Vascular Tumours of Skin and Soft Tissues

Dr. Thomas Mentzel, Friedrichshafen

Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas

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
- malignant

benign vascular Neoplasms

infantile haemangioma
congenital haemangioma
pyogenic haemangioma („capillary haemangioma“)
tufted haemangioma
spindle cell haemangioma
epithelioid haemangioma
others (microvenular, glomeruloid, actinic,
papillary, anastomosing haemangioma,
intravascular papillary endothelial hyperplasia,
epithelioid angiomatous nodule,
Littoral cell angioma of the spleen)

Borderline malignant vascular Neoplasms (Haemangioendotheliomas)

Kaposi sarcoma

kaposiform haemangioendothelioma

papillary intralymphatic angioendothelioma

retiform haemangioendothelioma

pseudomyogenic haemangioendothelioma

polymorphous haemangioendothelioma

composite haemangioendothelioma

malignant vascular Neoplasms

epithelioid haemangioendothelioma

angiosarcoma

- cutaneous angiosarcoma
  - idiopathic angiosarcoma
  - lymphedema associated angiosarcoma
  - radiation induced angiosarcoma
- angiosarcoma of soft tissues
  - epithelioid angiosarcoma

Benign Vascular Anomalies

Vascular Tumours

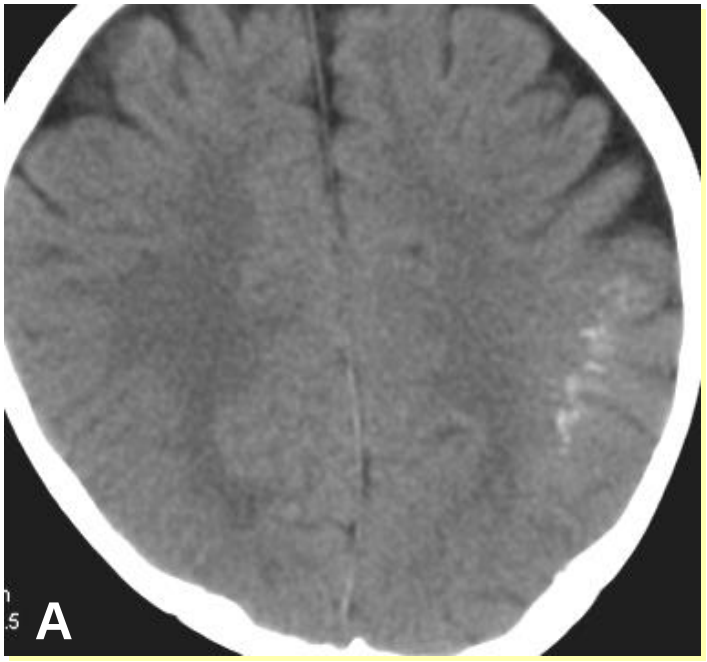
pyogenic granuloma
congenital haemangioma
infantile haemangioma
(proliferative phase
involuting phase
involuted phase)
Glut-1 positive
usually no treatment
antiangiogenic treatment
in problematic cases
(Propranolol)

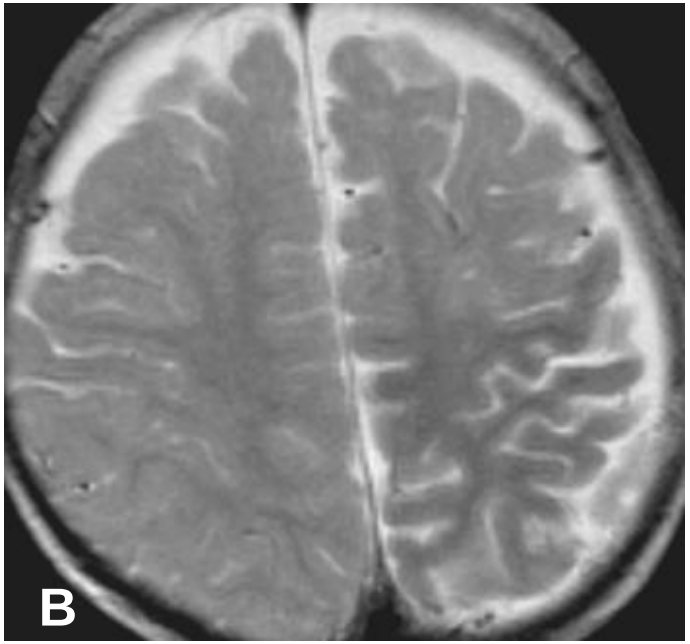
Vascular Malformations

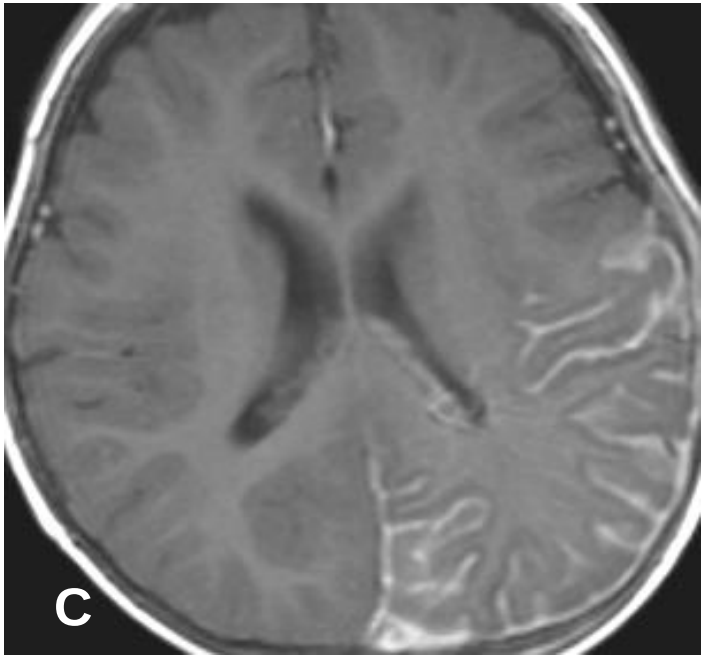
dysmorphogenesis
slow-flow lesions
(CM, LM, VM)
fast-flow lesions
(AM, AVM)
grow proportionally
with the patients
photocoagulation (CM)
sclerotherapy (LM, VM)
embolization (AM, AVM)
Rapamycin (LM)

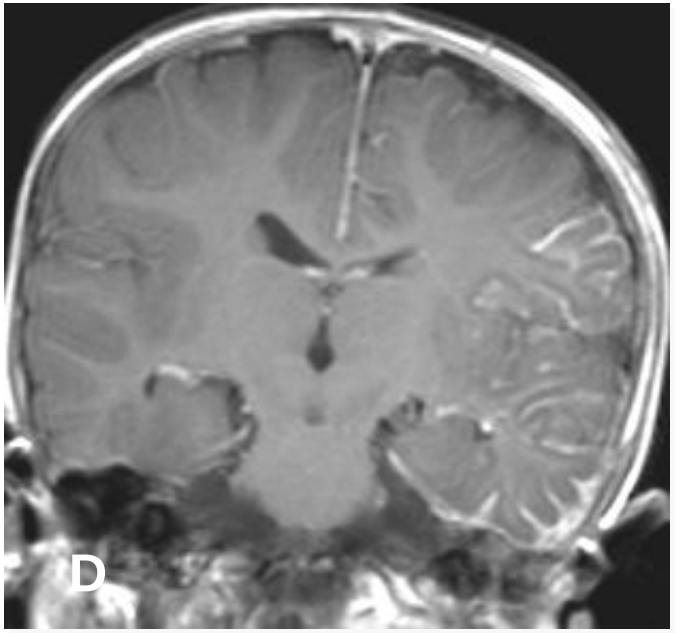
combined vascular Malformations

- associated overgrowth of soft tissue, skeleton
- Klippel-Trenaunay Syndrome
  - slow-flow anomaly, capillary-lymphatic MF
  - limb hypertrophy, limb hypotrophy
- Proteus Syndrome
  - progressive vascular, soft tissue, skeletal condition
- Maffucci Syndrome
  - vascular anomalies, enchondromas, exostoses
- Parkes Weber Syndrome
  - fast-flow anomaly, capillary-arteriovenous MF
  - symmetrically enlarged limb









Sturge-Weber Syndrome

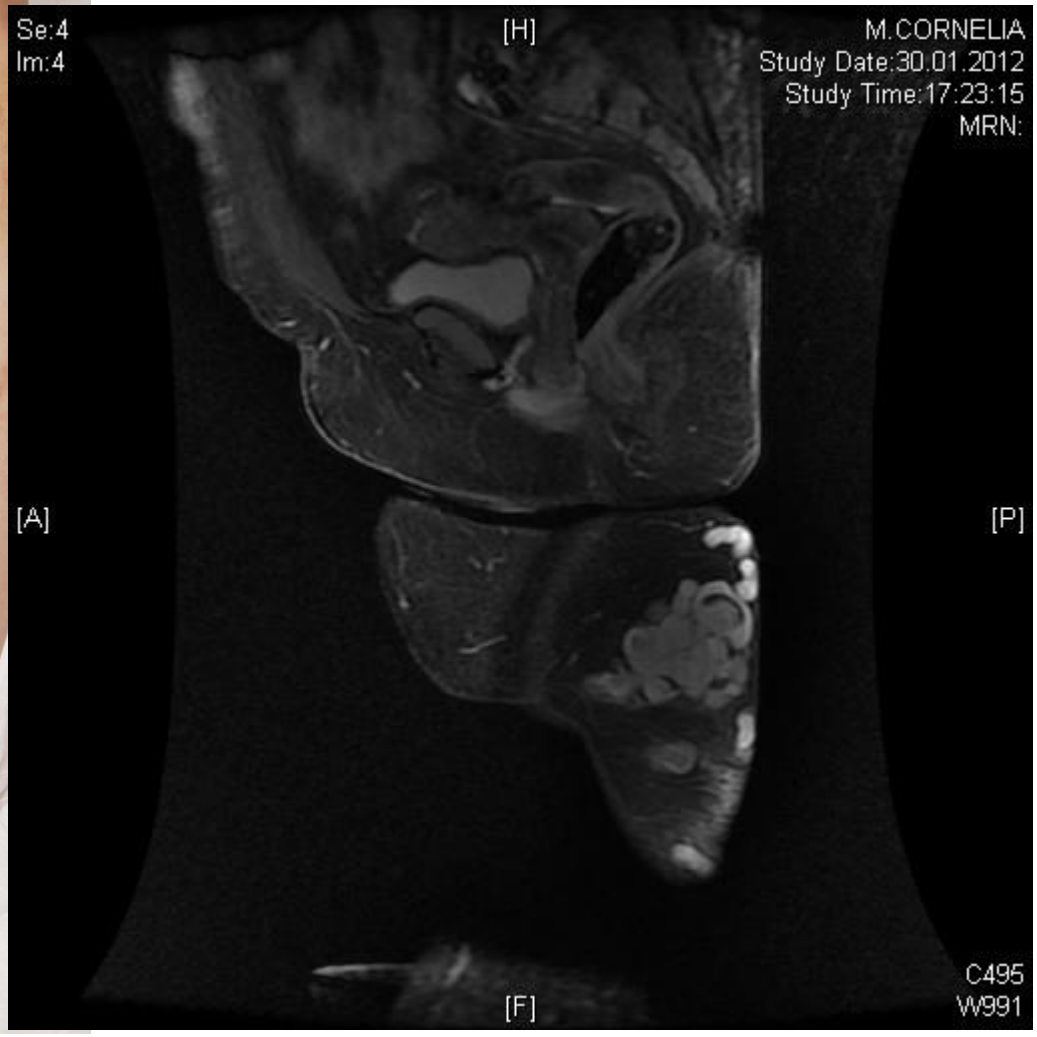
- facial, ocular,
- leptomeningeal CM

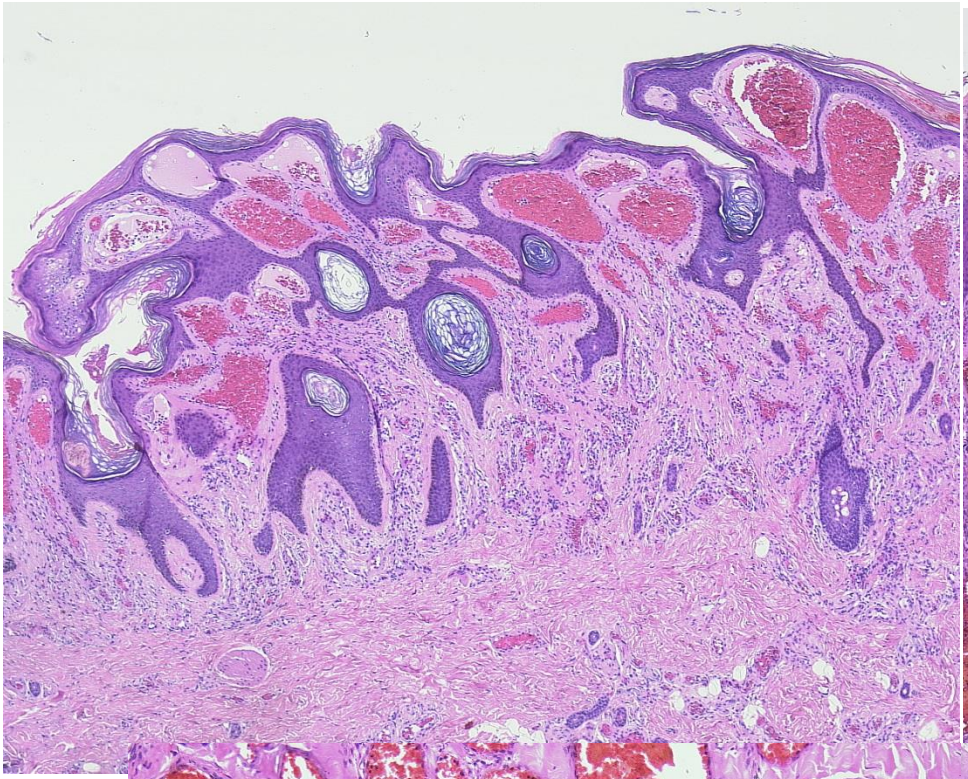
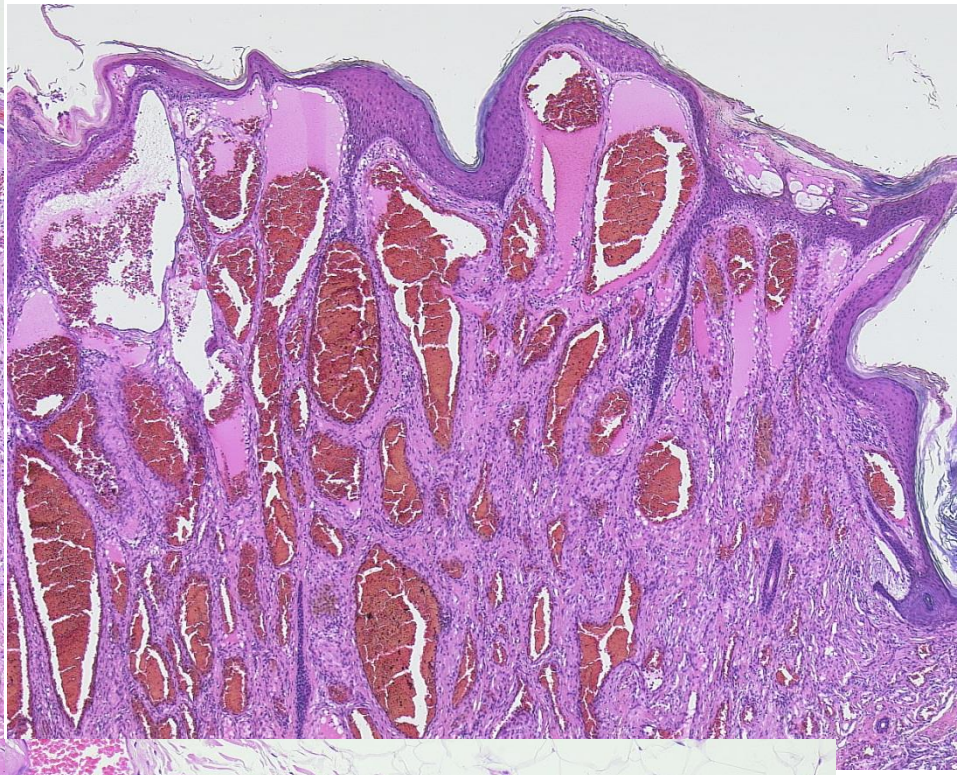
- 12/12, M
- A,B: CT (calcification atrophy)
- C,D: MRI (angiomatous leptomeningeal vessels)

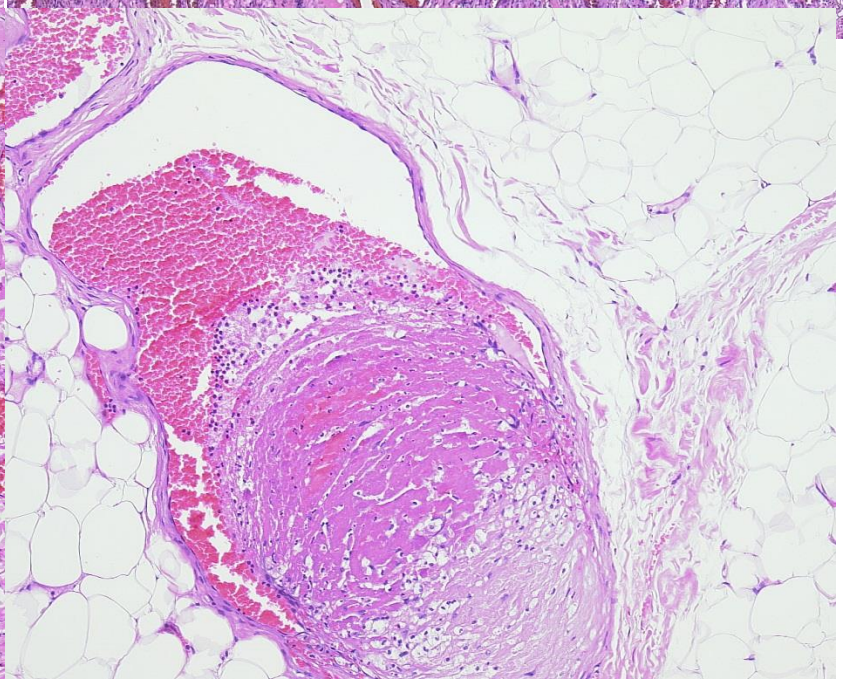
- *GNAQ* mut.

N Engl J Med 2013; 368: 1971

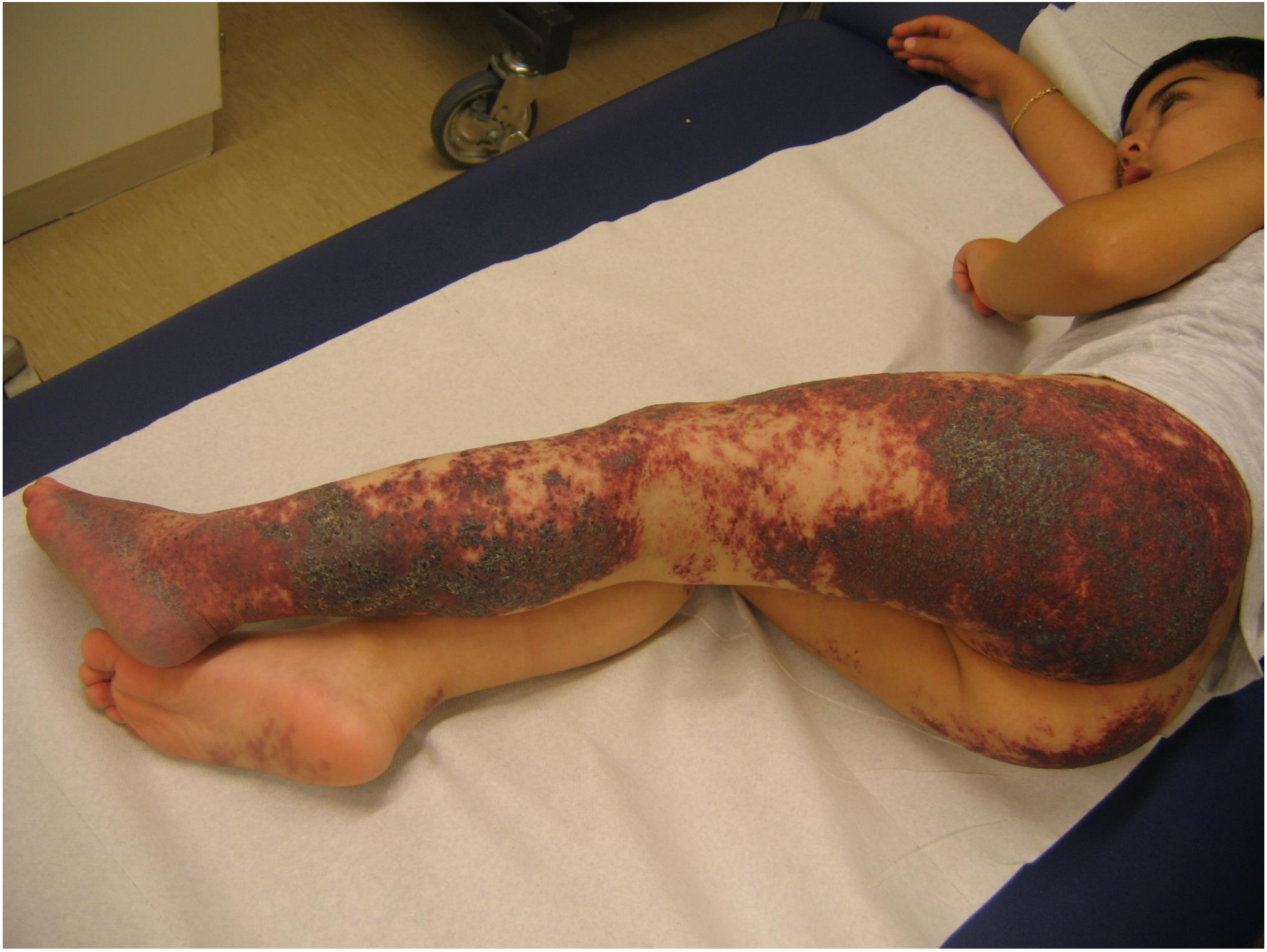
Klippel-Trenaunay Syndrome
F, 32 years

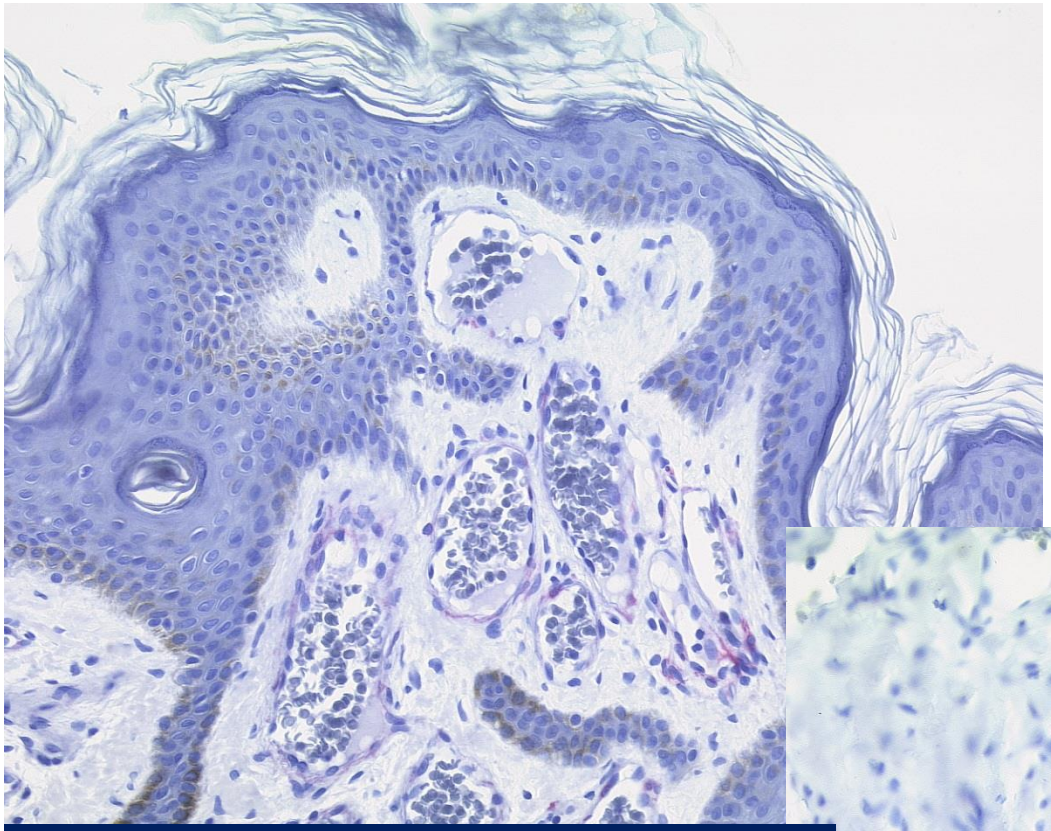


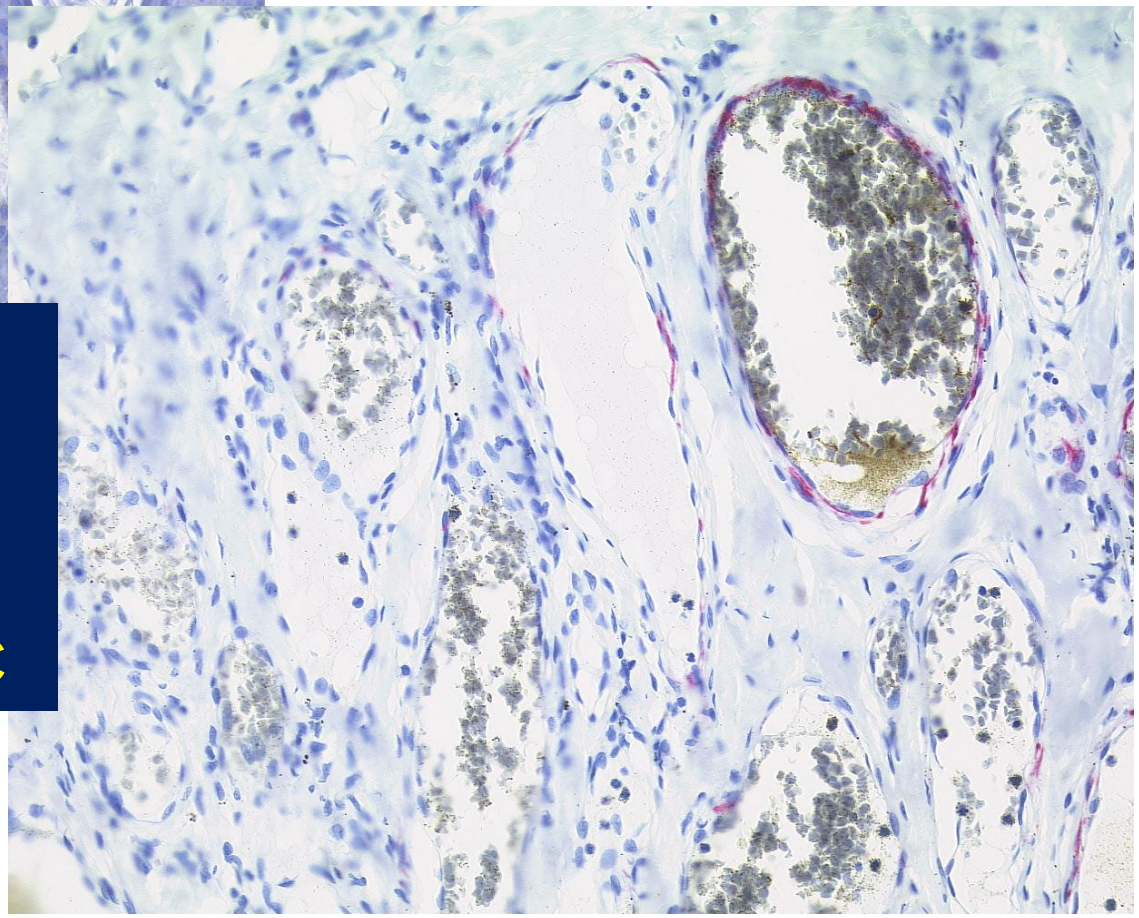





M, 8 years
capillary haemangioma?







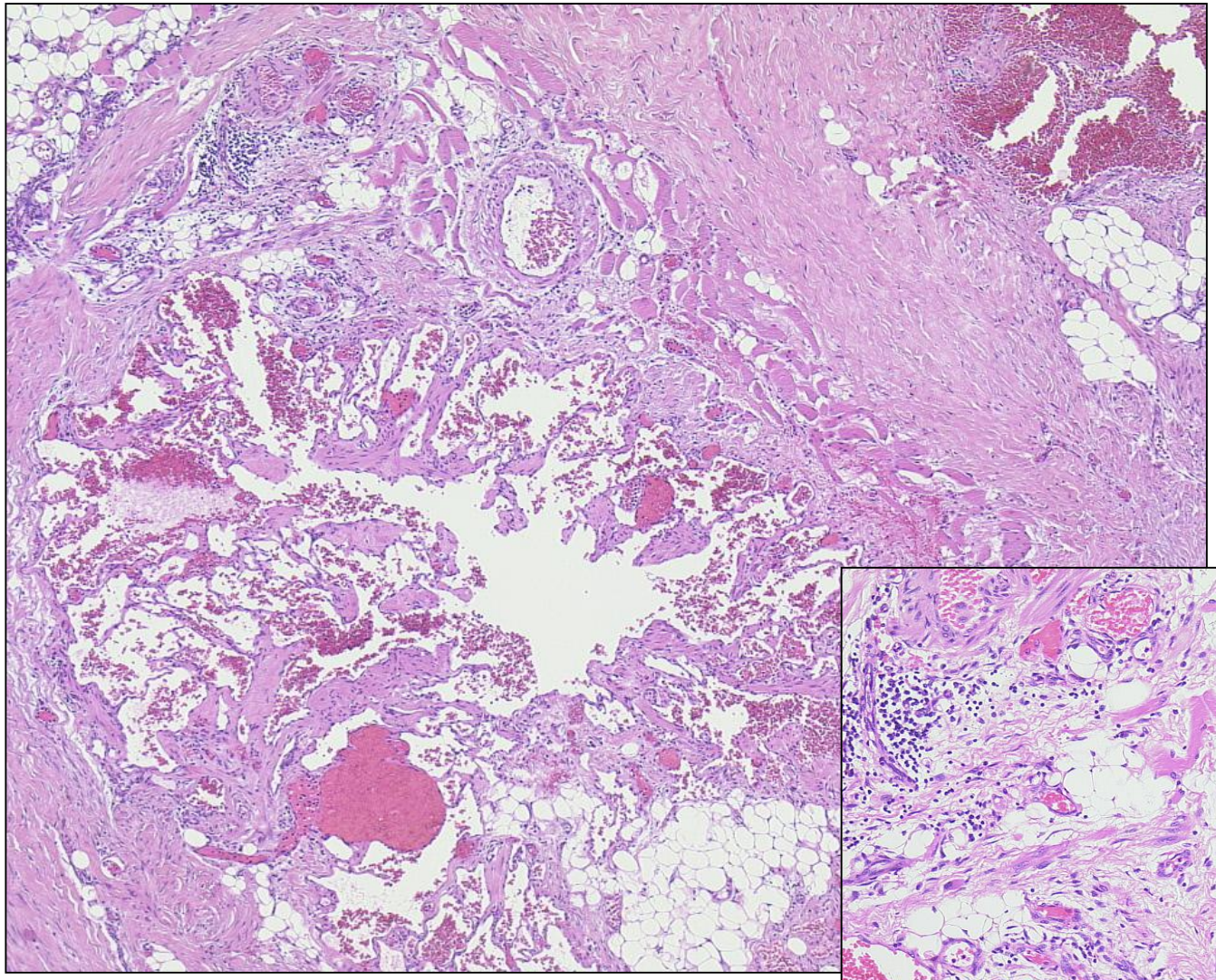
WT-1 (6F-H2)
cytoplasmic staining
of endotheliel cells
6F-H2, WT49, EP122
recommended by NordiQC

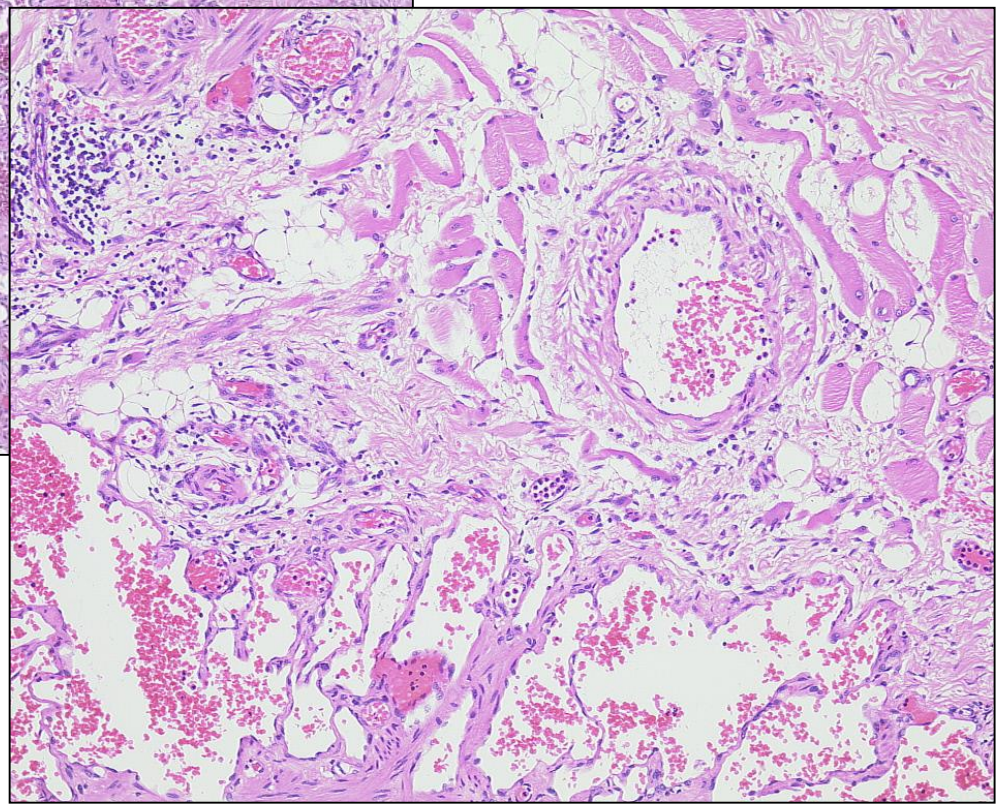
Lawley LP et al.:

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

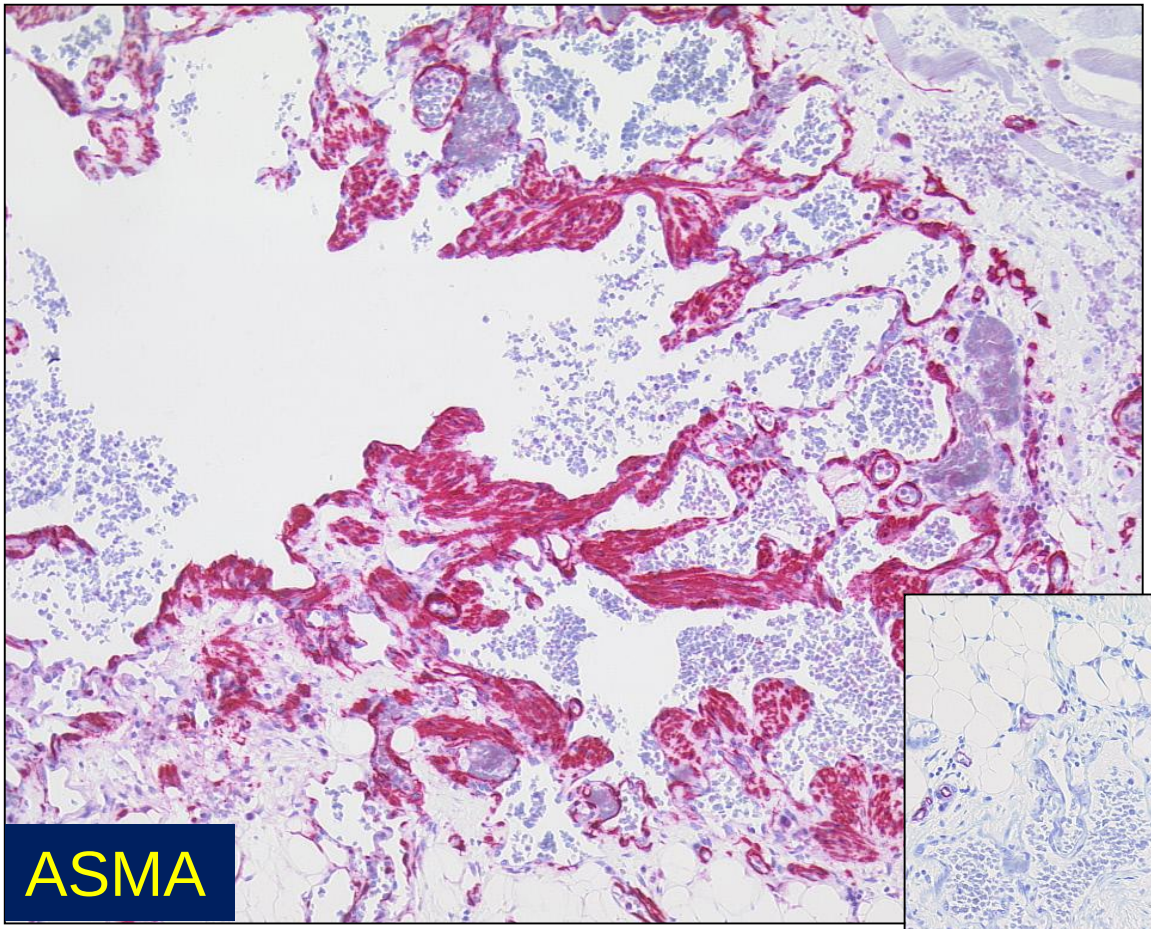
Arch Dermatol 2005; 141: 1297-1300

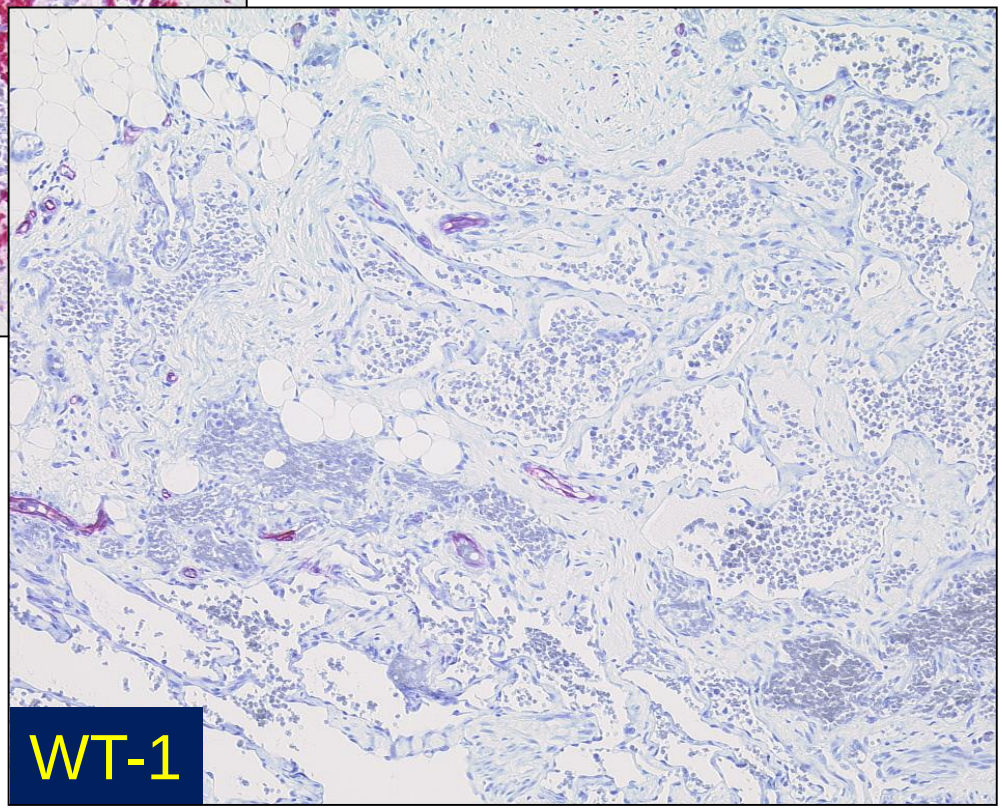
„Defects in WT1 signaling may underlie the inability of malformation endothelial cells to undergo physiologic apoptosis and remodeling.“





M, 21 years, large vascular lesion, trunk


ASMA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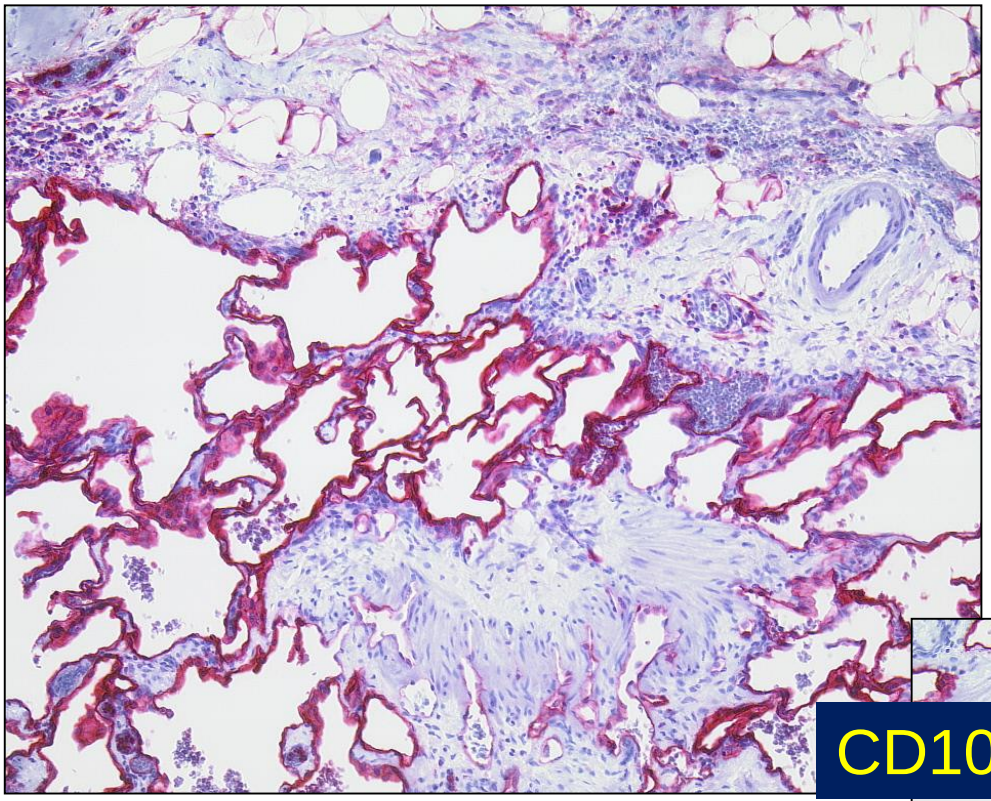
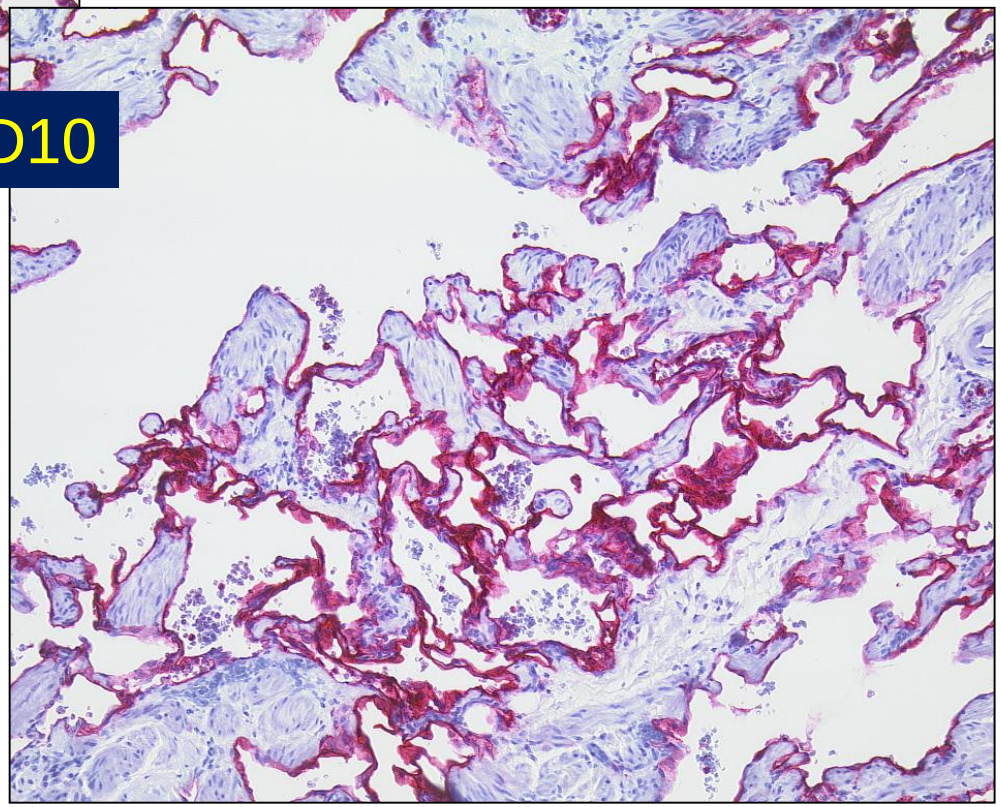


CD10



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

Virchows Arch (2009) 454:161–179
DOI 10.1007/s00428-008-0709-3

ORIGINAL ARTICLE

Vascular lesions of bone in children, adolescents, and young adults. A clinicopathologic reappraisal and application of the ISSVA classification

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Abstract Vascular lesions of bone are rare and their terminology is not standardized. Herein, we report 77 patients with such lesions in order to characterize their morphologic spectrum and the applicability of the International Society for the Study of Vascular Anomalies (ISSVA) classification. In this system, malformations are structural anomalies distinguishable from tumors, which are proliferative. The radiologic images/reports and pathologic materials from all patients were reviewed. All lesions were either restricted to bone or had minimal contiguous soft tissue involvement with the exception of some multifocal lymphatic lesions that extensively affected soft tissue and/or viscera. We found that certain lesions of bone often regarded as tumors should be classified as malformations. Malformations (n=46) were more common than tumors (n=31); lymphatic and venous malformations were equally frequent. In the tumor category, hemangioendothelioma and epithelioid hemangioma were the most common. We also describe new vascular entities that arise in or involve bone. Utilizing the ISSVA approach, the diverse and often contradictory terminology of vascular lesions of bone can be largely eliminated. Standardized nomenclature is critical for scientific communication and patient management, and we hereby recommend the ISSVA classification be applied to vascular lesions of bone, just as for skin, soft tissue, and viscera.

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Vascular malformations are more frequent than currently believed

- 77 patients
- lymphangiomas, venous haemangiomas, arterio-venous haemangiomas are in fact malformations
- haemangiomas are infantile, spindle cell and epithelioid haemangiomas

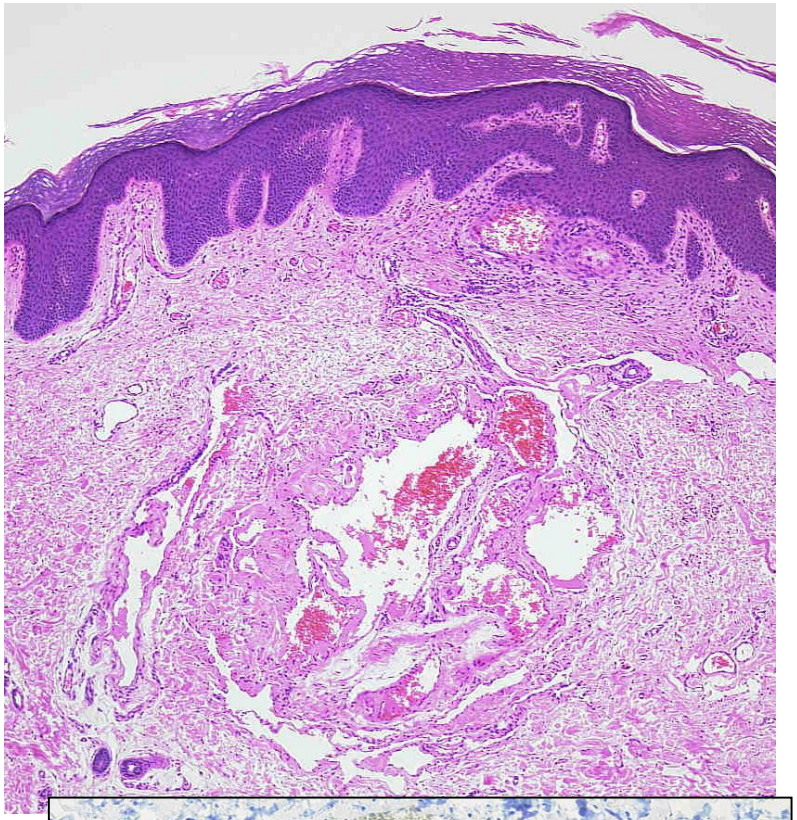
Vascular Malformations

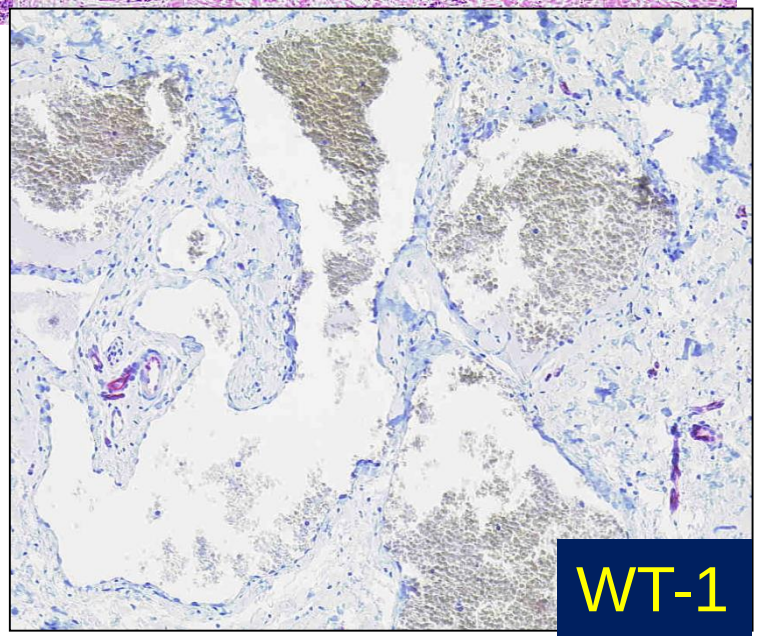
- relatively frequent (0.3% of population)
- genetically very heterogeneous
- disturbances in vessel development in the 4th-10th week of pregnancy
- manifestation often later
- no regression
- proper diagnosis also of underlying genetic changes is important for treatment

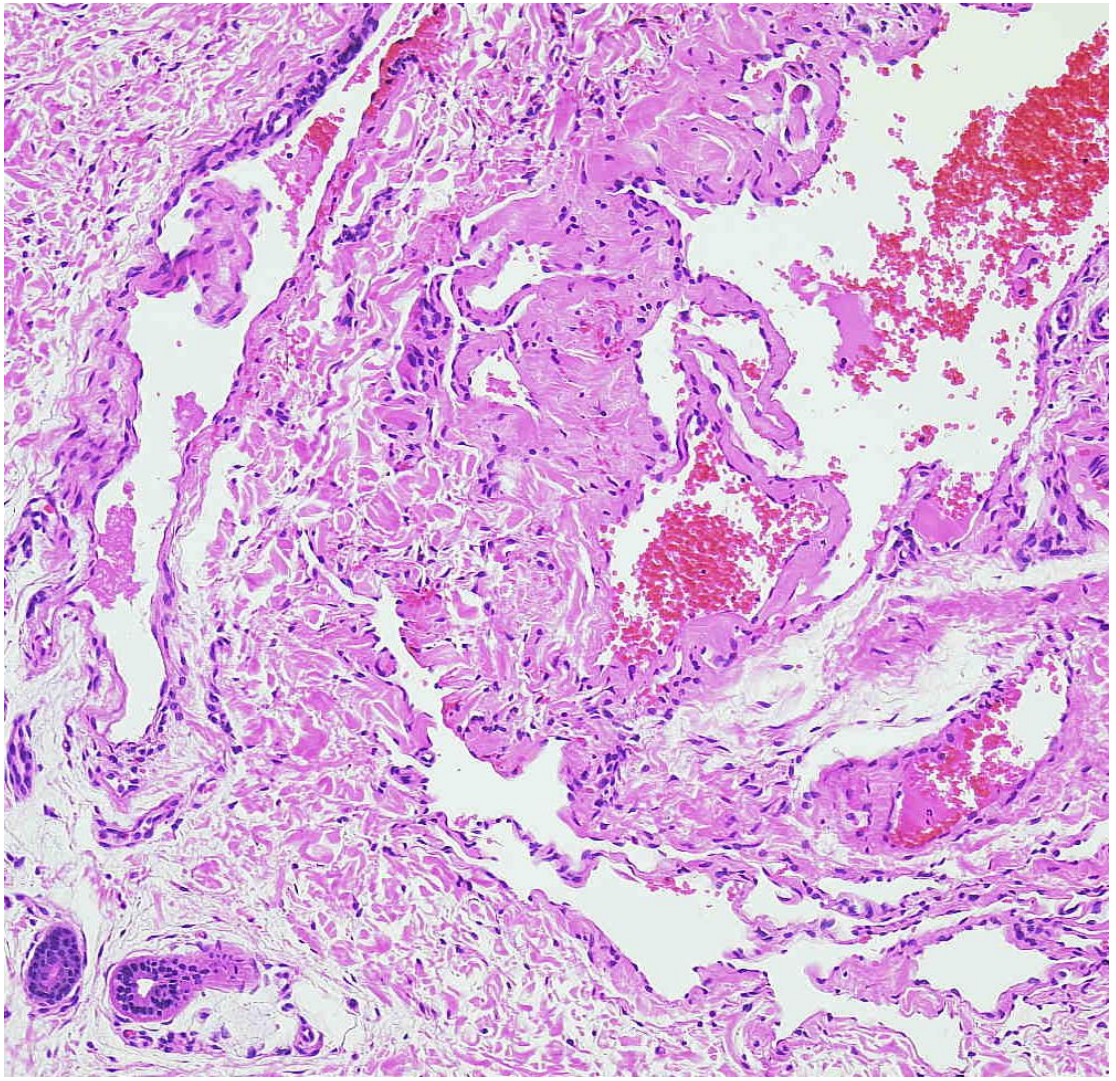
    Rapamycin in lymphangiomatous malformations

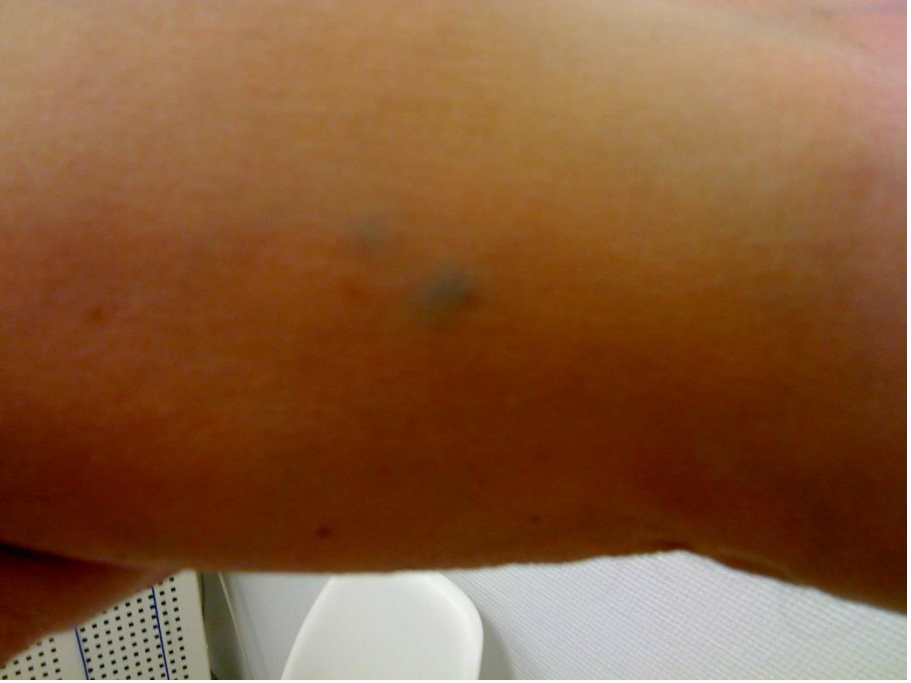
    Alpesilib in PIK3CA associated overgrowth syndroms (Nature 2018; 558: 540-546)

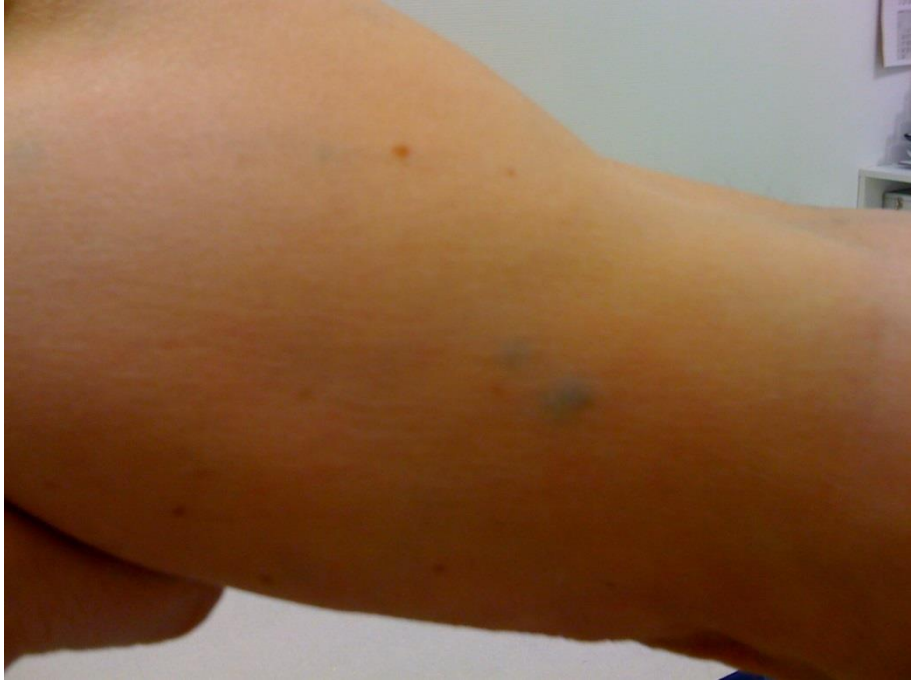
F, 23 years, popliteal fossa capillary-venous malformation



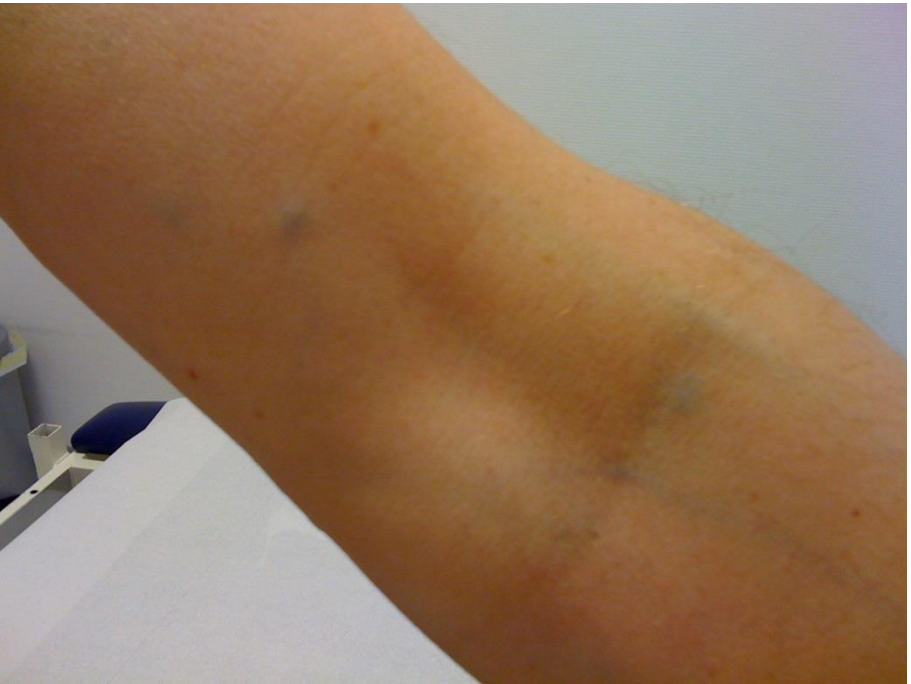


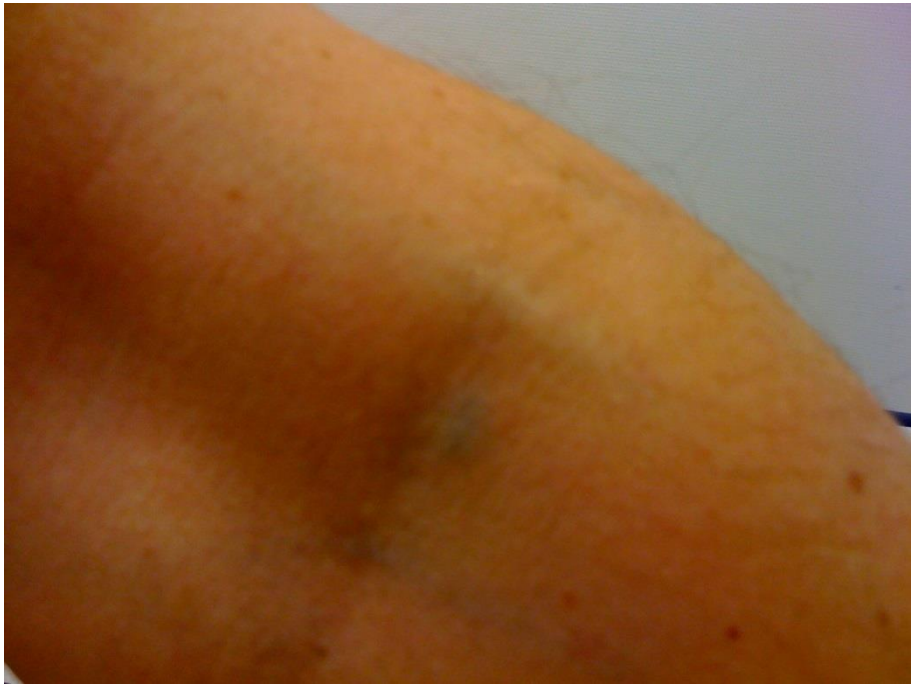


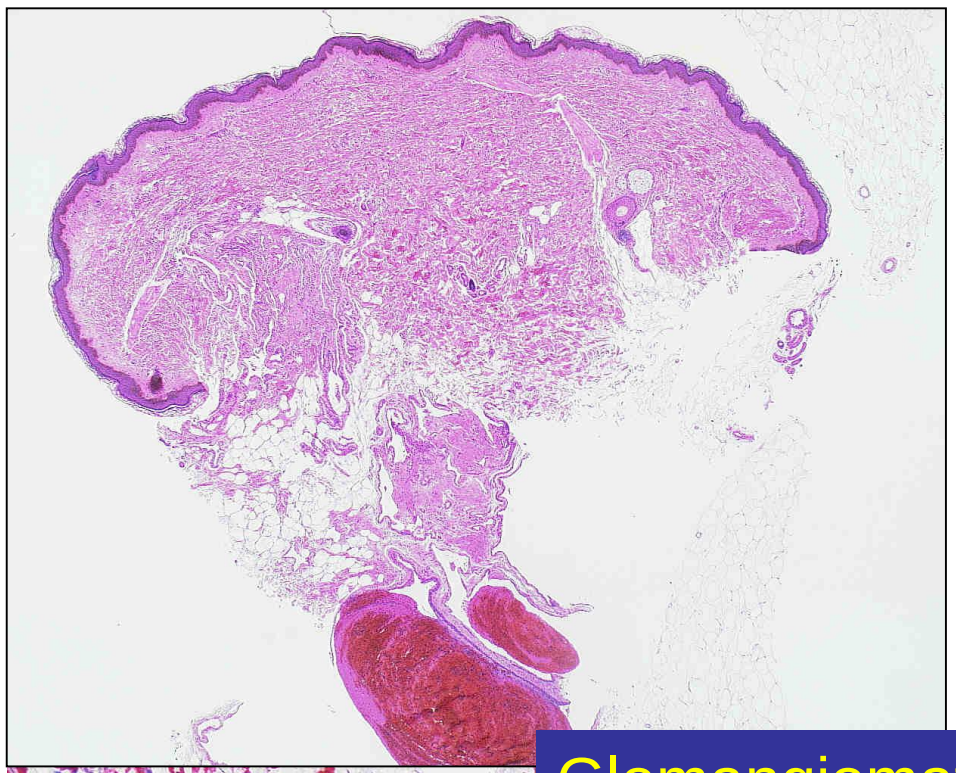


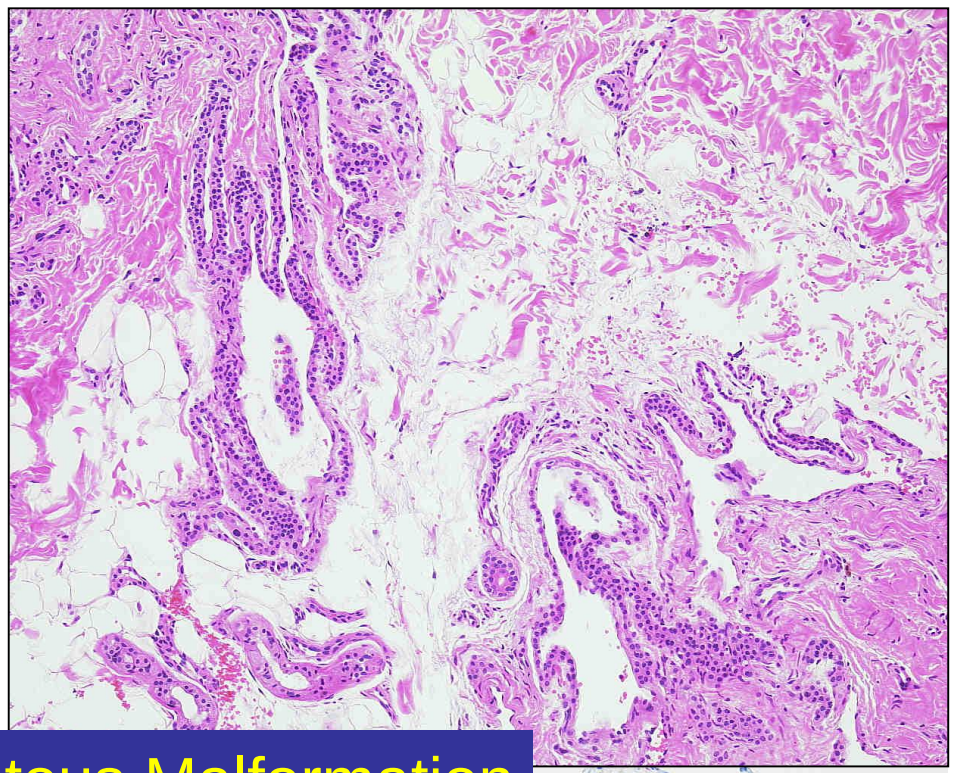


M, 50 years, multiple lesions, grow slowly, Kaposi´s sarcoma was suspected

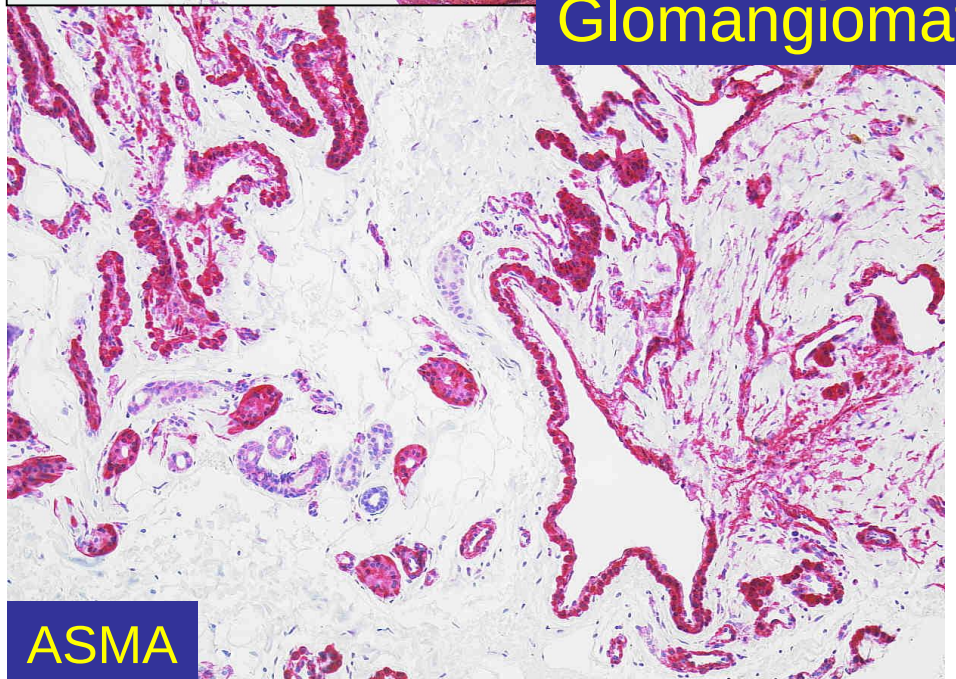


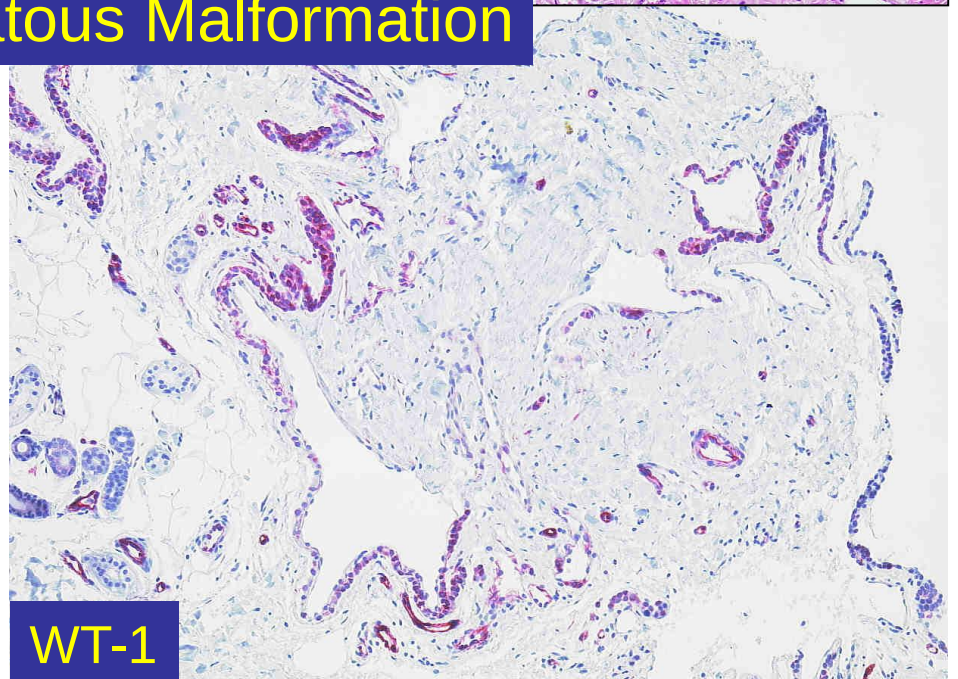


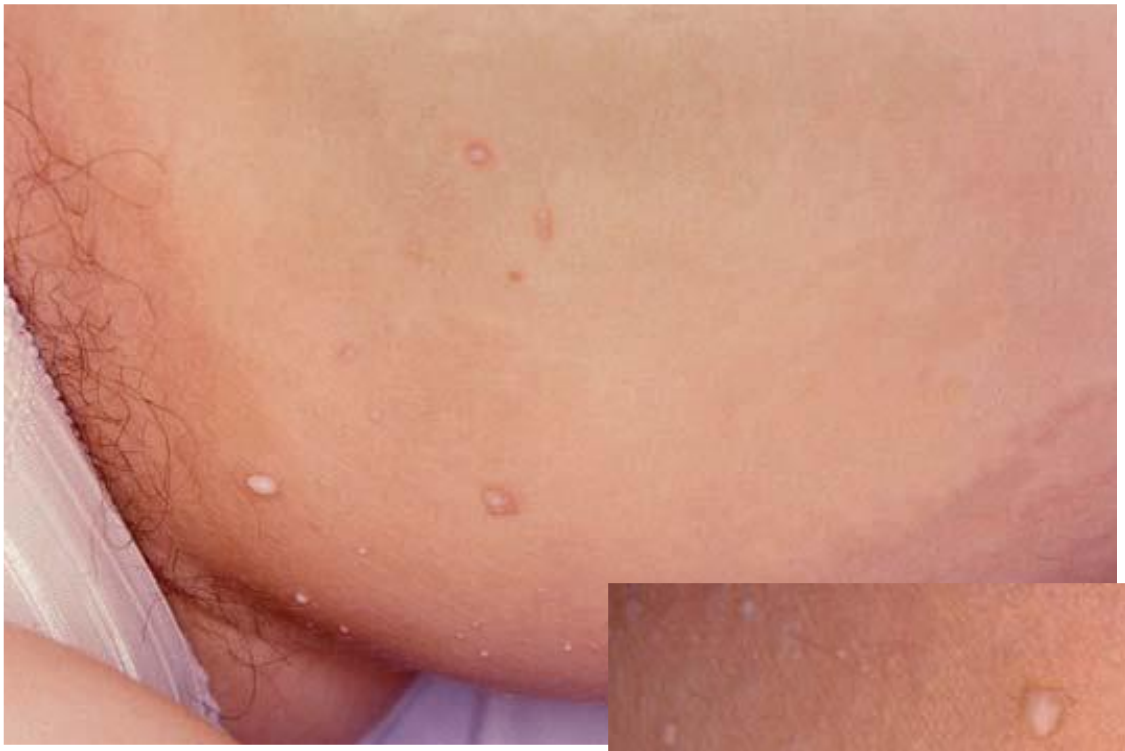


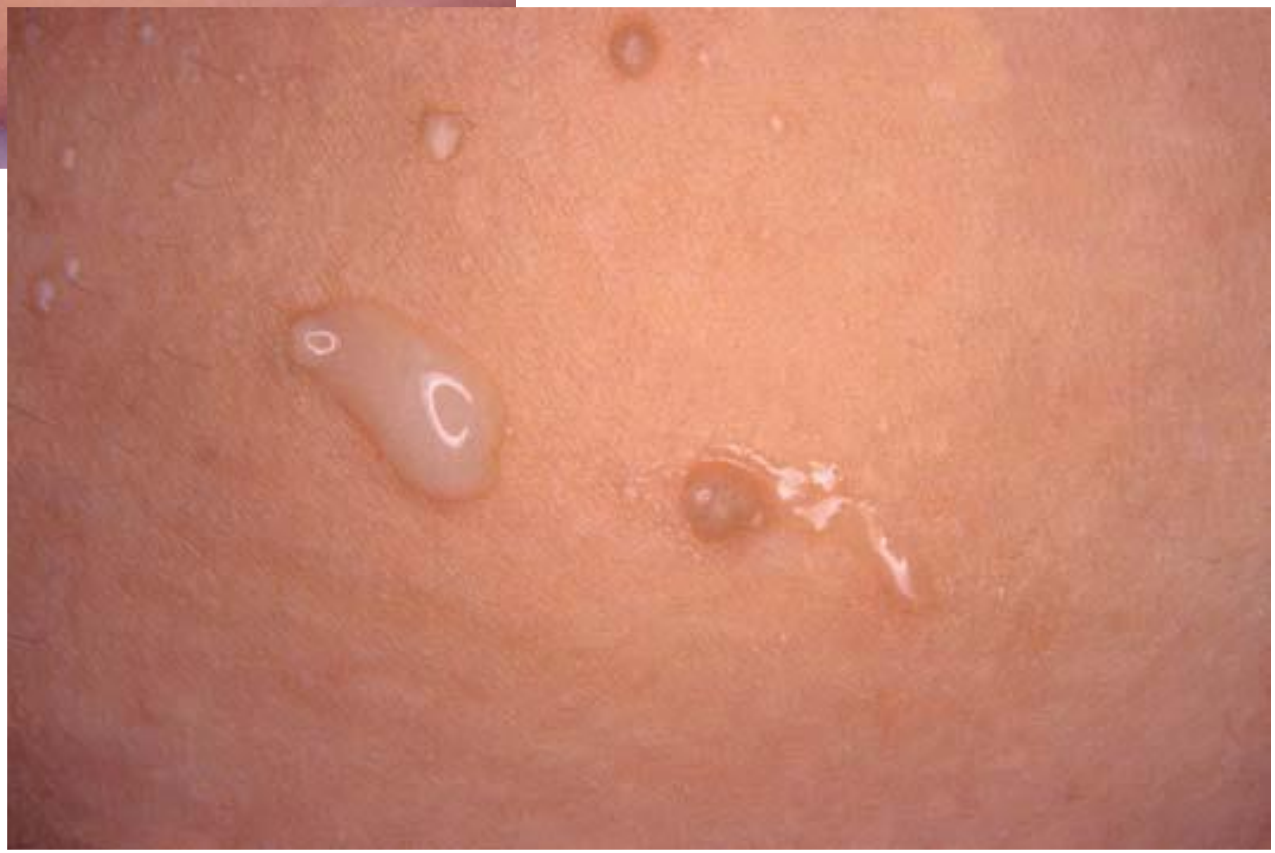


Glomangiomatous Malformation

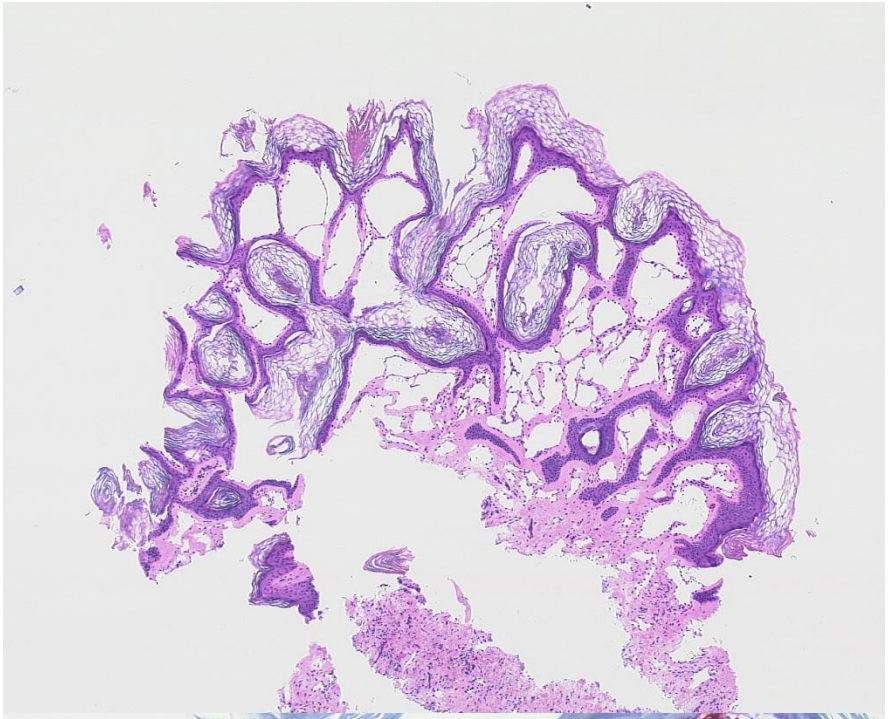


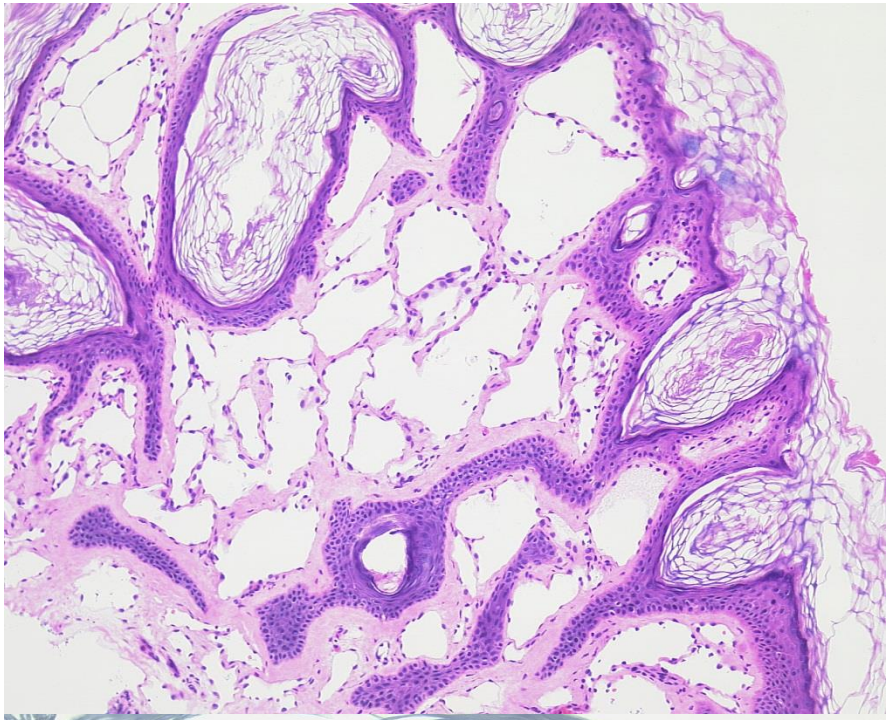


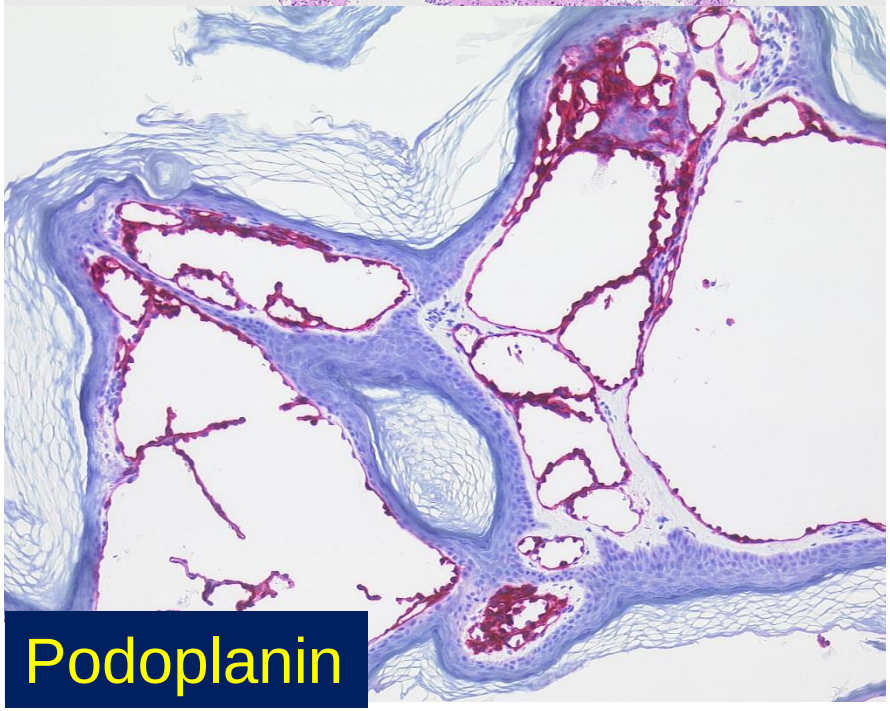




lymphangioma /
lymphangieectasia



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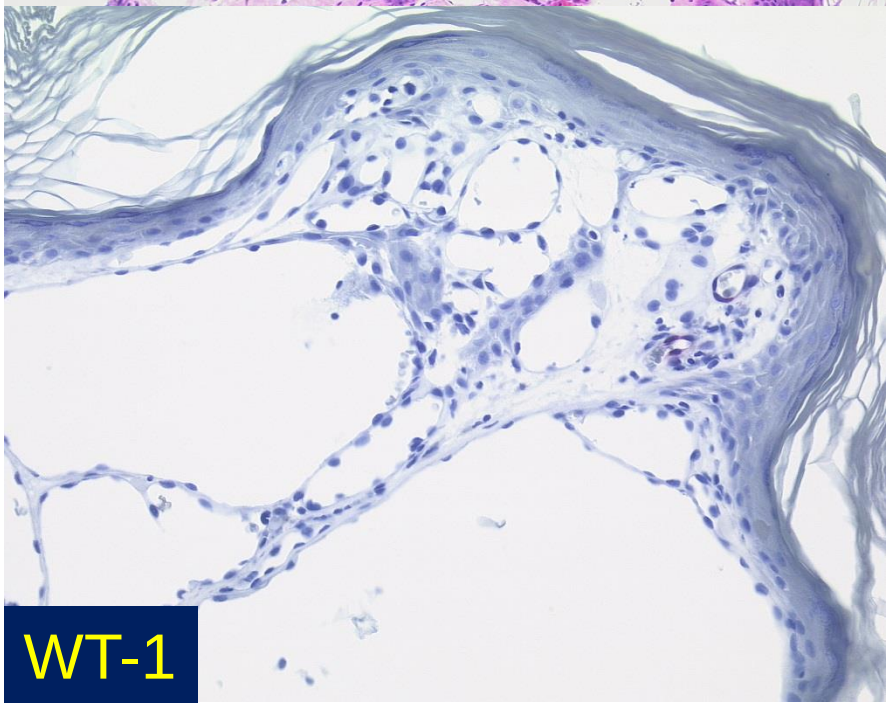
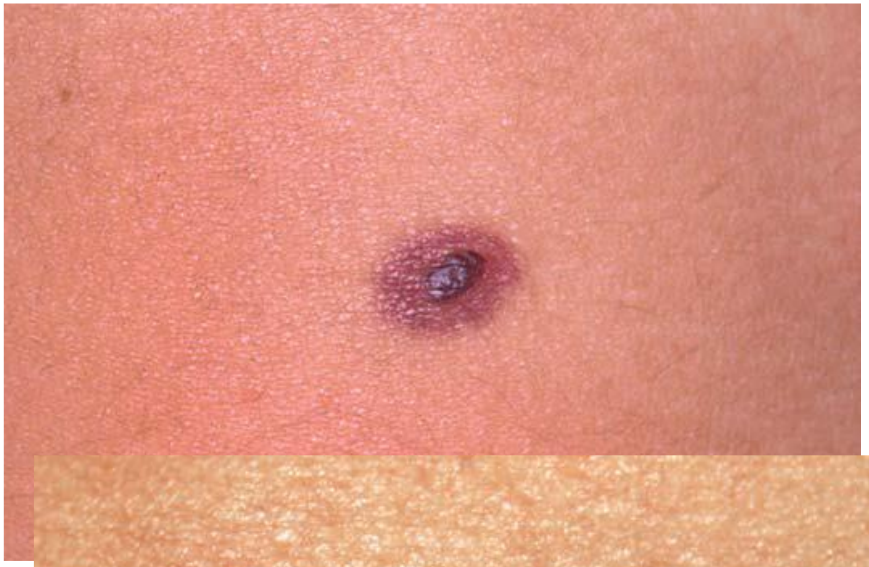

WT-1

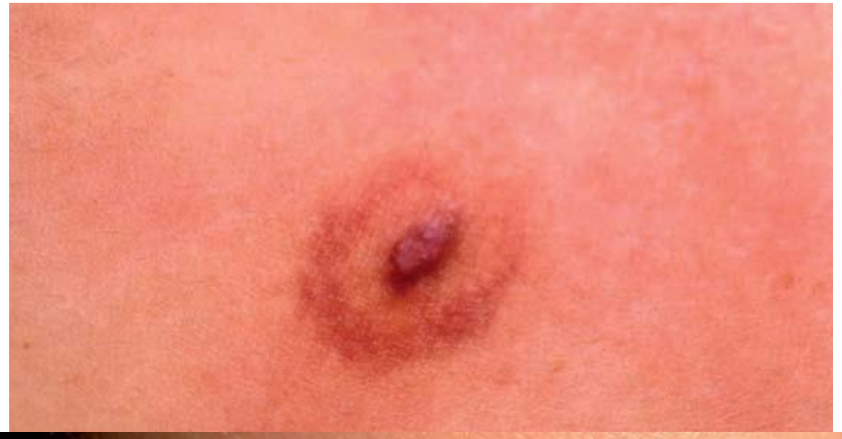
Hobnail Haemangioma

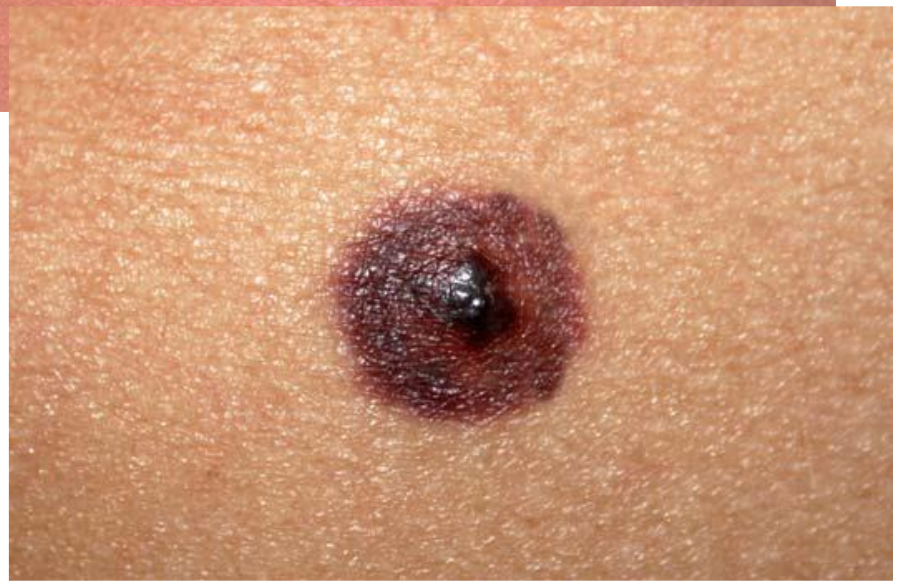
(„targetoid haemosiderotic haemangioma“)

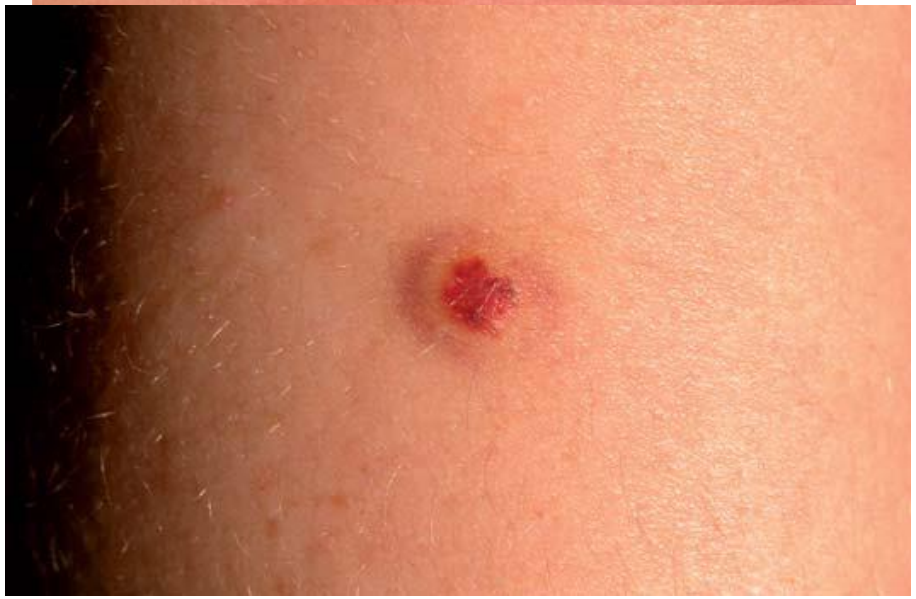
superficial haemosiderotic lymphovascular malformation

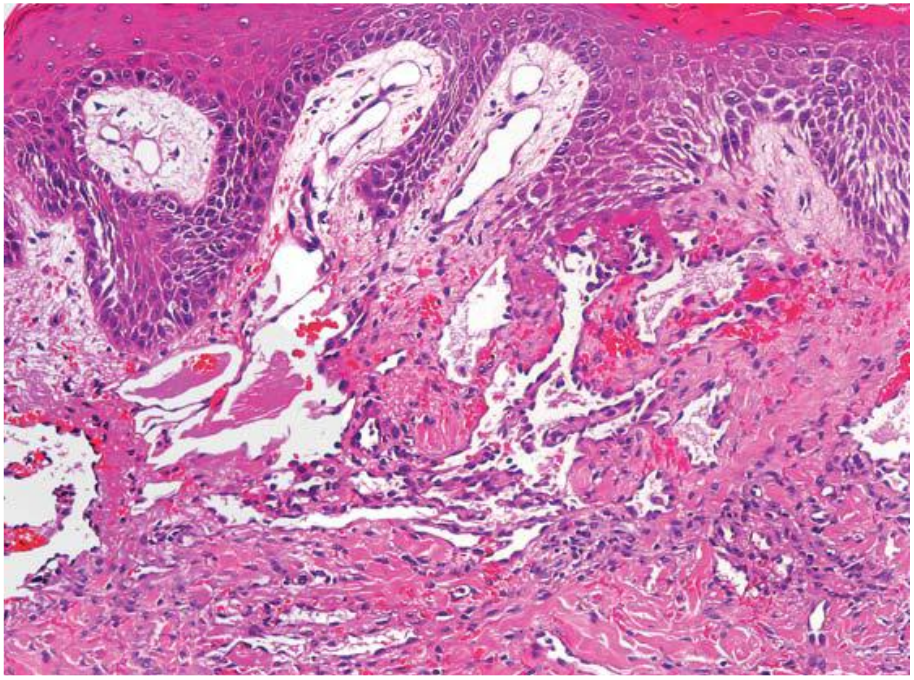
Joyce JC et al. Pediatr Dermatol 2014; 31: 281

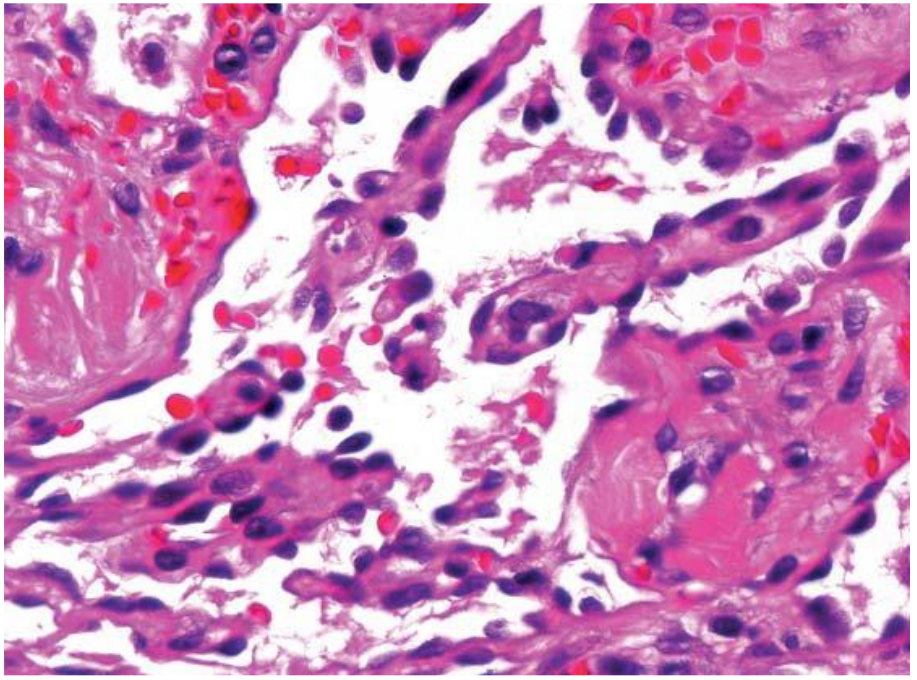


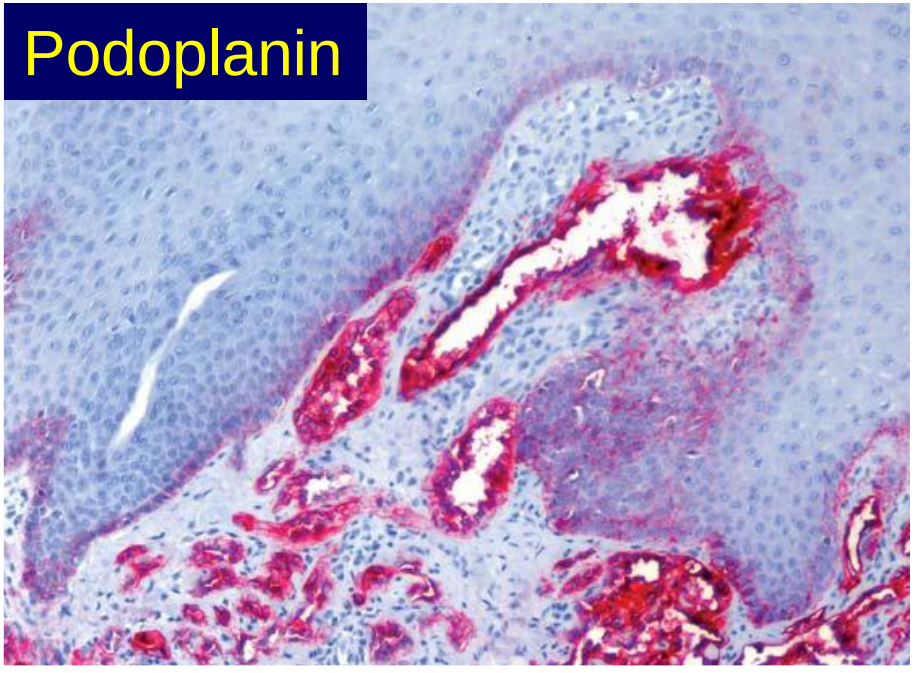


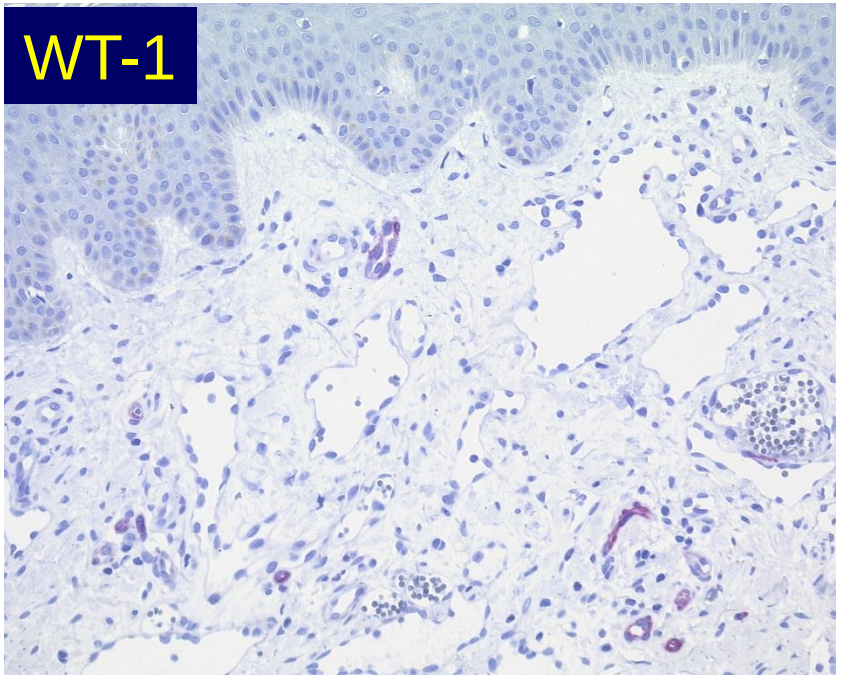




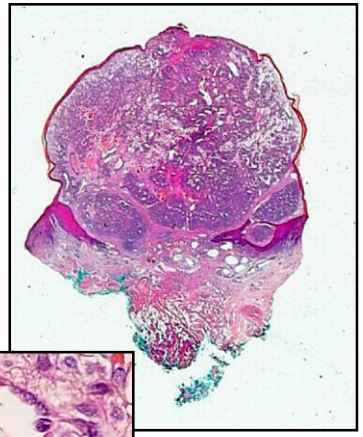


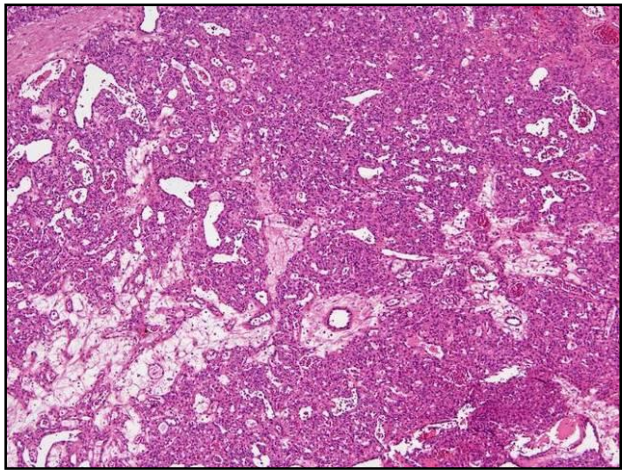


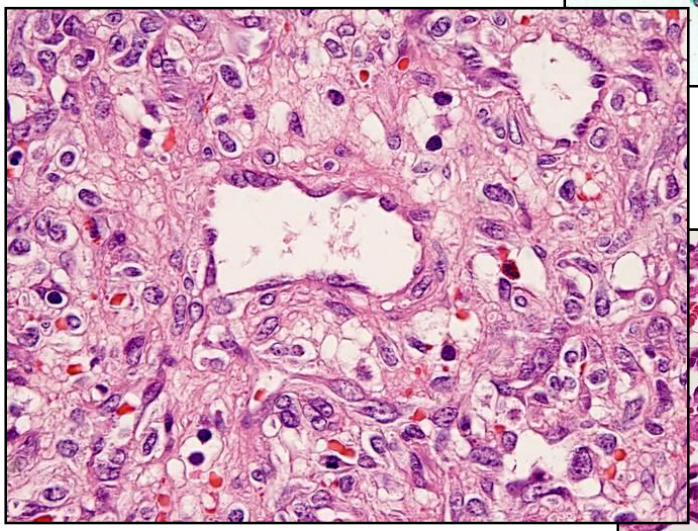

Podoplanin

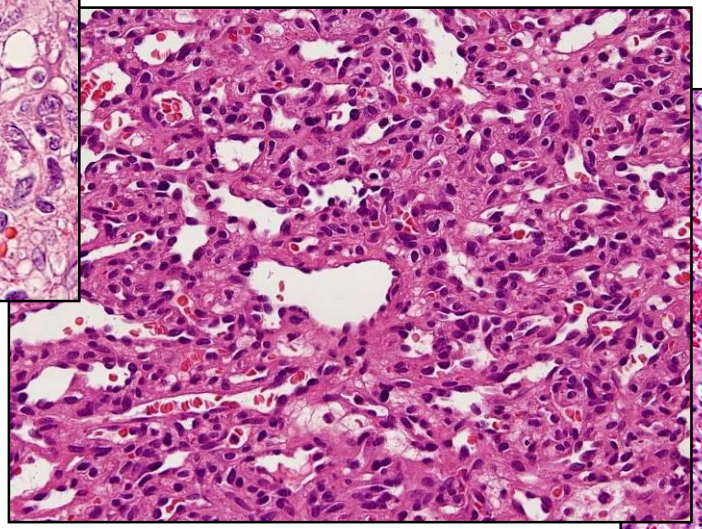

WT-1

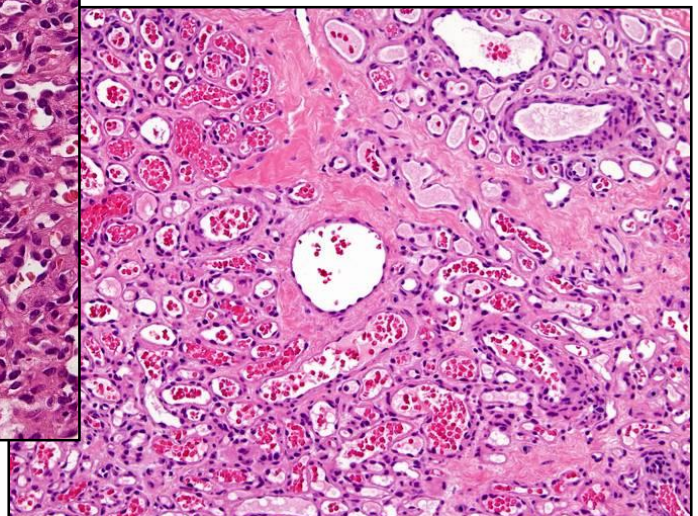
Differential Diagnosis: capillary vascular Malformation - pyogenic Granuloma («lobular capillary haemangioma»)



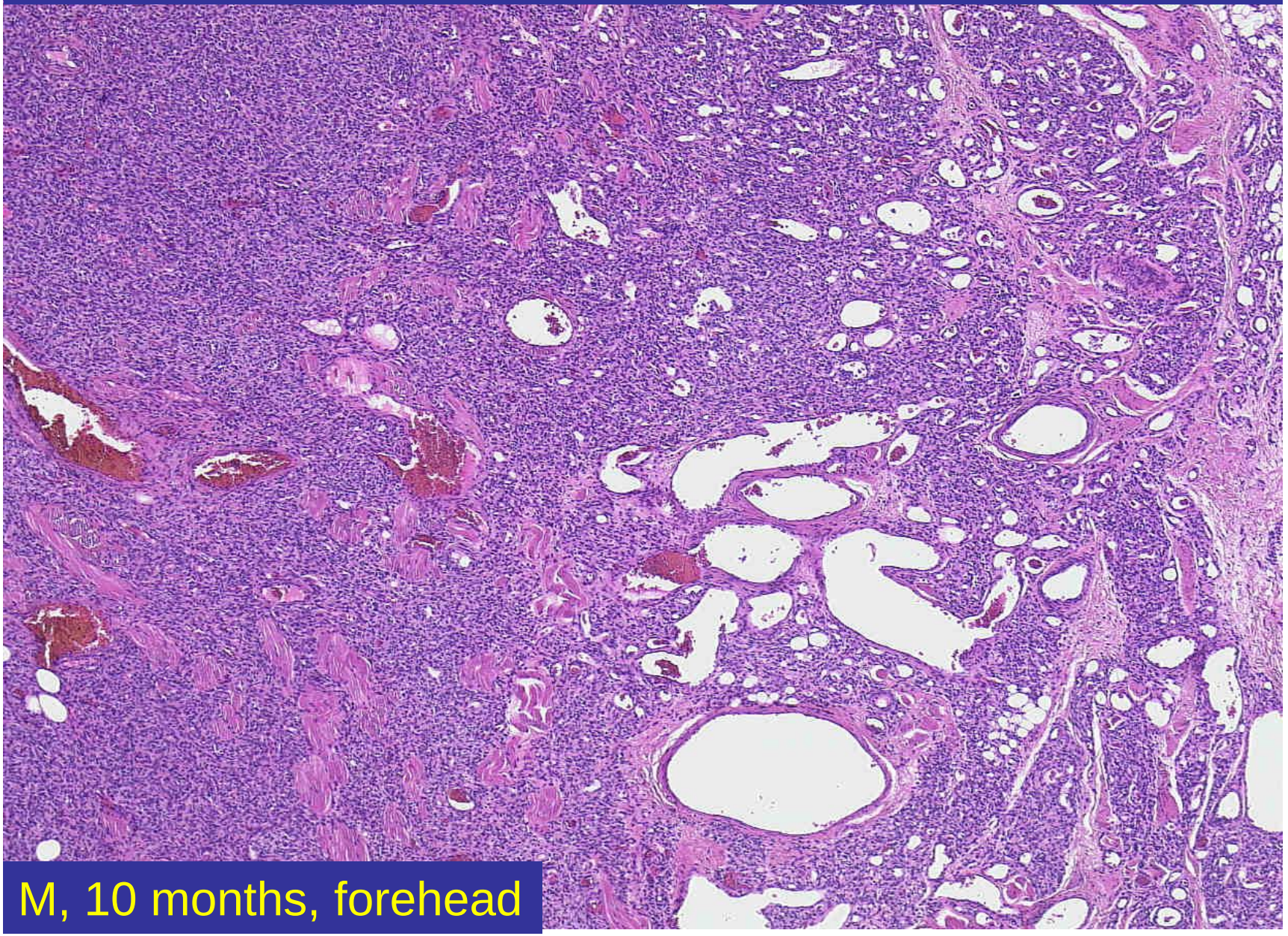




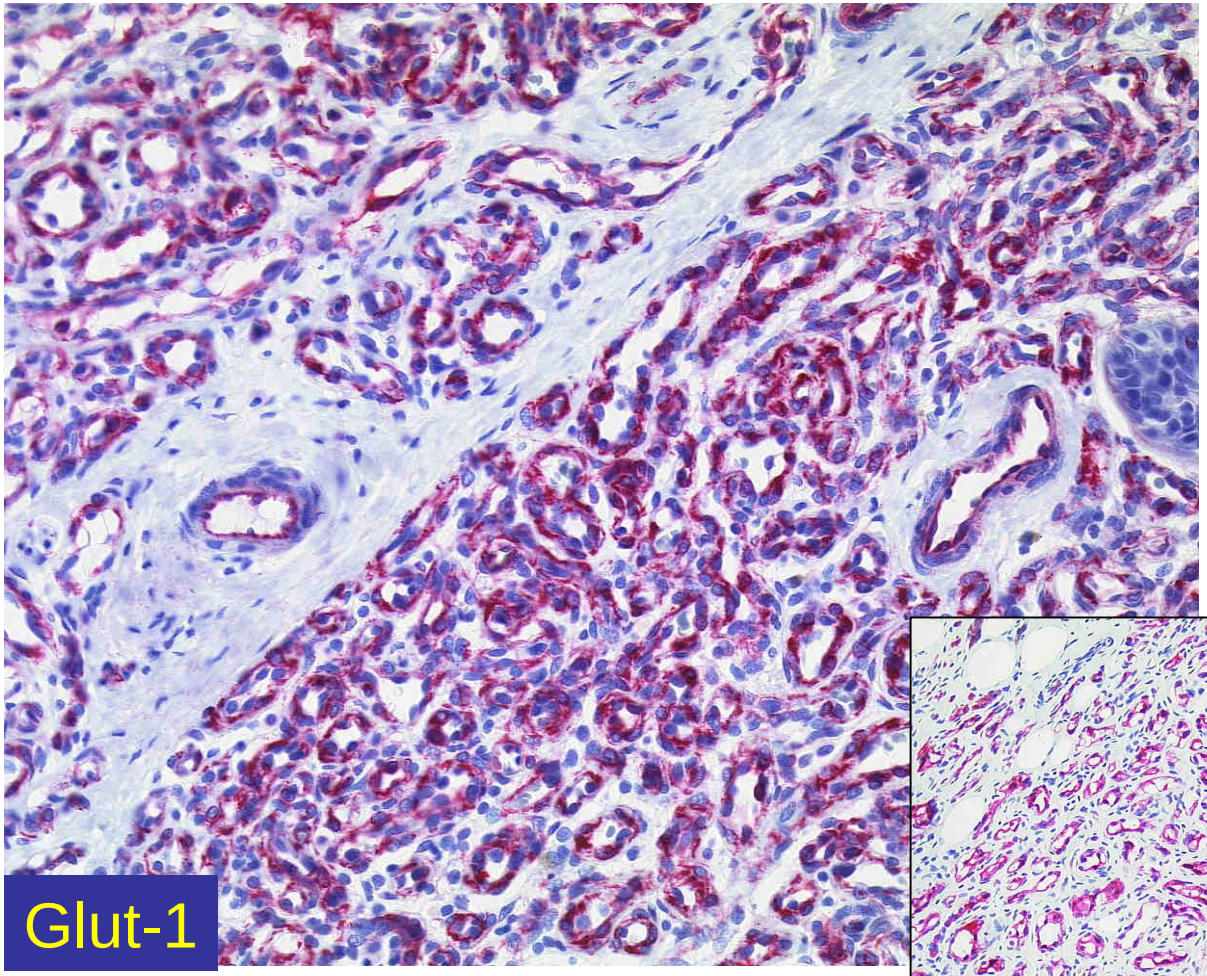


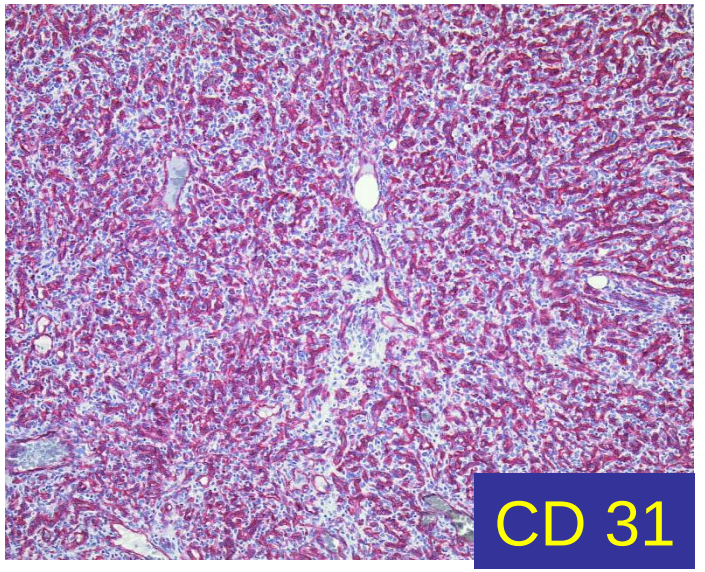


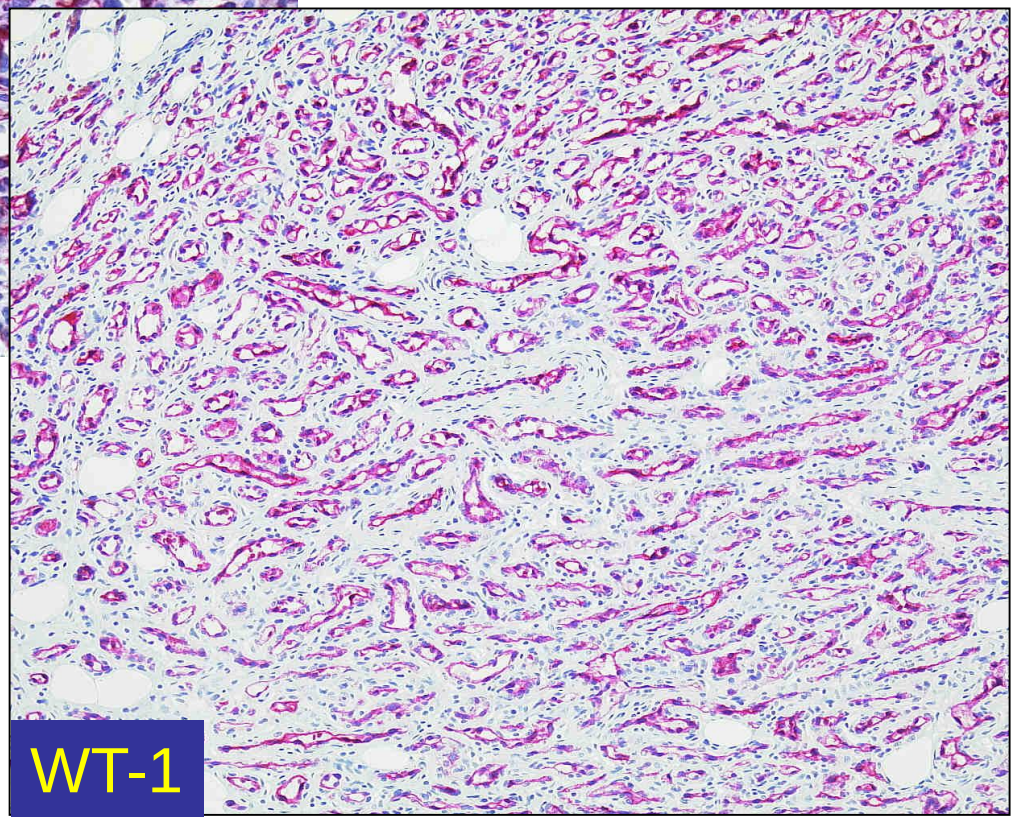
Differential Diagnosis: capillary vascular malformation - cellular infantile Haemangioma

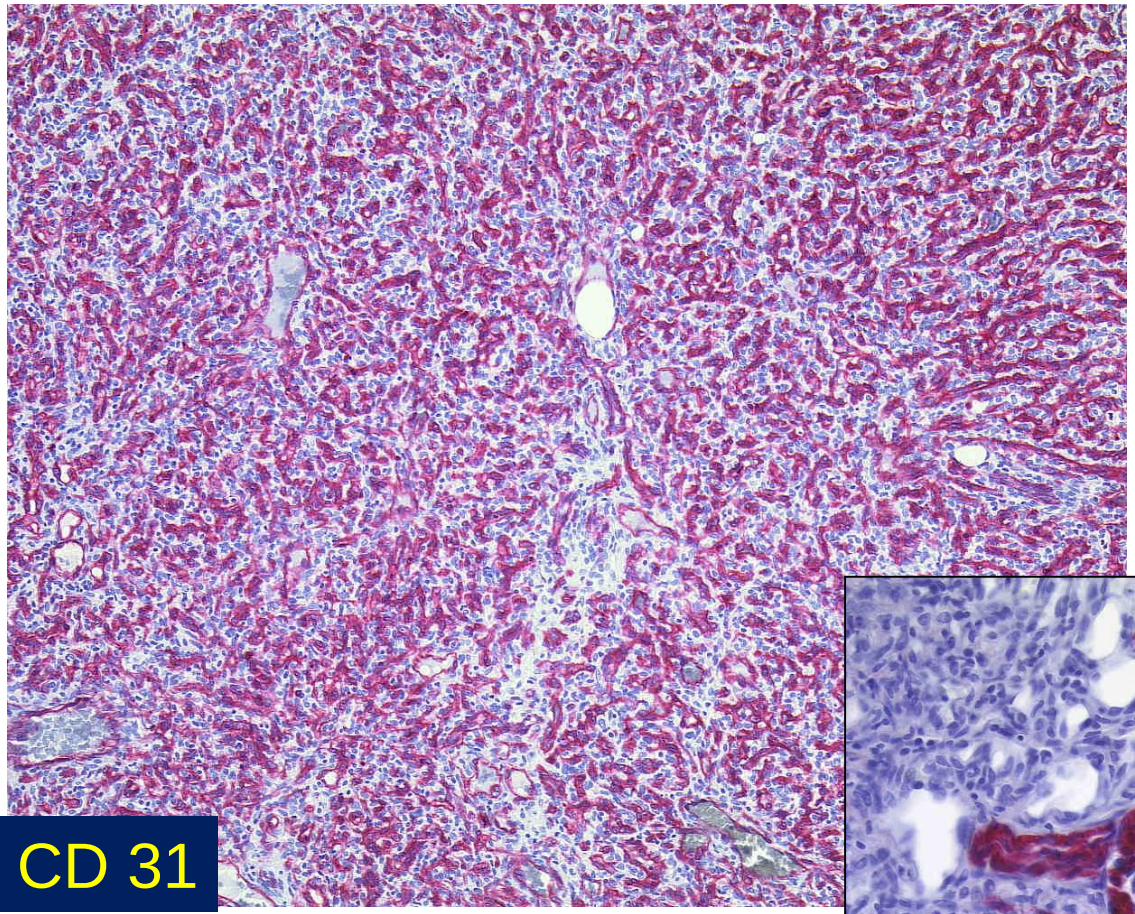


M, 10 months, forehead


Glut-1


CD 31


WT-1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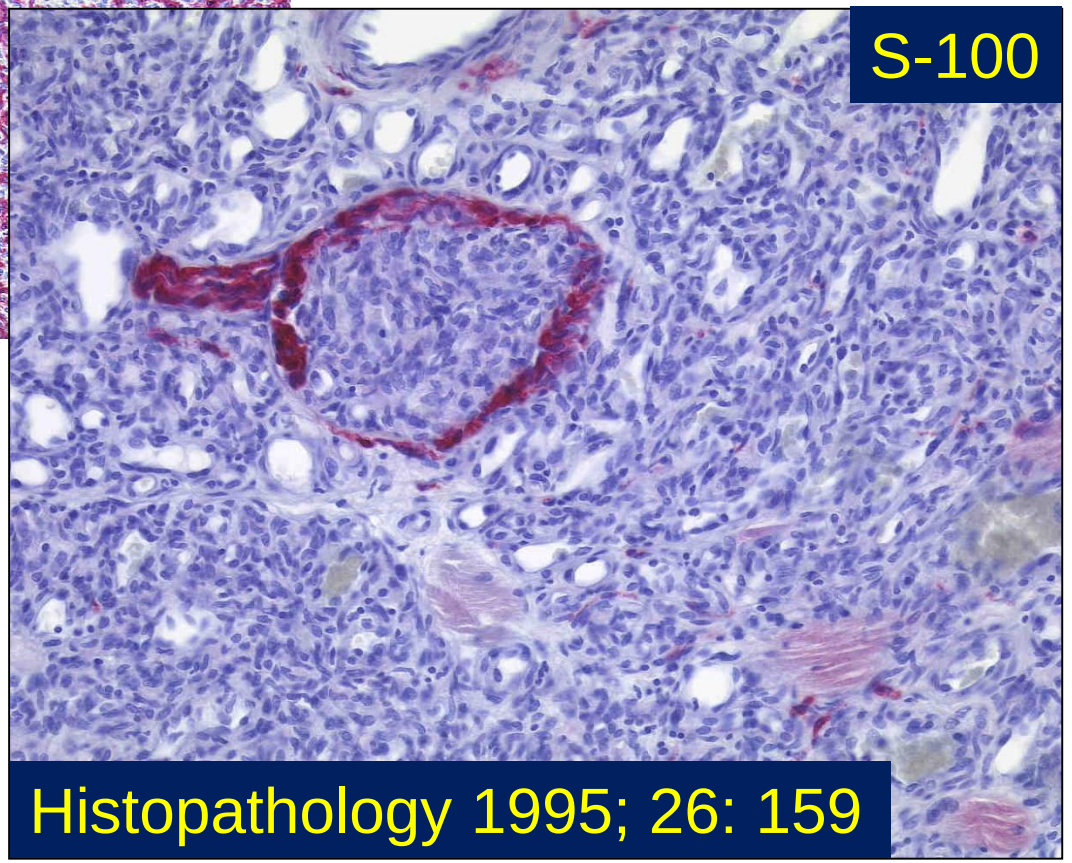
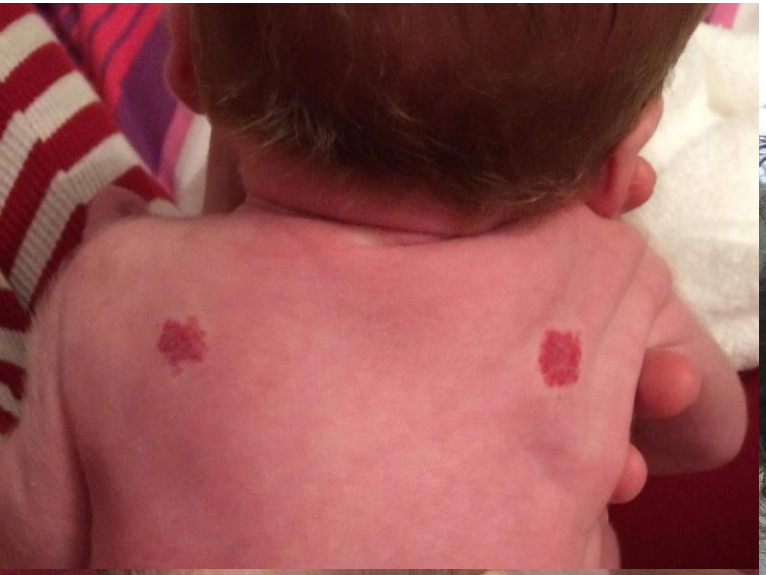
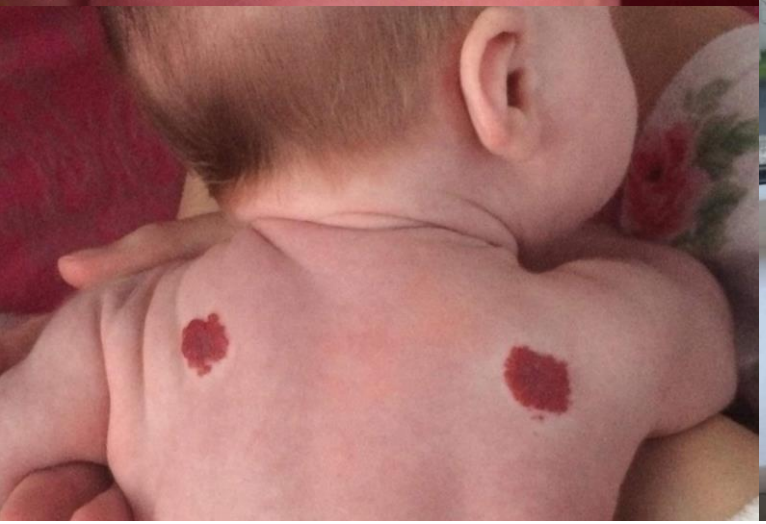
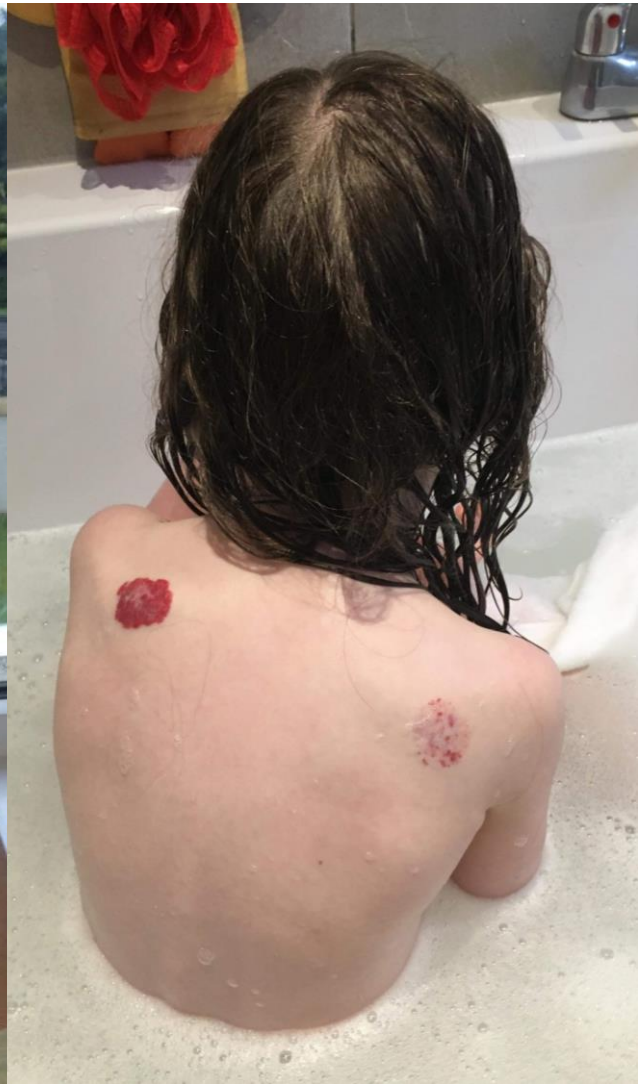

S-100
Histopathology 1995; 26: 159

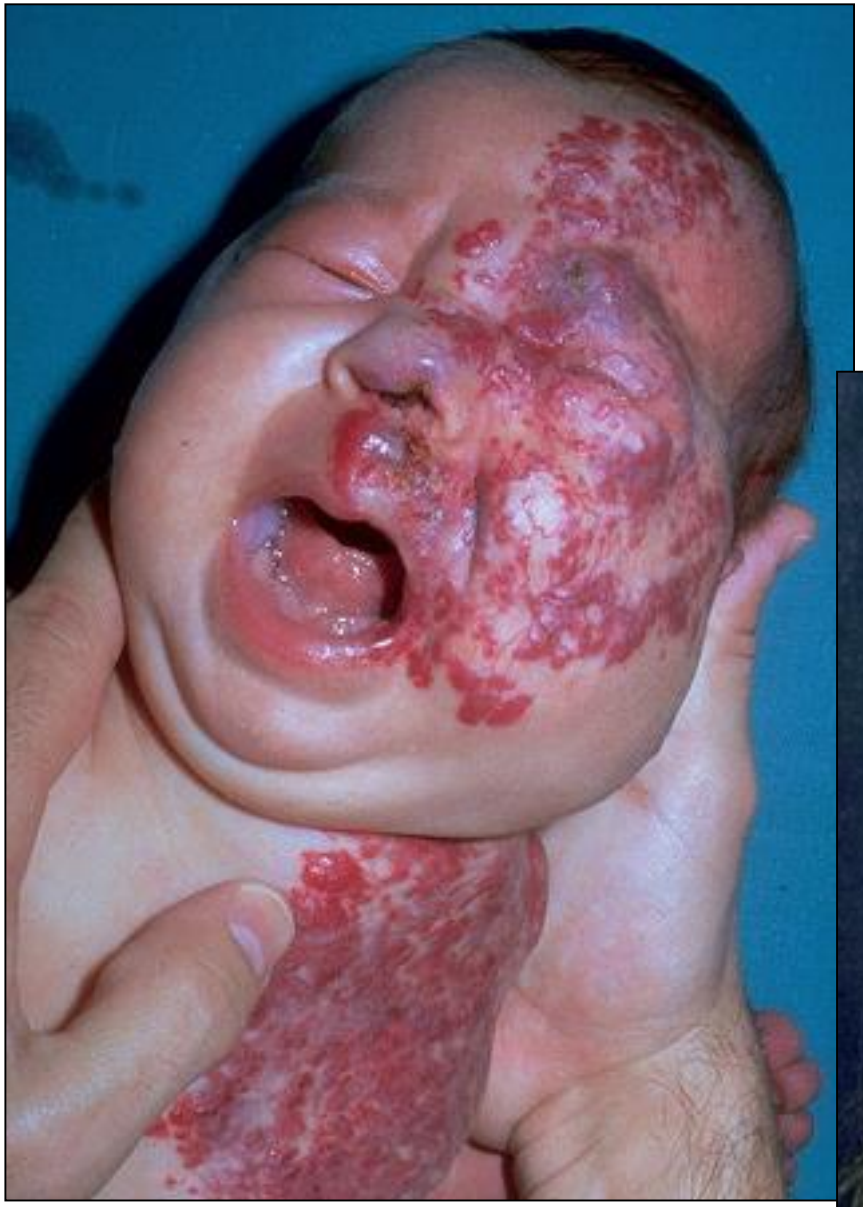
infantile Haemangioma

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

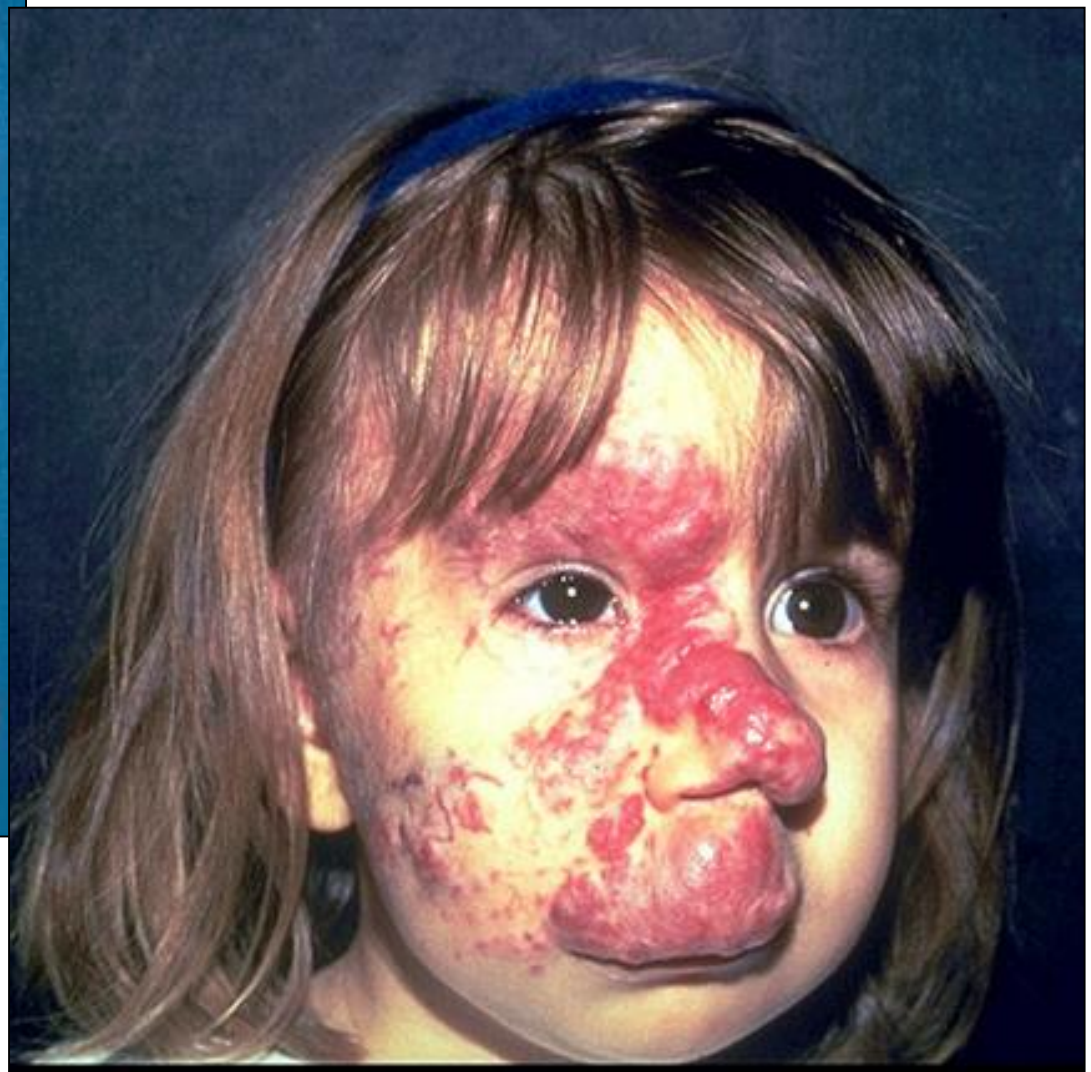








infantile
Haemangioma



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

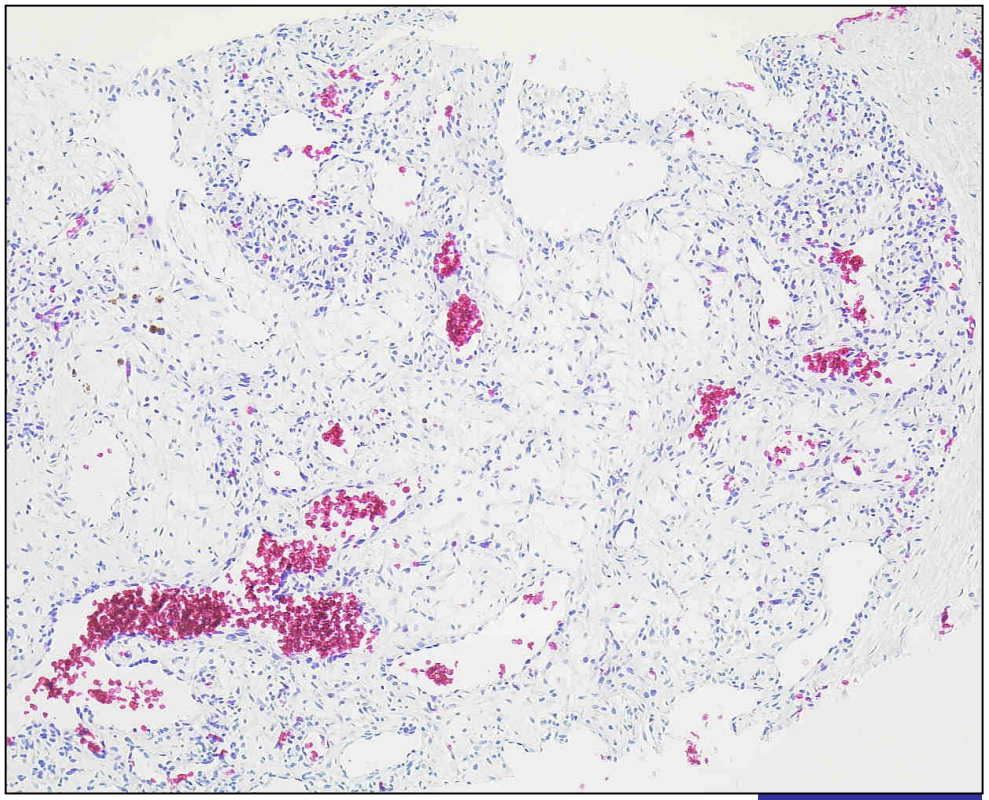
- Glut-1 **negative**
- rapid shrinking
- often thrombosis

Non Involuting CH

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

Partially Involuting CH

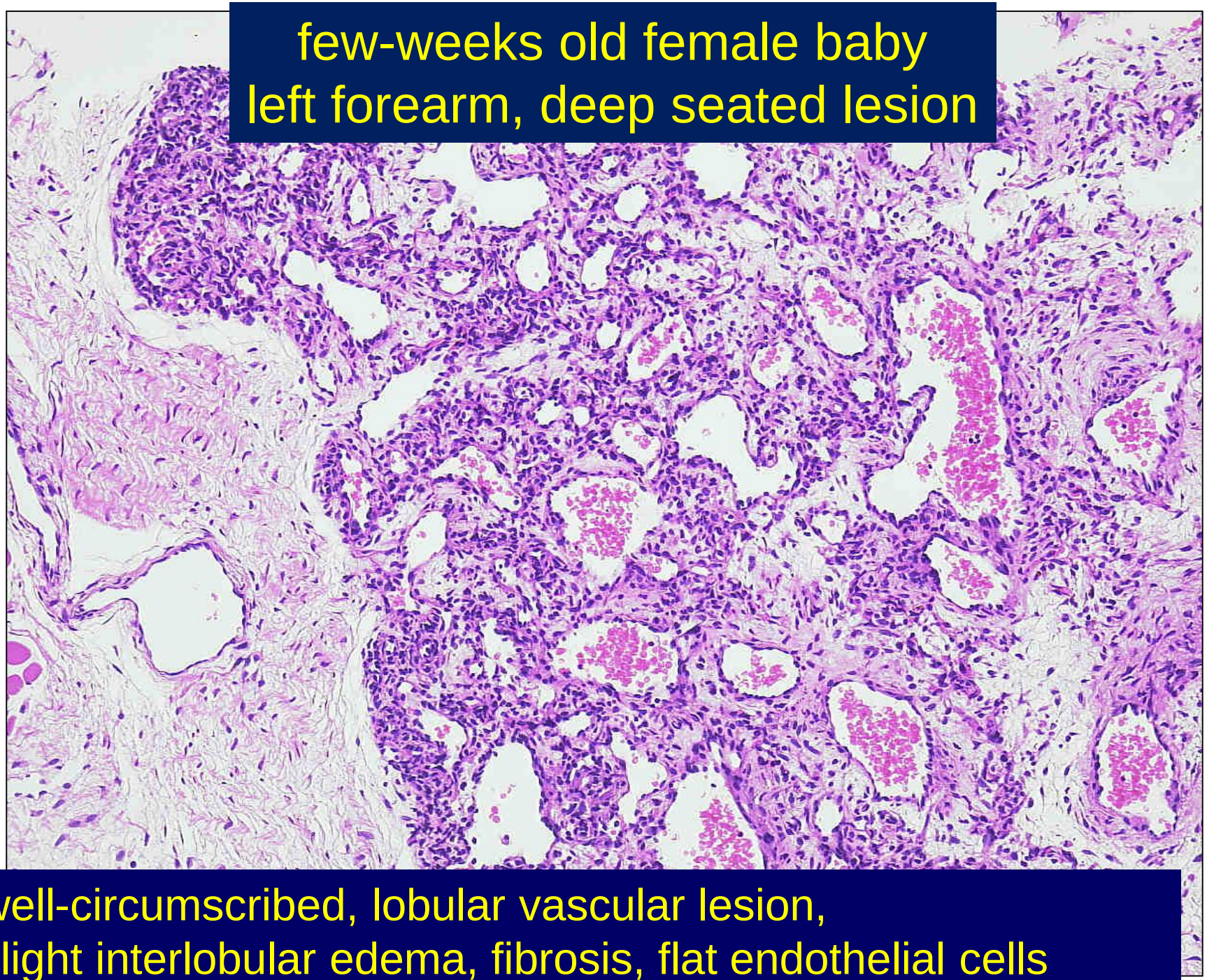
- Glut-1 **negative**



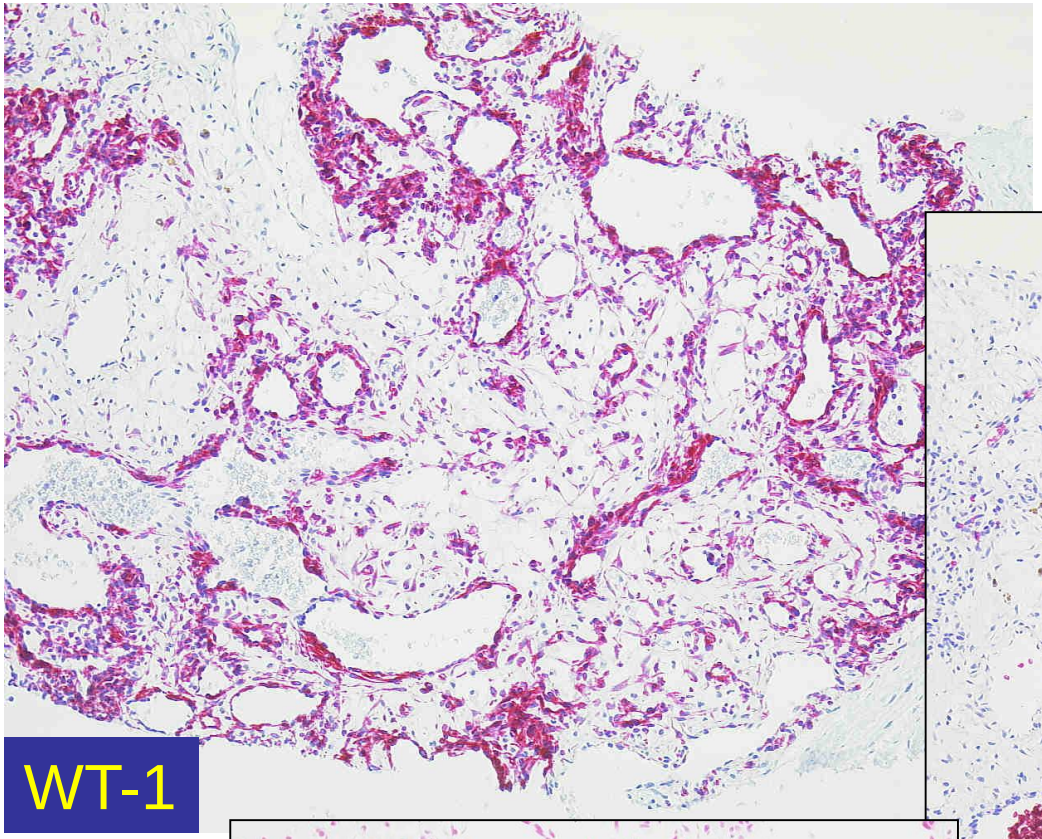
Glut-1

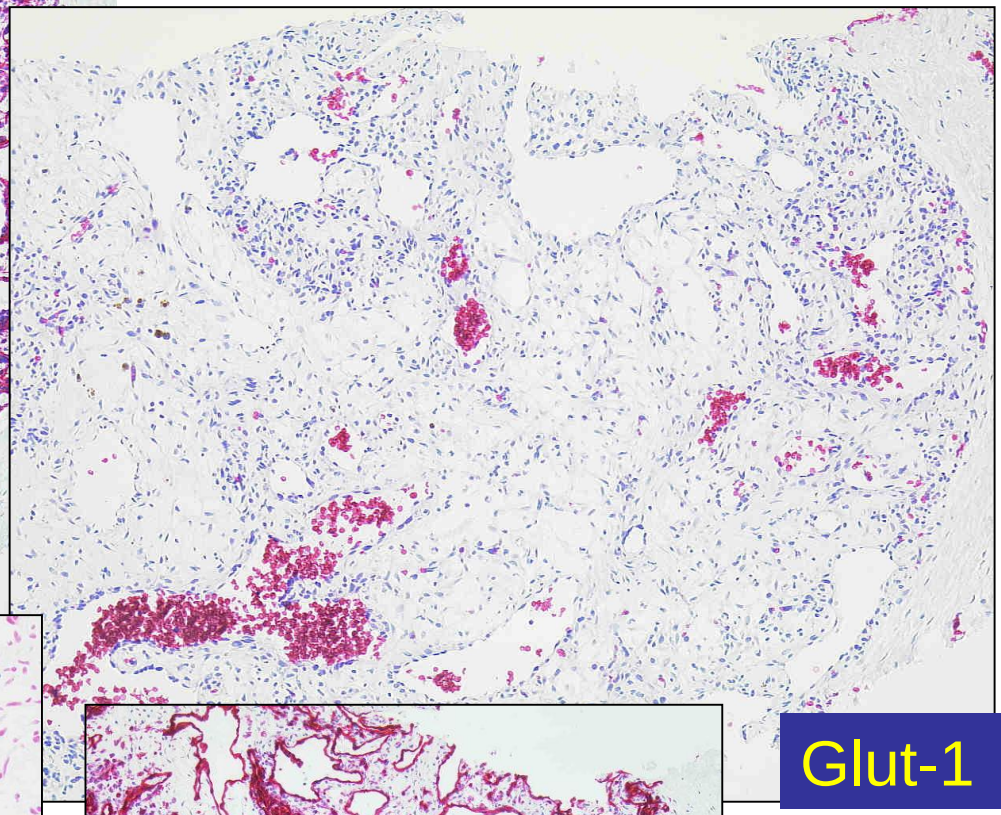
RICH	NICH
zonation	no zonation
small lobules	larger lobules
small capillaries	thicker-walled vessels
flat endothelia	prominent endothelia
interlobular fibrosis	intralobular fibrosis
haemosiderin deposits	no haemosiderin deposits

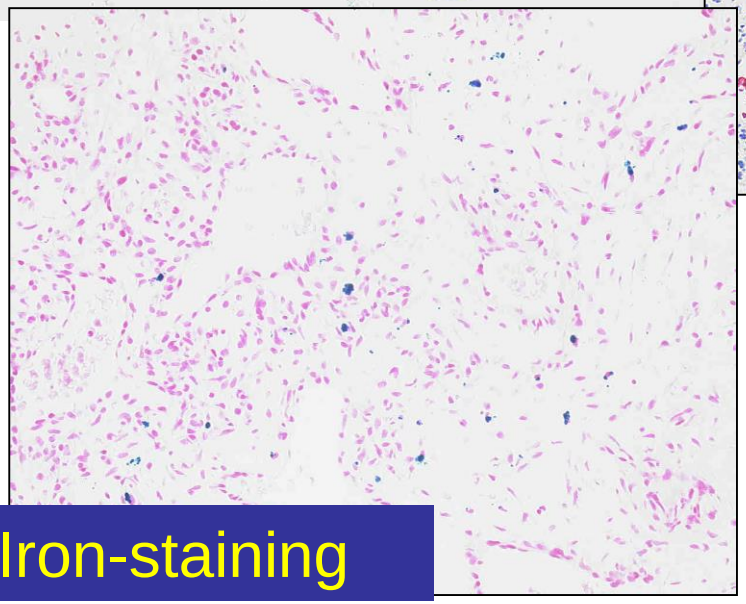
needs close clinicopathological correlation !

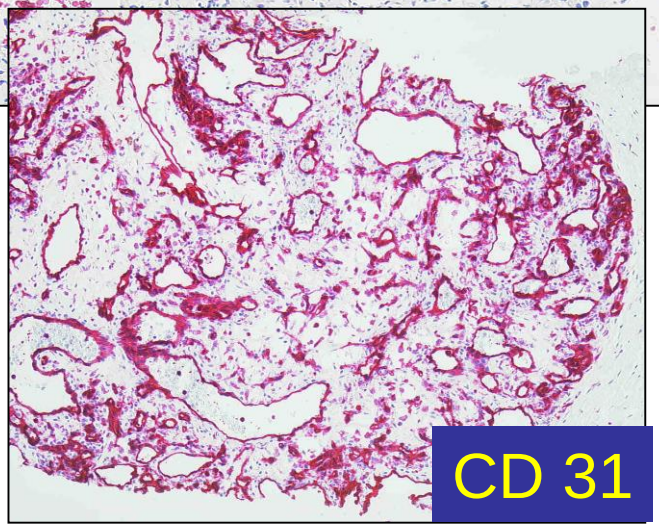

few-weeks old female baby
left forearm, deep seated lesion
well-circumscribed, lobular vascular lesion,
slight interlobular edema, fibrosis, flat endothelial cells

RICH









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

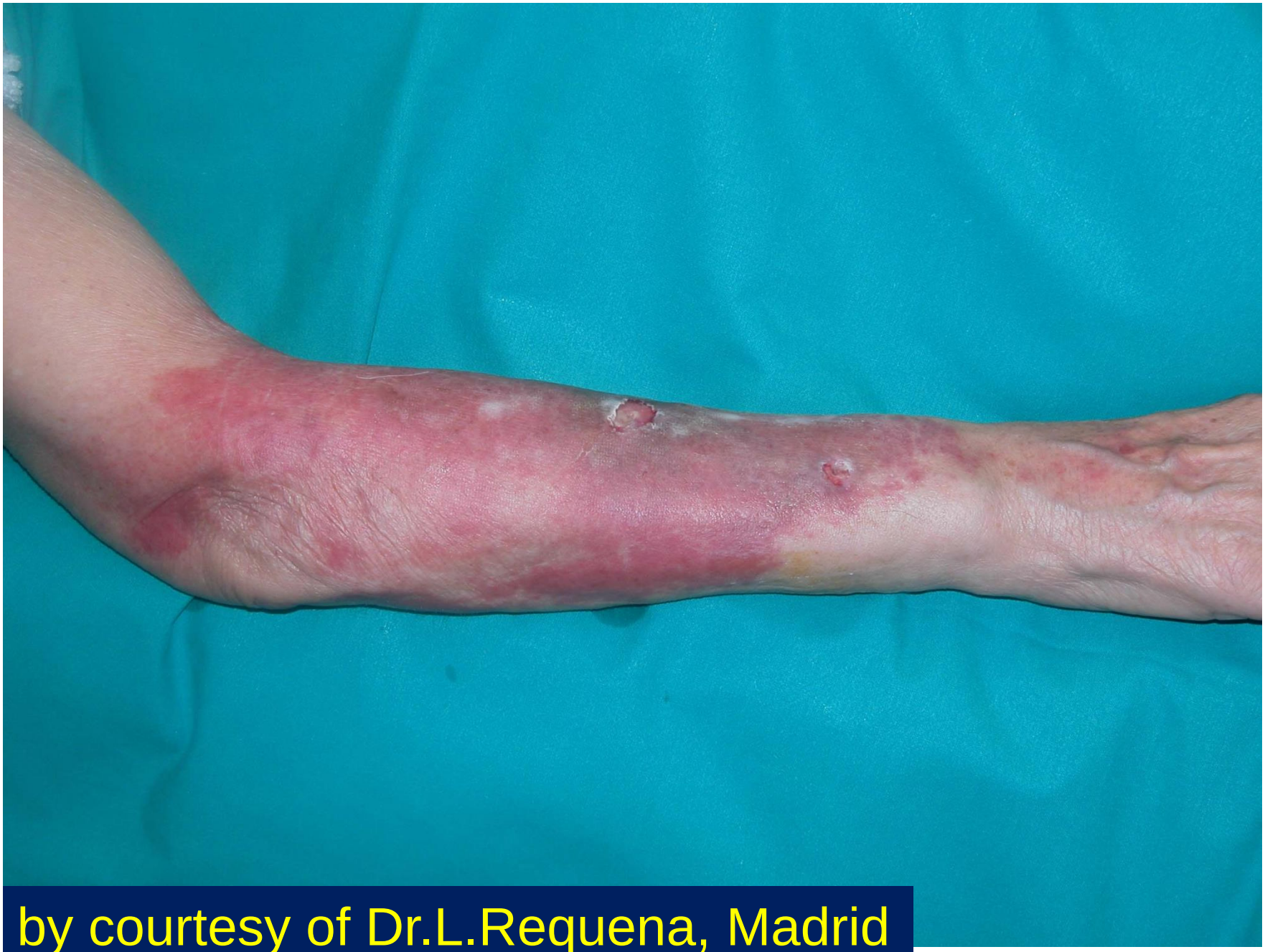
- diffuse dermal Angiomatosis
- reactive Angioendotheliomatosis
- Lymphangiomatosis (of the limbs)
- multifocal Lymphangioendotheliomatosis with thrombocytopenia
- prurigiform Angiomatosis
- bacillary Angiomatosis

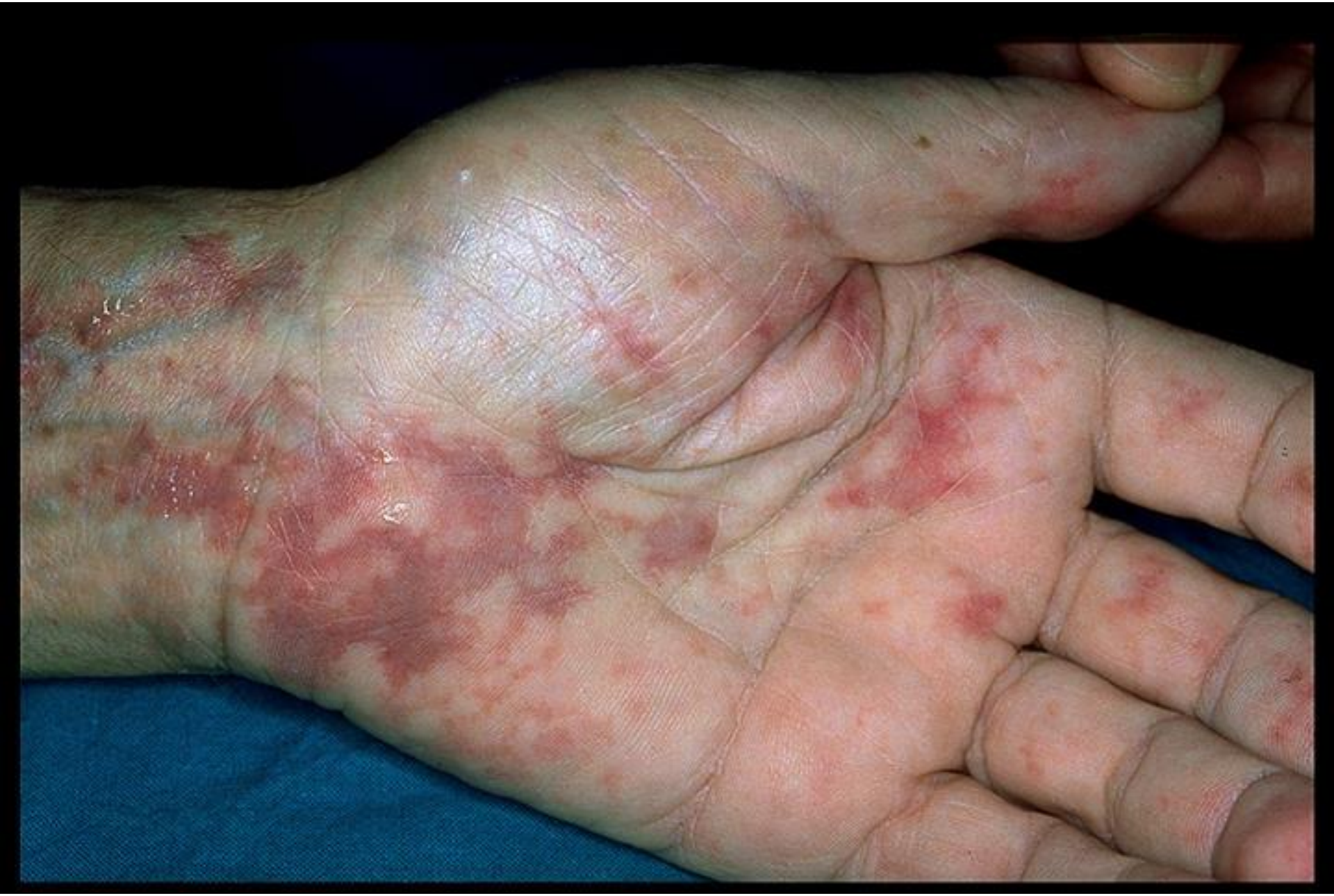
Diffuse Dermal Angiomatosis*

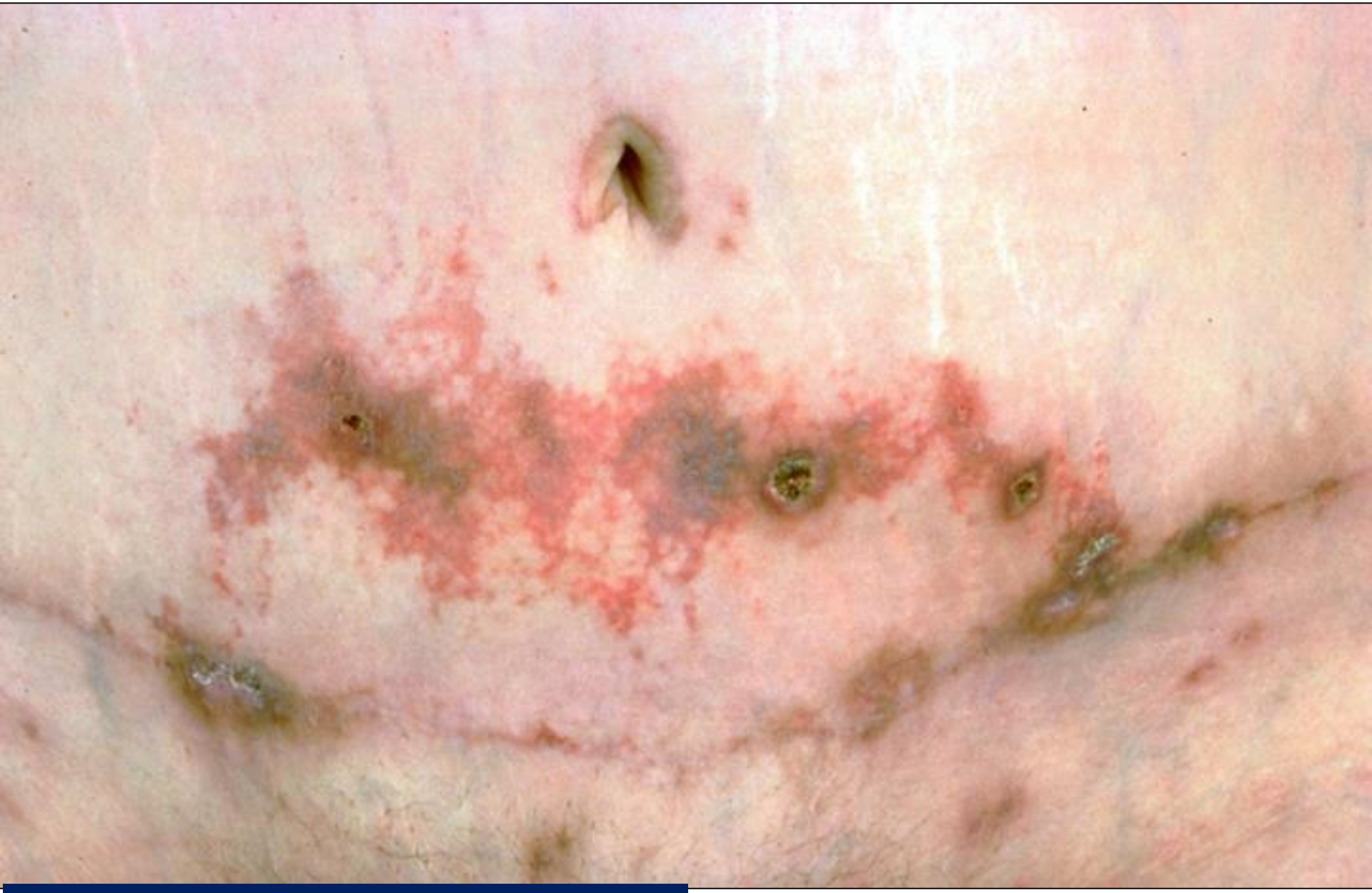
Clinicopathological Findings

- 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

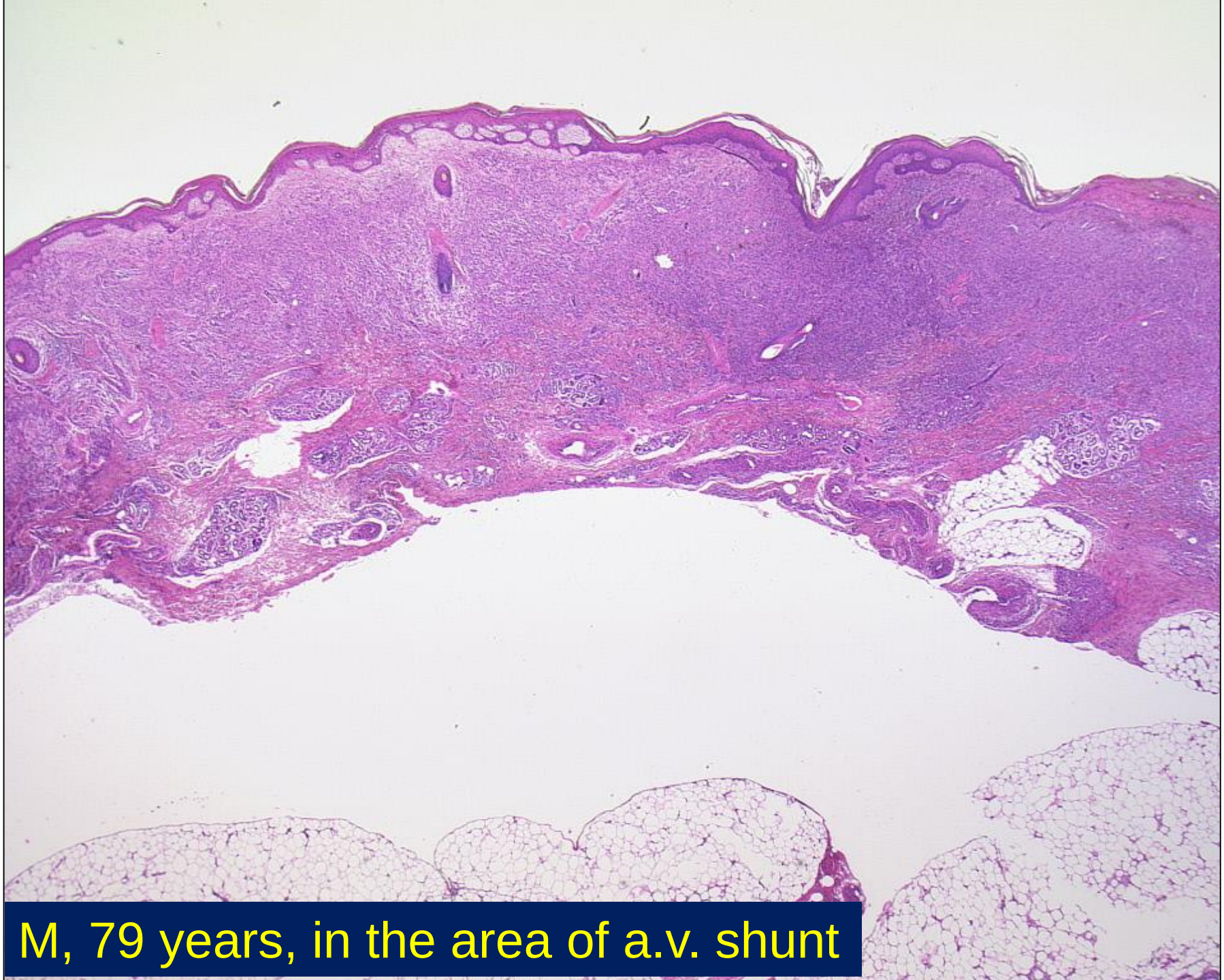
*** Kim S et al. Arch Dermatol 2002;138: 456**


by courtesy of Dr.L.Requena, Madrid

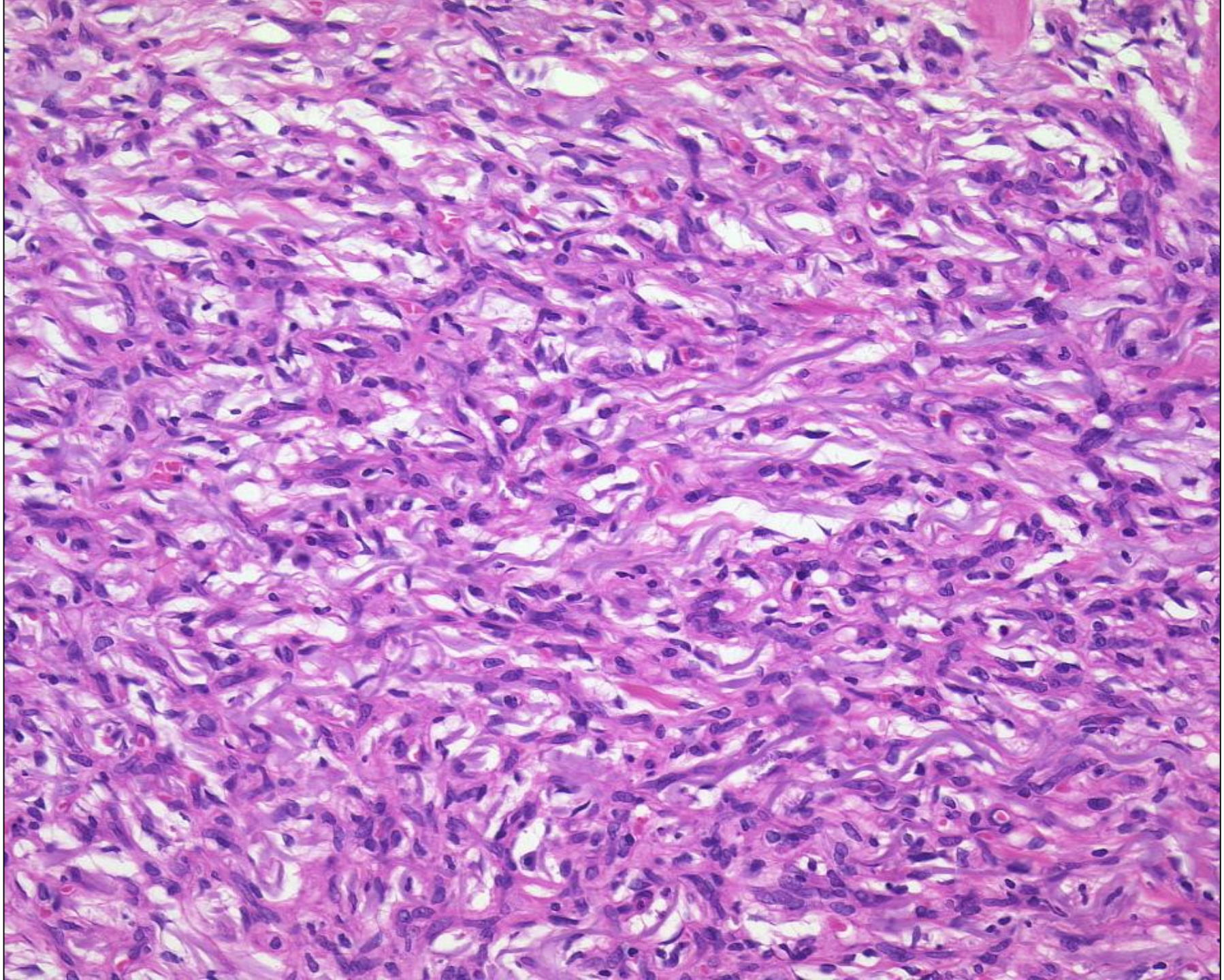


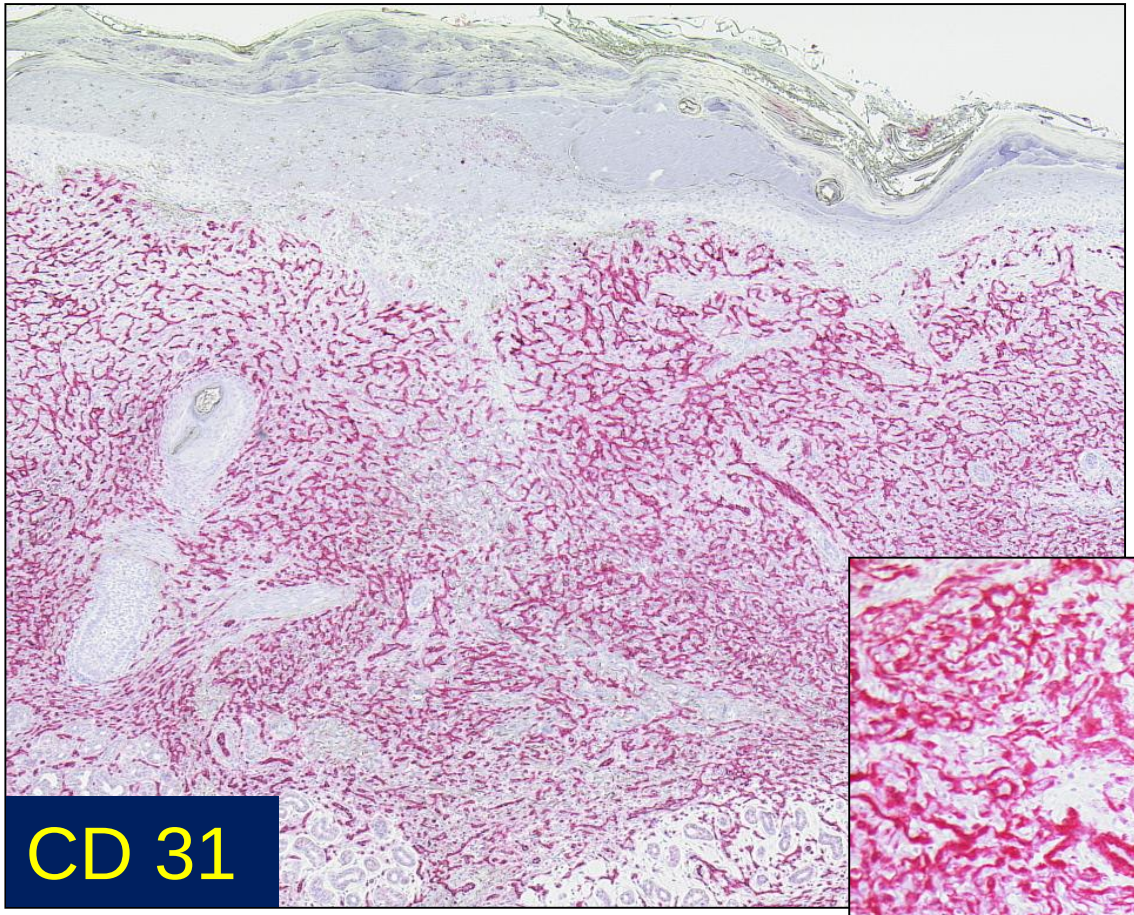


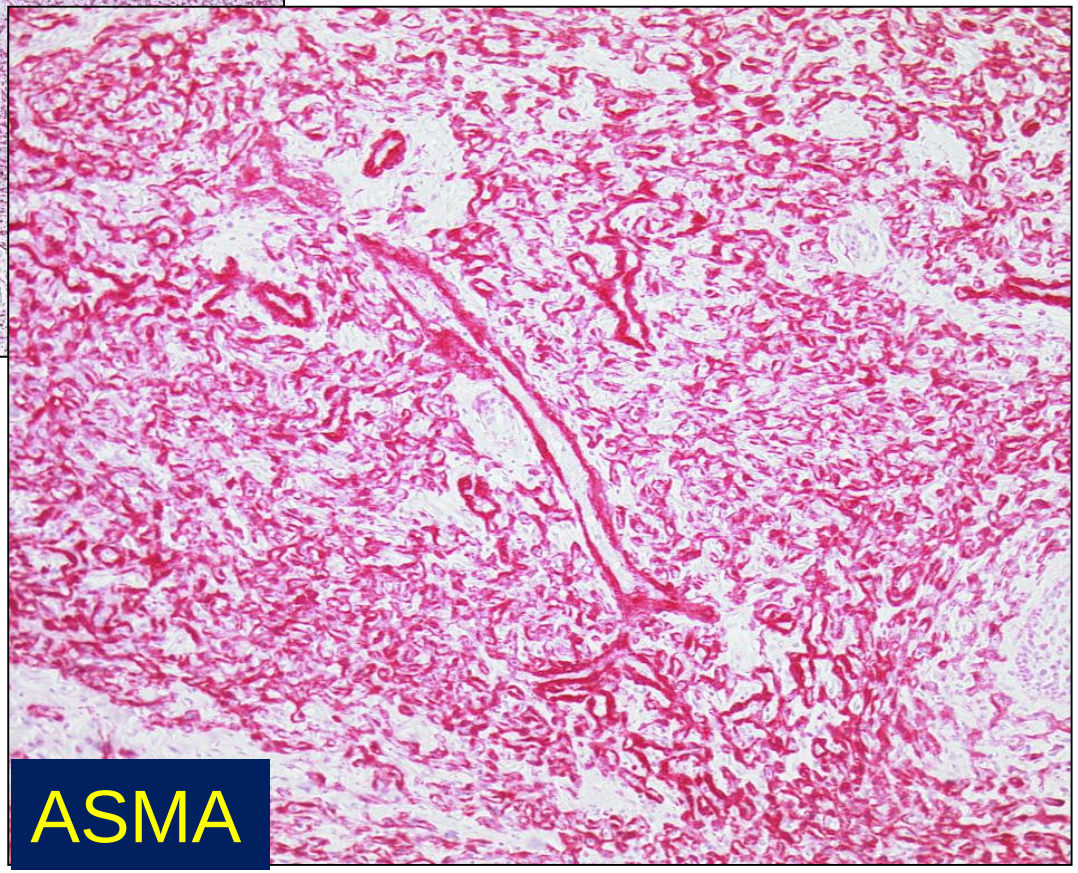
F, 43 years, previous liposuction
Hautarzt 2002; 53: 808



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




CD 31


ASMA

Diffuse Dermal Angiomatosis *versus* Reactive Angioendotheliomatosis

Related or identical ?

Reactive Angioendotheliomatosis:

cryoglobulinaemia, infection

intravascular endothelial proliferation

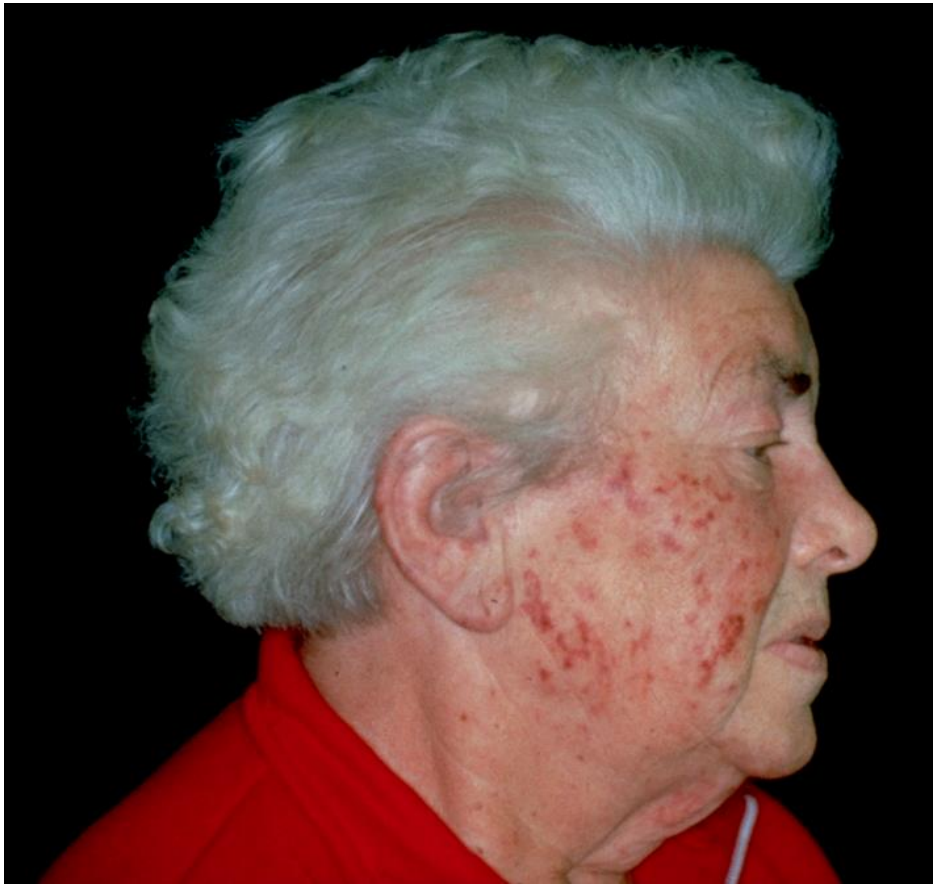
formation of capillary tufts

no proliferation of newly formed vessels

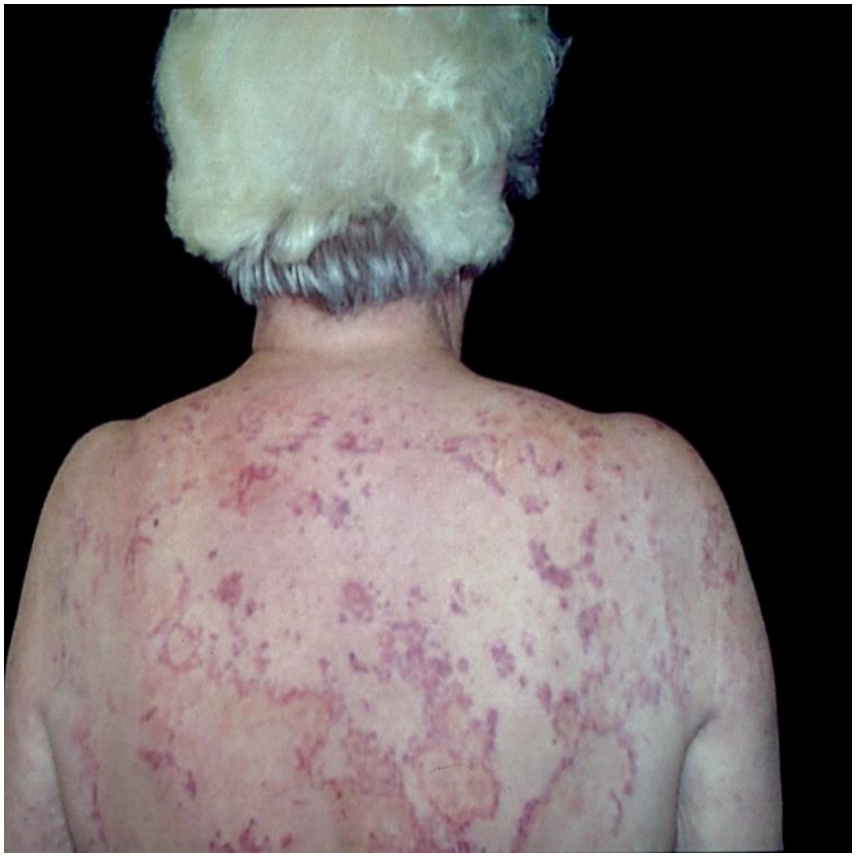
often fibrin thrombi

Related but not identical !

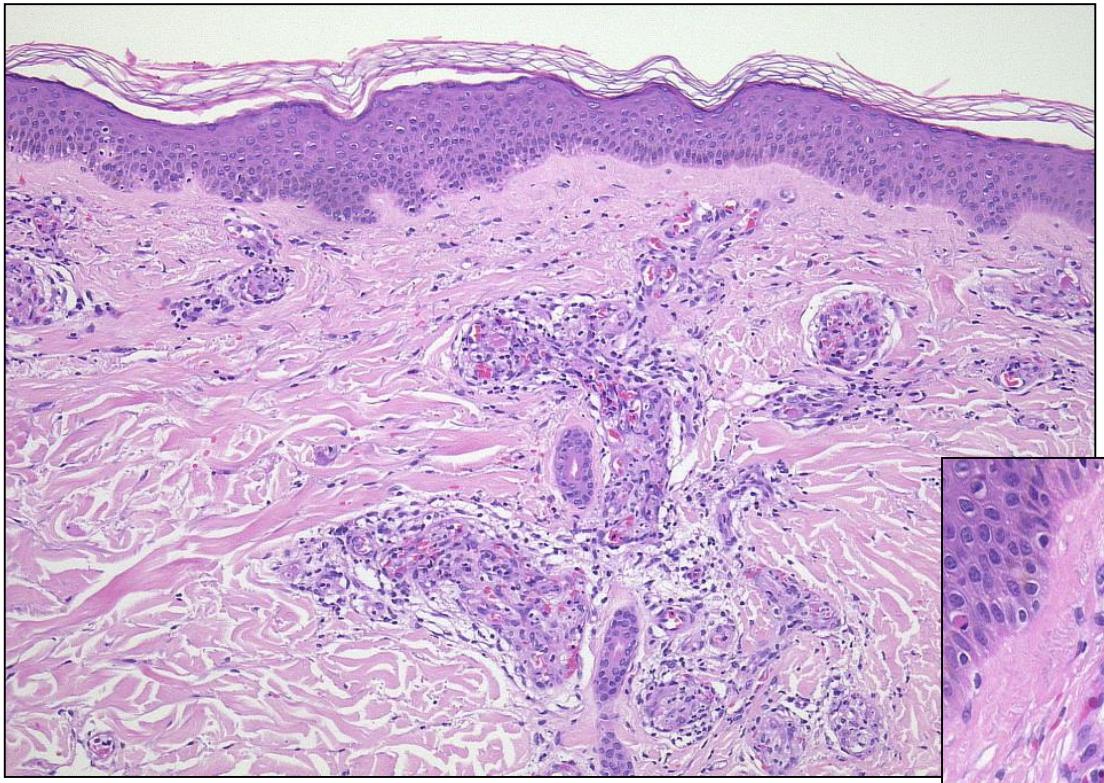
Reactive Angioendotheliomatosis

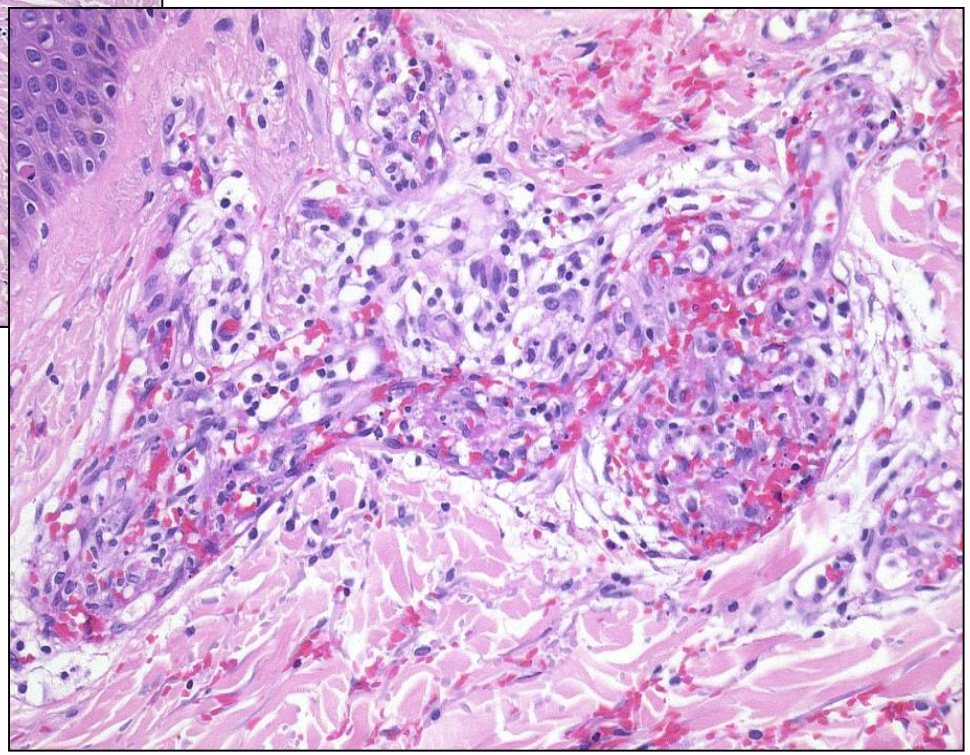


prolonged bacterial infection
following coronary bypass surgery
sudden eruption of erythemas

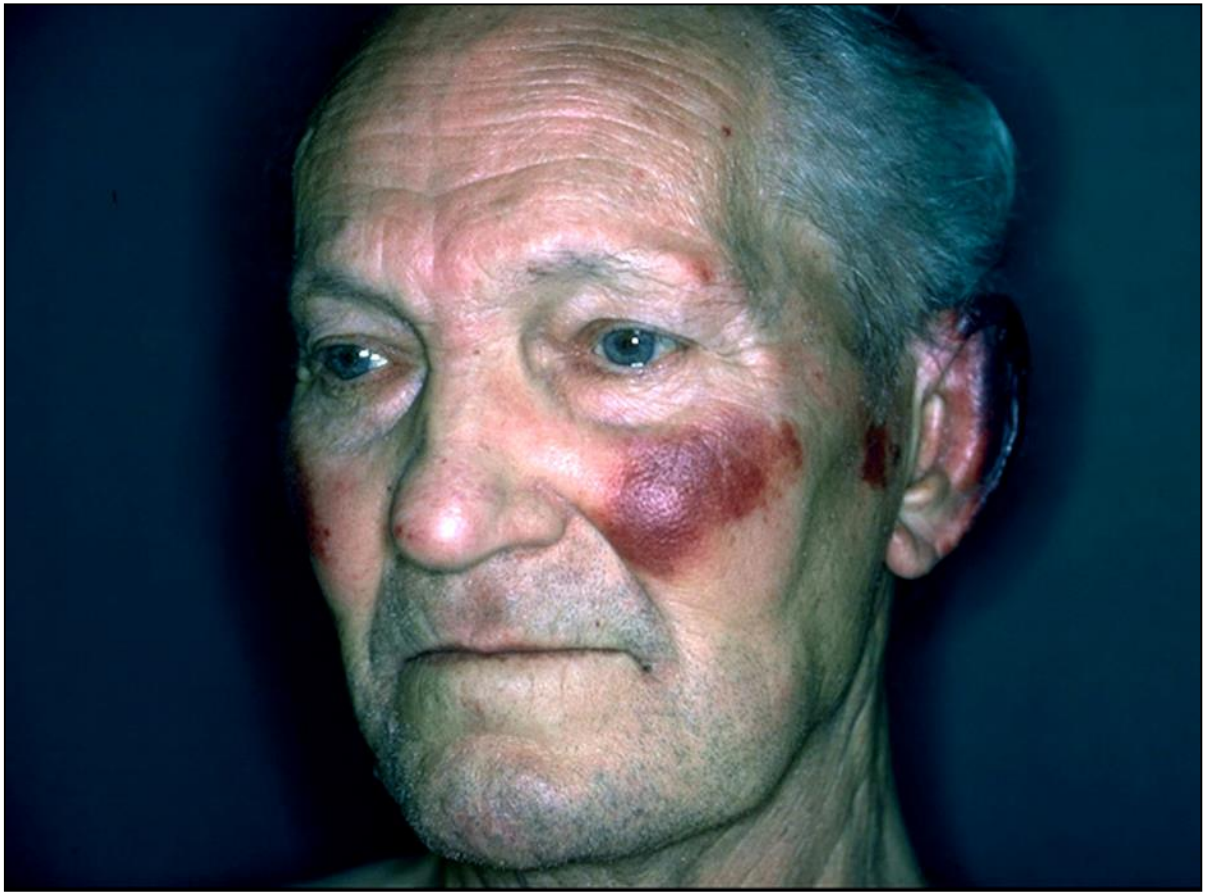


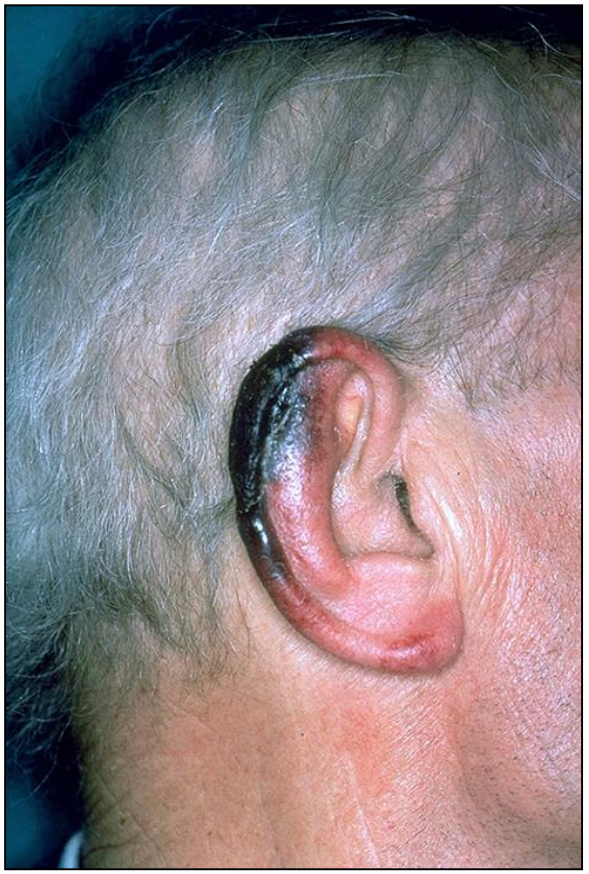
Reactive Angioendotheliomatosis



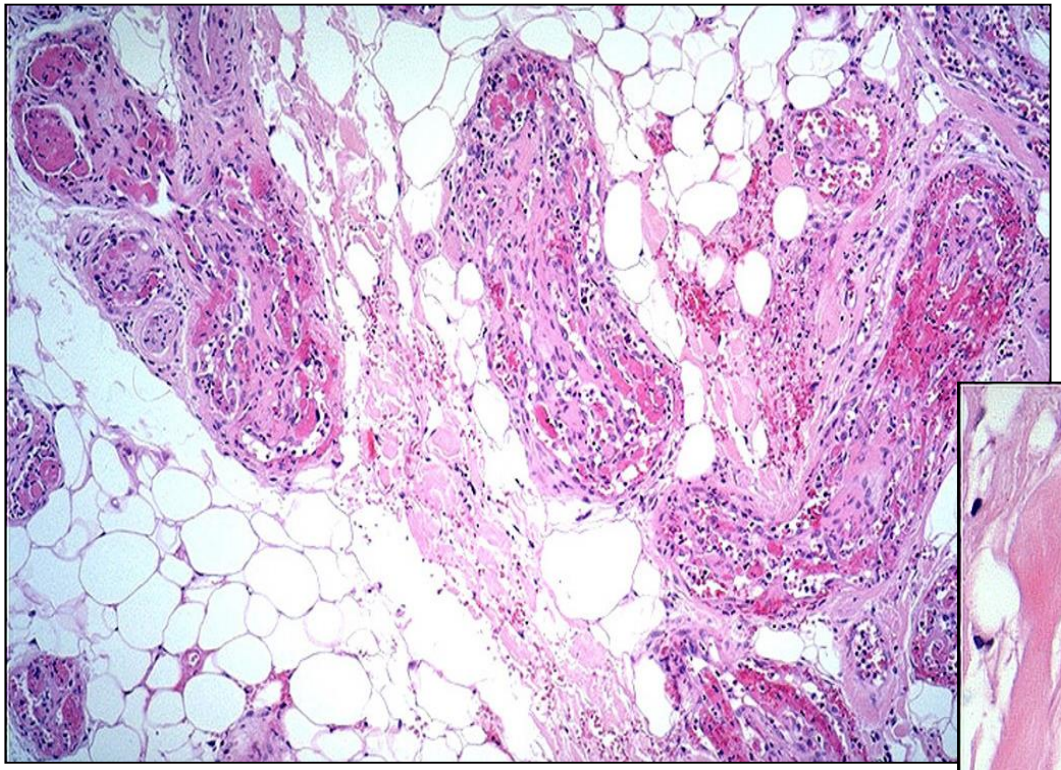


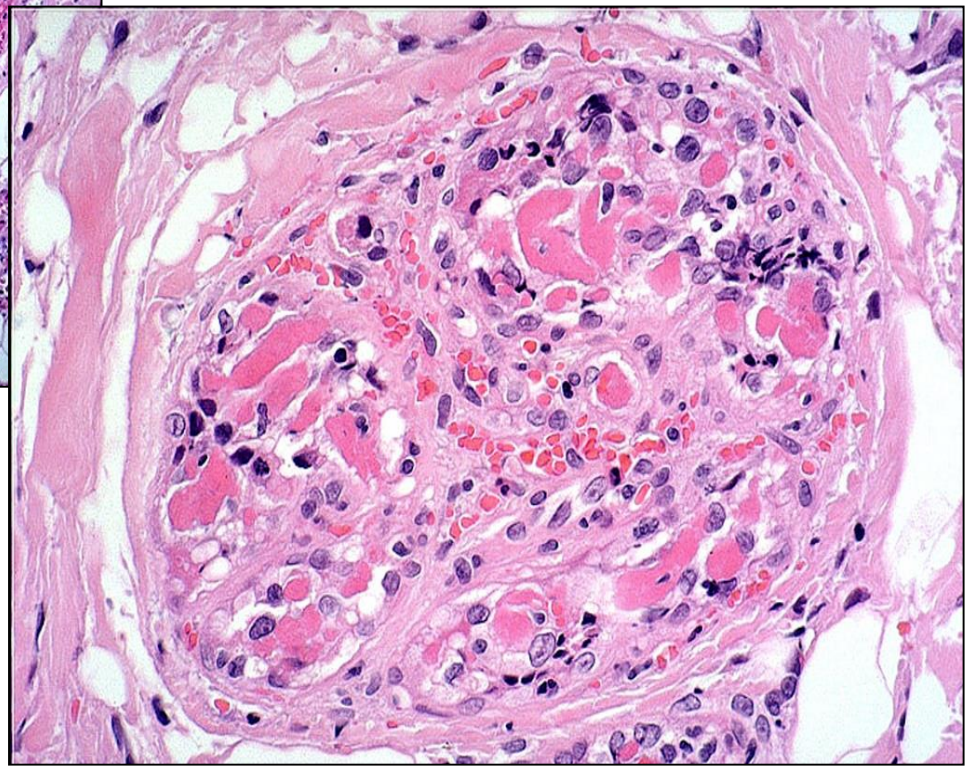
Reactive Angioendotheliomatosis in Cryoglobulinaemia



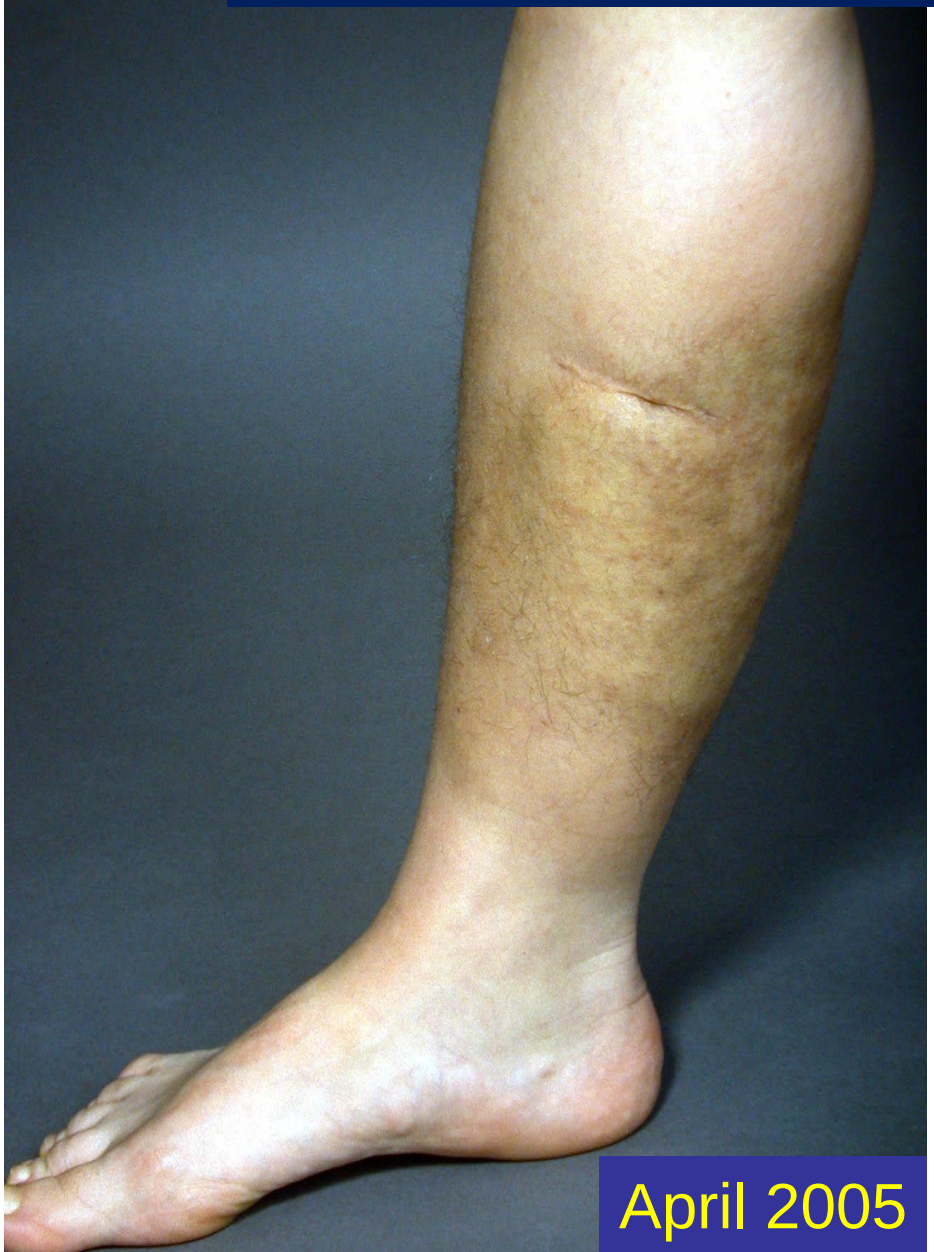


Reactive Angioendotheliomatosis in Cryoglobulinaemia

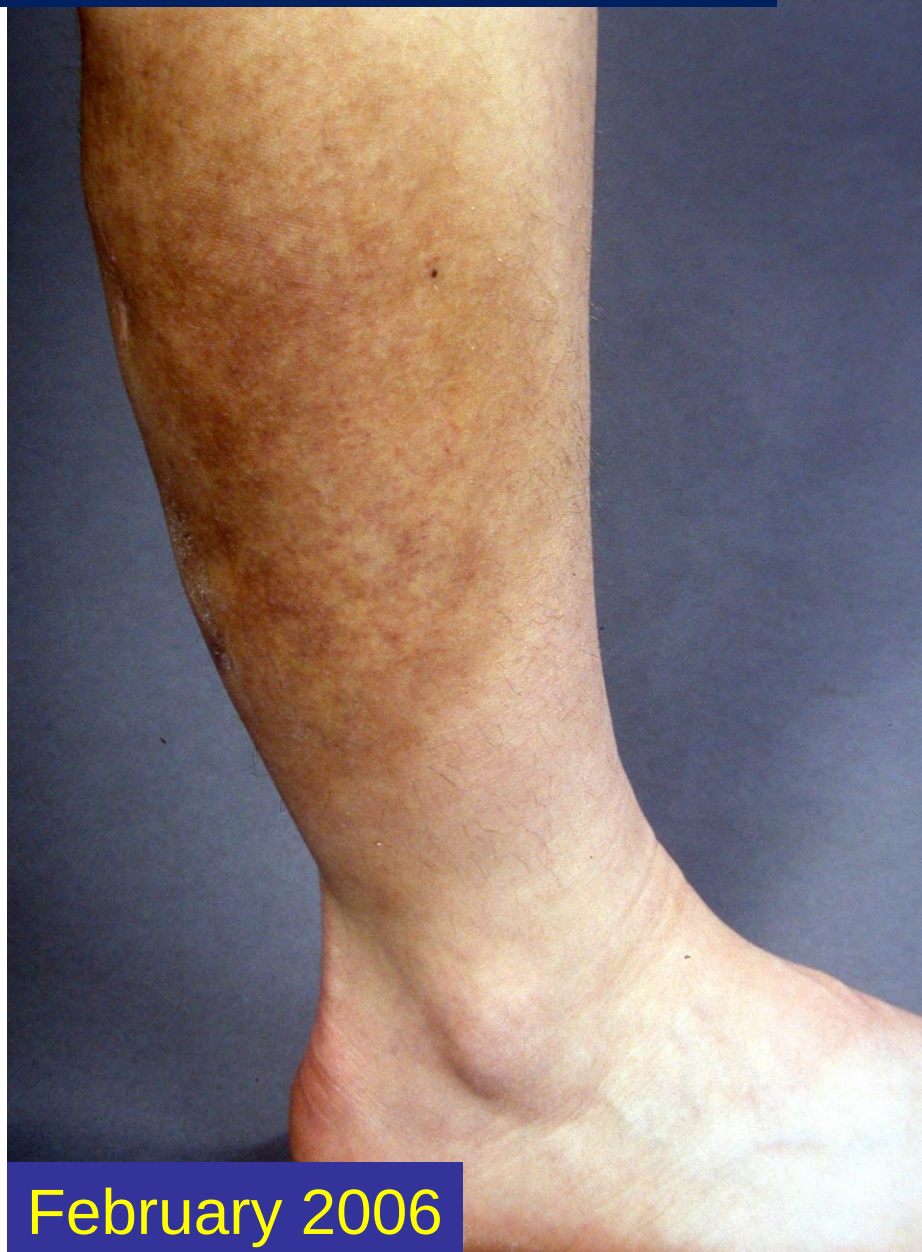




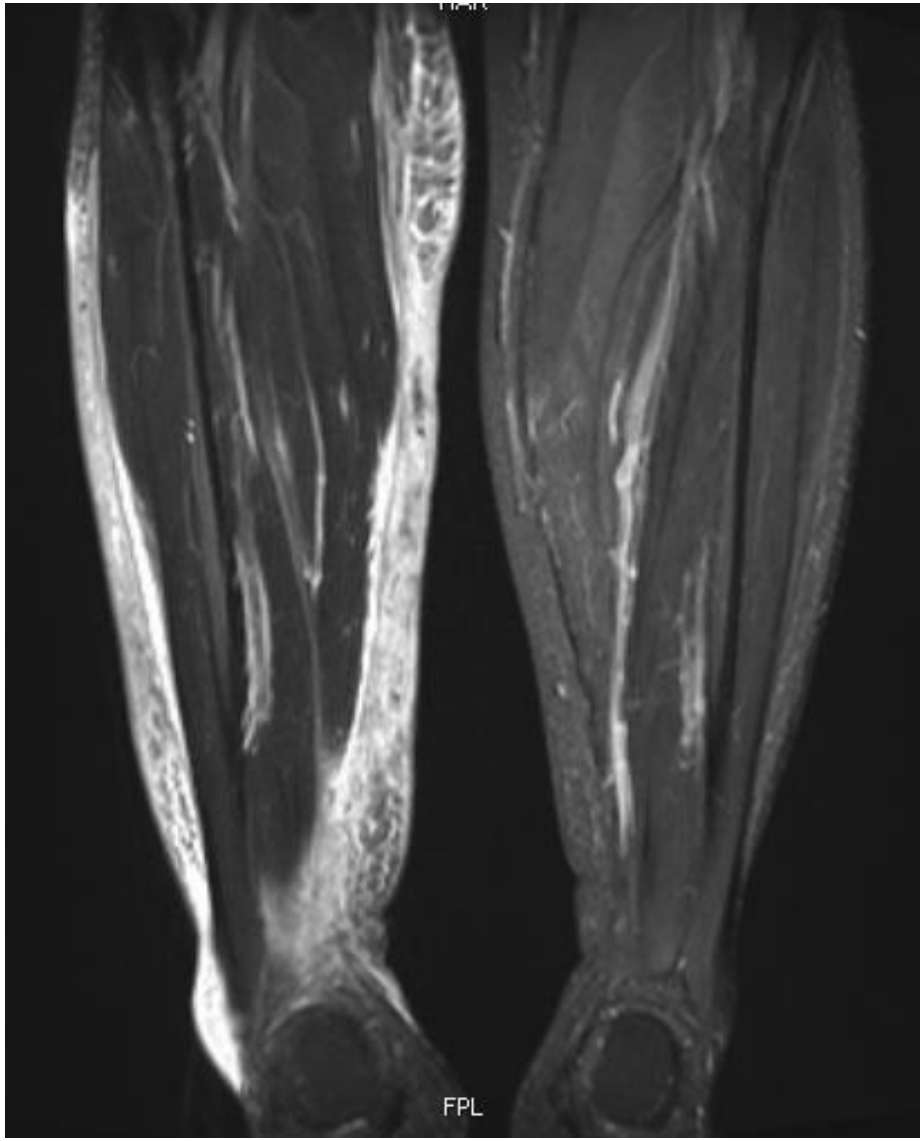
young female patient, since early childhood, slowly growing, indurated lesion



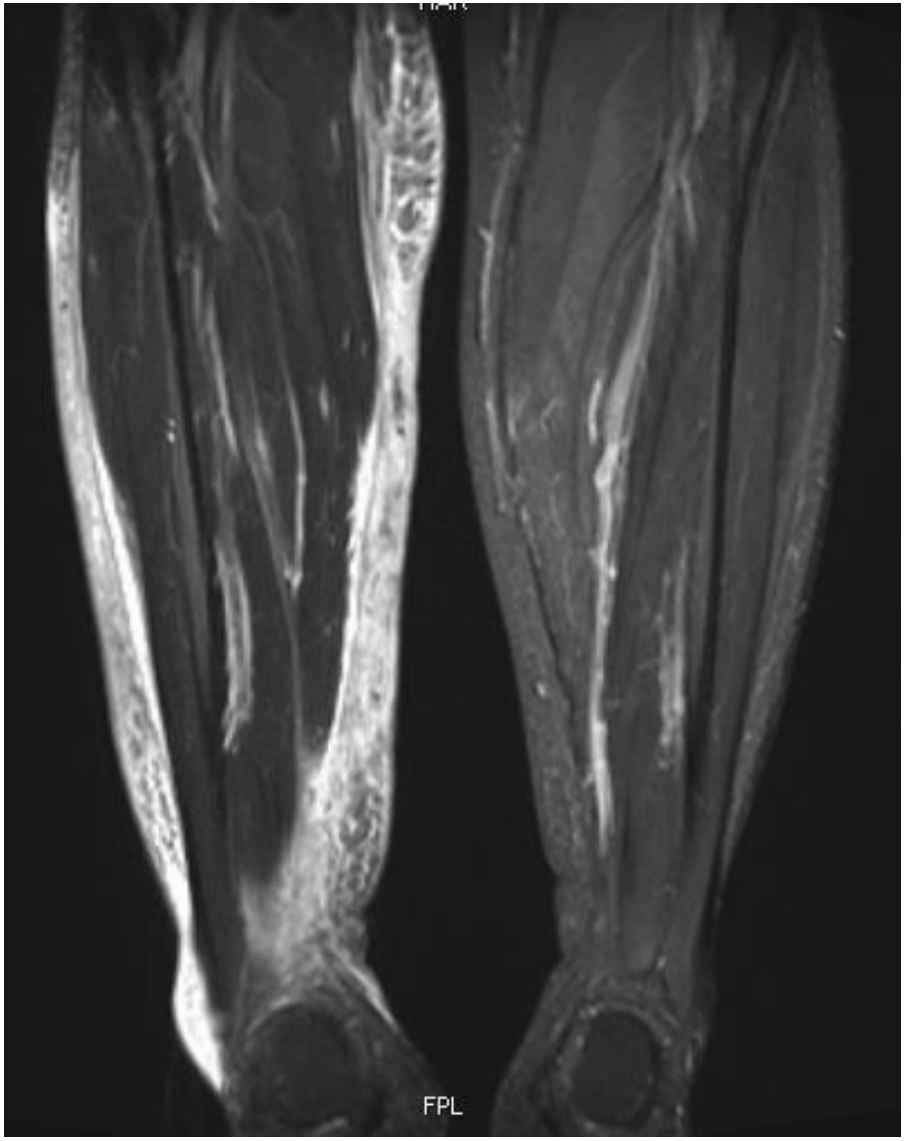
April 2005



February 2006



April 2005



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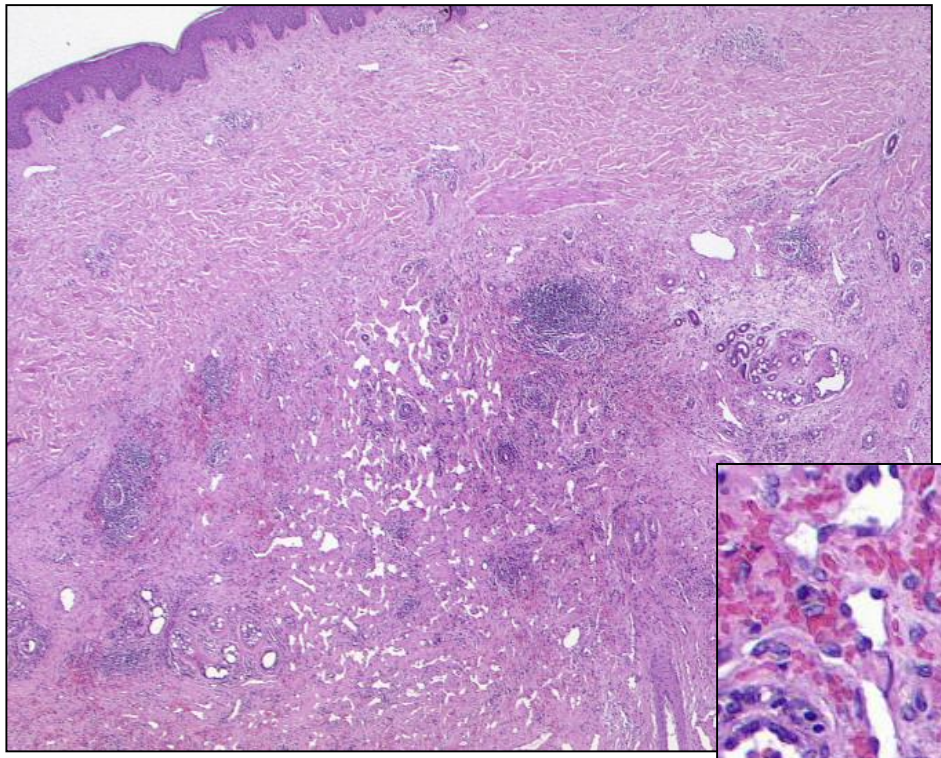
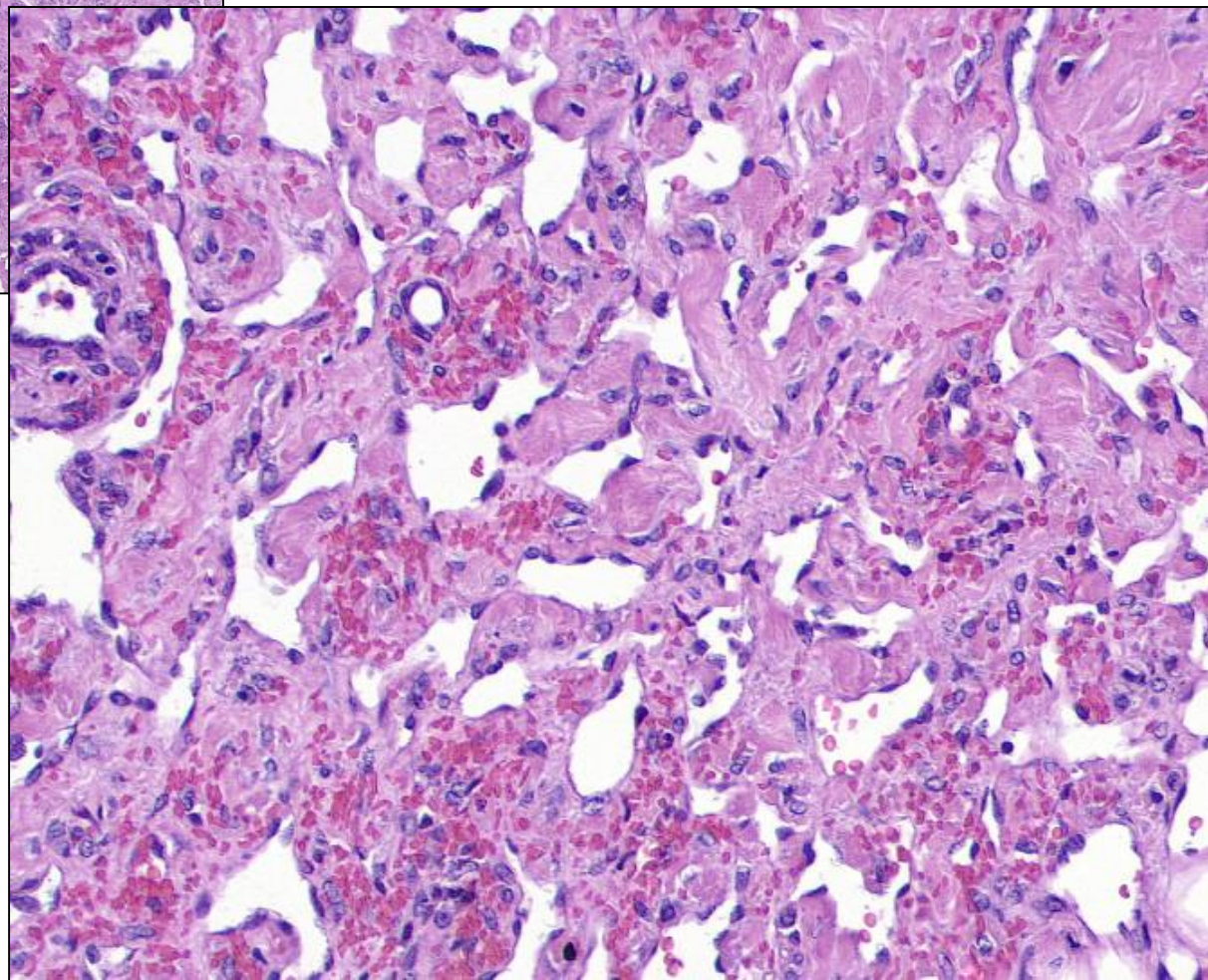
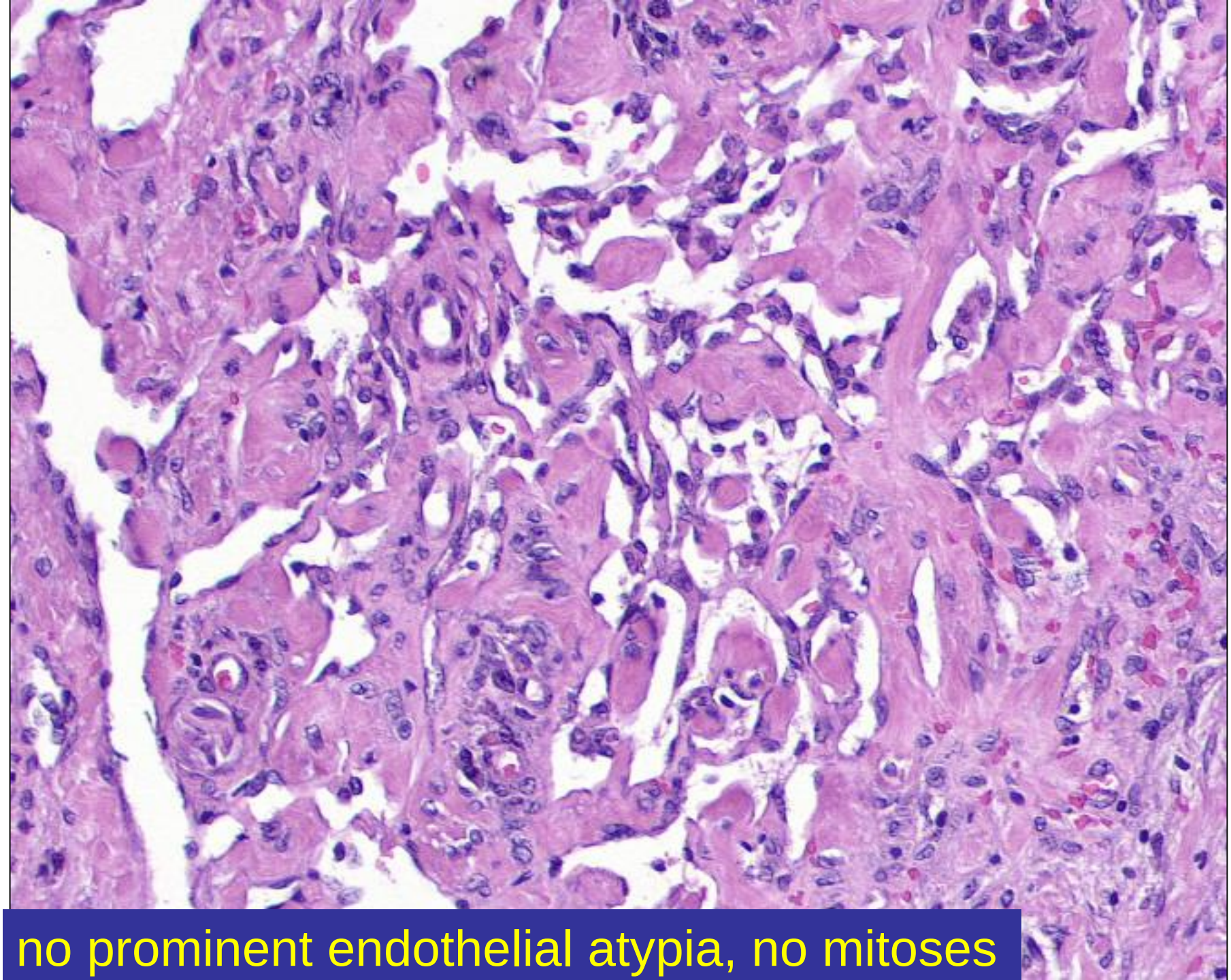
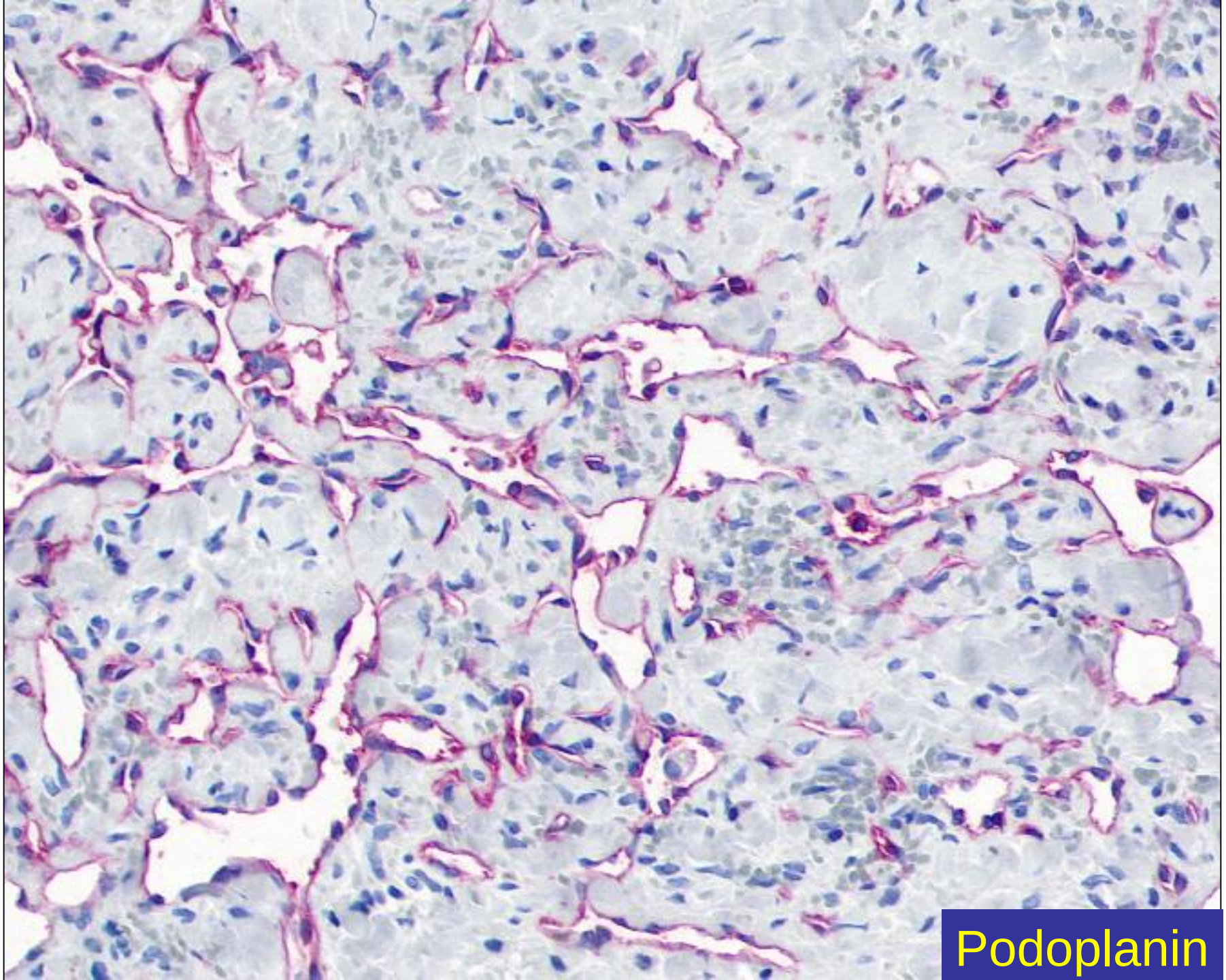
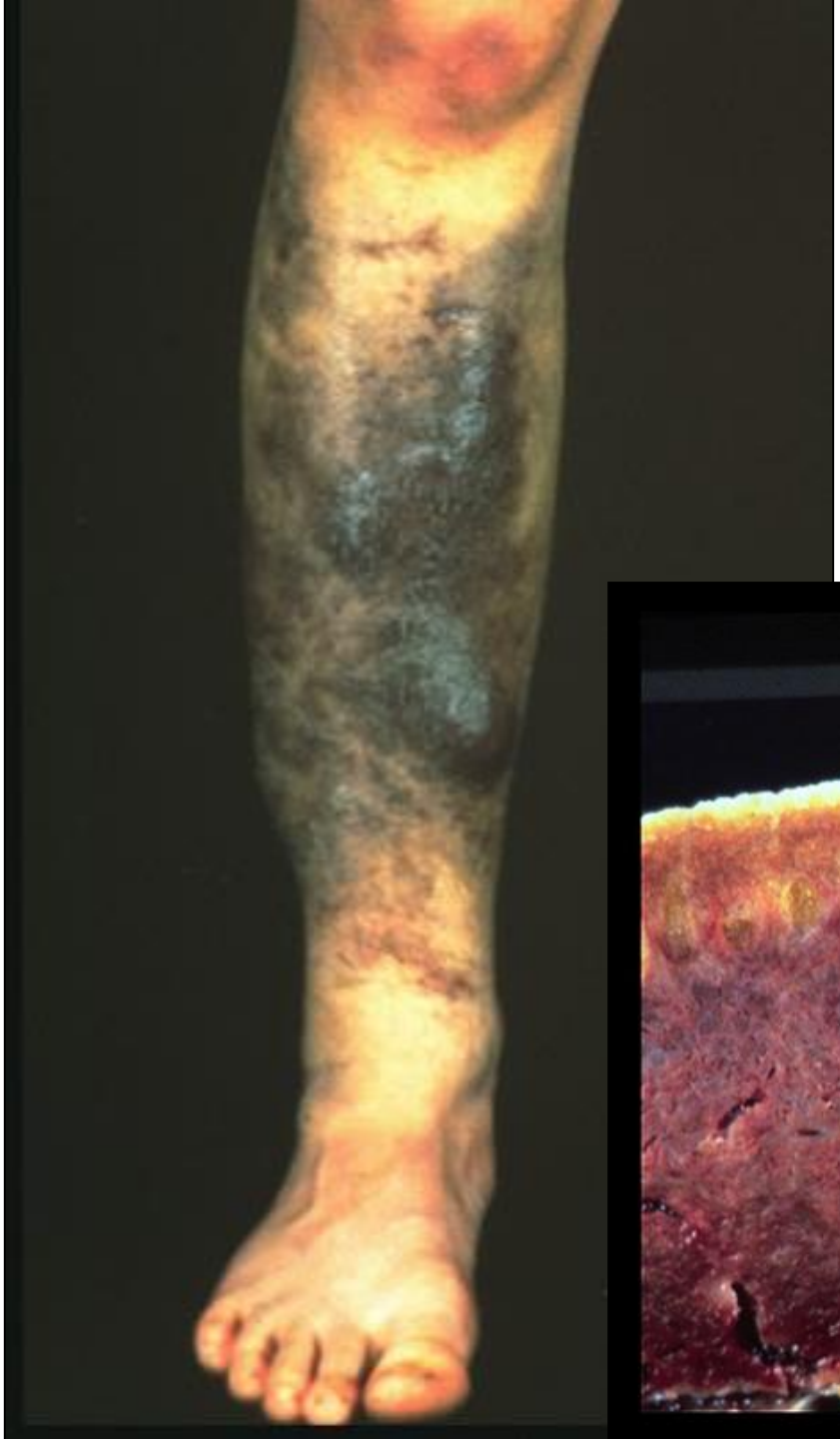


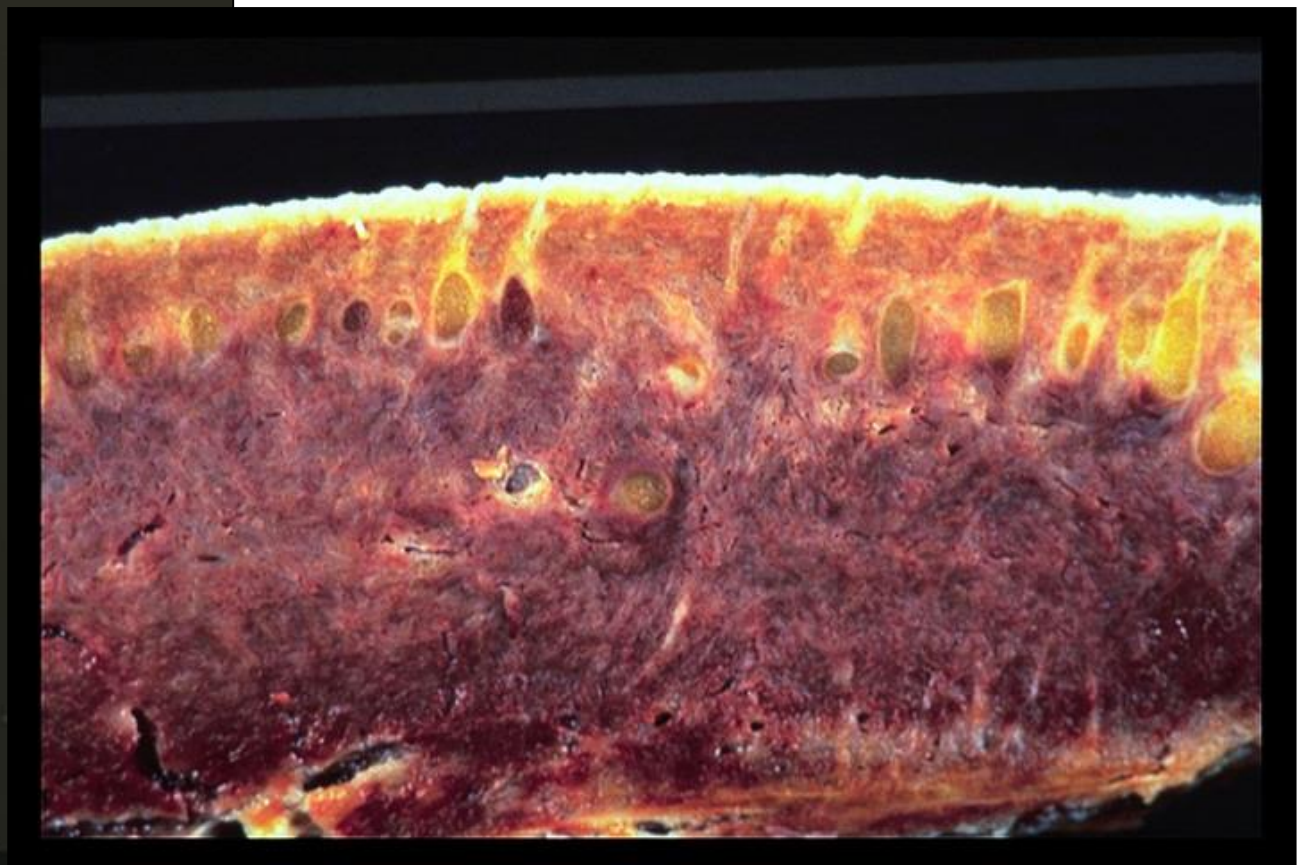



no prominent endothelial atypia, no mitoses


Podoplanin



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



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.*

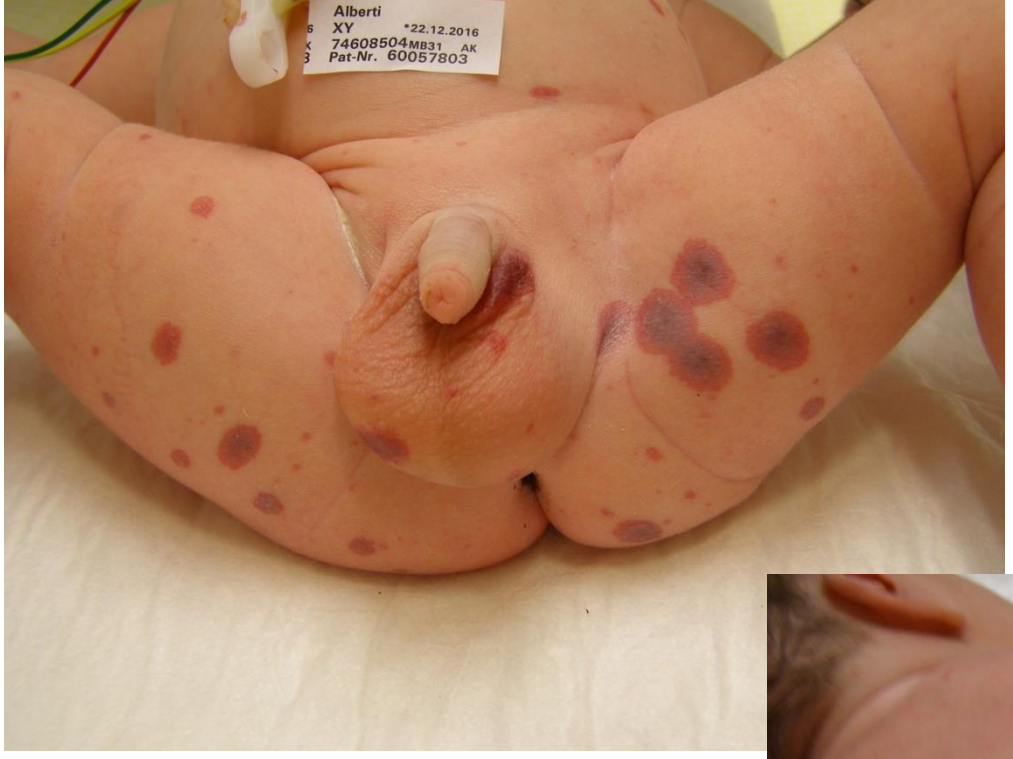
MULTIFOCAL VASCULAR tumors and malformations are relatively unusual among vascular anomalies, but are characteristic of several well-defined disorders. These include so-called neonatal hemangiomatosis (benign and disseminated),[1] blue rubber bleb nevus syndrome,[2] glomuvenous malformations,[3,4] Maffucci 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

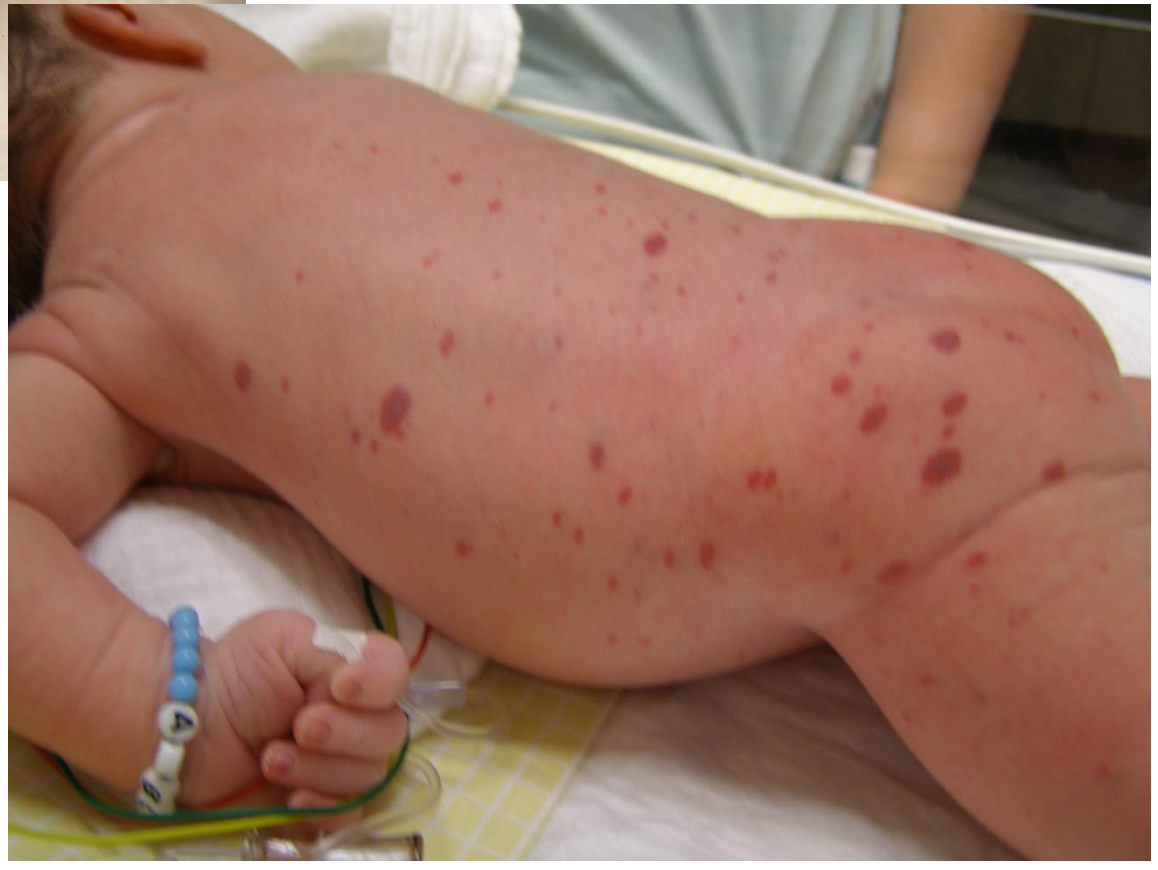
Three patients with an unusual and remarkably similar clinical presentation characterized by multiple discrete cutaneous and GI tract vascular anomalies associated with coagulopathy were identified independently at 3 different institutions. Medical records were reviewed, and hematoxylin-eosin–stained 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.

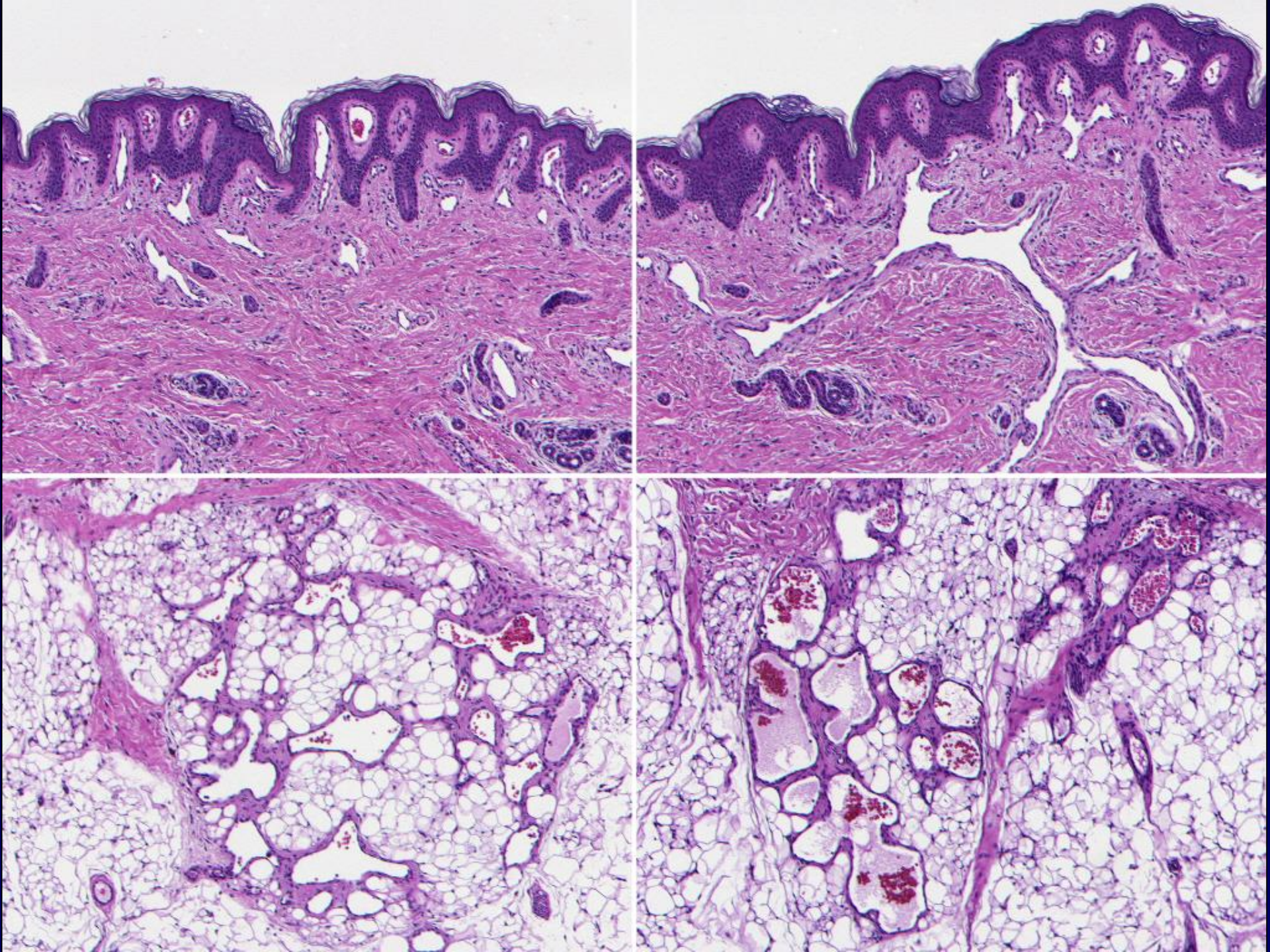
For immunofluorescent microscopy, paraffin-embedded sections (6-µm thickness) were deparaffinized, rehydrated, and treated with 0.01% protease XXIV (Sigma-Aldrich Corp,

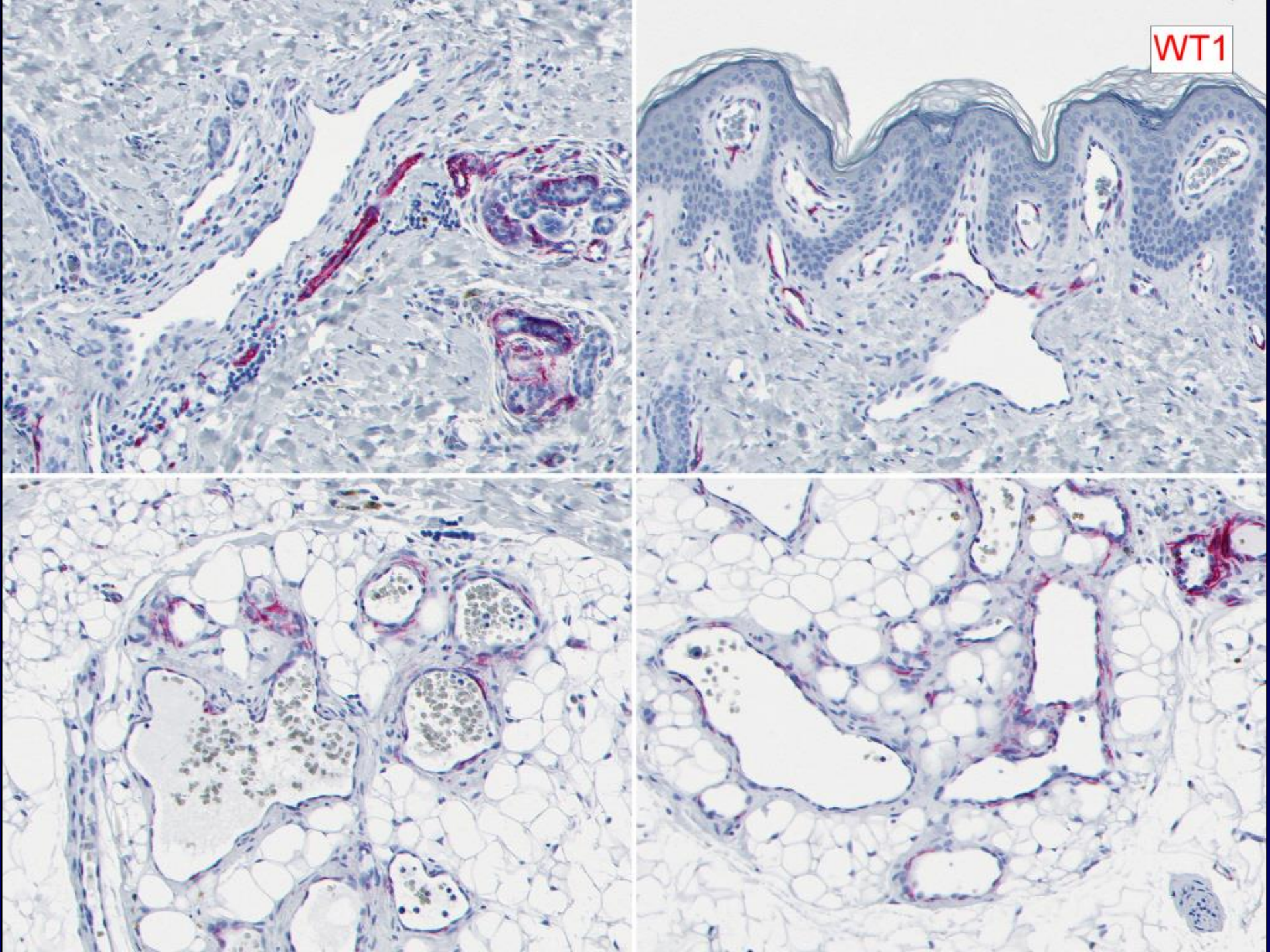
- 3 patients (2 M, 1 F, 5, 6, 13 years)
- hundreds of congenital skin plaques
- dilated vascular structures with hobnail endothelial cells, LYVE-1 +
- GI-vascular lesions with bleeding
- synovial vascular lesions (1 patient)
- significant thrombocytopenia
- vascular lesions of lymphatic diff.
- association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



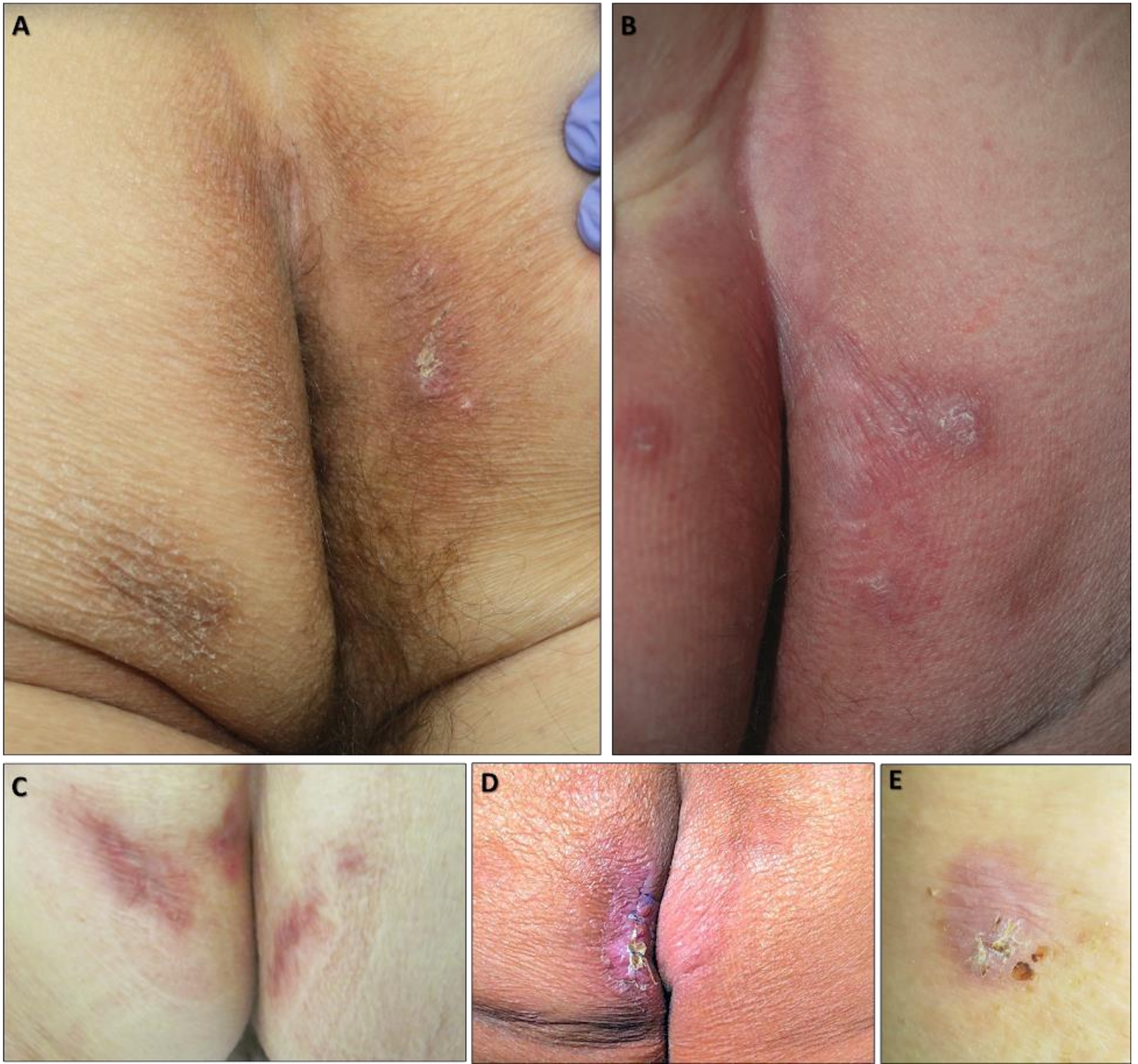


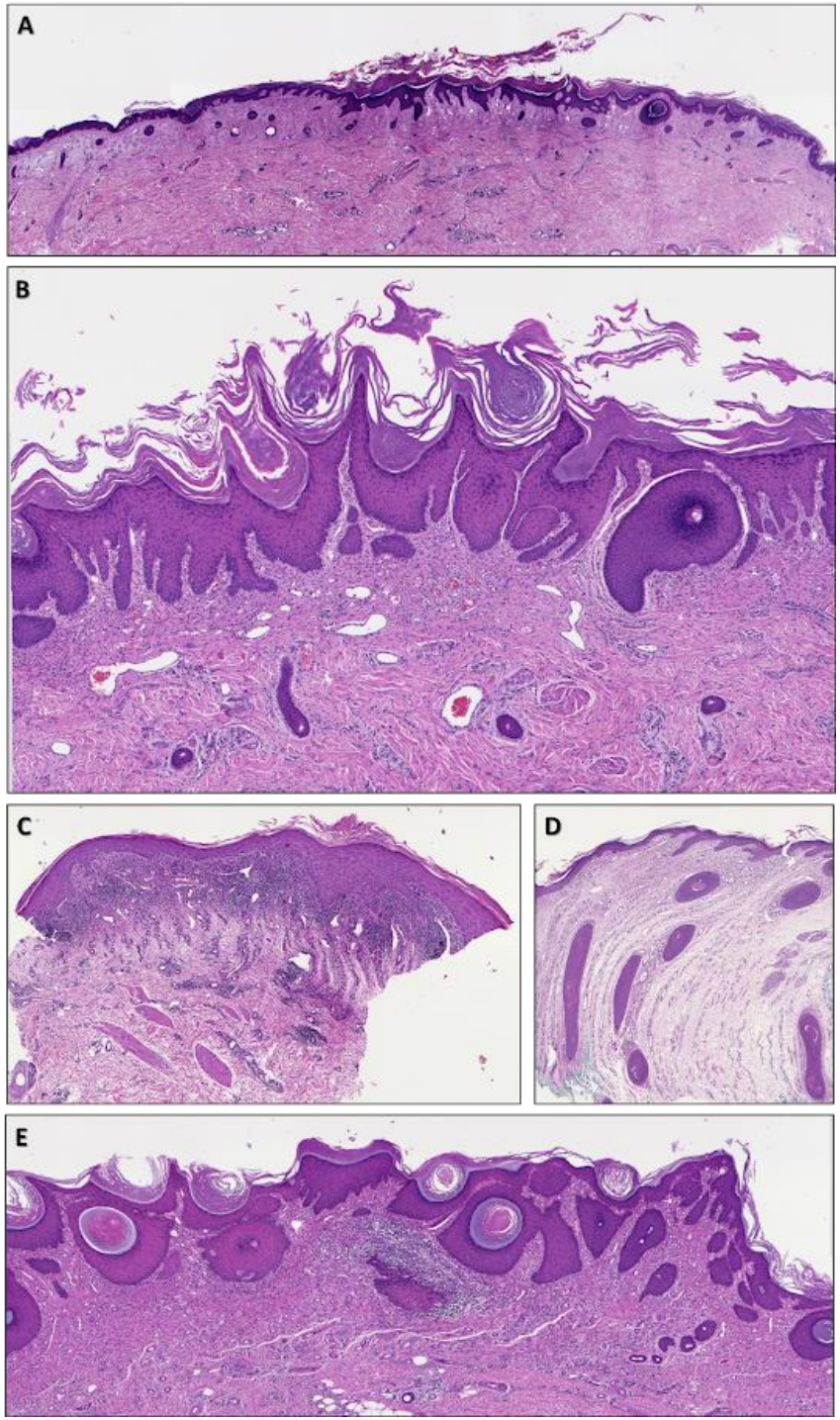

WT1

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
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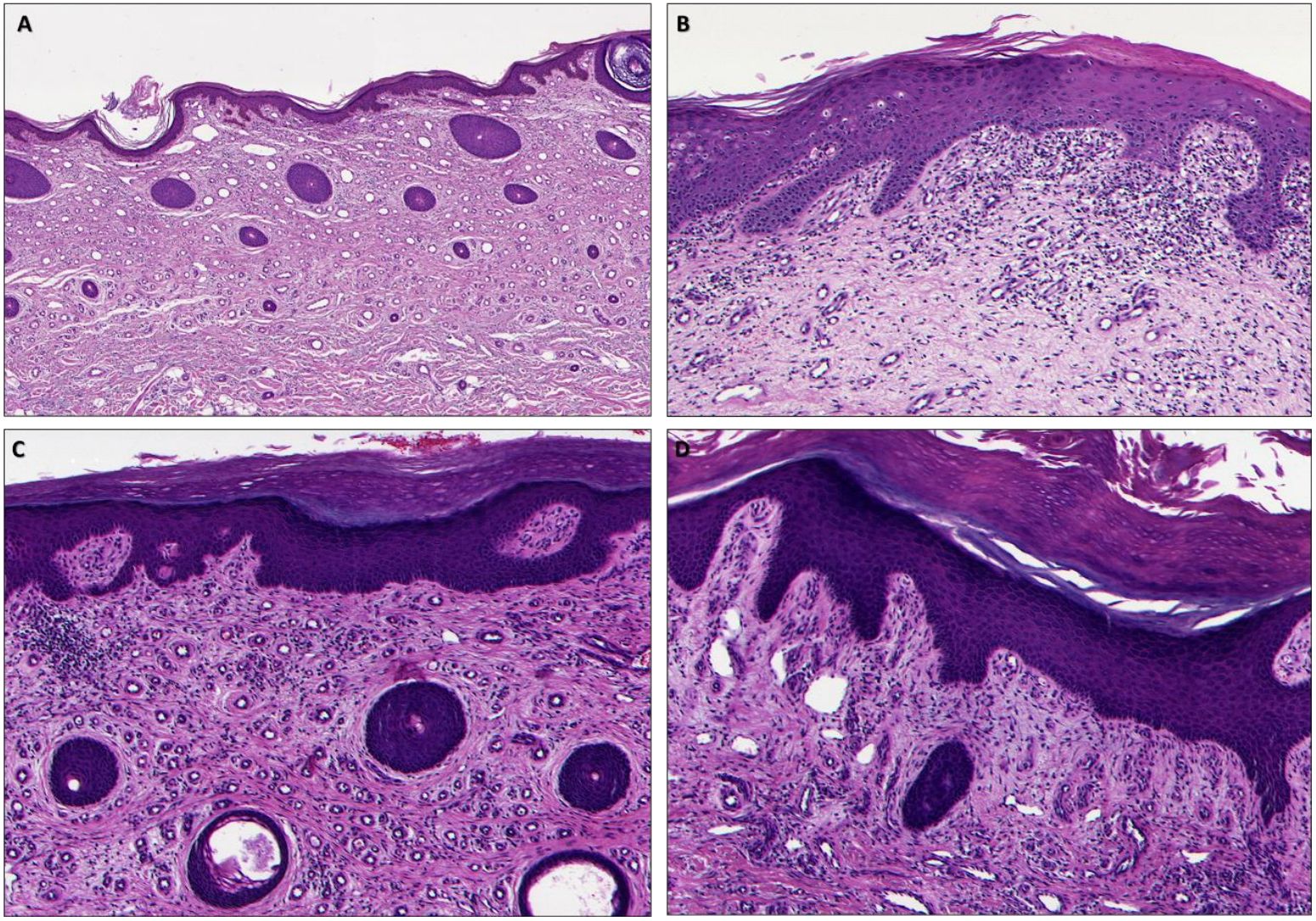
A
B
C
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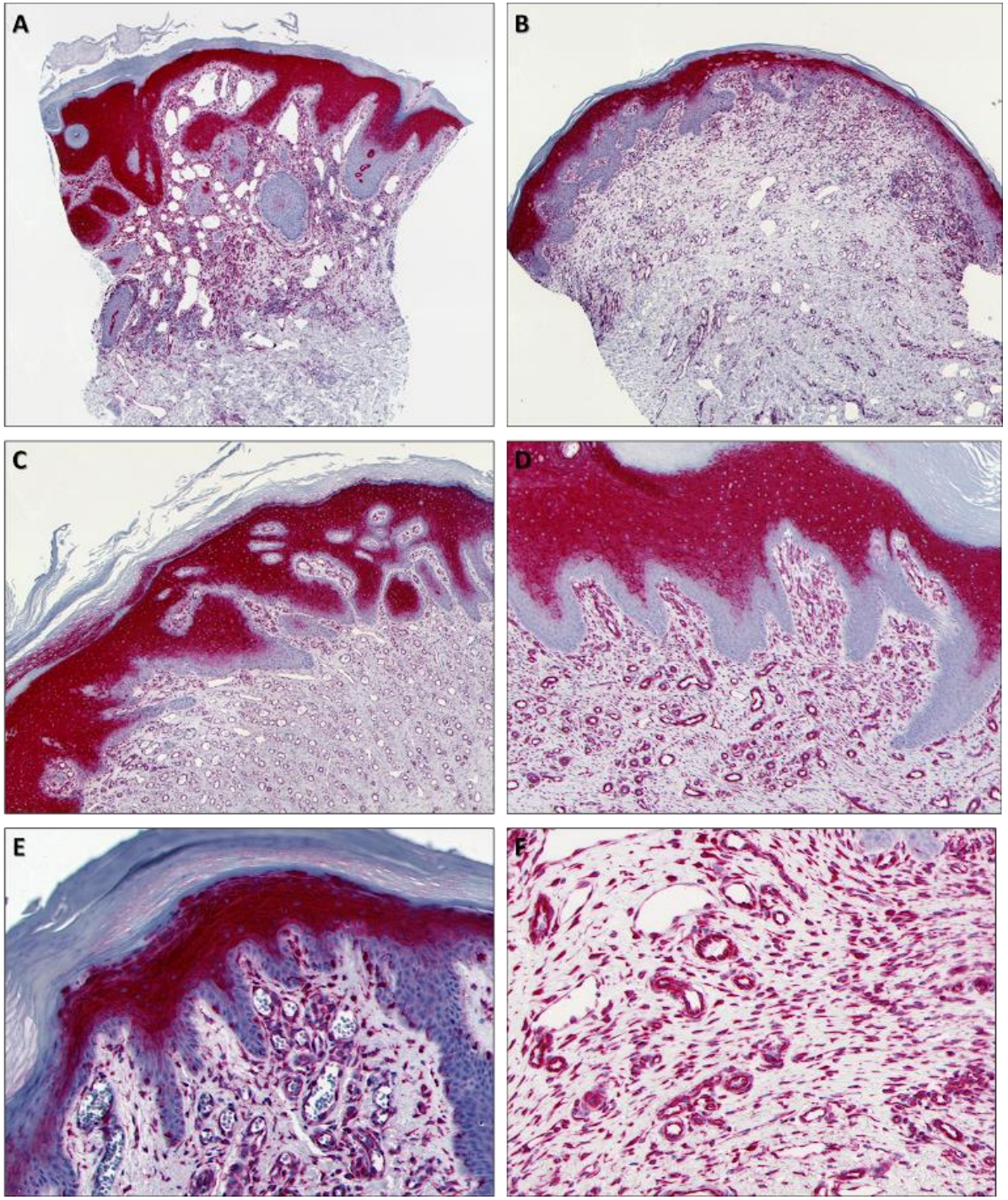
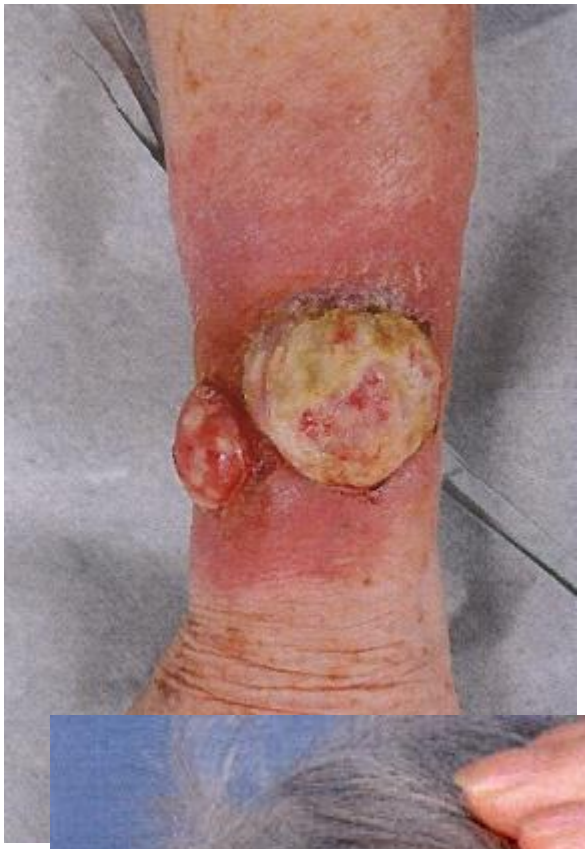
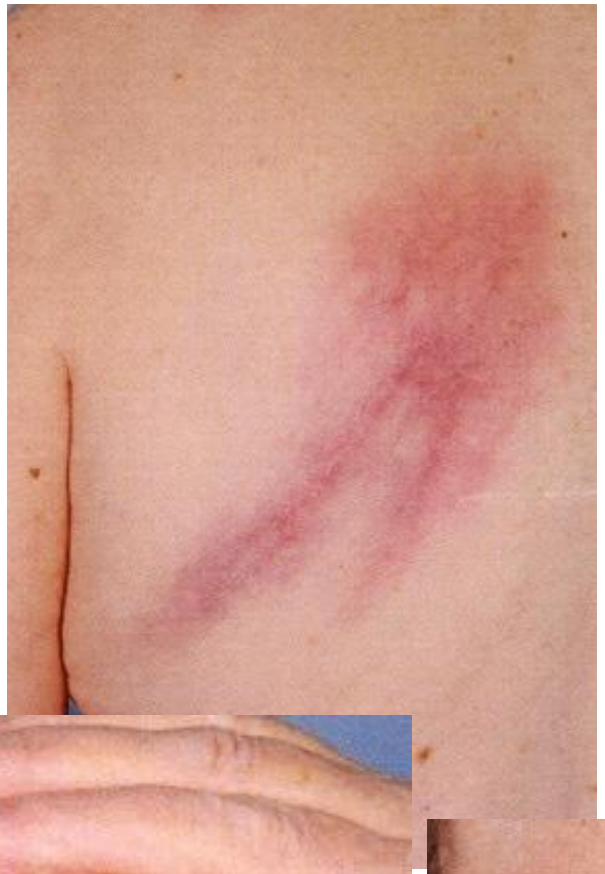
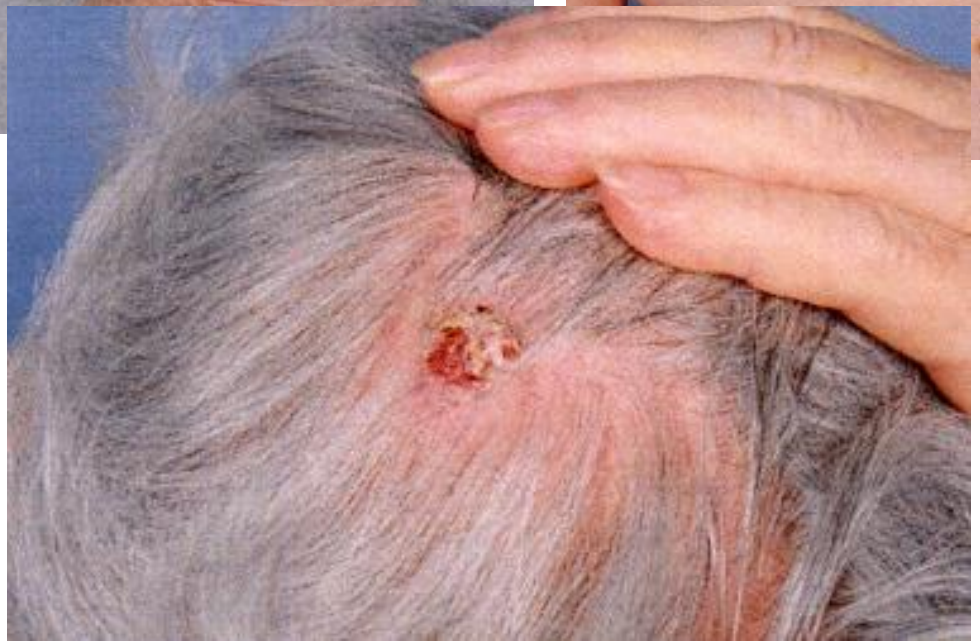
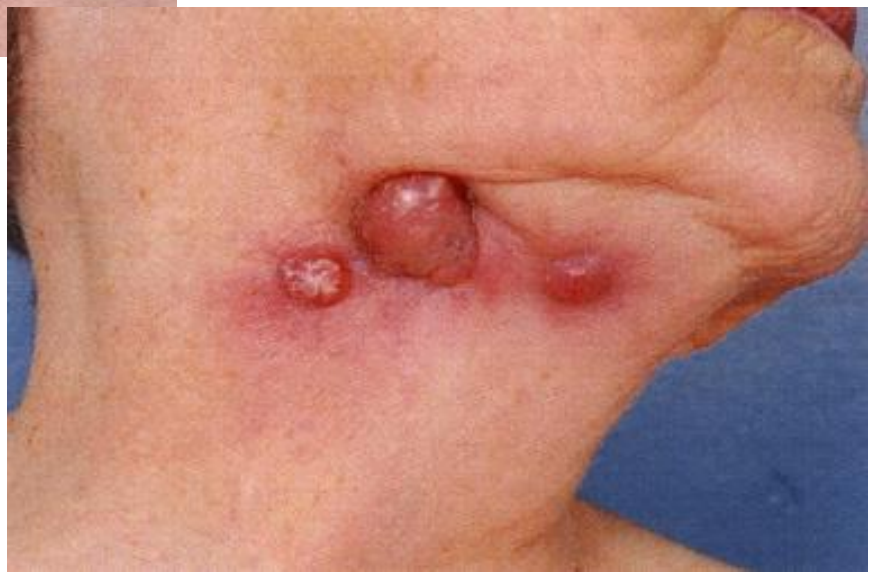


VEGF

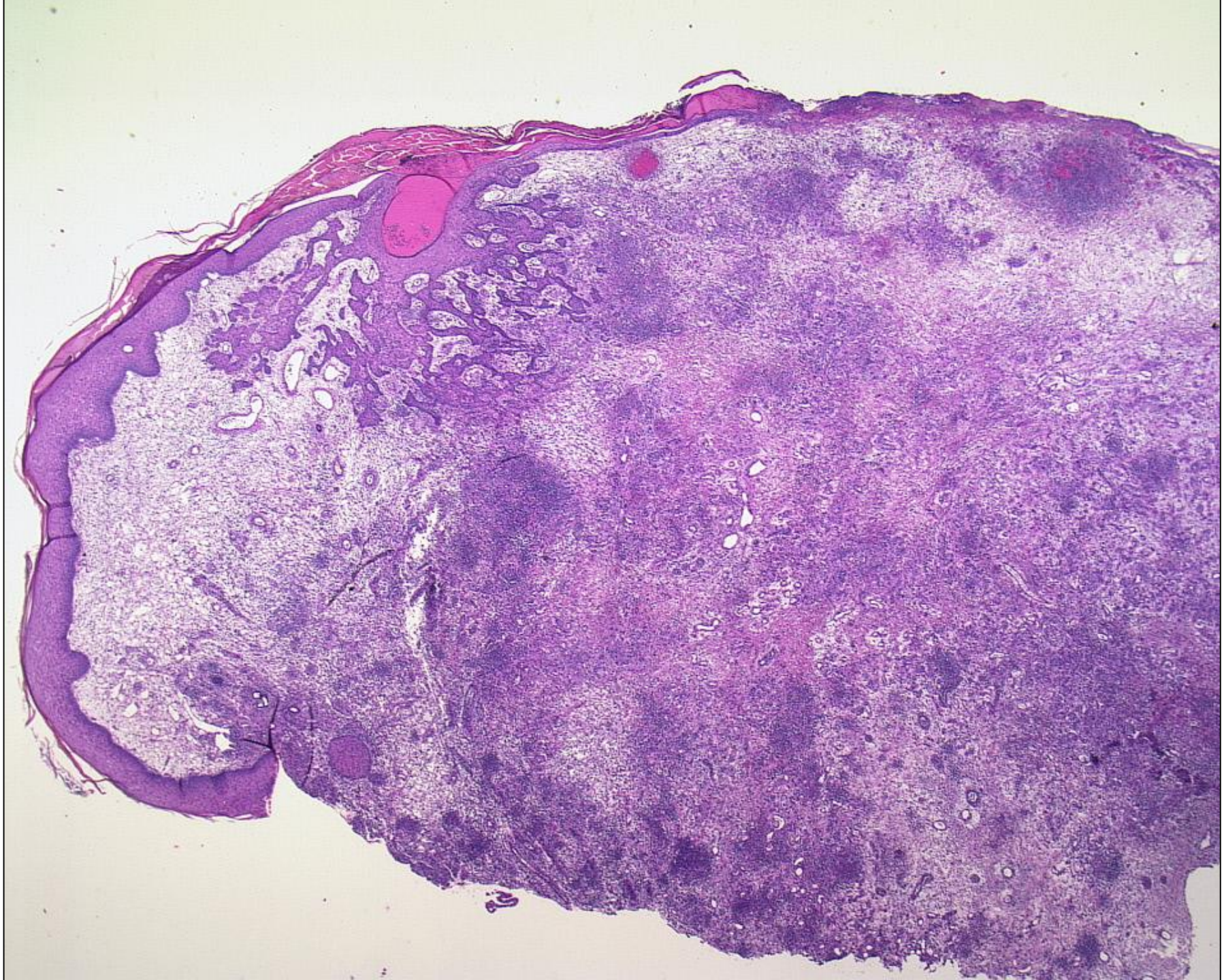


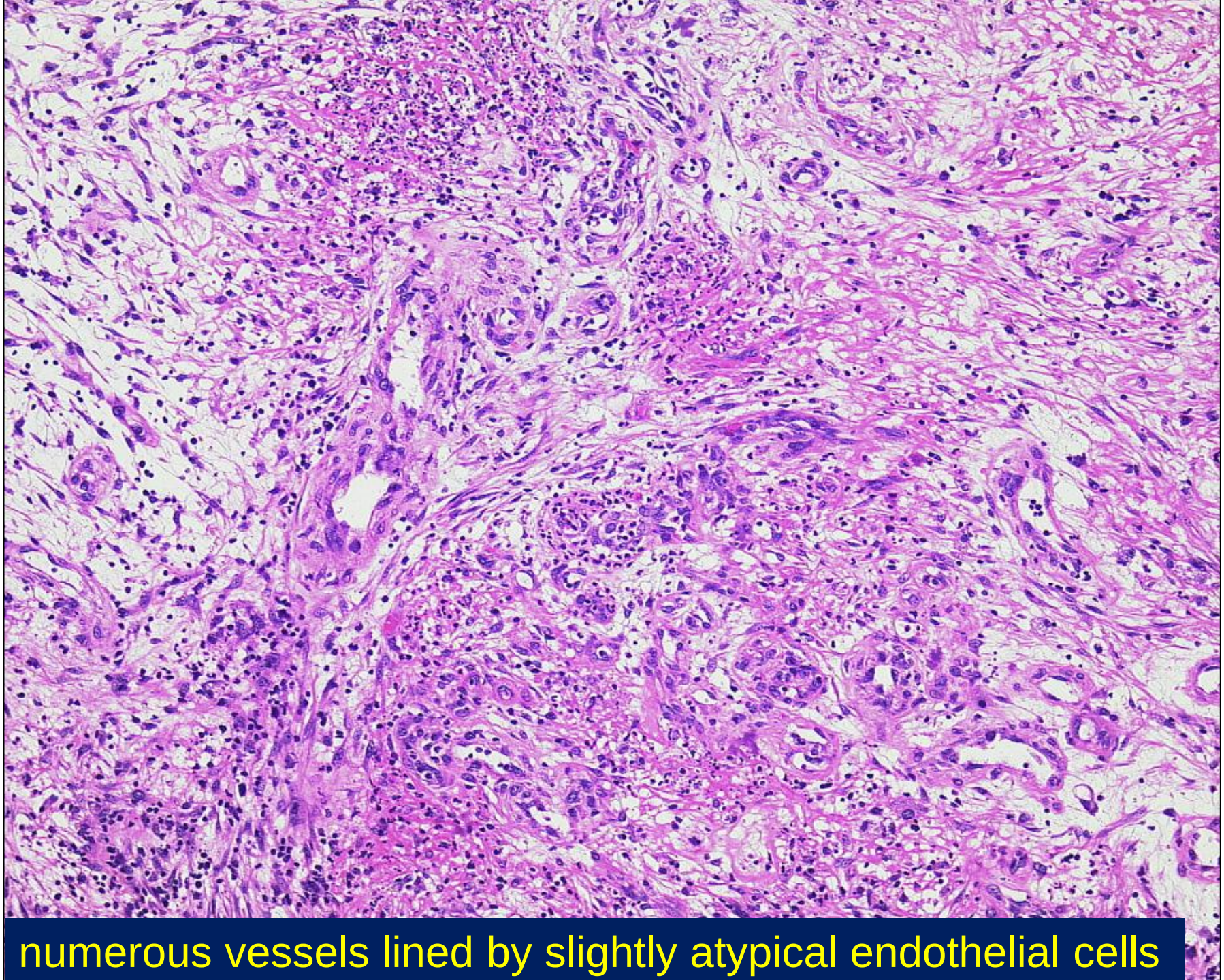




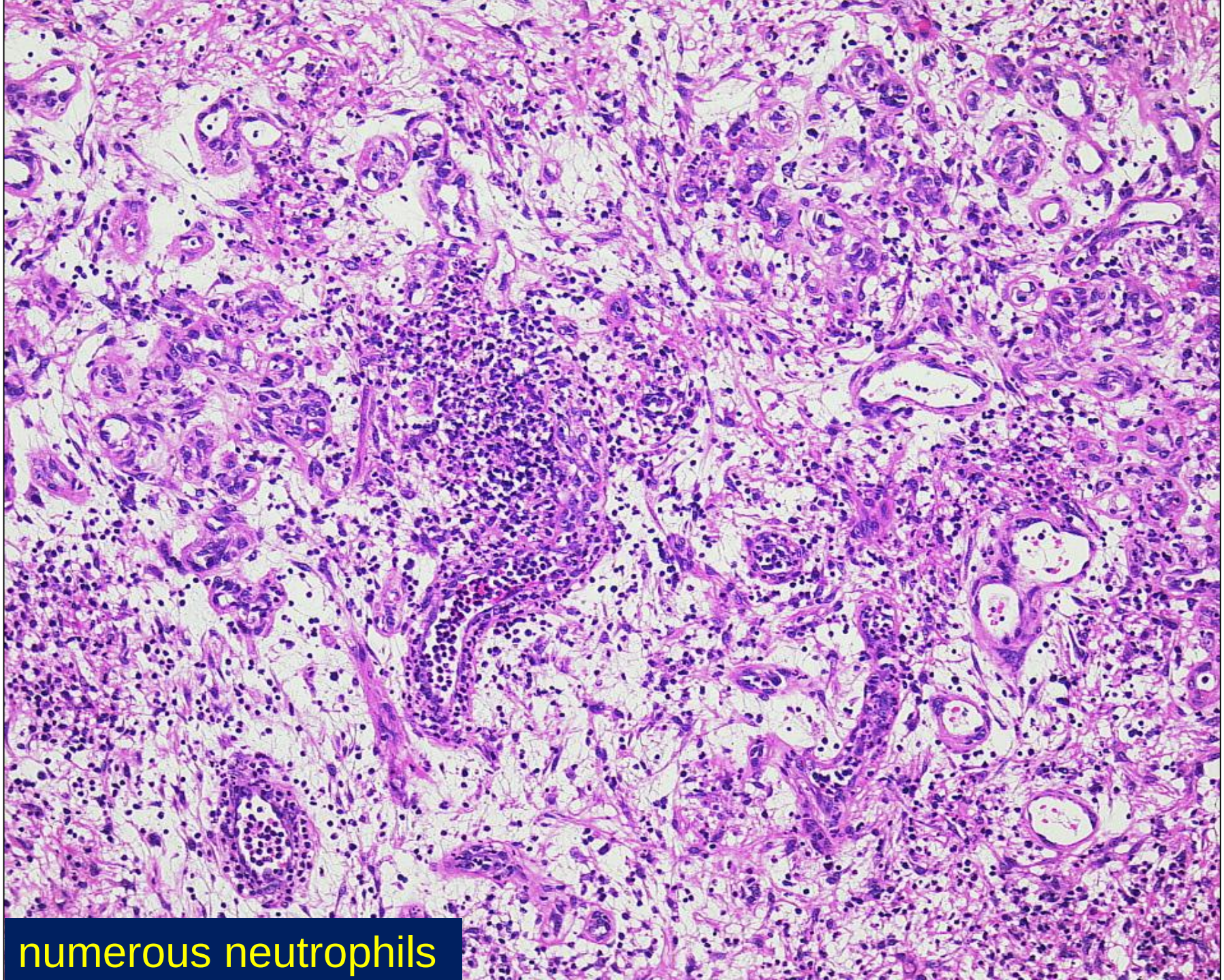


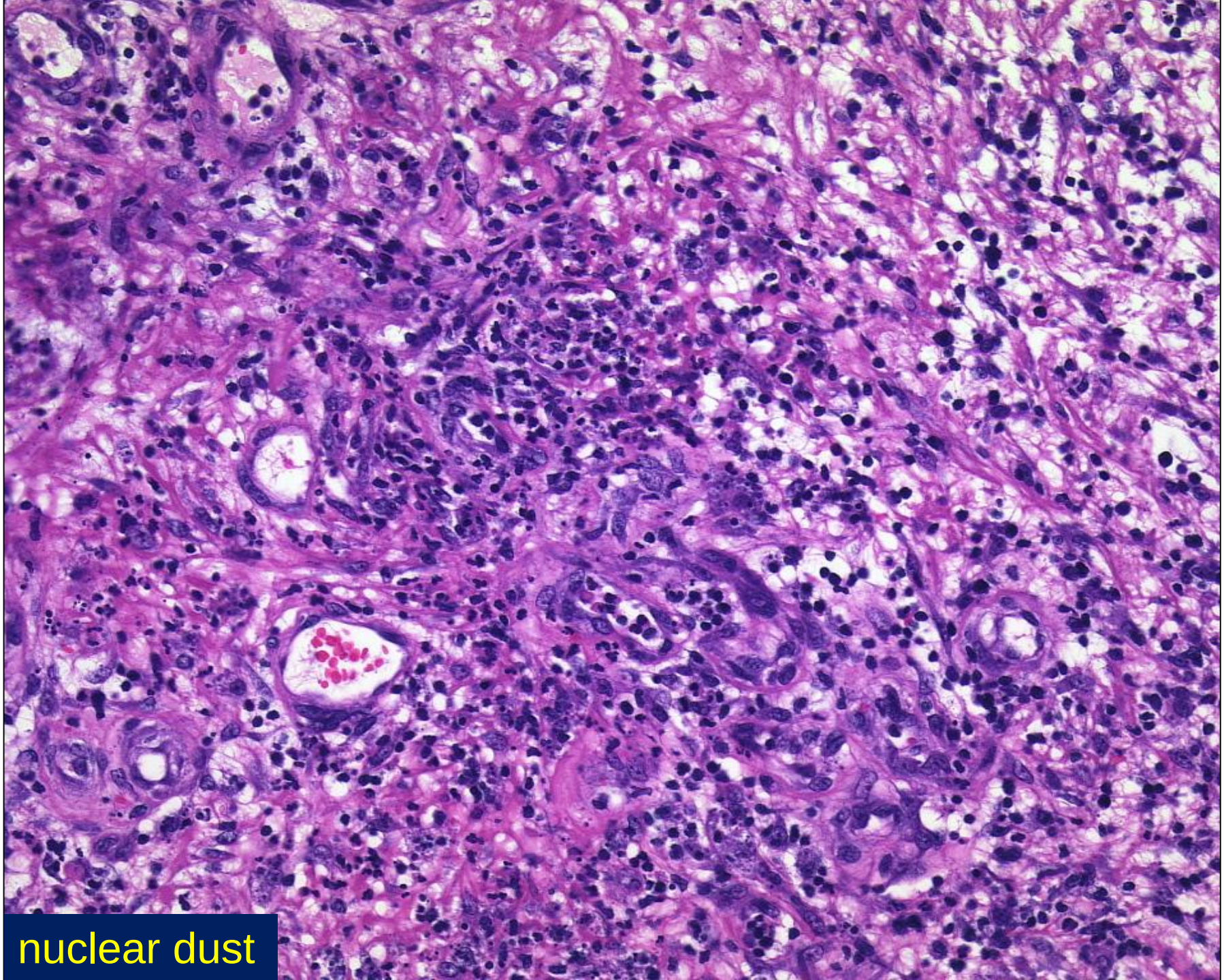
F, 81 years
previous breast cancer and CLL
since 6/12 nodular, ulcerated skin lesions
? angiosarcoma

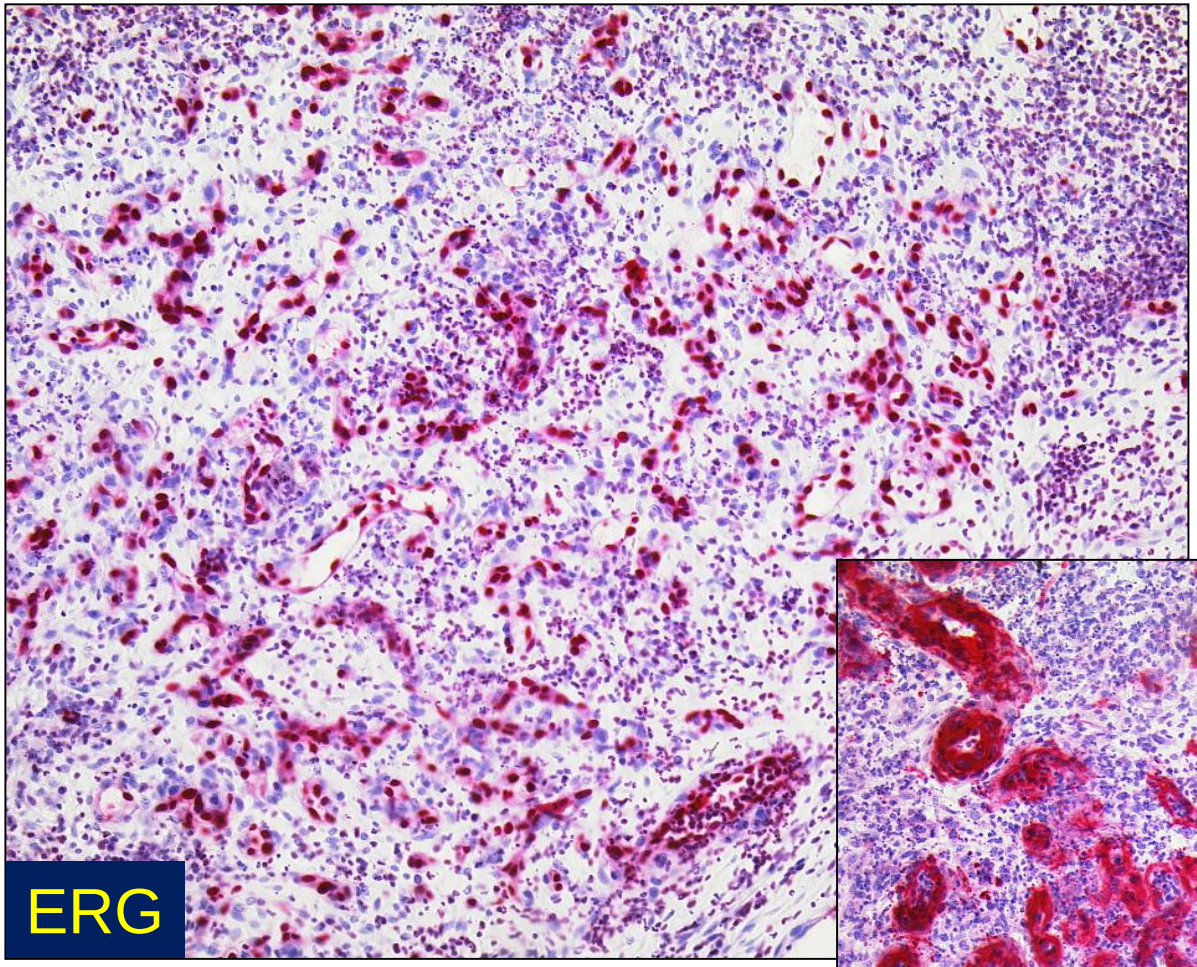


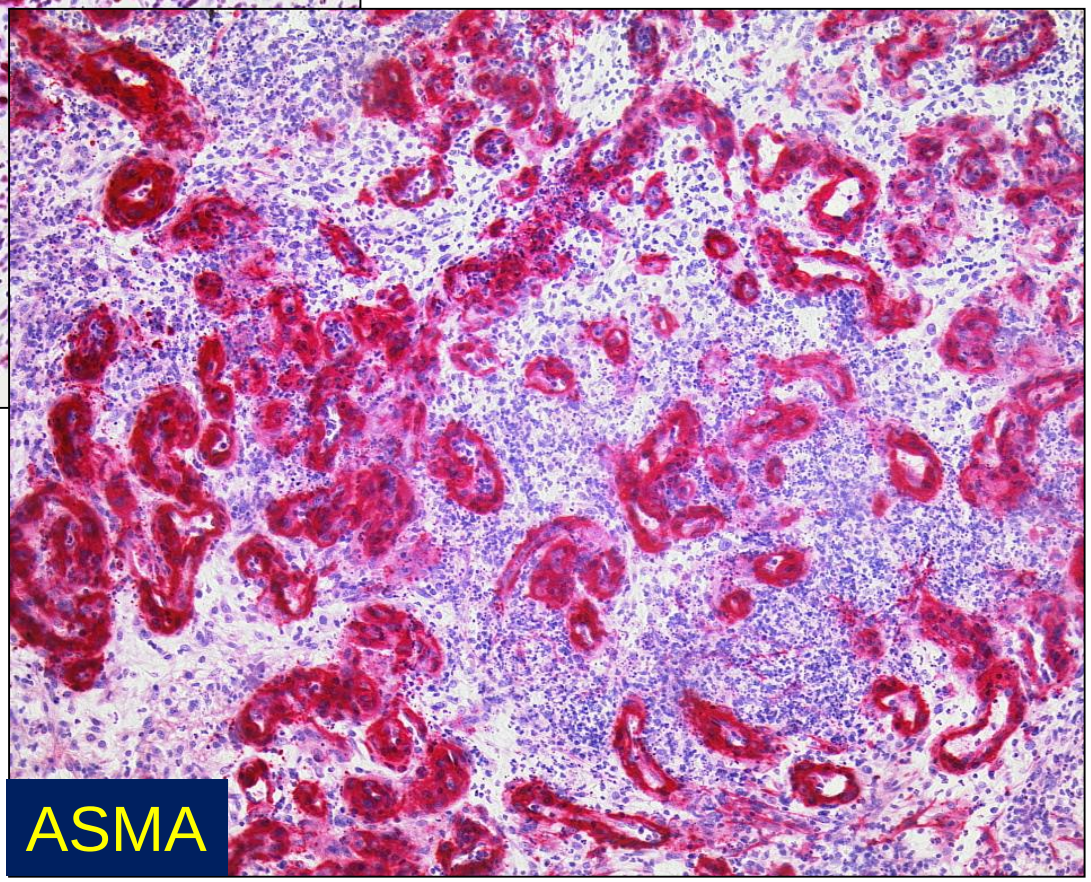


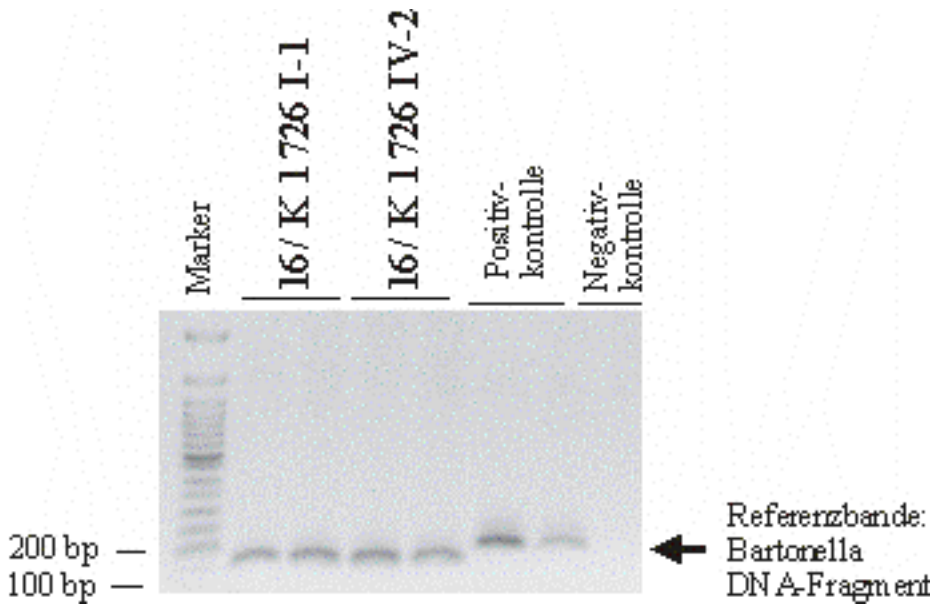
numerous vessels lined by slightly atypical endothelial cells


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

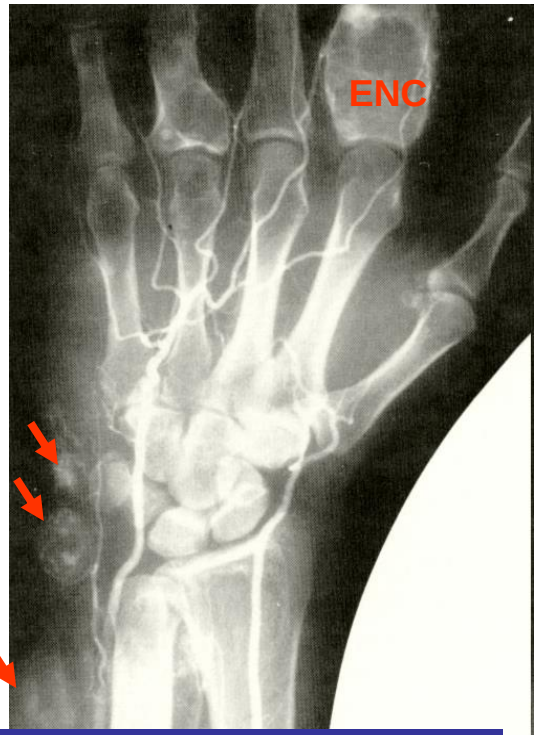
„Borderline“ malignant vascular tumours (Haemangioendotheliomas)

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 ⬆

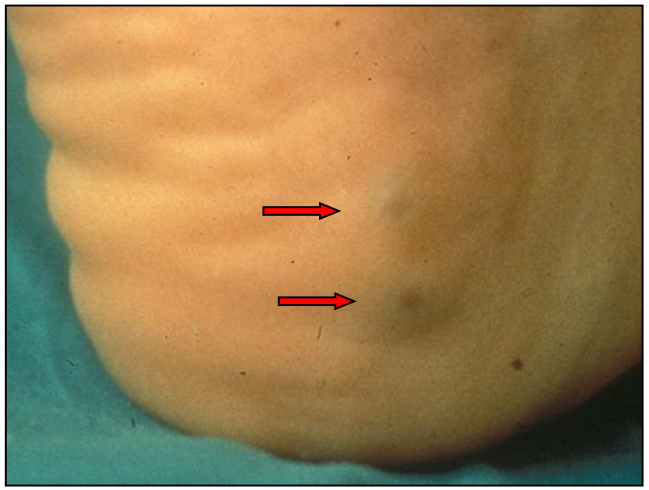
„Haemangioendothelioma“
Be specific !

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
- *IDH1/2* mutations



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



spindle cell Haemangioma

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

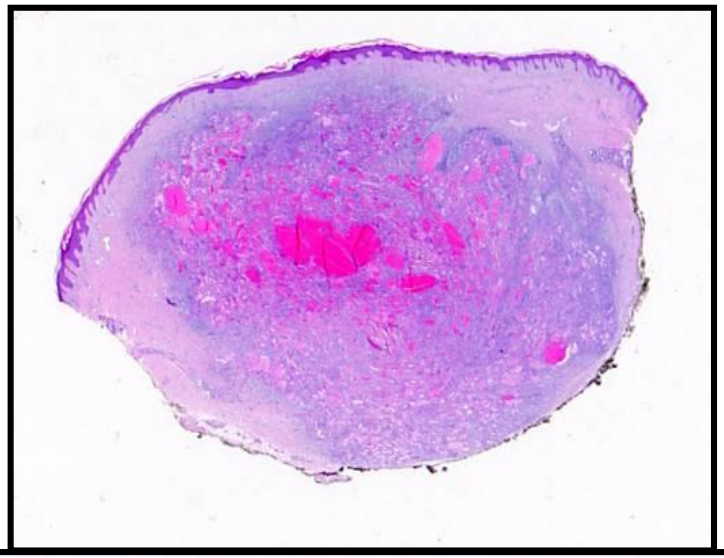
1. dilated, cavernous vascular spaces
2. bland spindle cells

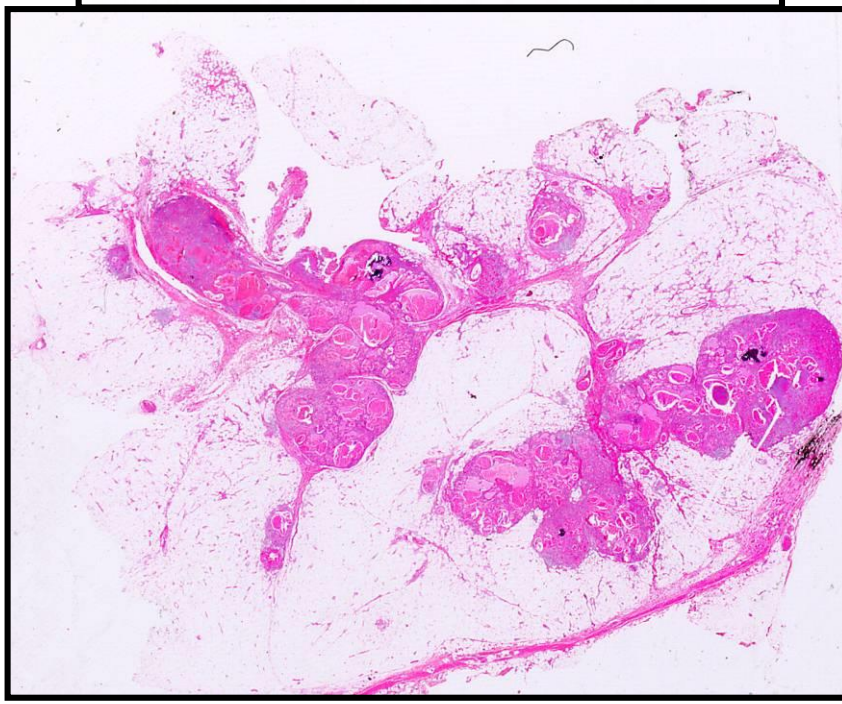
epithelioid endothelial cells (cytoplasmic vacuoles)

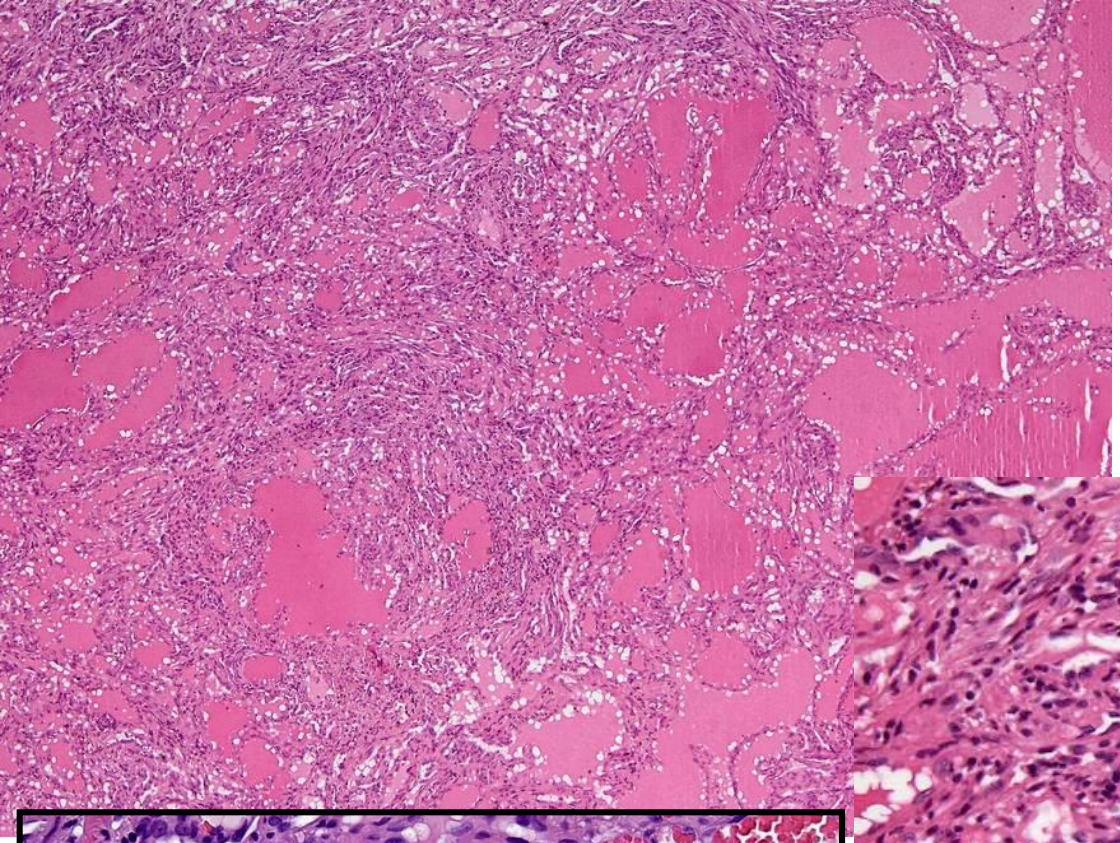
endothelial bridges

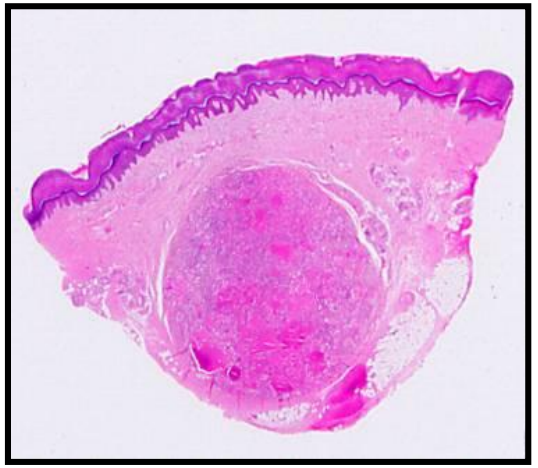
abnormal thick-walled vessels (vascular malformations)

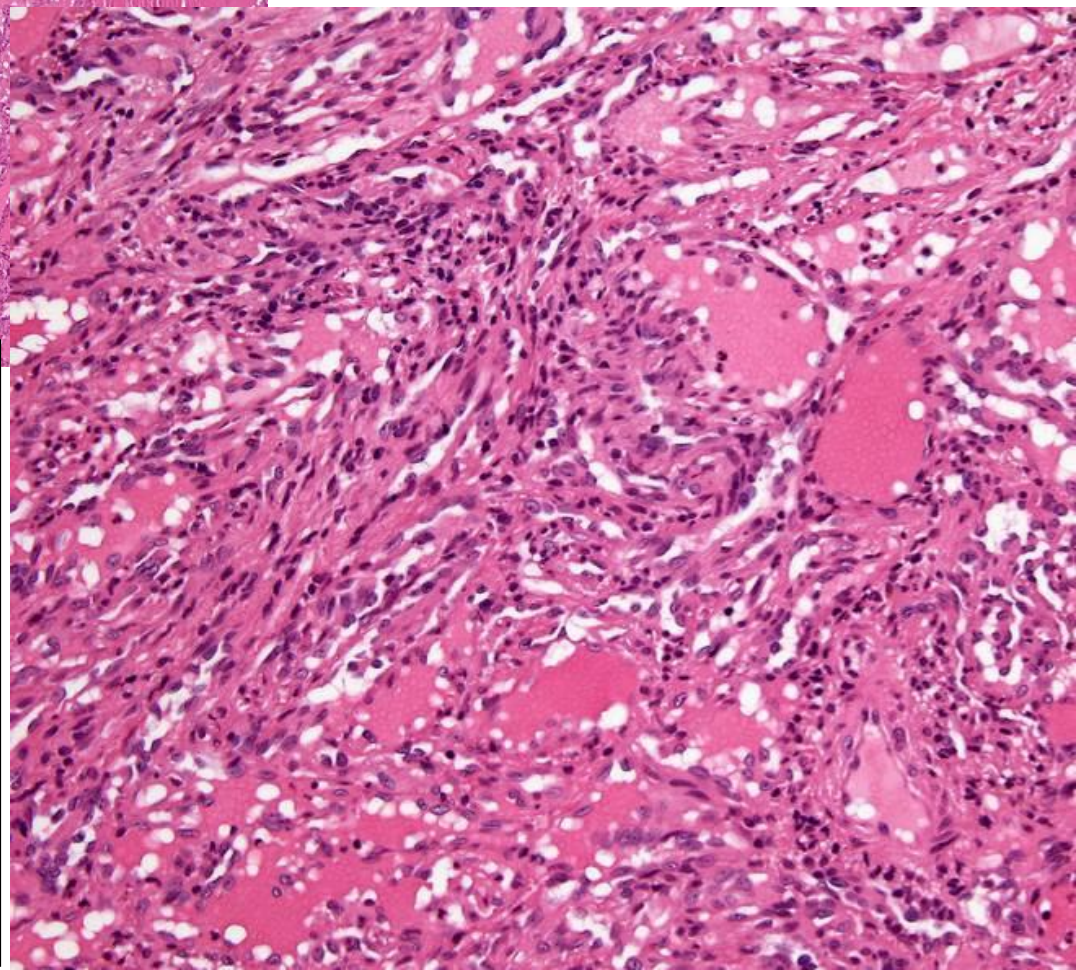
20-30% intravascular

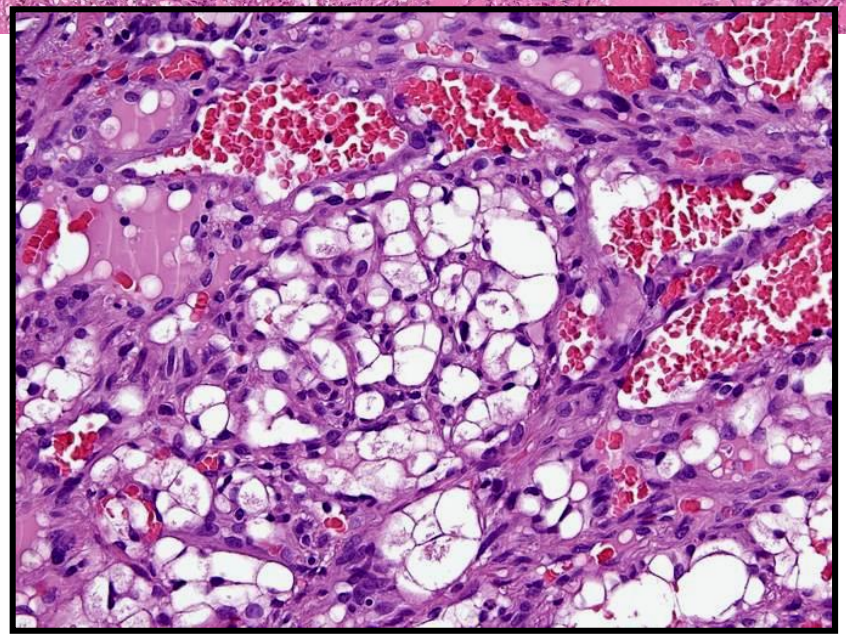


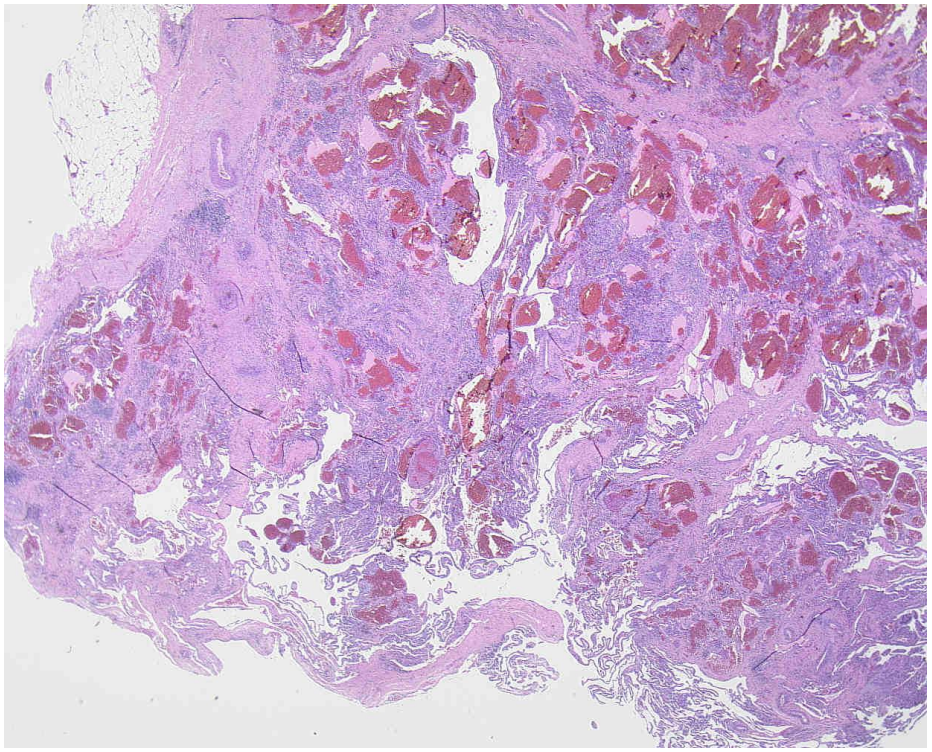


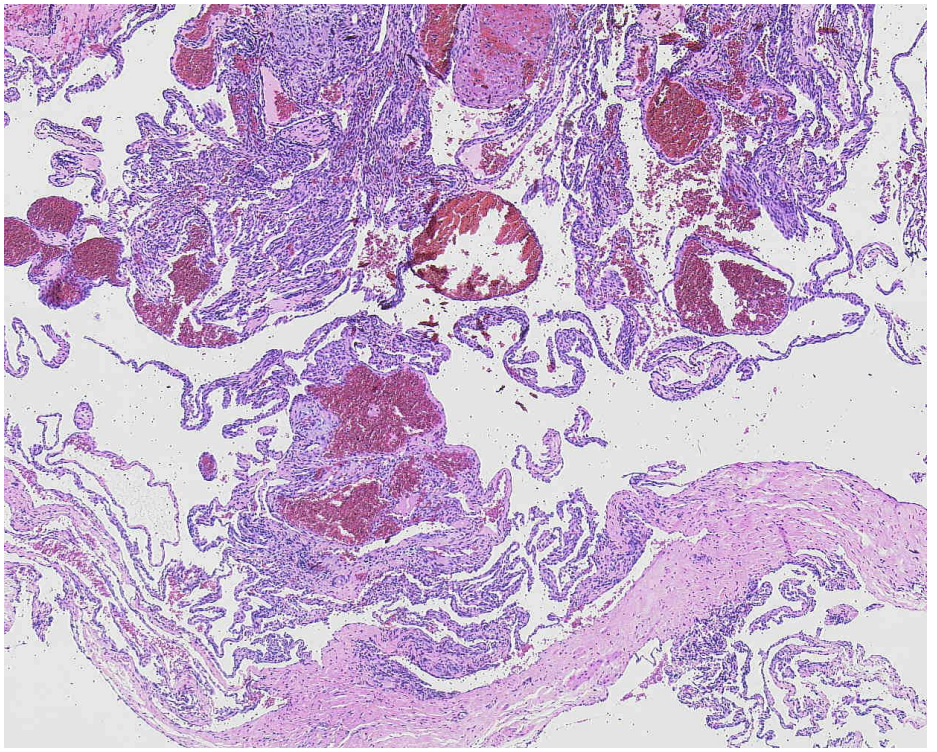


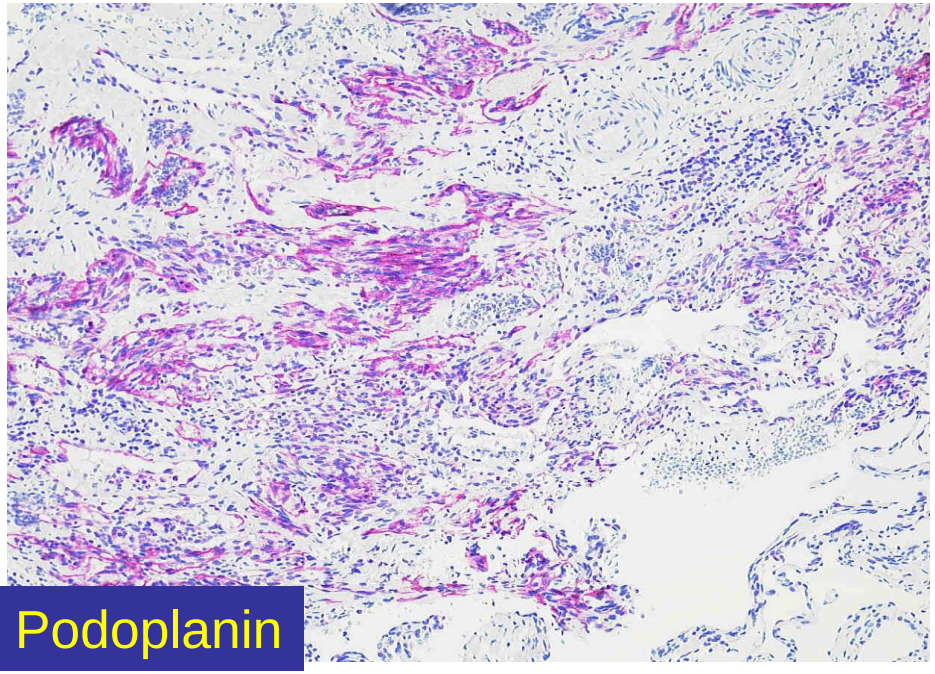


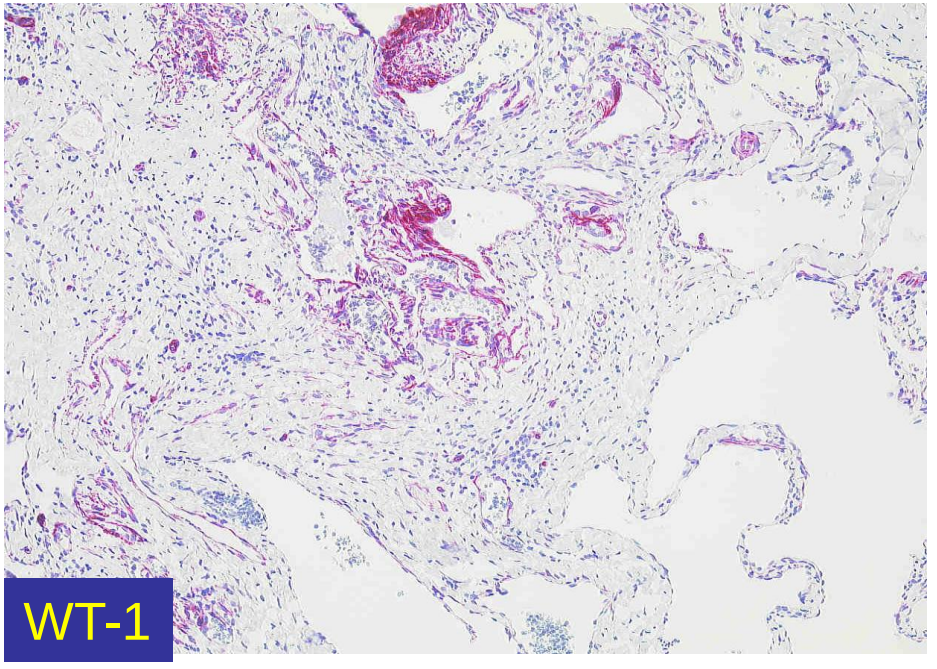









Podoplanin

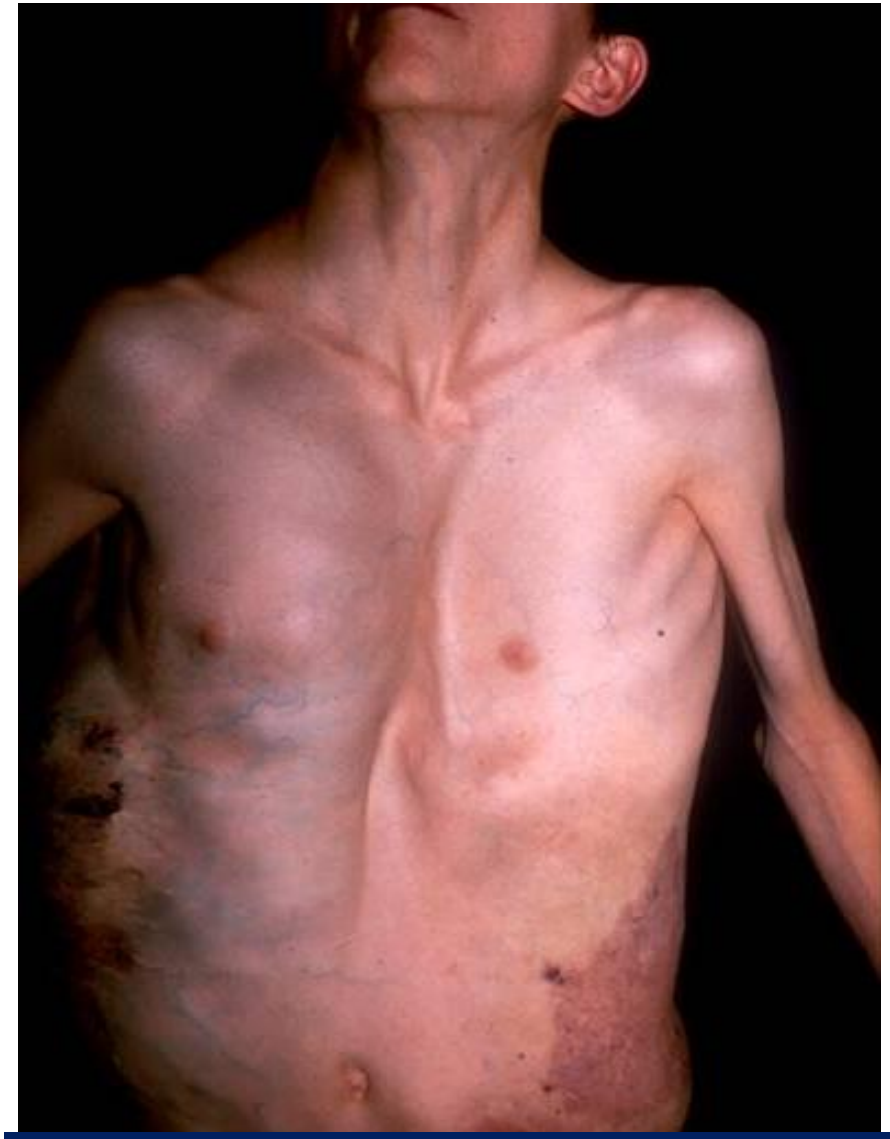

WT-1

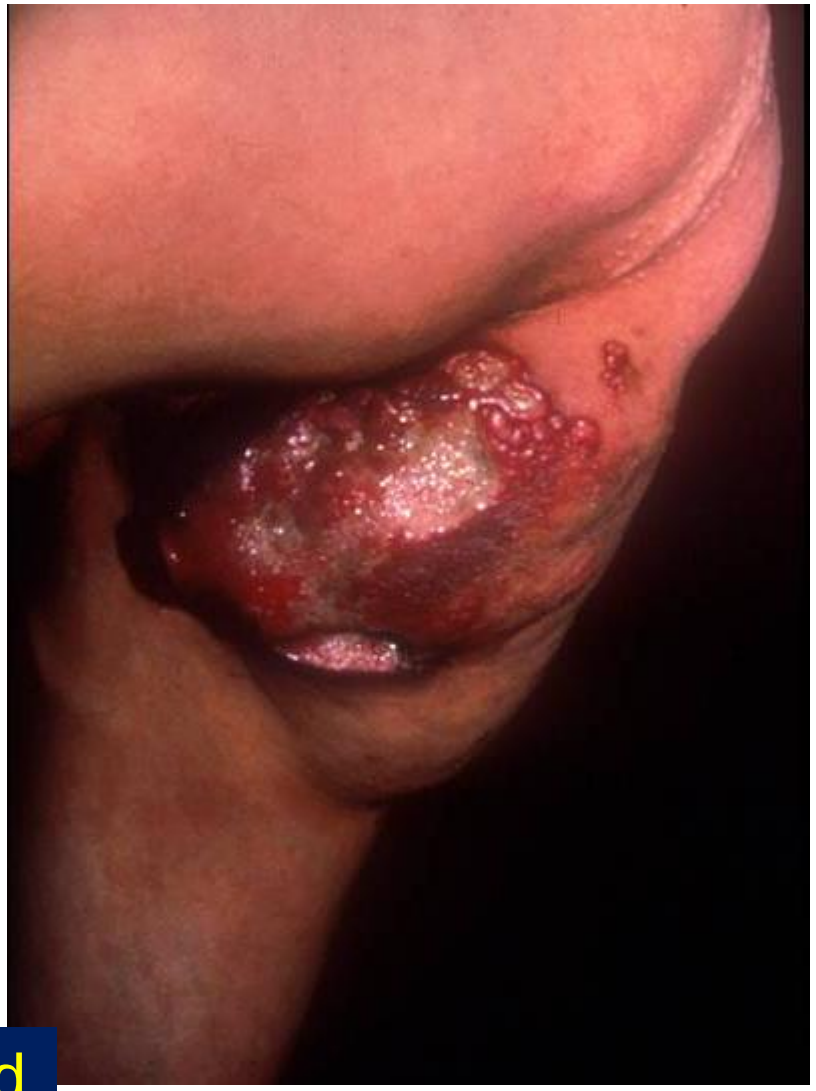
papillary intravascular Lymphangio-endothelioma* (Dabska´s Tumour)

- 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

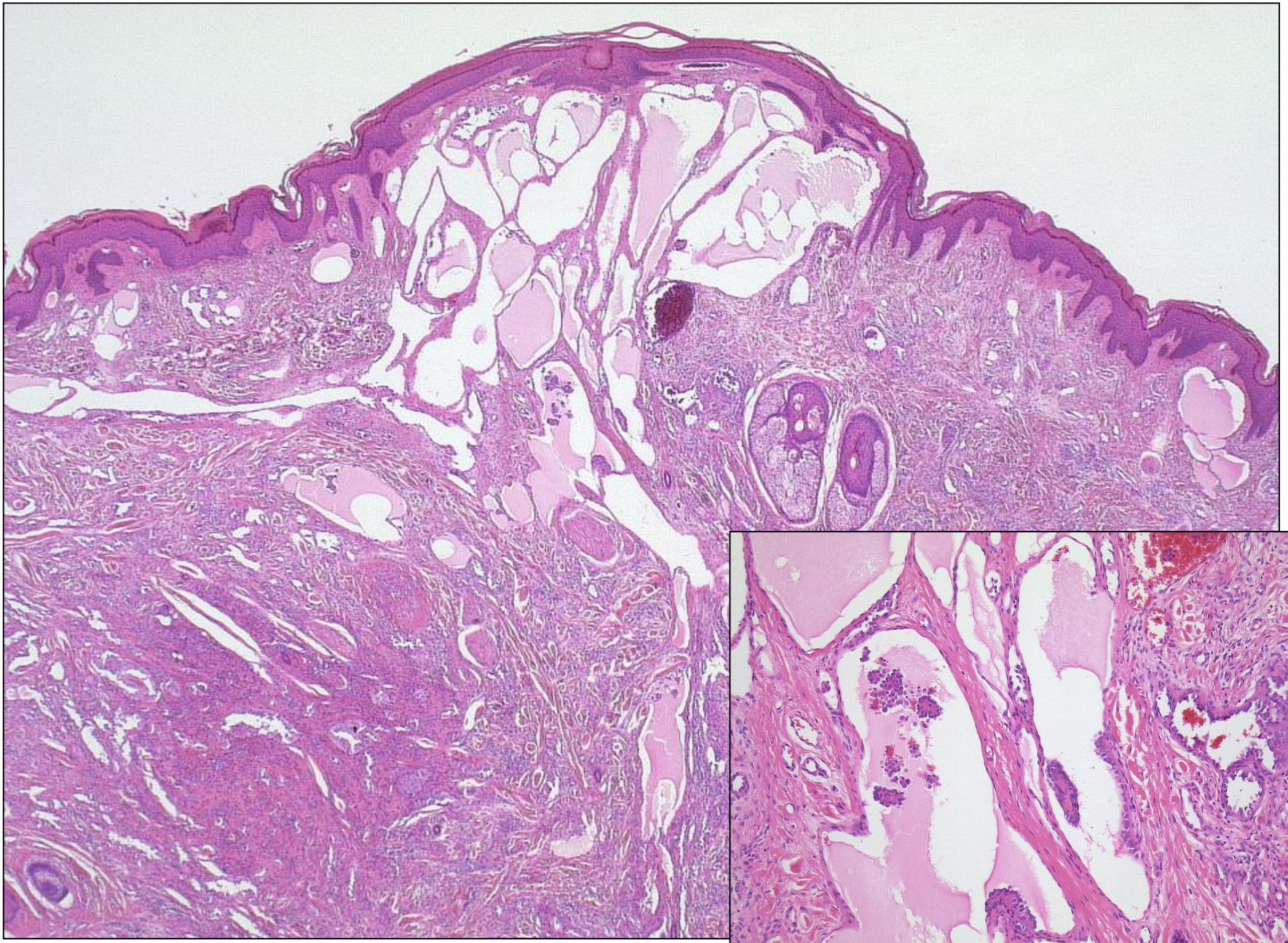
*** Fanburg-Smith JC et al. AJSP 1999; 23: 1004**

papillary intravascular Lymphangioendothelioma





by courtesy of Dr.L.Requena, Madrid

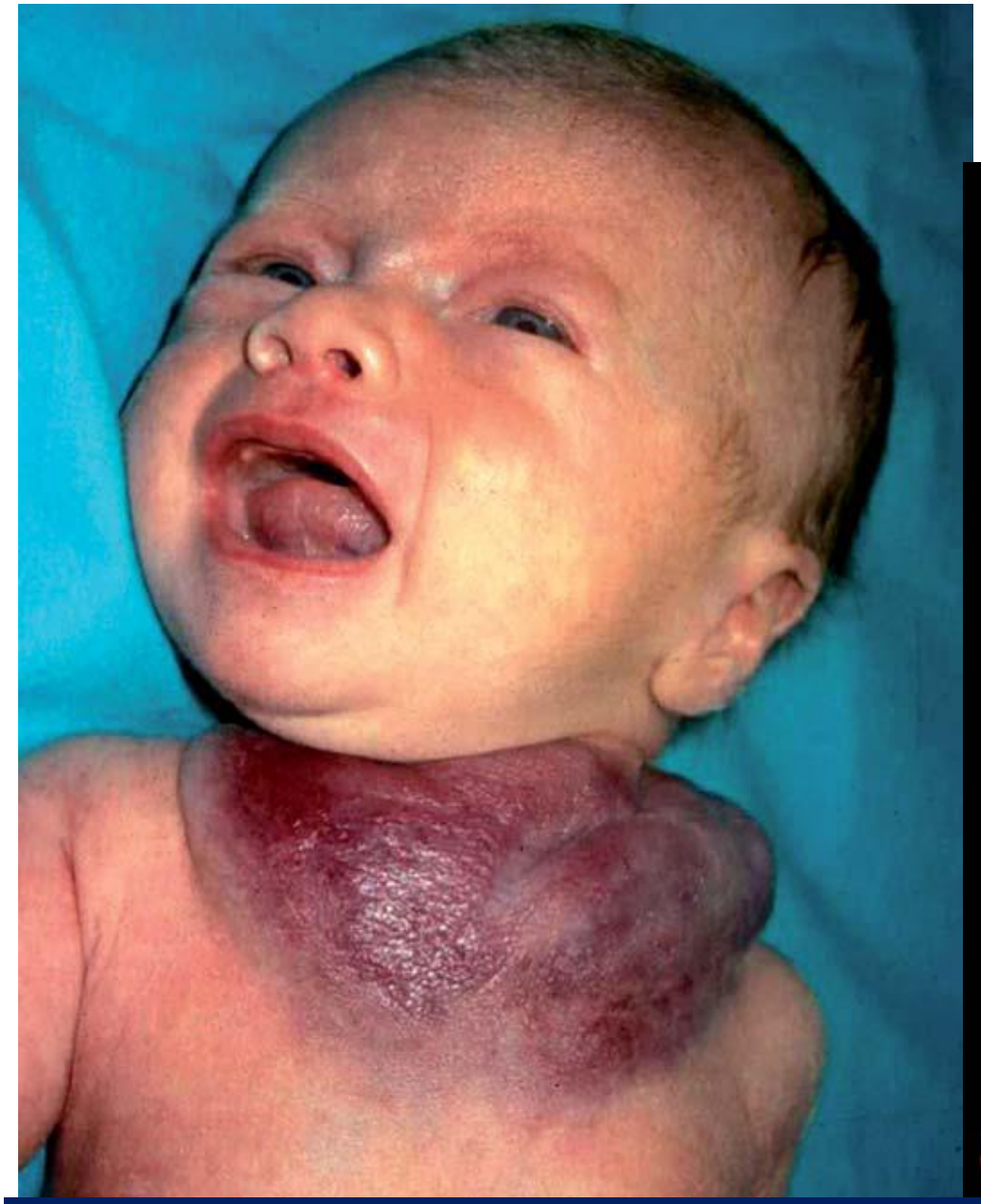


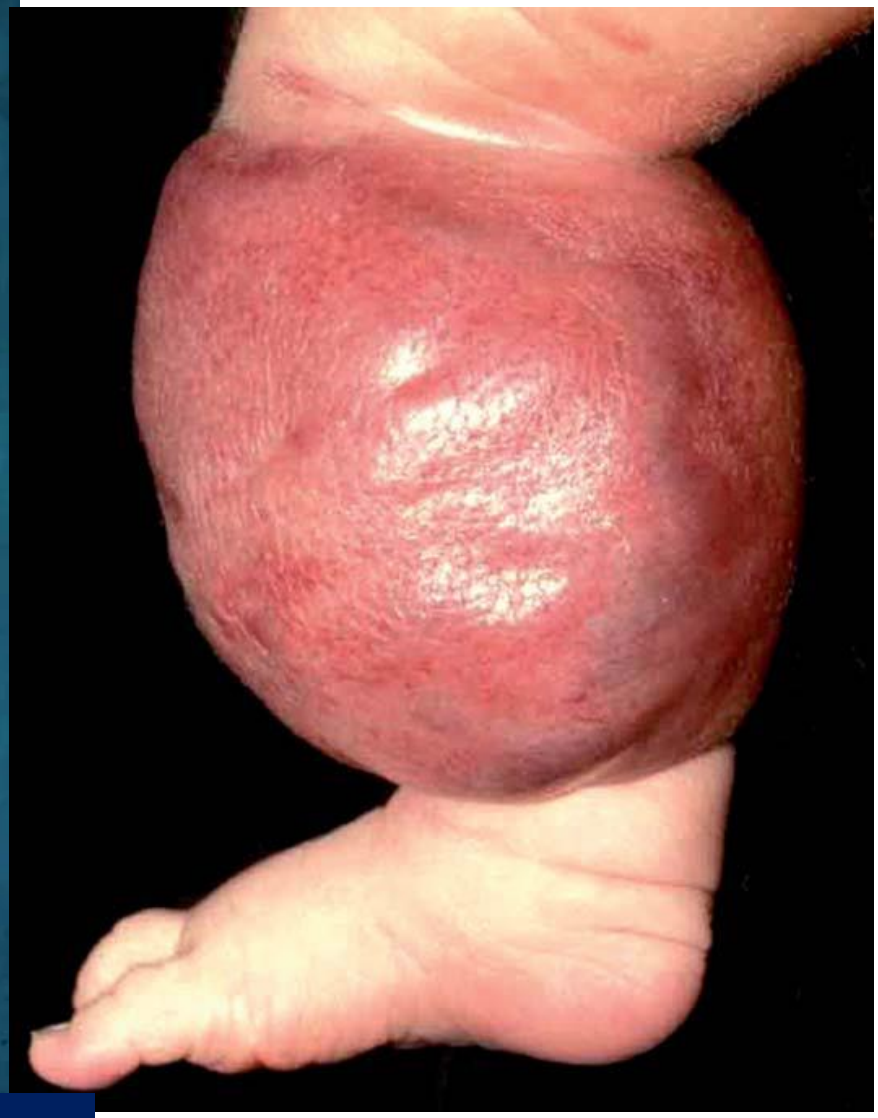
M, 15 years, thigh

kaposiform Haemangioendothelioma*

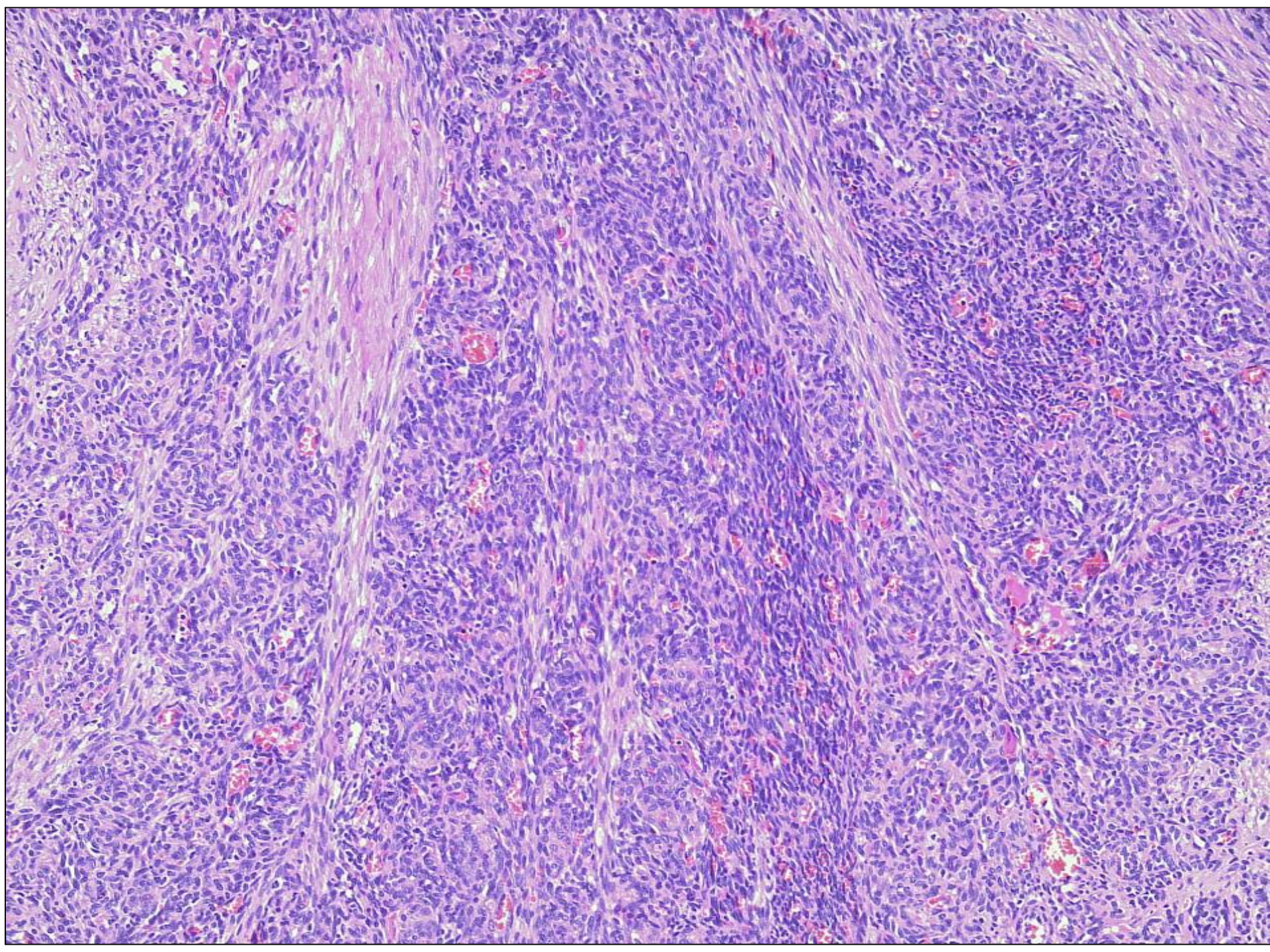
- children >> adults, retroperitoneum, extremities
- deep soft tissues >> dermal
- prognosis related to size and depth !
- locally aggressive, no metastases
- Cave: Kasabach Merritt syndrome
- cellular neoplasm, lobular growth
- bland spindled cells, fibrin thrombi
- focally podoplanin +, prox-1 +, LYVE-1 +
- associated lymphangiomatous changes
- spectrum with tufted haemangioma !

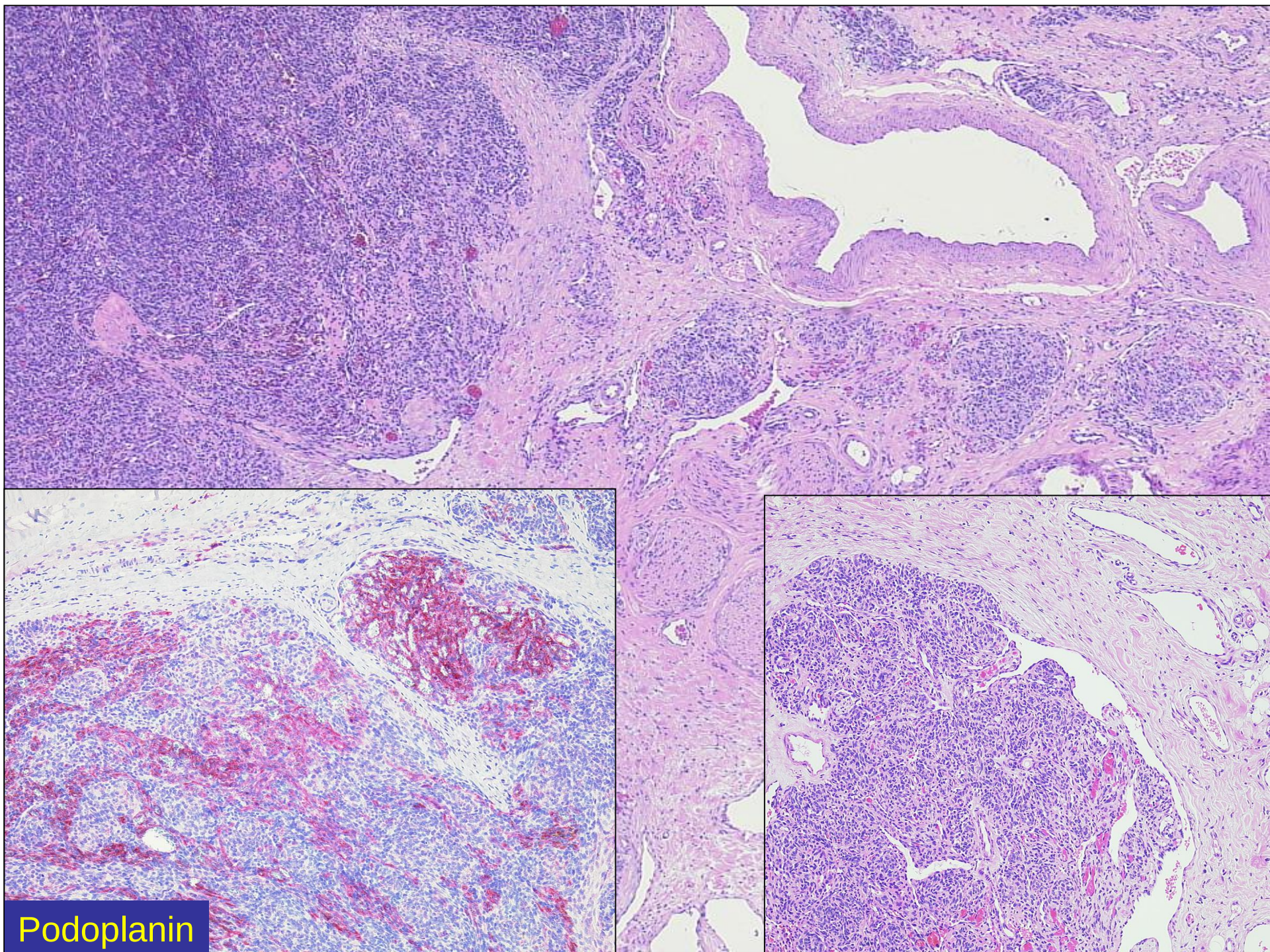
* Tsang WY, Chan JKC AJSP 1991; 15: 982
Zukerberg LR et al. AJSP 1993; 17: 321





by courtesy of Dr.L.Requena, Madrid

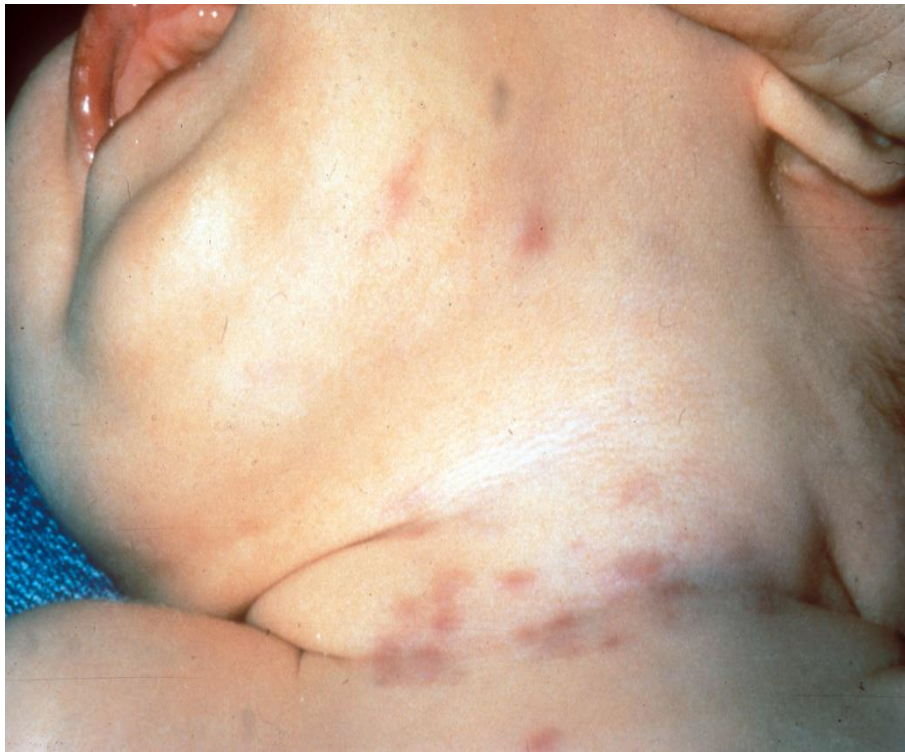



Podoplanin

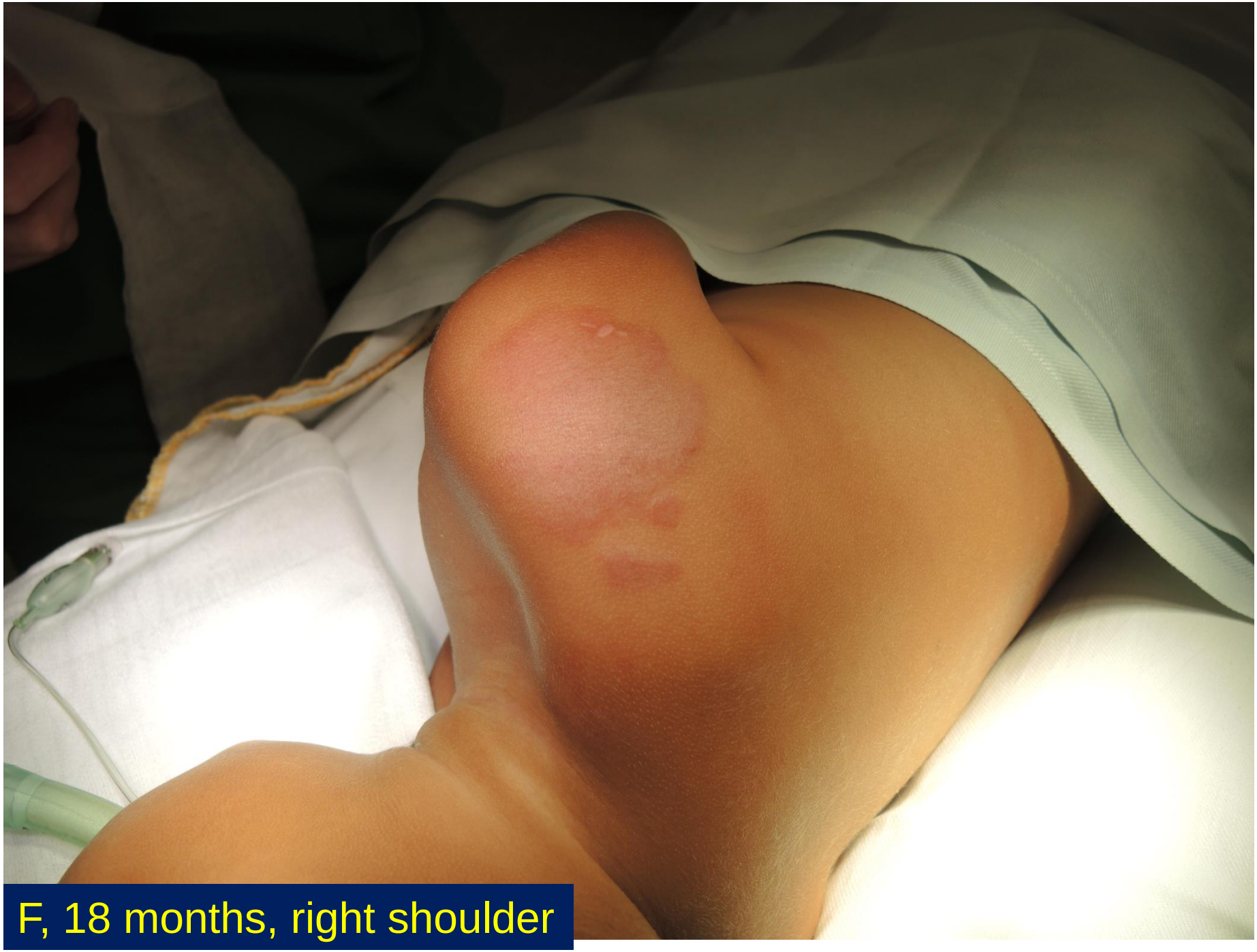
tufted Haemangioma

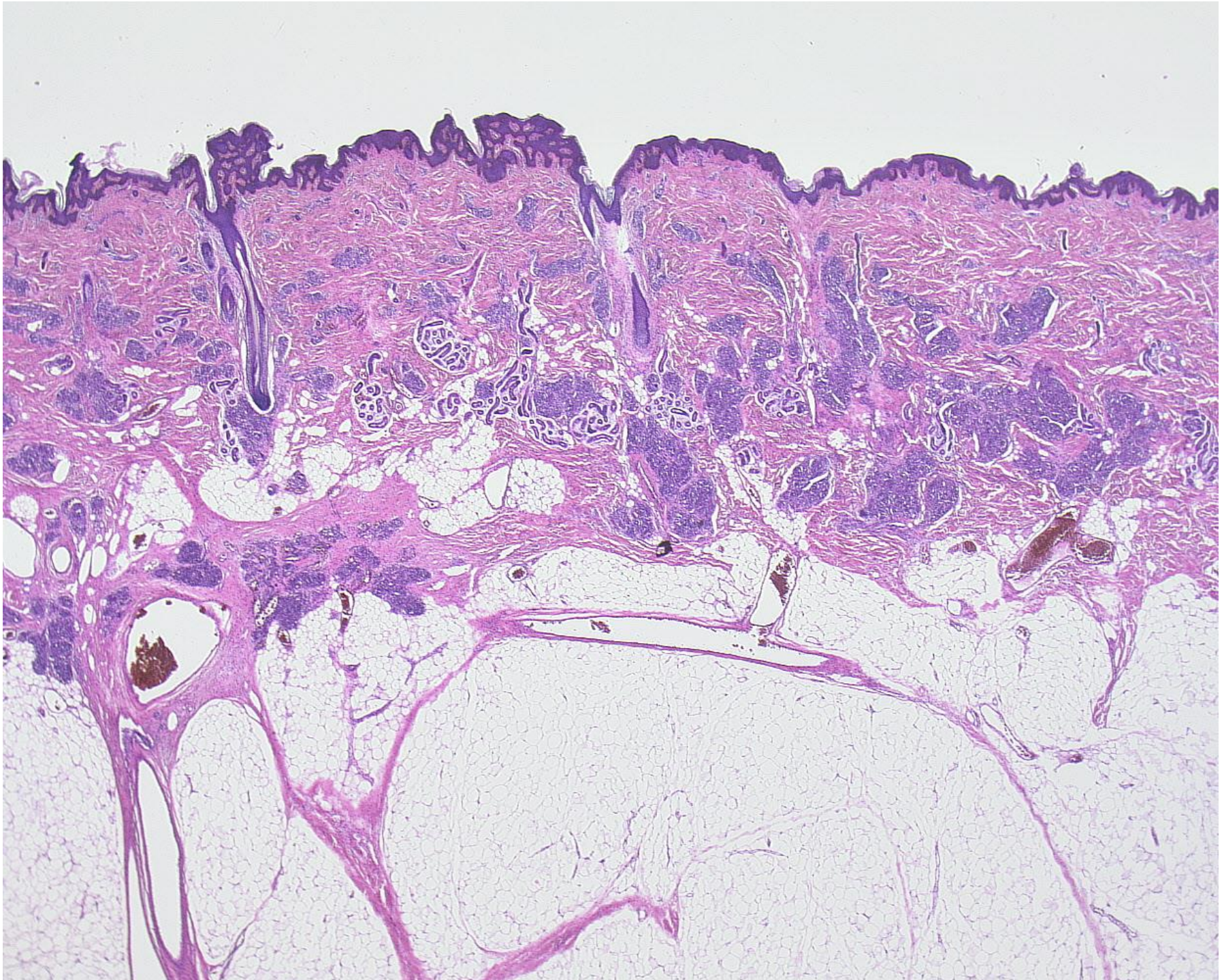
Pathological Findings

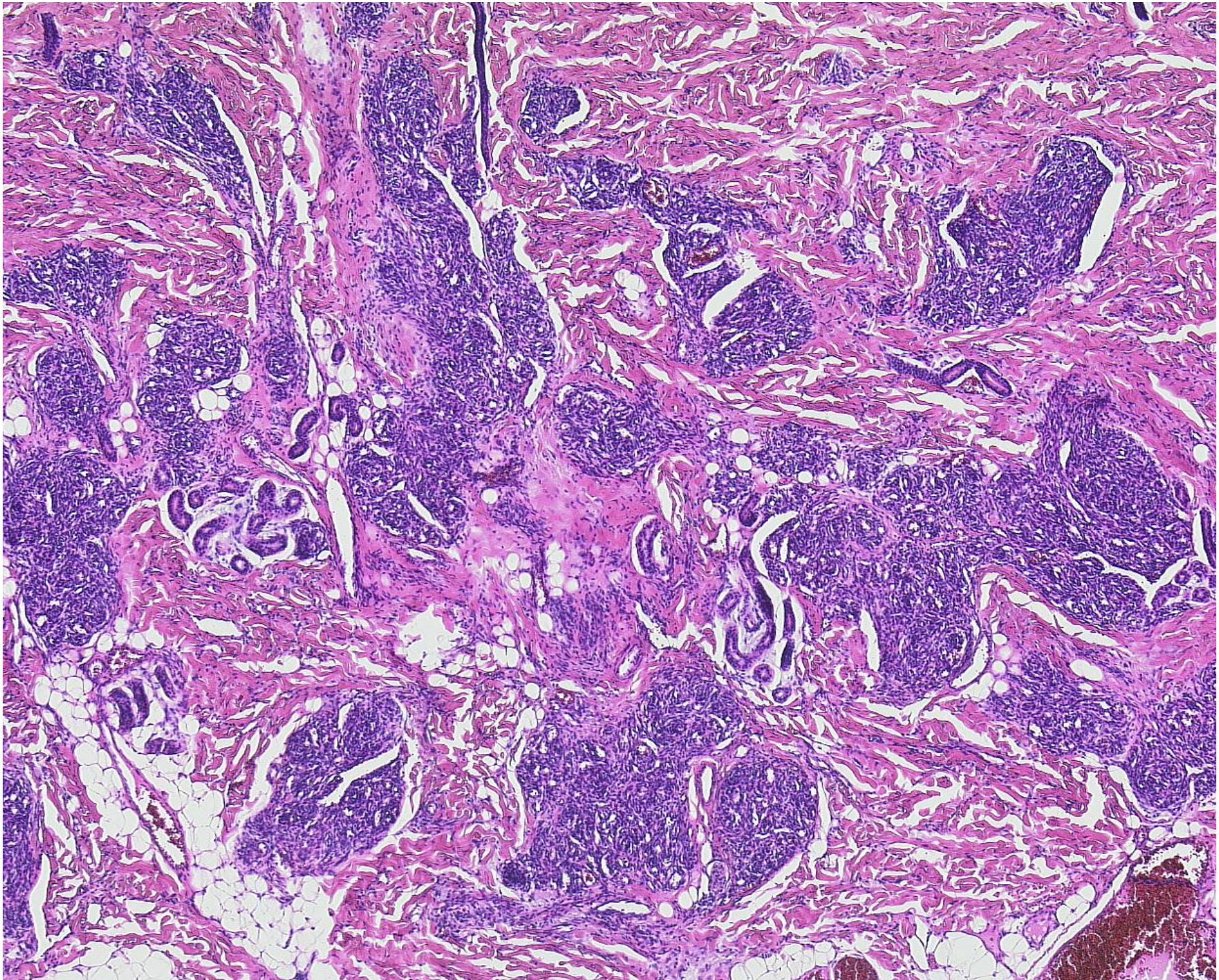
- infants, children >> adults
- head / neck, trunk
- slowly growing lesions
- cannon-ball distribution
- cellular vascular tufts
- peripheral lymphangio-matous changes
- CD31 +, ASMA +
- Podoplanin focal +
- spectrum with kaposiform haemangioendothelioma

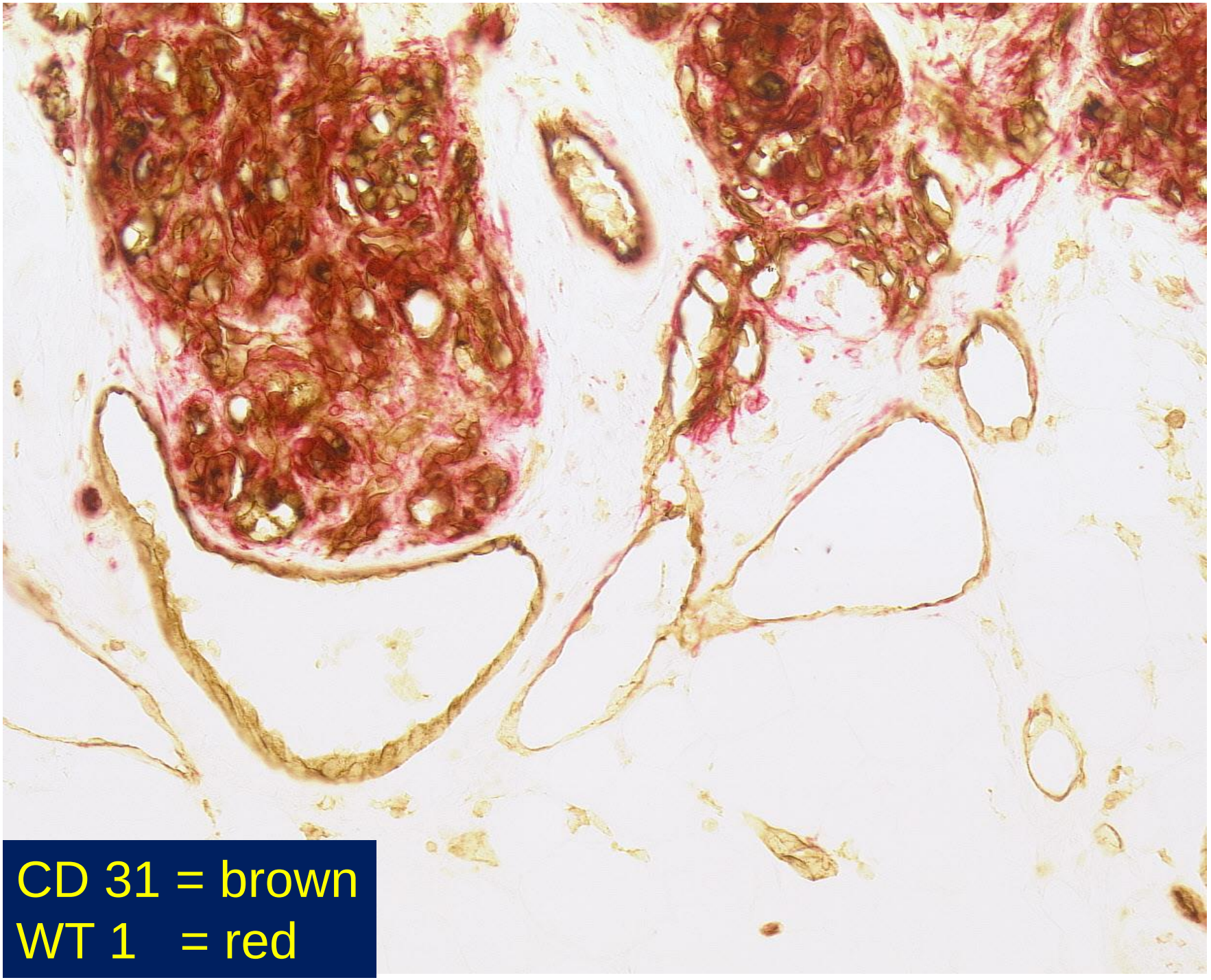


by courtesy of Prof.Dr.Fletcher
Boston, MA


F, 18 months, right shoulder






CD 31 = brown
WT 1 = red

kaposiform Haemangioendothelioma

- spectrum with tufted haemangioma
- peripheral lymphangiomatous changes
- expression of lymphatic markers
- loss / reduction of WT-1
- exhibit a lymphatic-blood phenotype
- Kasabach-Merritt syndrome due to abnormal lymphatic endothelium

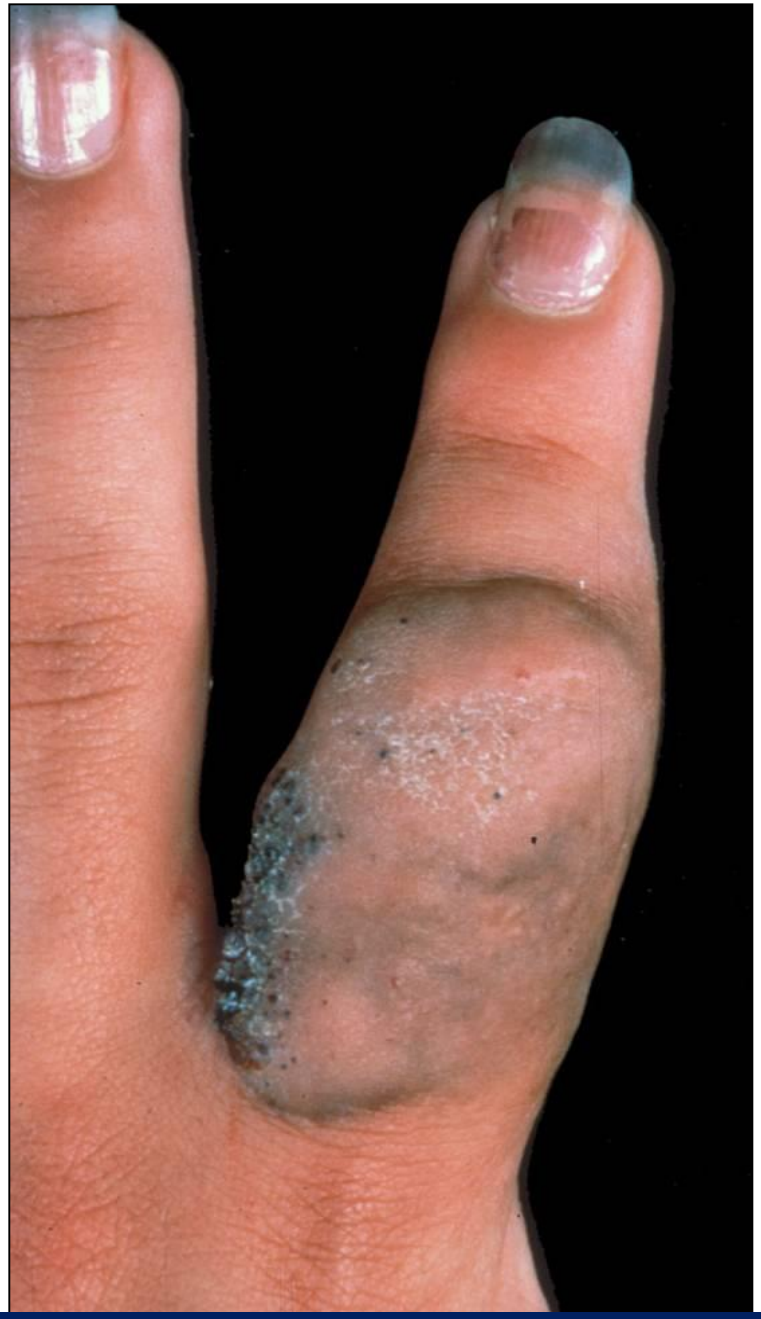
GNA14 somatic mutations causes congenital and sporadic vascular tumors by MAPK activation
Lim YH et al. Am J Hum Genet 2016; 99: 443-450
- point mutations in *GNA14* in tufted HE and KHE

Kaposiform hemangioendothelioma and tufted hemangioma – genetic analysis including genome-wide methylation profiling
Ten Broek RW et al. Ann Diagn Pathol 2019; 44: 151434
- 7 KHE, 3 TH
- *NRAS* mutation (1 TH), *CDKN2A* mutation (1 TH), *RAD50* mutation (1 KHE), no *GNA14* mutations
- similar methylation profile in TH and KHE
- 14 vascular malformations with different methylation profile

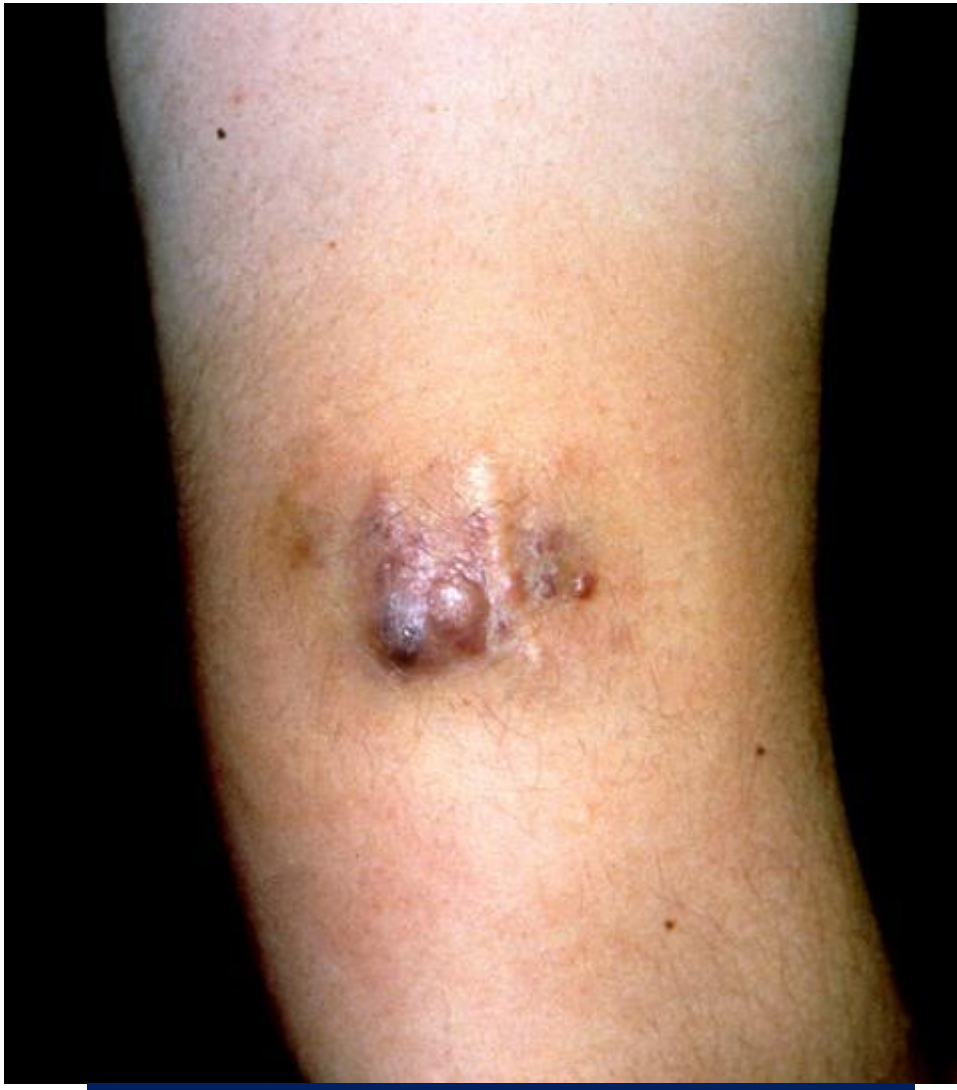
retiform Haemangioendothelioma*

- 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 +

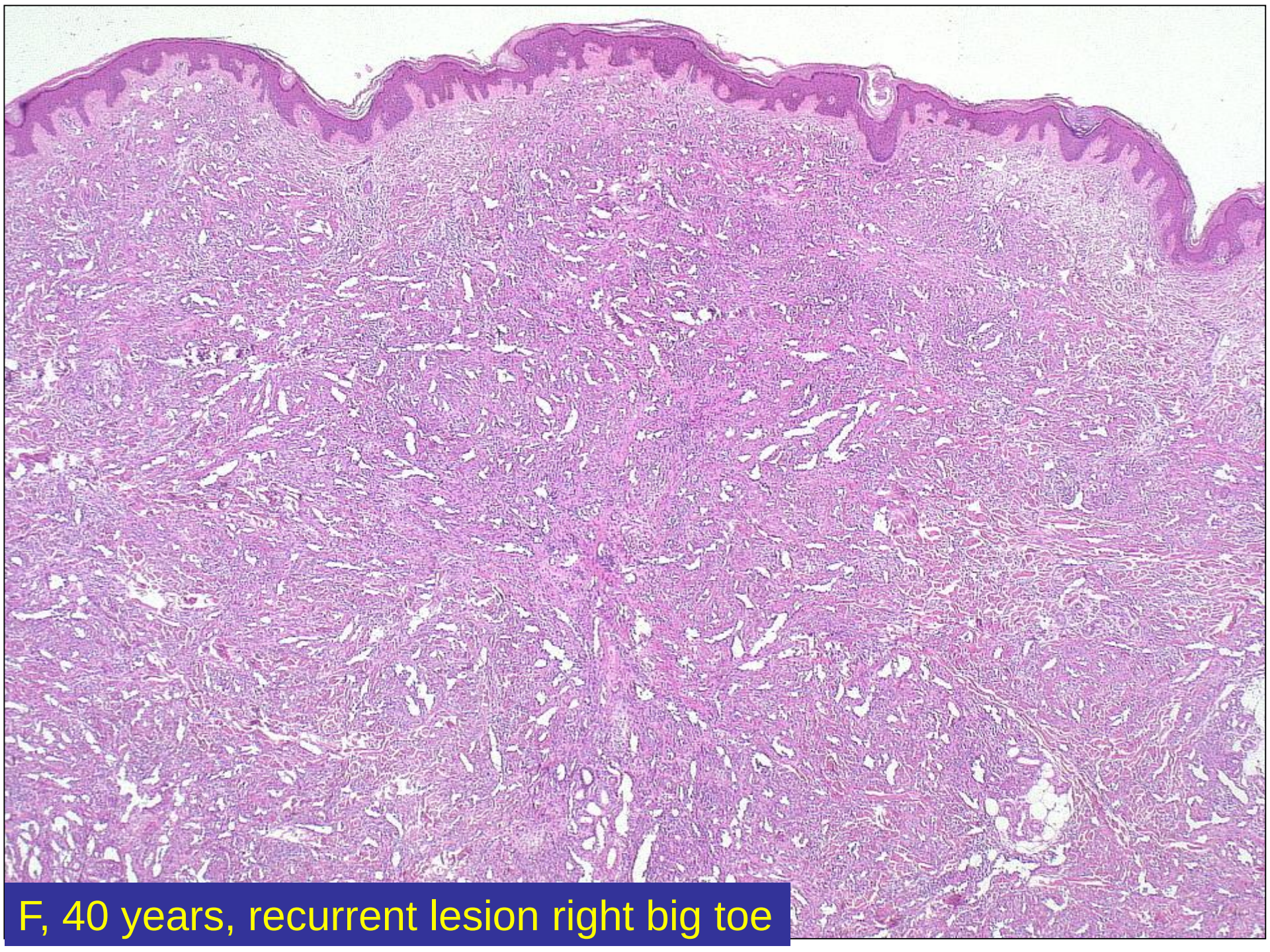
* Calonje E et al. AJSP 1994; 18: 115

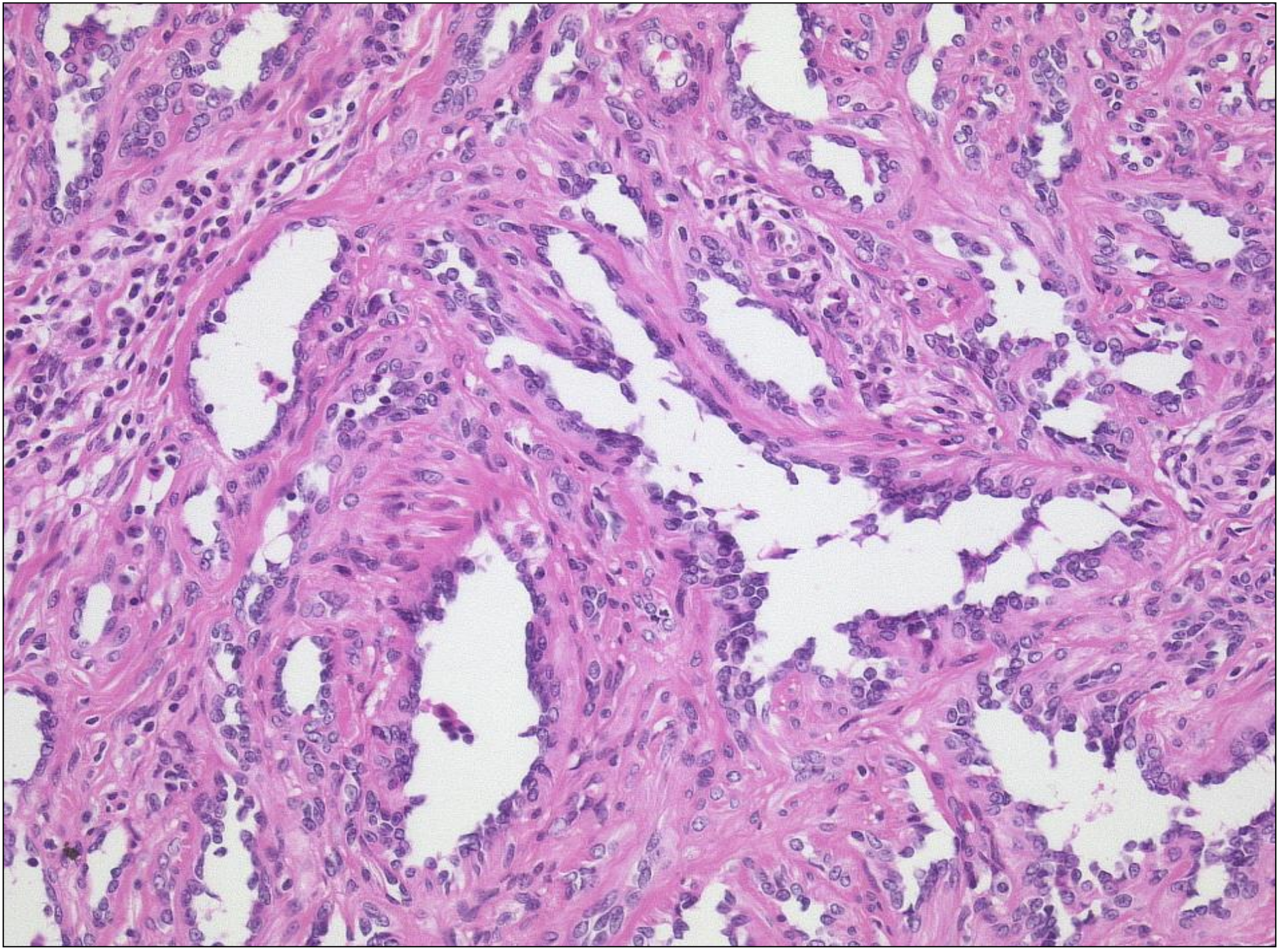


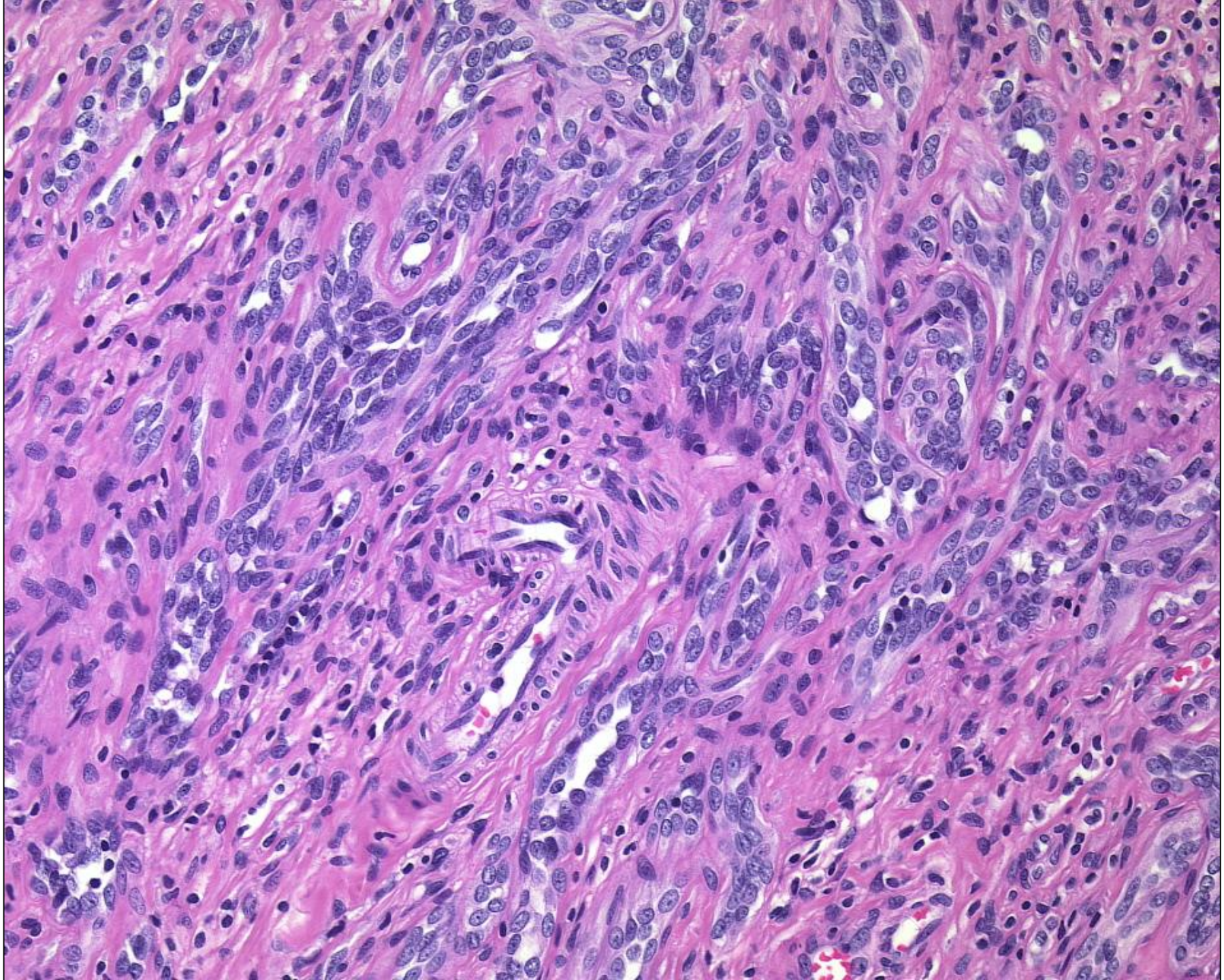
by courtesy of ProF.Dr.Fletcher, Boston

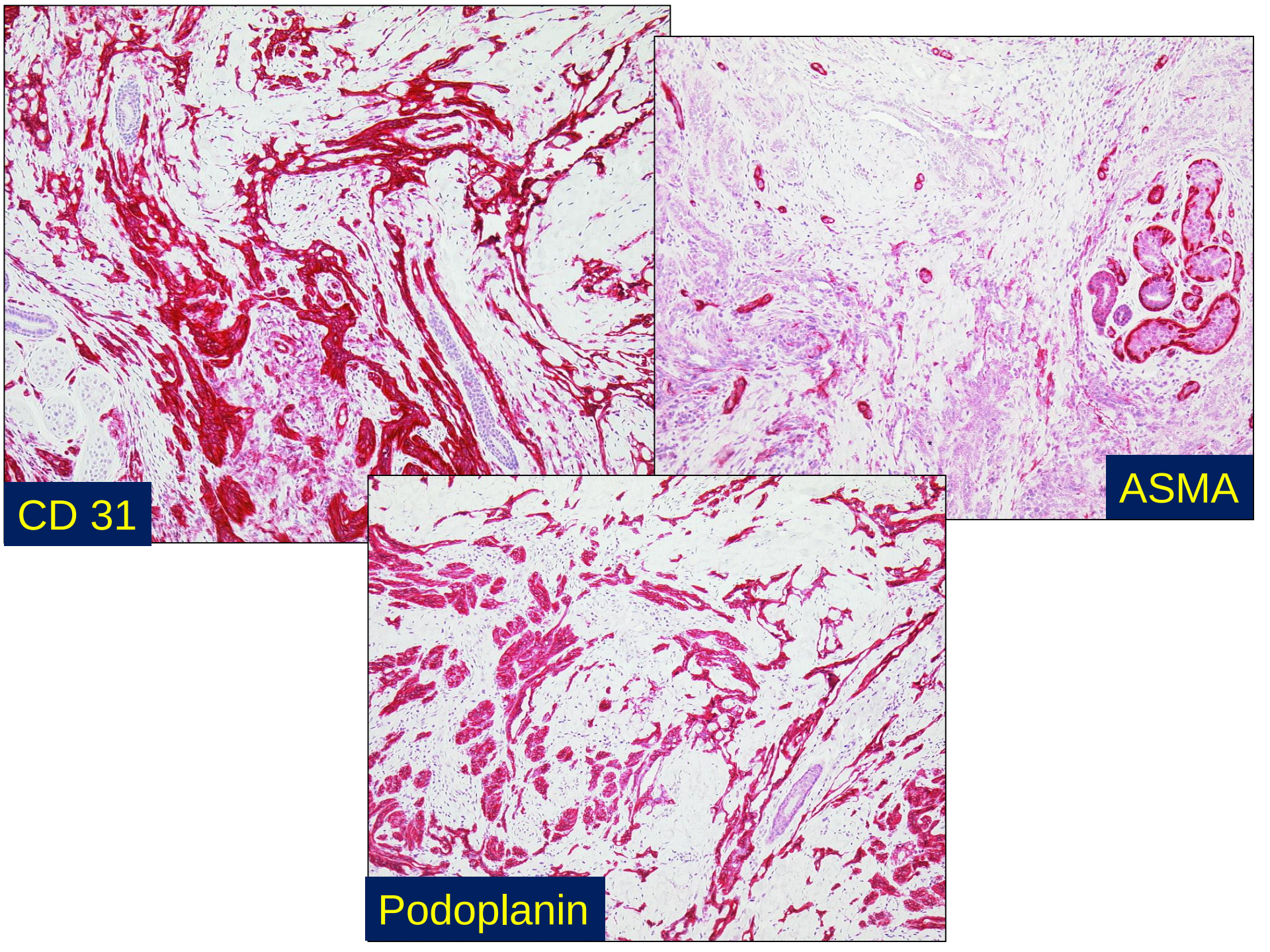


by courtesy of Dr.L.Requena, Madrid


F, 40 years, recurrent lesion right big toe





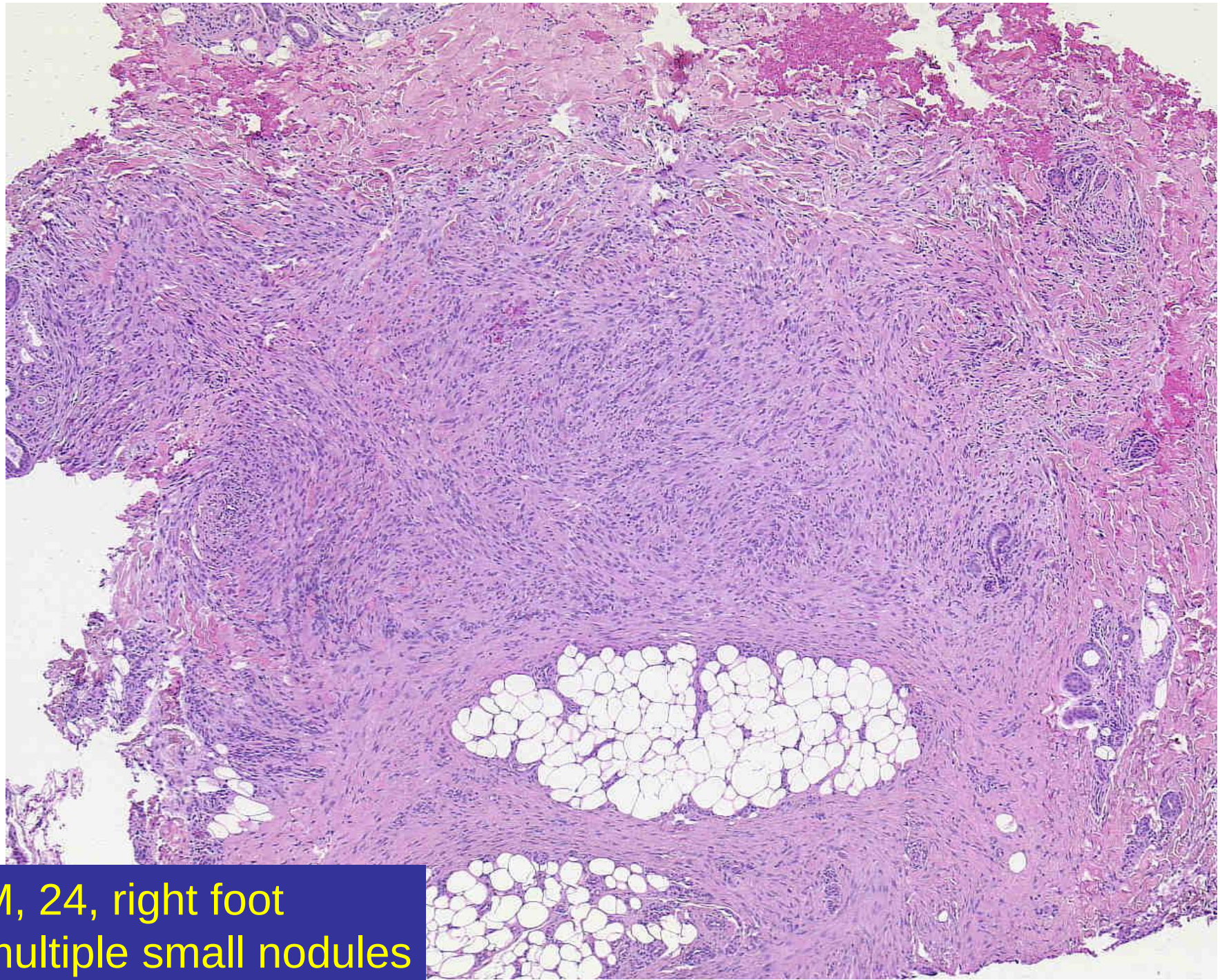

CD 31
ASMA
Podoplanin

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

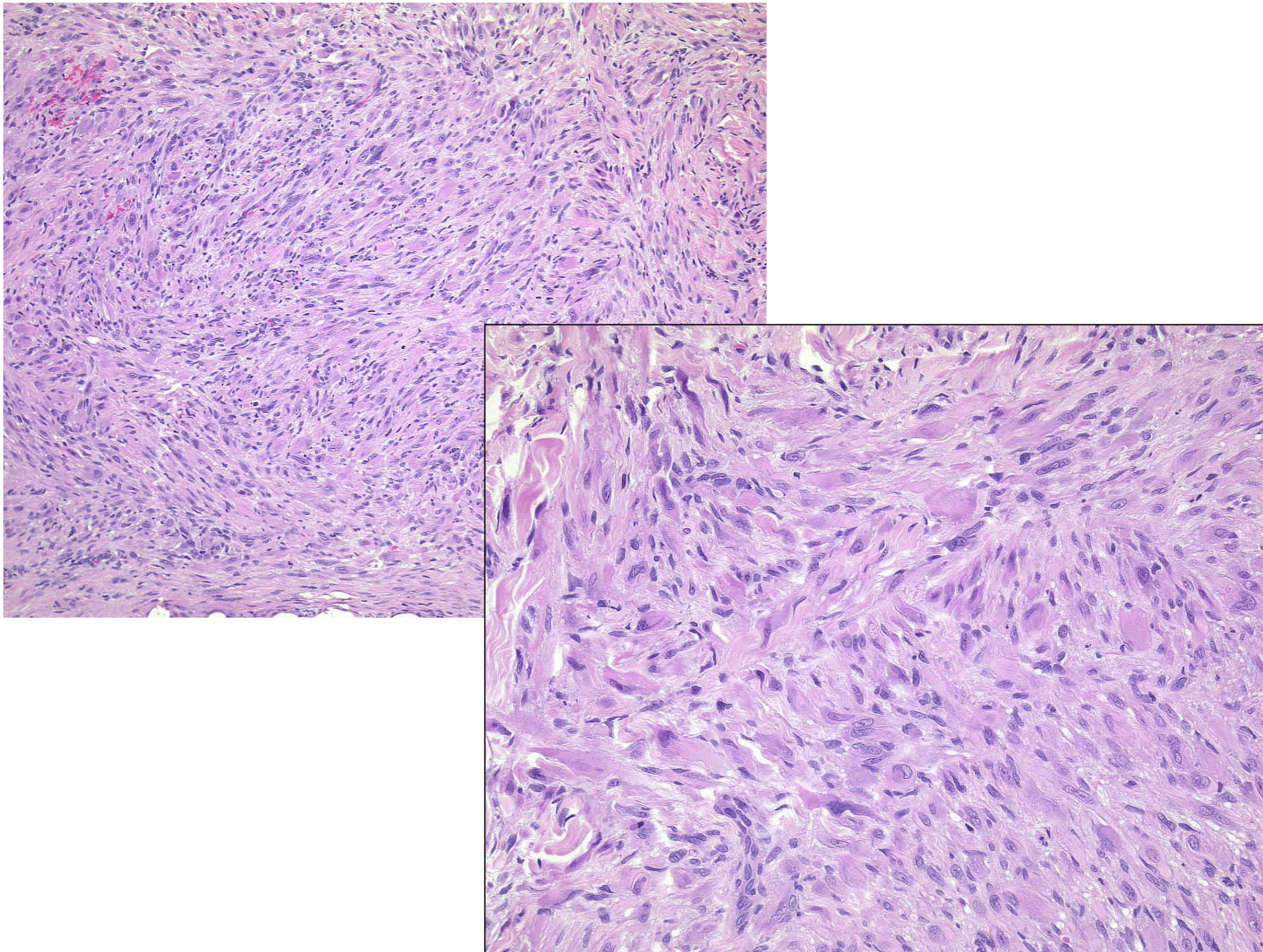
(„epithelioid sarcoma-like Hemangioendothelioma“)

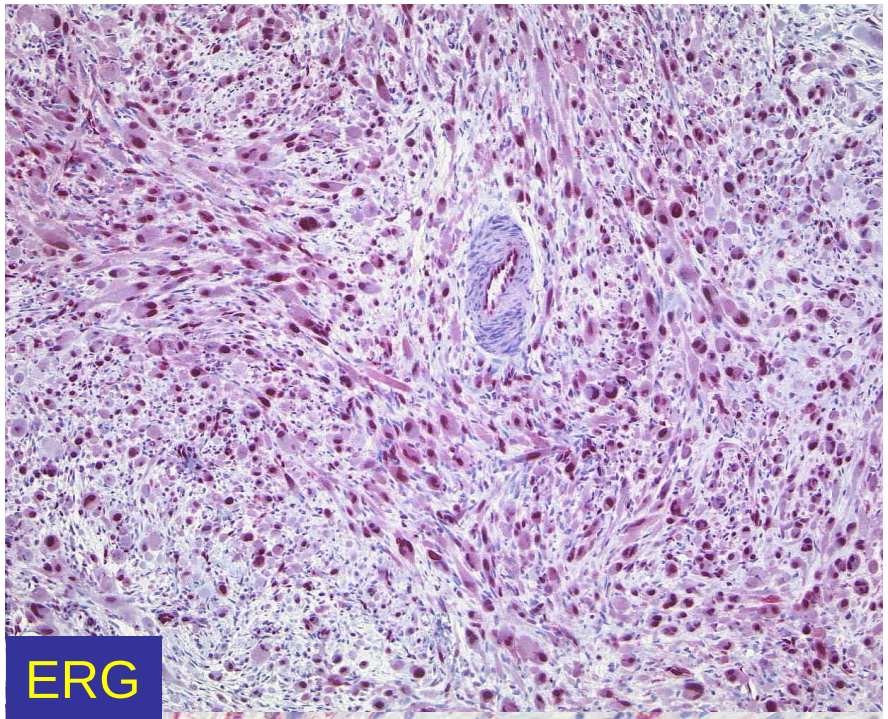
(Hornick JL, Fletcher CDM AJSP 2011; 35: 190)

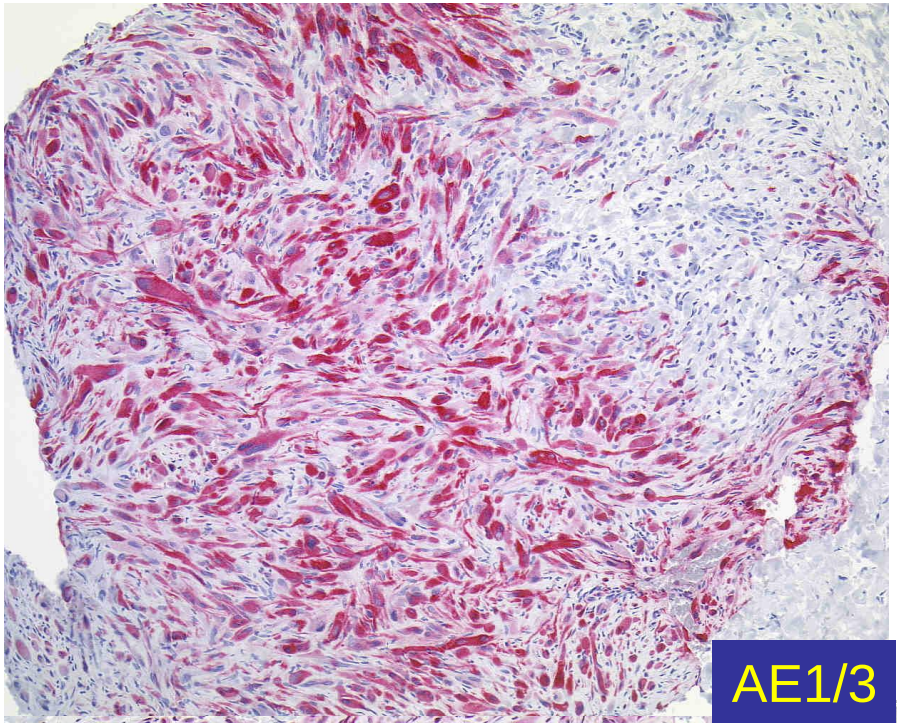
- 50 cases, 41 M, 9 F, 14 - 80 years
- extremities >> trunk, head / neck region
  dermis/subcutis > deep soft tissue > bone
- multifocal neoplasms (2-15 neoplasms) (66%)
- fascicles, sheets of plump spindled cells,
  few epithelioid cells, neutrophils
- AE1/3 +, MNF116 -, Fli-1 +, 22/47 CD 31 +,
  7/49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

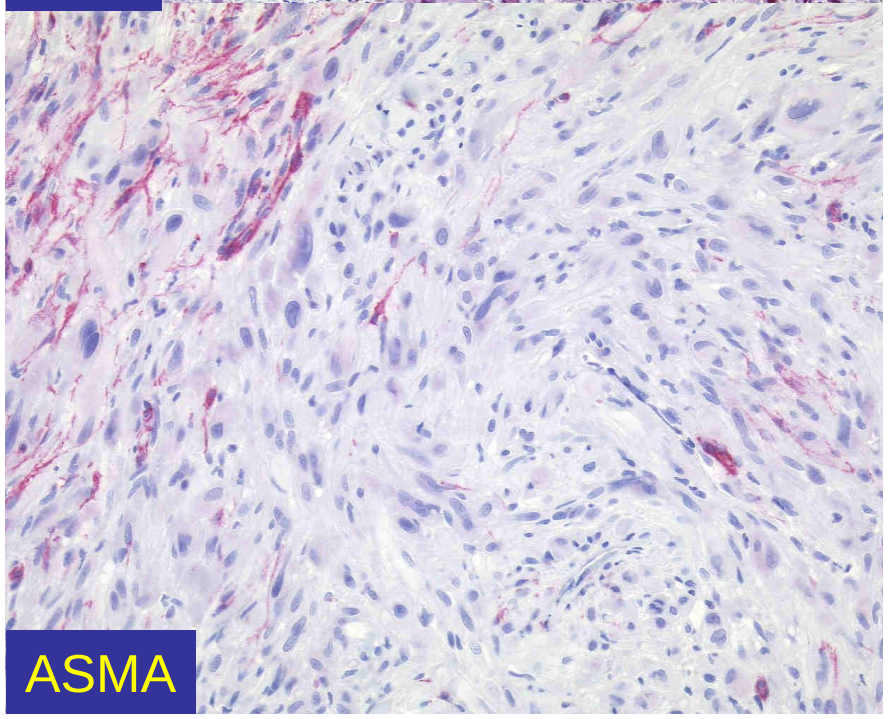


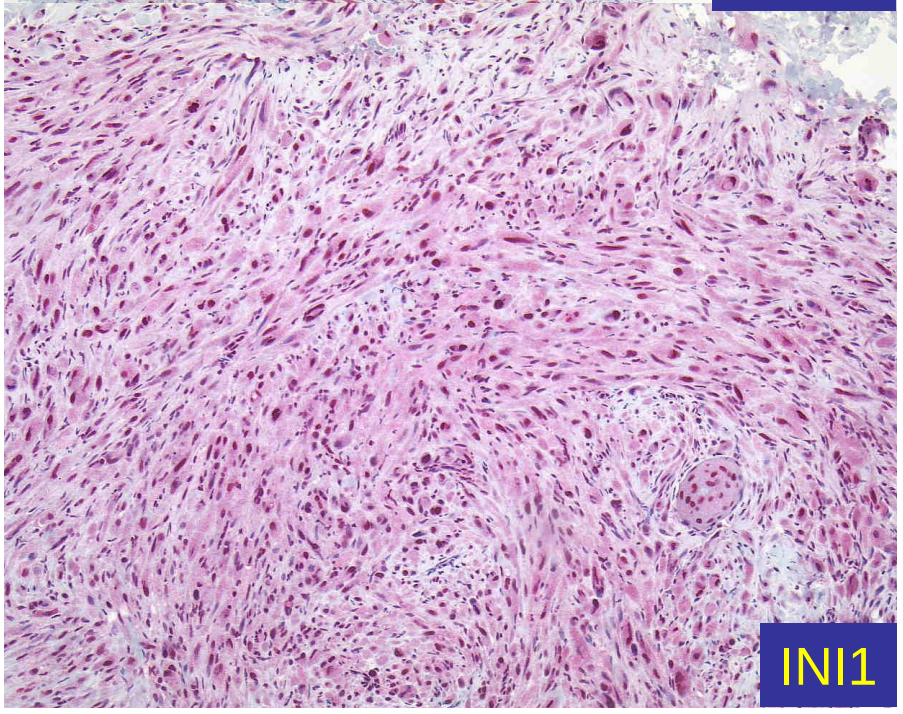
M, 24, right foot
multiple small nodules




ERG


AE1/3


ASMA


INI1

pseudomyogenic Haemangioendothelioma

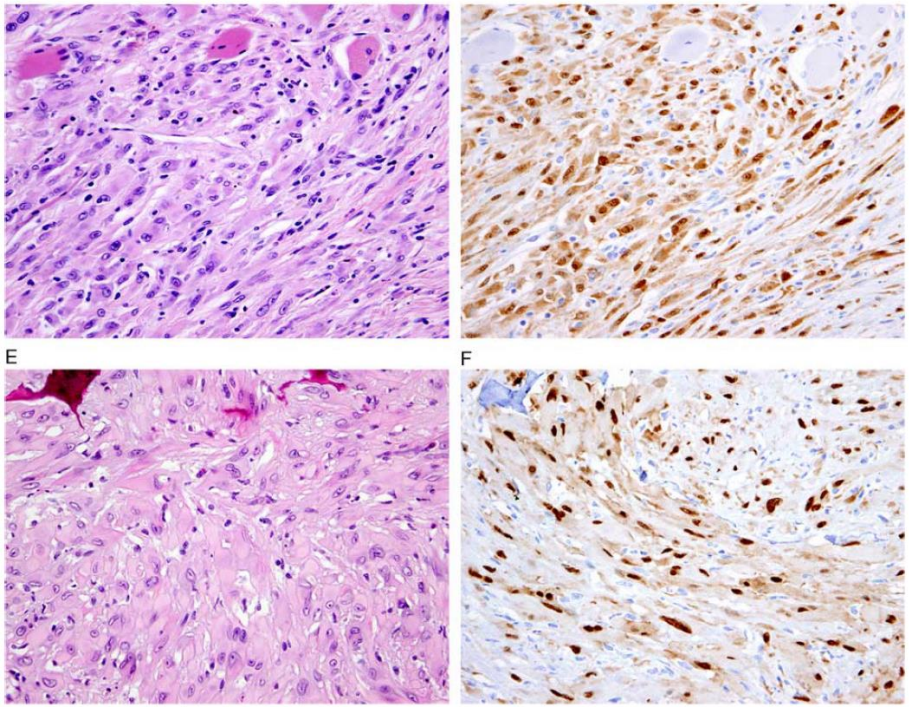
- t(7;19)(q22;q13) (Cancer Genetics 2011; 204: 211)
- *SERPINE1-FOSB* fusion (J Pathol 2014; 232: 534)
- *SERPINE1*: promotor for FOSB
- *FOSB*: encodes a transcription factor (FOS family)
  a component of the activating protein 1
- expanding the spectrum of genetic alterations in pseudomyogenic hemangioendothelioma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

INTERMEDIATE VASCULAR TUMOR
FOS-B POSITIVE

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

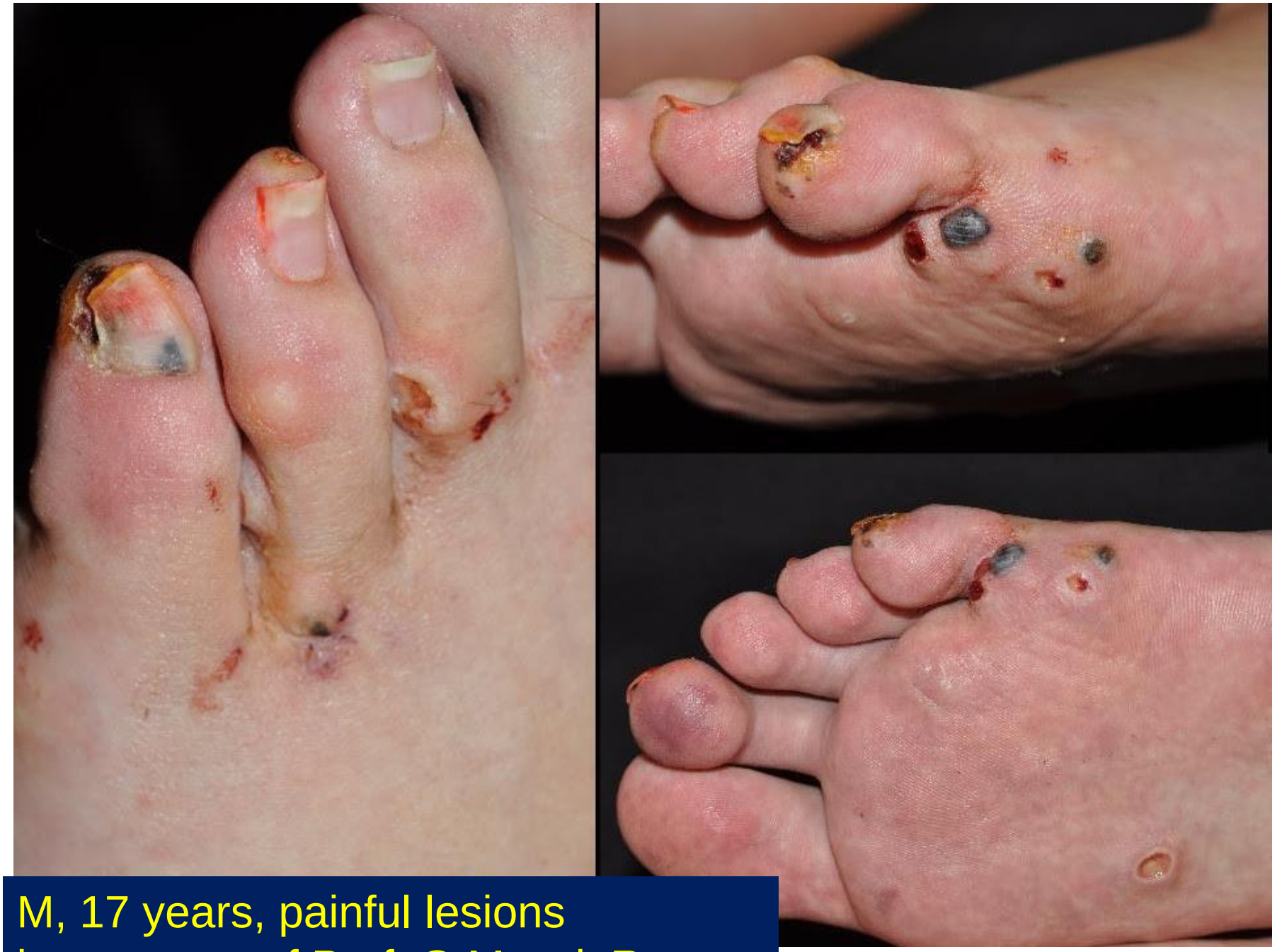
Diagnostic Pathology

RESEARCH Open Access

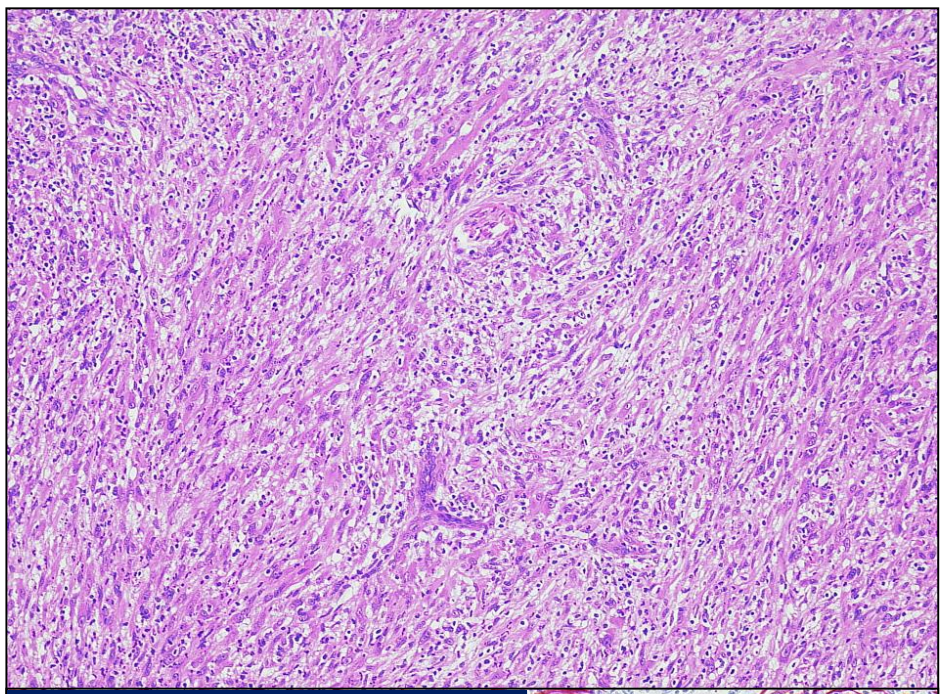
Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics

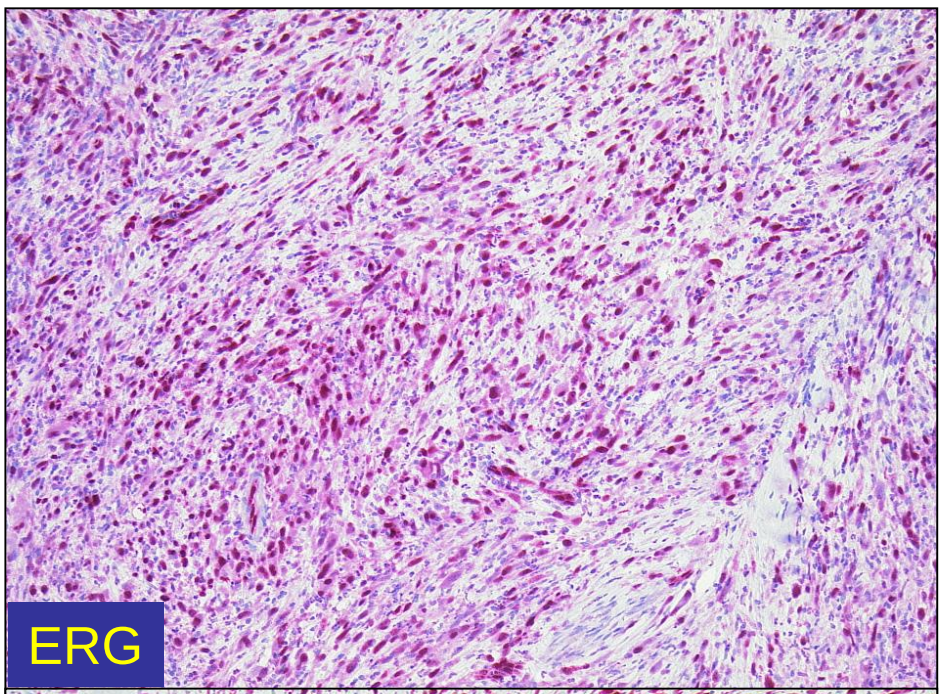
Shintaro Sugita[1], Hiroshi Hirano[1], Noriaki Kikuchi[1], Terufumi Kubo[1], Hiroko Asanuma[1], Tomoyuki Aoyama[1], Makoto Emori[2] and Tadashi Hasegawa[1*]

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

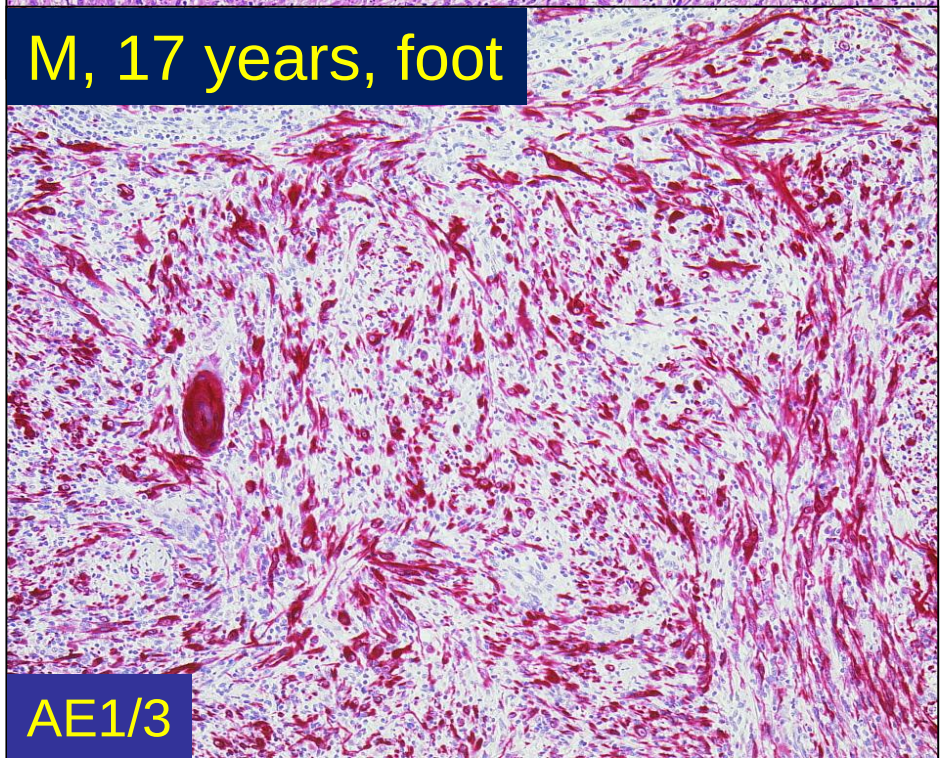


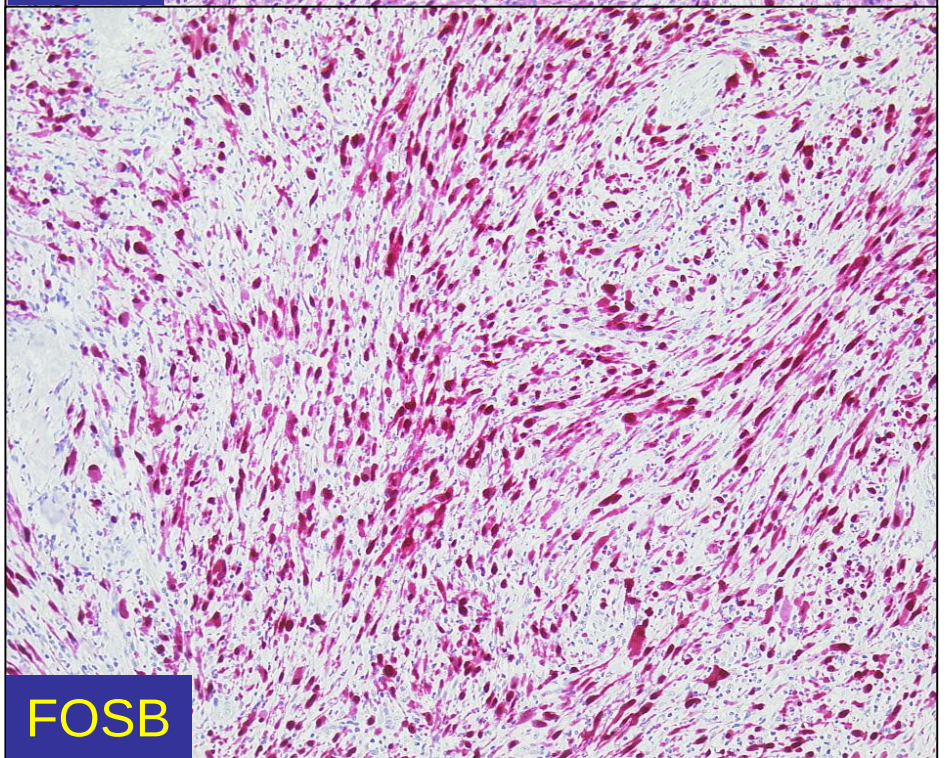
M, 17 years, painful lesions
by courtesy of Prof. G.Massi, Roma





M, 17 years, foot

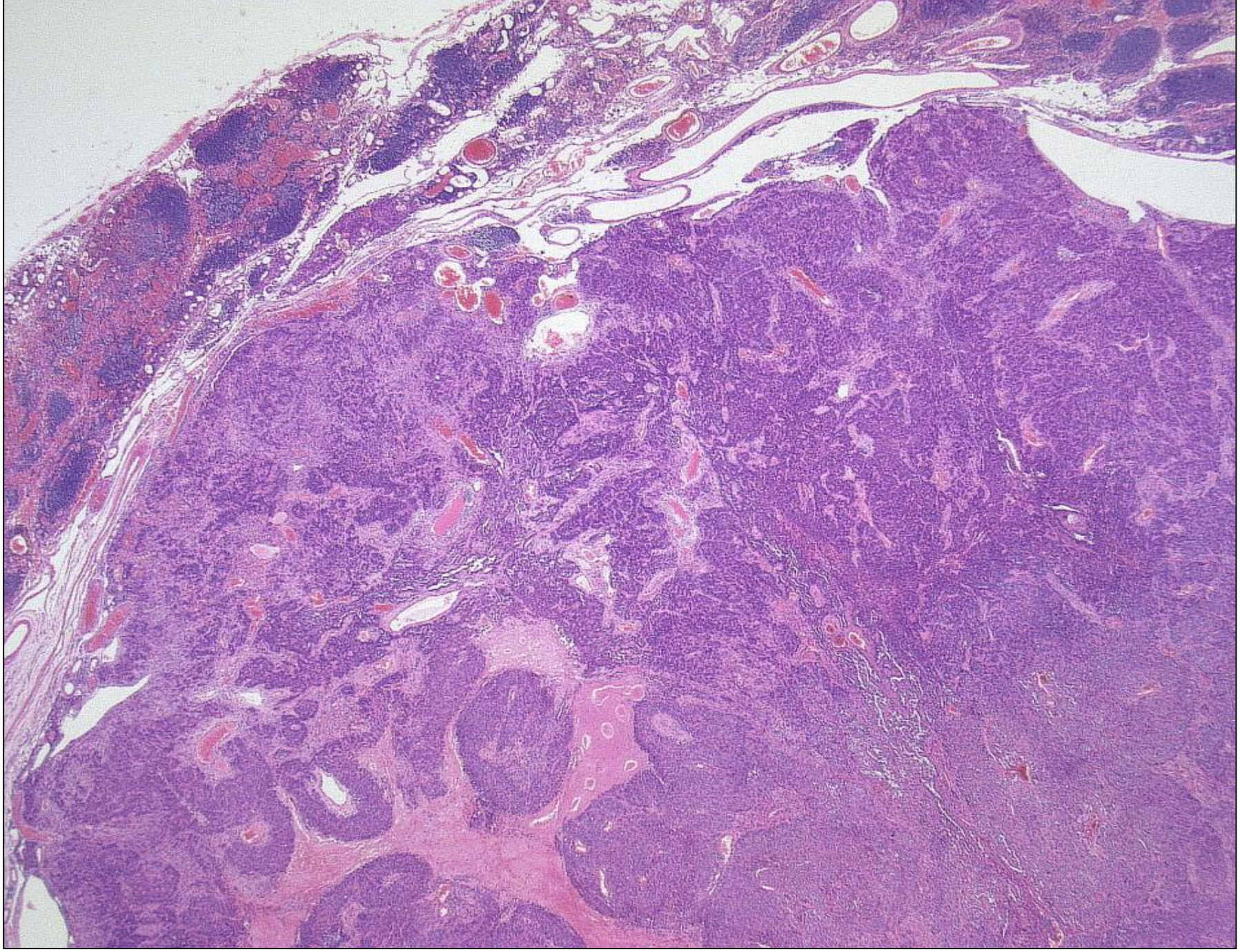




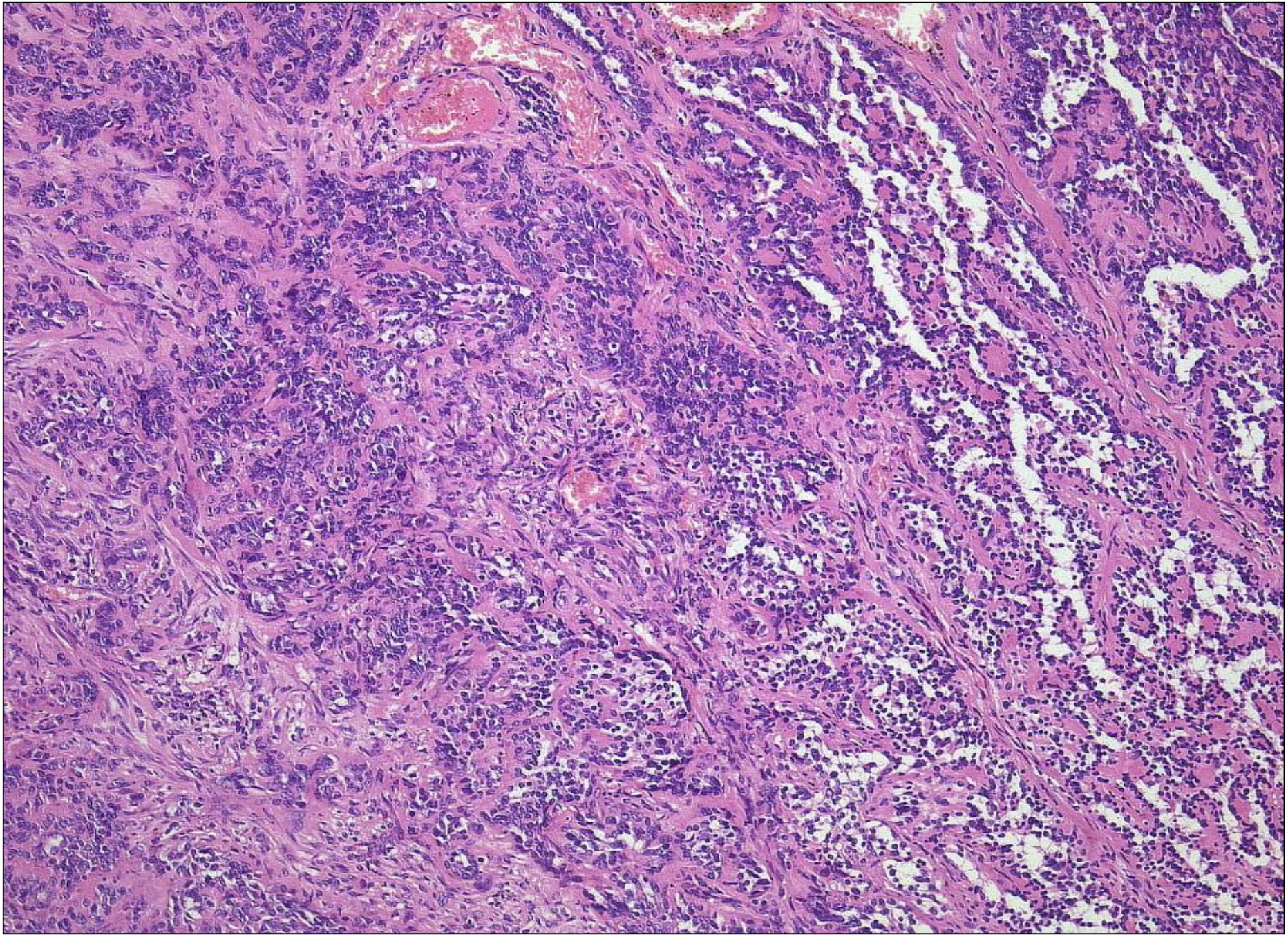
polymorphous Haemangioendothelioma*

- 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



by courtesy of Prof.Fletcher, Boston, MA



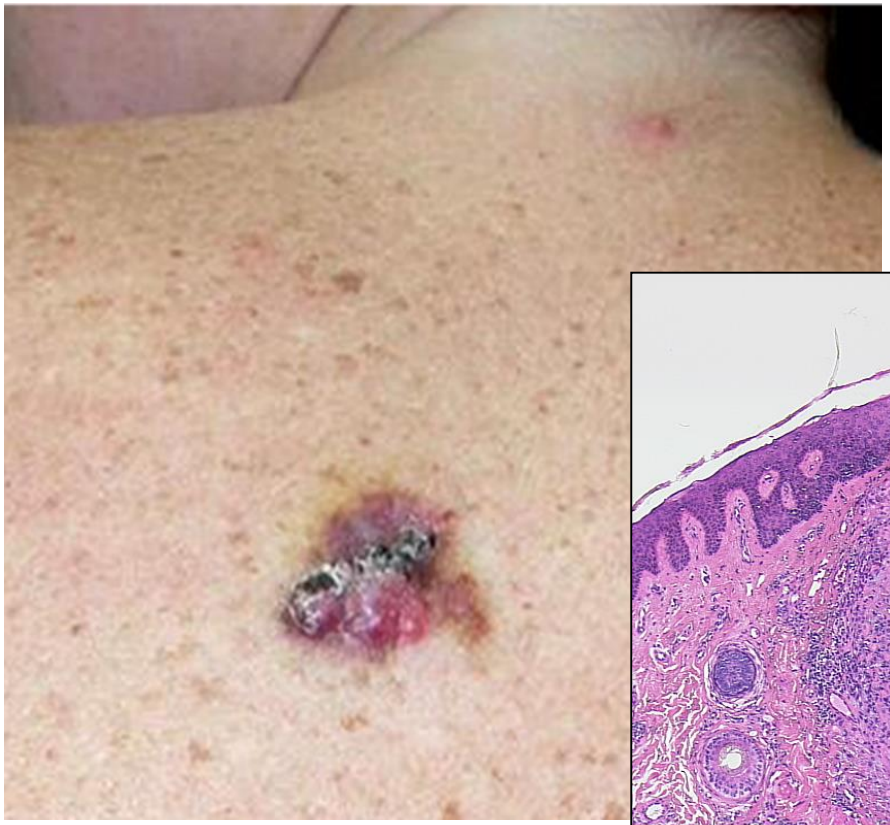
composite Haemangioendothelioma (Nayler SJ et al. AJSP 2000; 24: 352)

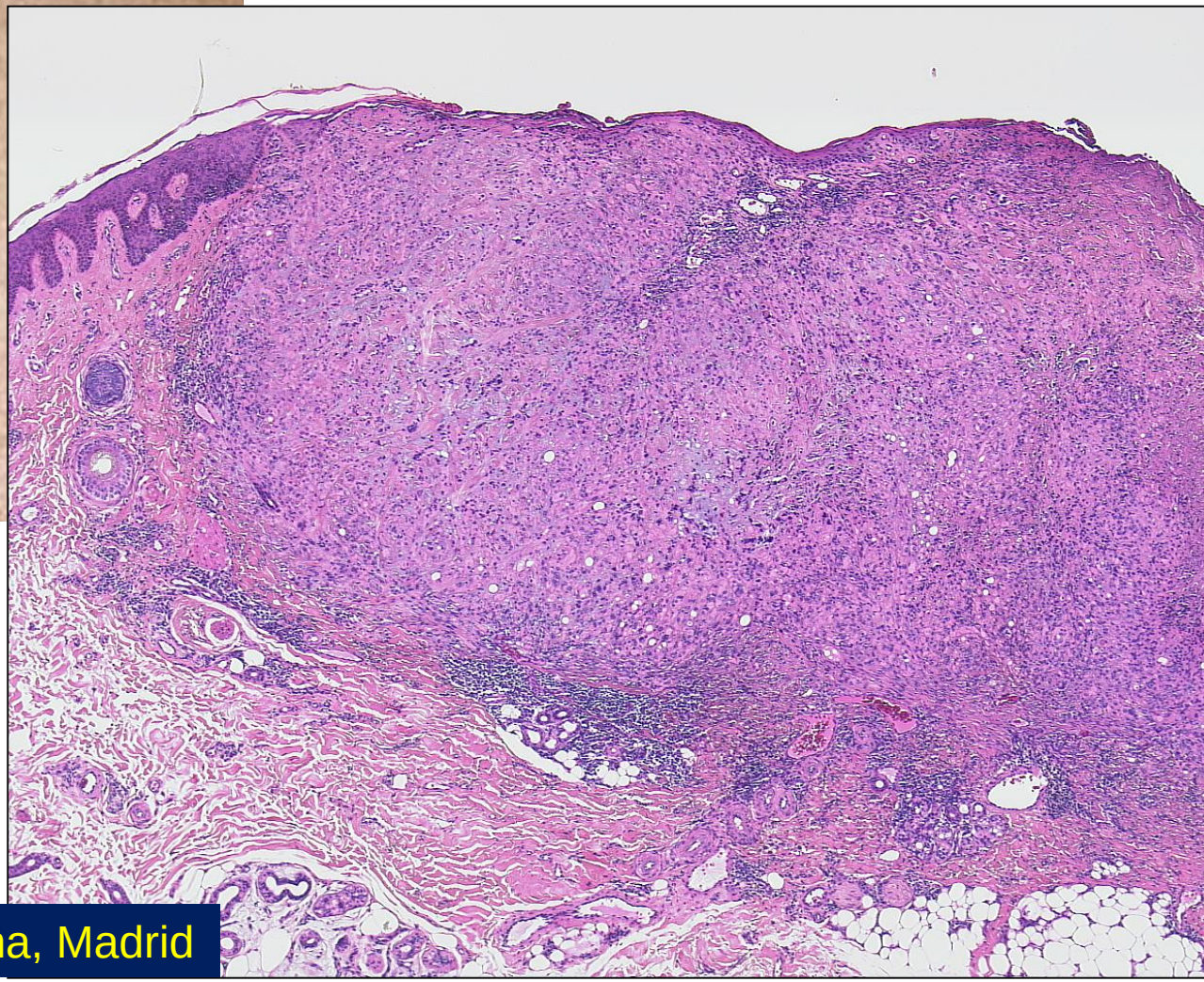
- adult patients
- mainly distal lower extremities > head / neck
- locally aggressive, 50% R, single MTS
- irregular admixture of:
  - haemangioma-like areas
  - low-grade areas (i.e. RHE-like)
  - malignant areas (i.e. EHE, AS)
- composite hemangioendothelioma with neuroendocrine marker expression: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

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%

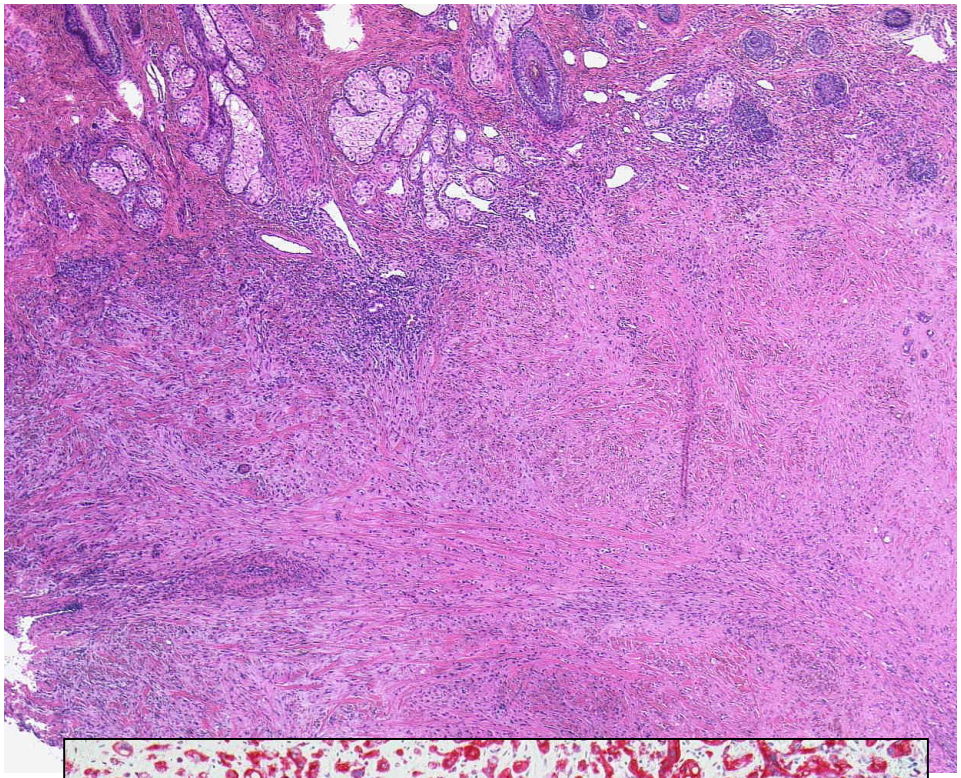
epithelioid Haemangioendothelioma

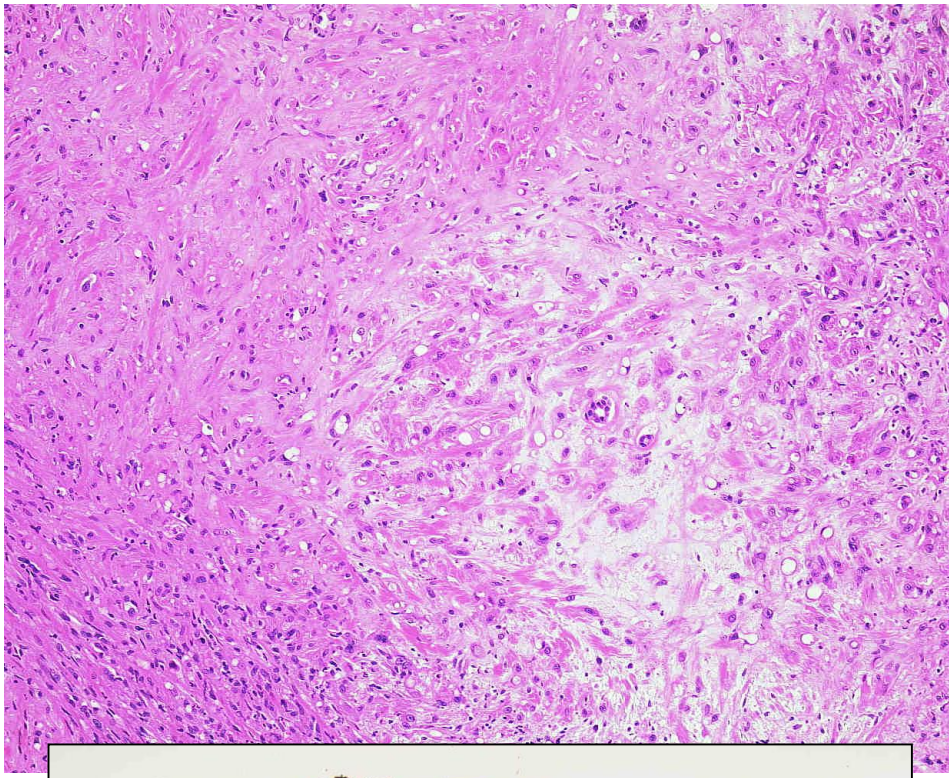


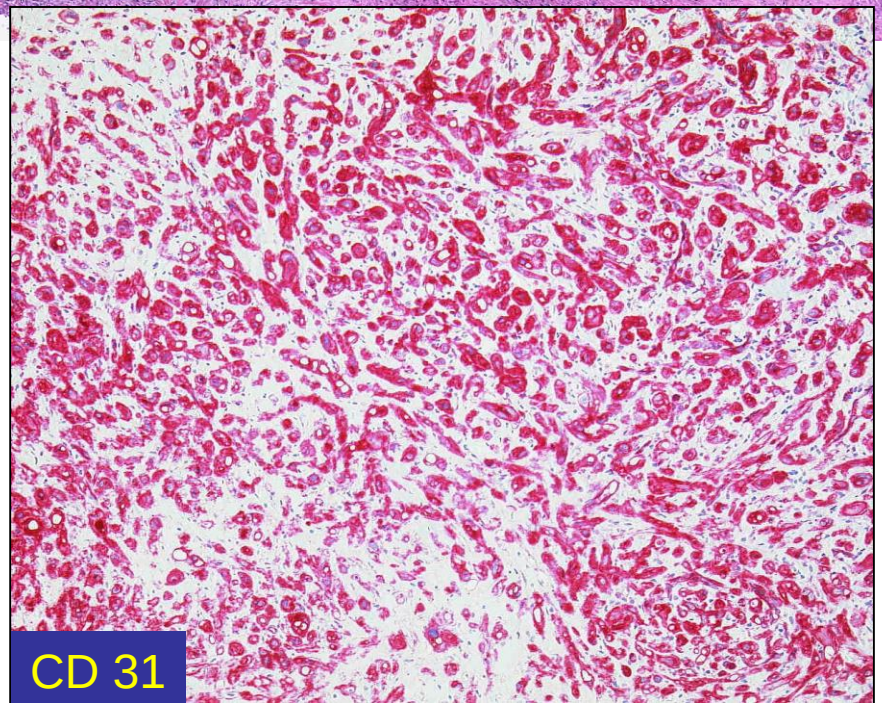


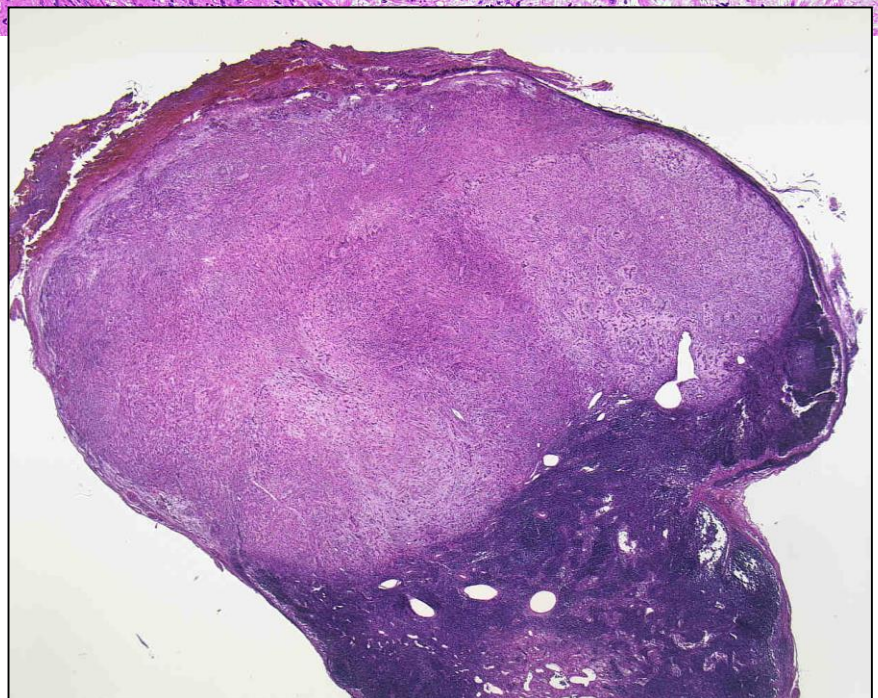
by courtesy of Dr.L.Requena, Madrid

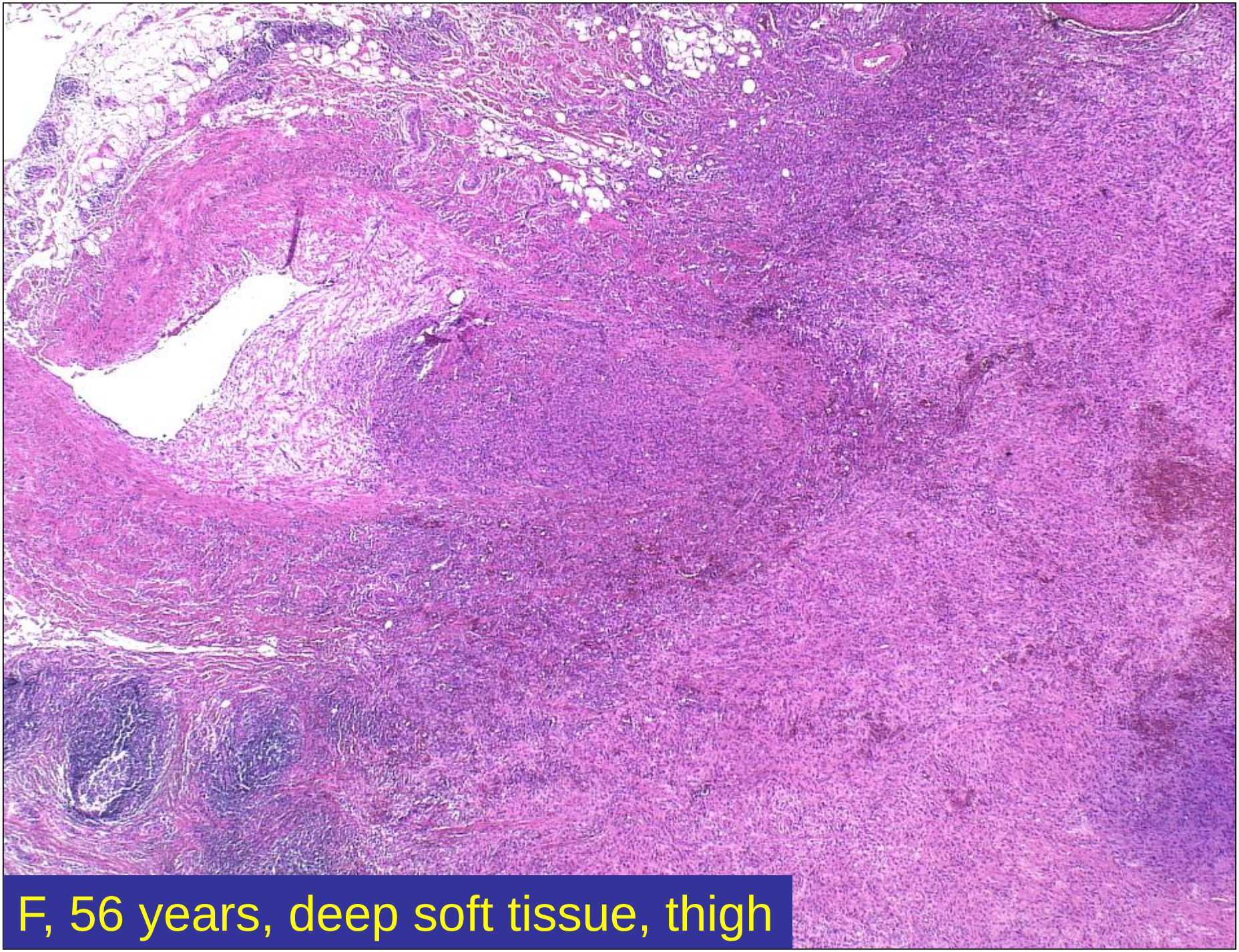
M, 9 years, painful erythematous plaque
cervical lymph node metastasis
J Cutan Pathol 2008; 35: 80

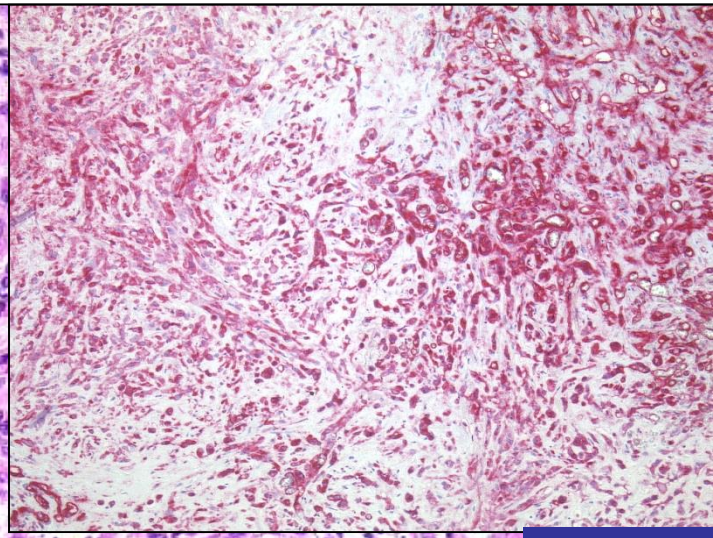





CD 31




F, 56 years, deep soft tissue, thigh



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,*]

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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

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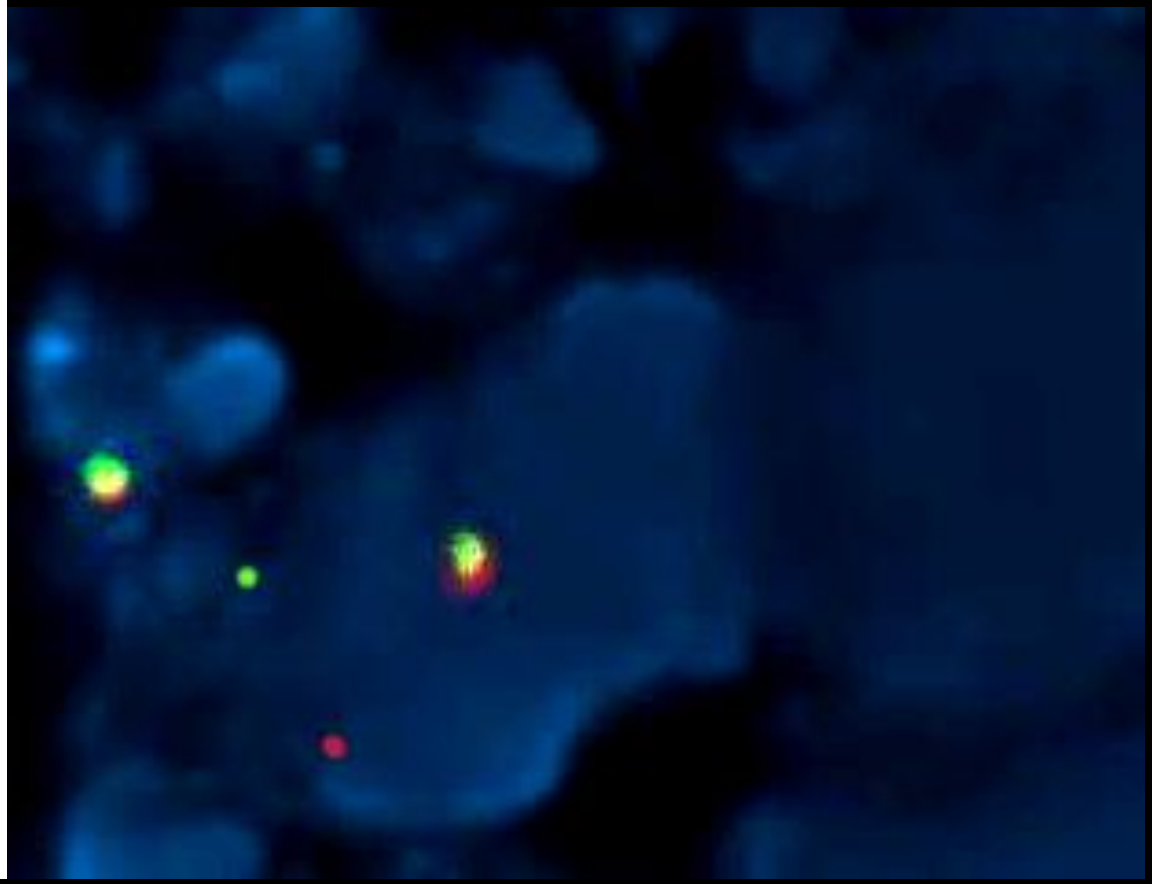
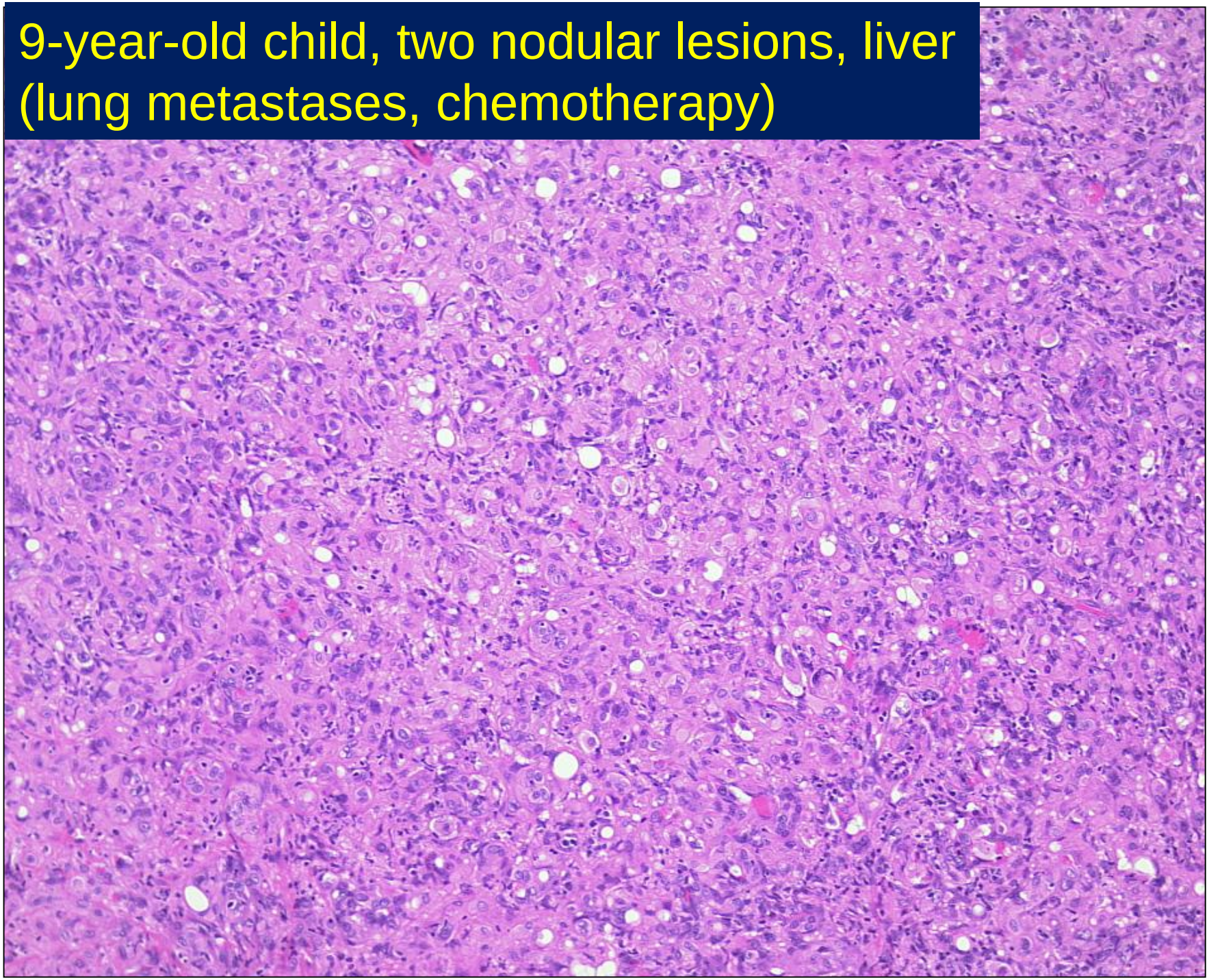
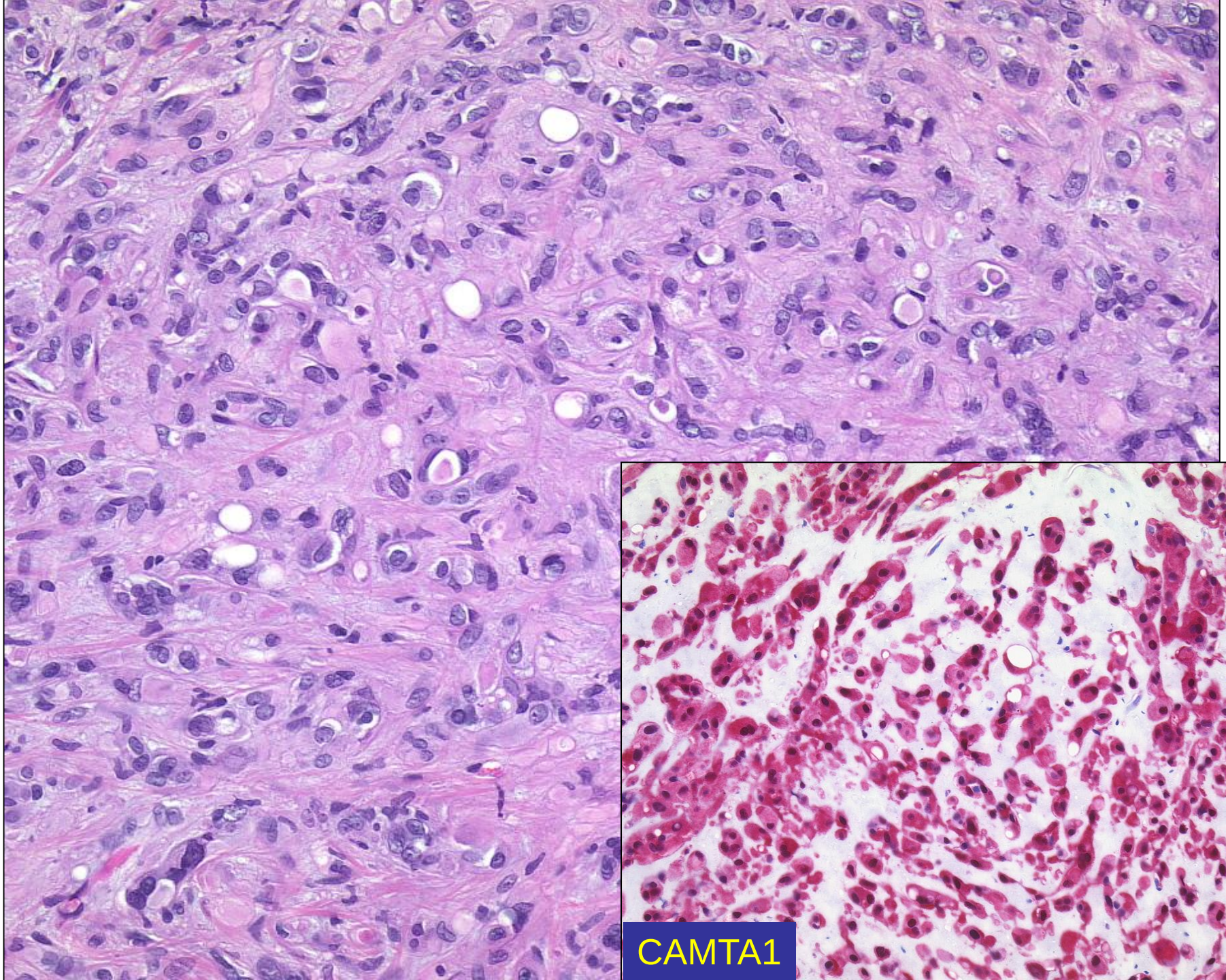
°Contributed equally to this work.

CAMTA1 **fusion probe**

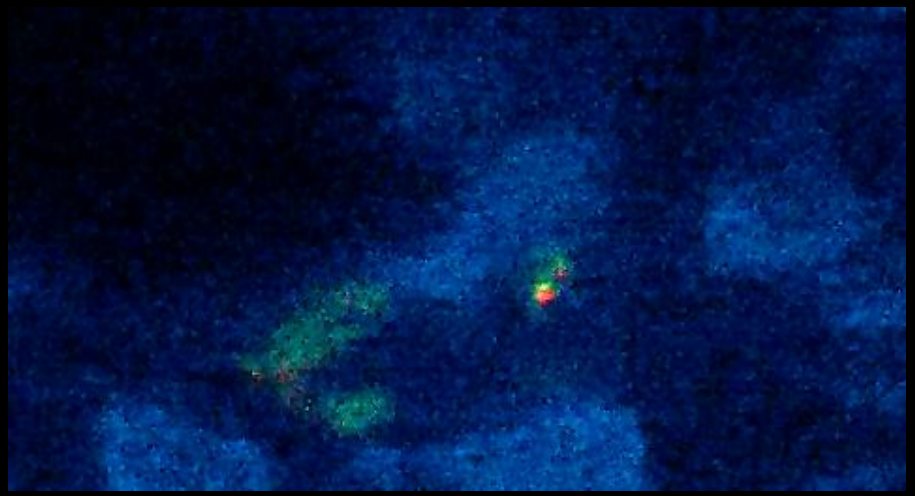


9-year-old child, two nodular lesions, liver (lung metastases, chemotherapy)




CAMTA1

t(1;3)(p36.3;q25) WWTR1-CAMTA1
dual color fusion probe



epithelioid Haemangioendothelioma
with *WWTR1-CAMTA1* fusion

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]

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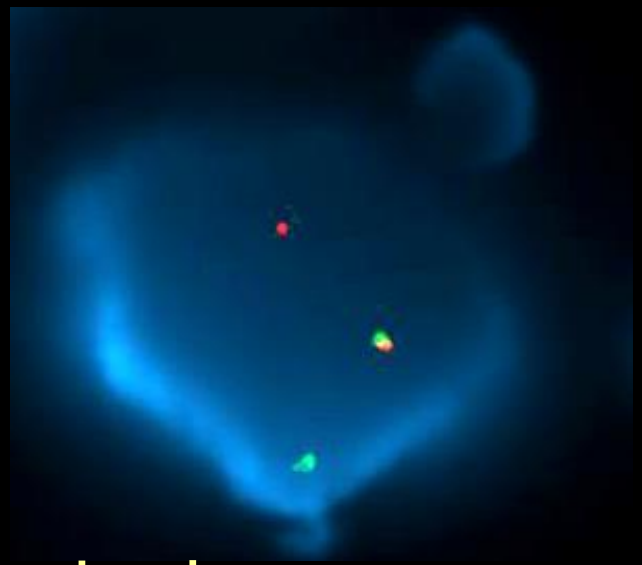
[8]Department of Pathology Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Abstract

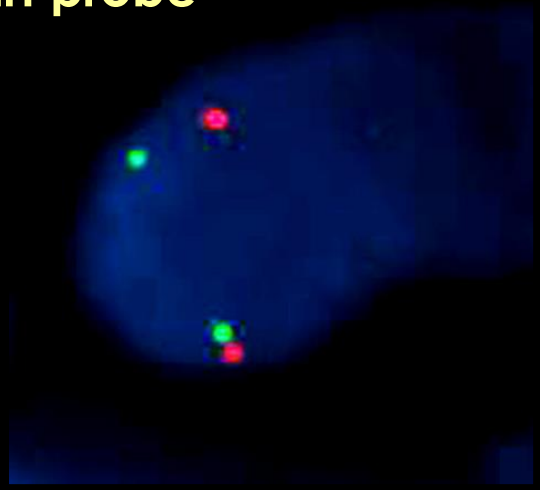
Conventional epithelioid hemangioendotheliomas (EHE) have a distinctive morphologic appearance and are characterized by a recurrent t(1;3) translocation, resulting in a *WWTR1-CAMTA1* fusion gene. We have recently encountered a fusion-negative subset characterized by a somewhat different morphology, 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

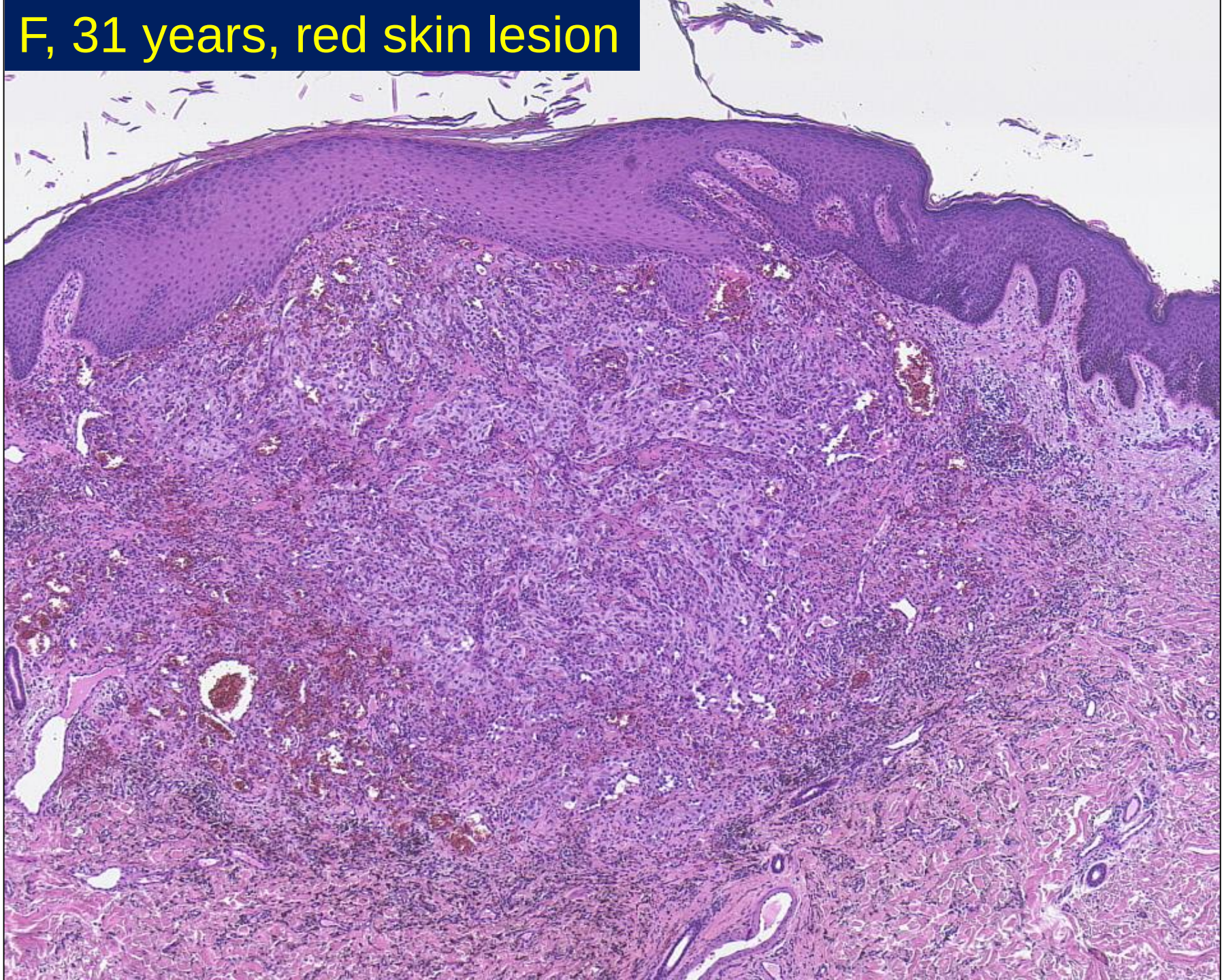
Correspondence: Cristina R Antonescu, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021, antonesc@mskcc.org; and Christopher DM Fletcher, Brigham and Women's Hospital, Boston, MA, cfletcher@partners.org.

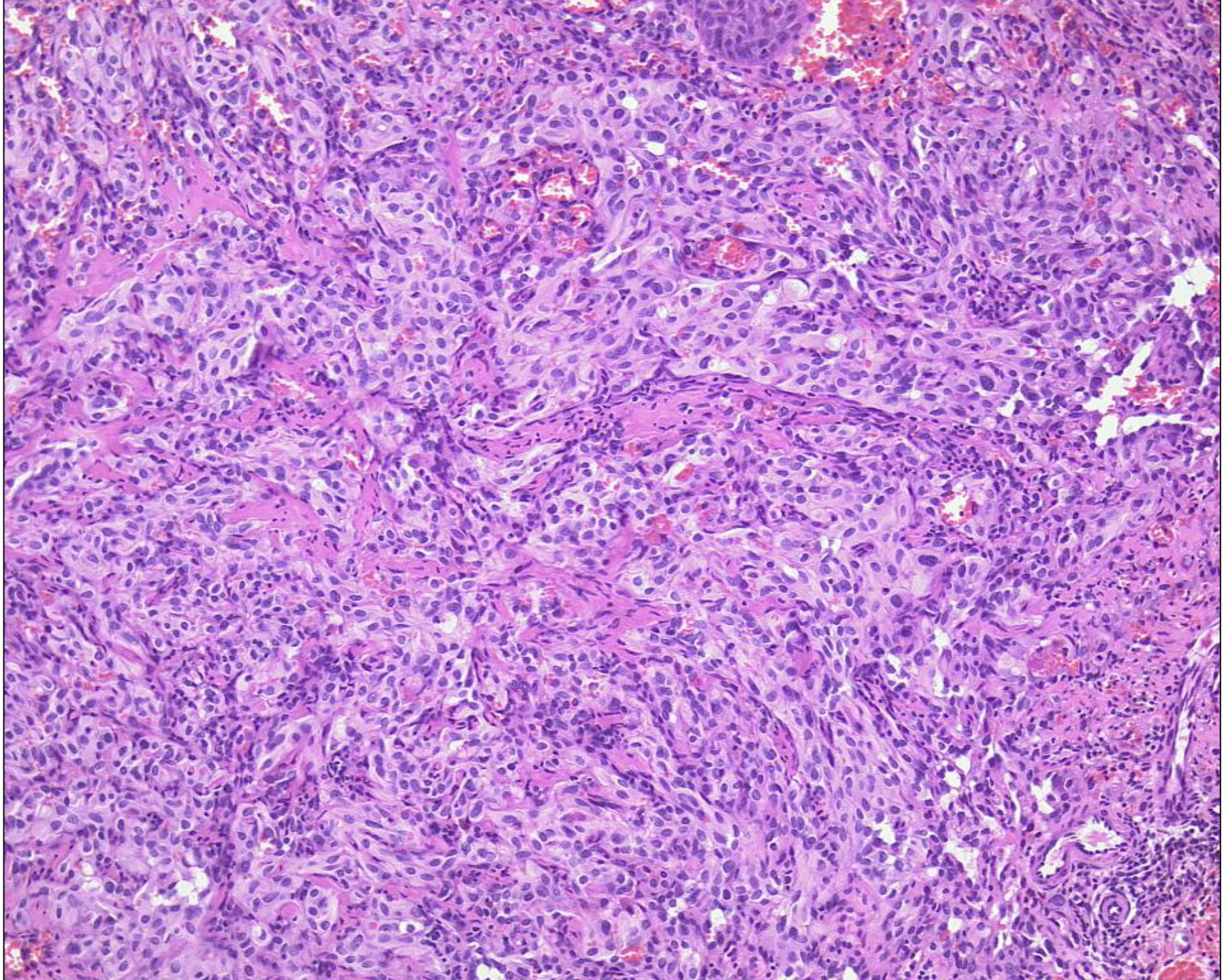
Conflict of interest: none



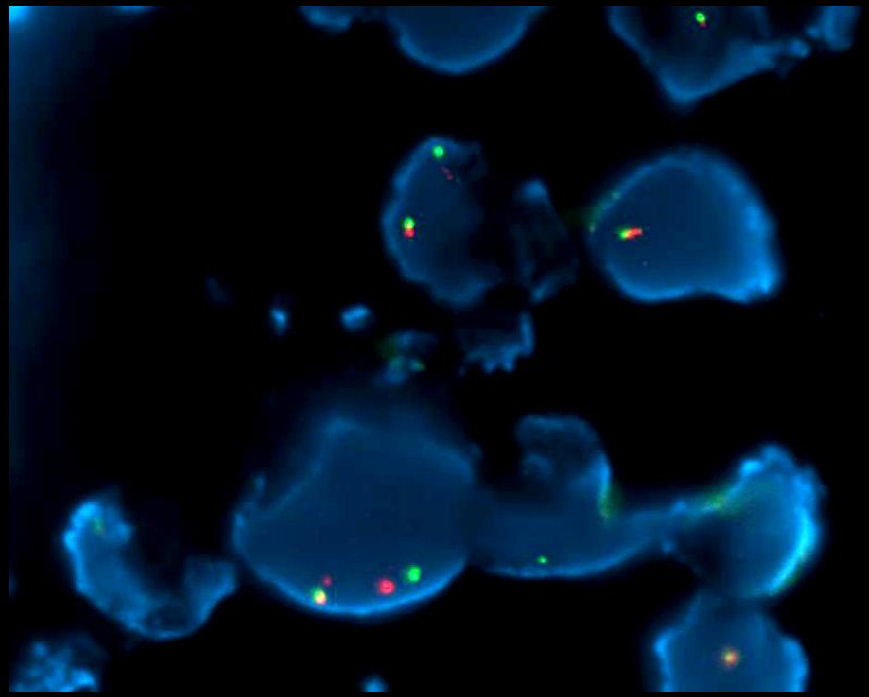
TFE3 **break-apart probe**




F, 31 years, red skin lesion



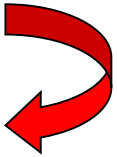
TFE3 dual color break-apart probe



epithelioid Haemangioendothelioma with *TFE3* break

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%

Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas

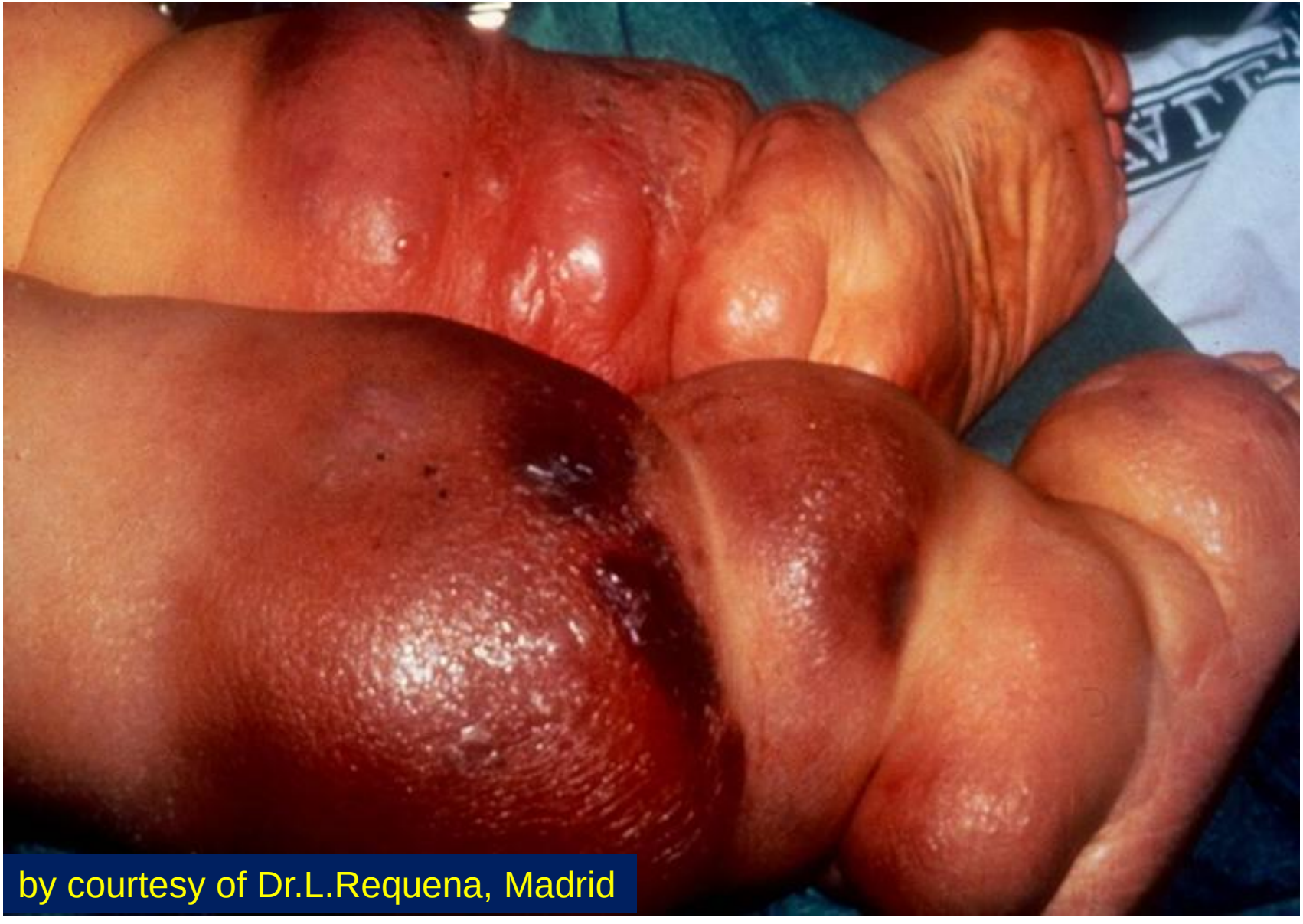
Angiosarcoma

Cutaneous Angiosarcoma

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

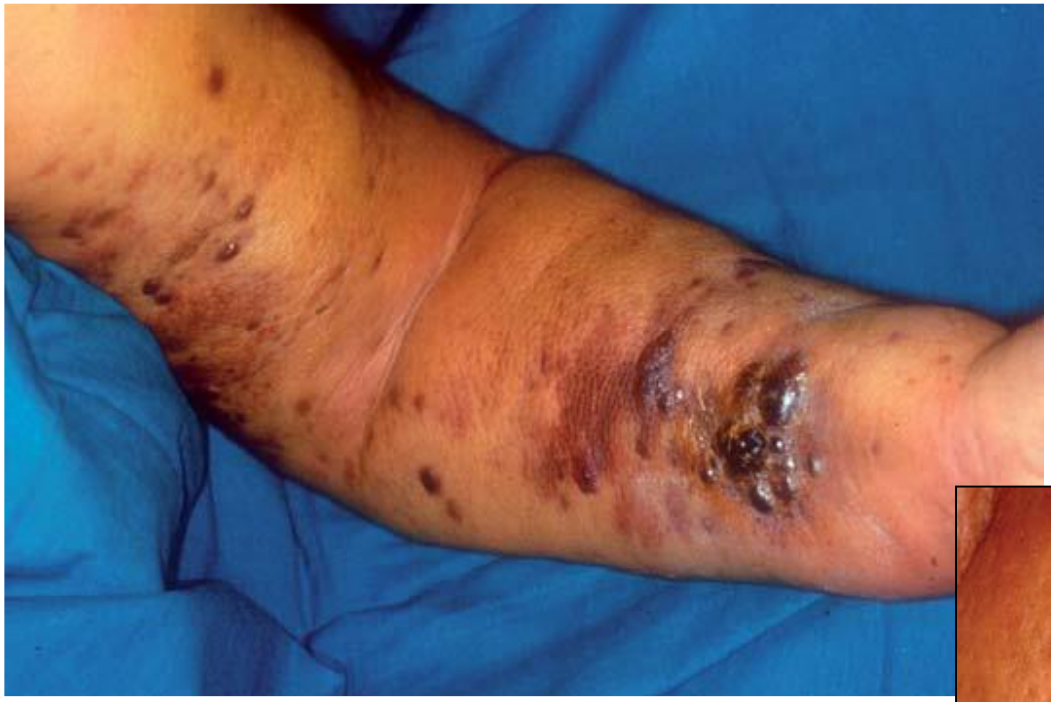
Angiosarcoma of Soft Tissues

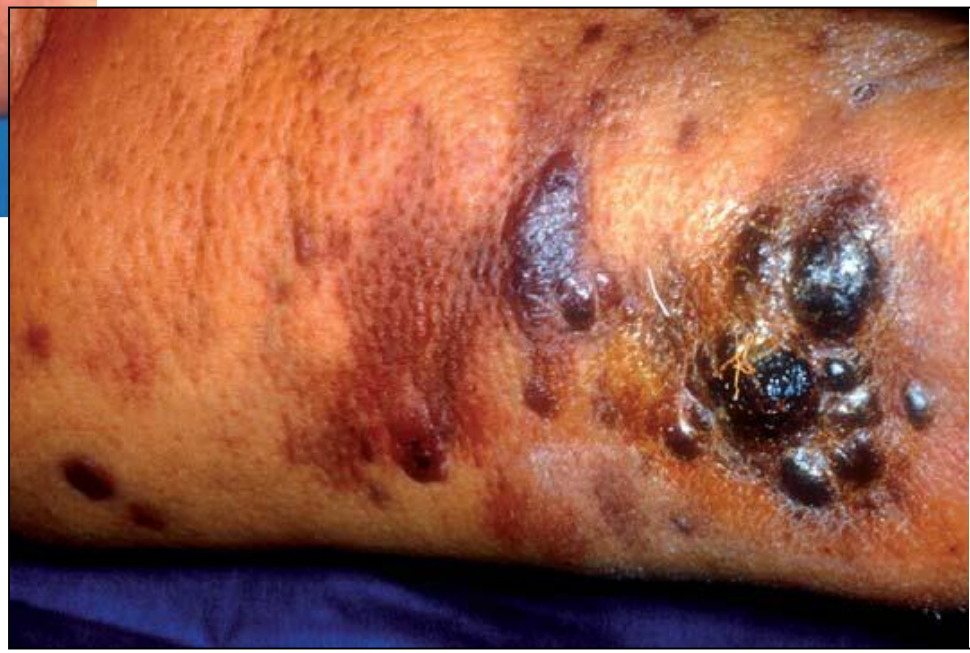
Lymphedematous Angiosarcoma (congenital chronic lymphedema)



by courtesy of Dr.L.Requena, Madrid

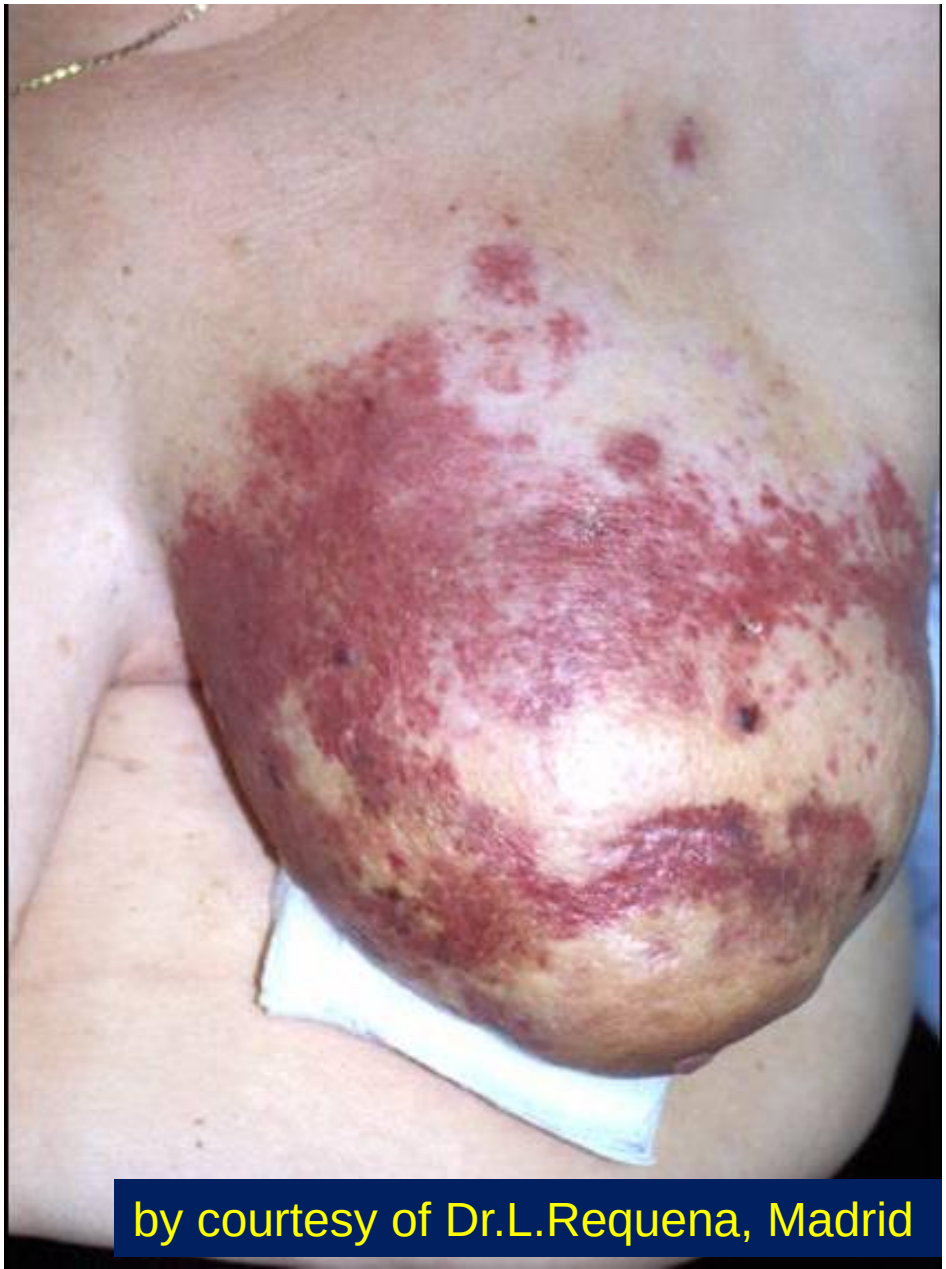
Lymphedematous Angiosarcoma (Stewart Treves Syndrome)

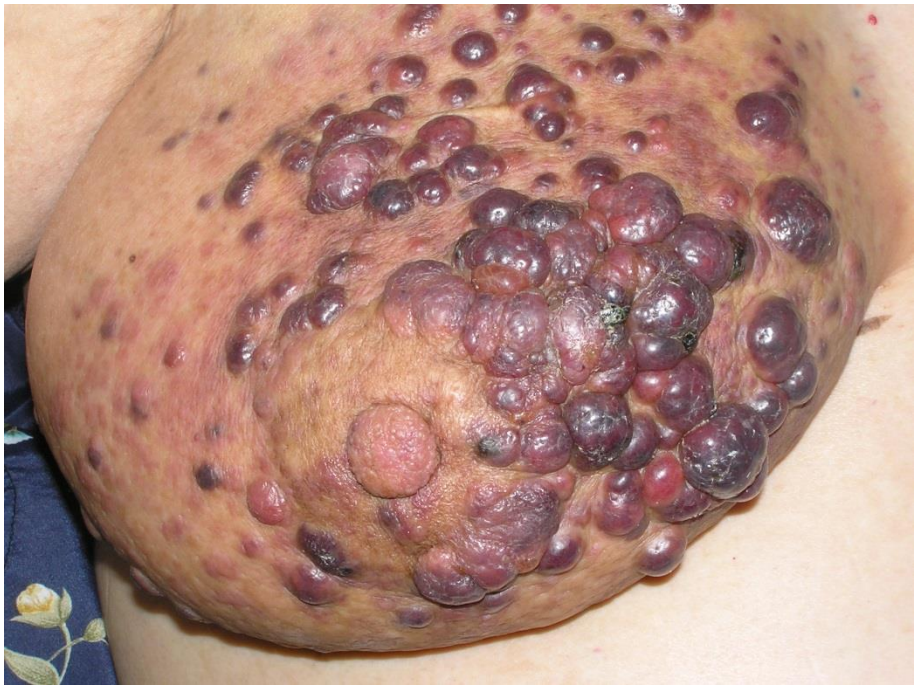




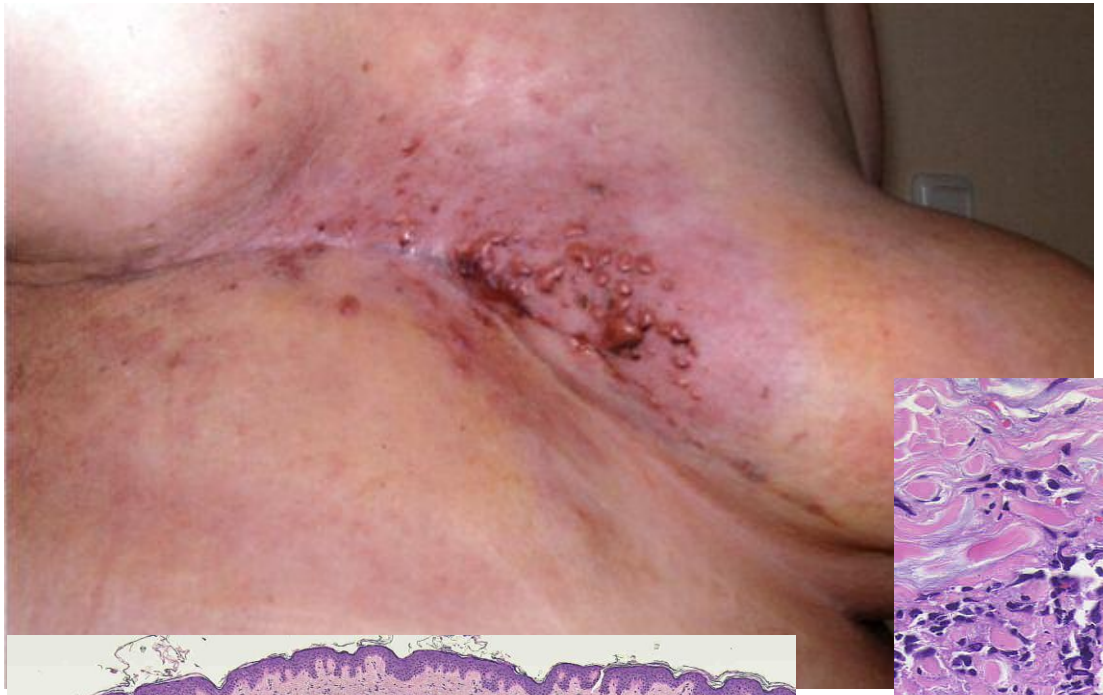
by courtesy of Dr.L.Requena, Madrid

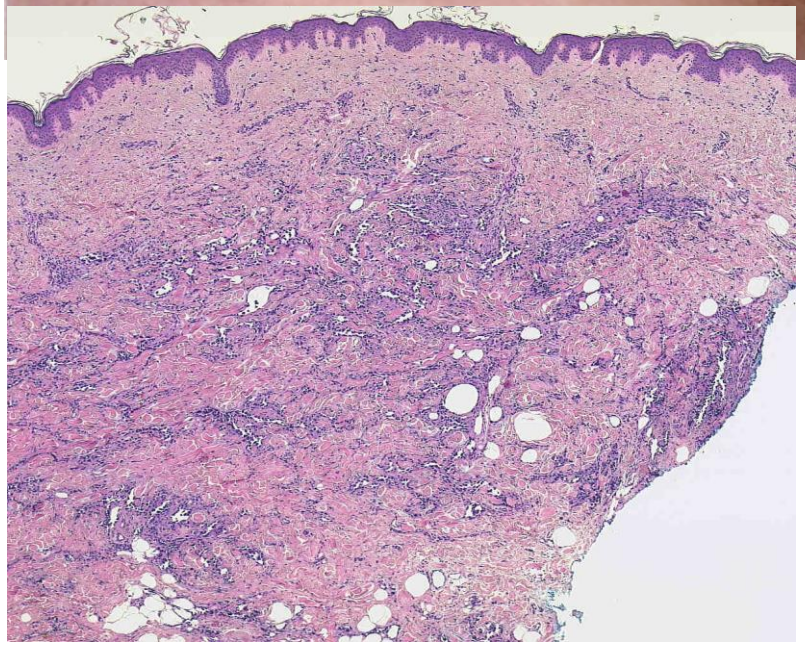
Postirradiation Angiosarcoma

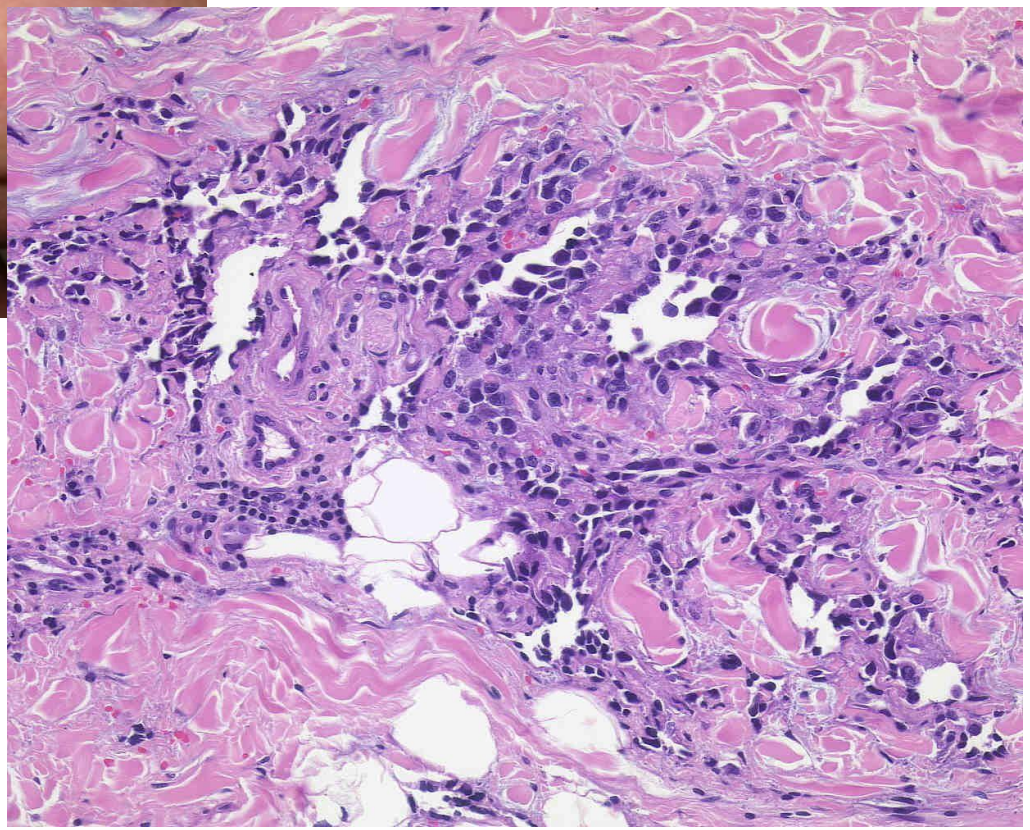


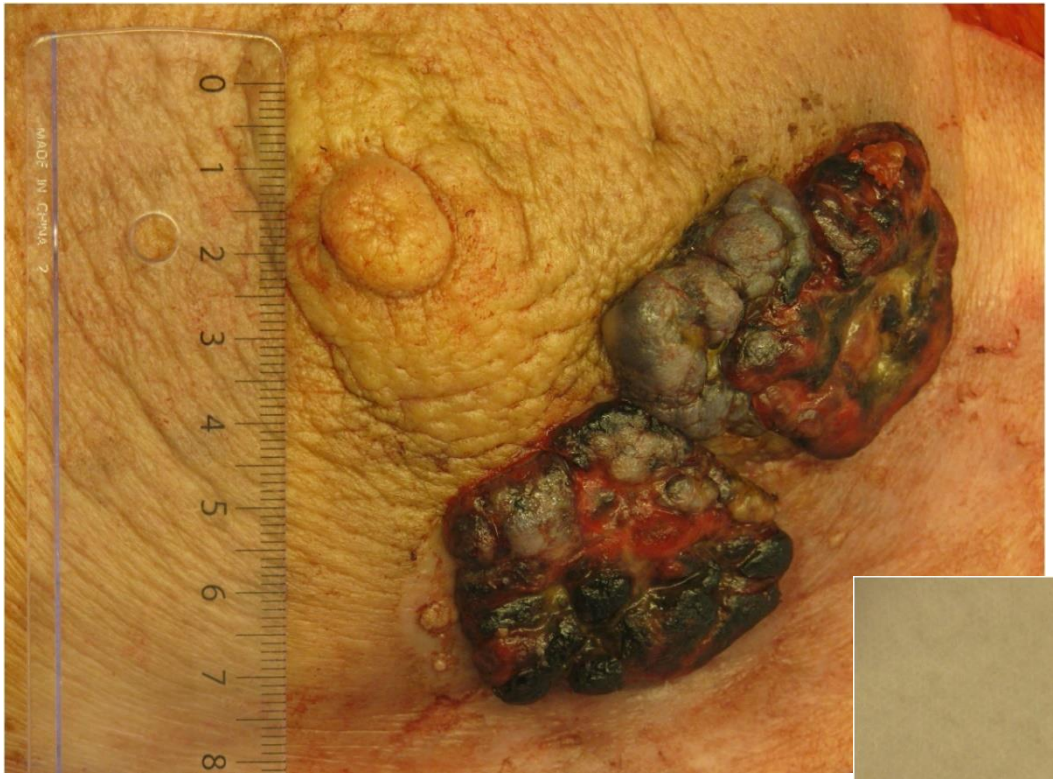


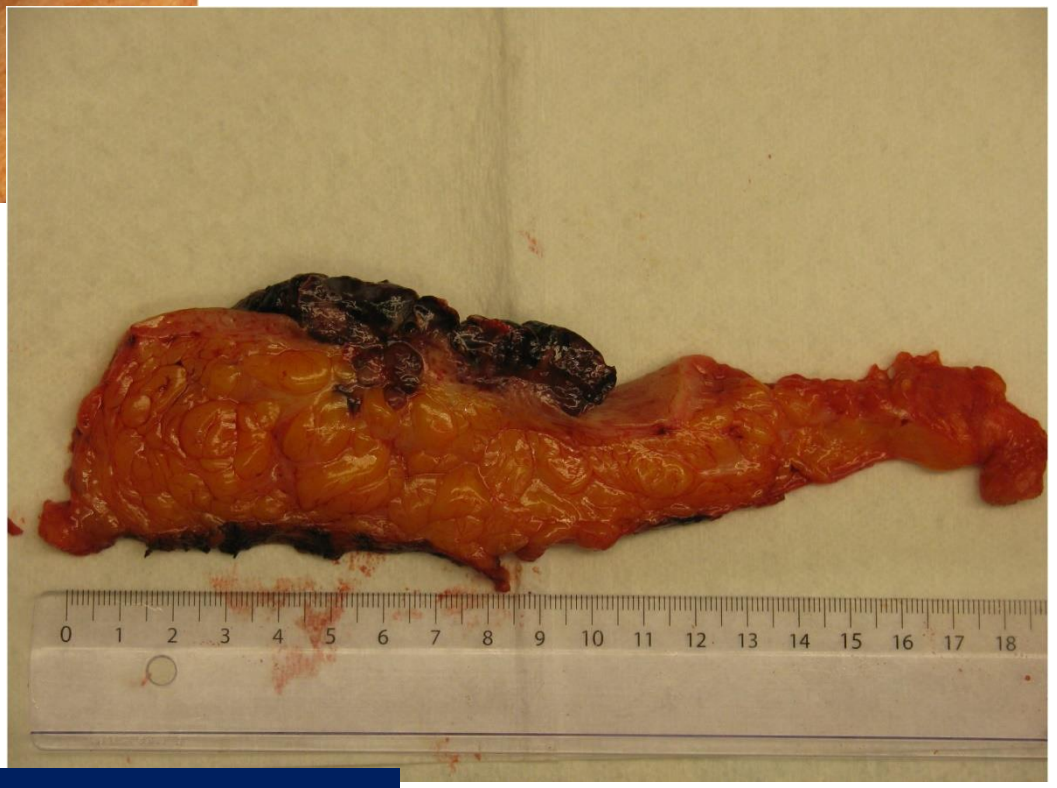
Postirradiation Angiosarcoma





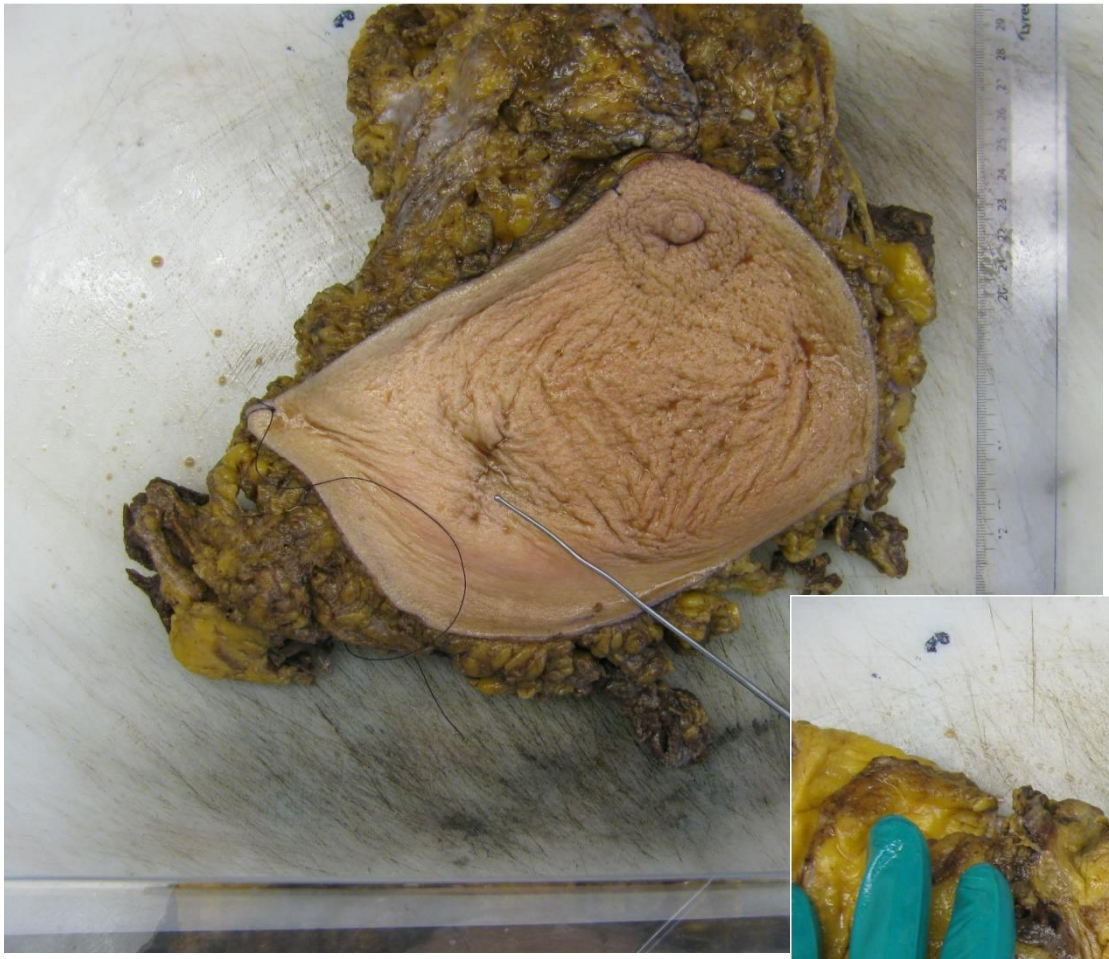


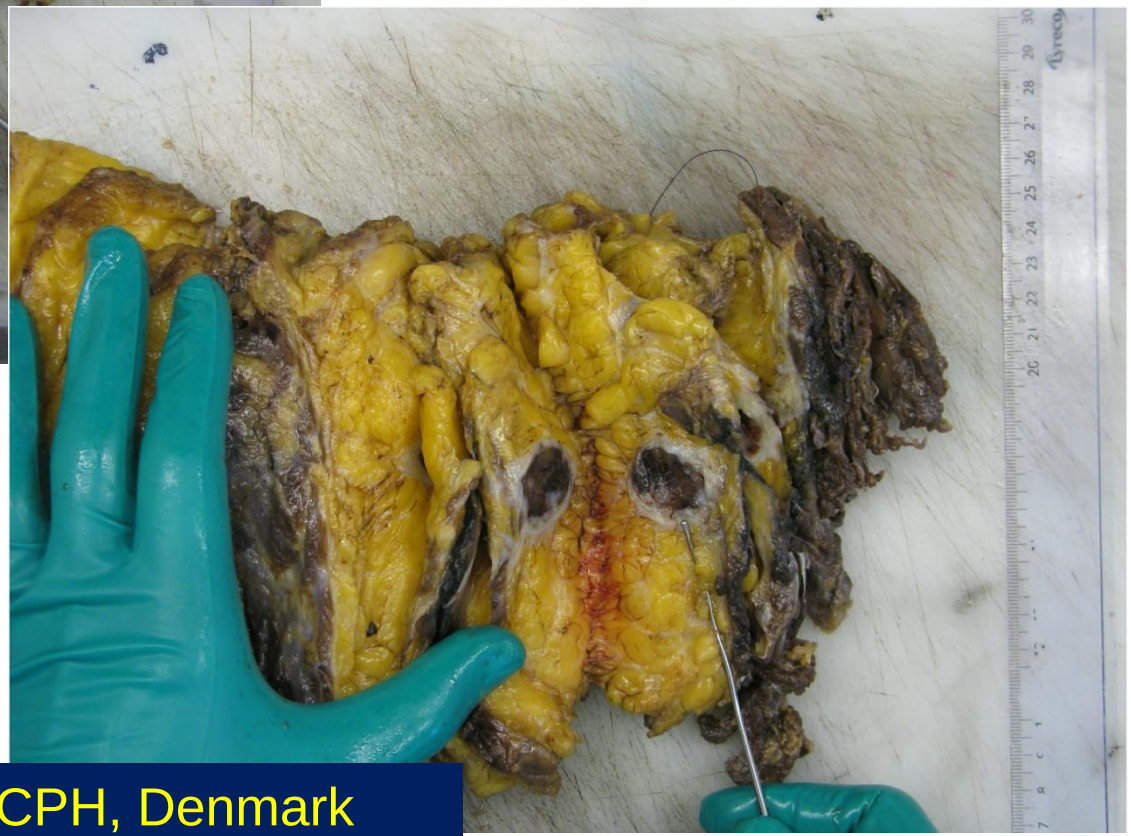




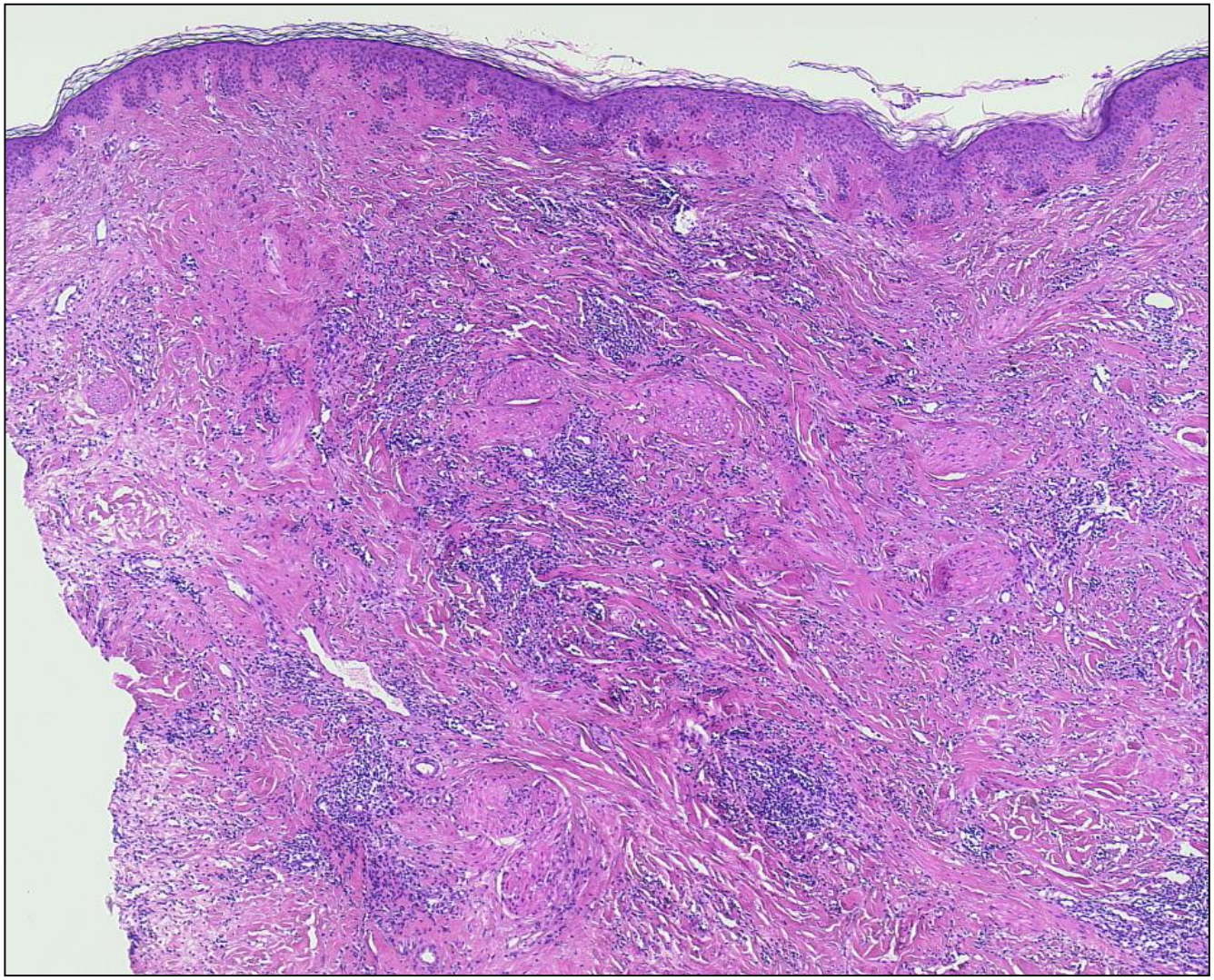
by courtesy of Dr. Katalin Kiss, CPH, Denmark

Radiation-associated parenchymal Angiosarcoma

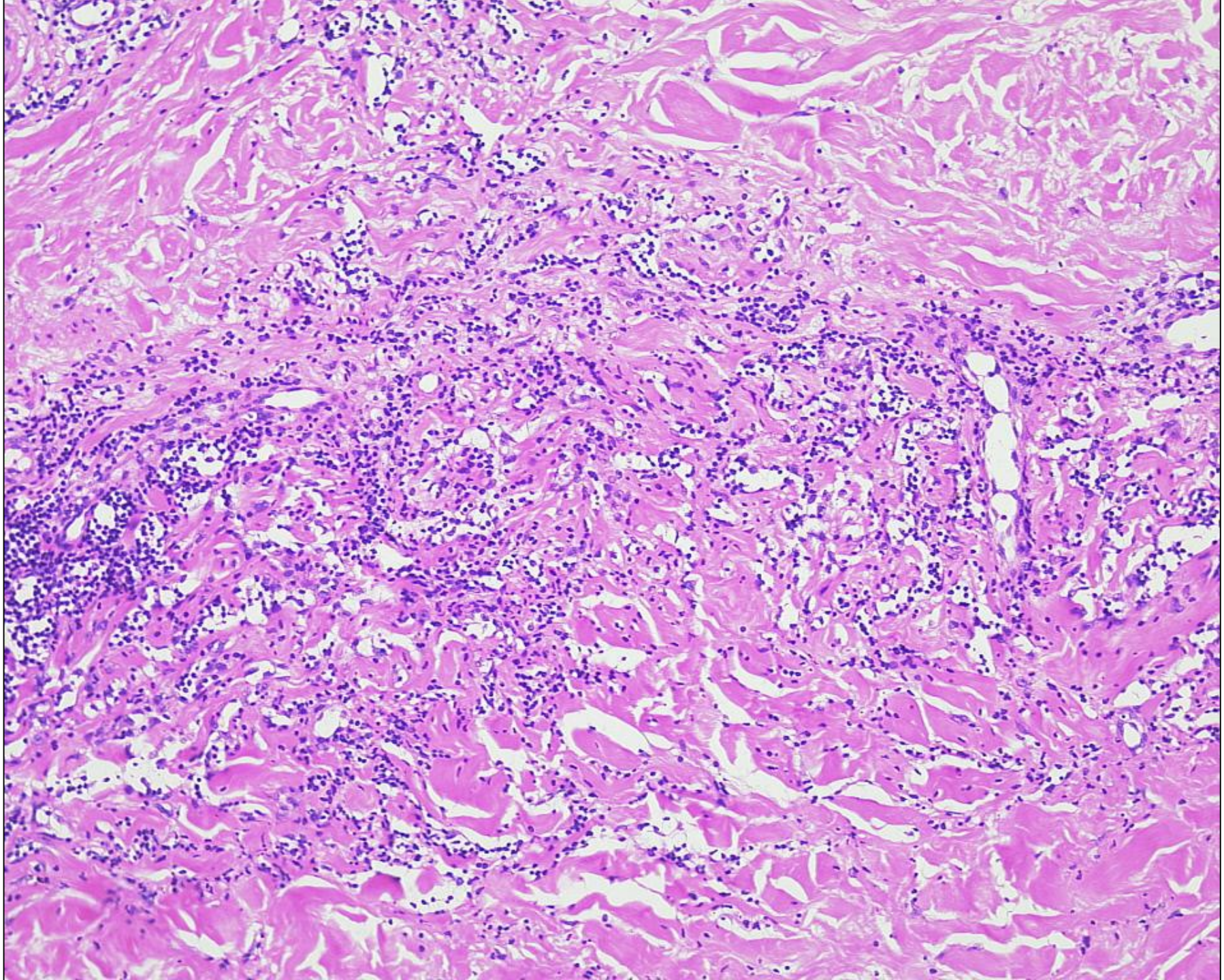


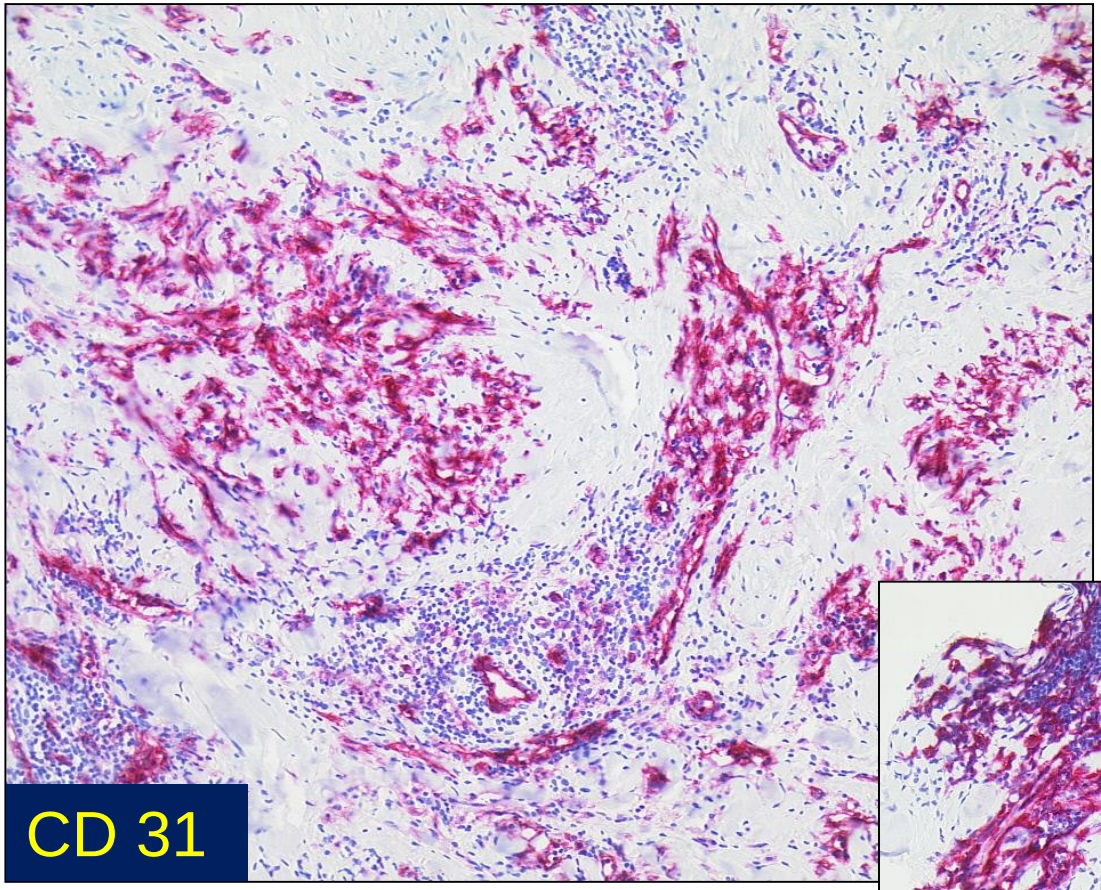


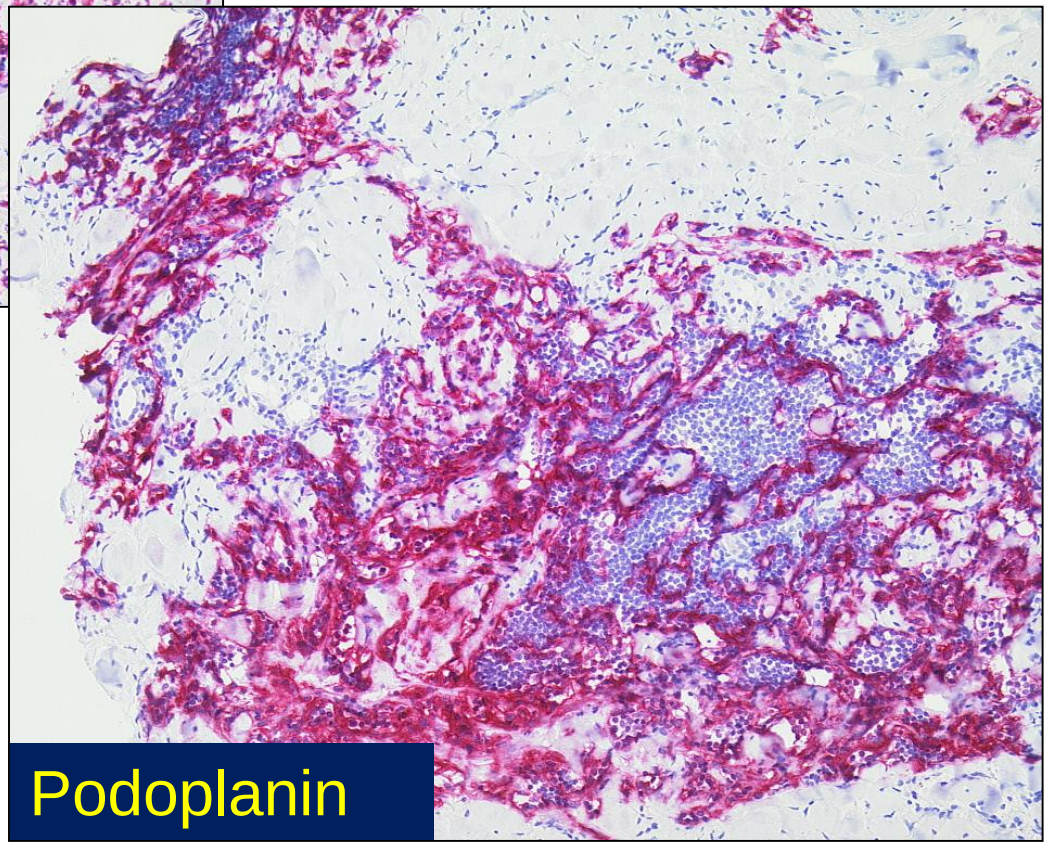
by courtesy of Dr. Katalin Kiss, CPH, Denmark

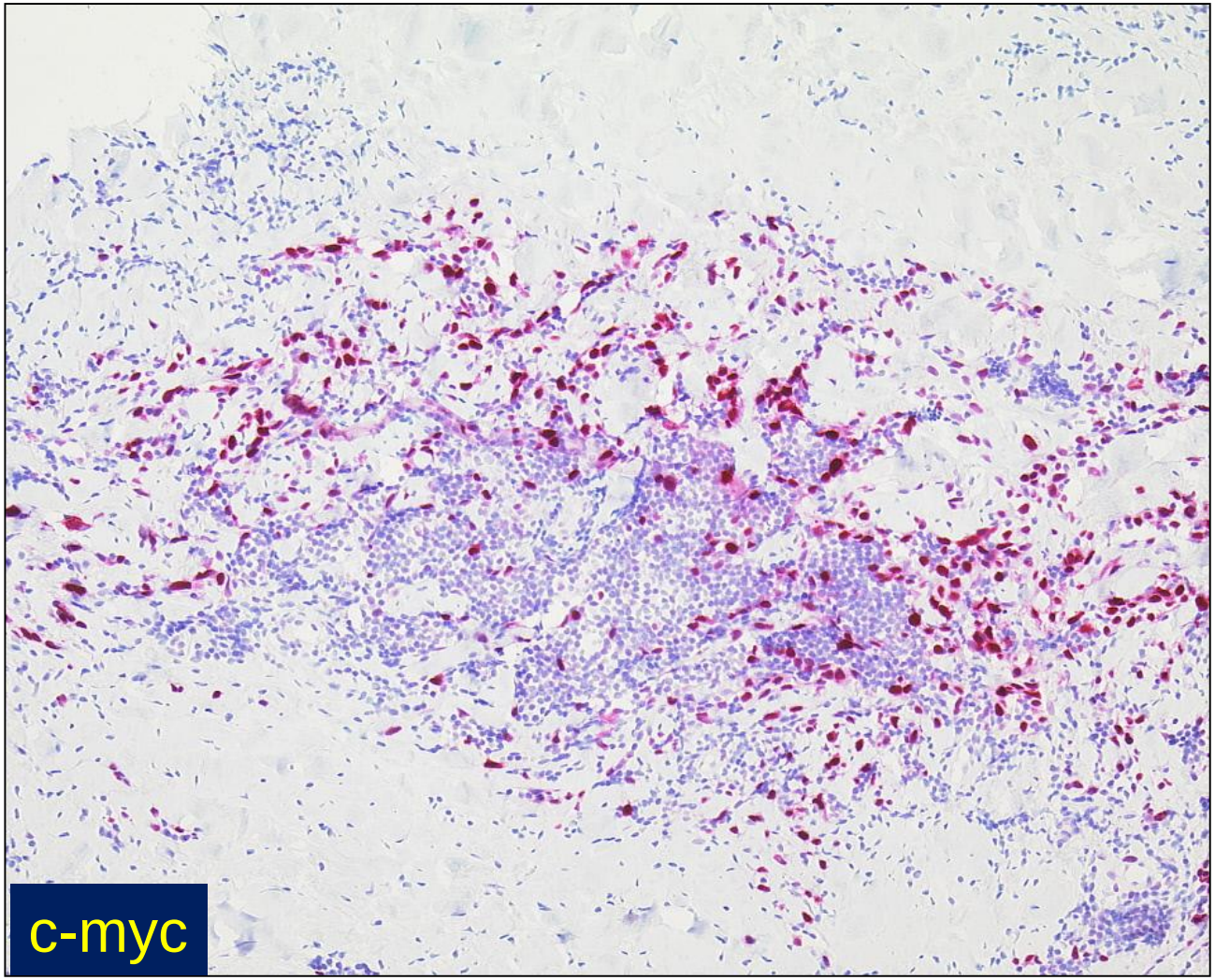


F, 62 years radiotherapy of breast cancer clinically inflammatory disorder was suspected



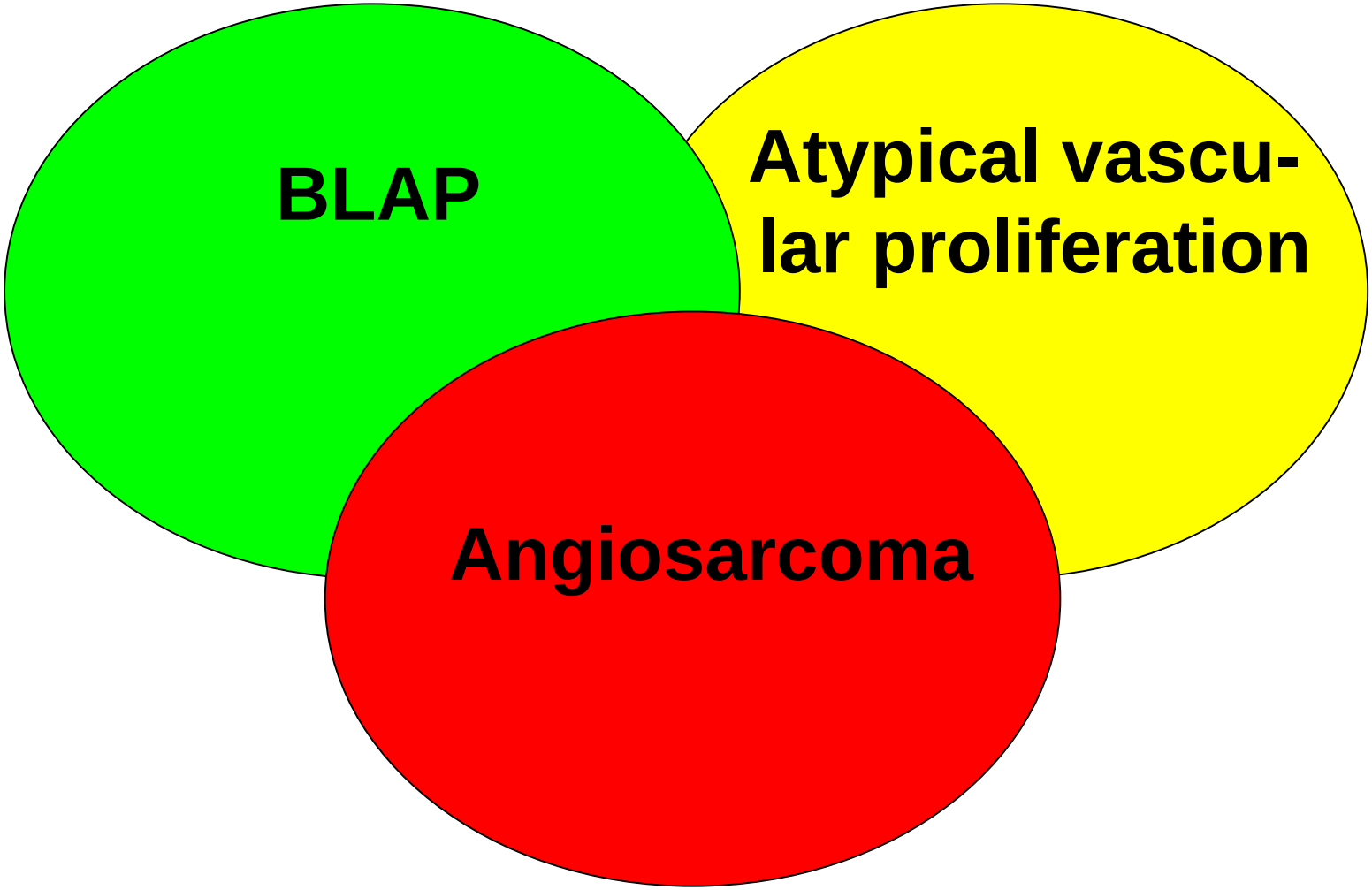

CD 31


Podoplanin



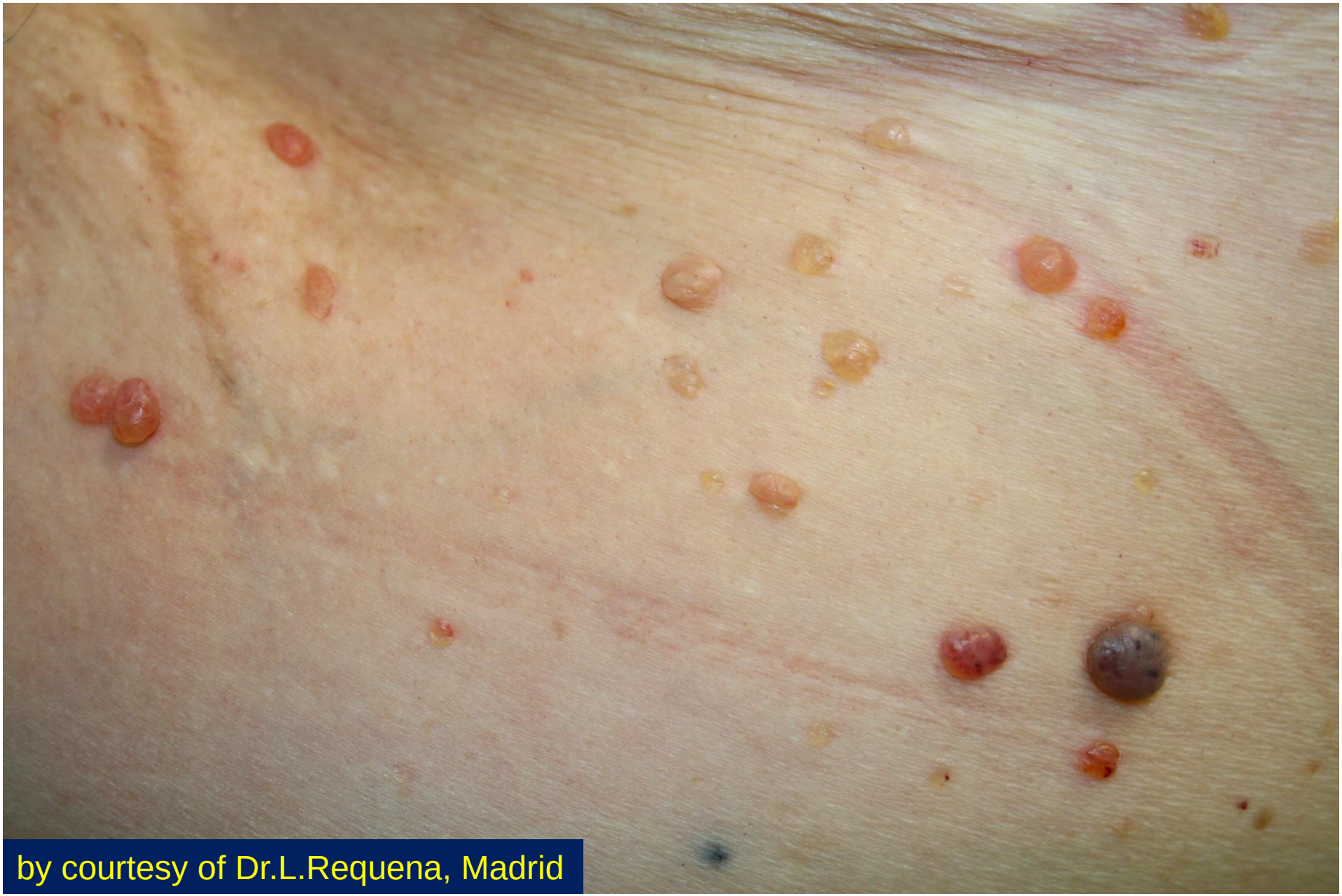
Radiation-associated angiosarcoma in the setting of breast cancer mimicking radiation dermatitis: a diagnostic pitfall
Daniels BH et al. J Cutan Pathol 2017; 44: 456-461

Vascular Proliferations after Radiotherapy*



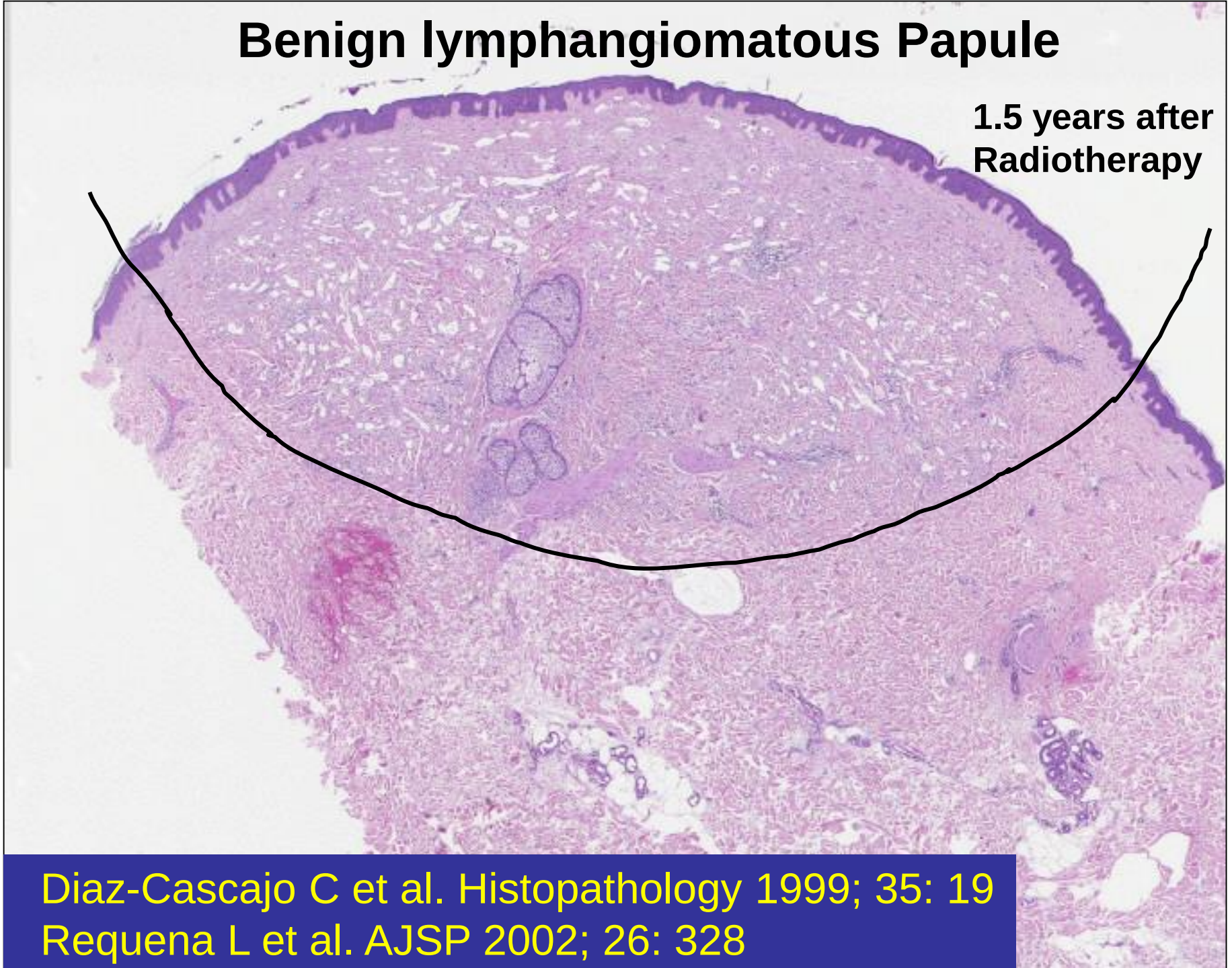
* Brenn T, Fletcher CDM AJSP 2005; 29: 983
Mattoch IW at al. JAAD 2007; 57: 126

Benign lymphangiomatous Papule



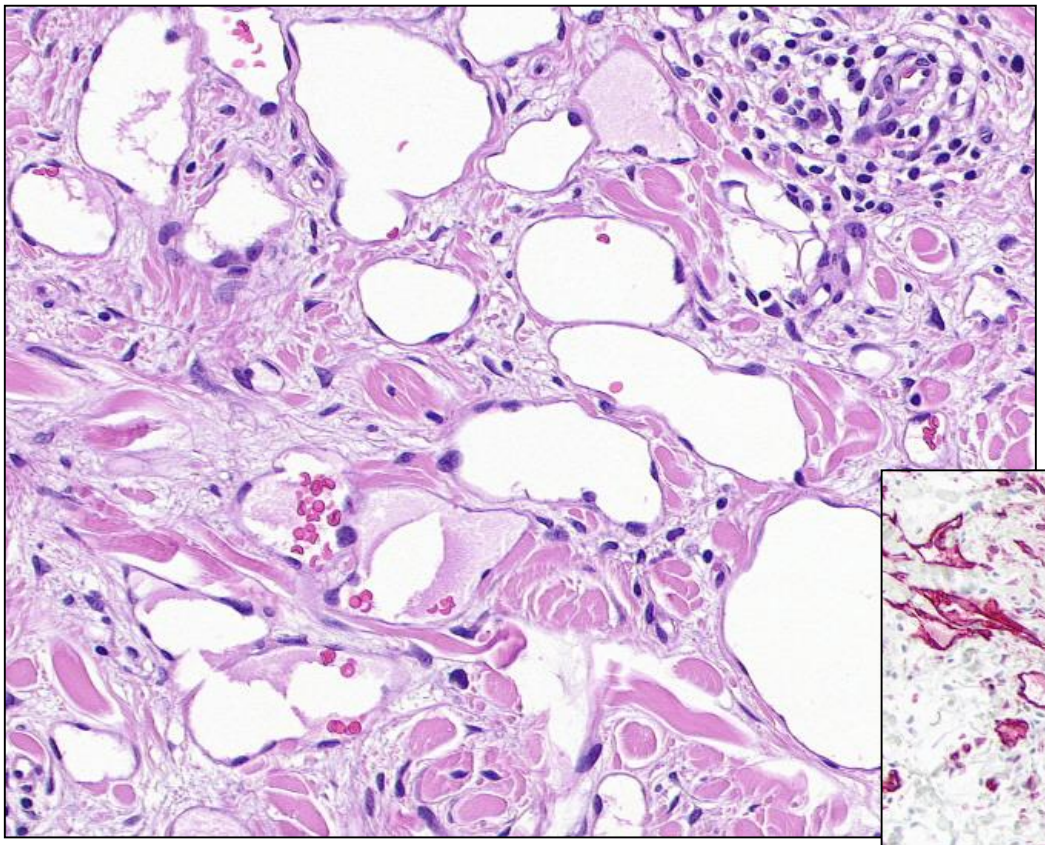
by courtesy of Dr.L.Requena, Madrid

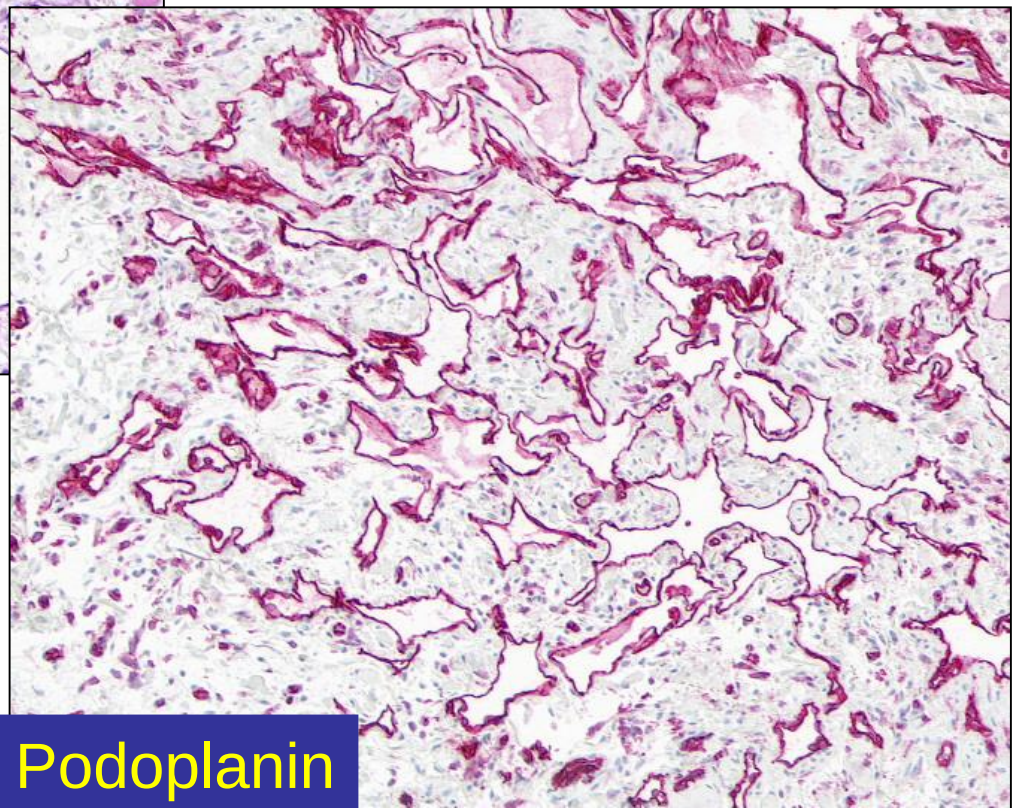
Benign lymphangiomatous Papule



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

Benign lymphangiomatous Papule





Podoplanin

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

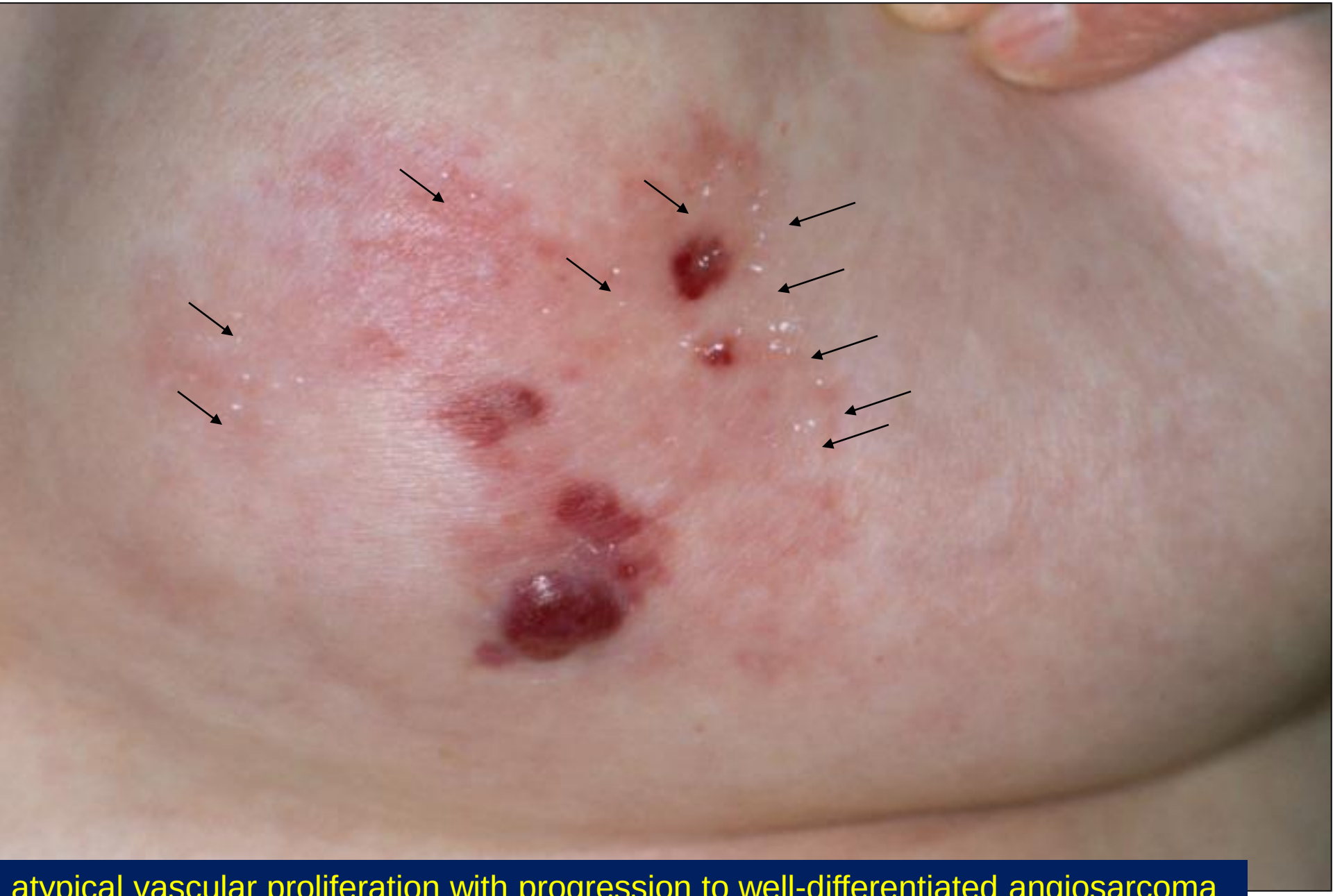
Clinicopathological Findings

- 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	+++	–

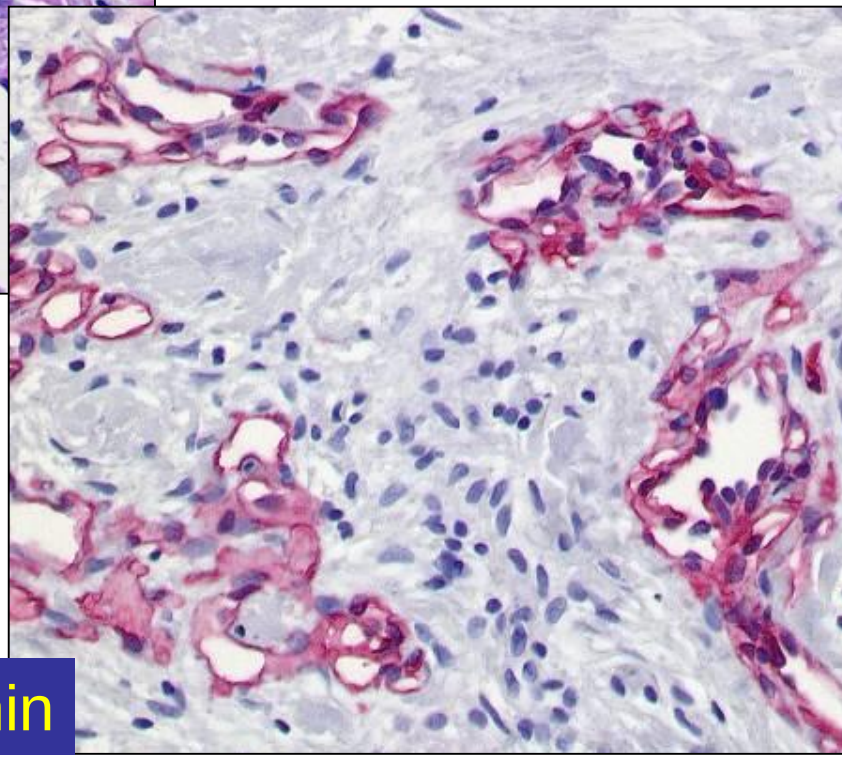
AVL, atypical vascular lesion; AS, angiosarcoma.



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

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

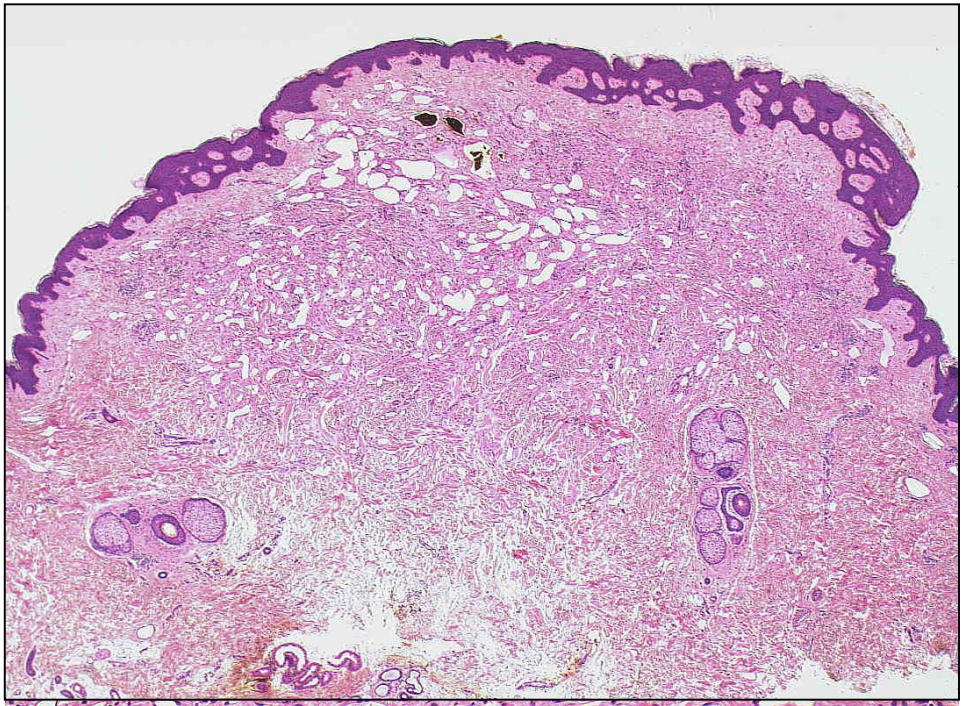
Guo T, Zhan L, Chang NE et al. Consistent MYC and FLT4 gene amplification in radiation induced angiosarcoma but not in other radiation-associated atypical vascular lesions.
Genes Chromosomes Cancer 2011; 50: 25-33

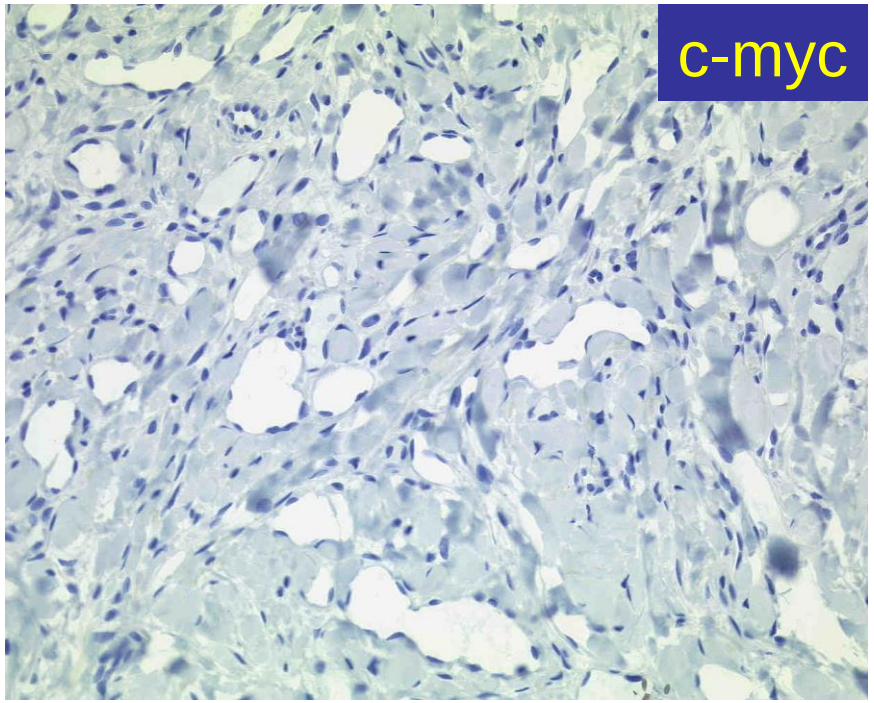
Cornejo KM, Deng A, Wu H et al. The utility of MYC and FLT4 in the diagnosis and treatment of postradiation atypical vascular lesion and angiosarcoma of the breast. Hum Pathol 2015; 46: 868-875

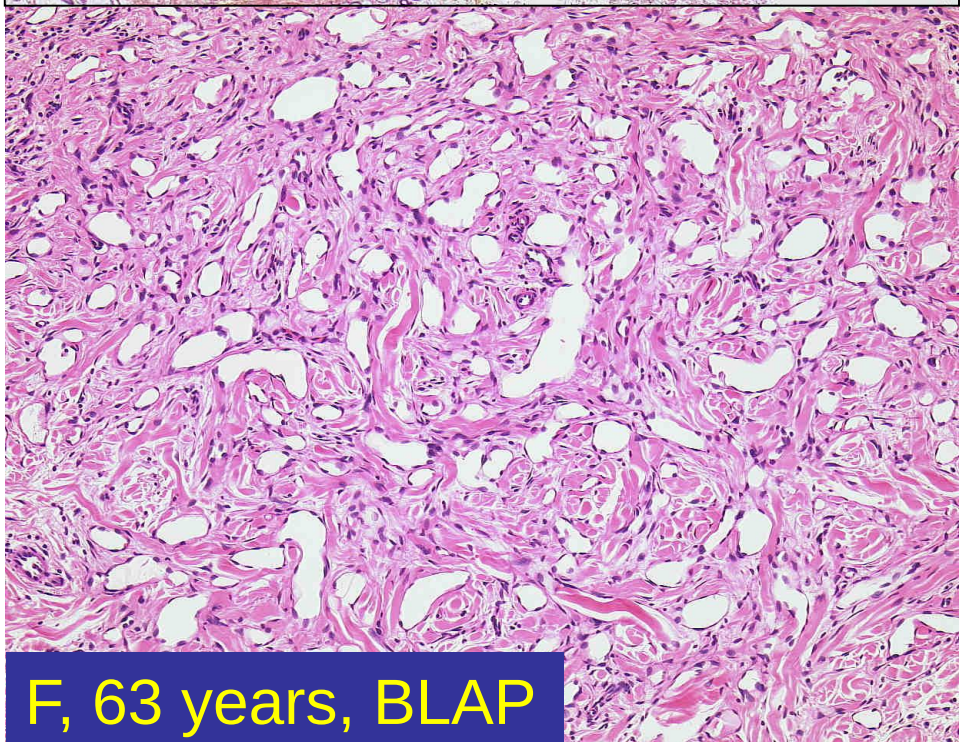
Fraga-Guedes C, Andre S, Mastropasqua MG et al. Angiosarcoma and atypical vascular lesions of the breast: diagnostic and prognostic role of MYC gene amplification and protein expression. Breast Cancer Res Treat 2015; 151: 131-140

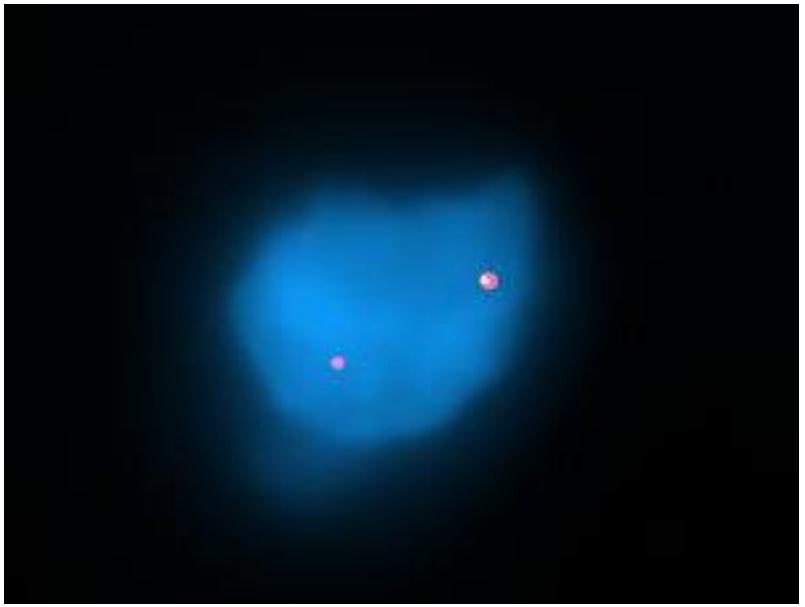
Results

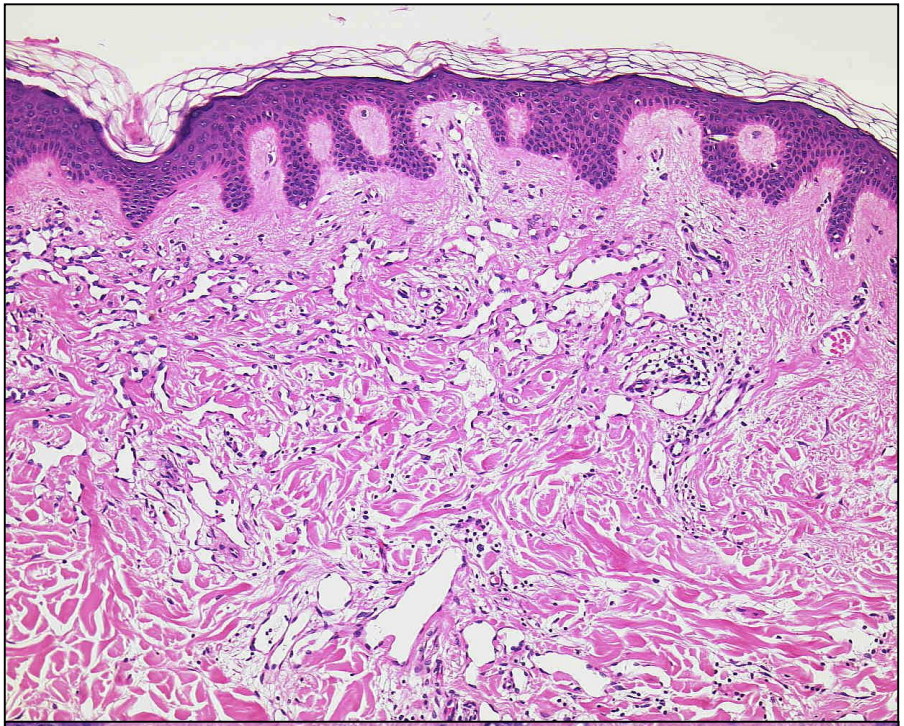
1. Control Cases
   - IM c-myc: 0/5 positive
   - IM prox-1: 1/5 focal positive
   - FISH c-myc: 0/5 positive
2. RT-associated slight vascular proliferation
   - IM c-myx: 0/11 positive
   - IM prox-1: 1/11 focal positive
   - FISH c-myc: 0/12 positive
3. RT-associated atypical vascular proliferation
   - IM c-myc: 1/16 focal positive
   - IM prox-1: 11/16 focal positive
   - FISH c-myc: 0/16 positive

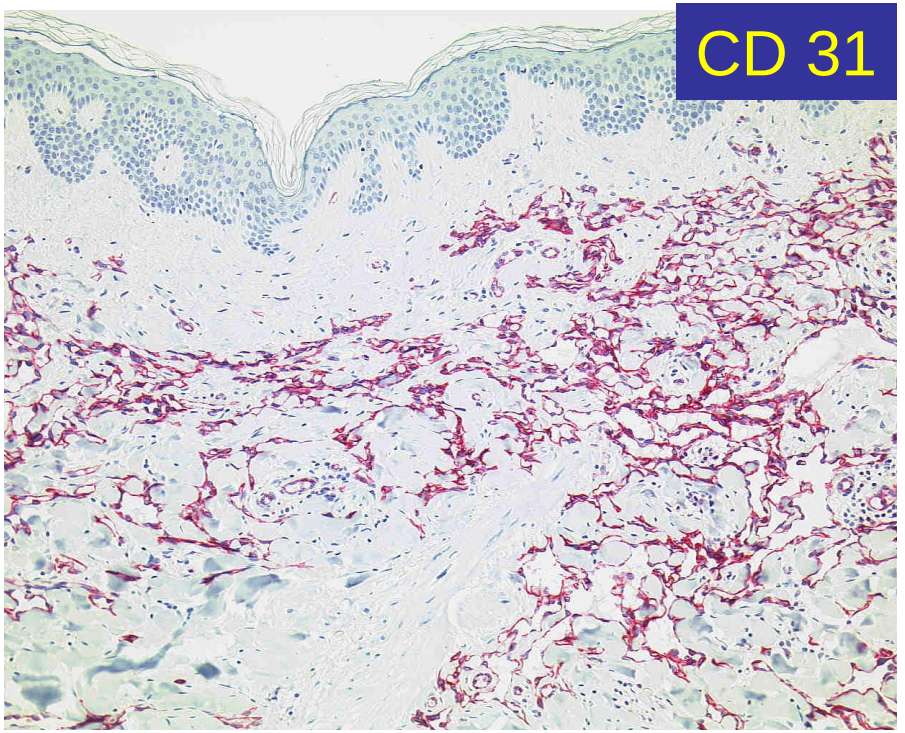


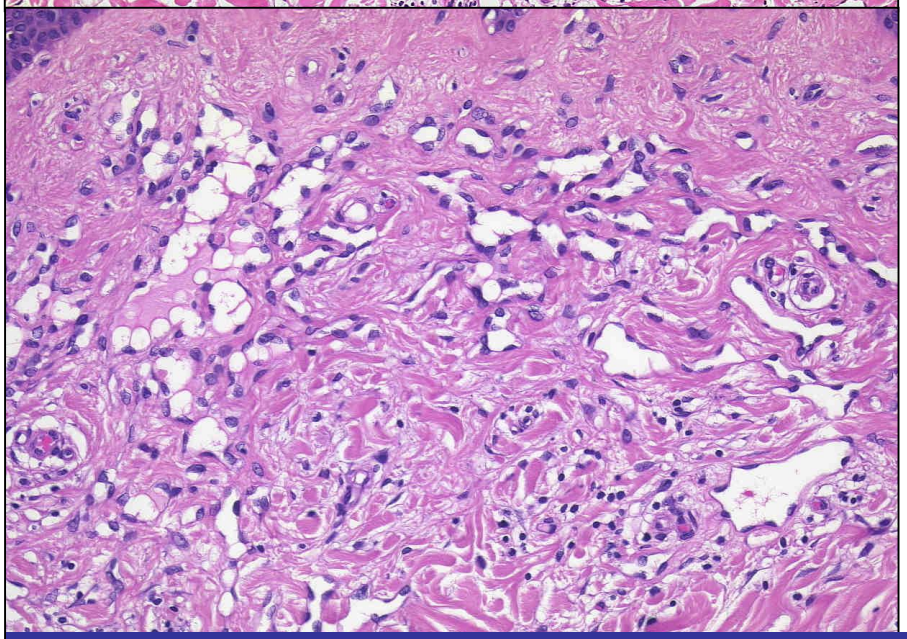

c-myc

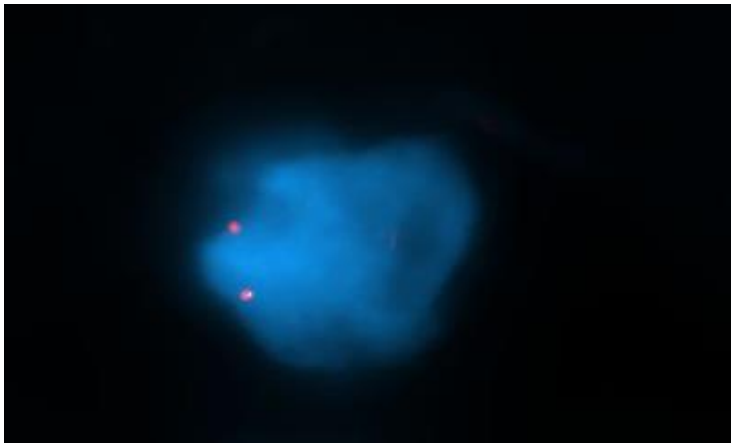

F, 63 years, BLAP







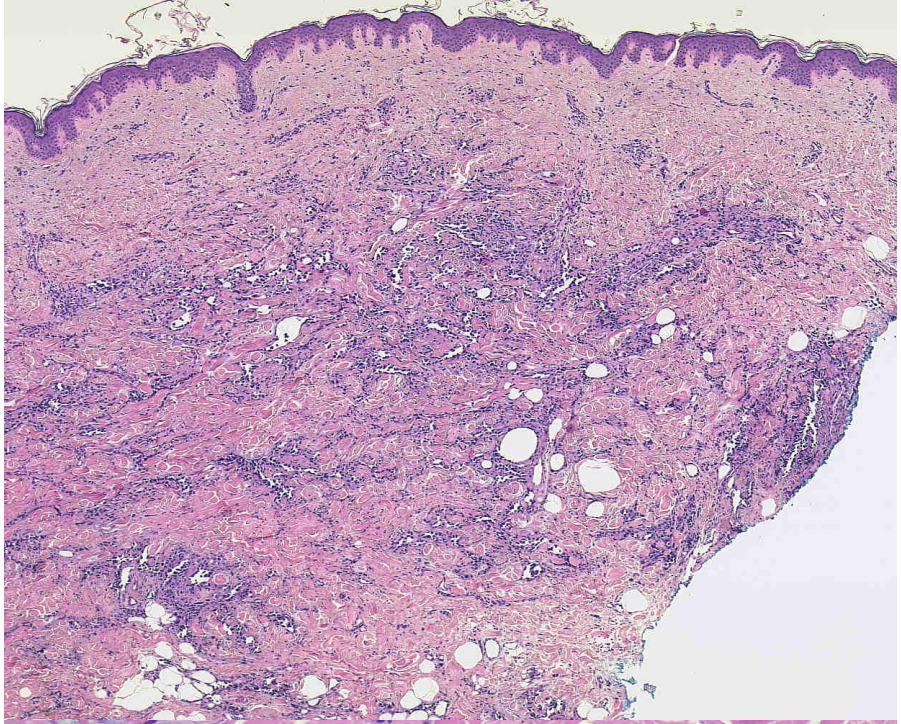


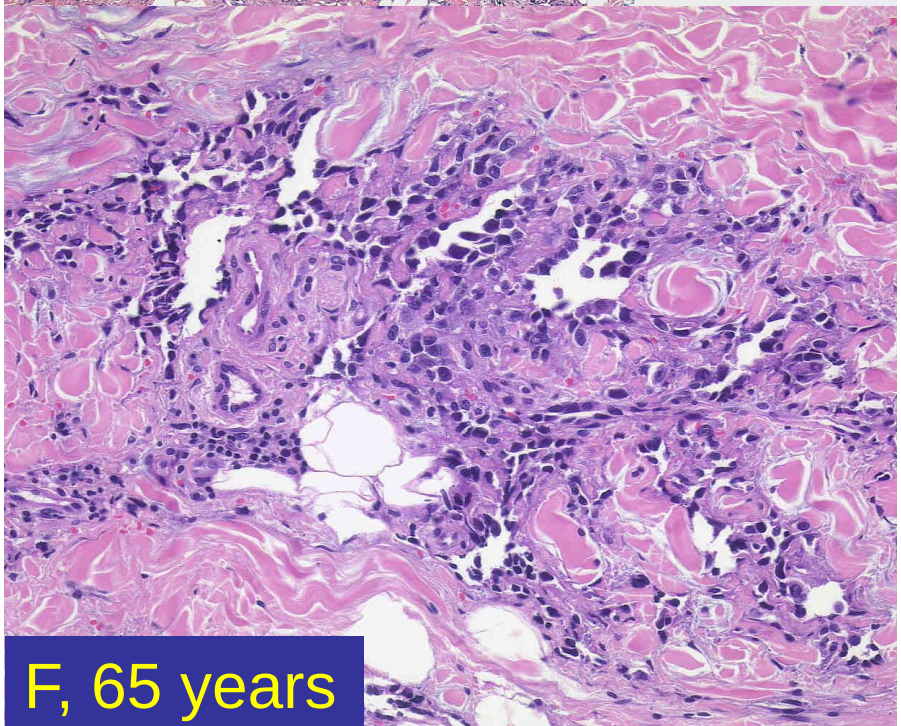


F, 65 years, AVL, NSR at 36/12

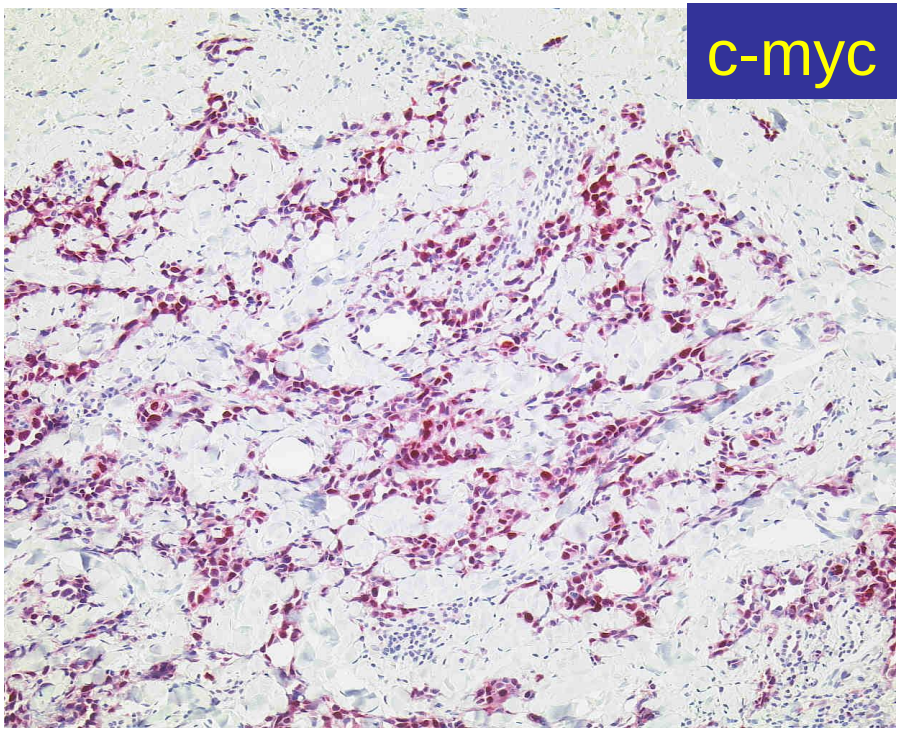
Results

4. RT-associated angiosarcoma
   - IM c-myc: 22/23 positive
   - IM prox-1: 15/21 positive
   - FISH c-myc: 25/25 positive
   - FISH c-myc: 0/4 positive in small vessels in the vicinity of angiosarcomatous areas
5. Angiosarcoma unrelated to radiotherapy
   - IM c-myx: 1/8 focal positive
   - IM prox-1: 1/8 focal positive
   - FISH c-myc: 0/8 positive

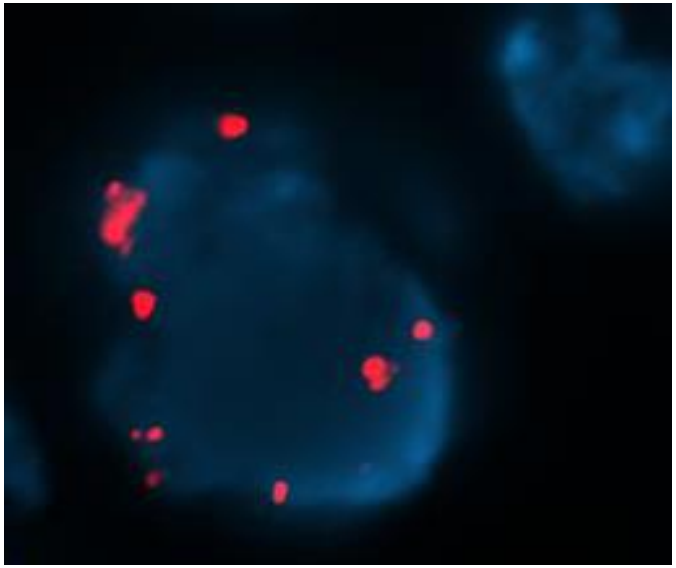


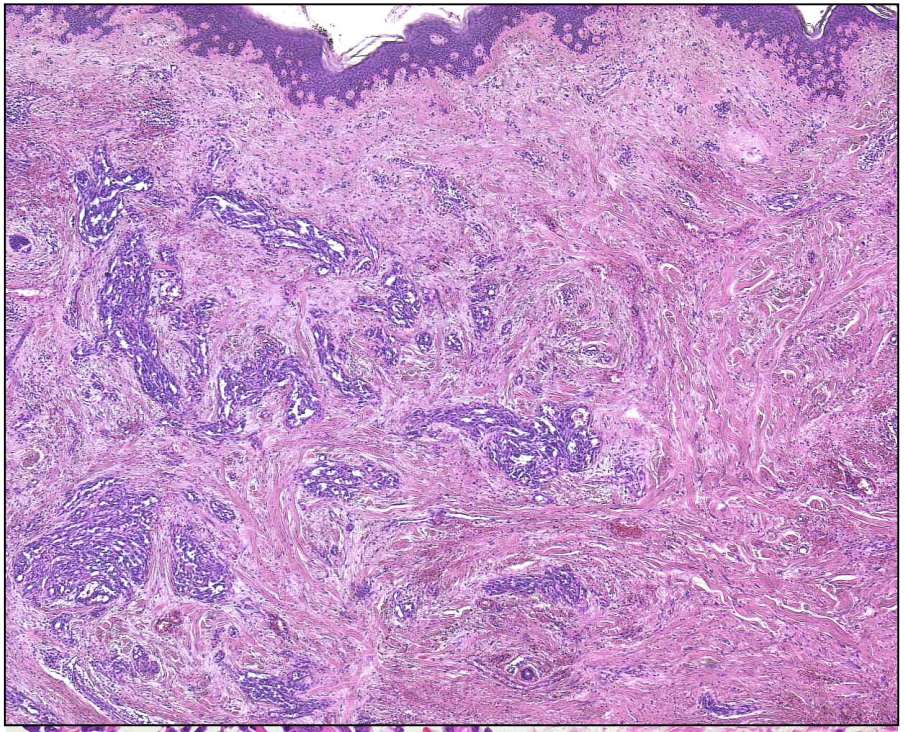


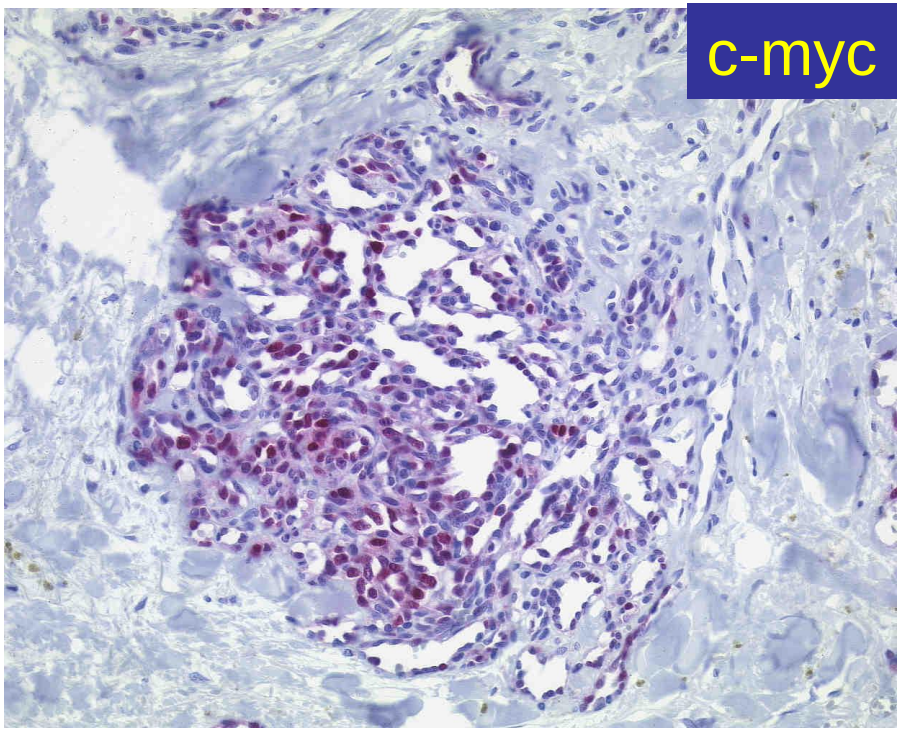
F, 65 years

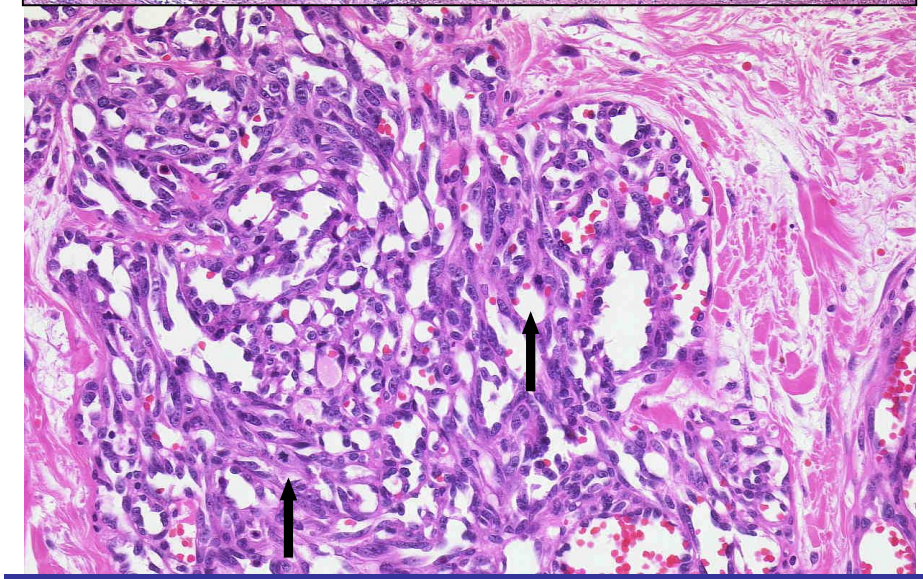


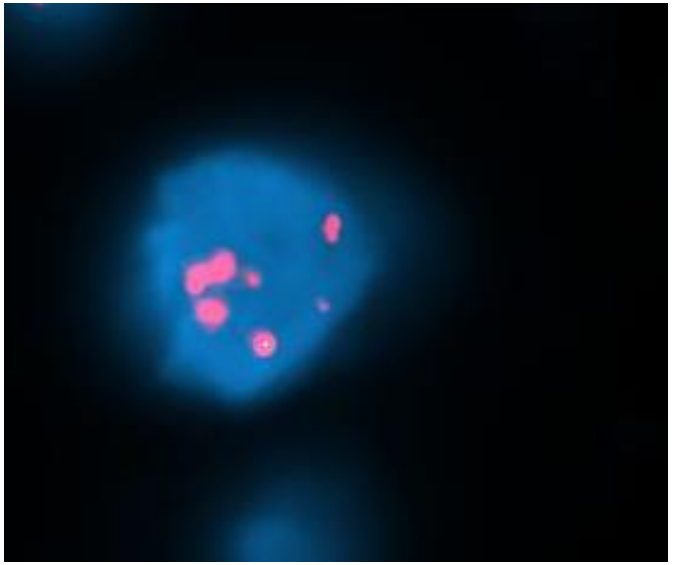
c-myc











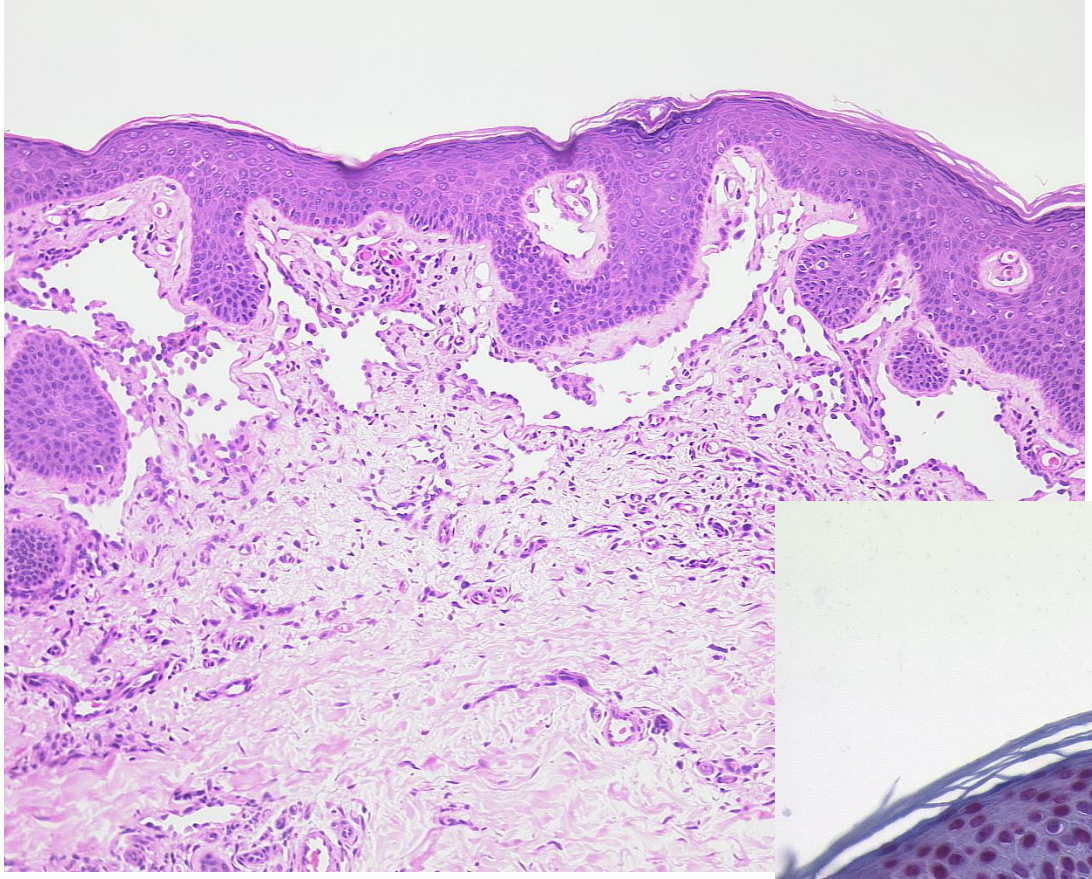
F, 67 years, breast cancer, RT in 2006
4 x 5 cm „lymphedema“ in 2009

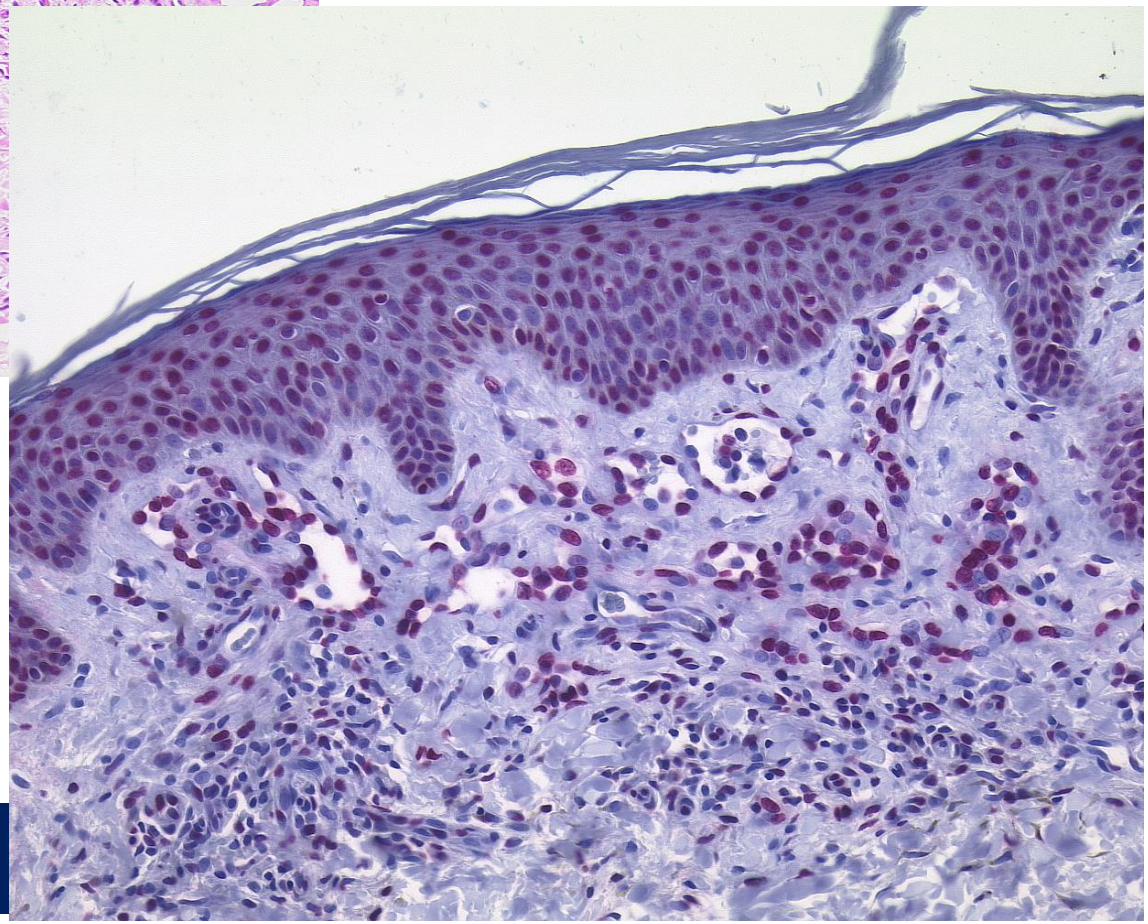
Reduced H3K27me3 expression in radiation-associated angiosarcoma of the breast

Mentzel T, Kiss K Virchows Arch 2018; 472: 361-368

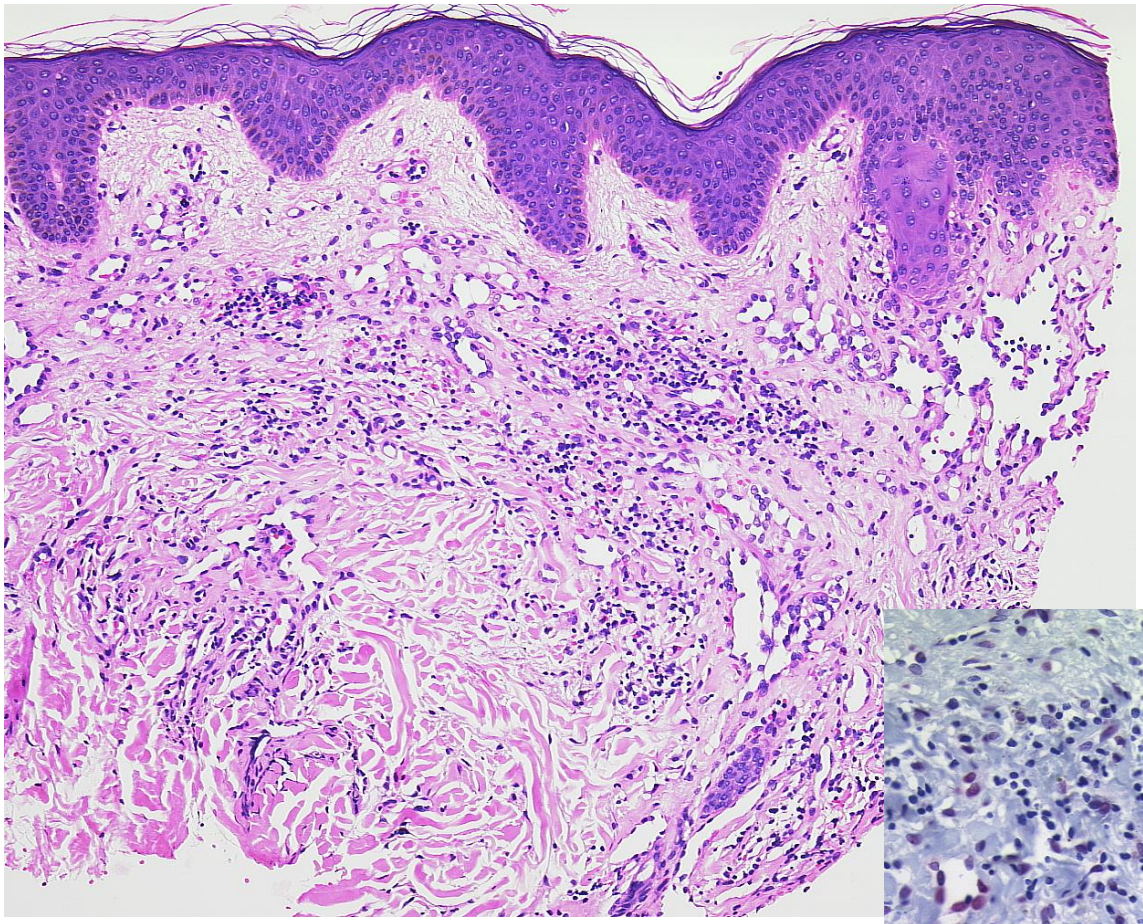
control cases (10):	H3K27me3 positive (x 8)
	H3K27me3 focally reduced (x 2)
RT-AVL (11):	H3K27me3 positive (x 8)
	H3K27me3 focally reduced (x 3)
RT-AS (20):	H3K27me3 negative (x 16)
	H3K27me3 focally reduced (x 4)
sporadic AS (8):	H3K27me3 positive (x 1)
	H3K27me3 focally reduced (x 4)
	H3K27me3 negative (x 3)

Hobnail Haemangioma

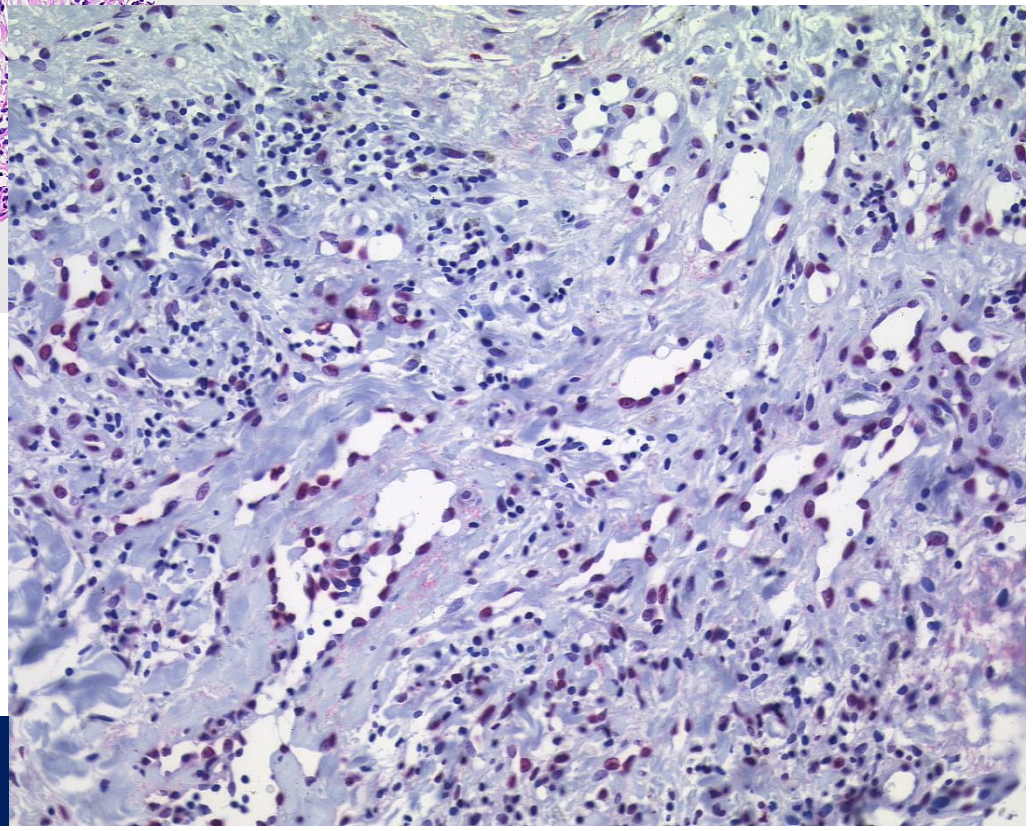




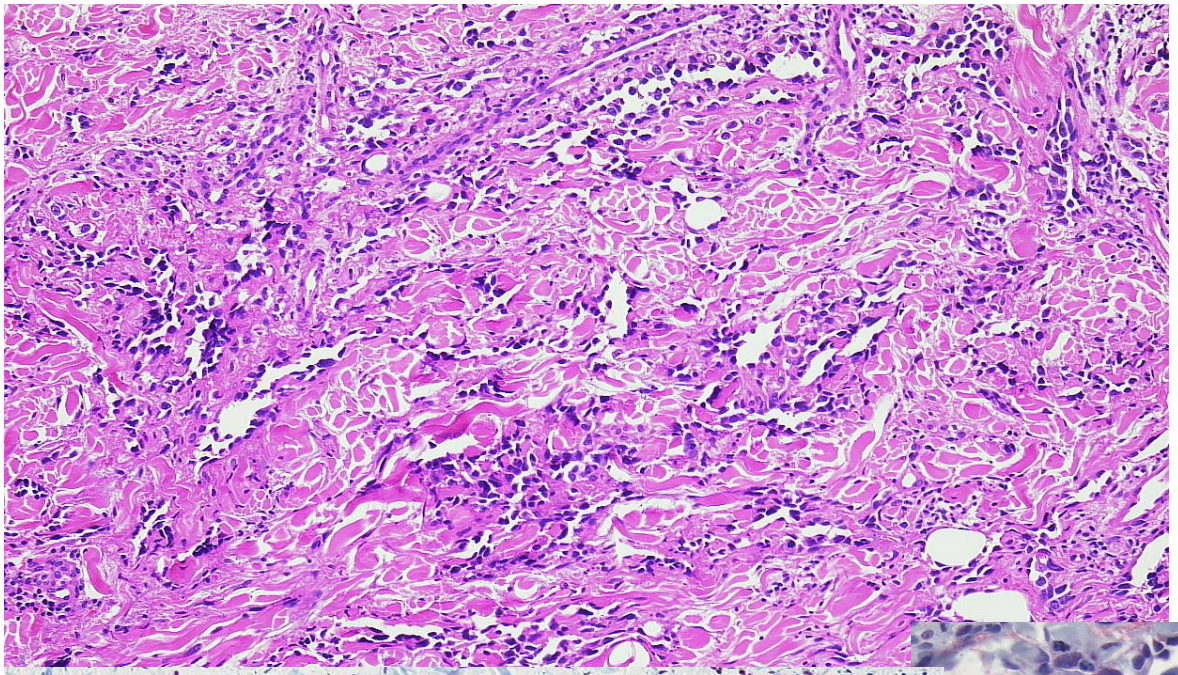
H3K27me3



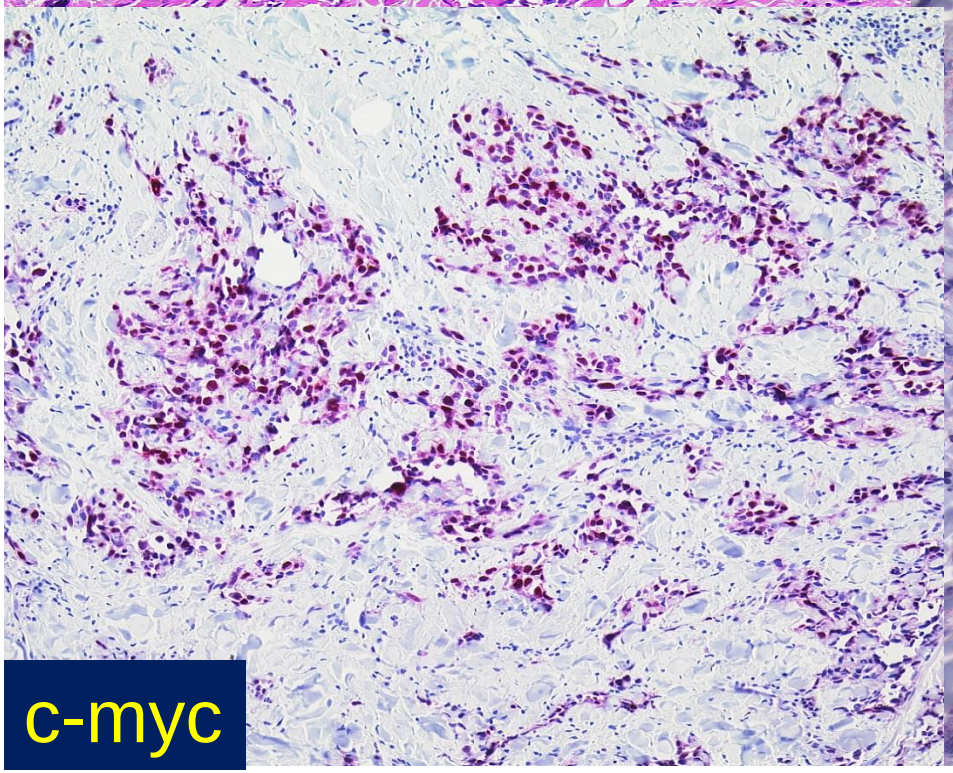
RT-associated AVP

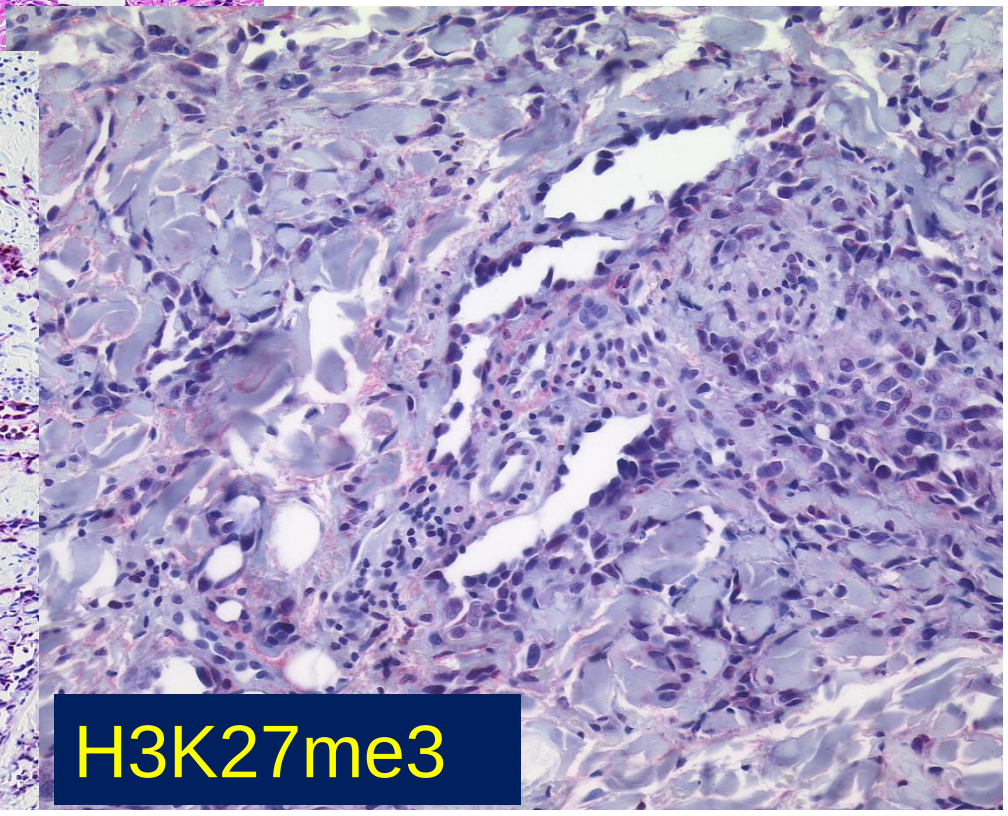


H3K27me3



RT-associated AS





Problematic issue: Incidence of postradiation Angiosarcoma

Marchal C et al. Int J ROBP 1999; 44: 113

9 AS on 18115 patients = 0.049%

Strobbe LJ et al. Breast Cancer RT 1998; 47: 101

estimated incidence is 0.16%

Hodgson NC et al. Am J Clin Oncol 2007; 30: 570

200.000 breast cancer patients (RT ?)

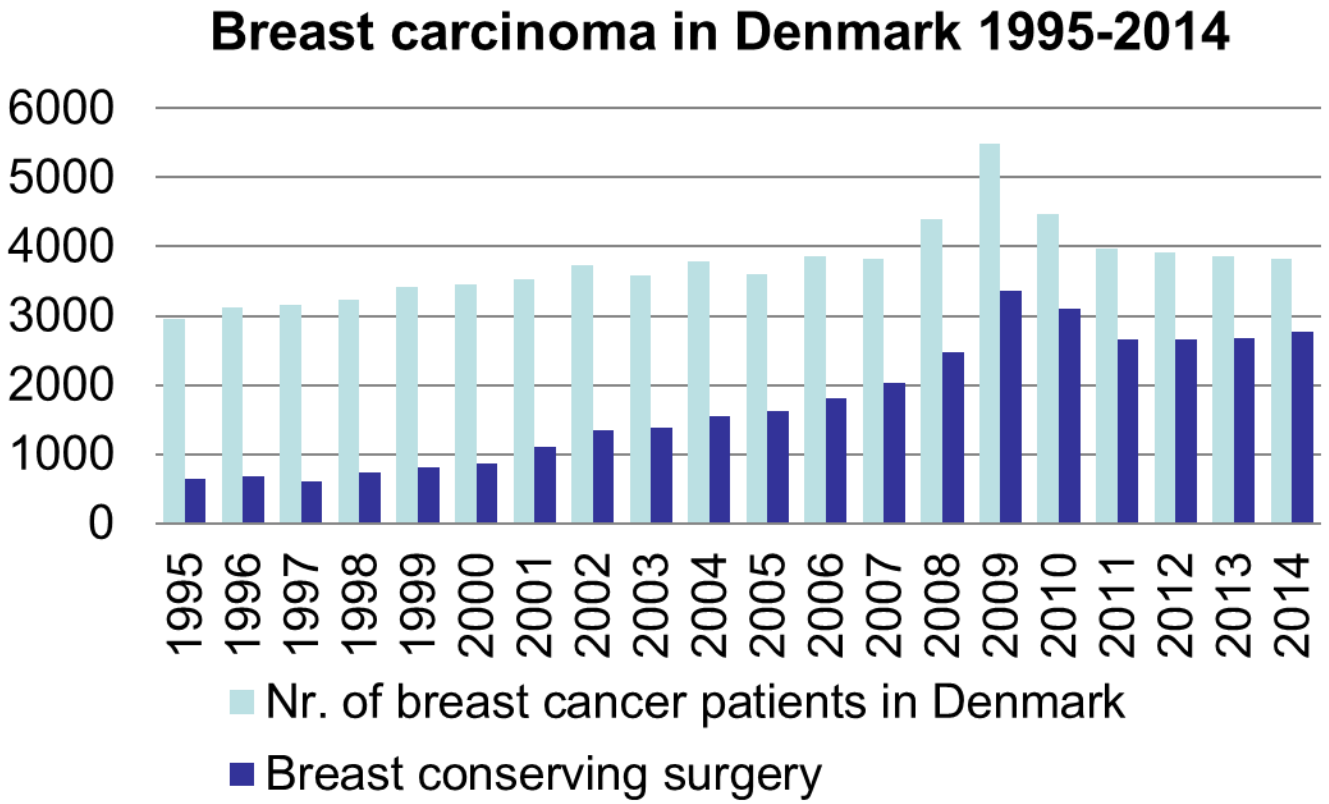
39 primary AS, 31 secondary AS

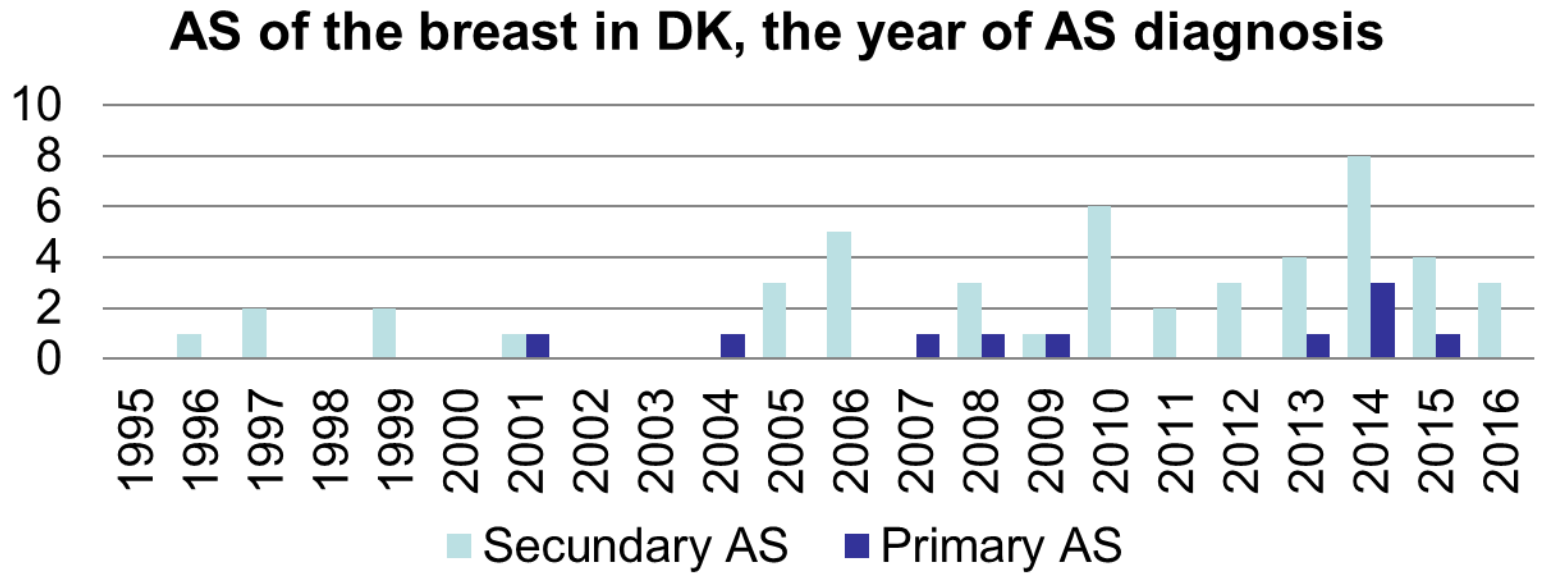
Flucke U Adv Anat Pathol 2013; 20: 407

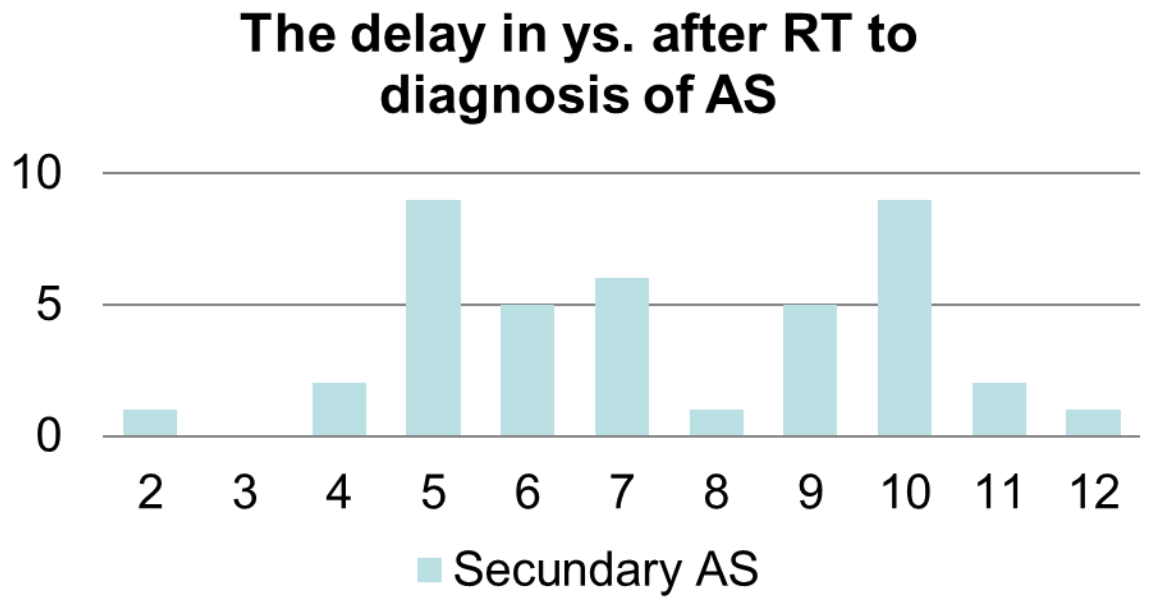
estimated rate 0.05% - 1.11%

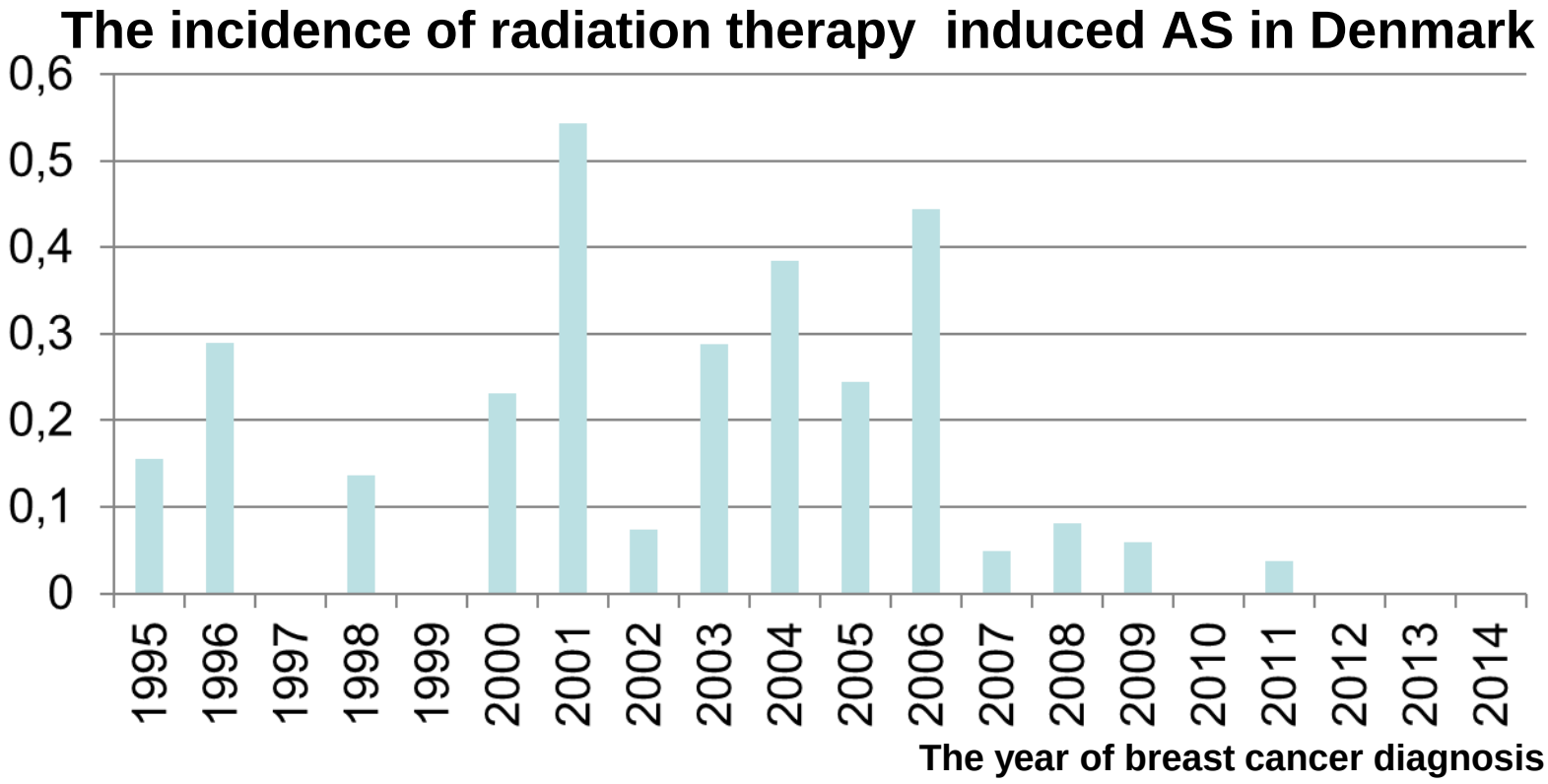
Hornick JL Practical Soft Tissue Pathology

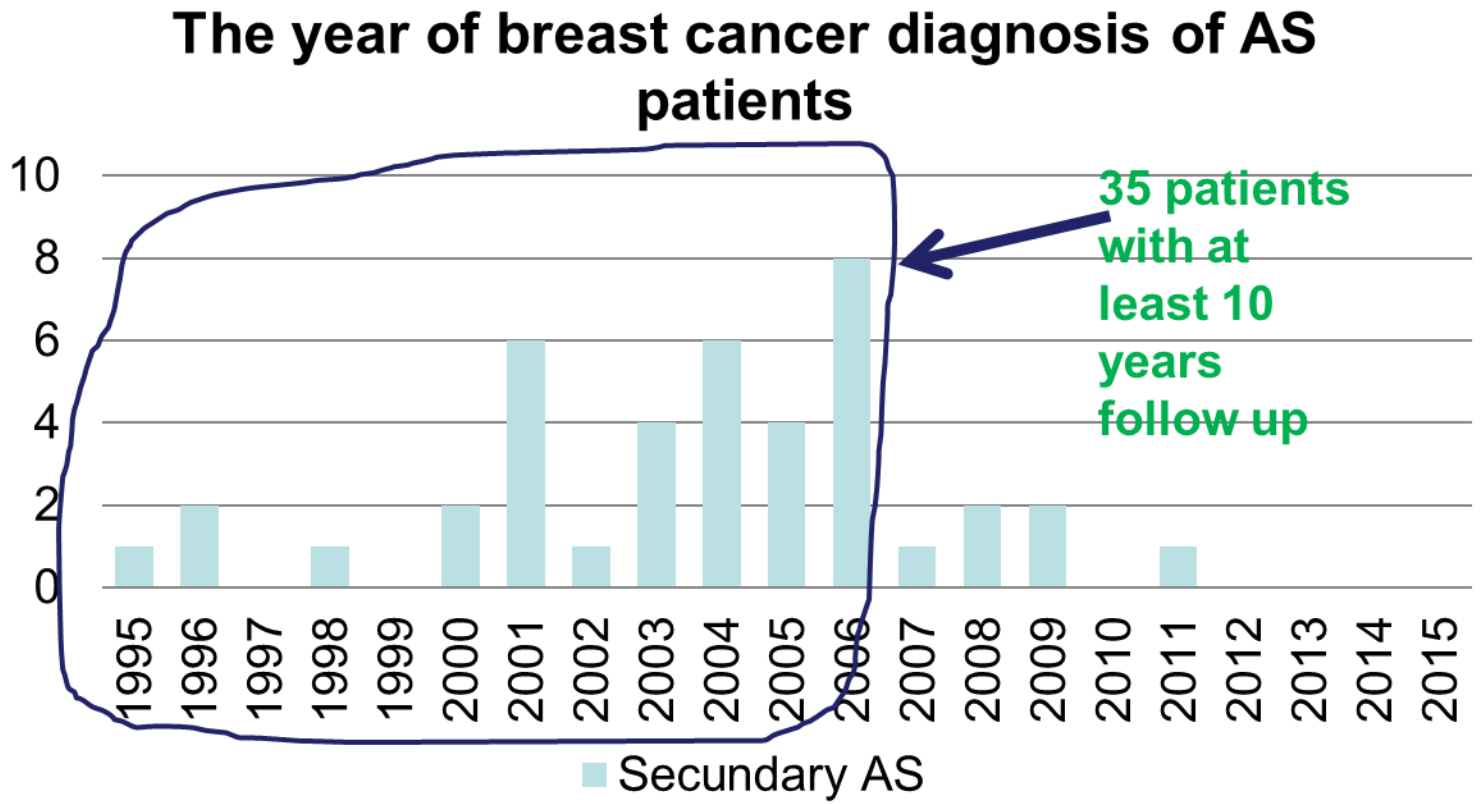
reported risk varies from 0.09% to 0.3%


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


The delay in ys. after RT to diagnosis of AS
10
5
0
2
3
4
5
6
7
8
9
10
11
12
Secundary AS


The incidence of radiation therapy induced AS in Denmark
0,6
0,5
0,4
0,3
0,2
0,1
0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
The year of breast cancer diagnosis



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


uticals, Inc.
Printed in U.S.A. E-674

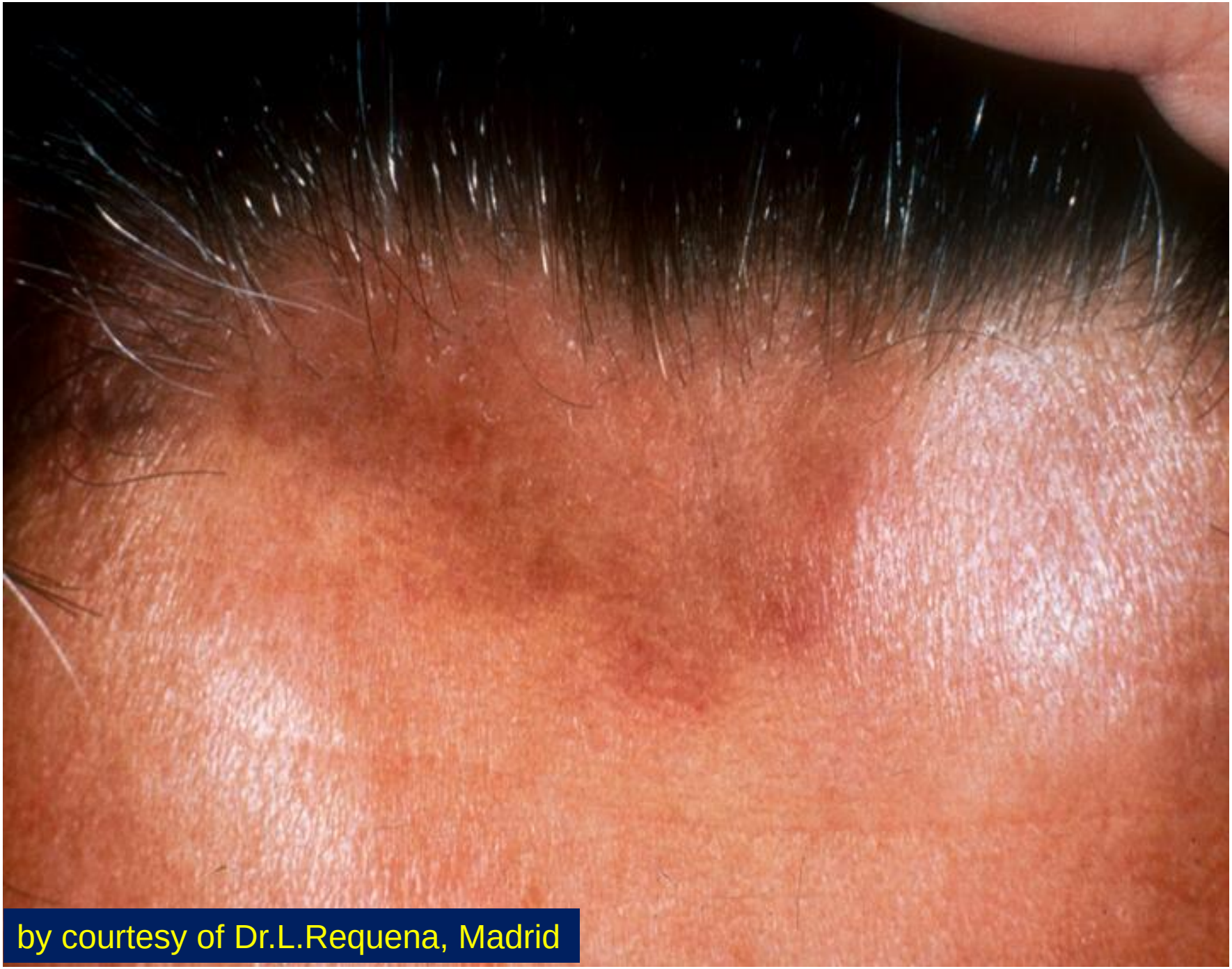
Conclusions

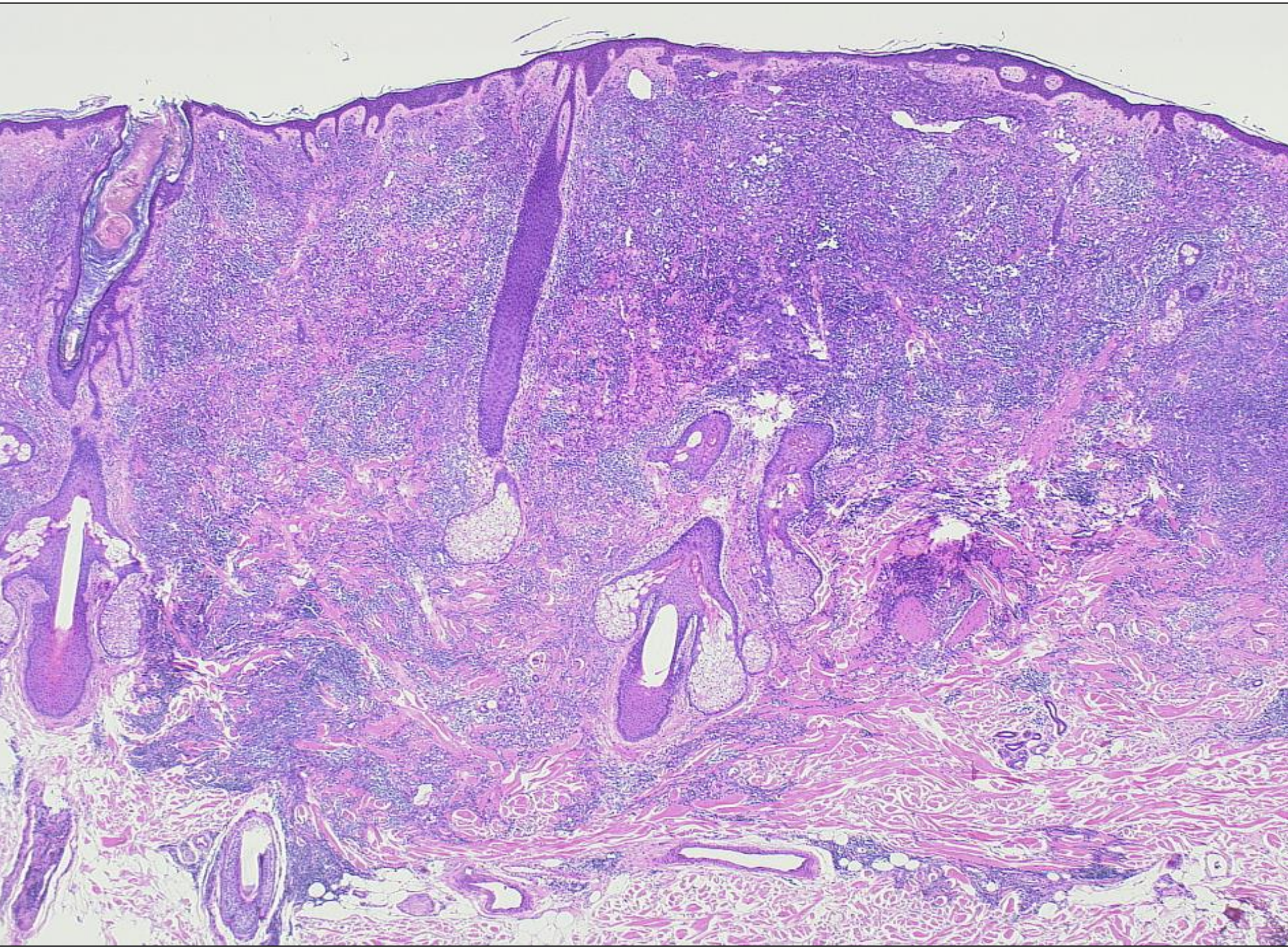
- all cutaneous vascular lesions after radiotherapy should be excised completely
- presence / absence of c-myc amplification / expression represents an additional finding in order to establish the correct dignity in RT-associated vascular lesions
- c-myc stainings may be used for mapping
- raises the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

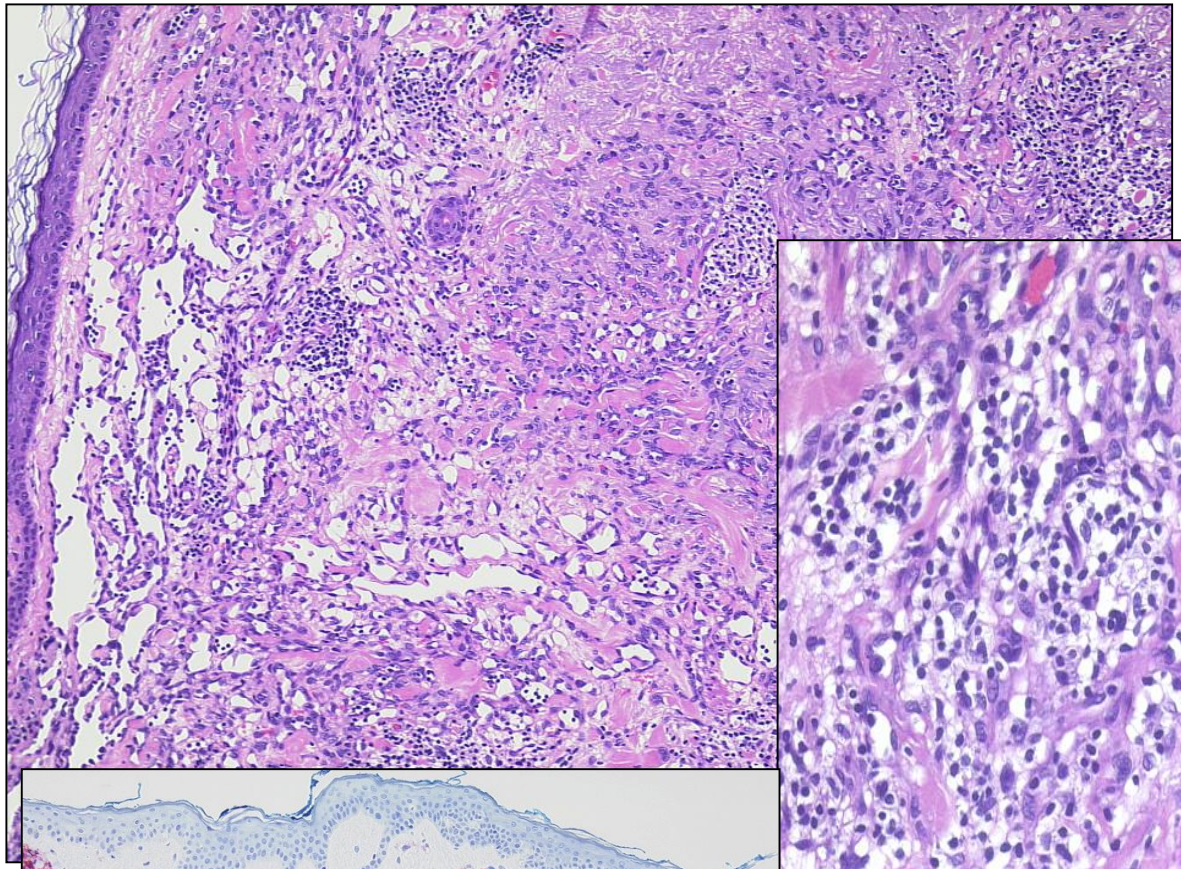
Cutaneous actinic Angiosarcoma

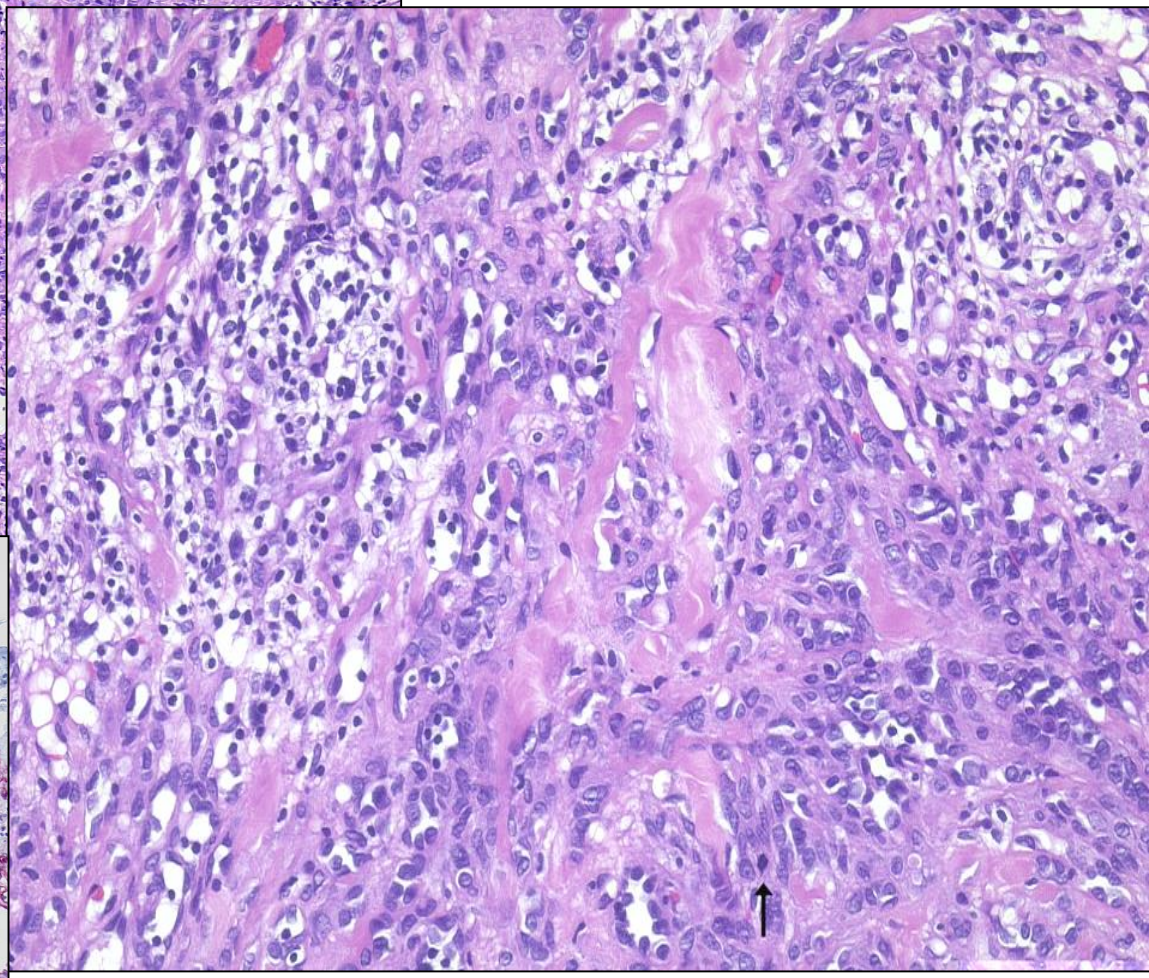
- irregular red plaques, nodular lesions, resembles inflammatory lesions, cut. lymphoma
- infiltrating, anastomosing vessels, atypical endothelial cells, mitoses, epithelioid morphology only rarely, prominent lymphocytic infiltrate
- CD31 +, CD34 -/+, D2-40+/-, Lyfe-1 +/-
- locally aggressive, many recurrences,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

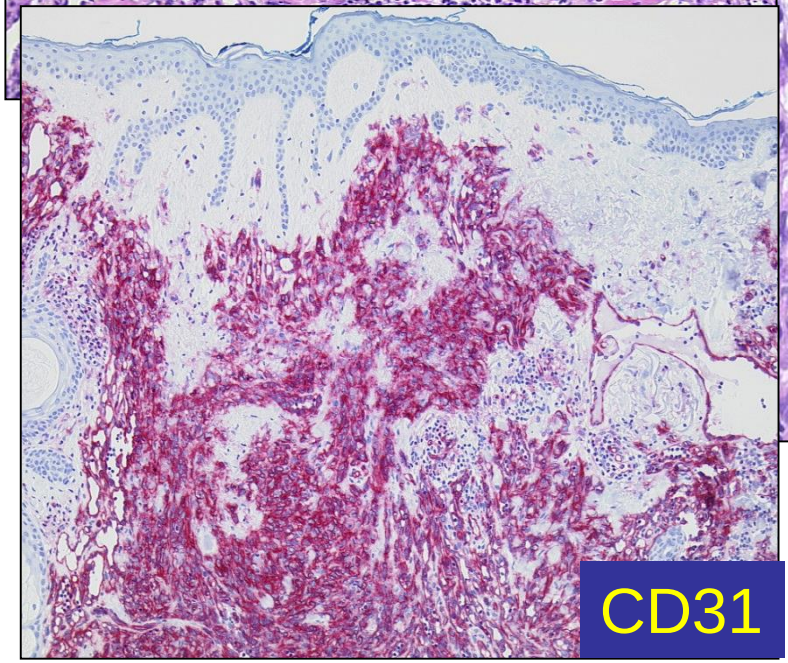
(Eur J Cancer 2008; 30: 639; Cancer 2005; 104: 361)

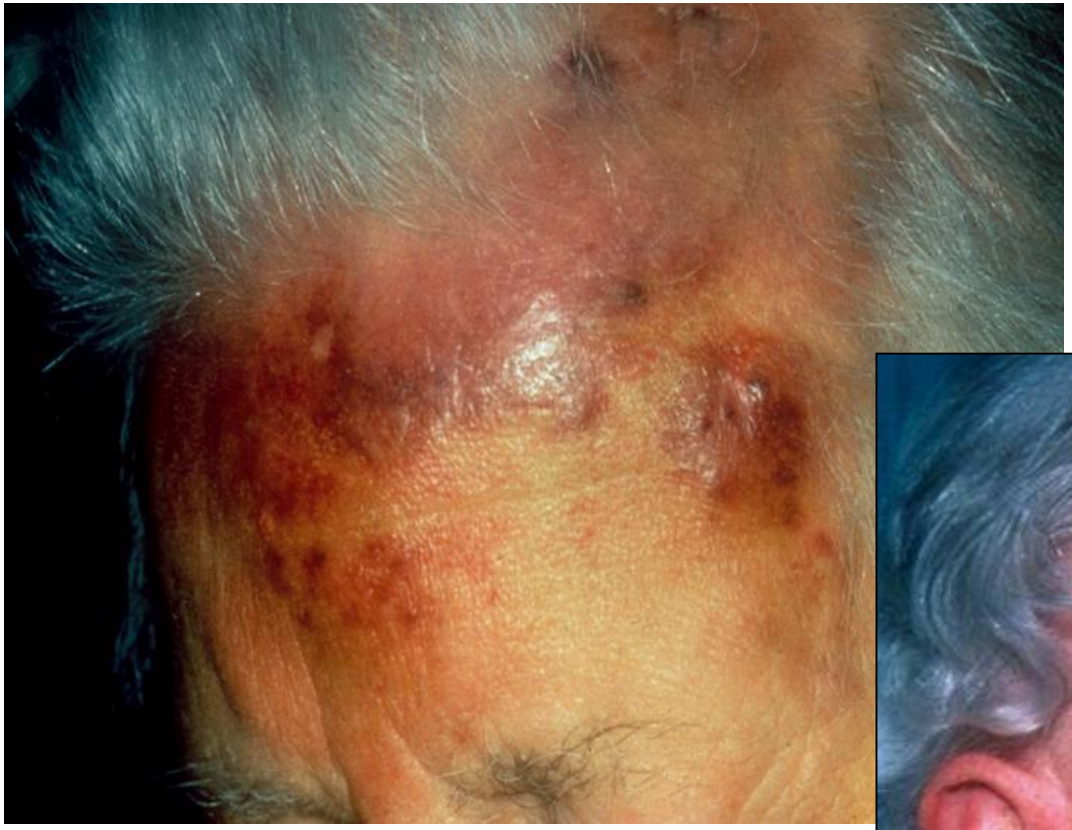

by courtesy of Dr.L.Requena, Madrid

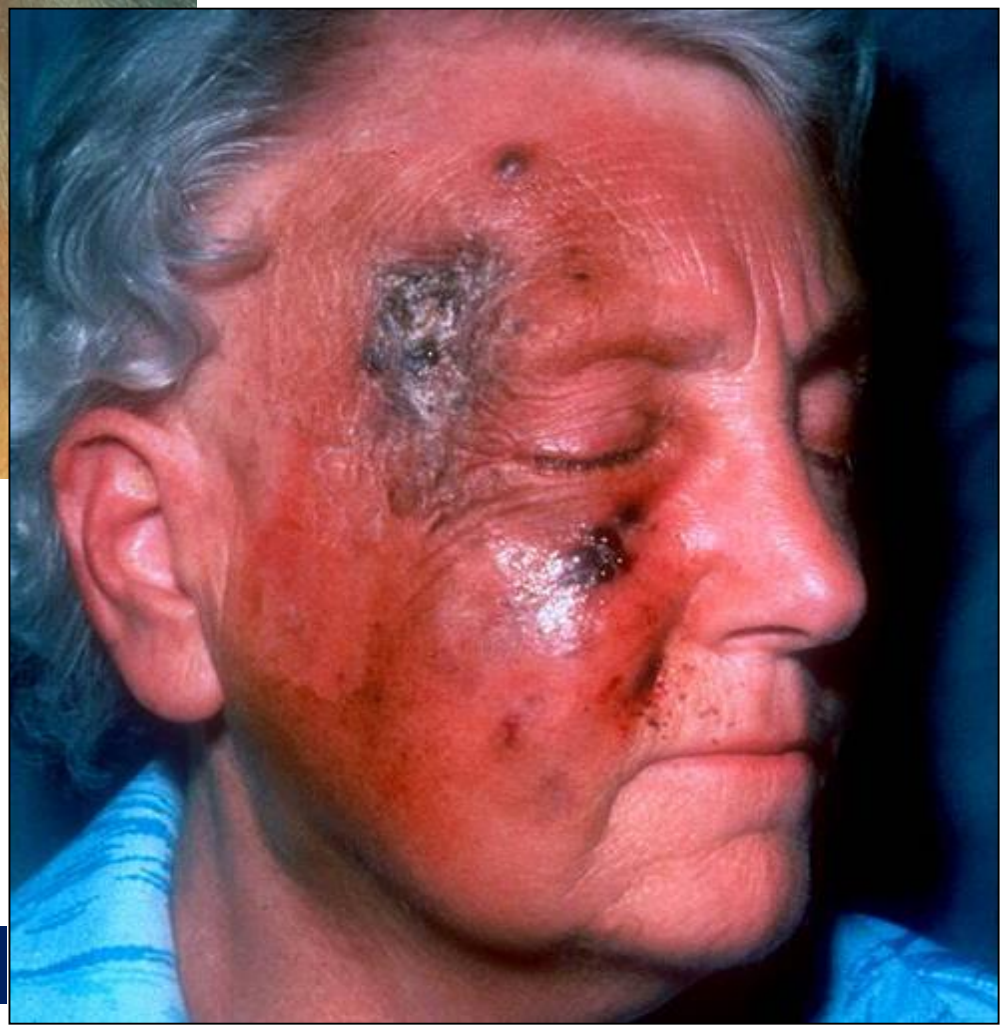




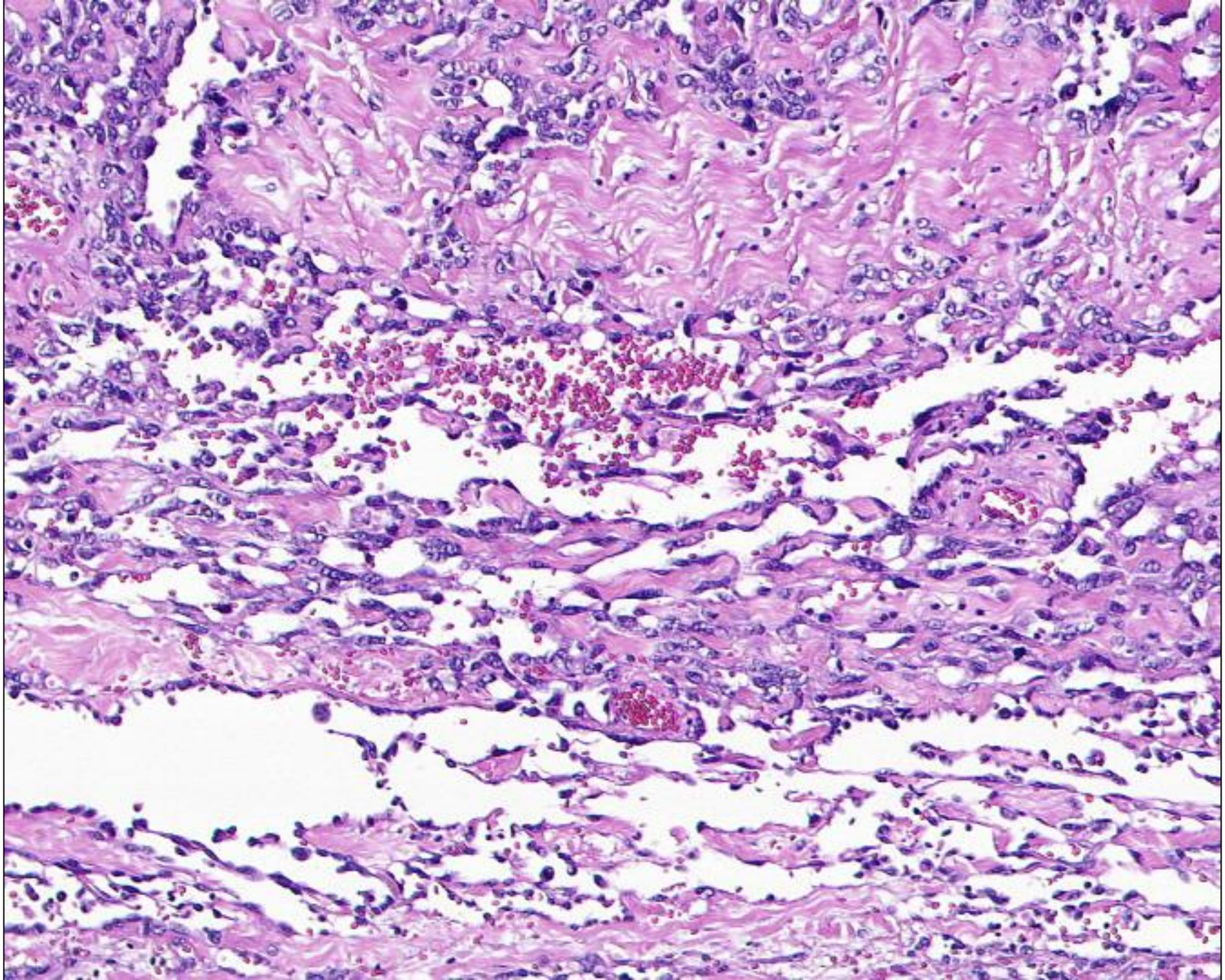


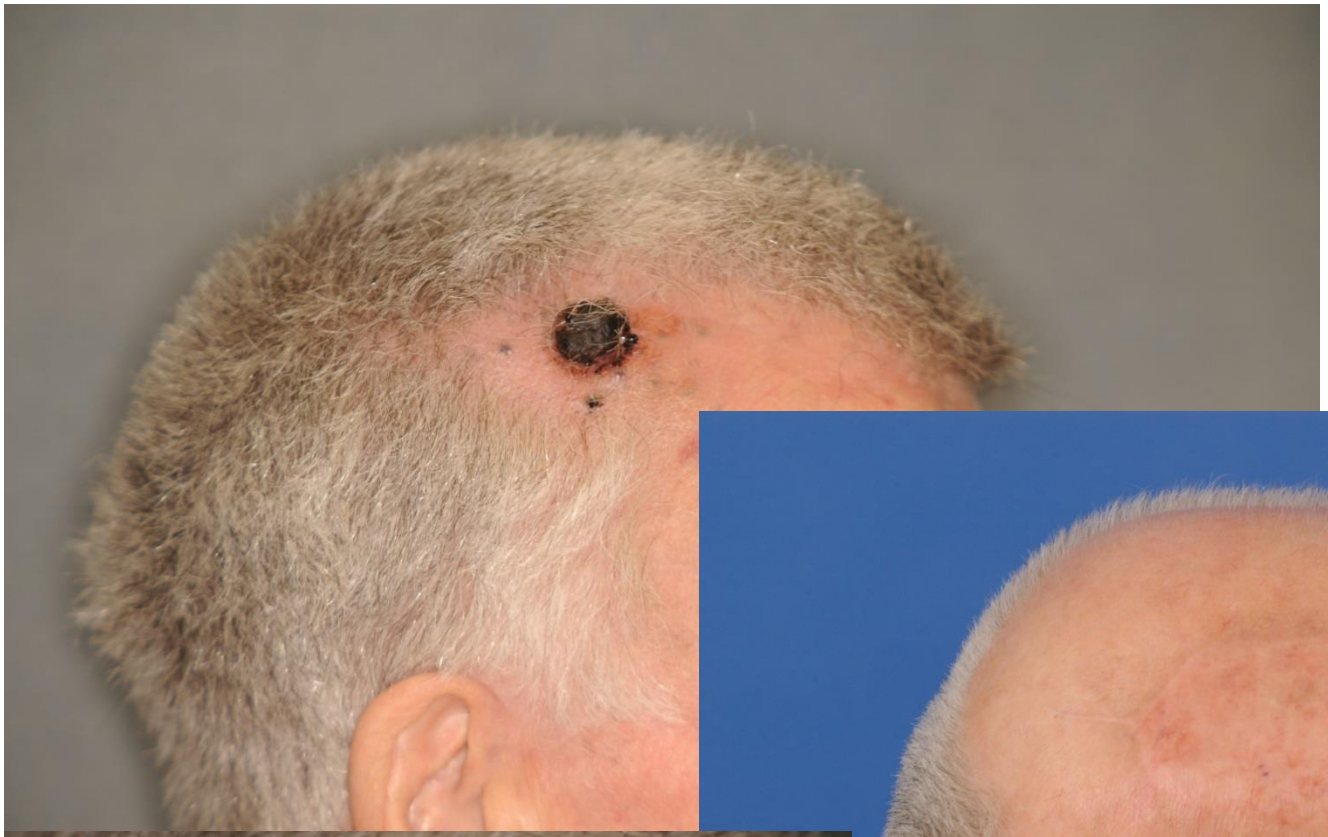

CD31

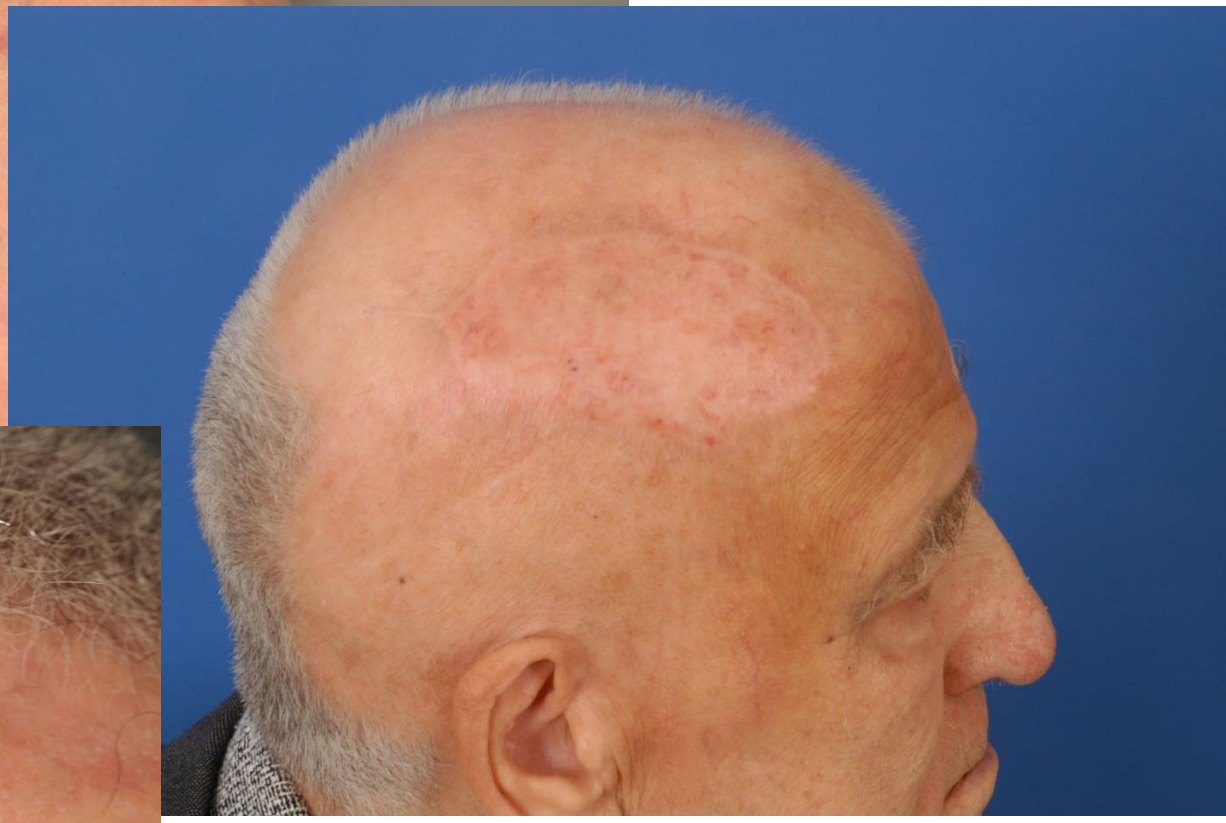


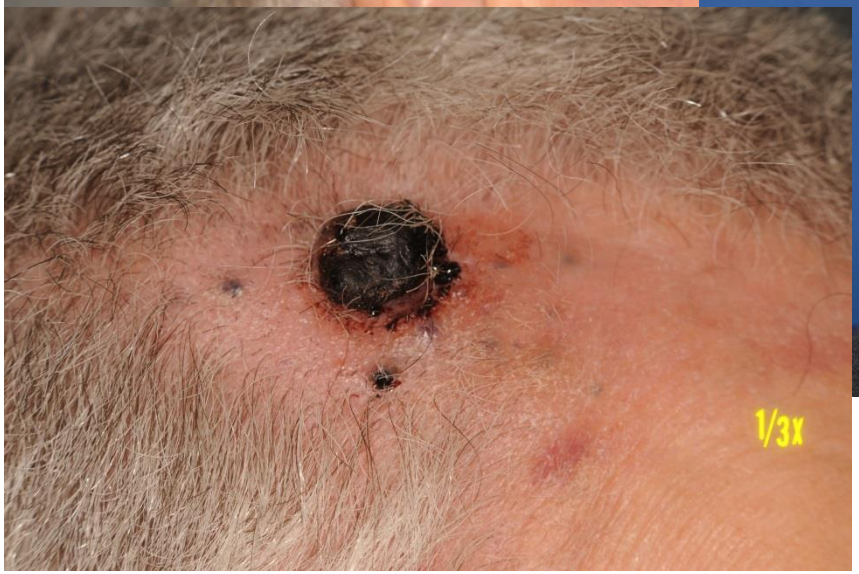


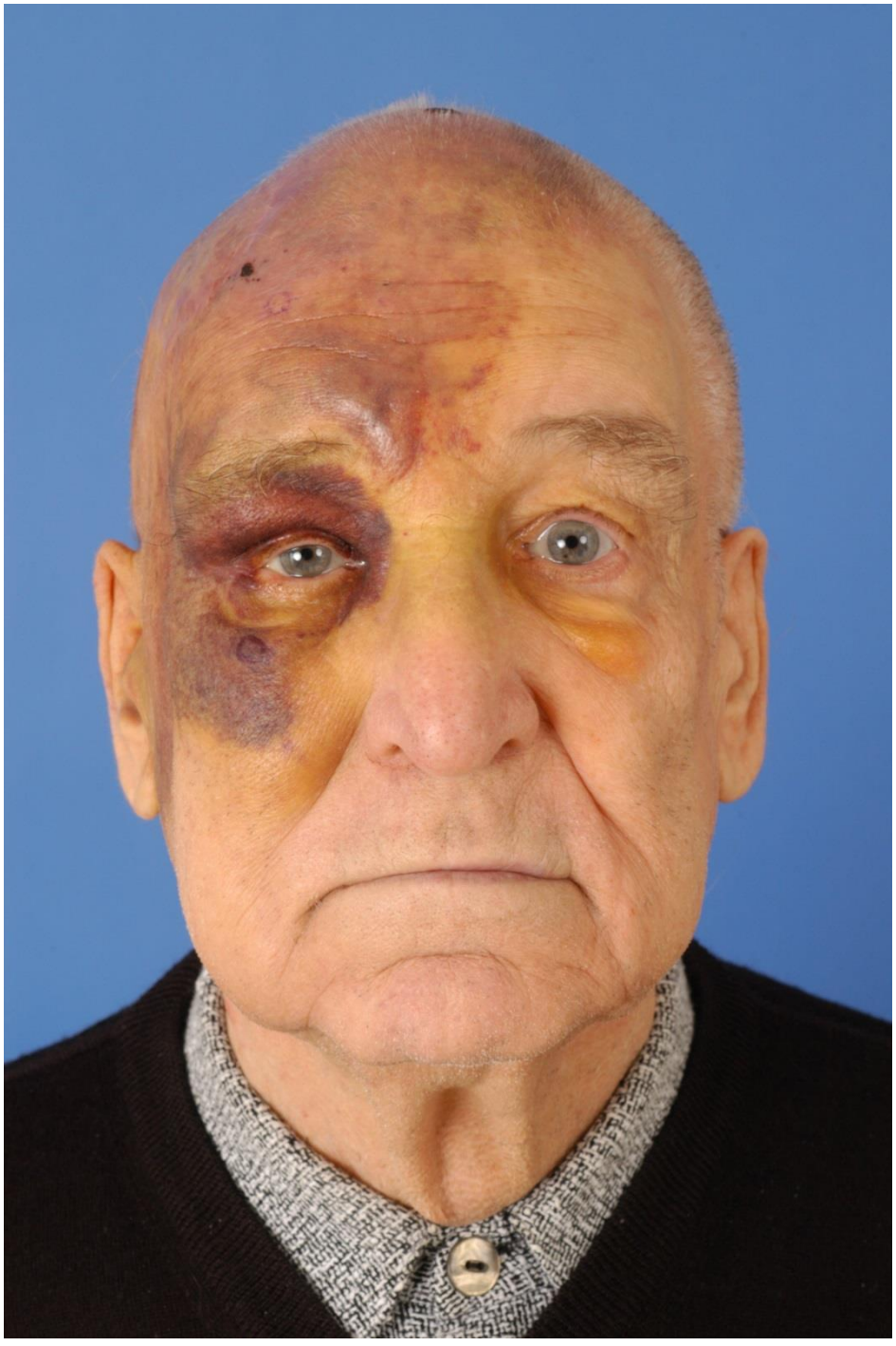
by courtesy of Dr.L.Requena, Madrid

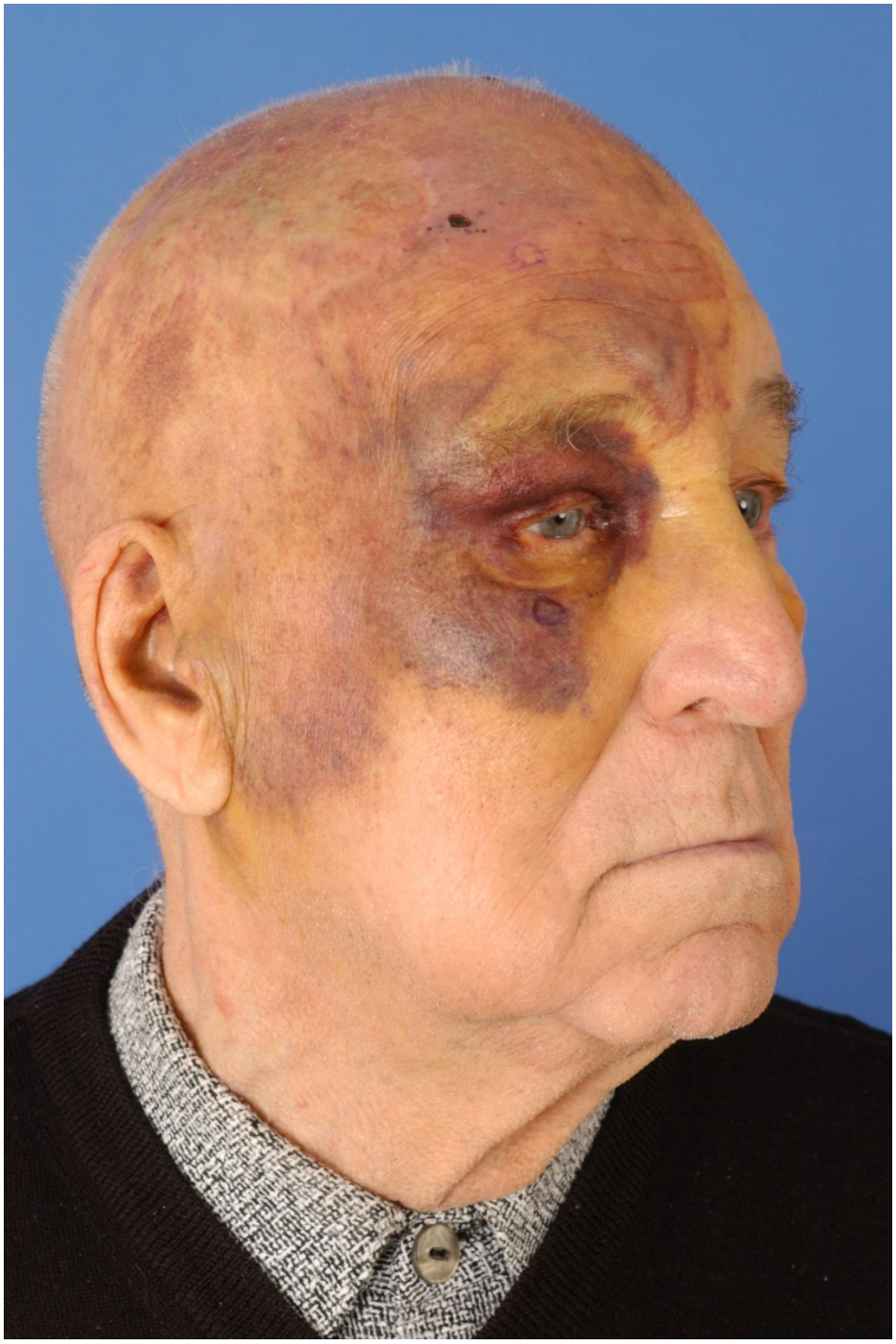







1/3x

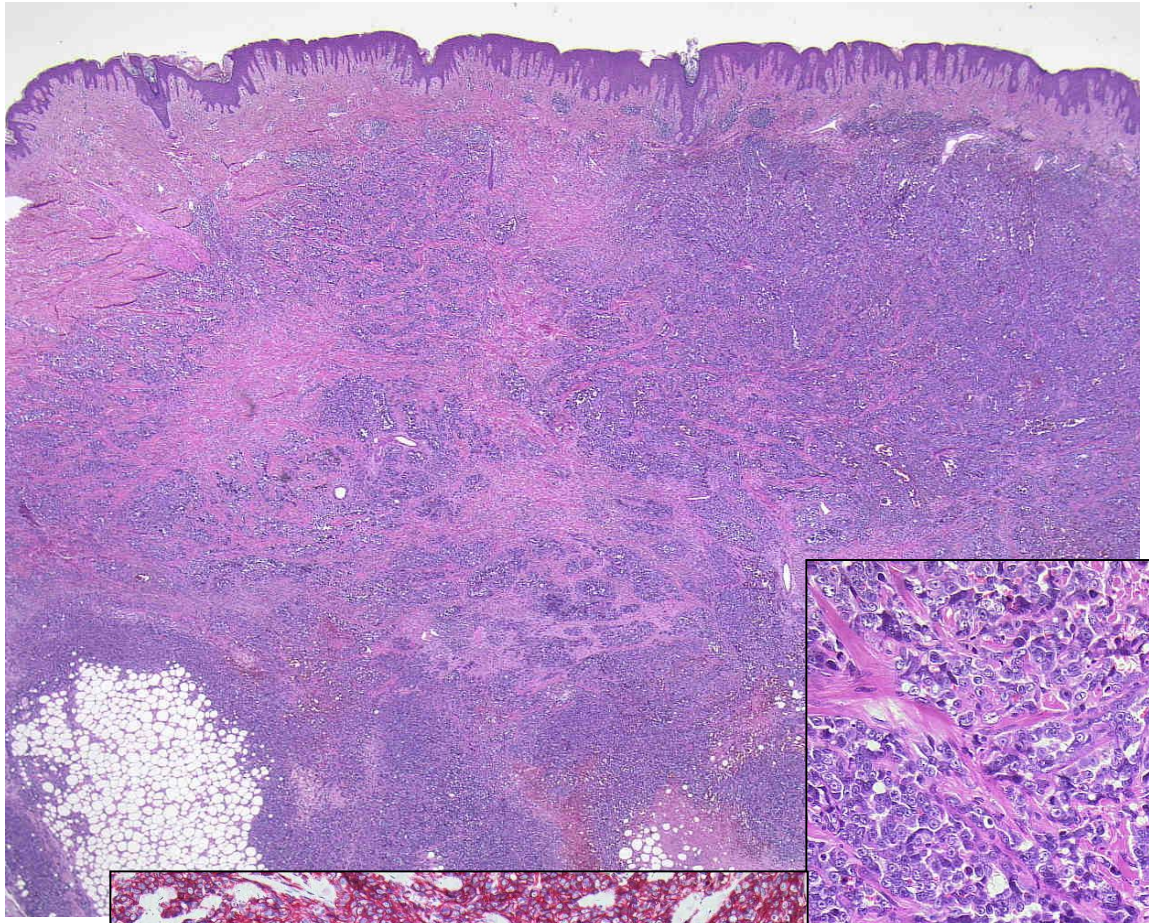




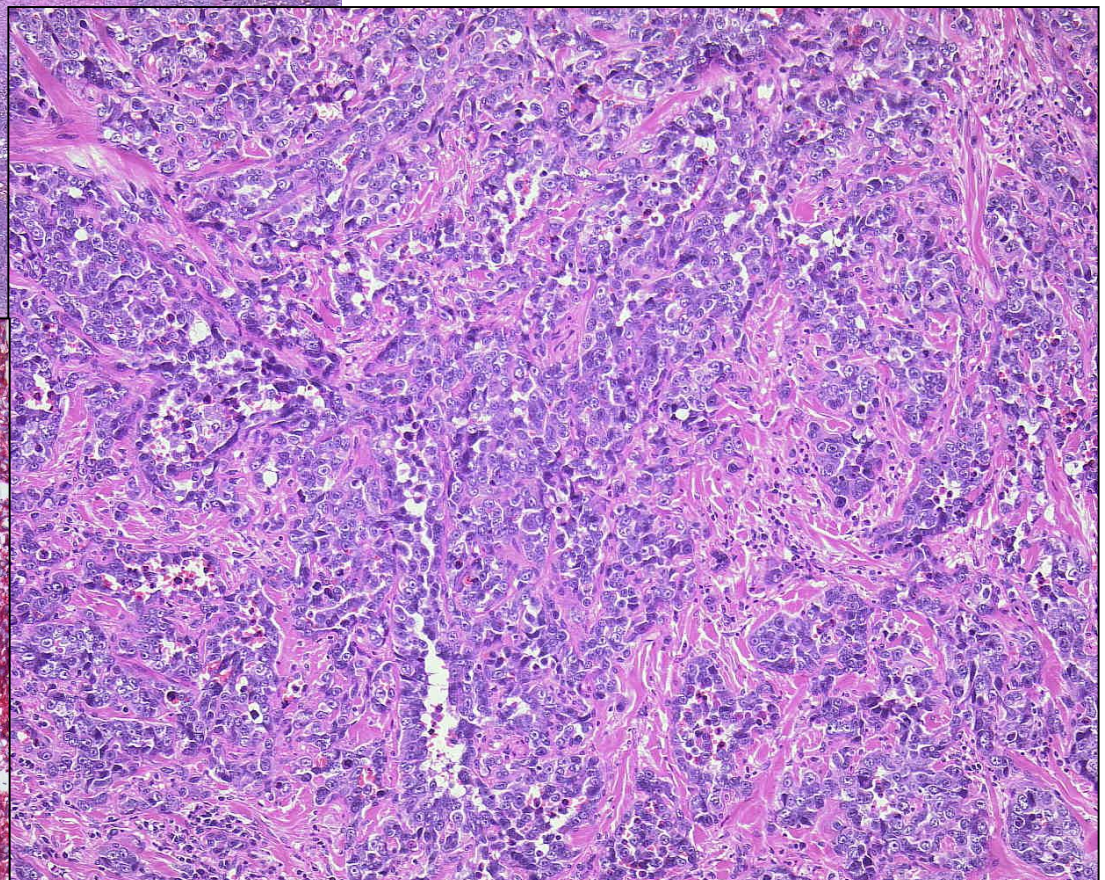
Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs

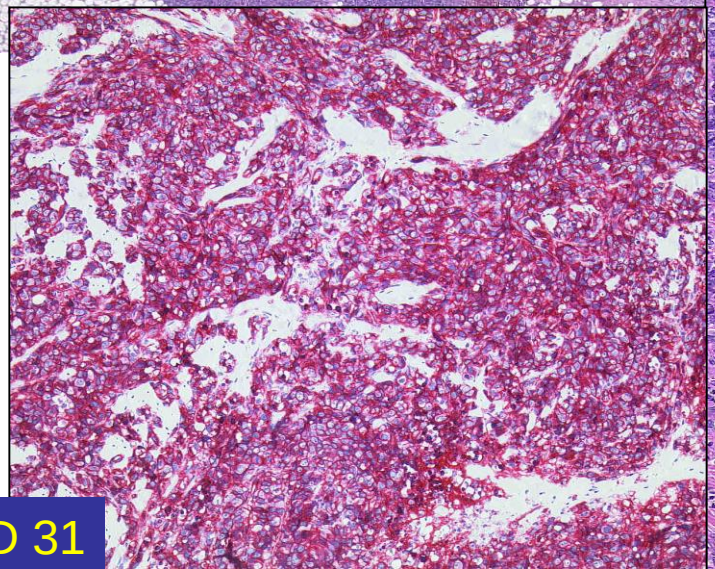
Suchak R et al. AJSP 2011; 35: 60

- 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

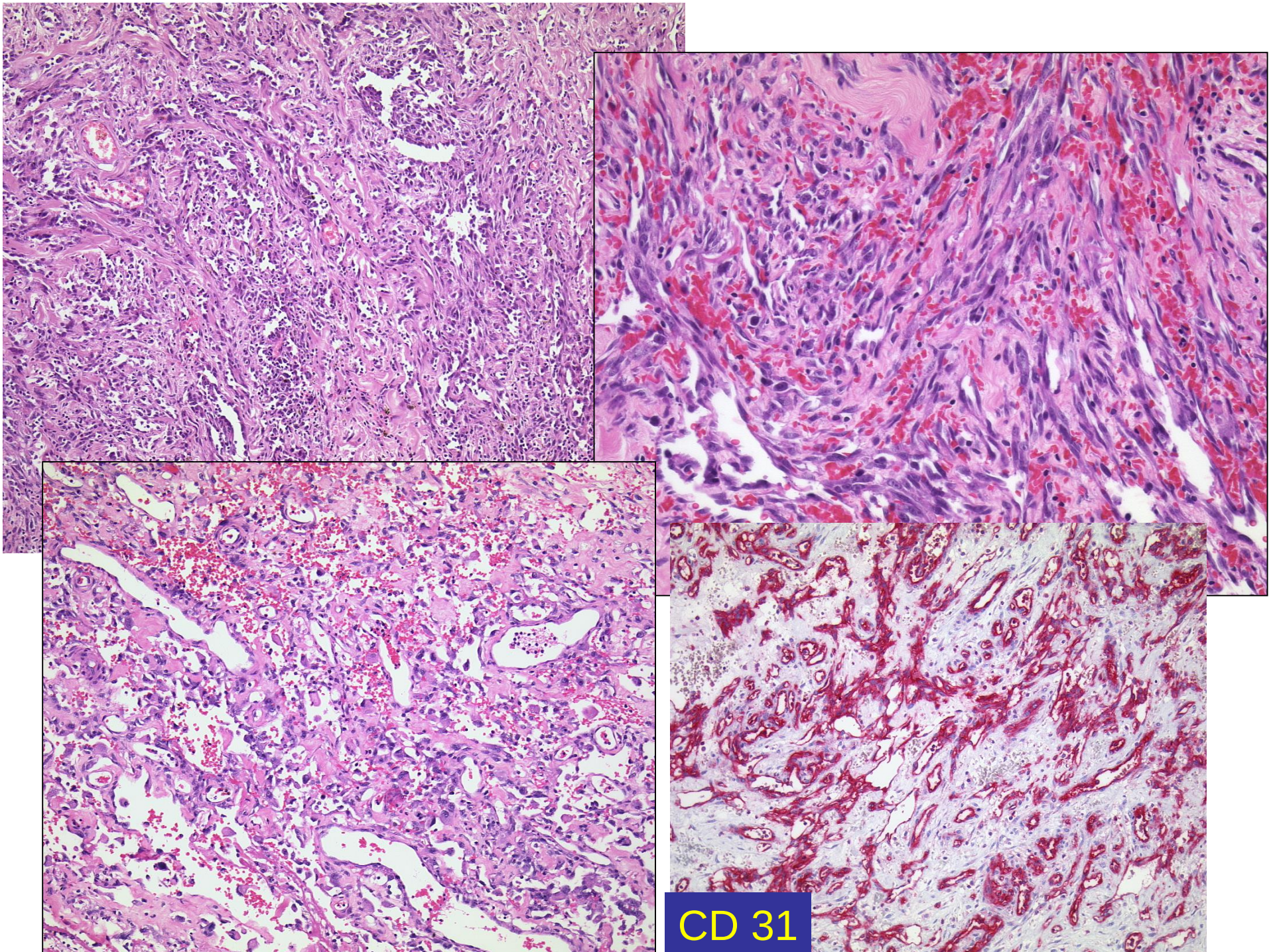
Conclusions: cutaneous Angiosarcoma

- 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)

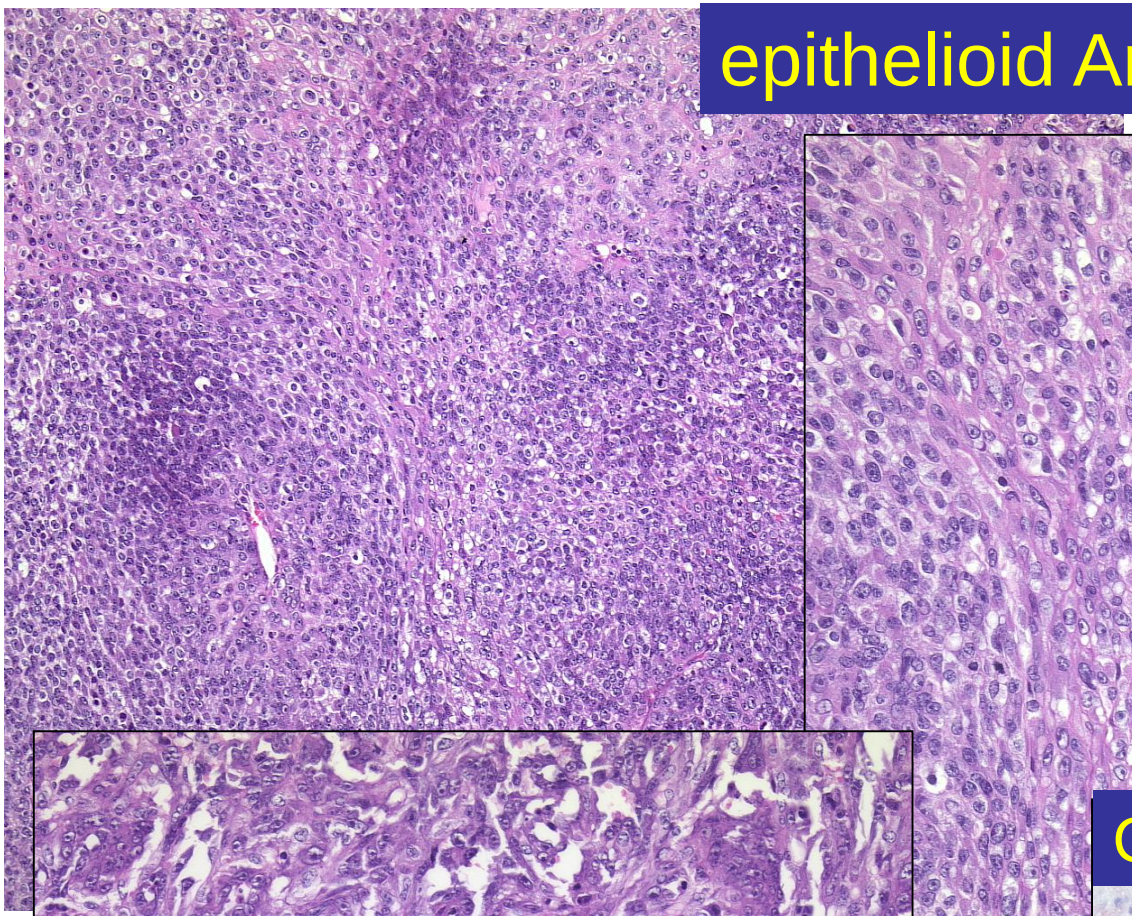
!!! Think on cutaneous angiosarcoma !!!

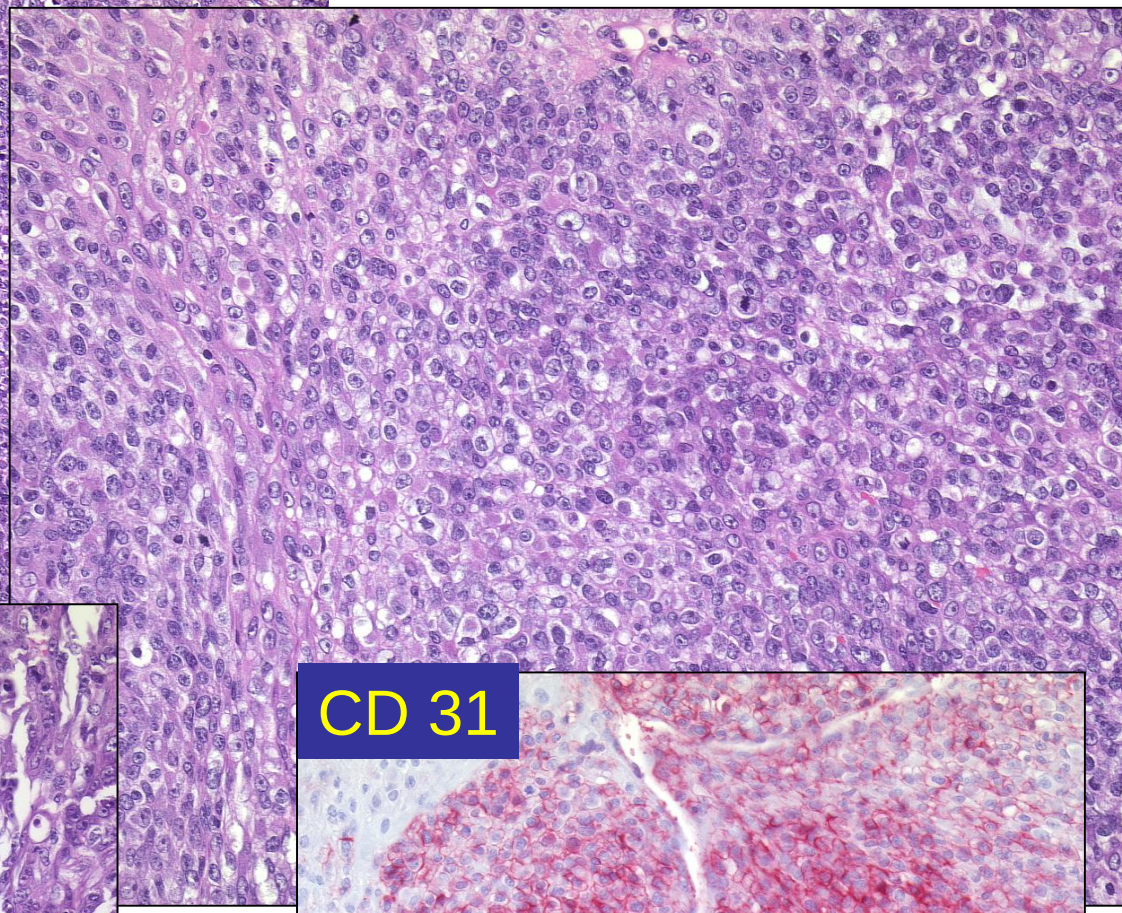
Angiosarcoma of Soft Tissues

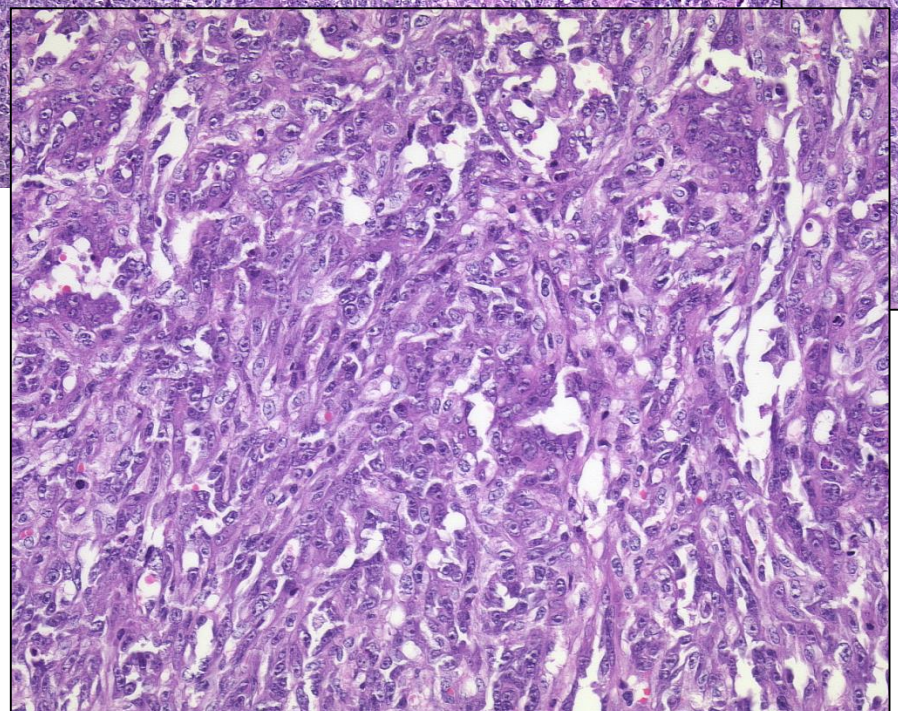
- very rare (< 1 % of all sarcomas)
- elderly patients, M > F
- lower > upper extremities, trunk > head
- rarely intraabdominal, retroperitoneal
- rarely multicentric
- very rarely in preexisting haemangiomas
- very rarely in nerve sheath tumours
- local recurrences in 20-30%
  metastases in 50%
  5-year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


CD 31

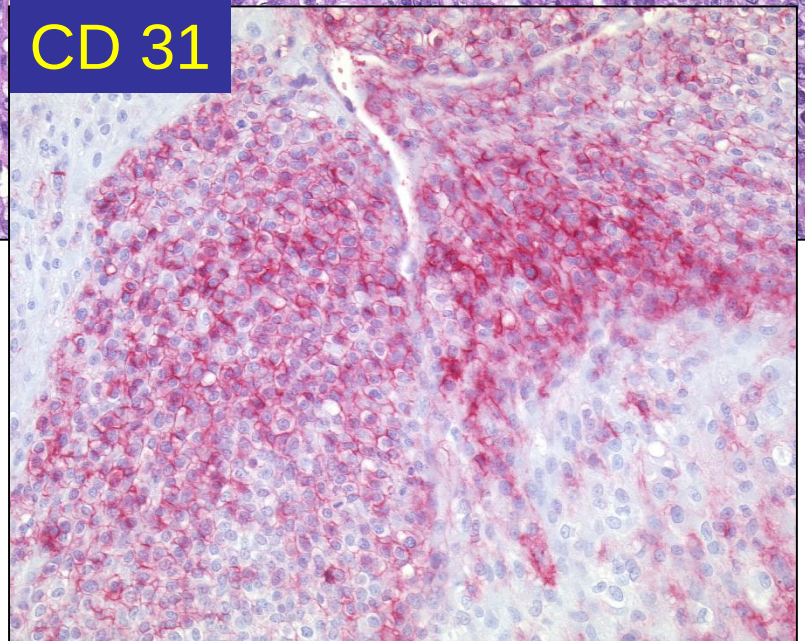
epithelioid Angiosarcoma

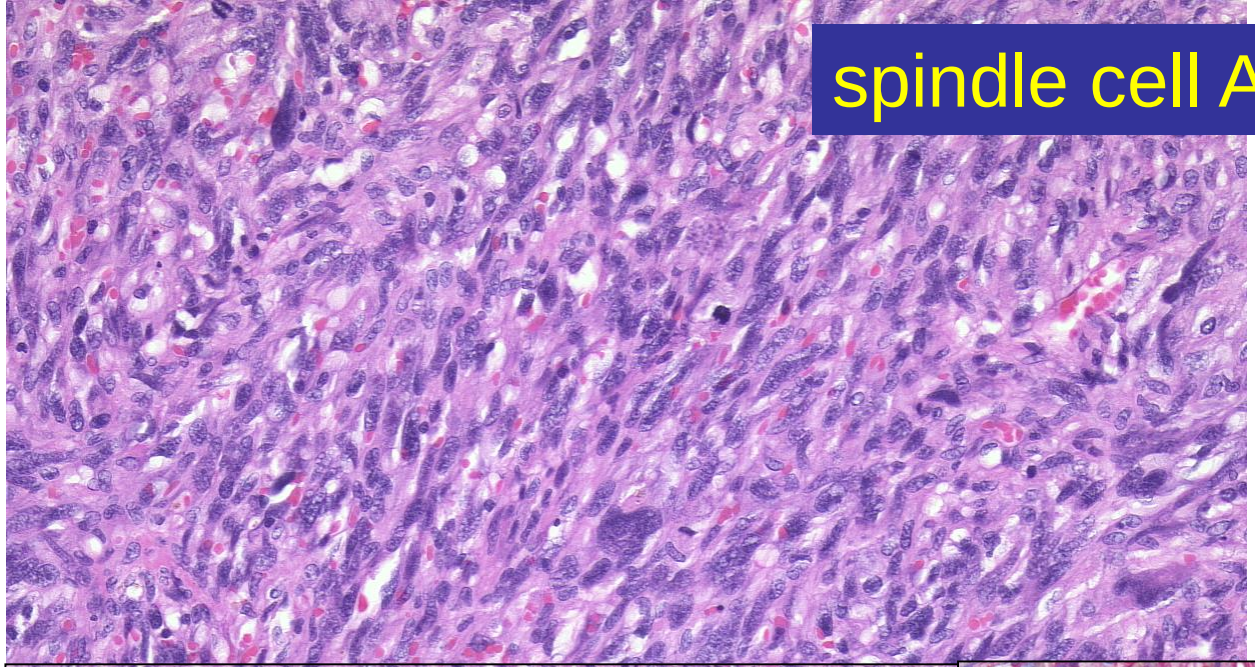




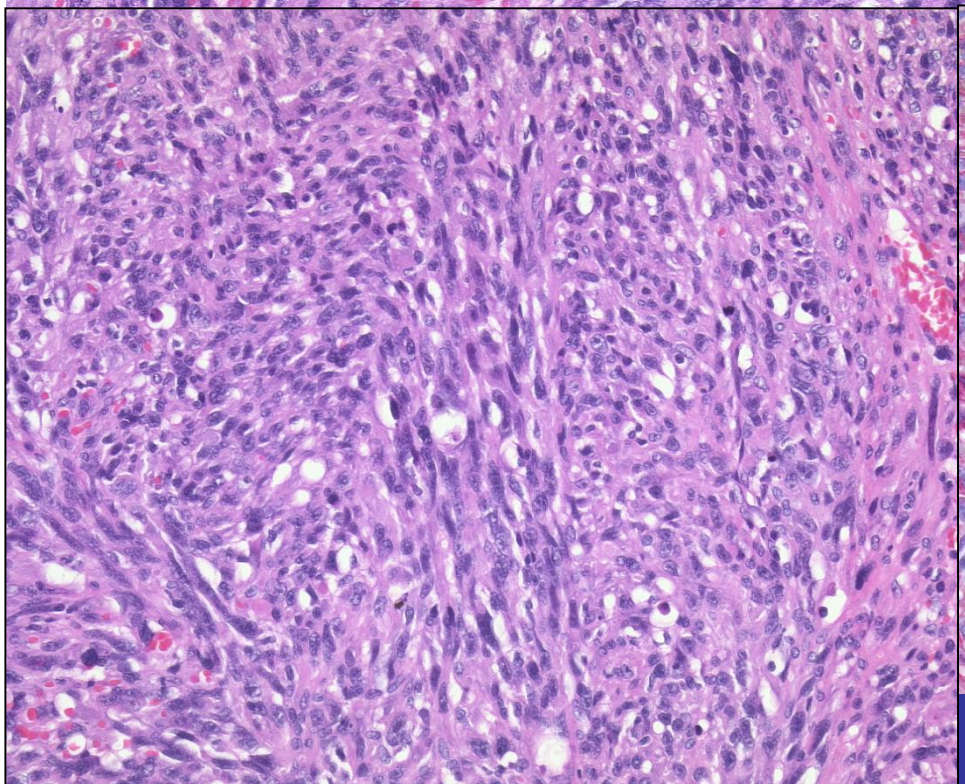


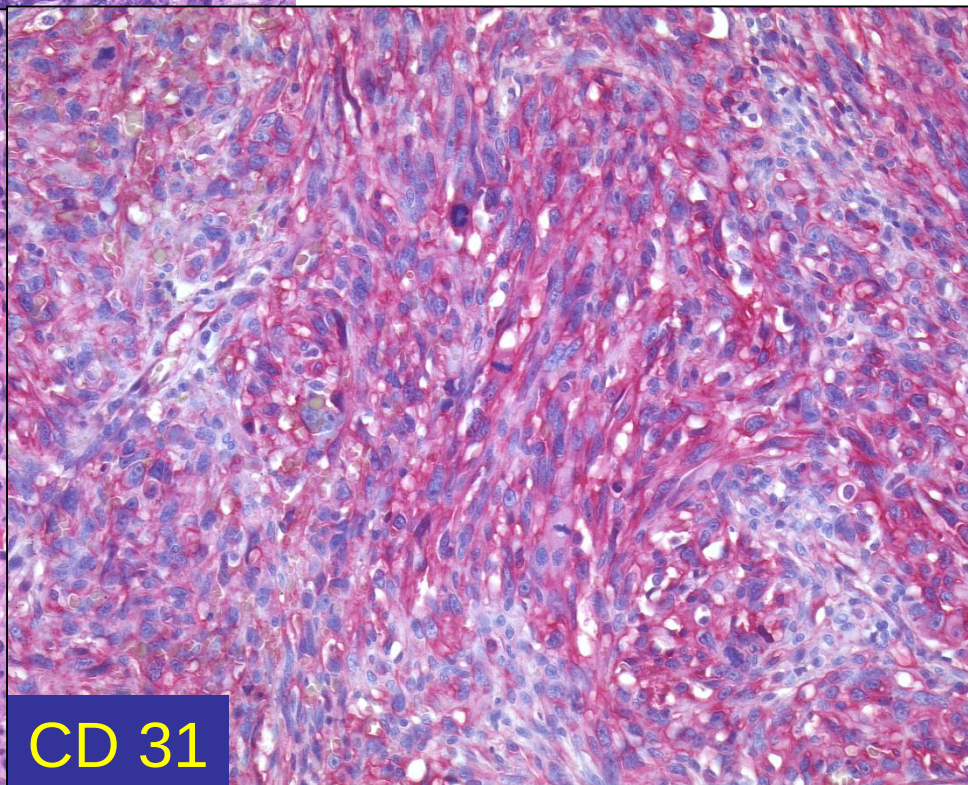
CD 31





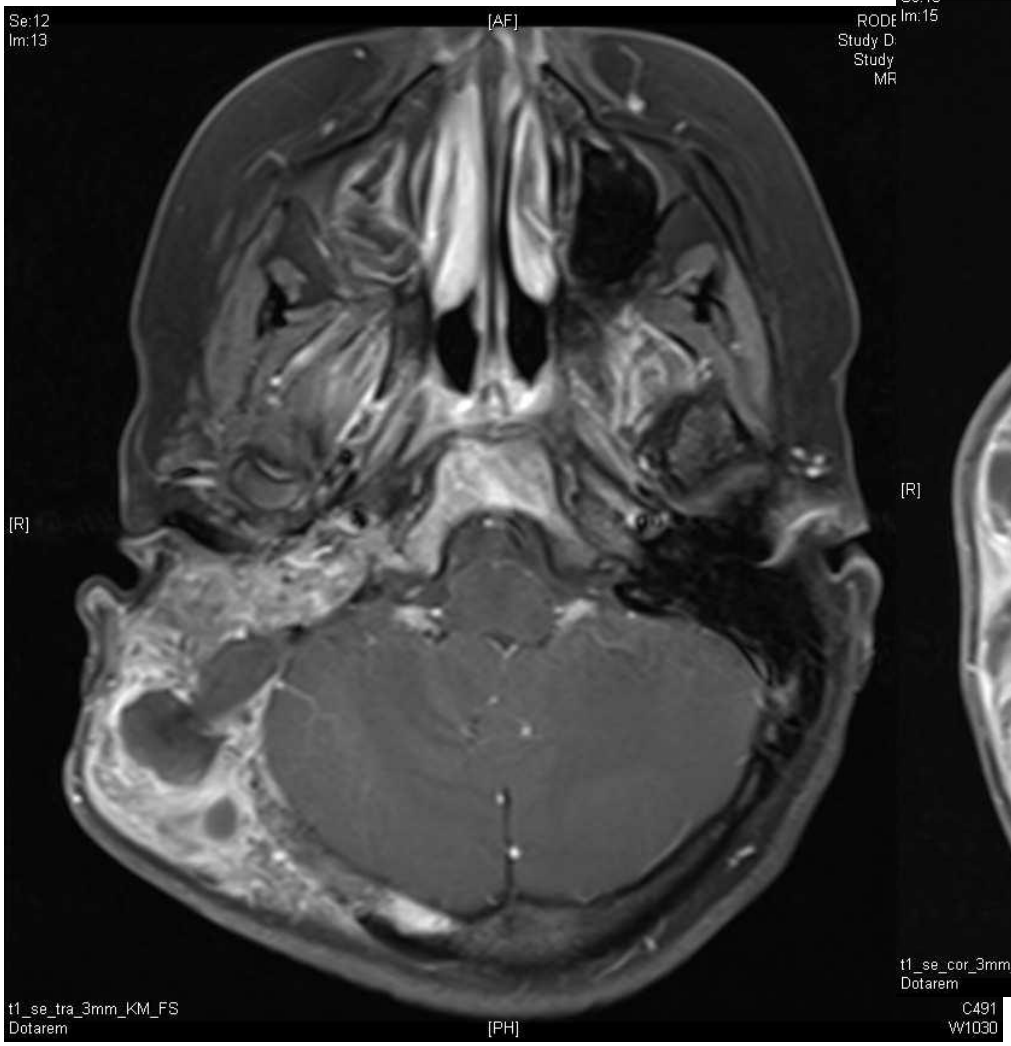
spindle cell Angiosarcoma

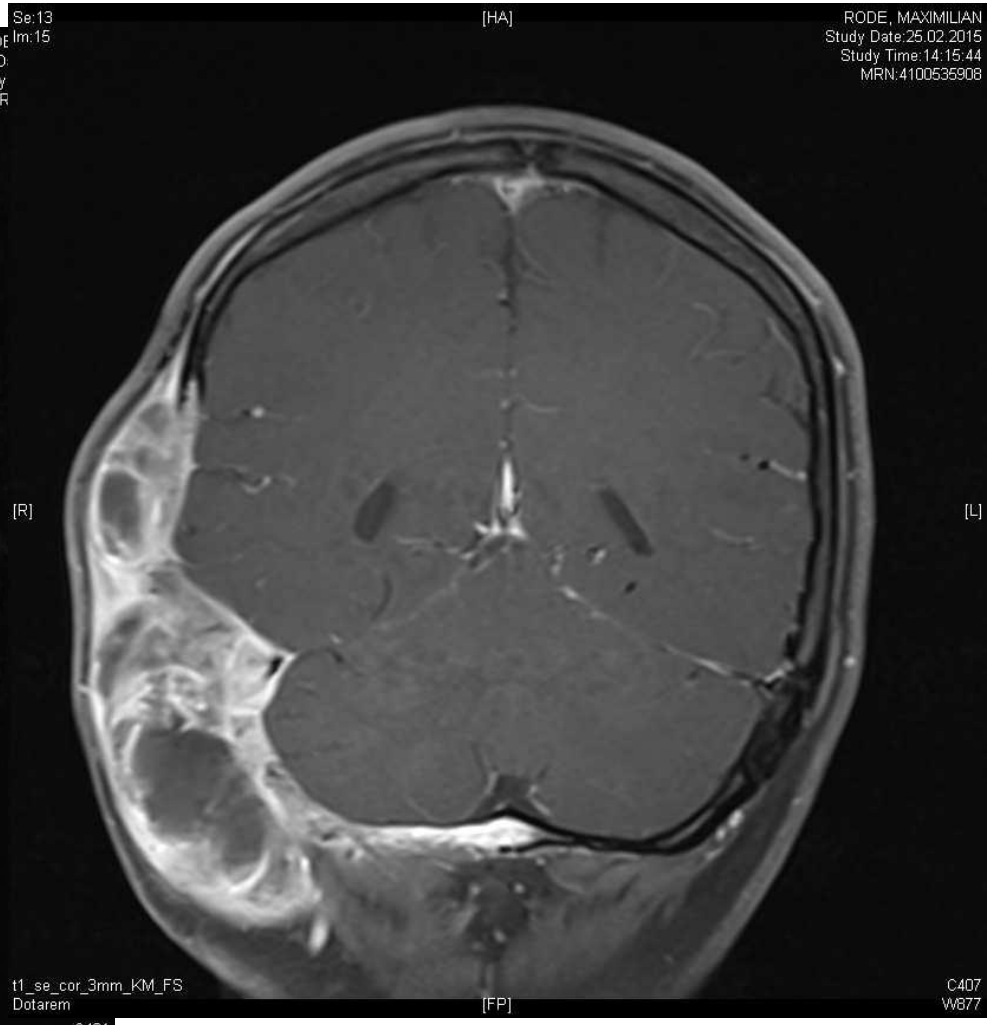


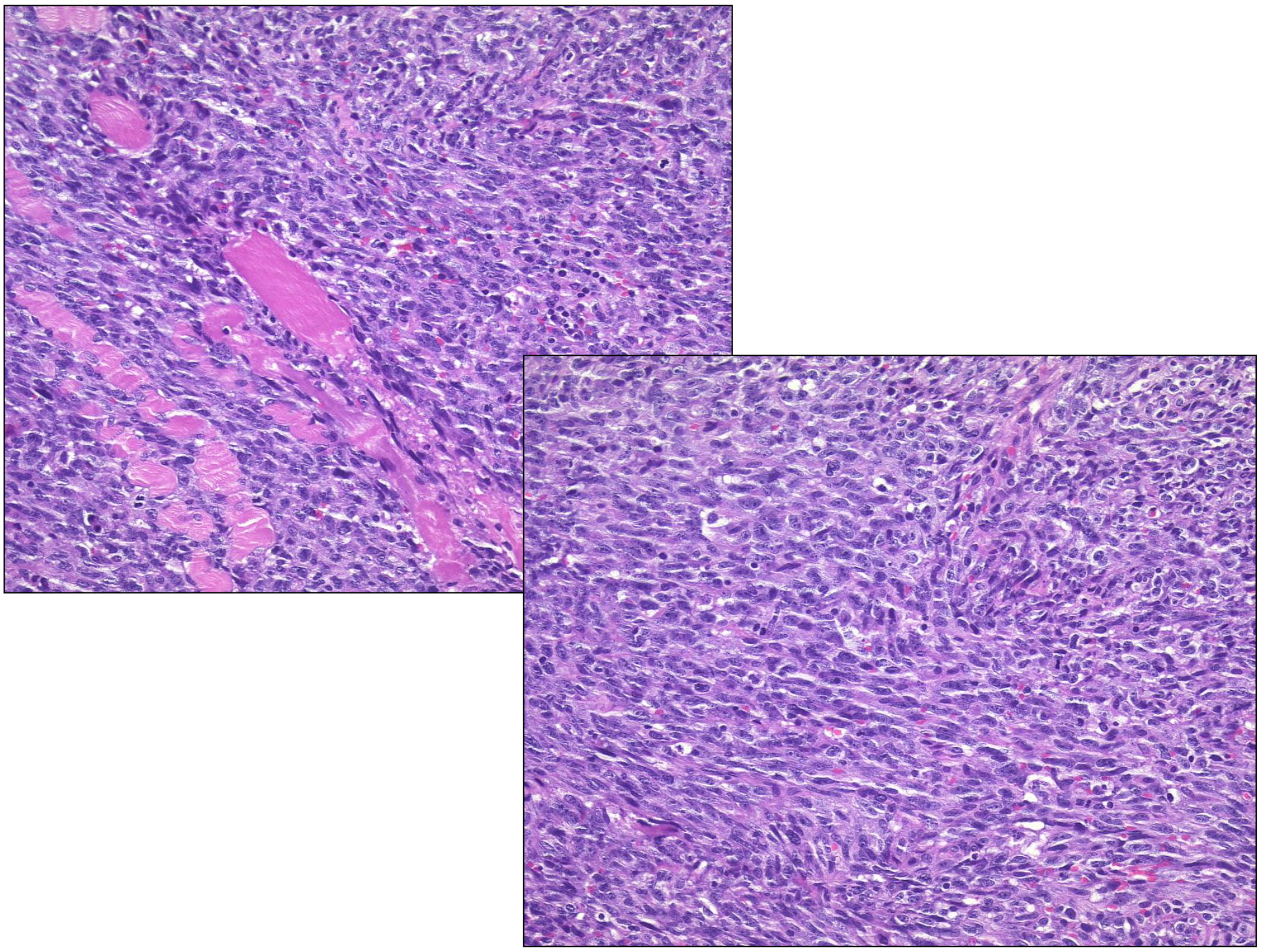


CD 31

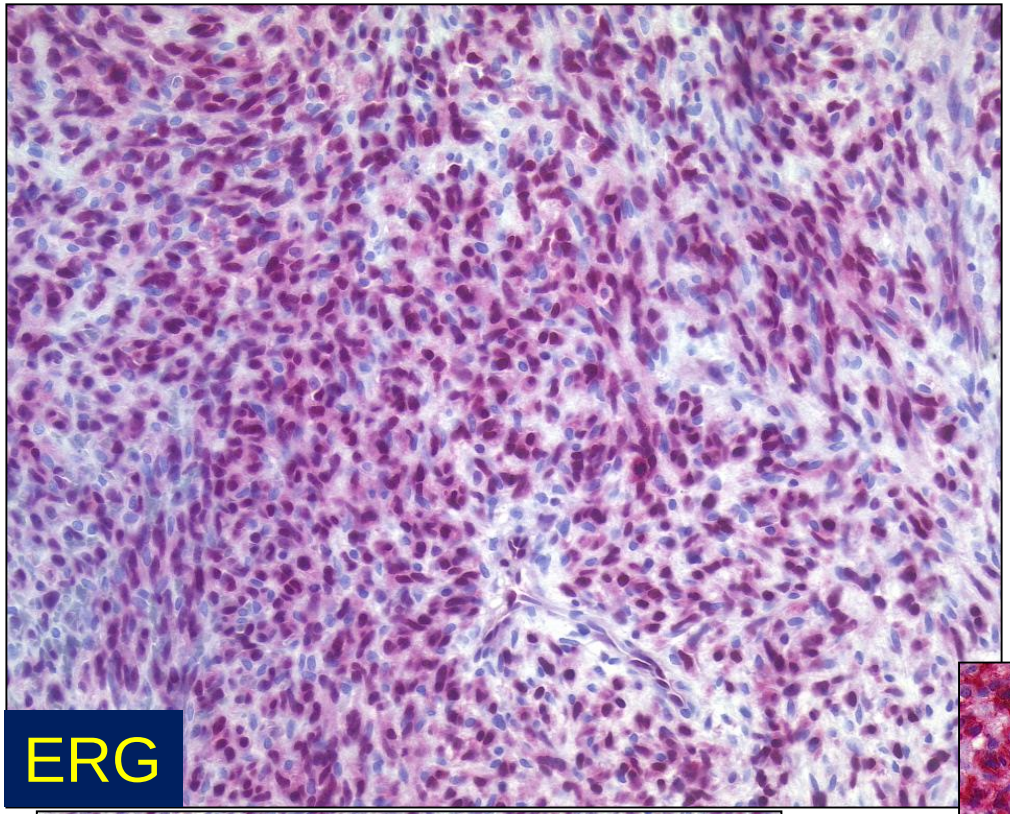
M, 14 years, scull,
huge tumour with bone destruction

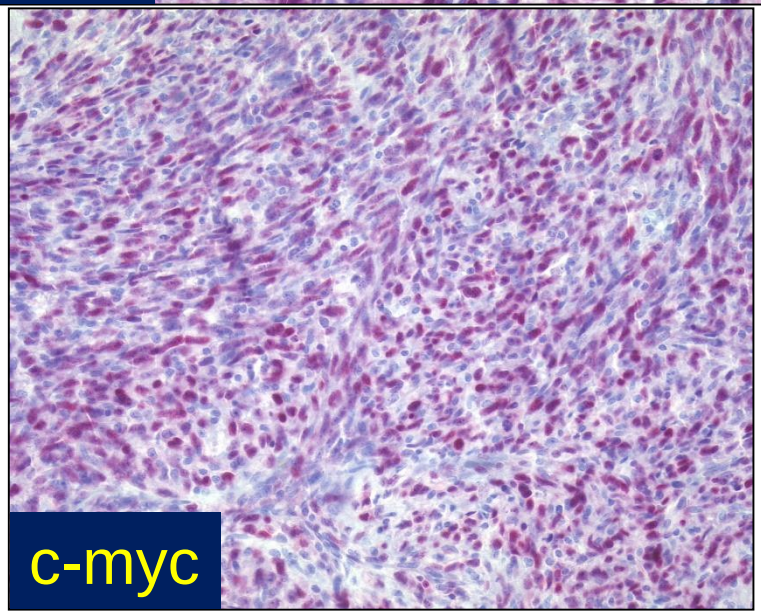


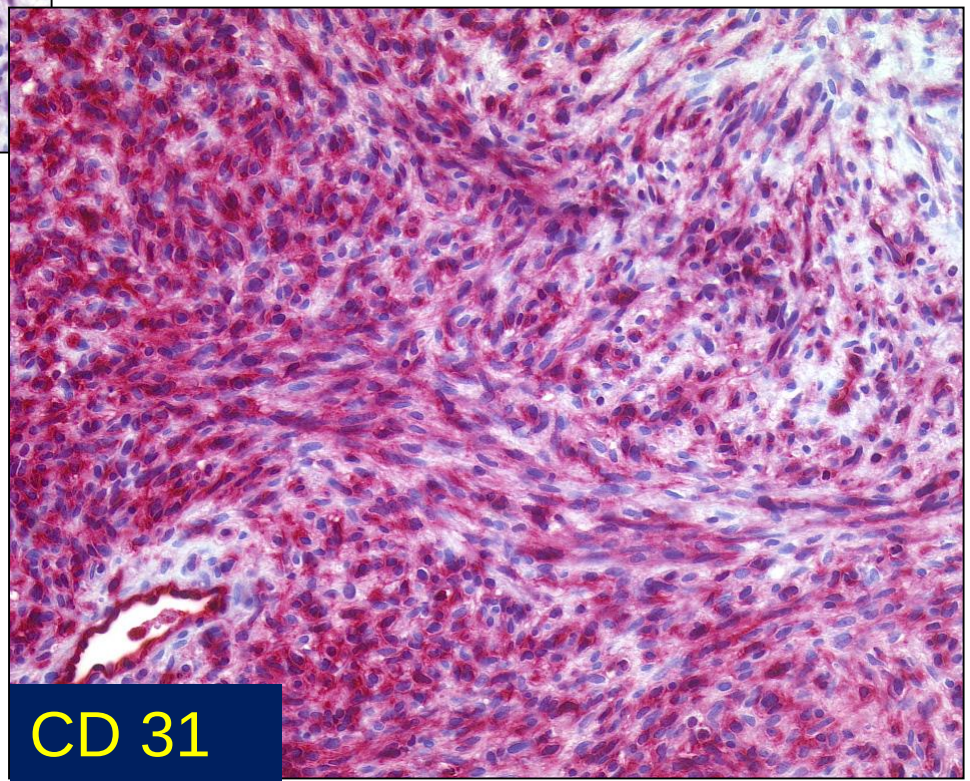


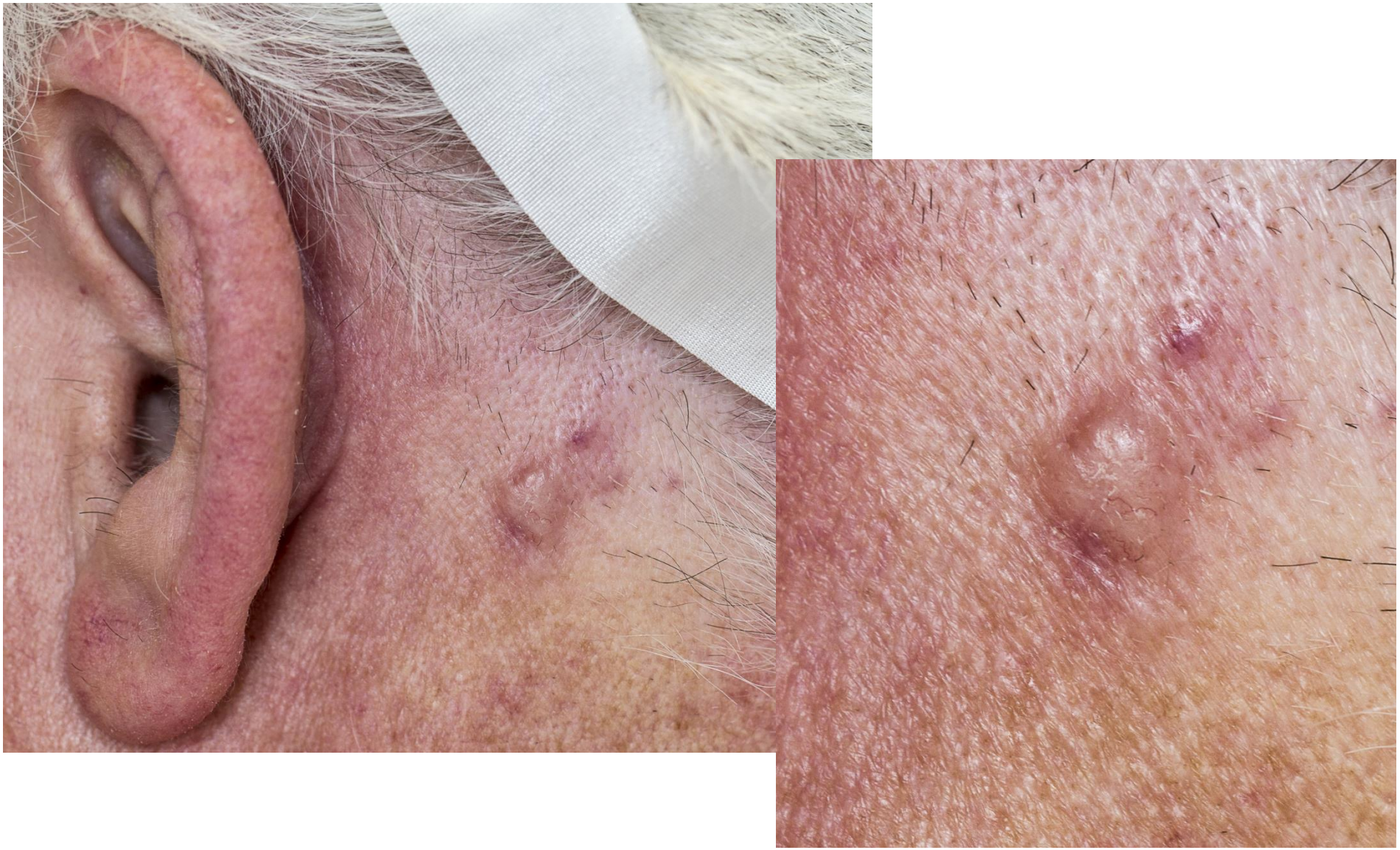


spindle cell angiosarcoma arising in a child

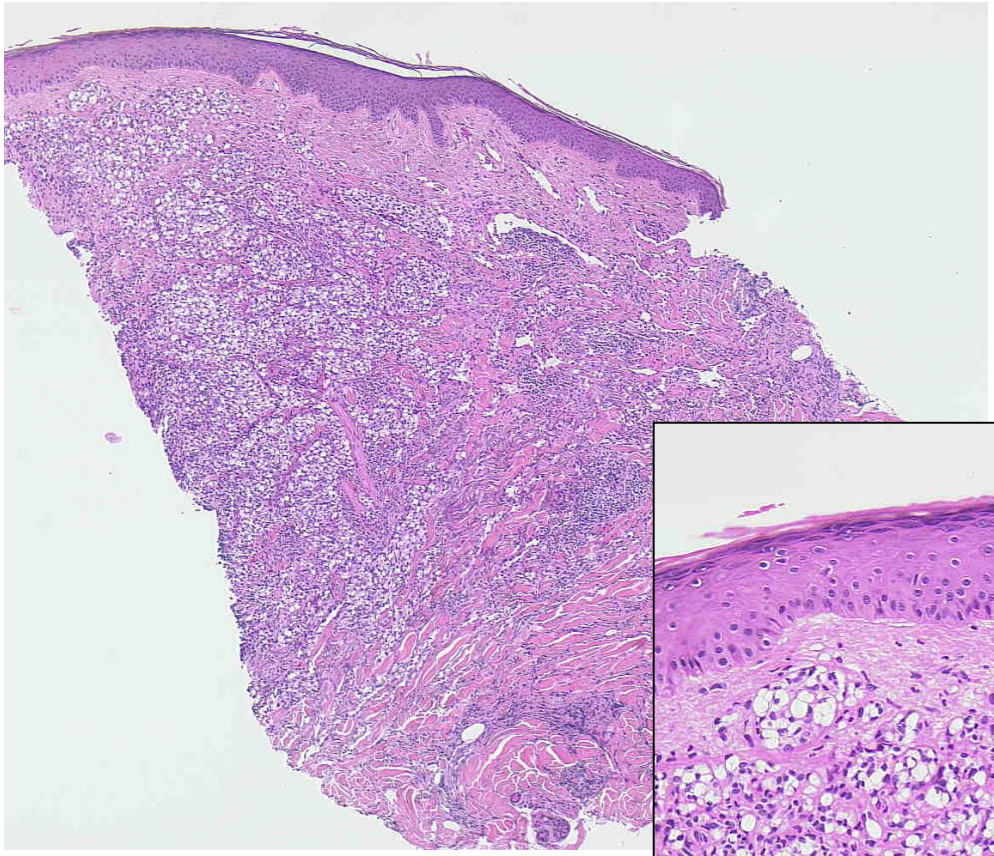


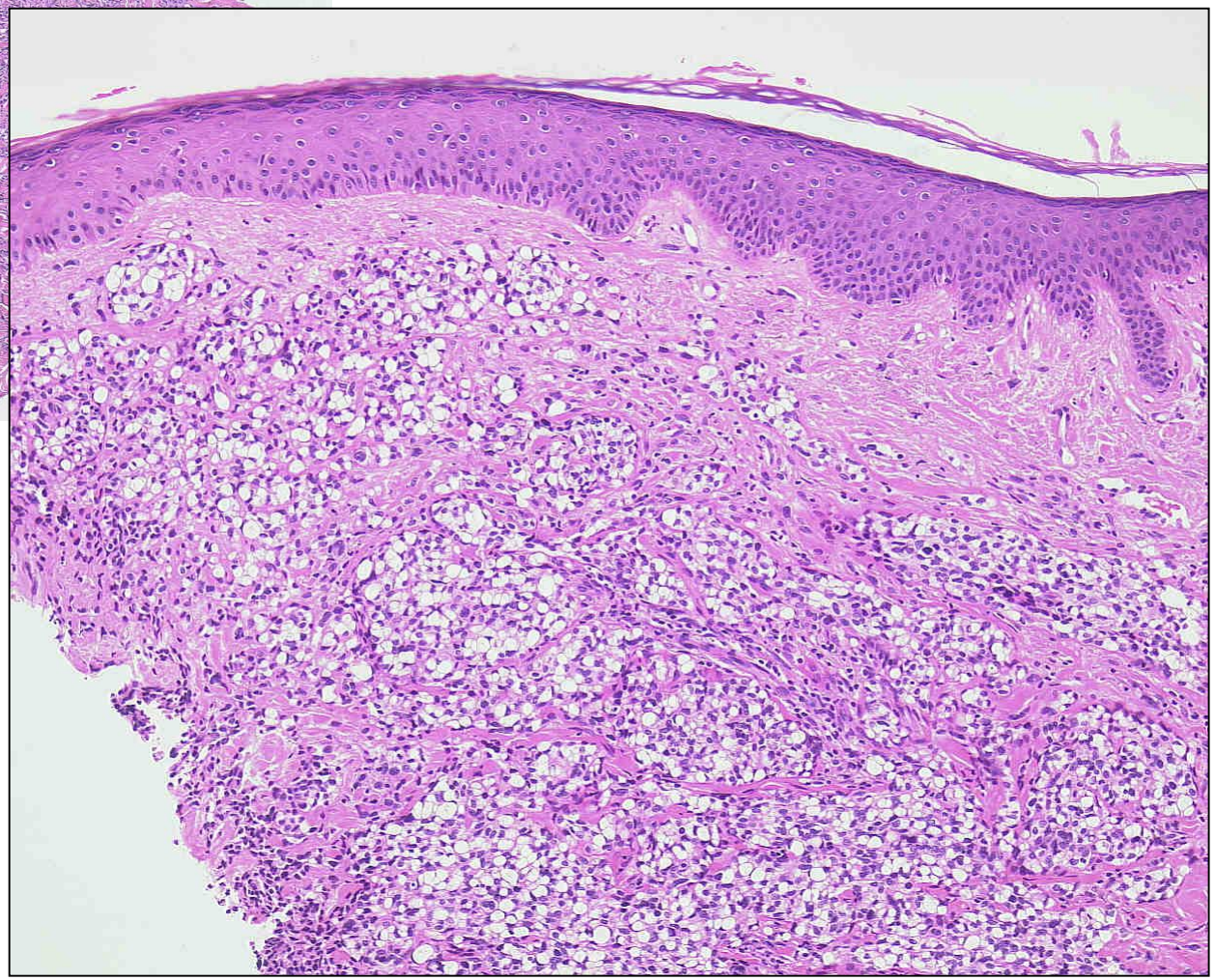


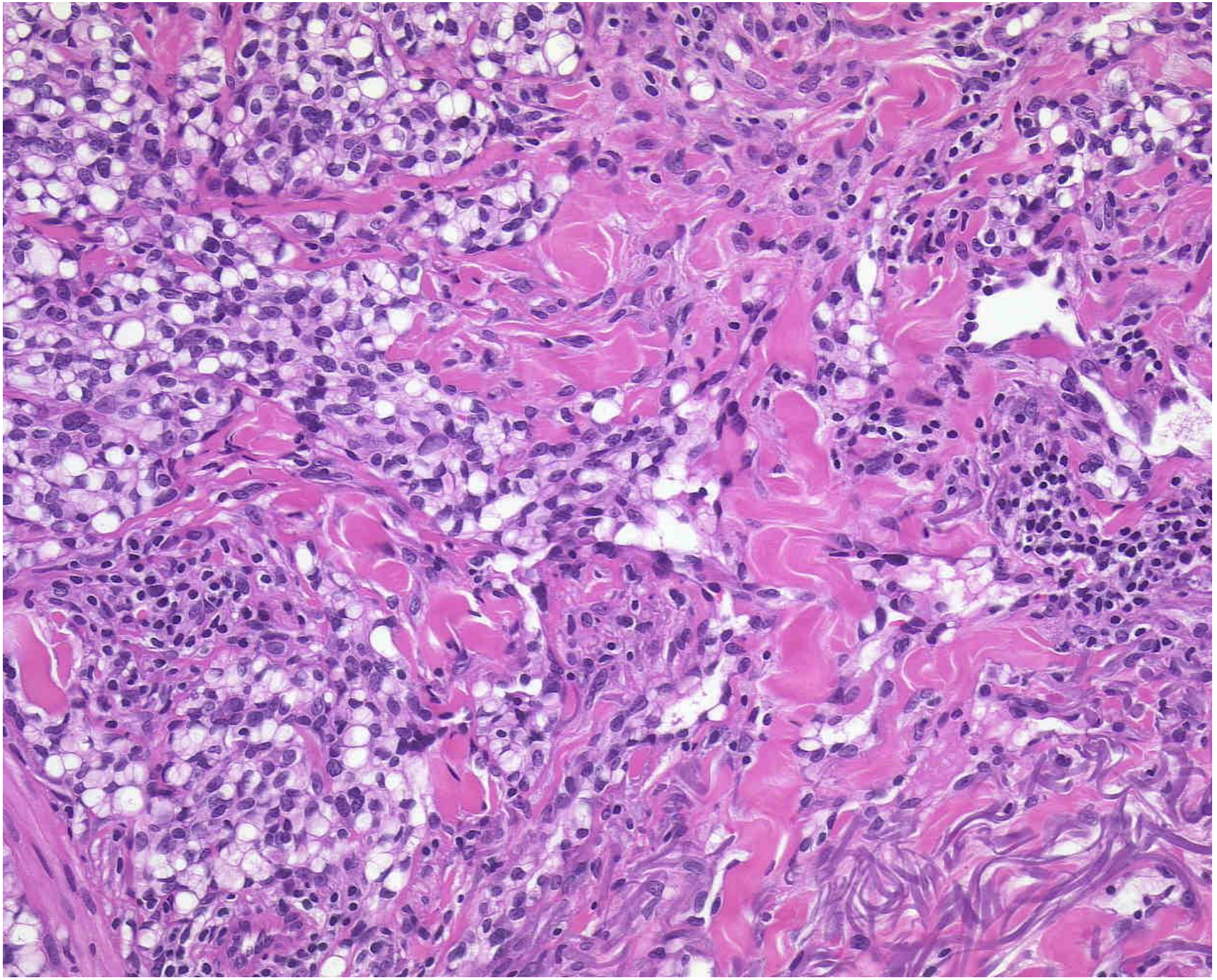


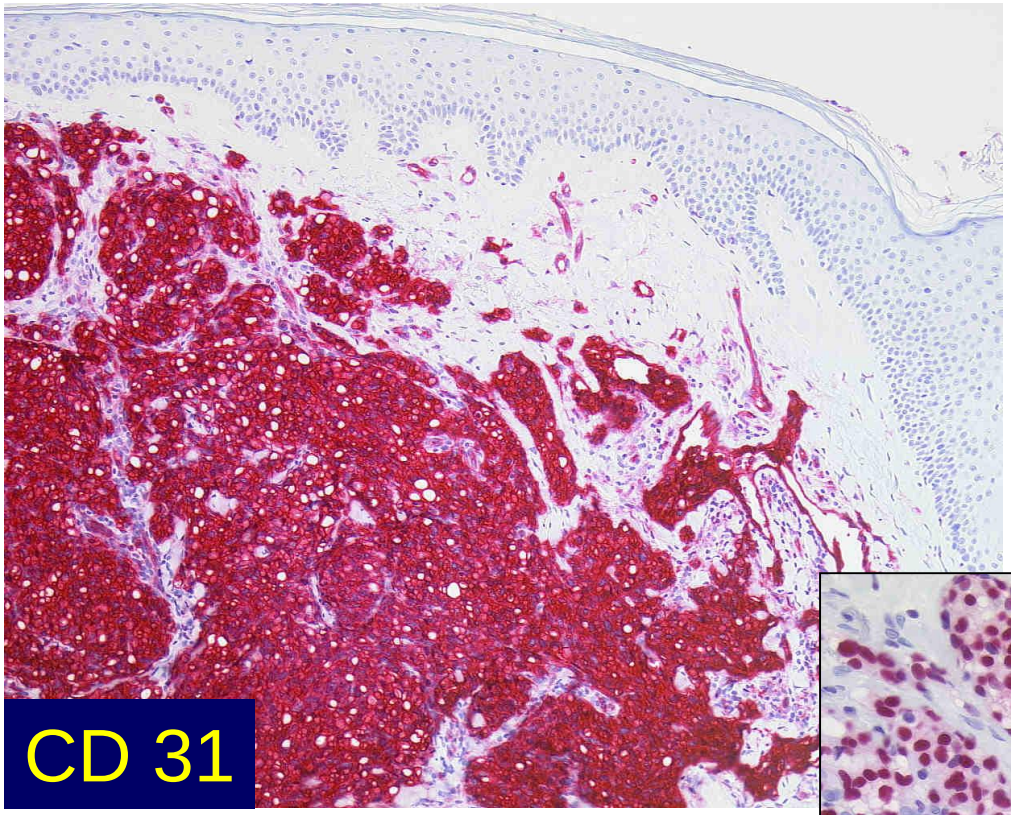


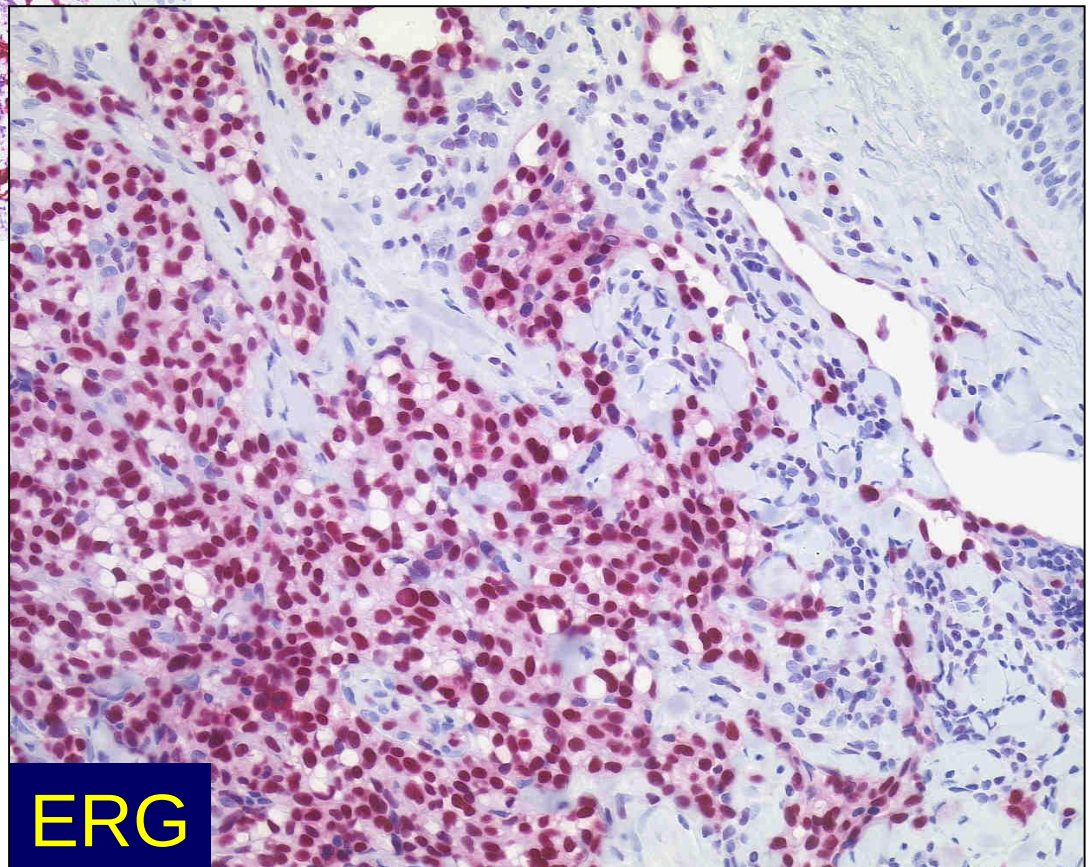
M, 74 years, BCC was suspected, biopsy







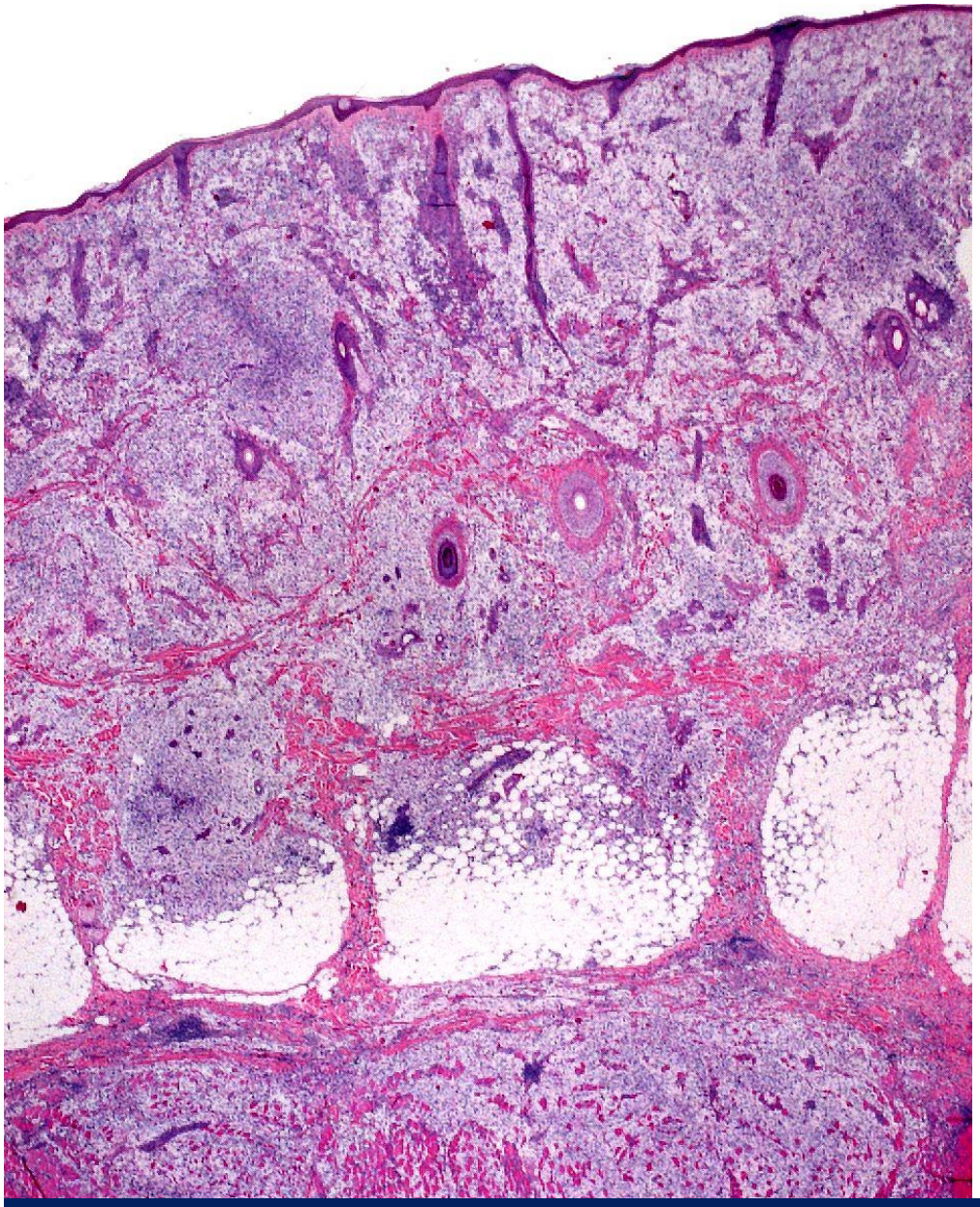

CD 31

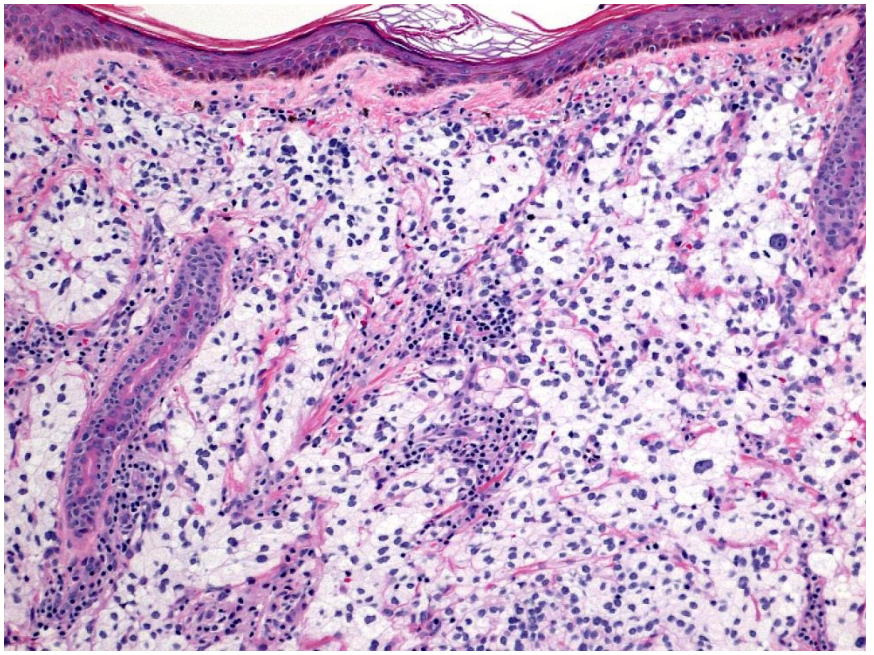

ERG

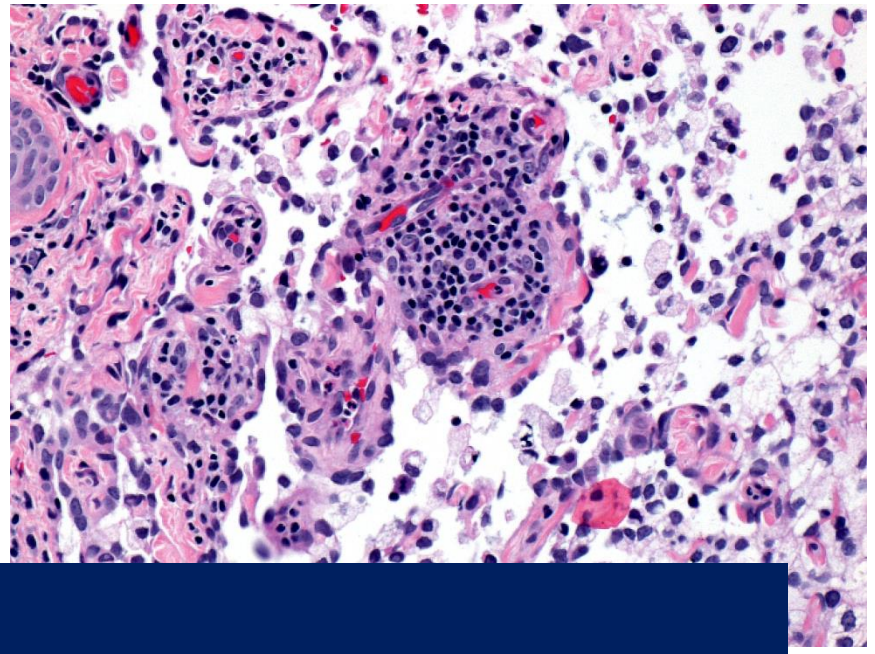
Signet ring cell Angiosarcoma

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

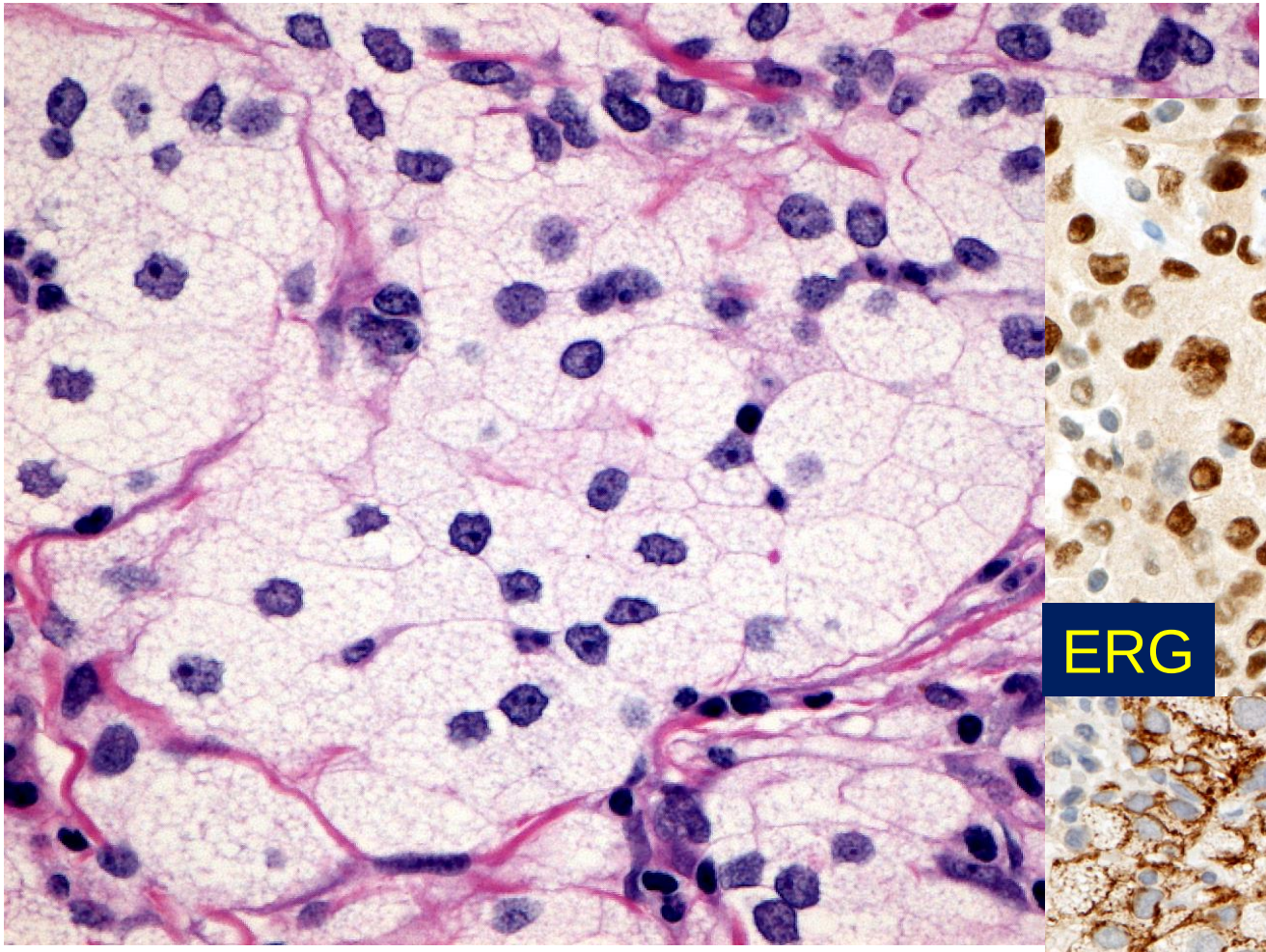
Wood et al. Histopathology 2015; 66: 856
(2 x signet ring AS, 2 x foamy cell AS,
1 x granular cell AS)

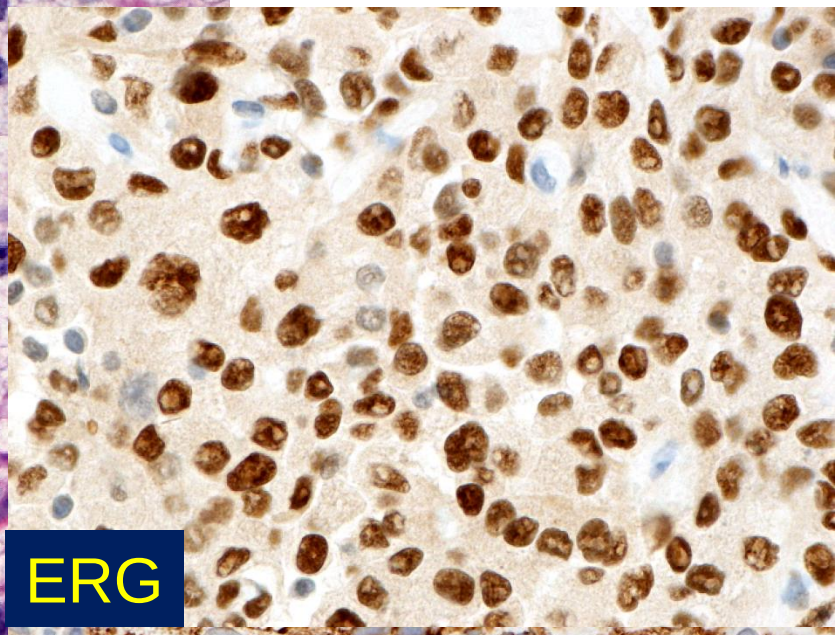


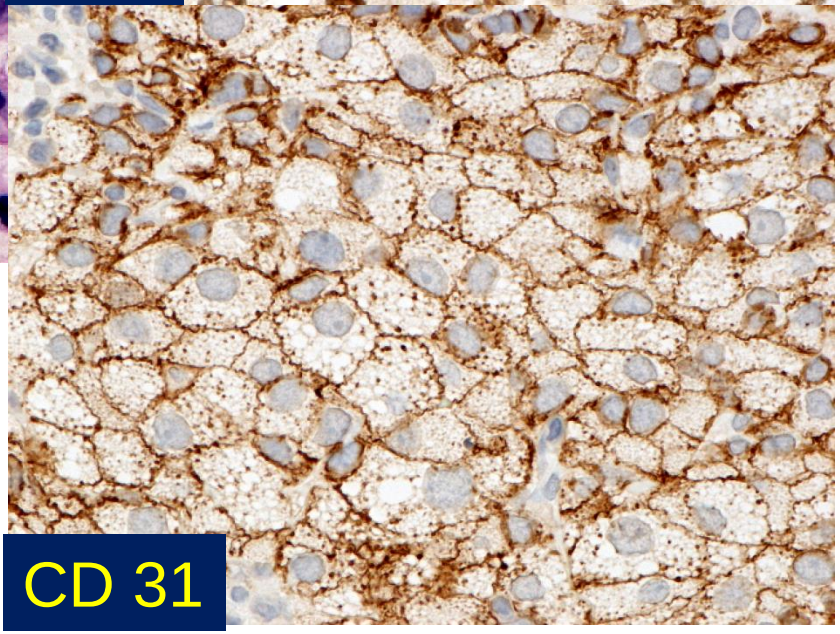




M, 68 years, large tumour, face
foam cell angiosarcoma (by courtesy of Dr.Th.Brenn, Calgary)

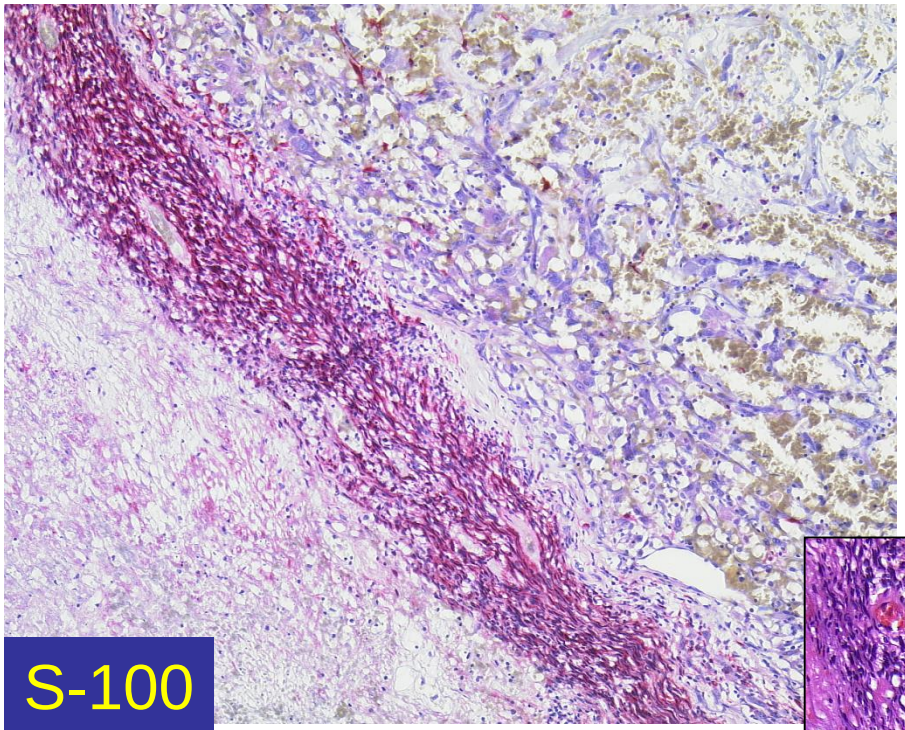


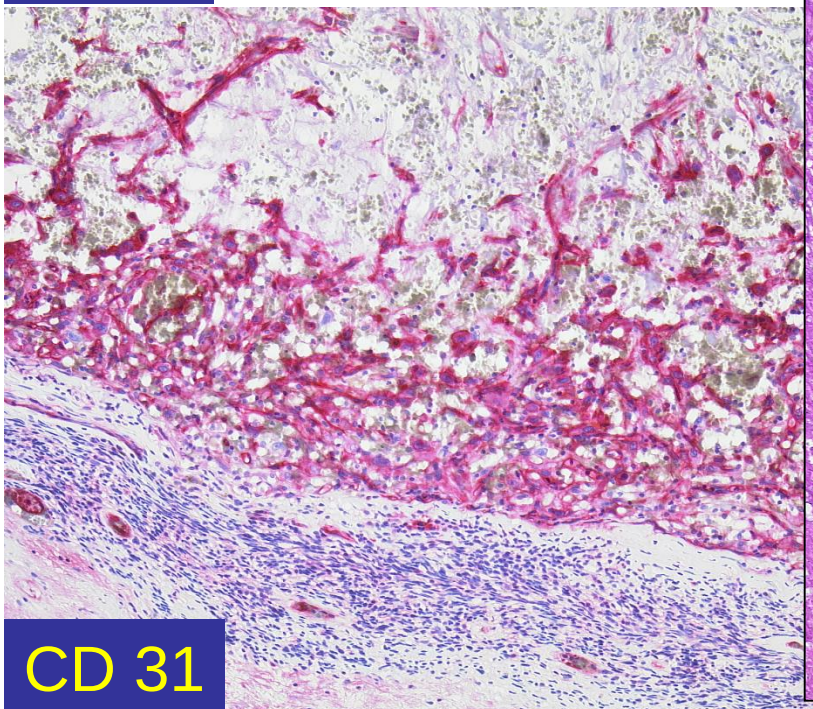

ERG

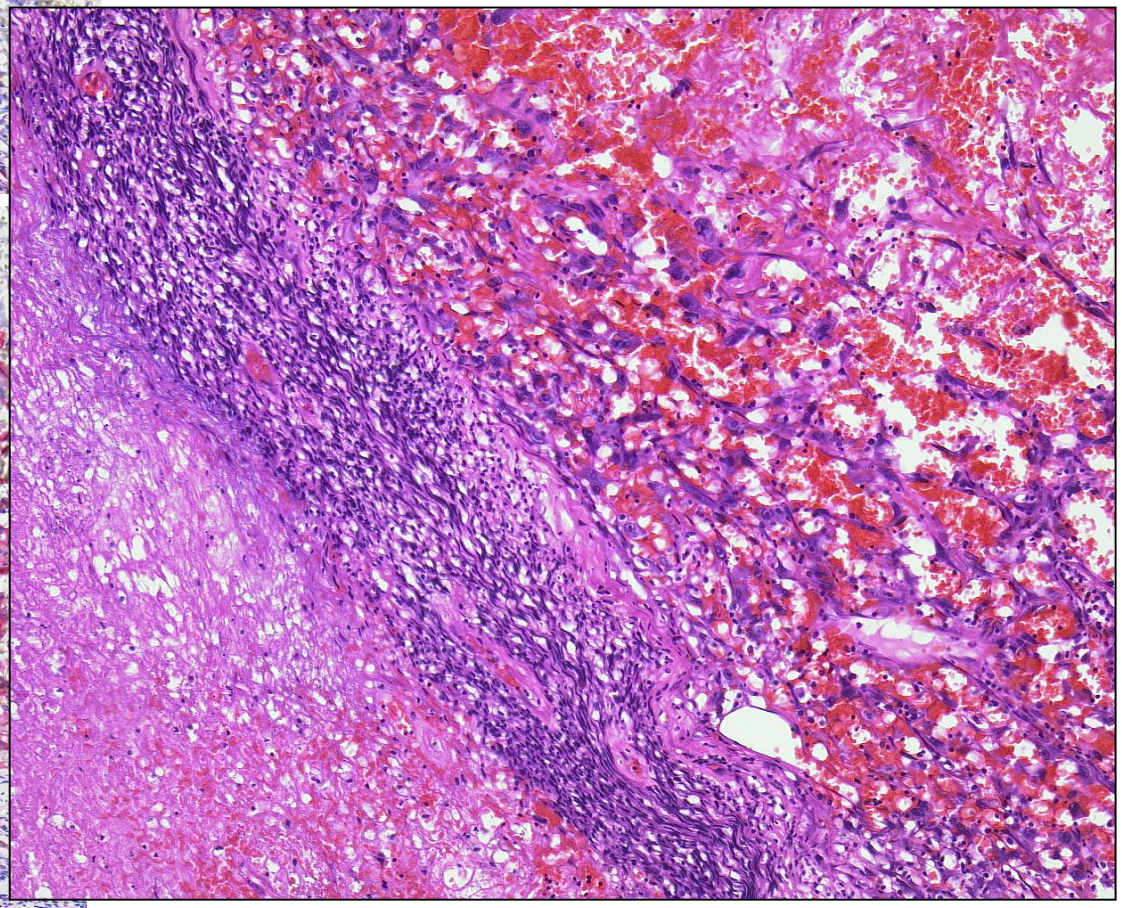

CD 31

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

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







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

- 12 atypical vascular lesions, 22 radiation induced AS
- gene expression profiling, FISH analysis, cell line studies and immunohistochemical studies have been performed
- podoplanin staining was negative in most angiosarcomas
- high level *MYC* amplification in all cases of angiosarcoma
- no *MYC* amplification in cases of atypical vascular lesions (dysregulated MYC expression promotes cell proliferation, represents an early oncogenic event)
- high level *FLT4* amplification in 25% of radiation induced AS (targeting *FLT4* as a potential therapeutic option)

KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors

CR Antonescu et al. Cancer Res 2009; 15: 7175-7179

- 39 cases, 22 primary and 17 secondary angiosarcomas
- 44% breast, 36% soft tissue/bone, 10% head, 10% visceral
- upregulation of *TIE1, KDR, SNRK, TEK*, and *FLT1*
- *KDR* mutations in 4 cases (breast, 2 primary, 2 secondary AS)
- all patients with *KDR* mutation developed distant metastases
- autophosphorylation of encoded proteins is blocked by *KDR* antagonists
- small molecule inhibitors i.e. Sunitinib, Sorafenib are effective

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

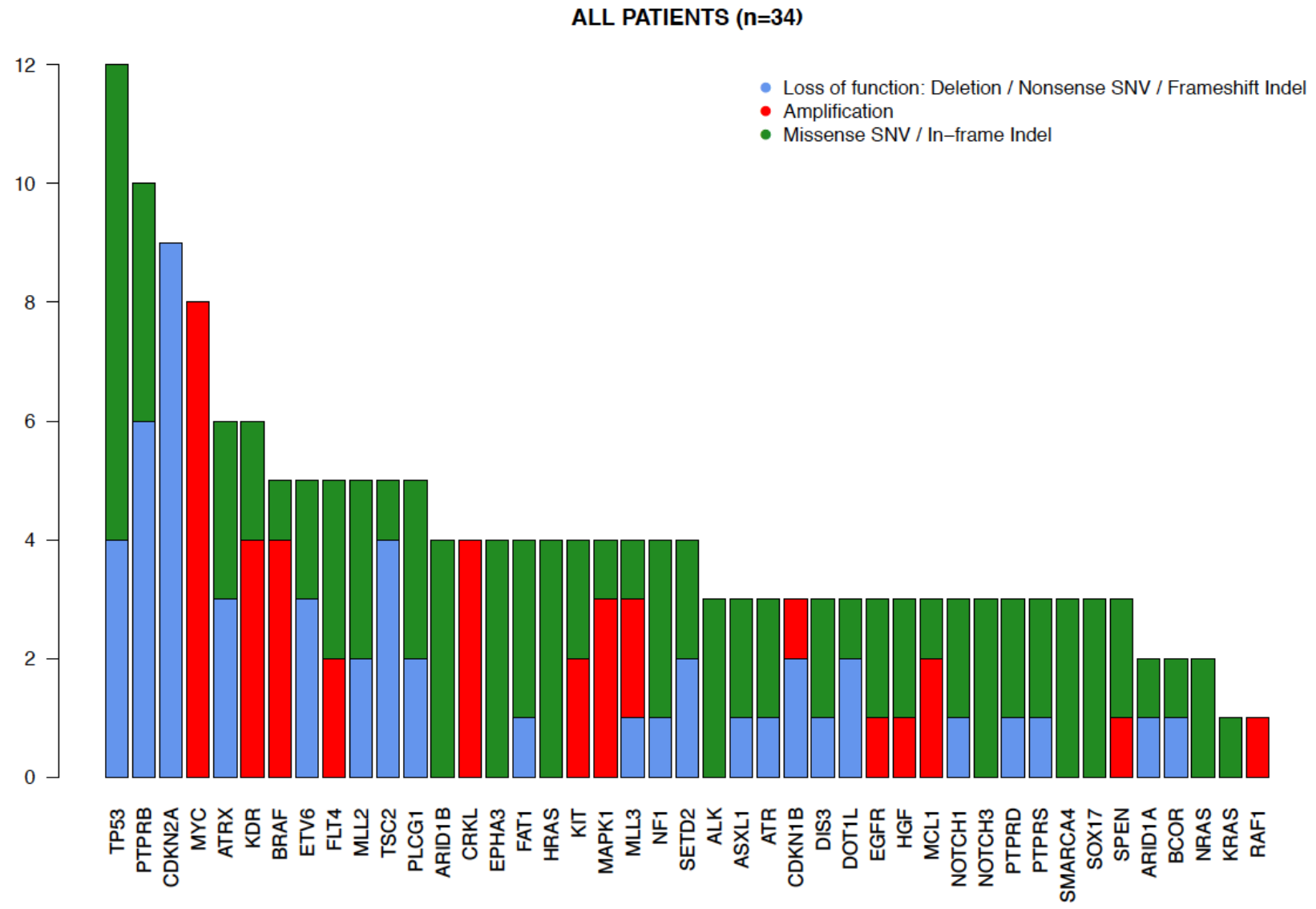
- *PLCG1* mutations in 9.5% of analysed cases
- *KDR* mutations in 7% of analysed cases
- *CIC* abnormalities in 9% of analysed cases
  (young patients, epithelioid cytomorphology
  poor prognosis)
- *MYC* amplification in 91% of RT-AS cases
- *MYC* amplification in 7% of primary angiosarcomas
- *FLT4* amplification in cases with *MYC* amplification

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

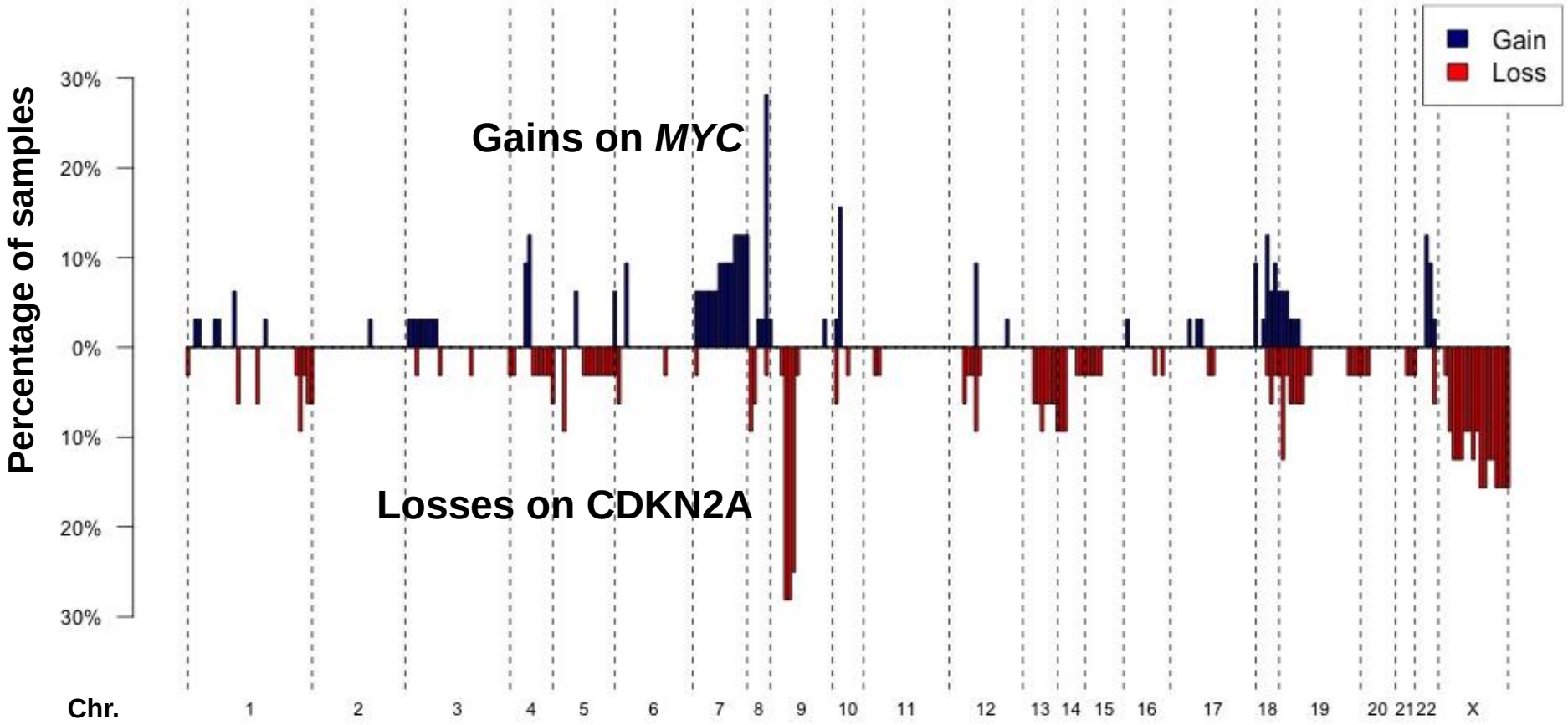
- 34 cases (24 F, 10 M)
- radiation-associated AS (7), actinic AS (9)
- MAPK pathway alterations in 53%
  (mutations in *KRAS, HRAS, NRAS, BRAF, MAPK1, NF1*,
  amplifications in *MAPK1/CRKL, CRAF, BRAF*)
- *TP53* mutations in 35%, losses of *CDKN2A* in 26%
- *MYC* amplification in 24% (88% radiation-associated AS)
- *PTPRB* mutations in 29%, *PLCG1 R707Q* mutations in 3%
- angiosarcomas are a genetically heterogenous group
- therapies inhibiting MAPK signaling may be promising

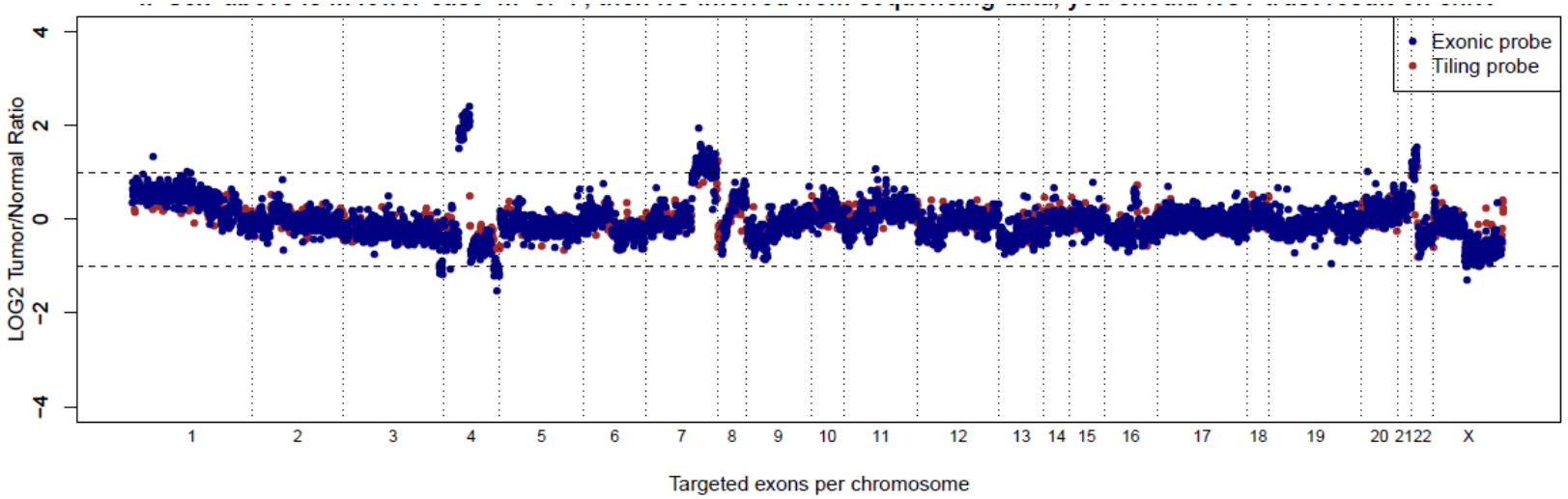
Figure 1. Distribution of genetic alterations in angiosarcoma samples



y-axis depicts the amount of tumour samples harboring the alteration

Figure 4. DNA copy number profiles of angiosarcoma samples





chr	genes	NExons	fc	p.adj
4q12	KIT	21	3.96*	0.0e+00
4q12	KDR	30	3.96*	0.0e+00
22q11	SMARCB1	9	2.48*	1.1e−06
7q34	BRAF	18	2.12*	1.0e−04
7q36	EZH2	19	2.12*	1.0e−04
7q36	MLL3	59	2.12*	1.0e−04
22q11	CRKL	3	2.00*	4.0e−04
22q11	MAPK1	8	2.00*	4.0e−04
7q32	SMO	12	1.98	4.2e−04
11q14	EED	12	1.49	1.5e−01
1p36	TNFRSF14	8	1.43	1.5e−01
1p36	PIK3CD	22	1.43	1.5e−01
1p36	MTOR	57	1.43	1.5e−01
1p36	SPEN	15	1.43	1.5e−01
1p36	SDHB	8	1.43	1.5e−01
1p36	ARID1A	20	1.43	1.5e−01
1p34	STK40	10	1.43	1.5e−01
1p34	MYCL1	3	1.43	1.5e−01
1p34	MPL	12	1.43	1.5e−01
1p34	MUTYH	16	1.43	1.5e−01

chr	genes	NExons	fc	p.adj
4q35	FAT1	26	−2.16*	6.1e−04
3q28	TP63	14	−2.04*	2.5e−03
Xq11	AMER1	1	−1.54	2.0e−01
Xq12	AR	8	−1.54	2.0e−01
Xq13	MED12	45	−1.54	2.0e−01
Xq21	ATRX	35	−1.54	2.0e−01
Xq22	BTK	18	−1.54	2.0e−01
Xq25	XIAP	6	−1.54	2.0e−01
Xq25	STAG2	33	−1.54	2.0e−01
Xq25	SH2D1A	4	−1.54	2.0e−01
4q13	EPHA5	18	−1.44	4.3e−01
4q21	FAM175A	9	−1.44	4.3e−01
4q24	TET2	9	−1.44	4.3e−01
4q31	INPP4B	23	−1.44	4.3e−01
4q31	FBXW7	11	−1.44	4.3e−01
4q12	PDGFRA	22	−1.31	9.3e−01
9p24	JAK2	23	−1.29	9.3e−01
9p24	CD274	6	−1.29	9.3e−01
9p24	PTPRD	35	−1.29	9.3e−01
9p21	CDKN2B	2	−1.29	9.3e−01

Case 4 shows amplification of *KDR* (*VEGR-R2*, chromosome 4)

Treatment of Angiosarcoma

- surgical treatment often frustrating
- *MYC* amplification in a number of AS
  - downregulation of thrombospondin 1 (endogenous inhibitor of angiogenesis)
  - therapeutic inhibition of MYC
- *FLT4* amplification: targeted therapy (Sorafenib)
- *KDR* mutations: KDR antagonists
- recurrent *PTPRB* and *PLCG1* mutations
  - Behjati S et al. Nat Genet 2014; driver mutations in angiogenesis signaling genes
- multiple lines of chemotherapy (Taxanes, Anthracyclines, Pazopanib…)

Vascular tumours of skin and soft tissues

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


SMILE!!!!
it confuses people