VASCULAR ANOMALIES (TUMORS AND MALFORMATIONS)

Soheil S Dadras MD-PhD

A TRIBUTE LECTURE

- Board-certified in Dermatology, Pathology and Dermatopathology
- Student of Drs. Wallace Clark and Thomas Fitzpatrick
- Founded Harvard Dermatopathology Training Program
- Unassuming international expert in melanoma (subtyping, AJCC, MITF), vascular lesions (GLUT-1)
- My mentor in dermatopathology, friend
- Established vascular anomaly clinic at MGH
  - MGH Pediatrics
- NIH Training grant at MGH CBRC (lymphatic endothelial cell biology, Dr. Michael Detmar)
- Introduced me to Dr. Paula E. North

Kupper T, Piris A, Kroshinsky D, Kaya G. In Memoriam-Martin C. Mihm, Jr. Dermatopathology (Basel). 2022 Sep 8;9(3):304-306.
Murphy GF. A Festschrift for Martin C. Mihm, Jr. J Cutan Pathol. 2010 Apr;37

Martin C. Mihm Jr., MD

March 15, 1934 - July 19, 2022

LEARNING TIPS, PITS AND HACKS

- Don’t call anything with blood vessels, “hemangioma” or “angioma”
- Use classification framework endorsed by the International Society for the Study of vascular Anomalies (ISSVA), www.issva.org
- Learn the clinical (biologic) behavior, histopathology, immunohistochemistry, and molecular genetic data (somatic and germline)
- Pathologist and dermatologist need to communicate to improve diagnostic accuracy
- Many textbooks lump unrelated entities into unnatural categories (e.g., McKee)
  - “Capillary hemangioma” most confusing
- Don’t be confused by hemangioma vs. malformation strict classification
  - Some show overlapping features
  - Use it as a biologic framework
- Attend an established multidisciplinary vascular anomaly clinic or start one(Lucile-Packard Children’s Hospital VAC, Bruckner, Lane and Dadras)
- Need Pathology to guide (not biopsy for NGS)

Angioma

- Benign cellular proliferation
- Mitotically active
- Congenital or acquired
- e.g., Infantile hemangioma

Malformation

- Error in vascular morphogenesis
- Mitotically inactive
- Usually evident at birth
- e.g., Venus malformation

ISSVA classification for vascular anomalies ©

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018)

This classification is intended to evolve as our understanding of the biology and genetics of vascular malformations and tumors continues to grow

Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined °**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° **defined as two or more vascular malformations found in one lesion**
* **high-flow lesions**

A list of causal genes and related vascular anomalies is available in Appendix 2

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.

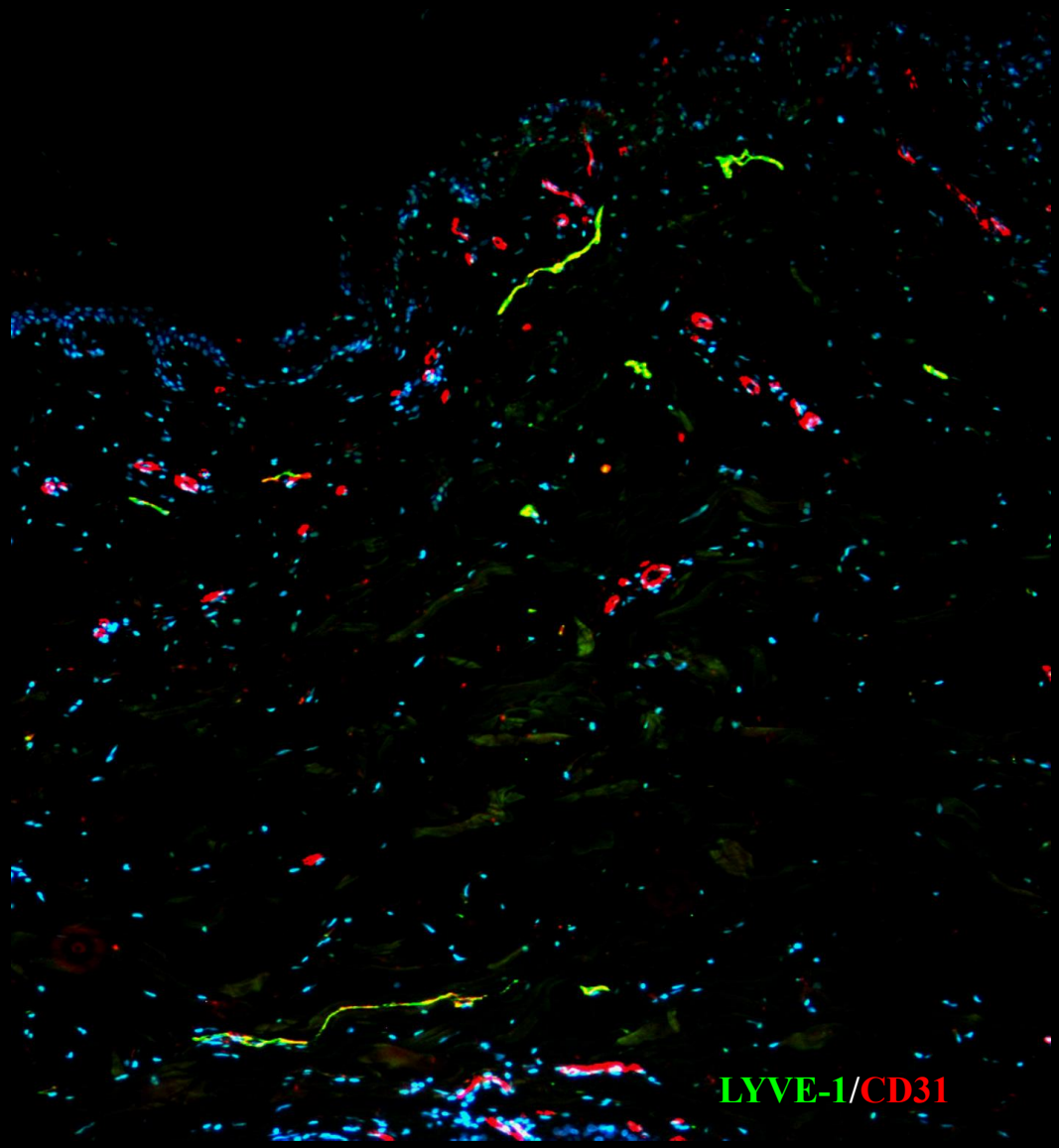
Abbreviations used

For more details, click on the underlined links

IMMUNOHISTOCHEMICAL MARKERS: BLOOD VS. LYMPHATIC

Marker	Lymphatic Vessels	Blood Vessels
Blood Vascular Specific		
CD34	-	+
CD44	-	+
PAL-E	-	+
Collagen type IV	-/(+)	+
Collagen type XVIII	-/(+)	+
Laminin	-/(+)	++
Neuropilin-1	-	+
Lymphatic Specific		
VEGFR-3	+	-
Podoplanin	+	-
SLC/CCL21	+	-
LYVE-1	+	-
Prox1	+	-
Panvascular		
CD31 (PECAM-1)	+	++
VEGFR-2	+	+
Factor VIII-related antigen	+	++

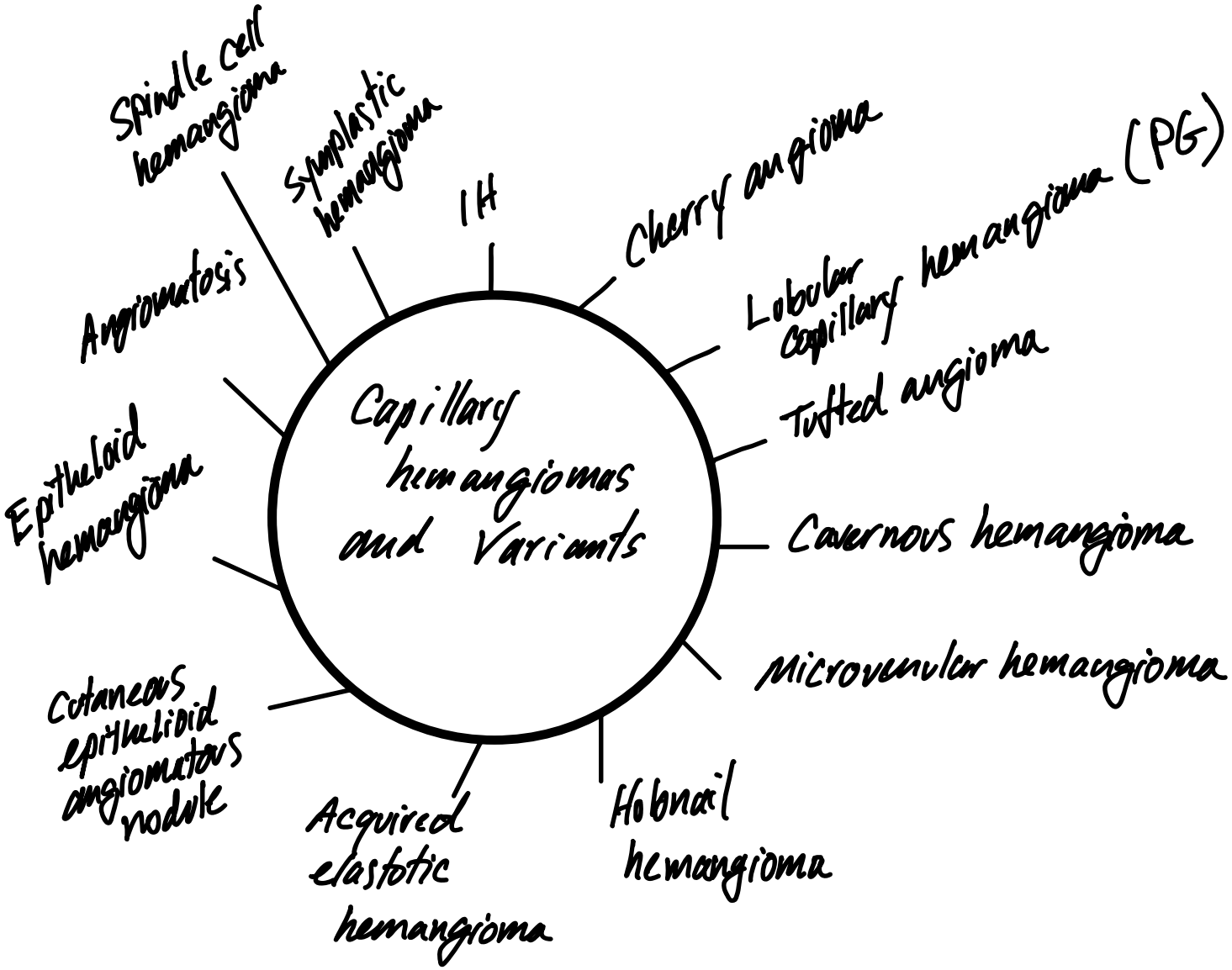
Dadras and Detmar, *Hem. Onc. of North Ame.* 2004



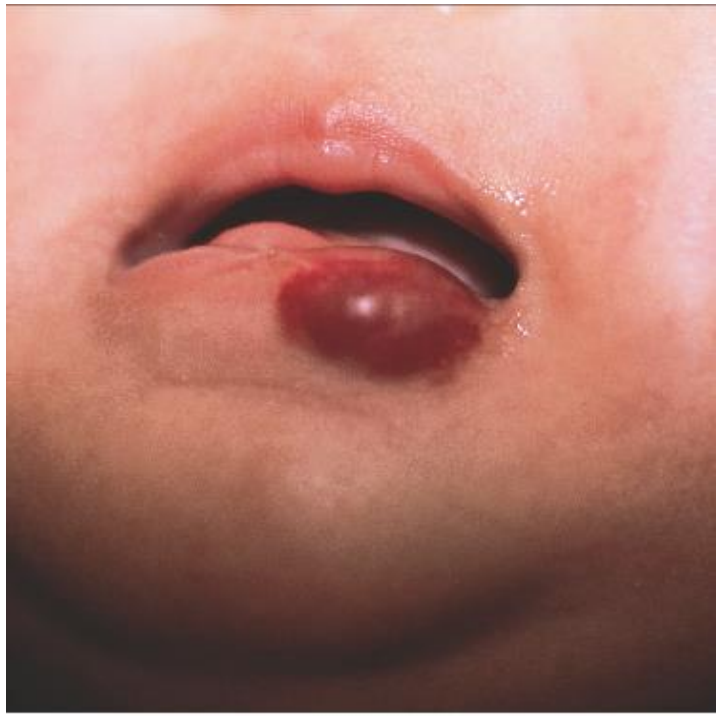
VASCULAR ANOMALIES

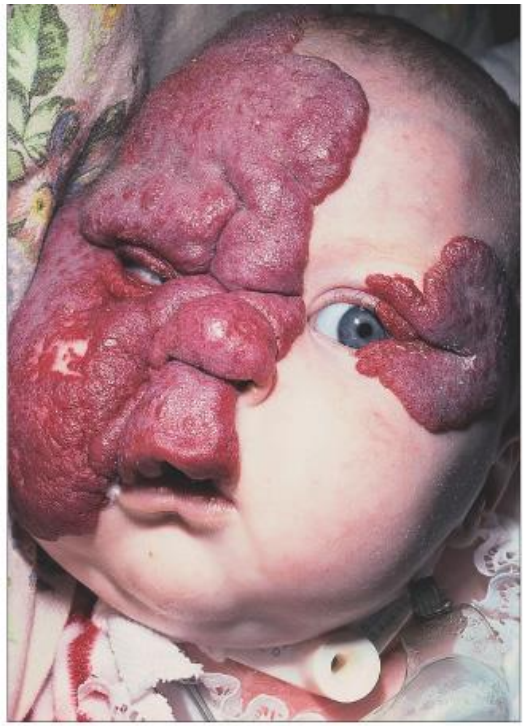
- Vascular proliferations
  - Intravascular papillary endothelial hyperplasia
  - Infantile hemangioma
  - Cherry angioma
  - Lobular capillary hemangioma (PG)
  - Microvenular hemangioma
  - Arteriovenous hemangioma
  - Bacillary angiomatosis
  - Angiolymphoid hyperplasia w eosinophilia
- Hamartomas/malformations
  - Lymphangioma
  - Venous capillary malformation
  - Venous lymphatic malformation
  - Nevus flammeus
- Low-grade/borderline tumors
  - Retiform hemangioendothelioma
  - Papillary intralymphatic angioendothelioma
  - Kaposiform hemangioendothelioma
  - Kaposi's sarcoma
  - Composite hemangioendothelioma
  - Giant cell angioblastoma
  - Pseudomyogenic hemangioendothelioma
- Malignant tumors
  - Epithelioid hemangioendothelioma
  - Angiosarcoma/lymphangiosarcoma
  - Multifocal lymphangiomatosis with thrombocytopenia
  - Atypical vascular proliferation after XRT
  - Lympahgiomatosis

‘CAPILLARY HEMANGIOMAS’

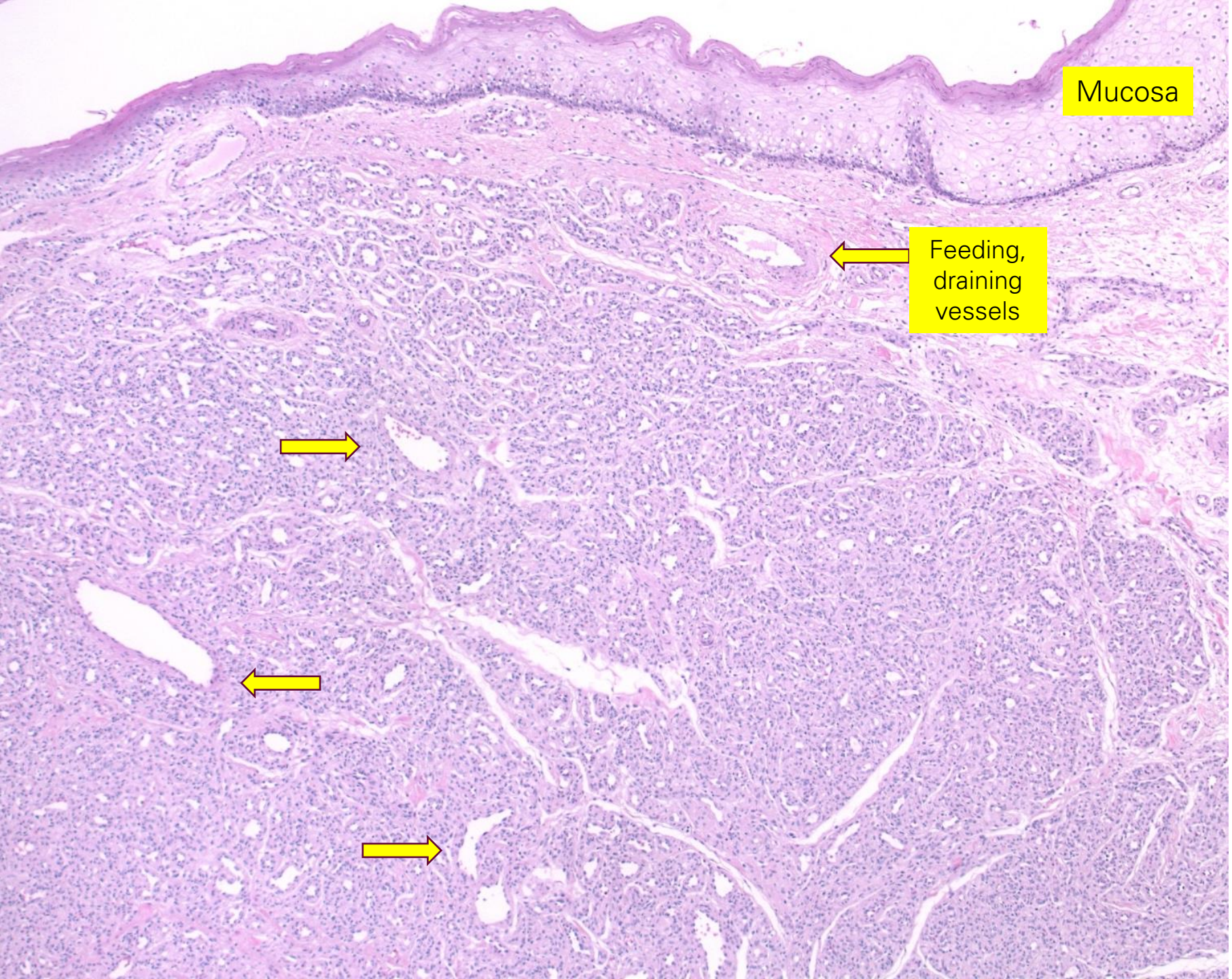


INFANTILE HEMANGIOMA

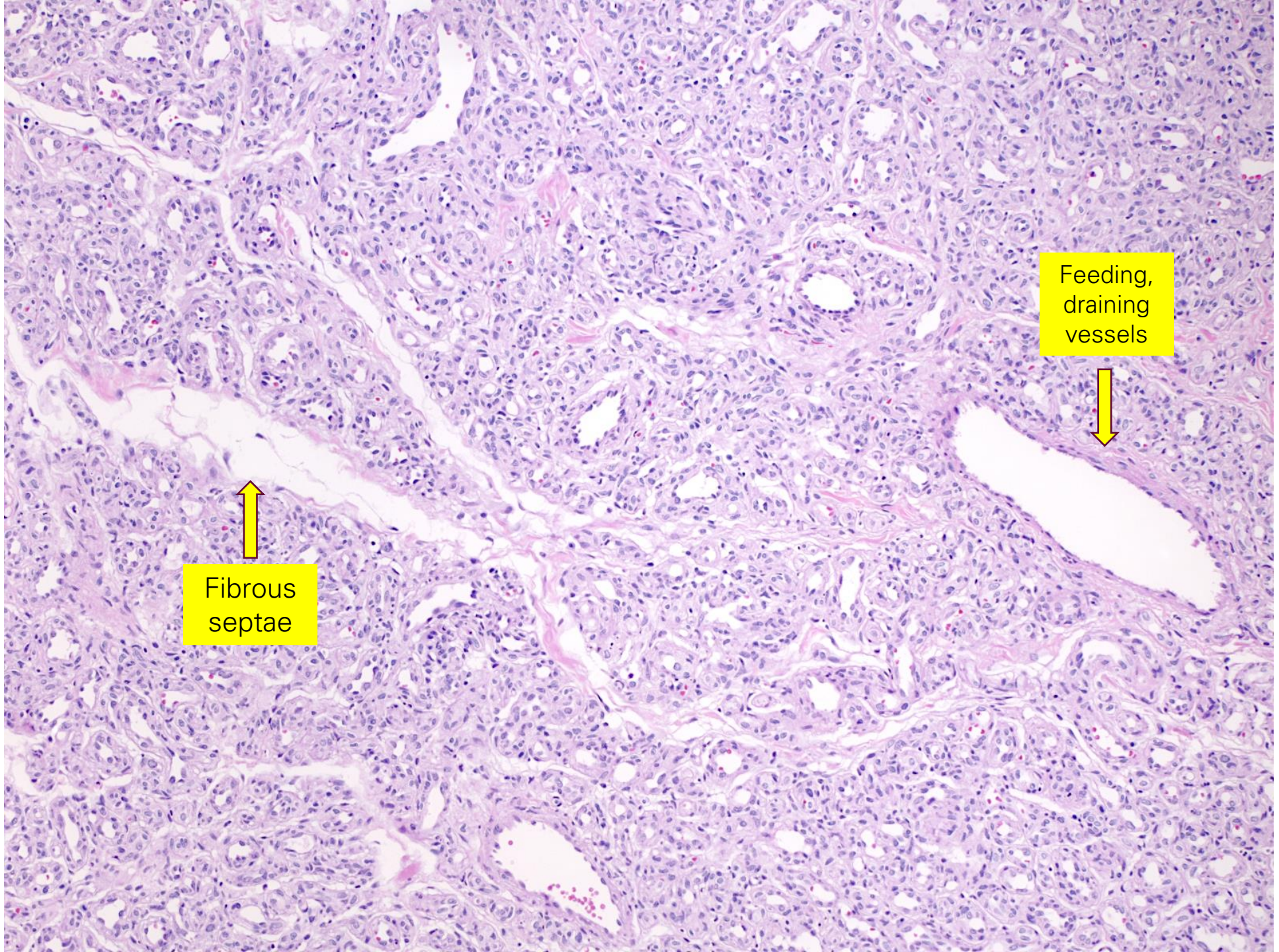


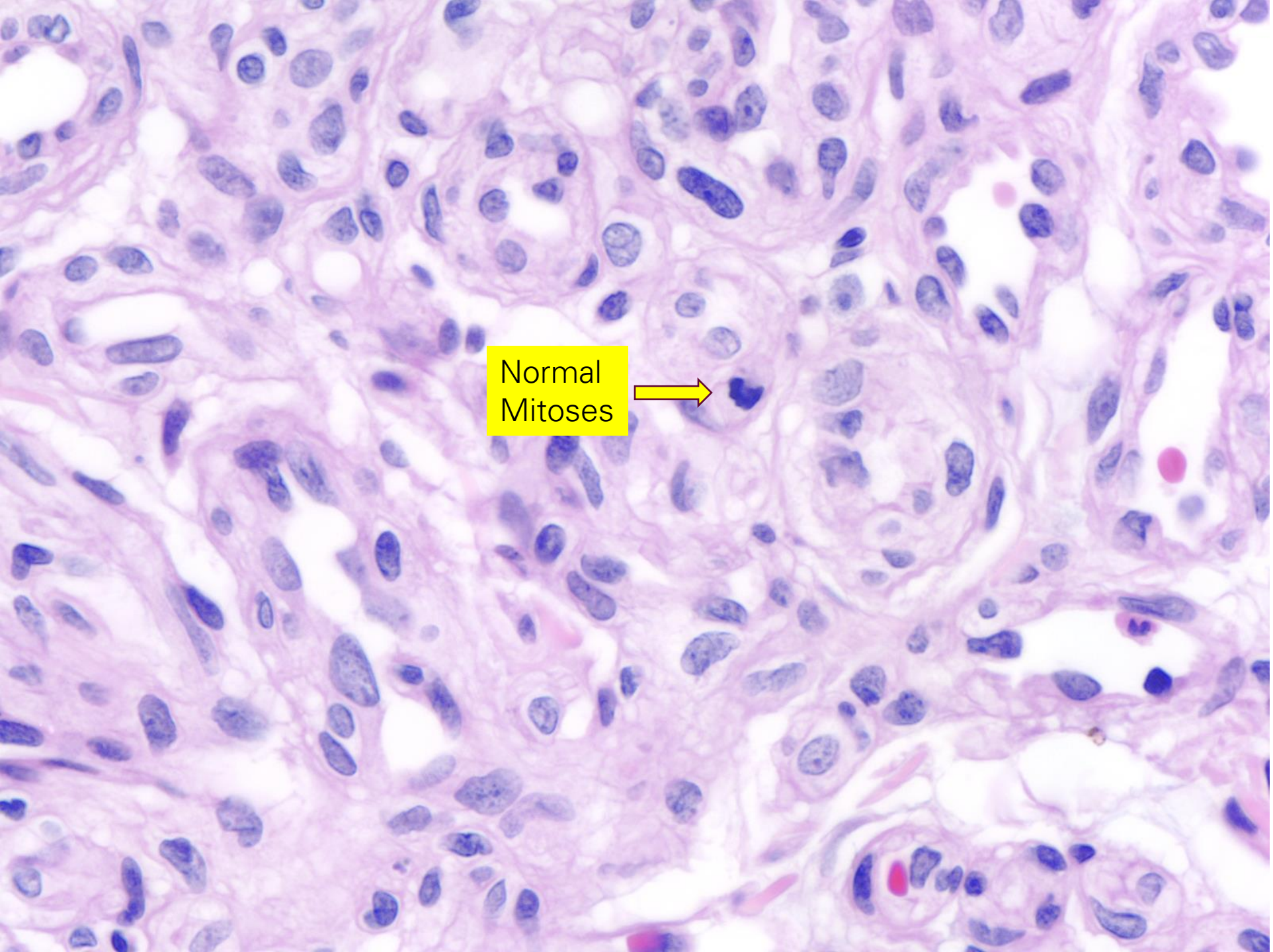


- Most common tumor of infancy and vascular tumor of childhood
- Absent at birth, develop within few weeks of life
- Females, head and neck
- Solitary, plaque, or multiple
- Growth pattern: proliferating, involuting and involuted
- DDX: congenital hemangiomas, LCH, congenital intramuscular hemangioma
- IHC: GLUT-1+, LYVE-1+ (proliferating phase), LeY+, WT-1+, Prox-1-
- Heterogenous tumor: endothelial cells, fibroblasts and pericytes



Intradermal or <u>submucosal</u>
Multinodular proliferation
Lobular configuration
Numerous, tightly packed capillary-sized blood vessels


Feeding, draining vessels
Fibrous septae



Endothelial cells
Pericytes
Fibroblasts
Mast cells

Do blood vascular tumors express lymphatic genes?

- Study of 62 lesions
- IHs in various growth stage
- PG, IMH, Cherry angioma
- LYVE-1 expression is lost during involution

www.modernpathology.org

Infantile hemangiomas are arrested in an early developmental vascular differentiation state

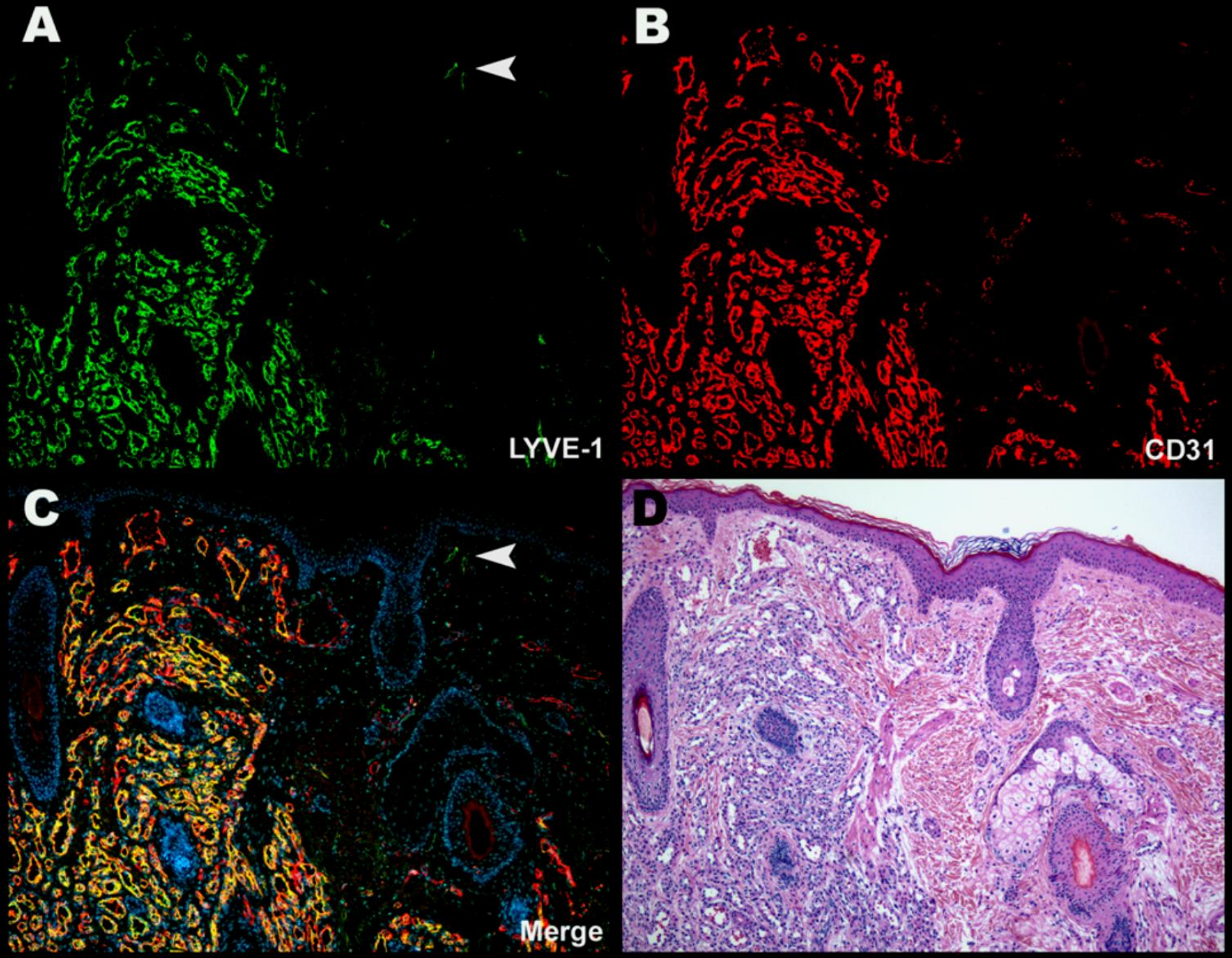
Soheil S Dadras[1,2], Paula E North[3], Jennifer Bertoncini[1], Martin C Mihm[2] and Michael Detmar[1]

[1]*Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA;* [2]*Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA and* [3]*Department of Pathology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR, USA*

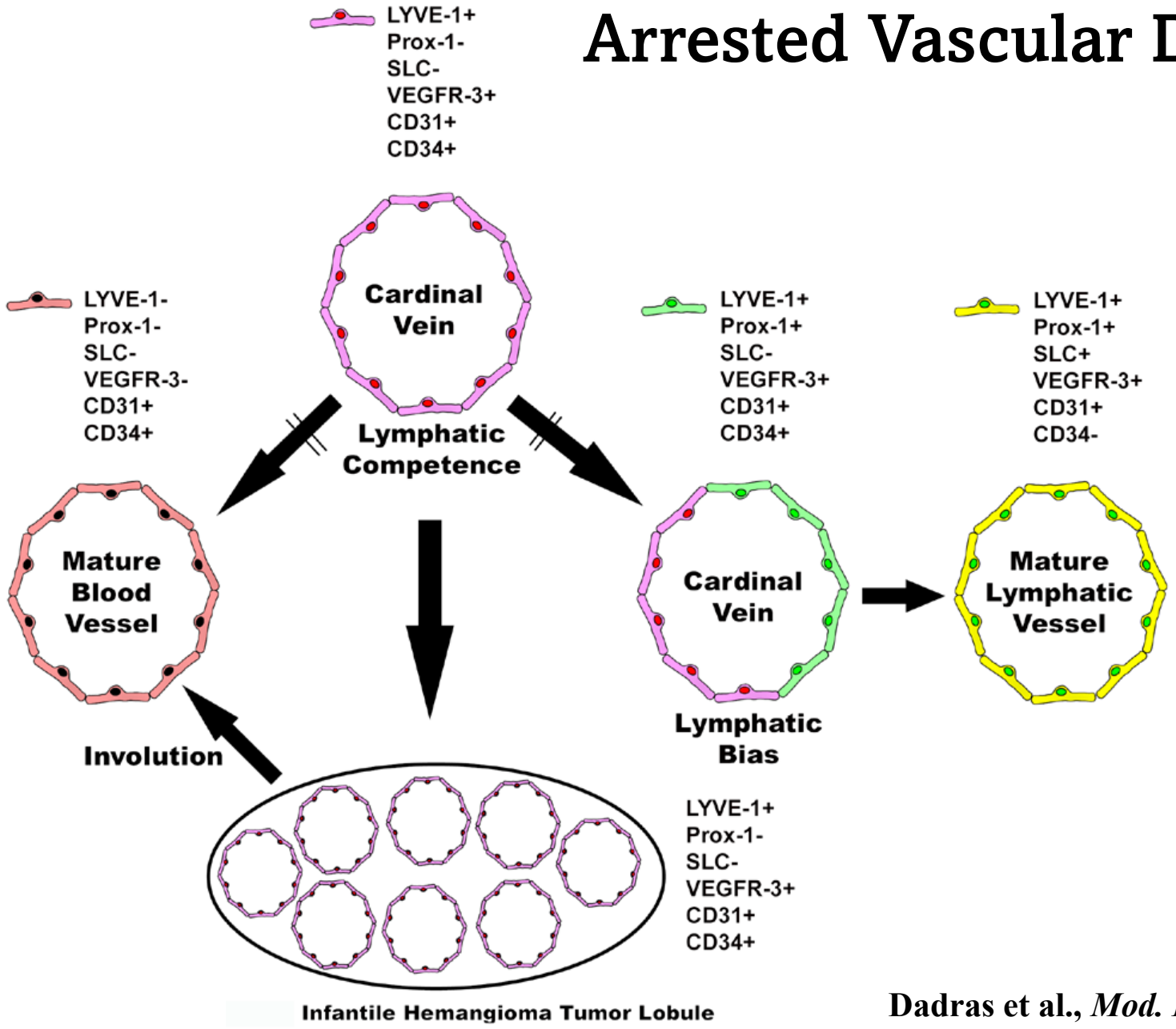
Infantile hemangiomas, the most common tumors of infancy, are vascular tumors characterized by rapid proliferation of endothelial cells during the first few months of postnatal life followed by slow spontaneous involution, whose molecular pathogenesis remains unclear. The recent identification of developmental expression of vascular lineage-specific markers prompted us to characterize infantile hemangiomas for the expression of lymphatic endothelial hyaluronan receptor-1 (LYVE-1), Prox-1, CD31 and CD34. We found that LYVE-1, a specific marker for normal and tumor-associated lymphatic vessels, was strongly expressed in tumor cells of infantile hemangiomas ($n=28$), but not in other vascular tumors including pyogenic granulomas ($n=19$, $P<0.0001$) or intramuscular hemangiomas ($n=9$), using LYVE-1/CD31 double immunostains. Whereas LYVE-1 expression was detected on the endothelial cells of all proliferating infantile hemangiomas, this lymphatic marker was absent from the lesional capillaries during involution in the majority of cases ($P=0.0009$). The majority of LYVE-1$^+$ endothelial cells also expressed CD34, but were negative for the lymphatic-specific homeobox protein Prox-1. Based on coexpression of both LYVE-1 and the blood vascular marker CD34, we propose that the endothelial cells in proliferating infantile hemangioma are arrested in an early developmental stage of vascular differentiation. The immature, incompletely differentiated immunophenotype of proliferating infantile hemangiomas may contribute to their rapid growth during the first few months of life.
Modern Pathology (2004) **17,** 1068–1079, advance online publication, 14 May 2004; doi:10.1038/modpathol.3800153

Keywords: infantile hemangioma; LYVE-1; Prox1; lymphangiogenesis

LYVE-1 Expression in Proliferating IH



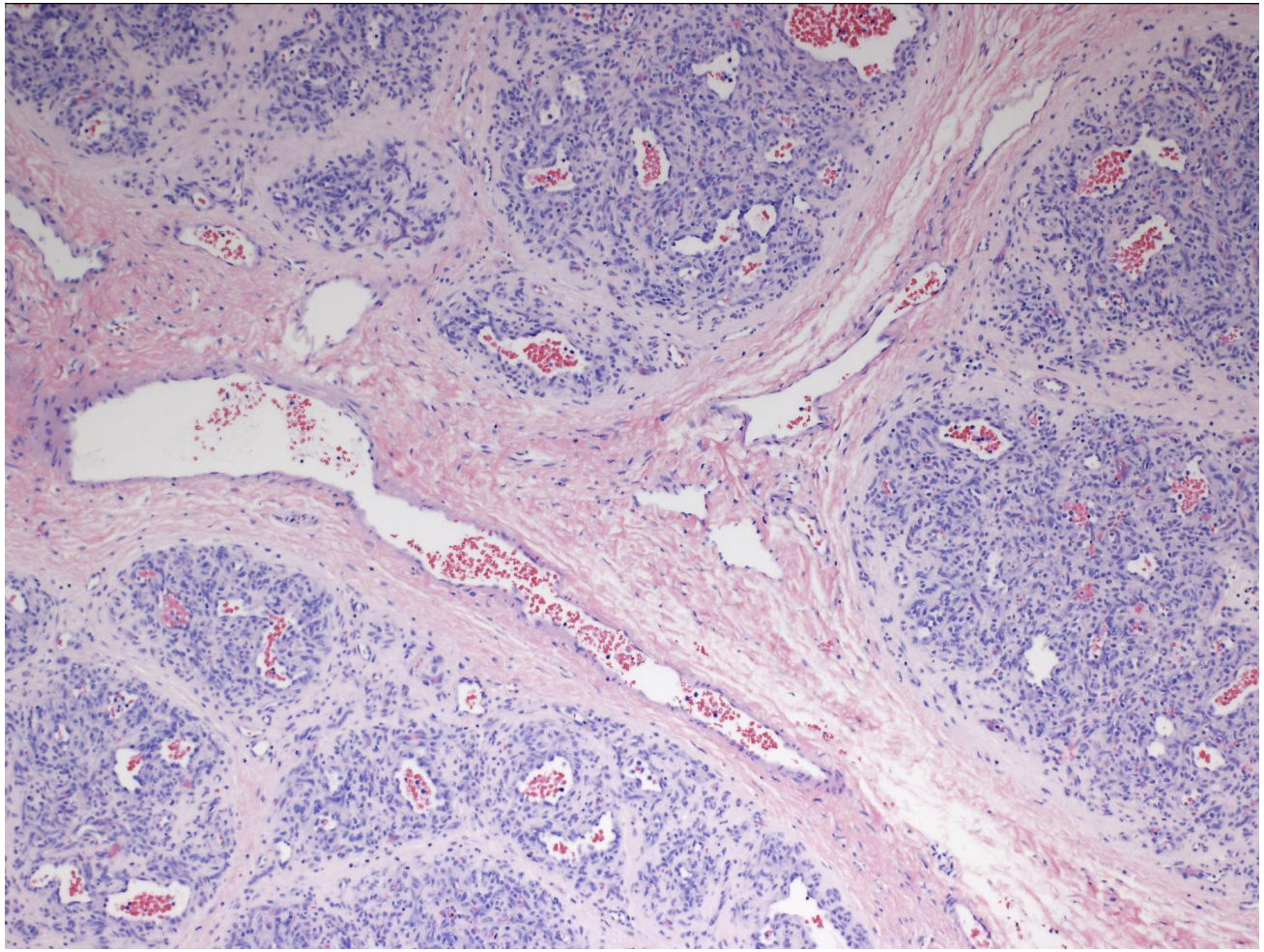
Arrested Vascular Development Hypothesis



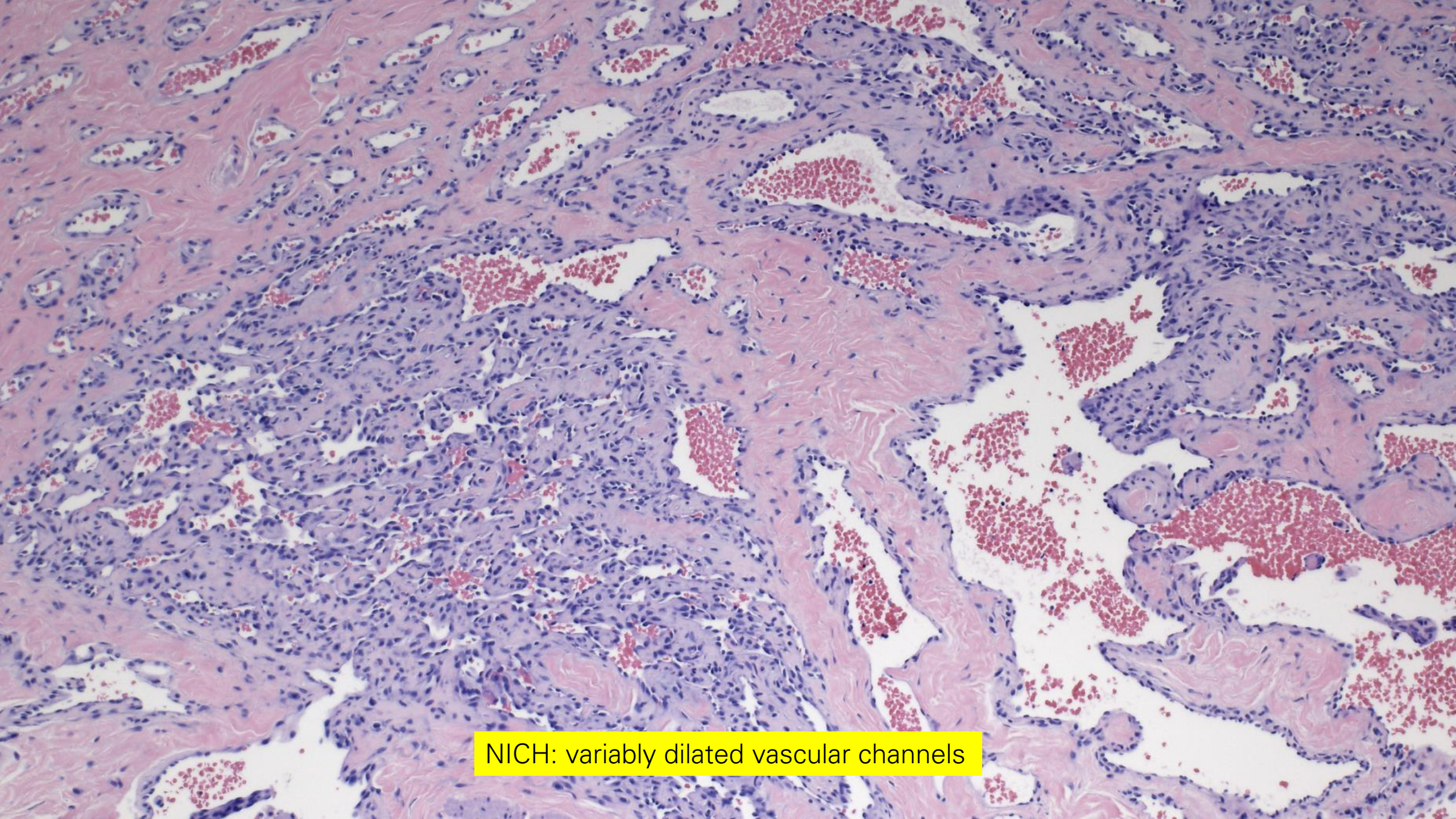
Dadras et al., *Mod. Path.* 2004

CONGENITAL HEMANGIOMAS

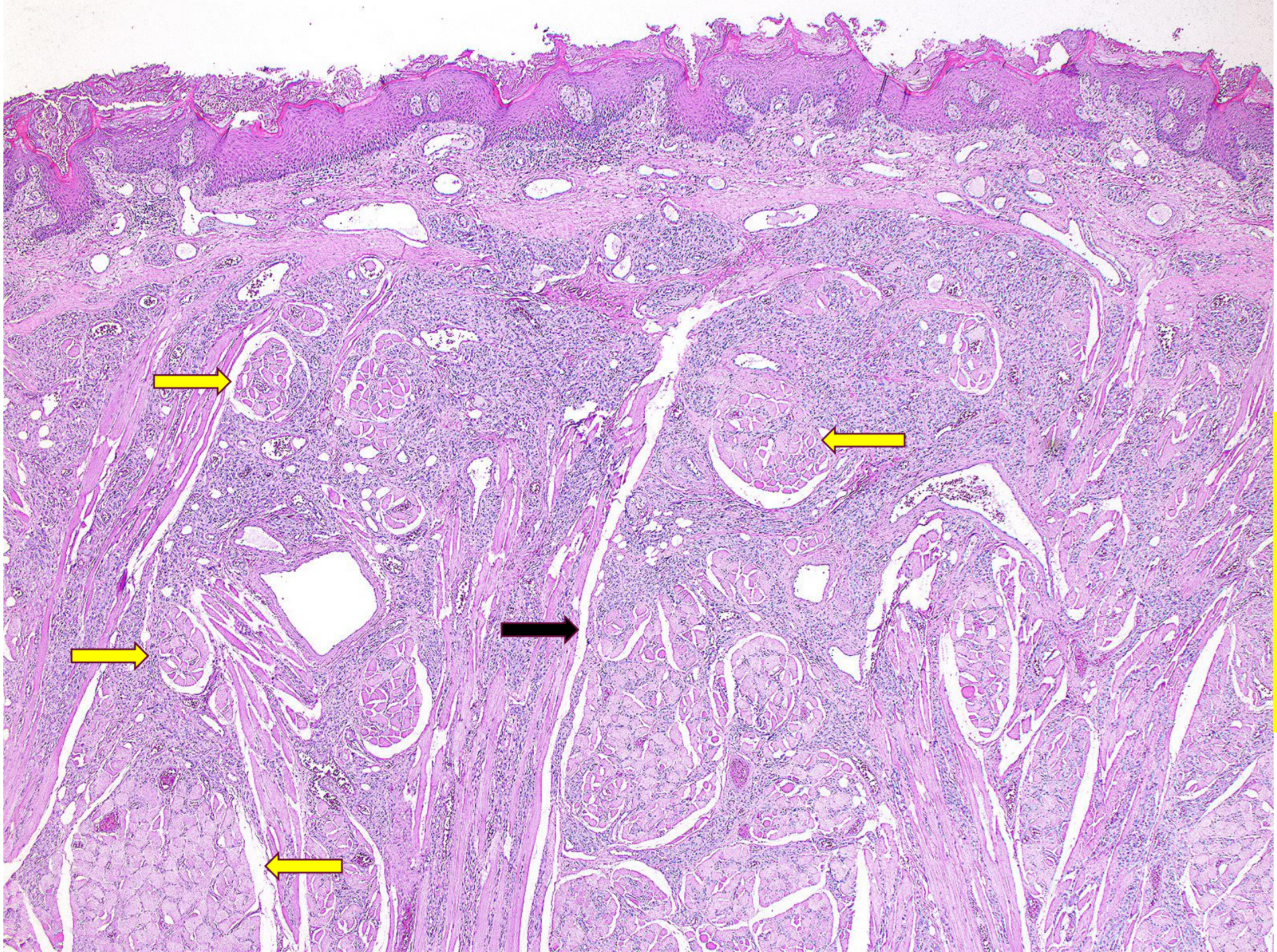
- Develop in-utero, fully developed at birth
- M=F incidence
- Clinical behavior:
  - Rapidly involuting (RICH)
  - Non-involuting (NICH)
  - Partially involuting (PICH)
- *GNAQ* and *GNA11* mutations
- DDX: infantile hemangioma, congenital intramuscular hemangioma
- IHC: GLUT-1-, LYVE-1-



RICH: Multinodular proliferation
Lobular configuration
Numerous, tightly packed capillary-sized blood vessels


NICH: variably dilated vascular channels

CONGENITAL INTRAMUSCULAR HEMANGIOMA



Maybe associated with thrombocytopenia

Unclassified vascular anomaly

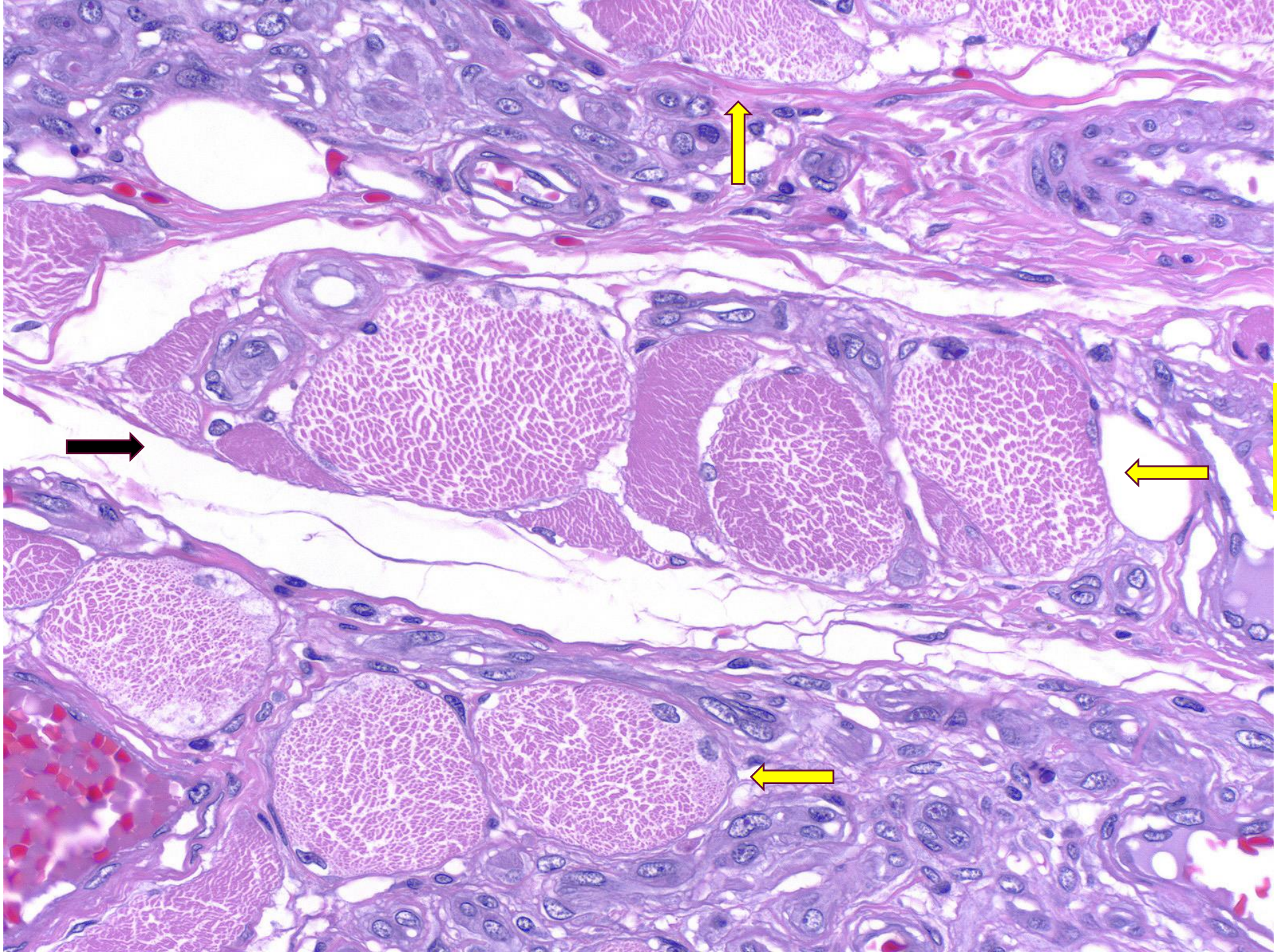
GLUT-1-

Lobules of tightly packed capillaries

Infiltrating bundles of skeletal muscle

Fibrous septae separate tumor lobules

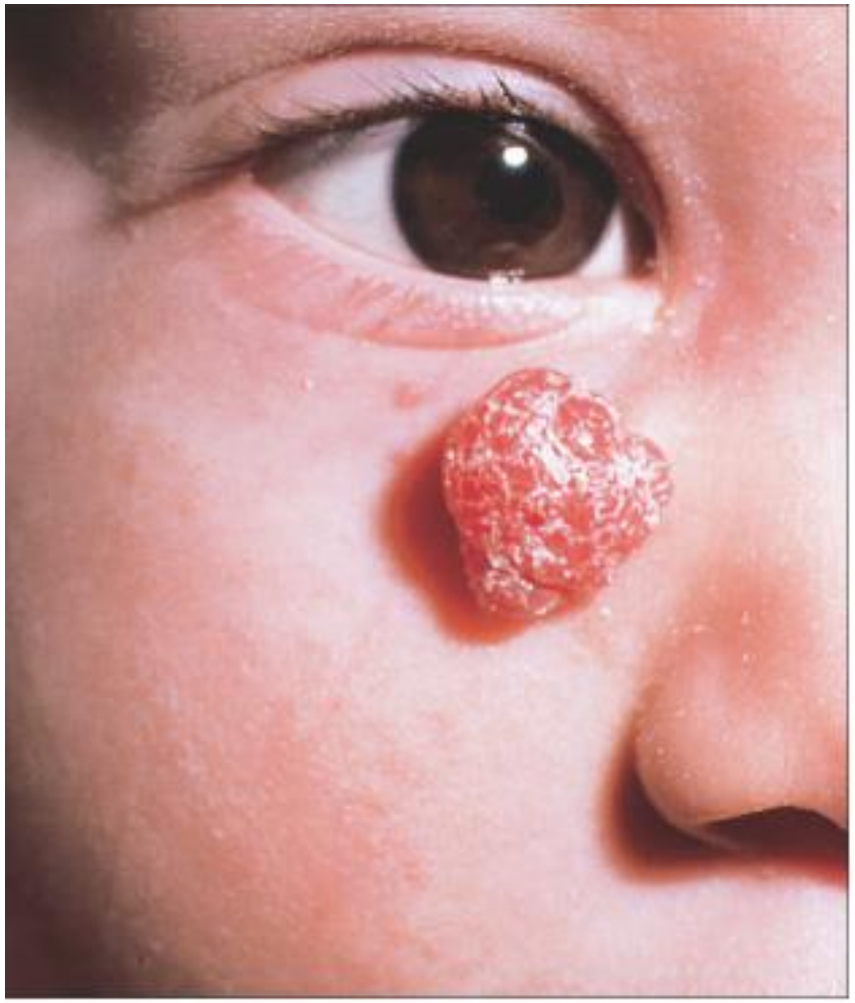
CONGENITAL INTRAMUSCULAR HEMANGIOMA



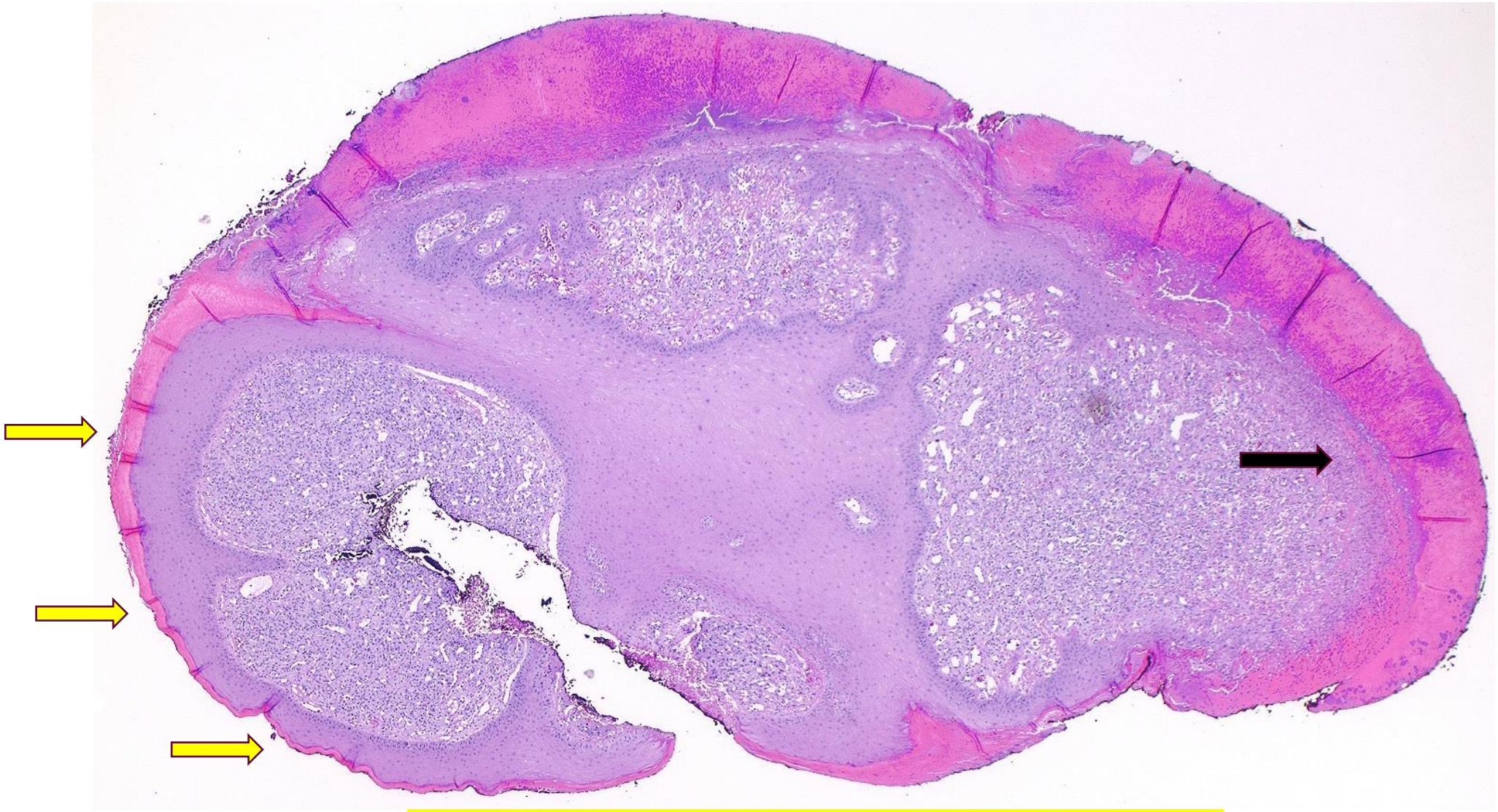
Intact bundles of skeletal muscle
Not destroyed

LOBULAR CAPILLARY HEMANGIOMA (PYOGENIC GRANULOMA)

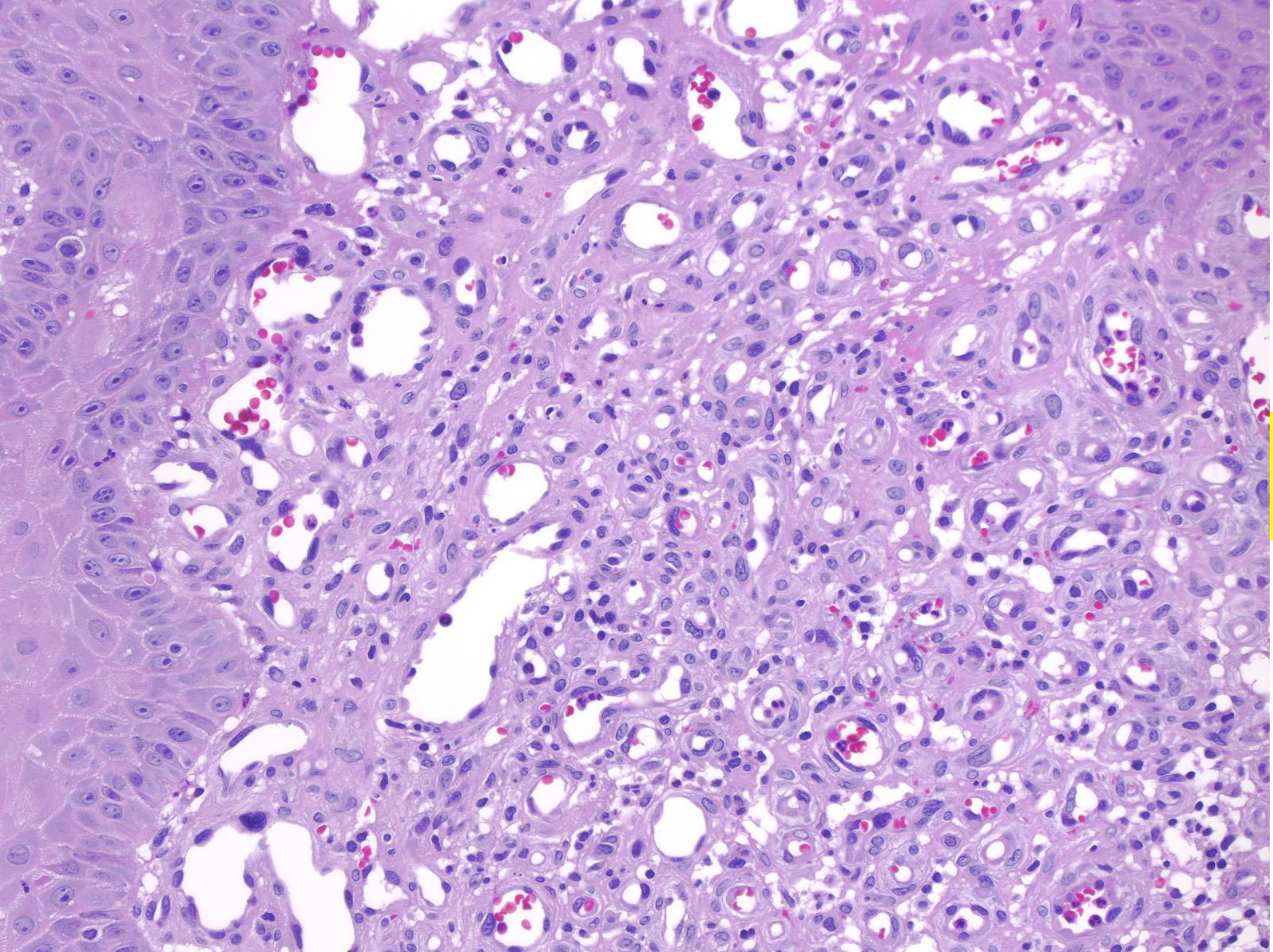
- Common, benign neoplasm
- Any age, M=F, head and neck >> limbs
- Local recurrence with multiple satellite lesions
- Pregnancy
- Variants:
  - Subcutaneous/deep (upper limbs) Intravascular (neck, upper extremities)
- DDX: infantile hemangioma, bacillary angiomatosis
- *RAS* and *BRAF* V600E mutations



ier - Bolognia, Jorizzo and Rapini: Dermatology - www.dermtext.com



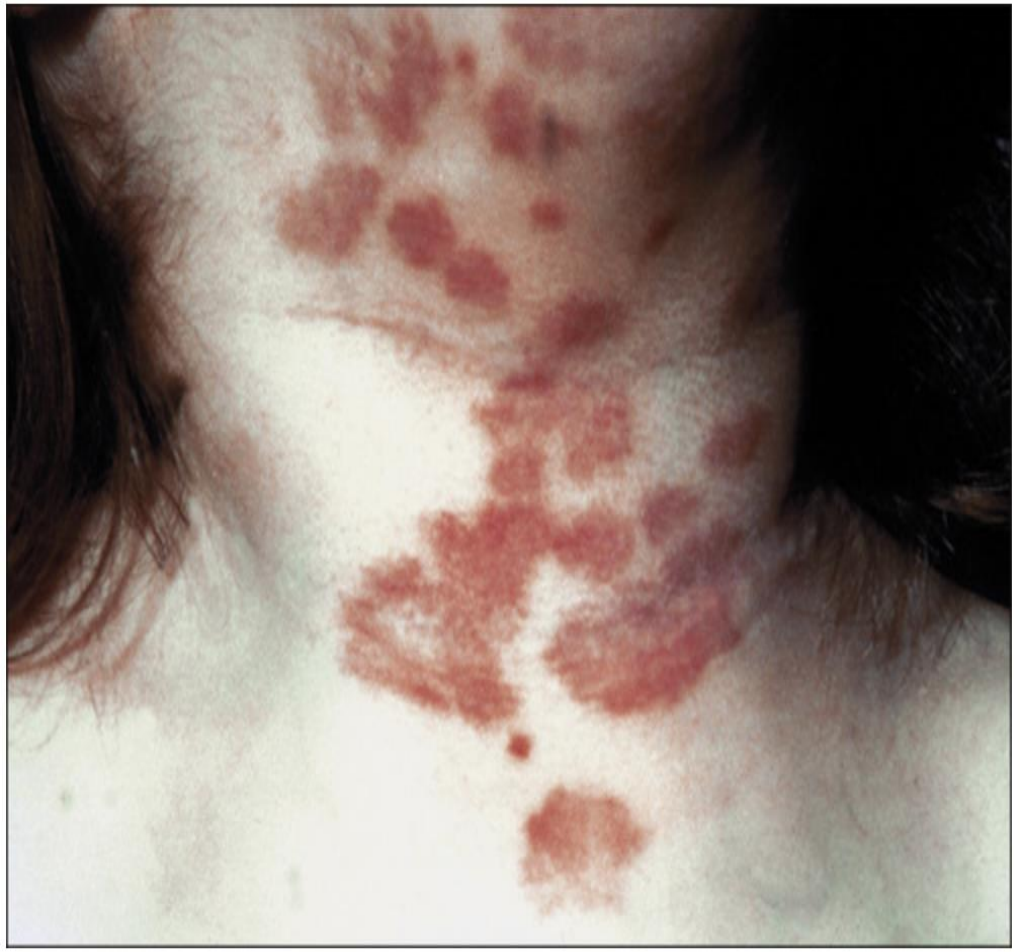
Exophytic lobulated dermal nodule
Ulcerated, well-formed collarette
Numerous capillaries
Edematous stroma with secondary inflammation

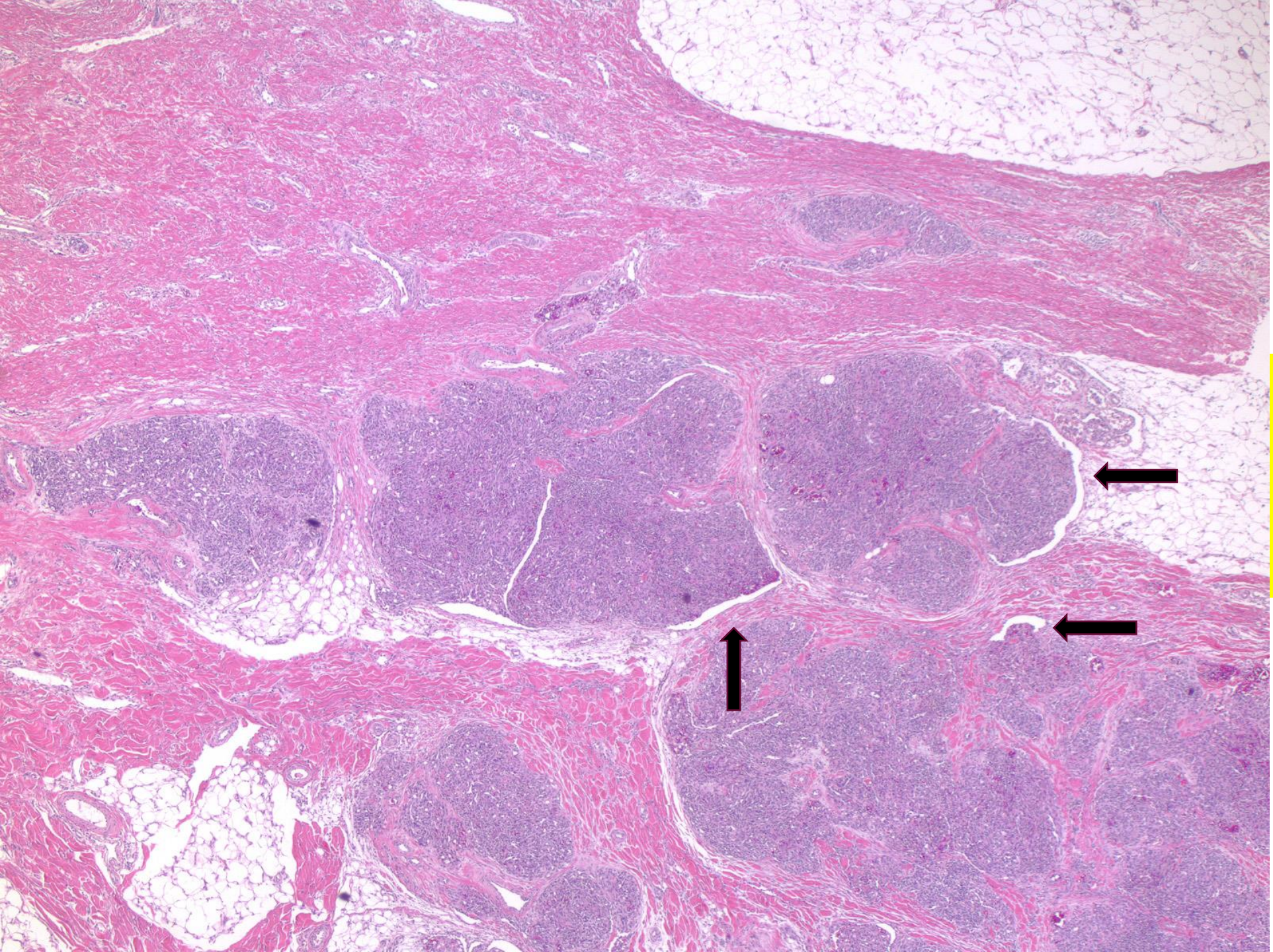


Capillaries form lobules
Mitoses
Minimal cytologic atypia

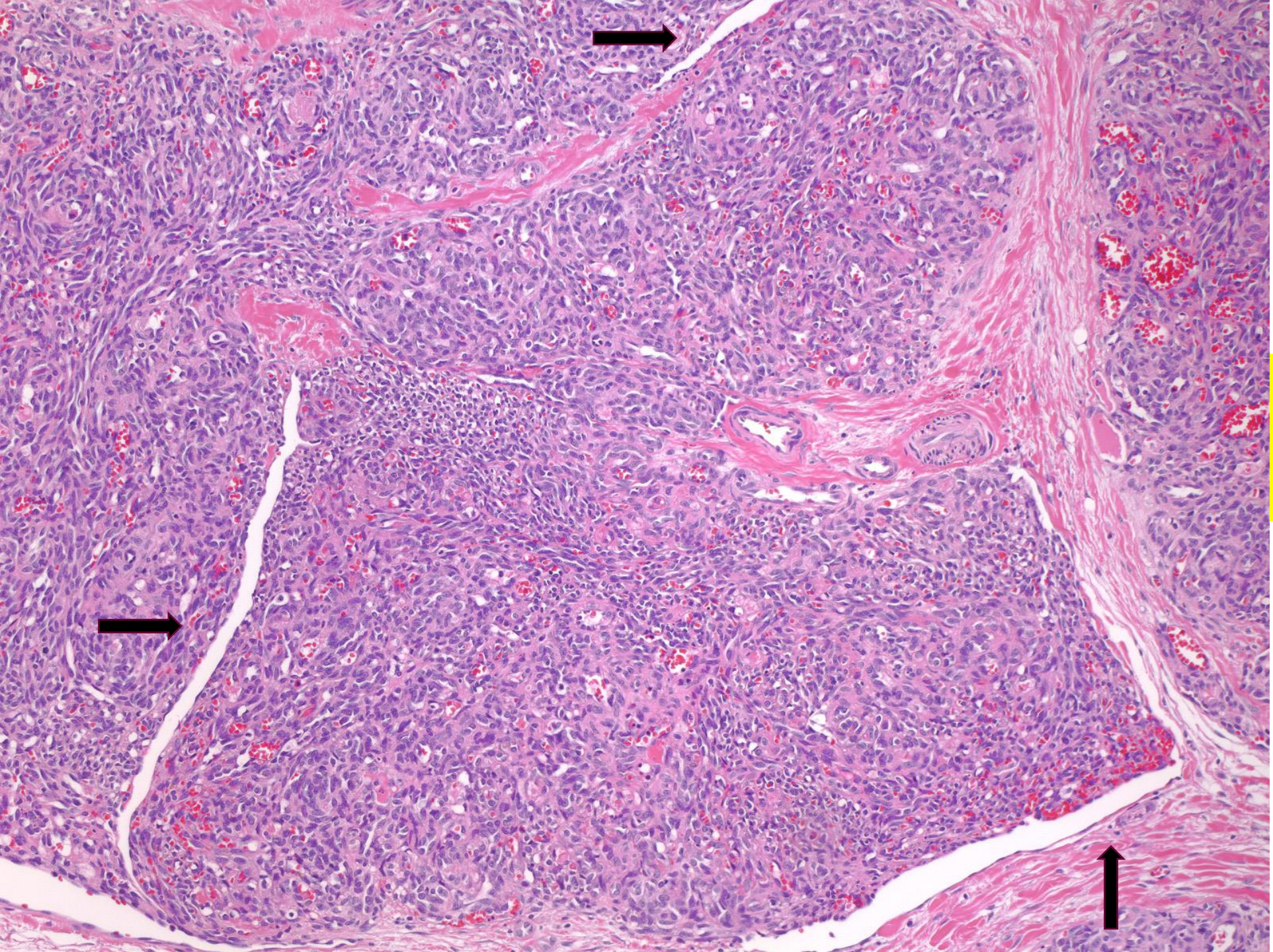
TUFTED ANGIOMA

- Any age, M=F, head and neck >> limbs
- First year of life, congenital (25%)
- Macules and plaque, red-purple
- Usually benign, can be complicated by
  - Consumptive coagulopathy (Kasabach-Merritt syndrome)
- DDX: LCH (deep), Kaposi sarcoma (rare in children)
- IHC: Prox-1, Podoplanin

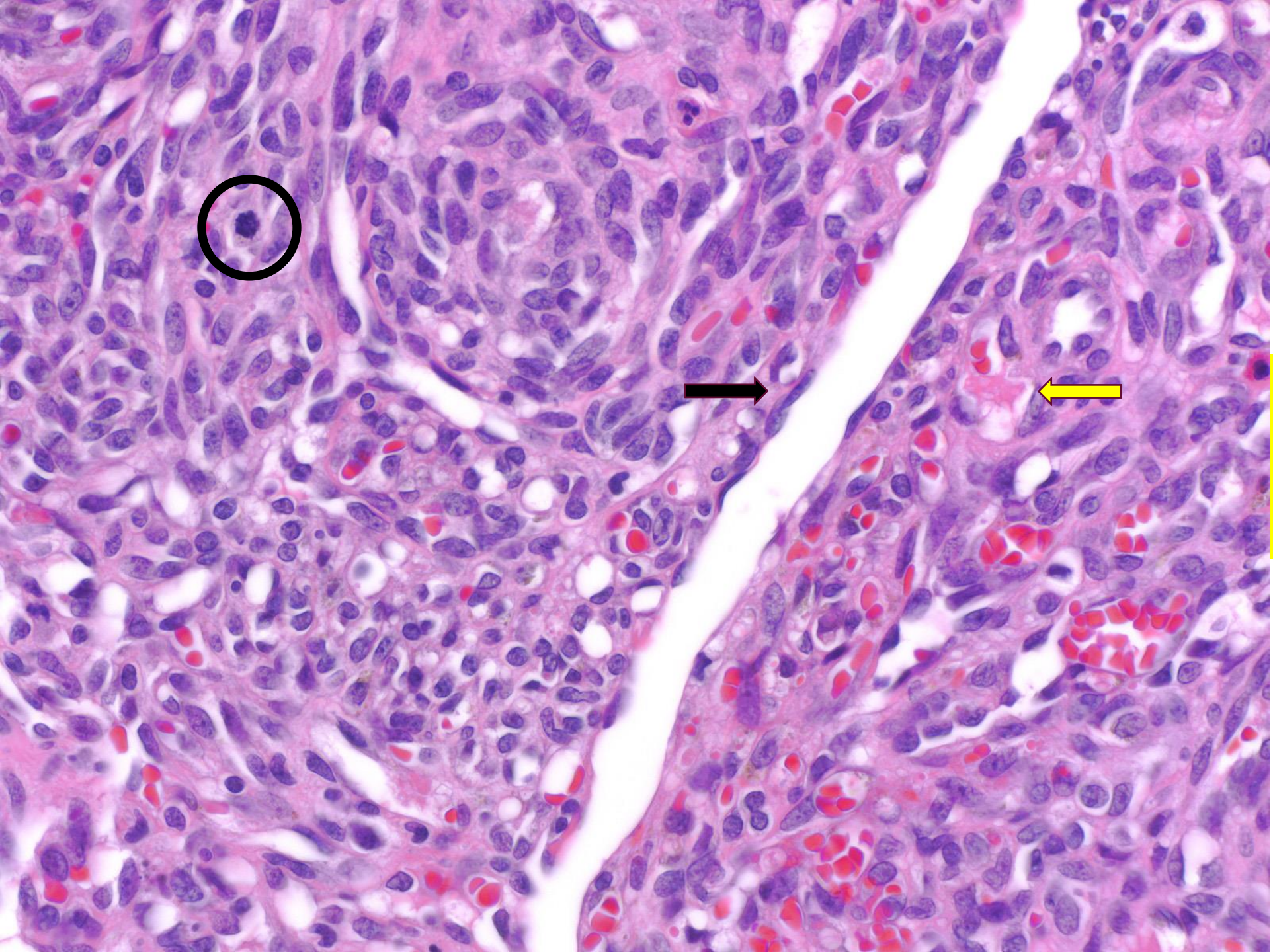




Well-formed, subcutaneous tumor nodules
Tiny holes suggest capillaries
Peripheral crescent shaped lymphatic space



Tightly knit capillaries form tumor nodules
Peripheral crescent shaped lymphatic space

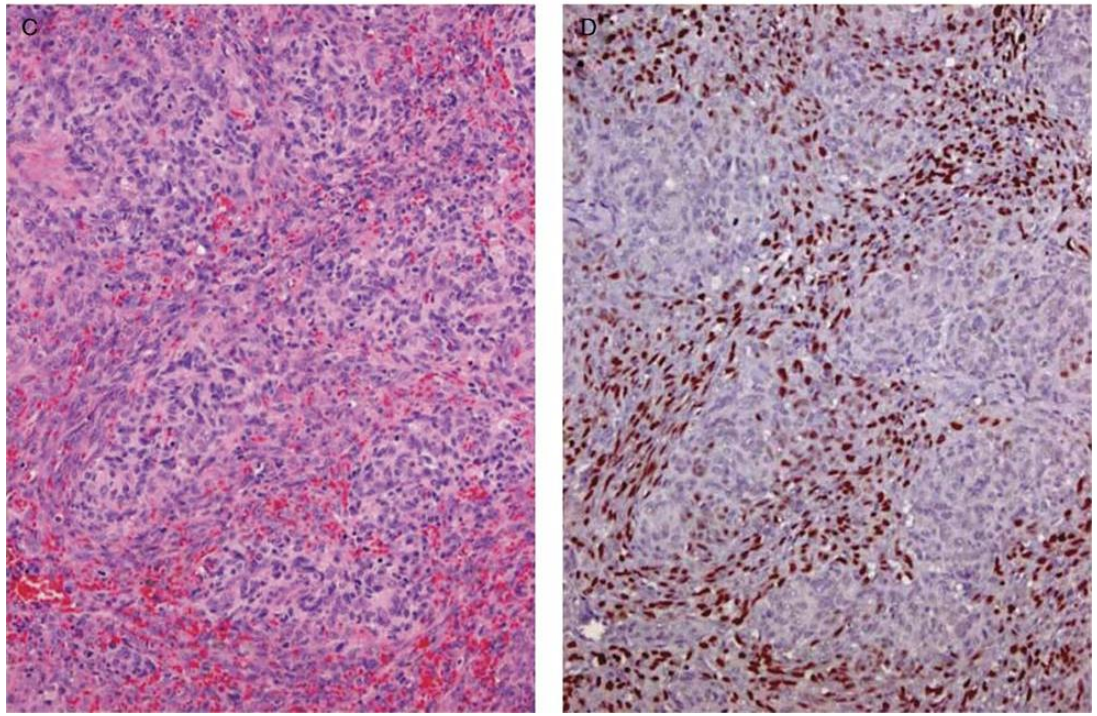


Peripheral lymphatic space, lined by attenuated endothelium
Microthrombi (consumptive coagulopathy)

- Mouse model: ectopic *Prox-1* expression
  - Local aggressive growth:
  - Dadras *et al*. (Detmar) *JID* 2008.
- KHE, TA, IH, PG and GT (n= 75)
- KHE and TA are closely related
- Shared an identical endothelial immunophenotype:
  - Glomeruloid cells negative: Prox-1, Podoplanin (D2-40) and LYVE-1
  - Spindle cells positive: Prox-1, Podoplanin (D2-40), LYVE-1, CD31 and CD34
- IHC DDX: IH, LCH negative for Prox-1 and Podoplanin (D2-40)

Expression of Prox1, Lymphatic Endothelial Nuclear Transcription Factor, in Kaposiform Hemangioendothelioma and Tufted Angioma

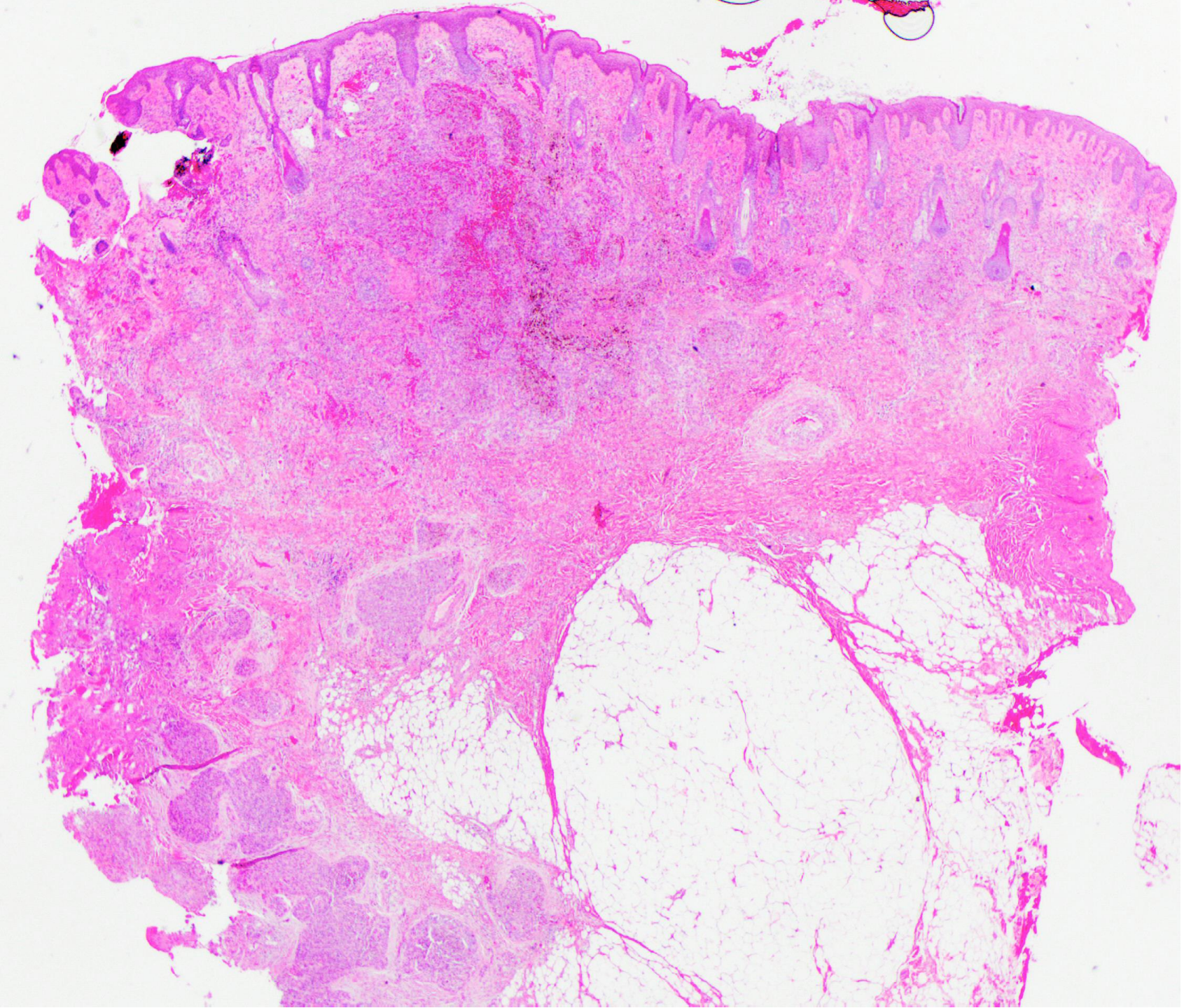
Aude Rimella Le Huu, MD,† ‡ Chris H. Jokinen, MD,§ Brian P. Ruben, MD, PhD,§ Martin C. Mihm, MD,‖ Sharon W. Weiss, MD,¶ Paula E. North, MD, PhD,# and Soheil S. Dadras, MD, PhD*†*



Glomerloid foci (central) : Negative

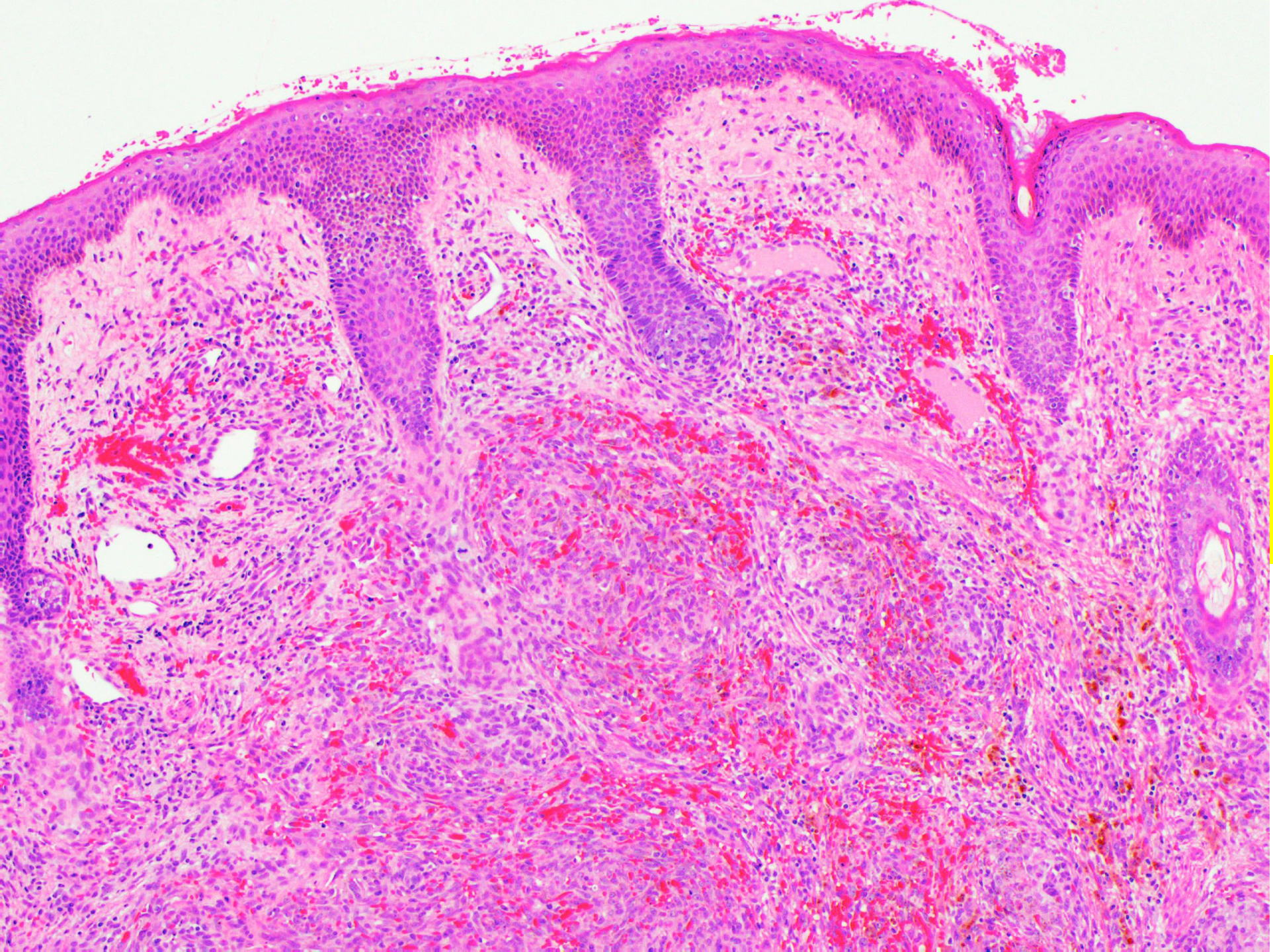
Spindle cells (peripheral): Positive

Am. J. Surg. Pathol. 2010



6-year-old girl with red-blue plaque on the face

Reticular dermal and deep subcutaneous tumor nodules
Hemorrhage, hemosiderosis

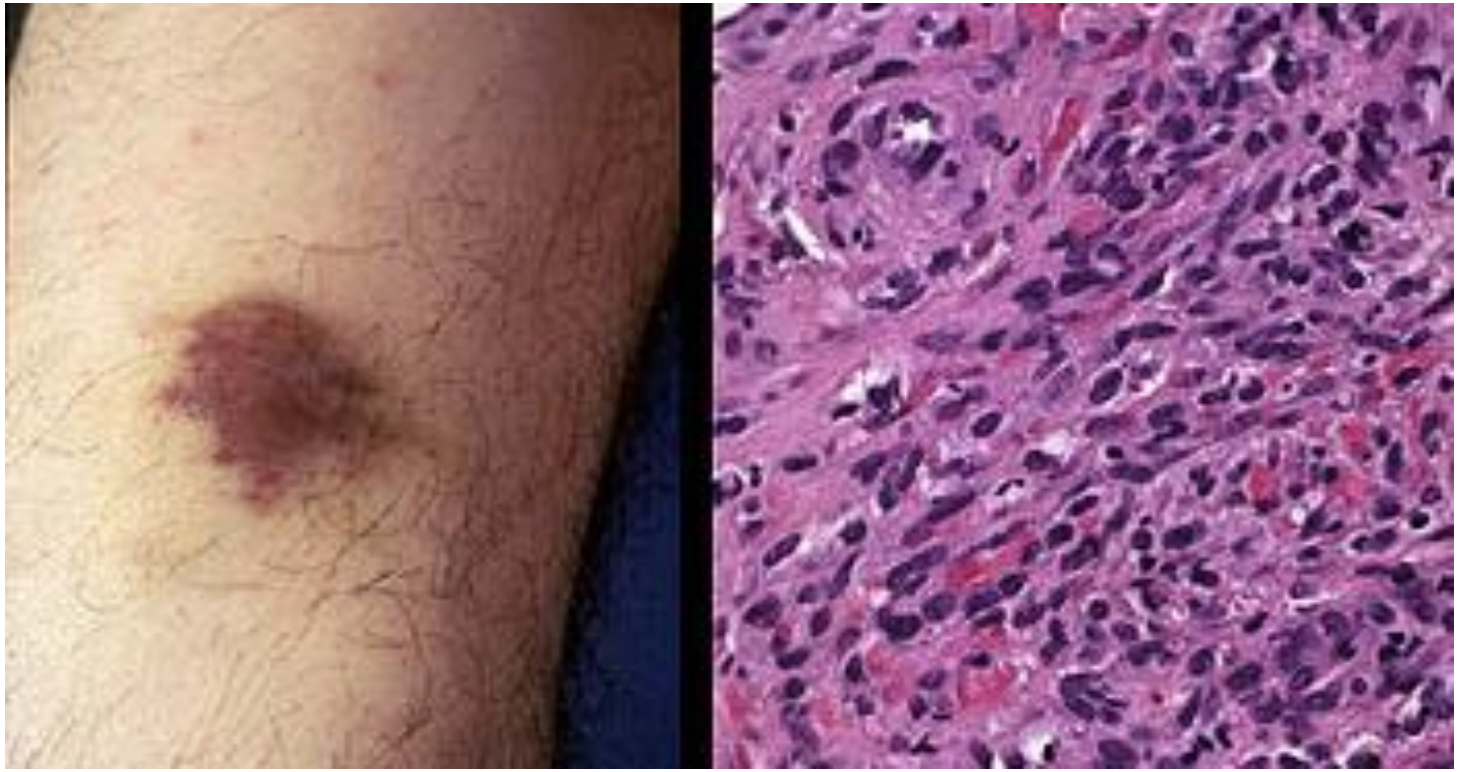


Reticular dermal and deep subcutaneous tumor nodules
Hemorrhage, hemosiderosis

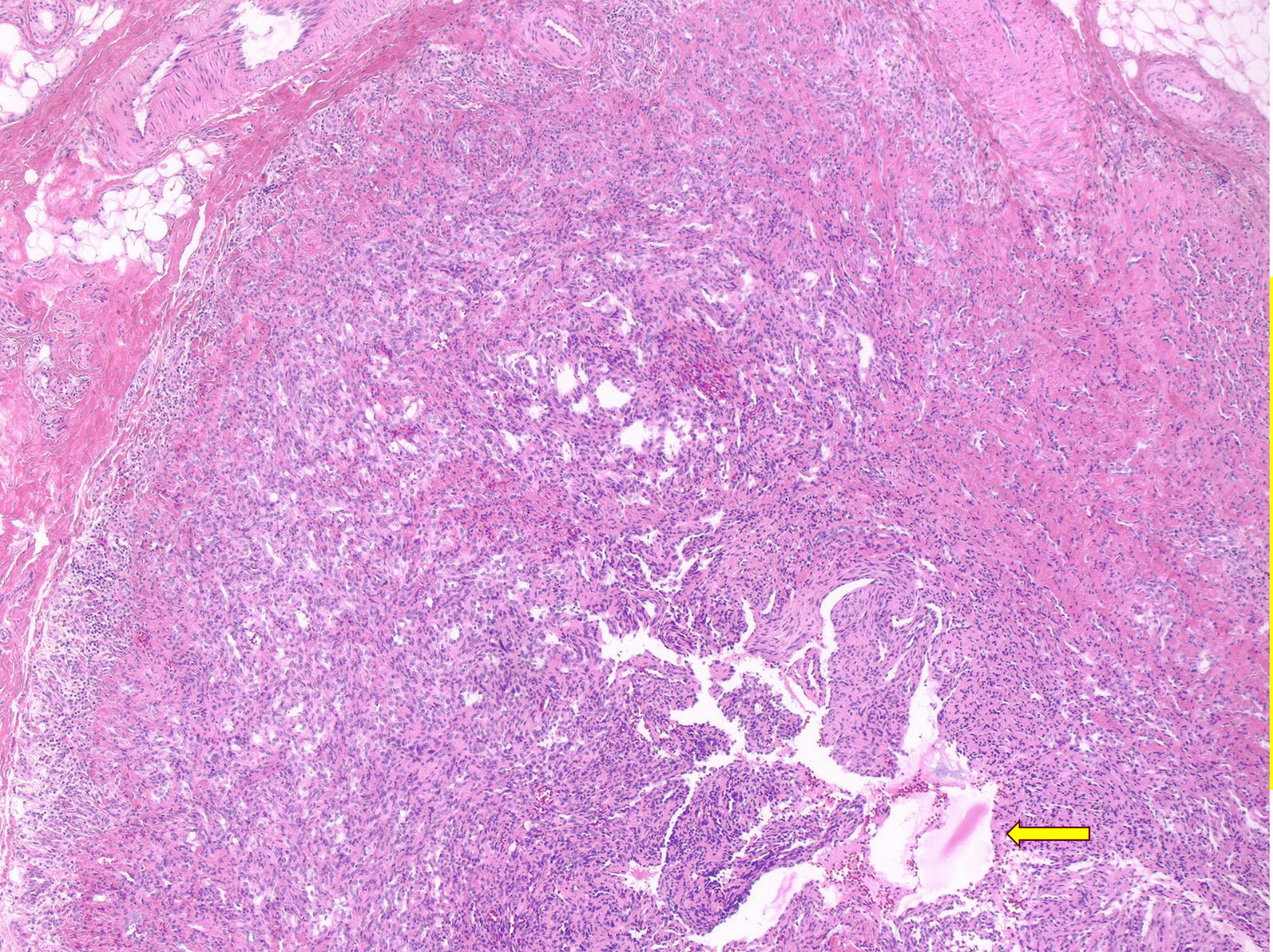
KAPSOIFORM HEMANGIOENDOTHELIOMA

Prox-1-negative glomeruloid foci

SPINDLE CELL HEMANGIOMA



- 1st three decades of life
- Distal extremities, red-blue painful nodule
- Associated (rare): Maffucci or Klippel-Trenaunay syndrome
- *IDH* R132C mutation
- DDX: Kaposi sarcoma, epithelioid hemangioendothelioma, (low-grade angiosarcoma)
- IHC: CD31+, CD34+
- Reticulin: shows vasoformative architecture

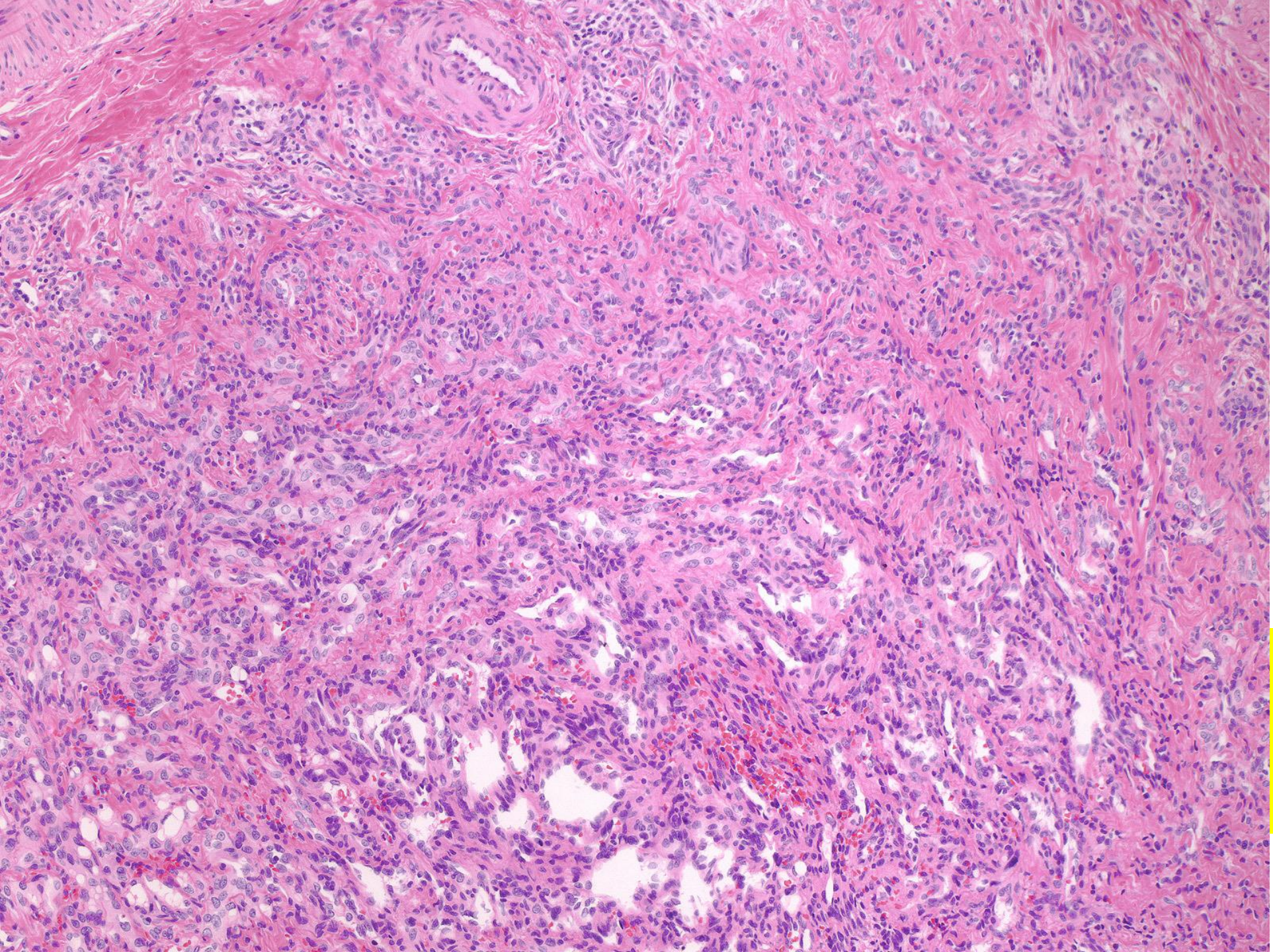


Subcutaneous mass

Dilated, irregular, cavernous vascular channels (malformation)

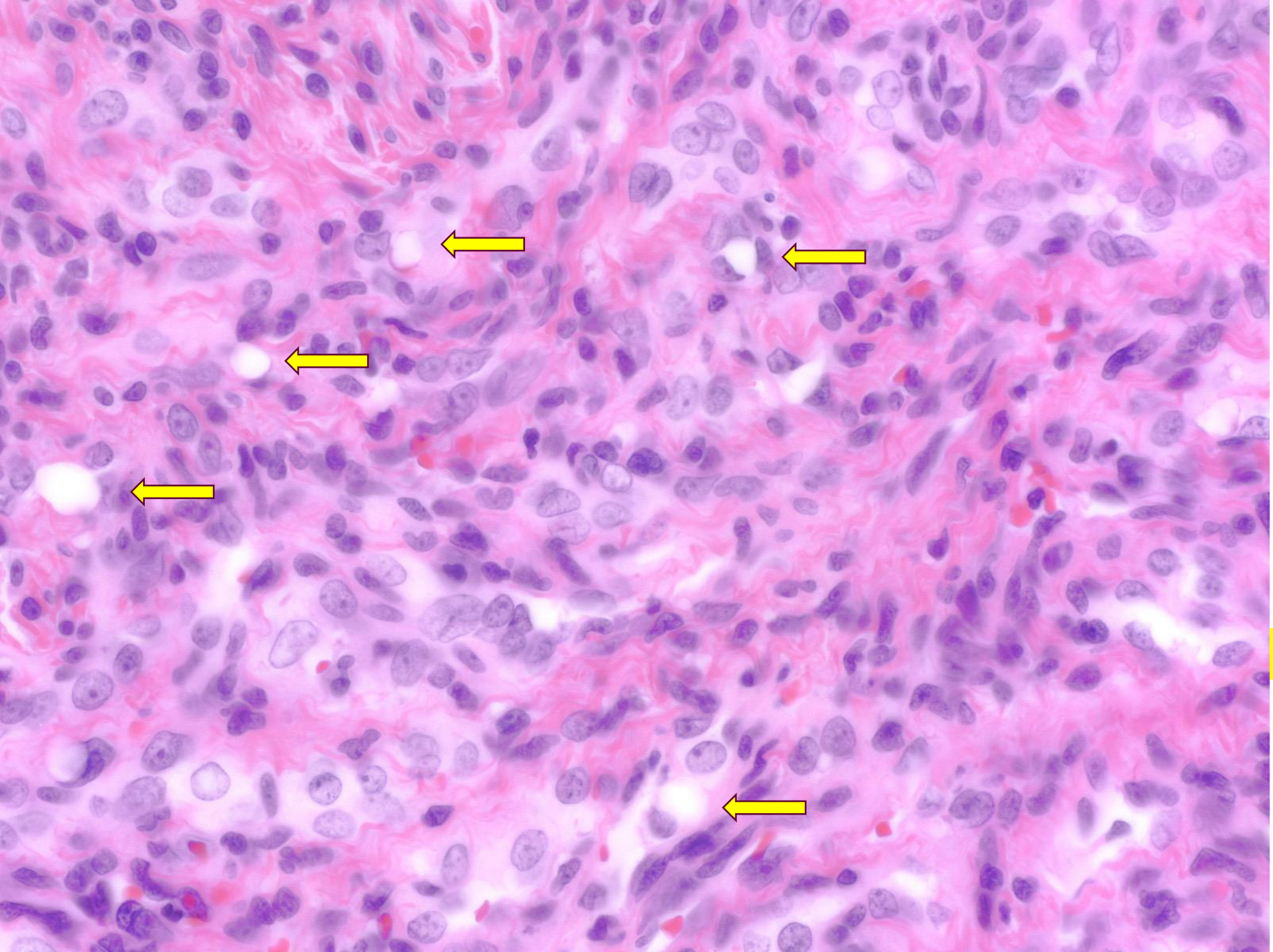
Bundles of smooth muscle around blood vessels (Not shown)

Thrombosis and papillary projections (Masson tumor, not shown)



Dilated, irregular, cavernous vascular channels (malformation)

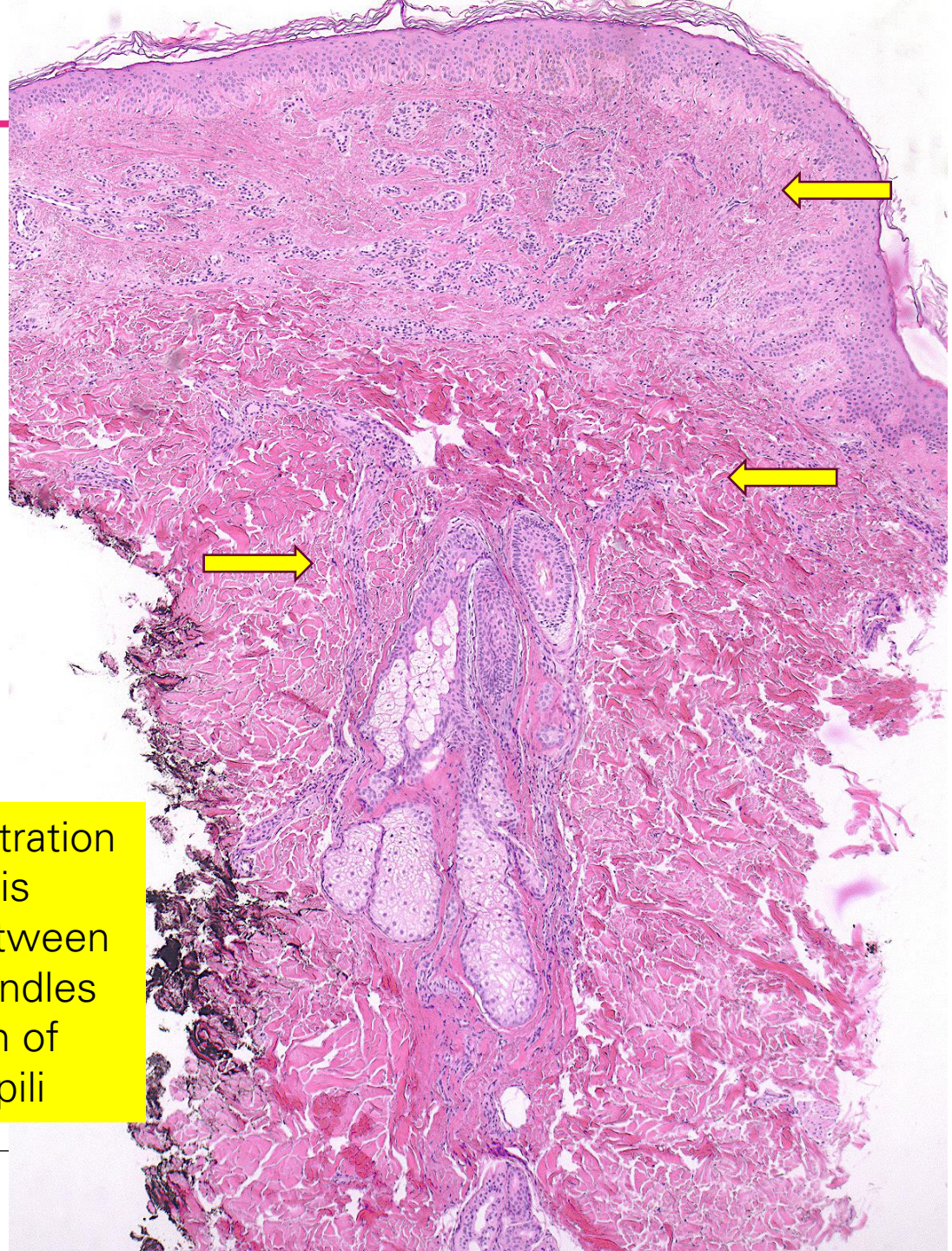
Short spindle cells



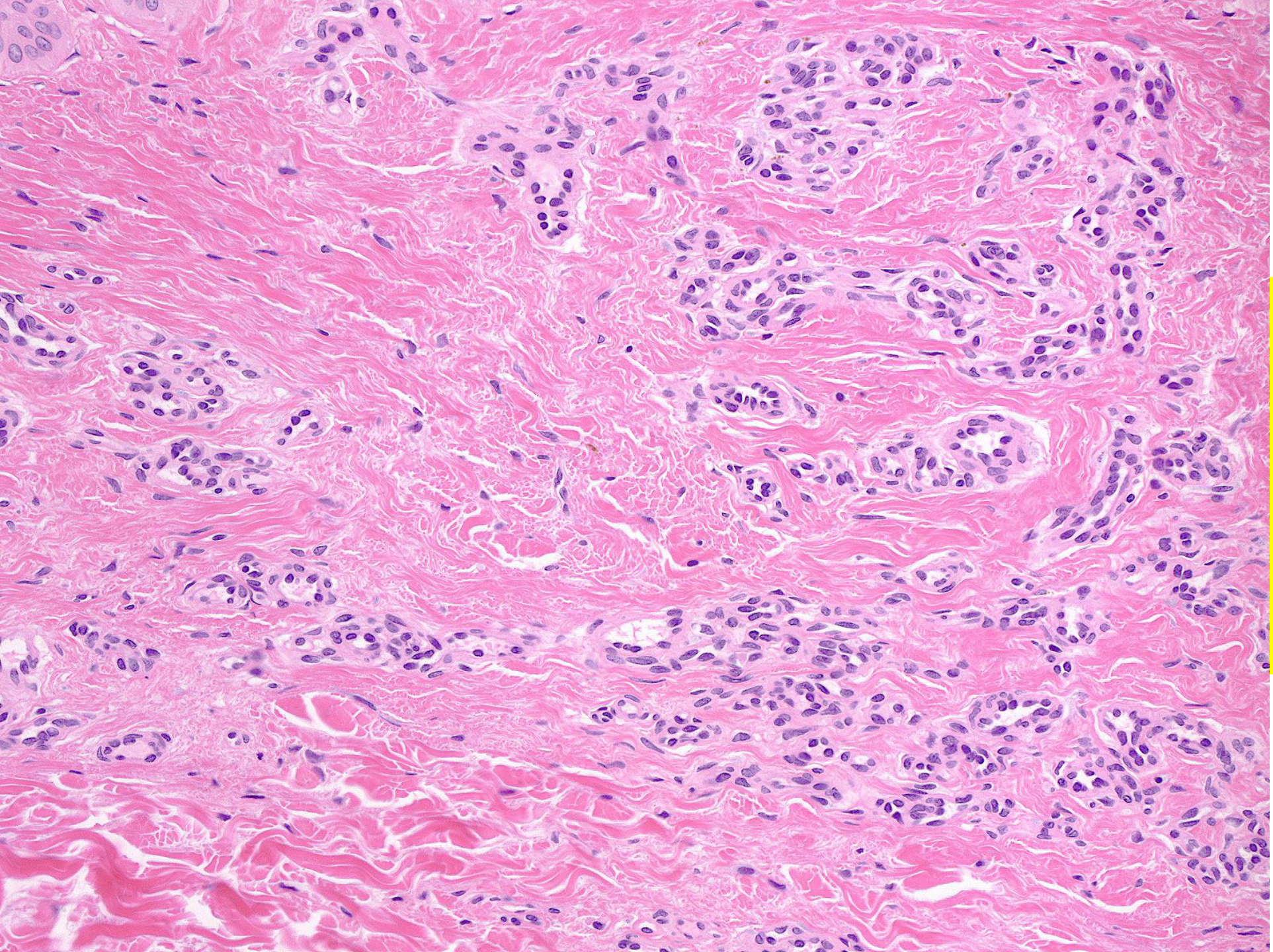
Intracytoplasmic lumina

MICROVENULAR HEMANGIOMA

- Limbs of young adults
- Red-bluish papule, nodule, or plaque
- Benign, recurrence is rare
- IHC: CD31+, CD34+, ERG+, WT1+
  - GLUT-1-, Podoplanin-
  - SMA+ pericytes surround vascular channels
- DDX: Kaposi sarcoma, (angiosarcoma)



Irregular infiltration of dermis
Dissects between collagen bundles
Infiltration of arrector pili



Irregular infiltration of dermis

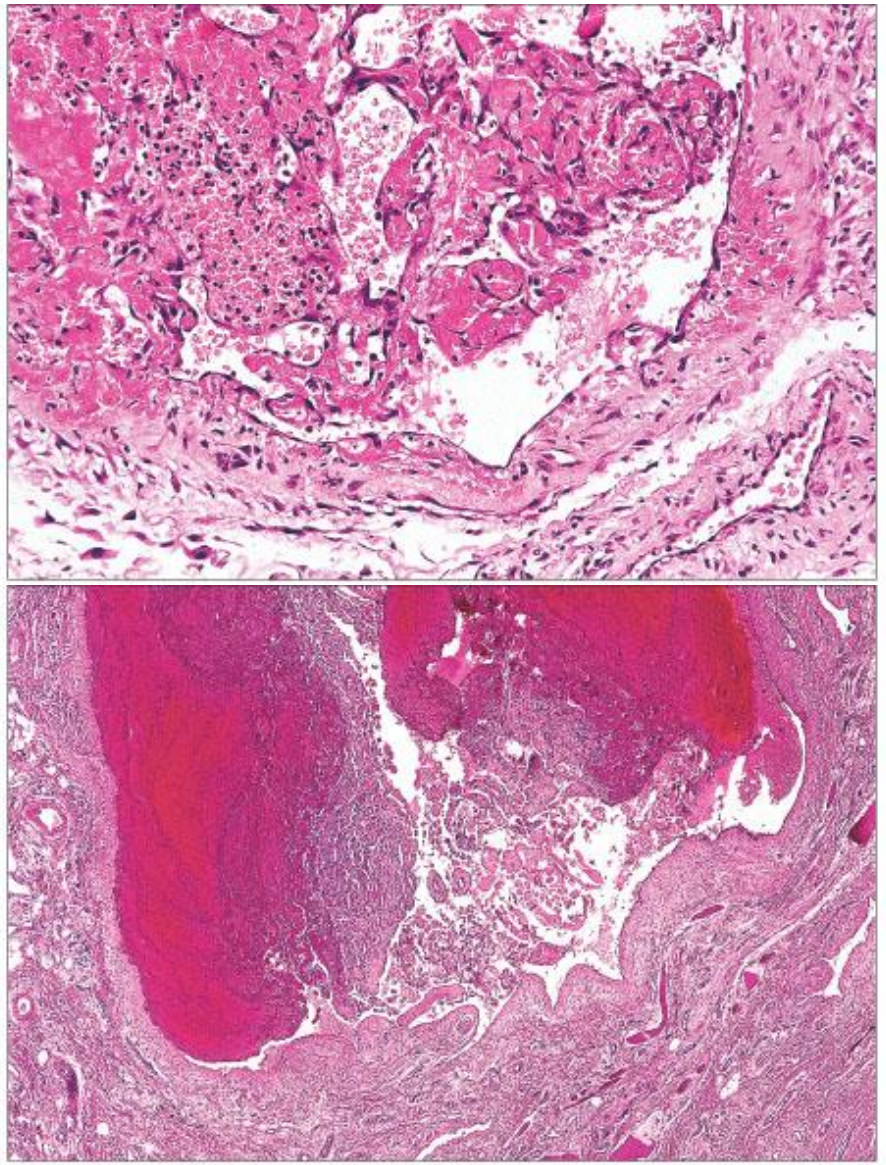
Dissects between collagen bundles

Round to slit-like lumina

Uniform plump endothelial monolayer

INTRAVASCULAR PAPILLARY ENDOTHELLIAL HYPERPLASIA (MASSON TUMOR)

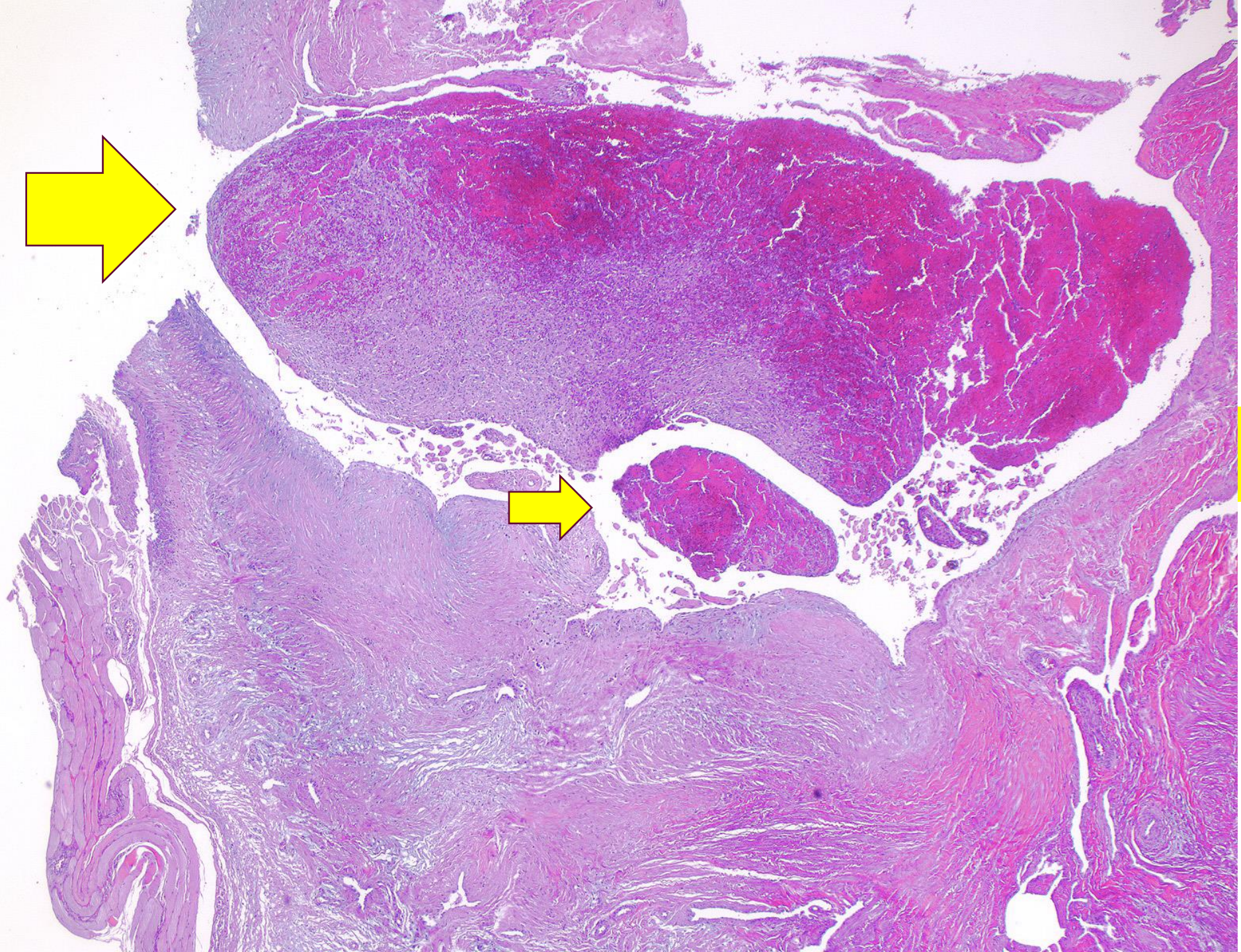
- Benign, common, slow growing cystic nodule
- Organizing thrombus
- Presents
  - Primary: head and neck or extremities of young females
  - Secondary (incidental): in other vascular tumors (spindle cell hemangioma)
- DDX: Angiosarcoma



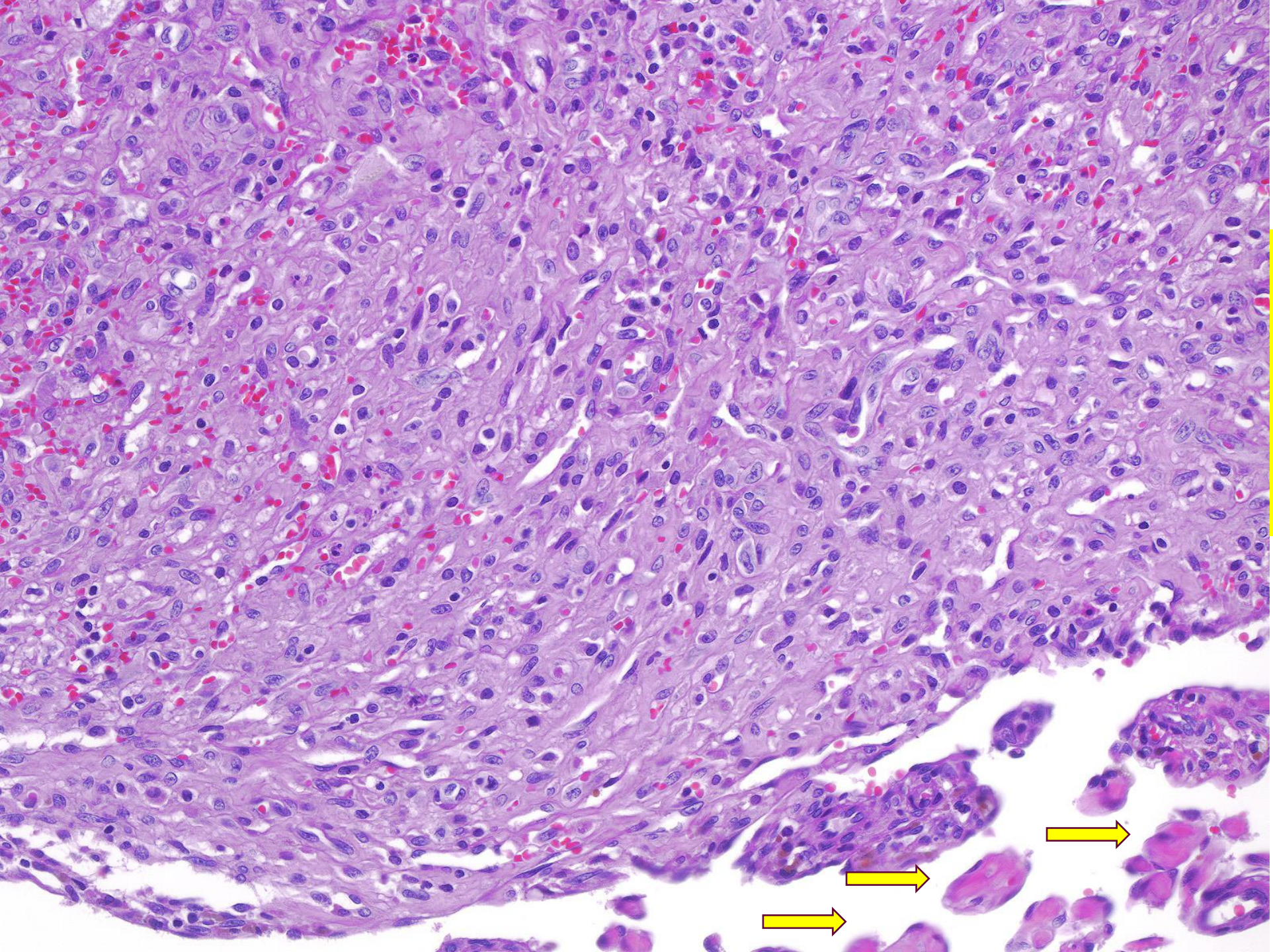
Numerous papillae in the lumen

Eosinophilic hyaline material covered by a single layer of endothelia

Organizing thrombus in a hemangioma



Organizing thrombus in a hemangioma



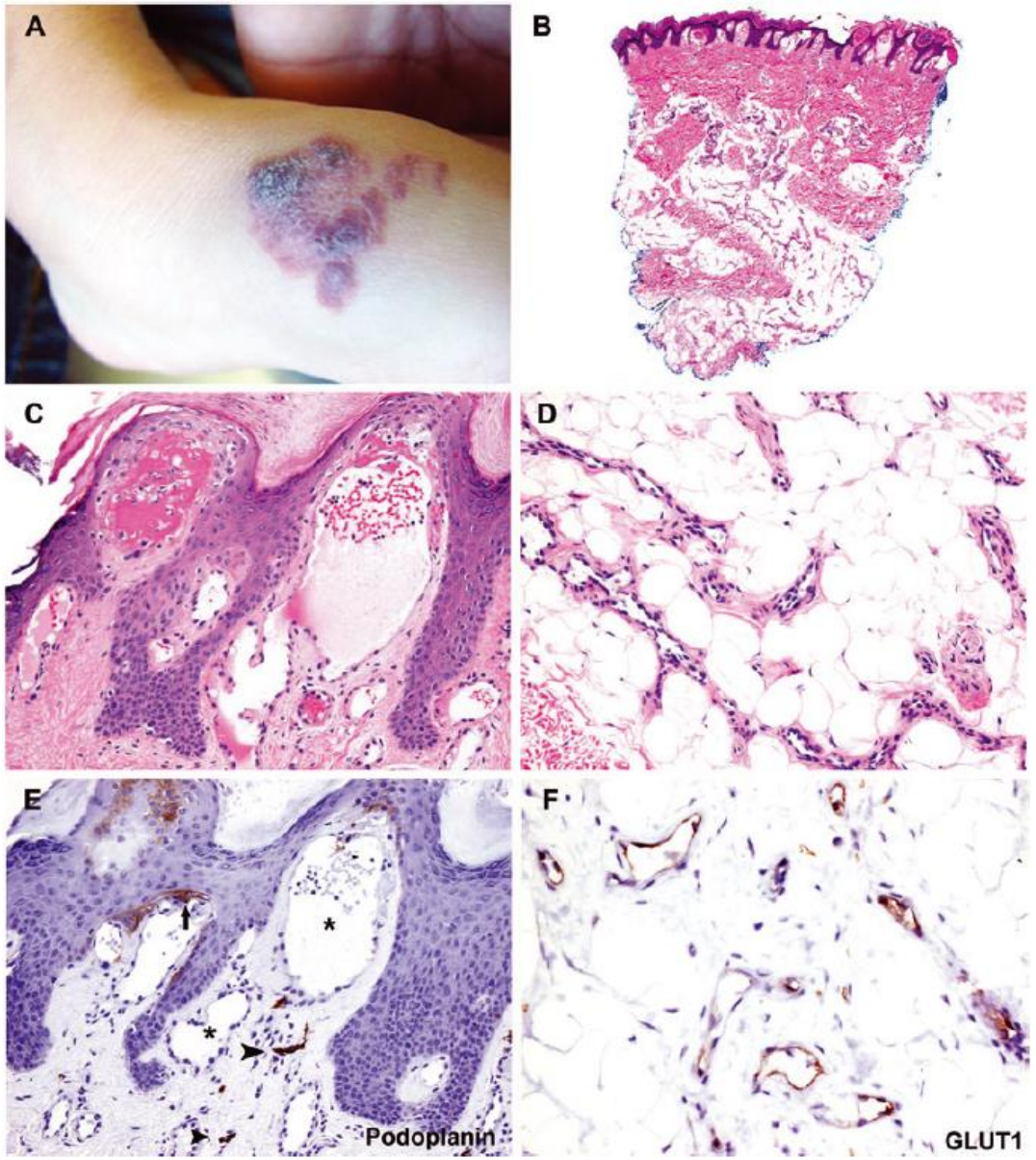
No atypia or multilayering

Numerous papillae in the lumen

Eosinophilic hyaline material

VERRUCOUS VENOUS MALFORMATION (VERRUCOUS HEMANGIOMA)

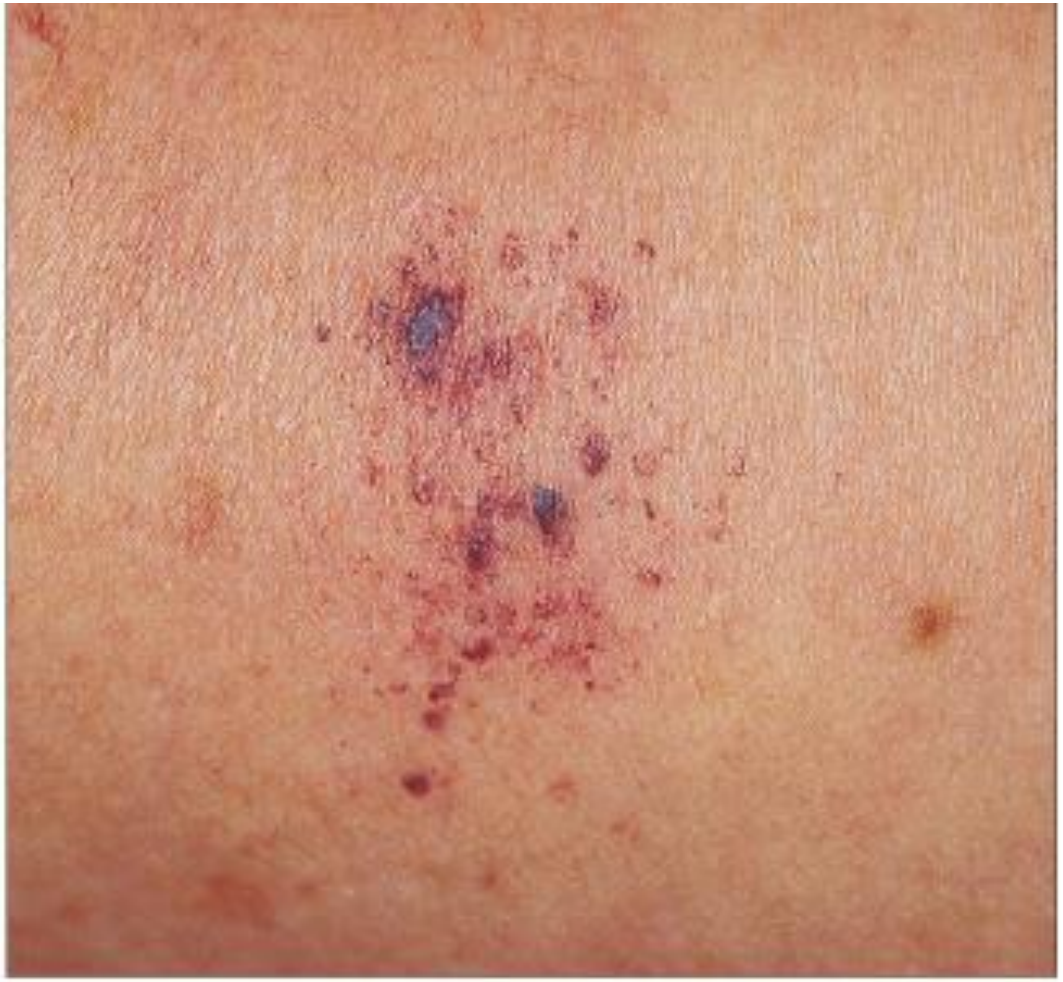
- Warty, dark blue-purple plaque
- Extremities, lower limbs of children
- Cutaneous lesions + spinal cord vascular malformation (Cobb syndrome)
- *MAP3K3* somatic mutation
- Resembles angiokeratoma (superficially)
  - Dilated, congested capillaries push up into dermis
  - Papillomatosis, acanthosis, hyperkeratosis (verrucous)
  - Subcutaneous component numerous capillaries
- IHC: GLUT-1+, WT-1-
- DDX: angiokeratoma

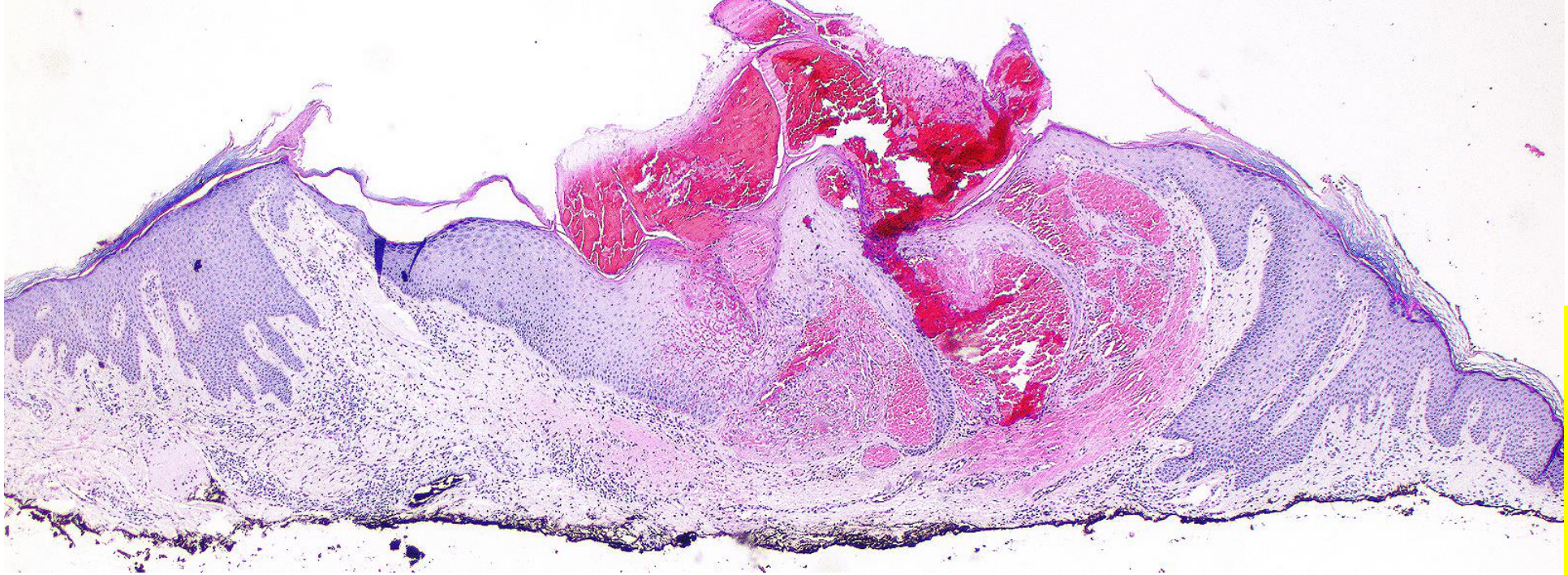


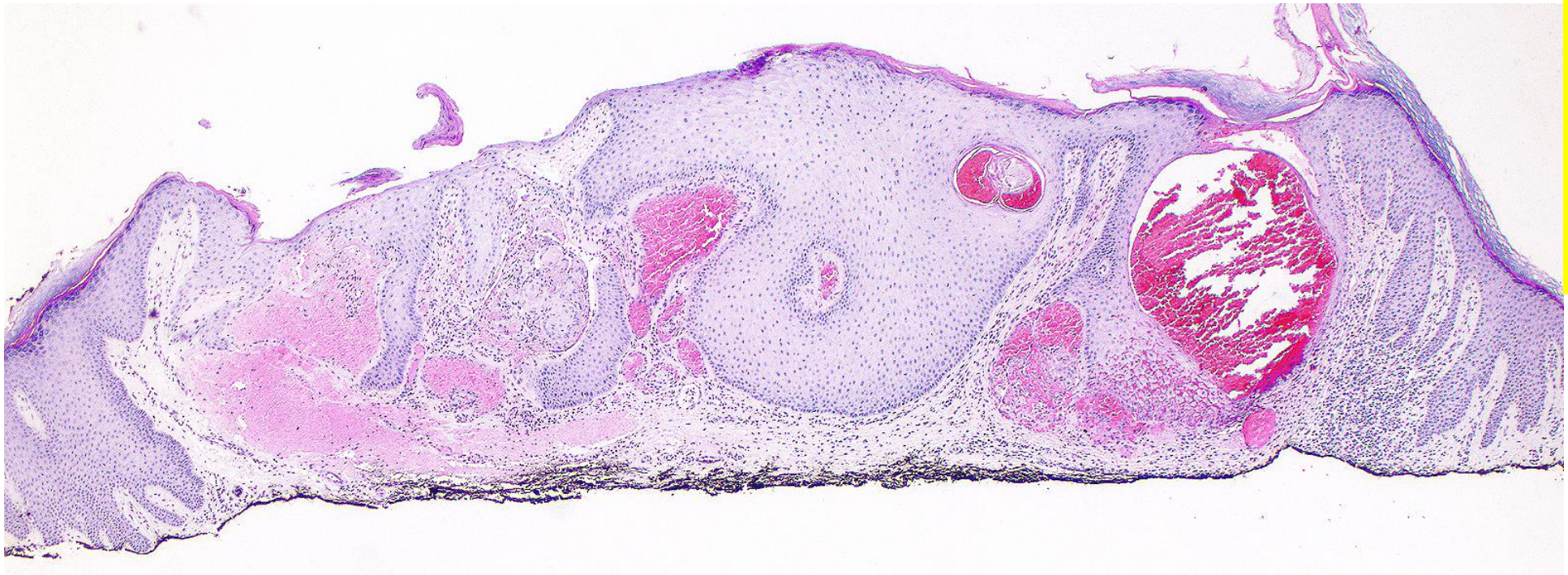
Verrucous hemangioma. Clairwood, Bruckner & Dadras. *JCP* 2011
Lucile-Packard Vascular anomaly clinic

ANGIOKERATOMA

- Clinical:
  - Of Fordyce: scrotum (old males), vulva (young females)
  - Of Mibelli: warty papules upper & lower extremities of children females
  - Circumscriptum: rare grouped papules, upper & lower extremities of children females
  - Corporis diffusum: red papules ‘bathing-trunk’ areas, associated with Anderson-Fabry’s disease (deficiency of lysosomal a-galactosidase A)
  - Solitary & multiple-wide age & anatomic site



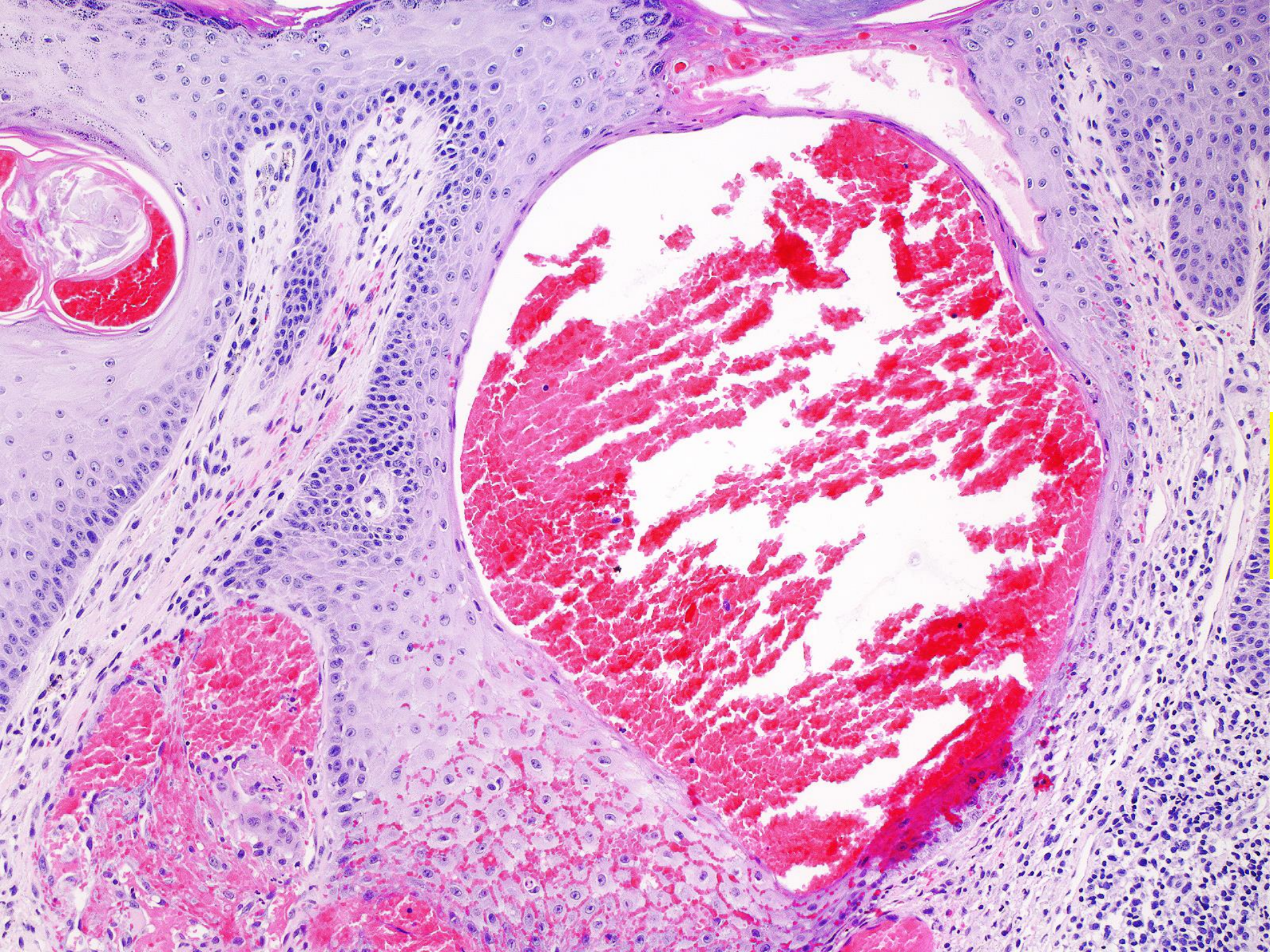




Congested small dilated blood vessels in papillary dermis

Push up into epidermis

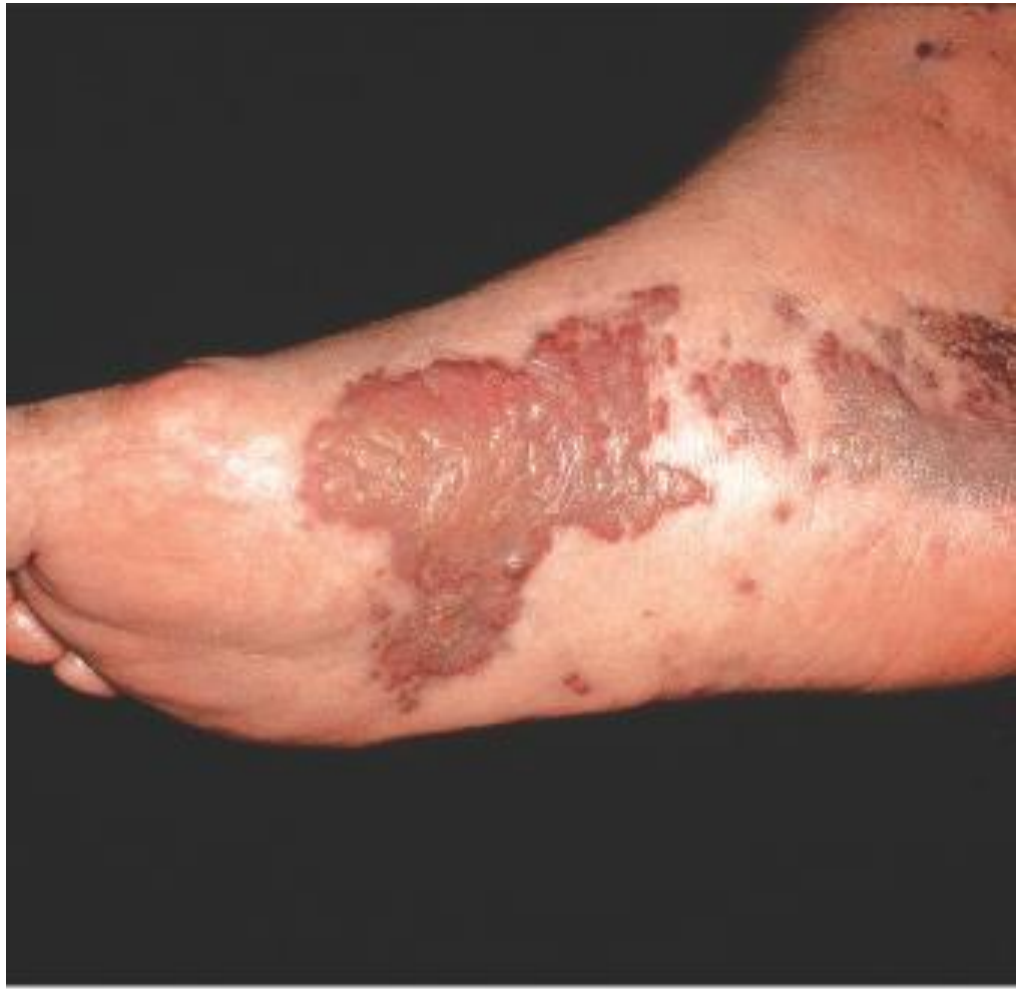
Overlying papillomatosis, acanthosis
Intracytoplasmic lipid vacuoles in endothelium pericytes, fibroblasts (in Anderson-Fabry's disease)



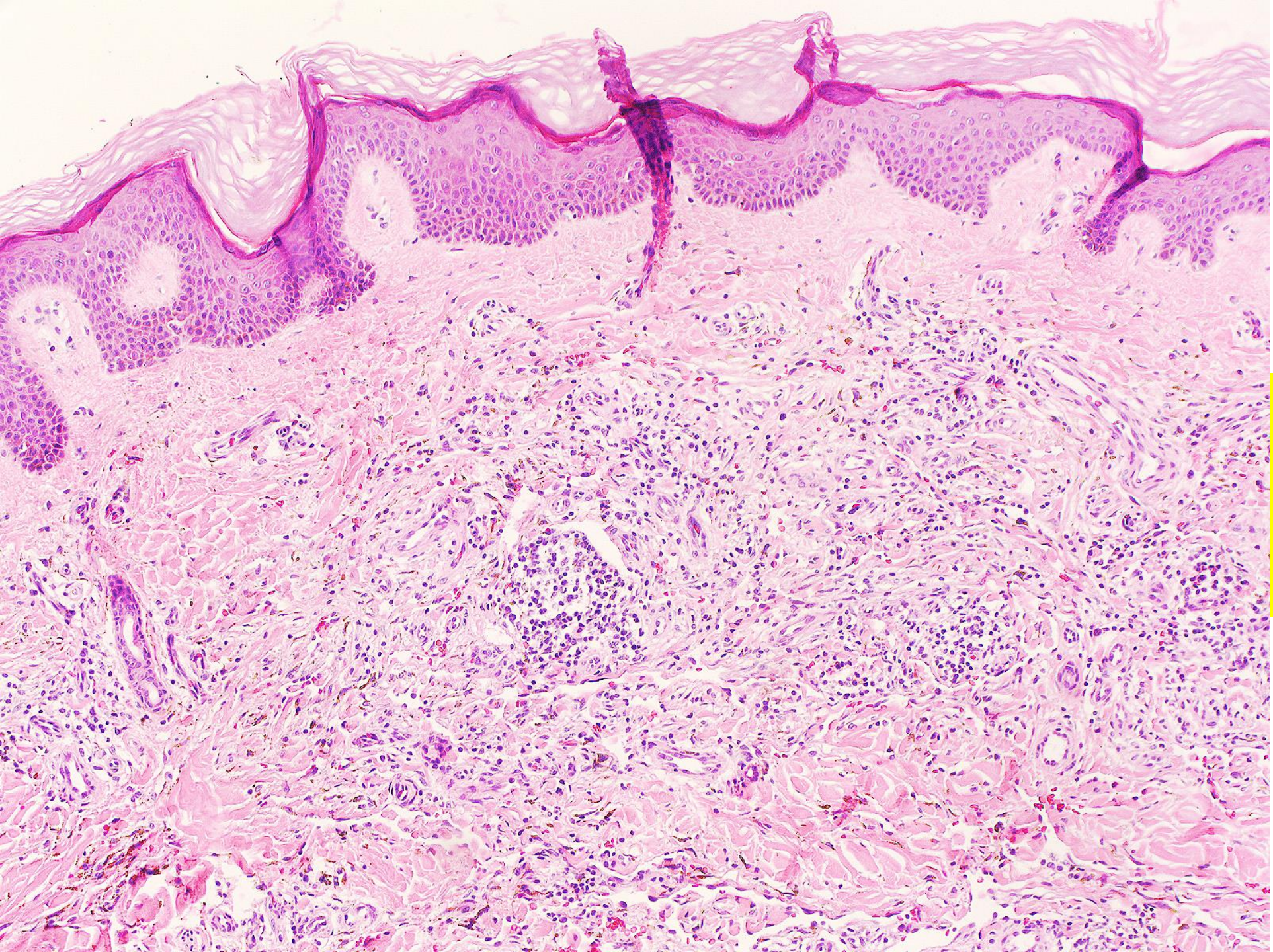
Congested small dilated blood vessels in papillary dermis
Appear to be in epidermis

KAPOSI SARCOMA

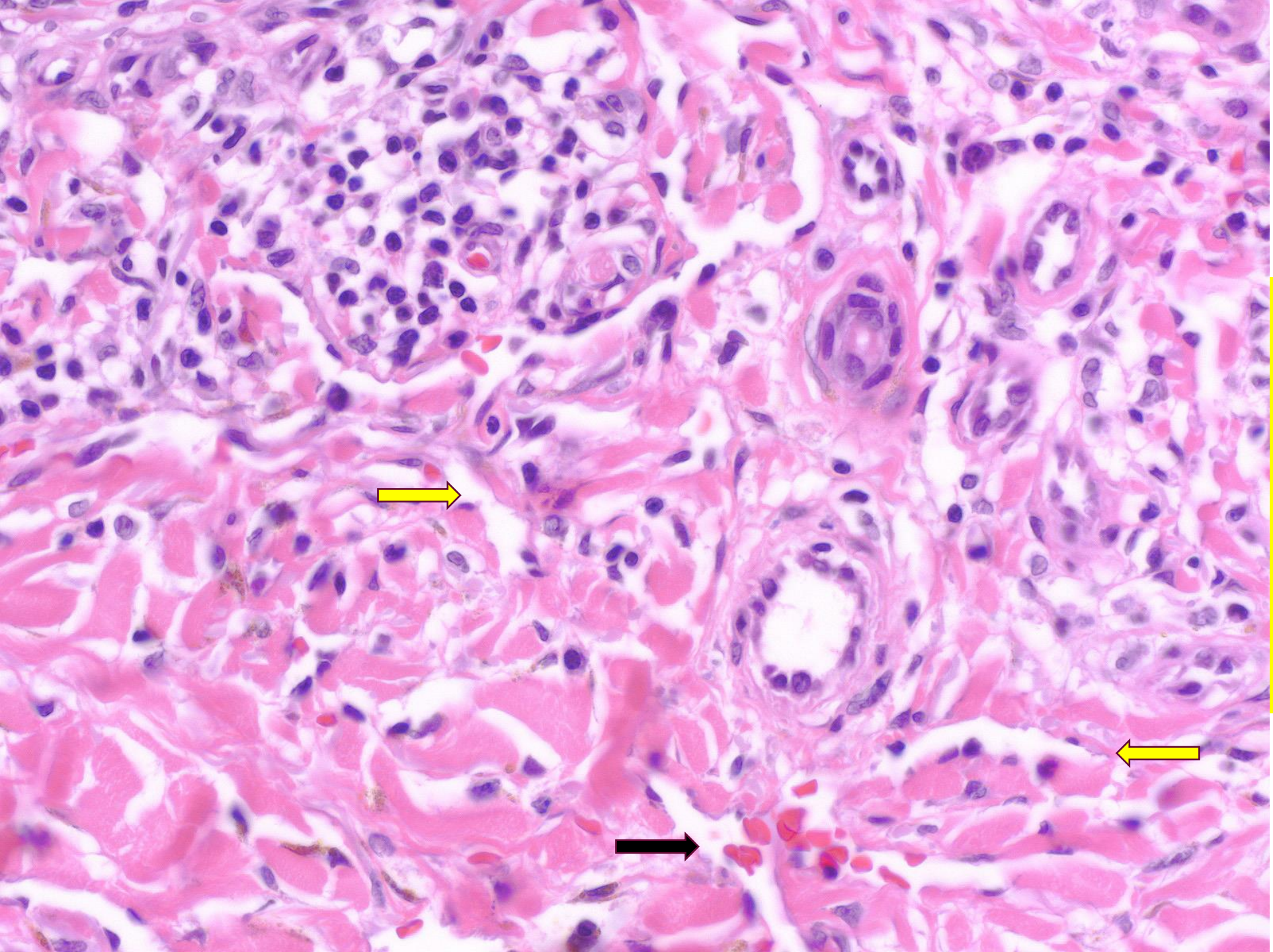
- Reactive vs. neoplastic
- Human herpesvirus (HHV-8, KS-associated herpesvirus)
- Clinical groups:
  - Classic: elderly male
  - AIDS-related: young adult males
  - Immune-associated: rare, kidney transplantation
  - African, sub-Saharan Central Africa
- Reddish-blue patch, nodule
- DDX: progressive lymphangioma, angiosarcoma, tufted angioma, KHE
- IHC: HHV8, CD31, CD34, D2-40



Isevier - Bolognia, Jorizzo and Rapini: Dermatology - www.der



Early patch stage:
Increased in dermal vessels
Slit-like lumina
Lymphocytes, plasma cells
Extravasated erythrocytes
Hemosiderosis



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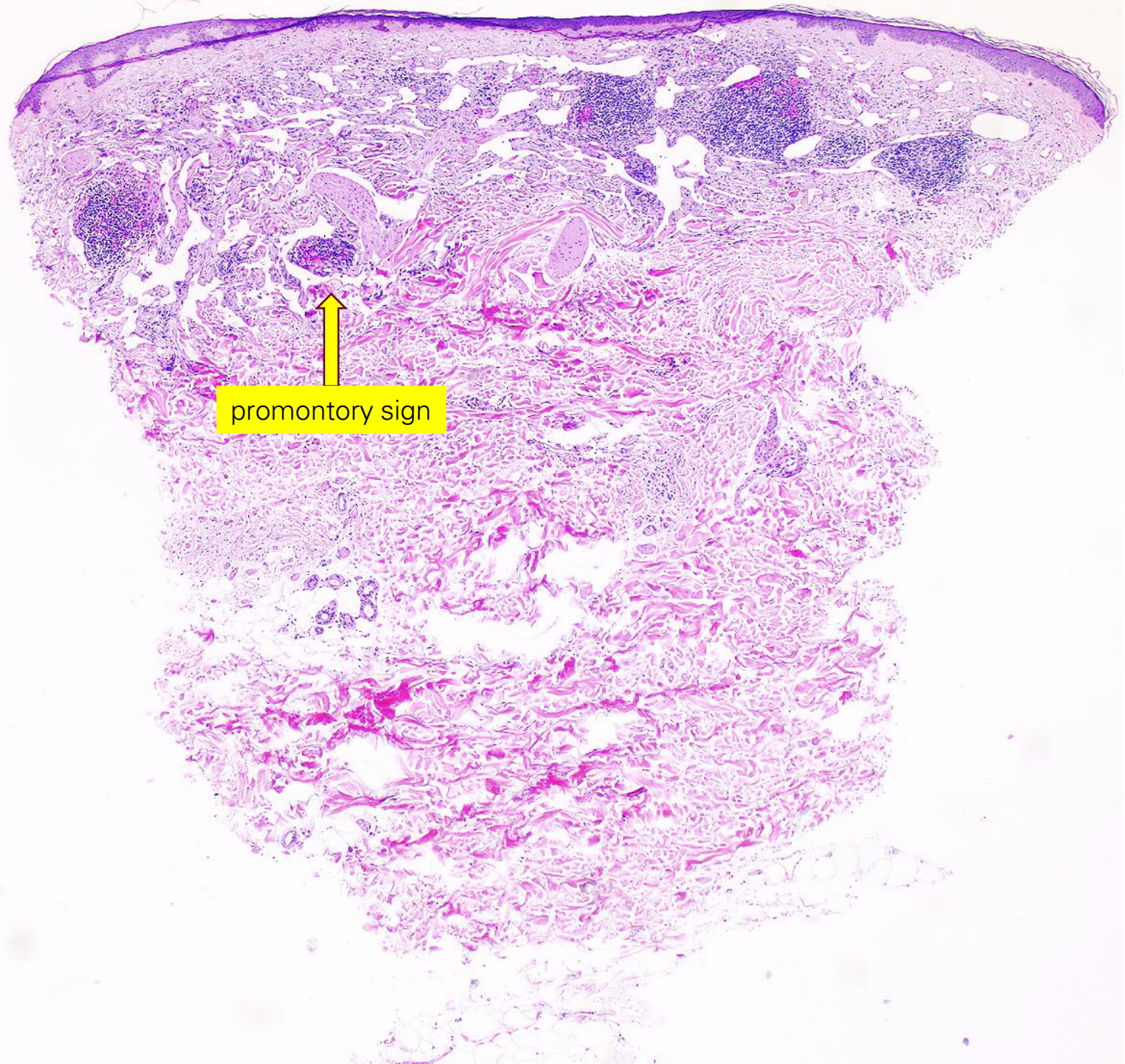


Plaque stage

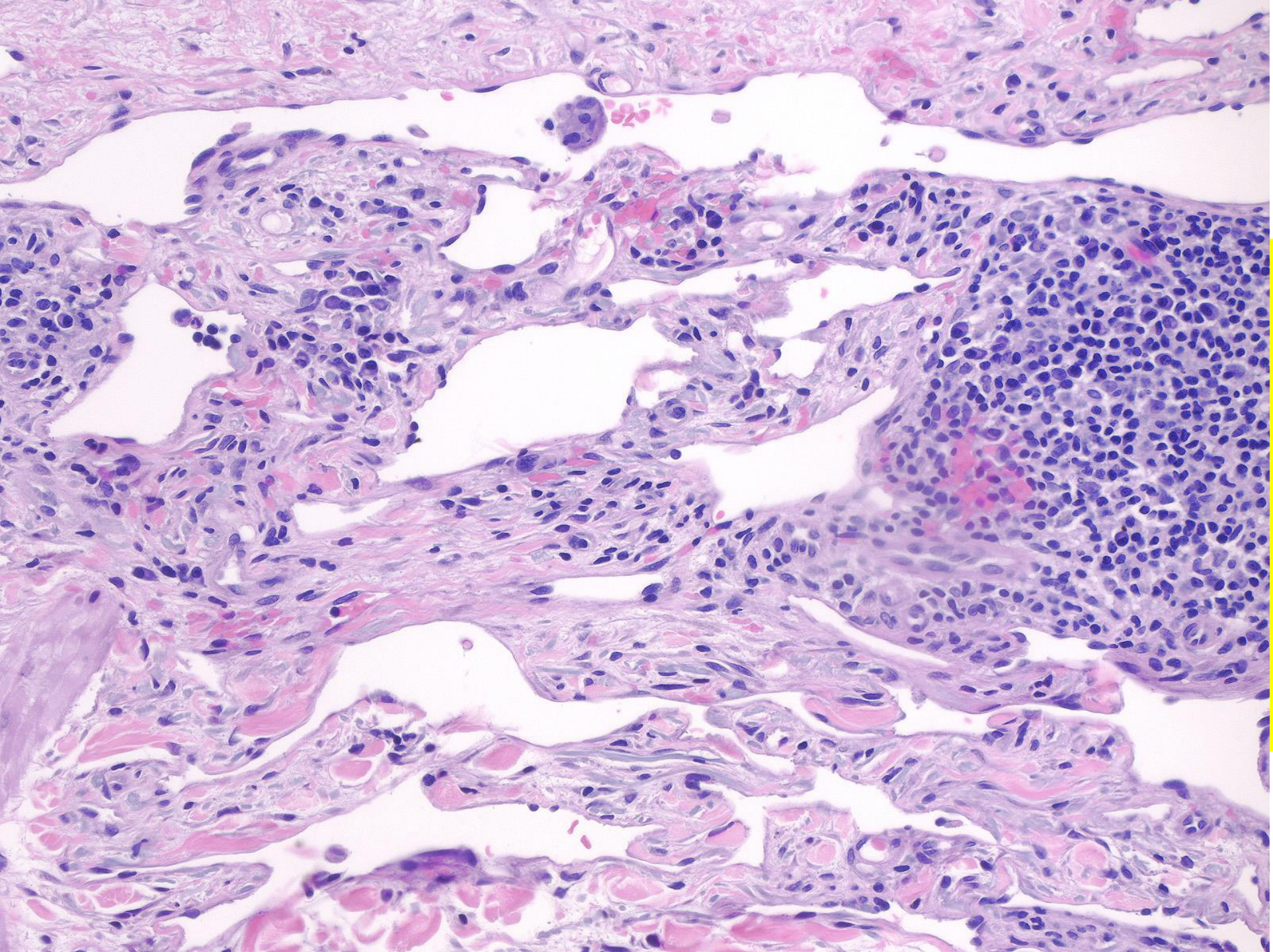
Numerous ill-formed vessels in dermis

Slit-like lumina

The promontory sign: new vessels ensheath pre-existent ones
Aggregates of lymphocytes, plasma cells

Extravasated erythrocytes

Hemosiderosis



Plaque stage

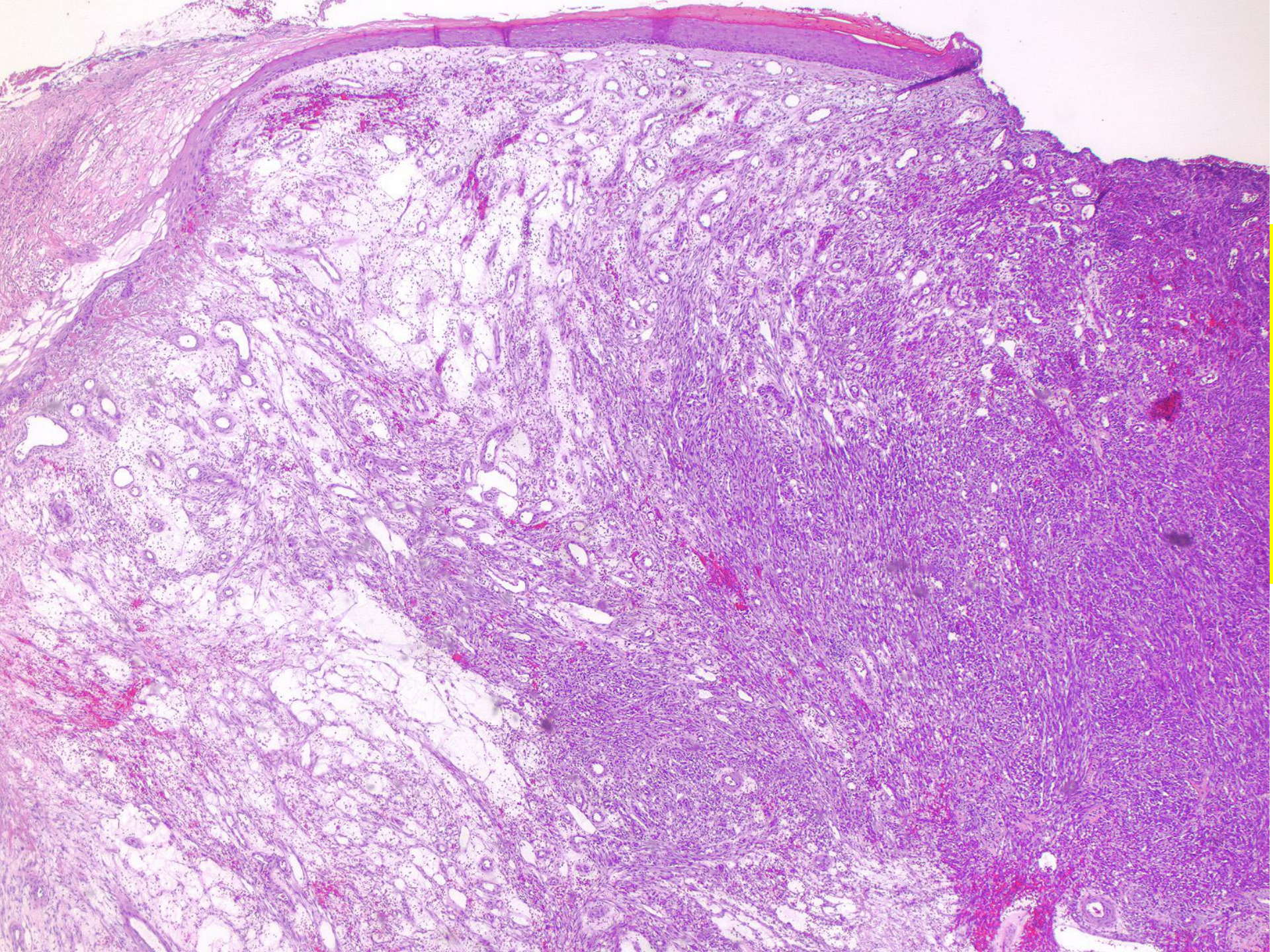
Numerous ill-formed vessels in dermis

Slit-like lumina

Aggregates of lymphocytes, plasma cells

Extravasated erythrocytes

Hemosiderosis

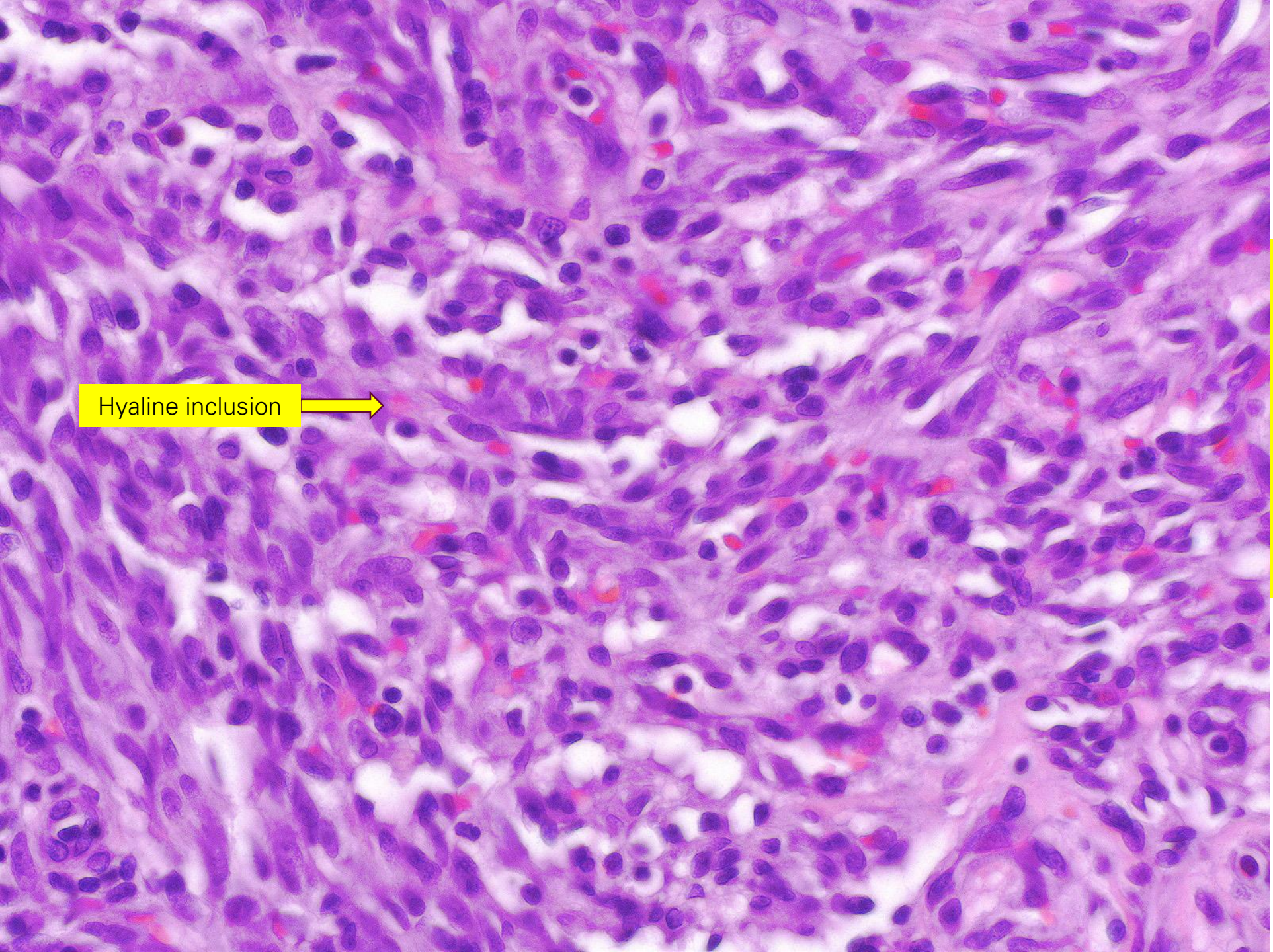


Nodular stage:

Ill-defined dermal mass

Slit-like lumina

Extravasated erythrocytes

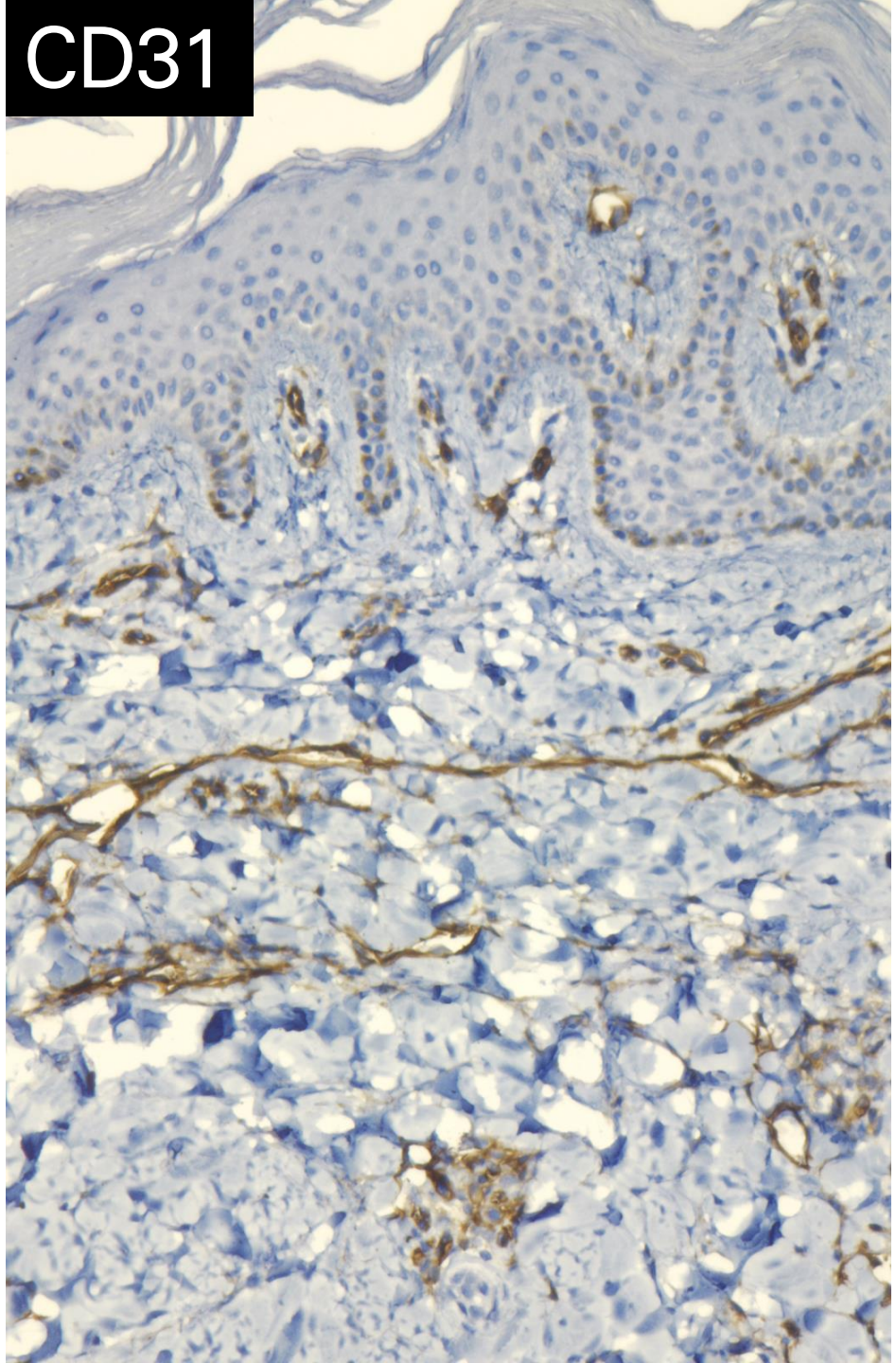


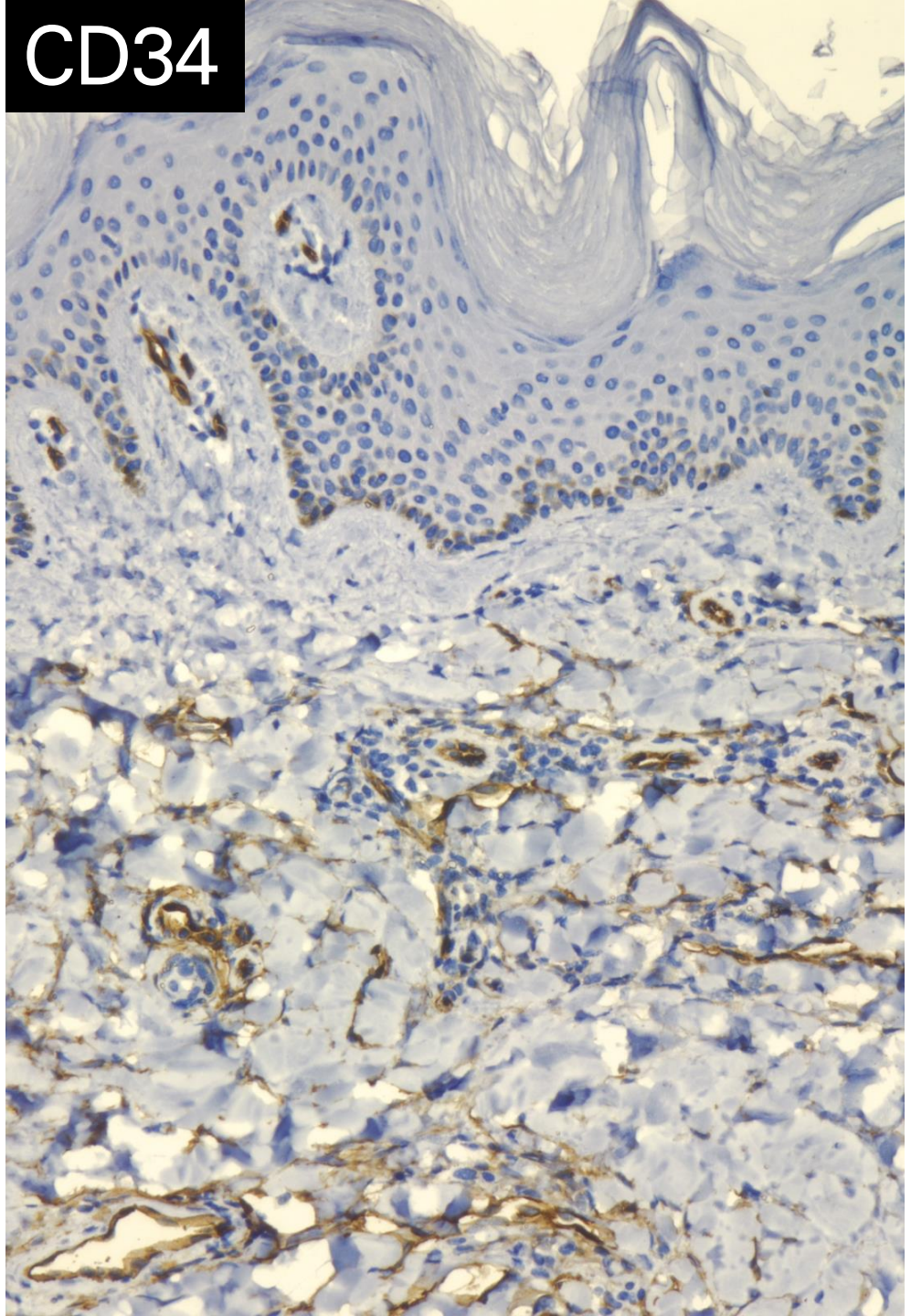
Numerous spindle cells with eosinophilic cytoplasm

Scattered lymphocytes

Extravasated erythrocytes

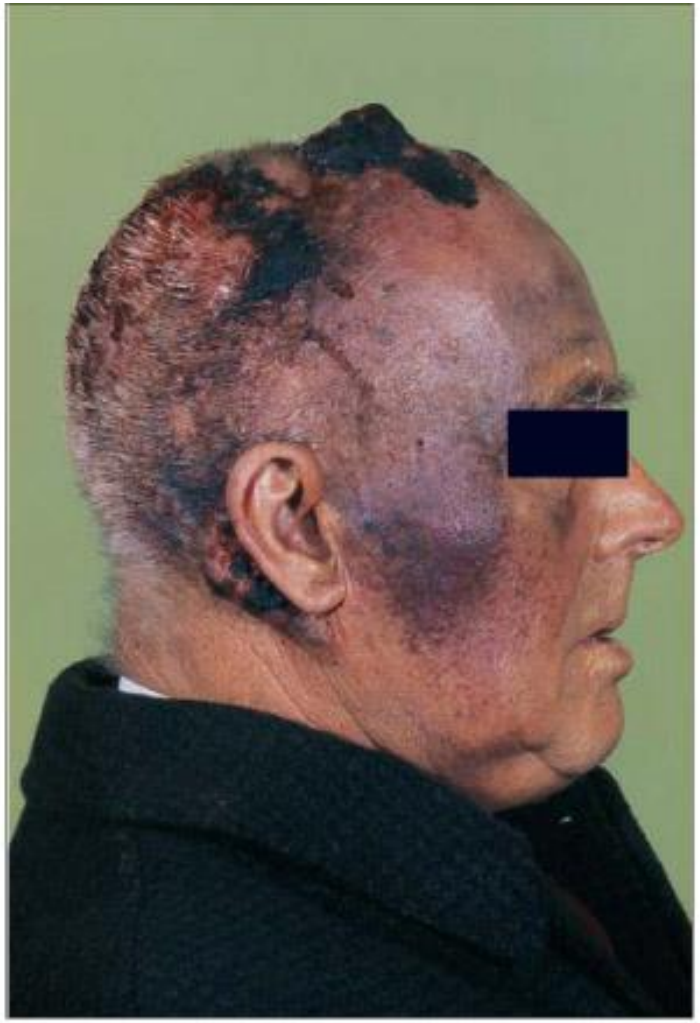
Hyaline inclusion

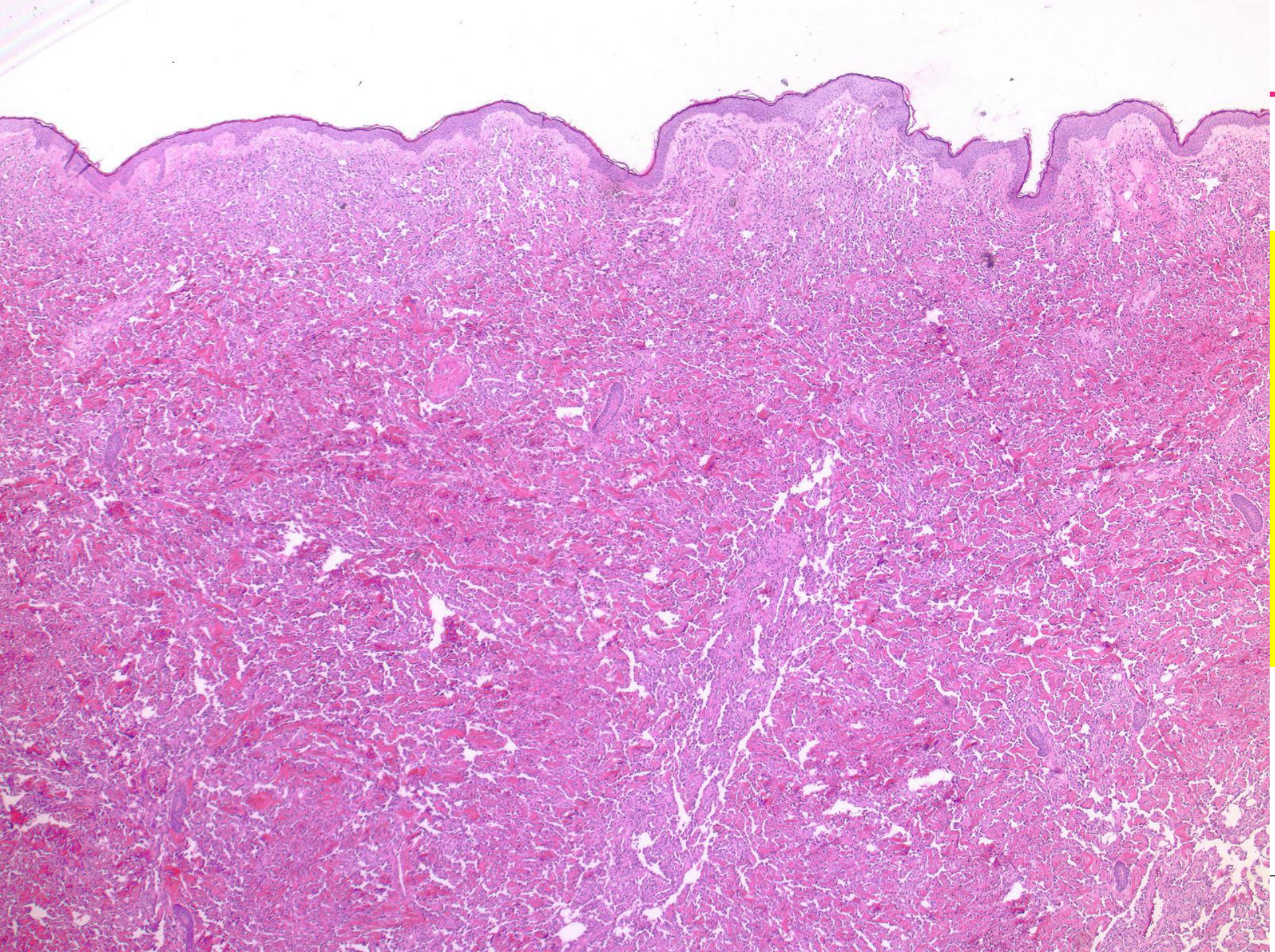

CD31


CD34

ANGIOSARCOMA

- Clinical settings
  - Idiopathic, head and neck, older adults
  - Lymphedema-associated, any age, limbs
  - Post-irradiation
- Bruise-like patches and plaques, hemorrhagic
- Many gene mutations (melanoma), ERK/MAPK pathway
- DDX: Kaposi sarcoma
- IHC: CD31+, CD34+, FLI1+, ERG+, HHV8-



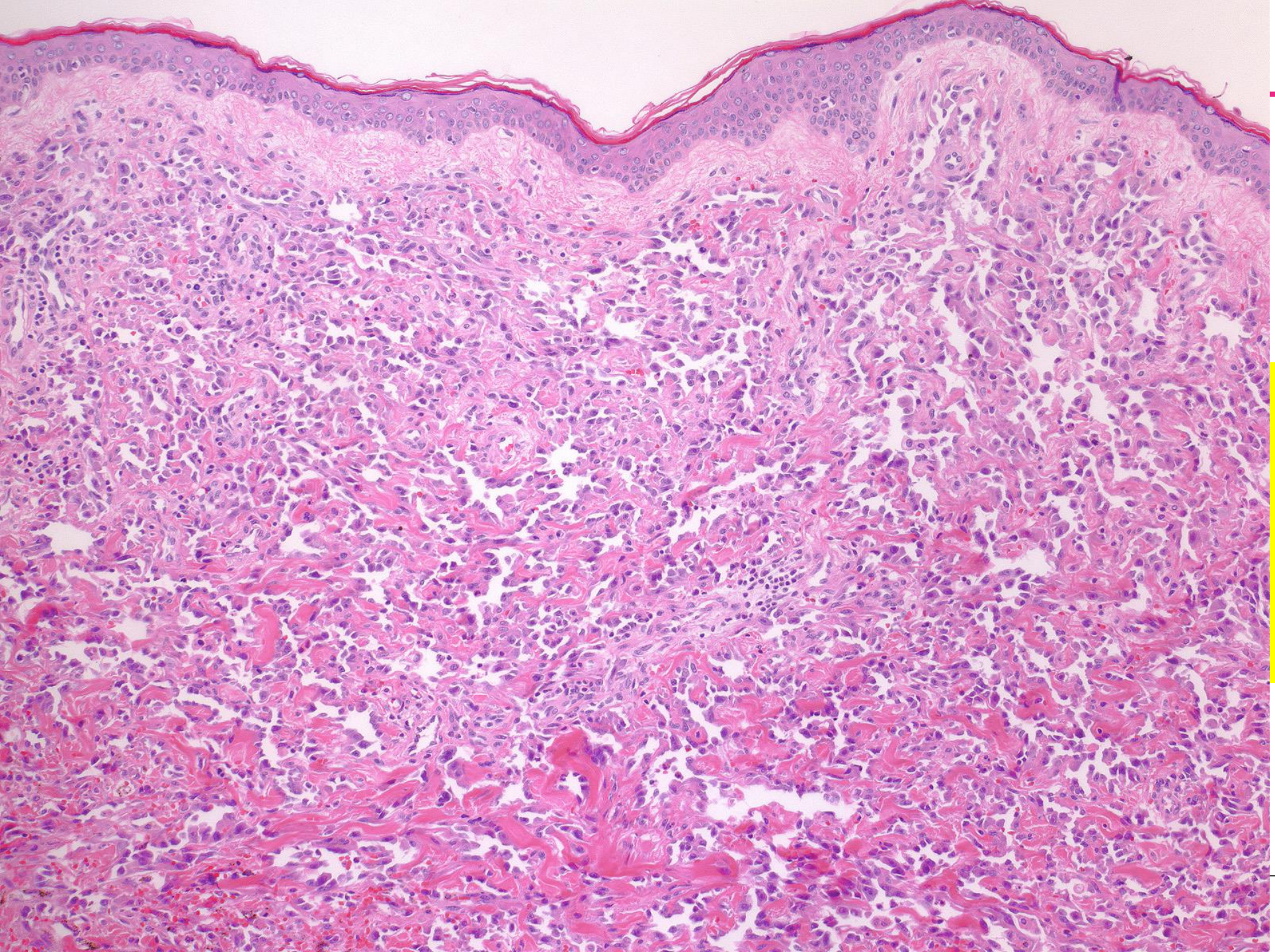


Ill-defined, infiltrating dermal mass

Destructive pattern, loss of adnexa

Vascular channels of varying caliber

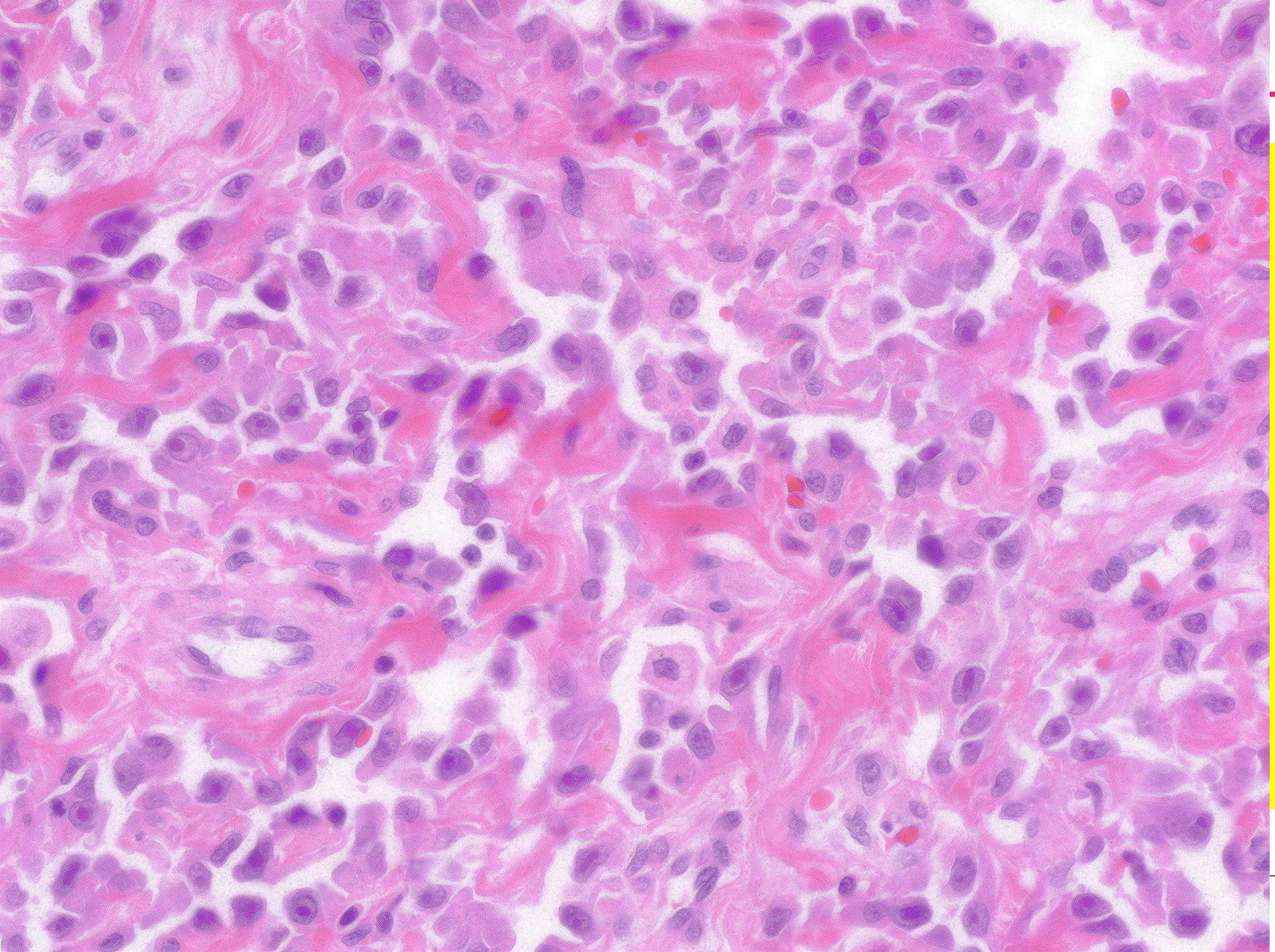
Dissecting vascular collagen bundles



Vascular channels of varying caliber

Dissecting vascular collagen bundles

Vascular space lined by multilayered endothelia



Dissecting vascular collagen bundles

Vascular space lined by multilayered endothelia

Plump, pleomorphic endothelia

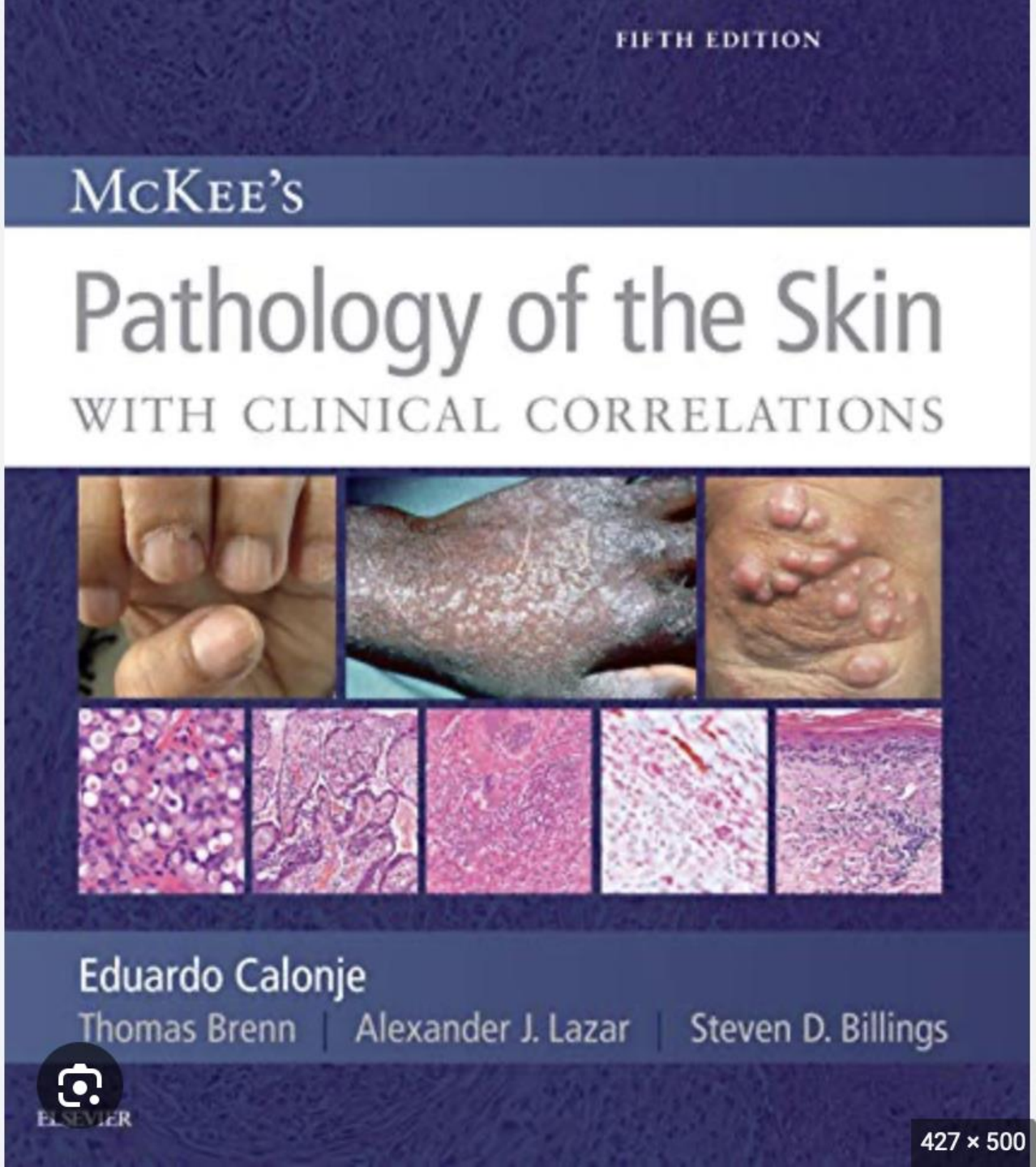
Forming papillae

Ample cytoplasm, round nuclei, open chromatin, prominent nucleolei

Mitoses

References

- *McKee's Pathology of the Skin* Eduardo Calonje
- ISSVA.org
- WHO Classification of Tumors (Skin Tumors 5th edition)
- Microscopic images: SS Dadras collection



Digital Skin Pathology

https://digitalskinpathology.com/

- Current lecture
- Examples of cases