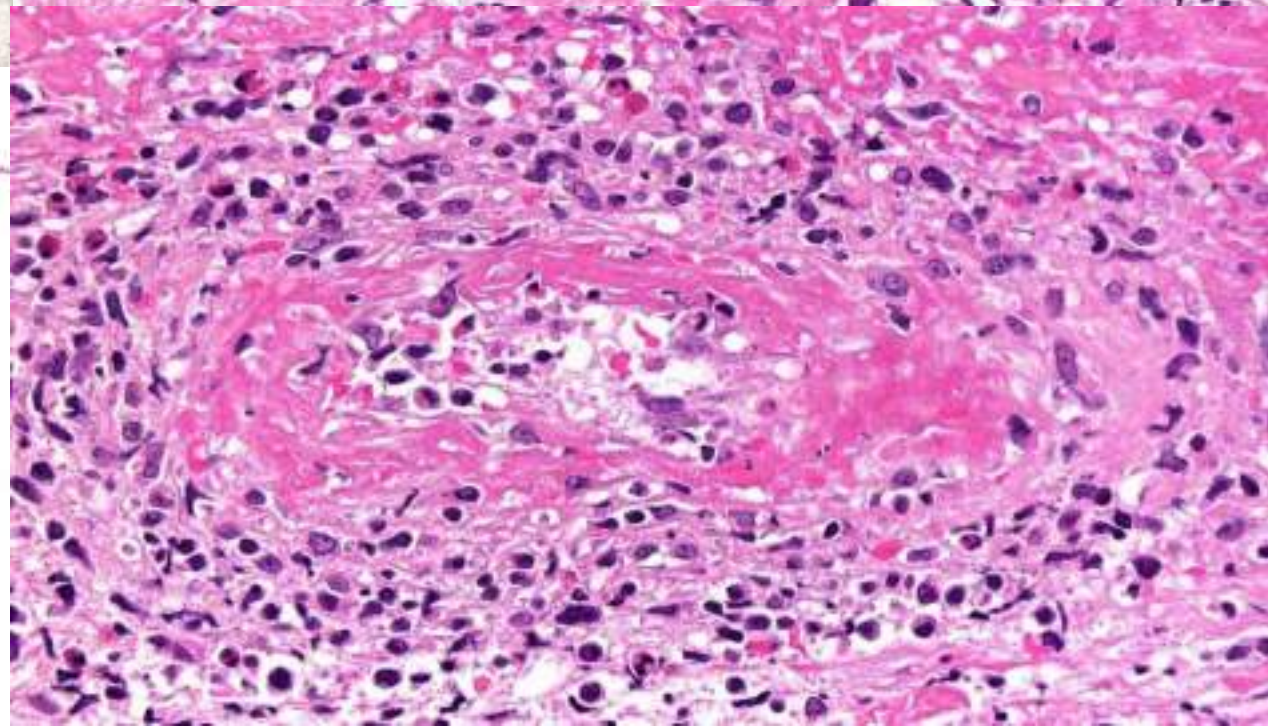
FIGURE 7. Histopathologic features of case 7 showing (A) Dense, wedge-shaped lymphoid infiltrates within the dermis with (B) prominent epidermotropism; (C) positive staining for CD56 and for (D) CD3 but (E) loss of CD5 expression.

"This cytotoxic variant of LyP may be histopathologically indistinguishable from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and may be the source of pitfalls in the diagnosis and classification. We propose the term **LyP type D** for this unusual variant of the disease. Accurate clinicopathologic correlation is required in this setting, with crucial implications regarding prognosis and management of patients."



Type E LyP ("angioinvasive")





Angioinvasive Lymphomatoid Papulosis

A New Variant Simulating Aggressive Lymphomas

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Abstract: Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders. Clinically, LyP is characterized by a variable number of self-healing papulo-nodular lesions, with the typical waxing and waning course. Histologically, 4 types (A, B, C, and D) have been delineated. Angioinvasive growth and large ulcers are rare findings in LyP and simulate aggressive lymphoma. We retrospectively analyzed the clinicopathologic and molecular features of angioinvasive LyP in a series of 16 patients. This new form of LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1 to 4 cm and an angiocentric and angiodestructive infiltrate of small-sized to medium-sized atypical lymphocytes expressing CD30 and frequently CD8. As in other forms of LyP, the lesions underwent spontaneous regression after a few weeks. Recurrences were common, but the prognosis was excellent with no extracutaneous spread or disease-related deaths. Complete remission occurred in 9 of 16 patients (56%). This LyP variant should be distinguished from aggressive forms of angiocentric and angiodestructive and cytotoxic T-cell lymphomas. We propose the term LyP type E for this clinically and histologically unusual variant.

Key Words: lymphoma, skin, CD8, CD30, lymphomatoid papulosis, cytotoxic lymphoma, angiotropic

(*Am J Surg Pathol* 2013;37:1–13)

Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders (CD30$^+$ LPD).[1,2] Histologically, 4 LyP types (A, B, C, and D) have been identified. Type A is characterized by the presence of large pleomorphic or anaplastic CD30$^+$ T cells scattered or in small clusters within the background of eosinophilic and neutrophilic granulocytes, histiocytes, and small lymphocytes. Type B shows epidermotropic infiltrates of small-sized to medium-sized lymphoid cells, with variable extent of CD30 expression. In type C, a nodular dense infiltrate of cohesive sheets of pleomorphic or anaplastic CD30$^+$ cells is present, and it usually contains only a few eosinophilic or neutrophilic granulocytes.[2–7] Recently, type D has been described, which displays an epidermotropic infiltrate of CD8$^+$ and CD30$^+$ small-sized to medium-sized lymphoid cells.[8] Within the same patient, different lesions may show different histologic types, either synchronously or metachronously.[9] The CD30$^+$ lymphoid cells may express CD4, CD8, or CD56, with CD4 immunoreactivity being the most common phenotype.[8,11] Independent of its histologic pattern and the immunophenotype, LyP is clinically characterized by a variable number of self-healing papulo-nodular lesions, with the typical waxing and waning course. The individual lesions undergo spontaneous regression within a few weeks, sometimes accompanied by ulceration on top of the lesions and occasionally leaving behind varioliform scars. Despite the presence of medium-sized to large-sized pleomorphic or anaplastic cells suggesting a highly malignant course, LyP exhibits a favorable prognosis and requires no aggressive treatment.[2,12,13]

We report a series of 16 patients with LyP who presented with a clinically and histologically unusual manifestation simulating highly aggressive angiocentric and angiodestructive T-cell lymphoma. These patients developed recurrent papular lesions that rapidly turned into hemorrhagic necrotic ulcers (eschar like) with a diameter of >1 cm and spontaneous regression, often leaving behind a scar. The typical features were rather large size of ulceration exceeding the size of the preexisting papule/nodule and presentation with only a few lesions at a given time. Histologically, predominantly angiocentric and angiodestructive infiltrates of CD30$^+$ and mostly CD8$^+$ lymphoid cells as well as necrotic areas were the hallmark. Remarkably, the skin lesions resolved spontaneously, and none of the patients manifested progressive disease with extracutaneous involvement or died

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Case 1 was presented by 1 of the authors (W.K.) at the Self Assessment Course of the XXIII annual meeting of the International Society of Dermatopathology (ISDP), 2002, in Siena, Italy.

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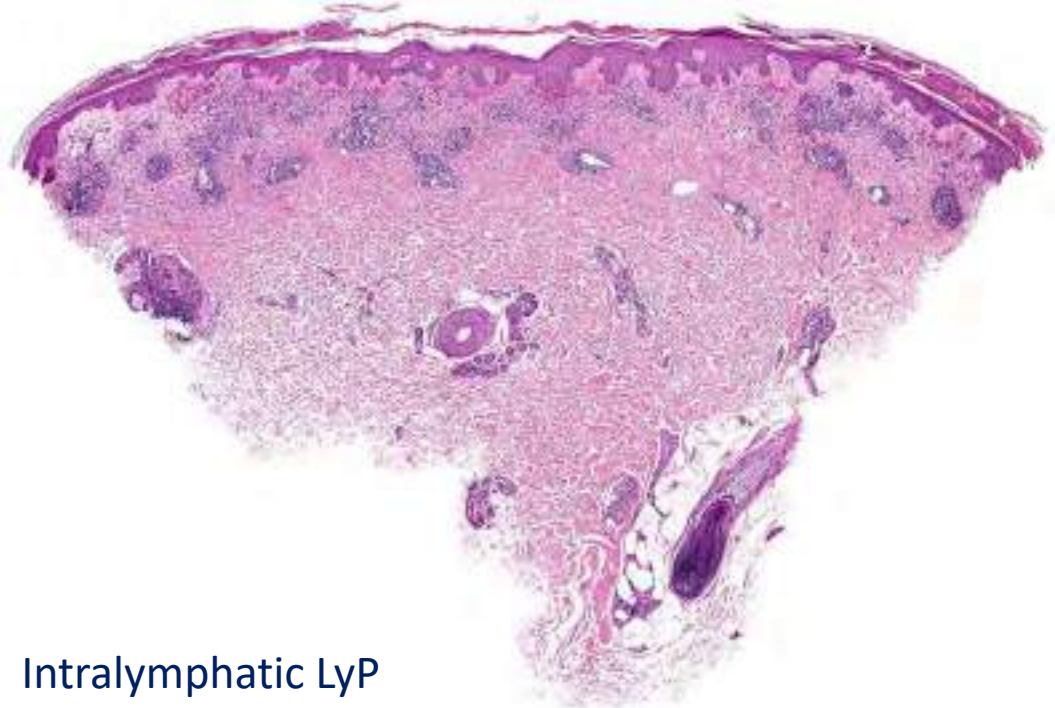
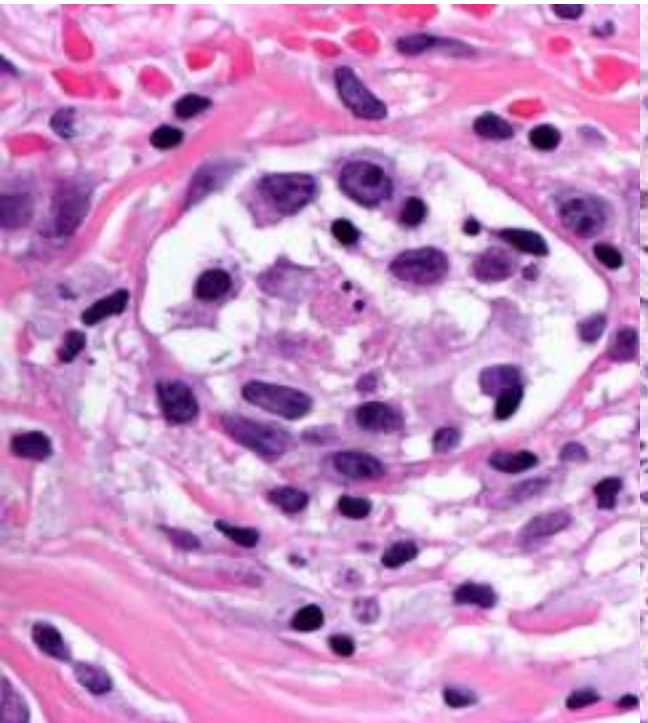
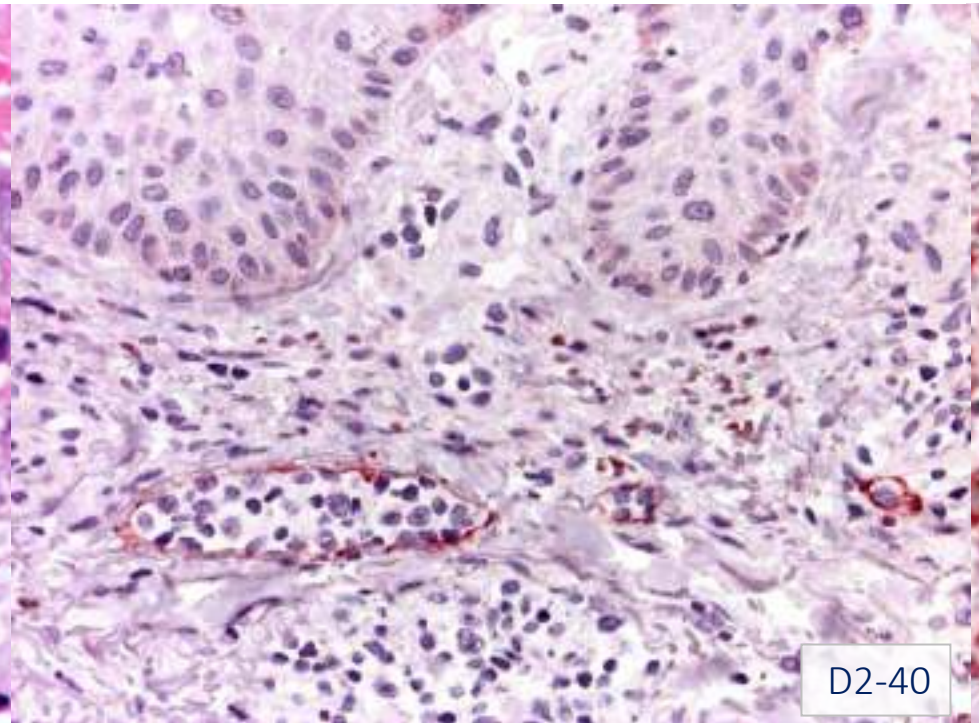
"We retrospectively analyzed the clinicopathologic and molecular features of angioinvasive LyP in a series of 16 patients. This new form of LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1 to 4 cm and an angiocentric and angiodestructive infiltrate of small-sized to medium-sized atypical lymphocytes expressing CD30 and frequently CD8. (…) We propose the term **LyP type E** for this clinically and histologically unusual variant."



Intralymphatic LyP





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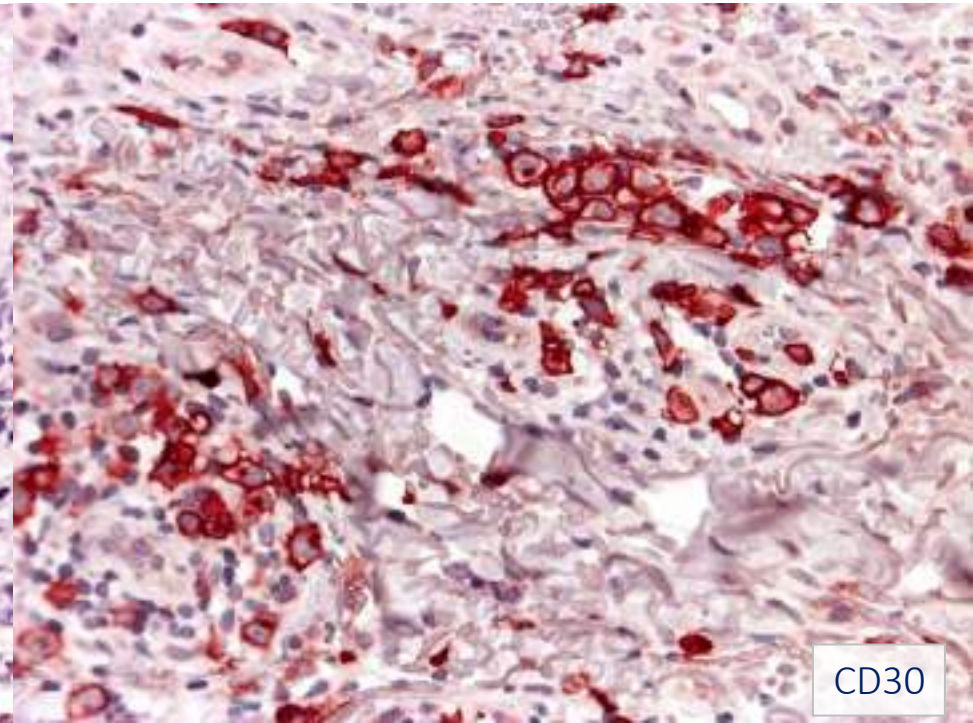
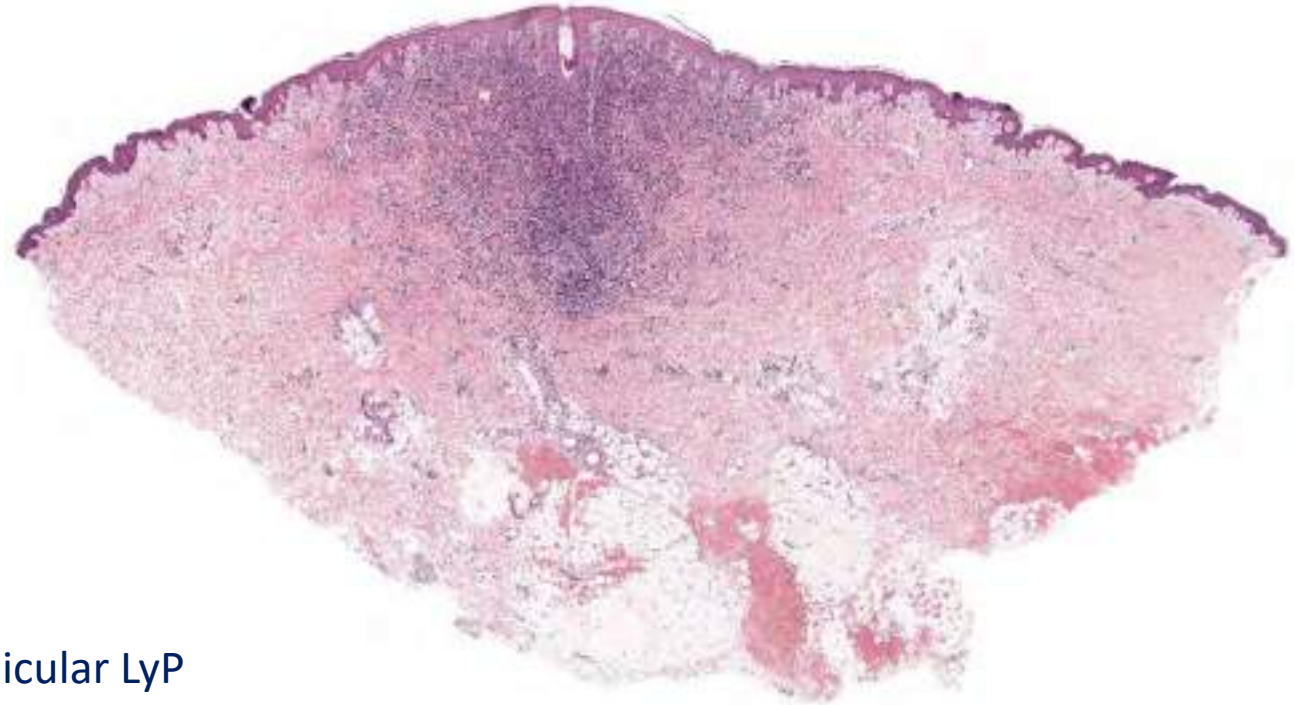
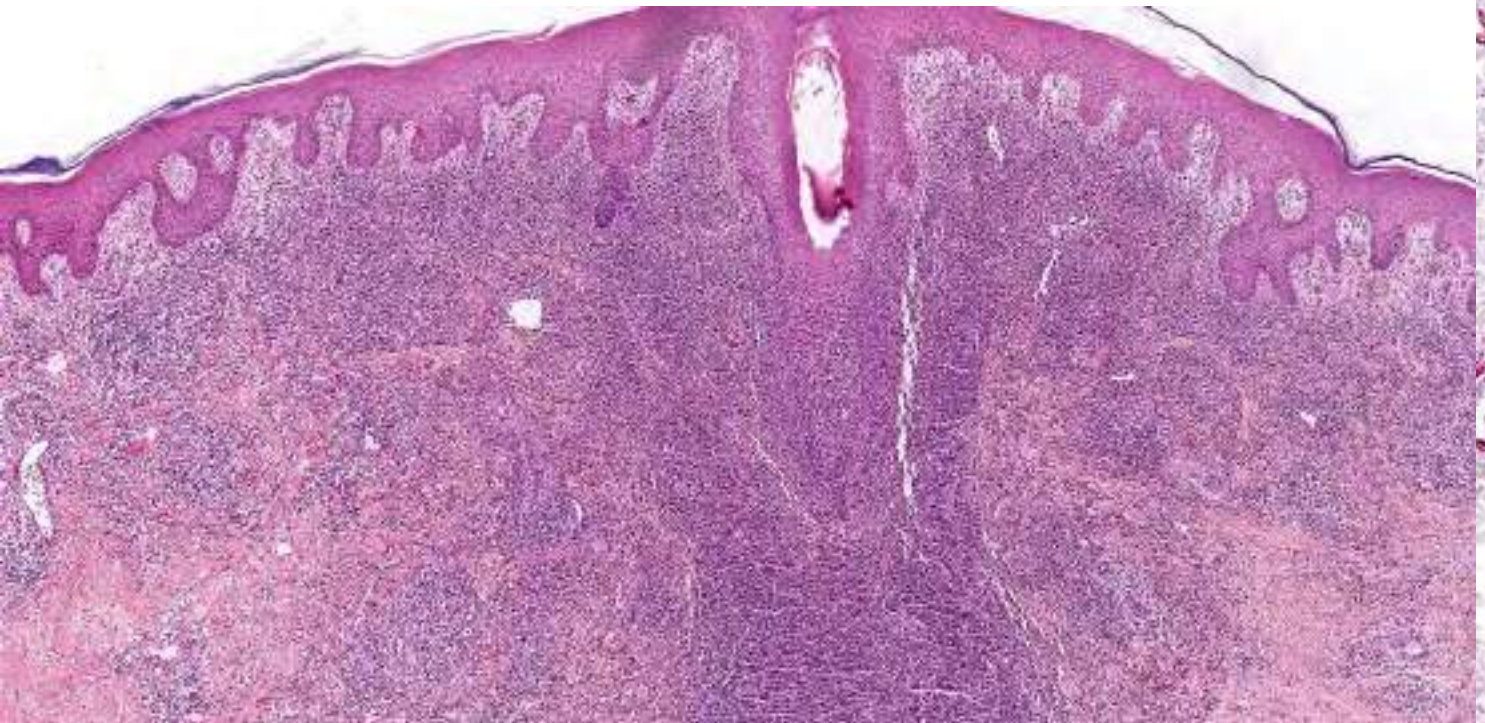
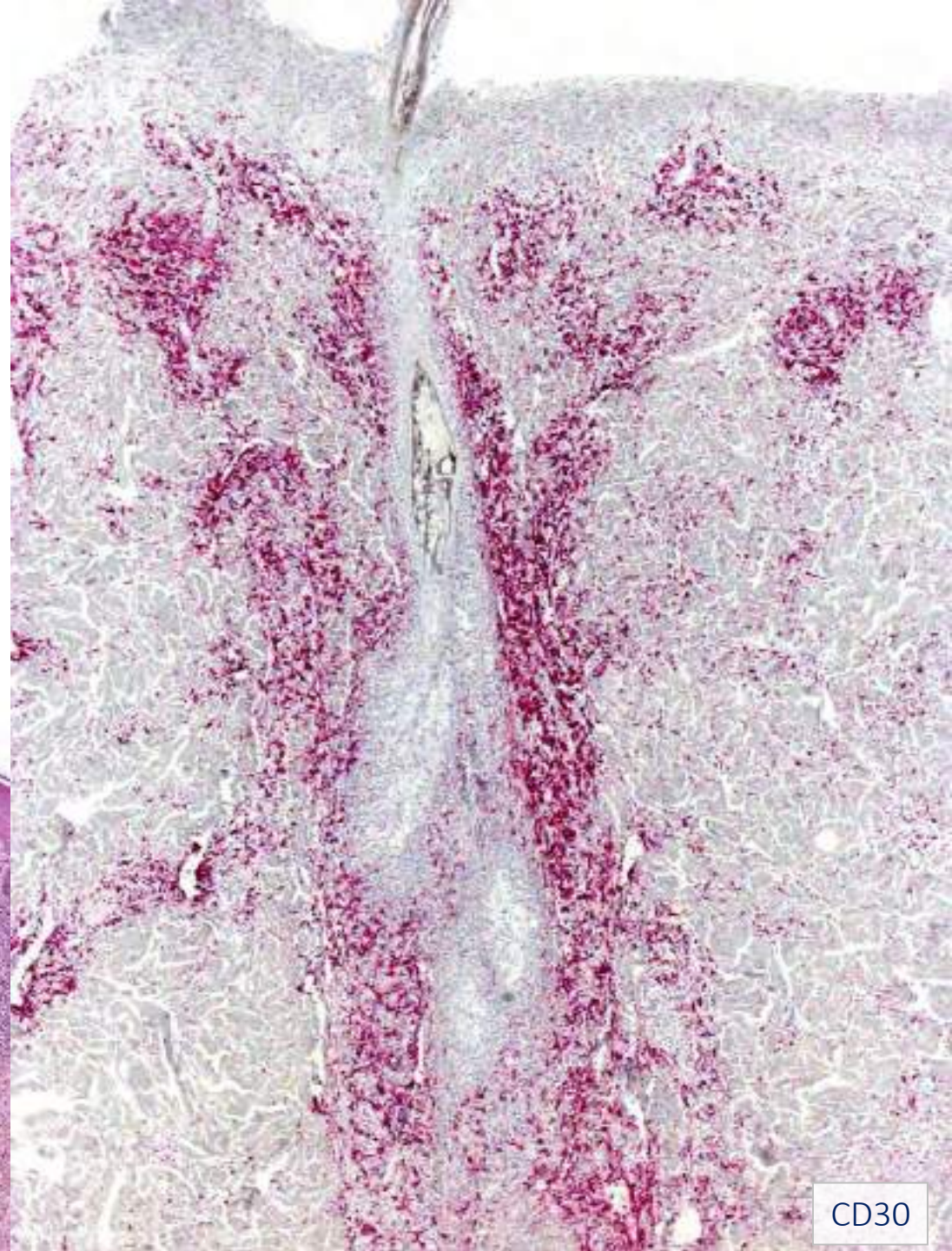


CD30



Follicular LyP





CD30

Follicular lymphomatoid papulosis revisited: A study of 11 cases, with new histopathological findings

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Background: Follicular lymphomatoid papulosis (LyP) describes a variant of LyP with perifollicular infiltrates and some degree of folliculotropism of $CD30^+$ atypical lymphocytes. So far, only a few cases of follicular LyP have been described.

Objective: Our goal was to study the clinicopathologic features of follicular LyP in a series of 11 cases (9 male, 2 female; age range 7–78 years; mean age 50 years).

Methods: In all, 113 cases of LyP were reviewed to select cases showing follicular involvement. Histology was correlated with the clinical data to exclude cases of $CD30^+$ anaplastic large-cell lymphoma or folliculotropic mycosis fungoides.

Results: Six cases were classified as type C and 3 as type A, whereas the remaining case manifested epidermotropism of small lymphocytes in a background of atypical type A lesion (overlapping type A/B). Perifollicular infiltrates of $CD30^+$ atypical lymphoid cells were seen in all 11 cases, with infiltration of the follicular epithelium in 8 cases. Hyperplasia of the follicular epithelium was observed in 4 cases, ruptured hair follicles in 3 cases, and follicular mucinosis in 2 cases. In addition to hair follicle infiltration, atypical cells were recognized within sebaceous glands in 2 lesions. New findings were presence of numerous intrafollicular neutrophils in 2 patients, who clinically had pustules in addition to papules. Other histopathological features encountered included perieccrine infiltration (n = 5), focal subcutaneous involvement (n = 4), granulomatous inflammation (n = 3), epidermal hyperplasia (n = 2), and 1 each of infiltration of muscle bundles, numerous eosinophils in the infiltrate, and angiocentricity.

Limitations: This was a retrospective study.

Conclusions: Follicular LyP is a variant of LyP with involvement of hair follicles, mostly in the form of perifollicular infiltrate with variable degree of folliculotropism. Other changes including hyperplasia of the follicular epithelium, rupture of hair follicle, and follicular mucinosis are less common. Rarely, intrafollicular pustules can be seen in the follicular epithelium, such lesions manifest clinically as pustules. (J Am Acad Dermatol 2013;68:809-16.)

Key words: CD30; follicular mucinosis; lymphoma; lymphomatoid papulosis; skin.

Several clinicopathological variants of lymphomatoid papulosis (LyP) have been delineated, sometimes occurring in the same individual. The commonest histopathological variants are LyP type A and C, which are characterized by wedge-shaped or nodular infiltrates of large pleomorphic or anaplastic $CD30^+$ lymphoid cells arranged as scattered atypical cells in the background of eosinophils and neutrophils (type A) or in cohesive sheets/nodules with more than 50% of atypical cells (type C) imitating $CD30^+$ anaplastic large-cell lymphoma.[1] Less common forms are LyP type B and the recently described type D, both showing an epidermotropic infiltrate of atypical lymphocytes with

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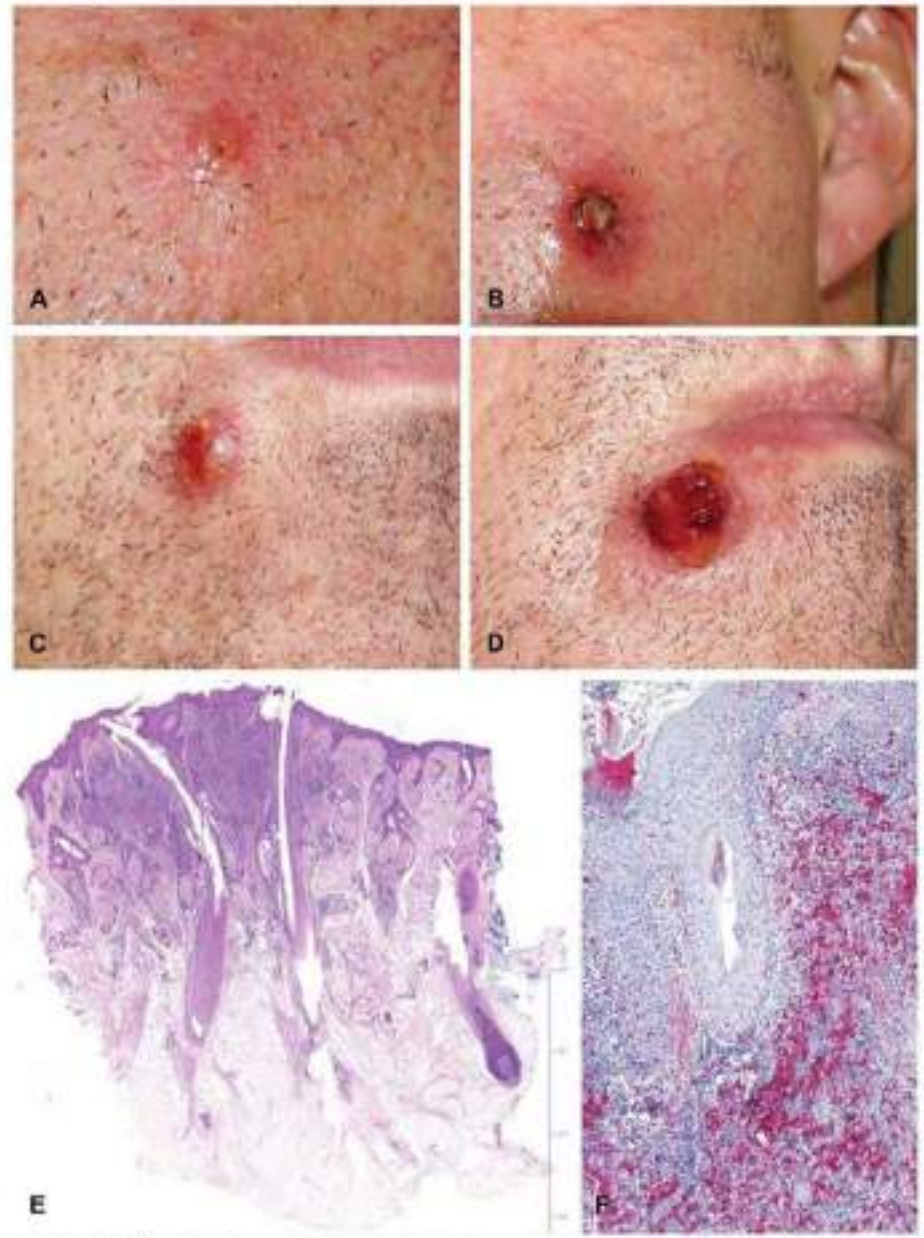
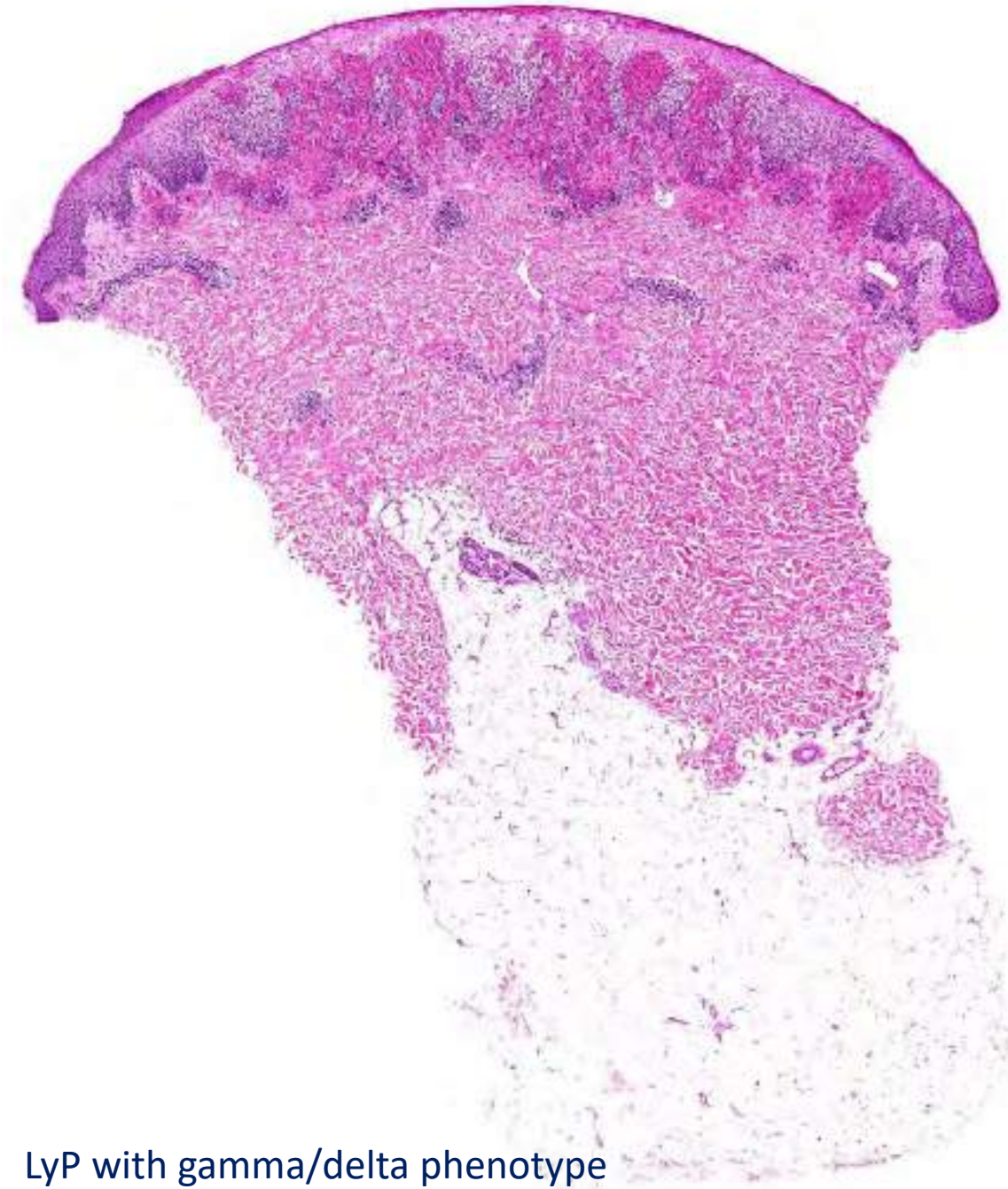
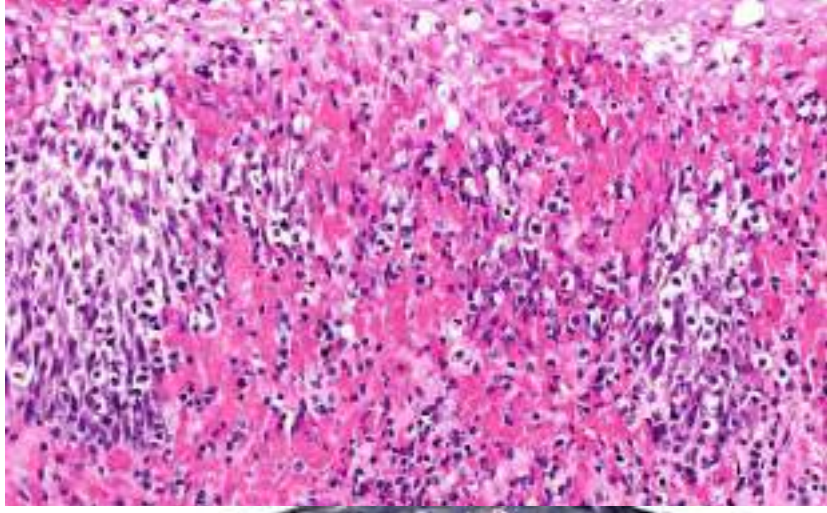
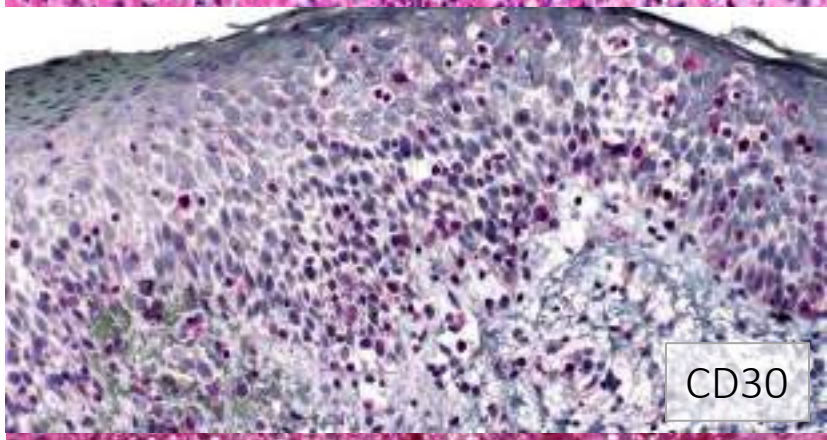
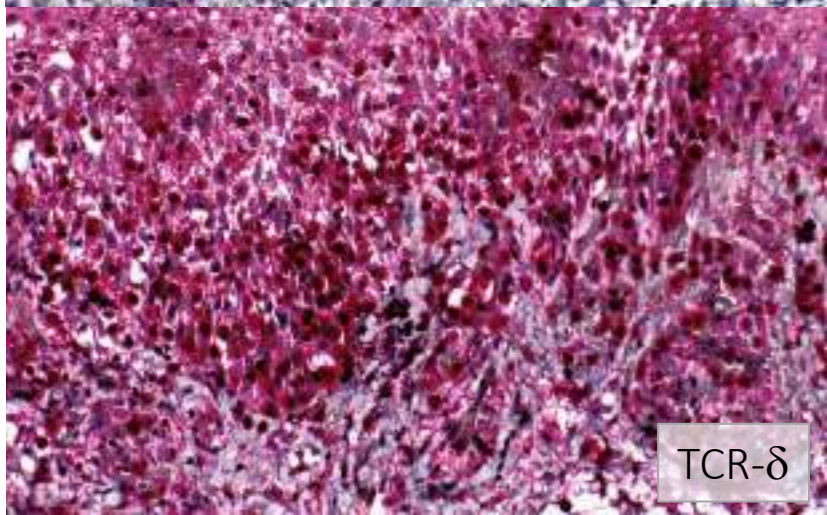


Fig 2. Follicular lymphomatoid papulosis (LyP). Lesions were localized to face (regional LyP) (**A** to **D**). Pustules are present (**A** and **C**). Histopathologically, there is perifollicular infiltrate composed of $CD30^+$ large cells along with numerous neutrophils and debris in cornified layer atop infundibulum of hair follicle (**E** and **F**) (case 9).

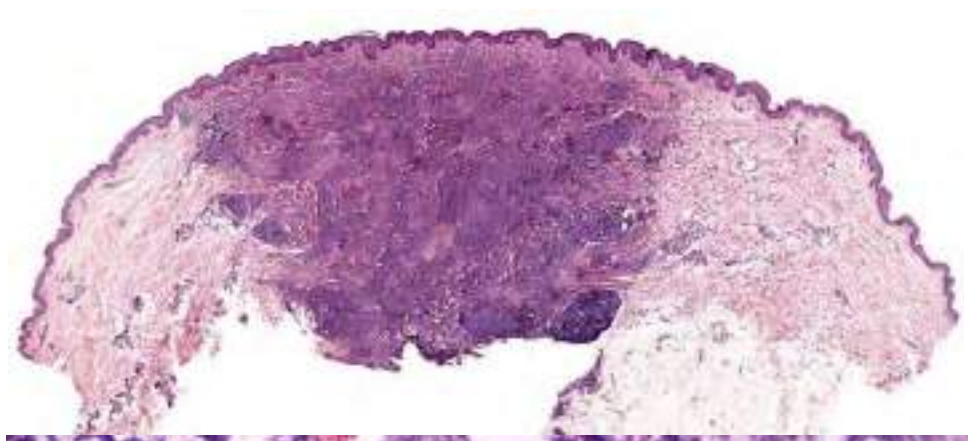


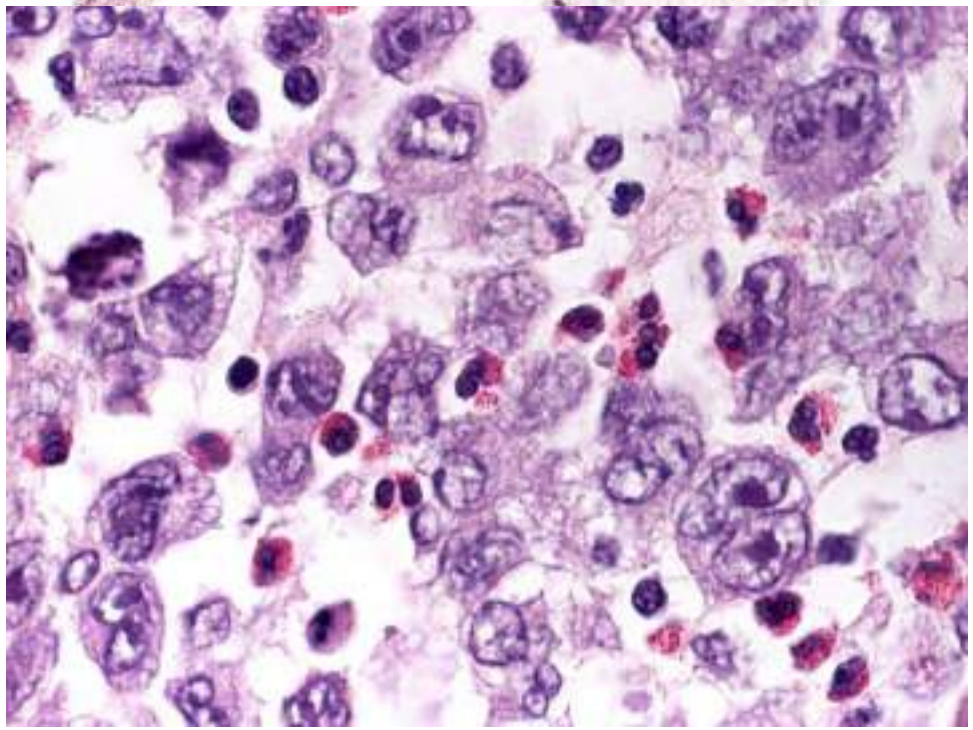






LyP with gamma/delta phenotype





The American Journal of Dermatopathology 16(1): 2–8, 1994

Primary Cutaneous Hodgkin's Disease

Unique Clinical, Morphologic, and Immunophenotypic Findings

Nicholas Sioutos, M.D., Helmut Kerl, M.D., Sharon B. Murphy, M.D., and Marshall E. Kadin, M.D.

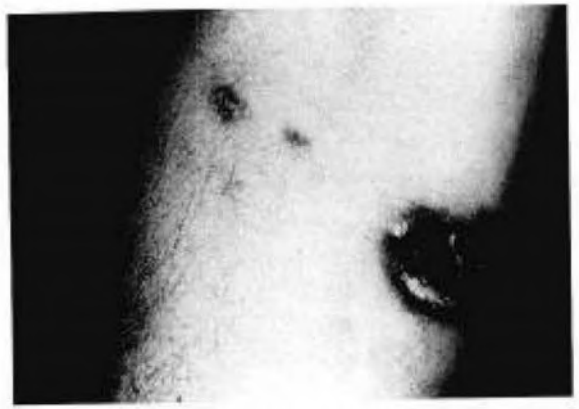
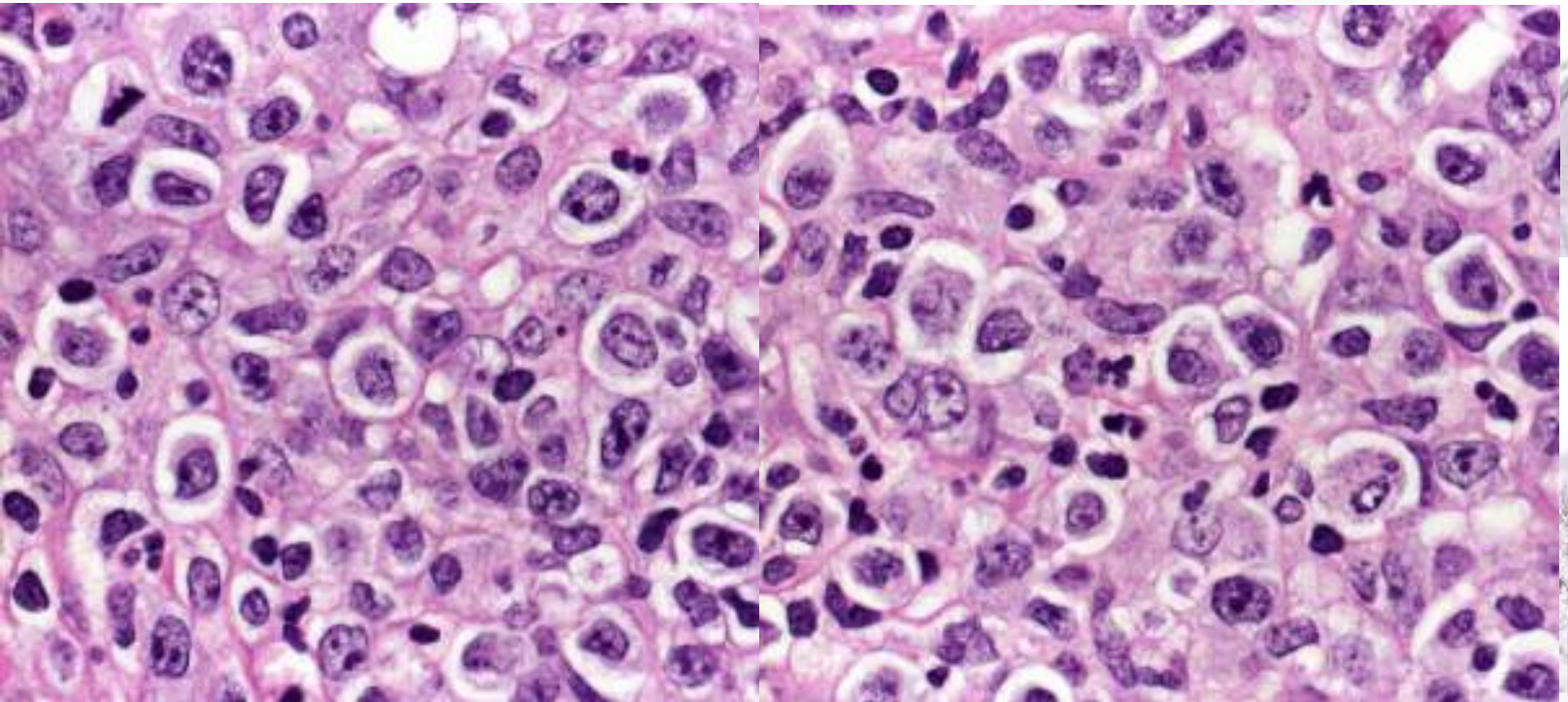


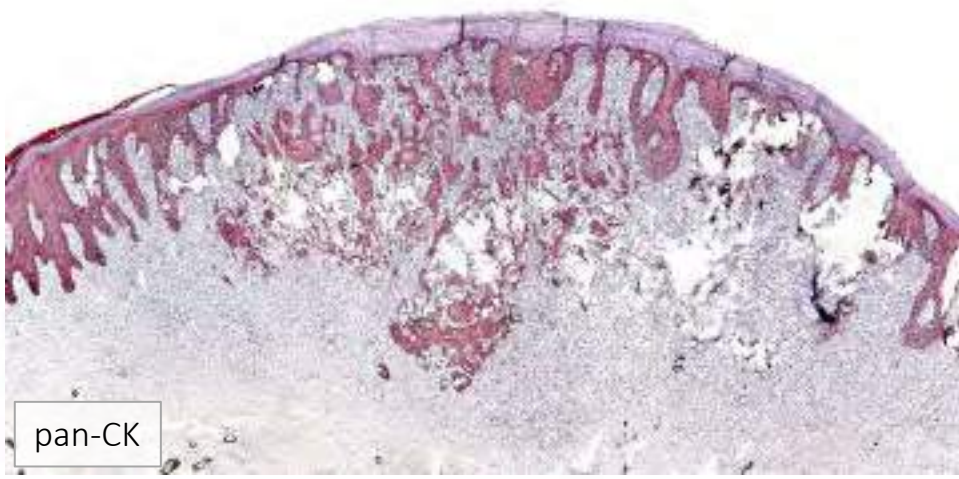
FIG. 1. Case 2: large tumor nodule and nearby papules on the right forearm.

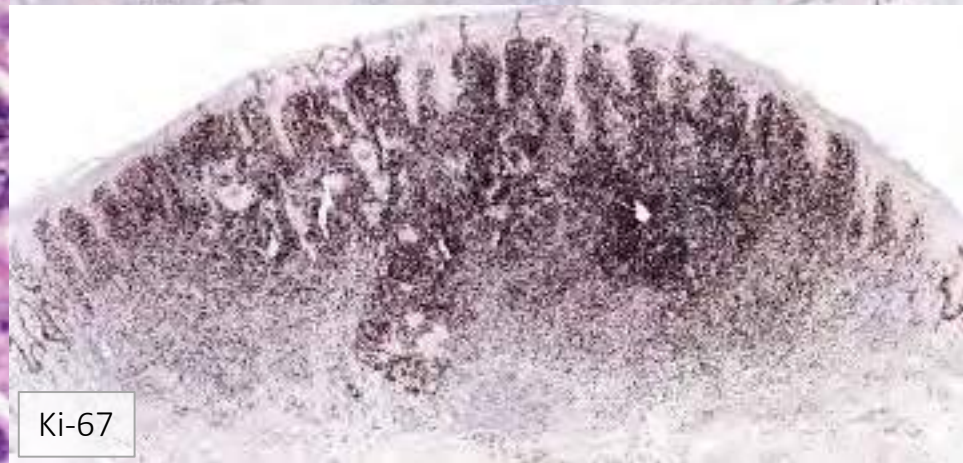
Hodgkin-lymphoma-like LyP

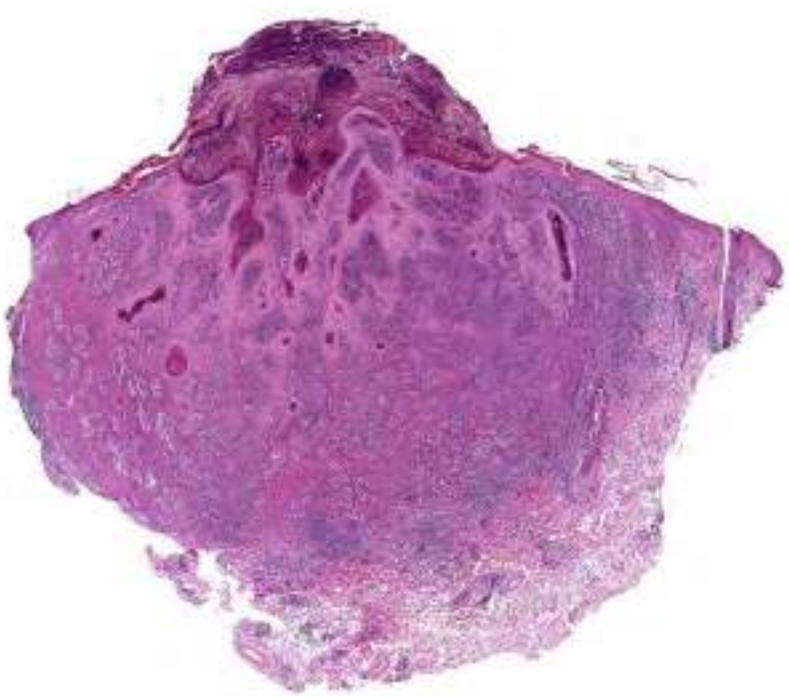
The patient subsequently developed several new papules and nodules on the same arm over a period of >20 years, always with similar histopathologic features and without systemic involvement ("regional" lymphomatoid papulosis).

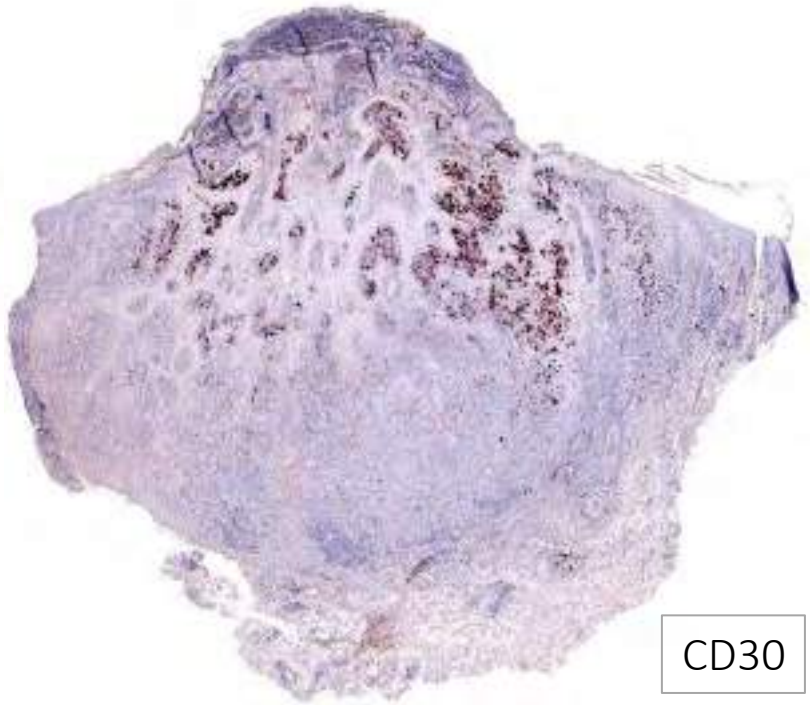
LyP with pseudoepitheliomatous hyperplasia

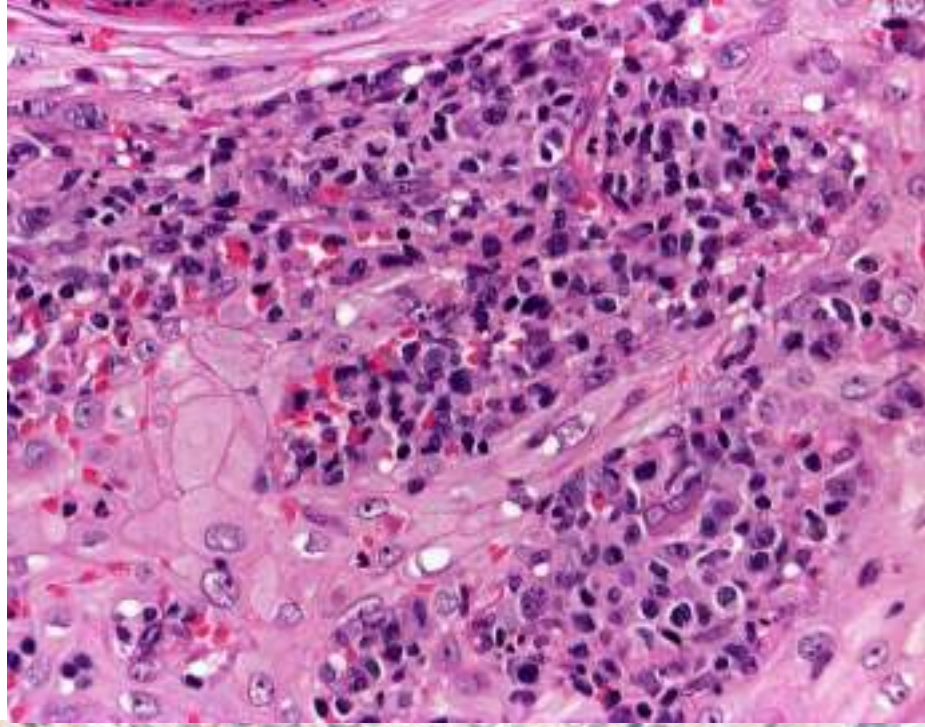












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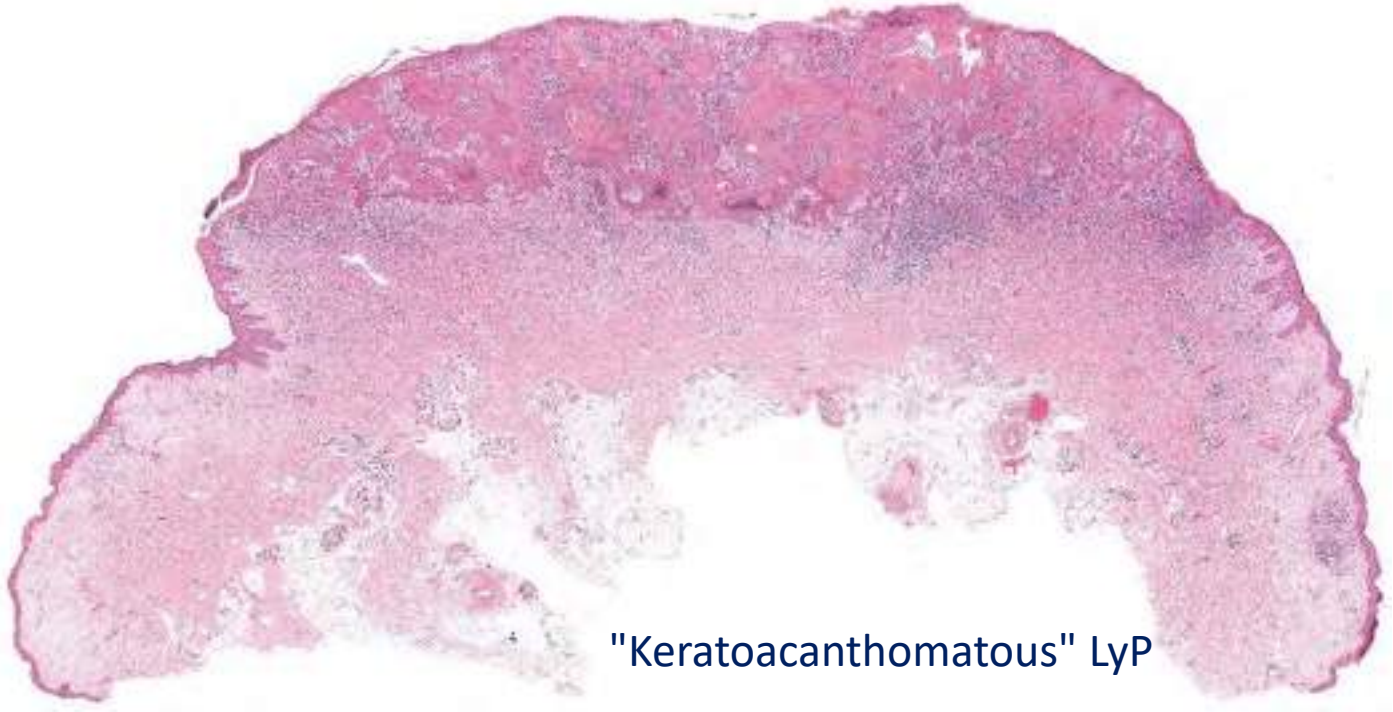
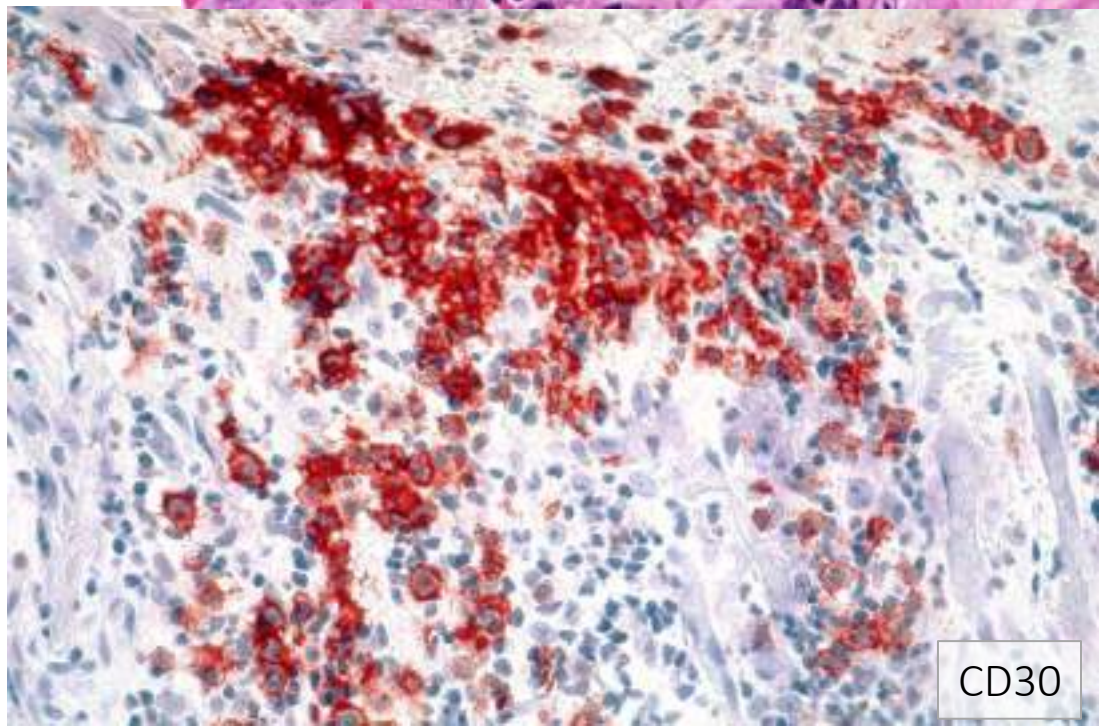


"Keratoacanthomatous" LyP



CD30

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Lymphomatoid papulosis with pseudocarcinomatous hyperplasia in a 7-year-old girl: a case report

Jingshu Xiong, Yiping Ma, Hao Chen, Xiulian Xu and Jianfang Sun

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Lymphomatoid papulosis (LyP) belongs to the group of cutaneous CD30+ lymphoproliferative disorders. Pseudocarcinomatous hyperplasia has rarely been reported in patients with LyP. In this report, we describe a case of LyP presenting as pseudocarcinomatous hyperplasia. The patient was a 7-year-old girl who presented with a recurrent papulonodular eruption on her face and trunk for 2 months. Histopathologic examination revealed an irregular growth of hyperkeratotic epidermis into the whole dermal layer with marked nests of squamous cells in the background of diffuse atypical lymphoid cells, eosinophils and neutrophils. The large atypical cells were positive for CD30 and CD5, but negative for CD4, CD7, CD8, CD20 and CD56. A TCR-γ clone was identified by polymerase chain reaction (PCR). The correct diagnosis in cases of LyP with overlying pseudocarcinomatous epithelial hyperplasia can be very difficult both clinically and histopathologically. Clinical and histopathologic characteristics should be integrated to avoid an erroneous diagnosis of squamous cell carcinoma or keratoacanthoma.

Keywords: cutaneous CD30+ lymphoproliferative disorders, keratoacanthoma, lymphoma papulosis, pseudocarcinomatous hyperplasia, squamous cell carcinoma

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Lymphomatoid papulosis (LyP) belongs to the group of cutaneous CD30+ lymphoproliferative disorders that includes primary cutaneous anaplastic large cell lymphoma and borderline CD30+ lesions. Pseudocarcinomatous hyperplasia has rarely been reported in patients with LyP. Rendering the correct diagnosis in cases of LyP with overlying pseudocarcinomatous epithelial hyperplasia can be very difficult both clinically and histopathologically. In particular, the epithelium in such cases can resemble squamous cell carcinoma or keratoacanthoma and, in some cases, the atypical lymphocytes are sparse or obscured by a dense infiltrate of eosinophils and neutrophils. We describe a case of LyP with pseudocarcinomatous hyperplasia that simulated an epithelial tumor.

Report of a patient

A 7-year-old girl presented with a recurrent papulonodular eruption on her face and trunk

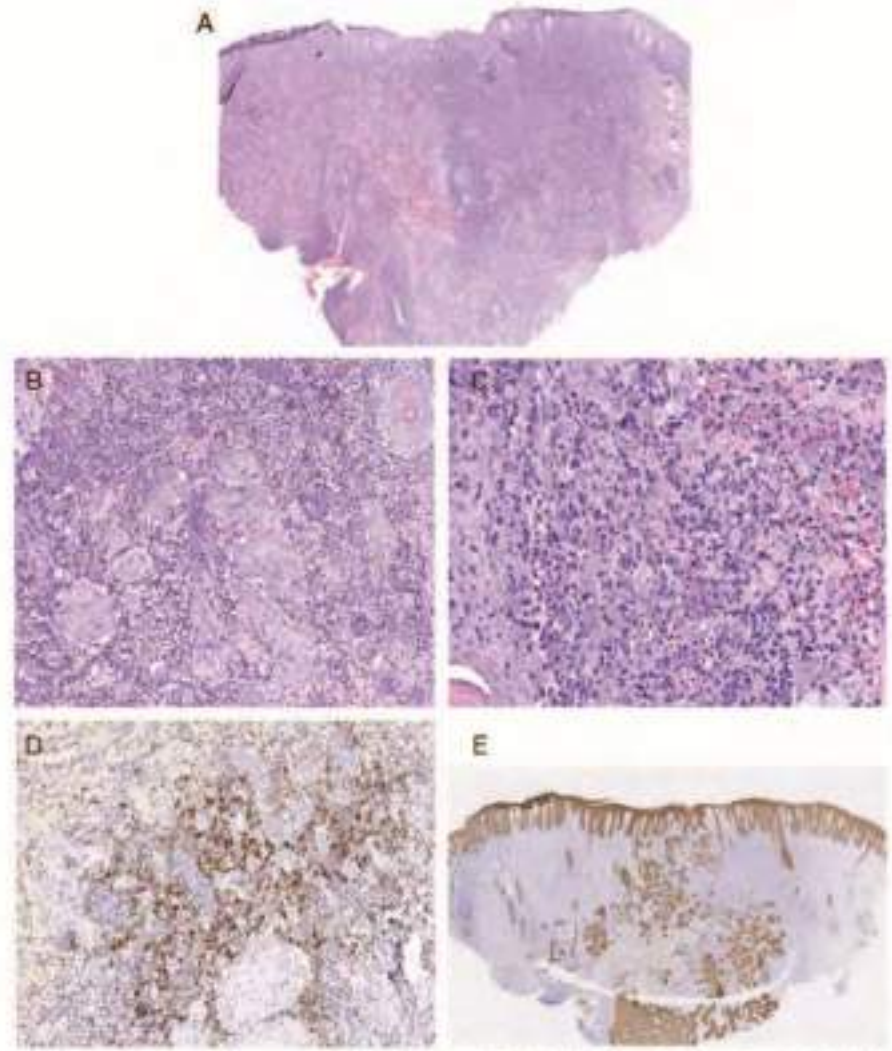
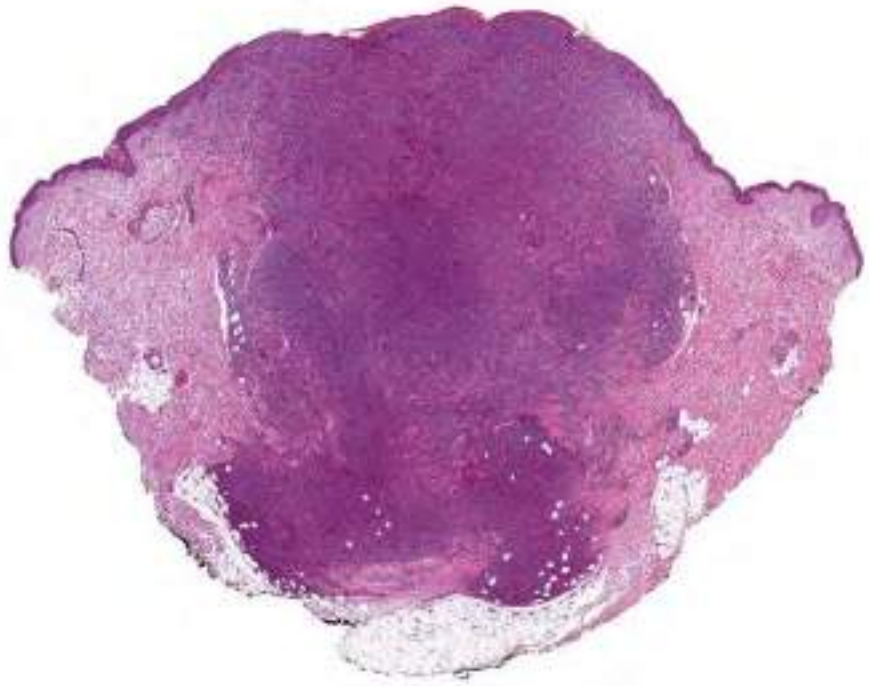
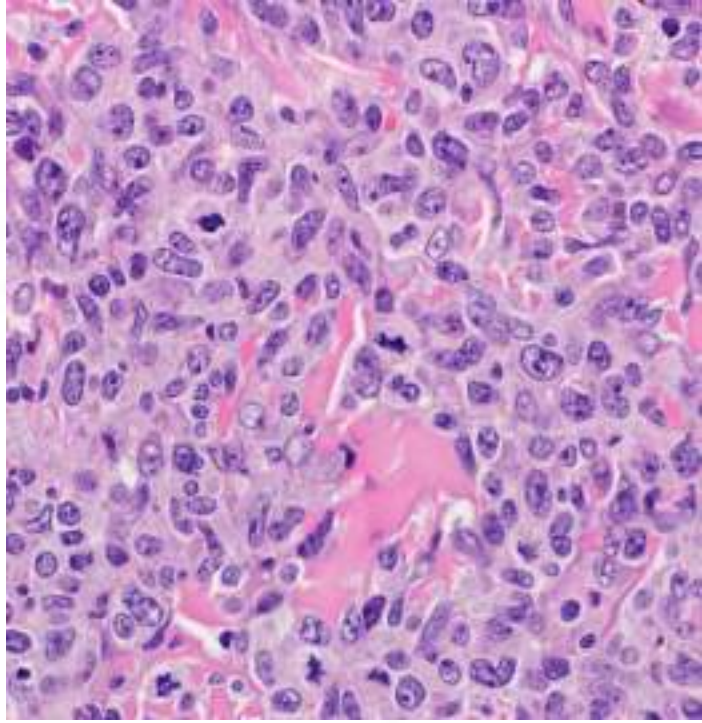
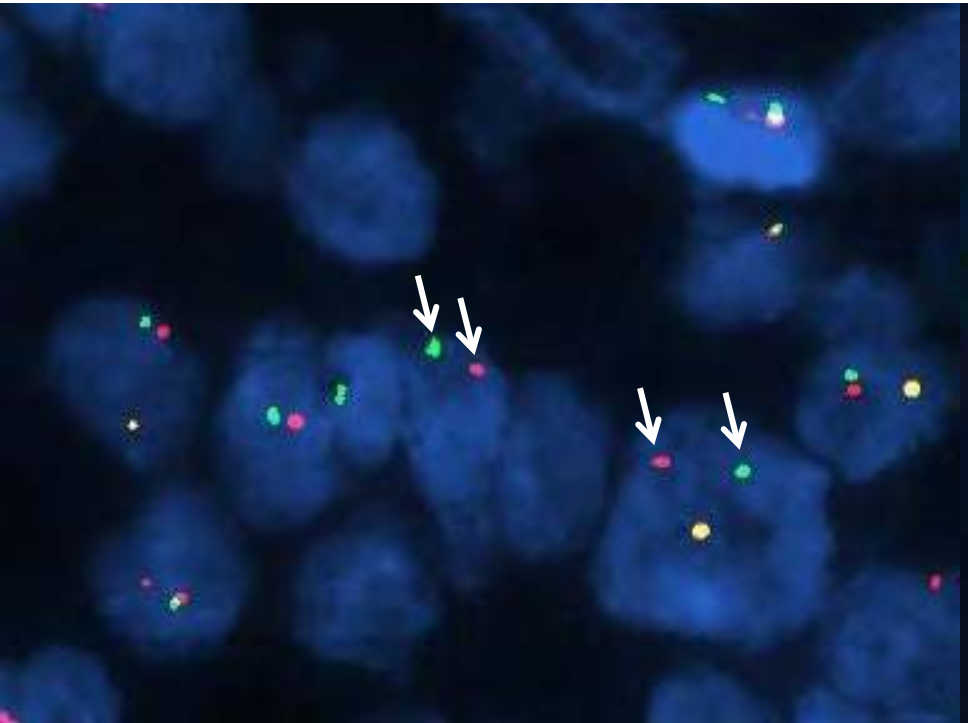


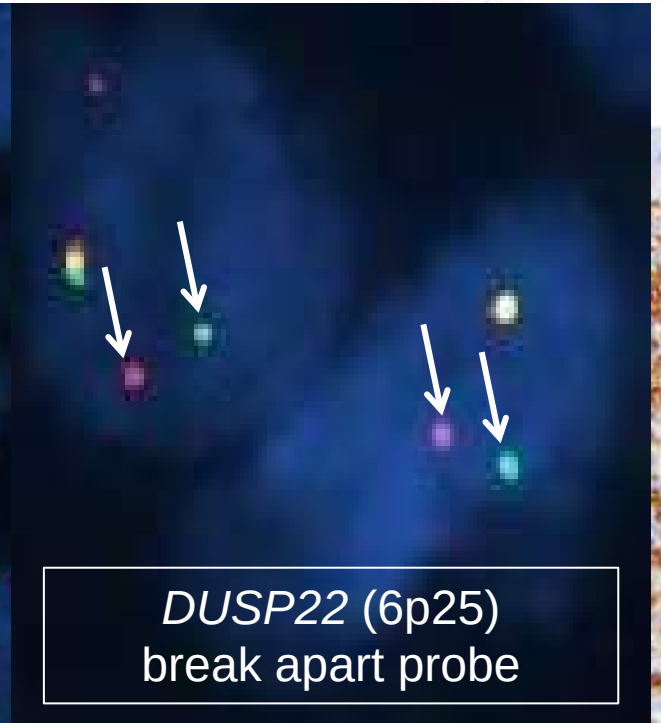
Fig. 2. A) Histopathology revealed nests of squamous cells that were diffusely distributed in the dermis with infiltrations of abundant lymphocytes, eosinophils and neutrophils [hematoxylin and eosin (H&E), ×10]. B) Nests of squamous cells in the dermis (H&E, ×40). C) Some lymphoid cells were obviously atypical with large and hyperchromatic nuclei (H&E, ×100). D) Immunohistochemical staining showed CD30+ large atypical cells (×100). E) Immunohistochemical staining: the cells were positive for CK (×10).

M, 56

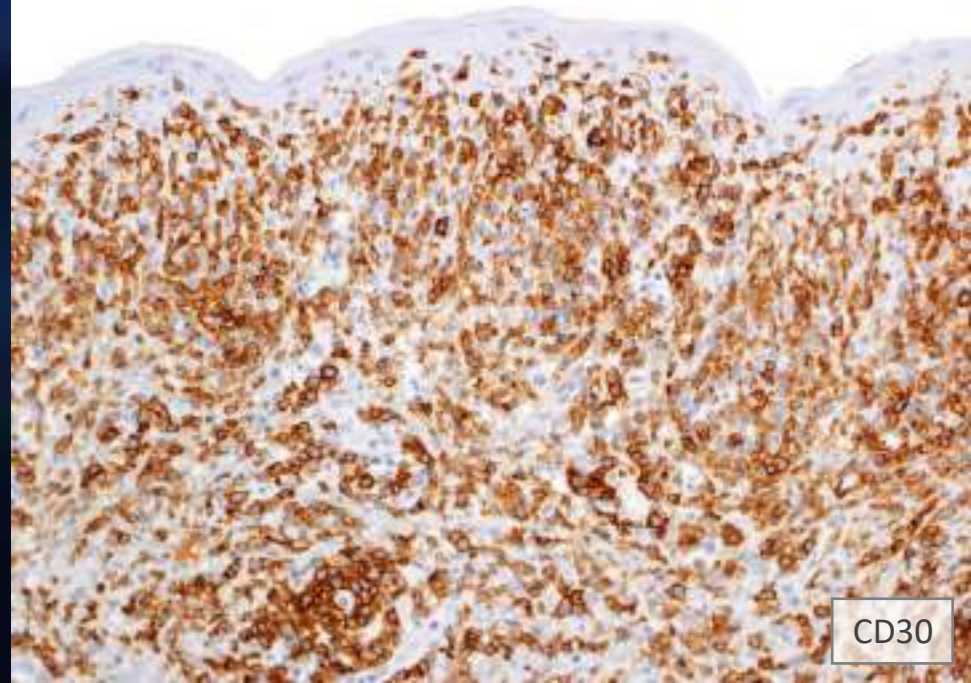




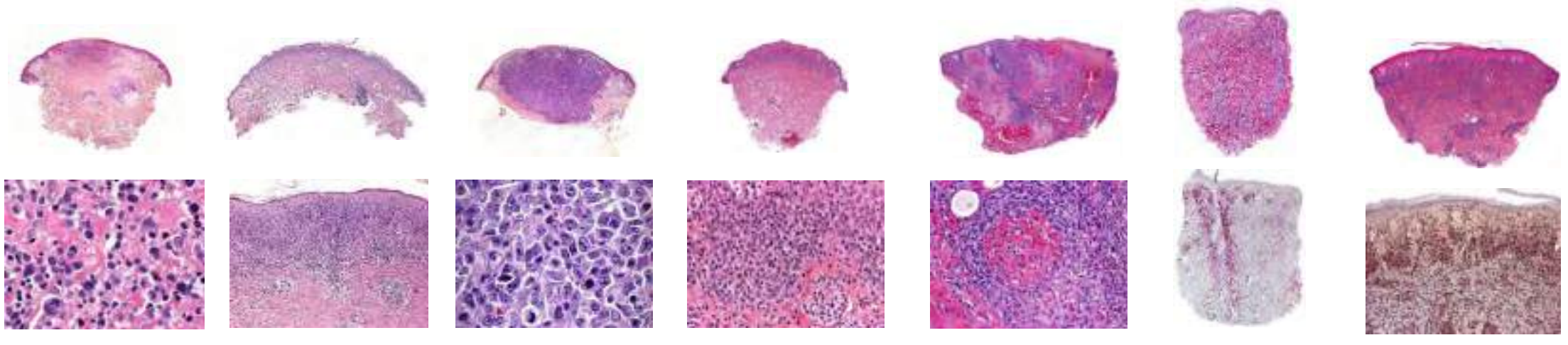




DUSP22 (6p25)
break apart probe

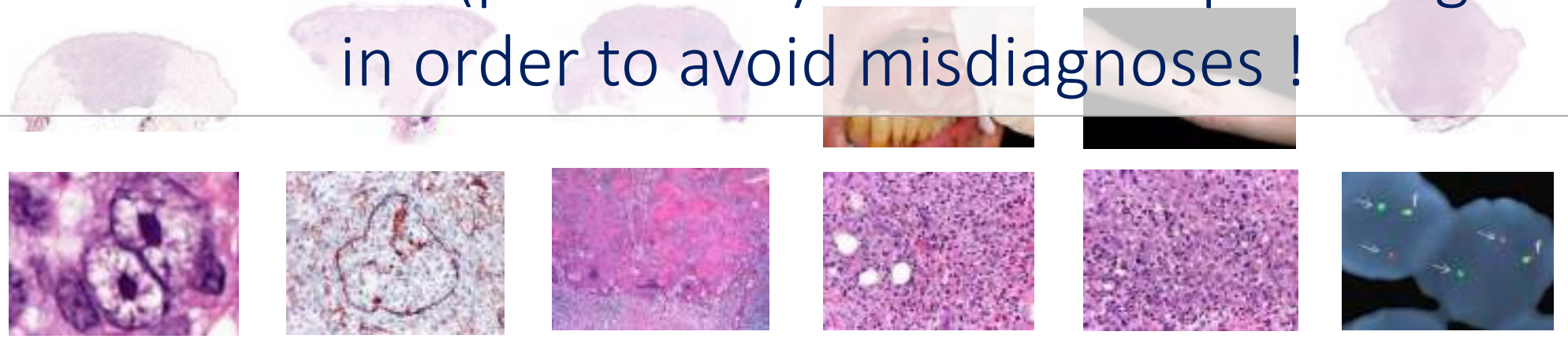


CD30



Type A
Type B
Type C
Type D
Type E
Type F
Type G

Subtypes of lymphomatoid papulosis are not a classification: Just a caveat (particularly for dermatopathologists) in order to avoid misdiagnoses !



Type H
Hodgkin-like

Type I
Intralymphatic

Type K
KA-like

Type M
Mucosal

Type R
Regional

Type 6
6p25.3
DUSP22-IRF4

Variants of lymphomatoid papulosis

- Many clinical or histopathological "types" of lymphomatoid papulosis have been described after the original report by Macaulay
- Clinically and prognostically no differences between the various types of lymphomatoid papulosis
- Some variants may be a chance finding (e.g., follicular LyP)
- The identification of different histopathological types of LyP is important exclusively for the diagnosis *(i.e., rule out other cutaneous lymphomas)*
- Not necessarily part of the histological report !!!

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Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin

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[2]Department of Dermatology, Medical University of Graz, Graz, Austria

Background: Cutaneous infections and inflammatory diseases may contain a significant number of CD30-positive cells, thus mimicking lymphomatoid papulosis (LyP) or anaplastic large cell lymphoma.
Methods: We reviewed our cases of non-neoplastic skin conditions with large, CD30-positive cells and searched the literature for similar cases.
Results: A total of 28 cases were included in the study: Milker's nodule (n = 8), Herpes simplex virus infection (n = 7), lymphomatoid drug reaction (n = 3), molluscum contagiosum (n = 3), nodular scabies (n = 2), leishmaniasis (n = 1), syphilis (n = 1), pernio (n = 1), ruptured infundibular cyst (n = 1) and pseudolymphoma in a scar (n = 1). CD30-positive cells were often arranged in clusters and revealed both Golgi and membrane positivity, similar to what was observed in LyP and CD30+ anaplastic large T-cell lymphoma.
Conclusions: Analysis of our data and of those published in the literature shows that viruses and drugs are the most common cause for occurence of large CD30-positive cells in cutaneous pseudolymphomatous infiltrates. Arrangement of these large, CD30-positive cells in small clusters is not unique to cutaneous CD30-positive lymphomas, and in many cases a precise diagnosis can be made only upon accurate clinicopathological correlation or using ancillary methods such as polymerase chain reaction analysis for viral DNA.

Werner B, Massone C, Kerl H, Cerroni L. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin.
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Expression of the CD30 antigen is the hallmark of a group of primary cutaneous T-cell lymphomas including the spectrum ranging from lymphomatoid papulosis (LyP) to primary cutaneous anaplastic large T-cell lymphoma (cALCL).[1,2] CD30-positivity on neoplastic cells of cutaneous malignant lymphomas, however, is not a feature exclusive to LyP and cALCL, as it can be observed in cases of Hodgkin's lymphoma involving secondarily the skin[3] as well as in several T-cell[4,5] and B-cell lymphomas,[6–8] natural-killer cell lymphomas[9,10] or even in granulocytic sarcoma.[11] Furthermore, in the past years, CD30-positive cells have been detected in several reactive lymphocytic infiltrates of the skin[12–32] and oral mucosa.[33]

We reviewed our cases of non-neoplastic (inflammatory or infectious) skin conditions in which large CD30-positive cells were detected among the infiltrating lymphocytes, analyzing the pattern of cell positivity and discussing the significance of the finding of CD30-positive lymphocytes in cutaneous lymphoid infiltrates.

Material and methods

Files from the Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz, Austria and cases sent in consultation to one of us (L. C.) were searched for pseudolymphomas (reactive benign inflammatory or infectious conditions) showing presence of large CD30-positive cells within the infiltrate. Biopsy specimens obtained in Graz were fixed in 10% buffered formalin and

Table 1. Reactive cutaneous infiltrates containing large CD30-positive lymphocytes included in our study

Condition	Number of cases
Milker's nodule	8
Herpes simplex virus or Varicella-Zoster virus infection	7
Lymphomatoid drug reaction	3
Molluscum contagiosum	3
Nodular scabies	2
Cutaneous leishmaniasis (oriental sore)	1
Syphilis (stage I)	1
Pernio	1
Re-excision scar of basal cell carcinoma	1
Ruptured infundibular cyst	1
Total	28

ORIGINAL ARTICLE

WILEY

A review of CD30 expression in cutaneous neoplasms

Franziska Kampa | Christina Mitteldorf

Abstract

Background: The surface protein CD30 is a therapeutic target of monoclonal antibody therapy. Knowledge of the frequency of CD30 expression and its prognostic relevance is therefore interesting, not only in lymphoproliferative disorders (LPD) but also in solid tumors of the skin.

Methods: A review was completed in PubMed for all published reports of CD30 expression in cutaneous lymphomas, mastocytosis, epithelial tumors and sarcomas from 1982 to April 2019. Only accessible articles in English and German were considered. Entities with an expected CD30 expression, such as CD30-positive LPD, were not evaluated.

Results: The electronic research identified 1091 articles and a further 24 articles were obtained from manual bibliographic reference. Overall 91 articles were included that examined CD30 expression in various entities of cutaneous neoplasms and matched the inclusion criteria.

Conclusion: Apart from cutaneous CD30-positive LPD, the best studied group for CD30 expression was mycosis fungoides (MF). CD30 positivity was found in 32% of classical (patch and plaque stage) and in 59.4% cases of transformed MF. CD30 was also frequently expressed in cutaneous mastocytosis (96.5%). In solid tumors, some single reports describe CD30 expression by tumor cells, but CD30 reactive lymphocytes were frequently observed in the tumor microenvironment (TME) especially in keratoacanthoma (KA).

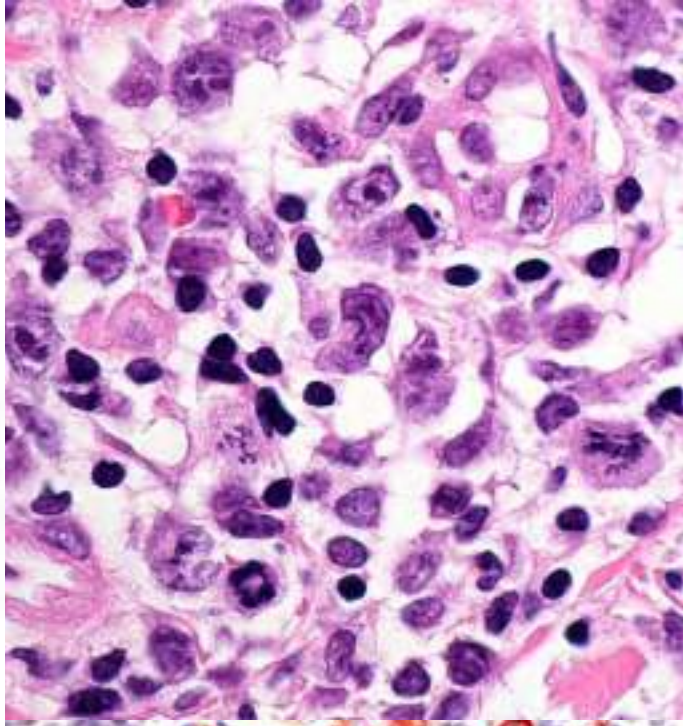
KEYWORDS

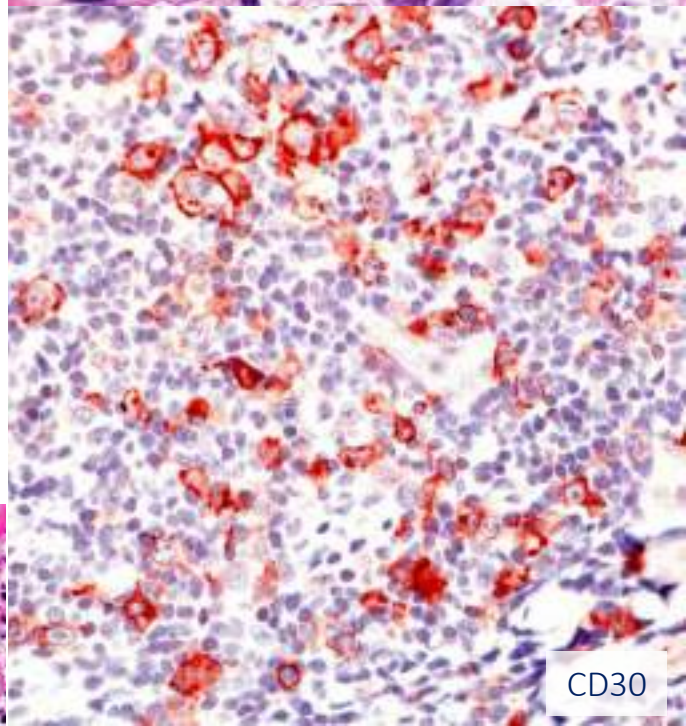
carcinoma, lymphoma, mastocytosis, mycosis fungoides, sarcoma

1 | INTRODUCTION

Apart from cutaneous CD30+ lymphoproliferative disorders, CD30 positivity was found in 32% of classical (patch and plaque stage) and in 59.4% cases of transformed MF.
CD30 was also frequently expressed in cutaneous mastocytosis (96.5%).
In solid tumors, some single reports describe CD30 expression by tumor cells.
CD30+ reactive lymphocytes were frequently observed in the tumor microenvironment, especially in keratoacanthoma. (*)

(*) beware of "keratoacanthomatous" LyP and cALCL !!

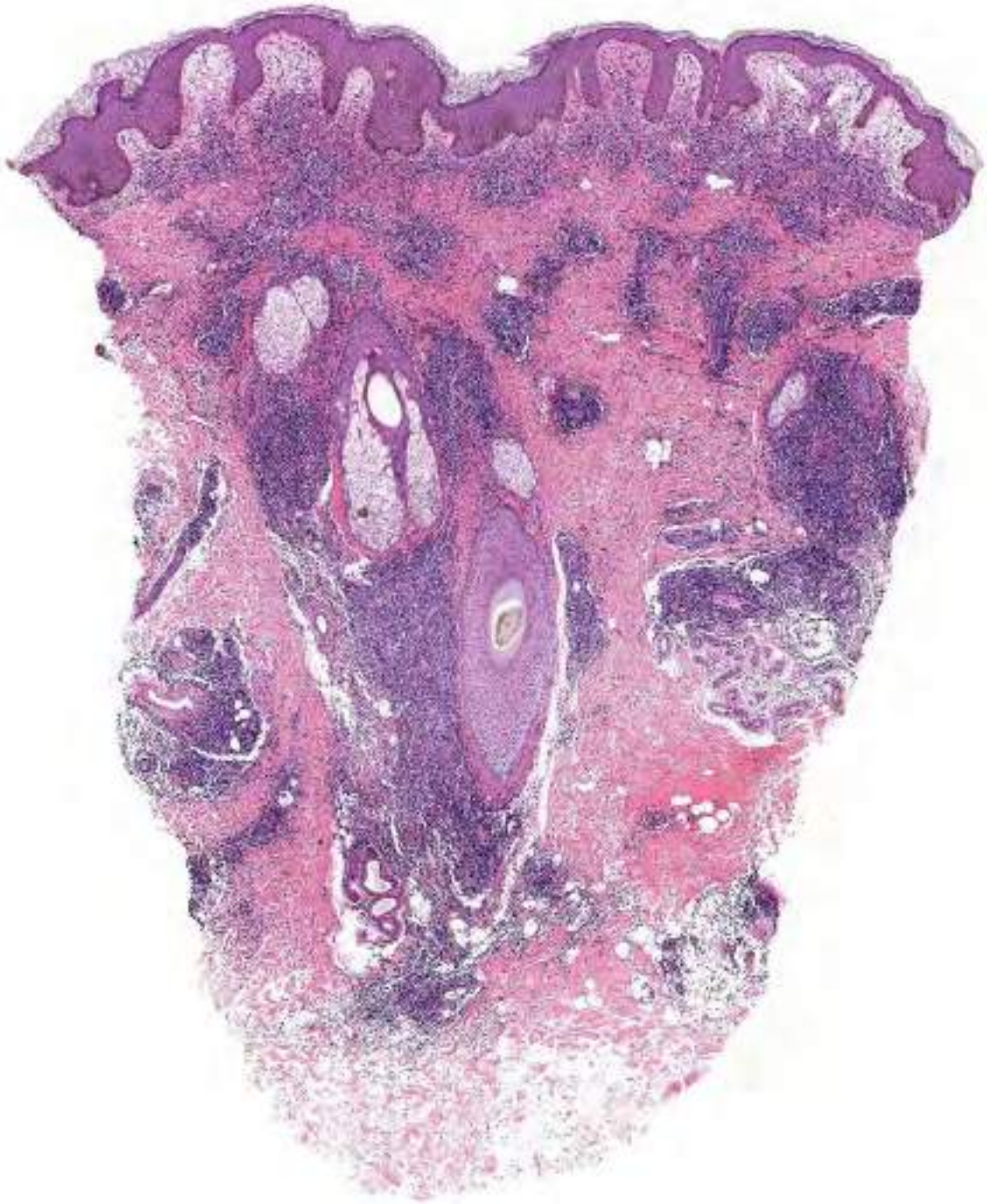


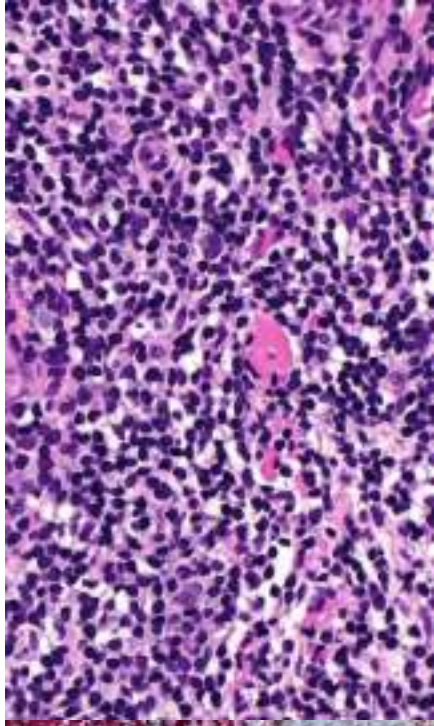


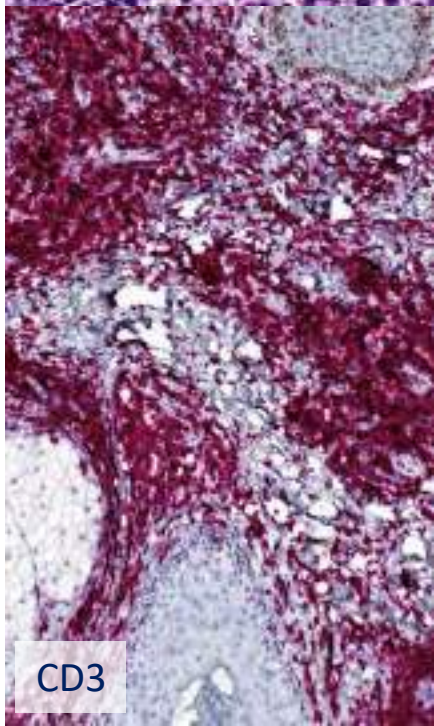
Herpes simplex

CD30

M, 53

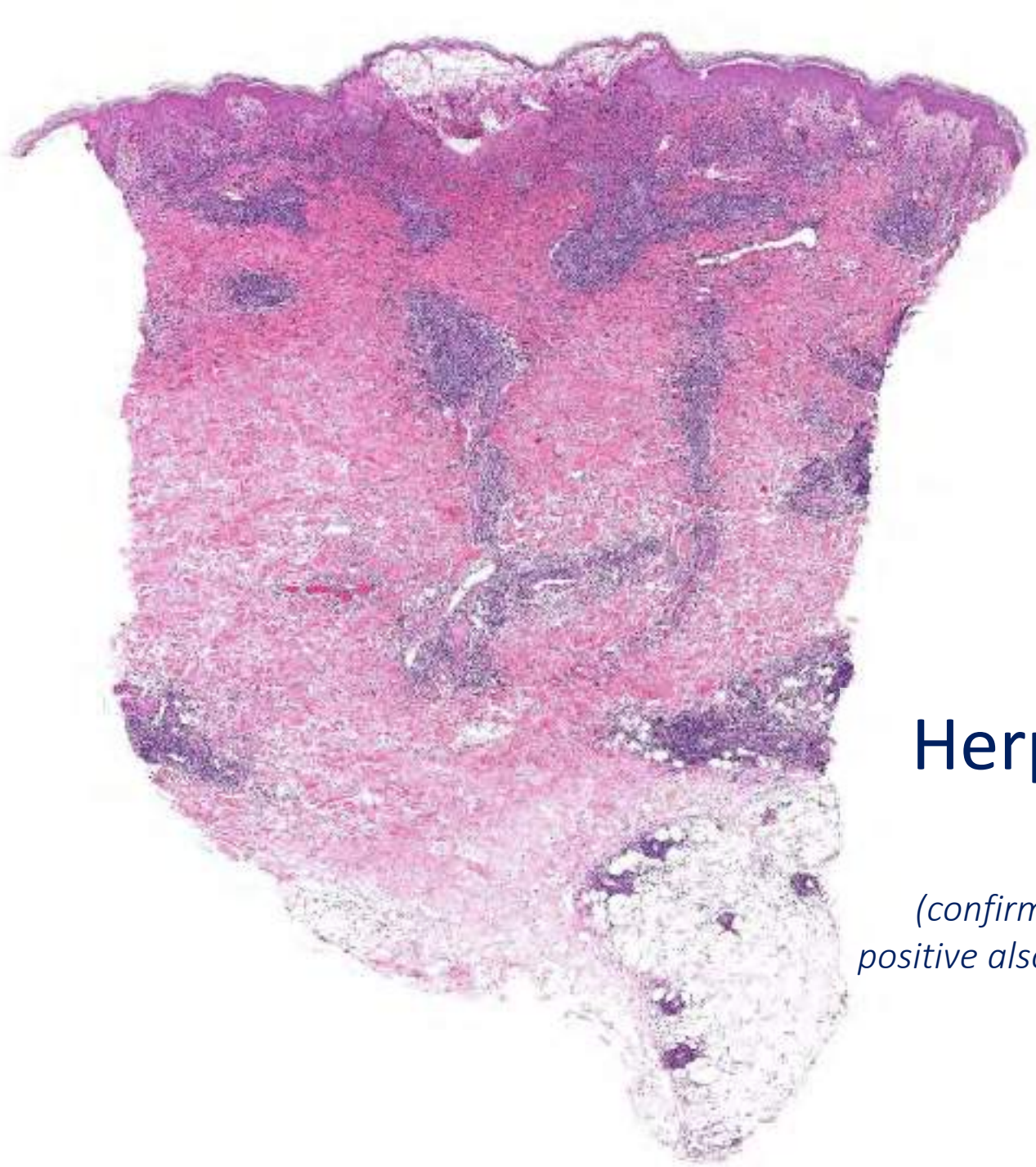


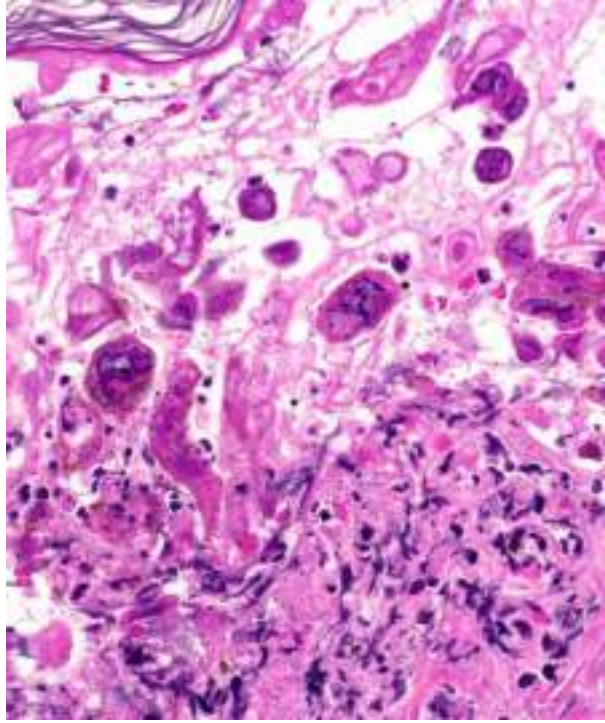




CD3

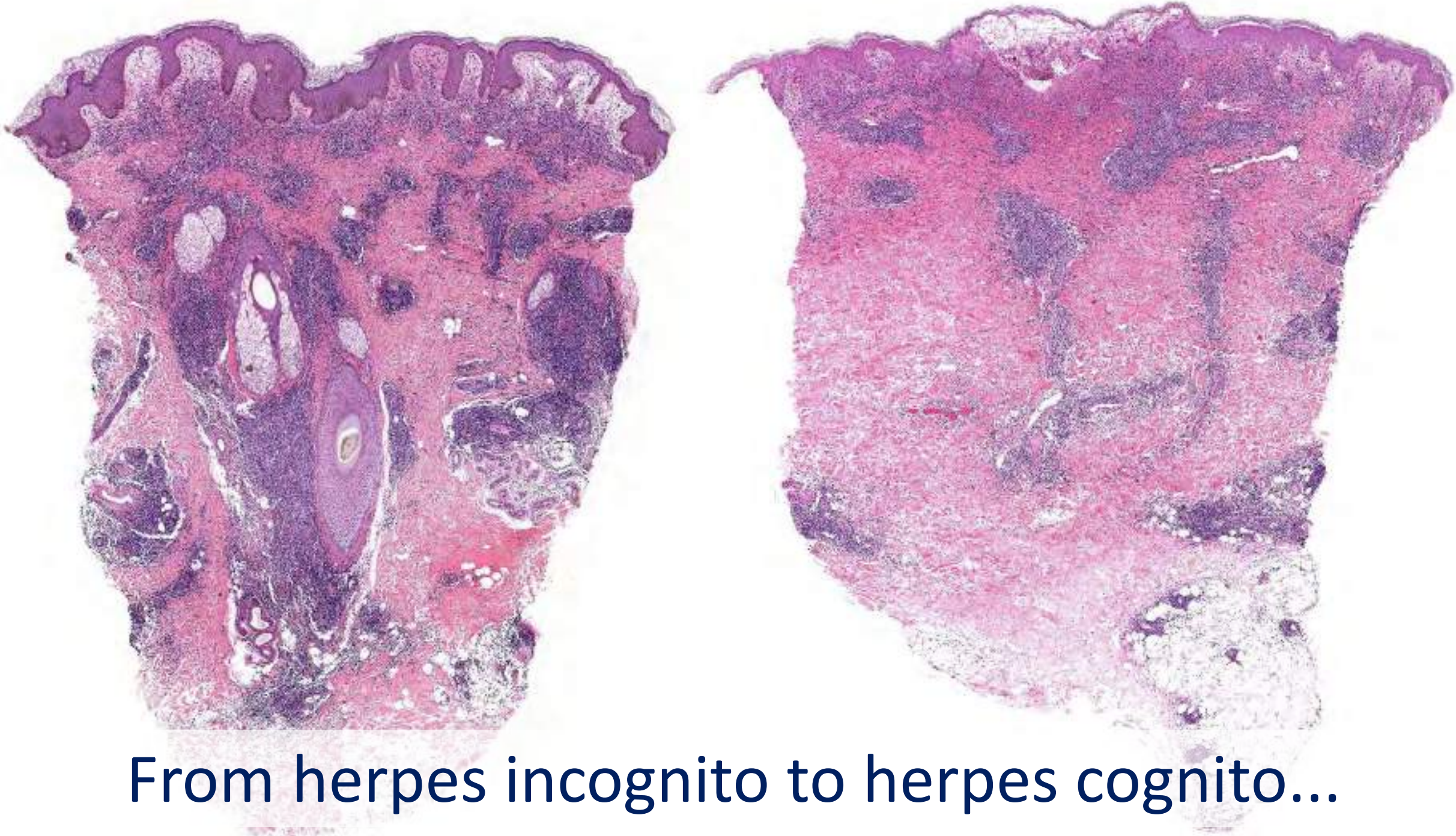
10 weeks later





Herpes simplex 1 infection

(confirmed by PCR, retrospectively positive also on the first biopsy specimen)



From herpes incognito to herpes cognito...

Histopathologic Features of Cutaneous Herpes Virus Infections (Herpes Simplex, Herpes Varicella/Zoster)

A Broad Spectrum of Presentations With Common Pseudolymphomatous Aspects

Bernd Leinweber, MD, Helmut Kerl, MD, and Lorenza Cerroni, MD

Abstract: Cutaneous eruptions caused by herpes simplex 1/2 (HSV-1/2) and herpes varicella/zoster (VZV) represent common dermatoses. In some cases, they present with atypical clinical and/or histopathologic features, including presence of dense lymphoid infiltrates with atypical lymphocytes simulating cutaneous lymphomas. In this study, we reviewed the biopsy specimens of 65 patients (33 males, 32 females; mean age, 61.2 years; median age, 62 years; age range, 19–96 years) with cutaneous eruptions caused by HSV-1/2 or VZV. Histologic examination revealed several atypical findings, including presence of dense lymphoid infiltrates, angiotropism, and atypical lymphocytes simulating malignant lymphoma. Immunohistochemistry performed in 22 cases showed a predominant T-cell infiltrate in the majority of cases with variable numbers of CD30+ and CD56+ cells. Two cases with a pseudolymphomatous appearance and small clusters of CD30+ cells revealed a monoclonal population of T lymphocytes by PCR analysis, underlying the difficulties in classification of these cases correctly. Our study indicates that cutaneous herpes infections can exhibit several atypical histopathologic, immunohistochemical, and molecular features, and that in given cases accurate clinicopathologic correlation and short-term follow-up controls are necessary for differentiation from cutaneous lymphoma.

Key Words: herpes simplex, herpes varicella/zoster, cutaneous pseudolymphoma

(Am J Surg Pathol 2006;30:50–58)

Cutaneous eruptions caused by herpes simplex 1/2 (HSV-1/2) and herpes varicella/zoster (VZV) represent common dermatoses. In most cases, a correct diagnosis can be made based on the characteristic clinical findings, and usually skin lesions are biopsied only in patients with uncommon clinical presentations.[1–3] In this context, it is well known that cutaneous herpes infections can present with atypical clinical features in patients with immunosuppression or with underlying hematologic diseases.[4–10,51] In these instances, the clinical diagnosis may be problematic, and the differential diagnosis includes cutaneous lymphoma or pseudolymphoma among others. In addition, histology of cutaneous herpes infections can vary to a great extent, ranging from lesions with purely epithelial involvement and sparse to absent inflammatory infiltrates, to cases with a florid pseudolymphomatous pattern simulating a malignant lymphoma. Indeed, in a recent article, Eddezzet-Hamdi et al reported a case of an obstructive mass in the nasopharynx caused by infection with HSV-1/2, with a clinical presentation simulating a malignant tumor, and a preliminary pathologic diagnosis of extranodal NK/T-cell lymphoma, nasal type.[26]

Occasionally, patients without preexisting diseases present with cutaneous HSV-1/2 or VZV infections that display atypical clinical and histologic findings suggestive of a cutaneous lymphoma. Indeed, in the past few months, one of us (L.C.) received 5 such cases for consultation (case nos. 27, 31, 49, 53, and 54), which had been previously misdiagnosed as malignant lymphoma (cutaneous CD30+ lymphoproliferative disorders: spontaneous lymphomatoid papulosis/anaplastic large cell lymphoma). In this study, we analyzed retrospectively the histopathologic features of 65 cases of cutaneous HSV-1/2 and VZV infections.

MATERIALS AND METHODS

Biopsy specimens from 65 patients (33 males, 32 females; mean age, 61.2 years; median age, 62 years; age range, 19–96 years) with cutaneous HSV-1/2 and VZV were included in the study (Table 1). All cases were retrieved from the files of the Division of Dermatopathology, Department of Dermatology, Medical University of Graz, Graz, Austria. Some of the cases had been sent in consultation cases. All diagnoses were reviewed by at least two independent dermatopathologists (B.L., L.C.). Diagnoses were based on clinical, histologic, immunohistochemical, molecular, and follow-up data.

Histology

All biopsy specimens were fixed in 10% buffered formalin, routinely processed, and subsequently embedded in paraffin. Sections were stained with hematoxylin and eosin and analyzed for the presence of several histopathologic features listed in Table 1.

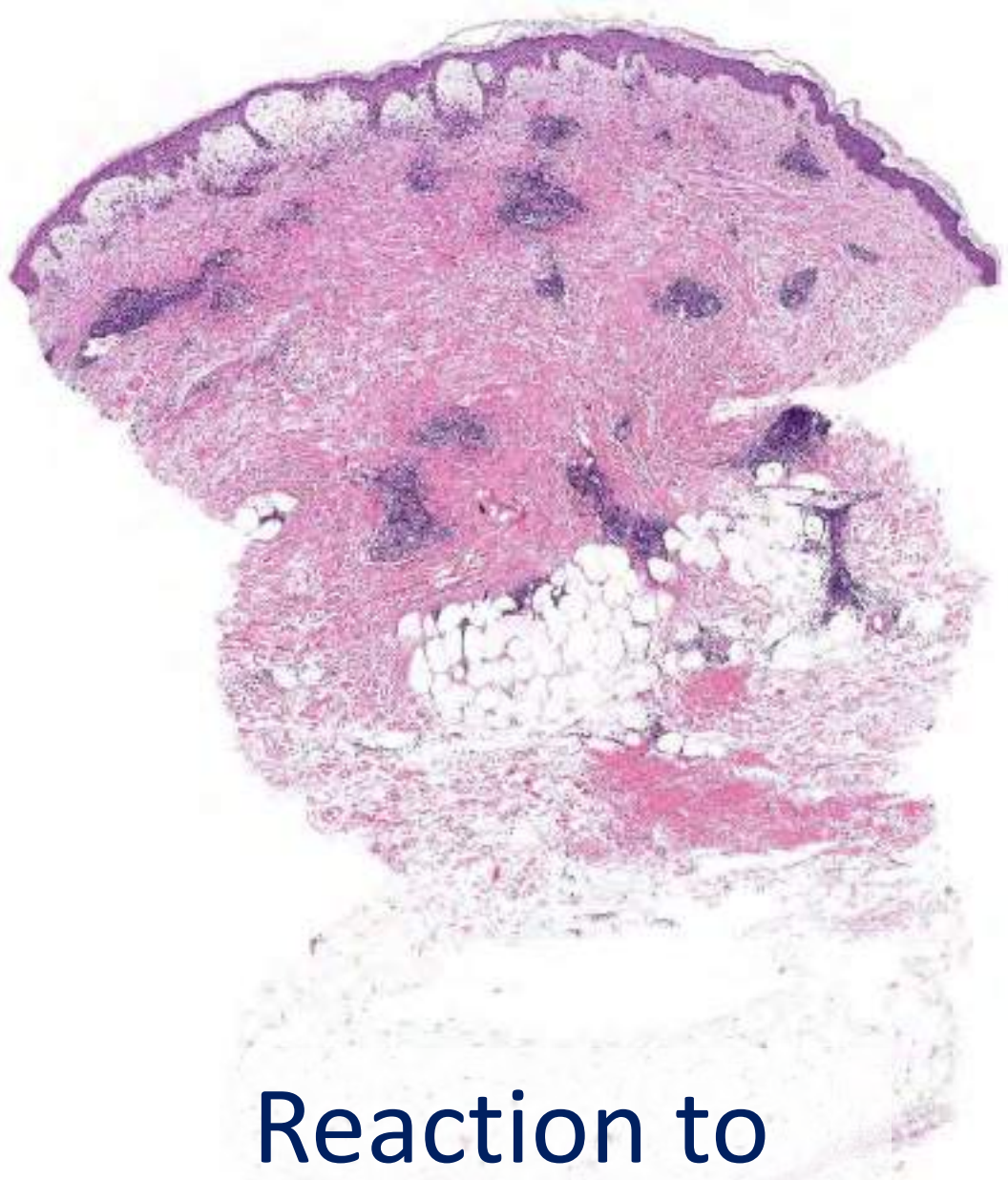
From the Department of Dermatology, Medical University of Graz, Graz, Austria.

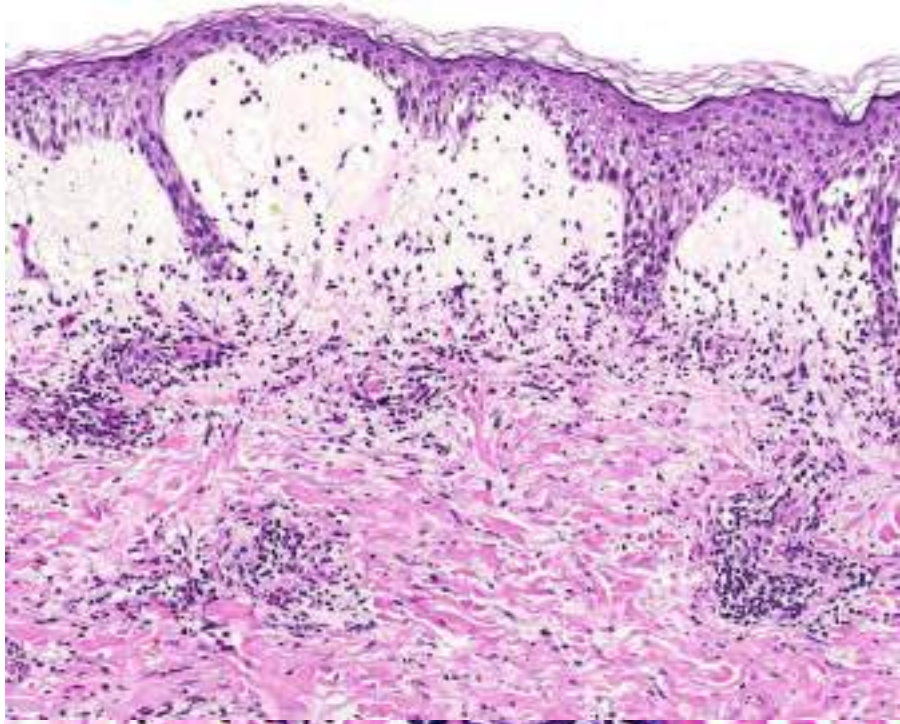
Reprints: Lorenza Cerroni, MD, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria (e-mail: lorenza.cerroni@medunigraz.at).

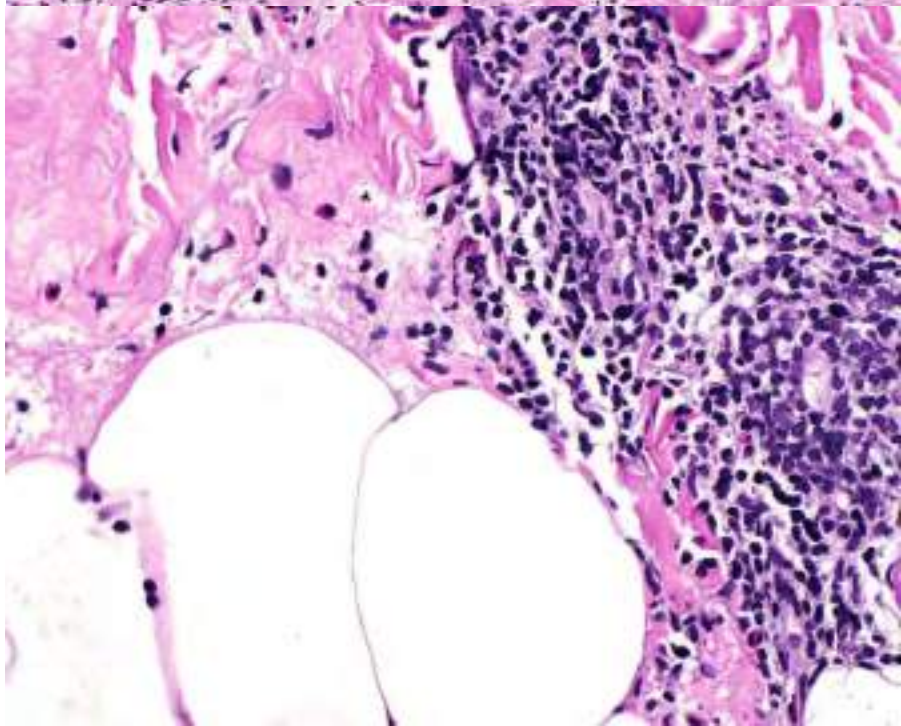
TABLE 2. Summary of Results of Immunohistologic and PCR Analyses

	Immunohistochemistry*								PCR		
Case No.	CD3	CD4	CD8	CD20	CD30	CD56	TIA1	CD123	Herpes Type	TCR	IgH
1	+++	++	+++	–	+/–	+/–	++	–	ND	ND	ND
5	ND	ND	ND	ND	ND	ND	ND	ND	VZV	ND	ND
8	+	+/–	+	+	+/–	+/–	++	–	ND	ND	ND
11	+++	+	++	+	+/–	+	++	–	ND	ND	ND
15	++	+	++	+	+/–	+/–	++	–	ND	ND	ND
16	++	++	++	+	–	+/–	++	–	ND	ND	ND
17	+++	+++	++	+	+/–	+/–	++	+/–	ND	ND	ND
18	+++	+++	++	+	+/–	++†	++	–	ND	ND	ND
24	+++	++	++	++	–	+	++	–	ND	ND	ND
25	+++	+	+++	+	+	–	++	–	ND	ND	ND
27	+++	ND	ND	++	+	+	ND	ND	HSV-1/2	P	P
28	+++	++	+++	++	+	+	+++	–	ND	ND	ND
29	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2 & VZV	ND	ND
31	+++	+	++	+/–	+/–	+	++	ND	VZV	P	P
34	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
36	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
37	+++	+	+++	+	+/–	–	+++	+/–	ND	ND	ND
39	+++	+	++	+	–	+/–	+	–	ND	ND	ND
40	+	+/–	+	+	+/–	–	+	–	ND	ND	ND
43	+++	++	++	+	+/–	+	++	–	ND	ND	ND
44	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2 & VZV	ND	ND
46	++	+	++	++	+	+/–	++	–	HSV-1/2	P	P
48	+++	++	++	+	+	+/–	++	–	VZV	ND	ND
49	ND	ND	ND	ND	+†	ND	ND	ND	HSV-1/2	M	P
50	+++	++	++	–	+	+	++	+/–	ND	ND	ND
53	+++	++	++	+	+†	–	++	ND	HSV-1/2	M	P
54	+++	++	+	+	+/–	ND	ND	ND	HSV-1/2	P	P
56	+++	ND	ND	–	–	ND	ND	ND	HSV-1/2	ND	ND
61	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
62	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
63	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
64	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND

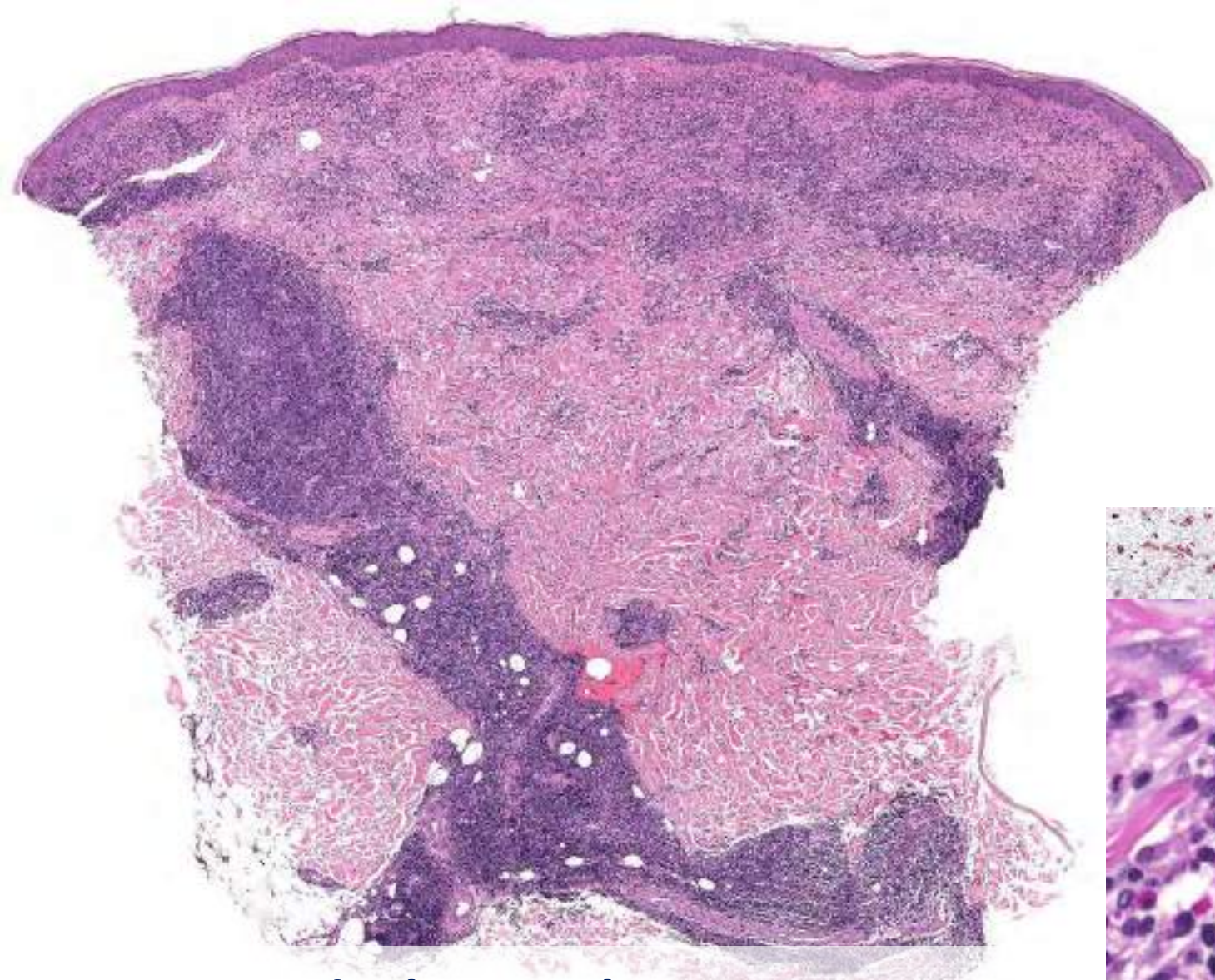
HSV-1/2, herpes simplex 1/2; VZV, varicella zoster virus; PCR, polymerase chain reaction; TCR, T-cell receptor; P, polyclonal; M, monoclonal; ND, not done.
*Rating immunohistochemistry: –, none; +/–, scattered to 5%; +, >5% to 25%; ++, >25% to 50%; +++, >50%.
†Clusters of positive cells.

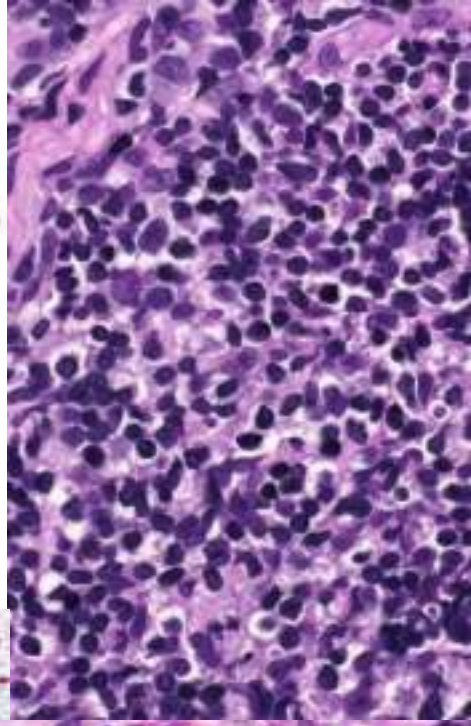


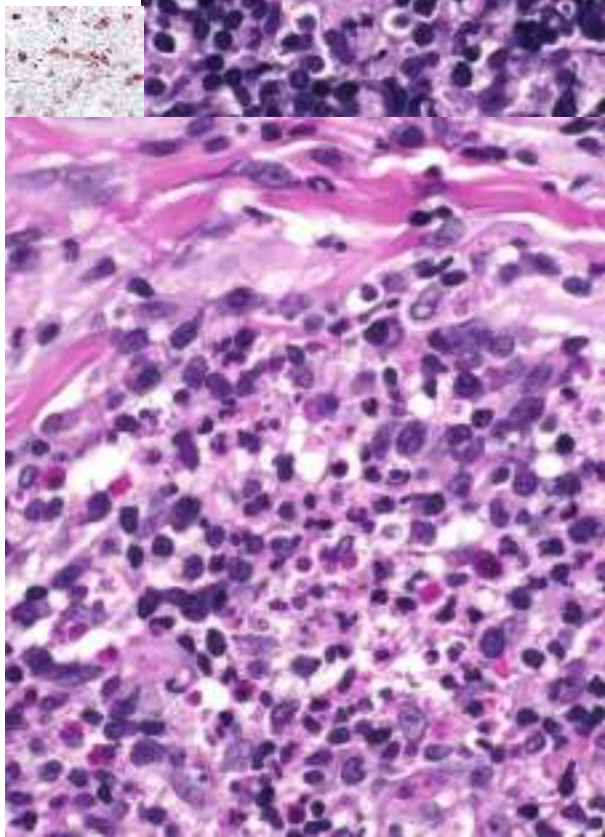




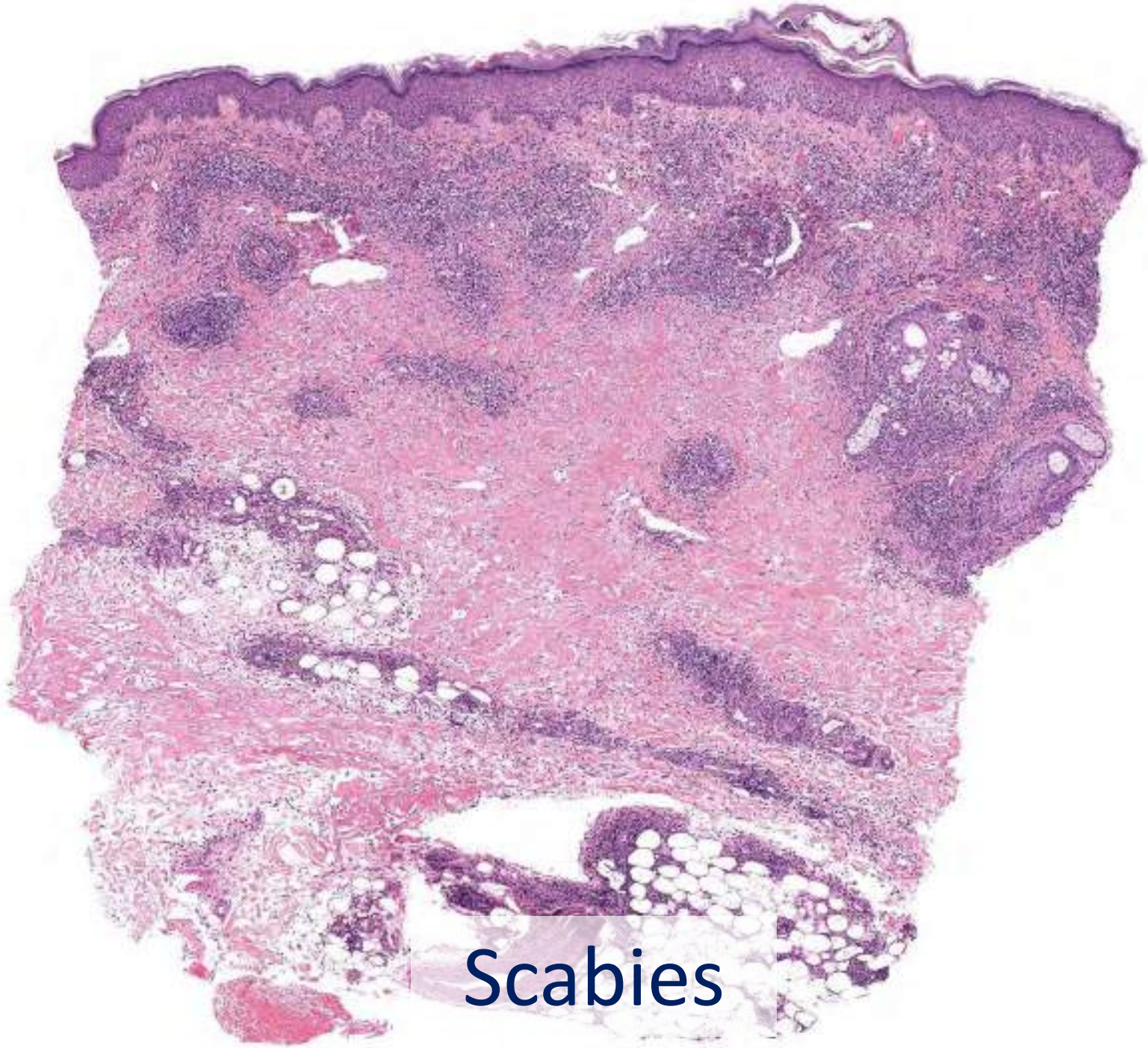
Reaction to artrhropod bite

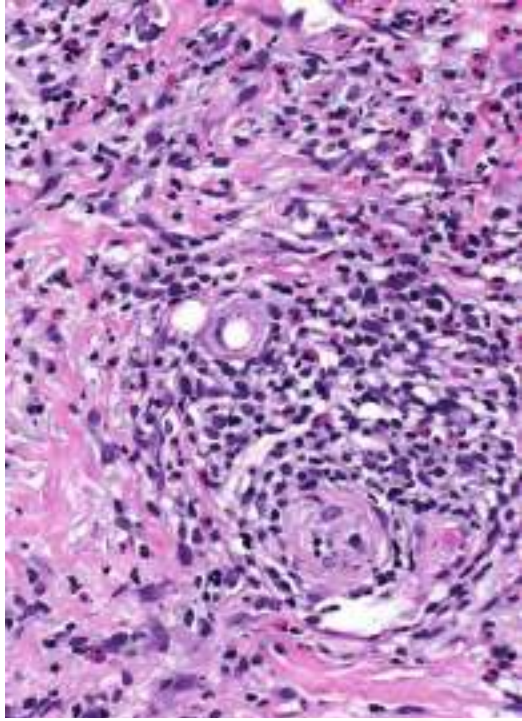


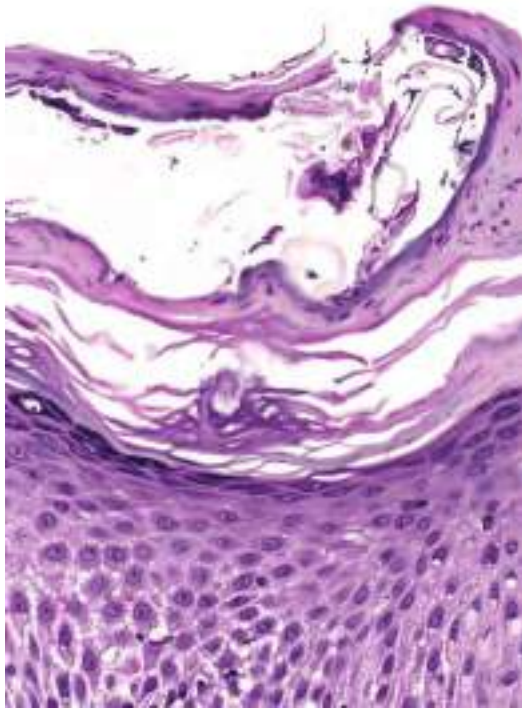




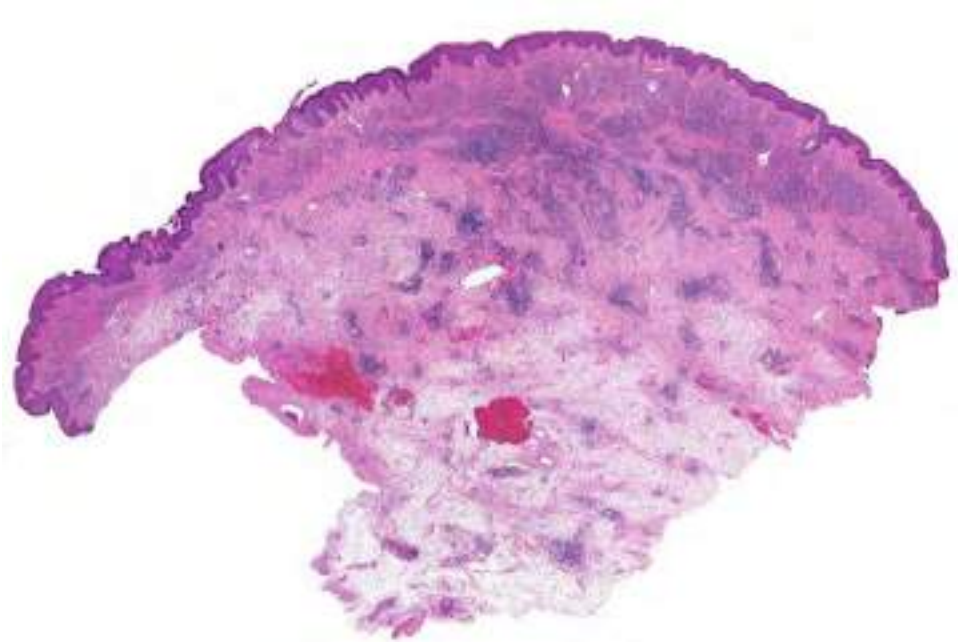
Pseudolymphomatous reaction to artrhropod bite

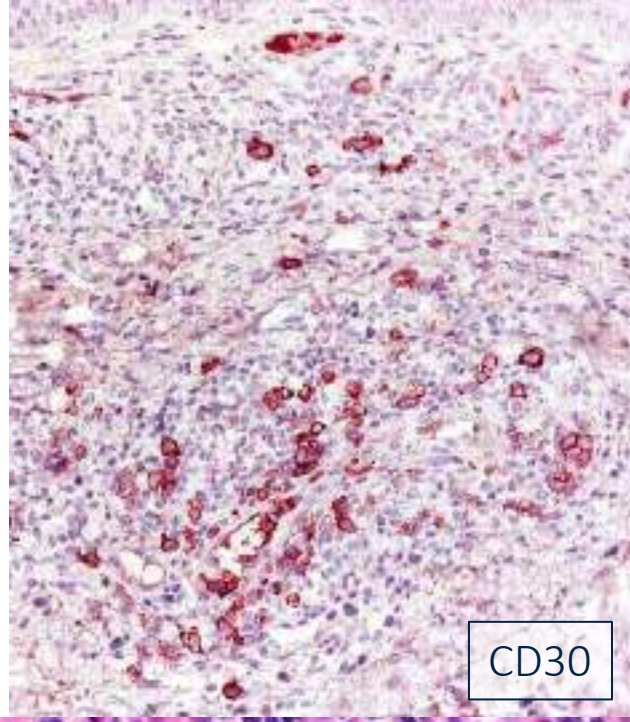






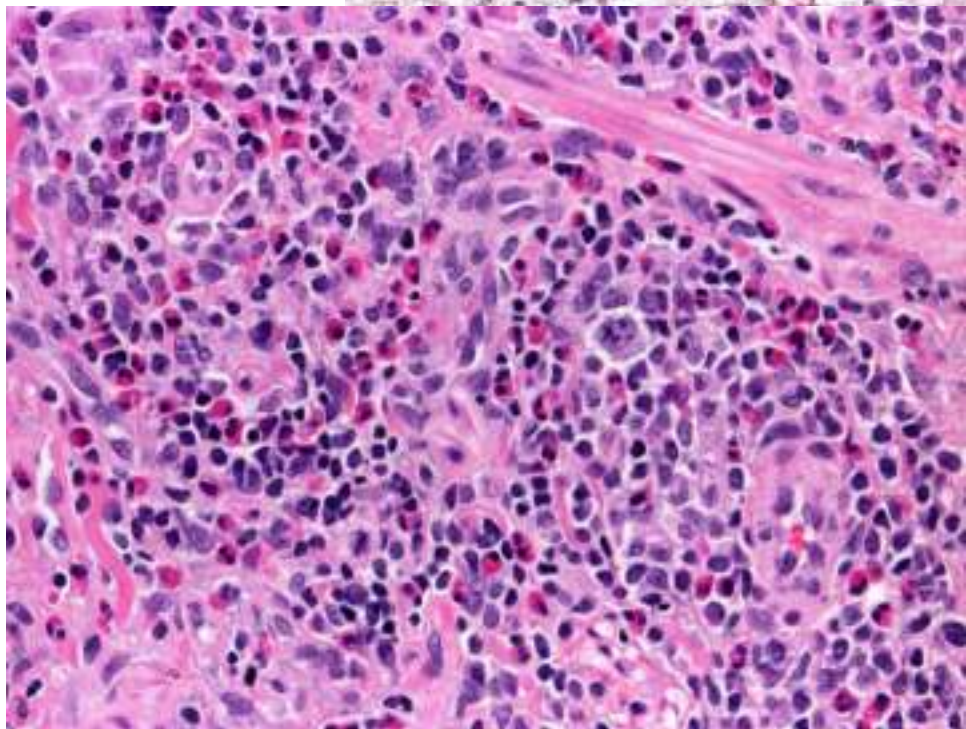
Scabies

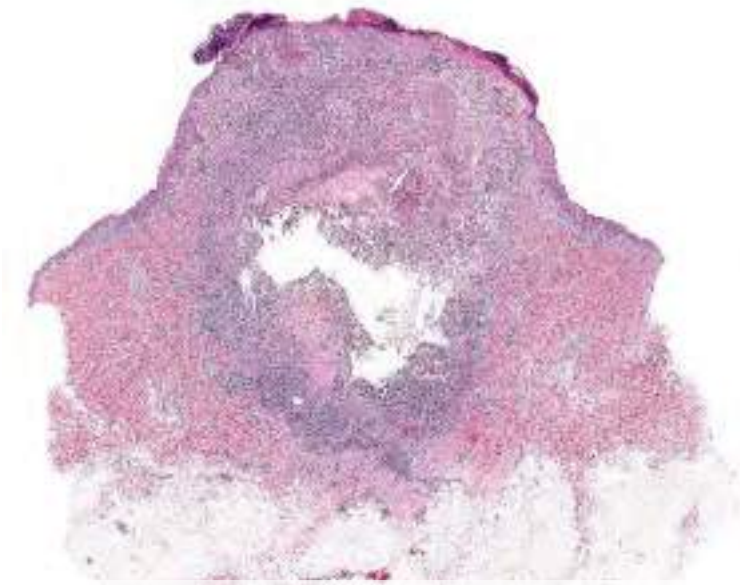




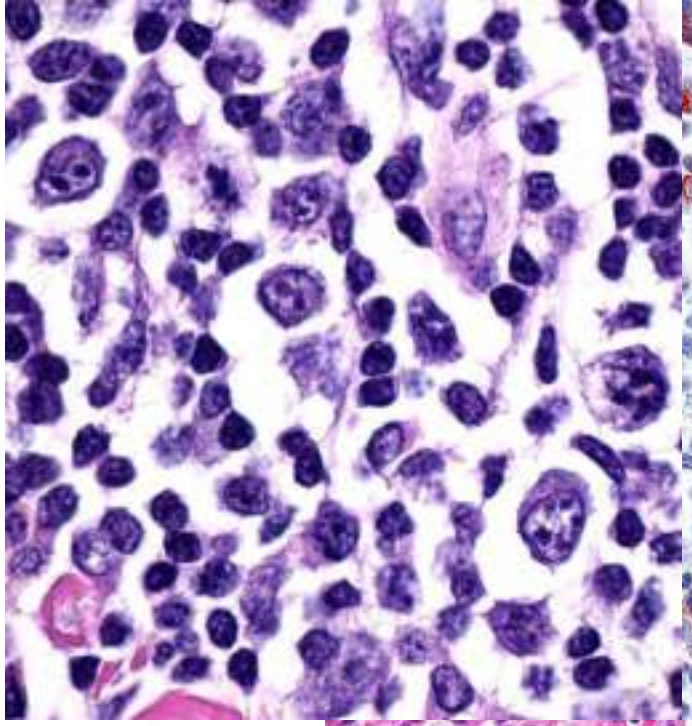
Nodular scabies

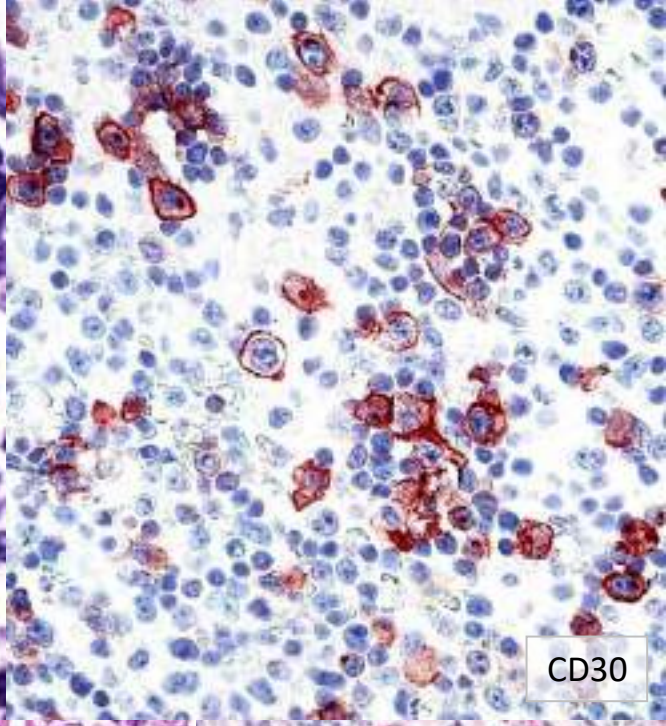
- Pruritic papules and small nodules with a predilection for the lower trunk, scrotum, and thighs; commonly observed in children
- May persist for several months and be not responsive to conventional treatment
- Mites are found in a minority of cases; it may represent a delayed hypersensitivity reaction similar to that found following other arthropod bites
- Activated, CD30+ cells may mimic lymphomatoid papulosis

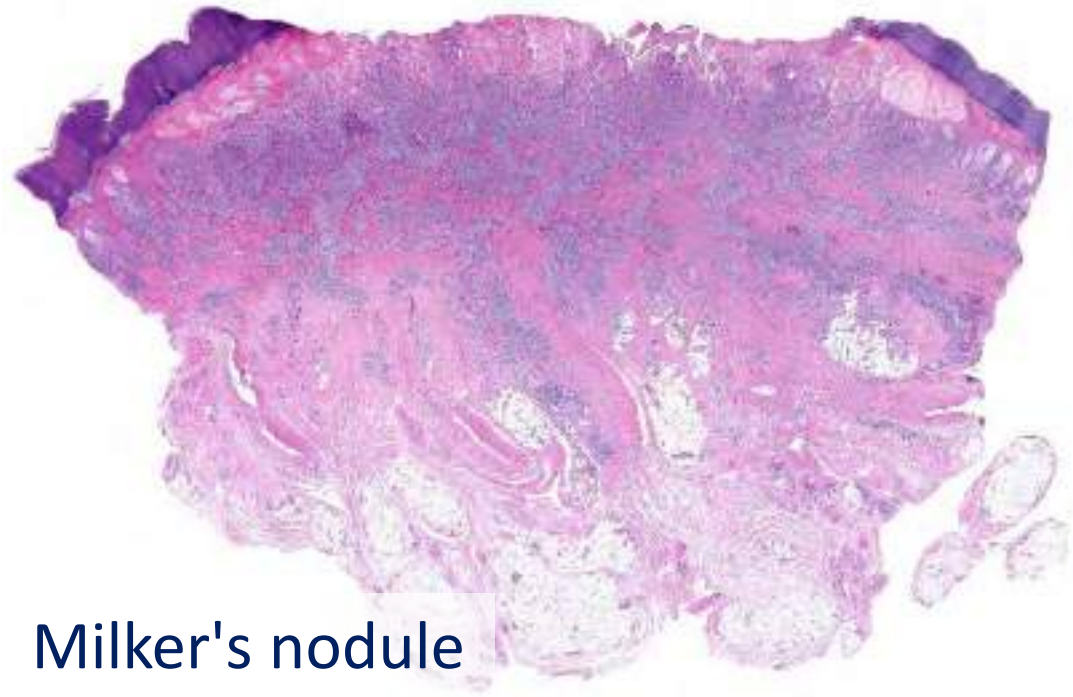




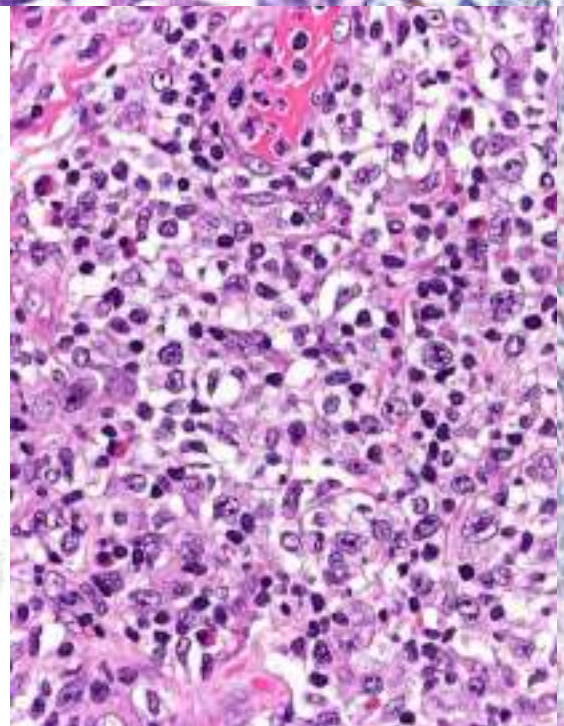
Molluscum contagiosum

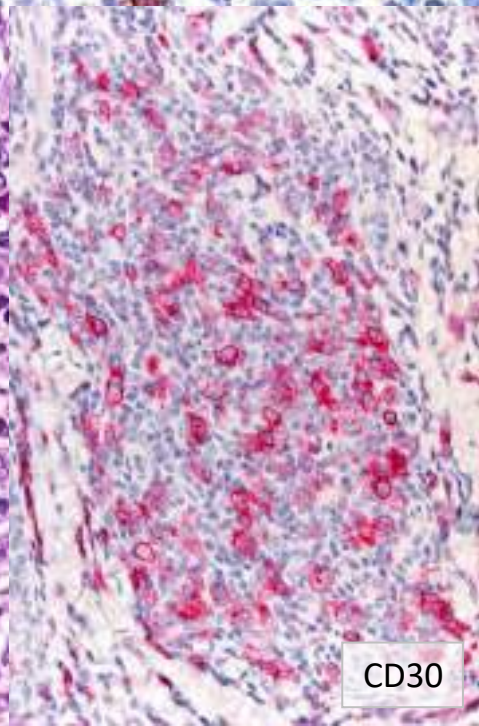


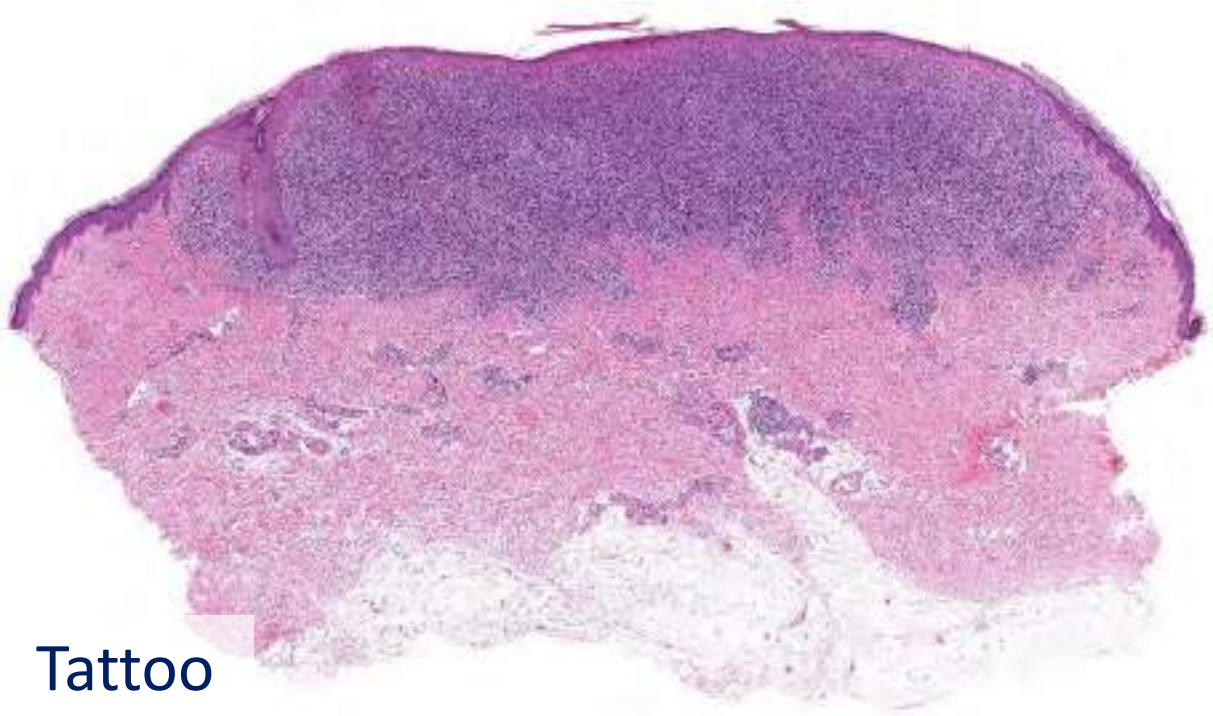




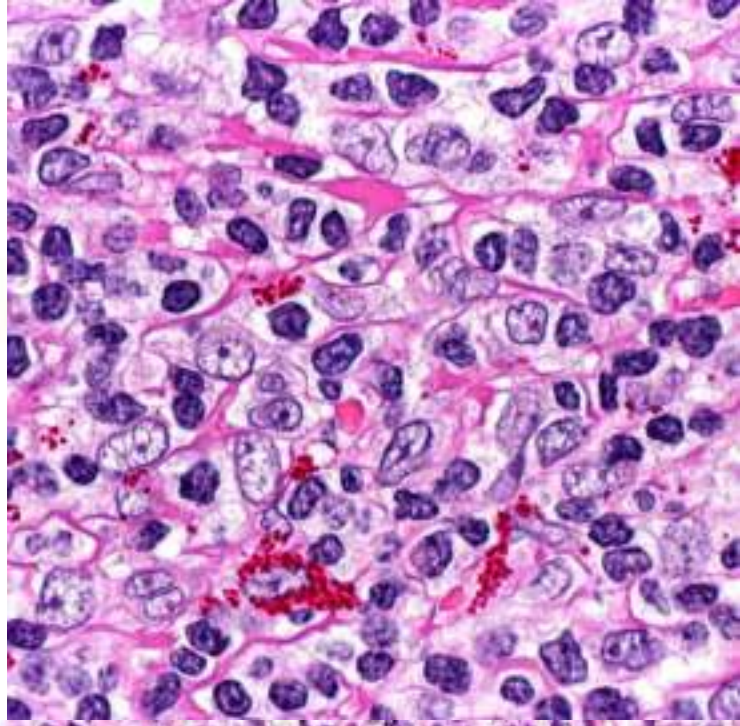
Milker's nodule



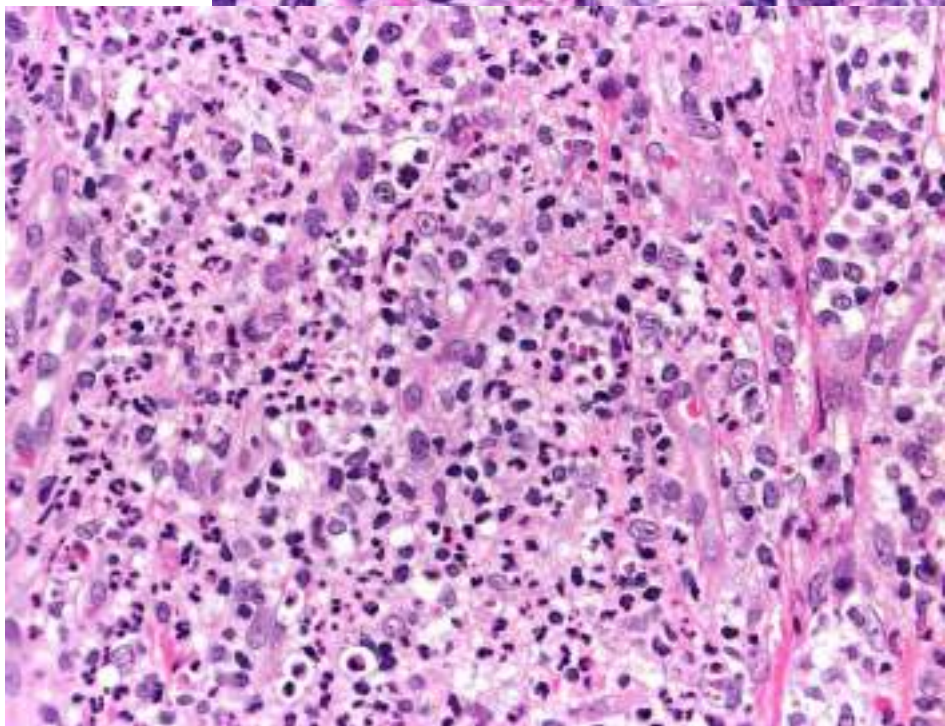




Tattoo

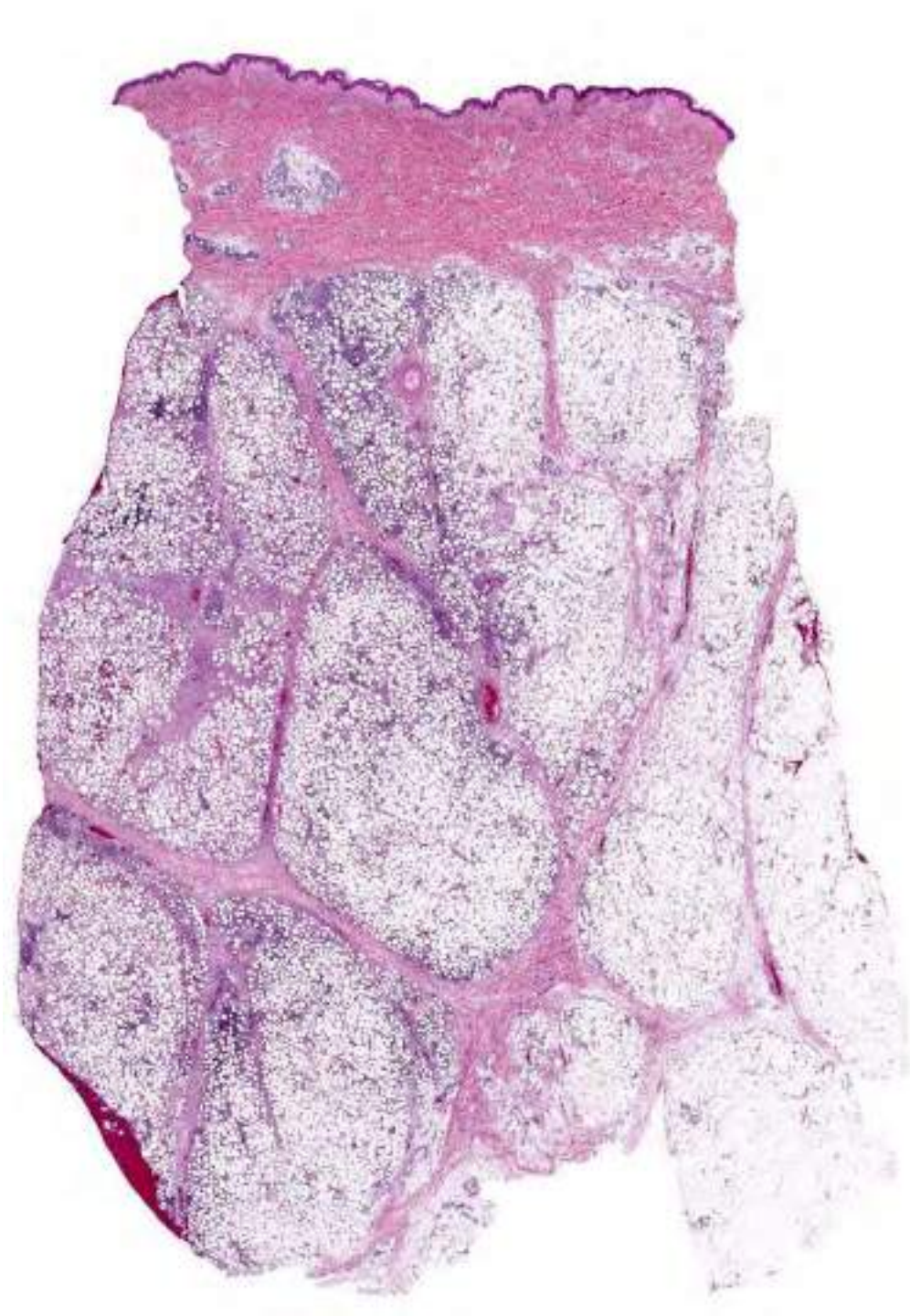


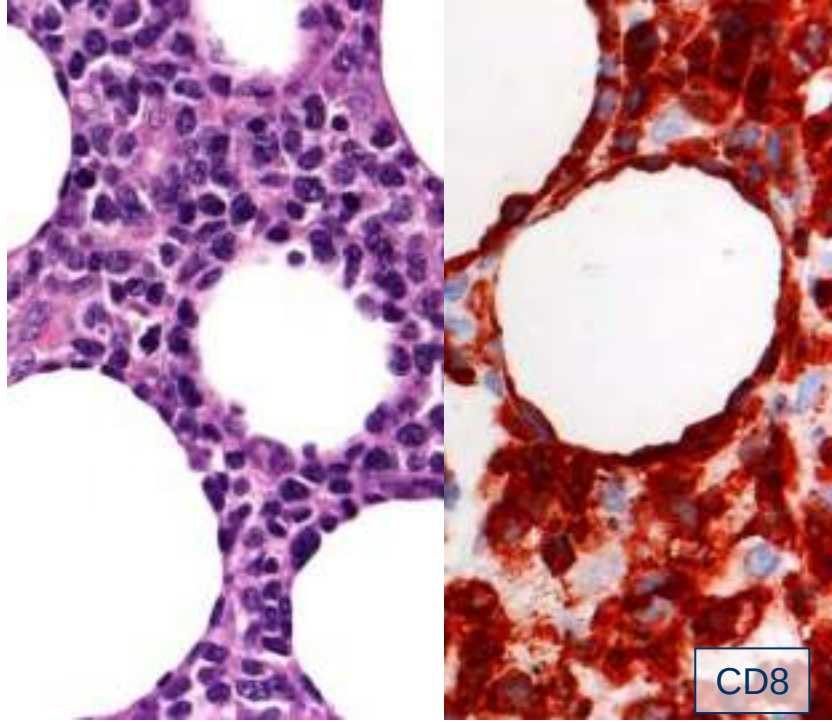
Folliculitis



CD30+ pseudolymphomas – Histopathological clues

- *Arthropod bites with CD30+ cells:* infiltrate wedge-shaped, may resemble LyP type A but limited number of atypical cells; usually no clusters of CD30+ cells; sometimes central scale crust; intracorneal cuniculum in scabies (rare!)
- *Herpes infections:* necrotic keratinocytes within epithelial structures (sometimes confined to follicles, eccrine coils)
- *Parapox virus:* large areas of haemorrhage, dilated vessels, irregular epithelial hyperplasia with focal areas of necrosis
- *Molluscum contagiosum:* typical molluscum bodies (may be found only in deeper sections!)
- *Drug eruptions with CD30+ cells:* infiltrate superficial, may resemble MF but more "atypical" than early MF



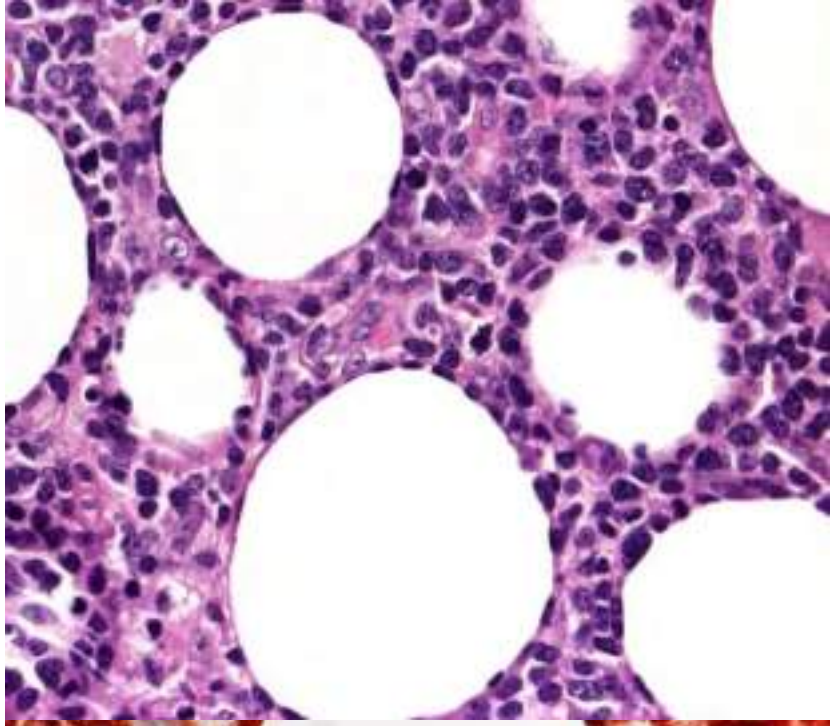


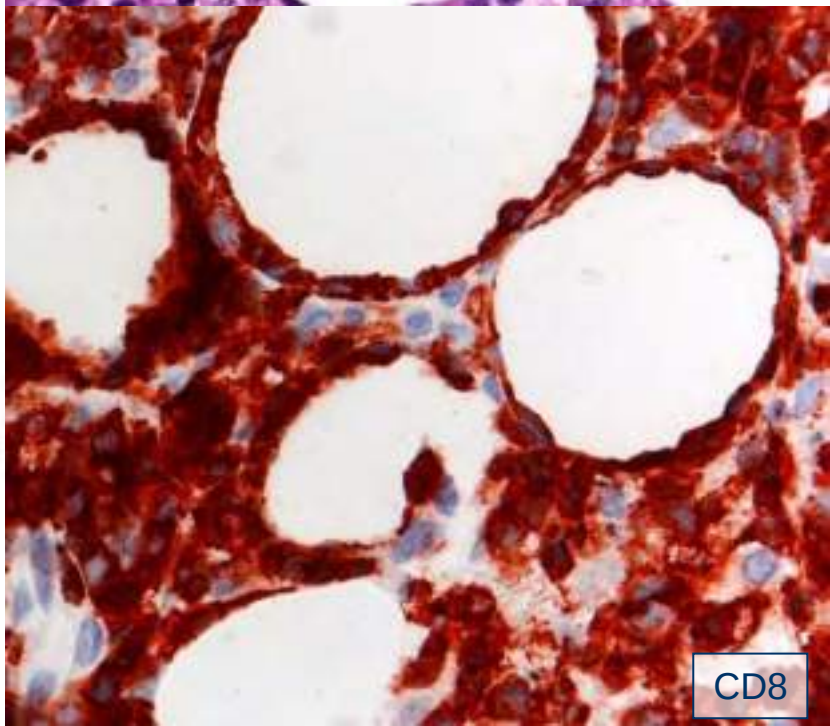
Subcutaneous panniculitis-like T-cell lymphoma

Exclusive involvement of subcutaneous fat (lobular panniculitis-like).

CD3+, CD4–, CD8+, CD56–, TIA1+, ßF1+, TCR γ/δ –; monoclonal TCR genes rearrangement.

Mutations in *HAVCR2Y82C* associated with younger age, development of hemophagocytic lymphohistiocytosis, and short relapse-free survival.




CD8

REGULAR ARTICLE

blood advances

Genetic profiles of subcutaneous panniculitis-like T-cell lymphoma and clinicopathological impact of *HAVCR2* mutations

Jiwon Koh,[1] Inseon Jang,[2] Seungchan Mun,[3-5] Chiwon Lee,[1] Hee Jeong Cha,[6] Young Ha Oh,[7] Jin Man Kim,[8] Jae Ho Han,[9] Jin Ho Paik,[10] Junhun Cho,[11] Young Hyeh Ko,[12] Chan-Sik Park,[13] Heounjeong Go,[14] Joongyung Huh,[15] Kwangsoo Kim,[5,16] and Yoon Kyung Jeon[1,4,6]

[1]Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea; [2]Department of Biomedical Research Innovation Medical Technology Research Institute, Seoul National University Hospital, Seoul, Republic of Korea; [3]Seoul National University Cancer Research Institute, Seoul, Republic of Korea; [4]Interdisciplinary Graduate Program in Cancer Biology, Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, Republic of Korea; [6]Department of Pathology, Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, Republic of Korea; [7]Department of Pathology, Hallym University Dan Hospital, Hallym University College of Medicine, Dan, Gyeonggi-do, Republic of Korea; [8]Department of Pathology, College of Medicine, Chungbuk National University, Cheongju, Republic of Korea; [9]Department of Pathology, Ajou University School of Medicine, Suwon, Gyeonggi-do, Republic of Korea; [10]Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Gyeonggi-do, Republic of Korea; [11]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [12]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; and [13]Translational Research, Department of Medicine & Advanced Technology, Seoul National University Hospital, Seoul, Republic of Korea

Key Points

- *HAVCR2*^{Y82C} mutation was found in 51% of SPTCL cases and was associated with younger age, systemic illness, and shorter RFS.
- *HAVCR2*^{Y82C} SPTCLs were enriched in inflammatory signaling and *HAVCR2*^{WT} SPTCLs showed higher CCR4 expression in the microenvironment.

Recent studies identified germline mutations in *HAVCR2* (encoding T-cell immunoglobulin mucin 3) as a genetic factor that predisposes to subcutaneous panniculitis-like T-cell lymphoma (SPTCL). However, the differences between *HAVCR2*-mutated (*HAVCR2*^{MUT}) and *HAVCR2* wild-type (*HAVCR2*^{WT}) SPTCLs remain unclear. A nationwide cohort of 28 patients with SPTCL diagnosed at 8 Korean institutions was established. Whole-exome sequencing and RNA-sequencing were performed on 8 patients in the discovery set. In the validation set, targeted gene sequencing or direct sequencing of *HAVCR2* was performed. Of 49 patients with available *HAVCR2* status, 25 (51.0%) were *HAVCR2*^{MUT}. *HAVCR2*^{MUT} was associated with younger age ($P < .001$), development of hemophagocytic lymphohistiocytosis or hemophagocytic lymphohistiocytosis-like systemic illness ($P < .001$), and short relapse-free survival (RFS) ($P = .025$). Most mutated genes in SPTCLs were involved in immune responses, epigenetic modifications, and cell signaling. Mutations in *UNC13D*, *PIAS3*, and *KMT2D* were more frequent in *HAVCR2*^{MUT} SPTCLs. At the gene expression level, *HAVCR2*^{MUT} SPTCLs were enriched in genes involved in IL-6/JAK-STAT3 signaling and in tumor necrosis factor-α signaling via NF-κB. CCR4 was significantly upregulated in *HAVCR2*^{MUT} SPTCLs both at the messenger RNA level and at the protein level. We established a risk stratification system for SPTCL by integrating clinical and histopathological features, including age and *HAVCR2* mutation status. This risk stratification system was strongly associated with RFS ($P = .030$). In conclusion, the *HAVCR2*^{Y82C} mutation was common in Korean patients with SPTCL and was associated with unique clinicopathological and genetic features. Combining clinicopathological parameters could aid in predicting prognosis for patients with SPTCL.

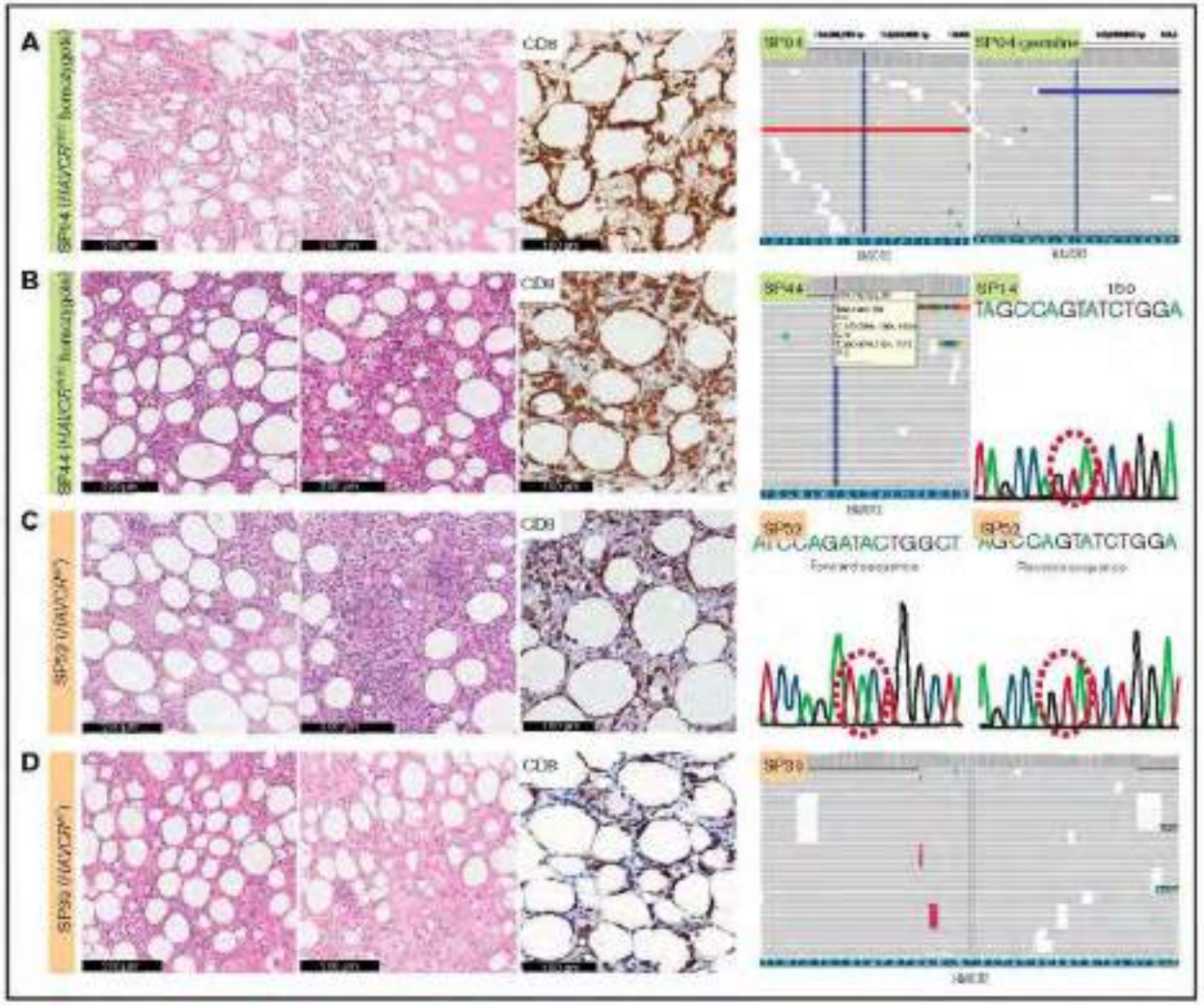
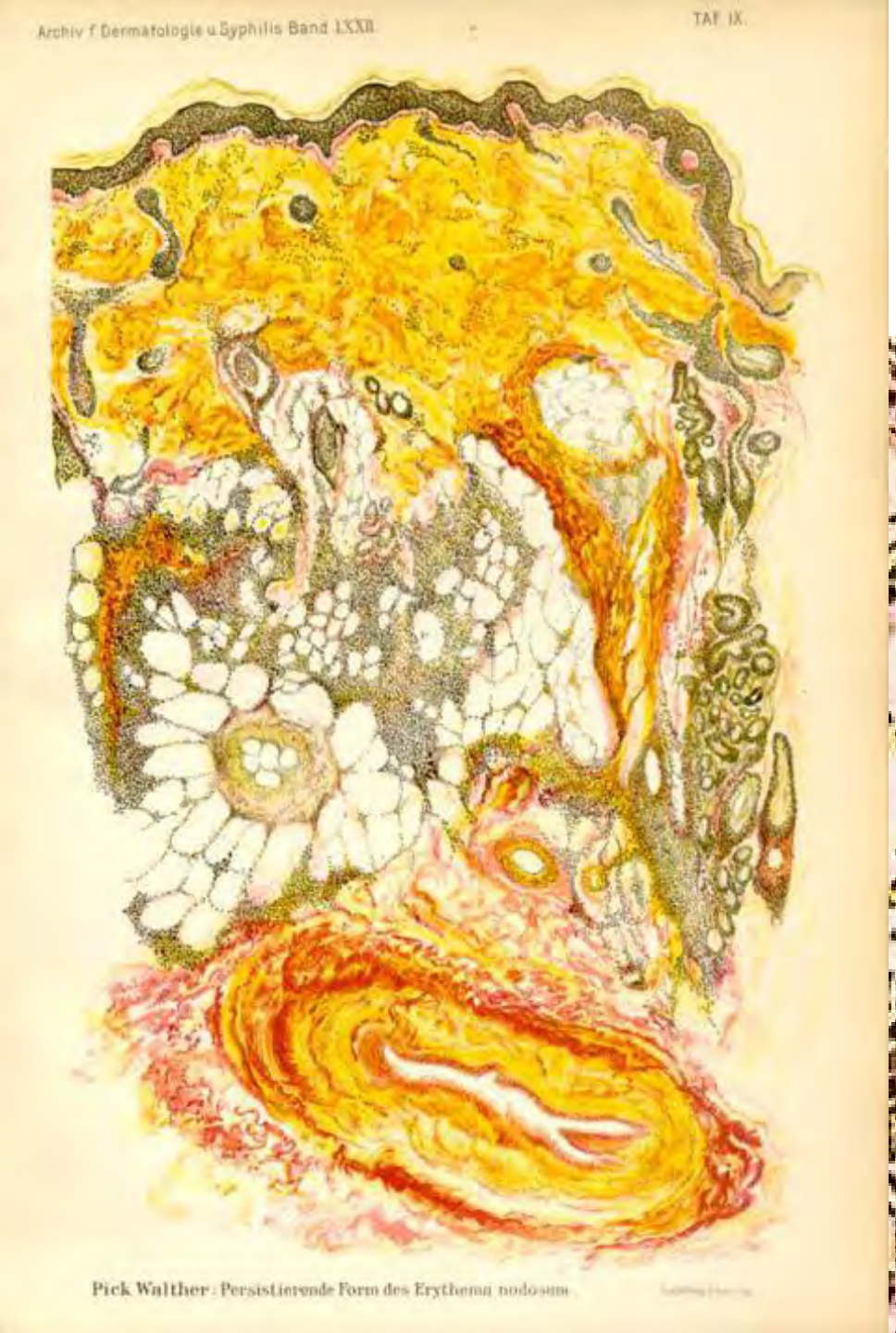
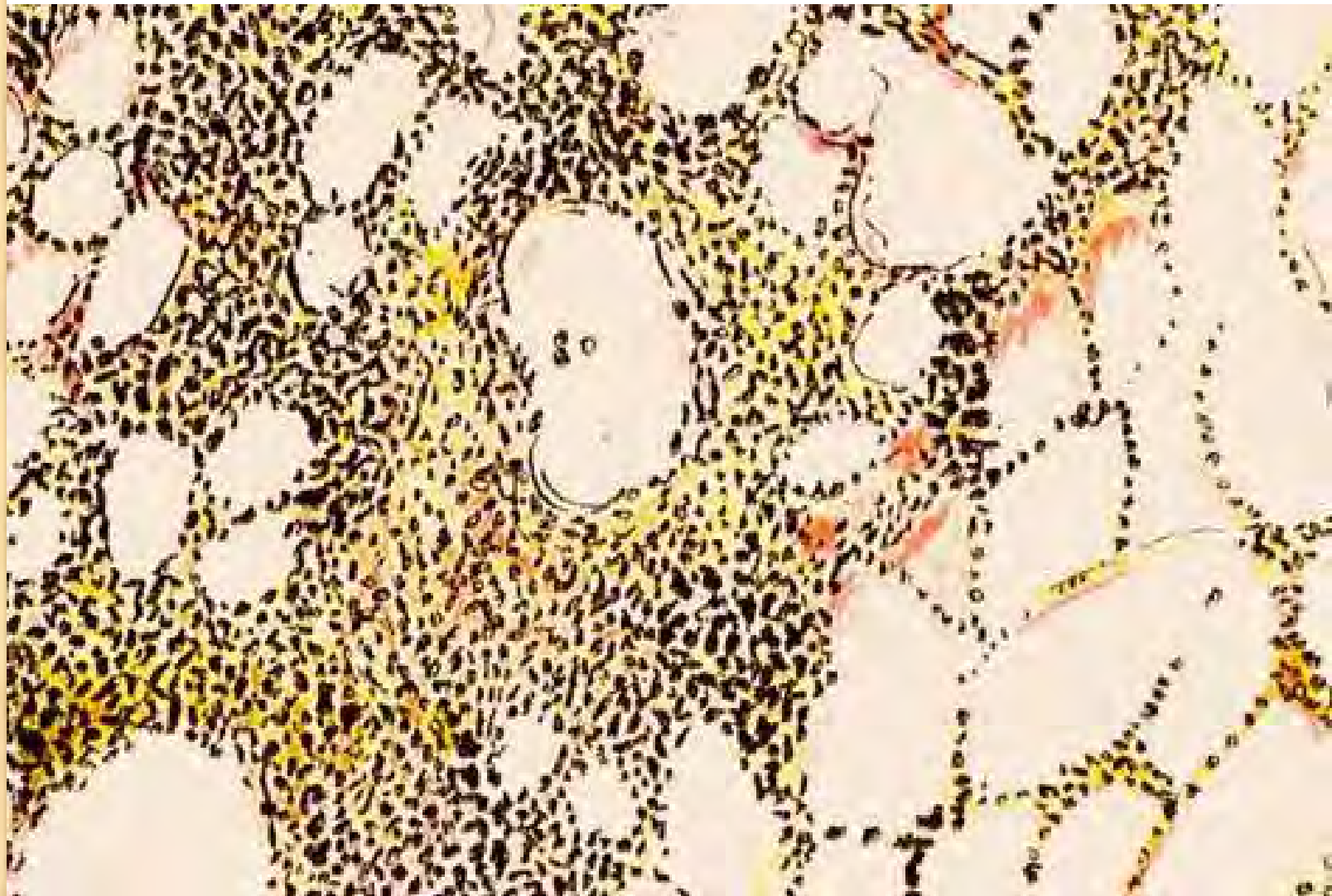


Figure 1. Histopathological features of SPTCLs and detection of *HAVCR2*^{Y82C} mutations. (A) Excisional biopsy specimen of a 19 year old female patient with an SPTCL (SP04) exhibited adipocytic rimming by CD8-positive lymphocytes along with prominent necrosis. This patient was confirmed by using WES to have a germline homozygous *HAVCR2*^{Y82C} mutation. (B) Lipogranulomatous inflammation was observed in a 64 year old female patient (SP44), and TGS revealed heterozygous *HAVCR2*^{Y82C} mutations. SP14 harbored heterozygous *HAVCR2*^{Y82C} mutations, which could be inferred from double peaks on the electropherogram. (C) A 45 year old female patient (SP52) with the *HAVCR2*^{WT} genotype had both necrosis and granuloma formation. (D) Lipogranulomatous inflammation was observed in the *HAVCR2*^{WT} SPTCL of a 53 year old woman (SP39).

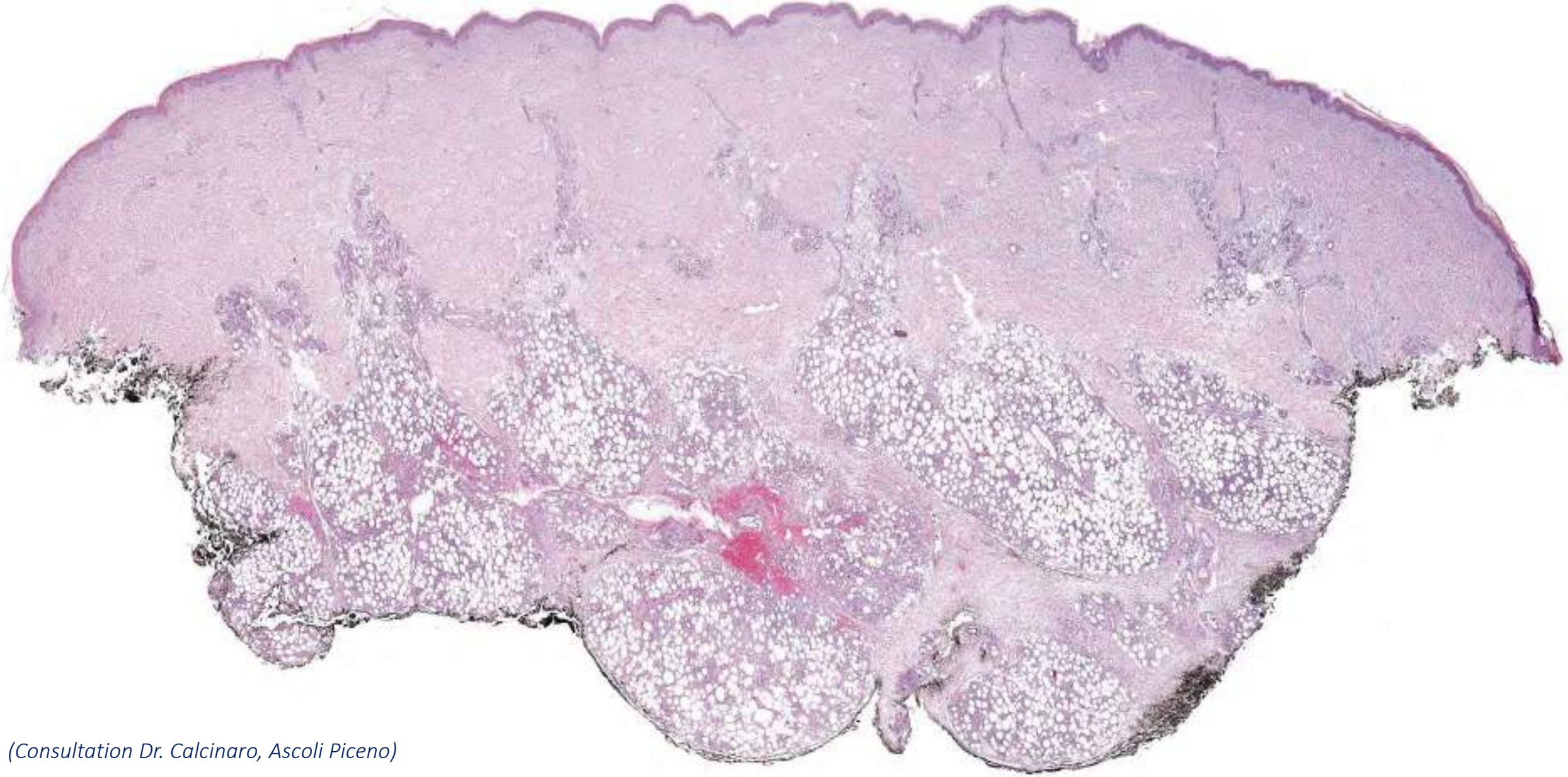
HAVCR2^{Y82C} was associated with younger age, development of hemophagocytic lymphohistiocytosis or hemophagocytic lymphohistiocytosis–like systemic illness, and short relapse-free survival (RFS).



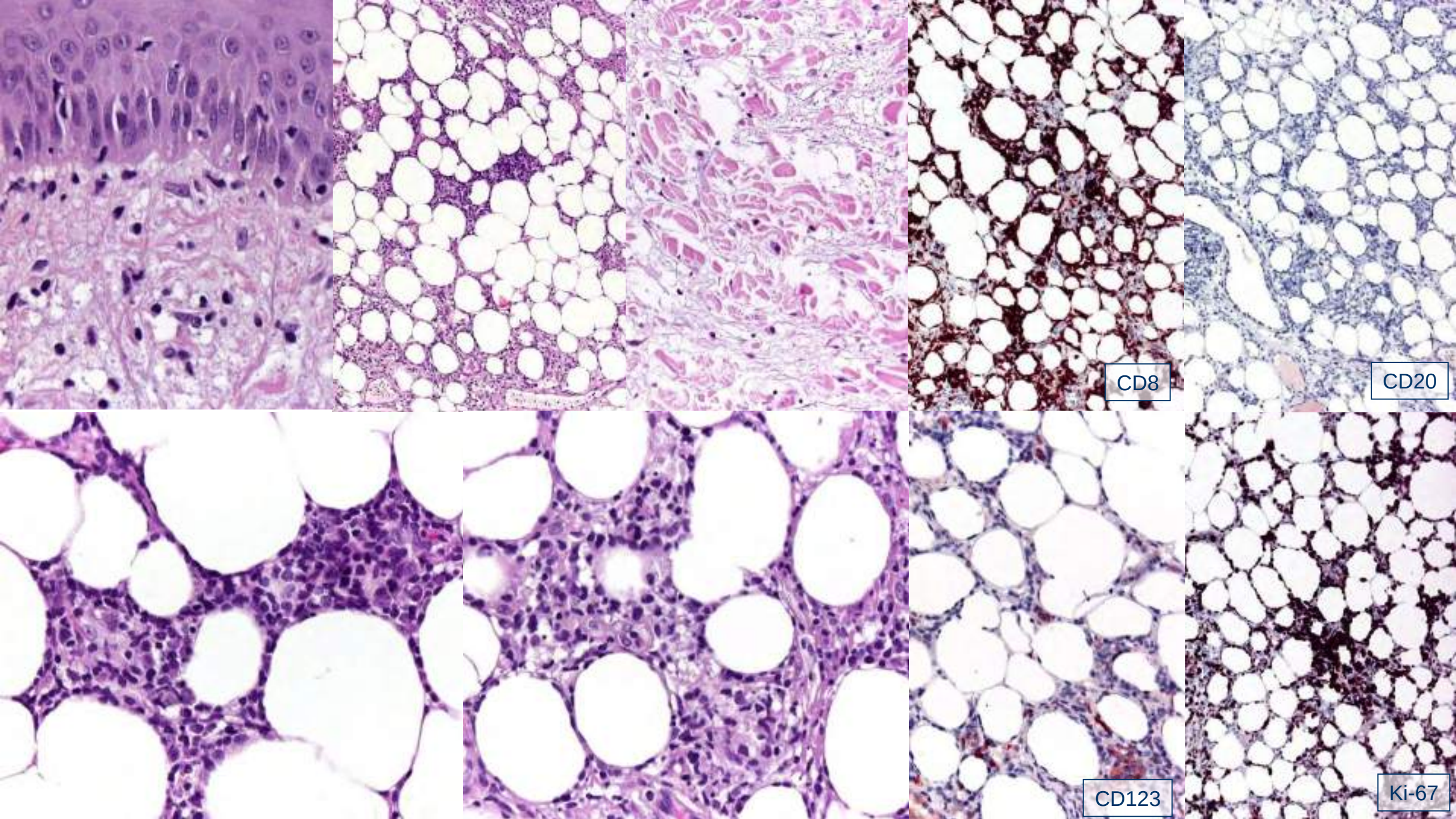
Pick W.
Persistent form of erythema nodosum
Arch Derm Syph 72, 1904



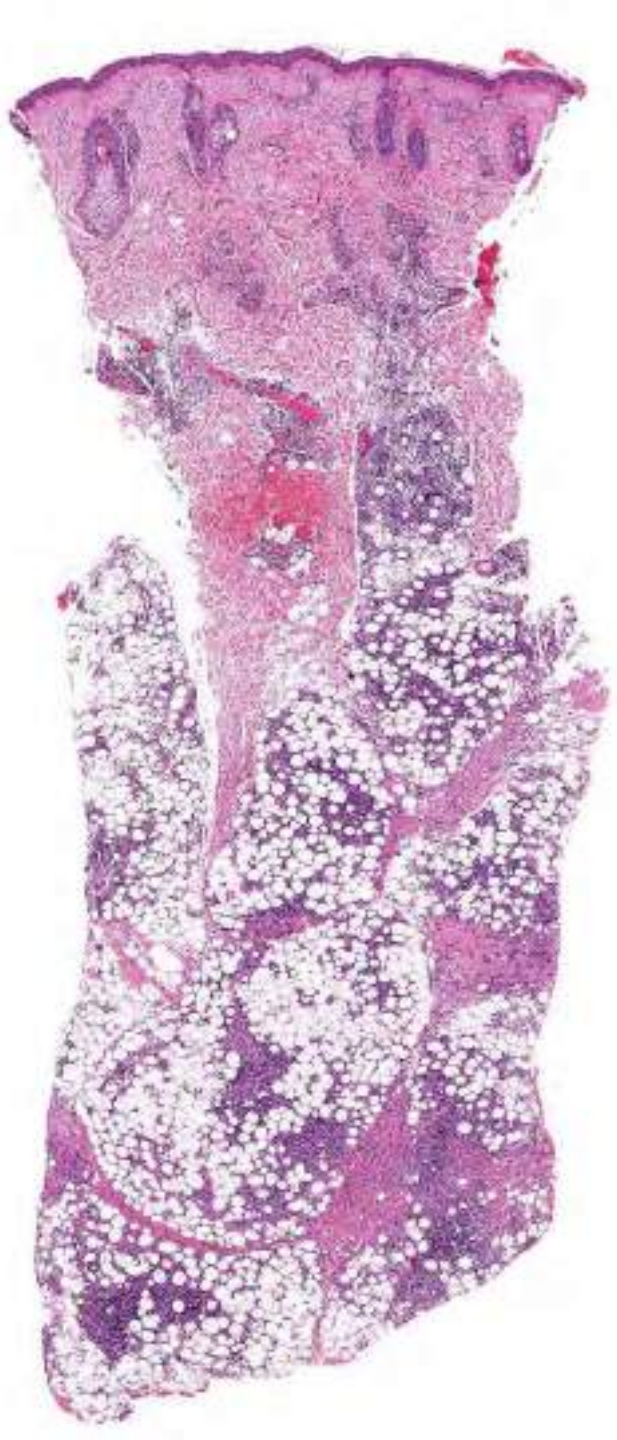
M, 36. Recurrent subcutaneous nodules, some with atrophic scars, for the last 14 years.

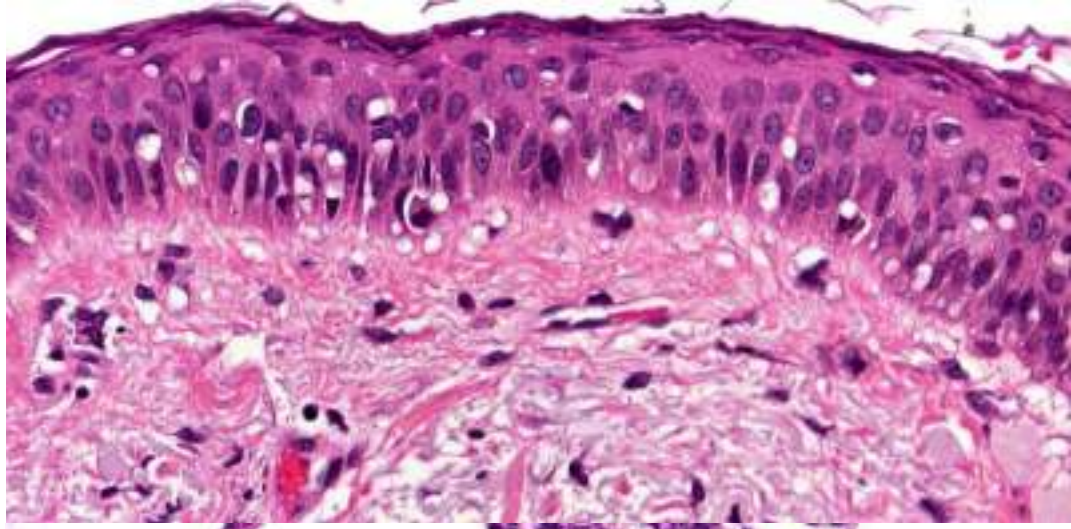


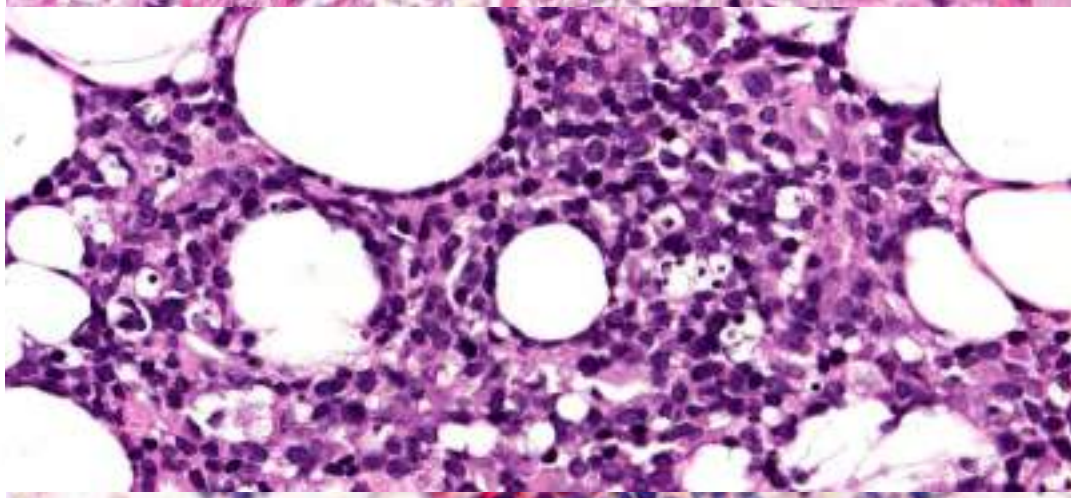
(Consultation Dr. Calcinaro, Ascoli Piceno)

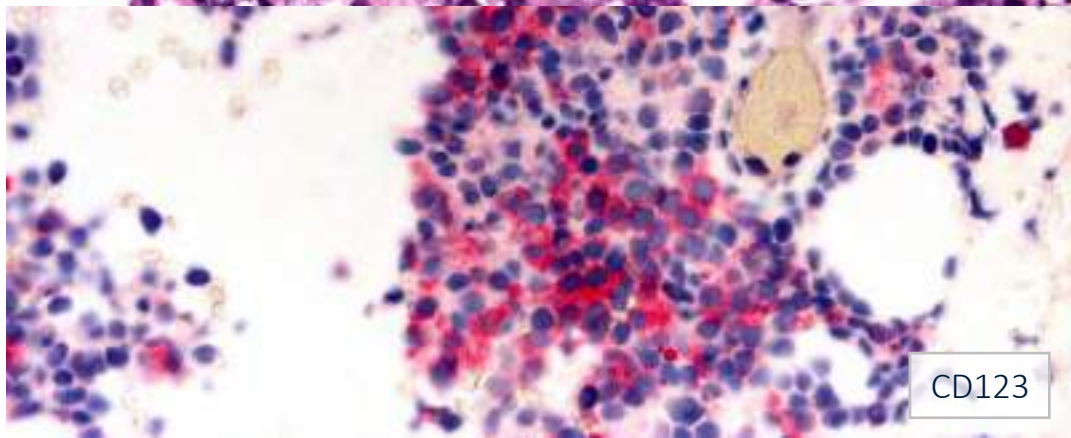

CD8
CD20
CD123
Ki-67

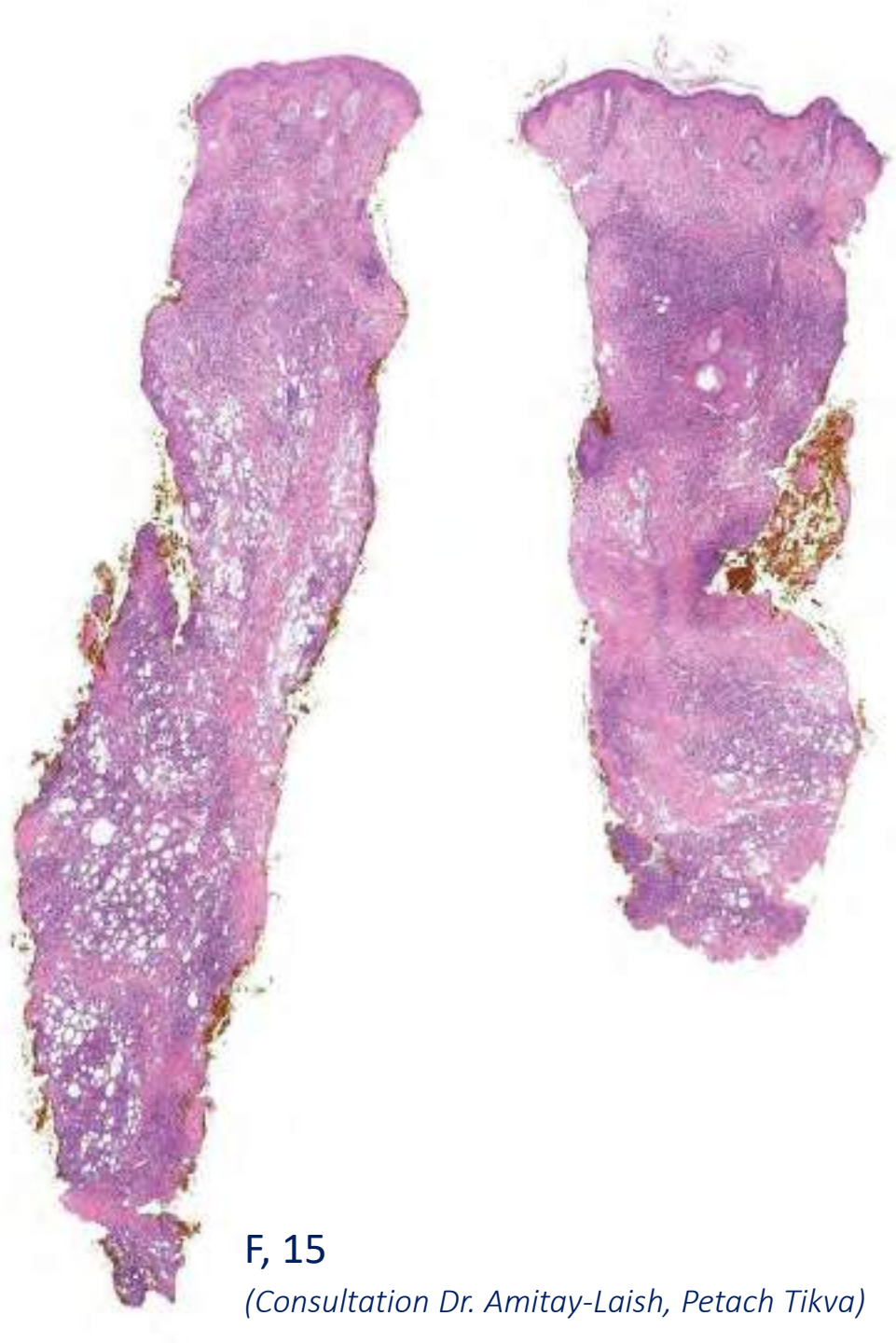
LE panniculitis

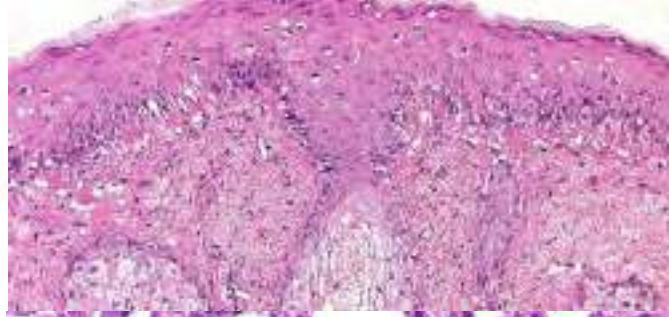


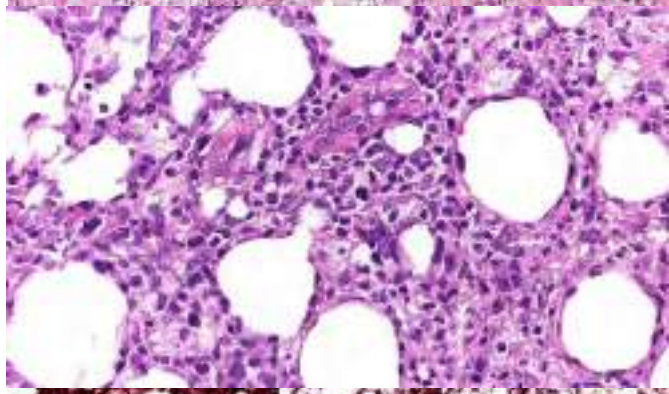


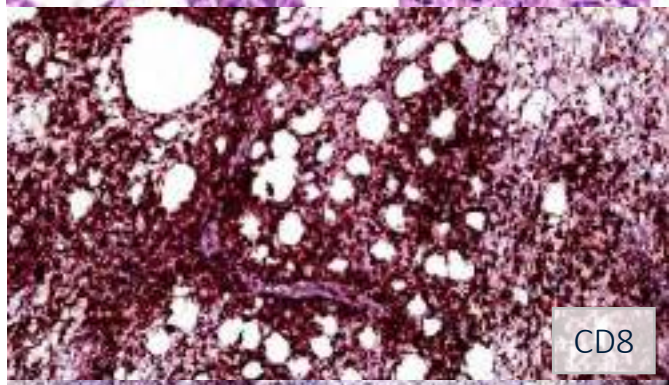


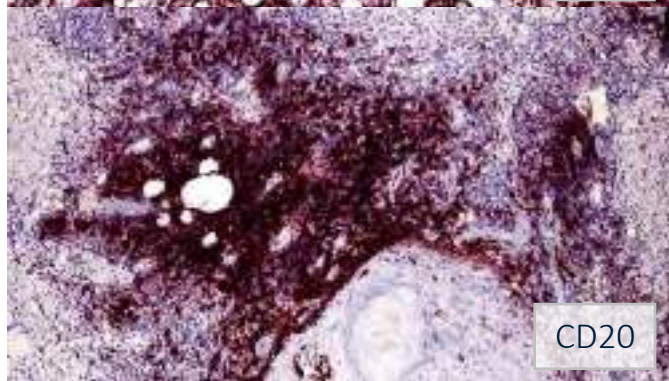

CD123











F, 15

(Consultation Dr. Amitay-Laish, Petach Tikva)

J Cutan Pathol 2005: 32: 396–404
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Lupus erythematosus panniculitis (lupus profundus): Clinical, histopathological, and molecular analysis of nine cases

Cesare Massone[1,2], Kazuo Kodama[1,3], Wolfgang Salmhofer[1], Riichiro Abe[3], Hiroshi Shimizu[3], Aurora Parodi[2], Helmut Kerl[1] and Lorenzo Cerroni[1]

[1]Department of Dermatology, Medical University of Graz, Graz, Austria,
[2]DiSEM, Section of Dermatology, University of Genoa, Genoa, Italy, and
[3]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background: The diagnosis of lupus erythematosus panniculitis (LEP) may be very difficult in cases in which involvement of the subcutaneous fat is the only manifestation of the disease. The main differential diagnosis is subcutaneous panniculitis-like T-cell lymphoma (SPTCL).
Methods: We performed a retrospective study reviewing the histopathologic features of 11 biopsy specimens from nine patients with LEP (M : F = 2 : 7; median age: 48 years; range: 20–71 years).
Results: Histopathologically, all biopsies revealed a lobular panniculitis, with concomitant septal involvement in 82% of them. Dermal changes included the presence of superficial and deep infiltrates (82%) and mucin deposition (73%). The majority of cases (73%) presented also some form of epidermal involvement. The subcutaneous infiltrate was composed of lymphocytes in all cases, admixed with plasma cells in 91% of cases. Lymphoid follicles with reactive germinal centers were detected in 45% of cases. Immunohistochemistry showed a predominance of α/β-T-helper and cytotoxic lymphocytes in 80% of cases admixed with B lymphocytes. The polymerase chain reaction analysis of the T-cell receptor (TCR)-γ gene showed a polyclonal smear in all cases.
Conclusions: Our study shows that the most useful histopathologic criteria for distinguishing LEP from SPTCL are the presence of involvement of the epidermis, lymphoid follicles with reactive germinal centers, mixed cell infiltrate with prominent plasma cells, clusters of B lymphocytes, and polyclonal TCR-γ gene rearrangement.

Massone C, Kodama K, Salmhofer W, Abe R, Shimizu H, Parodi A, Kerl H, Cerroni L. Lupus erythematosus panniculitis (lupus profundus): Clinical, histopathological, and molecular analysis of nine cases.
J Cutan Pathol 2005; 32: 396–404. © Blackwell Munksgaard 2005.

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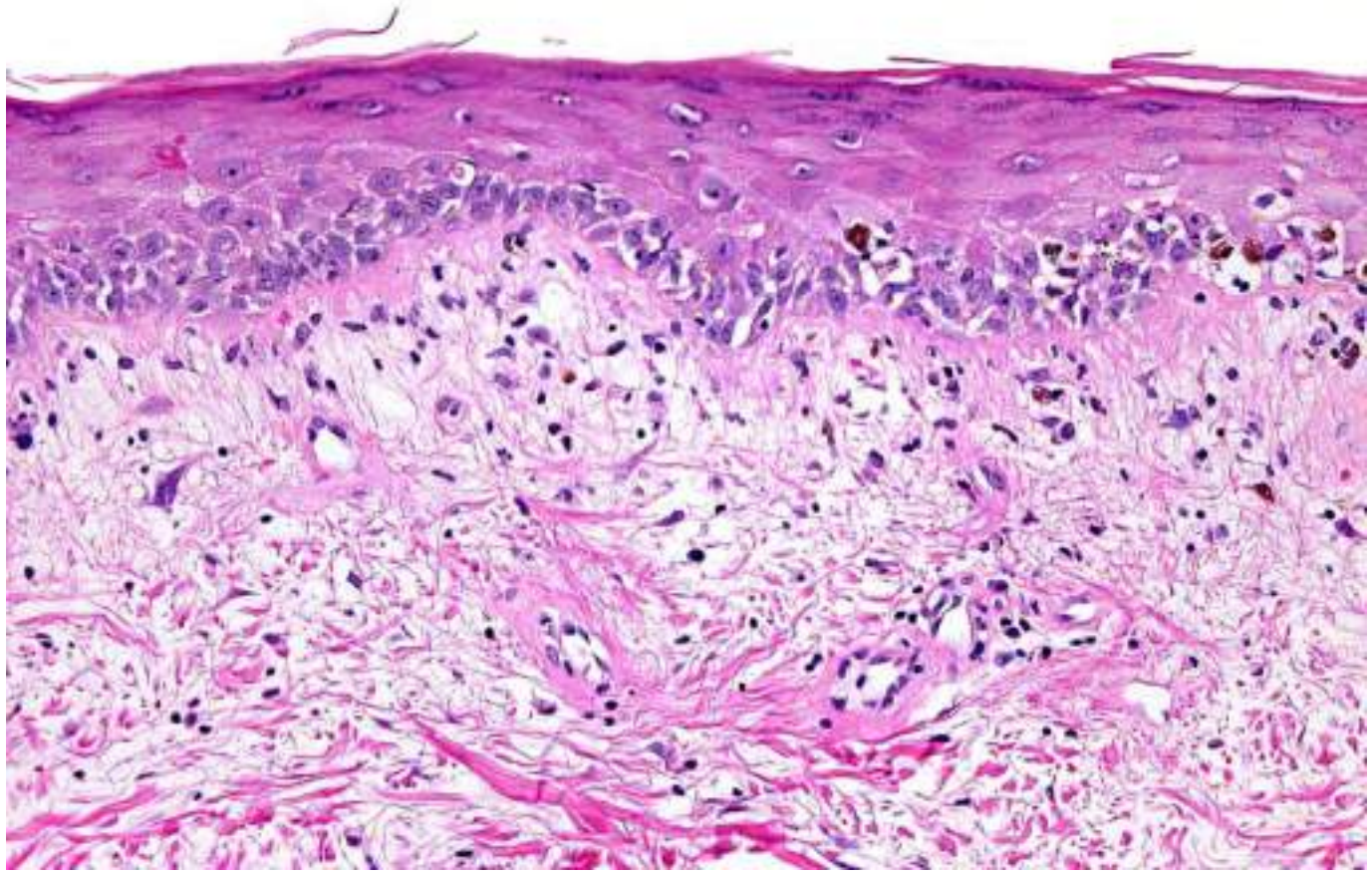
Lupus erythematosus panniculitis (LEP) (lupus profundus) is defined as a specific involvement of the subcutaneous fat in patients with lupus erythematosus (LE). It is a rare manifestation of the disease, occurring approximately in 1–3% of patients with cutaneous LE.[1,2] It may be observed in patients with discoid lupus erythematosus (DLE) or systemic lupus erythematosus (SLE)[3–5] or as an isolated phenomenon without systemic or other cutaneous findings.[3] The diagnosis of LEP may be especially problematic in cases in which the involvement of the subcutaneous fat is the only manifestation of the disease.[6] Especially differentiation from subcutaneous panniculitis-like T-cell lymphoma (SPTCL) may be extremely difficult, and recently, Magro and coworkers[7] suggested that LEP and SPTCL may belong to a spectrum of disease and introduced the term "subcutaneous T-cell lymphoid dyscrasia" to encompass these entities.

We performed a retrospective study on the clinical, histopathologic, and molecular features of nine



Epidermal involvement: 73%

Panniculitis in lupus erythematosus (lupus profundus)

- Patients with cLE may show prominent involvement of the subcutaneous fat (lupus profundus)
- May be concomitant to more conventional lesions of cLE (particularly CDLE but also SLE)
- The overlying skin may show features of cLE
- Histopathologically, pattern of a mainly lobular panniculitis with variable involvement of the septae ("mixed panniculitis") and with hyaline necrosis of the fat lobules
- Distinction from SPTCL is traditionally considered difficult; some biopsies show overlapping histopathological features of the two entities

Subcutaneous Panniculitis-Like T-Cell Lymphoma Versus Lupus Erythematosus Panniculitis: Distinction by Means of the Periadipocytic Cell Proliferation Index

Panitia Sathirannawin, MD, Pawadee Pattanaprichakul, MD,† Jitsupa Treetipsatit, MD,* Tawatchai Pongpruttipan, MD,* Sanya Sukpanichnant, MD,* Laura B. Placus, MD,‡ and Timothy H. McCalmont, MD‡*

Abstract: The distinction between subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and lupus erythematosus (LE) panniculitis is remarkably challenging. Rimming by lymphocytes with an elevated Ki-67 cell proliferation index has been forwarded as a potential diagnostic finding in biopsies of SPTCL but has not been rigorously compared with biopsies from patients with LE panniculitis. Nineteen and 17 examples of SPTCL and LE panniculitis, respectively, were evaluated for periadipocytic rimming by lymphocytes expressing Ki-67, CD8, and βF1 and the immature associated with LE, including clusters of CD123-positive cells. The identification of periadipocytic rimming using Ki-67, CD8, and βF1 held sensitivity of 79%, 100%, and 89.5% and specificity of 100%, 52.9%, and 88.2%, respectively ($P < 0.01$). CD123-positive cells were in both disorders. LE-like histopathology was commonly encountered in SPTCL. In conclusion, an elevated Ki-67 cell proliferation index with rimming is useful for distinguishing SPTCL from LE panniculitis. Notably, many features of LE panniculitis can also be encountered in SPTCL.

Key Words: subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus panniculitis, periadipocytic rimming, Ki-67 (MIB-1), CD123

(*Am J Dermatopathol* 2018;0:1–3)

INTRODUCTION

Periadipocytic rimming, defined as a string of lymphocytes that encircle individual adipocytes, is considered a significant diagnostic finding but is not a pathognomonic finding in subcutaneous panniculitis-like T-cell lymphoma (SPTCL) because this feature can be seen in other cutaneous lymphomas[1] and in some forms of lymphocytic panniculitis.[2] The distinction between SPTCL and lymphocytic panniculitis, in particular lupus erythematosus (LE) panniculitis, is often challenging. As an illustration of this difficulty, cases with overlapping features of both of these entities have been described.[3–7]

SPTCL is defined by the World Health Organization (WHO)/the European Organization for Research and Treatment of α/β T-c… CD8, C… cases o… CD20-p… stain of … immunity … diagn… edge, th… expres… and LE… by Linn… used to … has also … plasma… discord… both sh… SPTCL …

Case …
Histop…

… protocol at the University of California, San Francisco (UCSF #13-07951).

A search of the pathology files of the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University was performed from January 1999 to December 2009 for cases of SPTCL and LE panniculitis. The study consisted of 19 SPTCL and 17 LE panniculitis specimens retrieved from 18 and 17 patients, respectively.

TABLE 3. Calculated Sensitivity, Specificity, PPV, and PLR of Immunoreagents for Distinction of SPTCL and LE Panniculitis

Immunoreagents	SPTCL (n = 19)	LE (n = 17)	*P*	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	PLR (95% CI)
Ki-67 periadipocytic rimming, n (%)							
Positive	15 (78.9)	0 (0)	<0.001	79 (54.4–94)	100 (80.5–100)	100 (–)	—
Negative	4 (21.1)	17 (100)					
CD8 periadipocytic rimming, n (%)							
Positive	19 (100)	8 (47.1)	<0.001	100 (82.4–100)	52.9 (27.8–77)	70.4 (58.9–79.7)	2.1 (1.3–3.5)
Negative	0 (0)	9 (52.9)					
βF1 periadipocytic rimming, n (%)							
Positive	17 (89.5)	2 (11.8)	<0.001	89.5 (66.9–98.7)	88.2 (63.6–98.5)	89.5 (69.6–96.9)	7.6 (2–28.2)
Negative	2 (10.5)	15 (88.2)					
CD123 positive in clusters, n (%)							
Positive	7 (36.8)	12 (70.6)	0.04	70.6 (44–89.7)	63.2 (38.4–83.7)	63.2 (46.9–76.9)	1.9 (1–3.7)
Negative	12 (63.2)	5 (29.4)					

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The authors declare no conflicts of interest.

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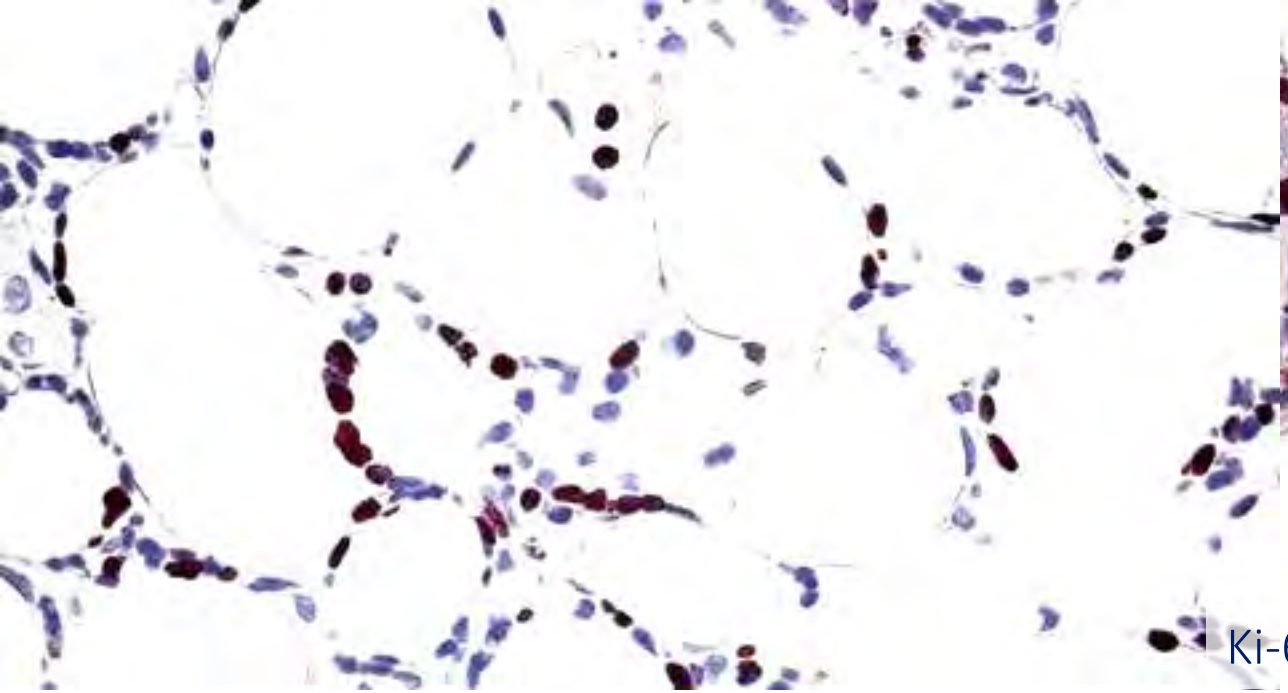
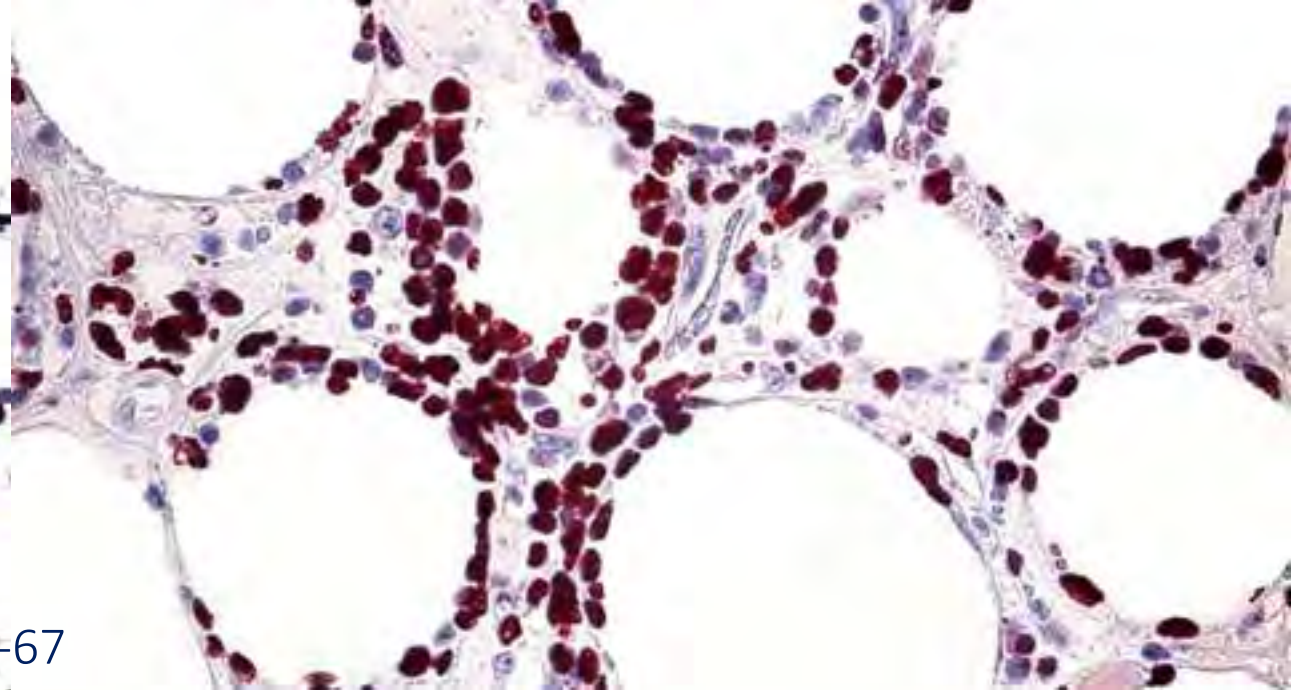
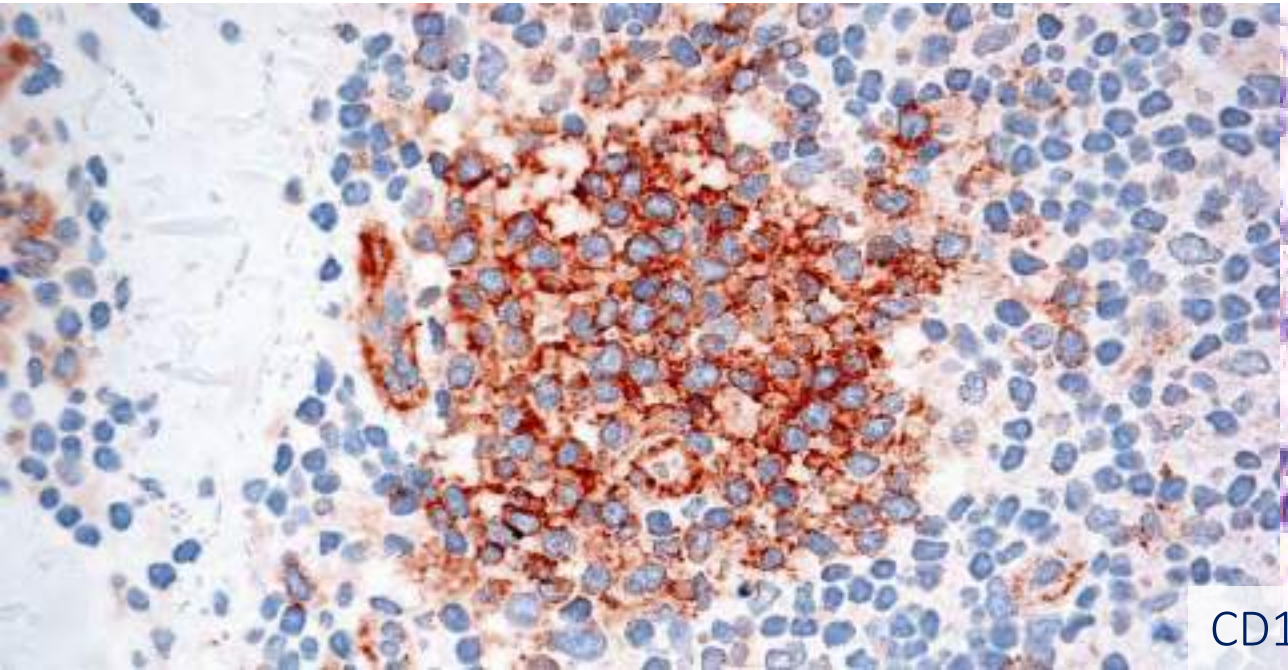


Ki-67

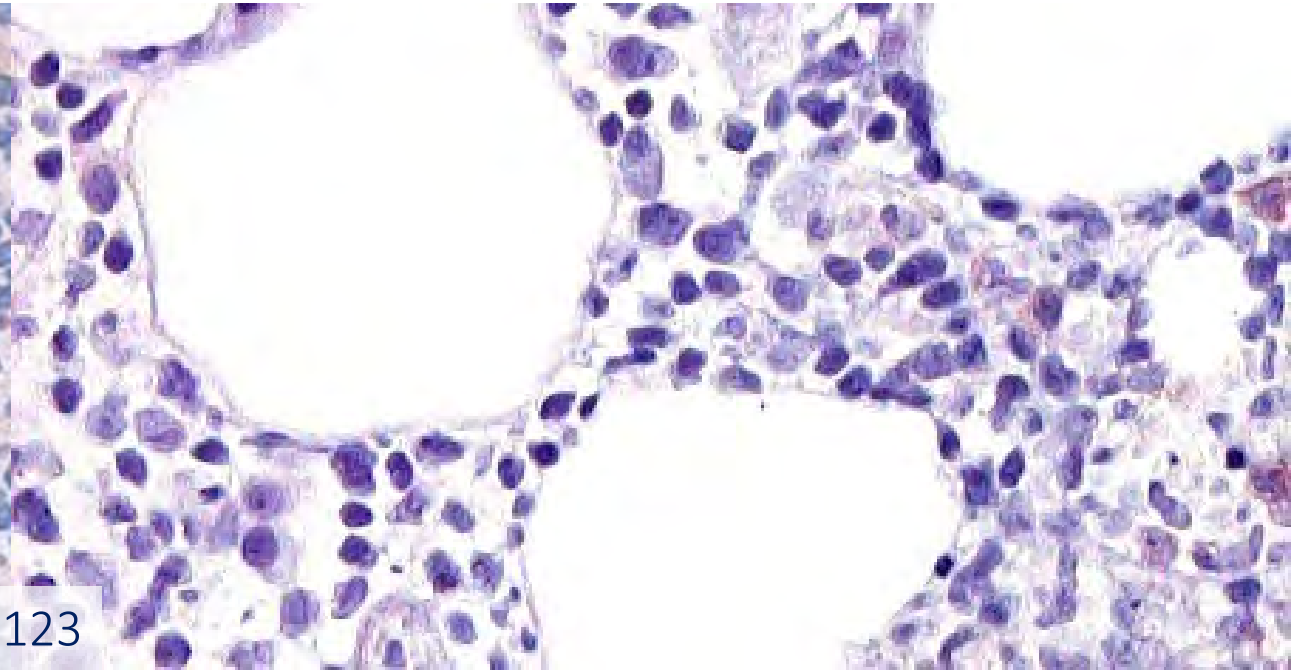


Lupus panniculitis

Subcutaneous panniculitis-like T-cell lymphoma



CD123



Lupus panniculitis

- Mostly lobular paniculitis
- Prominent necrosis
- Nuclear debris, degenerative changes
- Rimming of adipocytes by different cell types
- Nodules of B lymphocytes at the periphery of lobules
- Germinal centers frequent
- Mixed cell infiltrate; plasma cells frequent
- Fibrotic, enlarged septae
- Proliferation (Ki-67) low
- No proliferation "rimming"
- Clusters of CD123+ cells
- TCR: polyclonal

Subcutaneous T-cell lymphoma

- Mostly lobular panniculitis
- Prominent necrosis
- Nuclear debris, degenerative changes
- Rimming of adipocytes by atypical lymphocytes
- B lymphocytes few or absent
- Germinal centers absent
- Monomorphous lymphocytes; clusters of atypical cells
- Septae minimally or not enlarged
- Proliferation (Ki-67) high
- Proliferation "rimming"
- No (or small) clusters of CD123+ cells
- TCR: monoclonal

Subcutaneous Panniculitis-Like T-Cell Lymphoma With Overlapping Clinicopathologic Features of Lupus Erythematosus: Coexistence of 2 Entities?

Laura R. Pincus, MD, Philip E. LeBoit, MD,*† Timothy H. McCalmont, MD,*† Roberto Ricci, MD,‡ Carlo Buzio, MD,§ Lindy P. Fox, MD,* Fergus Oliver, MD,¶ and Lorenzo Cerroni, MD‖*

Abstract: We observed 5 patients with subcutaneous panniculitis-like T-cell lymphoma (SPTCL) who were unusual, in that they also exhibited features of lupus erythematosus (LE). This observation is in keeping with a recent study that reported an increased rate of autoimmune disease, including cutaneous lupus erythematosus (CLE), among patients with SPTCL. In all cases, attributes indicating SPTCL included an infiltrate of lymphocytes with pleomorphic nuclei involving subcutaneous lobules exhibiting a cytotoxic T-cell ($CD3^+CD8^+BF1^+$) immunophenotype. Additionally, a high proliferative rate and a monoclonal T-cell receptor-γ gene rearrangement were observed in most cases. The manifestations of LE in these patients included a spectrum of clinical and histopathological abnormalities. Clinical manifestations of LE included, in some patients, morphologic evidence of lupus erythematosus panniculitis (LEP) with subcutaneous nodules that healed with lipoatrophy on the face. In addition, all the patients exhibited serologic and/or extracutaneous end-organ abnormalities seen in patients with SLE, with 2 patients having sufficient findings to meet American College of Rheumatology criteria for SLE. Histopathological evidence of LE included vacuolar change at the dermal–epidermal interface in 3 patients, 2 of whom also showed interstitial deposition of mucin in the reticular dermis. One of these patients also had findings of LEP in the subcutaneous lobules with clusters of $CD123^+$ B cells partially arranged within germinal centers. In 2 patients in which neither the epidermis nor dermis was available for review, histopathological features of LE included in one patient, a few small clusters of $CD123^+$ plasmacytoid dendritic cells within the adipose tissue and, in the other patient, a positive direct immunofluorescence test (lupus band) on clinically uninvolved and lesional skin. Our study shows that some patients show overlap between SPTCL and LE. We suspect that these patients may suffer from both diseases concomitantly. Furthermore, patients with LE, particularly LEP, should be examined for evolution into SPTCL with biopsy of any subcutaneous lesion that is not typical of LEP. Additionally, screening for cutaneous LE and SLE could be considered in patients with SPTCL.

Key Words: cutaneous T-cell lymphoma, lupus erythematosus, lupus panniculitis, lupus profundus, subcutaneous panniculitis-like T-cell lymphoma

(*Am J Dermatopathol* 2009;31:520–526)

INTRODUCTION

A recent large European Organization for Research and Treatment of Cancer study of 63 patients with subcutaneous panniculitis-like T-cell lymphoma (SPTCL) indicated that 19% had an associated autoimmune disease, including 4 with systemic lupus erythematosus (SLE).[1] We encountered 5 patients in routine practice or in consultation who exhibited typical features of SPTCL but were unusual, in that they also had manifestations of lupus erythematosus (LE). The features of LE included a spectrum of findings from typical clinical cutaneous lesions, to serologic and extracutaneous end-organ abnormalities typical of SLE, to findings of LE seen on histopathological sections from skin biopsies.

Reports addressing a relationship between SPTCL and LE have focused primarily on delineating histopathological and clinical features that distinguish SPTCL from lupus erythematosus panniculitis (LEP).[2–5] Indeed, it can be very challenging to differentiate between SPTCL and LEP on histopathological grounds.[6,7] Microscopically, LEP is typically characterized by a lymphocytic infiltrate within subcutaneous lobules with little septal involvement, fat necrosis, and the presence of histiocytes containing karyorrhectic debris although these features can also be seen in SPTCL. Microscopic findings that can help in distinguish LEP from SPTCL include features typical of cutaneous LE in the epidermis and dermis, including vacuolar change at the dermal–epidermal interface, perifollicular lymphocytic infiltrates, and interstitial deposition of mucin in the reticular dermis. The presence in the subcutis of lymphoid follicles with reactive germinal centers, clusters of B lymphocytes, and a mixed infiltrate with prominent plasma cells also favors LEP.[4] A recently described clue to LEP is presence of clusters of $CD123^+$ plasmacytoid dendritic cells (pDCs) within the subcutaneous lobules and, if present, within the dermal infiltrate,

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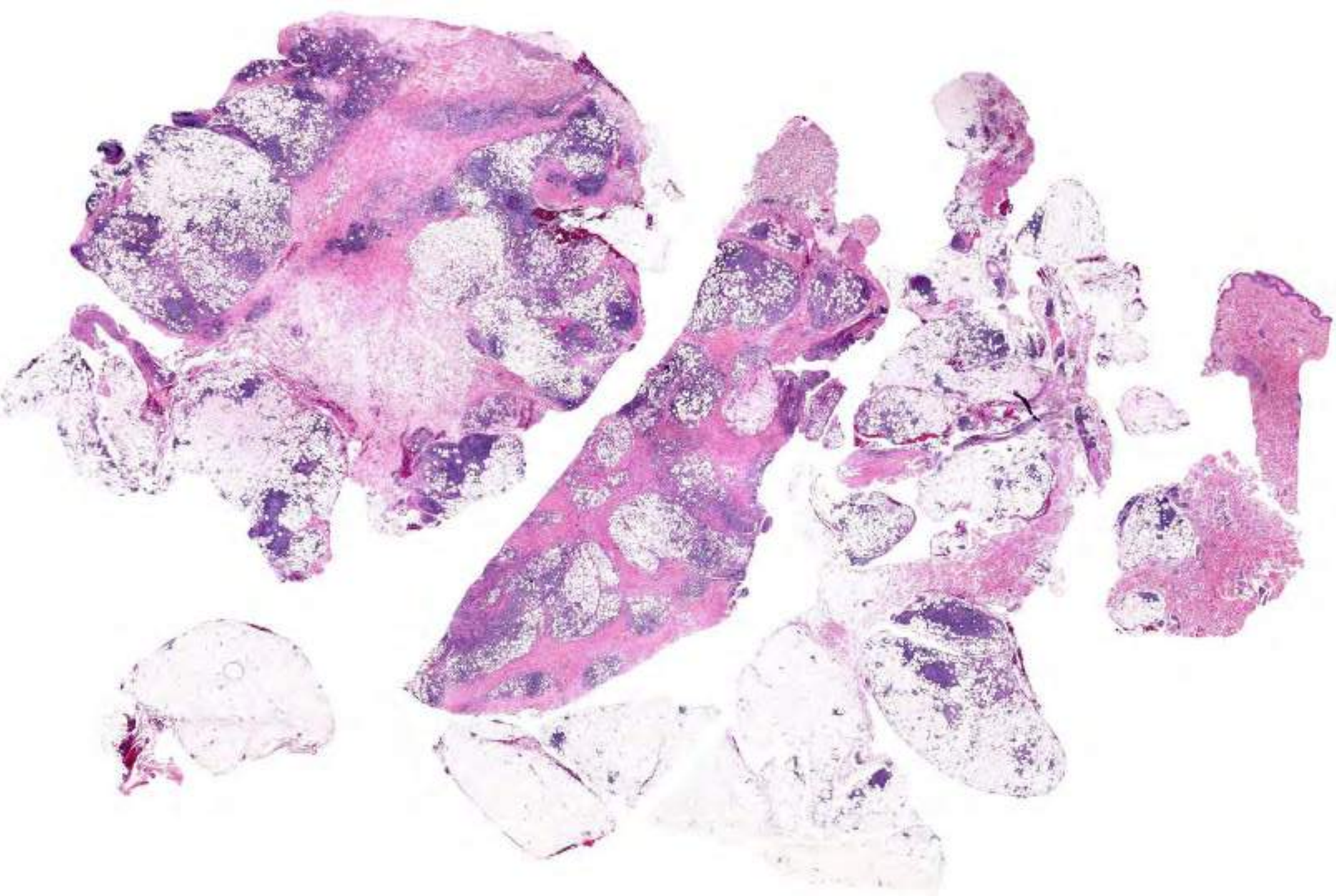
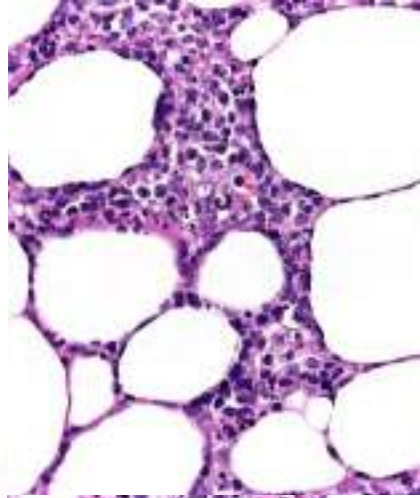
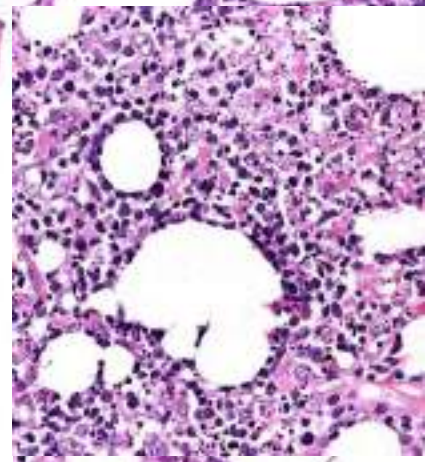
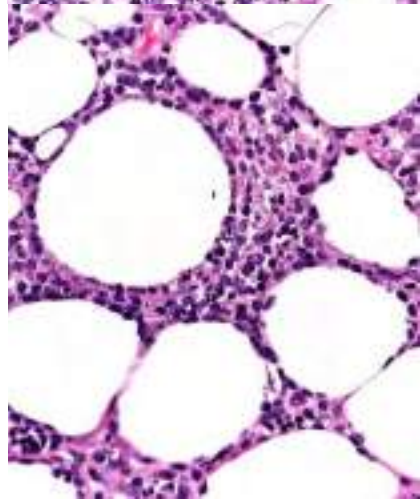
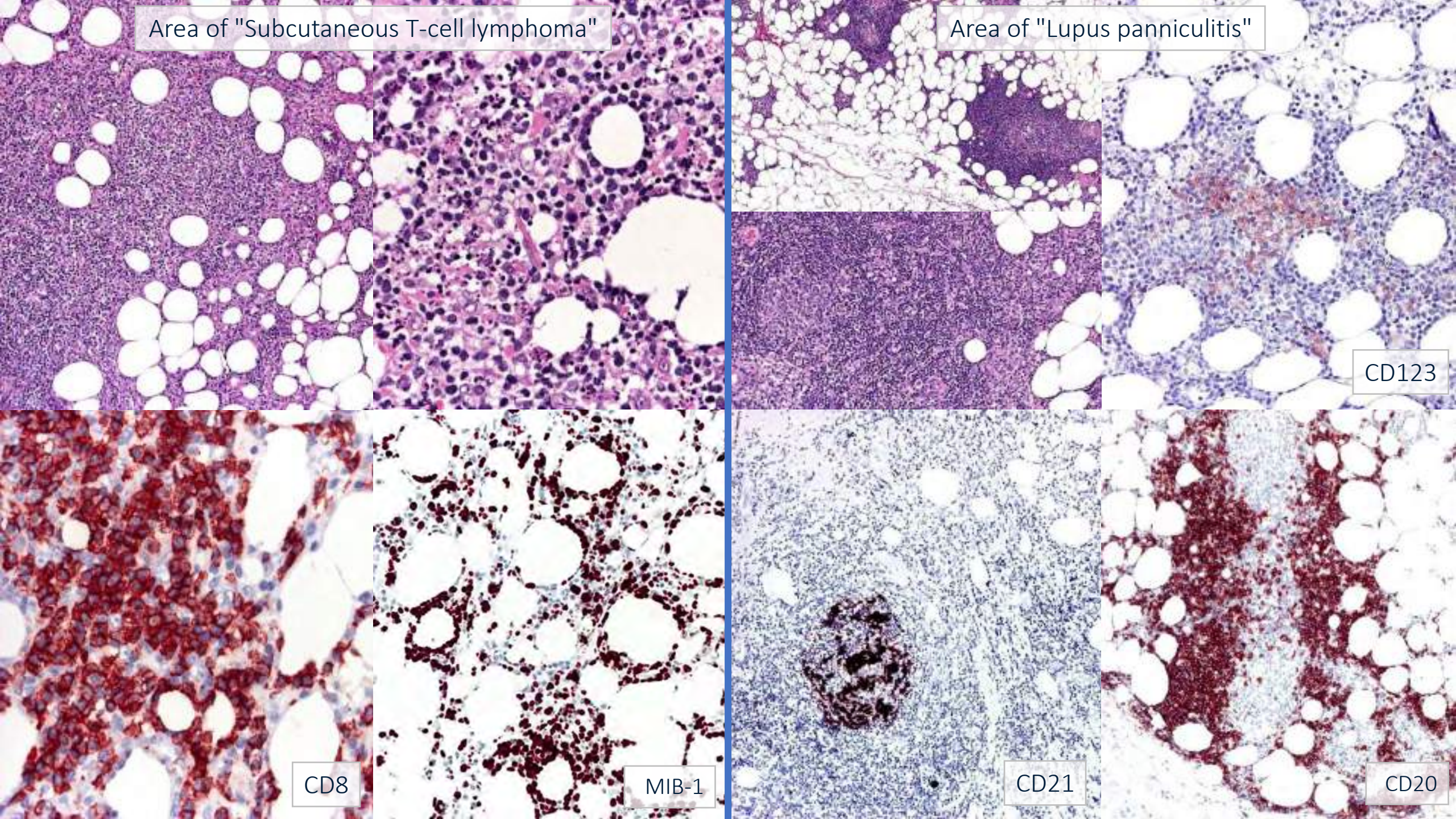
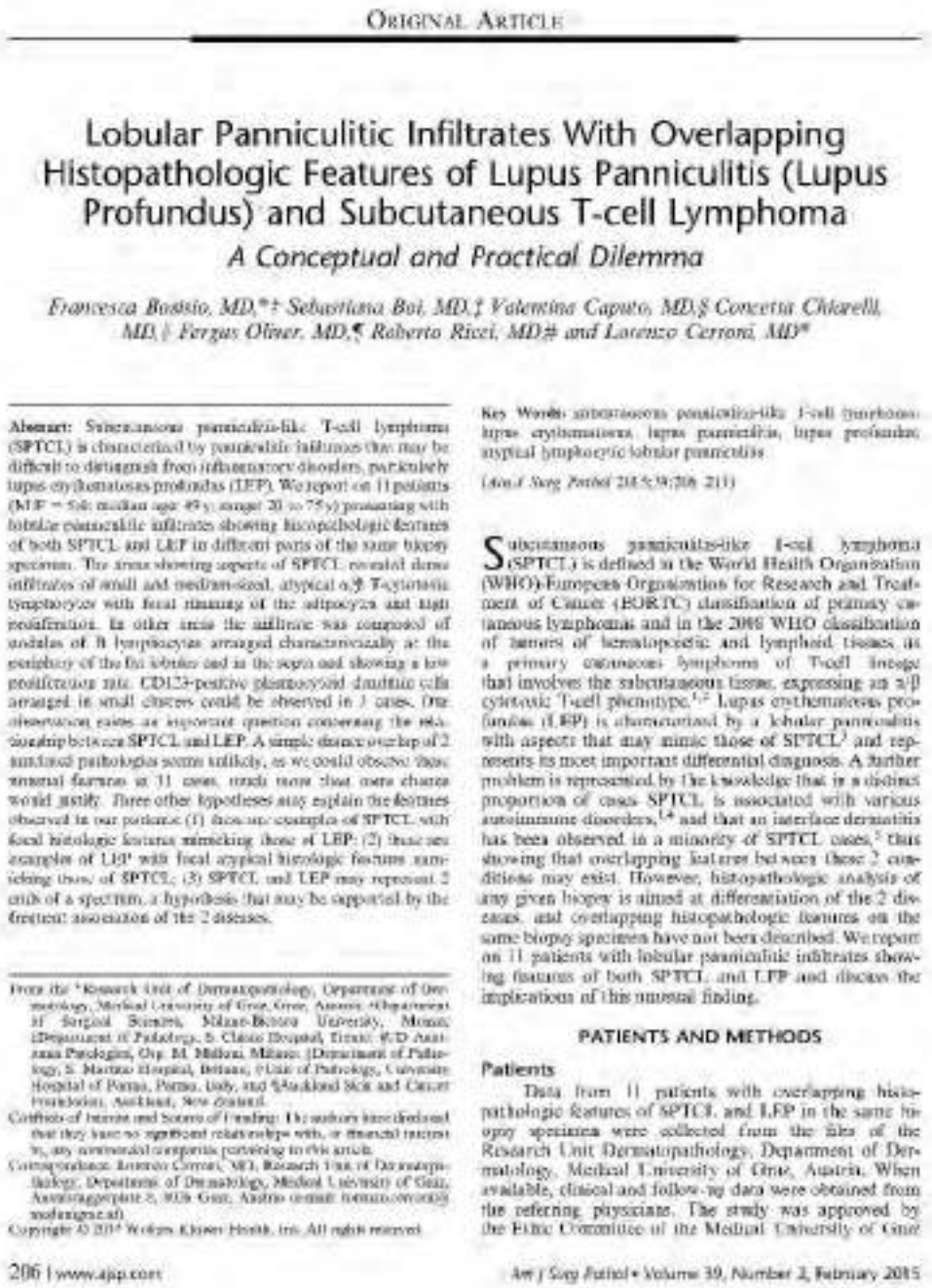
TABLE 1. Patient Data

	Patient				
	1	2	3	4	5
Age at diagnosis of SPTCL (yrs)/sex	52/F	22/M	22/F	20/F	20/F
Age at first presentation of clinical lesions (yrs)	37	20	NA	NA	15
Follow-up (mo)	A− (18): clinical remission after treatment with hydroxychloroquine 200 mg/d and methylprednisolone 1 mg/d	A− (19): clinical remission after treatment with hydroxychloroquine 200 mg/d	D+ (41)	NA	A− (30): clinical remission after treatment with vorinostat and currently on low-dose prednisone
Location/morphology of skin lesions	Extremities and face/ "panniculitis" with evolution in lipoatrophy	Bilateral cheeks/facial swelling with evolution in lipoatrophy	Extremities and face/ "panniculitis" with evolution in lipoatrophy	Extremities/ subcutaneous lesions	Abdomen and extremities/ subcutaneous nodules; focal erosions
Clinical features of LE	Skin lesions eventuated in lipoatrophy involving the face	Skin lesions eventuated in lipoatrophy involving the face	Skin lesions eventuated in lipoatrophy involving the face	dsDNA+	Episodic fevers
	ANA+	Episodic fevers	ANA+ 1:2560		Elevated ESR
	dsDNA+ (titer 1:80)	Lymphadenopathy	dsDNA+		Coombs-positive hemolytic anemia
	Interstitial nephropathy with proteinuria	Anemia	Episodic fevers		IgA nephropathy
	Anemia	Neutropenia	Renal failure requiring dialysis		Bilateral parotitis
	Anti-Ro+ (meets ACR criteria for LE)		Coombs-positive hemolytic anemia (meets ACR criteria for LE)		ASMA + (1:40 titer)
Histopathological features of LE seen in skin biopsies	DIF: junctional deposits of IgM and IgG on clinically uninvolved and lesional skin	A few small clusters of CD123 staining pDCs	Interface dermatitis	Interface dermatitis	Interface dermatitis
				Mucin deposition	Mucin deposition
				Substantial $CD20^+$ B-cell population, partially arranged within germinal centers	DIF: junctional deposits of IgG and C3 on lesional skin

A−, alive without signs of SPTCL; Anti-Ro, Anti-Ro antibodies; ASMA, anti–smooth muscle antibodies; D+, dead of hemophagocytic syndrome with SPTCL; ESR, erythrocyte sedimentation rate; F, female; M, male; NA, not available.


Area of "Subcutaneous T-cell lymphoma"
Area of "Lupus panniculitis"
CD123
CD8
MIB-1
CD21
CD20



ORIGINAL ARTICLE

Lobular Panniculitic Infiltrates With Overlapping Histopathologic Features of Lupus Panniculitis (Lupus Profundus) and Subcutaneous T-cell Lymphoma

A Conceptual and Practical Dilemma

Francesca Bonsito, MD,† Sebastiana Boi, MD,‡ Valentina Caputo, MD,§ Concetta Chiarelli, MD,‖ Fergus Oliver, MD,¶ Roberto Ricci, MD,# and Lorenzo Cerroni, MD**

Abstract: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is characterized by panniculitic infiltrates that may be difficult to distinguish from inflammatory disorders, particularly lupus erythematosus profundus (LEP). We report on 11 patients (M:F = 5:6; median age: 49 y; range: 20 to 75 y) presenting with lobular panniculitic infiltrates showing histopathologic features of both SPTCL and LEP in different parts of the same biopsy specimen. The areas showing aspects of SPTCL revealed dense infiltrates of small and medium-sized, atypical α/β T-cytotoxic lymphocytes with focal rimming of the adipocytes and high proliferation. In other areas the infiltrate was composed of nodules of B lymphocytes arranged characteristically at the periphery of the fat lobules and in the septa and showing a low proliferation rate. CD123-positive plasmacytoid dendritic cells arranged in small clusters could be observed in 3 cases. This observation raises an important question concerning the relationship between SPTCL and LEP. A simple chance overlap of 2 unrelated pathologies seems unlikely, as we could observe these unusual features in 11 cases, much more than mere chance would justify. Three other hypotheses may explain the features observed in our patients: (1) these are examples of SPTCL with focal histologic features mimicking those of LEP; (2) these are examples of LEP with focal atypical histologic features mimicking those of SPTCL; (3) SPTCL and LEP may represent 2 ends of a spectrum, a hypothesis that may be supported by the frequent association of the 2 diseases.

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Key Words: subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus, lupus panniculitis, lupus profundus, atypical lymphocytic lobular panniculitis

(Am J Surg Pathol 2015;39:206–211)

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined in the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas and in the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues as a primary cutaneous lymphoma of T-cell lineage that involves the subcutaneous tissue, expressing an α/β cytotoxic T-cell phenotype.[1,2] Lupus erythematosus profundus (LEP) is characterized by a lobular panniculitis with aspects that may mimic those of SPTCL[3] and represents its most important differential diagnosis. A further problem is represented by the knowledge that in a distinct proportion of cases SPTCL is associated with various autoimmune disorders,[1,4] and that an interface dermatitis has been observed in a minority of SPTCL cases,[5] thus showing that overlapping features between these 2 conditions may exist. However, histopathologic analysis of any given biopsy is aimed at differentiation of the 2 diseases, and overlapping histopathologic features on the same biopsy specimen have not been described. We report on 11 patients with lobular panniculitic infiltrates showing features of both SPTCL and LEP and discuss the implications of this unusual finding.

PATIENTS AND METHODS

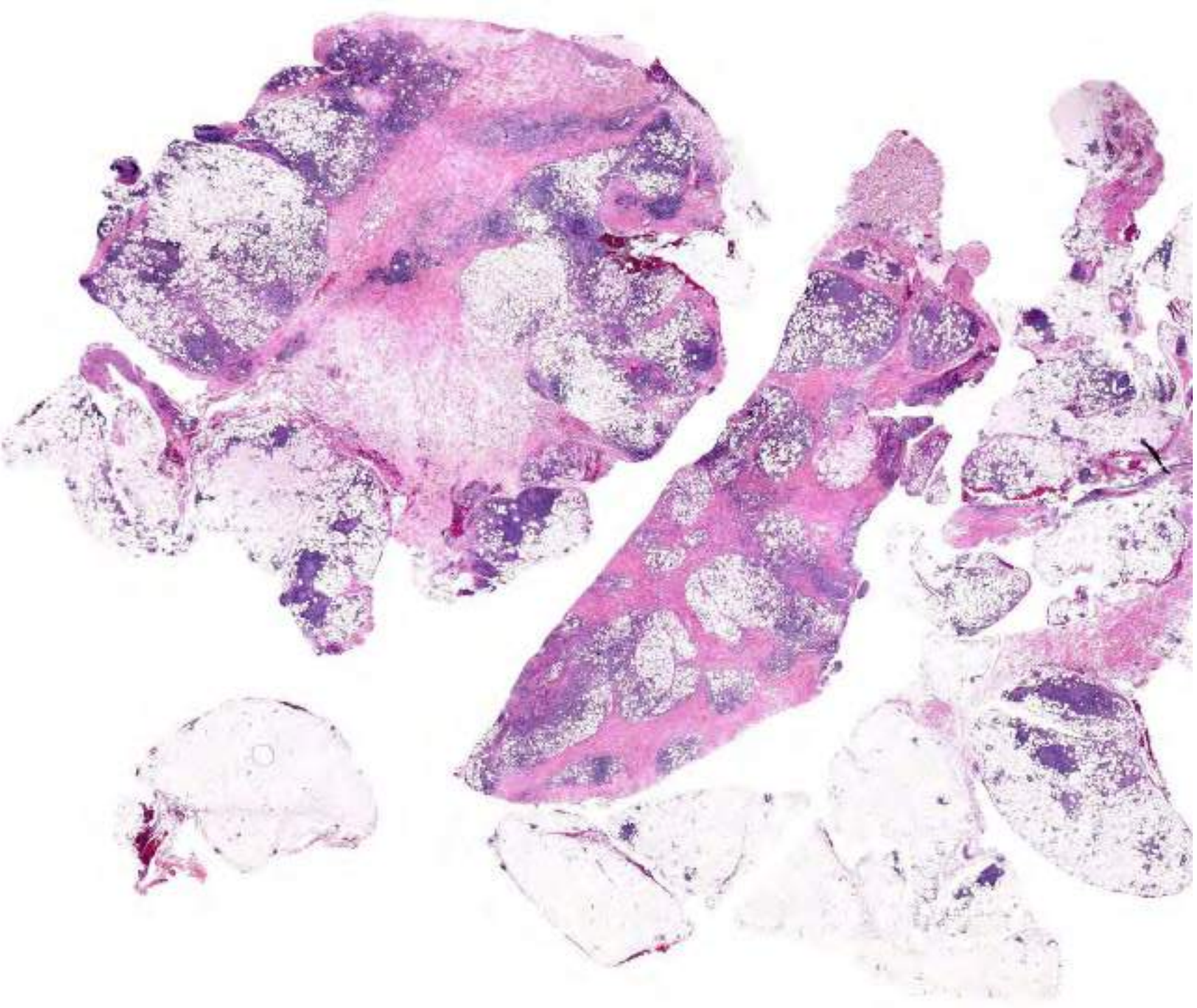
Patients

Data from 11 patients with overlapping histopathologic features of SPTCL and LEP in the same biopsy specimen were collected from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria. When available, clinical and follow-up data were obtained from the referring physicians. The study was approved by the Ethic Committee of the Medical University of Graz

11 patients

(M:F=5:6; median age: 49 y; range: 20 to 75 y)

A simple chance overlap of 2 unrelated pathologies seems unlikely, as we could observe these unusual features in 11 cases, much more than mere chance would justify. Three other hypotheses may explain the features observed in our patients: (1) these are examples of SPTCL with focal histologic features mimicking those of LEP; (2) these are examples of LEP with focal atypical histologic features mimicking those of SPTCL; (3) SPTCL and LEP may represent 2 ends of a spectrum, a hypothesis that may be supported by the frequent association of the 2 diseases.



Overlap SPTCL – LE panniculitis

Large biopsy specimens may show overlapping histopathologic and phenotypic features of both SPTCL and LEP.

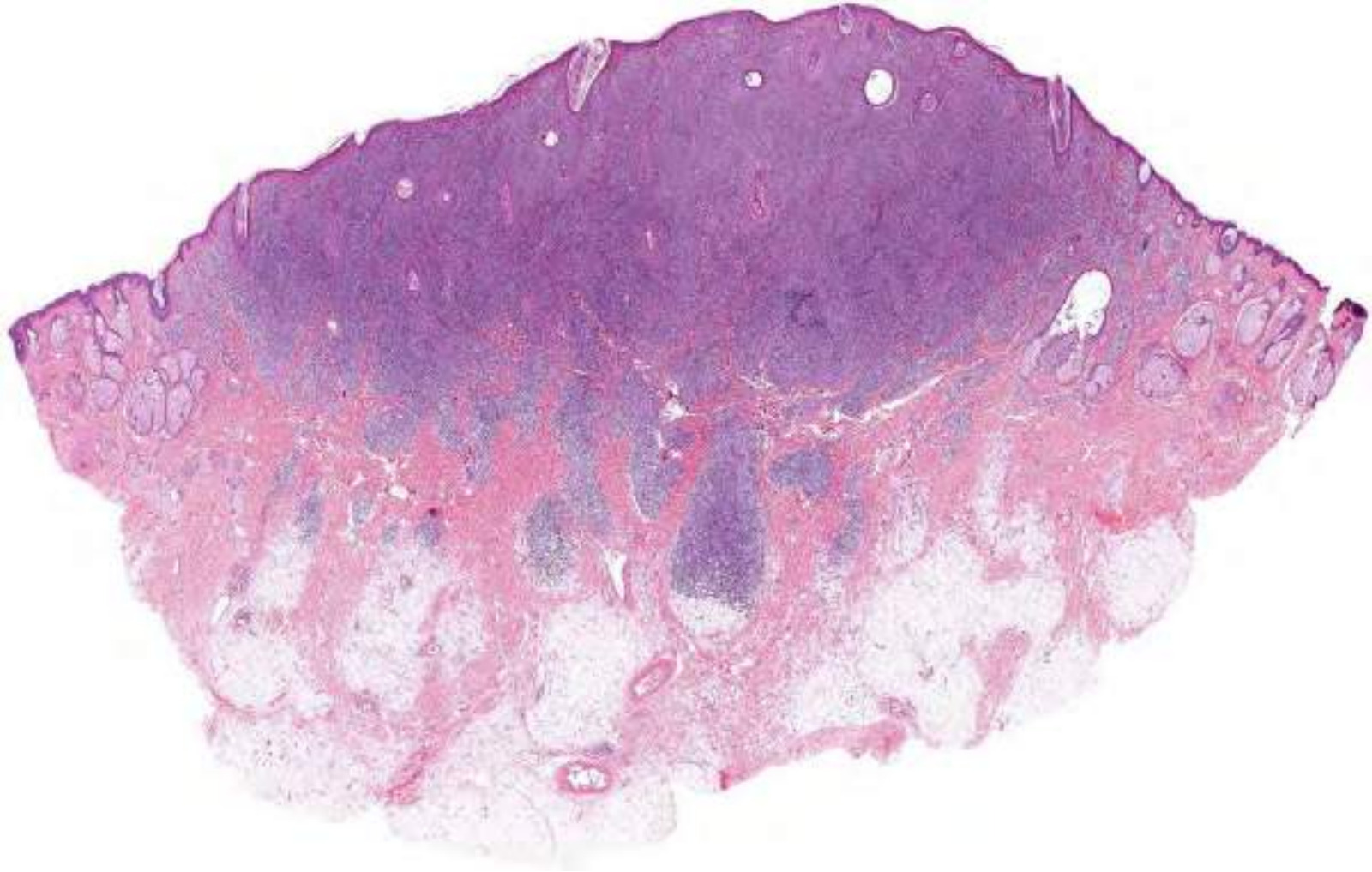
More cases than mere chance would justify.

A proportion of patients with "conventional" SPTCL shows clinical features of LE.

Relationship between the 2 diseases (if any) yet unclear.

May represent cases of "atypical" LEP, or early stages of SPTCL developing in patients with LEP, or SPCTL and LEP may represent to ends of a spectrum.

My current approach: these cases represent examples of "atypical" LE panniculitis and do not progress to clear-cut SPTCL.



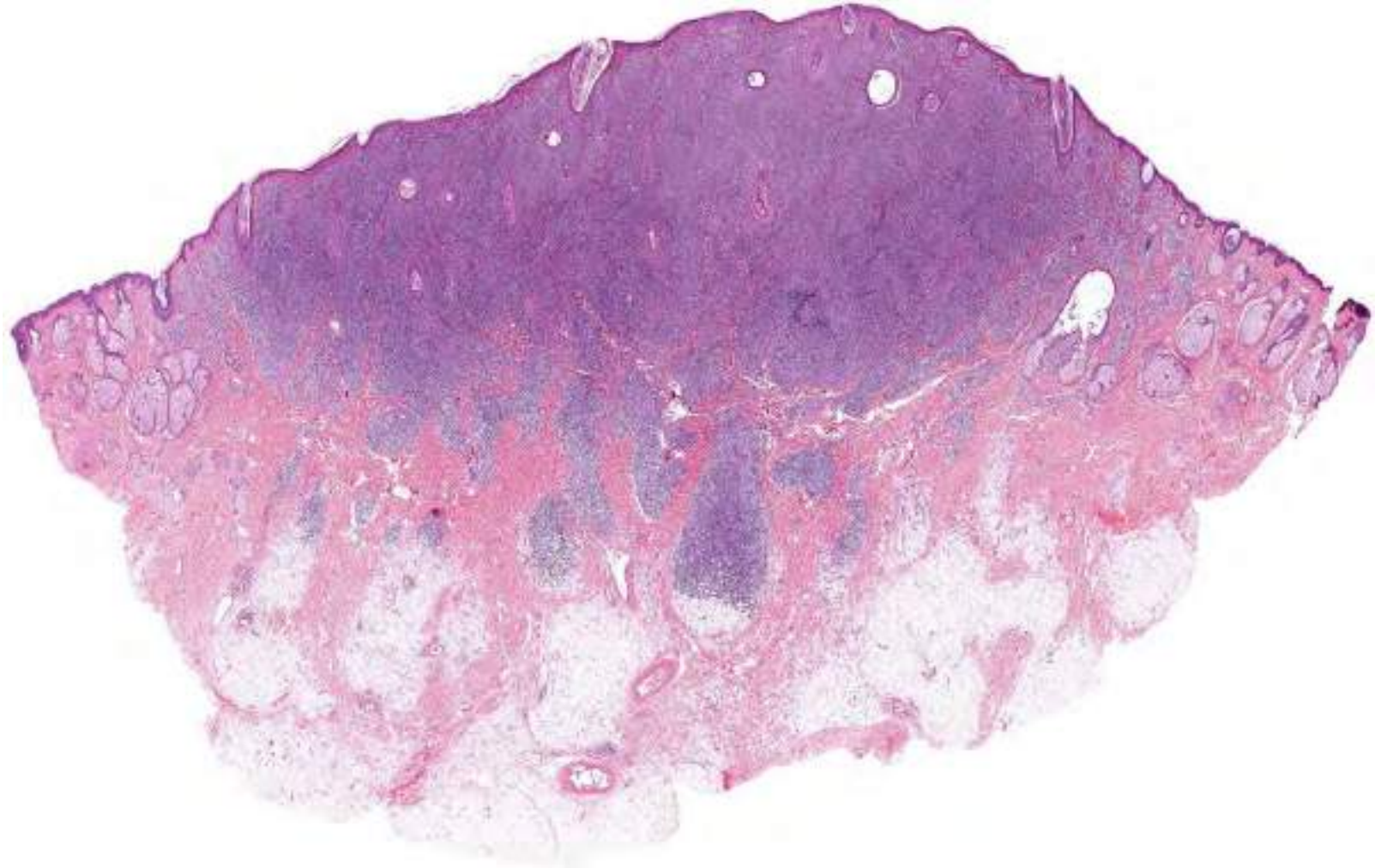
Cutaneous small-medium pleomorphic CD4+ T-cell lymphoproliferative disorder

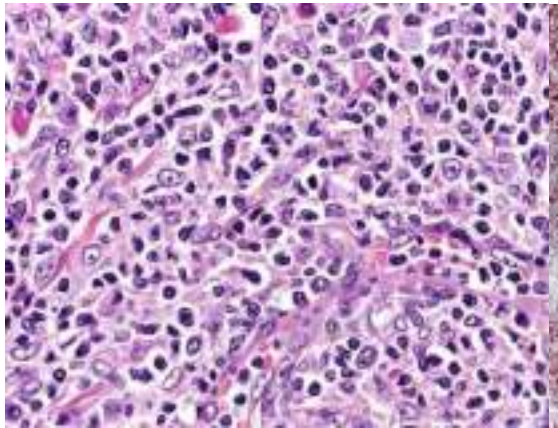
Solitary lesion (essential criterion) located mostly on the face.

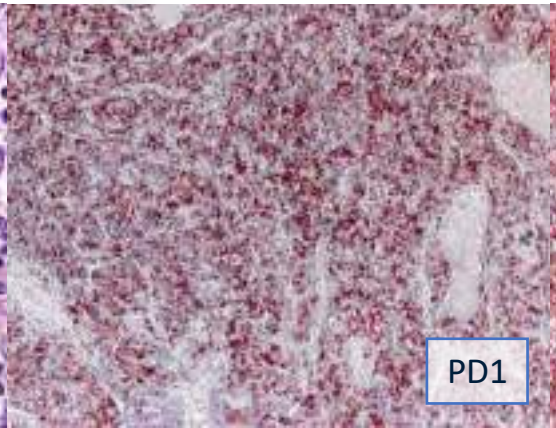
Mixed infiltrate with predominance of CD4+ lymphocytes with T_{FH} phenotype (PD1+).

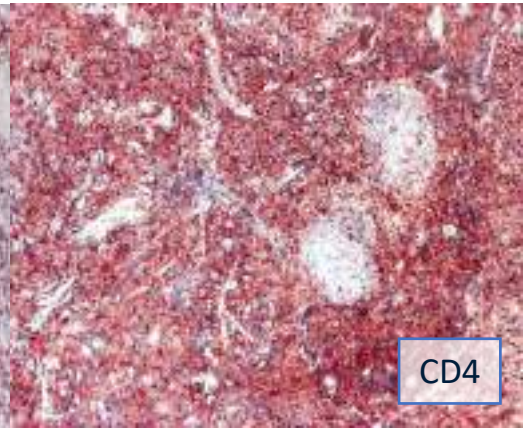
Large cells should not exceed 20%; Ki-67 should be <30%.

Indolent behavior, excellent prognosis.






PD1


CD4

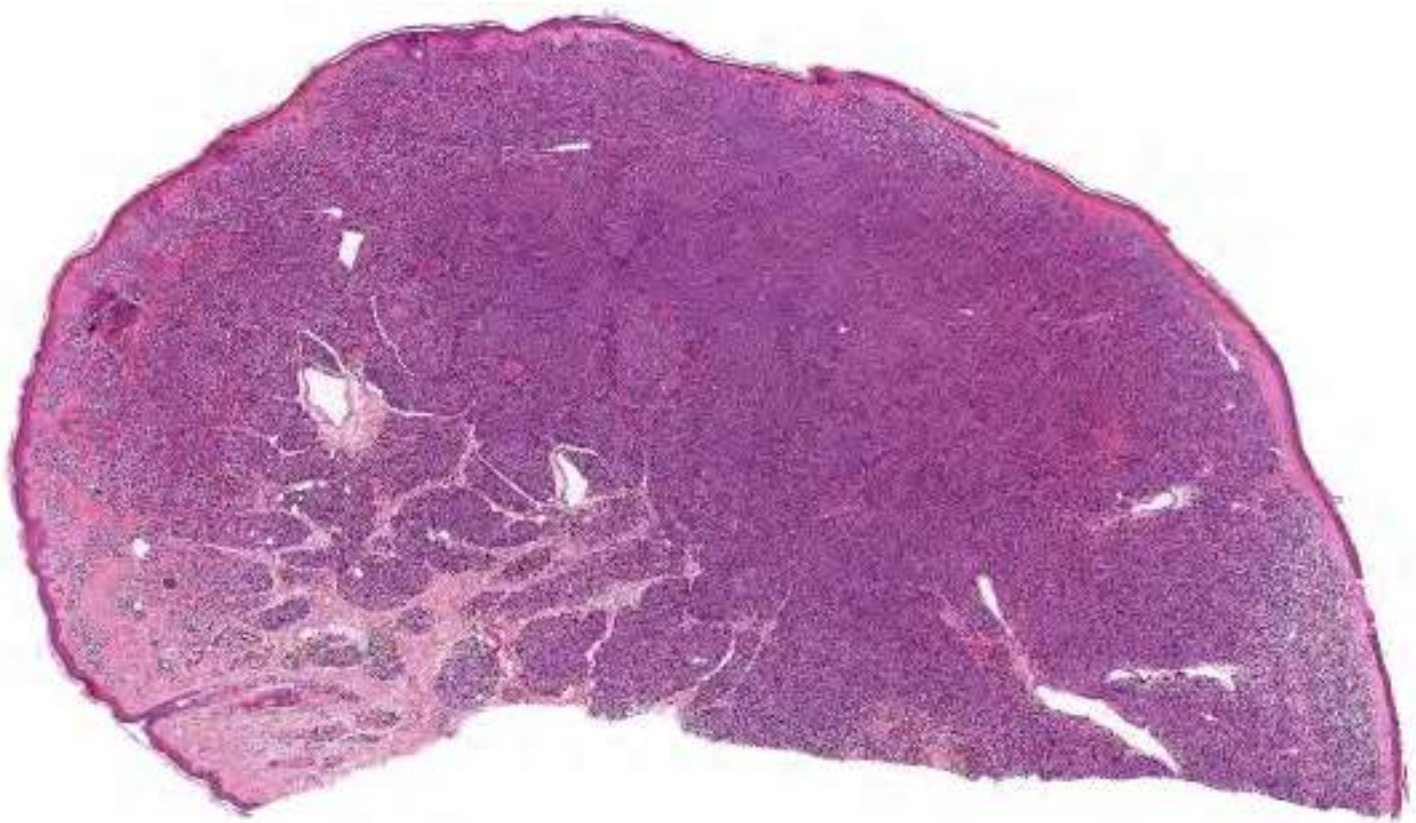
Primary Cutaneous CD4+ Small-/Medium-Sized Pleomorphic T-Cell Lymphoma: A Cutaneous Nodular Proliferation of Pleomorphic T Lymphocytes of Undetermined Significance? A Study of 136 Cases

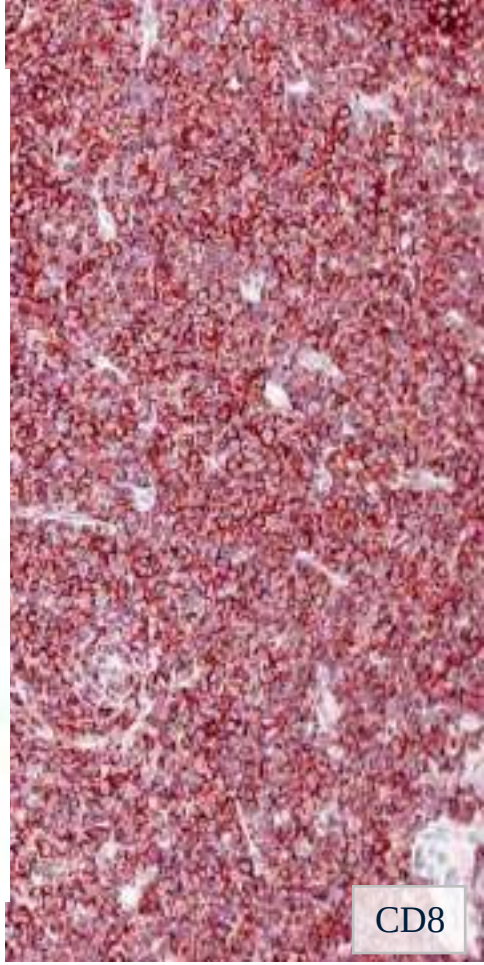
Dermatology

Original Paper

Solitary Small- to Medium-Sized Pleomorphic T-Cell Nodules of Undetermined Significance: Clinical, Histopathological, Immunohistochemical and Molecular Analysis of 26 Cases

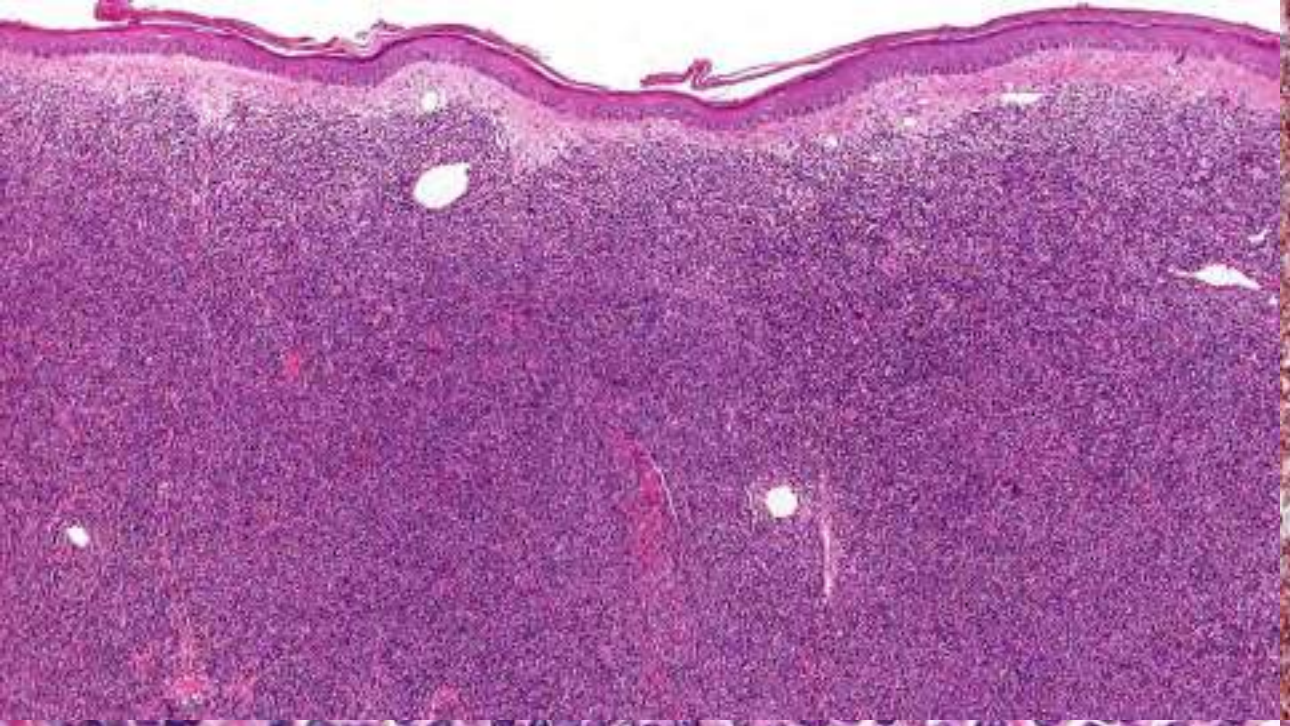
136 patients; 133 solitary lesion, 3 multiple (2 or 3 lesions)
Follow-up: 45 patients (median FU time: 63 months; range: 1–357 months)
41 CR (including 2 with multiple lesions)
4 persistent disease (2, 2, 4, and 16 months, respectively)

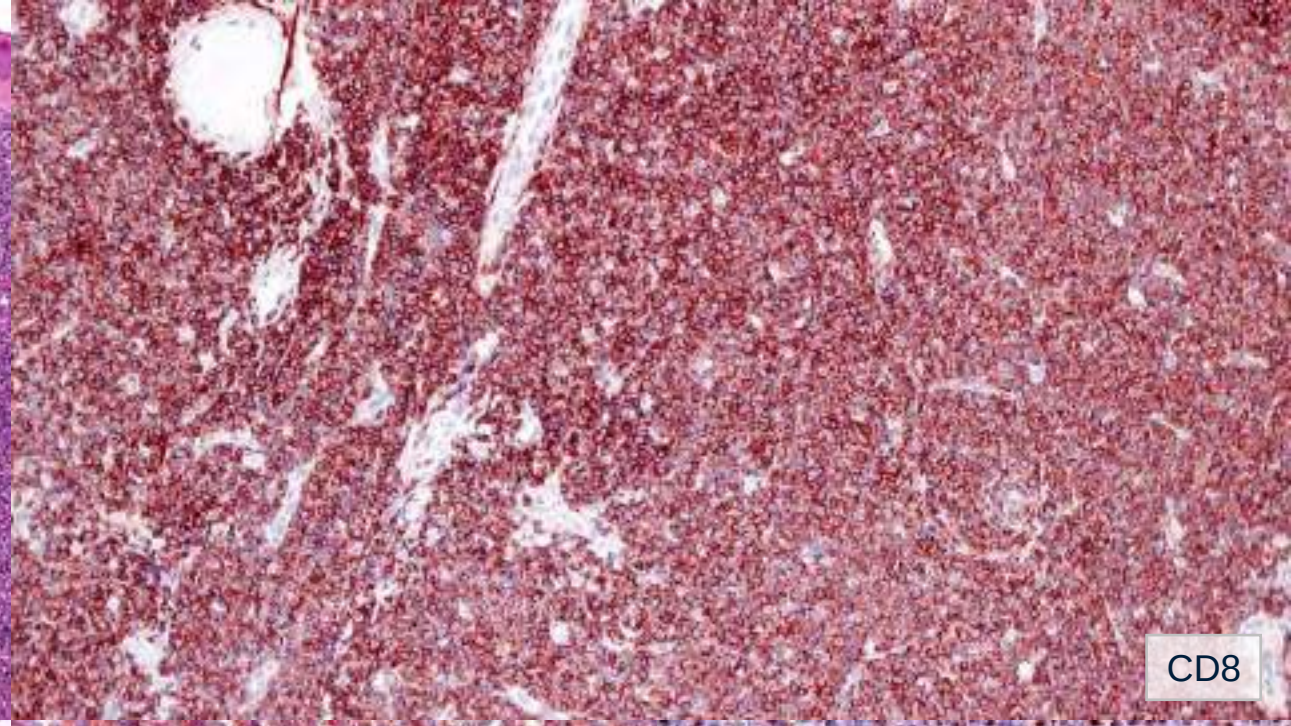




Acral CD8+ T-cell lymphoproliferative disorder

Lesions located mostly on the ear/face.
Monotonous proliferation of medium-sized CD8+ lymphocytes; dot-like CD68-positivity.
Main differential diagnoses: cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (clinical features, prominent epidermotropism), peripheral T-cell lymphoma, NOS (different phenotype), pcCD4+SMPTCLD (CD4+, frequent TFH phenotype).
Indolent behaviour, excellent prognosis.

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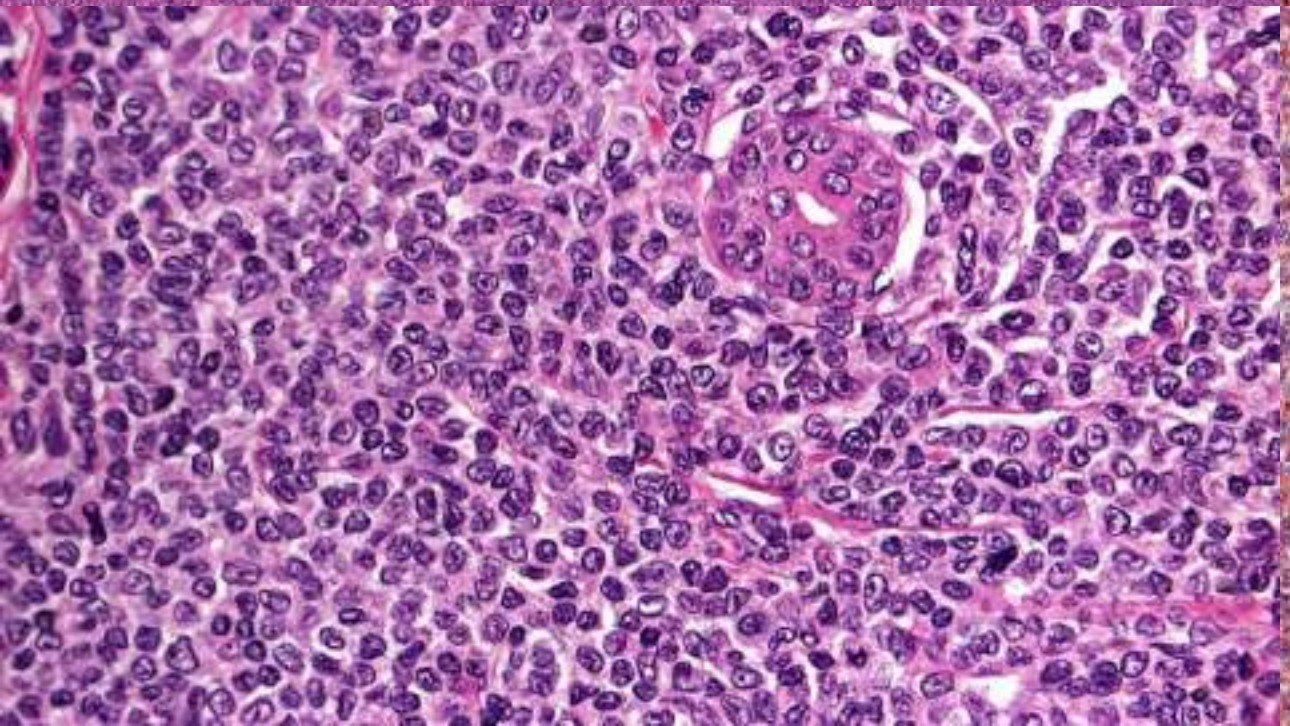

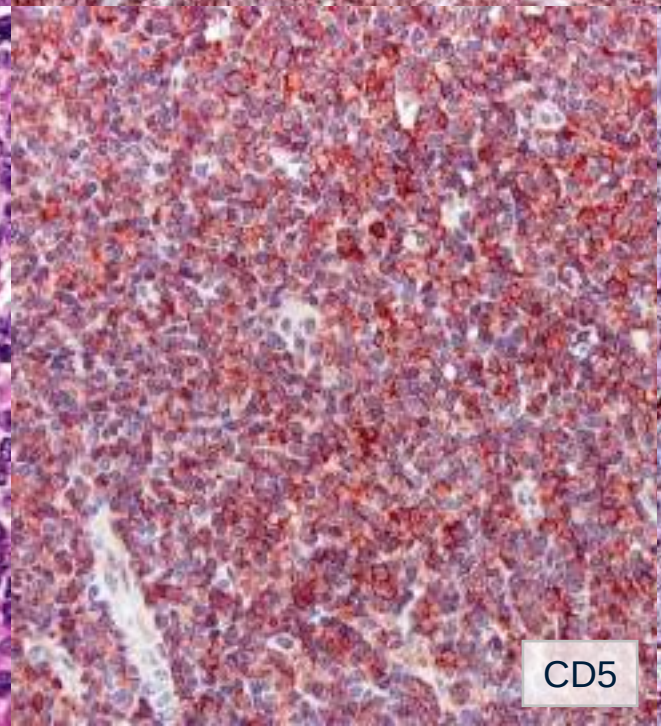
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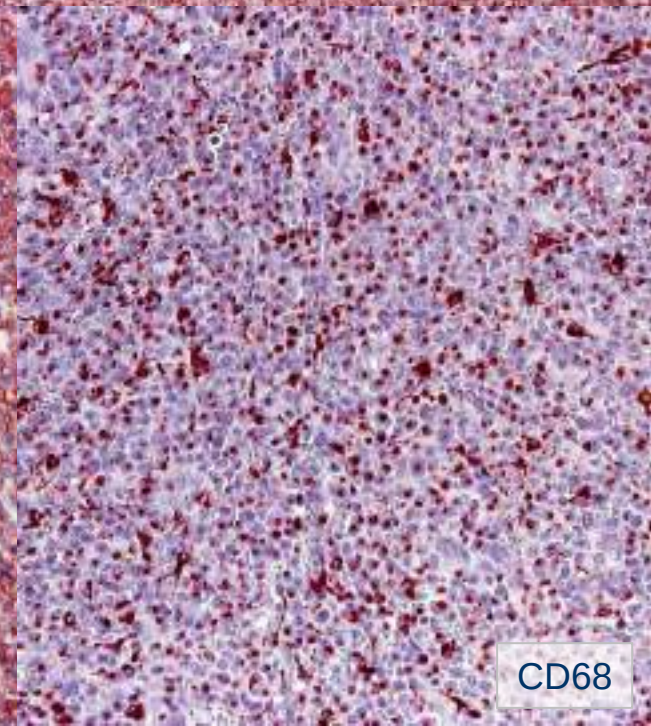
CD68

BJD
British Journal of Dermatology

Clinical, histopathological and prognostic features of primary cutaneous acral CD8$^+$ T-cell lymphoma and other dermal CD8$^+$ cutaneous lymphoproliferations: results of an EORTC Cutaneous Lymphoma Group workshop*

Werner Kempf,[1,2] Tony Petrella,[3] Rein Willemze,[4] Patty Jansen,[5] Emilio Berti,[6] Marco Santucci,[7] Eva Geissinger,[8] Lorenzo Cerroni,[9] Eve Maubec,[10] Maxime Battistella,[11] John Goodlad,[12] Emmanuella Guenova,[13,14] Katariina Lappalainen,[15] Annamari Ranki,[15] Paul Craig,[16] Eduardo Calonje,[17] Blanca Martin,[18] Sean Whittaker,[19] Reiko Oschlies,[20] Ulrike Wehkamp,[18] Jan P. Nicolay,[20] Marion Wobser,[21] Julia Scarabruck,[21] Nicola Pimpinelli,[22] Rudi Stadler,[23] Katrin Kerl-French,[24] Pietro Quaglino,[25] Jinran Lin,[26] Lianlian Chen,[27] Michaela Beer,[1] Patrick Emanuel,[28,29] Stephane Dalle[30] and Alistair Robson[31,32]

Linked Comment: J.E. Gru Br J Dermatol 2021; 186:769–771.

Abstract

Background The differential diagnosis of atypical dermal neutrophilic/histiocytic CD8$^+$ lymphocytic infiltrates includes a heterogeneous spectrum of lymphoproliferations with overlapping histological and phenotypic features, yet divergent clinical manifestations and prognosis. As these neoplasms are rare, more data on their clinicopathological presentation and course are needed.

Objectives To assess the clinical, histological and immunophenotypic features, outcomes of, and differences between dermal CD8$^+$ lymphoproliferations.

Methods Retrospective analysis of a series of 46 patients and biopsies by the International EORTC Cutaneous Lymphoma Group.

Results The dermal CD8$^+$ lymphoproliferations (*n* = 46) could be assigned to one of three groups: (i) cutaneous acral CD8$^+$ T-cell lymphoma (*n* = 31), characterized mainly by a solitary nodule arising at acral sites, a monomorphous dermal infiltrate of small-to-medium-sized CD8$^+$ lymphocytes with a characteristic dot-like pattern of CD68, a low proliferative rate and an excellent prognosis; (ii) primary cutaneous CD8$^+$ peripheral T-cell lymphoma, unspecified/NOS (*n* = 11), presenting with one or multiple rapidly evolving tumours, mostly medium-sized pleomorphic CD8$^+$ tumour cells with expression of several cytotoxic markers, and high proliferative activity; and (iii) cutaneous CD8$^+$ lymphoproliferations (*n* = 4), associated with congenital immunodeficiency syndromes in two patients with persisting localized or disseminated vesiculous or brownish plaques on the extremities, a histiocyte-rich infiltrate of mostly small CD8$^+$ lymphocytes with subtle atypia and a protracted course, and papular CD8$^+$ eruptions in two patients with acquired immunosuppression.

Conclusions A correlation of distinct clinical, histopathological and phenotypic features allows discrimination and assignment of dermal CD8$^+$ infiltrates into distinct disease entities. Primary cutaneous acral CD8$^+$ lymphoma, assigned a provisional category in current lymphoma classifications, is a distinct and reproducible entity. A correct diagnosis is crucial, to avoid unnecessarily aggressive treatment for indolent CD8$^+$ lymphoproliferations and to identify cases with underlying immunodeficiency or potential for distant relapse.

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Conflicts of interest
The author declares no conflicts of interest.

Data availability
Data are available in the Supporting Information.

1 Full list of affiliations is provided in Appendix 1.

*Plain language summary available online.

DOI: 10.1111/bjd.20831

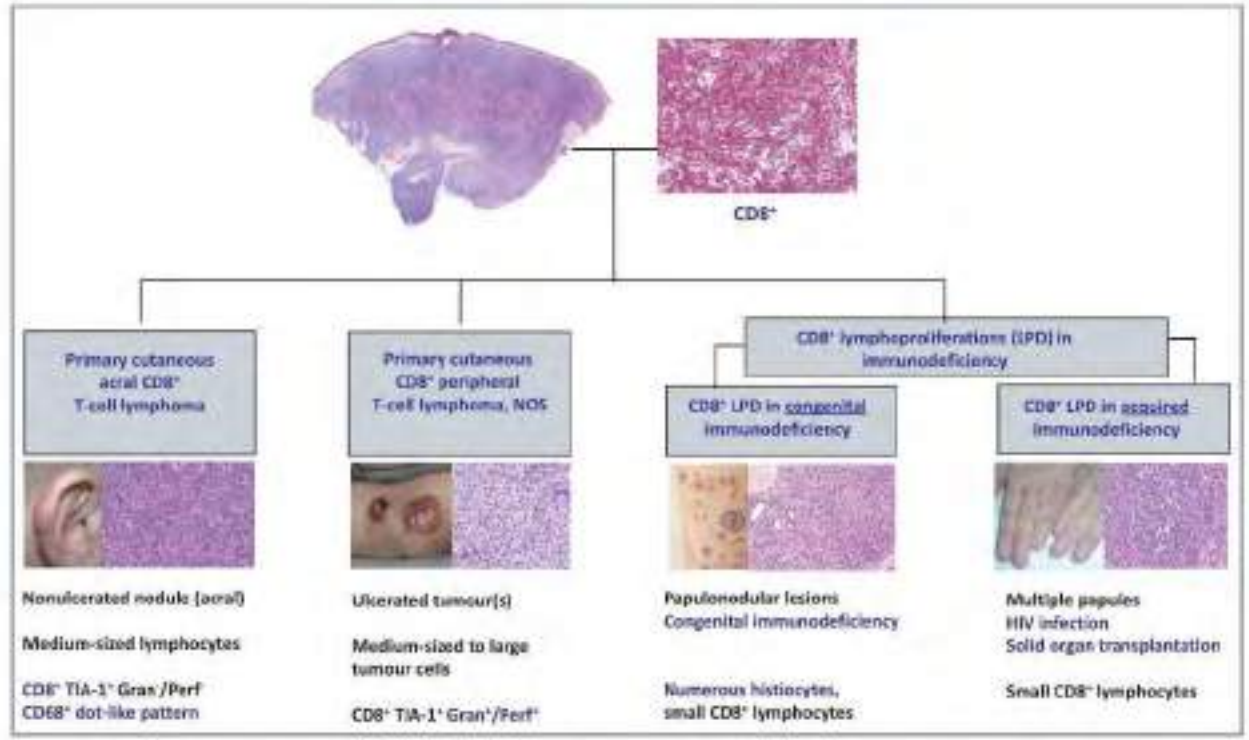
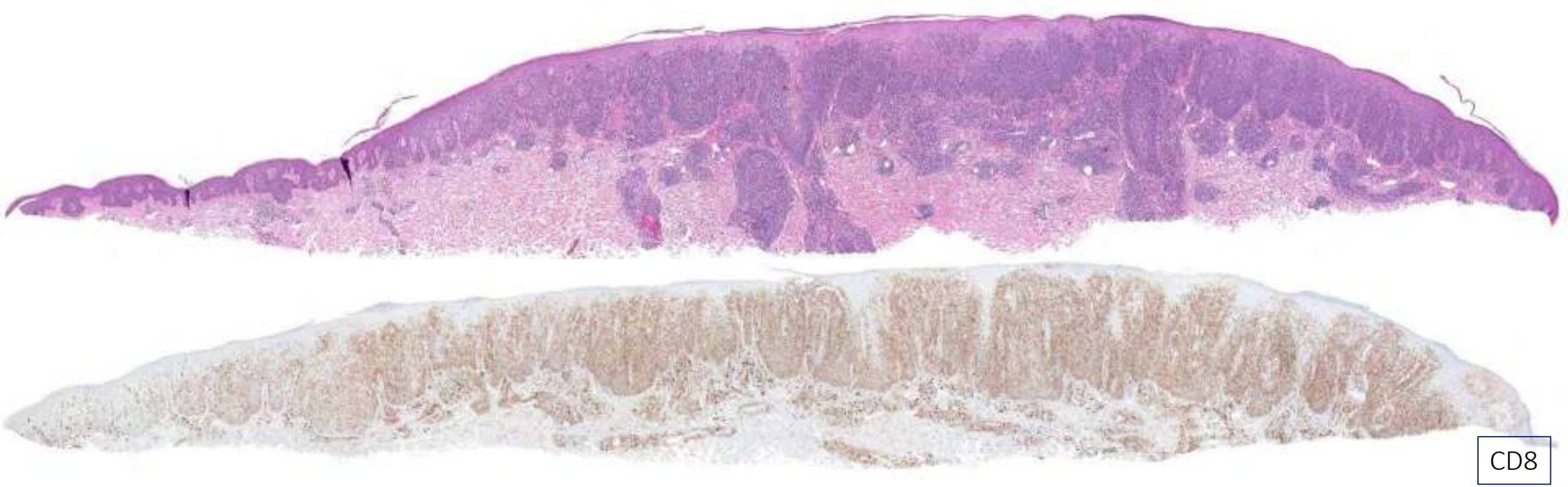


Figure 5 Differentiation of dermal small- to medium-sized CD8$^+$ infiltrates. Summary of the most relevant clinical, histological and immunophenotypic features for the differentiation of dermal CD8$^+$ infiltrates. Gran., granzyme B; NOS, not otherwise specified; Perf, perforin.



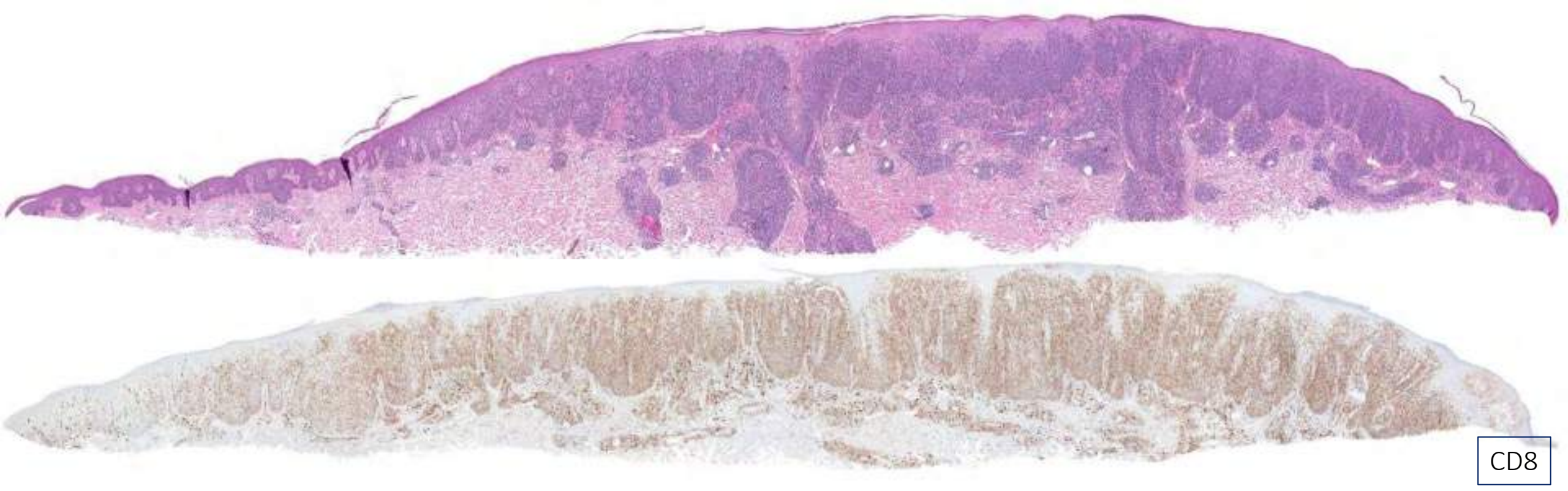
Aggressive epidermotropic CD8+ T-Cell Lymphoma

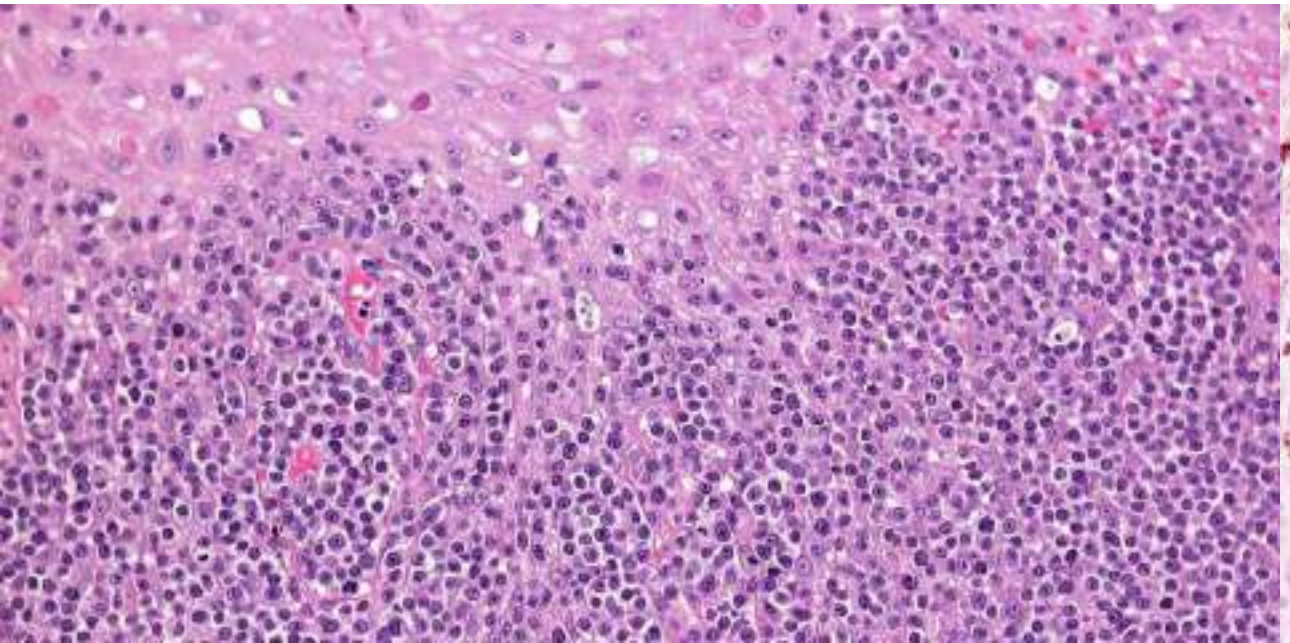
Clinically presents with the picture of so-called "generalized pagetoid reticulosis" (Ketron-Goodman).

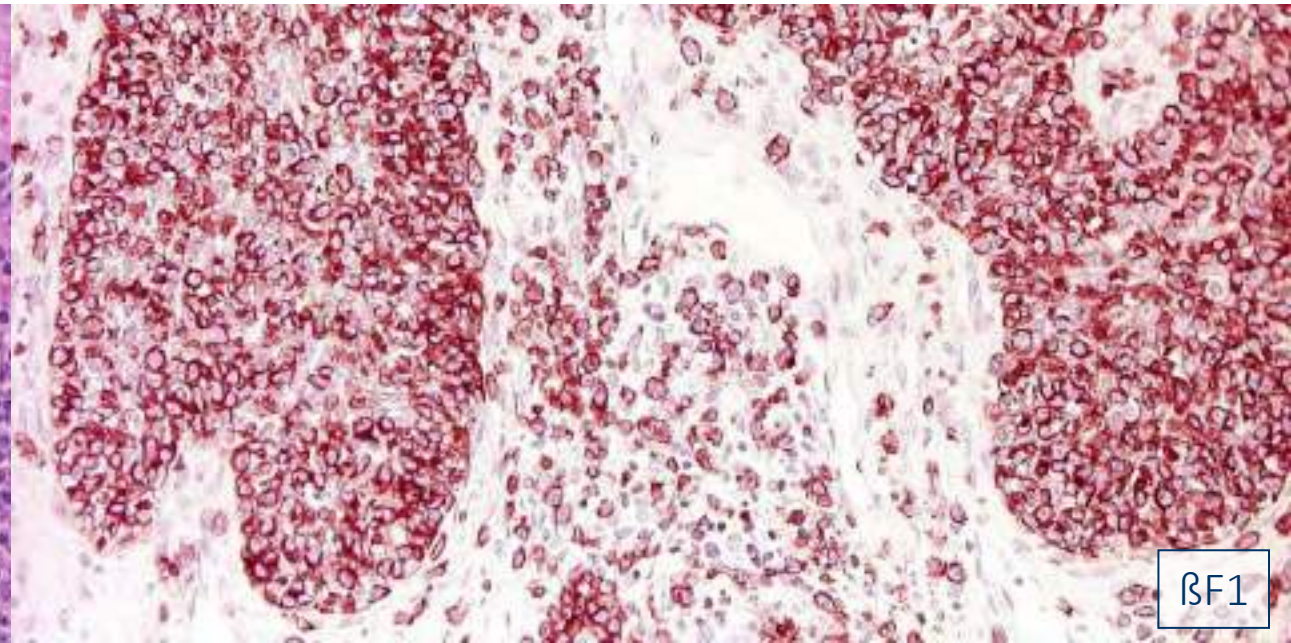
Prominent epidermotropism (may vary with biopsy site, time); CD8 expression may be weak in some cases; CD2, CD5 often negative; CD30 usually not expressed.

Main differential diagnoses: CD8+ MF (history, clinical presentation), LyP-D (history, CD30+), cutaneous γ/δ T-cell lymphoma (TCR-γ/δ+).

Aggressive behavior.


CD8




ßF1

American Journal of Pathology, Vol. 155, No. 2, August 1999

Primary Cutaneous CD8-Positive Epidermotropic Cytotoxic T Cell Lymphomas

A Distinct Clinicopathological Entity with an Aggressive Clinical Behavior

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Cutaneous T cell lymphomas (CTCL) generally have the phenotype of CD3+, CD4+, CD45RO+ memory T cells. CTCL expressing a CD8+ T cell phenotype are extremely rare and ill-defined. To elucidate whether these CD8+ CTCL represent a distinct disease entity, the clinical, histological, and immunophenotypical features of 17 CD8+ CTCL were reviewed. None of the 17 cases expressed markers characteristic of natural killer cells or γ/δ T cells. Nine of 17 cases showed the characteristic clinical and histological features as well as clinical behavior of well defined types of CTCL, such as mycosis fungoides (2 cases), pagetoid reticulosis (2 cases), lymphomatoid papulosis (2 cases), and CD30+ large T cell lymphoma (2 cases), all of which usually express a CD4+ T cell phenotype, and 1 case of subcutaneous panniculitis-like T cell lymphoma. The other 8 cases formed a homogeneous group showing a distinctive set of clinicopathological and immunophenotypical features, not consistent with that of other well defined types of CTCL. Clinical characteristics included presentation with generalized patches, plaques, papulonodules, and tumors mimicking disseminated pagetoid reticulosis; metastatic spread to unusual sites, such as the lung, testis, central nervous system, and oral cavity, but not to the lymph nodes; and an aggressive course (median survival, 32 months). Histologically, these lymphomas were characterized by band-like infiltrates consisting of pleomorphic T cells or immunoblasts, showing a diffuse infiltration of an acanthotic epidermis with variable degrees of spongiosis, intracpidermal blistering, and necrosis. The neoplastic cells showed a high Ki-67 proliferation index and expression of CD3, CD8, CD7, CD45RA, JH1, and TIA-1 markers, whereas CD2 and CD5 were frequently lost. Expression of TIA-1 pointed out that these lymphomas are derived from a cytotoxic T cell subset. The results of this and other studies reviewed herein suggest that these strongly epidermotropic primary cutaneous CD8+ cytotoxic T cell lymphomas represent a distinct type of CTCL with an aggressive clinical behavior. (Am J Pathol 1999, 155:683–692)

Recently, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group proposed a new classification for primary cutaneous T (CTCL) and B (CBCL) cell lymphomas.[1] This classification is based on a combination of clinical, histological, immunohistochemical, and genetic criteria and contains a number of well defined entities as well as some provisional forms. Well defined entities within the CTCL group include classical mycosis fungoides (MF), follicular MF, pagetoid reticulosis, Sézary's syndrome (SS), CD30+ primary cutaneous large T cell lymphomas (PC-LCL) and CD30− PC-LCL. Together they constitute about the 98% of CTCL in the Dutch registry.[1] In the overwhelming majority the neoplastic T cells have the phenotype of resting or activated CD4+ memory T cells (CD45RO+, CD29+). However, rare cases of CD8+ CTCL with the clinicopathological features of MF or pagetoid reticulosis,[2–4] were also reported. In 1960, Jansen[10] described a fulminant MF-like case in which the neoplastic T lymphocytes were CD8+. Since that initial report, other aggressive cases have been reported.[11–16] However, because of the small number and the heterogeneity in clinical presentation and course of the cases published so far, CD8+ CTCL were not included as a separate group in the EORTC classification for primary cutaneous lymphomas.

In the present study we discuss the clinical, histological, immunohistochemical, and molecular features of 17

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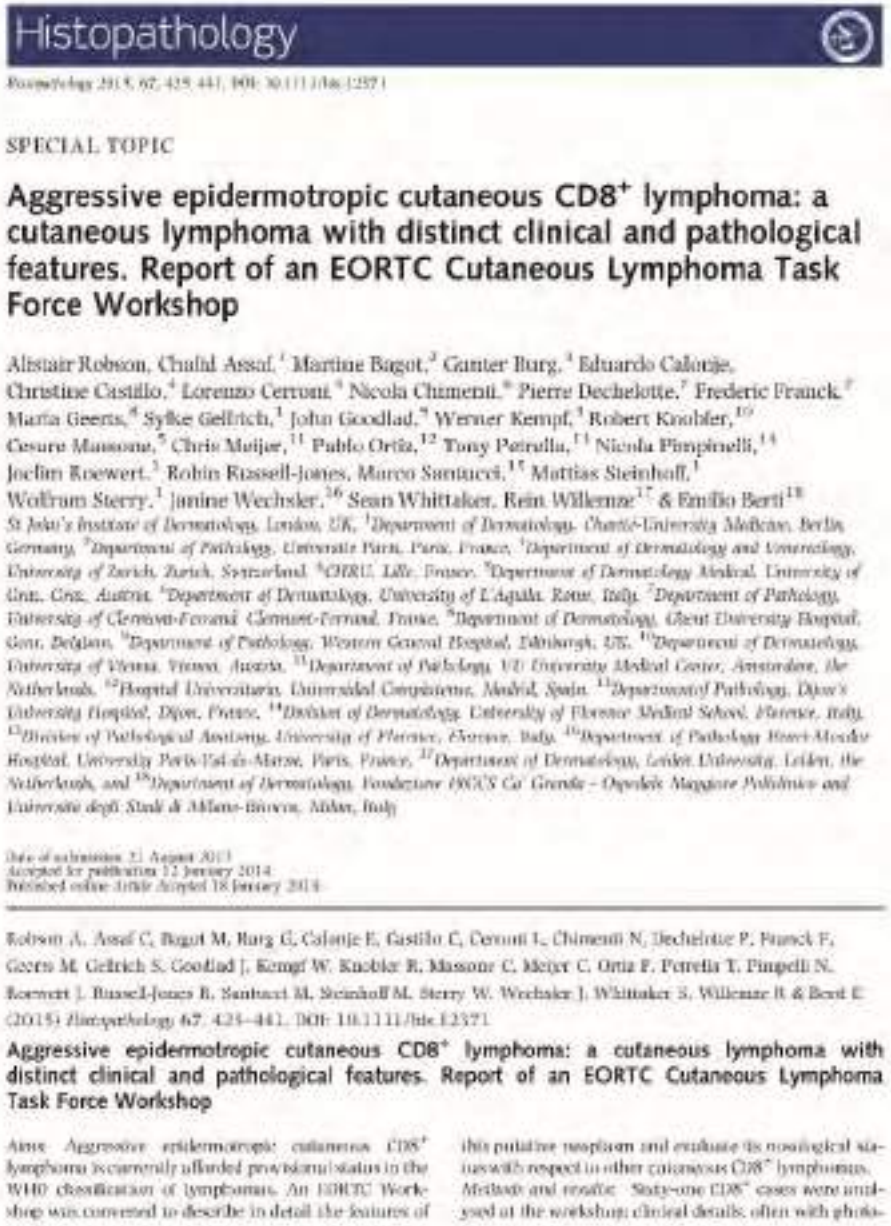
17 cases of CD8+ CTCL	
MF	2
Pagetoid reticulosis	2
Lymphomatoid papulosis	2
cALCL	2
SPTCL	1
Aggressive CD8+ CTCL:	8

CD2	2/7
CD3	8/8
CD4	0/7
CD5	2/7
CD7	6/7
CD8	8/8
CD30	0/7
CD45Ro	0/8
CD45Ra	7/8
TCRß	8/8
TIA-1	8/8
Granzyme B	2/8



Histopathology

SPECIAL TOPIC

Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop

Alistair Robson, Chalid Assaf,[1] Martine Bagot,[2] Gunter Burg,[3] Eduardo Calonje,[4] Christine Castillo,[5] Lorenzo Cerroni,[6] Nicola Chimenti,[7] Pierre Dechelotte,[8] Frederic Franck,[9] Maria Geerts,[10] Sylke Gellrich,[11] John Goodlad,[12] Werner Kempf,[13] Robert Knobler,[14] Cesare Massone,[15] Chris Meijer,[11] Pablo Ortiz,[12] Tony Petrella,[11] Nicola Pimpinelli,[14] Joelim Roewert,[3] Robin Russell-Jones, Marco Santucci,[15] Matthias Steinhoff,[1] Wolfram Sterry,[1] Janine Wechsler,[16] Sean Whittaker, Rein Willemze[17] & Emilio Berti[18]

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Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop

Aims: Aggressive epidermotropic cutaneous CD8+ lymphoma is currently afforded provisional status in the WHO classification of lymphomas. An EORTC Workshop was convened to describe in detail the features of this putative neoplasm and evaluate its nosological status with respect to other cutaneous CD8+ lymphomas. *Methods and results:* Sixty-one CD8+ cases were analysed at the workshop; clinical details, often with photo-

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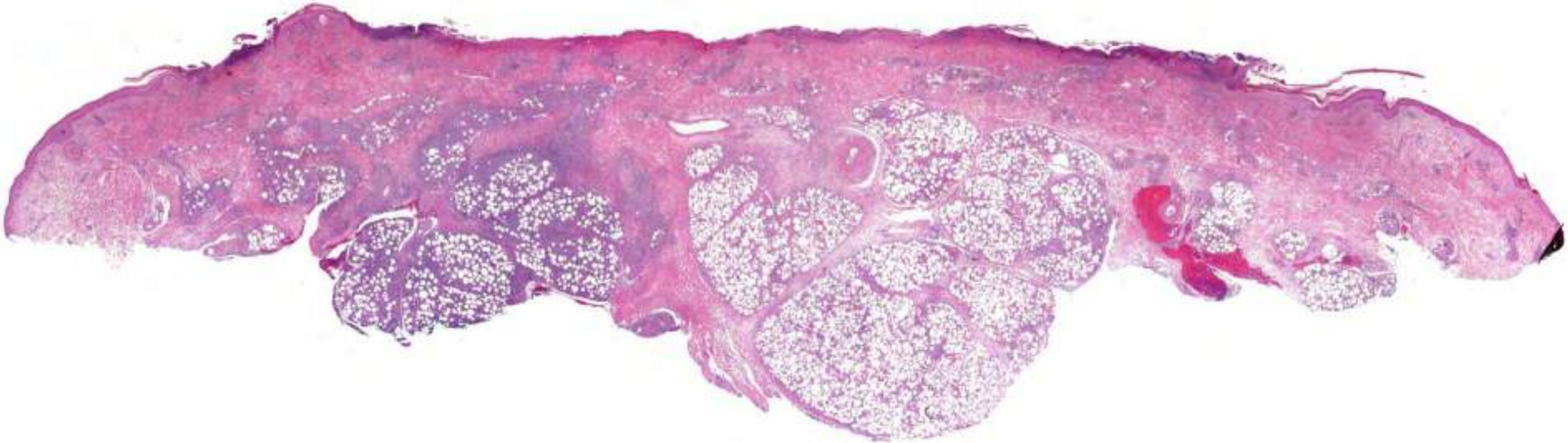
Eighteen cases had distinct features and conformed to the diagnosis of aggressive epidermotropic cutaneous CD8+ lymphoma.

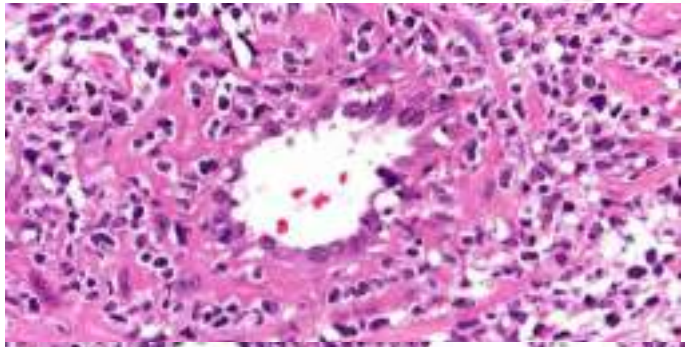
The patients typically present with widespread plaques and tumors, often ulcerated and hemorrhagic, and have striking pagetoid epidermotropism histologically.

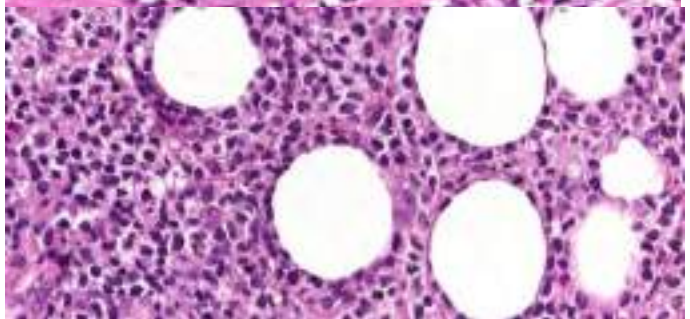
A CD8+ CD45RA+ CD45RO- CD2- CD5- CD56- phenotype, with 1 or more cytotoxic markers was found in 7/18 cases, with a very similar phenotype in the remainder.

The tumors seldom involve lymph nodes but mucosae and central nervous system involvement is not uncommon.

The prognosis is poor, with a median survival of 12 months.





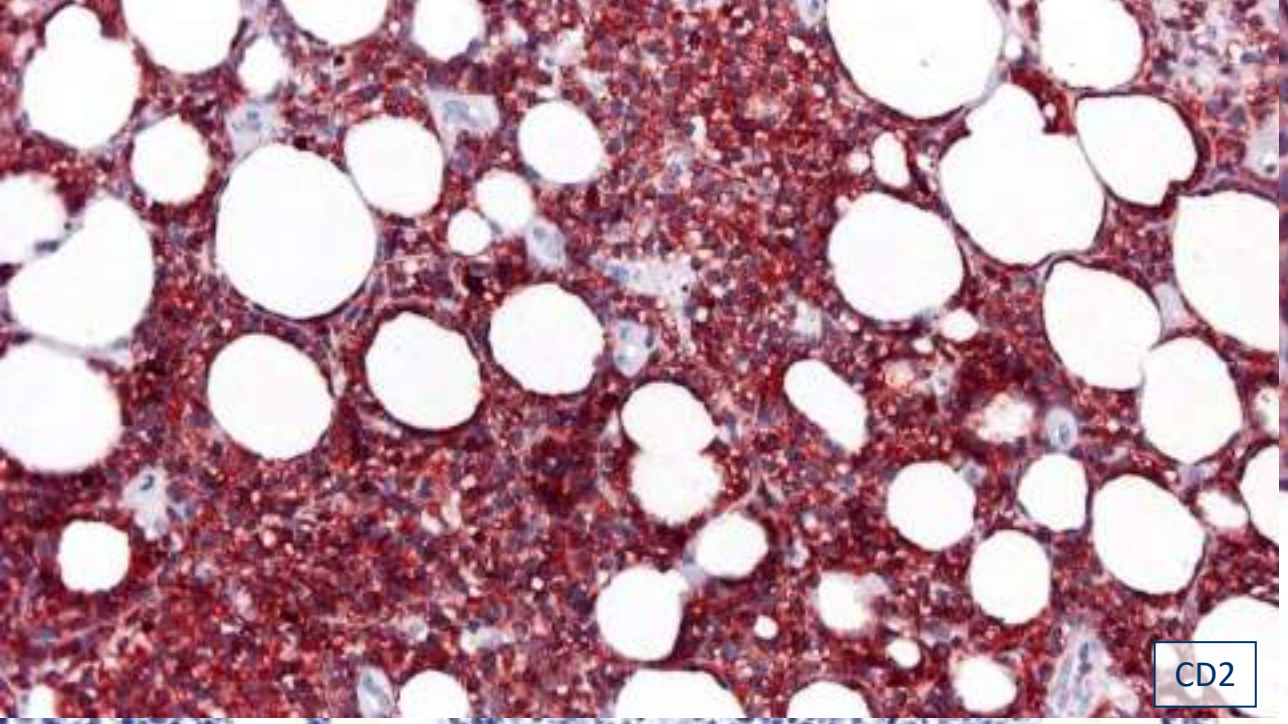


Cutaneous γ/δ T-cell lymphoma

Cases lumped in the past together with MF and SPTCL.

A γ/δ phenotype is not unique to cutaneous γ/δ T-cell lymphoma (MF, LyP, ALCL), but is never observed in reactive conditions.

Oft involvement of both epidermis and subcutaneous fat; angiocentricity / angiotropism; hemophagocytic syndrome (particularly in tumors involving the subcutaneous fat).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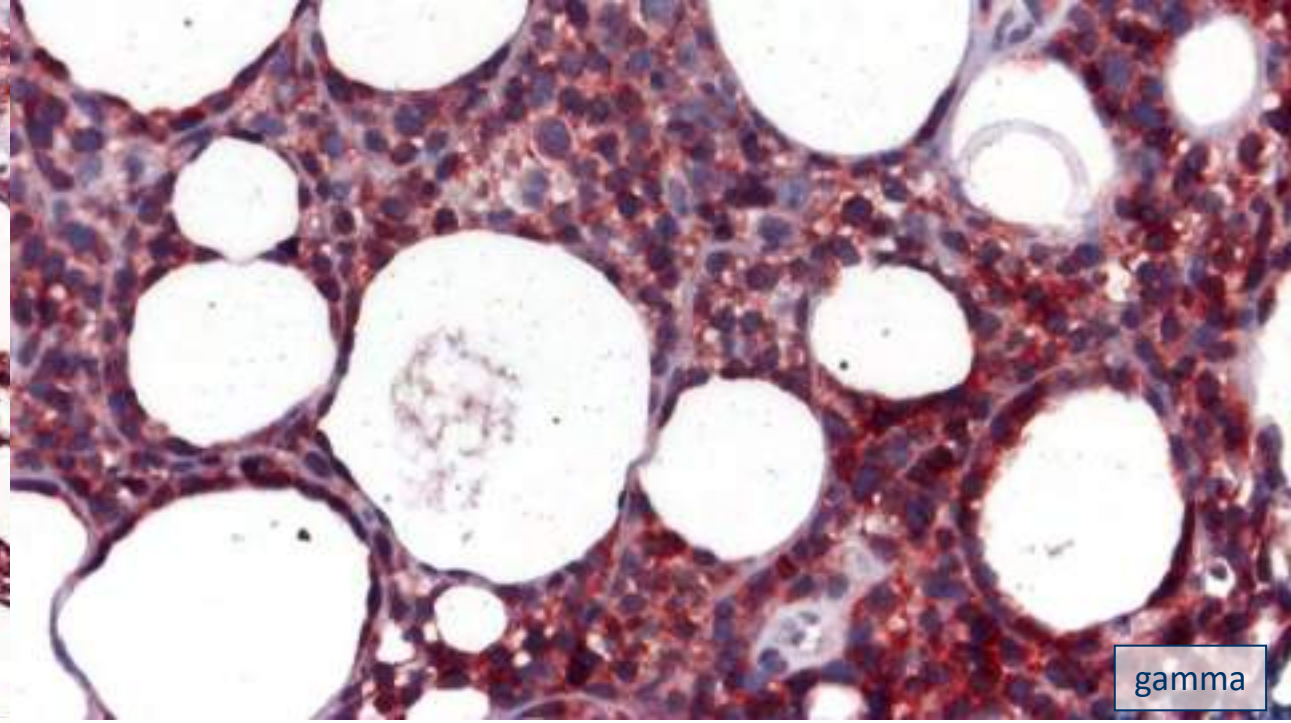
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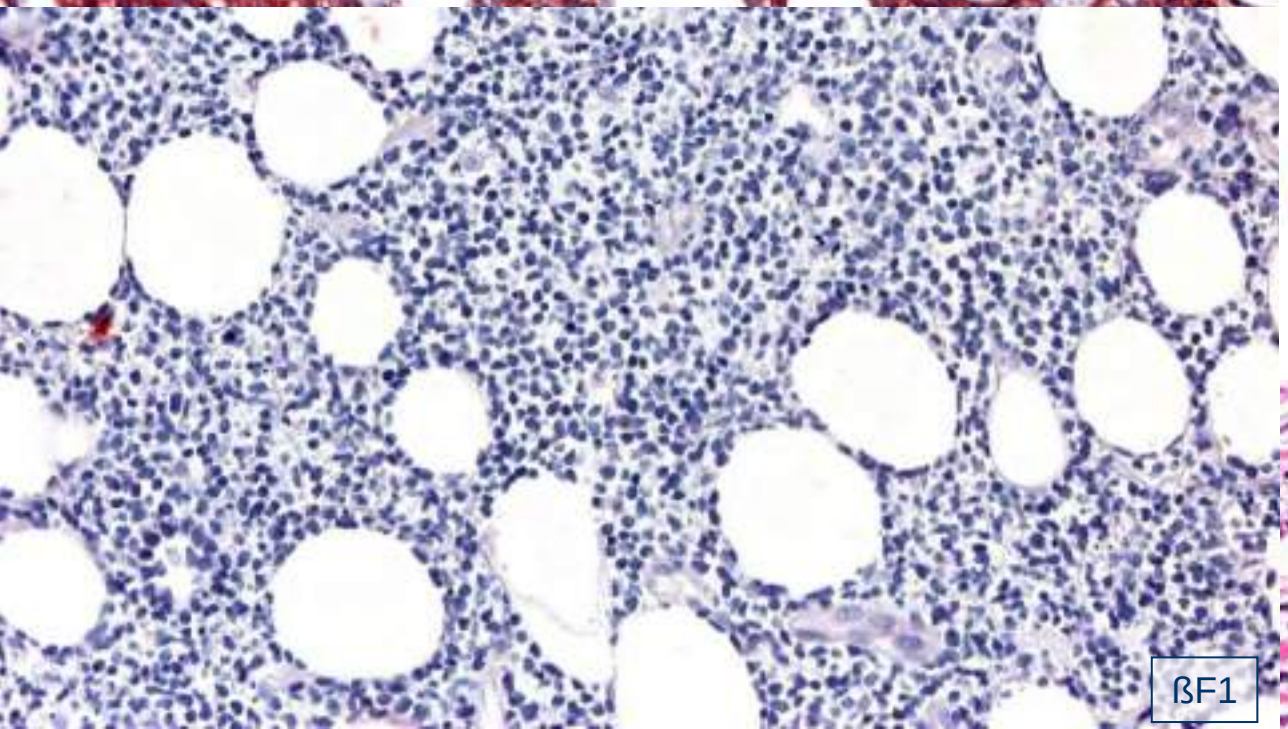
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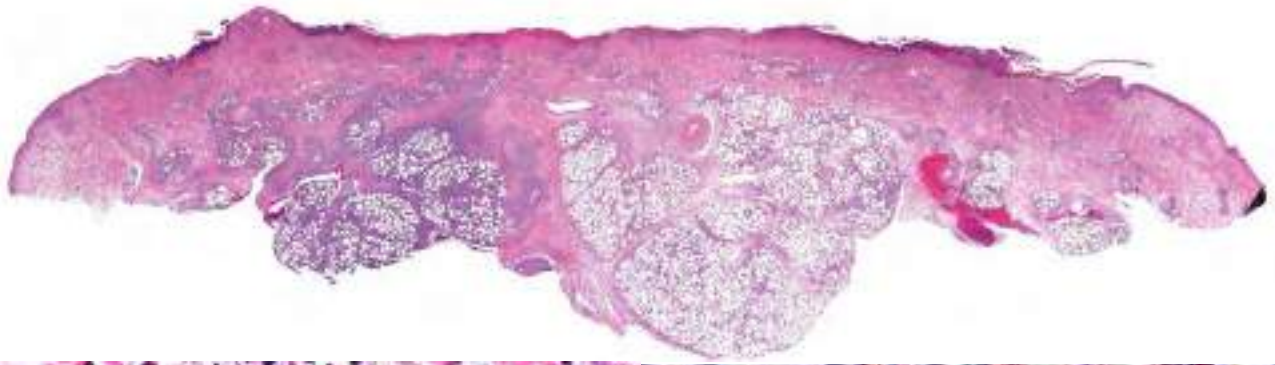
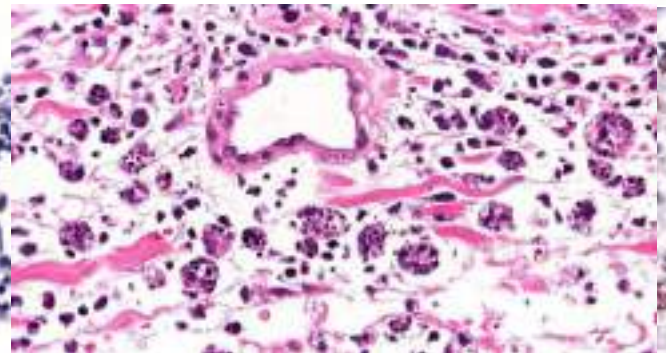
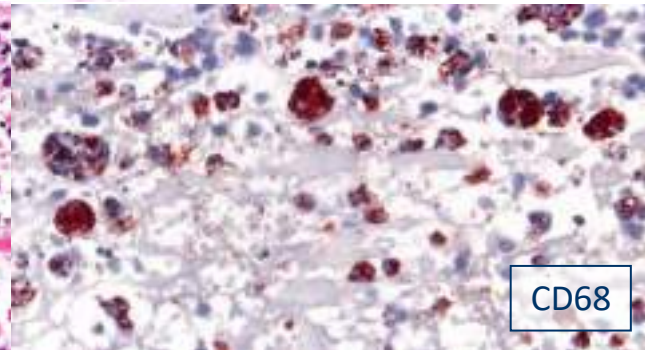
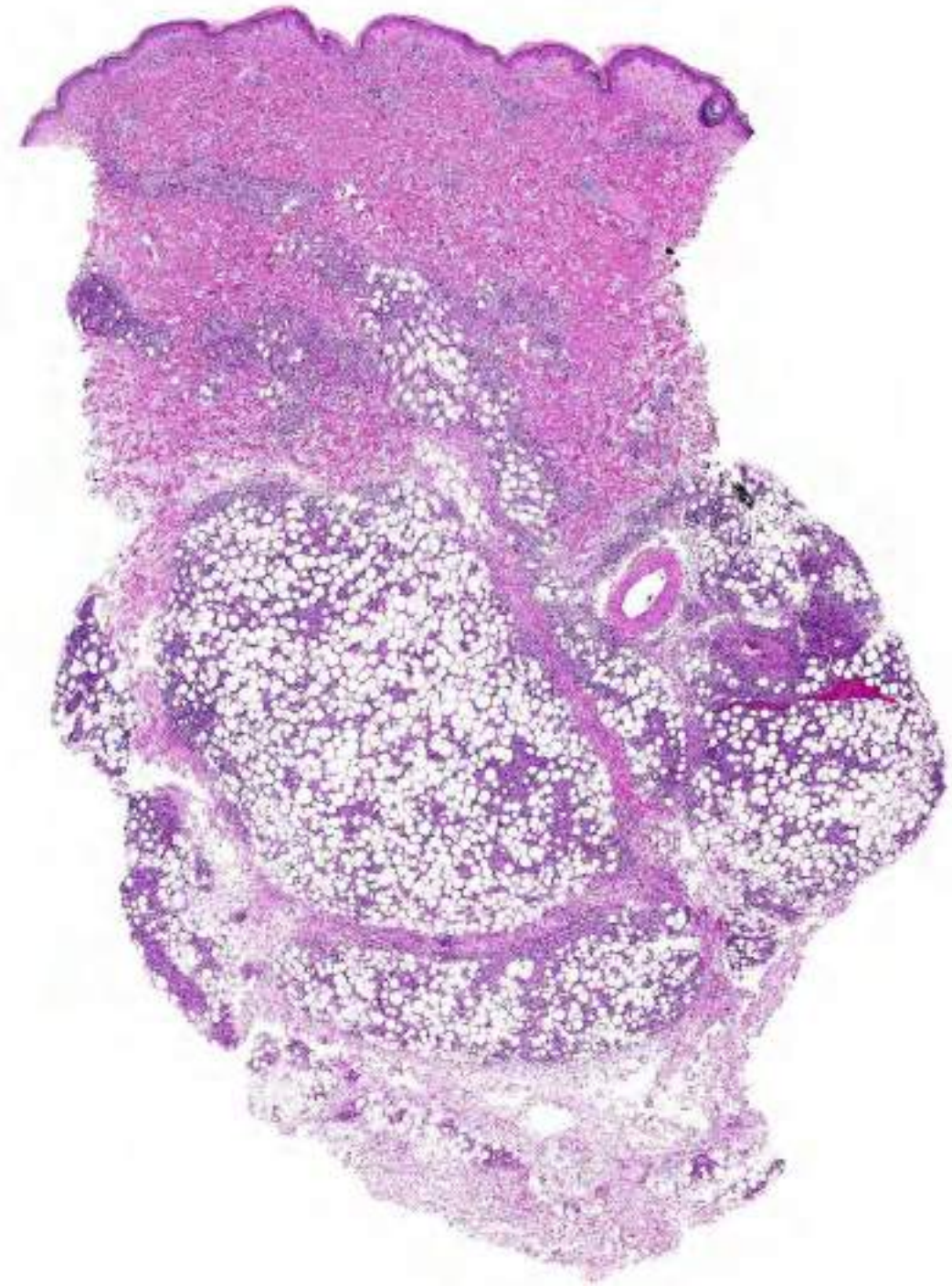
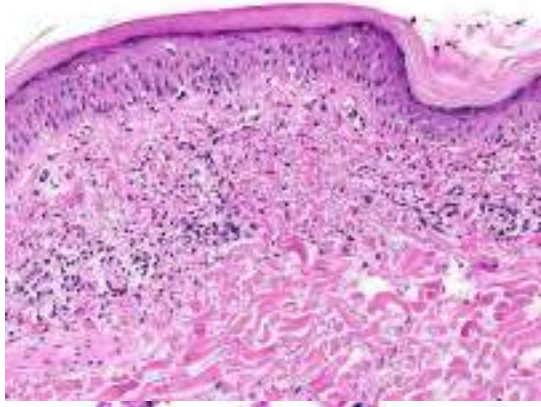
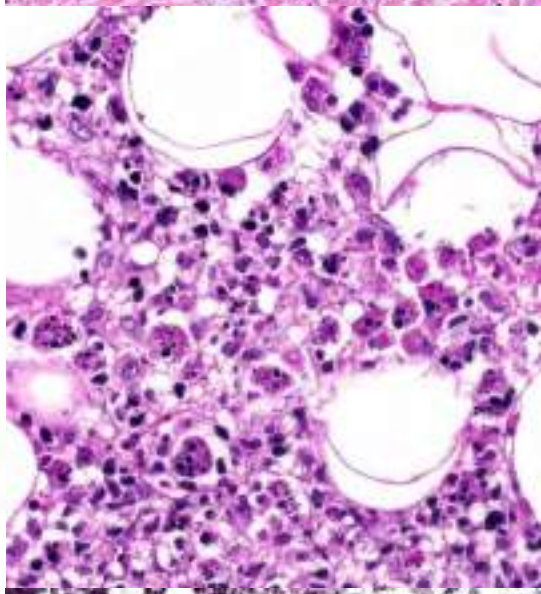


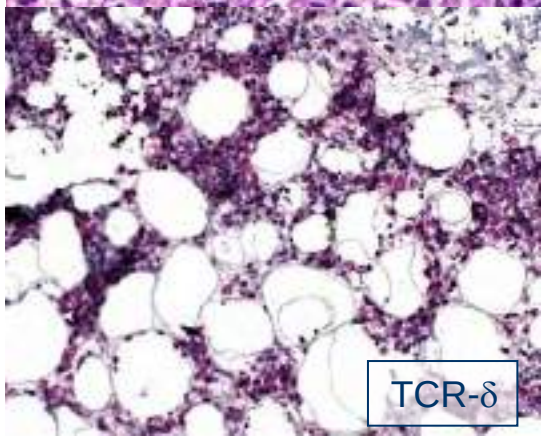


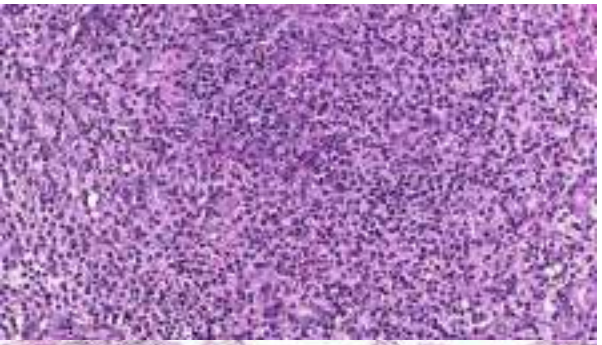

CD68

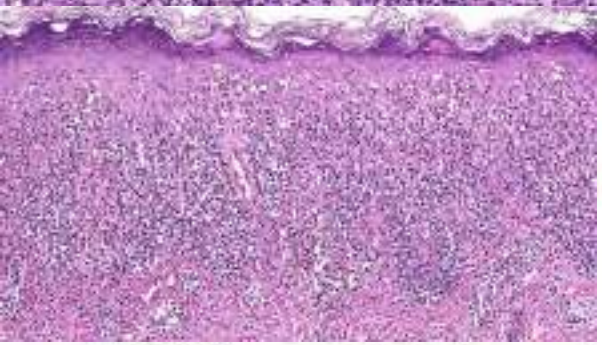


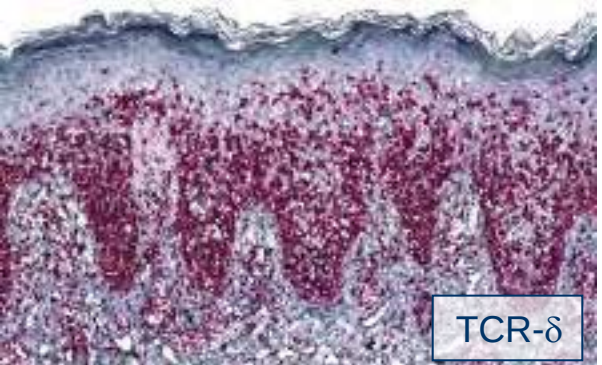


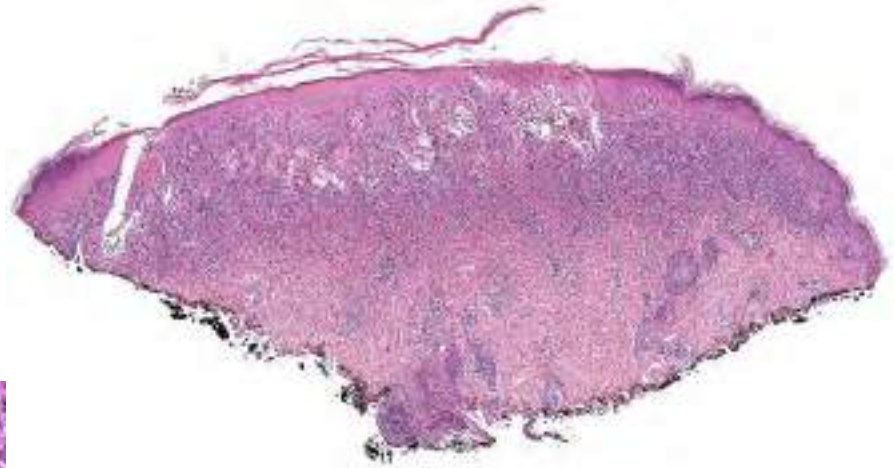


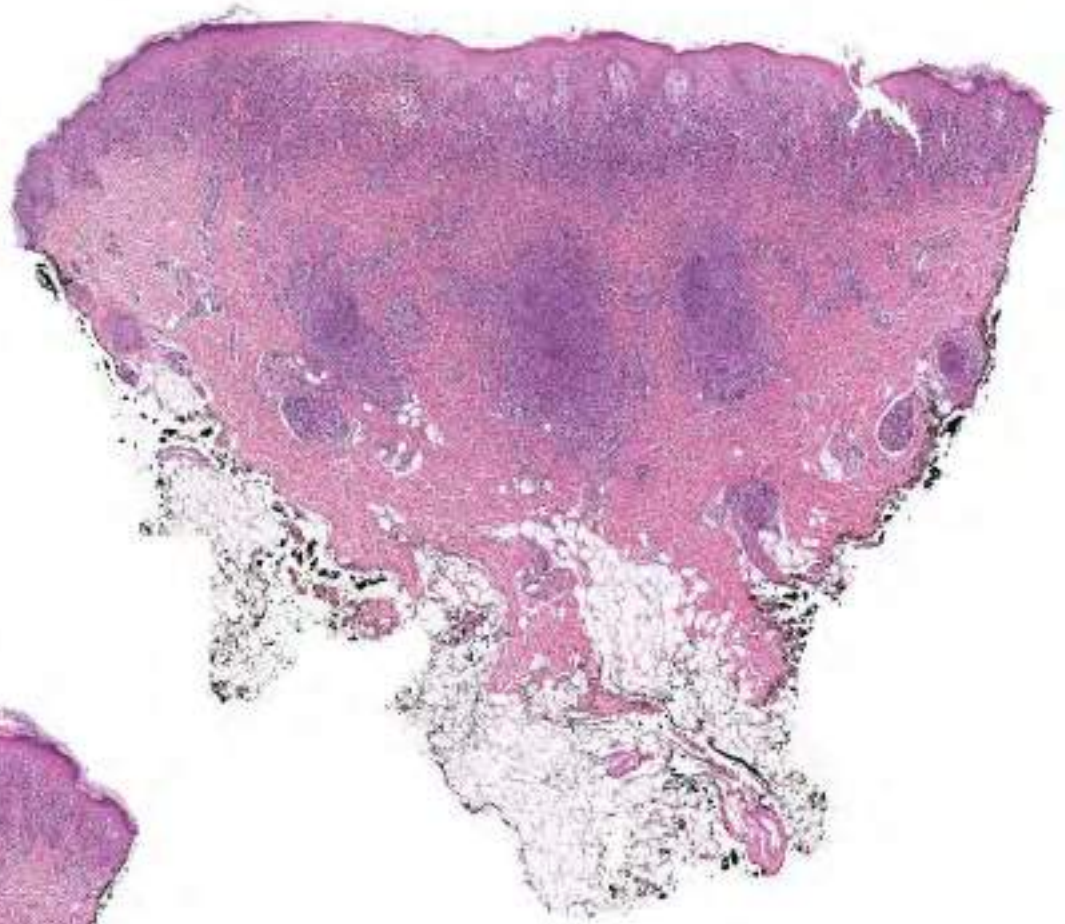

TCR-δ

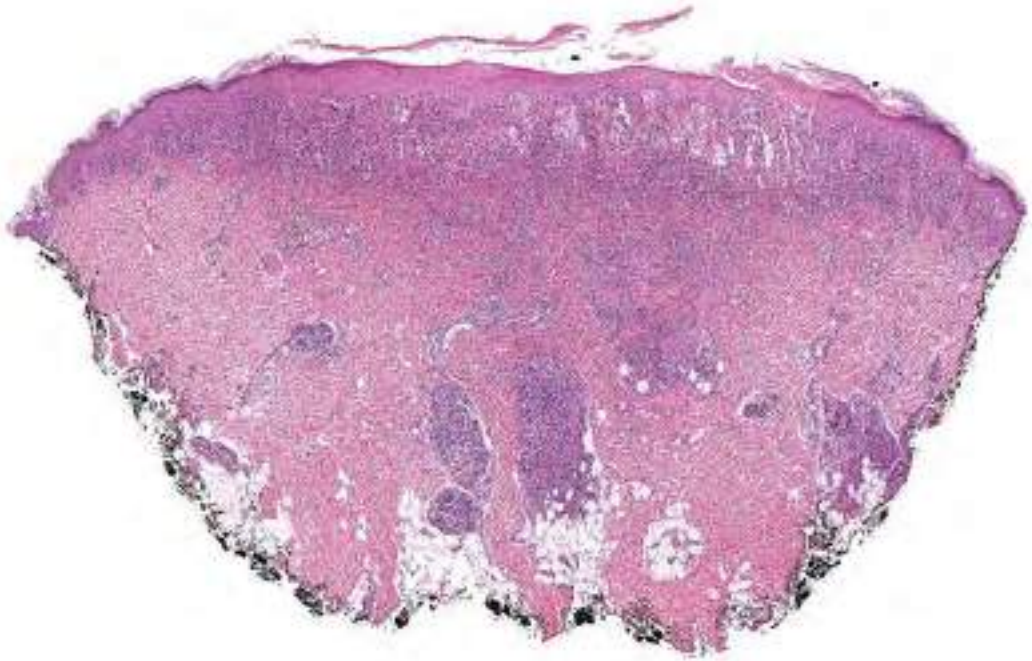


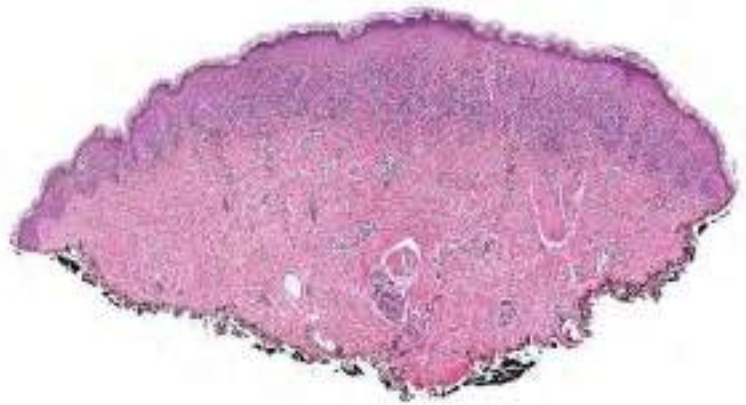



TCR-δ









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ARTICLE

OPEN

Cellular origins and genetic landscape of cutaneous gamma delta T cell lymphomas

Jay Daniels[1,7,14], Peter G. Doukas[1,15], Maria E. Martinez Escala[1], Kimberly G. Ringbloom[1], David J.H. Shih[2,3], Jingyi Yang[1], Kyle Tegtmeyer[1], Joonhee Park[1], Jane J. Thomas[1], Mehmet E. Selli[1], Can Altunbulakli[1], Ragul Gowthaman[4,5], Samuel H. Mo[6], Balaji Iothishankar[7], David R. Pease[1], Barbara Pro[8], Farah R. Abdulla[9], Christopher Shea[1], Nidhi Sahni[3,10,11,12], Alejandro A. Gru[13,14], Brian G. Pierce[4,5], Abner Louissaint Jr[15,16], Joan Guitart[1,14] & Jaehyuk Choi[1,2,16,17]✉

Primary cutaneous γδ T cell lymphomas (PCGDTLs) represent a heterogeneous group of uncommon but aggressive cancers. Herein, we perform genome wide DNA, RNA and T cell receptor (TCR) sequencing on 29 cutaneous γδ lymphomas. We find that PCGDTLs are not uniformly derived from Vδ2 cells. Instead, the cell-of-origin depends on the tissue compartment from which the lymphomas are derived. Lymphomas arising from the outer layer of skin are derived from Vδ1 cells, the predominant γδ cell in the epidermis and dermis. In contrast, panniculitic lymphomas arise from Vδ2 cells, the predominant γδ T cell in the fat. We also show that TCR chain usage is non-random, suggesting common antigens for Vδ1 and Vδ2 lymphomas respectively. In addition, Vδ1 and Vδ2 PCGDTLs harbor similar genomic landscapes with potentially targetable oncogenic mutations in the JAK/STAT, MAPK, MYC, and chromatin modification pathways. Collectively, these findings suggest a paradigm for classifying, staging, and treating these diseases.

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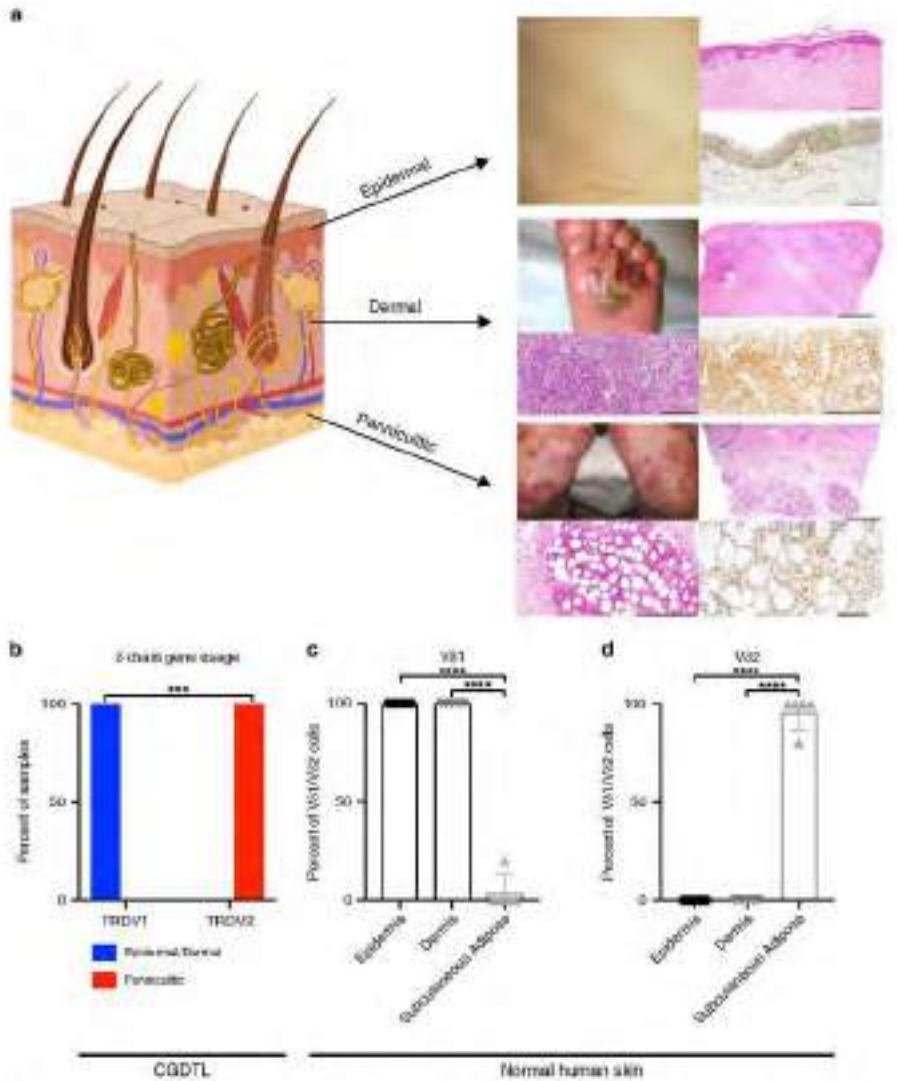
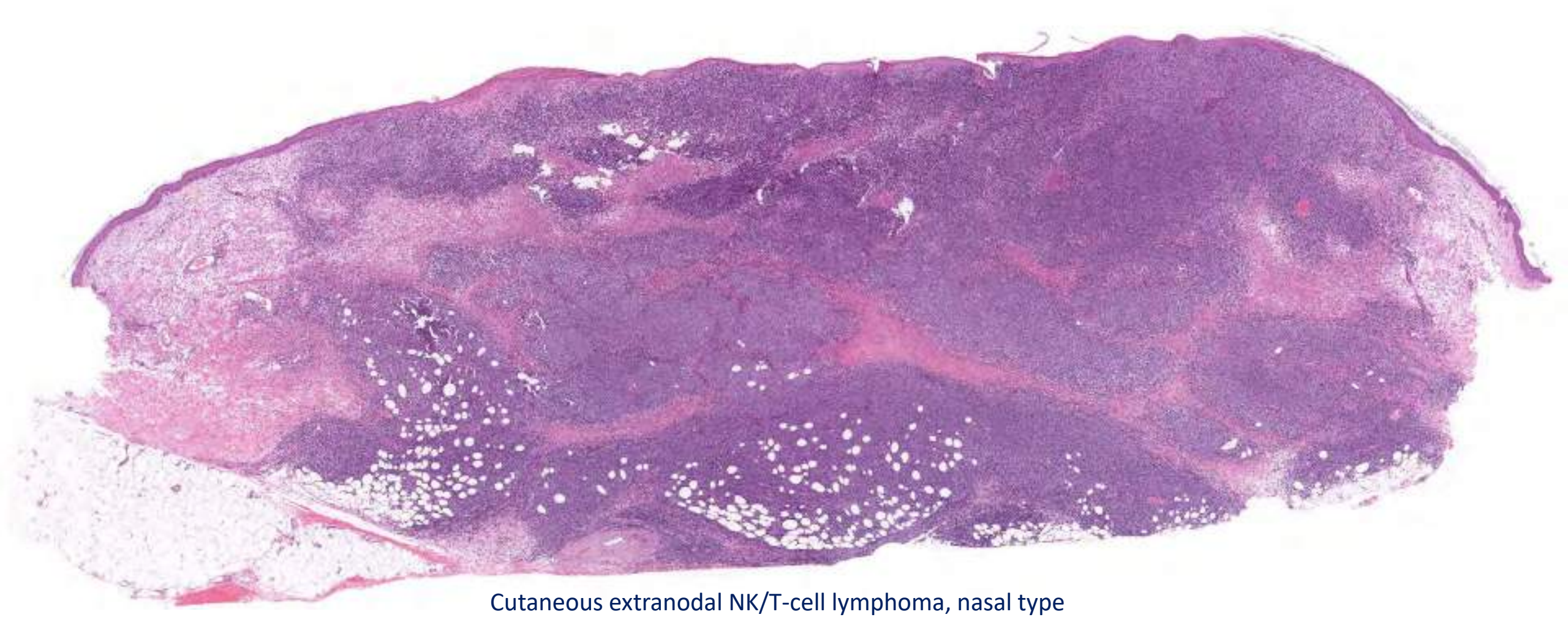


Fig. 1 Epidermal/dermal and panniculitic CGDTLs derived from distinct cells of origin. a Schematic highlighting distinct clinical and histological presentations of disease involving epidermis, dermis, or subcutaneous tissue. Clinical photographs of disease lesions, hematoxylin and eosin staining of biopsies, and γδ T cell receptor immunostaining (see "Methods" section) for representative patients with epidermal, dermal, and panniculitic disease are shown. Skin schematic created with BioRender. Scale bar represents 100 μm in bottom right epidermal panel, bottom left dermal panel, and bottom right panniculitic panel; 200 μm in top right epidermal panel, bottom right dermal panel, and bottom left panniculitic panel; 500 μm in top right dermal panel and top right panniculitic panel. **b** Frequency of δ chain usage by skin compartment in CGDTL as assessed by RNA-seq and high-throughput TCR-Seq. Lymphomas involving epidermis and/or dermis ($n = 8$) or subcutaneous tissue (panniculitic) ($n = 7$). *** Indicates P value = 0.0002, two-sided Fisher's exact test. **c**, **d** Flow cytometry analysis showing percentage of Vδ1 and Vδ2 T cells in normal human epidermis, dermis, and subcutaneous tissue ($n = 5$). Dots represent individual values, horizontal line represents mean, and error bars represent standard deviation. **** Indicates P value < 0.0001, one-way ANOVA followed by Tukey's multiple comparison test. Source data are provided as a source data file.

Vδ1 cells

Vδ2 cells



Cutaneous extranodal NK/T-cell lymphoma, nasal type

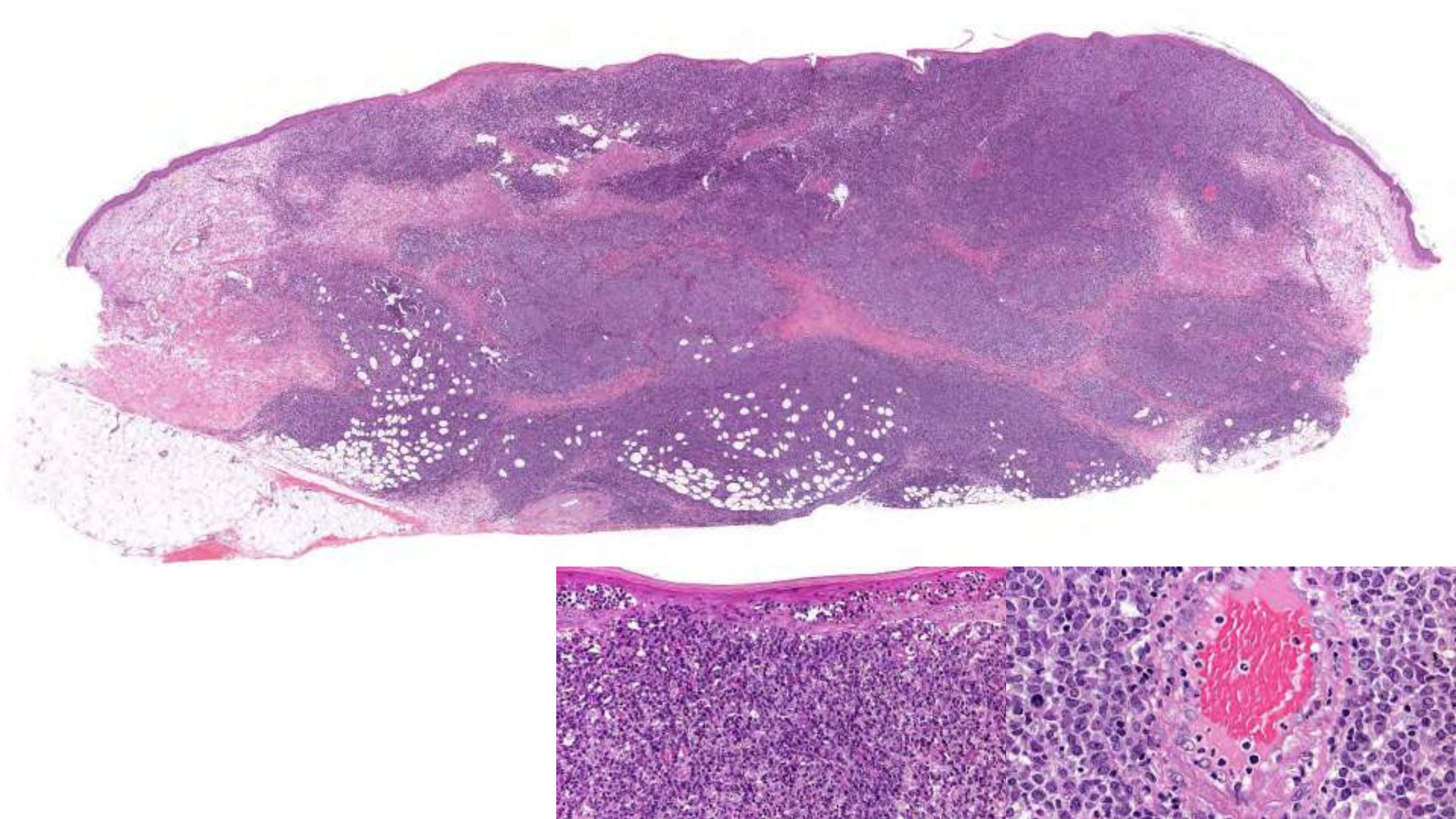
Nasal/perinasal erythematous, partly necrotic plaques ("lethal midline granuloma") and/or palatal ulcers; Persistent facial swelling is another typical presentation; non-descript patches, plaques and tumors on any region of the body.

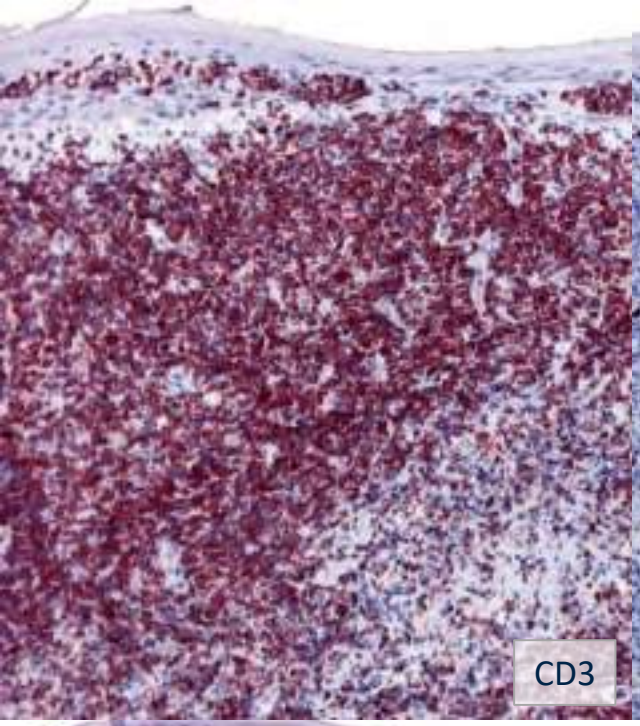
Cell morphology variable (small, medium, large).

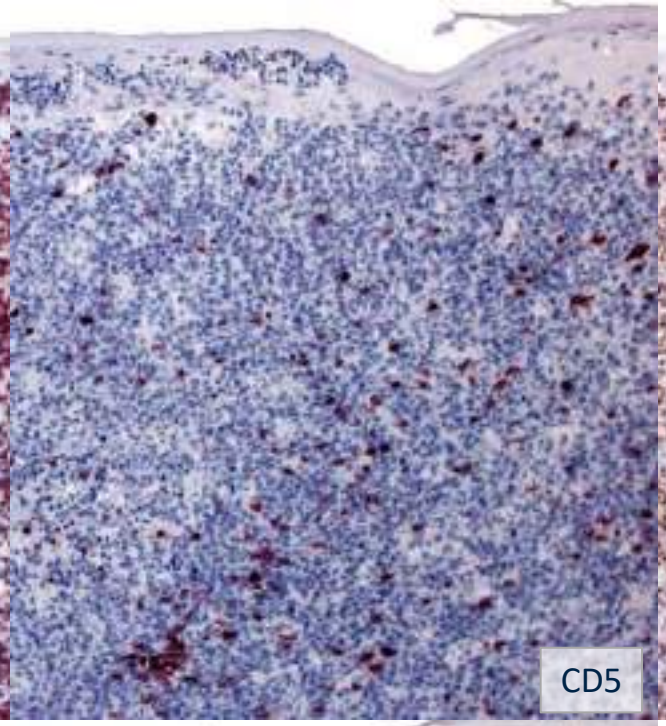
Phenotype: CD2+, CD3+, CD5-, CD4-, CD8-, ßF1-, TCRγ/δ-, CD56+, TIA-1+, Skin often CD2-, CD56-; CD30+ in approx. 30% of cases.

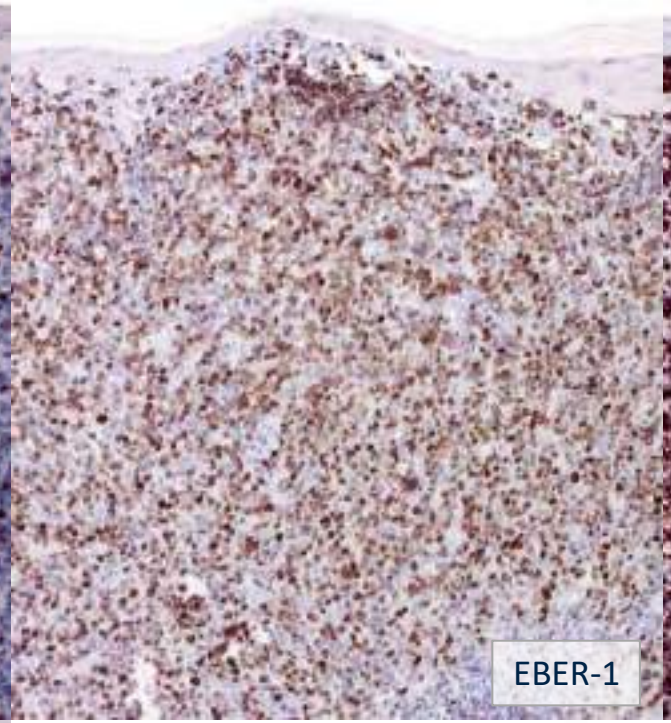
EBV-positivity (EBER-1) and expression of cytotoxic proteins pre-requisites for diagnosis!

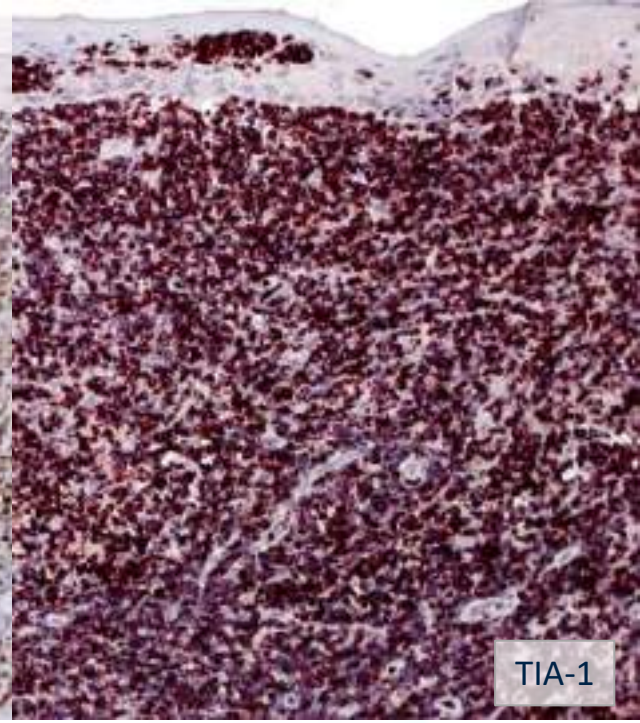
TCR genes rearranged in 10-40% of cases.

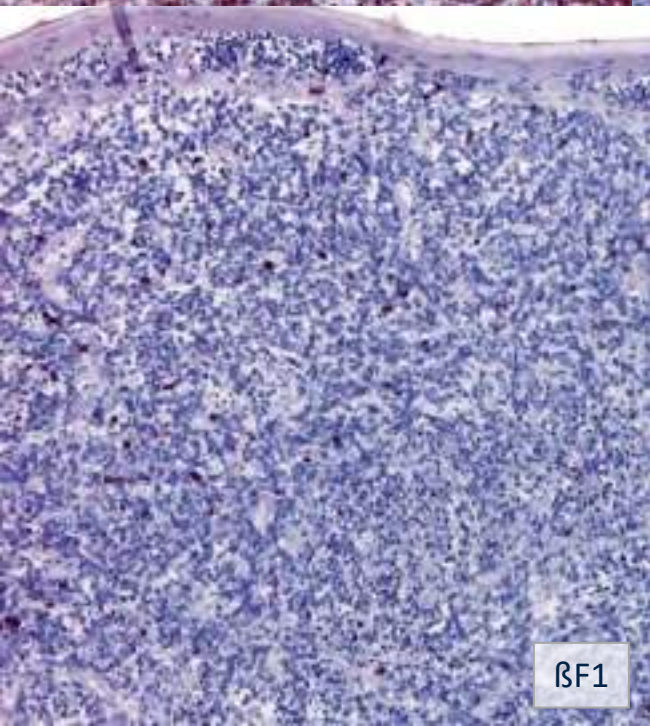


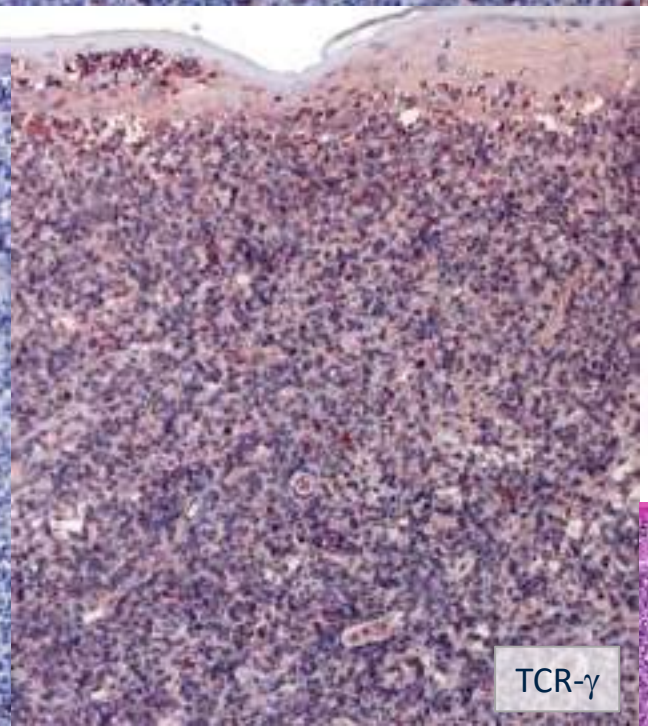

CD3

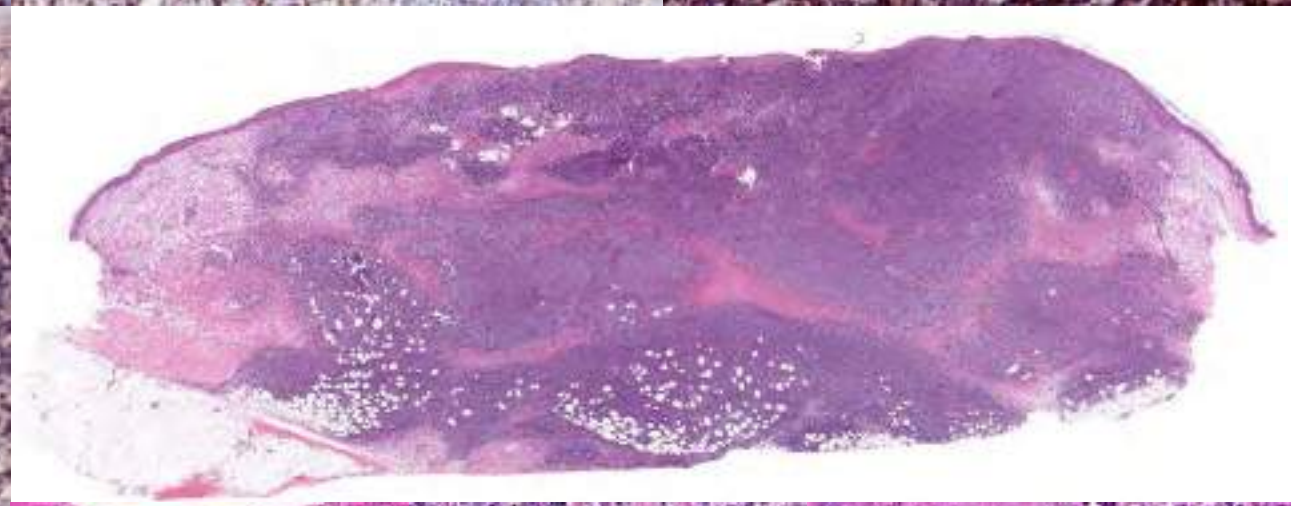

CD5

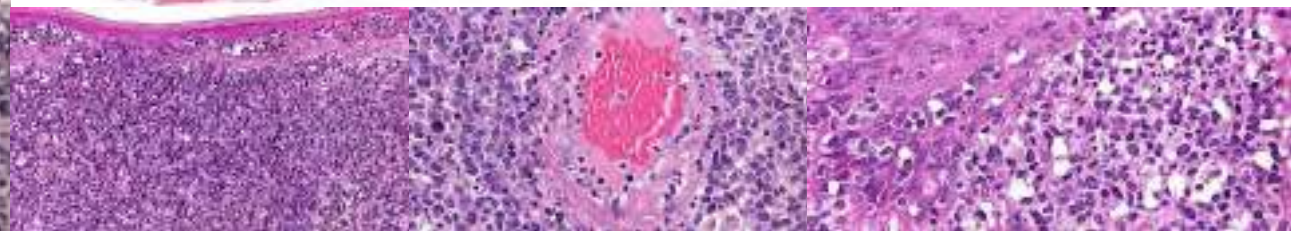

EBER-1


TIA-1


ßF1


TCR-γ





Extranodal NK/T-cell Lymphoma, Nasal Type

A Report of 73 Cases at MD Anderson Cancer Center

Shaoying Li, MD, Xiaoli Feng, MD,* Ying Li, MD,† Shuang Zhang, MD,† Zhuang Zuo, MD, PhD,* Pei Lin, MD,* Sergej Konoplev, MD, PhD,* Carlos E. Bueso-Ramos, MD, PhD,* Francisco Vega, MD, PhD,* L. Jeffrey Medeiros, MD,* and C. Cameron Yin, MD, PhD**

Abstract: Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is uncommon in the United States. We report 73 patients with ENKTL, including 49 men and 24 women (median age, 46 y). Sixty-three patients had nasal/upper aerodigestive tract disease; 10 had extranasal disease involving skin, small intestine, epiglottis, testis, adrenal glands, kidney, and breast. Complete staging data were available for 68 patients: 44 stage I/II and 24 stage IV. Fifteen of 69 (22%) had lymphadenopathy and 10/63 had bone marrow involvement. Histologically, 67/73 (92%) showed necrosis, and 48/70 (69%) had an angiocentric/angiodestructive growth pattern. The neoplastic cells showed a wide spectrum: medium sized (n = 34), mixed small and large (n = 21), large (n = 13), and small (n = 5). In situ hybridization for Epstein-Barr virus–encoded small RNA was positive in every case. Immunohistochemical studies showed expression of cytotoxic markers (100%), T-bet (96%), CD2 (96%), CD5 (92%), CD56 (90%), and BTS-1 (64%). Ki-67 was >80% in 46% cases. Therapy was known for 64 patients; 14 received only chemotherapy, 8 radiation alone, and 42 received combined radiation and chemotherapy. Median survival was 4.2 years, and 5-year overall survival was 46% (median follow-up, 3.5 y). Extranasal disease, high International Prognostic Index score, and high proliferation rate correlated with poorer prognosis. We conclude that ENKTL cases in the United States are similar to those reported in Asia and other countries. Absence of the angiocentric/angiodestructive pattern and presence of lymphadenopathy, features underemphasized in the literature, occurred in appreciable subsets of patients. The International Prognostic Index score, anatomic site of disease, and proliferation rate had prognostic value in this patient cohort.

Key Words: extranodal NK/T-cell lymphoma, nasal type, southern United States

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Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is a rare type of lymphoma that is endemic to East Asia and parts of Central and South America. Most (80% to 90%) patients present with nasal obstruction, sinusitis, ulcer, and epistaxis due to a destructive mass involving the midline facial tissues. ENKTL most often presents as a localized disease, clinical stage I-II; however, widespread dissemination can occur in a subset of patients. Occasionally, patients with ENKTL present with only extranasal sites of disease, most often skin, lung, and gastrointestinal tract, but a variety of other extranasal sites have been reported.[1–4]

Accurate diagnosis of ENKTL can be challenging, especially in small biopsy specimens or in frozen sections, as the neoplastic cells are often admixed with inflammatory cells and necrosis. An angiocentric and angiodestructive growth pattern is common and has been emphasized in the literature, but this pattern is not invariable.[1] Most cases of ENKTL are thought to be of NK-cell lineage or derived from an NK/T-cell precursor cell, but a subset of cases meets the criteria for T-cell lineage.[1] In the 2008 World Health Organization classification, presence of Epstein-Barr virus (EBV), usually shown by assessment for EBV-encoded small RNA (EBER), was included in the disease definition, and EBV has been implicated in disease pathogenesis.[5,6,12]

Although the clinicopathologic features of ENKTL are well recognized, most current data are derived from patient populations in endemic regions, particularly East Asia.[2,3,7] Data on patients with ENKTL in developed countries are limited.[8] In this study, we report the clinicopathologic and immunophenotypic features of a large series of patients with ENKTL at our institution in the United States.

MATERIALS AND METHODS

Case Selection

We searched the database of the Department of Hematopathology at The University of Texas MD Anderson Cancer Center from January 1, 1985 to March 31, 2012 for cases of ENKTL. The diagnosis was based on morphologic and immunophenotypic criteria as specified in the World Health Organization classification.[1] Clinical information was obtained by review of medical records.

73 cases

(63 nasal / upper aereodigestive tract, 10 extranasal including skin)

32 cases with incomplete data, lineage could not be assigned

24 cases (59%) of NK-cell lineage
17 cases (41%) of T-cell lineage

All cases positive for EBV (EBER-1)

Cutaneous epidermotropic lymphomas

Mycosis fungoides and variants

Conventional clinical presentation or features of solitary pagetoid reticulosis
Prominent ("pagetoid") epidermotropism observed mostly in cases with cytotoxic phenotype

Cutaneous γ/δ T-cell lymphoma (subset of cases)

Similar clinical presentation as advanced MF ("Ketron-Goodman" type of pagetoid reticulosis)
TCRγ+ or TCRδ+ cytotoxic phenotype pre-requisite for diagnosis; TCRß may be coexpressed
Aggressive behaviour *(cases reported as "indolent variant" indistinguishable from TCRγ/δ+ MF)*

Aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Similar clinical presentation as advanced MF ("Ketron-Goodman" type of pagetoid reticulosis)
CD8+ by definition (may be non-epidermotropic in given biopsies); TCRß+ / TCRγ– / TCRδ–
Aggressive behaviour

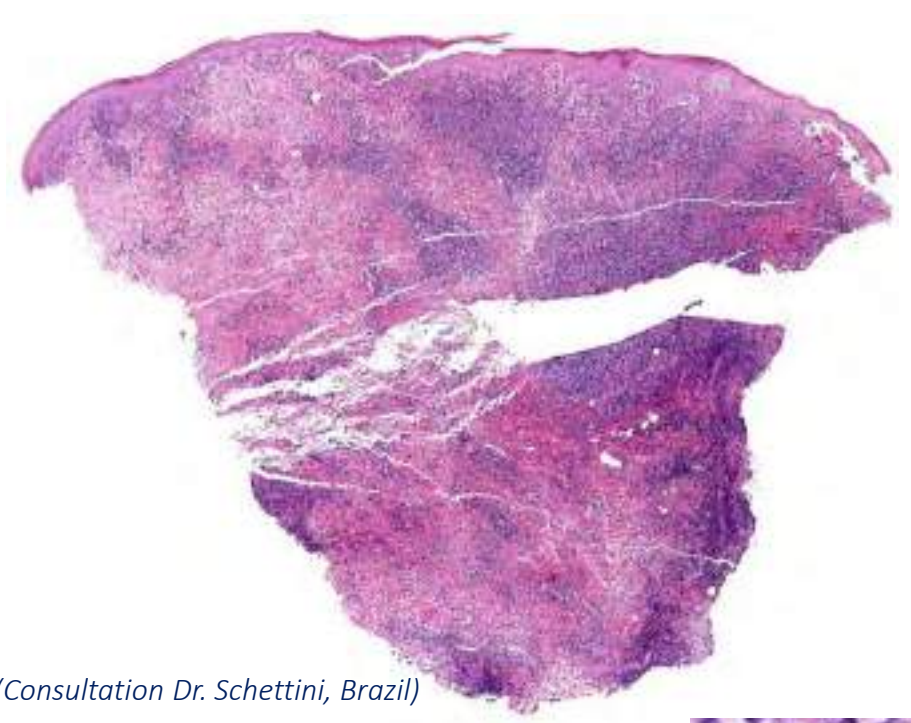
Lymphomatoid papulosis, type B or D

Waxing and waining papules and small nodules
Positivity for CD30 and CD4 (type B) or CD8 (type D) a pre-requisite for the diagnosis

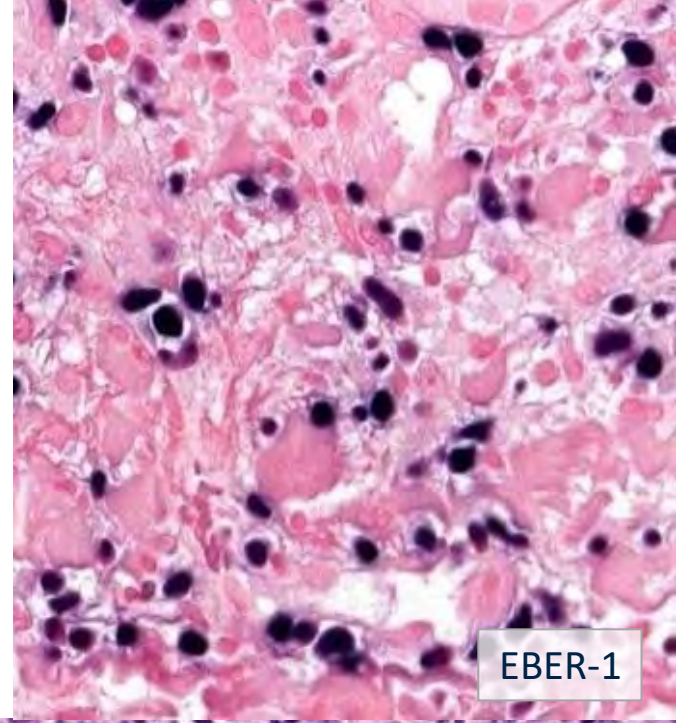
Extranodal NK/T-cell lymphoma, nasal-type (subset of cases)

Positivity for EBV a pre-requisite for the diagnosis (EBER-1+)
Epidermotropism less marked than in other epidermotropic lymphomas (may be absent)
Aggressive behaviour in the majority of cases

… and others, including some cutaneous B-cell lymphomas

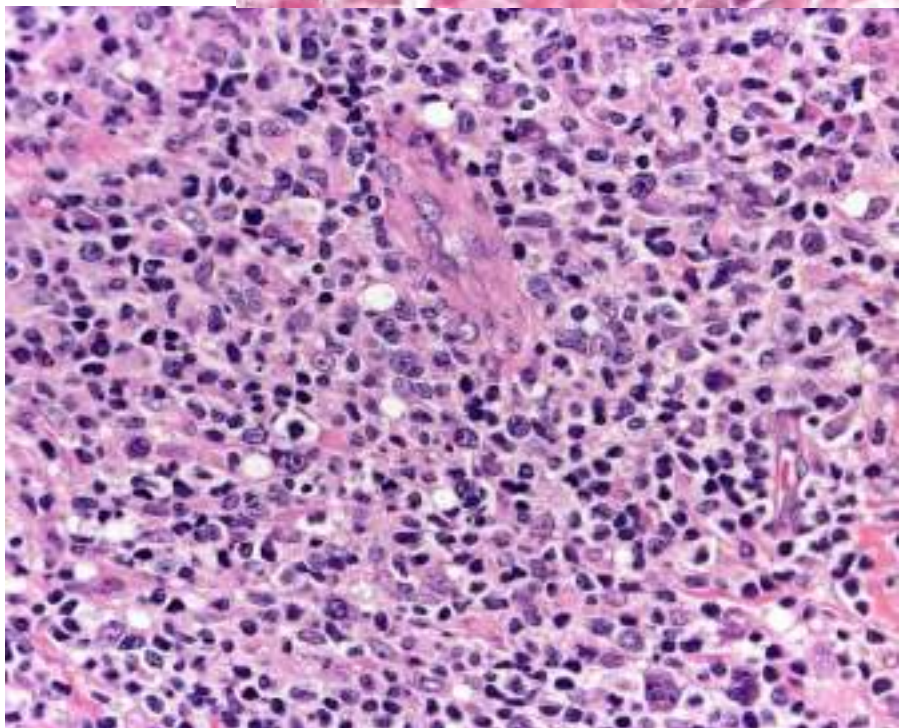


(Consultation Dr. Schettini, Brazil)



Hydroa vacciniforme lymphoproliferative disorder

- WHO 2024: included in the group of EBV+ T/NK-cell lymphoid proliferations and lymphomas of childhood
- Spectrum of clinicopathologic presentations from classic hydroa vacciniforme to severe hydroa vacciniforme and to hydroa vacciniforme-like T-cell lymphoma; genetic background plays a major role
- Hypersensitivity to sun and to insect bites
- Observed mainly in Asia, Mexico, Central- and South-America
- Primary cutaneous; variable clinical course but in HV-like T-cell lymphoma fatal outcome within 10-15 years



Clinicopathologic Features of Hydroa Vacciniforme–Like Lymphoma: A Series of 9 Patients

INTRODUCTION

MATERIALS AND METHODS

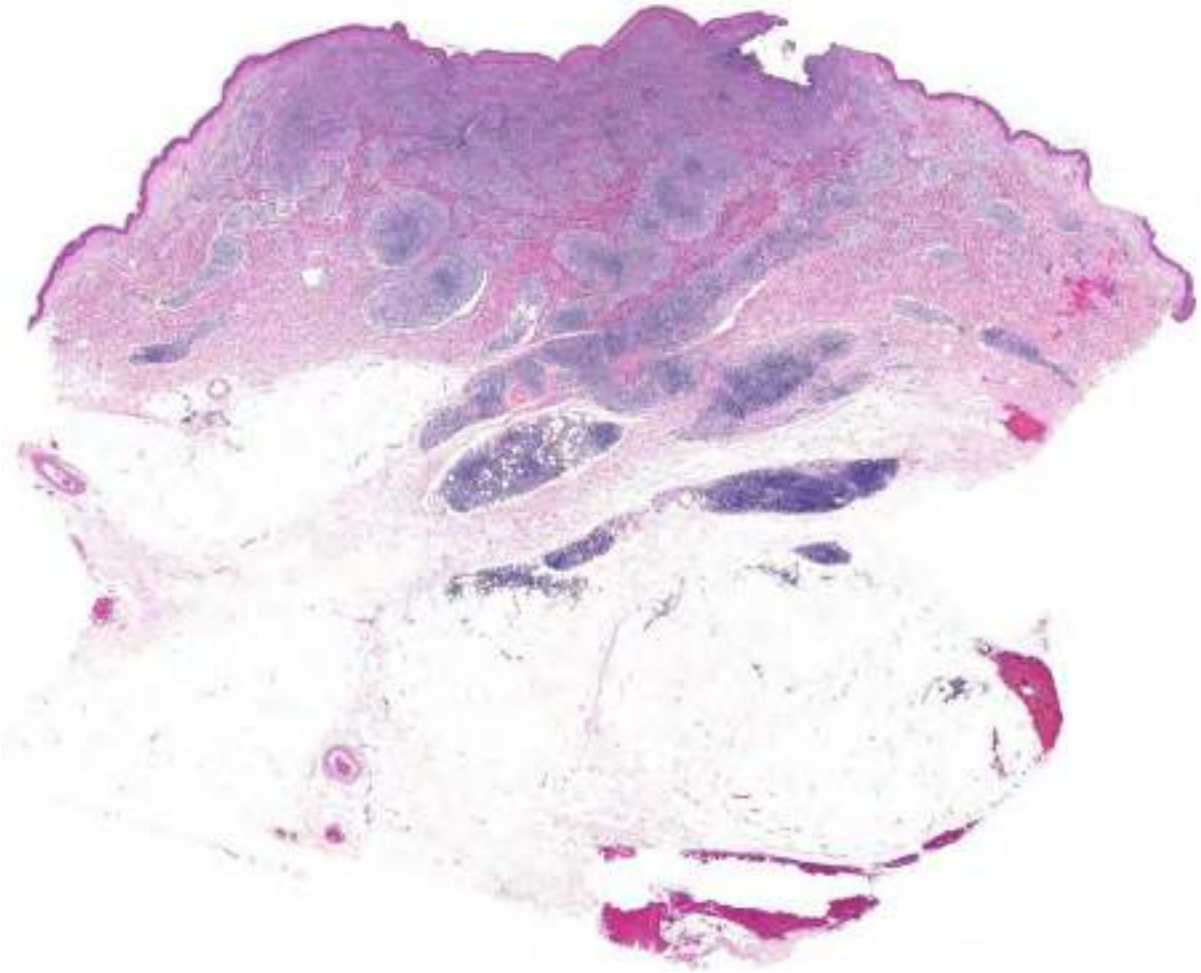
9 Mexican patients (M:F = 2:1; mean age, 14.5 years; median age, 13.3 years; age range, 4–27 years).

Facial edema in all cases.
No case with mosquito bite hypersensitivity.
All cases with extracutaneous involvement at first diagnosis and survival <6 months.

Always cytotoxic phenotype.
3 cases CD8+; 4 cases CD4-/CD8-; 2 cases CD8- with some CD4+ neoplastic cells.

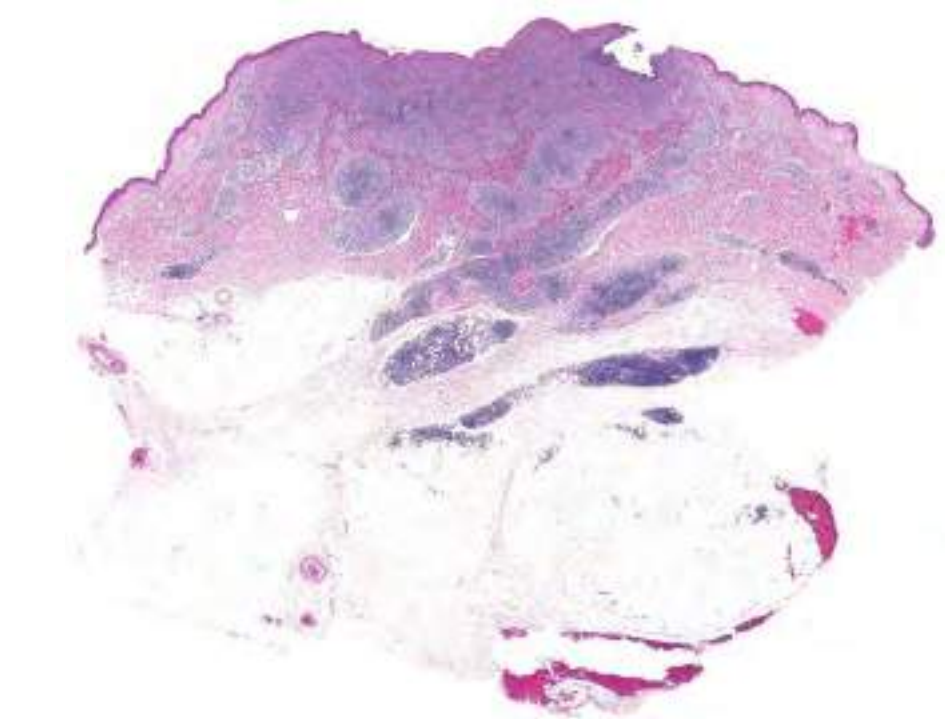
Cutaneous lymphomas

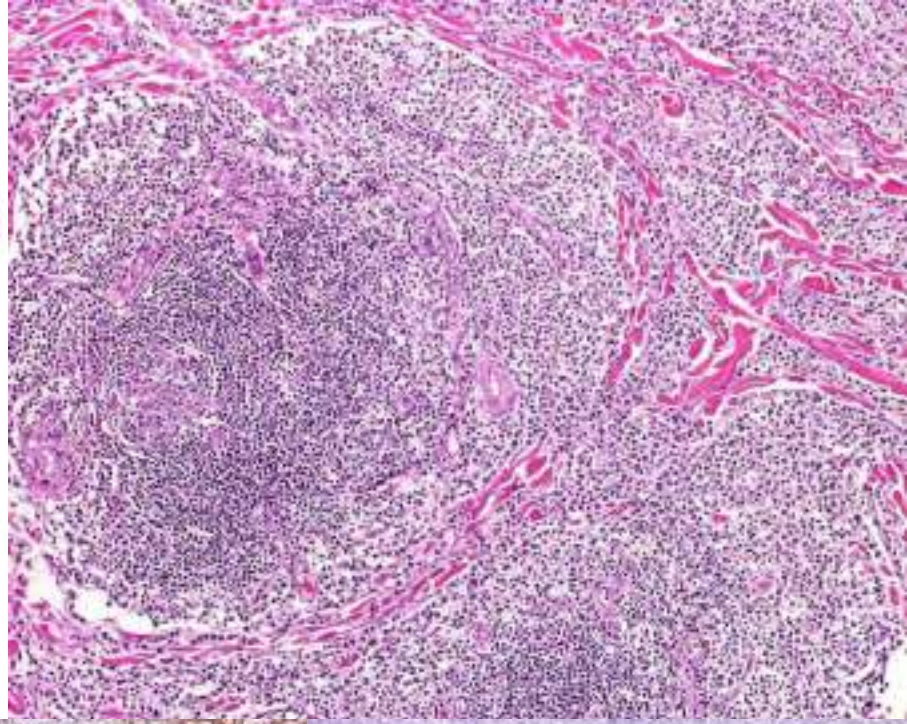
WHO 5ed	***International Consensus Classification 2022***
Mycosis fungoides & variants	Mycosis fungoides & variants
Sézary syndrome	Sézary syndrome
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
Cutaneous CD30+ lymphopr. disorders	Cutaneous CD30+ lymphopr. disorders
Cutaneous anaplastic large cell lymphoma	*Cutaneous anaplastic large cell lymphoma*
Lymphomatoid papulosis	*Lymphomatoid papulosis*
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Cut. extranodal NK/T-lymphoma, nasal-type	Cut. extranodal NK/T-lymphoma, nasal-type
Cutaneous γ/δ T-cell lymphoma	Cutaneous γ/δ T-cell lymphoma
Aggressive epidermotropic CD8+ CTCL	Aggressive epidermotropic CD8+ CTCL
SMPCD4+T-cell lymphoprolif. disorder	SMPCD4+T-cell lymphoprolif. disorder
Acral CD8+ T-cell lymphoproliferative disorder	Acral CD8+ T-cell lymphoproliferative disorder
Systemic chronic active EBV disease	Chronic active EBV infection
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Cutaneous marginal zone lymphoma	Cutaneous marginal zone lymphopr. disorder
Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma
Diffuse large B-cell lymphoma, leg-type	Diffuse large B-cell lymphoma, leg-type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
EBV+ mucocutaneous ulcer	EBV+ mucocutaneous ulcer

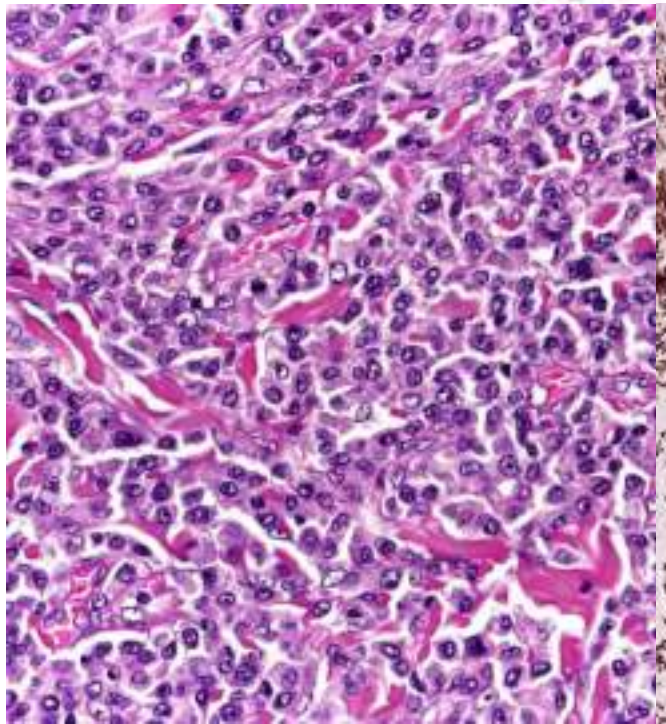


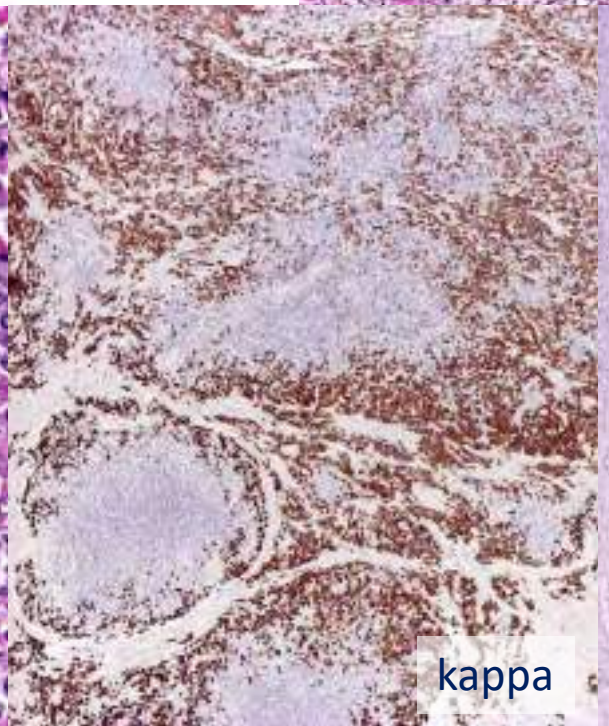
Cutaneous marginal zone lymphoproliferative disorder

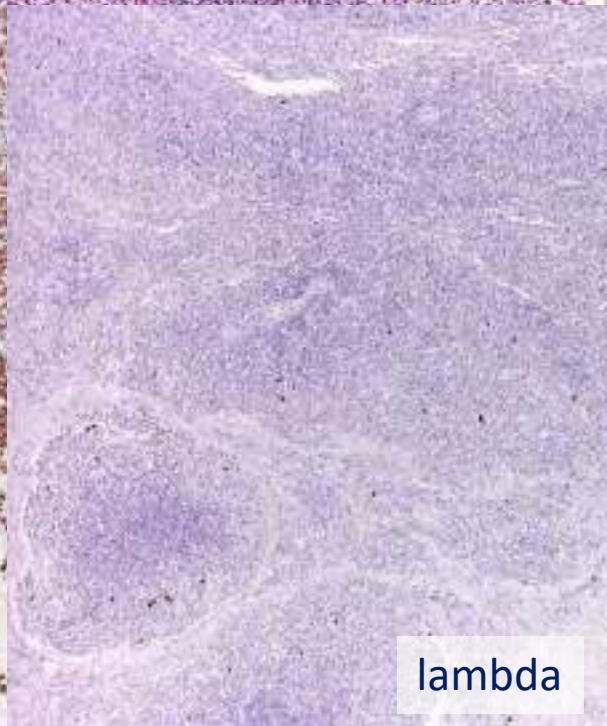
(Young) adults; may occur in children. Predominance of any given cell type (marginal zone cells, lymphoplasmacytoid cells, plasma cells, blastoid cells) does not influence prognosis
Conservative treatment; BM biopsy and staging investigations not necessary.
Histopathological worrying features: blastoid features in sequential biopsies; monomorphous, IgM+ infiltrates (non-class-switched MZLD). Class-switched cases: excellent prognosis; IgM+ cases: excellent prognosis, but extracutaneous dissemination possible.



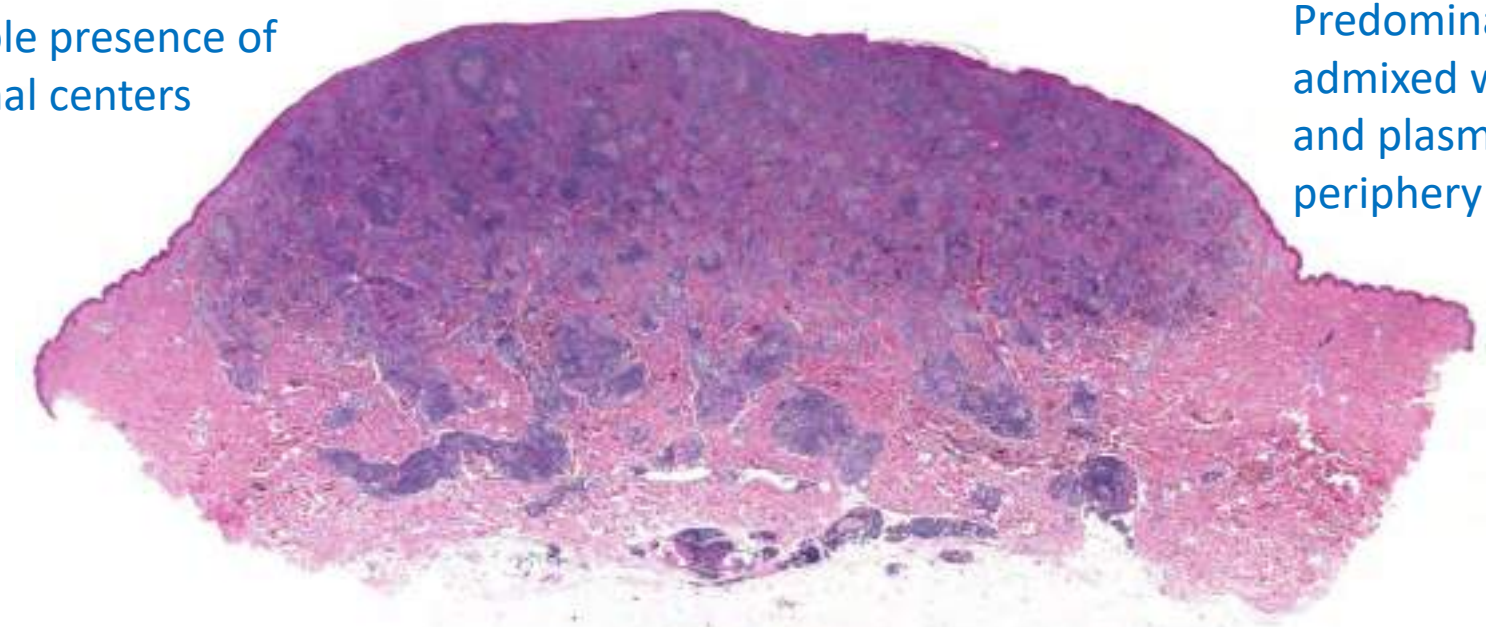




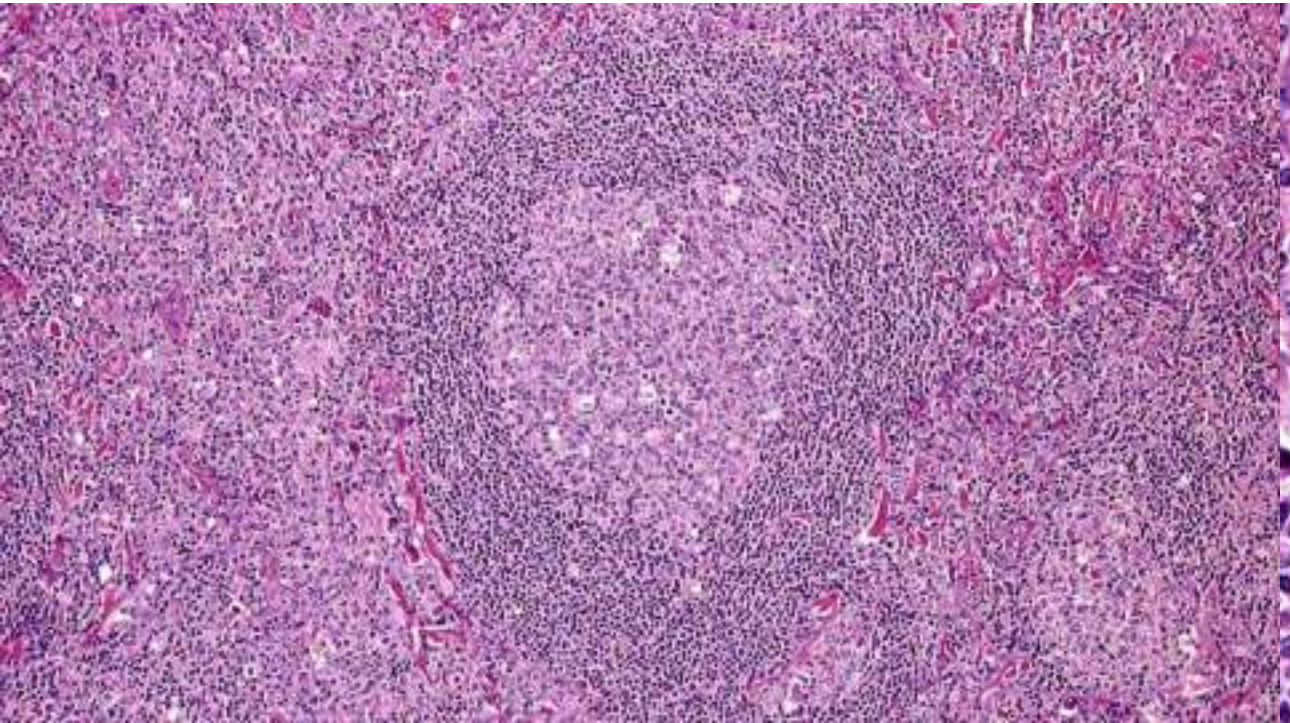

kappa

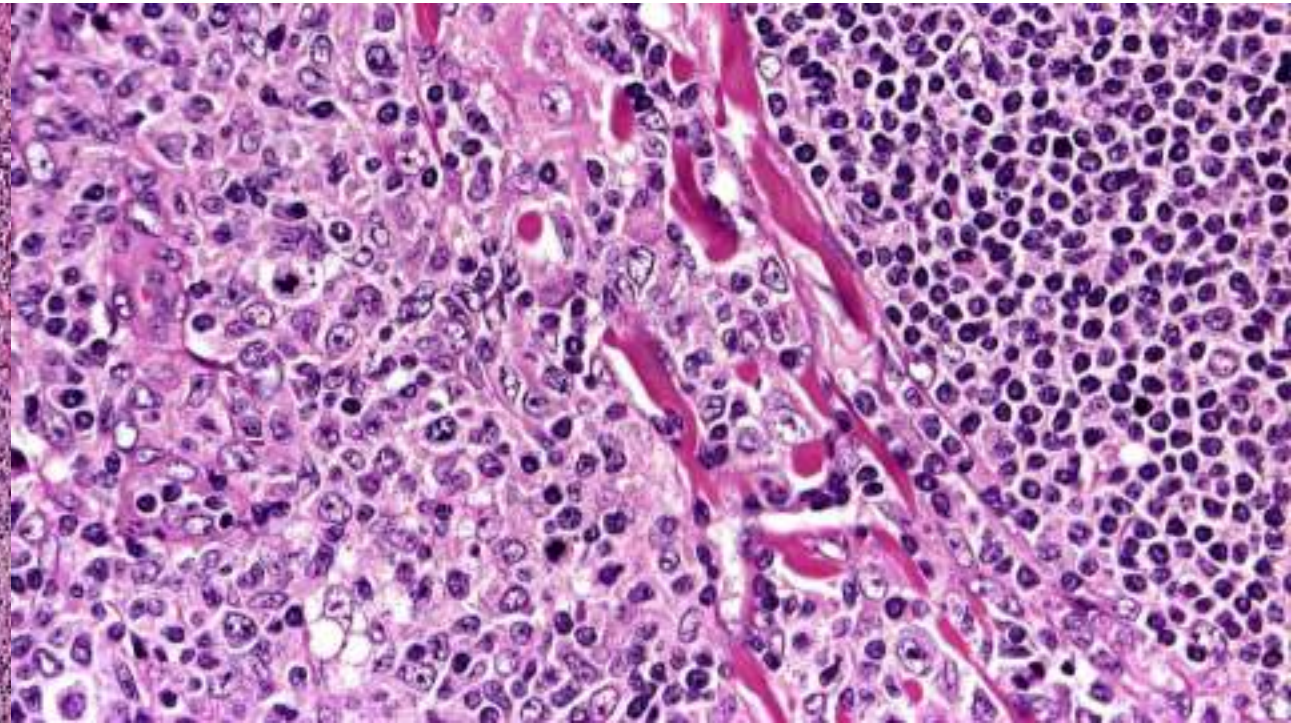

lambda

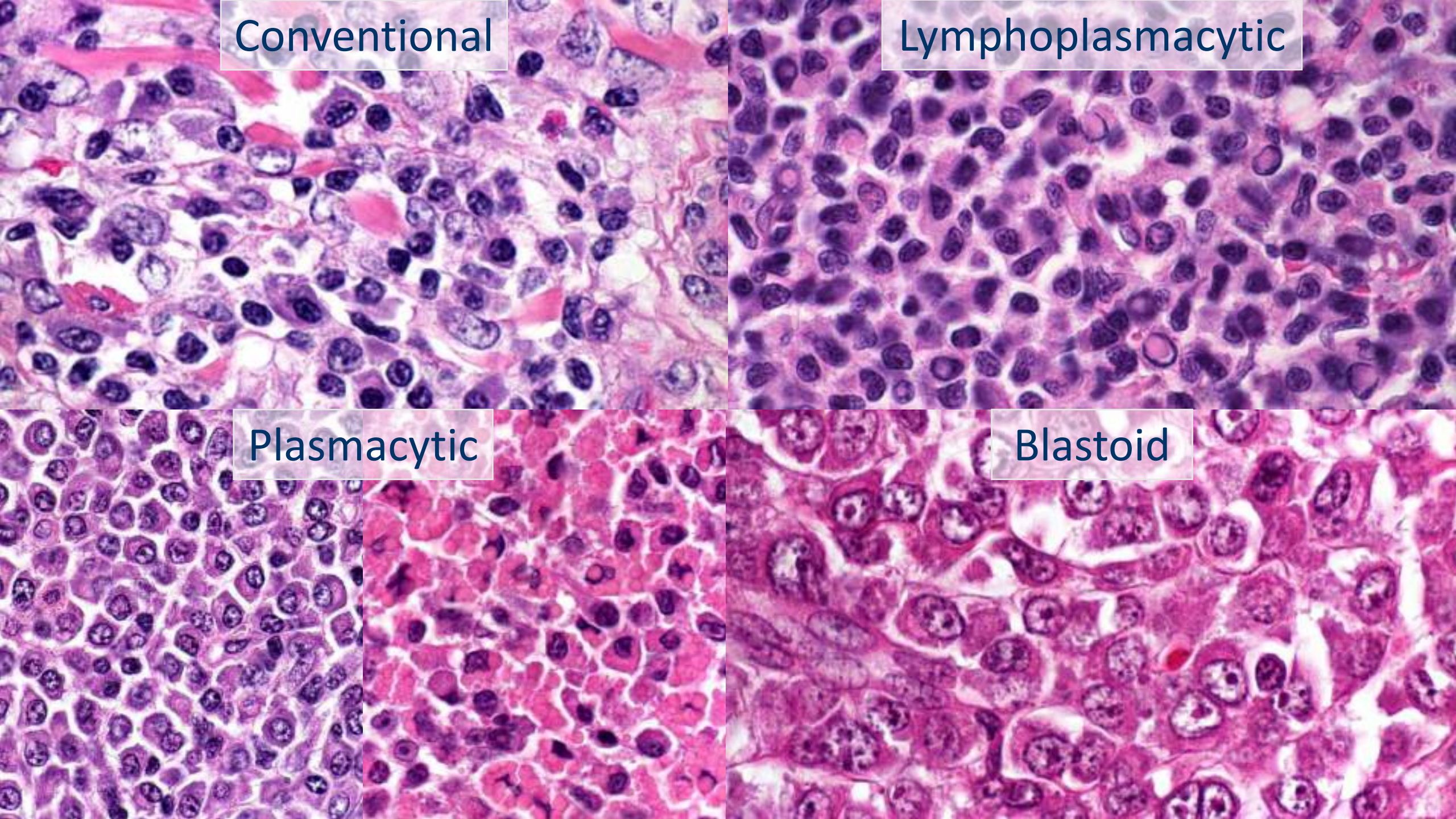
Almost invariable presence of reactive germinal centers



Predominance of reactive lymphocytes admixed with monoclonal marginal zone cells and plasma cells, usually arranged at the periphery of the infiltrate






Conventional
Lymphoplasmacytic
Plasmacytic
Blastoid

Journal of Cutaneous Pathology

Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma

Lorenzo Cerroni, Natalie Zöchling, Barbara Pütz and Helmut Kerl

Department of Dermatology, University of Graz, Austria

In past years, association of primary cutaneous B-cell lymphoma (CBCL) with infection by *Borrelia burgdorferi* has been reported in a few patients. The evidence for a pathogenetic role was based on clinical grounds or raised titre of antibodies in serum. Both methods, however, do not prove the association between the micro-organism and the CBCL, especially in countries where infection by *Borrelia burgdorferi* is endemic. Moreover, the exact percentage of *Borrelia burgdorferi*-positive CBCL is not known. We retrieved from our files 50 cases of CBCL to perform PCR analysis of *Borrelia burgdorferi* DNA on paraffin-embedded tissue sections. Only patients with primary CBCL were selected. In all cases, monoclonality of the infiltrate was confirmed by immunohistological pattern of immunoglobulin light chains or molecular analysis of J_H gene rearrangement, or both. Specific DNA sequences of *Borrelia burgdorferi* were identified in cutaneous lesions from 9 patients (follicle center lymphoma: 3/20; immunocytoma: 3/4; marginal zone B-cell lymphoma: 2/20; diffuse large B-cell lymphoma: 1/6). Specificity was confirmed by Southern blot hybridisation in all positive cases. We could show that *Borrelia burgdorferi* DNA is present in skin lesions from a small proportion of patients (18%) with various types of CBCL. Our results may have therapeutic implications. In analogy to *Helicobacter pylori*-associated MALT-lymphomas, which in some cases can be cured by eradication of *Helicobacter pylori* infection, a proportion of CBCL may be cured with antibiotic therapy against *Borrelia burgdorferi*. Although yet speculative, adequate antibiotic treatment for patients with primary CBCL should be considered before more aggressive therapeutic options are applied, particularly in countries where infection by *Borrelia burgdorferi* is endemic. PCR analysis of *Borrelia burgdorferi* DNA is a first test that should be performed in all patients with CBCL to identify those who more likely could benefit from an early antibiotic treatment.

Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma.
J Cutan Pathol 1997; 24: 457–461. © Munksgaard 1997.

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Accepted April 30, 1997

In past years, association of primary cutaneous B-cell lymphoma (CBCL) with infection by *Borrelia burgdorferi* has been reported in a few patients (1, 2). The evidence for a pathogenetic role was based on clinical grounds (B-cell lymphomas arising on skin affected by acrodermatitis chronica atrophicans) or raised titre of antibodies in serum. Both methods, however, do not prove the association between the micro-organism and the CBCL, especially in countries where infection by *Borrelia burgdorferi* is endemic. Moreover, the exact percentage of *Borrelia burgdorferi*-positive CBCL is not known. We retrieved from our files 50 cases of CBCL to perform PCR analysis of *Borrelia burgdorferi* DNA on paraffin-embedded tissue sections.

Material and methods

Selection of cases: Formalin-fixed, paraffin-embedded biopsy specimens from 50 patients with primary

Review Article

Chronic inflammatory disease, lymphoid tissue neogenesis and extranodal marginal zone B-cell lymphomas

Richard J. Bende, Febe van Maldegem, and Carel J.M. van Noesel

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ABSTRACT

Chronic autoimmune or pathogen-induced immune reactions resulting in lymphoid neogenesis are associated with development of malignant lymphomas, mostly extranodal marginal zone B-cell lymphomas (MZBCLs). In this review we address (i) chemokines and adhesion molecules involved in lymphoid neogenesis; (ii) the autoimmune diseases and pathogens which are associated with development of B-cell lymphomas; (iii) the molecular mechanisms involved in the initiation and progression of MZBCL; and (iv) 'potential' mouse models for MZBCL.

Key words: B-cell non-Hodgkin's lymphoma, extranodal marginal zone B-cell lymphoma, immunoglobulin, B-cell antigen receptor, inflammation, lymphoid tissue neogenesis.

Citation: Bende RJ, van Maldegem F, and van Noesel CJM. Chronic inflammatory disease, lymphoid tissue neogenesis and extranodal marginal zone B cell lymphomas. Haematologica 2009; 94:1659–1663. doi:10.3324/haematol.2009.009852

Lymphoid tissue neogenesis and ectopic germinal center formation

Inflammation is a local response to cellular injury and is initiated by macrophages and local epithelial and/or stromal cells that sense microorganisms and cell damage by pattern recognition receptors, i.e. the Toll-like receptors (TLRs), soluble intracellular NOD-like receptors and RIG-like helicases.[1] The triggered cells respond by secretion of a plethora of inflammatory mediators such as histamine, prostaglandins, leukotrienes, platelet-activating factors and typical pro-inflammatory chemokines and cytokines like IL-1β, IL-6, IL-8 (CXCL8) and TNF. These mediators, and in particular TNF, lead to endothelial activation and vasodilatation followed by a local efflux of circulating leukocytes. The first leukocytes arriving on site are granulocytes which combat the microbial invaders, while monocytes/macrophages clean up dead cells, including apoptotic granulocytes and destroyed tissue.[1] In parallel, dendritic cells (DCs) take up and process antigens (Ag) from the intruder, mature and migrate to a local lymph node to set off an adaptive immune response.

Chronic inflammatory conditions, due to improper eradication of pathogens, auto-immune processes or chronic allograft rejections, are associated with the genesis of organized lymphoid tissue. In recent years, a number of key molecular determinants operating during the generation of tertiary lymphoid tissue, have been identified. In the complex sequence of events, TNF is again one of the key molecules as it induces the production of CCL19 and CCL21 (SLC), which are important for the attraction of B- and T-lymphocytes.

The infiltrating lymphocytes switch on expression of membrane-bound lymphotoxin αβ (mLTαβ) when activated e.g. by Ag.[2] High levels of mLTαβ lead to lymphotoxin receptor (LTβ-R) ligation on stromal cells and/or macrophages and induce CXCL13 (BLC) production.[3] The basal production of CXCL13 mediates homing of B cells and induces the arrival B cells to further upregulate mLTαβ and probably also TNF. The enhanced interaction of CXCL13-producing stromal cells with the TNF- and mLTαβ- producing B cells promotes differentiation of resident stromal cells into follicular dendritic cells (FDCs) which start expressing characteristic molecules to trap immune complexes, i.e. the complement receptors CD21 and CD35 and the FcγR-IIB.[4,5] Subsequent production of CXCL13 by FDCs establishes a positive feedback loop essential for ectopic lymphoid tissue development, similar to embryonic lympho-organogenesis and normal follicle formation (Figure 1).[1,6] The importance of LT and TNF in this process has been demonstrated by transgenic expression of TNF, LTα and LTαβ in the pancreas and the kidneys, leading to formation of organized lymphoid tissue including FDC-containing follicles.[6,7] Transgenic expression of CCL21 alone, resulted in extensive lymphoid tissue development in the pancreas.[8] However, ectopic expression of CXCL12 (SDF), CCL19 or CXCL13 leads to attraction of lymphocytes, some compartmentalization but not to the genesis of FDC-containing follicles.[9]

Depending on the type of pathogen, i.e. differences in the Ag presentation mode and the combination of costimulatory molecules and cytokine signals, Ag presenting cells (APCs) guide T-cell differentiation into the direction of T-helper type 1 (Th1) or T-helper type 2 (Th2) cells. A Tol-polarized response depends

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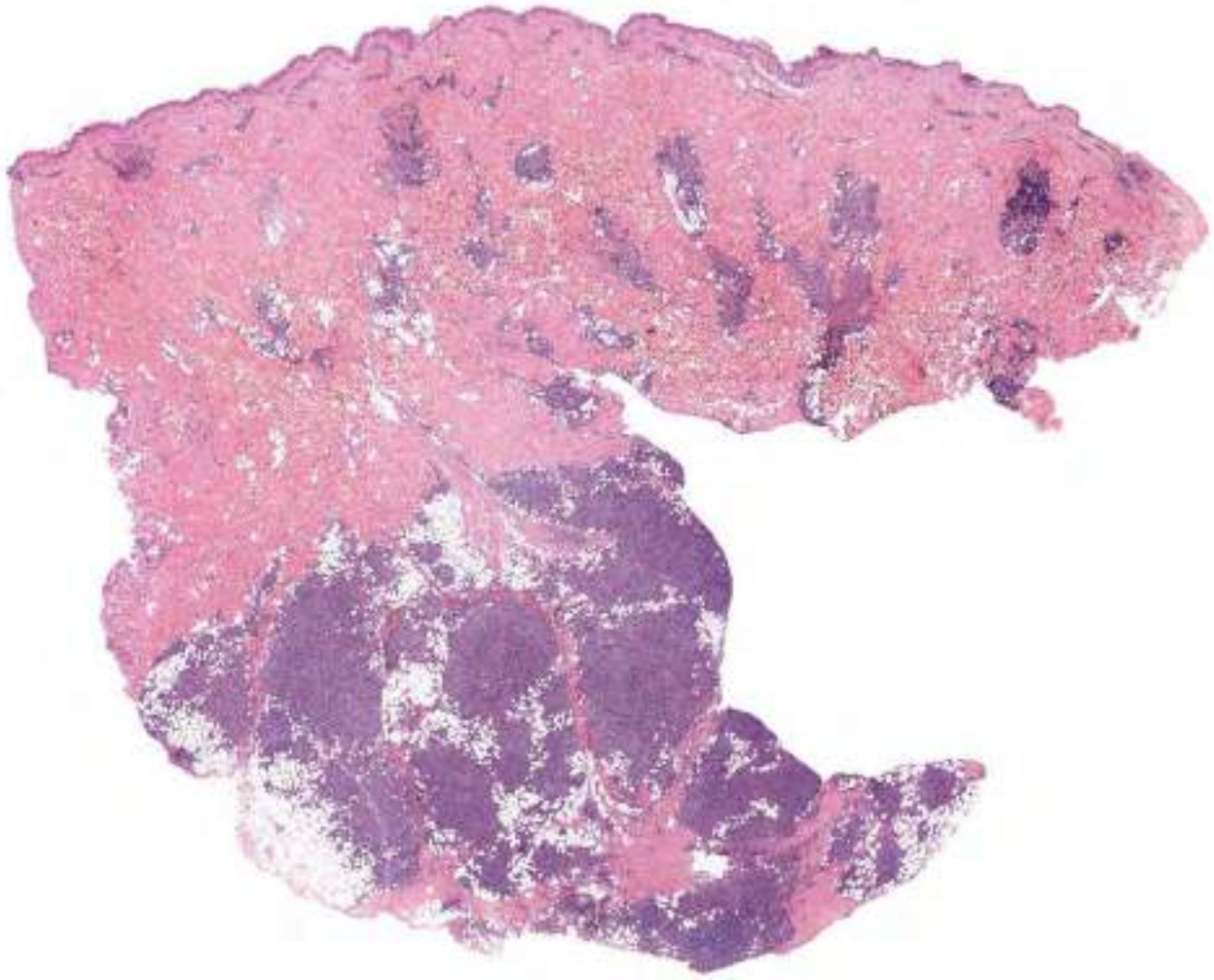
E-mail: c.j.vannoesel@amc.uva.nl

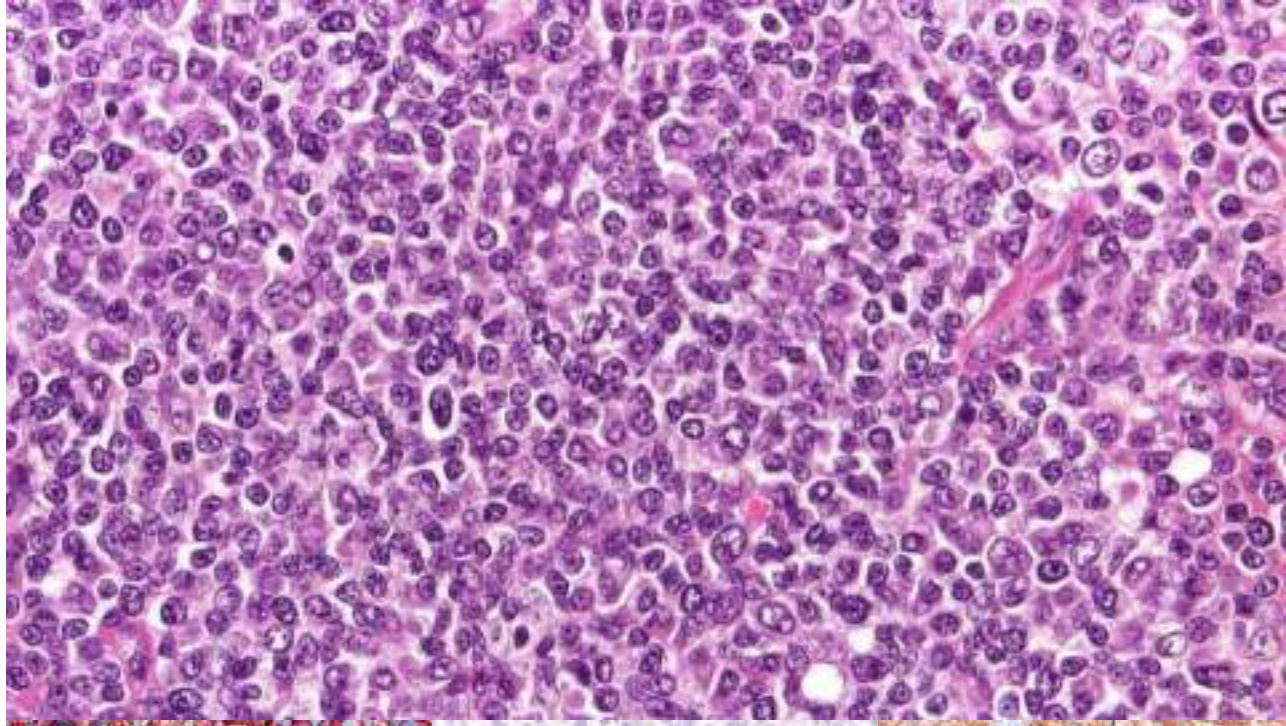
Cutaneous Marginal Zone Lymphomas Have Distinctive Features and Include 2 Subsets

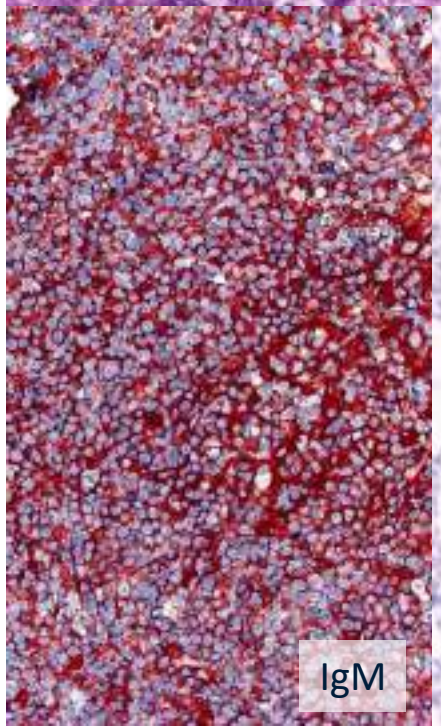
These findings support the presence of 2 types of cutaneous MALT lymphomas with the class-switched cases being the most distinctive but still sharing significant features with MALT lymphomas from other sites.

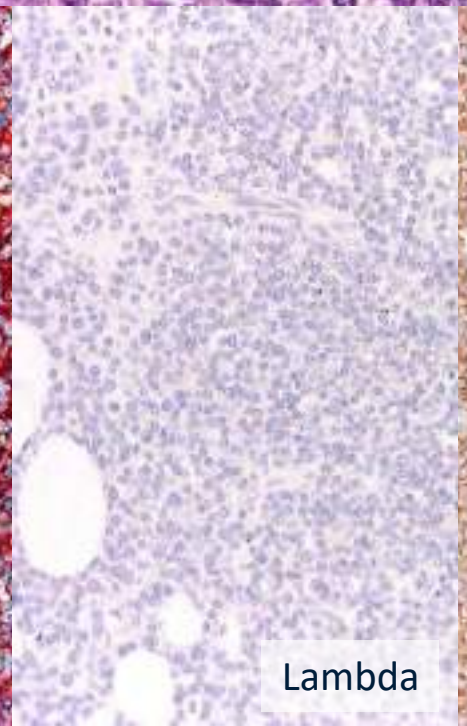
The class-switched cases had a predominance of T cells in 22 out of 23 cases, usually showed nodules and scattered small B cells often with IgD+ apparently nonneoplastic follicles, never showed a totally diffuse growth pattern, and lacked extracutaneous involvement. The IgM+ cases showed a predominance of B cells in 5 out of 6, a diffuse proliferation of CD20+ B cells in all, and extracutaneous disease in 3 out of 6.

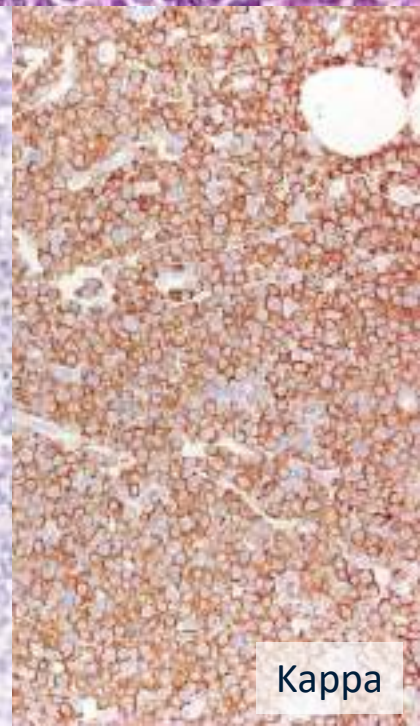
"non-class-switched" cutaneous marginal zone lymphoproliferative disorder (IgM+)











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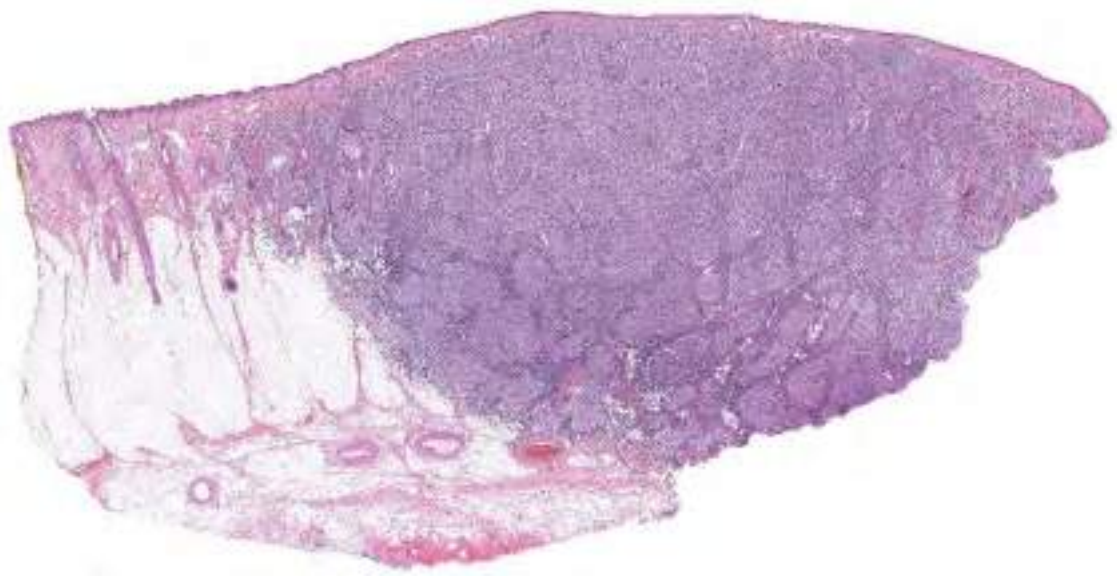
Cutaneous marginal zone lymphoproliferative disorder

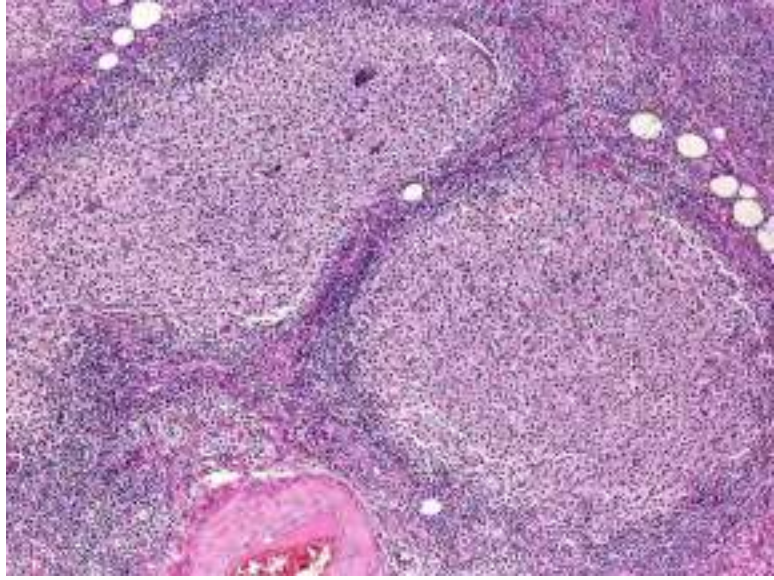
- Segregated from other MALT lymphomas, based on clinicopathologic features including mutational landscape.
- Now considered as a lymphoproliferative disorder rather than overt lymphoma.
- Two subtypes recognized distinguished principally based on whether class-chained switched or IgM+.
- IgM+ subtype requires greater concern about the possibility of concurrent or subsequent extracutaneous involvement.

35th Pezcoller Seminar – Surgical pathology of the skin: hot topics and slide seminars
Trento, May 9-10, 2024

Cutaneous lymphomas & pseudolymphomas 4

Lorenzo Cerroni

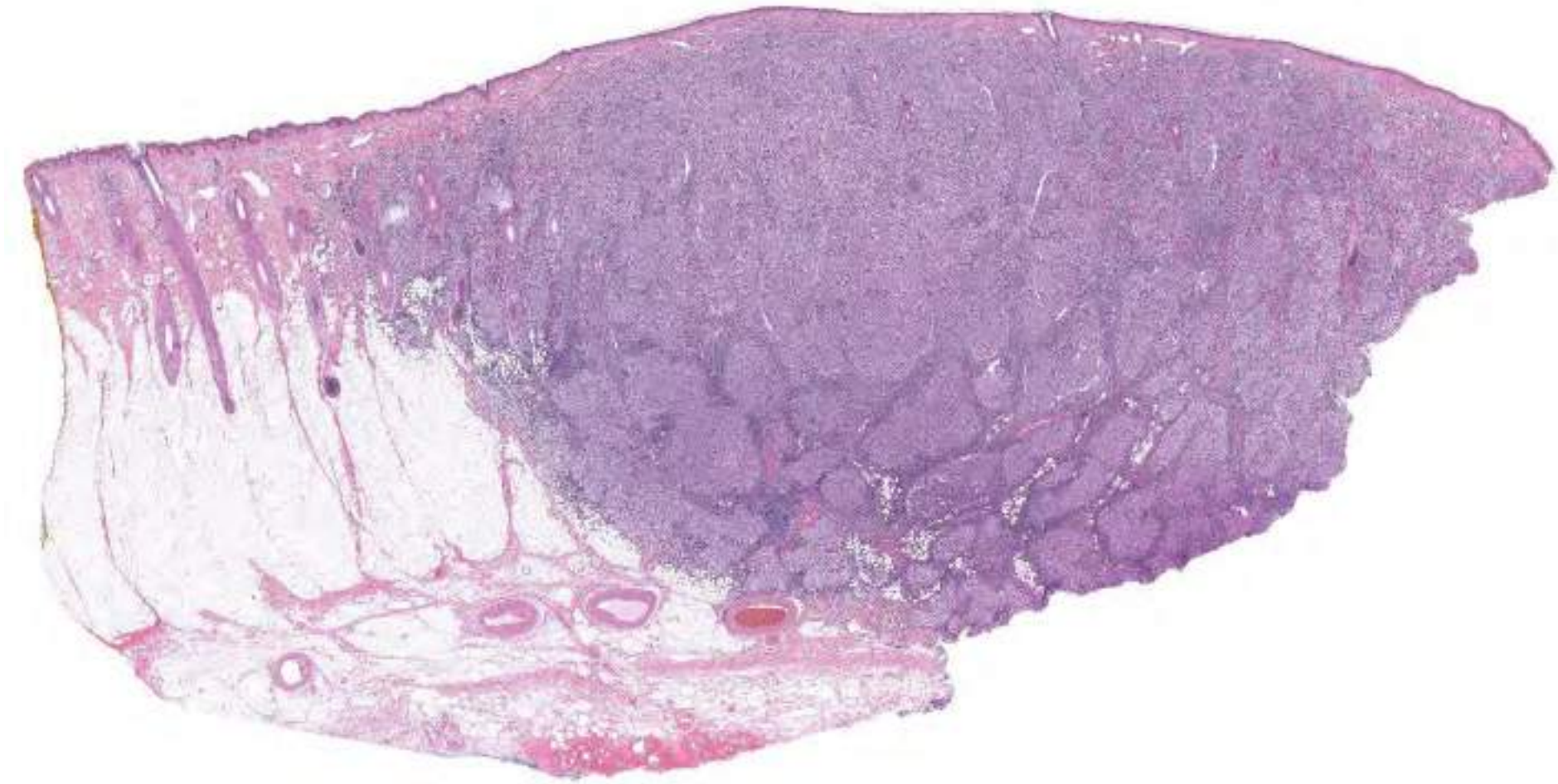


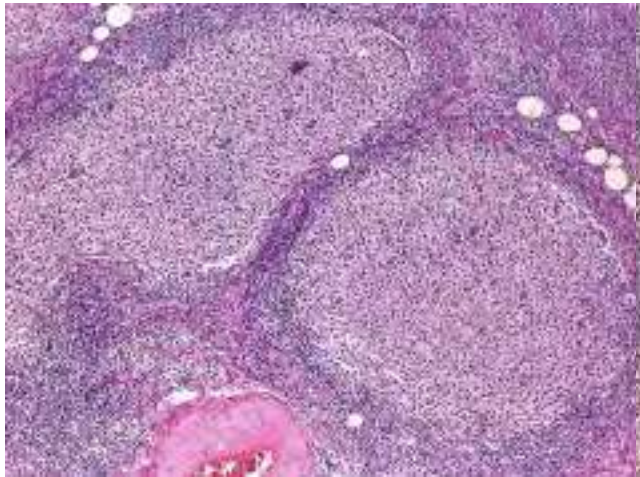


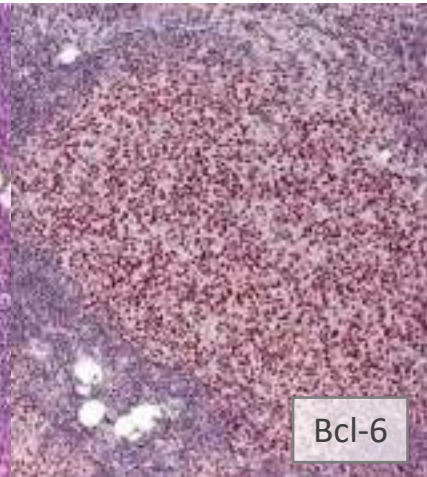
Cutaneous follicle center lymphoma

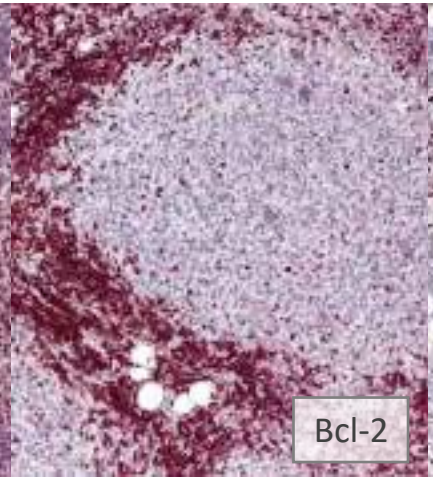
Most common type of cutaneous B-cell lymphoma. Adults; preferential locations: head & neck, trunk ("Crosti's lymphoma"). Staging mandatory; Bcl-2-positivity suspicious for (but not pathognomic of) secondary skin involvement. Indolent course irrespective of growth pattern (i.e., cases with diffuse infiltrates of large centrocytes are not classified as a high grade lymphoma). Differentiation from pcDLBCL, leg-type based on clinical presentation, cell morphology (predominance of centrocytes rather than of centroblasts & immunoblasts), and phenotype.

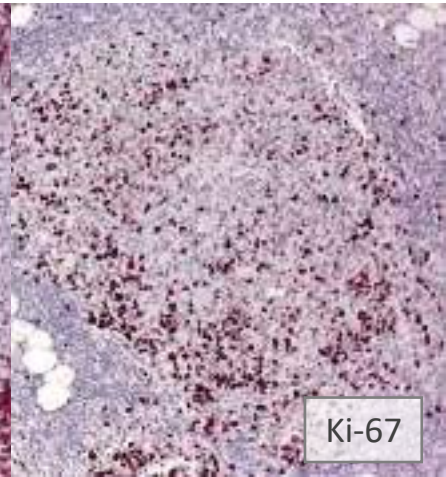
Deletion of chromosome 14q32.33 containing the oncogene *AKT1*, as well as the immunoglobulin heavy chain locus has been reported. Mutations in *CREBBP*, *KTM2D*, and *BCL2* much less frequently than in nodal follicular lymphoma. Mutations in *MYD88* and inactivation of *CDKN2A* and *CDKN2B* by deletion (9p21.3) or their promotor hypermethylation are not or only rarely found in PCFCL, in contrast to PCLBCL, leg type.

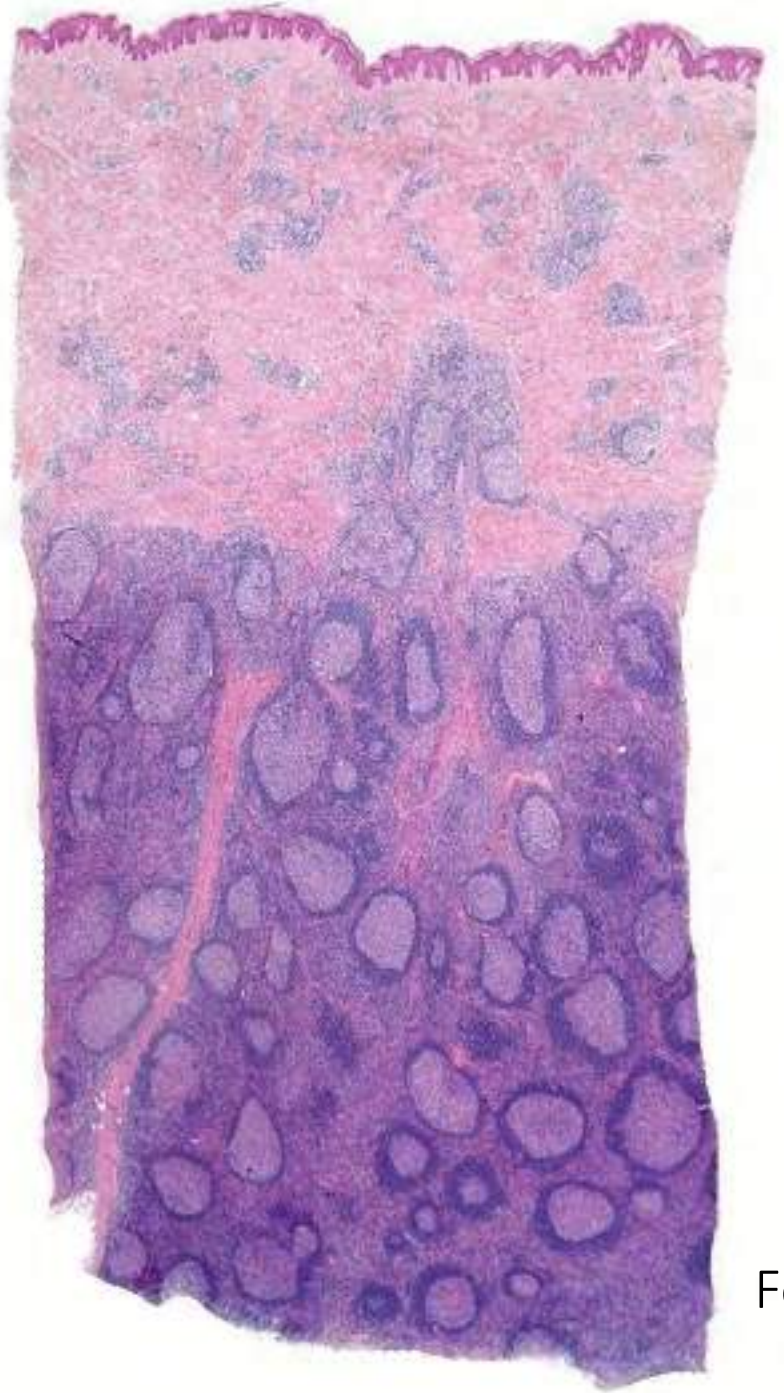




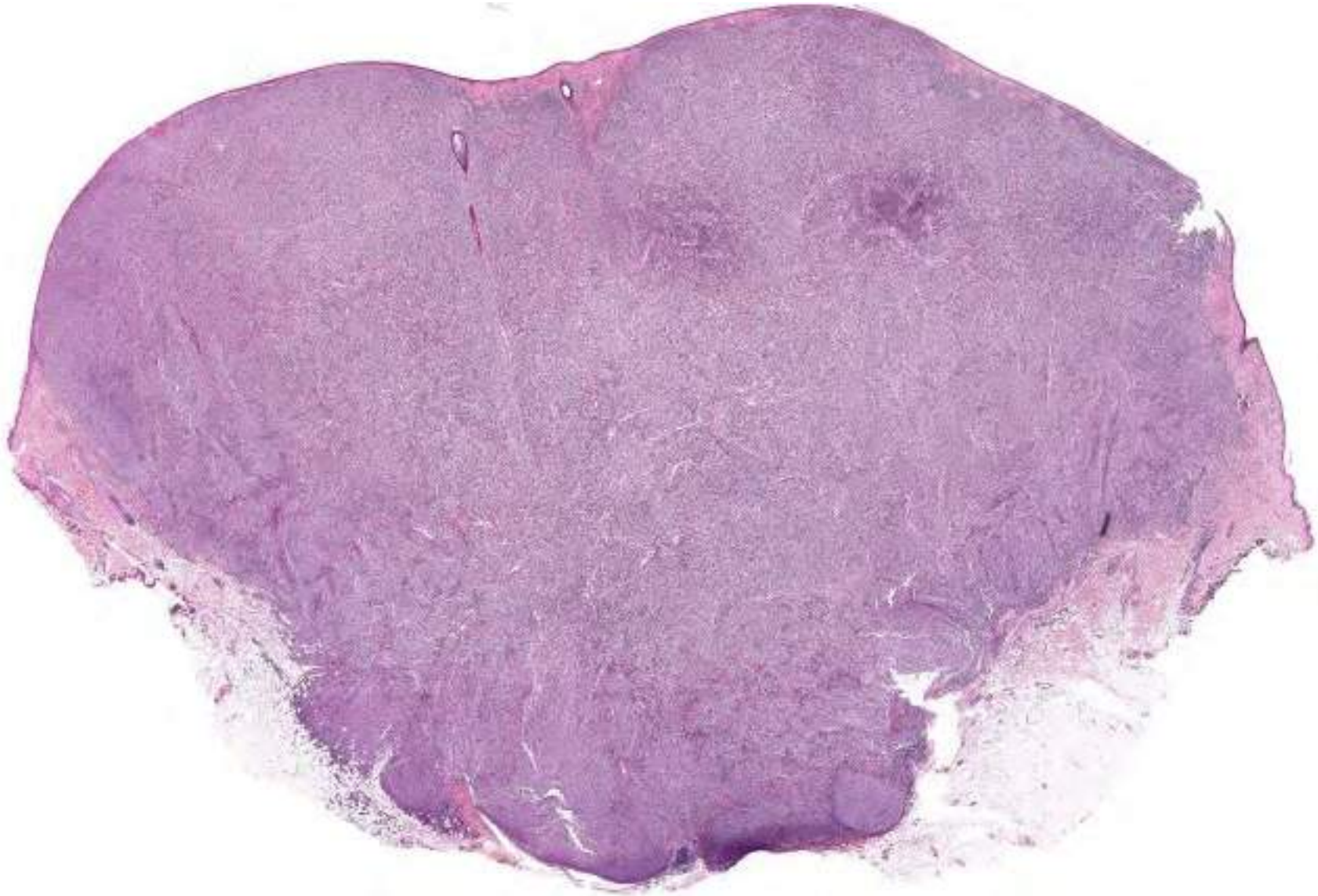

Bcl-6


Bcl-2

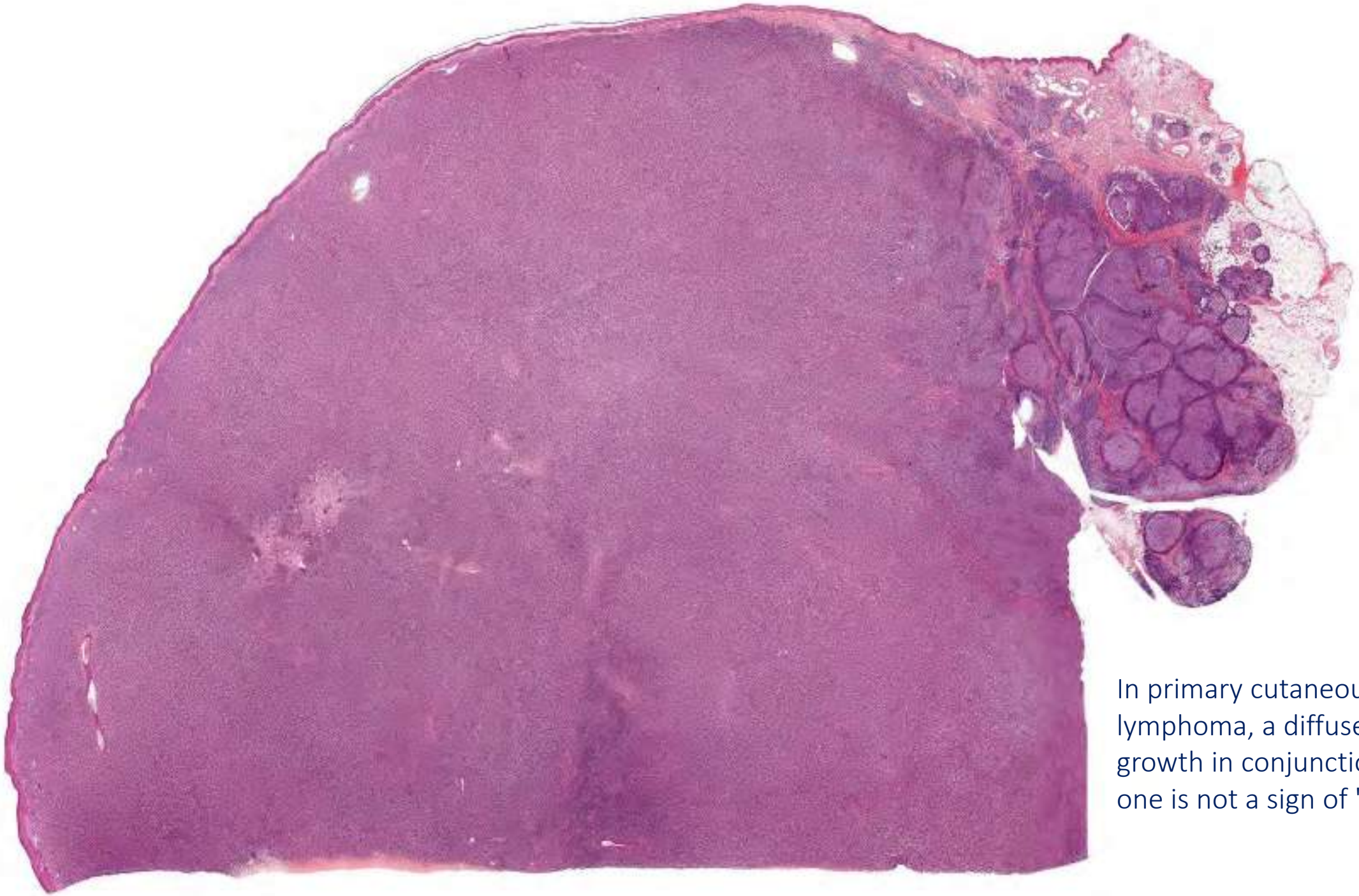

Ki-67



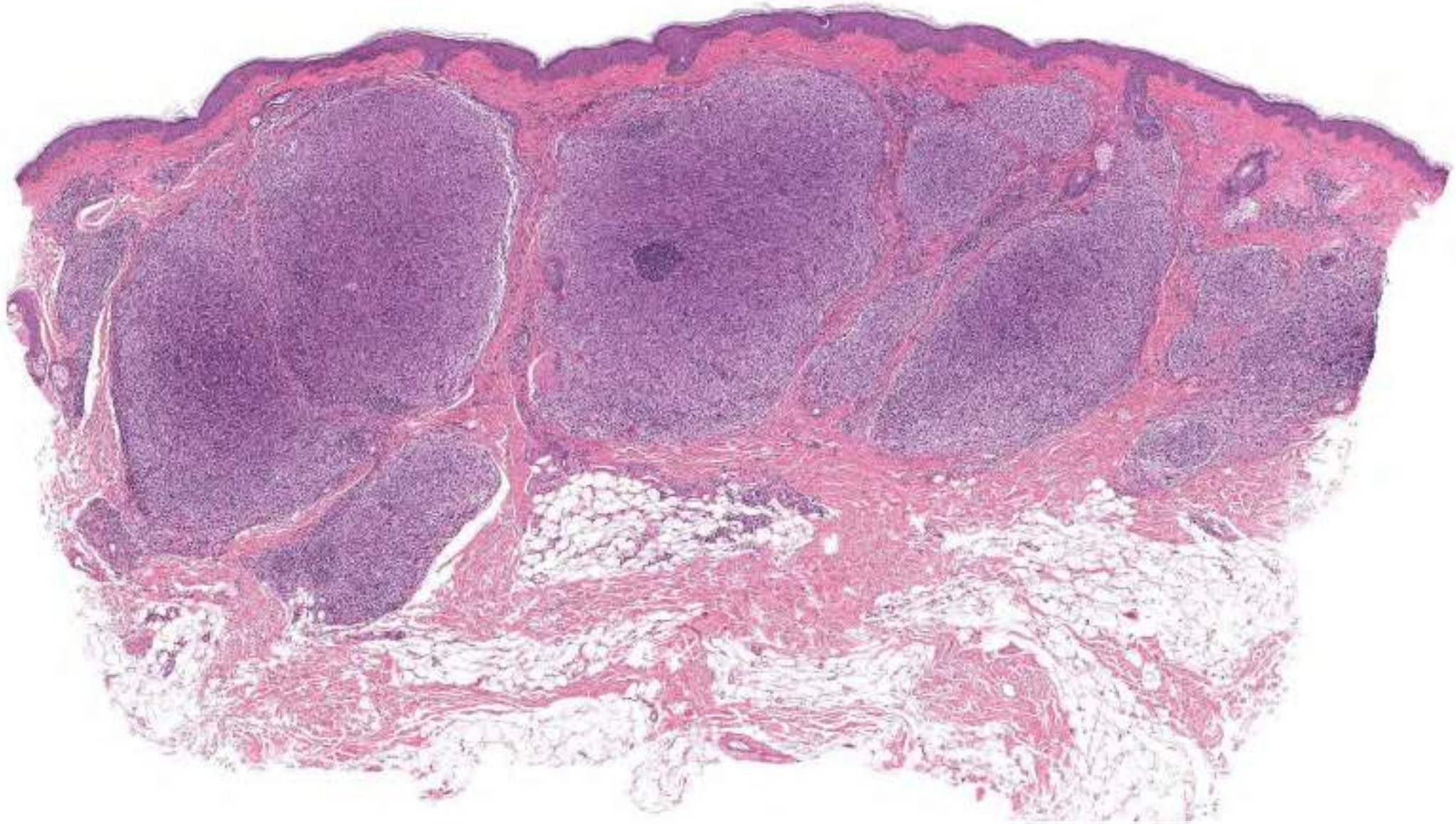
Follicular



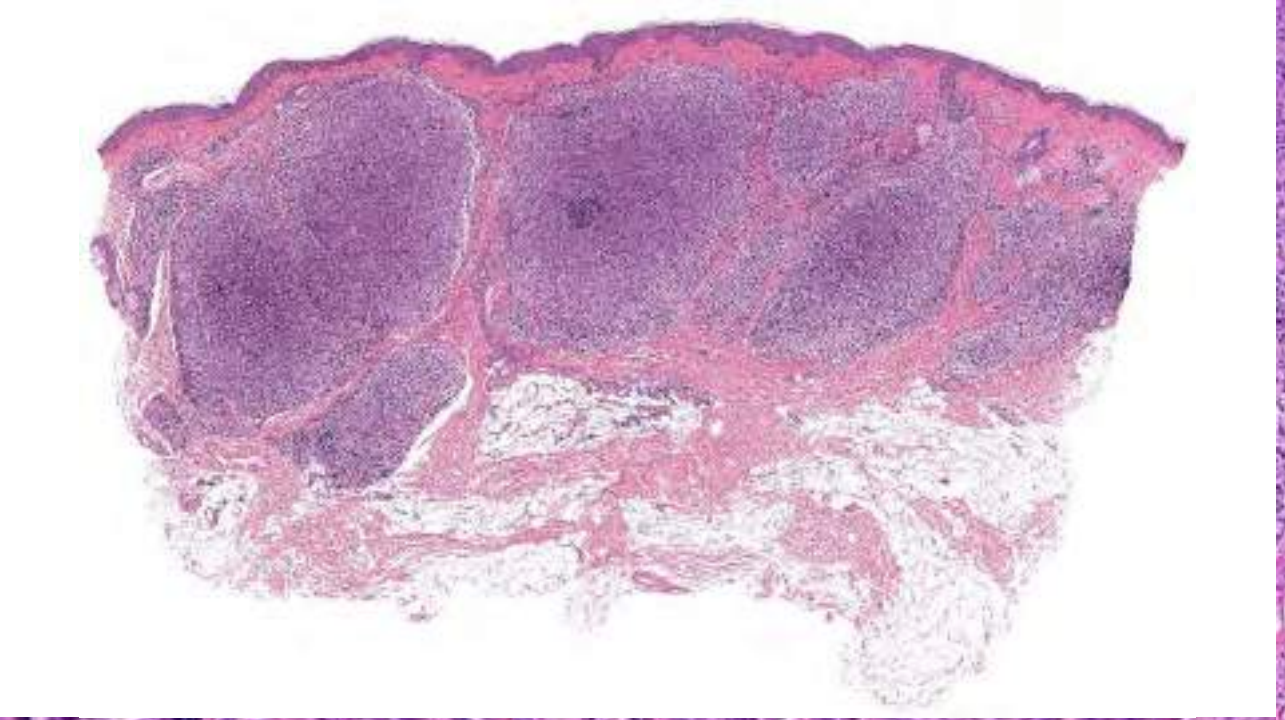
Diffuse

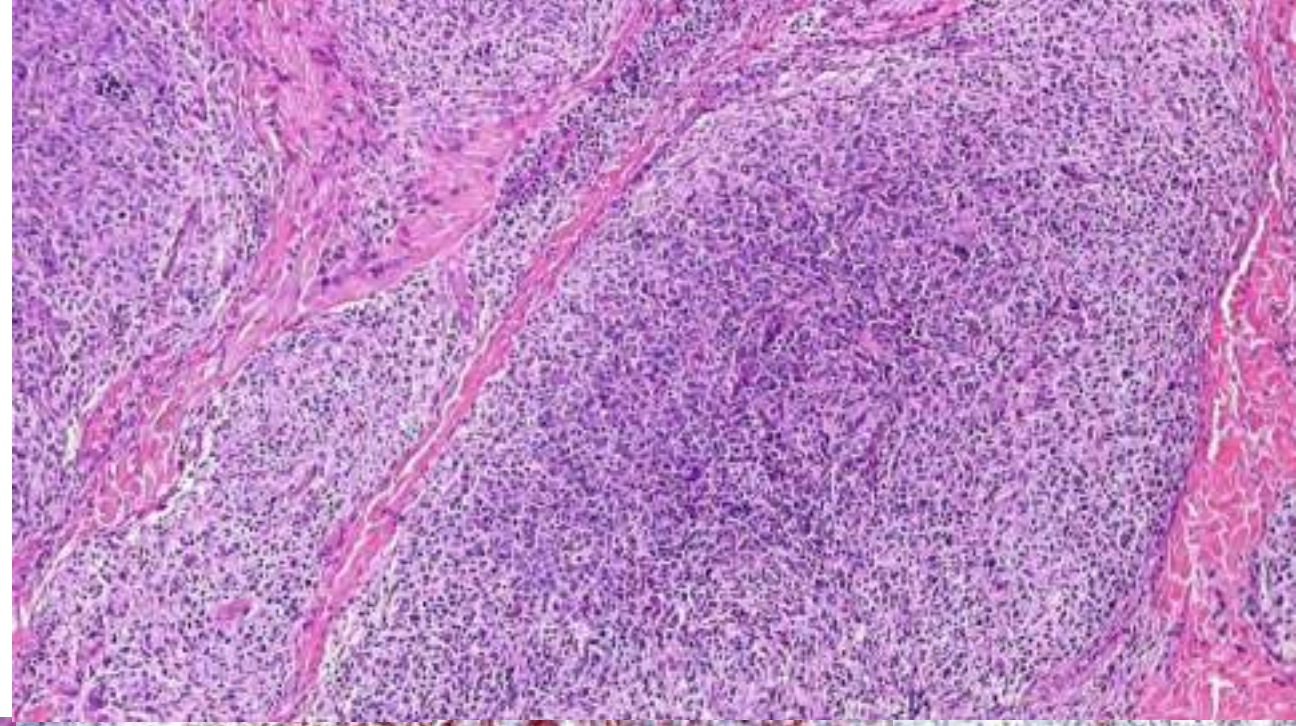


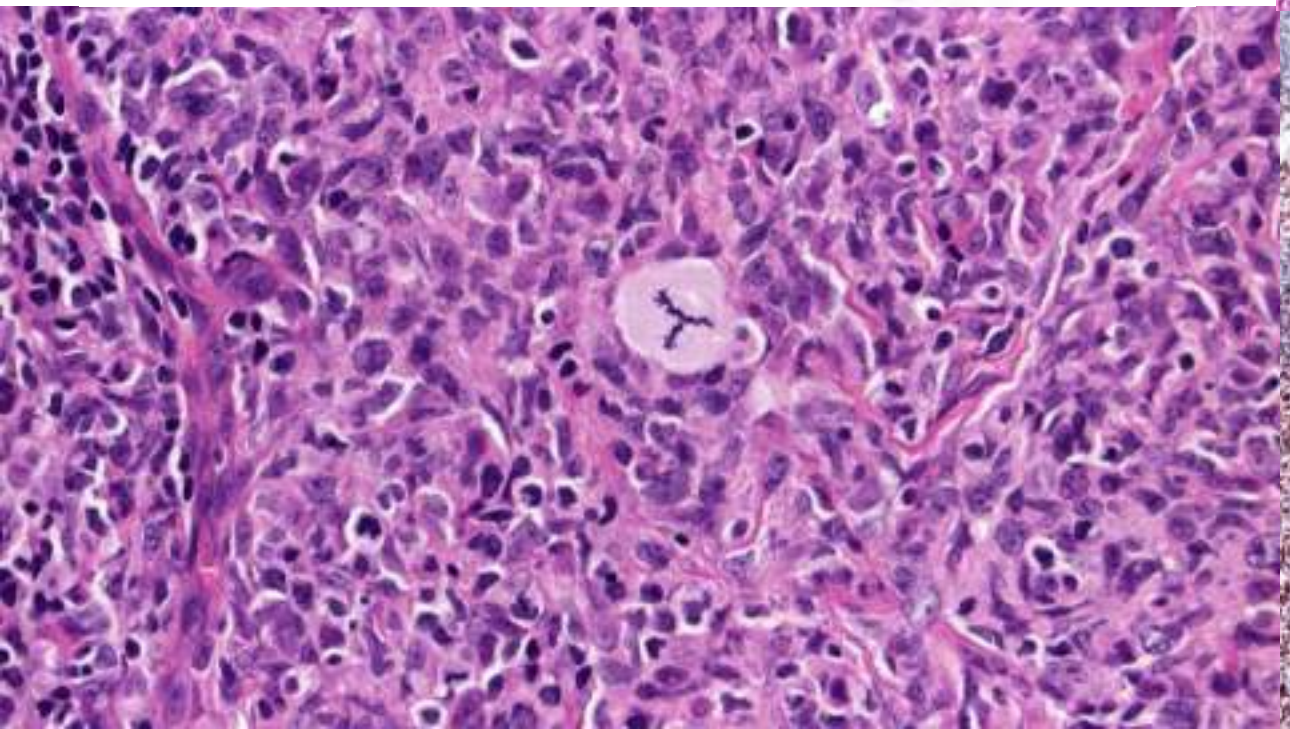
In primary cutaneous follicle center lymphoma, a diffuse pattern of growth in conjunction with a follicular one is not a sign of "progression".

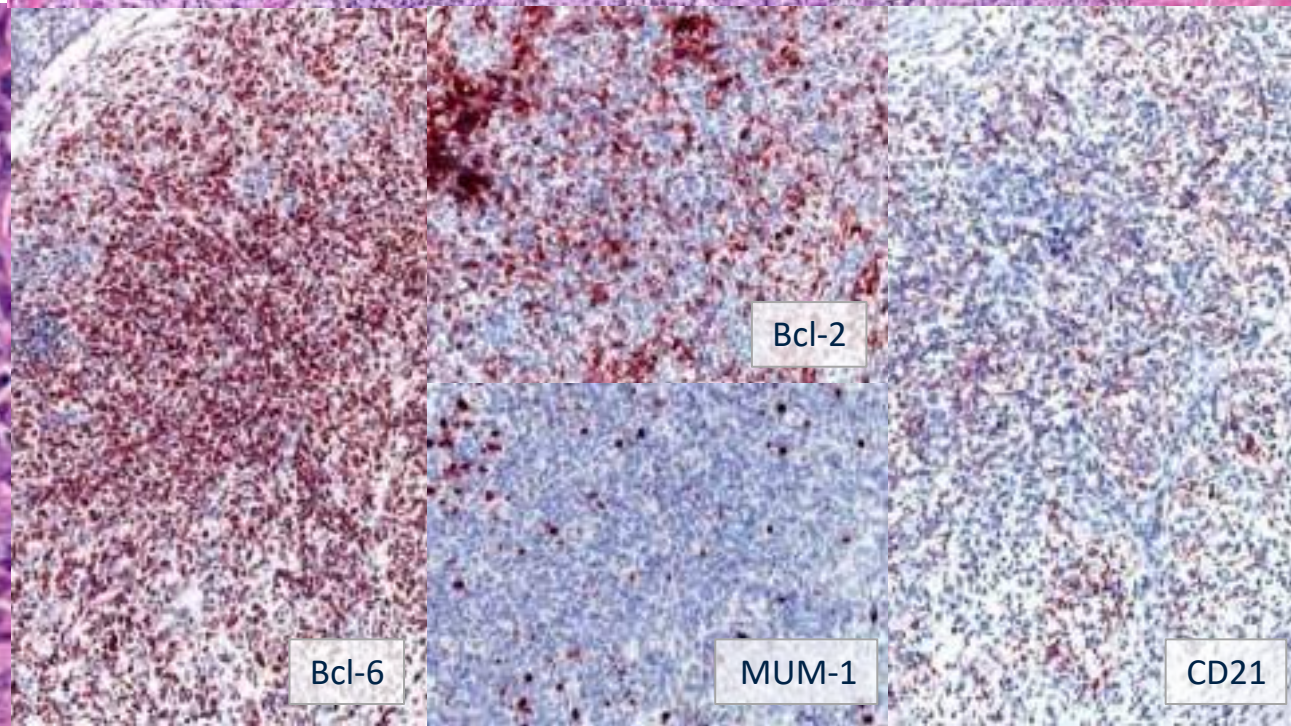


"Large cell lymphocytoma". In the past considered as a variant of the cutaneous pseudolymphomas; now included in the histopathological spectrum of cutaneous follicle center lymphoma.
Almost exclusively on the head & neck area; clinically often localized miliary lesions (similar to miliary and agminated cutaneous FCL). No association with *Borrelia* infection.

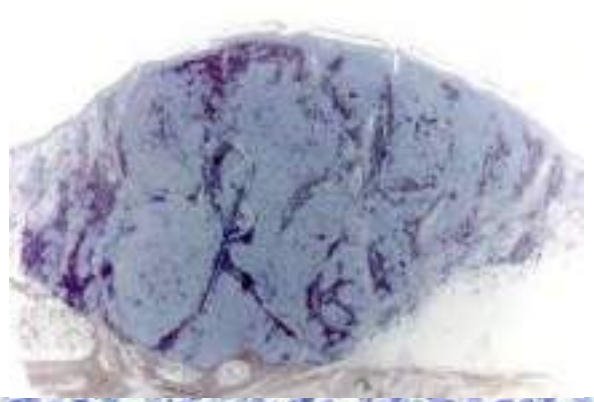


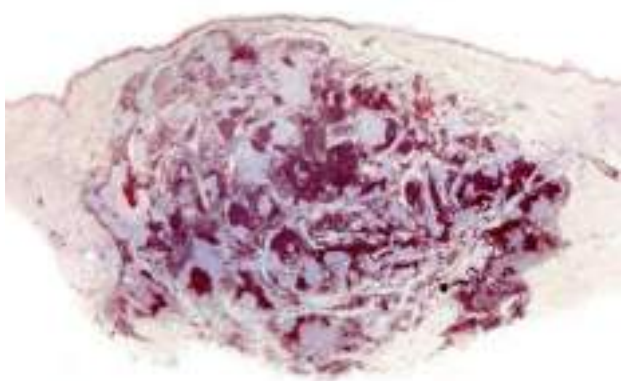


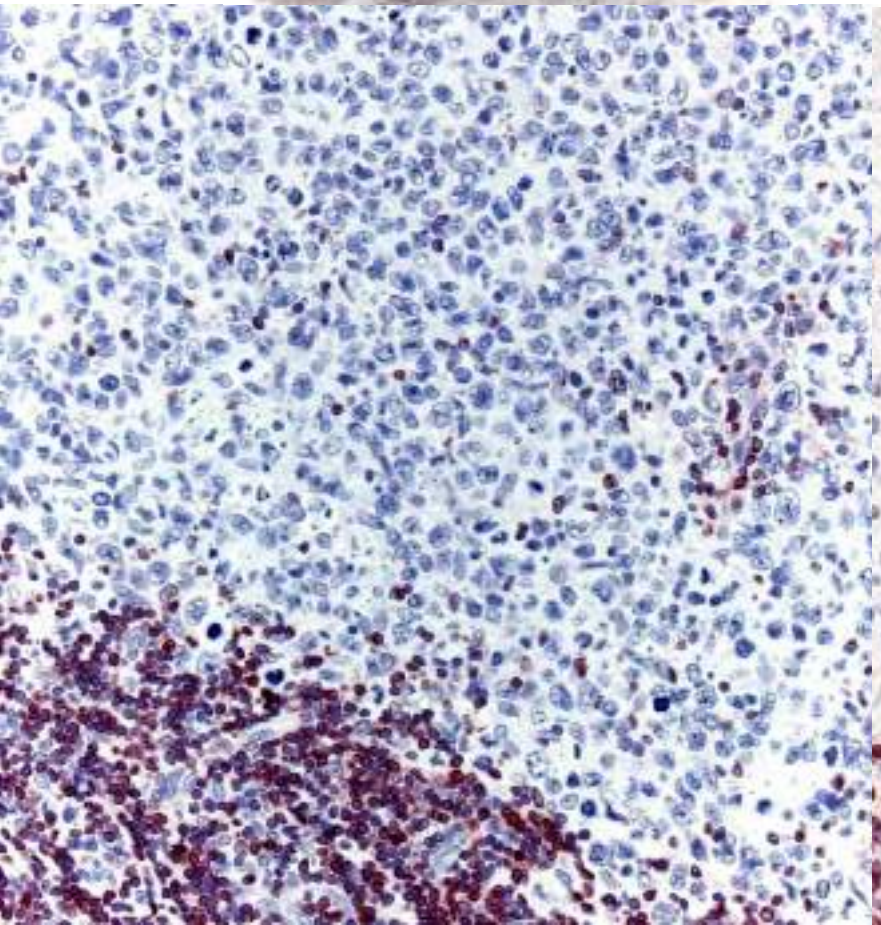


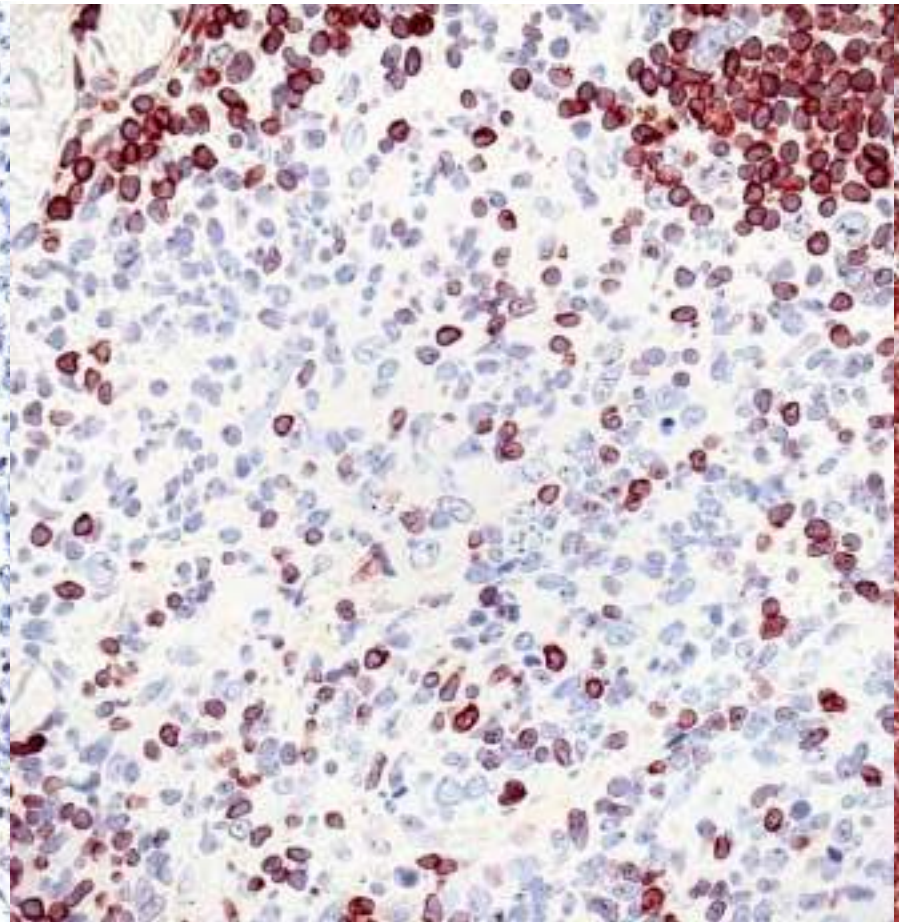

Bcl-6
Bcl-2
MUM-1
CD21

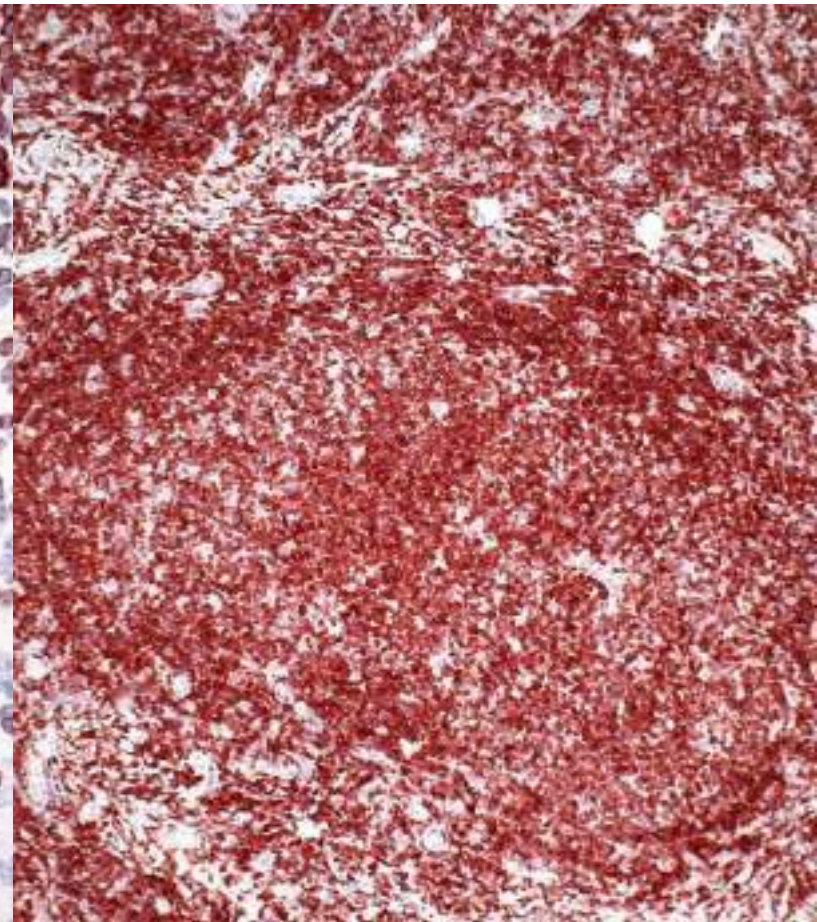
Patterns of Bcl-2 expression in primary cutaneous FCL

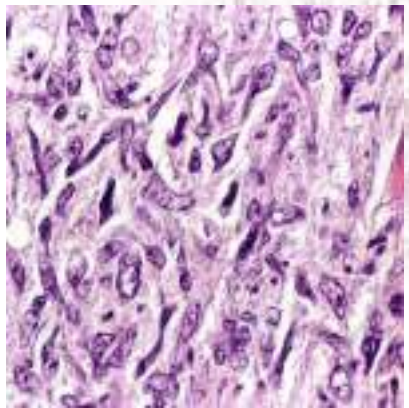




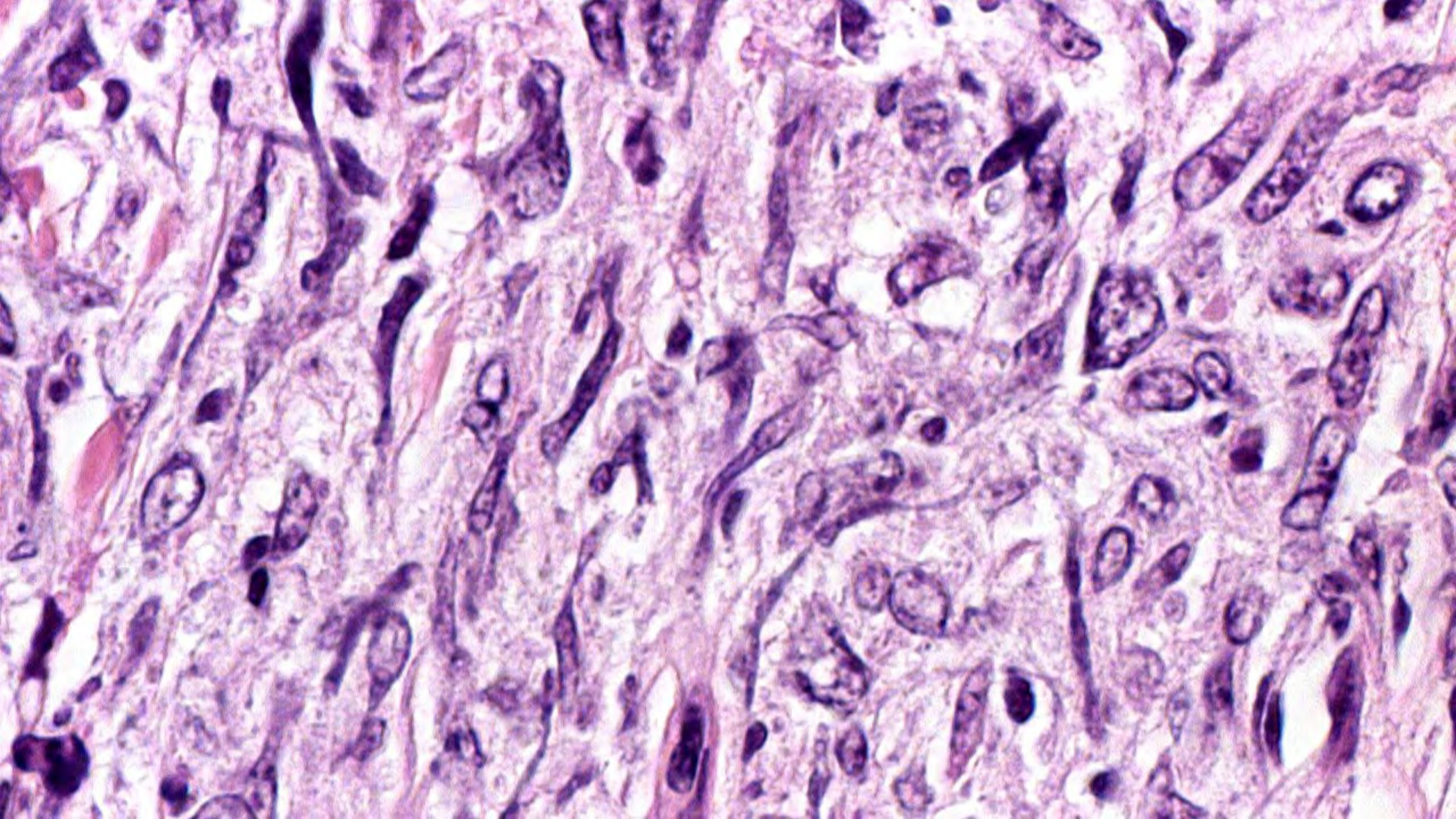








Spindled-cell cFCL



Cutaneous Spindle-Cell B-Cell Lymphomas

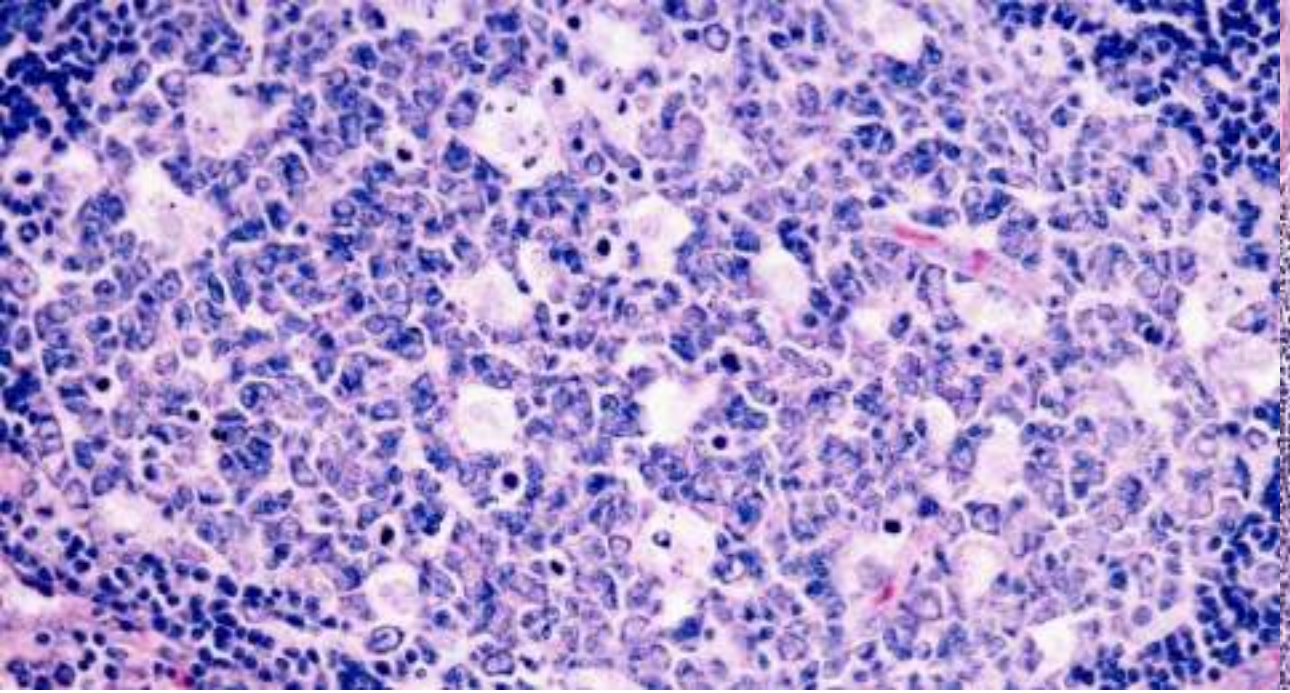
Most are Neoplasms of Follicular Center Cell Origin

24 cases (M:F = 18:6) (mean age 55 years). Head (12), trunk (8), lower extremities (4).

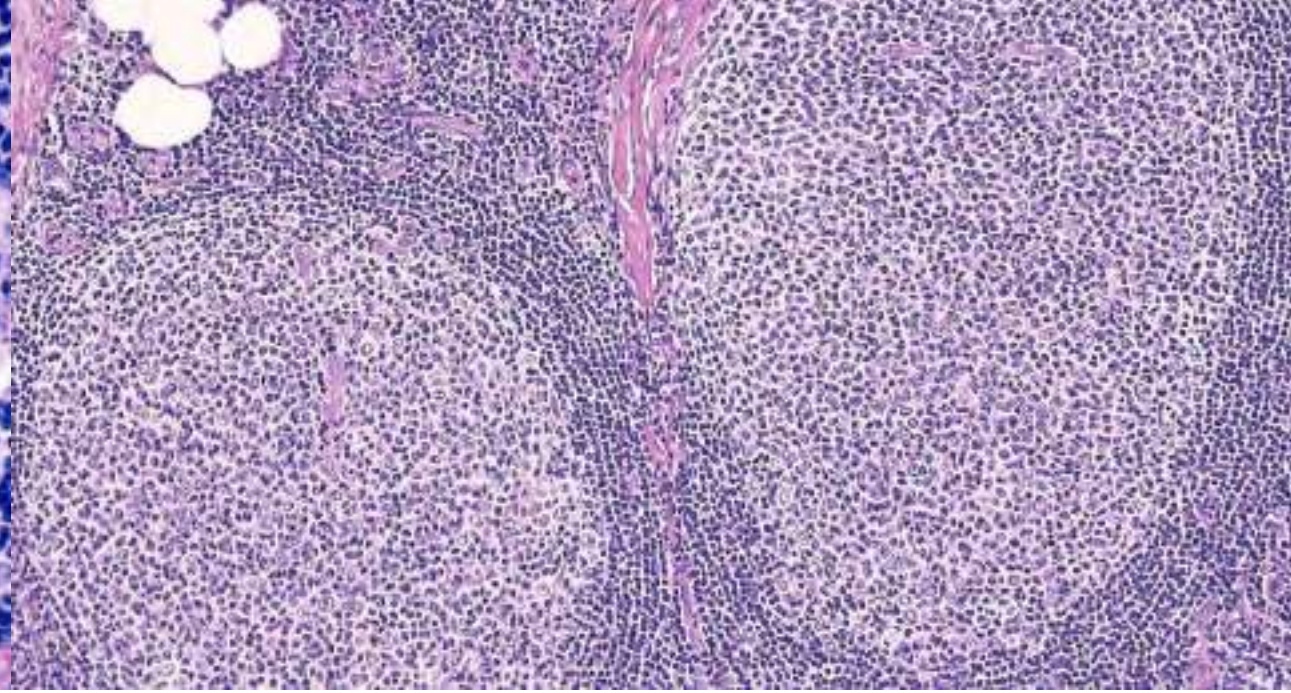
The neoplastic infiltrates comprised a mixture of medium-sized, visually prominent spindled cells (15% - 85% of the infiltrate) arranged in a fascicular pattern around nodular aggregates and admixed in a random manner between centrocyte/centroblast-like cells within these nodular collections. Immunohistochemical support for a follicular center cell origin was present in 22/24 cases, 1 was consistent with DLBCL-leg type and 1 defied precise classification, best fitting with intermediate-grade DLBCL-other.

Differential diagnosis of cutaneous lymphoid infiltrates with follicular pattern

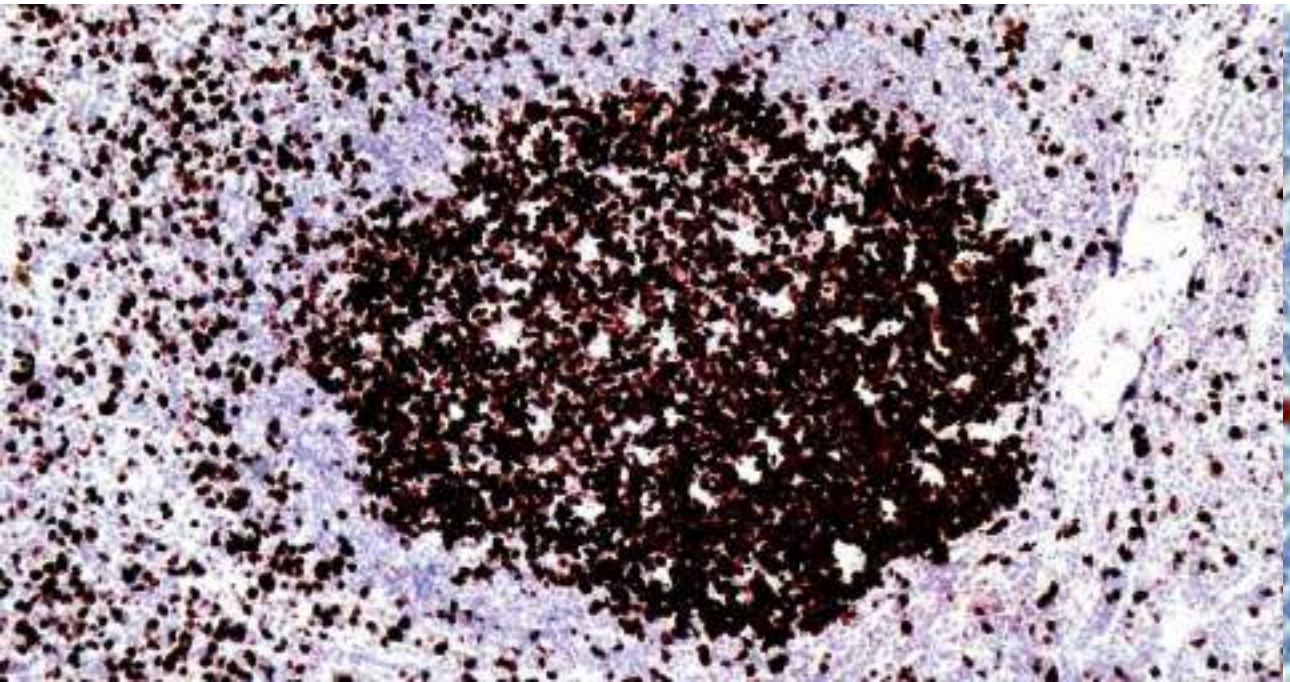
- *Reactive germinal centers:*
- Large numbers of tingible body macrophages and normal, well-formed mantle zone
- Clusters of Bcl6+ cells confined to the germinal centers
- High proliferation of the germinal centers
- Other clues specific to particular types of lymphocytoma (e.g., focal necrosis and histiocytes with a granular, basophilic cytoplasm in vaccination-induced pseudolymphoma)
- Beware of special locations in *Borrelia*-related lymphocytoma (e.g., earlobe, nipple, genital area)

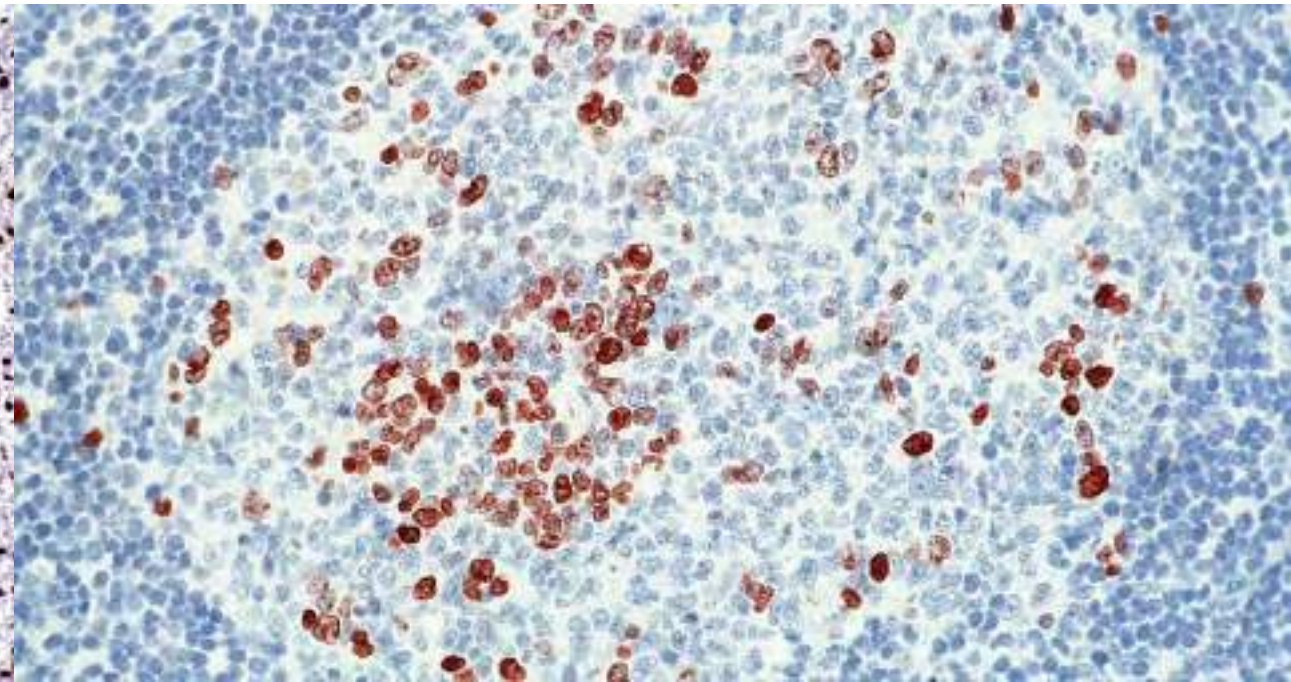


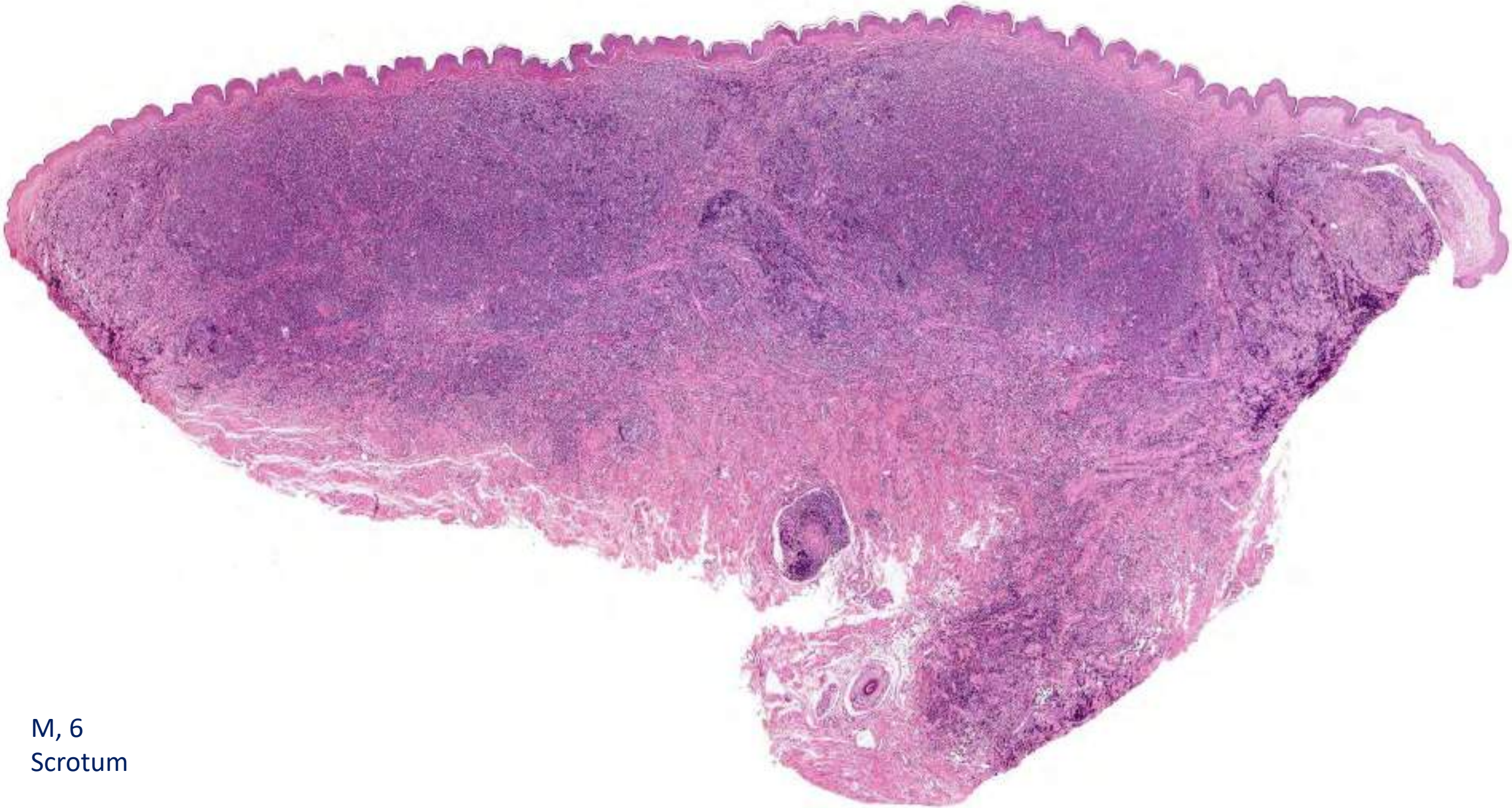
Reactive follicle



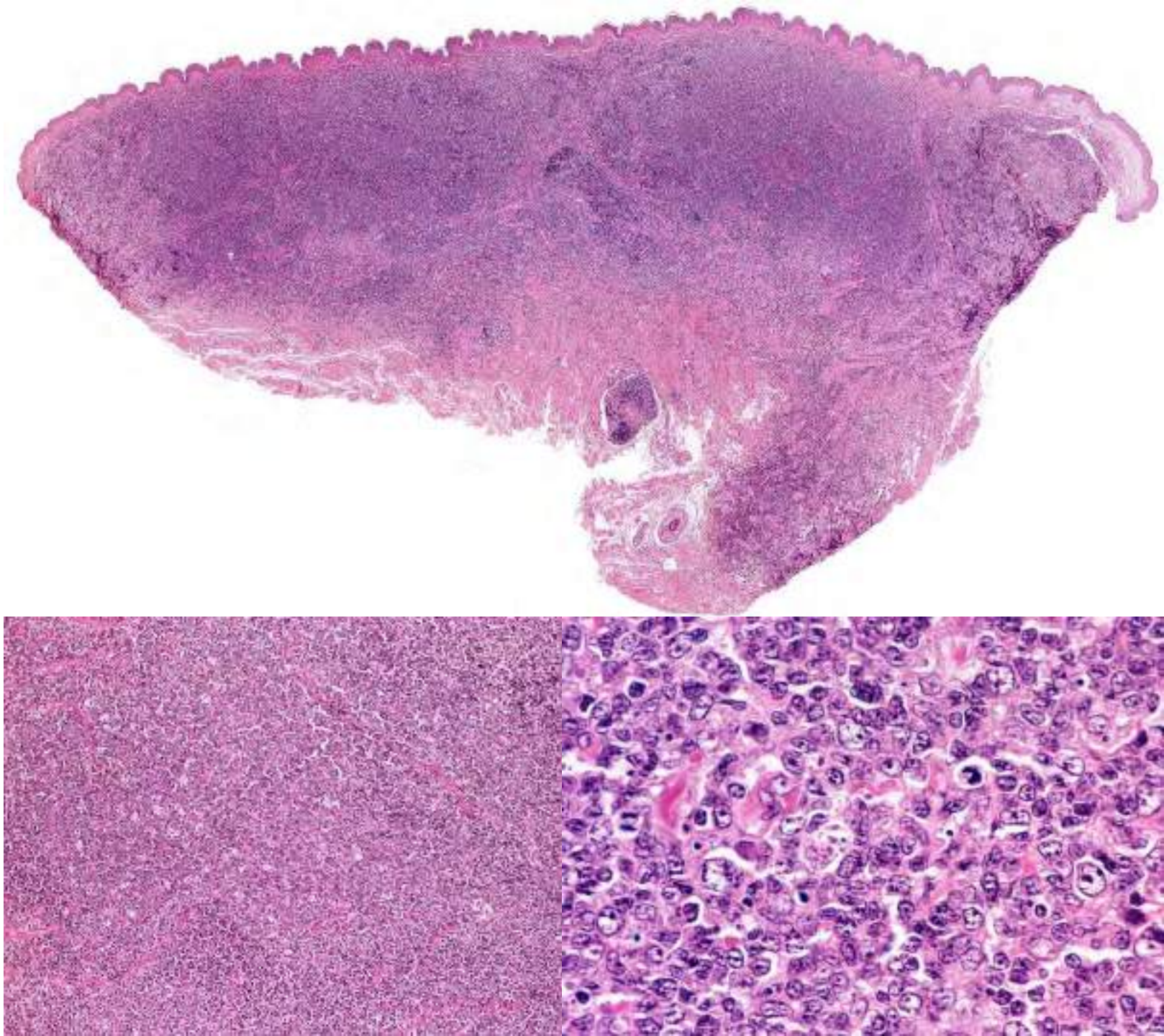
Neoplastic follicle

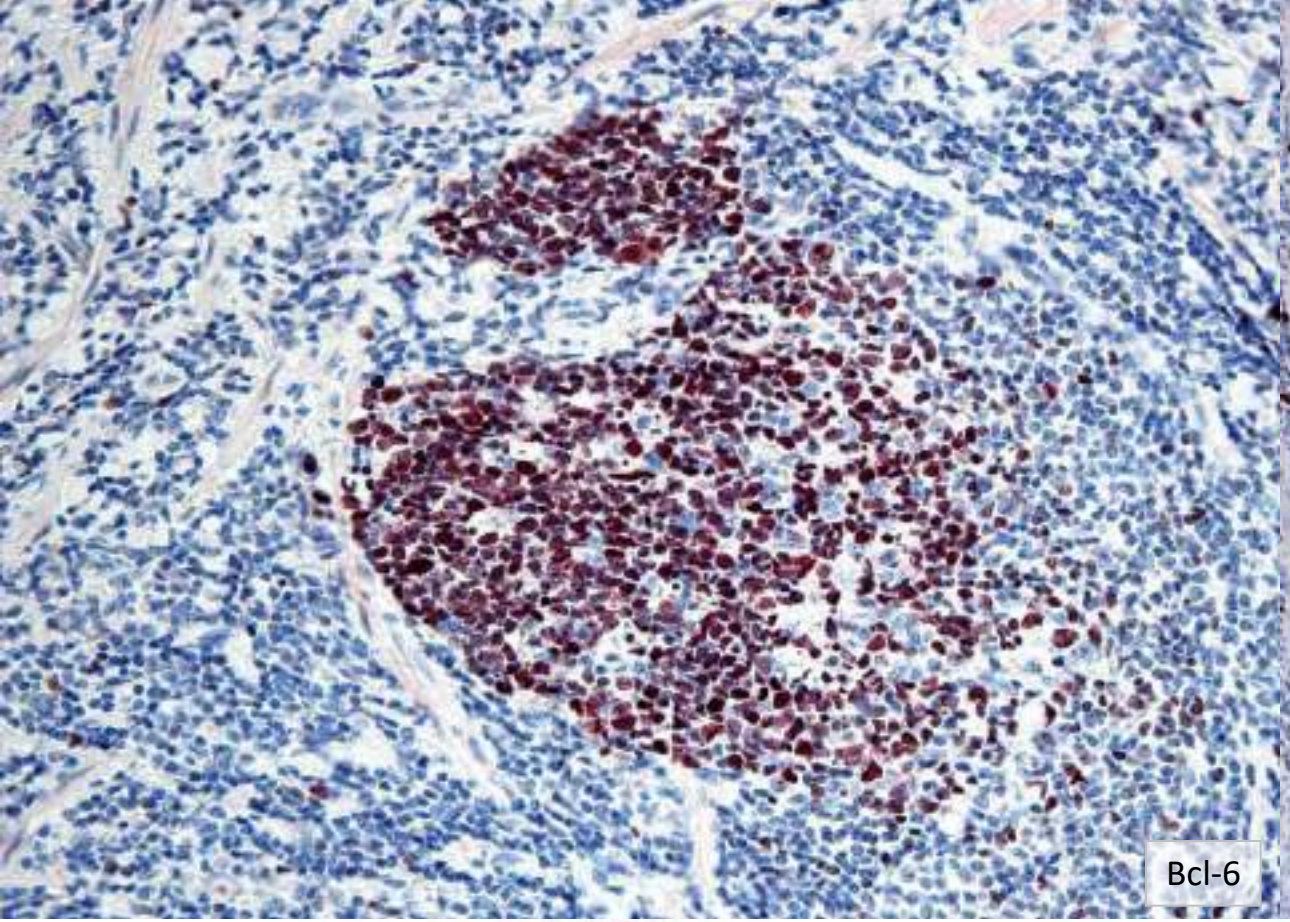


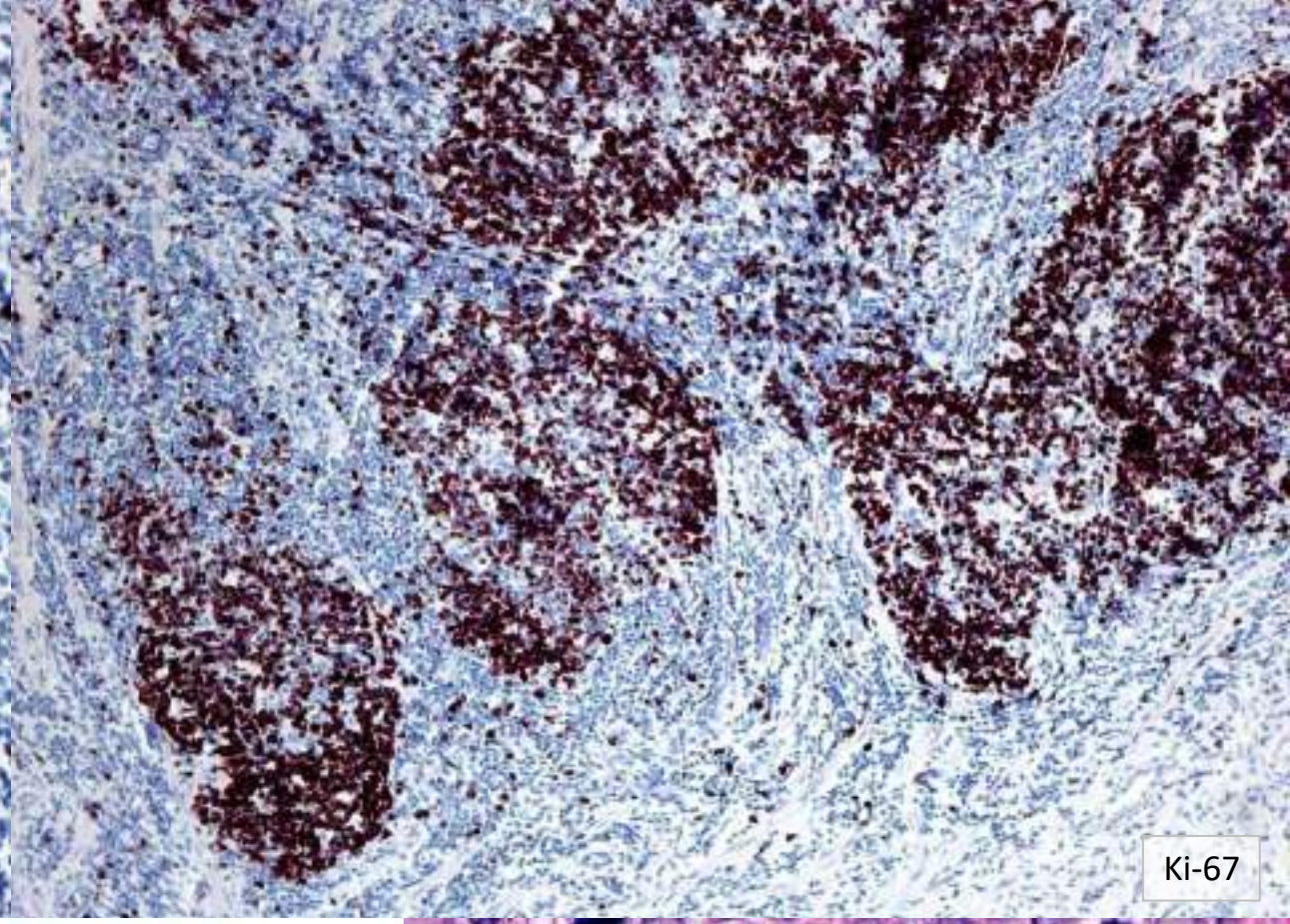


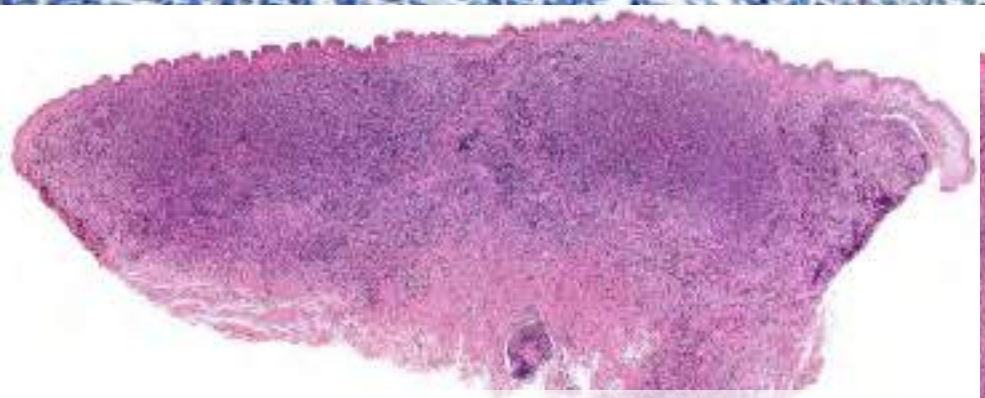


M, 6
Scrotum

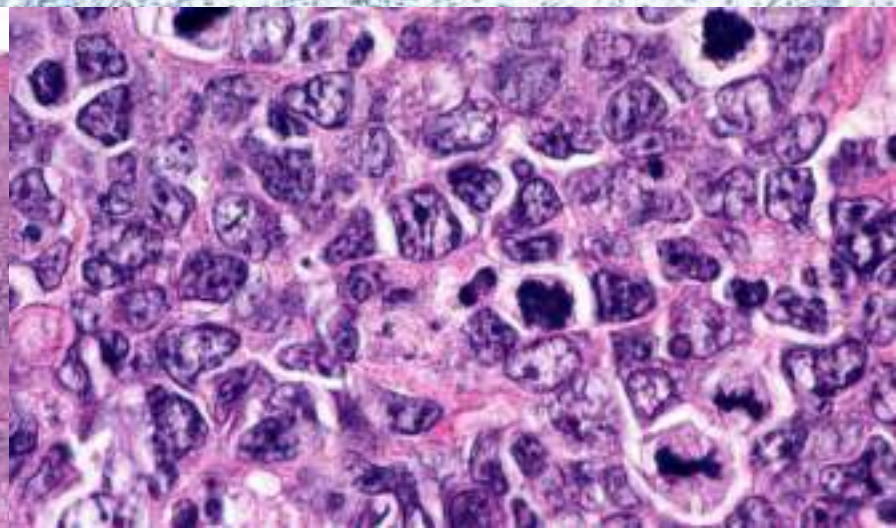








Borrelia lymphocytoma



Borrelia burgdorferi–associated lymphocytoma cutis simulating a primary cutaneous large B-cell lymphoma

"Because of this misleading histologic feature, a diagnosis of primary cutaneous large B-cell lymphoma was first suspected in both cases. In one case, successive recurrences led to aggressive therapies before the *B burgdorferi* infection was recognized."

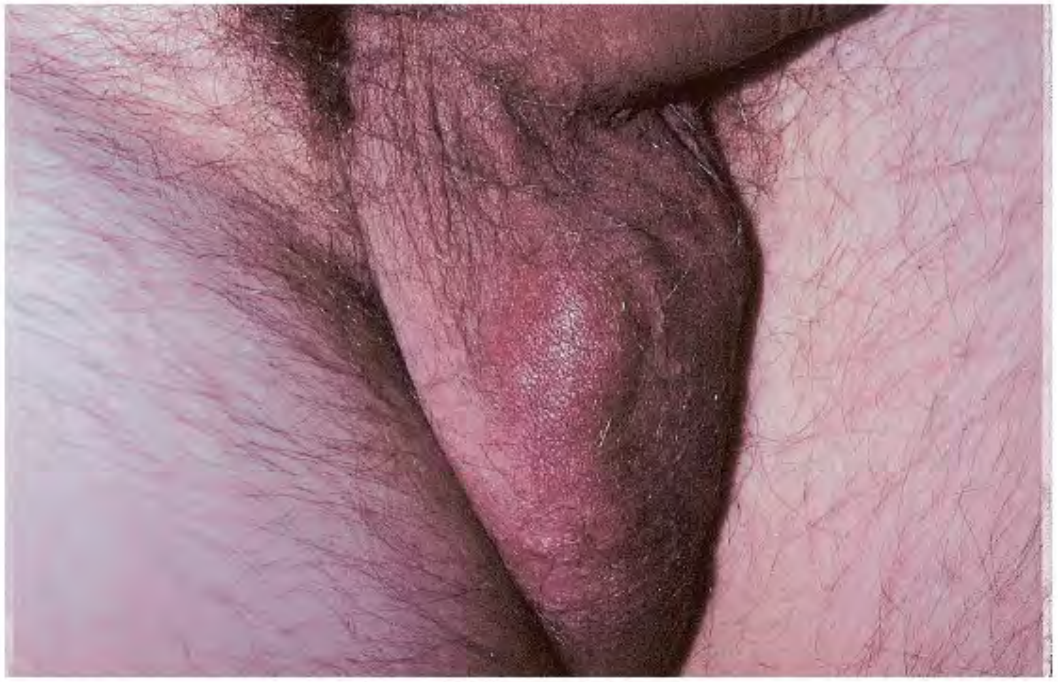


Fig 1. Case 1. Deeply infiltrated plaque on anterior part of scrotum.

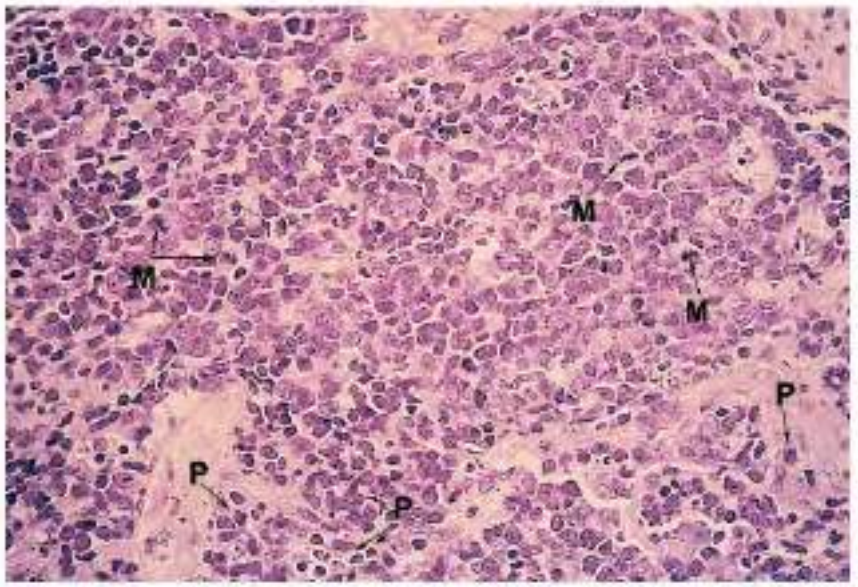
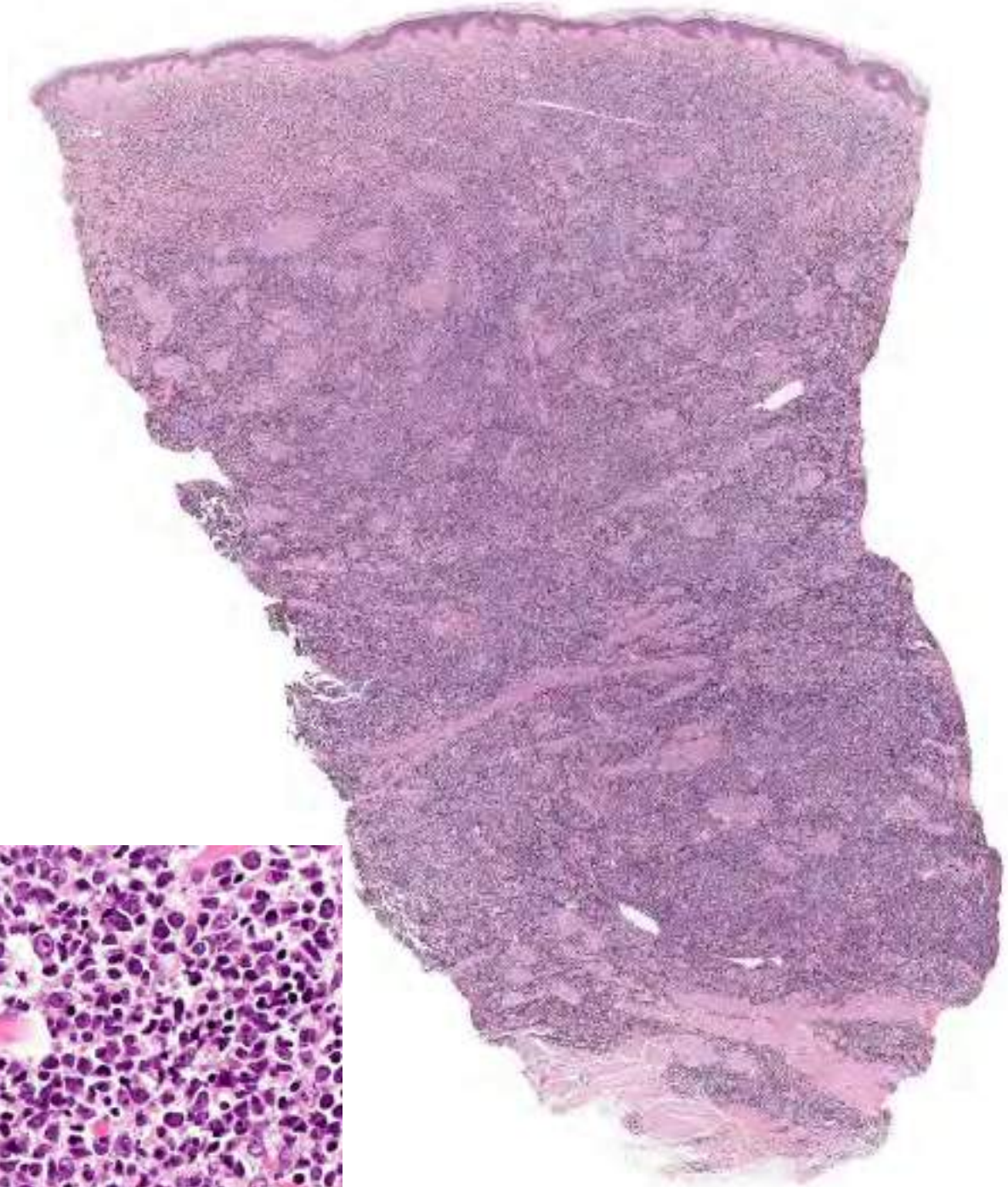
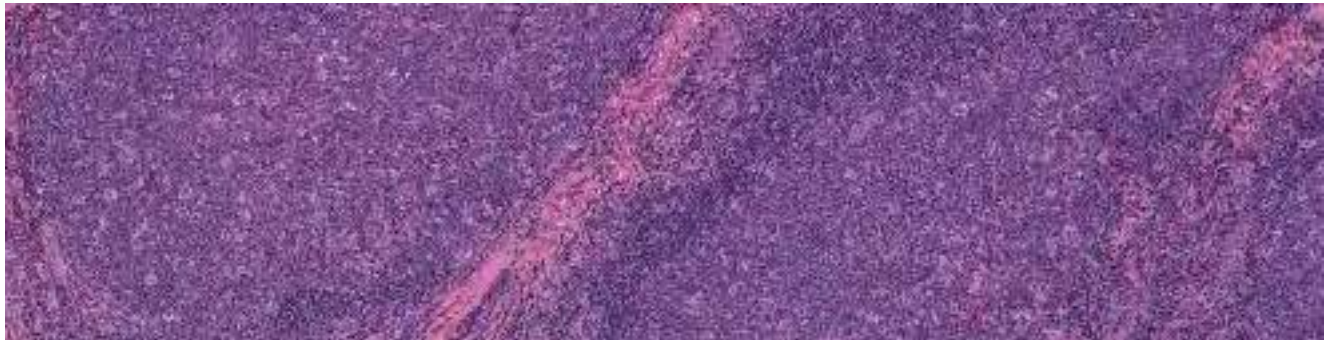


Fig 3. Case 1. Detail of Fig 2. Infiltrate is mainly composed of centroblasts; few immunoblasts and numerous mitoses *(M arrows)* are present. Some lymphocytes exhibit a plasmacytic differentiation *(P arrows)*. (Hematoxylin-eosin stain; original magnification ×200.)

"A surgical cutaneous excision associated with a testis biopsy was performed. (...) After a 15-month disease-free interval, the patient presented in July 1997 with an infiltrated plaque of 15x10 mm in diameter on the anterior part of the scrotum. A biopsy specimen confirmed the recurrence of the previously diagnosed tumor. Radiation therapy was performed in September 1997 with 6 meV for a total dose of 44 Gy in 20 fractions and resulted in a slow and complete resolution of the skin lesion within 2 months. However, a local recurrence with similar histologic features occurred 3 months later in the radiation field. The patient received 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. A complete response was achieved in July 1998. However, a scrotal nodule again reappeared in March 1999. (...) A complete resolution of the skin lesion was achieved after 3 weeks of therapy with amoxicillin, 3 g, administered daily. No relapse was observed after a follow-up period of 27 months."





Journal of
Cutaneous Pathology

Borrelia burgdorferi-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases

Lymphocytoma cutis (LC) is considered as the stereotypical example of the cutaneous B-cell pseudolymphomas. It can be induced by various antigenic stimuli including arthropod bites, vaccination, and drugs among others. In endemic regions, *Borrelia burgdorferi* is the principal causative agent for LC. We studied retrospectively 108 biopsies from 106 patients (male : female, 48 : 58; mean age, 44.6; median, 51.5; range, 3–81) with *B. burgdorferi*-associated LC retrieved from the files of the Department of Dermatology of the University of Graz (Austria). Only cases with a *B. burgdorferi* etiology (typical locations, positivity of serologic and/or polymerase chain reaction (PCR) tests, clinical history) were included in the study. Lesions were located on the nipple (63 cases), earlobe (18 cases), genital region (9 cases), and trunk or extremities (16 cases). PCR analysis of *B. burgdorferi* DNA was positive in 54 of 80 cases tested (67.5%). In 47 cases, we could retrieve data on serologic examination for *B. burgdorferi* antibodies performed at the time of diagnosis of LC. Positivity was found in 45 patients: IgG+/IgM+, 5 cases; IgG+/IgM−, 37 cases; IgG−/IgM+, 3 cases; IgG−/IgM−, 2 cases). Histology revealed dense lymphoid infiltrates with prominent germinal centers (GCs) in all cases. Atypical morphologic and/or immunophenotypic features of the GCs were commonly observed. In 5 cases, due to confluence of large follicles, the histopathologic pattern simulated that of a large B-cell lymphoma. PCR analysis of the IgH gene rearrangement performed in 35 cases showed a polyclonal pattern in 31 cases and a monoclonal band in 2. In summary, *B. burgdorferi*-associated LC can present with misleading histopathologic, immunophenotypic, and molecular features, and integration of all data is necessary for a correct diagnosis.

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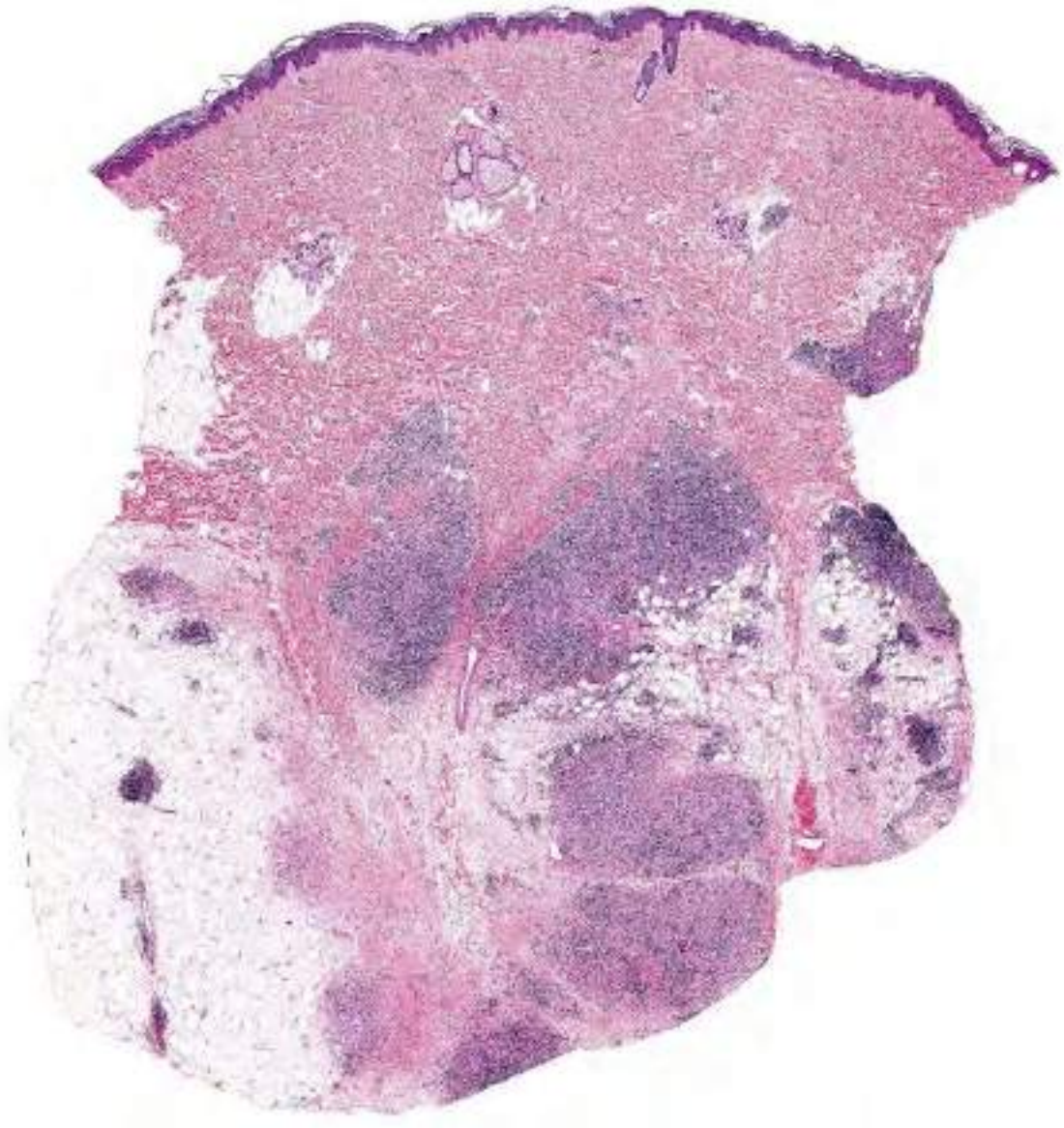
J Cutan Pathol 2004; 31: 232–240. © Blackwell Munksgaard 2003.

Lymphocytoma cutis (LC) is one of the most common types of cutaneous B-cell pseudolymphoma.[1,2] It can be induced by various antigenic stimuli, including arthropod bites,[3] vaccination,[4] and drugs[5] among others. In endemic regions, *Borrelia burgdorferi* infection is the most common causative factor.[6,7] These lesions are also designated "Borrelial lymphocytoma", and represent the least common manifestation within the

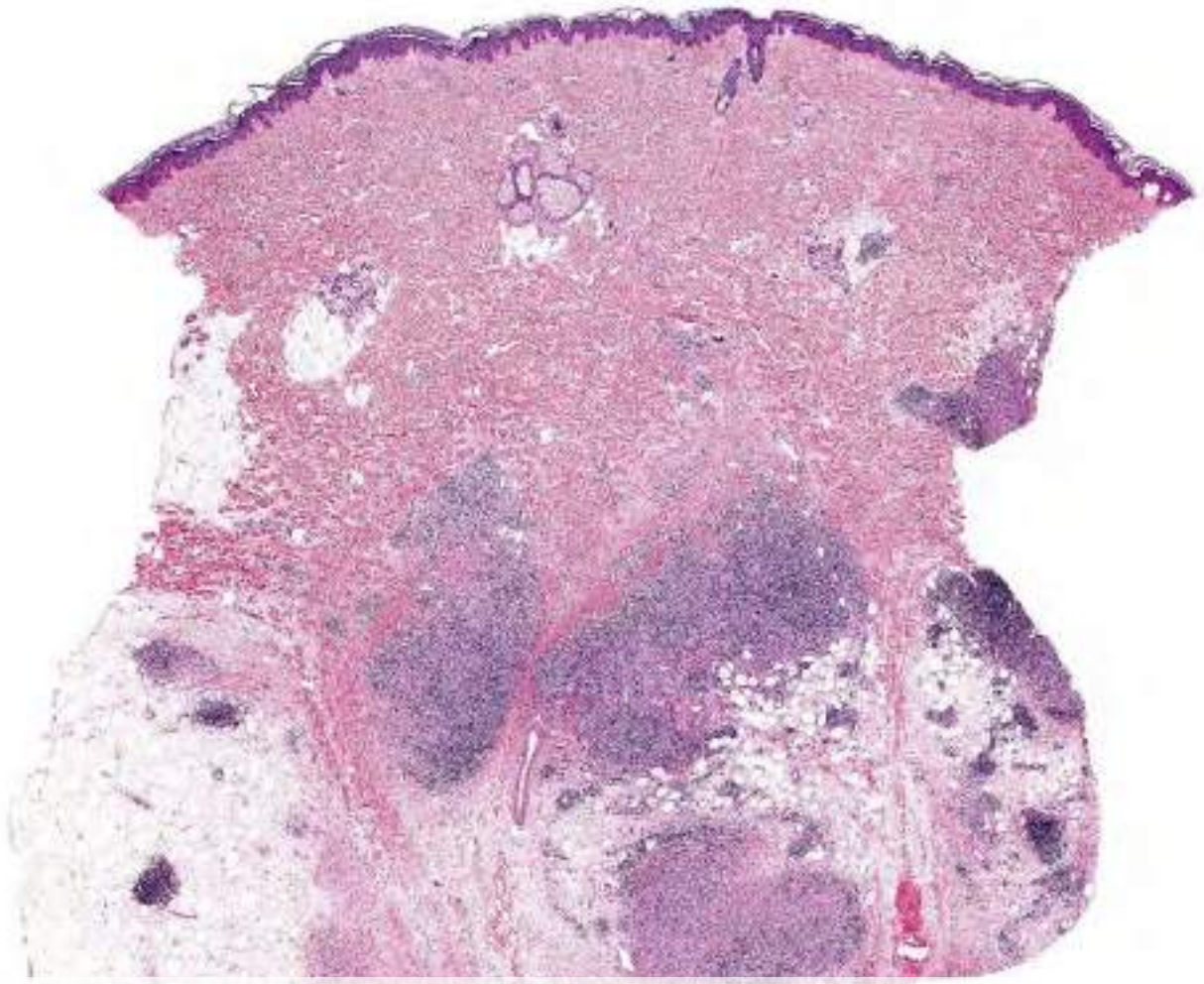
Nipple	59,4%
Earlobe	16,7%
Genital	8,5%
Other	10,0%

Exceptions to the rules

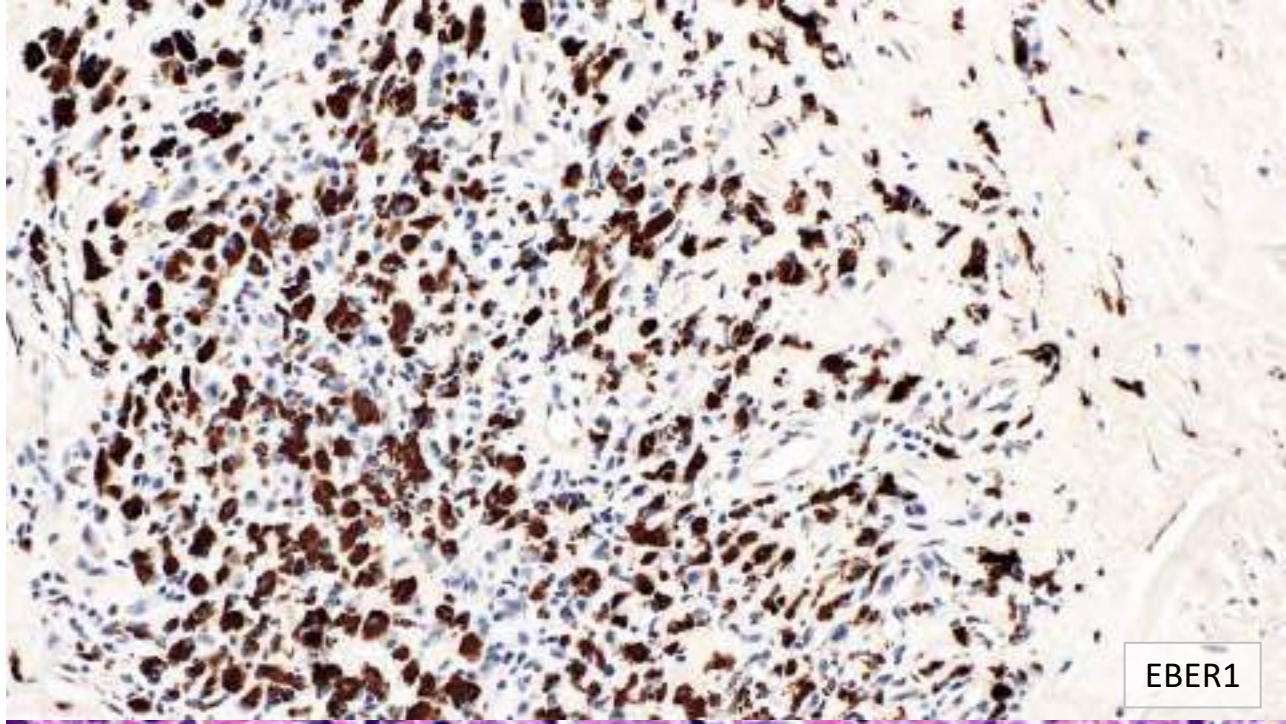
- Reactive germinal centers in *Borrelia*-induced lymphocytoma may miss a well-formed mantle and show confluence, mimicking the histopathological features of a diffuse large B-cell lymphoma
- High proliferation is usually a feature of malignant tumors, yet in lymphoid infiltrates with follicular pattern *reduced* proliferation of the lymphoid follicles is a clue for malignancy, whereas high (nearly 100%) proliferation is typical of reactive germinal centers

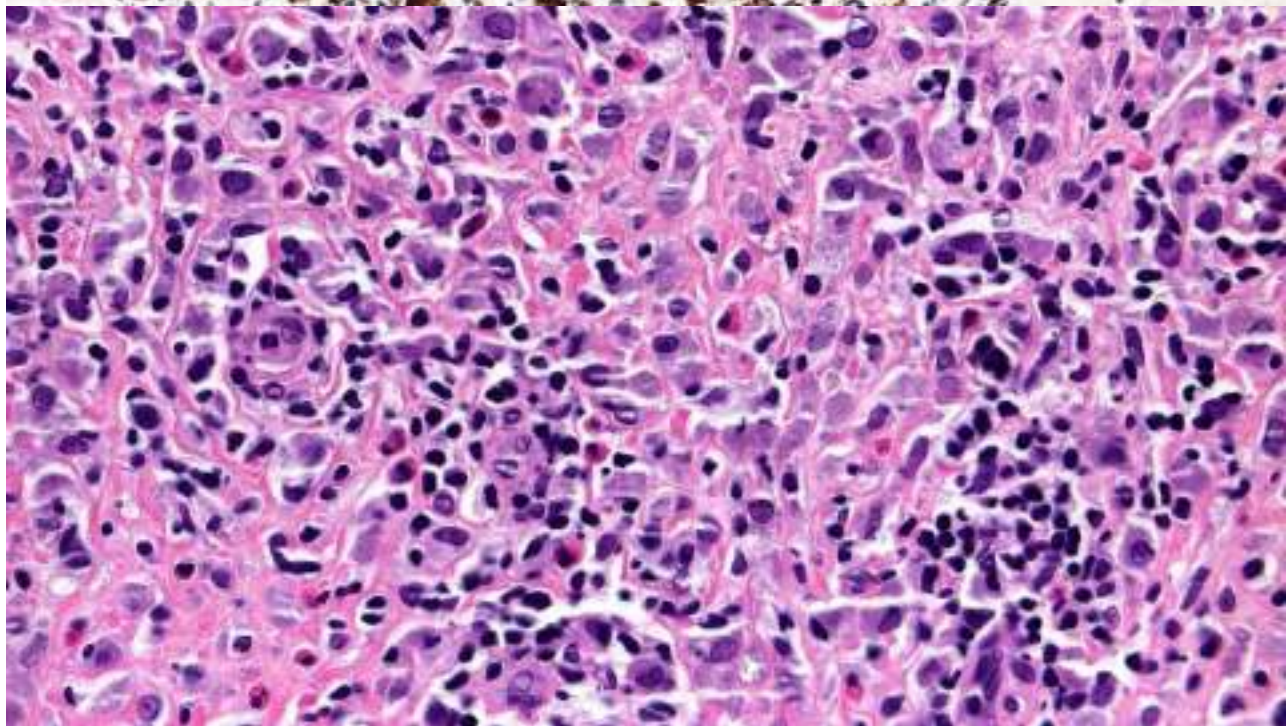


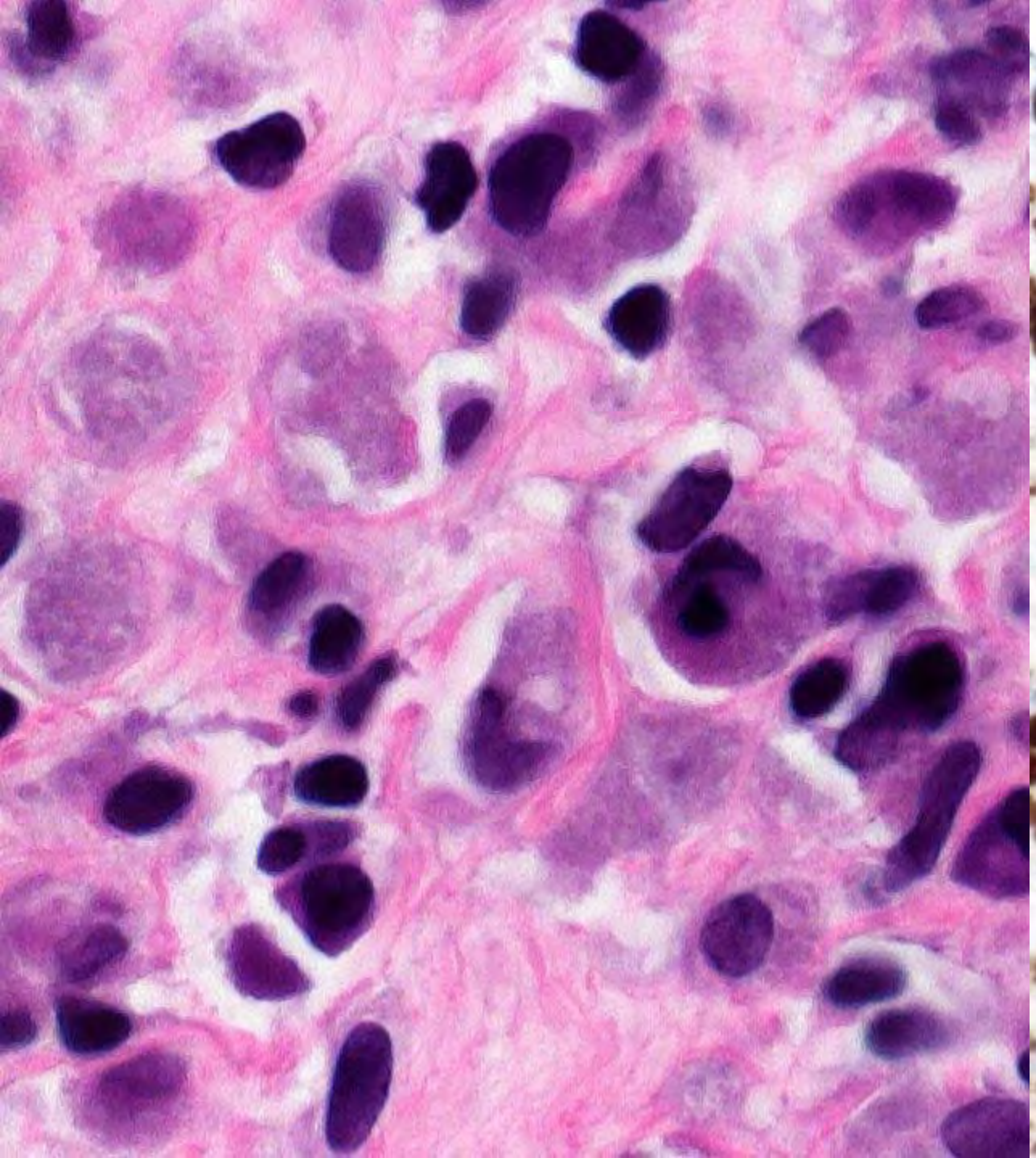
F, 42.
Subcutaneous nodule at the site of a hyposensitivity treatment.

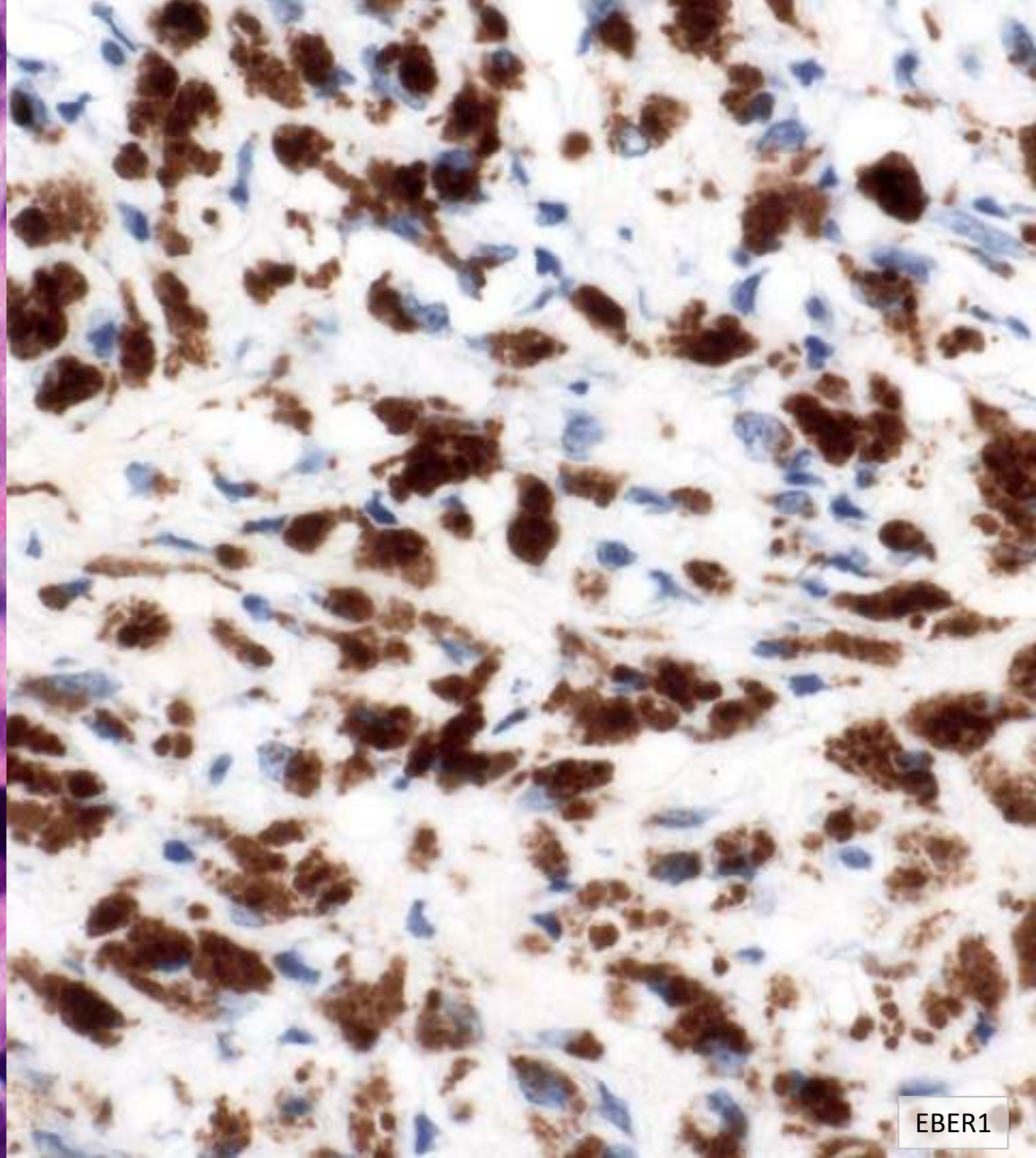


Pseudolymphoma at the site of vaccination








EBER1

Cutaneous B-cell Pseudolymphoma at the Site of Vaccination

Lorenzo Cerroni, MD, Riccardo G. Borroni, MD,*† Cesare Massone, MD,* Andreas Chott, MD,‡ and Helmut Kerl, MD**

Abstract: Pseudolymphomas are a rare complication of vaccination, presenting with dense lymphoid infiltrates and prominent follicular pattern. We report our observations on 4 patients with vaccination-induced B-cell pseudolymphoma (all females; age range 19 to 60 years; median: 34.5 years). Clinically 3 patients presented with subcutaneous nodules and 1 presented with a large, indurated, erythematous plaque. Histology revealed in all cases dense lymphoid infiltrates in the subcutaneous fat with prominent follicular pattern. The follicles displayed features of reactive germinal centers (normal mantle zone, presence of tingible body macrophages, normal proliferation). Necrotic areas surrounded by palisaded histiocytes were seen in 3 biopsies from 2 patients. A mixed-cell infiltrate with eosinophils and plasma cells was present in all cases. In addition, histiocytes with granular basophilic cytoplasm could be observed around the focal area of necrosis or within the inflammatory infiltrate. Follow-up was available for 3 patients. One patient was alive with persistent disease 6 months after the first observation. Two patients were treated with local radiotherapy and are alive and free of disease after 12 and 72 months, respectively. One of these two patients had a second pseudolymphoma on the contralateral arm after a new injection of vaccine. Cutaneous pseudolymphoma after vaccination should be distinguished histopathologically from low-grade cutaneous B-cell lymphomas (follicle center cell lymphoma, marginal zone lymphoma) and from other B-cell pseudolymphomas with prominent follicular pattern requiring different treatment (eg, *Borrelia burgdorferi*-induced lymphocytoma cutis).

Key Words: B-cell pseudolymphoma, vaccination, follicular pseudolymphoma, lymphocytoma, lymphadenosis benigna cutis

(*Am J Dermatopathol* 2007;29:538–542)

Adverse cutaneous effects of vaccinations include widespread and localized reactions. Mild erythema, edema, pain, and induration limited to the site of injection are commonly observed immediately after immunization and usually heal spontaneously. Less frequently, papules or subcutaneous nodules arise at the site of vaccination and may persist for months or years.[1,2] Histopathologically, they are characterized by either granulomas or lymphoid infiltrates with prominent germinal centers.[2–7] Typically, pseudolymphomas at the site of injection have been reported following administration of vaccines or allergens adsorbed to aluminum.[1,6,8,9]

We describe the clinical, histopathologic, immunophenotypic, and molecular biologic findings of 4 patients who developed cutaneous B-cell pseudolymphoma at the site of vaccination.

PATIENTS AND METHODS

Patients

Four patients with a diagnosis of pseudolymphoma occurring at the site of vaccination were included in the study. The diagnosis of pseudolymphoma was based on clinicopathologic features. Association with previous vaccination was documented in all patients.

Histology, Immunohistology, and Molecular Biology

All biopsy specimens were fixed in 4% buffered formalin, routinely processed, and subsequently embedded in paraffin. For routine histopathologic analysis, sections were stained with hematoxylin and eosin. All histopathologic sections were reviewed by at least two of us (L.C., R.G.B.). The following features were analyzed: location of the infiltrate, presence or absence of necrosis, sarcoidal or tuberculoid granulomas, germinal centers, degenerative fat changes, eosinophils, plasma cells, and histiocytes with granular basophilic cytoplasm. Standard immunohistology and molecular biology techniques [polymerase chain reaction (PCR) analysis of immunoglobulin (Ig) H gene rearrangement] were used as described previously.[10,11]

RESULTS

Clinical Features

The clinical features of our patients are summarized in Table 1. All patients included were women. Age ranged from 19 to 60 years (median: 34.5 years). The vaccine administered was for early summer meningoencephalitis (ESME) in 2 of 4 patients, tetanus in 1 patient, and hepatitis B virus in 1 patient. The site of injection, thus the site of occurrence of skin lesions, was the upper arm in all patients. Patient 2 presented with a pseudolymphoma after ESME vaccination on the left upper arm. She subsequently received a second injection of the

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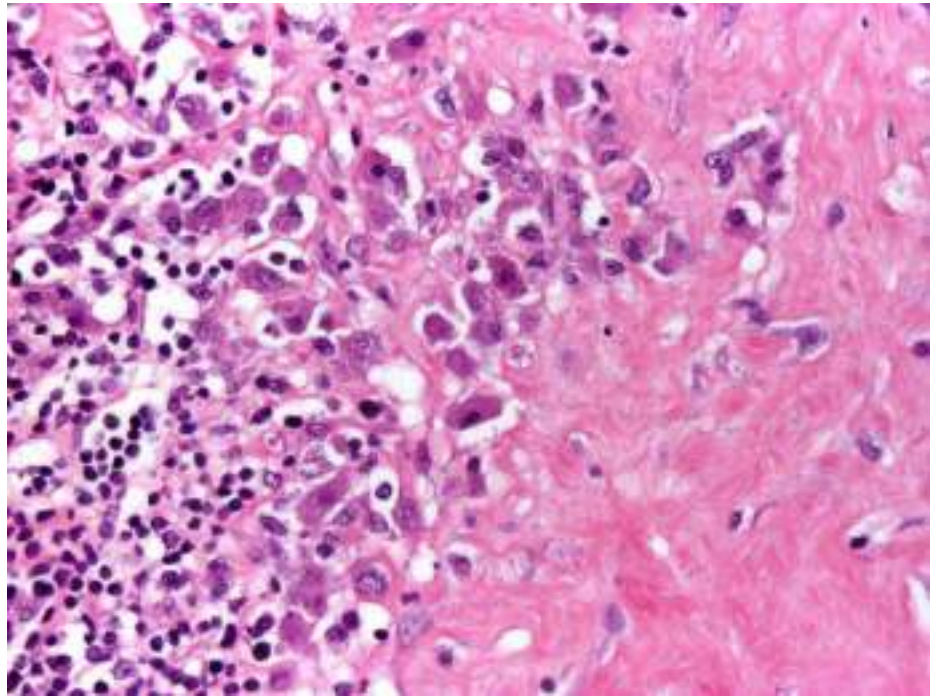
TABLE 2. Histopathologic Features of Pseudolymphomas at Site of Vaccination

Patient	Necrosis	Sarcoidal or Tuberculoid Granulomas	Germinal Centers	Eosinophils	Plasma Cells	Histiocytes With Granular Basophilic Cytoplasm	Degenerative Fat Changes	Polymerase Chain Reaction
1	—	—	+	+	+	+	+	P
2	—	—	+	+	+	+	+	P
2*	+	—	+	+	+	+	+	ND
2†	+	—	+/−	+	+	+	+	P
3	—	—	+	+	+	+/−	—	P
3*	+	—	+	+	+	+	+	ND
4	—	—	+	+	+	+	+	P

ND, not done; P, polyclonal smear.
*Persistent lesion at the same location.
†New lesion on the contralateral arm after a second injection of vaccine.

"Histiocytes with a granular, basophilic cytoplasm were observed in clusters and scattered throughout the infiltrates in all cases."



DOI: 10.1111/cup.13972

ORIGINAL ARTICLE

WILEY

EBER in situ hybridization in subcutaneous aluminum granulomas/lymphoid hyperplasia: A diagnostic clue to differentiate injection-associated lymphoid hyperplasia from other forms of pseudolymphomas and cutaneous lymphomas

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Abstract

Background: Subcutaneous vaccination or desensitization may induce persistent nodules at the injection sites. Without the knowledge of prior injection, histopathological work up may be challenging.

Objective: Aim of this study was to contribute to the histopathological work up of unclear subcutaneous nodules, especially their differentiation from cutaneous lymphoma.

Methods: We retrospectively reviewed clinical data and histopathological slides of four patients with subcutaneous nodules, which were suspected to suffer from cutaneous T- or B-cell lymphoma. Sections of these cases and 12 negative controls were stained with hematoxylin and eosin and a standardized immunohistochemical panel of B- and T-cell markers including EBER in situ hybridization as well as electron microscopy.

Results: In all cases, large histiocytes with granular cytoplasm compatible with intracellular aluminum hydroxide were present. EBER in situ hybridization revealed positive staining of these granular histiocytes while staining was absent in negative controls.

Limitations: Post hoc completion of medical history revealed that vaccination or specific immunotherapy had been applied before at the biopsy site in only three out of four patients; one patient was lost to follow-up.

Conclusion: EBER in situ hybridization is an adjunctive tool to differentiate aluminum induced granuloma/lymphoid hyperplasia from other forms of pseudolymphoma and cutaneous B- or T-cell lymphomas.

KEYWORDS
aluminum granuloma, EBER in situ hybridization, lymphoid hyperplasia, pseudolymphoma, RNA probe

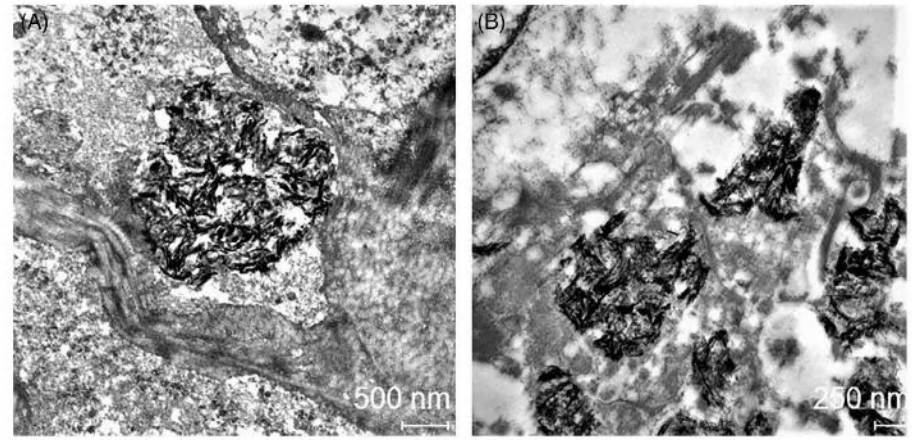
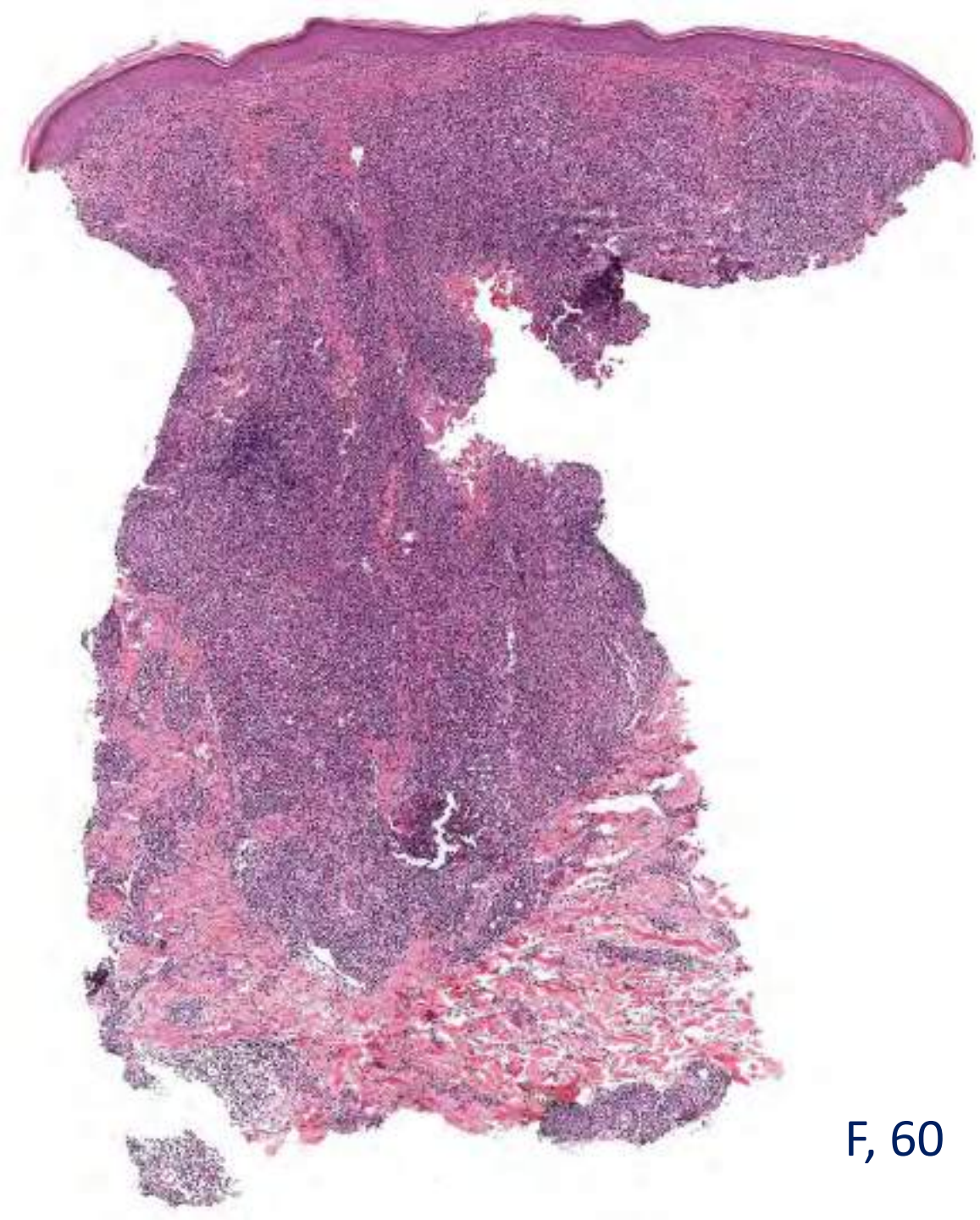


FIGURE 2 Aluminum granuloma. Electron microscopy exemplified by case 1. (A, B) In the cytoplasm of the histiocytes there are interwoven, filamentary or crystalline structures that correspond to the EBER positive signals



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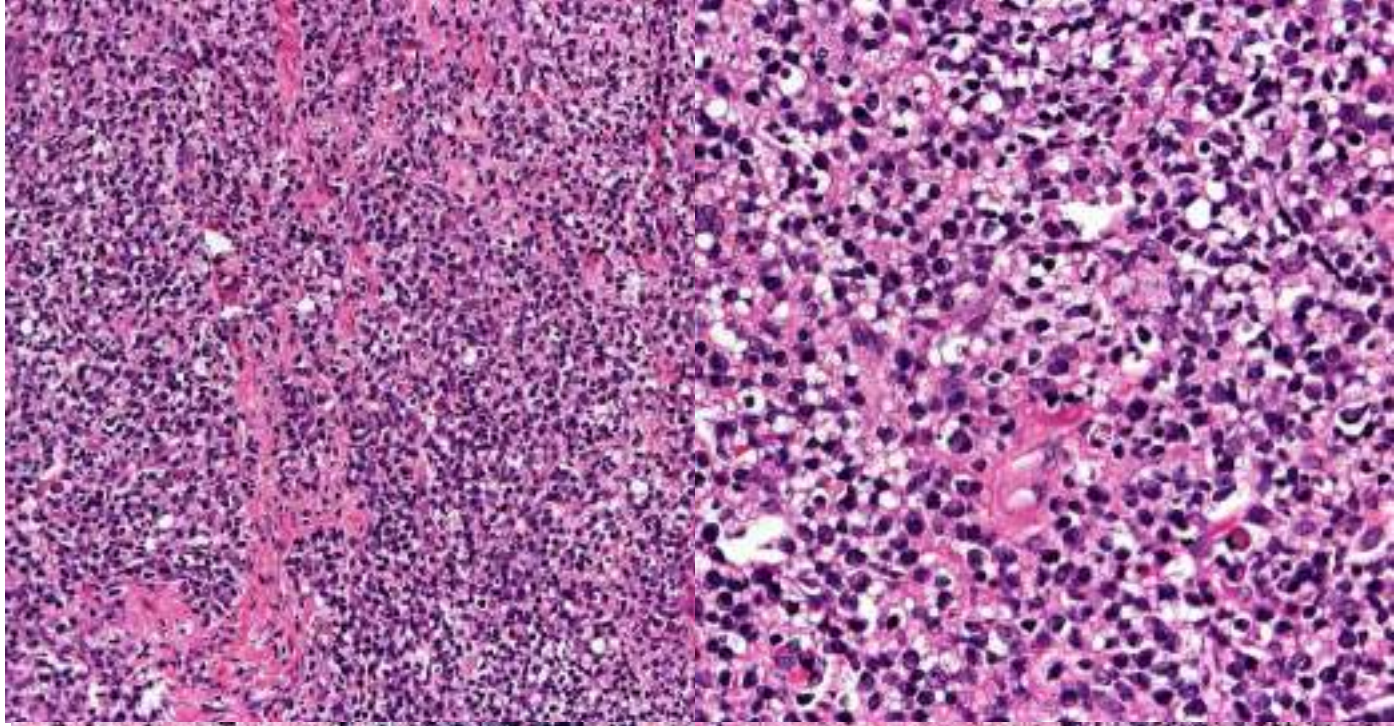
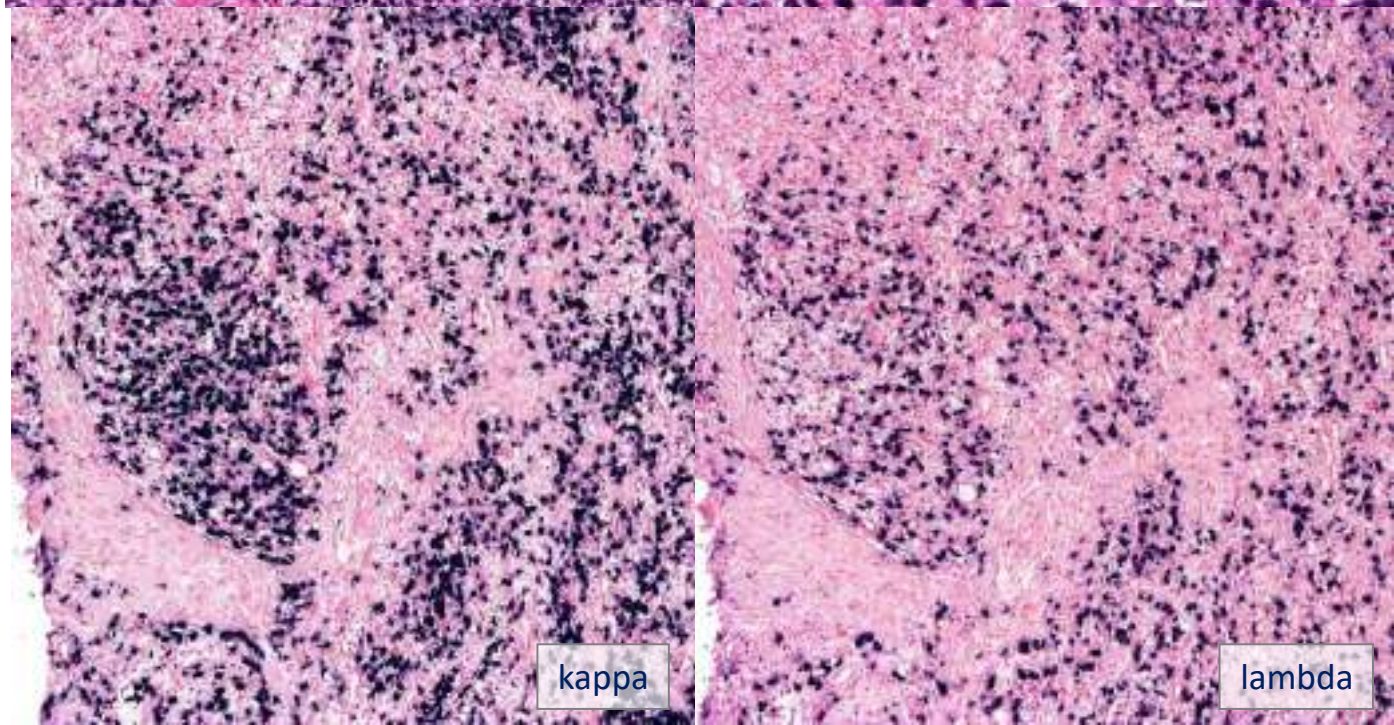
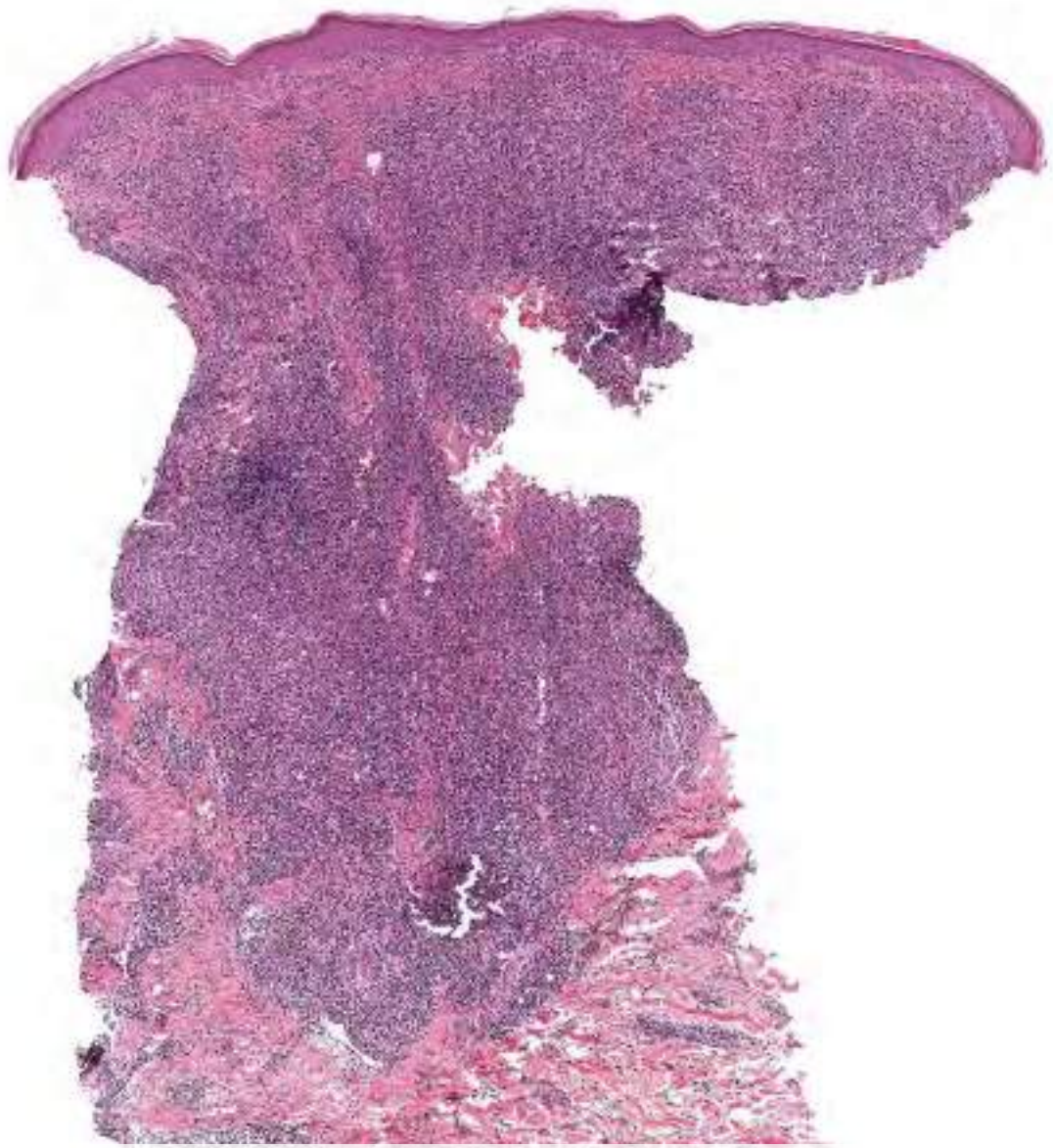
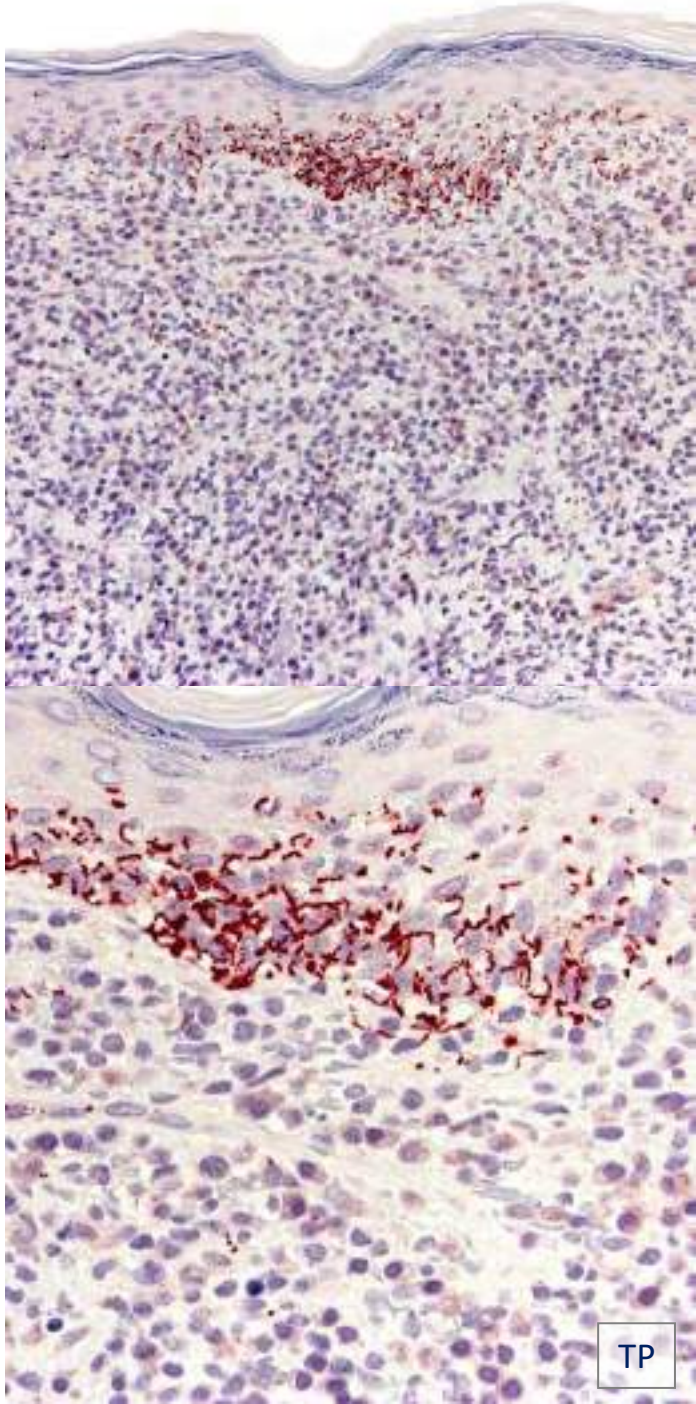
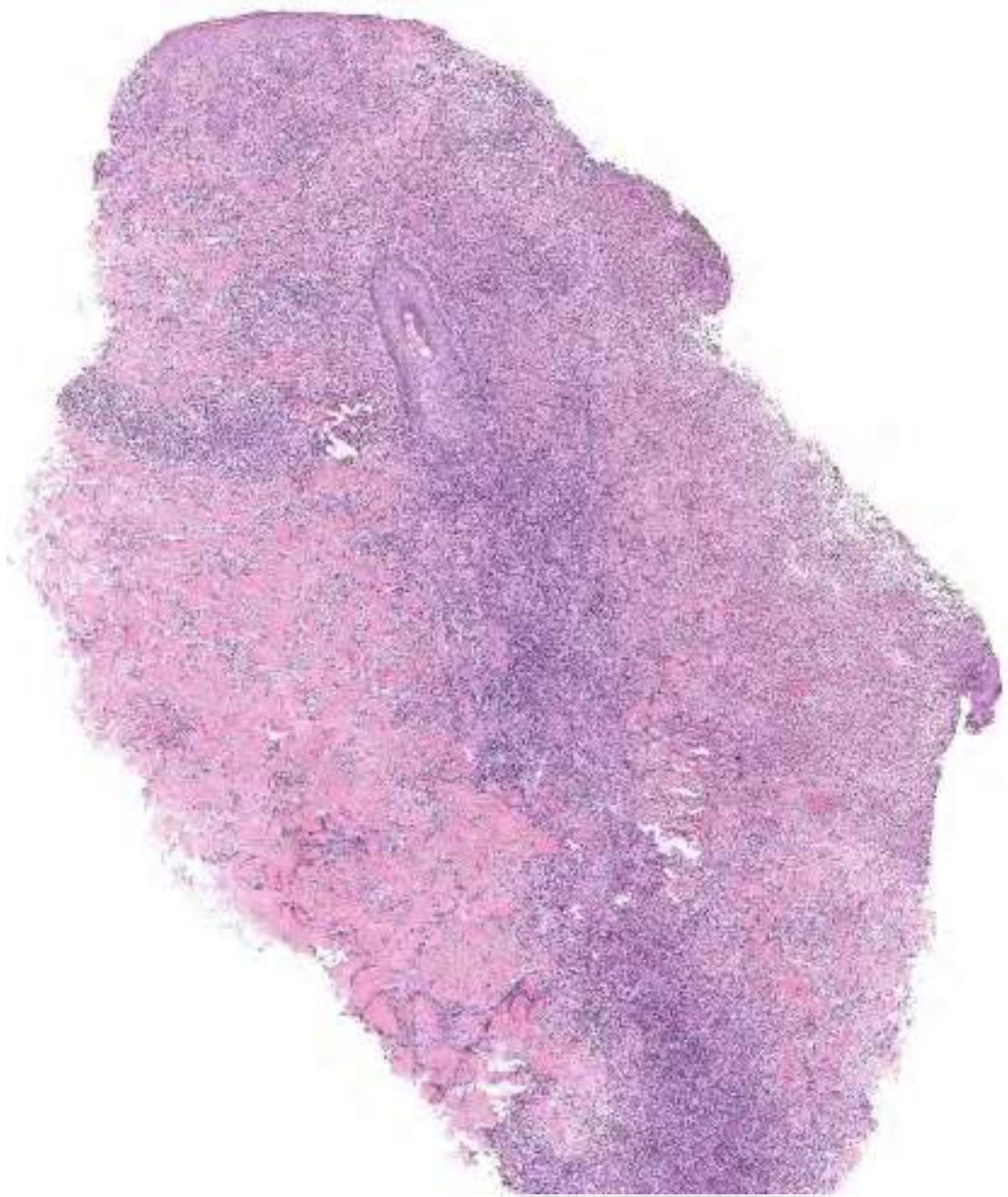


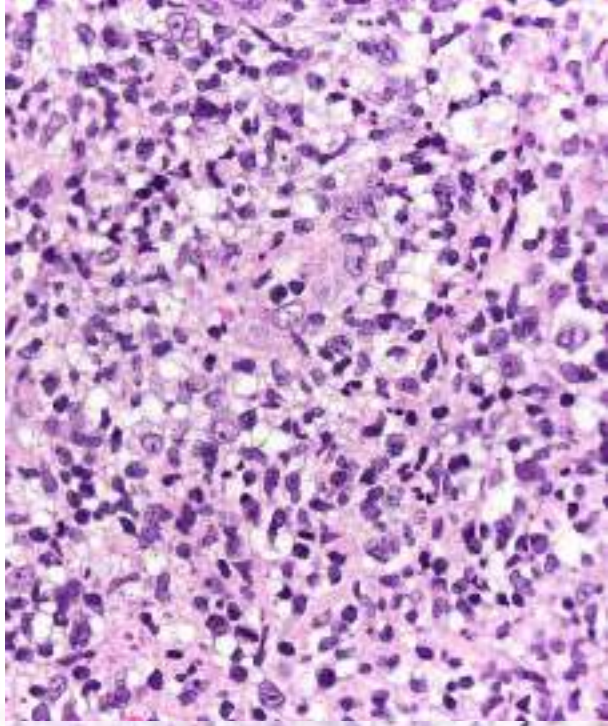


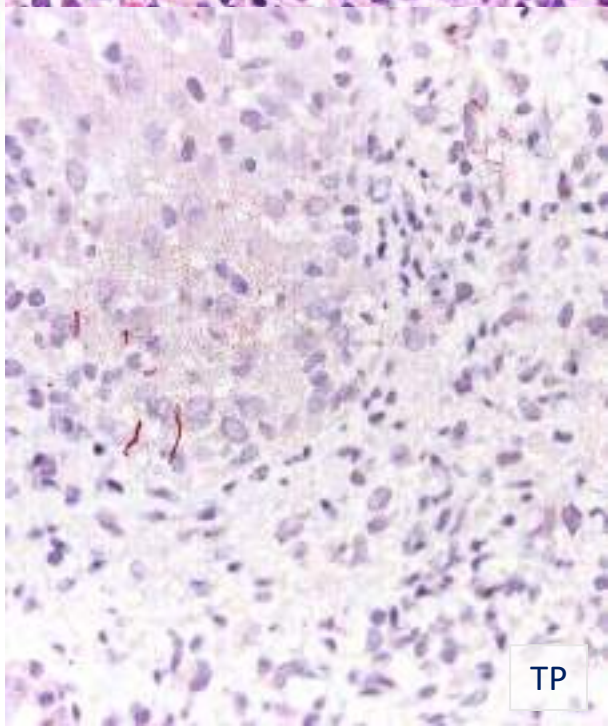


Secondary syphilis









Lues maligna in HIV+ patient

Secondary Syphilis Misdiagnosed as Lymphoma

D. R. Goffinet, M.D., C. Hoyt, M.D., and J. R. Eltringham, M.D., *Stanford*

In 1968 Stecmeier reviewed the histologic material of 600 patients with an initial biopsy diagnosis of Hodgkin's disease and found that three of the patients actually had either primary or tertiary syphilis as the correct diagnosis.[1] However, 25 years have elapsed since the generalized lymphadenopathy of secondary syphilis was last reported to have been misdiagnosed as one of the lymphomas, in particular giant follicle lymphoma.[2]

Since 1944 a new generation of physicians has been trained, some of whom have never seen a case of secondary syphilis. Therefore, attention is again called to the fact that syphilis is still a common disease that should be considered in the differential diagnosis of generalized lymphadenopathy. This report describes two patients seen recently, both of whom had syphilis, misdiagnosed in one case as giant follicle lymphoma and in the other confused with Hodgkin's disease.

Report of First Case

Case 1. A 31-year-old Negro man noted tender right inguinal lymphadenopathy in January 1968, but no penile lesions were present and a VDRL report was negative. Erythromycin was given orally for five days with prompt disappearance of all palpable lymph nodes.

The patient was then well until October 1968 when a slightly pruritic widespread papular skin eruption appeared, followed in about two weeks by generalized lymphadenopathy. The skin lesions were treated with cornstarch soaks. Biopsy of material from axillary and inguinal nodes in November was interpreted as giant follicle lymphoma, and the patient was subsequently referred to the Division of Radiation Therapy at Stanford University Medical Center for further evaluation and treatment. He was taking no medications, had not used Dilantin® and had no history of mononucleosis, cat scratches, sweats, or fevers.

The patient, who was healthy-appearing, had generalized lymphadenopathy, including palpable epitrochlear nodes, all less than 2.5 cm in size. There was a generalized papulo-squamous eruption, most prominent on the palms and trunk. The remainder of the examination, including neurological, disclosed no abnormality.

The Venereal Disease Research Laboratory Test (VDRL) was reactive to 1:128 dilution and the Fluorescent Treponema Antibody Test (FTA) was also positive. The Stanford surgical pathologists were of the opinion that the lymph node biopsy sections showed reactive hyperplasia.

The patient was sent back to the referring physician with a diagnosis of secondary syphilis. A Jarisch–Herxheimer reaction developed during penicillin therapy, and palpable adenopathy disappeared within three weeks. A repeat VDRL was nonreactive within three months.

Report of Second Case

Case 2. A 41-year-old single white man was well until January 1968 when he first noted small, painless, slowly enlarging masses on both sides of the neck. A generalized, erythematous and pruritic skin eruption was also noted. It cleared completely, without treatment, in a few days. There was no history of fevers, night sweats, diphenylhydantoin (Dilantin®) intake, cat scratches, mononucleosis, or penile lesions. A VDRL test had been negative in 1966, but the patient admitted to having both homosexual and heterosexual relations since that time.

After a March 1969 cervical lymph node biopsy was interpreted as showing Hodgkin's disease, the patient was transferred to the Palo Alto Veterans Administration Hospital for consideration of radiation therapy.

Except for generalized lymphadenopathy, including palpable epitrochlear nodes, no abnormality was noted on physical examination. All nodes were less than 2 cm in diameter. The liver and spleen were not palpable, and there were no skin lesions.

Results of blood cell count, urinalysis, determination of blood urea nitrogen, SGOT and electrolyte contents, and an x-ray film of the chest were all within normal limits. A VDRL test was reactive at 1:128 dilution and an FTA test was also positive.

The studies described in this paper were supported by research grants CA 09132 and CA 01395 from the National Cancer Institute.

From the Departments of Surgery (Dr. Goffinet), Medicine (Dr. Hoyt), and Radiology (Dr. Eltringham, Advanced Clinical Fellow, American Cancer Society), Stanford University Medical Center.

Submitted October 8, 1969.

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Biopsies of lymph nodes interpreted as lymphoma

British Journal of Dermatology (1976) **95**, 251.

Histology simulating reticulosis in secondary syphilis

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SUMMARY

Three cases of secondary syphilis are described in whom a skin biopsy was performed. In all, the histology bore a striking resemblance to that of malignant lymphoid neoplasm.

The classical cutaneous manifestations of secondary syphilis are usually easy to diagnose, especially when there is a good clinical history and the appropriate investigations are positive. If, however, the eruption is not characteristic, a skin biopsy may be carried out. We should like to report three cases where the histological appearances in isolation would have been misleading.

CASE REPORTS

Case 1

The patient, a 16-year-old girl, was admitted to hospital with a pyrexia and symptoms suggestive of a urinary tract infection. She was noted to have a widespread erythematous papular eruption involving face, trunk and limbs, which had been present for 3 weeks. There were no mucosal lesions. The inguinal lymph nodes were palpable.

Specific serology was as follows: VDRL slide test—positive. Cardiolipin Wassermann reaction—positive. Reiter protein complement fixation test—positive. A skin biopsy was reported as follows: The epidermis is hyper- and parakeratotic with marked epidermotropism of mononuclear lymphoid cells which are forming micro-abscesses in areas. There is inter- and intracellular oedema in the epidermis. In the dermis there is a dense infiltrate which predominantly is perivascular. There is no evidence of a vascular lesion. The infiltrate is composed of histiocytic cells, mononuclear cells, plasma cells and occasional neutrophil polymorphs. Scattered throughout there are large pleomorphic mononuclear cells with hyperchromatic nuclei and prominent nucleoli. Mitotic figures are occasionally found. These findings in the absence of a clinical history are compatible with the diagnosis of cutaneous lymphoid neoplasm.

Skin biopsies interpreted as lymphoma

Pseudolymphomatous syphilis

- Rare clinicopathologic presentation of secondary syphilis
- Solitary (rarely) or multiple papules, nodules and small tumors; may simulate MZLD, but plasma cells polyclonal
- In HIV+ patients with low CD4+ count may simulate a T-cell lymphoma (lues maligna)
- Some ulcera of primary syphilis may also be characterized by florid, pseudolymphomatous infiltrates
- Staining for *Treponema pallidum* represents a useful tool, but microorganisms may be only a few

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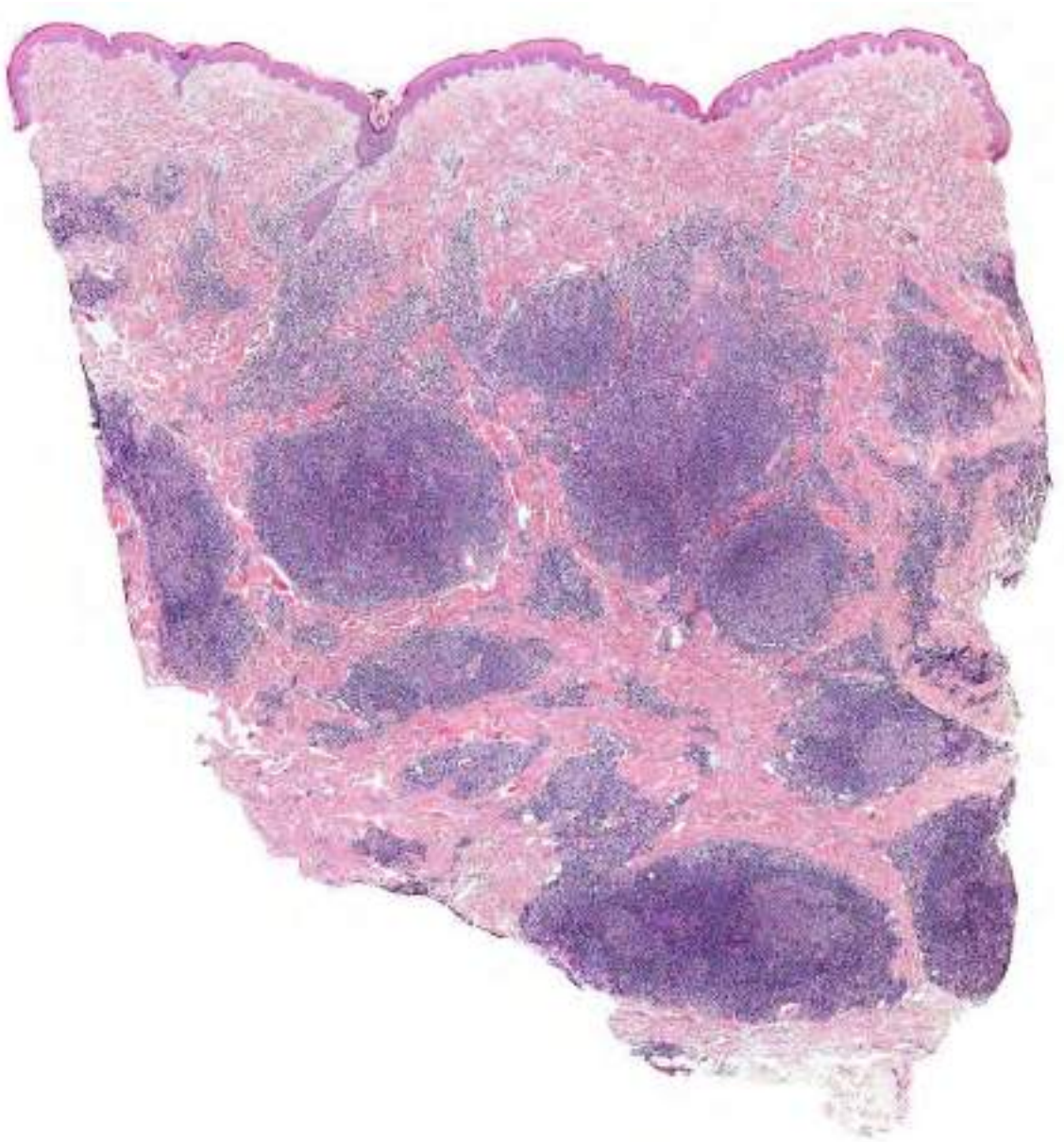

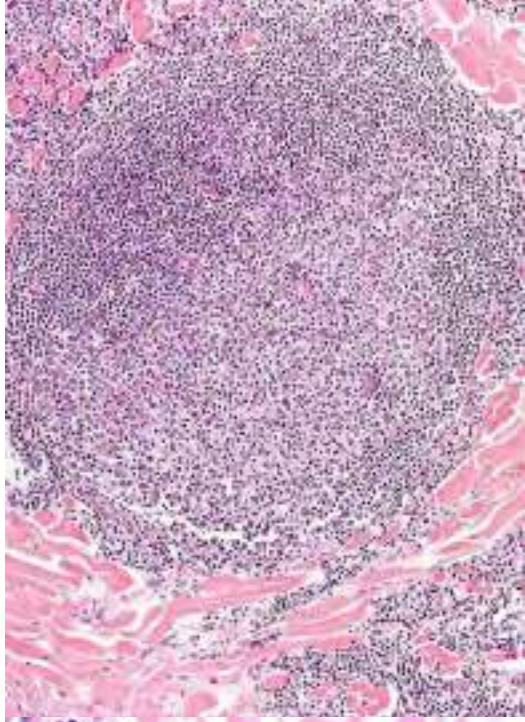

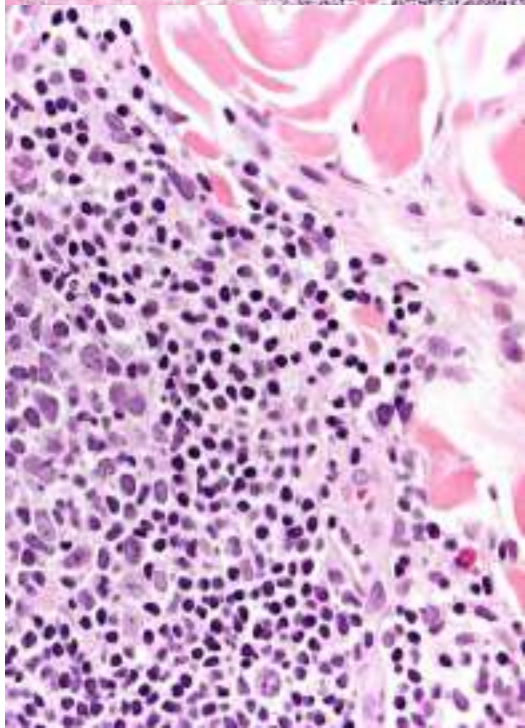

Pseudolymphoma after drug administration

Lymphomatoid drug eruption (B-cell pattern)

- Drug eruptions may occasionally mimic a cutaneous B-cell lymphoma (FCL-like or MZLD-like); The B-cell pattern is much less frequent than the T-cell pattern of drug-induced pseudolymphoma
- Sudden onset, localized or generalized distribution; Resolution upon discontinuation of the offending drug
- Cases with B-cell pattern present with nodular infiltrates, either with germinal centers or with clusters/sheets of monotypic plasma cells
- The germinal centers reveal reactive morphologic and phenotypic features

REVIEW ARTICLE

Australasian Journal of Dermatology

Drug-induced cutaneous pseudolymphoma: A systematic review of the literature

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Abstract

Drug-induced cutaneous pseudolymphoma (CPL) is a common form of pseudolymphoma and there are numerous drugs associated with it. In this study, we performed a systematic review of the literature by searching PubMed/Medline and Embase databases to determine the most common drugs responsible for CPL and to define the demographic, clinical, histopathological and immunopathological characteristics of patients (updated on 30 December 2020). From 883 initially found articles, 56 studies (89 reported cases) were included. The mean age of patients was 54.4 ± 17.7 (ranging 8–86) years, and 46 (51.7%) were men. The median time interval between drug intake and CPL occurrence was 120 days (range 1–7300 days). The shortest median time interval between taking the drug and the onset of the disease was observed among patients taking antidepressants (90 days) (range 7–540) and the longest median time interval was observed in individuals using immunomodulators (300 days) (range 3–7300). The most-reported drug categories causing CPL were anti-hypertensives (17.9%), anticonvulsants (14.6%), monoclonal antibodies (13.4%) and antidepressants (11.2%). Moreover, the most common drugs were phenytoin (6.7%), amlodipine (5.6%), fluoxetine (5.6%) and carbamazepine (4.4%). Histopathological evaluation of 76 cases revealed 62 (81.5%) reports of T-cell infiltrations. Furthermore, positive reports of CD4 (94.6%), CD8 (93.6%) and CD30 (87.5%) were noted. The lowest prevalence of CD30-positive reports was observed among monoclonal antibodies. In conclusion, anti-hypertensives, anticonvulsants, monoclonal antibodies and anti-depressants are the most common drugs responsible for CPL. It mostly presents in middle-aged patients with almost no gender difference as pruritic papules, nodules and plaques.

KEYWORDS

amlodipine, cutaneous pseudolymphoma, drug-induced, fluoxetine, phenytoin

Alumni of the Institute of Tehran University of Medical Sciences (IUMS), Department of Dermatology, Razi Hospital.

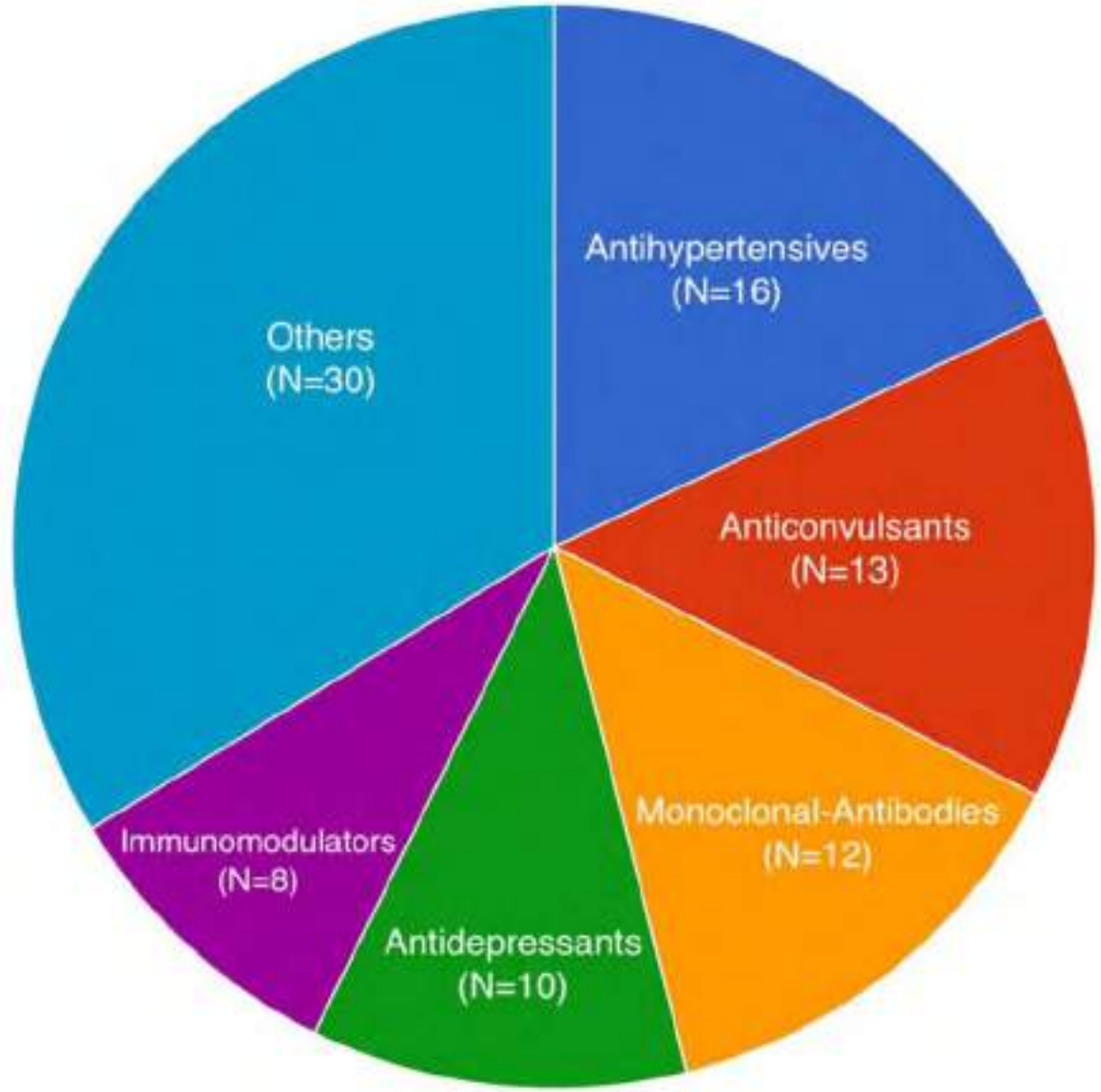

FIGURE 1 The culprit drug categories

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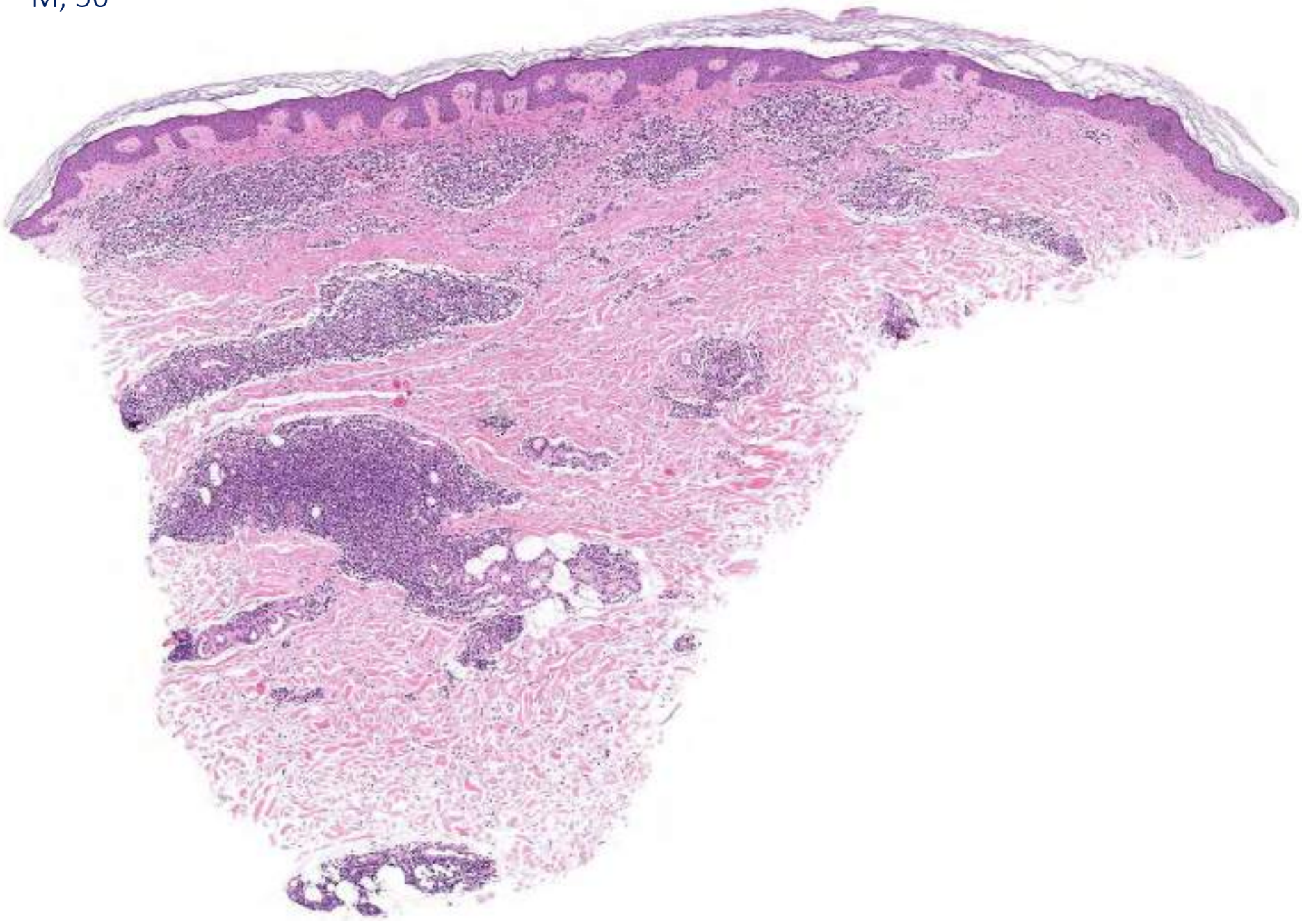
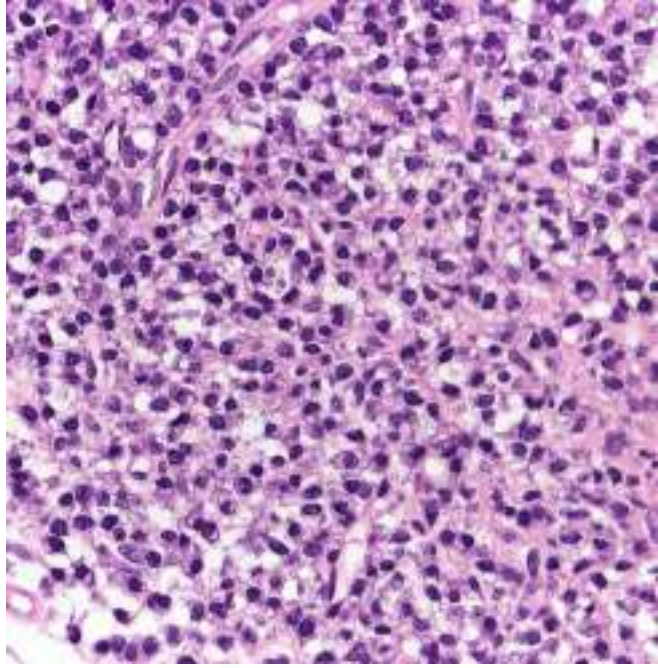
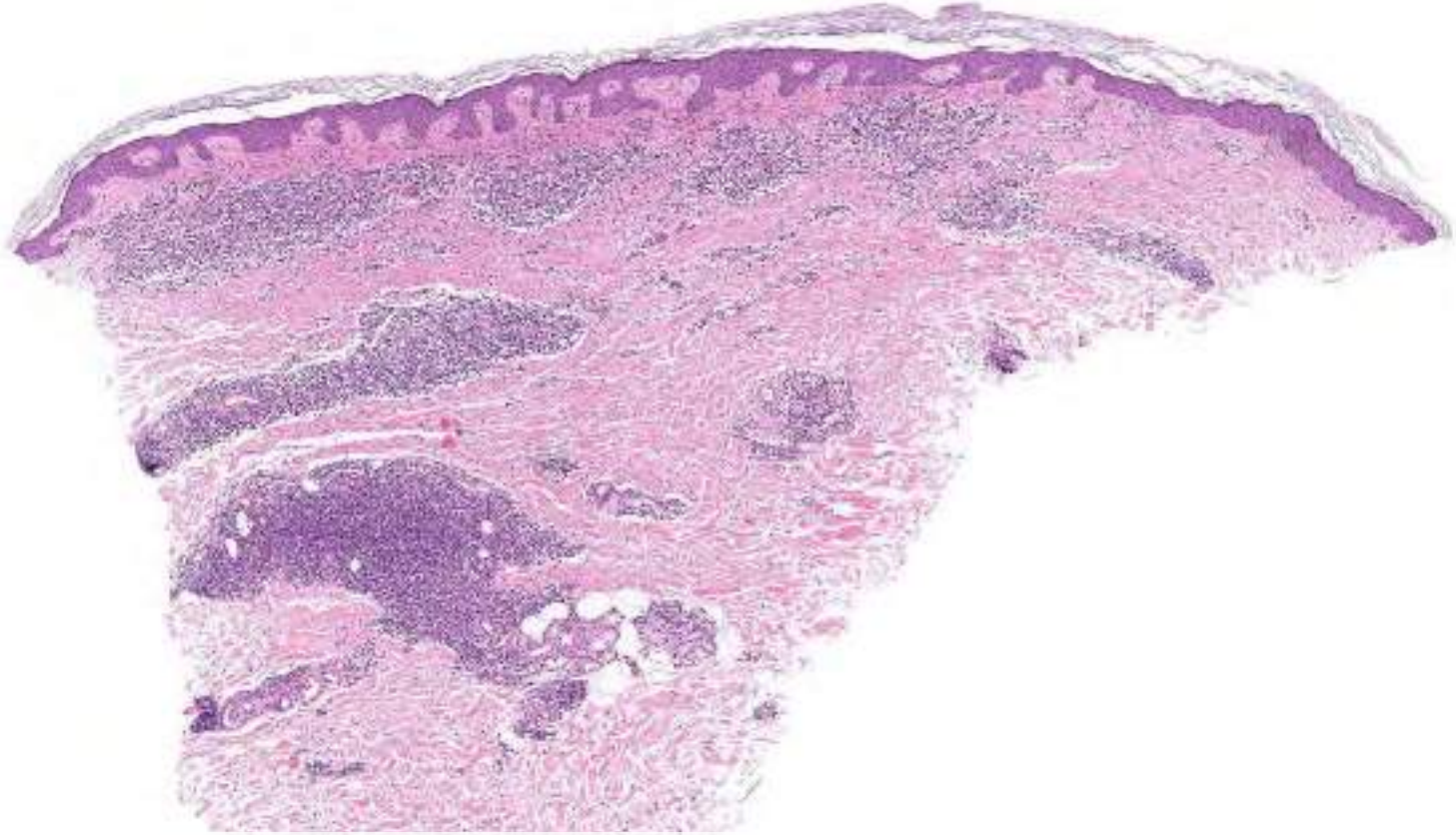




kappa

lambda



Pseudolymphoma after talimogene laherparepvec treatment for metastatic melanoma

kappa

lambda

personal fees from Berlin-Chemie Menarini, personal fees from Merck, personal fees from Regeneron, personal fees from Sanofi-Genzyme, personal fees from Amgen, personal fees from Boehringer Ingelheim, personal fees from Galapagos, personal fees from InflaRX, personal fees from Pfizer, personal fees from UCB, personal fees from Incyte and personal fees from Helm, outside the submitted work, and is a co-author of the article on development of the IsToDerm(QoL questionnaire.

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DOI: 10.1111/jdv.16660

Talimogene laherparepvec can initiate plasma cell invasion into infiltrated melanoma lesions – a case series

Editor

Talimogene laherparepvec (T-VEC) is a genetically engineered herpes simplex virus type 1 (HSV-1) and used in locally advanced melanoma patients. Its mode of action is not fully understood.[1,2] We present three cases where T-VEC caused intratumoral as well as polyclonal B-cell infiltration.

Case 1: A 76-year-old male patient presented with several firm, black-bluish papules on his right upper arm after a history of nodular melanoma (2.95 mm) on his right lower arm 2 years prior (Fig. 1a). Histopathology revealed cutaneous BRAF^{V600E} mutated melanoma metastases. Due to no signs of distant metastases, treatment with T-VEC (IMLYGIC®) was administered intralesionally according to recommended guidelines. Within 4 months, all lesions regressed leaving flat greyish macules that were excised (Fig. 1b).

Histology revealed dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis and superficial subcutis (Fig. 1c). Focal fibrosis and superficial clusters of melanophages were observed, and complexes of melanocytes were absent (Fig. 1d). By in situ hybridization and immunohistochemistry, the plasma cells were clonal, expressing light chain kappa and heavy chain IgG (Fig. 1e,f). Nine months later, two new papules on the right upper arm were excised. They showed the same infiltrate as mentioned above. Serum and urine protein electrophoresis was polyclonal. Quantification of IgG, IgA and IgM immunoglobulins as well as measurement of the serum free light chains lambda and kappa showed no pathologic findings. A

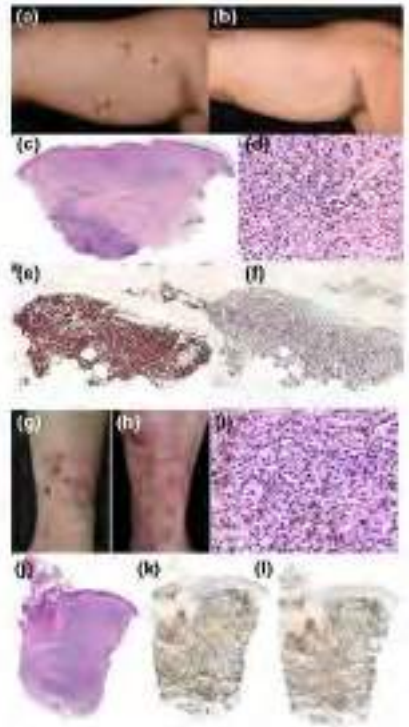


Figure 1 Clinical images and immunohistochemical pictures of case 1 and 2. (a) Black-bluish papules on right upper arm representing cutaneous melanoma metastases in December 2016. (b) Regression of all marked lesions in May 2017. (c) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis and superficial subcutis (original magnification 20×). (d) Focal fibrosis and small clusters of melanophages admixed with plasma cells, but no complexes of melanocytes (original magnification 200×). (e) Plasma cells are positive for kappa light chain (in situ hybridization; original magnification 100×). (f) Plasma cells are mostly negative for lambda light chain (in situ hybridization; original magnification 100×). (g) Red and black-bluish macules and papules on the left lower leg representing cutaneous melanoma metastases in August 2018. (h) Regressive lesions in Mai 2019. (i) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis (original magnification 20×). (j) Focal fibrosis and small clusters of melanophages admixed with plasma cells and lymphocytes, but no complexes of melanocytes (original magnification 200×). Polyclonal expression of kappa (k) and lambda (l) light chains of plasma cells (in situ hybridization; original magnification 20×).

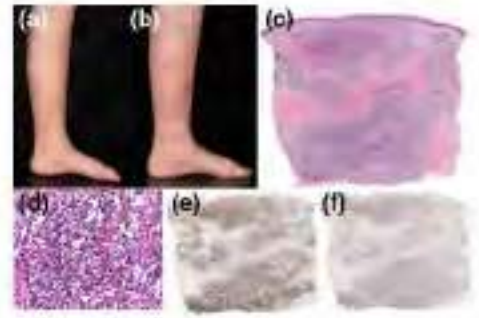
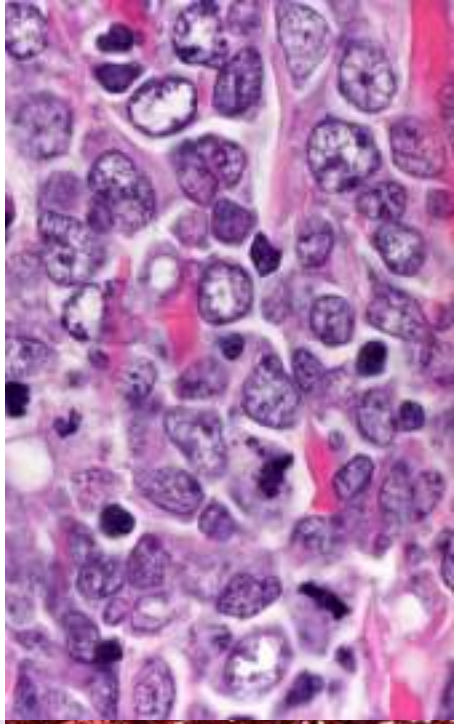


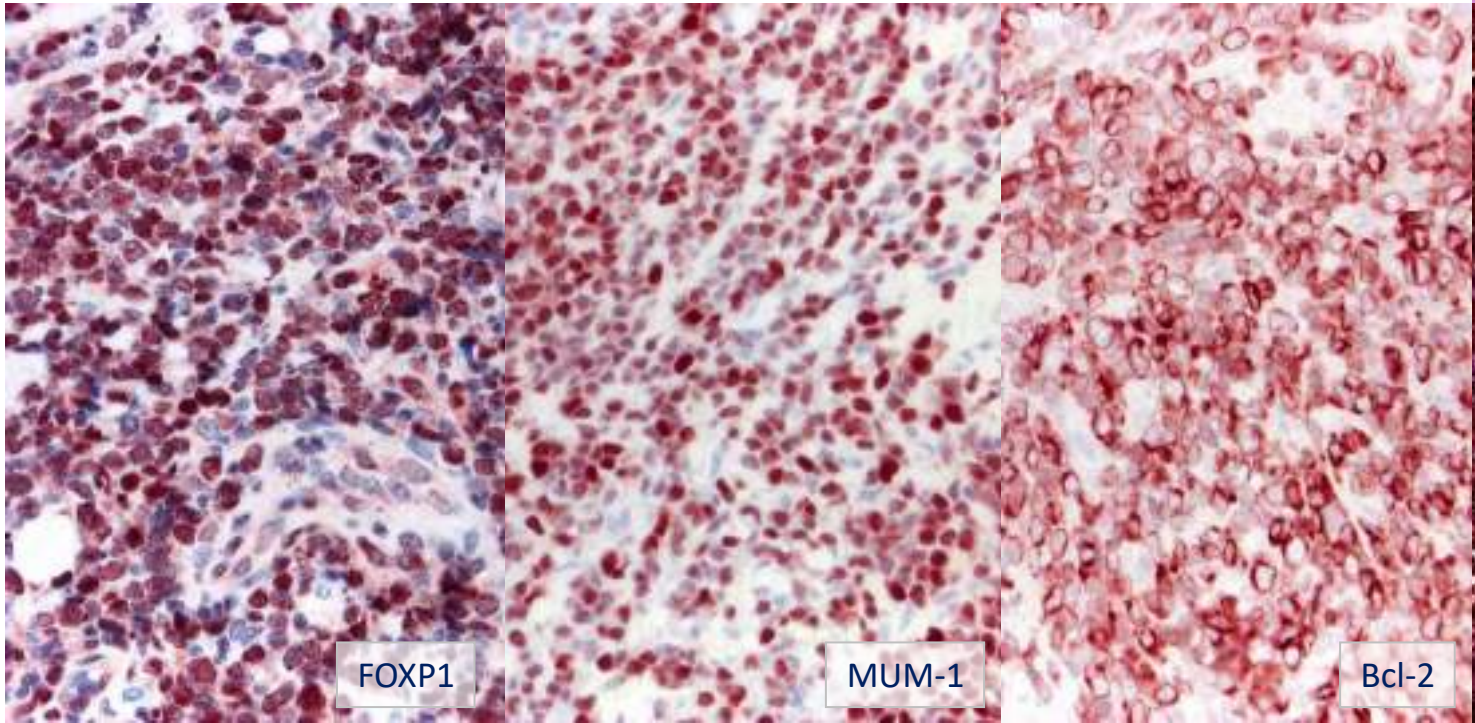
Figure 2 Clinical images and immunohistochemical pictures of case 3. (a) Black-bluish papules on the left lower leg representing cutaneous melanoma metastases in December 2017. (b) Regressive lesions in December 2018. (c) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis (original magnification 20×). (d) Focal fibrosis and plasma cells, but no complexes of melanocytes (original magnification 200×). (e) Plasma cells are positive for kappa light chain (in situ hybridization; original magnification 20×). (f) Plasma cells are mostly negative for lambda light chain (in situ hybridization; original magnification 20×).

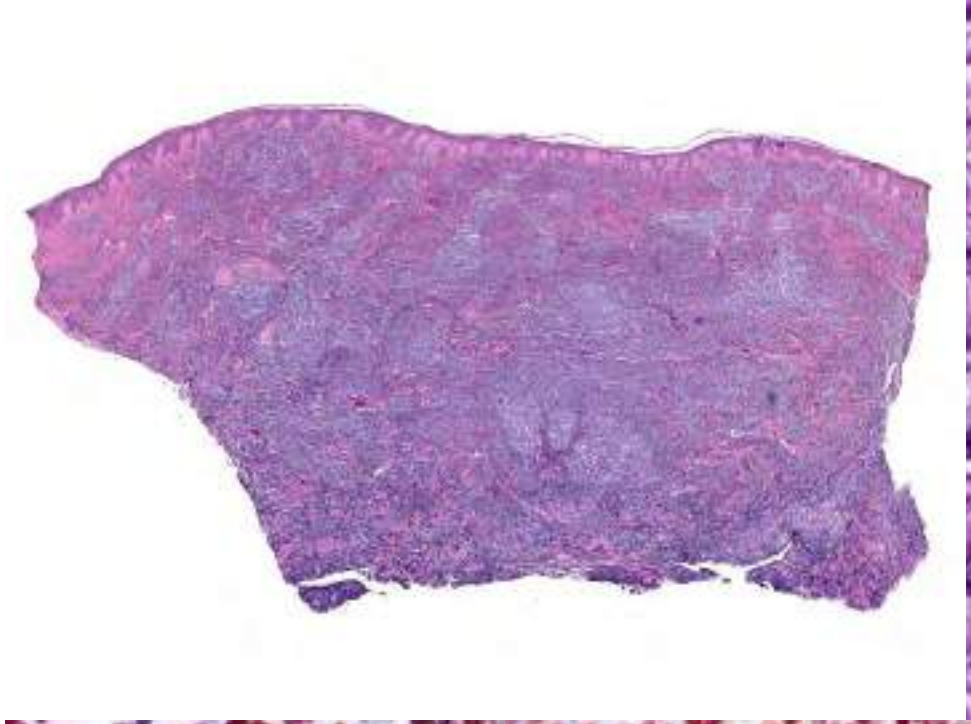
Primary cutaneous diffuse large B-cell lymphoma, leg-type

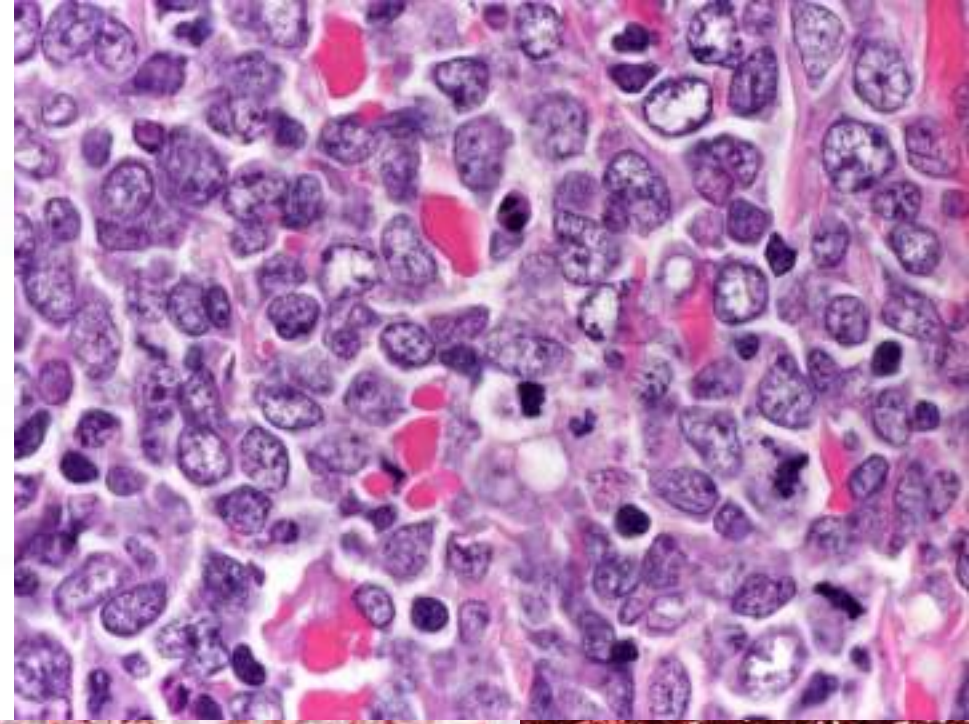
Edlerly patients; in >80% of cases located on the leg(s). Sheets of centroblasts and/or immunoblasts. Bcl2+, MUM1+, Bcl6+/-, FOXP1+, IgM+, MYC+/-, CD10-(+).

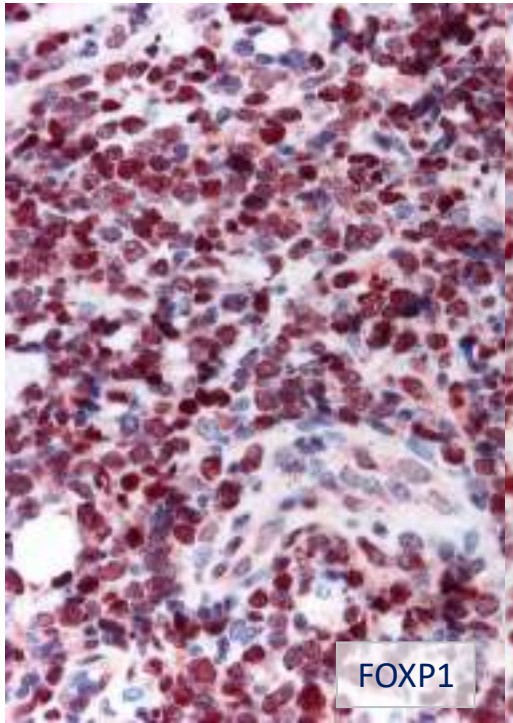
Chromosomal translocations involving *IGH* in 50%, *MYC* in 5-43% and *BCL6* in 23-50% are reported, as well as “double-hit” lymphomas with *MYC* and *BCL6* translocations (not of *BCL2*). Highly recurrent hotspot mutations in the adaptor molecule of the Toll-like receptor *MYD88* are found in ~70-75% of cases. The gene expression profile of PCLBCL-LT resembles activated B-cell–like DLBCL, similar to lymphomas arising in immunoprivileged sites such as primary DLBCL of the CNS and testis.







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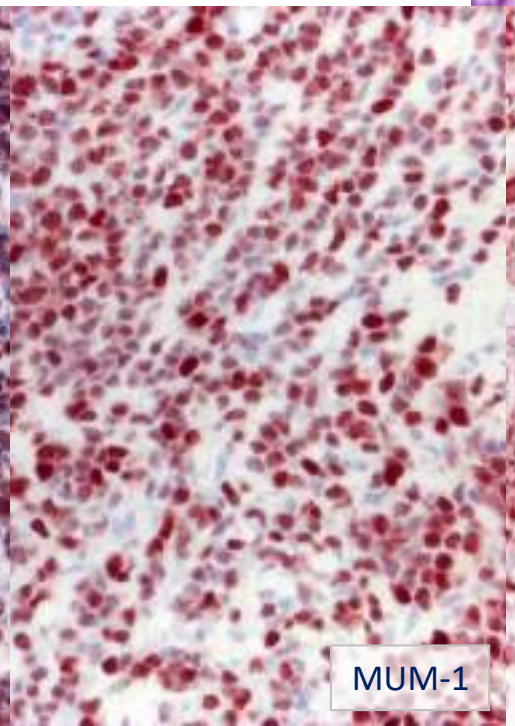
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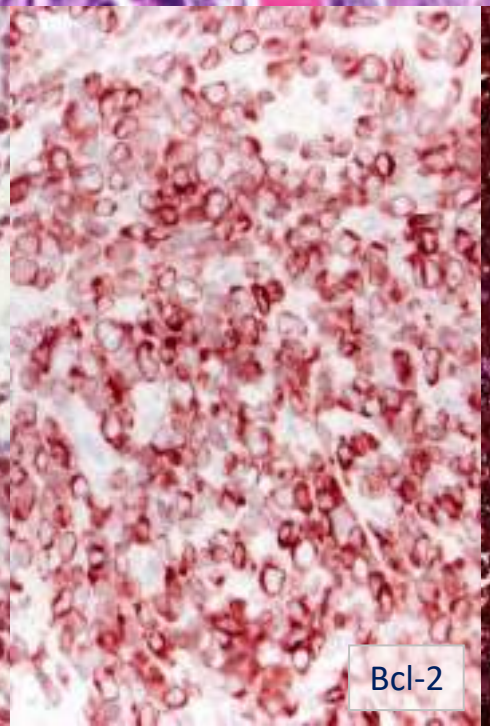
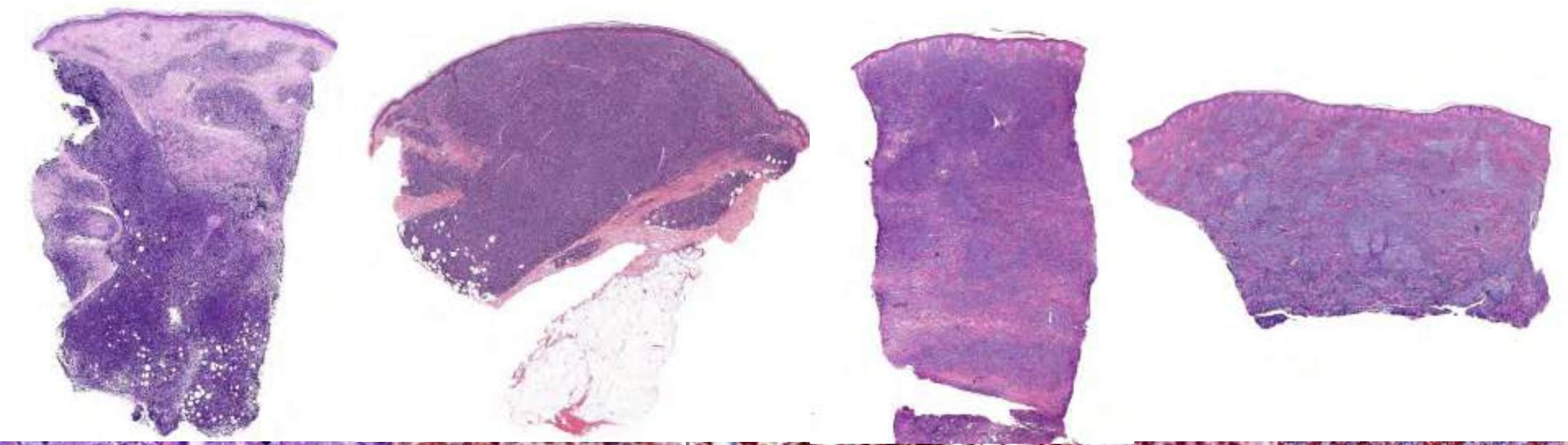
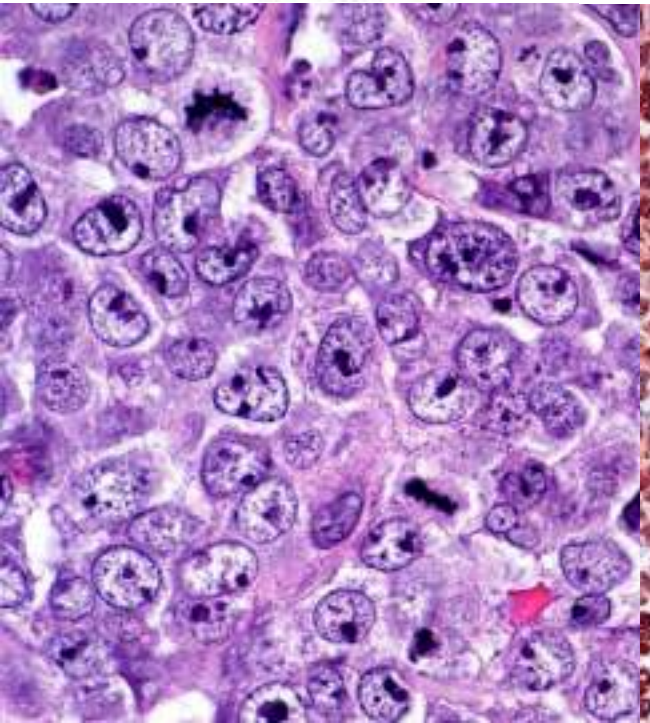
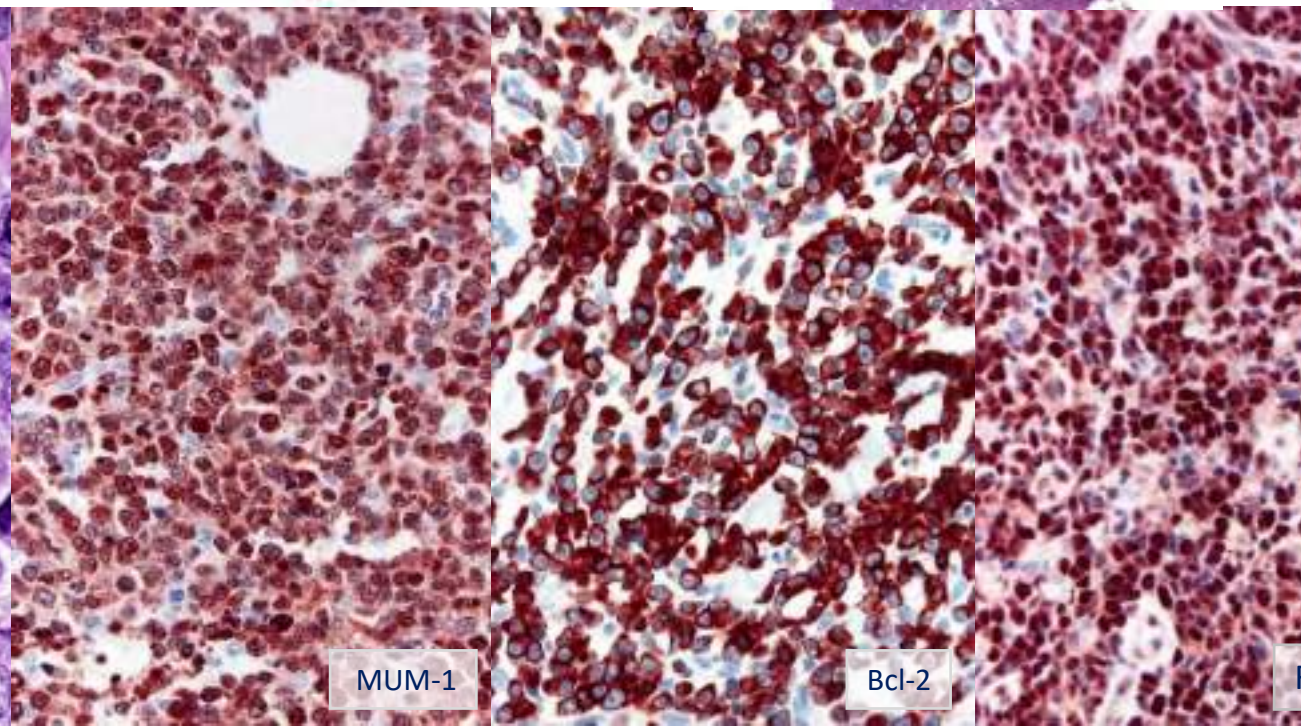
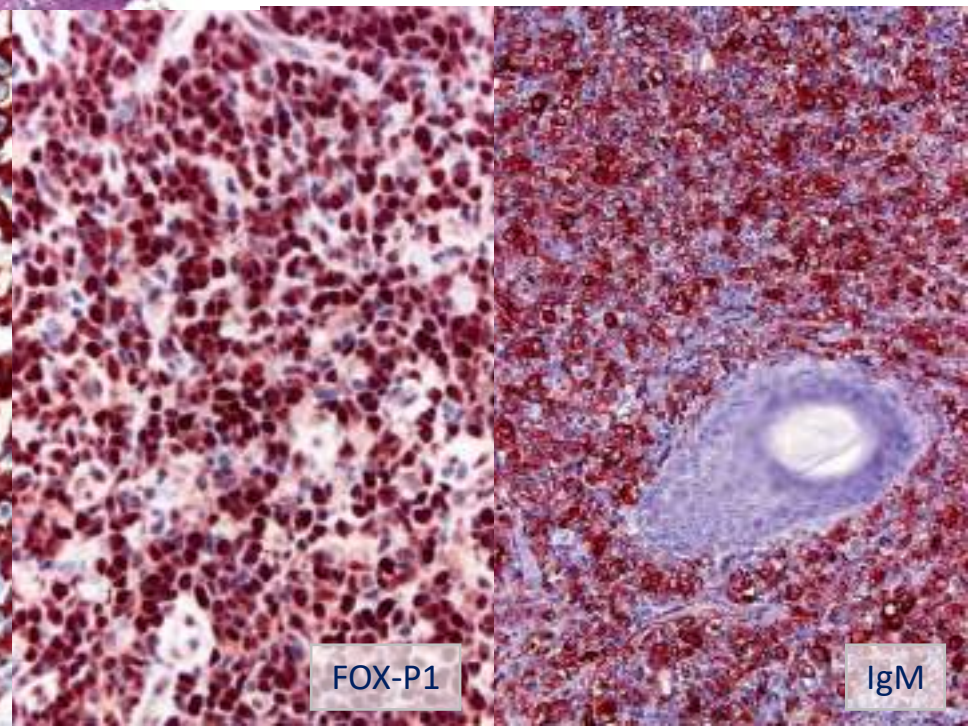

Bcl-2


IgM






MUM-1
Bcl-2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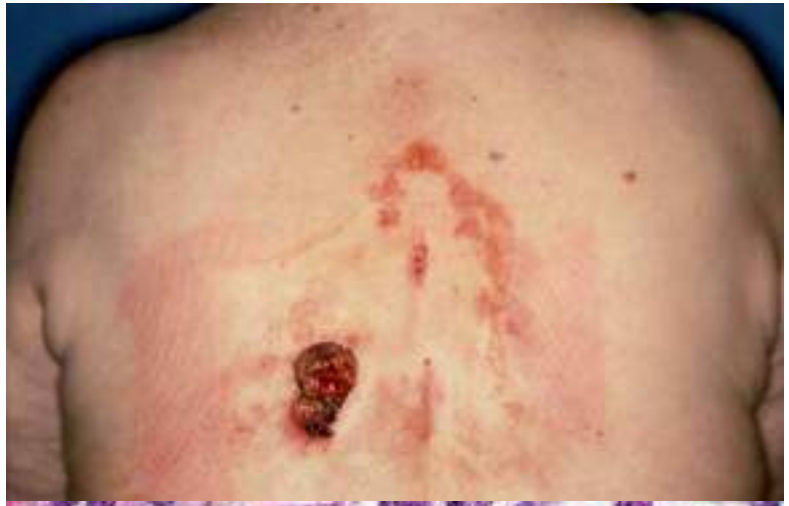
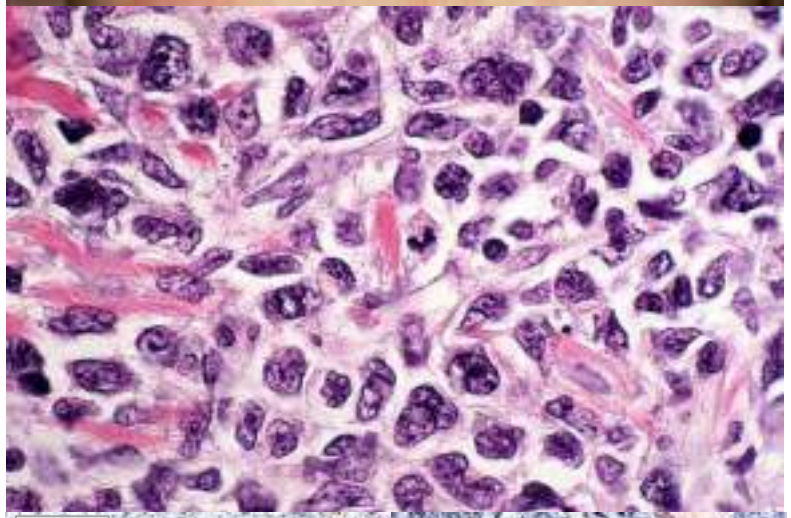
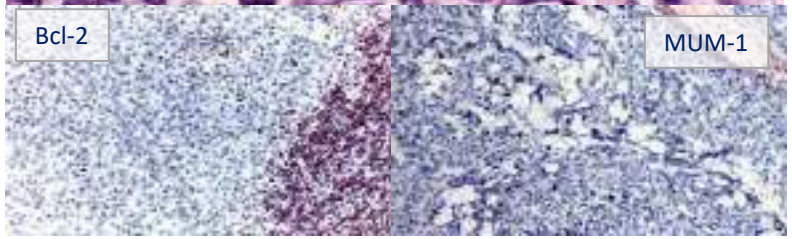
Follicle center lymphoma, diffuse type

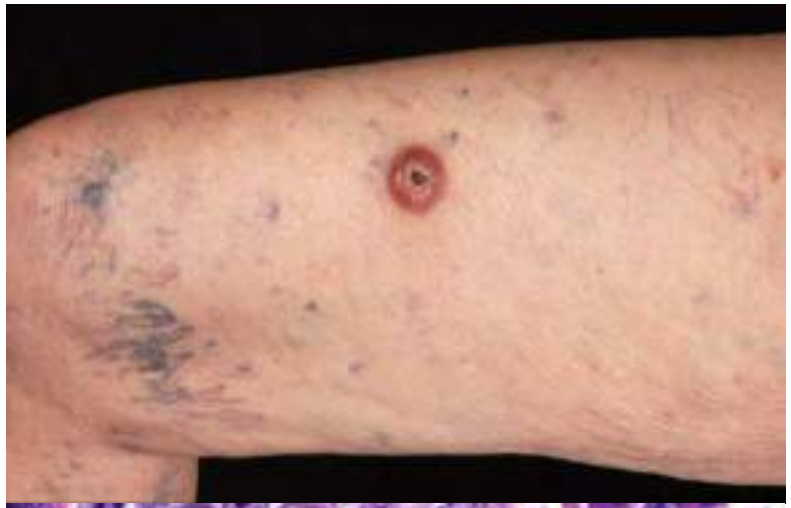


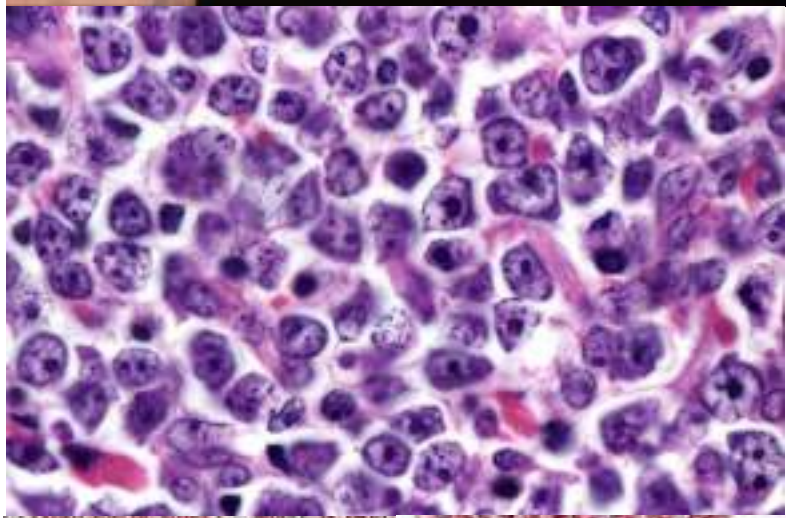


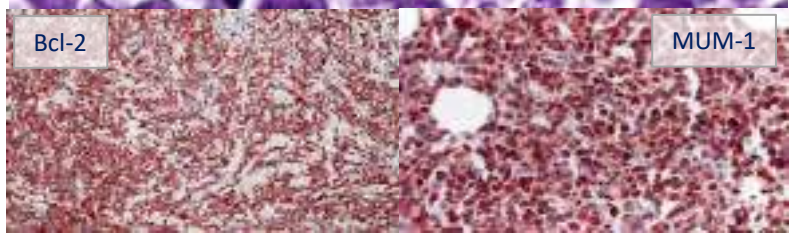


Non-aggressive treatment

Diffuse large B-cell lymphoma, leg type







Aggressive treatment

Atypical clinicopathologic presentation of primary cutaneous diffuse large B-cell lymphoma, leg type

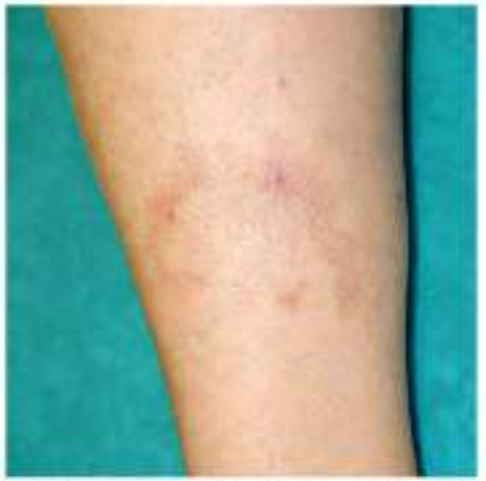


Fig 1. Primary cutaneous diffuse large B-cell lymphoma, leg type. Patient 1. Annular lesion on the leg. A small scar represents the site from which the biopsy specimen was obtained.

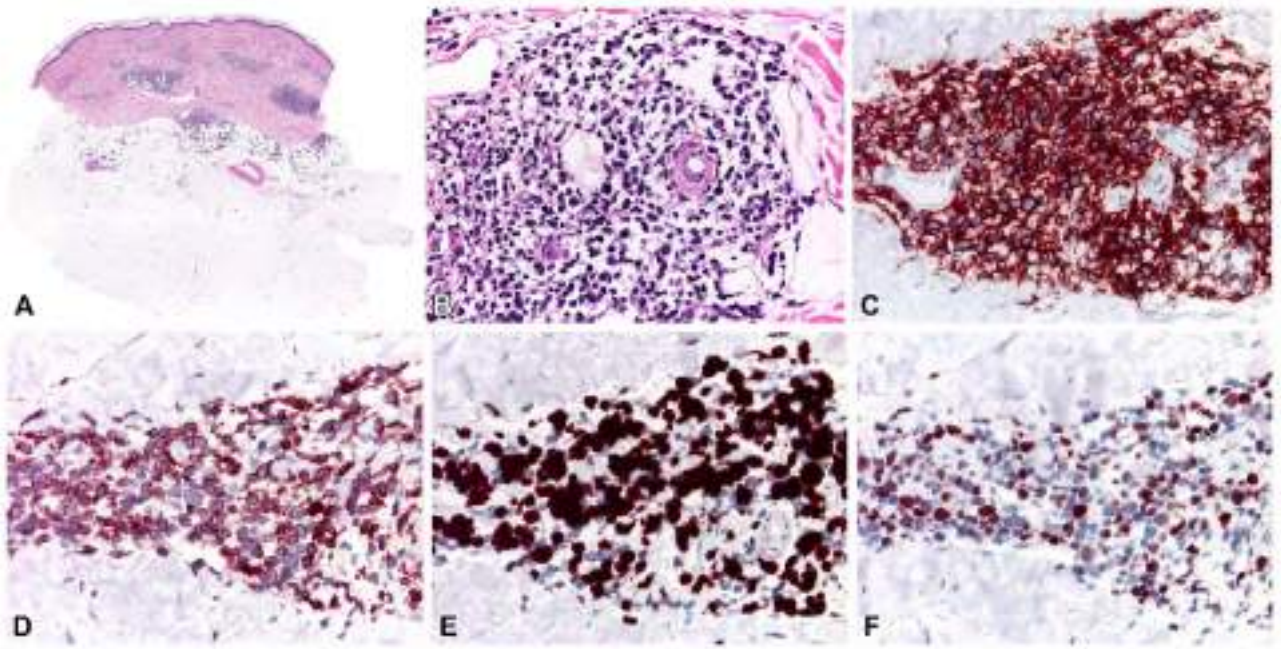
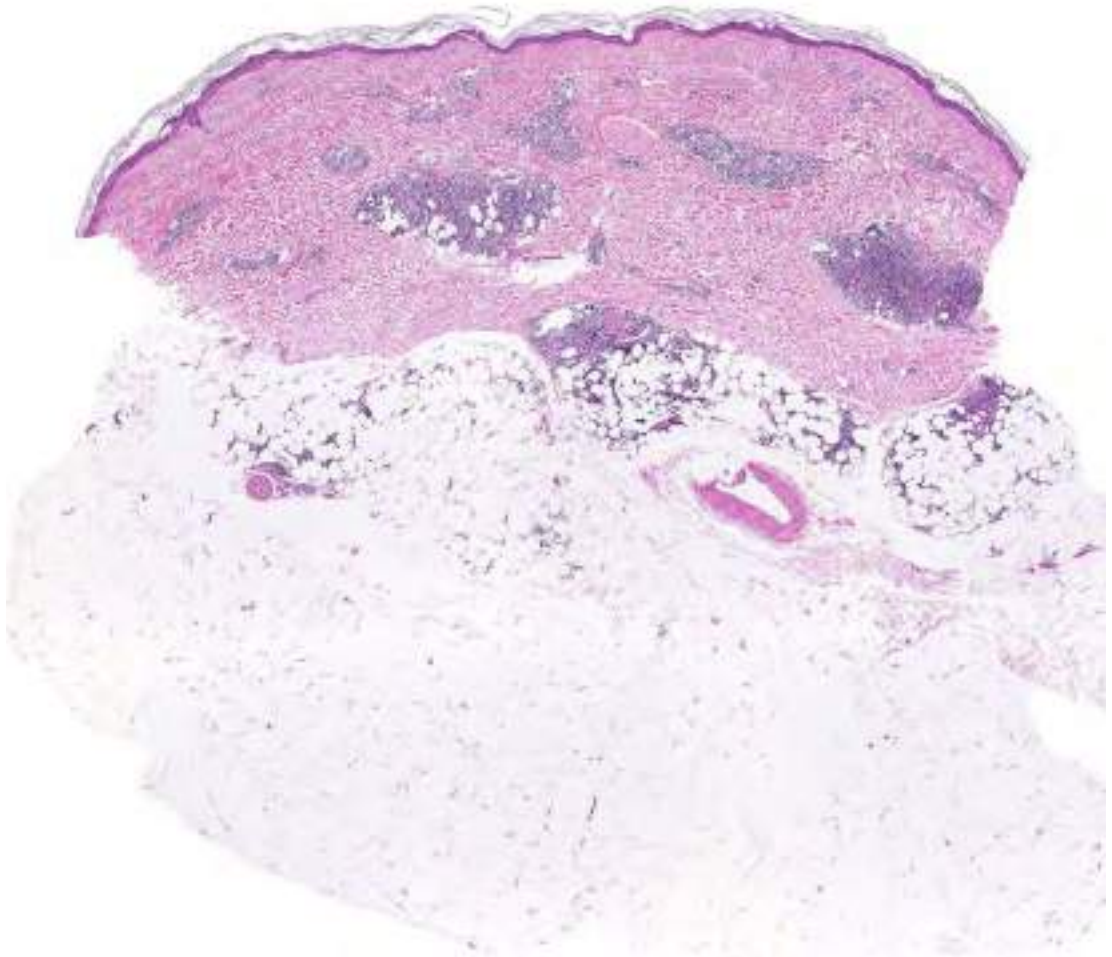
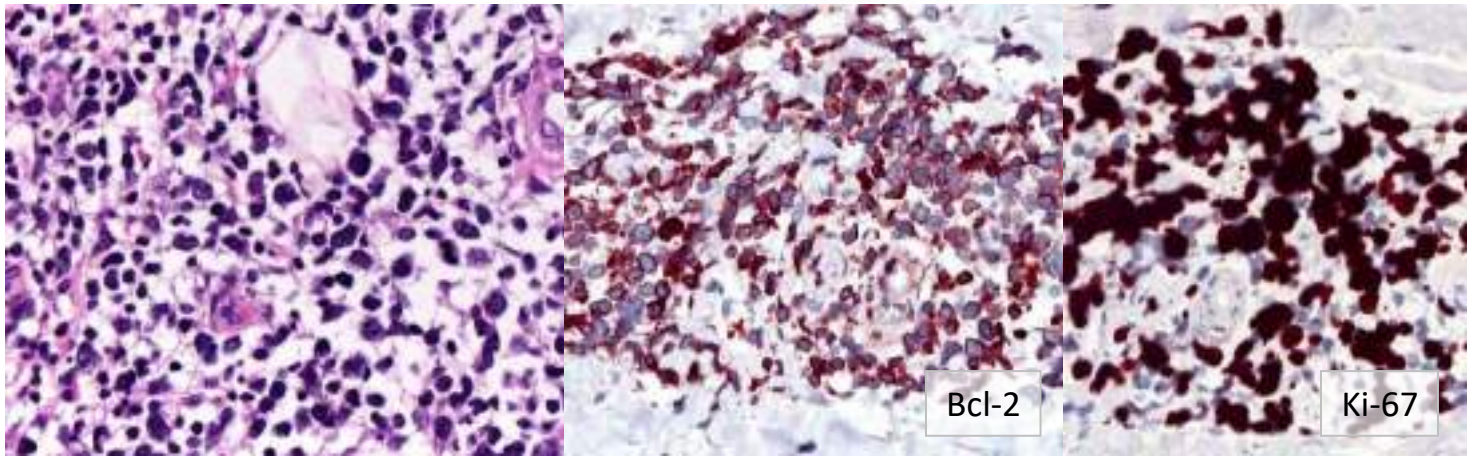
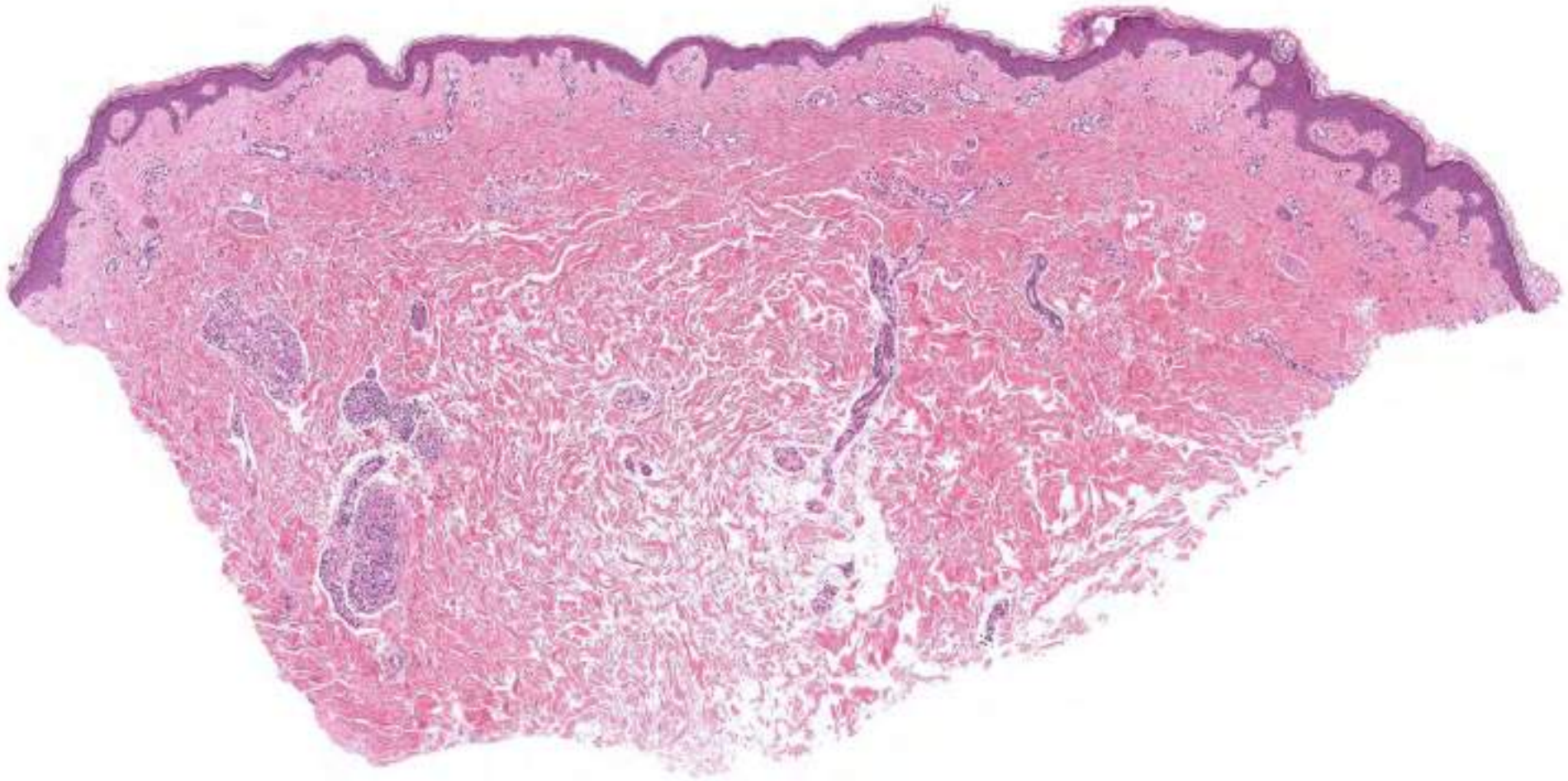


Fig 2. Primary cutaneous diffuse large B-cell lymphoma, leg type. Patient 1. Histopathologic and phenotypical studies reveal (**A**) a moderately dense, perivascular infiltrate (**B**) characterized by small lymphocytes admixed with several large cells. The cells are positive for (**C**) CD20, (**D**) Bcl-2, and (**E**) MUM-1 and (**F**) show a high proliferation as detected by the antibody Ki-67.

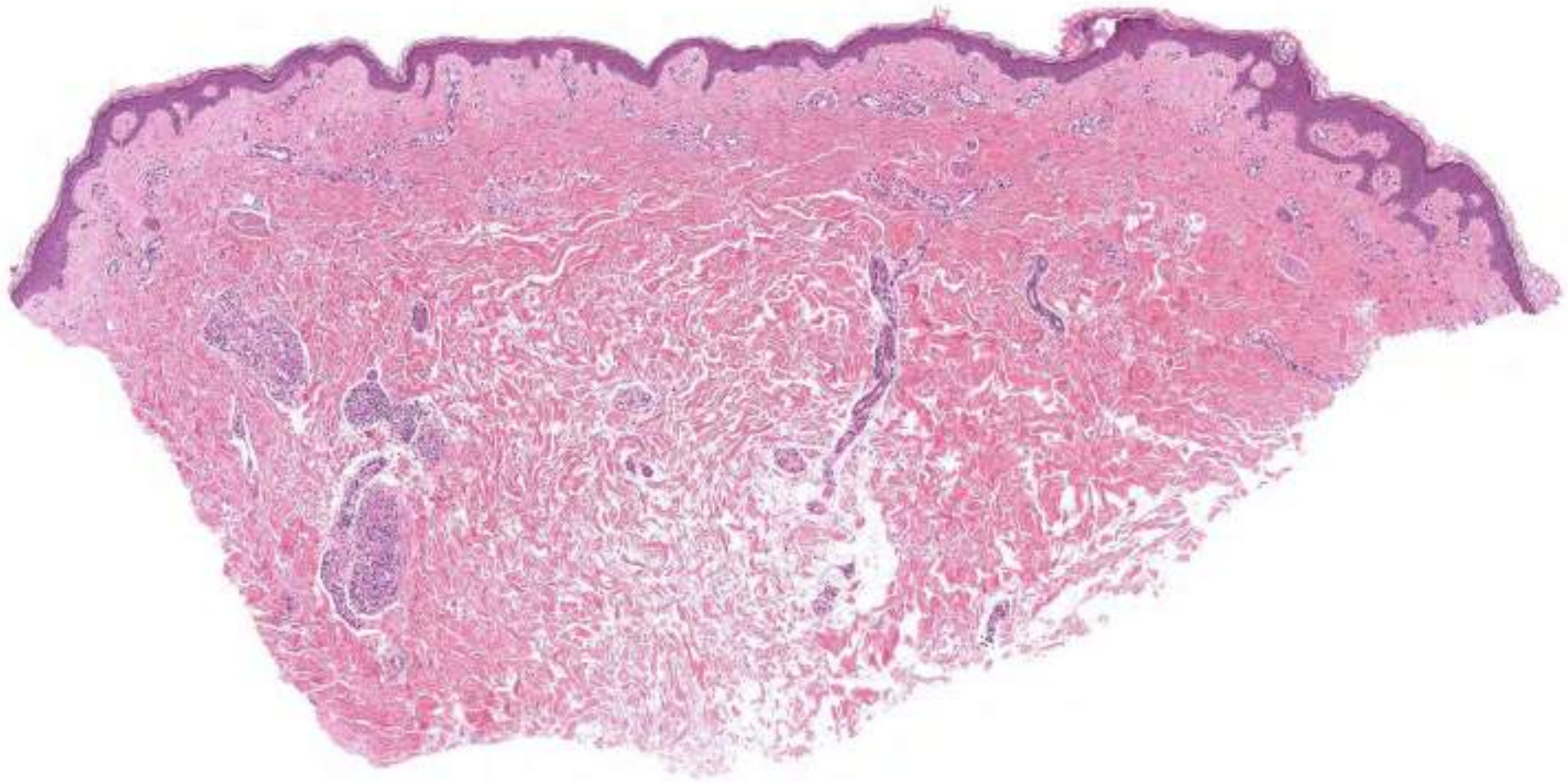


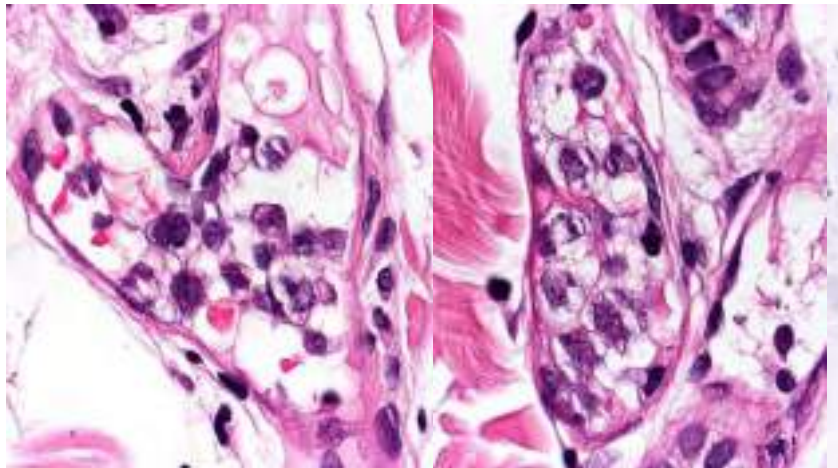

Bcl-2
Ki-67

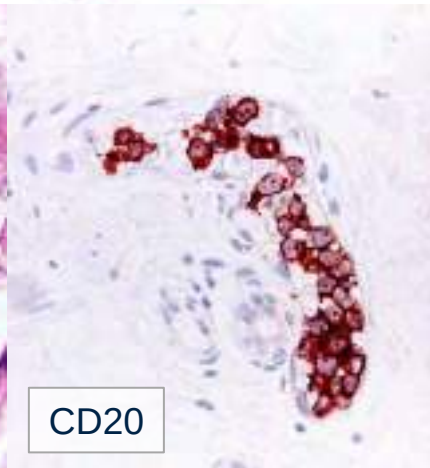


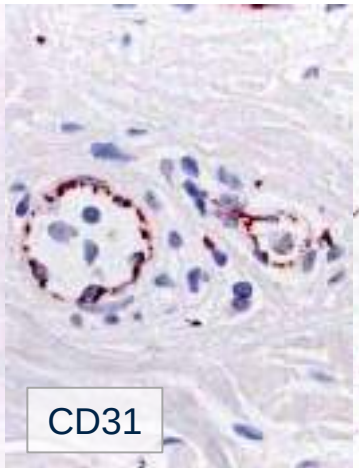
Intravascular diffuse large B-cell lymphoma

Rare variant of large B-cell lymphoma confined to the lumina of small blood vessels. Common involvement of skin and CNS ("Western variant "); multiorgan failure, haemophagocytic syndrome ("Asian variant"); a purely cutaneous variant, observed only in Western women, has a better prognosis. Sometimes diagnosed by "random" skin biopsy; located within haemangiomas in more cases than mere chance would explain. *MYD88 and CD79B* hot spot mutations are reported in 50% and almost 70% of cases, respectively. Morphologically indistinguishable from IV-NK/TCL.






CD20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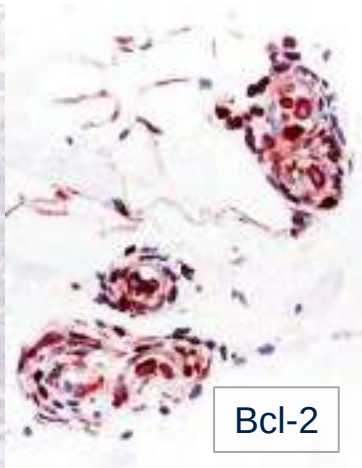
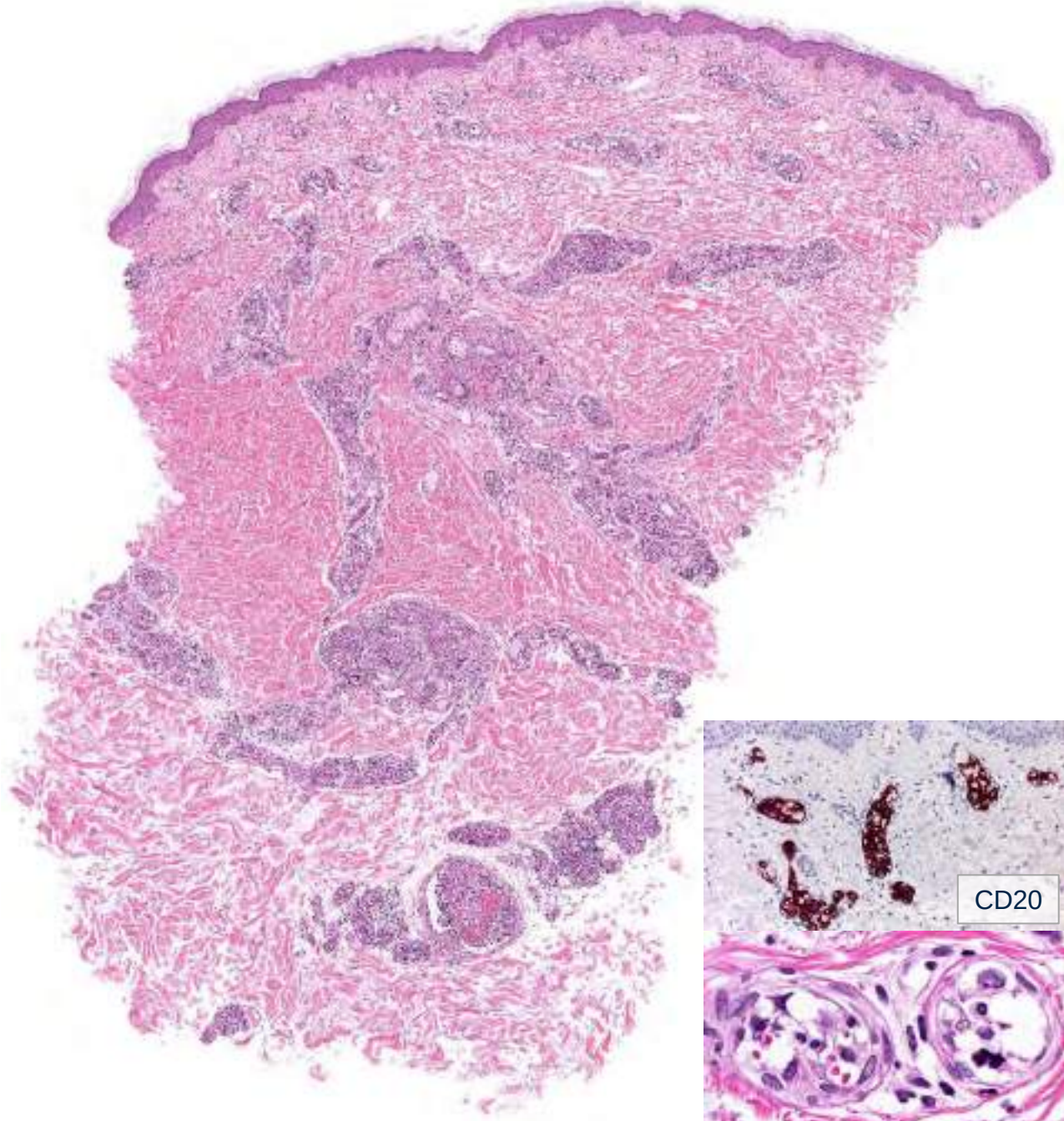

Bcl-2

F, 56

(Consultation Dr. Müller, Homburg/Saar)



Editorial

Dermatology

Dermatology 2004;209:79–80
DOI: 10.1159/000079687

Hemangiomas with a (Bad) Surprise

Lorenzo Cerroni

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Few lesions are less eye-catching for dermatologists and dermatopathologists than senile (cherry) hemangiomas. For one, they are among the most common benign neoplasms in the adult and elderly population, and two, they are devoid of any particular clinicopathologic or therapeutic problem: they are straightforward clinically, a glance diagnosis histopathologically, and treatment, if desired, is easy as well. In short, they are hardly the source of particular interest. And yet, in this issue of *Dermatology* 2 cases of cherry hemangioma or hemangioma-like skin changes draw the attention to these unremarkable neoplasms, showing that behind their innocent appearance sometimes the devil can hide. Our case [1] and that reported by Motegi et al. [2] show two different faces of the 'hemangiomas with a surprise': one characterized by colonization of preexisting cherry hemangiomas by neoplastic cells of an intravascular large B-cell lymphoma and the second showing an eruption of hemangioma-like skin lesions representing in truth skin involvement of angiotropic lymphoma. In both cases, the diagnosis was completely unexpected and represented a surprise, unfortunately a bad one, for the clinicians, the dermatopathologists and the patients.

Intravascular large B-cell lymphoma (also termed angiotropic lymphoma) is a malignant proliferation of large B lymphocytes within blood vessels. It was first described by Pfleger and Tappeiner in 1959 [3] and was formerly classified as a vascular neoplasm (malignant angioendotheliomatosis) [4]. It is considered as a subtype of extranodal diffuse large B-cell lymphoma [5]. This peculiar disease may arise de novo or in patients with preexisting cutaneous or, more often, nodal large B-cell lymphoma, in the latter instance probably representing a recurrence of the original malignancy rather than a second lymphoma [6, 7]. Neoplastic cells are positive for B-cell-associated markers, but a very rare T-cell variant of the disease has been reported [8]. Prognosis is usually very poor, with a median survival of about 12 months. The prognosis of cases limited to the skin may be better than that of the generalized (multisystem) disease, but only a very limited number of patients has been followed up to date.

The most common clinical presentation of intravascular large B-cell lymphoma is characterized by indurated, erythematous or violaceous patches and plaques, preferentially located on the trunk and thighs. The clinical appearance is not typical of lymphoma and may suggest a diagnosis of panniculitis or of purpura [9–13]. In rare cases, the skin may be the only affected site (primary cutaneous intravascular large B-cell lymphoma), though more often the lymphoma is disseminated, and neurologic symptoms as a sign of involvement of the central nervous system are commonly present [14]. Other organs that are frequently involved are the liver, lungs and kidneys. Systemic symptoms due to specific manifestations at extracutaneous sites are more likely to be caused by clots within the blood vessels and subsequent infarction of tissue than by destructive neoplastic growth.

Colonization of preexistent cutaneous hemangiomas, similar to that observed in our patient, has been described in 2 other cases [15–17]. Although this is an exceptional

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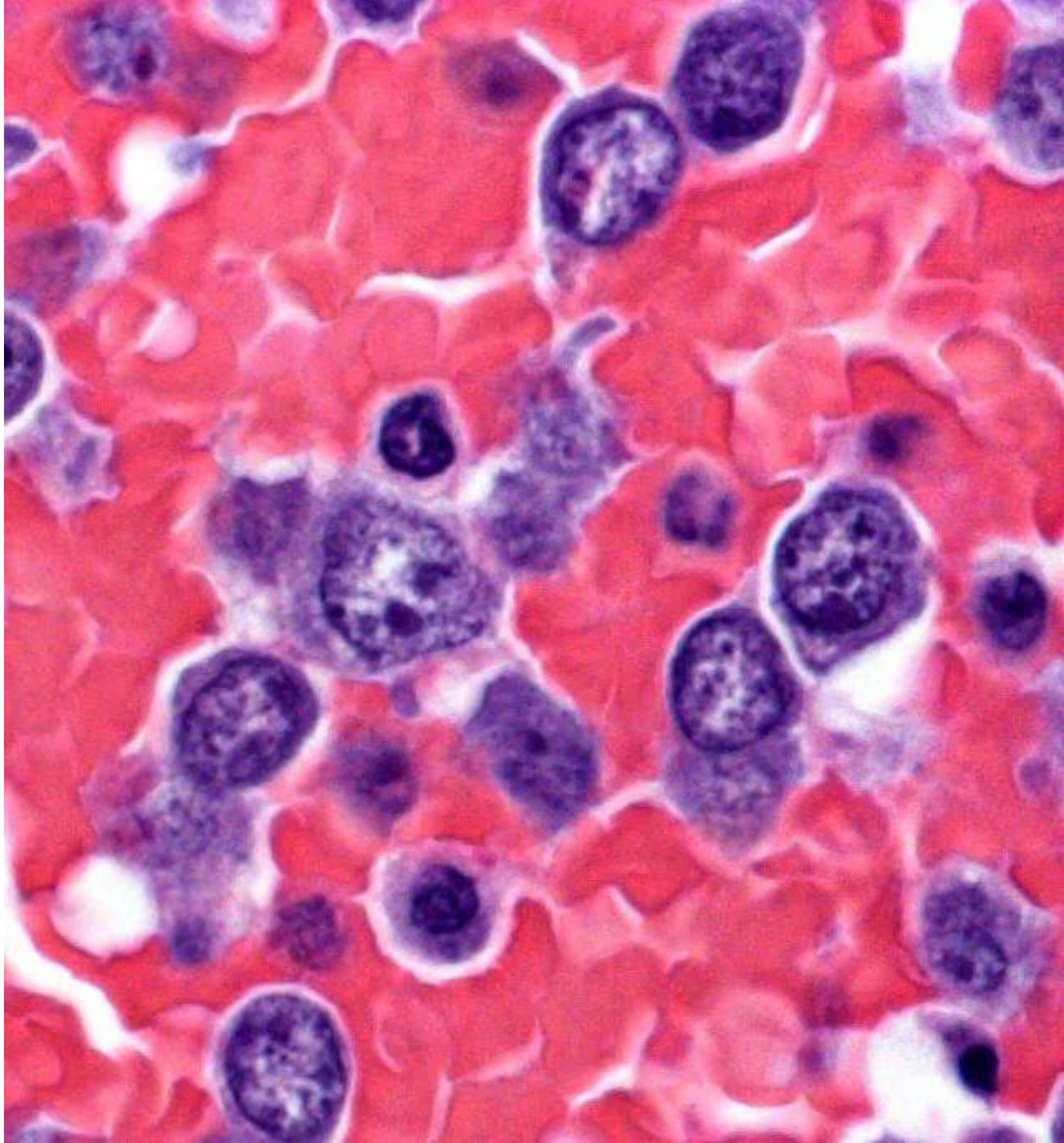

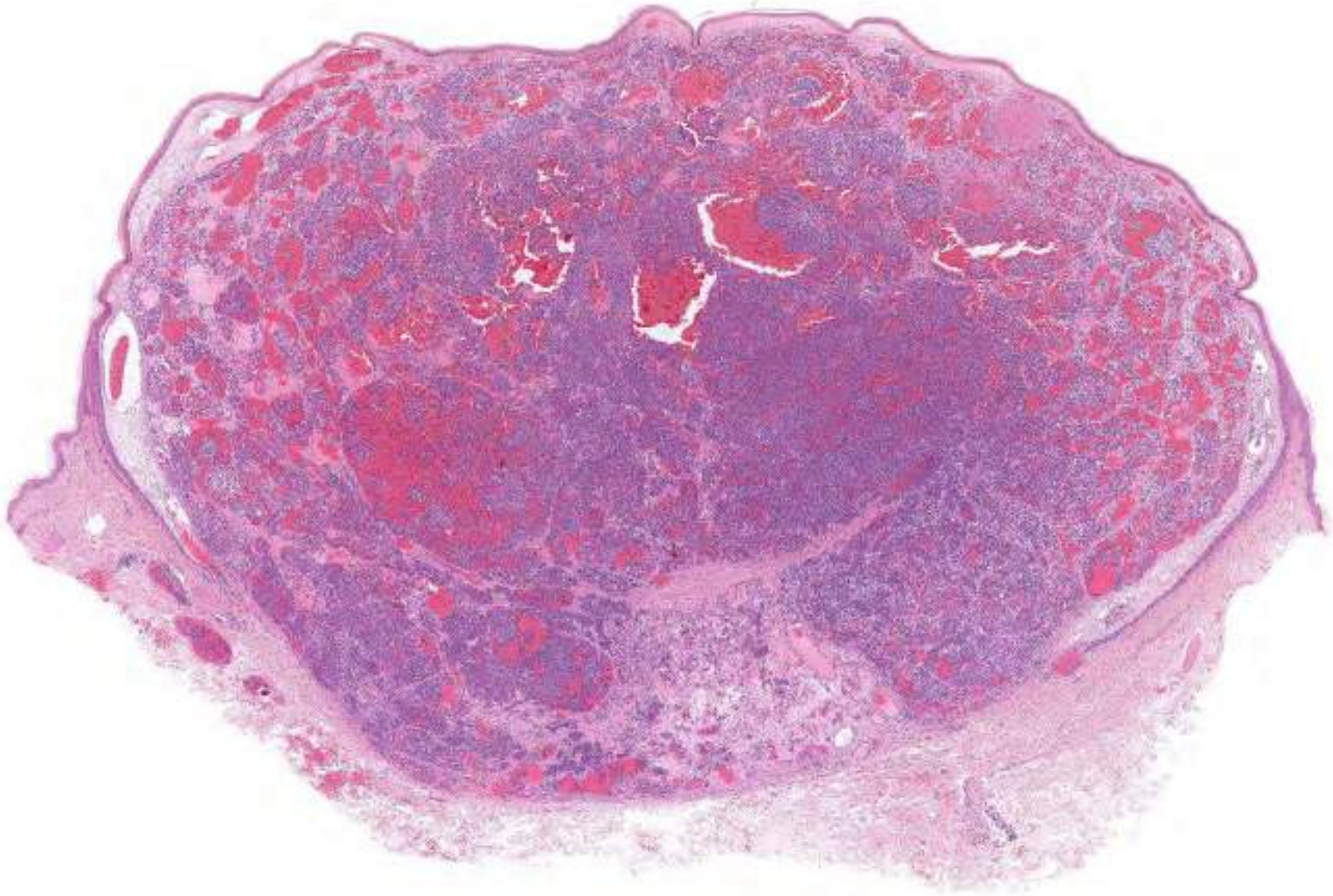

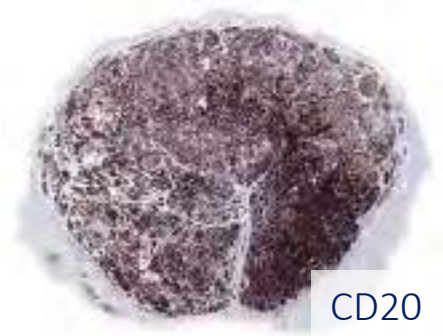
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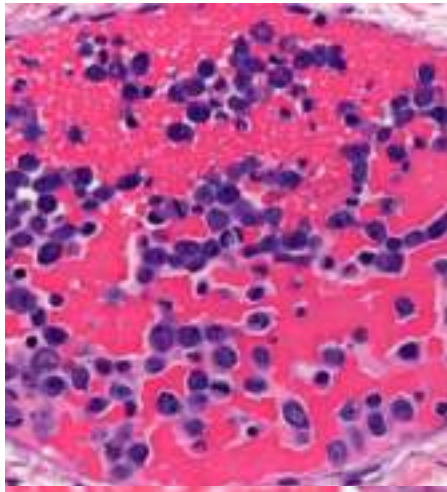

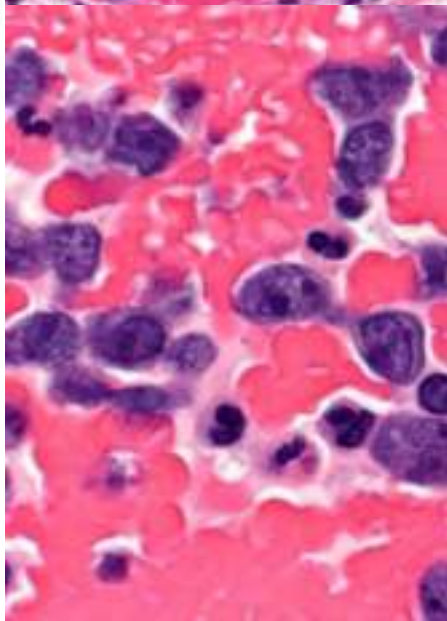

Dermatology

Case Report

Dermatology 2004;209:122–124
DOI: 10.1159/000078587

Intravascular Large B-Cell Lymphoma Colonizing Cutaneous Hemangiomas

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Key Words
Intravascular large B-cell lymphoma · Cherry hemangioma

Abstract
Intravascular large B-cell lymphoma is a malignant neoplasm characterized by the proliferation of large B cells (rarely of T lymphocytes) confined within the blood vessels. Although the disease can be limited to the skin, involvement of other organs is common. We report a case of intravascular large B-cell lymphoma colonizing the vessels of preexisting cutaneous cherry hemangiomas.

Intravascular large B-cell lymphoma (formerly malignant angioendotheliomatosis, angiotropic lymphoma) is a malignant neoplasm characterized by the proliferation of large B cells (rarely of T lymphocytes) confined within the blood vessels. Although the disease can be limited to the skin, involvement of other organs, especially the central nervous system, is common. We report a case of intravascular large B-cell lymphoma colonizing the vessels of preexisting cutaneous cherry hemangiomas.

Report of a Case

An 81-year-old woman with a history of malignant melanoma in 1999 (tumor thickness 4 mm; no extracutaneous involvement) presented to our department in April 2002 for a routine follow-up examination. Physical examination did not show any sign of recurrence of melanoma. She had several small senile (cherry) hemangiomas which had been present for many years. However, she had noticed that one of them located on the left upper arm had been slightly enlarging in the last few months and asked to have it removed for cosmetic reasons (fig. 1). The hemangioma was surgically removed, fixed in formalin and embedded in paraffin for routine histopathologic examination. Histology revealed the overall architecture of a capillary hemangioma. However, the vessels were filled with large atypical cells with cytomorphologic features of centroblasts and immunoblasts (fig. 2). Immunohistology showed that these cells were positive for CD45, CD20 and CD79a, and negative for CD3, CD5 and CD30. They were also negative for melanocytic markers (S-100, HMB-45, Melan-A) and for cytokeratin. Based on clinicopathologic features, a diagnosis of intravascular large B-cell lymphoma colonizing a preexistent hemangioma was made.

The patient was submitted to staging investigations that failed to reveal any extracutaneous involvement. Five more cutaneous hemangiomas were surgically removed (all of them located on the trunk). Histopathologic evidence of intravascular large B-cell lymphoma could be found in 2 of them (fig. 3). In contrast to the first lesion, colonization of the blood vessels in these 2 was only partial and limited to a part of the hemangioma. Surgical excision of 3 lesions clinically diagnosed as lipoma revealed the histopathologic features of angiolipoma, without any malignant lymphoid cells within or outside the vessels.

The patient declined any treatment, but was attending regular follow-up controls. At the last follow-up examination 9 months after the first diagnosis she complained of increasing fatigue, but did not show any central nervous system or systemic symptoms. She died at home 12 months after presentation, and the relatives denied authorization for autopsy.

Discussion

Intravascular large B-cell lymphoma is a very rare variant of large B-cell lymphoma frequently involving the skin, first described by Pfleger and Tappeiner in 1959 [1]. Clinically, lesions are often inconspicuous purpuric macules and plaques, and may be misdiagnosed as 'purpura' or 'panniculitis'. Colonization of preexistent hemangiomas has been described rarely in these patients and seems to be a peculiar clinicopathologic manifestation of this unusual lymphoma [2, 3].

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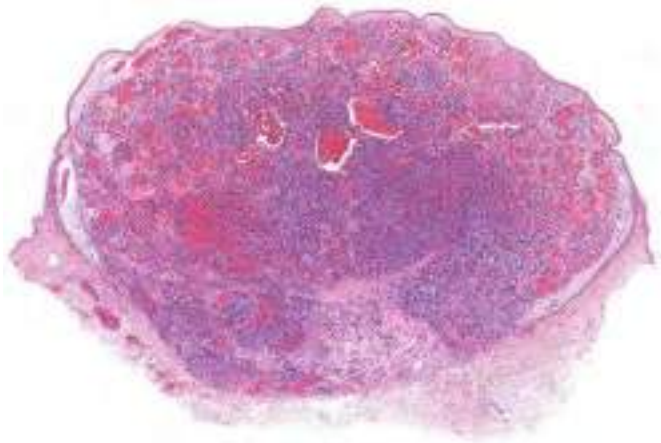
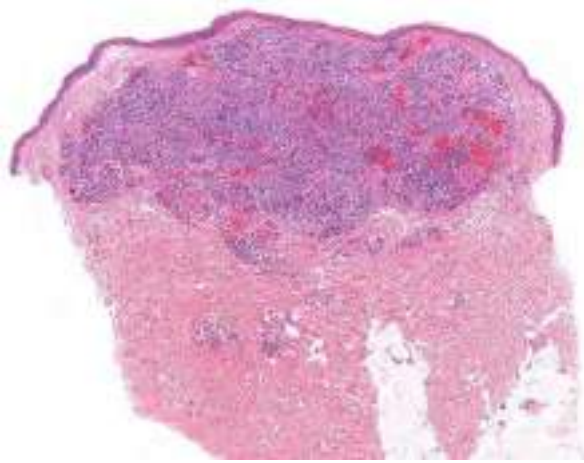
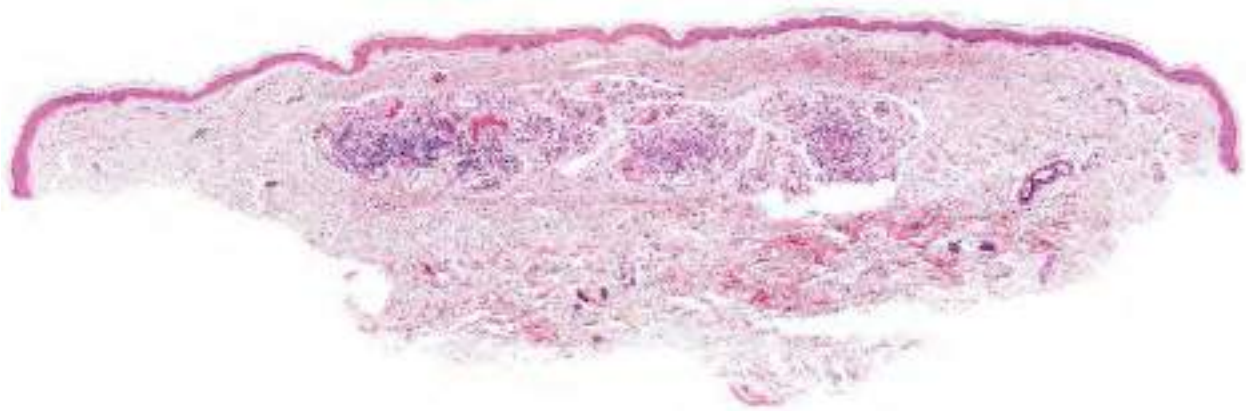
IVLBCL in 3/6 angiomas.
5/5 angiolipomas negative.
Normal skin at the side of involved angiomas did not show histopathological signs of intravascular lymphoma.







Main "intravascular" proliferation of cells

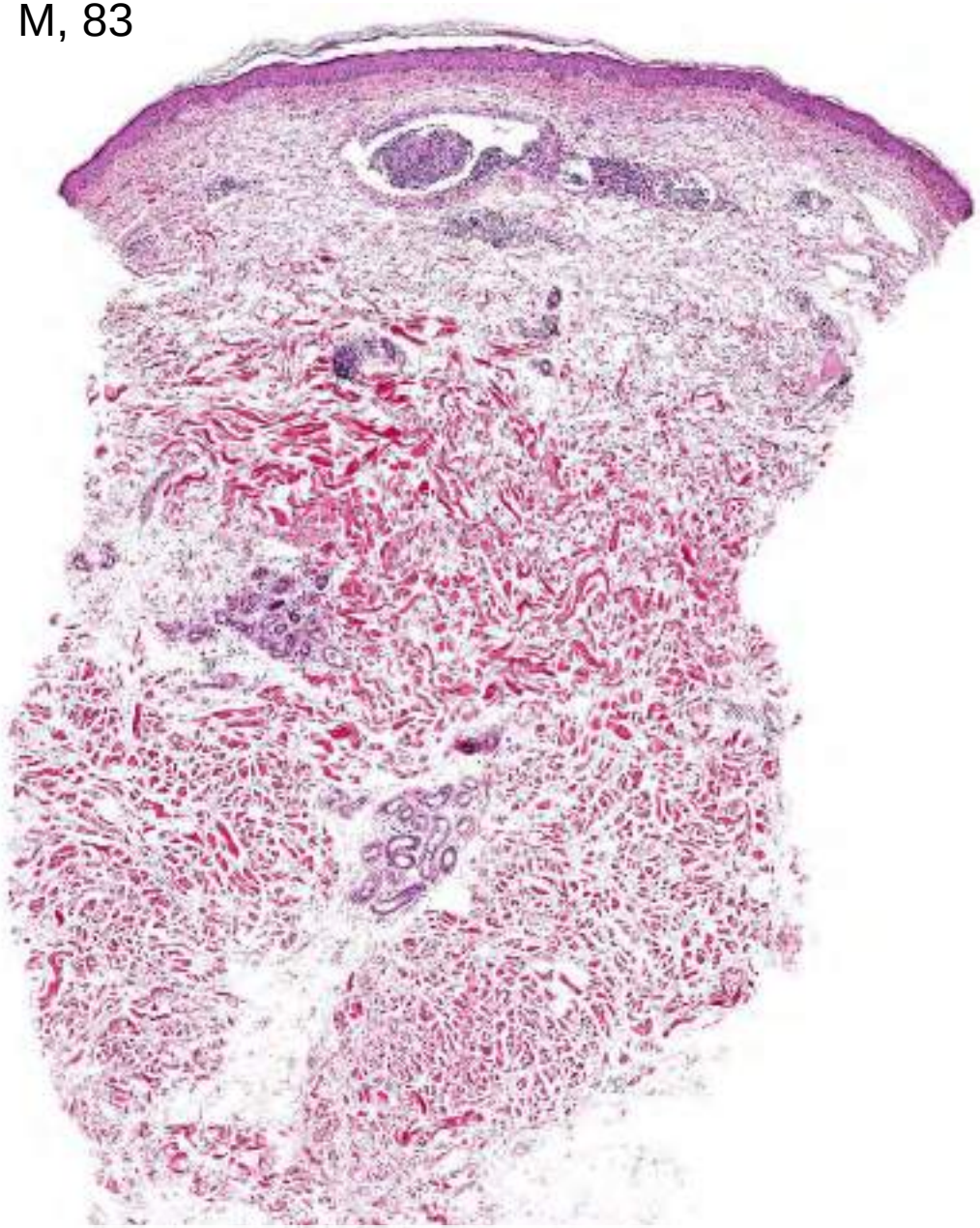
Within blood vessels

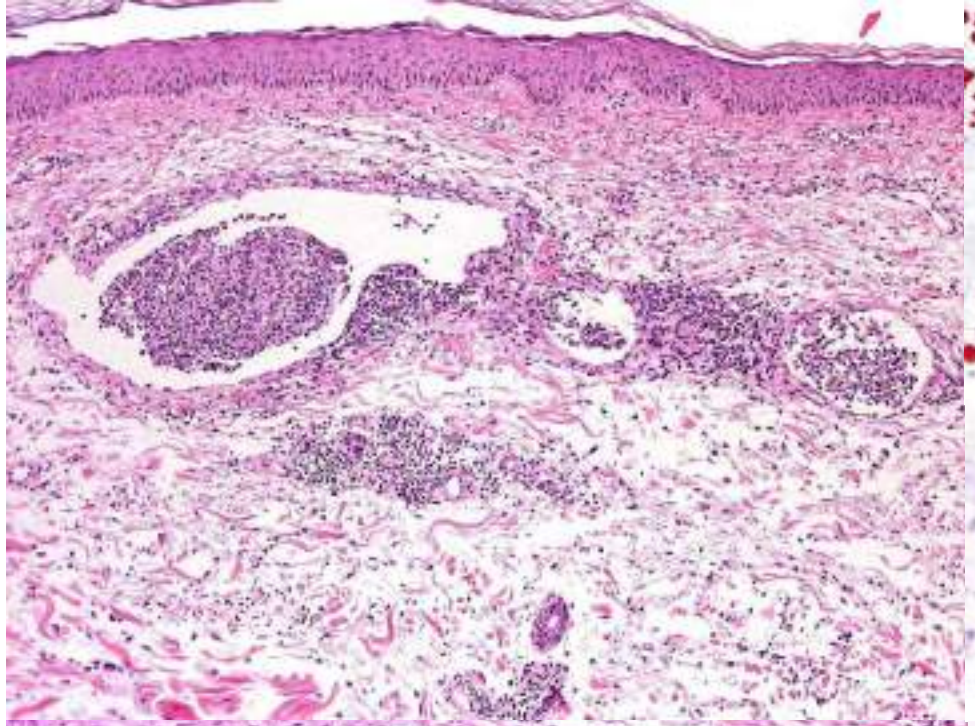
- B- and NK/T-cell intravascular diffuse large cell lymphoma
- Diffuse large B-cell lymphoma with intravascular component
- Intravascular angiosarcoma
- Reactive angioendotheliomatosis
- Rare cases of intravascular histiocytosis
- Merkel cell carcinoma (rare)

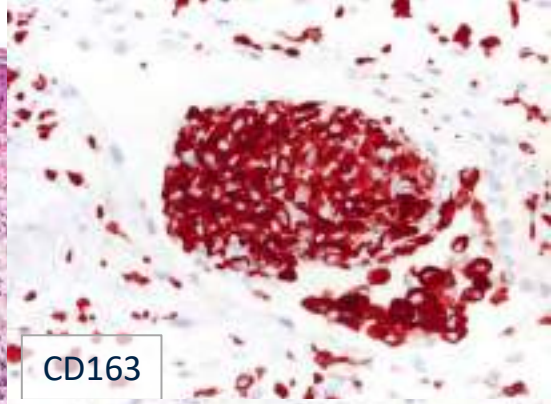
Within lymphatic vessels

- Intralymphatic cut. anaplastic large cell lymphoma / lymphomatoid papulosis
- Benign intralymphatic proliferation of large T-cell lymphoid blasts
- Intralymphatic histiocytosis
- Merkel cell carcinoma (common)
- Metastases of different types of carcinoma and of other malignant neoplasms

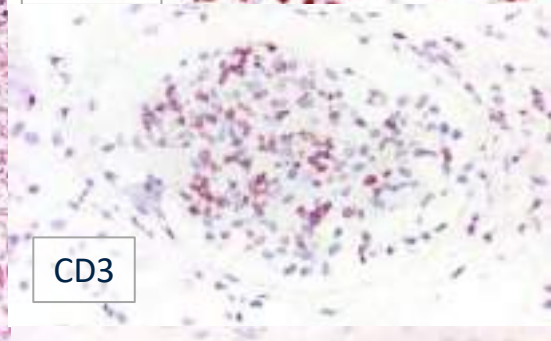
M, 83







CD163



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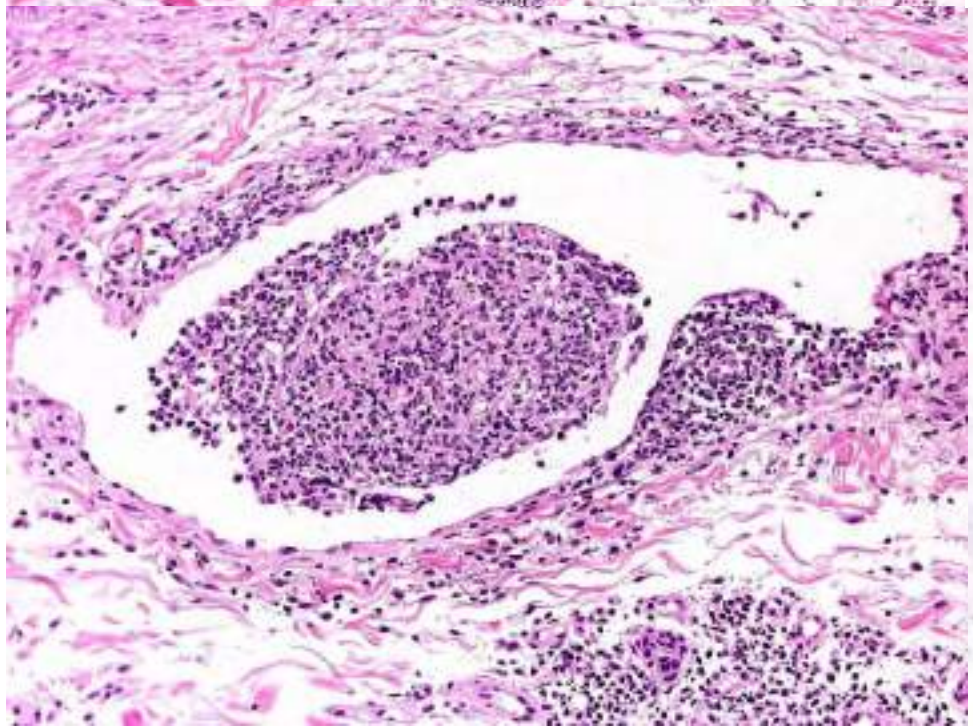
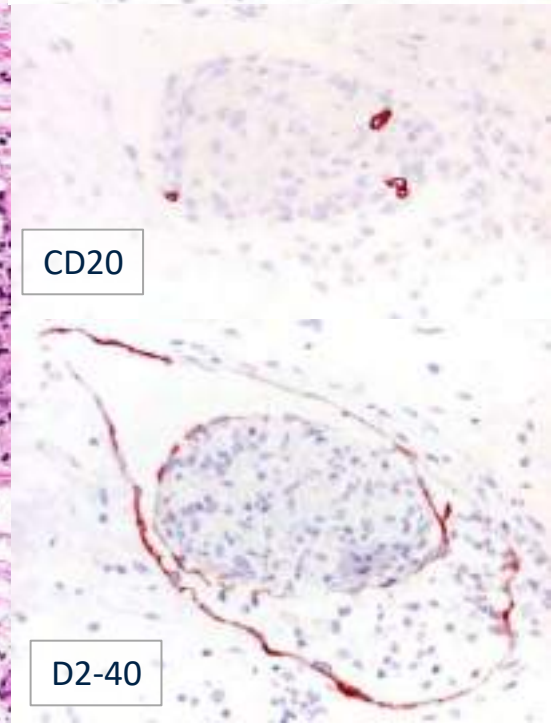


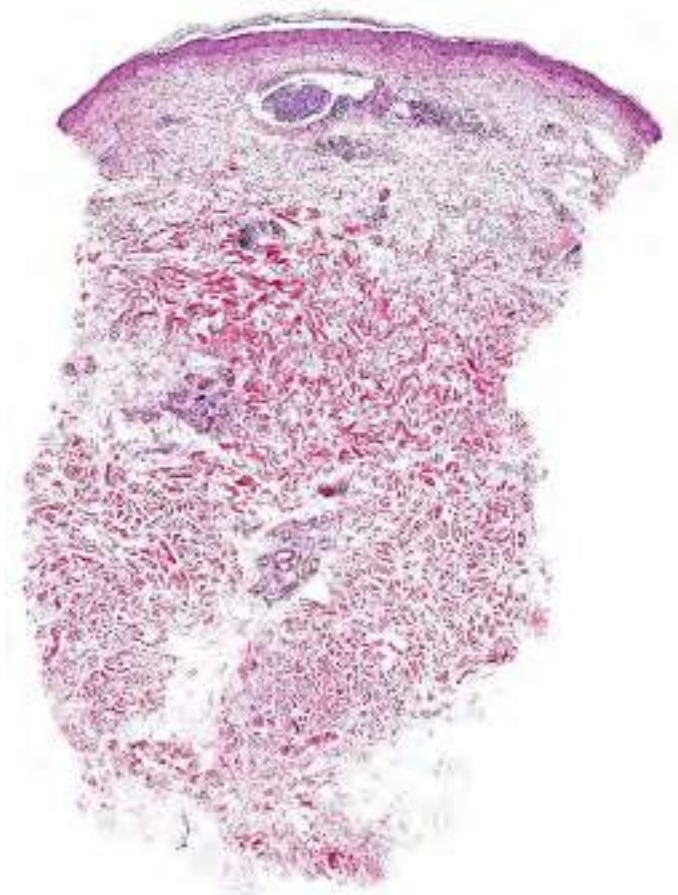


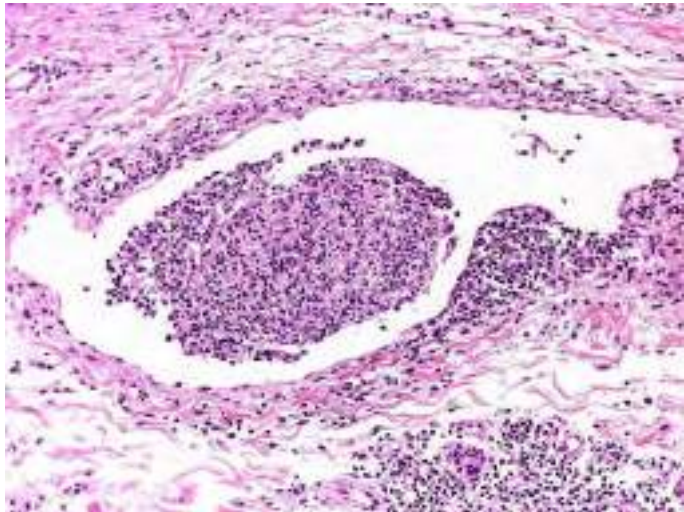
CD20

D2-40

Intralymphatic histiocytosis

- Known seronegative chronic polyarthritis
- Elevated CRP (111,1 mg/L)
- Duration of the skin lesions unknown





Intralymphatic histiocytosis

- Clusters of histiocytes within lymphatic vessels; may mimic intravascular large cell lymphoma (but it is intralymphatic)
- Cells CD68+, CD163+ and negative for lymphoid markers; vessels positive for podoplanin
- Association with rheumatoid arthritis more common than mere chance would explain (part of a macrophage activation syndrome?)
- "Localized" cases observed in different settings (particularly in chronic recurrent infections / inflammation, e.g. recurrent erysipelas)

Intralymphatic Histiocytosis. A Clinicopathologic Study of 16 Cases

Luis Requena, MD, Laila El-Shabrawi-Caelen, MD,† Sarah N. Walsh, MD,‡§¶ Sonia Segura, MD,‖ Mirjana Ziemer, MD,** Mark A. Hurt, MD,¶ Omar P. Sangüeza, MD,‡§ and Heinz Kutzner, MD††*

Abstract: Intralymphatic histiocytosis is a rare condition characterized by the presence of dilated lymphatic vessels containing aggregates of mononuclear histiocytes (macrophages) within their lumina. The phenomenon seems to occur almost exclusively within the reticular dermis. Although its pathogenesis remains uncertain, findings expand on the previously described morphologic and immunohistochemical features of intravascular histiocytosis. We also discuss the possible relationship between intralymphatic histiocytosis and the so-called reactive intravascular angioendotheliomatosis.

Key Words: intralymphatic histiocytosis, intralymphatic mucin-

TABLE 1. Clinical Data of 16 Patients With Intralymphatic Histiocytosis

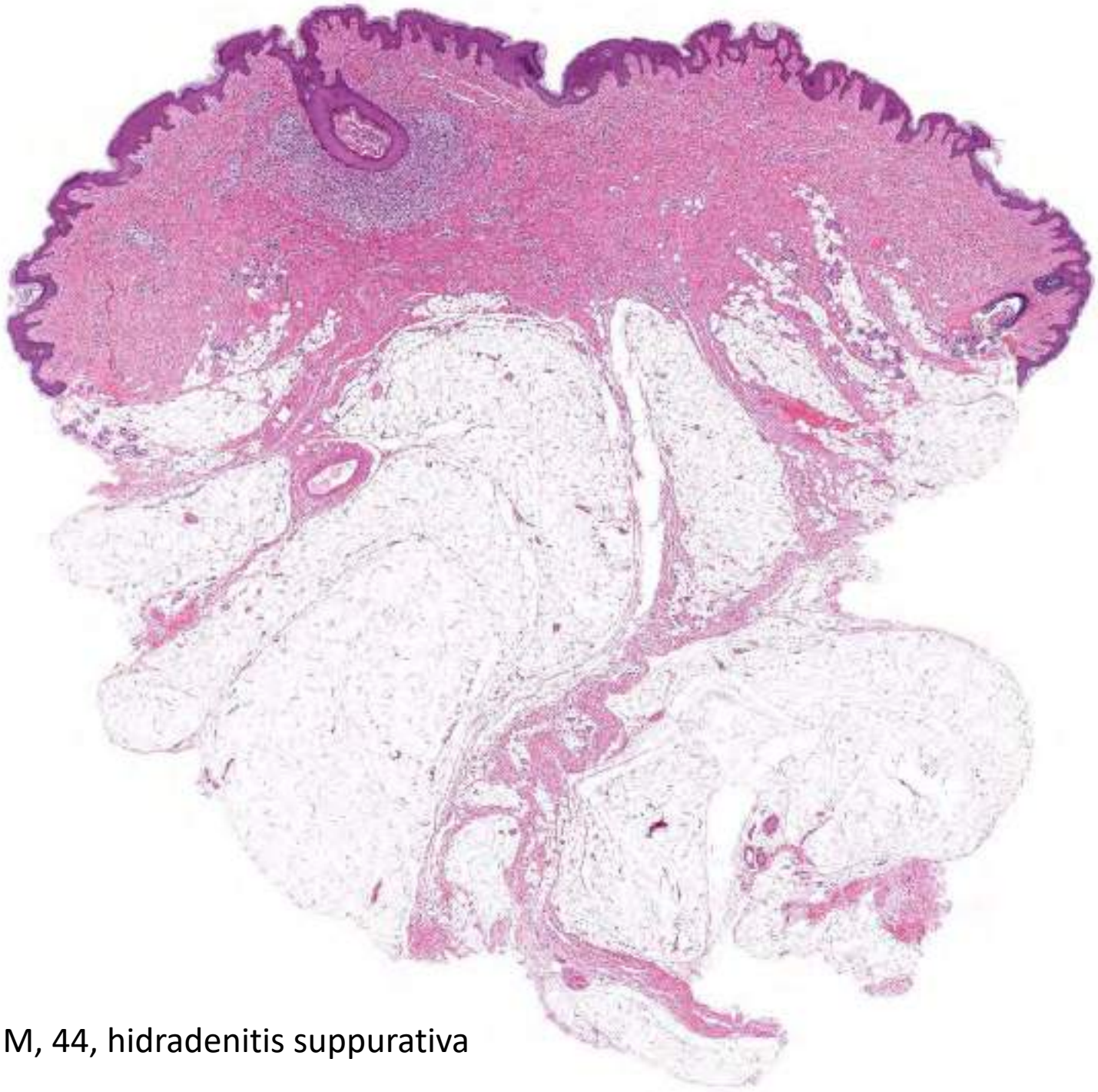
Case	Sex	Age (yrs)	Lesion Location	Clinical Features	Associated Diseases or Findings	Follow-up
1	F	79	Thighs, knees	Erythematous violaceous confluent patches	Rheumatoid arthritis	Lesions disappeared after knee joint replacement
2	F	46	Left lower leg	Poorly demarcated erythema	Rheumatoid arthritis Klippel–Trenaunay syndrome	N/a
3	M	48	Left chest, left thigh	N/a	N/a	N/a
4	F	84	Right arm	Indurated plaque: intravascular lymphoma?	None	Lesions have persisted
5	F	57	Left thigh	Erythema and induration	Merkel cell carcinoma at the same site of the original biopsy, rheumatoid arthritis, PCR negative for EBV, *Borrelia*, and *Treponema pallidum*	N/a
6	M	79	Abdominal skin	Multiple excoriated papules: scabies?	None	N/a
7	F	69	Right breast	Erythema on the surgical scar: carcinoma erysipeloides?	Previous right breast carcinoma	N/a
8	F	85	Left upper arm	Livid erythema: dermatomyositis?	PCR negative for *Borrelia*, *Streptococcus*, *Staphylococcus*, and *Bartonella*	N/a
9	F	66	Left breast	Livid erythematous patch	Excision of left breast carcinoma 9 yrs ago	N/a
10	F	78	Right elbow	Scaly induration: granuloma annulare, allergic eczema, herpes simplex?	None	N/a
11	M	63	Right hip	Indurated erythema of the surgical scar	The lesions developed on the scar after hip joint replacement with a metal prosthesis	N/a
12	F	75	Right upper arm	Livid erythema after insect bite: mycosis fungoides?	PCR negative for *Borrelia*and HHV-8, polyclonality of light chain expression (kappa and lambda light chains)	N/a
13	M	65	Right thigh	Erythema on the surgical scar	The lesions developed on the surgical scar after hip joint replacement with a metal prosthesis	N/a
14	F	84	Right upper arm	Persistent reticulate erythema	Rheumatoid arthritis, PCR negative for *Borrelia*, IgH and TCR clonality	N/a
15	M	68	Upper eyelid	Melkersson–Rosenthal syndrome?	Melanoma in situ in the overlying epidermis Unilateral eyelid swelling: histopathologically showing suppurative granuloma	N/a
16	M	73	Left upper arm	Large vascular radiating patch present for 2 months: angiosarcoma, inflammatory carcinoma, Kaposi's sarcoma?	Rheumatoid arthritis, malignant melanoma S/P lymphadenectomy	N/a

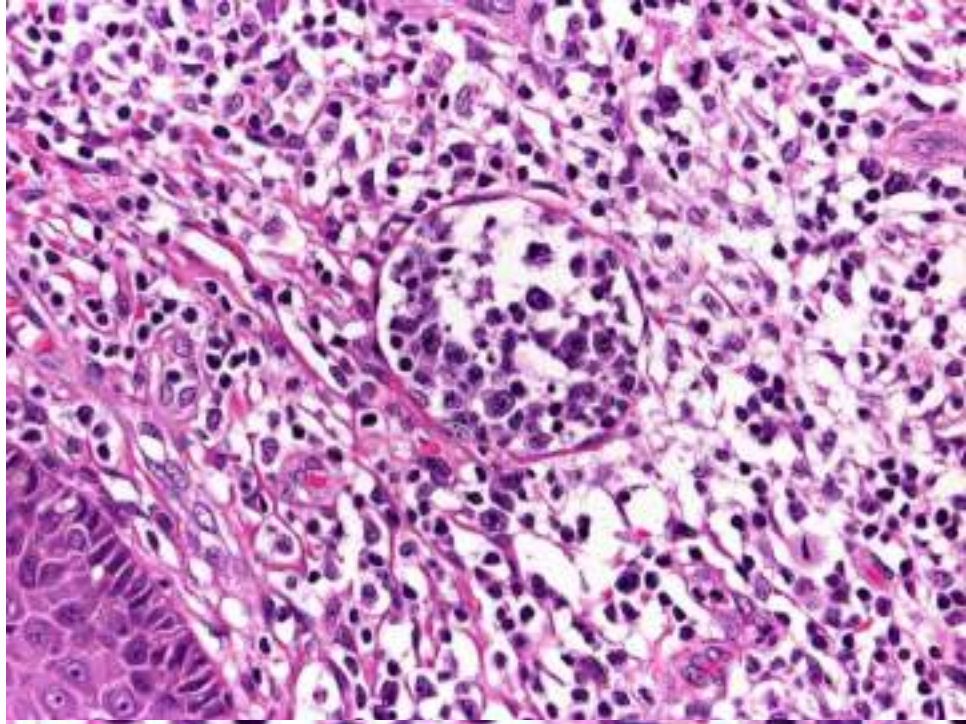
HHV-8, human herpesvirus 8; N/a: Not available; PCR, polymerase chain reaction; TCR, T-cell receptor; EBV, epstein-barr virus.

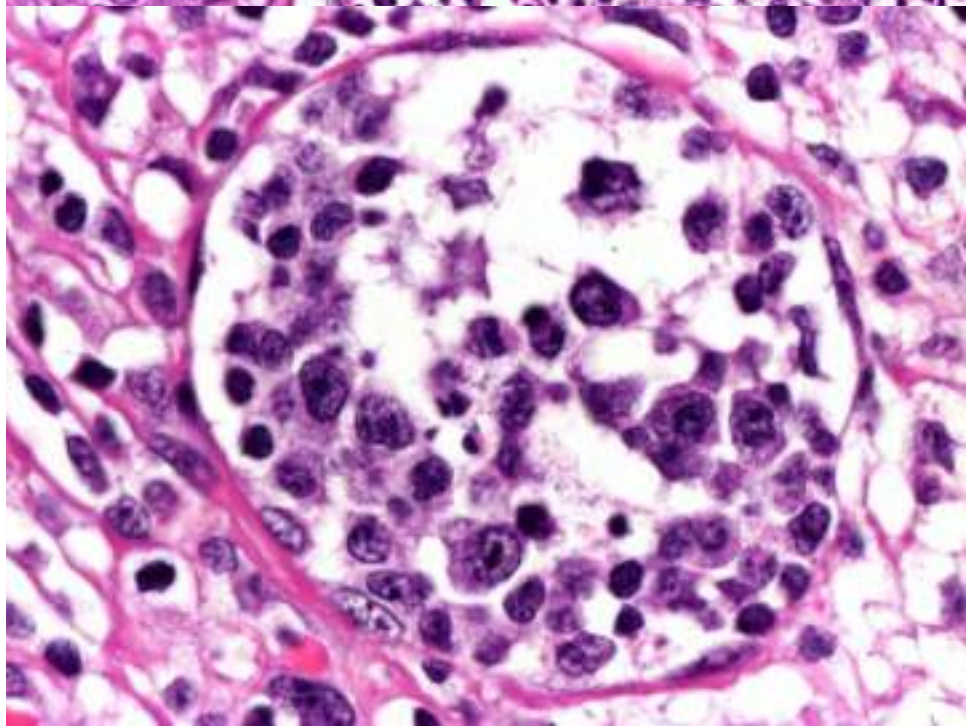
TABLE 2. Summary of the Cases of Intralymphatic Histiocytosis Previously Described in Literature

Case, Reference	Age (yrs)/Sex	Clinical Diagnosis	Histopathology/Immunohistochemistry	Associated Diseases
1, O'Grady et al[1]	70/F	Erythematous rash below the left knee	Intravascular collections of histiocytes (Mac 387 and Kp1 + histiocytes and F-VIII + endothelial cells)	ND
2, Rieger et al[2]	80/F	Red macules and plaques on face and arms	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *Ulex europaeus* + endothelial cells	Cardiac insufficiency osteoporosis, positive rheumatoid factor
3, Rieger et al[2]	77/F	Violaceous patches with livedo-like erythema on both elbows	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *U. europaeus* + endothelial cells)	Rheumatoid arthritis, bilateral breast cancer
4, Pruim et al[3]	63/M	Violaceous lesions with livedo-like erythema on the left elbow	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
5, Pruim et al[3]	59/F	Erythematous rash on the left wrist	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
6, Magro and Crowson[4]	82/M	Contact dermatitis on shoulder	Intravascular collections of histiocytes	Rheumatoid arthritis
7, Magro and Crowson[4]	46/M	Urticaria on buttocks, thighs, and lower back	Intravascular collections of histiocytes	Rheumatoid arthritis
8, Magro and Crowson[4]	41/F	Lymphoma on forearm	Intravascular collections of histiocytes	Rheumatoid arthritis
9, Takiwaki et al[5]	69/F	Indurated erythema and papules on the elbow	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
10, Takiwaki et al[5]	74/M	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
11, Takiwaki et al[5]	66/F	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
12, Takiwaki et al[5]	62/F	Erythema and confluent papules on forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
13, Okazaki et al[6]	52/M	Livedo-like erythema with vesicles on lower leg	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis
14, Asagoe et al[7]	17/M	Painful induration of the scrotum	Intravascular collections of histiocytes (CD68 + histiocytes and CD31 + D2-40 endothelial cells)	Tonsillitis
15, Catalina-Fernández et al[8]	50/F	Erythematous plaques with livedo-like pattern on shins	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, fibromyalgia
16, Okamoto et al[9]	75/F	Violaceous, infiltrated erythema on left forearm	Intralymphatic collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, lymphedema
17, Mensing et al[10]	68/F	Reticular, bizarre-shaped livid macules on the face, livid macules on the face, back, and thighs	Intravascular collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells	Heart attack, diabetes
18, Waranabe et al[11]	75/M	Erythematous nodules on the left knee	Intravascular collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Orthopedic metal implants

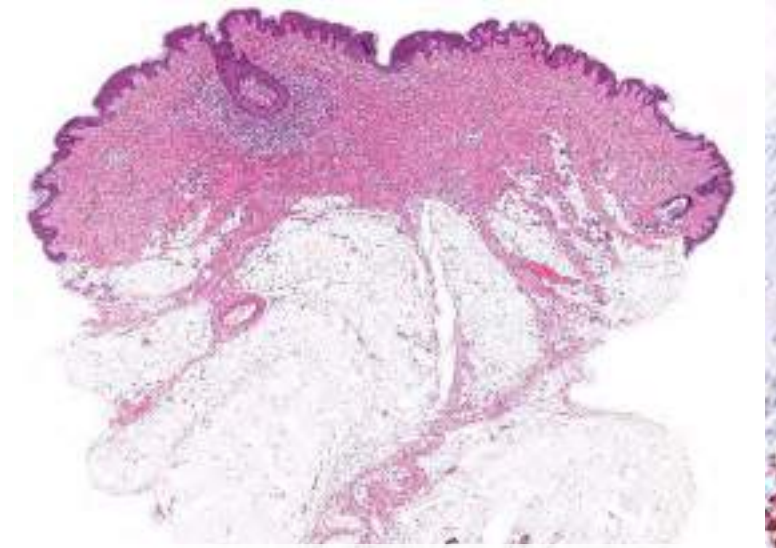
F-VIII, factor-VIII–related antigen; F, female; M, male; ND, not described.



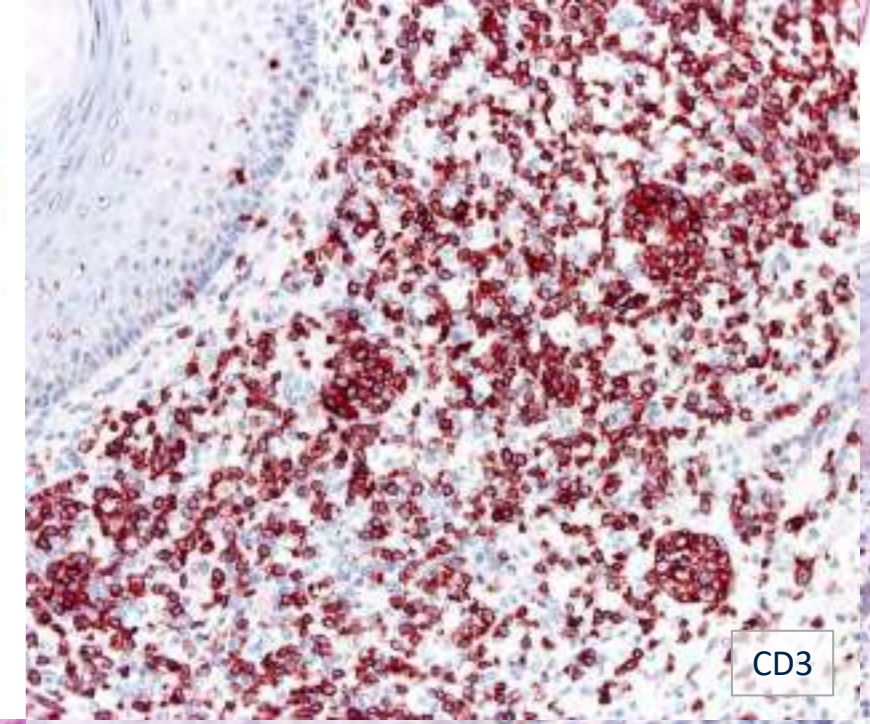


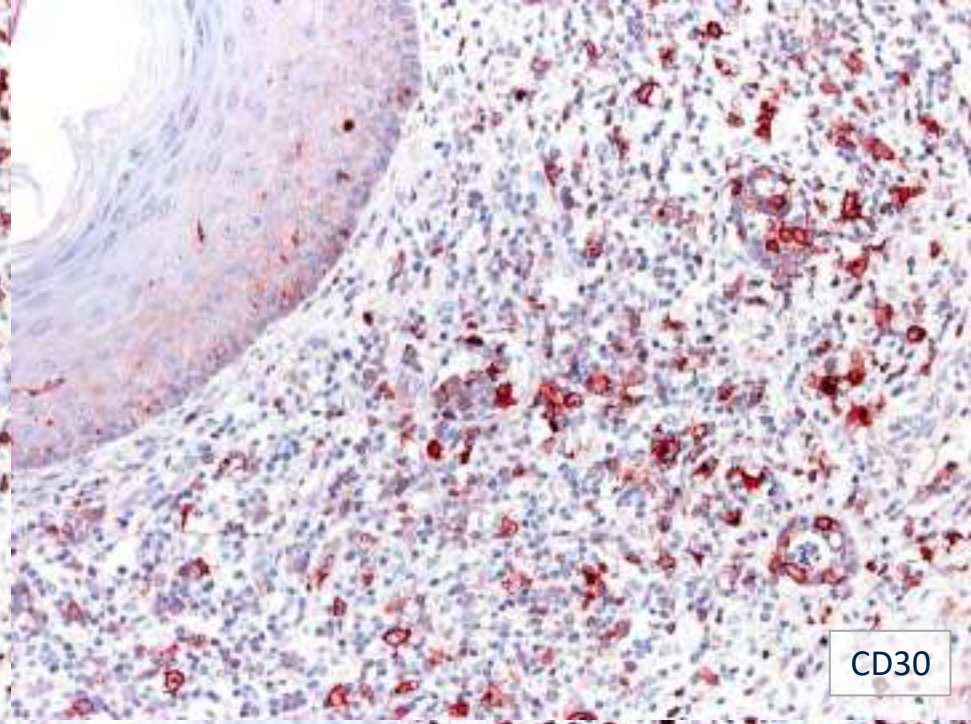


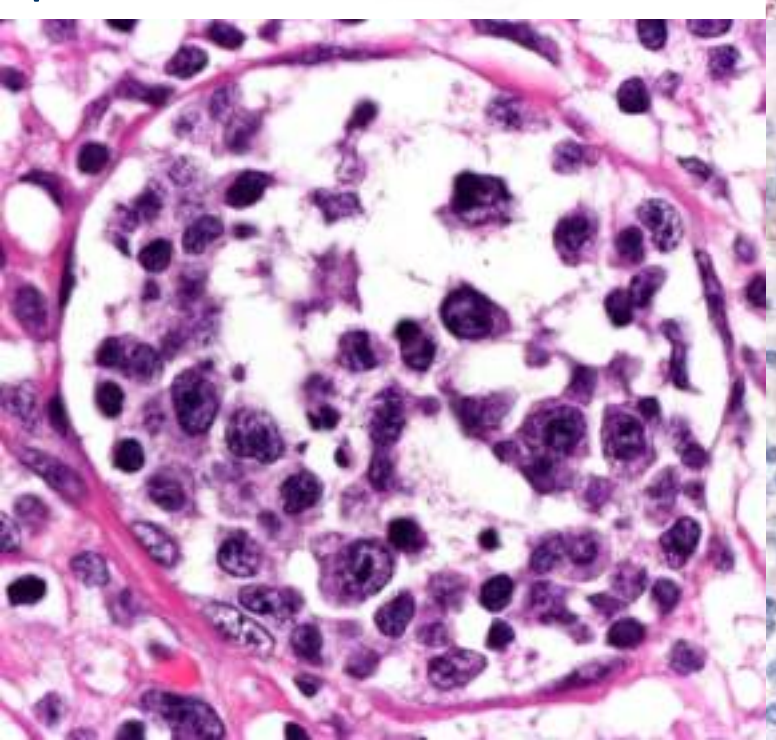
M, 44, hidradenitis suppurativa

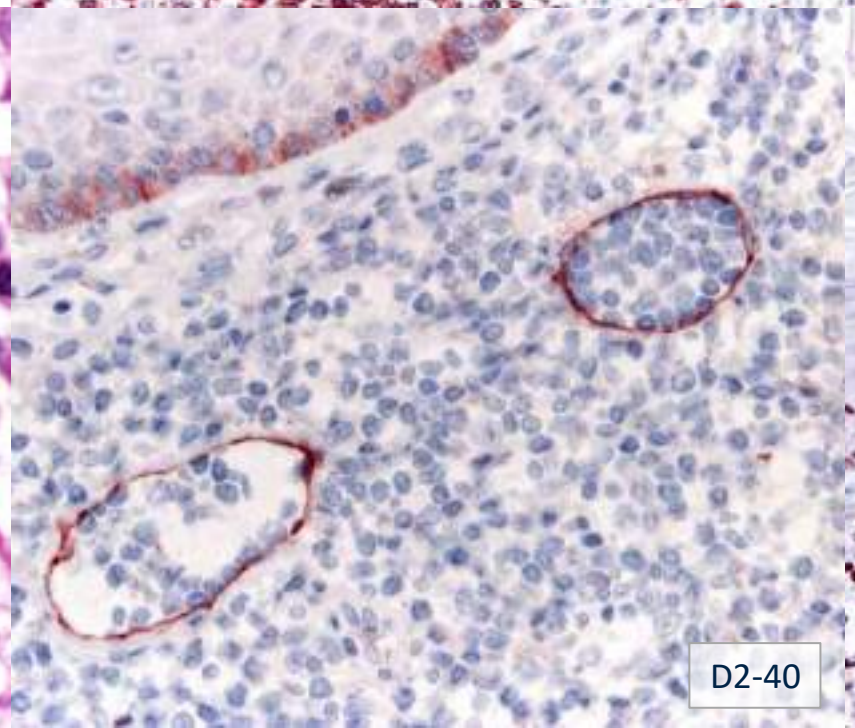


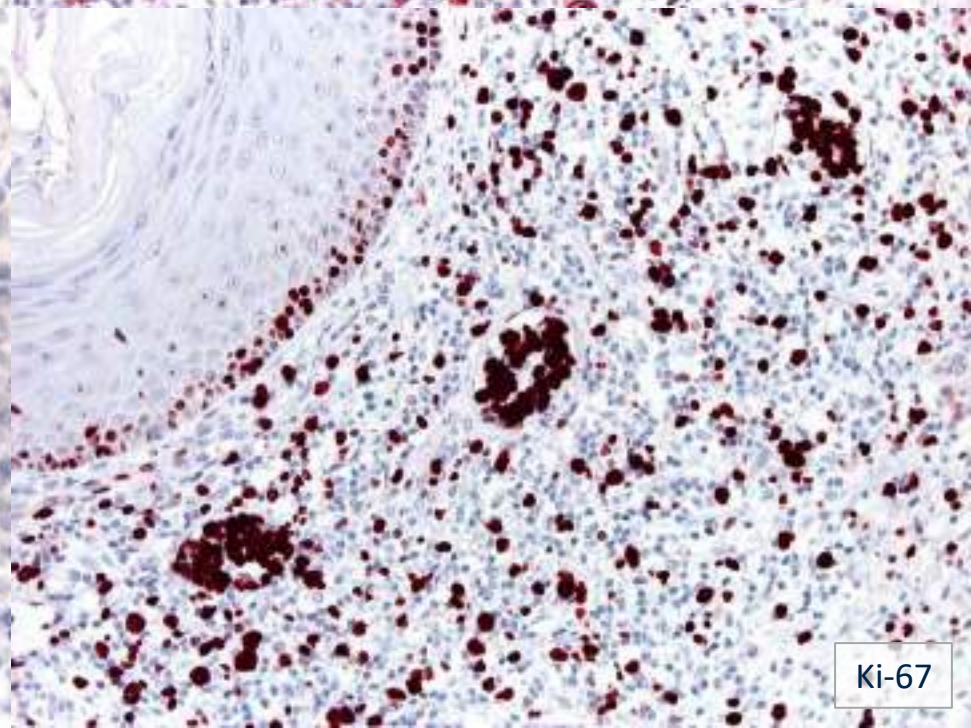
Benign intralymphatic proliferation of T-cell blasts











Intralymphatic Proliferation of T-cell Lymphoid Blasts in the Setting of Hidradenitis Suppurativa

Paola Calamaro, MD†‡ and Lorenzo Cerroni, MD**

Abstract: Intralymphatic proliferation of T-cell lymphoid blasts (IPTCLBs) is a rare, recently described entity, associated with cutaneous inflammatory conditions and characterized by intralymphatic proliferation of highly proliferating, blastoid T lymphocytes expressing CD30, thus mimicking an intravascular lymphoma. In all reported cases, the intralymphatic proliferation was associated with an underlying inflammatory condition, with no clonal T-cell receptor rearrangement, no signs of systemic or cutaneous lymphoma, and excellent prognosis. The authors present a new case of IPTCLB arising in a patient with hidradenitis suppurativa. Histological examination revealed a dilated follicle embedded within a fibrotic stroma surrounded by a dense lymphoid infiltrate characterized by the presence of dilated small vessels filled with atypical medium-to-large sized blastoid lymphocytes expressing a $CD4^+$ T phenotype. There was also expression of CD30, but negativity for cytotoxic markers and Epstein-Barr virus. The proliferation index was high and the vessels showed expression of D2-40, confirming their lymphatic nature. No signs of systemic lymphoma could be detected after routine investigations, and the patient is alive and in good general health. IPTCLB is a rare benign entity that presents with worrying, potentially misleading histopathological features that mimic those observed in intravascular lymphoma. Careful histological and phenotypic investigations and correlation with the clinical features are necessary for a proper diagnosis.

Key Words: intralymphatic proliferation of T-cell lymphoid blasts, intravascular large cell lymphoma, intralymphatic histiocytosis, T-cell pseudolymphoma

(*Am J Dermatopathol* 2016;38:536–540)

Intralymphatic proliferation of T-cell lymphoid blasts (IPTCLBs) is a recently described entity characterized by the presence of large, blastoid T lymphocytes within lymphatic vessels, often with CD30 expression. Although it mimics histologically an intravascular lymphoma (IVL), it is considered to be a benign condition because of the lack of clinical signs of lymphoma, the lack of clonal rearrangement of the TCR genes, and the favorable follow-up.[1]

To date, only few cases of IPTCLB have been reported in the literature, associated with different inflammatory conditions.[2–7] We present a new additional case occurring in a young male patient in the setting of hidradenitis suppurativa.

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The authors declare no conflicts of interest.

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CASE REPORT

A 25-year-old man with long-standing hidradenitis suppurativa of the inguinal region was referred to our department for surgical treatment. Histological examination of the biopsy specimens revealed typical features of hidradenitis suppurativa, characterized by cystic-dilated hair follicles associated with fibrosis and variably dense perifollicular infiltrates composed mainly of lymphocytes and histiocytes.

In one of the specimens, a dilated follicle embedded within a fibrotic stroma was surrounded by a dense lymphoid infiltrate (Figs. 1A, B), characterized by the presence of dilated small vessels filled with atypical medium-to-large sized blastoid lymphocytes (Figs. 1C, D). The atypical cells were positive for CD2, CD3 (Fig. 2A), CD4 (Fig. 2B), CD5, and beta-F1, and negative for CD8, TIA-1, CD56, TCR-gamma, and CD20. Expression of CD30 was observed in many of the atypical lymphocytes (Fig. 2C). Epstein-Barr virus-encoded small RNA (EBER-1) in situ hybridization was negative. Staining for Ki-67 revealed a high proliferation index (>90%) of the intralymphatic cells (Fig. 2D). The atypical lymphocytes were arranged within D2-40–positive vessels (Fig. 3), thus confirming the intralymphatic distribution of the cells. Besides the intralymphatic blastoid cells, a dense infiltrate of predominantly small lymphocytes admixed with some larger blastoid cells was present around the dilated follicle (Figs. 1A–D). The phenotype of these cells was similar to that of the intralymphatic ones, and some of them were positive for CD30 as well (Figs. 2A–C). The Ki-67 index in this component was lower (approximately 20%) (Fig. 2D).

Routine investigations were negative. The patient is alive in good general health 7 months after presentation.

DISCUSSION

Our patient showed an IPTCLB in the setting of chronic inflammation because of hidradenitis suppurativa. IPTCLB is a benign condition characterized by the proliferation of large, atypical lymphoid cells within lymphatic vessels. Although the histopathologic features may arise the suspicion of intravascular large cell lymphoma, all reported cases occurred in the background of an inflammatory disorder, without clinical signs of lymphoma and with a favorable outcome.[1,7] So far, only 7 cases of IPTCLB have been reported, 6 of them with cutaneous localization, and 1 arising within an endometrial polyp (Table 1).[1–7] Although the first description is considered to be that by Beyaert et al in 2007,[1] Ackerman and Taniuchi[8] described a similar case in 1977 under the term "pseudoleukemia cutis." The pseudolymphomatous inflammatory infiltrate was arising in the background of molluscum contagiosum, and the pictures presented in their report show histopathological features virtually identical to those observed in

TABLE 2. Histopathologic Criteria for the Diagnosis of ILPTCB

Presence of histopathological features of an inflammatory skin disorder (eg, lichen sclerosus, granuloma pyogenicum, etc)
Clusters of large atypical lymphoid cells confined to D2-40 + lymphatic vessels; scattered atypical extravascular cells common
T-cell phenotype without aberrant features (no loss of pan-T-cell markers; no aberrant double positivity/negativity of CD4 and CD8)
Lack of positivity for Epstein-Barr virus (EBER-1 negativity)
Polyclonality of the infiltrate as detected by polymerase chain reaction

Benign intralymphatic proliferation of blasts

- Most reported cases observed in a "microorganism-rich" environment (also at extracutaneous sites!)
- May be related to a local infection triggering the activation and proliferation of a T-cell subclone trafficking to and from the regional lymph nodes
- Usually CD30+ T-cell phenotype with high Ki-67; cytotoxic markers negative; no association with EBV; polyclonal pattern of the TCR genes
- Positive staining for podoplanin in affected vessels rules out intravascular NK/T large cell lymphoma
- Presence of a prominent inflammatory response outside of the affected vessels rules out intralymphatic cALCL (LyP may remain a differential diagnosis, but features of the background condition usually allow a clear-cut distinction)

PSEUDOLEUKEMIA CUTIS

Report of a Case in Association with Molluscum Contagiosum

A. BERNARD ACKERMAN, MD, AND EUGENE V. TANSKI, MD

Histologic sections from a solitary cystic cutaneous lesion that showed atypical mononuclear cells in the dermis and within blood vessels were diagnosed by several general pathologists and dermatopathologists as leukemia cutis. The patient, who had no other cutaneous lesions, was consequently submitted to an extensive investigation for leukemia, which proved negative. Additional and deeper sections from the original block revealed that the cellular infiltrate so suspicious of leukemia cutis was secondary to rupture of a lesion of molluscum contagiosum. The correct histopathologic diagnosis, therefore, was pseudoleukemia cutis. The lessons of the case are that 1) further study of the specimen, solitary as it was and asymptomatic as the patient was, would have obviated worry and the expense and inconvenience of an extensive systemic investigation, and that 2) the diagnosis of leukemia cutis should never be made solely on the basis of histologic sections of skin, but rather after examination of blood and bone marrow.

Cancer **40:813–817, 1977.**

CERTAIN CAVEATS PERTAINING TO THE INTERpretation of histopathology of the skin cannot be emphasized too firmly or too often. One such caution relates to making an unqualified diagnosis of leukemia cutis solely on the basis of histologic findings in a lesion of the skin. The consequences of such premature conclusions are here reported in a case that may be as instructive to others as it was to us.

CASE REPORT

A 37-year-old woman had a "cyst" of 11 months duration on the right lower eyelid. It was removed *in toto* by surgical excision and histologic sections were interpreted by a general pathologist as leukemia cutis. For greater certainty, the slides were sent in consultation to the Armed Forces Institute of Pathology (AFIP Accession No. 1475626) where a diagnosis of "malignant neoplastic infiltrate, probably granulocytic leukemia, eyelid" was also made. A diagnosis (#1122-74) of "metastatic lesion, lymphoma or lymphomatoid papulosis" was rendered by the Department of Eye Pathology of the Northwestern University School of Medicine. The Dermatopathology Section of the Skin and Cancer Unit of New York University School of Medicine also interpreted the changes as those of leukemia cutis. All saw a moderately dense, mixed infiltrate of lymphocytes, histiocytes, plasma cells, eosinophils, and especially atypical mononuclear cells throughout the dermis. In addition to their interstitial distribution, the atypical mononuclear cells were found in large numbers within widely dilated endothelial-lined spaces (Fig. 1a & b)

Despite the fact that the cutaneous lesion was solitary, and solely on the basis of the histologic diagnosis of leukemia cutis, which had been concurred in by most of the pathologists who had examined the tissue, the patient (a doctor's wife) was admitted to the M.D. Anderson Tumor Institute for thorough systemic investigation. Findings of complete routine examination and special studies of the blood and bone marrow were completely normal.

Perplexed by the contradiction between the dire histologic interpretation and the negative clinical and other laboratory findings, we obtained the original block of the cutaneous specimen and cut deeper sections through it. To our amazement, and embarassment, those sections revealed molluscum bodies within the cornified cells of an epithelial, cyst-like structure (Fig. 2) that had ruptured. In these sections, too, within the lumina of the dilated blood vessels surrounding the cystlike lesion of molluscum contagiosum, there were many of those atypical mononuclear cells that were previously so misleading (Fig. 3a & b)

DISCUSSION

One may only wonder worriedly about the phenomenon of rupture of a lesion of molluscum

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Accepted for publication November 30, 1976.

Perplexed by the contradiction between the dire histologic interpretation and the negative clinical and other laboratory findings, we obtained the original block of the cutaneous specimen and cut deeper sections through it. To our amazement, and embarassment, those sections revealed molluscum bodies within the cornified cells of an epithelial, cyst-like structure (Fig. 2) that had ruptured. In these sections, too, within the lumina of the dilated blood vessels surrounding the cystlike lesion of molluscum contagiosum, there were many of those atypical mononuclear cells that were previously so misleading (Fig. 3a & b)

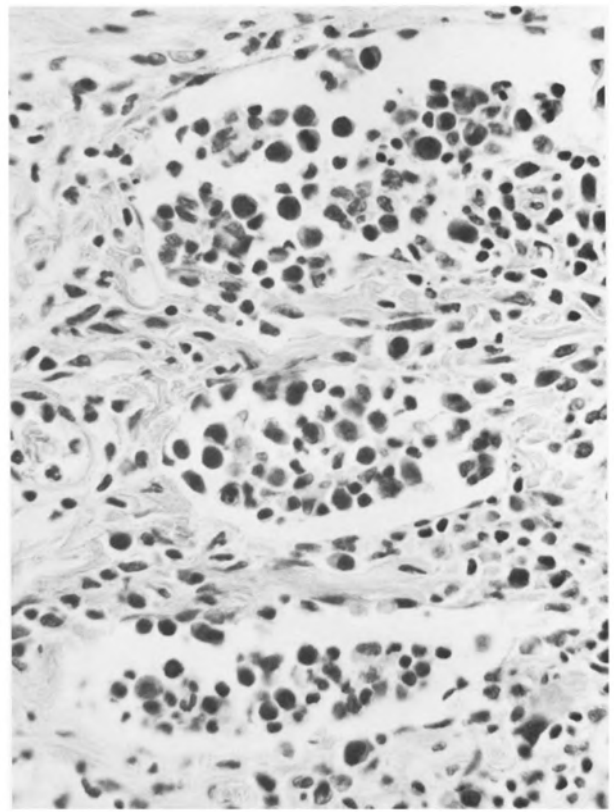
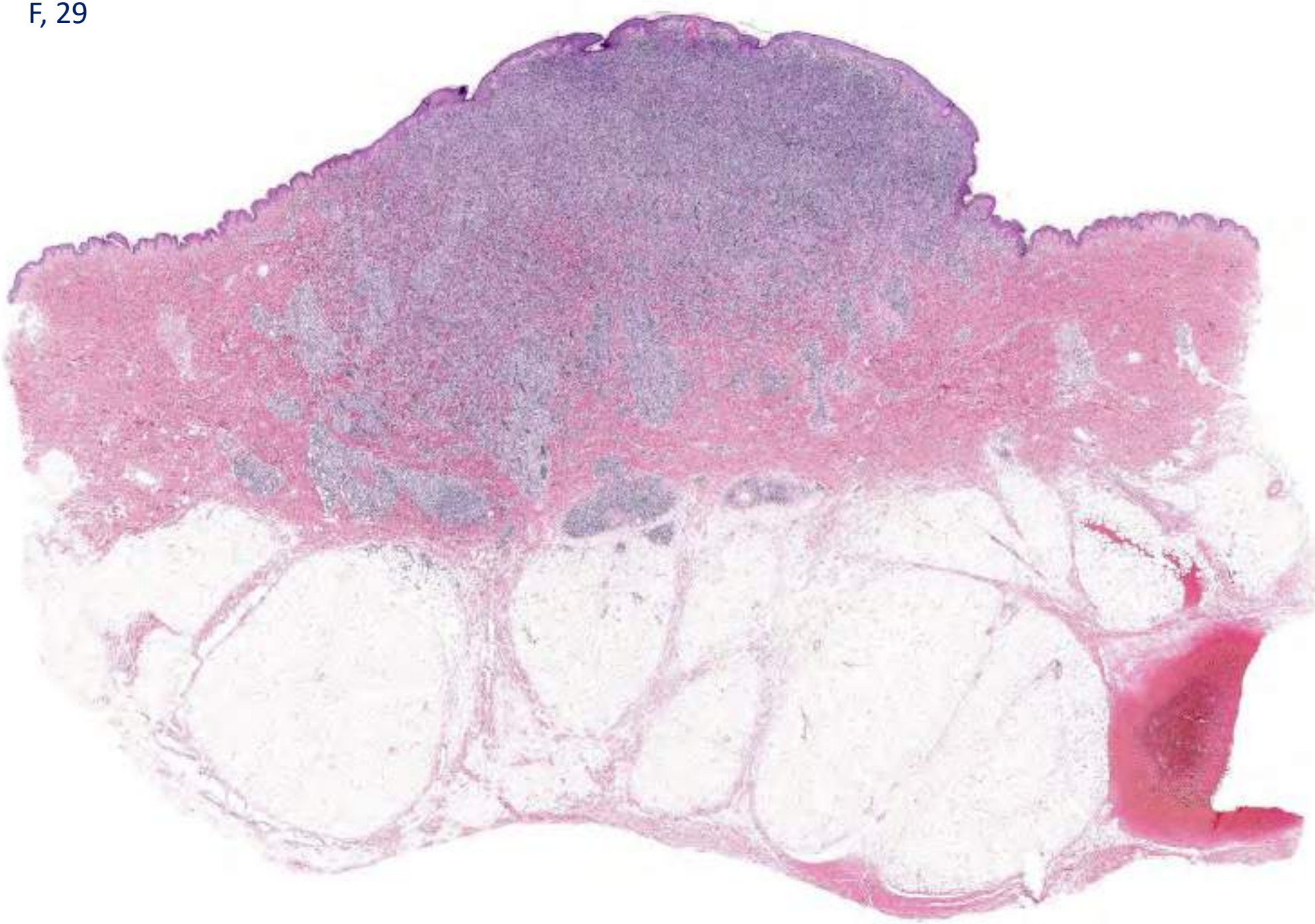
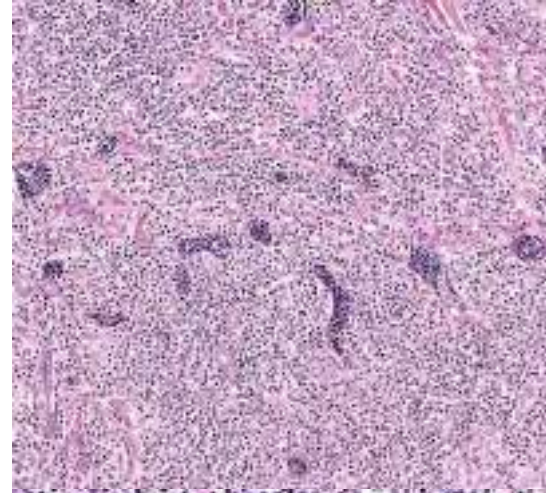
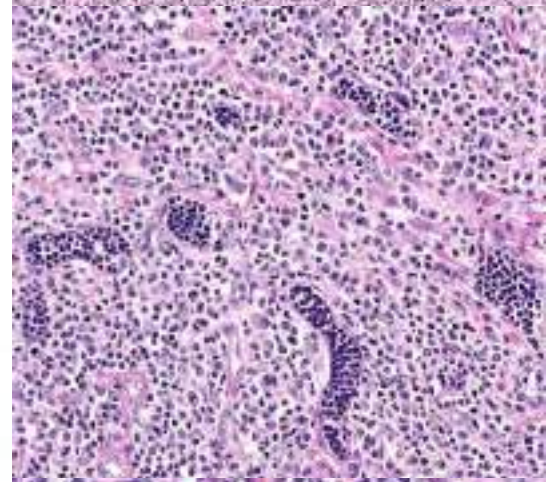


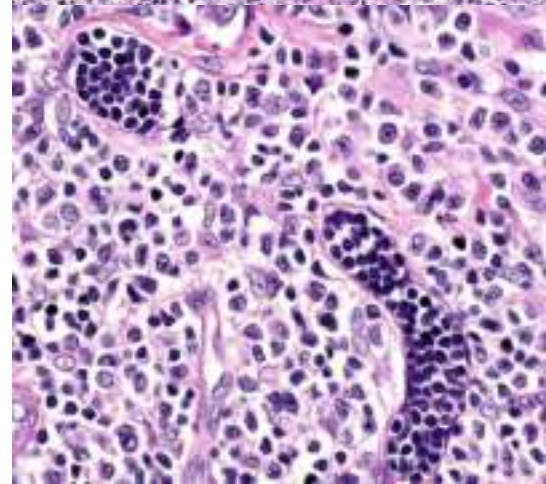
FIG. 1b. Higher power of Fig. 1a showing atypical mononuclear cells in the stromal infiltrate and within three vascular spaces (×680).

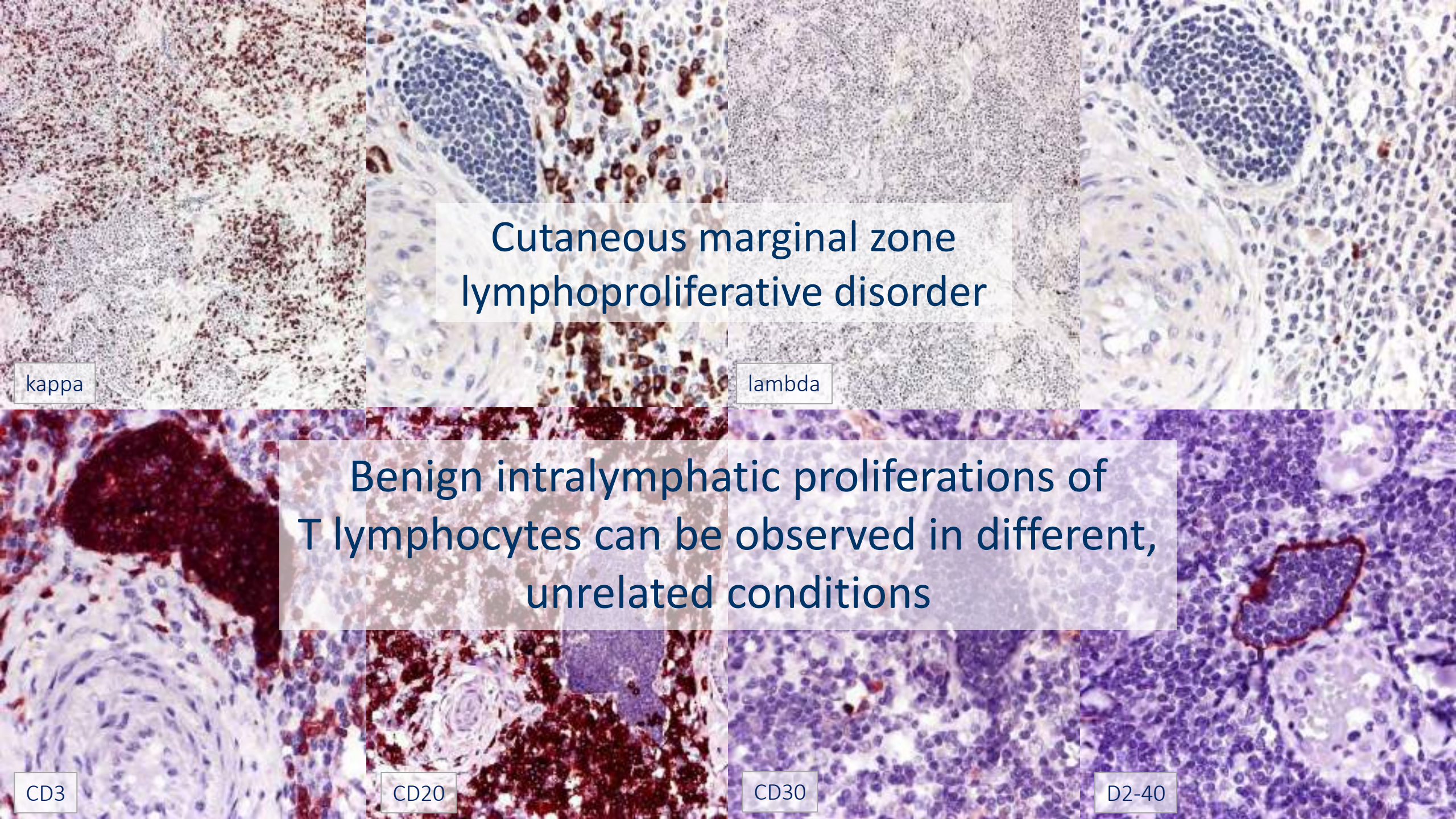
F, 29



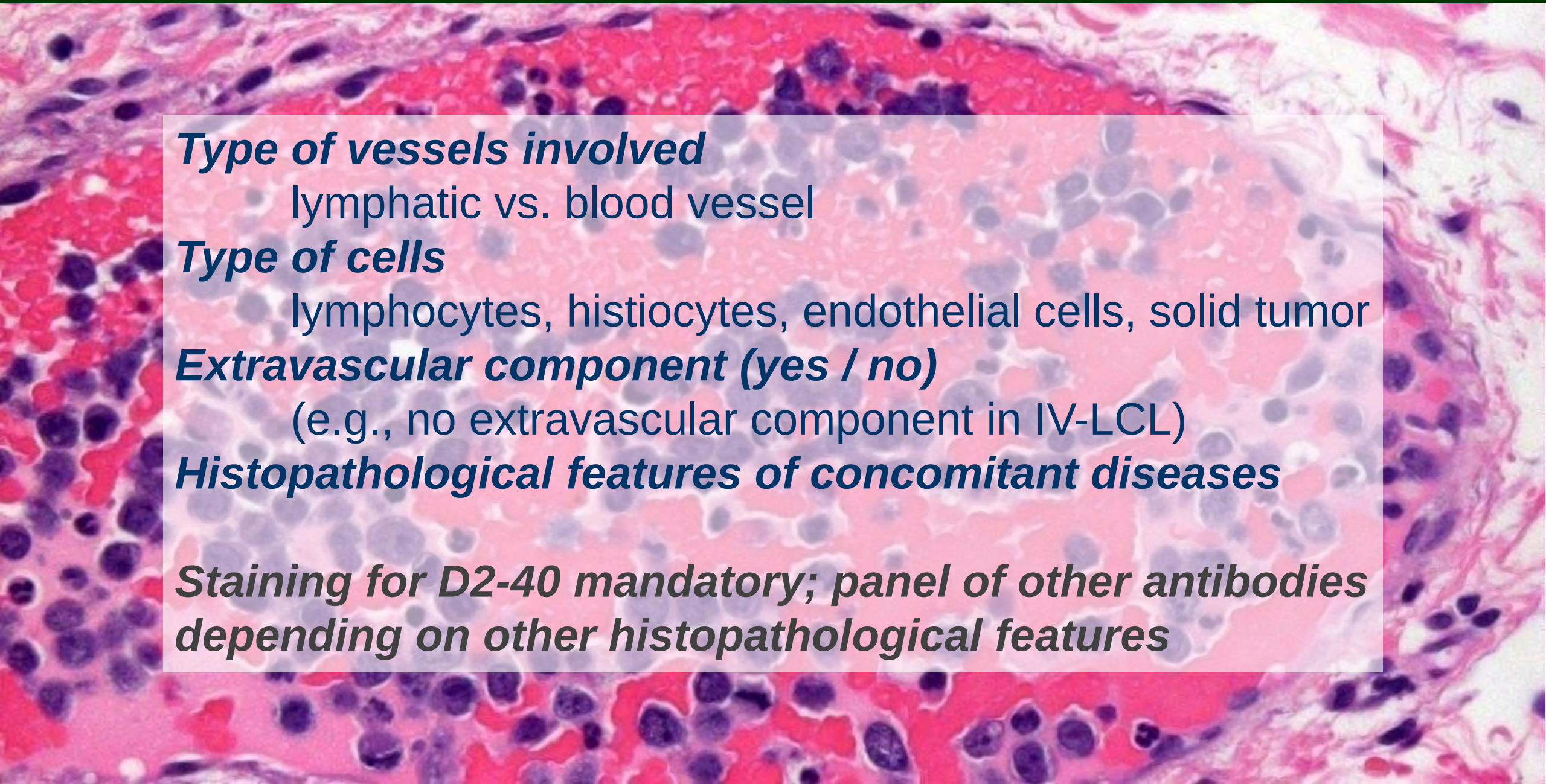







Cutaneous marginal zone lymphoproliferative disorder
kappa
lambda
Benign intralymphatic proliferations of T lymphocytes can be observed in different, unrelated conditions
CD3
CD20
CD30
D2-40

Approach to diagnosis of intraluminal cells



Type of vessels involved

lymphatic vs. blood vessel

Type of cells

lymphocytes, histiocytes, endothelial cells, solid tumor

Extravascular component (yes / no)

(e.g., no extravascular component in IV-LCL)

Histopathological features of concomitant diseases

Staining for D2-40 mandatory; panel of other antibodies depending on other histopathological features