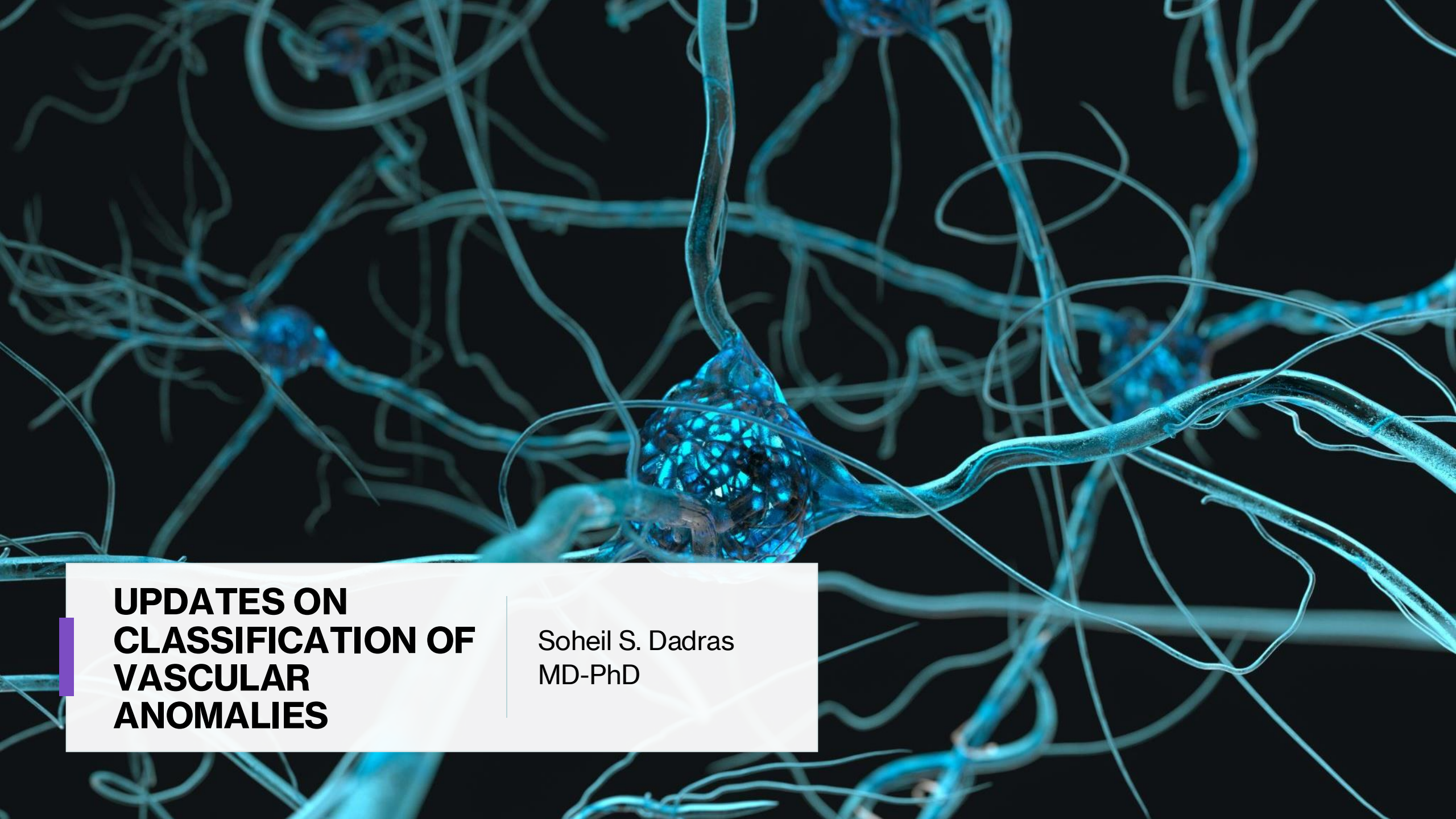


UPDATES ON CLASSIFICATION OF VASCULAR ANOMALIES

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)
- Established vascular anomaly clinic at MGH Pediatrics
- My mentor in dermatopathology, friend

March 15, 1934 - July 19, 2022

Martin C. Mihm Jr., MD

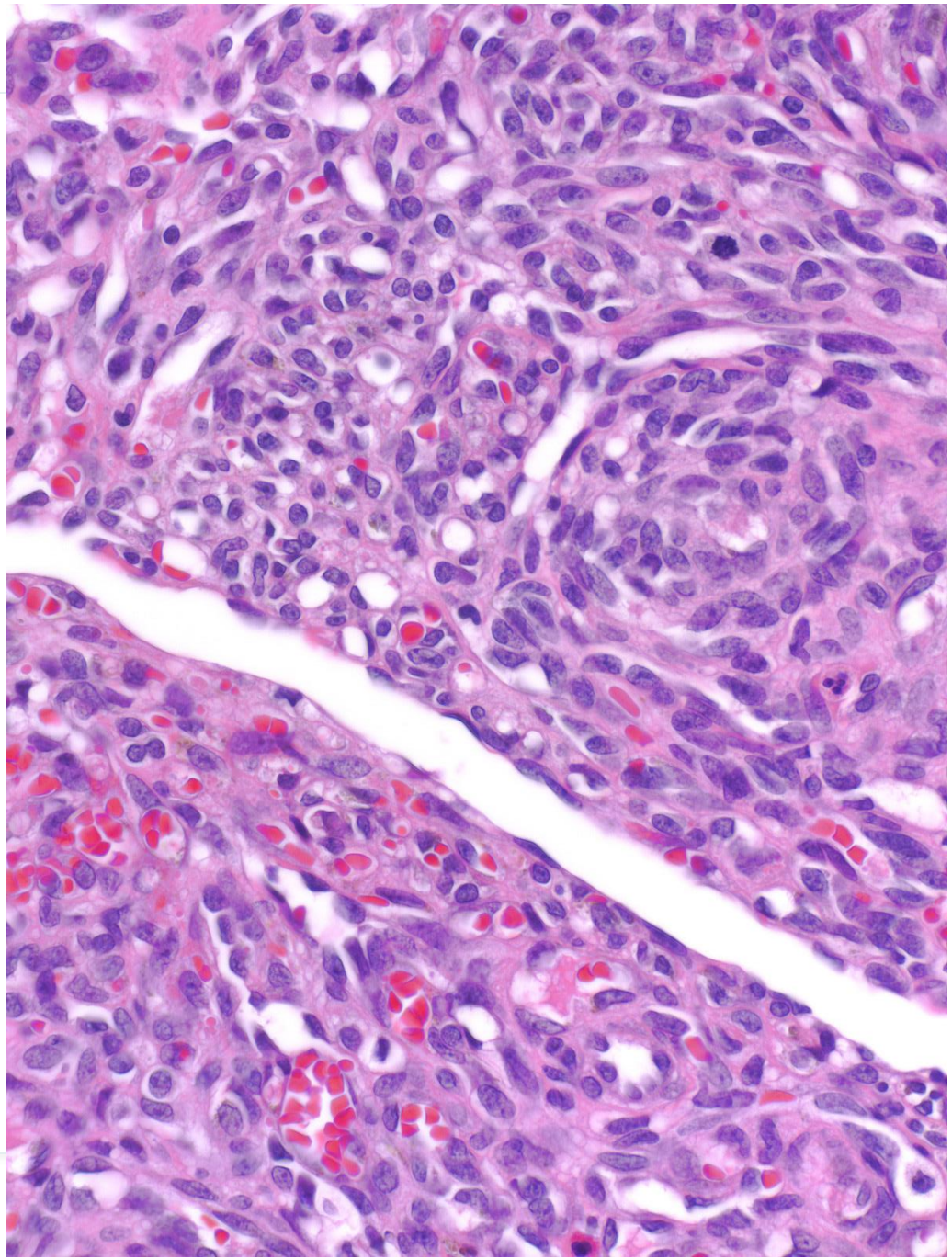
Kupper T, Piris A, Kroshinsky D, Kaya G. In Memoriam-Martin C. Mihm, Jr. Dermatopathology (Basel). 2022 Sep 8;9(3):304-306.
Murphy GF. A Festschrift for Martin C. Mihm, Jr. J Cutan Pathol. 2010 Apr;37

Who is most qualified to speak on the pathology of vascular anomalies?

- Usually, expect ...
  - Soft tissue pathologist? Or Pediatric pathologist? A (pediatric) dermatopathologist?
- An orphan field
- NIH Training grant (Dadras) at MGH CBRC (lymphatic endothelial cell biology, Dr. Michael Detmar)
- Introduced to Dr. Paula E. North
  - Started a series of large studies in expression of endothelial makers in vascular anomalies
- Established the VAC at Lucille-Packard (Stanford) in 2005 (Bruckner, Lane and Dadras)

What are the objectives?

- Improve diagnostic accuracy (reduce our send-out cases)
  - Pathologists can play a critical role in the early stage of diagnosis
  - Facilitate communications via multidisciplinary Vascular Anomaly Clinic
  - New targeted therapies (NGS needed)
- Introduce classification framework
  - The International Society for the Study of Vascular Anomalies; https://www.issva.org
- Online resource: https://digitalskinpathology.com



How are vascular anomalies classified?

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

Causal genes of vascular anomalies

(appendix 2b, ISSVA May 2018)

Gene	Syndrome/Diagnosis
IDH1, IDH2	Maffucci , spindle cell hemangioma
KIF11	Microcephaly ± chorioretinopathy, lymphedema, or mental retardation
KRIT1	Cerebral cavernous malformation
Malcavernin	Cerebral cavernous malformation
MAP2K1	Arteriovenous malformation (AVM), arteriovenous fistula
MAP3K3	Verrucous venous malformation
MYC	Post-radiation angiosarcoma
NPM11	Maffucci
PDCD10	Cerebral cavernous malformation
PIK3CA	Common cystic lymphatic malformation Common venous malformation Klippel-Trenaunay Megalencephaly-capillary malformation-polymicrogyria Fibroadipose vascular anomaly

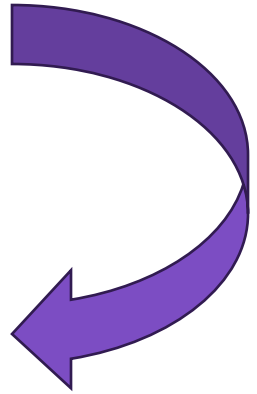
What are the biological basis for classification?

Hemangioma

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

Malformation

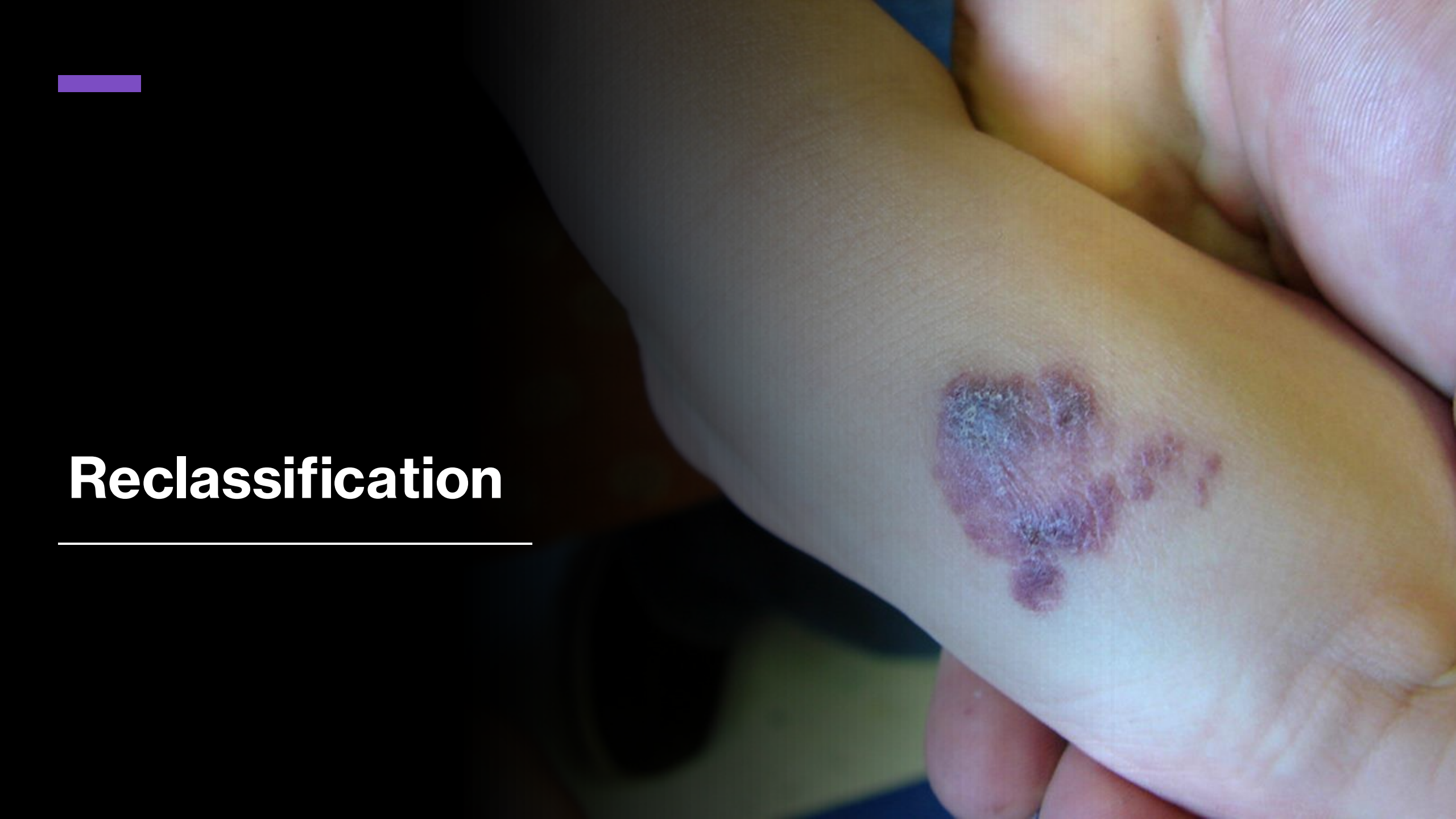
- Errors in vascular morphogenesis
- Mitotically inactive
- Usually evident at birth
- e.g., Venous malformation

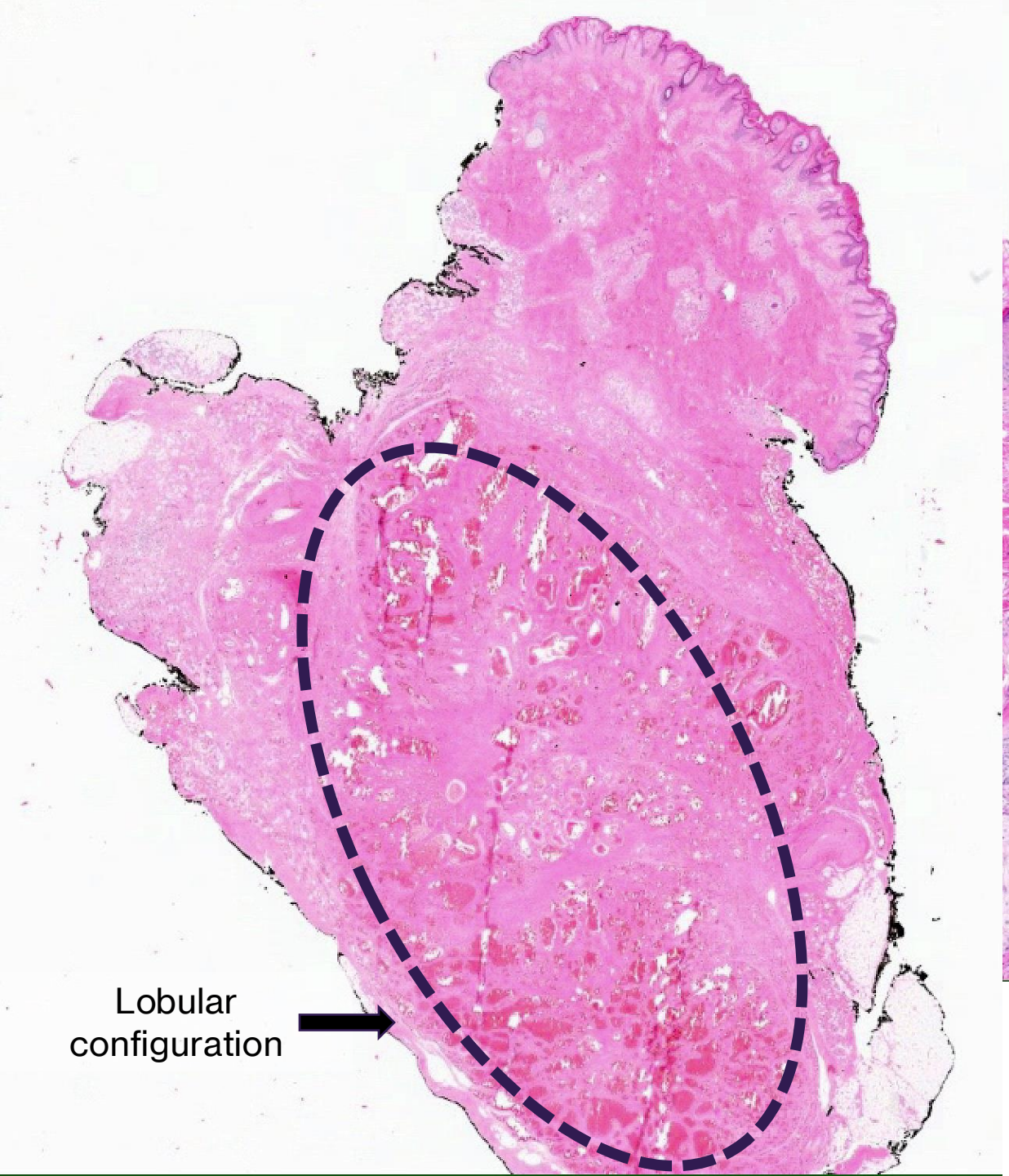


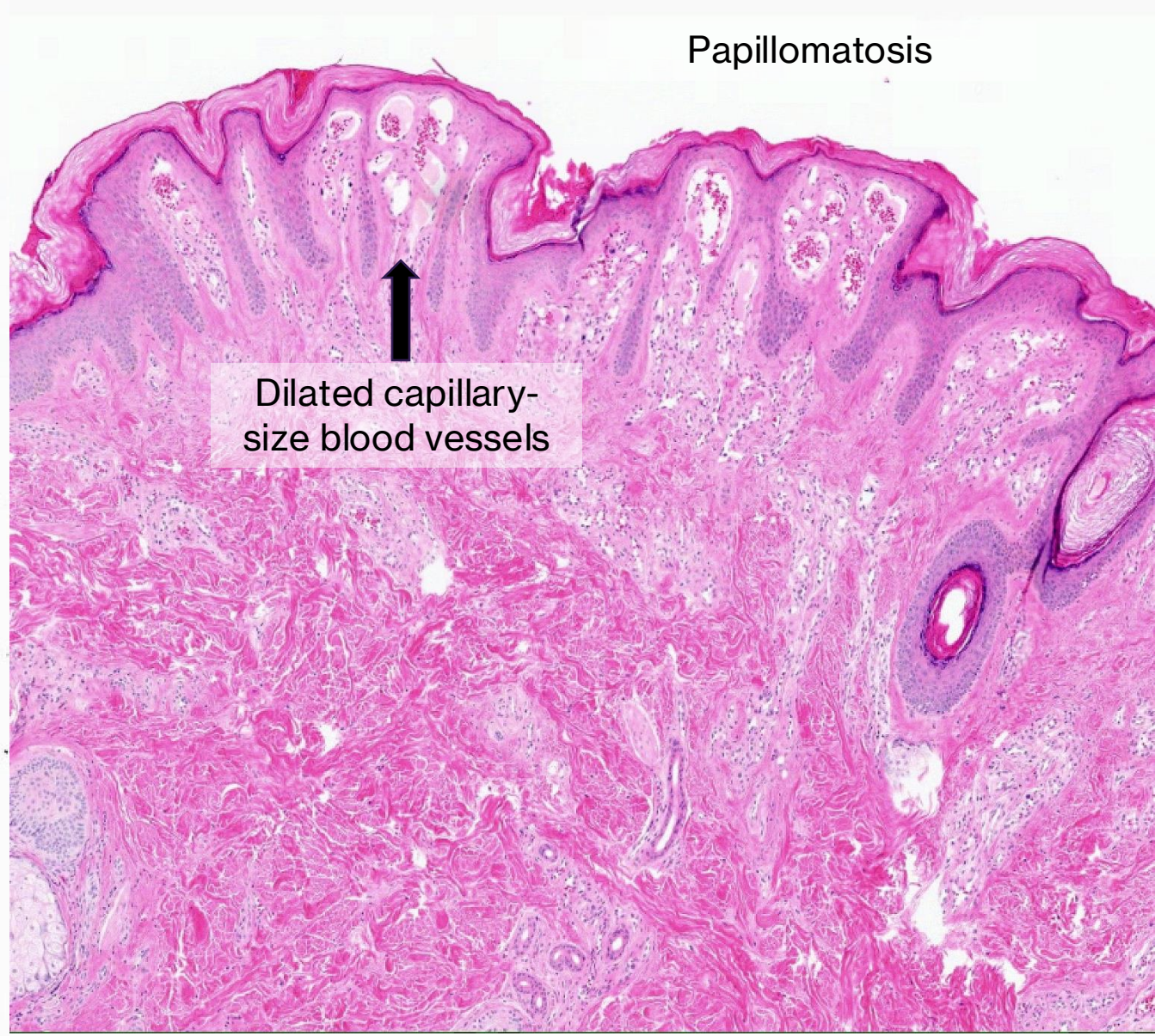
±Overlapping features

Molecular pathology

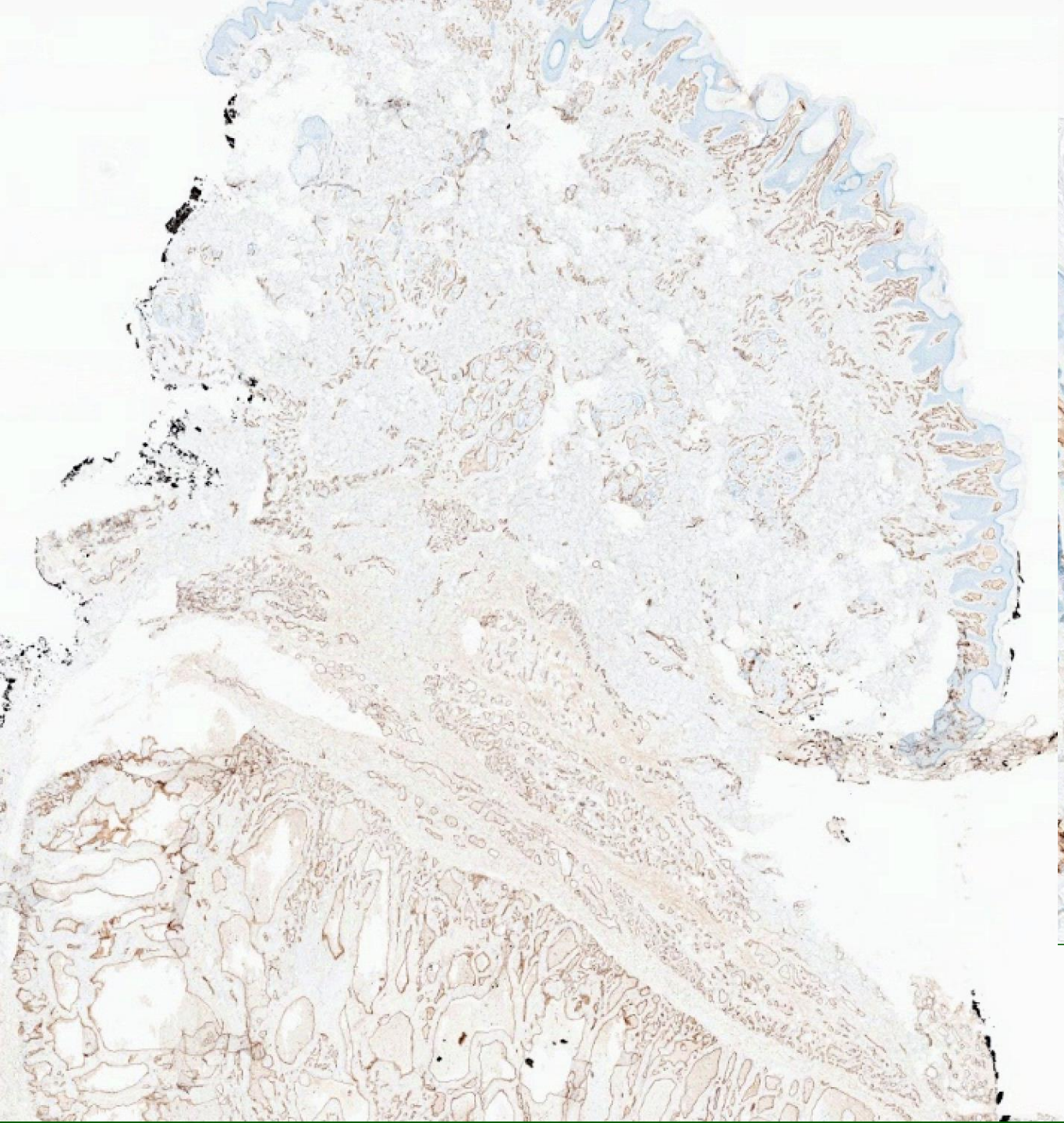
Reclassification

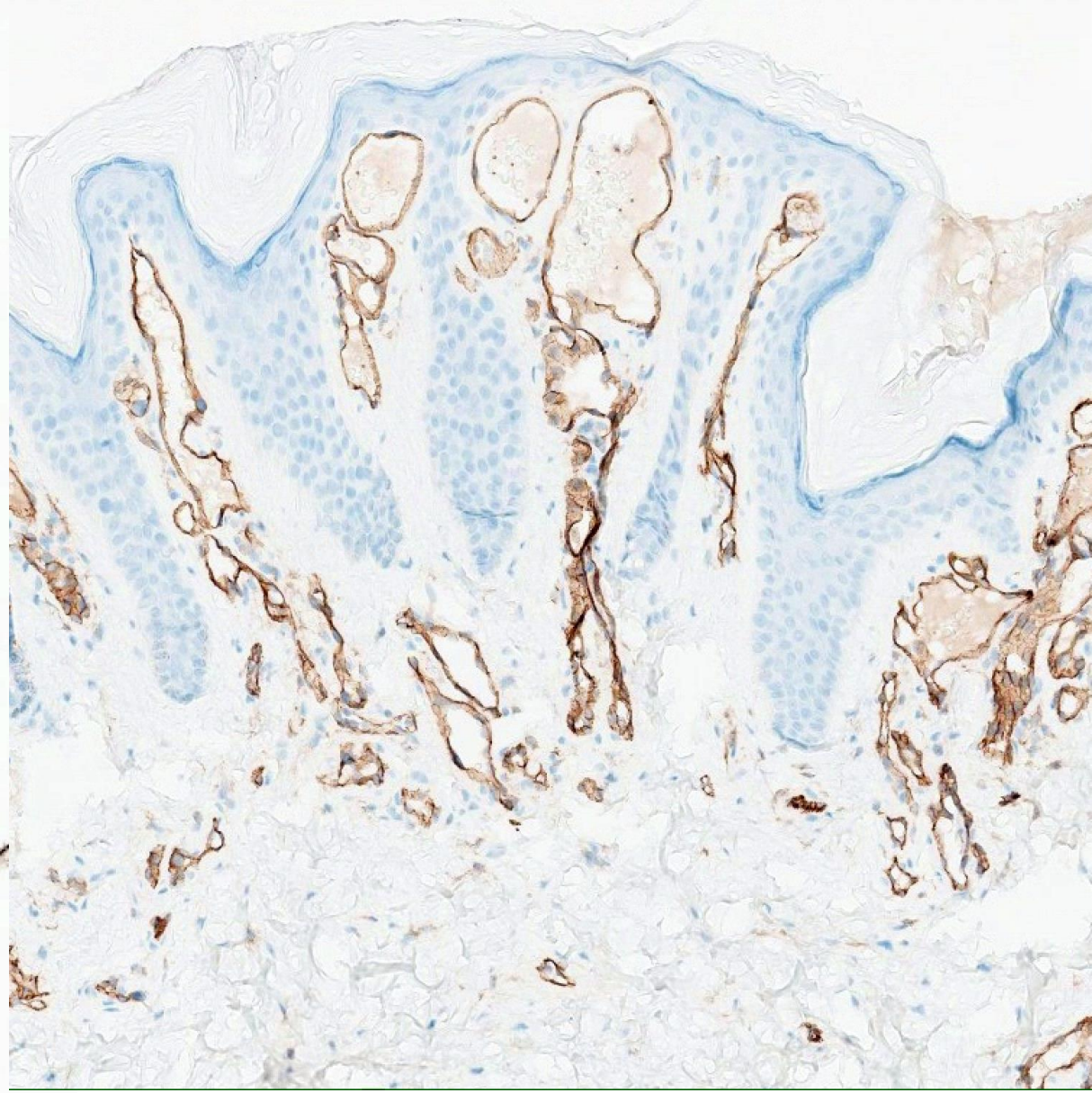






15-year-old male, Right Wrist
Ganglion cyst

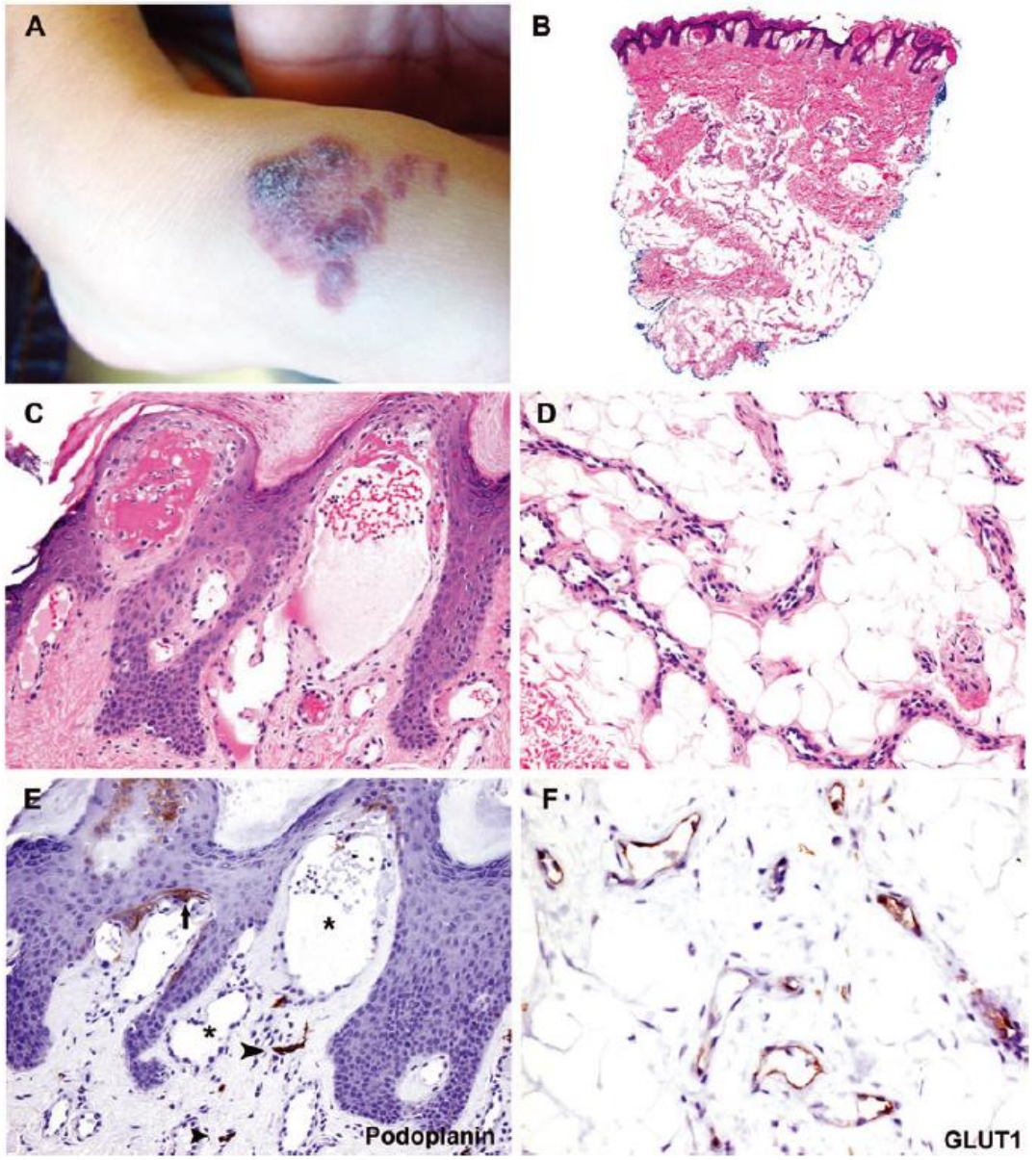




CD31+; ERG+; GLUT1-

VERRUCOUS VENOUS MALFORMATION (VERRUCOUS HEMANGIOMA)

- *MAP3K3* missense somatic mutation
- Resembles angiokeratoma (superficially)
  - Dilated, congested capillaries push up into dermis
  - Papillomatosis, acanthosis, hyperkeratosis (verrucous)
  - Subcutaneous component numerous capillaries
- DDX: angiokeratoma, infantile hemangioma (GLUT1+)
- IHC: GLUT1- (focal+), WT1±



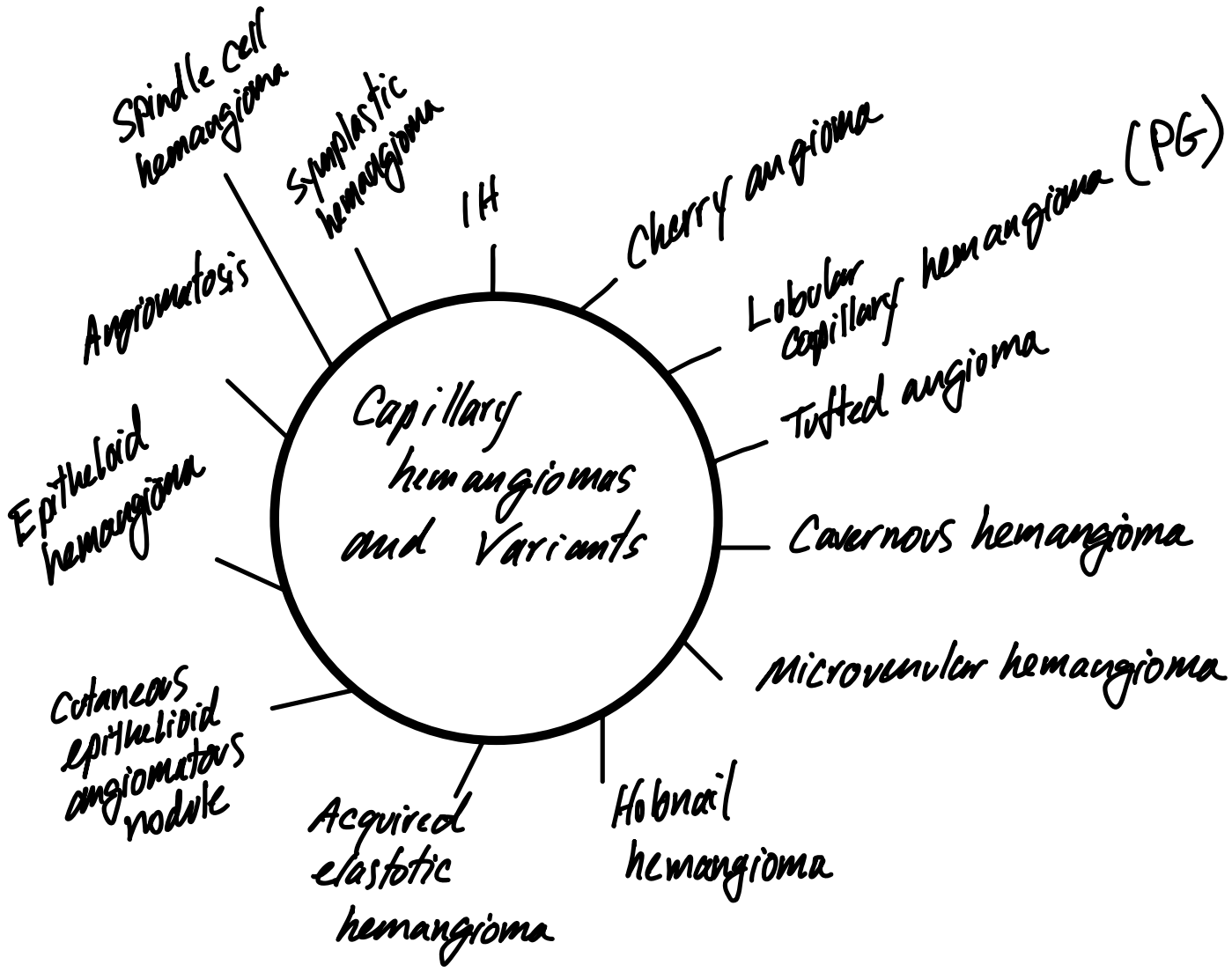
Verrucous hemangioma. Clairwood, Bruckner & Dadras. *JCP* 2011
Lucile-Packard Vascular Anomaly Clinic

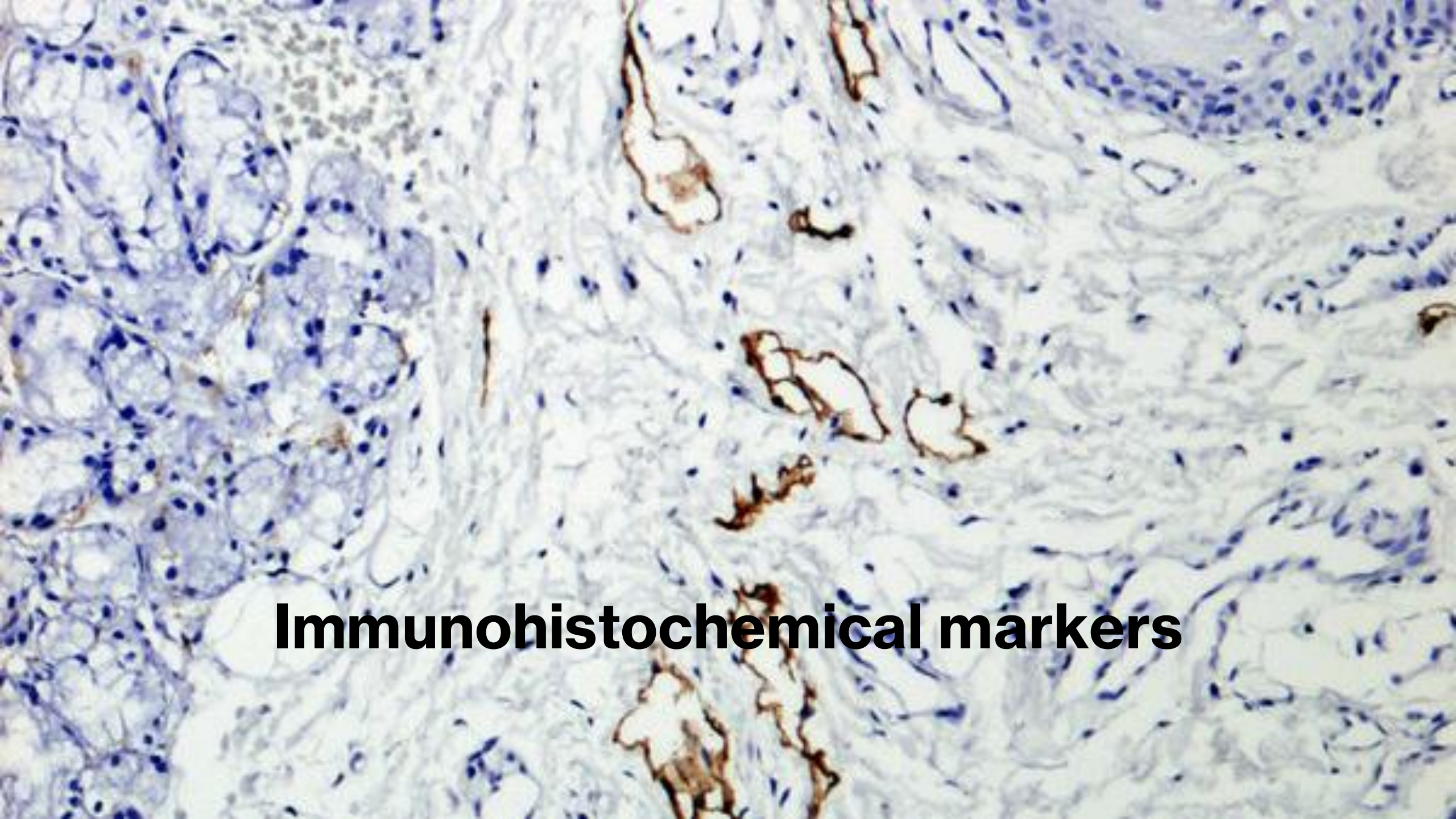
How are vascular neoplasms classified? (clinical context)

Benign	Hemangioma, e.g., Infantile hemangioma, TA
Borderline	Hemangioendothelioma, e.g., Epithelioid hemangioendothelioma, KHE, KS
Malignant	Angiosarcoma, epithelioid hemangioendothelioma

‘CAPILLARY HEMANGIOMAS’

- Avoid diagnostic term ‘hemangioma’
- Confusing
- Non-specific
- Provides no prognostic information





Immunohistochemical markers

Podoplanin (D2-40)

- Commercially available, most used lymphatic marker

Vascular Biology, Atherosclerosis and Endothelium Biology

Up-Regulation of the Lymphatic Marker Podoplanin, a Mucin-Type Transmembrane Glycoprotein, in Human Squamous Cell Carcinomas and Germ Cell Tumors

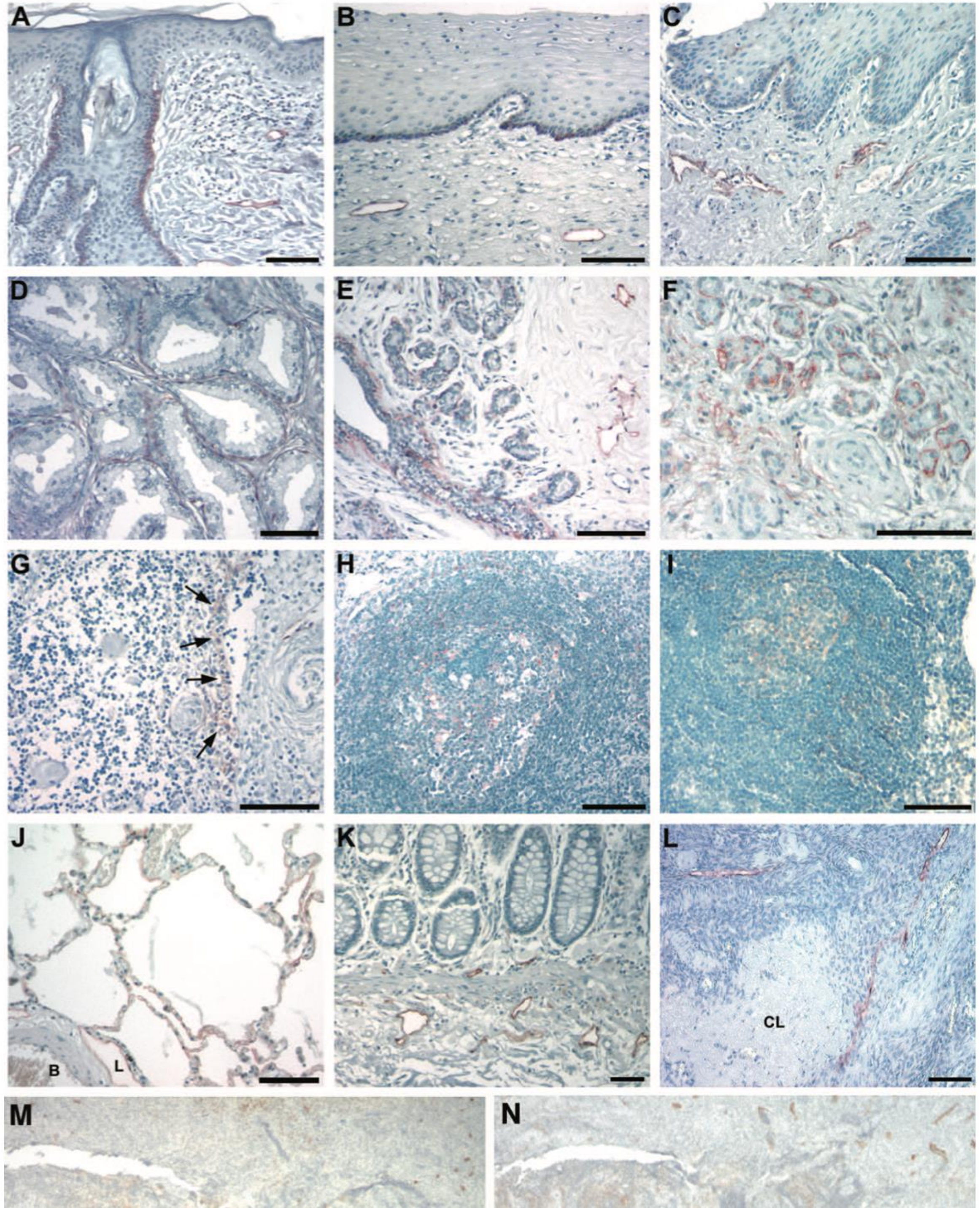
Vivien Schacht,* Soheil S. Dadras,*† Louise A. Johnson,‡ David G. Jackson,‡ Young-Kwon Hong,* and Michael Detmar*§

From the Cutaneous Biology Research Center and the Department of Pathology,† Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts; the Weatherall Institute of Molecular Medicine,‡ John Radcliffe Hospital, Headington, Oxford, United Kingdom; and the Institute of Pharmaceutical Sciences,§ Swiss Federal Institute of Technology Zurich, Zurich, Switzerland*

The mucin-type glycoprotein podoplanin is specifically expressed by lymphatic but not blood vascular endothelial cells in culture and in tumor-associated lymphangiogenesis, and podoplanin deficiency results in congenital lymphedema and impaired lym-

planin in tumor progression, and they also identify the first commercially available antibody for the specific staining of a defined lymphatic marker in archival human tissue sections, thereby enabling more widespread studies of tumor lymphangiogenesis in human cancers. *(Am J Pathol 2005, 166:913–921)*

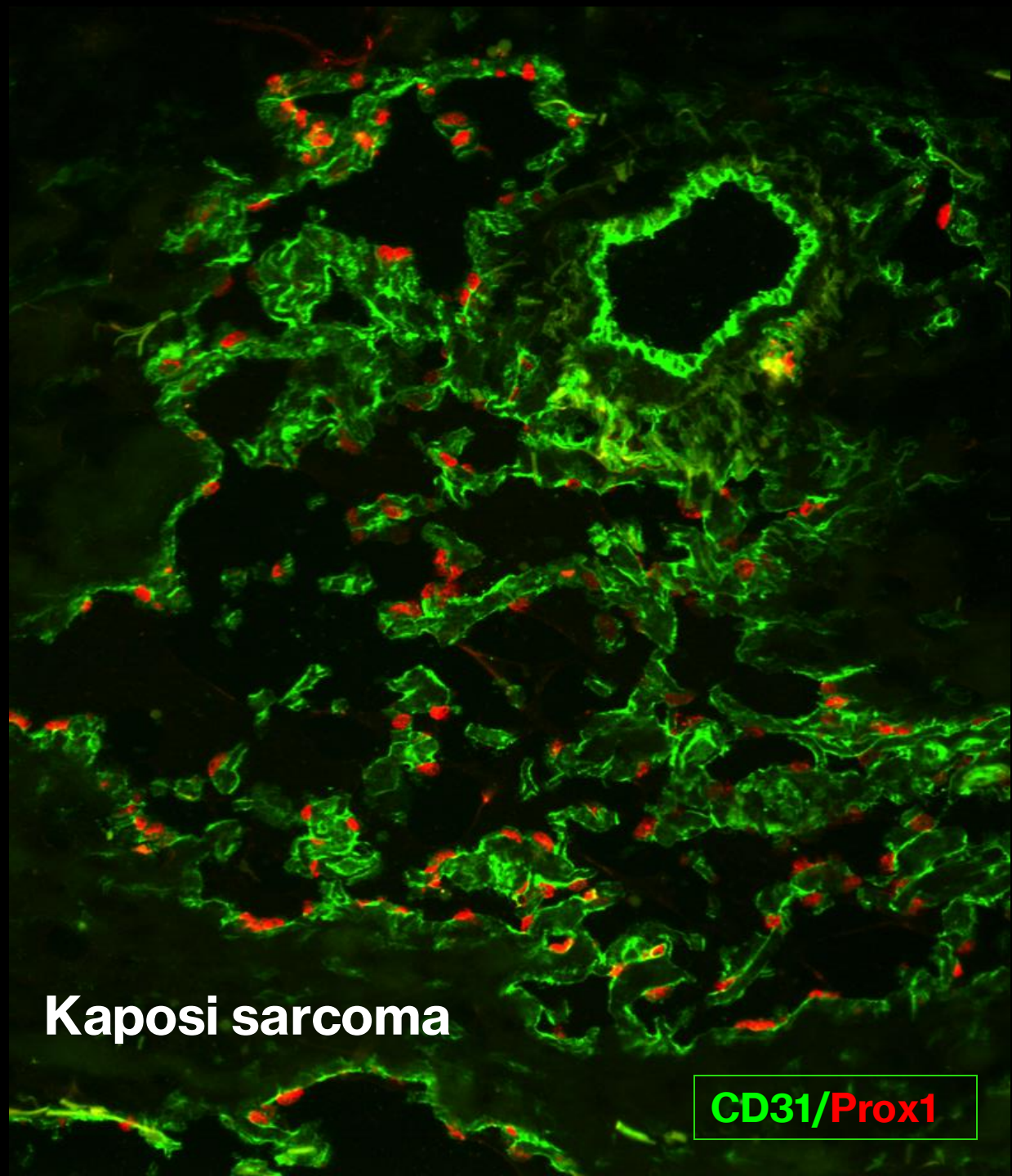
Lymphatic vessels play an important role in the maintenance of tissue homeostasis[1] and in the transport of immune cells,[2] but they also serve as the primary conduit for malignant tumor cell metastasis to regional lymph nodes.[3] Although there is considerable evidence, obtained in genetic and xenotransplant tumor models, that tumor lymphangiogenesis promotes lymphatic tumor spread,[3,4] it has remained controversial whether human tumors might actively induce lymphangiogenesis, and

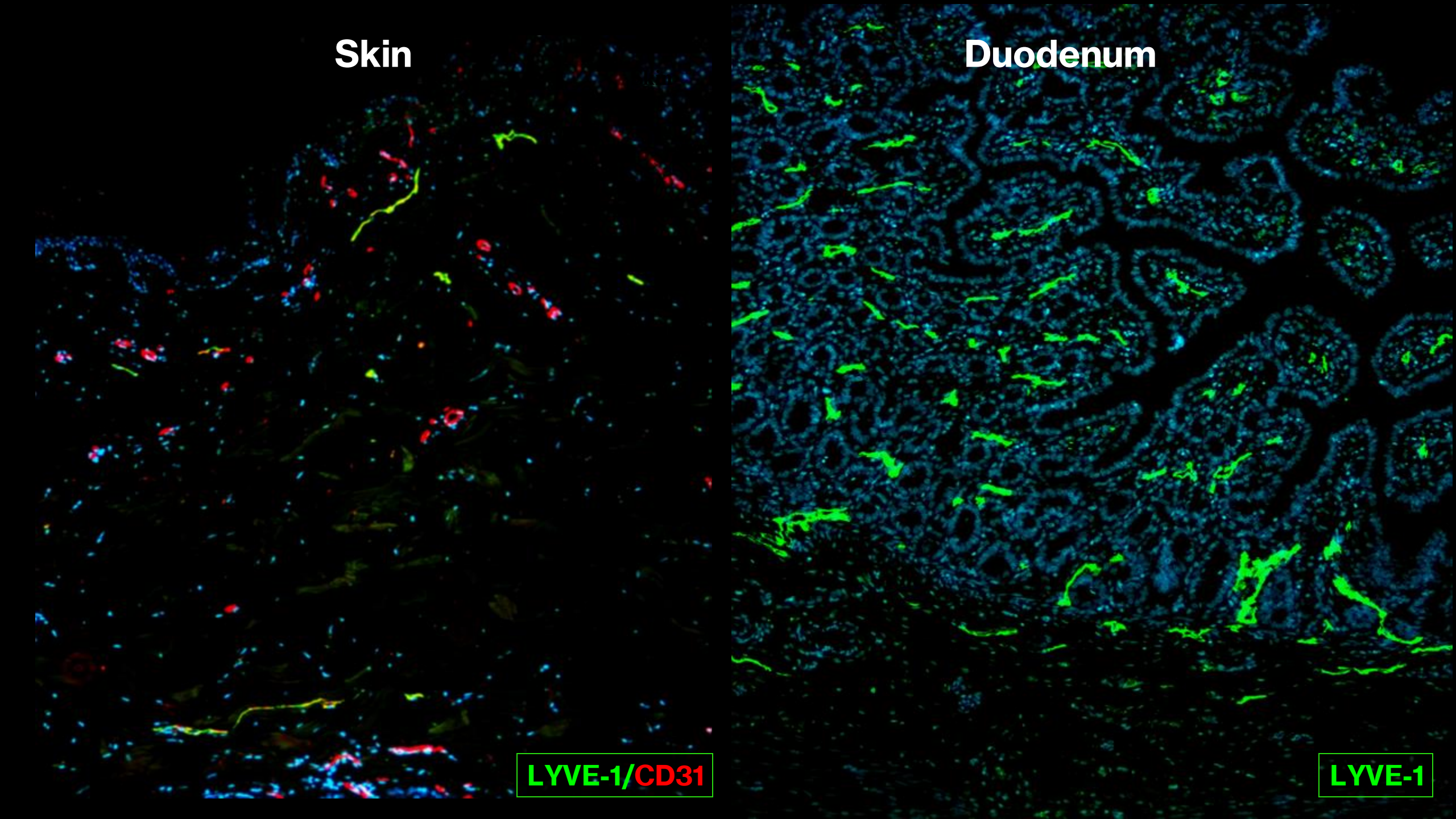


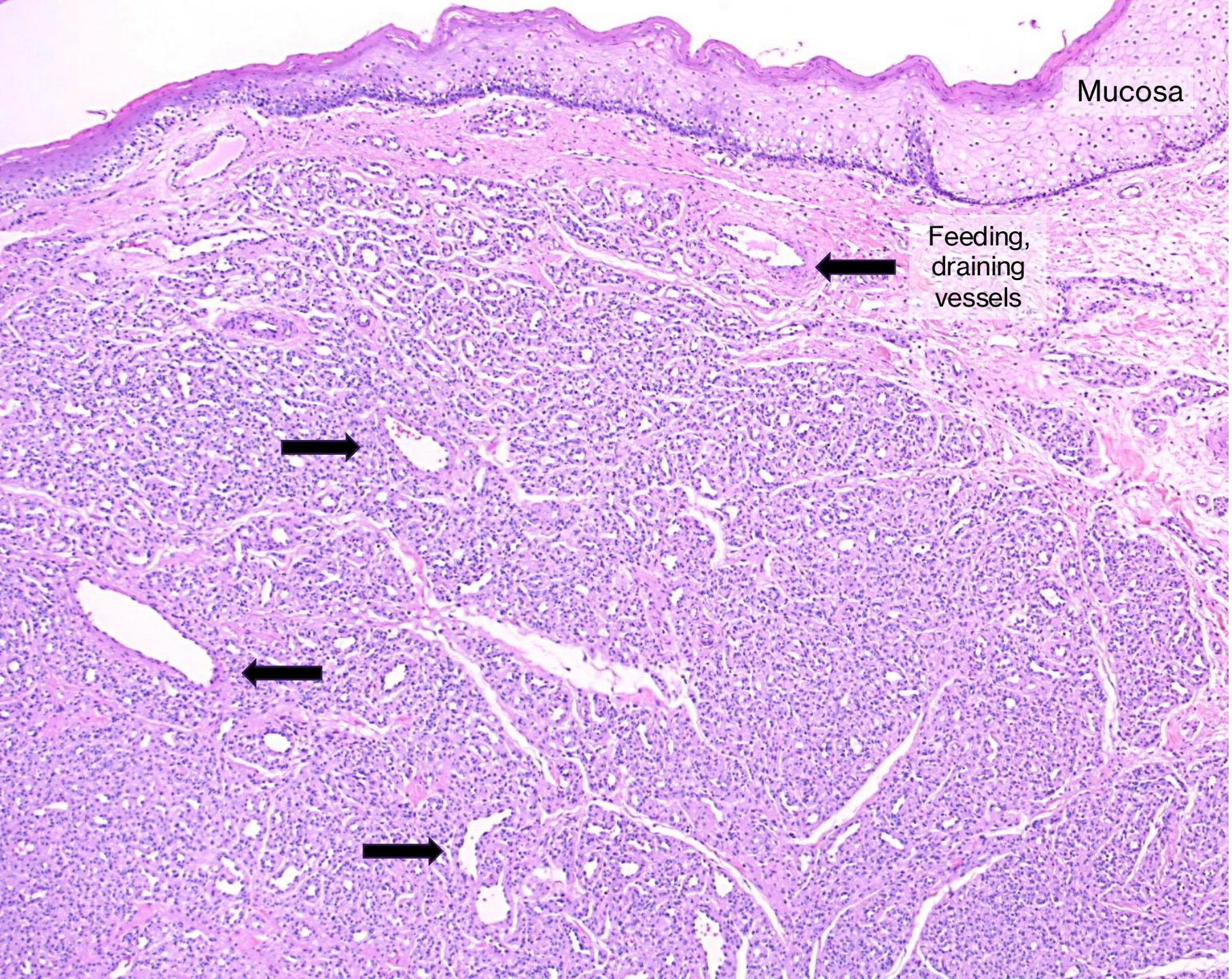
IMMUNOHISTOCHEMICAL MARKERS: BLOOD VS. LYMPHATIC

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 (D2-40)	+	-
SLC/CCL21	+	-
LYVE-1	+	-
Prox1	+	-
Panvascular		
CD31 (PECAM-1)	+	++
VEGFR-2	+	+
Factor VIII-related antigen	+	++

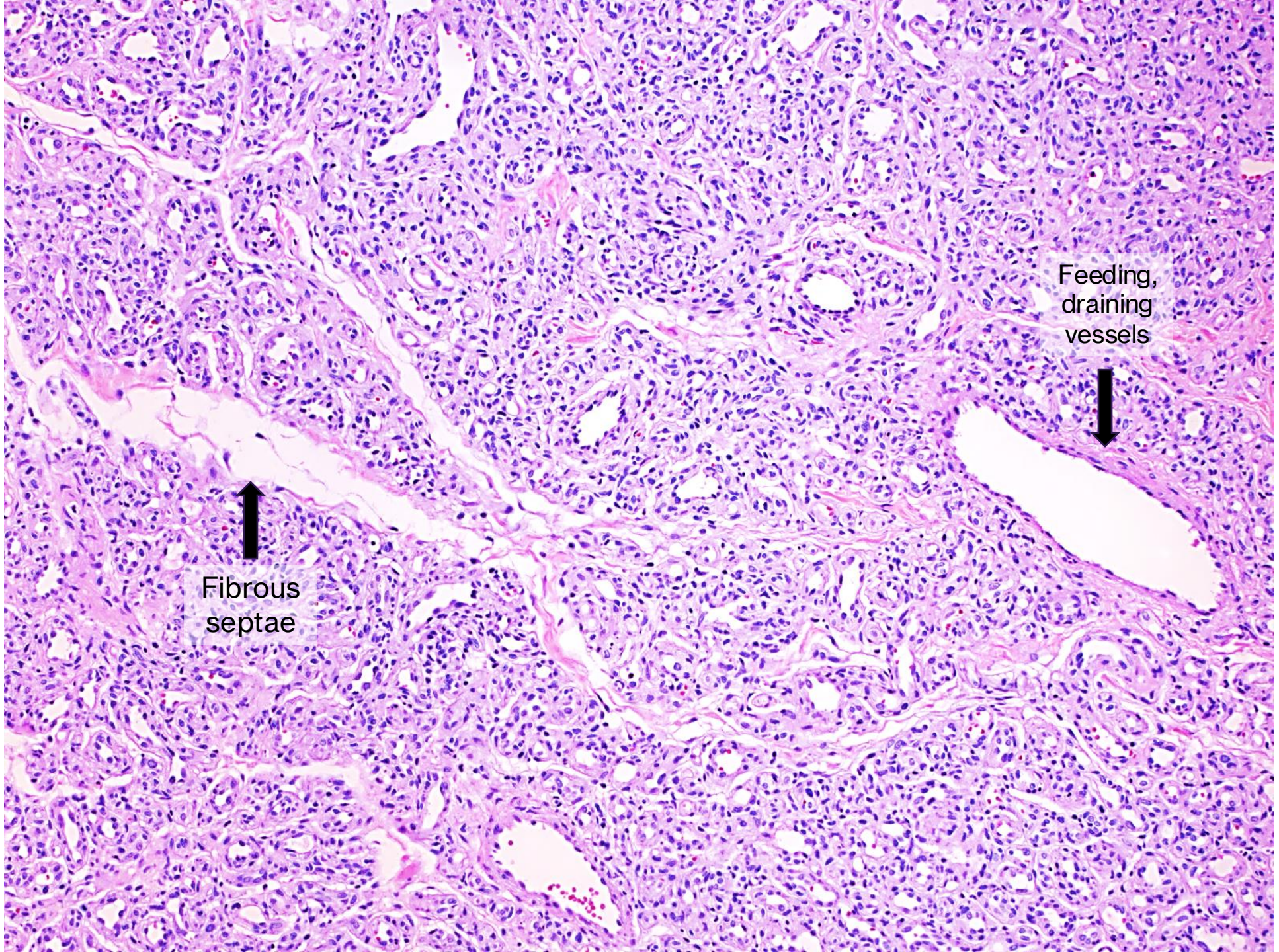
Dadras and Detmar, *Hem. Onc. of North Ame.* 2004

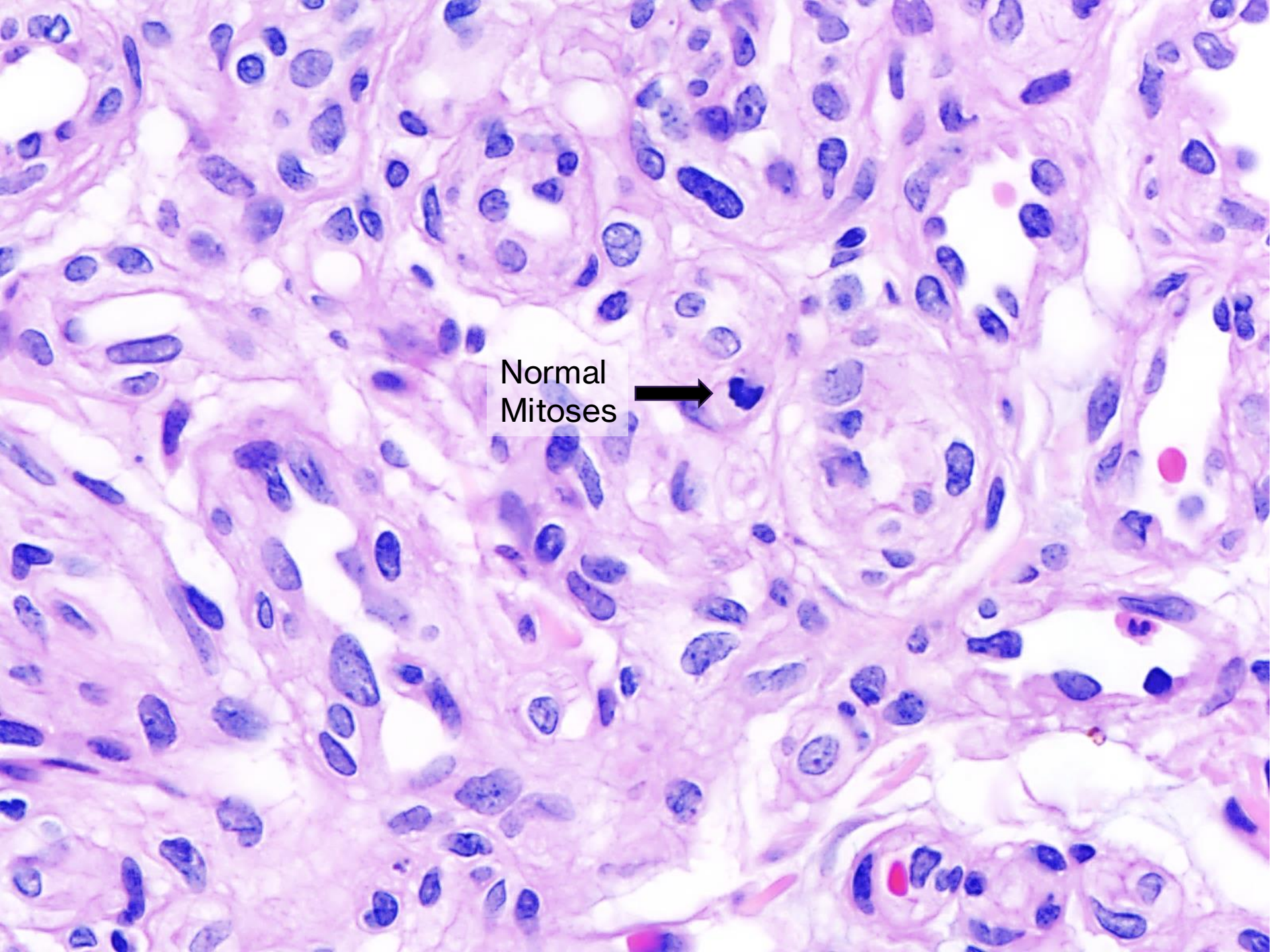



Skin
LYVE-1/CD31
Duodenum
LYVE-1



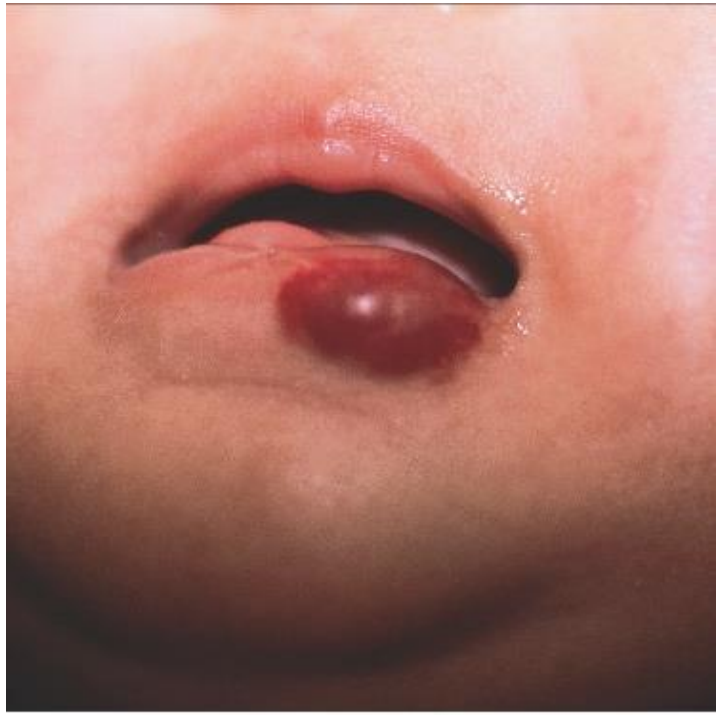
Intradermal or <u>submucosal</u>
Multinodular proliferation
Lobular configuration
Numerous, tightly packed capillary-sized blood vessels

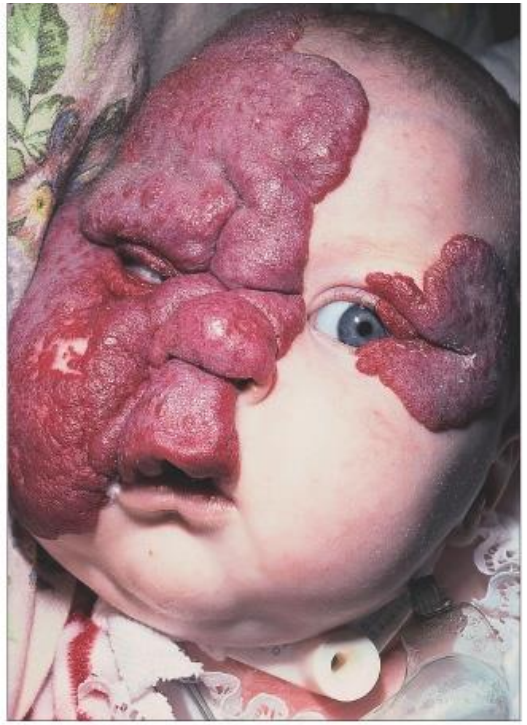

Feeding, draining vessels
Fibrous septae



Heterogenous tumor of:
Endothelial cells
Pericytes
Fibroblasts
Mast cells

INFANTILE HEMANGIOMA





- 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-

Do blood vascular tumors express lymphatic genes?

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

www.modernpathology.org

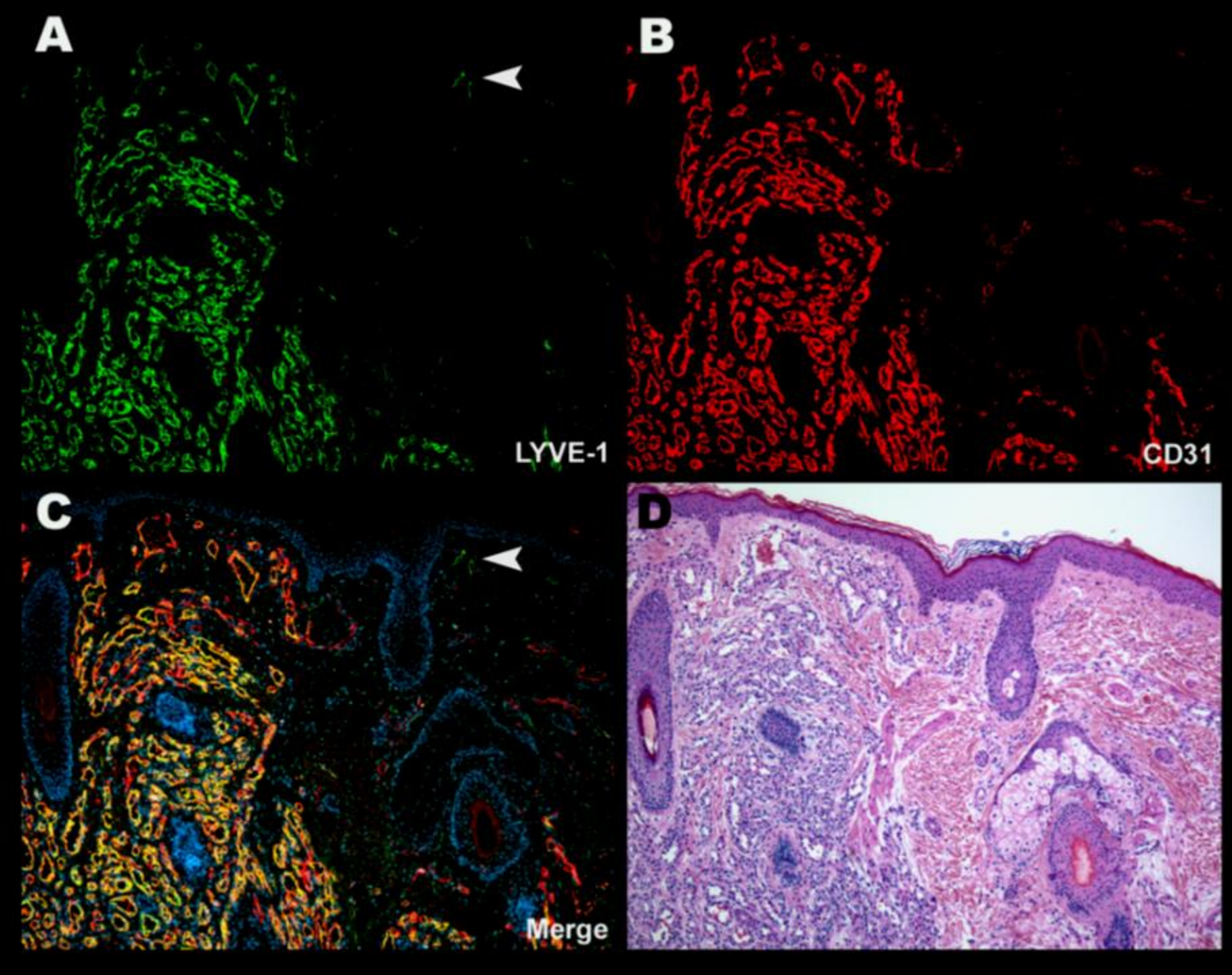
Infantile hemangiomas are arrested in an early developmental vascular differentiation state

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*

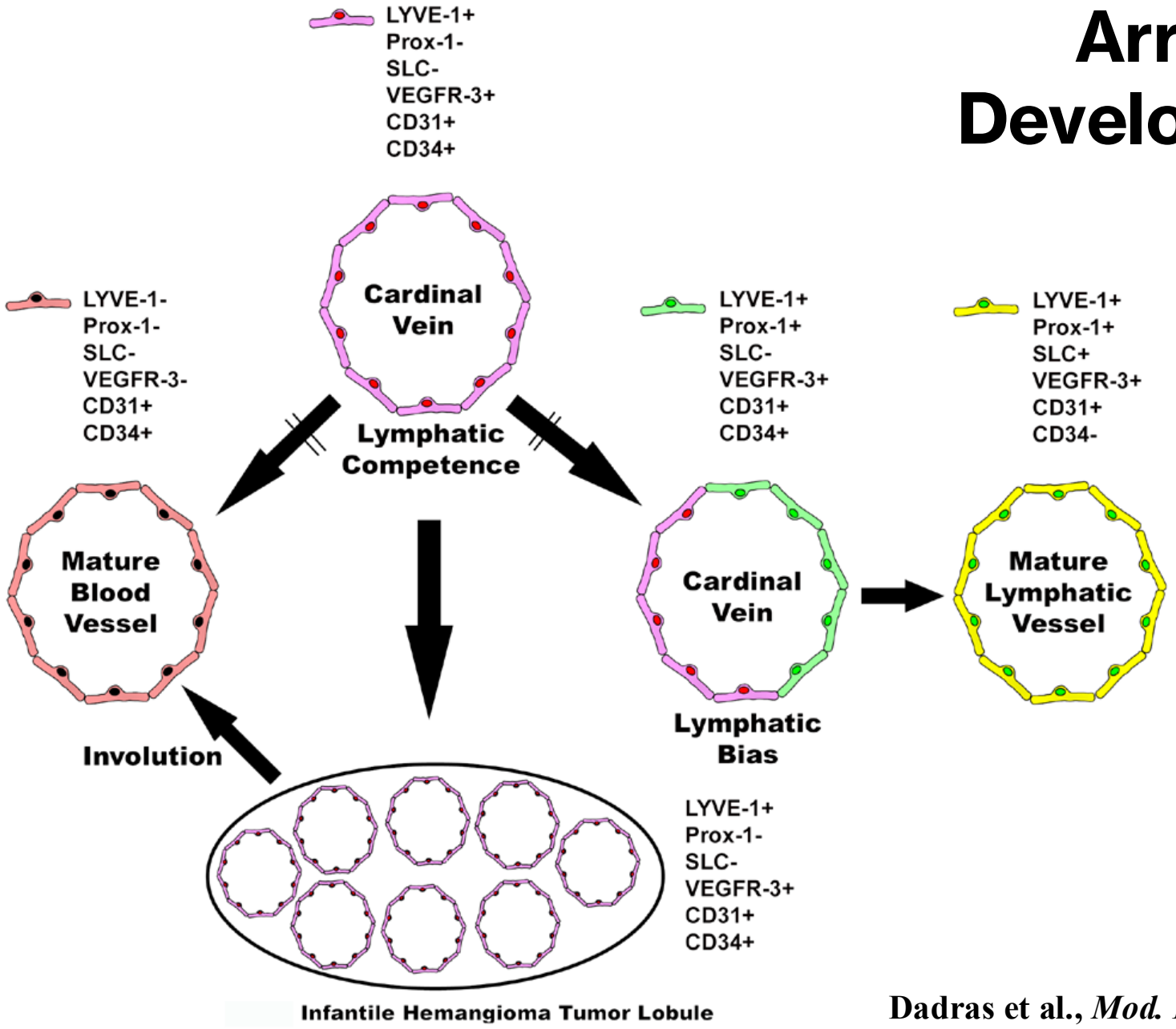
Infantile hemangiomas, the most common tumors of infancy, are vascular tumors characterized by rapid proliferation of endothelial cells during the first few months of postnatal life followed by slow spontaneous involution, whose molecular pathogenesis remains unclear. The recent identification of developmental 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

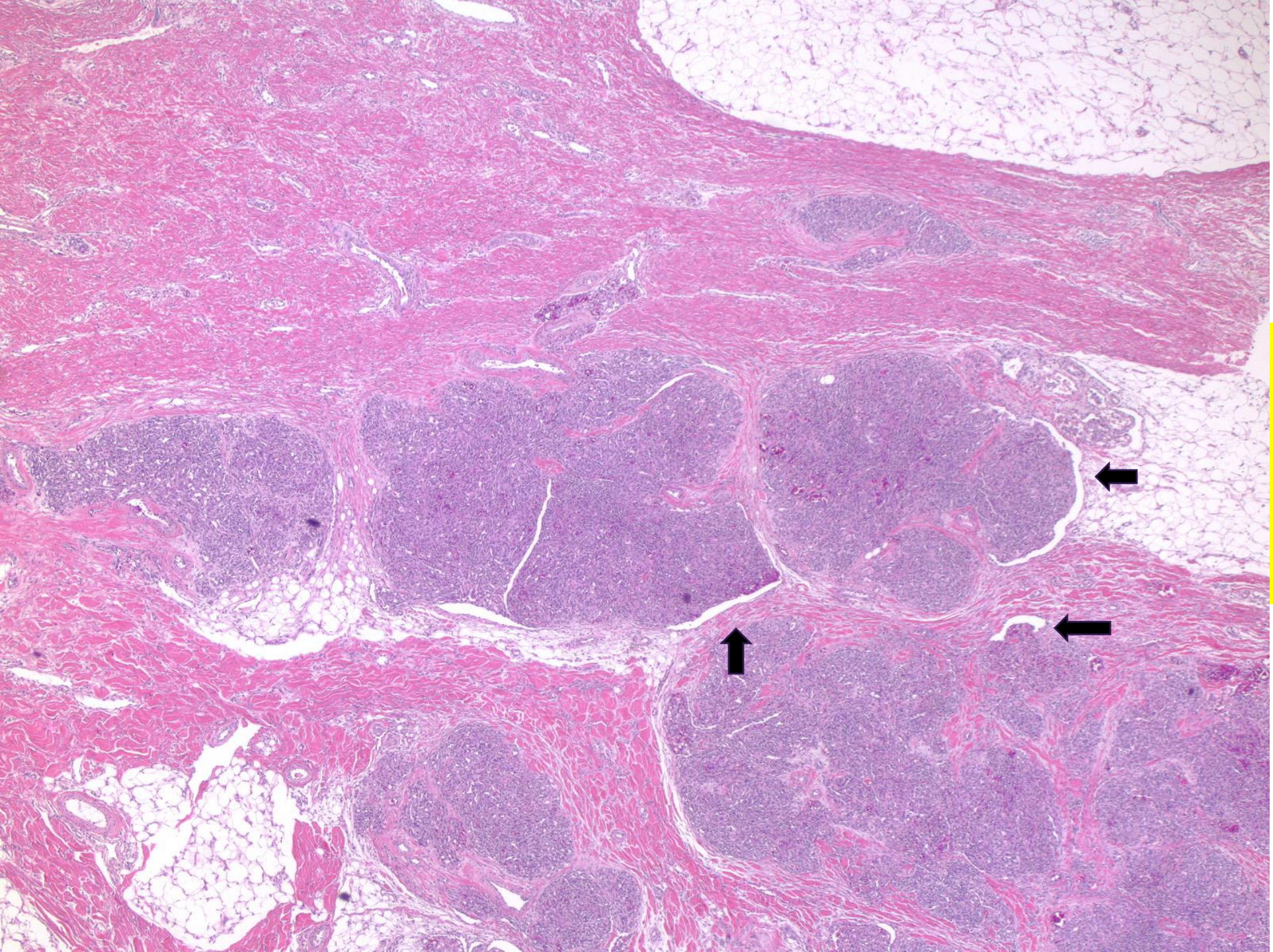


LYVE-1 Expression in Proliferating Infantile Hemangioma

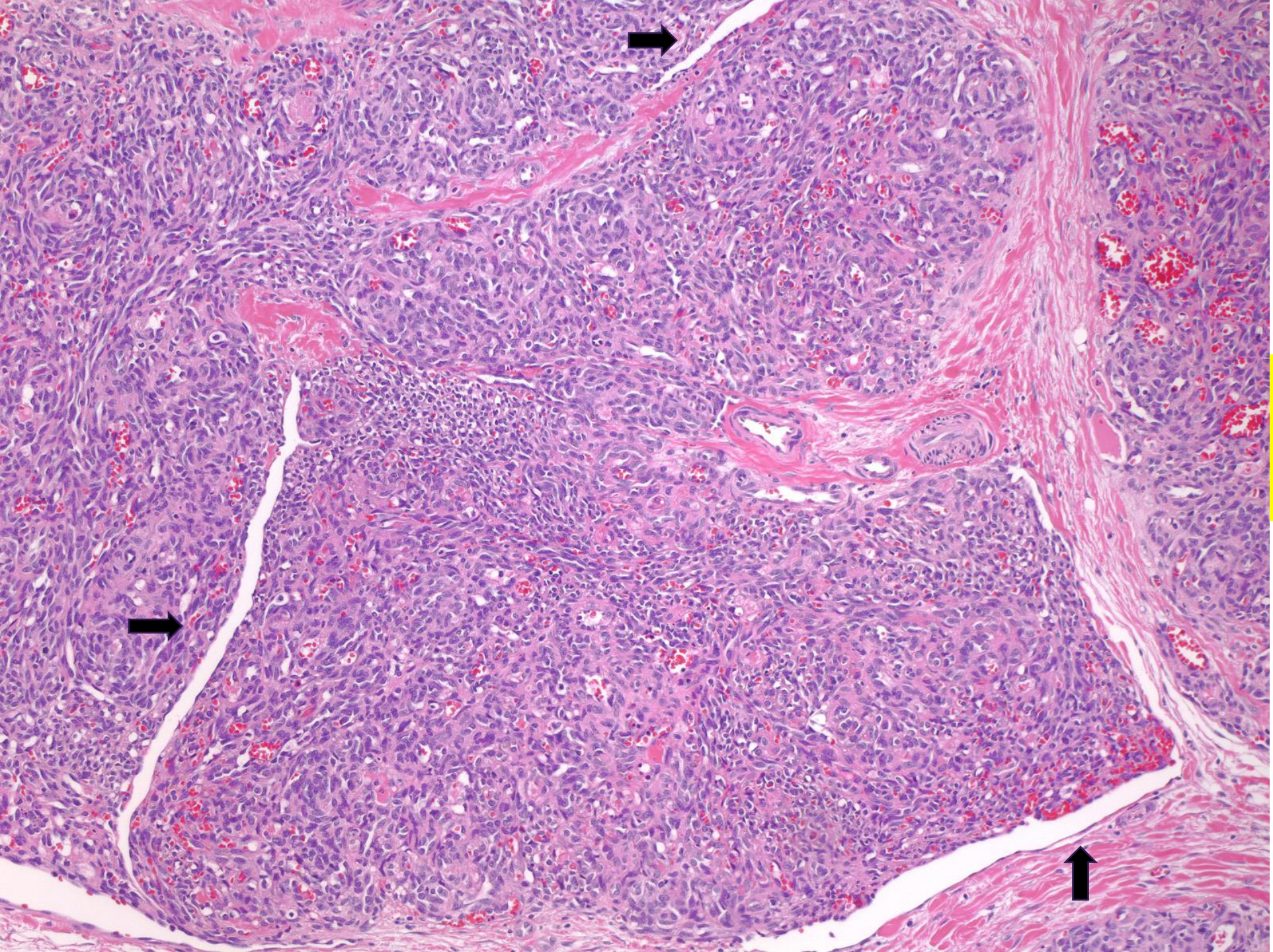
Arrested Vascular Development Hypothesis



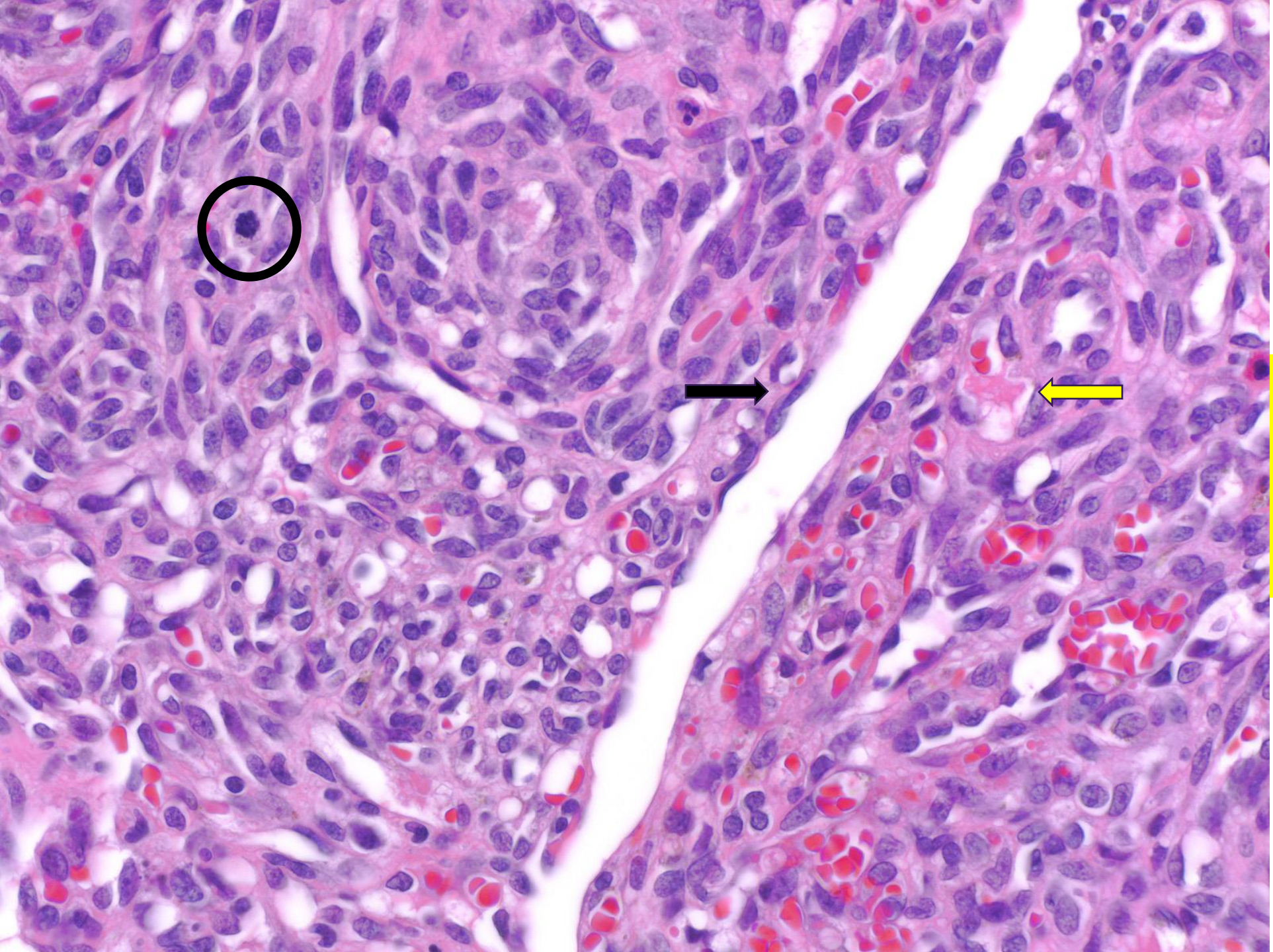
Dadras et al., *Mod. Path.* 2004



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



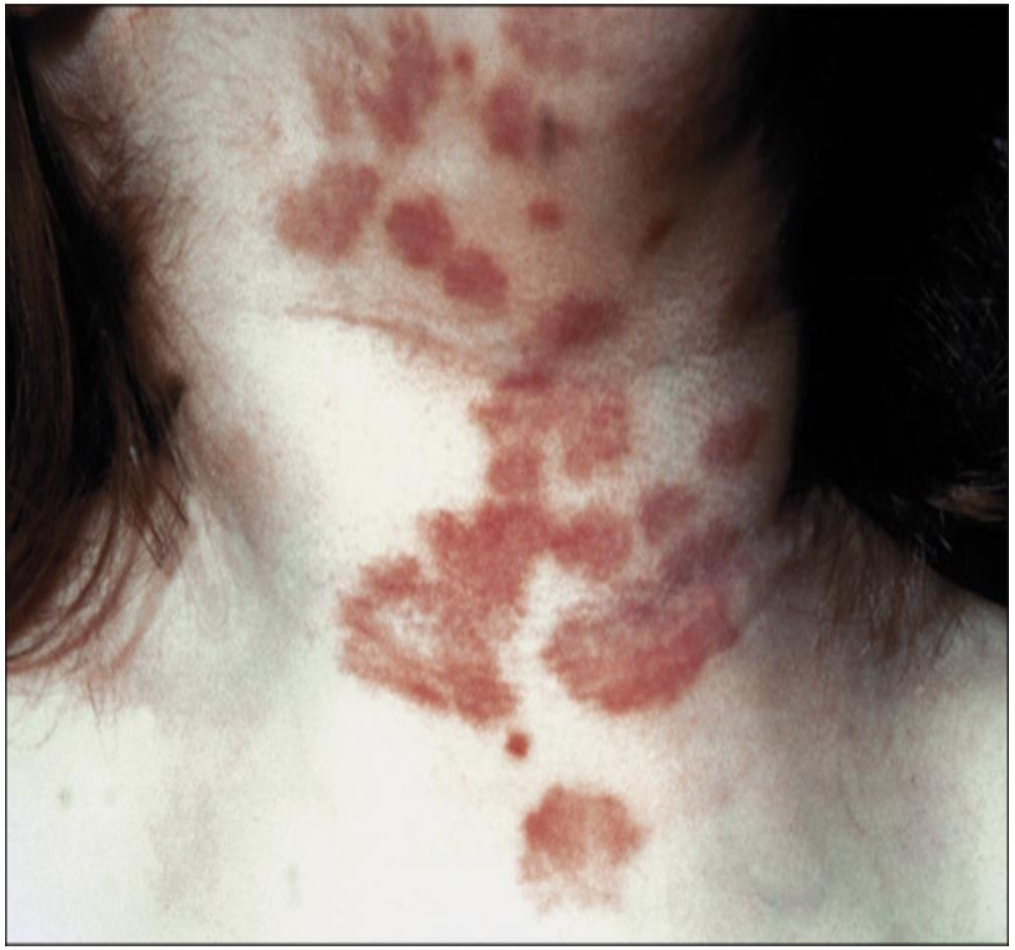
Tightly knit capillaries form tumor nodules
Peripheral crescent shaped lymphatic space



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

TUFTED ANGIOMA

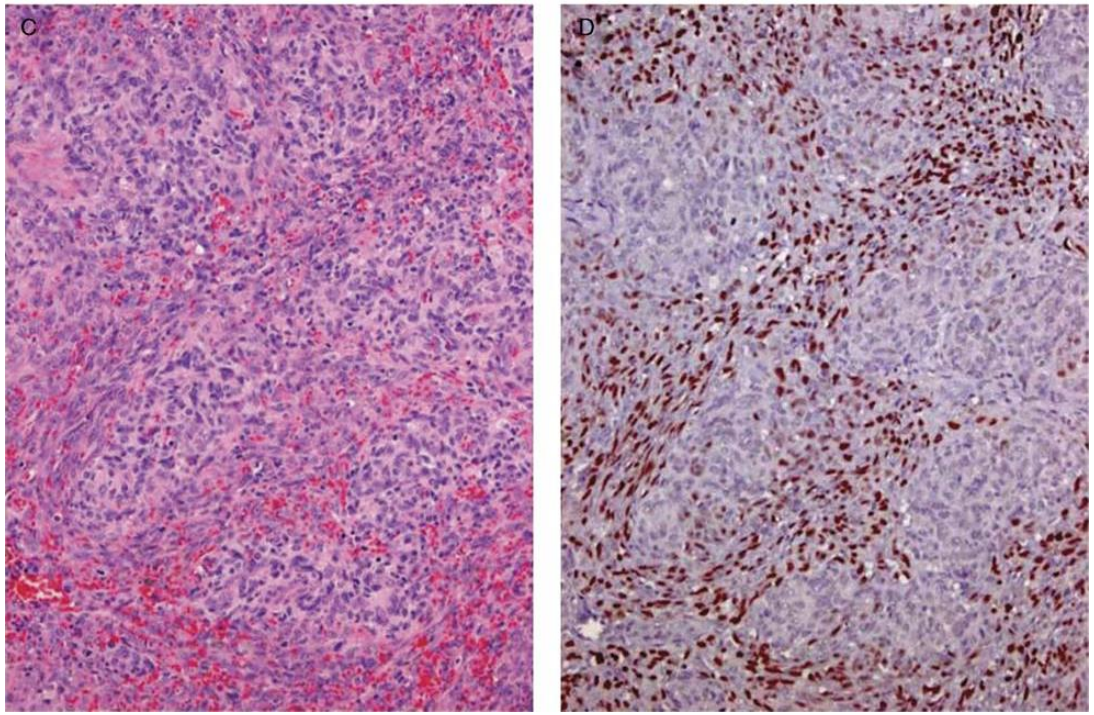
- Any age, M=F, head and neck >> limbs
- First year of life, congenital (25%)
- Macules and plaque, red-purple
- Usually benign, can be complicated by
  - Consumptive coagulopathy (Kasabach-Merritt syndrome)
- DDX: LCH (deep), Kaposi sarcoma (rare in children)
- IHC: Prox-1+, Podoplanin+



- 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

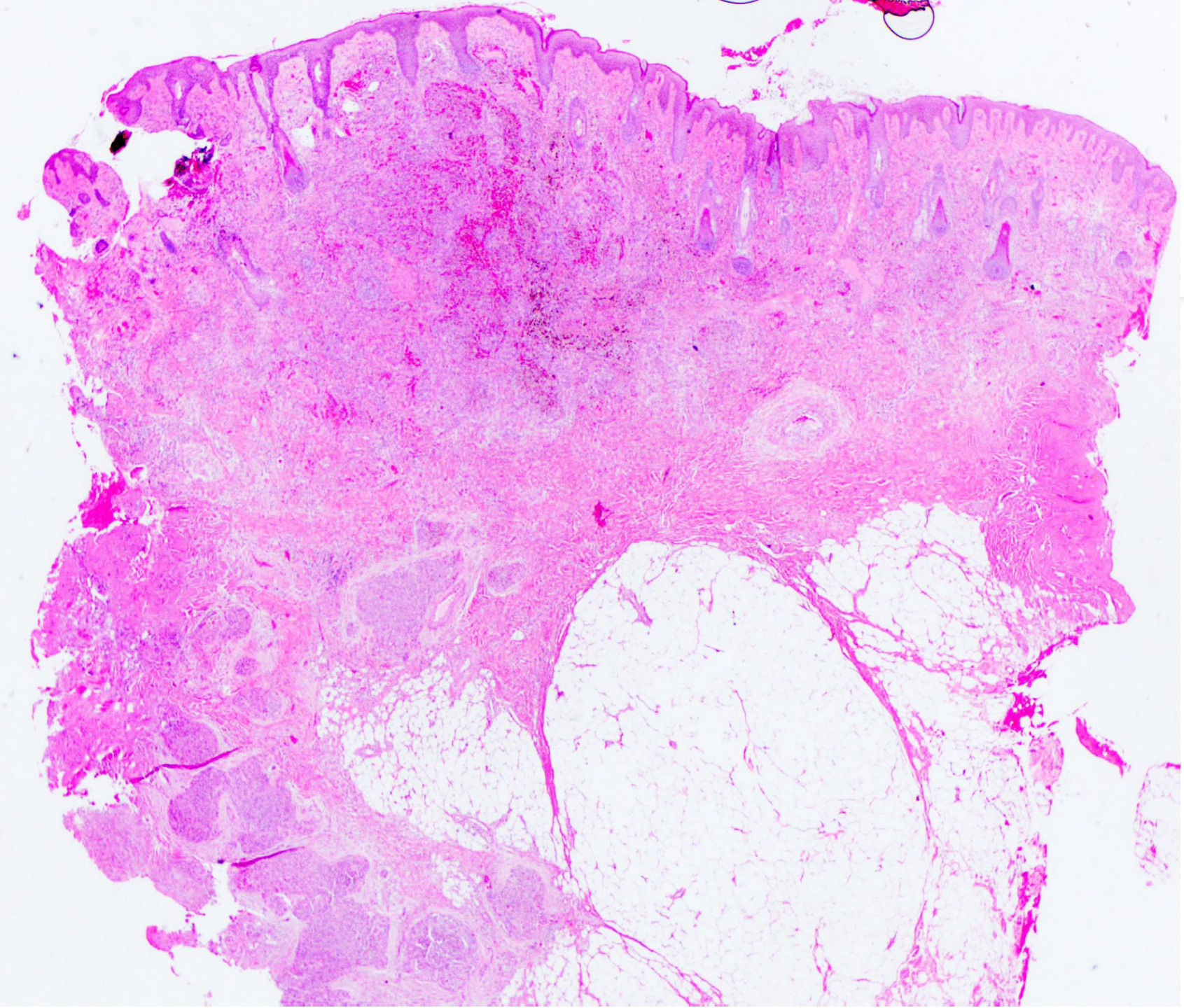
Aude Rimella Le Huu, MD,† ‡ Chris H. Jokinen, MD,§ Brian P. Ruben, MD, PhD,§ Martin C. Mihm, MD,‖ Sharon W. Weiss, MD,¶ Paula E. North, MD, PhD,# and Soheil S. Dadras, MD, PhD*†*



Glomeruloid foci (central) : Prox1 Negative

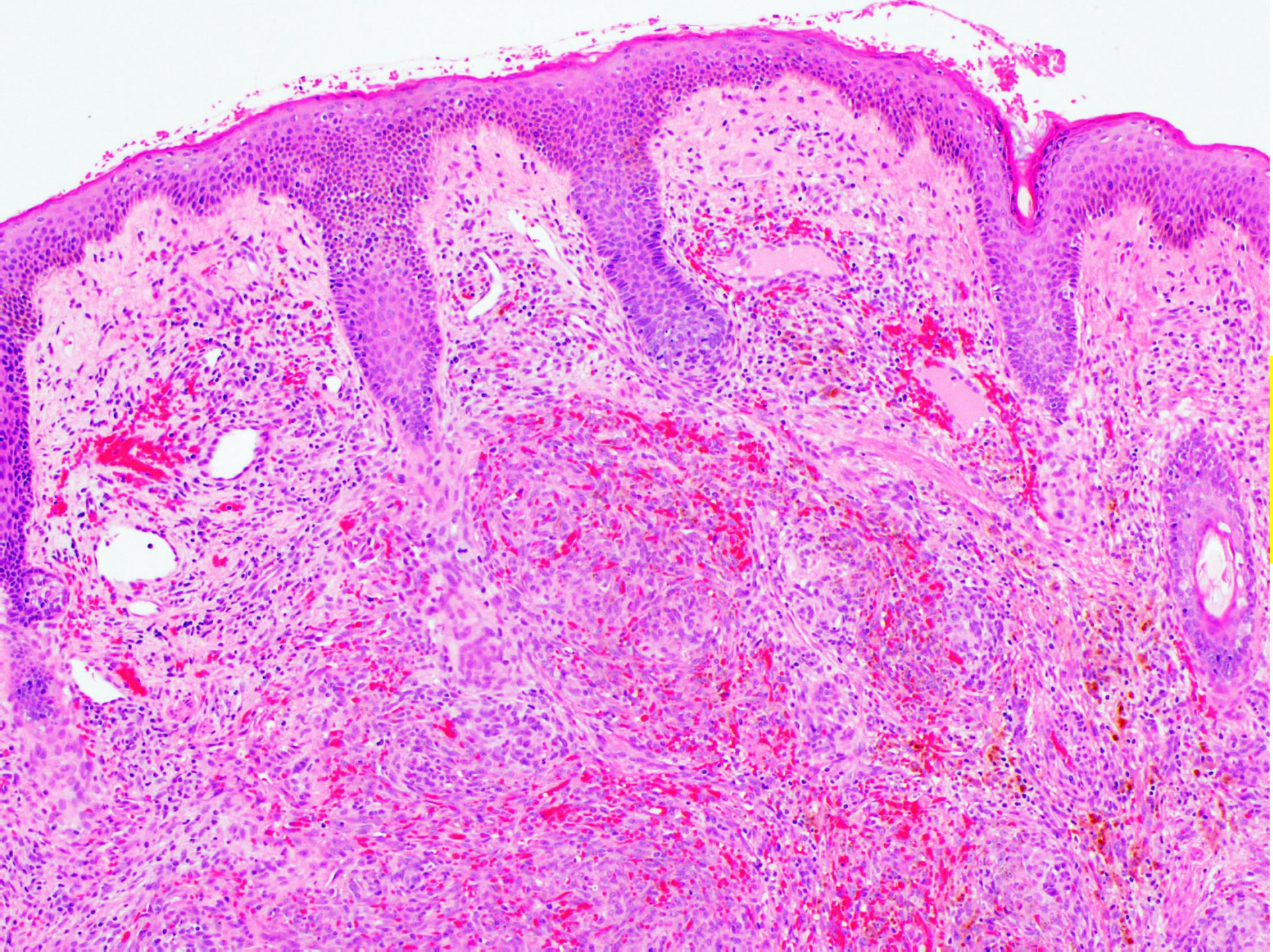
Spindle cells (peripheral): Prox1 Positive

Am. J. Surg. Pathol. 2010



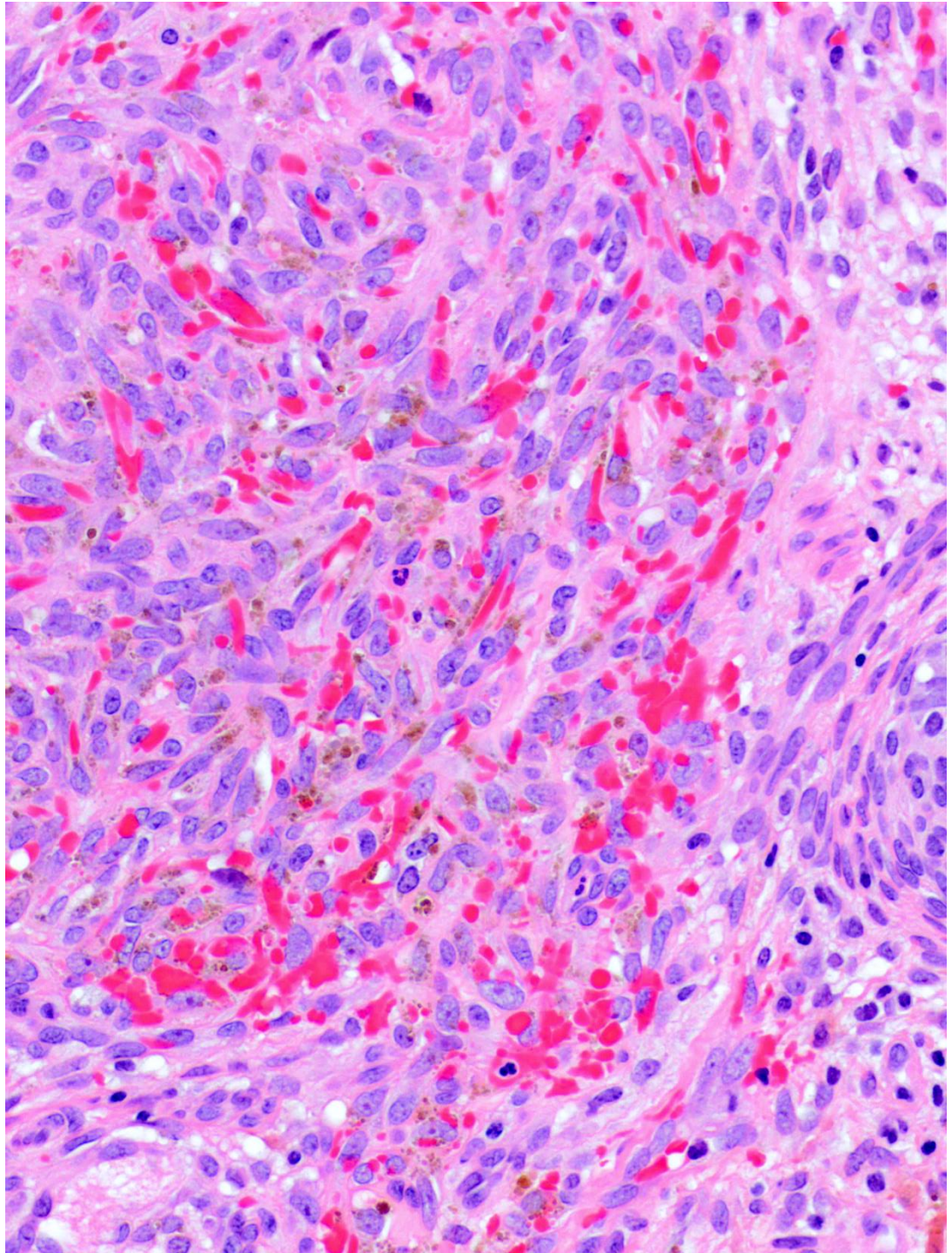
6-year-old girl with red-blue plaque on the face

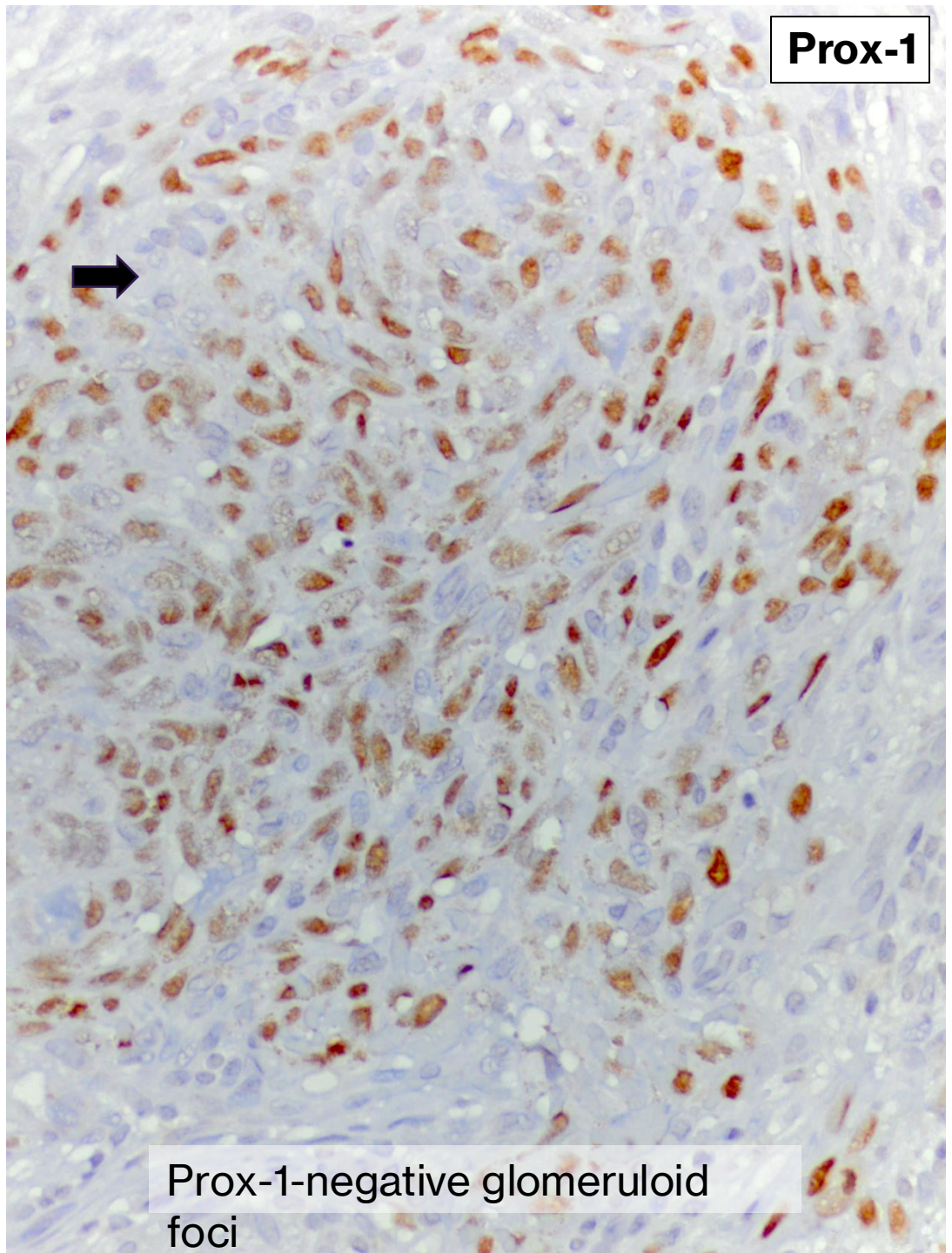
Reticular dermal and deep subcutaneous tumor nodules
Hemorrhage, hemosiderosis



Reticular dermal and deep subcutaneous tumor nodules
Hemorrhage, hemosiderosis

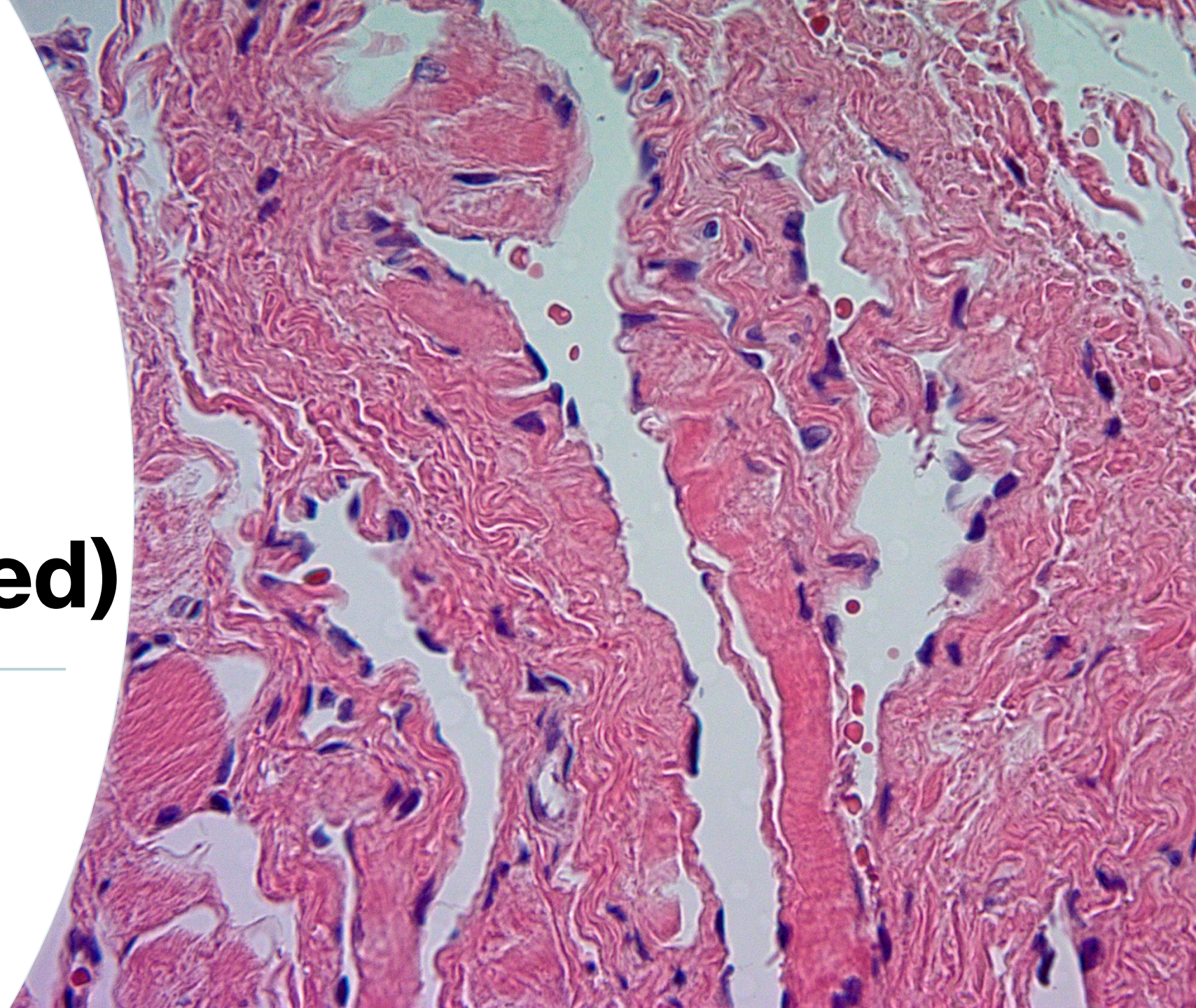
KAPSOIFORM HEMANGIOENDOTHELIOMA

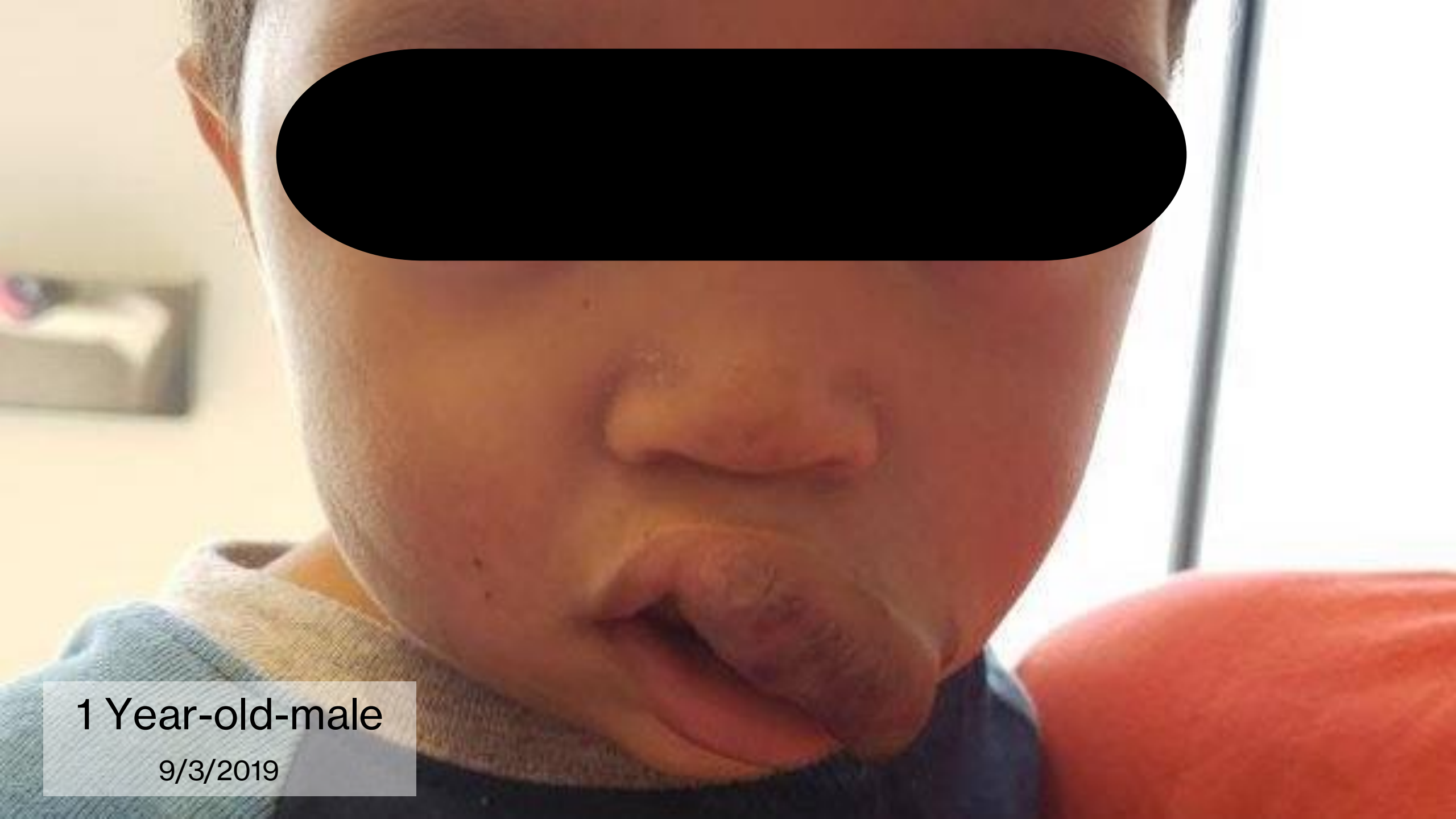


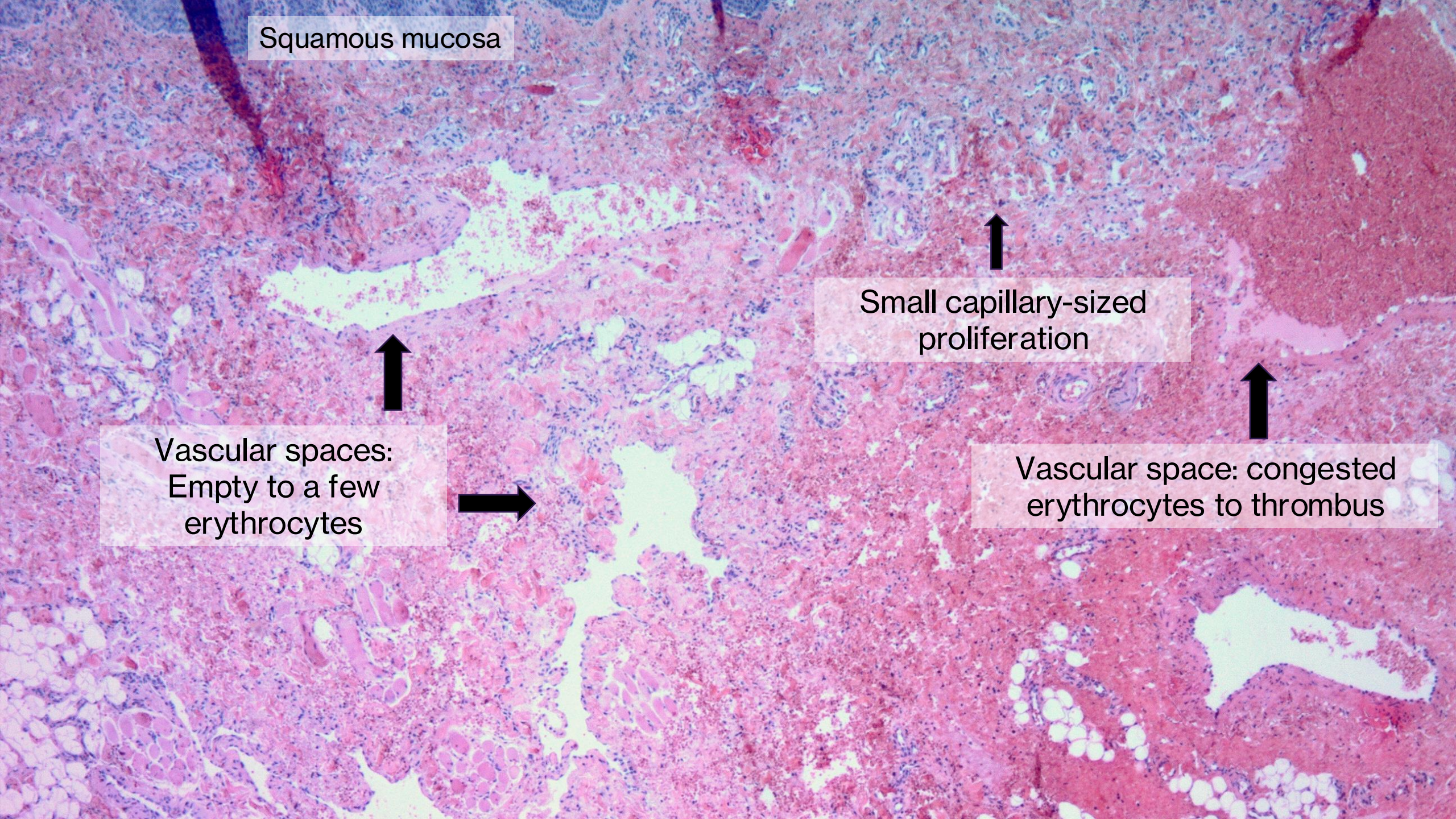


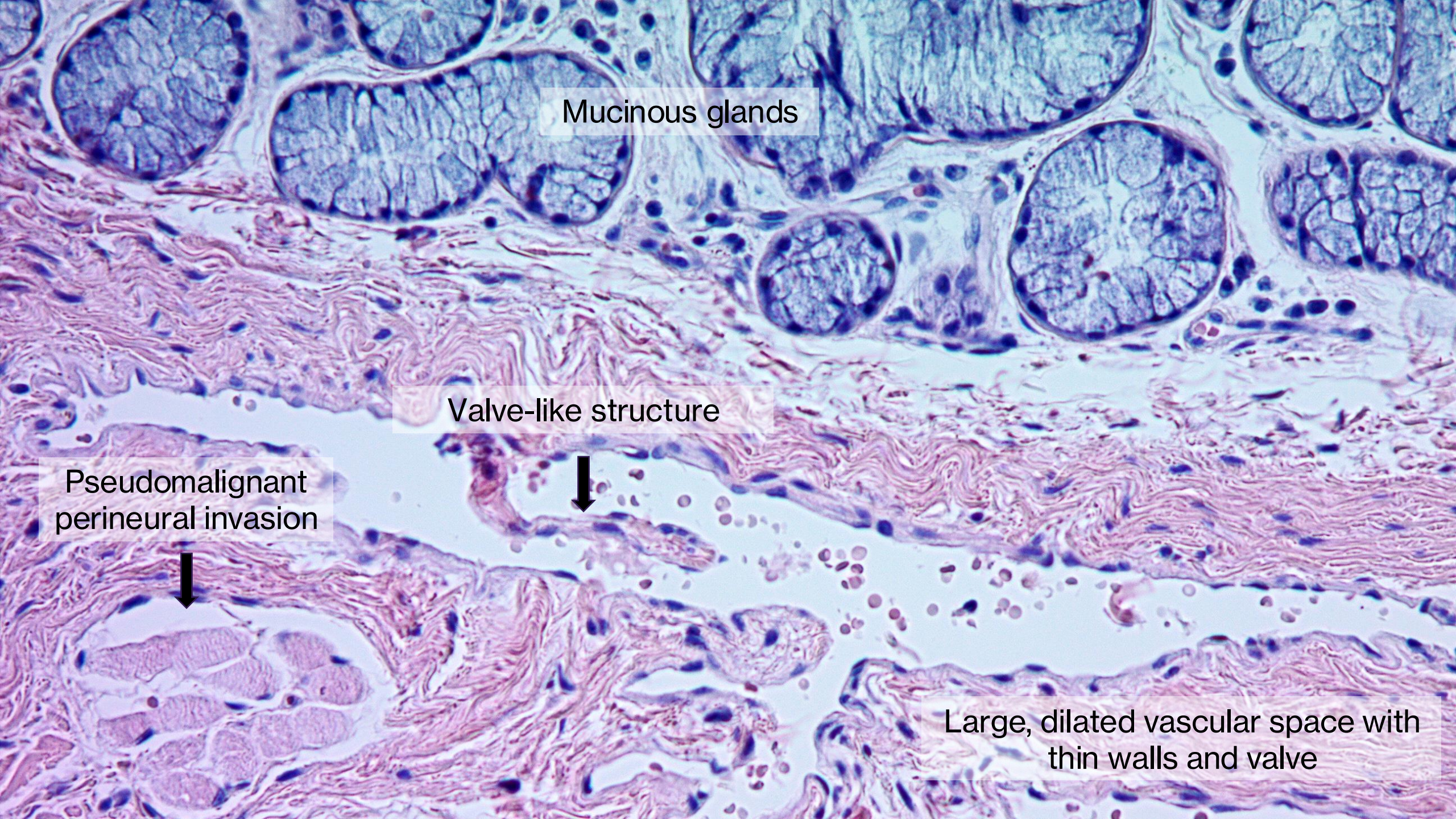
Prox-1-negative glomeruloid foci

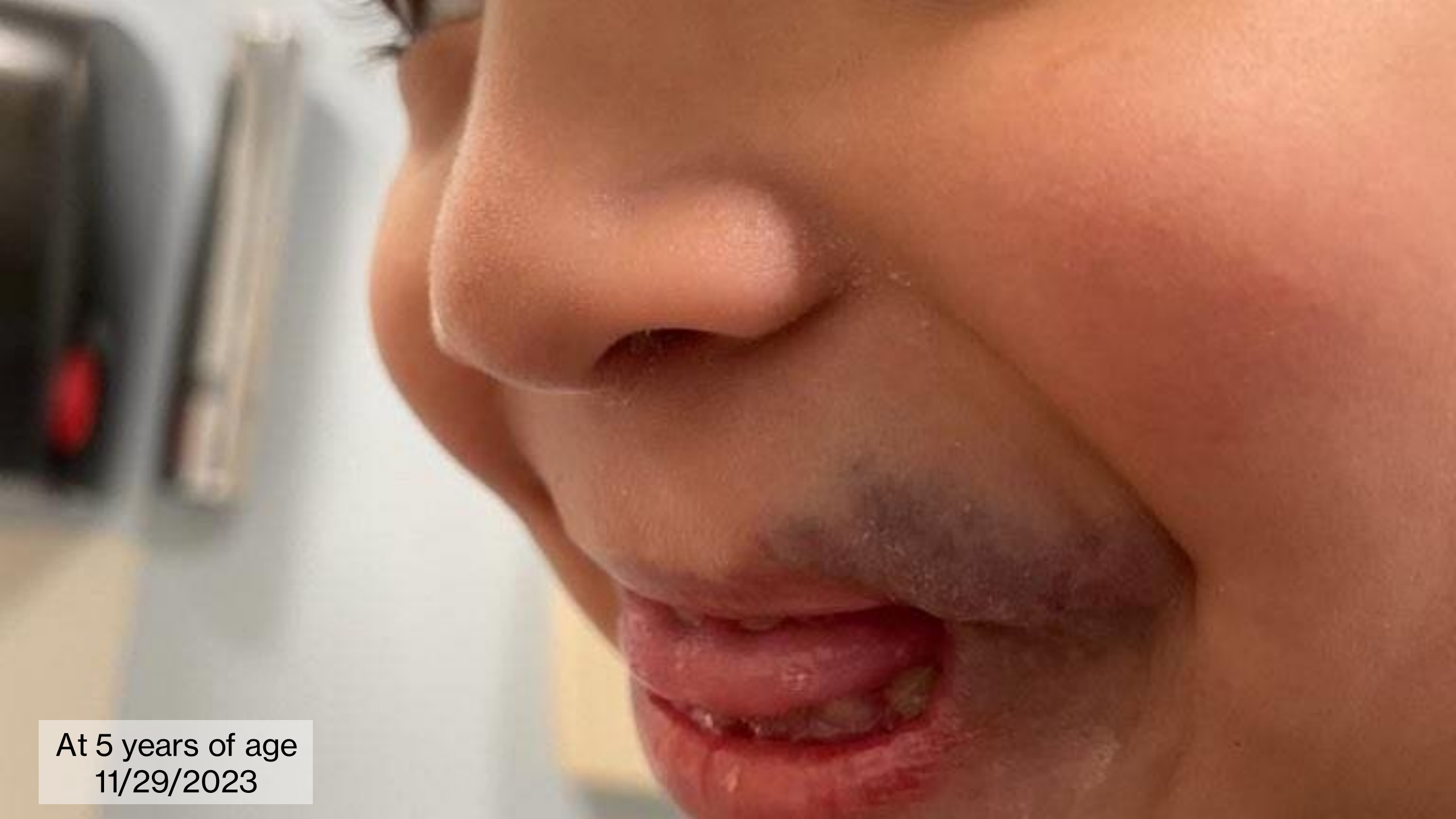
Diagnosis (misclassified)




1 Year-old-male
9/3/2019

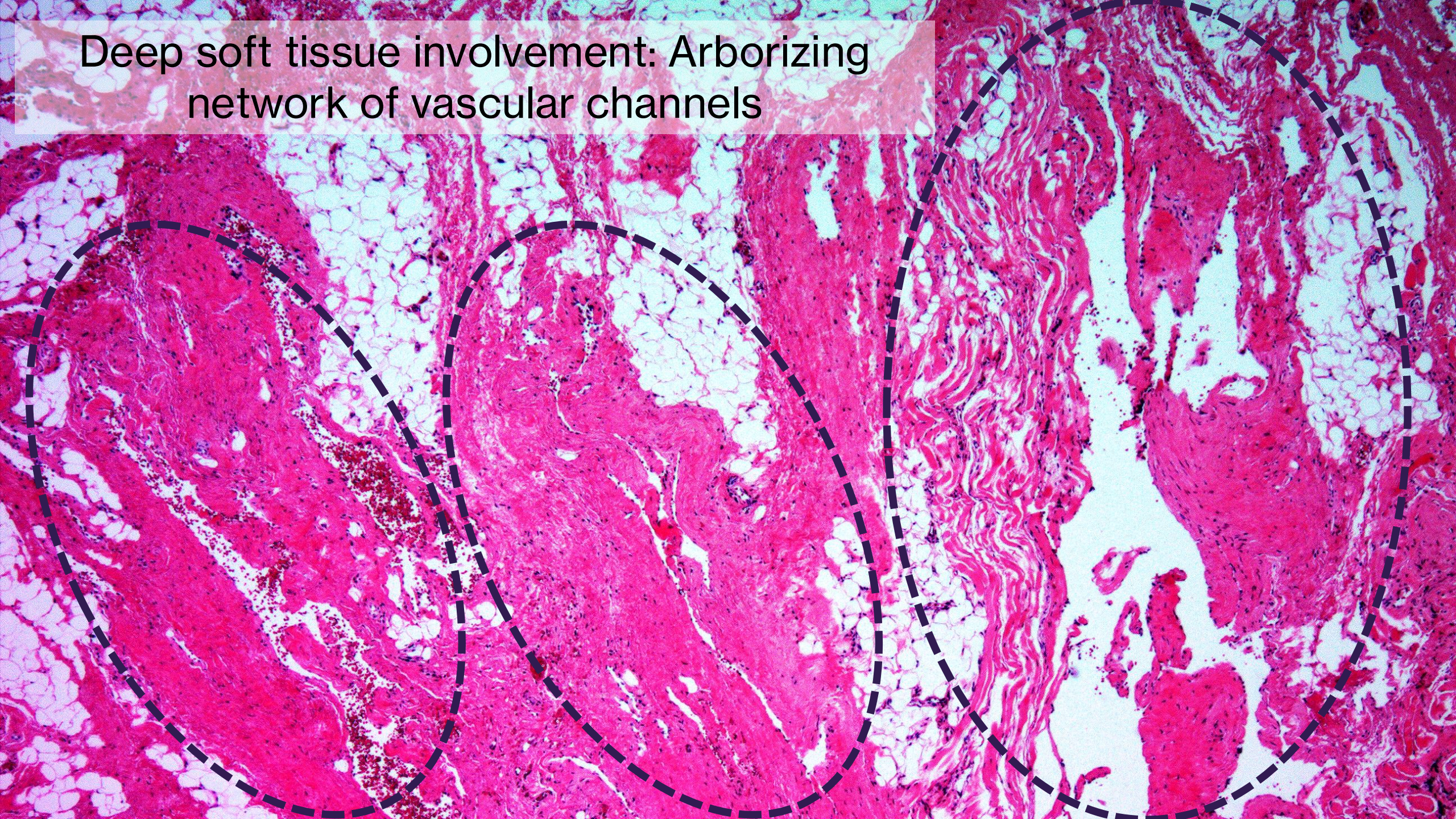

Squamous mucosa
Small capillary-sized proliferation
Vascular spaces: Empty to a few erythrocytes
Vascular space: congested erythrocytes to thrombus

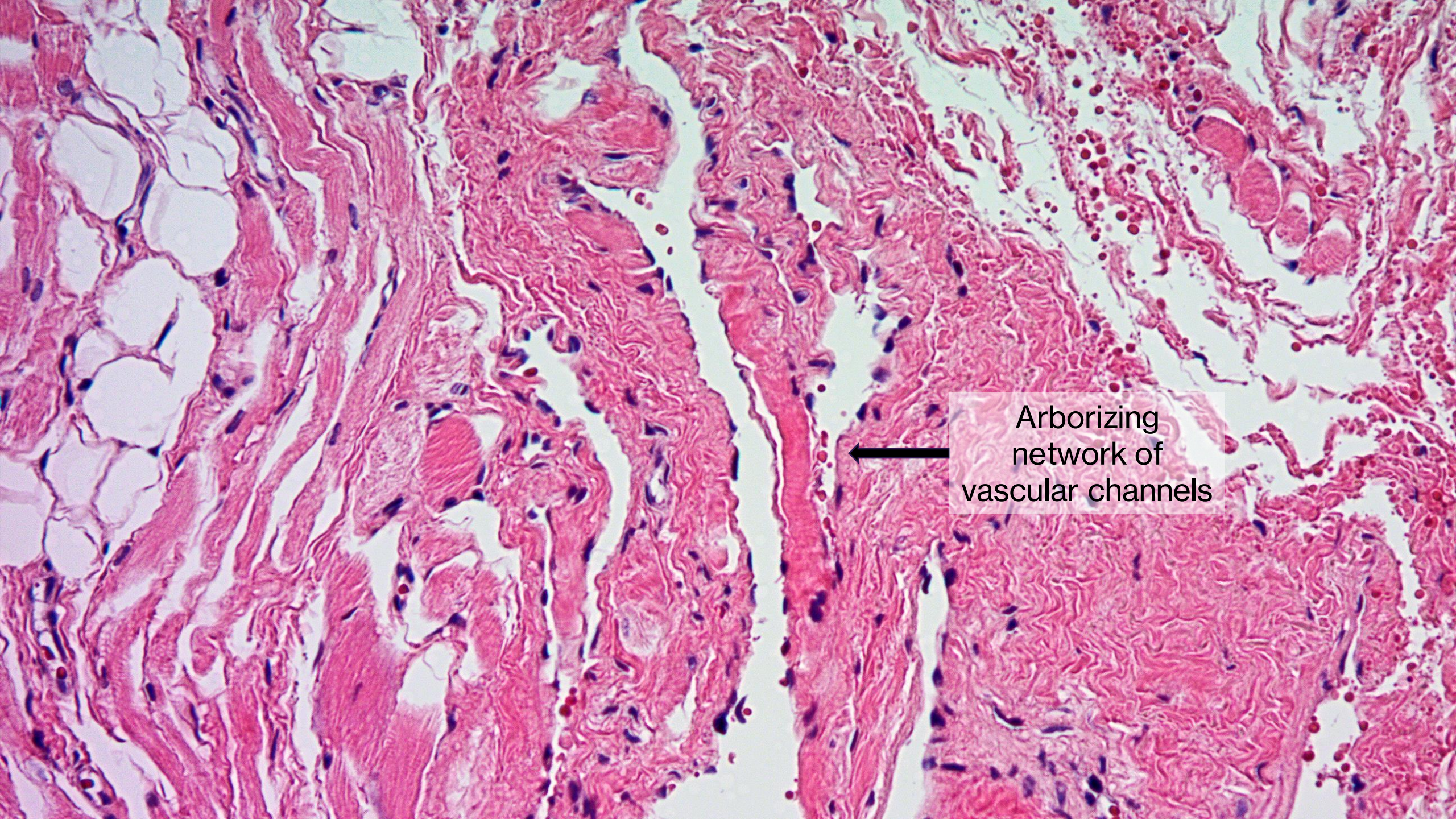

Mucinous glands
Valve-like structure
Pseudomalignant perineural invasion
Large, dilated vascular space with thin walls and valve

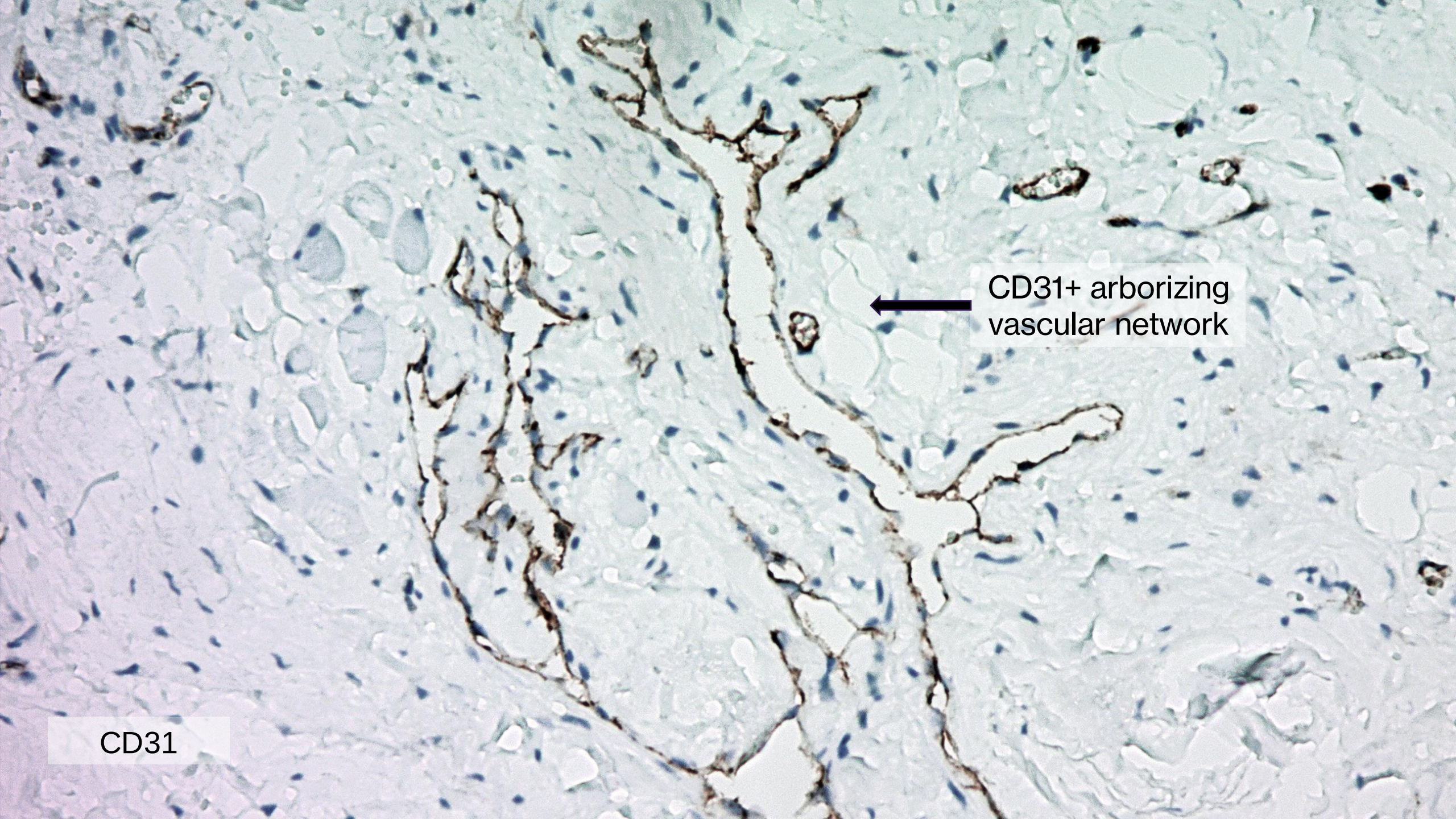


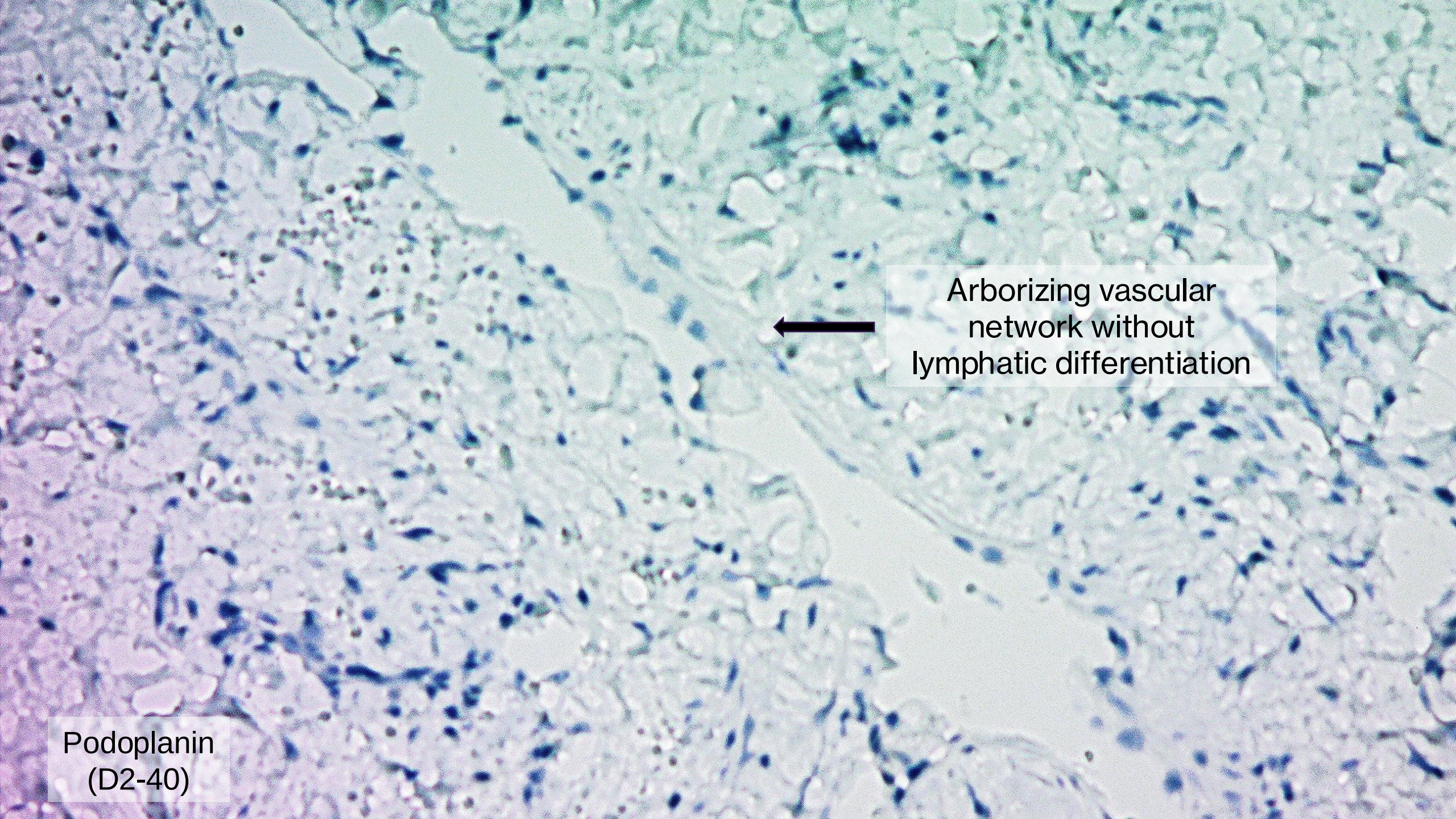
At 5 years of age
11/29/2023

Deep soft tissue involvement: Arborizing network of vascular channels




Arborizing
network of
vascular channels


CD31+ arborizing
vascular network
CD31


Arborizing vascular network without lymphatic differentiation
Podoplanin (D2-40)

- **Clinical Information:** 5-year-old male with vascular lesion of the lip that has been a diagnostic challenge. It was initially considered to benign hemangioma (including on path from first excision), but after a poor response to propranolol the diagnosis was reconsidered. A second excision sample from 2020 was more consistent with a venous malformation, but a lymphatic component couldn't be excluded.

- **DIAGNOSIS:**

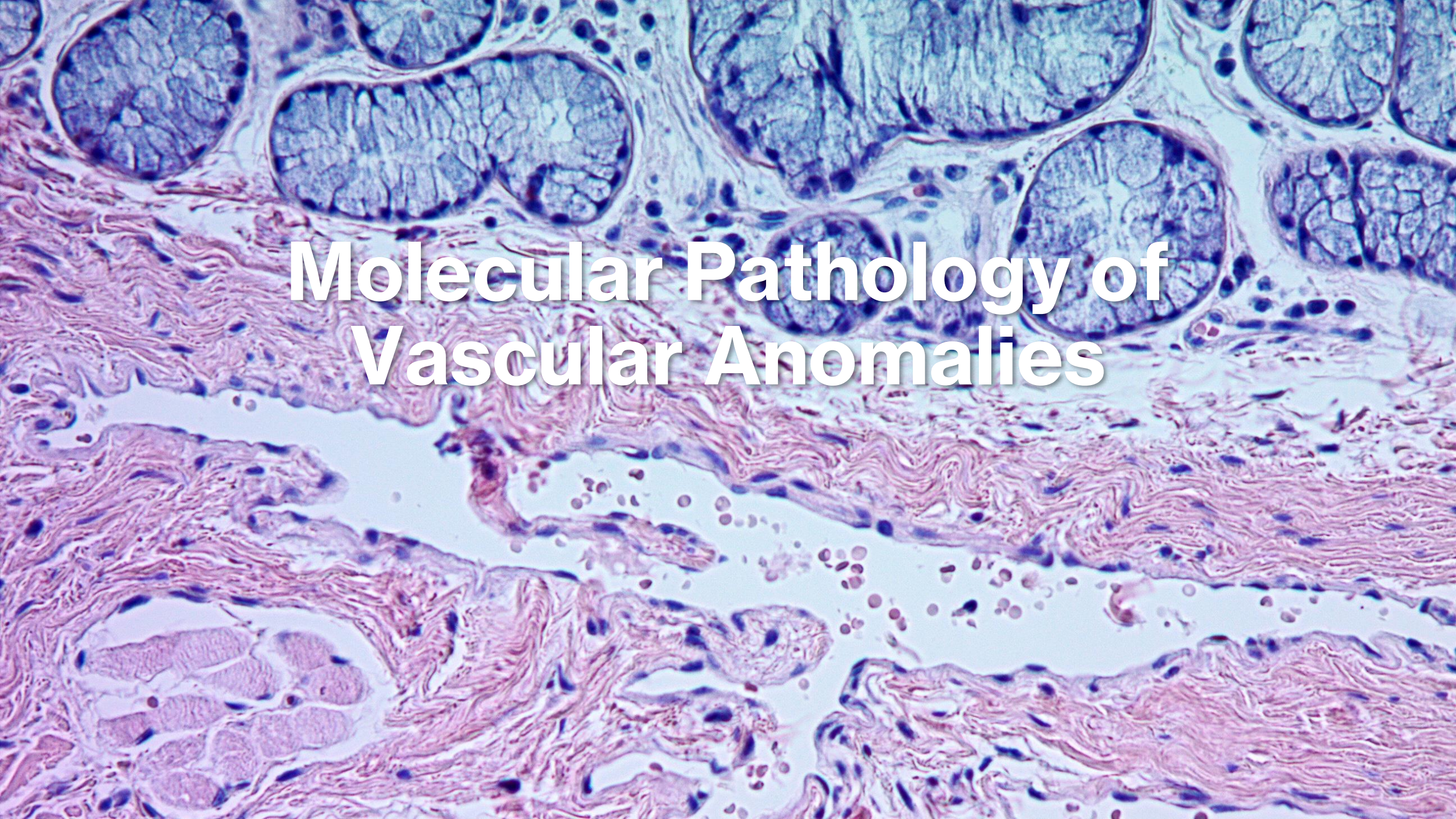
  Skin, Left Upper Lip, Excision :

  - Venous malformation without lymphatic component.

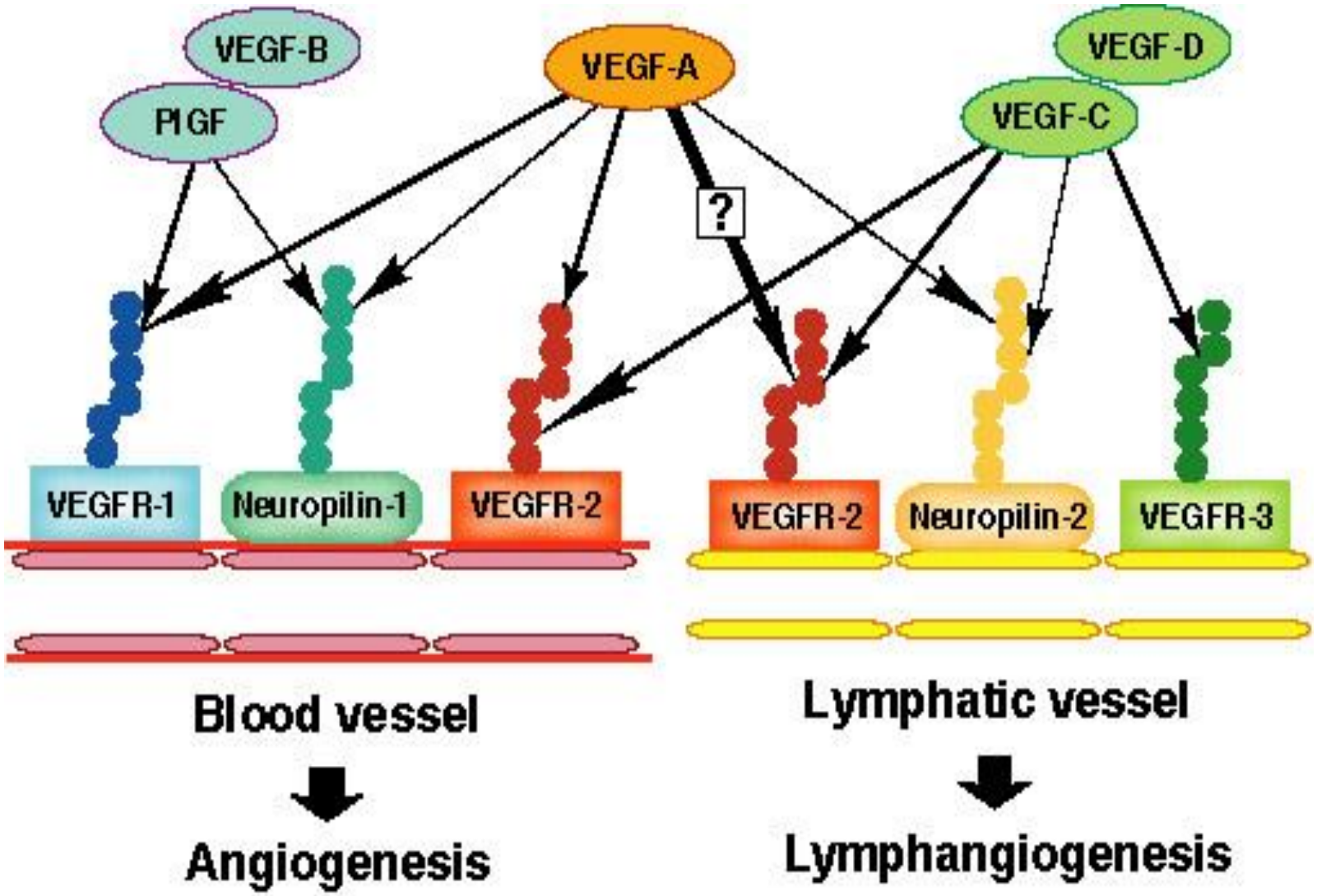
  Comment: Per the request of Dr. X, the current excision was reviewed. The prior excisions from 2019 and 2022 were also reviewed in conjunction. All three excisions demonstrate similar features of vast areas of cystically dilated venous structures that are collapsed or contain fibrin thrombi.

  By immunohistochemistry, CD31 highlights numerous collapsed venous structures while Podoplanin (D2-40) is negative for lymphatic differentiation.

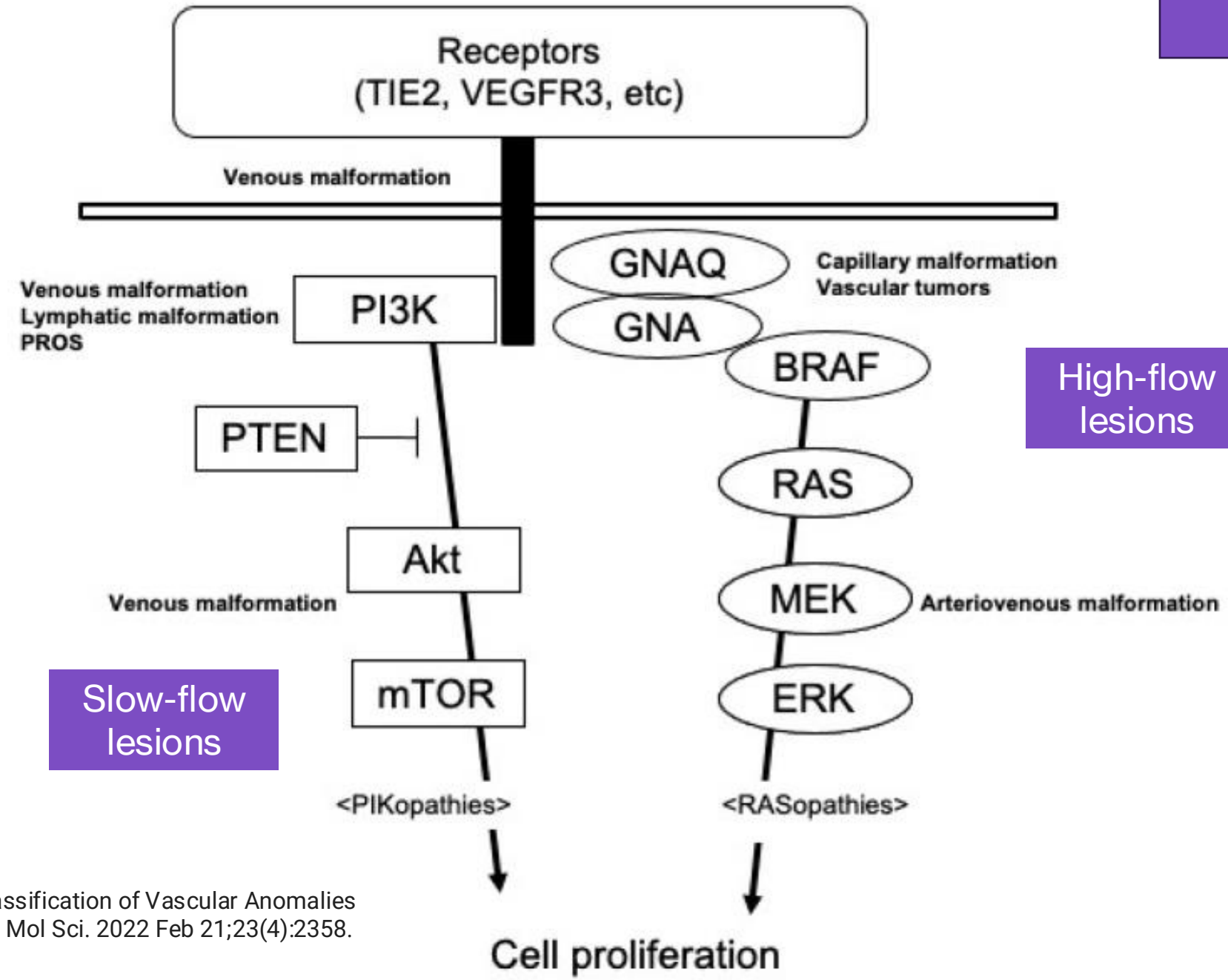
- **Minimal Diagnostic Criteria:**
  - Large, empty dilated vascular spaces with thin walls and valve-like structures
  - Immunohistochemistry (IHC) markers (Podoplanin, PROX-1, & LYVE-1) are negative for lymphatic component
- **Differential Diagnosis:**
  - Venous lymphatic malformation (IHC markers positive for lymphatic differentiation)
  - Microcystic lymphatic malformation
  - Sinusoidal malformation (hemangioma)



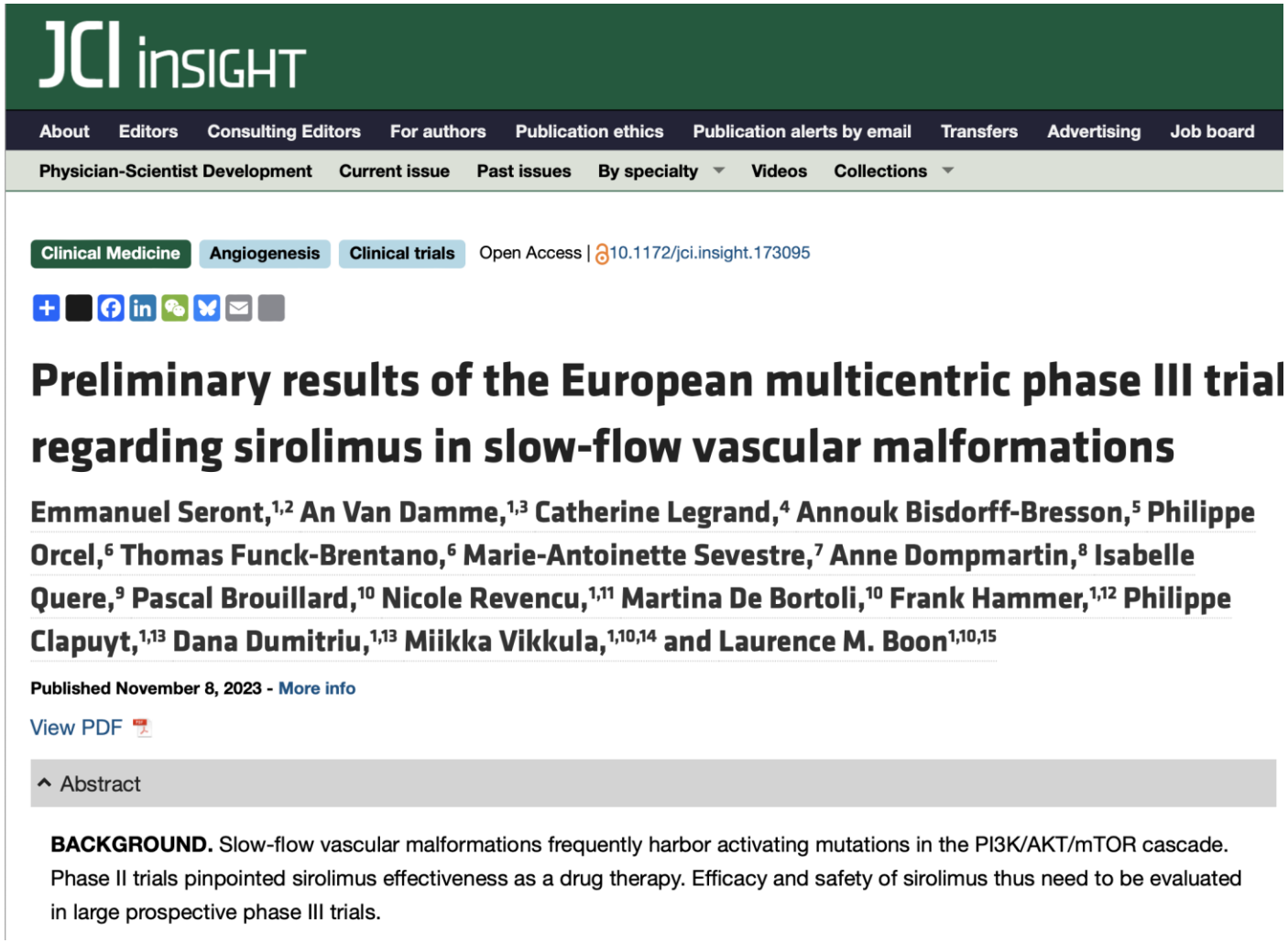
Molecular Pathology of Vascular Anomalies



Specific regulation of lymphangiogenesis and angiogenesis by VEGF family members and their receptors:



Kunimoto K, *et al*. ISSVA Classification of Vascular Anomalies and Molecular Biology. Int J Mol Sci. 2022 Feb 21;23(4):2358.



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Preliminary results of the European multicentric phase III trial regarding sirolimus in slow-flow vascular malformations

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Abstract

BACKGROUND. Slow-flow vascular malformations frequently harbor activating mutations in the PI3K/AKT/mTOR cascade. Phase II trials pinpointed sirolimus effectiveness as a drug therapy. Efficacy and safety of sirolimus thus need to be evaluated in large prospective phase III trials.

Efficacy of Sirolimus in the treatment of vascular malformations

- Harbor activating mutations in the PI3K/AKT/mTOR
- mTOR inhibitor
- Patients enrolled
  - Pediatrics, 31
  - Adults, 101
- Initiated in 2016
- Clinical improvement in 85% of patients