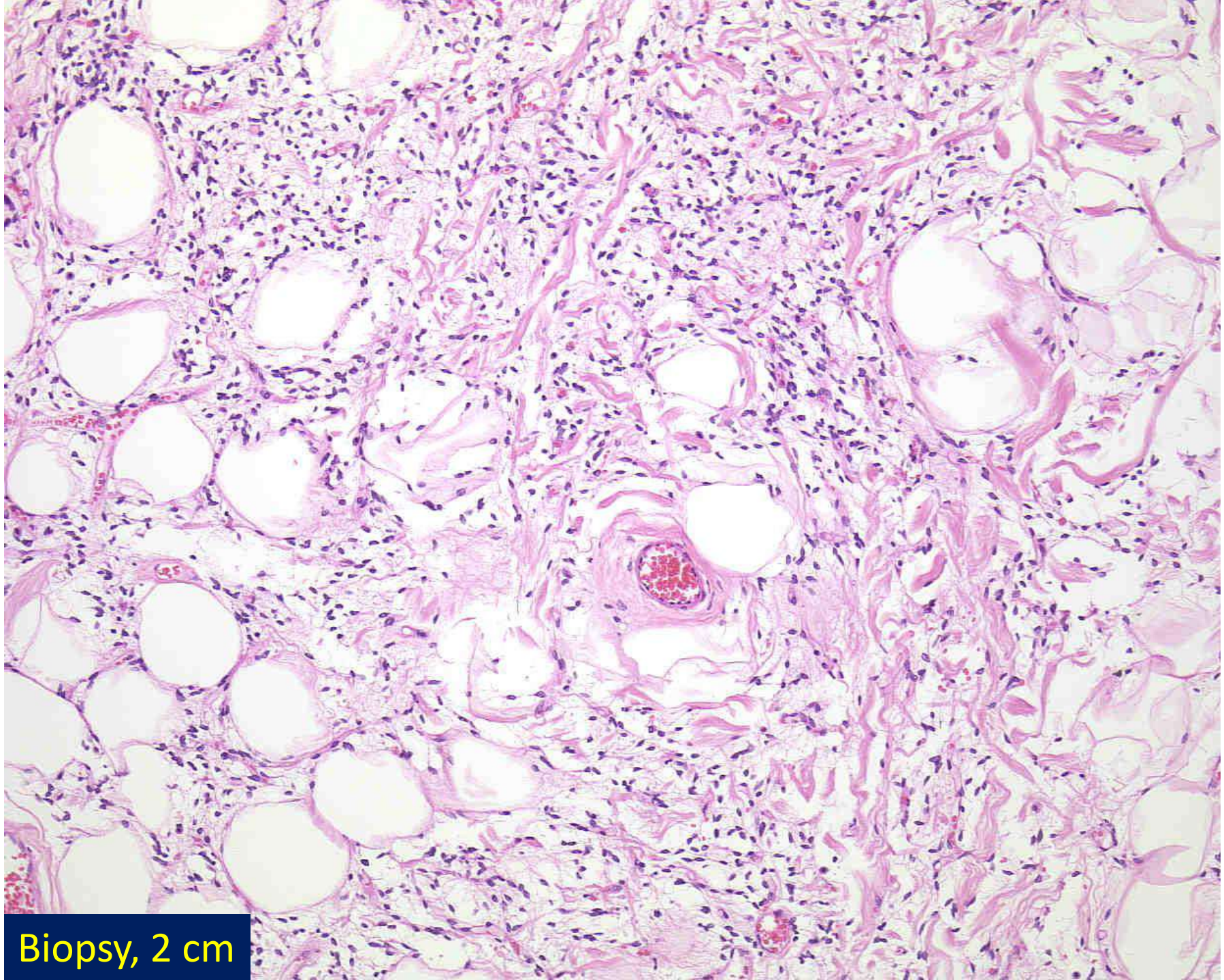
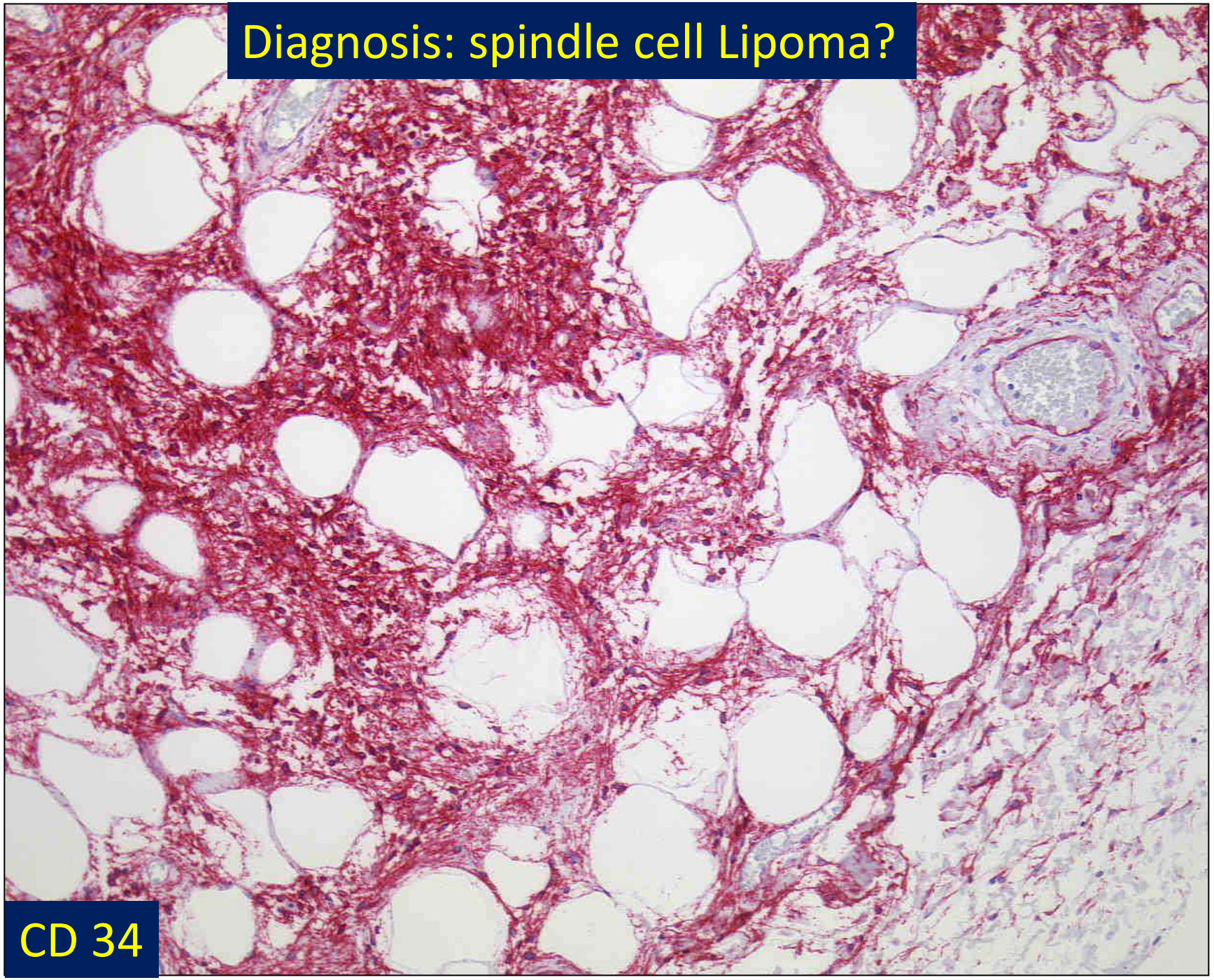
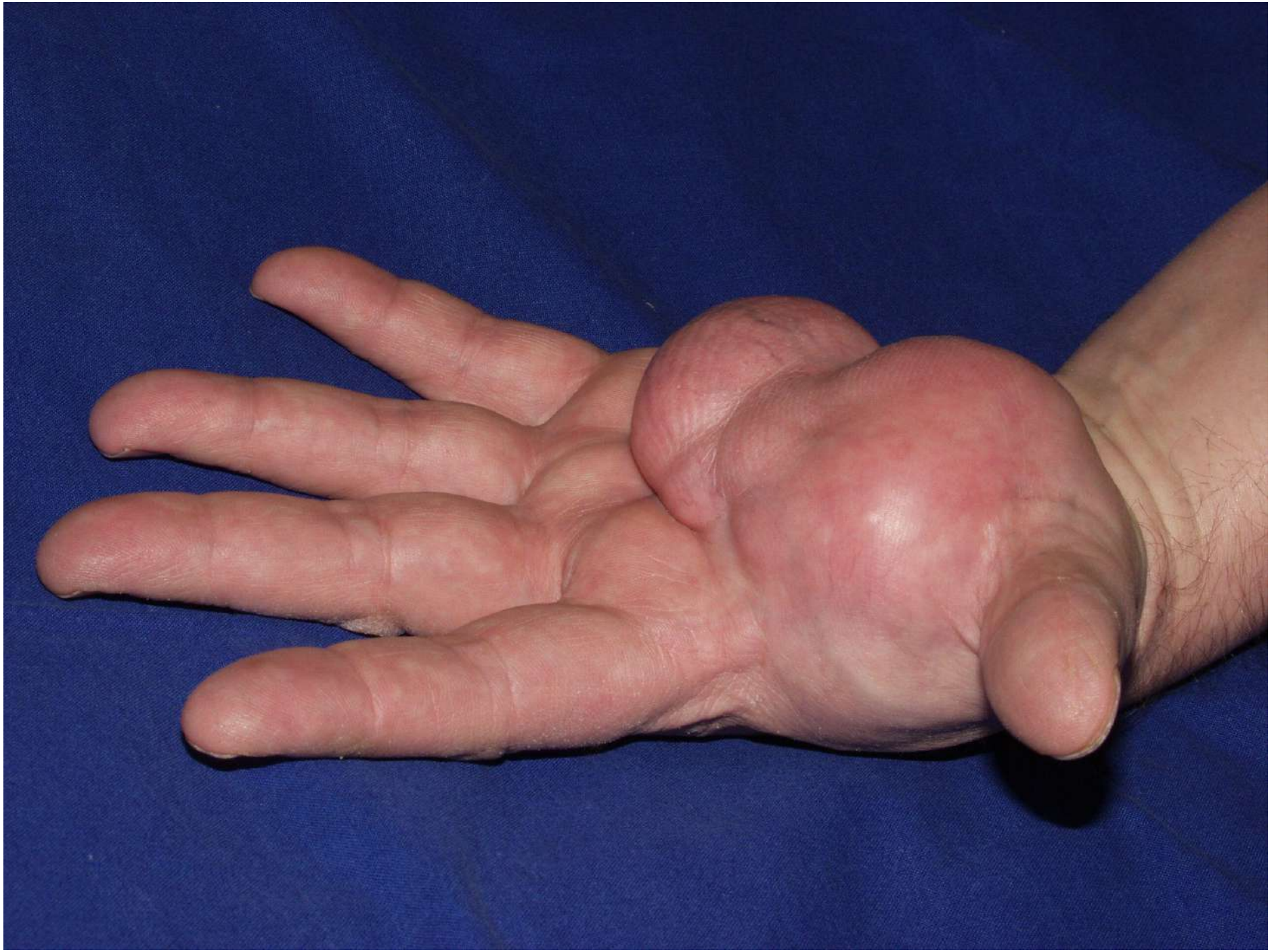
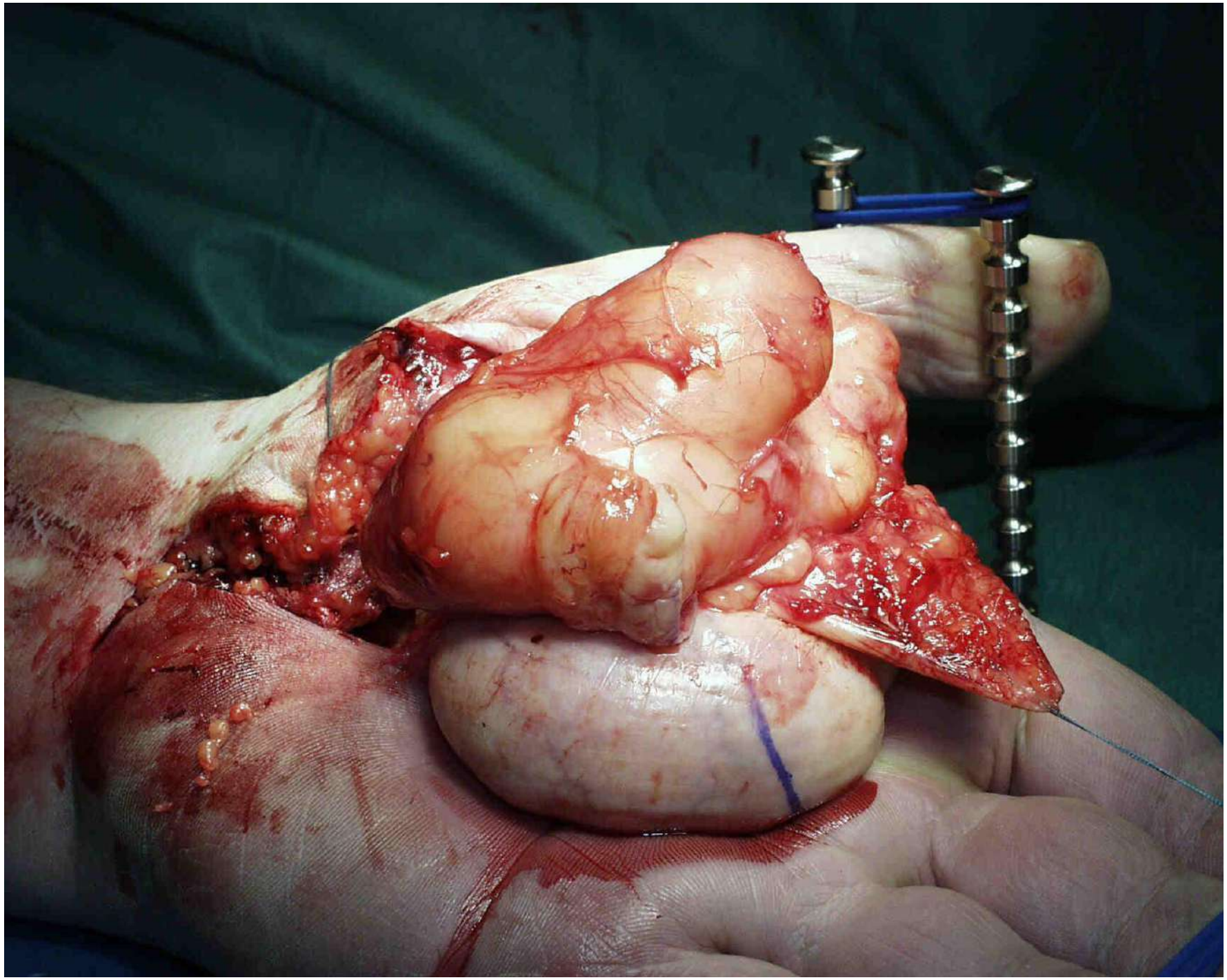
- M, 54 years
- left hand, exophytic growing neoplasm
- slowly enlarging neoplasm (5 years !)
- 9 x 9 cm, soft consistency
- biopsy
- complete excision
- no recurrence at 5 years

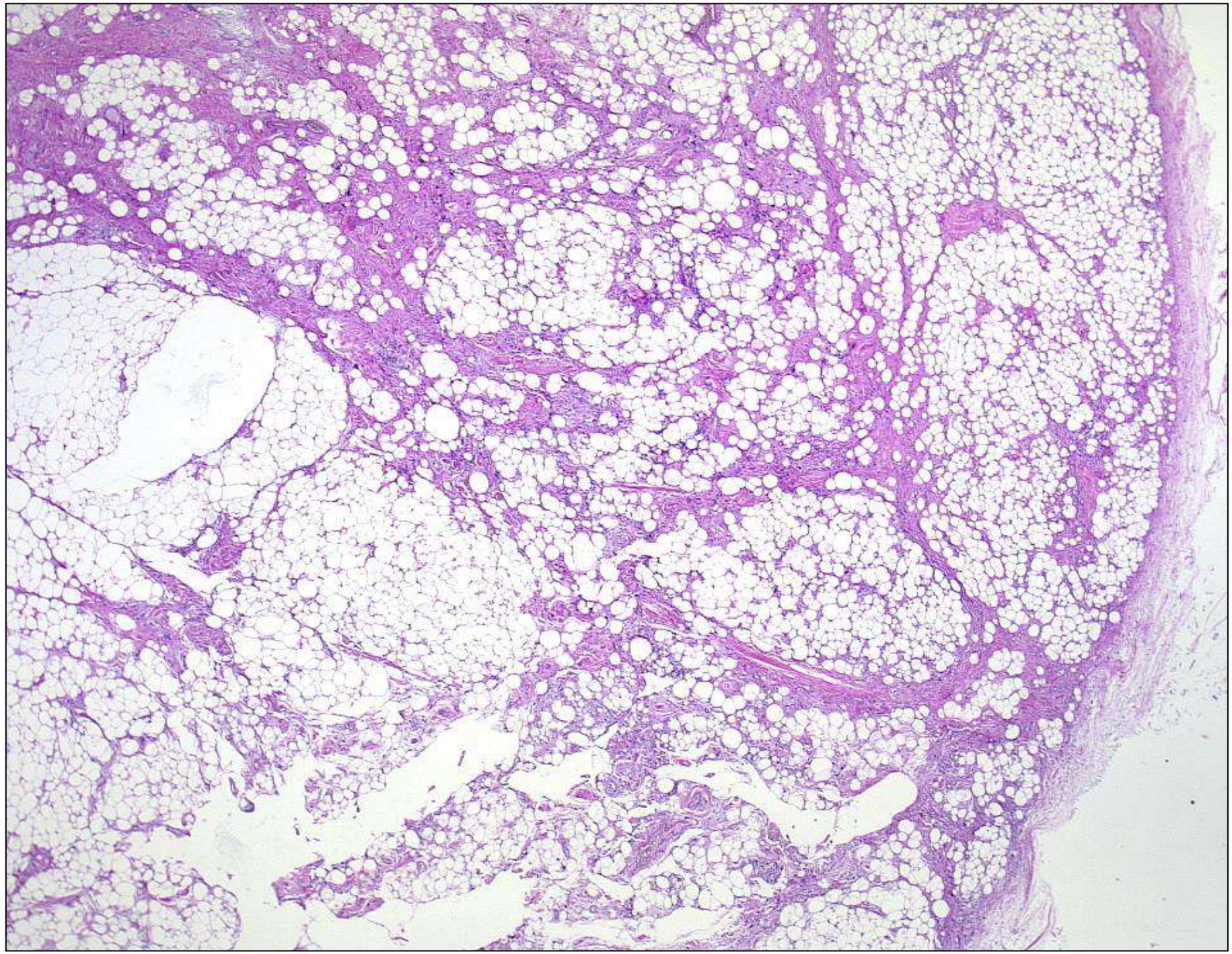

Biopsy, 2 cm

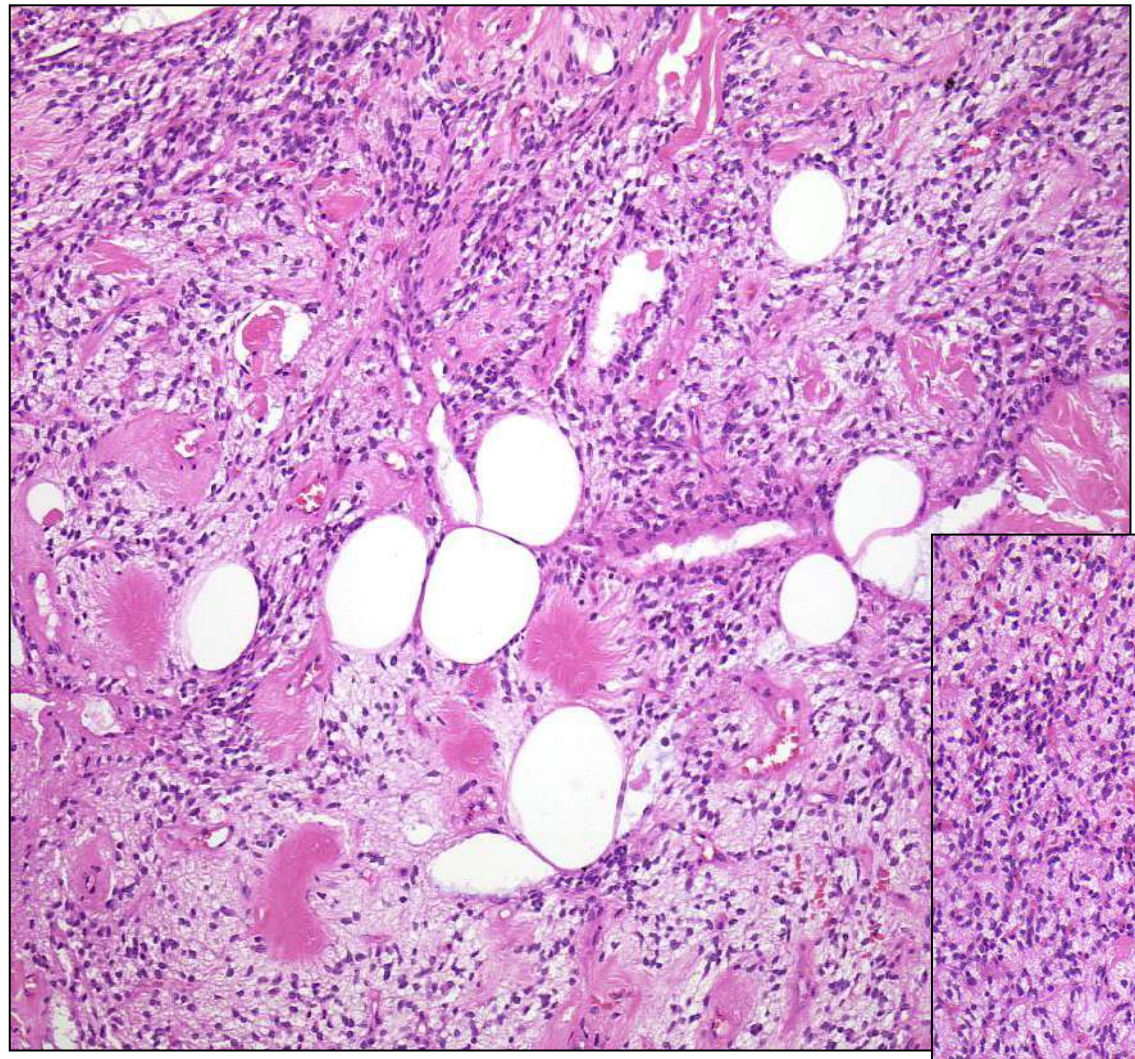

Diagnosis: spindle cell Lipoma?
CD 34

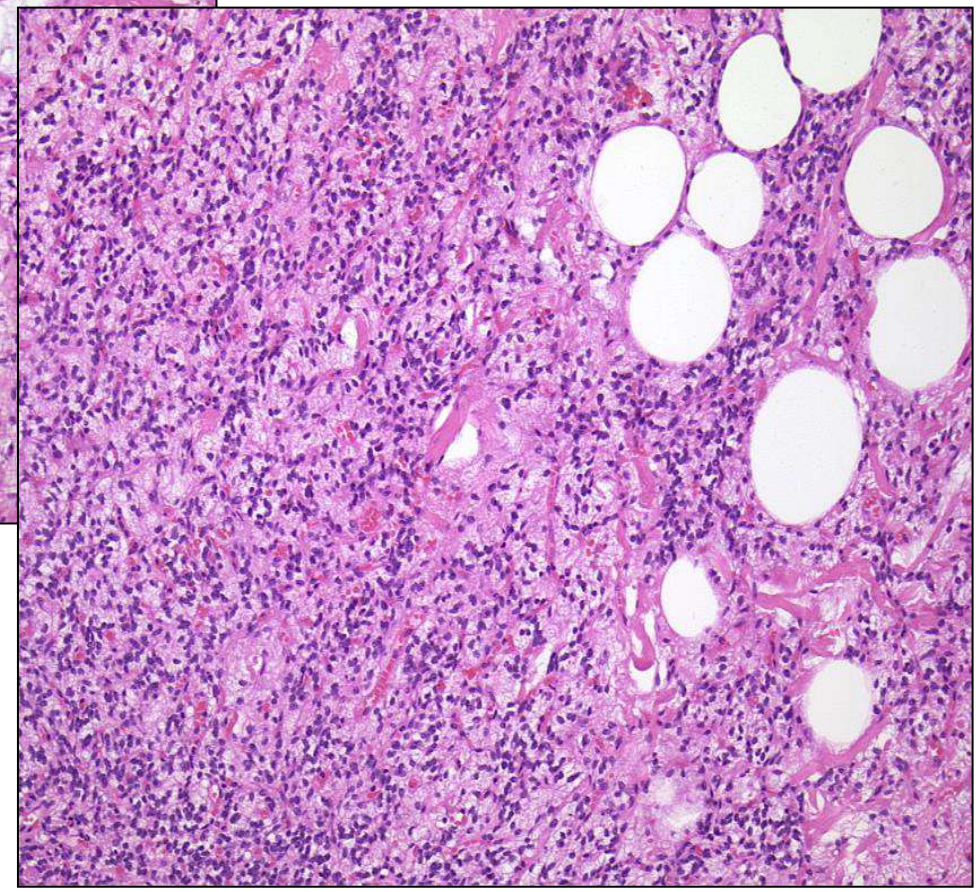
**Clinician: „You must be wrong with your diagnosis, do you want to see the patient?“**

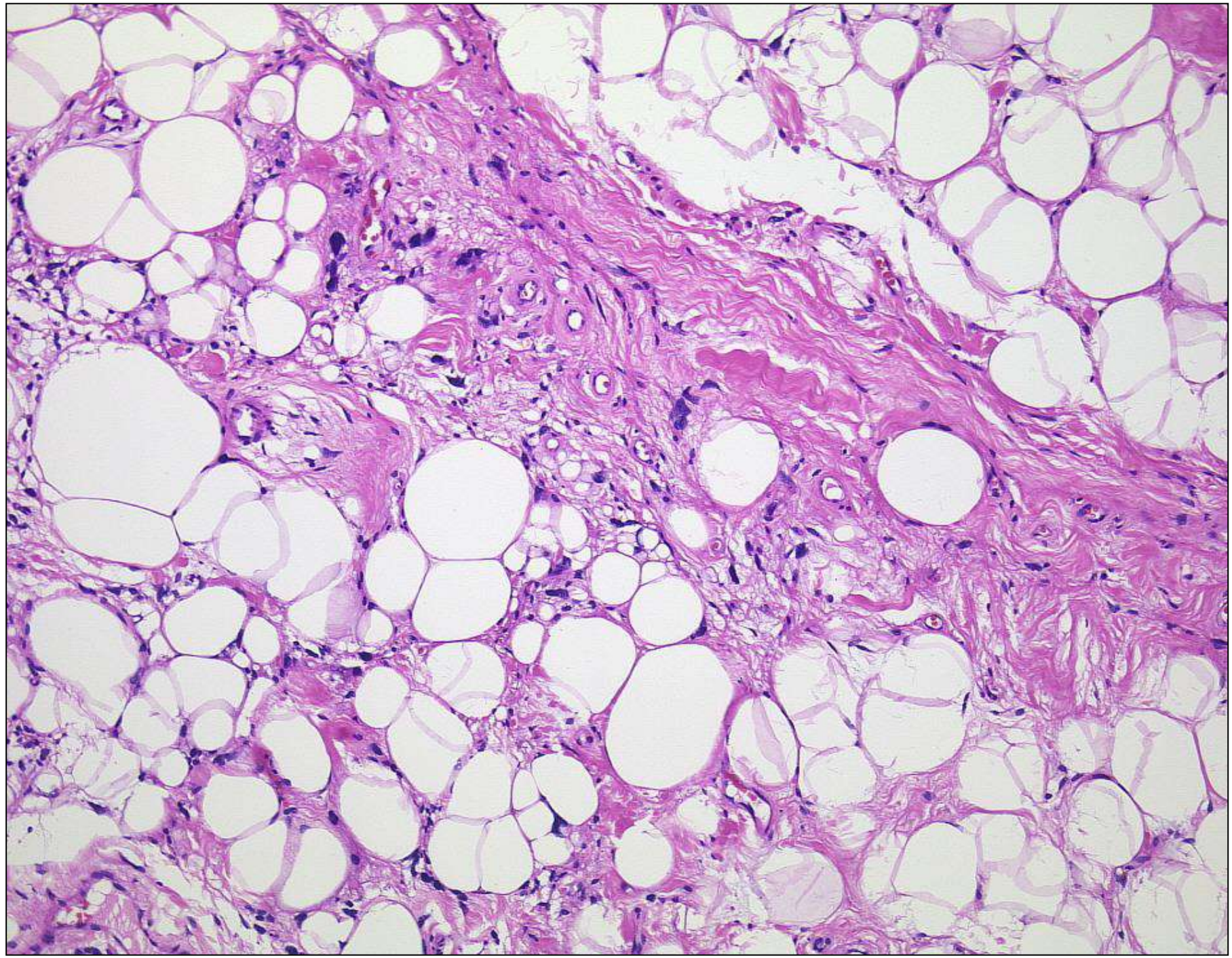


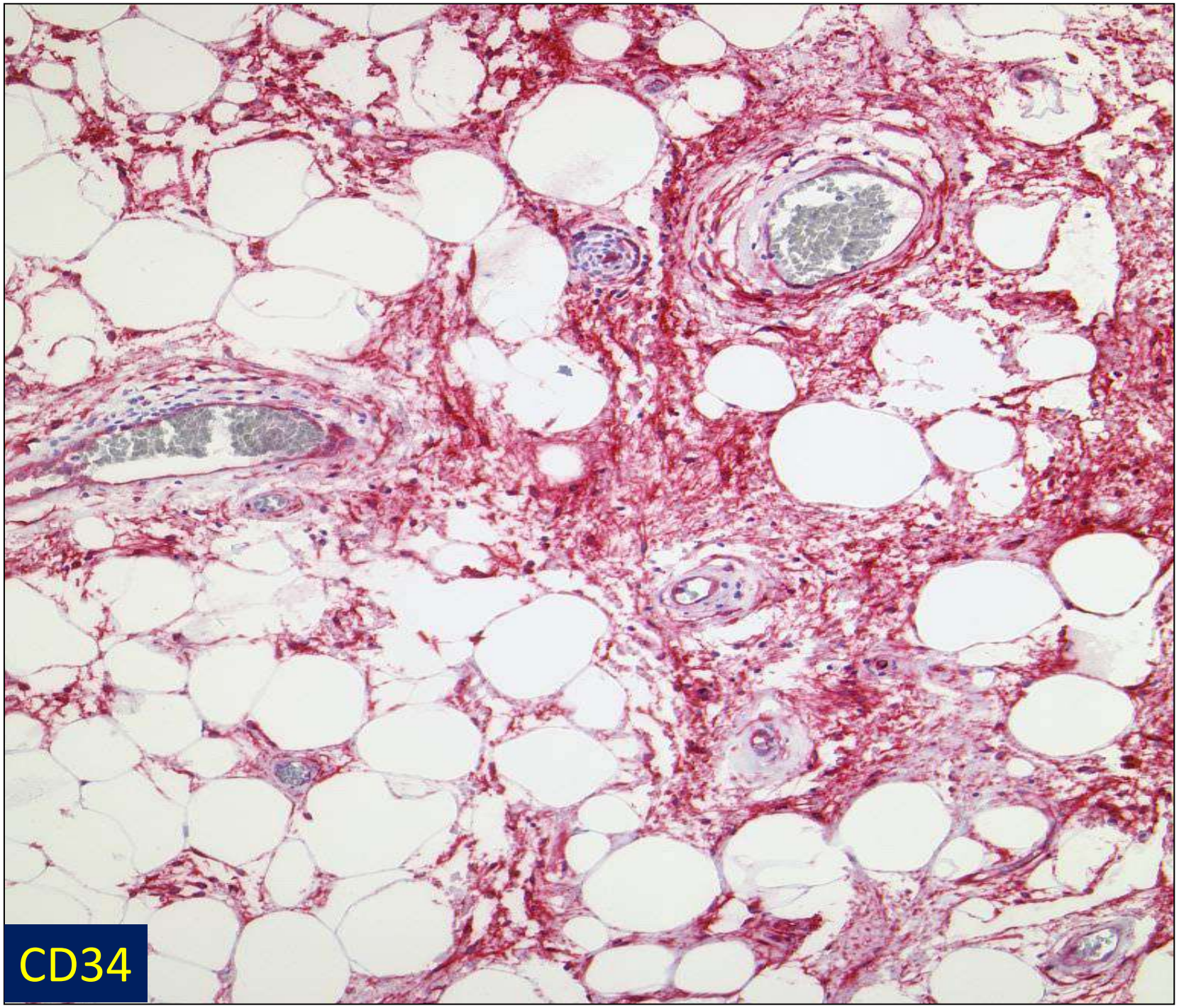


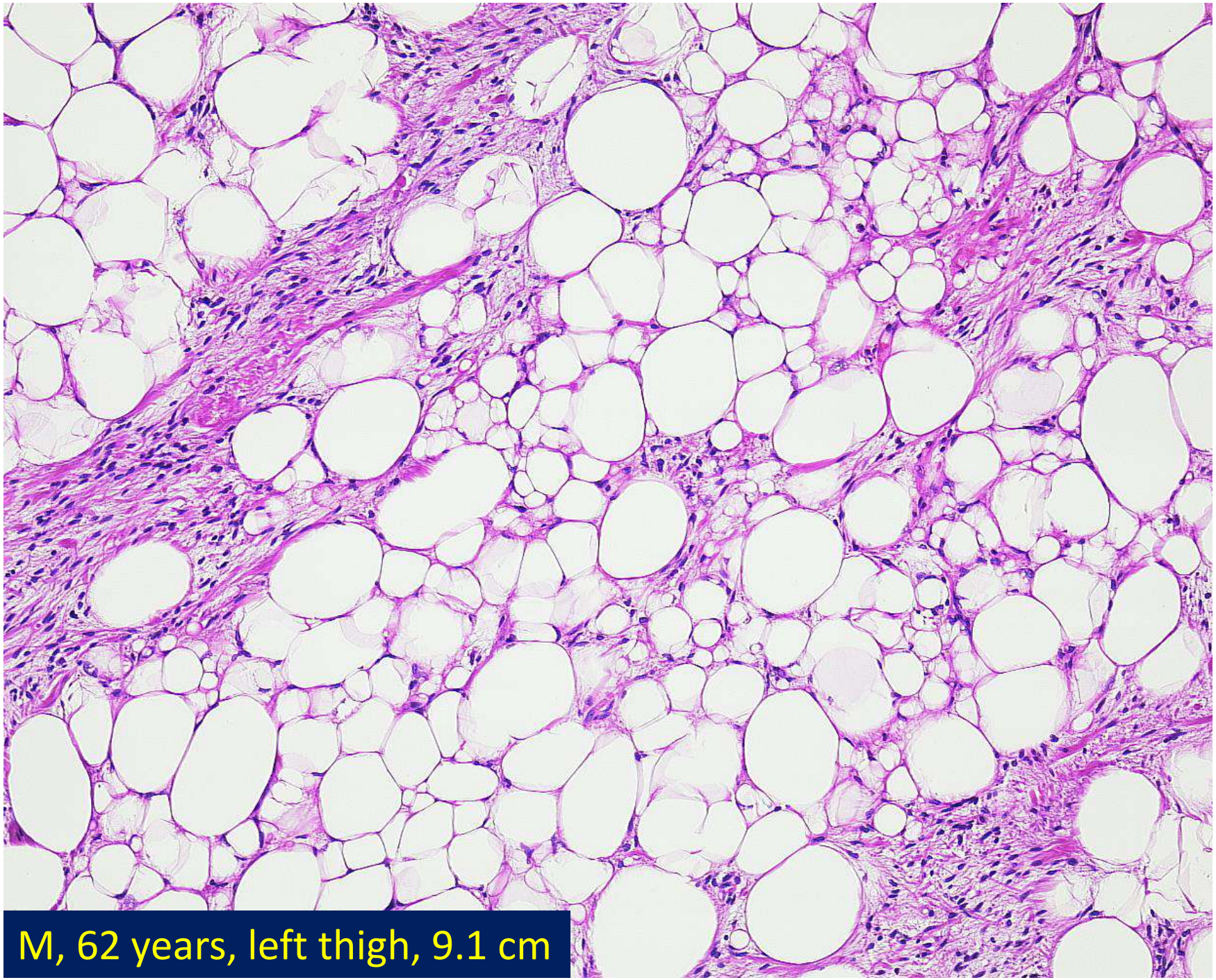


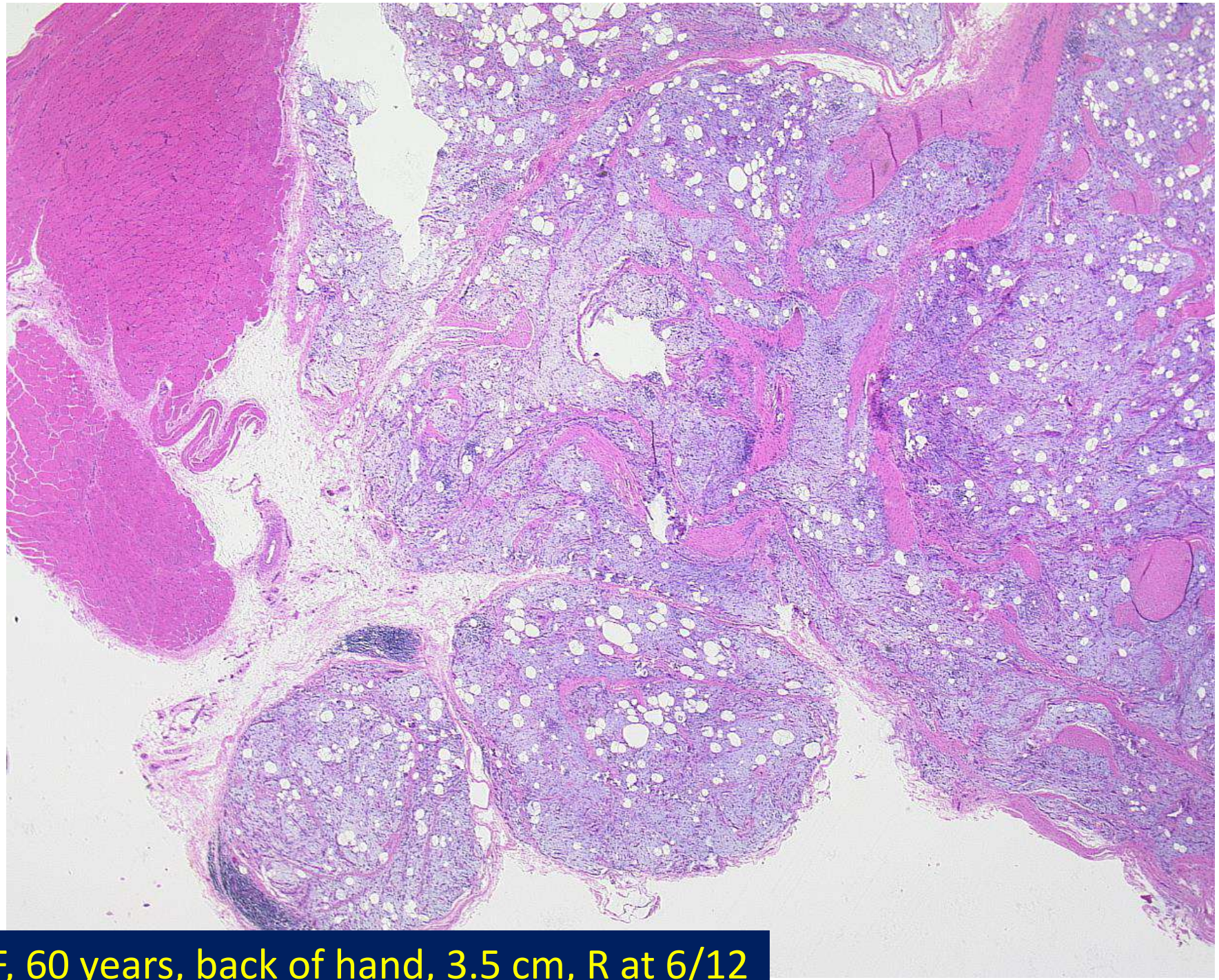




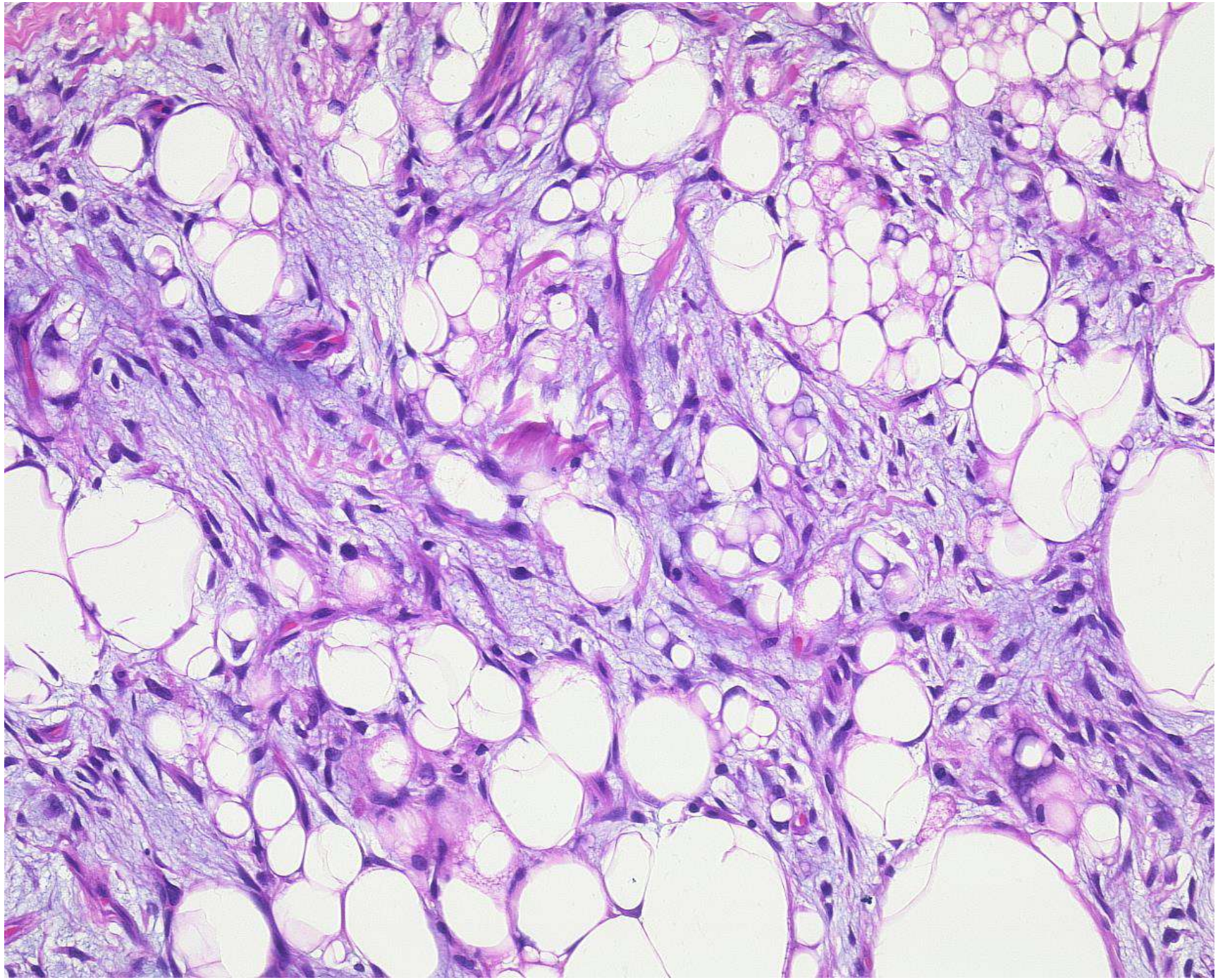


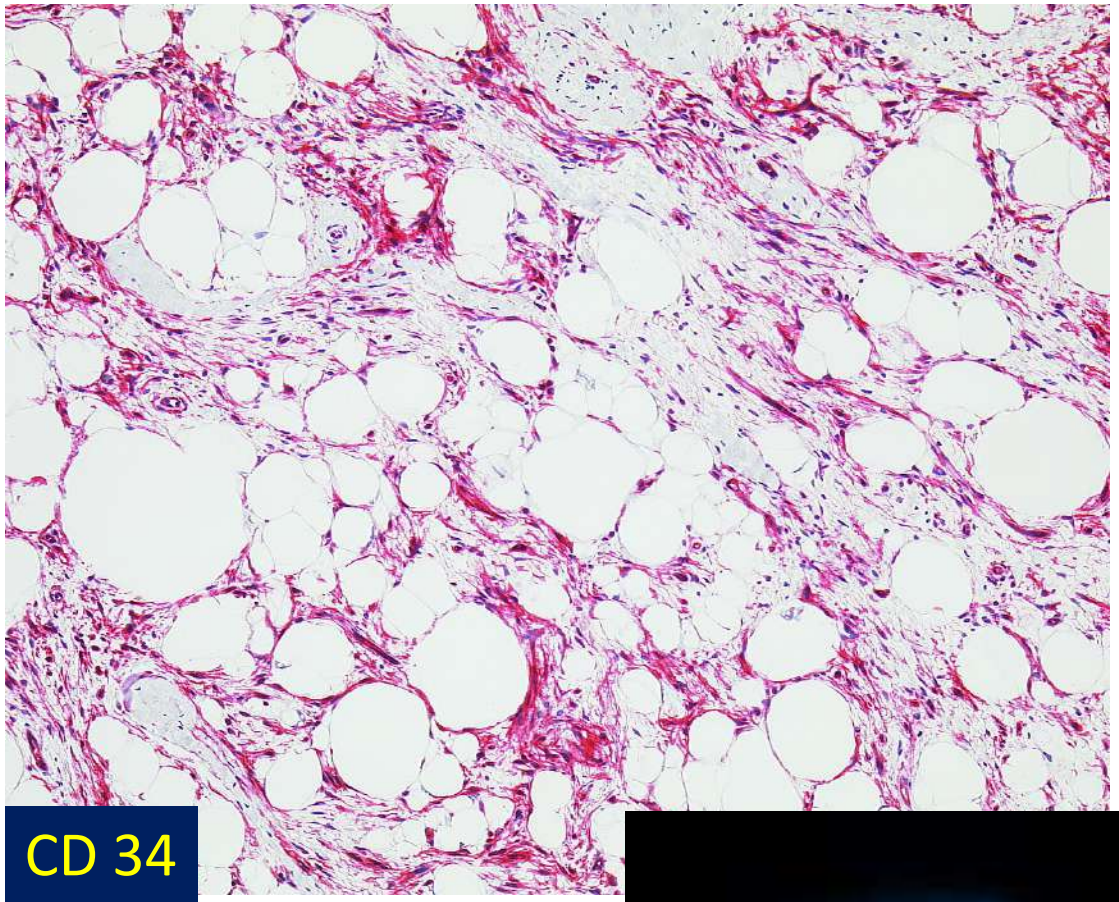

CD34


M, 62 years, left thigh, 9.1 cm

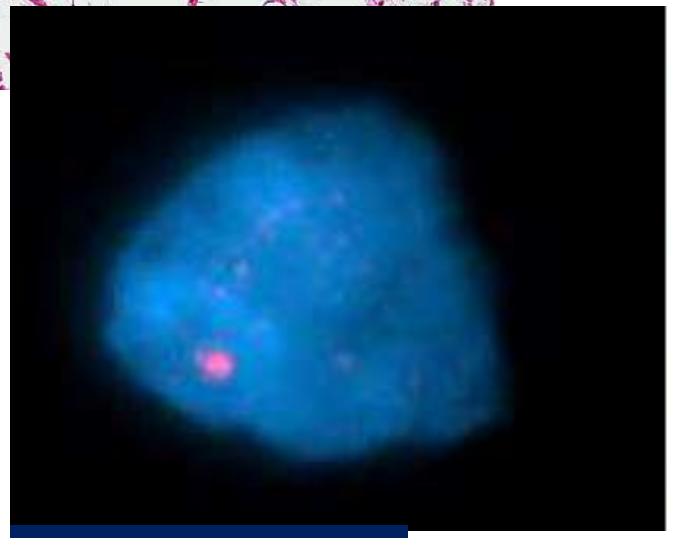


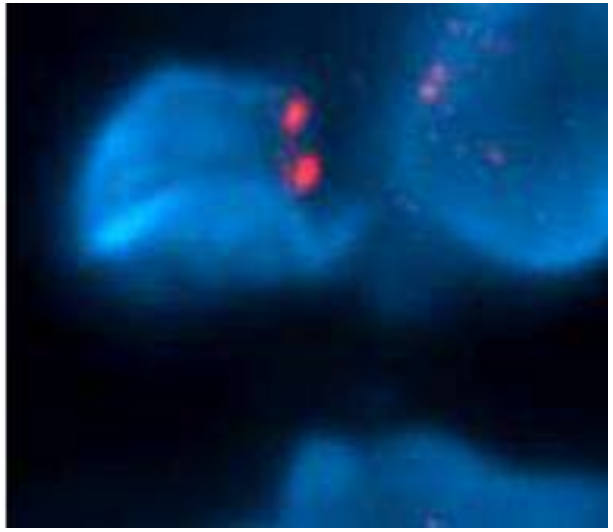
F, 60 years, back of hand, 3.5 cm, R at 6/12





CD 34





Rb-1 Deletion

# Atypical Spindle Cell Lipomatous Tumor

## *Clinicopathologic Characterization of 232 Cases Demonstrating a Morphologic Spectrum*

*Brian Marino-Enriquez, MD, PhD,* Alessandra F. Nascimento, MD,* Azra H. Ligon, PhD,* Cherwei Liang, MD,† and Christopher D.M. Fletcher, MD, FRCPath**

The classification of atypical adipocytic neoplasms with cell features remains challenging. To better define a group of low-grade lipomatous neoplasms, we present the clinical, histologic, and immunohistochemical characteristics of a large series of 232 atypical spindle cell lipomatous tumors. The lesions affected 140 males and 92 females, at an age of 56 years (range, 6–87 y), clinically presenting as a new, or enlarging mass with a median size of 5 cm. The most frequent distribution of the tumors was wide, predominating in the trunk and limb girdles (147 cases, 63%), mainly in the hands and feet (17% and 11%, respectively), with equal distribution between subcutaneous and deeper locations. Microscopic examination revealed a spectrum of histologic appearances. All consisted of a poorly marginated proliferation of mildly atypical spindle cells set in a fibrous or myxoid stroma, with a prominent admixed adipocytic component showing a range in adipocyte size and scattered nuclear atypia, focally with multivacuolated or multivacuolated lipoblasts. The intensity and the relative proportion of the different cell types were very variable. Tumor margins were often ill-defined with invasion into surrounding tissues. Two tumors showed morphologic features reminiscent of dedifferentiation. By immunohistochemistry, the neoplastic spindle cells expressed MDM2 (54%), S100 protein (40%) and, less frequently, desmin (8%). Expression of Rb was lost in 37% of cases examined, and CDK4 were never overexpressed and FISH for MDM2 amplification was consistently negative, highlighting biological differences from atypical lipomatous tumor/well-differentiated liposarcoma. The morphologic differential diagnosis of atypical spindle cell lipomatous tumor is broad, and includes spindle cell lipoma, diffuse neurofibroma, nonmyxoid type myofibroblastoma, dermatofibrosarcoma protuberans, fat-forming solitary fibrous tumor, and morphologically low grade malignant peripheral nerve sheath tumor. Most patients underwent surgical excision of the primary mass. With a median follow-up of 4 years (range, 1 mo to 20 y), 87% of patients (63/72) were alive with no evidence of recurrence or metastatic disease. Local recurrence of the tumor was observed in 12% of patients (9 out of 72, multiple in 3 of them) at intervals between 6 months and 17 years after resection of the primary tumor. None of the patients developed tumor metastasis or died of disease. Identification of the neoplastic adipocytic component admixed with spindle cells, and recognition of the range of histologic appearances are key for the diagnosis of atypical spindle cell lipomatous tumor. Whereas the risk of metastatic dissemination is minimal, there is a non-negligible risk for local recurrence (13%) which warrants surgical resection with clear margins whenever feasible.

**Key Words:** soft tissue, liposarcoma, atypical lipomatous tumor, spindle cell liposarcoma, dedifferentiated liposarcoma, atypical spindle cell lipomatous tumor

(*Am J Surg Pathol* 2017;41:234–244)

Atypical spindle cell lipomatous neoplasms were first described by Dei Tos et al[1] in 1994, in a series of 6 cases designated spindle cell liposarcoma. Microscopically, spindle cell liposarcoma shows distinctive morphology, with atypical spindle cells and a variably prominent adipocytic component. Locally aggressive growth and local recurrence were common, whereas dedifferentiation and metastasis occurred rarely.[1] At that time, spindle cell liposarcoma was considered a morphologic variant of well-differentiated liposarcoma, given its overlapping clinicopathologic characteristics and distinct morphology. Additional examples of spindle cell lipomatous tumor have been reported since, as isolated case reports or as part of small series of atypical lipomatous tumor/well-differentiated liposarcoma.[2–5]

Over the last 2 decades, the classification of atypical and malignant adipocytic tumors has evolved, thanks to a better biological understanding, with substantial con-

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Presented at the 94th United States and Canadian Pathology Meeting, March 2005, San Antonio, TX.

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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92 F, 140 M, 6-87 years
median size 5 cm
limbs, limb girdles (63%)
head/neck (10%)
genital area (7%)
trunk (6%), back (6%)…
poorly marginated
atypical spindled cells +
atypical lipogenic cells
variable cellularity
local recurrence 12%
(3 x multiple)

subcutis > deep soft tissues >> visceral
admixture of atypical spindled + lipogenic cells
low cellularity (62%) > high cellularity (38%)
mild atypia (52%) > prominent atypia (28%)
uni- or multivacuolated lipoblasts (45%)
rare mitoses, no tumour necrosis
purely mxoid to collagenous stroma
CD 34 + (64%), S-100 + (40%), desmin + (22%),
Rb loss (57%), no tumour MDM2 and CDK4 +
FISH analysis: no *MDM2/CDK4* amplification
loss of Rb-1 locus in 71%
monosomy 7 in 43%

# DD atypical spindle cell lipomatous Tumour

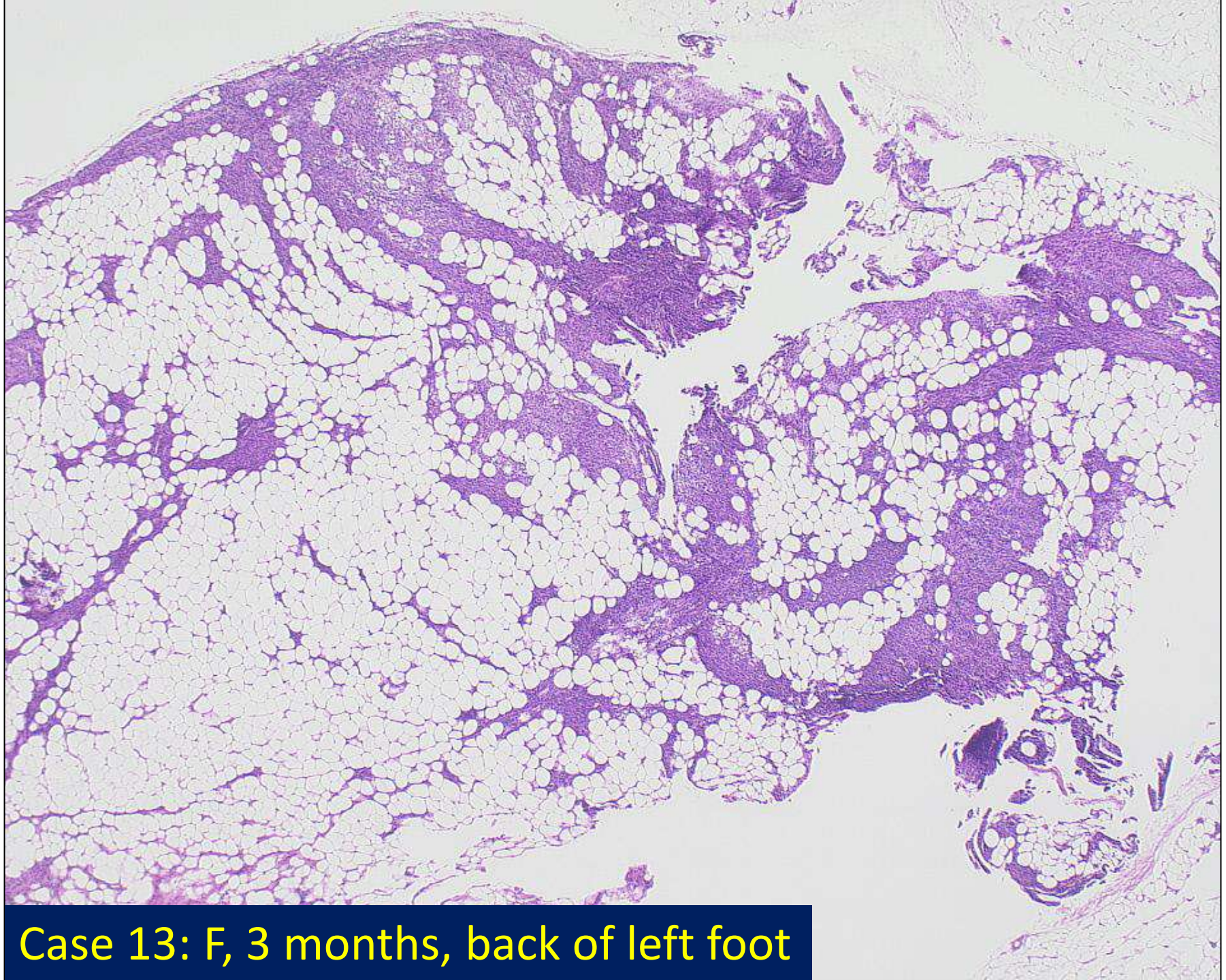
| | |
|---|---|
| spindle cell lipoma: | elderly male patients, neck, encapsulated, no atypia |
| ALT: | *MDM2 / CDK4* amplification<br>no *Rb-1* deletion |
| DDLS: | deep soft tissue<br>abrupt transition, more atypia<br>*MDM2 / CDK4* amplification |
| spindle cell myxoid LS: | young patients, vasculature<br>t(12;16), t(12;22) |

(Alaggio R et al. AJSP 2009; 33: 645)

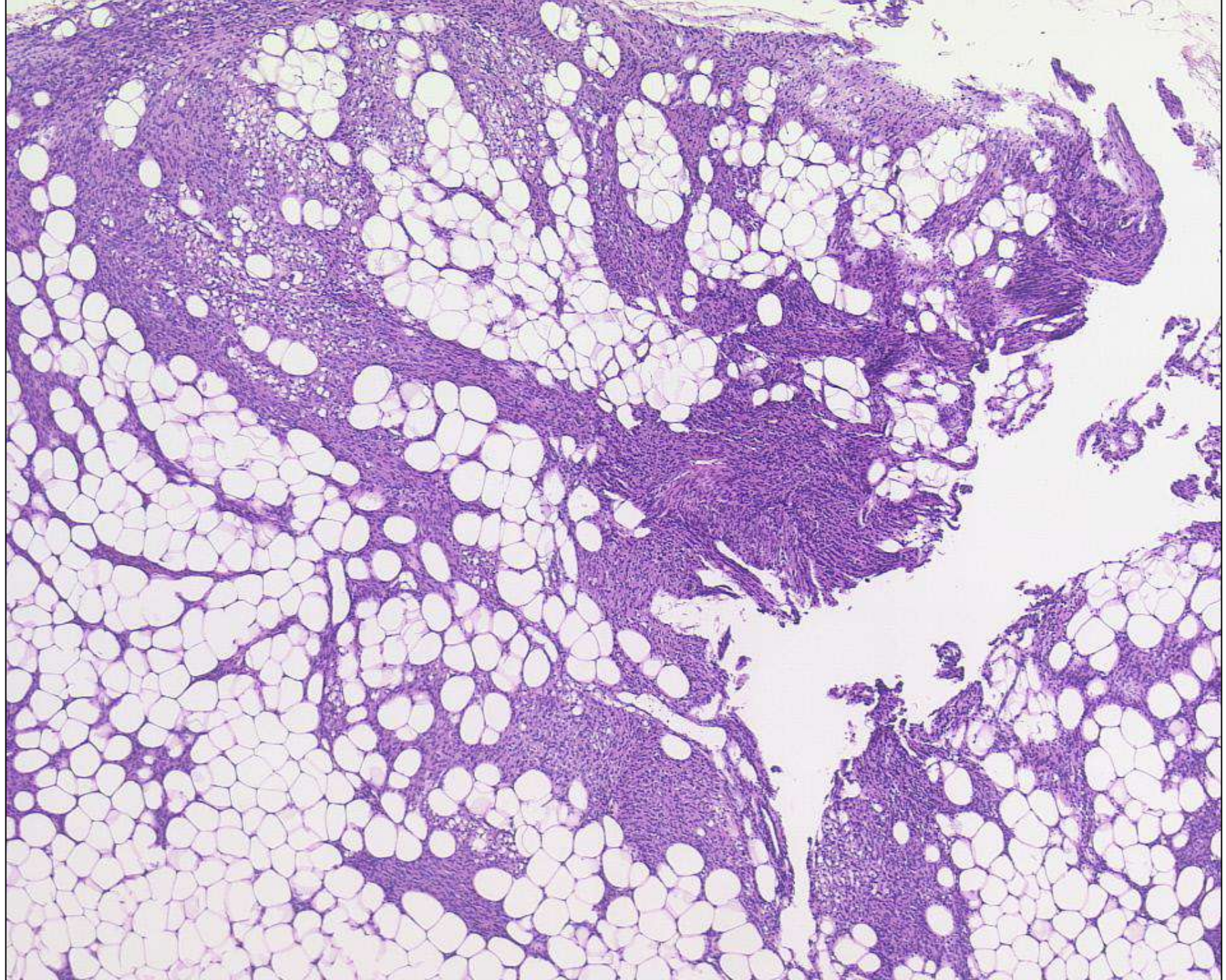
lipomatous SFT, diffuse neurofibroma, DFSP, mammary-type myofibroblastoma, MPNST

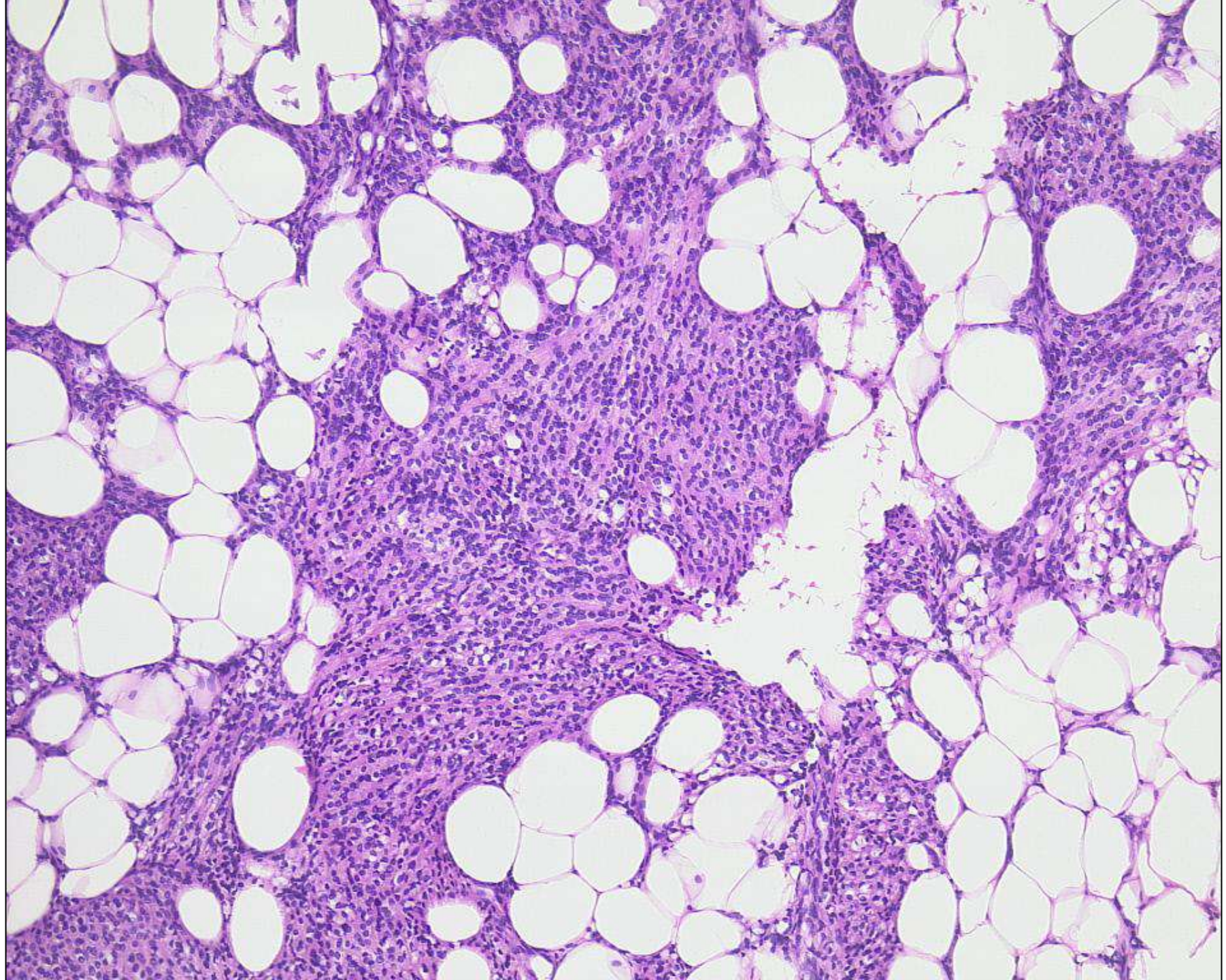
# Conclusions Case 12

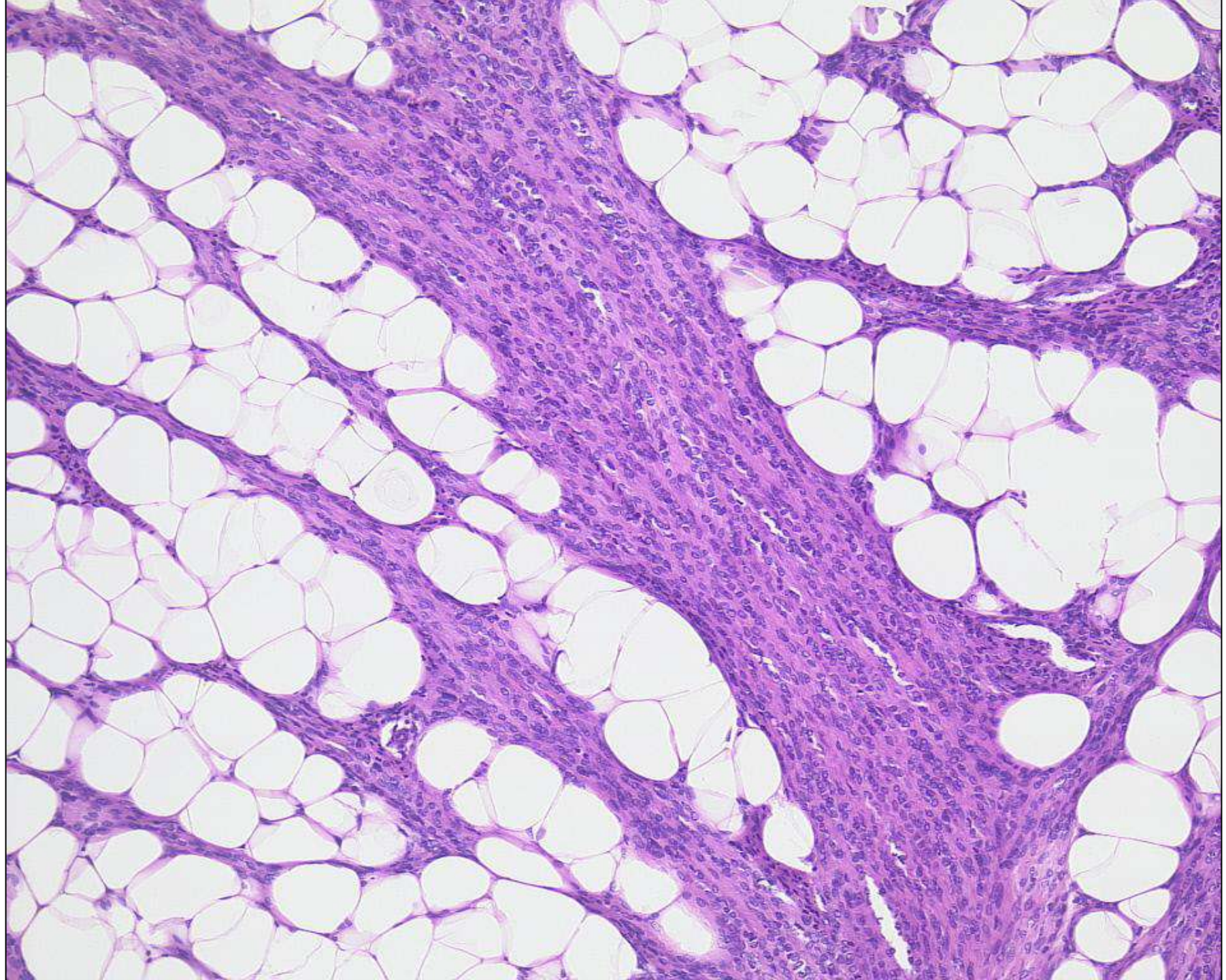
ASCLTs are…
distinct category of adipocytic neoplasms
represent clinically low-grade neoplasms
require surgical excision with clear margins
low risk for local recurrence
very low risk for dedifferentiation
include „fibrosarcoma-like“ lipomatous neoplasms
often adult males with predilection for the limbs
variable proportions of atypical spindled cells,
adipocytes, lipoblasts myxoid/coll. stroma
CD 34 +, Rb -, MDM2 -, CDK4 -

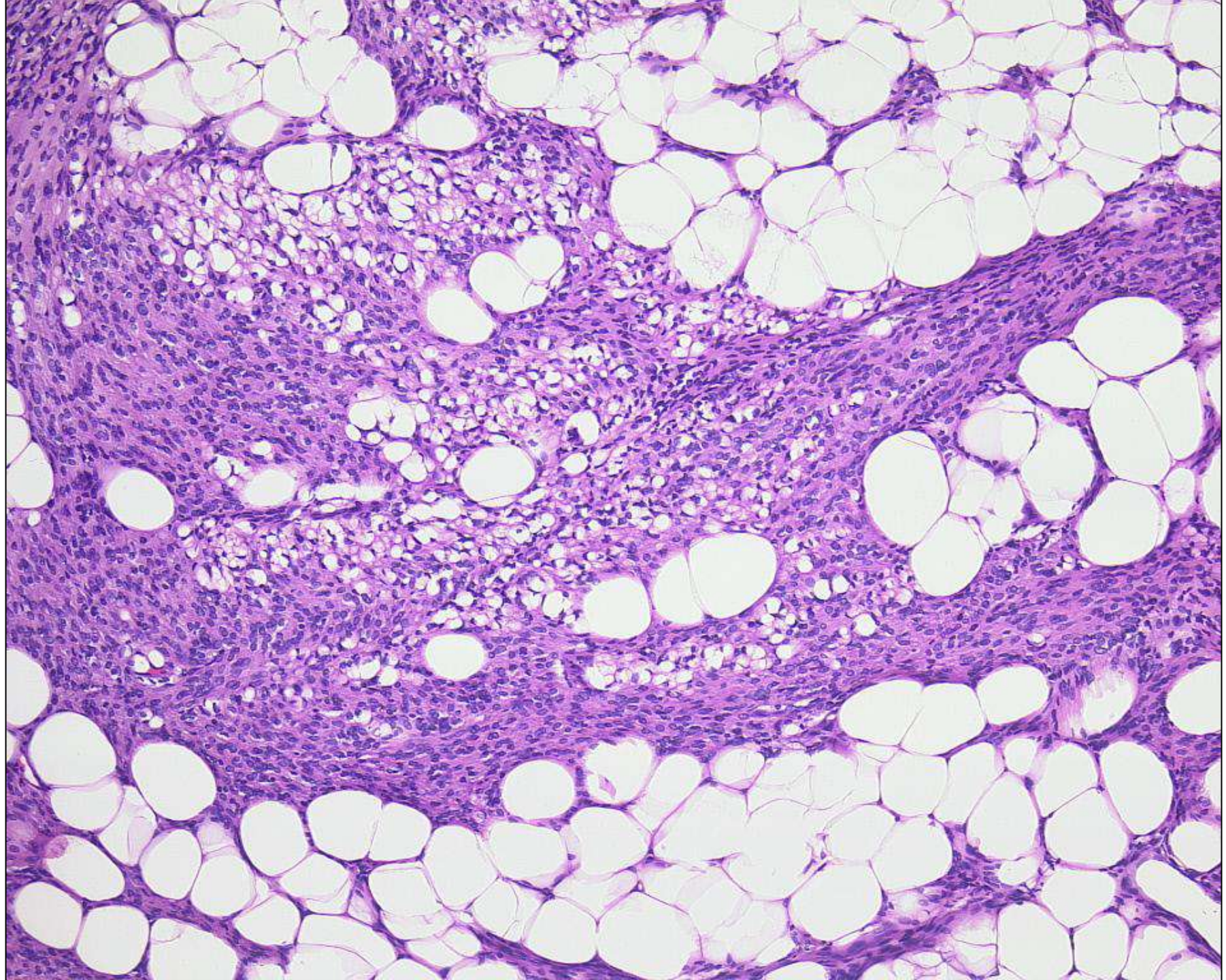


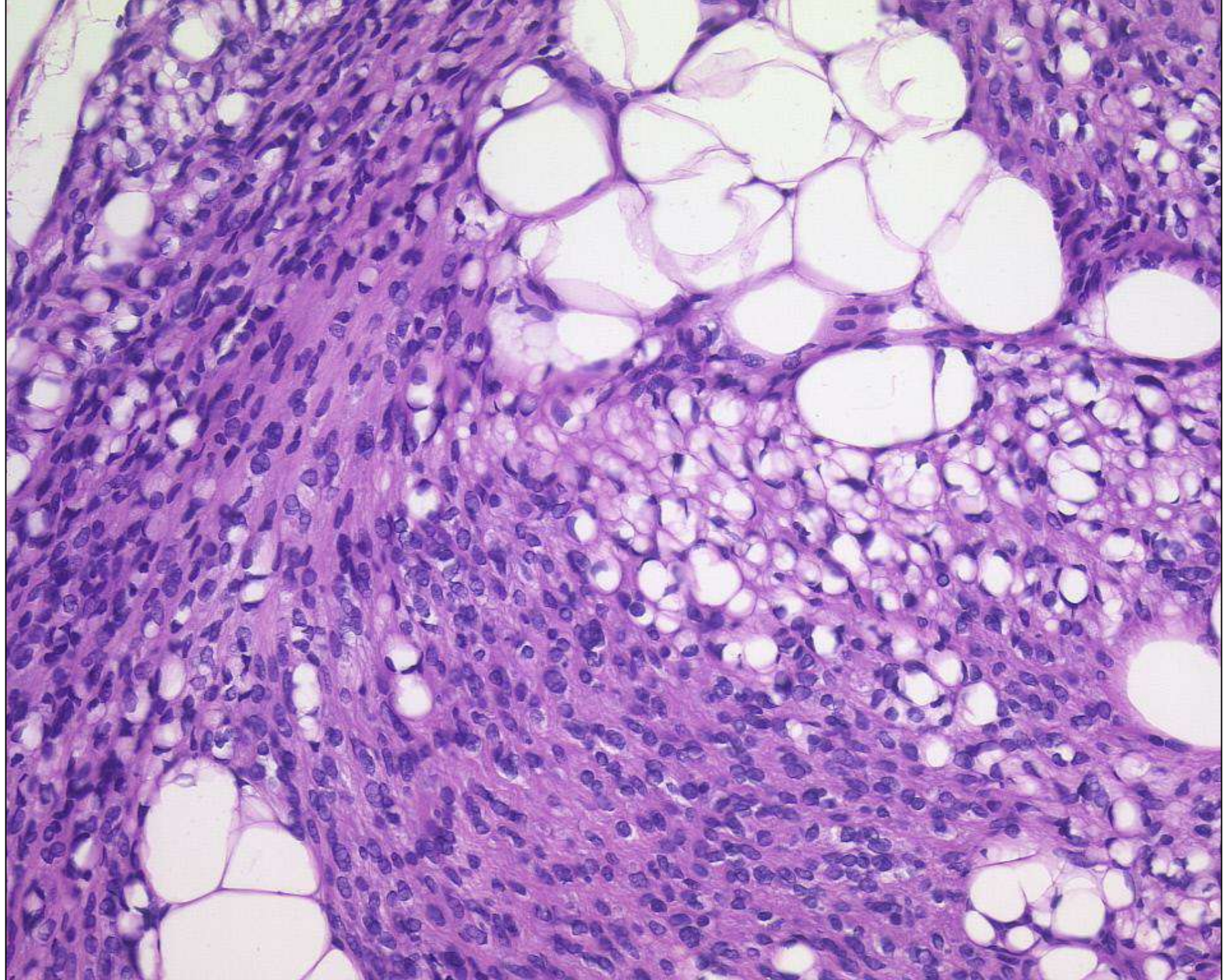
Case 13: F, 3 months, back of left foot

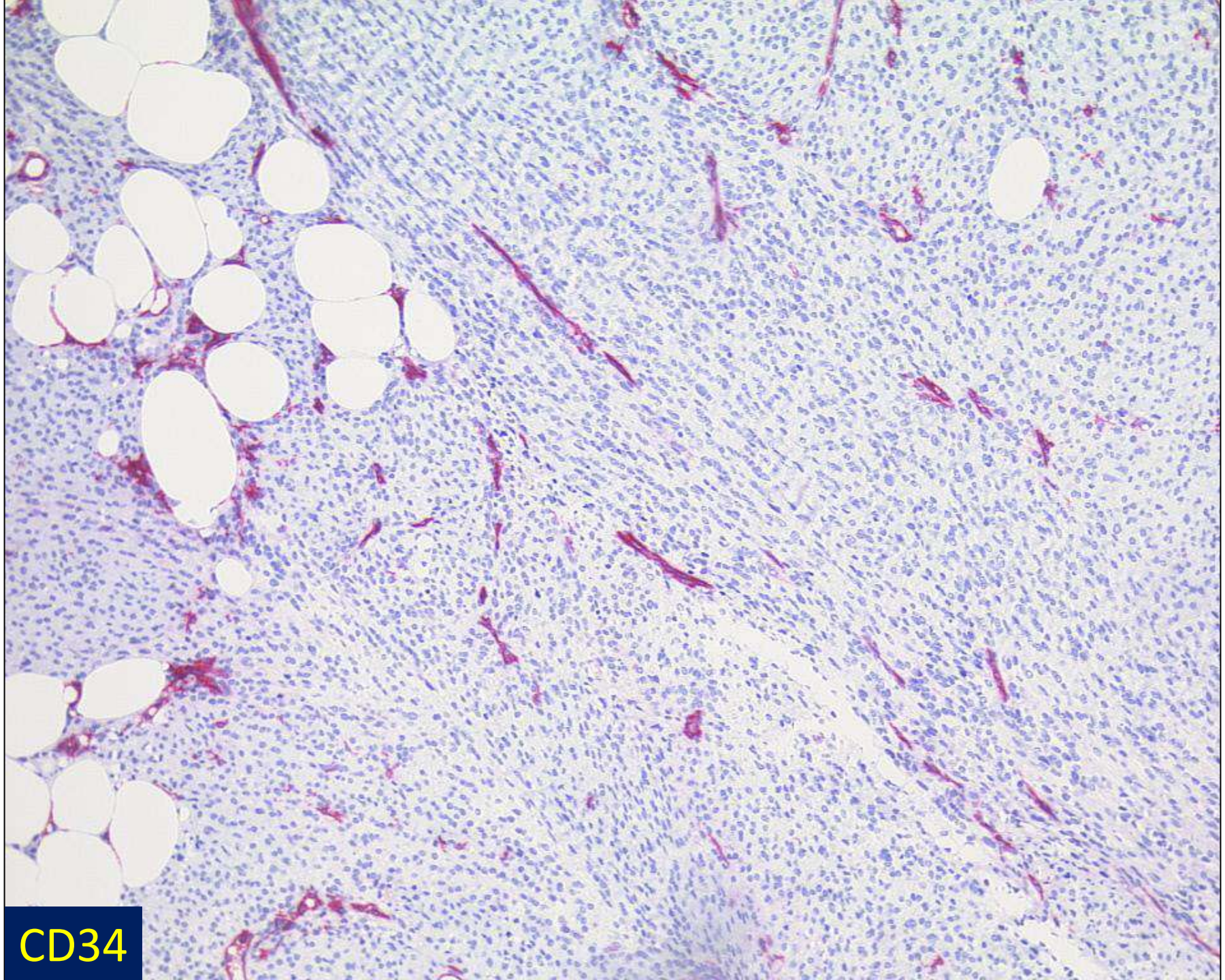


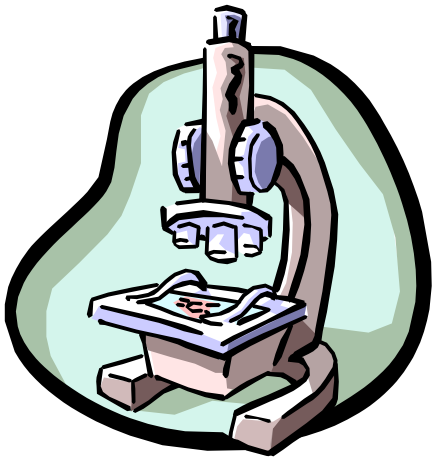









CD34



# Diagnosis Case 13

## Lipofibromatosis

# A clinicopathologic study of 45 pediatric soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis

Fetsch J et al. Am J Surg Pathol 2000; 24: 1491-1500

32 M, 12 F, 1 ?, 8 tumours were present at birth, 1 - 7 cm

distal extremities >> trunk/head

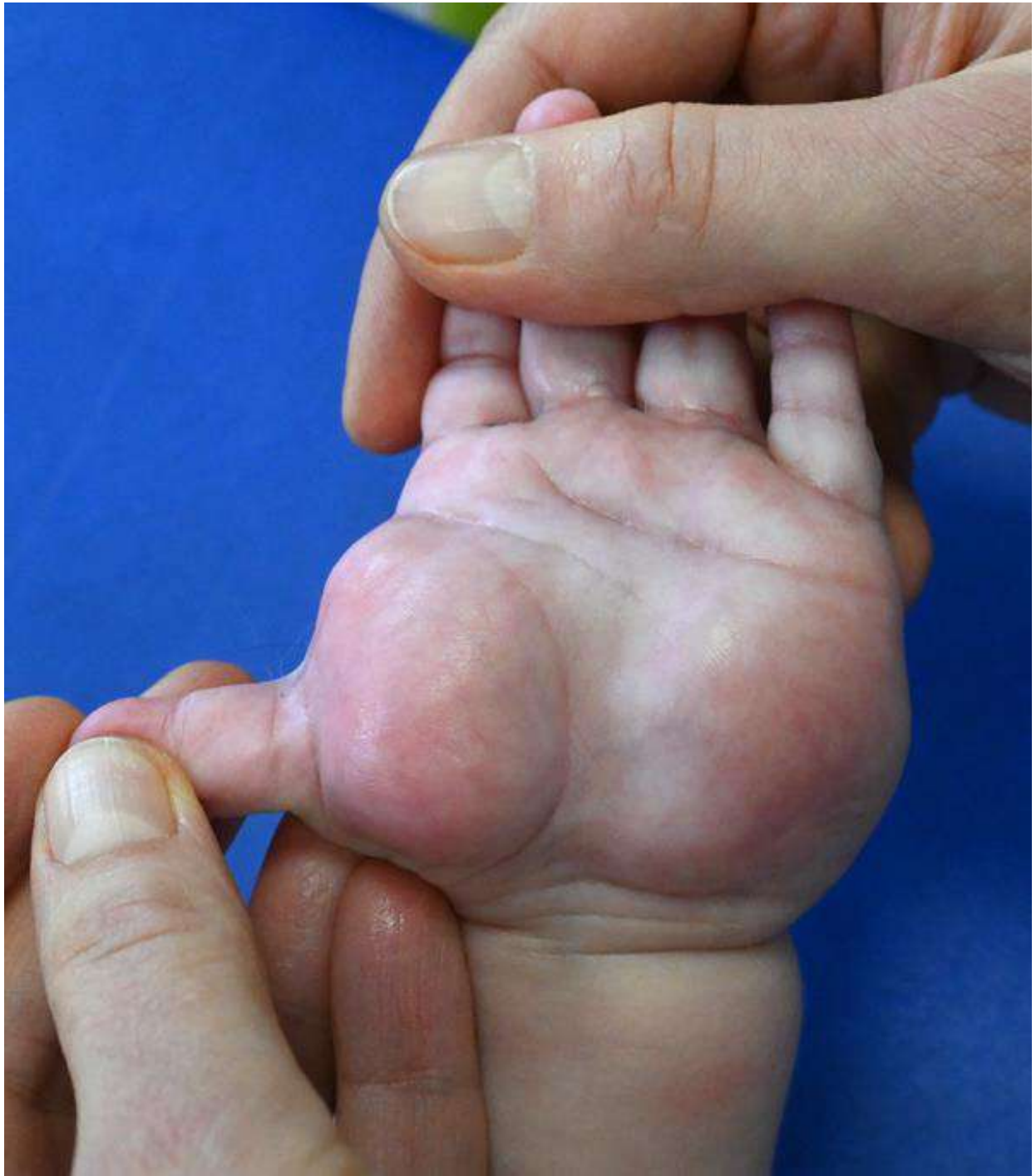
abundant adipose tissue + spindle shaped fibroblastic elements

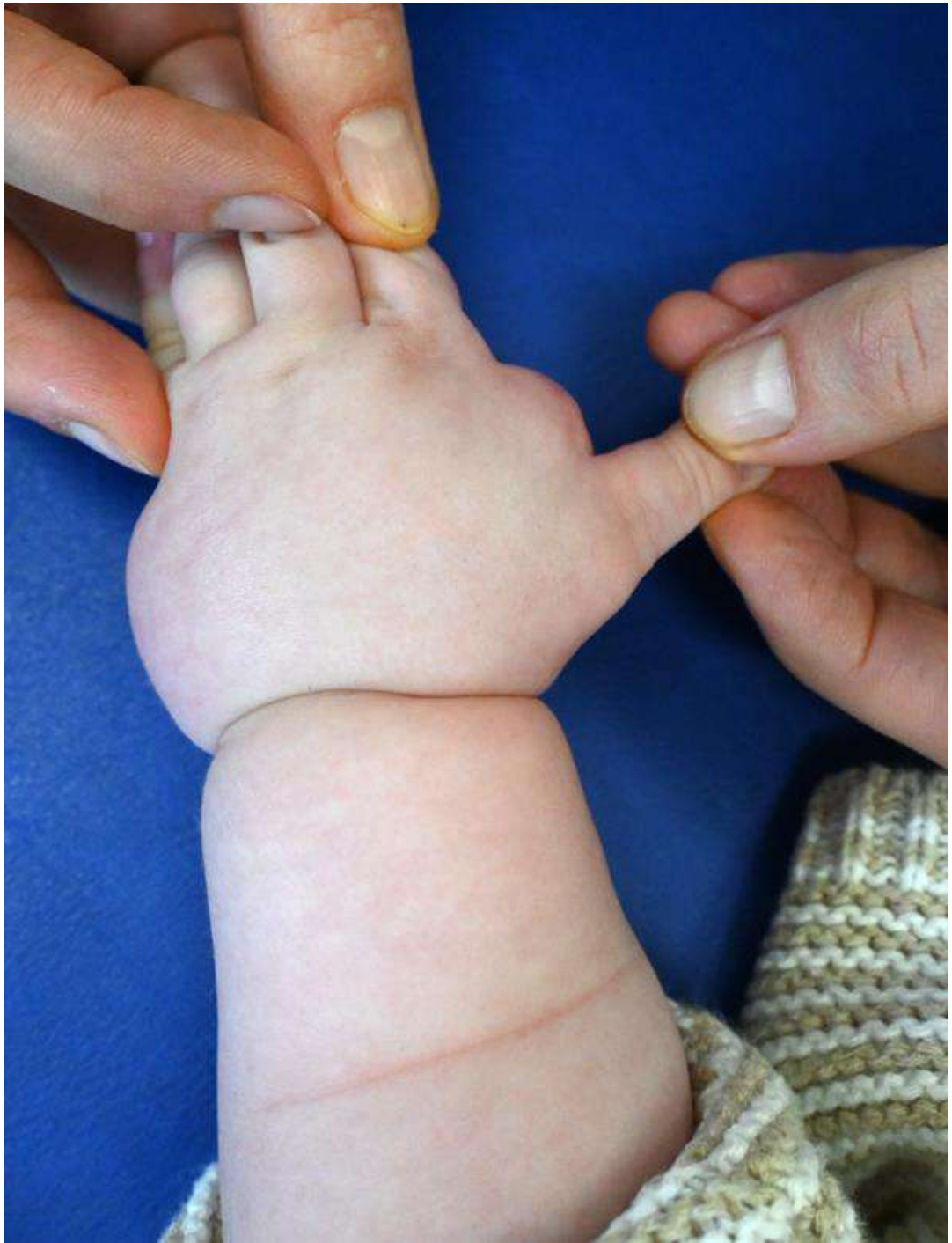
limited cytologic atypia and proliferative activity

small collections of univacuolated cells (lipoblast-like cells)

focal expression of CD34, CD99, ASMA (desmin -)

regrowth/persistent disease in 17/22 patients (72%)





**Chromosomal rearrangements in lipofibromatosis**

Kenney B et al. Cancer Genet Cytogenet 2007; 179: 136-139

5-year-old boy

three way t(4;9;6) translocation

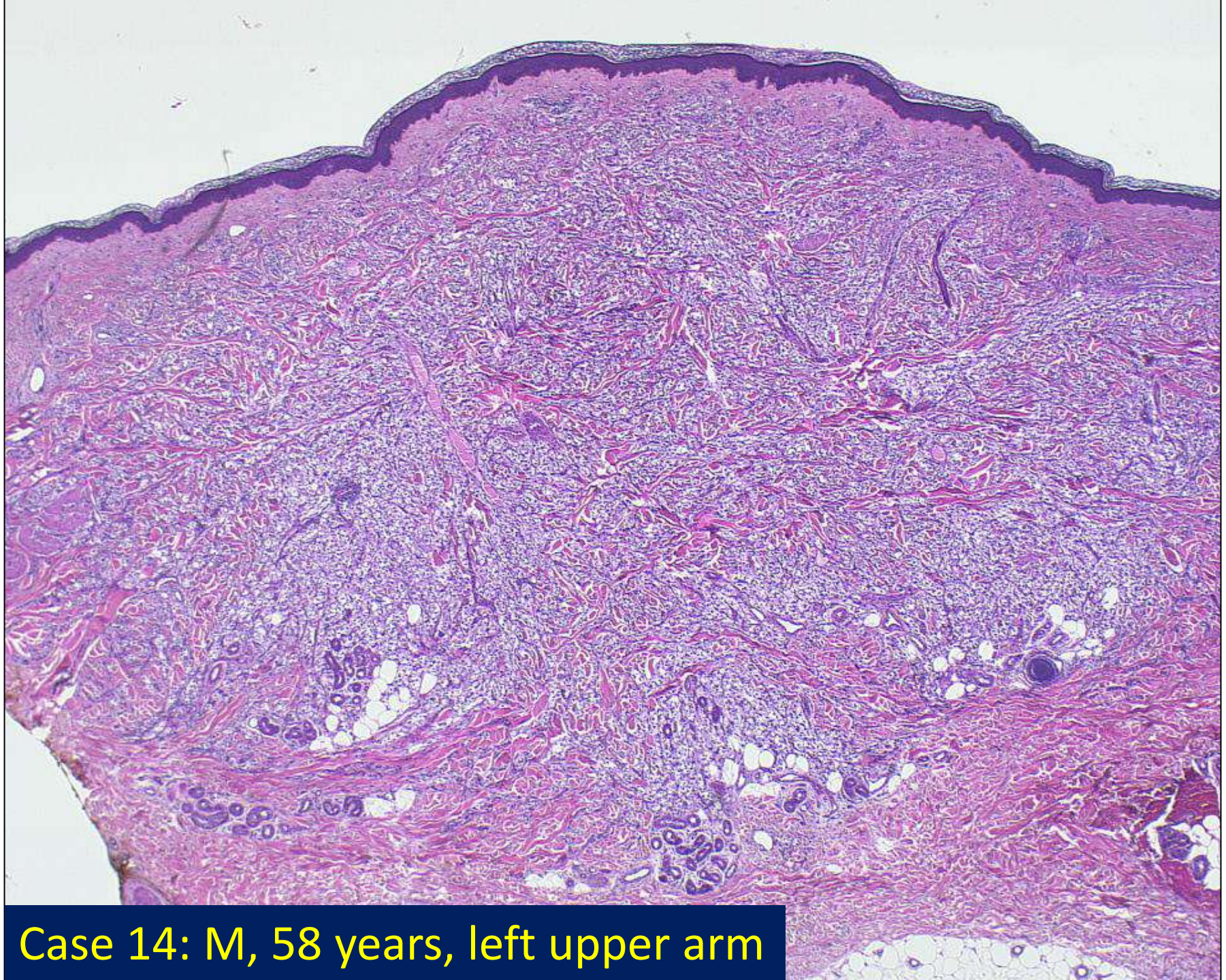
**Aberrant receptor tyrosine kinase signaling in lipofibromatosis: a clincopathological and molecular genetic study in 20 cases**

Al-Ibraheemi et al. Mod Pathol 2019; 32: 423-434

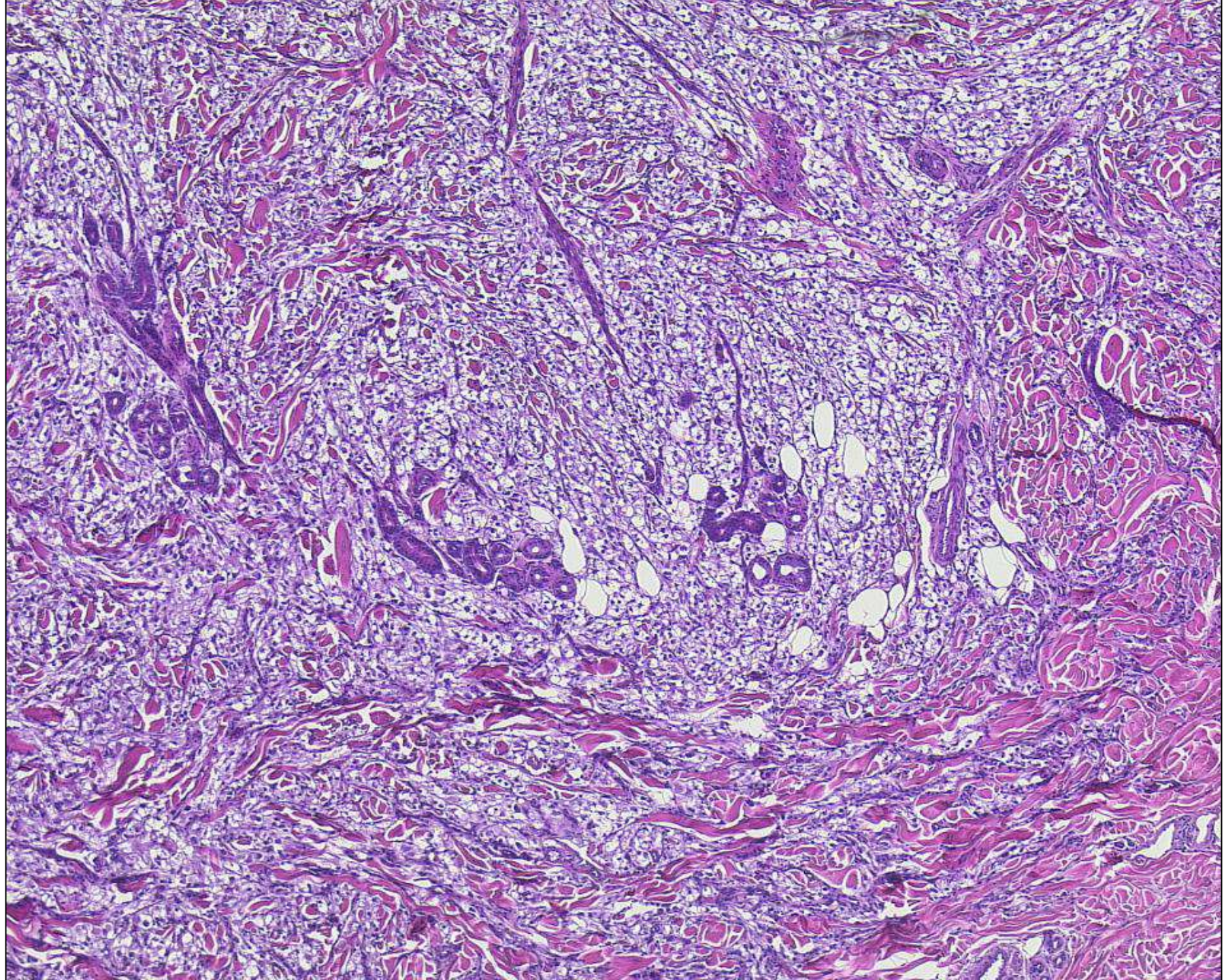
14 M, 6 F, 1 month-14 years

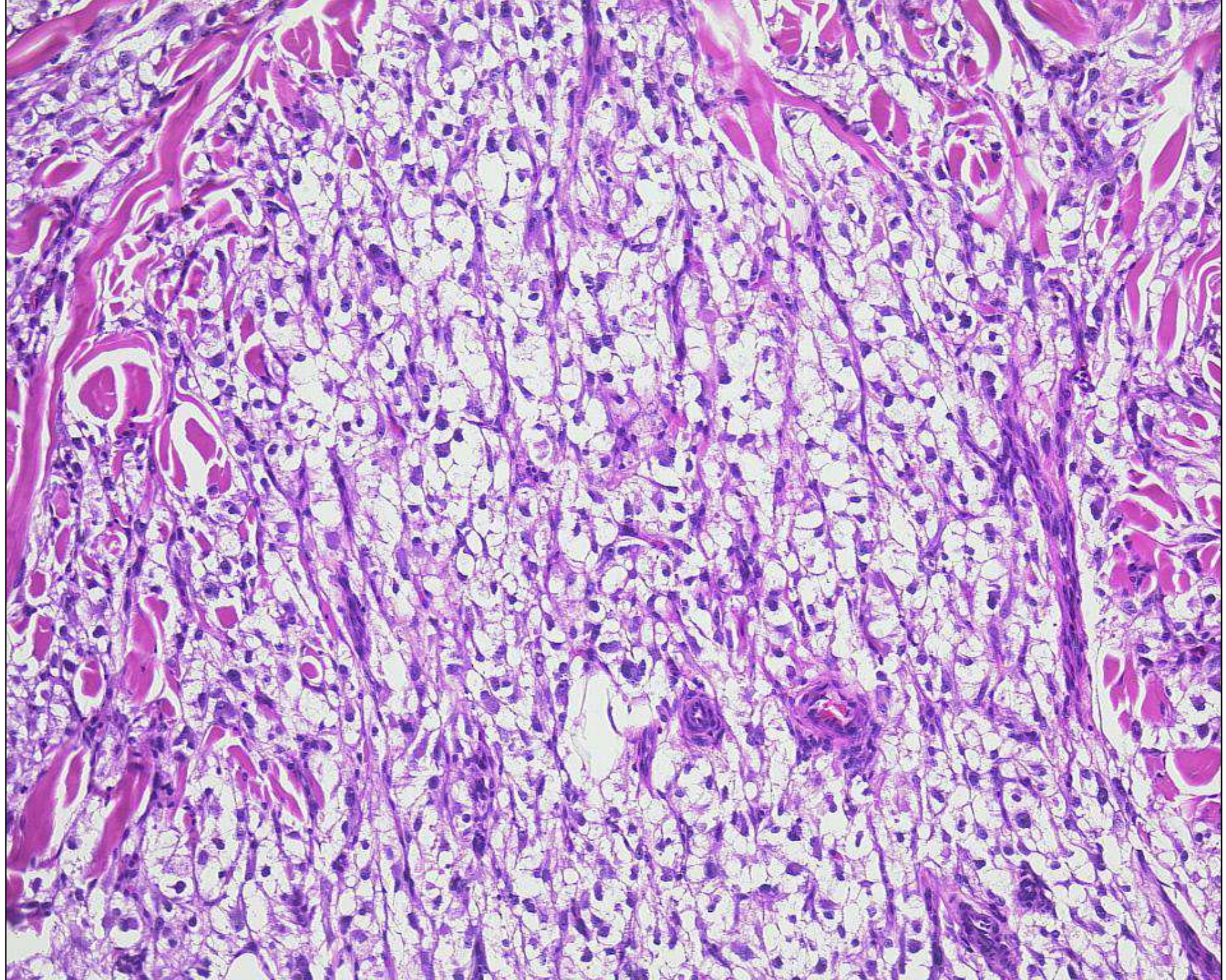
*FN1::EGF* in 4 cases (similar to calcifying aponeurotic fibroma)

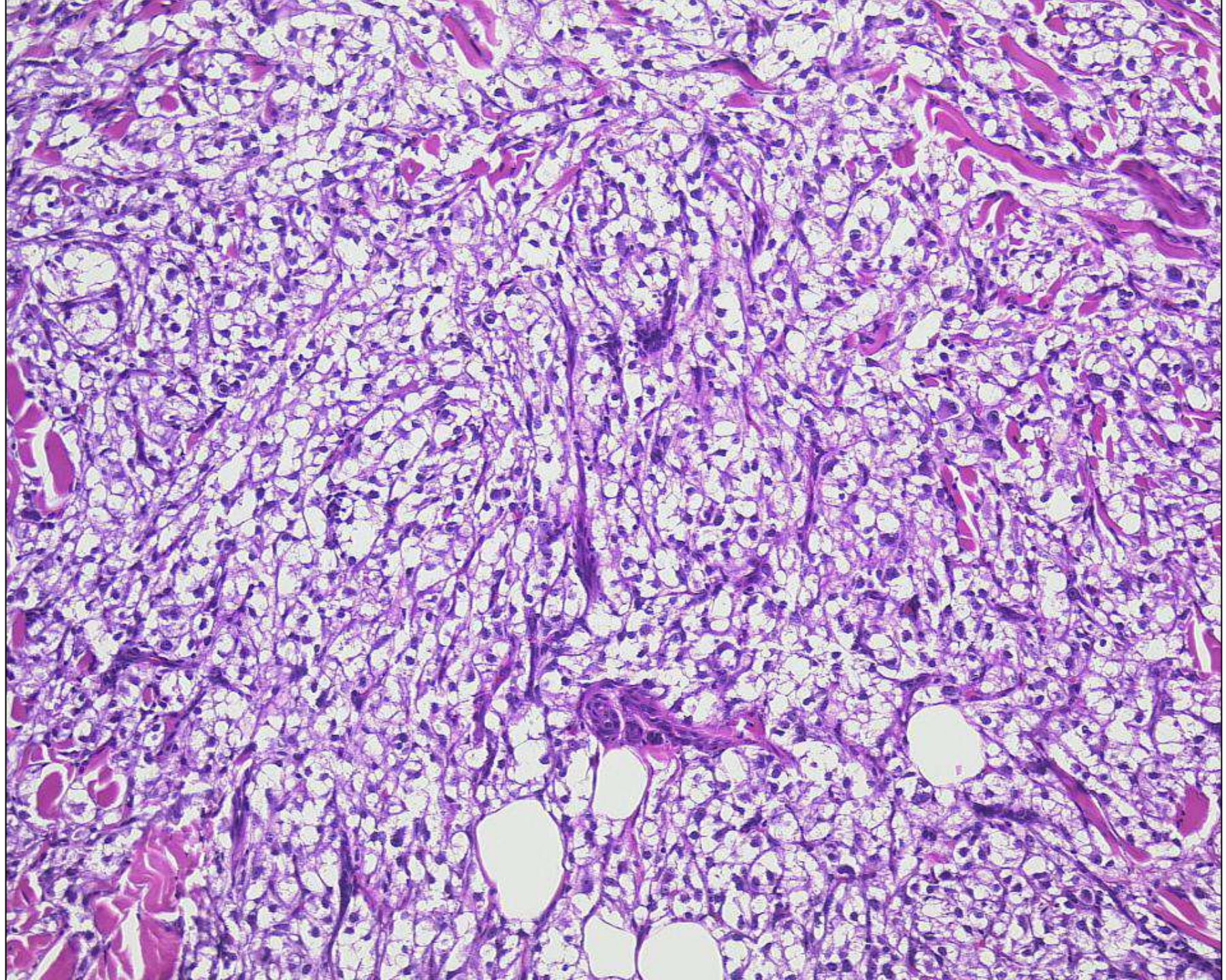
activation of the PI3K/Akt/mTOR pathway

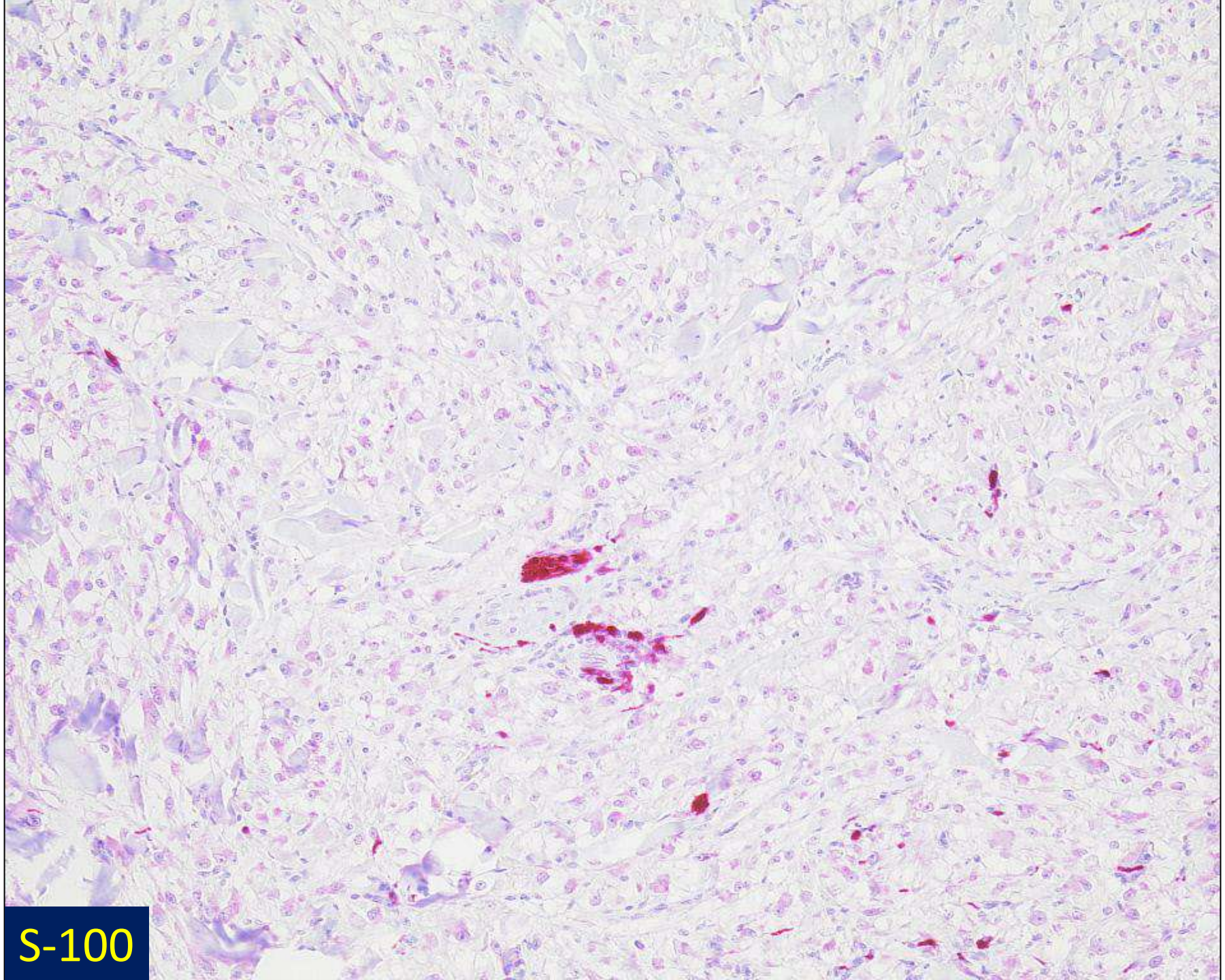


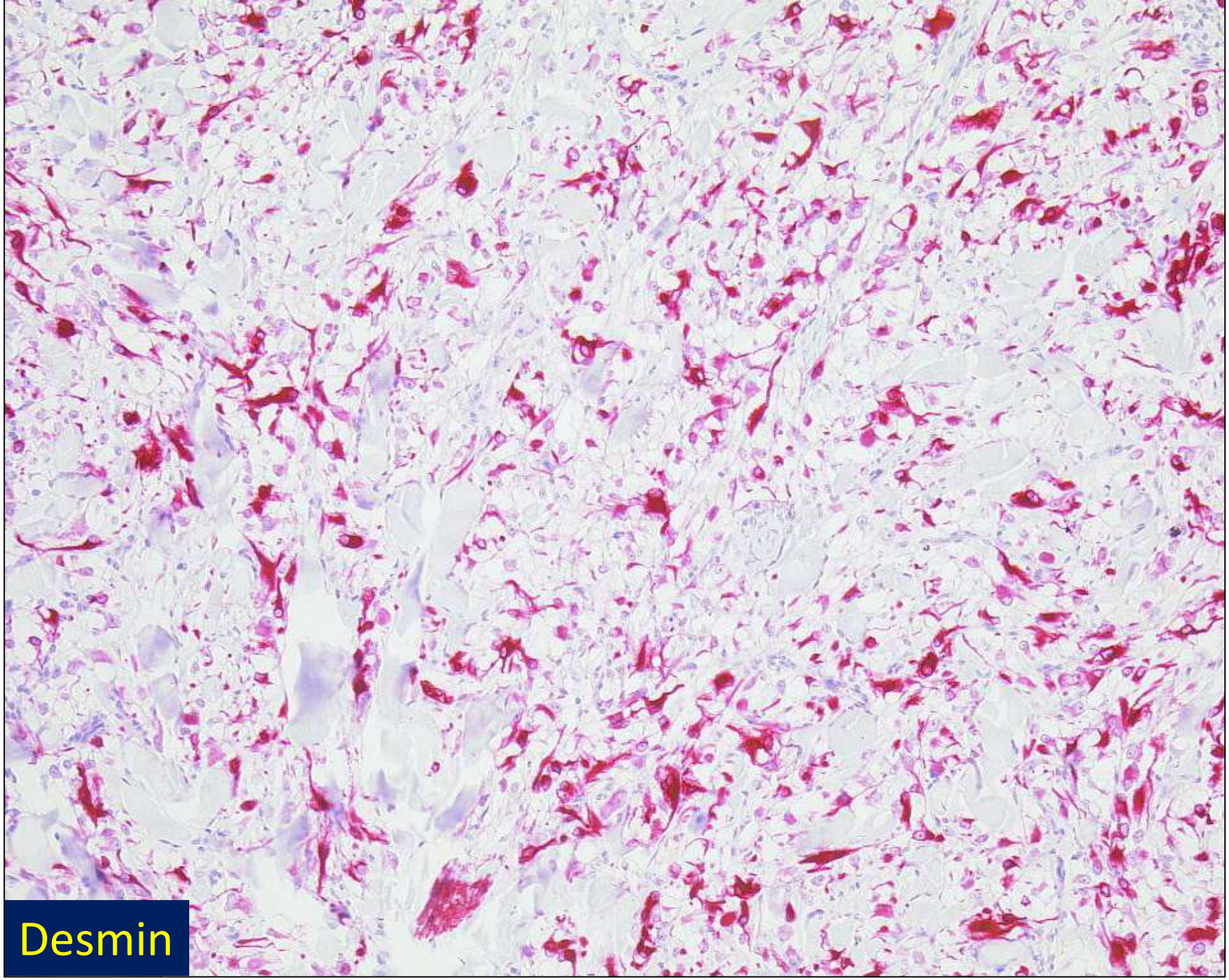
Case 14: M, 58 years, left upper arm

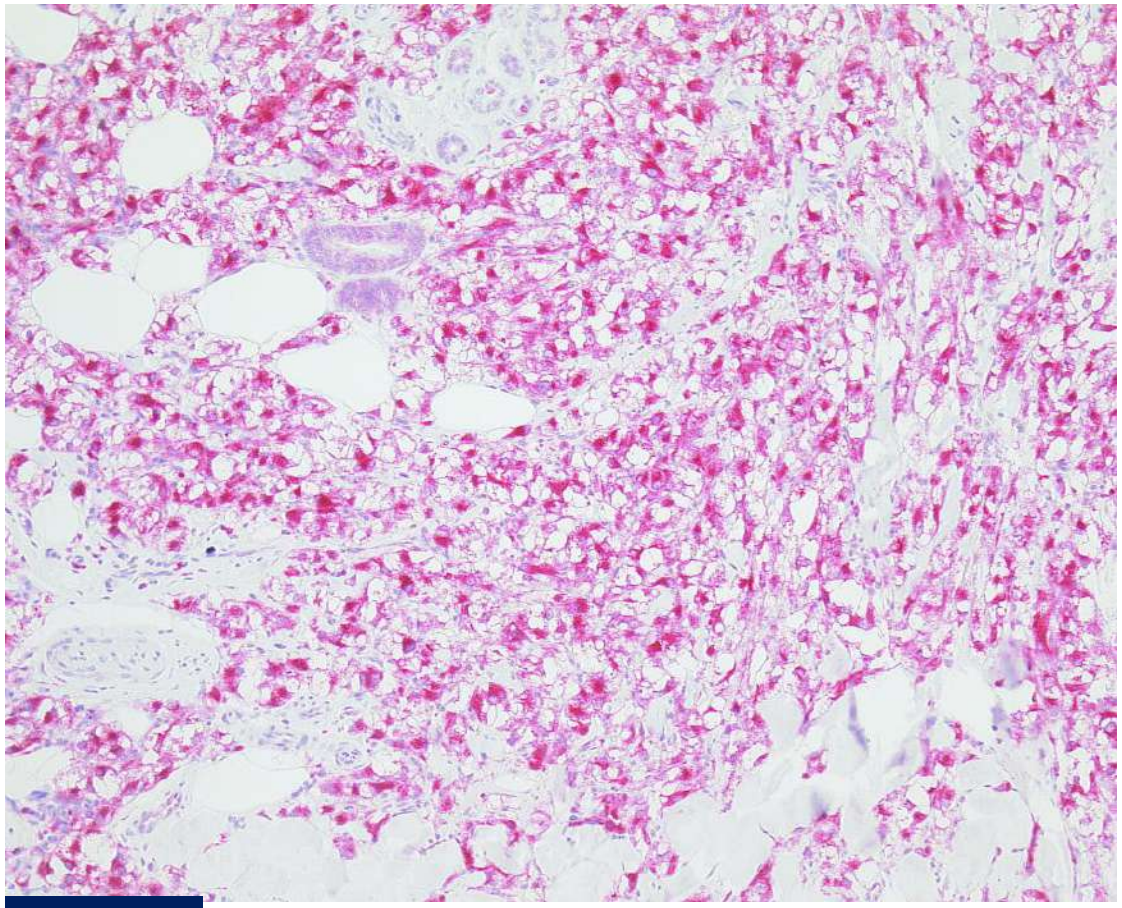




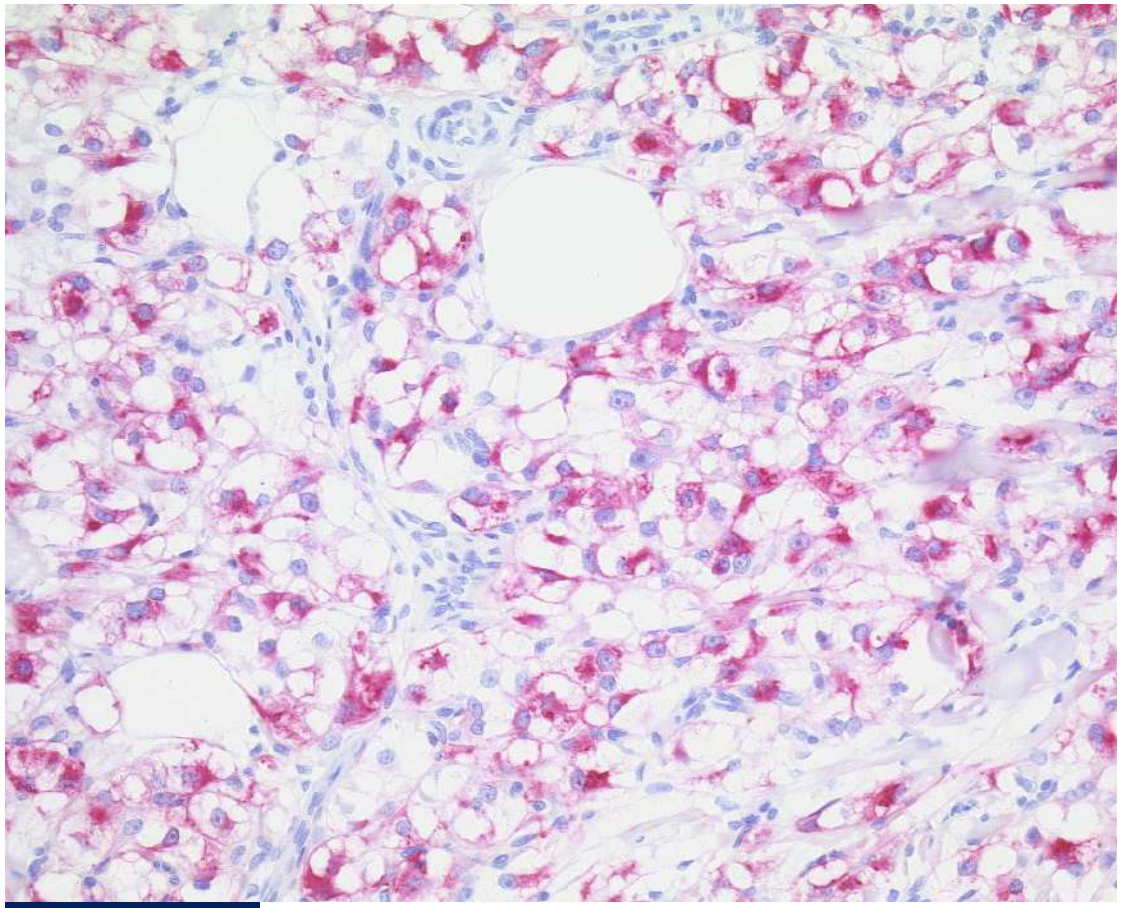



S-100

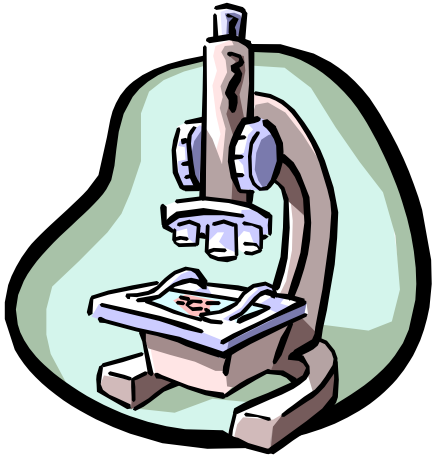

Desmin



NKIC3



HMB-45



# Diagnosis Case 14

## cutanous PEComa

# PEComa

## (neoplasms with perivascular epithelioid cell differentiation)

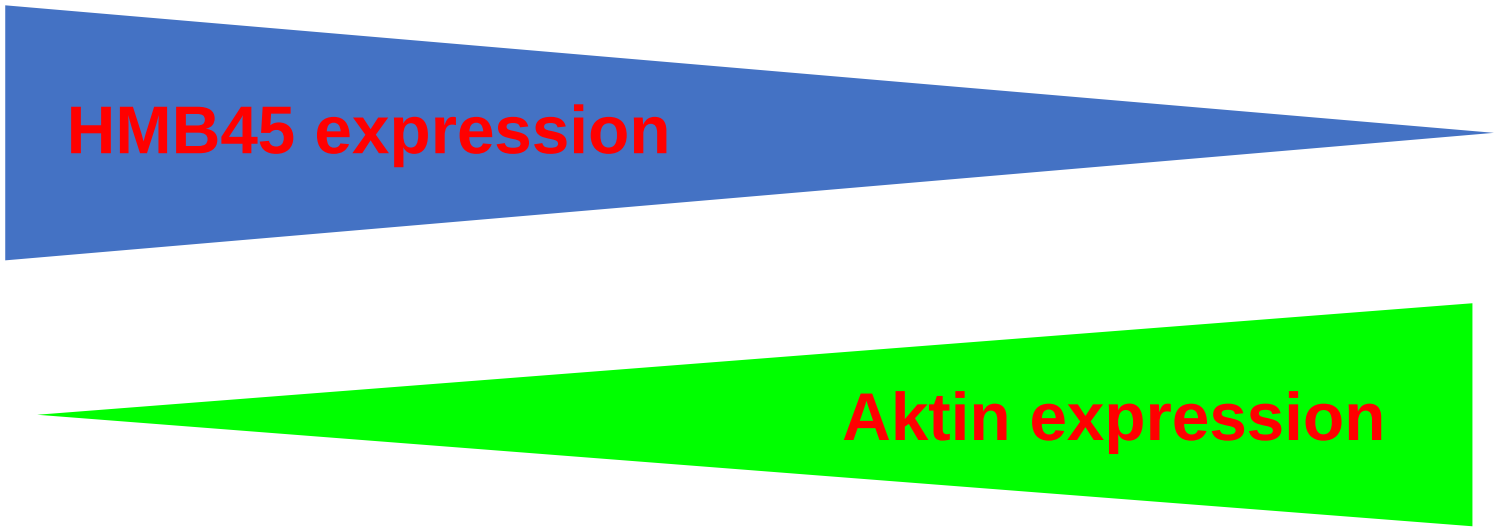
- heterogenic family of neoplasms
- adult patients, F >> M
- angiomyolipoma, clear cell „sugar“ tumour, extrapulmonal clear cell „sugar“ tumour, lymphangioleiomyomatosis, uterine PEComa, PEComa of the skin and soft tissues
- broad anatomic distribution
- *TSC* aberrations in some neoplasms
- subset with *TFE3* gene fusions (TFE3 +)

# PEC - perivascular epithelioid cell

- „histogenesis“ ?, no nonneoplastic PECs
- epithelioid, spindled tumor cells
- clear, granular, pale eosinophilic cytoplasm
- round / oval, centrally lokalised nuclei
- network of thin-walled vessels
- perivascular growth
- expression of myogenic and melanocytic markers
- chromosomal aberations (loss of 16p, 19, 17p, 1p, 18p, gains of X, 12q, 3q, 5, 2q)

# PEComas – broad morphological spectrum (Bonetti F et al. Adv Anat Pathol 1997; 4: 343)

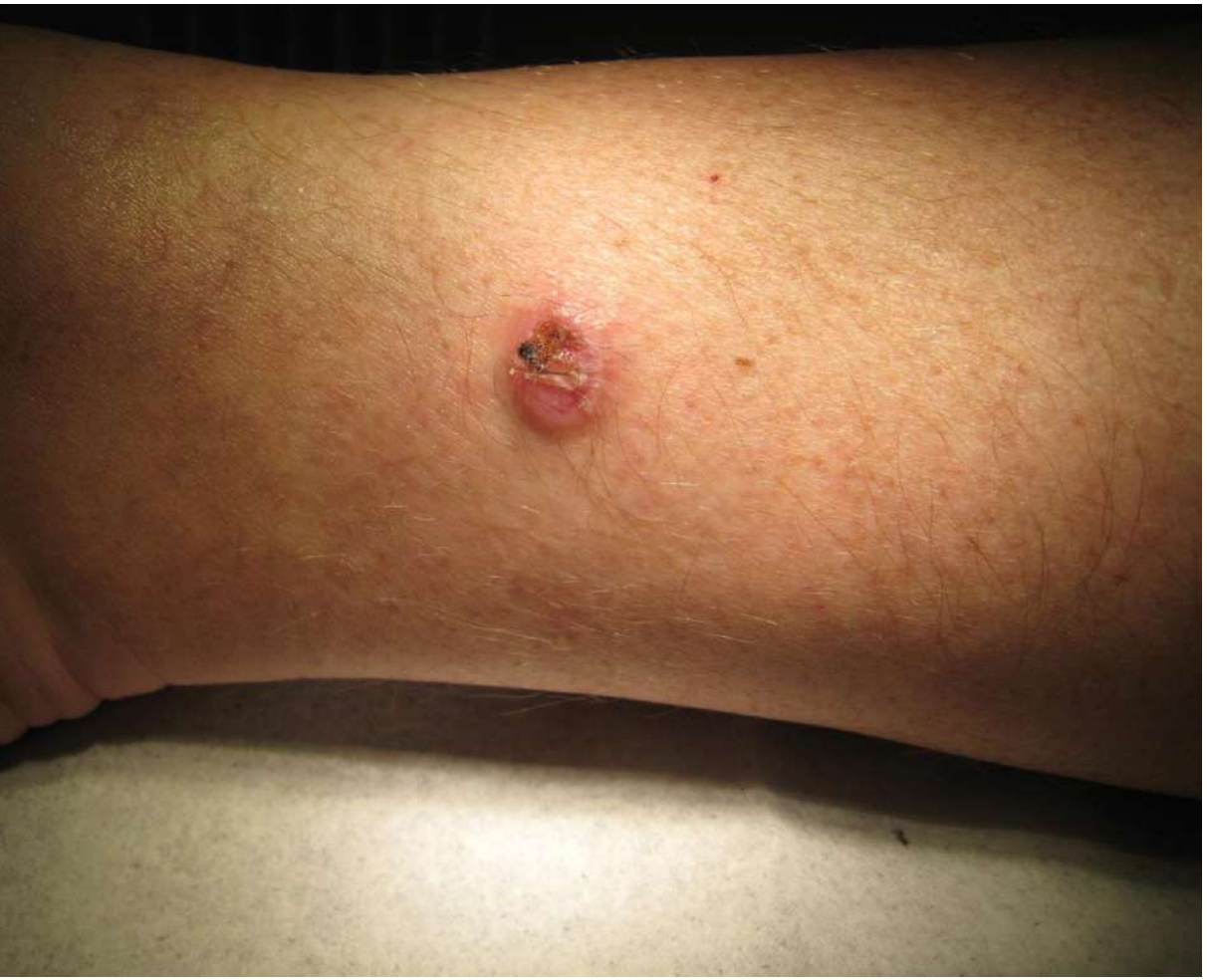
**round, cells cells** **spindled, eosinophilic cells**



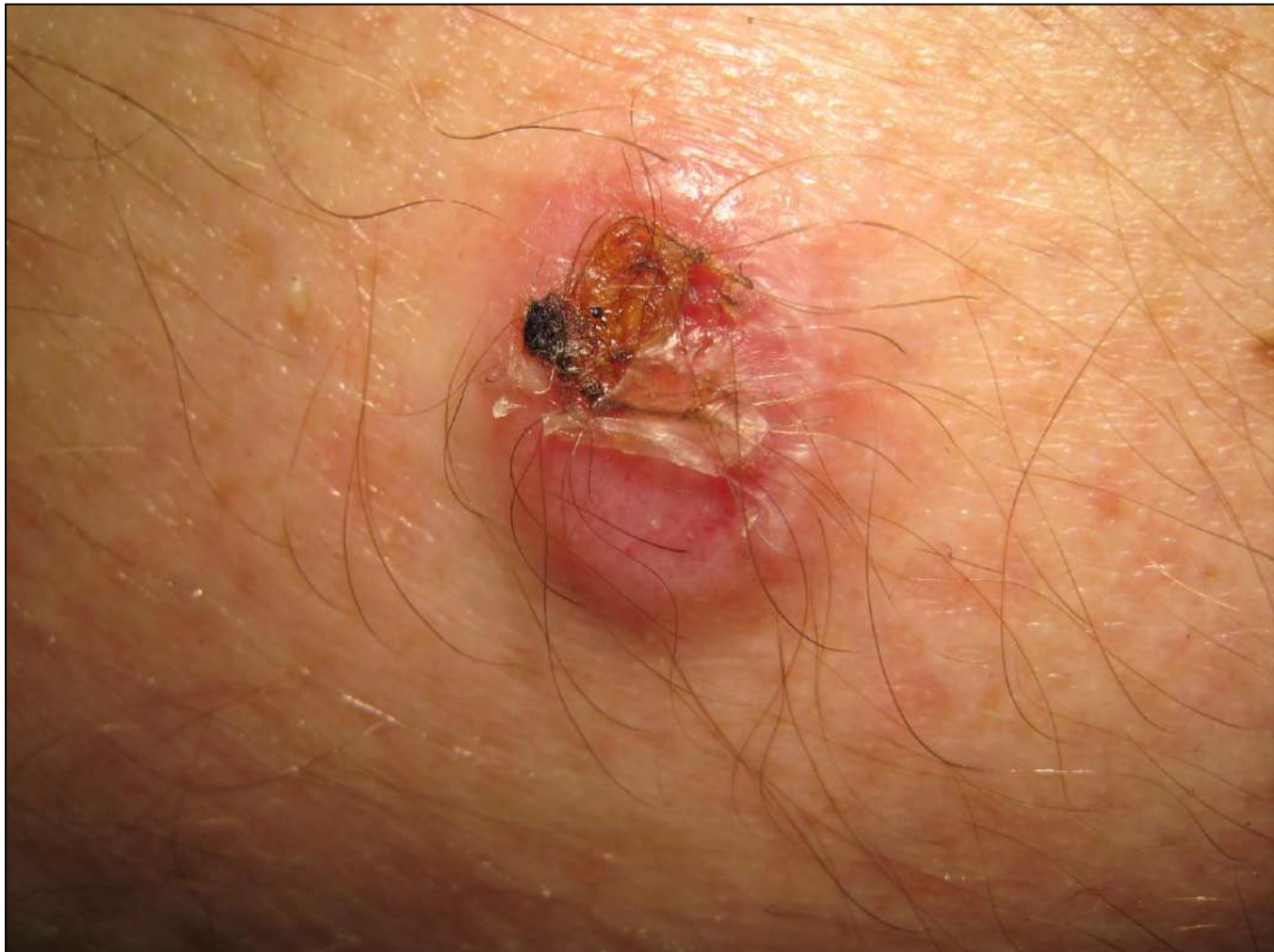
# Cutaneous PEComa*

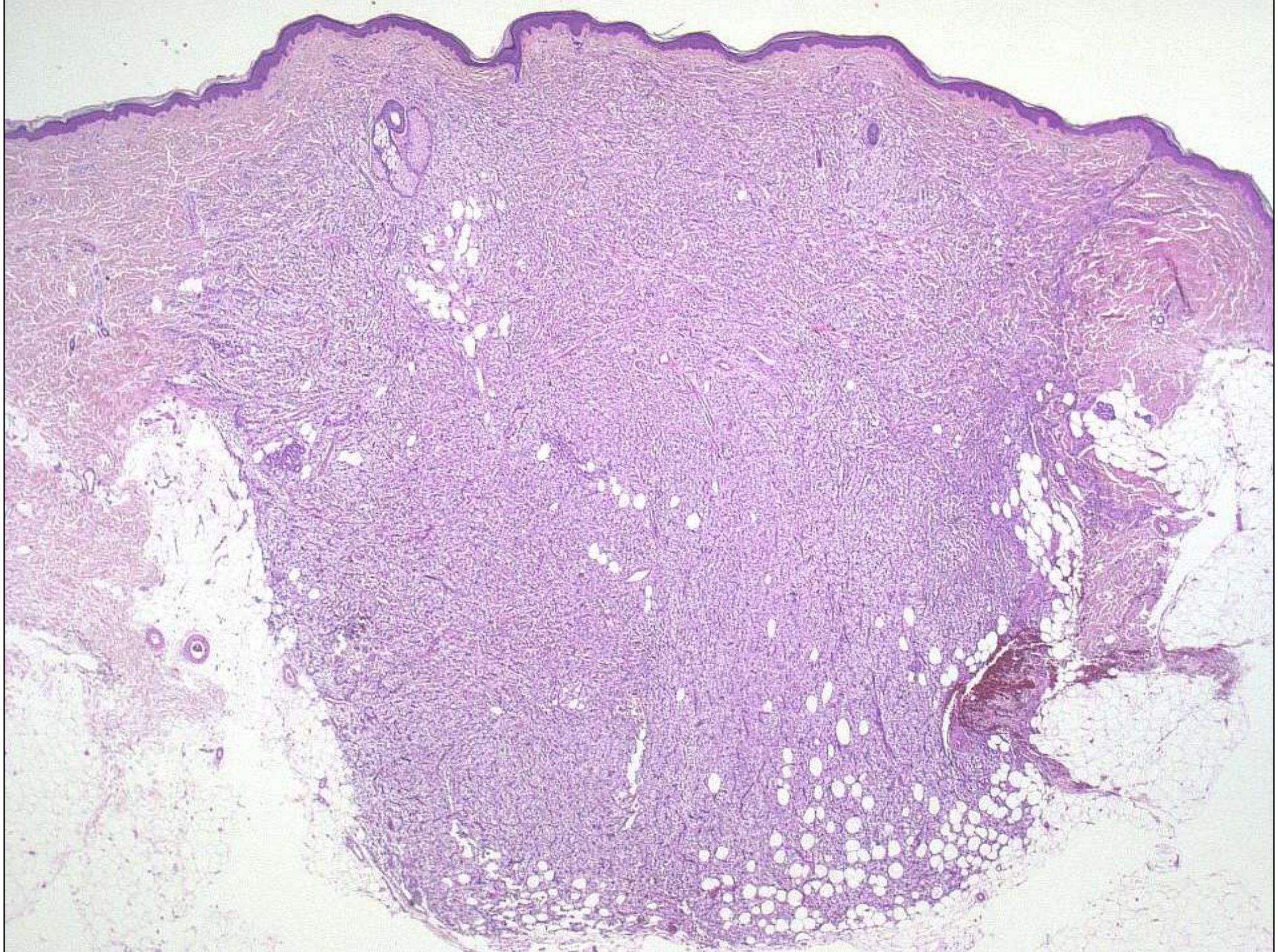
- 15 F, 2 M,  15-81 years
- 15 x extremities (lower > upper), 2 x back
- dermal neoplasms, extension into subcutis
- network of capillaries, perivascular growth
- epithelioid > spindled tumour cells
- clear > granular, pale eosinophilic cytoplasm
- HMB45 +, MiTF1 +, NKIC3 +, Melan-A +/-,
  S-100 -, ASMA + (2), desmin +(6), CK -, h-caldesmon -, calponin –

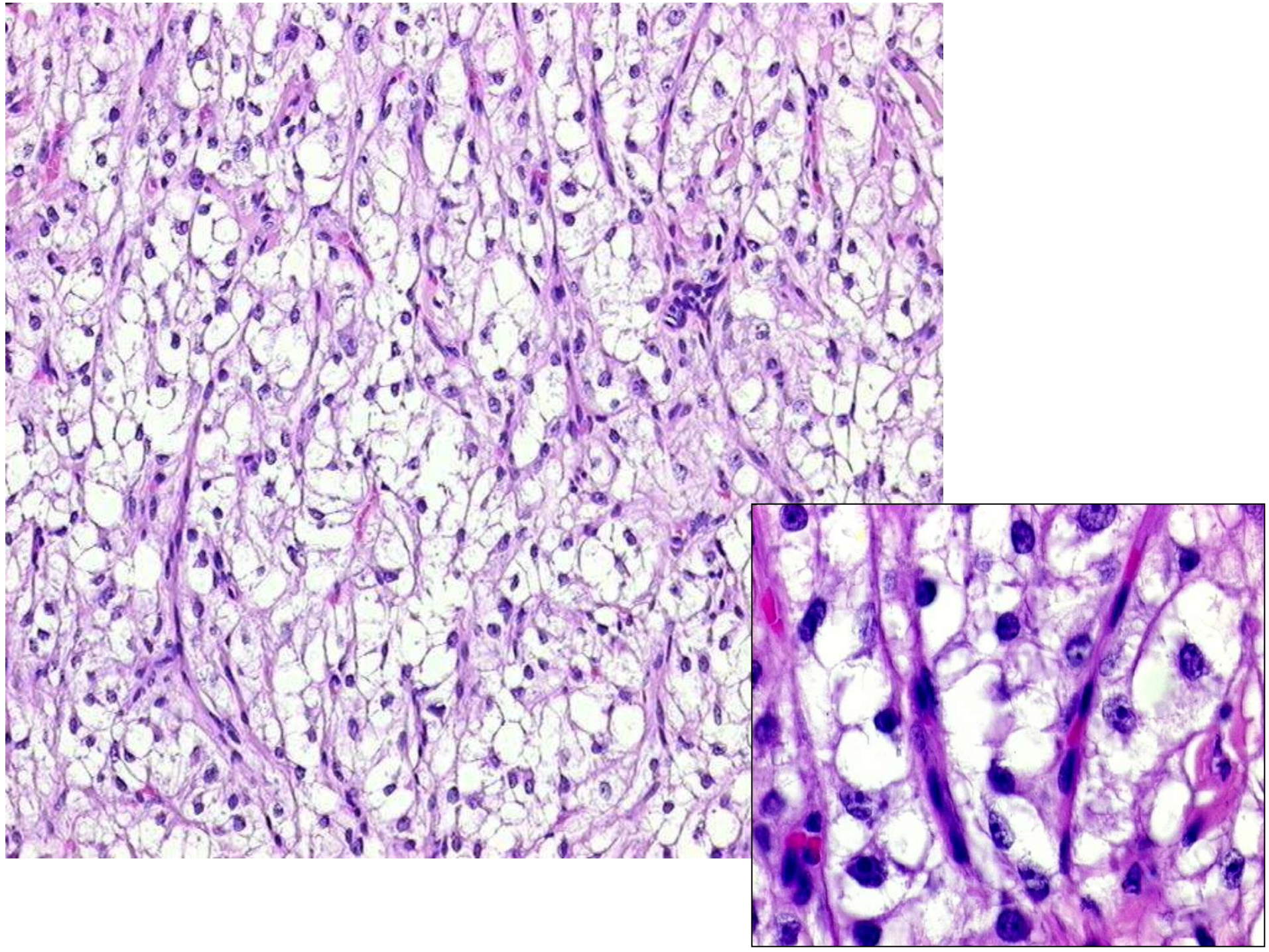
* Mentzel T et al. Histopathology 2005; 46: 498
  Liegl B et al. AJSP 2008; 32: 608

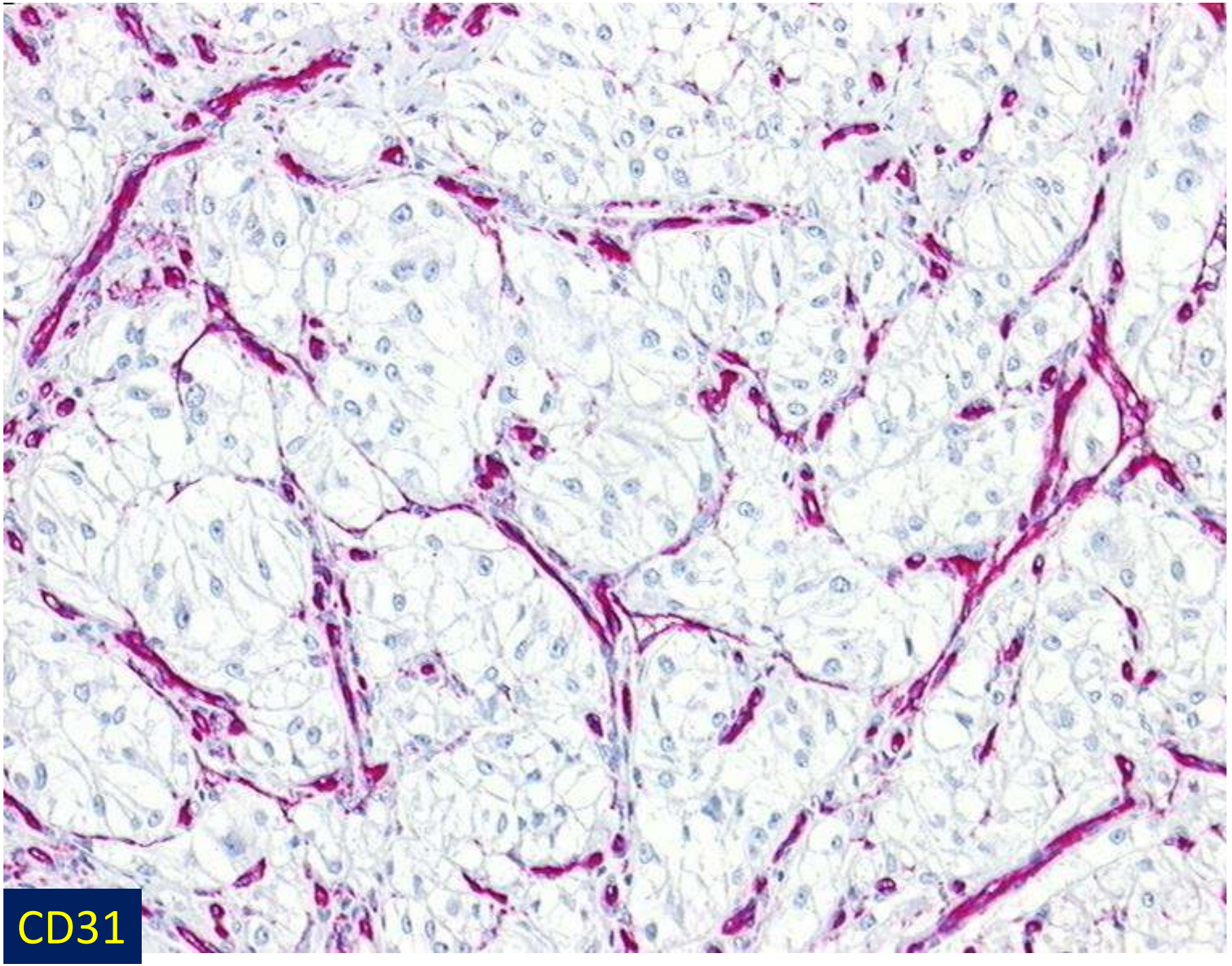


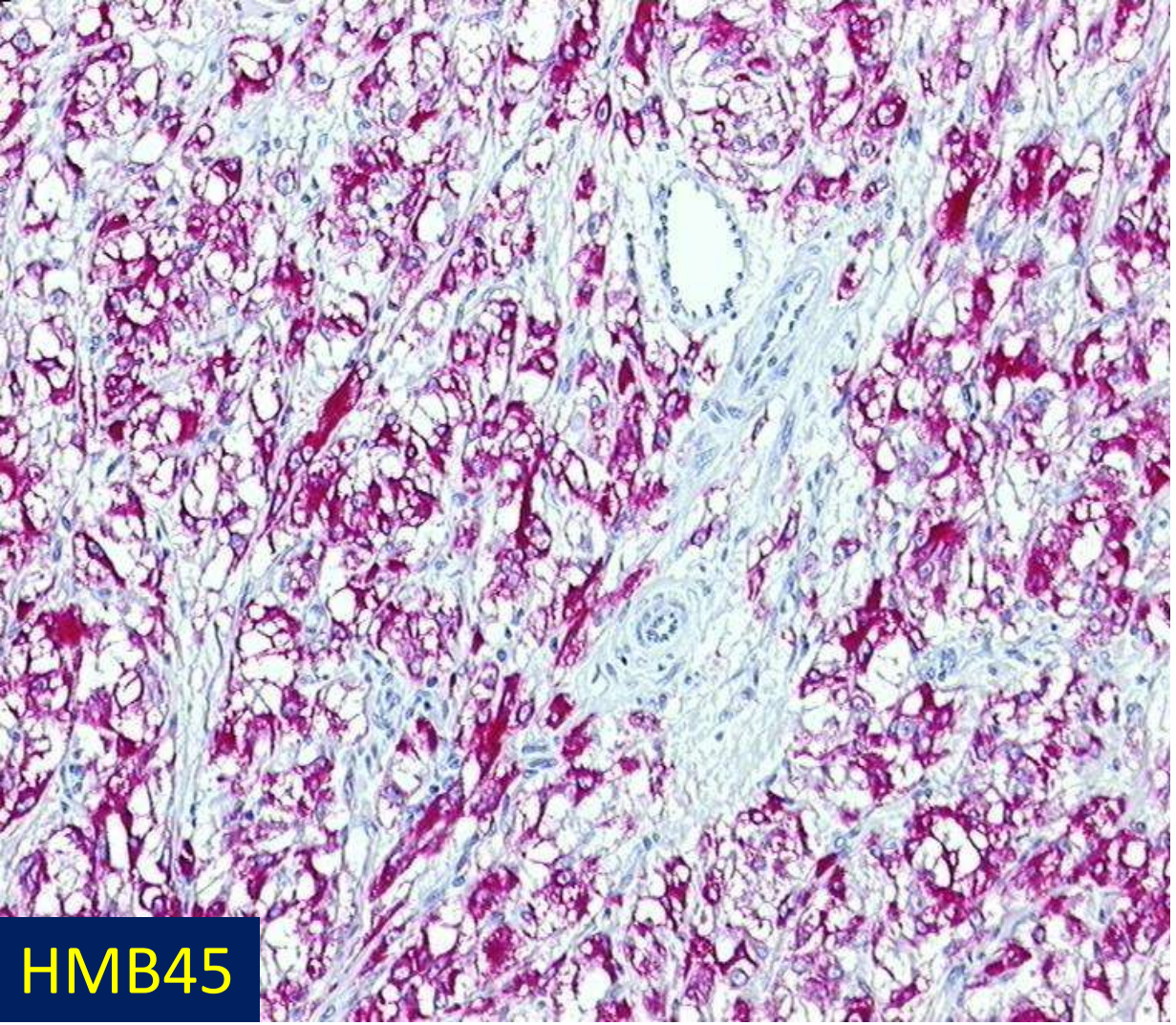
# M, 41 Jahre

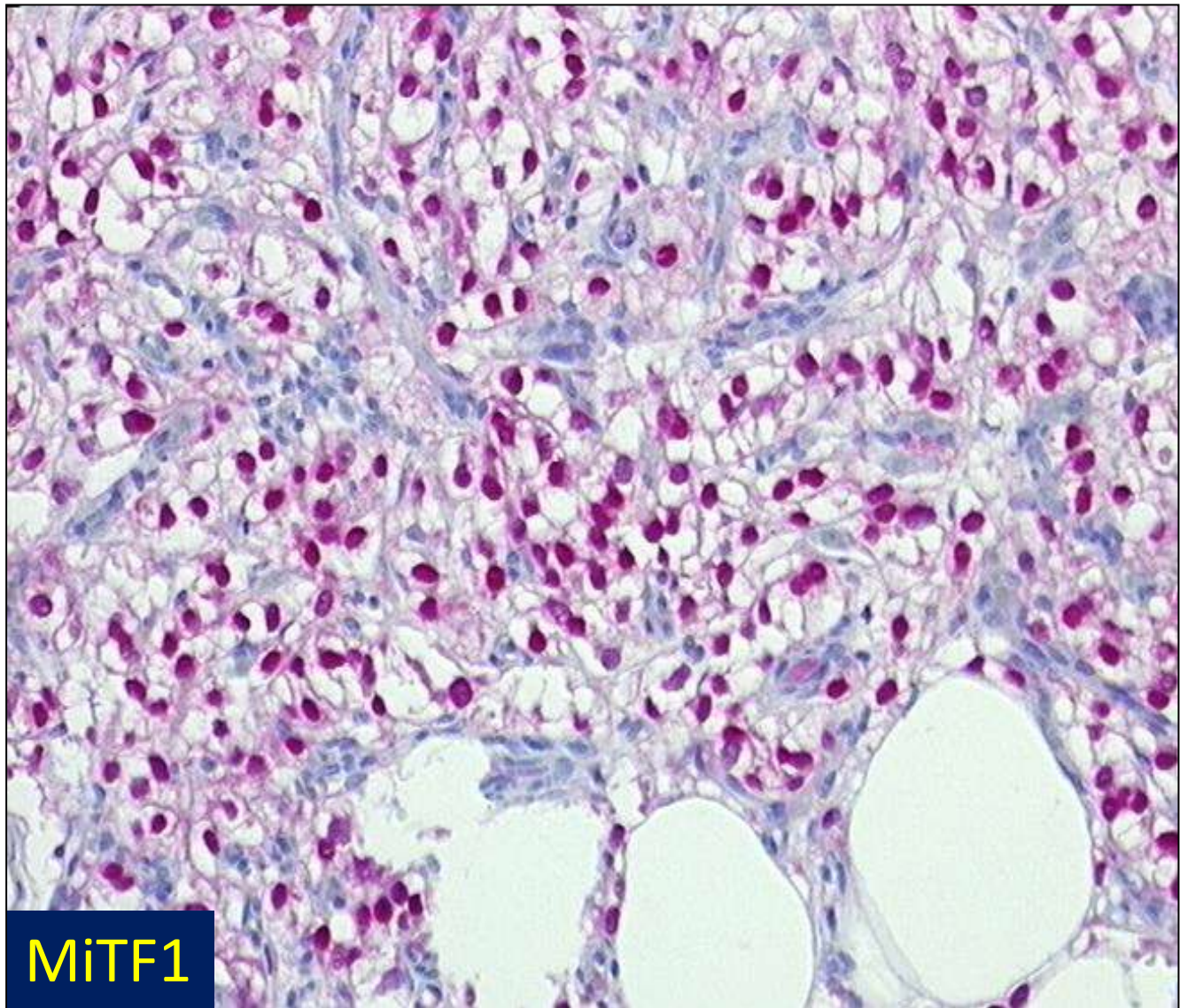


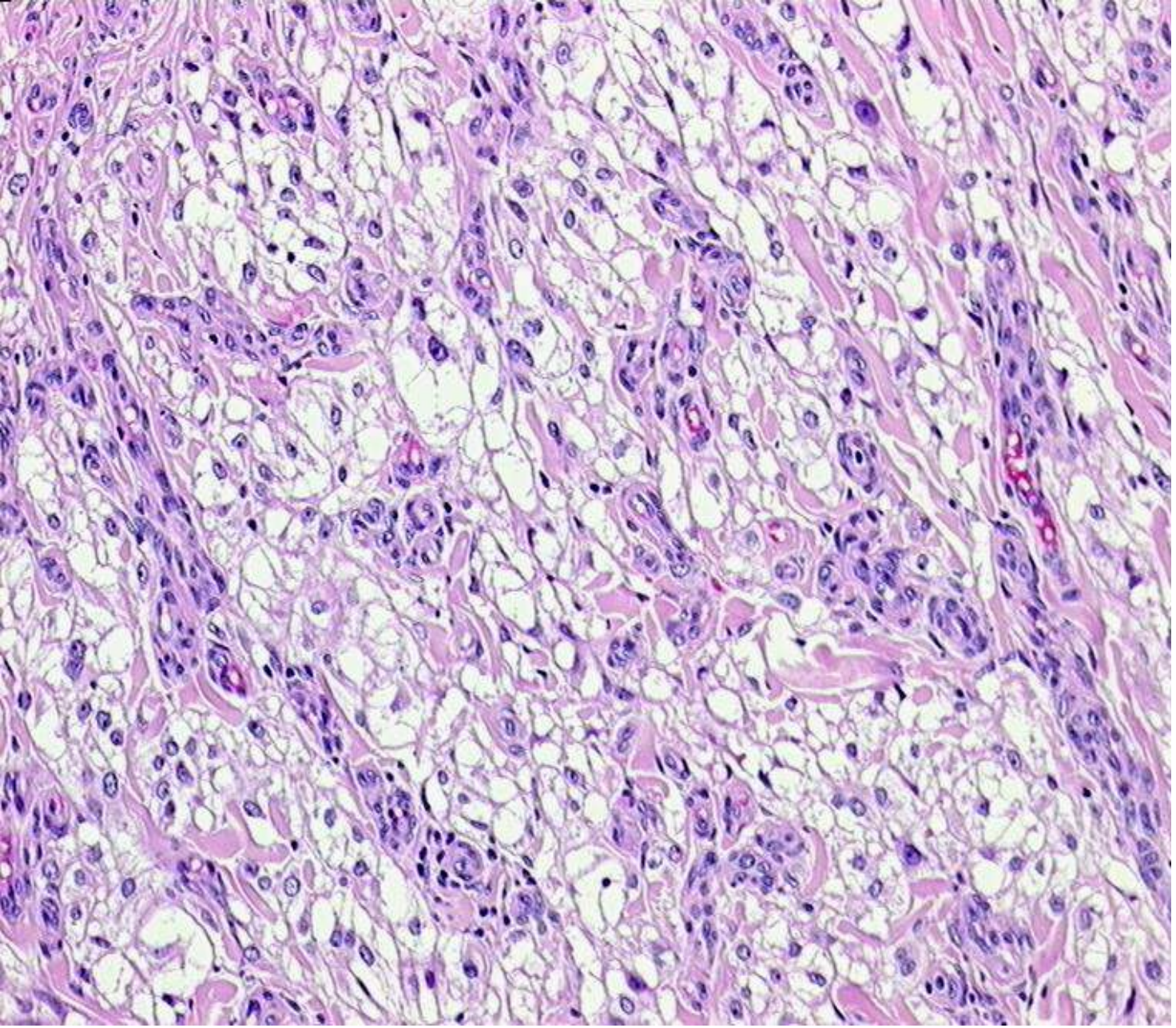


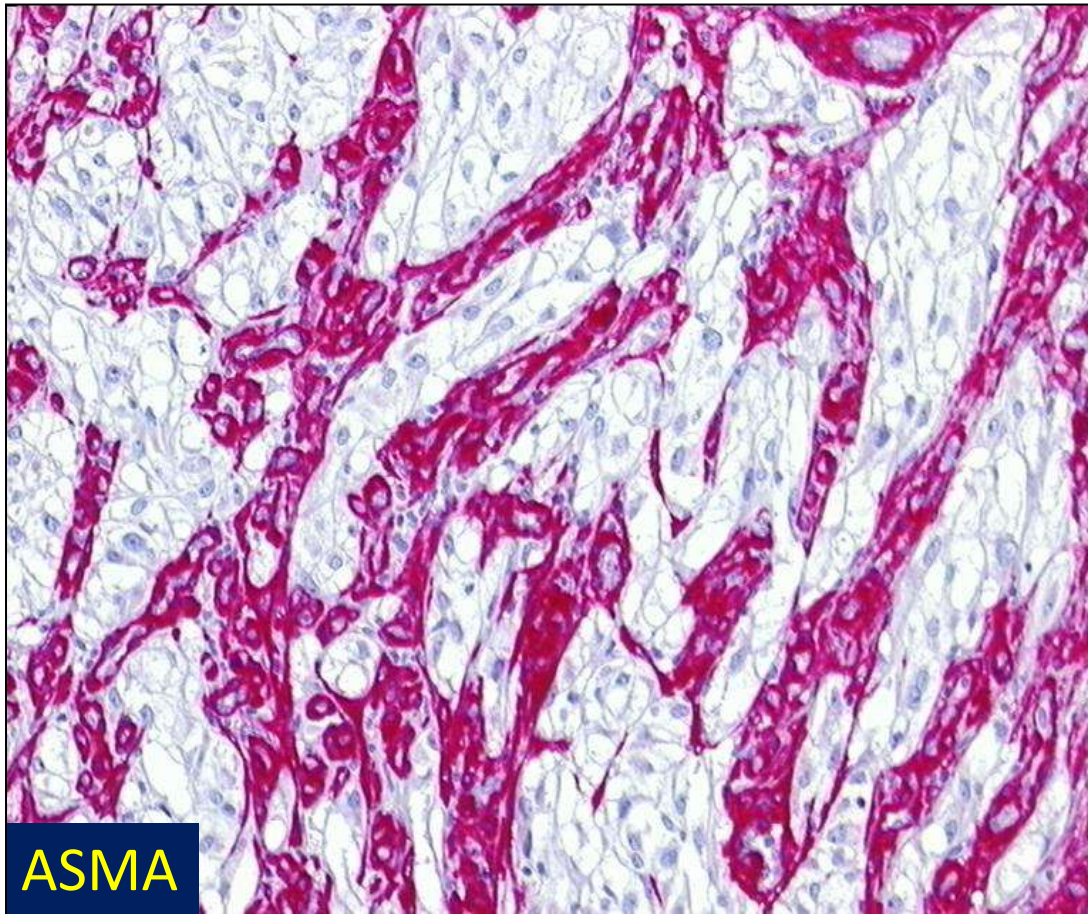


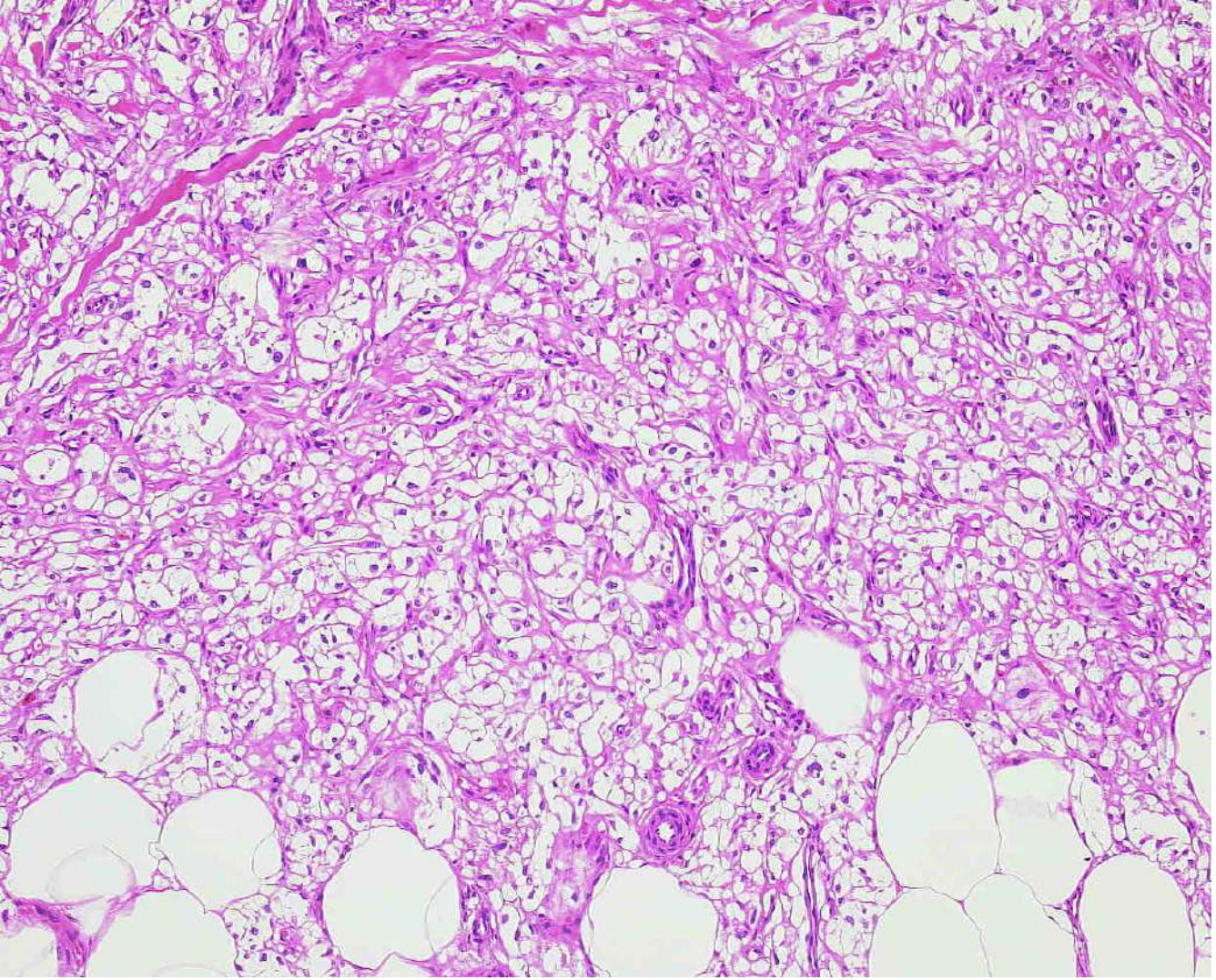

CD31

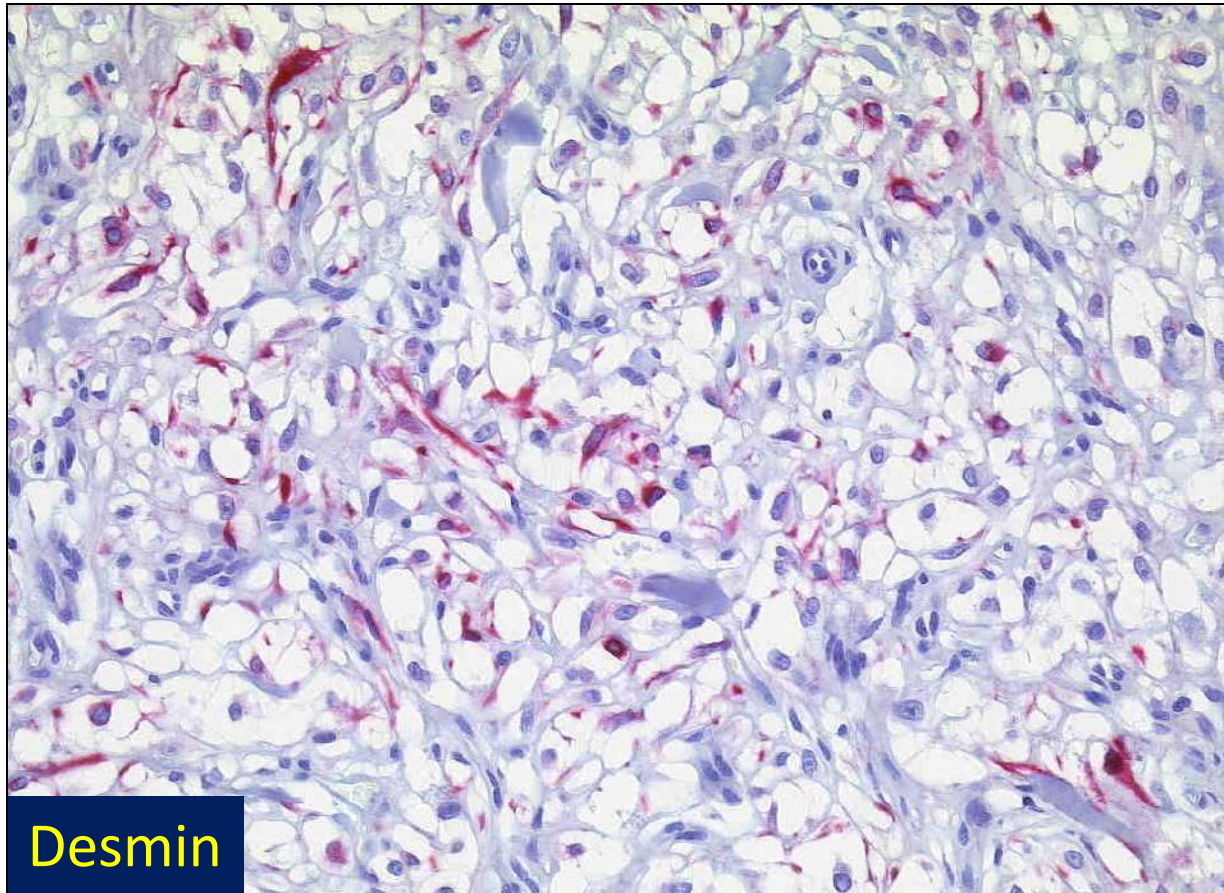

HMB45


MiTF1




ASMA




Desmin

**Cutaneous PEComa does not harbour *TFE3* gene fusions: immunohistochemical and molecular study of 17 cases**

Llamas-Velasco M et al. Histopathology 2013; 63: 122-129

12 F, 5 M, median age: 49.5 years

clear cell / epithelioid or monomorphous clear cell pattern

TFE 3 -, SOX10 -

FISH-assay for *TFE3* rearrangement was negative

# DD: cutaneous PEComa

- clear cell dermatofibroma
- dermal clear cell neoplasm
  (AJDP 2004; 26: 273)

  large clear cells, vesicular nuclei

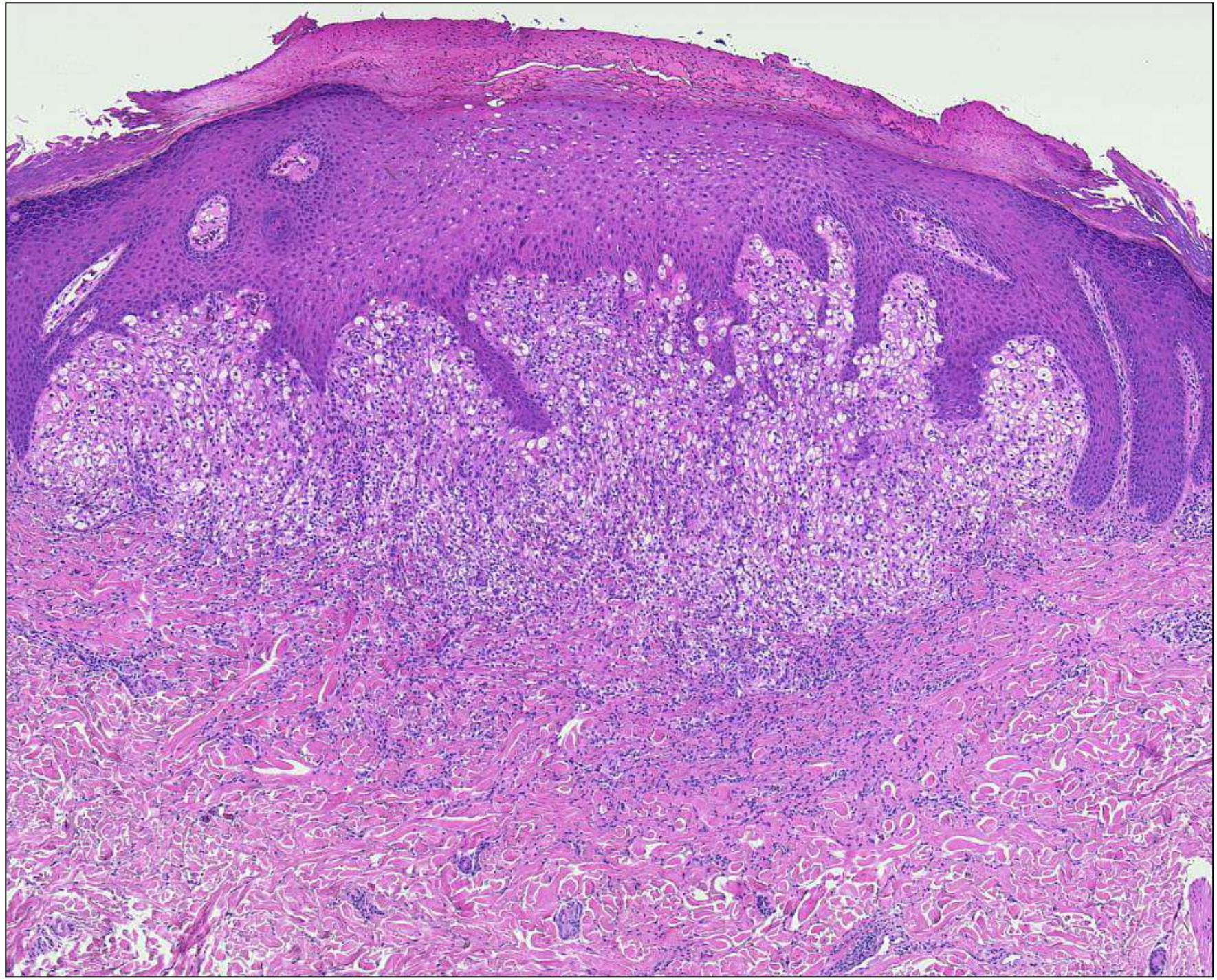
  NKIC3 +, melanocytic markers -
- clear cell AFX
- primary carcinoma / MTS of carcinoma
- clear cell sarcoma

# DD: cutaneous PEComa

**Clear cell dermatofibroma**
**(Zelger BW et al. AJSP 1996; 20: 483)**

- epidermal hyperplasia
- rarely subcutaneous infiltration
- no network of capillaries
- no perivascular growth
- melanocytic markers -

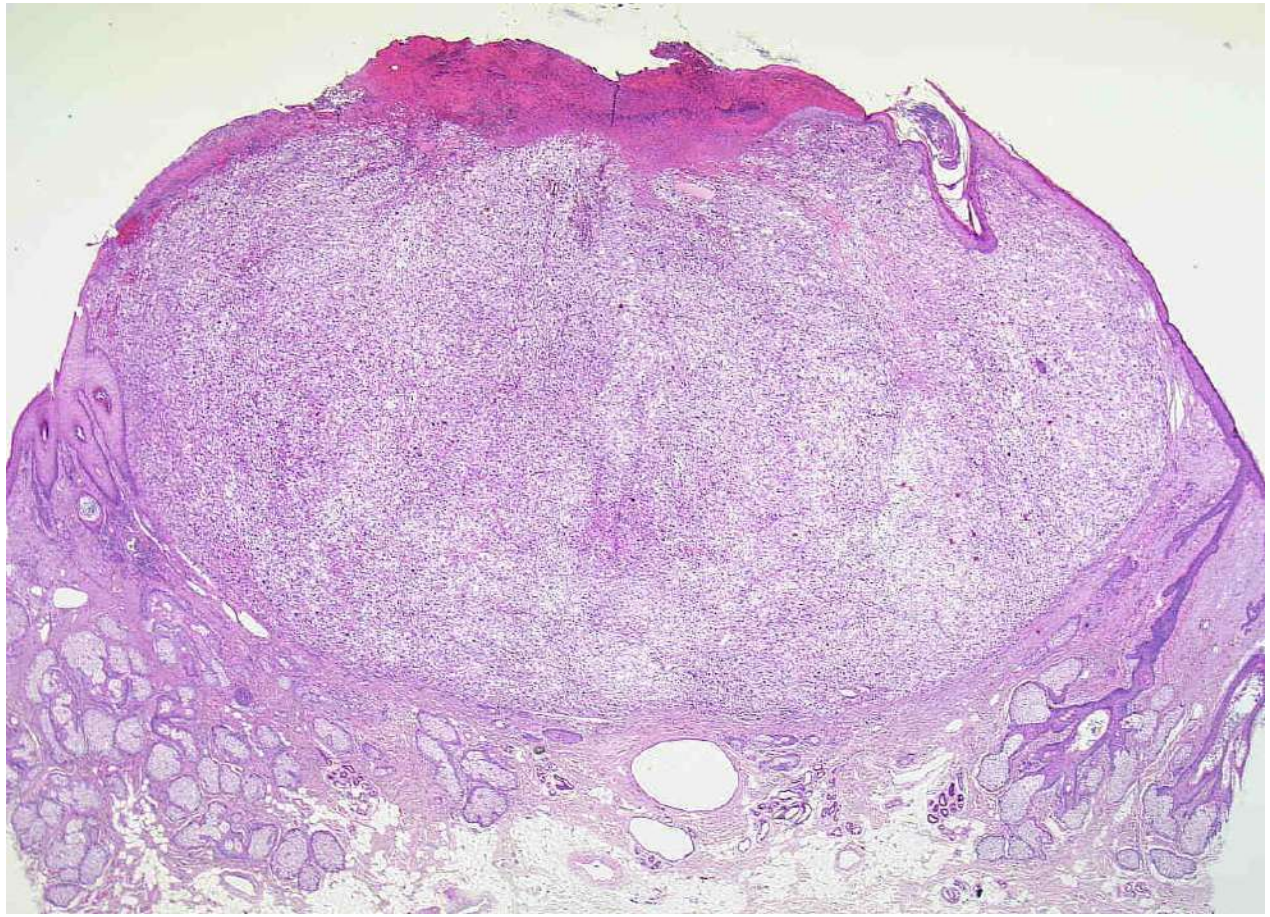
?

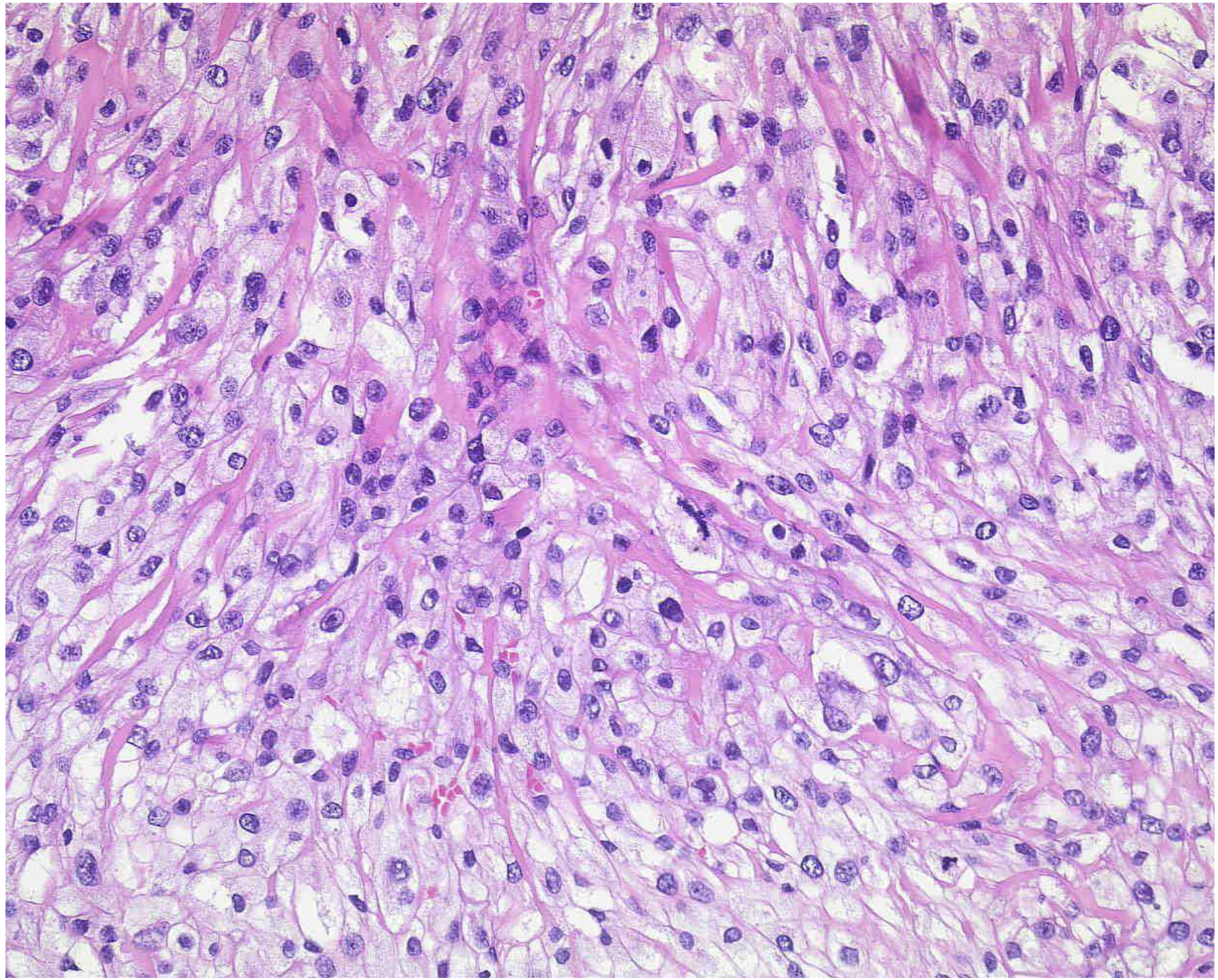


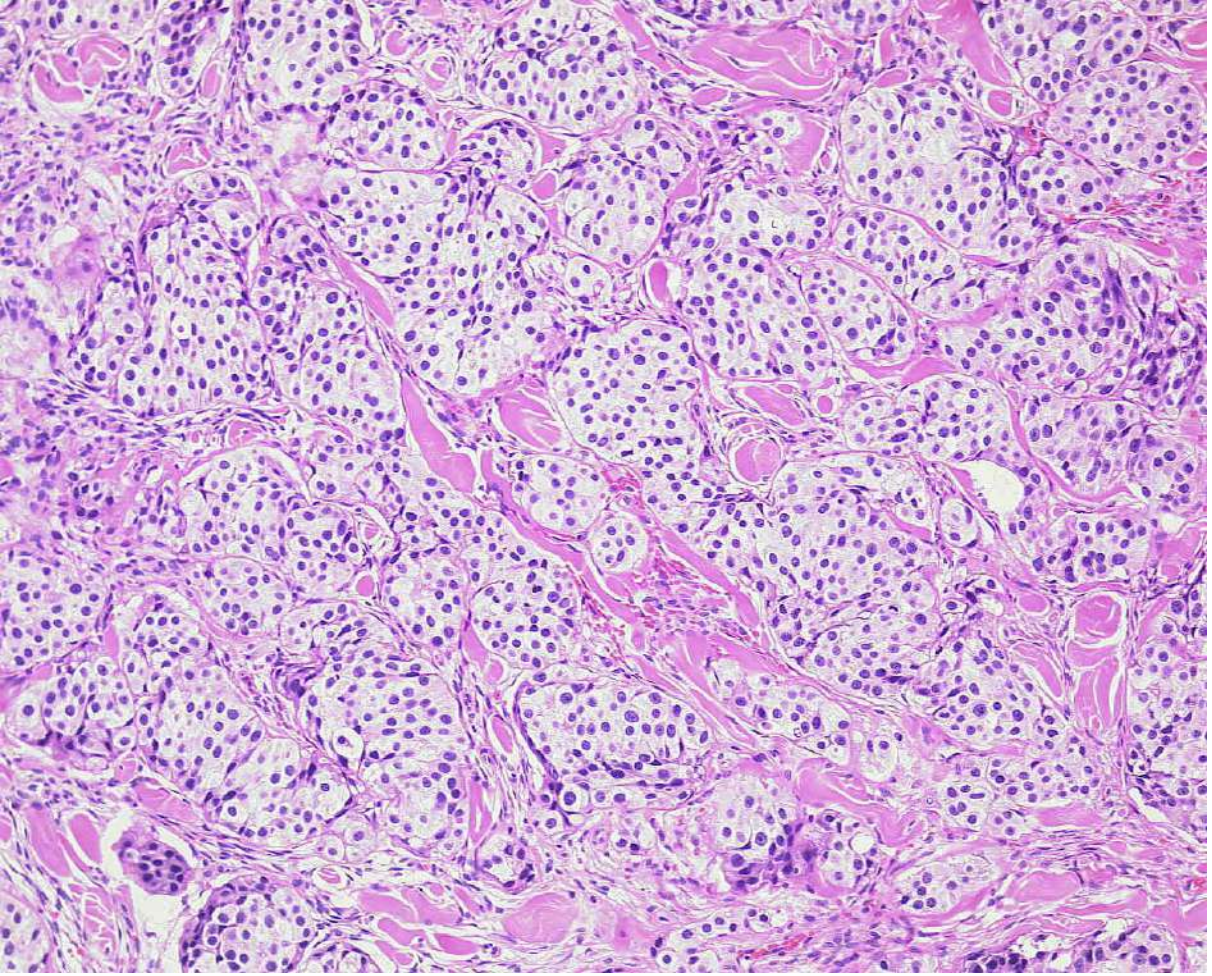
# DD: cutaneous PEComa

**Clear cell atypical fibroxanthoma**

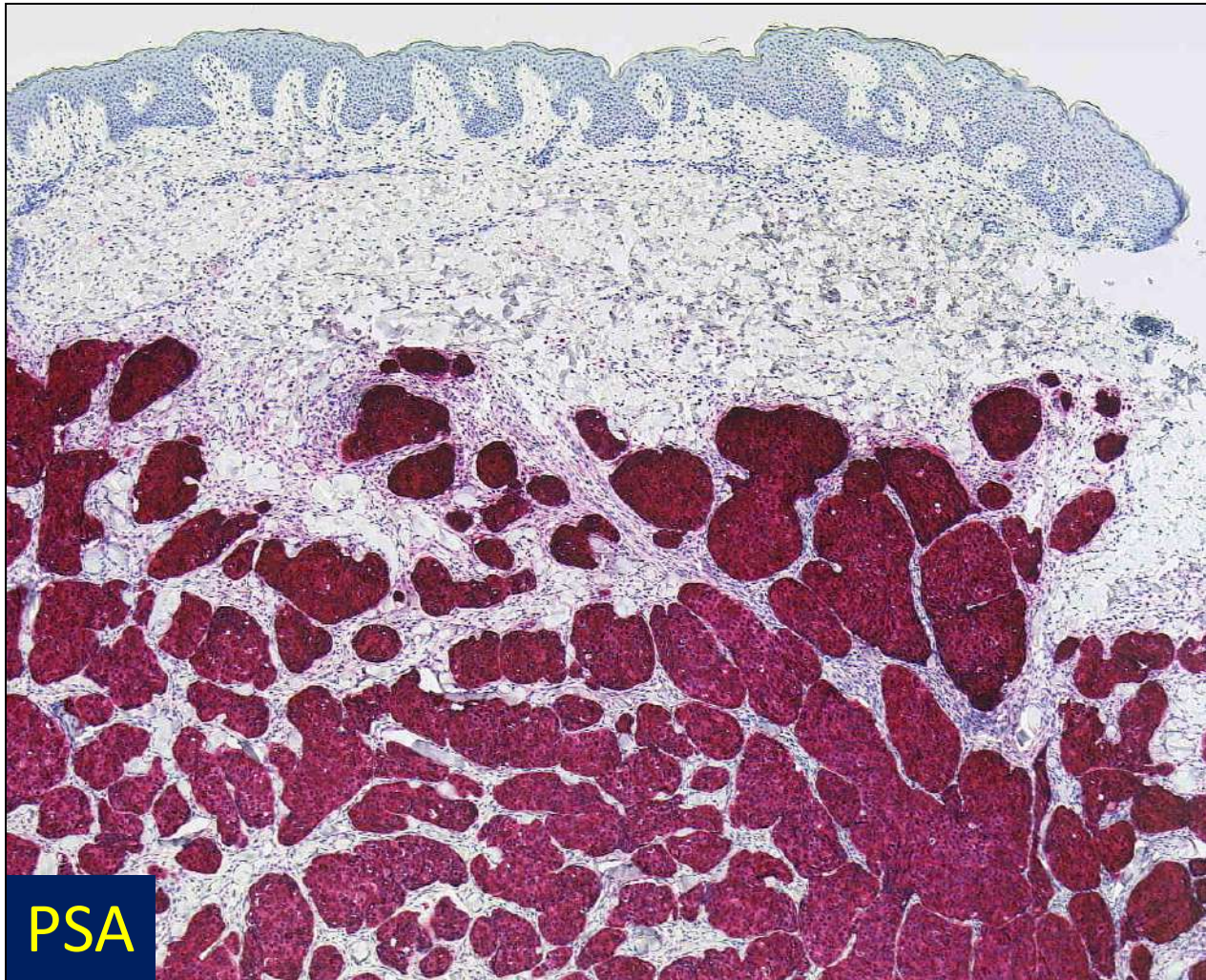
- elderly patients
- face
- sun-damaged skin
- atypical cells
- many mitoses
- numerous mitoses
- melanocytic markers negative

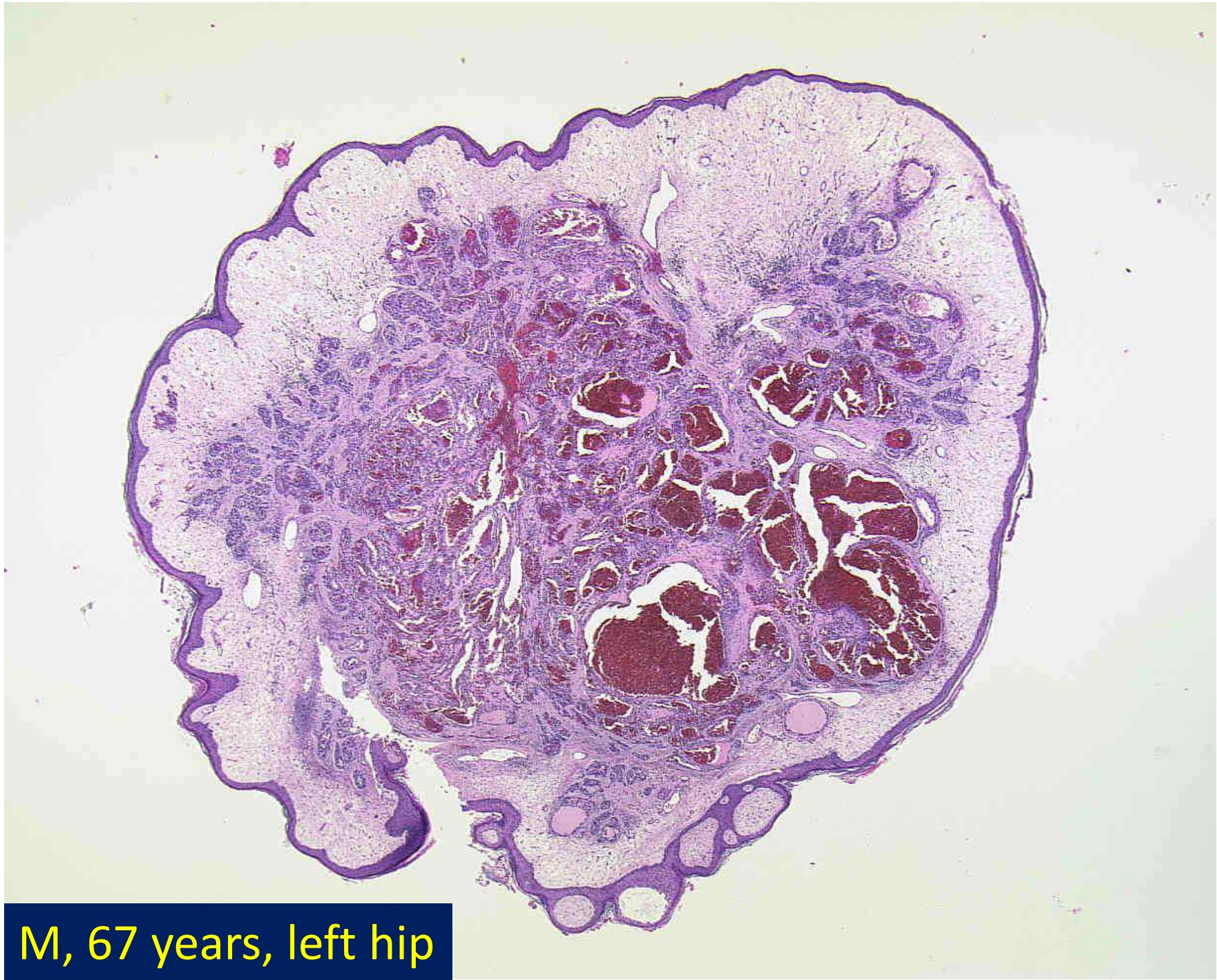






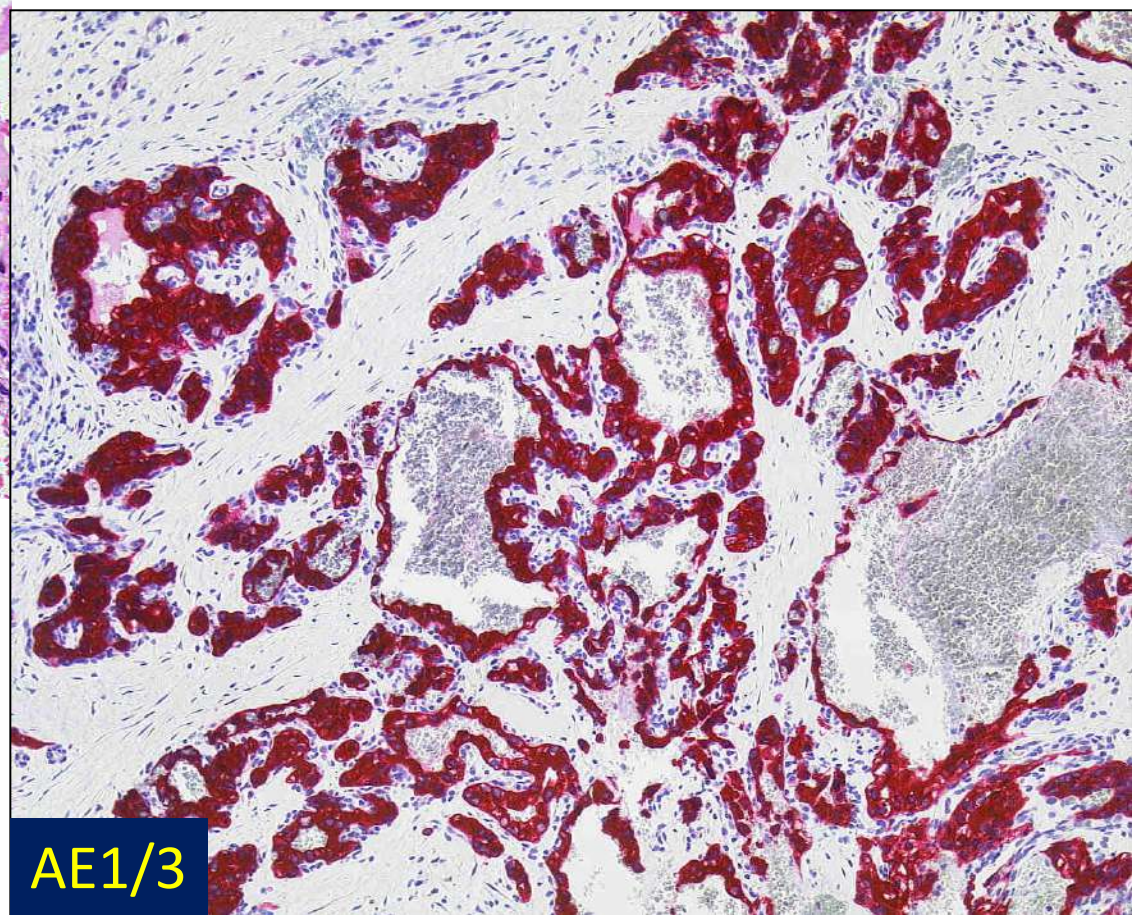
M, 65 years, left groin



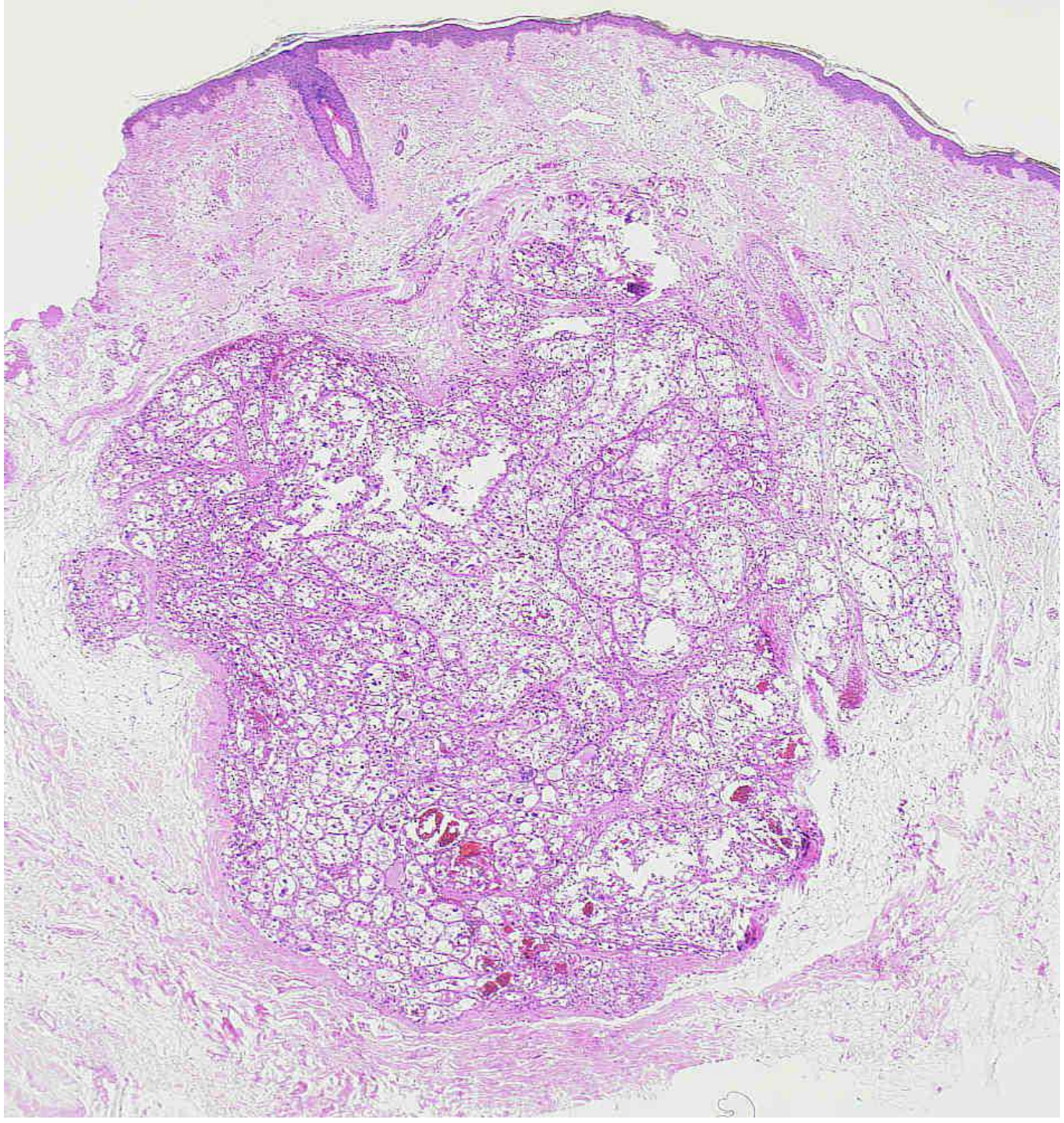


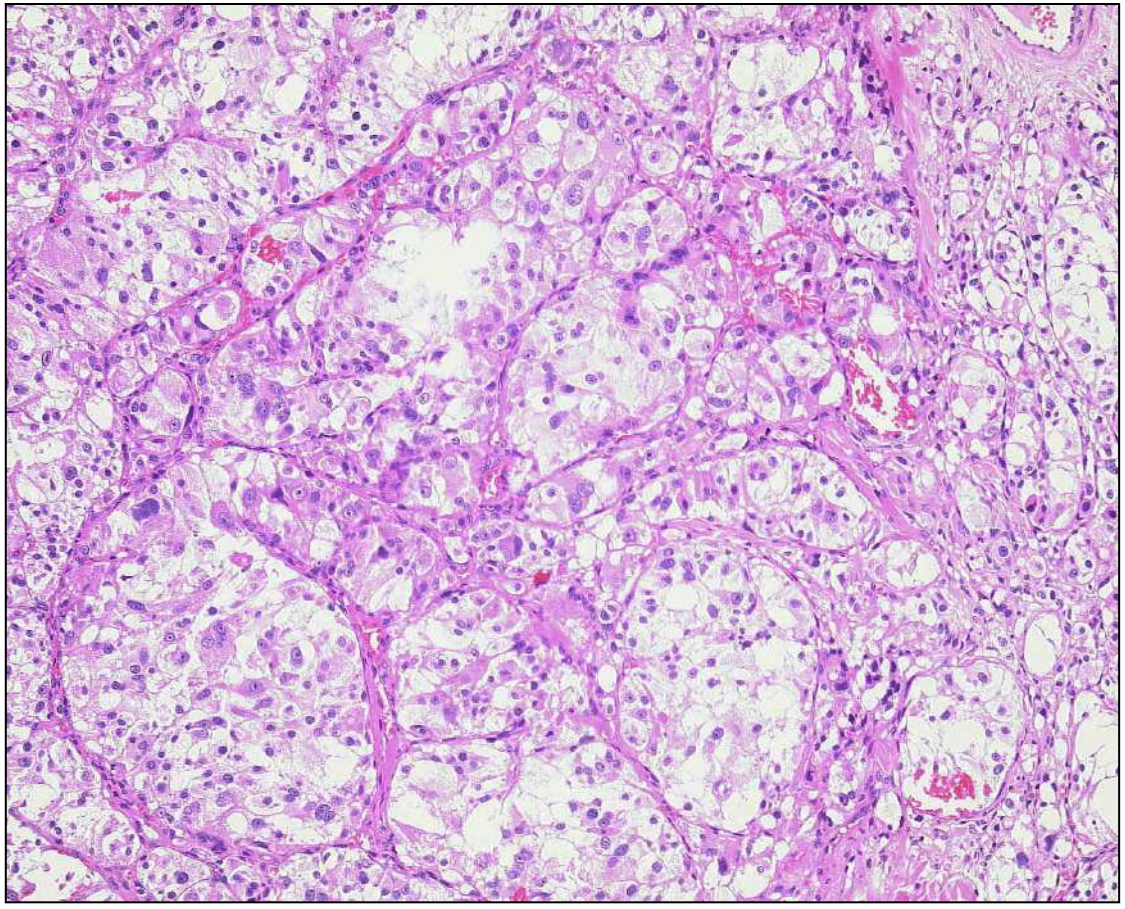
M, 67 years, left hip

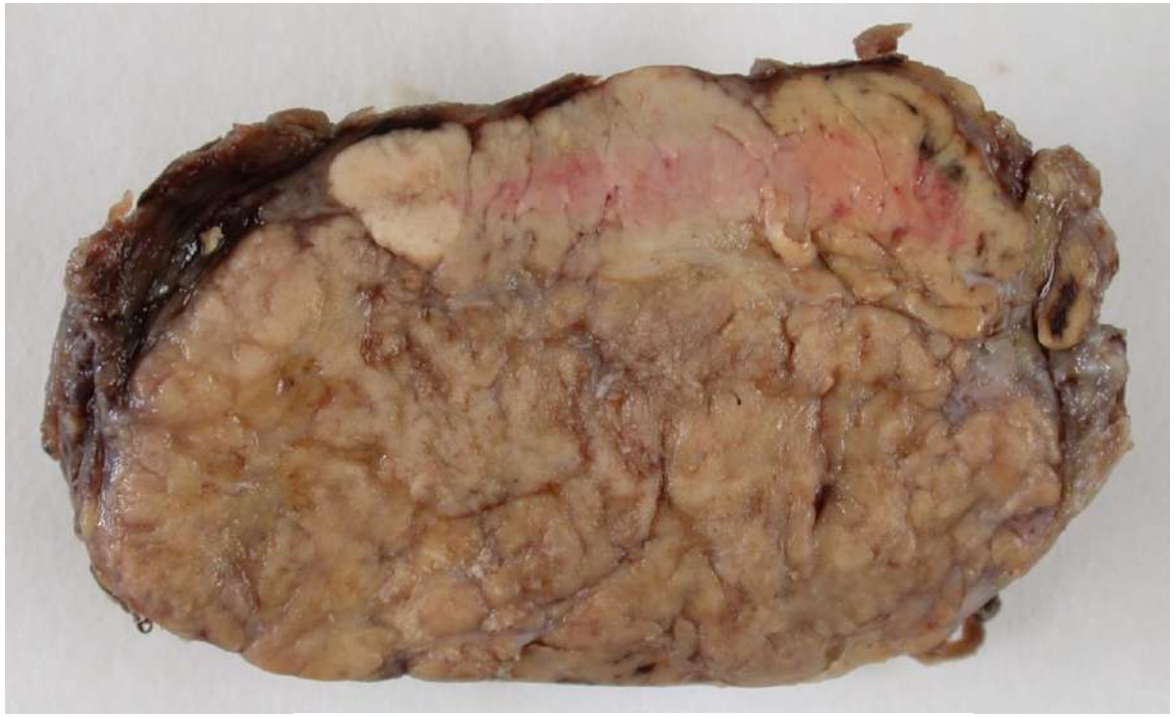
# History of renal cancer

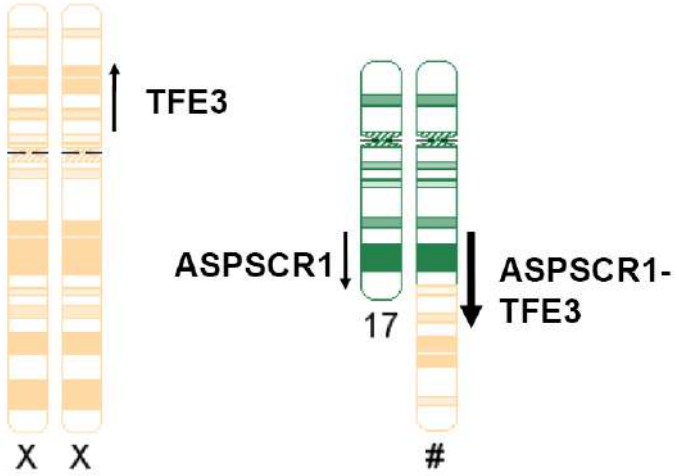


M, 38 years, scalp

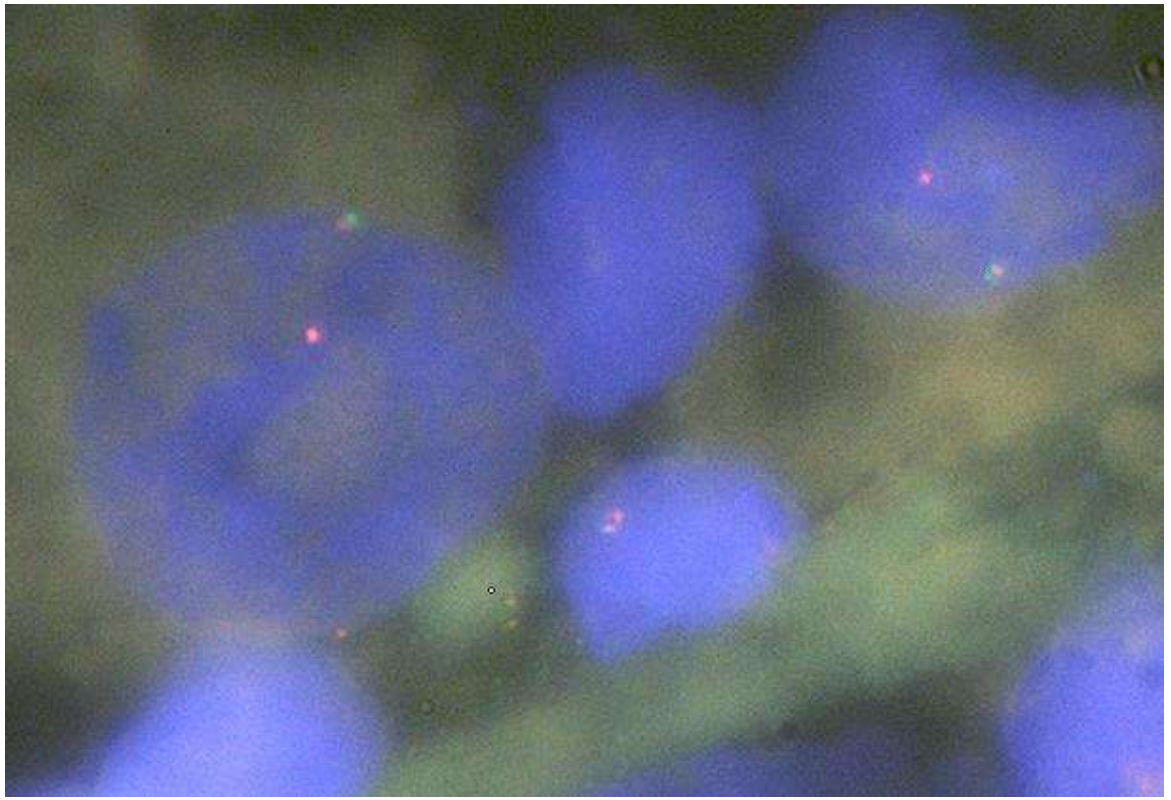









left calf, 9 cm mass
2 years before
multiple MTS (lung,
skin, nose….)
**metastasizing alveolar soft part sarcoma**



# PEComa with *ASPSCR1::TFE3* fusion: expanding the molecular spectrum of TFE3-rearranged PEComa with an emphasis on overlap with alveolar soft part sarcoma

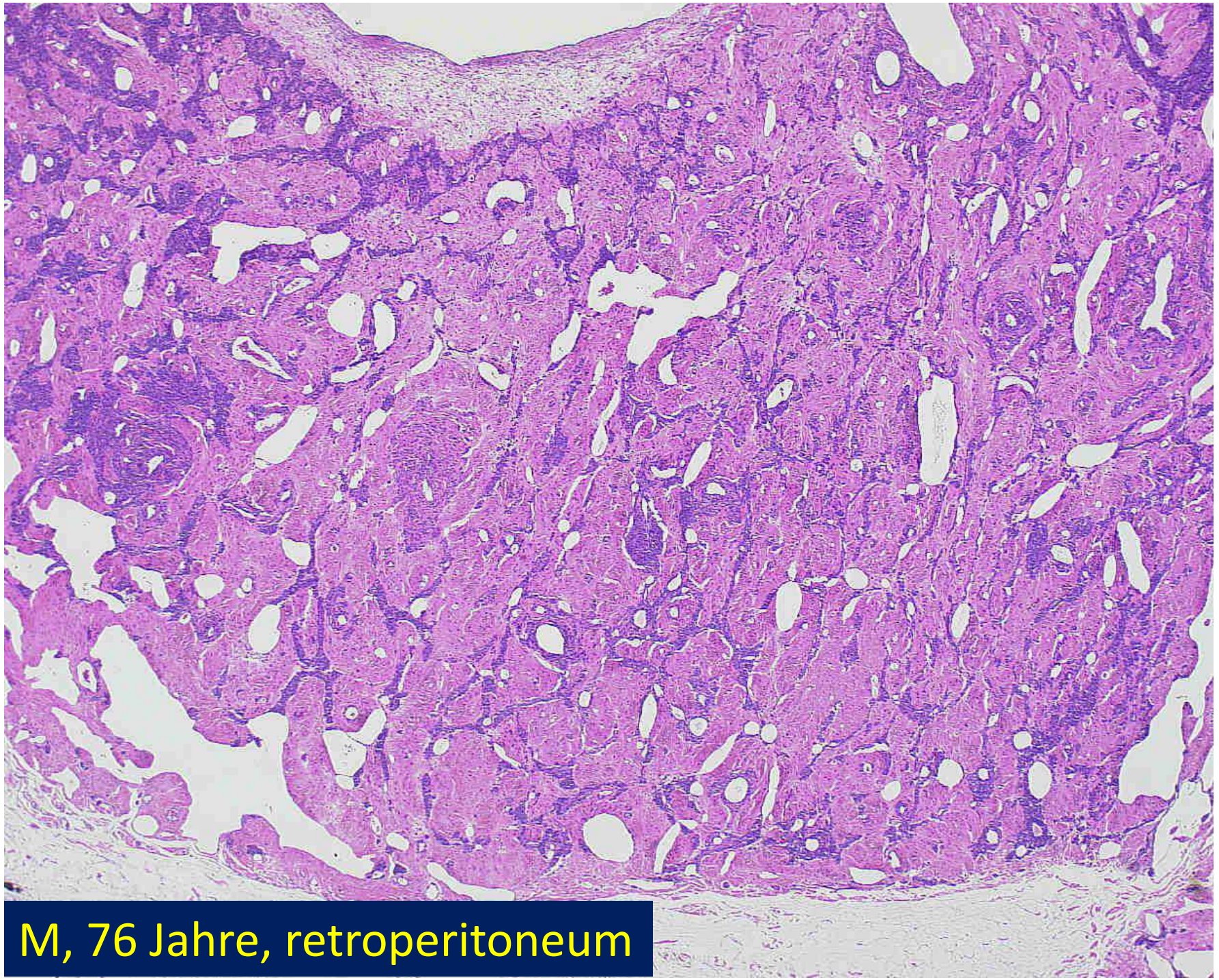
Zhao M et al. Histopathology 2024; 84: 482-491

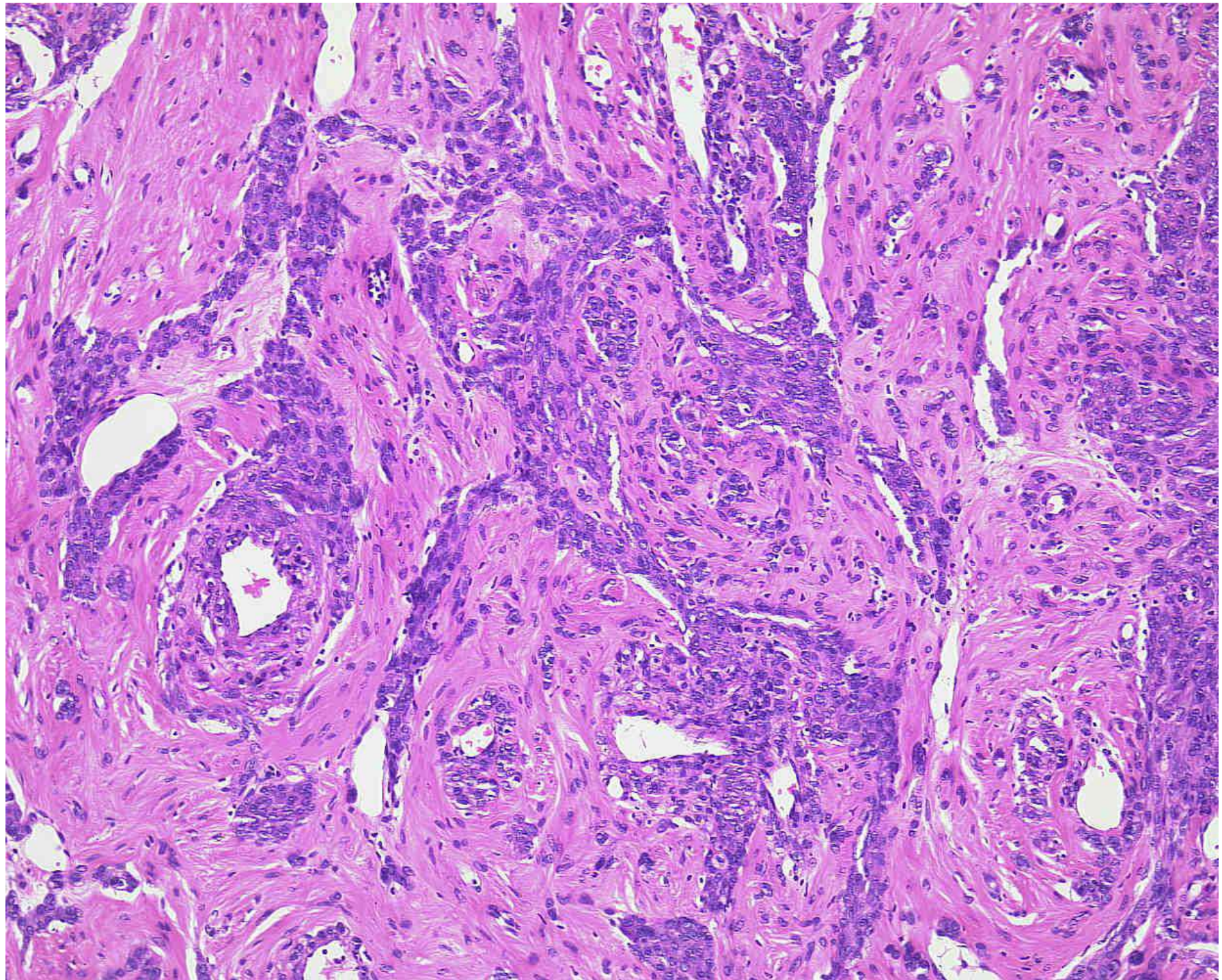
2 F, 1 M, 21-51 years
rectum, kidney, cervix
epithelioid clear tumour cells
delicate vascular network
Melan-A +, ASMA +, TFE3 +
*ASPSR1::TFE3* fusion

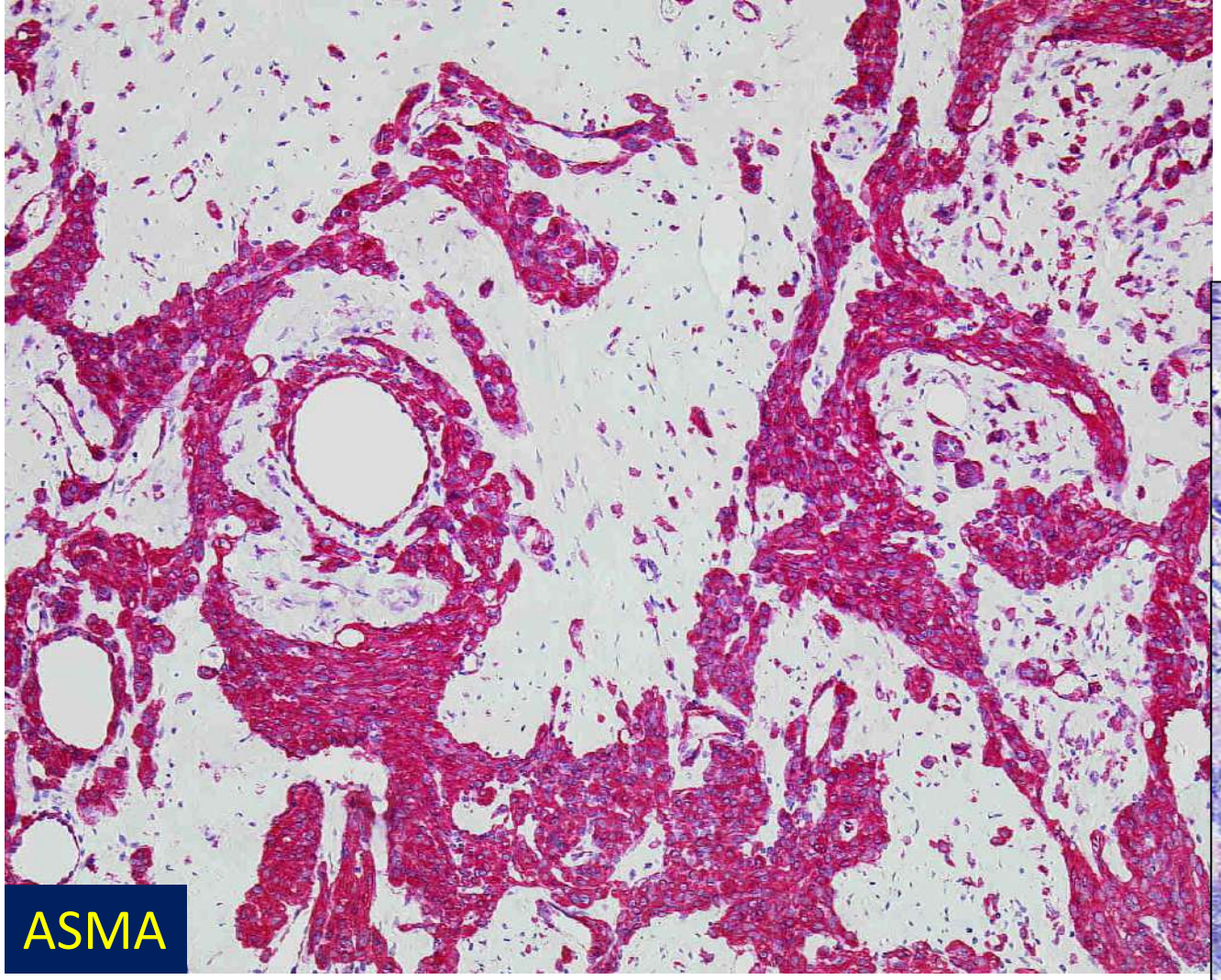
# sclerosing PEComa

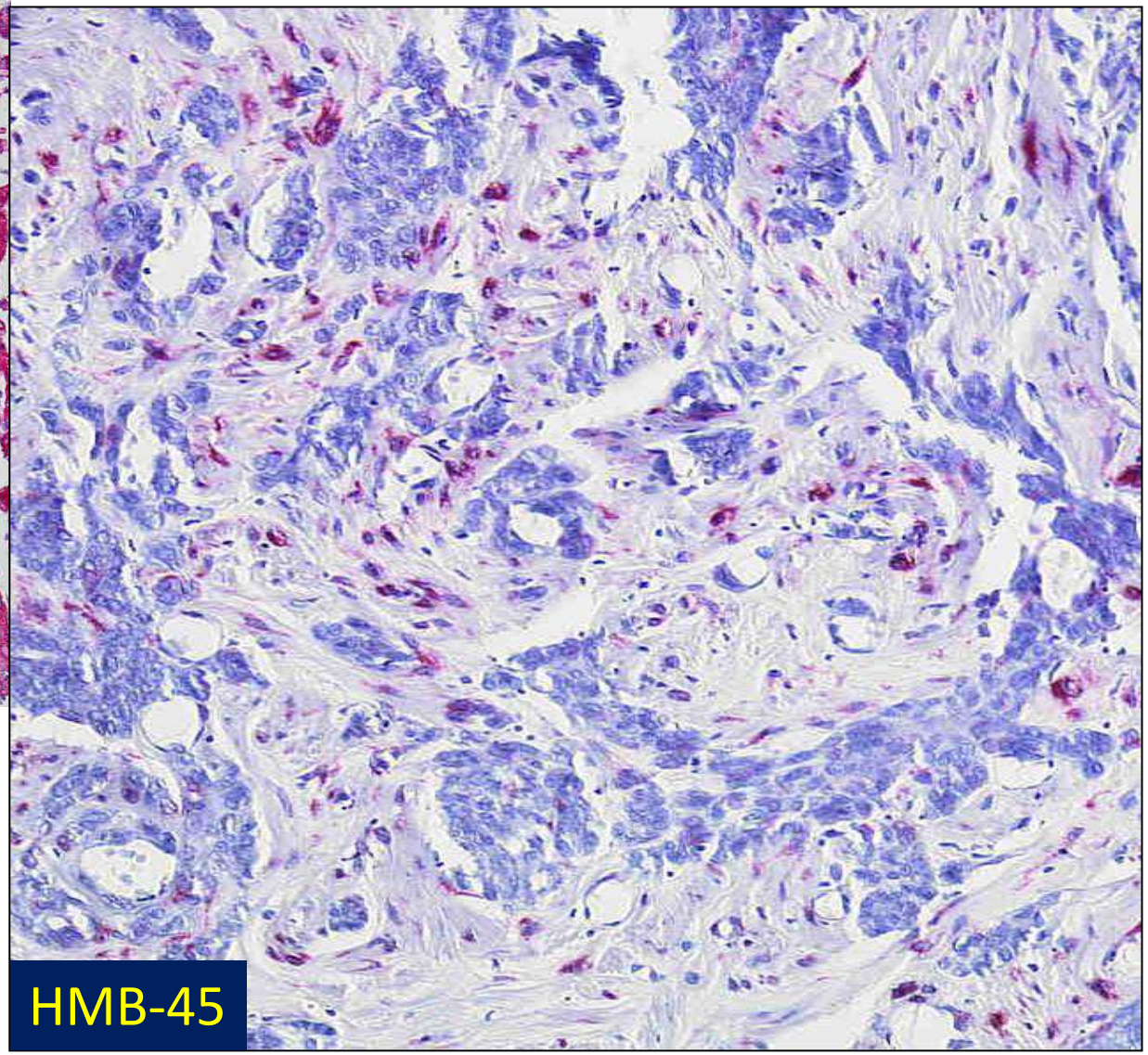
JL Hornick, CDM Fletcher AJSP 2008; 32: 493

- 13 patients, F, 34-73 years
- 1 patient with tuberous sclerosis
- retroperitoneum (10), pelvis, uterus, abdominal wall
- well-circumscribed neoplams (11)
- tumour size 4.5 – 28 cm
- multiple MTS in one case


M, 76 Jahre, retroperitoneum




ASMA


HMB-45

# Melanotic PEComa: a rare but distinctive subtype analyzed in a series of 7 cases

(de la Fourchardiere et al. Am J Surg Pathol 2024; 48: 88-96)

21-82 years, pelvis (2), gallbladder, cervix, eyelid,
epidural space, femur

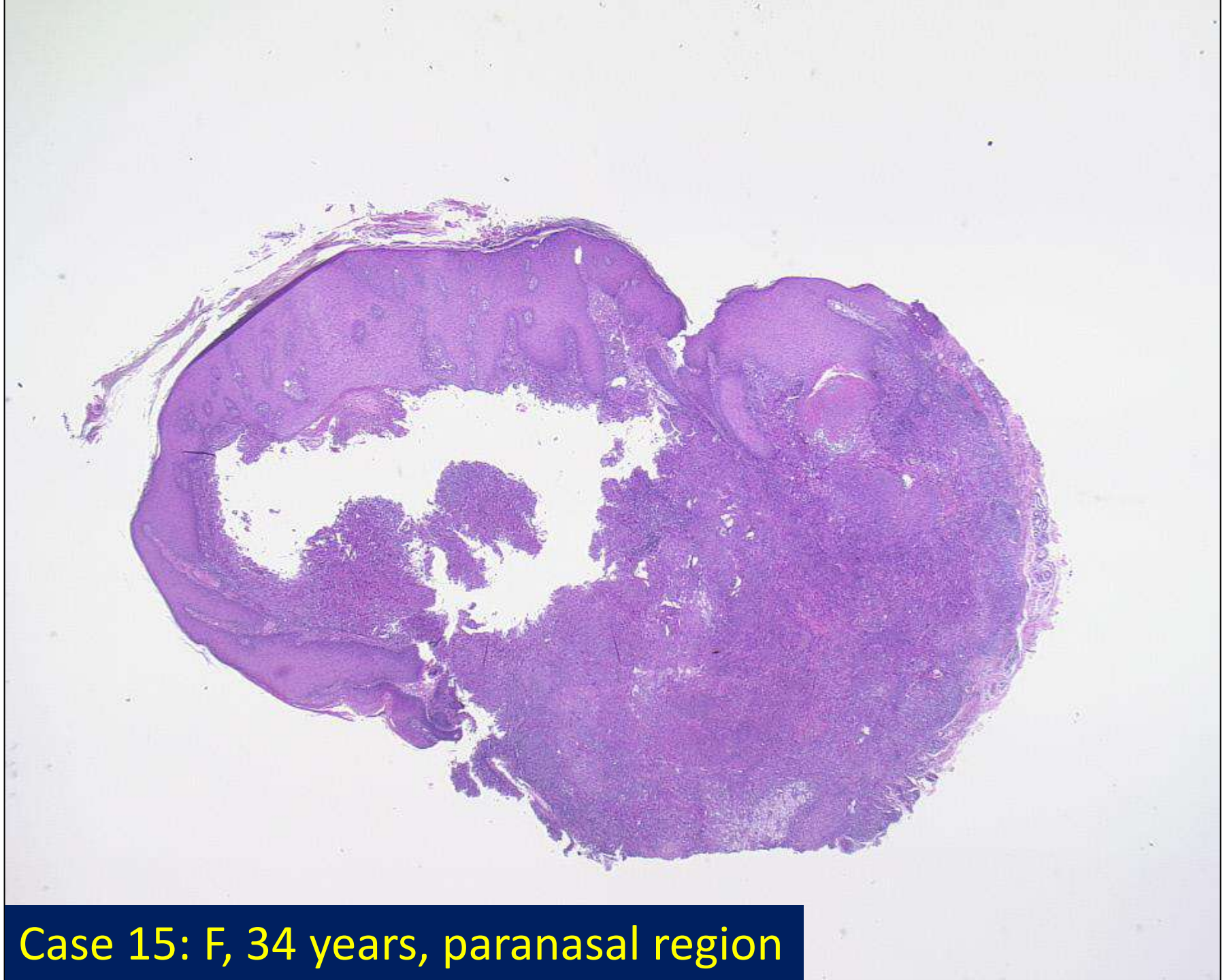
heavily pigmented neoplasms

variably sized cells with granular > clear cytoplasm

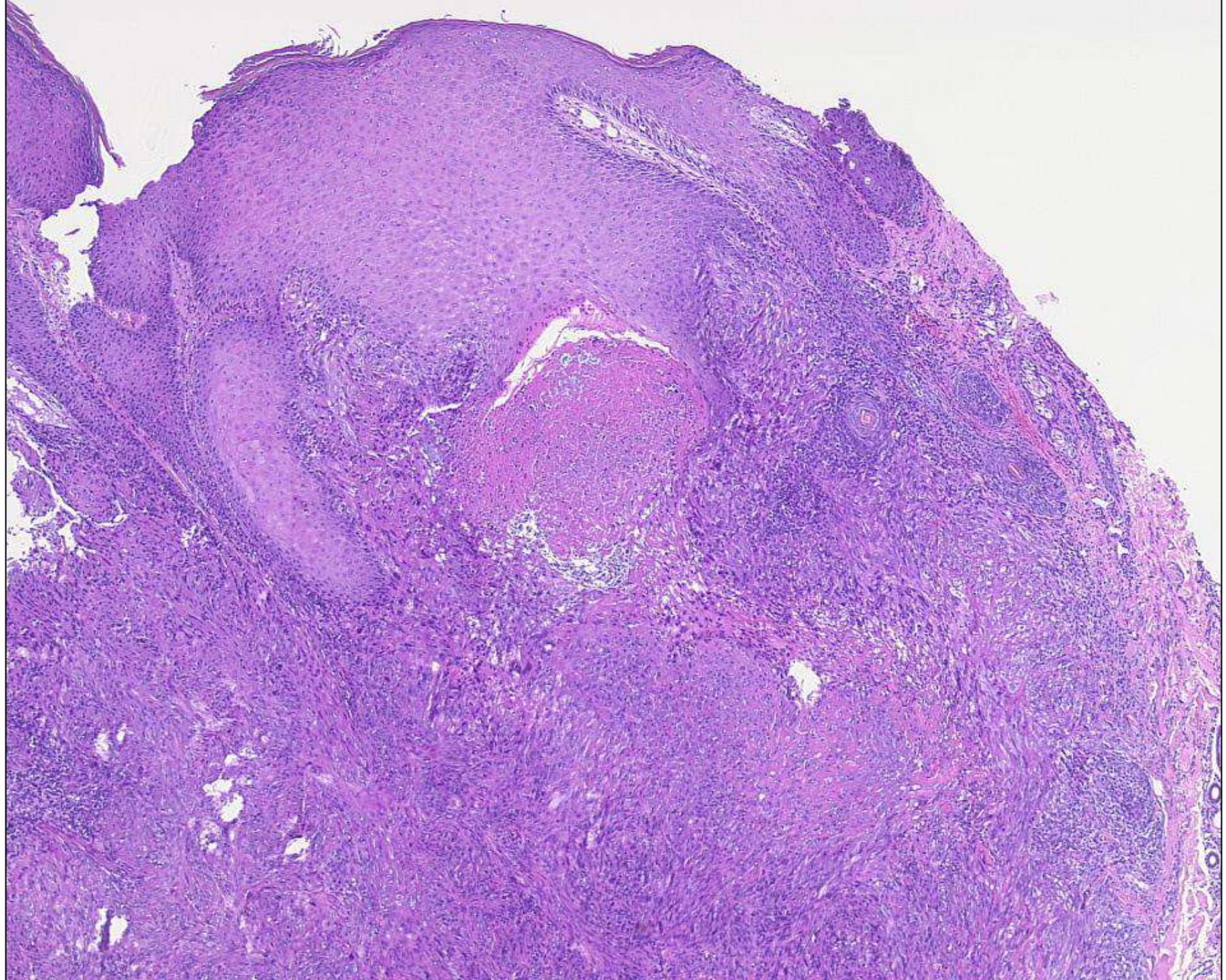
HMB45 +, 6/7 TFE3 +, Melan-A -, S-100 -, desmin -, ASMA -

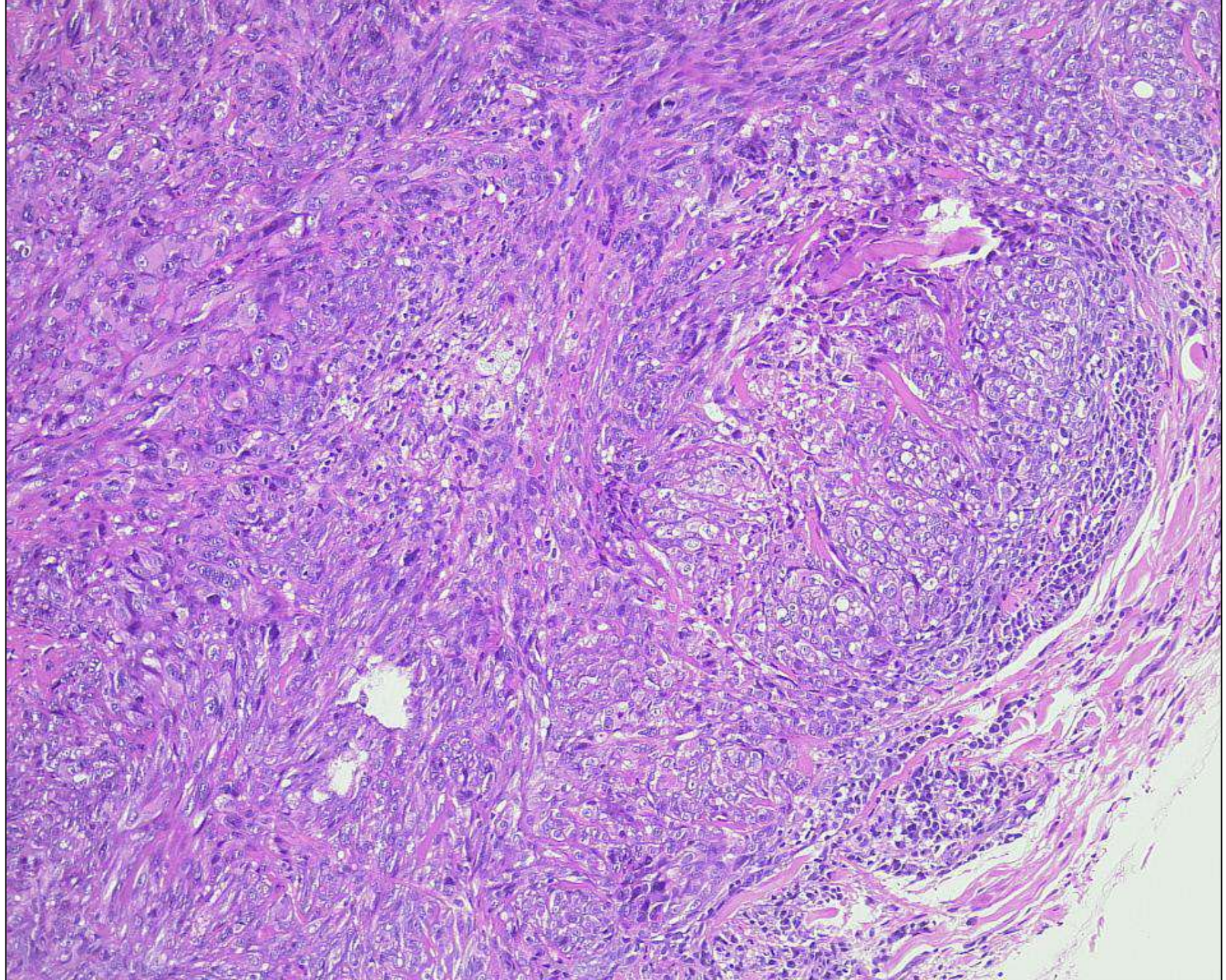
*TFE3* rearrangement in 5/7 cases

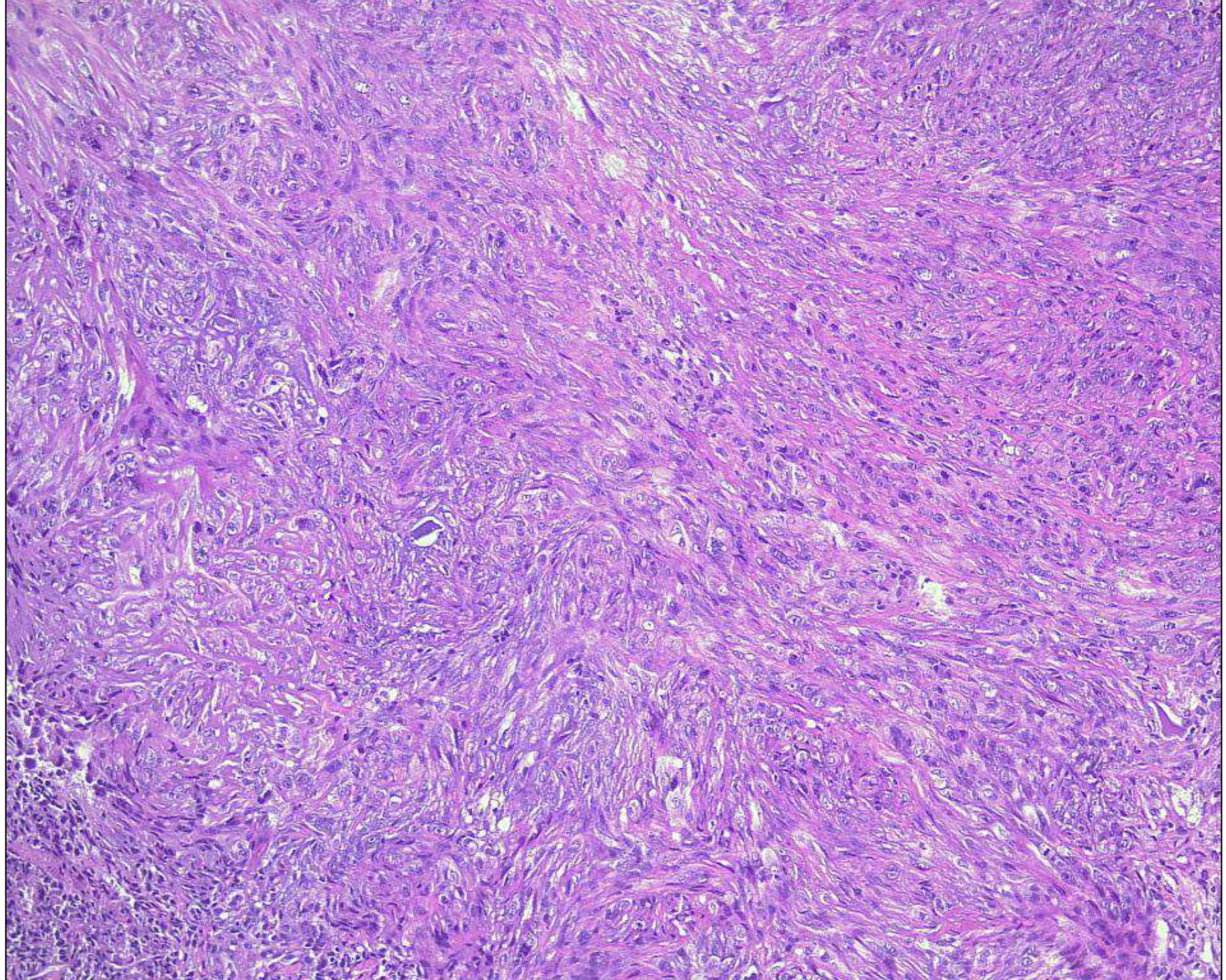
*SFPQ::TFEB* in TFE3 negative case (patient died of disease)

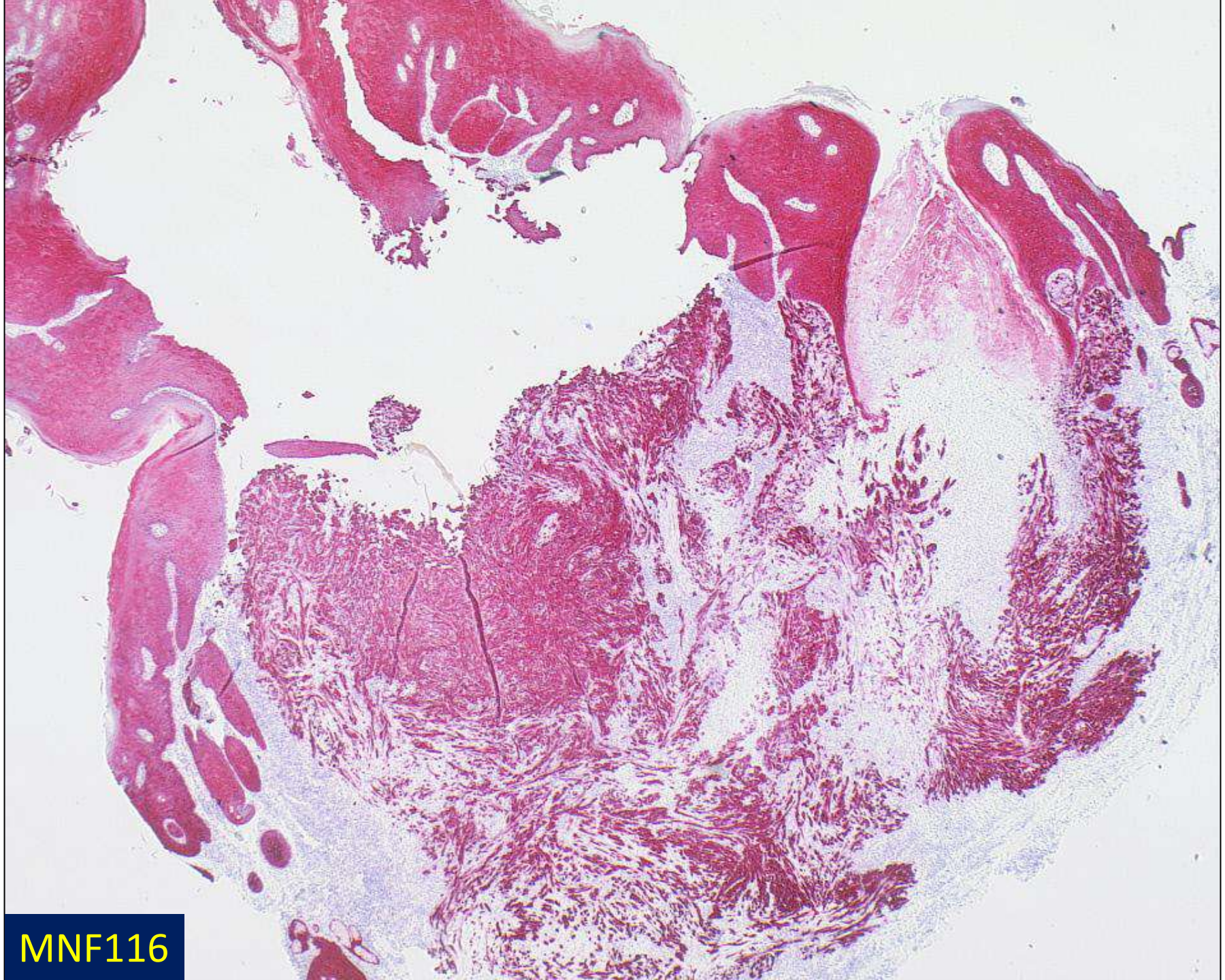


Case 15: F, 34 years, paranasal region



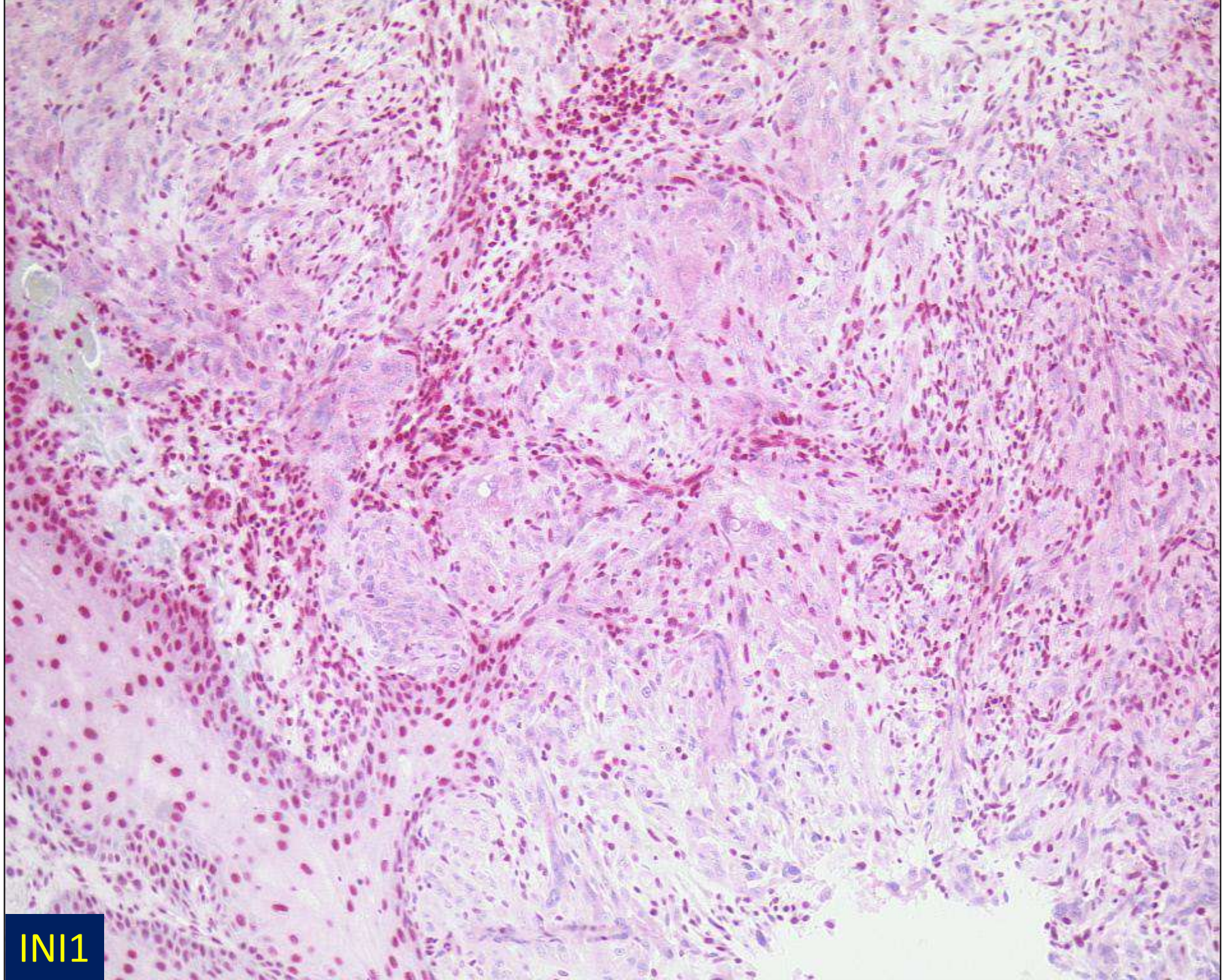


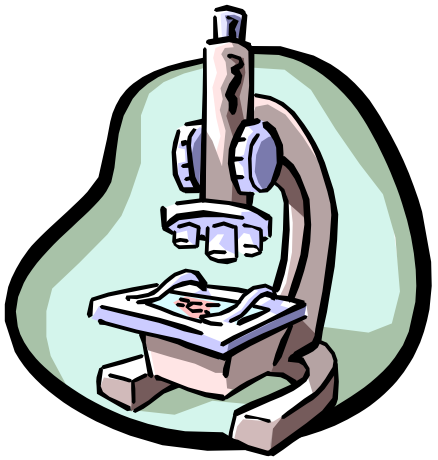



MNF116

Diagnosis:

poorly differentiated squamous cell carcinoma
in a young patient…


INI1



# Diagnosis Case 15

## epithelioid Sarcoma

Reprinted from CANCER, Vol. 26, No. 5, November 1970. 

# EPITHELIOID SARCOMA

## *A Sarcoma Simulating a Granuloma or a Carcinoma*

F. M. ENZINGER, MD

**This article reviews the pathologic features and the behavior of 62 cases of a peculiar form of sarcoma that has repeatedly been confused with a chronic inflammatory process, a necrotizing granuloma, and a squamous cell carcinoma. The tumor occurs chiefly in young adults (median age 23 years) and most commonly affects the soft tissues of the hand, the forearm, and the pretibial region. It tends to grow in a nodular or multinodular manner along fascial structures and tendons, often with central necrosis of the tumor nodules and ulceration of the overlying skin. Most of the tumors grow slowly, and many of our cases had been present for months or years prior to surgery. Microscopically, the tumor consists of irregular nodular masses of large, deeply acidophilic polygonal cells merging with spindle cells, frequently associated with large amounts of hyalinized collagen. Follow-up information on 54 patients (87%) revealed slow, relentless clinical course with frequent recurrence (85%) and late metastasis (50%). Cure may be achieved by wide local excision at early stage of disease.**

THIS IS A REVIEW OF OUR EXPERIENCE WITH a distinctive but rare type of sarcoma that is likely to be confused with a variety of benign and malignant conditions, especially a granulomatous process, a synovial sarcoma, or an ulcerating squamous cell carcinoma. The characteristic nodular arrangement and the epithelioid appearance of the tumor cells, the early necrosis, and the frequent involvement of tendons and fascial structures were the the principal features of the neoplasm that led to errors in evaluation and diagnosis.

Initially we were under the impression that a tumor of this type had not been previously described, but a search of the literature revealed similar cases among reviews of synovial sarcoma. In 1938, Berger[3] described a "distinctive and peculiar" variant of synovial sarcoma affecting the common extensor tendon of the right wrist. Although follow-up was incomplete, the tumor recurred rapidly after enucleation and necessitated amputation of the forearm. De Santo et al.[4] reported a similar appearing tumor in the flexor tendon of the ring finger that was interpreted as an atypical synovial sarcoma with "polygonal and polyhedral cells bearing a striking resemblance to epithelium." A group of related or identical tumors designated by Bliss and Reed[5] as "large cell sarcomas of tendon sheath," has recently been reported. Their tumors were attached to the tendons of the hand and wrist and clinically and histologically showed "a remarkable resemblance to benign giant cell tumors of tendon sheath."

### MATERIALS AND METHODS

Clinical records and microscopic sections of 62 tumor cases submitted to the Armed Forces Institute of Pathology (AFIP) by military, Veterans Administration, and civilian hospitals over a period of 25 years (1945 through 1969) and coded under a number of different diagnoses were reviewed and analyzed (Table 1A, 1B). Follow-up information was obtained on 54 of the 62 patients. The follow-up period ranged from 1 year to 26 years and averaged 7 years (median 5 years). In all cases, hematoxylin-eosin stains were available. In selected cases, the following staining techniques were utilized: the Masson trichrome,

From the Armed Forces Institute of Pathology, Washington, D. C.
Address for reprints: F. M. Enzinger, MD, Armed Forces Institute of Pathology, Washington, D. C. 20305.
The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.
Received for publication April 18, 1970.



FIGURE 1. First page of Enzinger's original publication on epithelioid sarcoma.





ES 7198

The American Journal of Surgical Pathology
14): 241-263, April
© 1985 Raven Press, New York

Donald R. Chase, M.D.

Franz M. Enzinger, M.D.

# Epithelioid sarcoma

## Diagnosis, prognostic indicators, and treatment*,†

ABSTRACT A retrospective review of 241 cases of epithelioid sarcoma reaffirmed the propensity of this tumor to occur in the distal extremities of young adults. The tumor was generally firm and nontender, and involved the dermis, subcutis or deeper soft tissues, particularly fascial planes, aponeuroses, and tendon sheaths. Follow-up data, available in 202 cases (84%), showed a 77% recurrence and a 45% metastatic rate. The most common initial sites of metastasis were lymph nodes (48%) and lungs (25%). A more aggressive course was associated with a proximal or axial tumor location, increased size and depth, hemorrhage, mitotic figures, necrosis, or the presence of vascular invasion. More favorable behavior was observed when the tumor arose in younger individuals, in distal extremities, or in females between the ages of 10 and 49. (The last observation calls for further work with steroid receptors.) Radical excision or amputation still appears to be the initial treatment of choice, though adjunctive high-dose radiotherapy to the excision site may prove to be of additional value.

From the Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, D.C.
Assistant Professor of Pathology (DRC), Loma Linda University School of Medicine, Loma Linda, California; Chairman (FME), Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, D.C.
* 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 Army or the Department of Defense.
† Presented in part before the Annual Meeting of the International Academy of Pathology (United States-Canadian Division), Toronto, March 12, 1985.

### INTRODUCTION

Since its first detailed description in 1970,[6] epithelioid sarcoma has been accepted as a unique soft tissue sarcoma which typically pursues an indolent, relentless clinical course with numerous recurrences, and frequently culminates in regional lymph node or pulmonary metastasis. Its microscopic appearance may frustrate the surgical pathologist, often mimicking necrobiotic granuloma, nodular fasciitis, benign and malignant fibrous histiocytoma, synovial sarcoma, "amelanotic" melanoma, ulcerated squamous cell carcinoma, and other benign or malignant processes.

Epithelioid sarcoma usually occurs in the soft tissues of young adults, particularly involving the hands and forearms, and produces multinodular masses of epithelial-appearing cells having a tendency to grow along fascial planes, aponeuroses, and tendon sheaths. It involves the viscera only secondarily. Unusual primary sites include the penis[15,27] and vulva.[11,13] Many case reports and review articles have been written, stressing different features of the tumor.[1-3,6-15,17-23,25-37] Medenica has observed damage to tumor cells immediately adjacent to surrounding cuffs of lymphocytes and proposed that the slow growth of the neoplasm might be related to the high efficacy of lymphocyte-mediated defenses.[23] Another report shows a poorer prognosis in recurrent cases or in those showing vascular invasion or lymph node metastasis.[30] Still other papers have detailed the tumors cytologic and radiologic features.[1,20] Al-

POLISH MEDICAL JOURNAL, Vol. X, No. 1/1971
(Translated from Nowotwory, Vol. XI, No. 1—2/1961

*Józef Laskowski*

# *SARCOMA APONEUROTICUM*

Z Zakładu Patologii Instytutu Onkologii
im. Marii Skłodowskiej-Curie w Warszawie
Dyrektor: prof. dr med. *J. Laskowski*
Kierownik Zakładu Patologii: prof. dr med. *J. Laskowski*

W roku 1948 miałem możność klinicznego i histopatologicznego badania przypadku guza ręki, który przedstawiał poważne trudności diagnostyczne. Ostatecznie uświadomiłem sobie, że utkanie nowotworu jest mi nieznane i że nie jestem w stanie bliżej określić jego natury tkankowej. Z konieczności zatem ograniczyłem się do ogólnikowego rozpoznania nienabłonkowego nowotworu złośliwego. Preparat mikroskopowy powędrował za granicę, gdzie jeden z profesorów, cieszący się wielkim autorytetem, rozpoznał nietypową postać czerniaka. Z opinią tą nie mogłem się zgodzić: ani obraz kliniczny, ani mikroskopowy nie przemawiały za czerniakiem. Wprost nawet przeciwnie — wskazywały na to, że nie jest to czerniak. Dalszy przebieg choroby i pomyślny wynik leczenia potwierdziły moje stanowisko. Zgodnie z przyjętym w Zakładzie Patologii Instytutu Onkologii zwyczajem zaliczyliśmy przypadek do rzędu zagadkowych i wymagających gromadzenia dalszego materiału. W ciągu lat blisko 12 udało mi się zebrać 7 tego rodzaju guzów. Dzisiaj mogę z pewnością powiedzieć, że omawiany nowotwór ma swoją odrębną charakterystykę biologiczną i morfologiczną, wobec czego uzasadnionym jest jego wyodrębnienie jako oddzielnej i dotychczas nieznanej jednostki onkologicznej.

Przede wszystkim należy podkreślić wśród chorych znaczną przewagę mężczyzn. Na 7 zarejestrowanych przypadków było aż 6 mężczyzn i tylko 1 kobieta. Nowotwór występuje u ludzi fizycznie pracujących, których ręce narażone są na urazy. W wywiadach chorzy podkreślali przebycie wielokrotnych urazów, które jakoby poprzedzały zjawienie się guza. Rozpiętość wieku chorych wahała się od 23 do 56 lat. Nowotwór umiejscawiał się na dłoni, przy czym jego punktem wyjścia była tkanka rozścięgna i pokrewnych struktur. W ostatnich jednak czasach spotkałem przypadek 56-letniego mężczyzny, u którego nowotwór umiejscowiony był na pięcie. Wynika z tego, że dłoń nie jest jedynym umiejscowieniem, lecz tylko lokalizacją najczęstszą.

Proces nowotworowy rozwija się w tkankach głębokich od strony powierzchni dłoniowej ręki i, jak to podają chorzy, przybiera postać nie tyle guza, ile chrząstkowato twardego zgrubienia czy też nacieku. Pokrywająca skóra jest zgrubiała i nadmiernie zrogowaciała. Najczęściej nowotwór rozwija się u podstawy V lub IV palca. W jednym przypadku zmiana umiejscowiona była bliżej nadgarstka.

Wzrost guza odznacza się powolnością; stopniowo nacieka on otoczenie, w tym również pokrywającą go skórę. Jak zaznaczyłem — ma on raczej wygląd bardzo twardego nacieku, stopniowo gubiącego się w otocze-

*JÓZEF LASKOWSKI*

# APONEUROTIC SARCOMA

Department of Pathology, Institute of Oncology in Warsaw

On the basis of histoclinical analysis of 7 cases recorded in the Institute of Oncology in Warsaw (Poland) in the period of 1949—1960 a new type of mesenchymal neoplasm originating from the aponeuroses and related structures has been distinguished. The tumor was situated almost exclusively on the palmar aspect of the hand just beneath the skin and appeared in the form of a flat, very hard infiltration. The growth was very slow and after some years a slit-like deep ulceration with sharply outlines borders appeared in the skin of the palm, usually in the middle portion of the tumor. It was remarkable that this lesion affected mostly manual workers. Trauma seems to play an important role in the pathogenesis of the neoplasm. The patients recorded so far were aged 23—56 years. Microscopically, the neoplasm was composed of spindle cells intermingled with those of epithelioid appearance. The tumor shows a tendency to become fibrotic and to invade diffusely deep the adjacent tissues. Therefore contractures similar to those of Dupuytren sometimes do occur. The course of the disease is slow, lasting many years. The neoplasm is locally malignant, the borders are not sharply delineated and it is very prone to recur. In some cases the neoplasm metastasizes through the lymphatic or blood vessels. However, the results of treatment are encouraging if radical surgery is performed based on the knowledge of the biology of the tumor. Electroexcision and electrocoagulation, removal of the lesion together with the corresponding fingers and metacarpal bones (possibly the formation of what is called "small hand") and at least amputation of the forearm can be taken into consideration. So far this neoplasm was falsely diagnosed as: malignant melanoma, malignant synovioma, squamous carcinoma, inflammatory process.

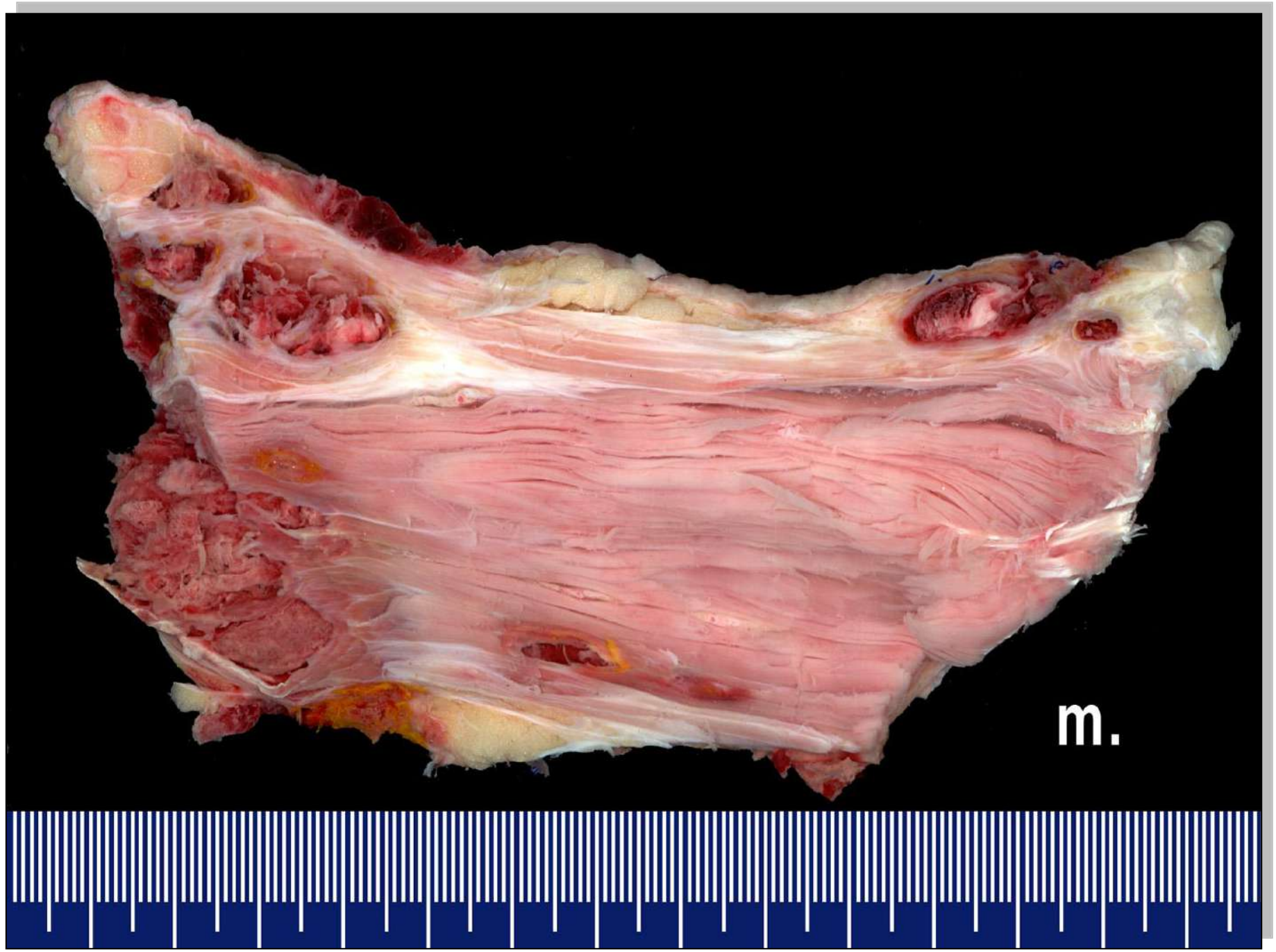
In 1948 I studied clinically and histopathologically a tumor of the hand which caused considerable diagnostic difficulties. Finally I became aware that the neoplastic tissue is unknown to me and that I am unable to determine its nature. Of necessity I confined myself to the vague diagnosis of a nonepithelial malignant neoplasm. The microscopic slide was mailed abroad where one of the professors of high authority recognized an atypical form of melanoma. I did not agree with this opinion: neither clinical data nor the morphological pattern supported the diagnosis of a melanoma. On the contrary, it indicated that it is no melanoma. The further course of the disease and the favorable effect of therapy confirmed my opinion. According to the principle accepted in the Institute of Oncology we classified this case to the enigmatic ones and decided to collect further material. I succeded in collecting seven cases of tumors of this type within almost 12 years. At present I can claim with certainty that this neoplasm

# Epithelioid Sarcoma: A sarcoma simulating a granuloma or a carcinoma

F.M.Enzinger Cancer 1970; 26: 1029

- „acidophilic fascial Sarcoma“
- 62 cases, M > F
- x = 23 years
- hand, forearm, lower leg
- nodular / multinodular growth along tendons, neurovascular structures
- 85% R, 30% MTS, 20% DOD

M, 43 years, slowly growth within months


m.

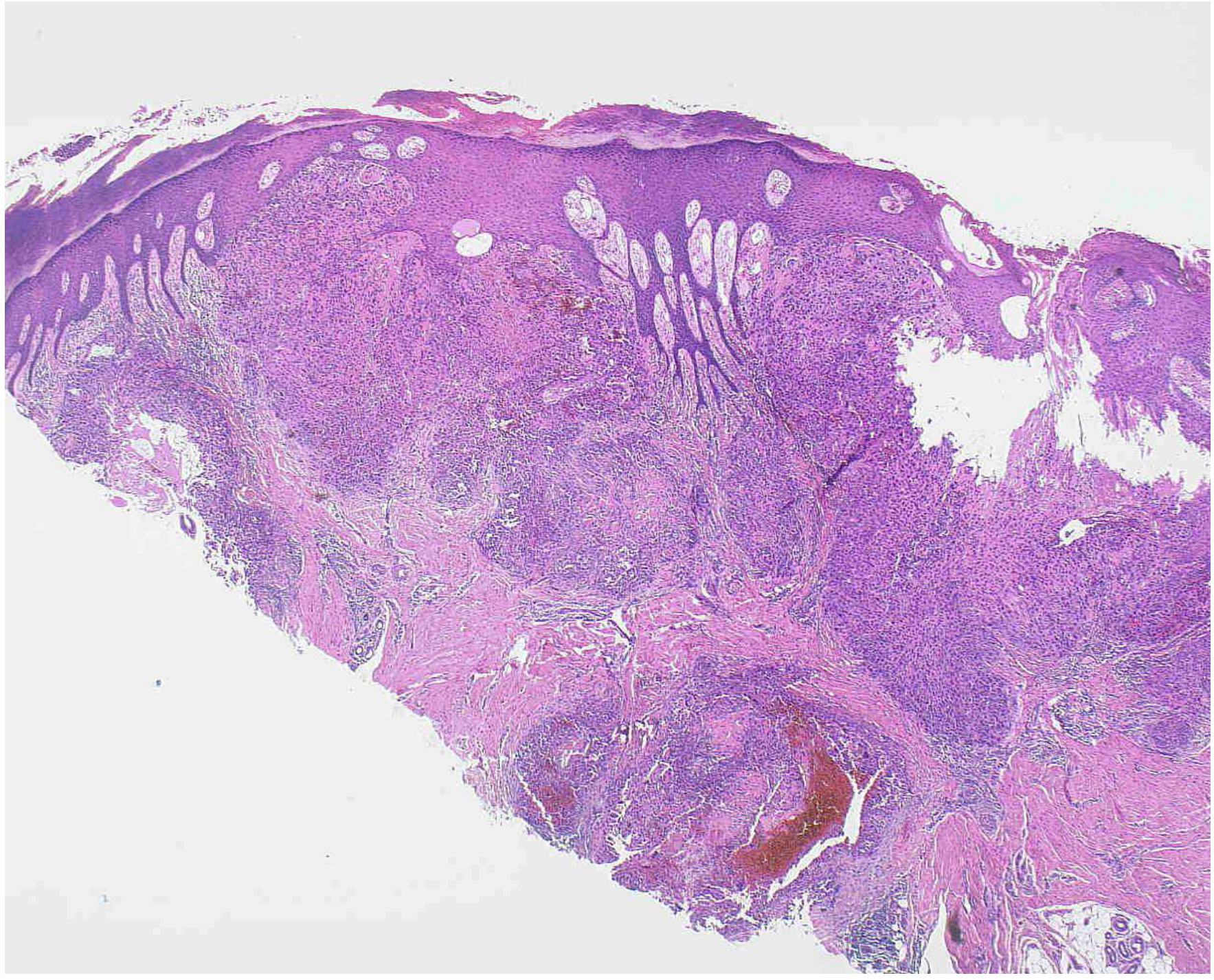
# Histology / Immunohistochemistry

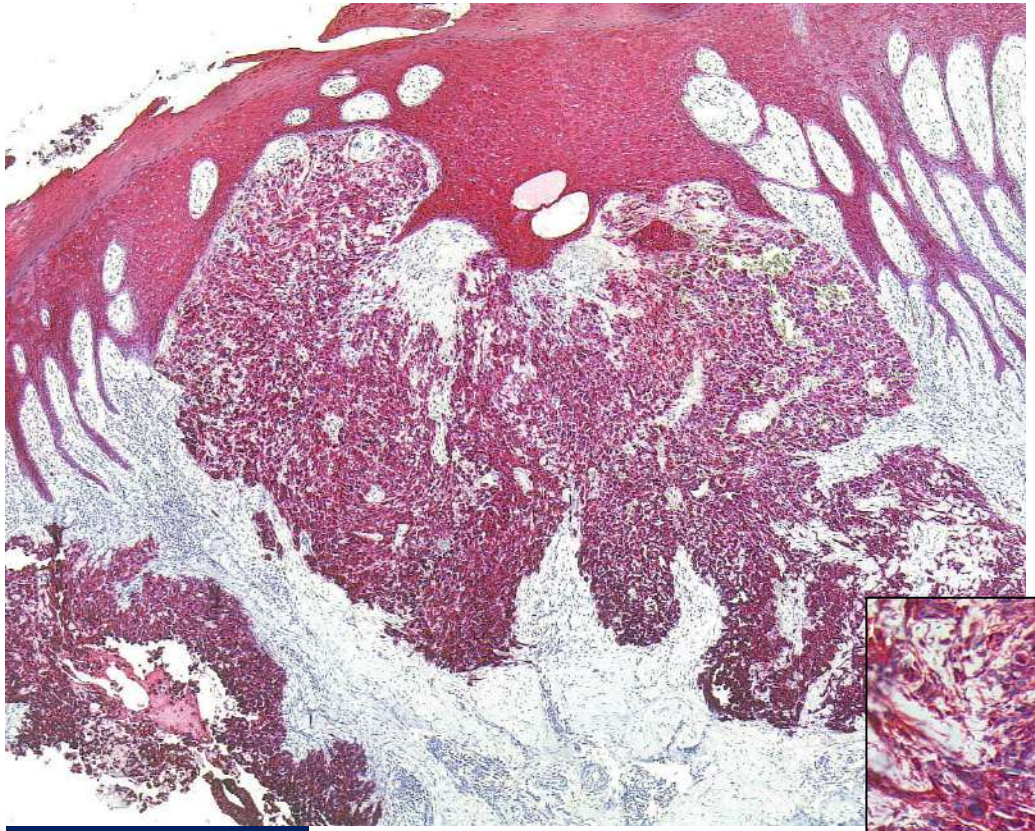
- nodular growth, central necrosis
- polygonal, epithelioid, spindled tumour cells
  slight atypia, scattered mitoses
- desmoplasia: fibroma-like variant
  pseudovascular clefts: angiomatoid variant
  calcification, ossifications, rare myxoid areas
- vimentin +, EMA +, pancytokeratin +, CD34 + (50%)

CK 8 +, CK 14 +, CK 19 +

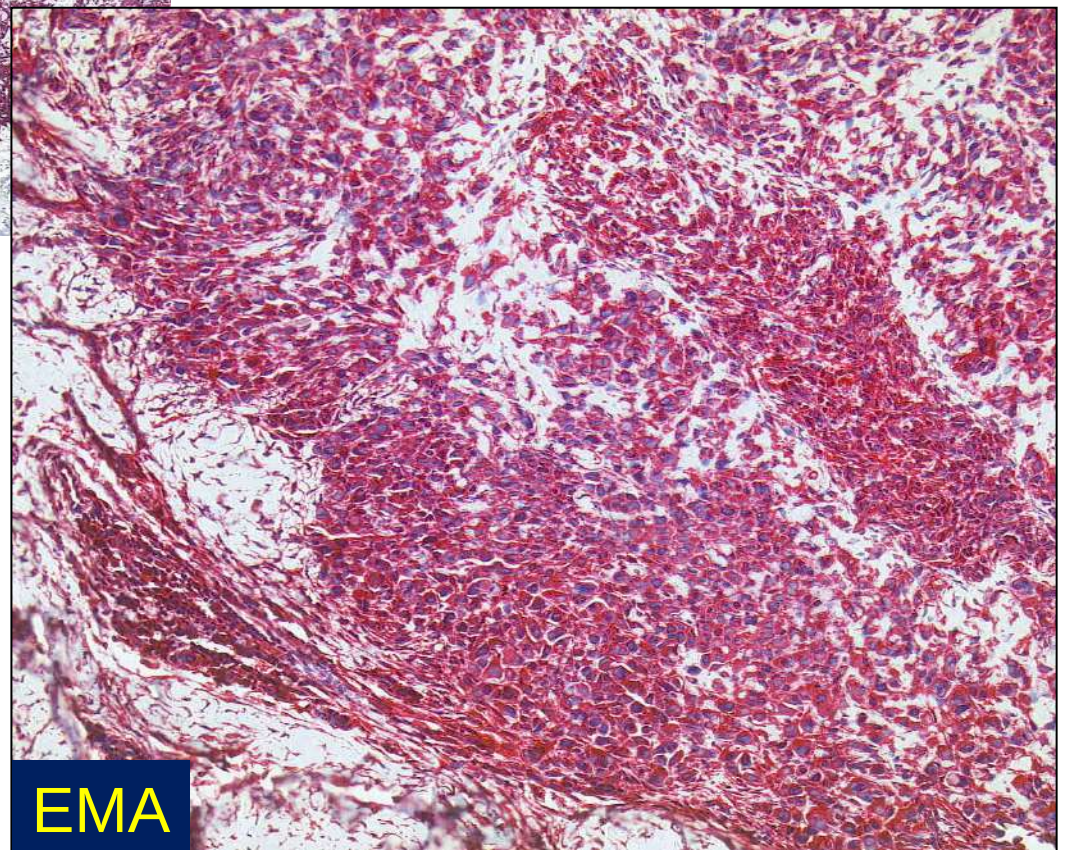
ERG + (38%, Miettinen et al. AJSP 2013; 37: 1580-1585)

CK 7 -, CK 20 -, CK 5/6 -, S-100 -, CD31 -

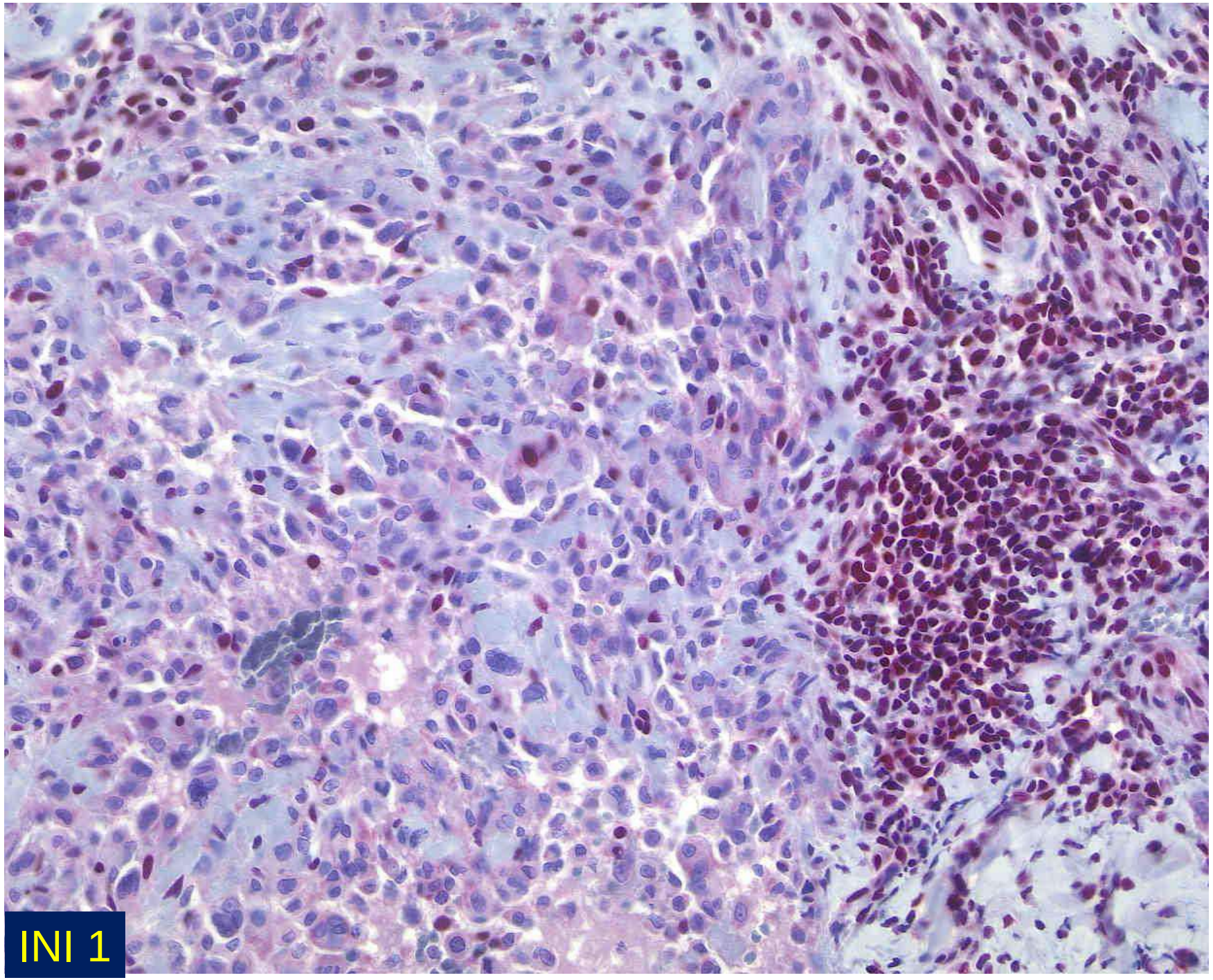




MNF 116



EMA


INI 1

# *SMARCB1/INI1* tumor suppressor gene is frequently inactivated in epithelioid sarcomas

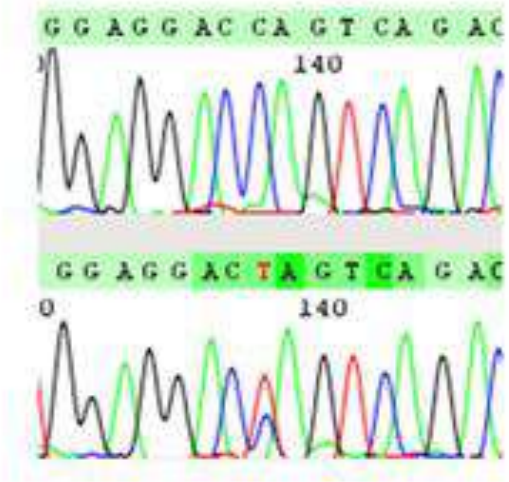
P Modena et al. Cancer Res 2005; 65: 4012

- long arm of chromosome 22
- suppressorgene, inhibition of proliferation
- induction of „cellular senescence“
- modulation of actin cytoskeleton
- inactivation in epithelioid sarcoma
- point mutation in renal / extrarenal malignand rhabdoid tumour

# Infrequent *SMARCB1/INI1* gene alteration in ES

## U. Flucke et al. Hum Pathol 2009; 40: 1361

| Case | Sex | Age | Site | INI/BAF47 AB | Genetic alteration |
|---|---|---|---|---|---|
| 1 | Male | 15 | foot | - | - |
| 2 | Male | 47 | not known | - | - |
| 3 | Male | 63 | finger | + | - |
| 4 | Female | 22 | perineum | - | C>T transition |
| 5 | Male | 52 | wrist | - | - |
| 6 | Male | 22 | finger | - | - |
| 7 | Male | 73 | finger | - | - |
| 8 | Female | 25 | pretibial | - | - |
| 9 | Male | 21 | upper arm | - | - |
| 10 | Female | 19 | vulva | - | - |
| 11 | Male | 53 | hand | - | - |
| 12 | Female | 46 | vulva | - | - |
| 13 | Female | 46 | hand | - | - |
| 14 | Female | 16 | lower leg | - | no DNA available |
| 15 | Male | 55 | knee | - | no DNA available |

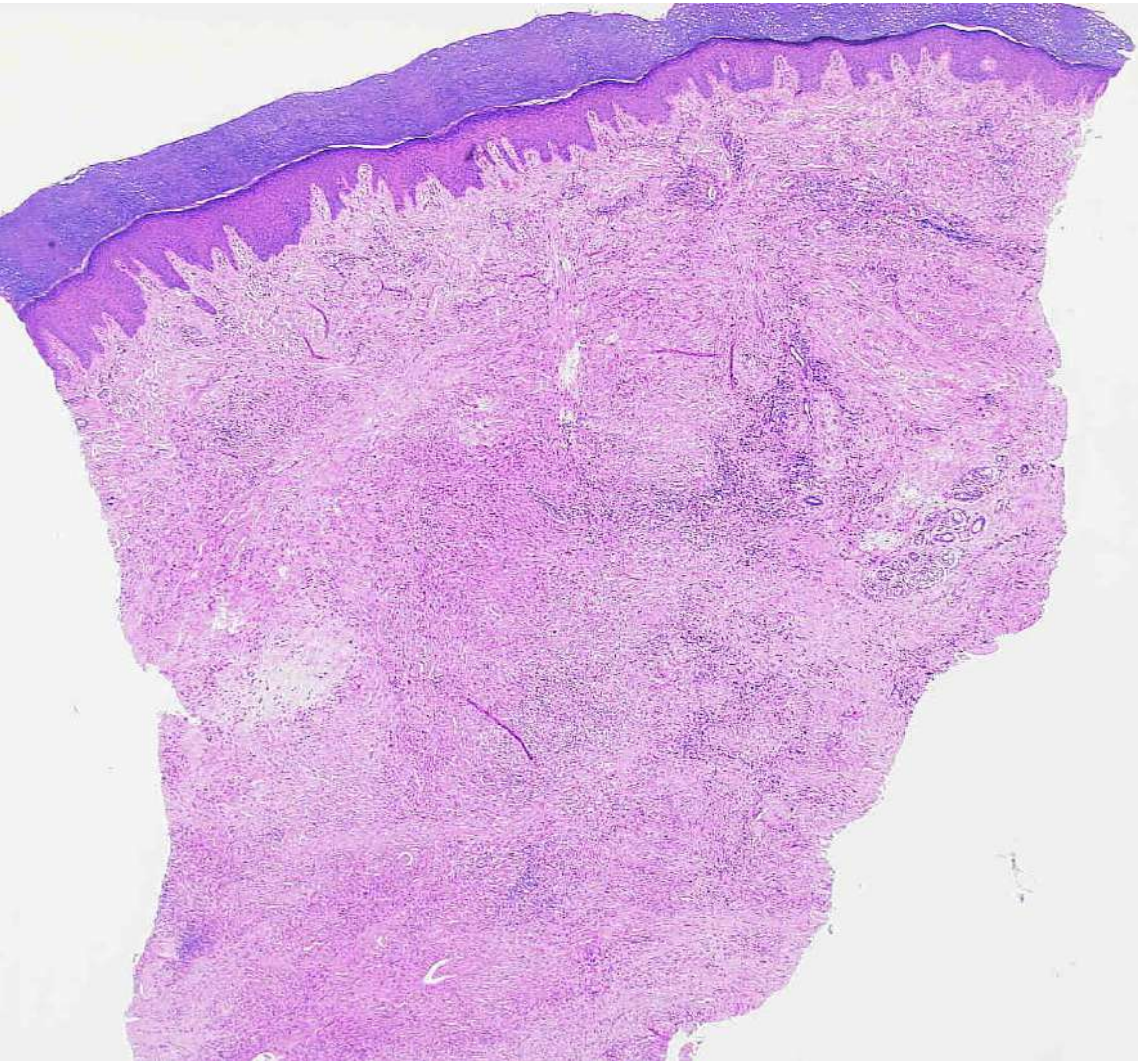



C>T transition of exon 6 at position 257 where CAG codon changed to stopcodon TAG

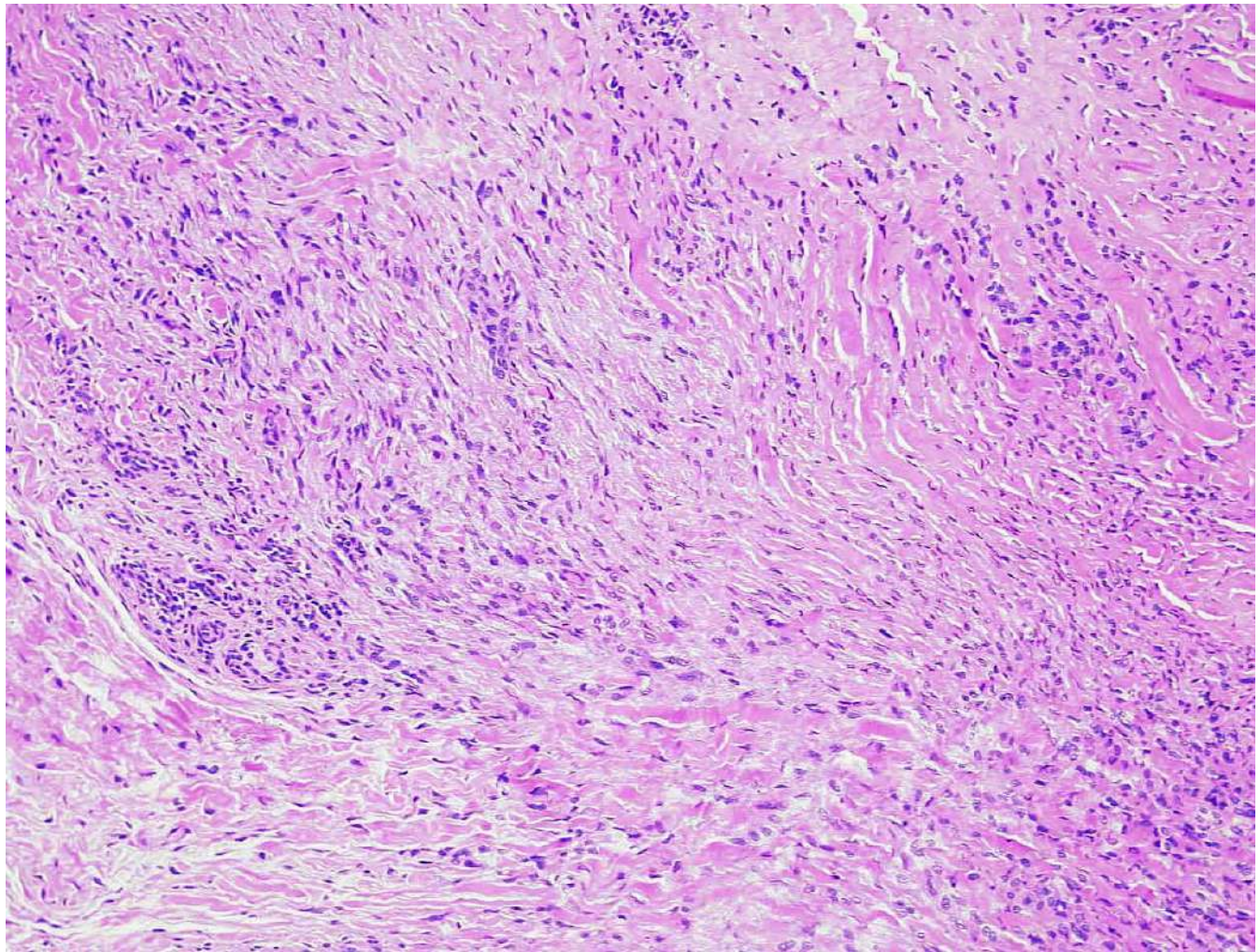
# epithelioid Sarcoma - Variants

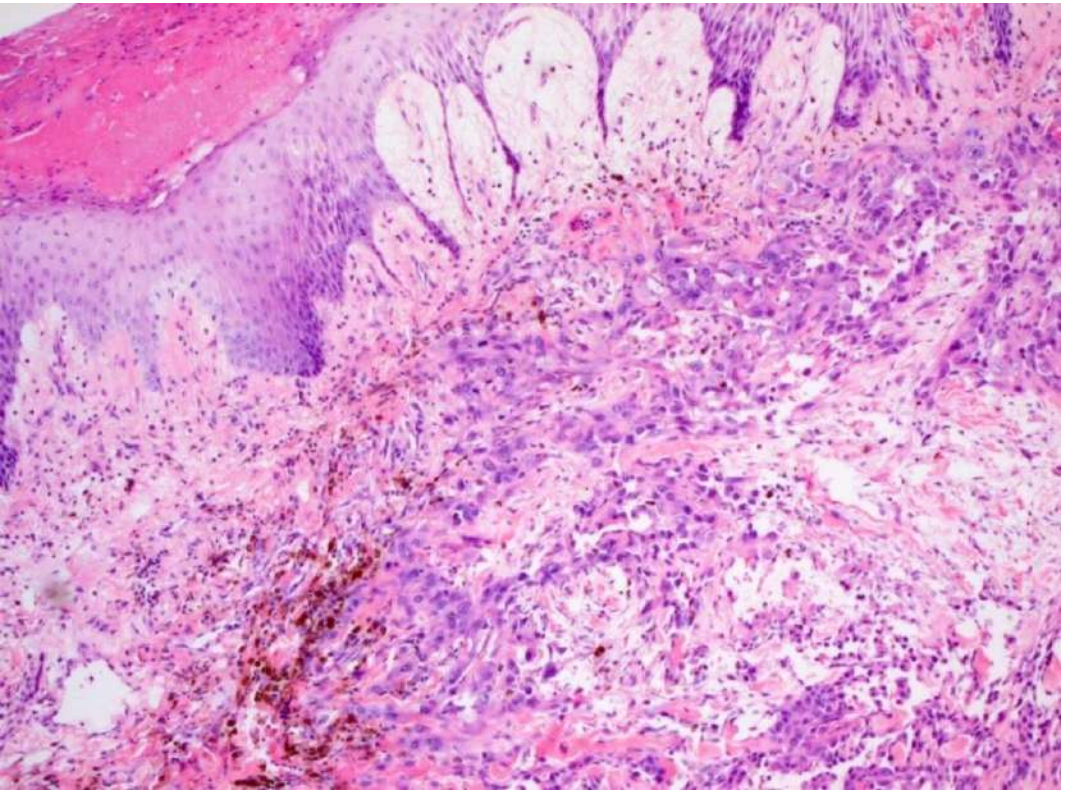
1. Fibroma-like variant
   spindled > epithelioid cells, storiform growth
   DD: dermatofibroma, fibroma
2. Angiomatoid variant
   cystic, blood filled spaces
   DD: EHE, epithelioid angiosarcoma
3. Myxoid variant
   DD: Myxofibrosarcoma…
4. Proximal (large cells) variant
   nodular, sheeth-like growth
   large, rhabdoid tumour cells, necrosis
   DD: epith.AS, MTS-CA, rhabdoid Tumour

# Spectrum of epithelioid Sarcoma

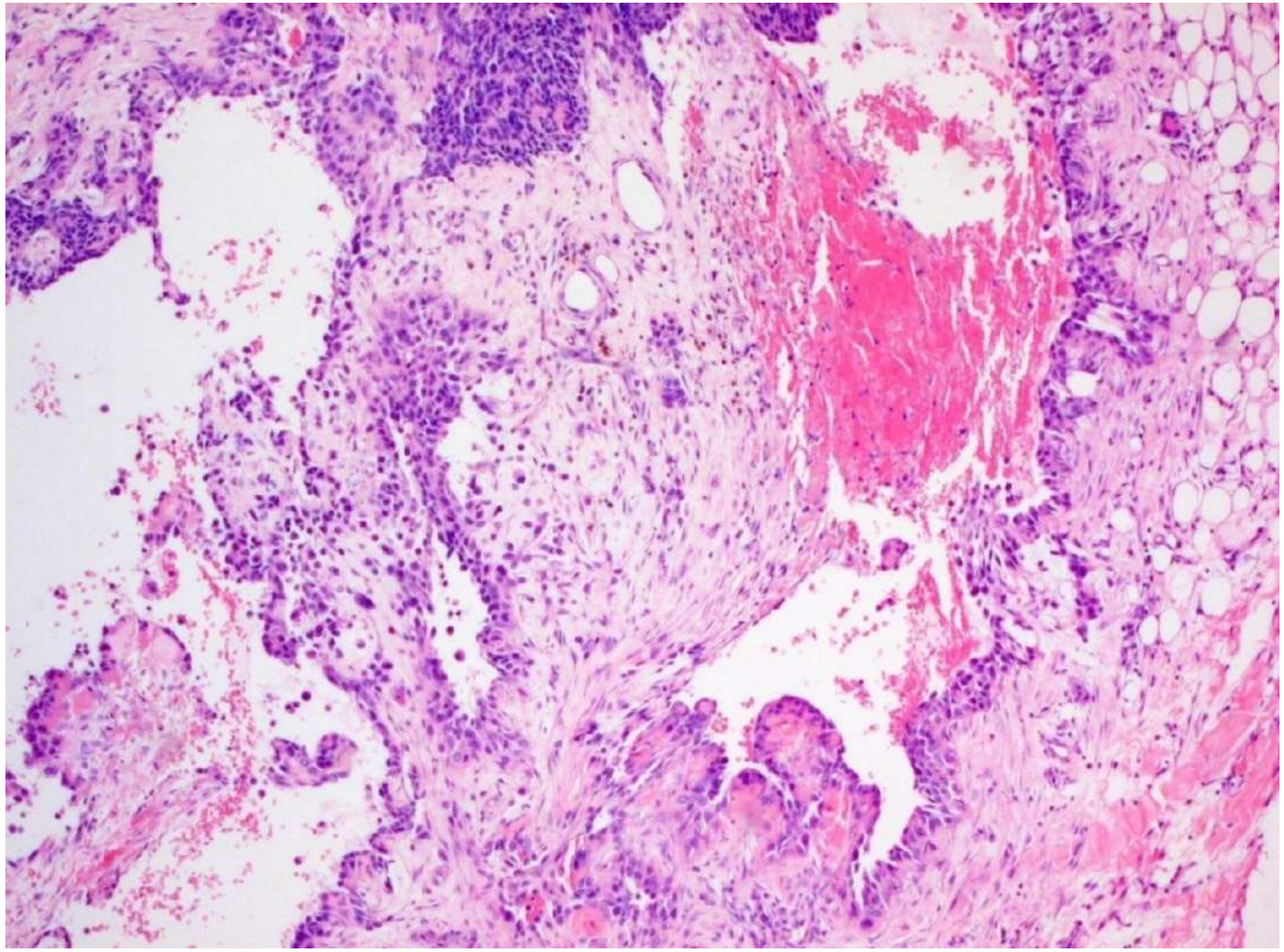


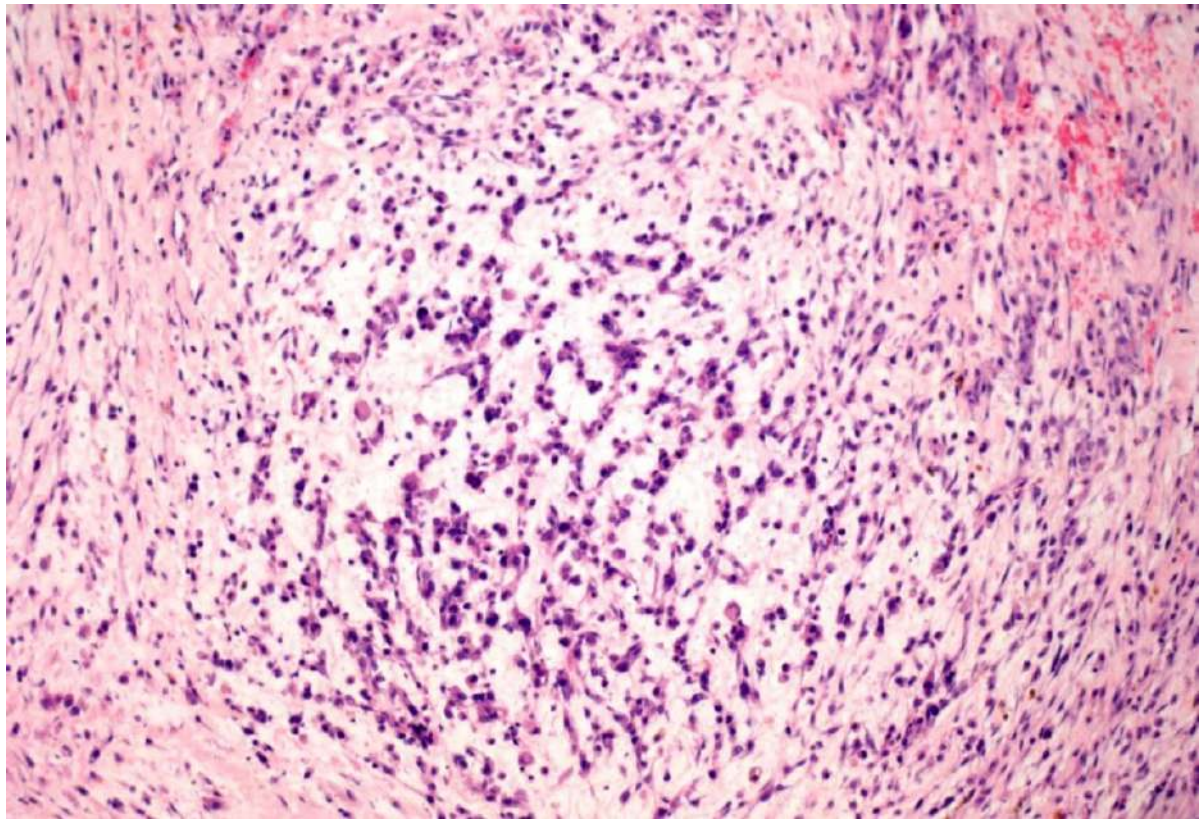
fibroma-like variant



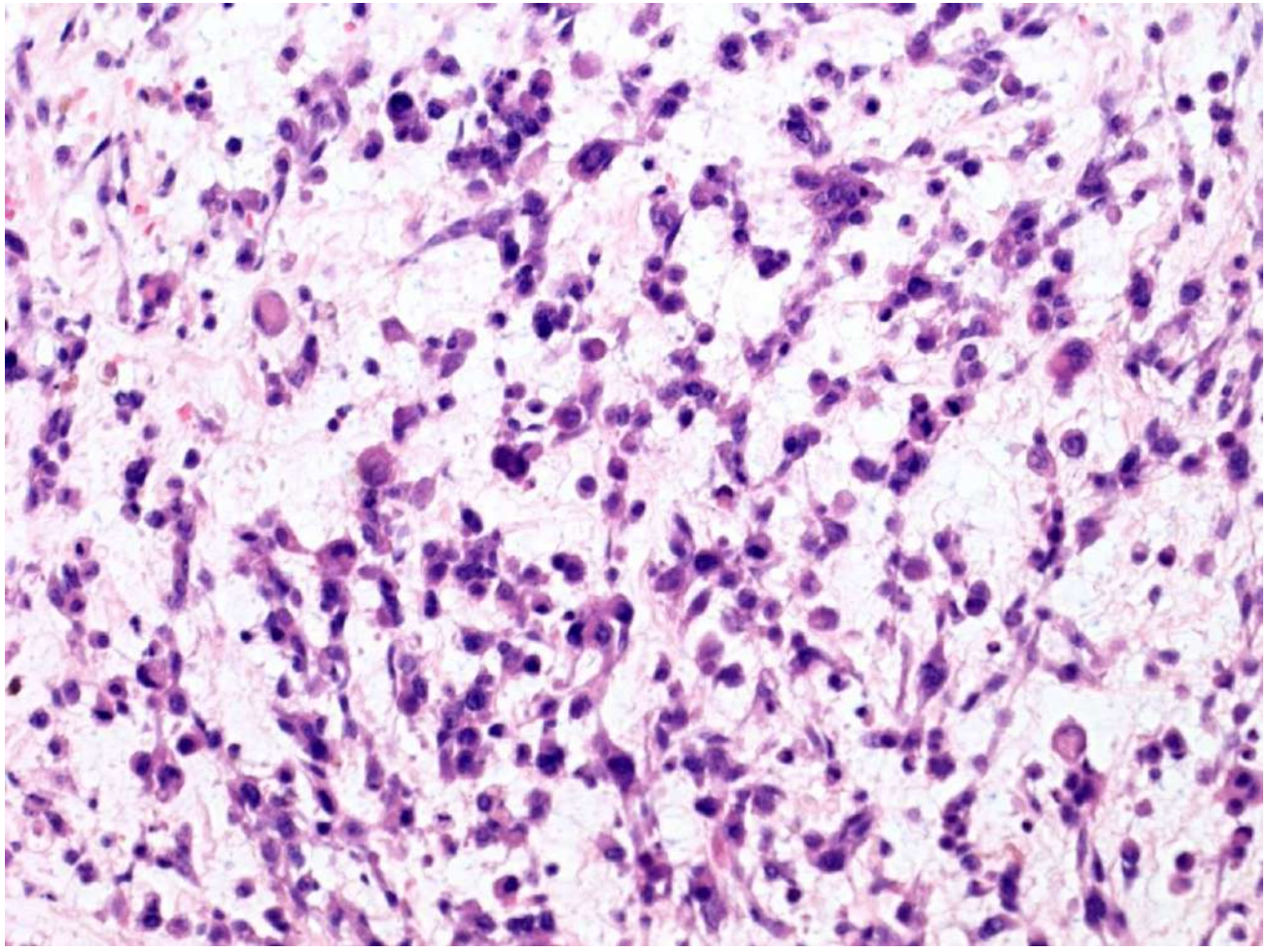


# angiomatoid variant





myxoid variant



# proximal-type epithelioid Sarcoma

older age group than distal type

deep soft tissue, pelvis, perineum, intracavitary

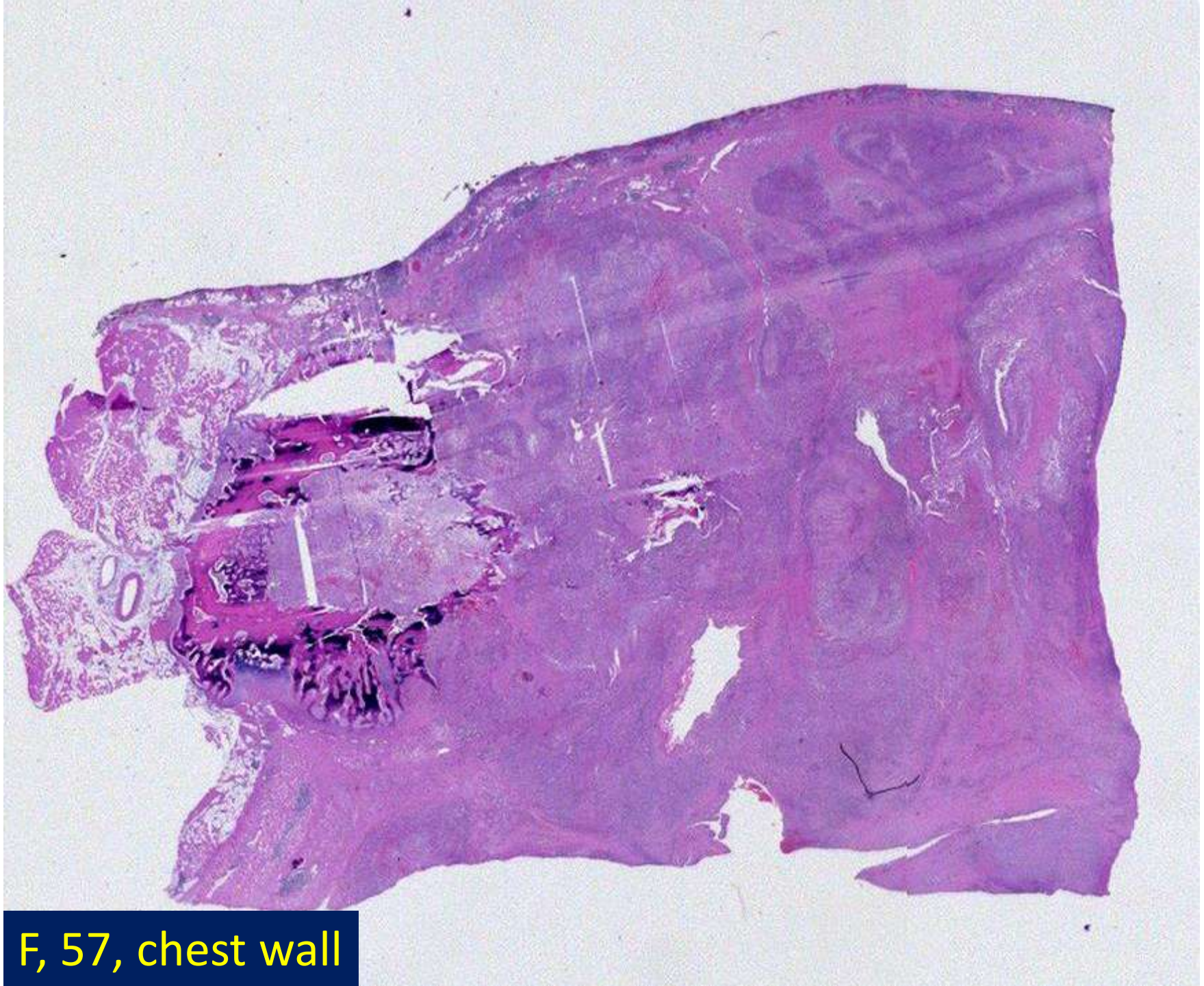
represents morphological form of progression

aggressive clinical course

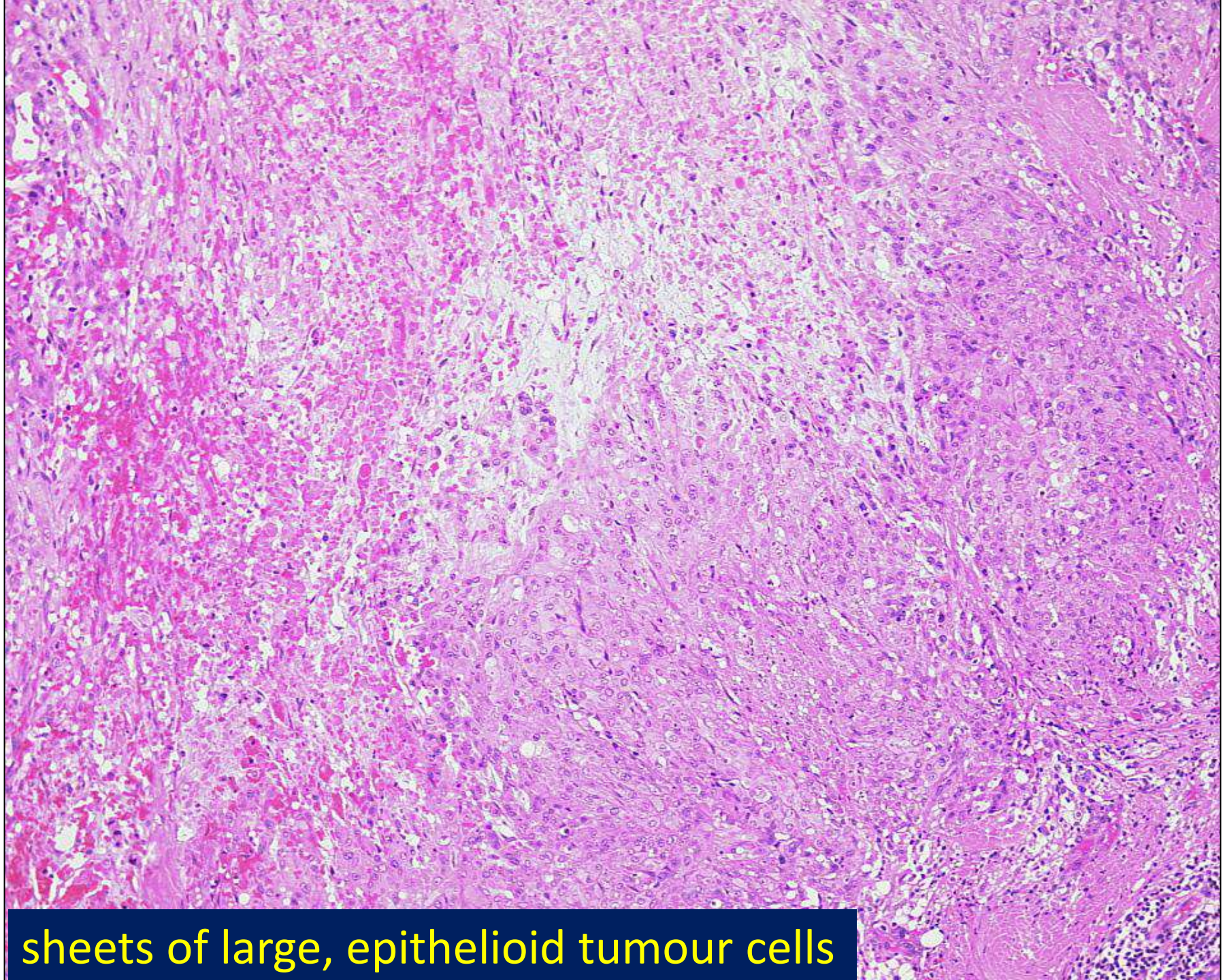
inactivation of *INI1/SMARCB1* (ch 22q11)

IM: positive: vimentin, EMA, cytokeratin
CD34 (50%)
desmin rarely
ERG (10-60%)

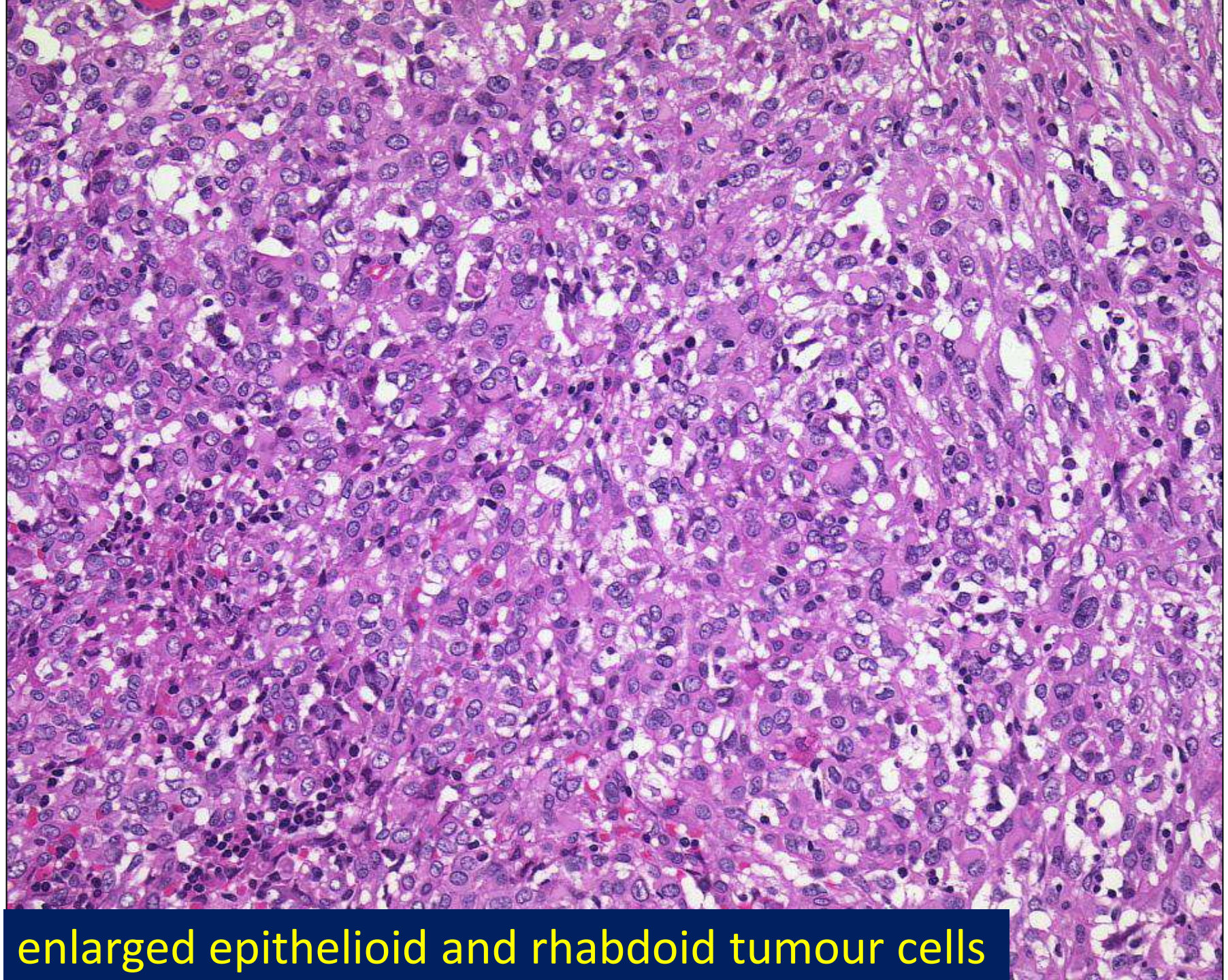
negative: INI1
CD31



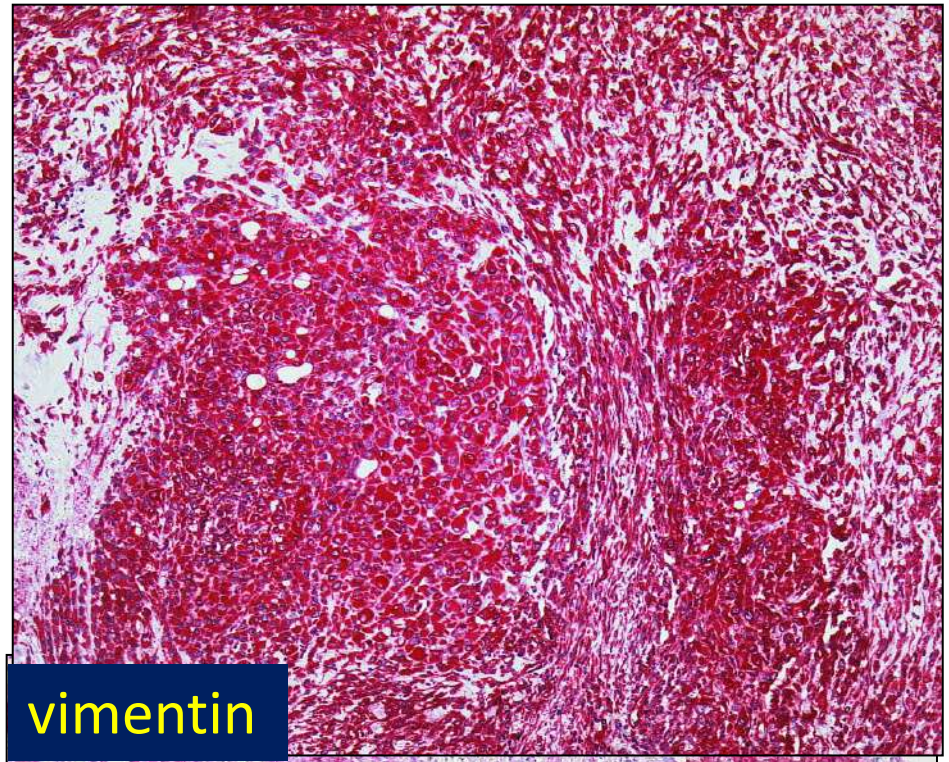
F, 57, chest wall

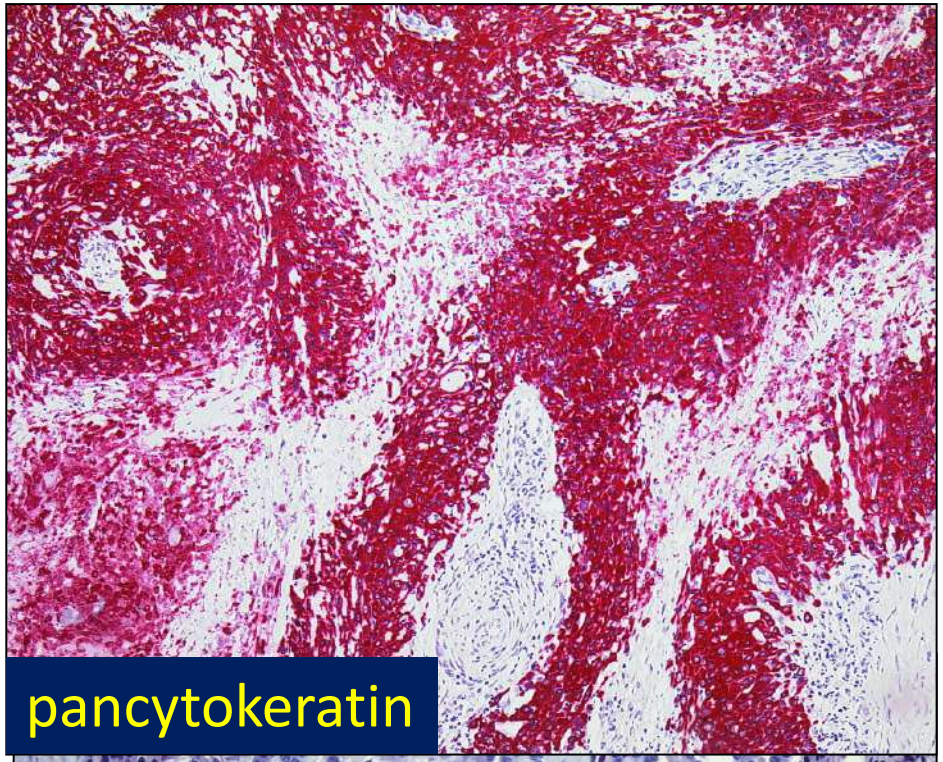


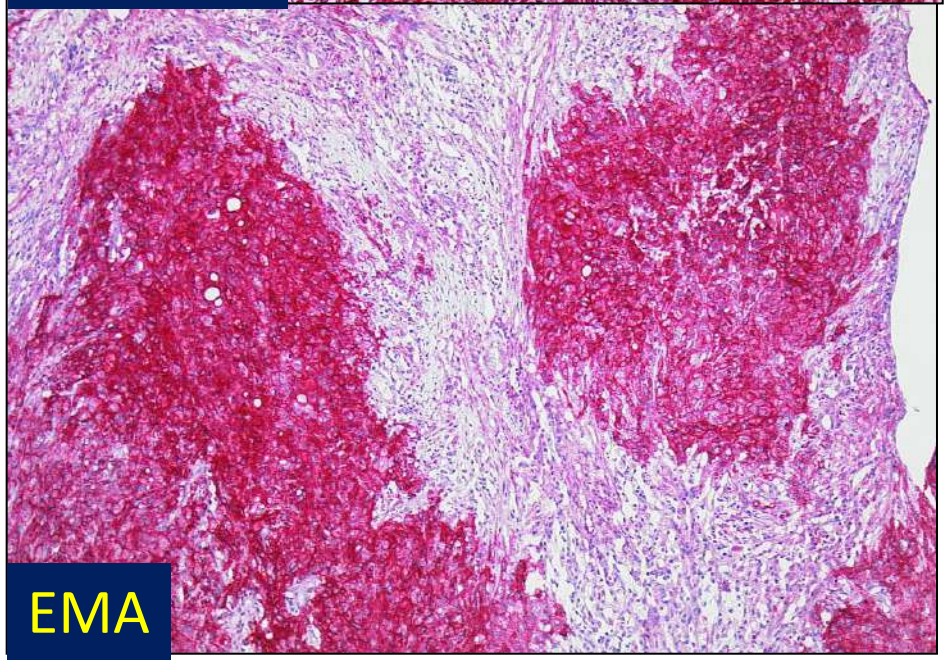
sheets of large, epithelioid tumour cells

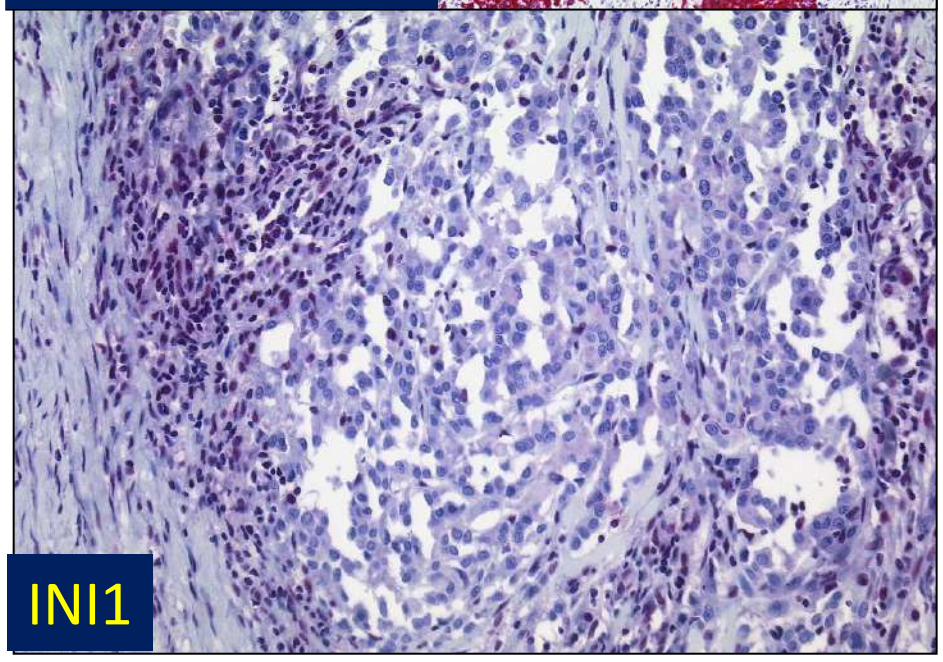


enlarged epithelioid and rhabdoid tumour cells

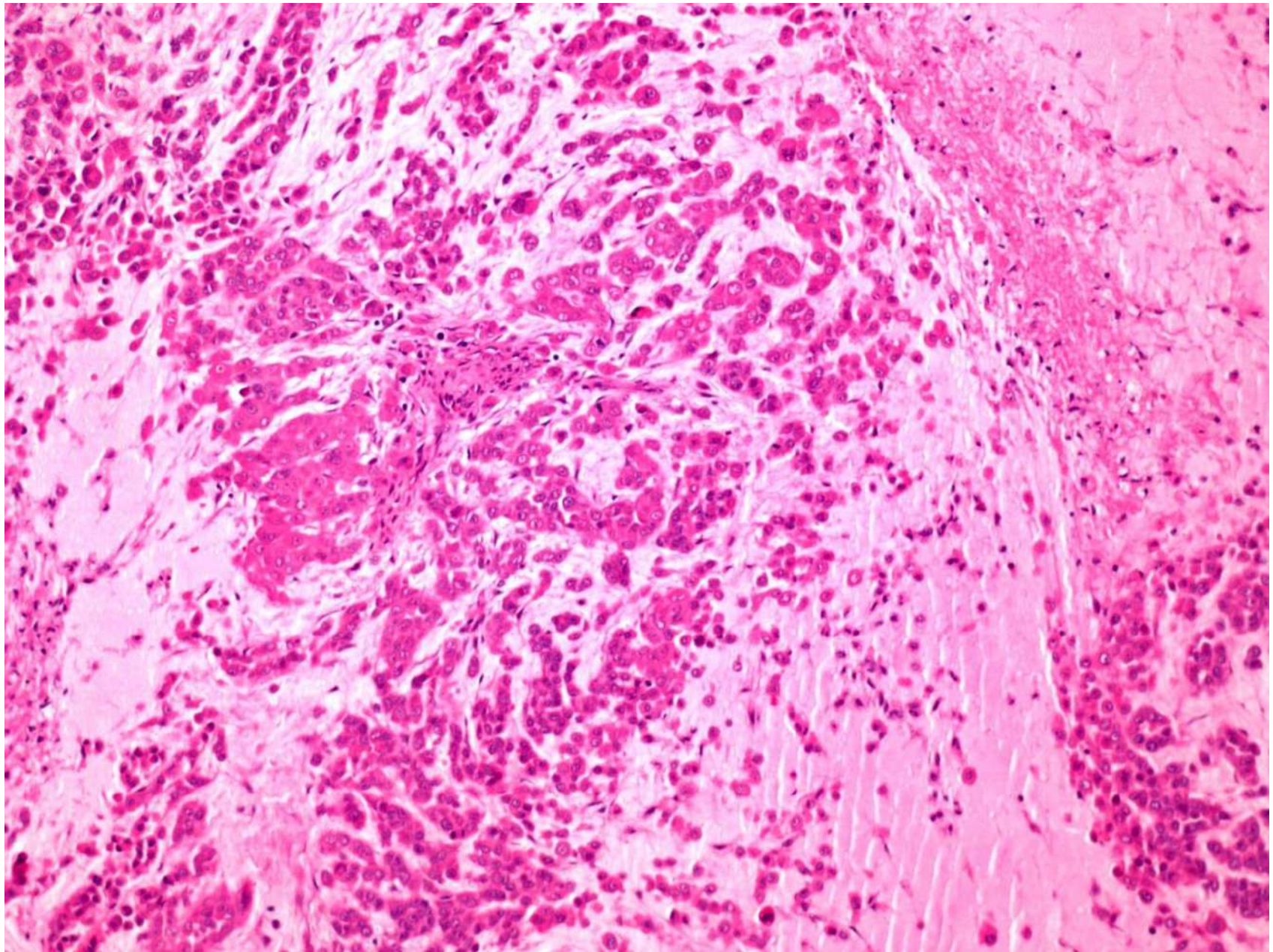

vimentin

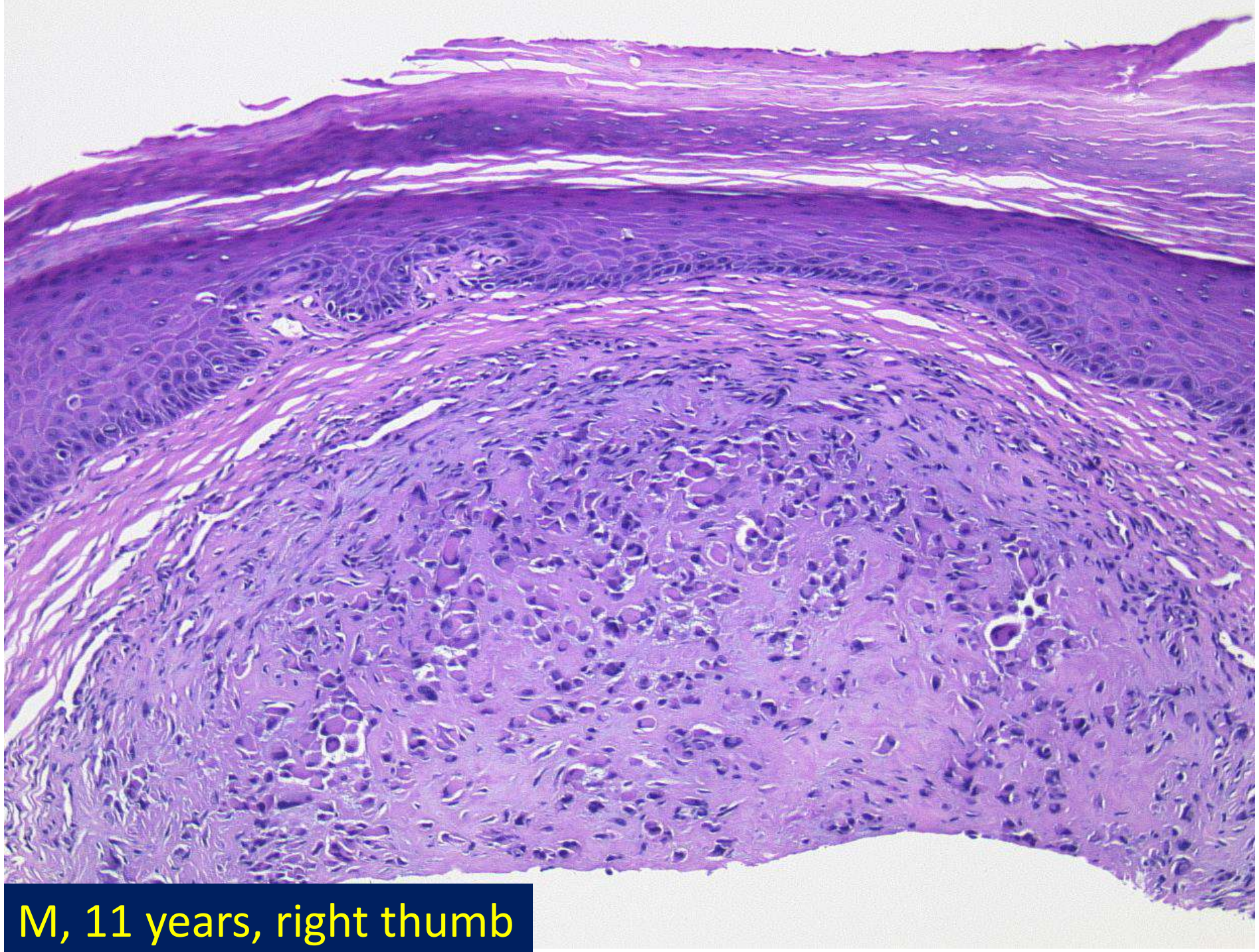

pancytokeratin


EMA

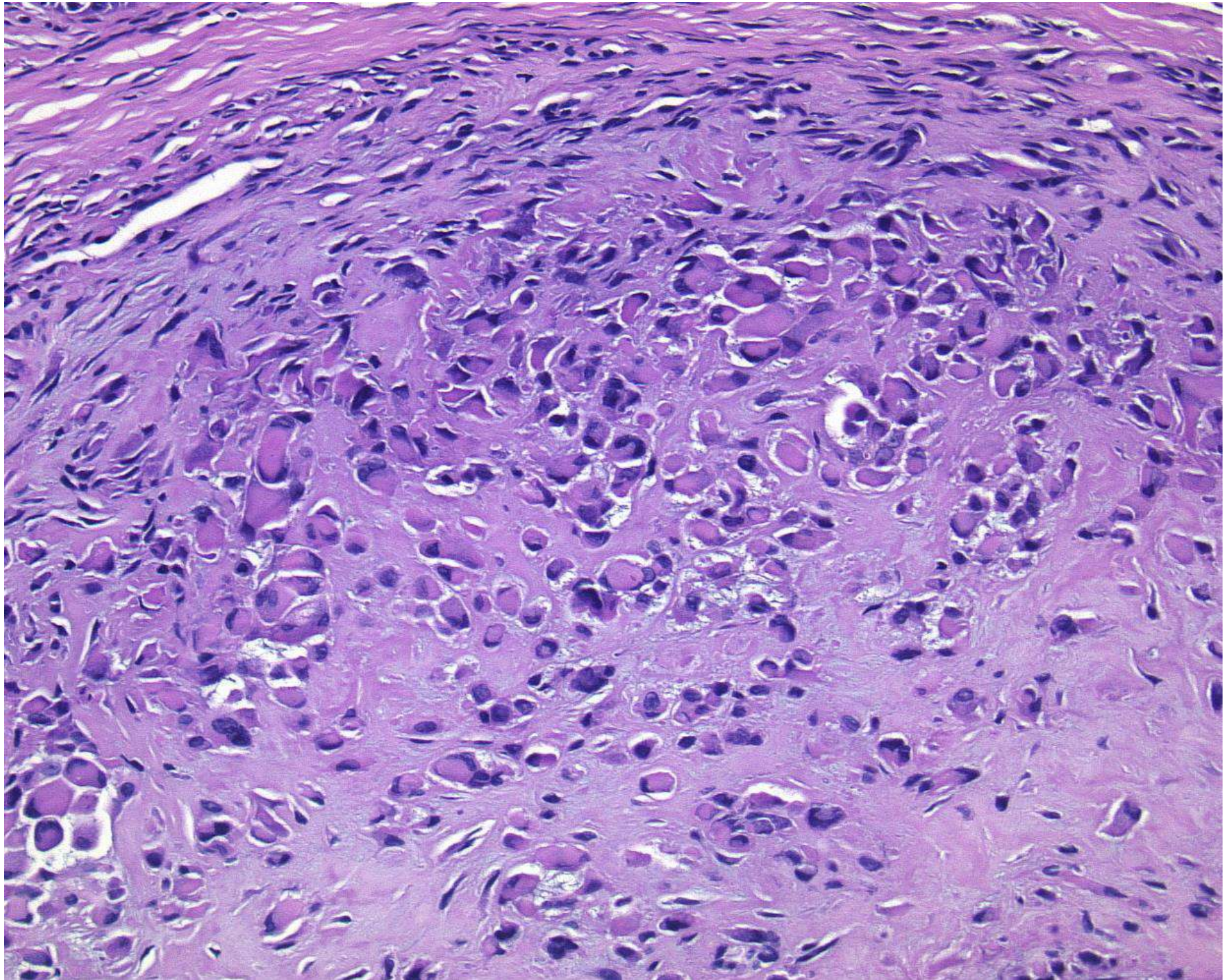

INI1

# proximal-type myxoid variant

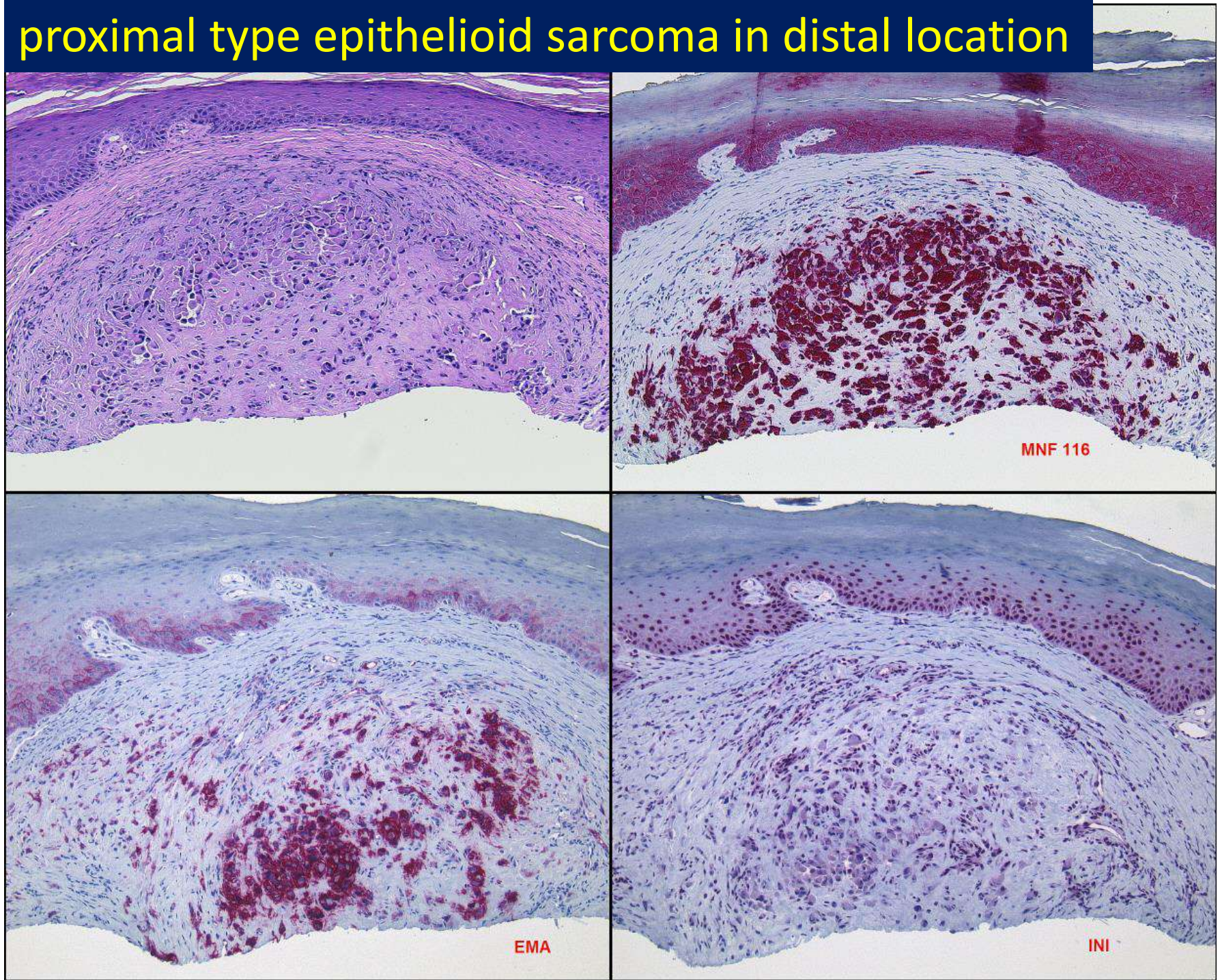




M, 11 years, right thumb



# proximal type epithelioid sarcoma in distal location



# Relationship of epithelioid sarcoma and proximal-type epithelioid sarcoma

Proximal-type epithelioid sarcoma represents the morphological form of progression of epithelioid sarcoma….

# Molecular profiling and immunohistochemical characterization unveils differences between classic-type and proximal-type epithelioid sarcoma

(F Cappello et al. USCAP 2023)

11 classic-type epithelioid sarcoma

8 proximal-type epithelioid sarcoma

classic-type ES: expression of genes involved in cell adhesion and migration
GATA3 -, CDH2/N-Cadherin 4/6 +

proximal-type ES: expression of genes involved in chromatin remodeling and cell cycle regulation
GATA 3 5/8 +, CDH2/N-Cadherin -

**„Classic-type and proximal-type epithelioid sarcoma represent two biologically distinct entities based on their different transcriptional profiles!“**

# DD: proximal-type epithelioid Sarcoma

epithelioid haemangioendothelioma:

no solid growth, CD31 +

epithelioid angiosarcoma:

cytoplasmic vacuoles, erythrocytes, CD31 +

epithelioid MPNST (INI1 loss in 50%):

mixed growth (nests, cords), S-100 +

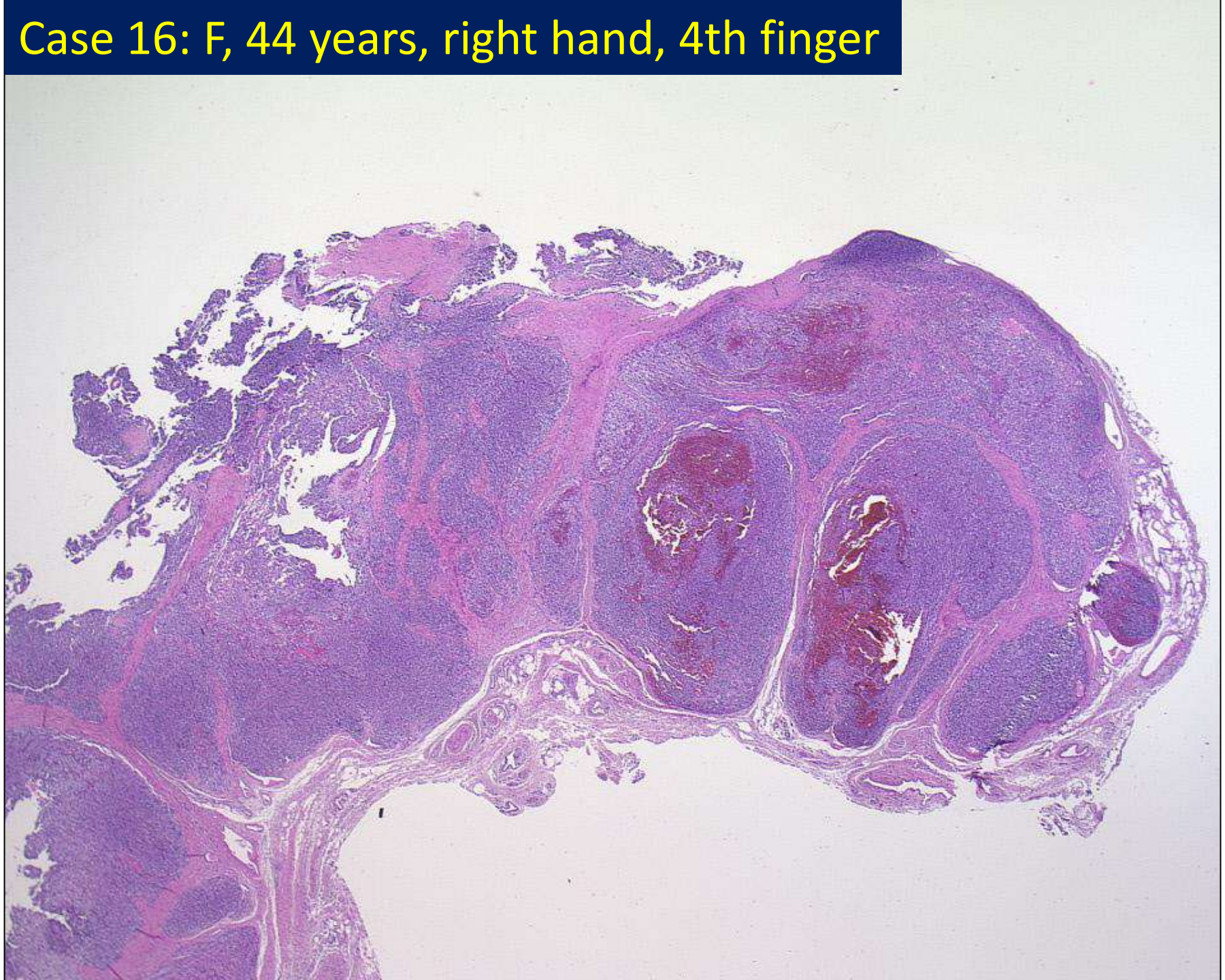
malignant rhabdoid tumour:

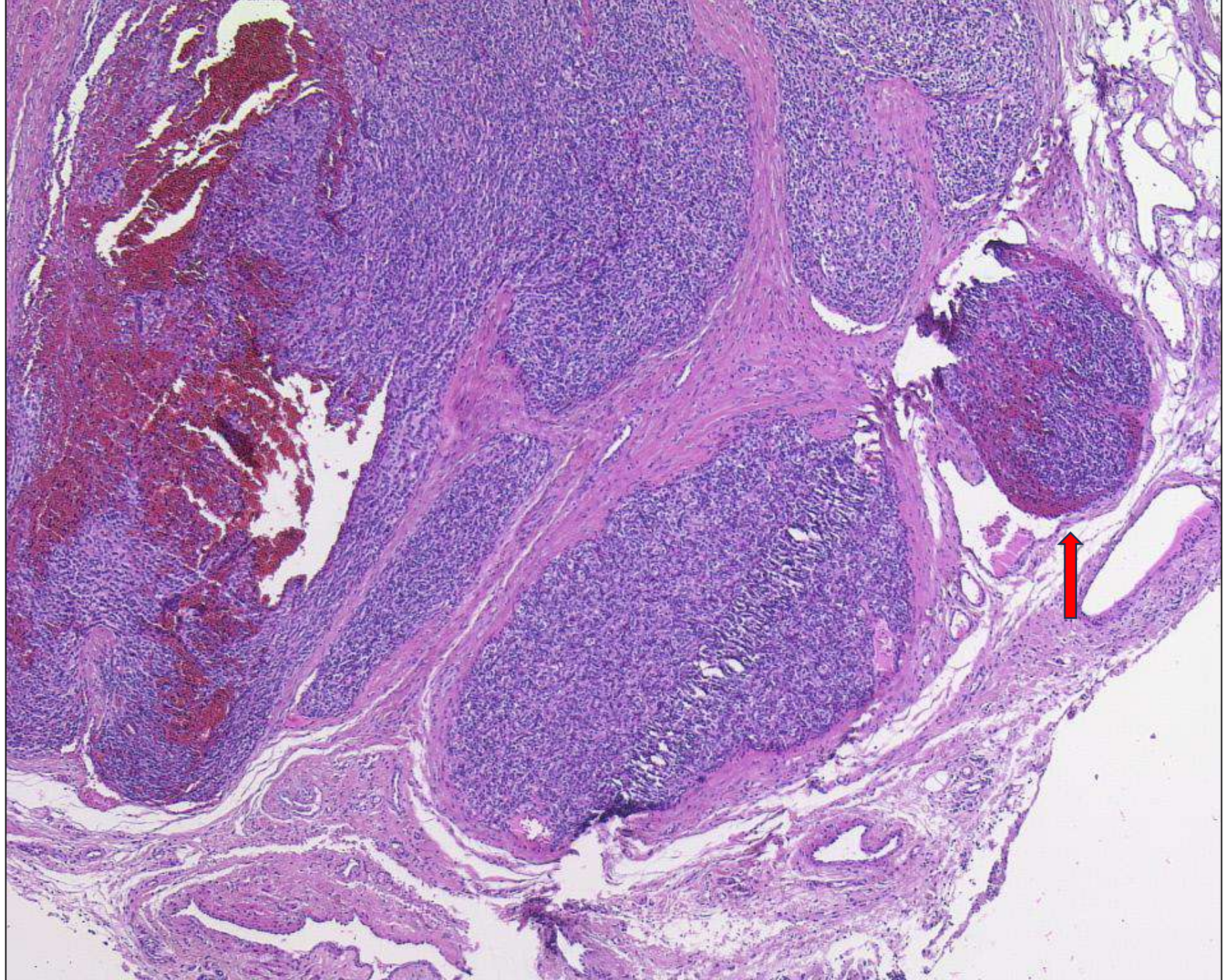
infants, CD 34 -

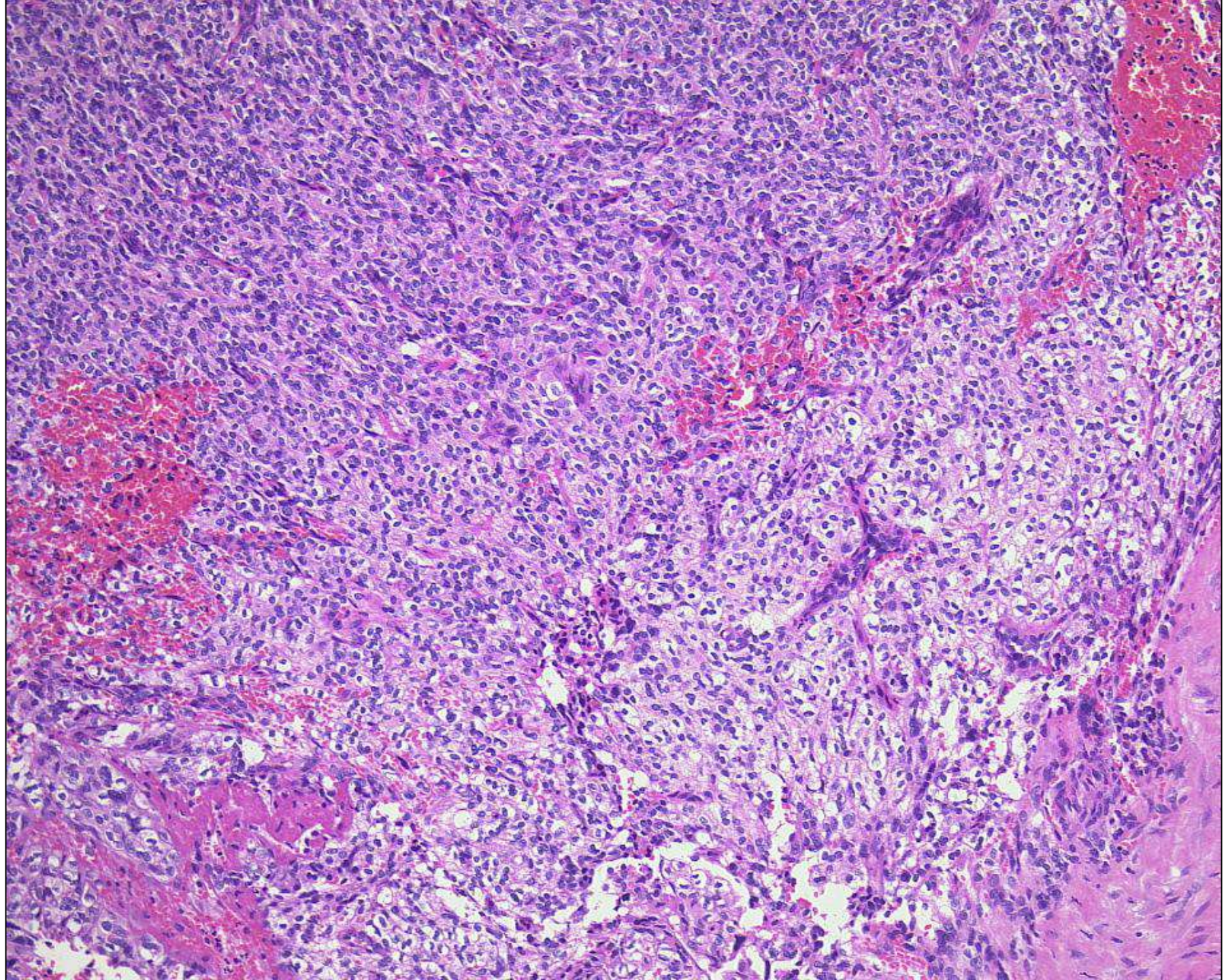
myoepithelial tumours (may show INI1 loss):

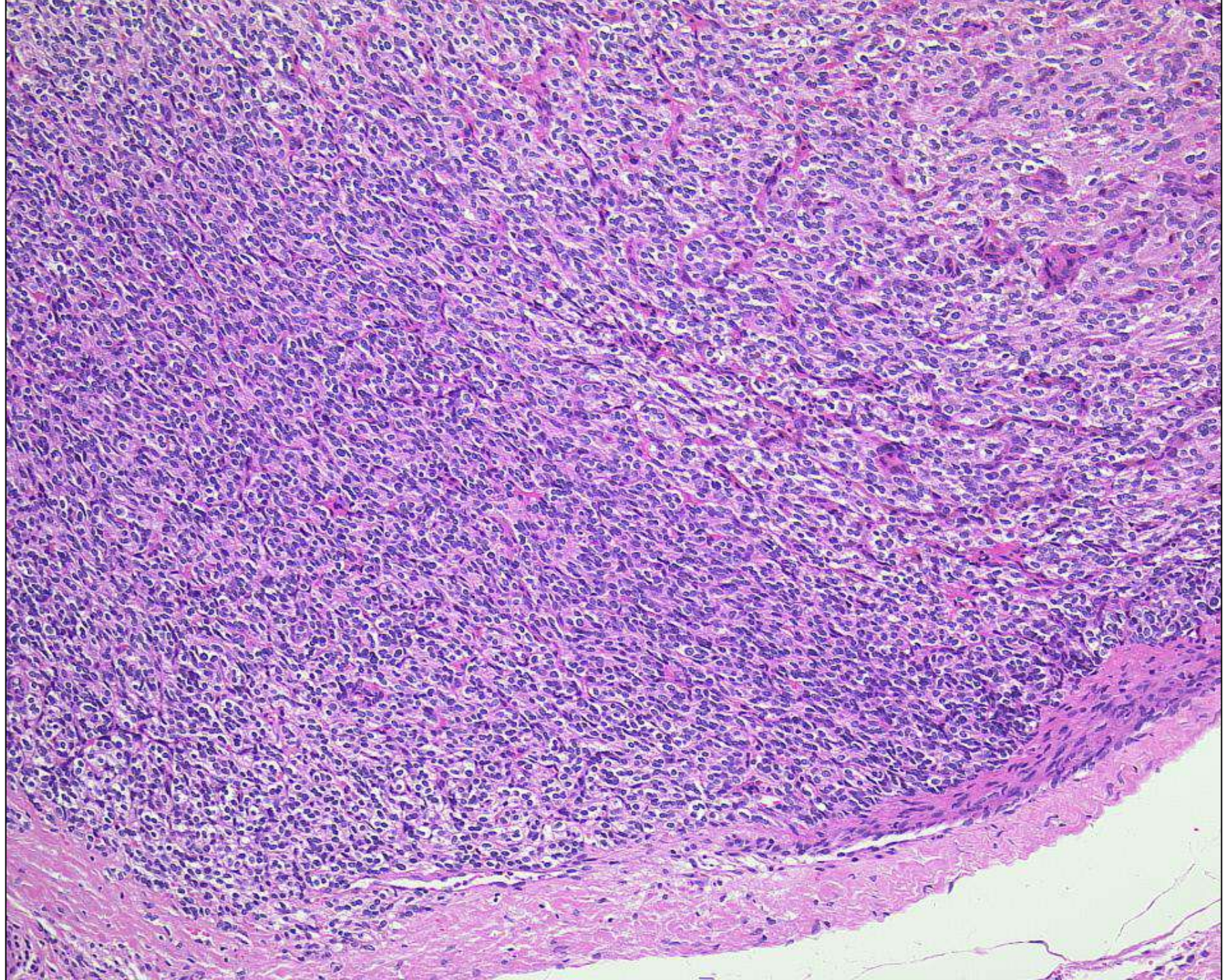
myxoid stroma, duct formation, more heterogenous, *EWSR1* rearrangement

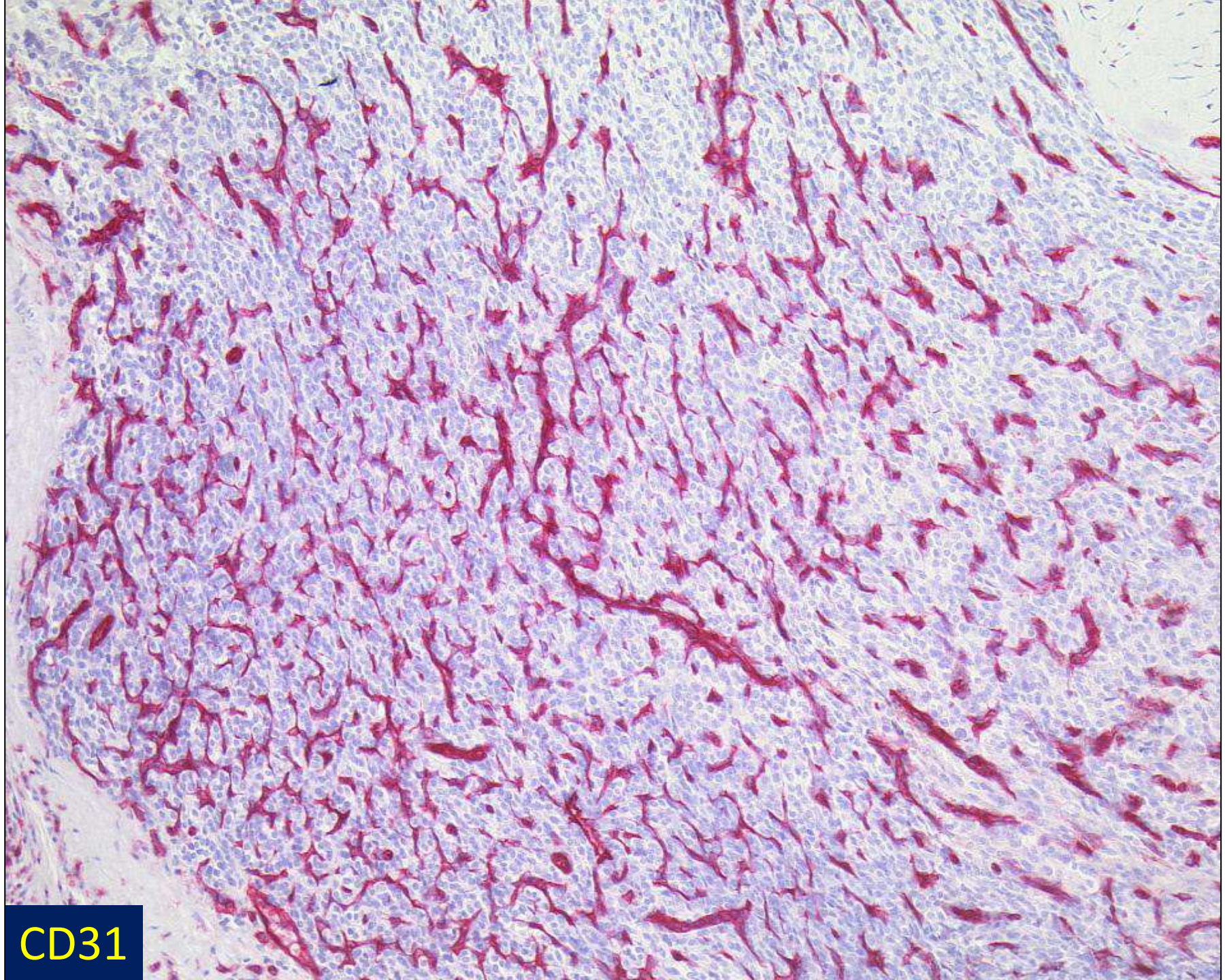
# Case 16: F, 44 years, right hand, 4th finger

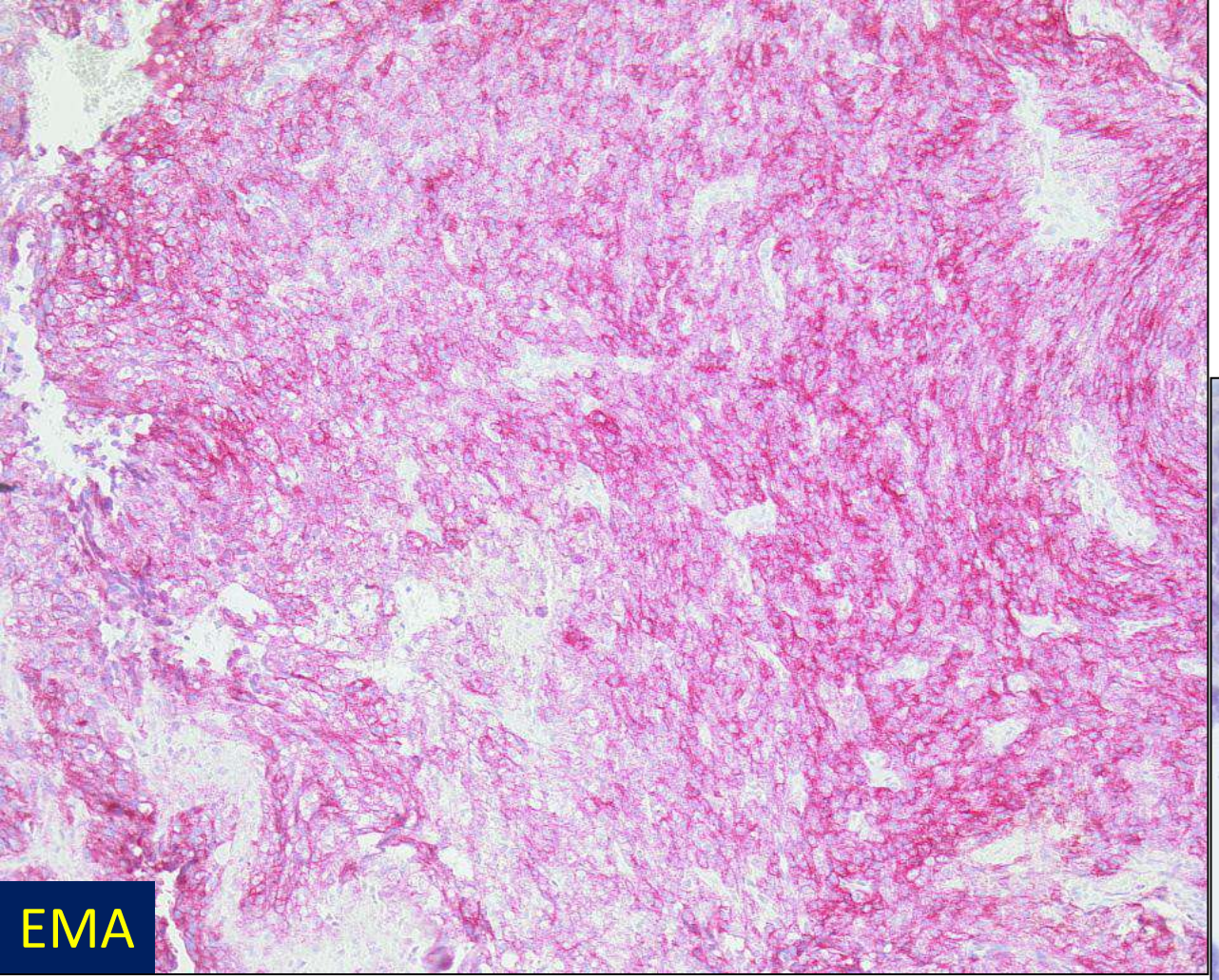


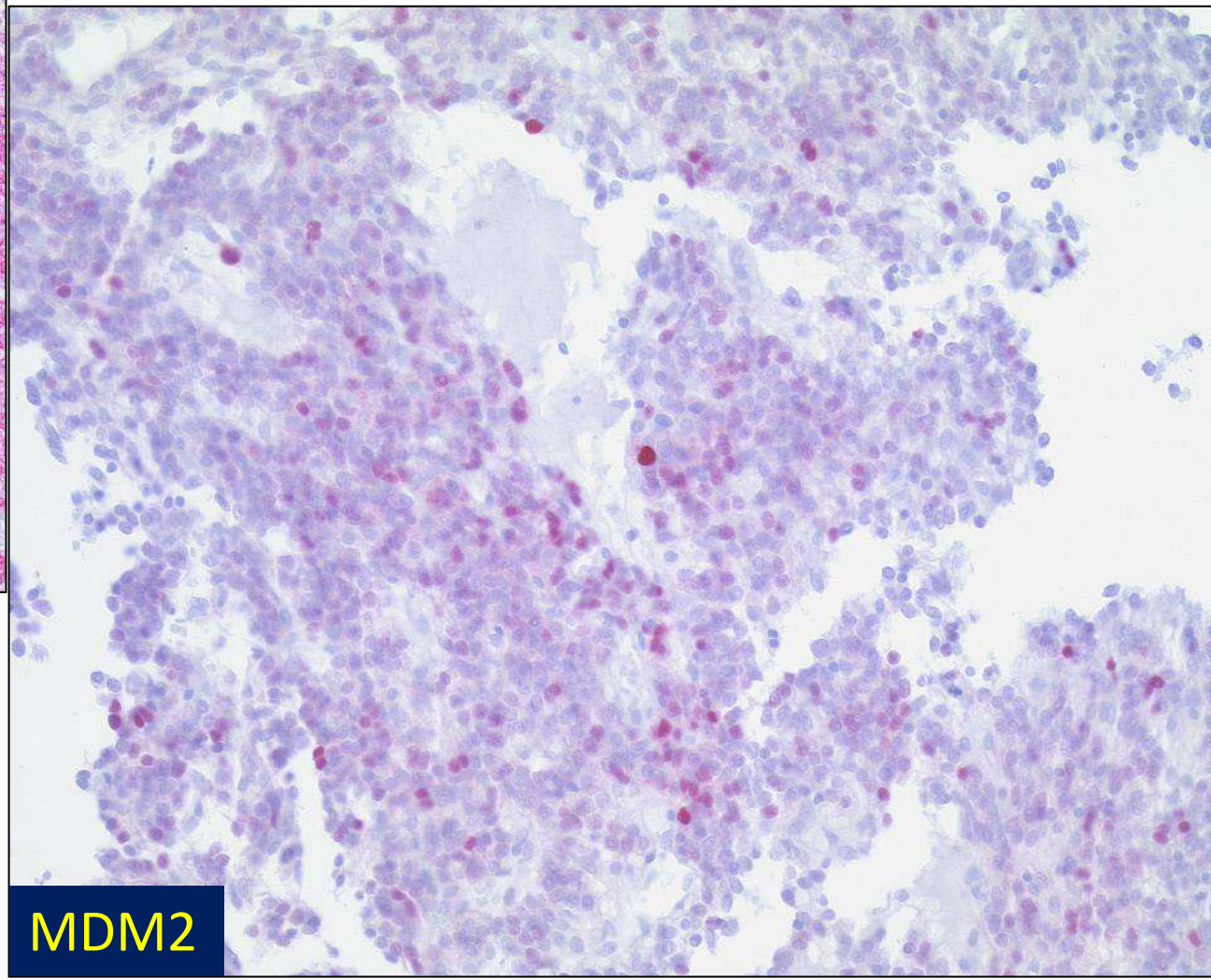


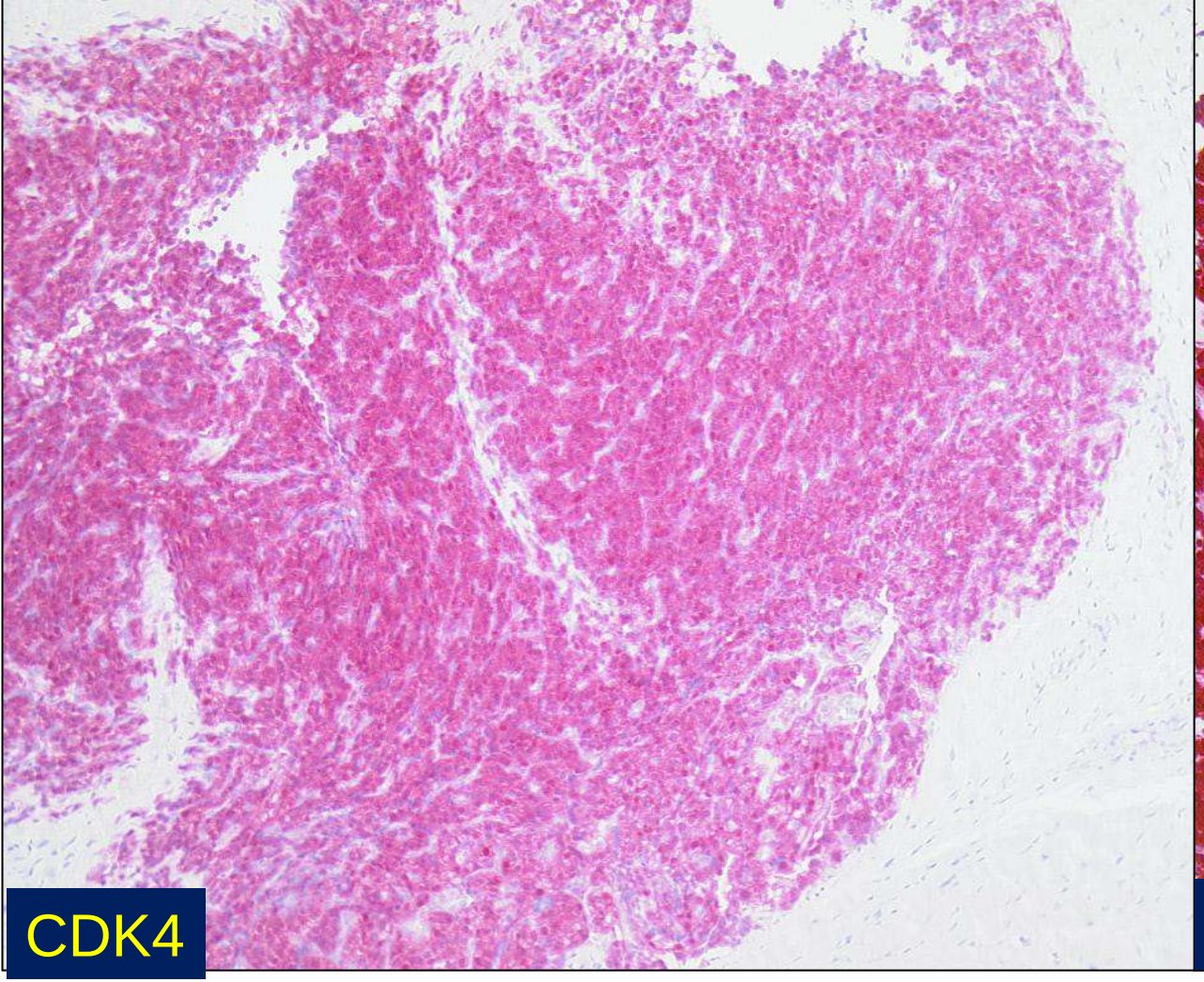


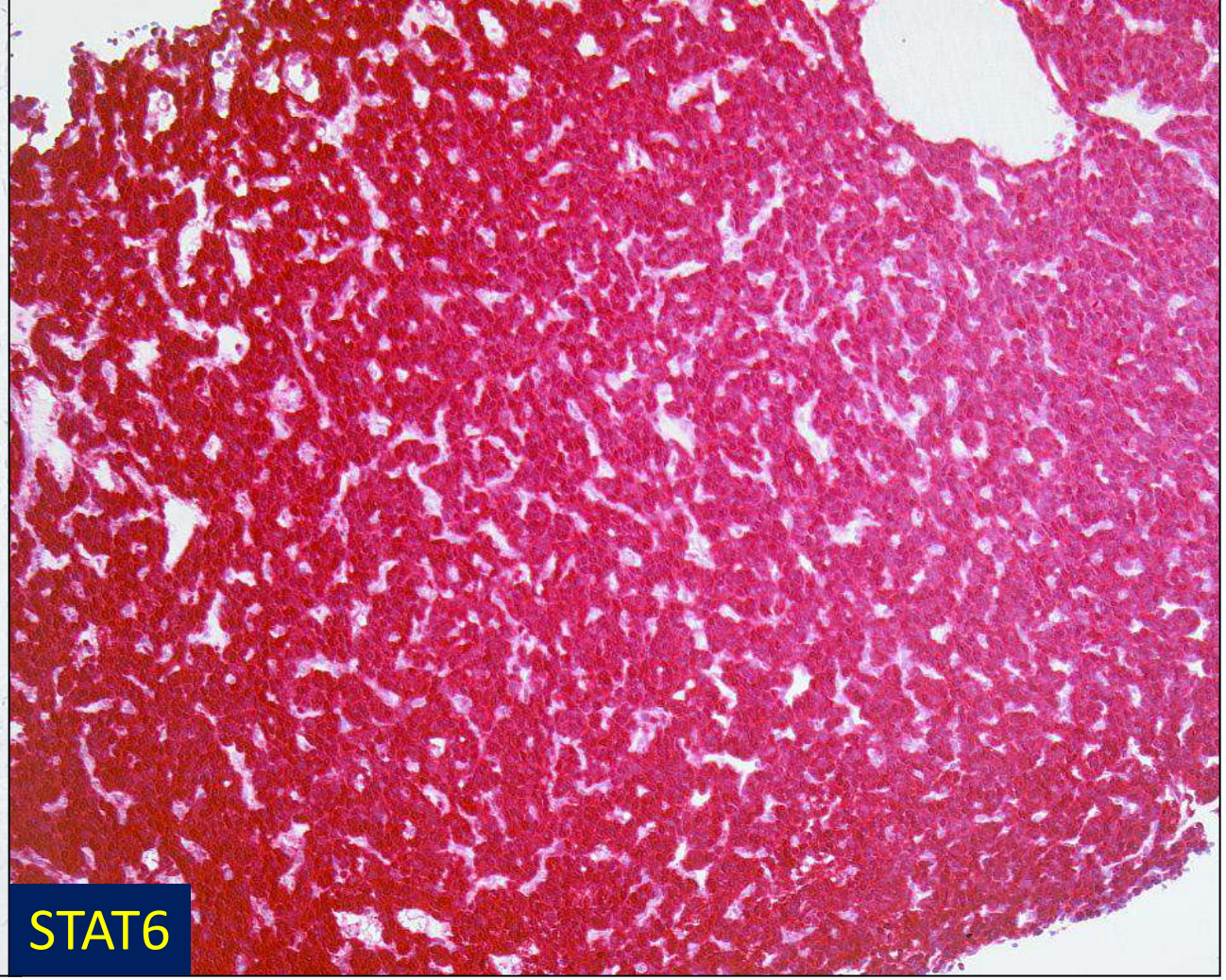



CD31

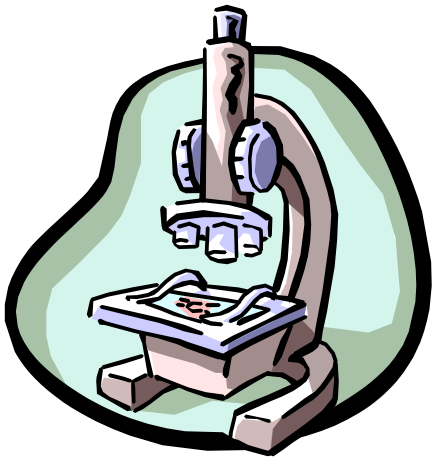

EMA


MDM2




FISH-Analysis:
*STAT6-GLI1-DDIT3- HMGA2-CDK4-MDM2* amplification
(Prof.Antonescu CR, New York)



# Diagnosis Case 16

## *GLI1*-amplified soft tissue neoplasm

# GLI1-altered epithelioid soft tissue neoplasms

**A distinct malignant epithelioid neoplasm with *GLI1* gene rearrangements, frequent S100 protein expression and metastatic potential: expanding the spectrum of soft tissue neoplasms defined by *GLI1* gene fusions**

Antonescu CR et al. AJSP 2018; 42: 553-560

6 cases, 4 F, 2 M, 16-79 years
lower extremities, retroperitoneum, trunk, head/neck
lymph node metastases (3), lung metastases (1)
monomorphic epithelioid phenotype
nest or cord-like architecture, capillary network
S-100 + (4/6); *GLI1* fusions with *ACTB, PTCH1, MALAT1*

**GLI1 amplifications expand the spectrum of soft tissue neoplasms defined by GLI1 gene fusions**

Agaram NP et al. Mod Pathol 2019; 32: 1617-1626

10 cases, 5 F, 5 M, 4-65 years

limbs, trunk, head and neck

epithelioid tumour cells, nested growth pattern

increased nuclear pleomorphism, many mitoses

necrosis, lymphovascular invasion

*GLI1* amplification, coamplification of *MDM2, CDK4, STAT6*

*GLI1* amplification represents an alternative genetic mechanism of *GLI1* oncogenic activation

**Head and neck mesenchymal neoplasms with GLI1 gene alterations. A pathologic entity with distinct histologic features and potential for distant metastasis**

Xu B et al. Am J Surg Pathol 2020; 44: 729-737

11 cases (8 x tongue, 1-65 years)

multinodular growth, delicate vascular network

momotonous round to ovoid nuclei, pale/clear cytoplasm

*GLI1* fusions (7 x), coamplification *GLI1/MDM2/CDK4* (4 x)

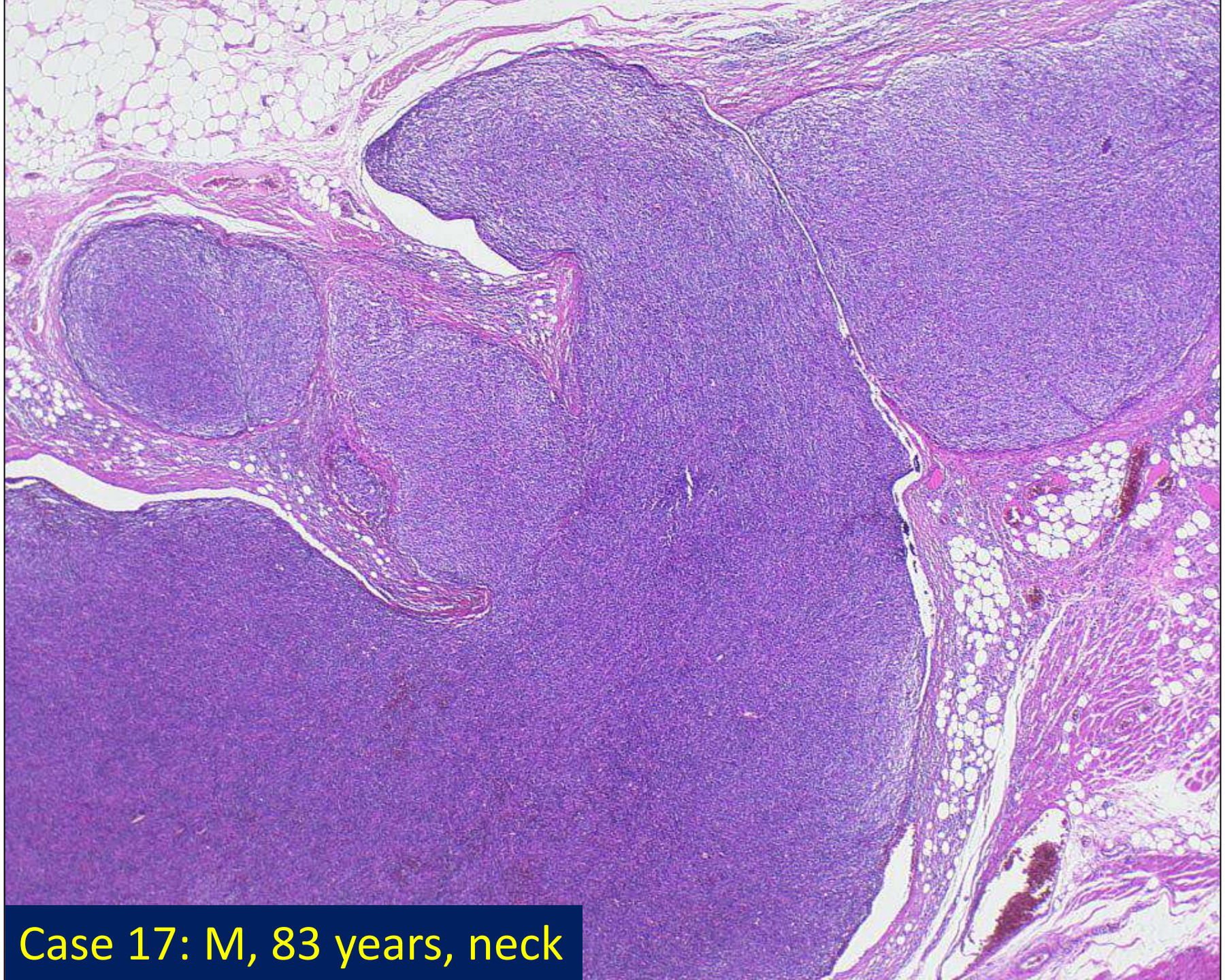
S100 +, CD56 +, CDK4/MDM2/STAT6 + in amplified cases

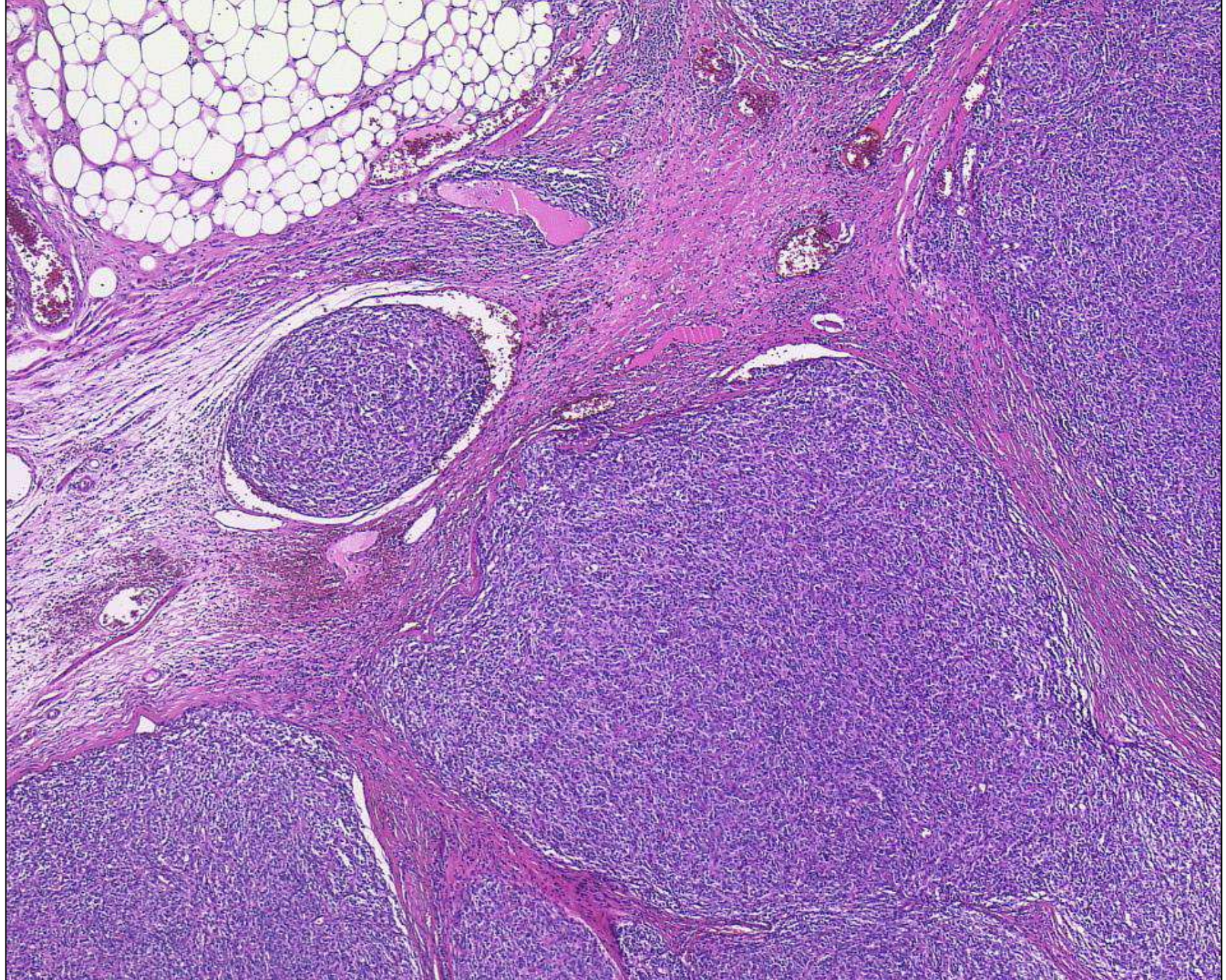
distant metastases in 2 out of 6 patients with follow-up

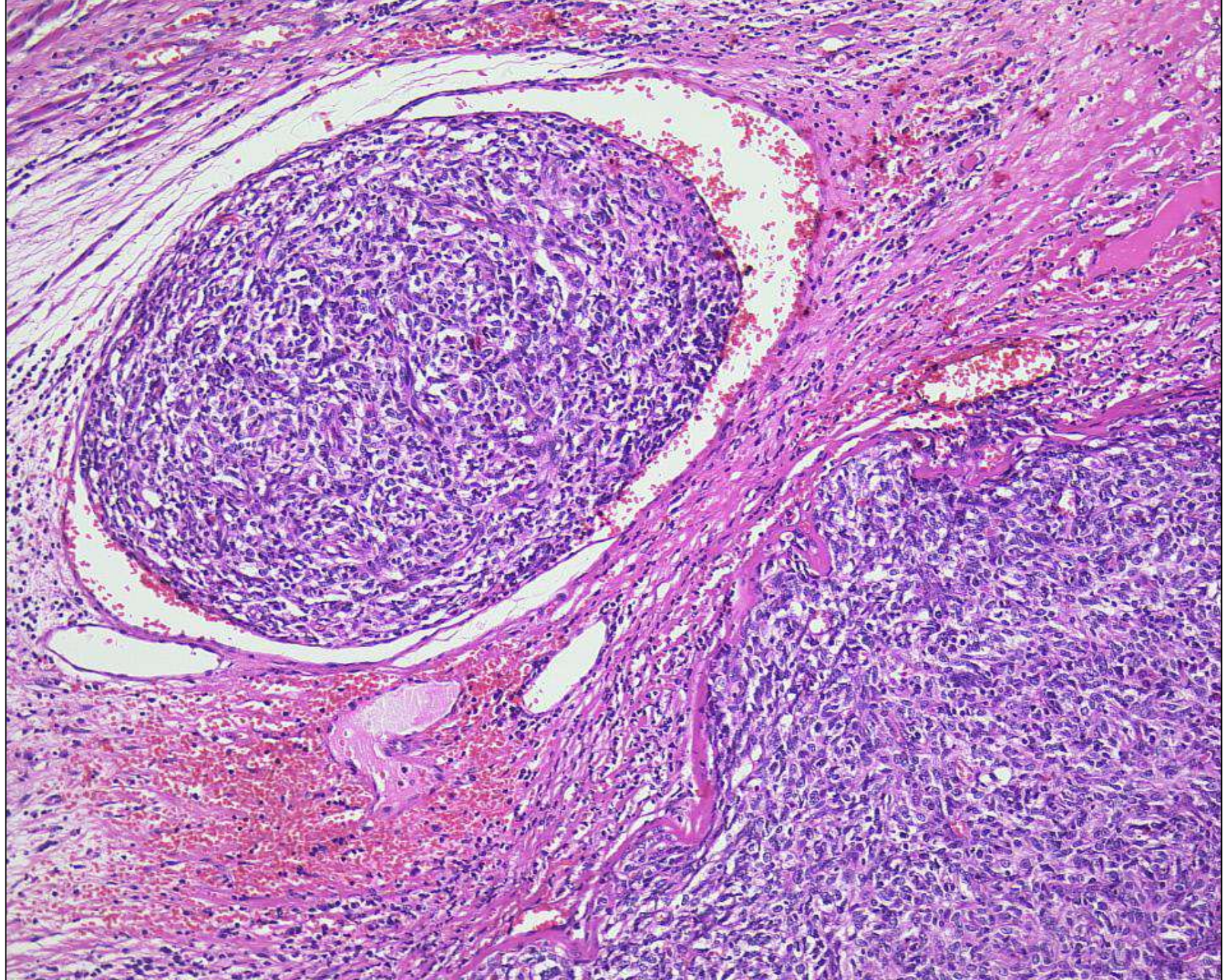
**Distinctive nested glomoid neoplasm. Clinicopathologic analysis of 20 cases of a mesenchymal neoplasm with frequent *GLI1* alterations and indolent behavior**

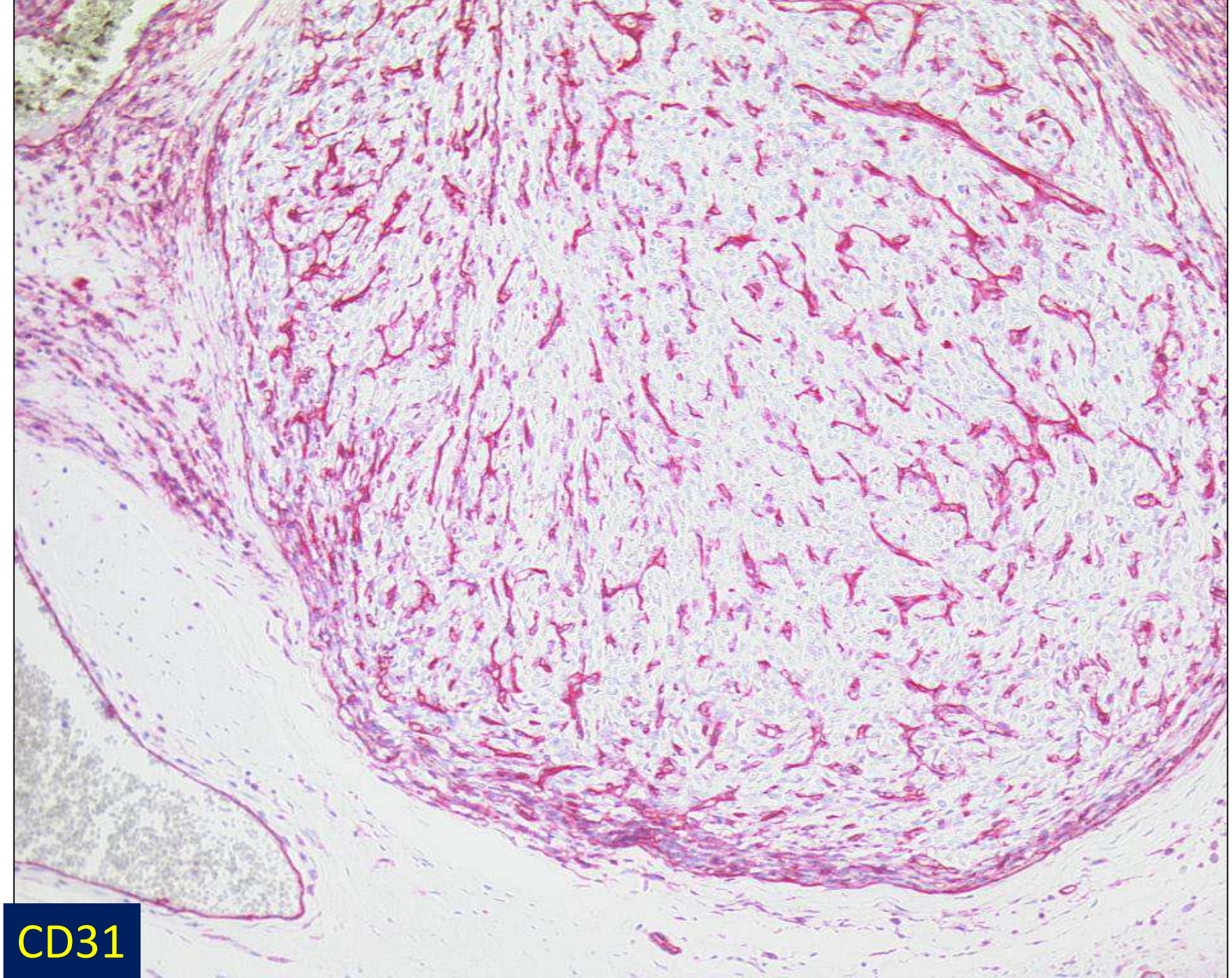
Papke DJ et al. Am J Surg Pathol 2023; 47: 12-23

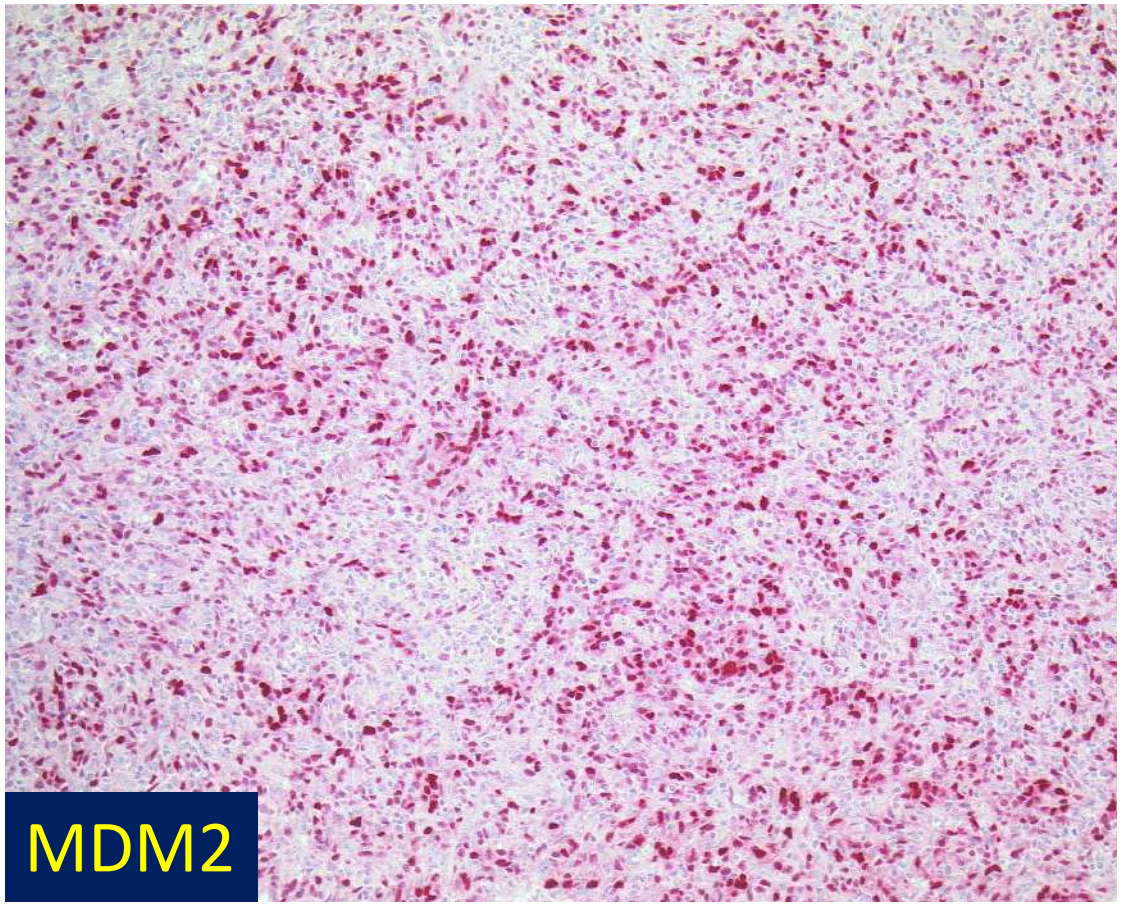
20 cases, (11 F, 9 M), congenital to 74 years, 0.9 - 11.1 cm
trunk (7), lower (5) and upper limbs (3), tongue (4), neck (1)
nests of round to ovoid tumour cells
network of capillaries, perivascular growth
microcysts (8), myxoid stroma (5), clear cells (7)
MDM2 + (47%), S100 + (26%), STAT6 + (20%), CK (10%)
*GLI1* alterations (16)
    *GLI1* rearrangements (10)
    *GLI1* amplifications (6)
local recurrences (30%), no MTS, no DOD

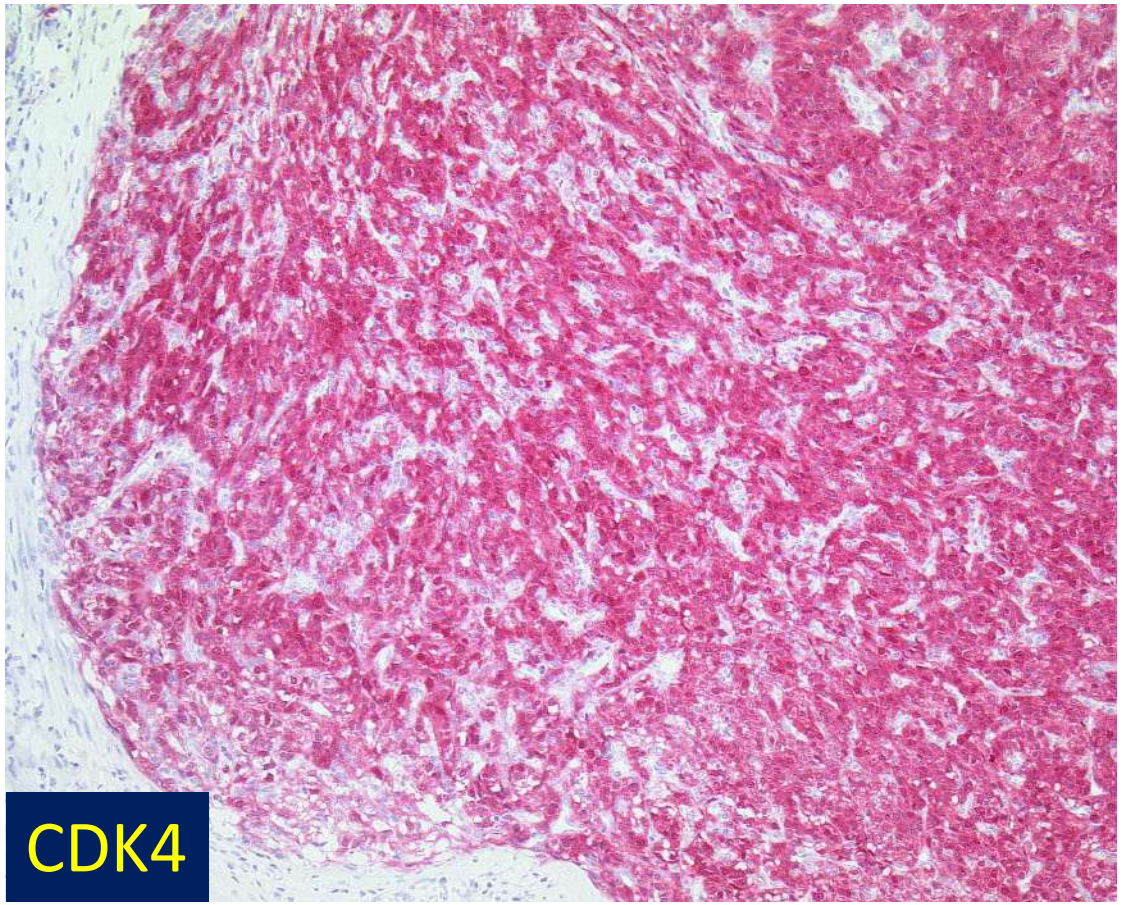

Case 17: M, 83 years, neck

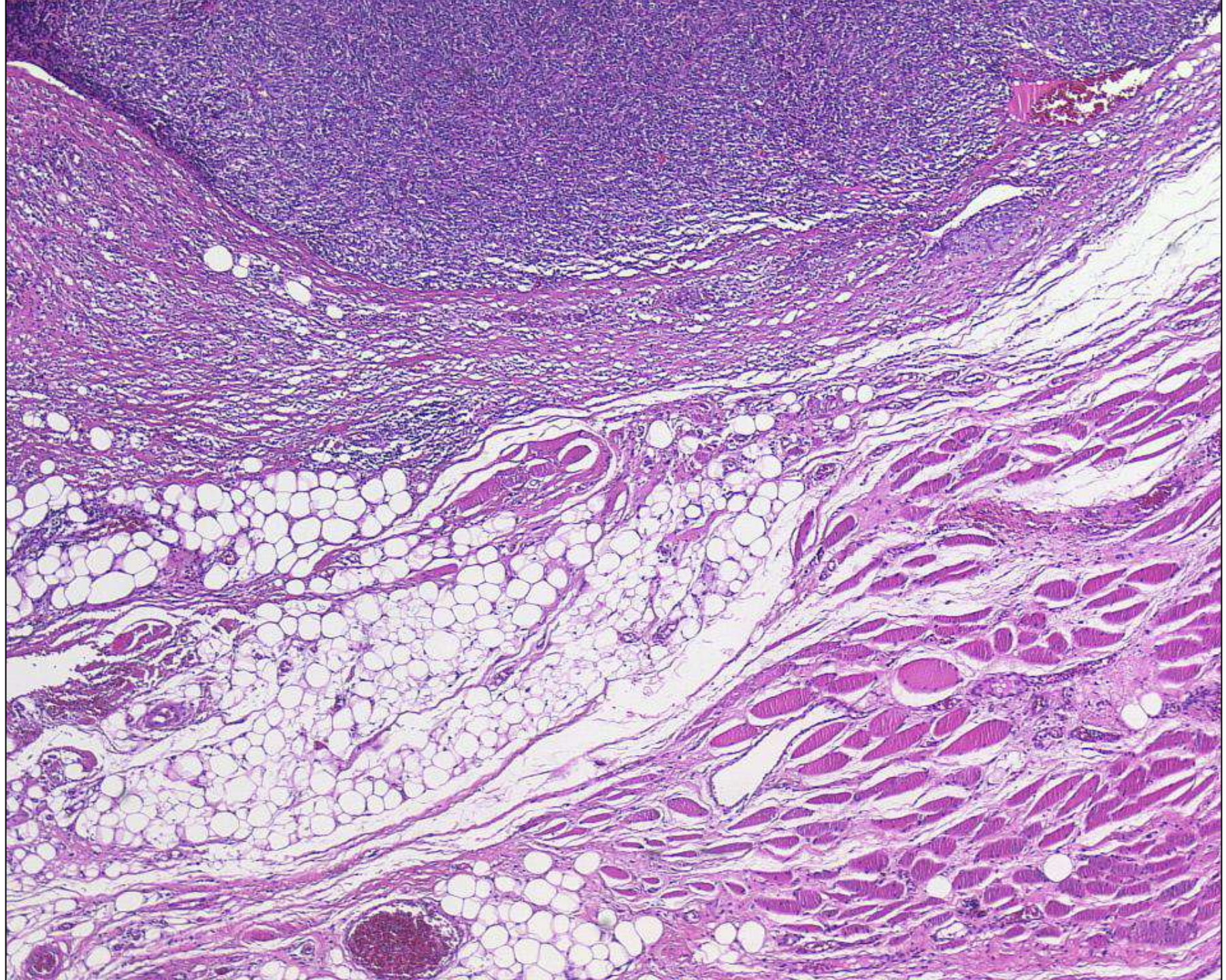


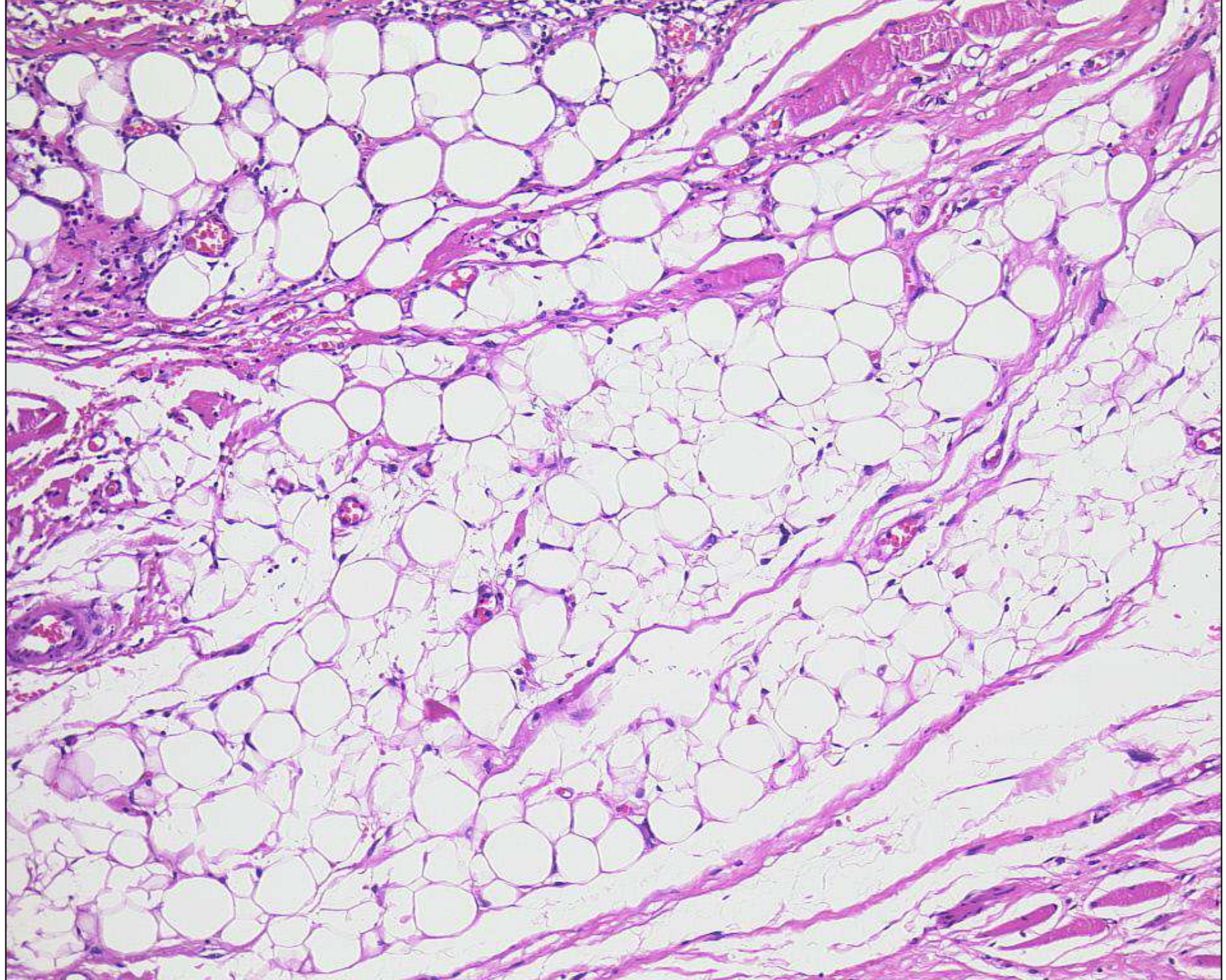


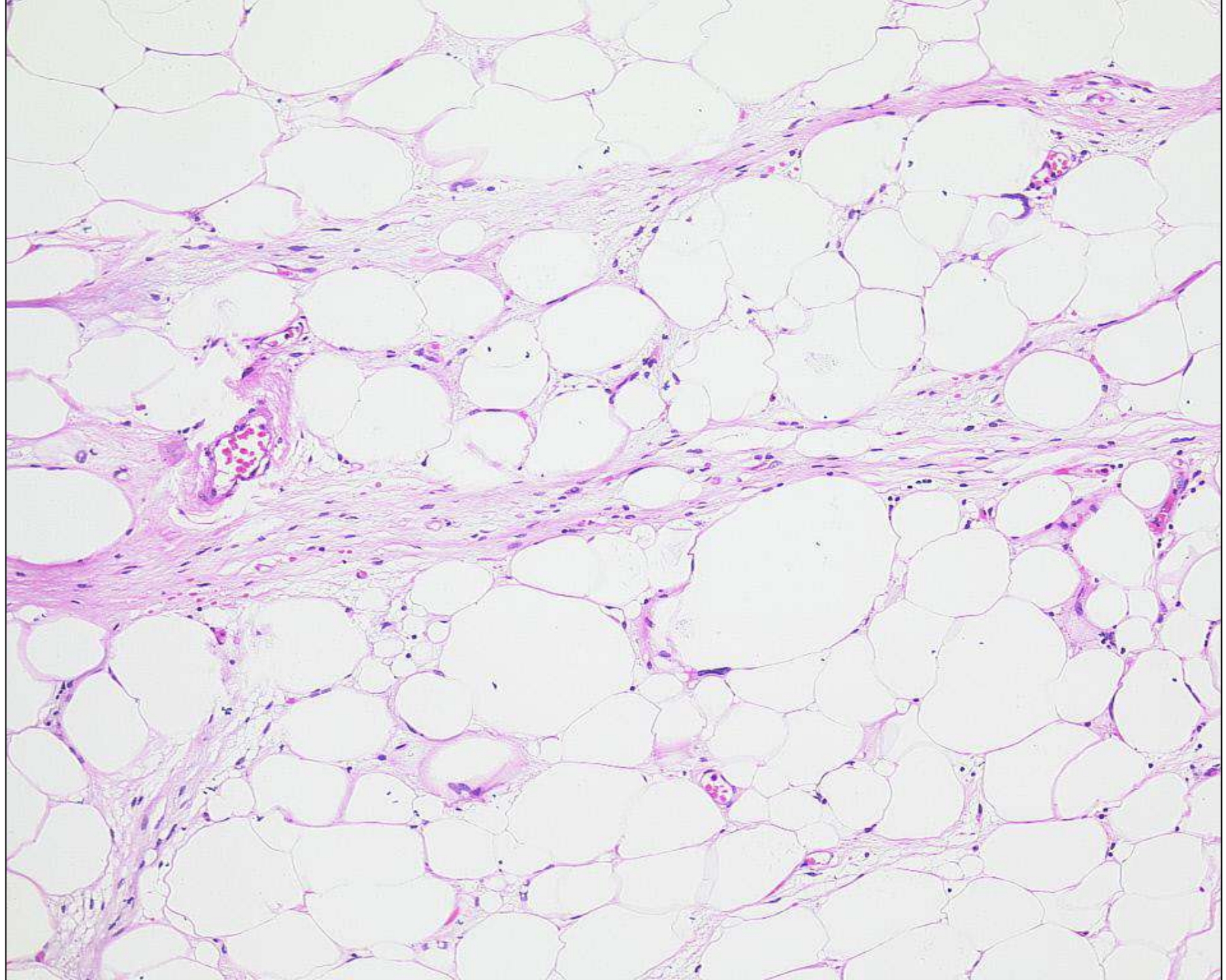

CD31

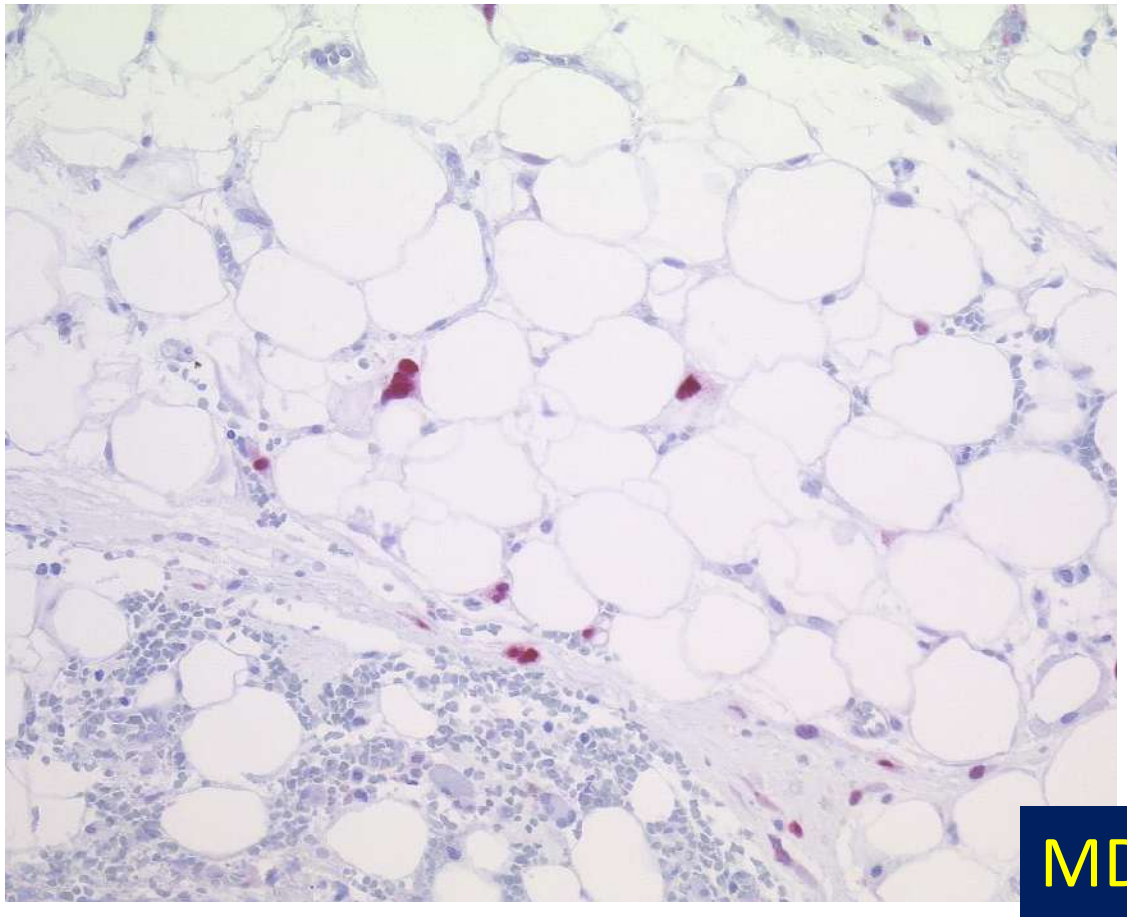

MDM2

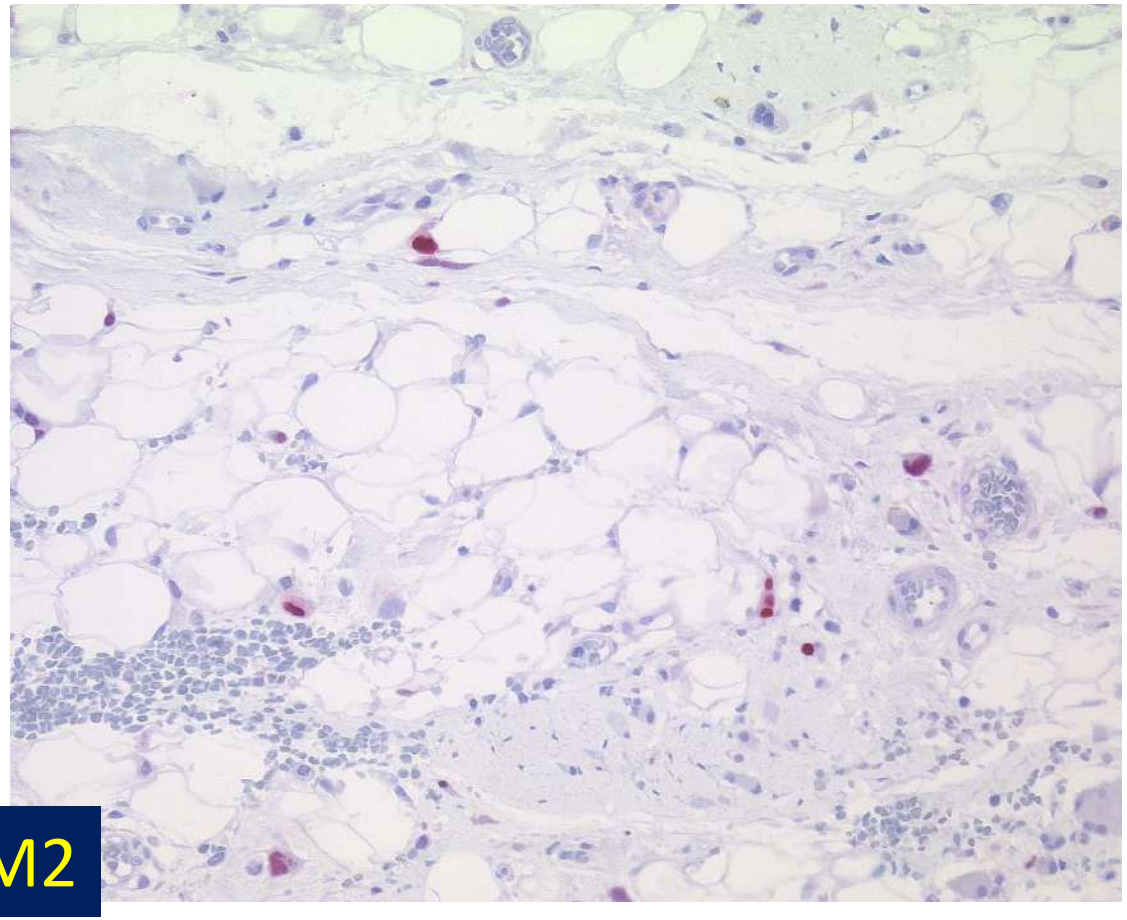

CDK4



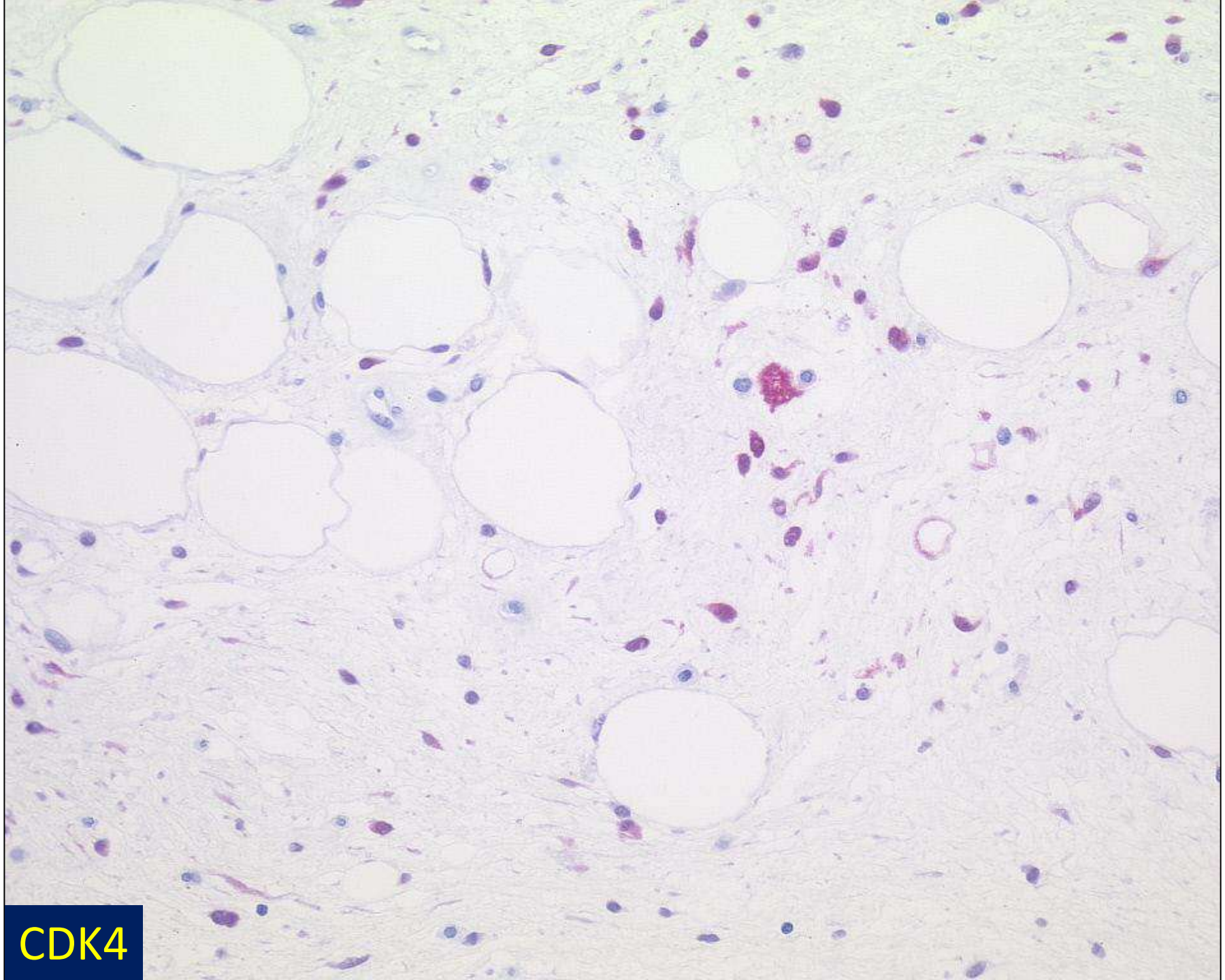


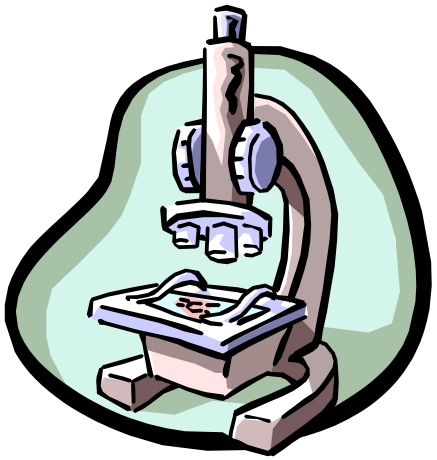






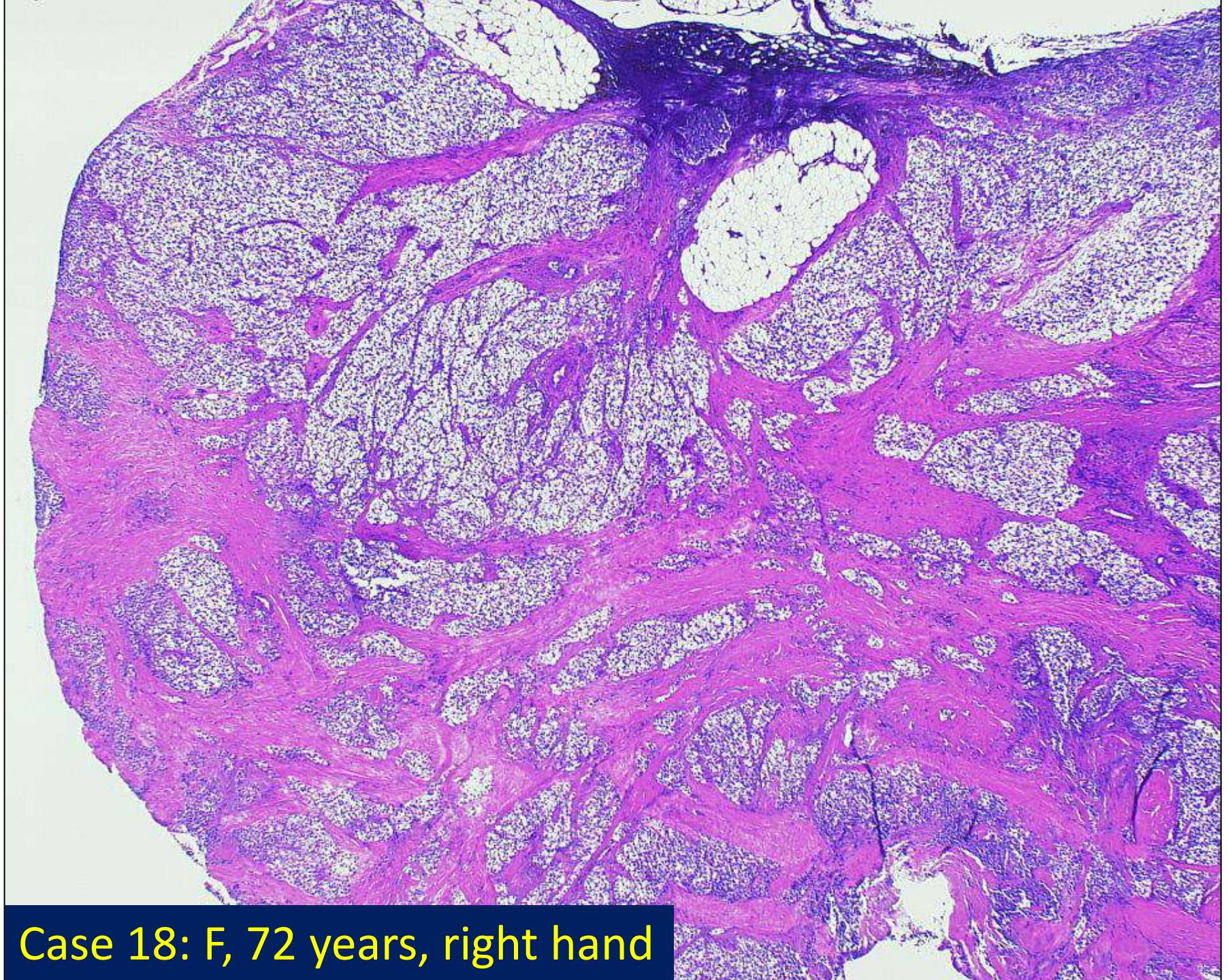
MDM2


CDK4

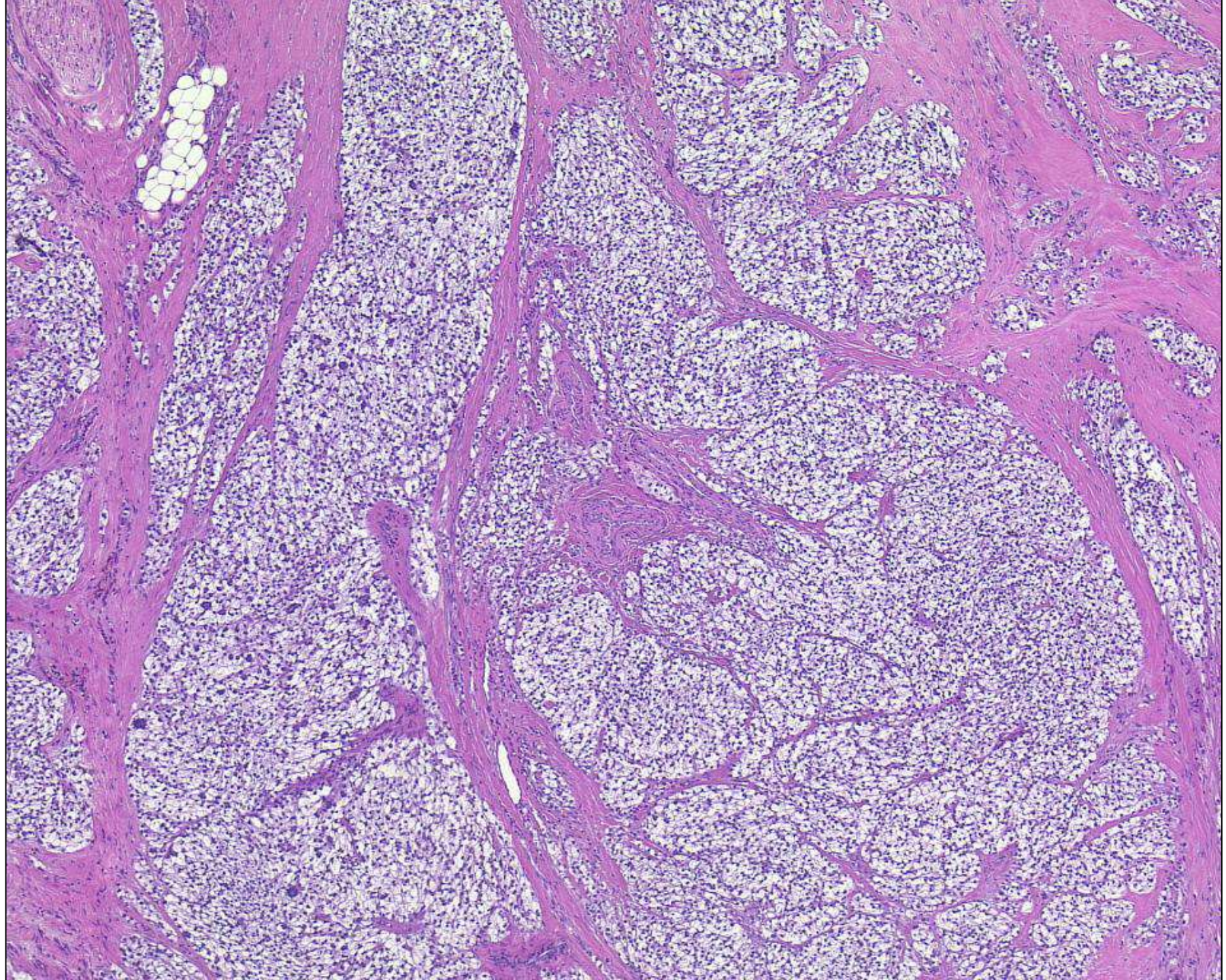


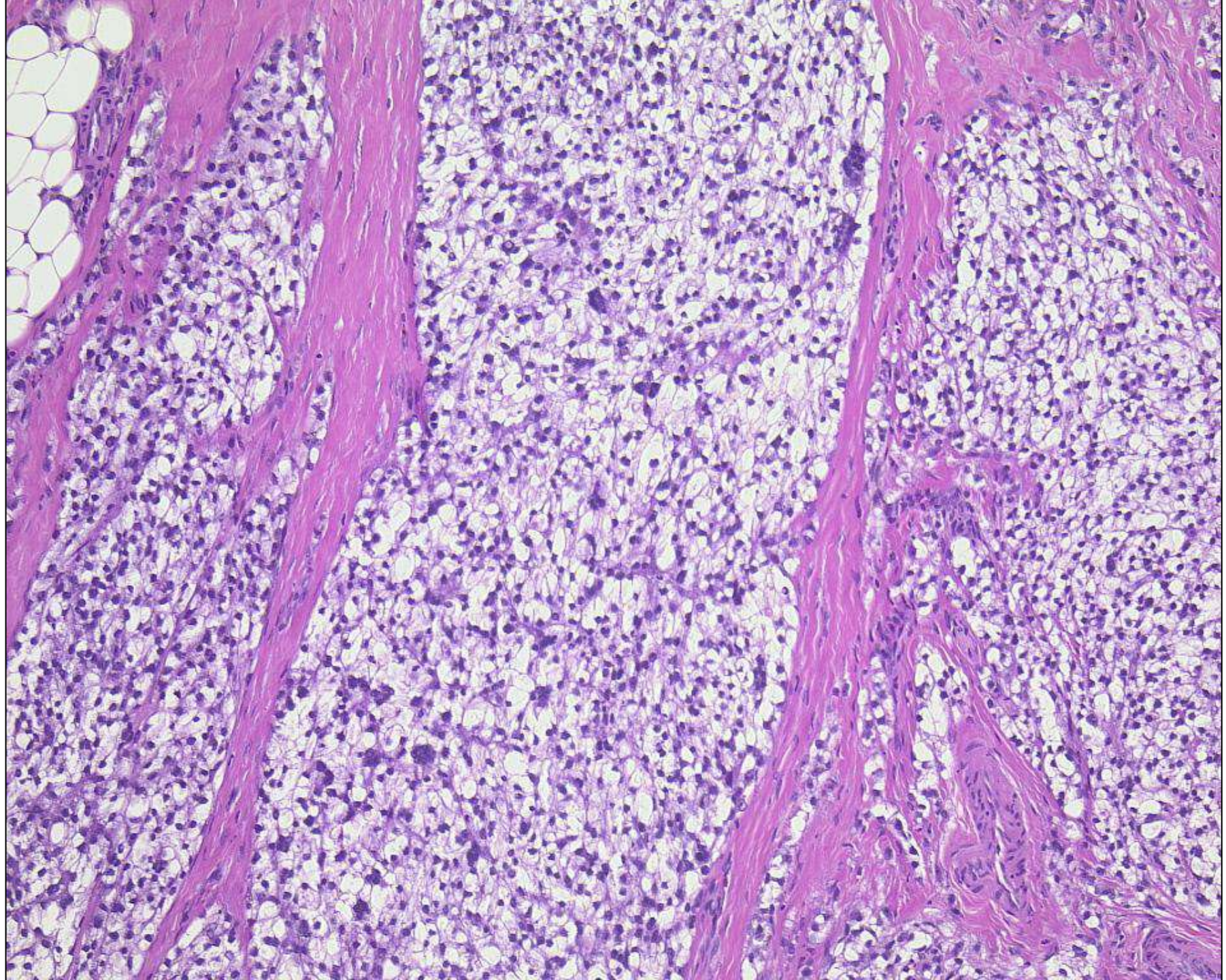
# Diagnosis Case 17

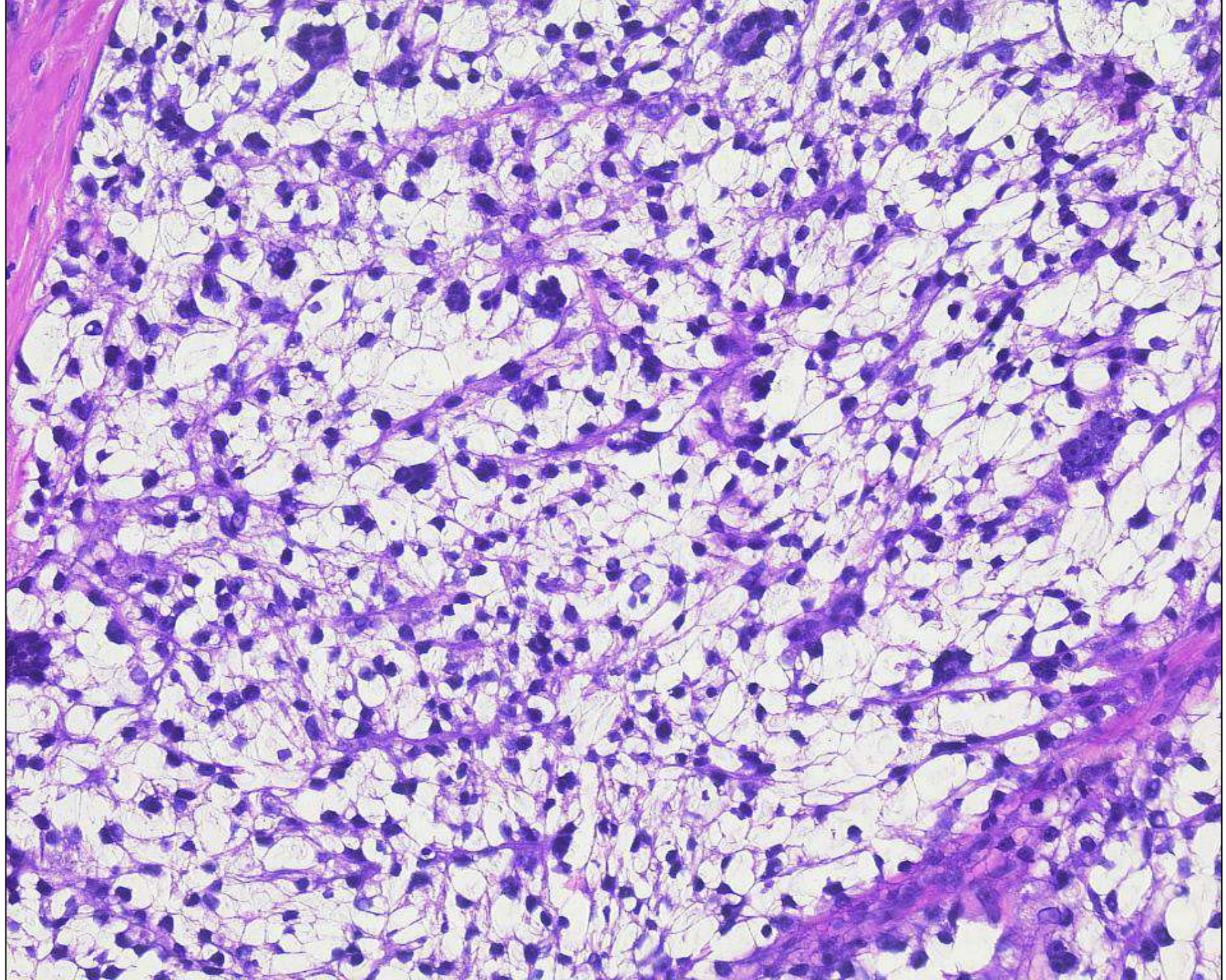
**dedifferentiated Liposarcoma with distinctive nested glomoid neoplasm-like features**

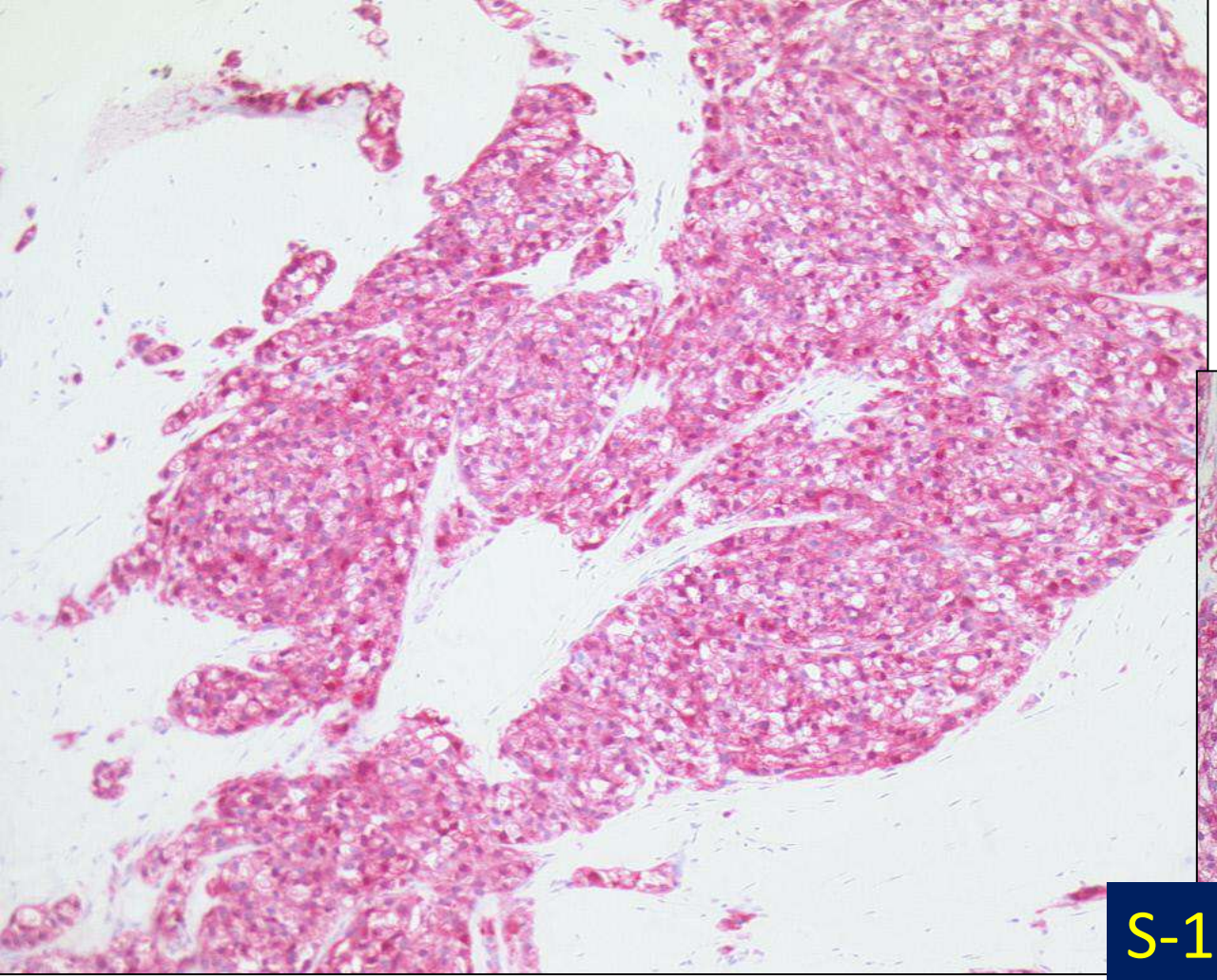


Case 18: F, 72 years, right hand

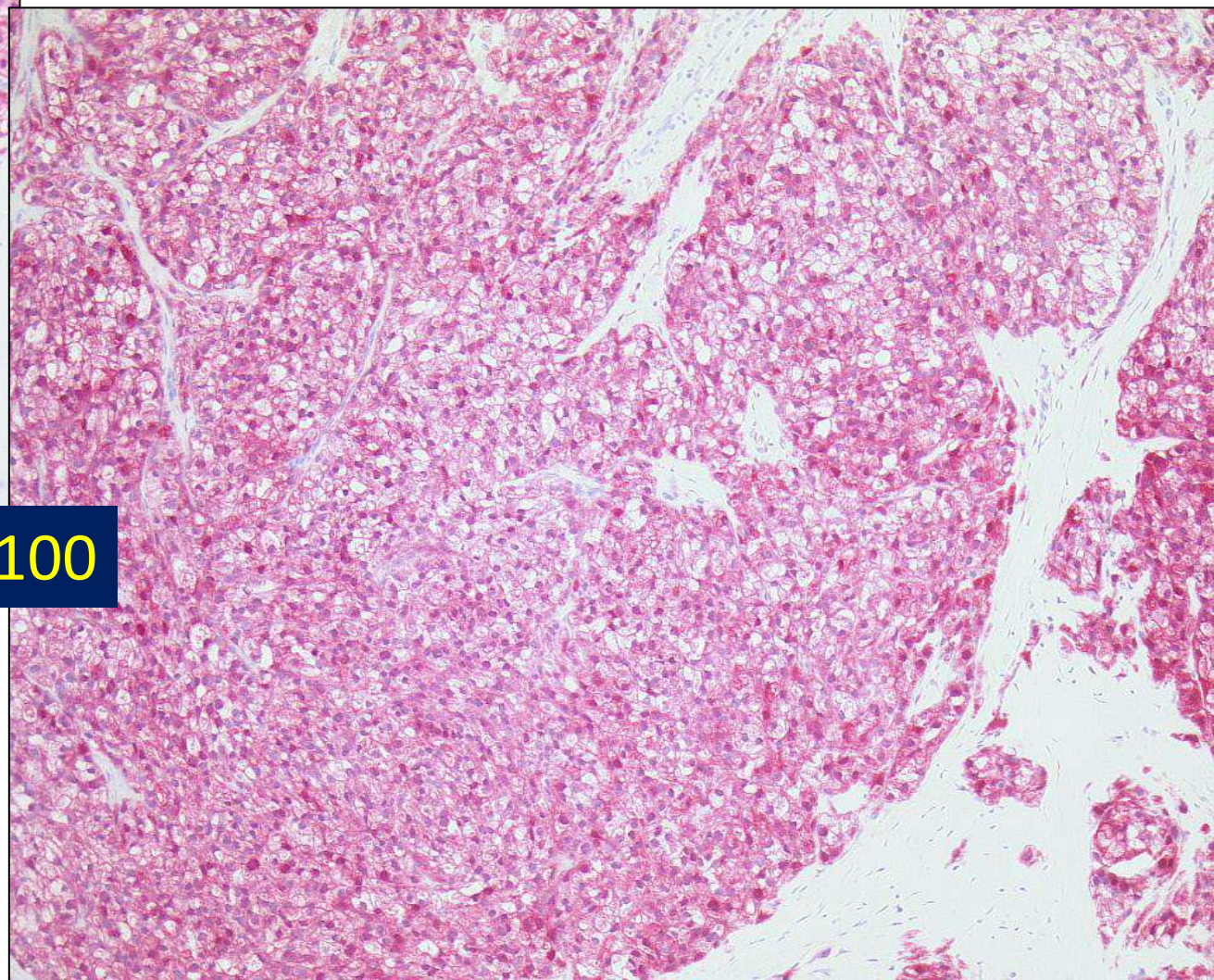


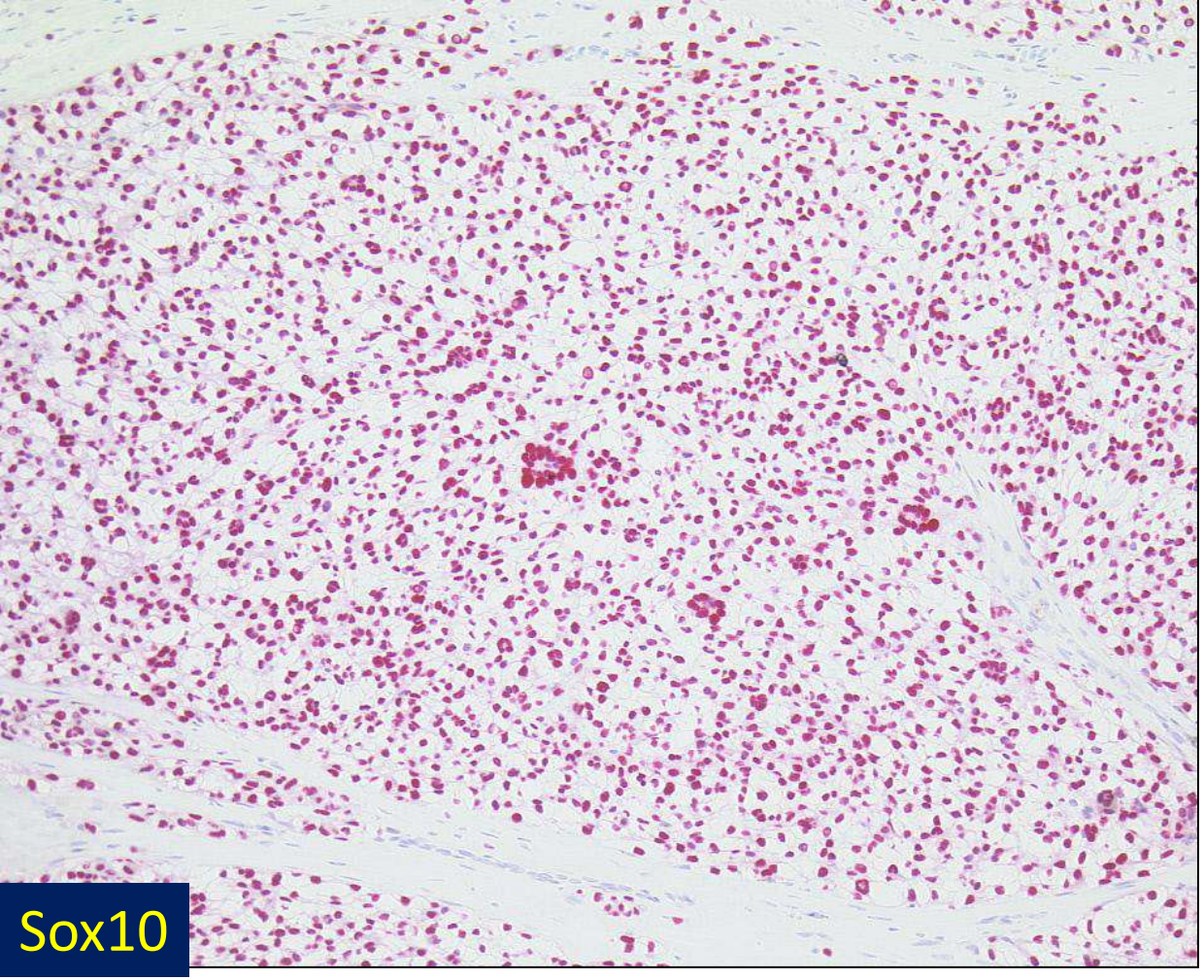


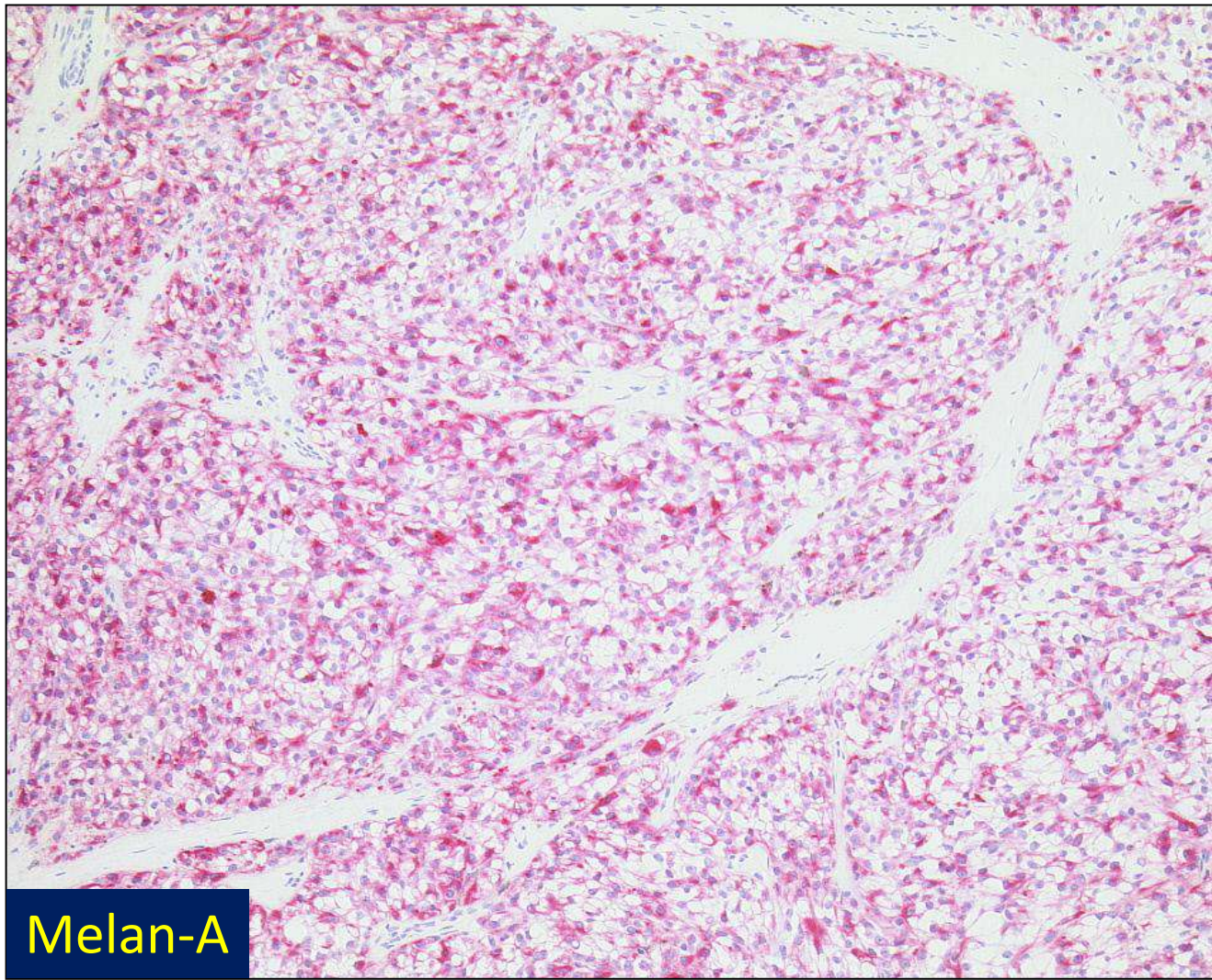




S-100




Sox10


Melan-A

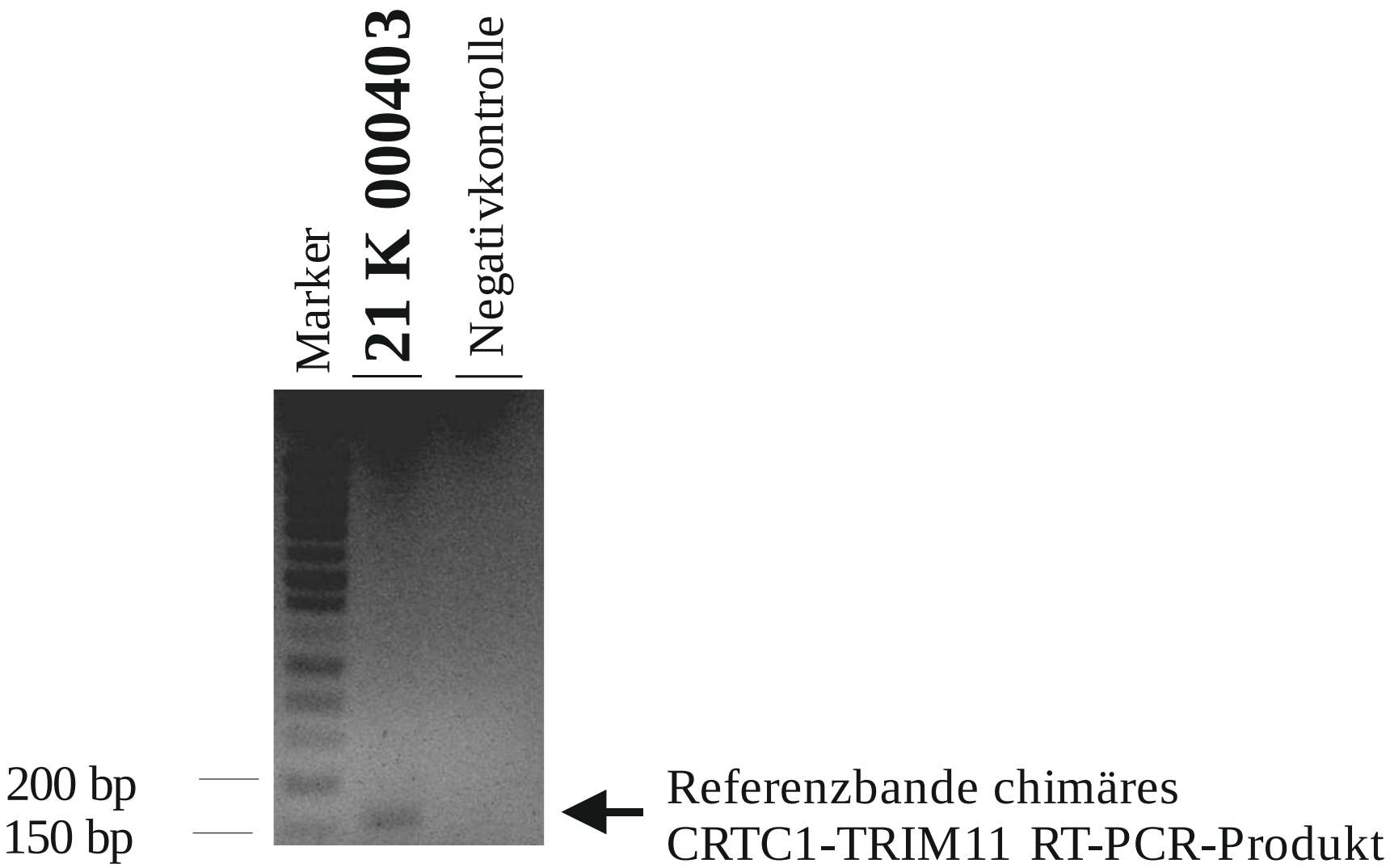
**Diagnosis:**

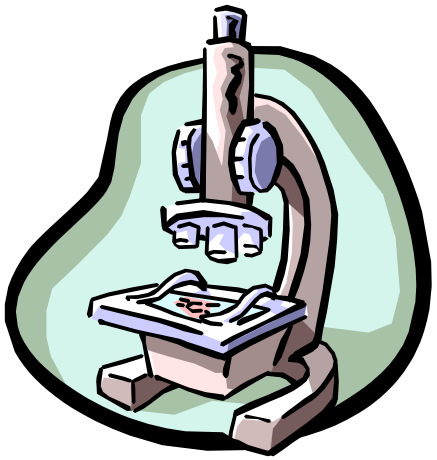
**Clear cell sarcoma…**

**But**

**RT-PCR: no *EWS* or *ATF1* translocation**

# CRTC1-TRIM 11 RT-PCR





# Diagnosis Case 18

## Cutaneous melanocytoma with *CRTC1::TRIM11* fusion

# Cutaneous melanocytoma with *CRTC1-TRIM11* fusion

recently described, rare neoplasm
children, adults
wide variety of anatomic locations
low-grade neoplasms (R and MTS are rare)
Differential diagnosis:

- cellular blue naevus
- metastatic and dermal melanoma
- paraganglioma-like dermal melanocytic TU
- clear cell sarcoma

# Cutaneous melanocytoma with *CRTC1-TRIM11* Fusion: Report of 5 cases resembling clear cell saroma

Cellier L et al. AJSP 2018; 42: 382-391

3 F, 2 M, 25-82 ys, extremities (3), trunk (1), neck (1)
nodular, dermal neoplasms, nests and bundles of spindled, epithelioid tumour cells,
multinucleated giant cells,
cytological atypia, mitoses, necrosis (2)
positive staining of melanocytic markers
*CRTC1-TRIM11* fusion, nuclear TRIM11 +
no *EWS* translocation
no local recurrence, no metastasis (3-72/12)

*CRTC1-TRIM11* fusion defined melanocytic tumors:
A series of four cases
(Ko JS et al. J Cutan Pathol 2019; 46: 810-818)

A case report of cutaneous melanocytoma with
*CRTC1-TRIM11* fusion: is CMCT different from
clear cell sarcoma of soft tissue?
(Kashima J et al. Pathol Int 2019; 69: 496-501)

Dermal melanocytic tumor with *CRTC1-TRIM11* fusion:
report of two additional cases with review of the
literature of an emerging entity
(Parra O et al. J Cutan Pathol 2021; 48: 915-924)

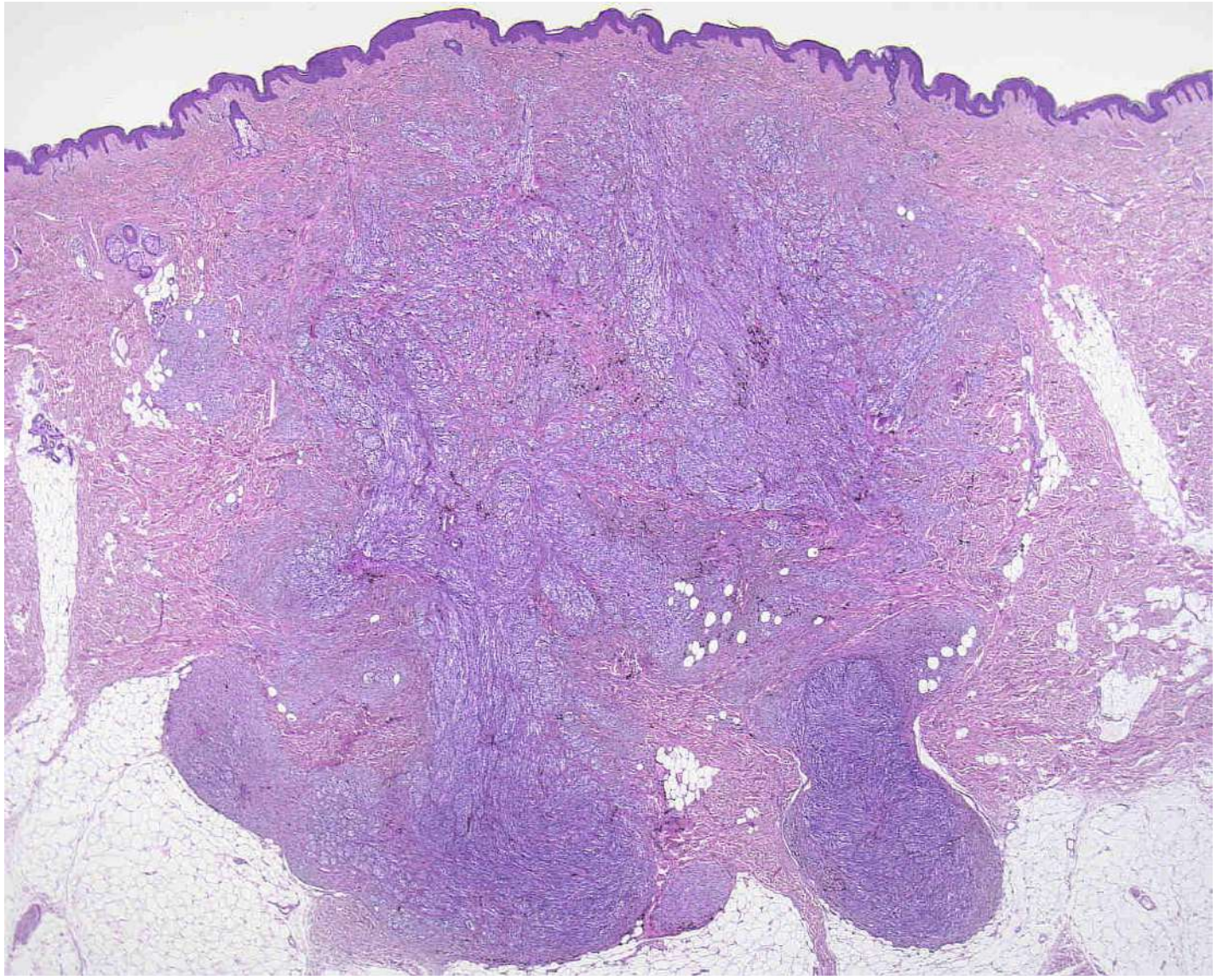
Cutaneous melanocytic tumor with *CRTC1::TRIM11*
fusion and prominent epidermal involvement
Vest BE et al. J Cutan Pathol 2022; 49: 1025-1030

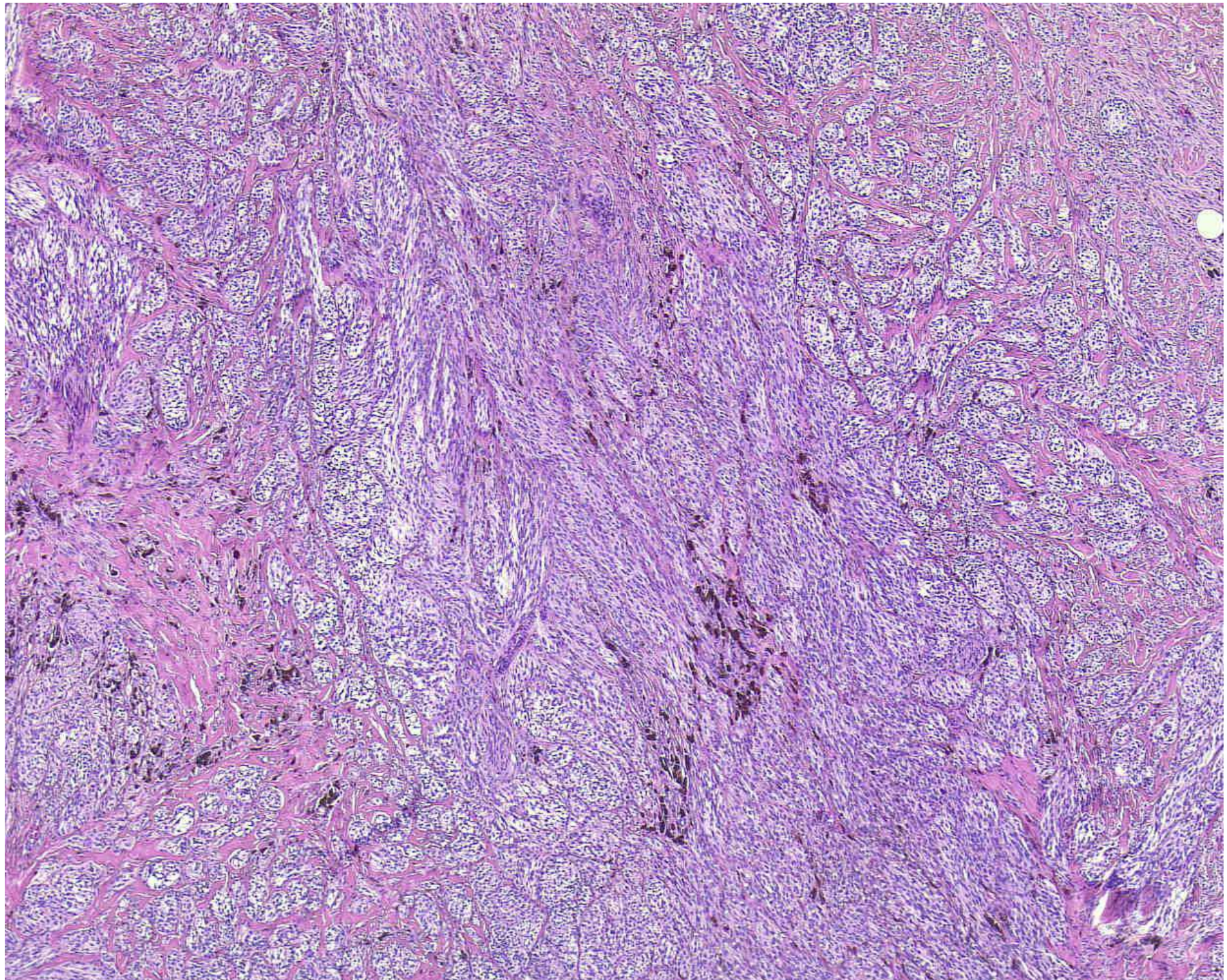
# Cutaneous melanocytoma with *CRTC1::TRIM11* Fusion: An emerging entity analyzed in a series of 41 cases

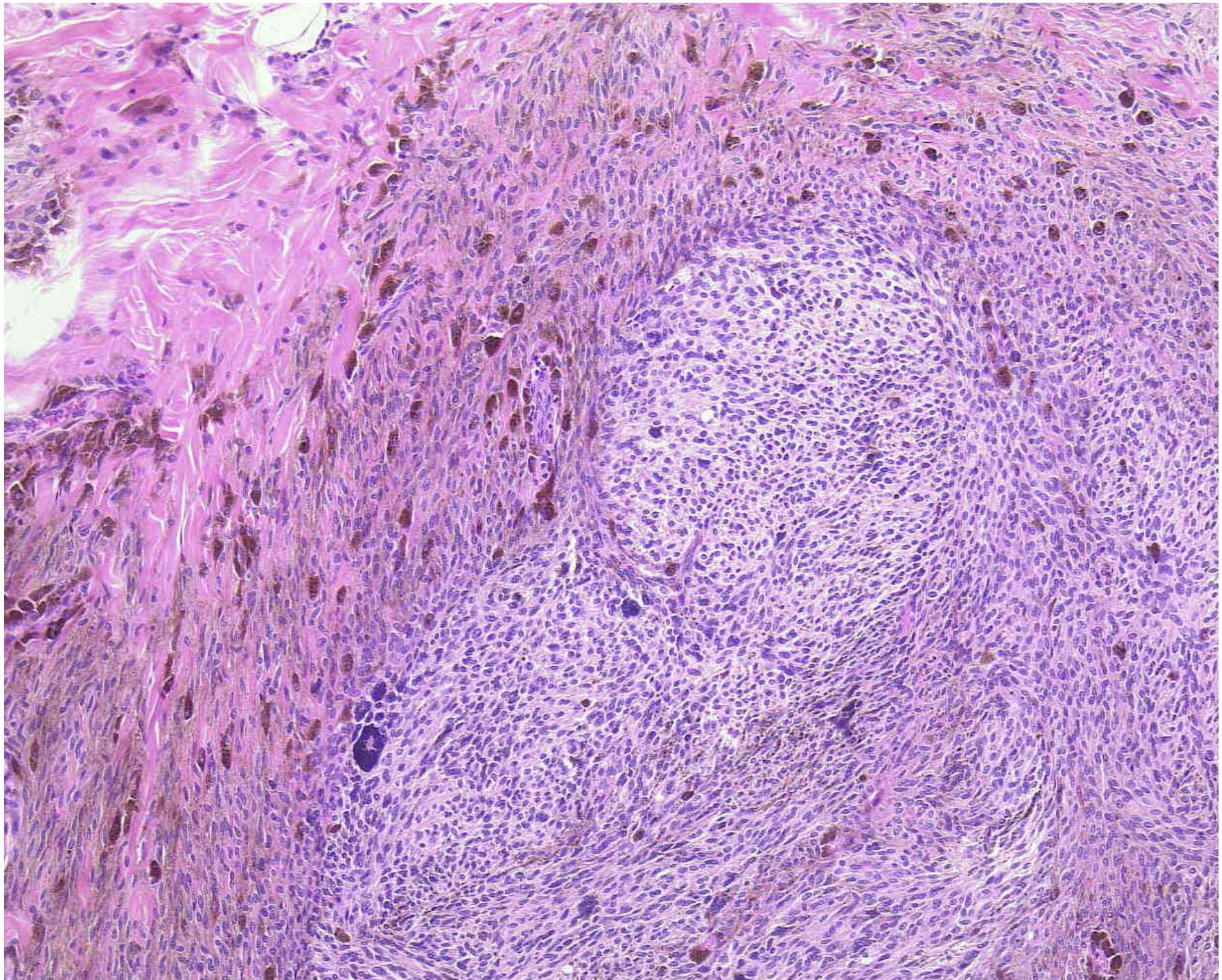
Hanna J et al. Am J Surg Pathol 2022; 46: 1457-1466

23 F, 18 M, 11-87 years (mean age: 44 years)
limbs (36), trunk (8), mucosa (2), head (1), ? (4)
dermis, sometimes exophytic growth, nodular lesions
intersecting nests and bundles
low mitotic activity (< 5 mitoses/10 hpf), necrosis (2)
Sox10 +, S-100 focally +, Melan-A focally +, TRIM1 +
*CRTC1-TRIM11* fusion
20/22 cases free of disease (12-168 months FU)
1 local recurrence at 6/12
1 multiple nodal metastases at 13/12

# DD: Cutaneous melanocytoma with *CRTC1::TRIM11* fusion: cellular nevus blue





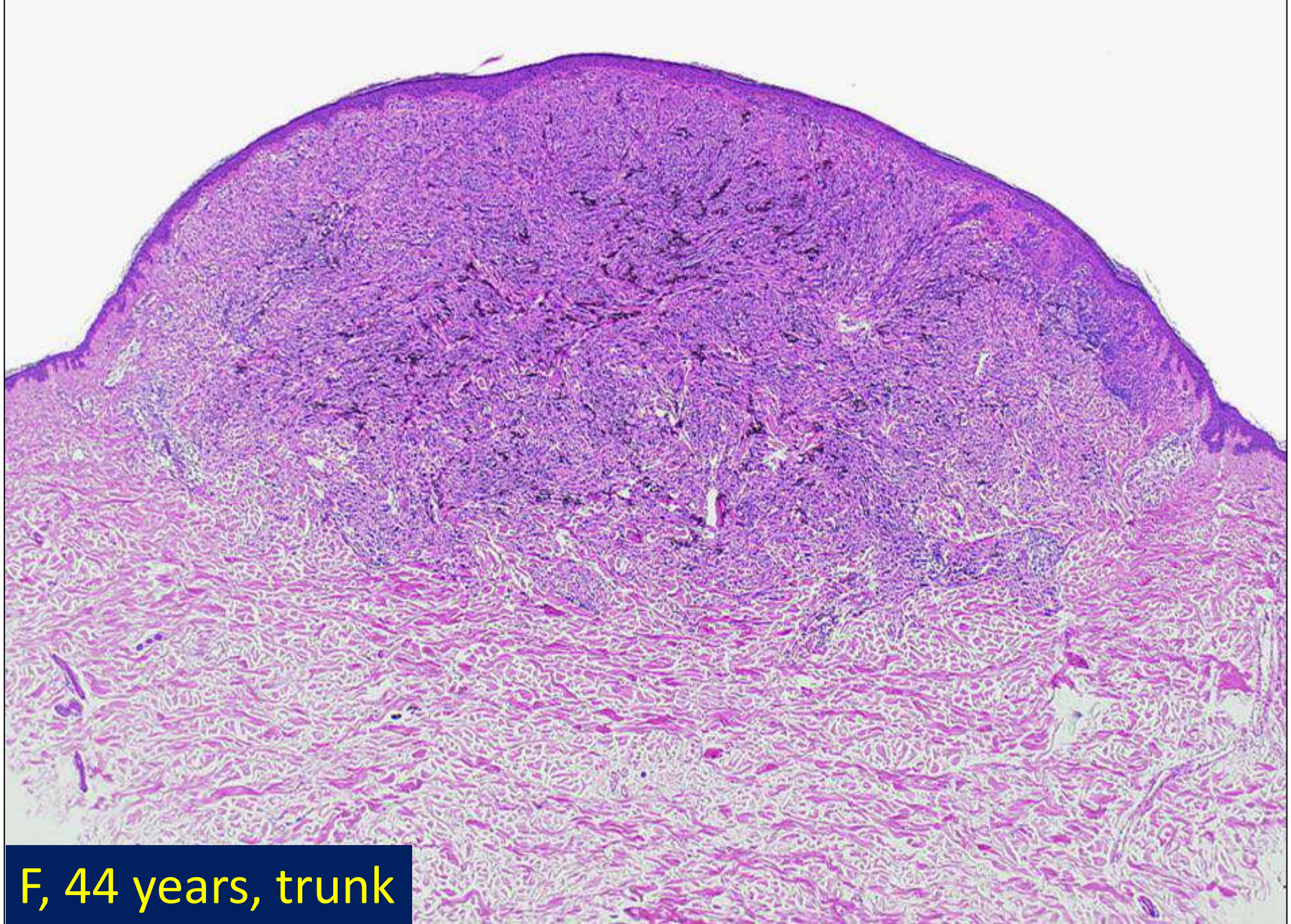


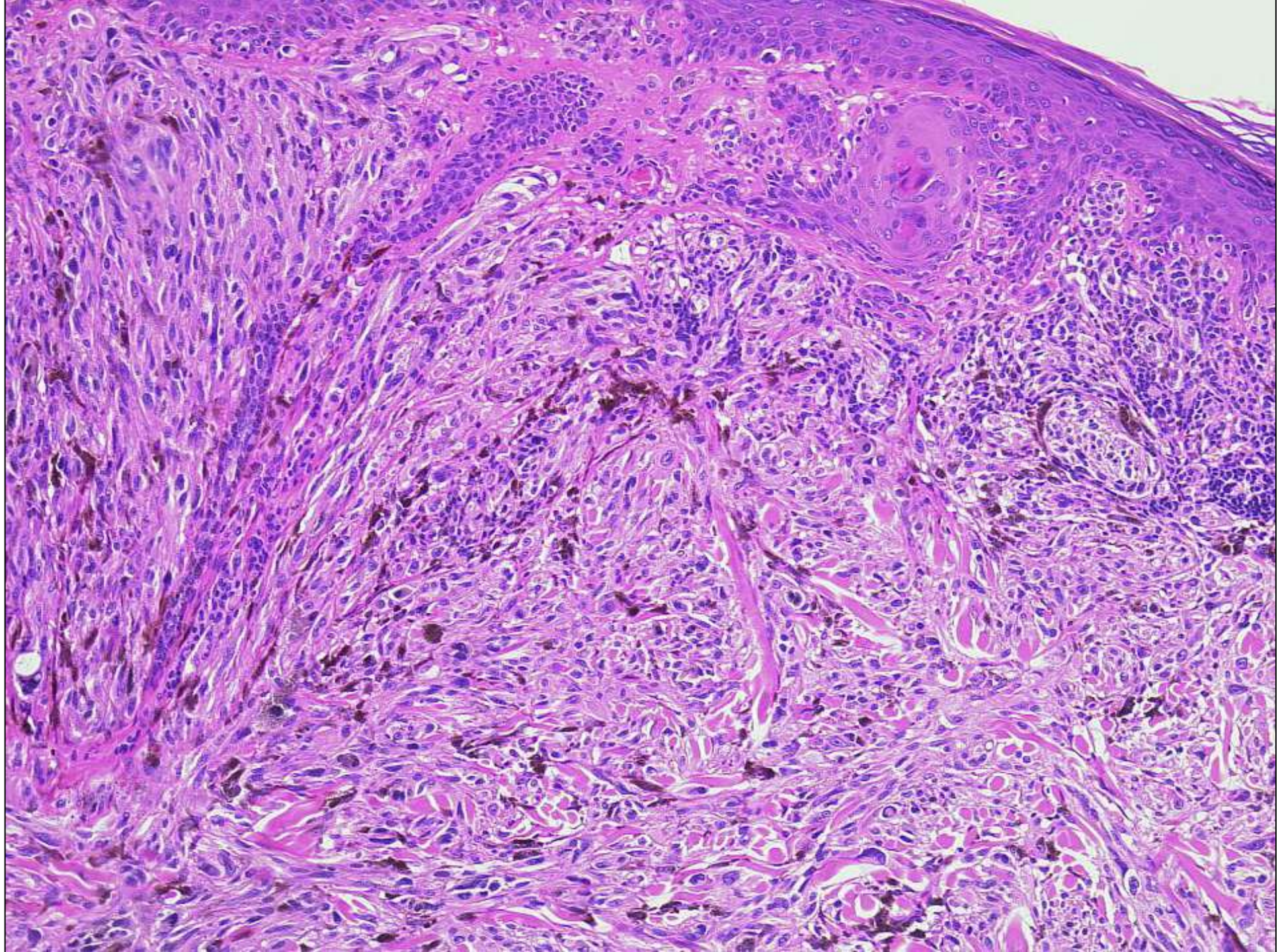
# DD: Cutaneous melanocytoma with *CRTC1::TRIM11* fusion: metastatic and primary dermal melanoma

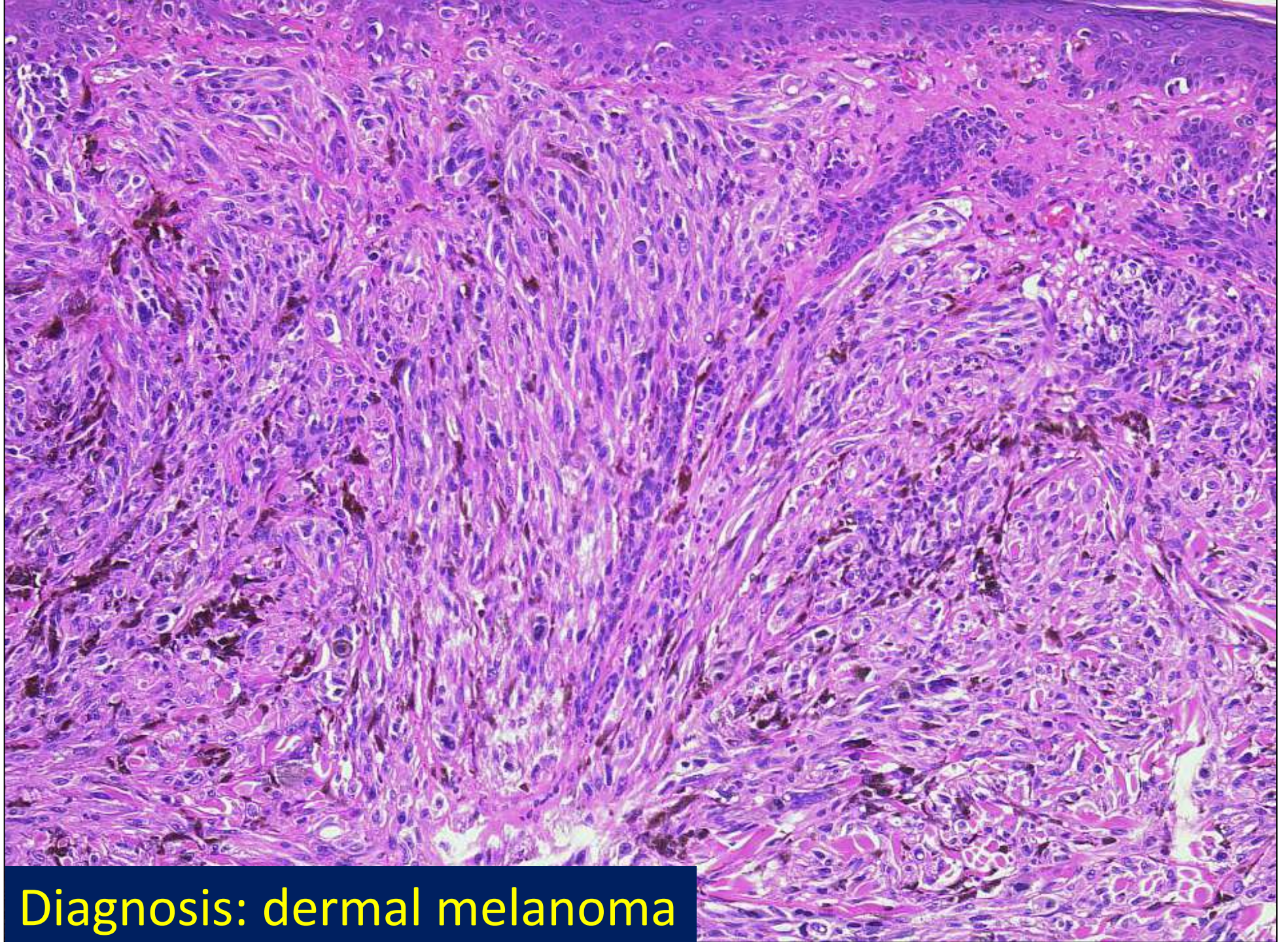
intersecting nests and bundles

uniformity of the cytology

*CRTC1::TRIM11* fusion


F, 44 years, trunk

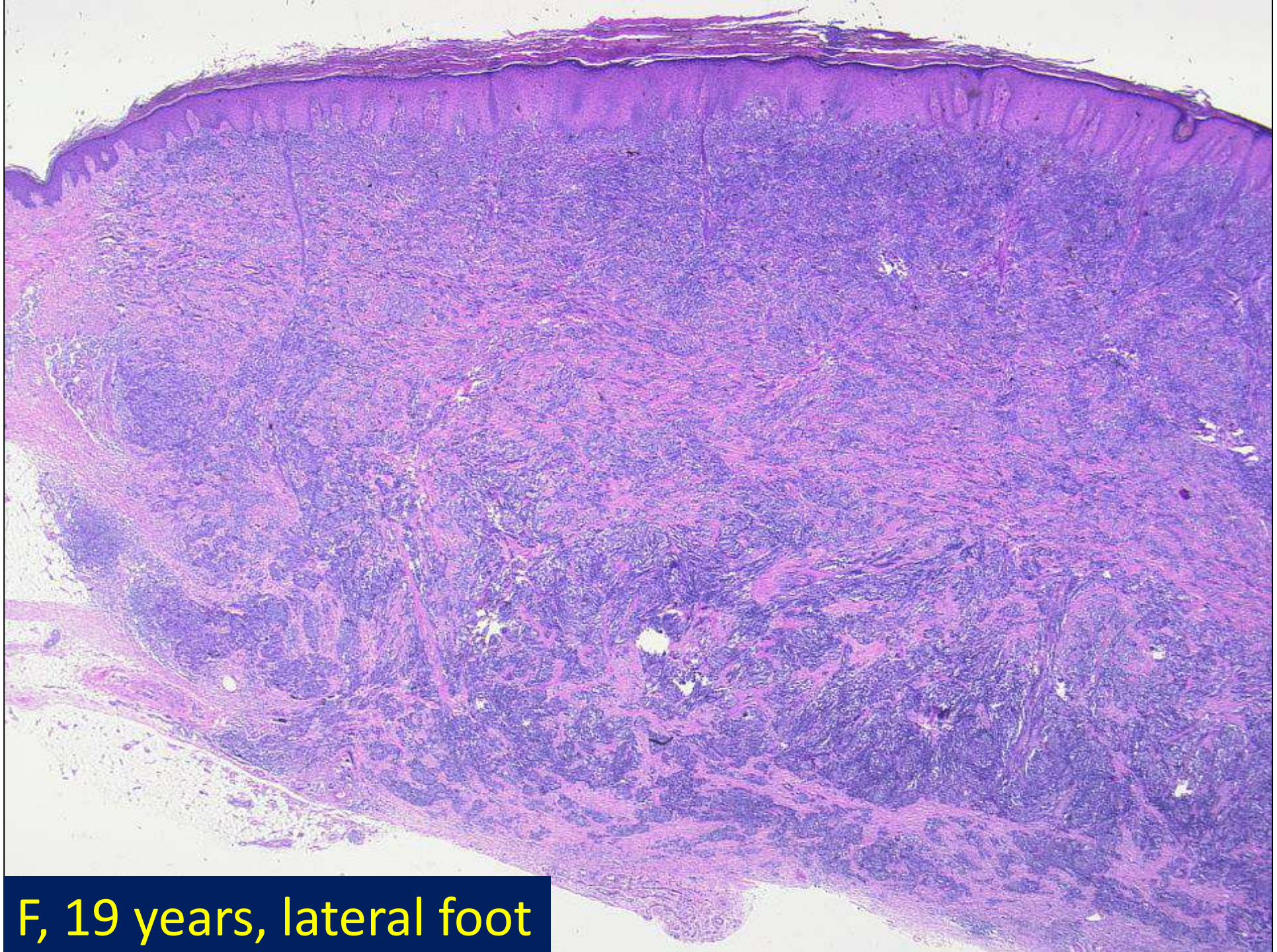



Diagnosis: dermal melanoma

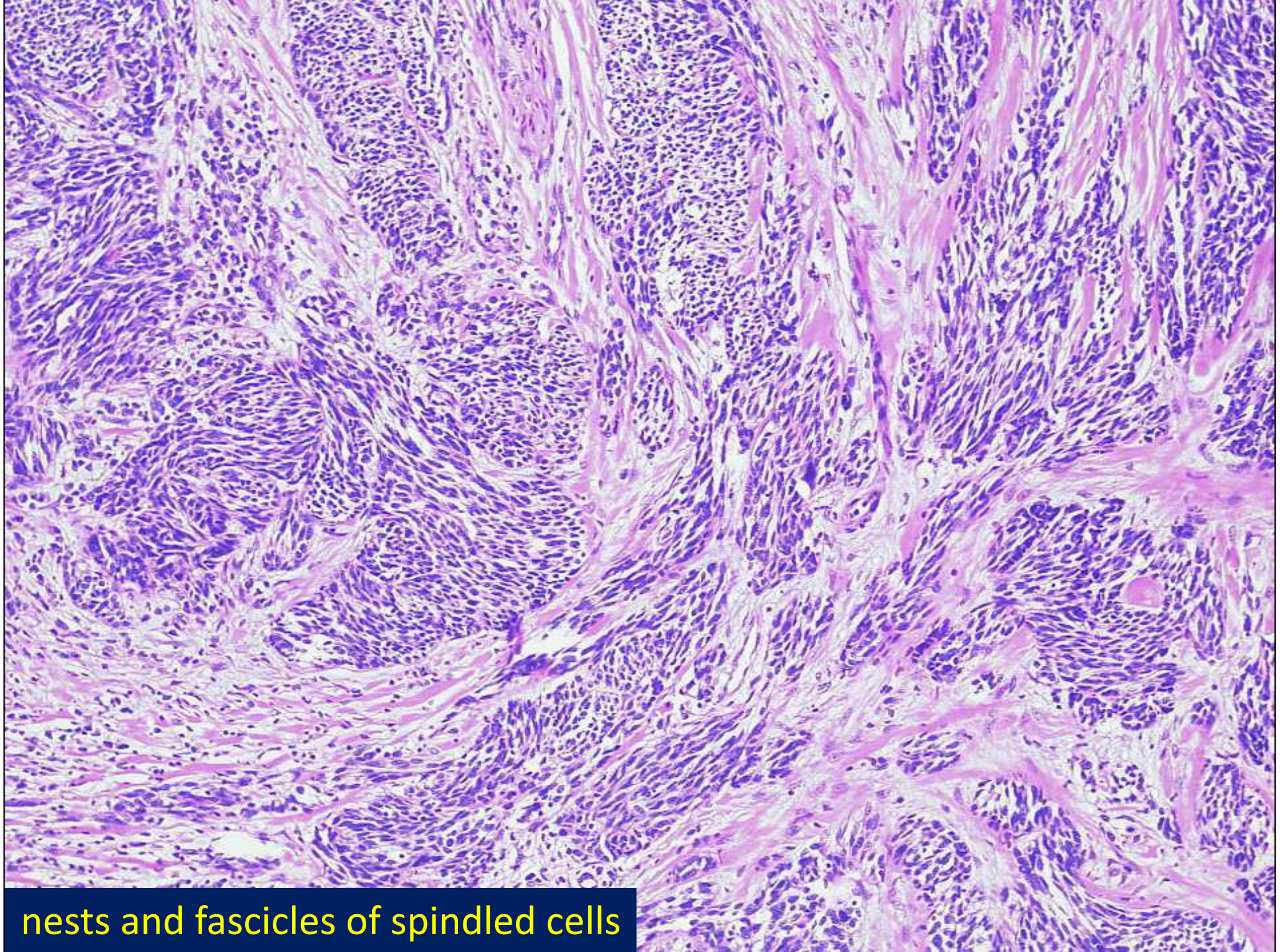
# DD: Cutaneous melanocytoma with *CRTC1::TRIM11* fusion: Paraganglioma-like dermal melanocytic tumor

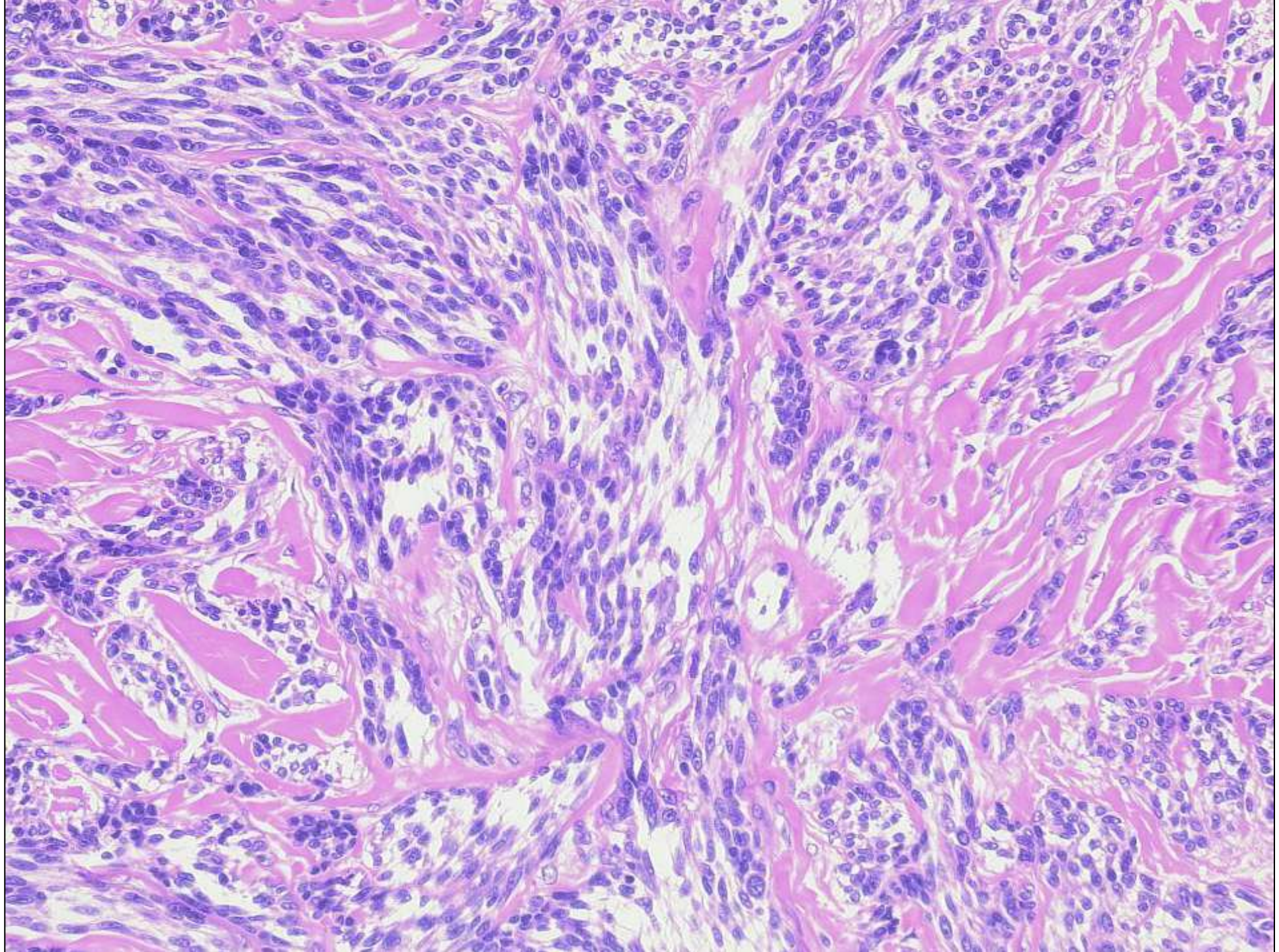
(Deyrup A et al. Am J Surg Pathol 2004; 28: 1579-1586)

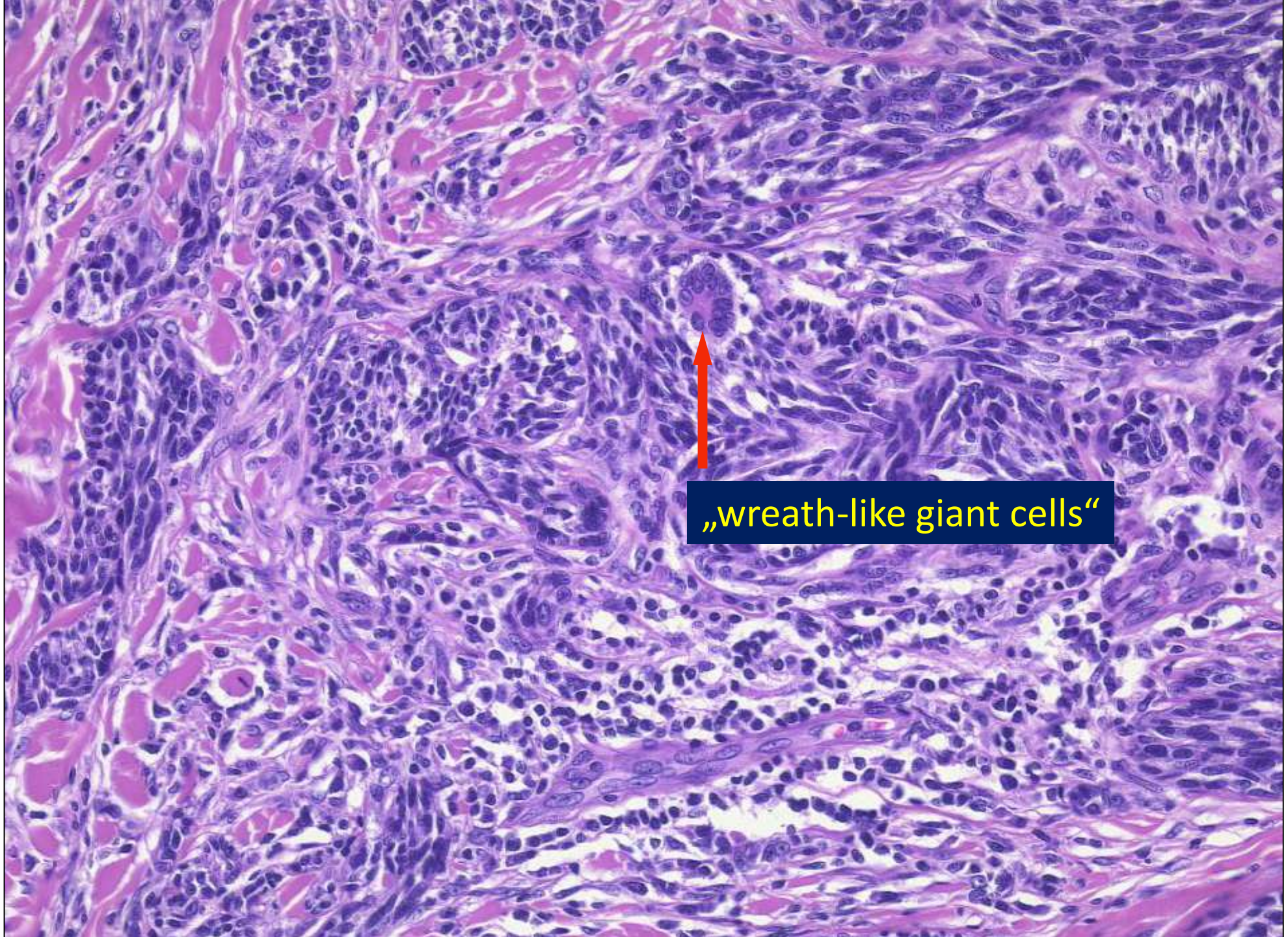
6 F, 2 M, 18-53 years
nodular, multinodular (3)
mild atypia, low proliferative activity
similar immunophenotype
intact EWS locus
But: no testing of *CRTC1-TRIM11* fusion

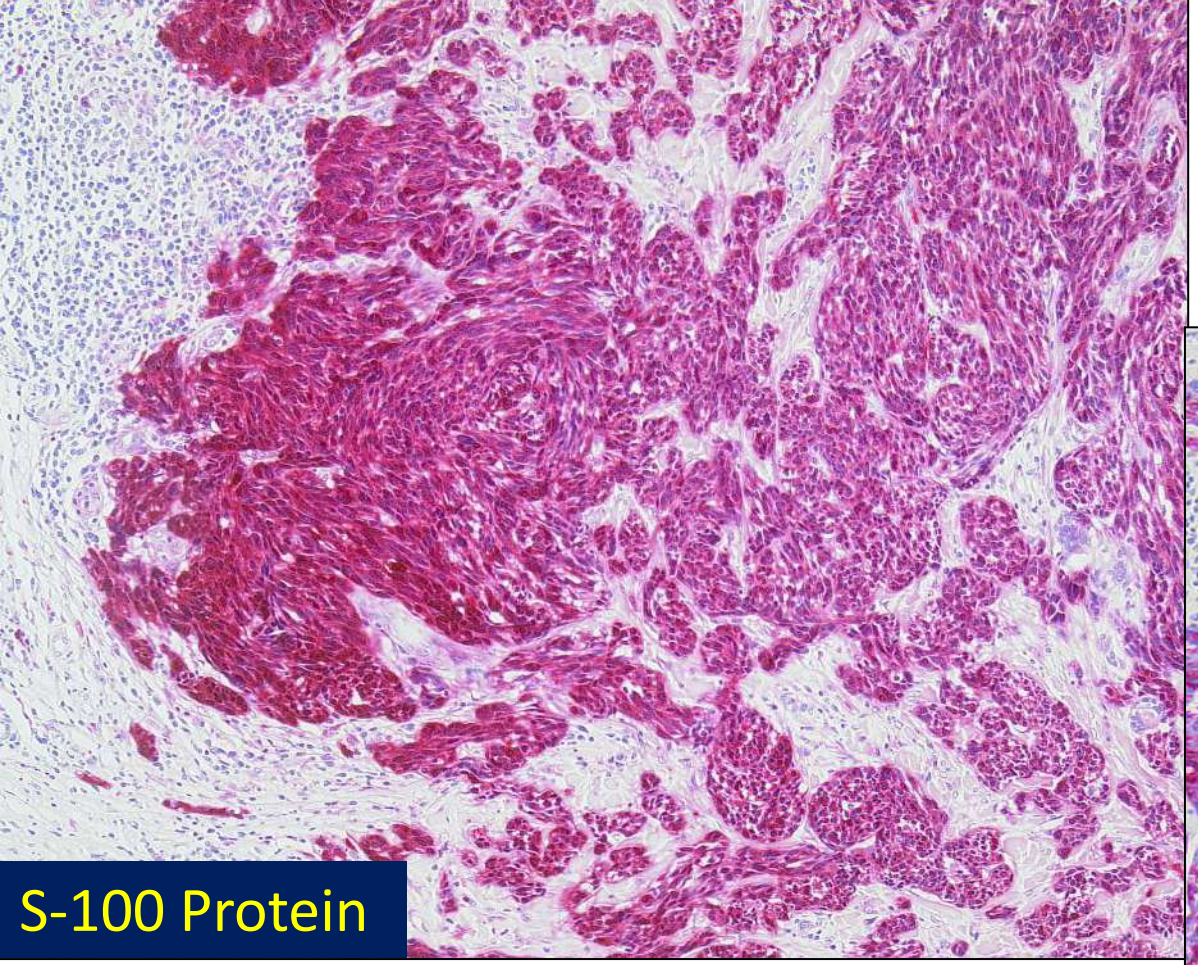


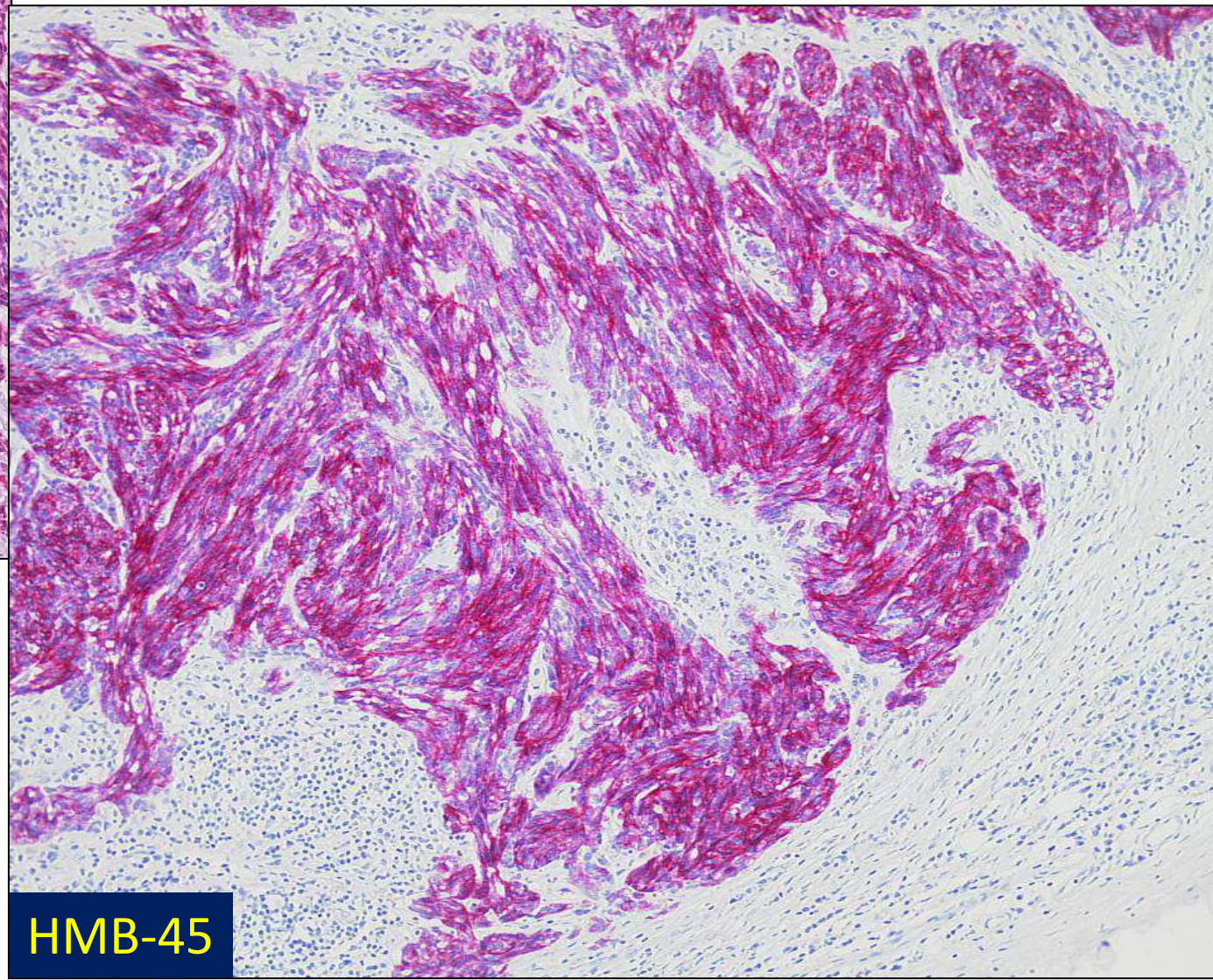
F, 19 years, lateral foot


nests and fascicles of spindled cells

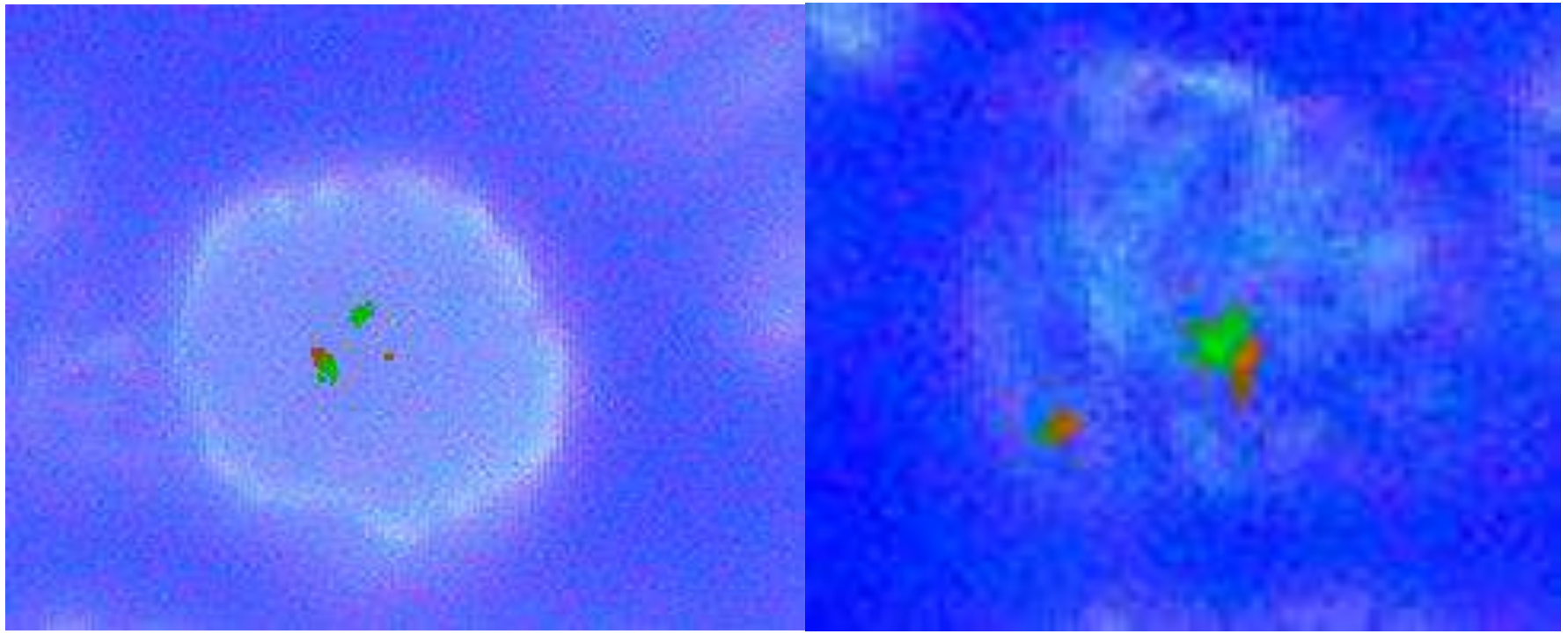



„wreath-like giant cells“

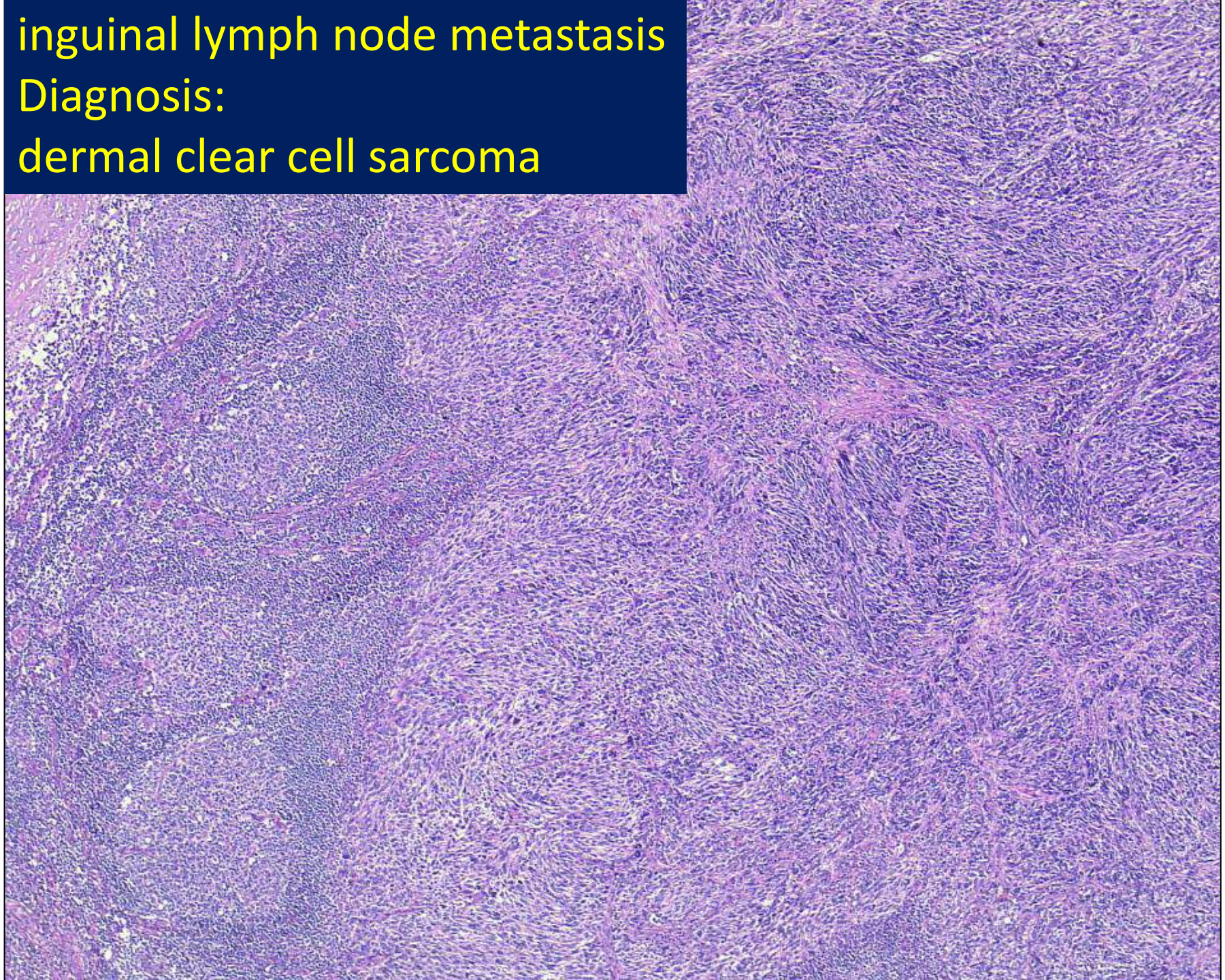

S-100 Protein

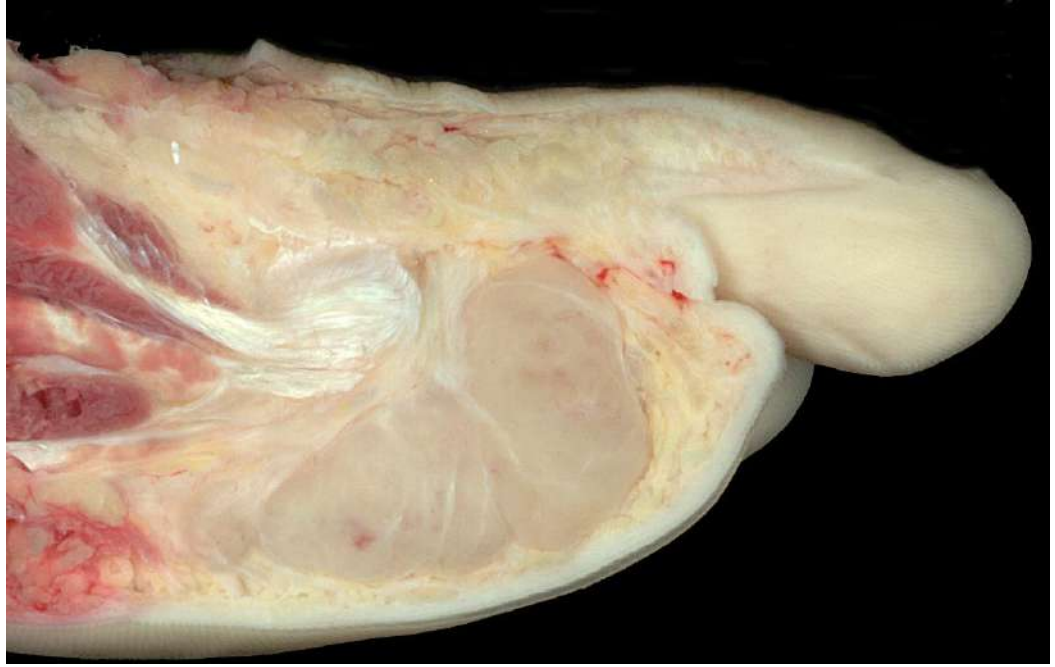

HMB-45

# FISH Analysis for the evidence of *EWS* translocation with a *EWS*-break apart probe

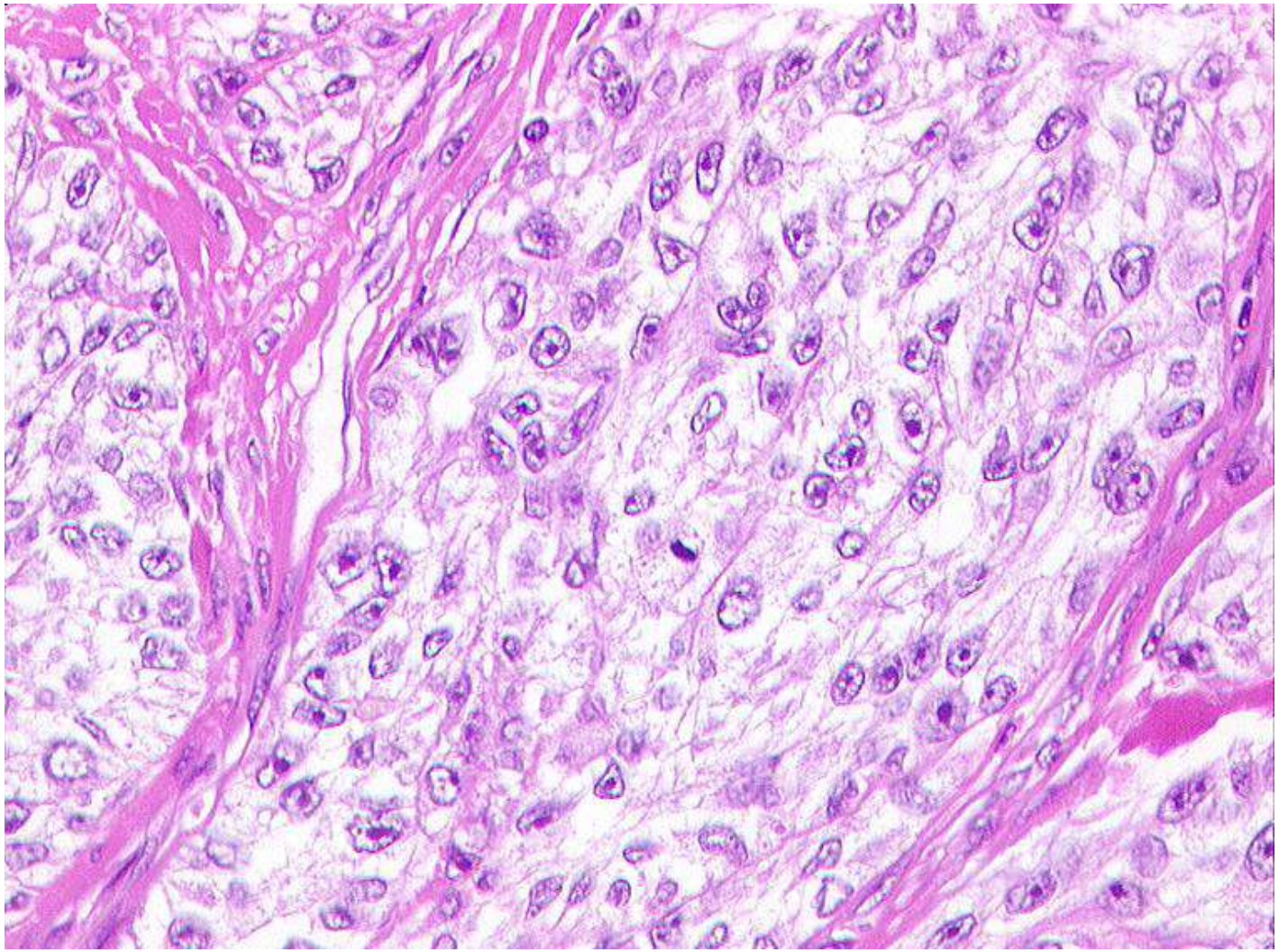


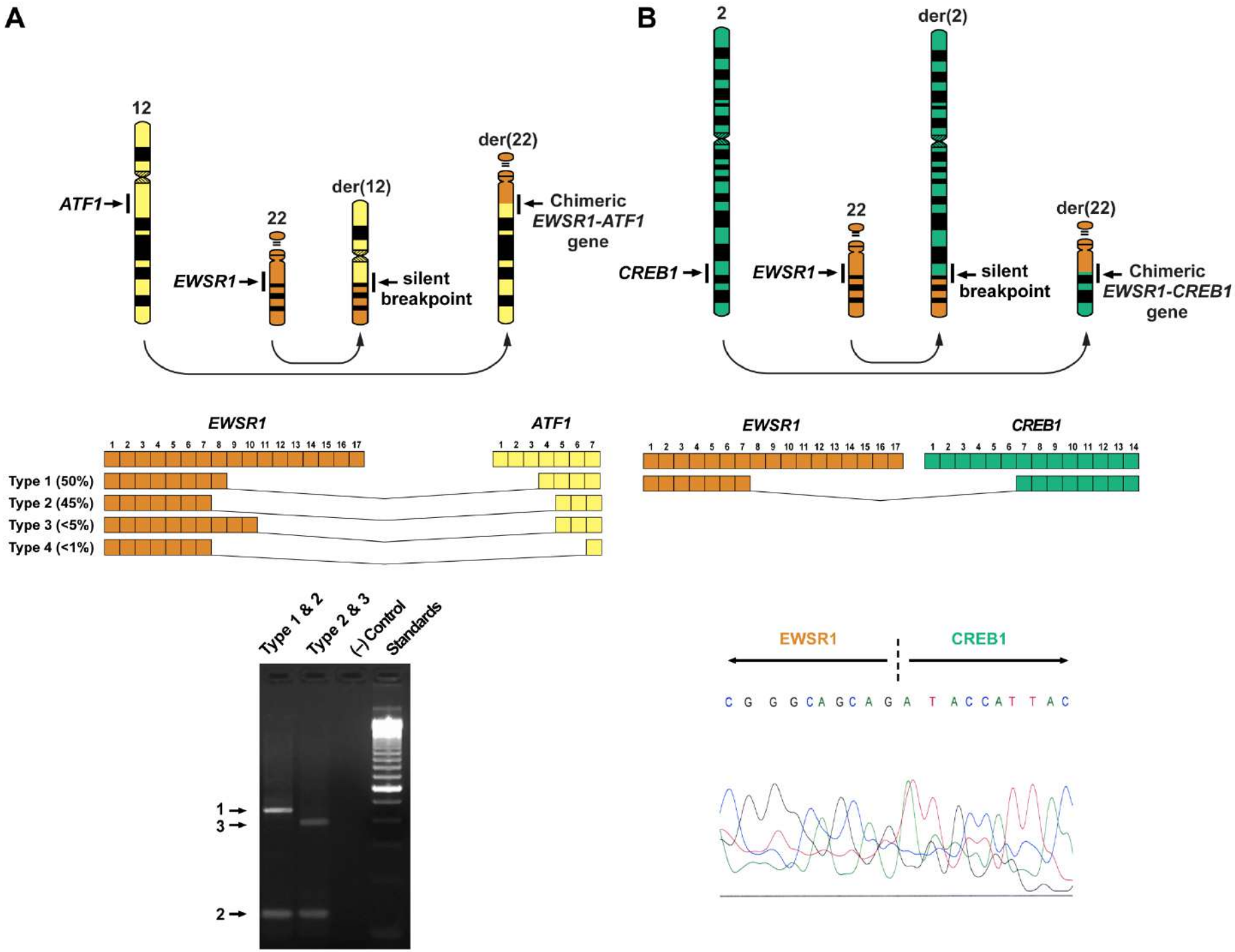
inguinal lymph node metastasis
Diagnosis:
dermal clear cell sarcoma





M, 42 years




A
12
ATF1
22
EWSR1
der(12)
silent breakpoint
der(22)
Chimeric EWSR1-ATF1 gene
EWSR1
ATF1
Type 1 (50%)
Type 2 (45%)
Type 3 (<5%)
Type 4 (<1%)
Type 1 & 2
Type 2 & 3
(–) Control
Standards
1
3
2
B
2
CREB1
22
EWSR1
der(2)
silent breakpoint
der(22)
Chimeric EWSR1-CREB1 gene
EWSR1
CREB1
EWSR1
CREB1
C G G G C A G C A G A T A C C A T T A C

# Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

*Markus Hantschke, MD,* Thomas Mentzel, MD,* Arno Rütten, MD,* Gabriele Palmedo, PhD,* Eduardo Calonje, MD,† Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD**

**Abstract:** Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a rare tumor and in the majority of cases presents a characteristic reciprocal translocation *t*(12;22)(q13;q12) that results in fusion of the *EWS* and *ATF1* genes. Although the melanocytic differentiation of CCS is indisputable, its precise lineage remains unclear. Typically, the slowly growing tumor affects the extremities of adolescents or young adults, especially around the ankle and foot. CCS is classically regarded as a deep soft tissue tumor associated with tendons or aponeuroses. This traditional view is put into perspective by the description of primary CCS of the gastrointestinal tract that may have a variant fusion gene *EWSR1-CREB1*. We describe 12 cases of cutaneous CCS and discuss the differential diagnoses. These 12 cases share an identical immunohistochemical profile with MM and thus can easily be confused with a dermal variant of spindle cell MM or metastasis of MM. The patients' ages ranged from 6 to 74 years (median: 25 y), and there was a female predominance (10 females, 2 males). Most tumors (n = 9) were located on the extremities, 2 tumors arose on the back, and 1 on the abdomen. The mean tumor size was 0.97 cm (range, 0.4 to 1.7 cm). Six cases showed invasion of the subcutis, the other 6 cases were entirely dermal. Tumor necrosis was evident in 2 cases, melanin pigment in 2 cases, and ulceration in 1 tumor. All cases showed uniform nests and fascicles of pale spindled or slightly epitheloid cells with finely granular eosinophilic or clear cytoplasm. There was fair pleomorphism with plump spindled nuclei and significantly prominent nucleoli. Multinucleated wreath-like tumor giant cells were observed in two-thirds of cases, but were usually present only focally. The dense cellular aggregates were encased by delicate fibrous septa. The stroma showed a sclerotic reticulated pattern. Partly, the nests of spindle cells bordered the epidermis, prima vista mimicking junctional nests of melanocytes. The specific translocation pattern was confirmed in all cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.

**Key Words:** clear cell sarcoma, melanoma of soft parts, melanoma

(*Am J Surg Pathol* 2010;34:216–222)

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Funding: This work partially supported by NIH 1P50CA09345-01A1 (Lazar).

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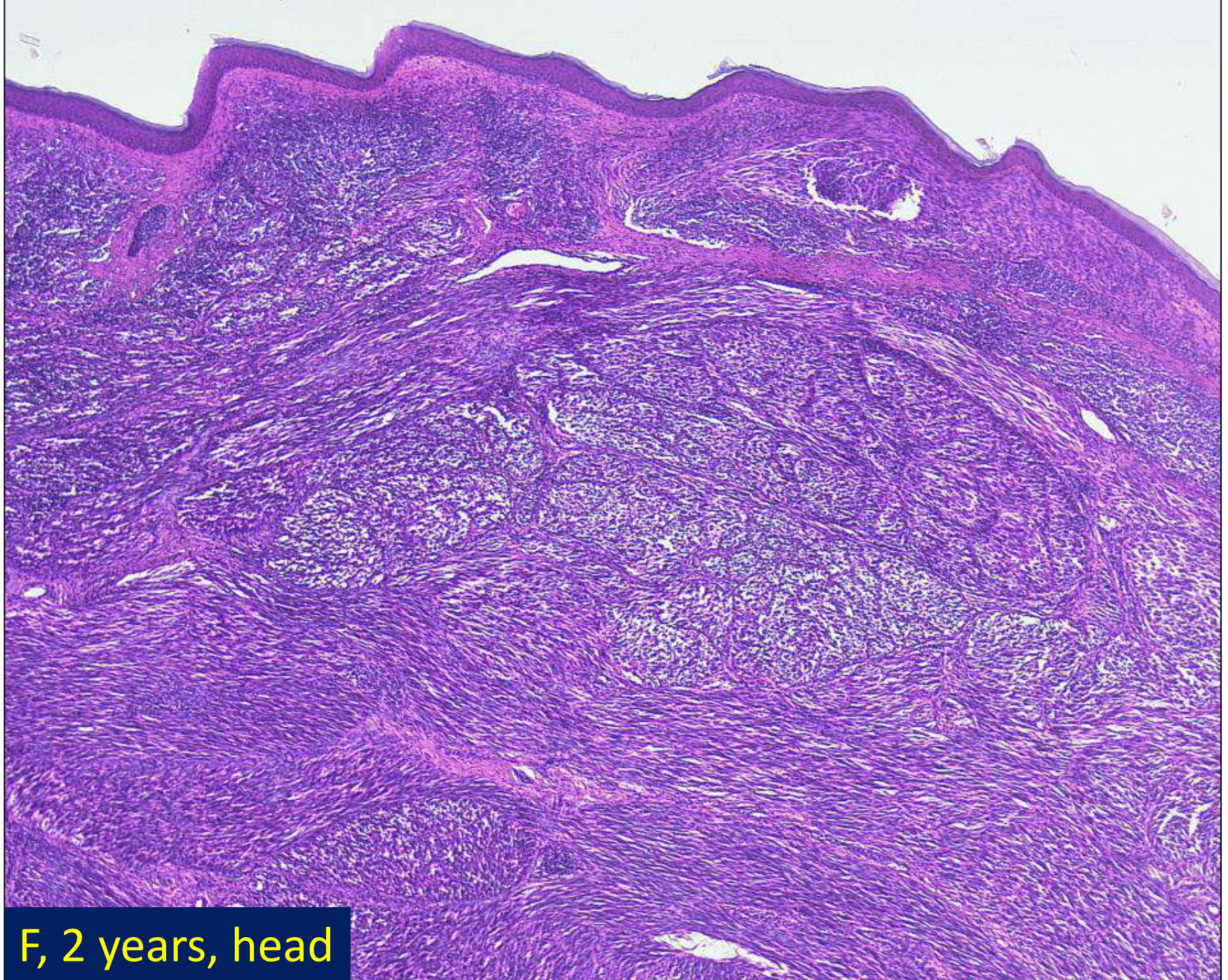
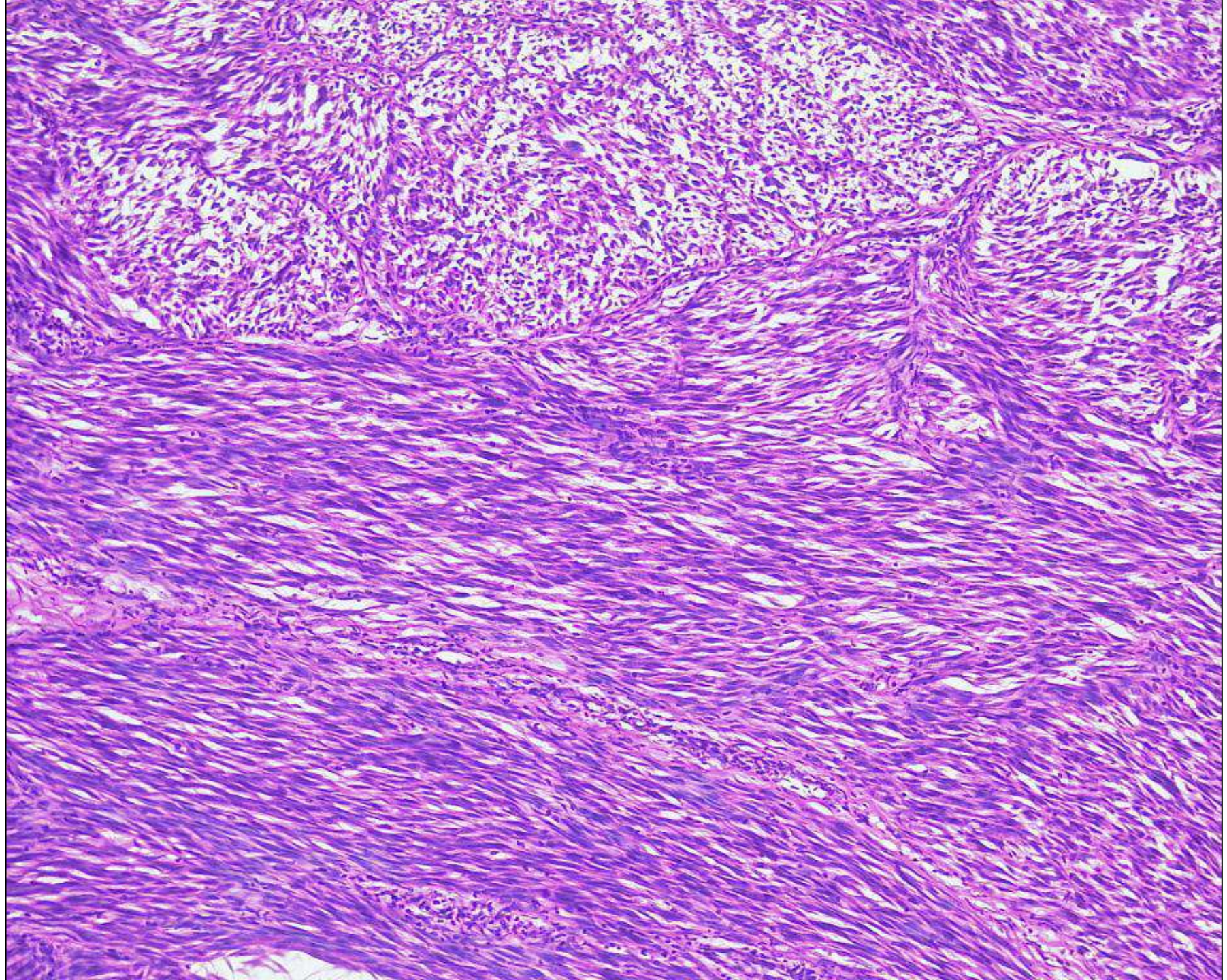
Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a unique sarcoma initially described by Franz Enzinger in 1965.[10] The tumor has a proclivity to involve the tendons and aponeuroses of distal extremities of adolescents or young adults, with a peak incidence in the third and fourth decade and a slight female predominance. The tumor is usually deep seated and characterized by multiple local recurrences with late metastases and a high rate of tumor deaths. Pathologic findings include fascicles and nests of pale fusiform and epitheloid tumor cells with clear or finely granular, eosinophilic cytoplasm and elongated oval nuclei with prominent nucleoli, and scattered mitoses. The cellular aggregates are encased by delicate fibrous septa and in two-thirds of cases multinucleated giant cells are observed. CCS shows consistent evidence of melanocytic differentiation. By electron microscopy, melanosomes in varying stages of development can be identified in the majority of the cases.[3,13,15,19] Immunohistochemically, distinction from MM is not possible because both tumors share positivity for the melanocytic markers S-100, HMB-45, MelanA, and microphthalmia transcription factor. As the histologic and immunohistochemical features of CCS overlap with those of cutaneous spindle cell melanoma and occult metastatic melanoma, the differential diagnosis between these entities is still problematic with profound clinical consequences.[8,26] Characteristically, cytogenetic analysis of CCS indicates in most cases the presence of a reciprocal translocation, *t*(12;22)(q13;q12) that has not yet been identified in malignant melanoma.[23] The gene fusion product involves the *EWS* (22q12) and *ATF1* (12q13) genes. This translocation has been detected cytogenetically in about 75% of reported cases of CCS. In addition, another fusion of *EWS* to *CREB1*, a gene at 2q13, has been found

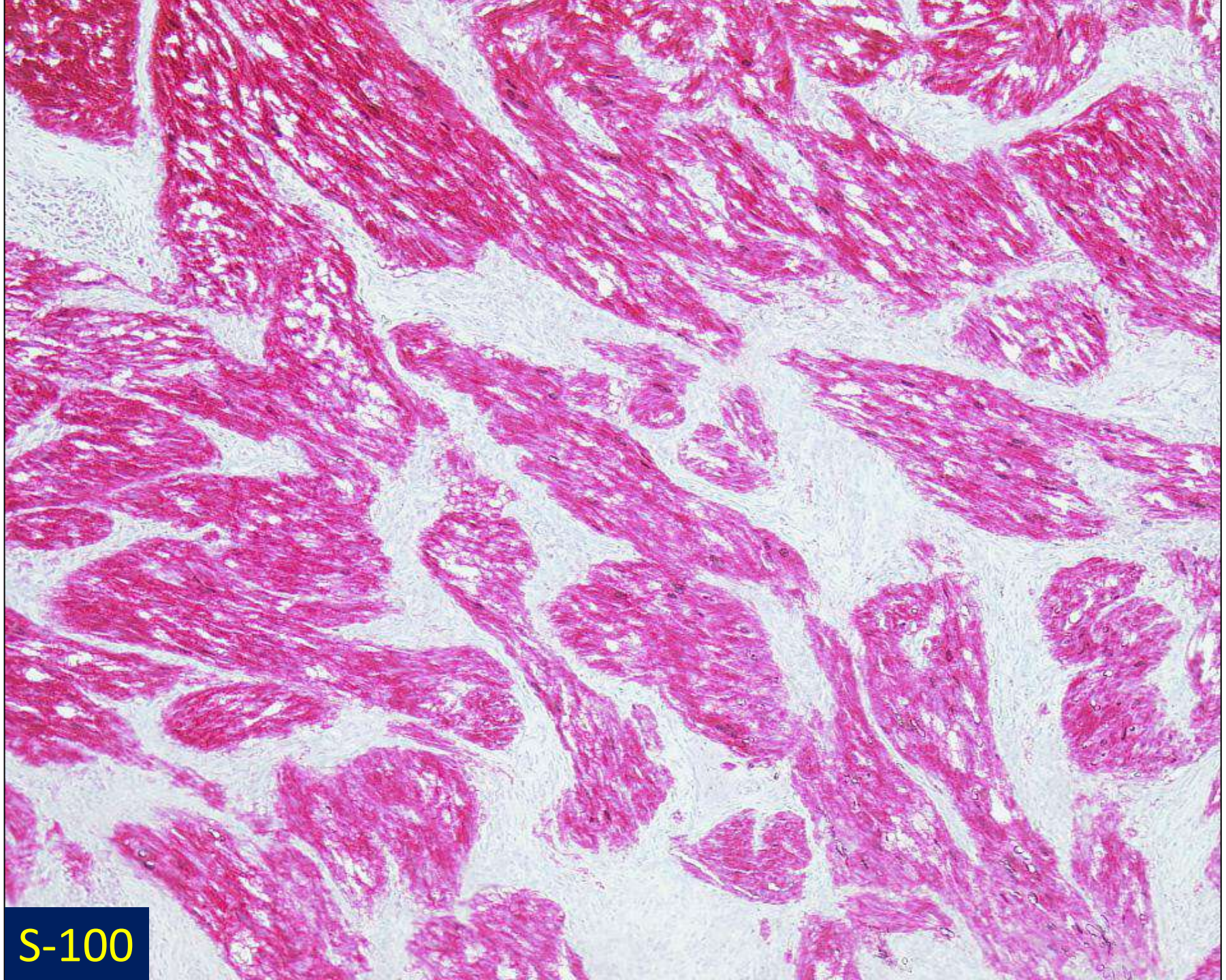
# Compound clear cell sarcoma of the skin - A potential diagnostic pitfall: Report of a series of 4 new cases and a review of the literature

B Luzar et al. Am J Surg Pathol 2020; 44: 21-29

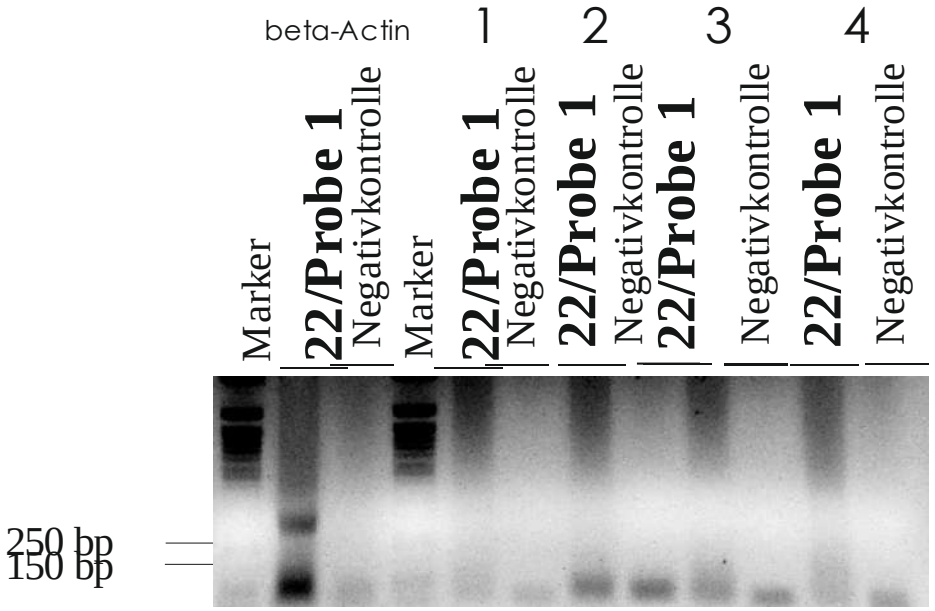
- M, 17-71 years, lower extremities (2), head (1), trunk (1), 8 - 55 mm
- 3 primary tumour, 1 skin metastasis
- typical features in the dermis + intraepidermal component (nests of spindled and epithelioid tumour cells)
- *EWSR1* rearrangement in all 4 cases


F, 2 years, head



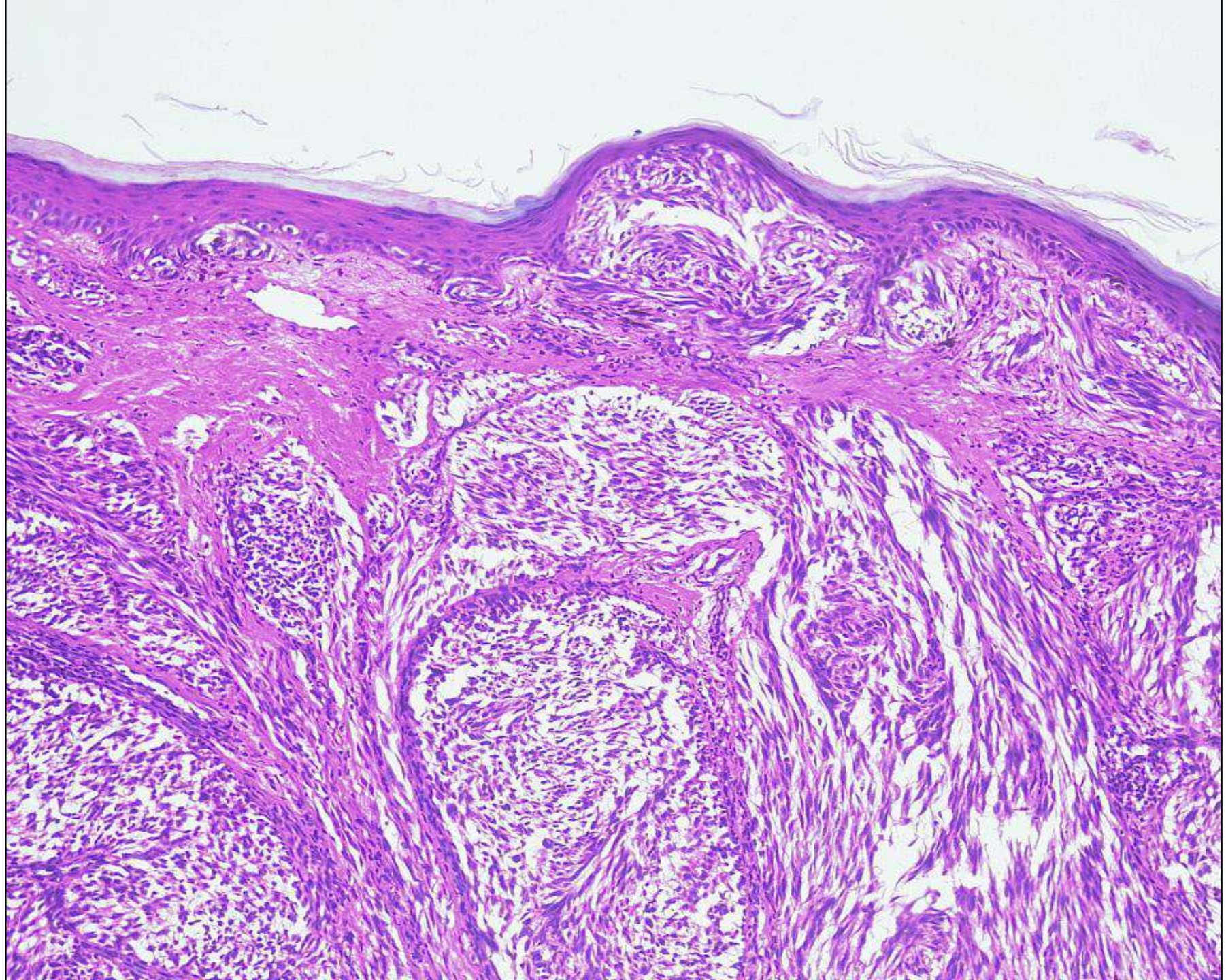

S-100

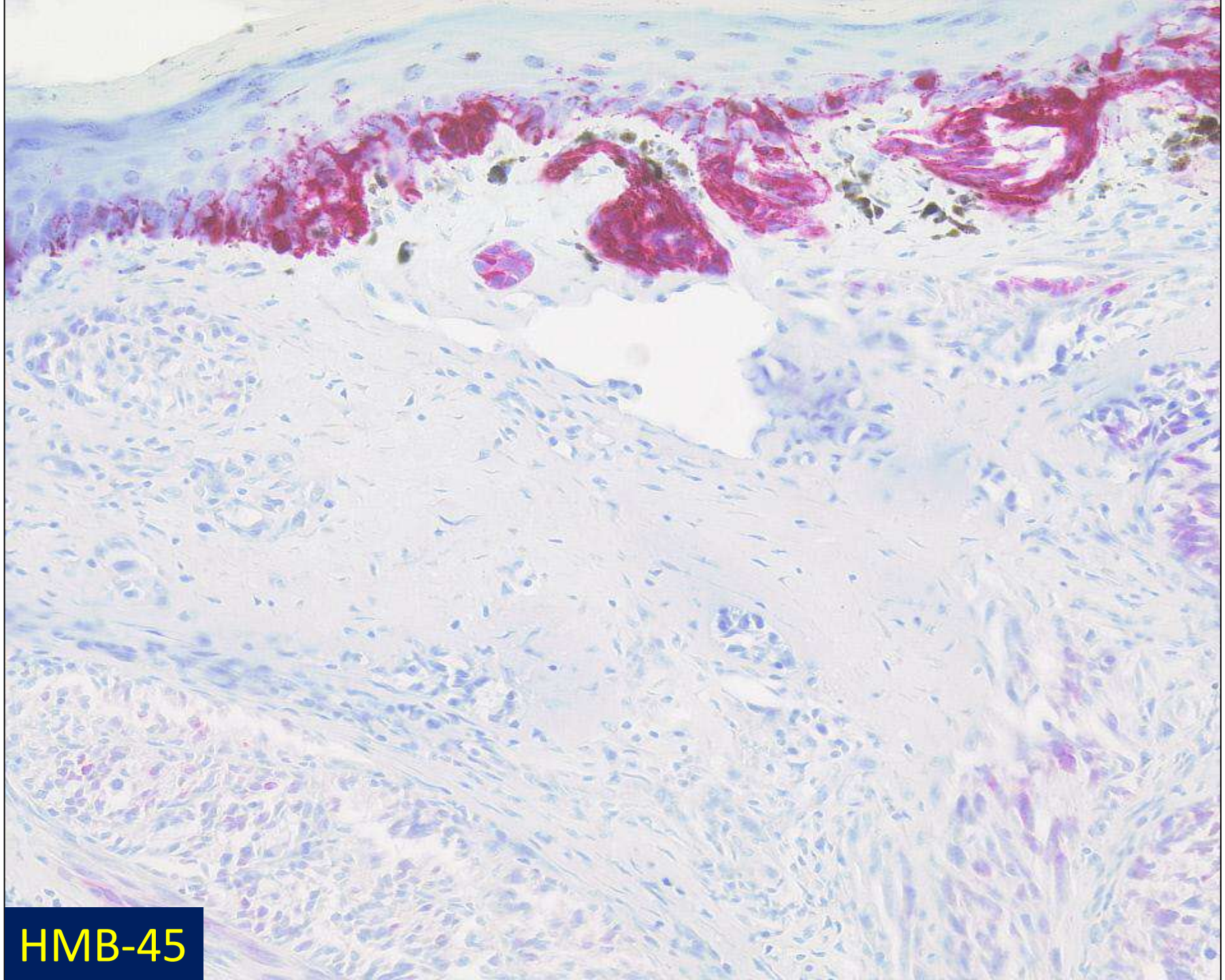
RT-PCR for fusion of EWS Exon 7-ATF1 Exon 5 with beta-Actin as control of amplification




1=EWS Exon 8/ATF1 Exon 4
2=EWS Exon 7/ATF1 Exon 5
3=EWS Exon 9/ATF1 Exon 7
4=EWS Exon 7/CREB1Exon 7

Referenzbereich chimäres
EWS-ATF und EWS-CREB1
RT-PCR-Produkt




HMB-45

# Cutaneous melanocytoma with *CRTC1::TRIM11* Fusion: An emerging entity analyzed in a series of 41 cases

Hanna J et al. Am J Surg Pathol 2022; 46: 1457-1466

„CCS represents the entity morphologically closest to cutaneous melanocytoma with *CRTC1-TRIM11* fusion“

„deeper anatomic location, multinucleated giant cells and, in some cases, prominent clear cell morphology in CCS“

„molecular confirmation will still be needed“

# MITF pathway-activated melanocytic tumours

Clear cell tumor with melanocytic differentiation and *MITF-CREM* translocation: a novel entity similar to clear cell sarcoma
(de la Fouchardiere A et al. Virchows Archiv 2021; 479: 841

Clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation: report of 7 cases of a novel entity
(de la Fouchardiere A et al. Am J Surg Pathol 2021; 45: 962)

*MED15::ATF1*-rearranged tumor: a novel cutaneous tumor with melanocytic differentiation
(Ko JS et al. Mod Pathol 2024; online ahead of print)

5-16 years, high proliferative activity

Case 3: lymph node metastases

# What defines a neoplasm?

characteristic clinical features ?

characteristic morphology ?

typical immunophenotype ?

characteristic molecular features ?

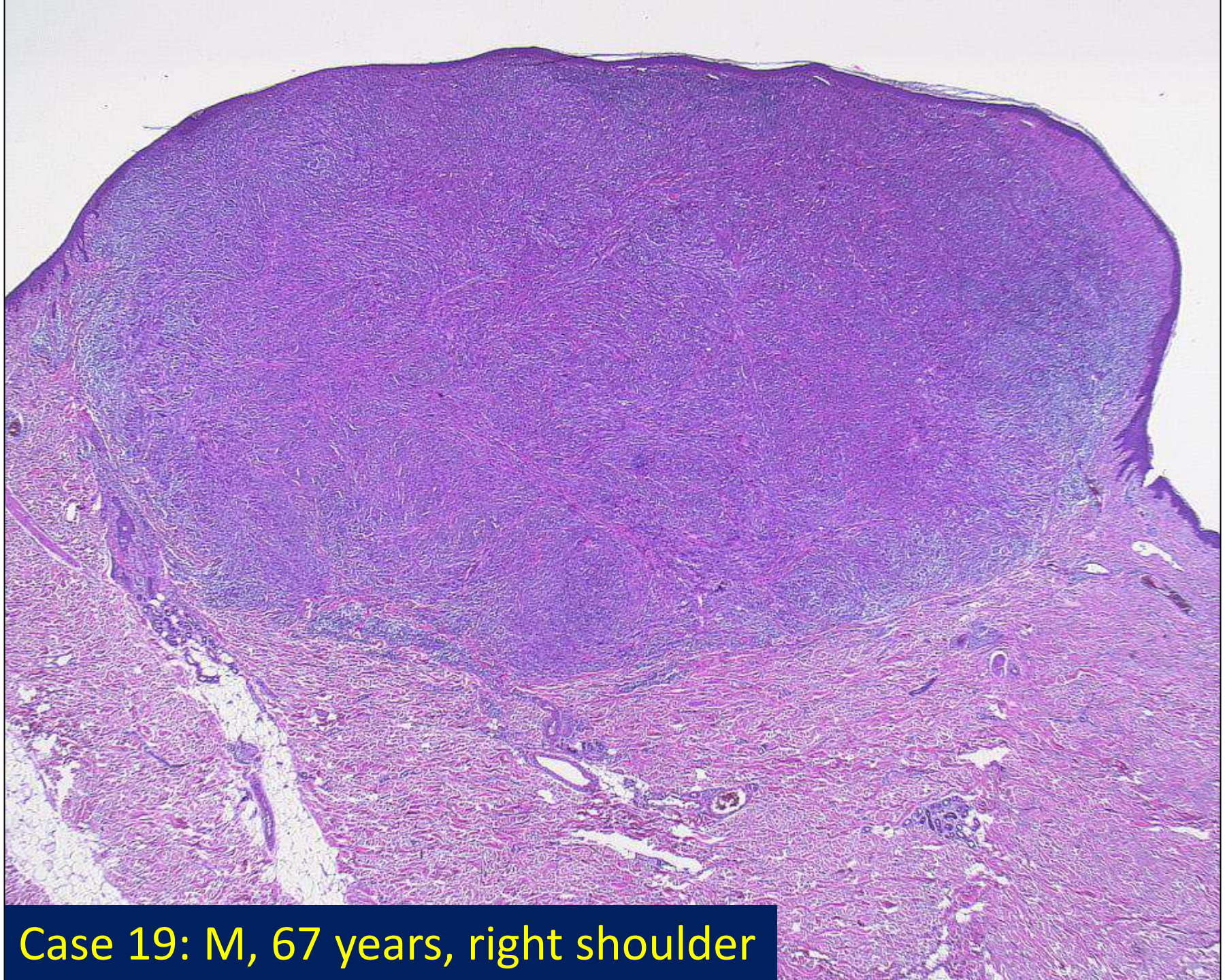
characteristic methylation pattern?

# Cutaneous melanocytoma with *CRTC1::TRIM11* Fusion

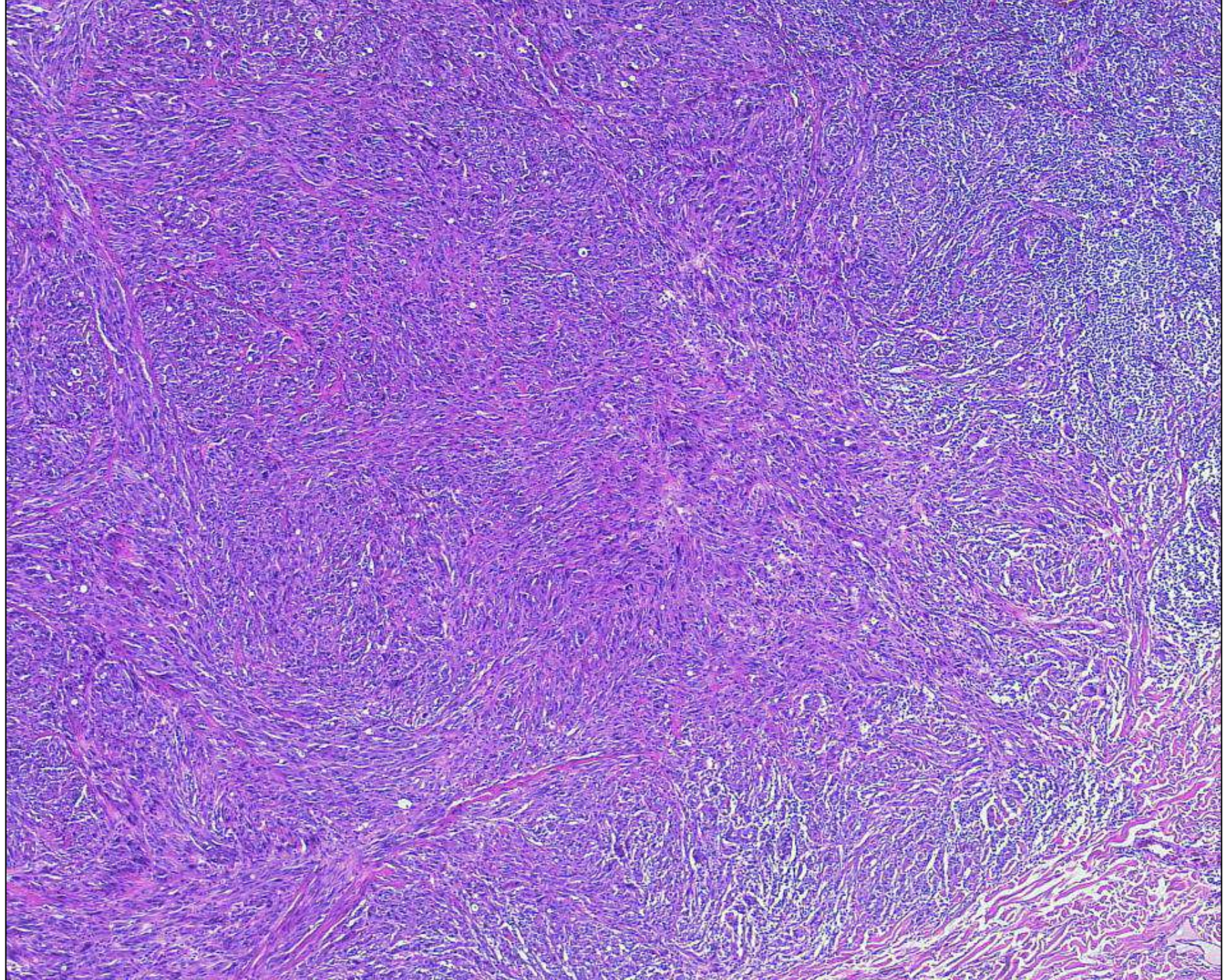
unique nosologic entity ?

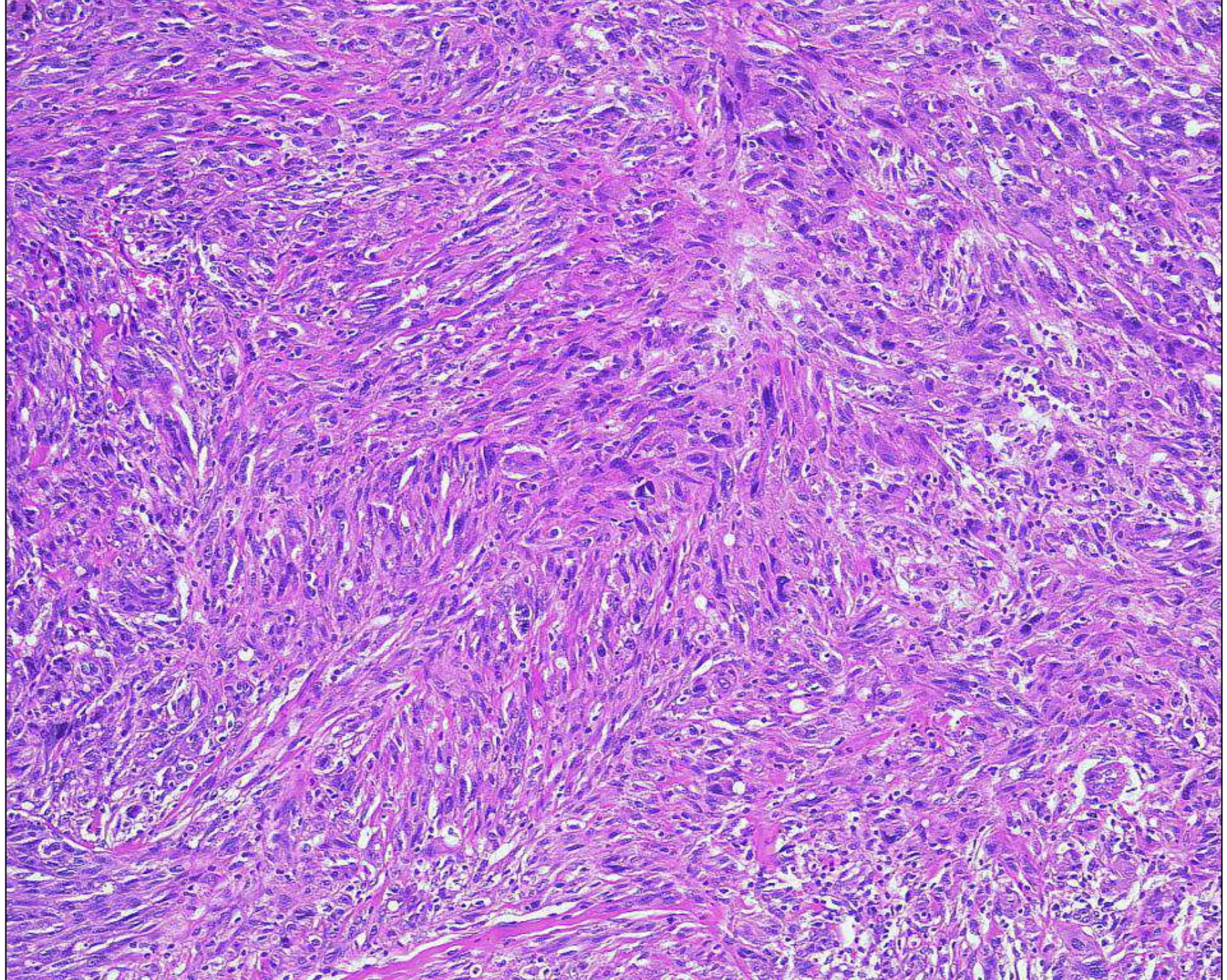
CCS with *CRTC1::TRIM11* fusion ?
(and better prognosis)

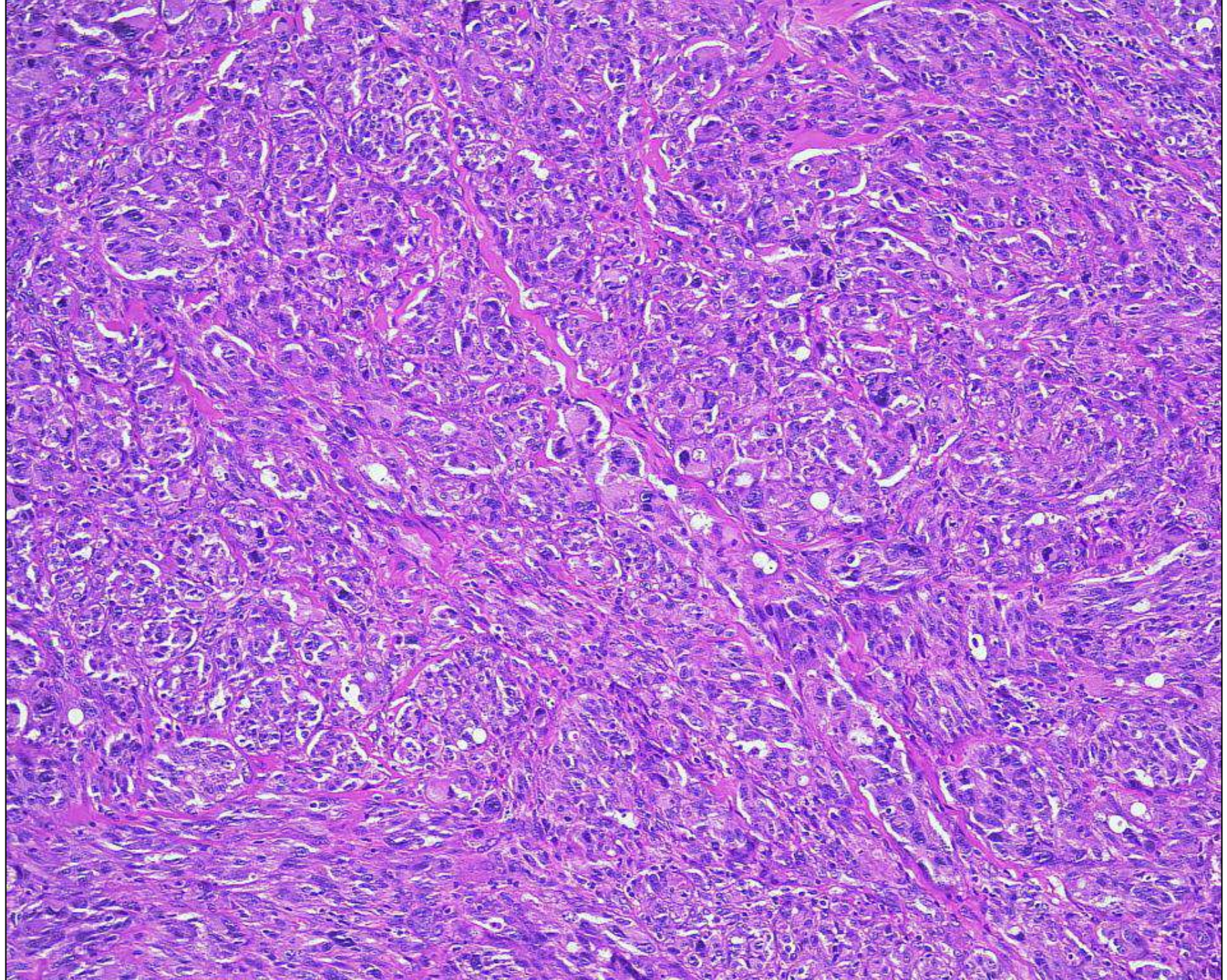
???

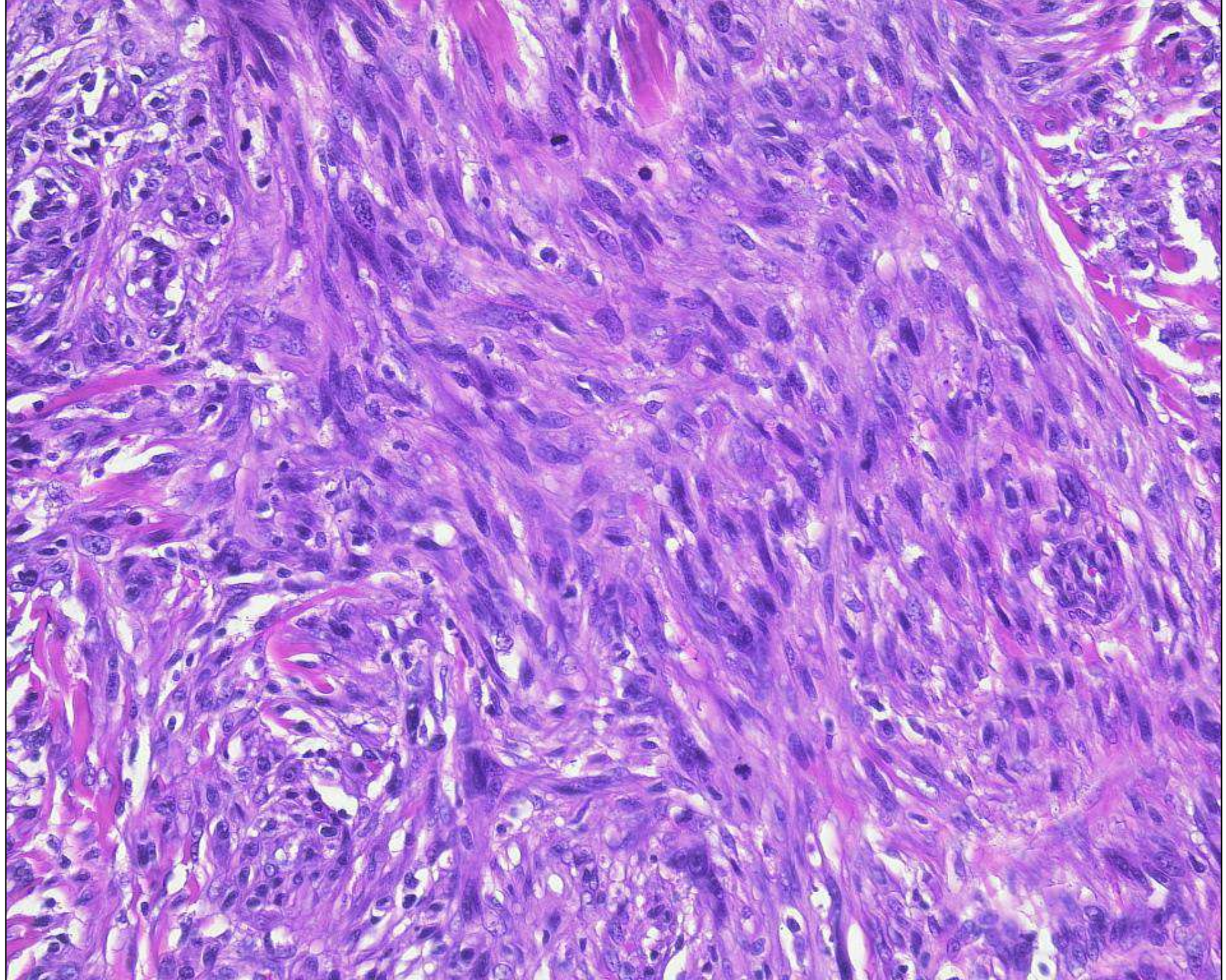


Case 19: M, 67 years, right shoulder



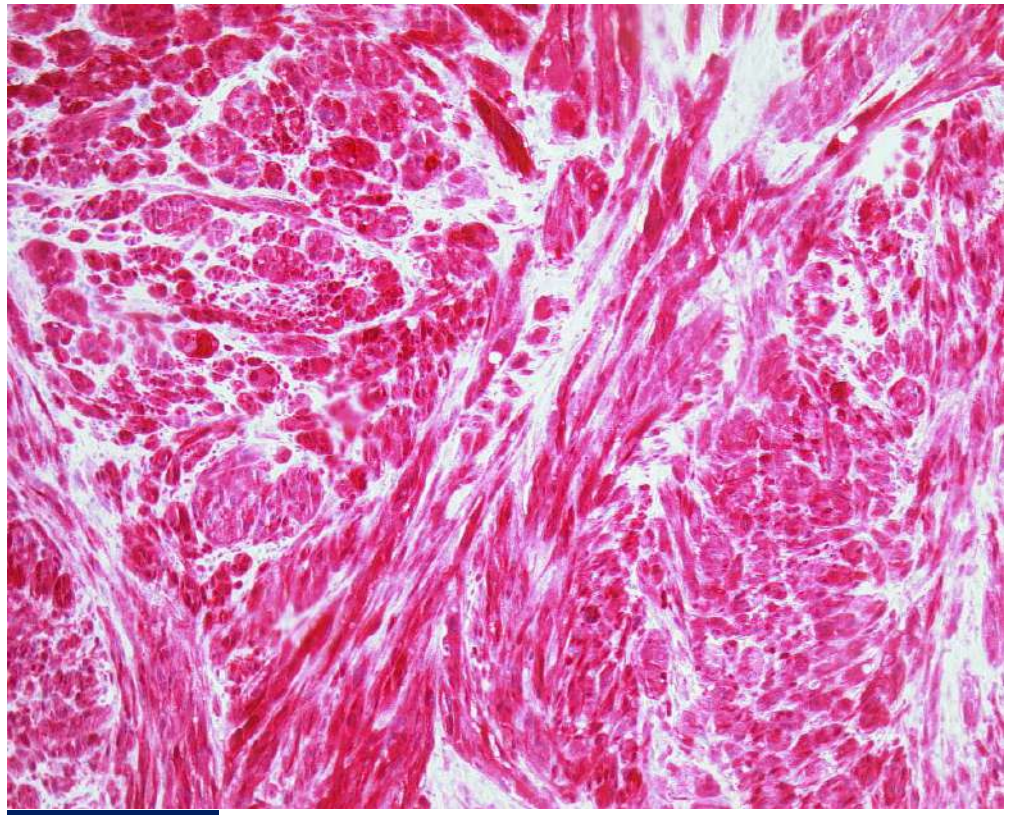




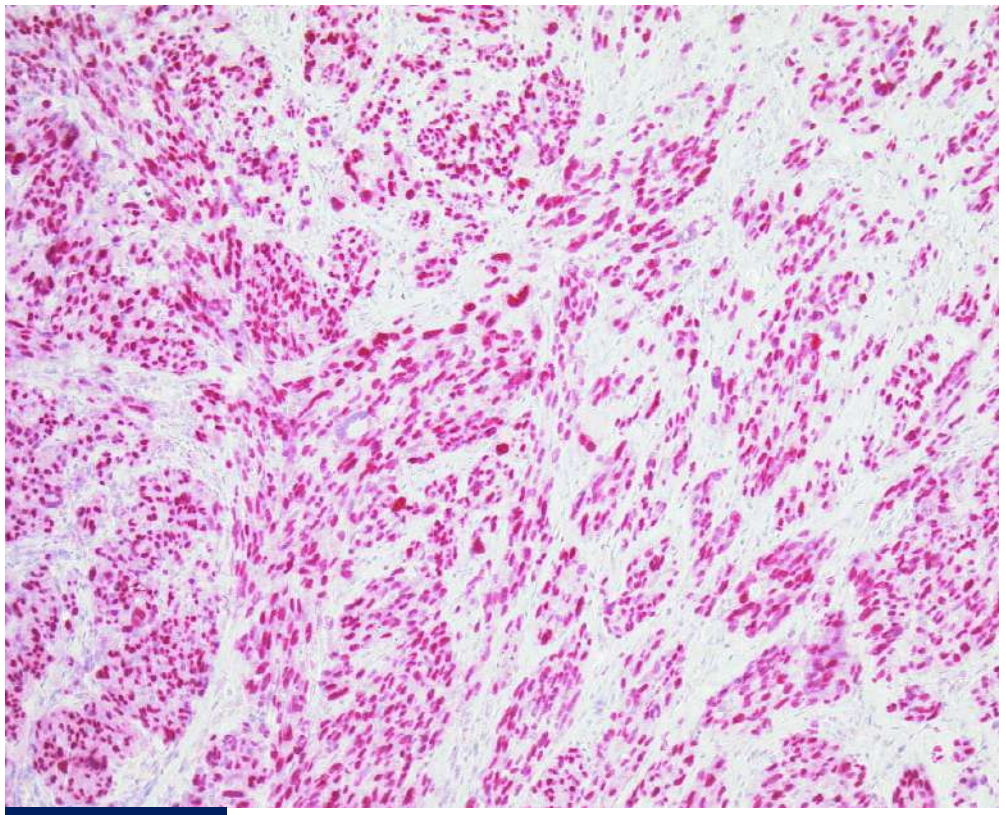


Diagosis Case 19:

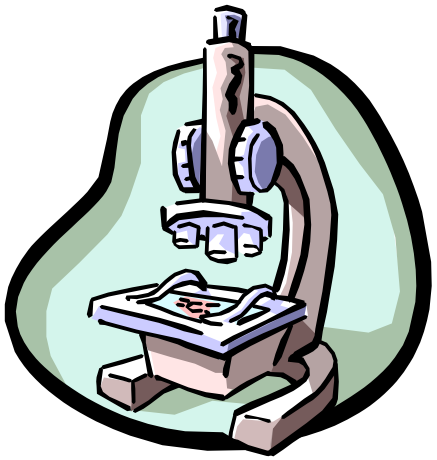
undifferentiated pleomorphic sarcoma
(superficial „MFH“)



S-100



Sox10



# Diagnosis Case 19

## sarcomatoid malignant Melanoma

**Metastatic malignant melanoma with complete loss of differentiation markers (undifferentiated/dedifferentiated melanoma): analysis of 14 patients emphasizing phenotypic plasticity and the value of molecular testing as surrogate diagnostic marker**

Agaimy A et al. Am J Surg Pathol 2016; 40: 181-191

undifferentiated/spindle cell sarcoma morphology

S-100 -, Melan-A -, HMB-45 -, Sox10 -

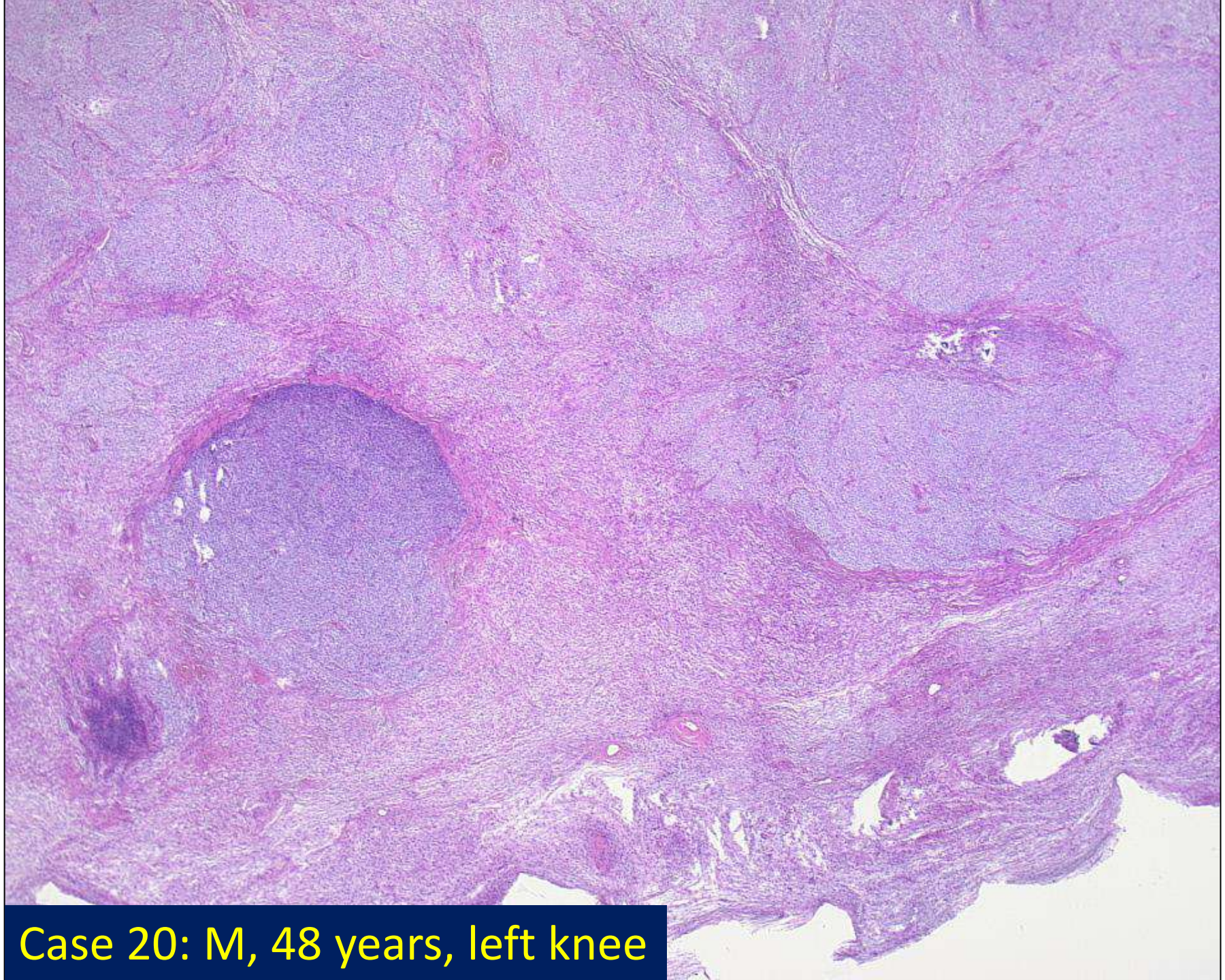
*BRAF* mutation (5), *NRAS* mutation (5)

**Prame expression is a useful tool in the diagnosis of primary and metastatic dedifferentiated and undifferentiated melanoma**

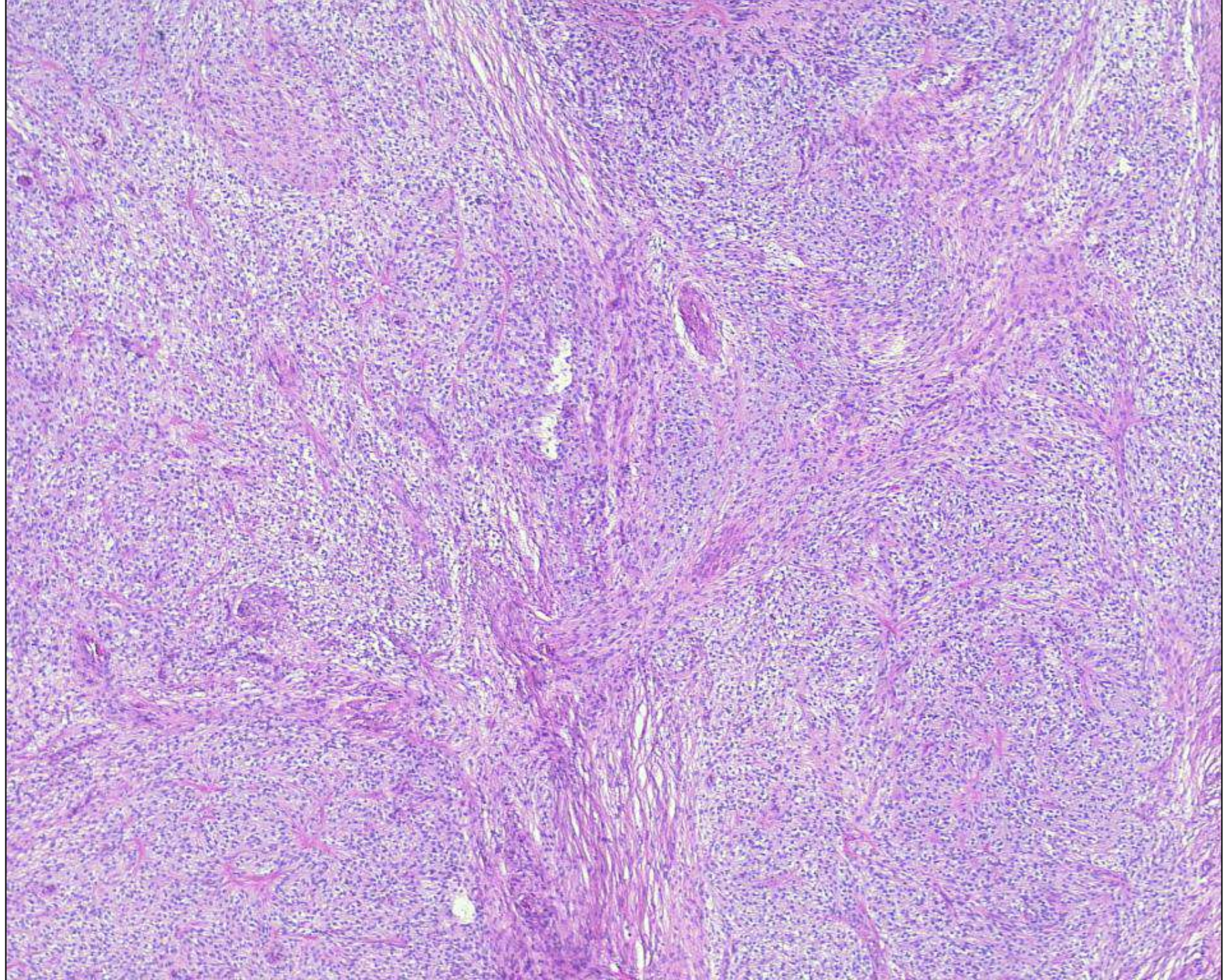
Hornick JL et al. Am J Surg Pathol 2023; 47: 1390-1397

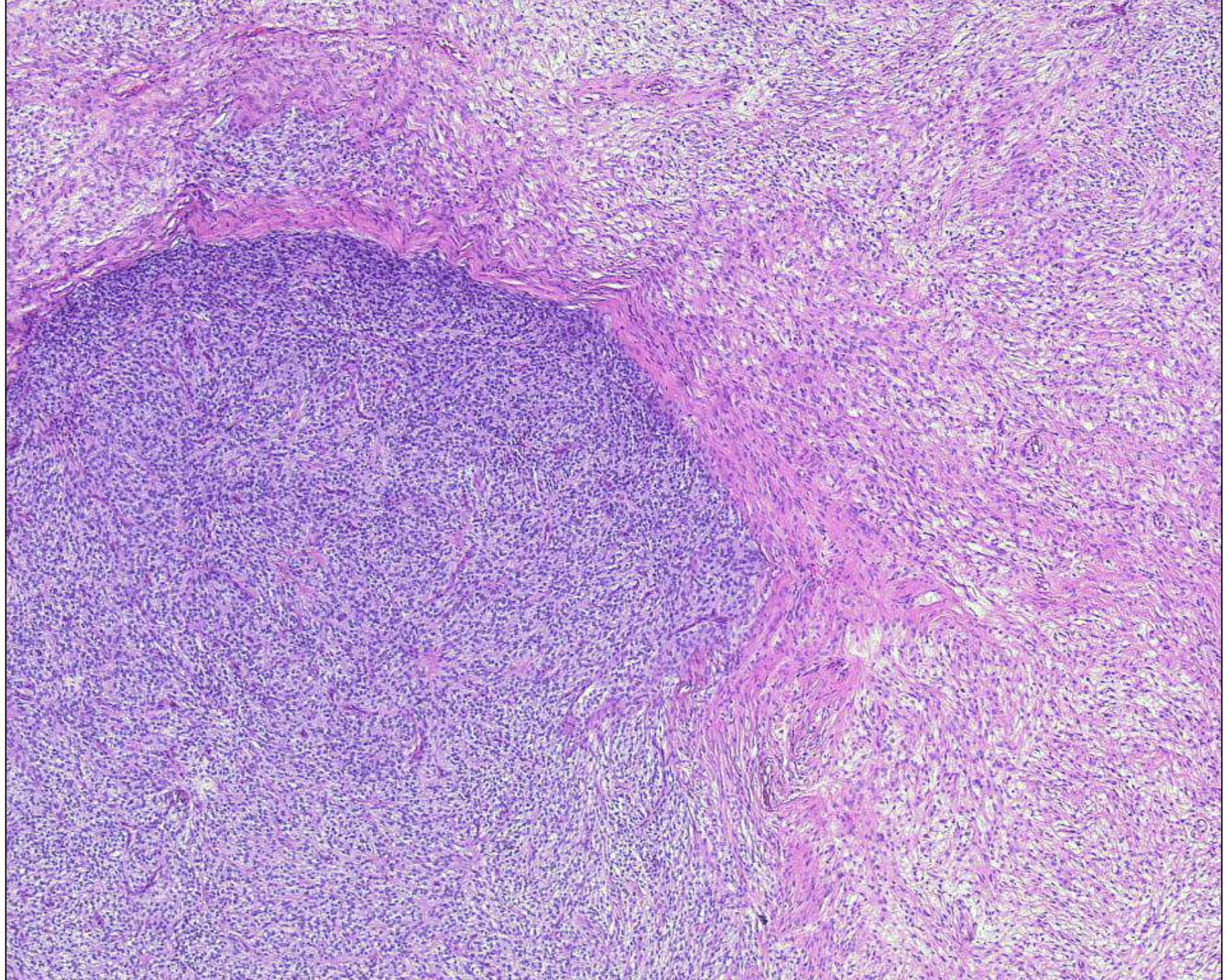
11 primary and 10 metastatic cases: strong nuclear PRAME expression

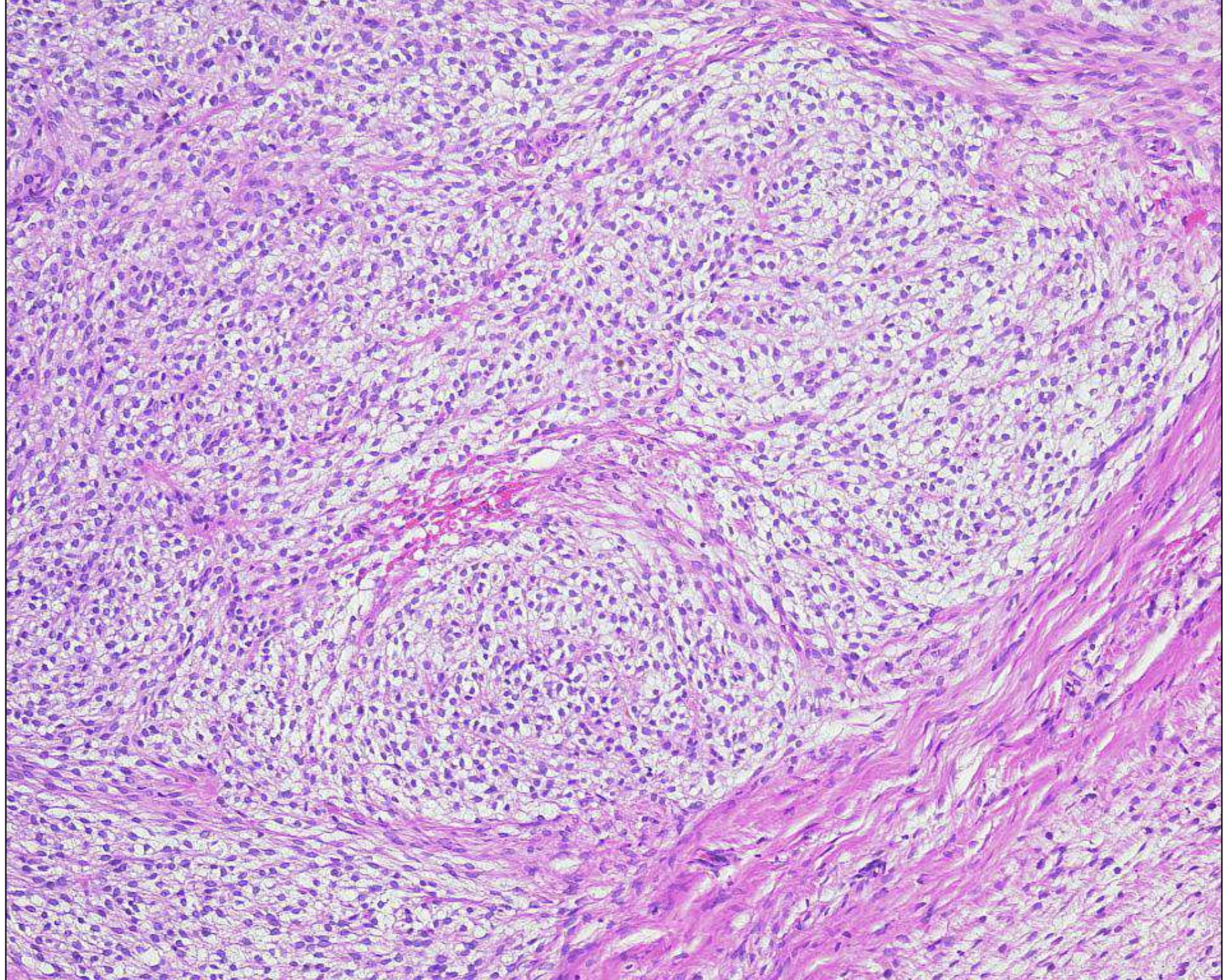
AFX and PDS PRAME -, weak and patchy +

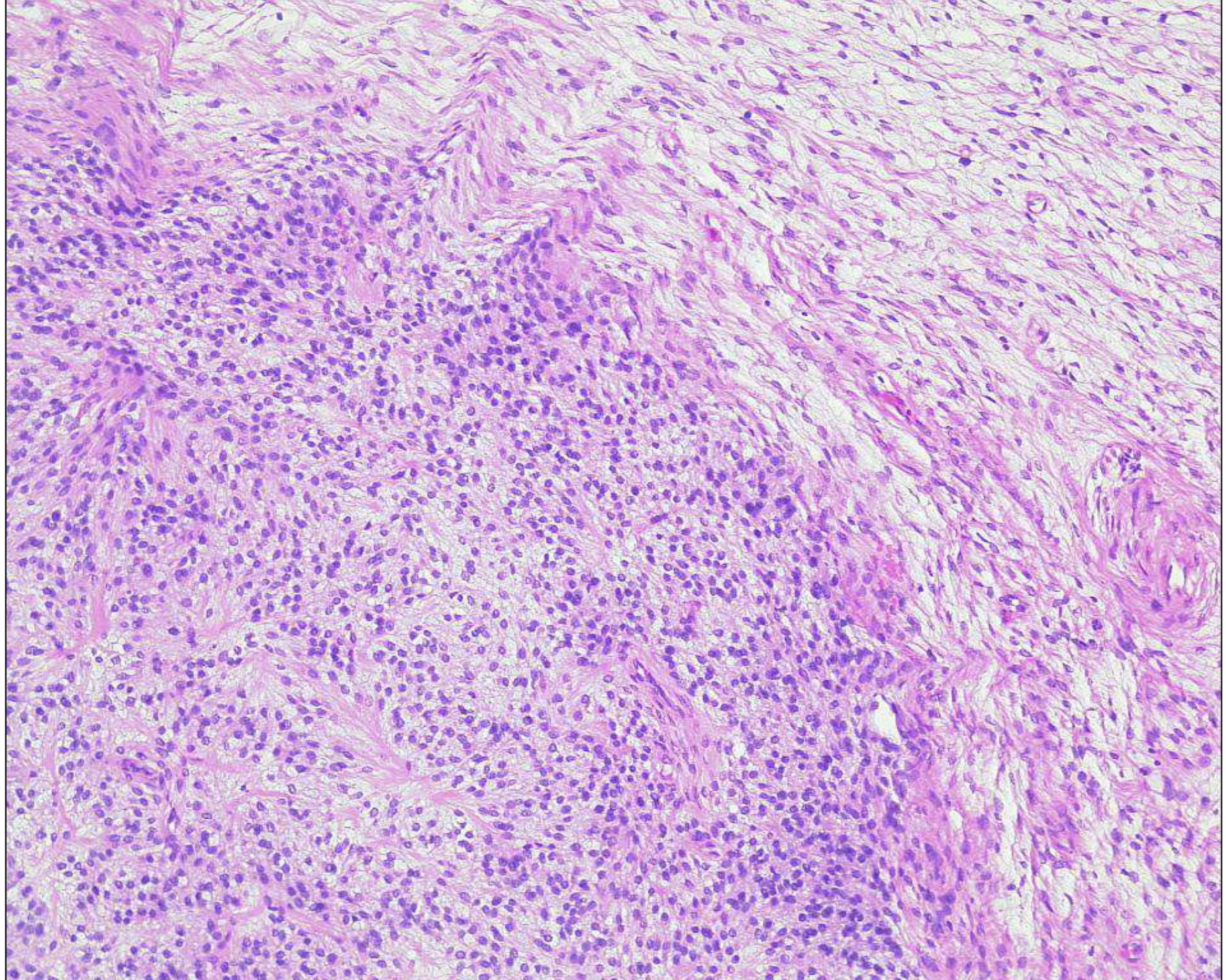


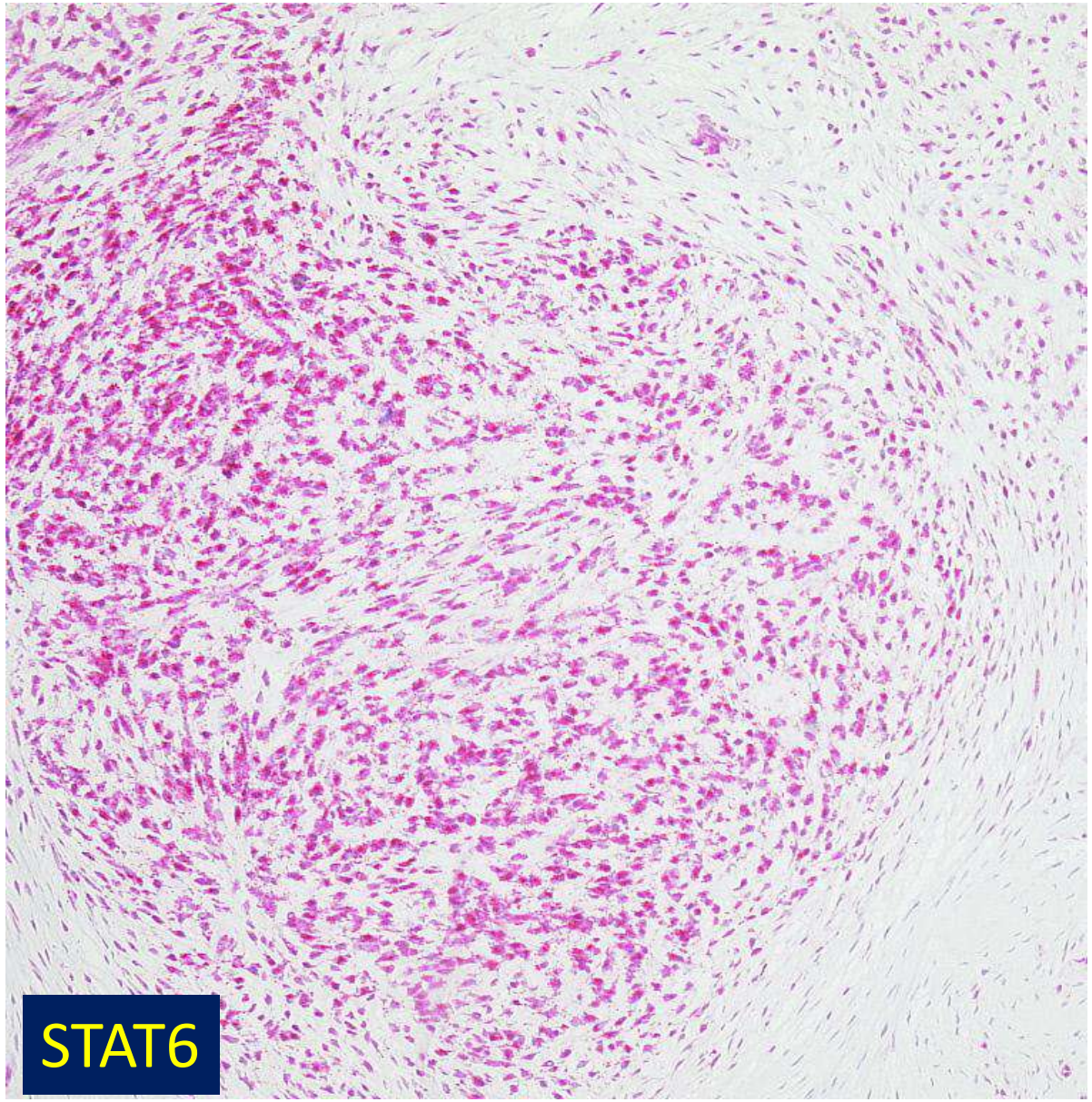
Case 20: M, 48 years, left knee

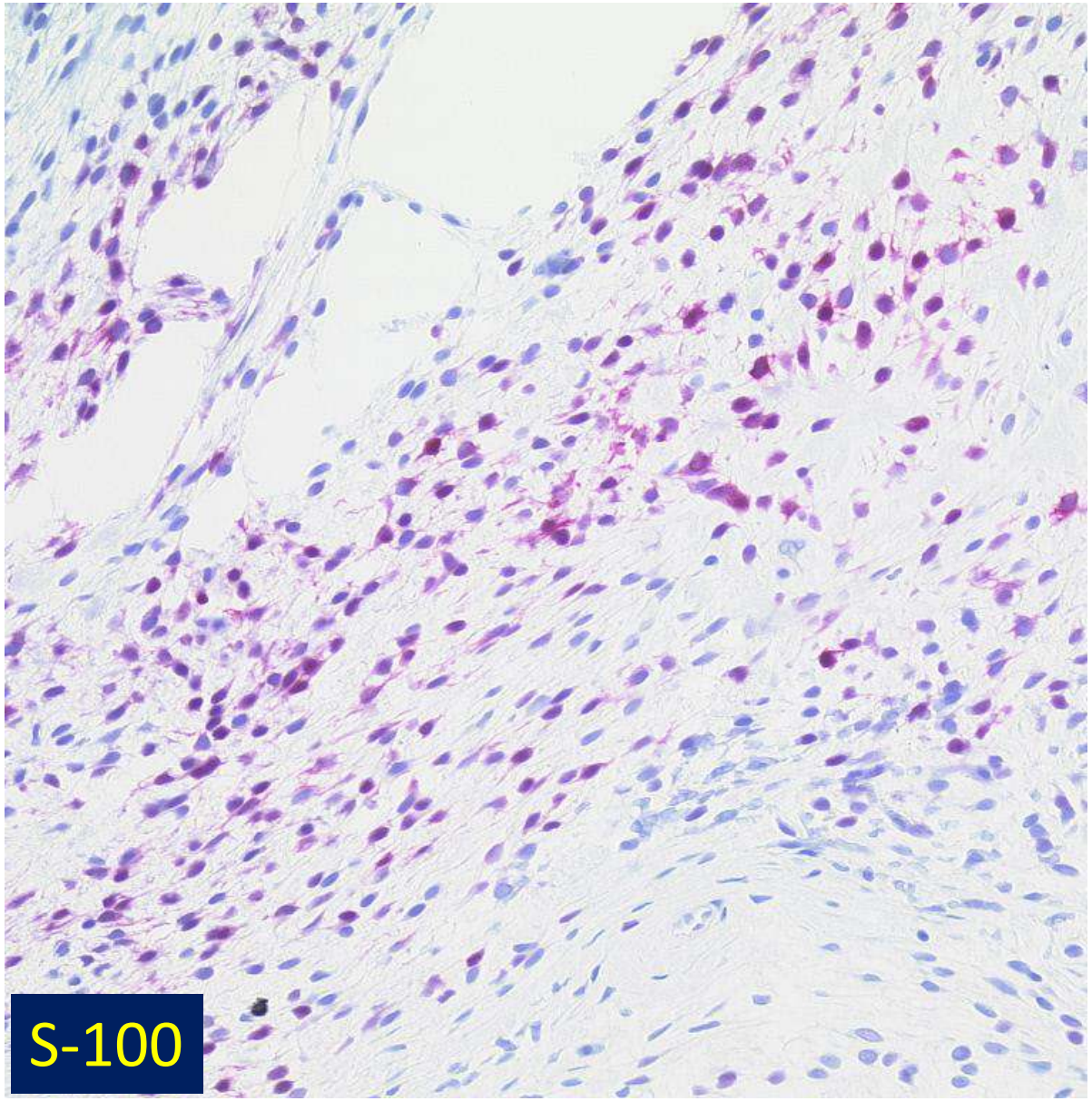




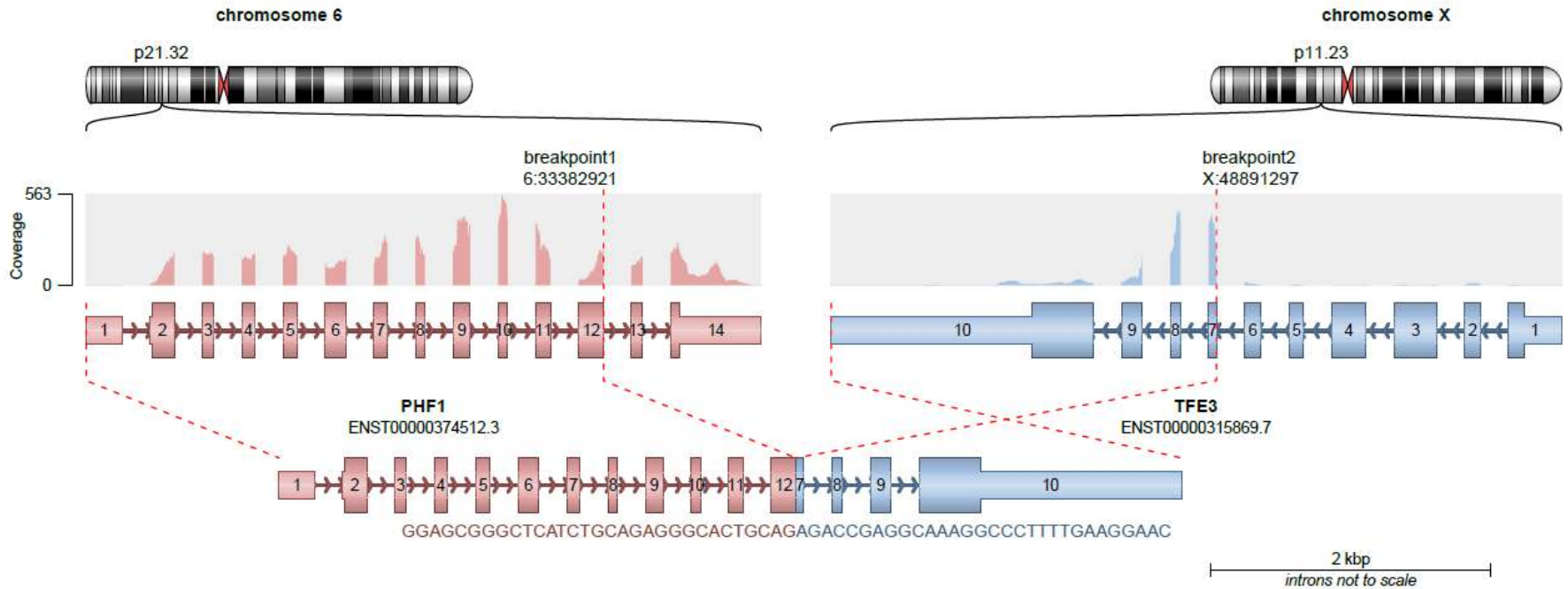


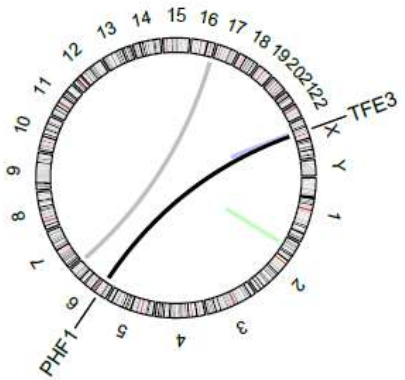


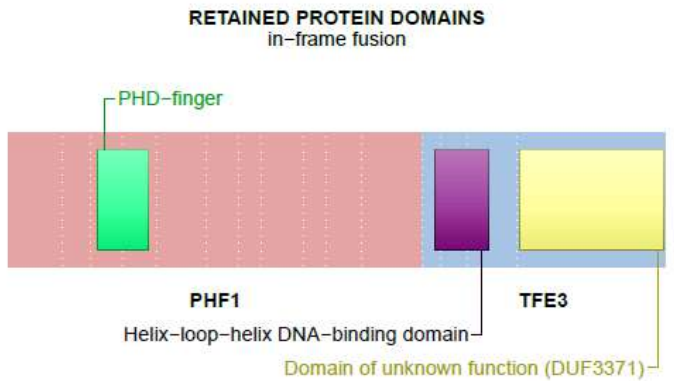



CD 31 -, ASMA -, Calponin -, CK -, HPCA1 -, EMA -, MUC4 -, desmin -



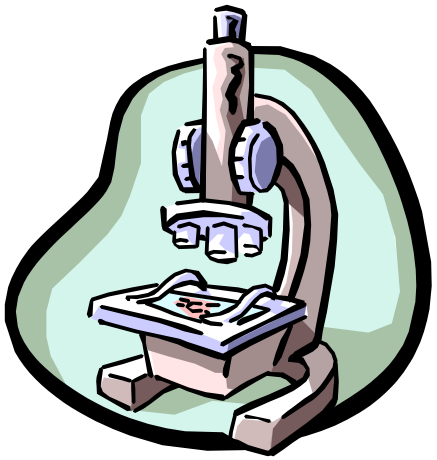




**SUPPORTING READ COUNT**

Split reads at breakpoint1 = 28
Split reads at breakpoint2 = 60
Discordant mates = 39

translocation deletion
duplication inversion

by courtesy of Prof. Dr. A.Agaimy, Erlangen, Germany

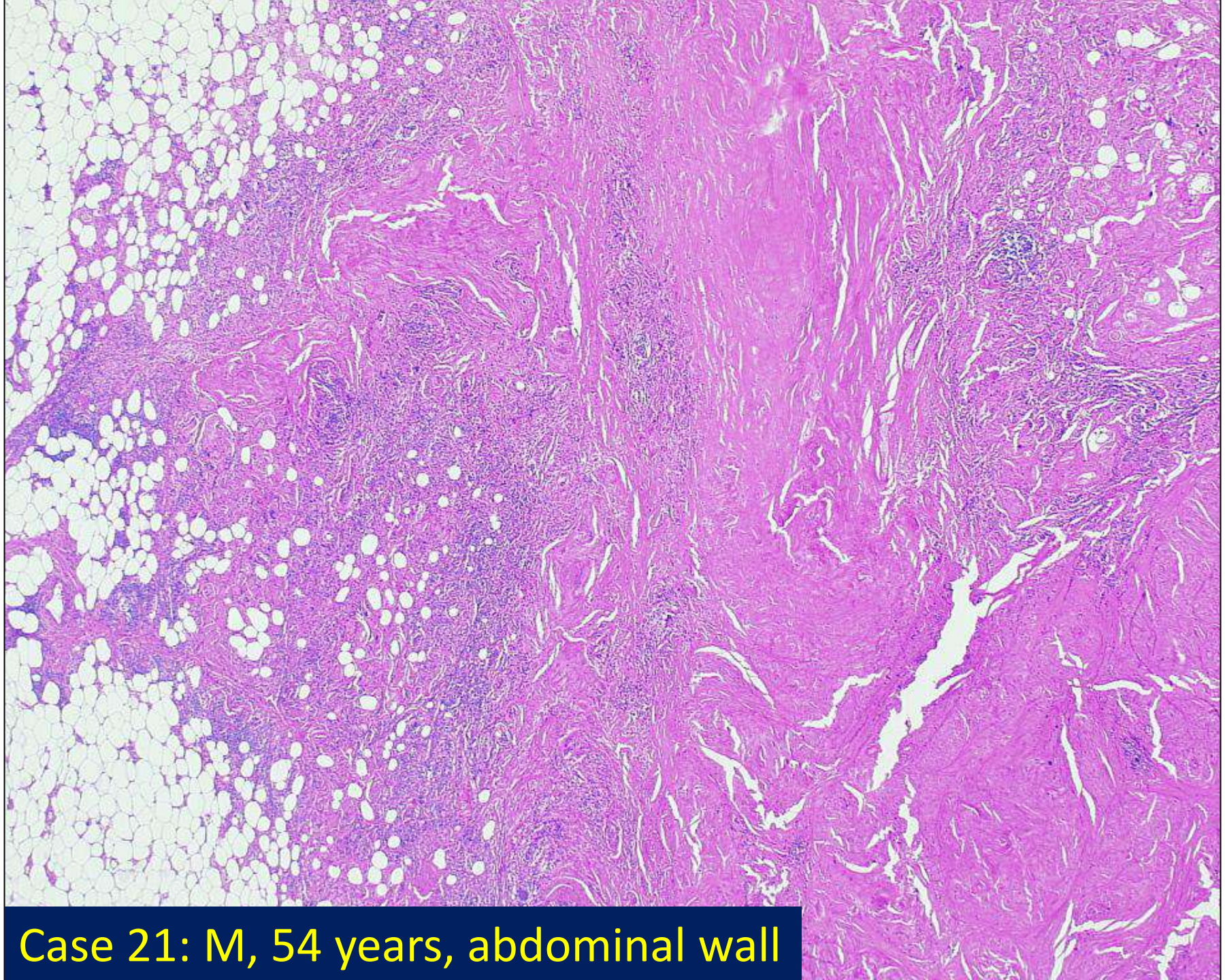


# Diagnosis Case 20

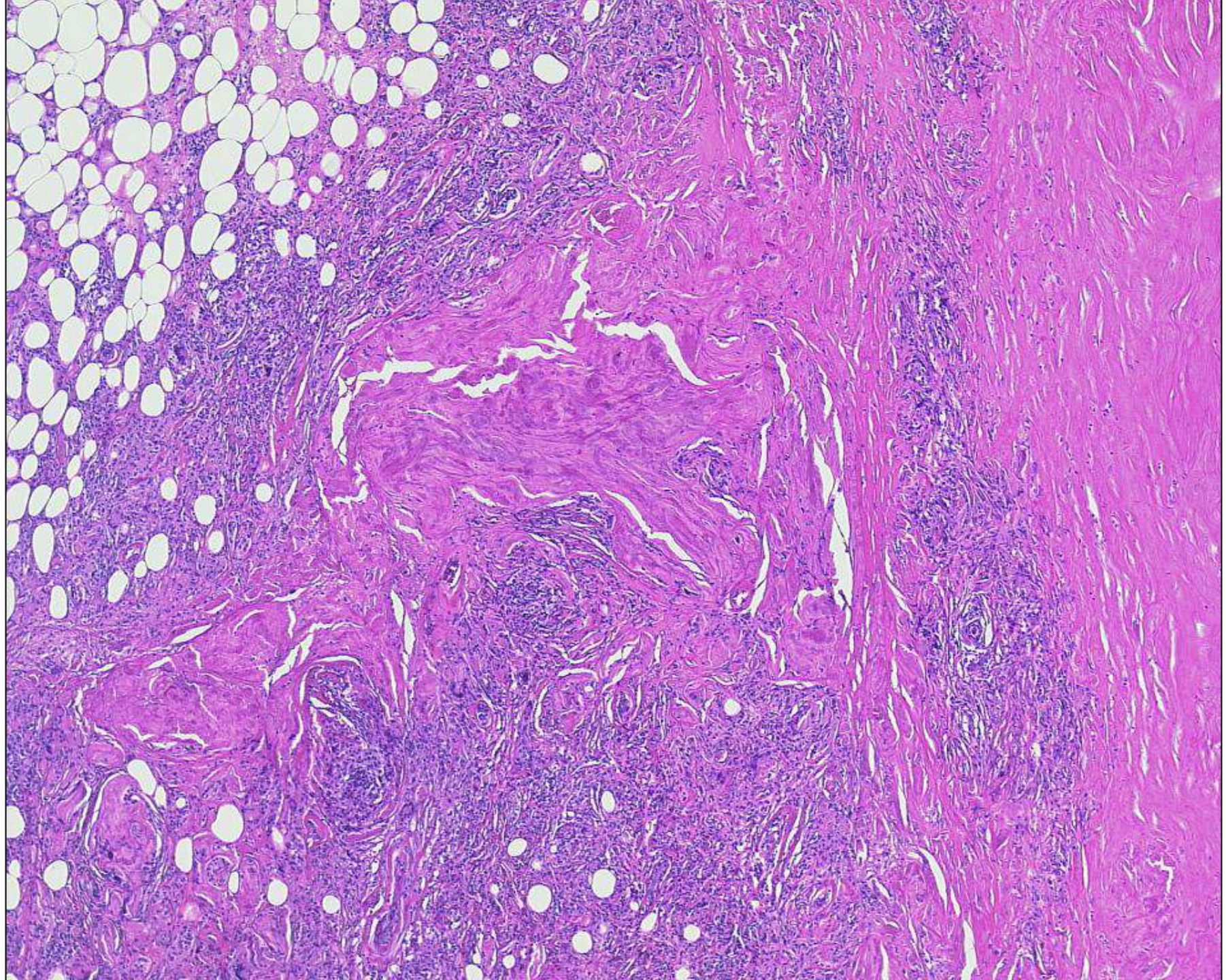
## ossifying fibromyxoid Tumour (without bone)

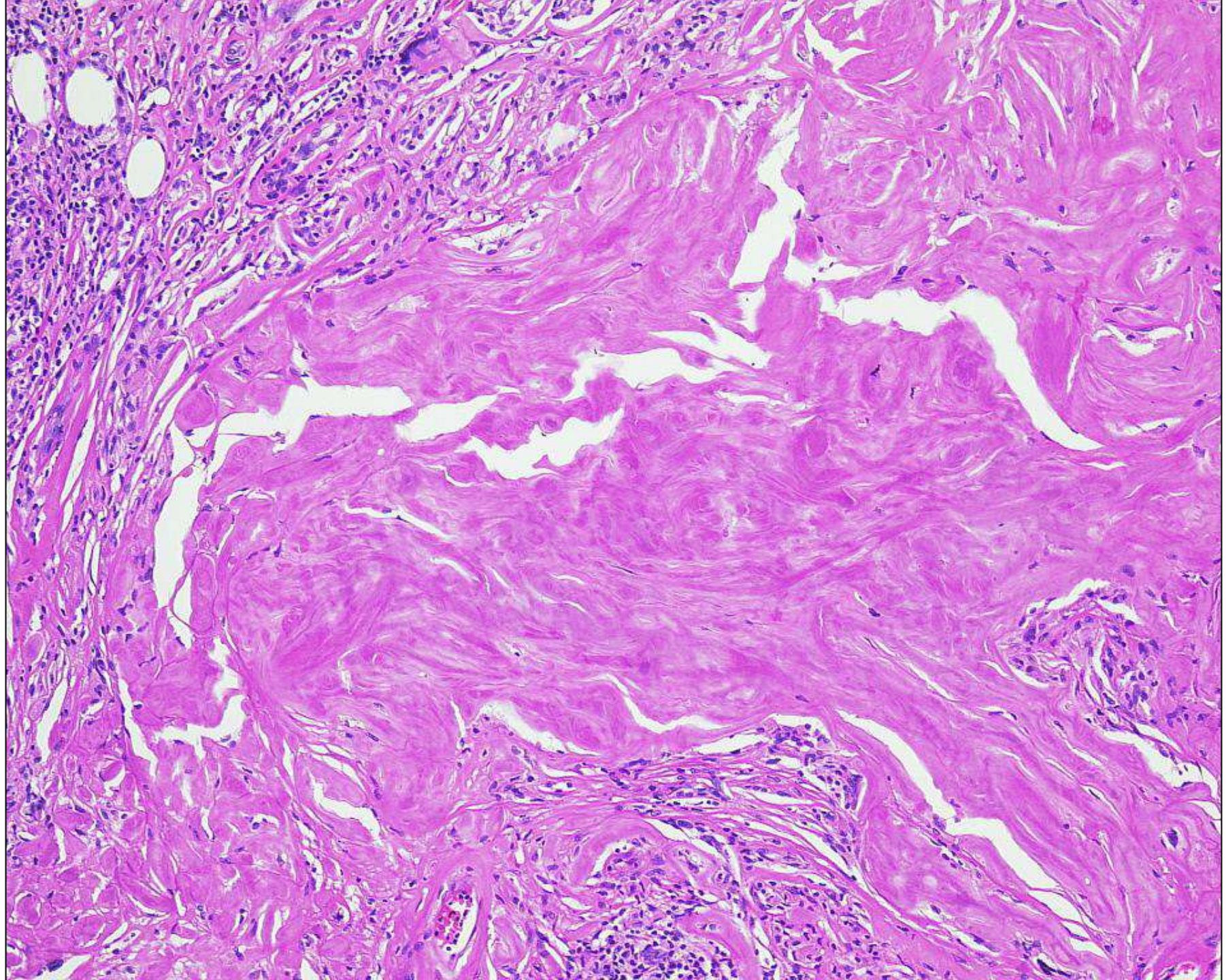
# ossifying fibromyxoid Tumour

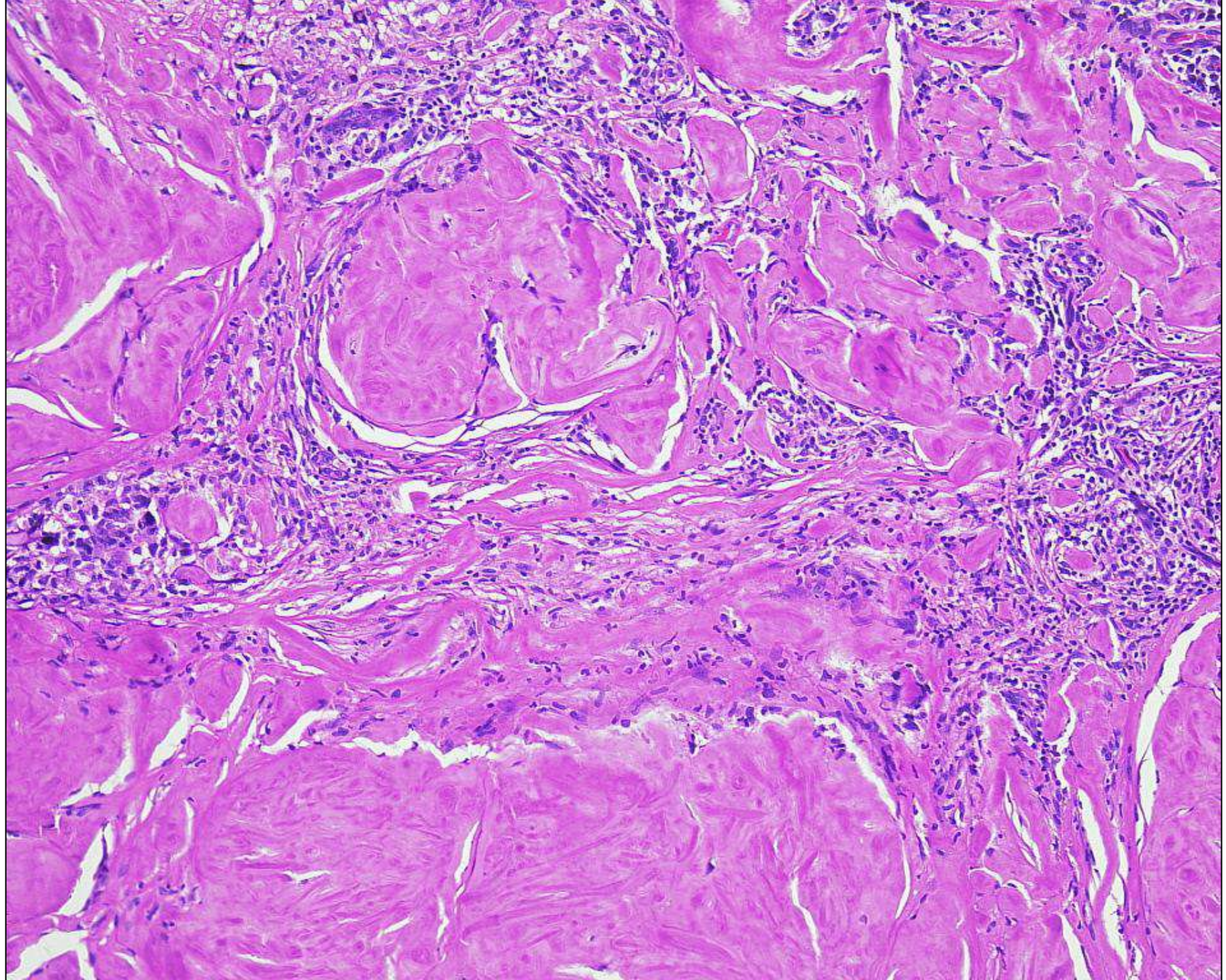
adult patients, subcutis > deep soft tissue, extremities > head, trunk
MRI: well-circumscribed, lobulated, peripheral calcification/ossification
uniform round to spindled tumour cells, cords, nests, sheets
variable cellularity, low mitotic activitiy
fibrous and myxoid stroma
fibrous septa, capsule, pseudocapsule
peripheral shell of metaplastic bone
S-100 + (65%), desmin + (50%), EMA +/-, CK +/-, ASMA +/-
INI1 - in 75%
most commonly *PHF1* fusions

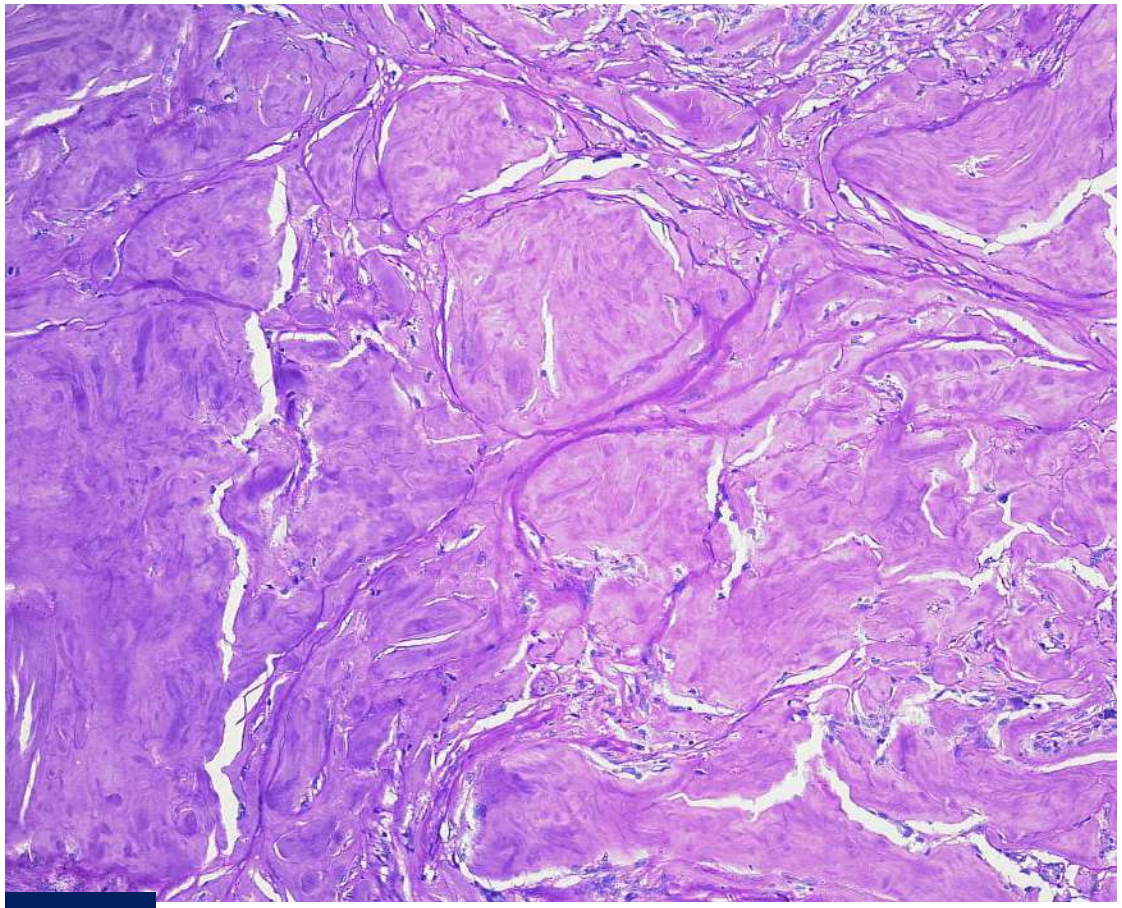


Case 21: M, 54 years, abdominal wall

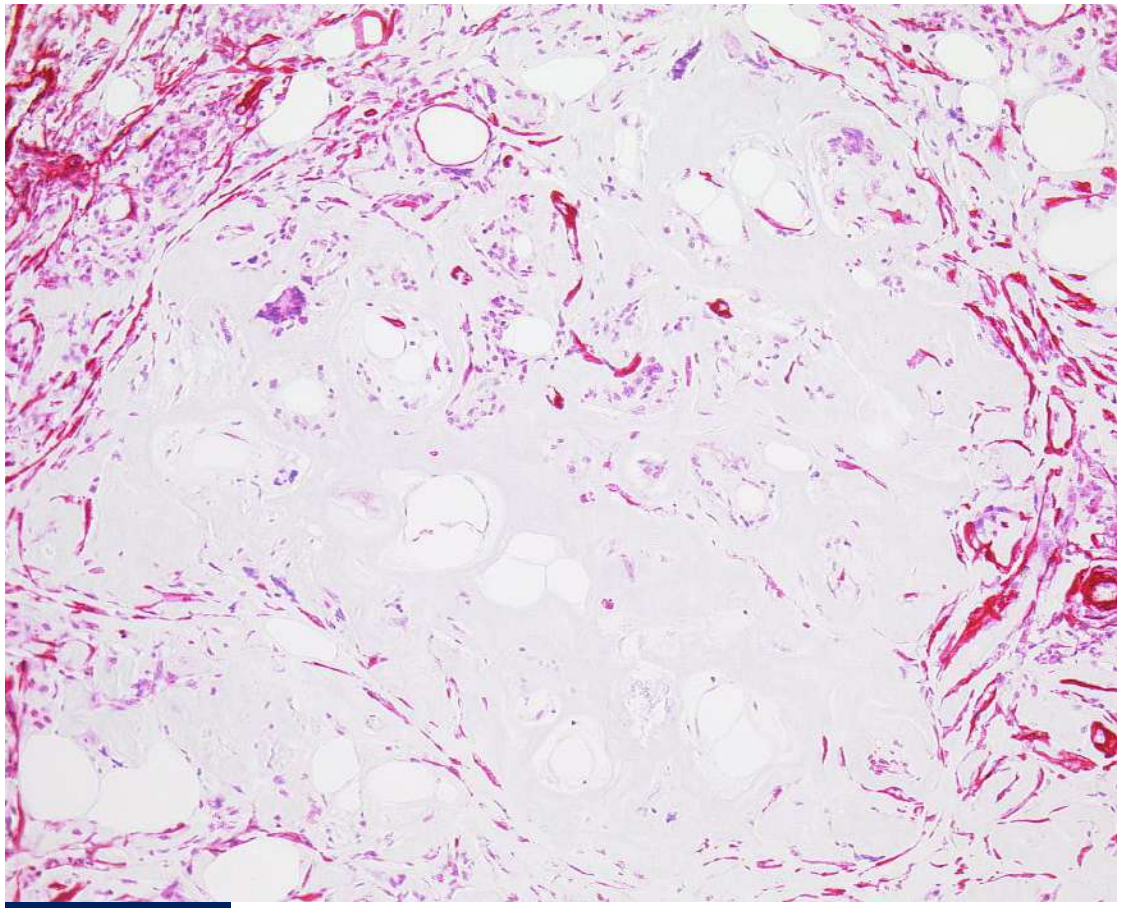




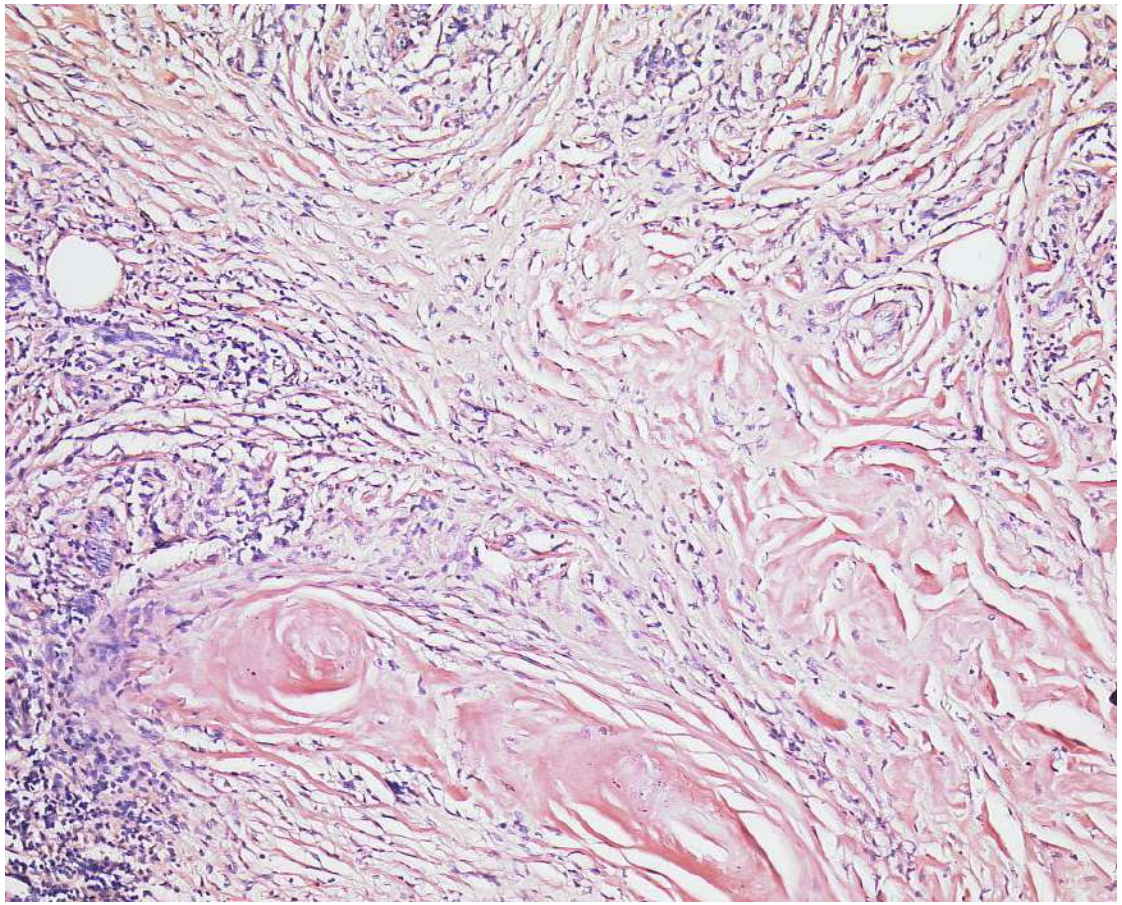


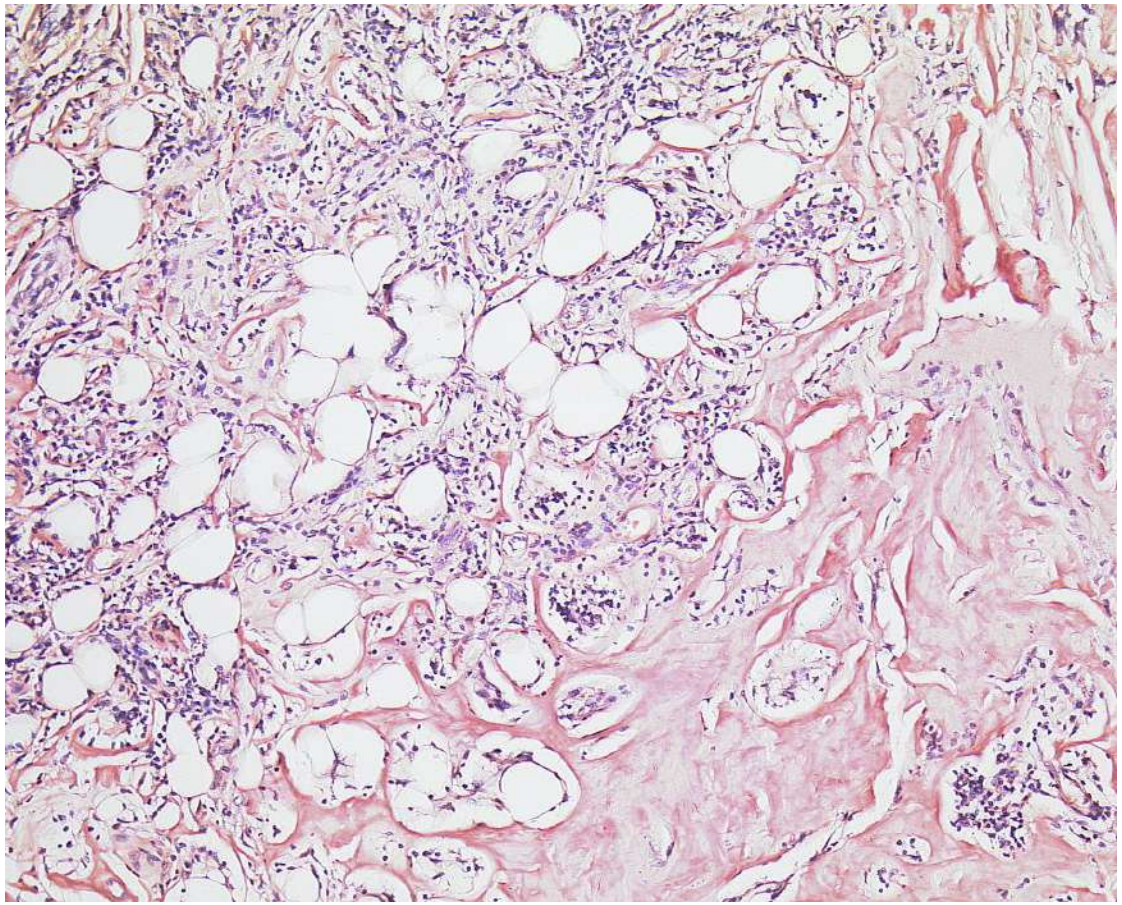


PAS

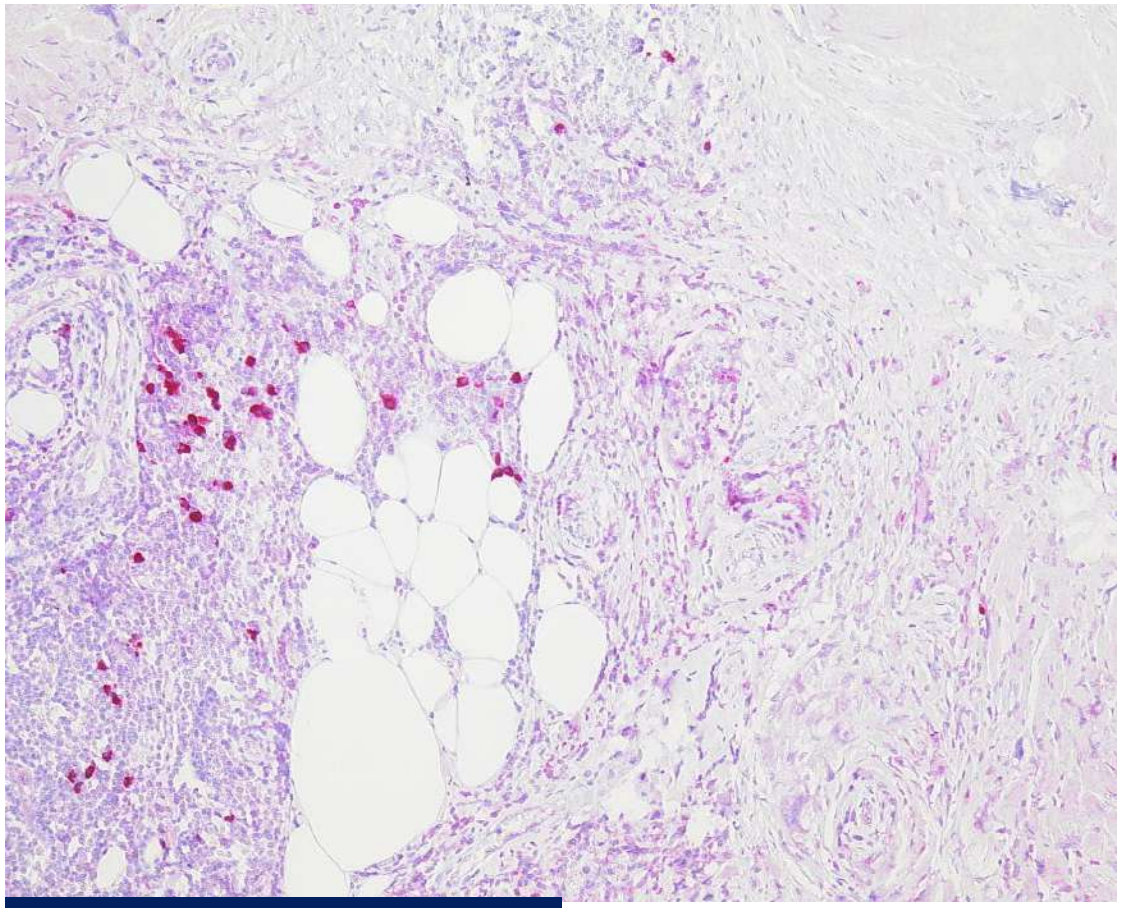


ASMA

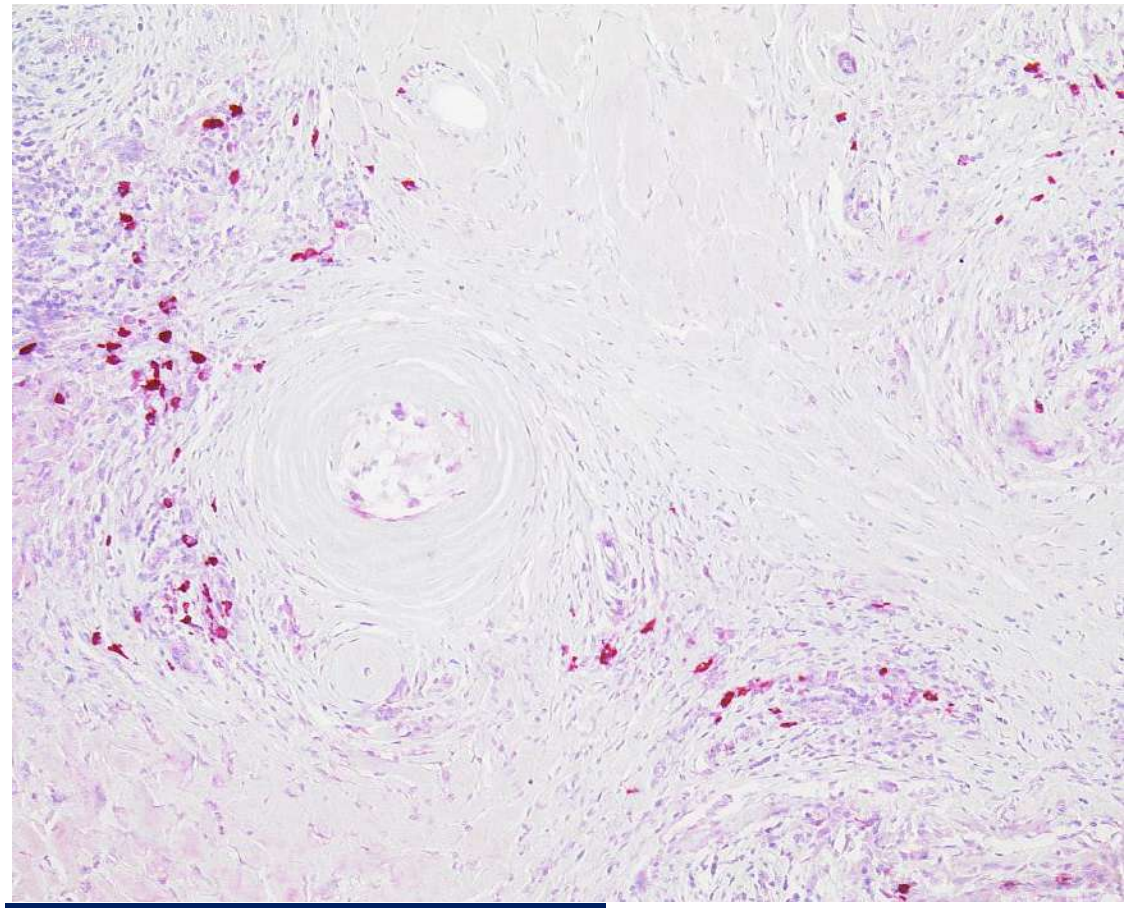




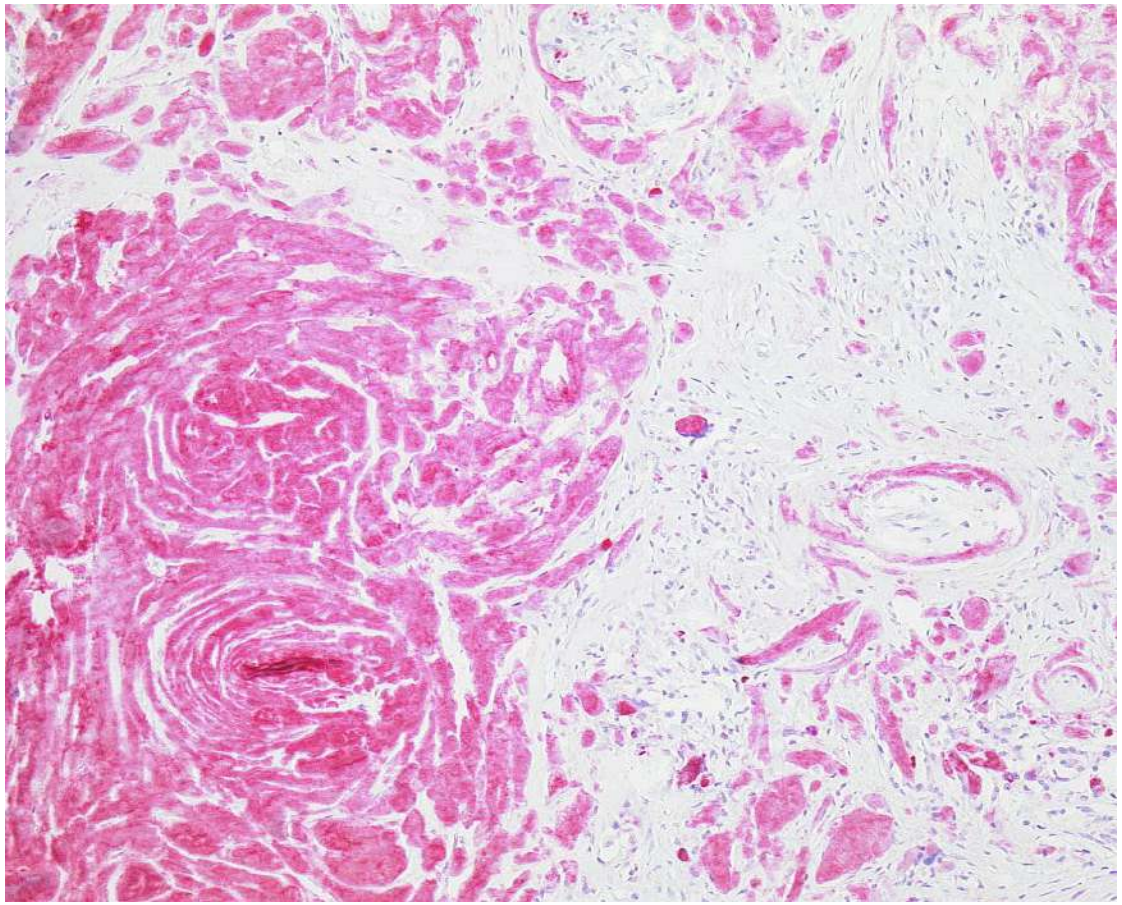
Congored

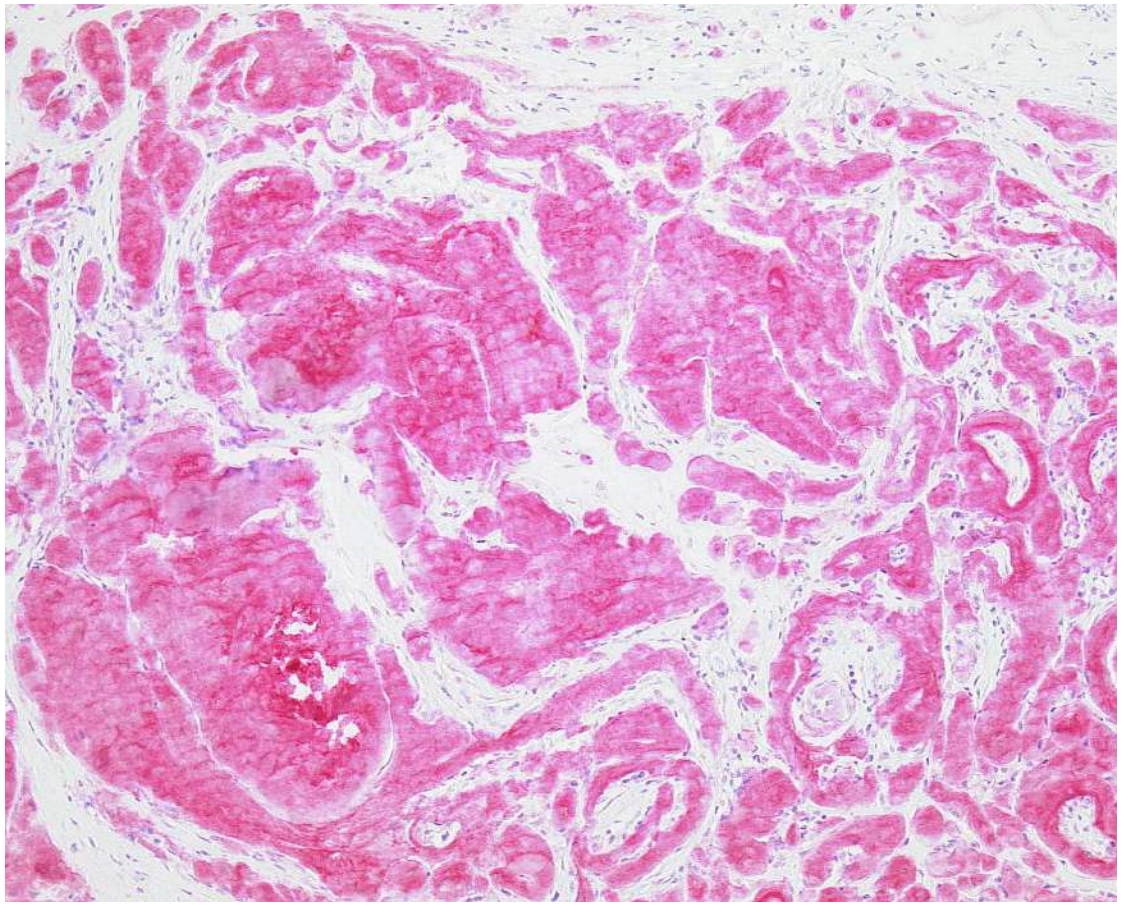


kappa light chain



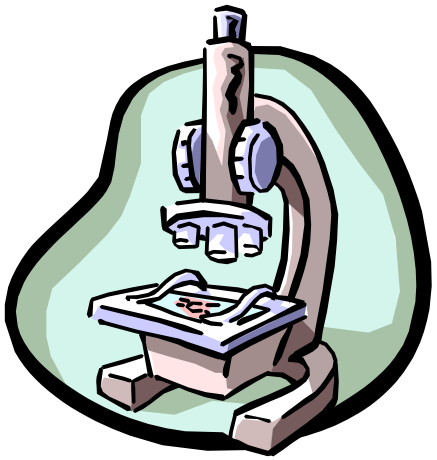
lambda light chain





Insulin antibody


Patient is suffering from
Diabetes Type 1
since many years…
Insulin injection since years



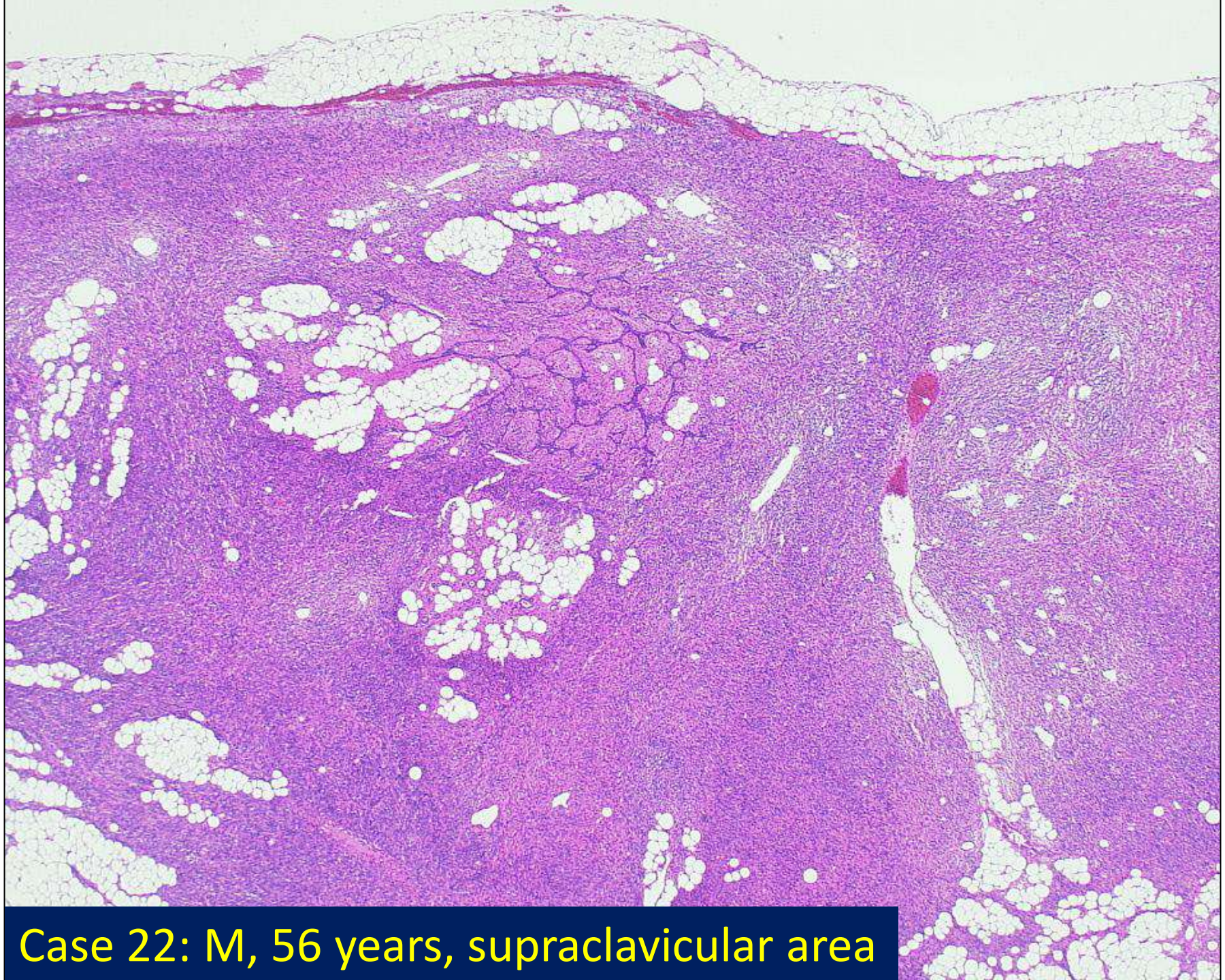
# Diagnosis Case 21

**nodular amyloidosis at the site of insulin injection**

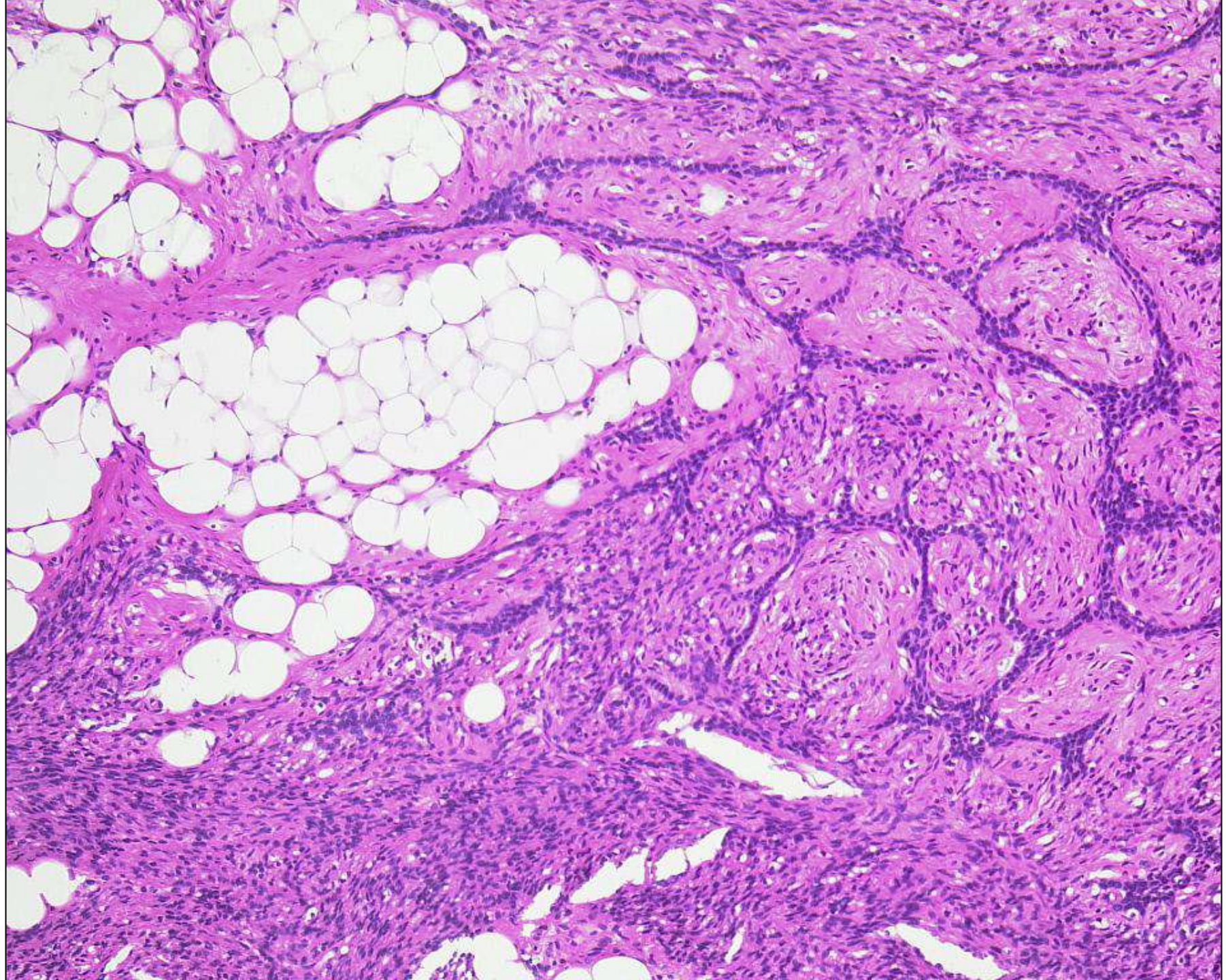
**Nodular amyloidosis at the sites of insulin injections**

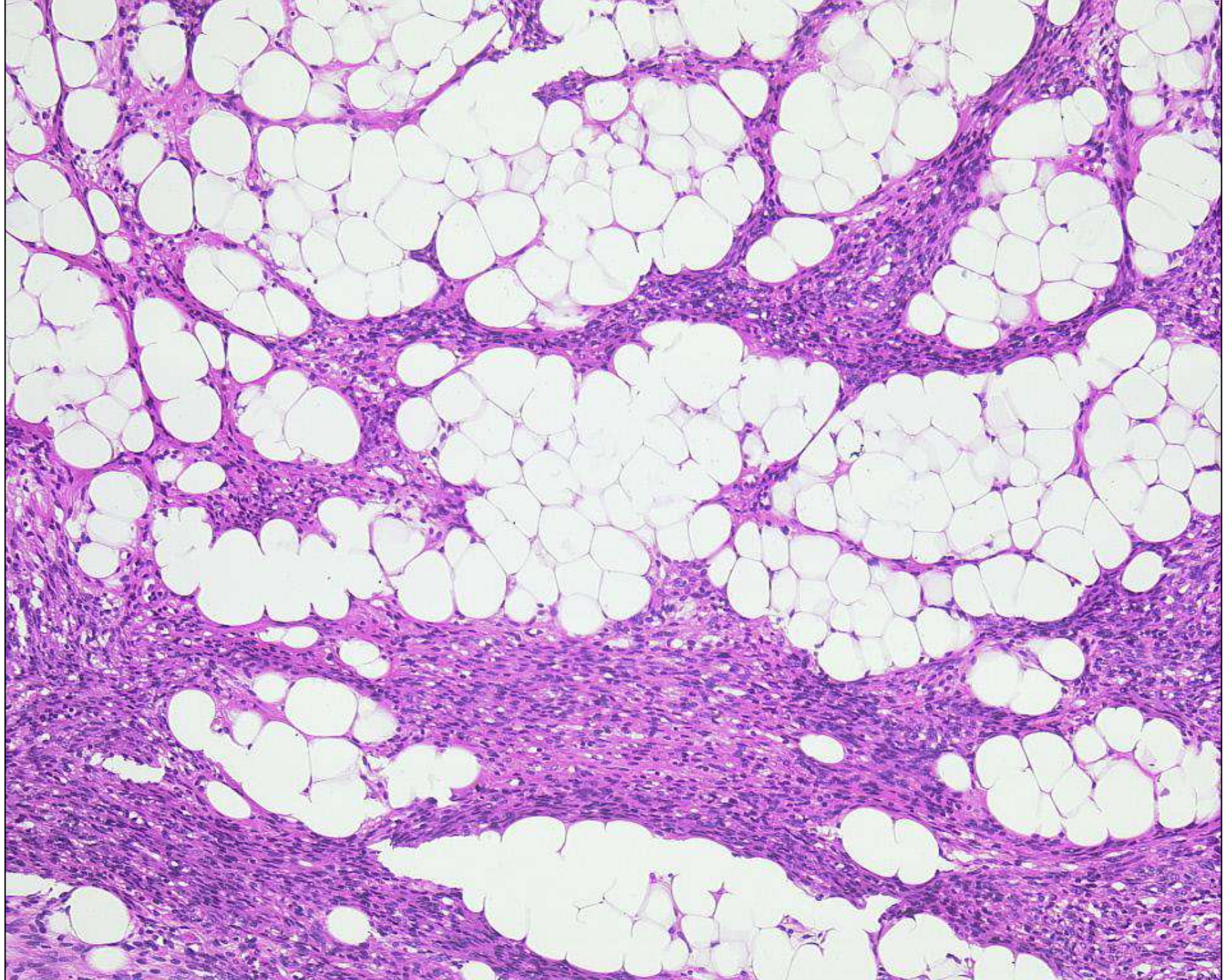
Bernardez C et al. J Cutan Pathol 2015; 42: 496-502

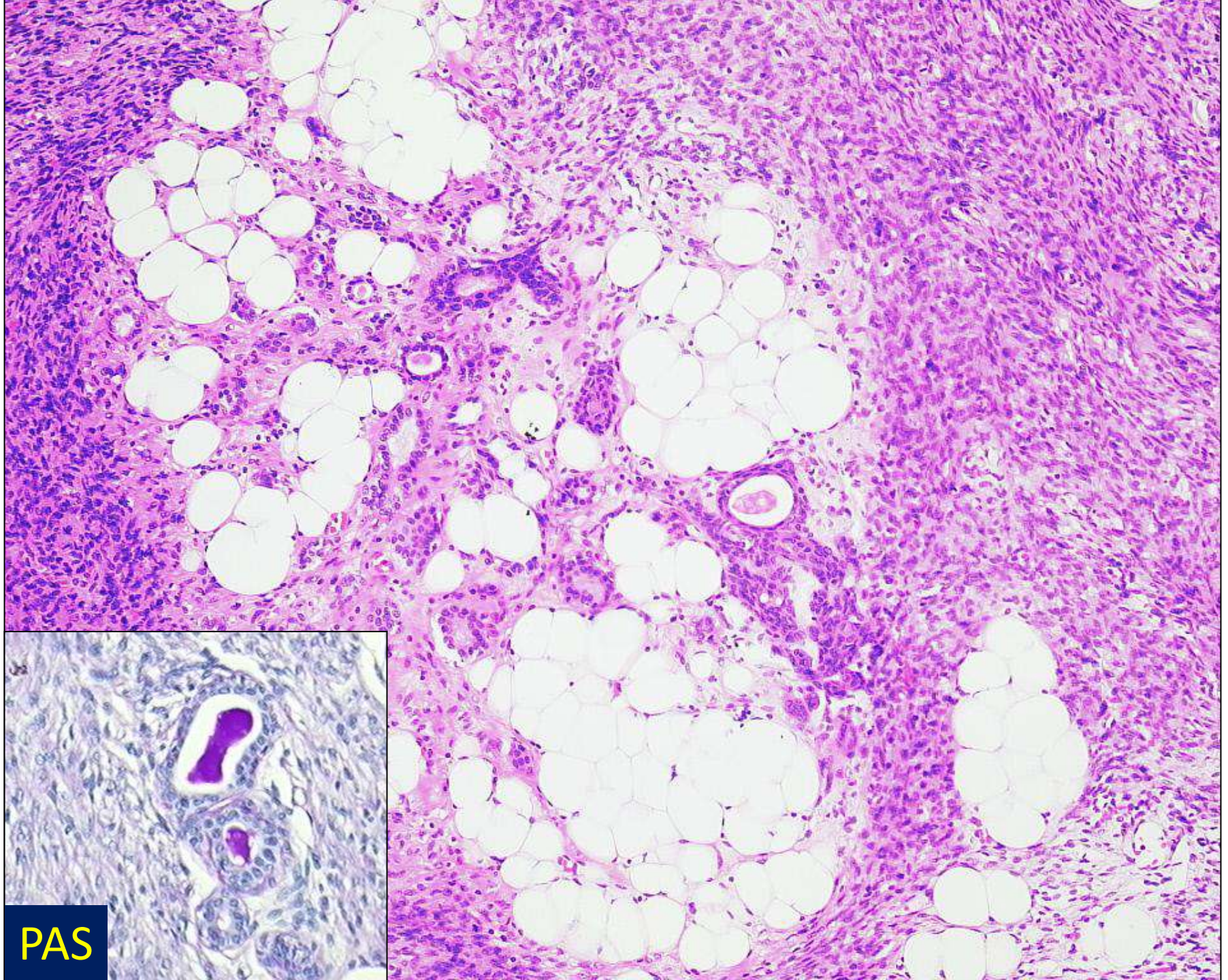
2 diabetic patients
longstanding subcutaneous insulin treatment
subcutaneous nodules at the sites of injection
eosinophilic and amorphous masses
Congored +, amyloid P-substance +, insulin antibody
Amyloid is characterized by fibrillary ultrastructure
> 20 proteins are possible precursors
„The amyloidoses are a group of protein misfolding diseases characterized by the accumulation in extracellualar spaces of insoluble fibrillar protein“

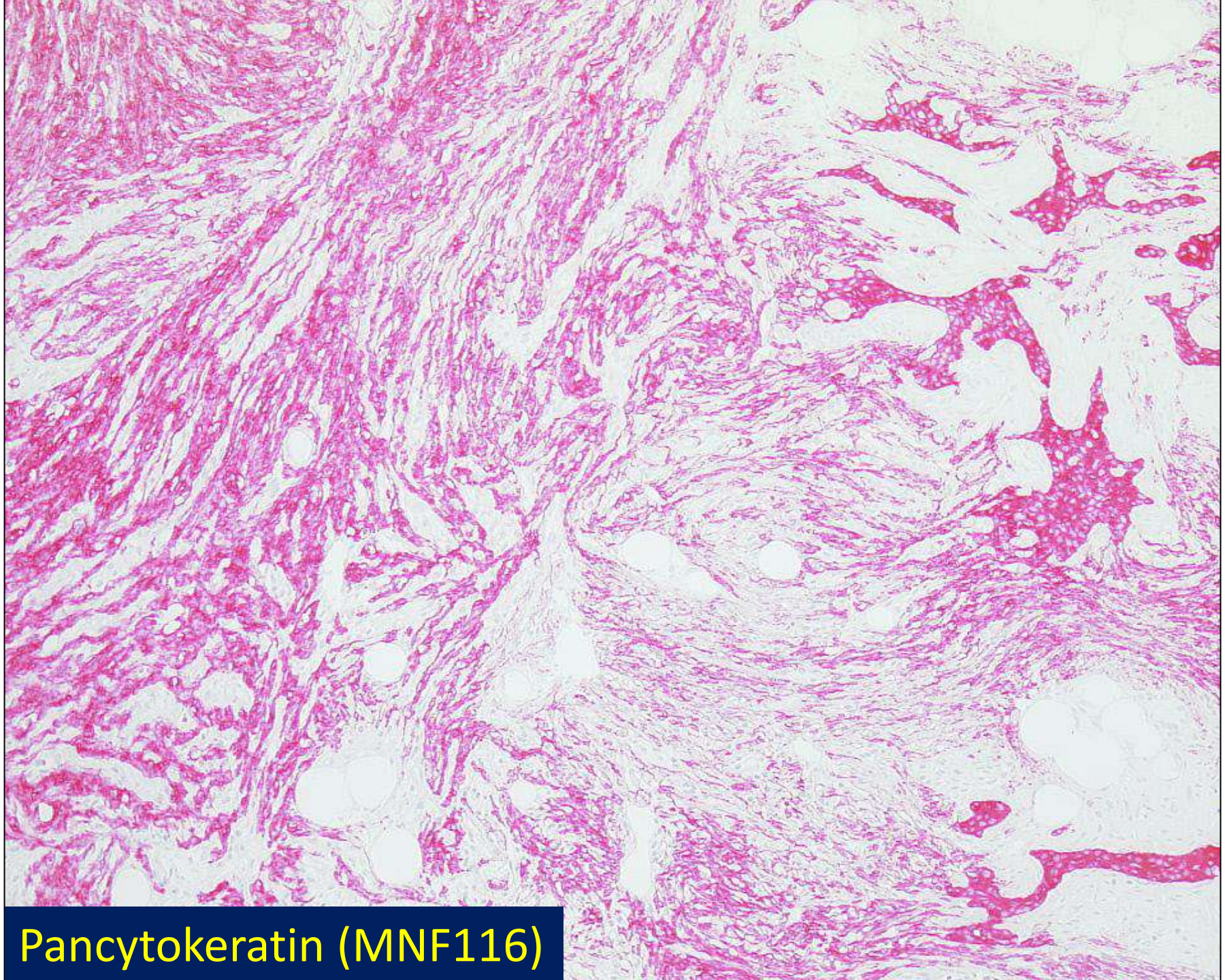


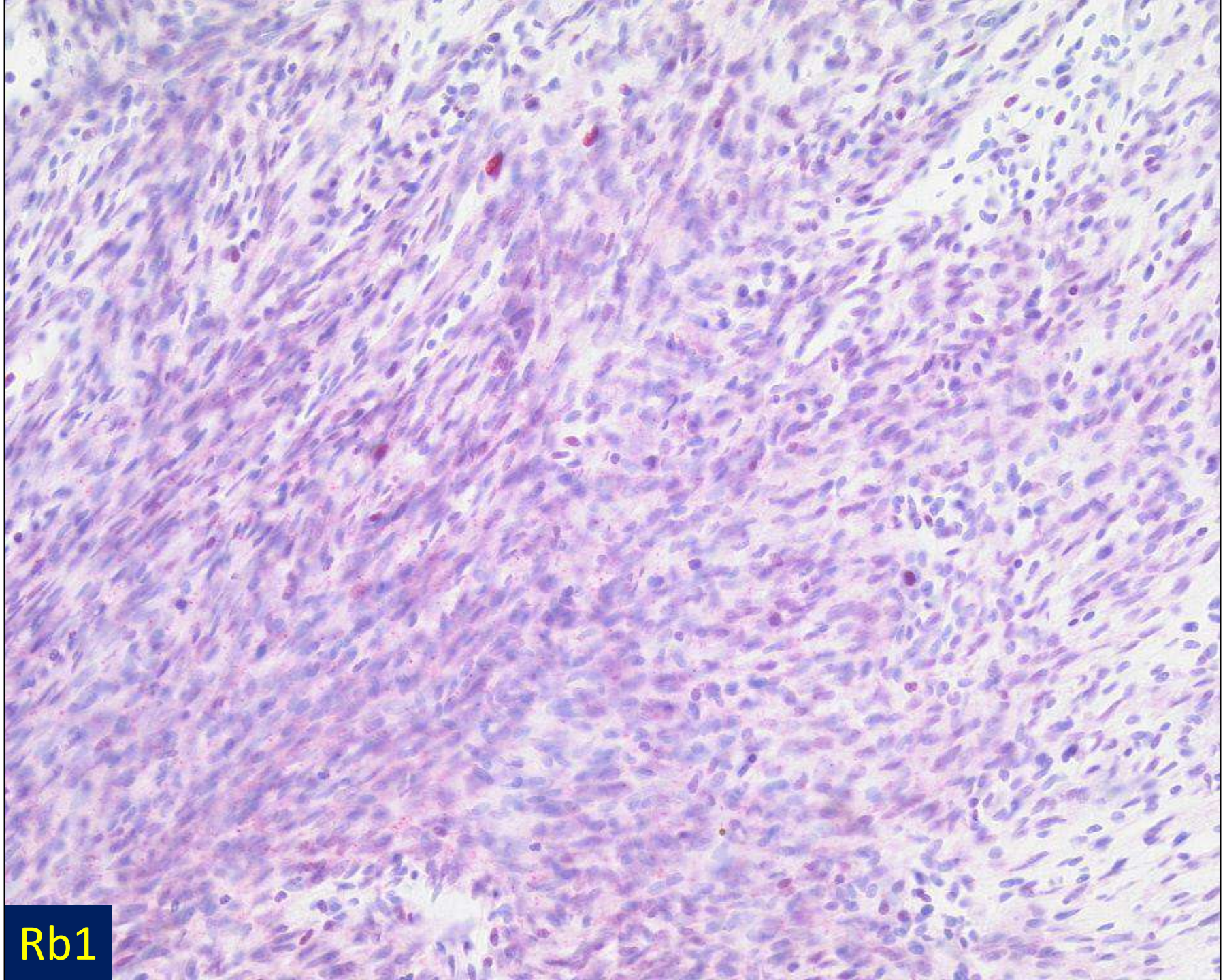
Case 22: M, 56 years, supraclavicular area



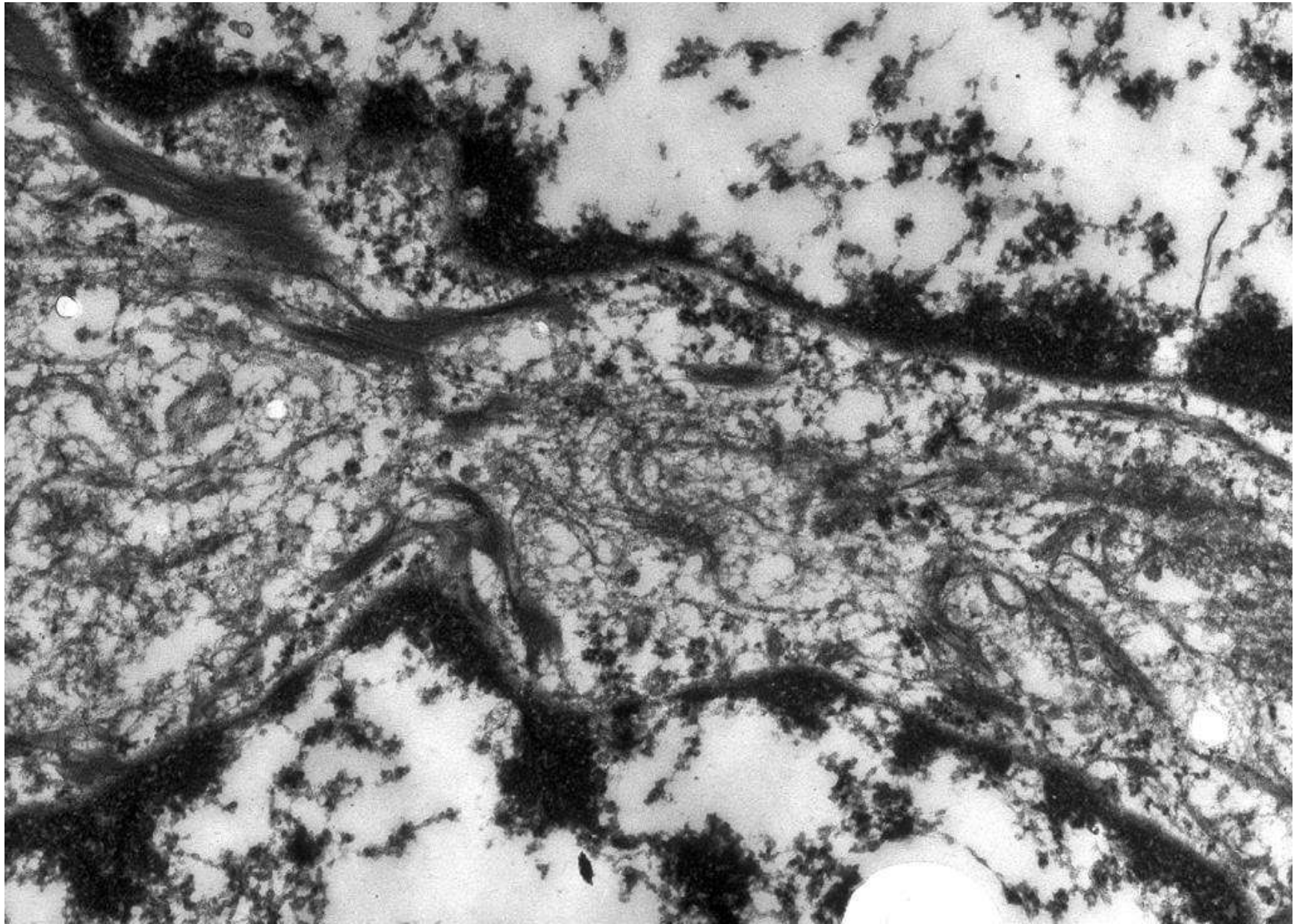


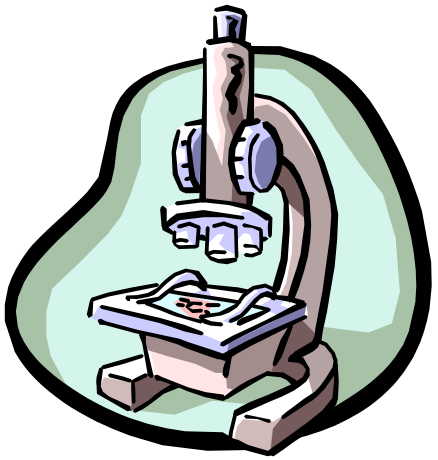

PAS


Pancytokeratin (MNF116)


Rb1

# EM Findings: tonofilaments, desmosomes





# Diagnosis Case 22

## Branchioma
## (ectopic hamartomatous Thymoma)

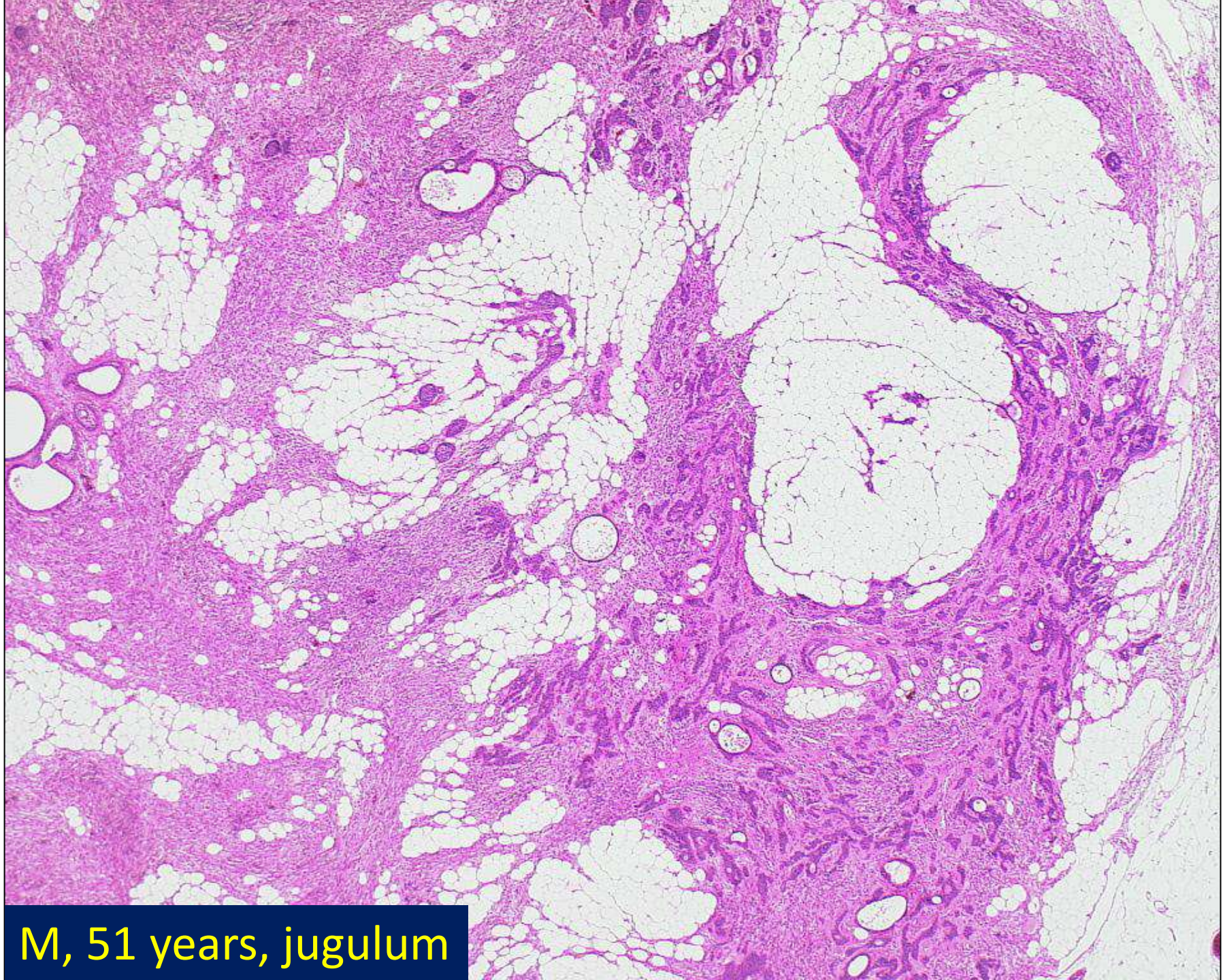
# Branchioma

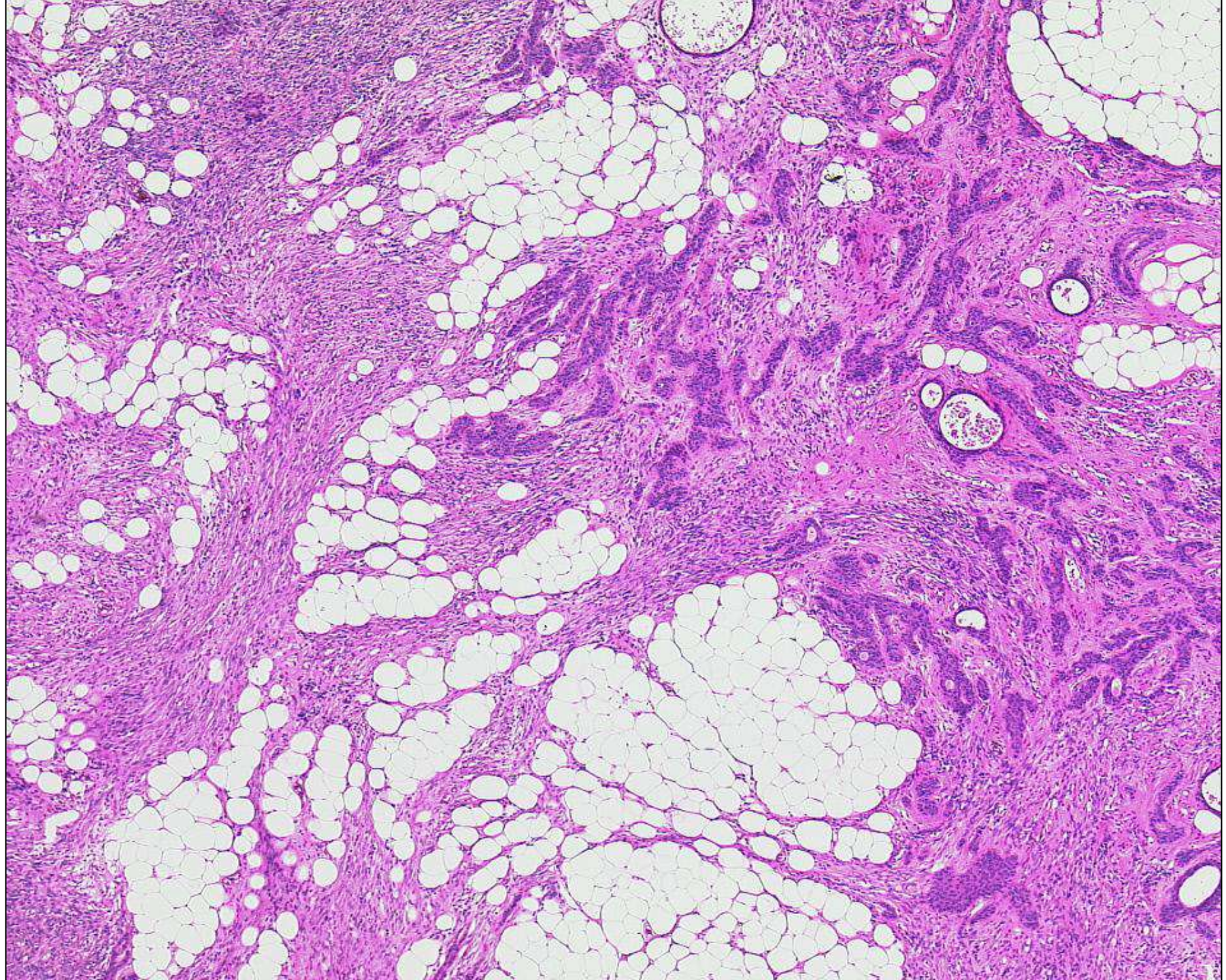
- Smith PC, McClure J J Clin Pathol 1982; 35: 1074
  unusual subcutaneous mixed tumour exhibiting adipose, fibroblastic and epithelial components
- Rosai J et al. AJSP 1984; 8: 501
  „ectopic hamartomatous thymoma“ - thymic origin ?
- Fetsch JF, Weiss SW Hum Pathol 1990; 21: 662
  arises from the 3rd/4th pharyngeal pouch, cervical sinus
- Chan JKC, Rosai J Hum Pathol 1991; 22: 349
  thymic or related branchial pouch differentiation
- Michal M et al. Histopathology 1996; 29: 549
  heterotopic salivary differentiation is suggested
- Fetsch JF et al. AJSP 2004; 28: 1360
  no true evidence of thymic differentiation, branchial anlage mixed tumour

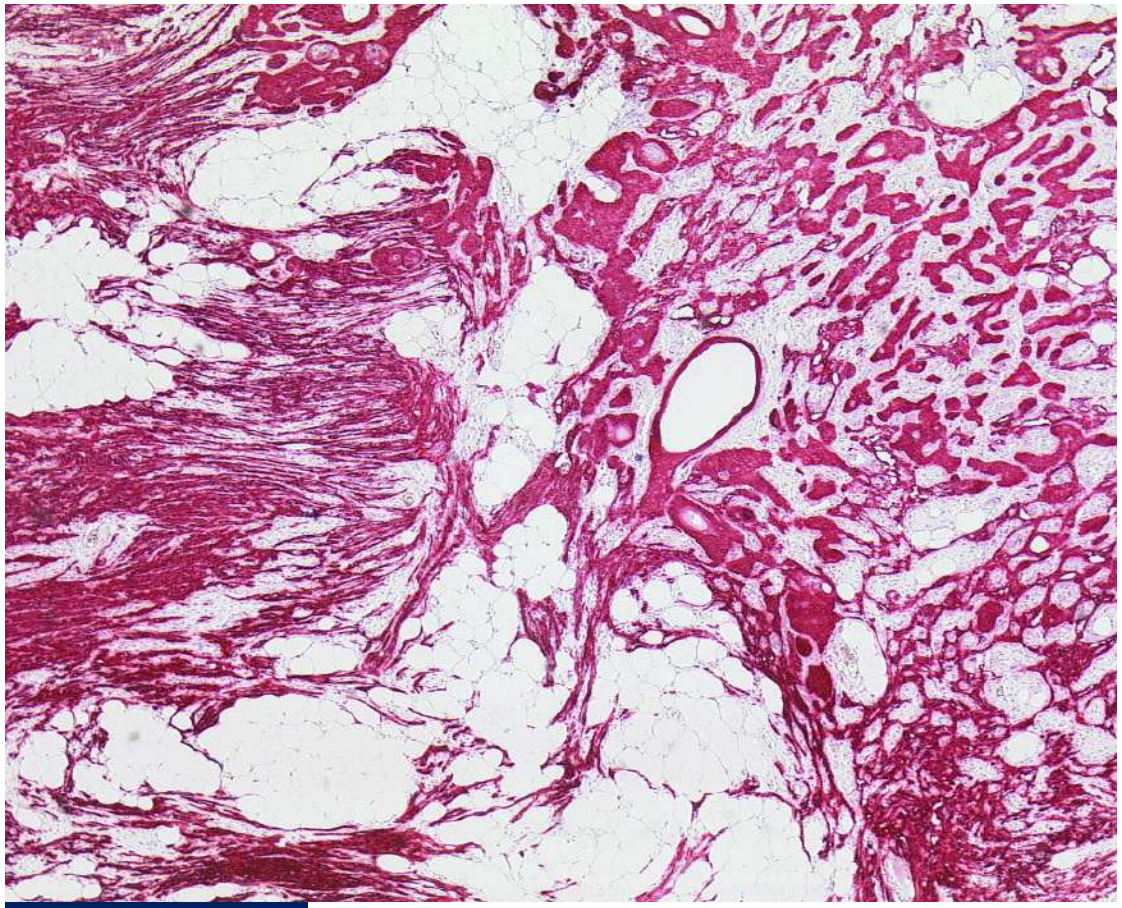
# Branchioma

## Pathological Findings

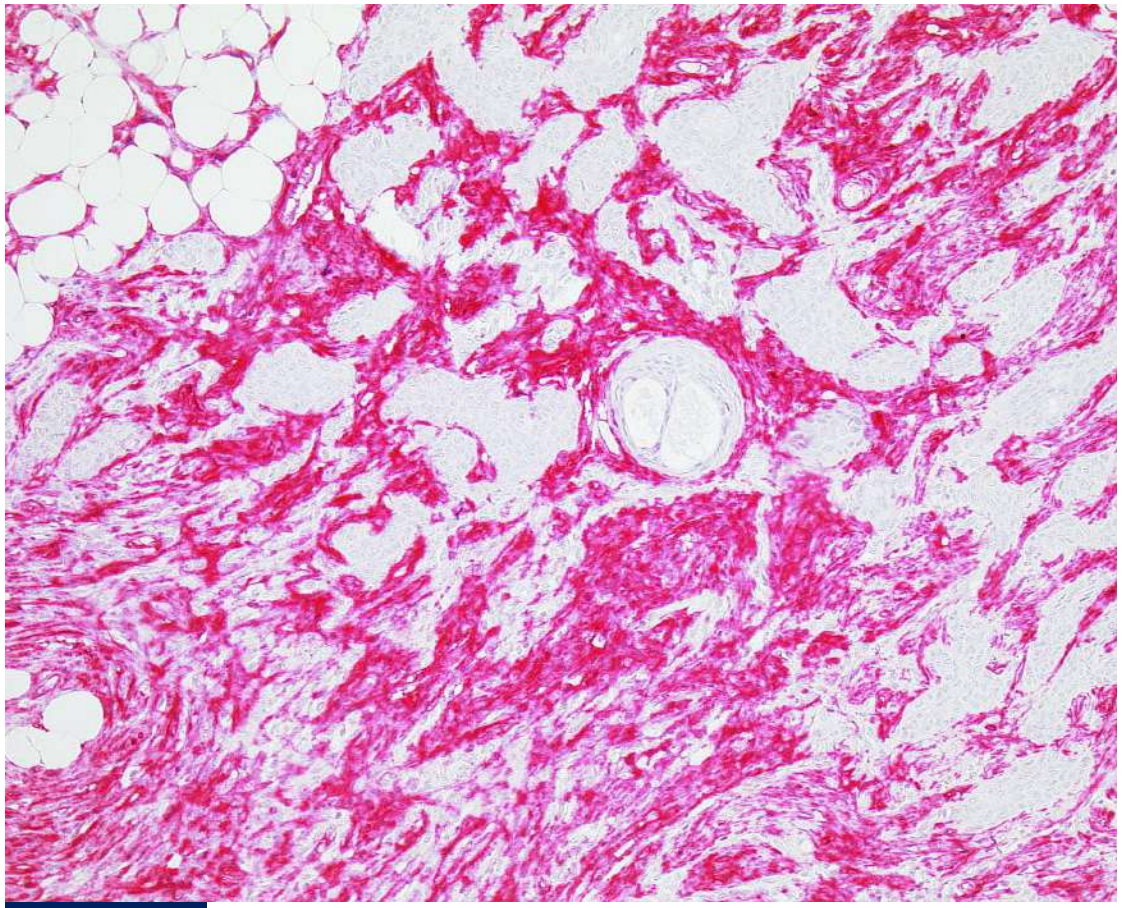
- well-circumscribed lesions, 1.5 – 19 cm
- fibroblast-like, bland spindled cells showing myoepithelial phenotype (AJSP 2004; 28: 1360)
- epithelial structures (tubules, glands squamous areas, cysts, trabecular network)
- mature adipocytes, scattered lymphocytes
- rarely myoid/ clear cell differentiation
- very rarely carcinomatous features
- vimentin +, CK +, CD34 + stromal cells


M, 51 years, jugulum





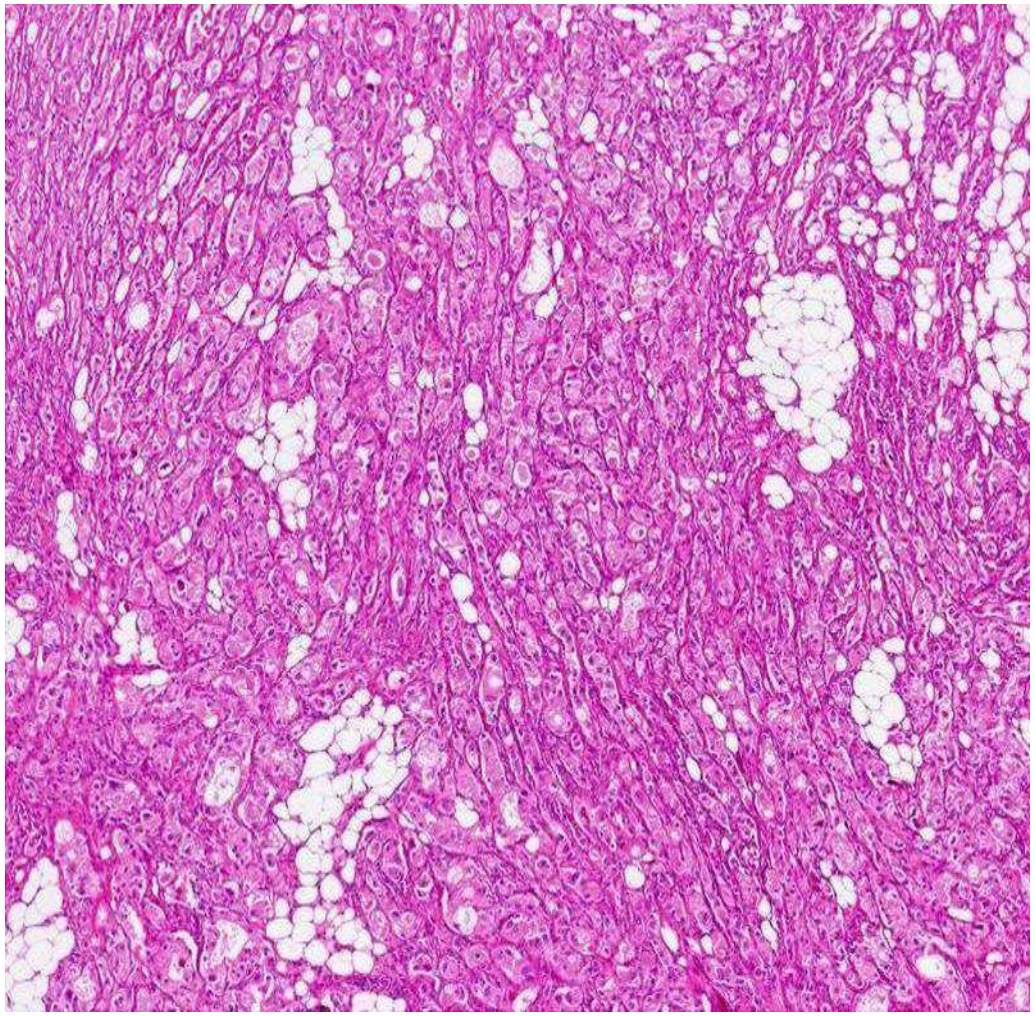
MNF116

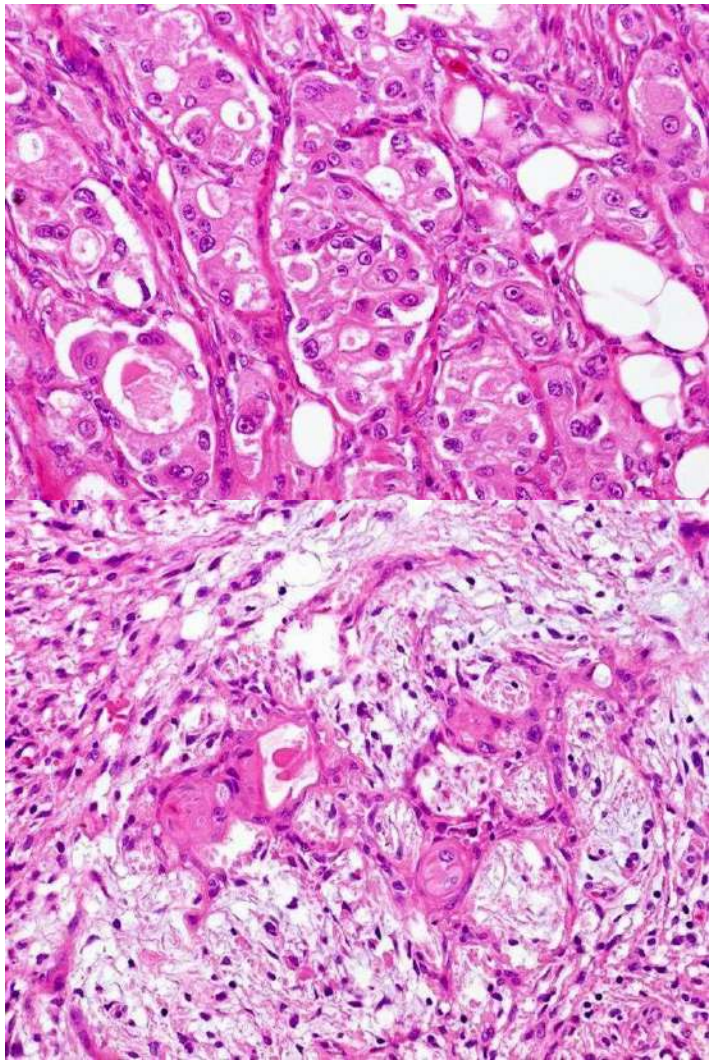


CD34

# Carcinoma arising in ectopic hamartomatous thymoma

(Michal M et al. Zentralbl Pathol 1993; 139: 381-386





# Branchioma: immunohistochemical and molecular genetic study of 23 cases highlighting frequent loss of retinoblastoma 1 immunoexpression

Bradova M et al. Virchows Archiv 2024; 484: 103-117

21 M, 2 F, 31-80 years, 10-80 mm, simple excision, no R, no MTS
supraclavicular (11), suprasternal (8), chest wall (2), neck (1), back (1)
admixture of spindle cells, epithelial cells, adipose tissue
neuroendocrine morphology (1), myoid differentiation (1)
multinucleated giant cells (1), prominent clear cells (1)
carcinoma in the background of branchioma (3)
AE1/3 +, p63 + (spindled + epithelial cells)
CD34 + (spindled cells), Rb1 - (13/15 cases)

Case 1: *MSH6, PETEN, KRAS* mutations
Case 2: *BMPR1A, TET2* mutations
Case 14: *BRCA1* mutation
Case 20: *FANCG* mutation
Case 21: variants of unknown significance (*PHOX2B, XRCC2, PLCG2*)
Case 22: *NF2, NF1* mutations
Case 19: *HRAS, PIK3CA, CHD2, SLIT2* mutations
(CA ex branchioma)
C. 14,18: deletion of *RB1*

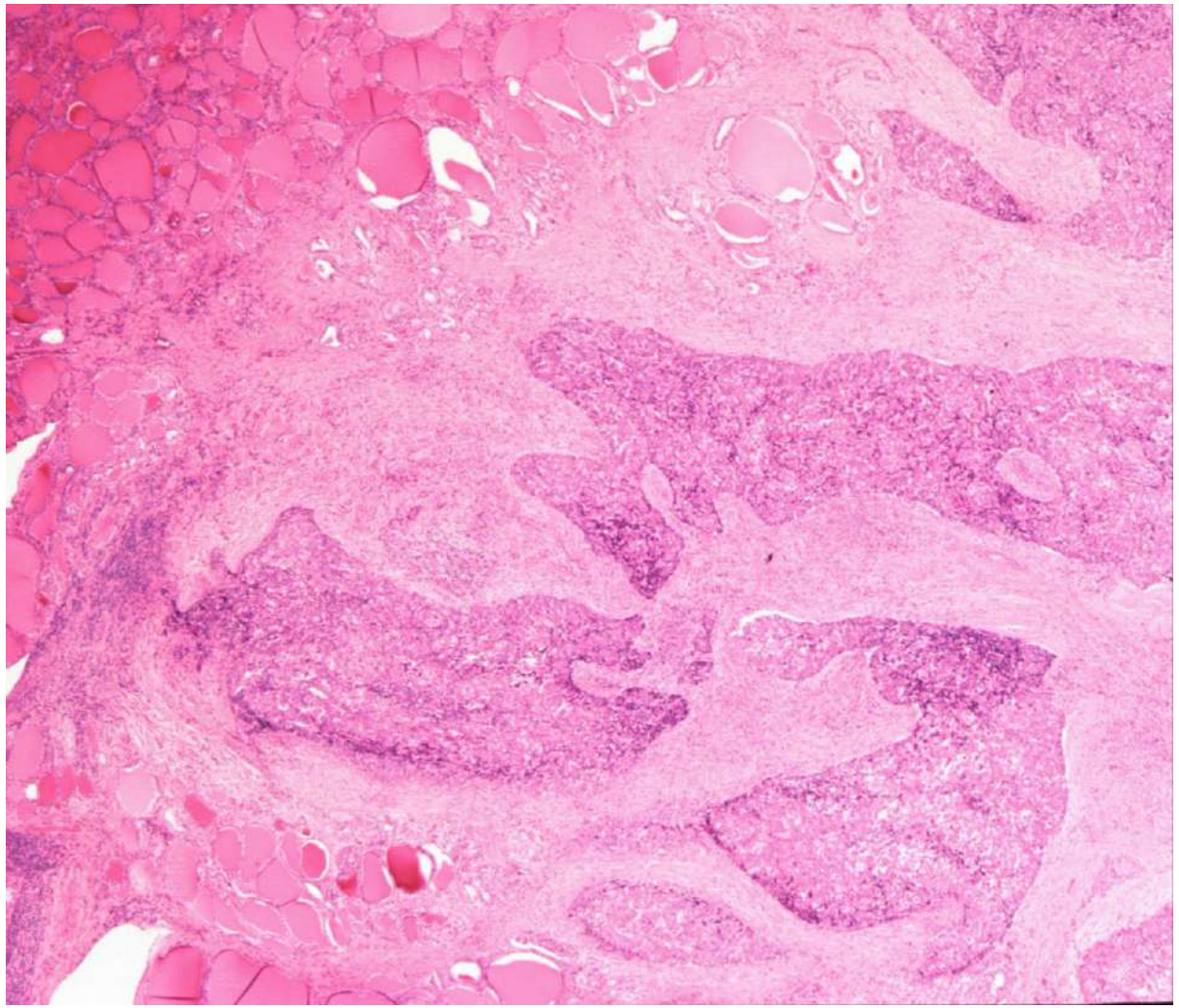
# DD: Branchioma

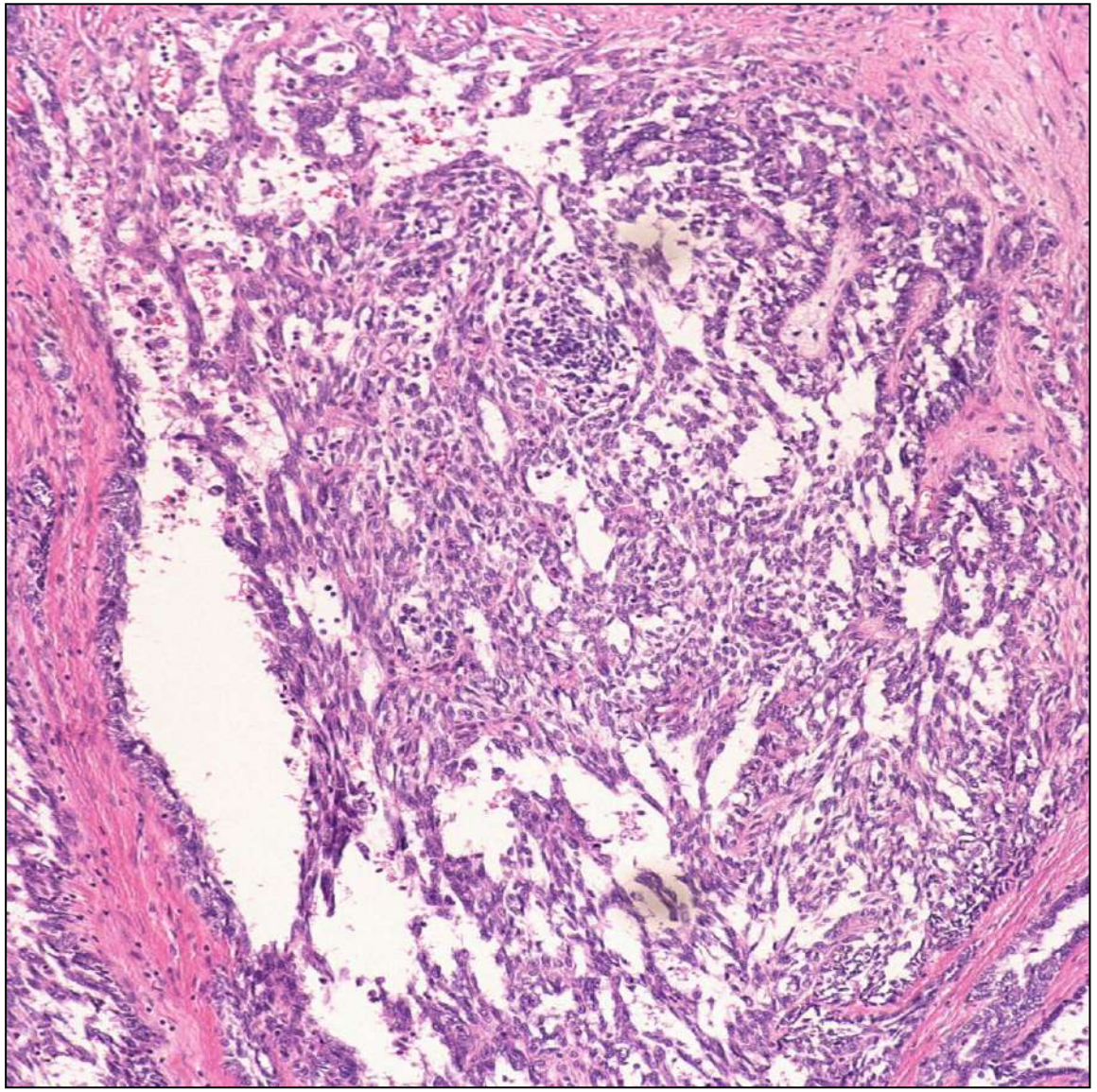
- poorly differentiated squamous cell carcinoma (mitoses, necrosis)
- MPNST (MPNST with glands)
- biphasic synovial sarcoma
- mixed tumour of the skin
- thymolipoma
- ectopic cervical thymoma
- SETTLE
- CASTLE

# Spindle epithelial tumour with thymus-like differentiation (SETTLE)

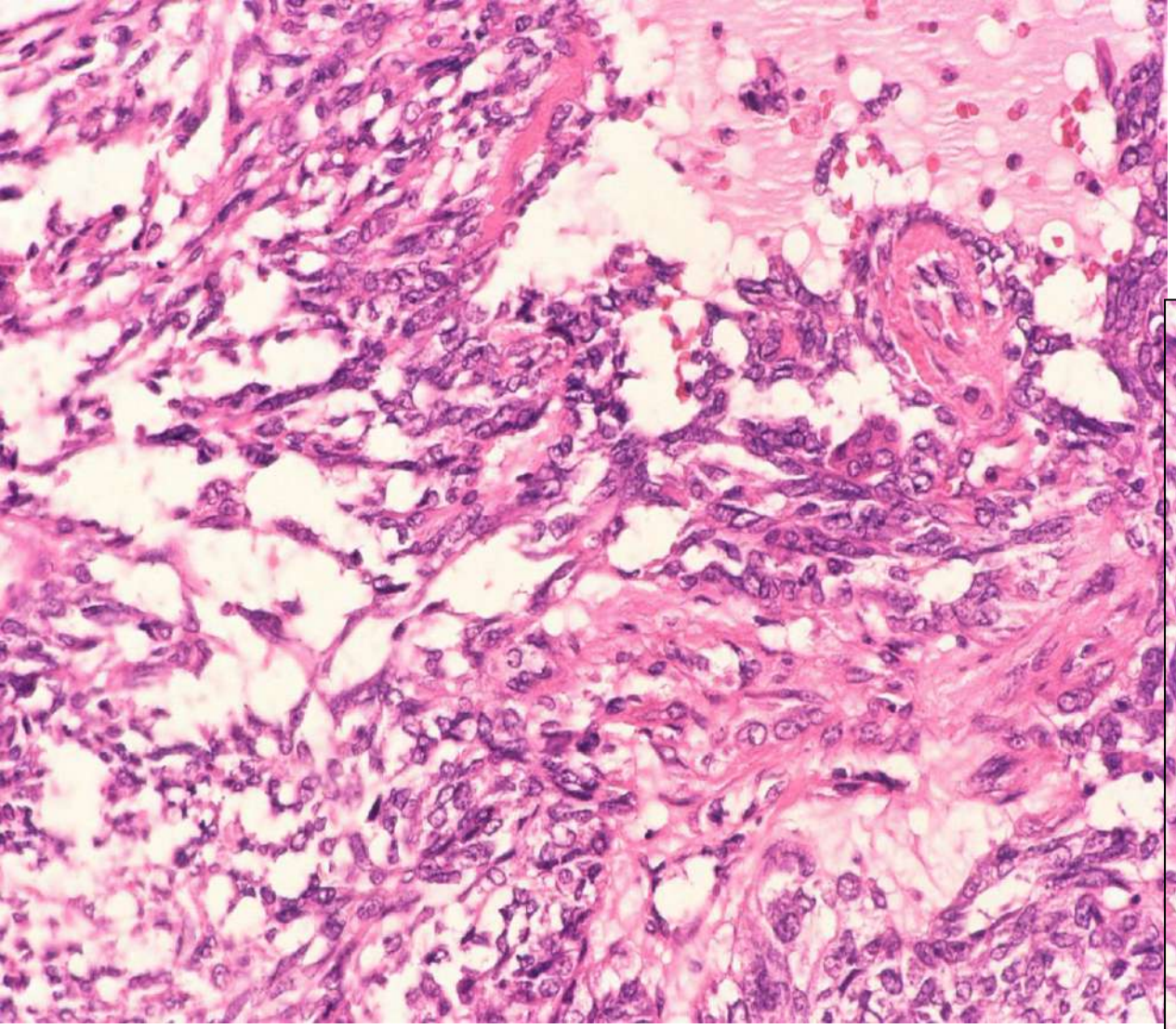
- children, young adults, thyroid nodule
- spindled cells, epithelial cells
- sclerotic bands, reticular pattern
- homogenous cytokeratin expression
- rare monophasic spindle cell differentiation
- rare myoepithelial differentiation
- documented Ki-*ras* gene mutation
- no convincing proof of thymic differentiation
- 5/15 MTS, 3/15 DOD

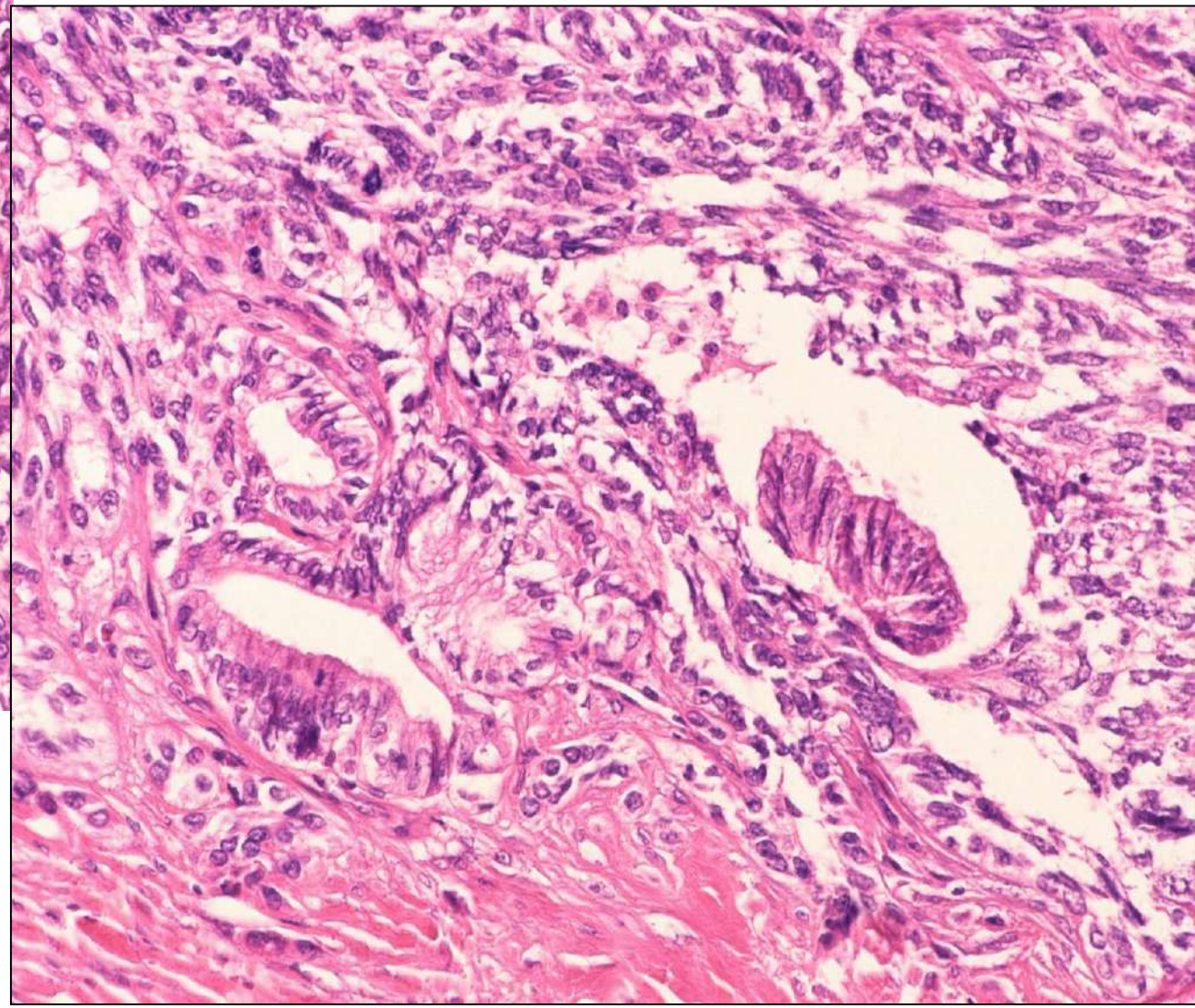
# Spindle epithelial tumour with thymus-like differentiation (SETTLE)*





* by courtesy of Prof.J.K.C Chan, Hong Kong

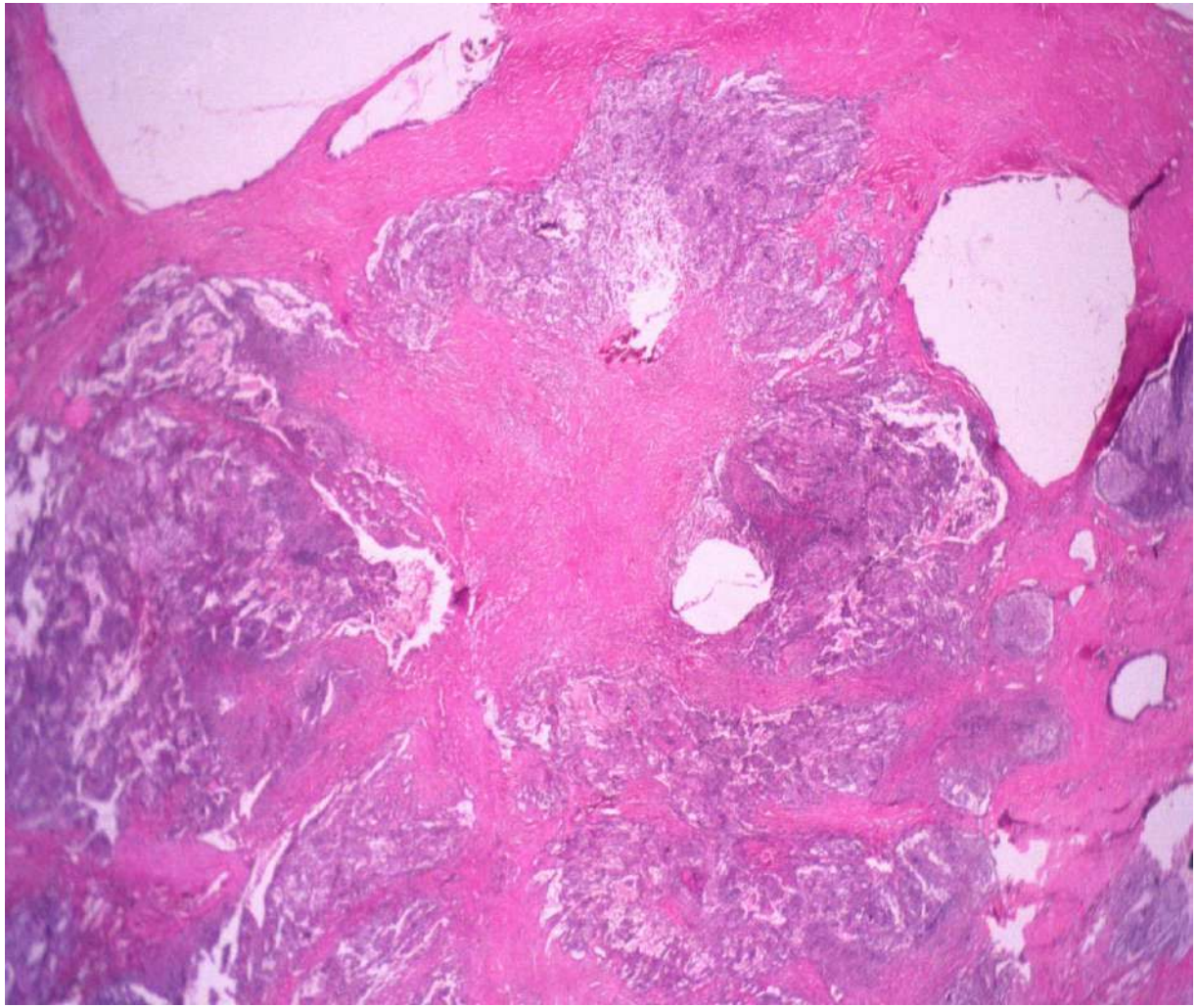


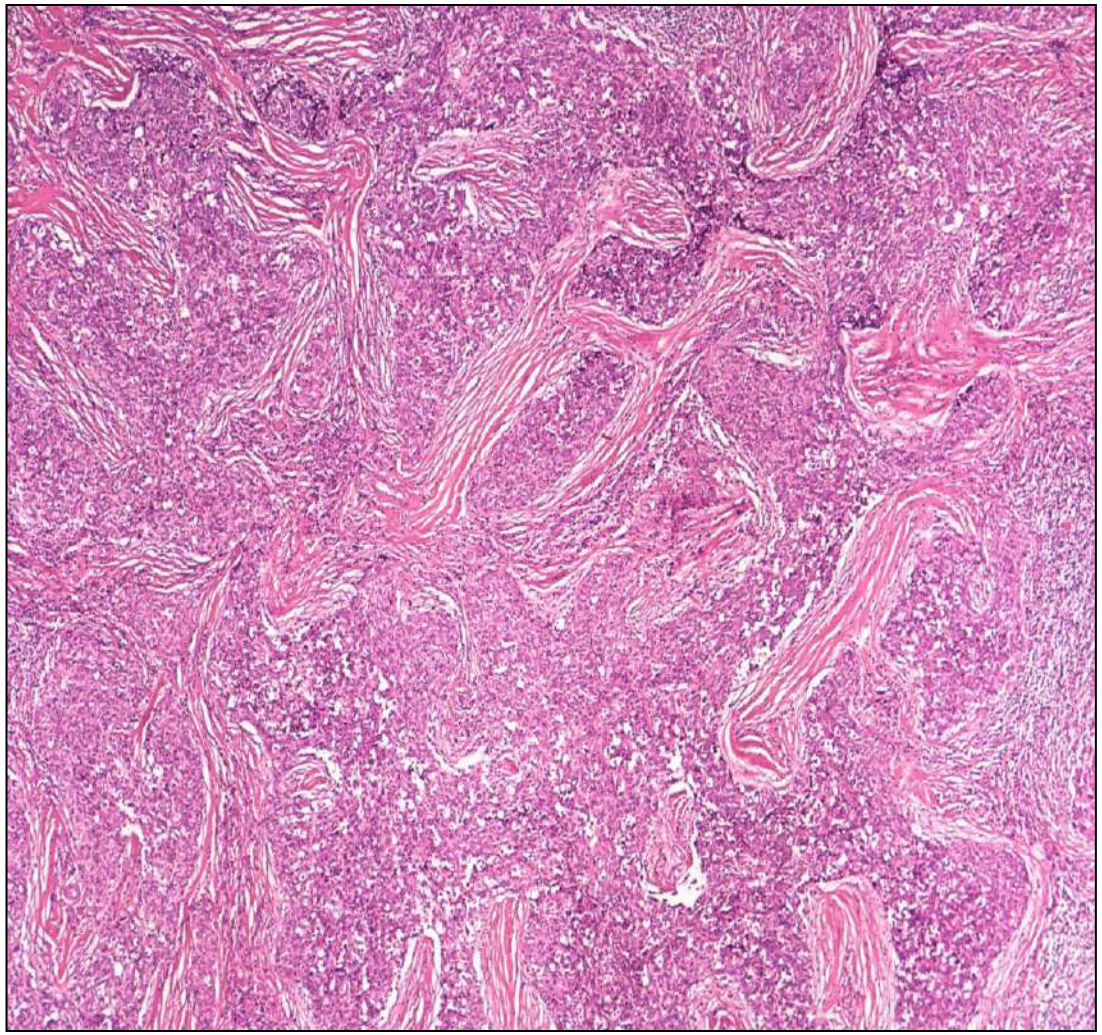


# Carcinoma showing thymus-like differentiation (CASTLE)

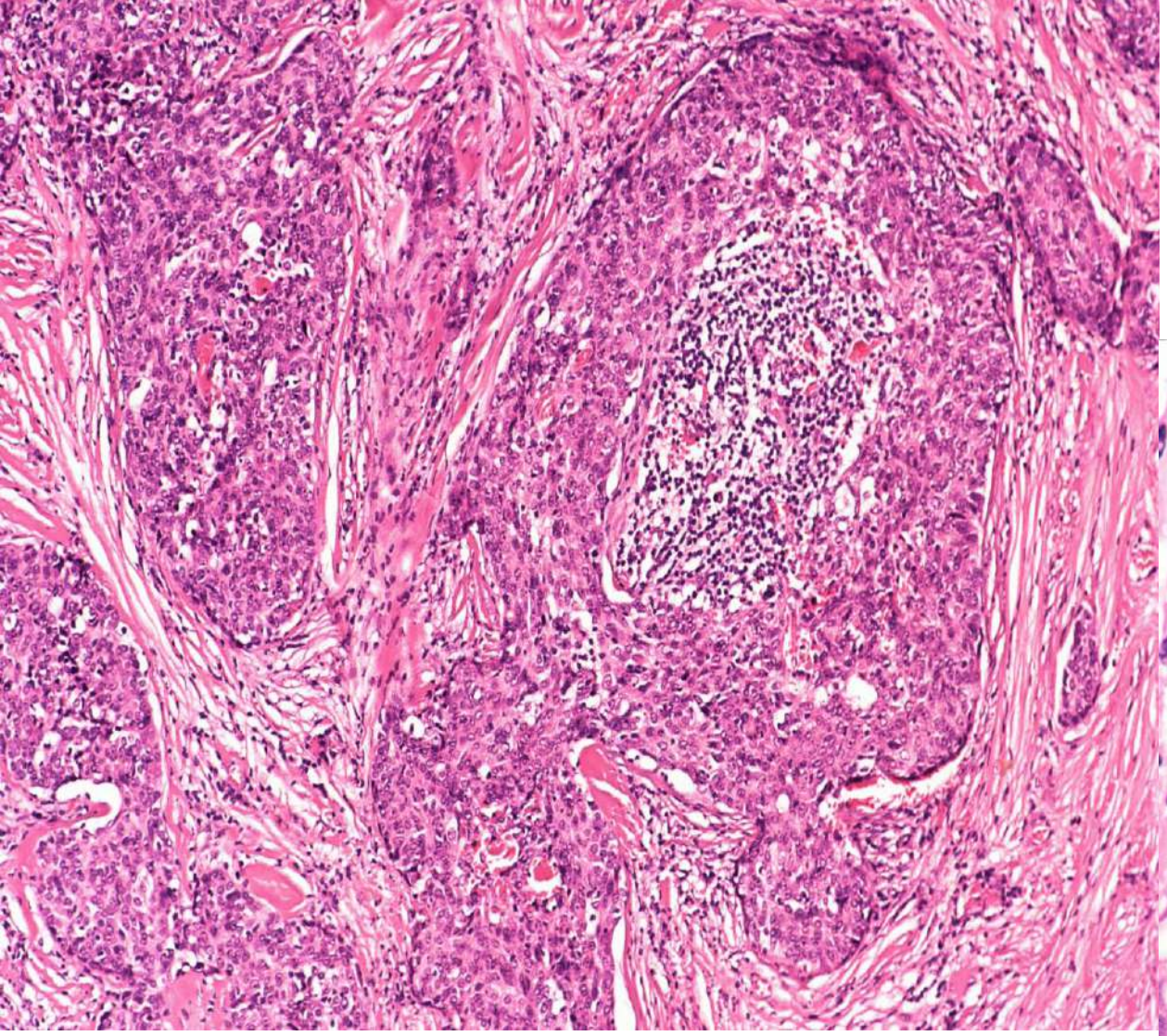
- adult patients, thyroid or neck mass
- lobular pattern, fibrous septa
- atypical cells with indistinct borders, vesicular nuclei and prominent nucleoli
- focal squamous differentiation
- lymphocytes, plasma cells
- CK +, thyroglobulin -, calcitonin -
- increased risk for R and MTS

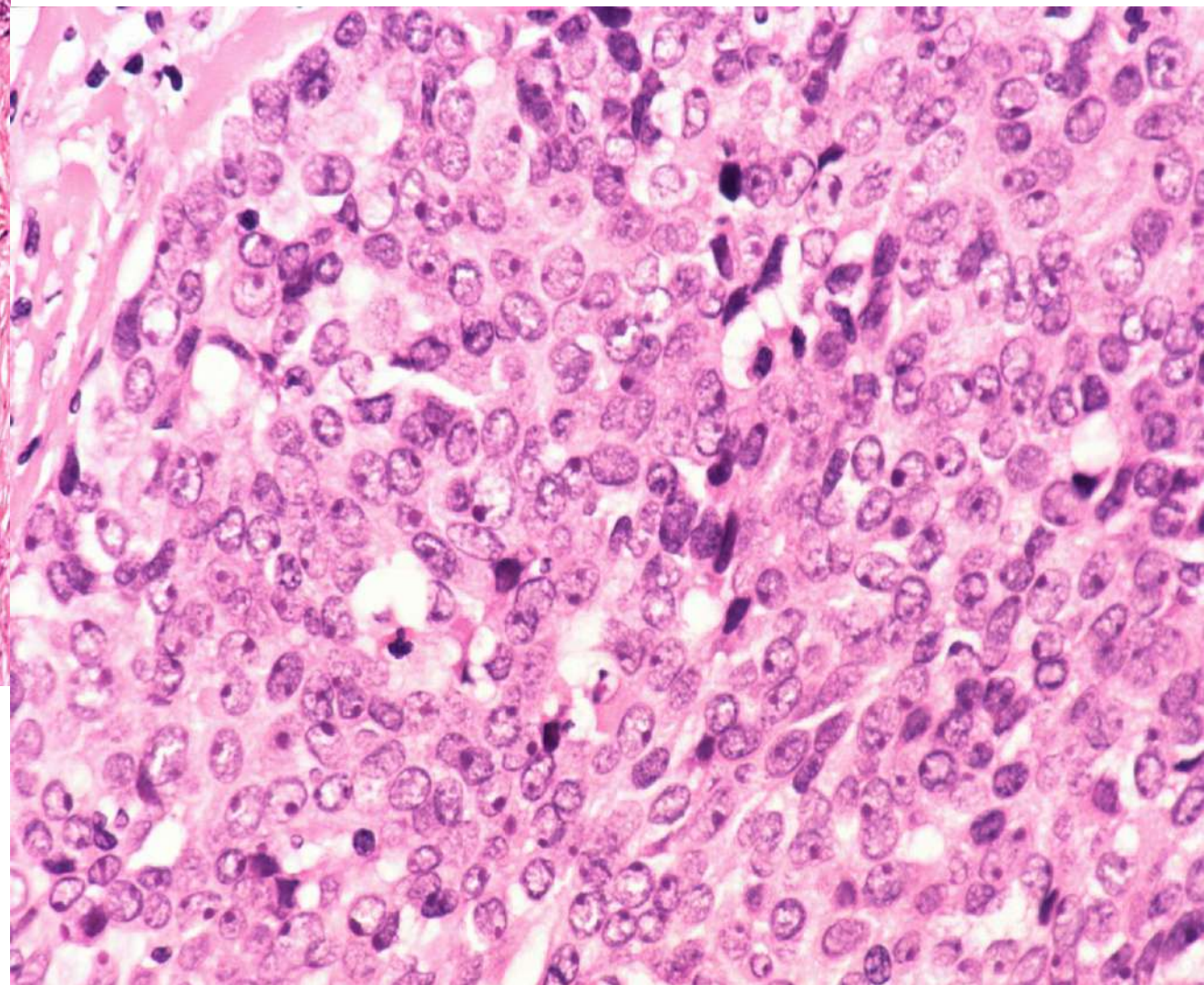
# Carcinoma showing thymus-like differentiation (CASTLE)*

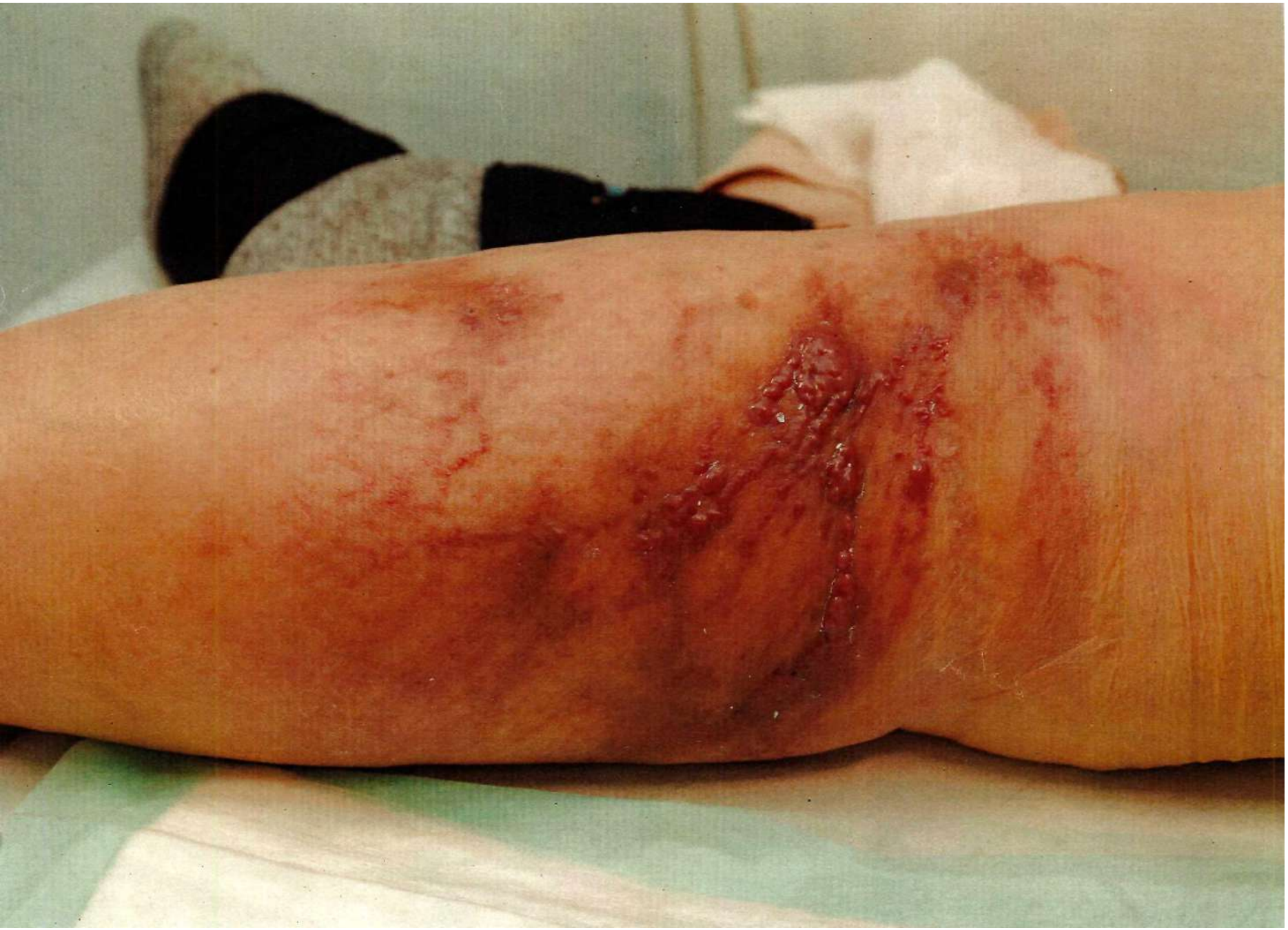




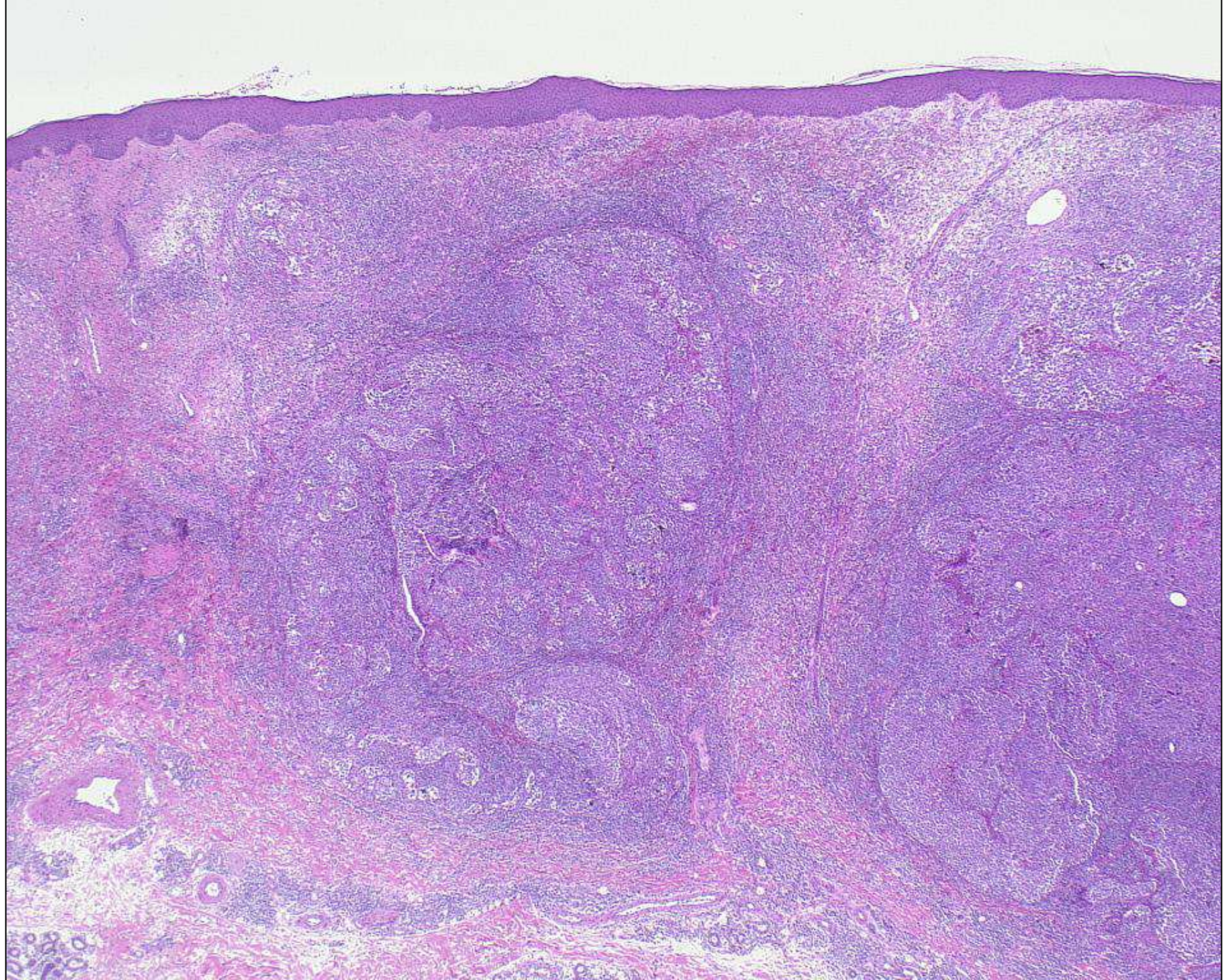
* by courtesy of Prof.J.K.C Chan, Hong Kong

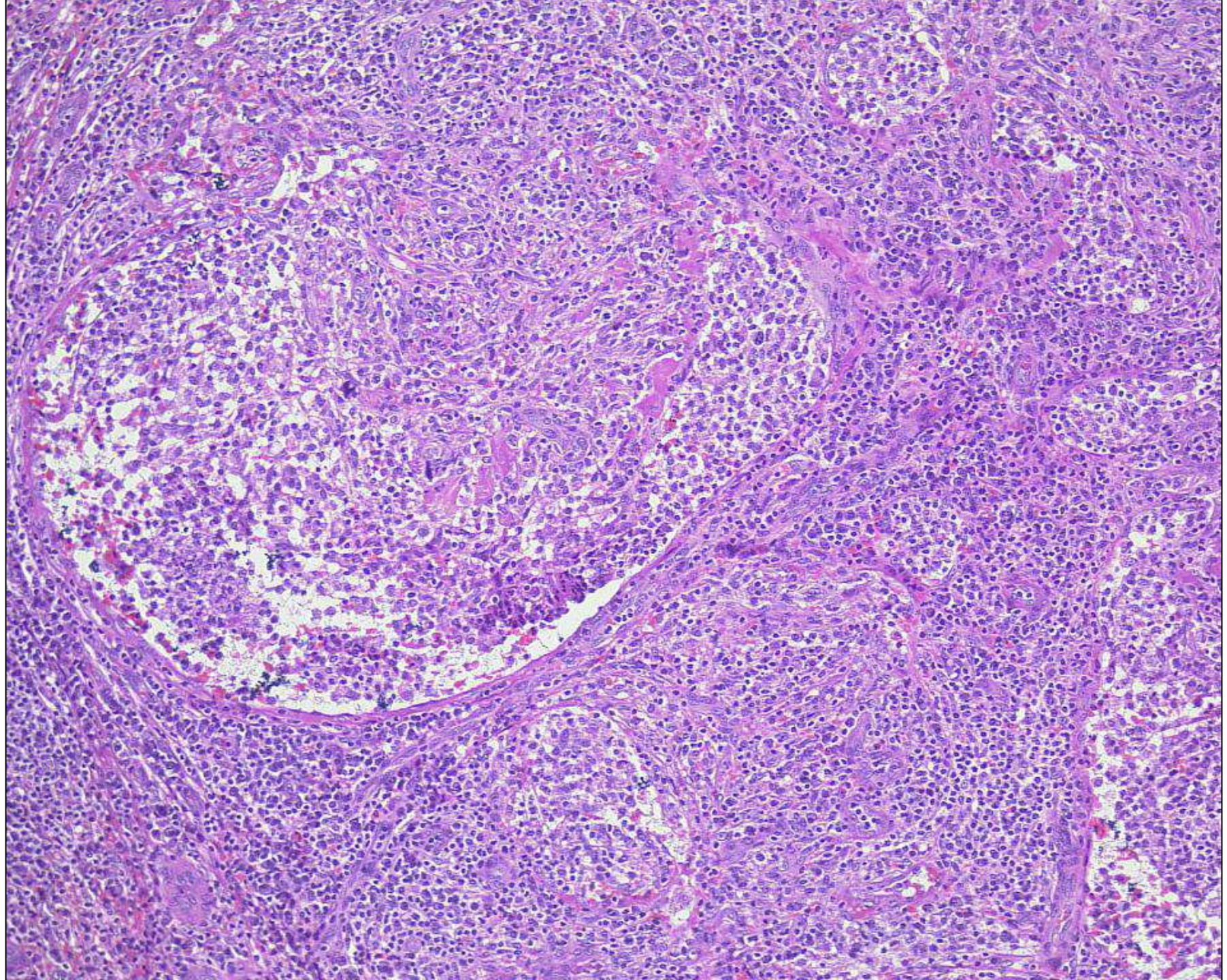


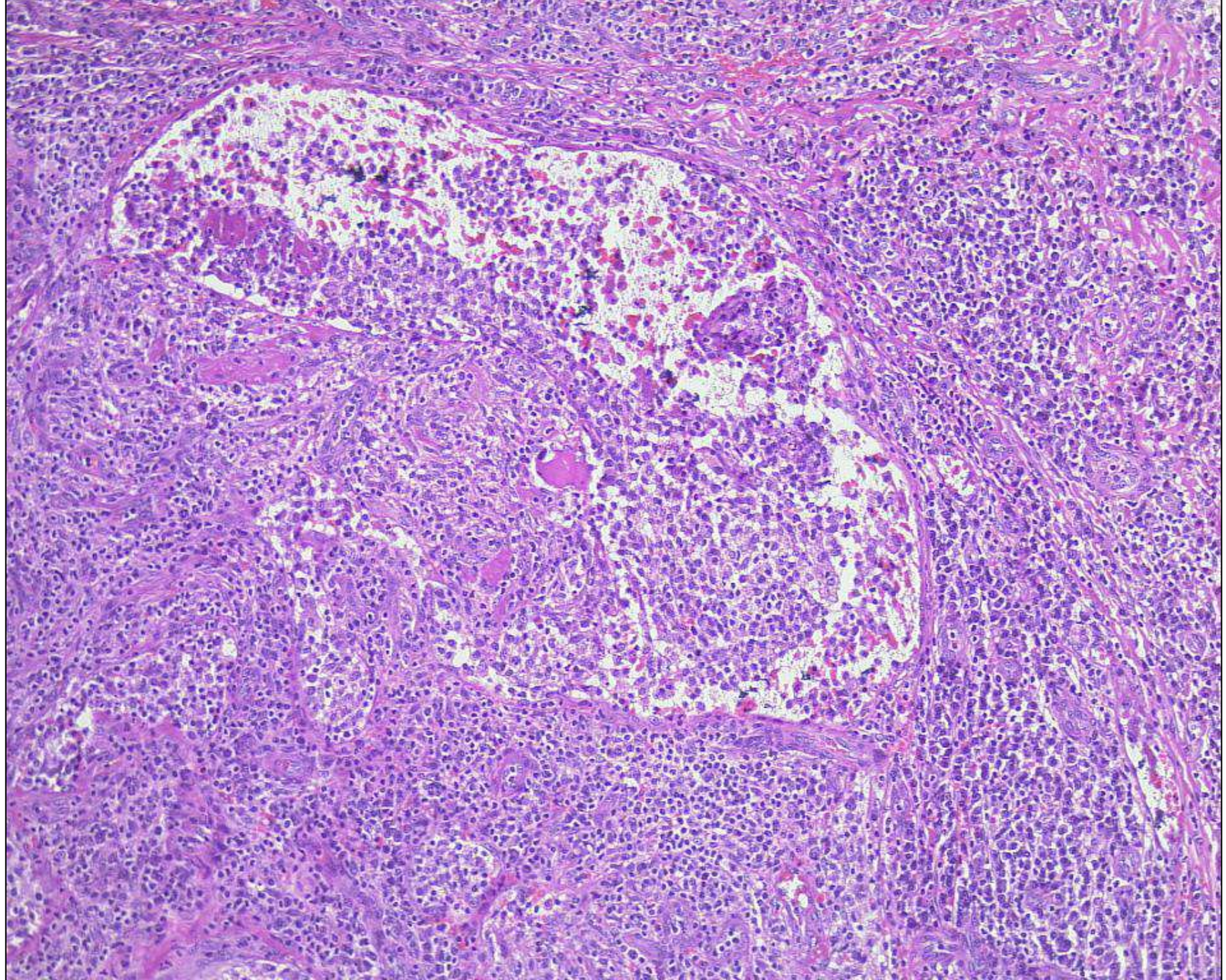


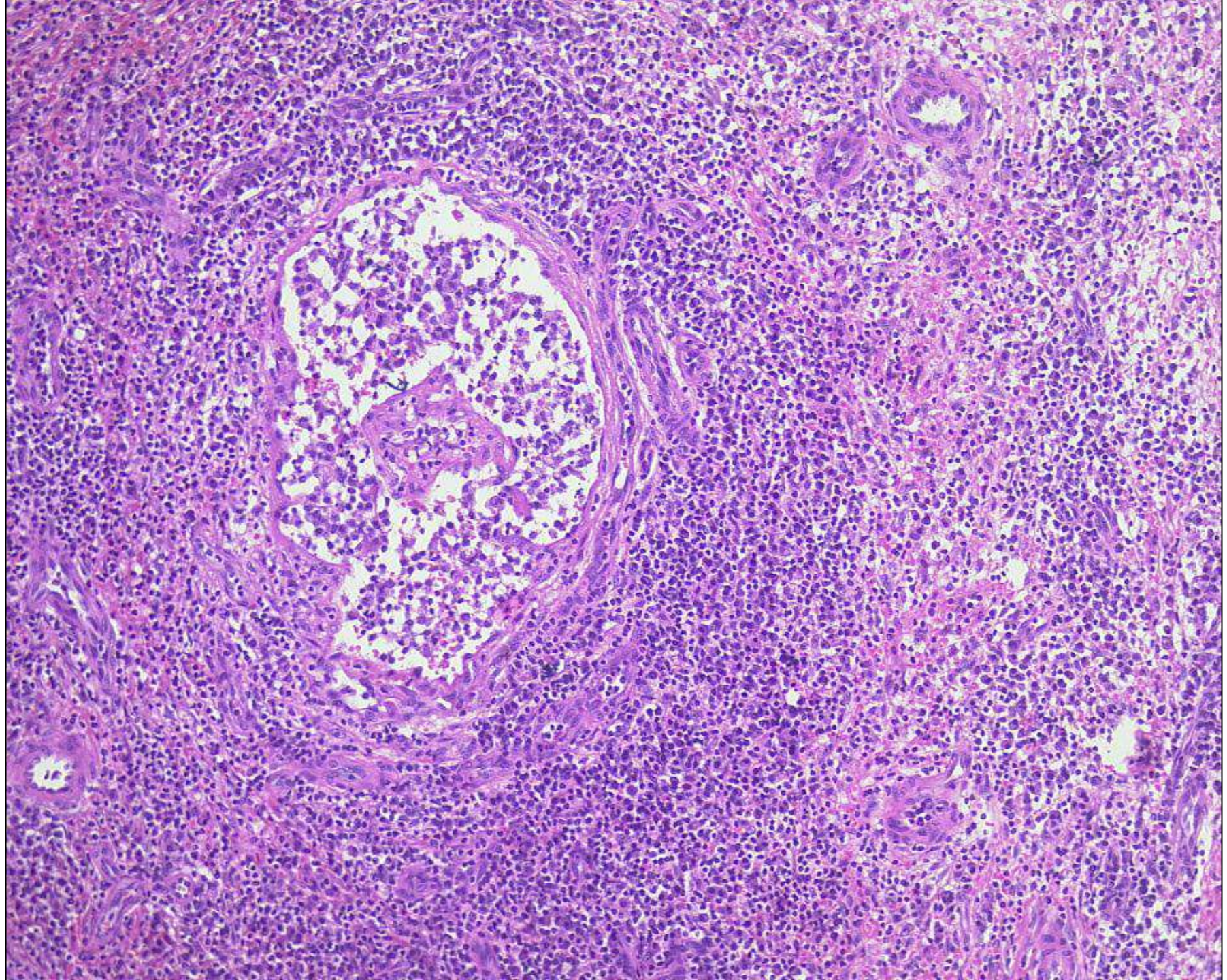


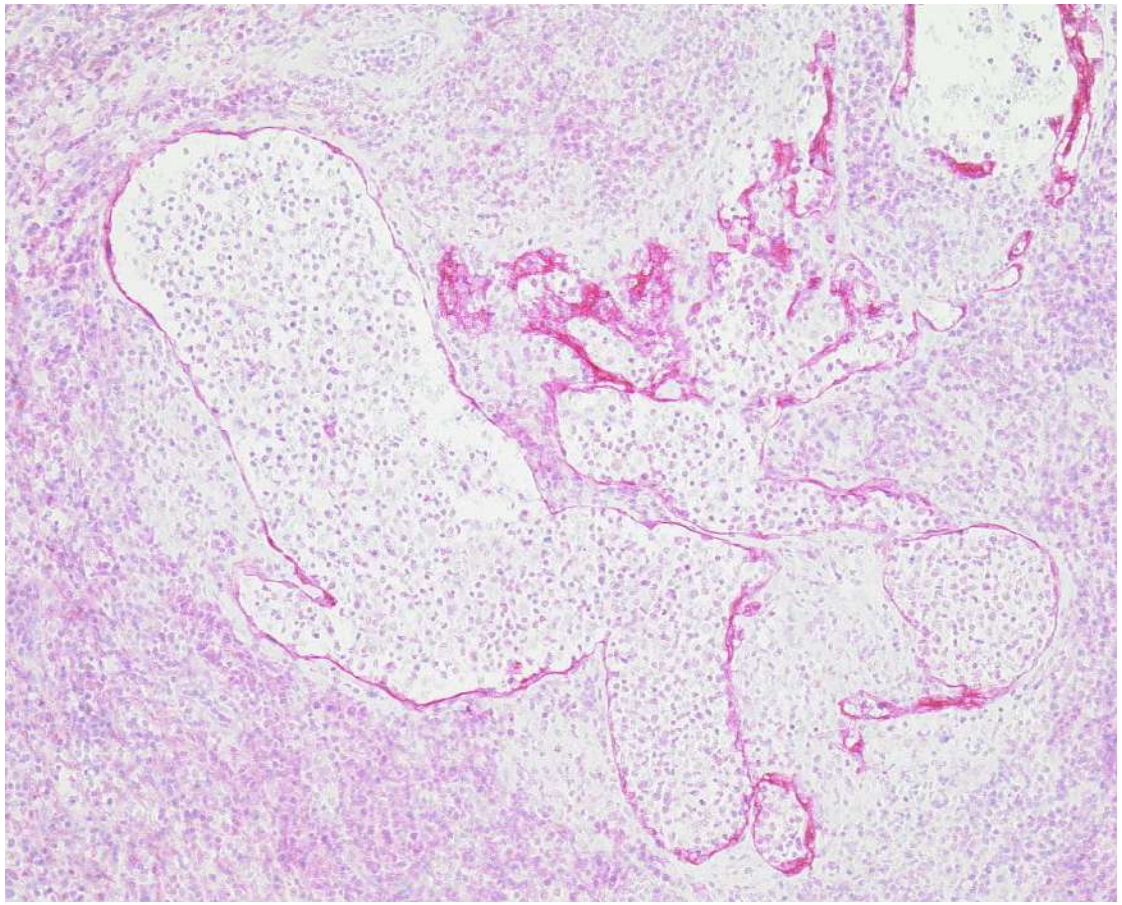
Case 23:
M, 82 years
left lower leg
previous TEP knee

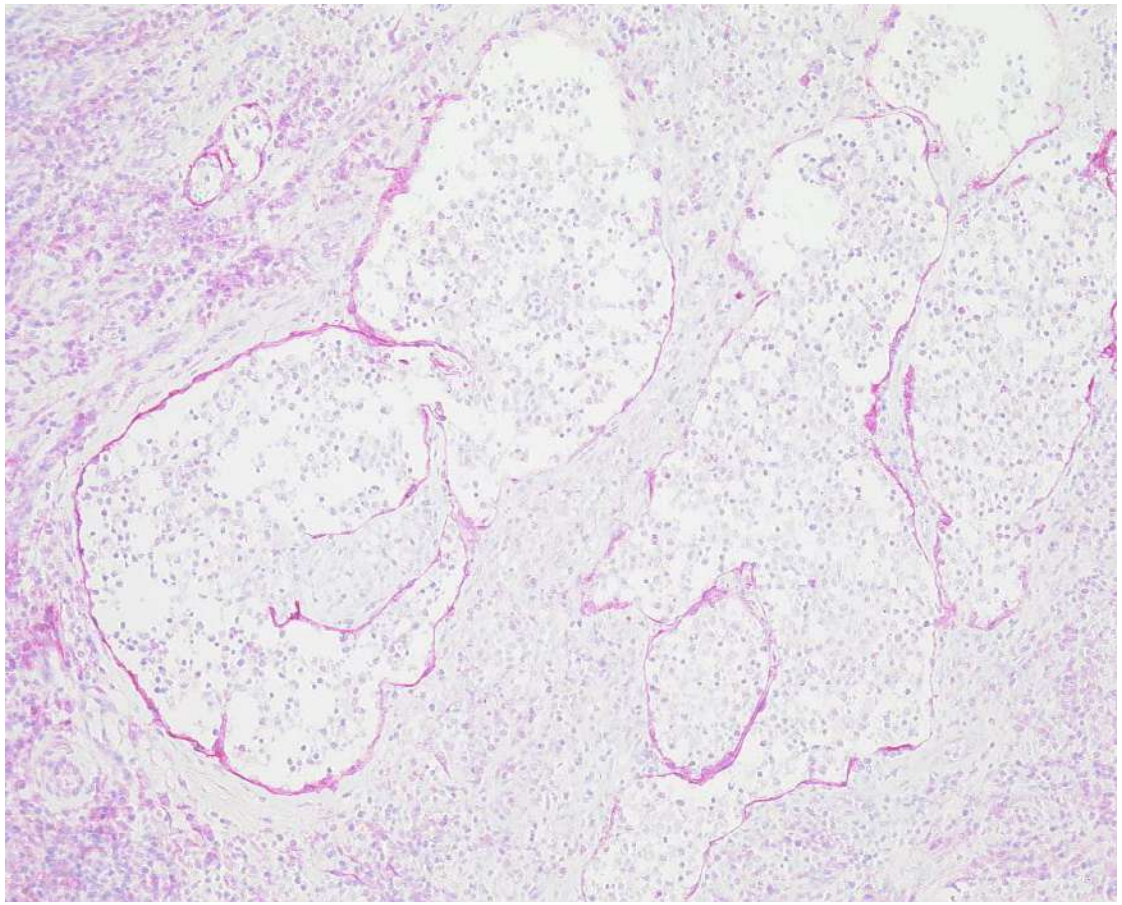




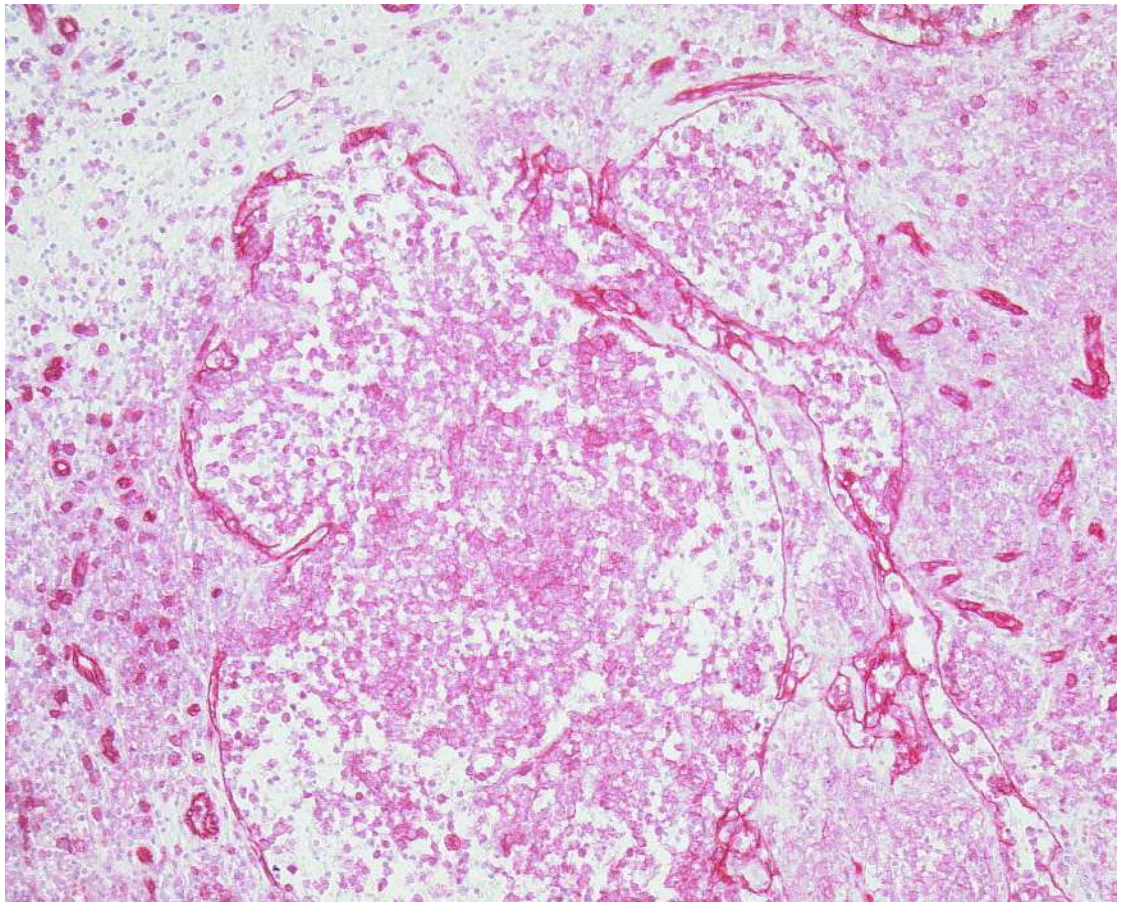


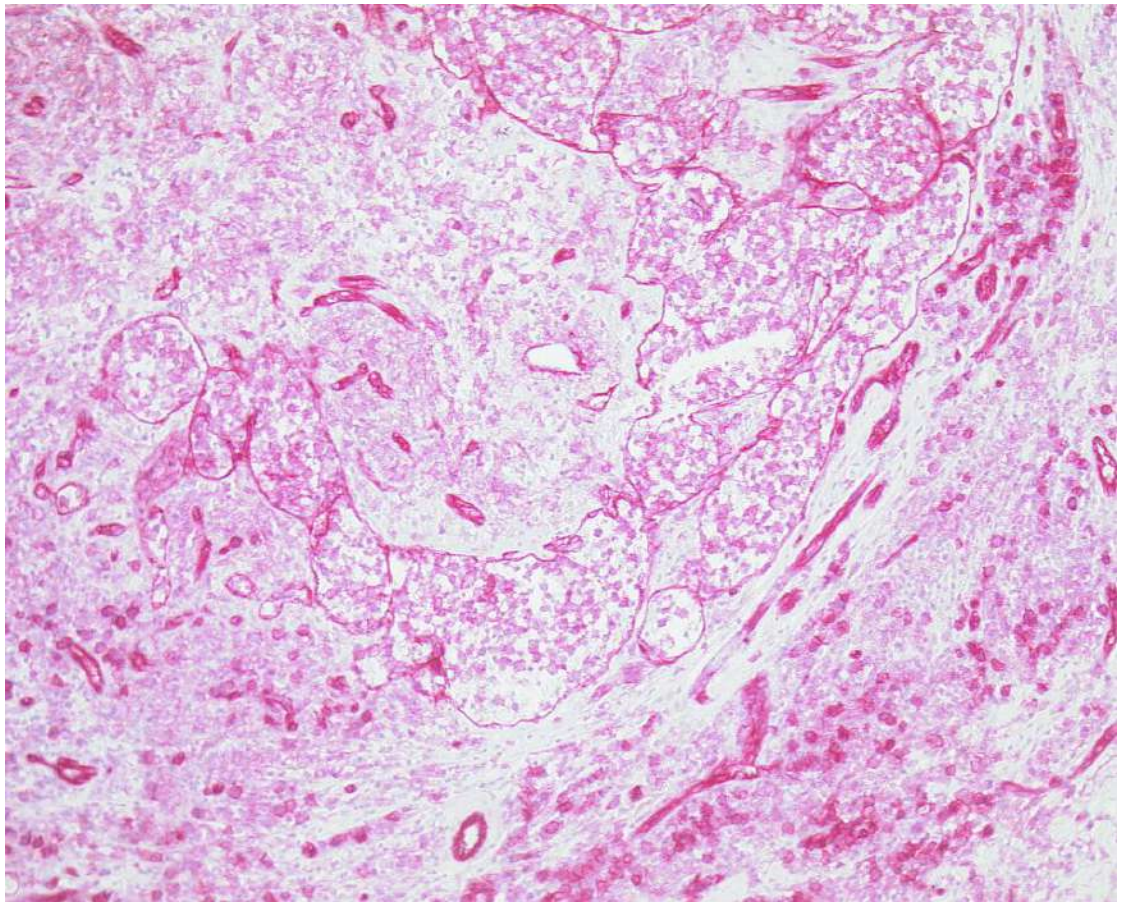




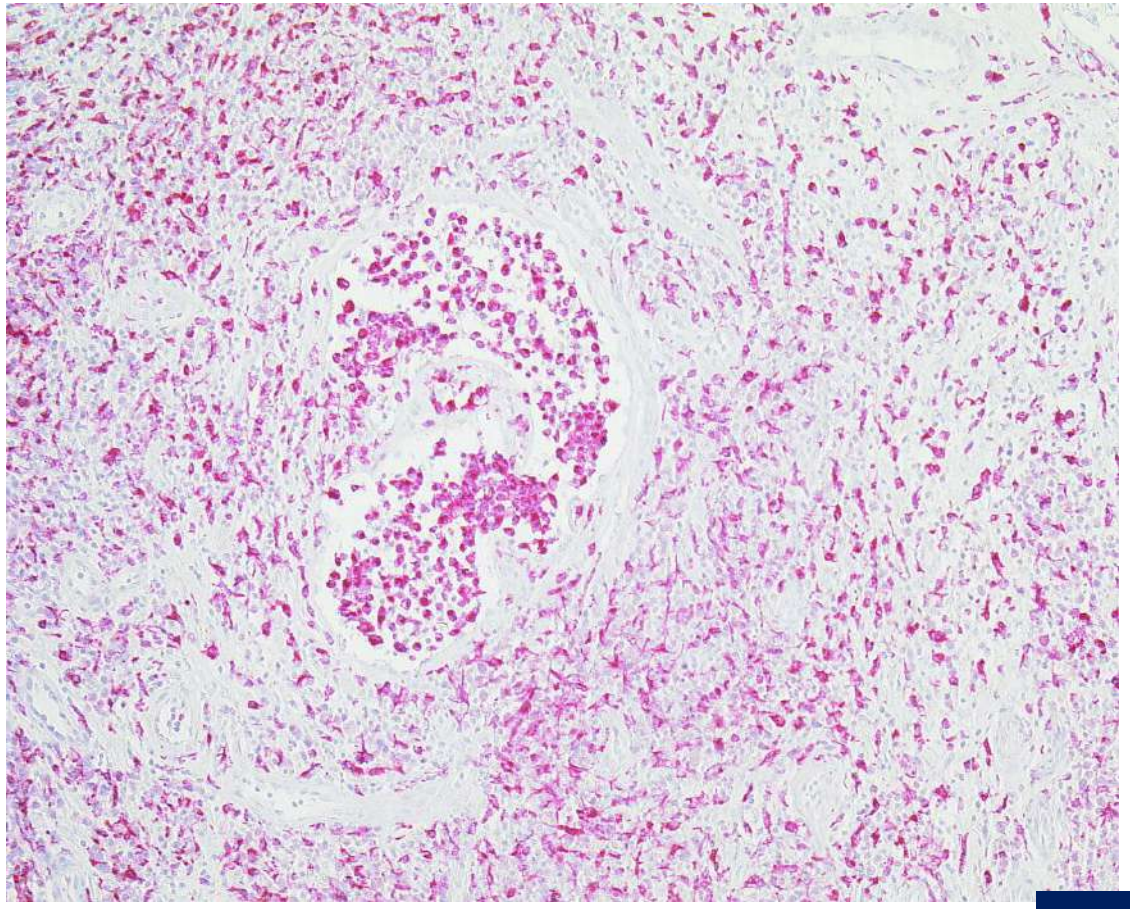


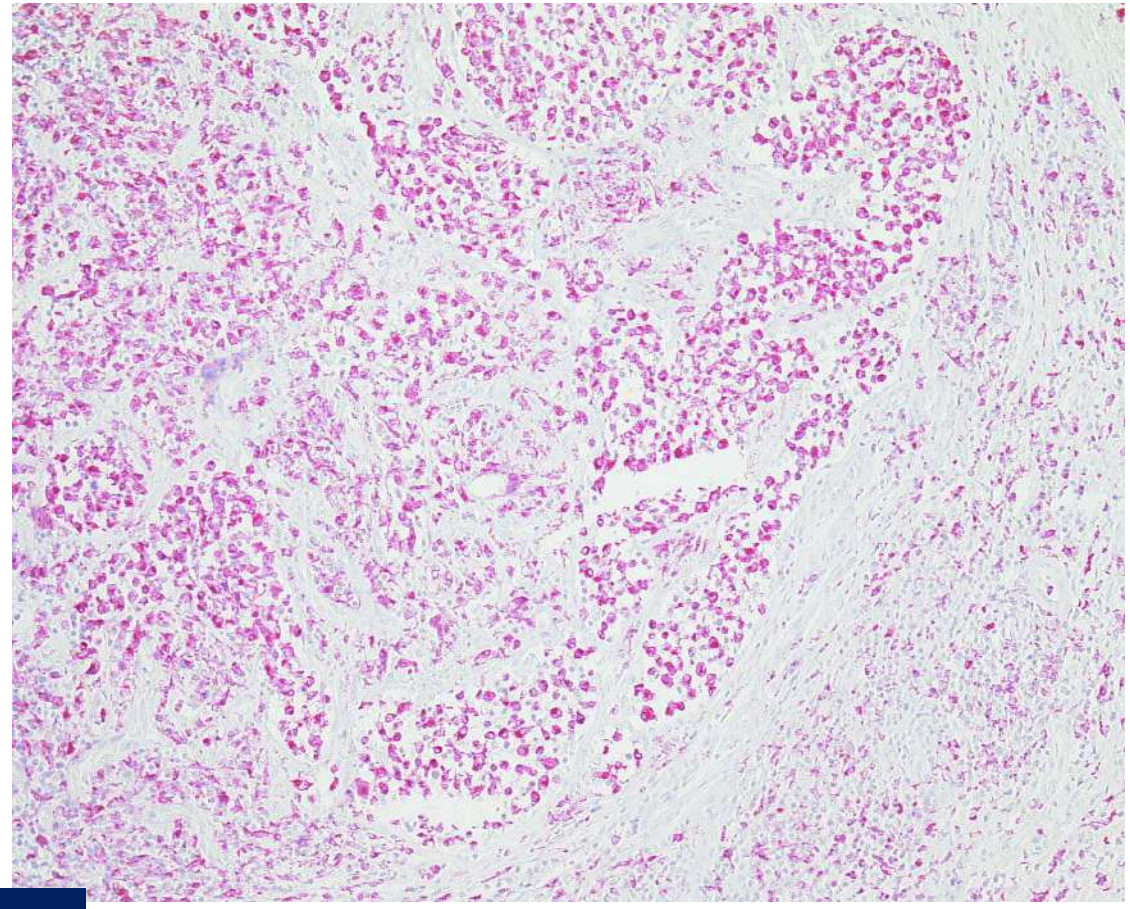
Podoplanin (D2-40)





CD31





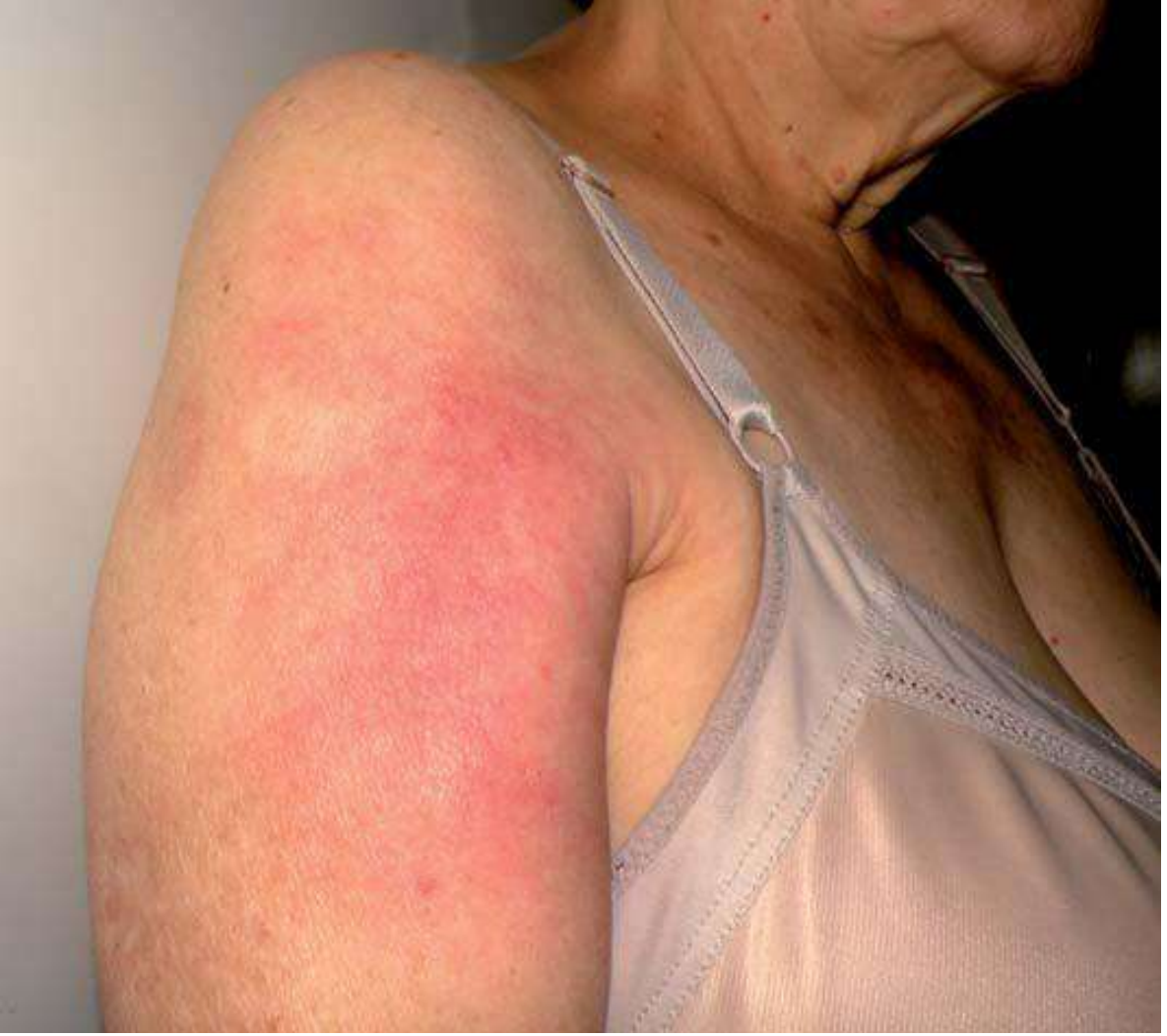
CD68

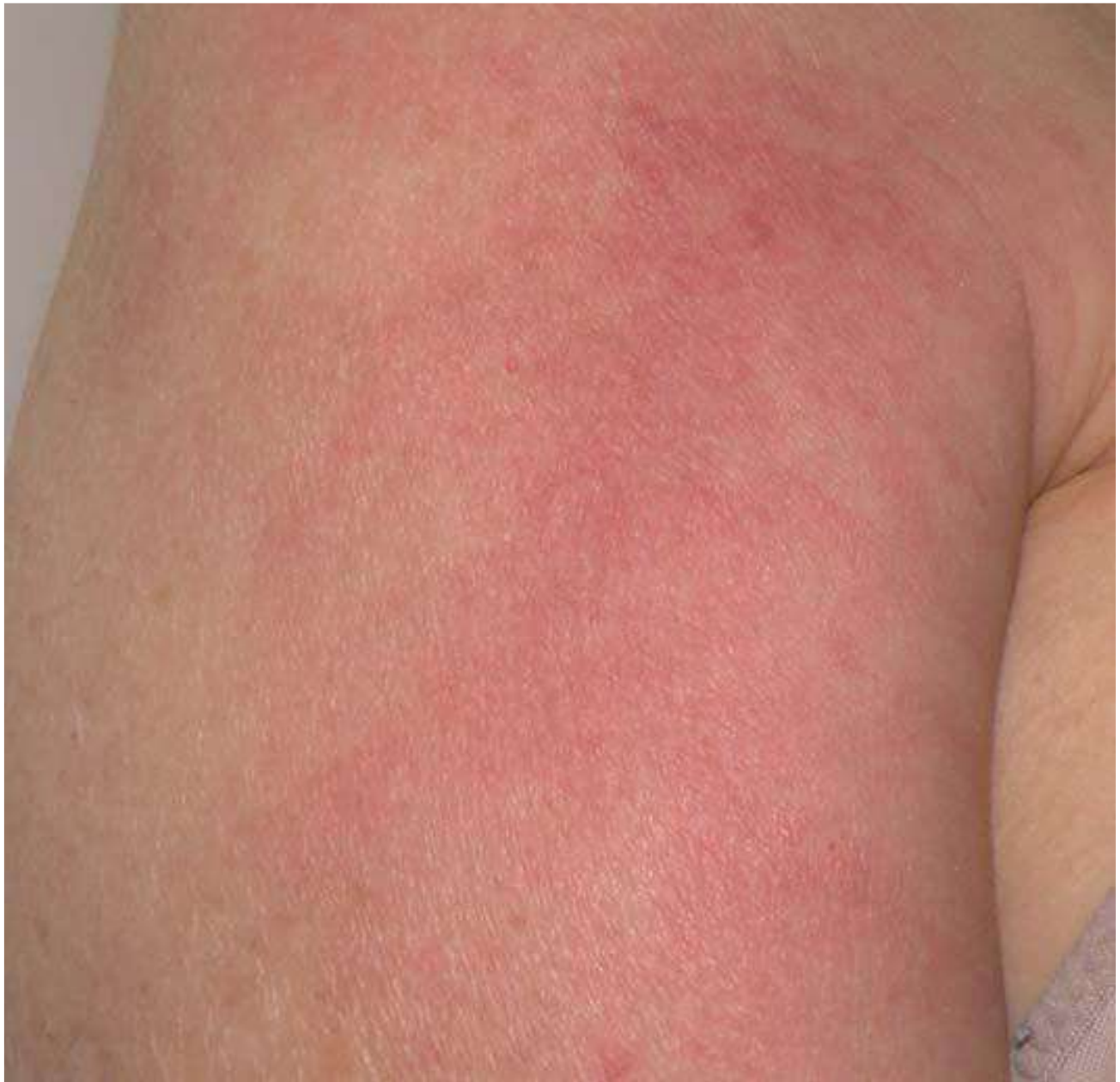
CD20 -, CD2 -, CD30 -

# Diagnosis Case 23: intralymphatic Histiocytosis

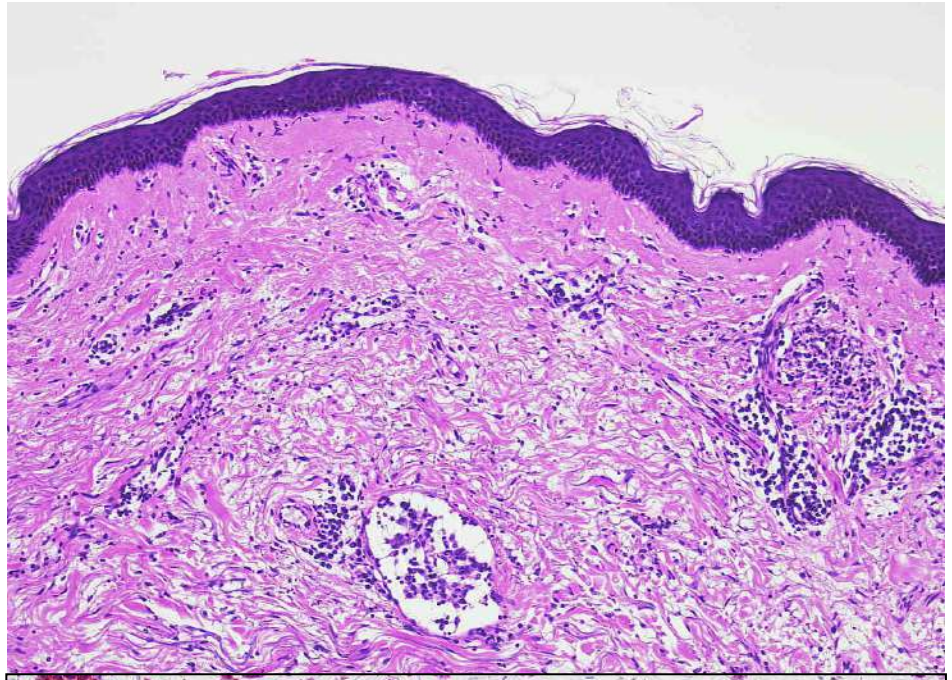
(Requena L et al. AJDP 2009; 31: 140-151)

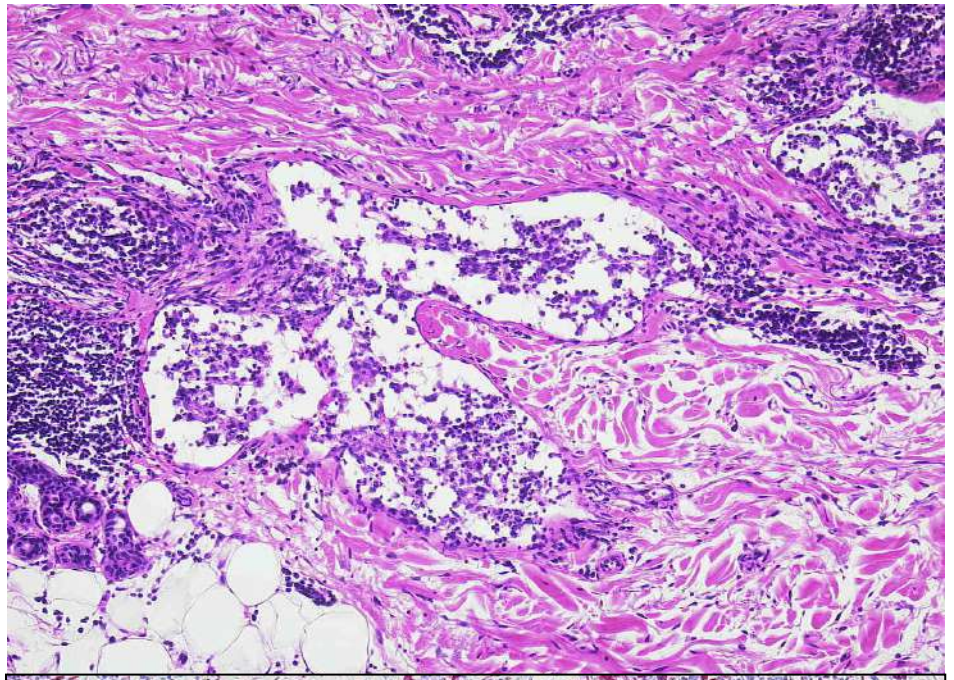
- 16 cases, F > M, upper > lower extremities
- dermal lesions (stratum retikulare)
- ill-defined, erythematous plaques
- dilated lymphatic vascular spaces (podoplanin + endothelial cells)
- intravascular histiocytes
  (CD 68 +, CD 14 +, CD 31 +)
- associated inflammatory infiltrate
- associated rheumatism in 50% of cases !
- relationship with metal implant (Int J Dermatol 2014; 53: e365)
- indolent but chronic course

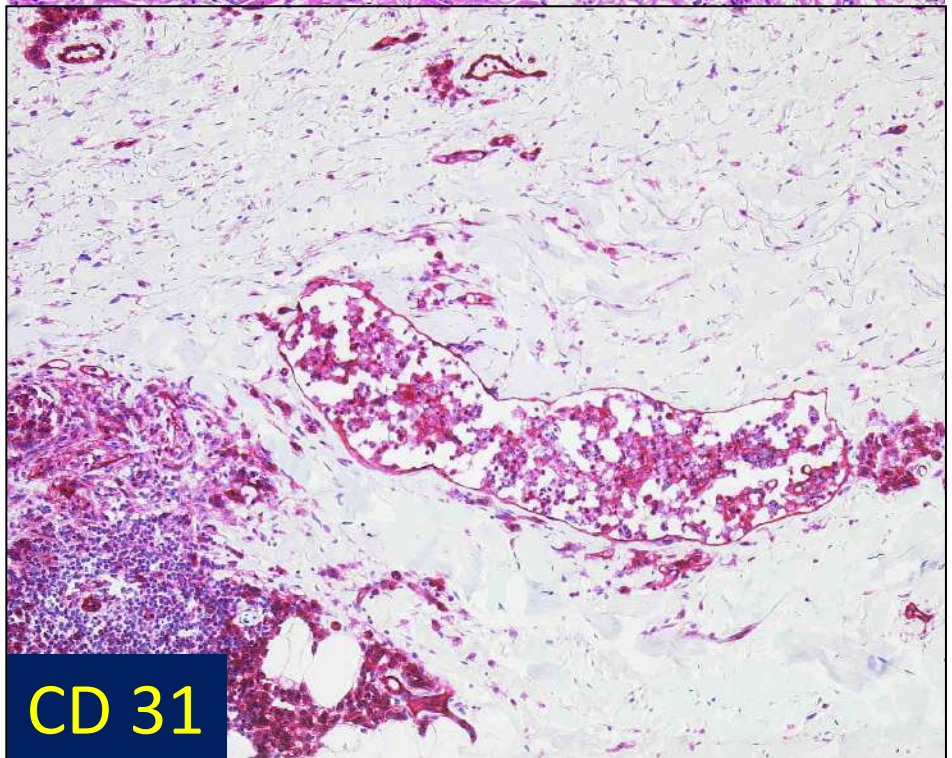


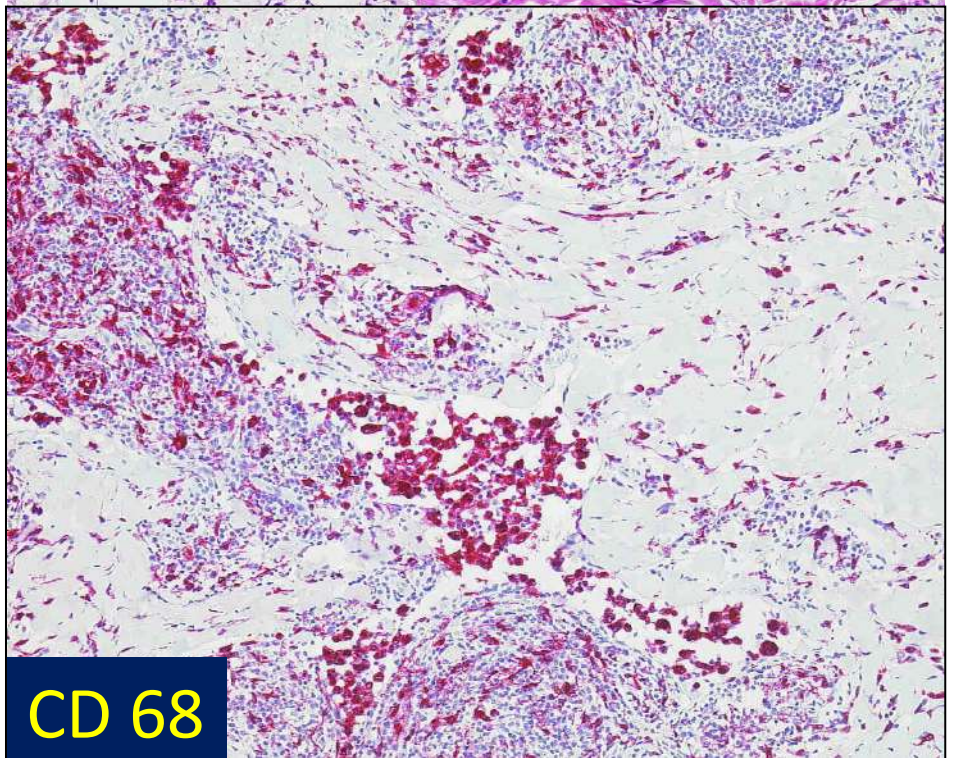


by courtesy of Dr. L. Requena, Madrid, Spain






CD 31


CD 68

# Many thanks for your attention…