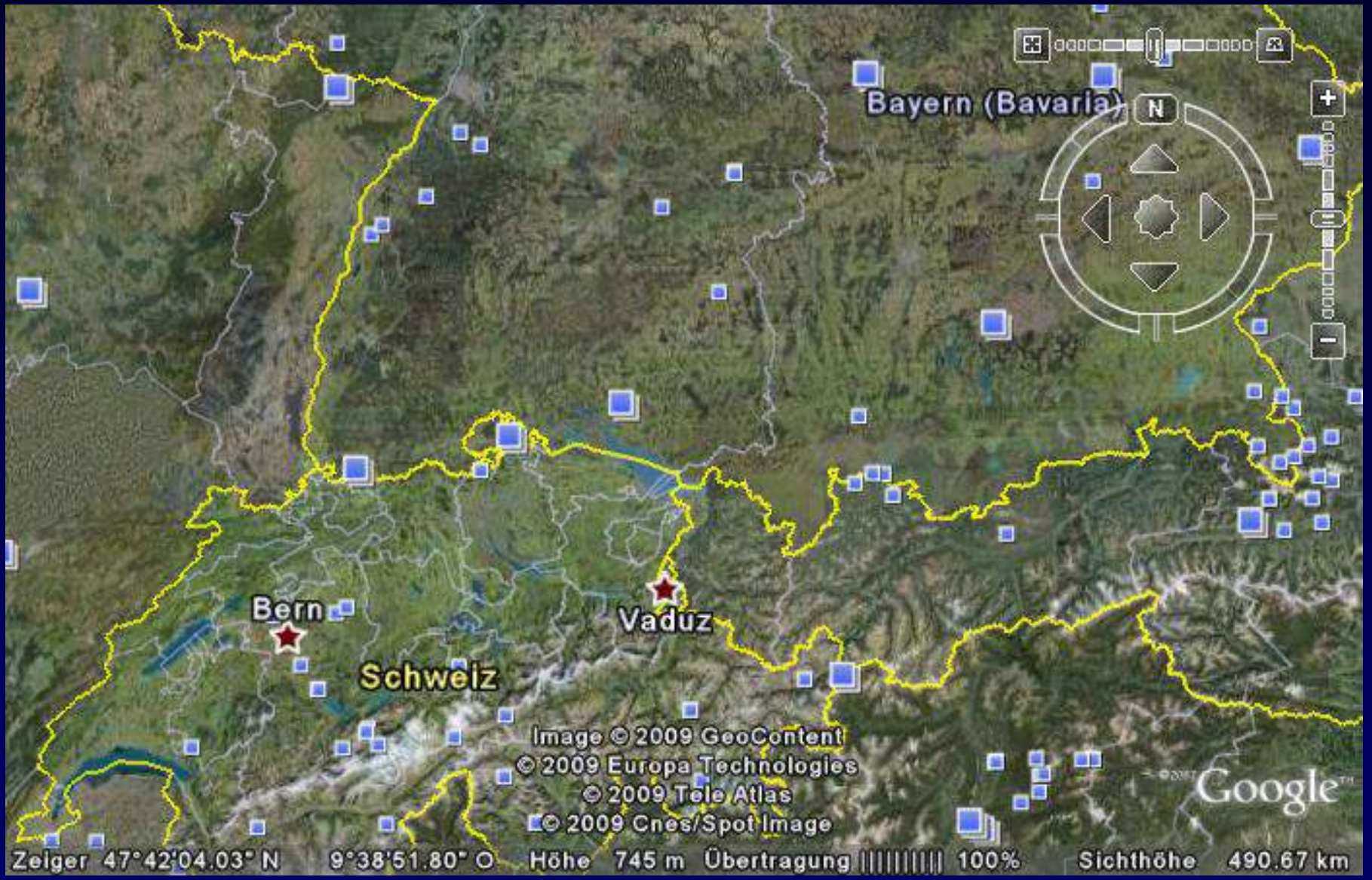
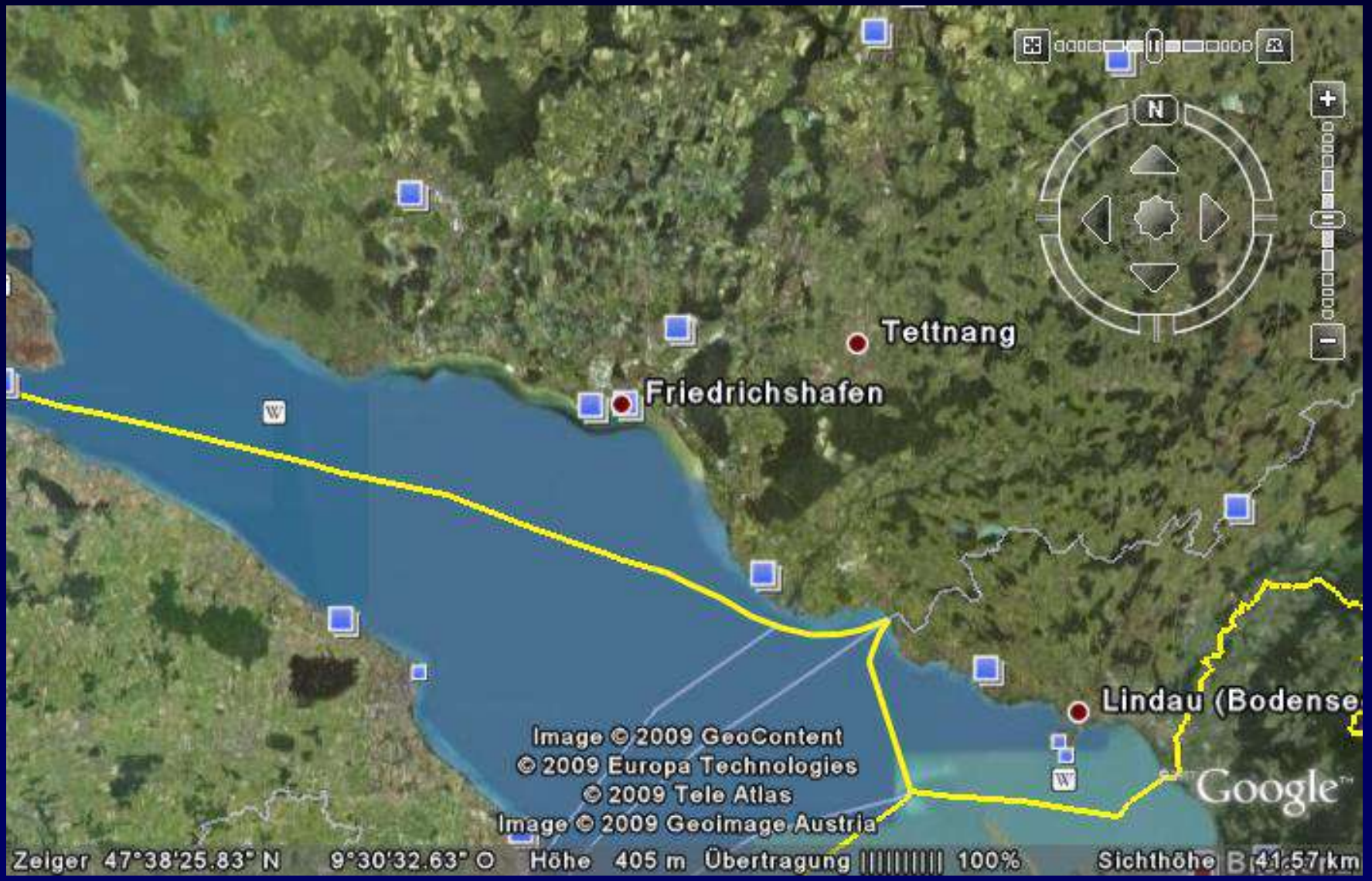
Vascular Tumours of Skin and Soft Tissues

Dr. Thomas Mentzel

MVZ Dermatopathologie Friedrichshafen / Bodensee PartG


Bayern (Bavaria)
N
Bern
Vaduz
Schweiz
Image © 2009 GeoContent
© 2009 Europa Technologies
© 2009 Tele Atlas
© 2009 Cnes/Spot Image
Google
Zeiger 47°42'04.03" N 9°38'51.80" O Höhe 745 m Übertragung 100% Sichthöhe 490.67 km


Tettnang
Friedrichshafen
Lindau (Bodense
Image © 2009 GeoContent
© 2009 Europa Technologies
© 2009 Tele Atlas
Image © 2009 Geoimage Austria
Google
Zeiger 47°38'25.83" N 9°30'32.63" O Höhe 405 m Übertragung 100% Sichthöhe 41.57 km


N
Image © 2009 GeoContent
© 2009 Tele Atlas
Google
Zeiger 47°40'41.53" N 9°28'48.95" O Höhe 414 m Übertragung 100% Sichthöhe 871 m

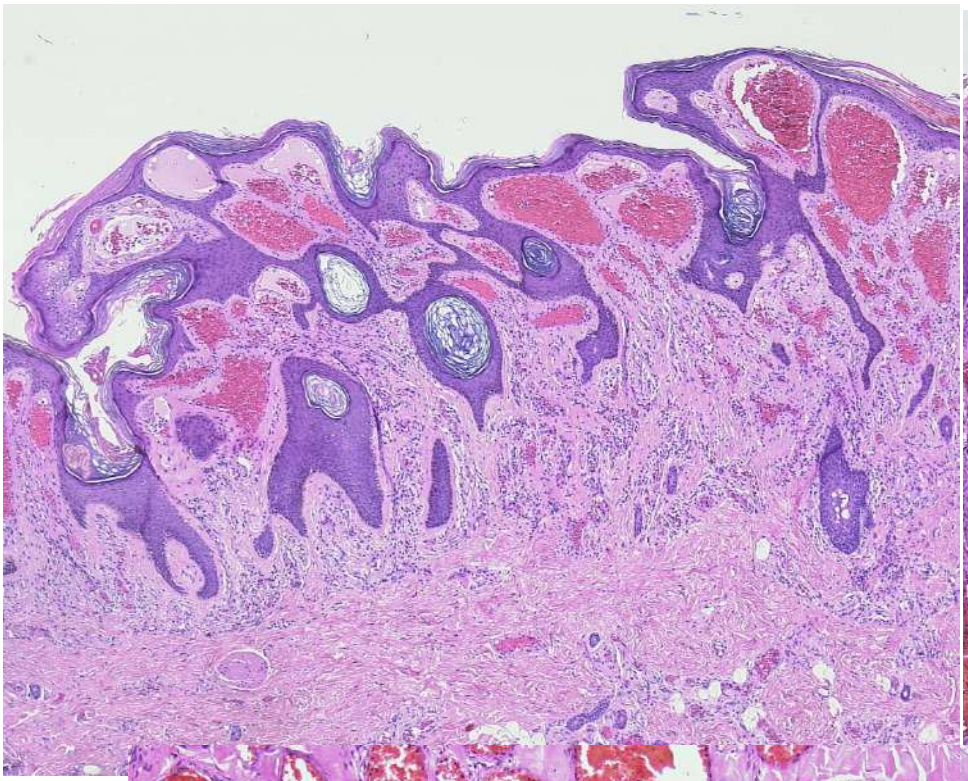
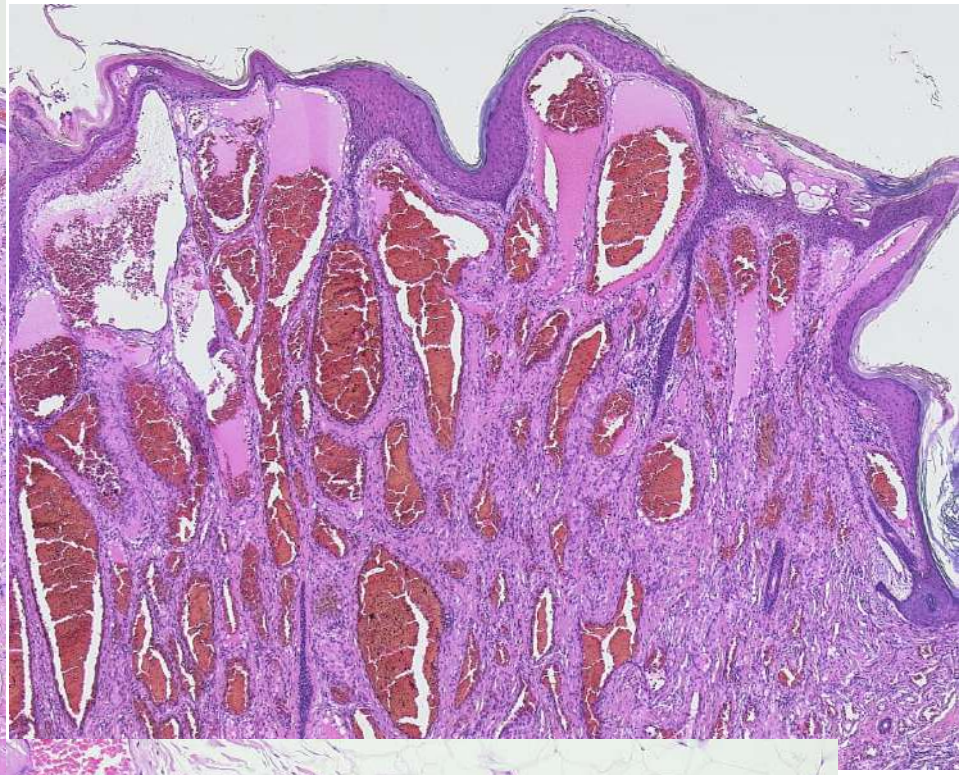
ISSVA Classification of vascular Tumours (Melbourne 2014, update 2018)

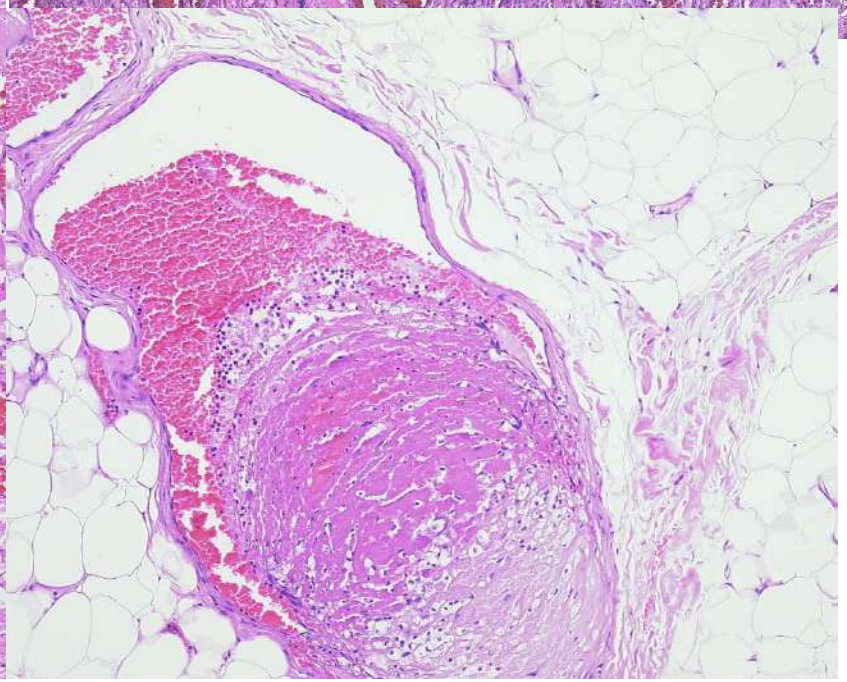
vascular Malformations
- simple (capillary, lymphatic, venous, arteriovenous, arteriovenous fistula)
- combined of major named vessels
- associated with other anomalies

vascular Neoplasms
- benign
- locally aggressive / borderline (Kaposi sarcoma, haemangioendotheliomas)
- malignant (epithelioid HE, angiosarcoma)

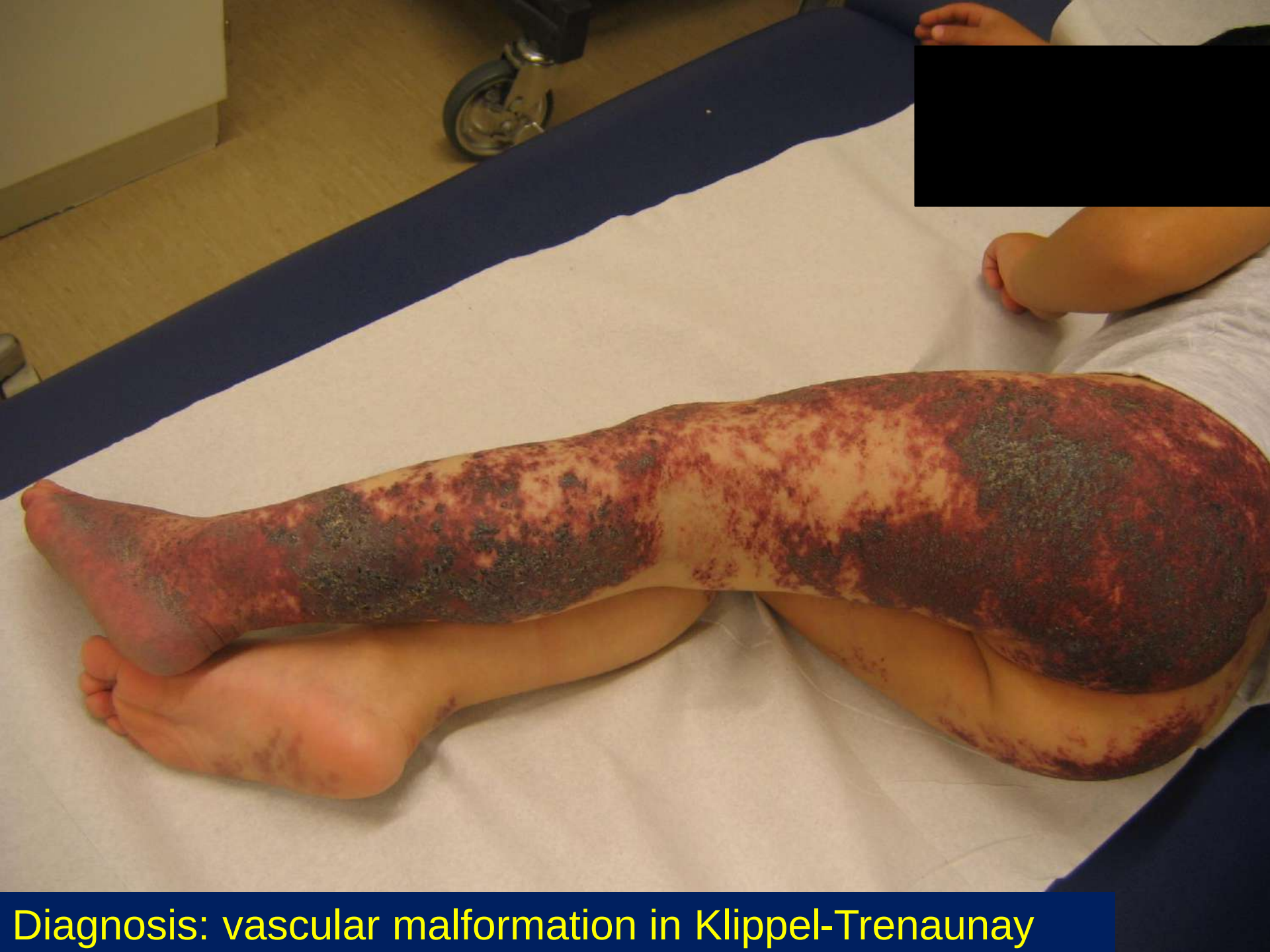
Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas



M, 8 years, left thigh, biopsy
capillary haemangioma?



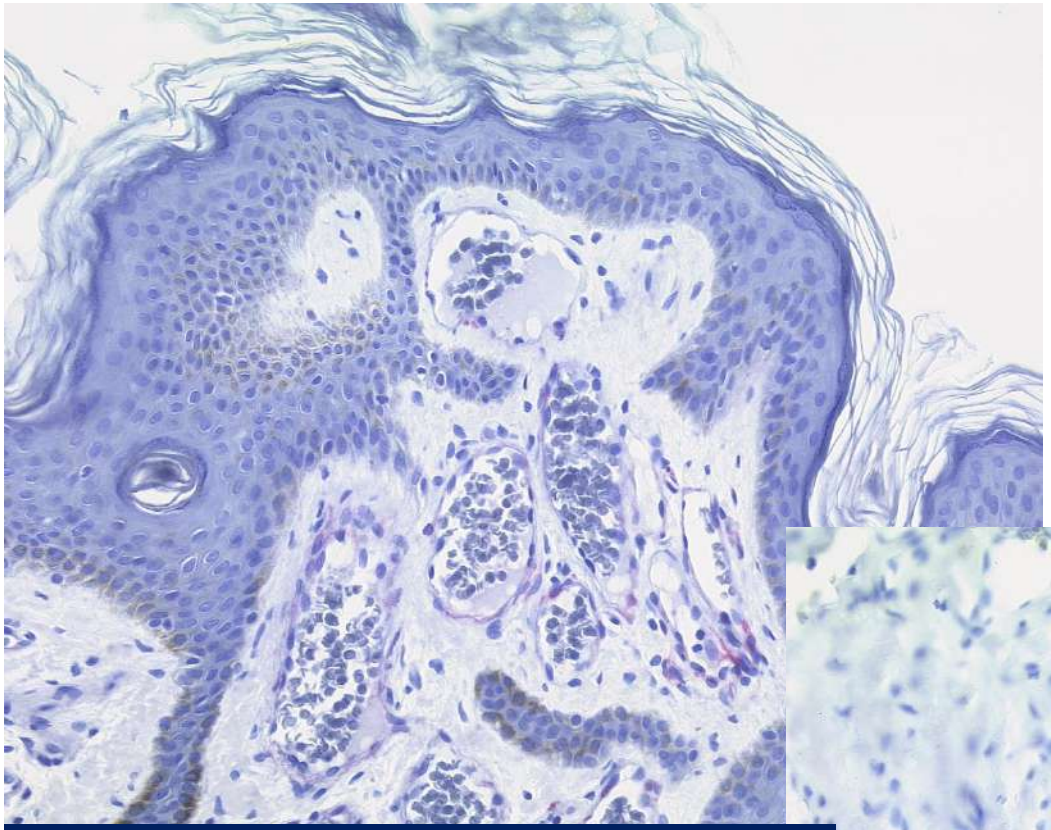
Diagnosis: vascular malformation in Klippel-Trenaunay

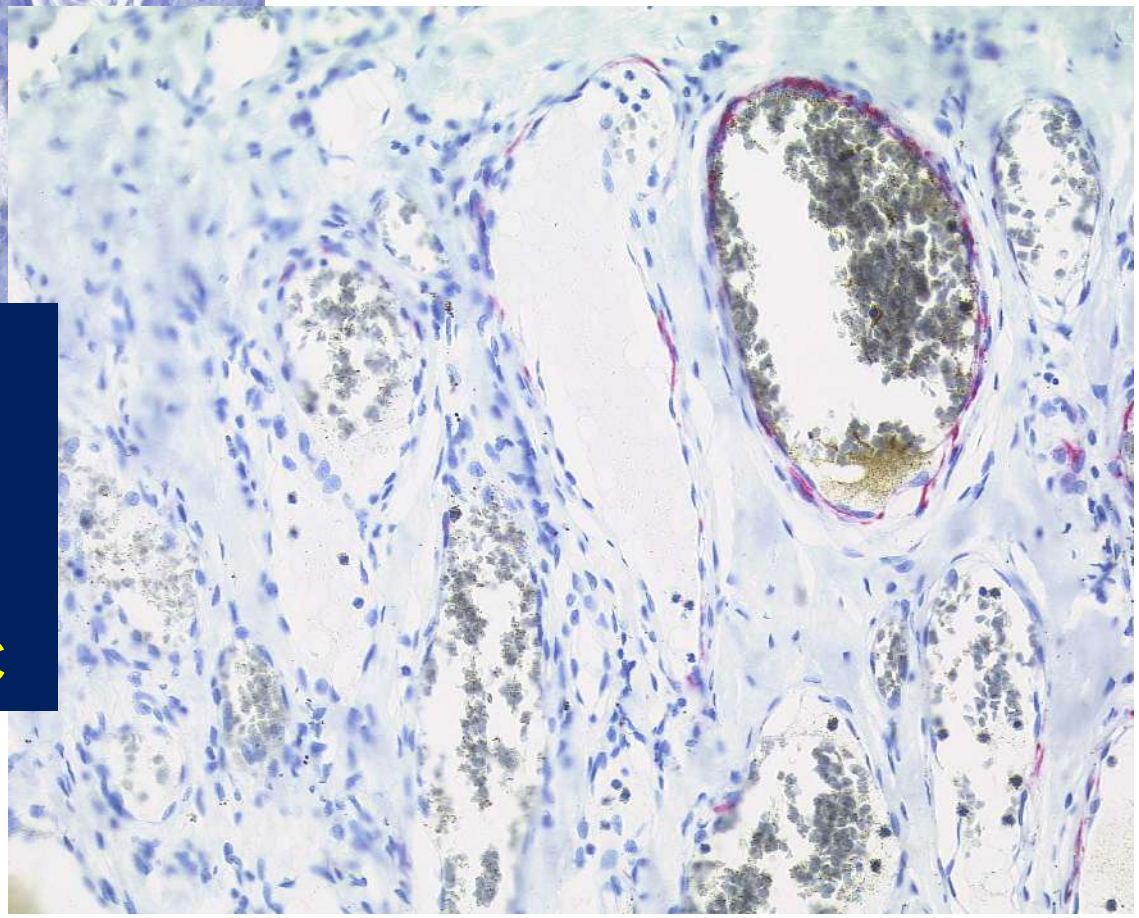
Lawley LP et al.:

Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions.

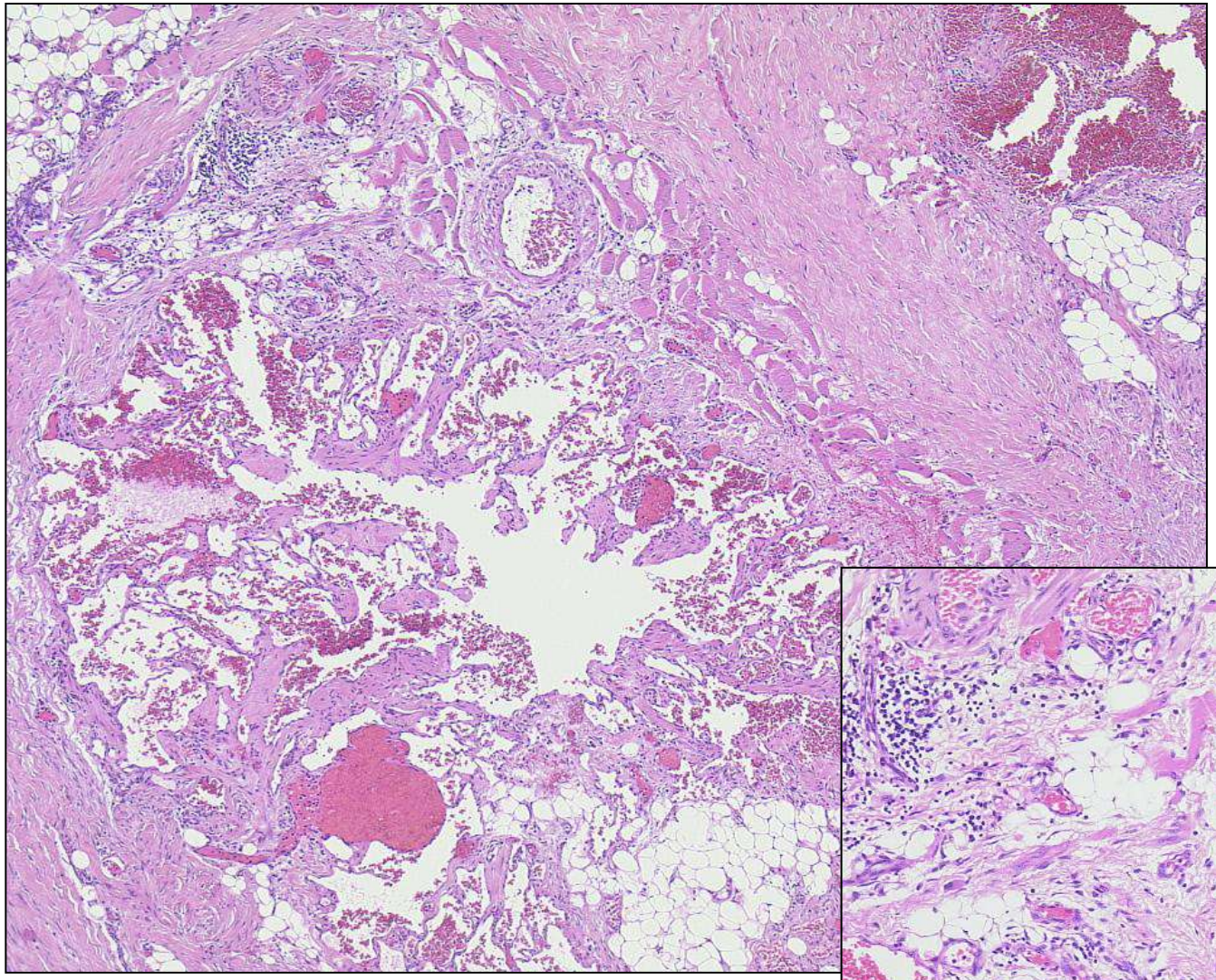
Arch Dermatol 2005; 141: 1297-1300

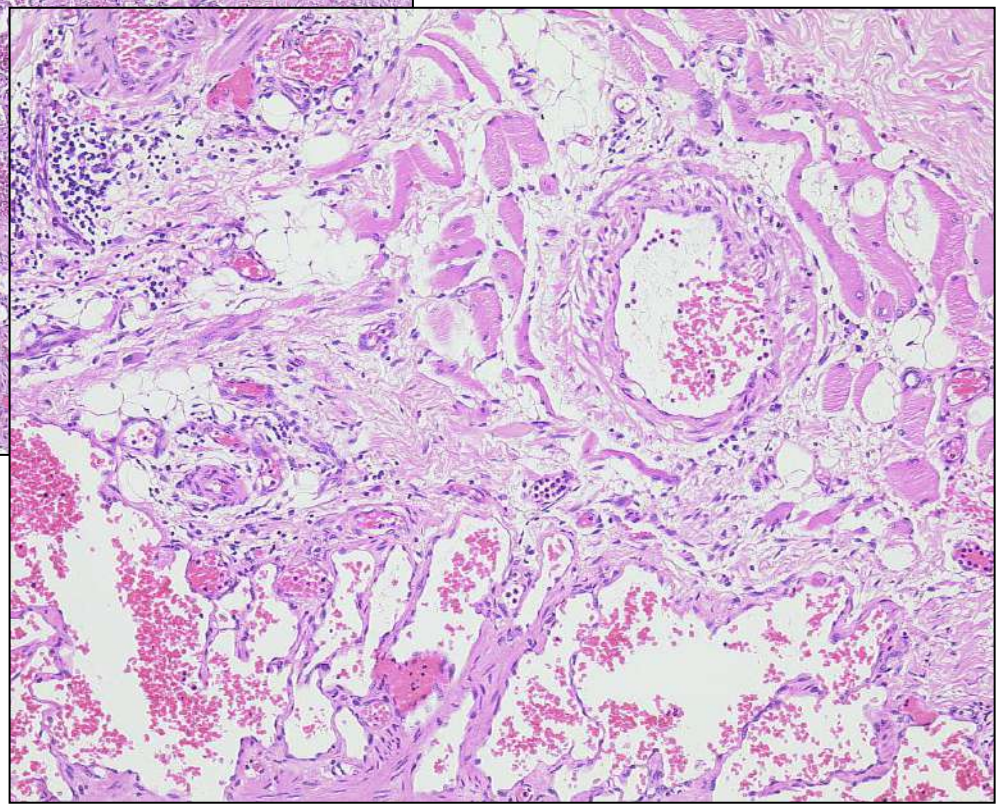
„Defects in WT1 signaling may underlie the inability of malformation endothelial cells to undergo physiologic apoptosis and remodeling.“



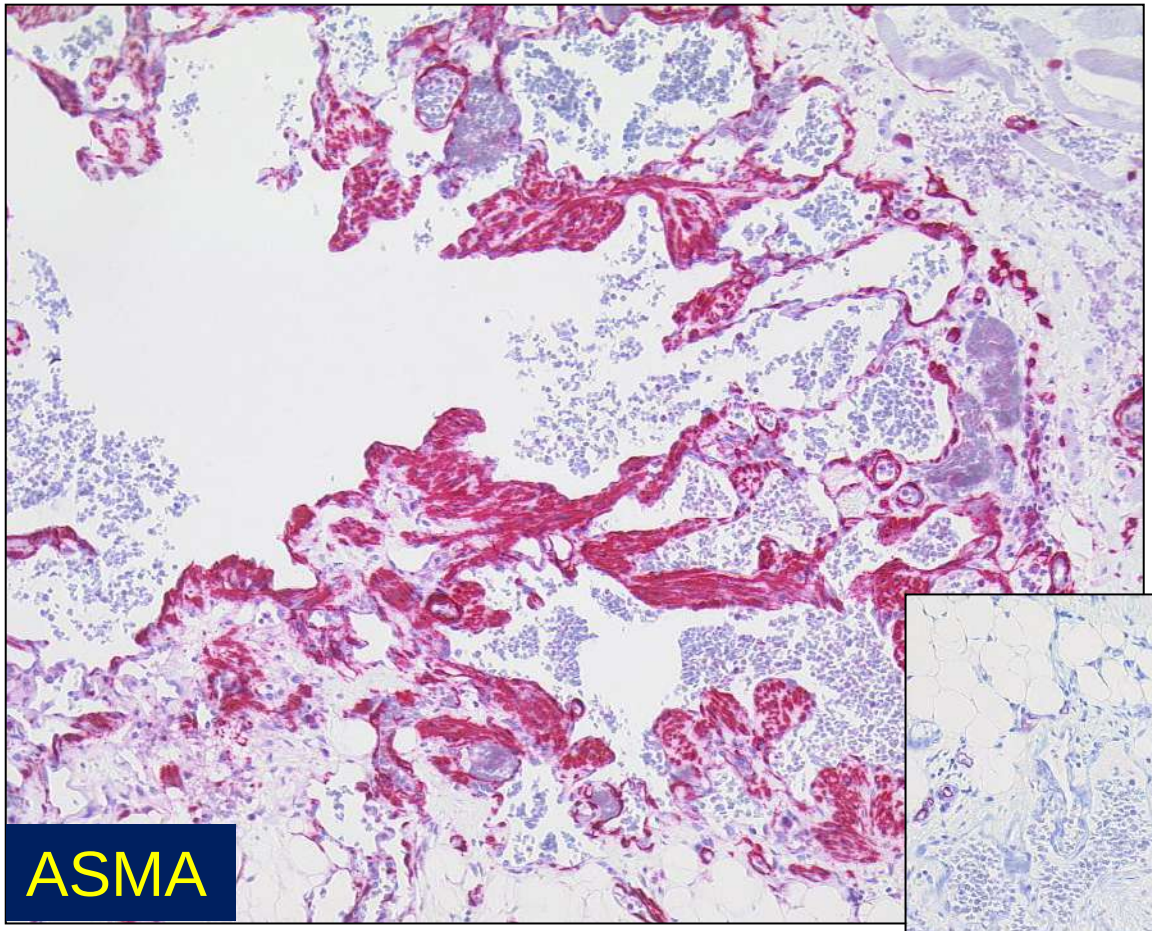


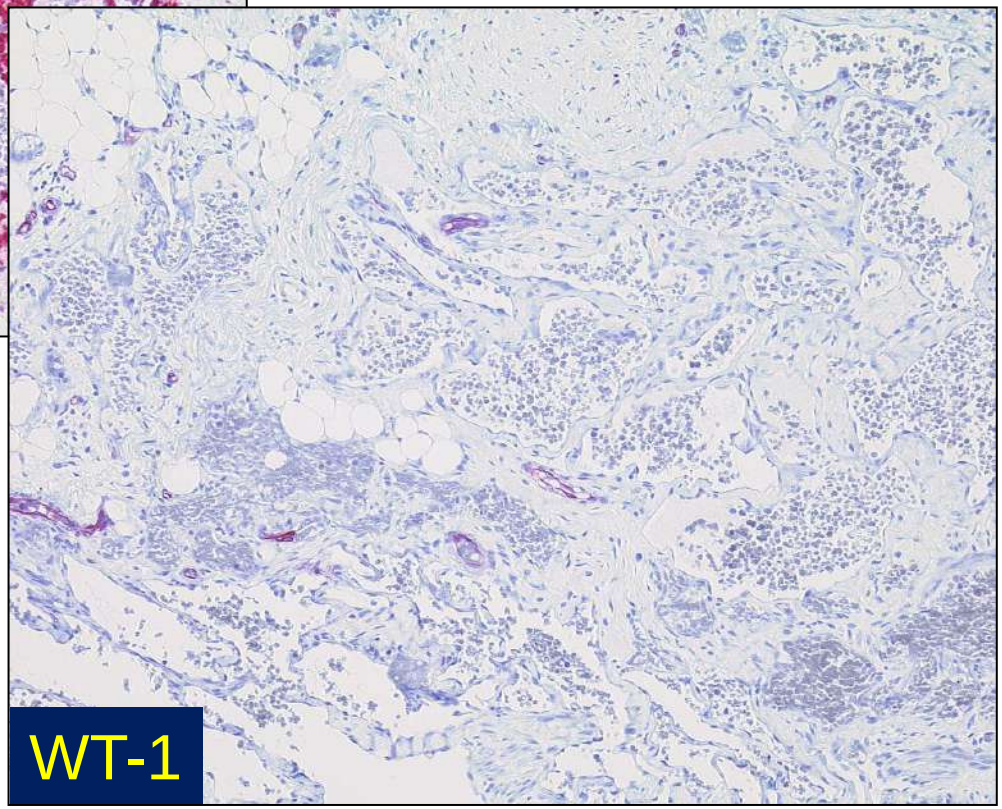
WT-1 (6F-H2, N-terminus)
cytoplasmic staining
of endotheliel cells
6F-H2, WT49, EP122
recommended by NordiQC

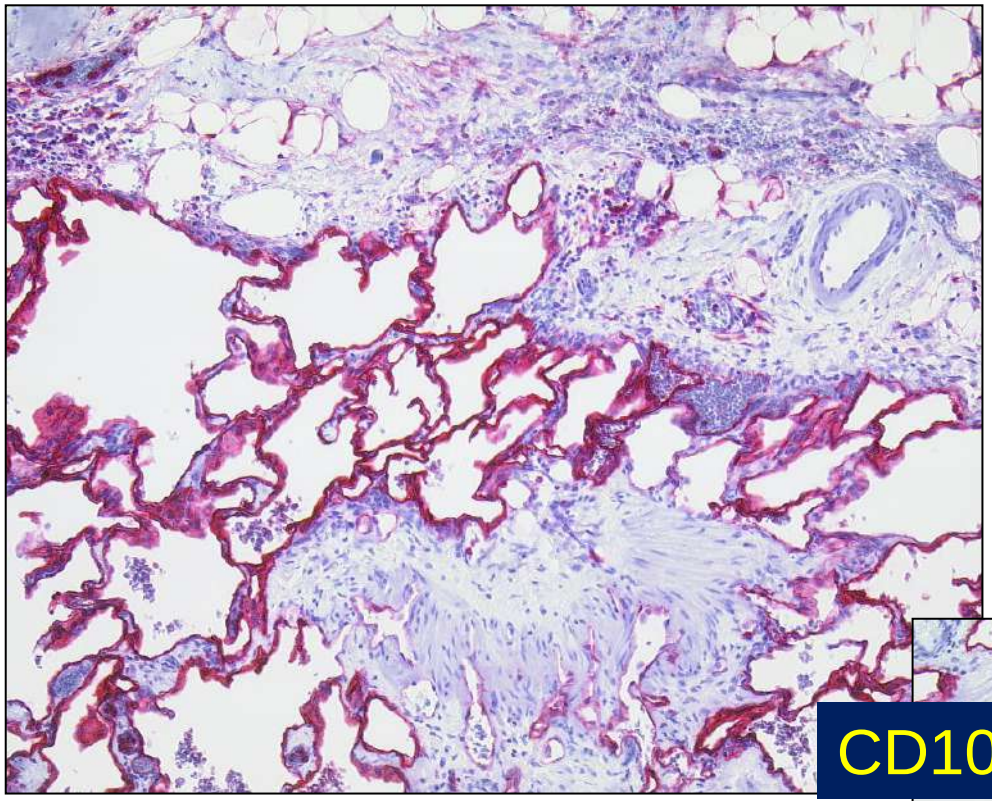




M, 21 years, large vascular lesion, trunk

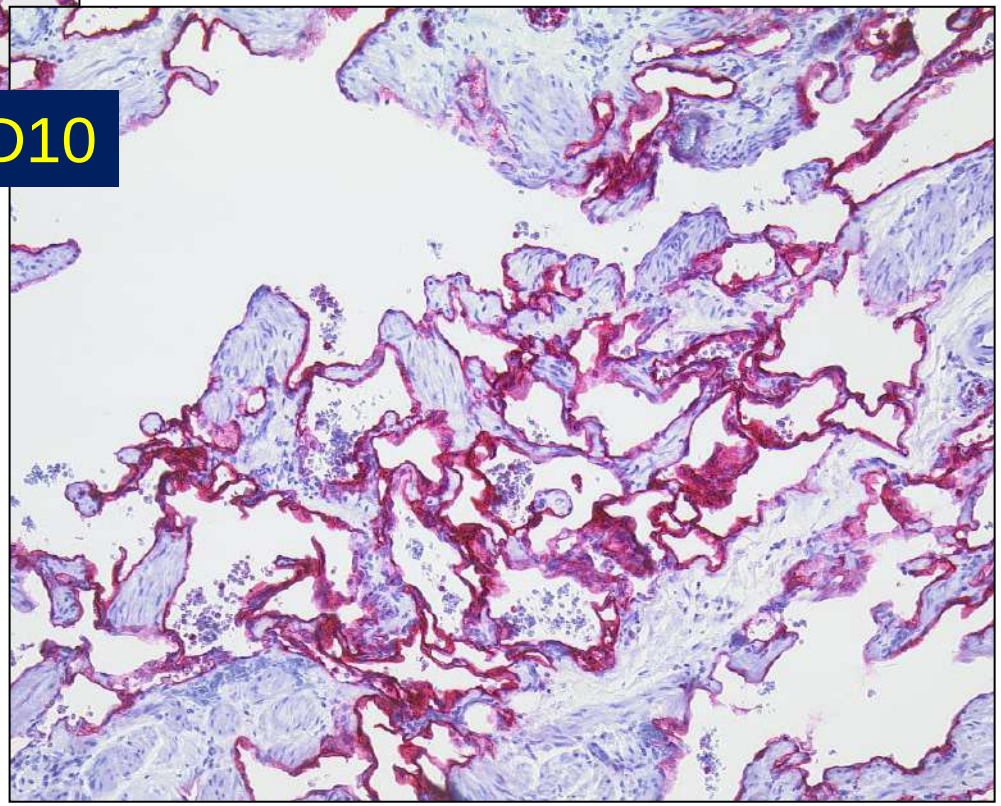

ASMA


WT-1



CD10

CD10 is expressed in endothelial cells of vascular malformations
Mod Pathol 2018; 31: 578A



Vascular Malformations

- relatively frequent (0.3% of population), genetically very heterogeneous
- disturbances in vessel development in the 4th-10th week of pregnancy, manifestation often later, no regression
- proper diagnosis also of underlying genetic changes is important for treatment

    Rapamycin in lymphangiomatous malformations
    Alpesilib in PIK3CA associated overgrowth syndroms (Nature 2018; 558: 540-546)

Vascular Malformations + Genetics

PIK3CA-mutations: PROS-PIK3CA associated overgrowth syndrome (Alpesilib treatment)

- CLOVES syndrome (congenital lipomatous proliferation, vascular MF, epidermal naevi, scoliosis)
- Megalencephaly-capillary malformation
- Dysplastic Megalencephaly
- CLAPO syndrome (capillary MF lower lip, lymphatic MF head/neck, overgrowth)

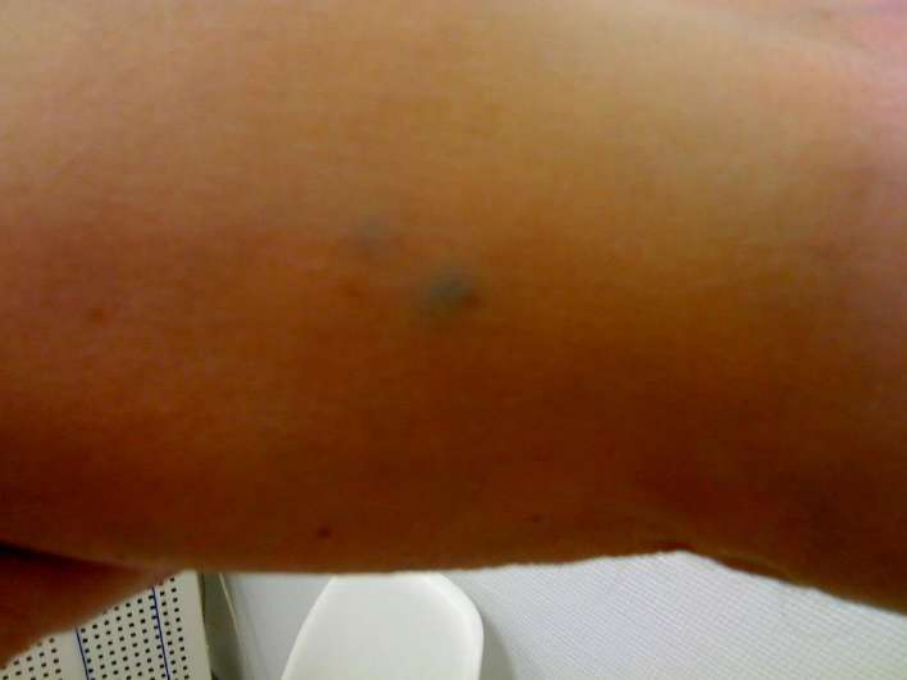
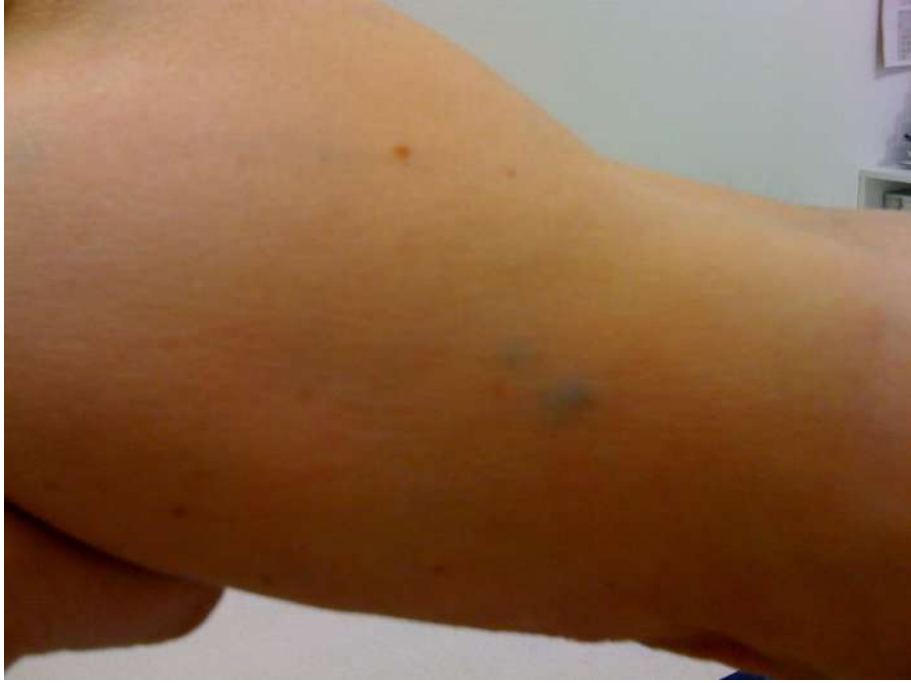
RASA1 mutations
- CM-AVM syndrome (elongated vessels)
- Parkes-Weber syndrome (arteriovenous MF + overgrowth)

GNAQ/GNA11 mutations
- Sturge-Weber syndrome
- capillary MF + overgrowth of the extremities

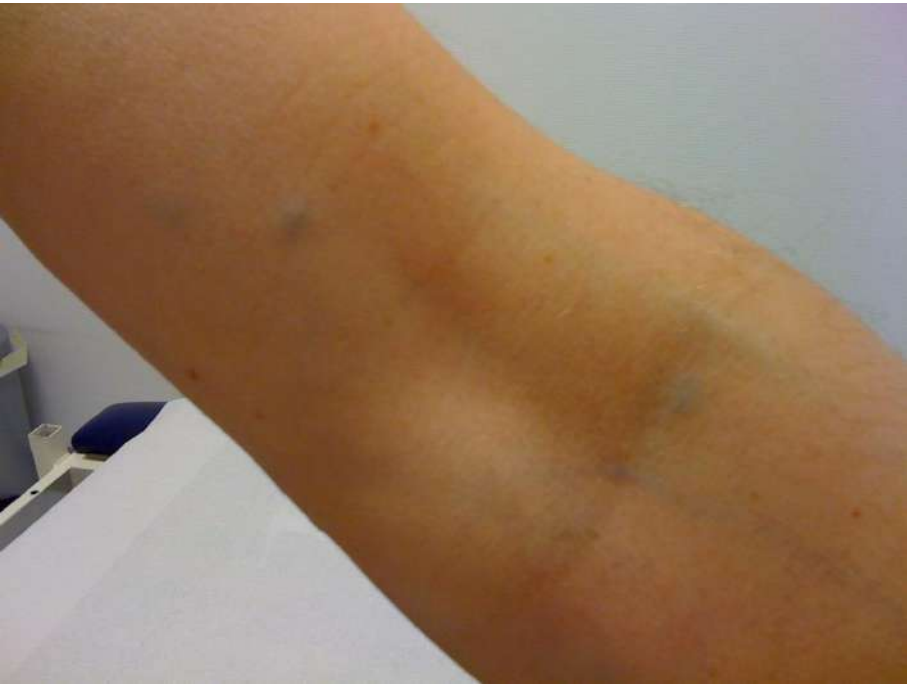
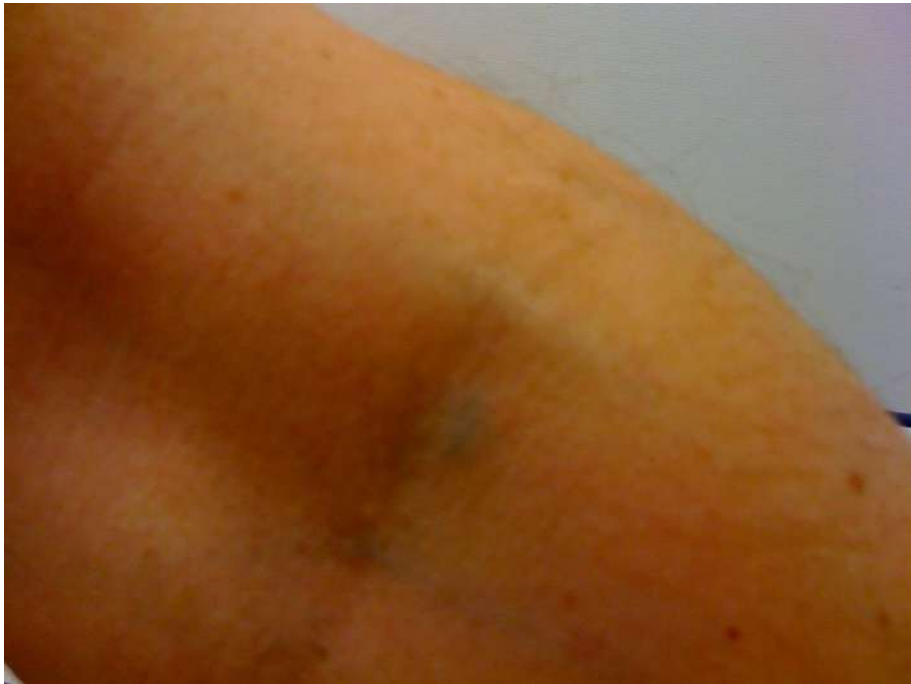
IDH1/2 mutations
- Mafucci syndrome

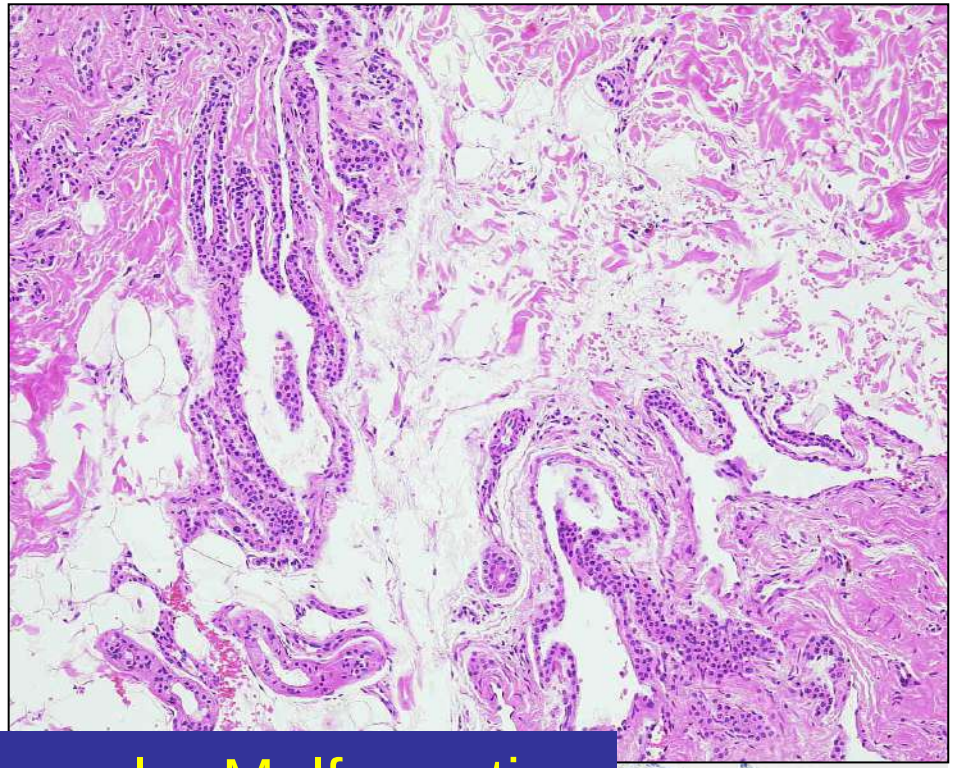
PTEN mutations
- PTEN hamartomatous syndrome

AKT1 mutations
- Proteus syndrome

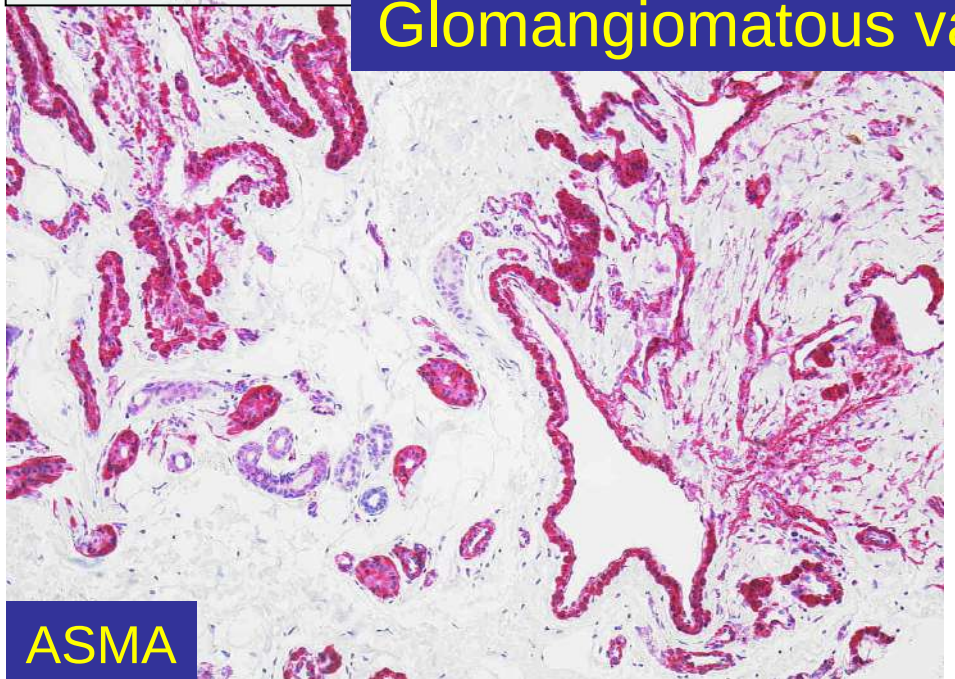



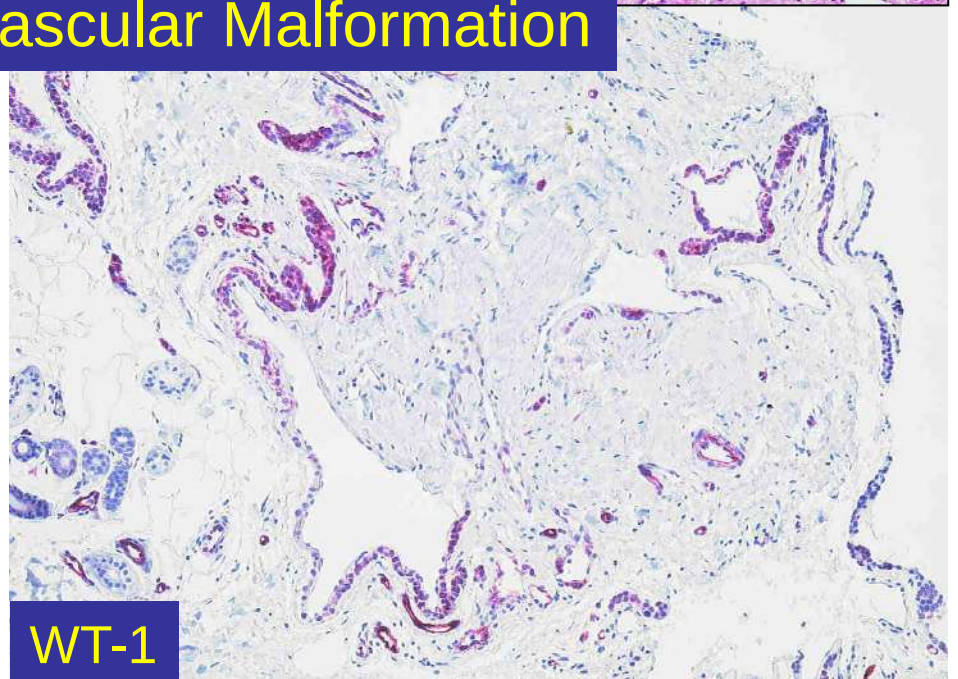
M, 50 years, multiple lesions, grow slowly, Kaposi´s sarcoma was suspected

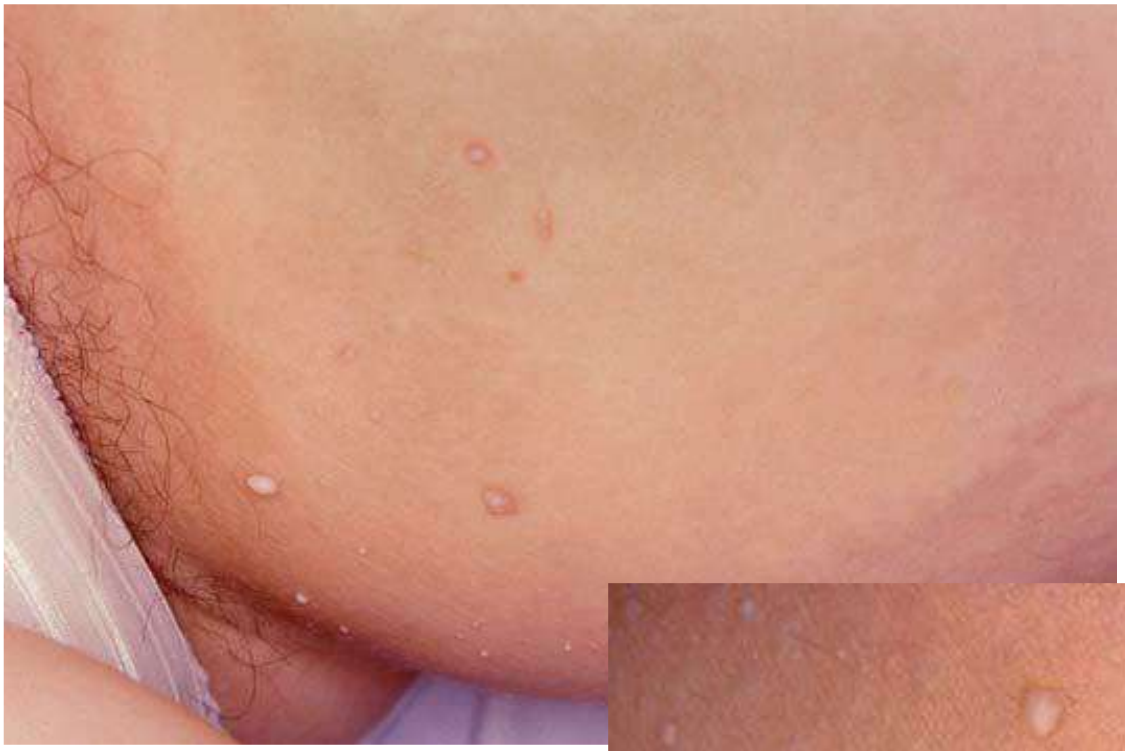



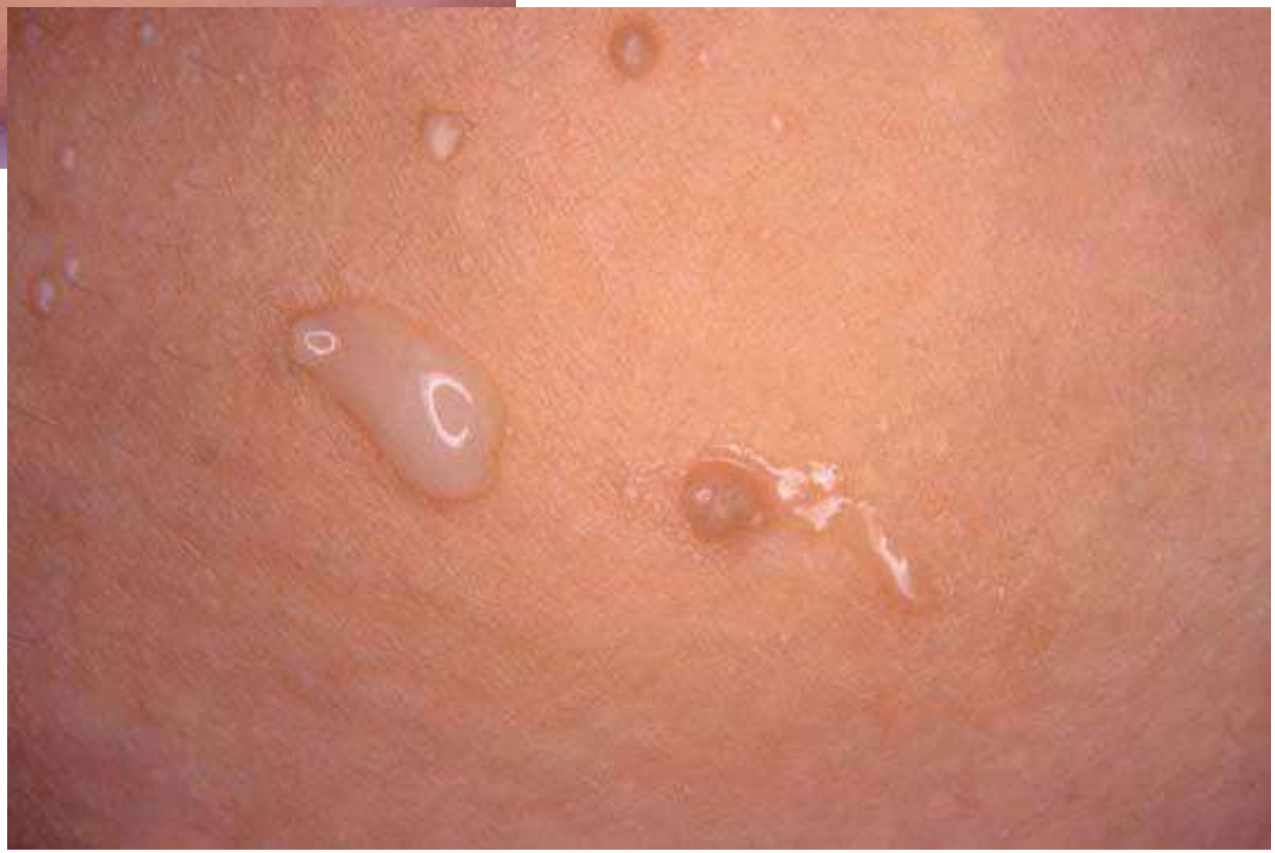


Glomangiomatous vascular Malformation

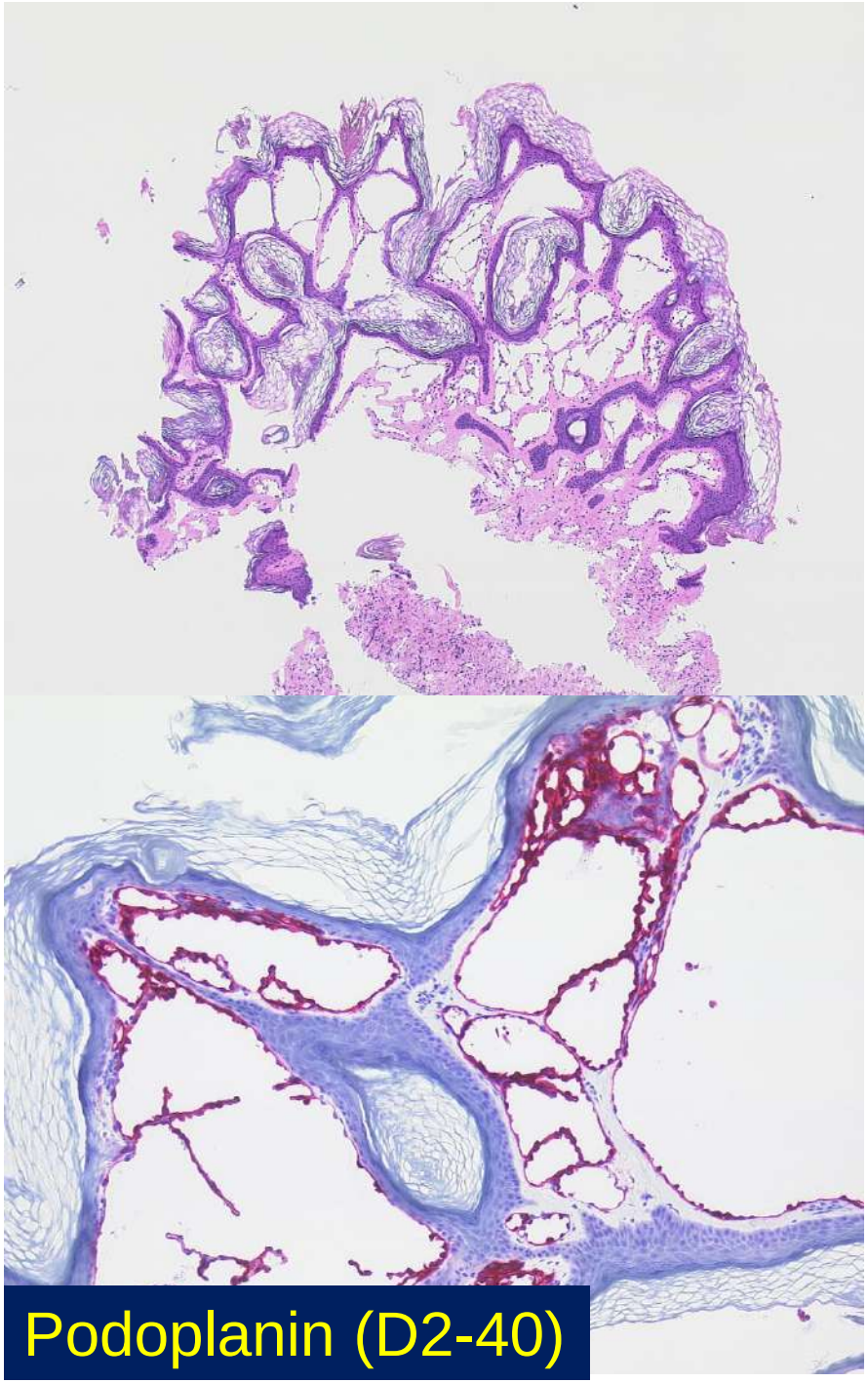


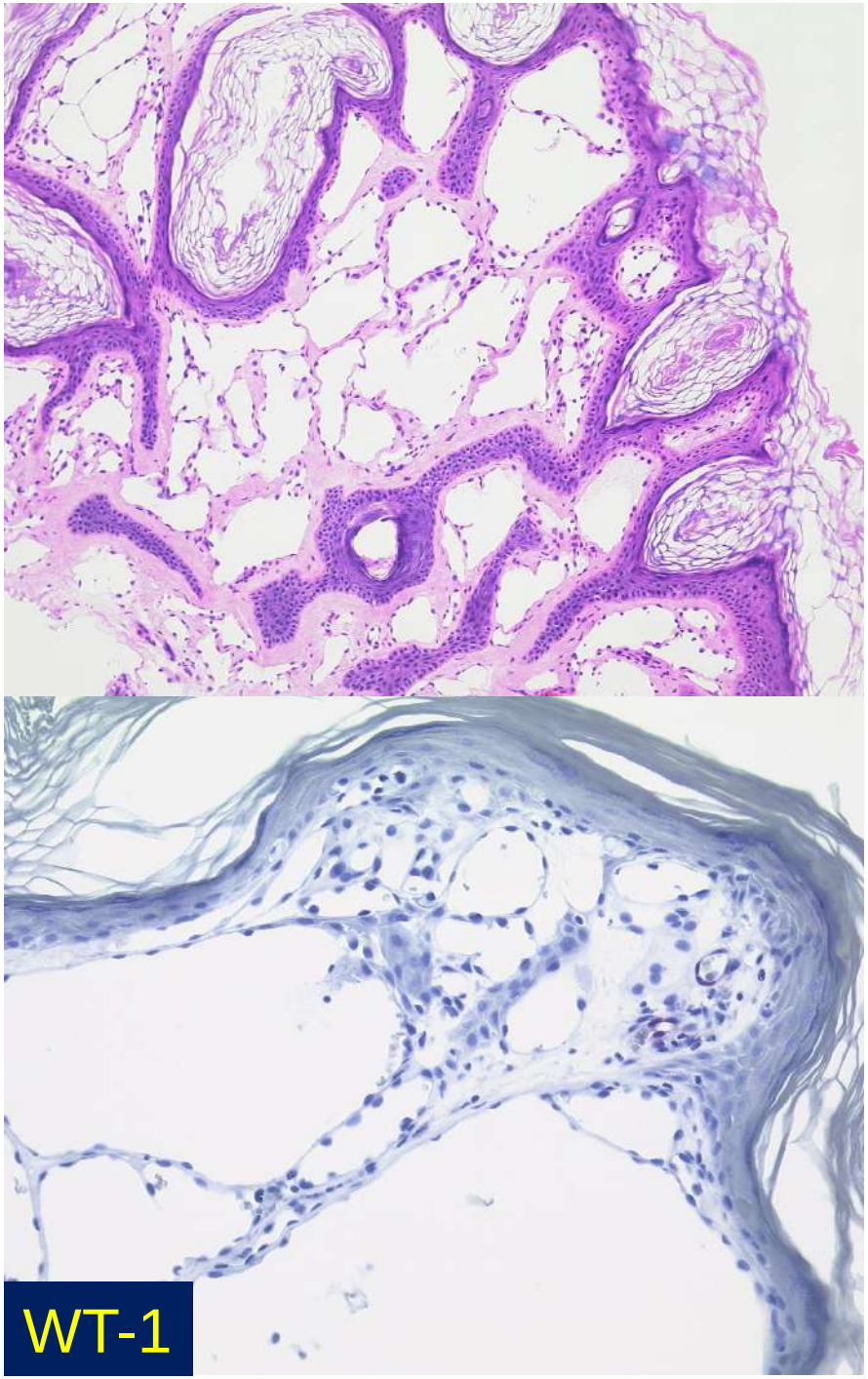






lymphangioma /
lymphangieectasia

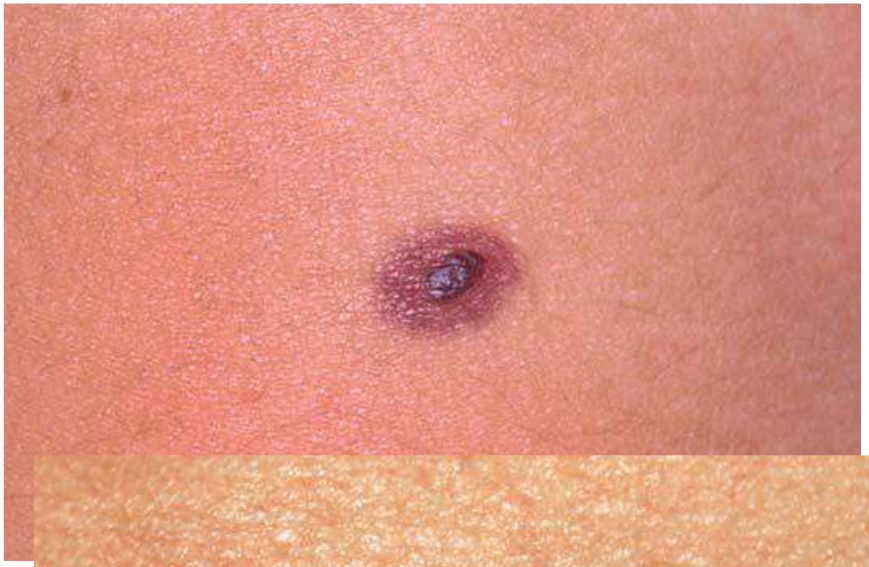

Podoplanin (D2-40)

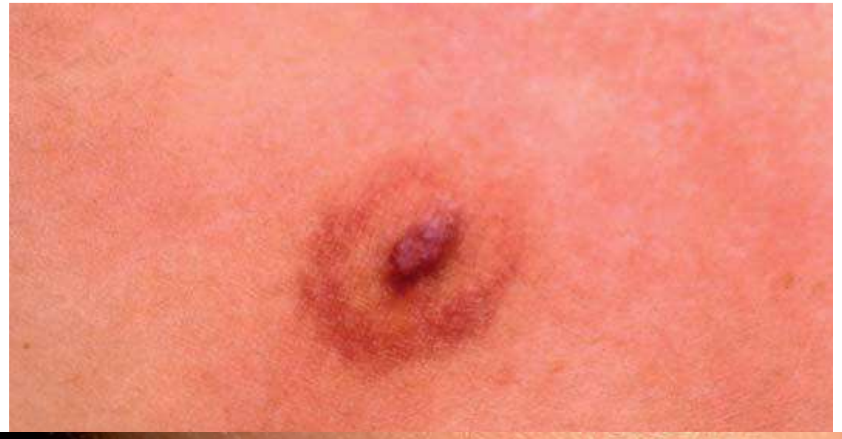

WT-1

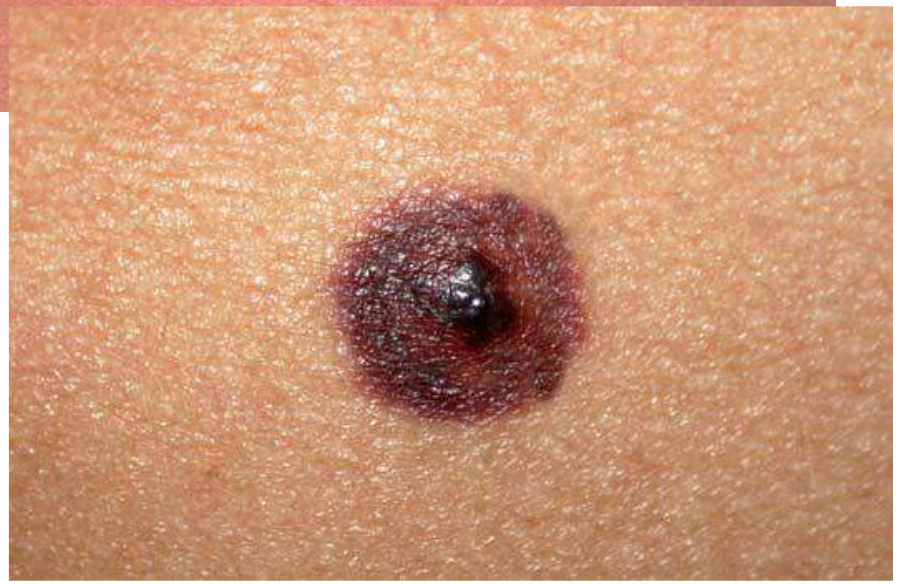
Superficial haemosiderotic lymphovascular Malformation

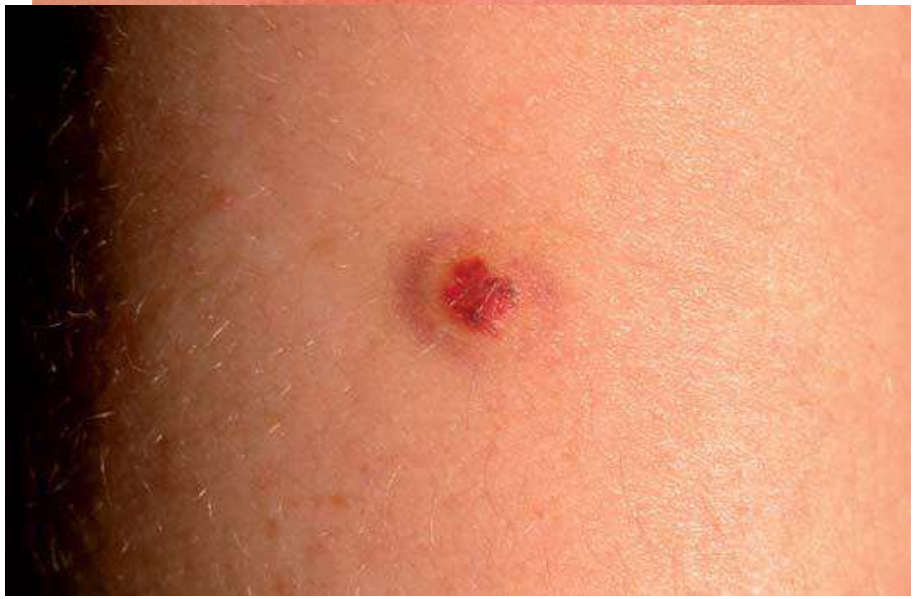
(„targetoid haemosiderotic haemangioma“
„hobnail haemangioma“)

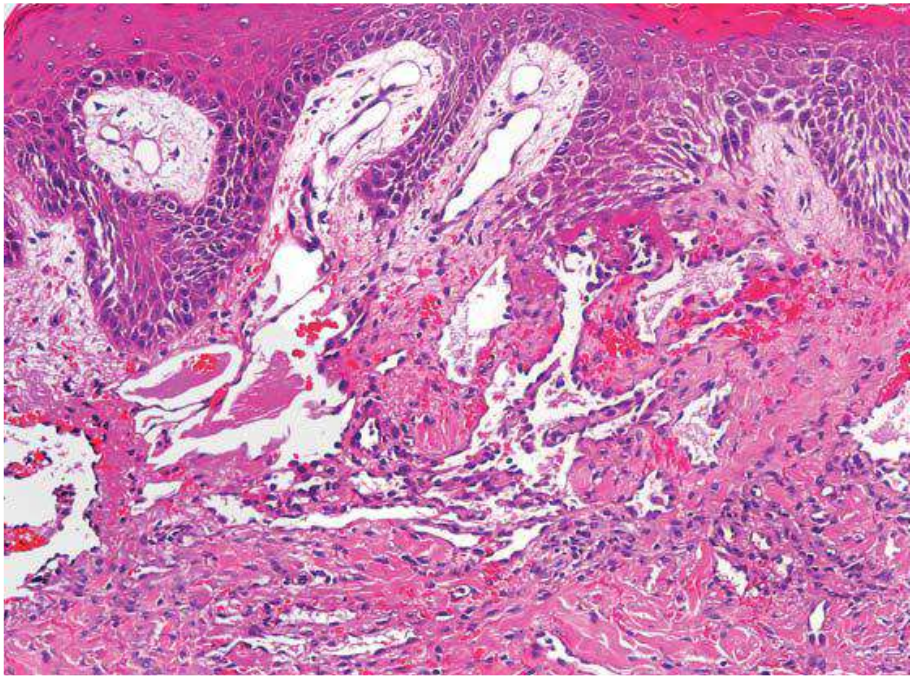
Joyce JC et al. Pediatr Dermatol 2014; 31: 281

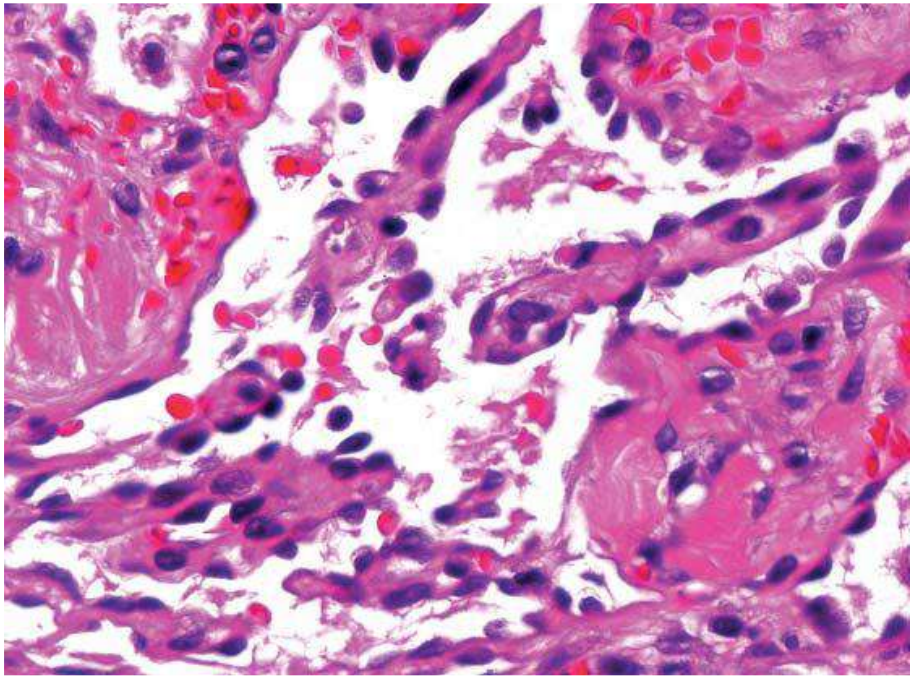


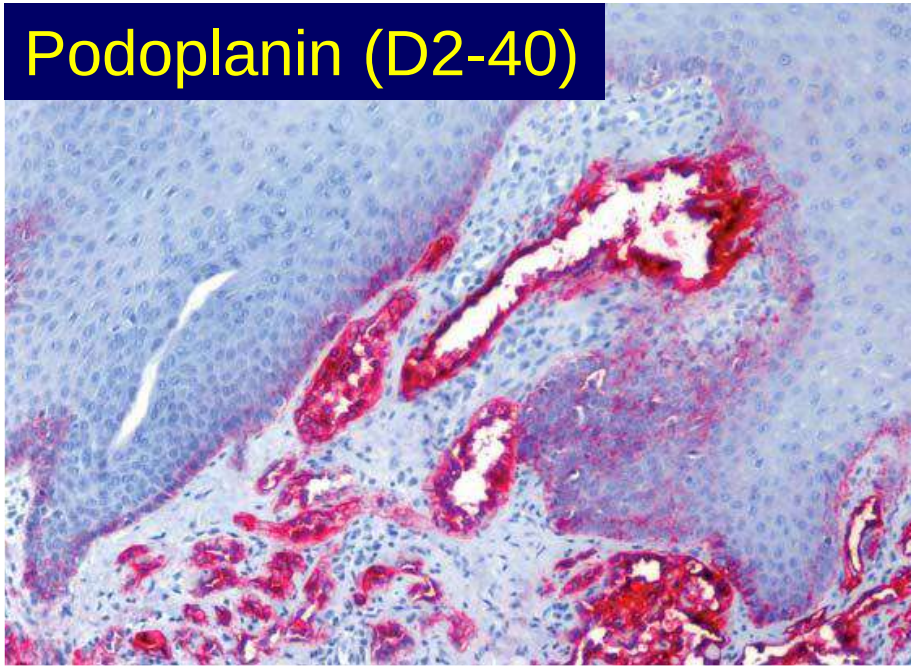


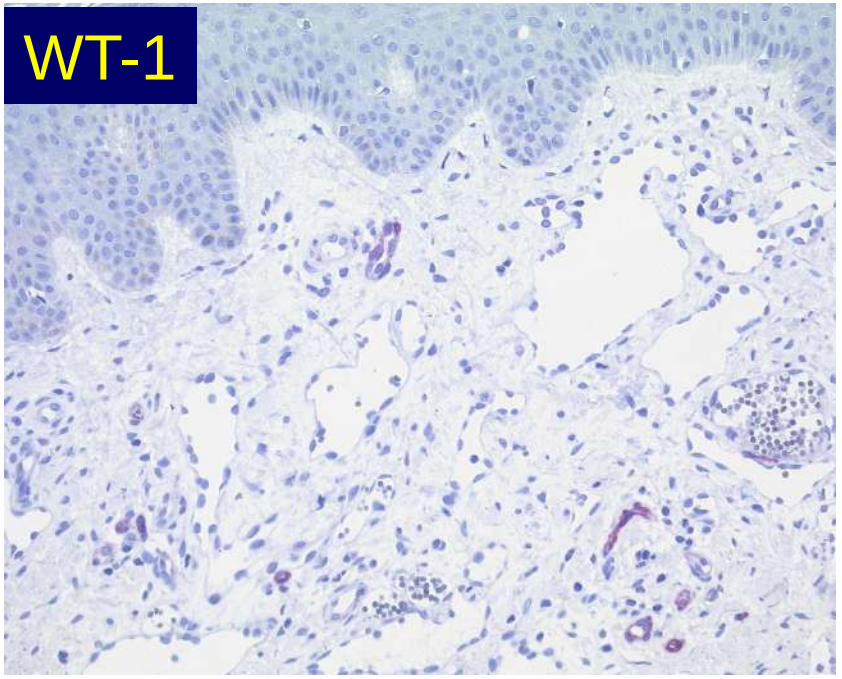




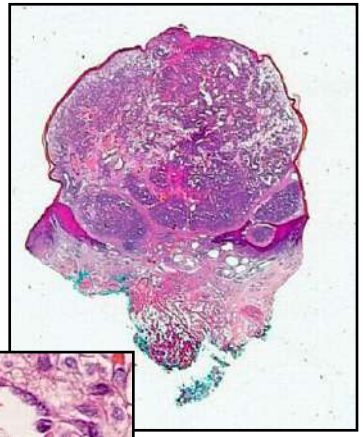


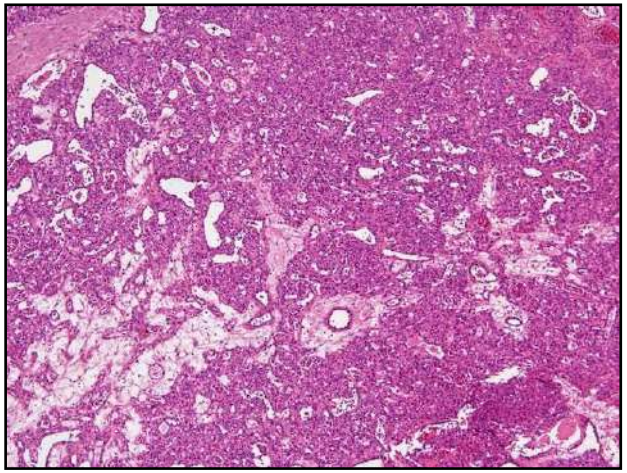


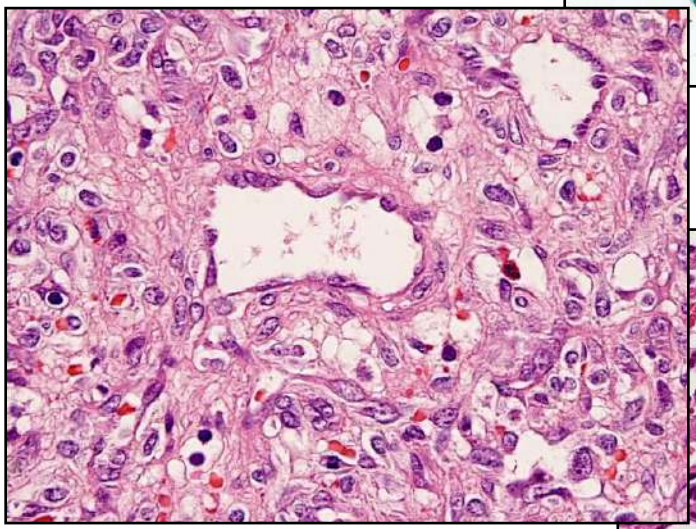

Podoplanin (D2-40)

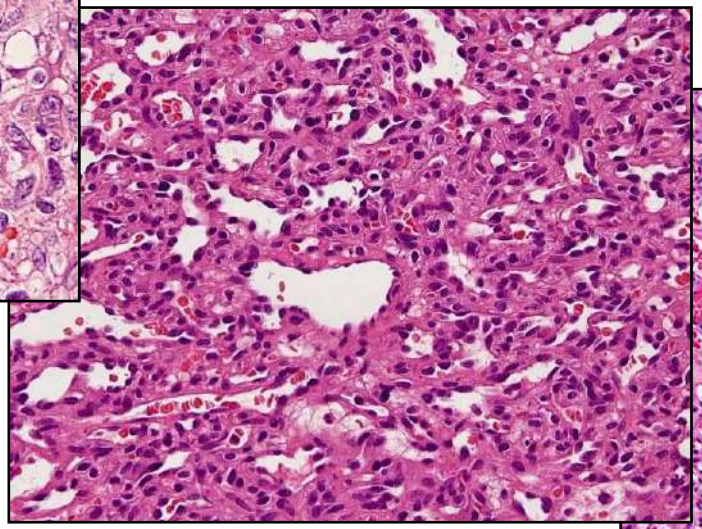

WT-1

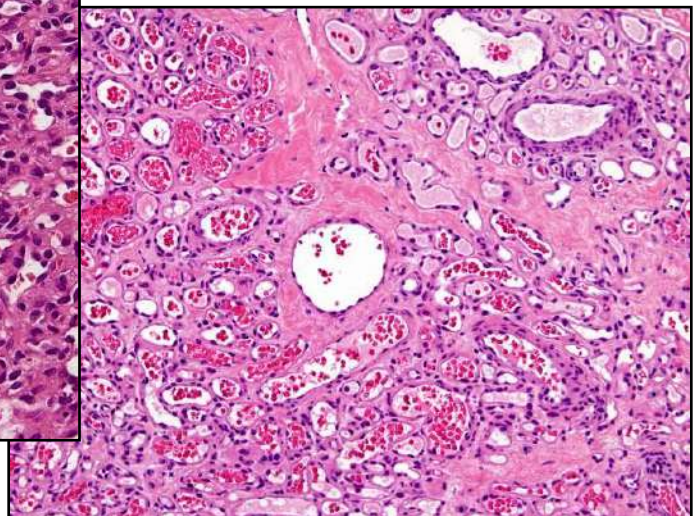
Differential Diagnosis: capillary vascular Malformation - pyogenic Granuloma («lobular capillary haemangioma»)



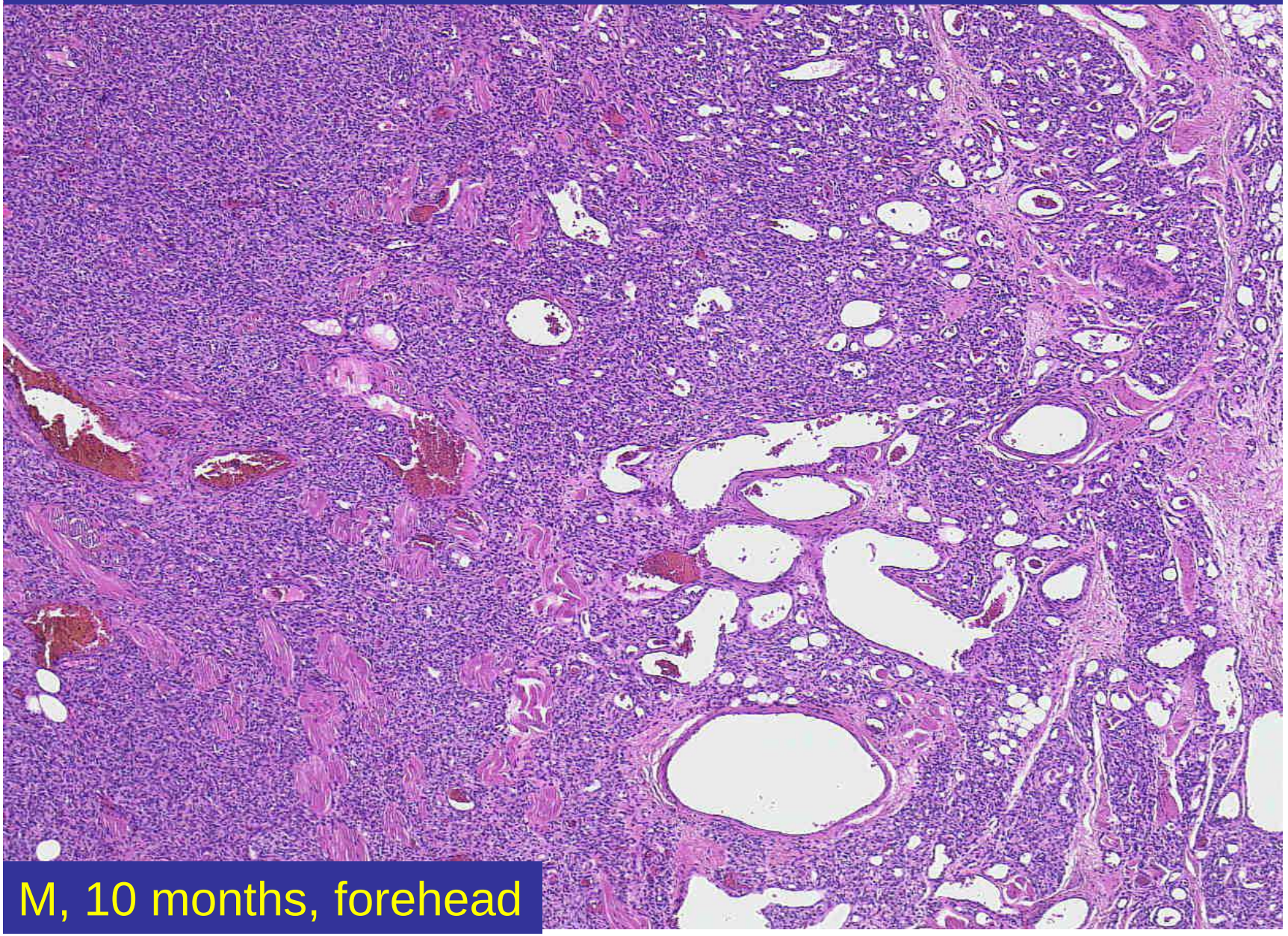




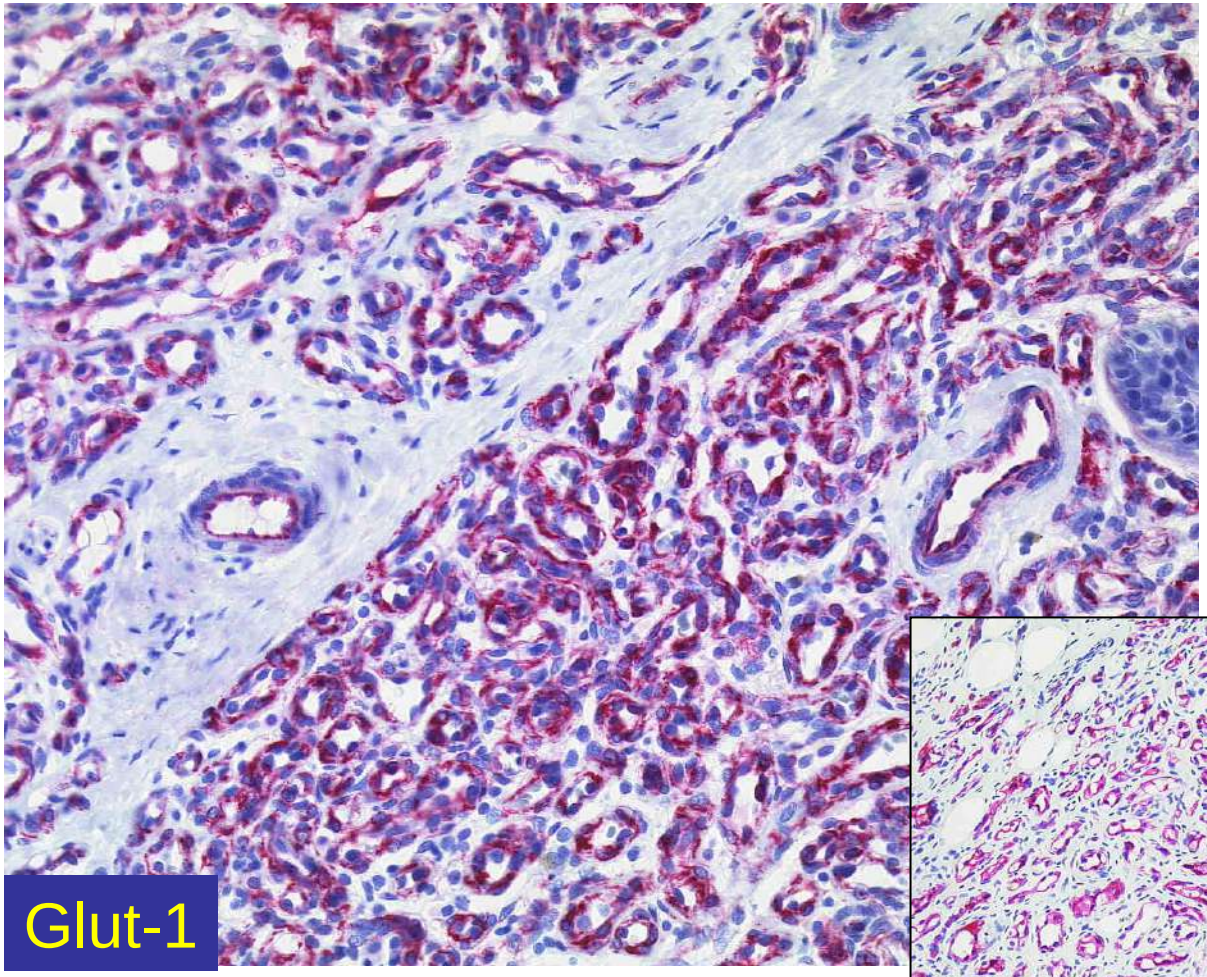


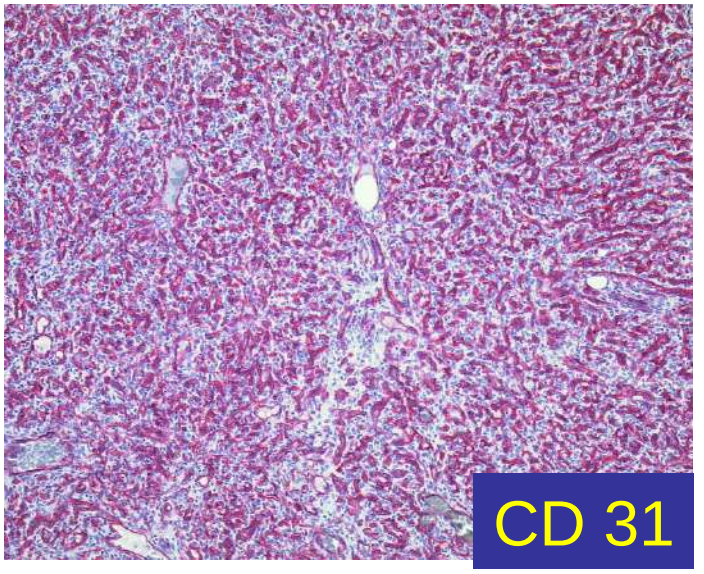


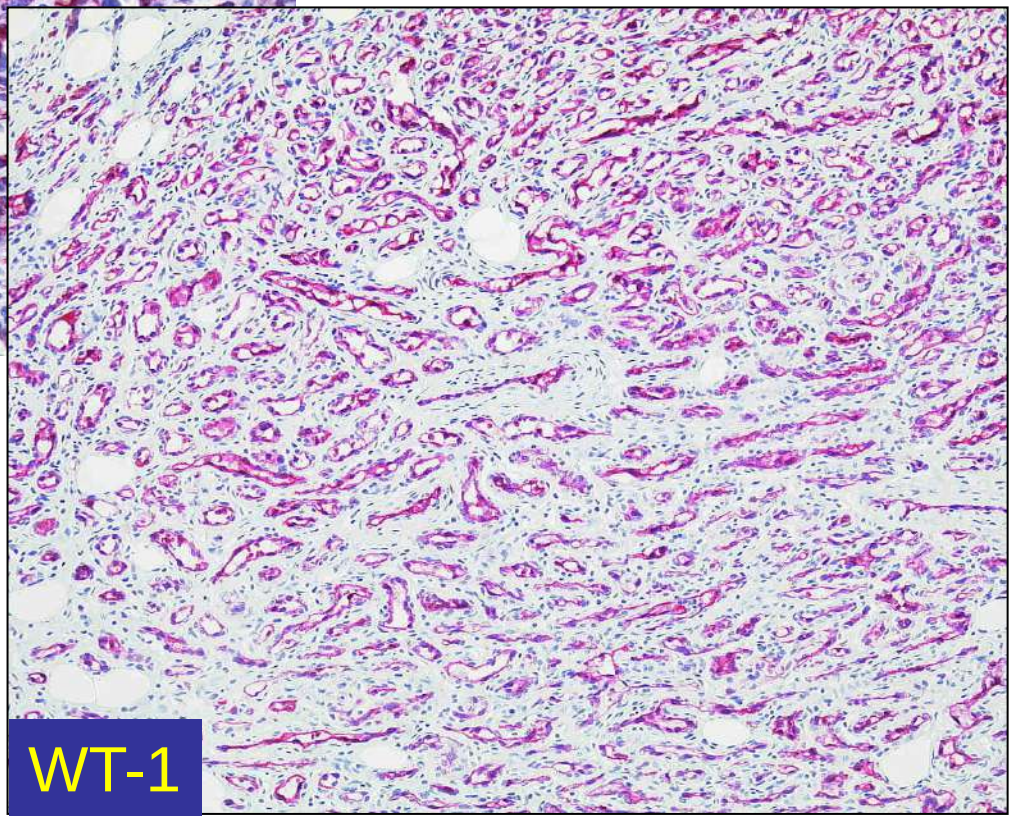
Differential Diagnosis: capillary vascular malformation - cellular infantile Haemangioma



M, 10 months, forehead

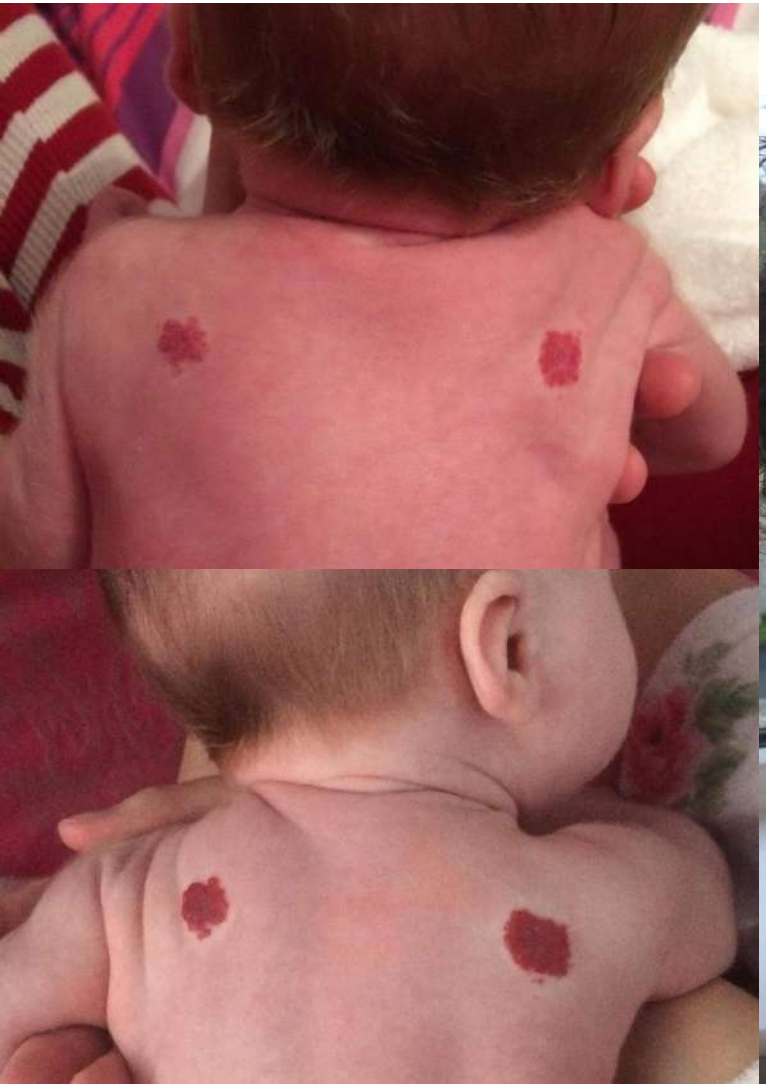

Glut-1


CD 31


WT-1

infantile Haemangioma

commonest benign tumour of childhood (4-5%)
rapid proliferative growth phase
slow involution phase
superficial, deep, mixed
localized, segmental, multifocal
frequent head / neck region
lobular, cellular, capillary proliferation
Glut-1+ (placental differentiation, hypoxia induces angioneogenesis)
vascular markers +
complete layer of ASMA-positive myopericytes



Complications

infiltrative growth

superinfection, ulceration

PHACE (posterior fossa malformations, haemangiomas
arterial anomalies, cardiac defects,
eye abnormalities, sternal clefting) Syndrom

involvement of visceral organs

prominent scarring, destruction

increased risk in segmental and multifocal
haemangiomas

sucessful treatment with Propranolol!

Cellular infantile Haemangioma: Glut-1 +

DD: Congenital Haemangioma

Rapidly Involuting CH

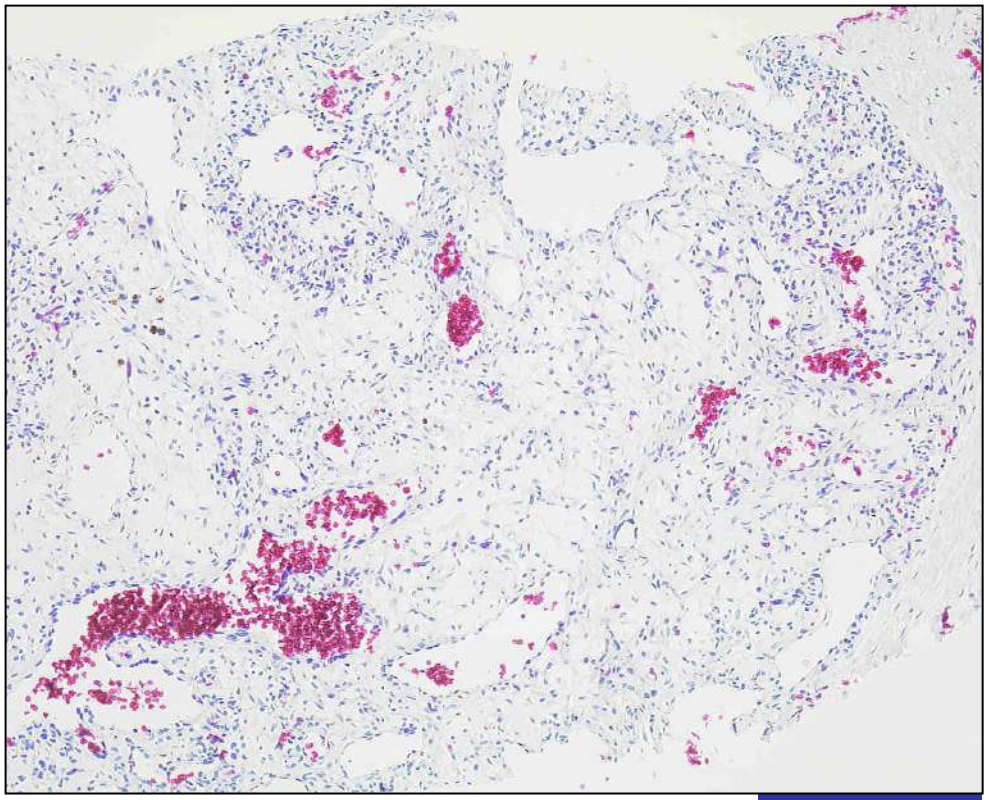
- Glut-1 **negative**
- rapid shrinking
- often thrombosis

Non Involuting CH

- Glut-1 **negative**
- persist over time
- grow proportionaly with the child
- arteriolobular fistulae

Partially Involuting CH

- Glut-1 **negative**



Glut-1

The histopathology of congenital haemangioma and its clinical correlations: a long-term follow-up study of 55 cases

S El Zein et al. Histopathology 2020; 77: 275

- histopathological features **are similar** in all three subtypes
- histopathological features are related to the time since disease onset
- RICH, NICH, and PICH **are a single entity**
- intralobular expression of podoplanin was related with thrombocytopenia

Differential Diagnosis

infantile HE: **Glut-1 +, WT-1 +**
(Propranolol sensitive)

congenital HE: **Glut-1 -, WT-1 +**

vascular MF: **Glut-1 -, WT-1 -,**
CD10 +

Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas

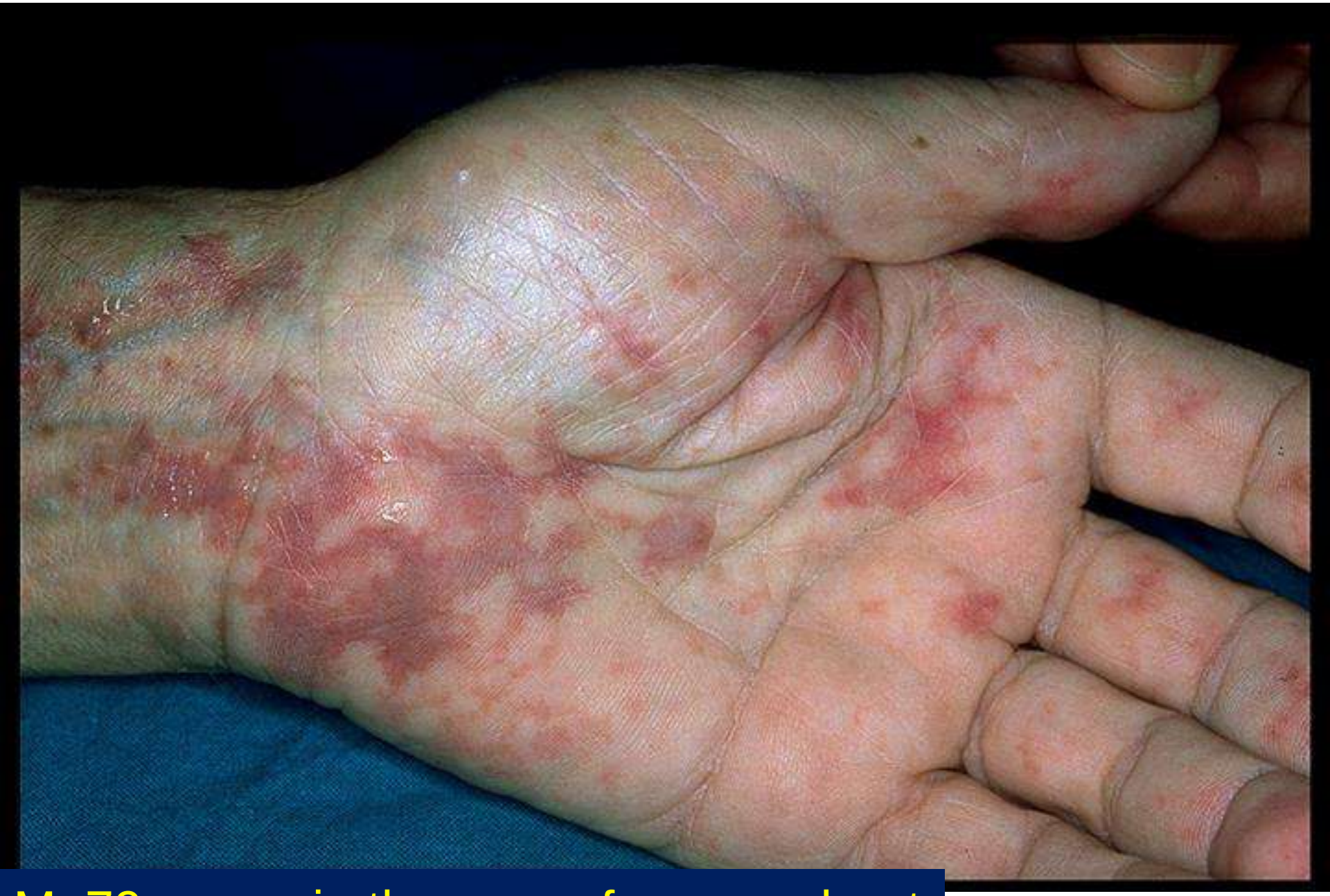
Angiomatoses

- diffuse dermal Angiomatosis
- reactive Angioendotheliomatosis
- Lymphangiomatosis (of the limbs)
- multifocal Lymphangioendotheliomatosis with thrombocytopenia
- prurigiform Angiomatosis
- bacillary Angiomatosis
- kaposiform Lymphangiomatosis

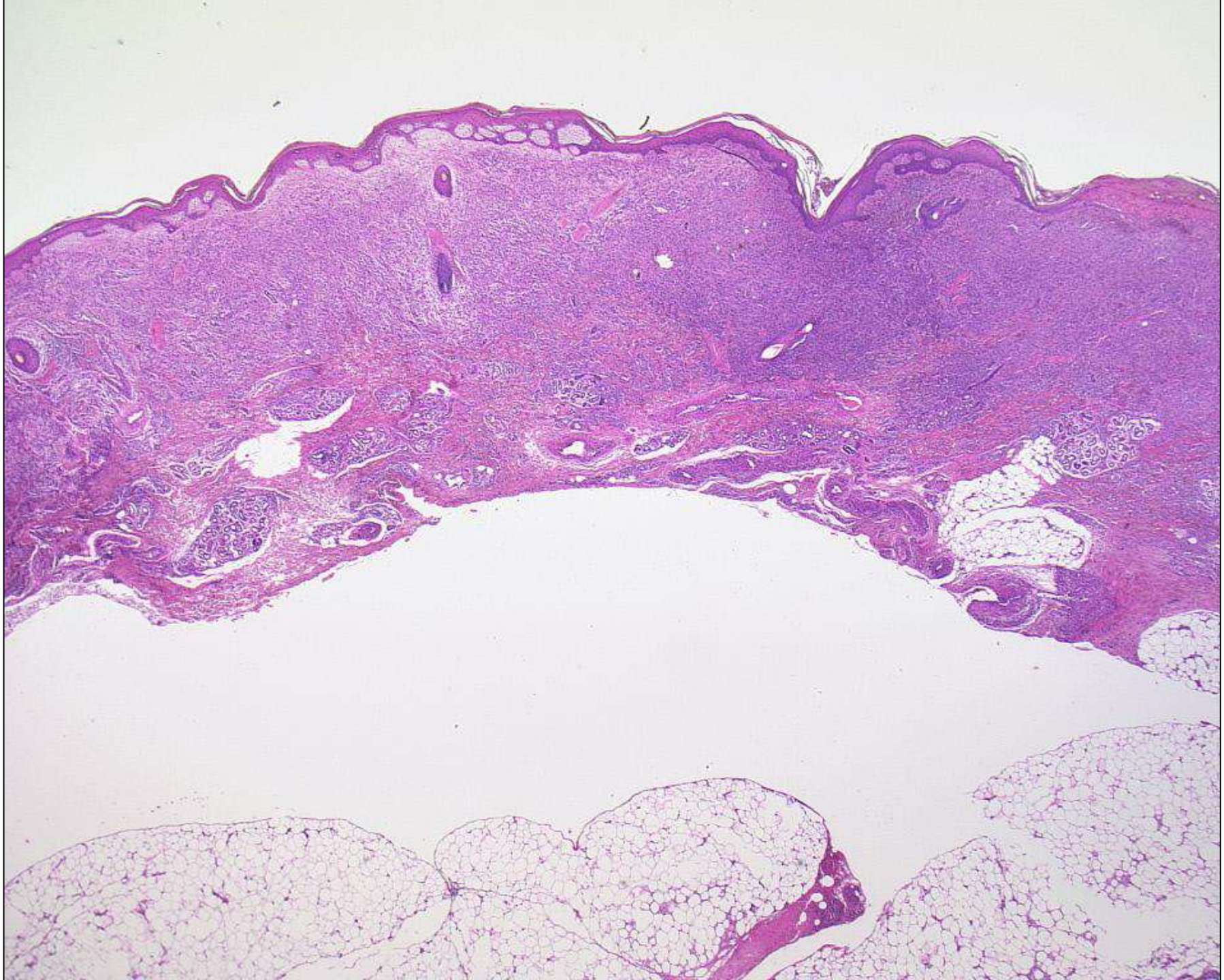
(dermis, ST, lung, mediastinum, spleen, skeleton

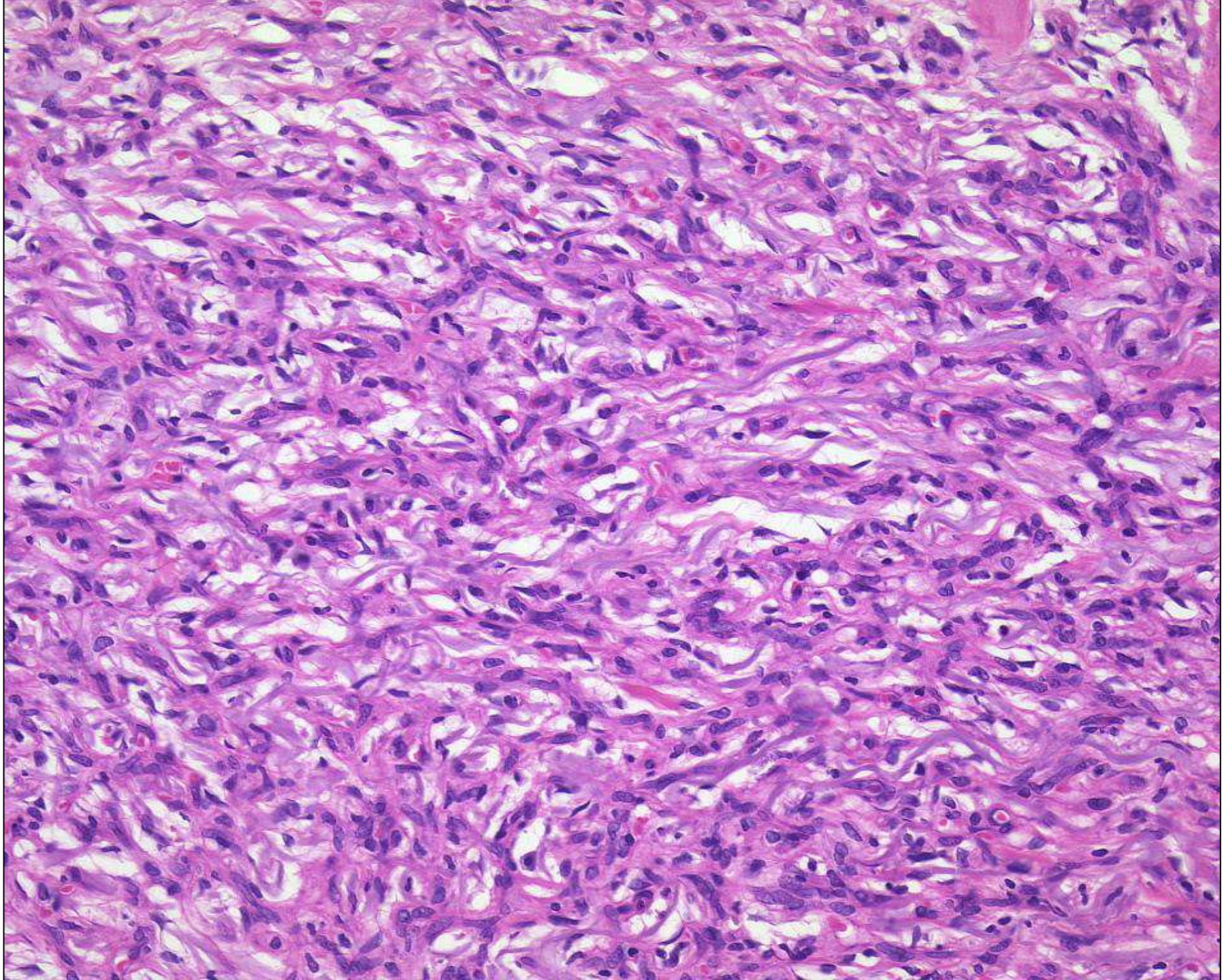
dilated lymphatics + haemosiderotic spindled endothelial cells

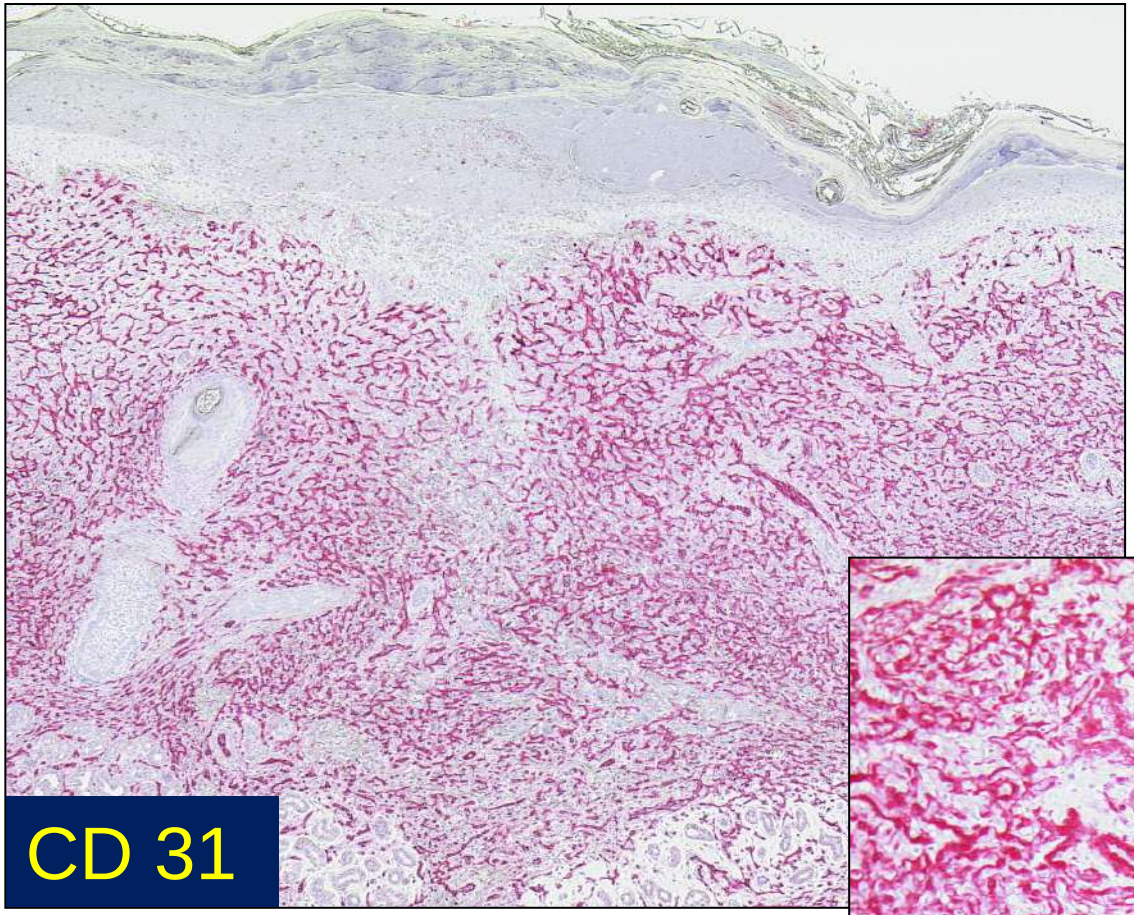
activating *NRAS* mutation, AJSP 2022; 46: 963)

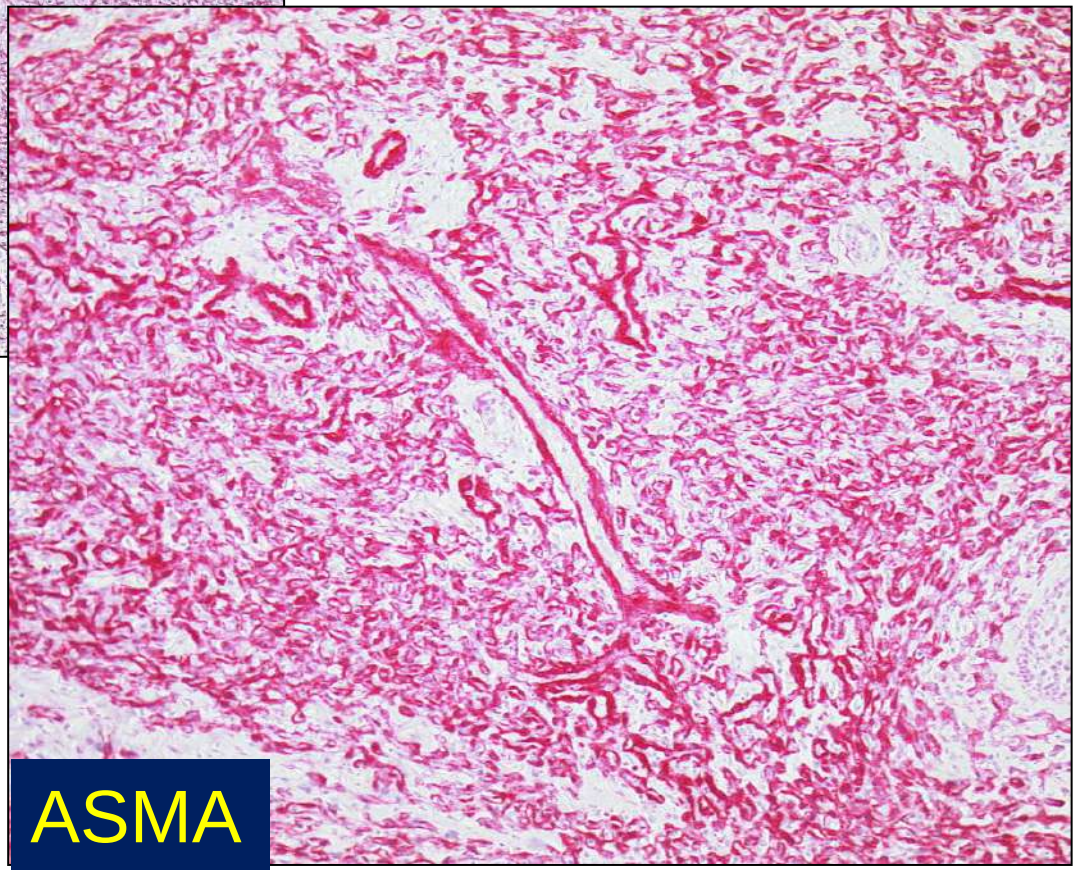


M, 79 years, in the area of an a.v. shunt






CD 31


ASMA

Diffuse Dermal Angiomatosis*

Clinicopathological Findings

- elderly patients, rapid growth
- large, ulcerated, red-violet plaques
- distal to a.v. fistula, severe atherosclerosis
- may show spontaneous regression
- diffuse proliferation of narrow vessels
- newly formed dermal vessels
- CD31 + endothelial cells, ASMA + pericytes
- mitoses, spindled cells, fibrosis
- biologically benign vascular lesion

*** Kim S et al. Arch Dermatol 2002;138: 456**

Diffuse Dermal Angiomatosis *versus* Reactive Angioendotheliomatosis

Related or identical ?

Reactive Angioendotheliomatosis:

cryoglobulinaemia, infection

intravascular endothelial proliferation

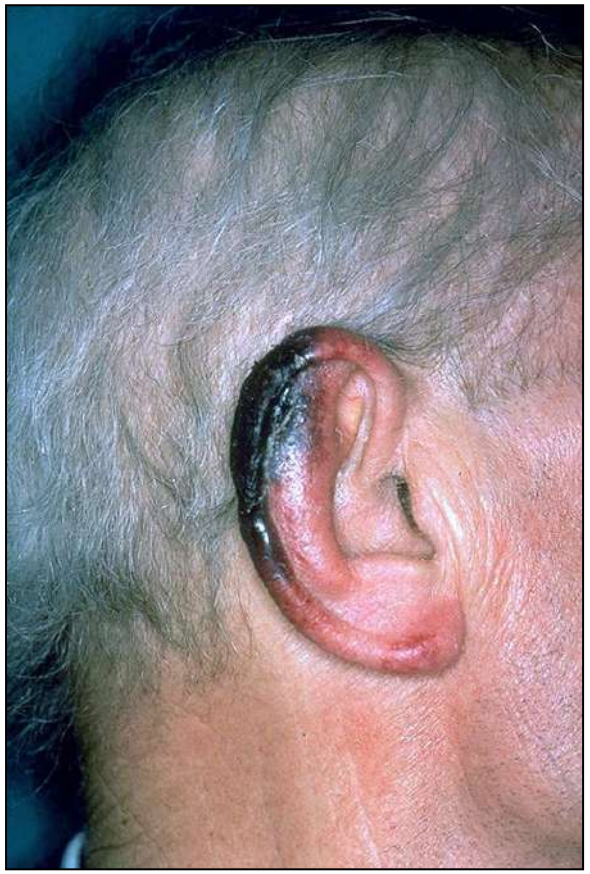
formation of capillary tufts

no proliferation of newly formed vessels

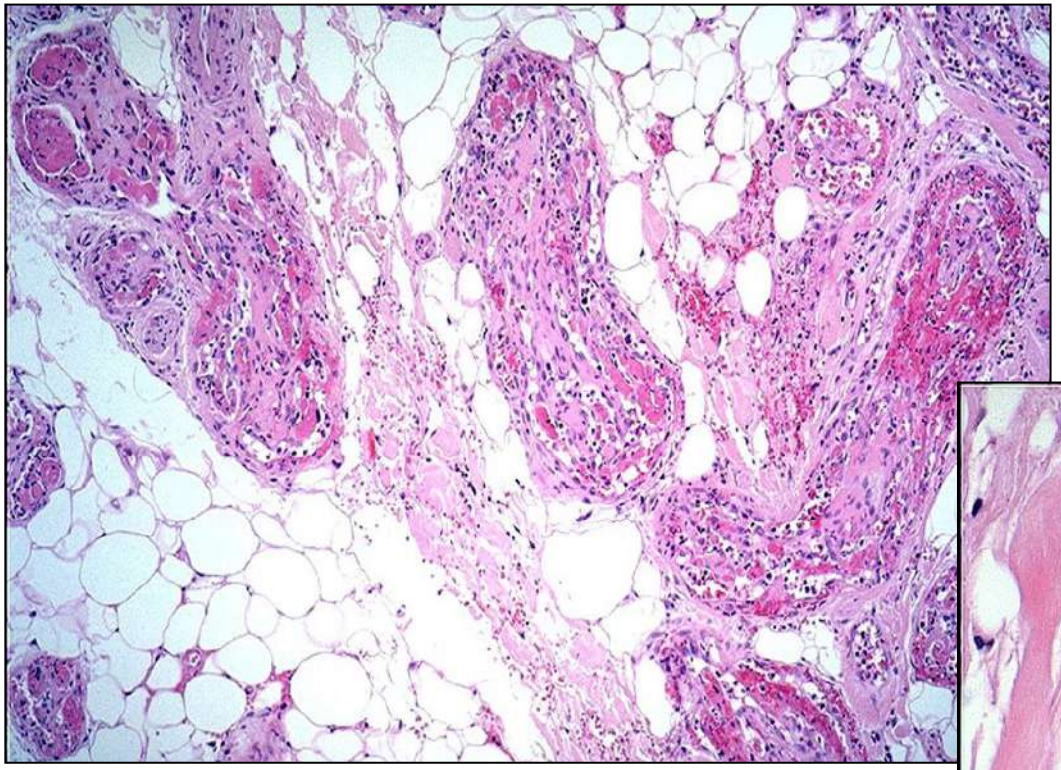
often fibrin thrombi

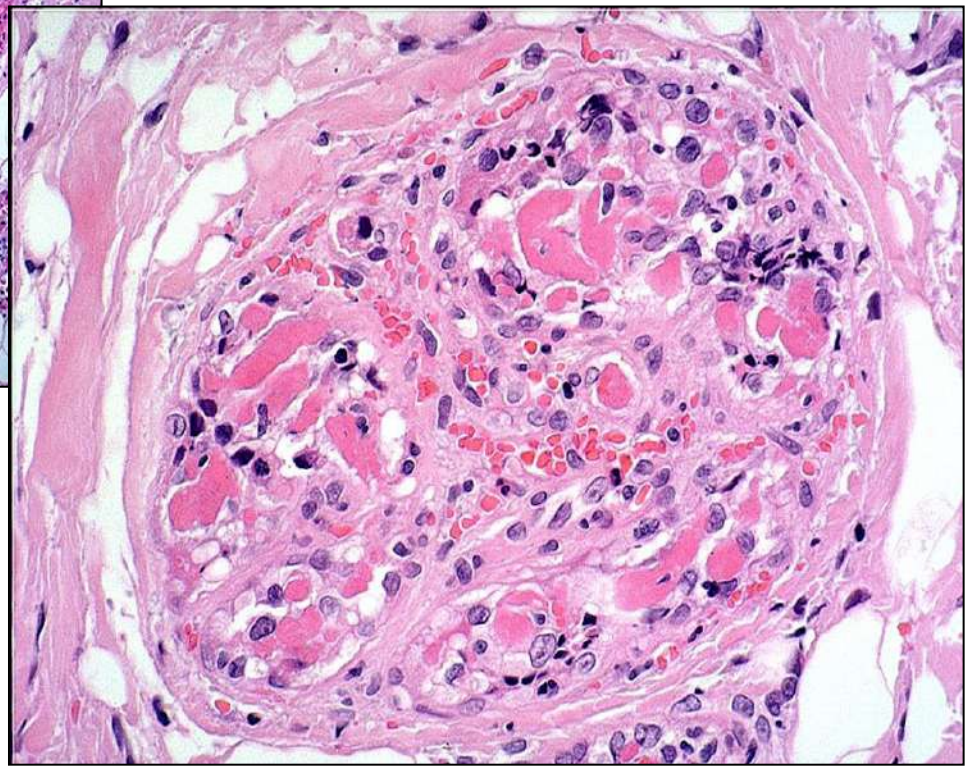
Related but not identical !

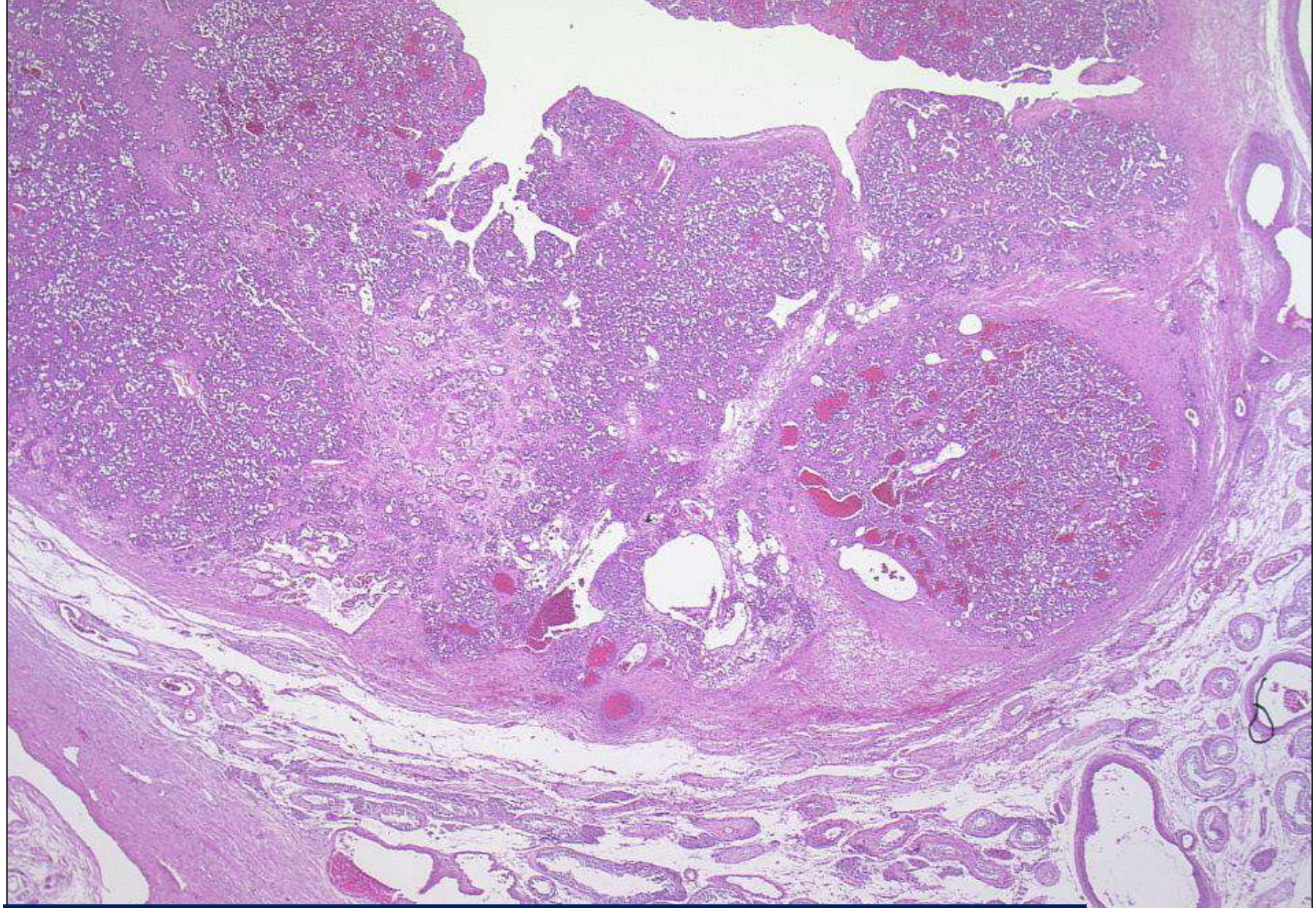
Reactive Angioendotheliomatosis in Cryoglobulinaemia



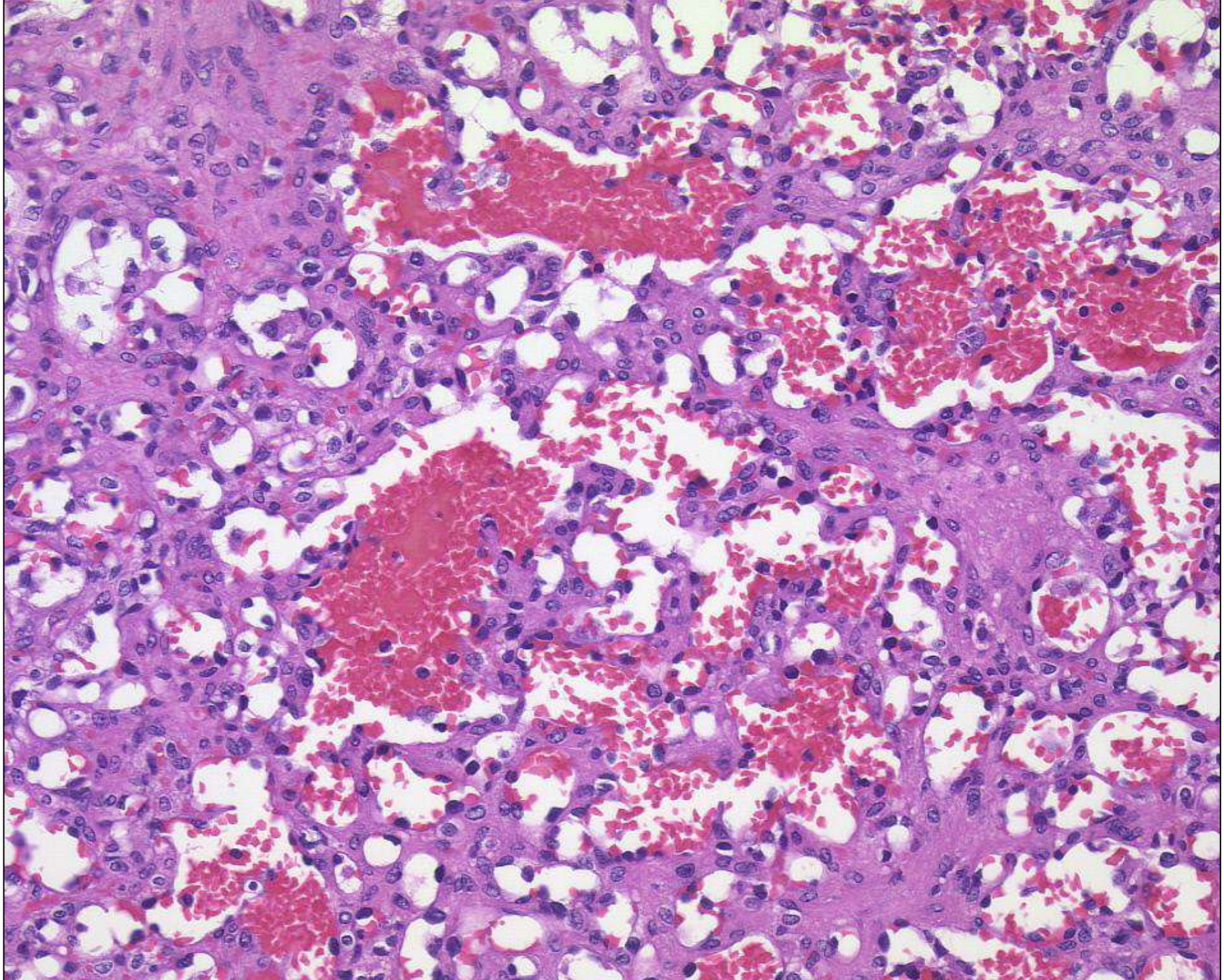
Reactive Angioendotheliomatosis in Cryoglobulinaemia

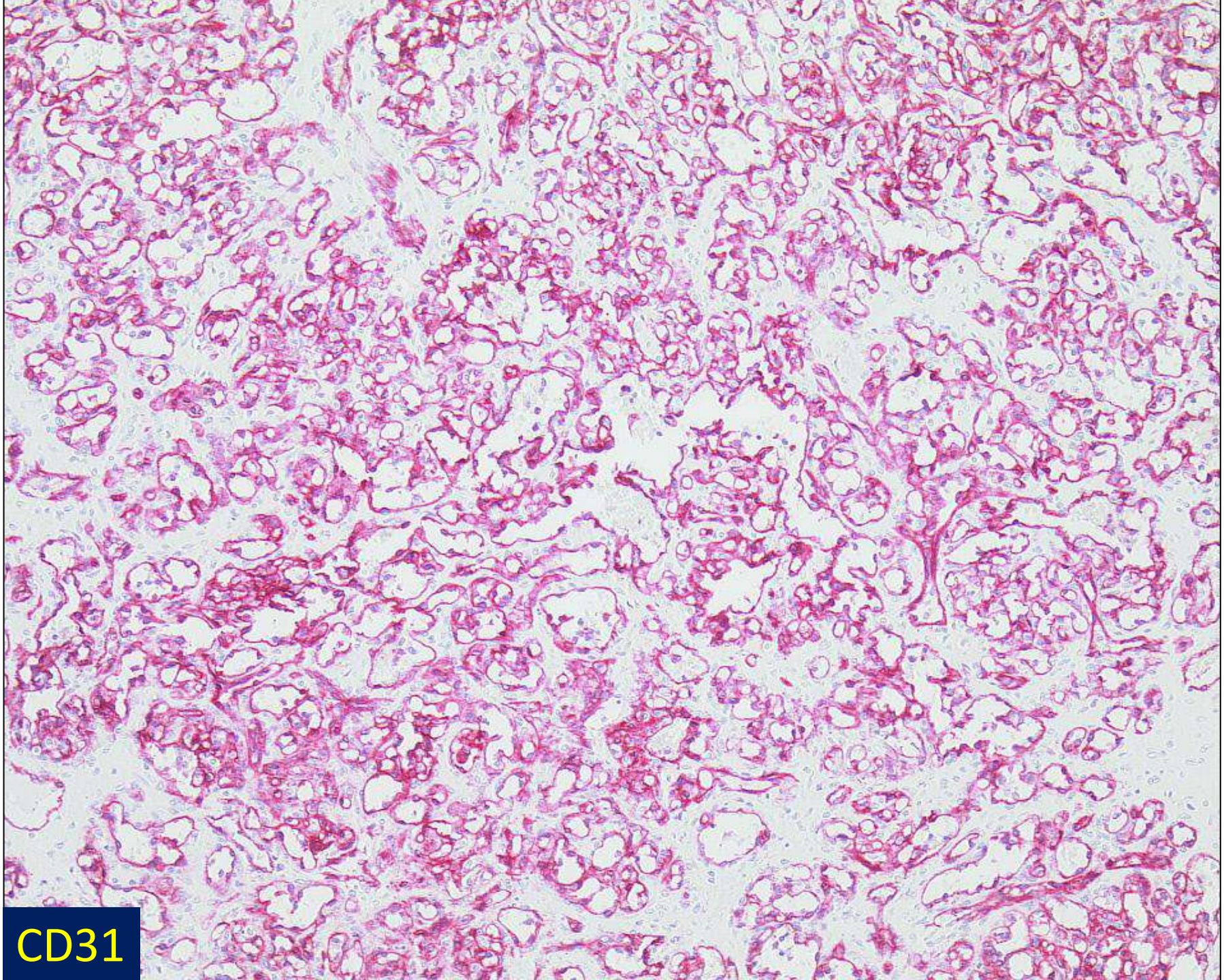






M, 74 years, right testis
(by courtesy of Prof.E.Montgomery, U.S.A.)




CD31

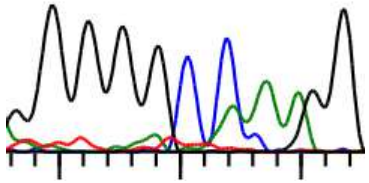
Ergebnis der molekularpathologischen Untersuchung des GNAQ Gens
(Guanine nucleotide-binding protein Q polypeptide, OMIM-Nummer 600998)
Histologie-Nummer 18/K 3781

Mutationsstatus		
Sequenzierung von	**DNA**	**abgeleitete Aminosäuresequenz**
GNAQ Exon 5 (Codon 209)	A 626 C	Q209H

Die arabischen vierstelligen Zahlen bezeichnen die betroffenen Nukleotide, die arabischen dreistell igen Zahlen die betroffenen Codons, die Buchstaben die entsprechenden Nukleotide (A-Adenin, C-Cytosin, G-Guanin, T-Thymin) bzw. Aminosäuren: A-Alanin, R-Arginin, N-Asparagin, D-Asparaginsäure, C-Cystein, E-Glutaminsäure, Q-Glutamin, G-Glycin, H-Histidin, I-Isoleucin, K-Lysin, M-Methionin, F-Phenylalanin, P-Prolin, S-Serin, T-Threonin, W-Tryptophan, Y-Tyrosin, V-Valin.
Nach:"Guidelines for mutation nomenclature" der "Human Genome Variation Society" (HGVS; www_hgvs.org/)

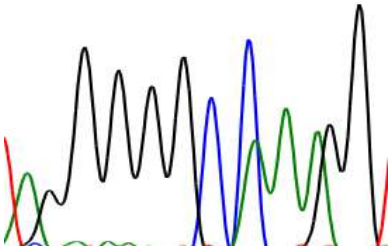
Prof. Dr. Mentzel / Dr. Palmedo 09.01.2018

18 / K 3781
Fall 2B



G G GGCCMA A G

Wildtyp



GGGGCCAA A G

Anastomosing hemangioma of the genitourinary tract: a lesion mimicking angiosarcoma.
(Montgomery E, Epstein JL AJSP 2009; 33: 1364)

Anastomosing hemangioma arising in unusual locations: a clinicopathologic study of 17 soft tissue cases showing predilection for the paraspinal region
(John I, Folpe AL AJSP 2016; 40: 1084)

Recurrent GNAQ mutations in anastomosing hemangiomas.
(Bean GR et al. Mod Pathol 2017; 30: 722)

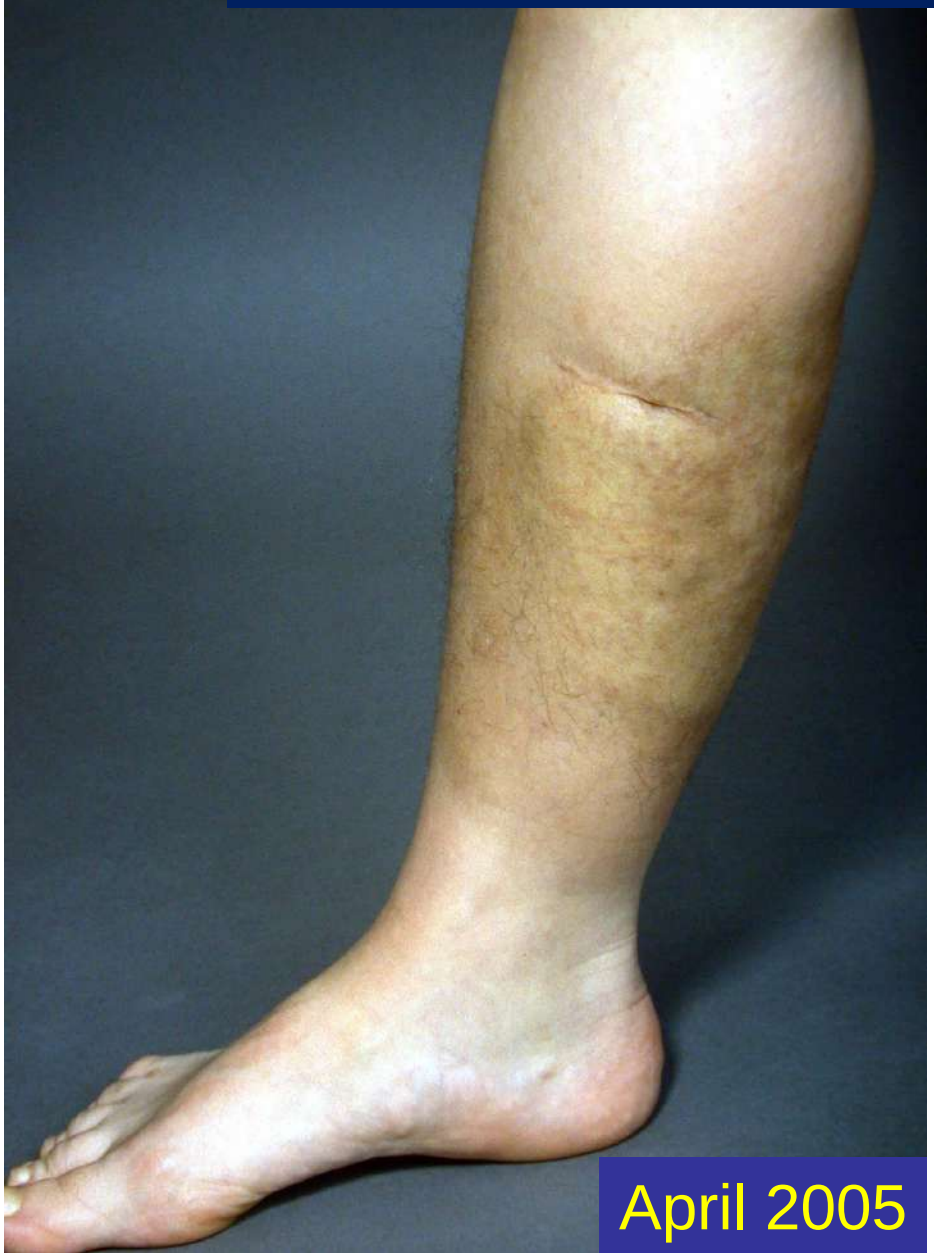
anastomosing Haemangioma

- genital area, visceral organs, skin, soft tissues, children, adults
- solitary, multiple, circumscribed, infiltrative
- dilated, anastomosing vessels,

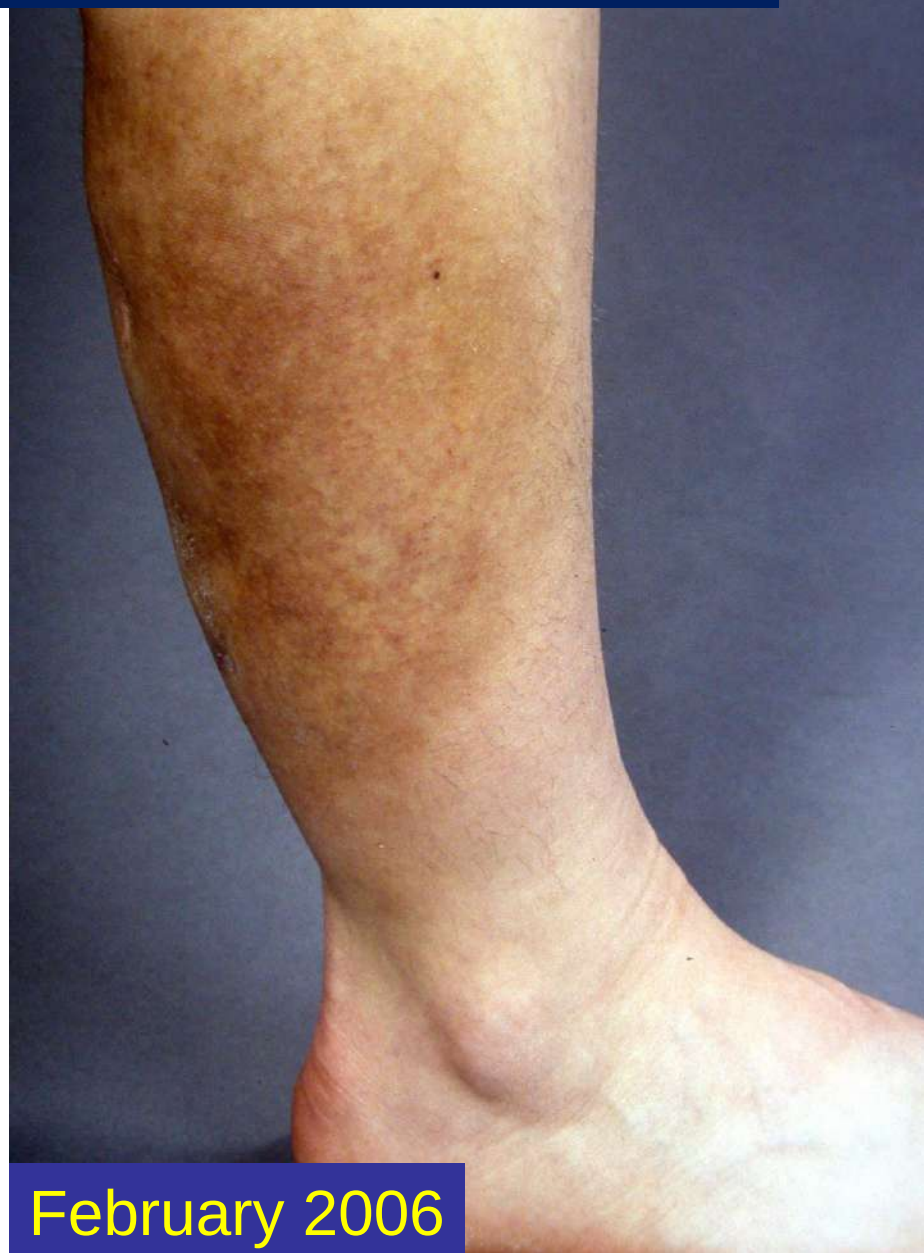
  enlarged, hobnail-like endothelial cells
- hyaline globuli, extramedullary haematopoesis, lipomatous metaplasia,

  few mitoses, no endothelial multilayering
- activating *GNAQ* or *GNA14* mutations

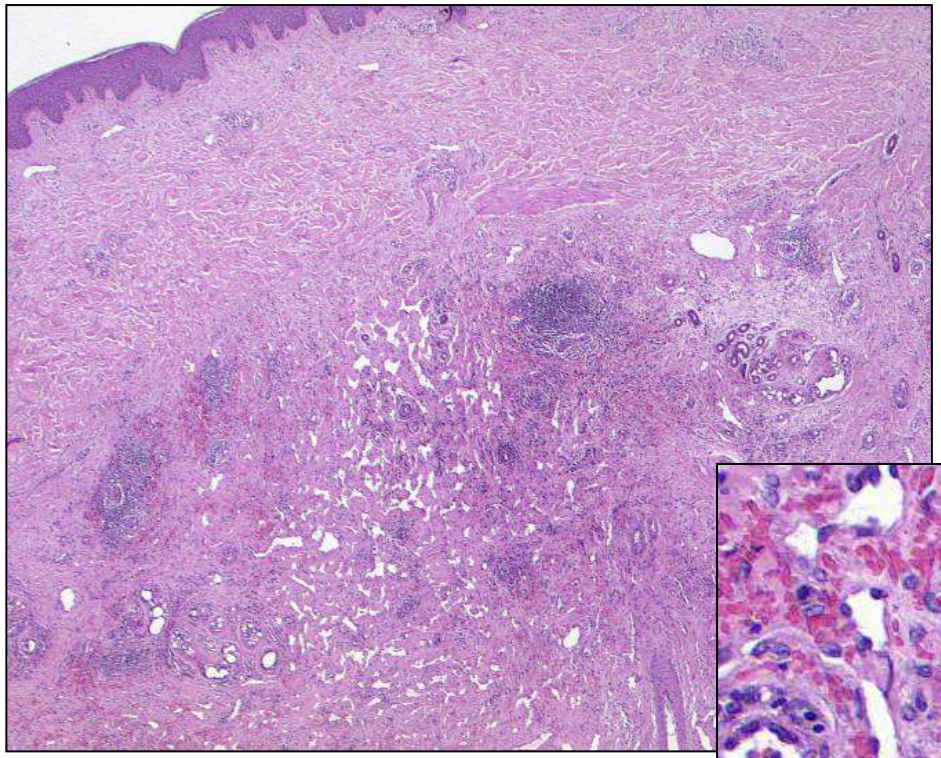
young female patient, since early childhood, slowly growing, indurated lesion

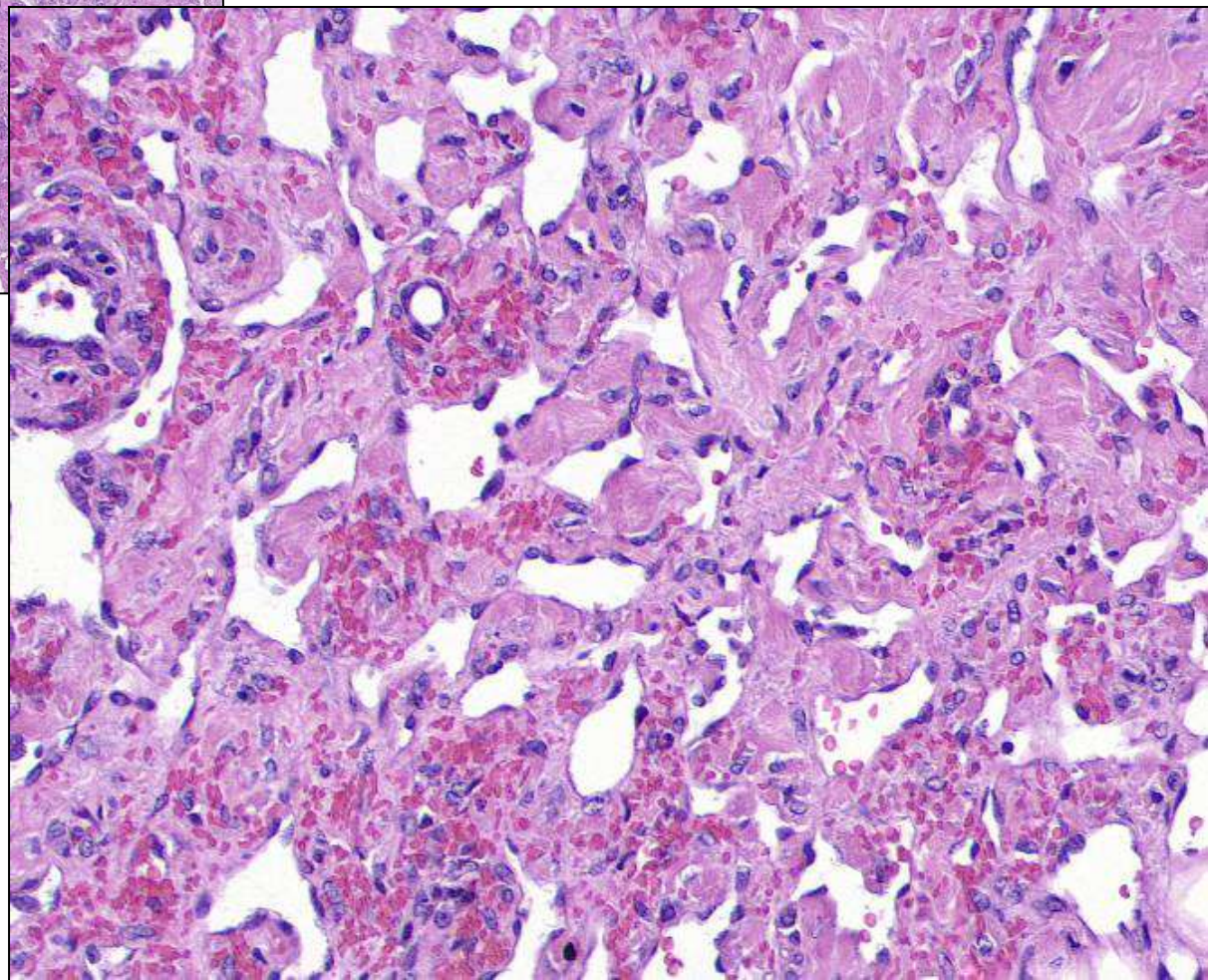


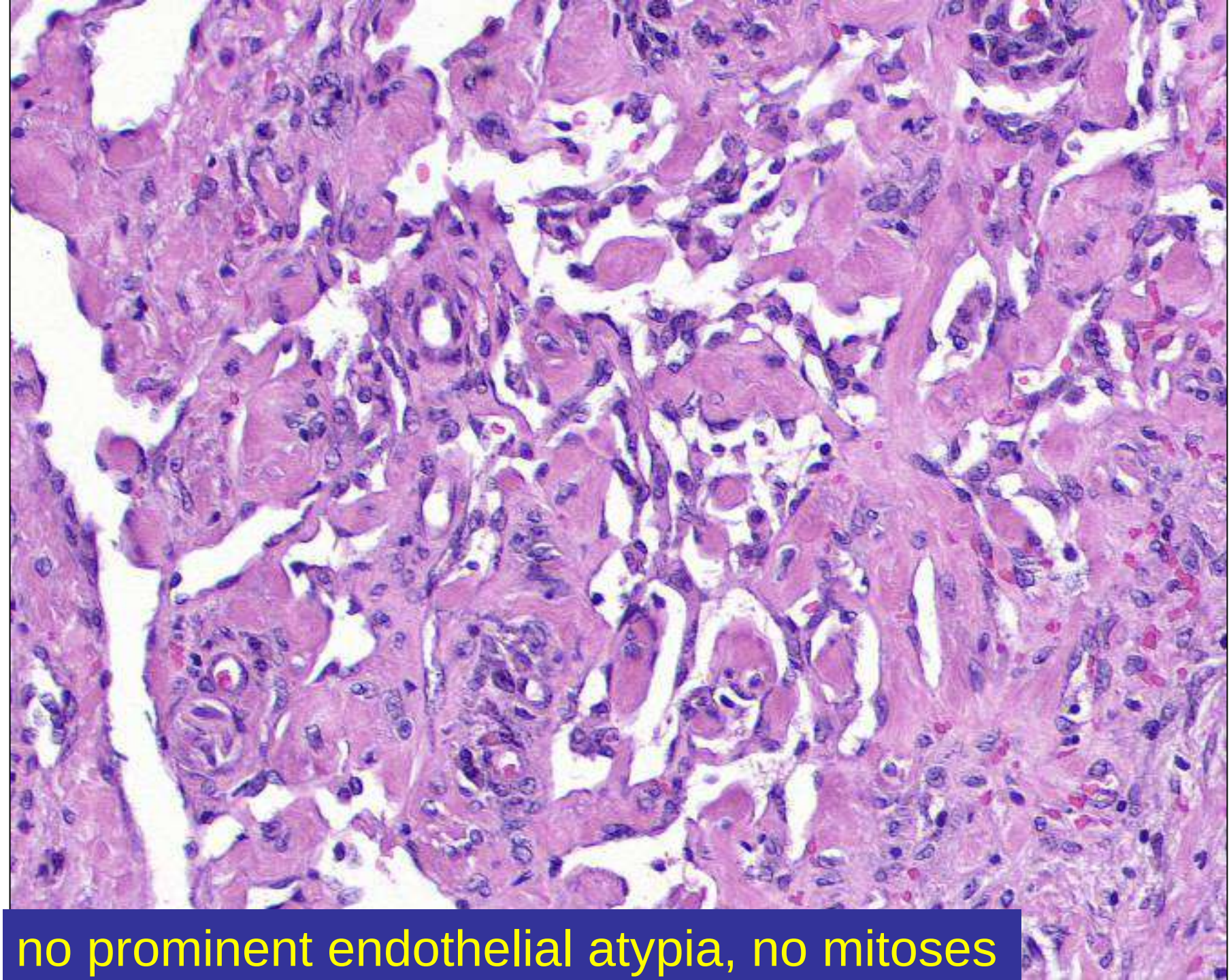
April 2005

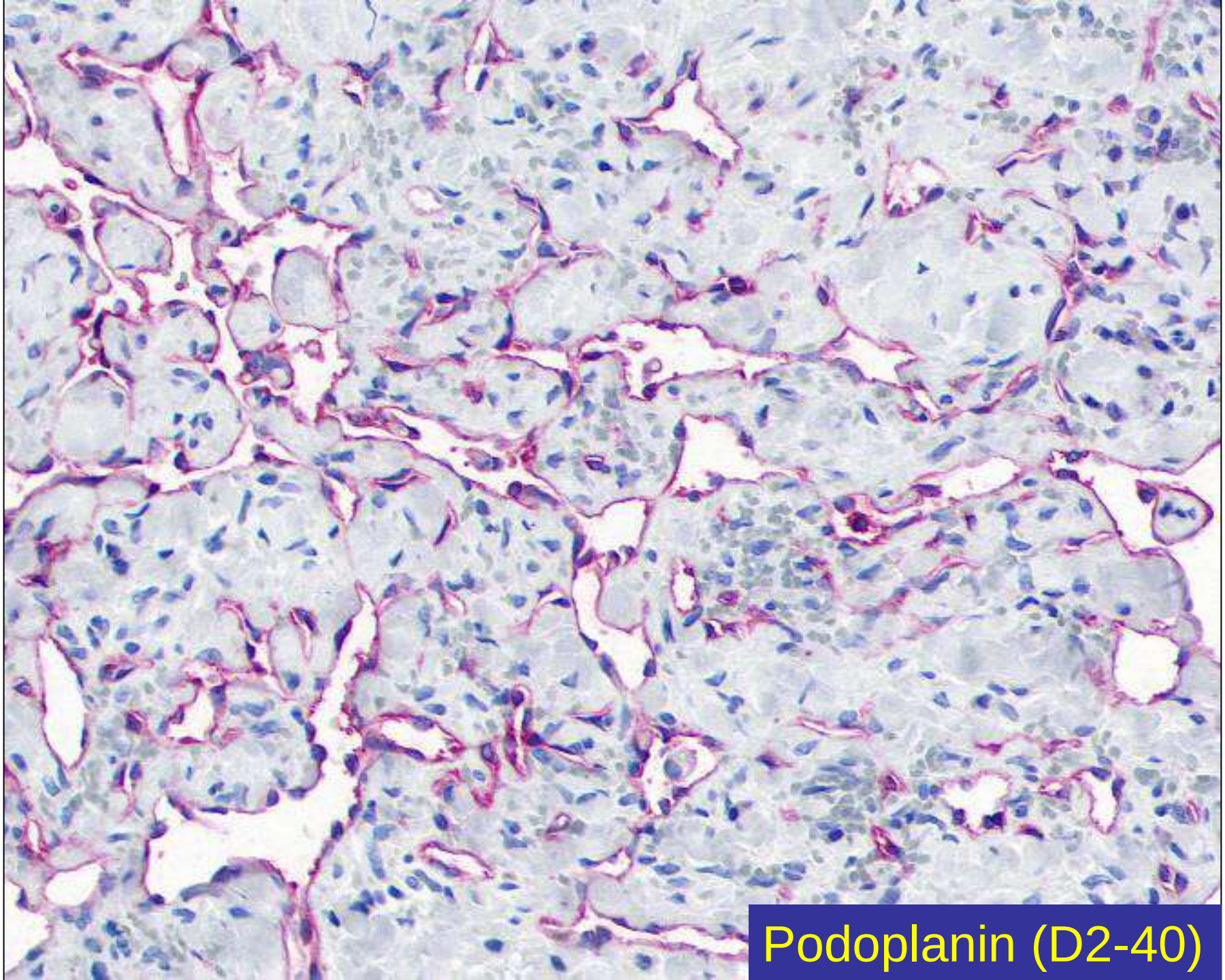


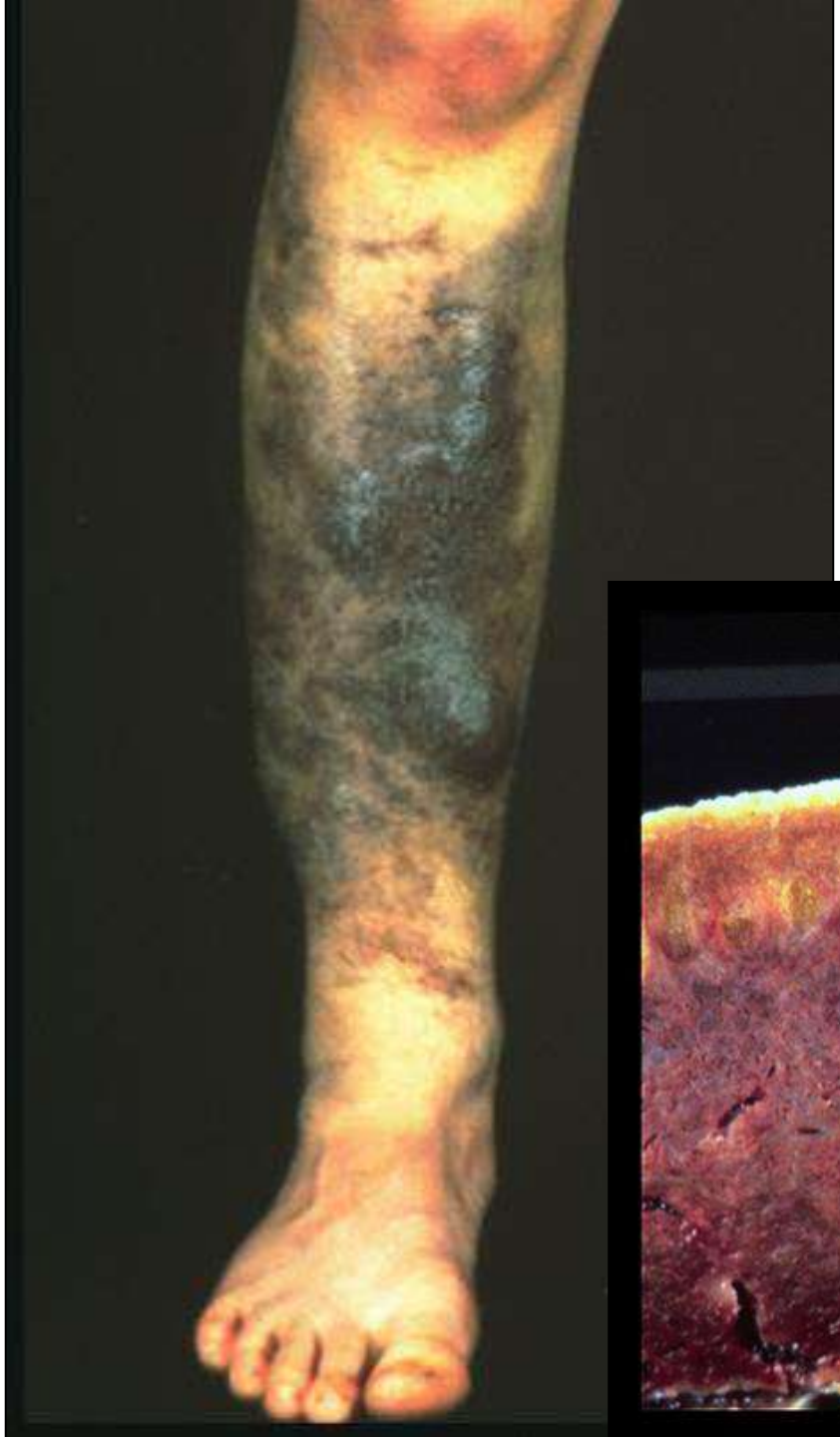
February 2006



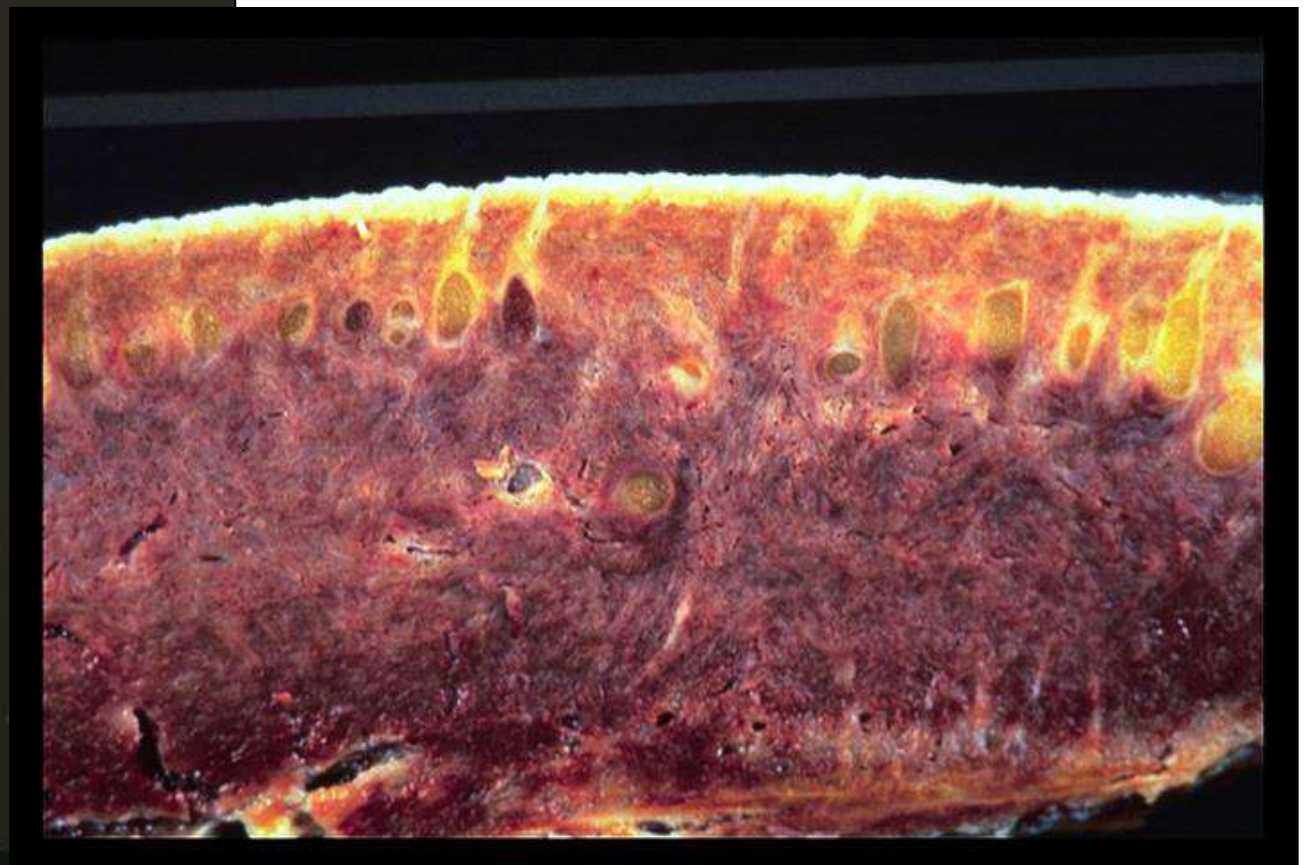



no prominent endothelial atypia, no mitoses


Podoplanin (D2-40)



Lymphangiomatosis of the limbs (courtesy of Prof.Fletcher, Boston) AJSP 1995; 19: 125-133 (no systemic involvement, benign clinical course)



OBSERVATION

Multifocal Lymphangioendotheliomatosis With Thrombocytopenia

A Newly Recognized Clinicopathological Entity

Paula E. North, MD, PhD; Teri Kahn, MD; Maria R. Cordisco, MD; Soheil S. Dadras, MD, PhD; Michael Detmar, MD; Ilona J. Frieden, MD

Background: Severe thrombocytopenic coagulopathy may complicate platelet-trapping vascular tumors such as kaposiform hemangioendothelioma and tufted angioma. Low-grade, chronic consumptive coagulopathy may occur with extensive venous and lymphatic malformations. We have also observed patients with rare multifocal, congenital skin and gastrointestinal (GI) tract vascular anomalies of distinctive and remarkably similar appearance, all associated with coagulopathy. We studied the clinical and histopathologic features of 3 patients demonstrating this previously uninvestigated phenomenon.

Observations: All 3 patients presented with hundreds of congenital red-brown skin plaques as large as a few centimeters, with similar lesions throughout the GI tract and severe GI tract bleeding. One patient had synovial involvement. All had significant thrombocytopenia, with prothrombin and partial thromboplastin times and fibrinogen levels near the reference range. Corticosteroids and/or interferon alfa treatment resulted in equivocal or no improvement. Skin lesions from all 3 patients were histologically distinctive and similar, including dilated, thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells (10%-15% immunoreactive for Ki-67), most displaying intraluminal papillary projections. Immunoreaction for the lymphatic marker LYVE-1 was uniformly present.

Conclusions: We propose the term *multifocal lymphangioendotheliomatosis with thrombocytopenia* to distinguish this newly recognized clinicopathological entity. These congenital lesions, like tufted angioma and kaposiform hemangioendothelioma, show lymphatic differentiation, strengthening the association between abnormal lymphatic endothelium and coagulopathy.

Arch Dermatol. 2004;140:599-606

From the Departments of Pathology and Otolaryngology, the University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock (Dr North); the Department of Dermatology, The Cleveland Clinic, Cleveland, Ohio (Dr Kahn); the Hospital Nacional de Pediatria, Buenos Aires, Argentina (Dr Cordisco); the Cutaneous Biology Research Center, Massachusetts General Hospital and Harvard Medical School, Boston (Drs Dadras and Detmar); and the Departments of Pediatrics and Dermatology, University of California–San Francisco Medical Center (Dr Frieden). *The authors have no relevant financial interest in this article.*

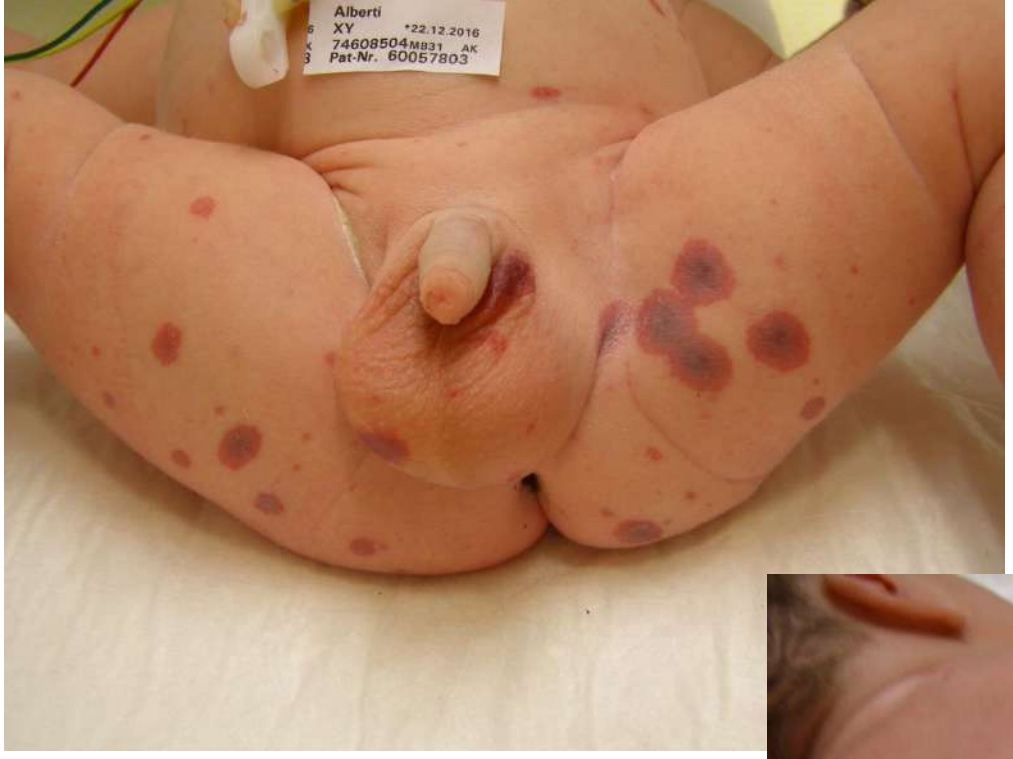
MULTIFOCAL VASCULAR tumors and malformations are relatively unusual among vascular anomalies, but are characteristic of several well-defined disorders. These include so-called neonatal hemangiomatosis (benign and disseminated),[1] blue rubber bleb nevus syndrome,[2] glomuvenous malformations,[3,4] Maffucci syndrome,[5] hereditary hemorrhagic telangiectasia,[6-8] familial cutaneocerebral capillary malformations,[9,10] and familial multiple mucocutaneous venous malformations.[11,12] We herein describe 3 patients with an entirely different disorder, characterized by multiple congenital and progressive cutaneous and gastrointestinal (GI) tract vascular lesions with occasional involvement of other anatomic sites, coagulopathy, and distinctive histopathologic features resembling those of solitary acquired lesions recently classified as *benign lymphangioendothelioma*[13] and previously as *acquired progressive lymphangioma*.[14] We propose the term *multifocal lymphangioendotheliomatosis with thrombocytopenia* to describe this unique and potentially life-threatening condition.

METHODS

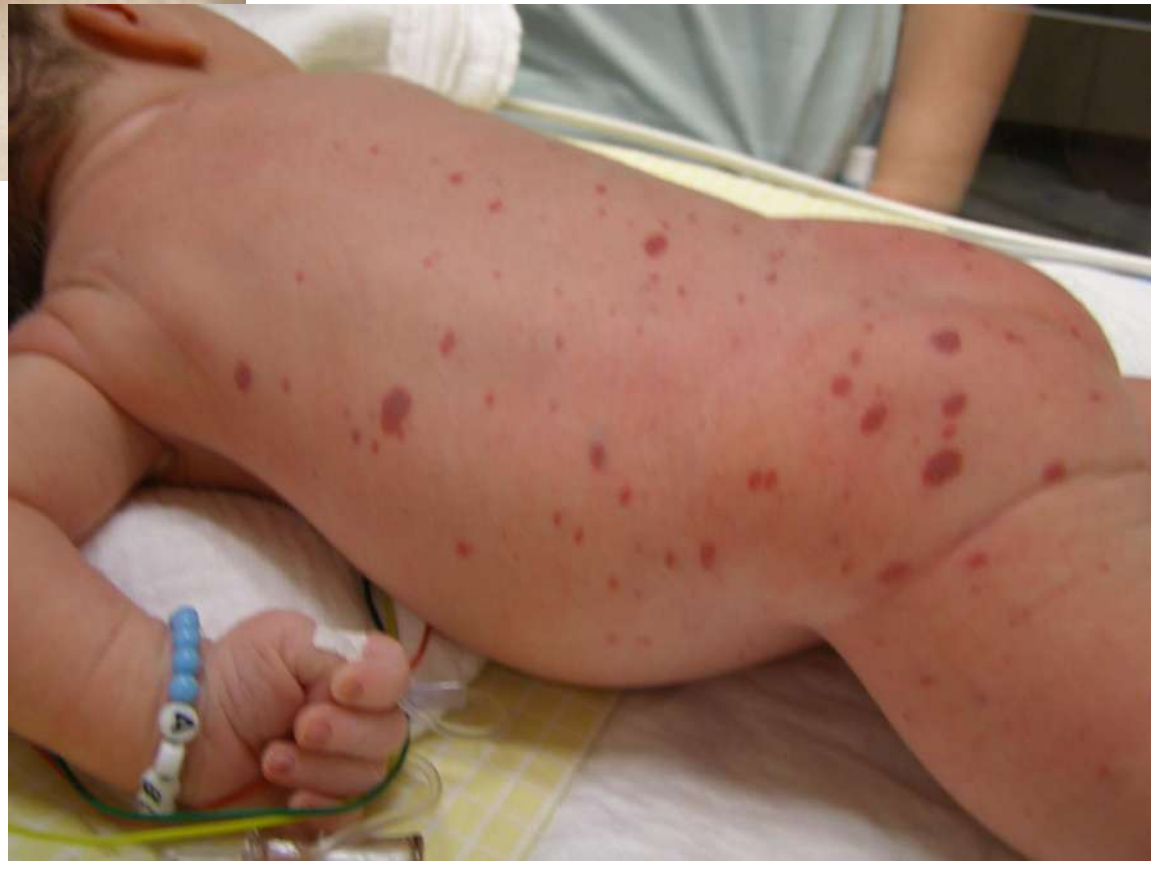
Three patients with an unusual and remarkably similar clinical presentation characterized by multiple discrete cutaneous and GI tract vascular anomalies associated with coagulopathy were identified independently at 3 different institutions. Medical records were reviewed, and hematoxylin-eosin–stained tissue sections were reviewed and compared by one of us (P.E.N.). Biopsy specimens included skin samples of the lower back and right hip synovium (patient 1, aged 5-6 years), a punch biopsy specimen from a left buttock lesion (patient 2, aged 6 years), and a resection specimen from the cheek (patient 3, aged 13 years 9 months). Histochemical, immunohistochemical, and immunofluorescent studies, including evaluation for expression of the lymphatic marker LYVE-1,[15] were performed.

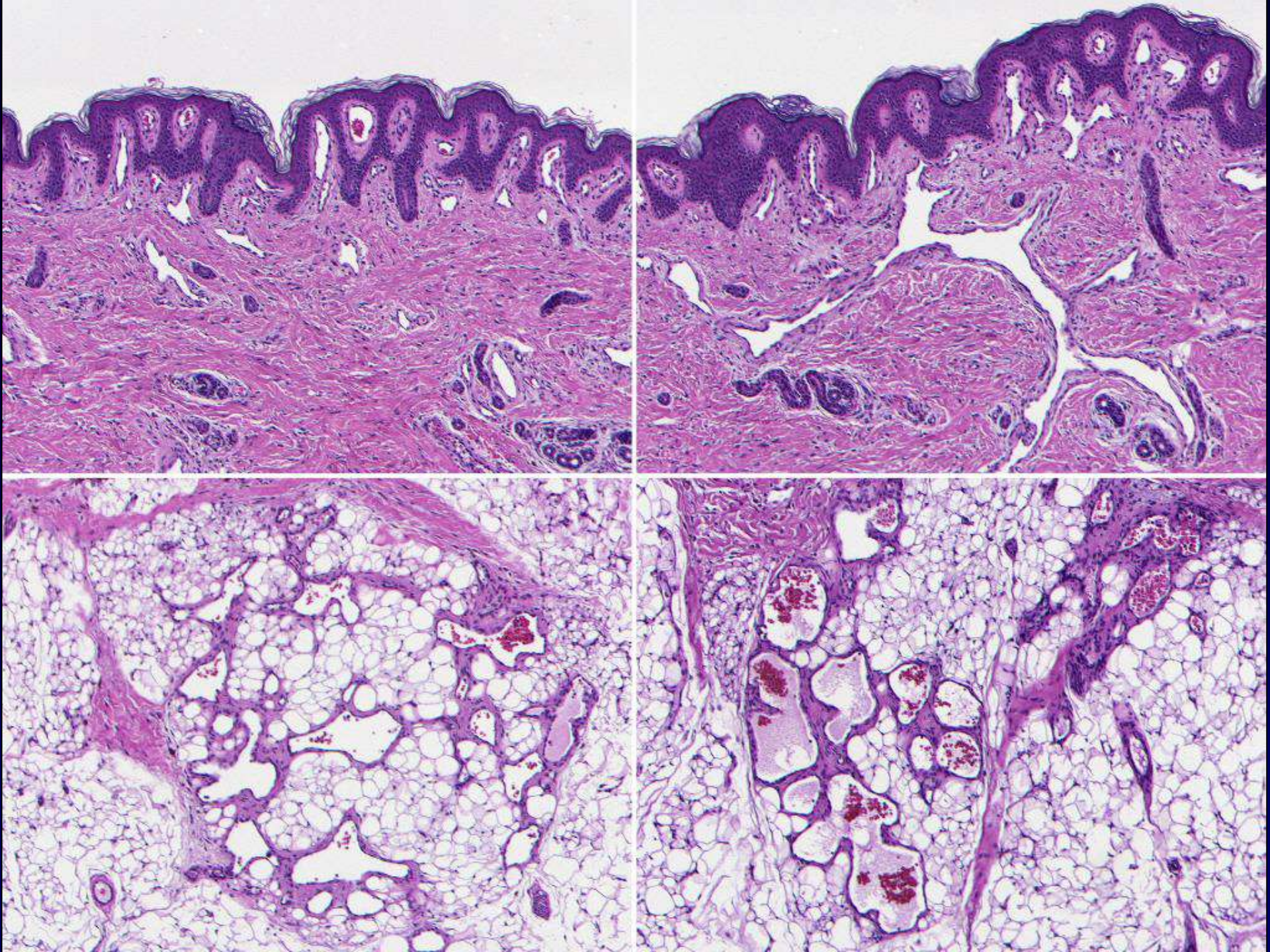
For immunofluorescent microscopy, paraffin-embedded sections (6-μm thickness) were deparaffinized, rehydrated, and treated with 0.01% protease XXIV (Sigma-Aldrich Corp,

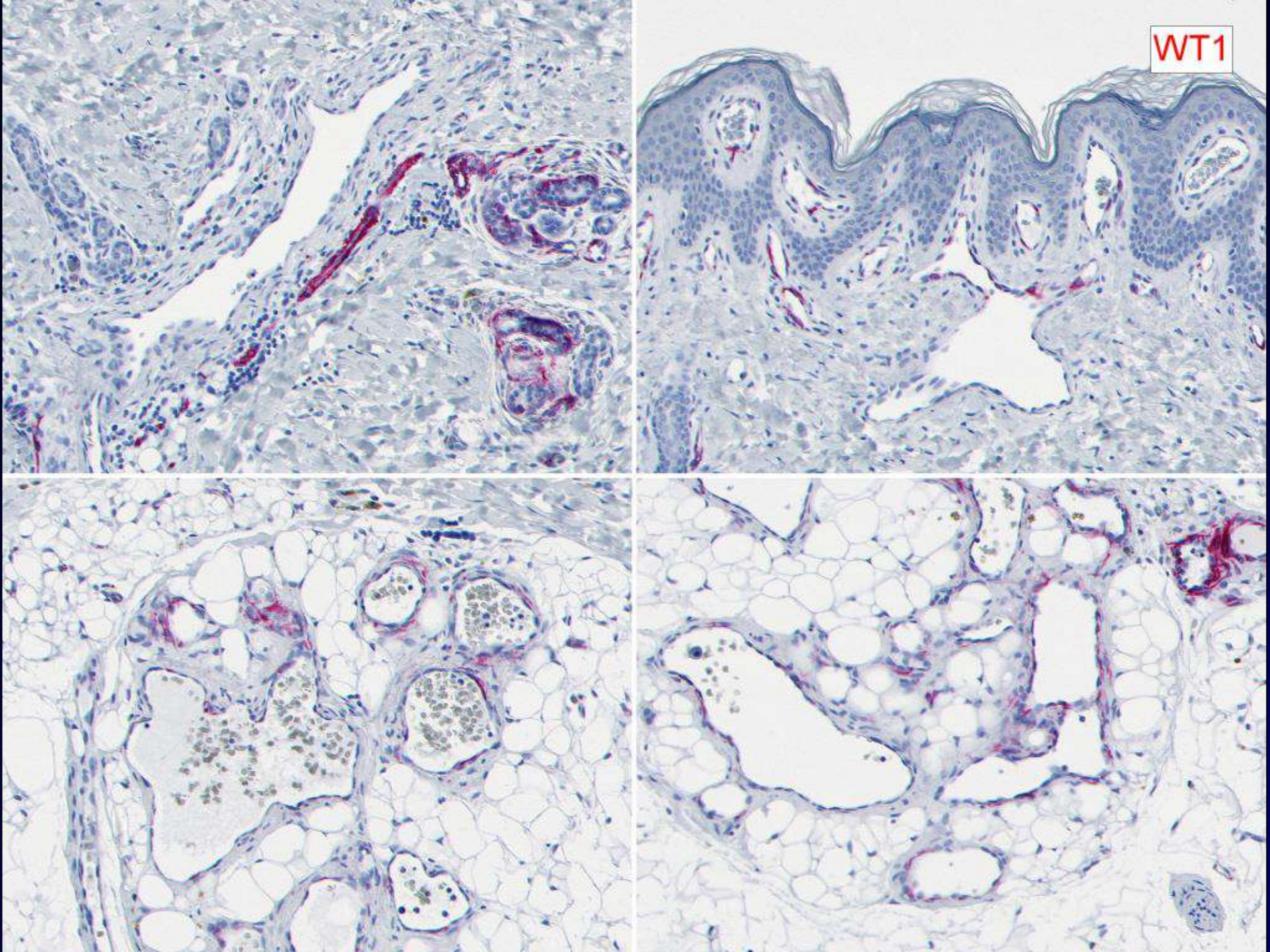
- 3 patients (2 M, 1 F, 5, 6, 13 years), hundreds of congenital skin plaques
- dilated vascular structures with hobnail endothelial cells, LYVE-1 +
- GI-vascular lesions with bleeding, synovial vascular lesions (1 patient)
- significant thrombocytopenia (vascular lesions of lymphatic diff.)
- association of abnormal lymphatic endothelium and coagulopathy
- represents a vascular malformation



M, newborn, multifocal haemangiomatosis of the skin and visceral organs (spleen), disseminated intravascular coagulation, thrombocytopenia



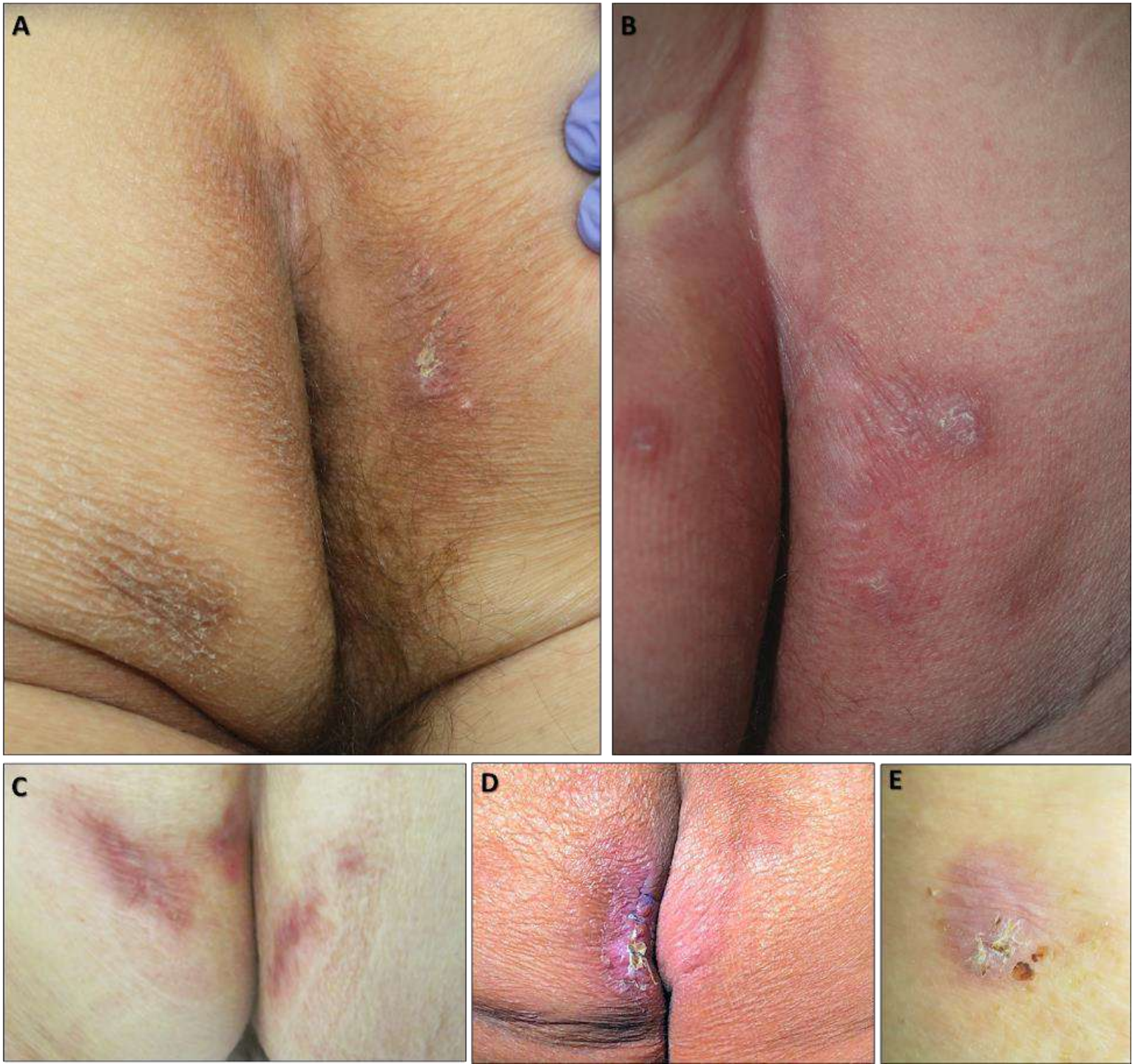


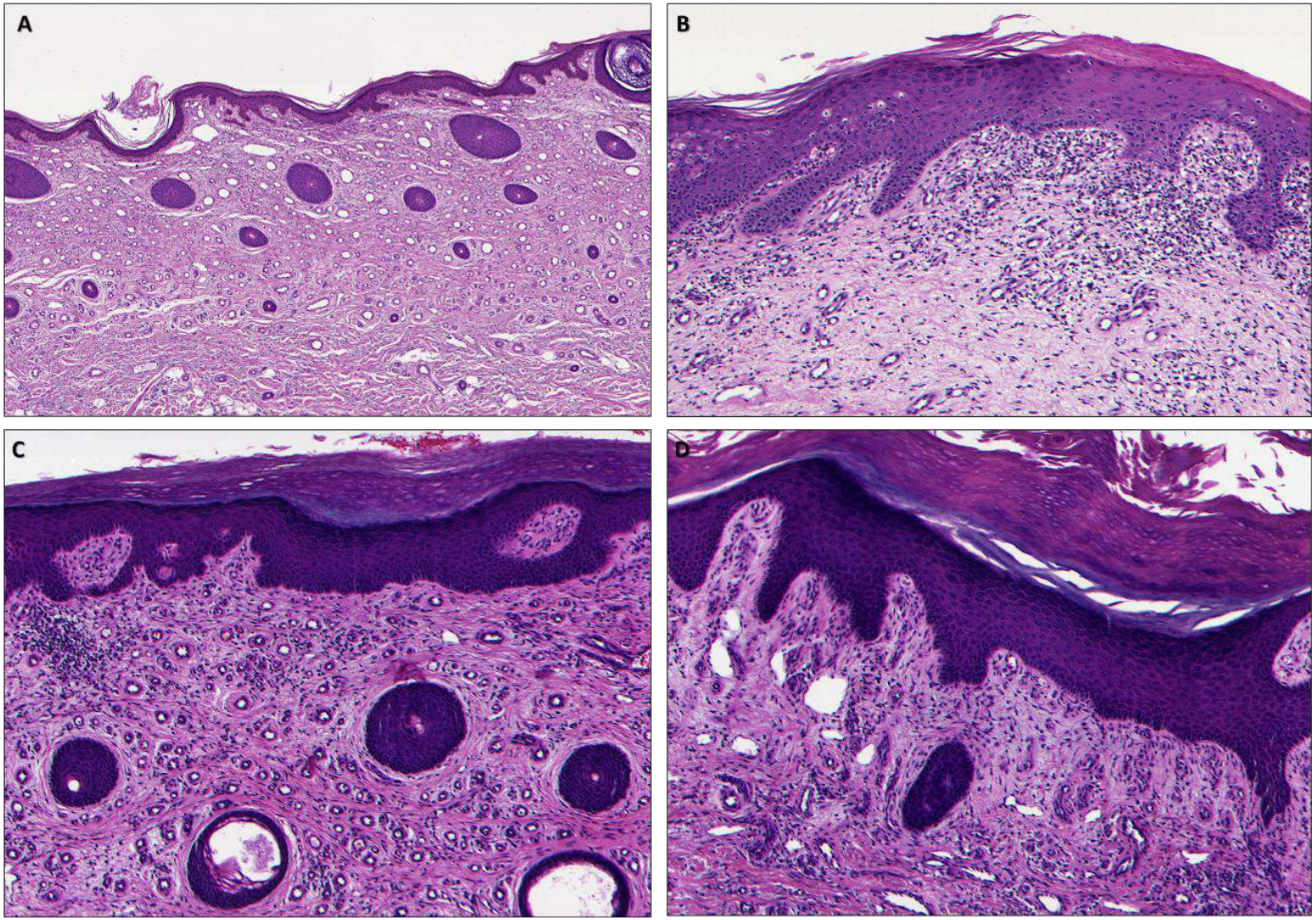

WT1

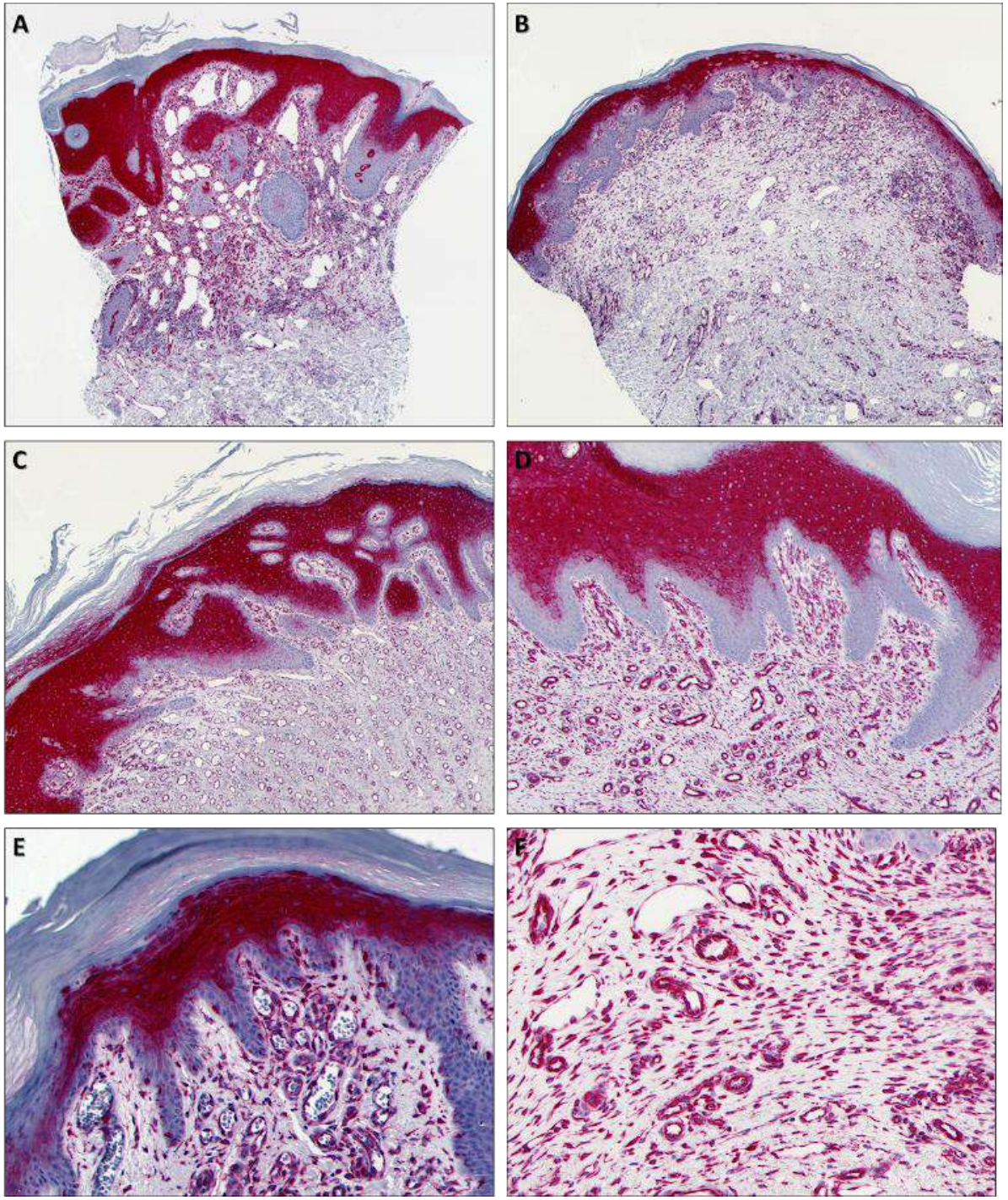
Prurigiform angiomatosis and endothelial growth factors: a distinct reactive angioproliferation in the skin

(Ortins-Pina A et al. Am J Dermatopathol 2020; 42: 29-34)

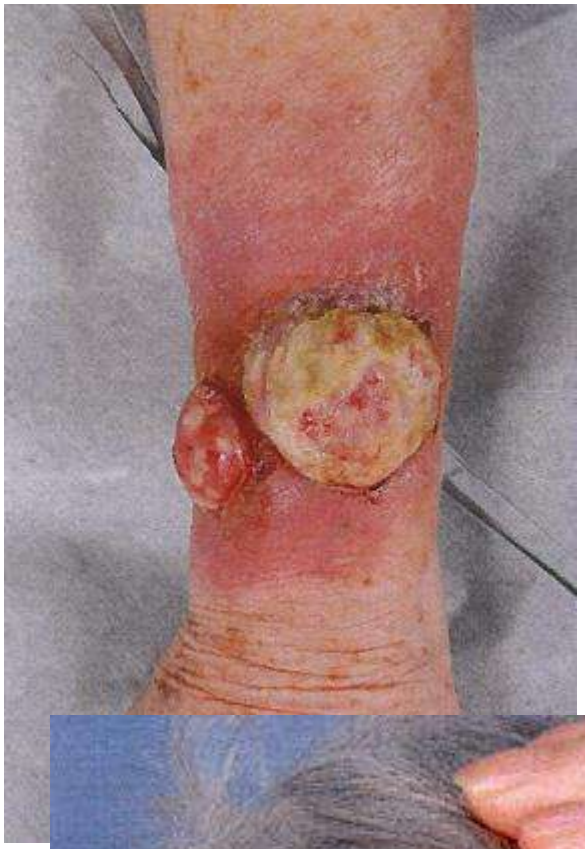
- non-neoplastic, reactive increase of vessels
- elderly patients, M > F, buttock, intergluteal fold, erythematous / brown plaques
- epidermis hyperplasia with VEGF secretion and increase of organoid vessels
- band- or plaque-like, dermal vascular proliferation inflammatory cells, fibrosis
- mechanical injury, inflammation are triggers of angiogenesis driven by epidermal VEGF expression
- no topical treatment

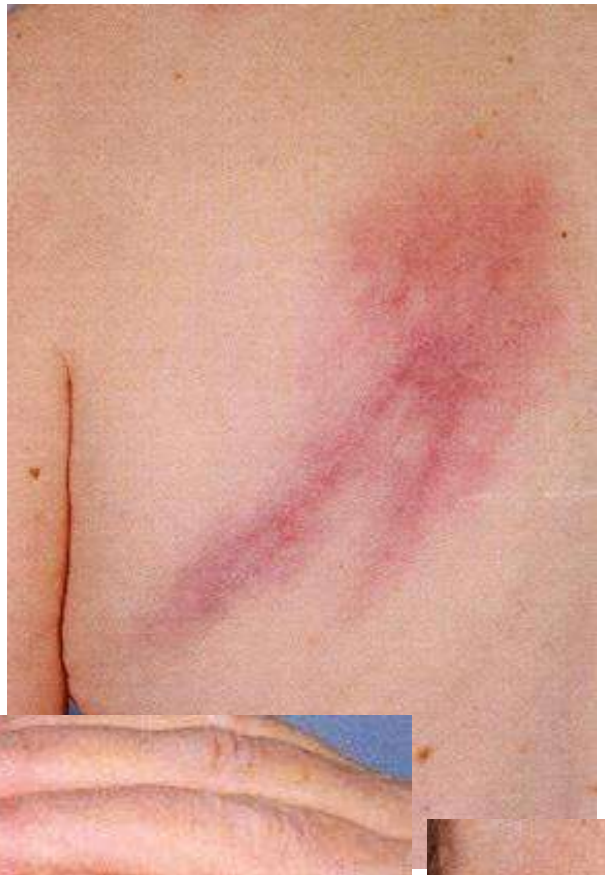

A
B
C
D
E

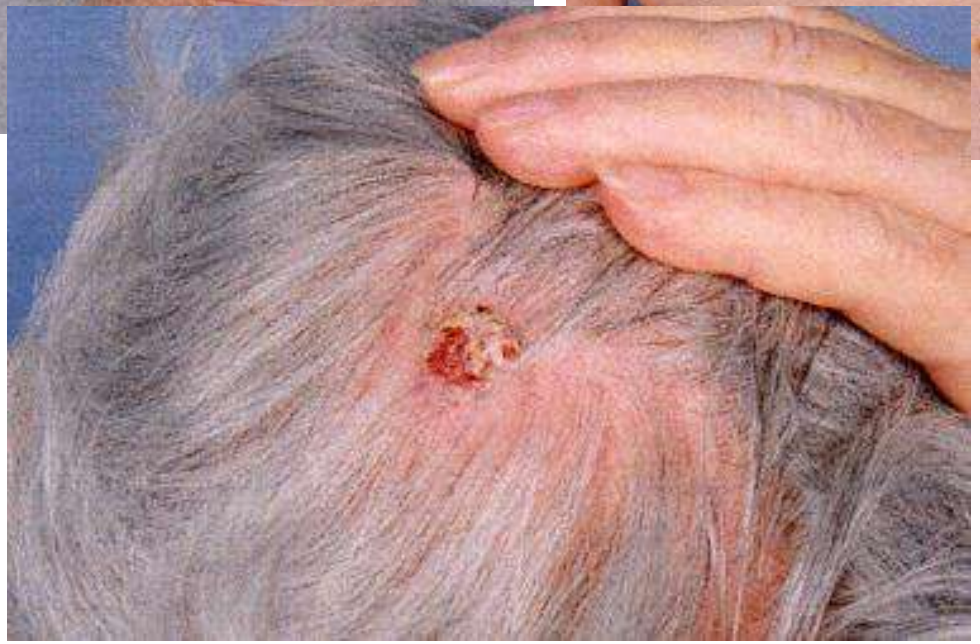

A
B
C
D

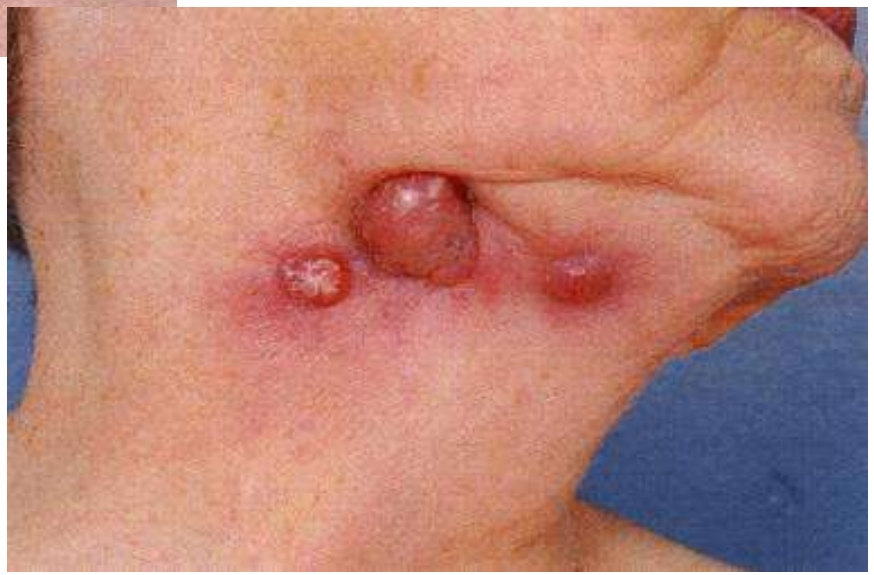


VEGF

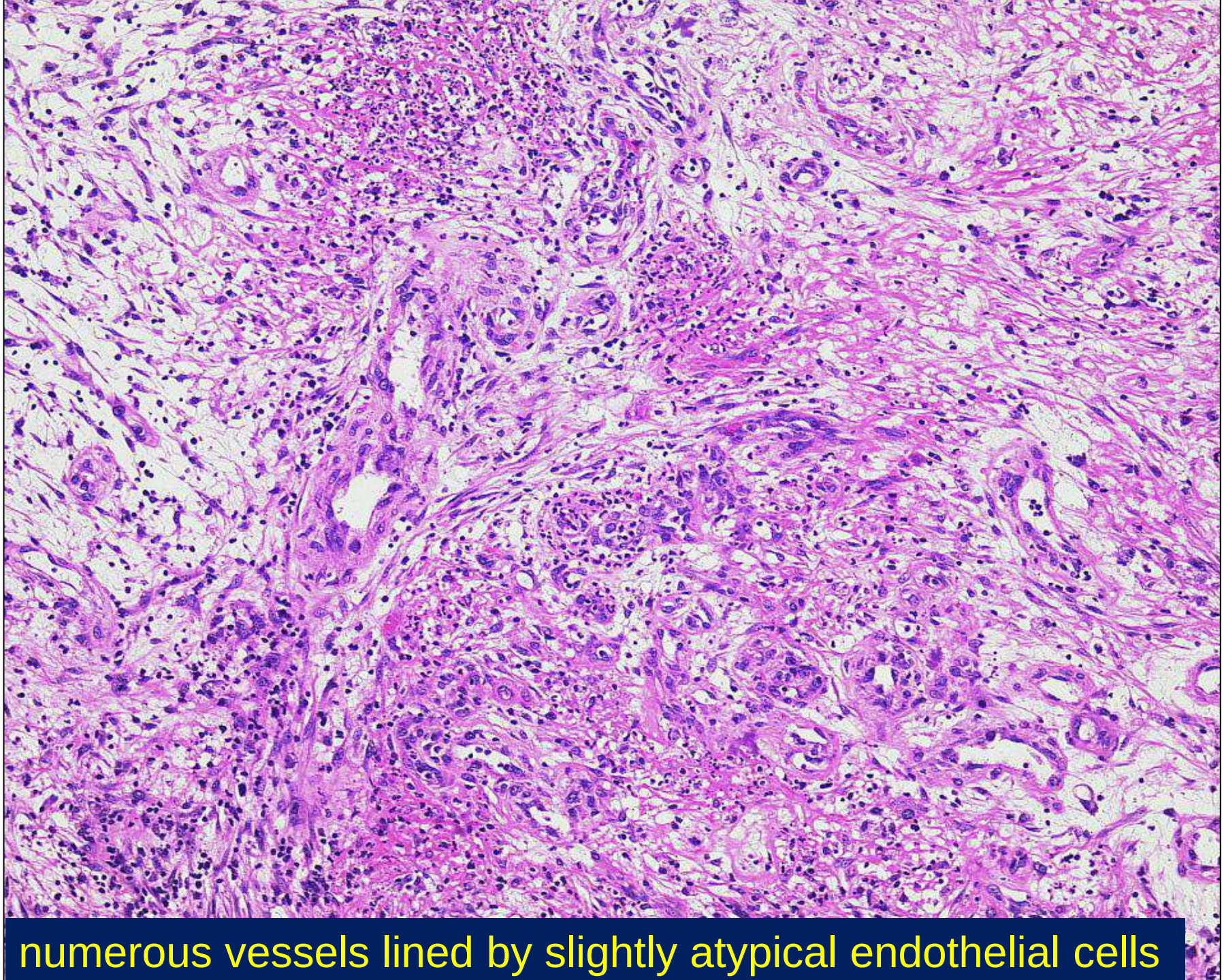




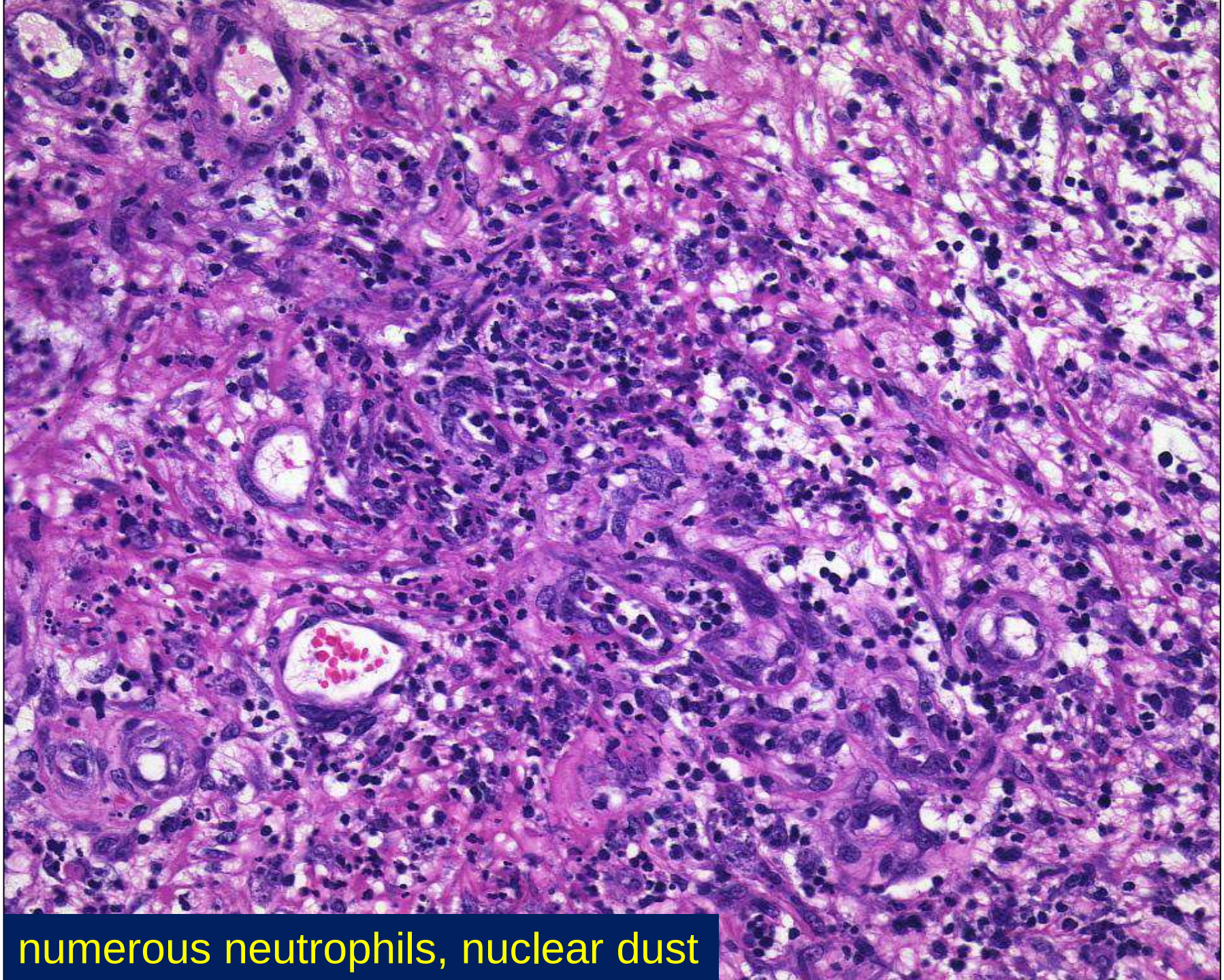


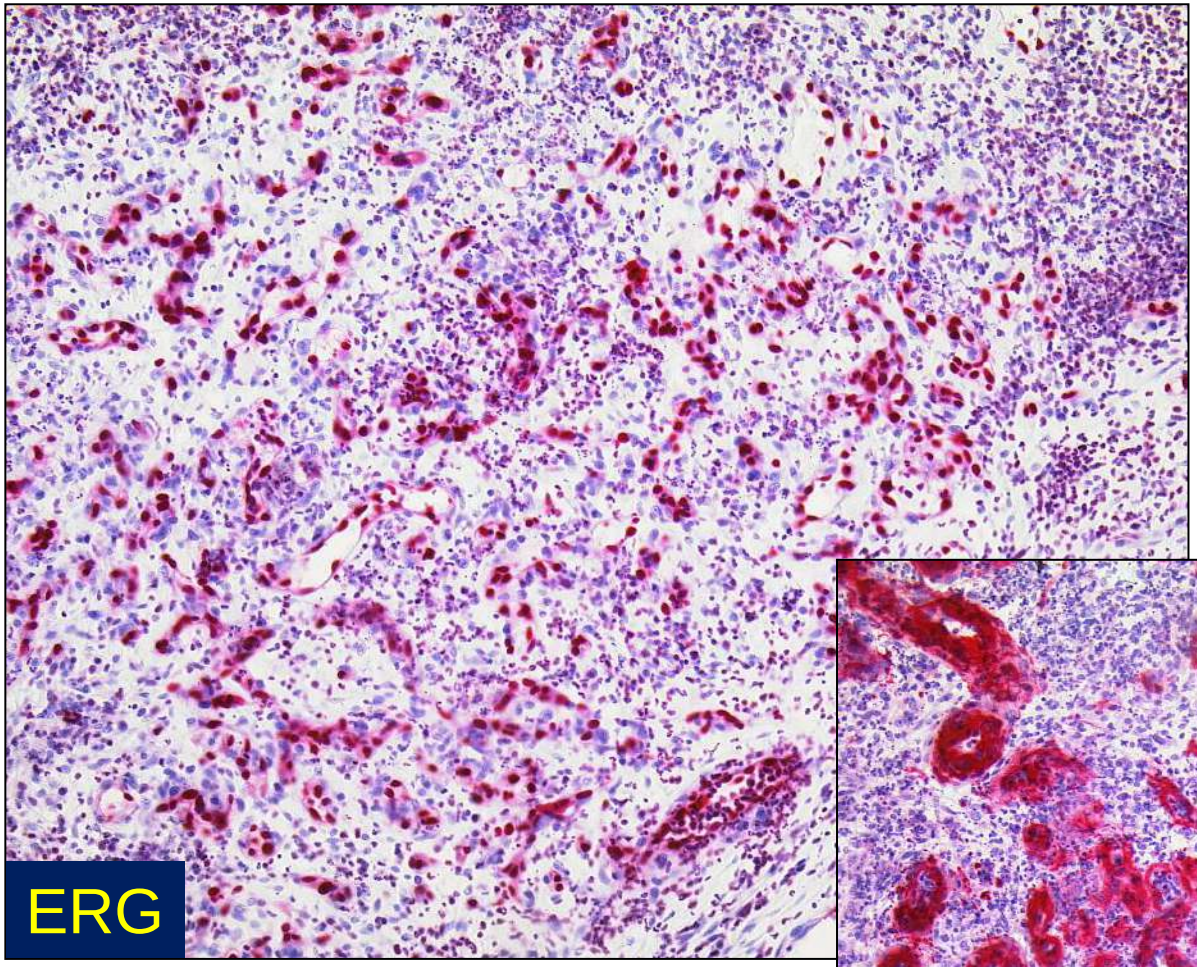


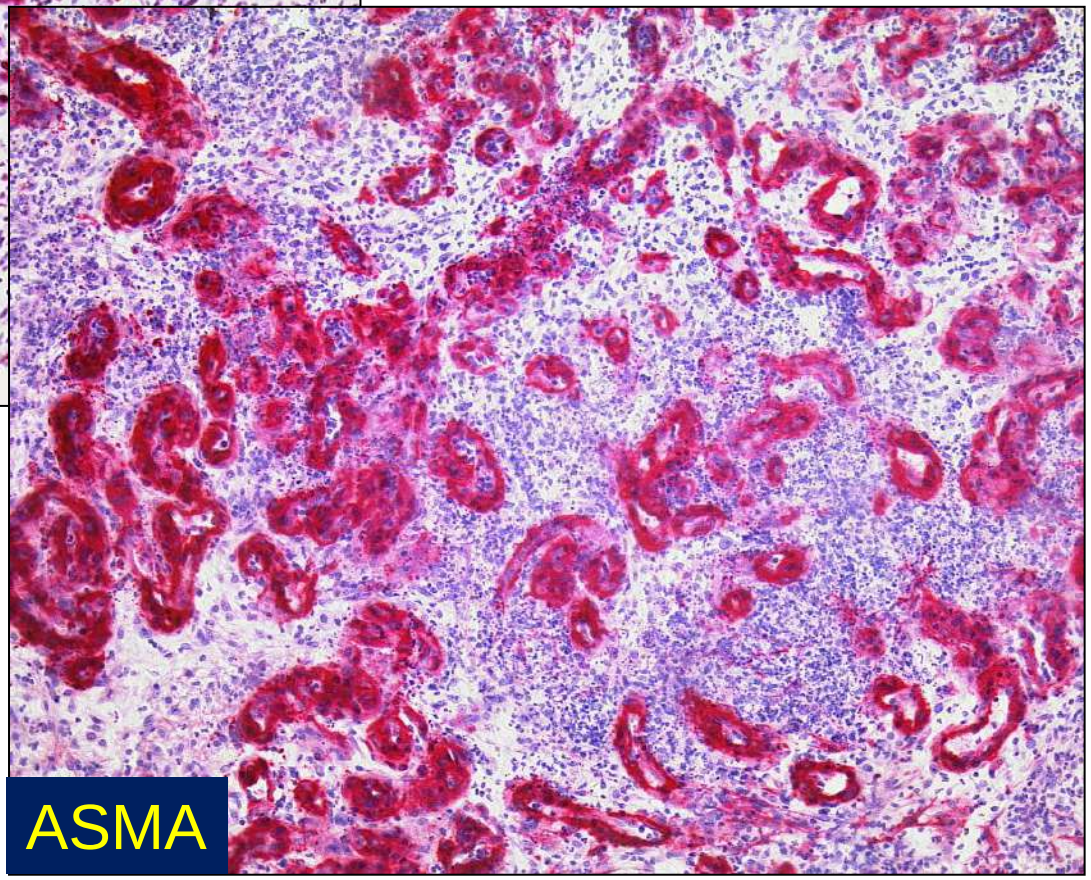
F, 81 years
previous breast cancer and CLL
since 6/12 nodular, ulcerated skin lesions
? angiosarcoma

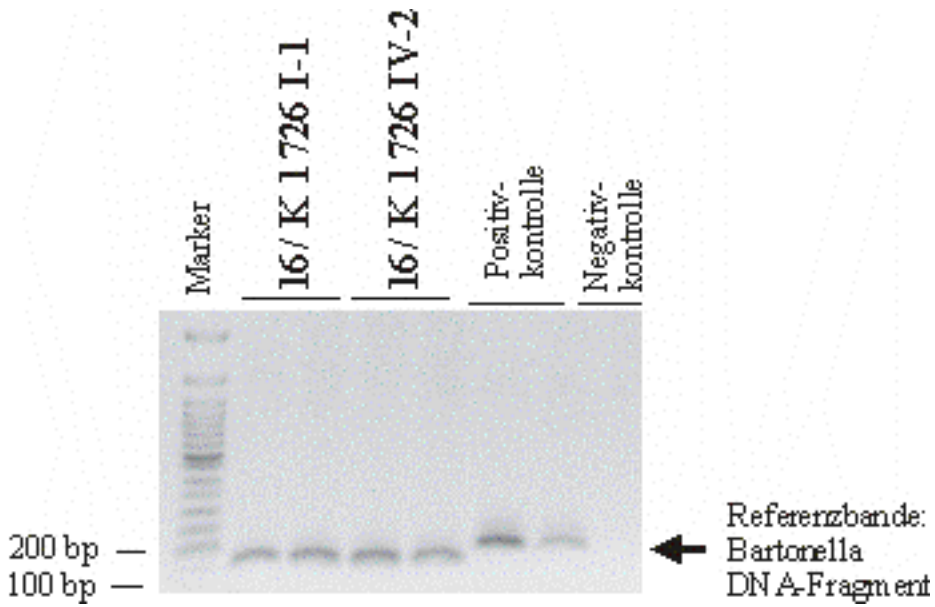


numerous vessels lined by slightly atypical endothelial cells


numerous neutrophils, nuclear dust


ERG


ASMA



Sequenzvergleich:

16/ K 1726 I	GCCTTCGGGCGATCTCTTACAATAAGCCCTTTGGGACTTTAAGGAAGACACTTTTGTGT	60
B. quintana	GCCTTCGGGCGATCTCTTACAATAAGCCCTTTGGGACTTTAAGGAAGACACTTTTGTGT	429

bacillary Angiomatosis

- tumour-like vasoproliferative lesion
- Bartonella henselae (quintana)
- often in immunosuppressed patients
- skin > lymph node, spleen
- often multiple dermal nodules
- lobular vascular proliferation

  epithelioid endothelial cells, neutrophils,

  extracellular amorphous material
- excellent response to erythromycin

Vascular Tumours of Skin and Soft Tissues

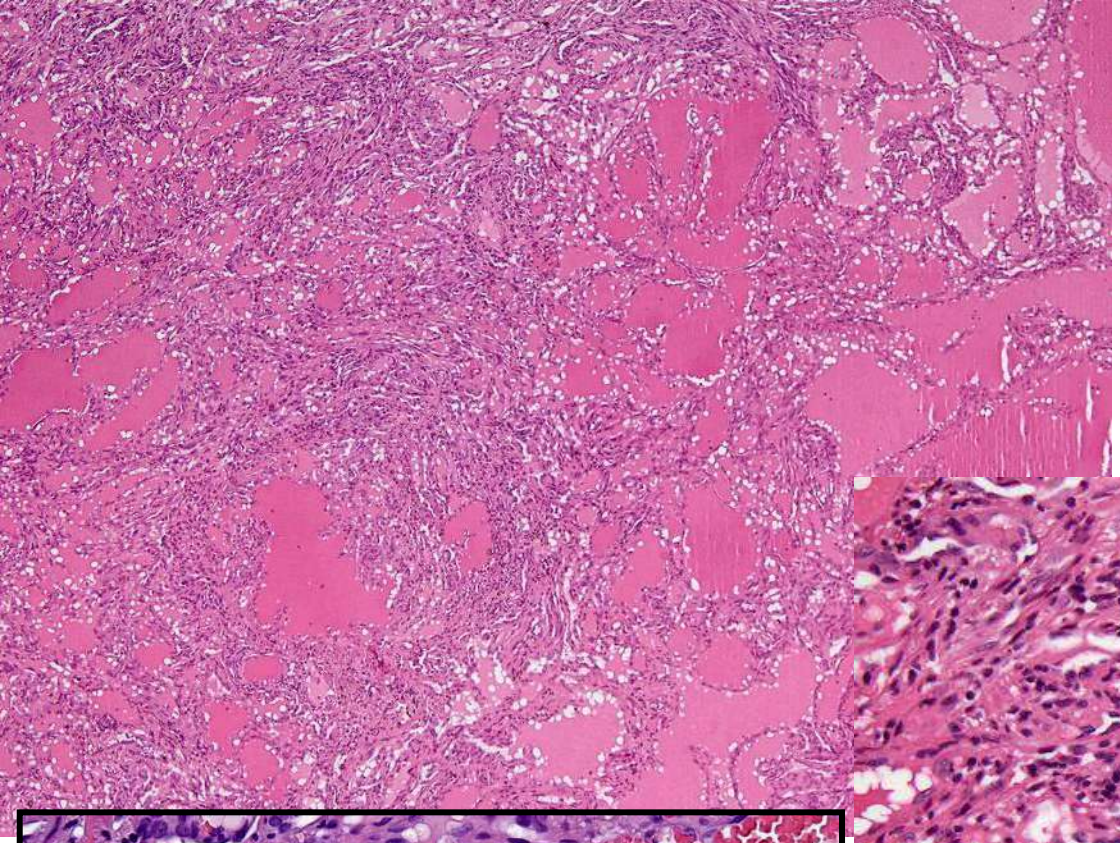
- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas

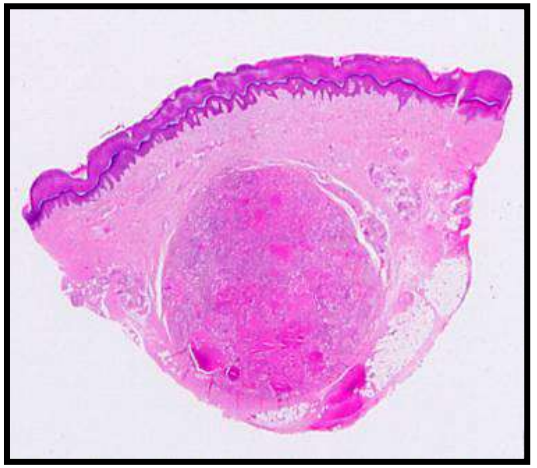
„Borderline“ malignant vascular tumours
Haemangioendotheliomas

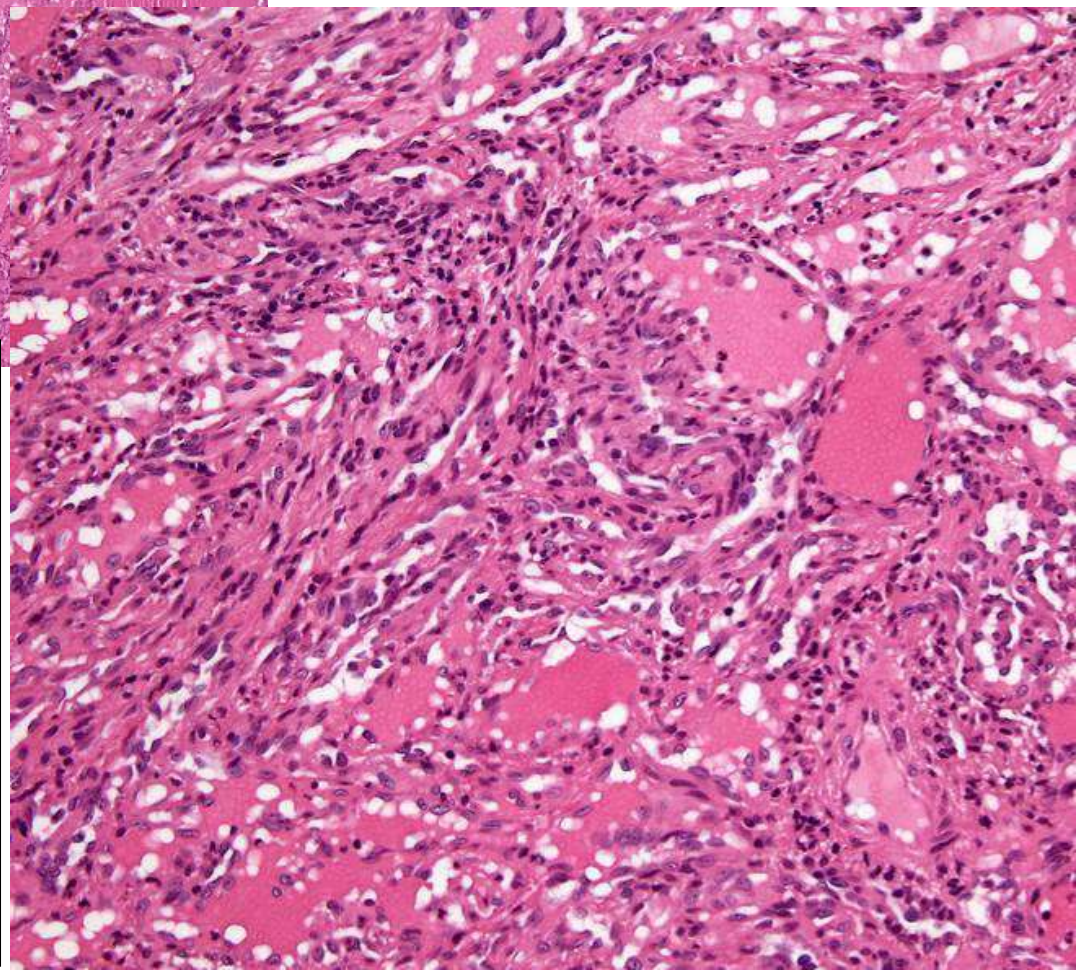
Mallory EB J Exp Med 1908; 10: 575

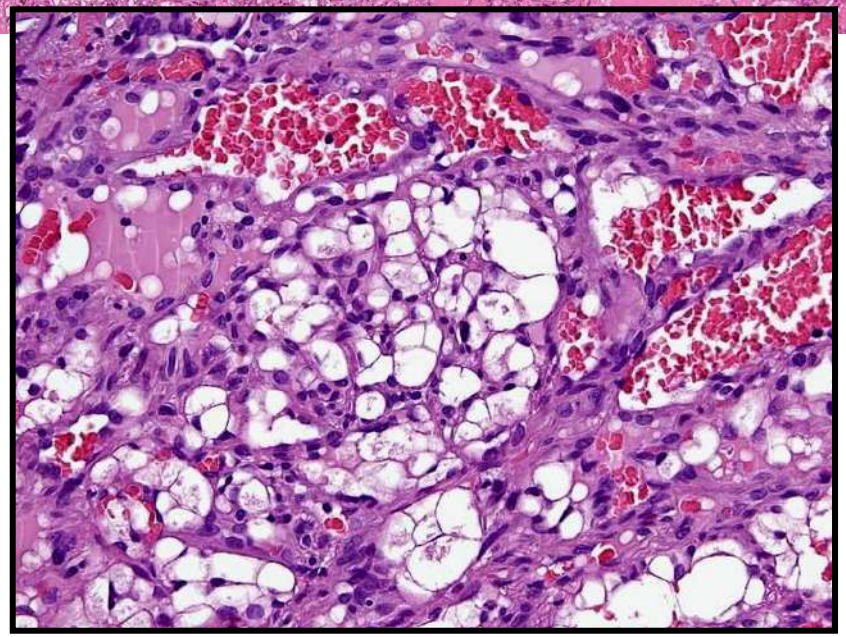
spindle cell HE	spindle cell haemangioma	⬇
Dabska Tumour	PILA, lymphatic tumour	⬇
kaposiform HE	locally aggressive	⬇
retiform HE	locally aggressive, rare MTS	
polymorphous HE	locally aggressive, rare MTS	
composite HE	locally aggressive, rare MTS	
pseudomyogenic HE	locally aggressive, rare MTS	
epithelioid HE	malignant neoplasm	⬆

„Haemangioendothelioma“
Be specific !



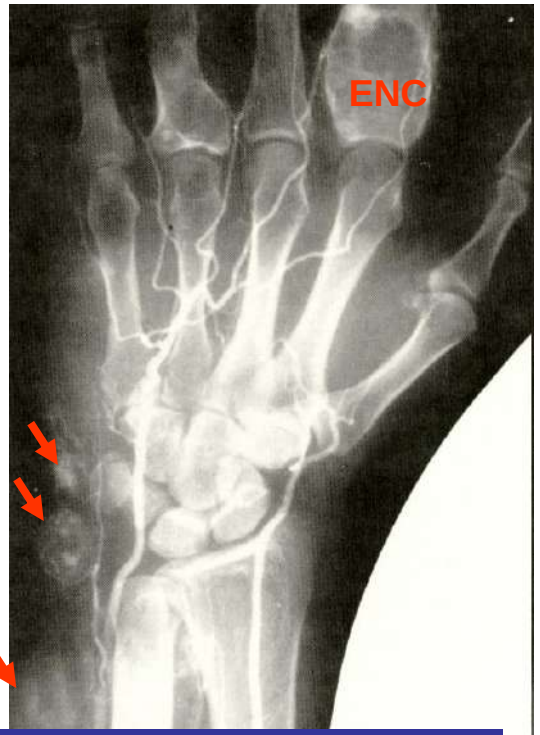




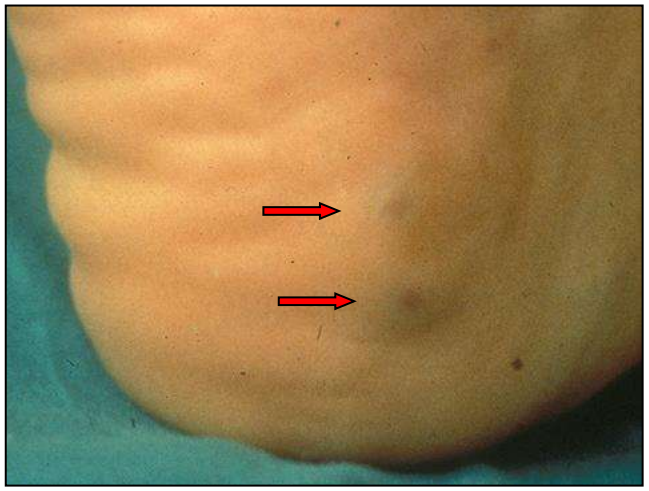


spindle cell Haemangioma

- children, young adults, also in elderly patients
- 10% of cases: associated abnormalities (lymphedema, Maffucci Syndrom, Klippel-Trenaunay Syndrom)
- dermis / subcutis of distal extremities
- 50% of cases: multiple lesion, mostly in one anatomic region
- no progression, no metastases
- small (< 2 cm), often painful, blue, dermal nodules
- *IDH 1/2* mutations



SCH in Maffucci Syndrome
AJSP 1996; 20: 1196-1204



spindle cell Haemangioma

- haemorrhagic, dermal and / or subcutaneous nodules
- well-circumscribed, unencapsulated

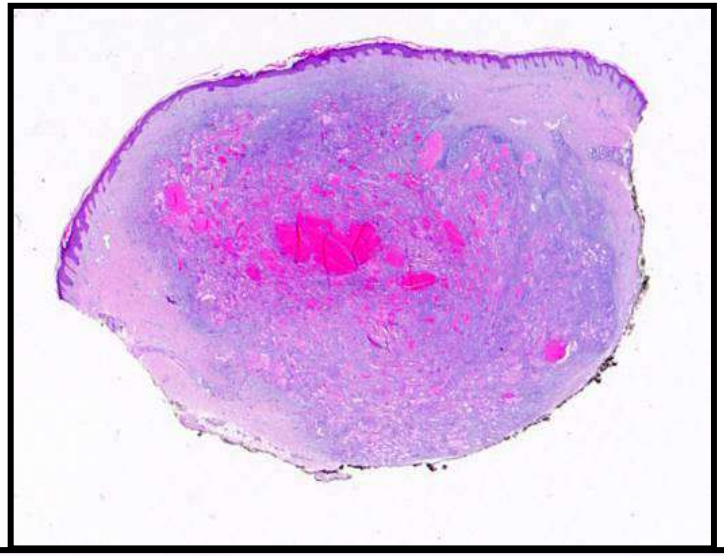
  1. dilated, cavernous vascular spaces
  2. bland spindle cells

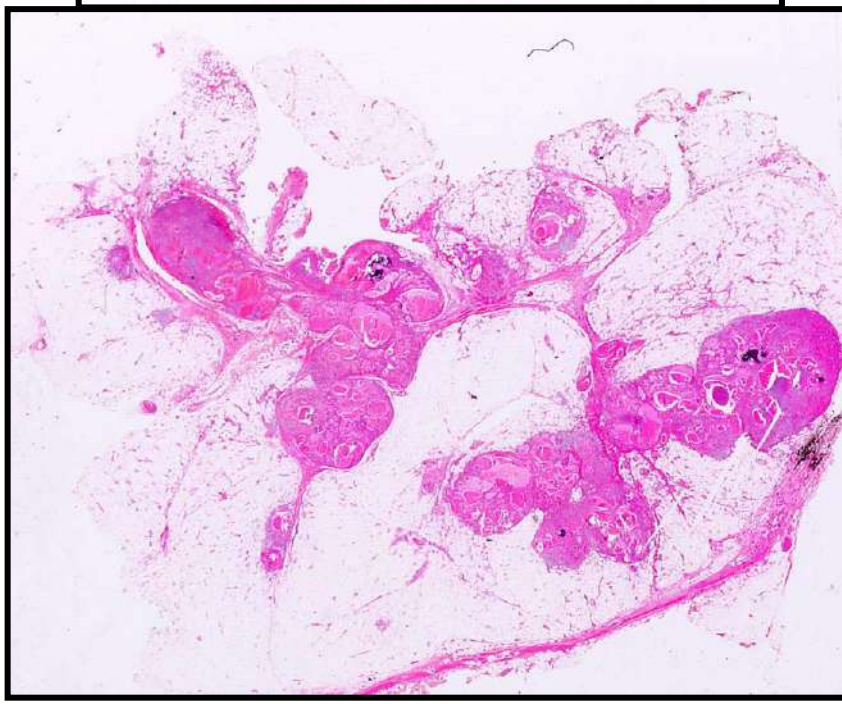
epithelioid endothelial cells (cytoplasmic vacuoles)

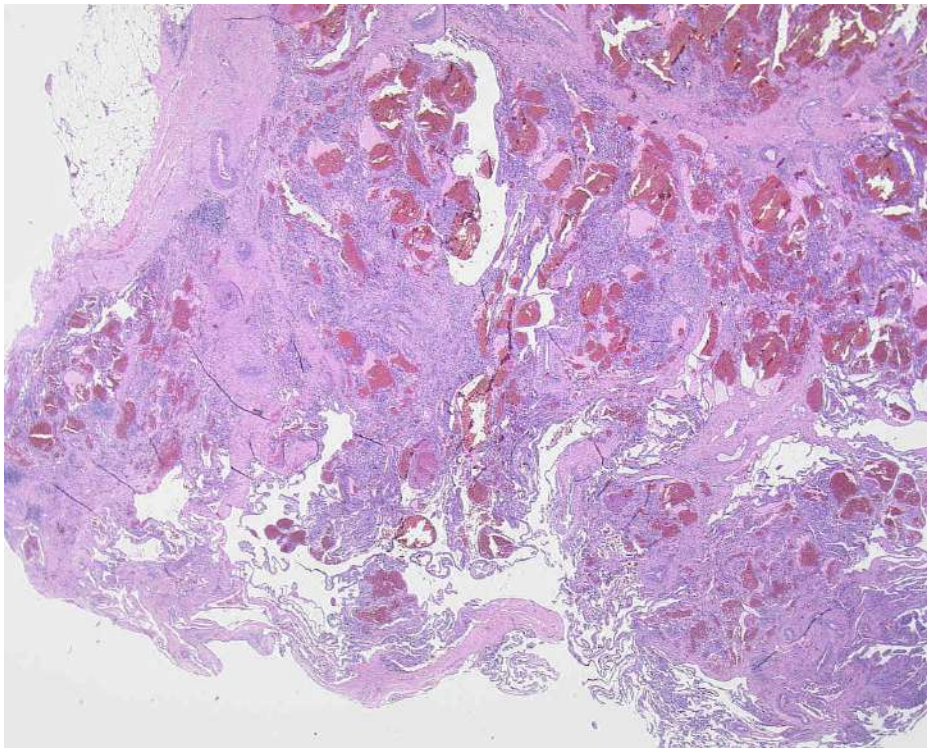
endothelial bridges

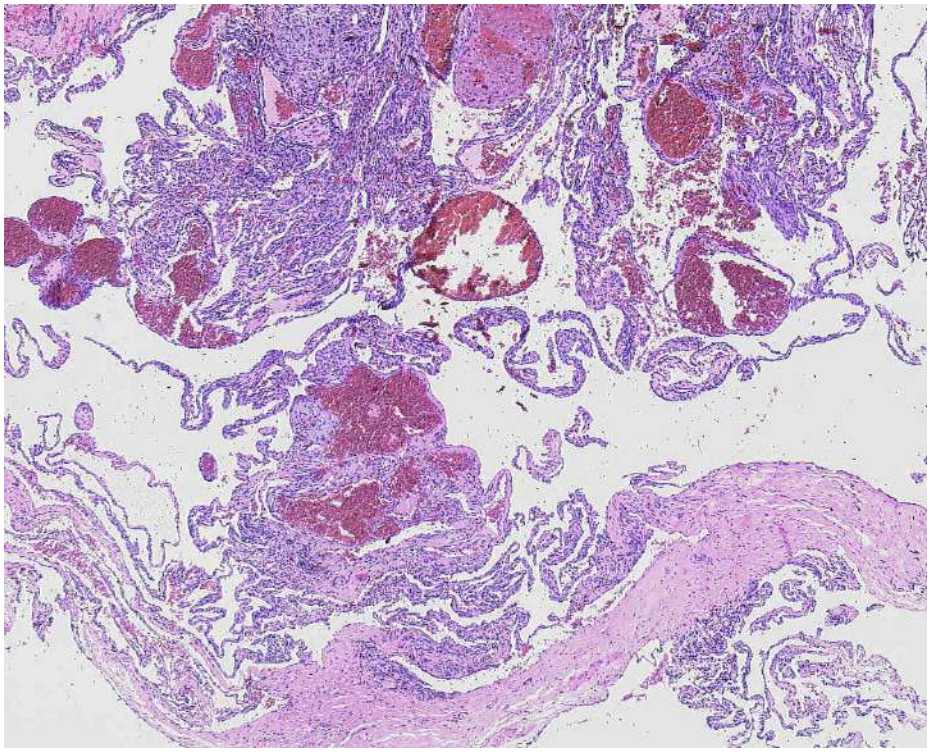
abnormal thick-walled vessels (vascular malformations)

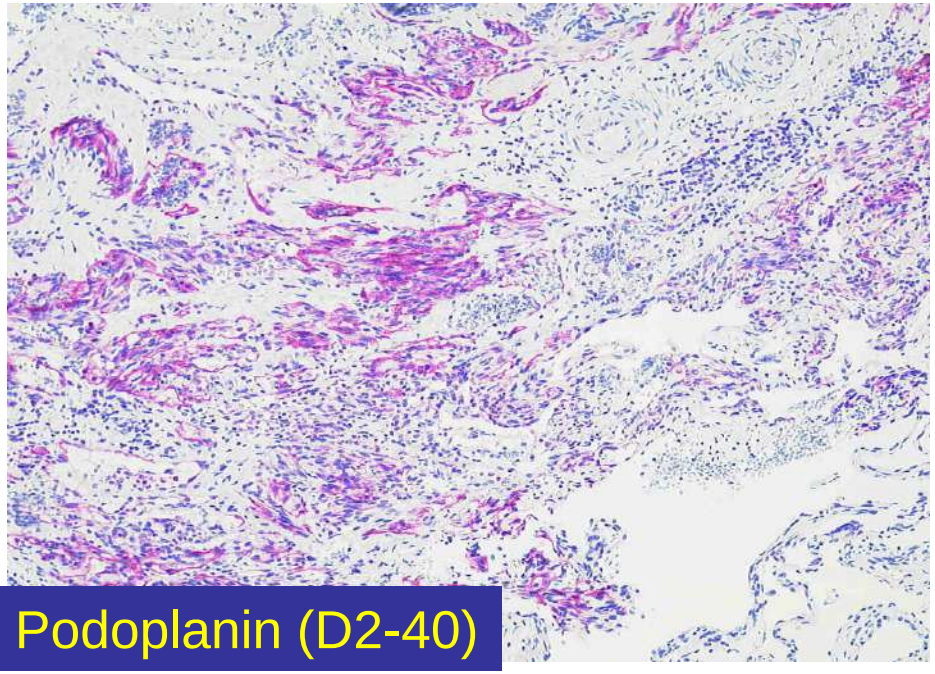
20-30% intravascular



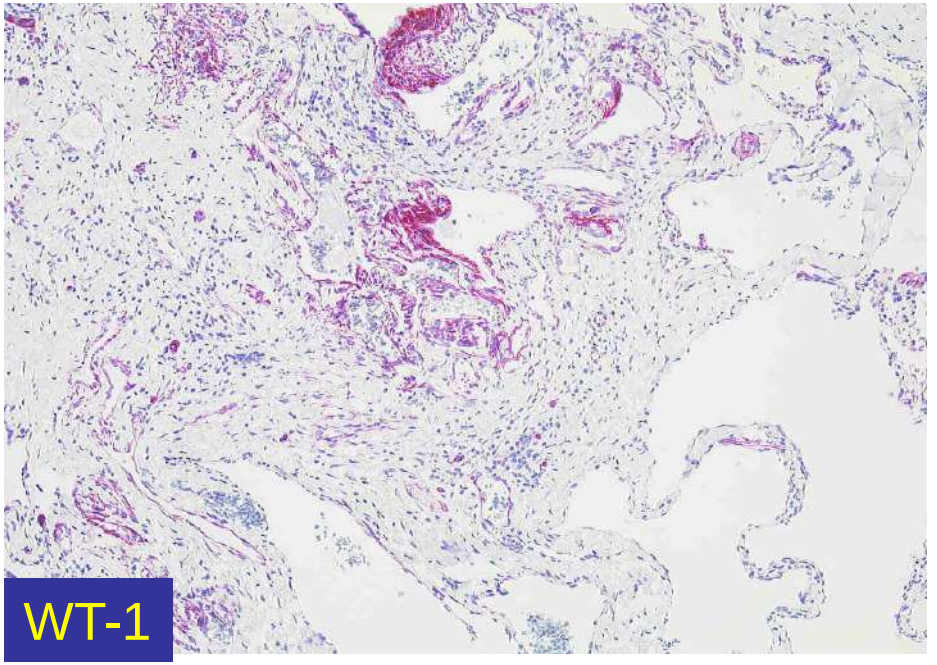








Podoplanin (D2-40)



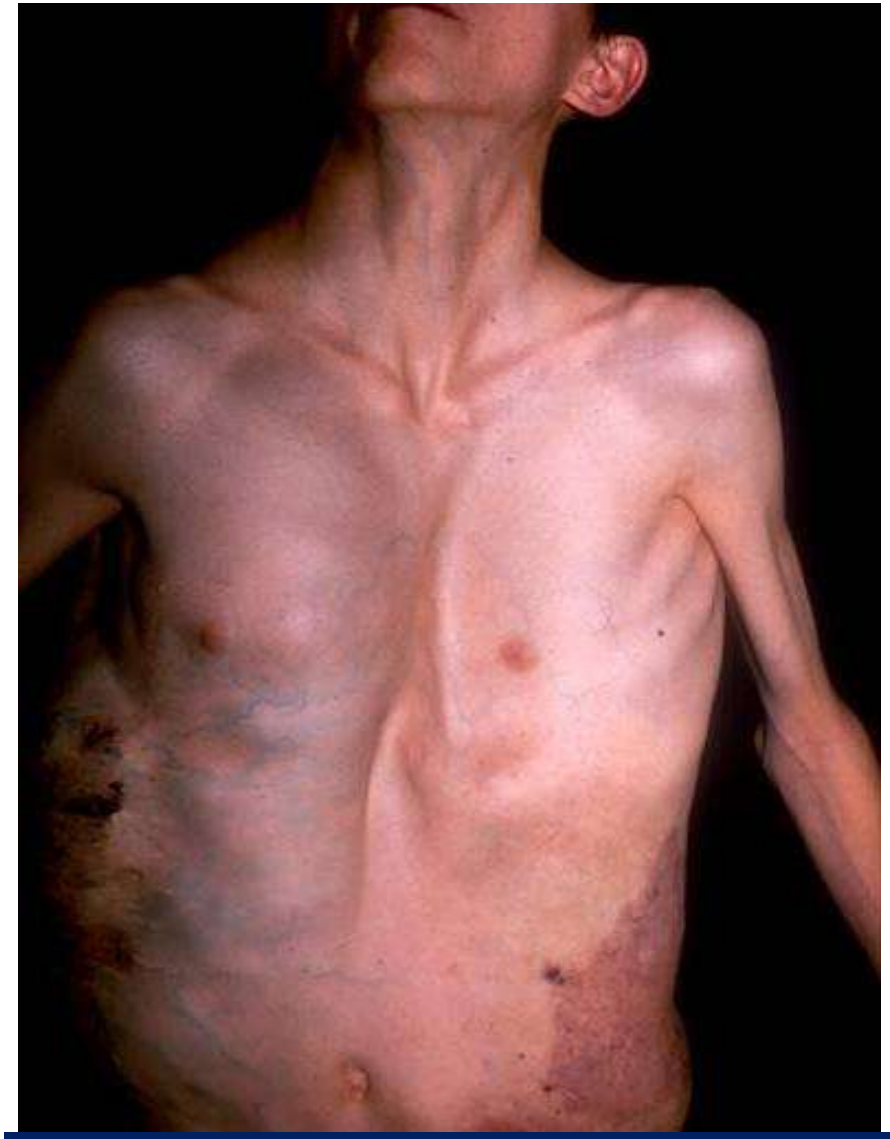
WT-1

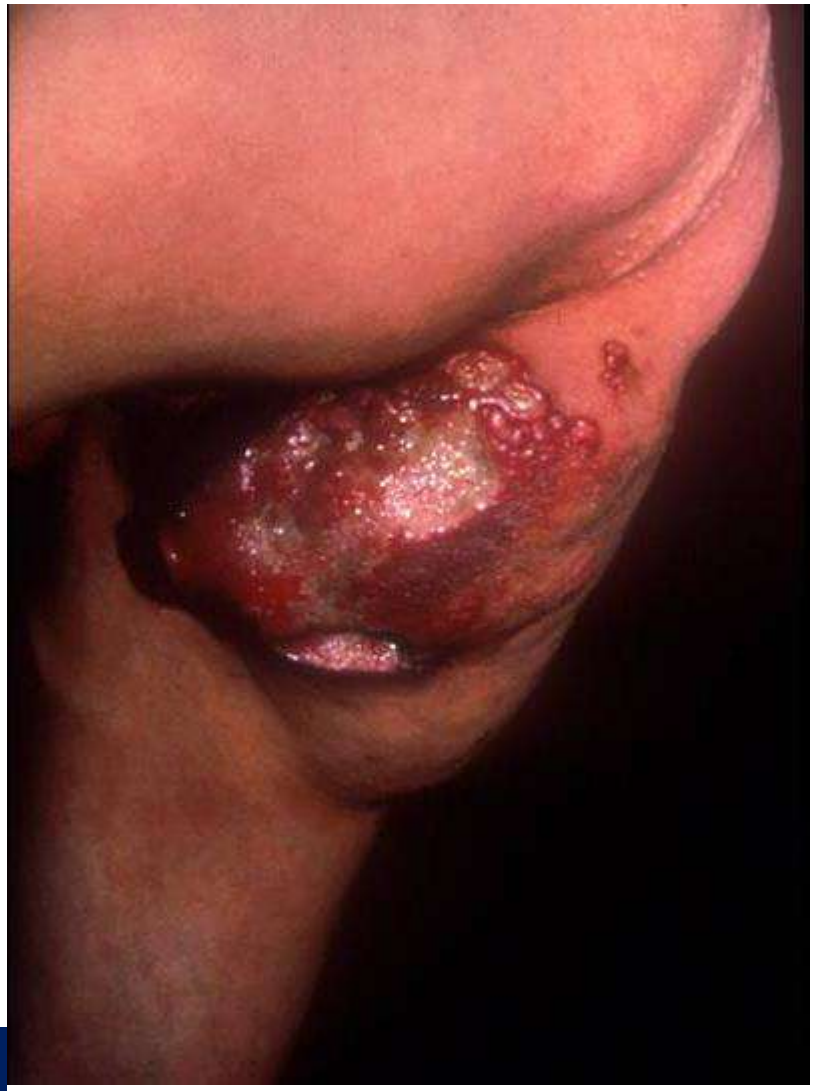
papillary intravascular Lymphangio-endothelioma* (Dabska´s Tumour)

- children and young adults, locally aggressive, good prognosis, no metastases
- lymphangioma-like vascular spaces, prominent, hobnail endothelial cells, intravascular papillae (coll.core, hobnail cells)
- no surrounding actin + myopericytes, foci of lymphatic infiltrate

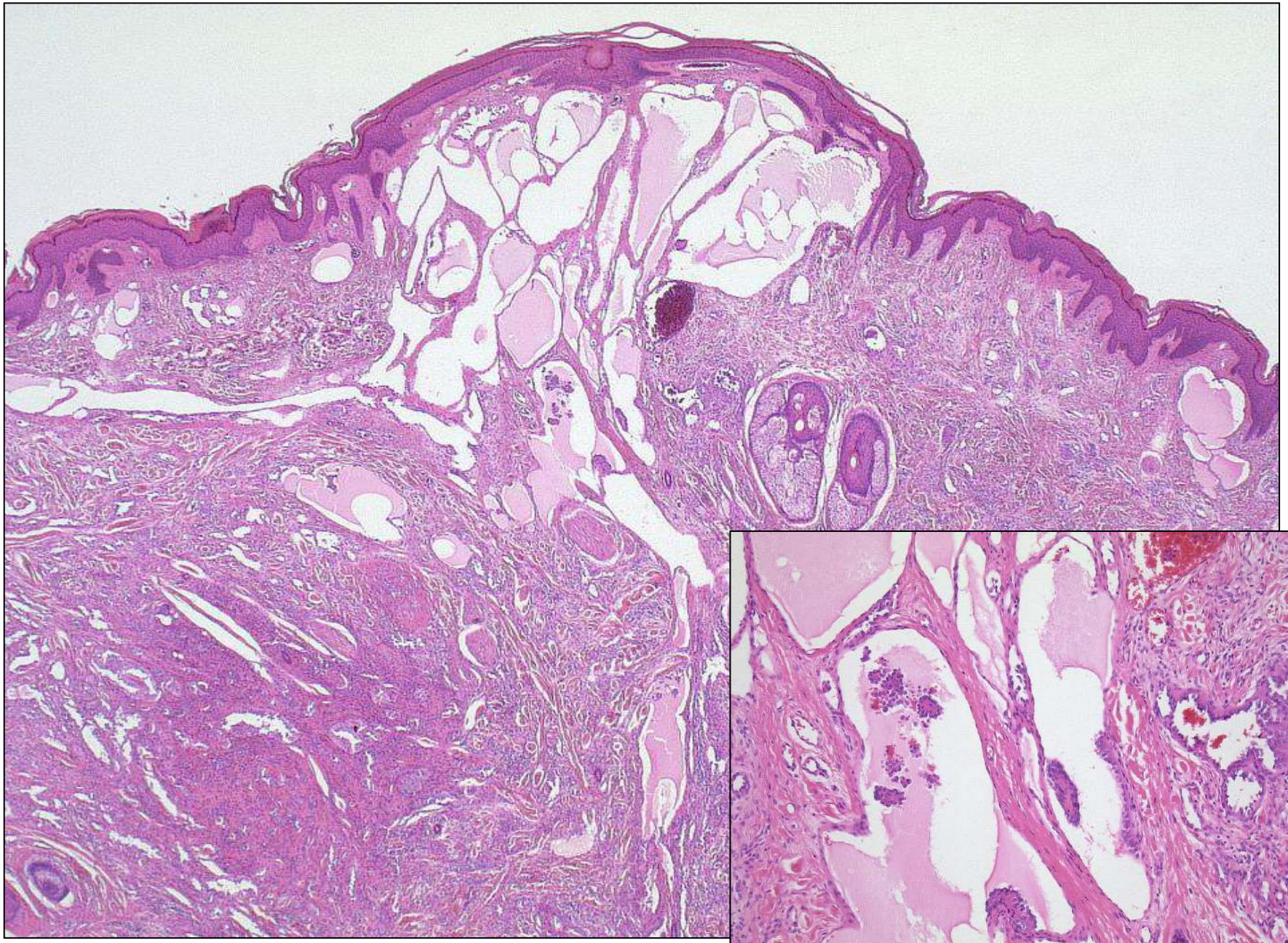
*** Fanburg-Smith JC et al. AJSP 1999; 23: 1004**

papillary intravascular Lymphangioendothelioma

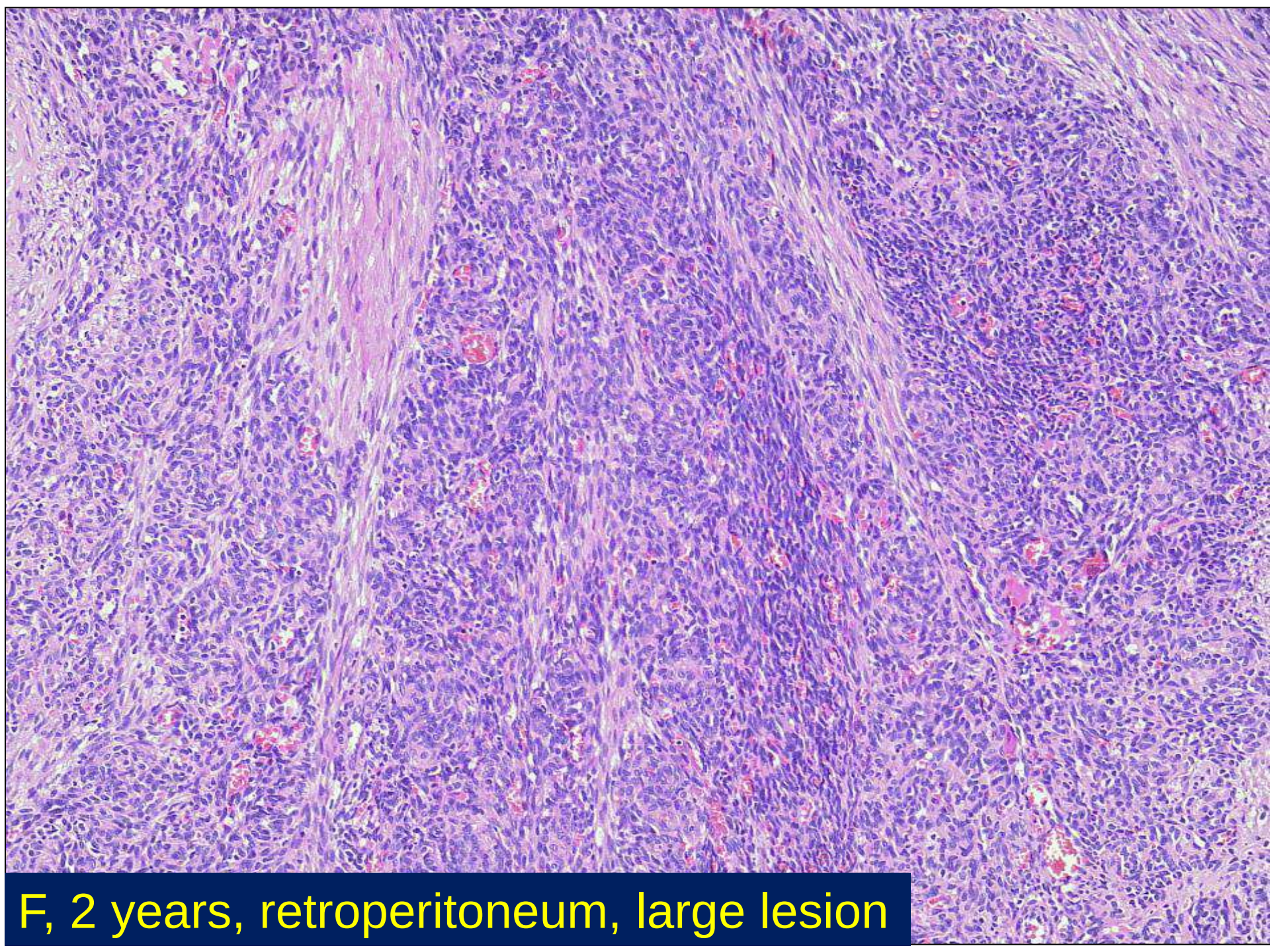


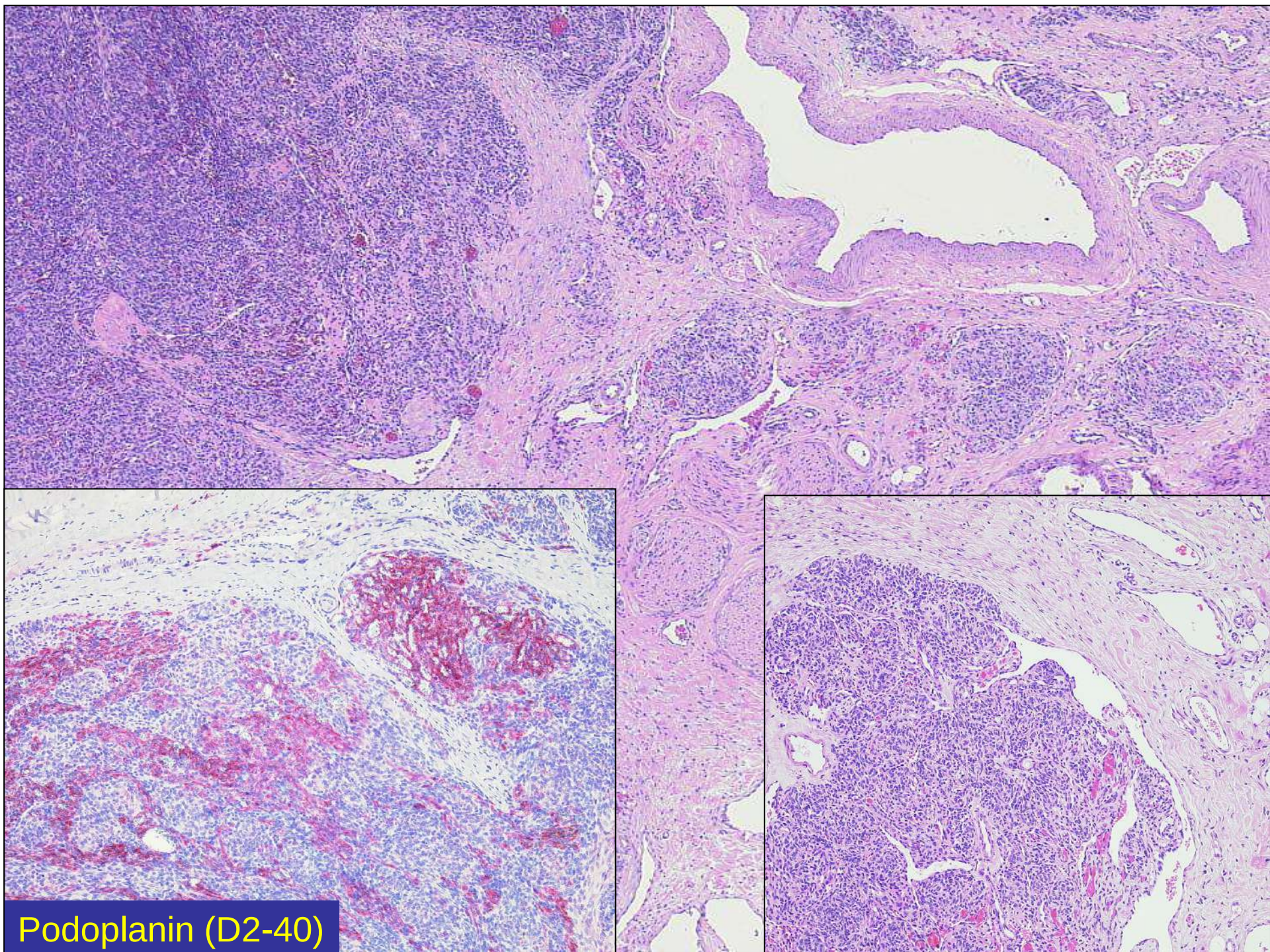


courtesy of Dr.L.Requena, Madrid



M, 15 years, thigh


F, 2 years, retroperitoneum, large lesion

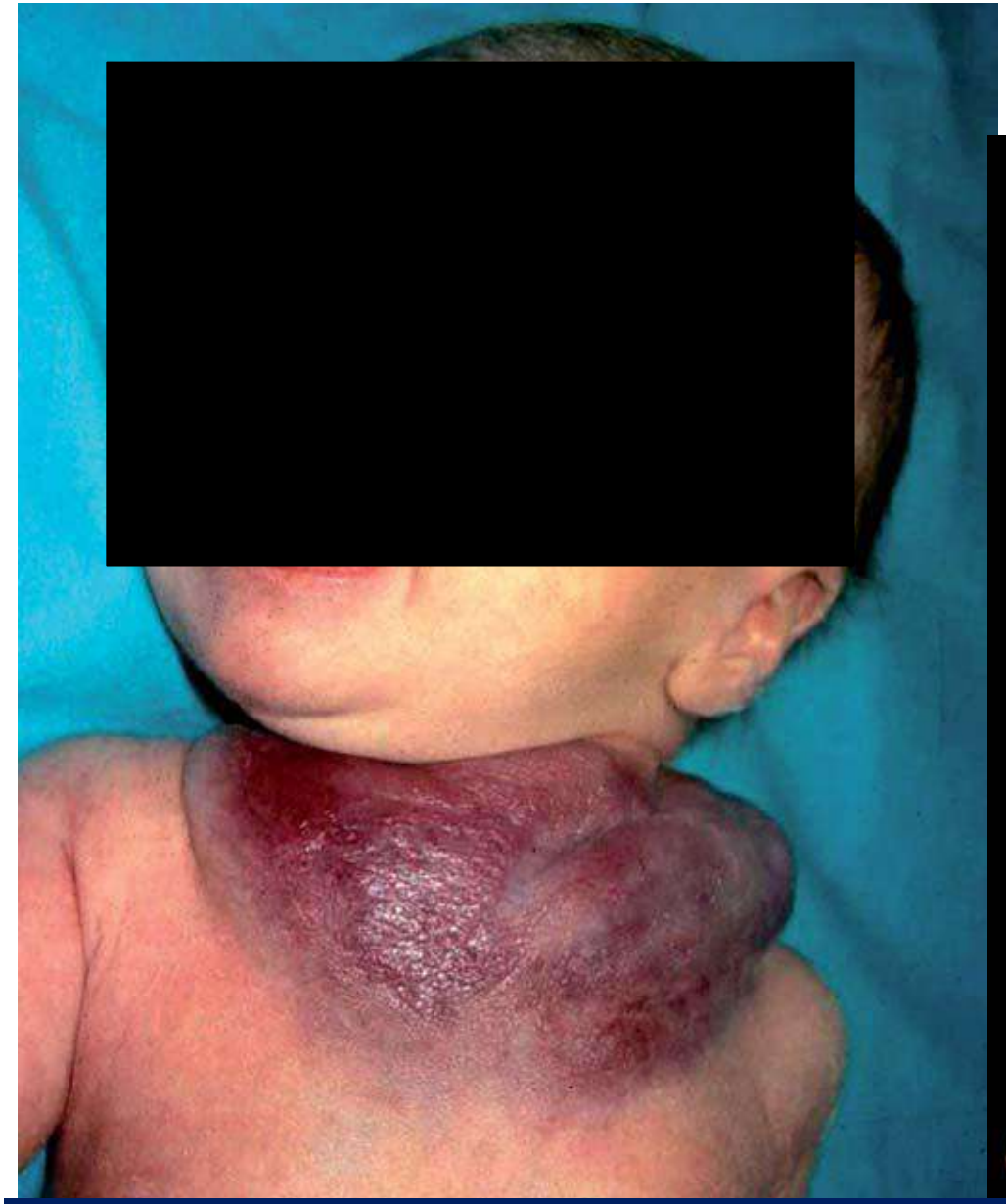

Podoplanin (D2-40)

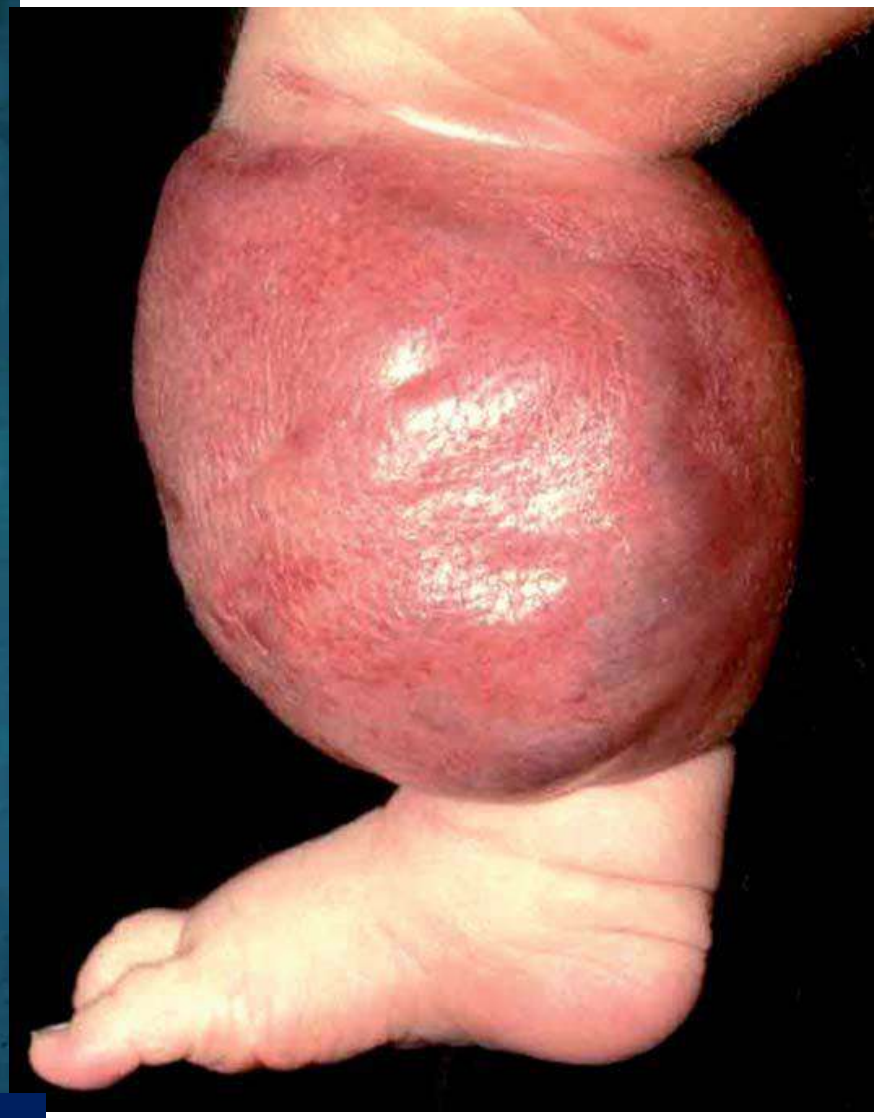
kaposiform Haemangioendothelioma*

- children >> adults, retroperitoneum, extremities
- deep soft tissues >> dermal
- prognosis related to size and depth !
- locally aggressive, no metastases

  Cave: Kasabach Merritt syndrome
- cellular neoplasm, lobular growth
- bland spindled cells, fibrin thrombi
- focally podoplanin +, prox-1 +, LYVE-1 +
- associated lymphangiomatous changes
- spectrum with tufted haemangioma !

* Tsang WY, Chan JKC AJSP 1991; 15: 982
Zukerberg LR et al. AJSP 1993; 17: 321



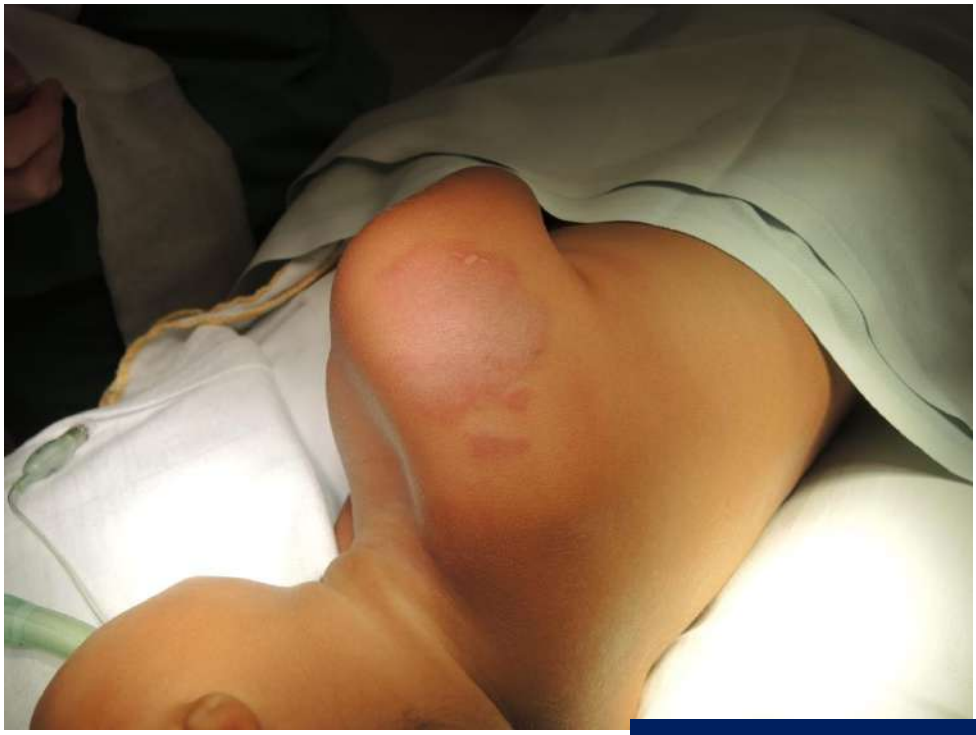


courtesy of Dr.L.Requena, Madrid

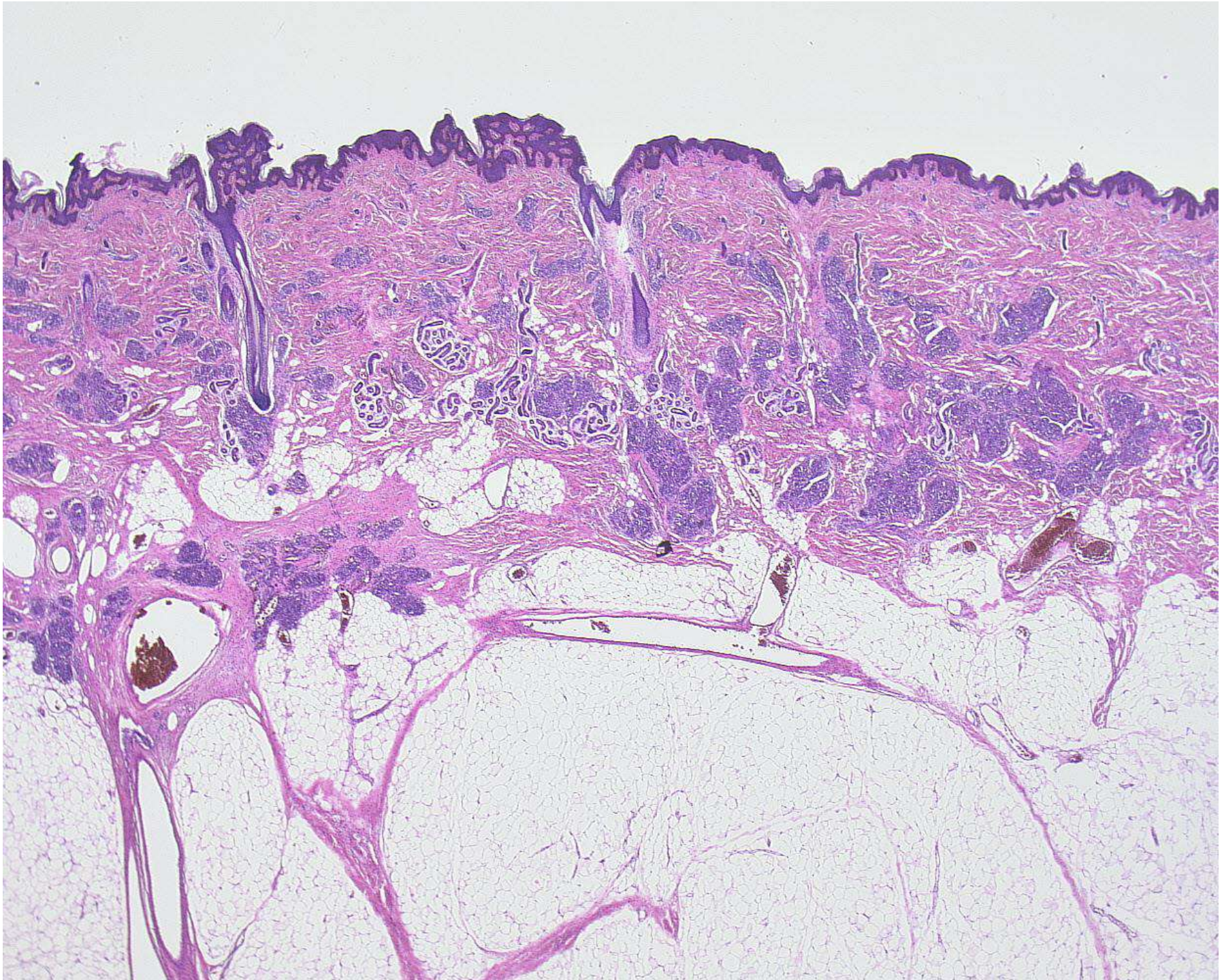
tufted Haemangioma

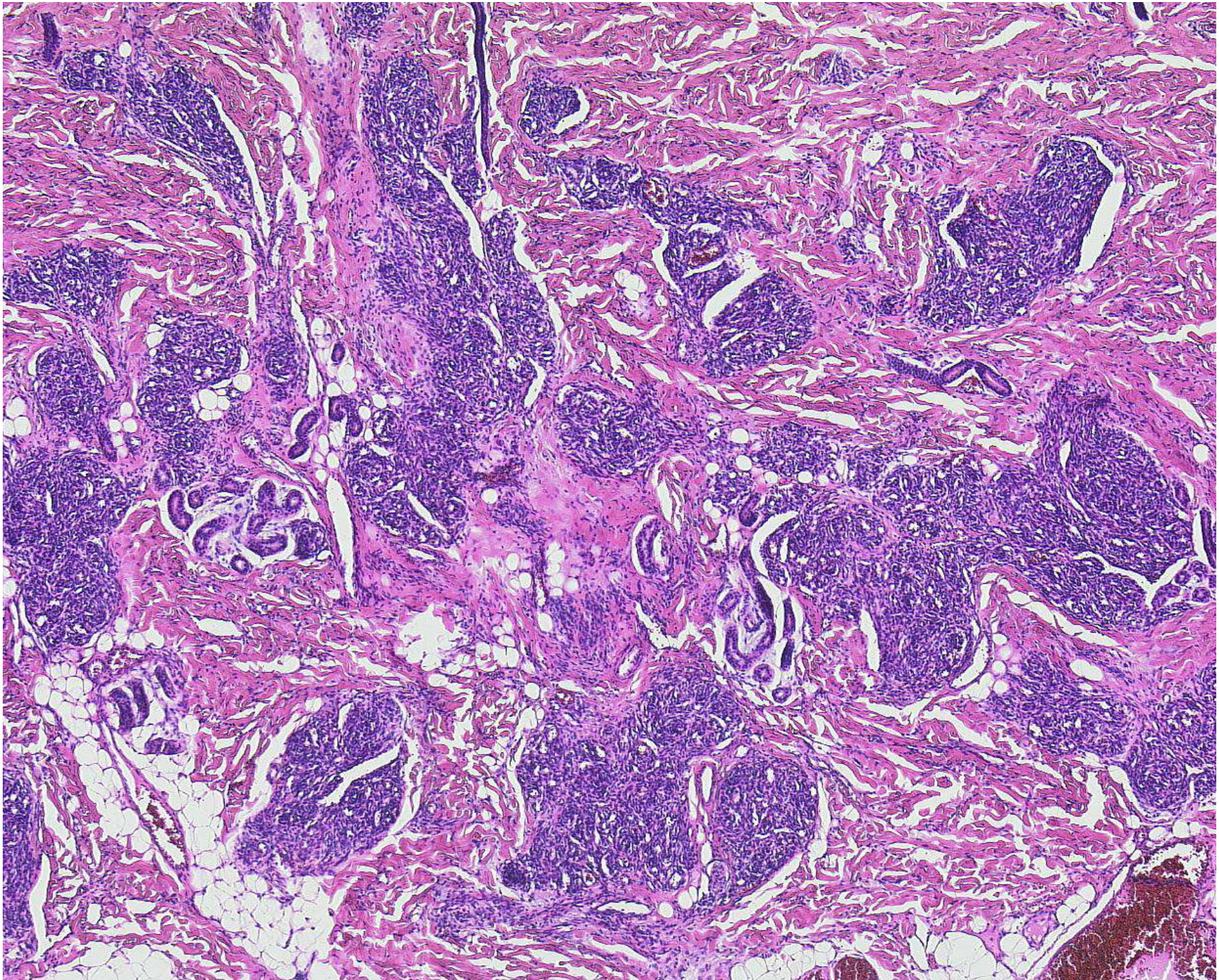
Pathological Findings

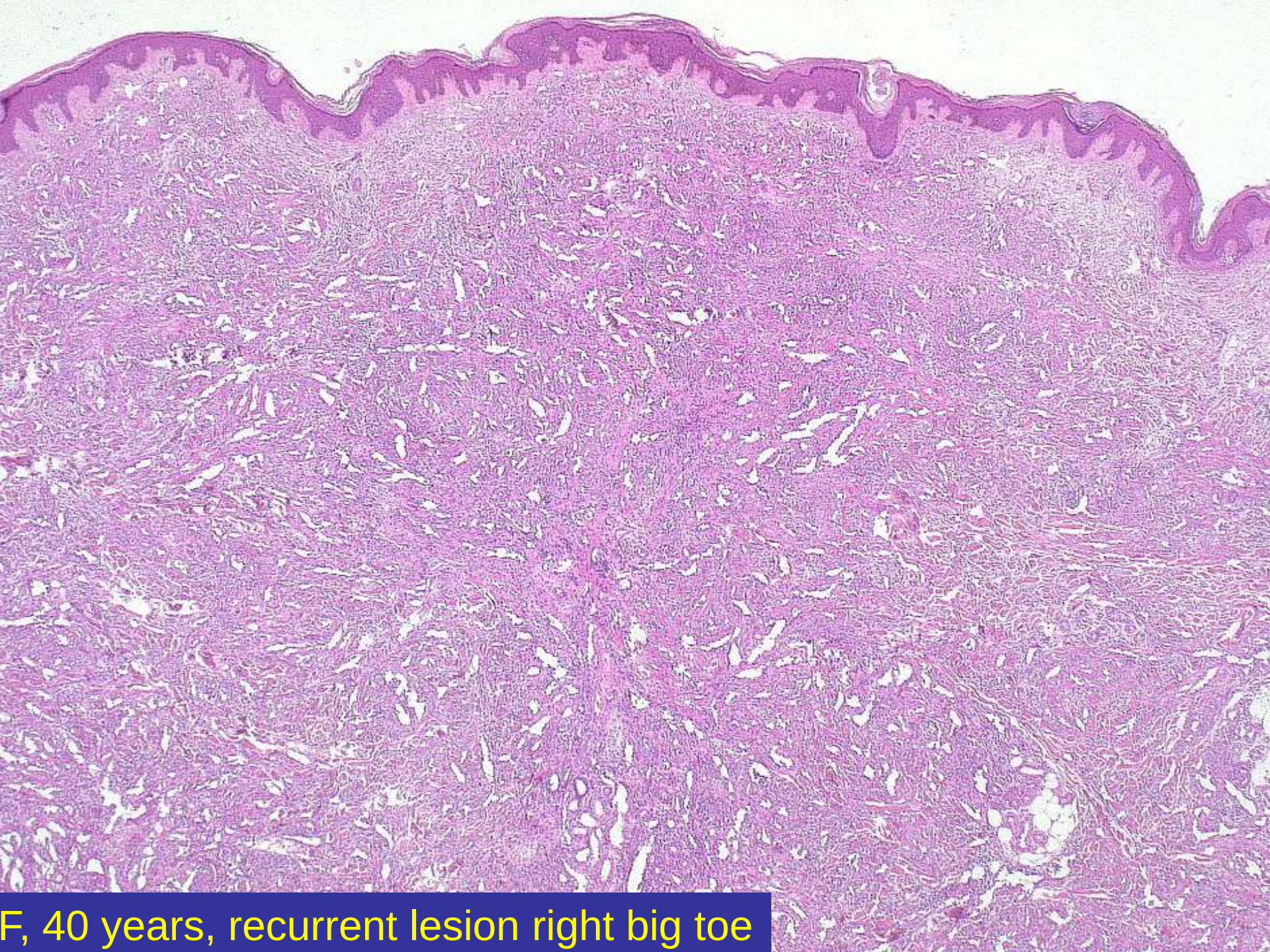
- infants, children >> adults
  head / neck, trunk
- slowly growing lesions
- cannon-ball distribution
  of cellular vascular tufts
- peripheral lymphangio-
  matous changes
- CD31 +, ASMA +
  Podoplanin focal +
- spectrum with kaposiform
  haemangioendothelioma



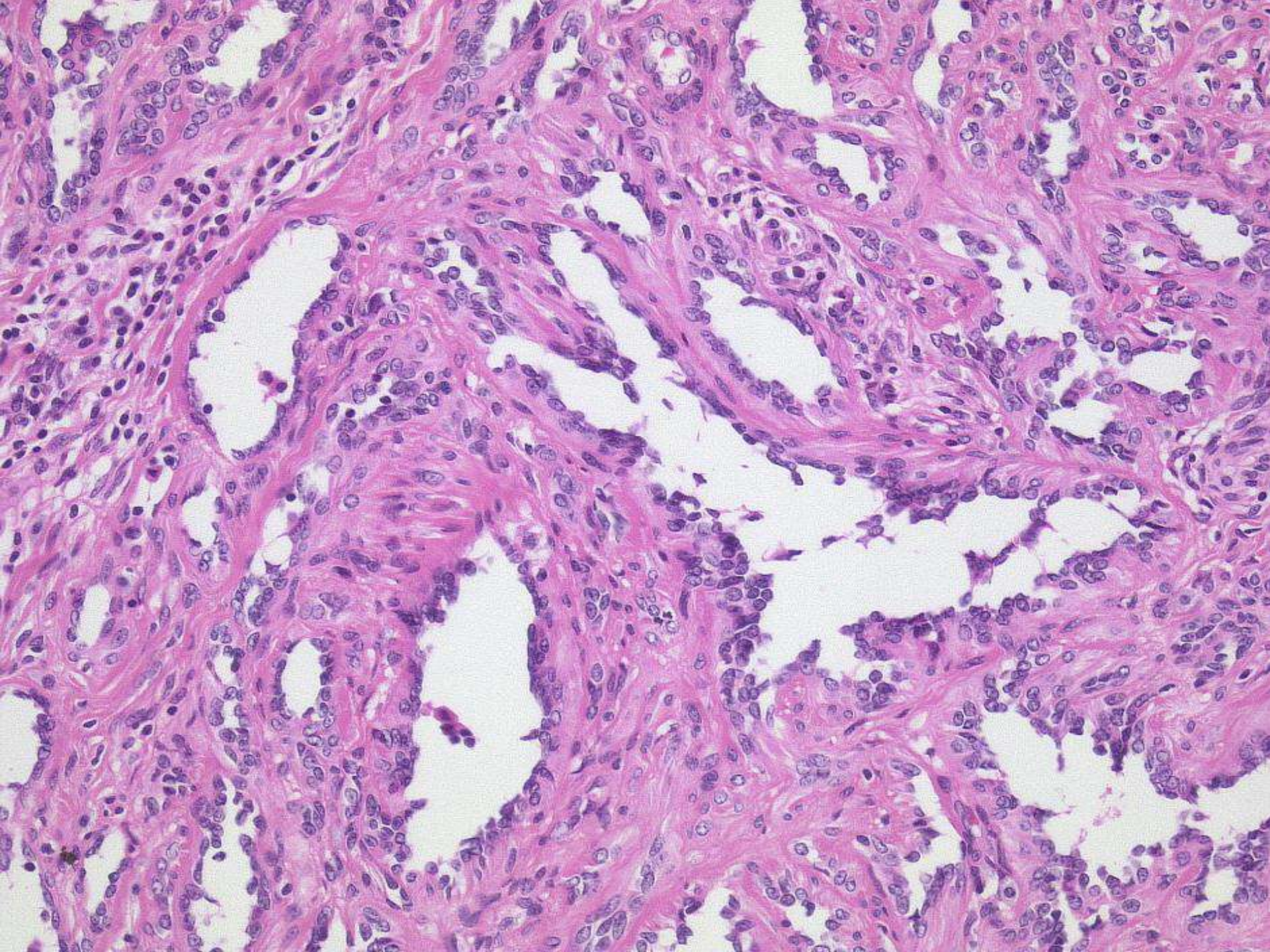
F, 18 months







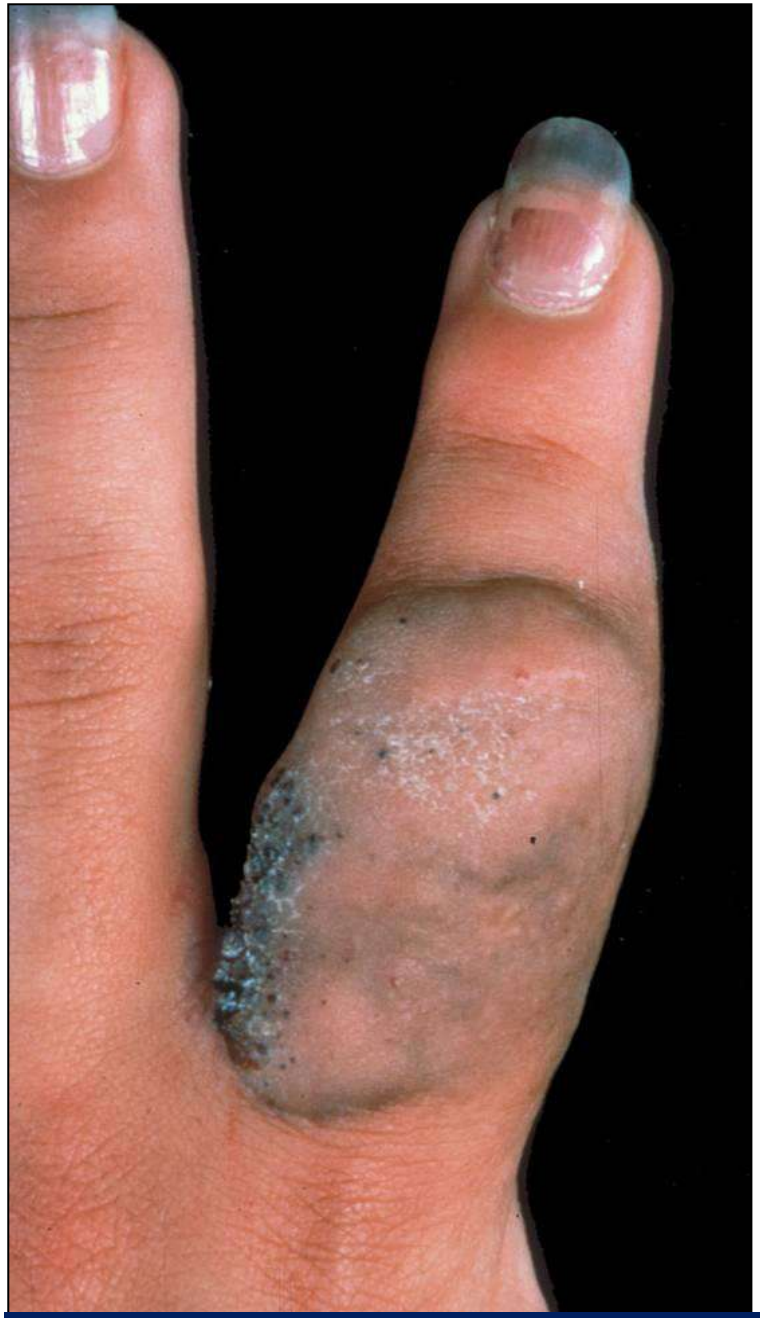
F, 40 years, recurrent lesion right big toe



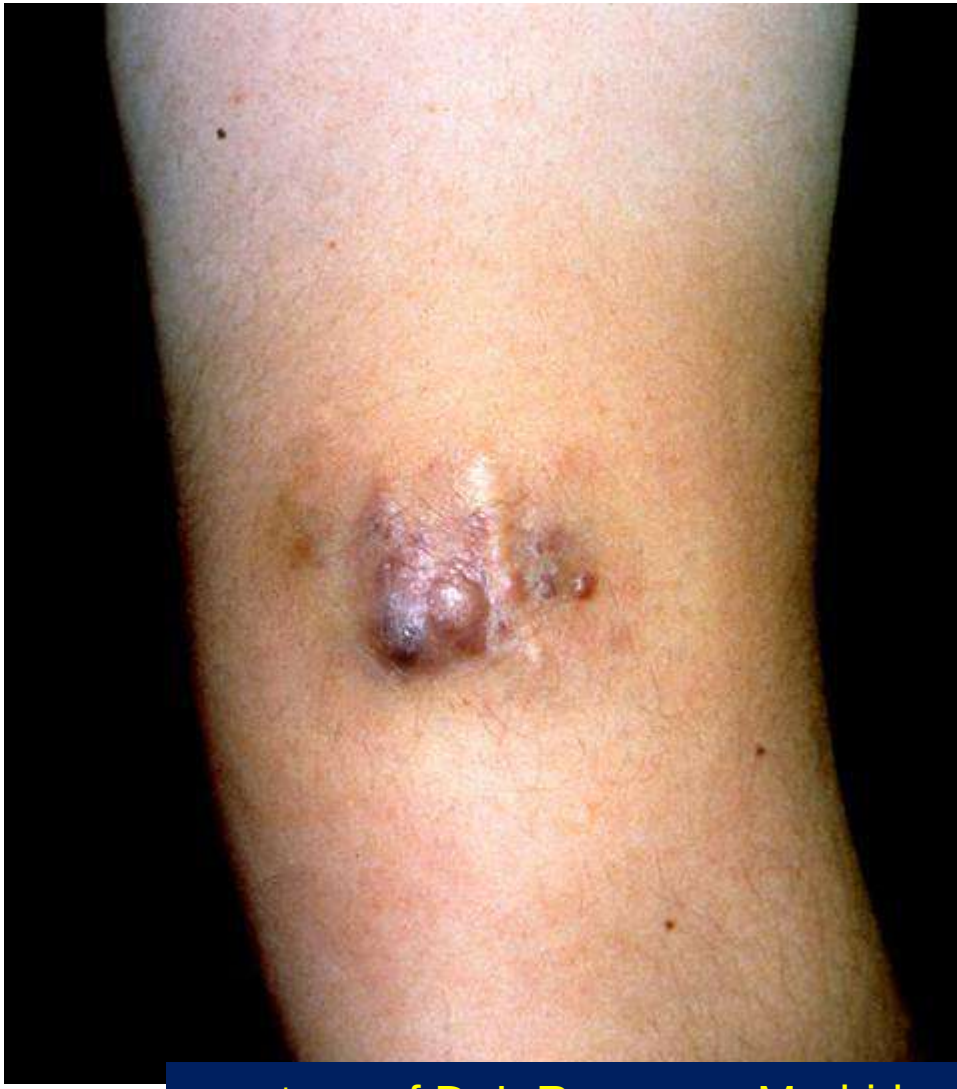
retiform Haemangioendothelioma*

- young adults, dermis, subcutis,
  often distal extremities
- slowly growing red-bluish plaques, nodules
- destructive growth, many R, rare metastases
- very rarely multiple lesions
- retiform vascular channels
  hobnail endothelial cells, solid foci possible,
  associated lymphocytes
- CD31 +, CD34 -/+, VEGFR +, D2-40 +

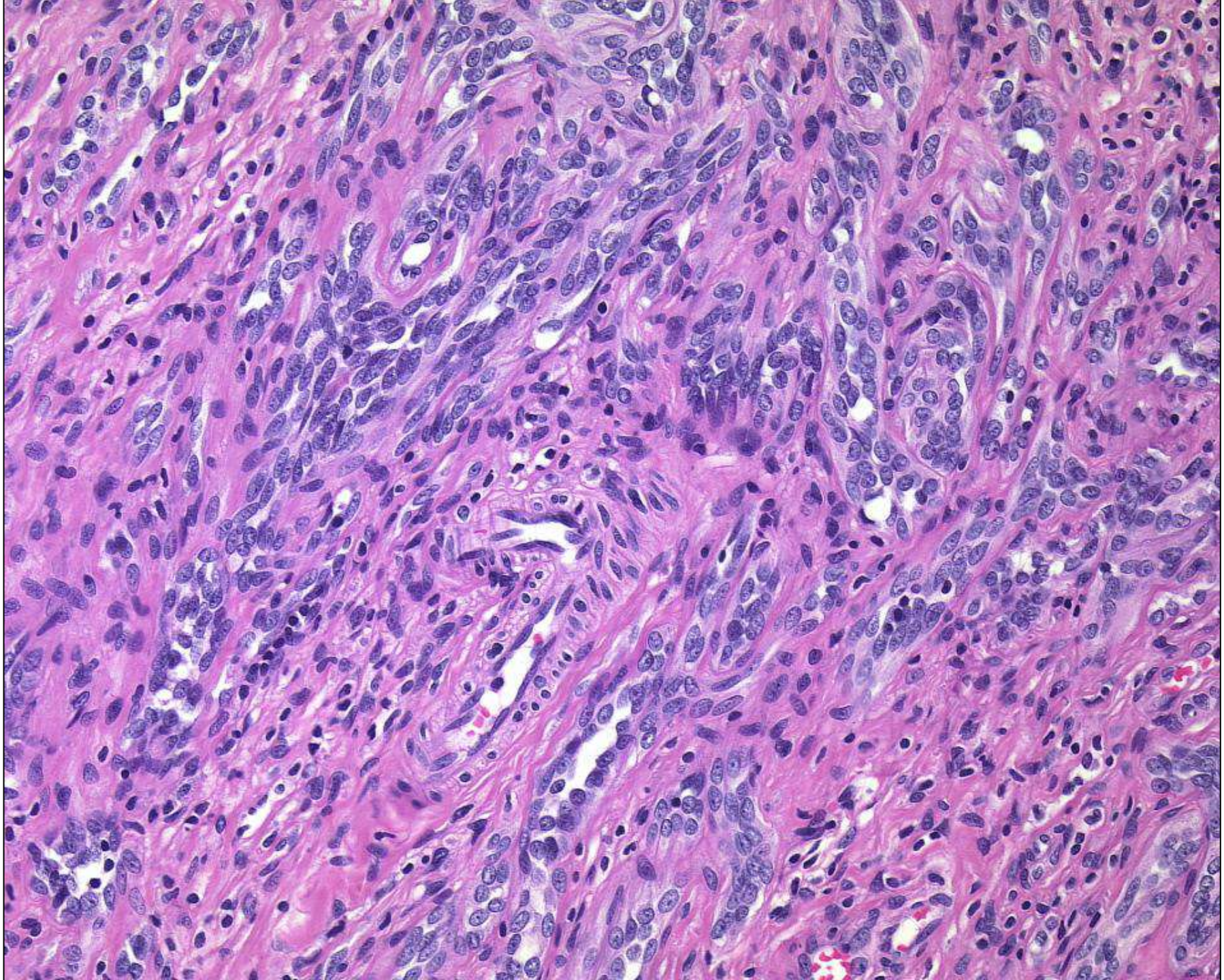
* Calonje E et al. AJSP 1994; 18: 115

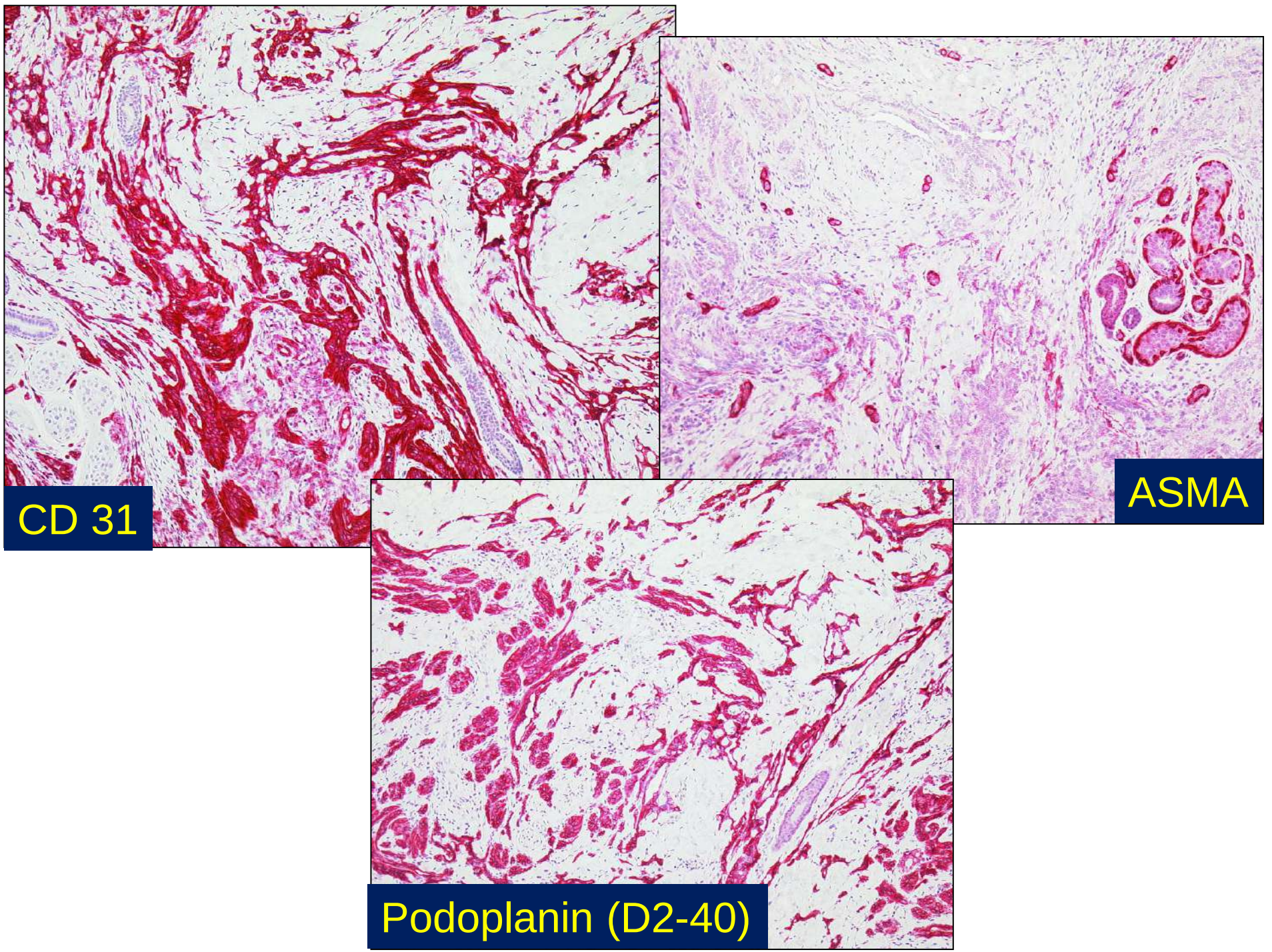


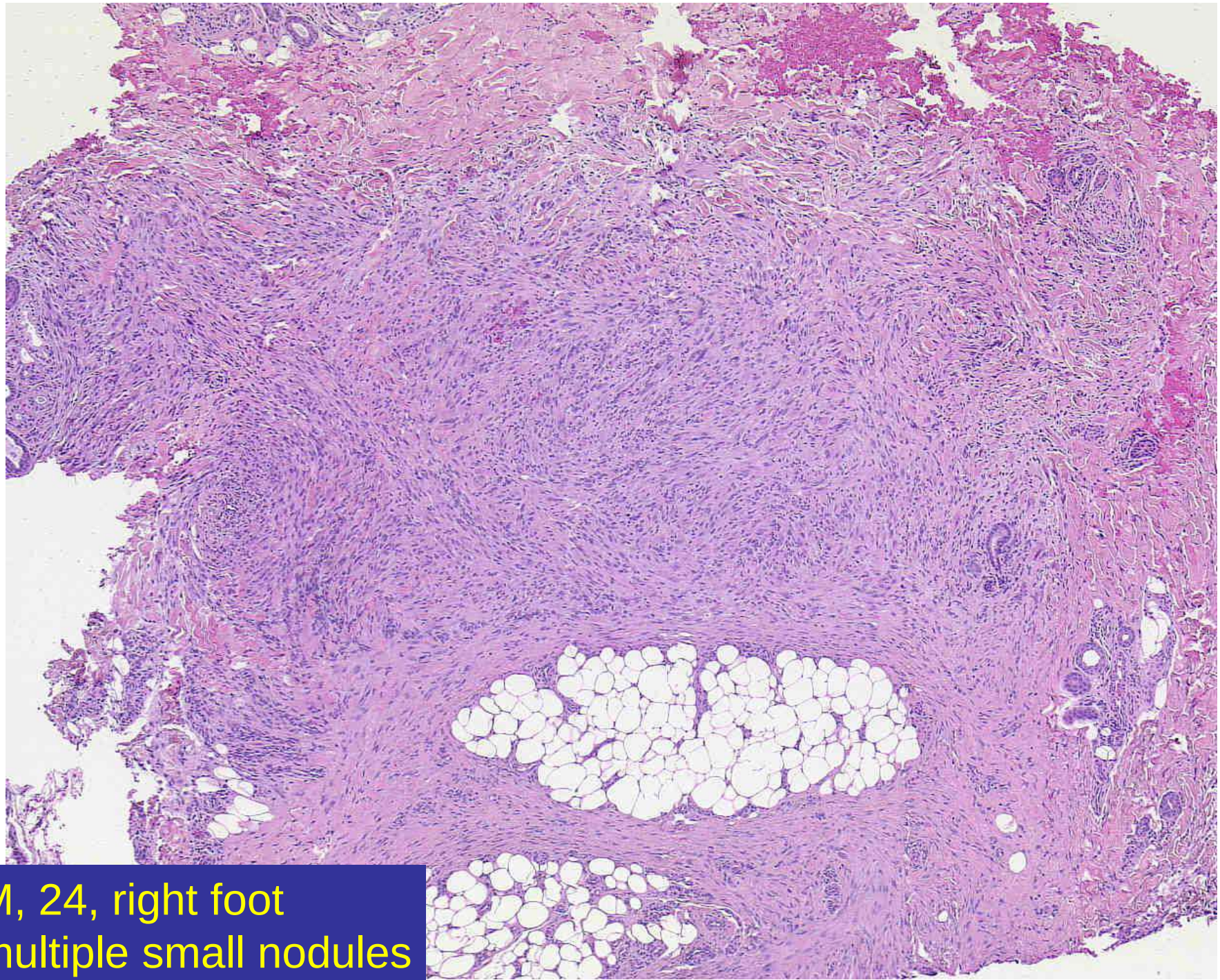
courtesy of ProF.Dr.Fletcher, Boston



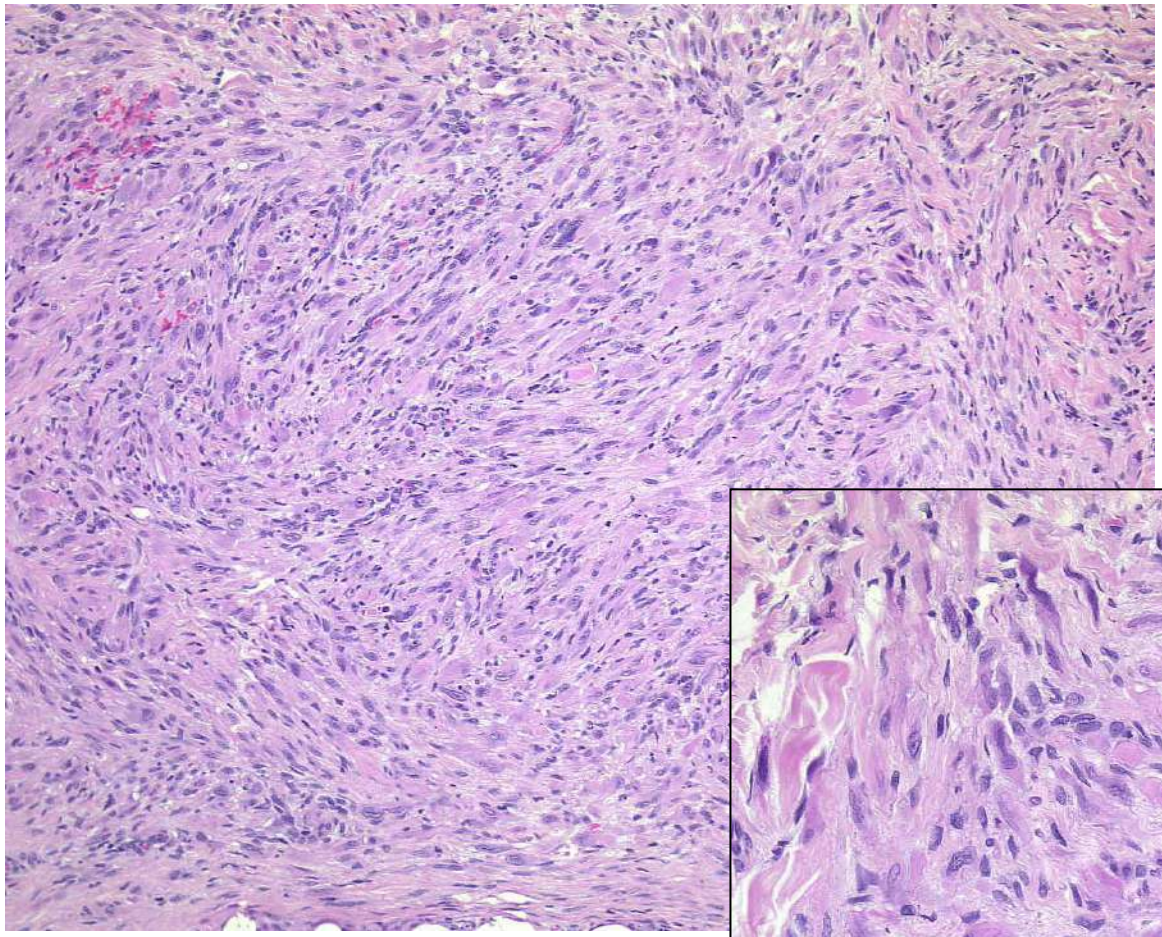
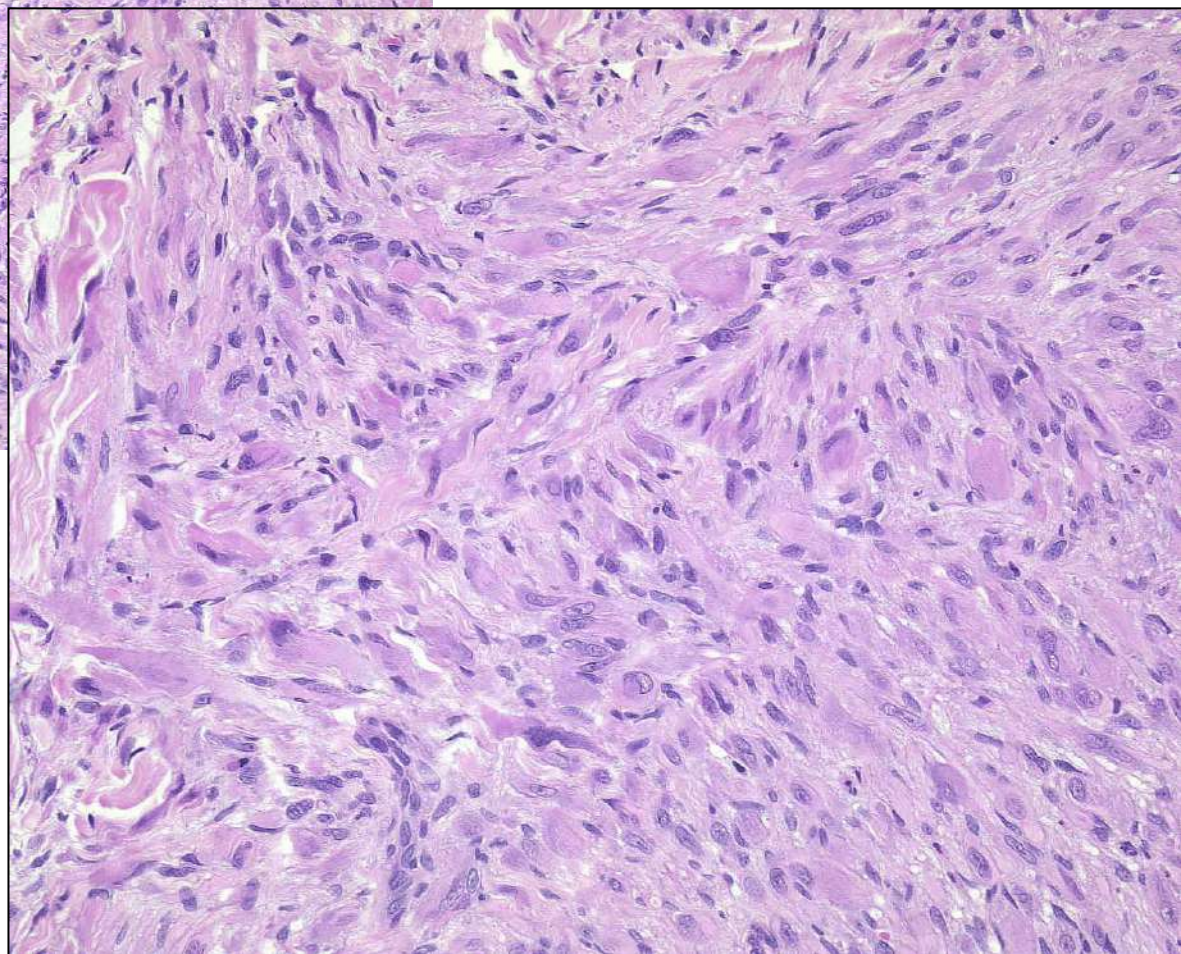
courtesy of Dr.L.Requena, Madrid

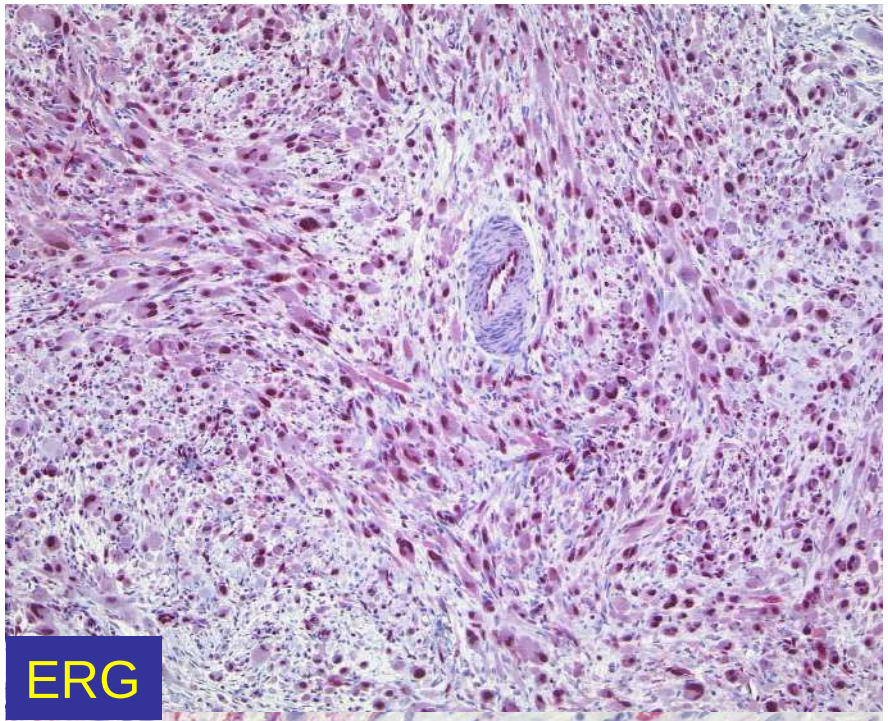


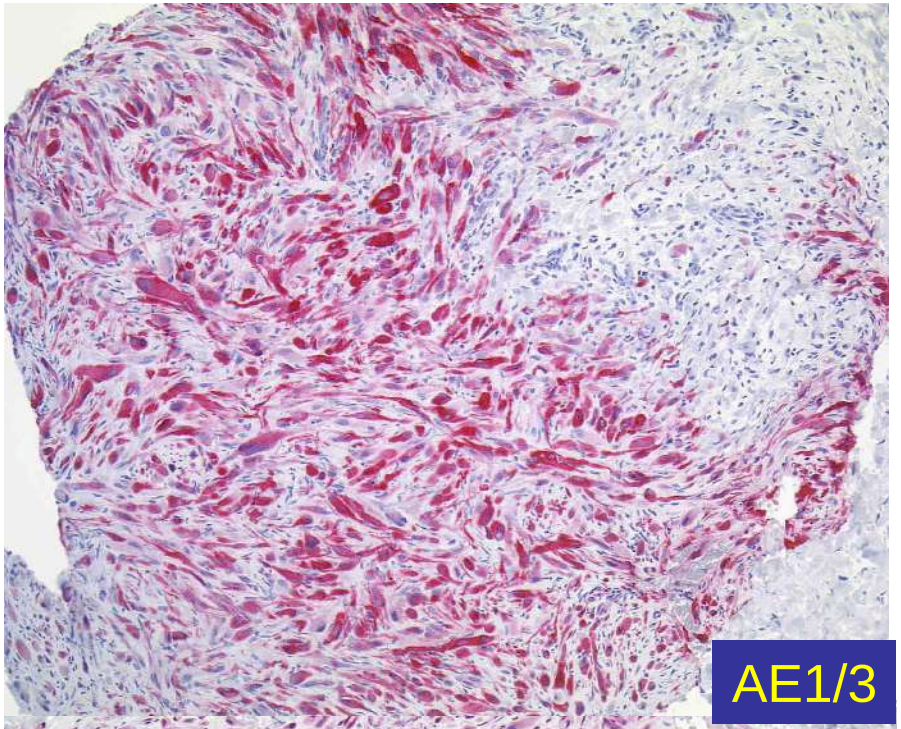

CD 31
ASMA
Podoplanin (D2-40)

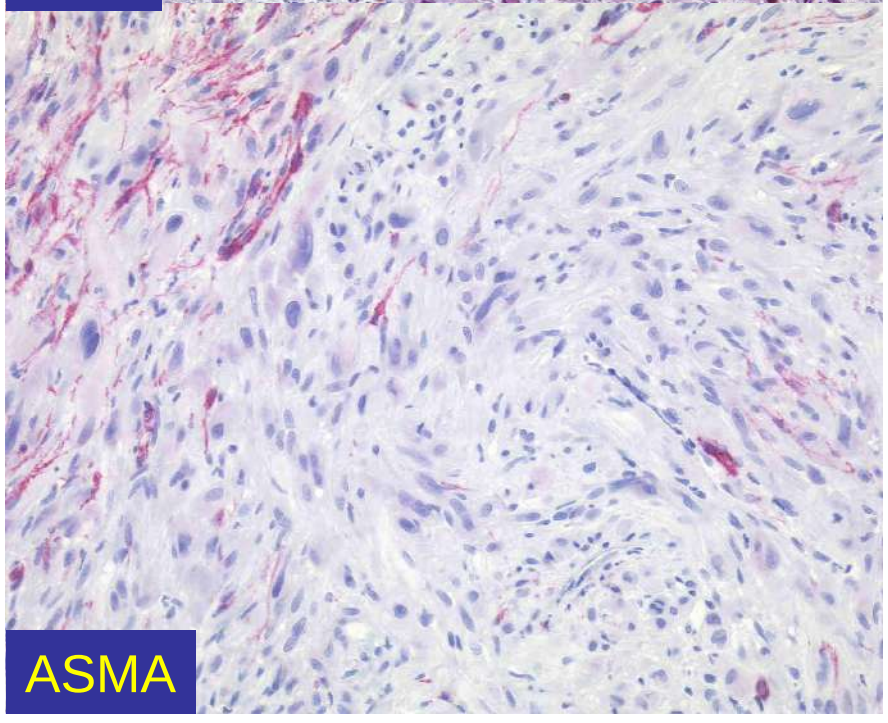


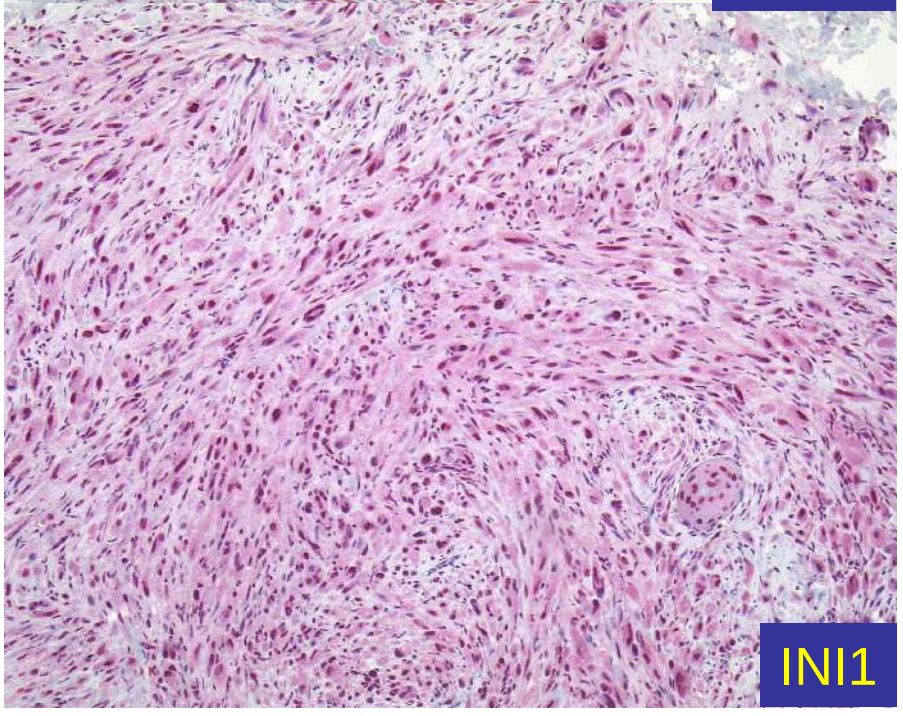
M, 24, right foot
multiple small nodules


ERG


AE1/3


ASMA


INI1

pseudomyogenic Hemangioendothelioma: A distinctive, often multicentric tumor with indolent behavior

(„epithelioid sarcoma-like Hemangioendothelioma“)

(Hornick JL, Fletcher CDM AJSP 2011; 35: 190)

- 50 cases, 41 M, 9 F, 14 - 80 years
- extremities >> trunk, head / neck region
  dermis / subcutis > deep soft tissue > bone
- multifocal neoplasms (2-15 neoplasms) (66%)
- fascicles, sheets of plump spindled cells,
  few epithelioid cells, neutrophils
- AE1/3 +, MNF116 -, Fli-1 +, 22/47 CD 31 +,
  7/49 EMA +, CD 34 -, INI1 +, S-100 -
- local recurrence (58%), MTS (2 x)

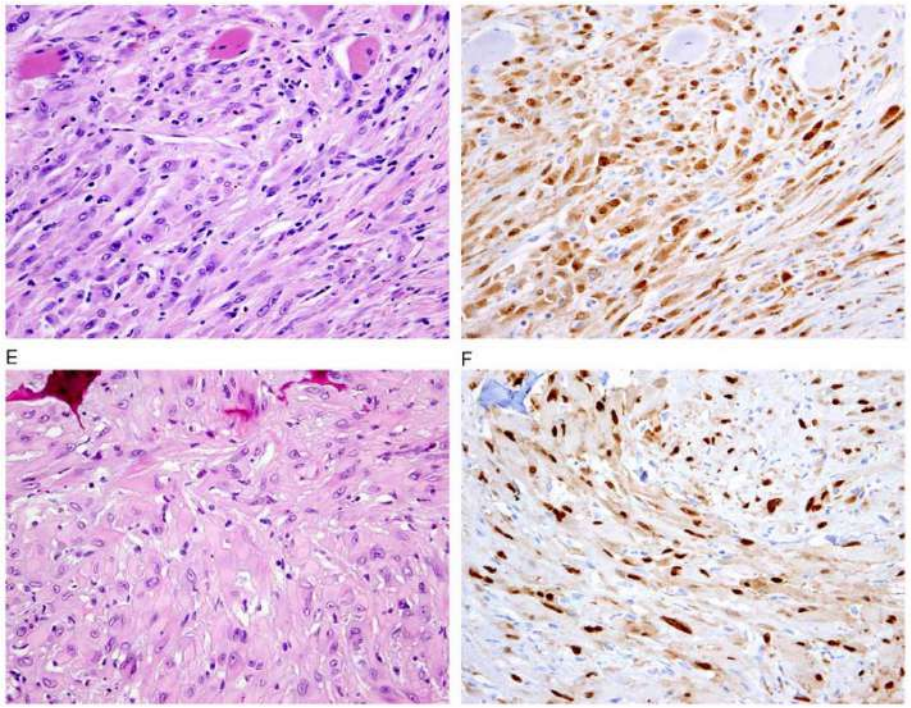
pseudomyogenic Haemangioendothelioma

- t(7;19)(q22;q13) (Cancer Genetics 2011; 204: 211)
- *SERPINE1-FOSB* fusion (J Pathol 2014; 232: 534)
- *SERPINE1*: promotor for FOSB
- *FOSB*: encodes a transcription factor (FOS family)
  a component of the activating protein 1
- expanding the spectrum of genetic alterations in pseudomyogenic hemangioendothelioma with recurrent novel *ACTB-FOSB* gene fusion (Agaram NP et al. Am J Surg Pathol 2018; 42: 1653)

FOS-B in vascular neoplasms

Pseudomyogenic hemangioendothelioma (PHE)

t(7;19)*SERPINE1-FOSB*



Hung et al, 2017

Journal of Pathology
J Pathol 2014; **232**: 534–540
Published online 29 January 2014 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4322

ORIGINAL PAPER

A novel *SERPINE1–FOSB* fusion gene results in transcriptional up-regulation of *FOSB* in pseudomyogenic haemangioendothelioma

Charles Walther,[1,2]* Johnbosco Tayebwa,[1] Henrik Lilljebjörn,[1] Linda Magnusson,[1] Jenny Nilsson,[1] Fredrik Vult von Steyern,[3] Ingrid Øra,[4] Henryk A Domanski,[2] Thoas Fioretos,[1] Karolin H Nord,[1] Christopher DM Fletcher[5] and Fredrik Mertens[1]

Sugita *et al. Diagnostic Pathology* (2016) 11:75
DOI 10.1186/s13000-016-0530-2

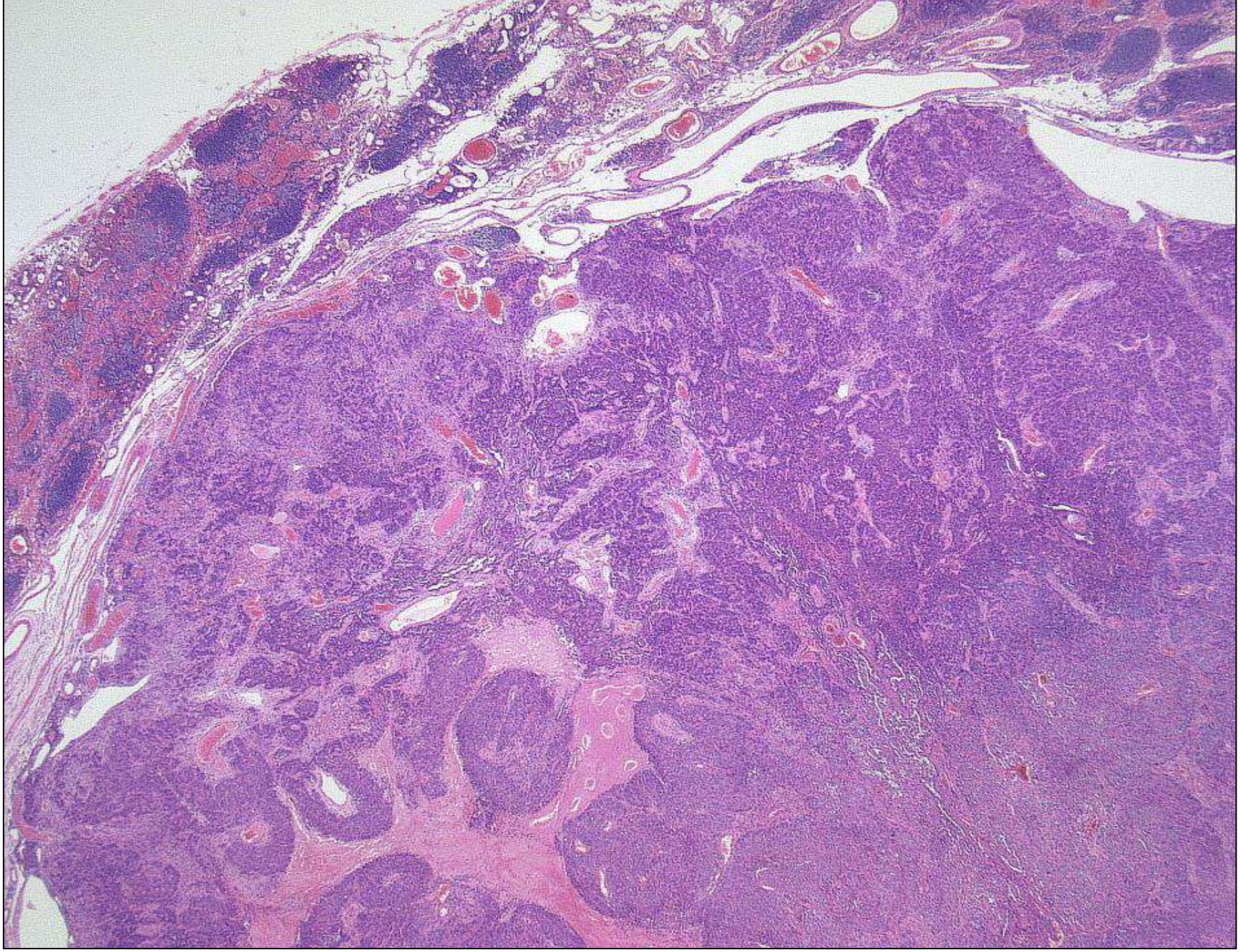
Diagnostic Pathology

RESEARCH Open Access

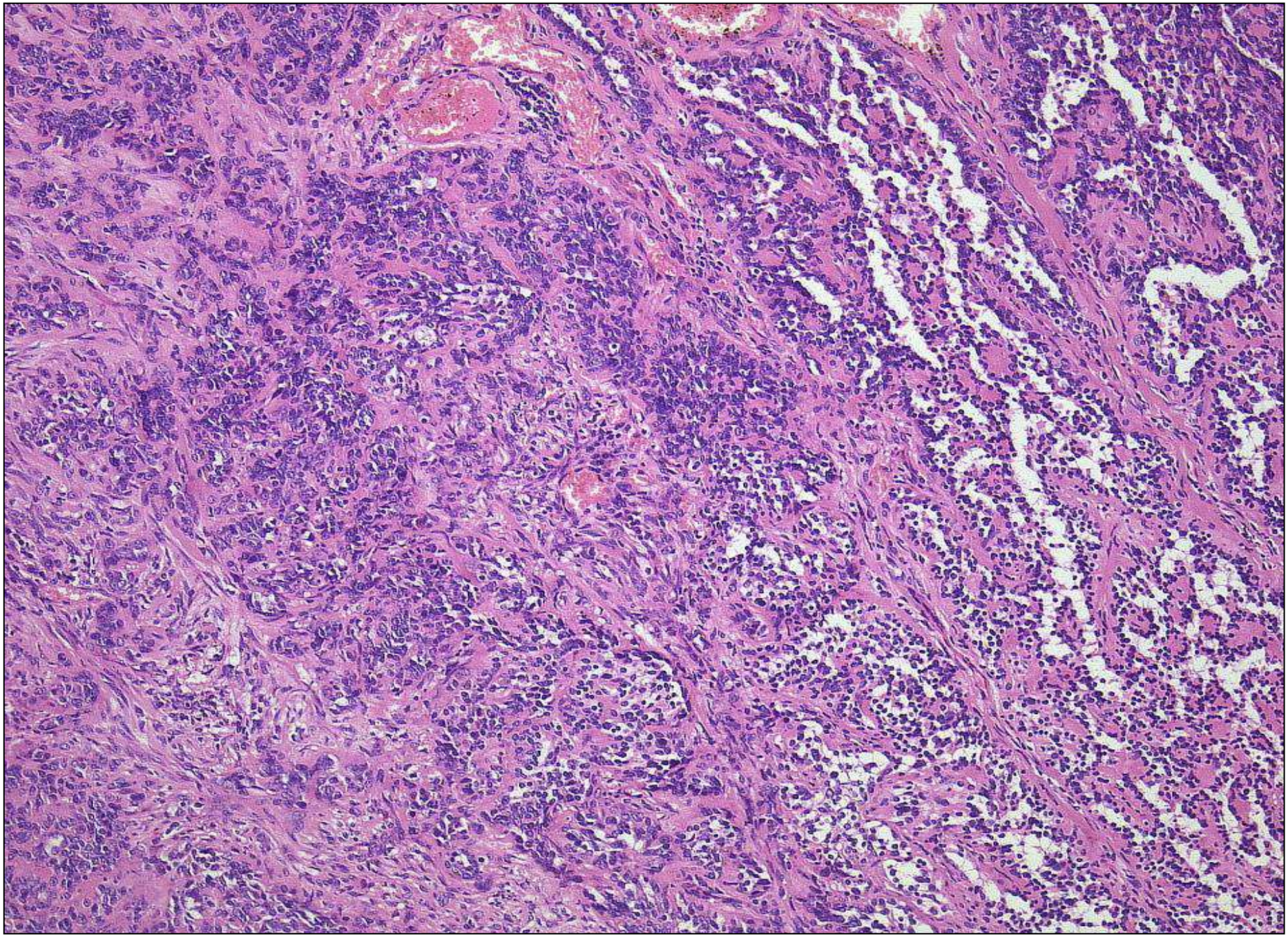
Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics

Shintaro Sugita[1], Hiroshi Hirano[1], Noriaki Kikuchi[1], Terufumi Kubo[1], Hiroko Asanuma[1], Tomoyuki Aoyama[1], Makoto Emori[2] and Tadashi Hasegawa[1*]

FOSB immunohistochemistry useful marker
strong nuclear expression > 95% of cases



courtesy of Prof.Fletcher, Boston, MA

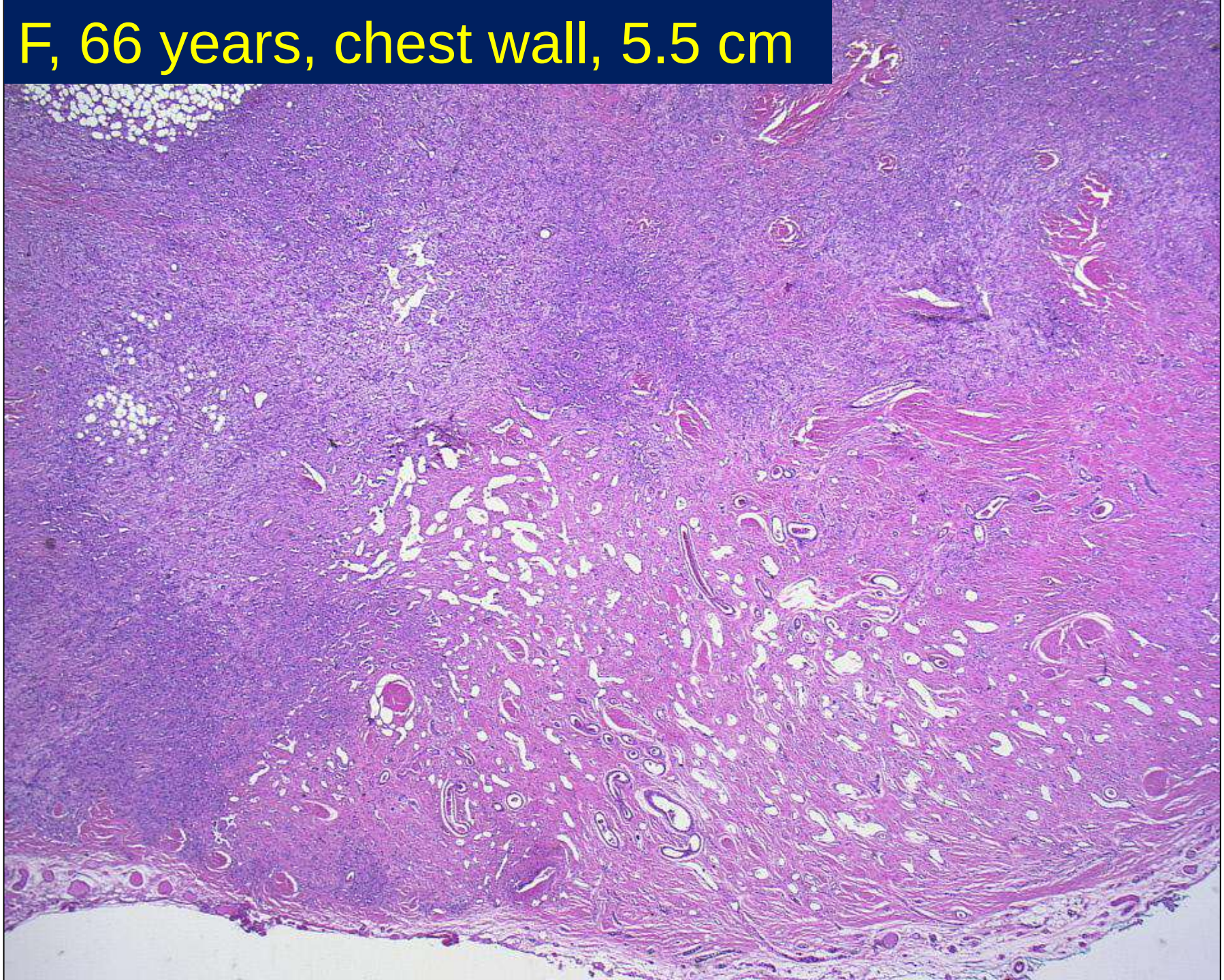


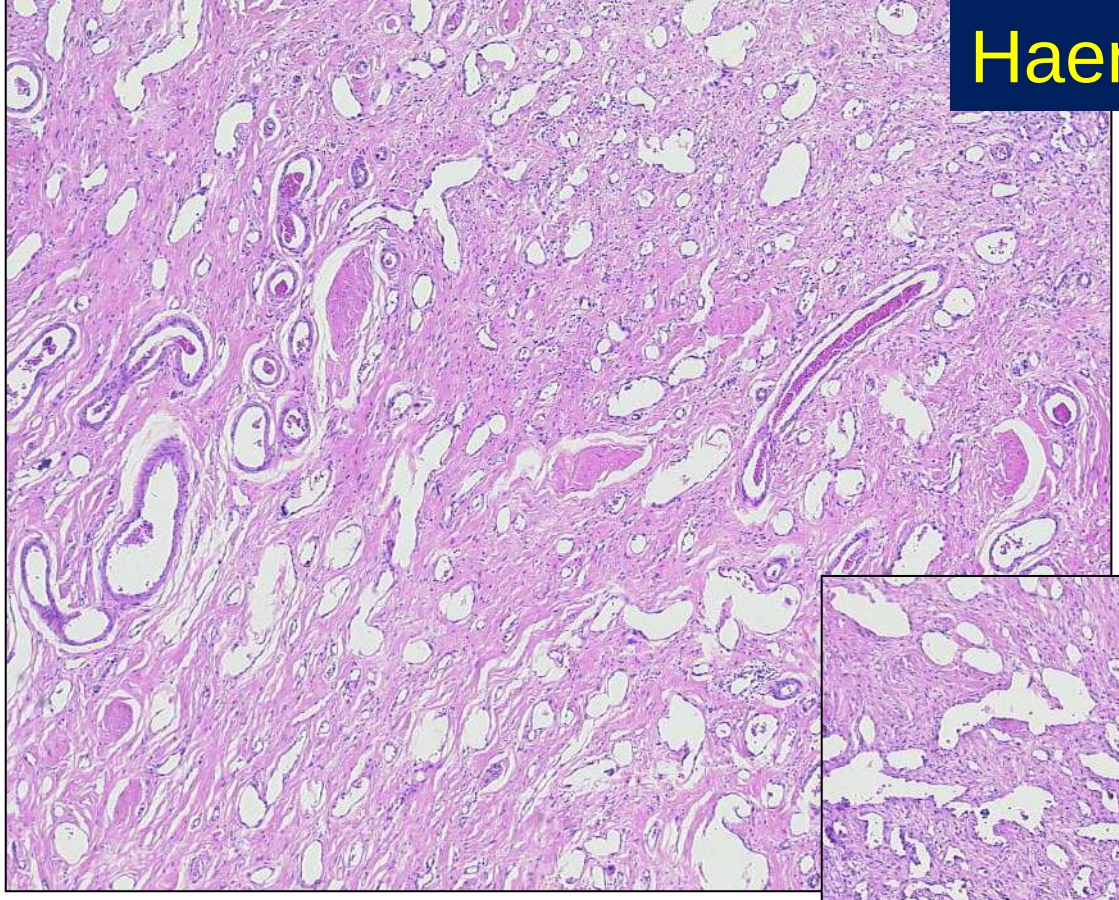
polymorphous Haemangioendothelioma*

- extremely rare neoplasm
- adult patients
- lymph node > soft tissue
- retiform and solid areas
- enlarged, but uniform hobnail cells

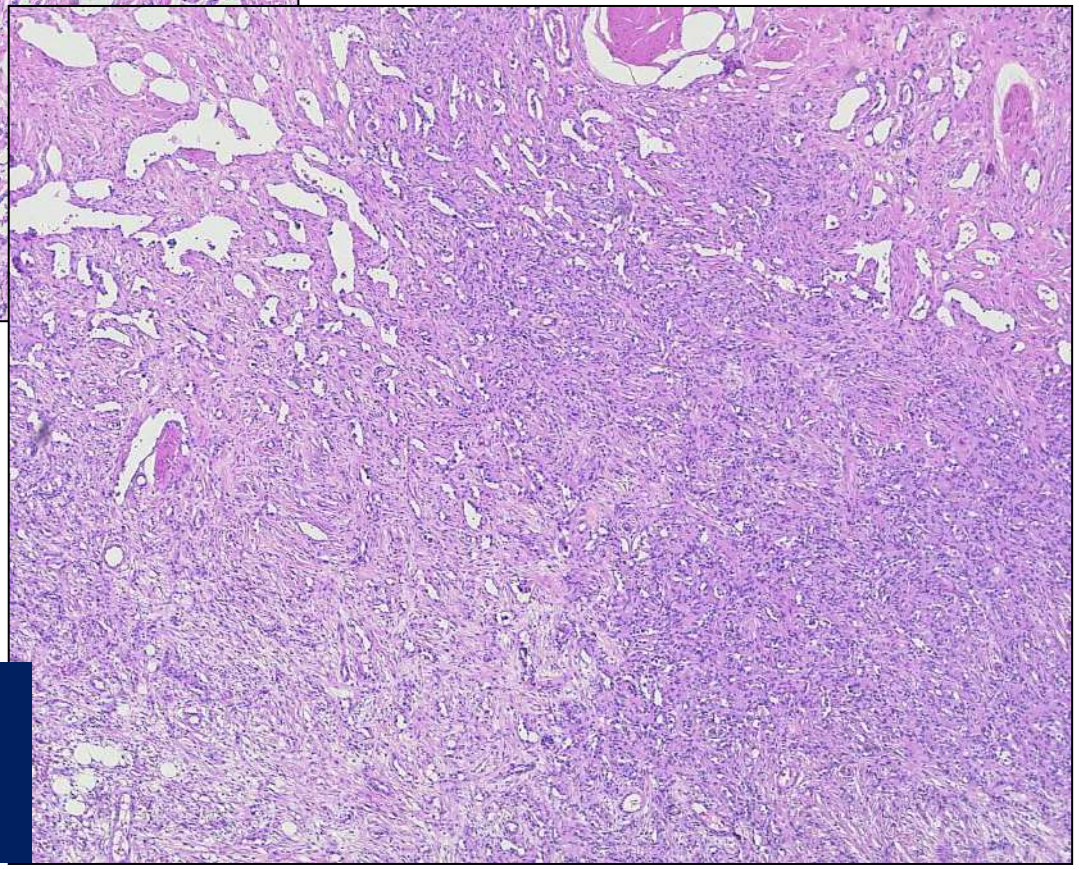
* Chan JKC et al. AJSP 1992; 16: 335
Nascimento AG et al. AJSP 1997; 21: 1083

F, 66 years, chest wall, 5.5 cm

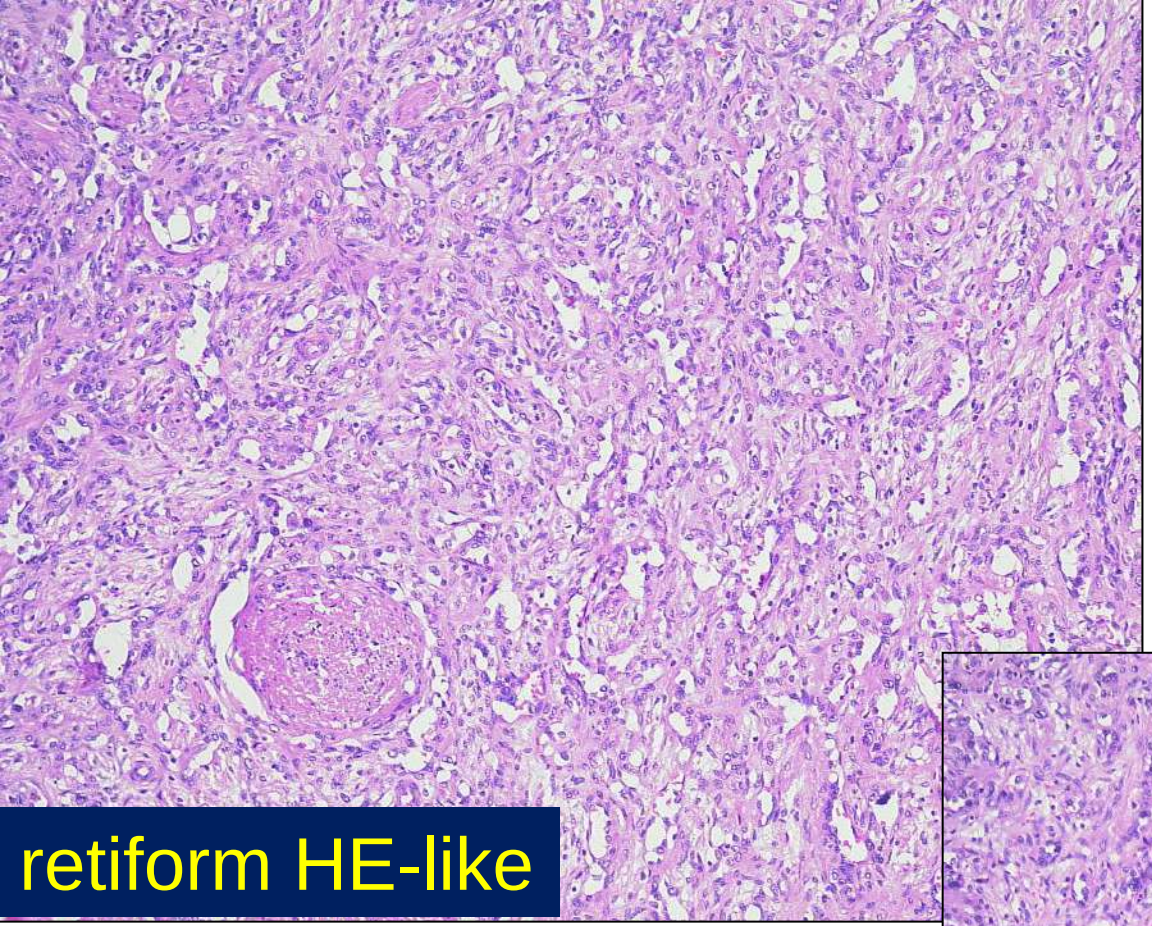




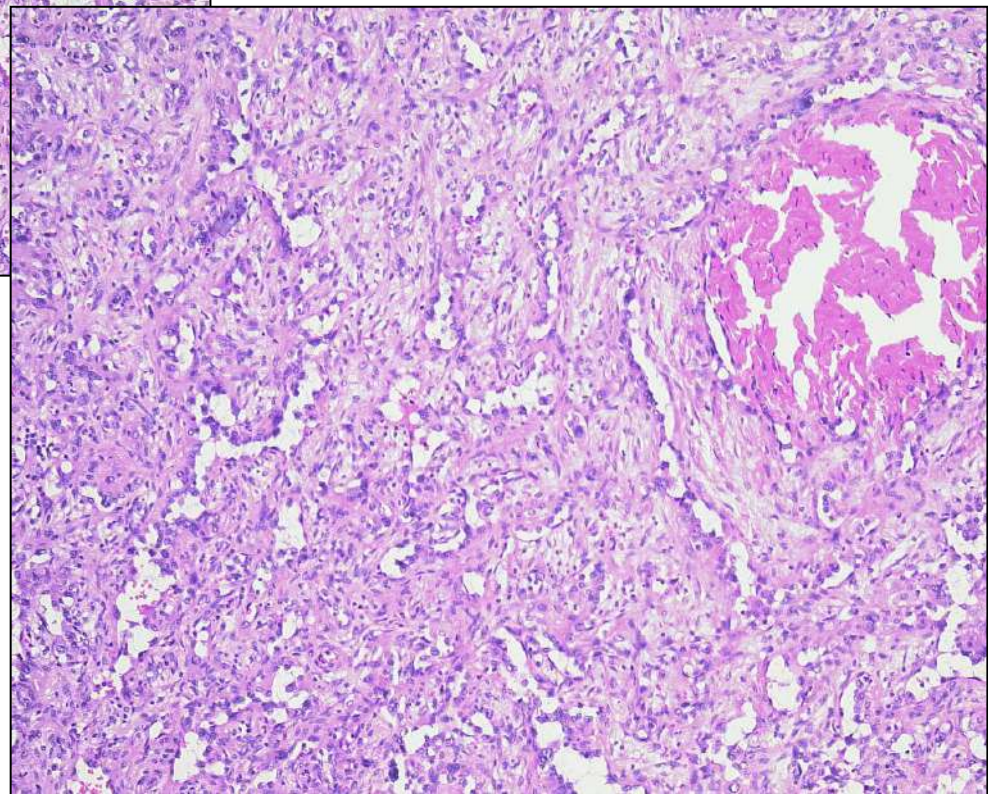
Haemangioma-like

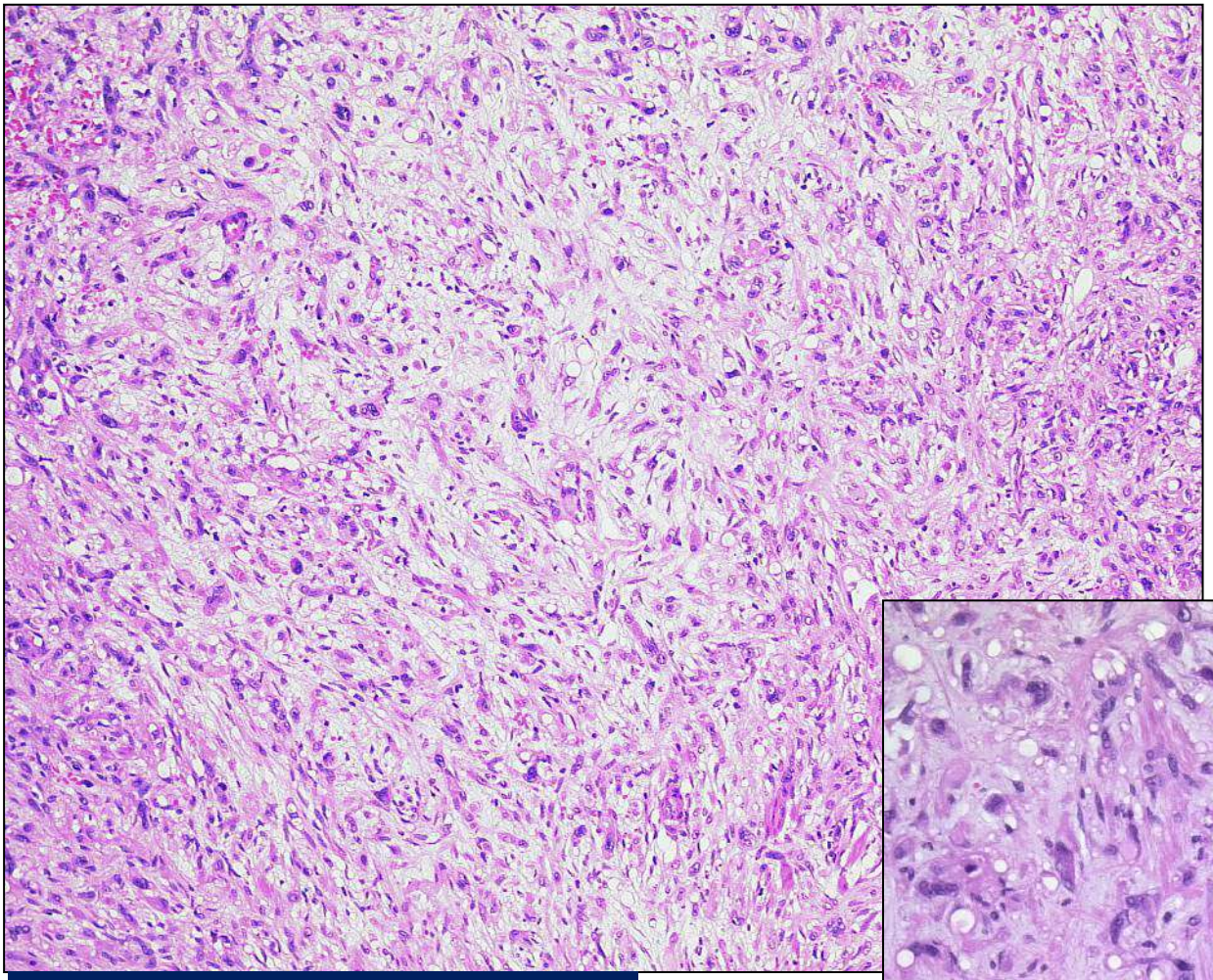


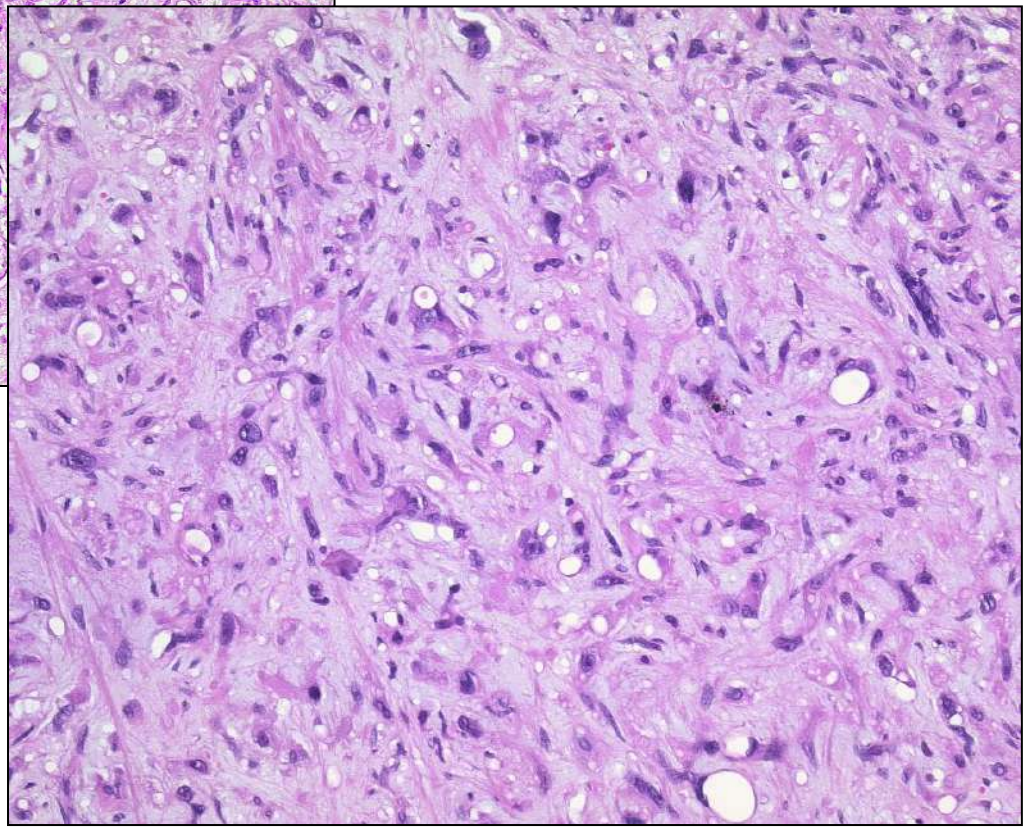
Haemangioma-like + infiltrating component



retiform HE-like







epithelioid HE-like

composite Haemangioendothelioma (Nayler SJ et al. AJSP 2000; 24: 352)

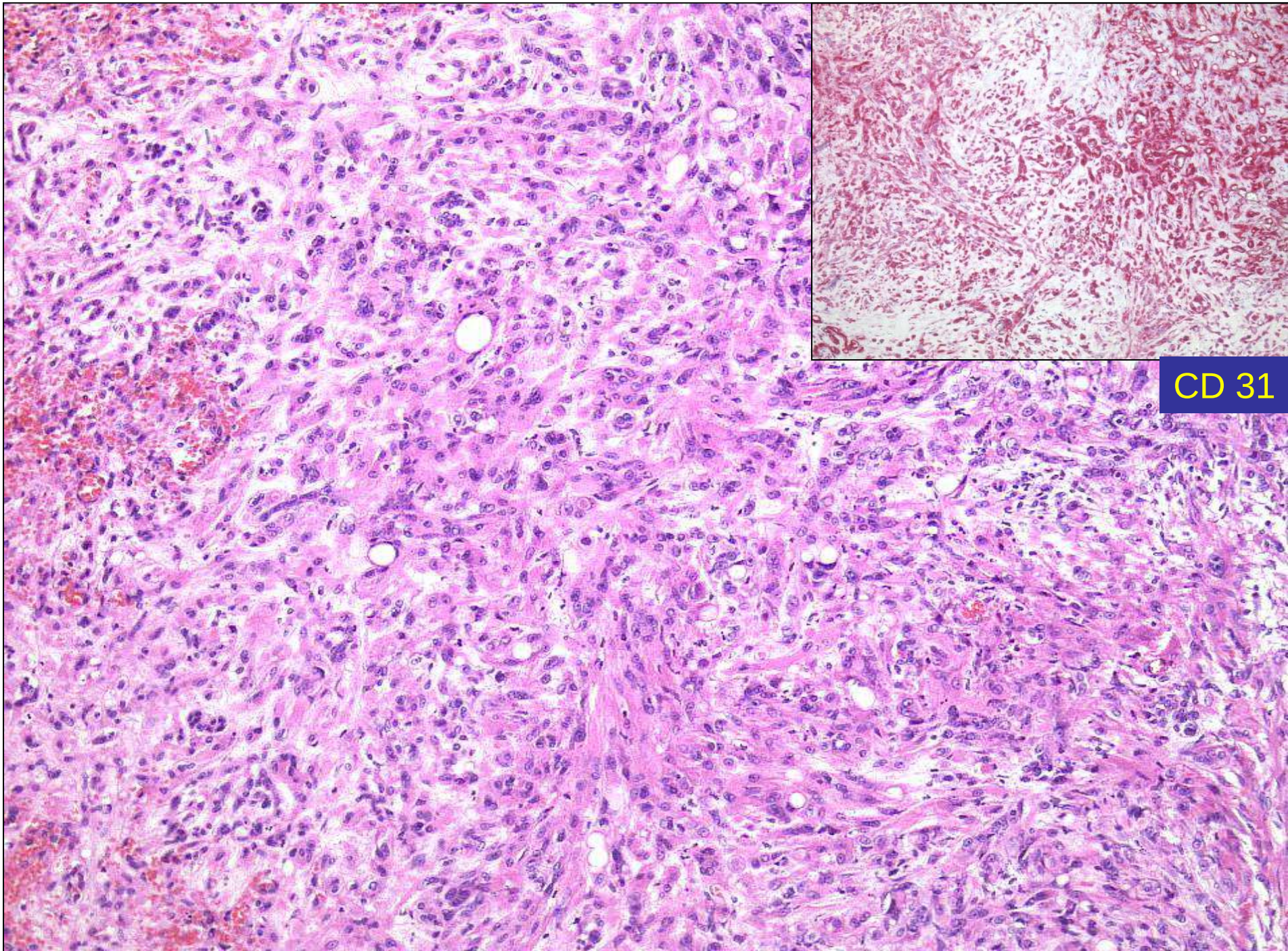
- adult patients
- mainly distal lower extremities > head / neck
- locally aggressive, 50% R, single MTS
- irregular admixture of:
  - haemangioma-like areas
  - low-grade areas (i.e. RHE-like)
  - malignant areas (i.e. EHE, AS)
- composite hemangioendothelioma with neuroendocrine marker expression: an aggressive variant (Mod Pathol 2017; 30: 1589)

Recurrent *YAP1* and *MAML2* gene rearrangements in retiform and composite hemangioendothelioma

Antonescu CR et al. AJSP 2020; 44: 1677

13 RHE, 10-55 years; 11 CHE, 7-68 years
skin, soft tissues, extremities > head / neck
M, 37 years, CHE with neuroendocrine differentiation (pancreas, liver, lung)
5/13 RHE and 3/11 CHE *YAP1* rearrangement
5 cases showed *YAP1-MAML2* fusion
PTBP1-MAML1 fusion in neuroendocrine CHE
close relationship between RHE and CHE
neuroendocrine CHE appears a distinct subset

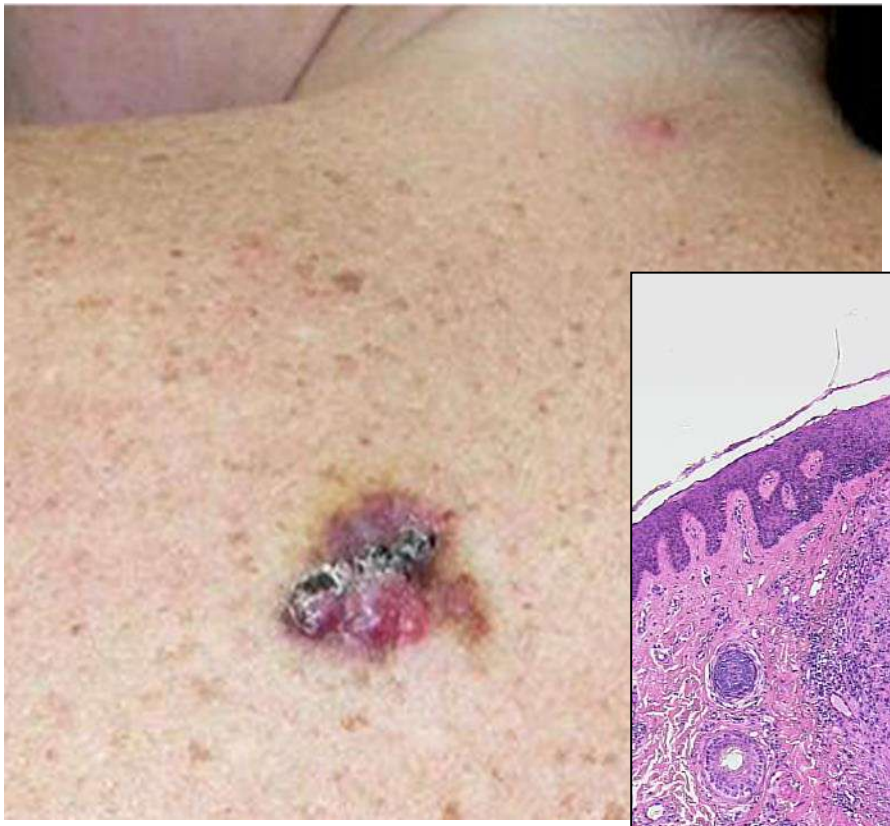
F, 56 years, deep soft tissue, thigh

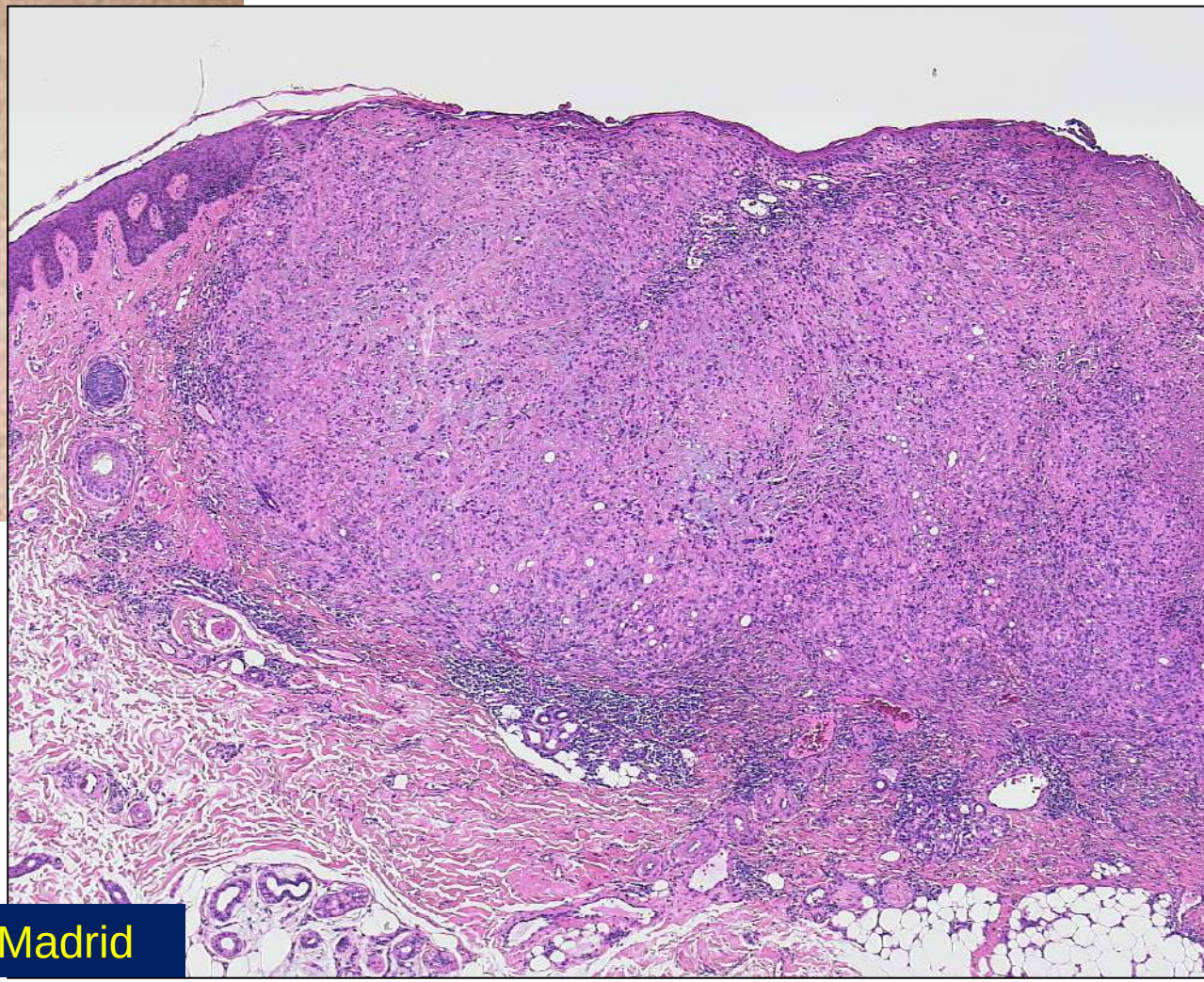

CD 31

epithelioid Haemangioendothelioma

- adults, rarely in childhood
- solid > multicentric, soft tissues > skin
- arise from large vessels in 50% of cases
- ill-defined, infiltrative neoplasms
- nests, cords, trabeculae, epithelioid cells, cytoplasmic vacuoles (with erythrocytes), myxohyaline stroma
- endothelial markers +, podoplanin + in 40%, CK + in 25%

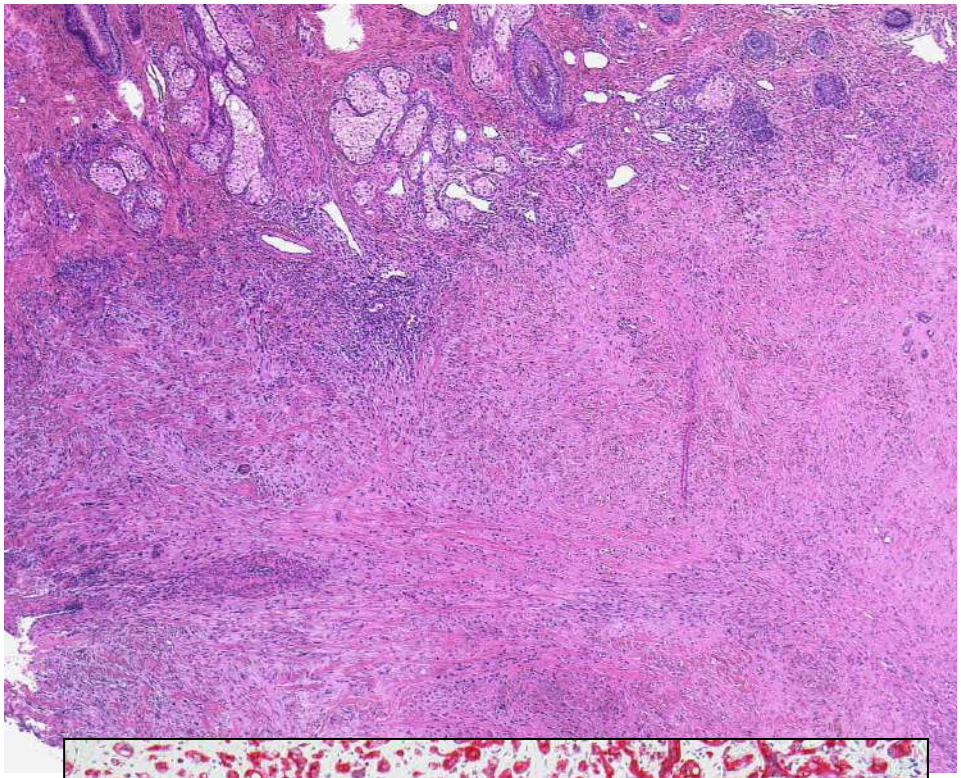
epithelioid Haemangioendothelioma

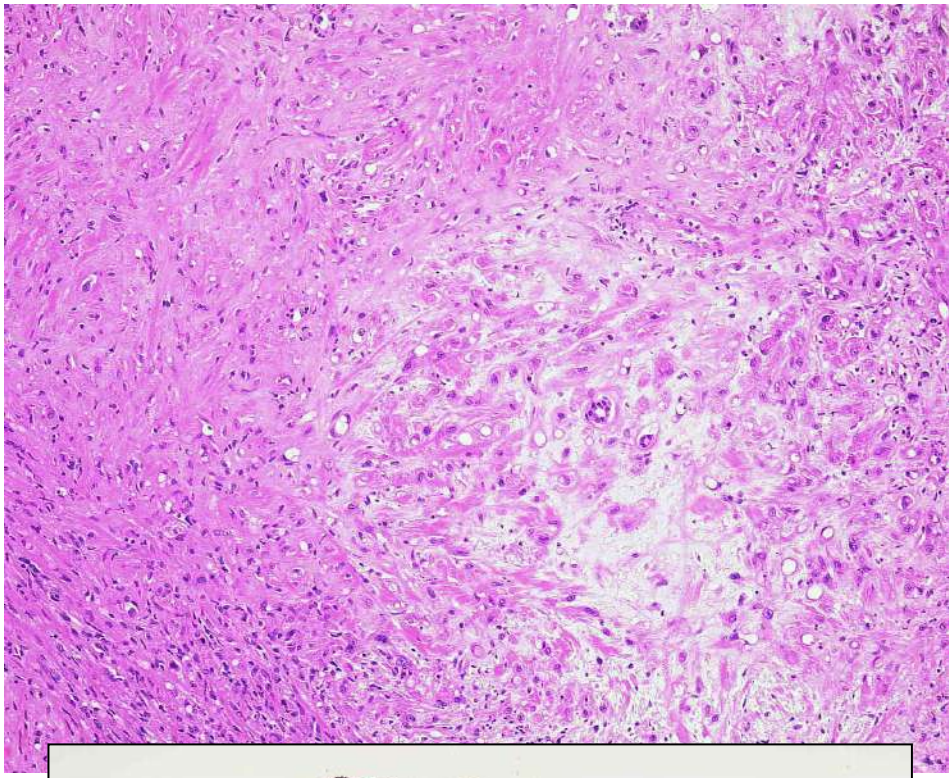


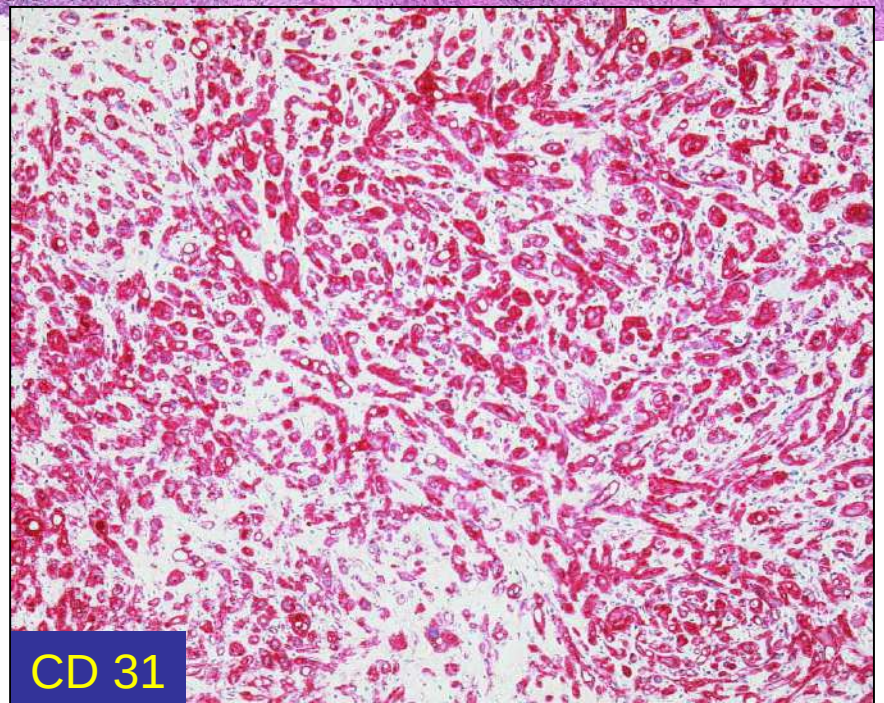


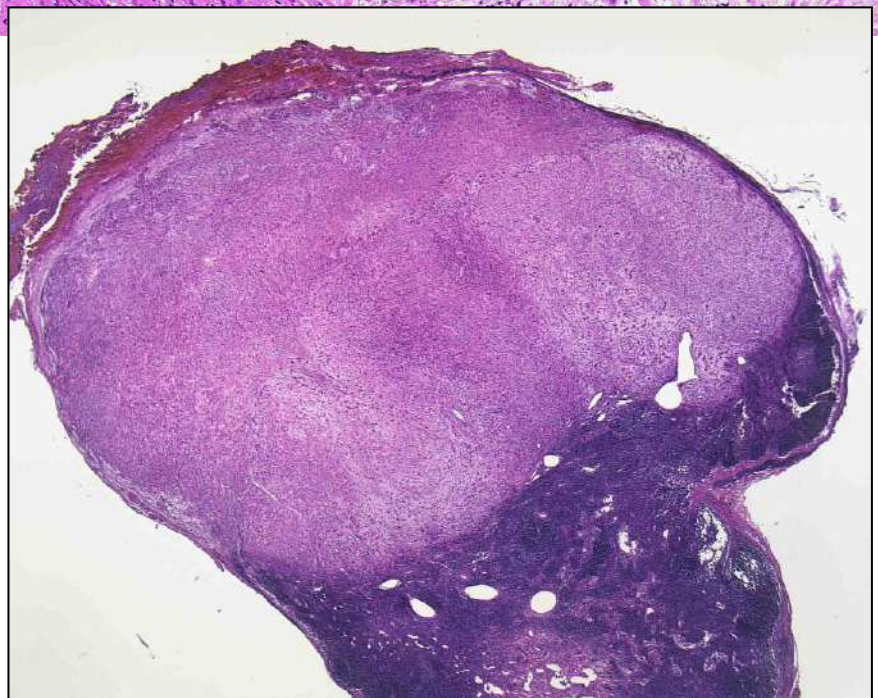
courtesy of Dr.L.Requena, Madrid

M, 9 years, painful erythematous plaque
cervical lymph node metastasis
J Cutan Pathol 2008; 35: 80






CD 31



epithelioid Haemangioendothelioma

Errani C et al. Genes Chromosomes Cancer 2011; 50: 644-653

- EHE (17), epithelioid haemangioma (13), epithelioid AS (5), pseudomyogenic HE (4)
- t(1;3)(p36.3;q25), *WWTR1-CAMTA1* fusion present only in cases of EHE
- *WWTR1-CAMTA1* oncogenic function

Doyle LA et al. Am J Surg Pathol 2016; 40: 94

- nuclear expression of CAMTA1 distinguishes EHE from histologic mimics
- rabbit polyclonal antibody (Novus Biologicals) is highly sensitive (85%) and specific

Published in final edited form as:
Genes Chromosomes Cancer. 2011 August ; 50(8): 644–653. doi:10.1002/gcc.20886.

A Novel *WWTR1-CAMTA1* Gene Fusion is a Consistent Abnormality in Epithelioid Hemangioendothelioma of Different Anatomic Sites

Costantino Errani[1,2,^,*], **Lei Zhang**[1,*], **Sung Yun Shao**[1], **Mihai Hajdu**[1], **Samuel Singer**[3], **Robert G Maki**[4], **John H Healey**[2], and **Cristina R Antonescu**[1,*]

[1]Department of Pathology, Sloan-Kettering Cancer Center, New York, NY, USA

[2]Department of Orthopaedic Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[3]Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[4]Department of Medicine/Pediatrics, Mount Sinai School of Medicine, New York, NY, USA

[^]Visiting Research Fellow from the Musculoskeletal Oncology Department, Istituto Ortopedico Rizzoli, Via Pupilli nr. 1, Bologna, Italy

Abstract

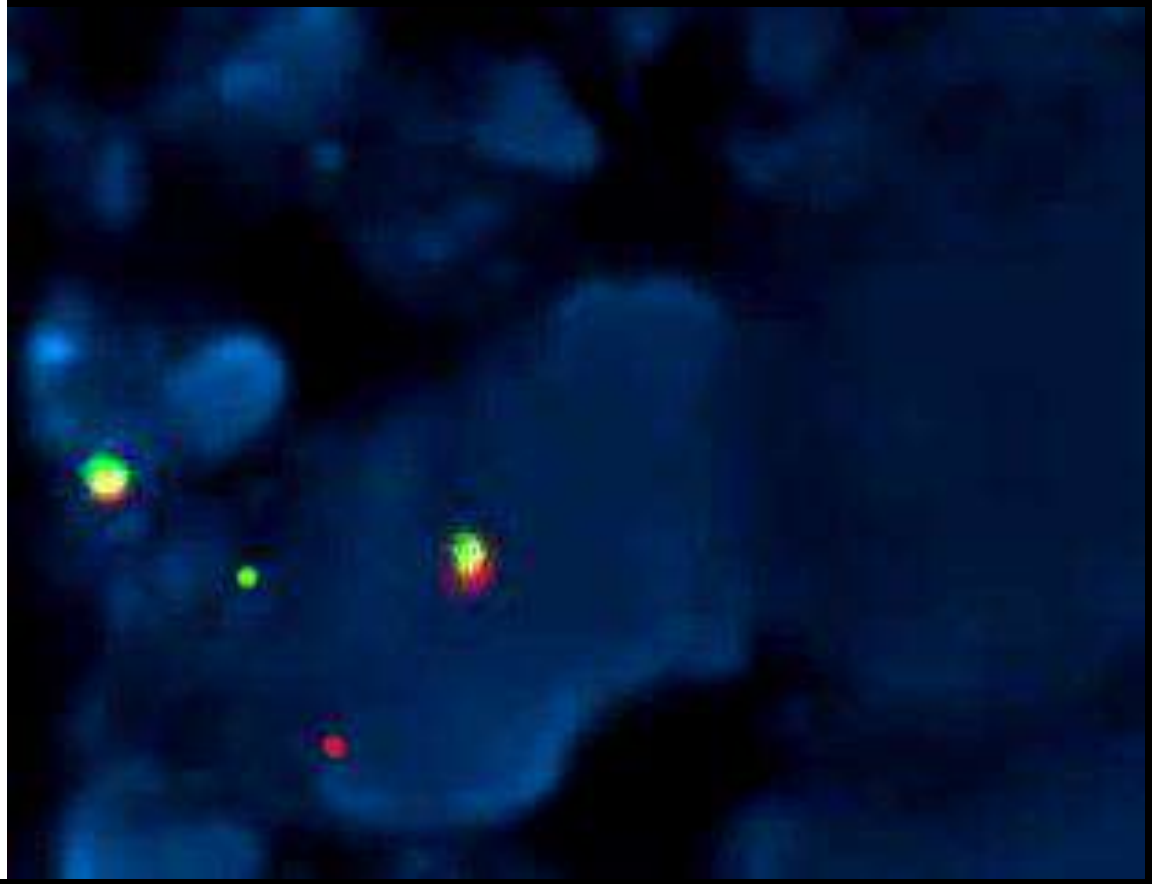
The classification of epithelioid vascular tumors remains challenging, as there is considerable morphologic overlap between tumor subtypes, across the spectrum from benign to malignant categories. A t(1;3)(p36.3;q25) translocation was reported in two cases of epithelioid hemangioendothelioma (EHE), however, no follow-up studies have been performed to identify the gene fusion or to assess its prevalence in a larger cohort of patients. We undertook a systematic molecular analysis of 17 EHE, characterized by classic morphologic and immunophenotypic features, from various anatomic locations and with different malignant potential. For comparison we analyzed 13 epithelioid hemangiomas, five epithelioid angiosarcomas and four epithelioid sarcoma-like EHE. A fluorescence in situ hybridization (FISH) positional cloning strategy, spanning the cytogenetically defined regions on chromosomes 1p36.3 and 3q25, confirmed rearrangements in two candidate genes from these loci in all EHE cases tested. None of the other benign or malignant epithelioid vascular tumors examined demonstrated these abnormalities. Subsequent RT-PCR confirmed in three EHE the *WWTR1-CAMTA1* fusion product. *CAMTA1* and *WWTR1* have been previously shown to play important roles in oncogenesis. Our results demonstrate the presence of a *WWTR1-CAMTA1* fusion in all EHE tested from bone, soft tissue and visceral location (liver, lung) in keeping with a unique and specific pathological entity. Thus, FISH or RT-PCR analysis for the presence of *WWTR1-CAMTA1* fusion may serve as a useful molecular diagnostic tool in challenging diagnoses.

INTRODUCTION

Epithelioid vascular tumors encompass a wide histologic spectrum, including epithelioid hemangioma (EH), a benign tumor; epithelioid hemangioendothelioma (EHE), a low grade malignant tumor; and epithelioid angiosarcoma (E-AS), a high grade malignant tumor (Wenger and Wold, 2000; O'Connell et al., 2001; Fletcher et al., 2002). Although some of

[*]Correspondence to: Cristina R Antonescu, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York 10021 NY, USA. antonesc@mskcc.org.
[^]Contributed equally to this work.

CAMTA1 **fusion probe**



Novel *YAP1-TFE3* fusion defines a distinct subset of epithelioid hemangioendothelioma (Antonescu CR et al. Genes Chromosomes & Cancer 2013; 52: 775-784)

- t(11;X)(q13;p11) with *YAP1-TFE3* fusion
- *YAP1-TFE3* oncogenic function
- young patients
- well-formed vasoformative vascular structures, more solid growth
- abundant pale eosinophilic cytoplasm
- strong nuclear TFE3 expression, TFE3 immunohistochemistry is not specific

Published in final edited form as:
Genes Chromosomes Cancer. 2013 August ; 52(8): 775–784. doi:10.1002/gcc.22073.

Novel *YAP1-TFE3* Fusion Defines a Distinct Subset of Epithelioid Hemangioendothelioma

Cristina R Antonescu[1], **Francois Le Loarer**[1], **Juan-Miguel Mosquera**[2], **Andrea Sboner**[2,3], **Lei Zhang**[1], **Chun-Liang Chen**[1], **Hsiao-Wei Chen**[1], **Nursat Pathan**[4], **Thomas Krausz**[5], **Brendan C Dickson**[6], **Ilan Weinreb**[7], **Mark A Rubin**[2], **Meera Hameed**[1], and **Christopher DM Fletcher**[8]

[1]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

[2]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY

[3]Institute for Computational Biomedicine, Weill Medical College of Cornell University, New York, NY

[4]Department of Pathology, Raritan Bay Medical Center, Raritan Bay, NJ

[5]Department of Pathology, University of Chicago, Chicago, IL

[6]Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

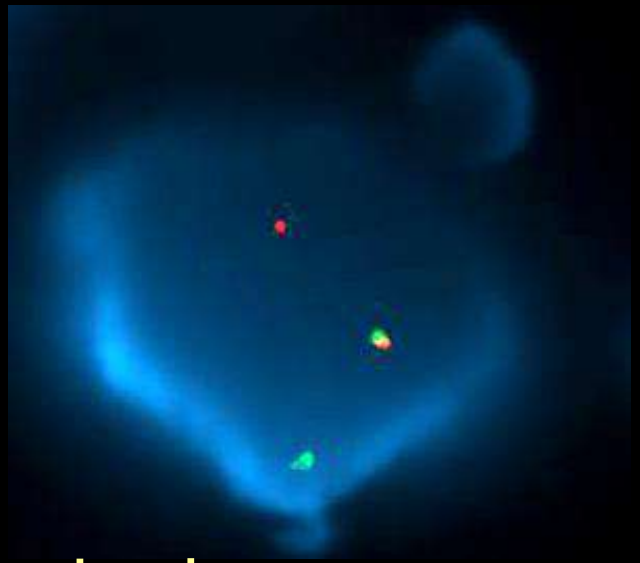
[7]Department of Pathology, University Health Network and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

[8]Department of Pathology Brigham & Women's Hospital and Harvard Medical School, Boston, MA

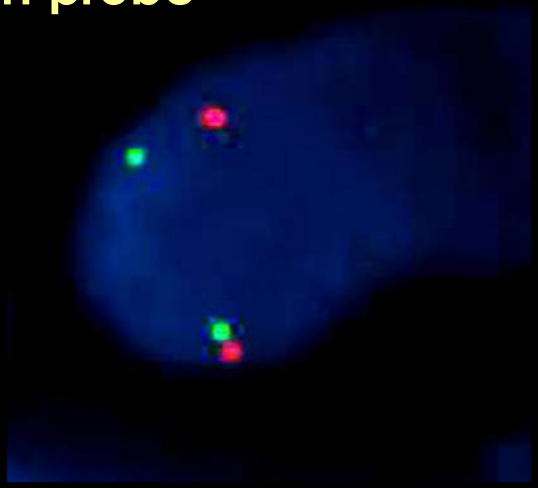
Abstract

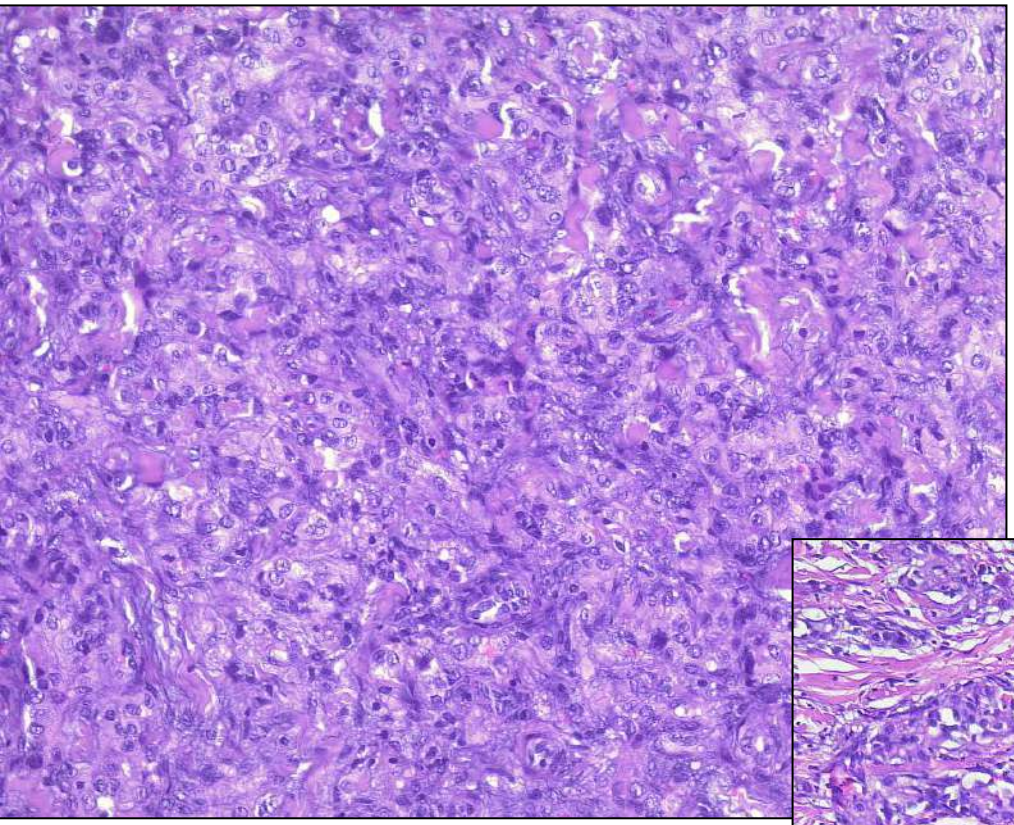
Conventional epithelioid hemangioendotheliomas (EHE) have a distinctive morphologic appearance and are characterized by a recurrent t(1;3) translocation, resulting in a *WWTR1-CAMTA1* fusion gene. We have recently encountered a fusion-negative subset characterized by a somewhat different morphology, including focally well-formed vasoformative features, which was further investigated for recurrent genetic abnormalities. Based on a case showing strong TFE3 immunoreactivity, FISH analysis for *TFE3* gene rearrangement was applied to the index case as well as to 9 additional cases, selected through negative *WWTR1-CAMTA1* screening. A control group, including 18 epithelioid hemangiomas, 9 pseudomyogenic HE and 3 epithelioid angiosarcomas, was also tested. *TFE3* gene rearrangement was identified in 10 patients, with equal gender distribution and a mean age of 30 years old. The lesions were located in somatic soft tissue in 6 cases, lung in 3 and one in bone. One case with available frozen tissue was tested by RNA sequencing and FusionSeq data analysis to detect novel fusions. A *YAP1-TFE3* fusion was thus detected, which was further validated by FISH and RT-PCR. *YAP1* gene rearrangements were

Correspondence: Cristina R Antonescu, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021, antonesc@mskcc.org; and Christopher DM Fletcher, Brigham and Women's Hospital, Boston, MA, cfletcher@partners.org.
Conflict of interest: none

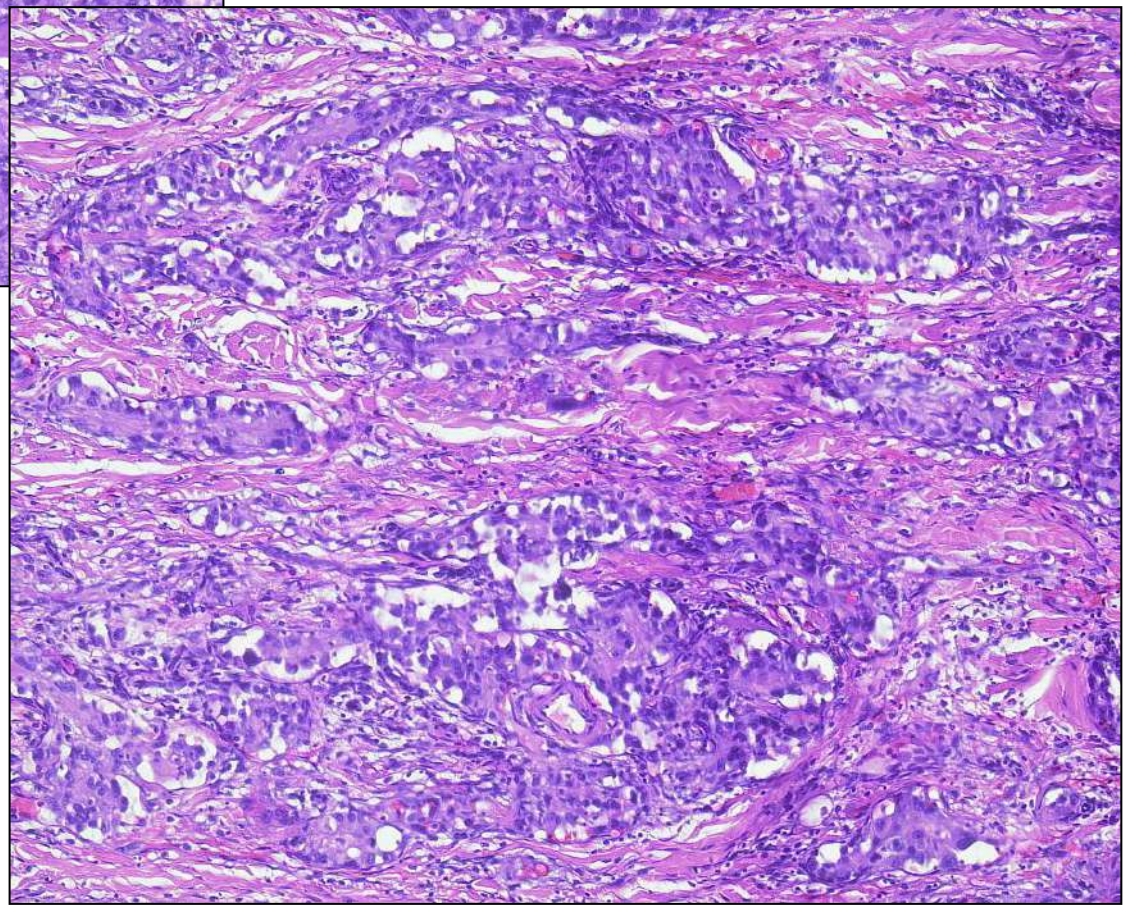


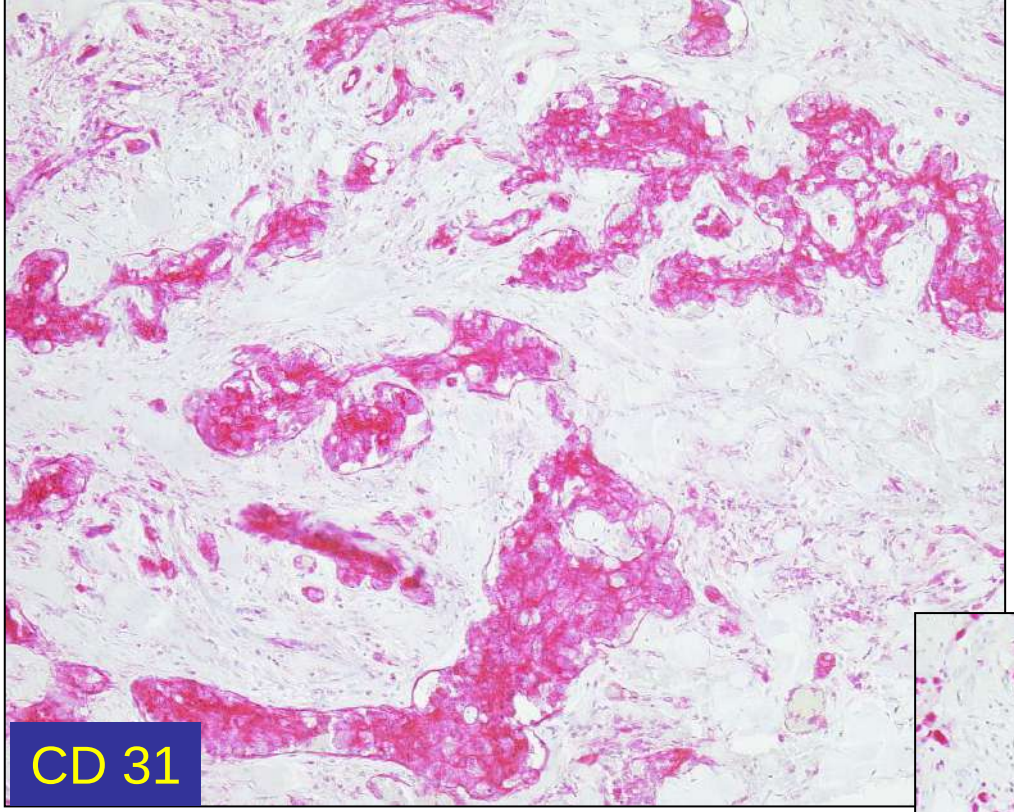
TFE3 **break-apart probe**





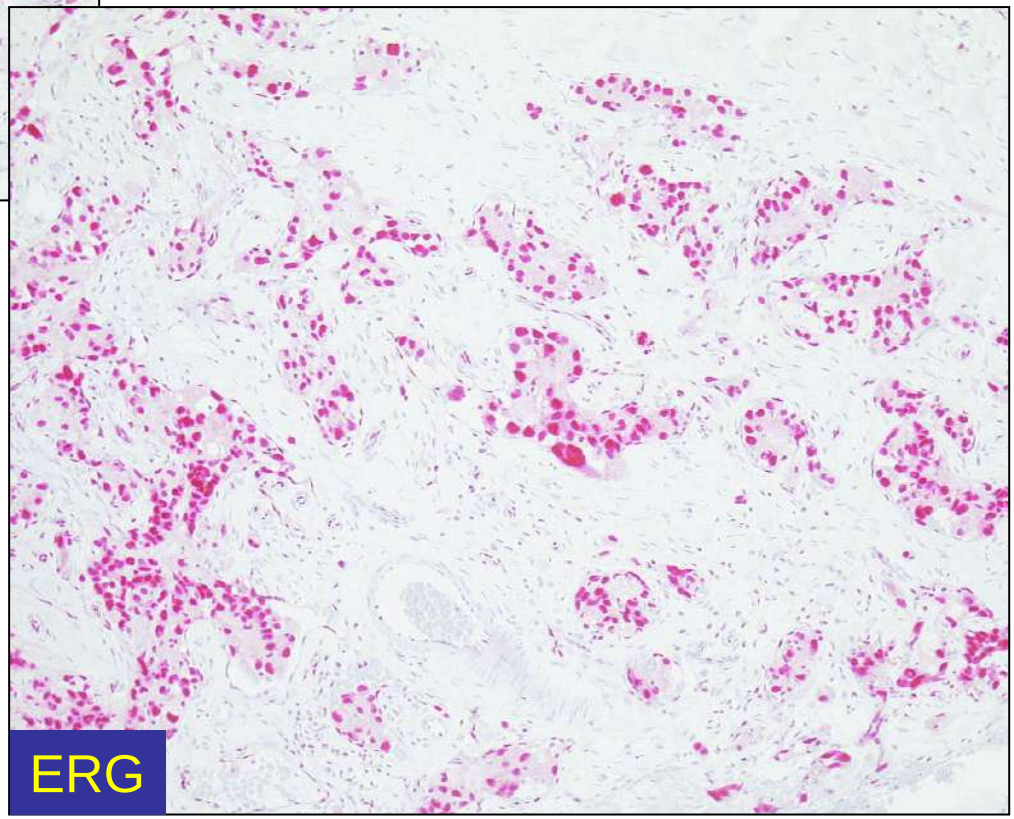
F, 43 years,
cccipital region





Archer expanded sarcoma fusionplex analysis: *YAP1::TFE3* fusion

Diagnosis: epithelioid EHE with *YAP1::TFE3* fusion



Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets

E Rosenbaum et al. Mod Pathol 2020; 33: 591-602

- 93 translocation positive cases
- 83 patients with *WWTR1-CAMTA1* gene fusion
- 10 patients with *YAP1-TFE3* gene fusion
- ***WWTR1-CAMTA1* fusion: 59% 5-year survival**
  ***YAP1-TFE3* fusion: 86% 5-year survival**
- multifocality, pleural involvement, lymph node and distant metastases are adverse prognostic factors
- more than half of the analysed cases showed additional genetic changes

epithelioid Haemangioendothelioma

many recurrences
20-30% MTS
10-20% DOD

true malignant
vascular neoplasm
(better prognosis
in dermal EHE)

size > 3 cm,
> 3 mitoses/50 hpf
(Deyrup AT et al.
AJSP 2008; 32: 924)

high risk tumours
5-year survival 59%

Clinicopathological characterization of epithelioid hemangioendothelioma in a series of 62 cases: a proposal of risk stratification and identification of a synaptophysin-positive aggressive subset

(Shibayama T et al. Am J Surg Pathol 2021; 45: 616)

62 cases, CAMTA1 subtype (59), TFE3 subtype (2)

22 cases atypical histology (>2 mitoses/mm^2, high nuclear grade, necrosis)

DOD (11 cases, 18%), 5-year survival 78.8%

> 3 cm, histological atypia = shorter survival

3-tired risk assessment system

low-risk (5-ys. 100%), intermediate risk (5-ys. 81.8%), high-risk (5-ys. 16.9%)

4 cases synaptophysin + = high-risk lesions, aggressive clinical course

Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas

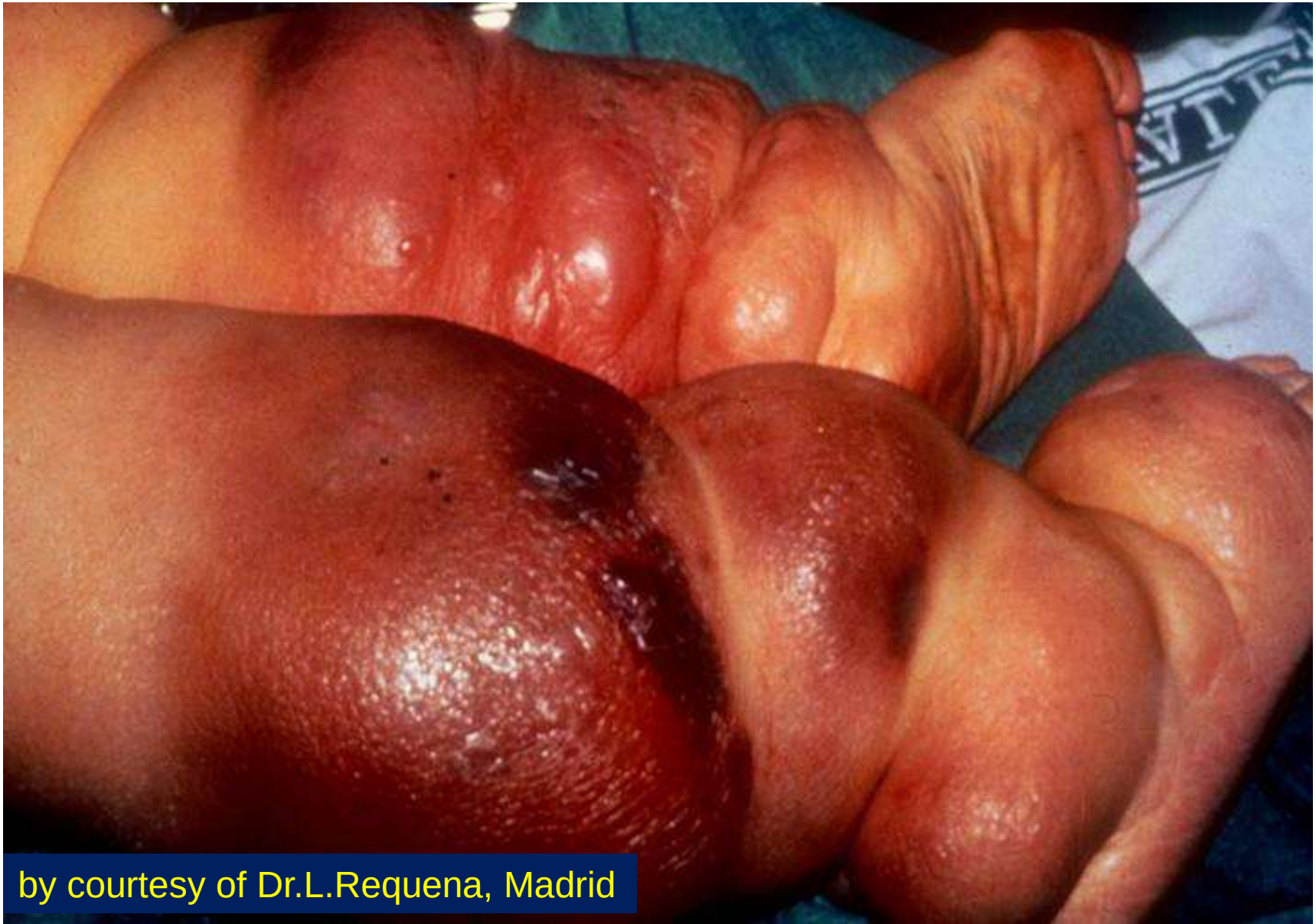
Angiosarcoma

Cutaneous Angiosarcoma

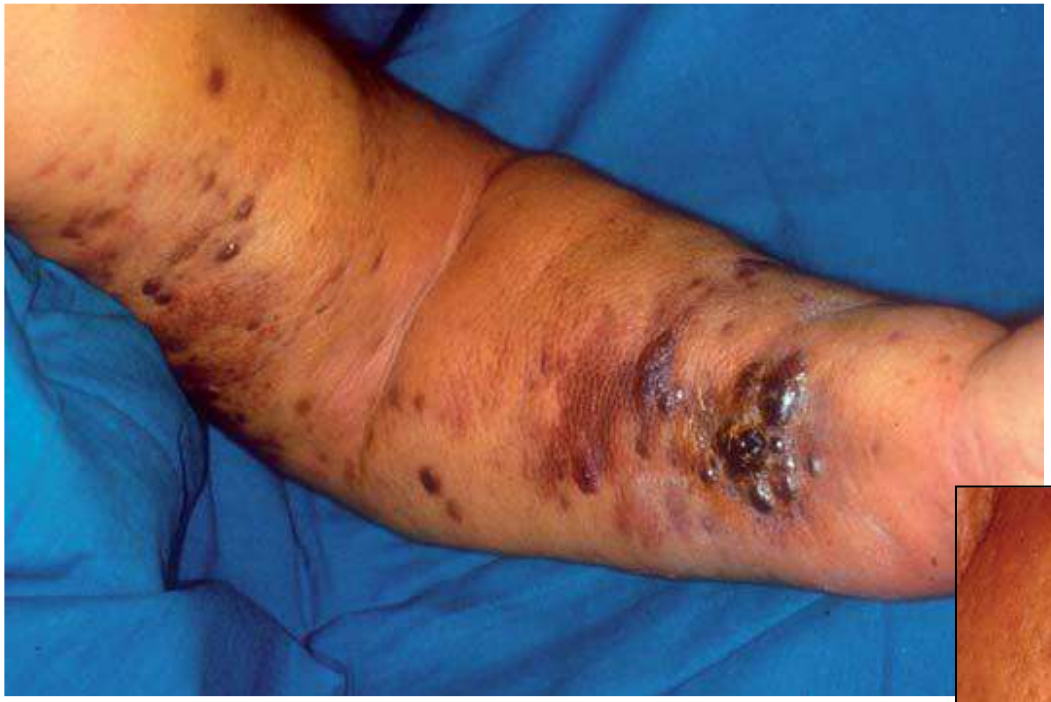
- lymphedematous angiosarcoma
- postirradiation angiosarcoma
- (idiopathic) actinic angiosarcoma

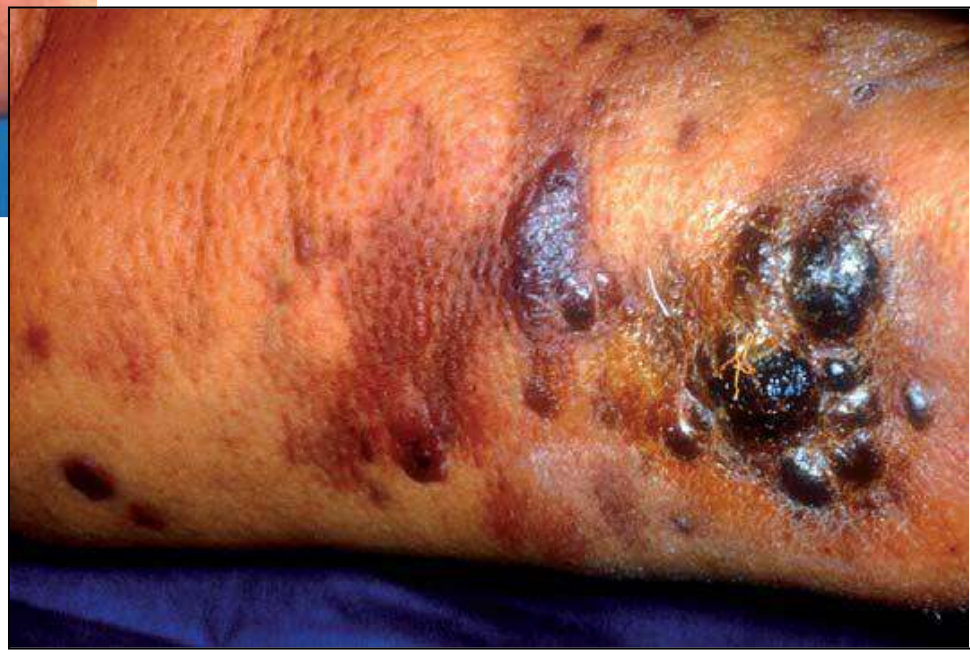
Angiosarcoma of Soft Tissues

Lymphedematous Angiosarcoma (congenital chronic lymphedema)



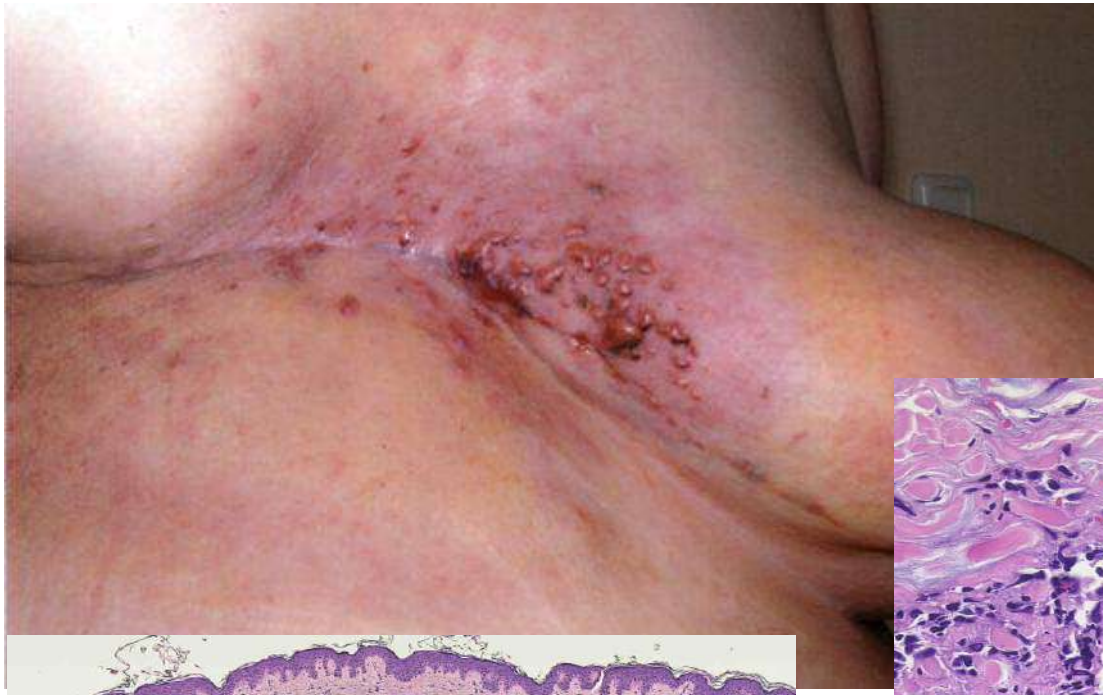
Lymphedematous Angiosarcoma (Stewart Treves Syndrome)

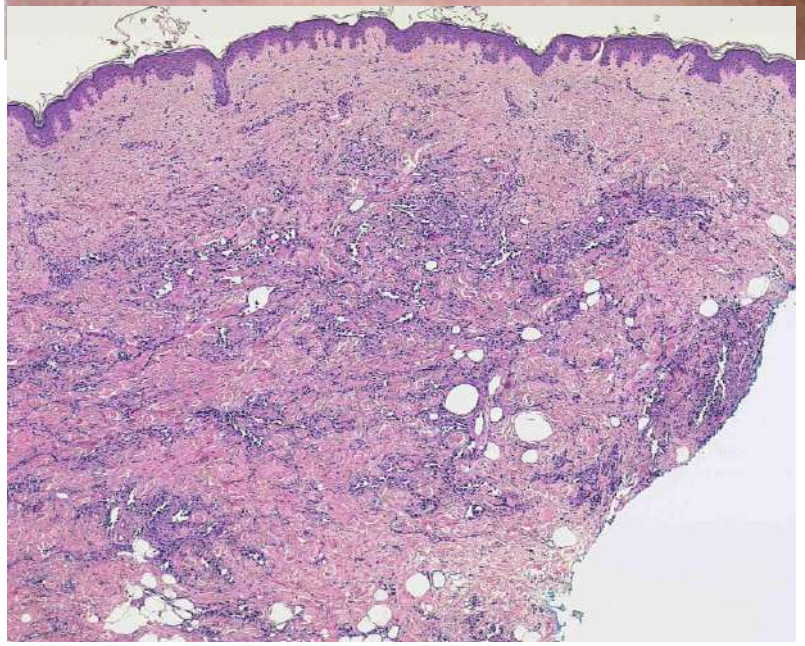


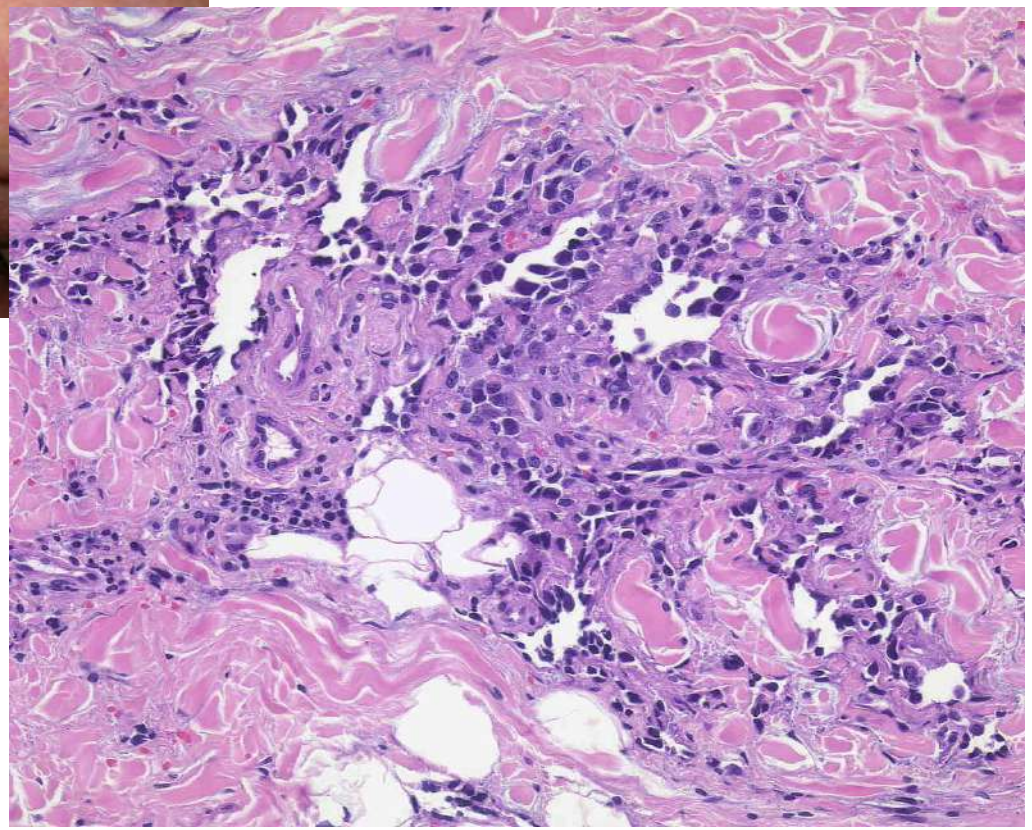


by courtesy of Dr.L.Requena, Madrid

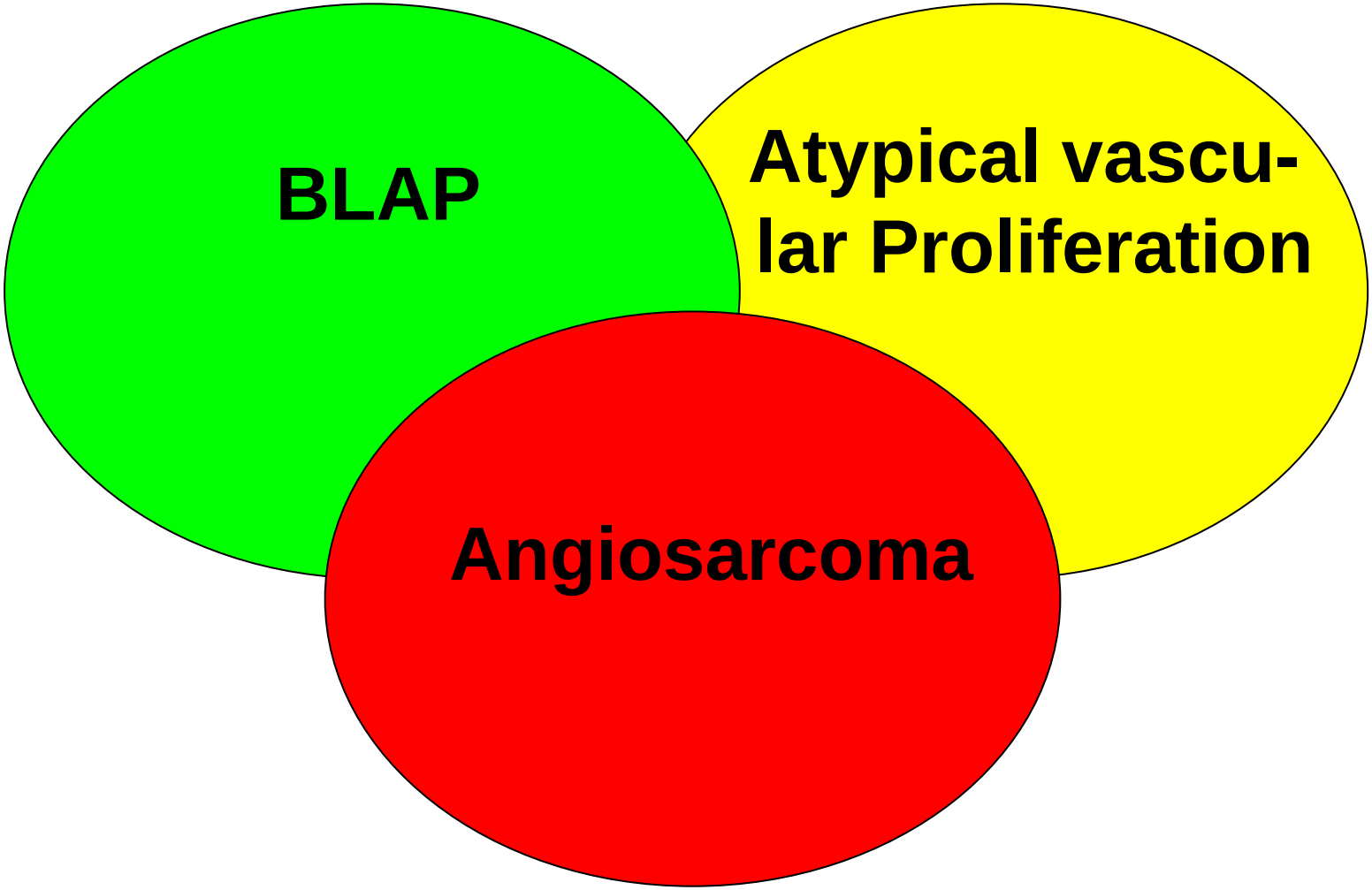
Postirradiation Angiosarcoma





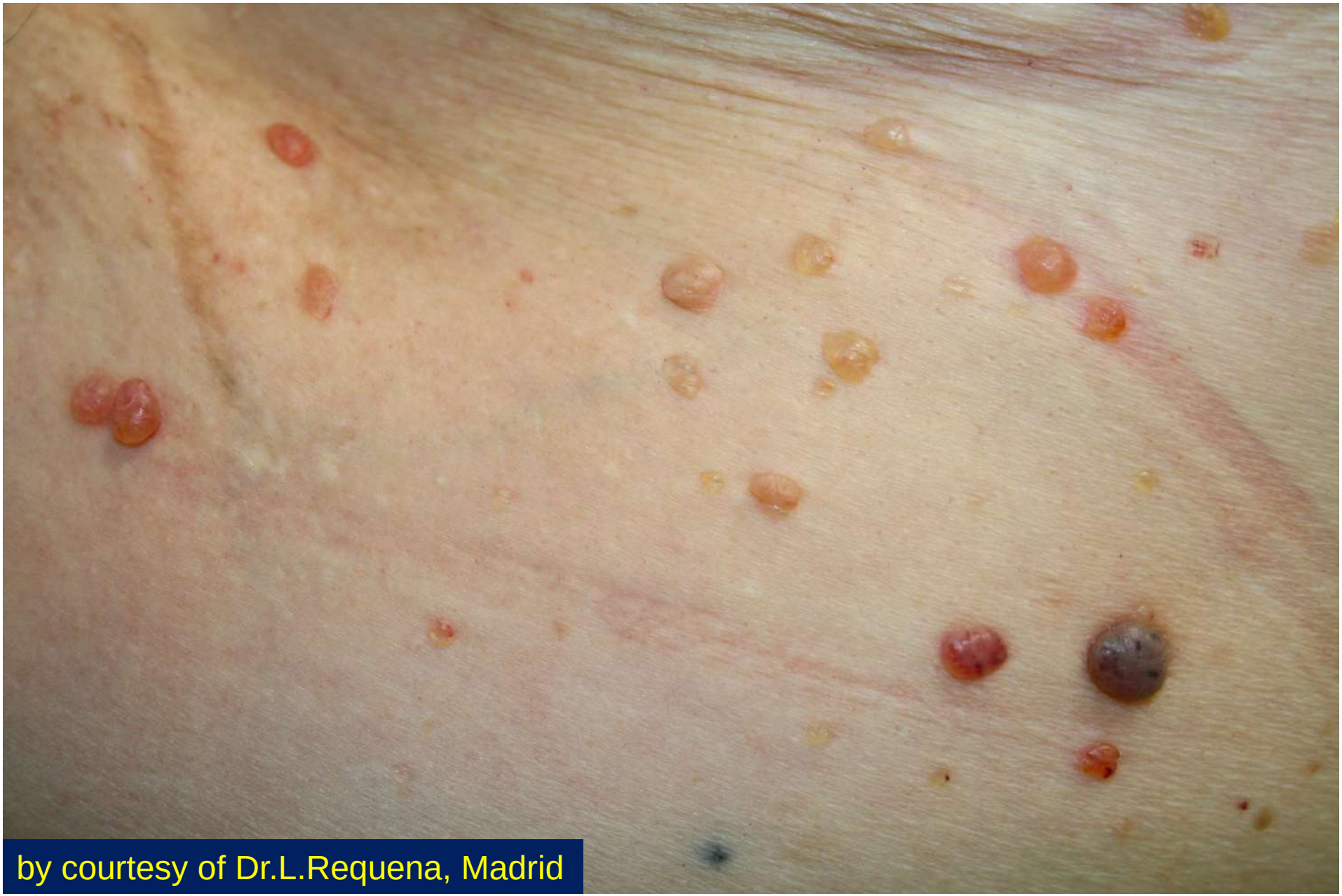


Vascular Proliferations after Radiotherapy*



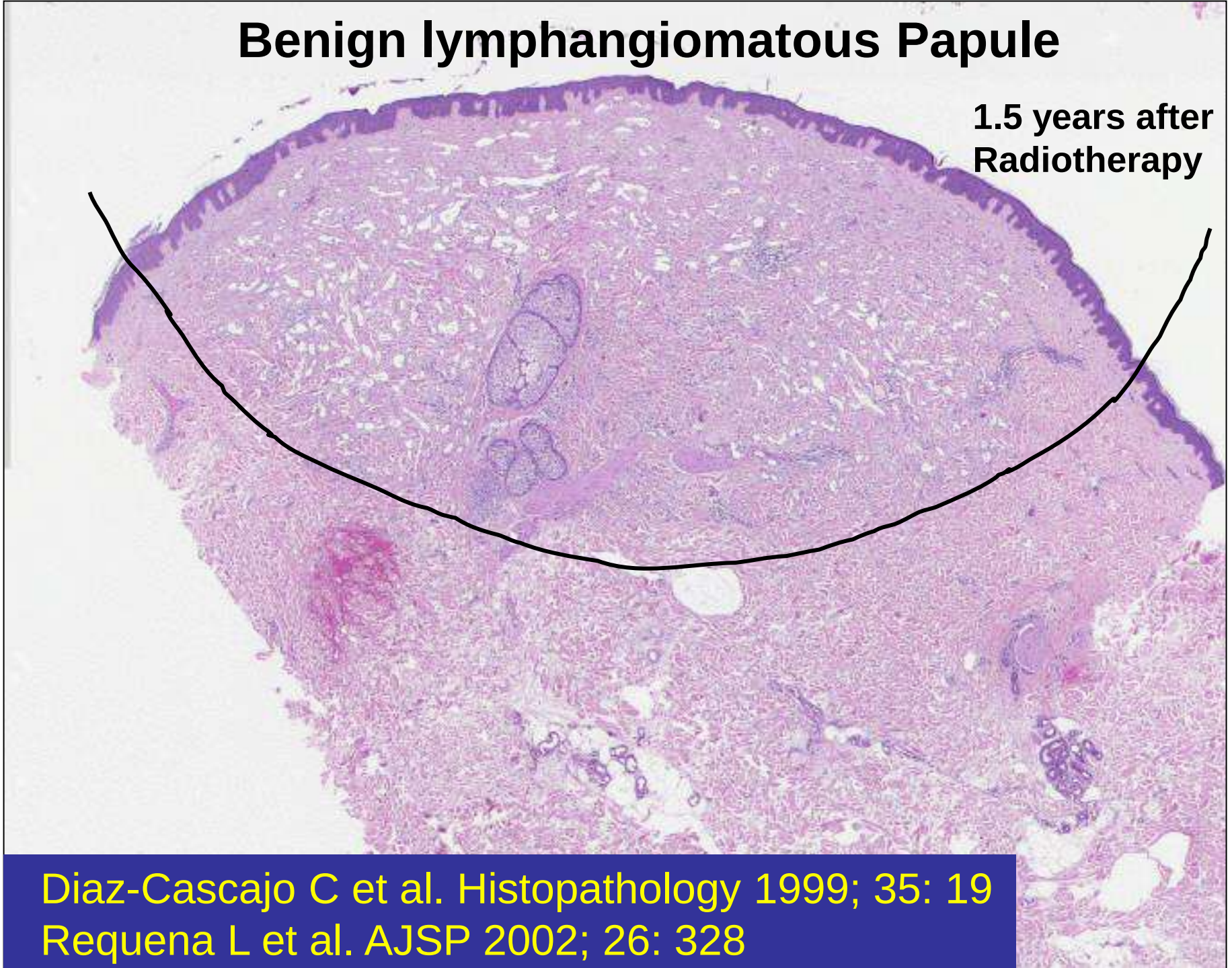
* Brenn T, Fletcher CDM AJSP 2005; 29: 983
Mattoch IW at al. JAAD 2007; 57: 126

Benign lymphangiomatous Papule



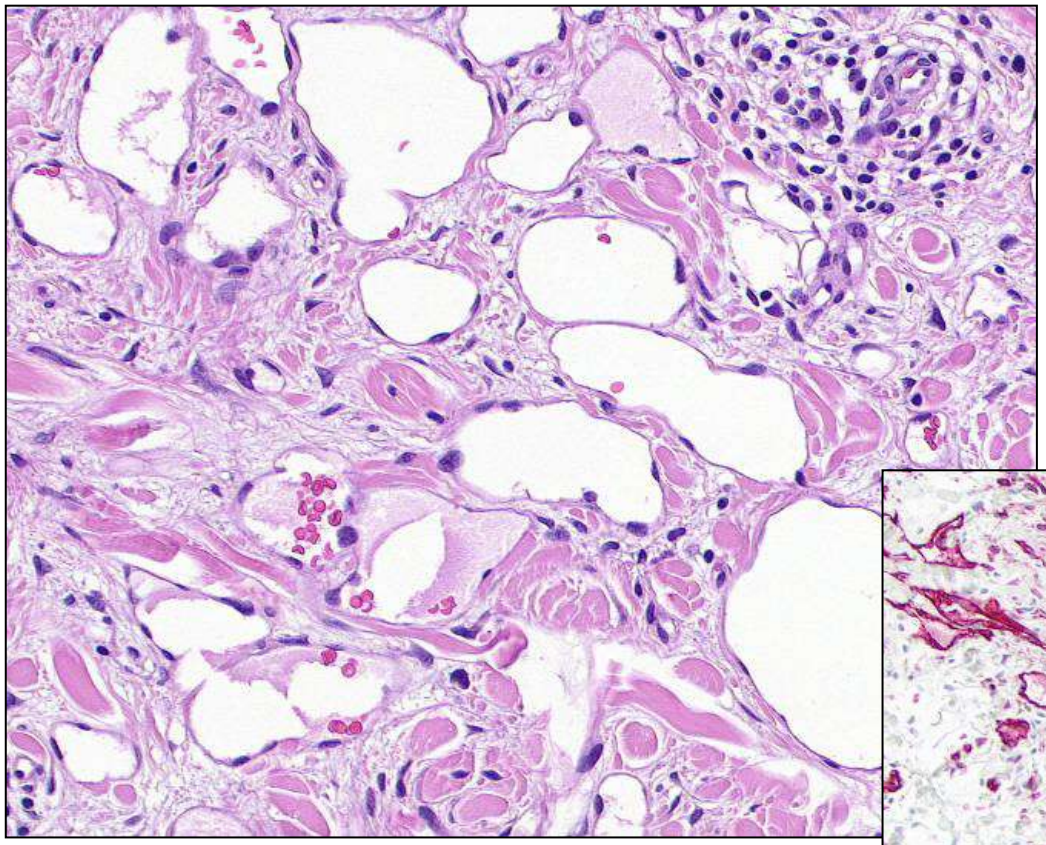
by courtesy of Dr.L.Requena, Madrid

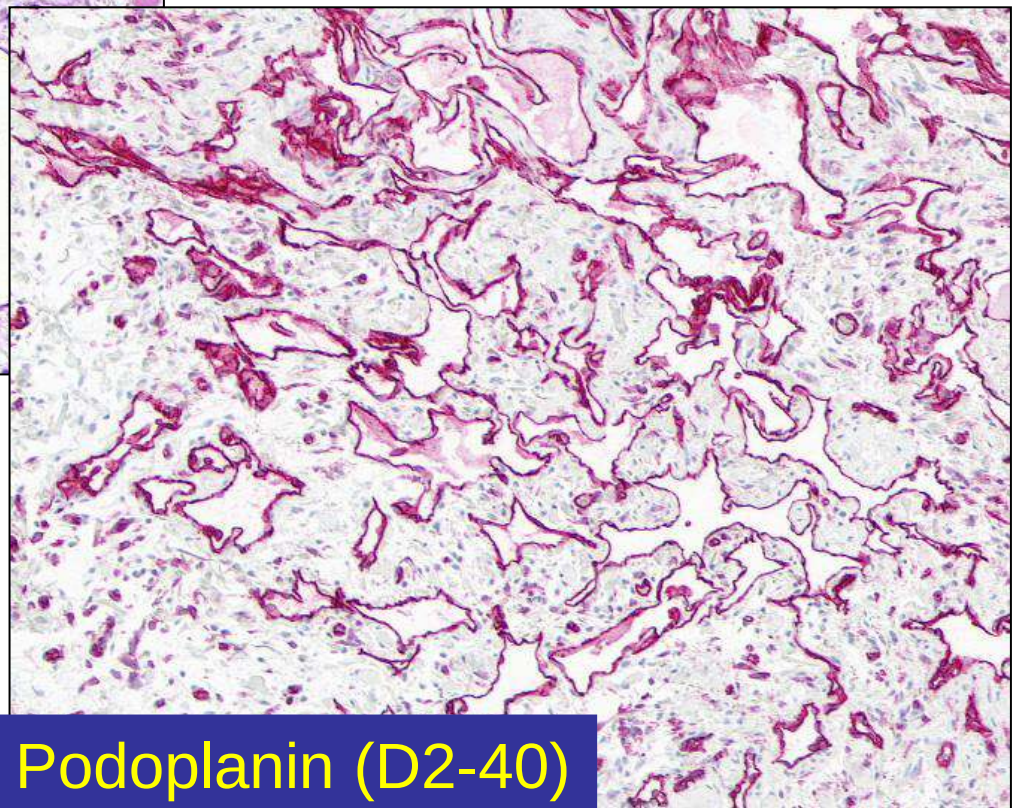
Benign lymphangiomatous Papule



Diaz-Cascajo C et al. Histopathology 1999; 35: 19
Requena L et al. AJSP 2002; 26: 328

Benign lymphangiomatous Papule





Podoplanin (D2-40)

Atypical vascular proliferation after RT
(Fineberg S, Rosen PP AJCP 1994; 102: 757)

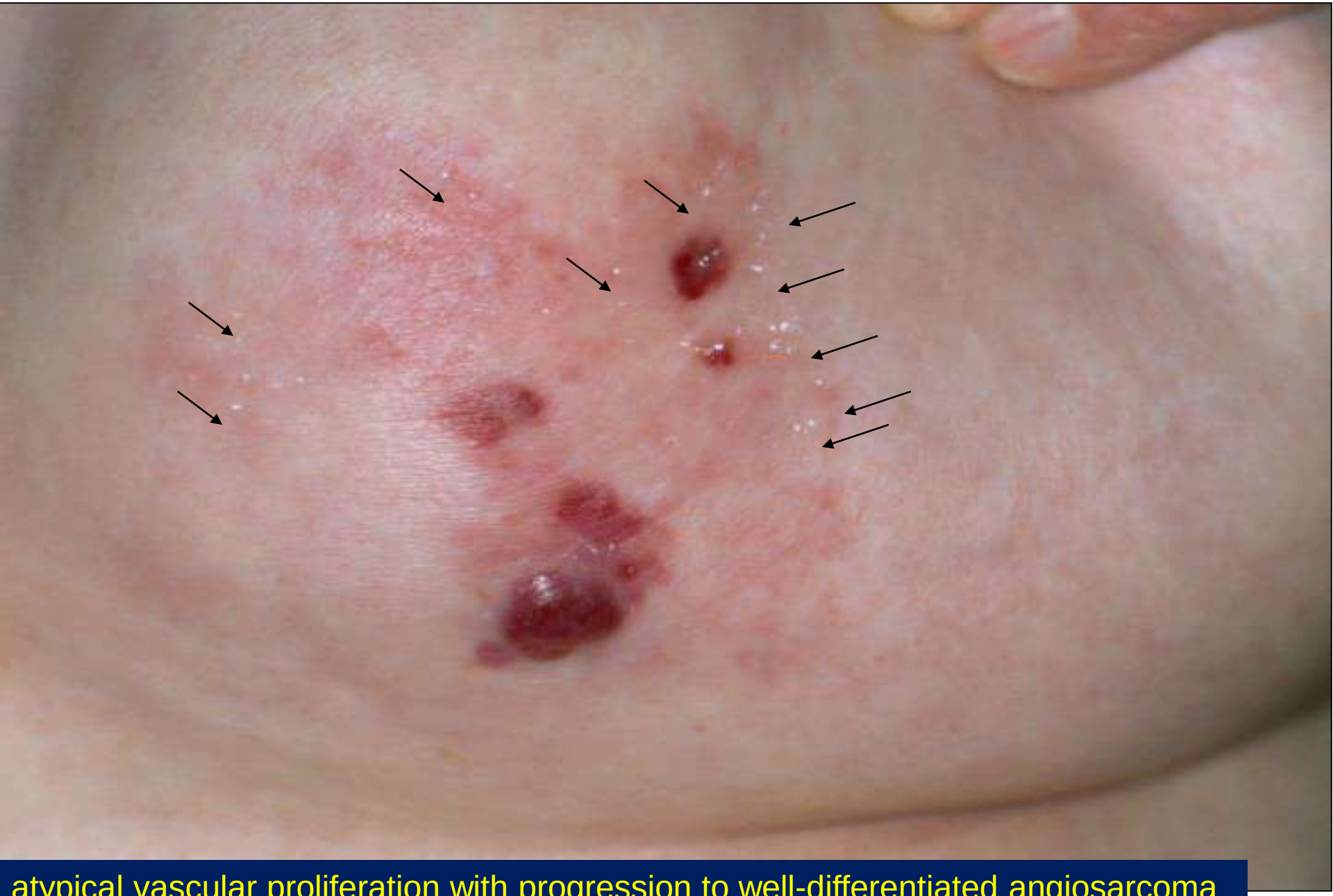
Clinicopathological Findings

- brown to erythematous papules / nodules
- single or multiple, circumscribed lesions
- anastomosing vessels, endothelial cells with hyperchromatic nuclei, no prominent nucleoli
- chronic inflammation
- no significant atypia, no mitoses
- no papillary endothelial proliferation
- no „blood lakes“, no infiltration of subcutis

Table 1. Histopathological features that help distinguish atypical vascular lesions from angiosarcoma (from Fineberg and Rosen[25])

Histopathological feature	AVL	AS
Infiltration into subcutis	–	+++
Papillary endothelial hyperplasia	–	+++
Prominent nucleoli	–	+++
Mitotic figures	–	+++
Significant cytological atypia	–	+++
'Blood lakes'	–	++
Dissection of dermal collagen	±	+++
Anastomotic vessels	++	+++
Hyperchromatic endothelial cells	+++	++
Chronic inflammation	+++	+
Relative circumscription	+++	–
Projections of stroma into lumen	+++	–

AVL, atypical vascular lesion; AS, angiosarcoma.

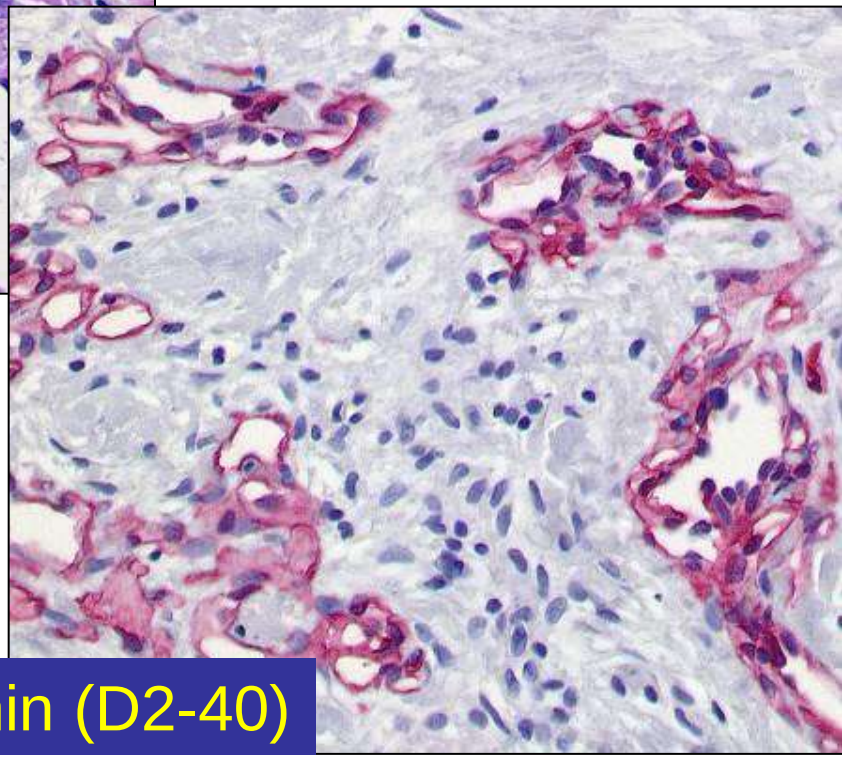


atypical vascular proliferation with progression to well-differentiated angiosarcoma (by courtesy of Prof.Dr.Metze, Münster, Germany)

hyperchromatic endothelial cells

multiple lesions 11 years after radiotherapy

AVP with transition into well-diff. AS



Podoplanin (D2-40)

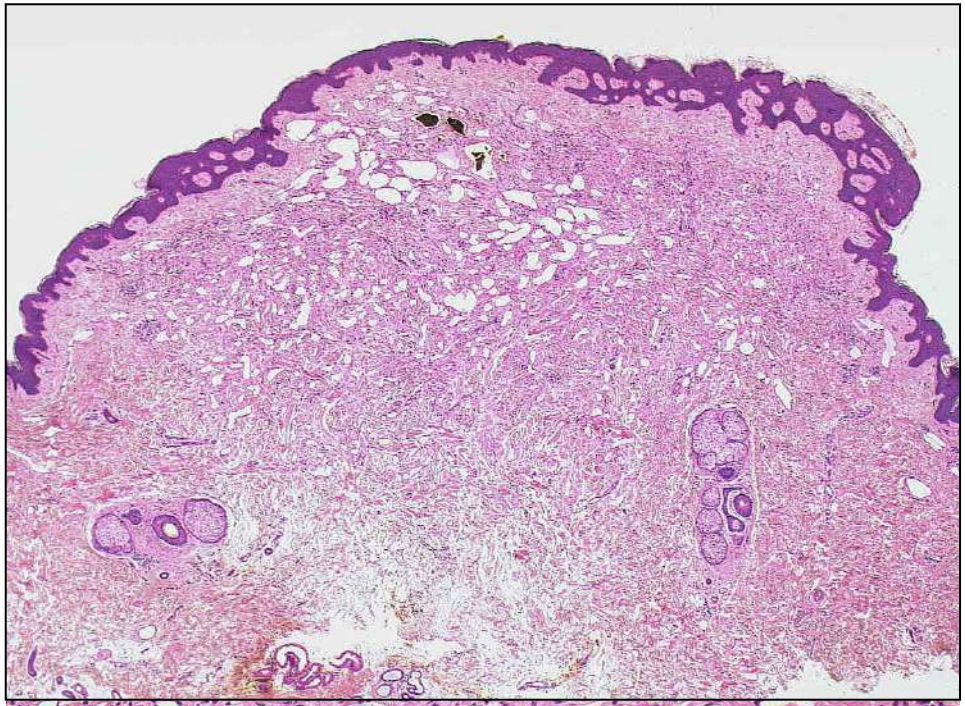
Mentzel T, Schildhaus HU, Palmedo G, Büttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol 2012;25(1):75-85

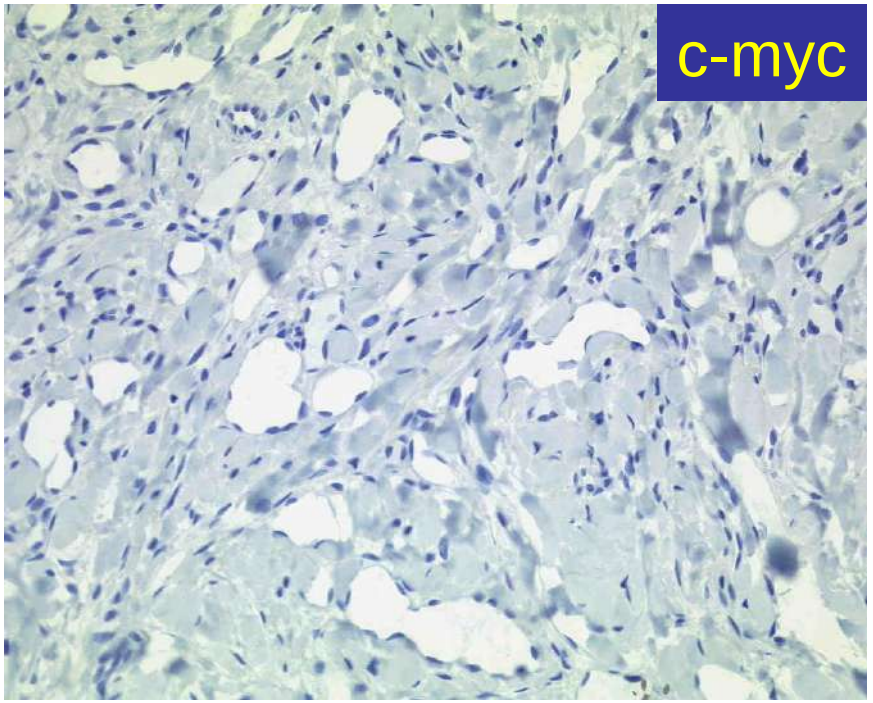
Fernandez AP, Sun Y, Tubbs RR, Goldblum JR, Billings SD. FISH for MYC amplifiation and anti-MYC immunohistochemistry: useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. J Cutan Pathol 2012;39(2):234-242

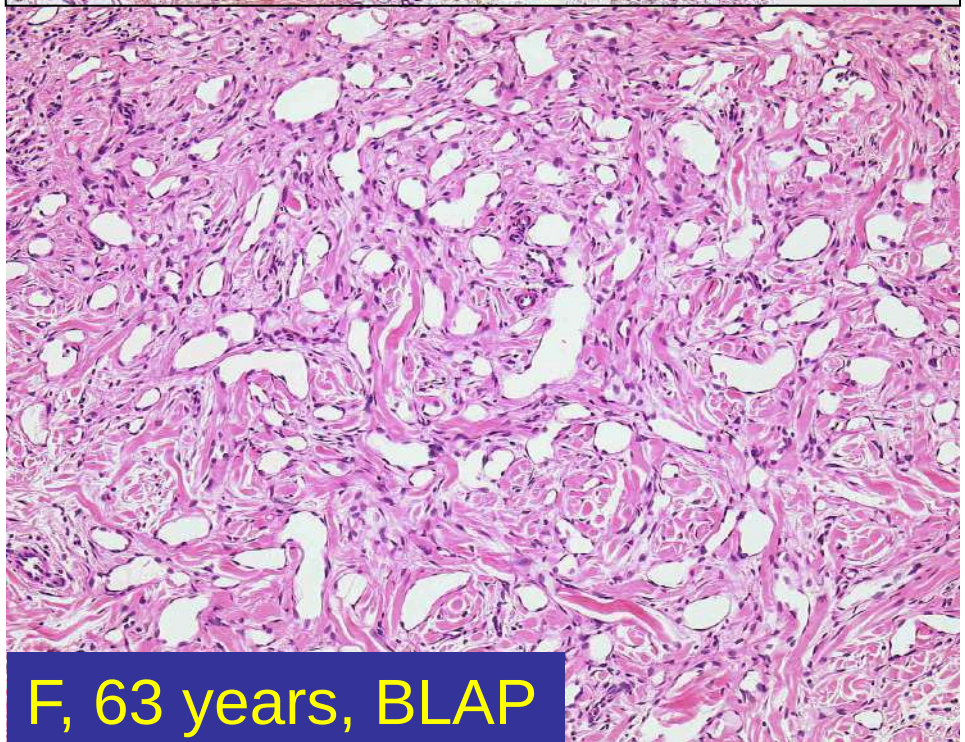
Guo T, Zhan L, Chang NE et al. Consistent MYC and FLT4 gene amplification in radiation induced angiosarcoma but not in other radiation-associated atypical vascular lesions.
Genes Chromosomes Cancer 2011; 50: 25-33

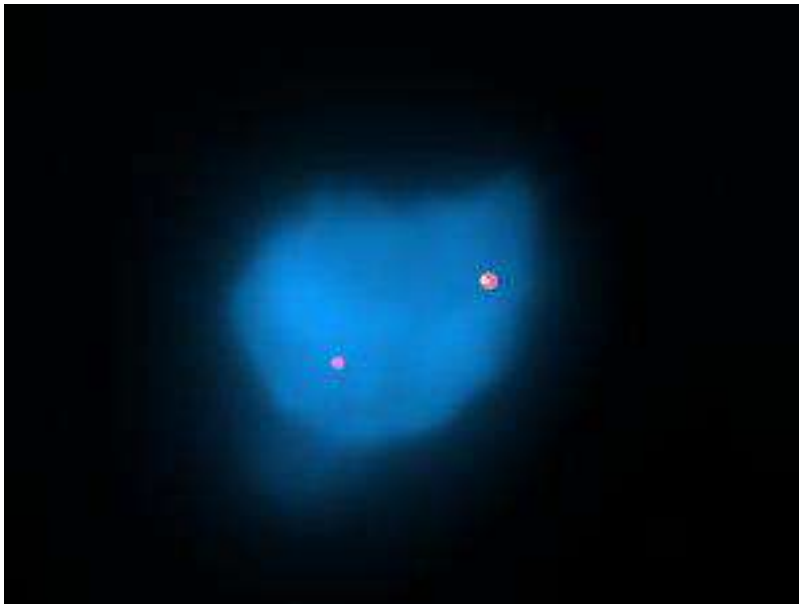
Cornejo KM, Deng A, Wu H et al. The utility of MYC and FLT4 in the diagnosis and treatment of postradiation atypical vascular lesion and angiosarcoma of the breast. Hum Pathol 2015; 46: 868-875

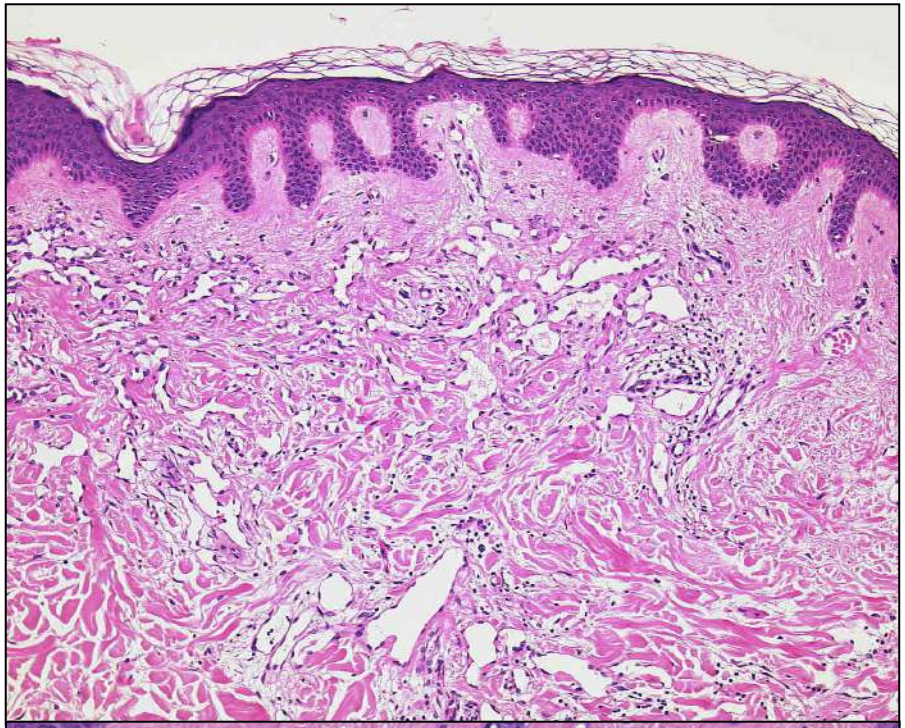
Fraga-Guedes C, Andre S, Mastropasqua MG et al. Angiosarcoma and atypical vascular lesions of the breast: diagnostic and prognostic role of MYC gene amplification and protein expression. Breast Cancer Res Treat 2015; 151: 131-140

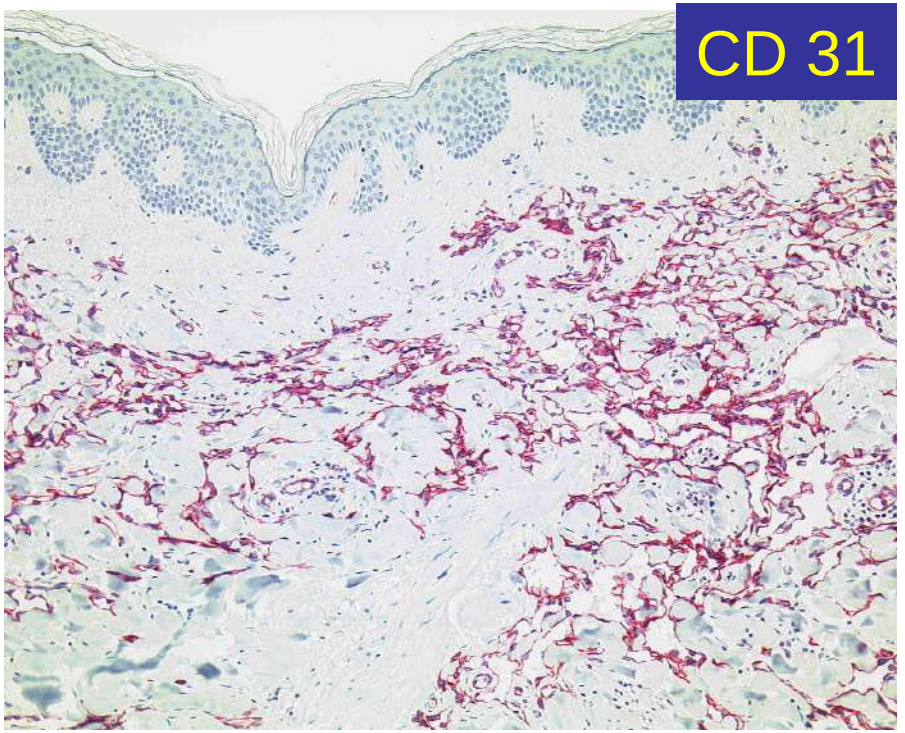


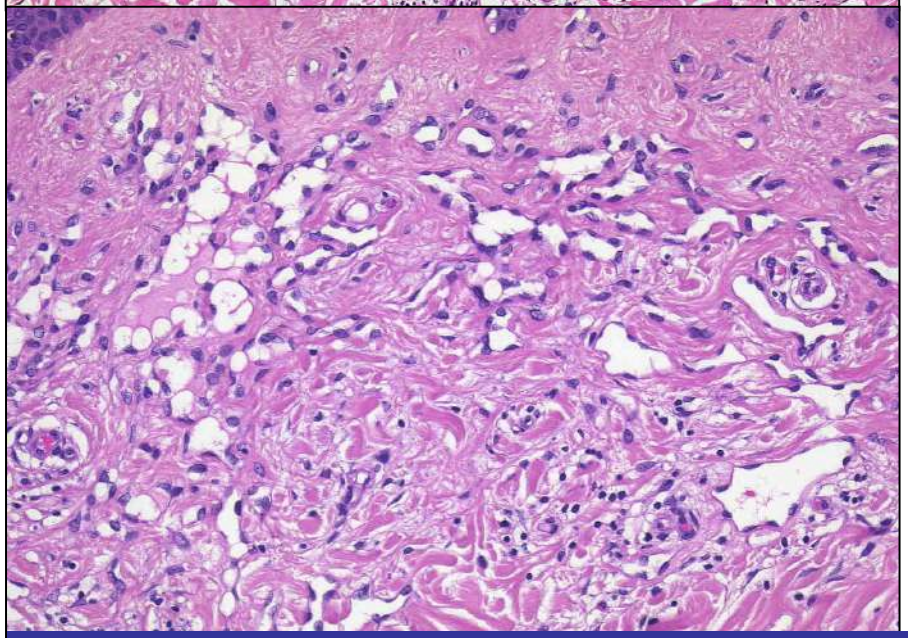

c-myc

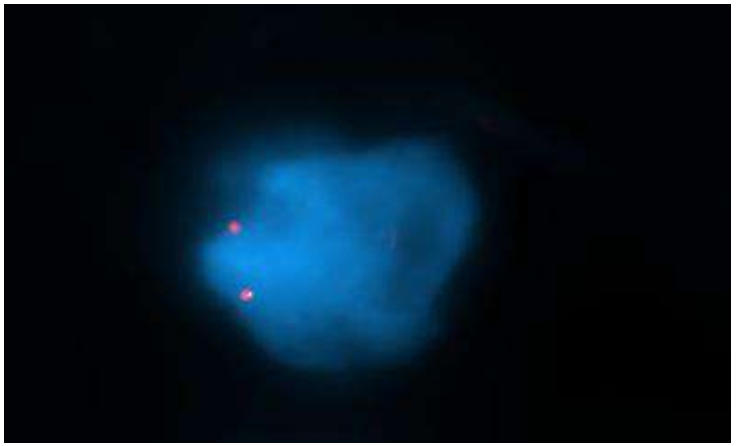

F, 63 years, BLAP



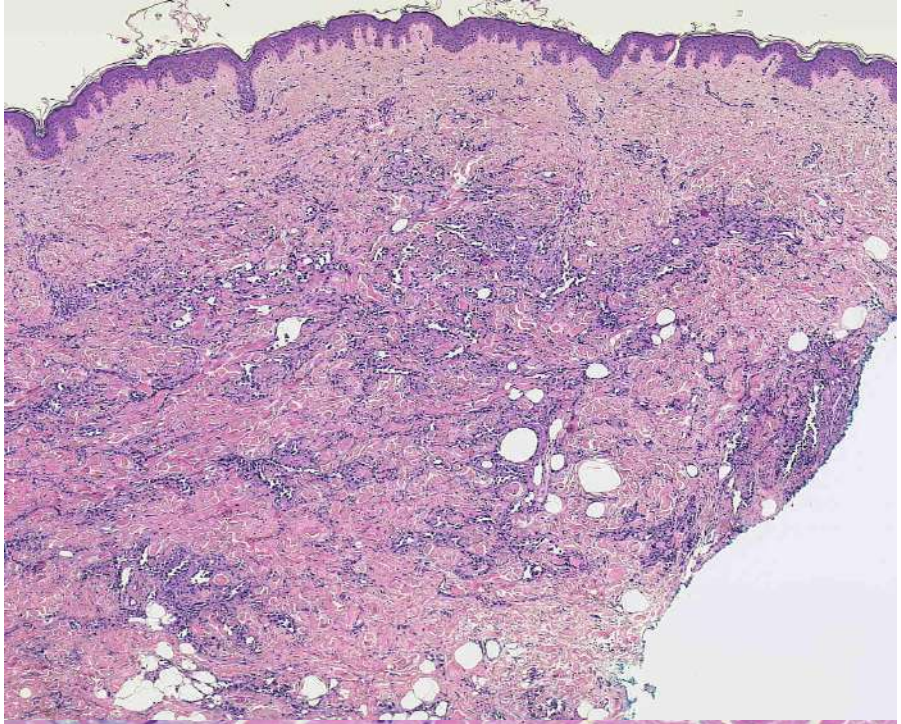


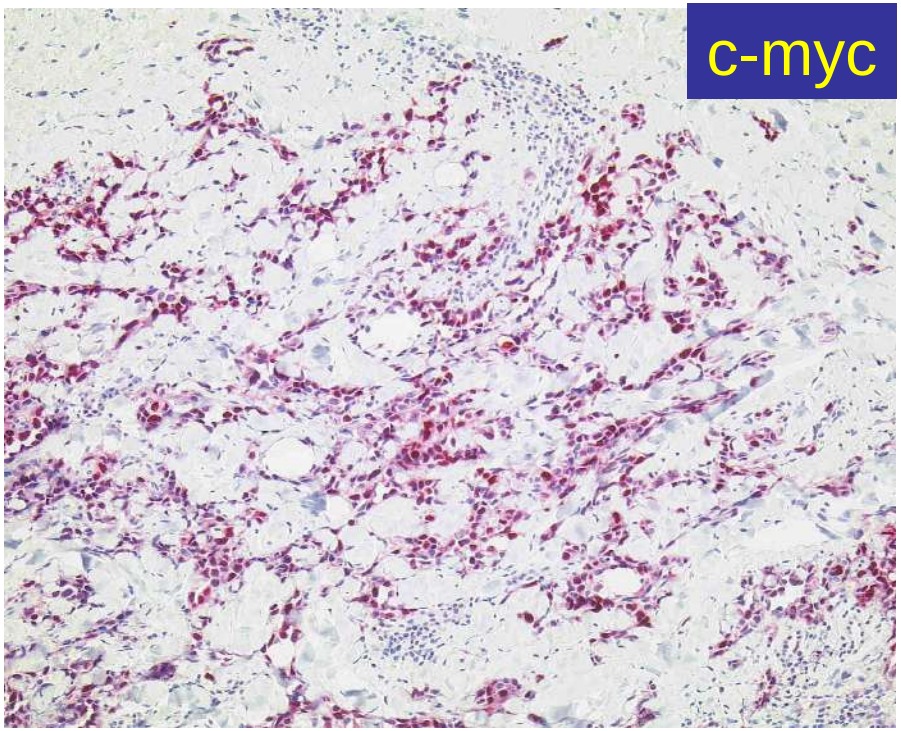


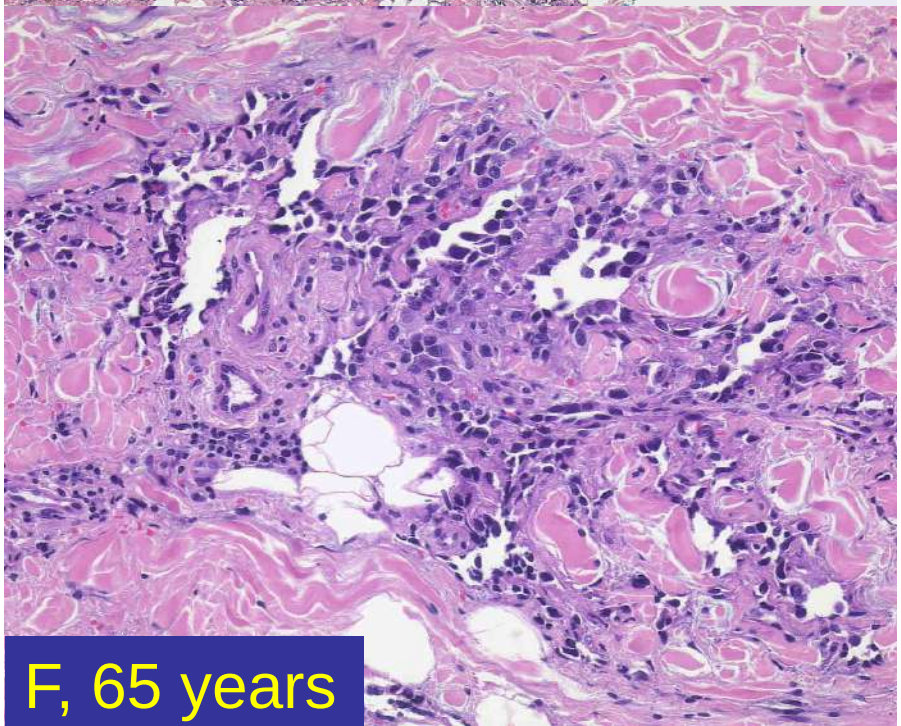


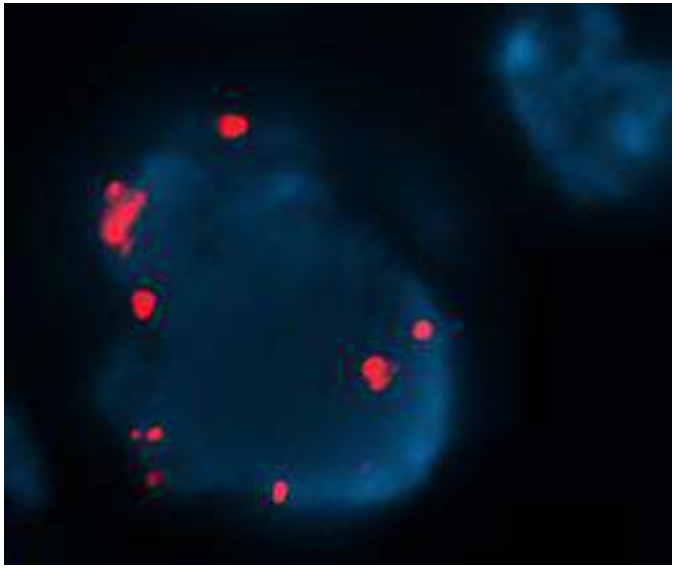


F, 65 years, AVL, NSR at 36/12



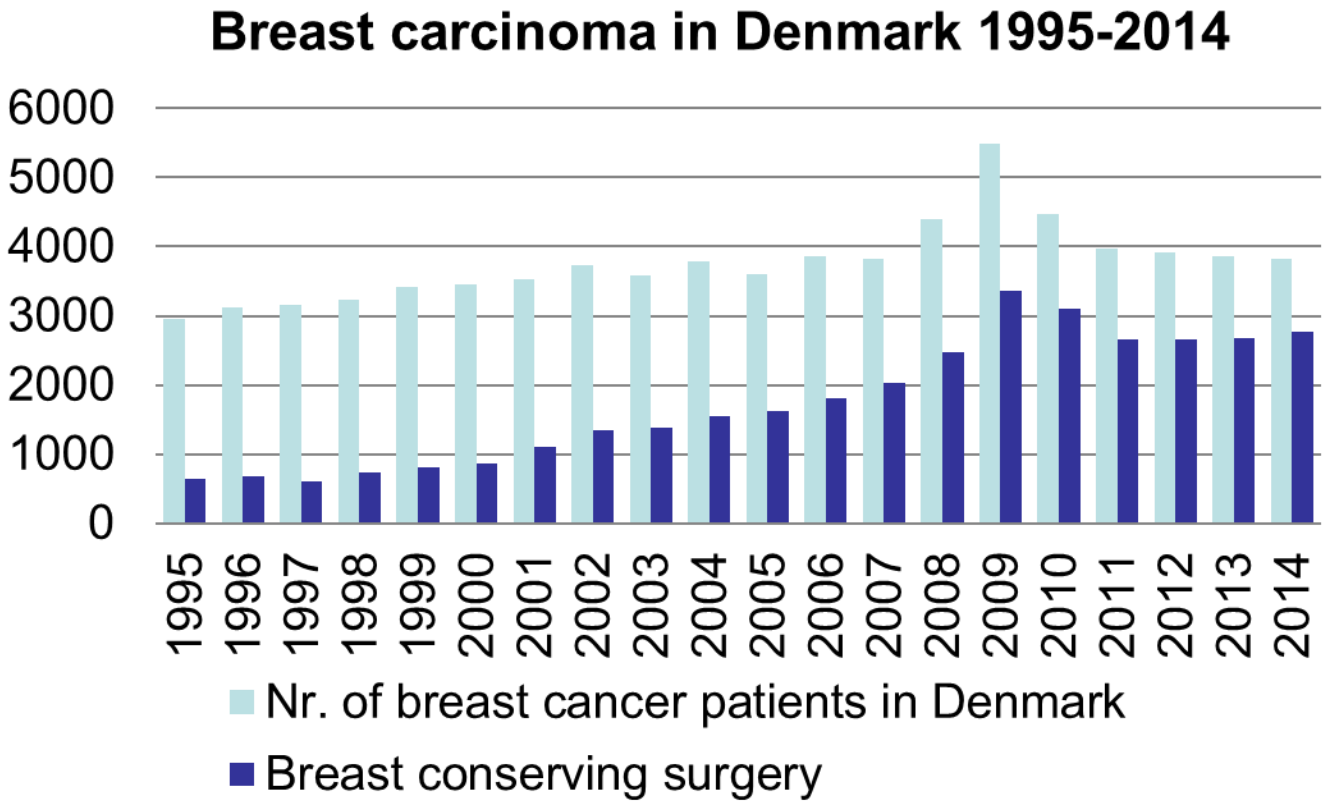

c-myc

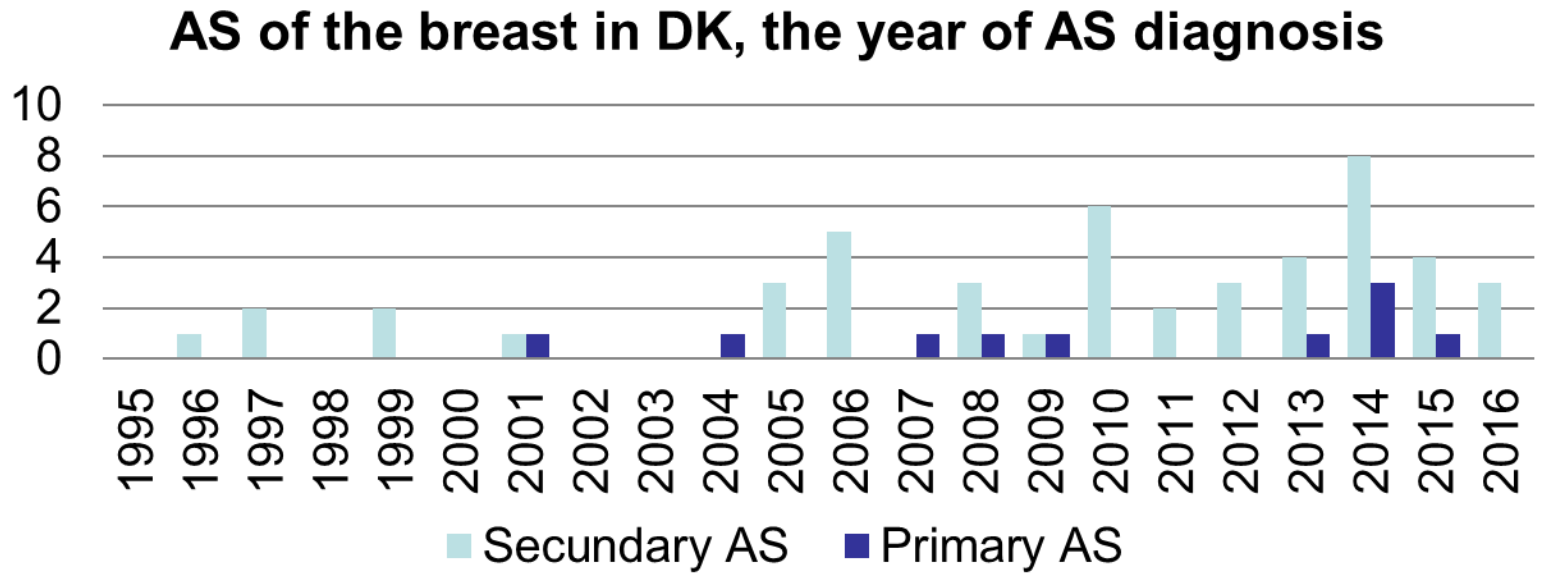

F, 65 years

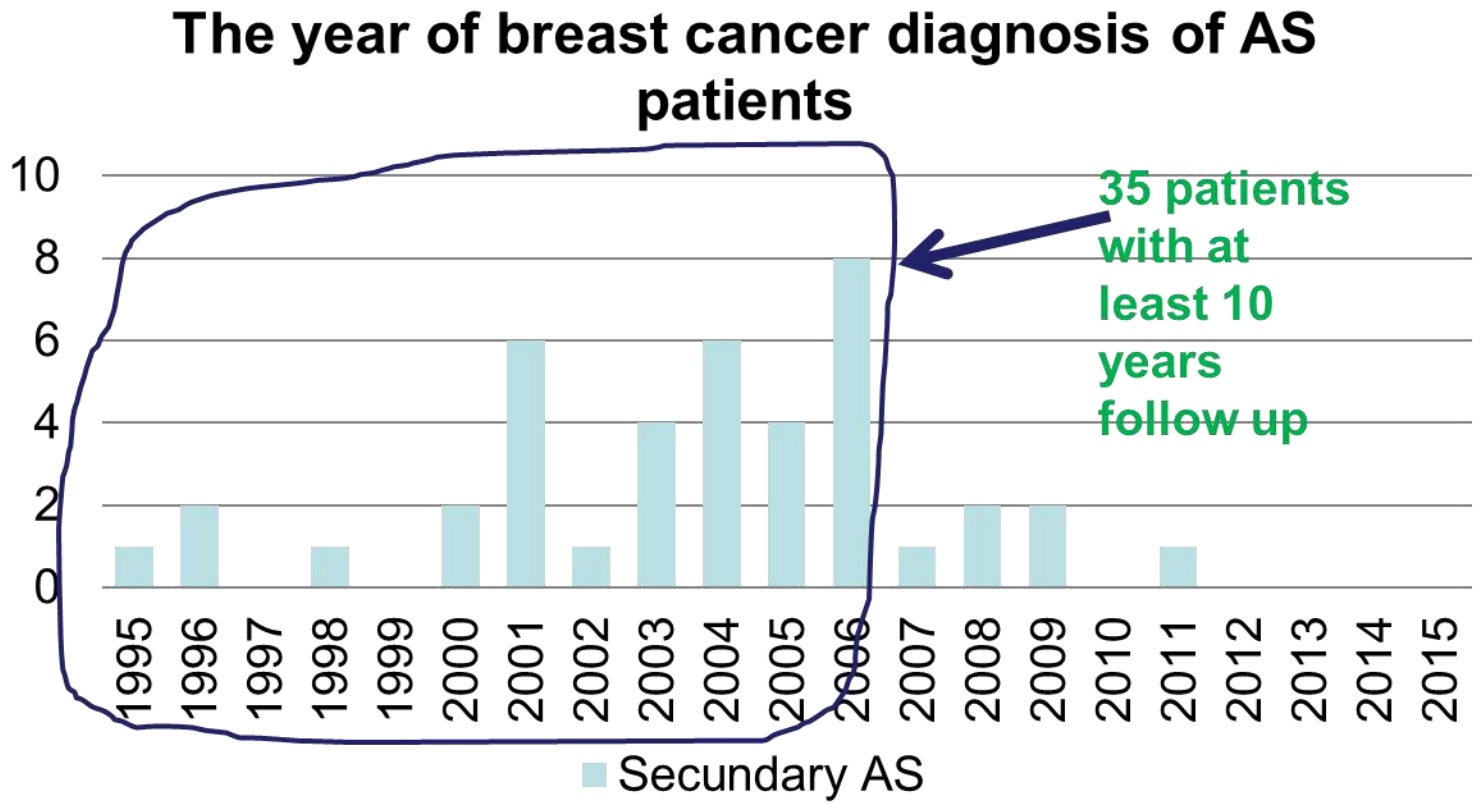


Problematic issue: Incidence of postradiation Angiosarcoma

Marchal C et al. Int J ROBP 1999; 44: 113
9 AS in 18115 patients = 0.049%
Strobbe LJ et al. Breast Cancer RT 1998; 47: 101
estimated incidence is 0.16%
Flucke U Adv Anat Pathol 2013; 20: 407
estimated rate 0.05% - 1.11%
Hornick JL Practical Soft Tissue Pathology
reported risk varies from 0.09% to 0.3%


Breast carcinoma in Denmark 1995-2014
6000
5000
4000
3000
2000
1000
0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Nr. of breast cancer patients in Denmark
Breast conserving surgery


AS of the breast in DK, the year of AS diagnosis
10
8
6
4
2
0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Secundary AS
Primary AS

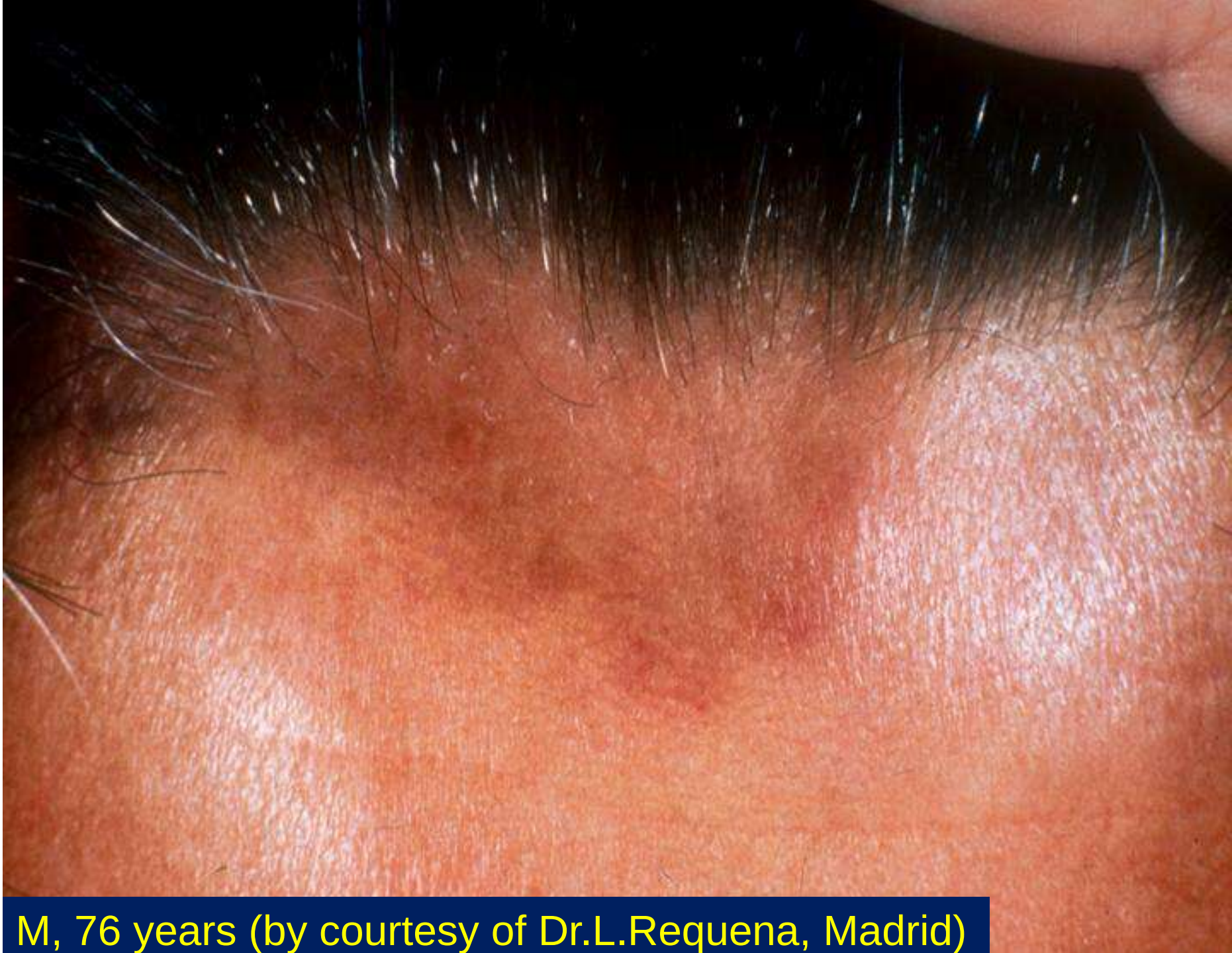


1995-2006: **13.150 patients received radiotherapy**
35 patients developed AS within follow-up period
incidence of RT-induced AS 0.266%
9 patients developed other sarcomas
incidence of RT-induced sarcomas 0.319%

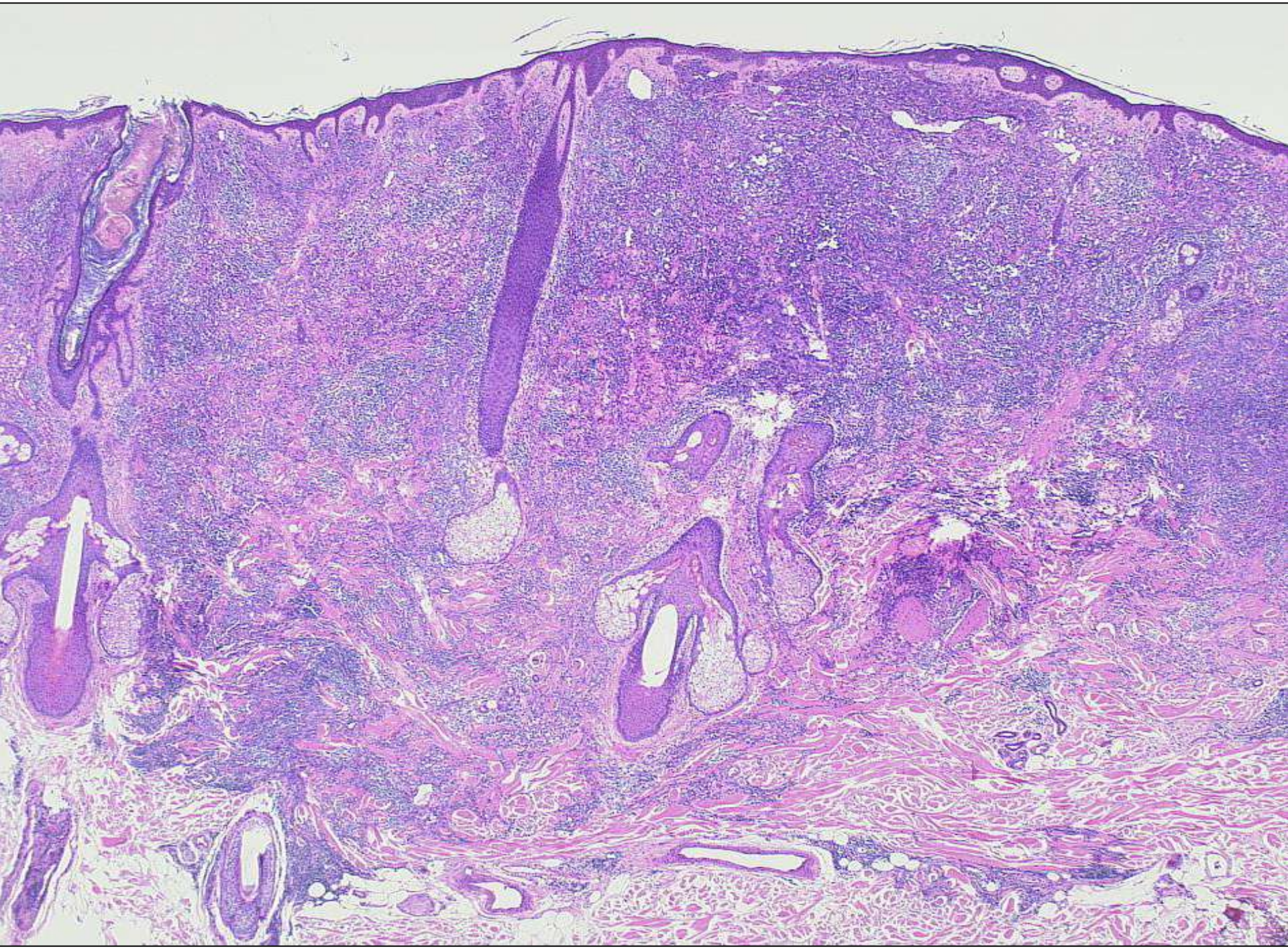
Katalin Kiss et al. Mod Pathol 2017; 132A: 517

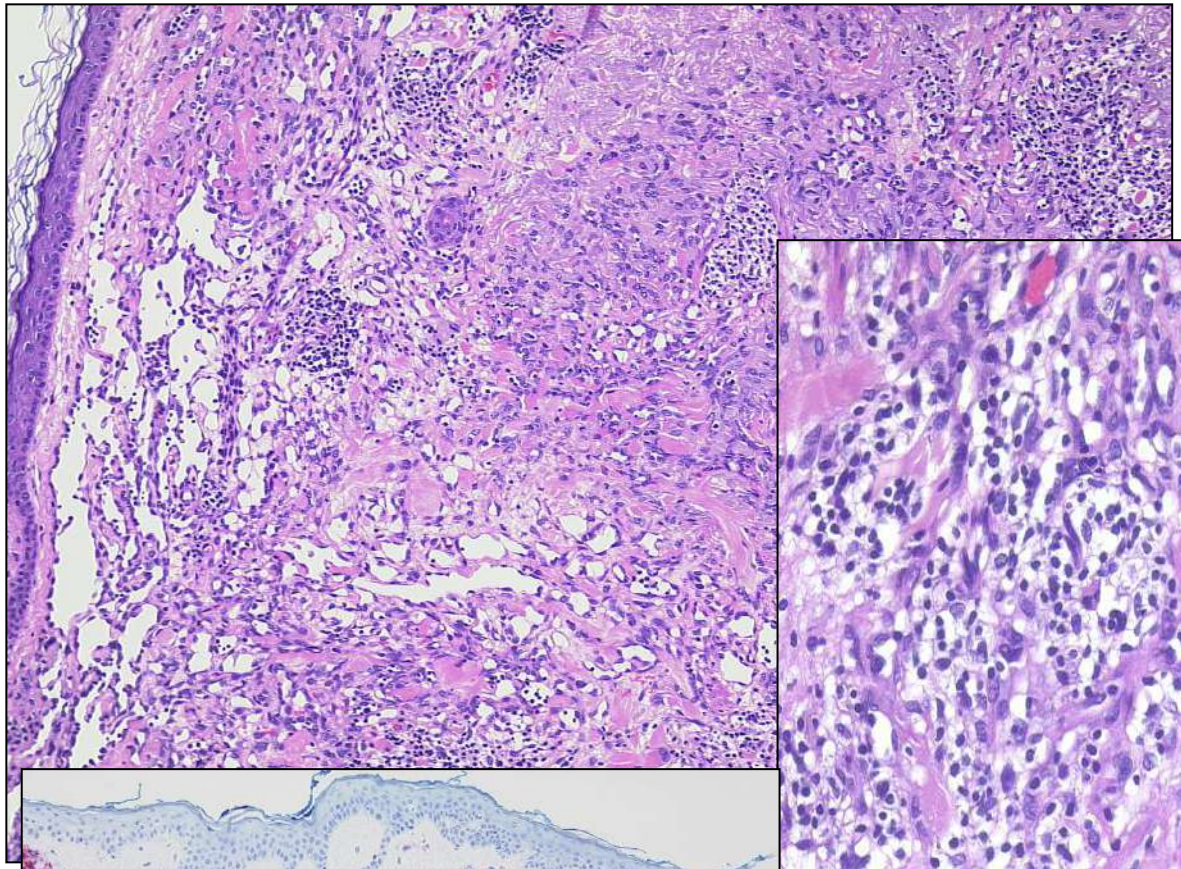
Conclusions

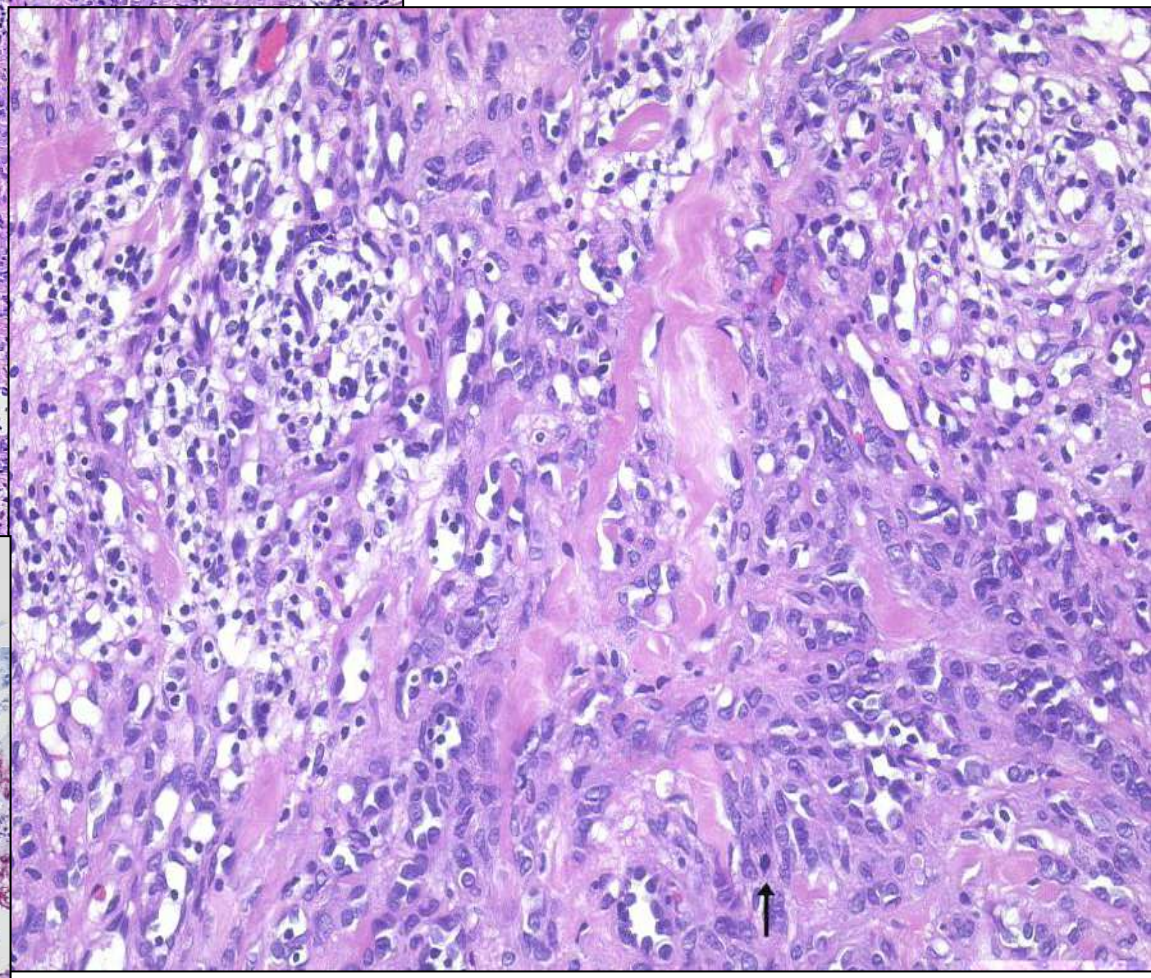
- all cutaneous vascular lesions after radiotherapy should be excised completely
- presence / absence of c-myc amplification / expression represents an additional finding in order to establish the correct dignity in RT-associated vascular lesions
- c-myc stainings may be used for mapping
- raises the possibility of new potential therapeutic options (*MYC / FLT4* amplification) i.e. Sorafenib
- extended follow-up studies are necessary

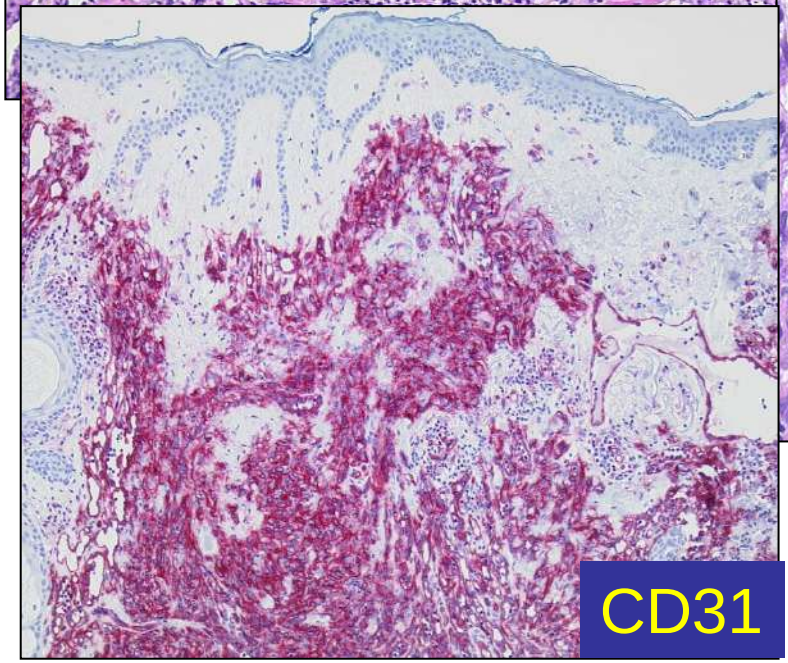


M, 76 years (by courtesy of Dr.L.Requena, Madrid)





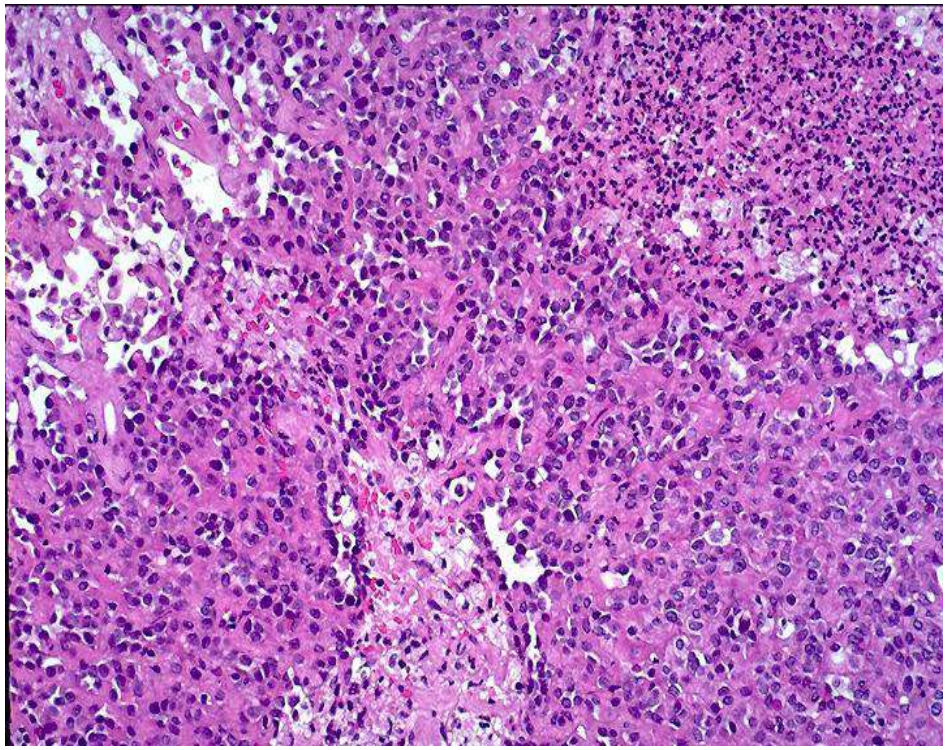


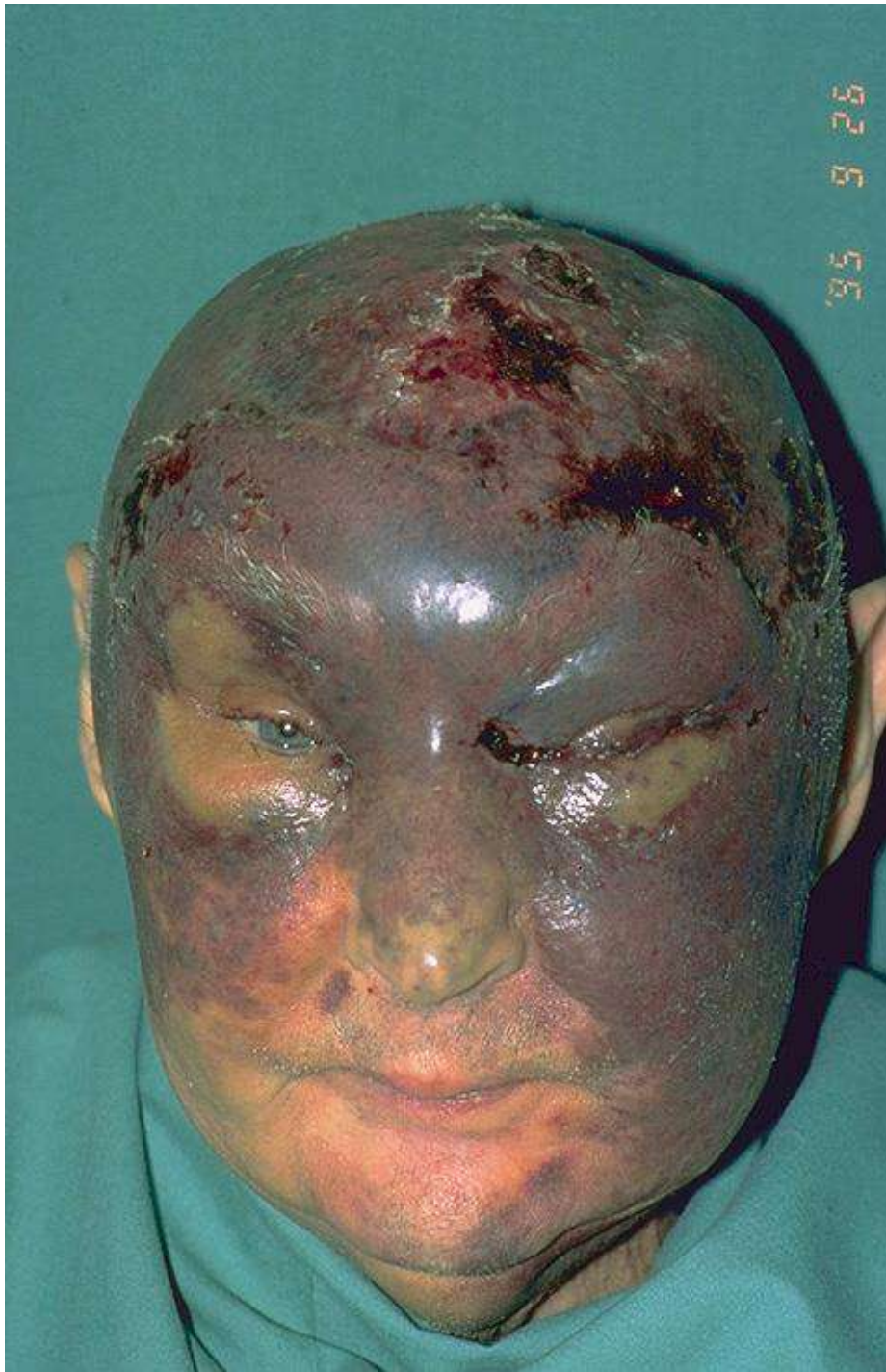

CD31

Cutaneous actinic Angiosarcoma

- irregular red plaques, nodular lesions, resemble inflammatory lesions, cut. lymphomas
- infiltrating, anastomosing vessels, atypical endothelial cells, mitoses, epithelioid morphology only rarely, prominent lymphocytic infiltrate
- CD31 +, CD34 -/+, D2-40+/-, Lyfe-1 +/-
- locally aggressive, many recurrences, late metastases, 5-years survival 15-30%
- adjuvant therapy: i.e. Paclitaxel, Thalidomide

(Eur J Cancer 2008; 30: 639; Cancer 2005; 104: 361)

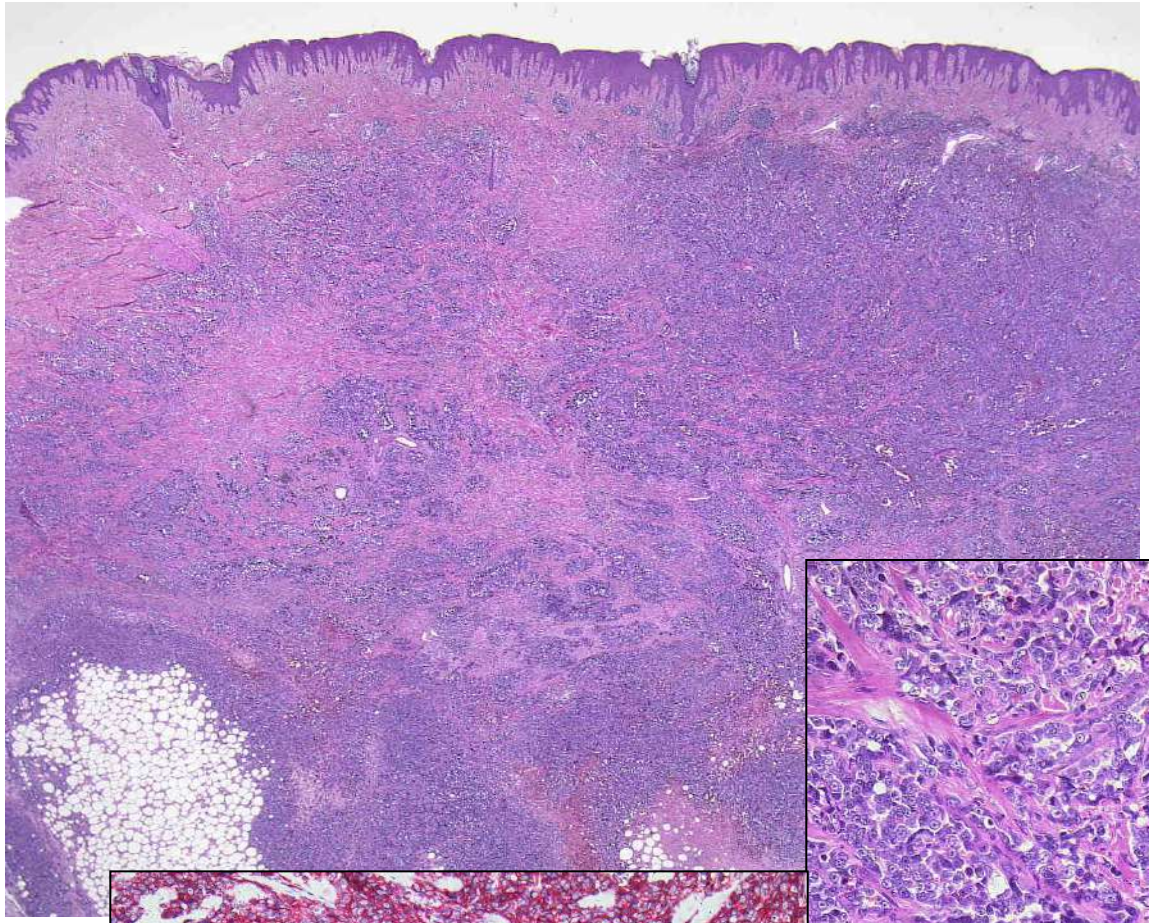




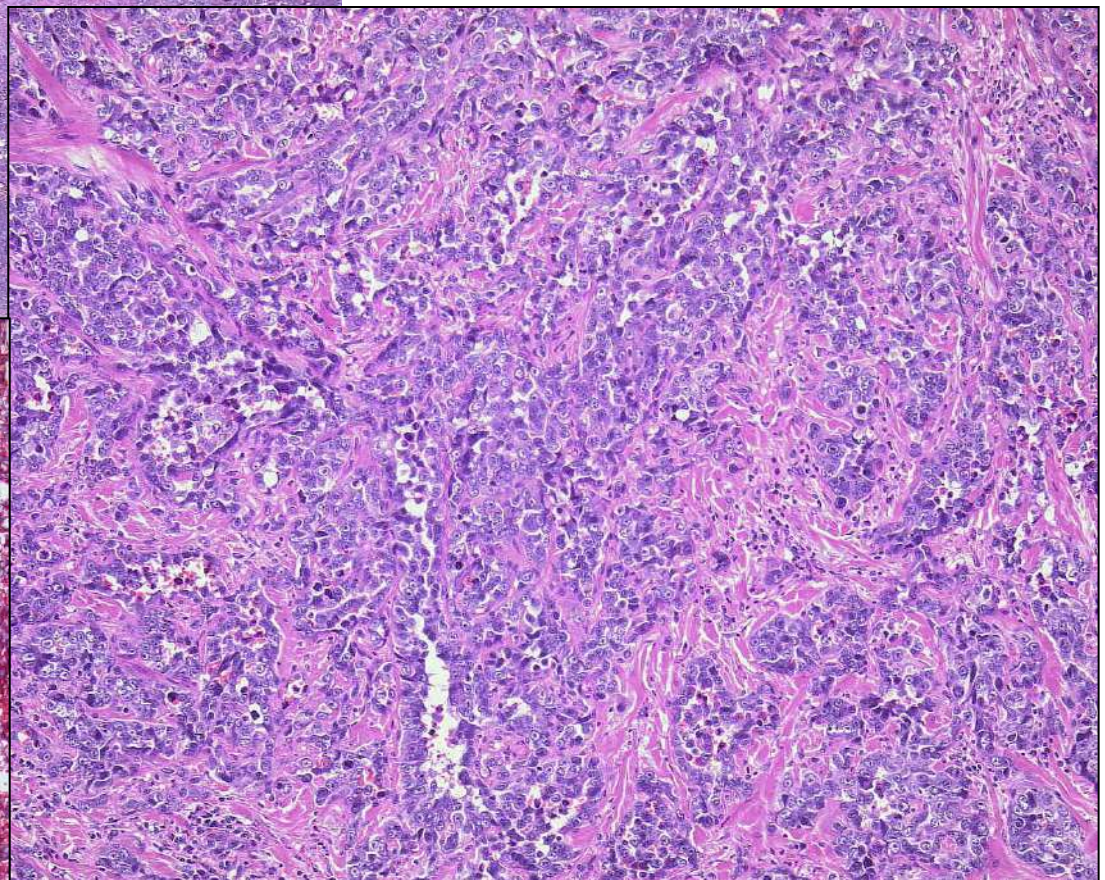
Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs

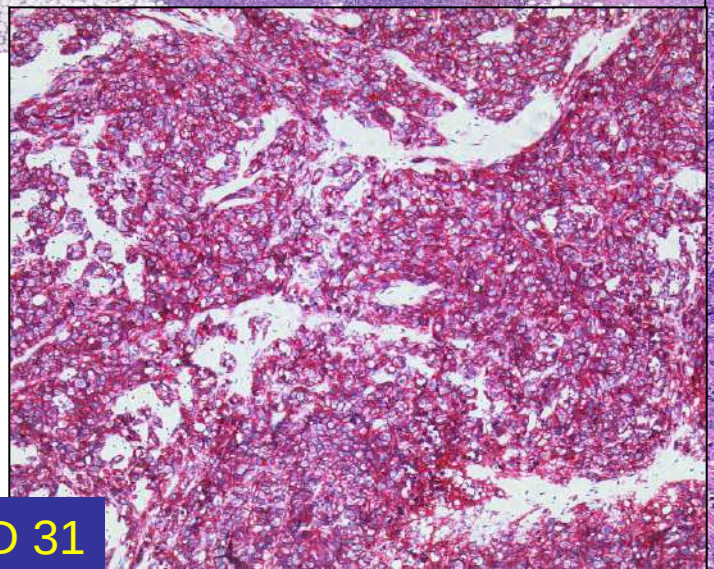
Suchak R et al. AJSP 2011; 35: 60

- 13 cases, x = 66 years, extremities (10)
- solitary (10), multicentric (3)
- dermis, infiltration of subcutis
- confluent areas of epithelioid tumour cells
- atypia, mitoses, necrosis (40%)
- CD 31 +, Fli-1 +, CK in 2/3 +
- 6/11 MTS, 6/11 DOD



F, 88 years
abdominal wall





CD 31

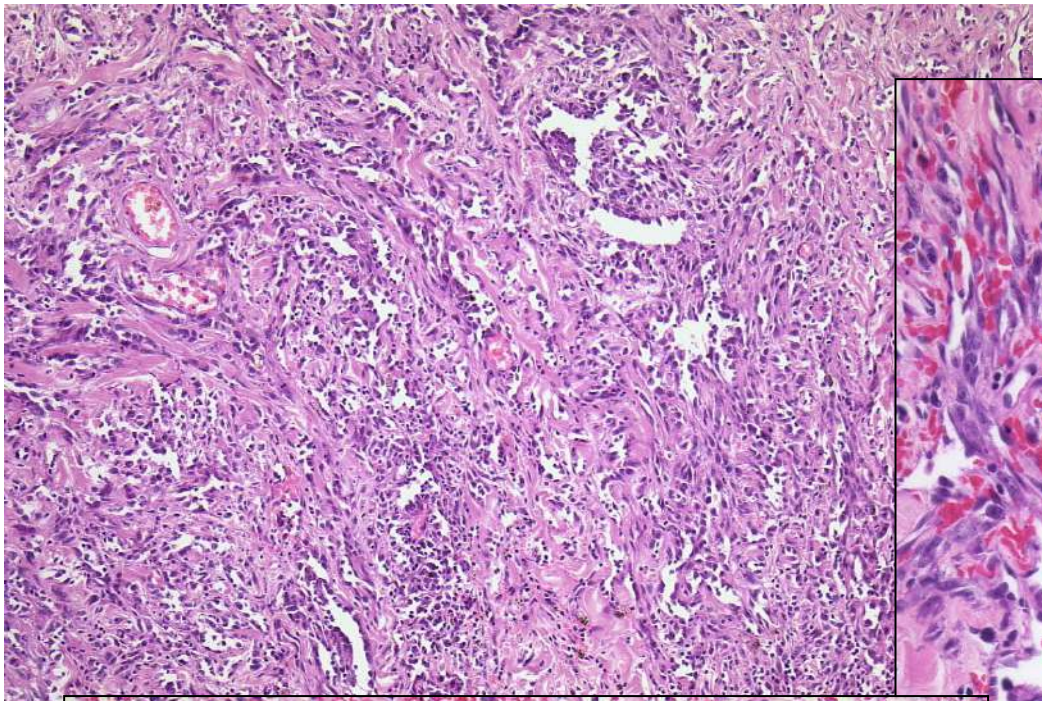
Conclusions: cutaneous Angiosarcoma

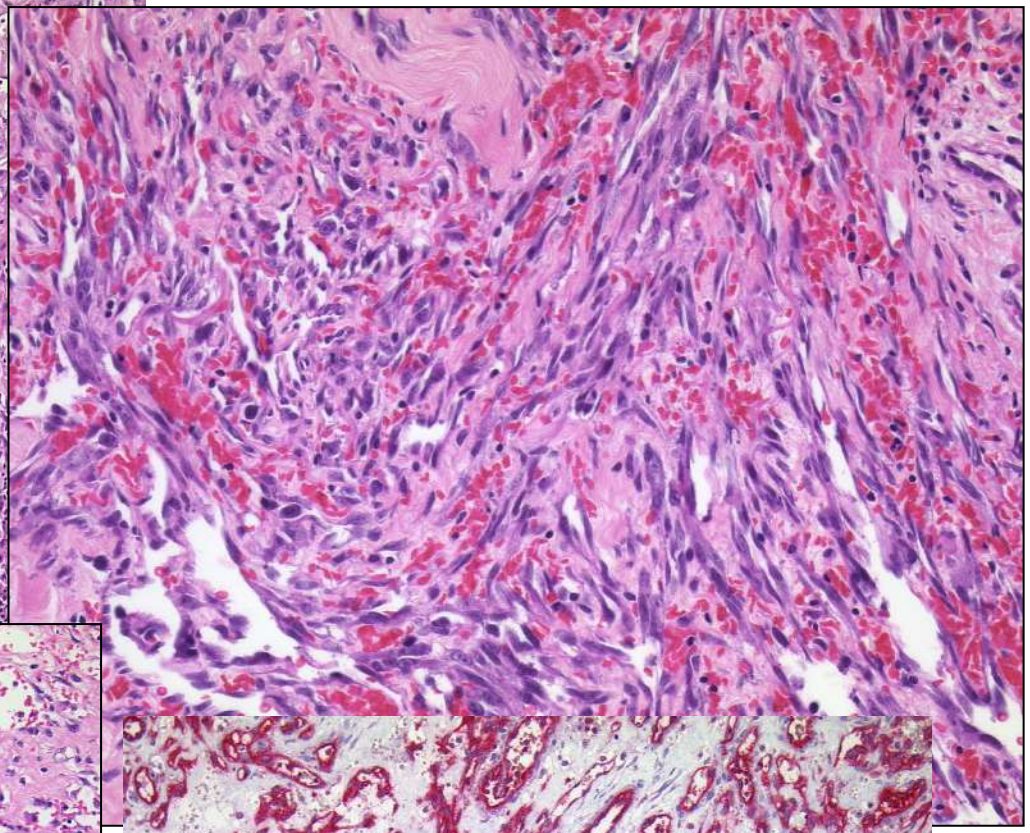
- varying clinical presentation mimicking an inflammatory disorder, cut. lymphoma
- often prominent inflammation
- clinically very aggressive neoplasms
- morphological grading has no prognostic influence (AJSP 2008; 32: 1896)
- rare epithelioid angiosarcoma has a worse prognosis (AJSP 2011; 35: 60)

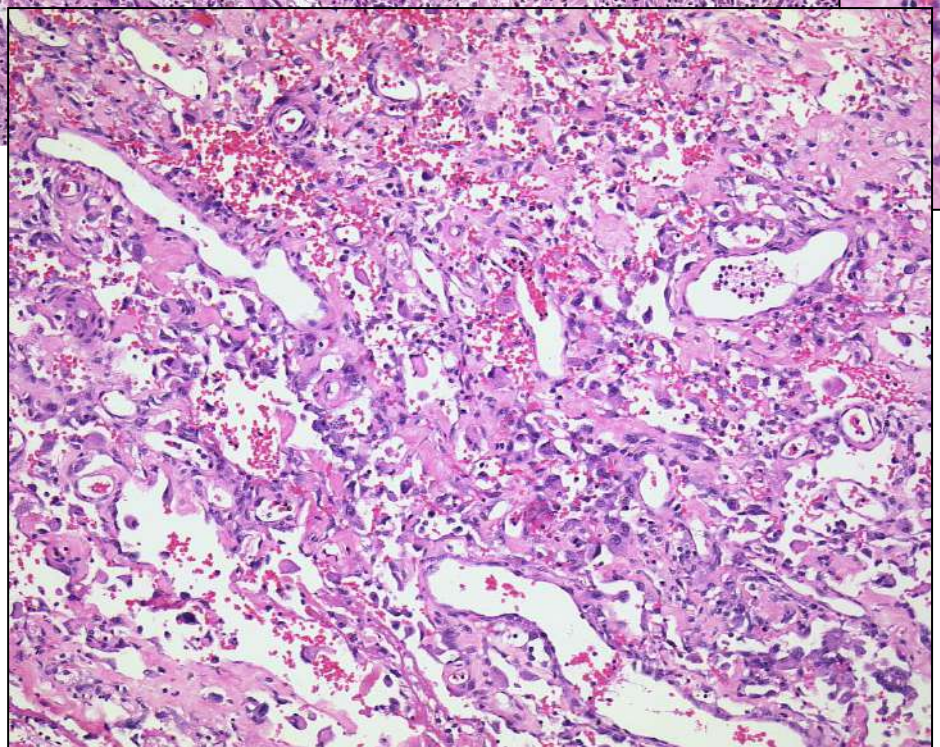
!!! Think on cutaneous angiosarcoma !!!

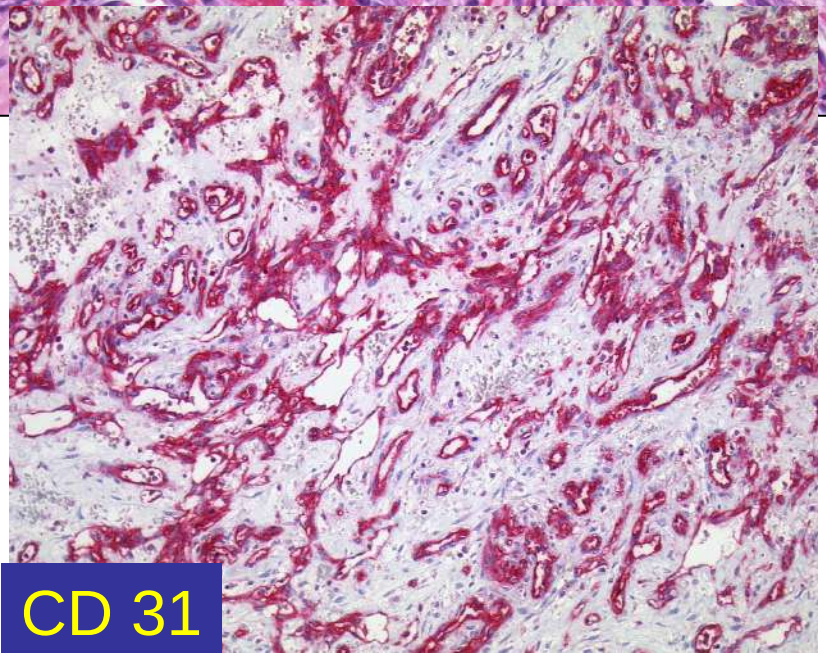
Angiosarcoma of Soft Tissues

- very rare (< 1 % of all sarcomas)
- elderly patients, M > F,
  lower > upper extremities, trunk > head
- rarely intraabdominal, retroperitoneal
- rarely multicentric
- very rarely in preexisting haemangiomas
- very rarely in nerve sheath tumours
- local recurrences in 20-30%
  metastases in 50%
  5-year survival 20-30%
  aggressive surgery



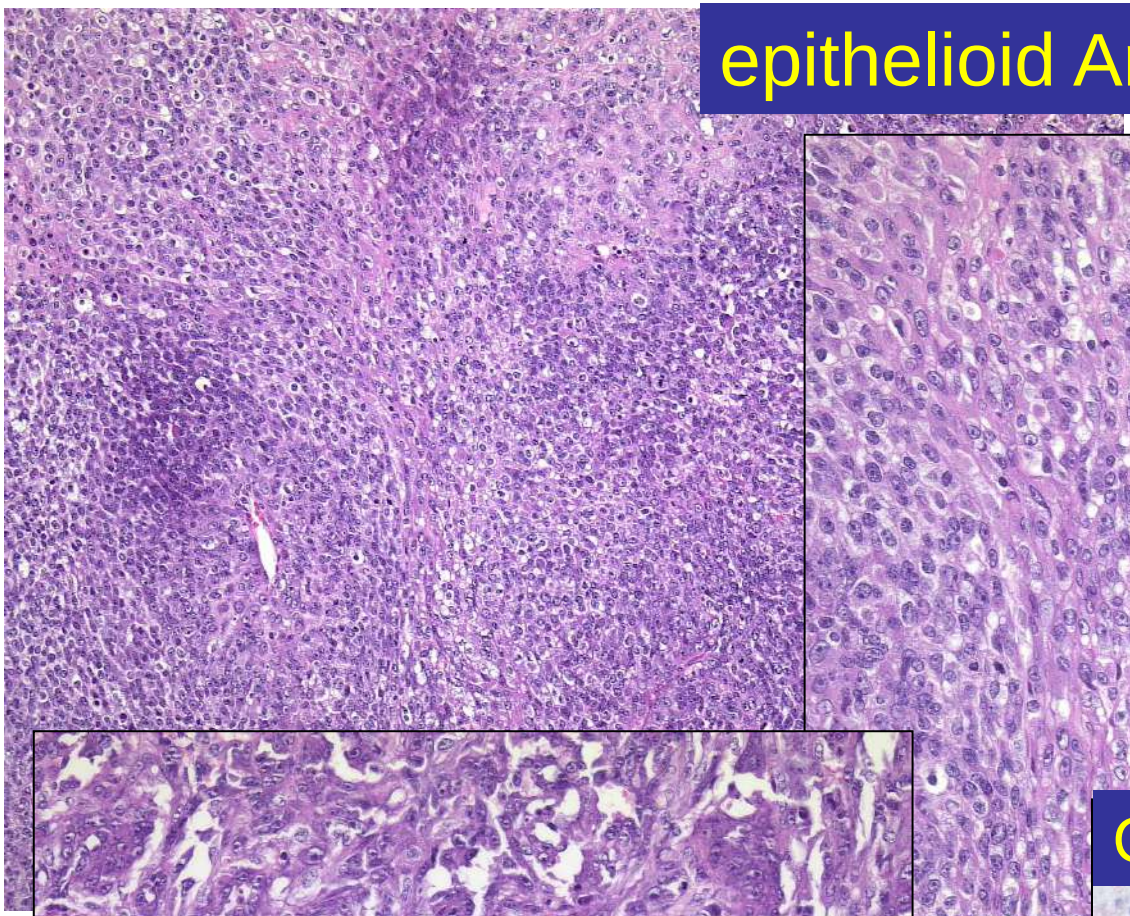


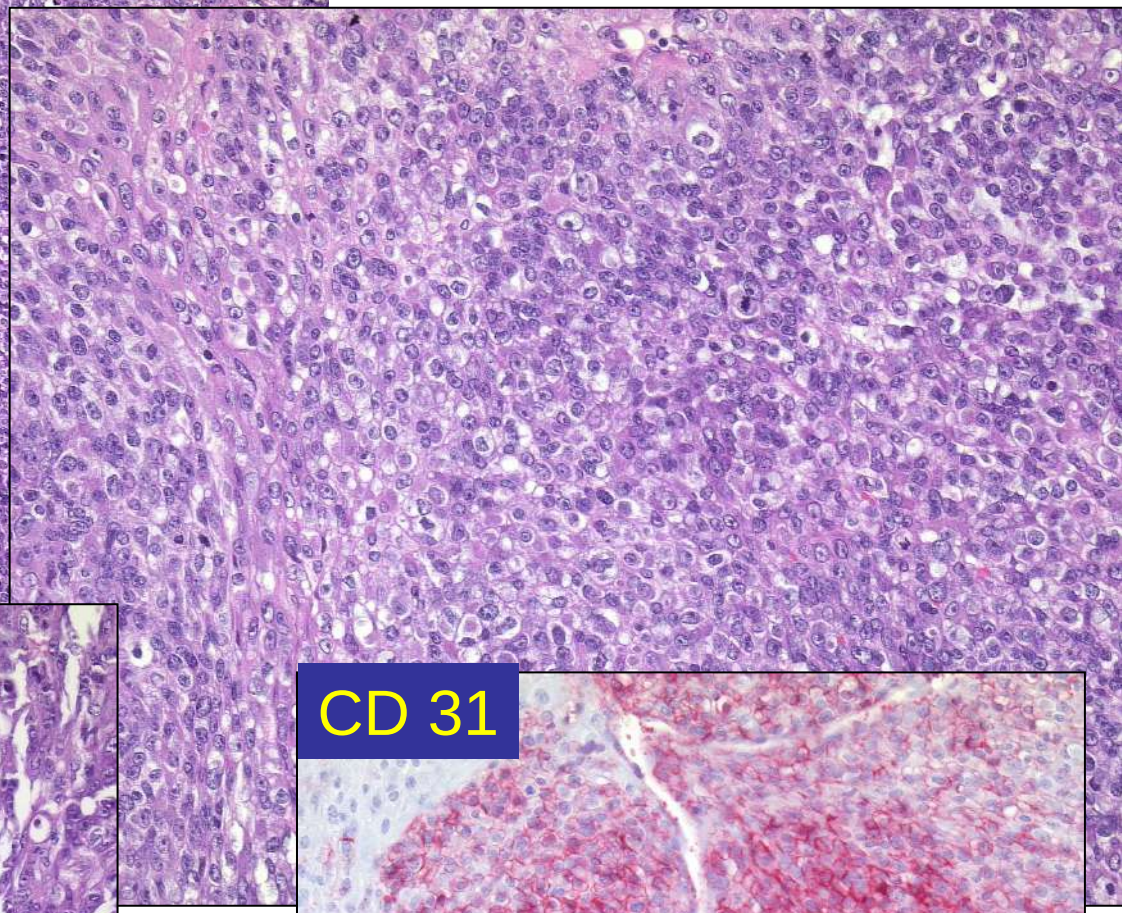


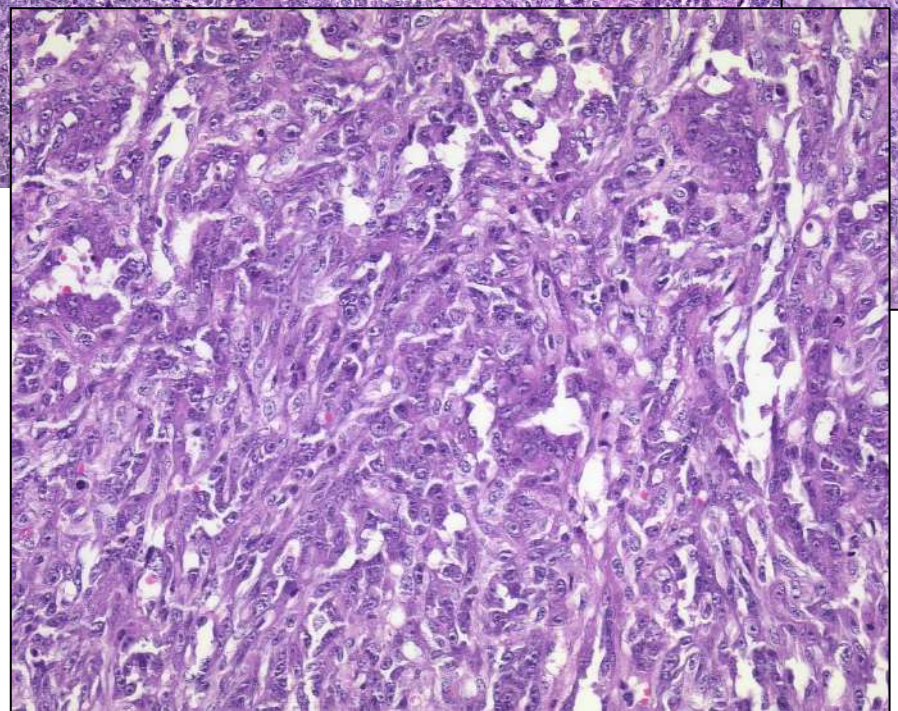


CD 31

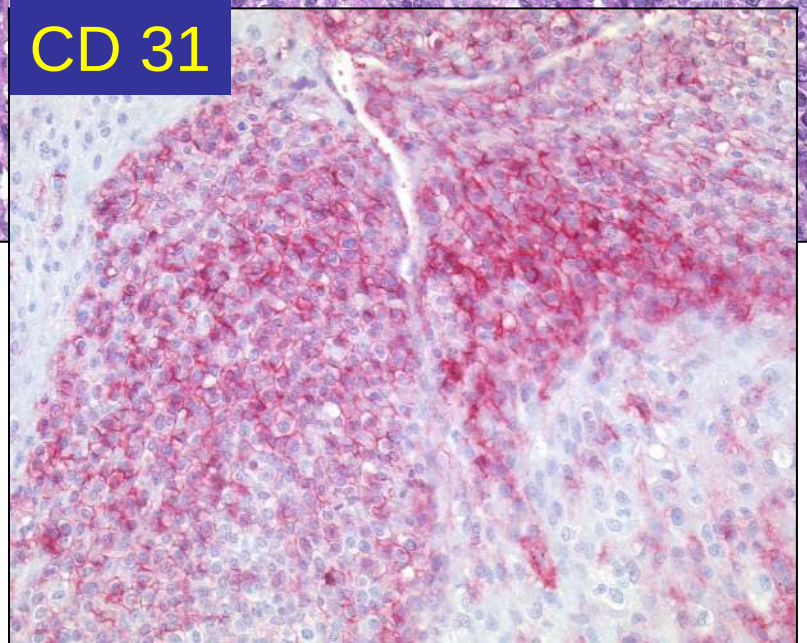
epithelioid Angiosarcoma

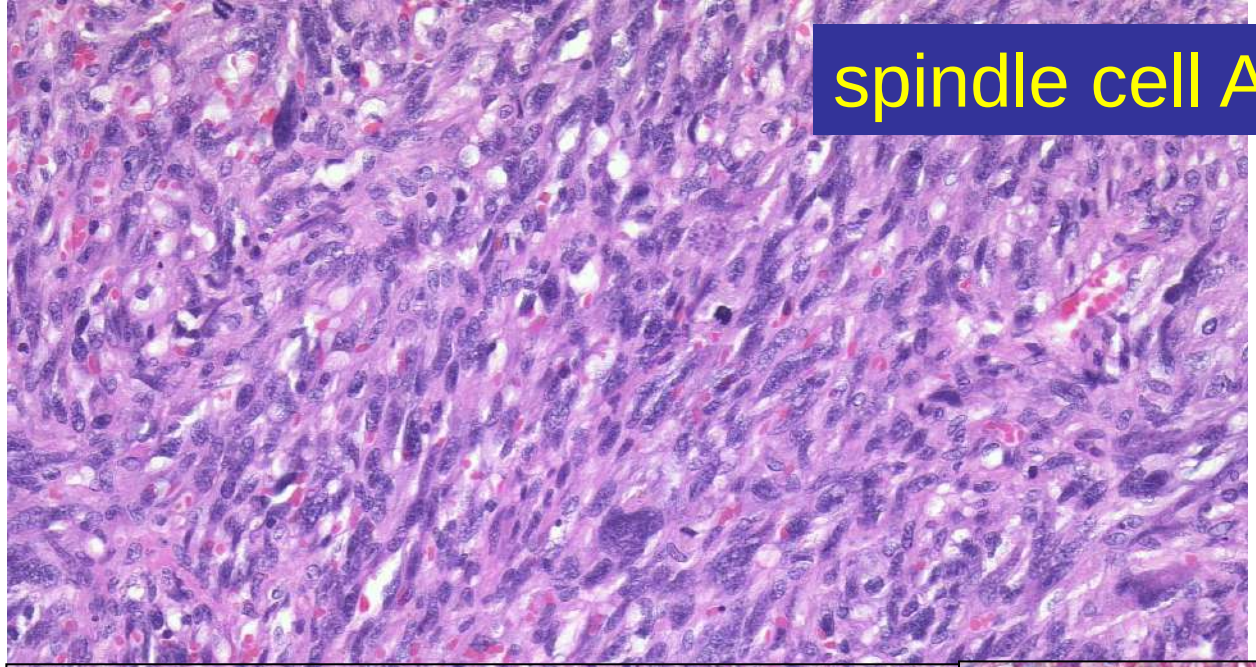




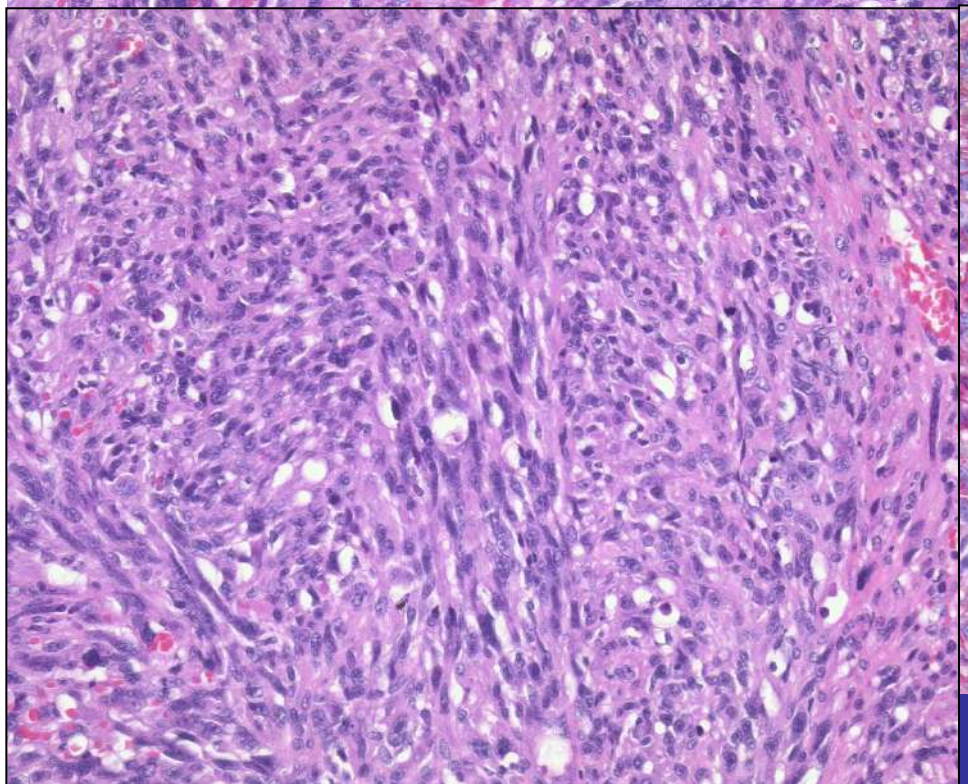


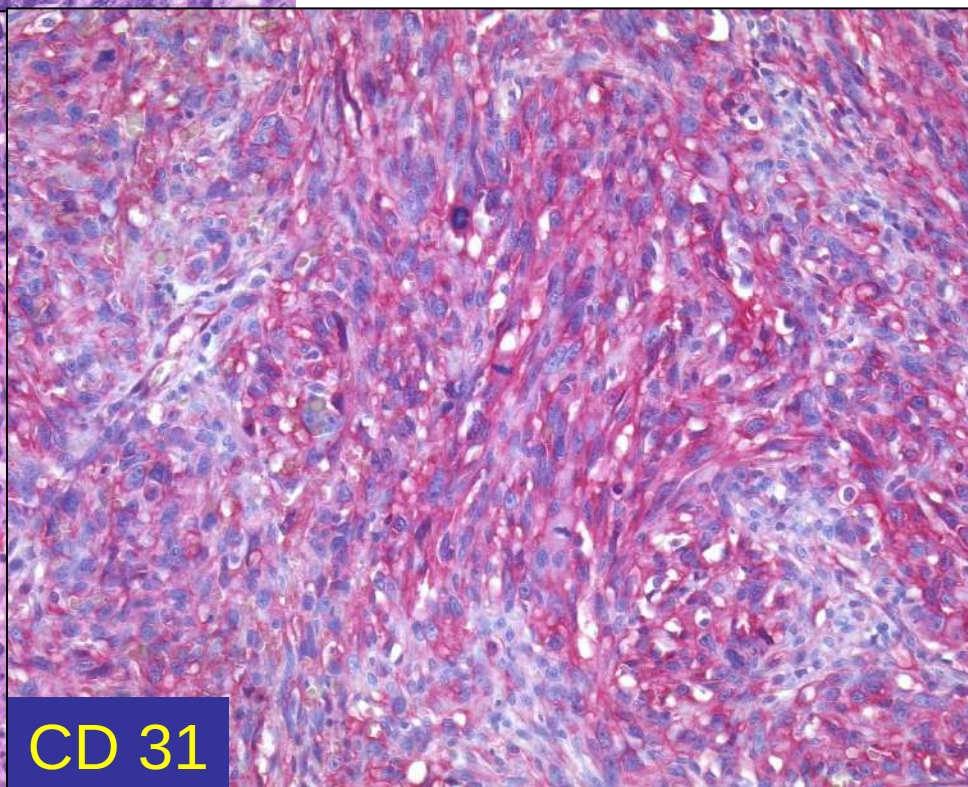
CD 31



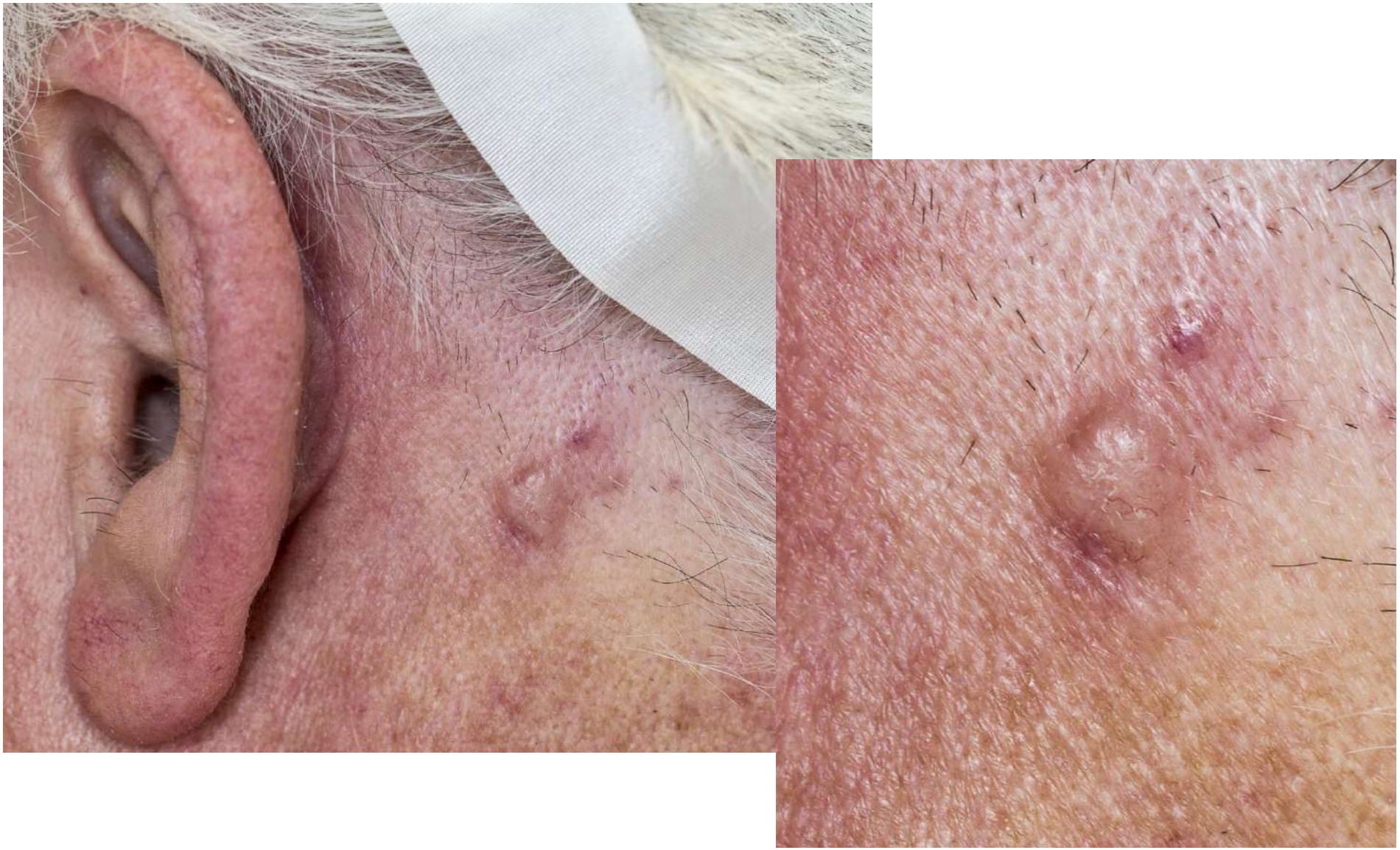


spindle cell Angiosarcoma

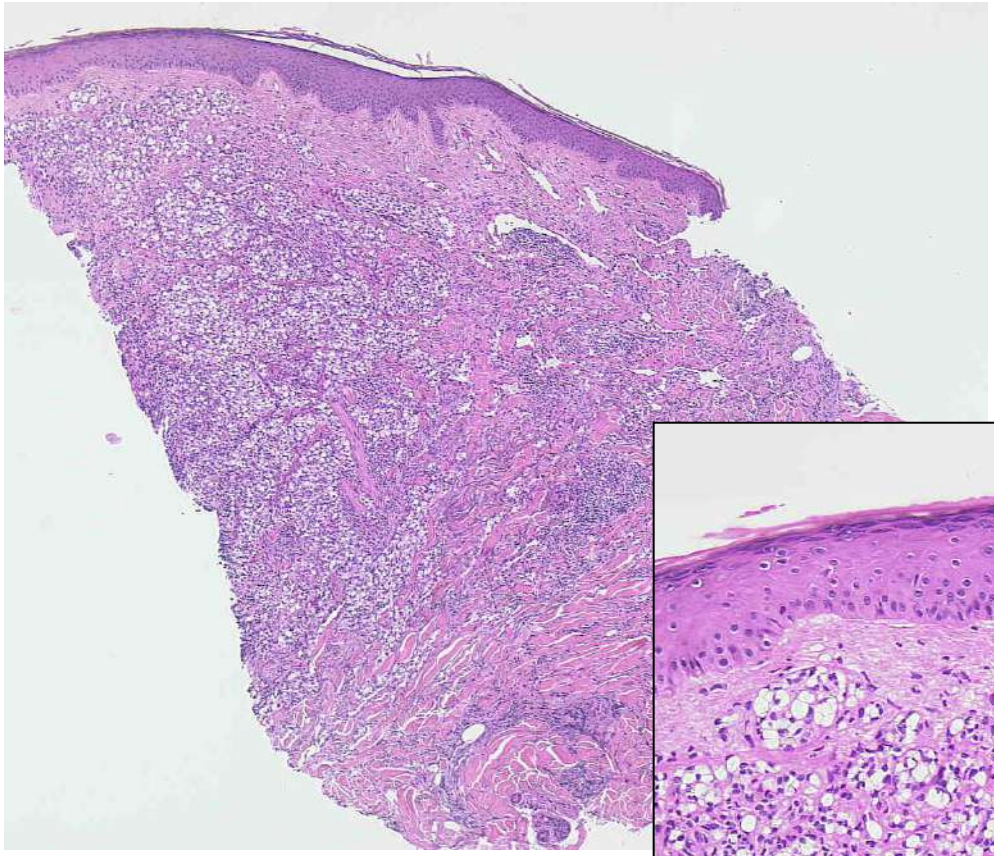


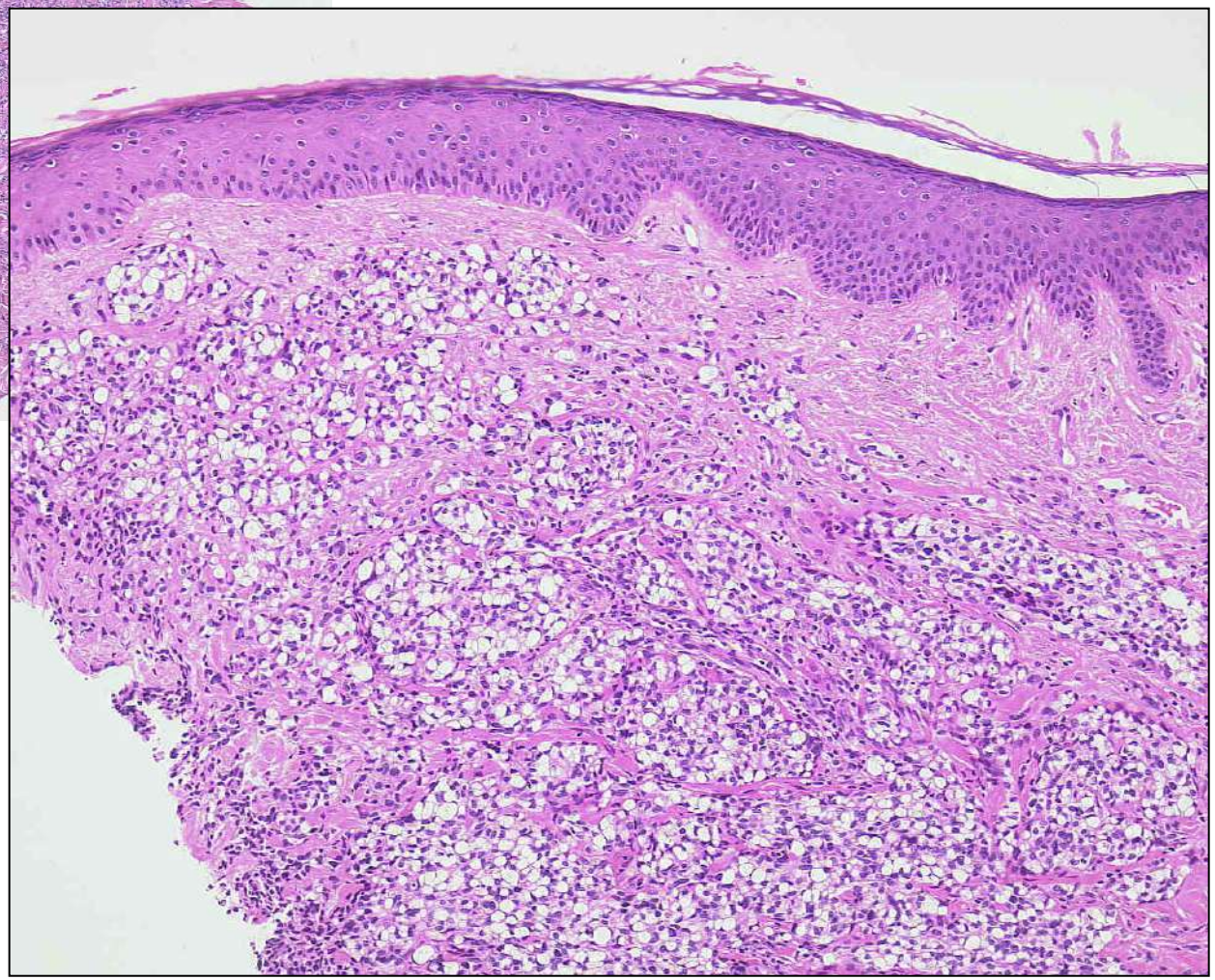


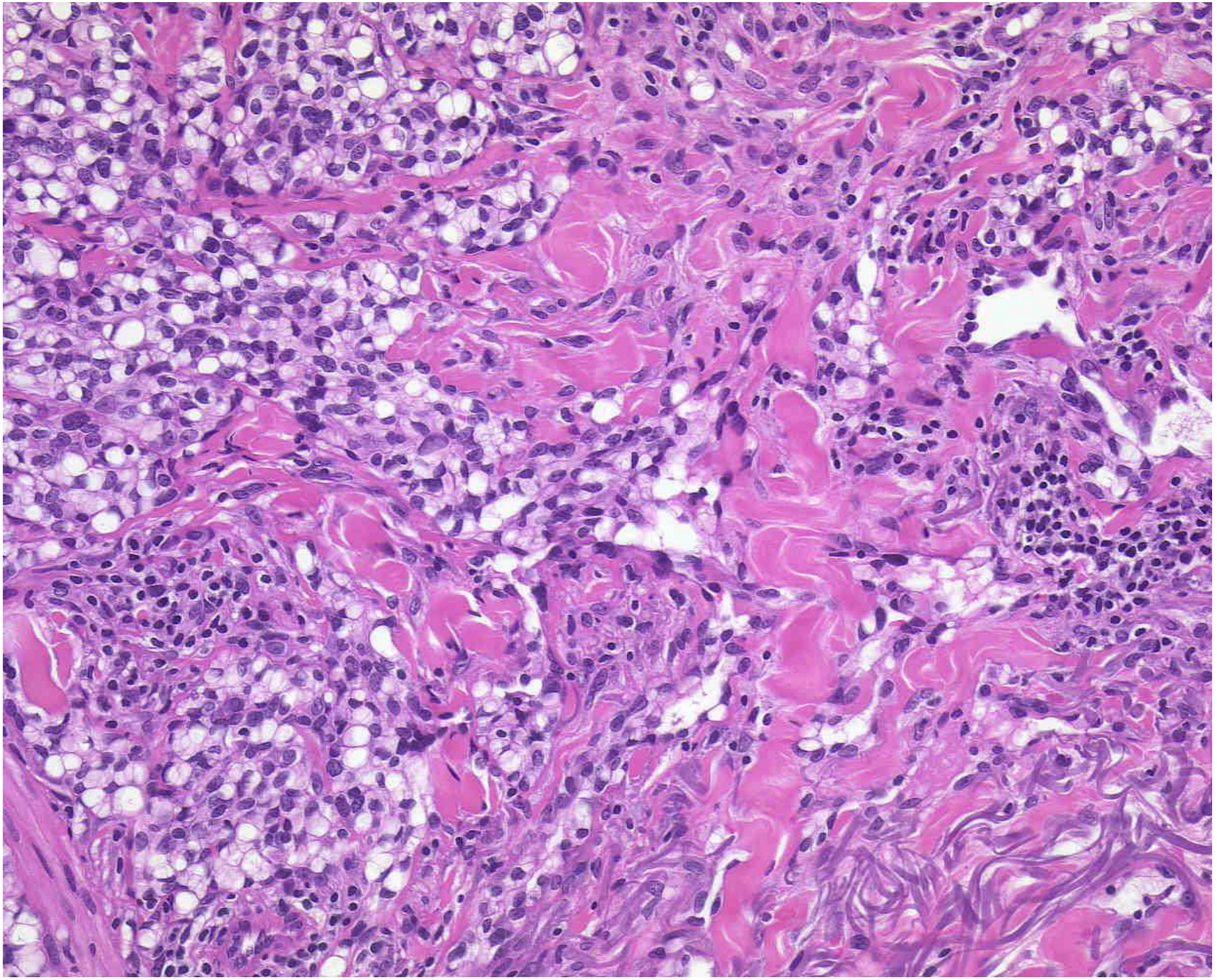
CD 31

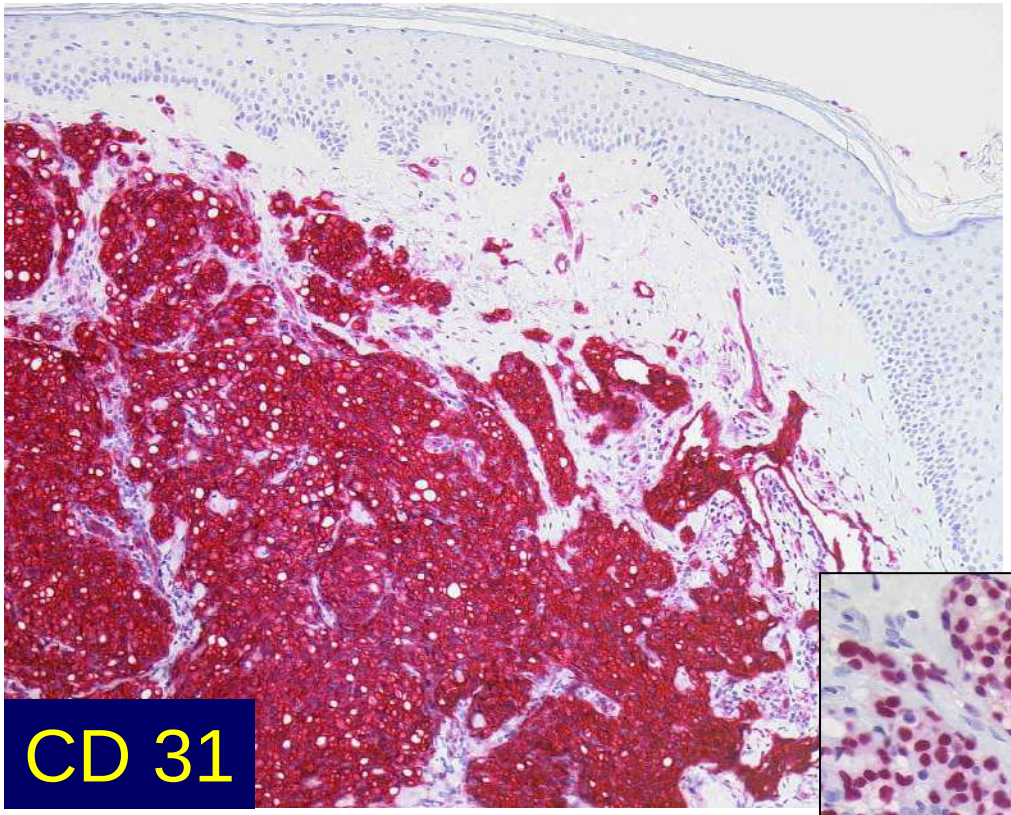


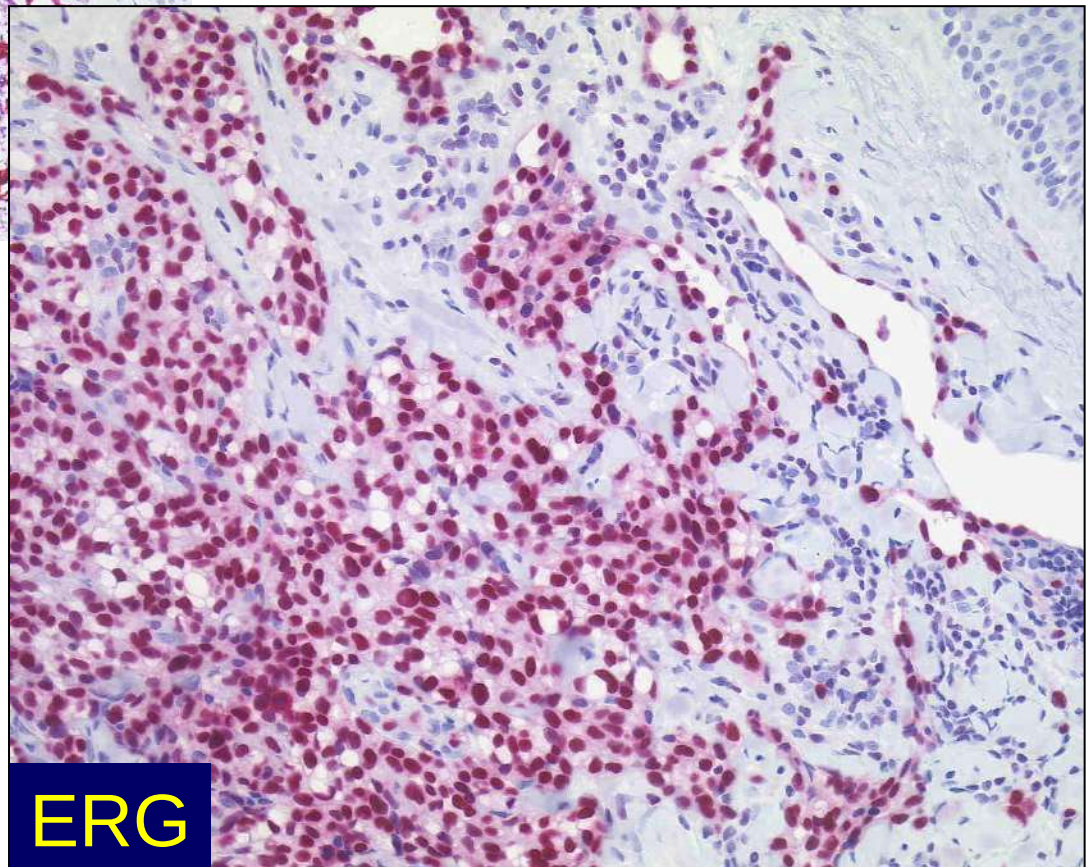
M, 74 years, BCC was suspected, biopsy







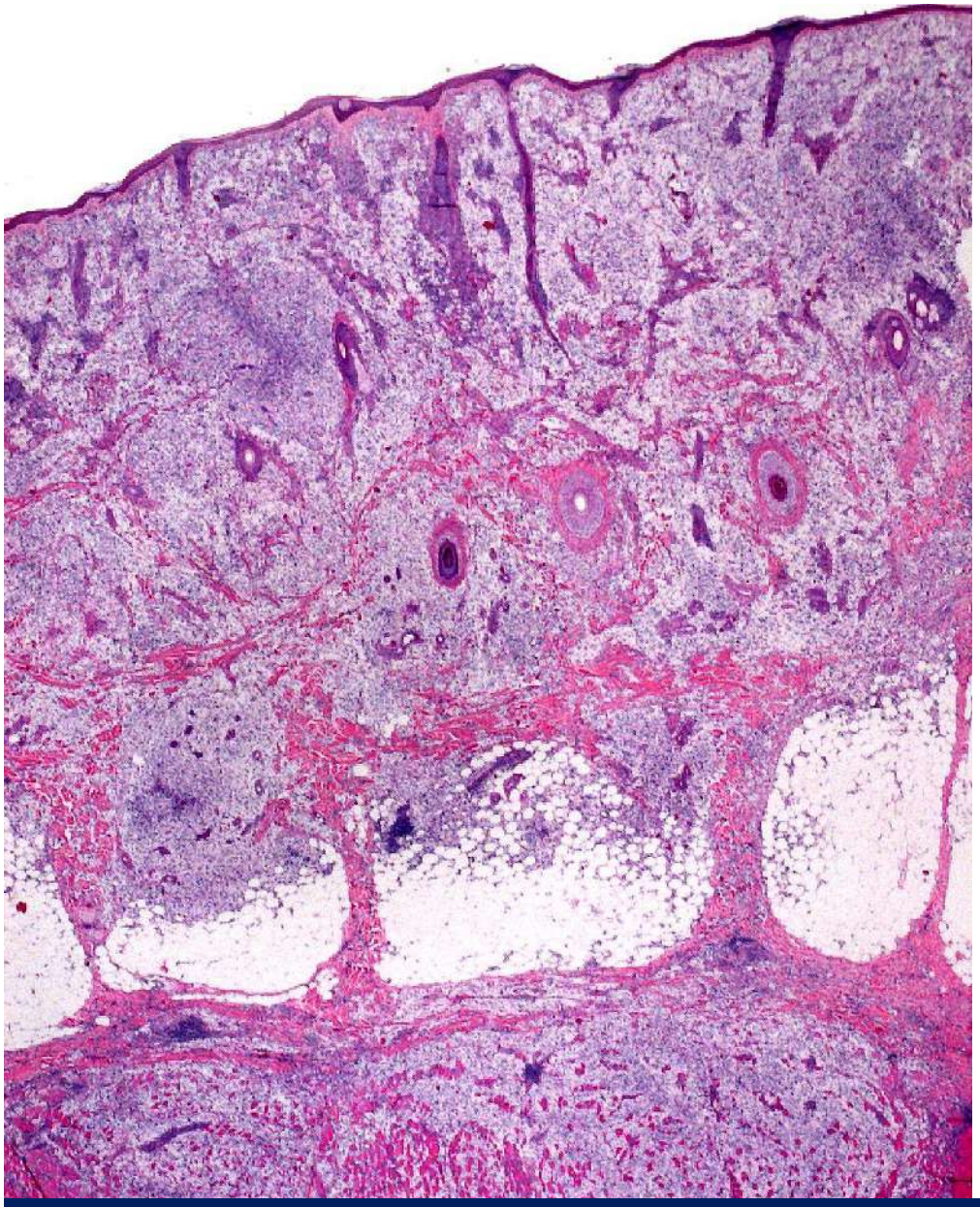

CD 31

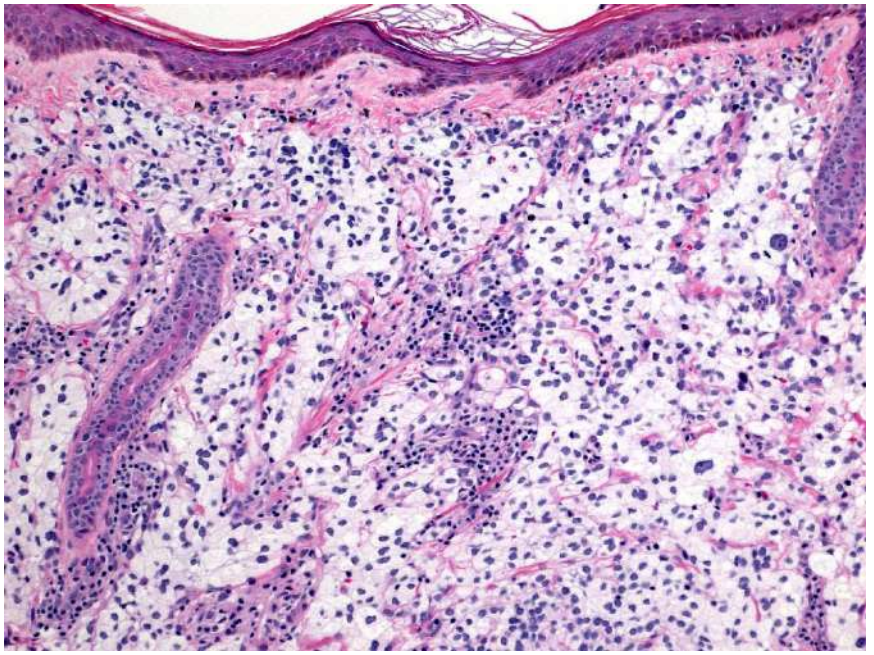

ERG

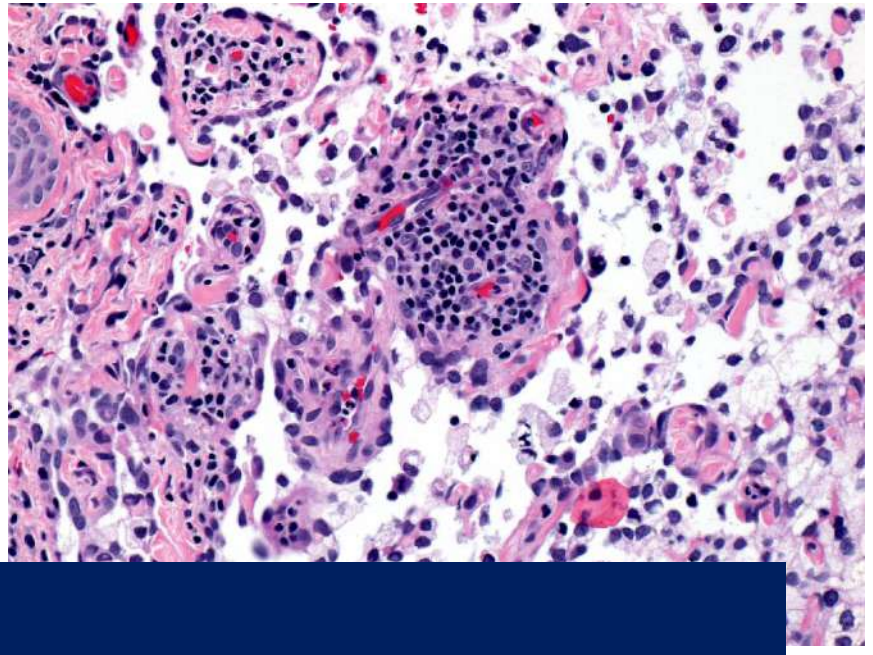
Signet ring cell Angiosarcoma

Salviato T et al. AJDP 2013; 35: 671
- two cases, F, 68 years, M, 85 years
- parietal, retroauricular skin
- CD 31+, CD 34 +, Podoplanin +

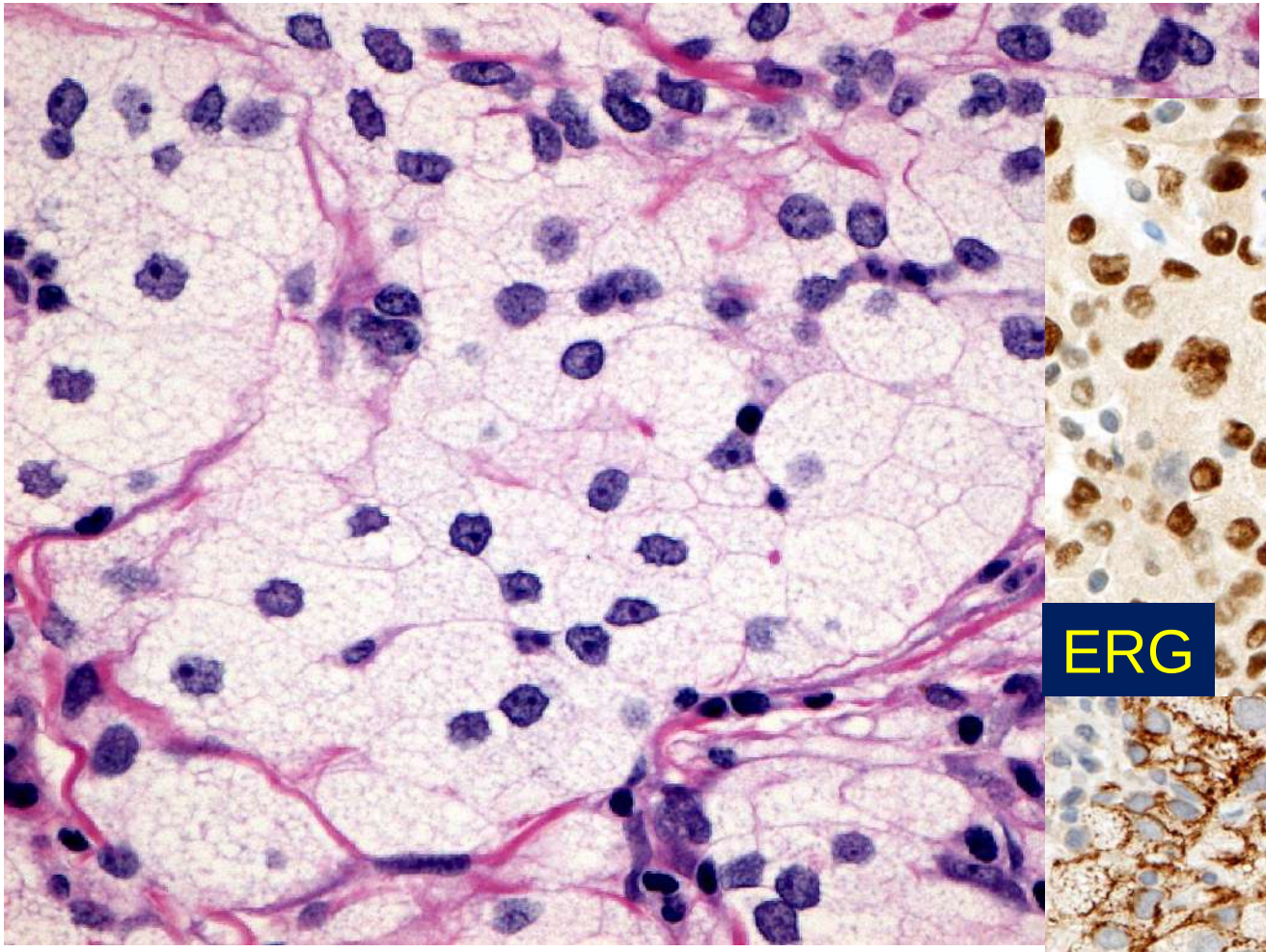
Wood et al. Histopathology 2015; 66: 856
(2 x signet ring AS, 2 x foamy cell AS,
1 x granular cell AS)

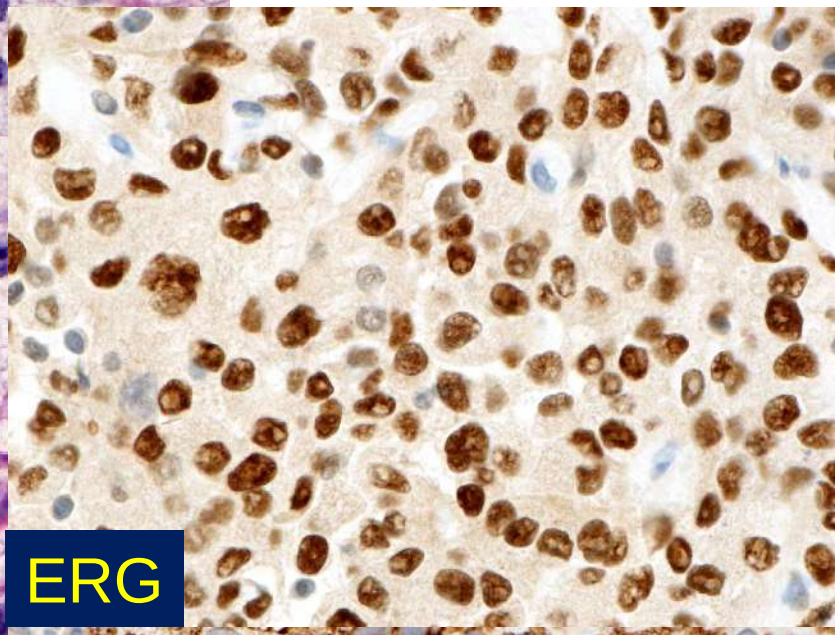


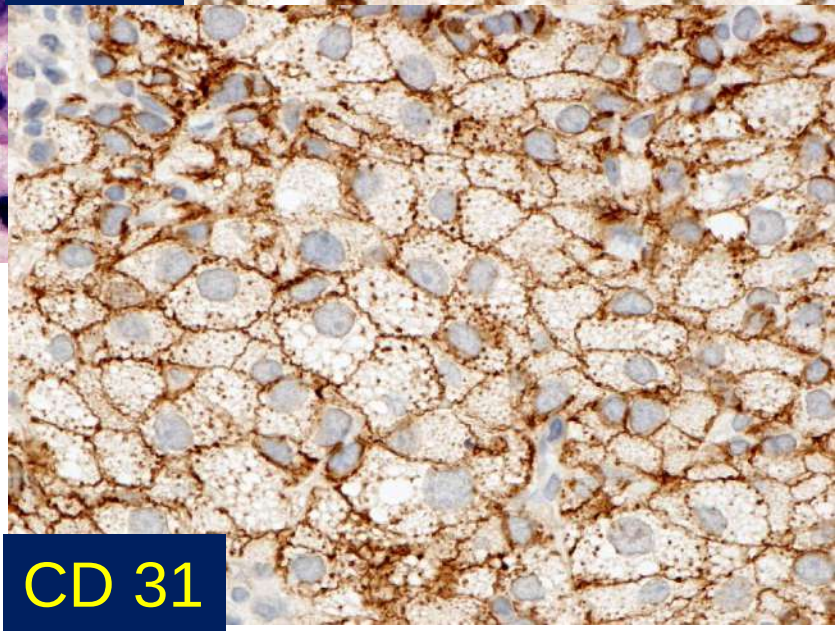




M, 68 years, large tumour, face
foam cell angiosarcoma (by courtesy of Dr.Th.Brenn, Calgary)

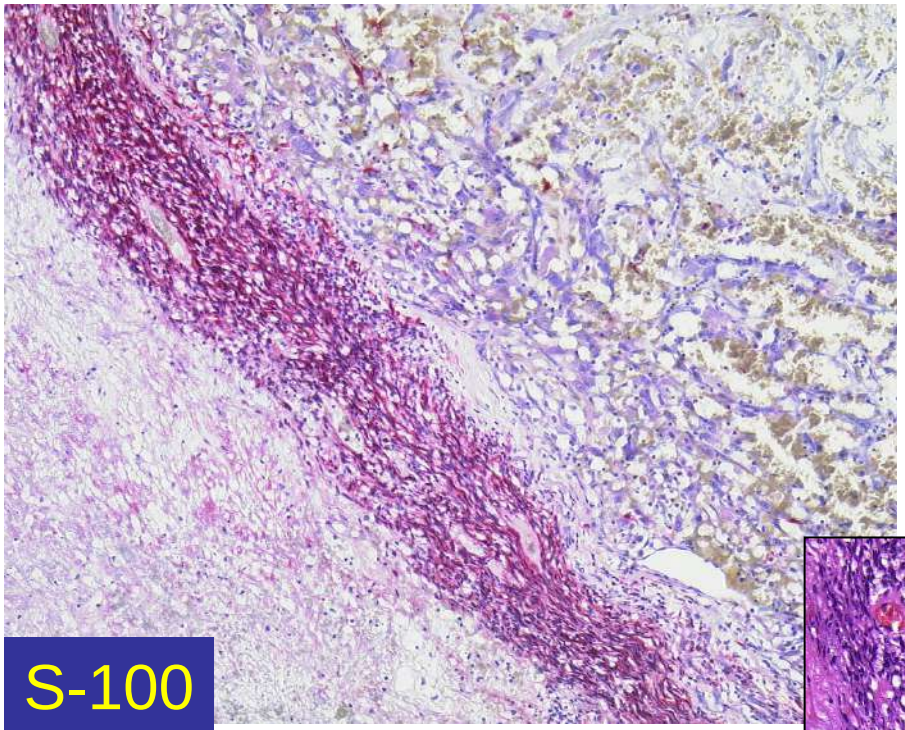


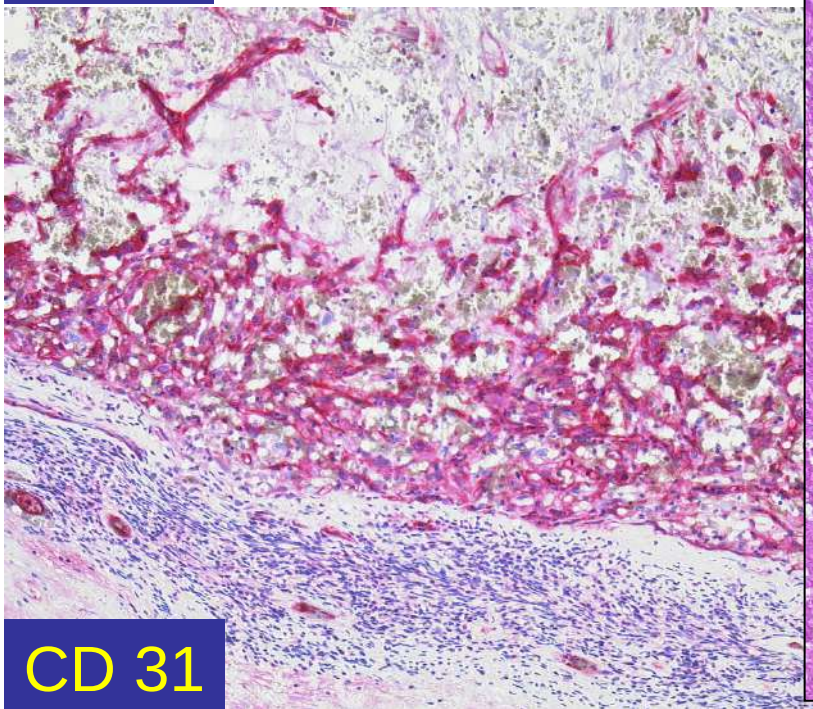

ERG

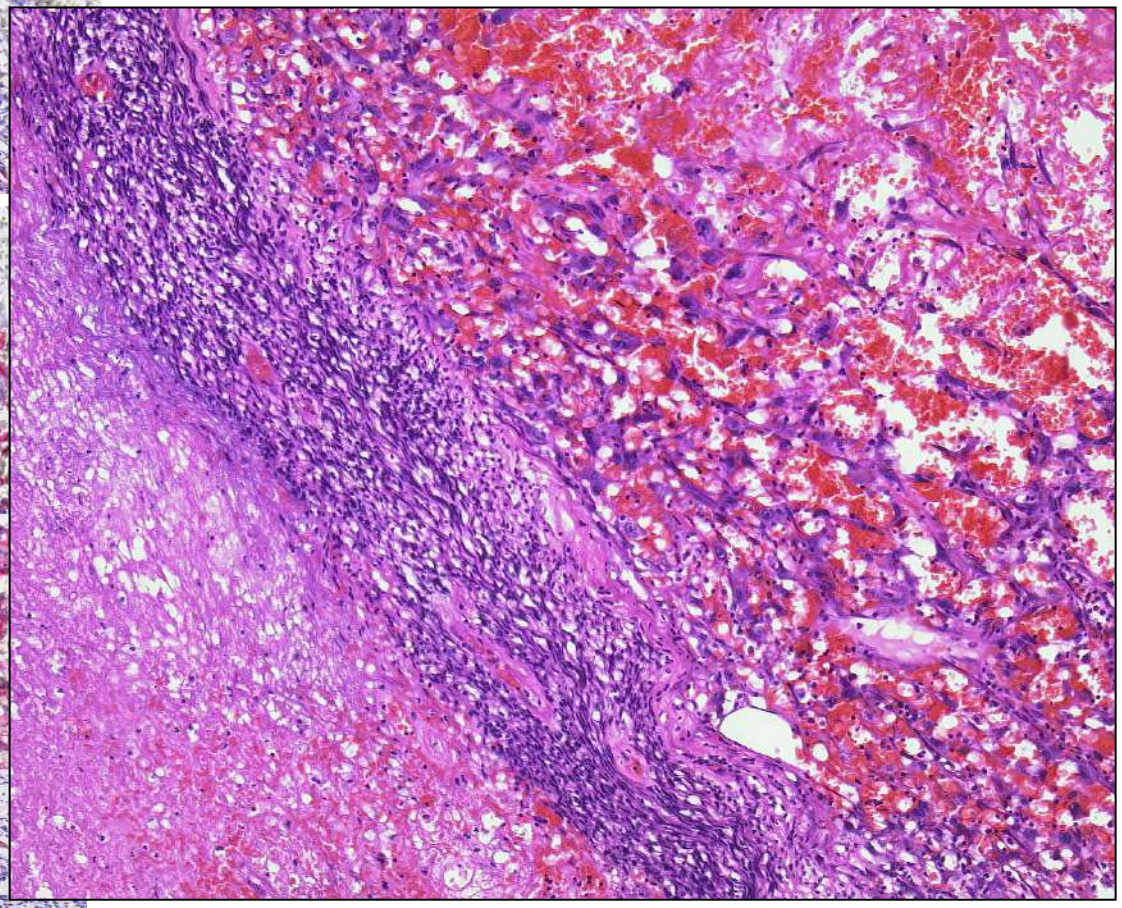

CD 31

Angiosarcoma in a pre-existing schwannoma
F, 73 years, neck

(Mentzel T, Katenkamp D Histopathology 1999; 35: 114)







Histopathologic grading in angiosarcoma

WHO-classification 2019:

grade does not correlate with prognosis

Primary angiosarcoma of the breast: clinico-pathologic analysis of 49 cases, suggesting that grade is not prognostic

Nascimento AF et al. AJSP 2008; 32: 1896

Histopathologic grading is of prognostic significance in primary angiosarcoma of breast: proposal of a simplified 2-tier grading system

Kuba MG et al. AJSP 2023; 47: 307-317

low-grade:	no / < 10% of solid foci
	< 10 mitoses/mm^2
	no tumour necrosis
high-grade:	> 10% of solid foci
	> 10 mitoses/mm^2
	tumour necrosis

low-grade angiosarcoma of the breast

5-year survival: 74%

high-grade angiosarcoma of the breast

5-year survival: 38%

PIK3CA and *KDR* alterations were identified in angiosarcomas of the breast with worse prognosis

Molecular Pathology of Angiosarcoma

Array-CGH analysis identifies two distinct subgroups of primary angiosarcoma

SLJ Verbeke et al. Genes Chromosomes Cancer 2015; 54: 72

- bone (13) and soft tissue (5) neoplasms
- array-CGH, FISH analysis and IM have been performed
- group 1: complex genetic profile
  (disrupted Rb pathway in 55%, lack of CDKN2A expression)
- group 2: few genetic aberrations only
  (*MYC* amplification, *FLT4* coamplification,
  high level amplification of 2q, 17q)
- no genetic differences between bone and soft tissue AS

Consistent *MYC* and *FLT4* gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions
T Guo et al. Genes Chromosomes Cancer 2011; 50: 25-33

***KDR* activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors**
CR Antonescu et al. Cancer Res 2009; 15: 7175-7179

Recurrent CIC gene abnormalities in angiosarcomas: A molecular study of 120 cases with concurrent investigation of PLCG1, KDR, MYC, and FLT4 gene alterations (120 cases)
Huang SC et al. Am J Surg Pathol 2016; 40: 645-655

Targeted massively parallel sequencing of angio-sarcomas reveals frequent activation of the mitogen activated protein kinase pathway
R Murali et al. Oncotarget 2015; 6: 36041

DNA methylation profiling identifies distinct clusters in angiosarcoma

Weidema ME et al. Clin Cancer Res 2020; 26: 93

36 primary angiosarcomas
6 visceral AS, 5 soft tissue AS, 14 radiation-induced AS,
11 UV-induced AS
DNA methylation revealed two main clusters (A,B)
and four subclusters
A1: UV-induced AS
A2: radiation-induced AS
B: visceral and soft tissue AS
Cluster A: increased chromosomal instability
better overall survival compared with cluster B

Conclusions: Vascular tumours of skin and soft tissues

- recognition of vascular malformations
- angiomatoses are a heterogeneous group
- haemangioendotheliomas are a hetero-genous group of vascular neoplasms
- AVL after RT should be handled cautiously
- angiosarcomas may mimic inflammation / cutaneous lymphoma / pseudolymphoma
- broad morphological spectrum of AS
- AS are heterogeneous genetically


SMILE!!!!
it confuses people