FEB 2019 DIAGNOSIS LIST

6351: hemophagocytic lymphohistiocytosis [bone marrow/hematopathology]
6352: progressive lymphangioma (benign lymphangioendothelioma) [skin/dermatopathology]
6353: malignant atrophic pustolosis (Degos disease) [skin/dermatopathology]
6354: alveolar soft part sarcoma [soft tissue/soft tissue pathology]
6355: primary liver carcinoma: inhibin positive “solid follicular/cystic” (cholangioblastic) variant cholangiocarcinoma [liver/neoplastic liver pathology]
6356: melanotic schwannoma [soft tissue/soft tissue pathology AND neuropathology]
6357: metastatic prostatic adenocarcinoma [bladder/GU pathology]
6358: invasive melanoma, balloon cell type [skin/dermatopathology]
6359: SMARCA4-deficient undifferentiated uterine sarcoma [uterus/GYN pathology]
6360: conventional mantle cell lymphoma with leukemic presentation [peripheral blood AND bone marrow/hematopathology]

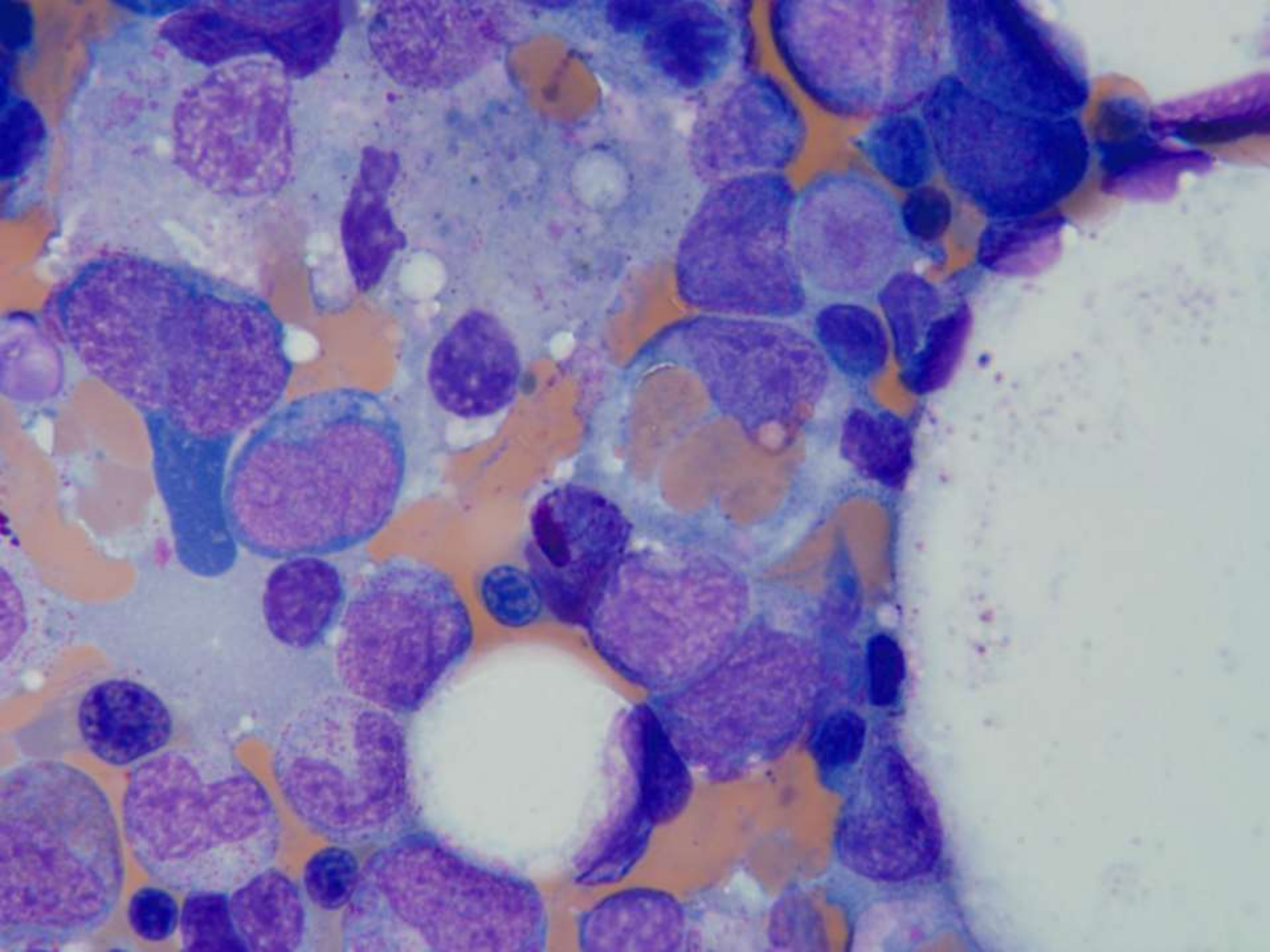
SB 6351

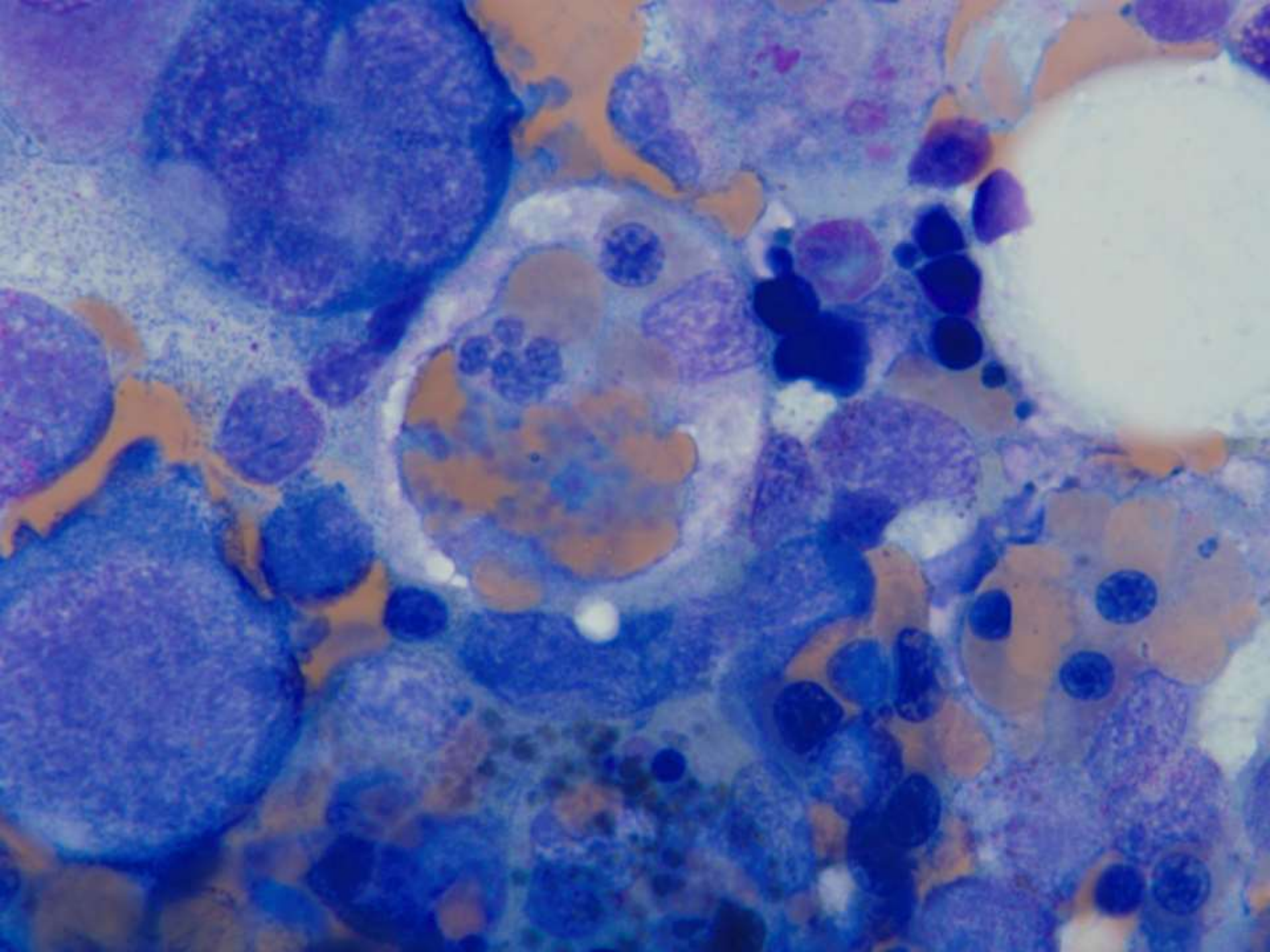
Charles Lombard; El Camino Hospital

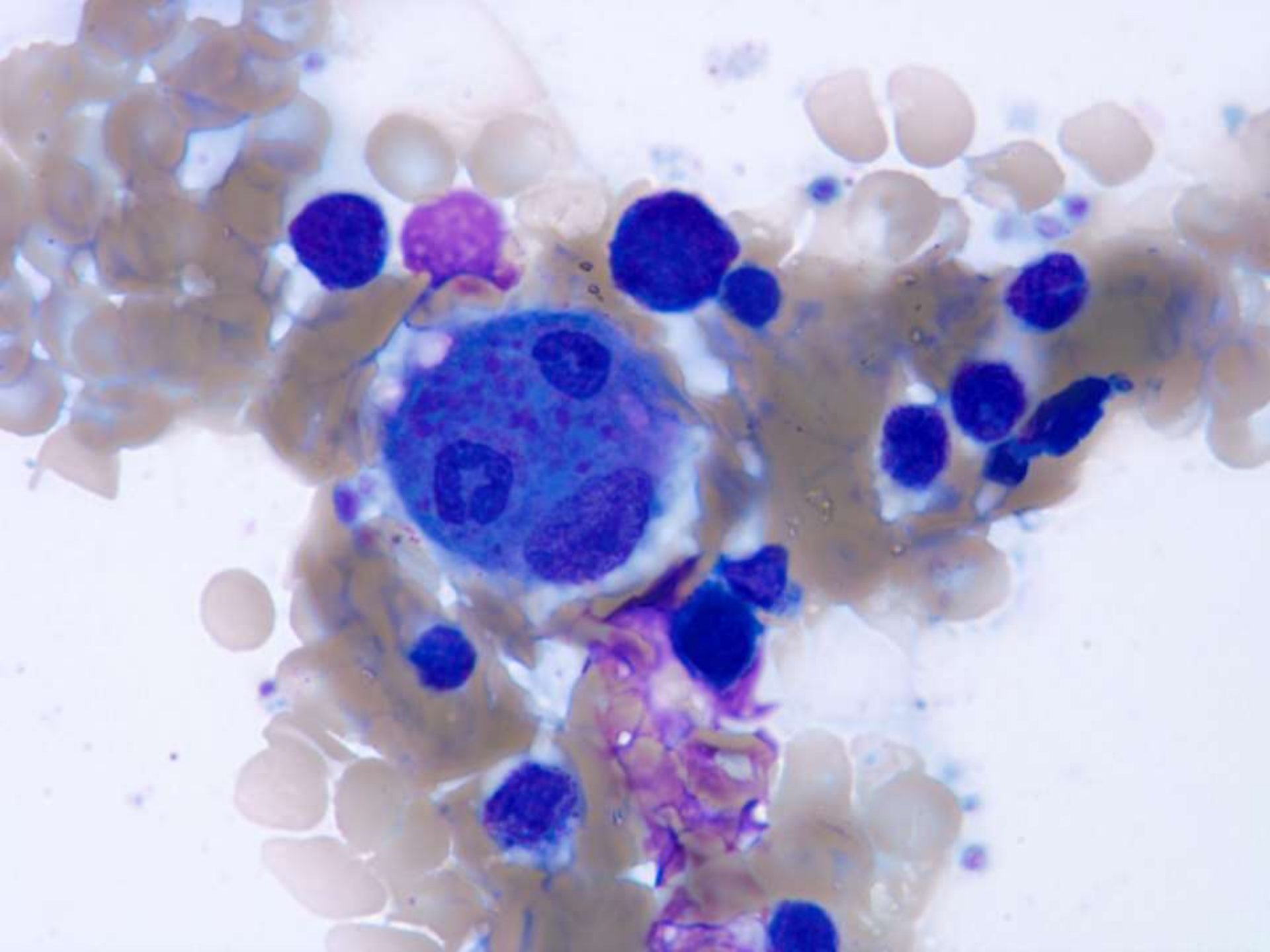
61-year-old male with NMDAR auto-immune encephalitis and pancytopenia. Bone marrow aspirate/biopsy performed: DRESS syndrome?

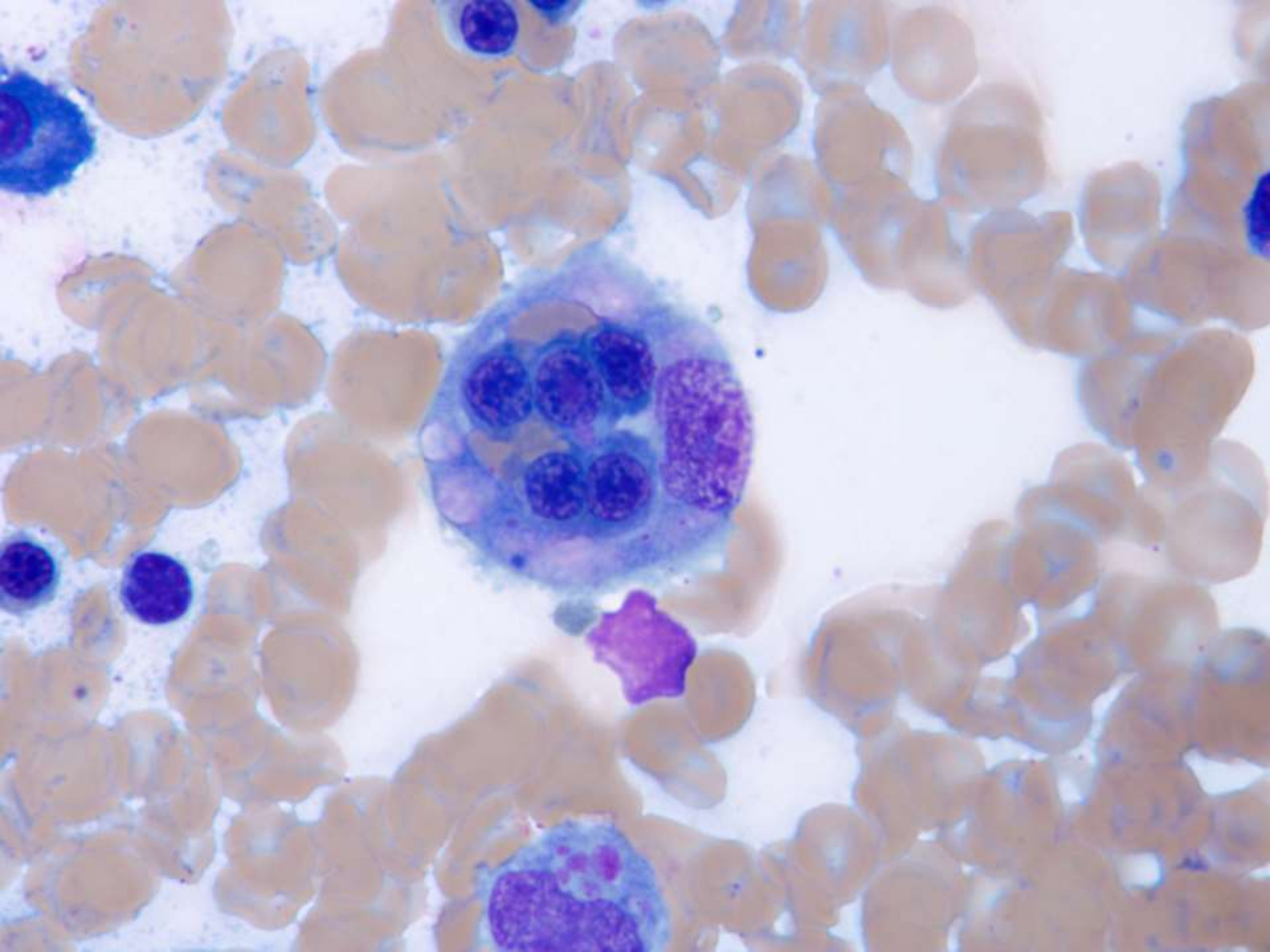
CBC

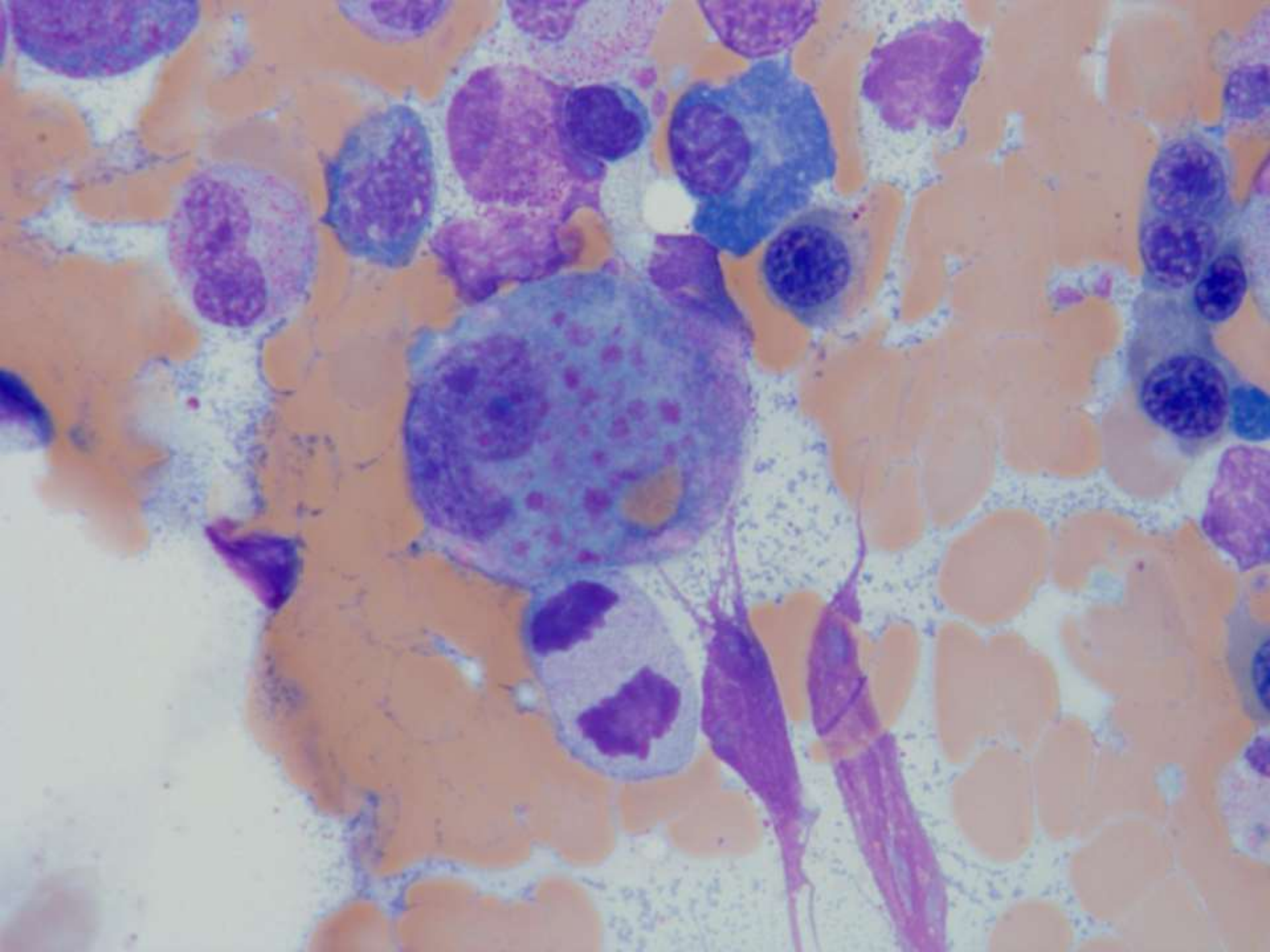
- WBC: 1.84 (4.5-11)
  - 84% neutrophils, 10 % lymphs, 4% mono 2% myelocytes
  - IGF: 3.3%
- Hg/Hct: 7.3/21.9
- Platelets: 54,000

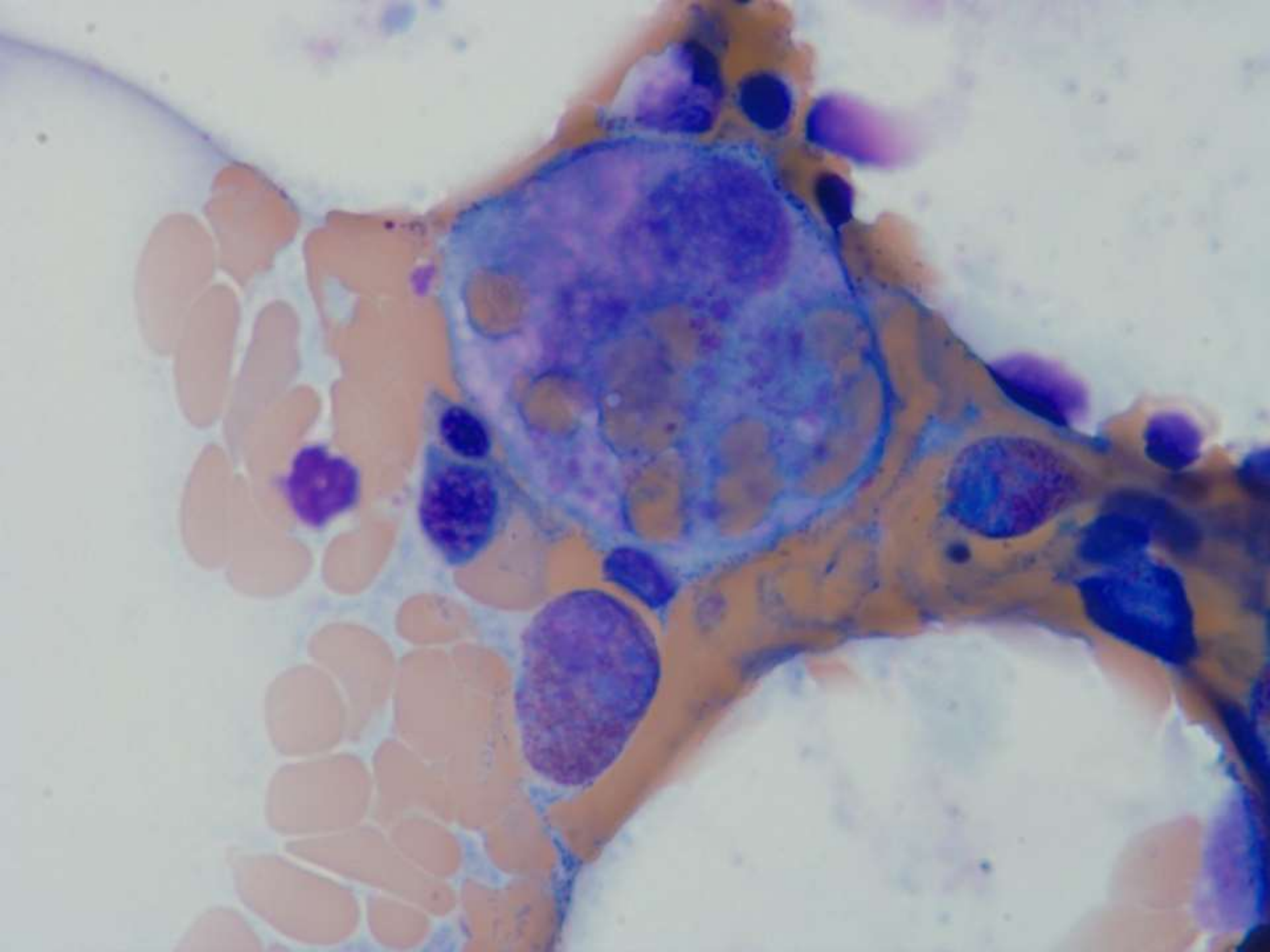


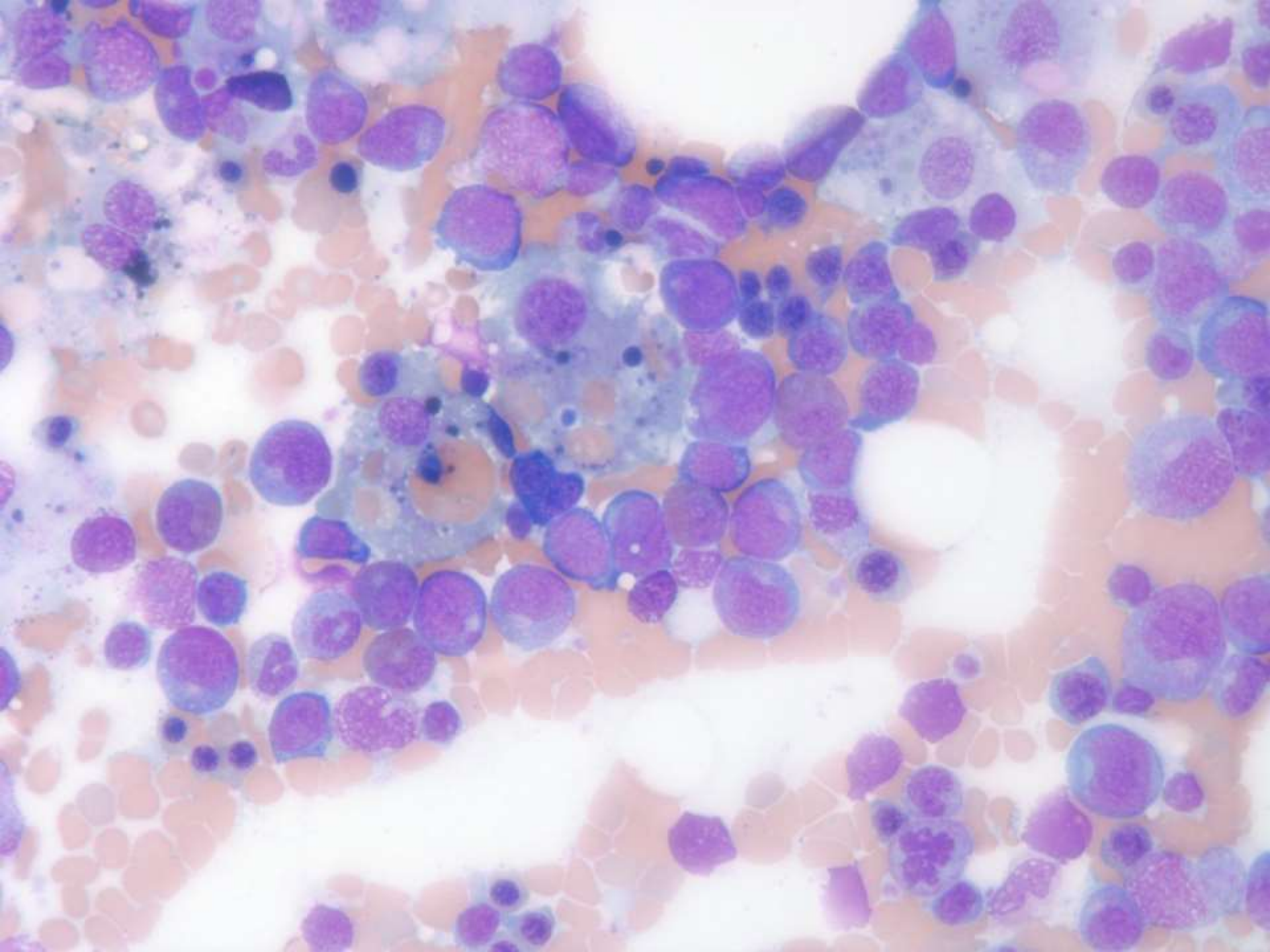


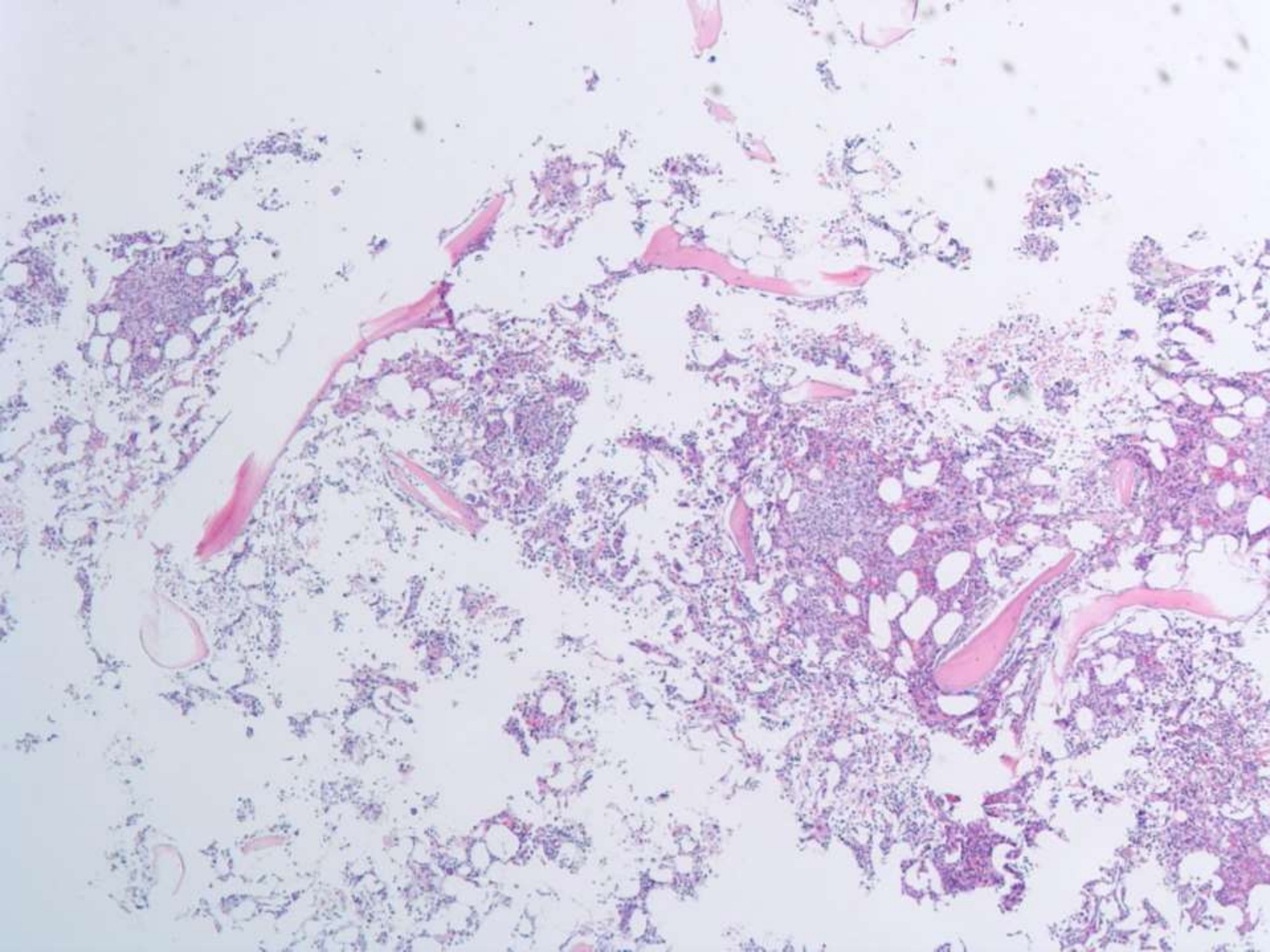


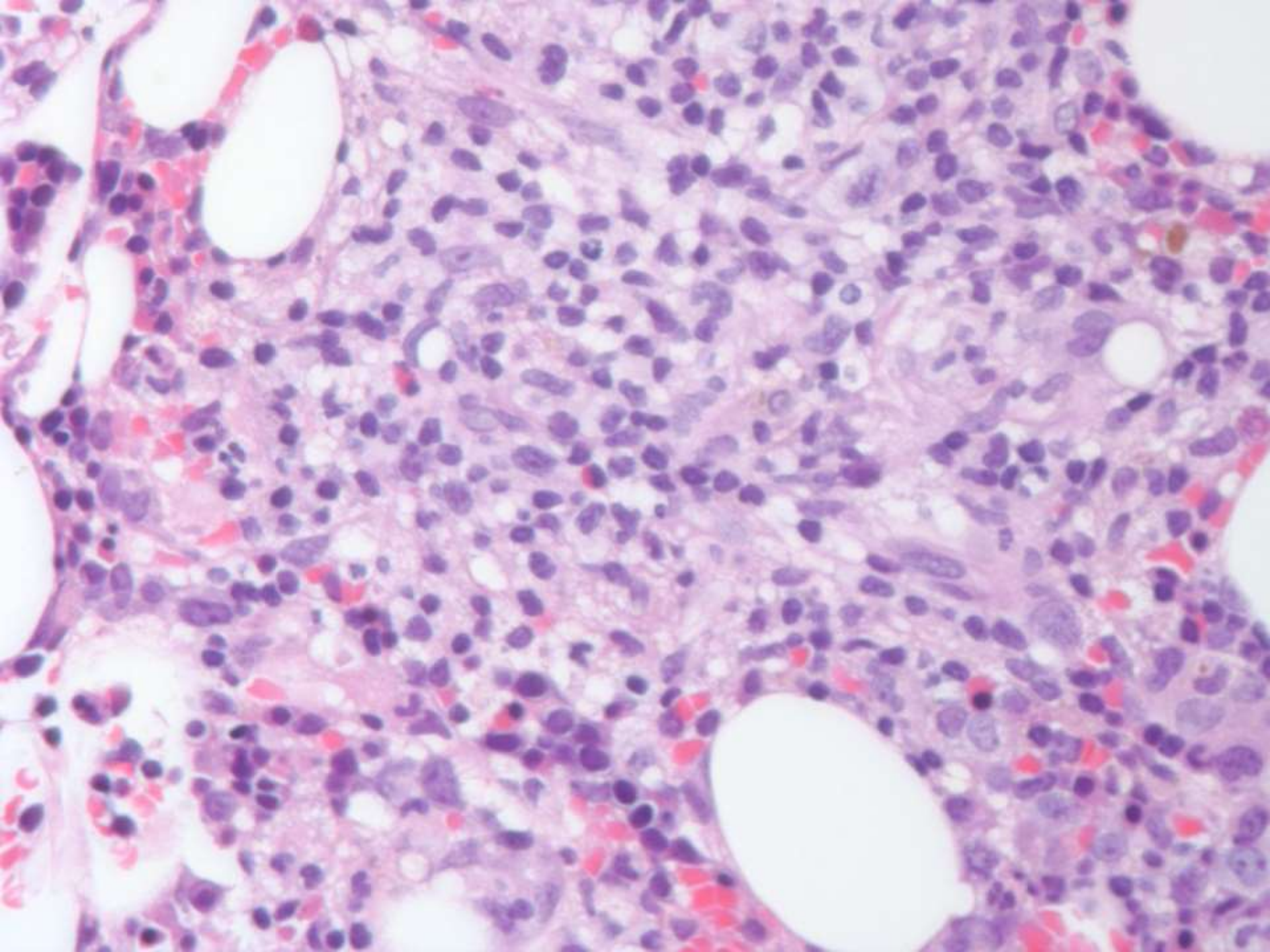


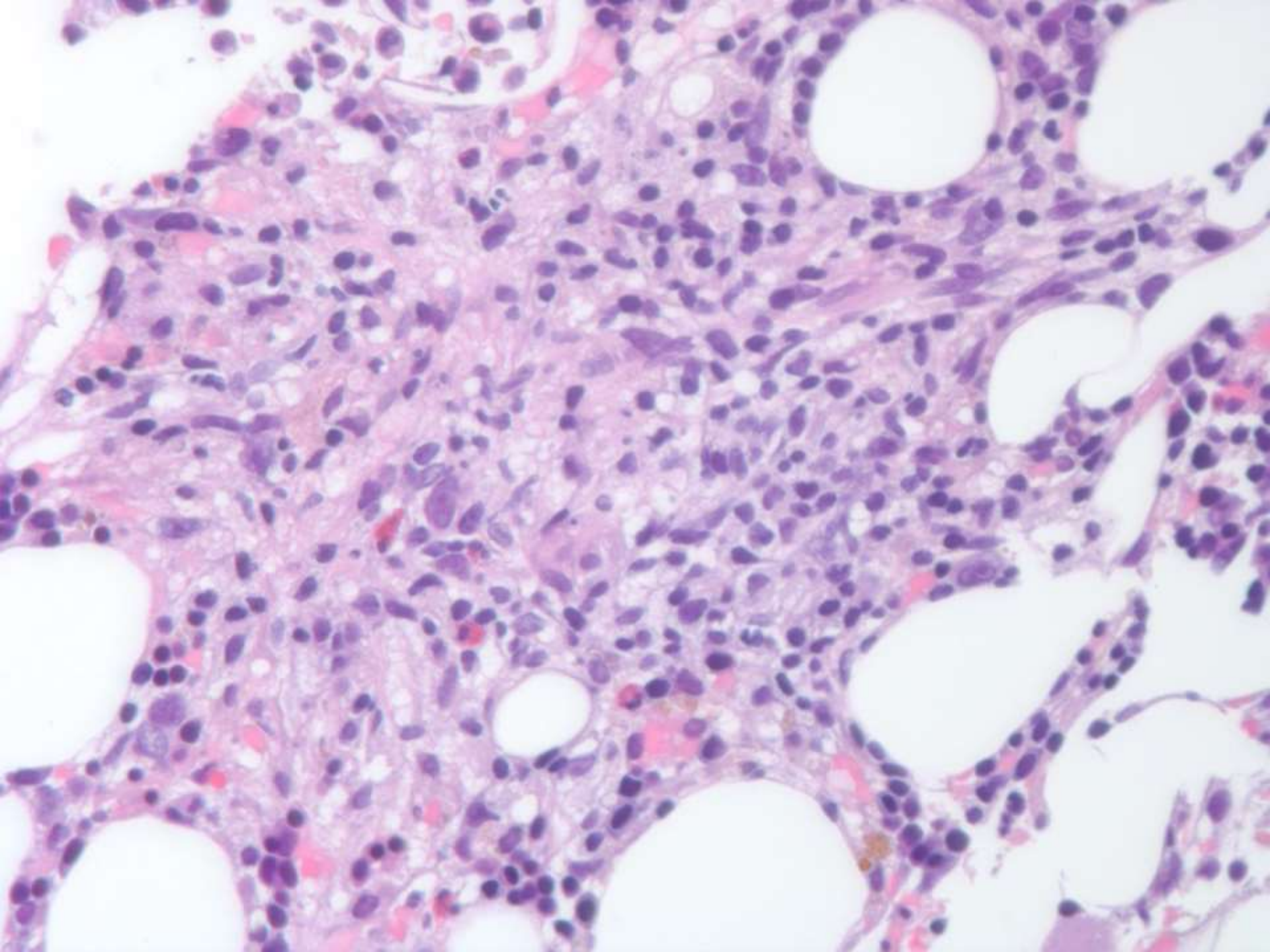


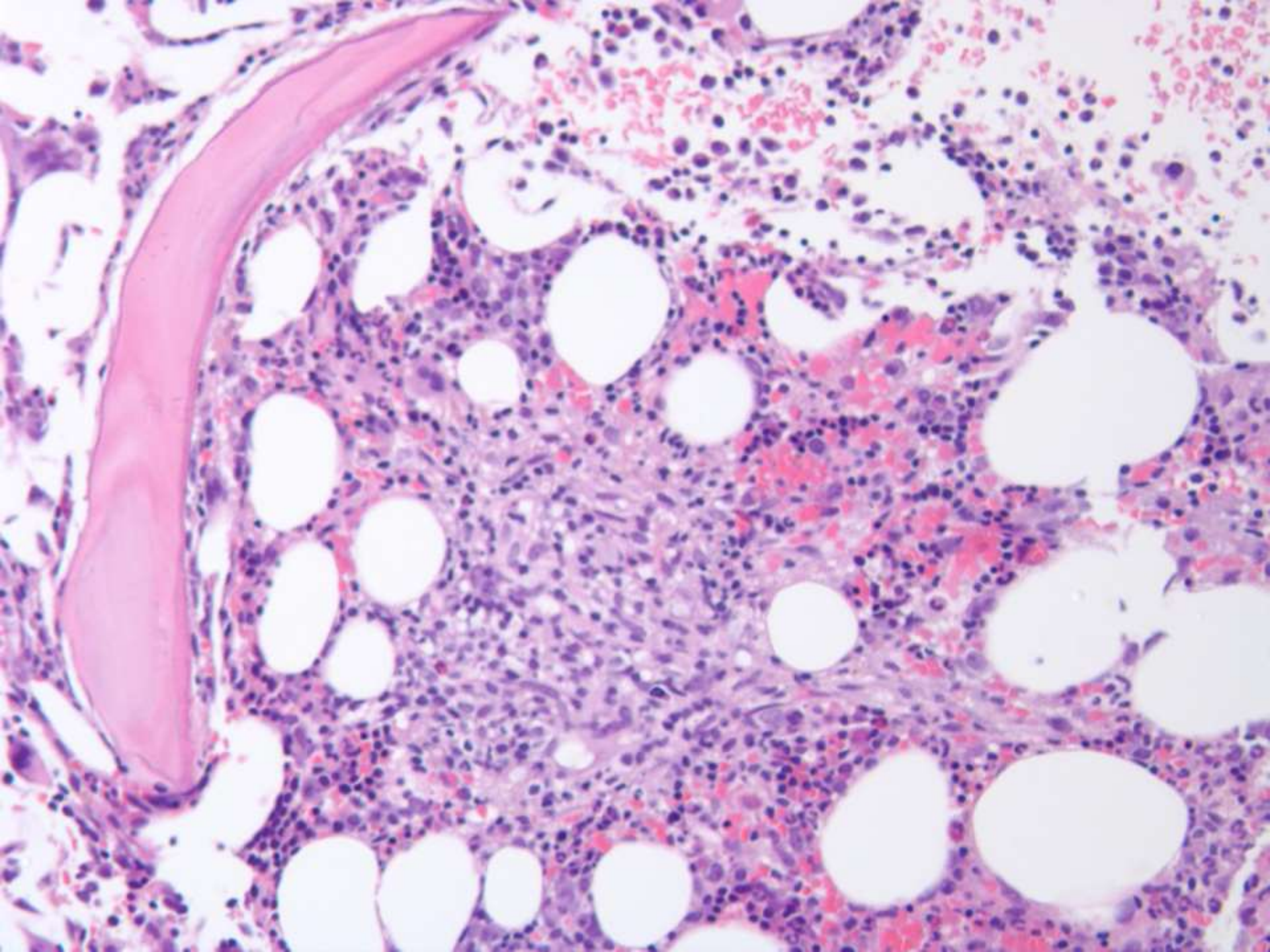


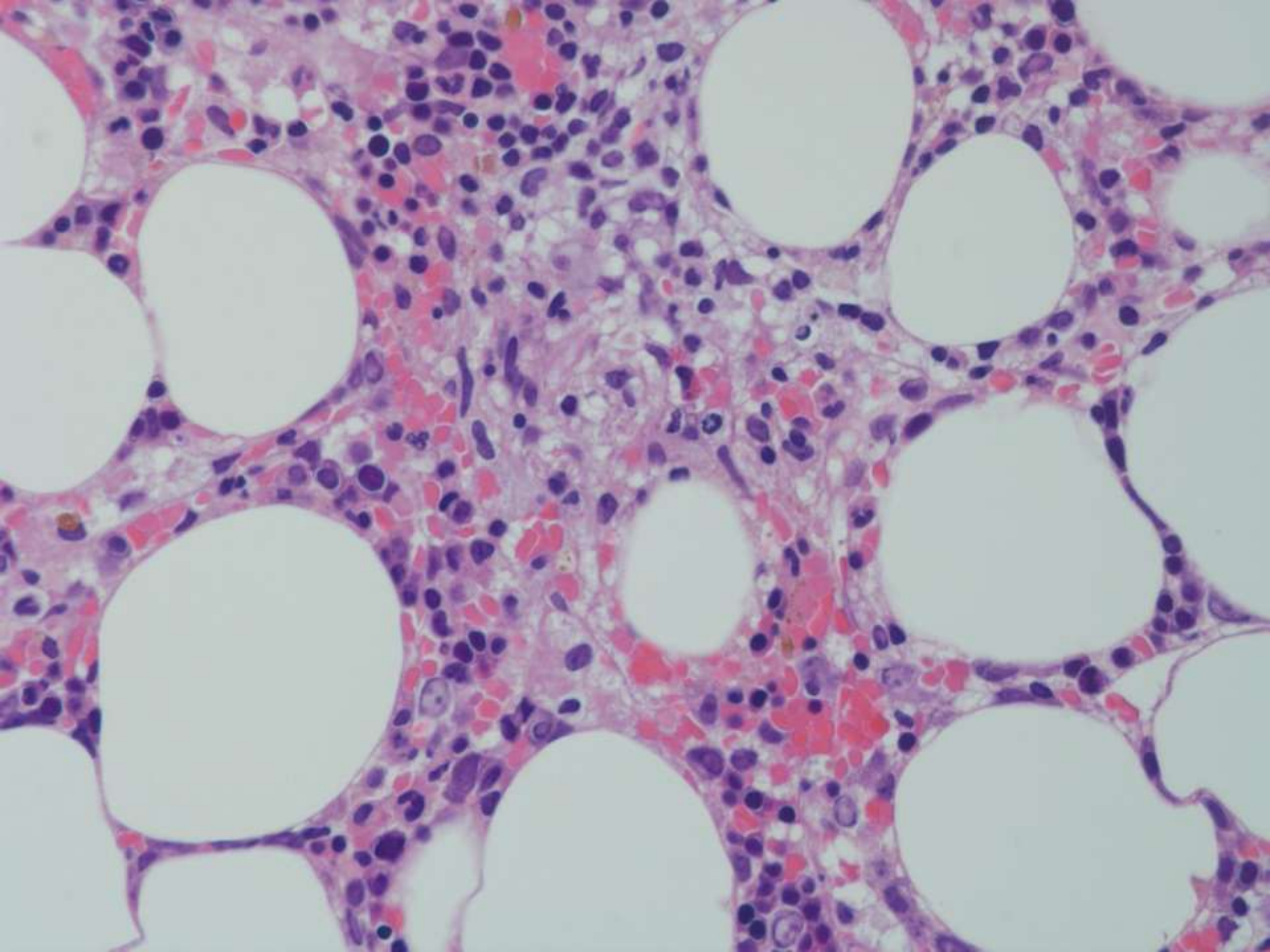












Diagnosis?

Summary of BM findings

- Peripheral blood with neutropenia, anemia, thrombocytopenia
- Bone marrow (normo to slightly hypocellular) with increase histiocytes with phagocytosis of red cell, neutrophils, and platelets
- Bone marrow with poorly formed noncaseating granulomas (AFB/GMS negative)
- Stress dyserythropoiesis without overt dysplasia
- No increase in blasts/reticulin

Need to evaluate for HLH syndrome Patient Results

- Fever: Present
- Splenomegaly: Absent
- Cytopenias: All 3 cell lines
- Elevated Ferritin: 3,146
- Decreased Fibrinogen 162 (190-440)
- Triglycerides: normal
- Soluble CD25: Elevated
- Hemophagocytosis identified in BM bx

- Need 5 criteria
  - 6 criteria met

Pt. expired day following BM bx

Hemophgocytic Lymphohistiocytosis (HLH)

- Life threatening syndrome with uncontrolled ineffective immune response
- Group of conditions with similar end-stage
- Triggered in majority by infection
- Results in severe hyperinflammation
- Familial forms associated with impaired function of NK/cytotoxic T cells

HLH: Classification

- Familial HLH
- Immune deficiency syndrome associated HLH
- Acquired HLH
  - Macrophage activation syndrome
  - Infection associated (usually viral, but also bacterial, fungal, and parasitic)
  - Malignancy associated (T/NK, ALCL, MM, AMoL, Germ cell, thymoma, carcinoma

Acquired HLH
Macrophage activation syndrome

- Acquired HLH associated with autoimmune diseases
- Strong association with systemic juvenile idiopathic arthritis
  - Decreased expression of perforin on CD8+ T cells thought to be responsible for MAS
  - MAS may lead to DIC
- Other autoimmune diseases including lupus are less commonly associated with HLH

HLH: Clinical

- Most cases in pediatric population
- Signs/Symptoms
  - Fever
  - Anemia
  - HSM,LN
  - Neurologic
    - Seizures
    - Cranial N palsy
  - Pulmonary infiltrated
  - Renal/Multiorgan failure
  - Cutaneous maculopapular eruptions/diffuse erythroderma

Diagnostic criteria

- Molecular identification of mutations associated with familial/autoimmune HL H or
- Detection of 5/8 of the following:
  - Fever
  - Splenomegaly
  - Cytopenias
  - Hypertriglyceridemia +/or hypofibrinogenemia
  - Elevated ferritin
  - Elevated soluble CD25
  - Low/absent NK cell cytotoxicity
  - Hemophagocytosis on BM/Spleen/LN biopsies

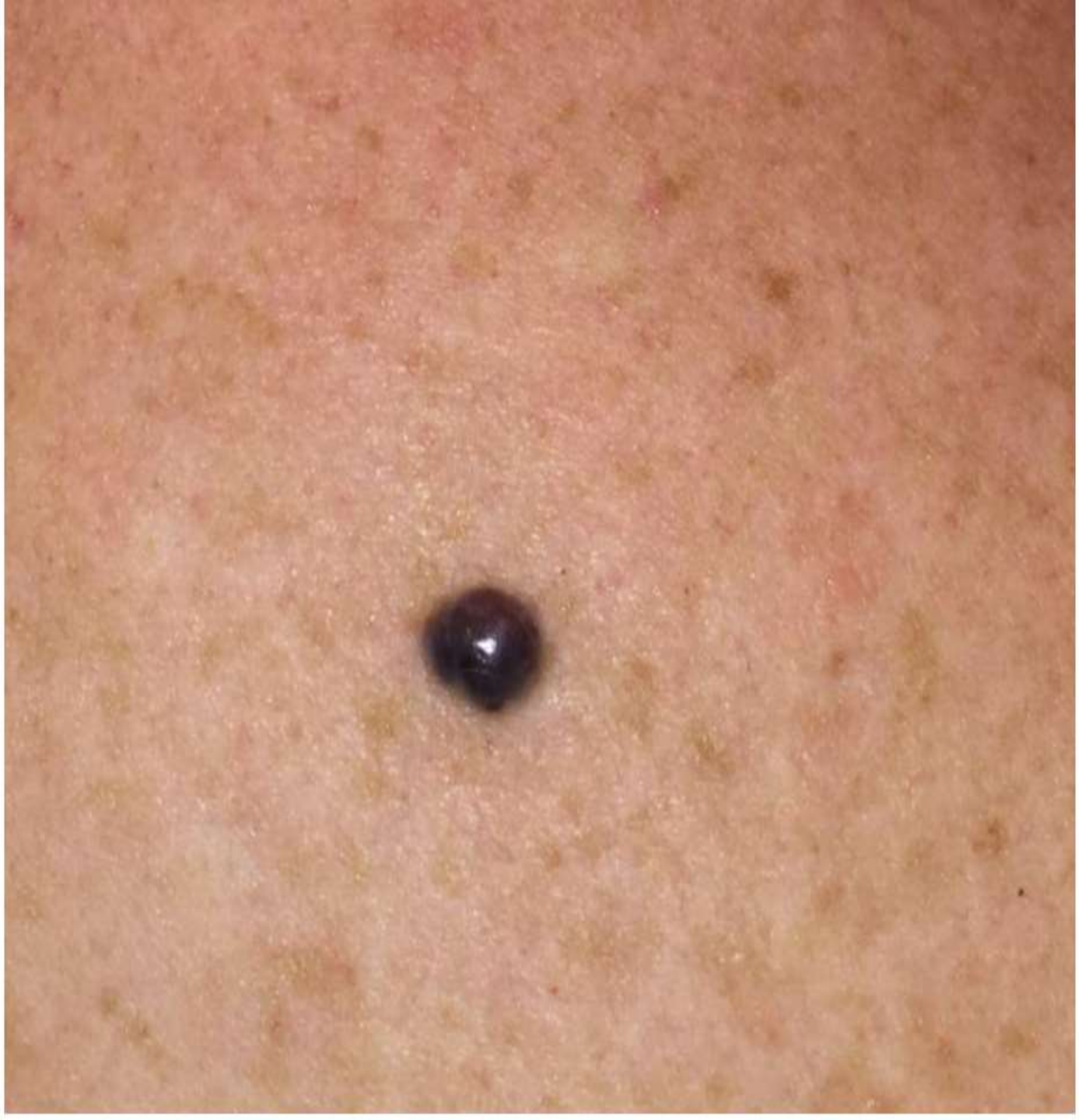
Molecular testing in suspected HLH

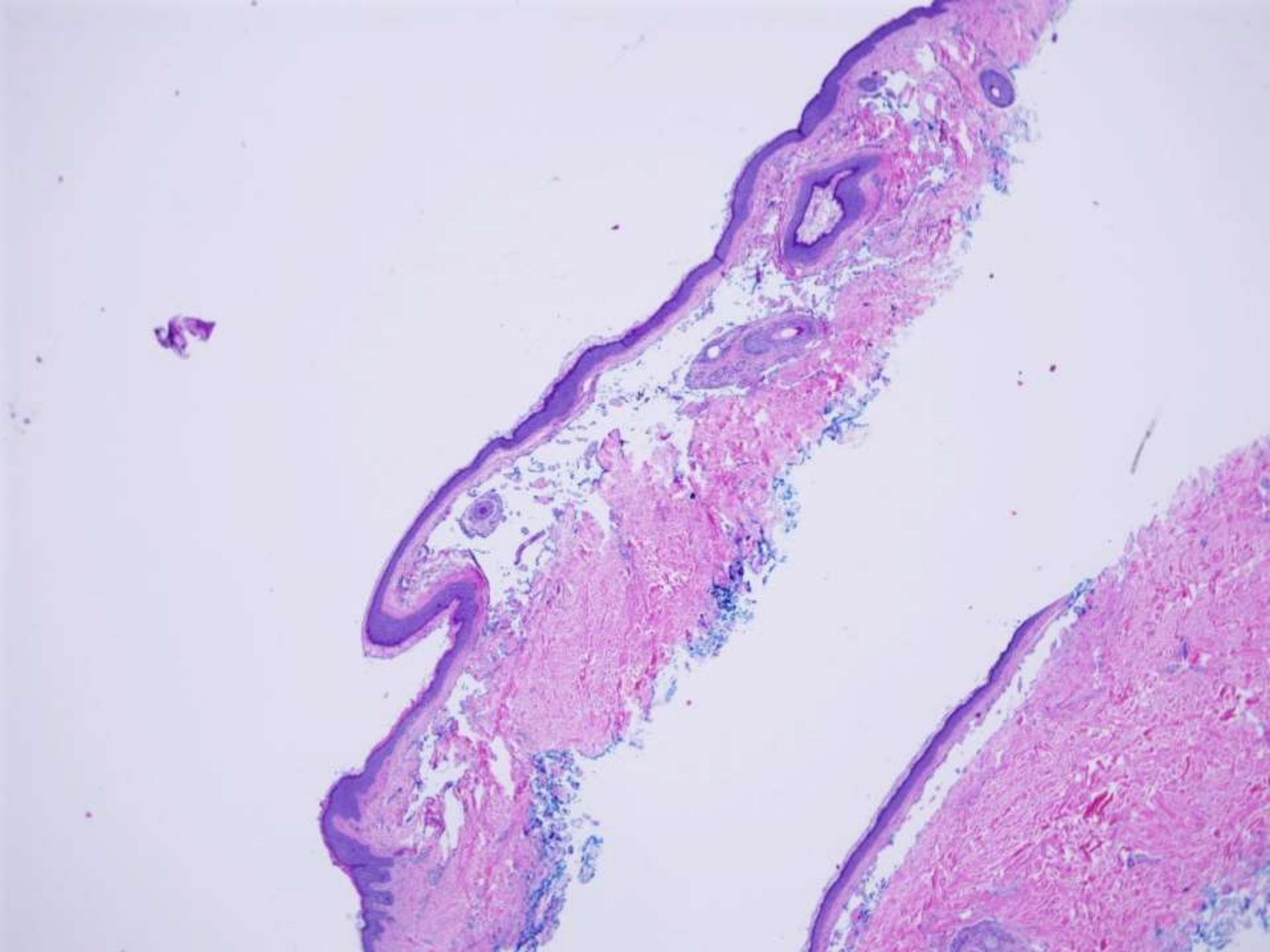
- Genes involved in familial HLH
  - PRF1, UNC13D, STX11, STXBP2
- Genes involved in immune deficiency syndrome associated HLH
  - LYST, RAB27A, AP3B1, SH2D1A, XIAP

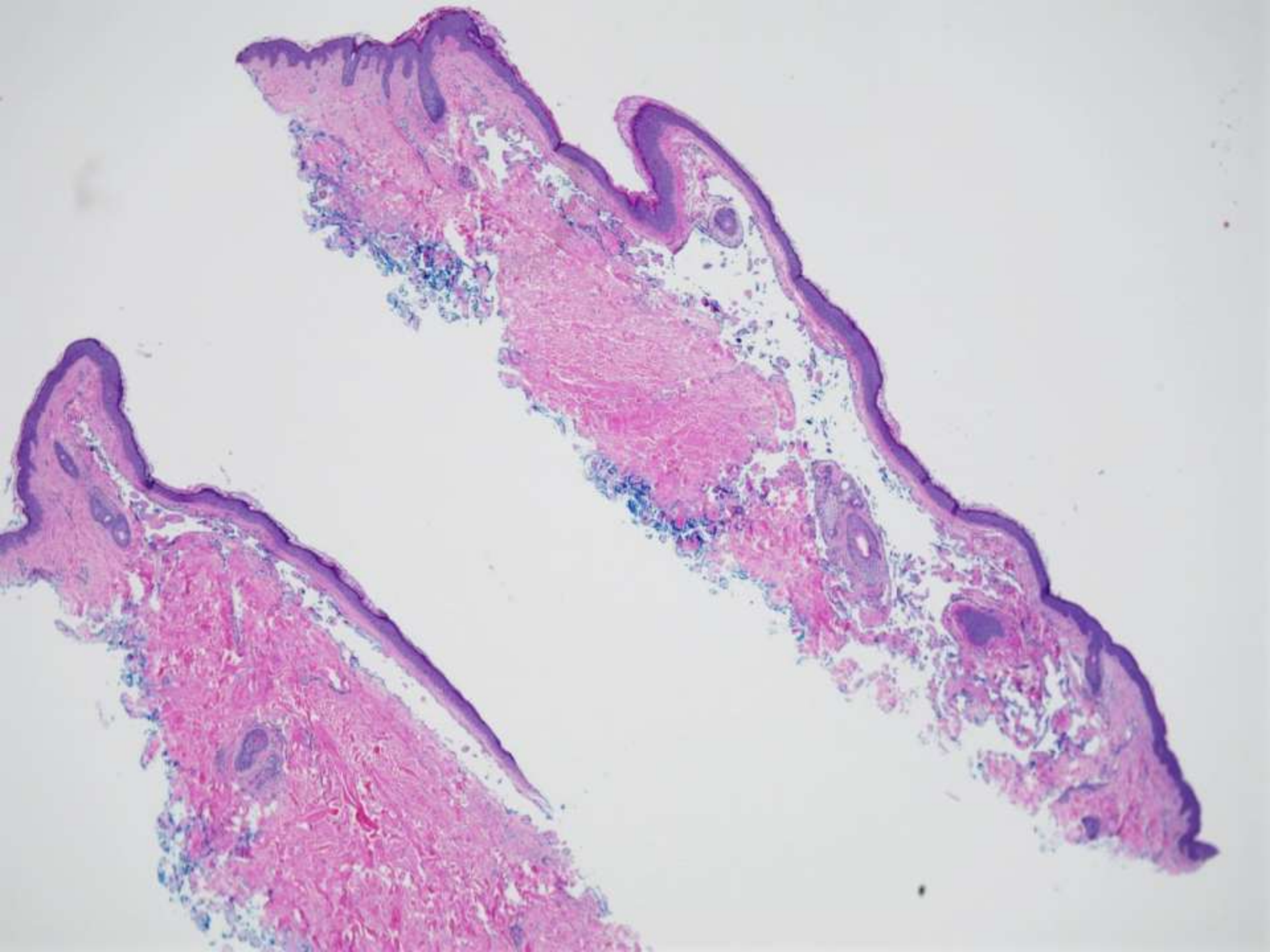
SB 6352

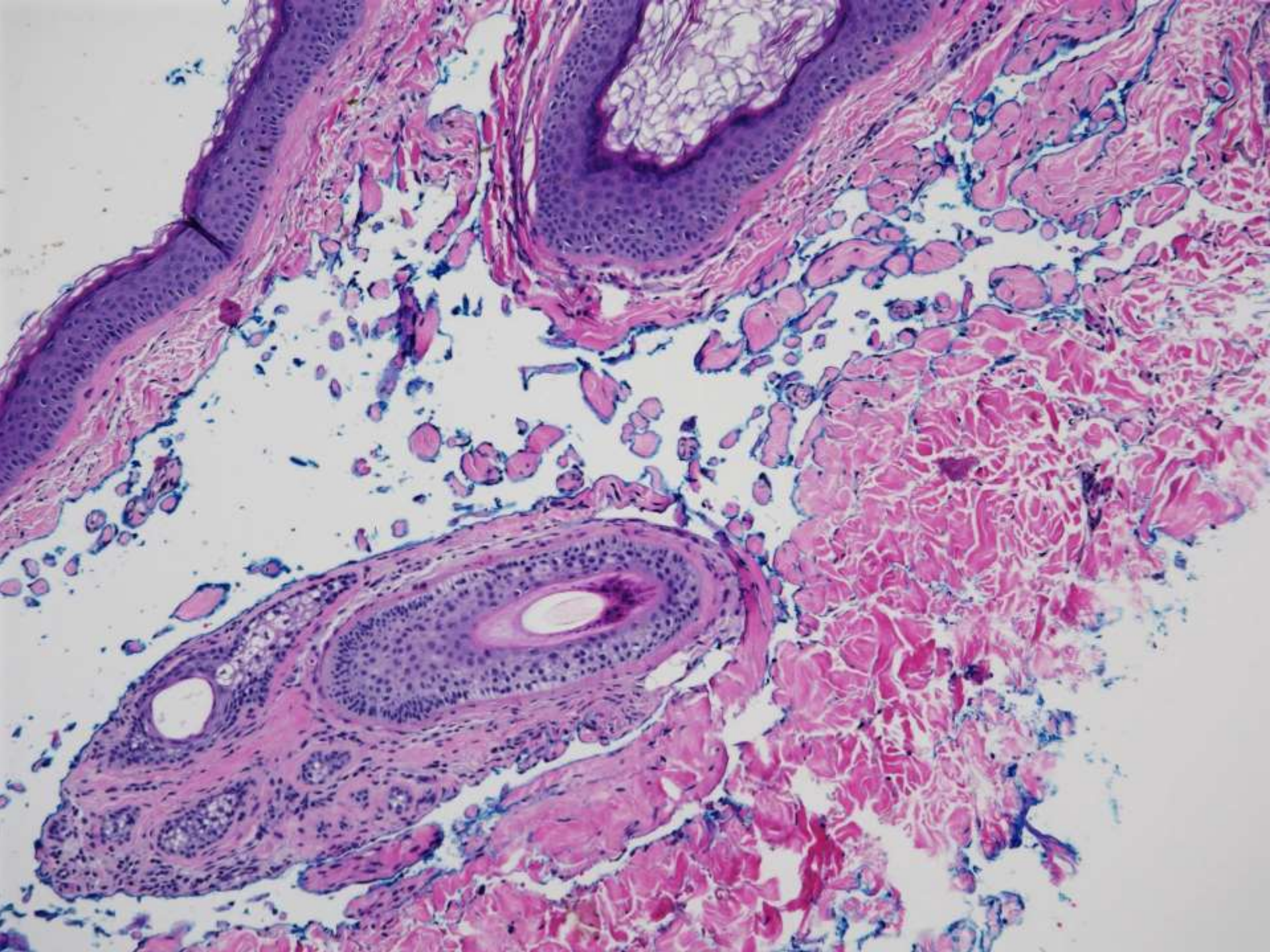
Sebastian Fernandez-Pol/Kerri Rieger/Roberto Novoa; Stanford

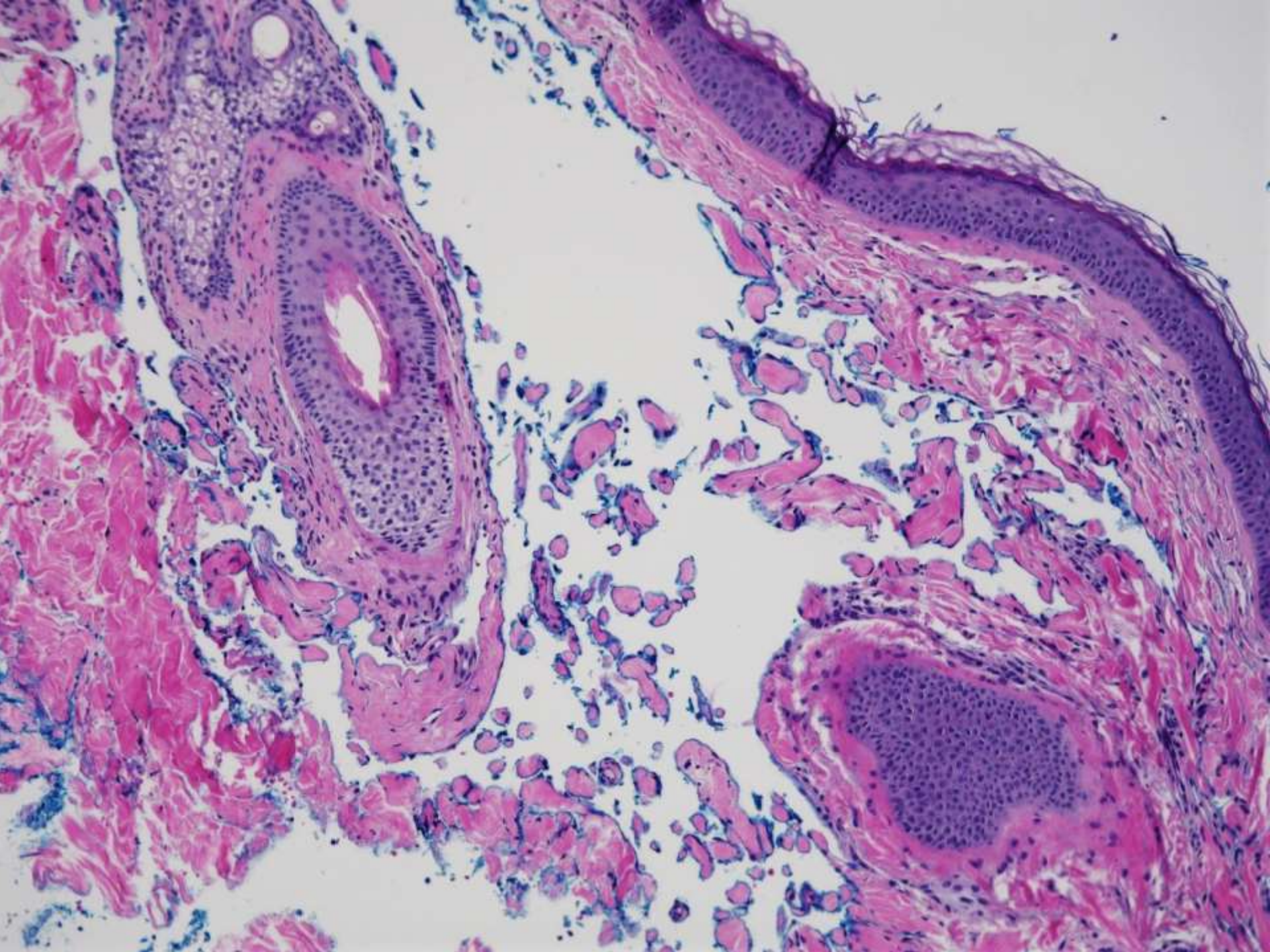
44-year-old female with 0.4x0.4cm purple papule.

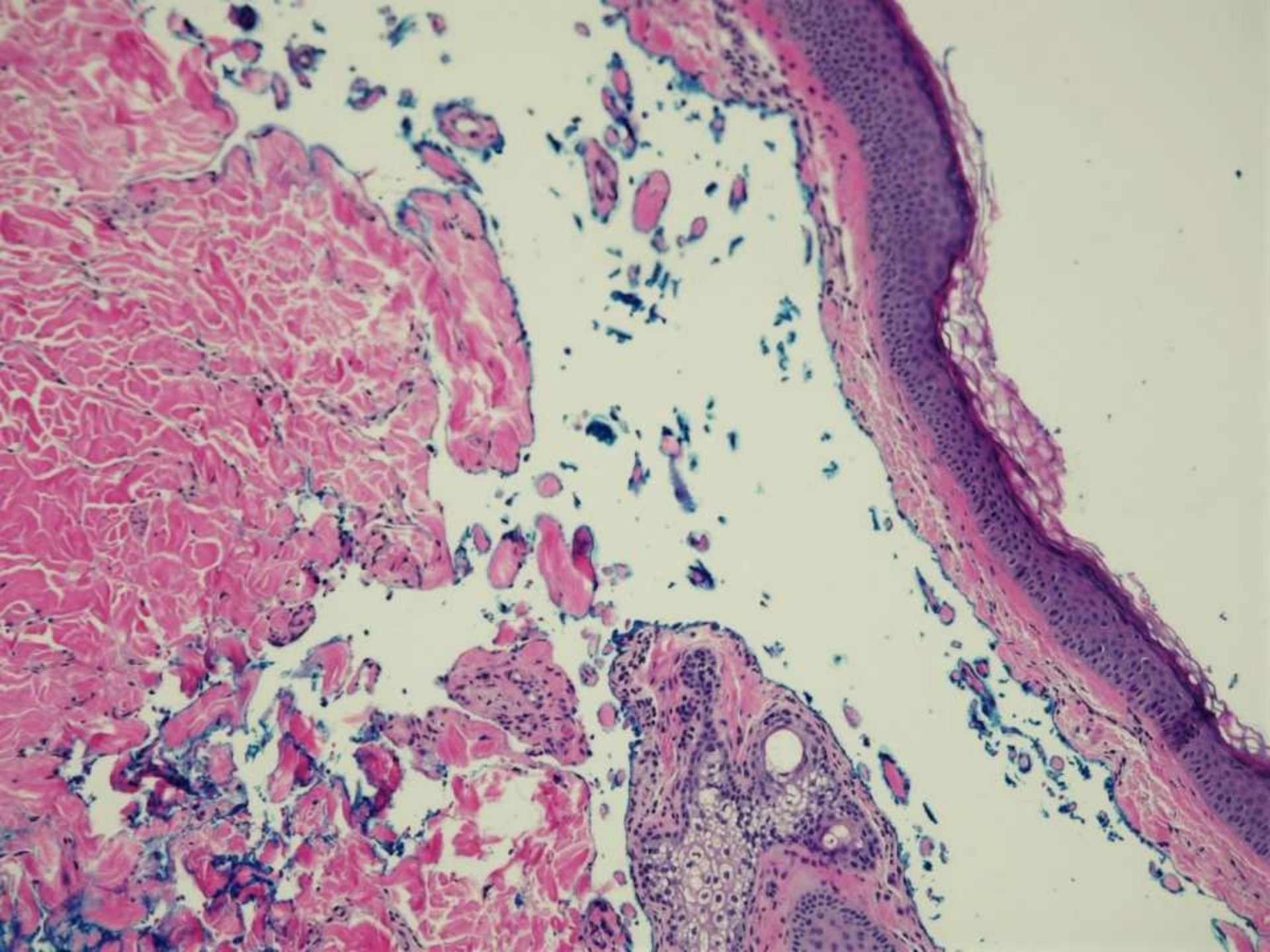


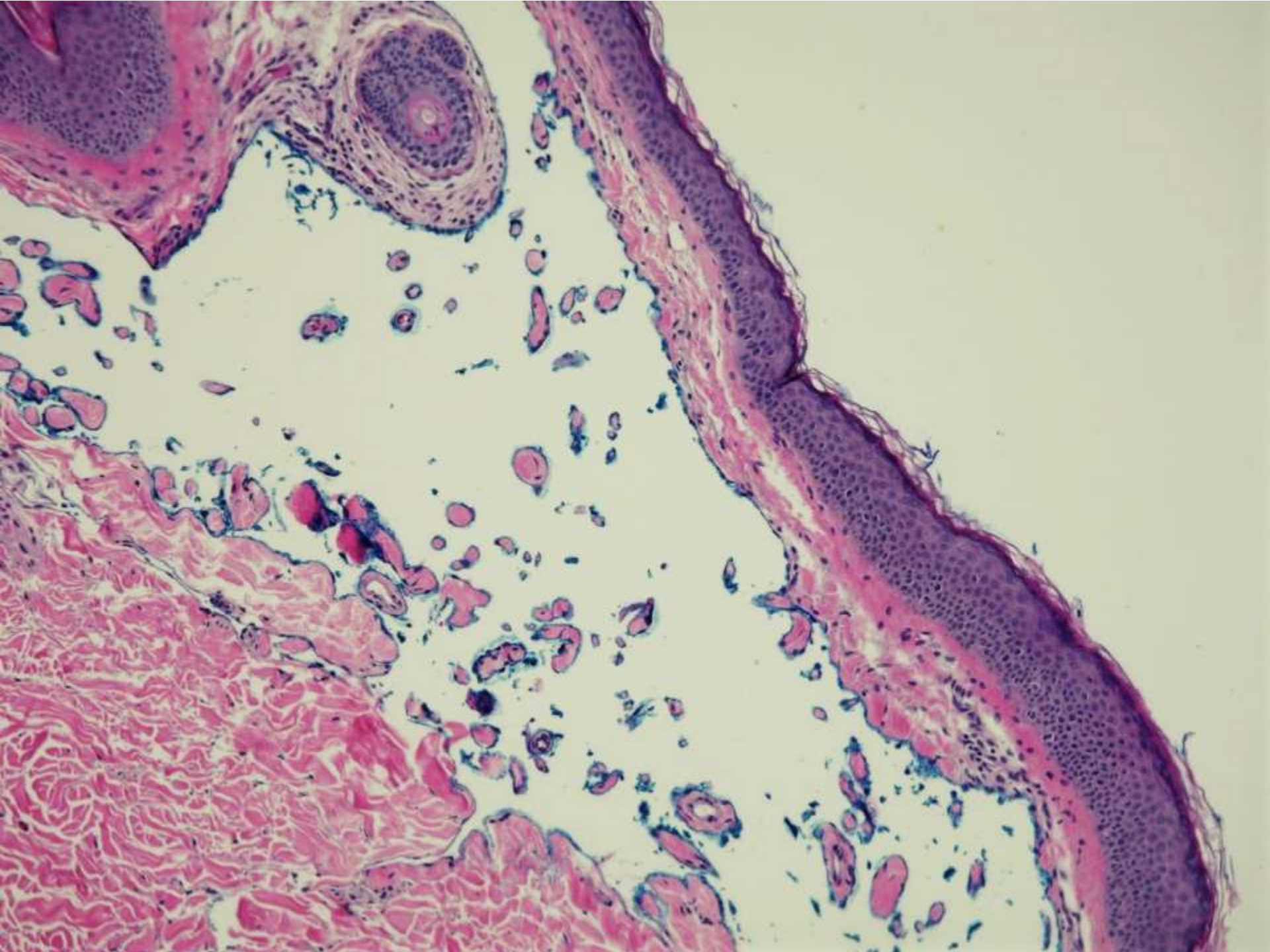


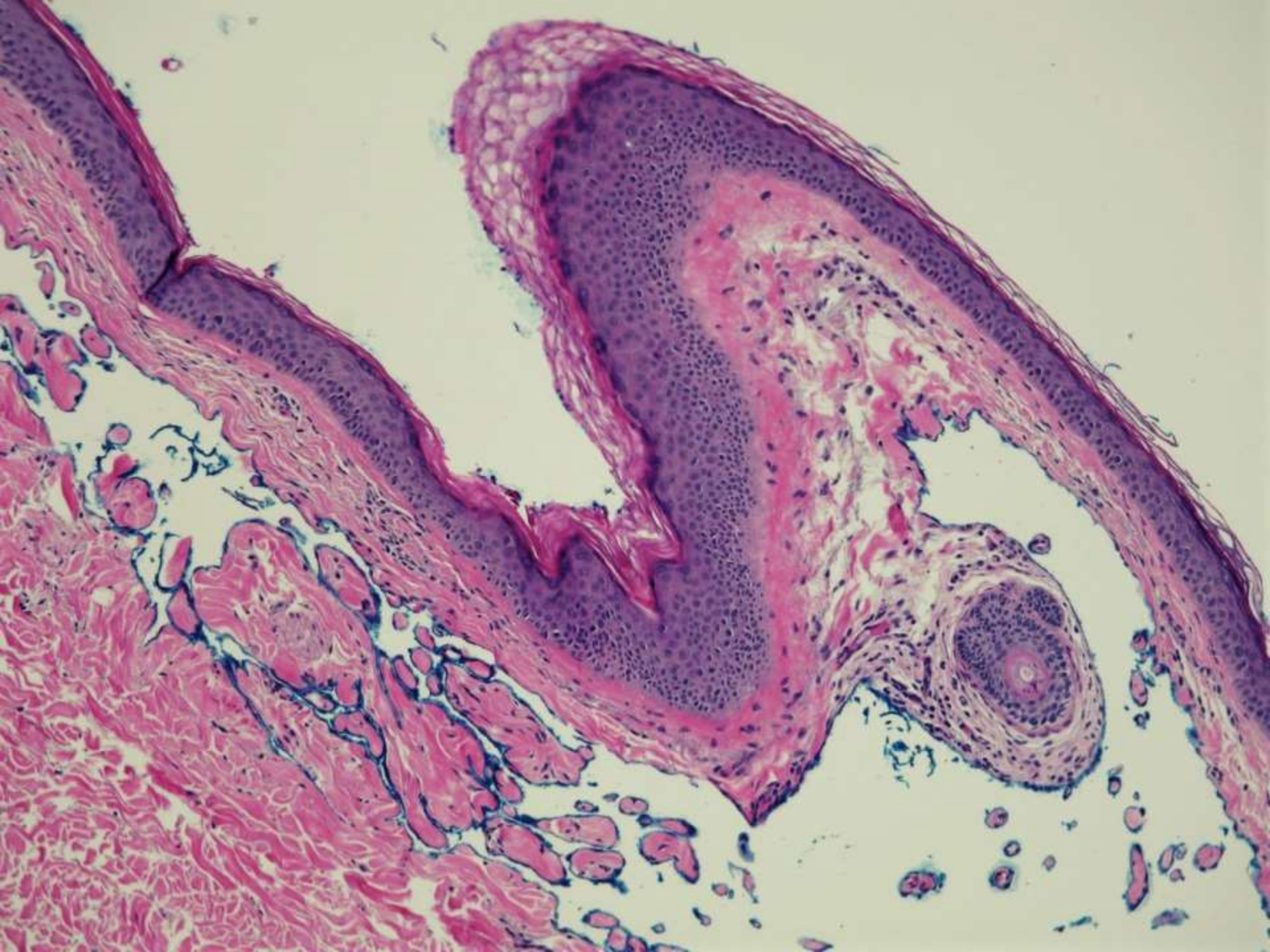


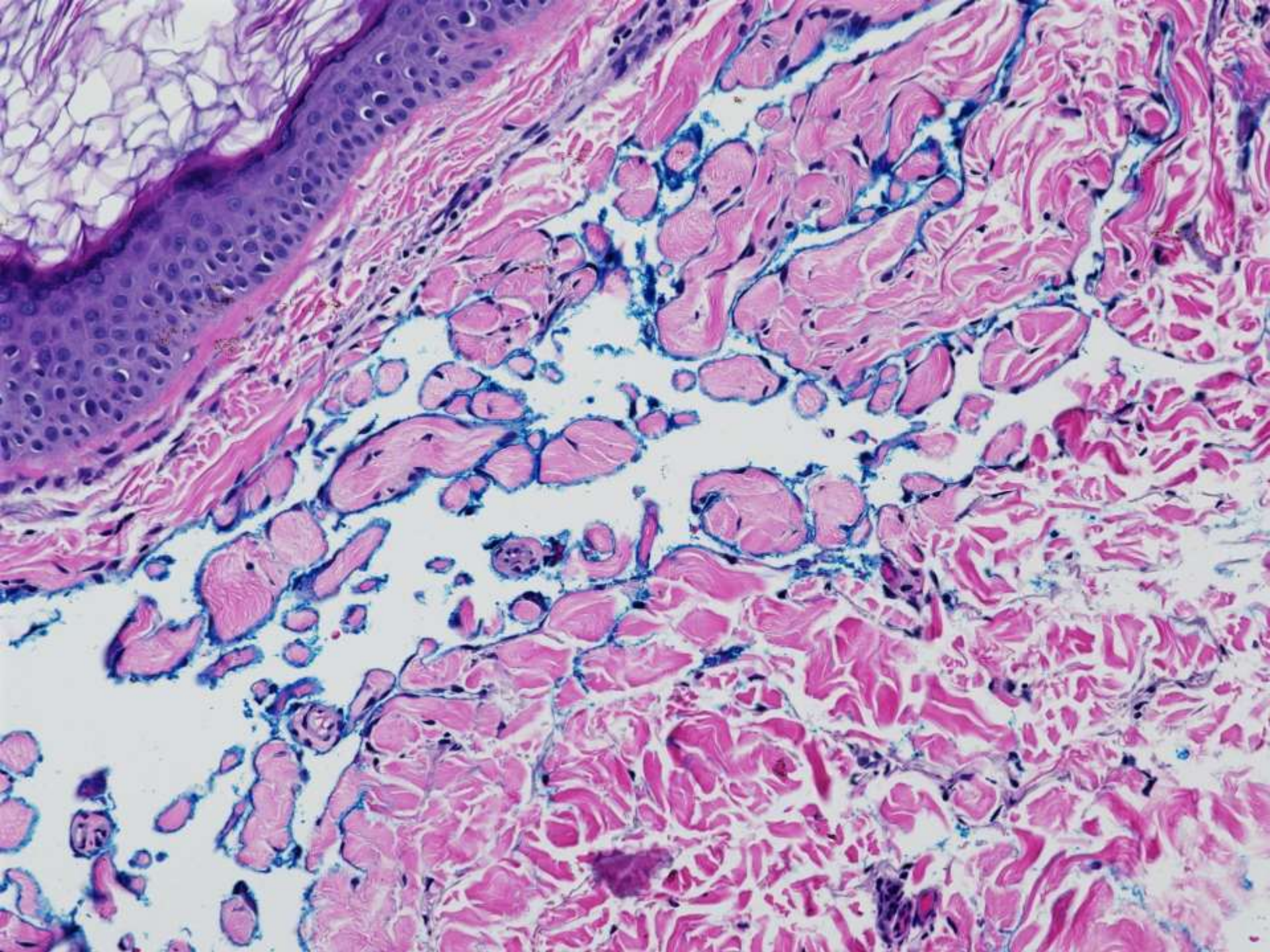


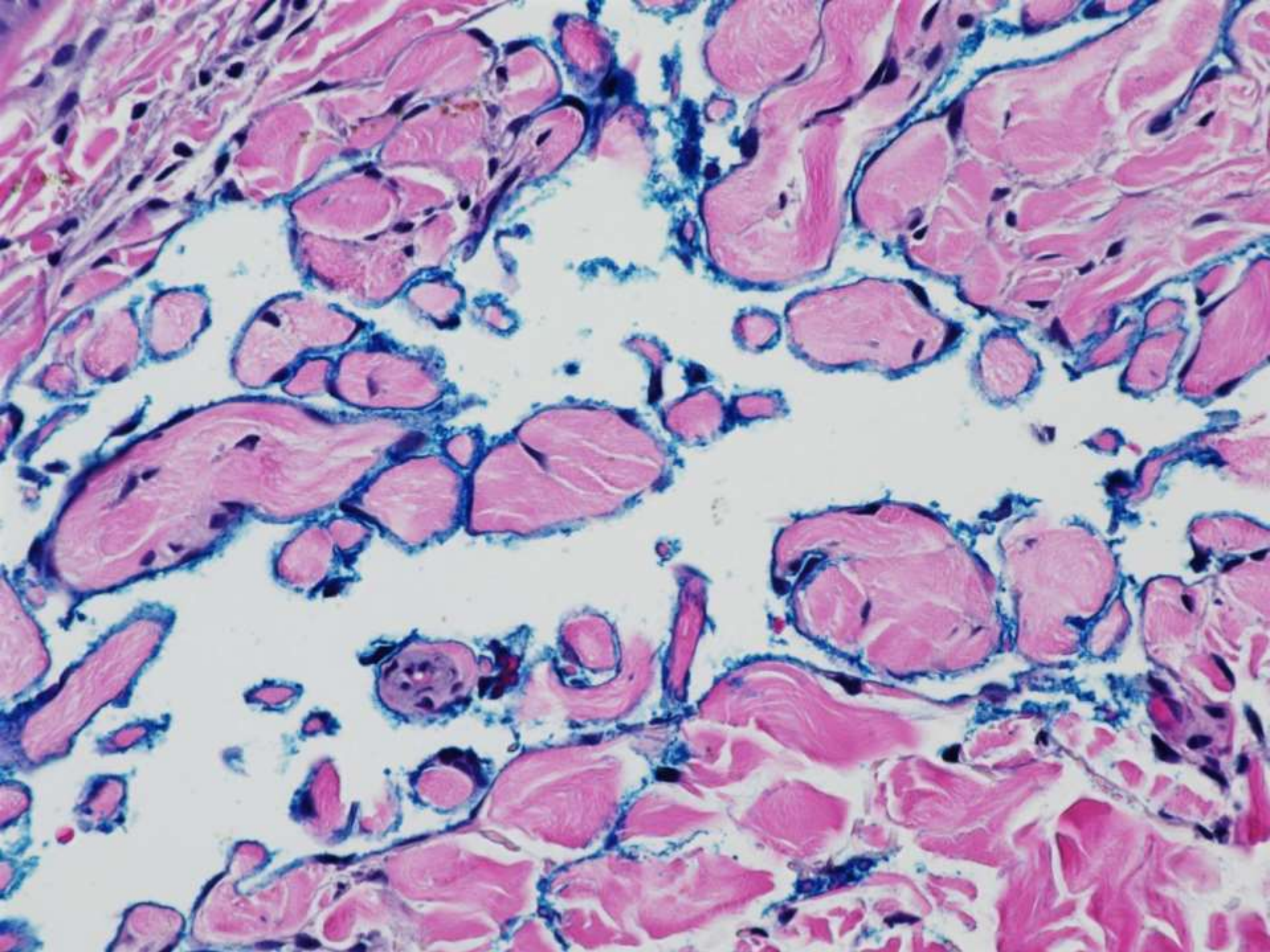


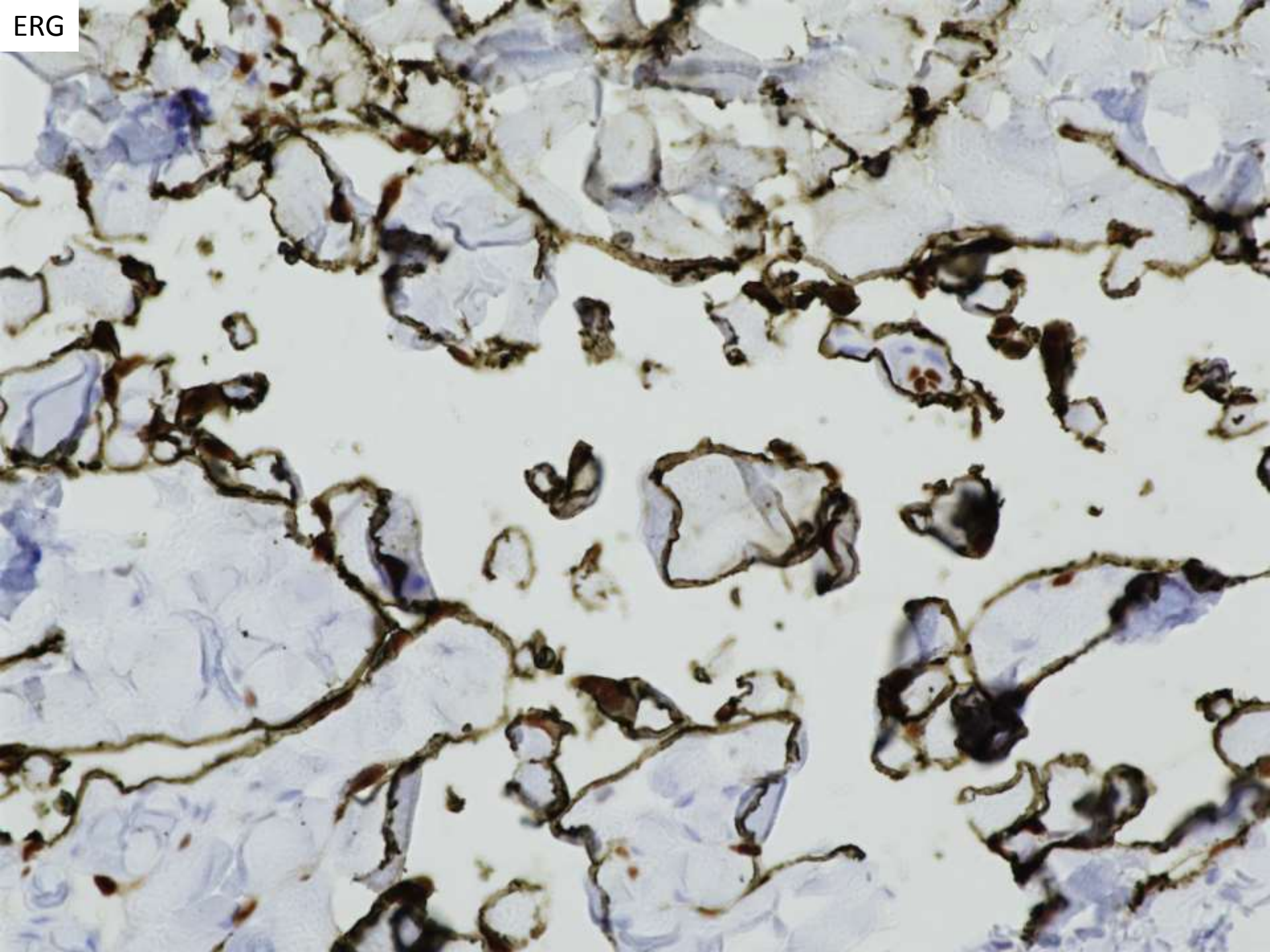











ERG

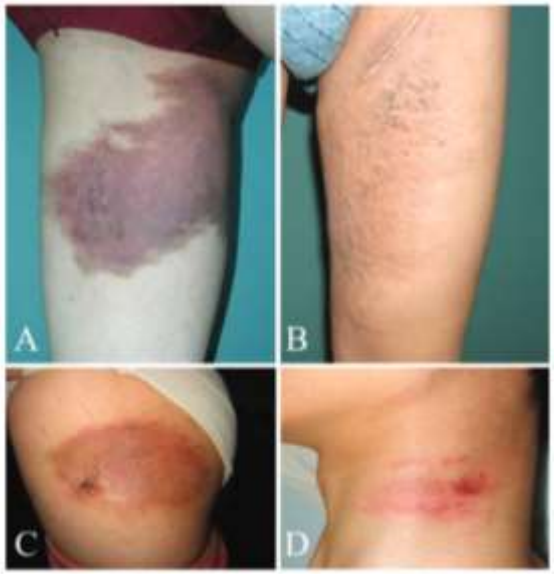
Diagnosis?

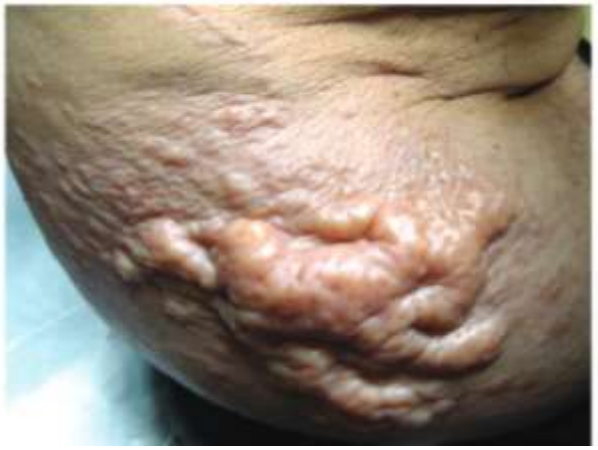
Differential diagnosis

- Atypical vascular lesion
- Well-differentiated angiosarcoma
- Kaposi's sarcoma
- **Benign lymphangioendothelioma (Acquired progressive lymphangioma)**

Benign lymphangioendothelioma

- Median age, 52 yrs; range, 5–90 yrs
- Varied sites of involvement
- Slowly growing,solitary, erythematous to hyperpigmented,flat or slightly elevated patch or plaque
- Largest reported thus far was 60 cm

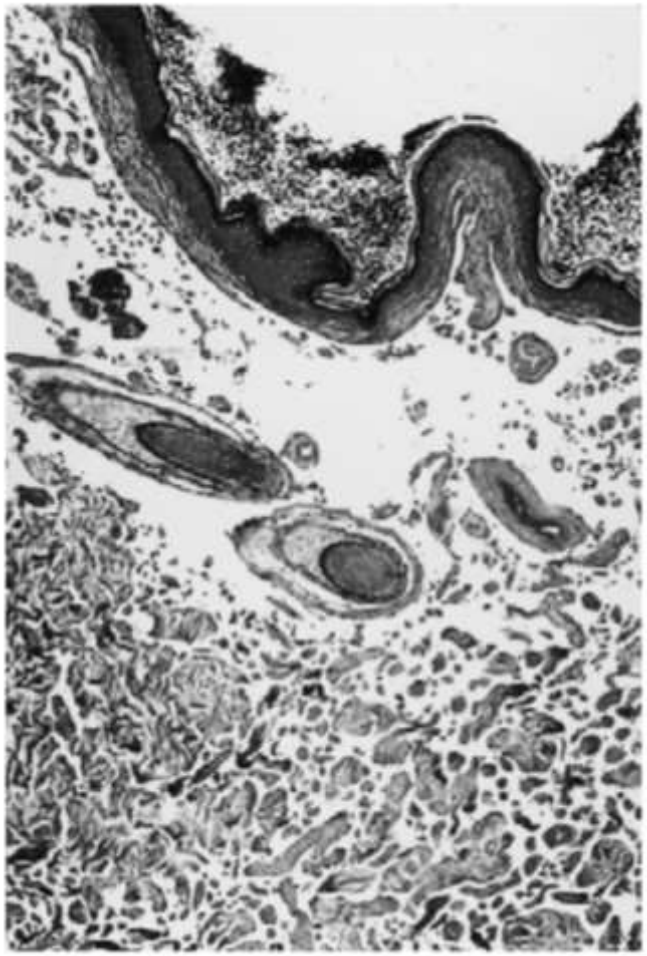




Schnebelen AM, Page J, Gardner JM, Shalin SC. Benign lymphangioendothelioma presenting as a giant flank mass. J Cutan Pathol. 2015 Mar;42(3):217-21.

Benign lymphangioendothelioma

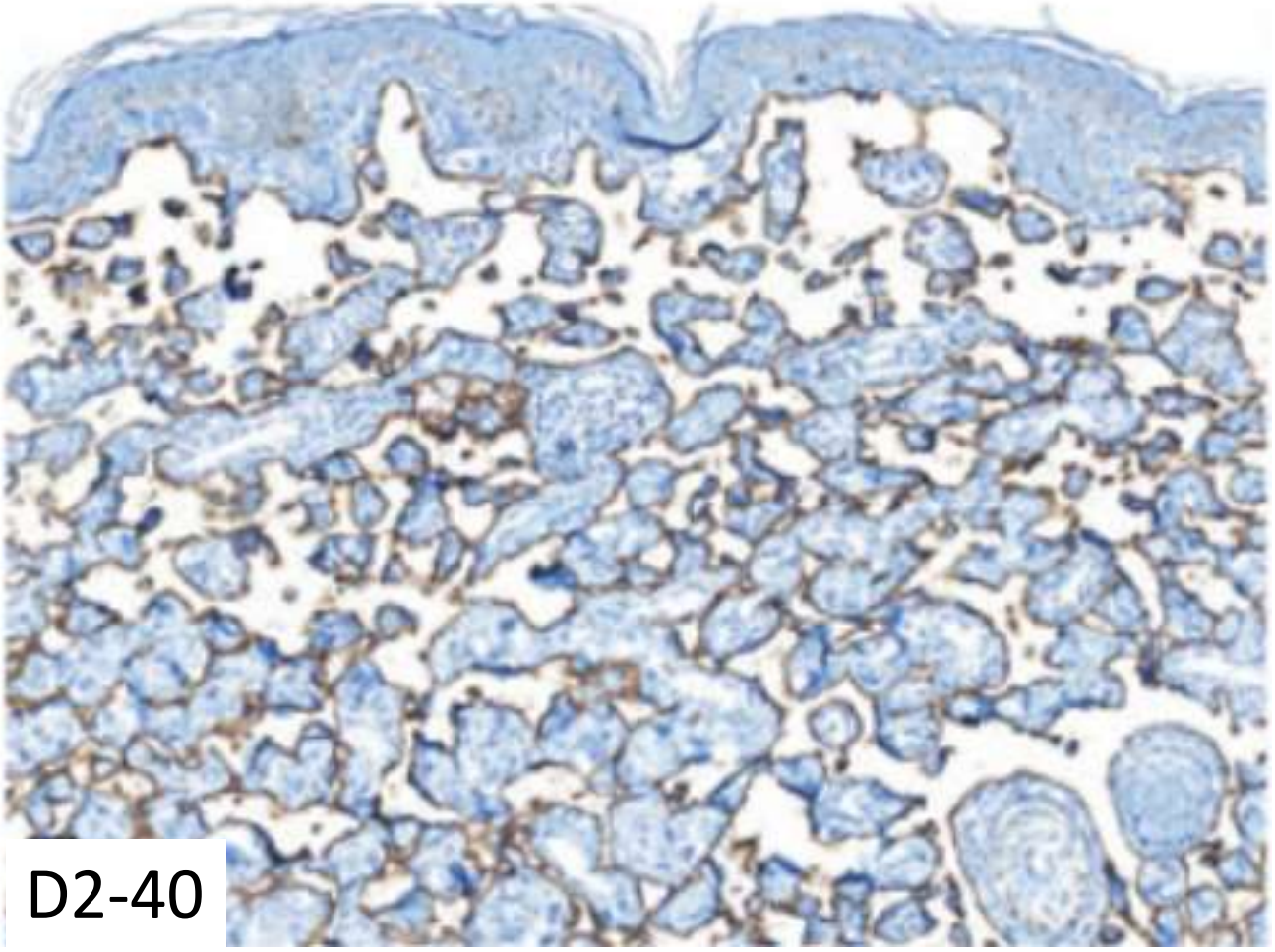
- Abundant anastomosing vessels that lined by flattened endothelial cells and that dissect dermal collagen
- Vessels ramify in the dermis and occasionally extend into the subcutis
- Vessels are filled with clear fluid
- No atypia, mitotic activity, or solid areas of growth



Guillou L, Fletcher CD: Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma. Am J Surg Pathol. 24 (8):1047-1057

Benign lymphangioendothelioma (acquired progressive lymphangioma)

- CD34+
- CD31+
- D2-40+
- Prox1+

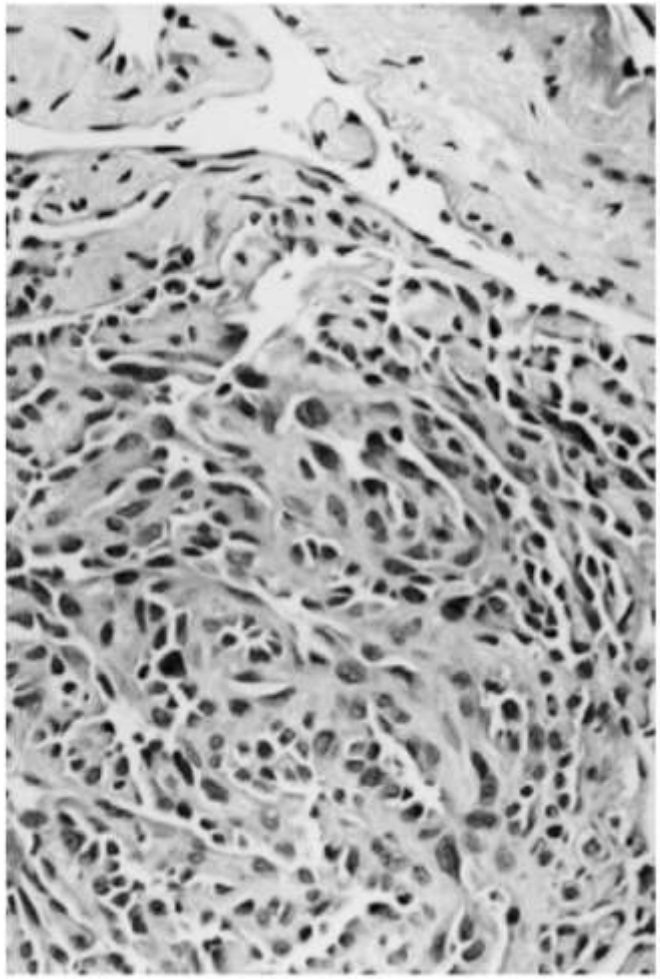


D2-40

Wang L, Chen L, Yang X, Gao T, Wang G. Benign lymphangioendothelioma: a clinical, histopathologic and immunohistochemical analysis of four cases. J Cutan Pathol. 2013;40:945–949.

Clinical behavior

- Benign clinical course with no evidence of metastasis



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Benign lymphangioendothelioma versus angiosarcoma

	Angiosarcoma	**Benign lymphangioendothelioma**
Clinical setting	Lymphedema-associated Radiation-associated	All ages
Site	Face, neck, scalp	Outside of the head and neck region
Clinical appearance	Reddish blue plaque or multiple raised bluish nodules	Slow-growing, gradually enlarging, solitary patch or raised nodule

	Angiosarcoma or Kaposi sarcoma	Benign lymphangioendothelioma
Cytology and architecture	Ill-defined Branching Variable cytologic atypia Multilayering Micropapillary tufting	Thin and discontinuous smooth muscle layer
Intravascular and extravascular erythrocytes	Common	Absent
Hemosiderin deposition	Common	Absent
Mixed or plasma cell-rich inflammation	Common	Absent
Spindle cell and/or epithelioid component	Common	Absent
MYC gene amplification	Present in a subset	Absent

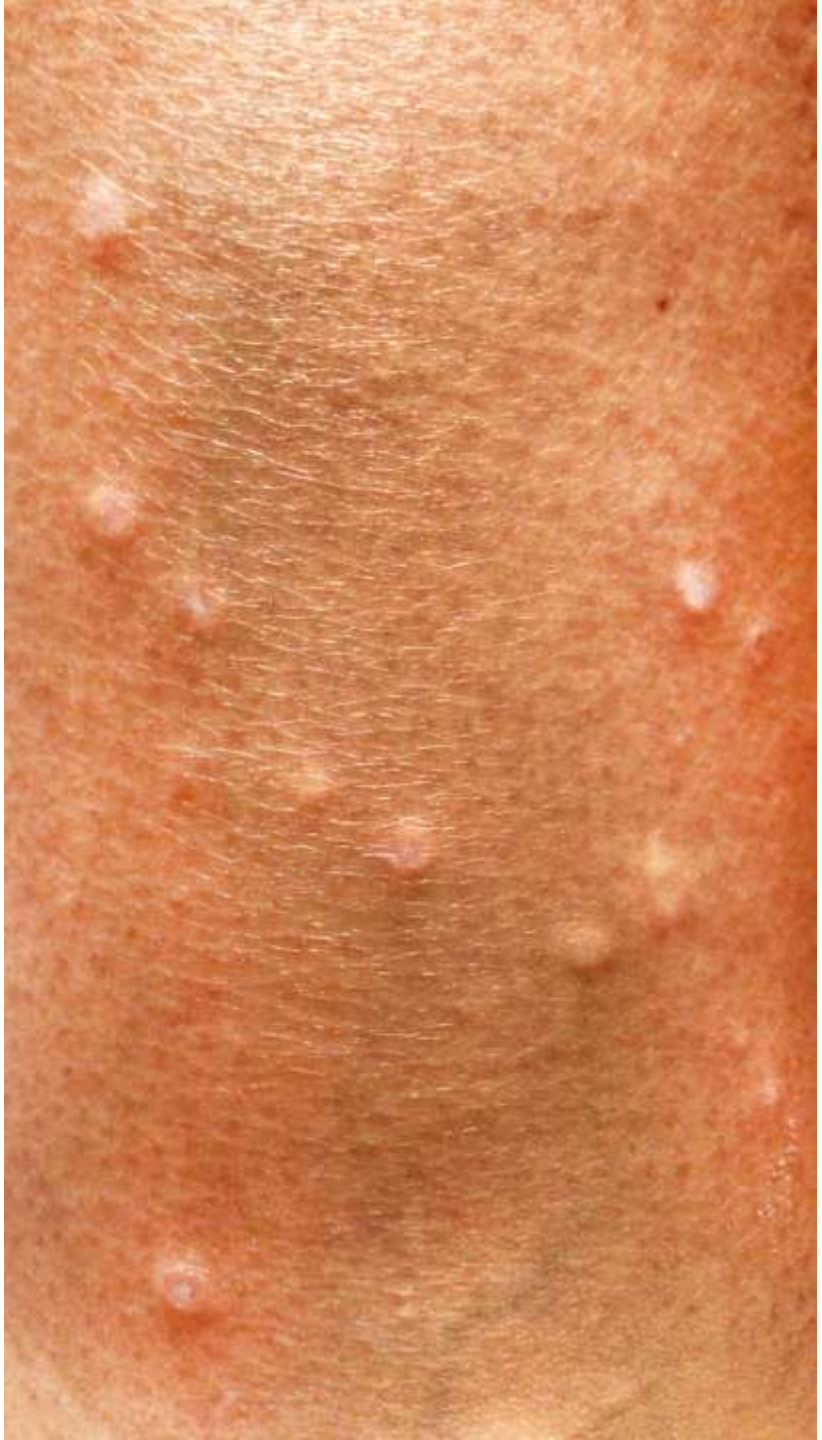
References

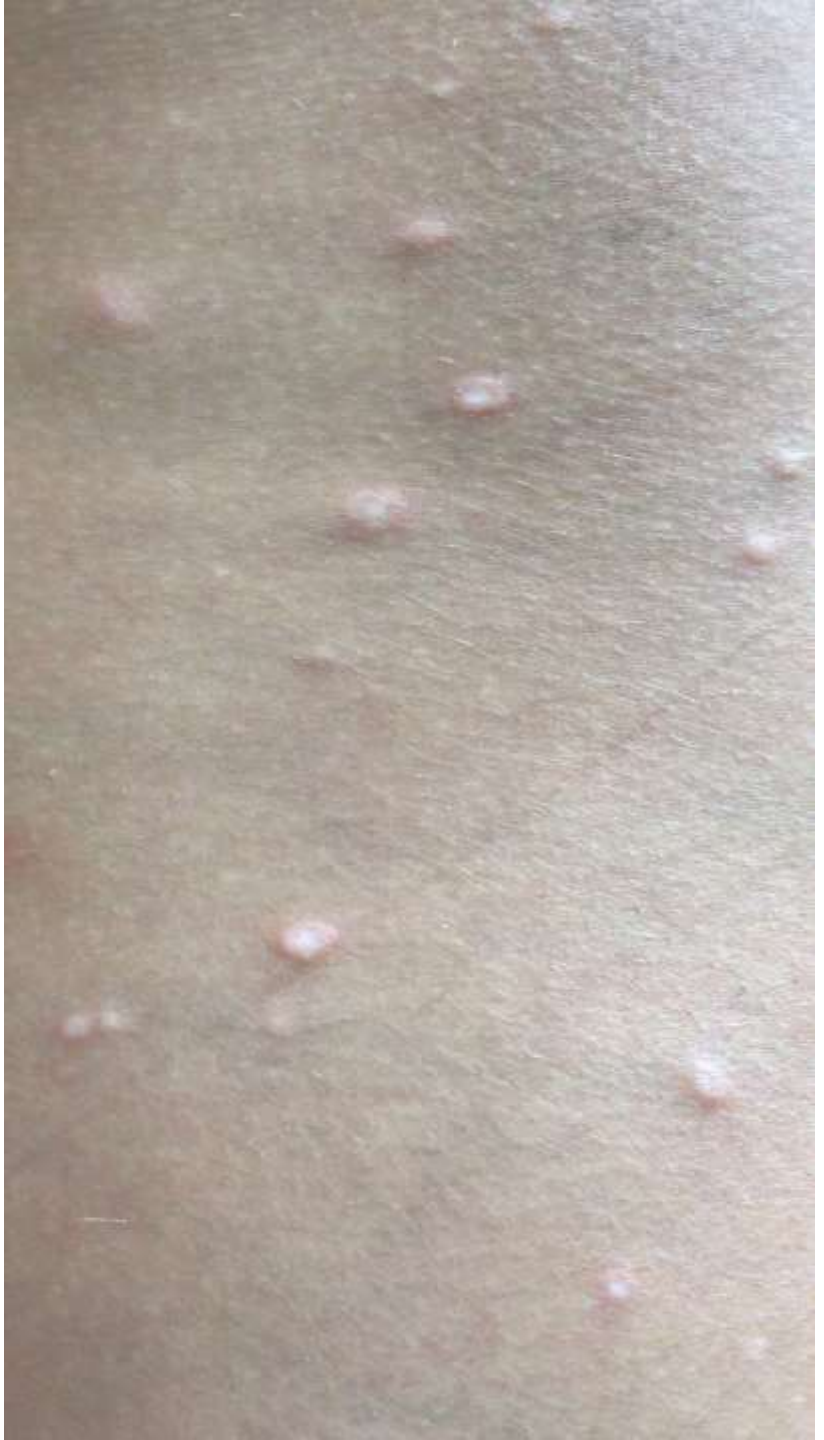
1. Guillou L, Fletcher CD: Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma. Am J Surg Pathol. 24 (8):1047-1057. PMID: 10935645
2. Schnebelen AM, Page J, Gardner JM, Shalin SC. Benign lymphangioendothelioma presenting as a giant flank mass. J Cutan Pathol. 2015 Mar;42(3):217-21.

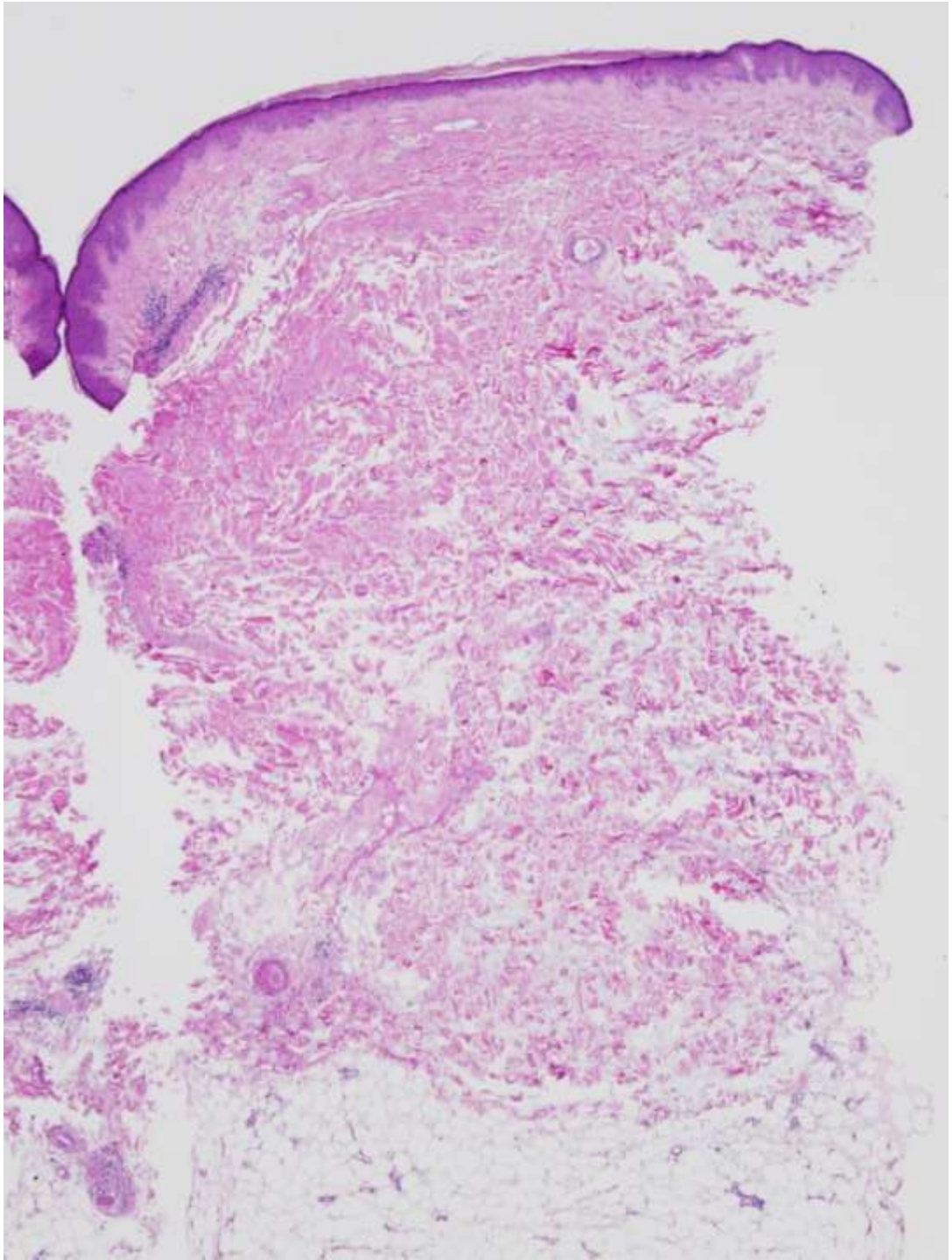
SB 6353

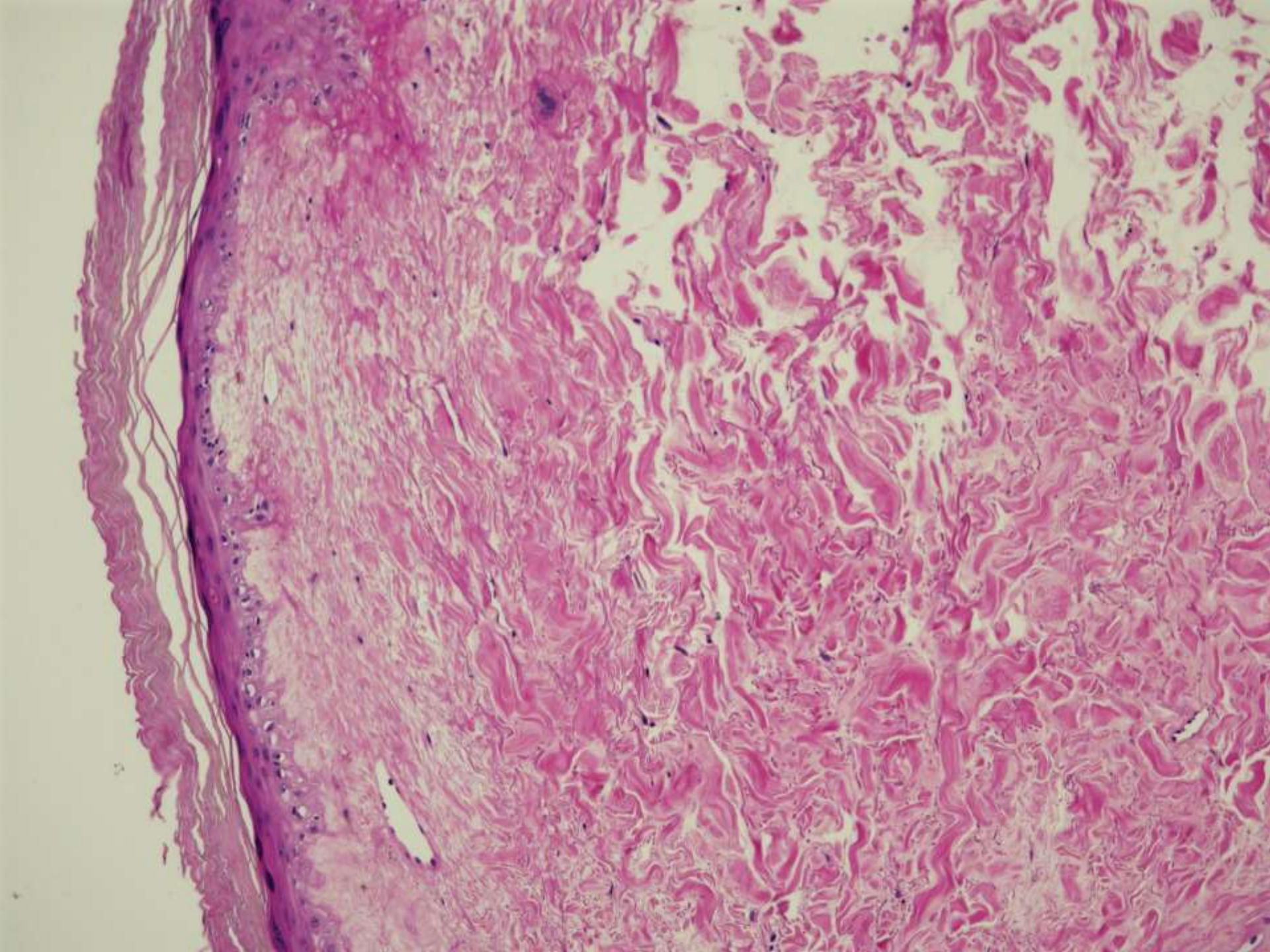
Sebastian Fernandez-Pol/Kerri Rieger/Roberto Novoa; Stanford

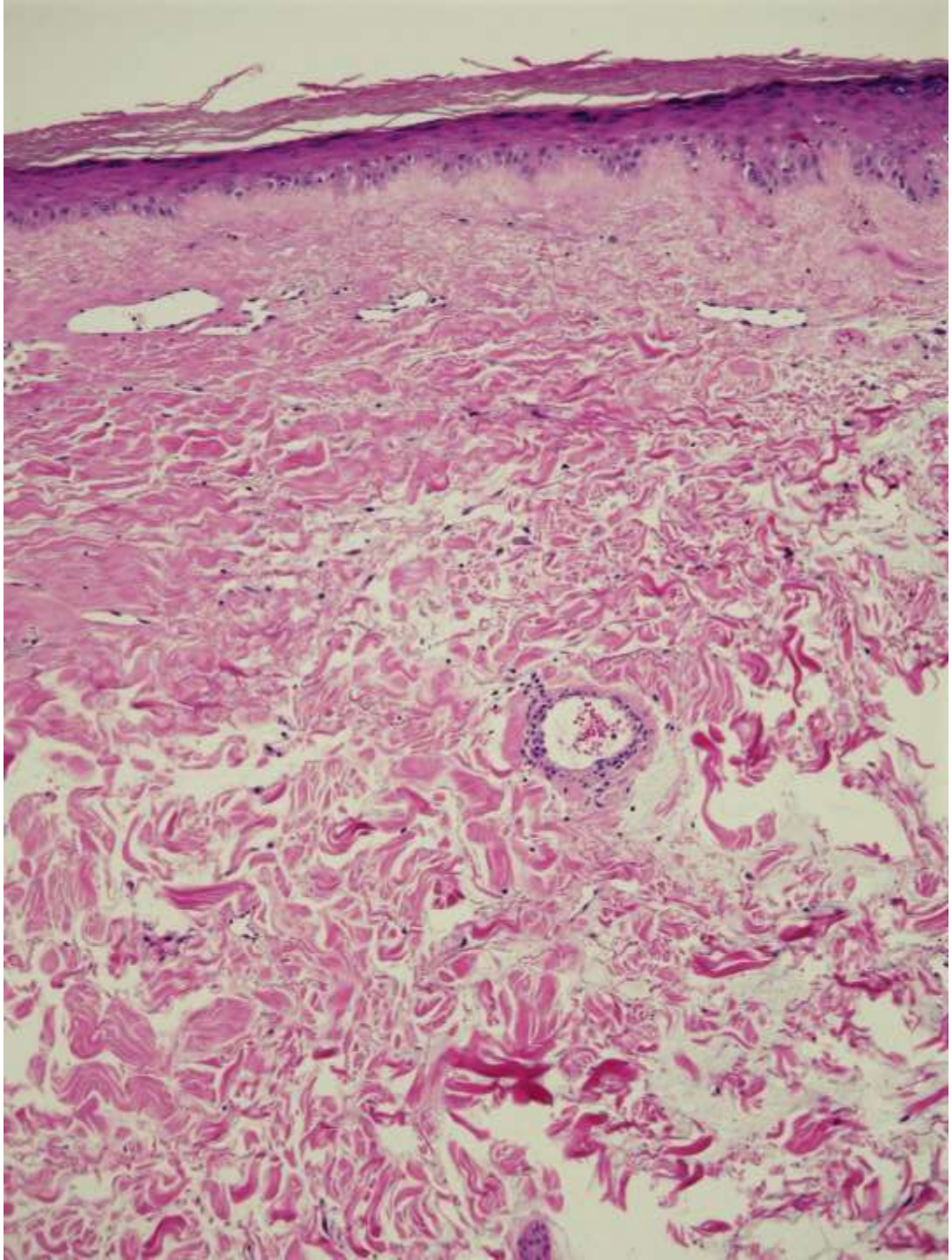
15-year-old female who developed waxing and waning neurologic symptoms in May 2017 involving mainly cranial nerves. In March 2018 she complained of foot numbness, progressive lower limb weakness eventually requiring use of a wheelchair. In addition she develops loss of sphincter control and marked stiffness. Skin lesions appeared in September 2017 characterized by macules and papules on both lower limbs, then appearing on the trunk and upper limbs and sparing the face. The lesions are non-painful and non-itching.

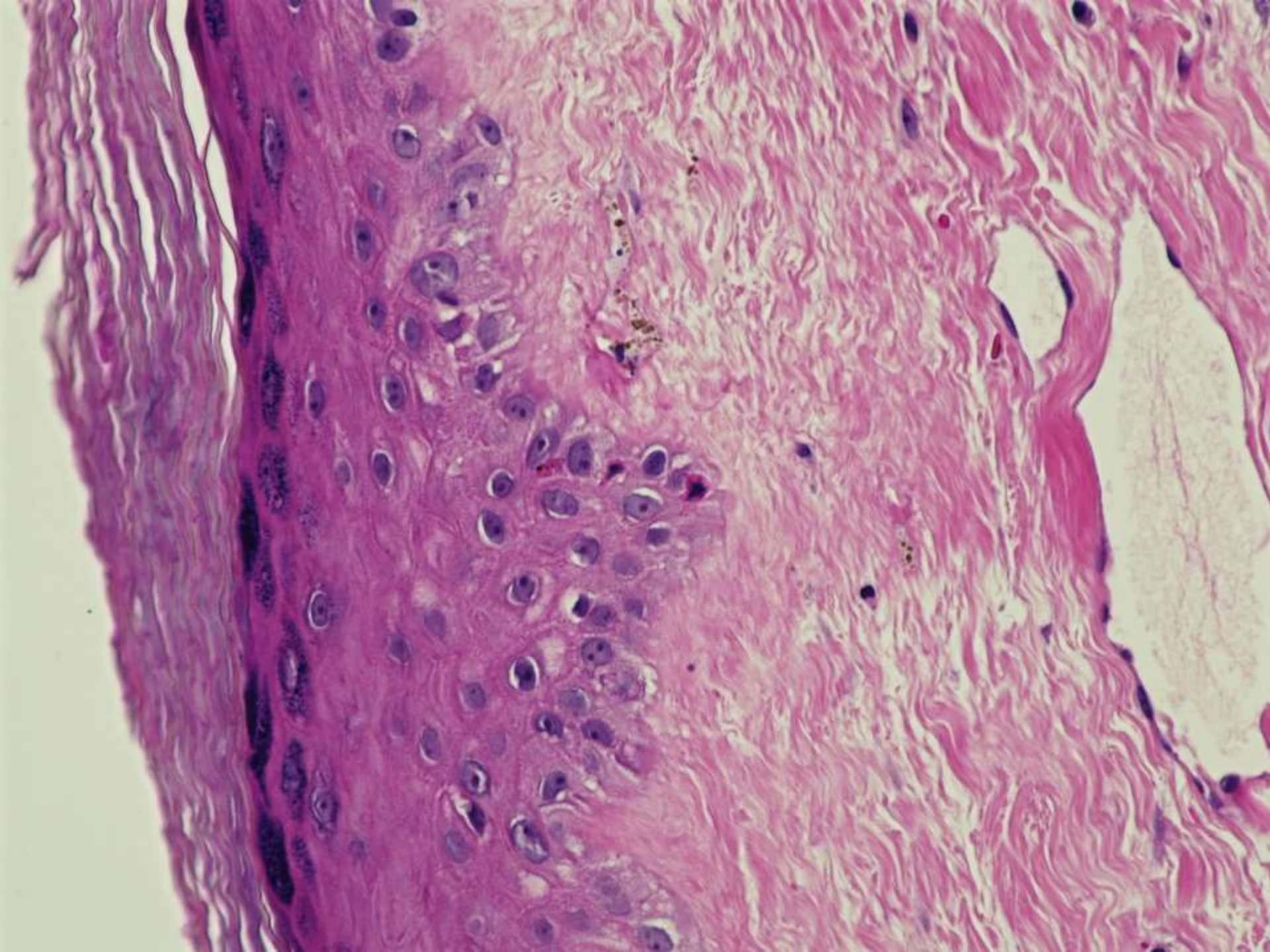


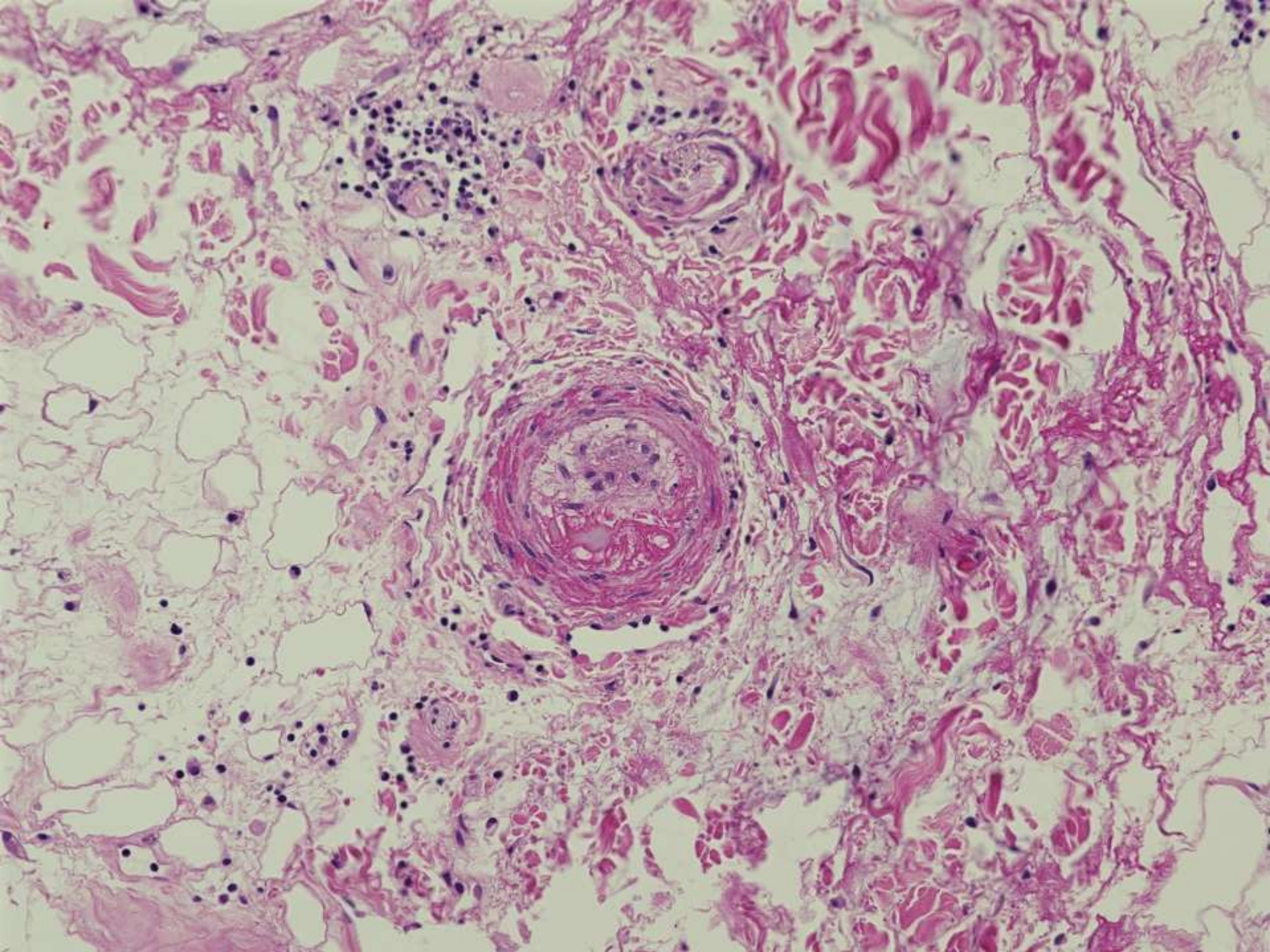


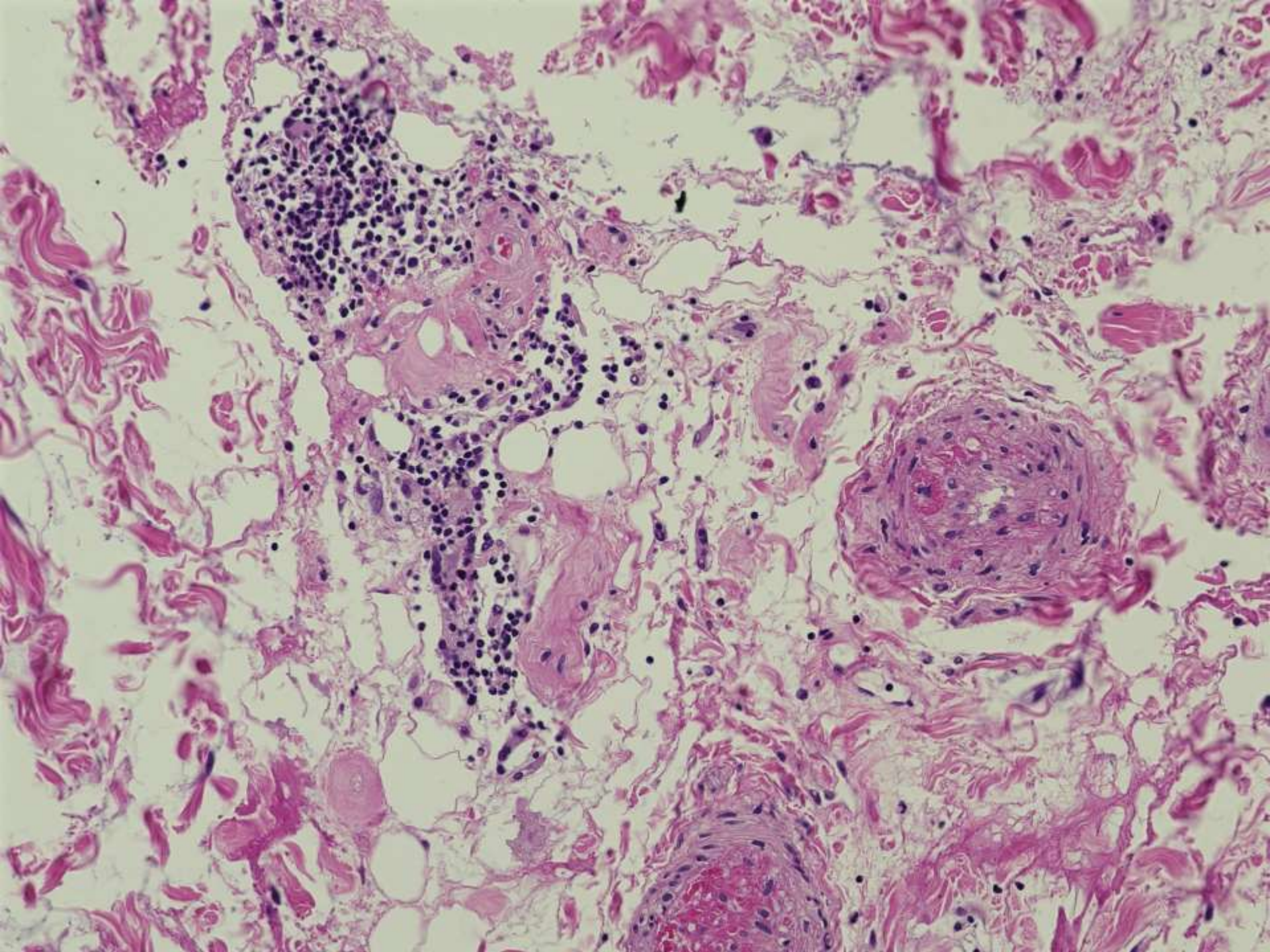


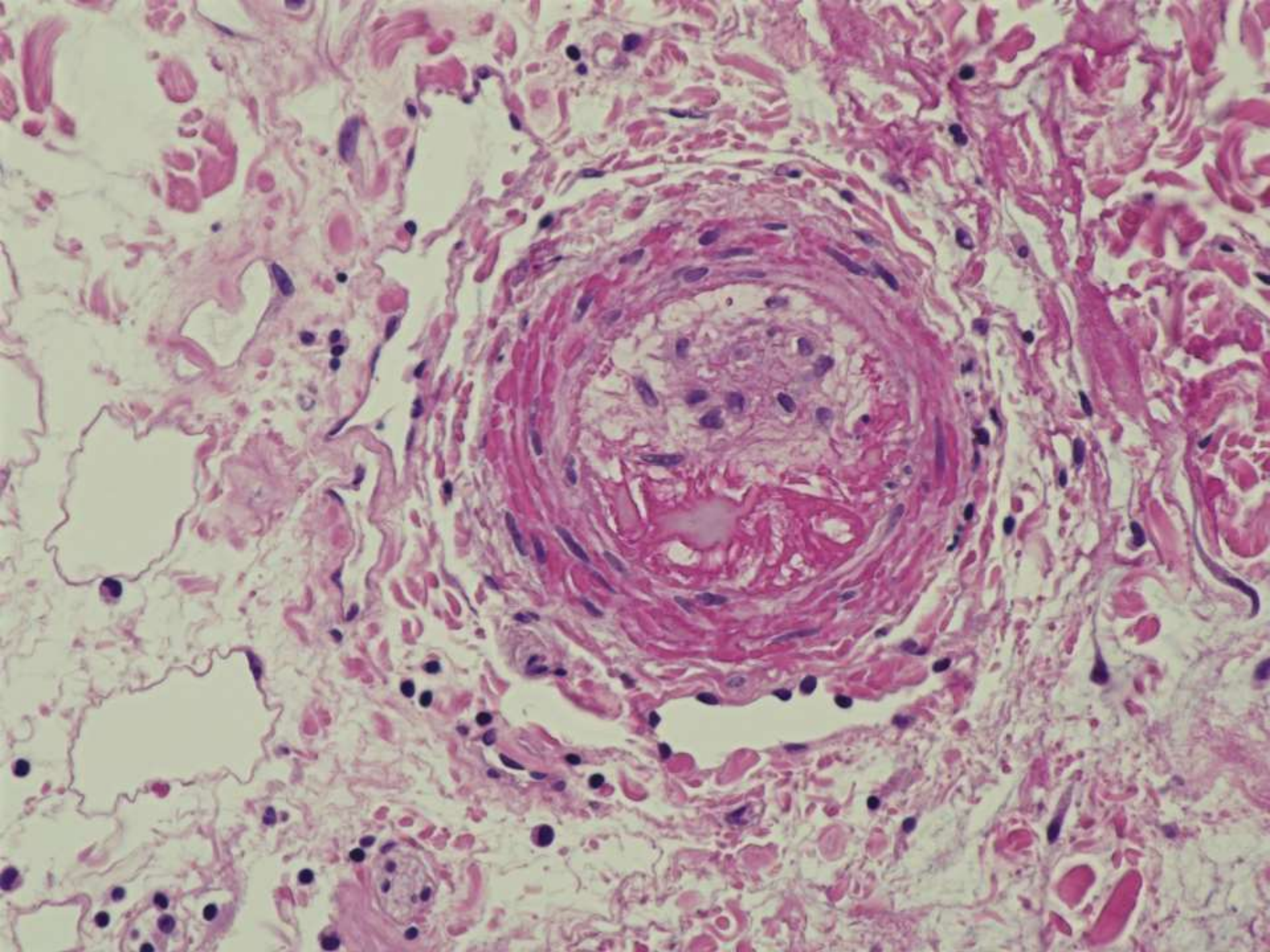


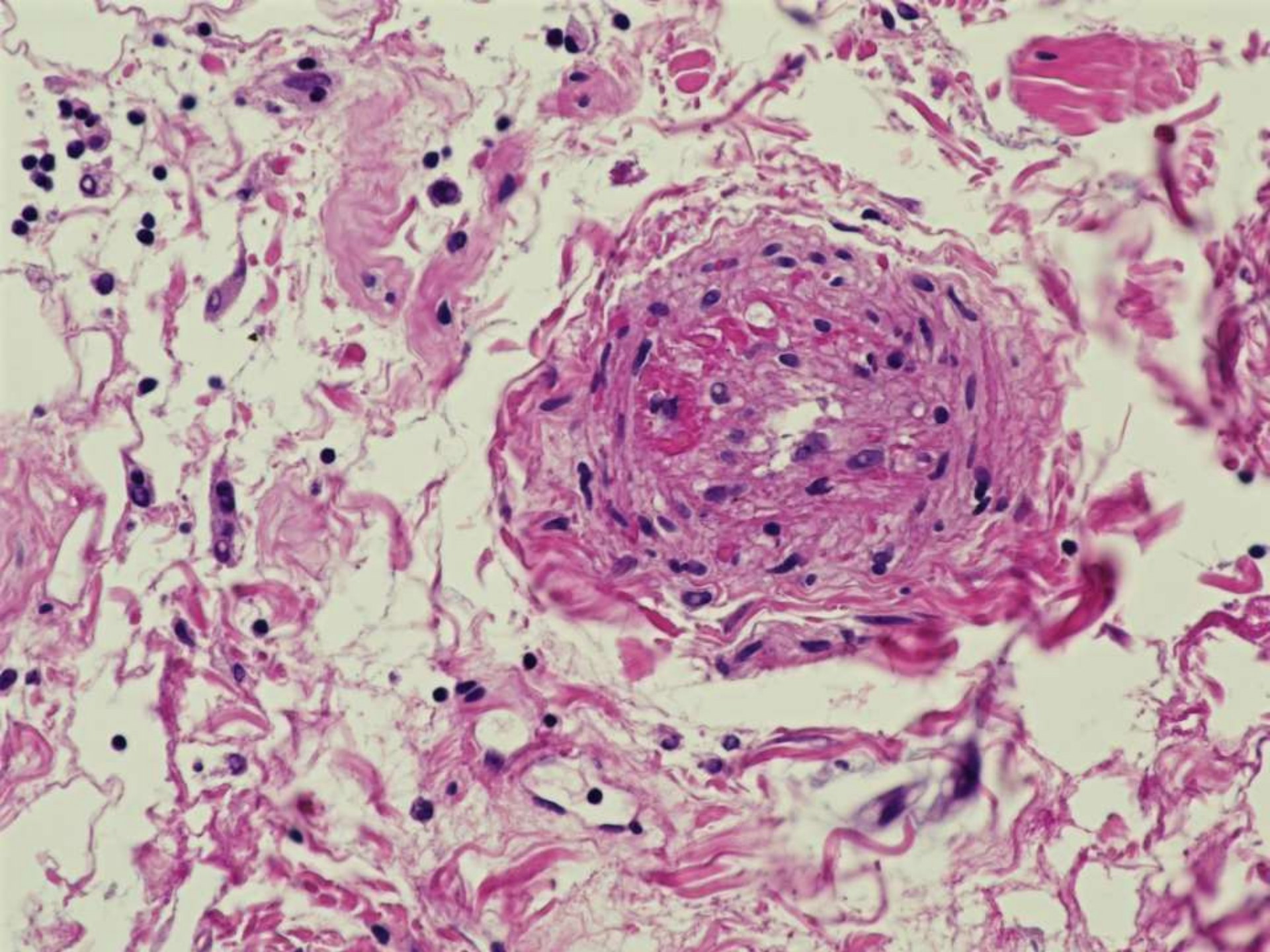


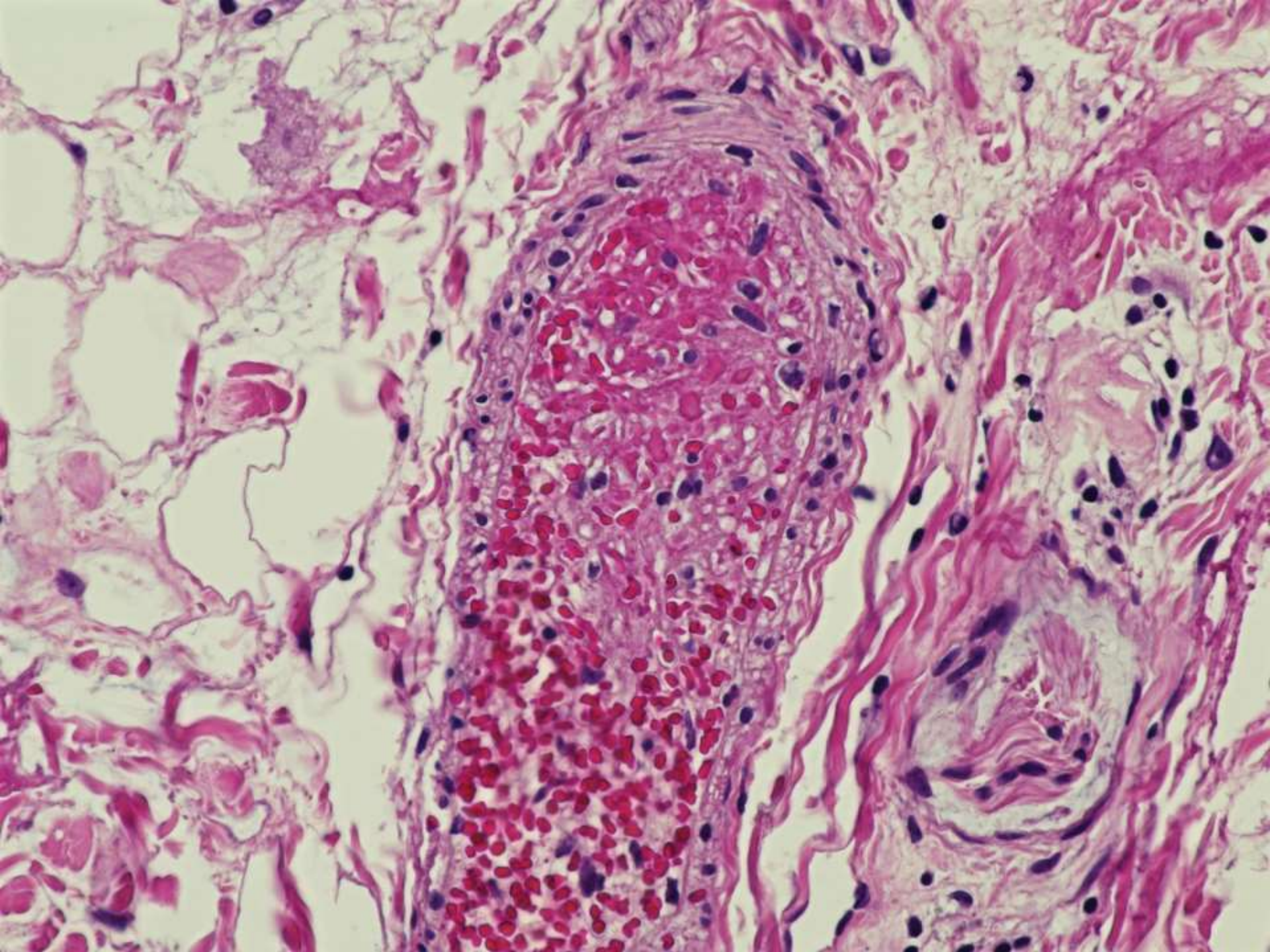


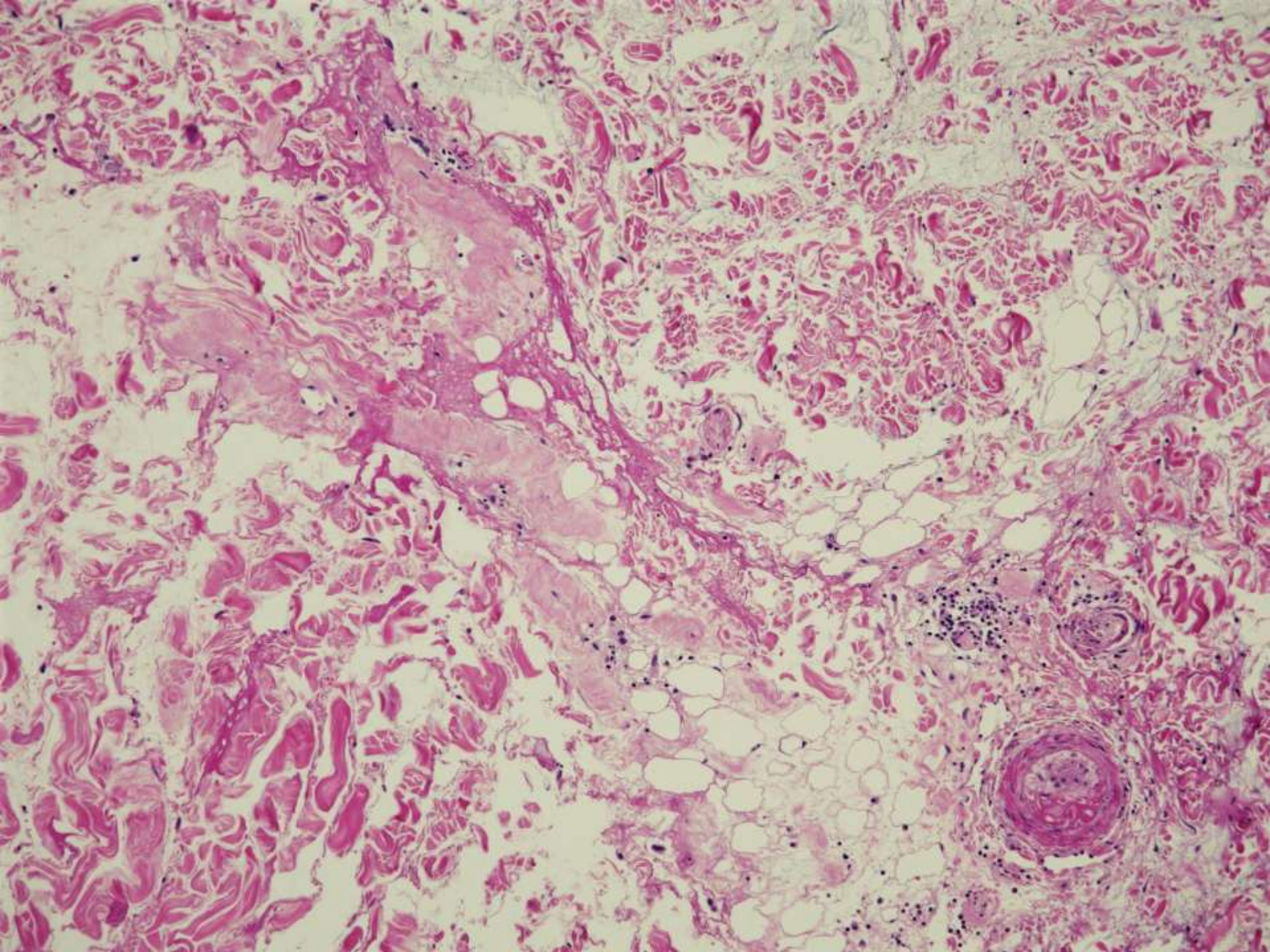


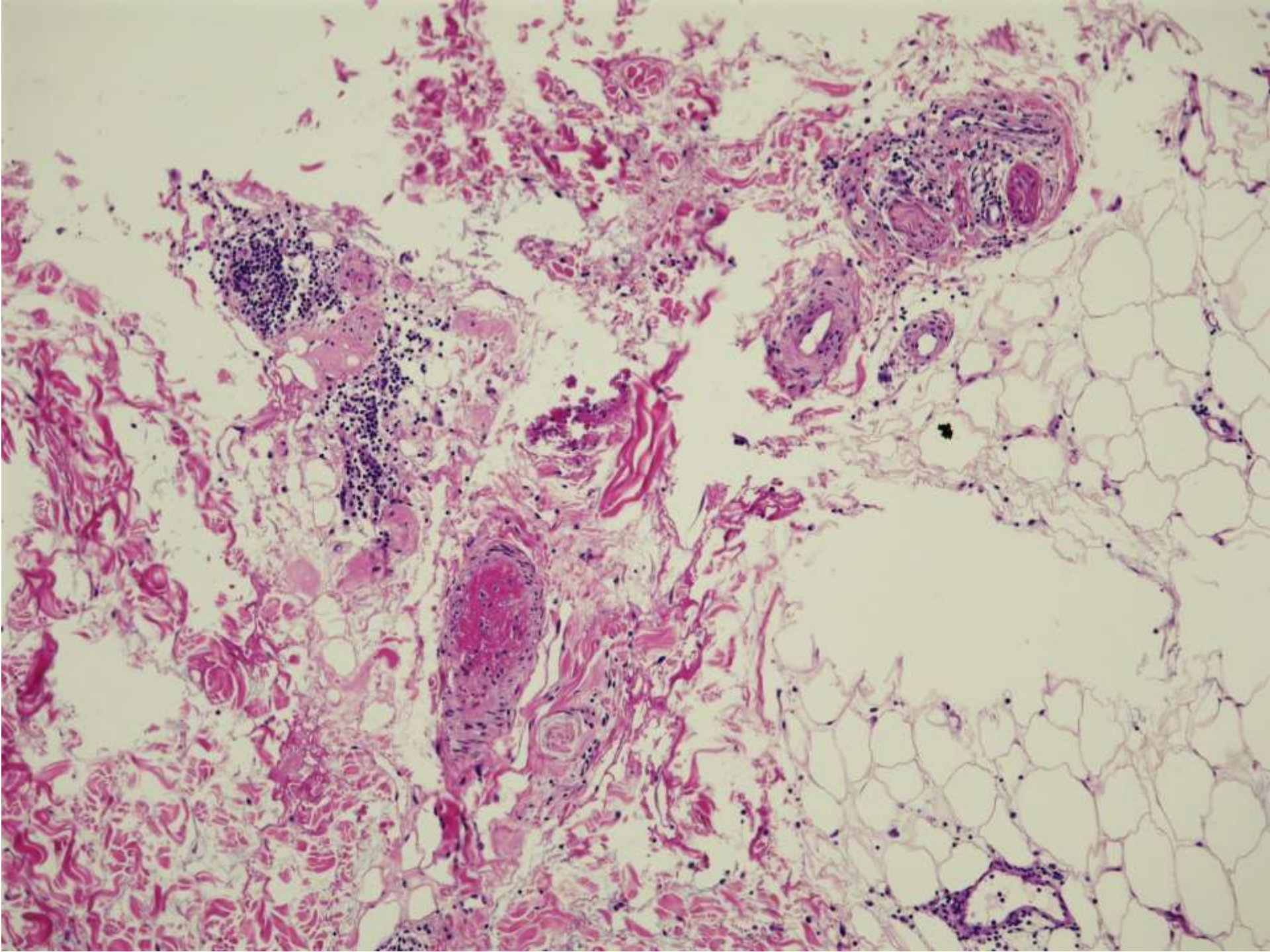


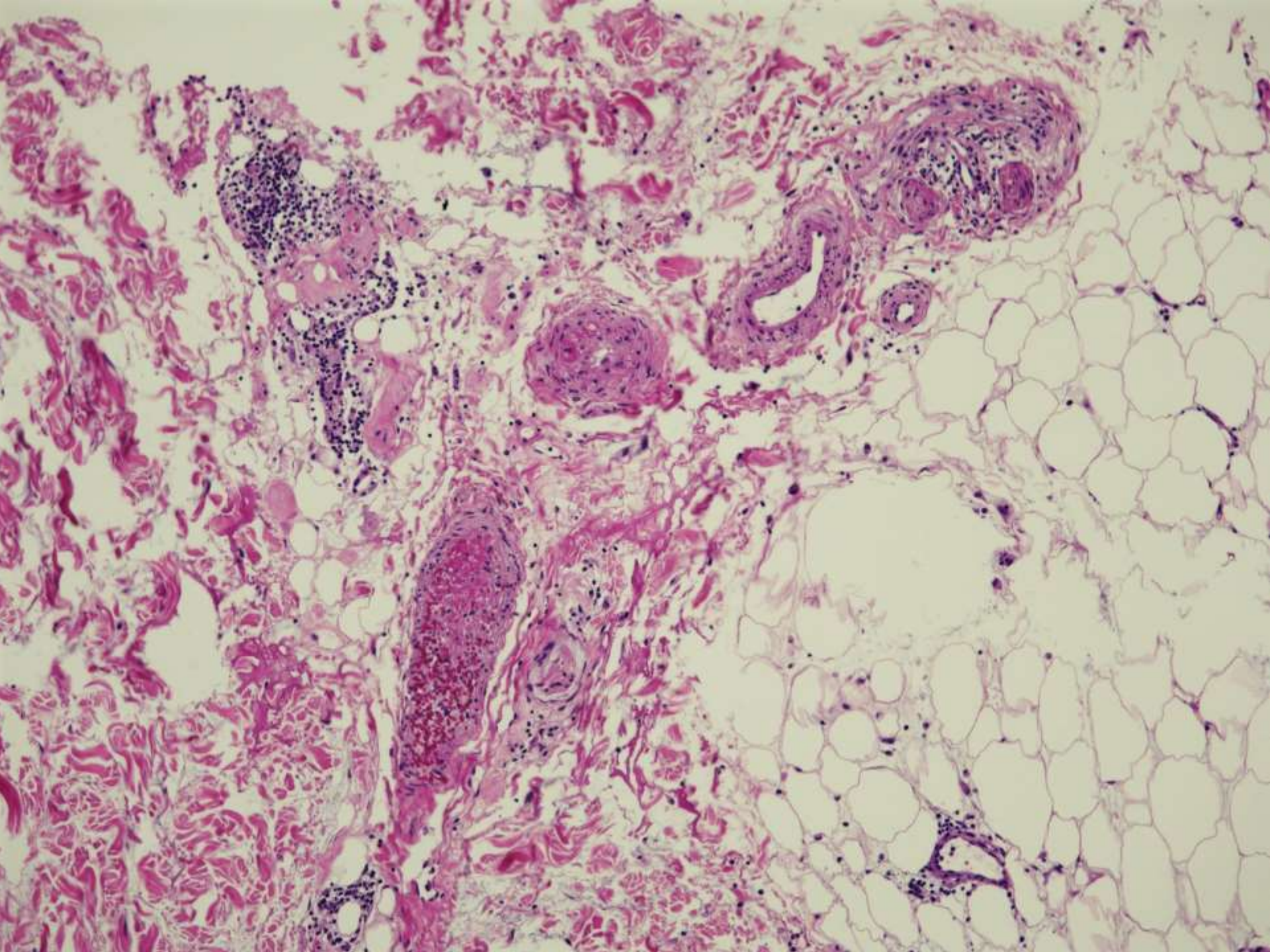


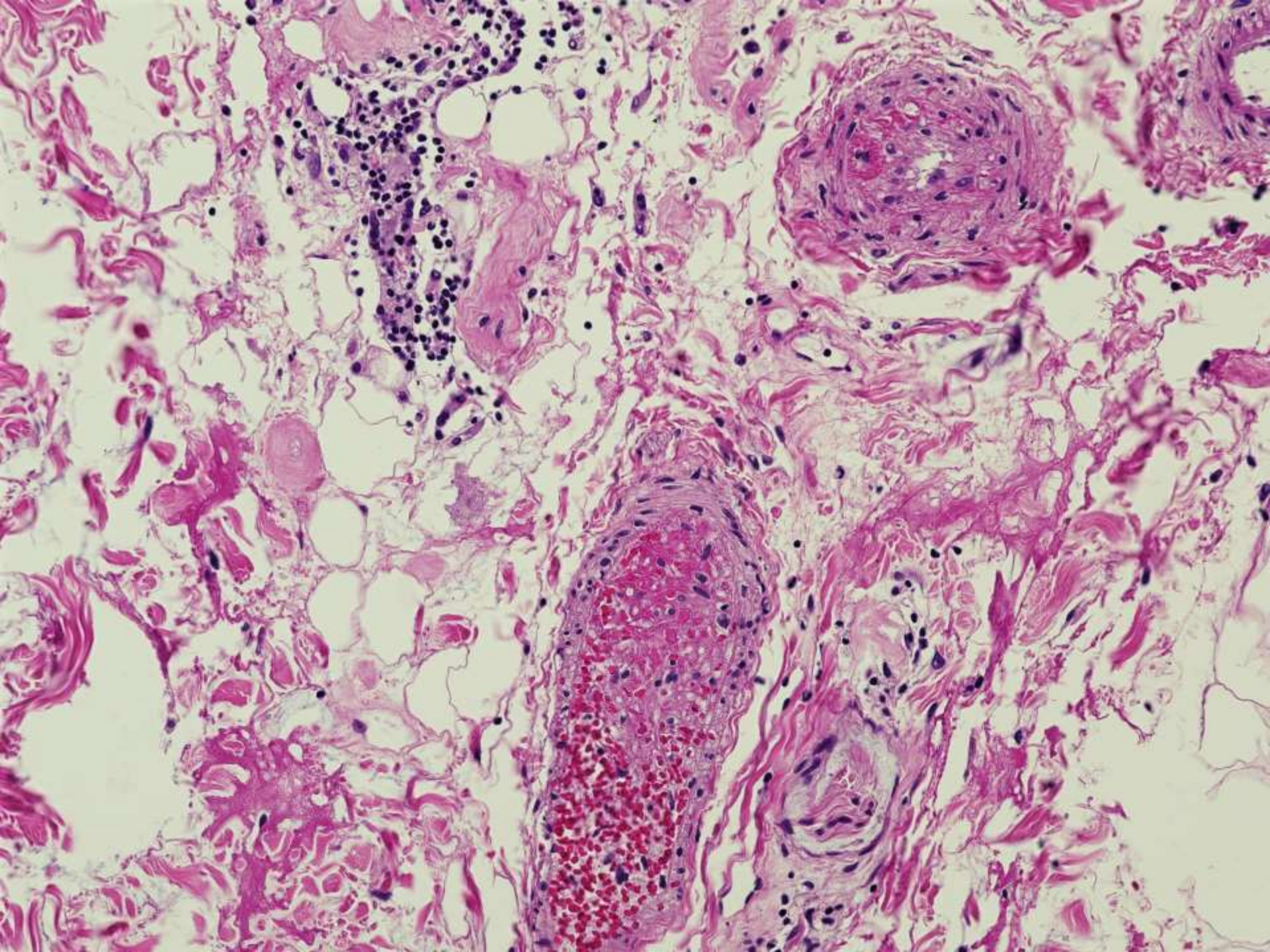








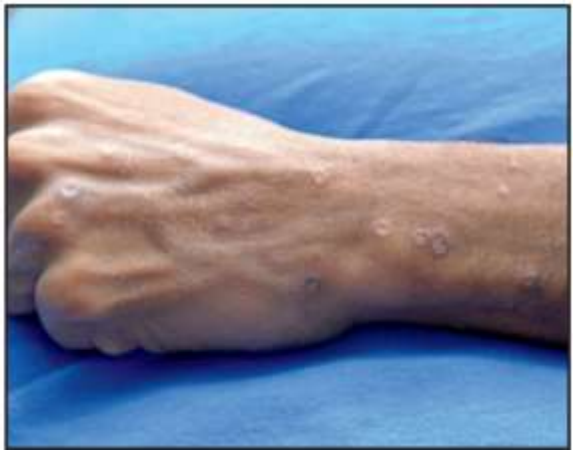


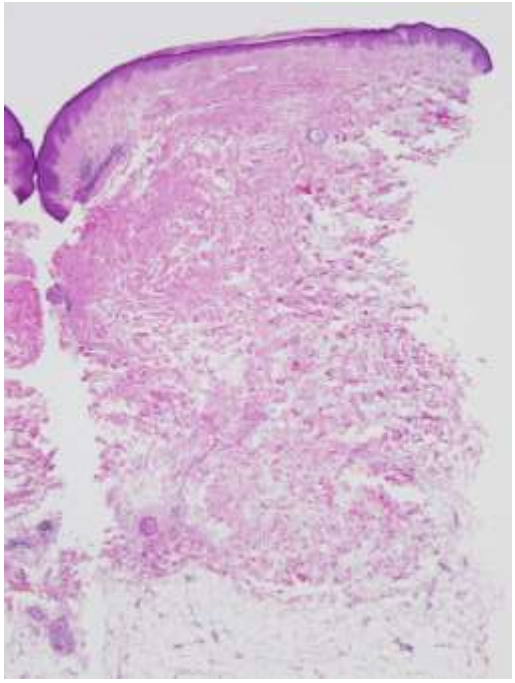


Diagnosis?

Malignant atrophic papulosis (MAP)

- Also known as Degos disease
- Known by unique skin presentation
  - Central porcelain-white atrophic lesions with telangiectatic rim
- Two variants:
  - Cutaneous MAP (can progress to systemic)
  - Systemic MAP affects GI, CNS, lungs, other internal organs
- Possible association with autoimmune or thrombotic disorders including scleroderma, lupus erythematosus, and antiphospholipid antibody syndrome

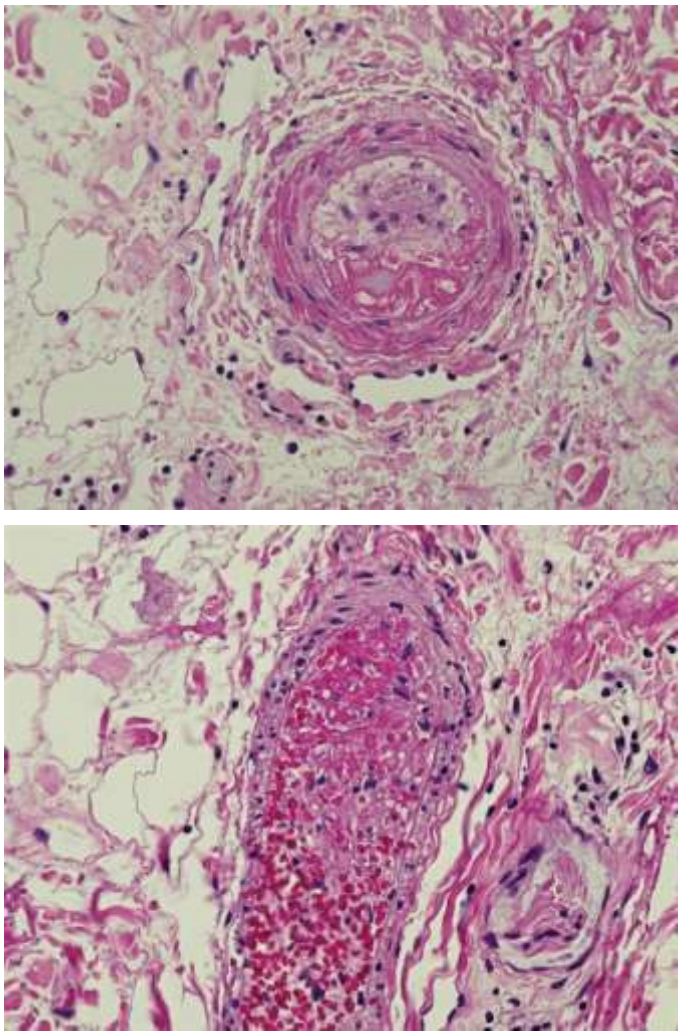




Magro, et al: Degos disease: a C5b-9/interferon-alpha-mediated endotheliopathy syndrome. Am J Clin Pathol 2011, 135:599–610.
Huang et al. Pediatric Malignant Atrophic Papulosis. Pediatrics. 2018; 141(s5):e20164206

Histology of malignant atrophic papulosis (MAP)

- Pauci-inflammatory thrombogenic microangiopathy with endothelial cell injury



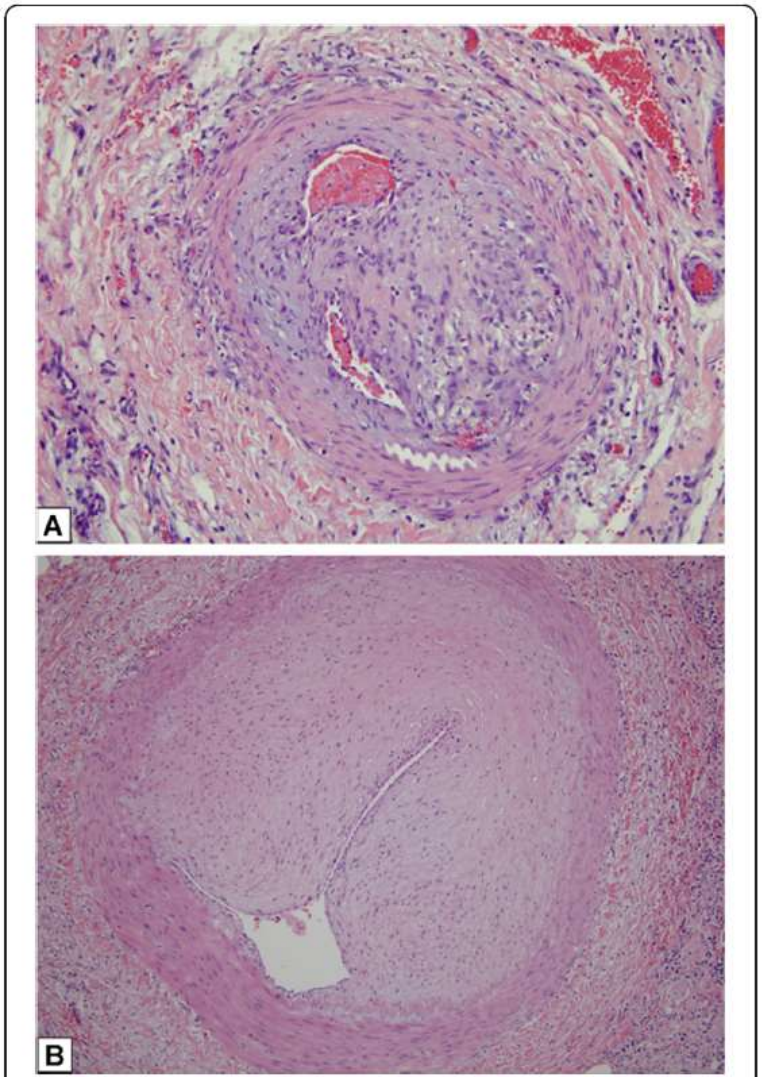
Huang Y-C, Wang J-D, Lee F-Y, et al. Pediatric Malignant Atrophic Papulosis. Pediatrics. 2018; 141(s5):e20164206

Submucosal vessels from intestinal resection

Fibro-obliterative arteriopathy

Pre-eculizumab humanized mAbagainst complement protein C5

2 years of eculizumab



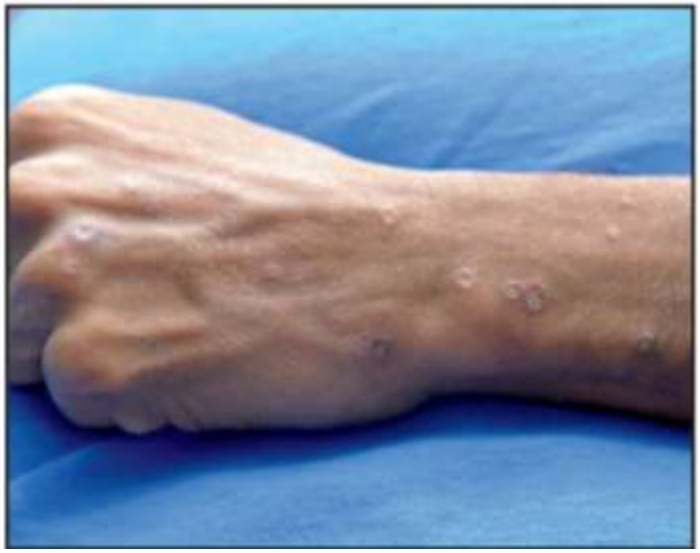
Magro CM, Wang X, Garrett-Bakelman F,et al. The effects of Eculizumab on the pathology of malignant atrophic papulosis. Orphanet J Rare Dis. 2013;8:185

Malignant atrophic papulosis (MAP)

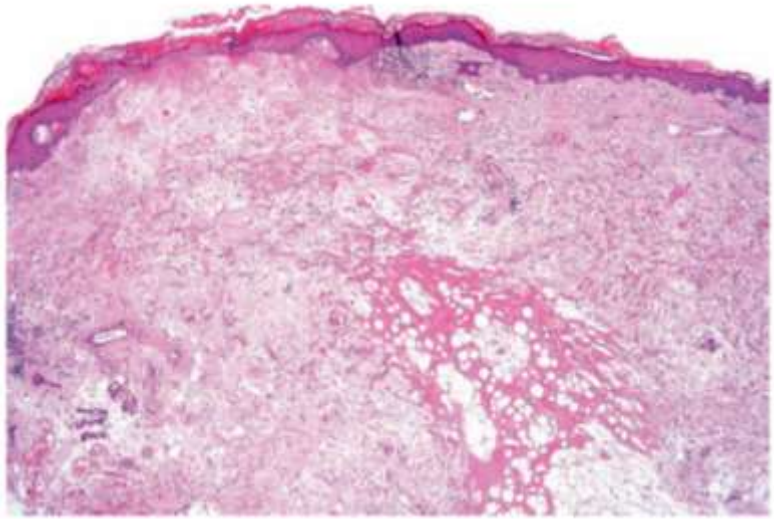
- Pathophysiology unknown
  - Possibly a vascular injury syndrome characterized by high expression of IFN-α
  - Component C5b-9 complex deposition
  - Anti-endothelial antibodies may play a role

Magro, et al: Degos disease: a C5b-9/interferon-alpha-mediated endotheliopathy syndrome. Am J Clin Pathol 2011, 135:599–610.

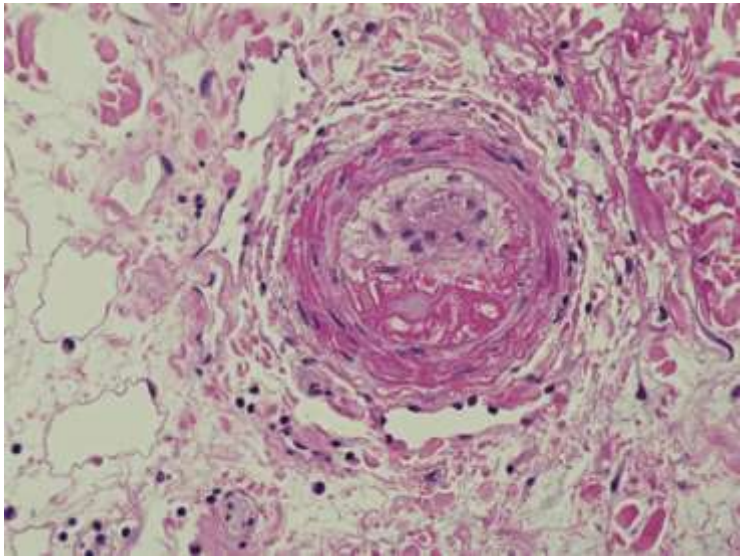
Malignant atrophic papulosis



- Rare microangiopathy
- Clinical presentation is highly suggestive but not specific
- Vascular thrombosis with minimal inflammation and wedge-shaped zone of dermal infarction
- Can have similar lesions in gastrointestinal tract
- Eculizumab may be of clinical benefit



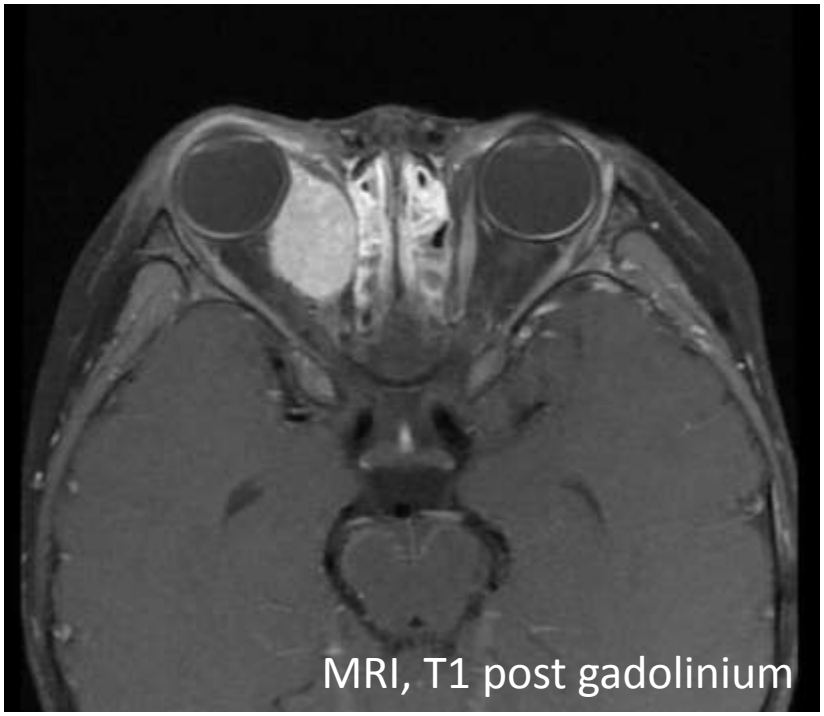
McKee's 4th Edition

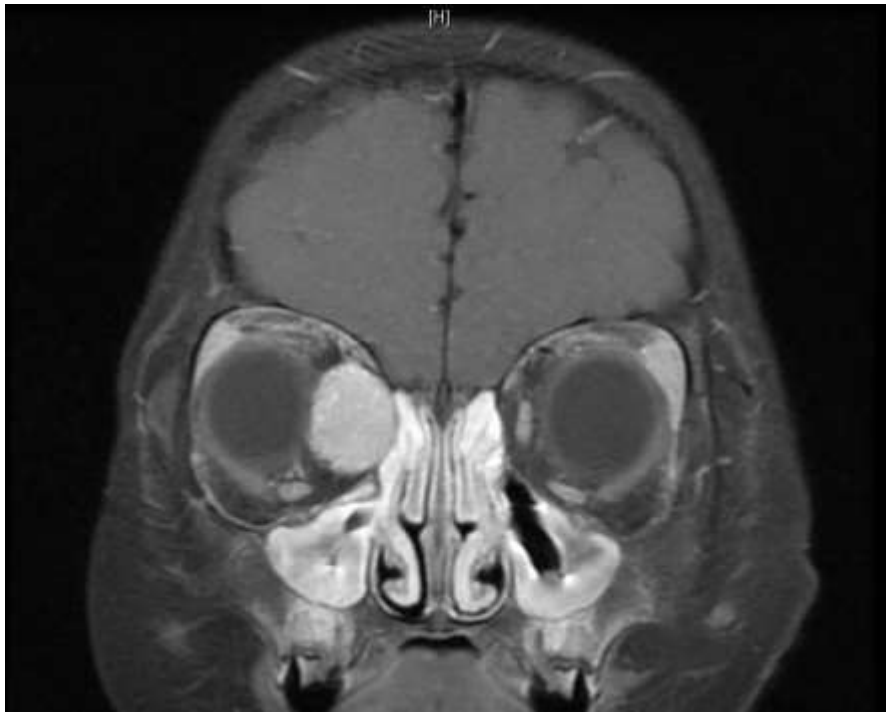


SB 6354

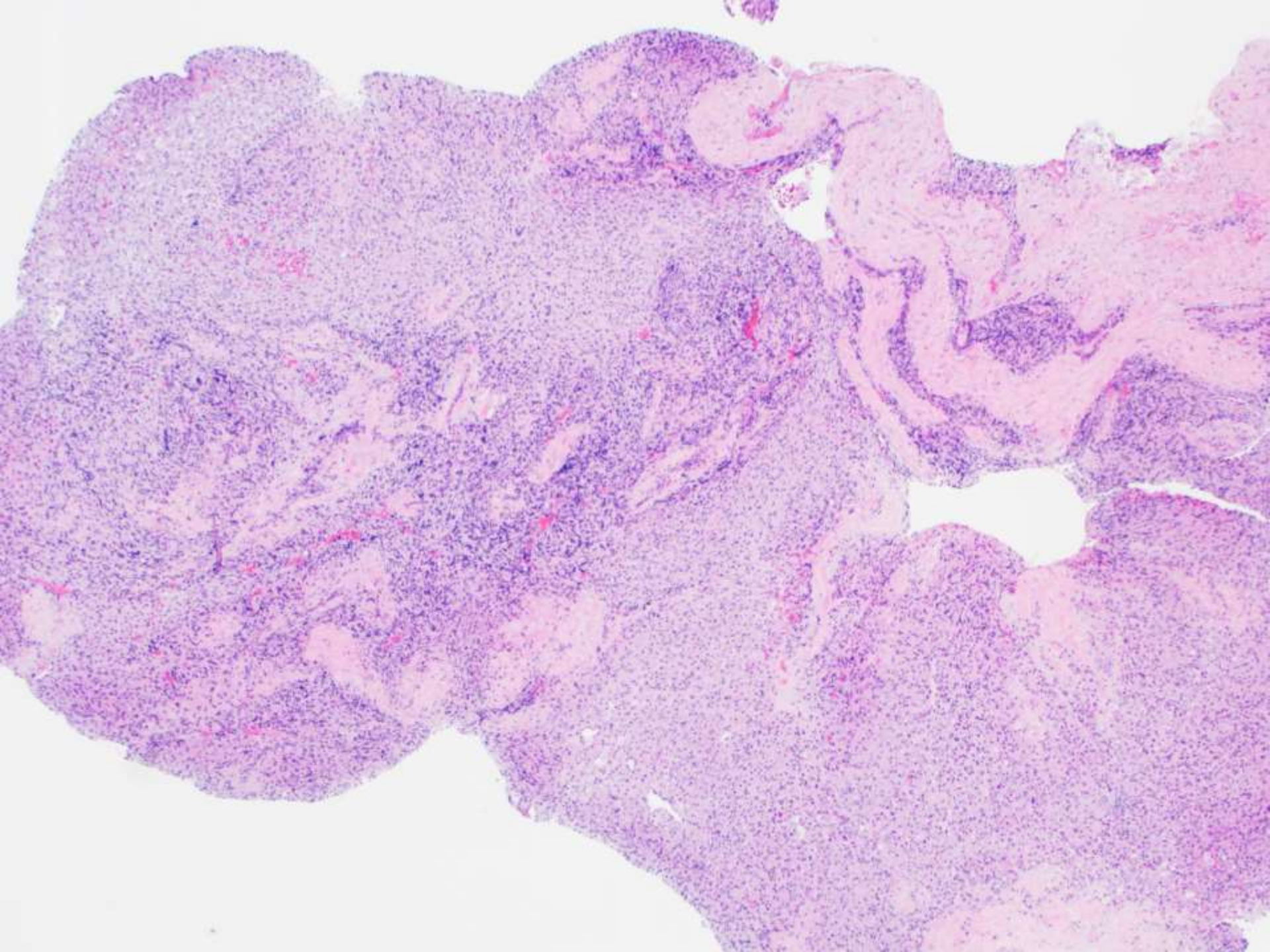
Romain Cayrol/Donald Born; Stanford

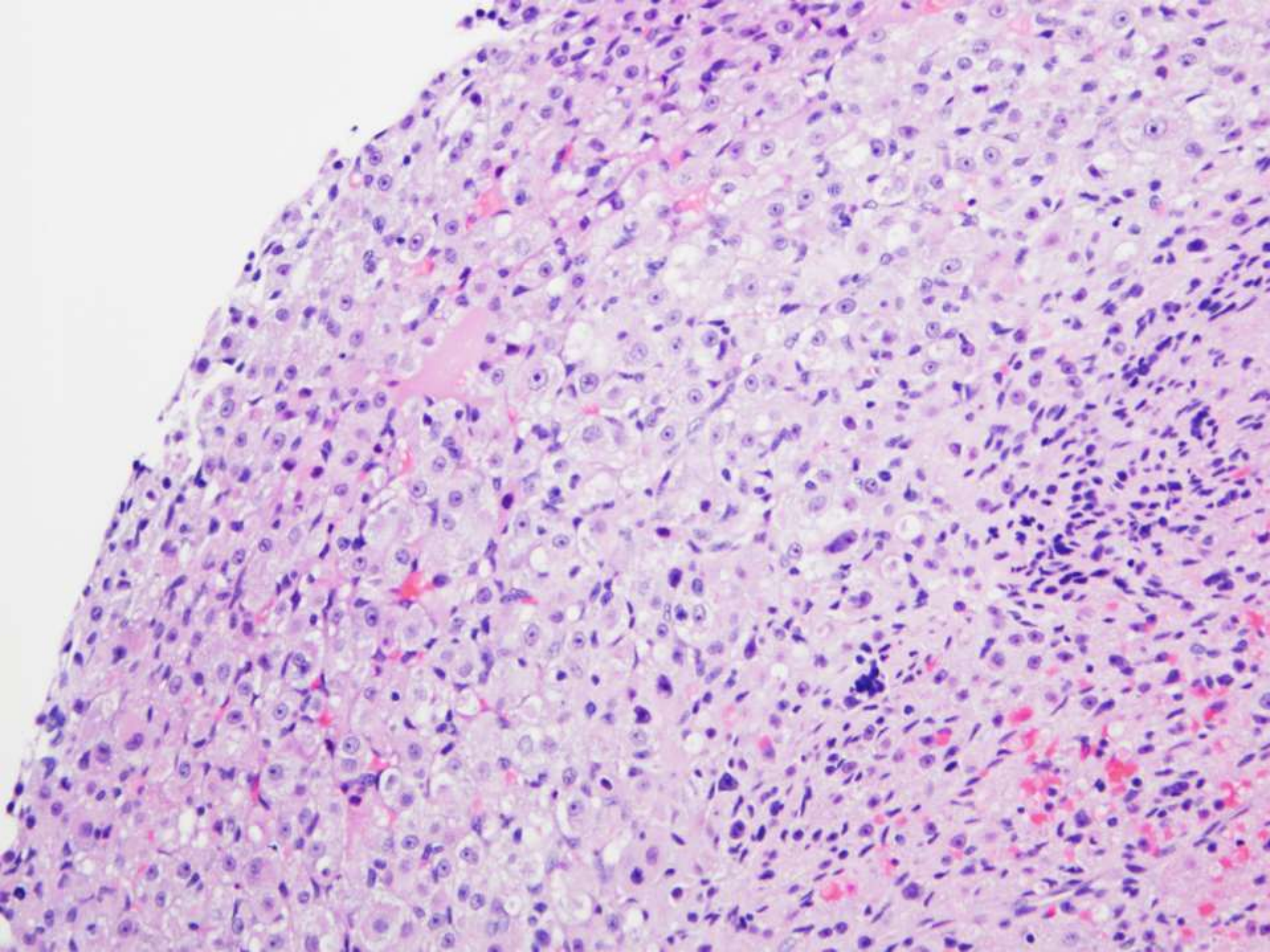
2-year-old boy with an orbital mass.

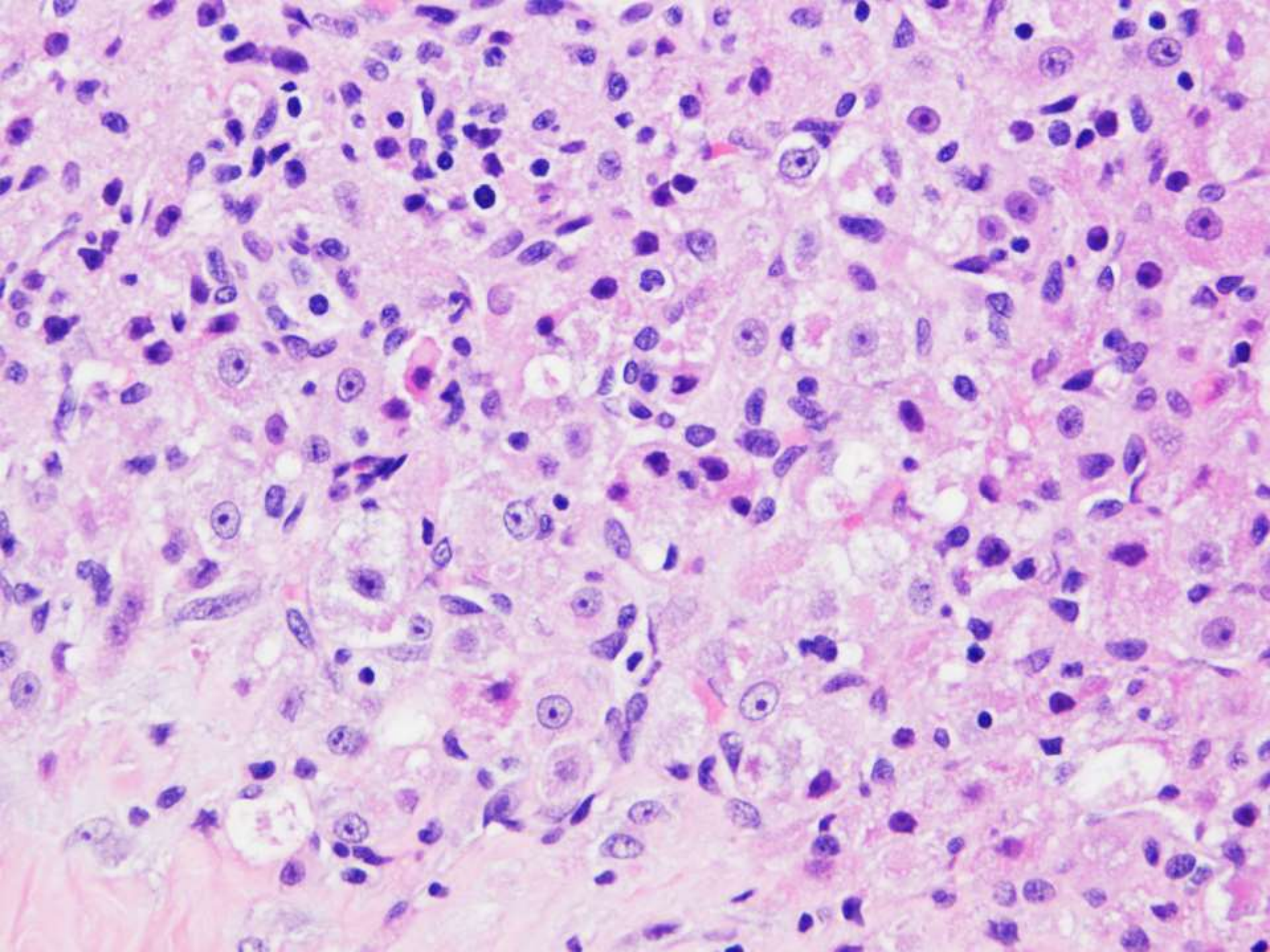


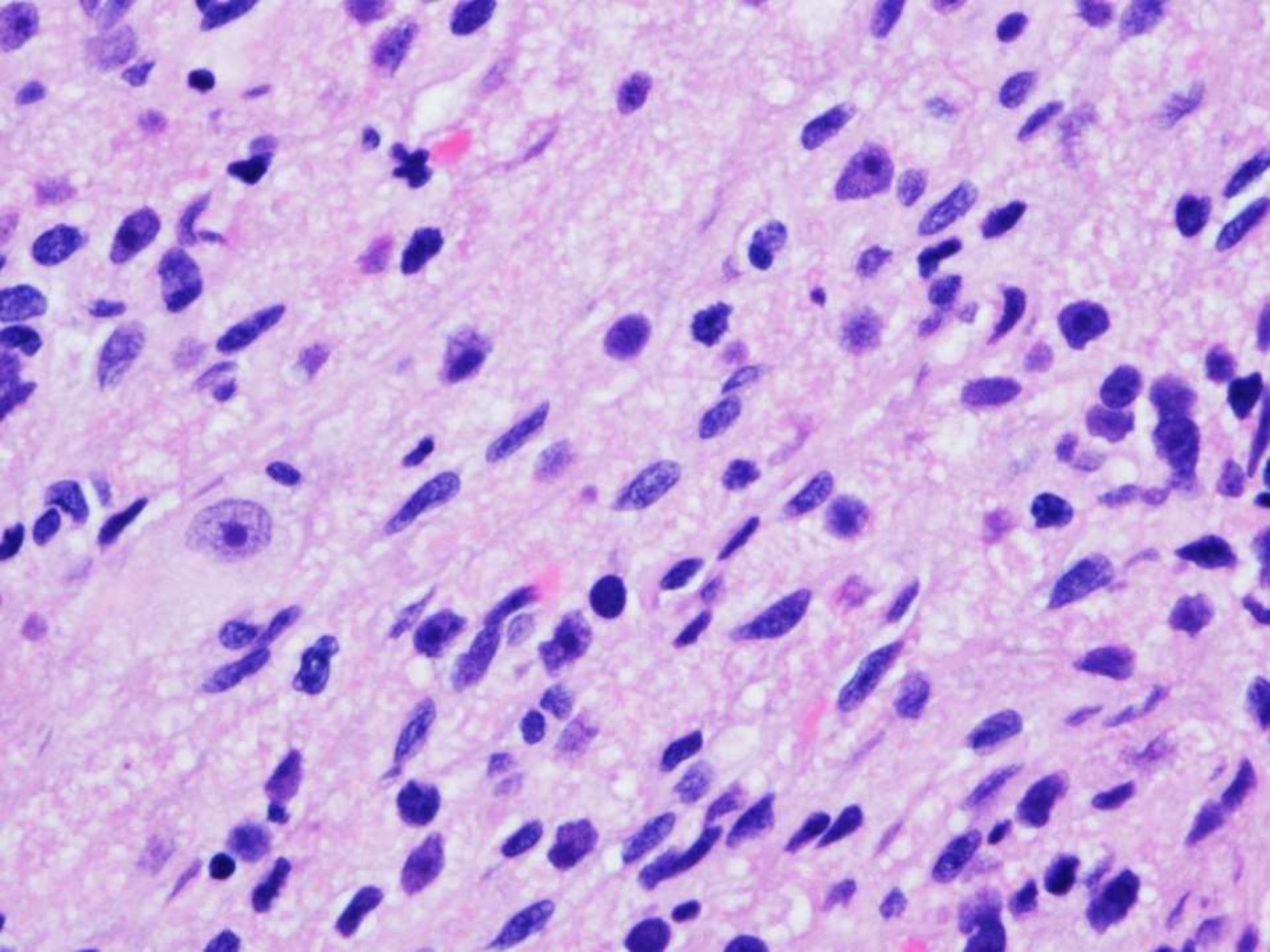


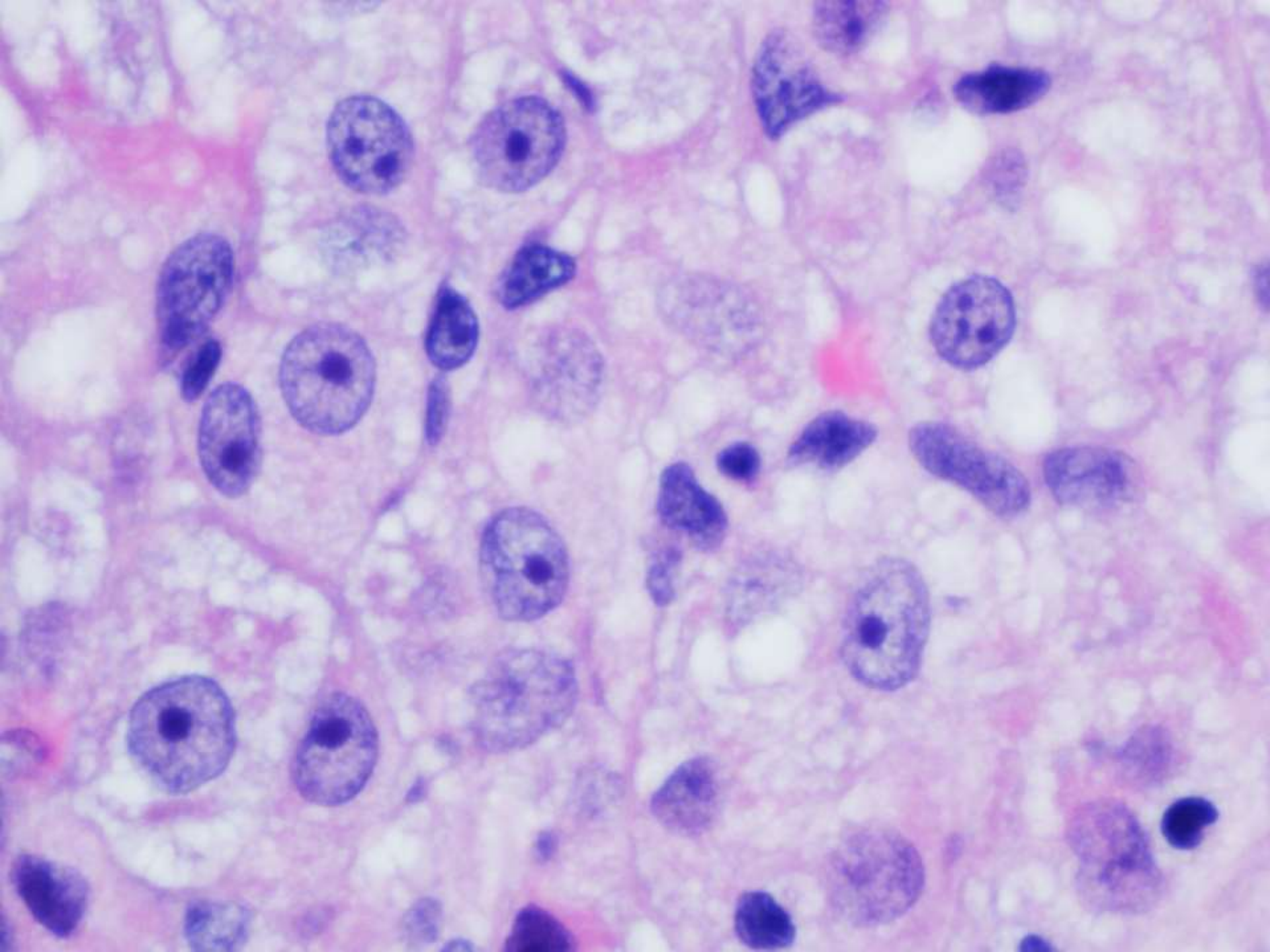
- Two year old boy with a 25 x 18 x 16 mm enhancing lesion of the right medial intraconal space



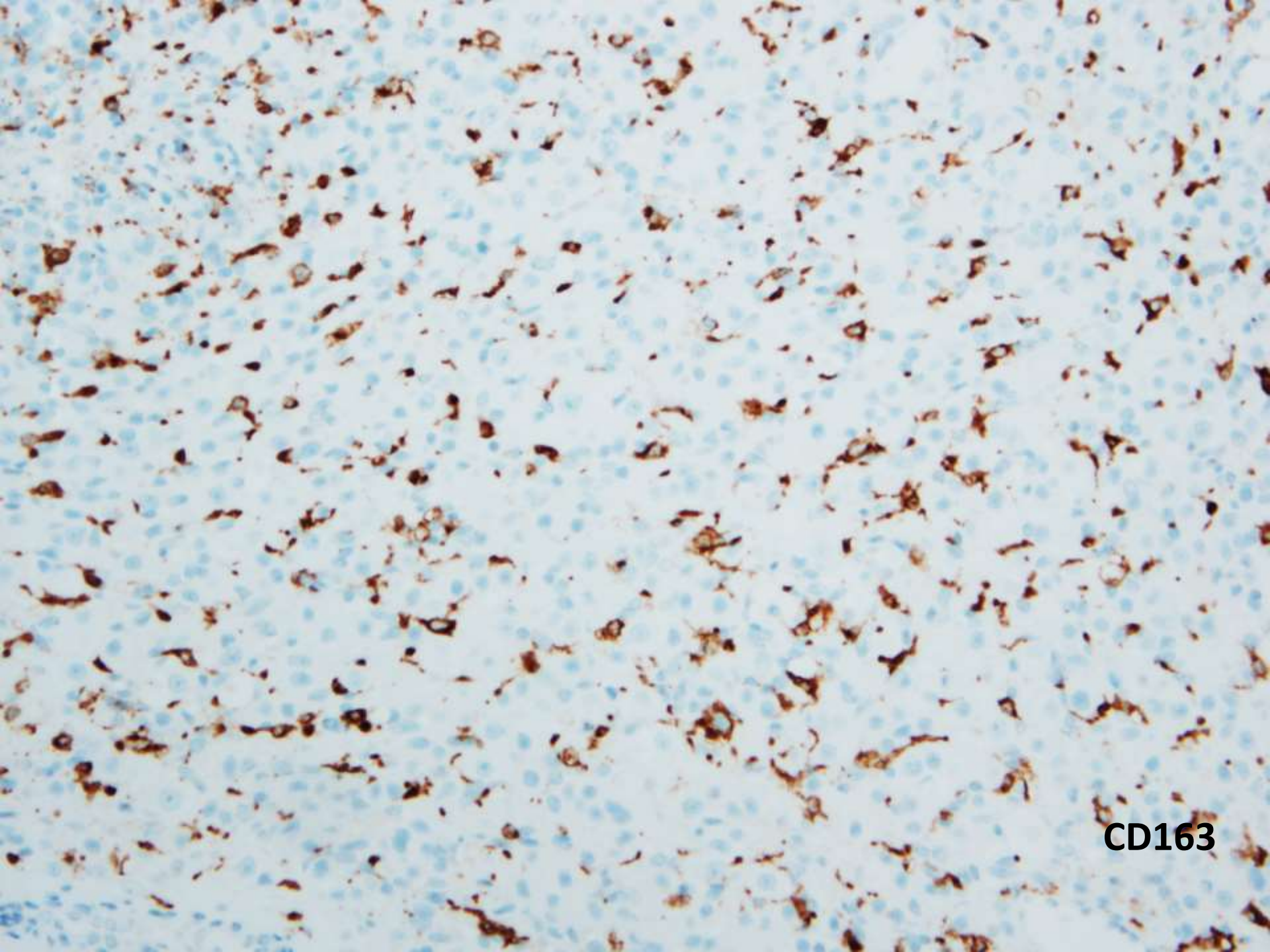


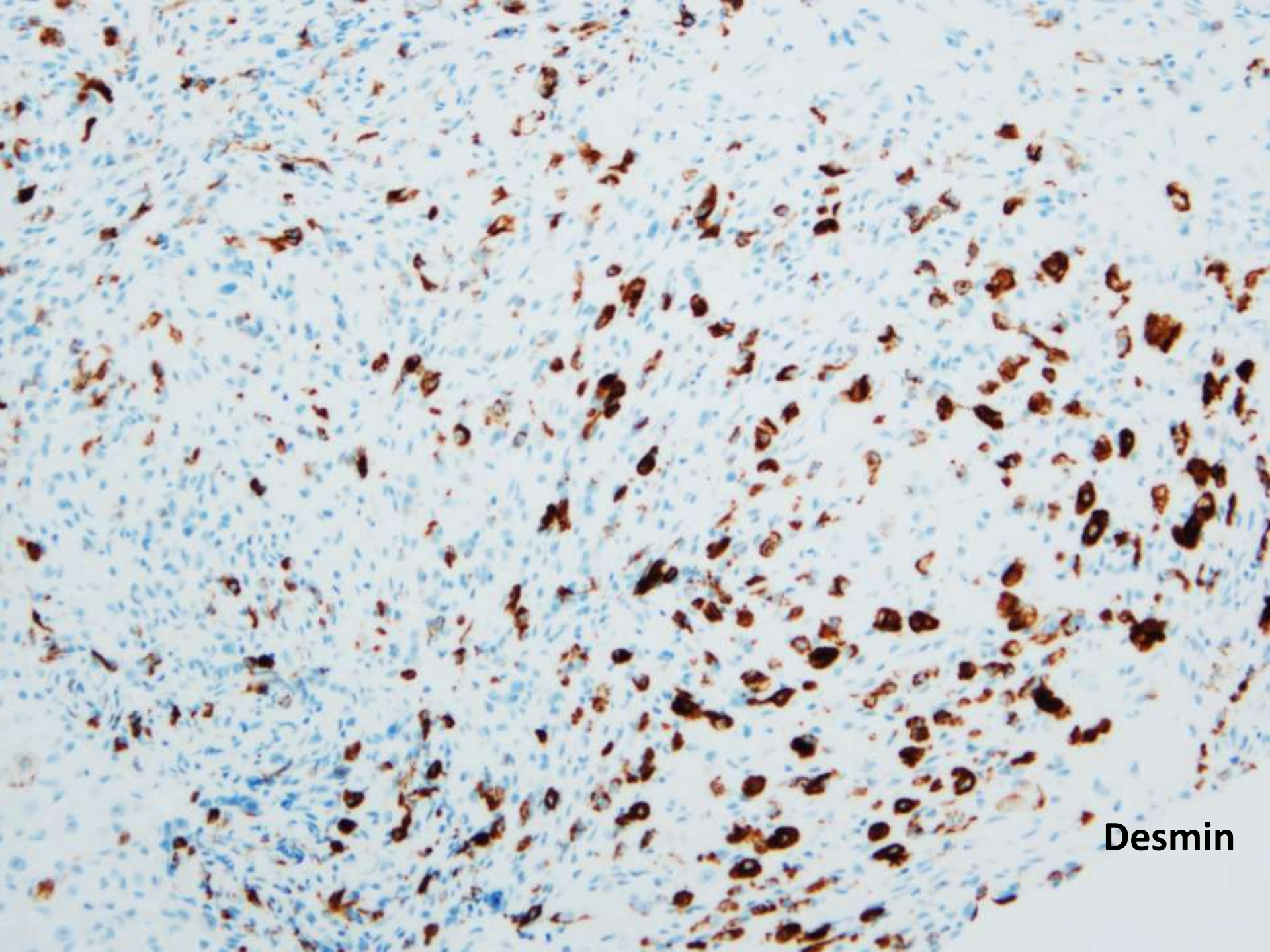


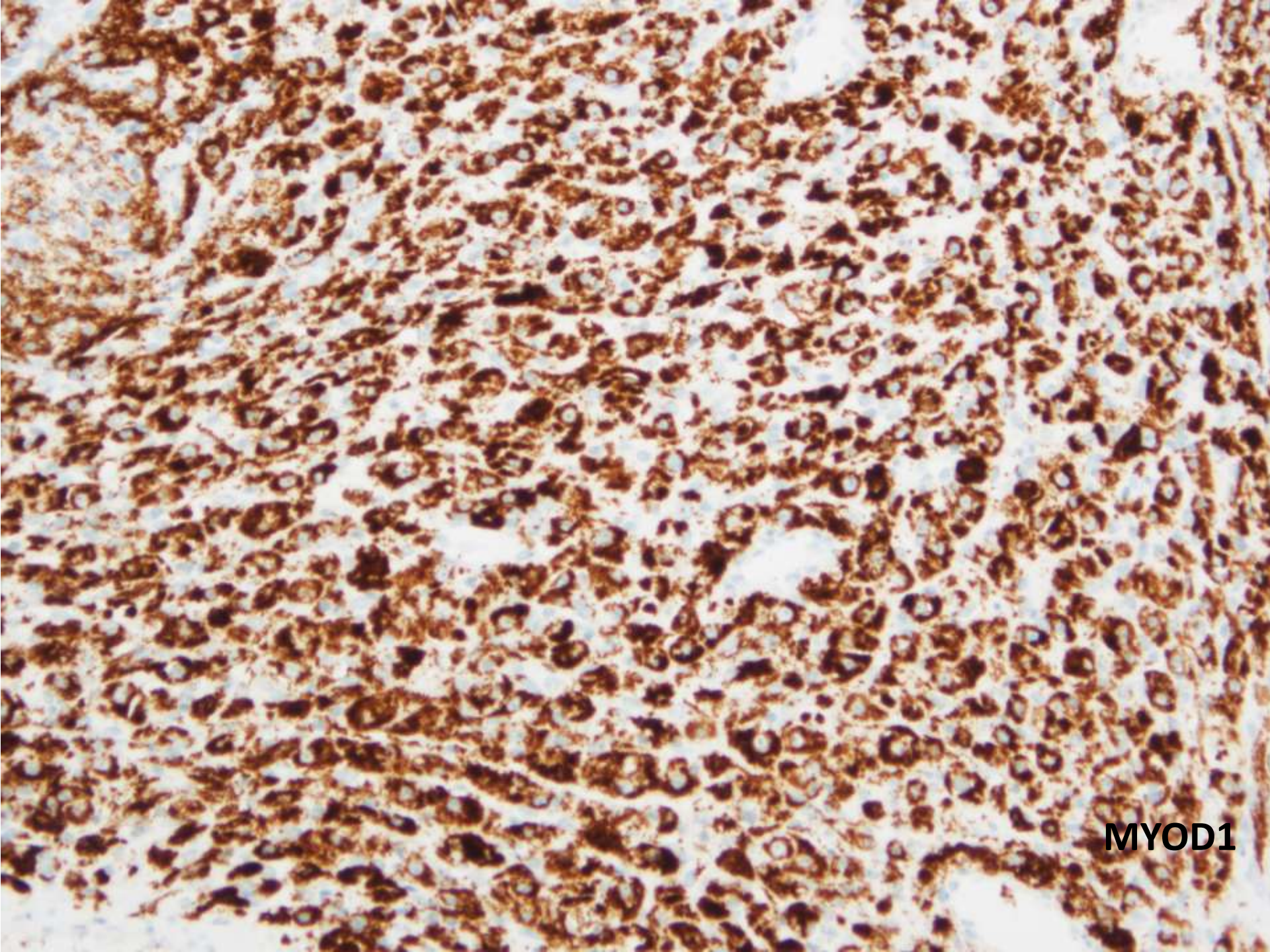


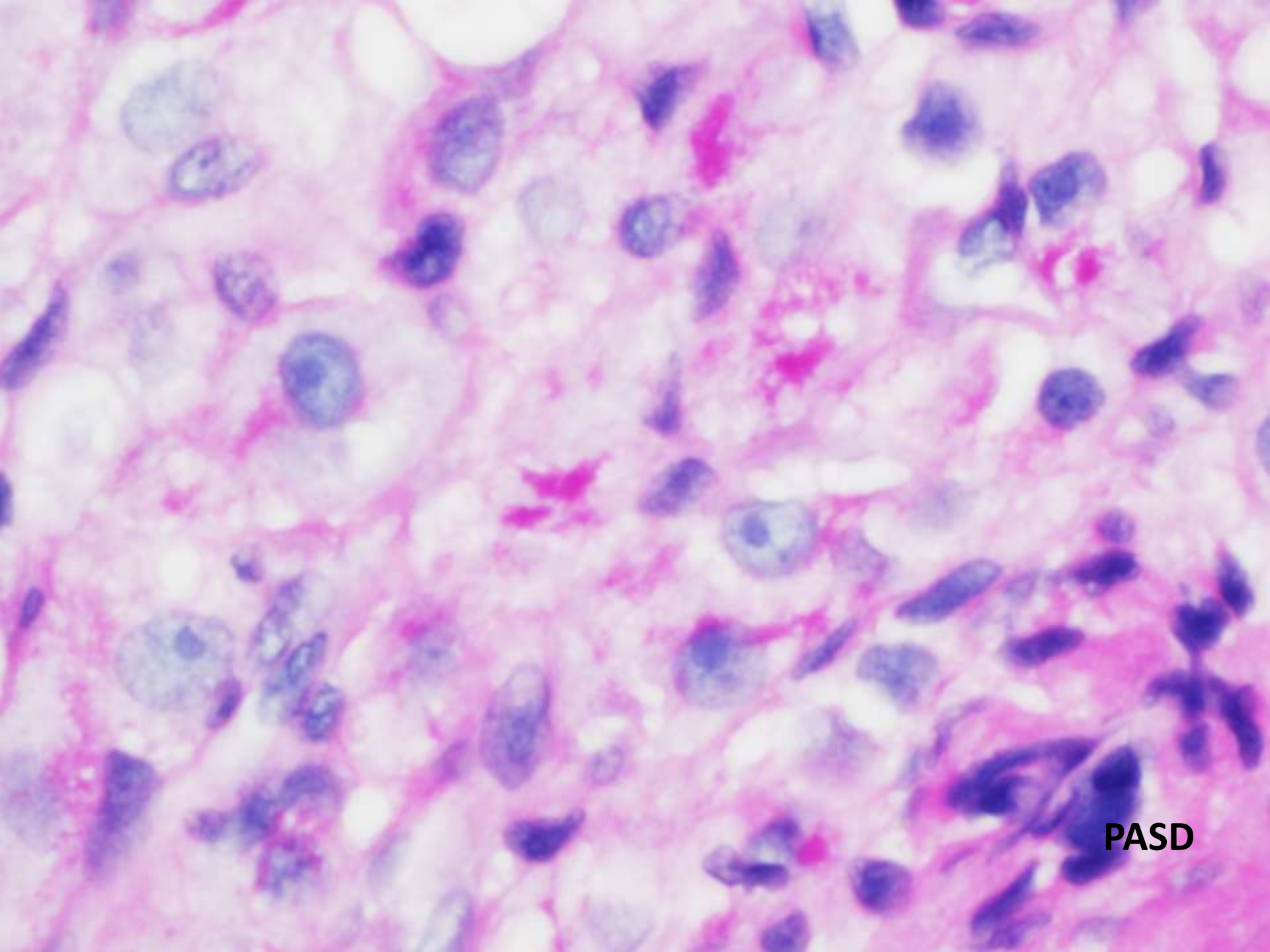



CD68


CD163

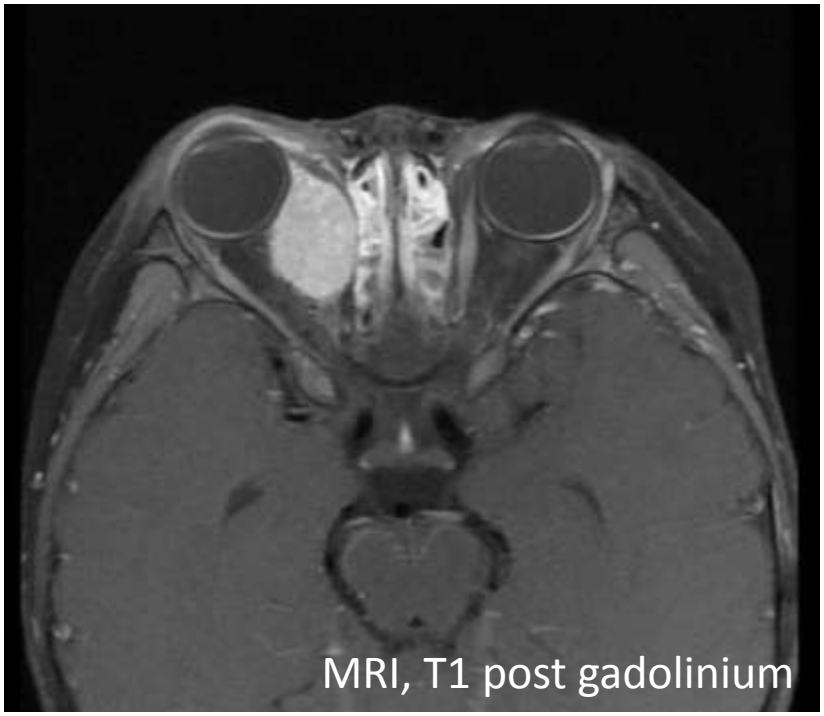

Desmin

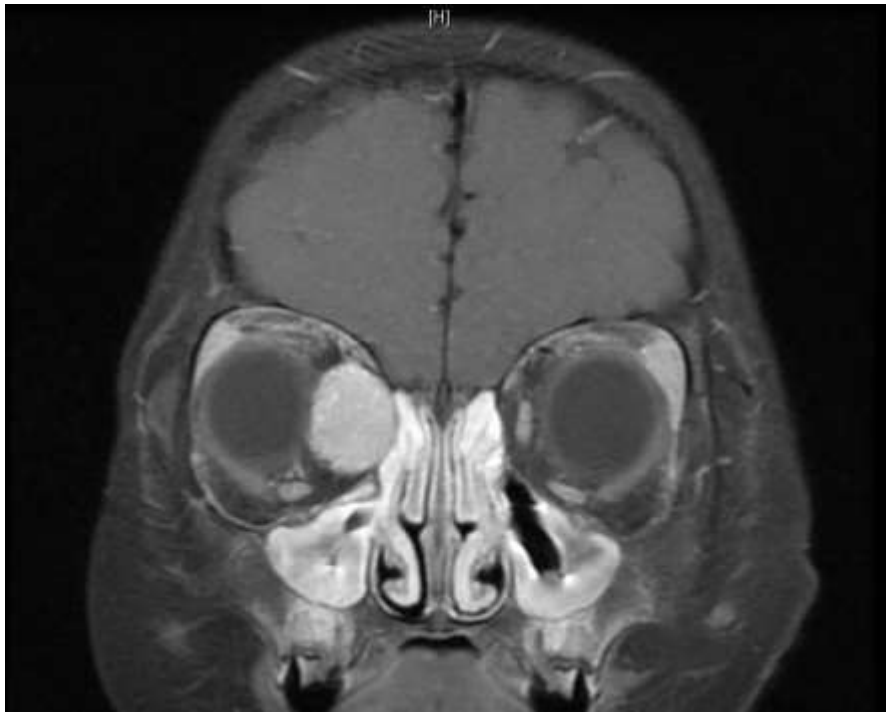

MYOD1


PASD

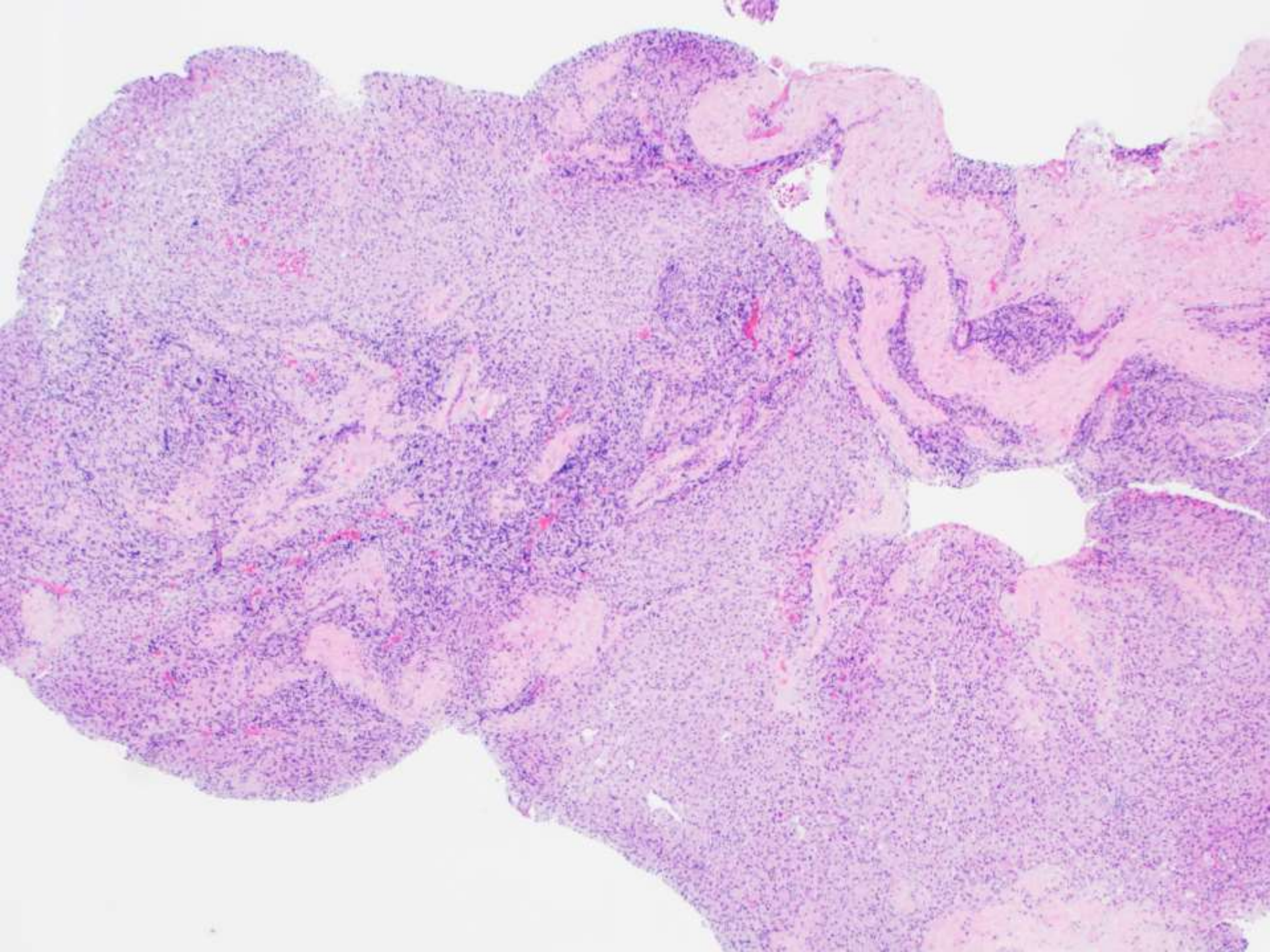
- Negative stains:
  - Ckmix, EMA, S100, Sox10, Myogenin, Sall4, INI-1 (retained), Stat6, Synaptophysin, Chromogranin, Inhibin, HMB45, Pax8, Factor XIIIa, Nestin

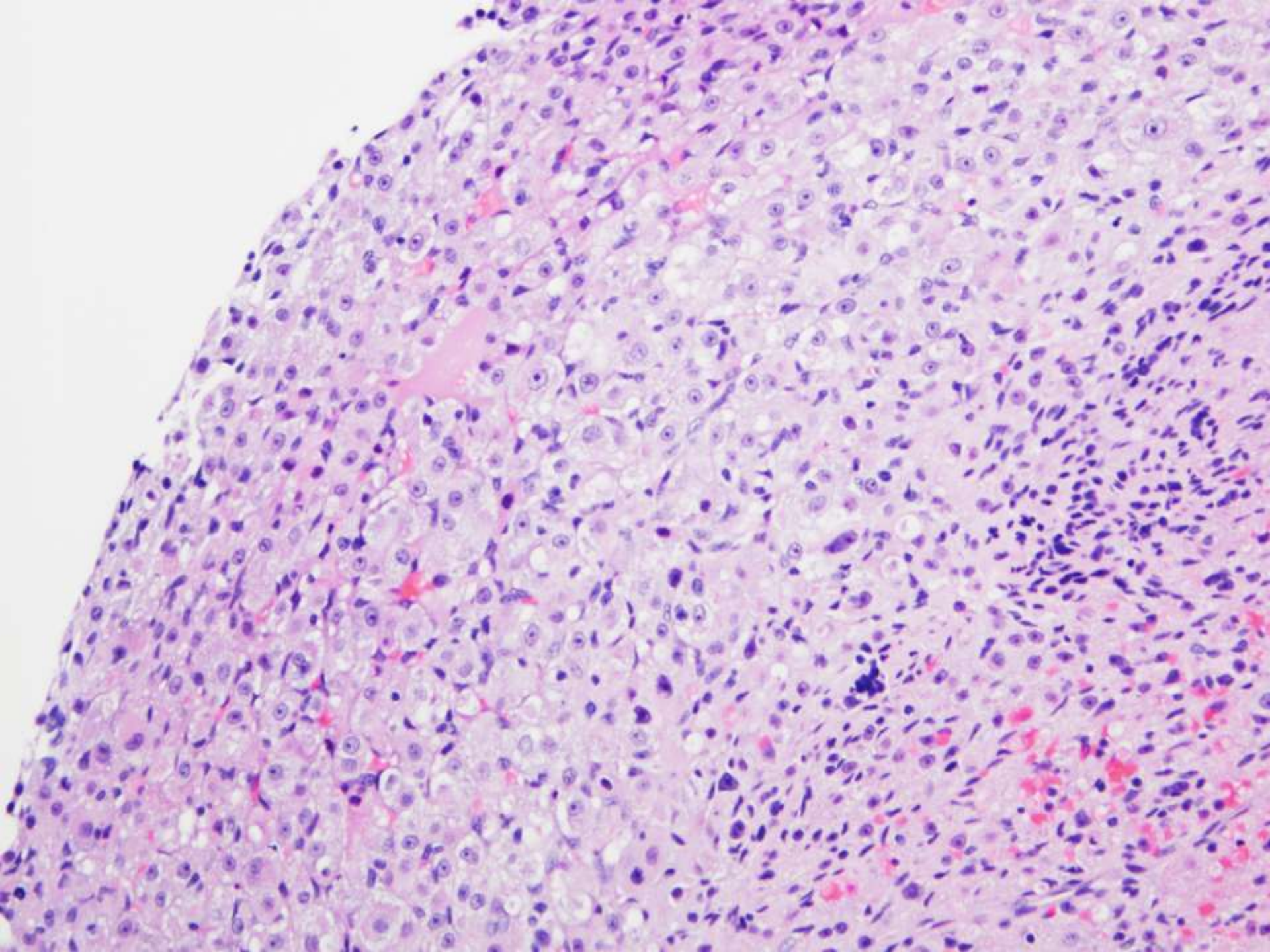
Diagnosis?

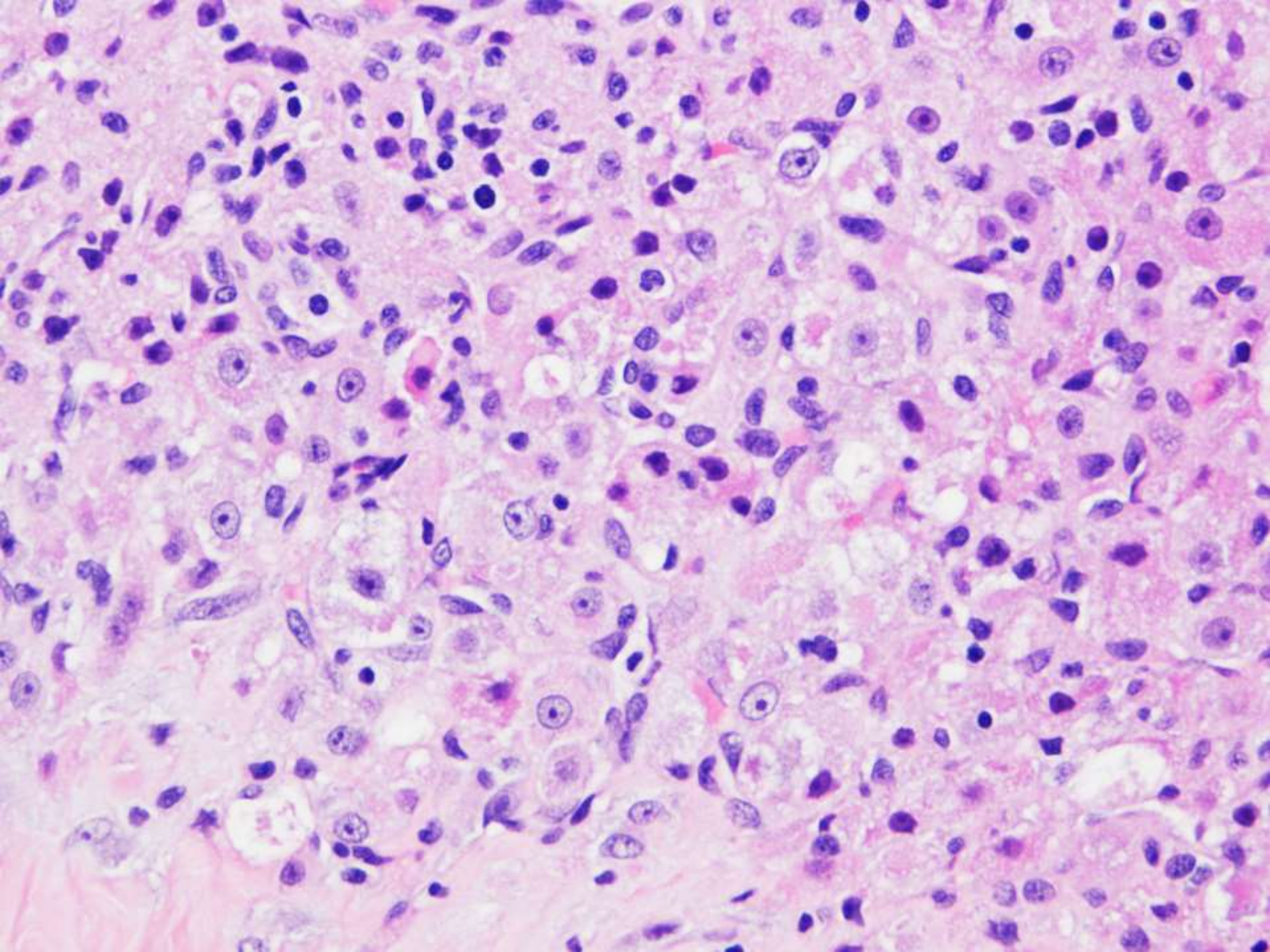


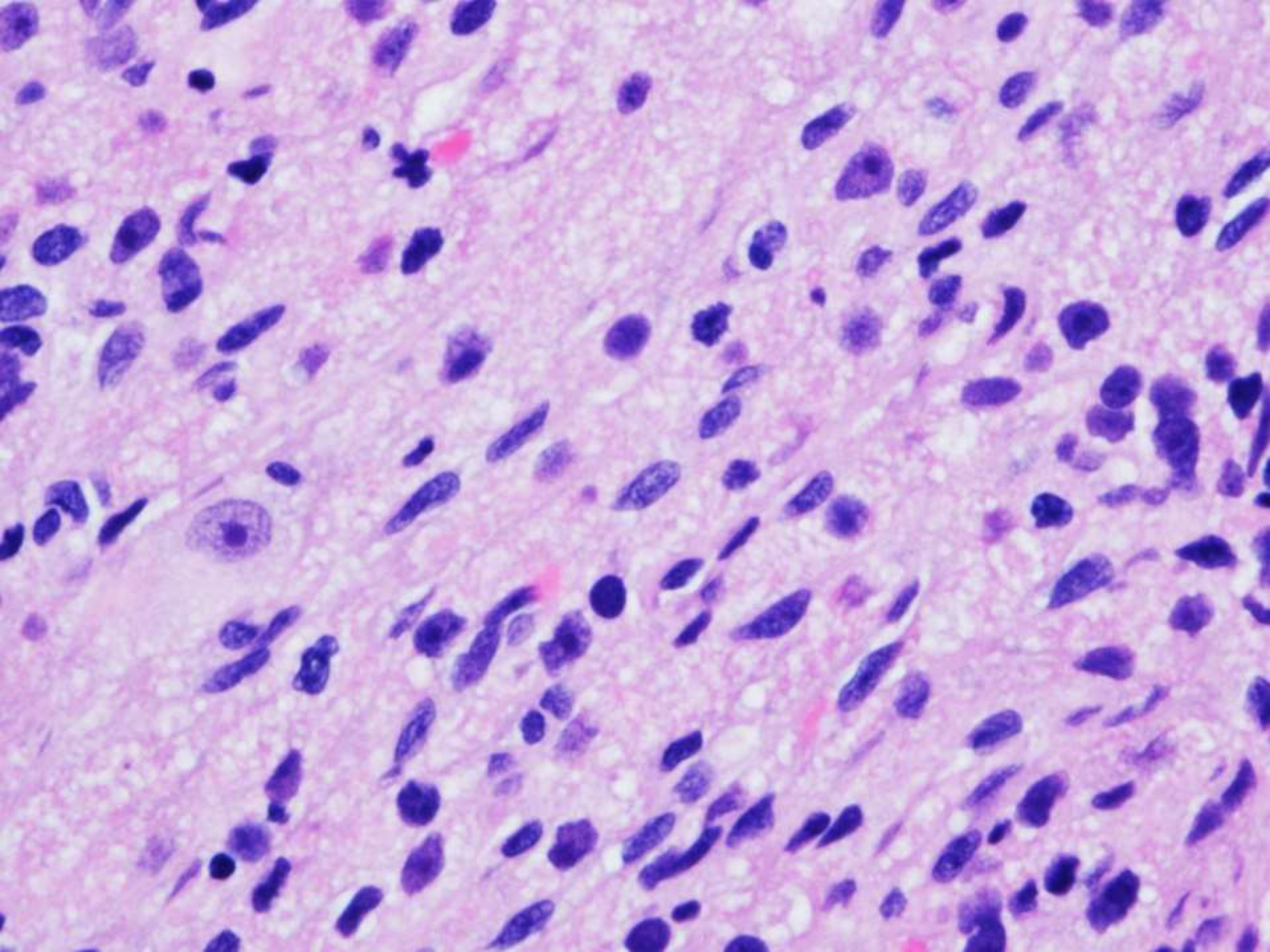


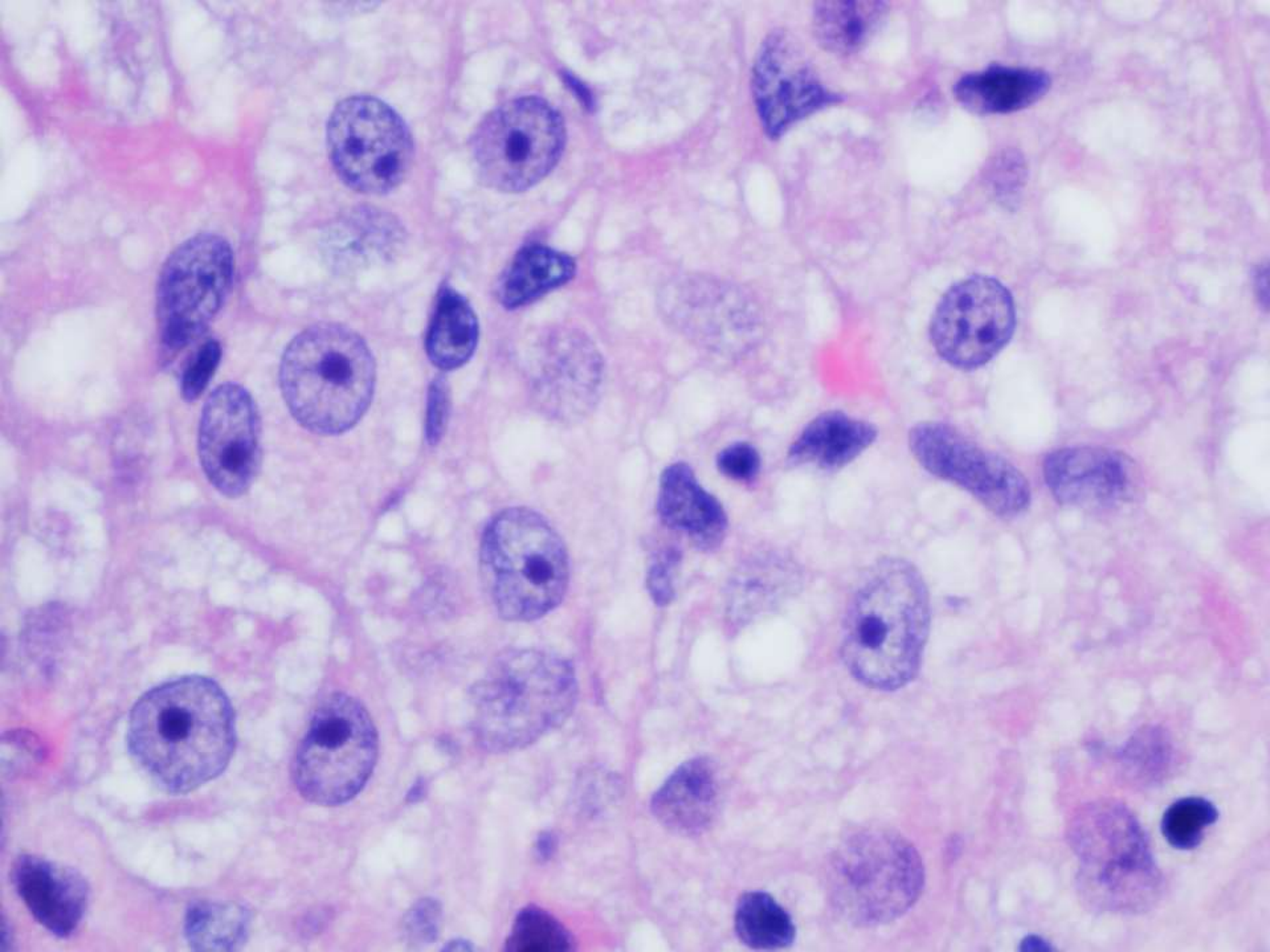
- Two year-old boy with a 25 x 18 x 16 mm enhancing lesion of the right medial intraconal space
- Mild proptosis and tortuous conjunctival vessels

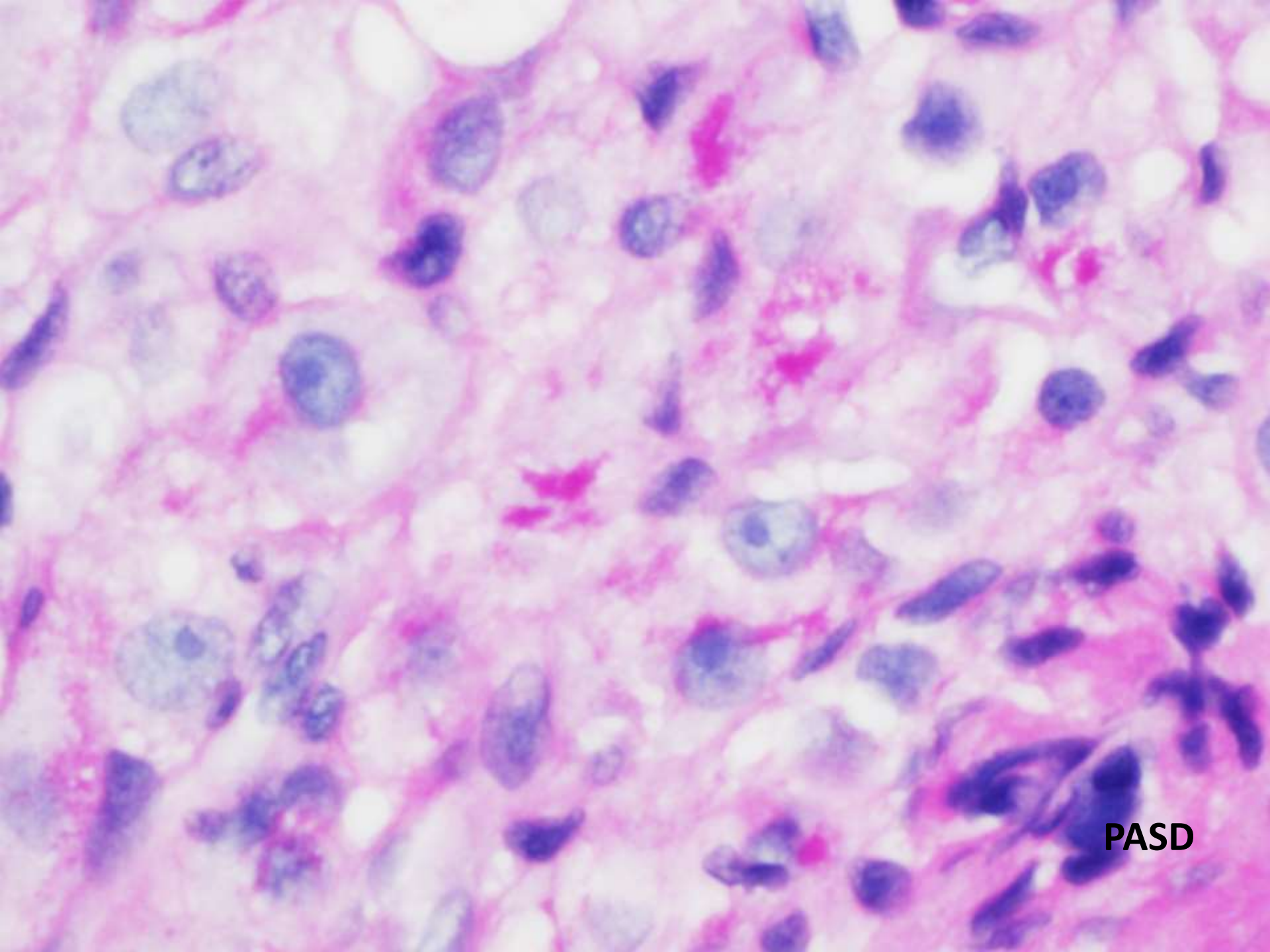




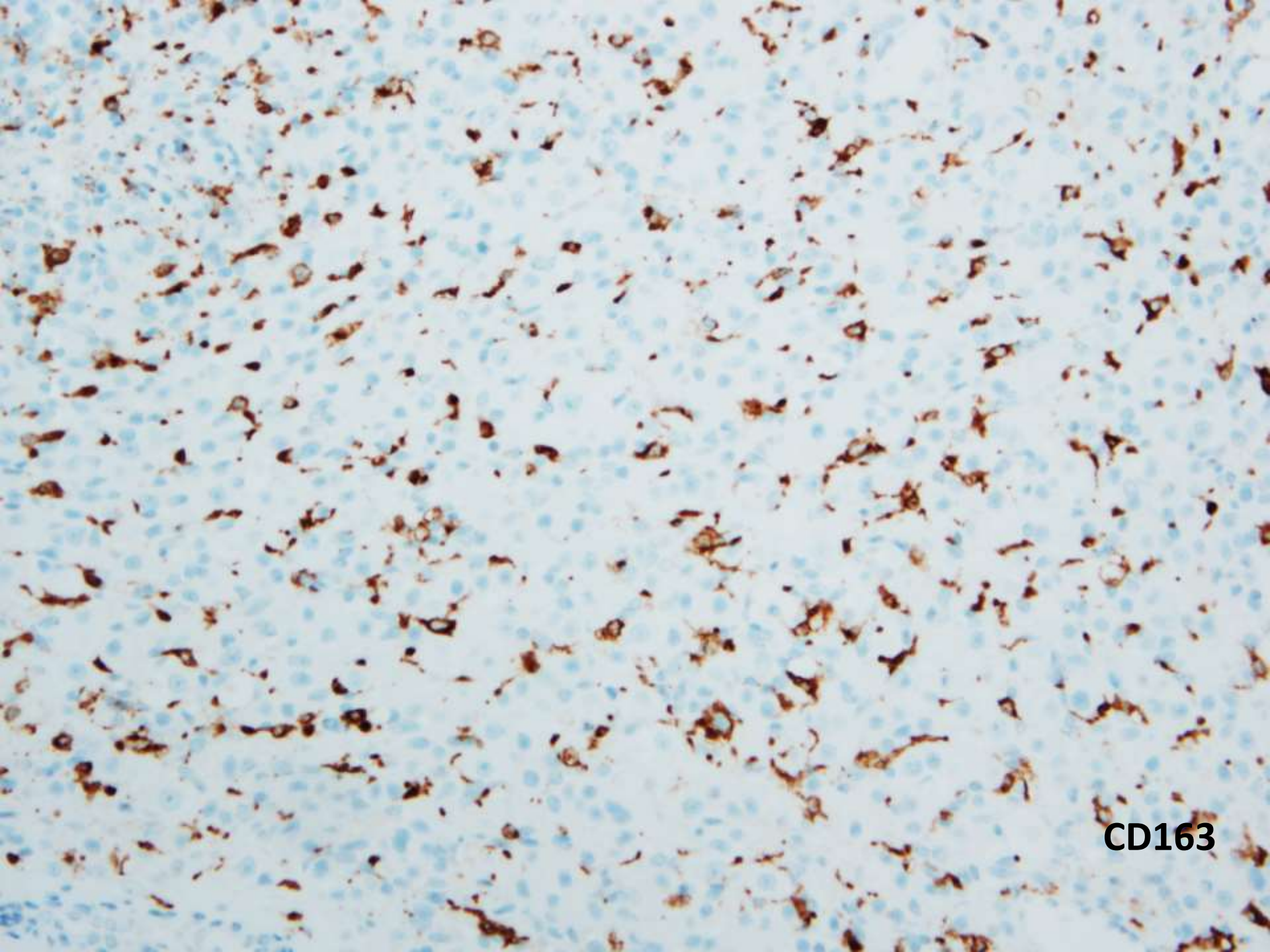


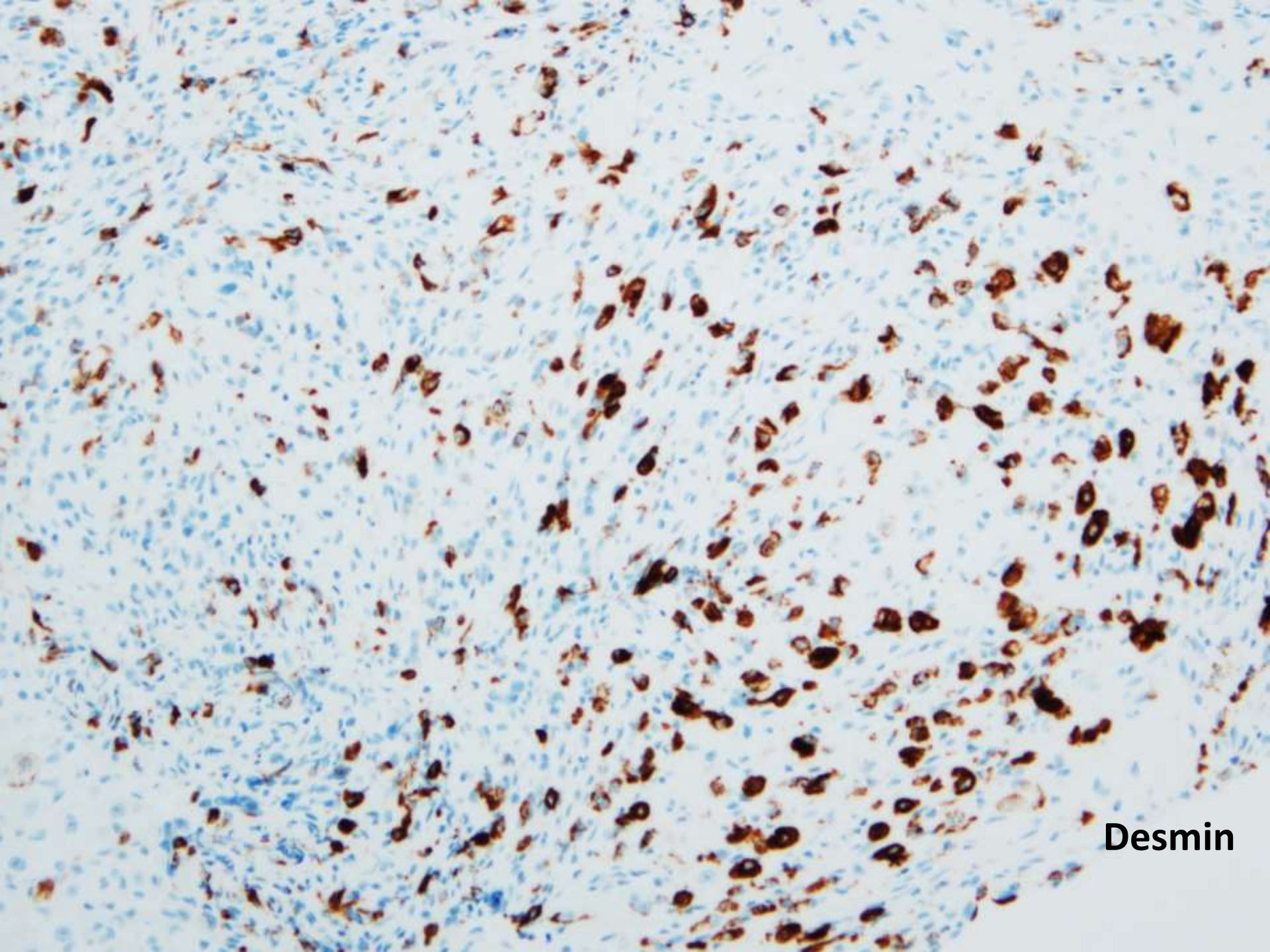


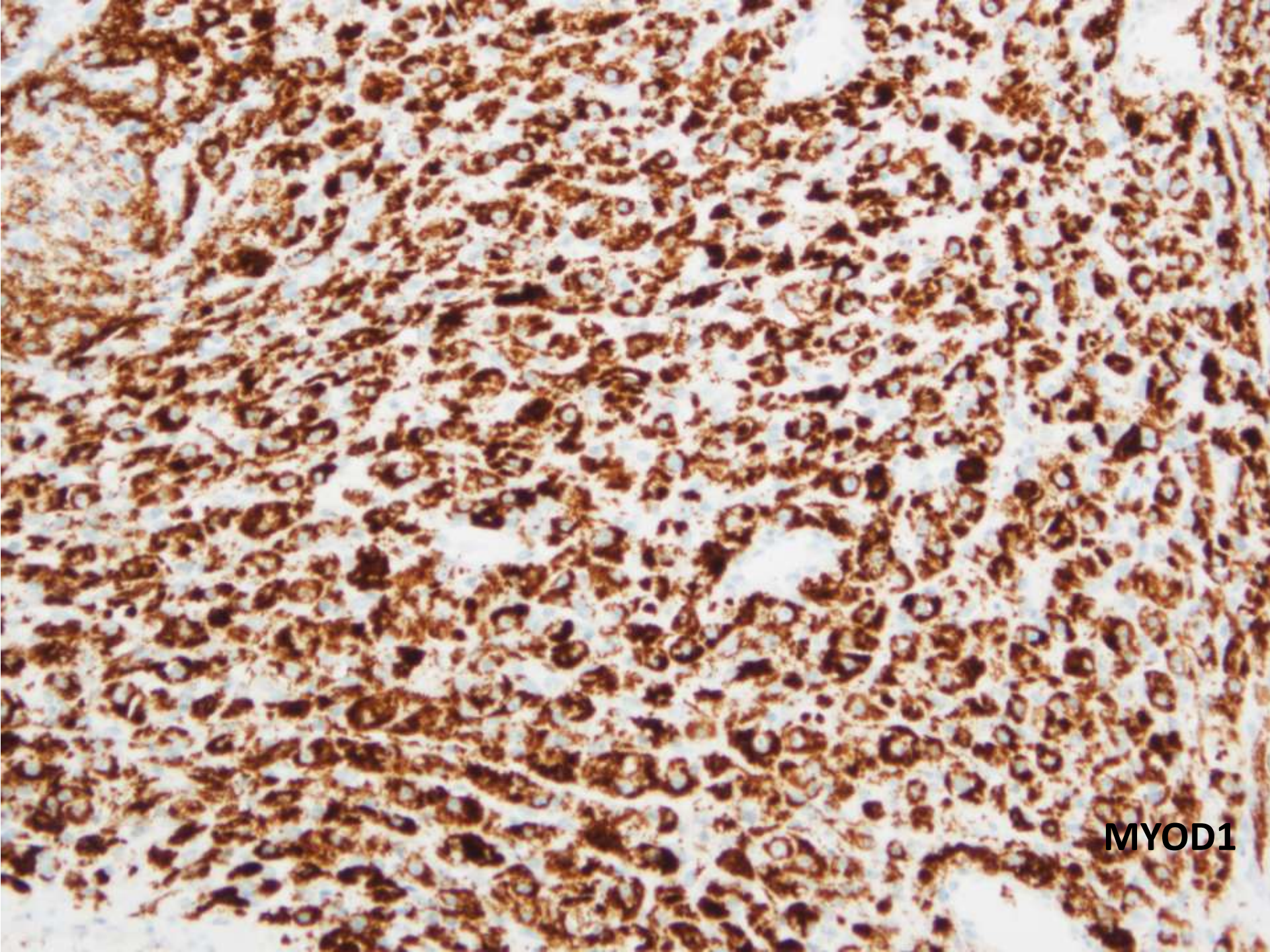



PASD


CD68

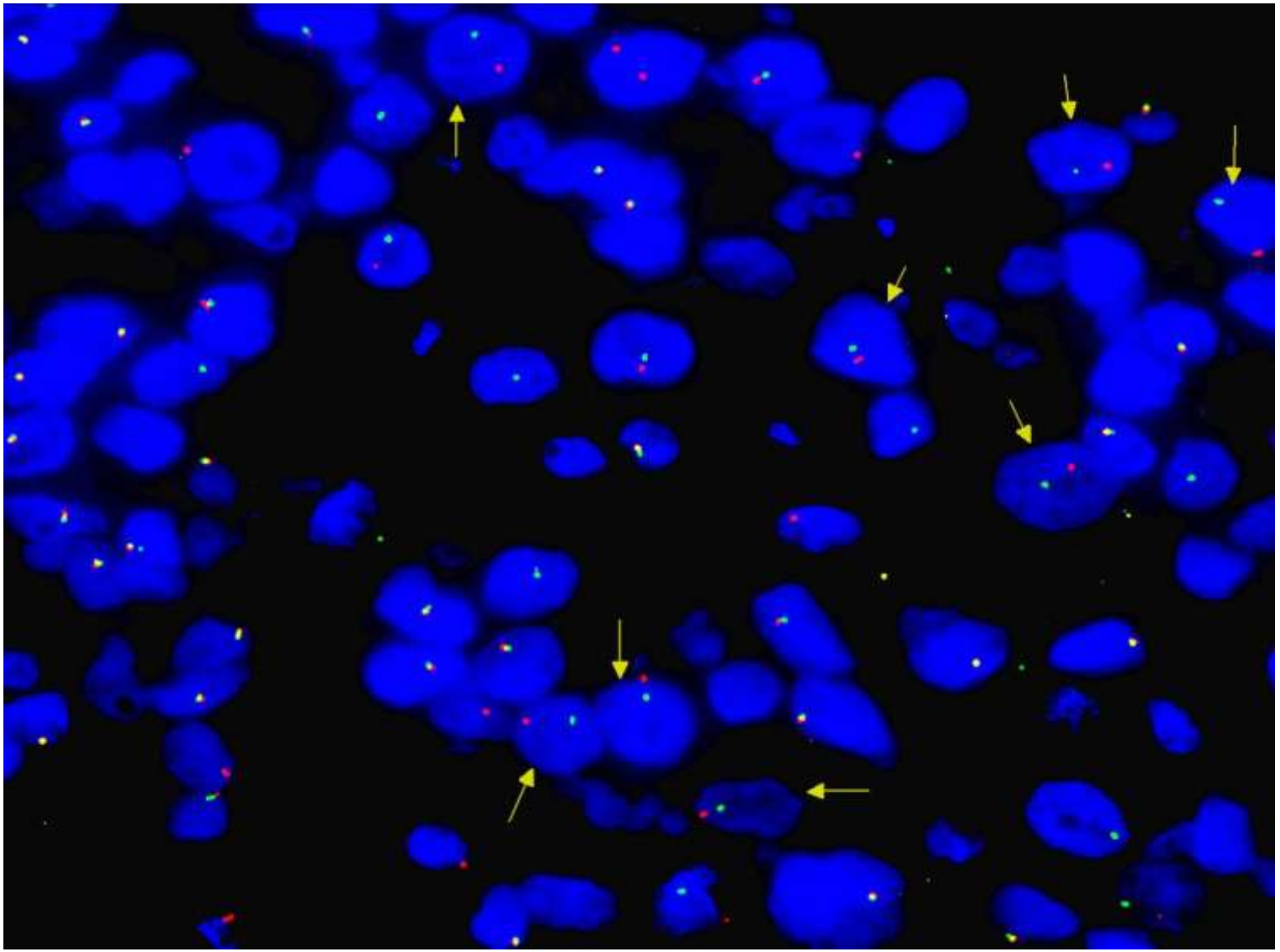

CD163


Desmin


MYOD1

- Negative stains:
  - Ckmix, EMA, S100, Sox10, Myogenin, Sall4, INI-1 (retained), Stat6, Synaptophysin, Chromogranin, inhibin, HMB45, Pax8, Factor XIIIa, Nestin

- Molecular studies:
  - FISH break apart probe positive for TFE-3 t(X; 17)



DIAGNOSIS

- ORBIT, RIGHT INTRACONAL MASS, BIOPSY
  - ALVEOLAR SOFT PART SARCOMA
  - FISH POSITIVE FOR TFE-3 TRANSLOCATION

ALVEOLAR SOFT PART SARCOMA (ASPS)

- EPIDEMIOLOGY
  - 0.2-0.9% of soft tissue sarcoma
  - Most common in 15-35 age group, rare below 5 and after 50,
  - F>M

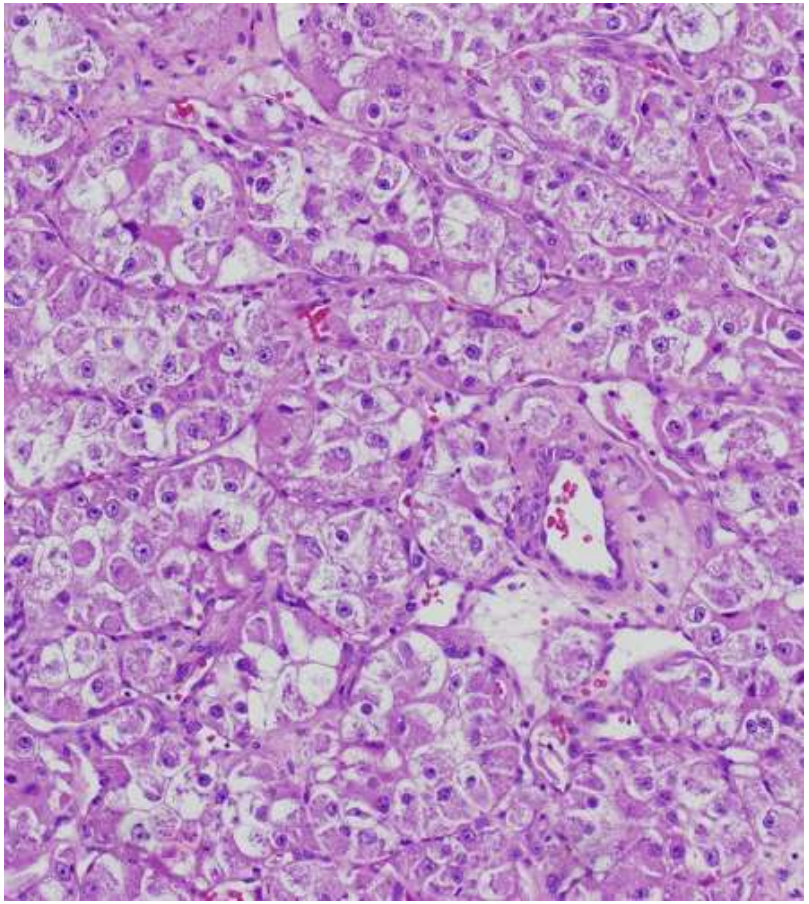
- LOCATION
  - Deep soft tissue thigh, buttock, head and neck (tongue and orbit) and other unusual locations
    - Metastatic disease: lung, bone and brain

- CLINICAL
  - Slowly growing, painless mass, somewhat indolent (short term stable disease)

- IMAGING
  - High T1 and T2 signals on MRI
  - Contrast enhancing lesion, differential often with vascular lesions

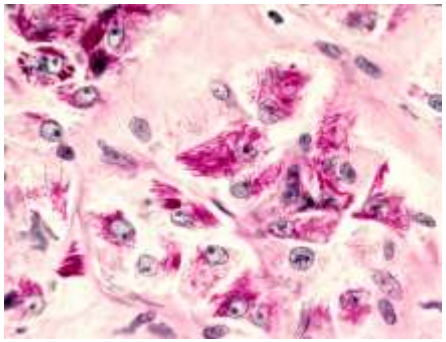
ALVEOLAR SOFT PART SARCOMA

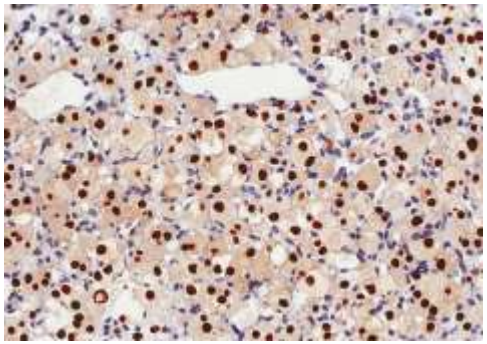
- MACROSCOPY
  - Poorly circumscribed, soft, pale grey-yellow, +/- necrosis and hemorrhage
- MICROSCOPY
  - Large, uniform, epithelioid cells with abundant eosinophilic, granular cytoplasm arranged in nests or alveolar structures (may be absent in children) separated by delicate sinusoidal vessels
  - Central nuclei with one or two nucleoli
  - Multinucleation can occur
  - Mitoses are uncommon, vascular invasion is common

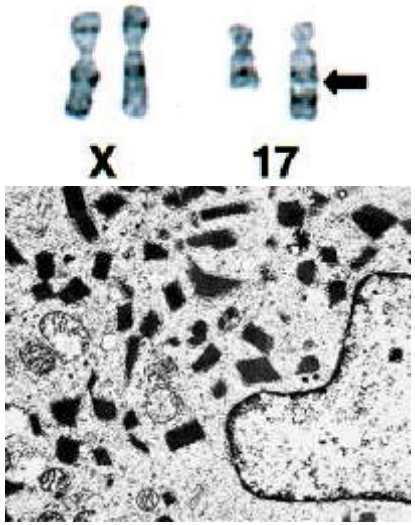


ALVEOLAR SOFT PART SARCOMA

- SPECIAL STAINS
  - Rhomboid or rod shape intra-cytoplasmic inclusions (PASD+)
- IMMUNOHISTOCHEMISTRY
  - TFE3+, CD147+, Desmin (50% of the cases), +/- S100, +/- SMA, EMA-, keratins-
- ELECTRON MICROSCOPY
  - Membrane bound rhomboid/rectangular crystal with a periodic lattice of rigid fibrils (5-7 nm) every 10 nm (CD147+)
- MOLECULAR
  - t(X; 17) - ASPL/ASPSCR1-TFE3 fusion





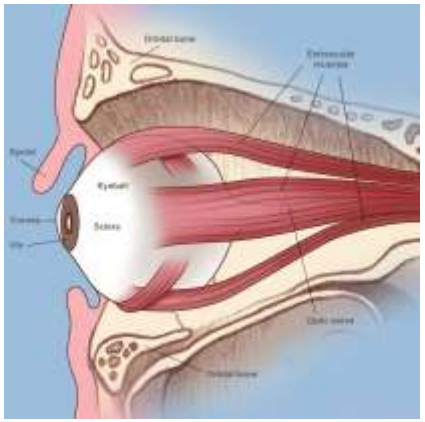


ALVEOLAR SOFT PART SARCOMA

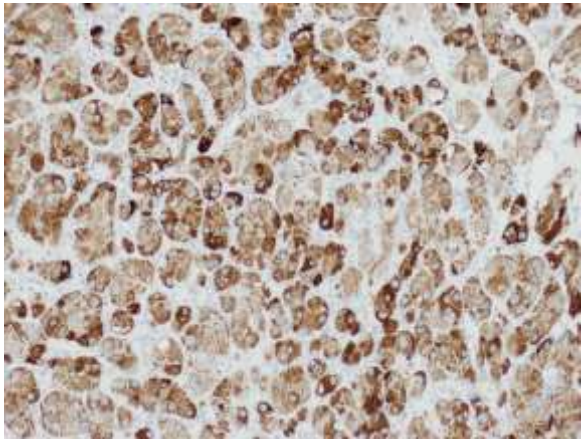
- DIFFERENTIAL DIAGNOSIS
  - Paraganglioma, granular cell tumor, renal cell carcinoma, alveolar rhabdomyosarcoma, hepatocellular carcinoma, melanoma, and adrenal cortical carcinoma
- PROGNOSIS
  - 1/3 have metastatic disease either at presentation or years after the initial resection, long term follow up is required.
  - Patient age at presentation, tumor size, and presence of metastasis at diagnosis
- TREATMENT
  - Surgery with negative margins and\or systemic treatment (VEGF-R predominant TKI, ICI under study)

ALVEOLAR SOFT PART SARCOMA

- Orbit:
  - Younger patients (< 15 year-old)
  - Often involves extra-ocular muscle
  - Early symptoms (proptosis, gaze deviation)
    - Smaller tumor size, < 5 cm
  - Better prognosis



- Some reports have noted a granular MyoD1 staining in ASPS



Follow-up

- Staging
  - No systemic disease
- Parents have since elected to pursue a surgical resection at UCSF
  - Globe, medial rectus muscle, and proximal optic nerve segment were sacrificed
  - Pathology showed ASPS
    - Margins close, but negative.
- Discussed in tumor board and it was recommended to do close serial follow up

References

- Does alveolar soft-part sarcoma exhibit skeletal muscle differentiation? An immunocytochemical and biochemical study of myogenic regulatory protein expression. Wang NP, Bacchi CE, Jiang JJ, McNutt MA, Gown AM. Mod Pathol. 1996 May;9(5):496-506.

- Immunohistochemical profile of myogenin and MyoD1 does not support skeletal muscle lineage in alveolar soft part sarcoma. Gómez JA, Amin MB, Ro JY, Linden MD, Lee MW, Zarbo RJ. Arch Pathol Lab Med. 1999 Jun;123(6):503-7.

- Alveolar Soft Part Sarcoma. Jaber OI, Kirby PA. Arch Pathol Lab Med. 2015 Nov;139(11):1459-62.

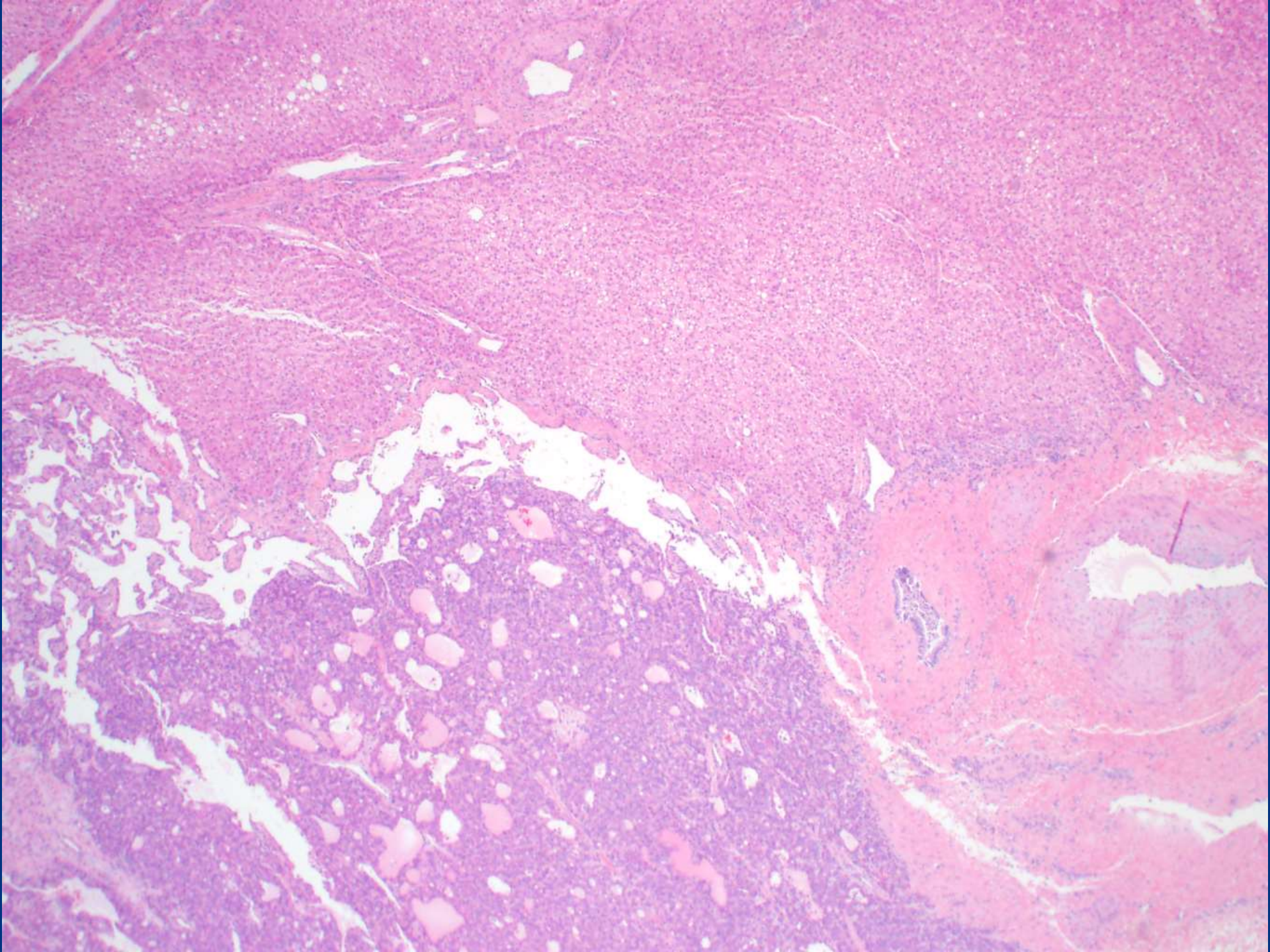
- Orbital alveolar soft part sarcoma: A report of 8 cases and review of the literature. Hei Y, Kang L, Yang X, Wang Y, Lu X, Li Y, Zhang W, Xiao L. Oncol Lett. 2018 Jan;15(1):304-314.

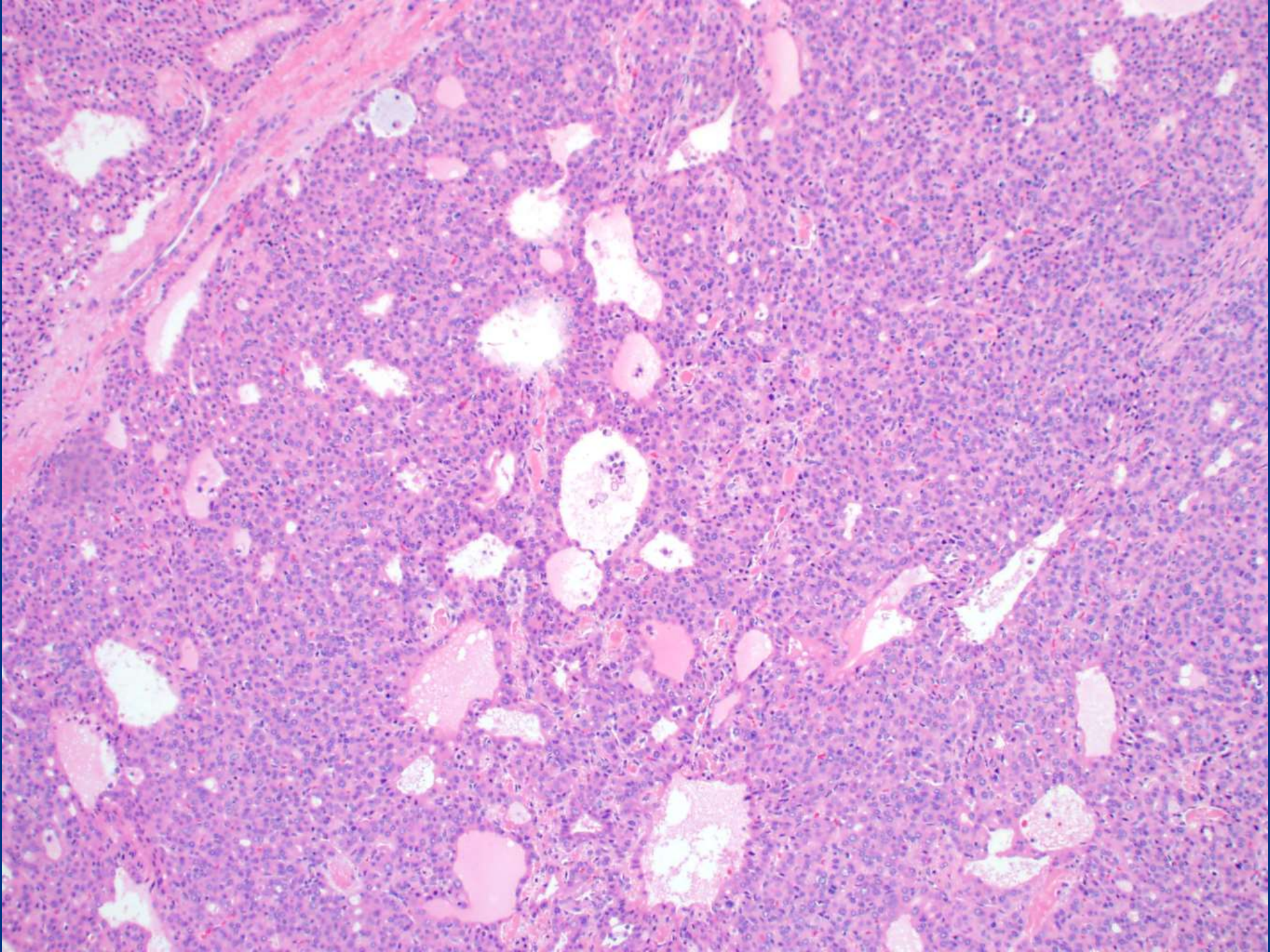
- Diagnosis, Prognosis, and Treatment of Alveolar Soft-Part Sarcoma: A Review. Paoluzzi L, Maki RG. JAMA Oncol. 2018 Oct 18. doi: 10.1001

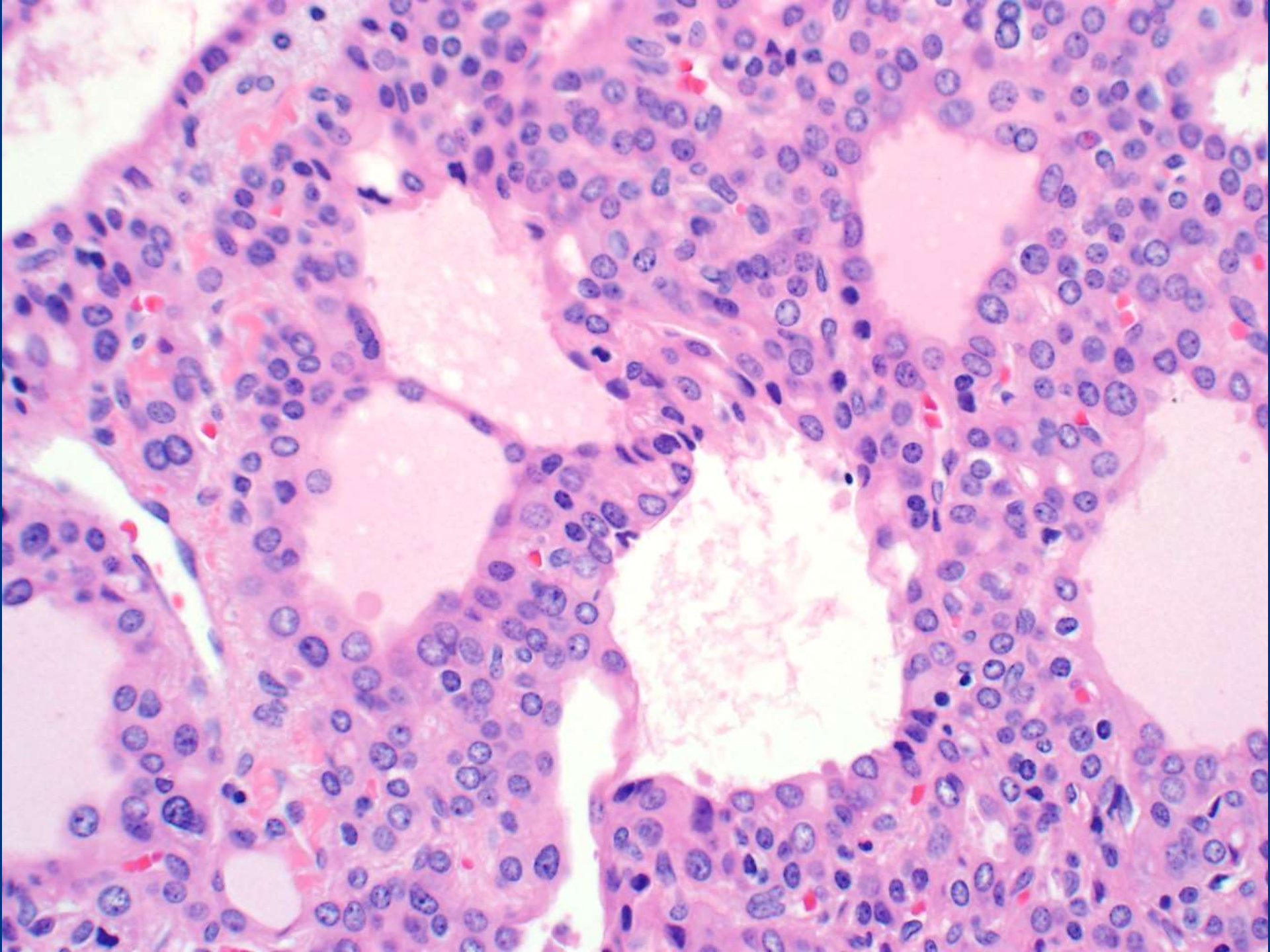
SB 6355

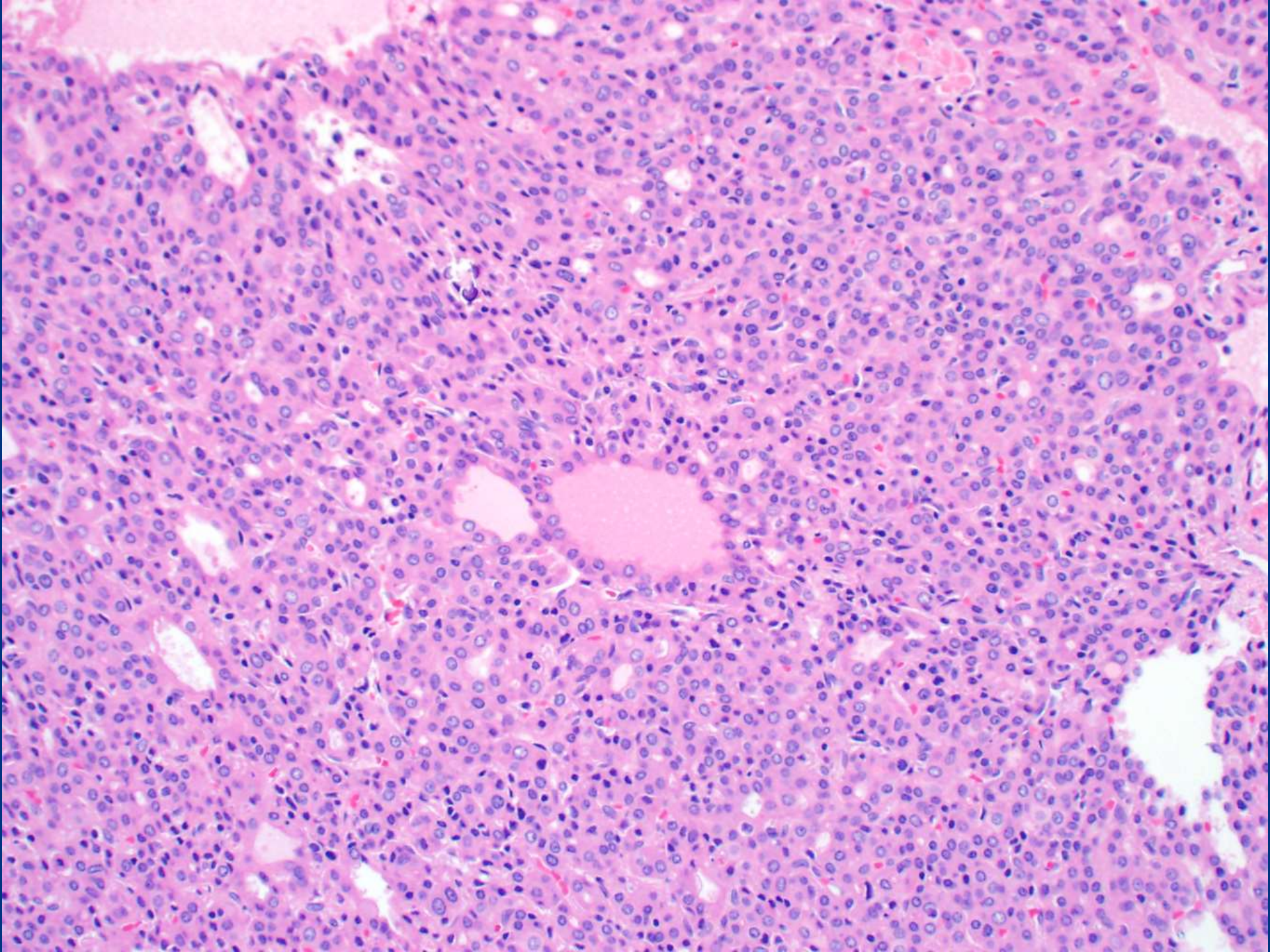
Sanjay Kakar; UCSF

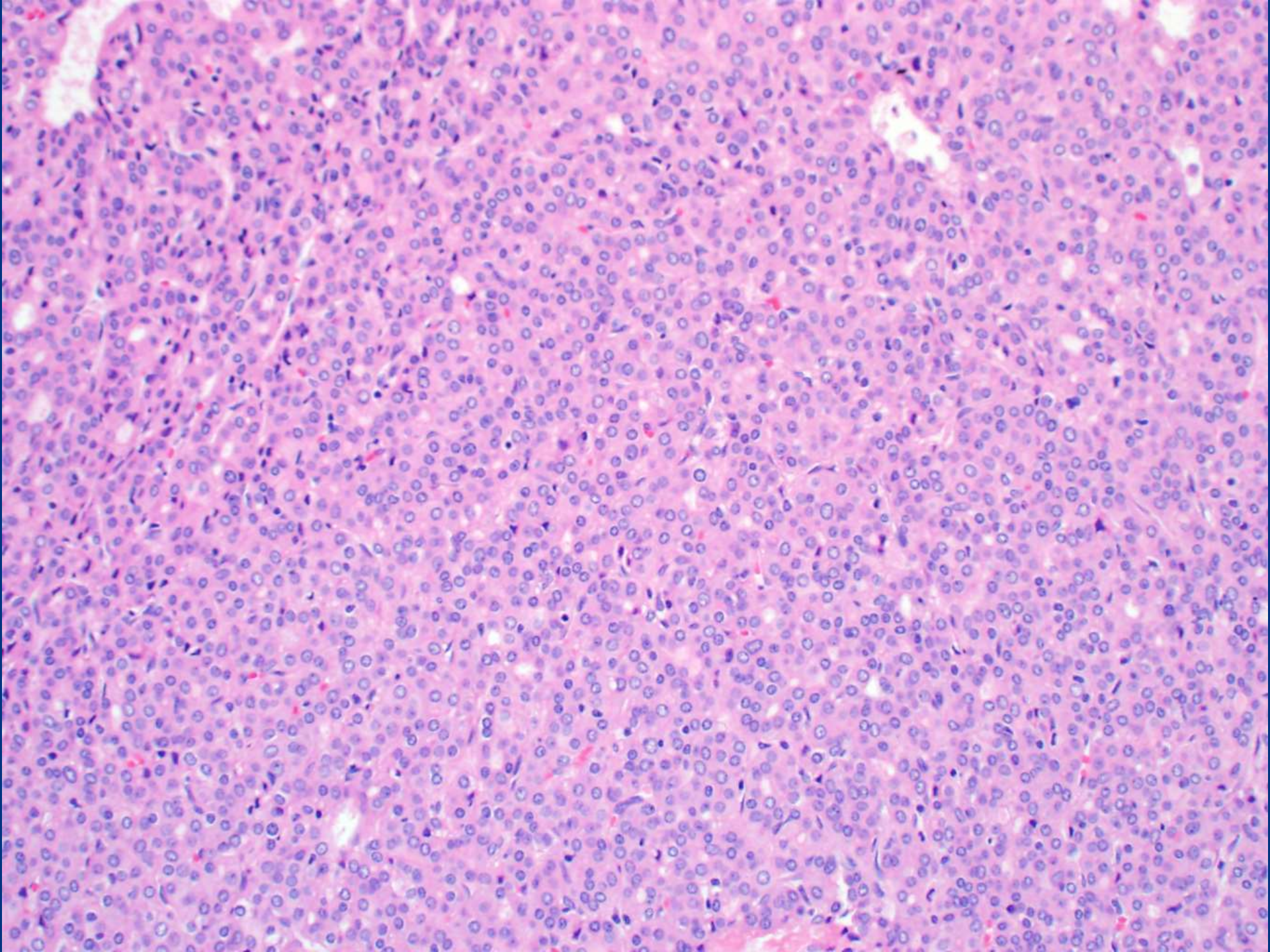
28-year-old female with h/o cervical dysplasia, obesity, and hypothyroidism. Resection for 13cm liver mass. No other known mass lesions.

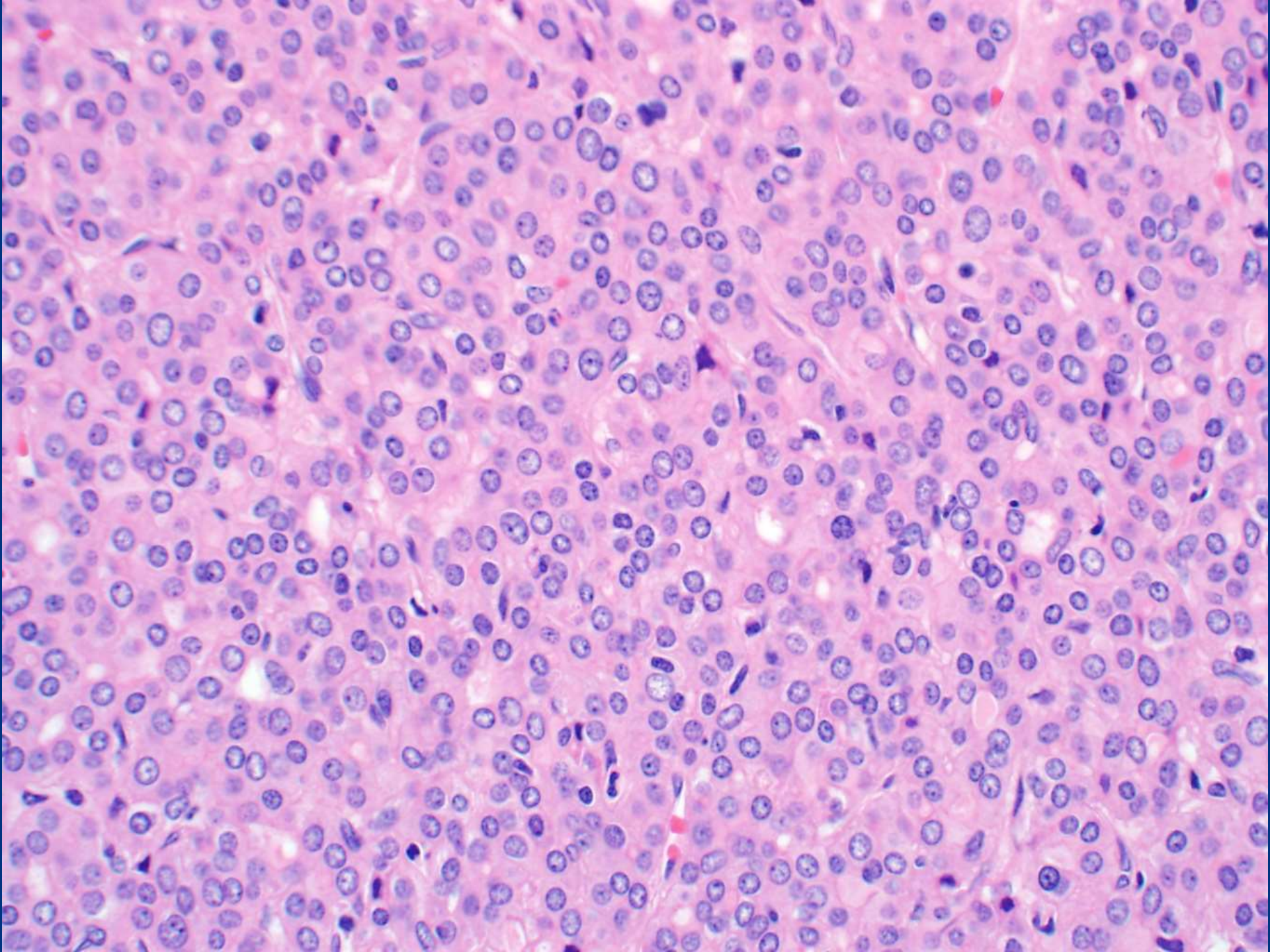


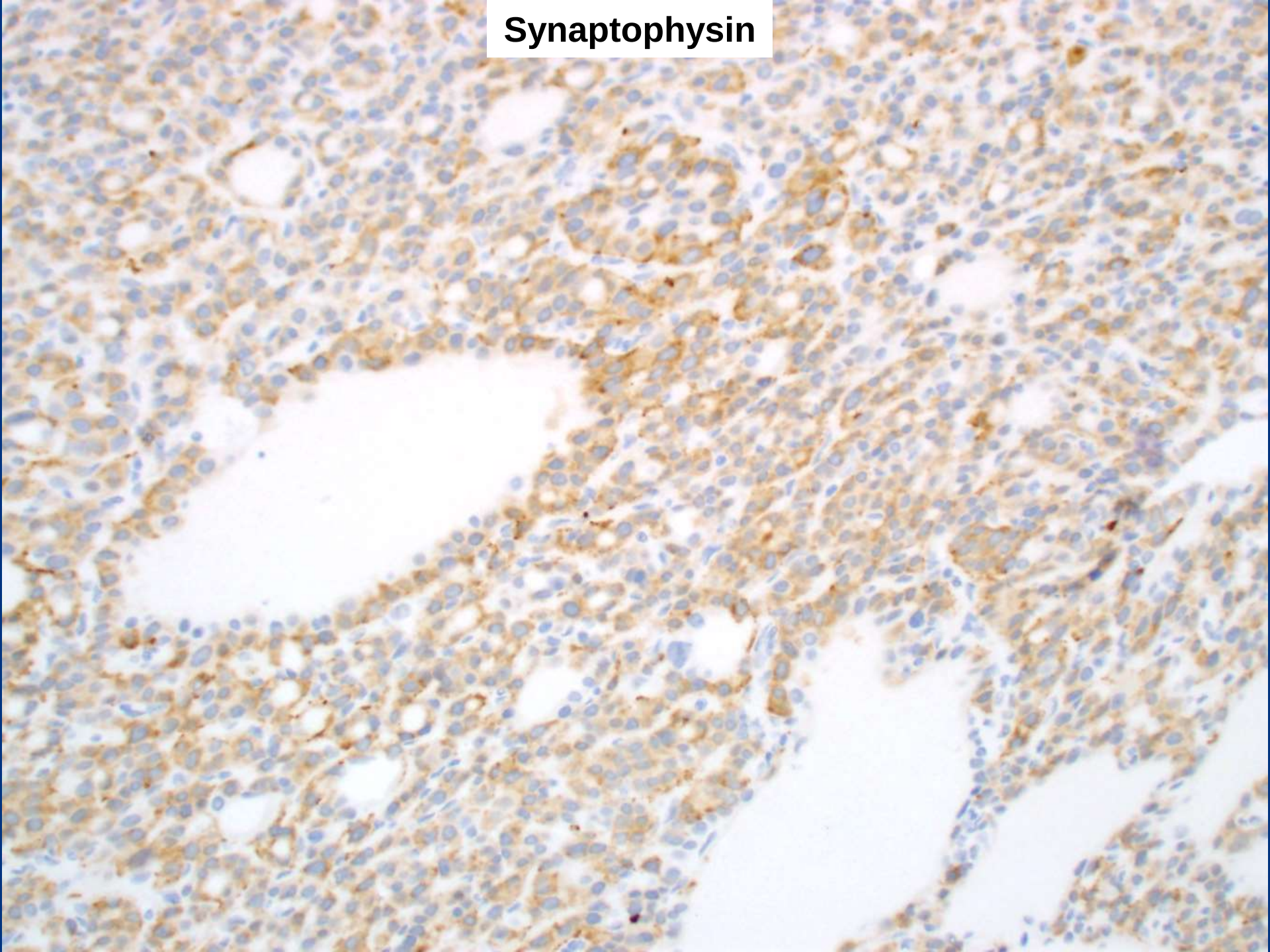


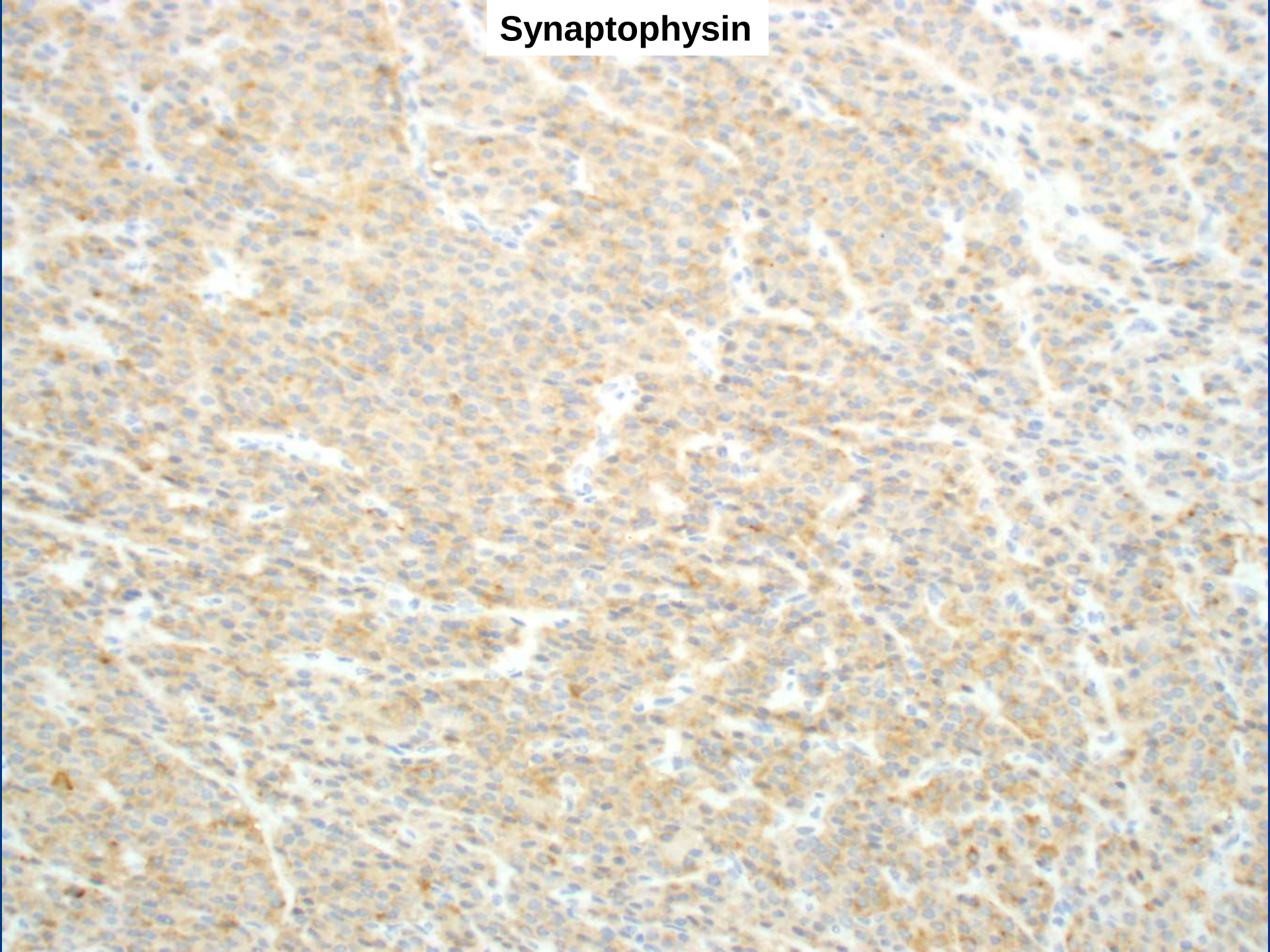


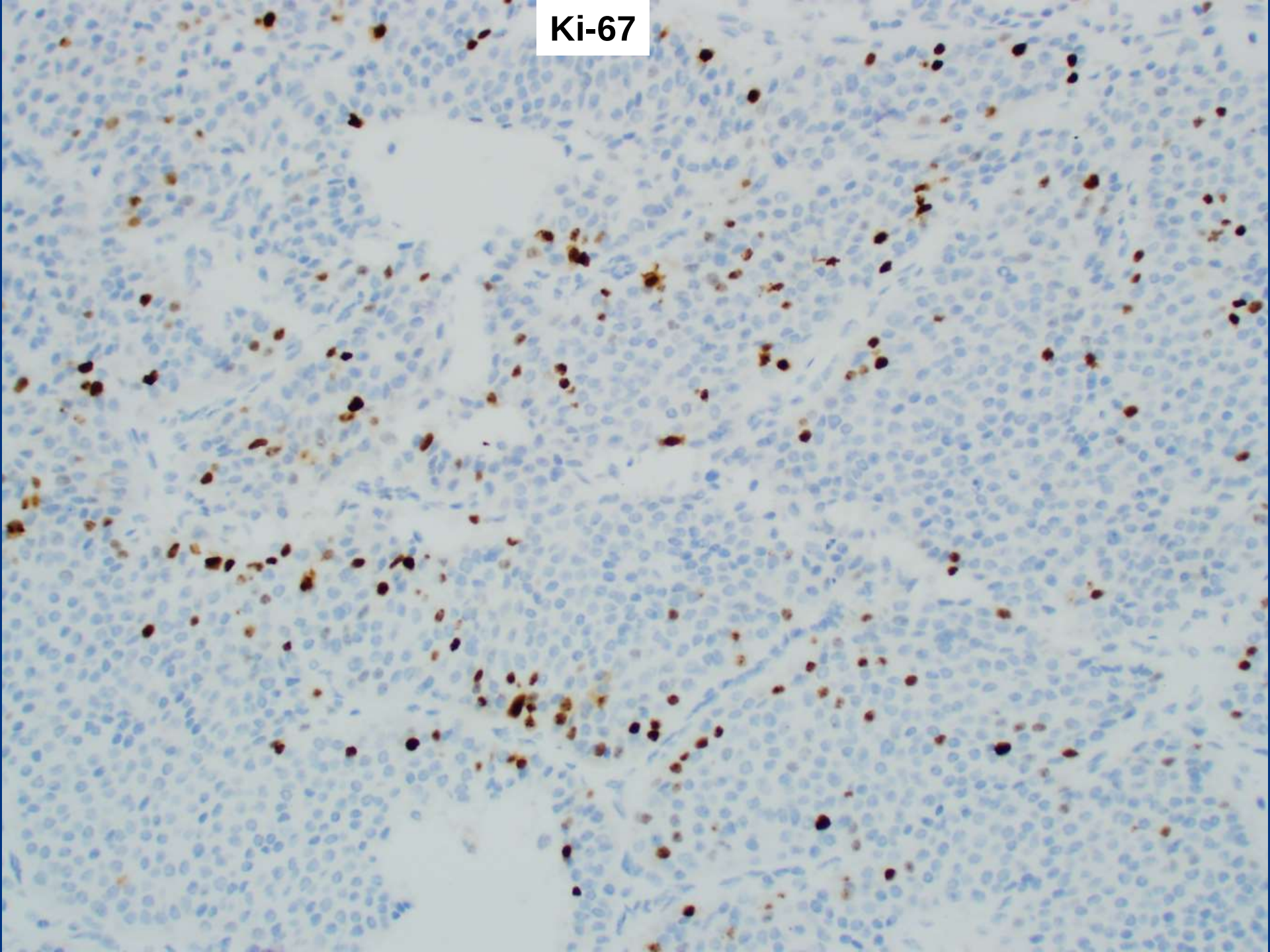







Synaptophysin


Synaptophysin


Ki-67

Immunohistochemistry

Marker	Result
Epithelial (panCK, CK7)	Positive
CK20, CDX2	Negative
Hepatocellular: HepPar, Arg-1, GPC-3	Negative
Chromogranin, CD56	Negative
ER, PR, GATA3	Negative
PAX8, TTF-1	Negative
DPC4	Intact
SF1, CD117, SOX10	Negative
D2-40, WT1	Negative

Diagnosis?

SB 6355: Differential diagnosis

- Neuroendocrine neoplasm
- Metastatic carcinoma
- Non-epithelial tumor
- Primary liver carcinoma
- Diagnosis unknown

Search

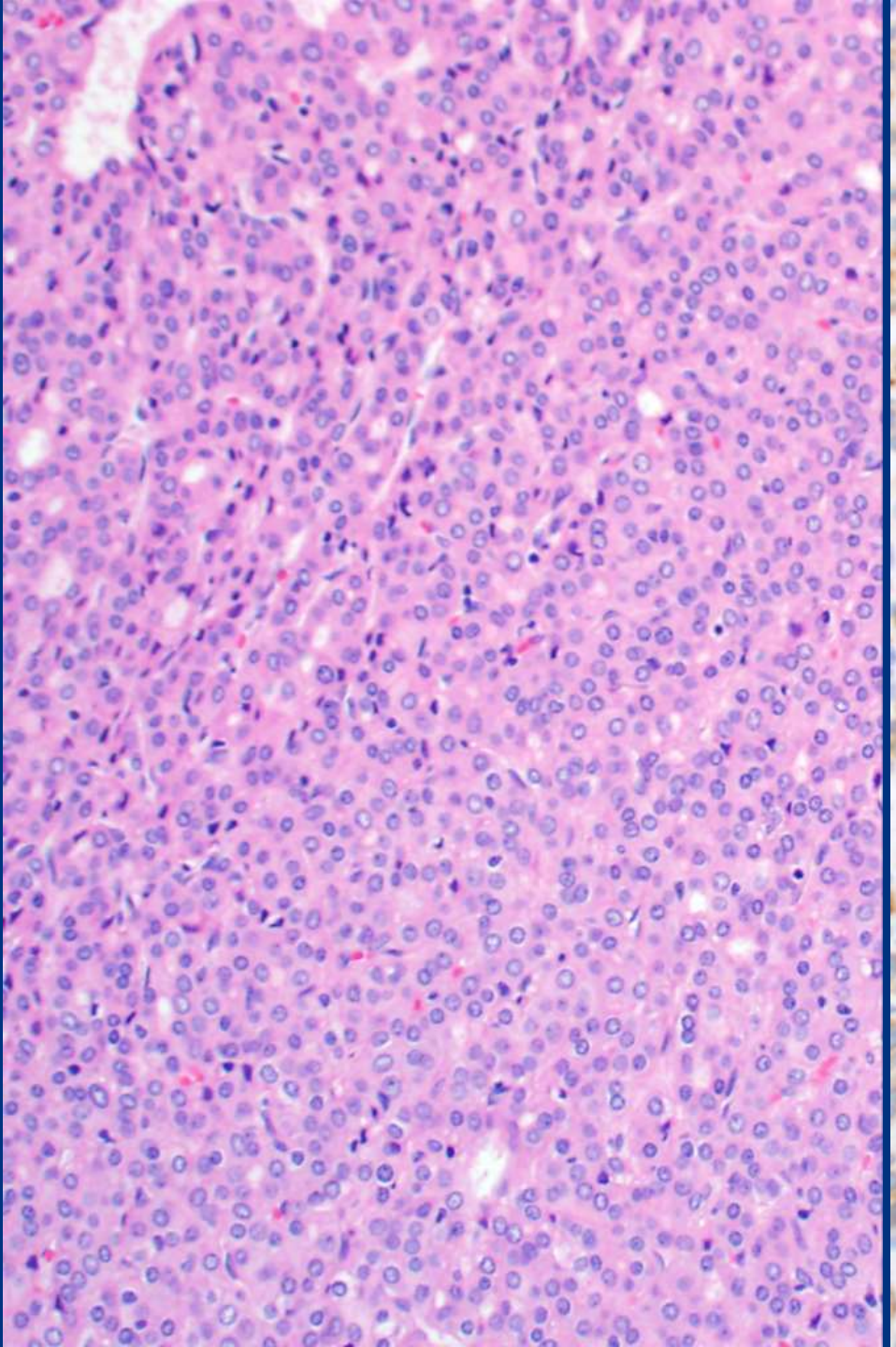
Database of cases from 1959 to the present

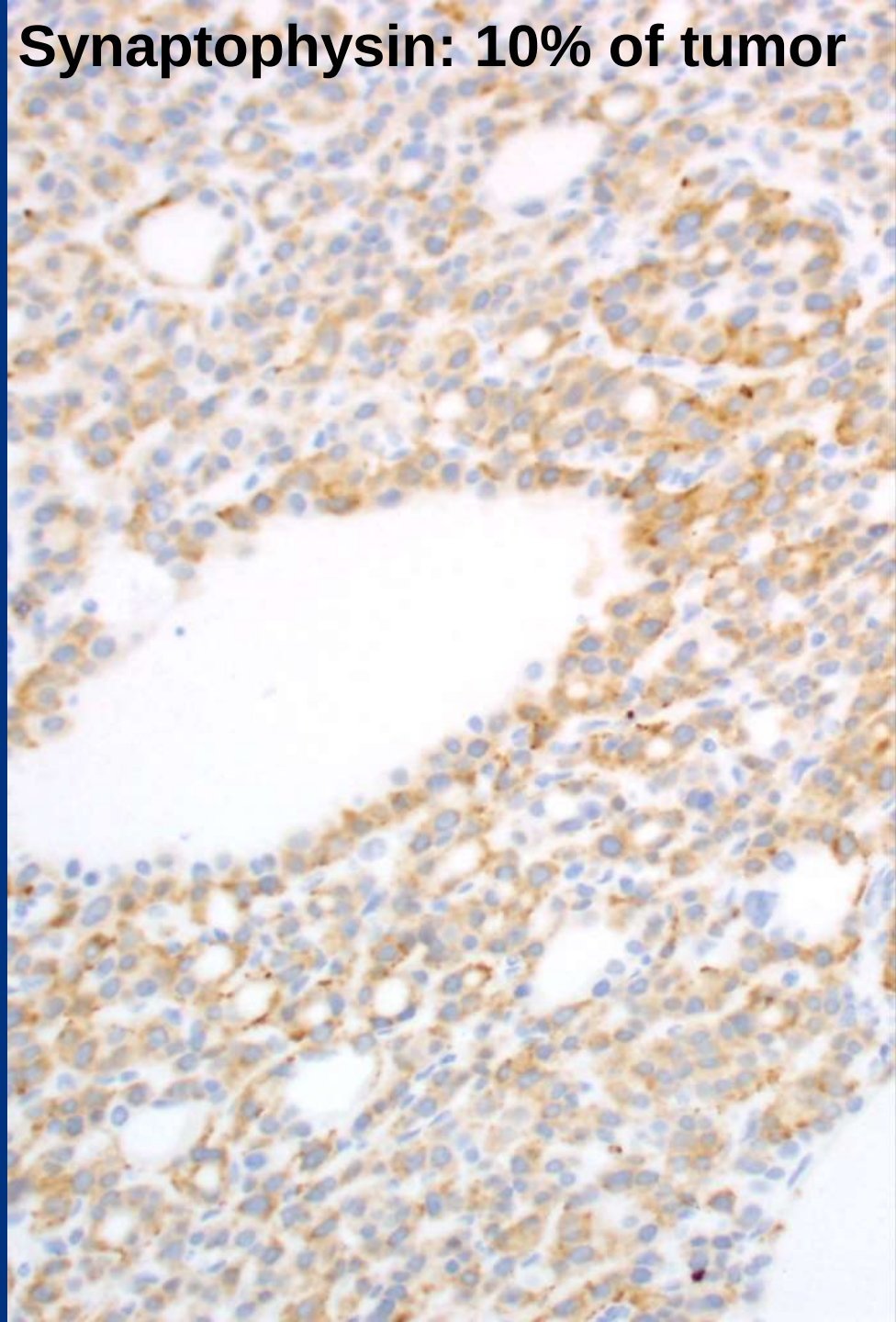
Unknown

Submit

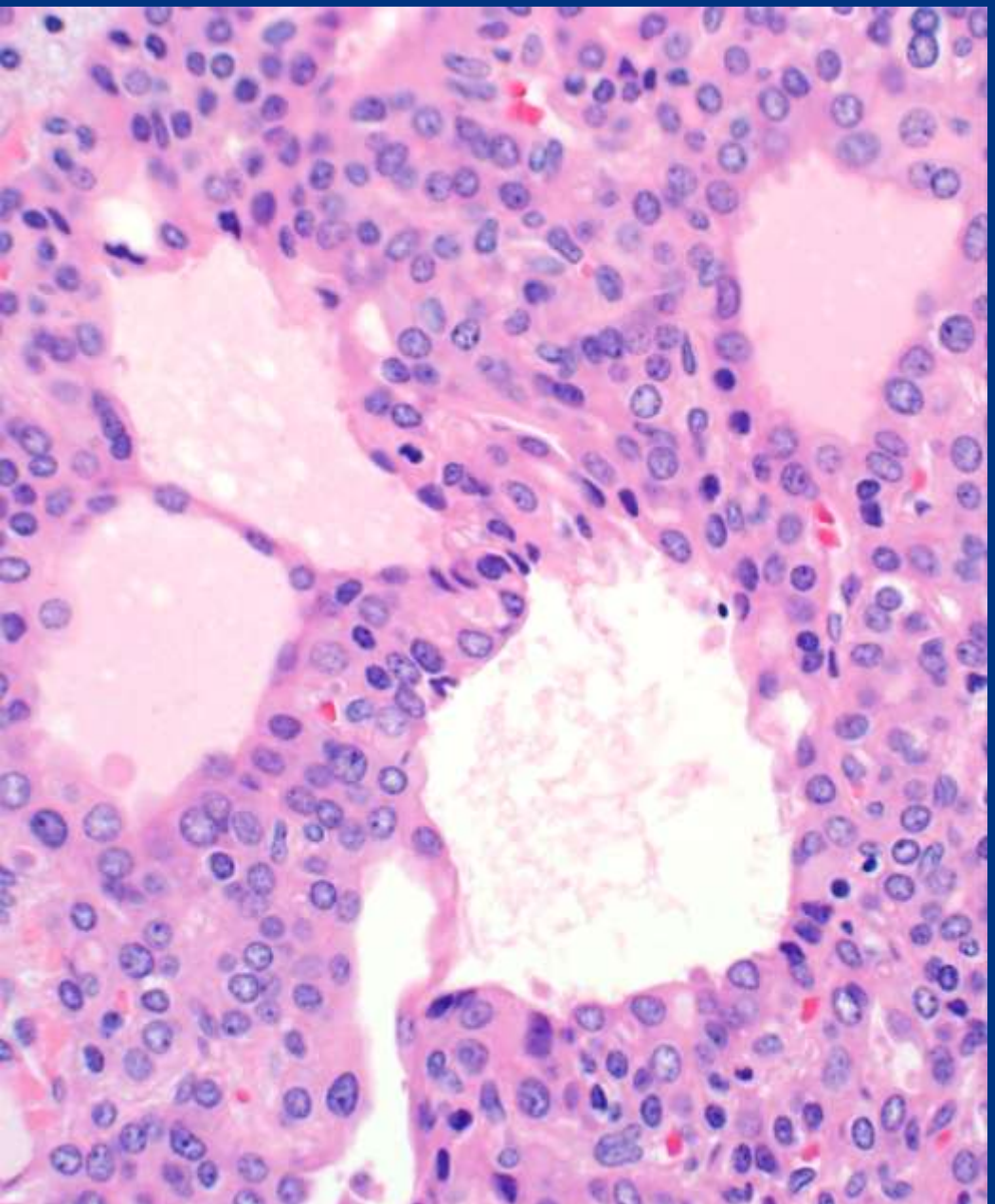
Search results

CASE ID#	ORGAN	DIAGNOSIS
5284	Brain	Metastatic melanoma, primary site unknown
5346	Heart	Metastatic poorly differentiated carcinoma of unknown origin
5510	Joint & Synovium	Xanthogranulomatous reaction to unknown amorphous material, right hip
1710	Liver	Drug induced liver disease (unknown agent)
4833	Placenta	Villitis of unknown origin
4982	Retroperitoneum	Granulosa cell tumor, retroperitoneum (previous TAH-BSO with unknown pathology)

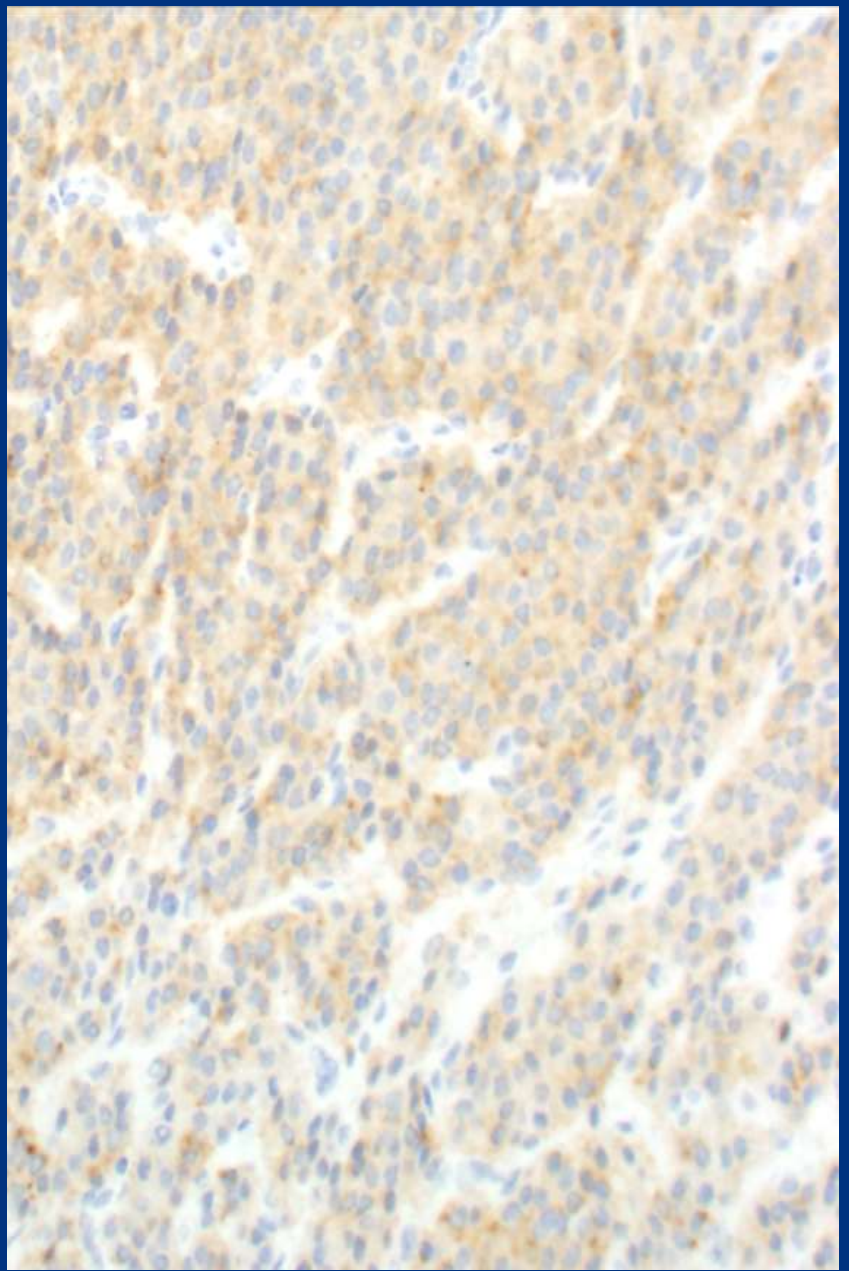



Synaptophysin: 10% of tumor

Cyst-like



Synaptophysin



Differential diagnosis

- Neuroendocrine neoplasm
- Metastatic carcinoma
- Non-epithelial tumor
- Primary liver carcinoma

Immunohistochemistry

Marker	Result
Epithelial (panCK, CK7, CK19)	Positive
CK20, CDX-2	Negative
ER, PR, GATA3	Negative
PAX8, TTF-1	Negative
DPC4	Intact
D2-40, WT1	Negative

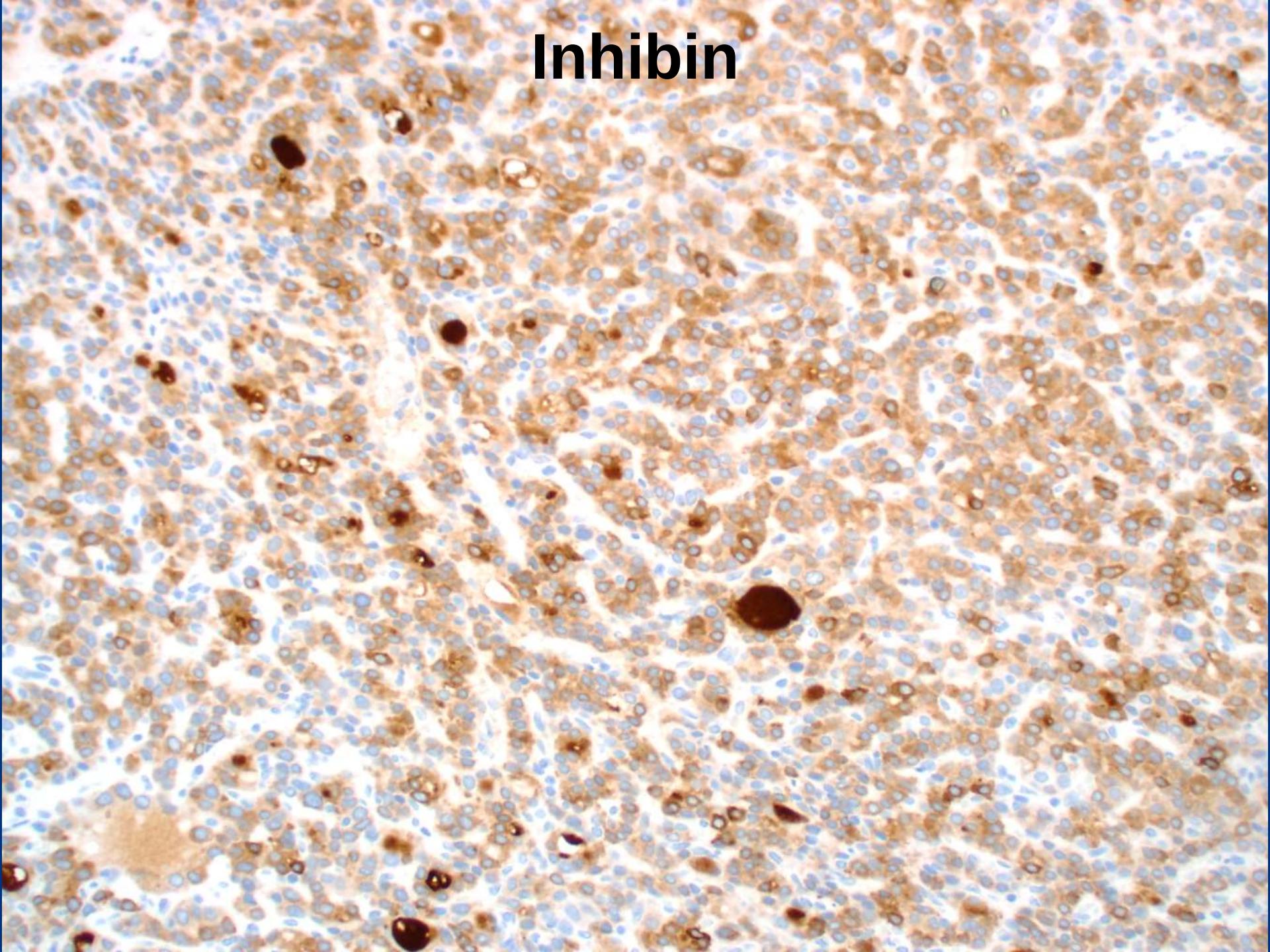
Differential diagnosis

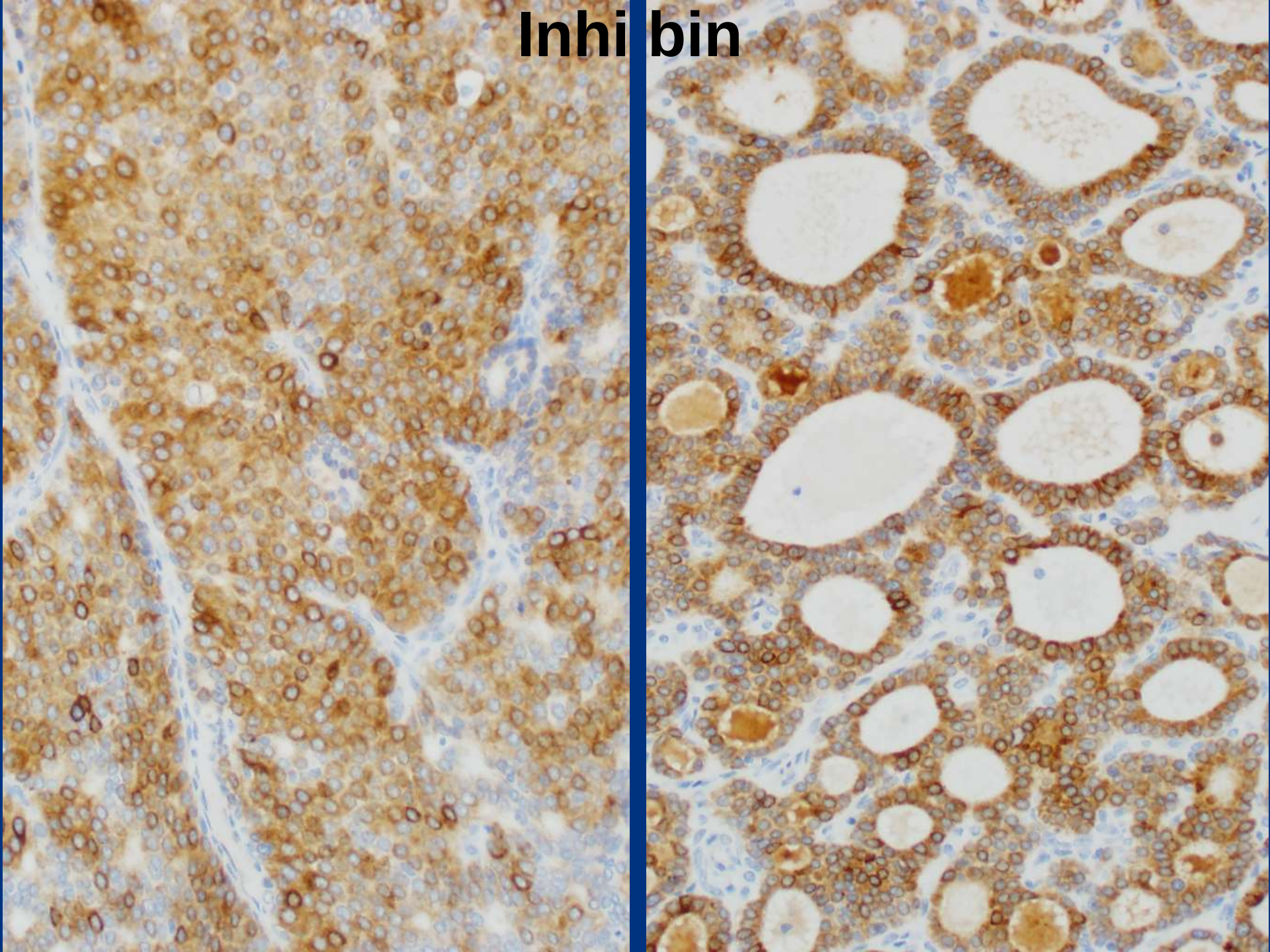
- Neuroendocrine neoplasm
- Metastatic carcinoma
- Non-epithelial tumor
- Primary liver carcinoma

Non-epithelial tumor

Marker	Result
Melanoma (S-100, Melan A)	Negative
GIST (DOG1, KIT)	Negative
Germ cell tumor SALL4, PLAP, OCT4	Negative
Sex cord stromal tumor FOXL2, calretinin, WT-1, SF-1	Negative

Inhibin




Inhi bin

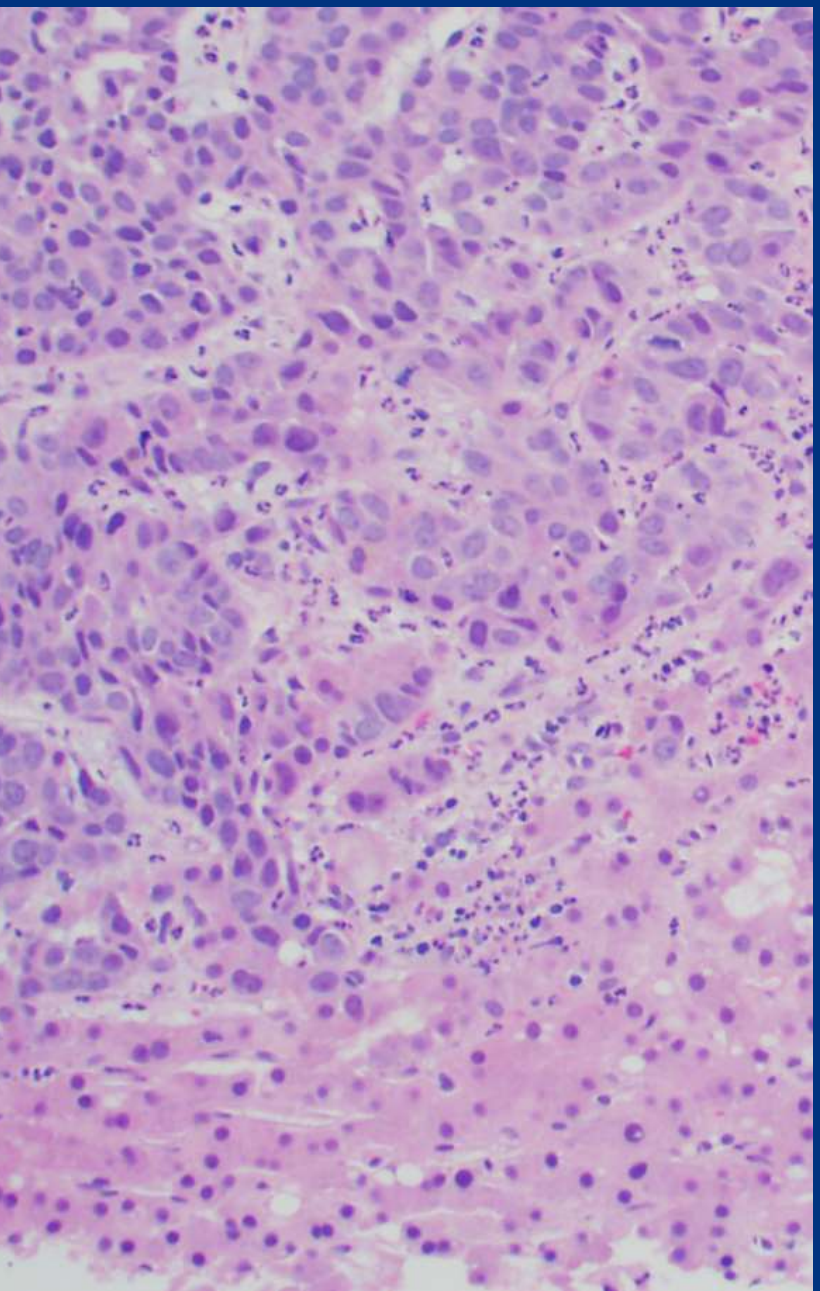
Differential diagnosis

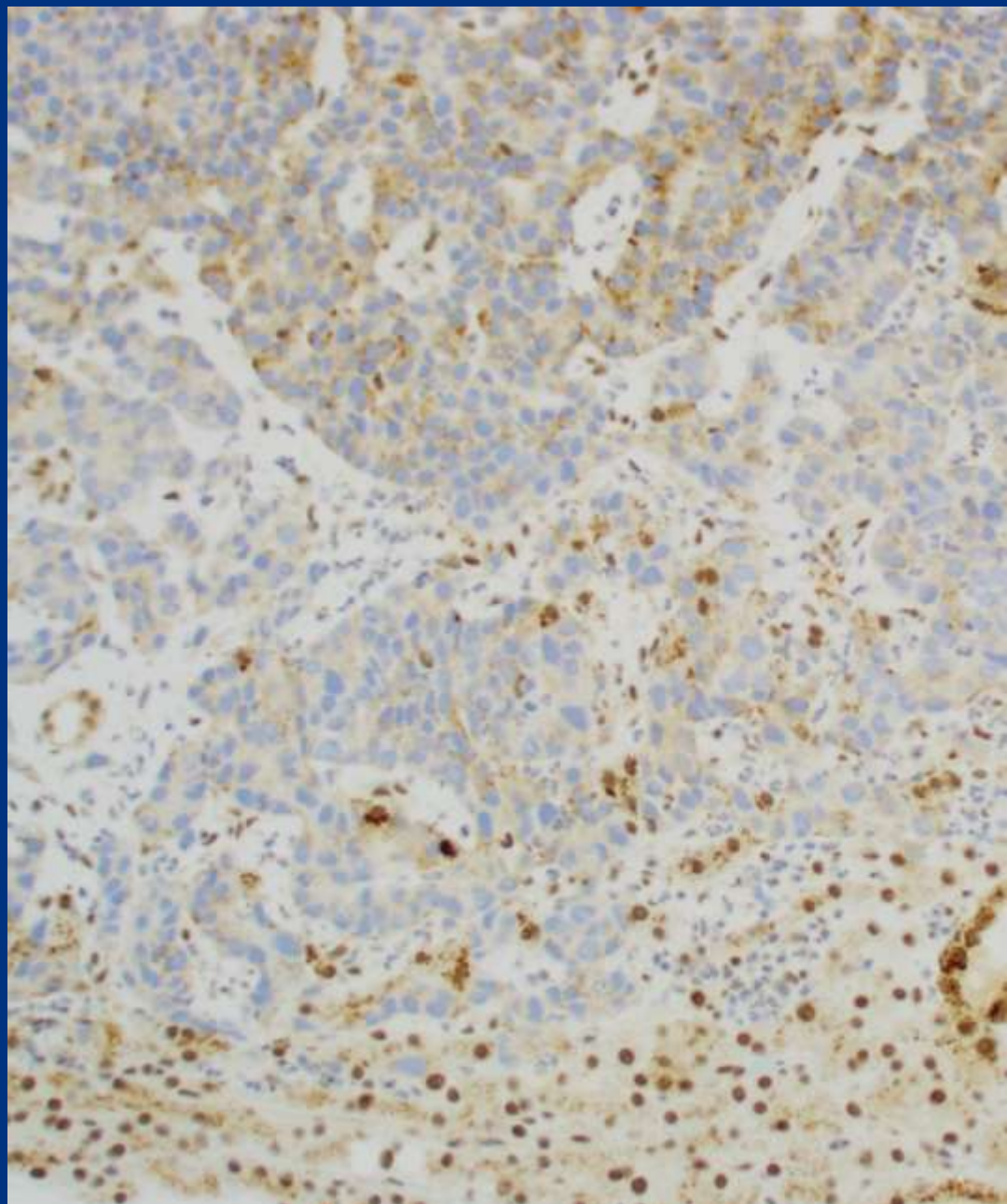
- Neuroendocrine neoplasm
- Metastatic carcinoma
- Nonepithelial tumor
- Primary liver carcinoma

Primary liver carcinoma

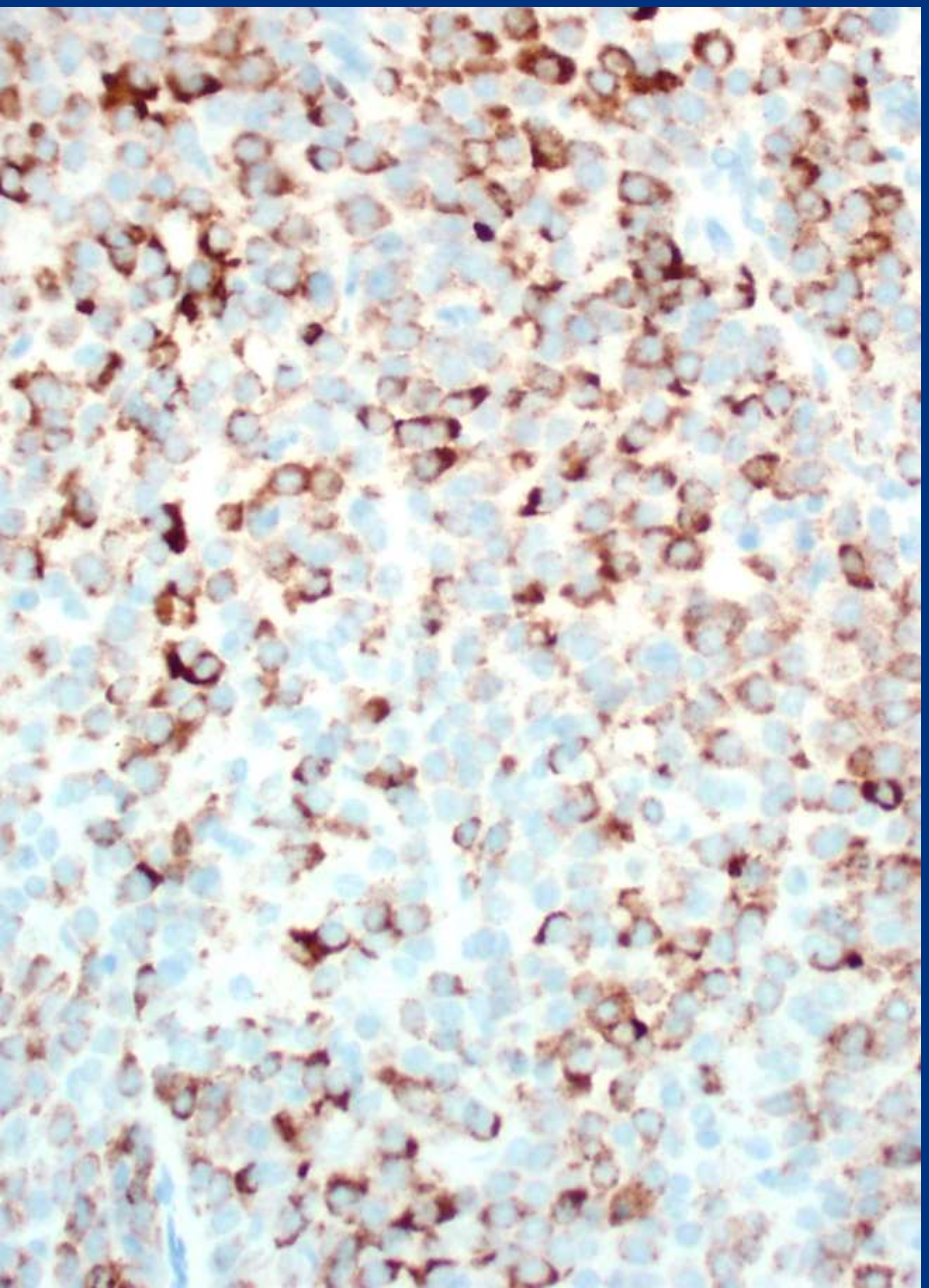
Diagnosis	IHC results
Hepatocellular carcinoma	Hep Par 1, arginase-1, glypican-3, pCEA negative
Intrahepatic cholangiocarcinoma	CK7, CK19: positive Other markers: BAP1 Albumin in situ hybridization

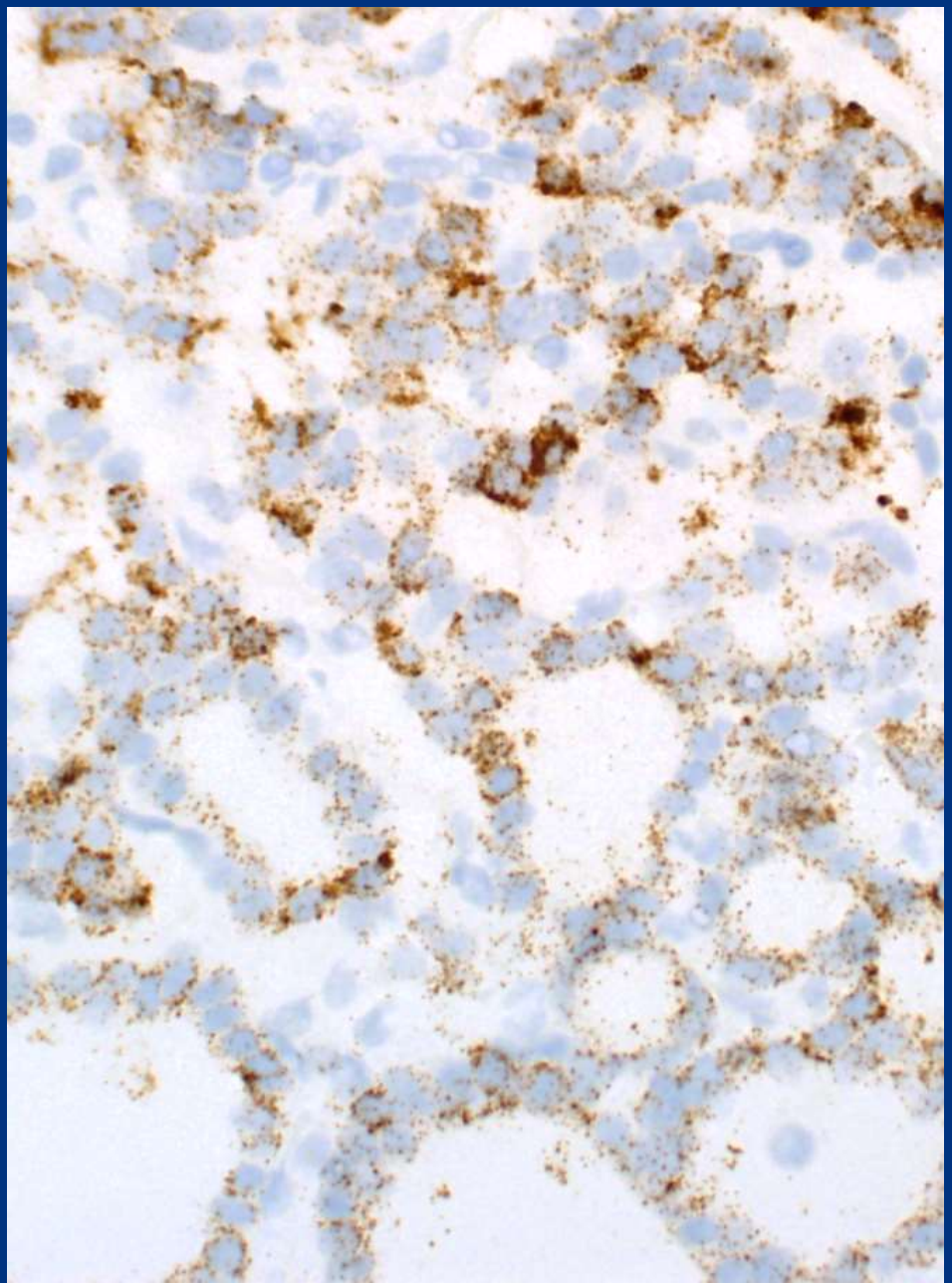
BAP1 loss in ICC





Albumin ISH: solid and cystic areas





Diagnosis?

- Primary liver carcinoma with inhibin and weak synaptophysin staining
- ? Variant of intrahepatic cholangiocarcinoma

Molecular changes in ICC

Molecular changes	Frequency
IDH1/IDH2	12-36%
BAP1	19-25%
PBRM1	11-17%
***FGFR2* fusion**	13%

None of these changes were present in this tumor

Virchows Arch. 2005 May;446(5):560-5. Epub 2005 Apr 7.

Hepatic adenocarcinoma expressing inhibin in a young patient on oral contraceptives.

Vrettou E[1], Hytiroglou P, Sikas N, Soultoyannis I, Goodman ZD.

Ann Hepatol. 2012 Nov-Dec;11(6):961-5.

Thyroid-like cholangiocarcinoma of the liver: an unusual morphologic variant with follicular, trabecular and insular patterns.

Chablé-Montero F[1], Shah B S A, Montante-Montes de Oca D, Angeles-Ángeles A, Henson DE, Albores-Saavedra J.

Int J Surg Pathol. 2018 Oct;26(7):649-654. doi: 10.1177/1066896918769381. Epub 2018 Apr 18.

Thyroid-Like Intrahepatic Cholangiocarcinoma: Report of a Case and Review of the Literature.

Chen SH[1,2], Zheng ZY[1], Wang HL[3], Yu YH[1], Zeng DH[1], Qu LJ[1], Ye XZ[1].

Hum Pathol. 2017 Apr;62:232-241. doi: 10.1016/j.humpath.2017.02.001. Epub 2017 Feb 21.

Molecular and cytogenomic profiling of hepatic adenocarcinoma expressing inhibinA, a mimicker of neuroendocrine tumors: proposal to reclassify as "cholangioblastic variant of intrahepatic cholangiocarcinoma".

Braxton DR[1], Saxe D[2], Damjanov N[3], Stashek K[4], Shroff S[4], Morrissette JD[5], Tondon R[4], Furth EE[6].

Clinical course

Series	Outcome
Braxton, Hum Pathol 2017 (n=3)	2 had metastatic disease on follow-up, died within 4 years of diagnosis
UCSF series (n=4)	1 had metastatic disease

Diagnosis

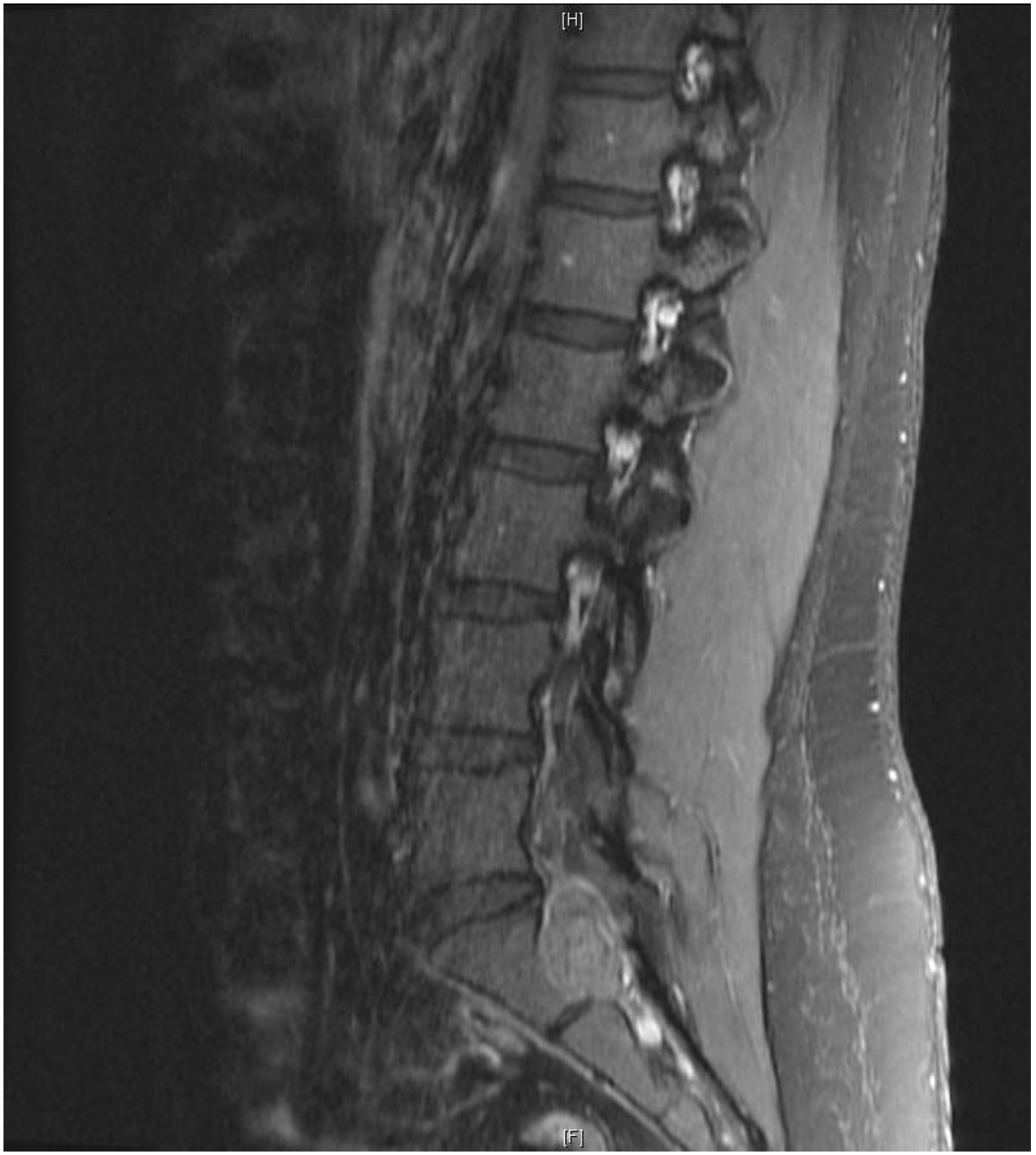
"Solid-cystic variant of intrahepatic cholangiocarcinoma"

- **Young women**
- **Inhibin positivity**
- **Lacks typical molecular changes of ICC**
- **"Cholangioblastic": not preferred**

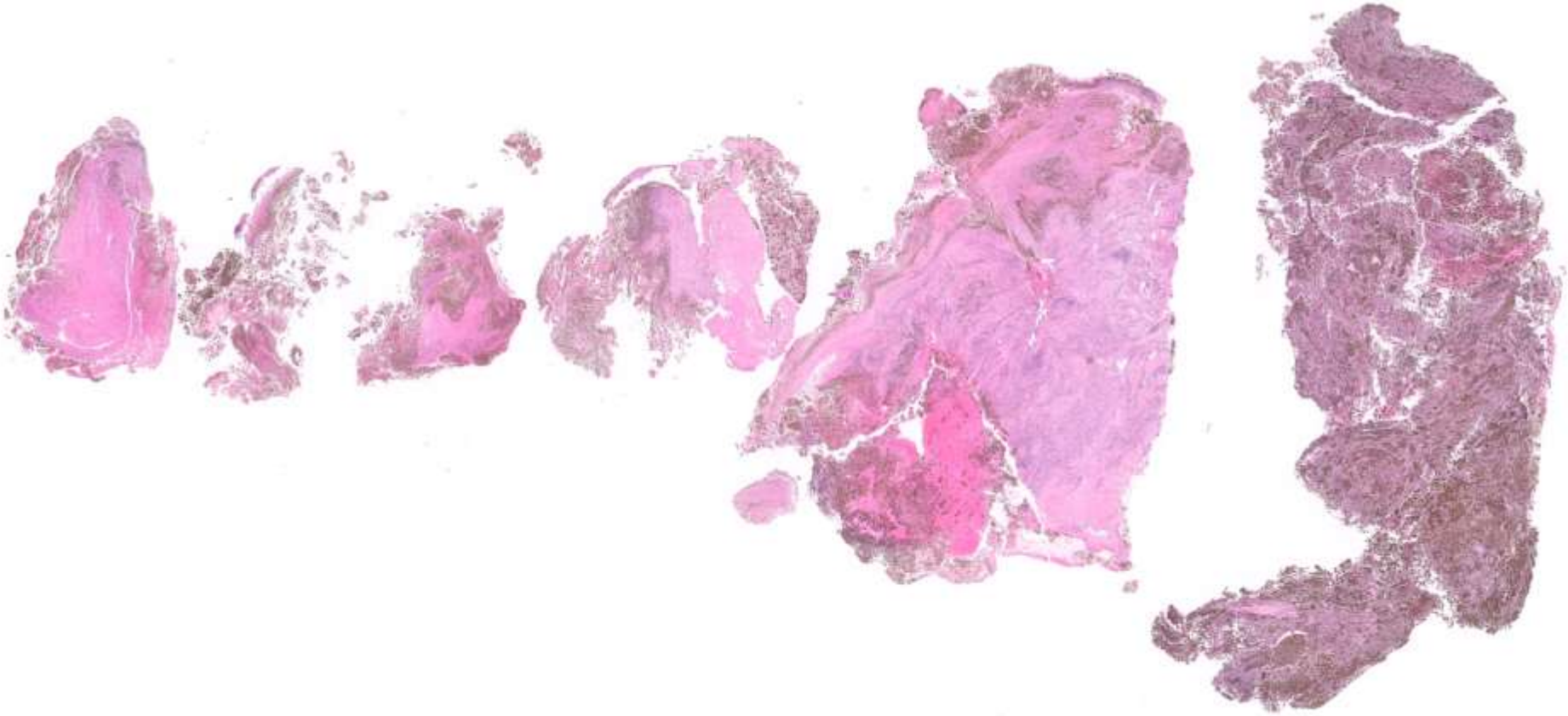
SB 6356

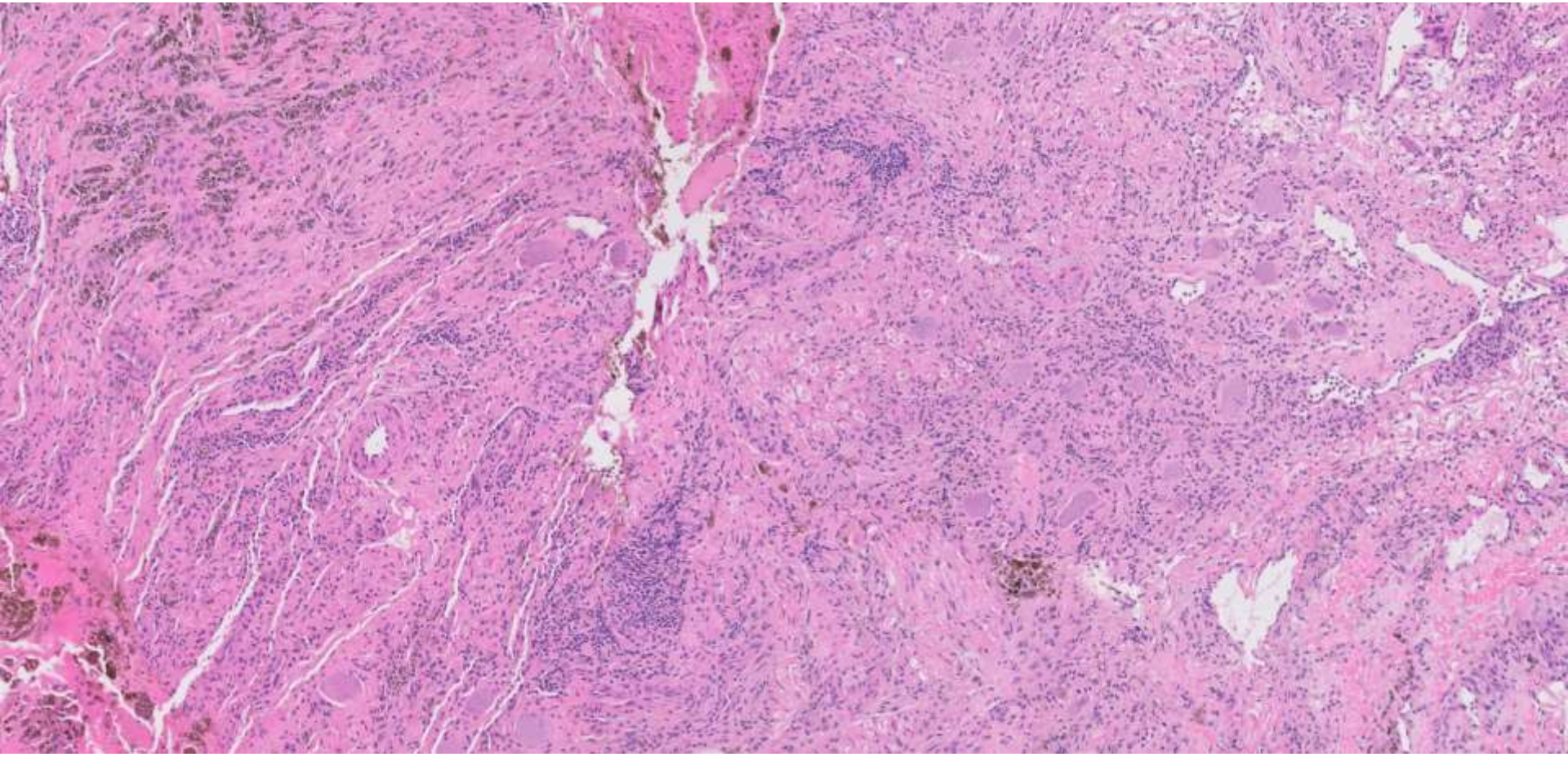
Jeff Cloutier/Hannes Vogel; Stanford

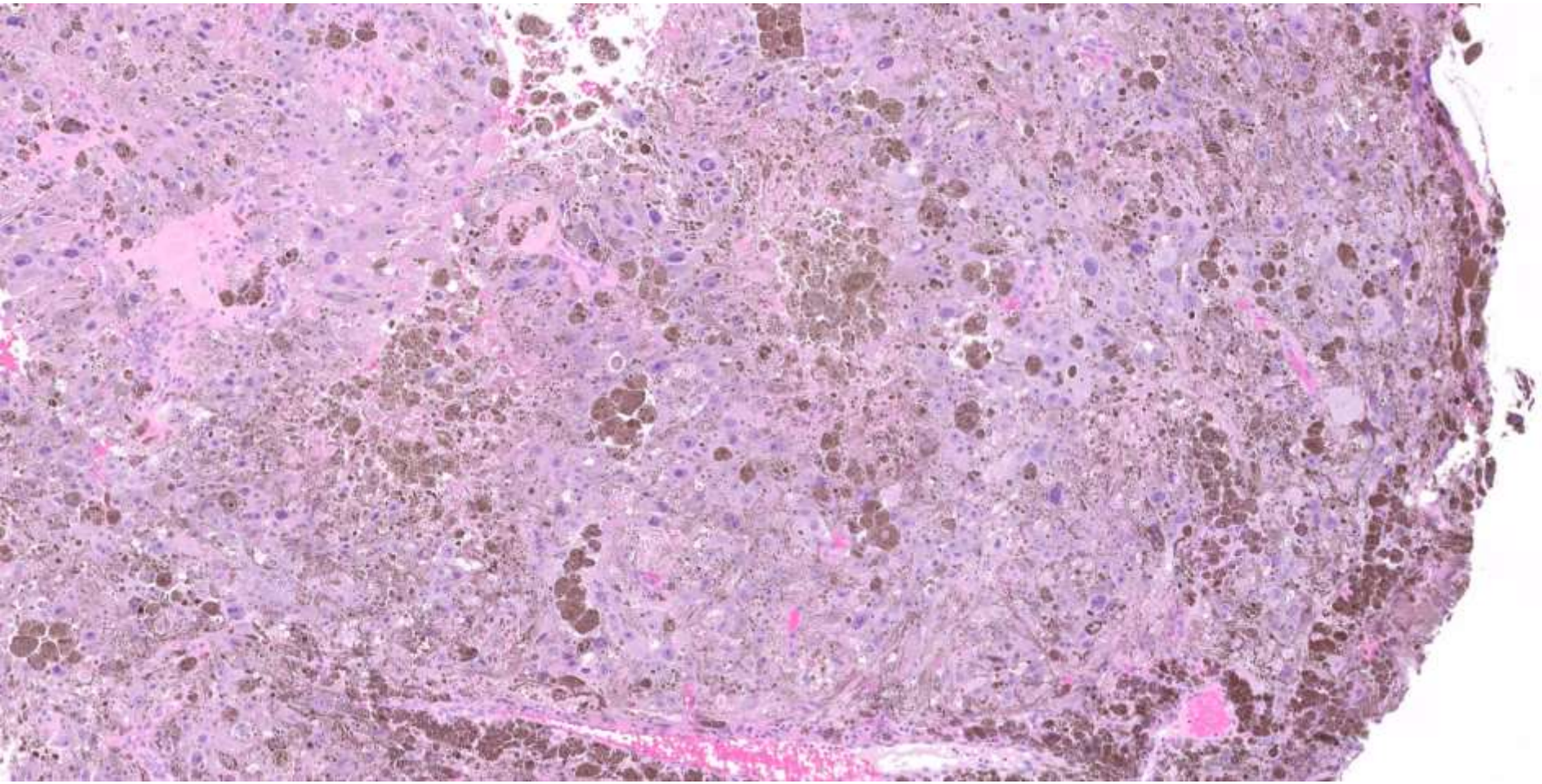
18-year-old female with h/o progressive lower back pain over past 8 months and recent increased difficulty with urination. MRI: 2.9cm mass identified filling right S1 subarticular space, intimately associated with the exiting right S1 nerve root.

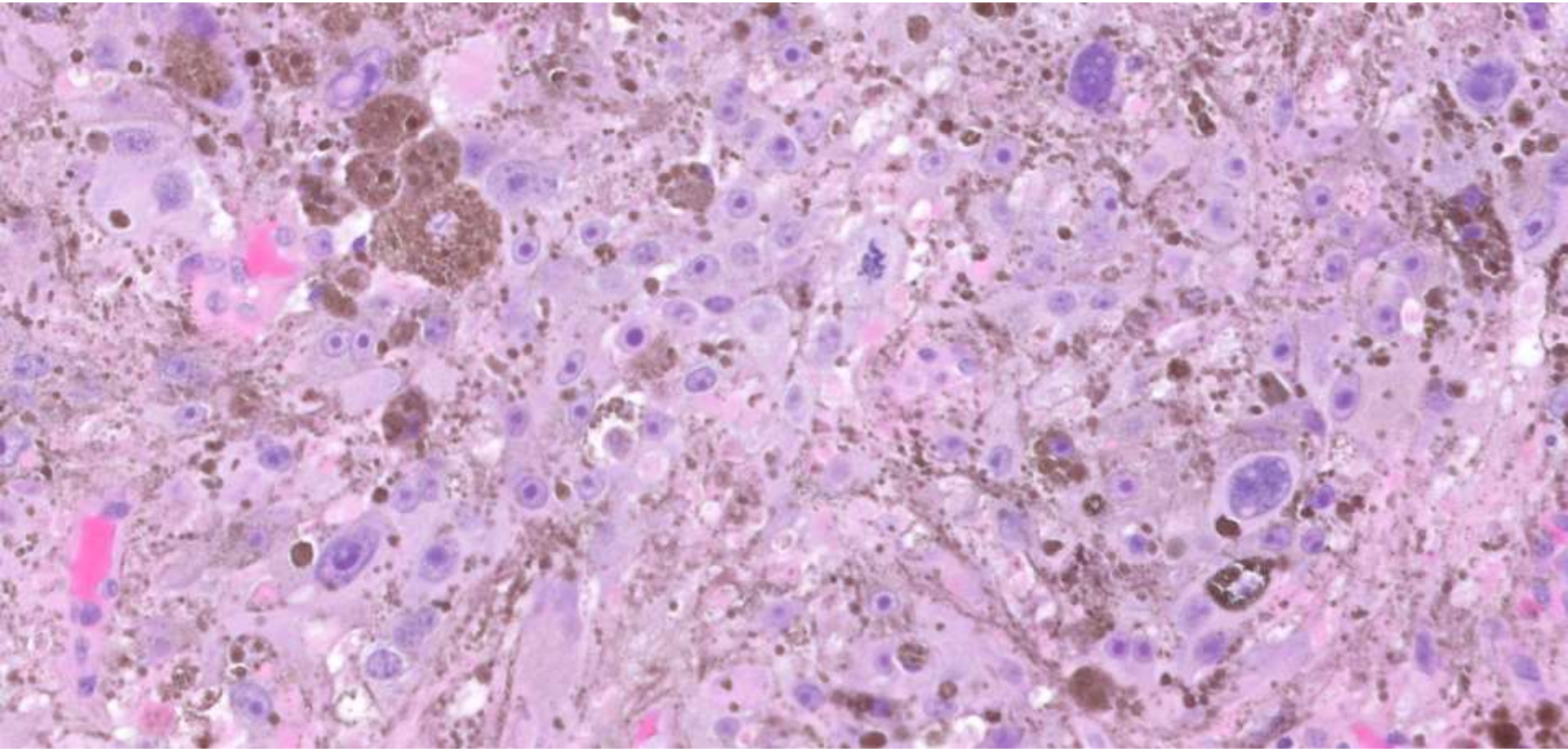


MRI: 2.9 cm mass filling the right S1 subarticular space, intimately associated with the exiting right S1 nerve root

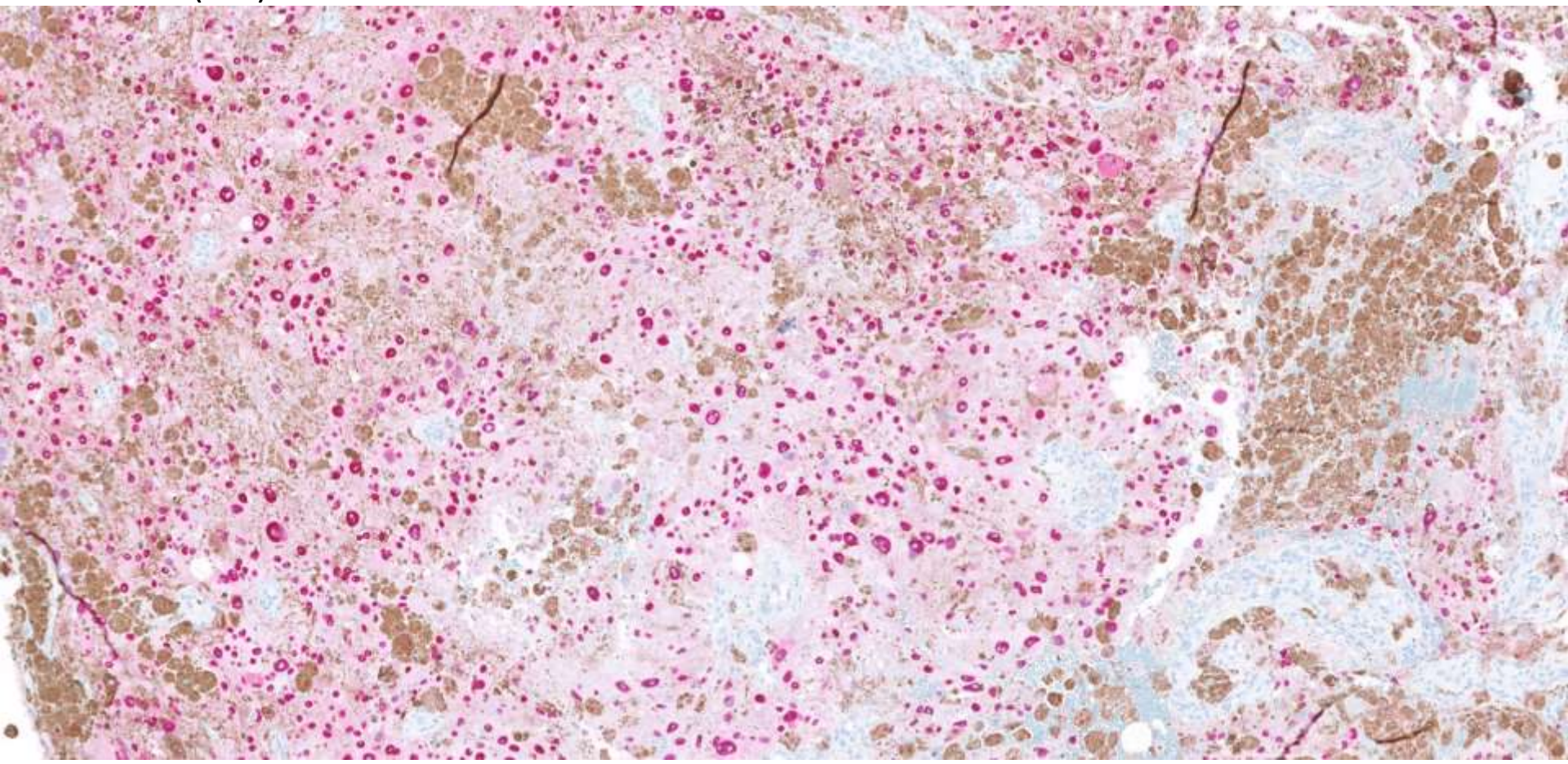




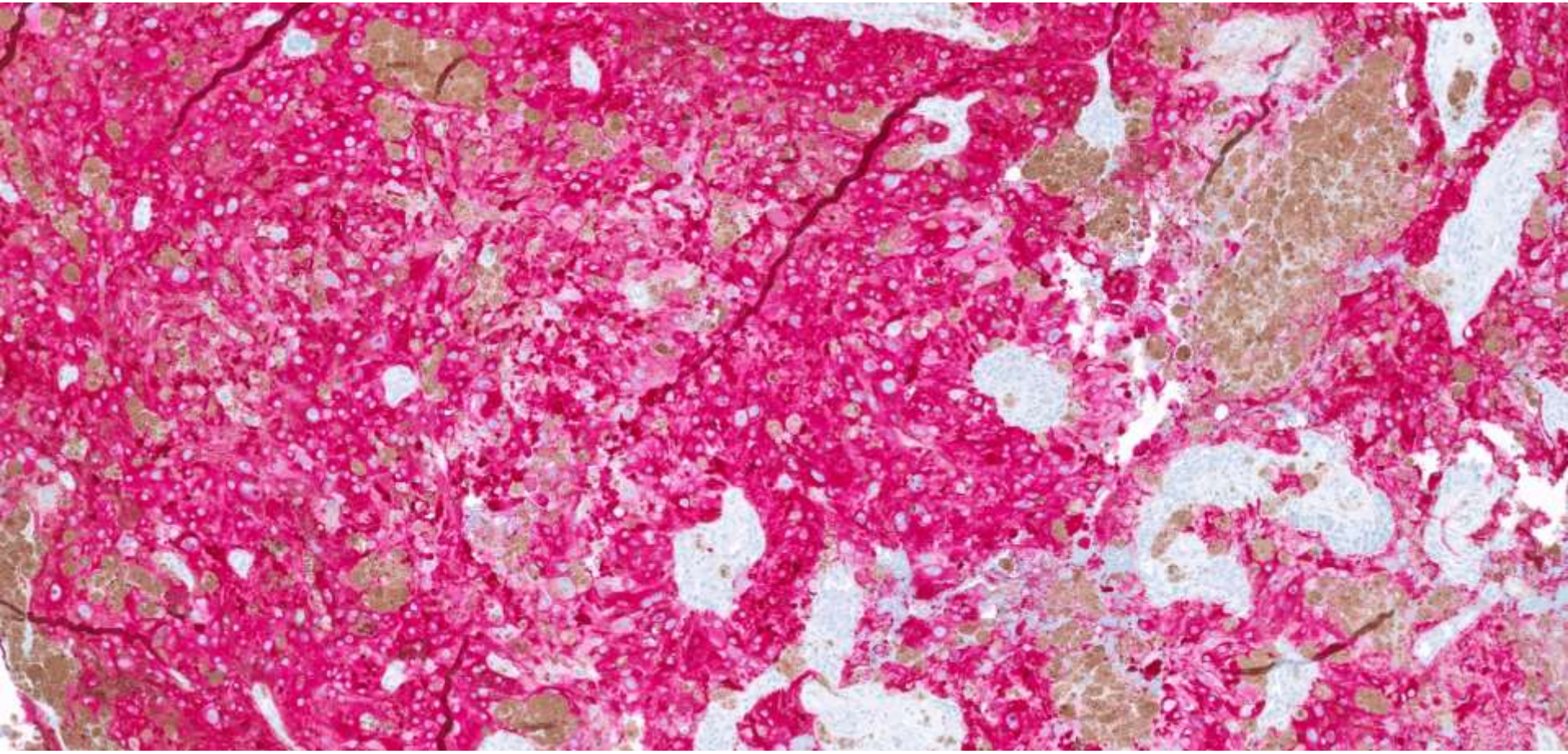




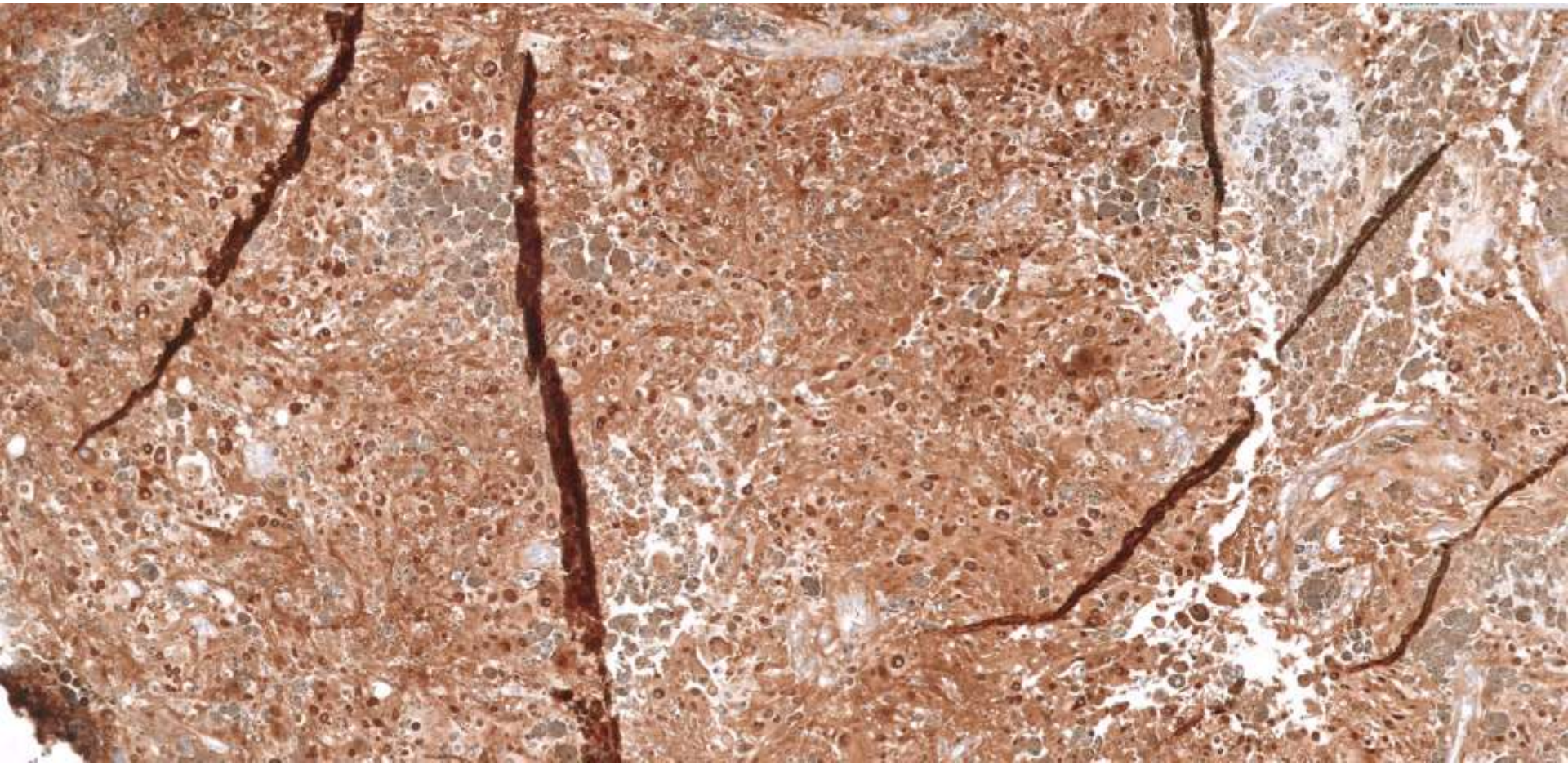
SOX-10 (red)



MelanA (red)



S100



Diagnosis?

Dx: Malignant melanotic schwannian tumor (i.e. melanotic schwannoma)

MMST

- Nerve sheath tumor of melanin-producing Schwann cells
- An uncommon neoplasm: <1% of all nerve sheath tumors (~200 cases reported)
- First described in 1932 as a “malignant melanotic tumor of ganglion cells”
- Subsequently termed “melanocytic schwannoma” in 1975
- In 2014, authorities argued for reclassification as “malignant melanotic schwannian tumor” due to malignant potential

Alexiev BA, Chou PM, Jennings LJ. Pathology of Melanotic Schwannoma. Arch Pathol Lab Med. 2018 Jan 26.

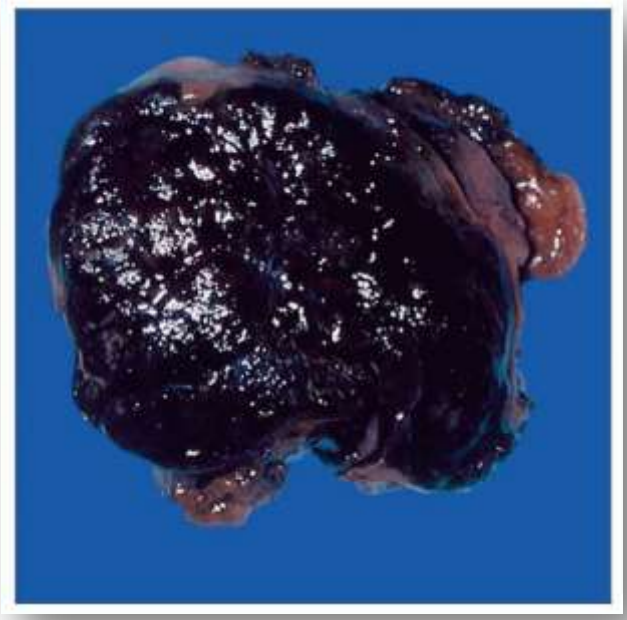
Clinical features

- Young patients (mean age = 38 years)
- Arises in peripheral nervous system, especially paraspinal sympathetic chain
- Can cause adjacent bone erosion or destruction
- Local recurrence common and metastatic potential (lung and pleura)

Alexiev BA, Chou PM, Jennings LJ. Pathology of Melanotic Schwannoma. Arch Pathol Lab Med. 2018 Jan 26.

Gross features

- Solitary, round/ovoid tumor
- Well circumscribed
- Most are >5 cm
- Gray to pitch black, consistency of tar
- Infrequently cystic



Histologic features

- Interlacing fascicles or nests
- Plump spindle and epithelioid cells with vesicular chromatin
- Severe cytologic degenerative atypia
  - markedly enlarged nuclei, nuclear hyperchromasia, irregular nuclear borders
- Macronucleoli
- Variable melanin pigment (in tumor cells and melanophages)
- Psammomatous calcifications (“Psammomatous MMST”)
- Low mitotic rate

Immunohistochemistry

- IHC profile identical to melanoma
- Positive:
  - S100
  - SOX10
  - HMB-45
  - Melan-A
  - MITF

Genetics of MMST

- Most are sporadic
- 50% of “psammomatous MMST” associated with Carney complex
  - Inactivating mutation in Ch17 gene *PRKAR1A*
  - Spotty skin pigmentation, cardiac myxomas, endocrine tumors (adrenal cortex, pituitary, testis, thyroid)
- Can be seen in patients with NF1

Prognosis

- Local recurrence rate: 15-35%
- Metastasis rate: 26-44% (in 5 years)
- Mortality rate: 15%
- Clinicopathologic evaluation poorly predicts tumor behavior
- Mitotic rate >2/10 HPF correlated with metastasis

Malignant Melanotic Schwannian Tumor

A Clinicopathologic, Immunohistochemical, and Gene Expression Profiling Study of 40 Cases, With a Proposal for the Reclassification of "Melanotic Schwannoma"

Jorge Torres-Mora, MD, Sarah Dry, MD,† Xinmin Li, PhD,† Scott Binder, MD,† Mitual Amin, MD,‡ and Andrew L. Folpe, MD**

Torres-Mora J, Dry S, Li X, Binder S, Amin M, Folpe AL. Malignant melanotic schwannian tumor: a clinicopathologic, immunohistochemical, and gene expression profiling study of 40 cases, with a proposal for the reclassification of "melanotic schwannoma". Am J Surg Pathol. 2014 Jan;38(1):94-105.

Differential diagnosis

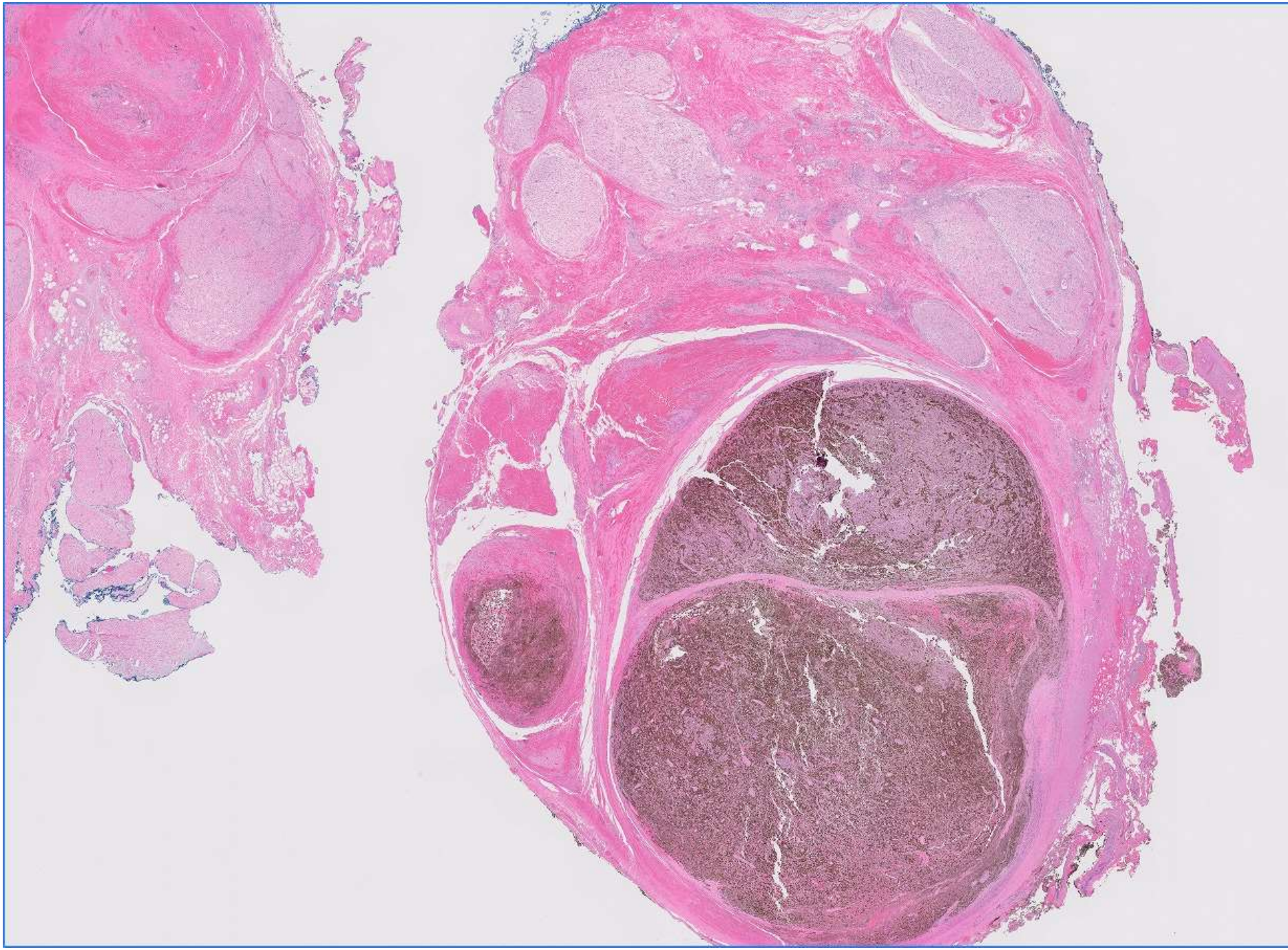
- Malignant melanoma
- Melanocytoma
- Pigmented neurofibroma
- Pigmented dermatofibrosarcoma protuberans

DDX: Malignant melanoma

- A crucial diagnosis to rule out
- MMST is favored of melanoma if:
  - Tumor arises in ganglia
  - Psammoma bodies are present
  - Evidence of pericellular basement membrane (by collagen IV IHC or reticulin stain)
  - Negative for $BRAF^{V600E}$ mutation (vs present in 90% of melanomas)
- Clinical correlation is essential

Follow up

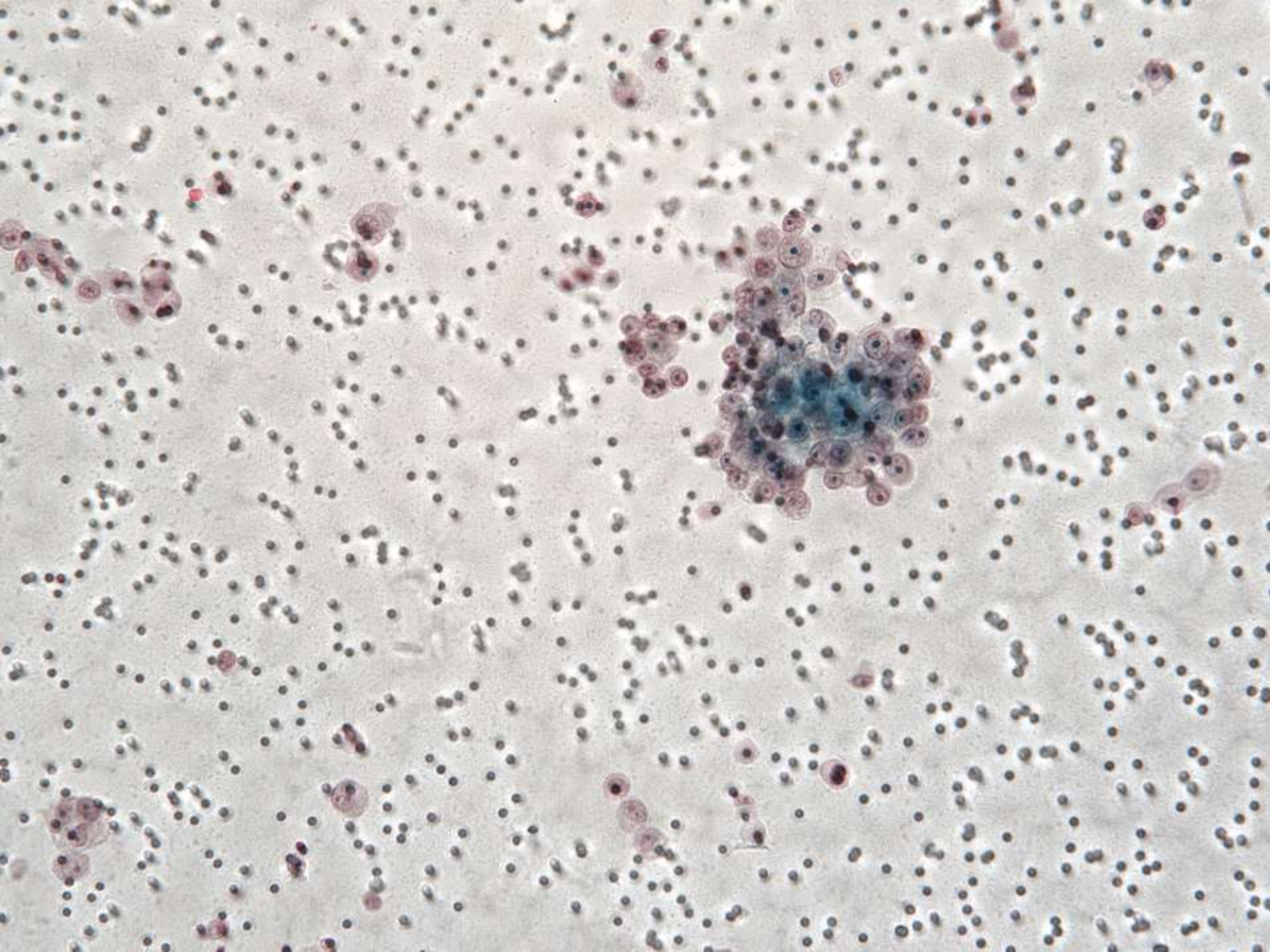
- Re-resection of residual tumor with positive margin near nerve root
- Post-operative CyberKnife radiosurgery
- Stanford Solid Tumor Actionable Mutation Panel (STAMP):
  - CHECK2 c.715G>A 47% (unknown significance)
  - EPHA2 c.1072G>A 48% (unknown significance)
  - NTRK1 c.1237G>C 41% (unknown significance)

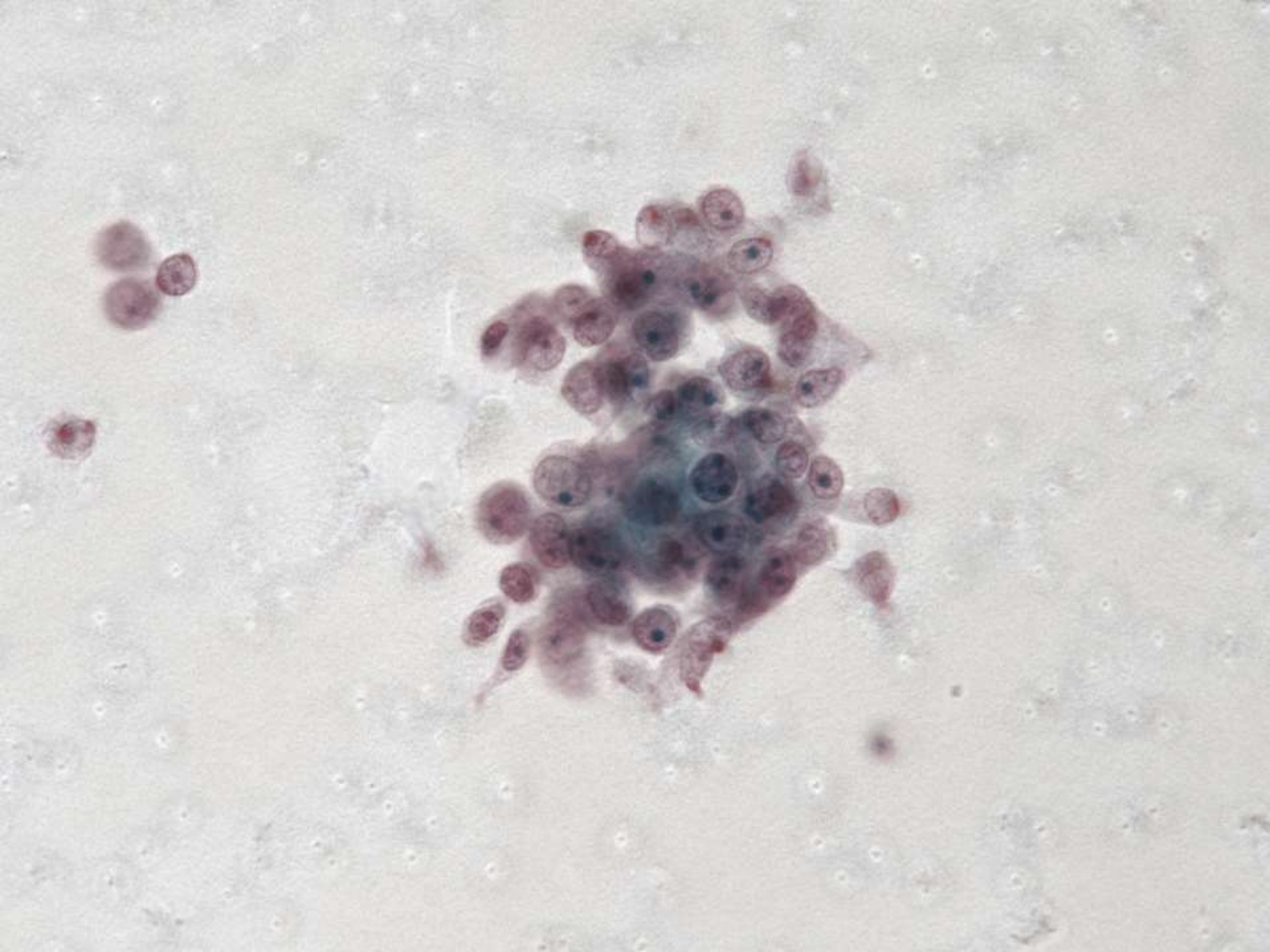


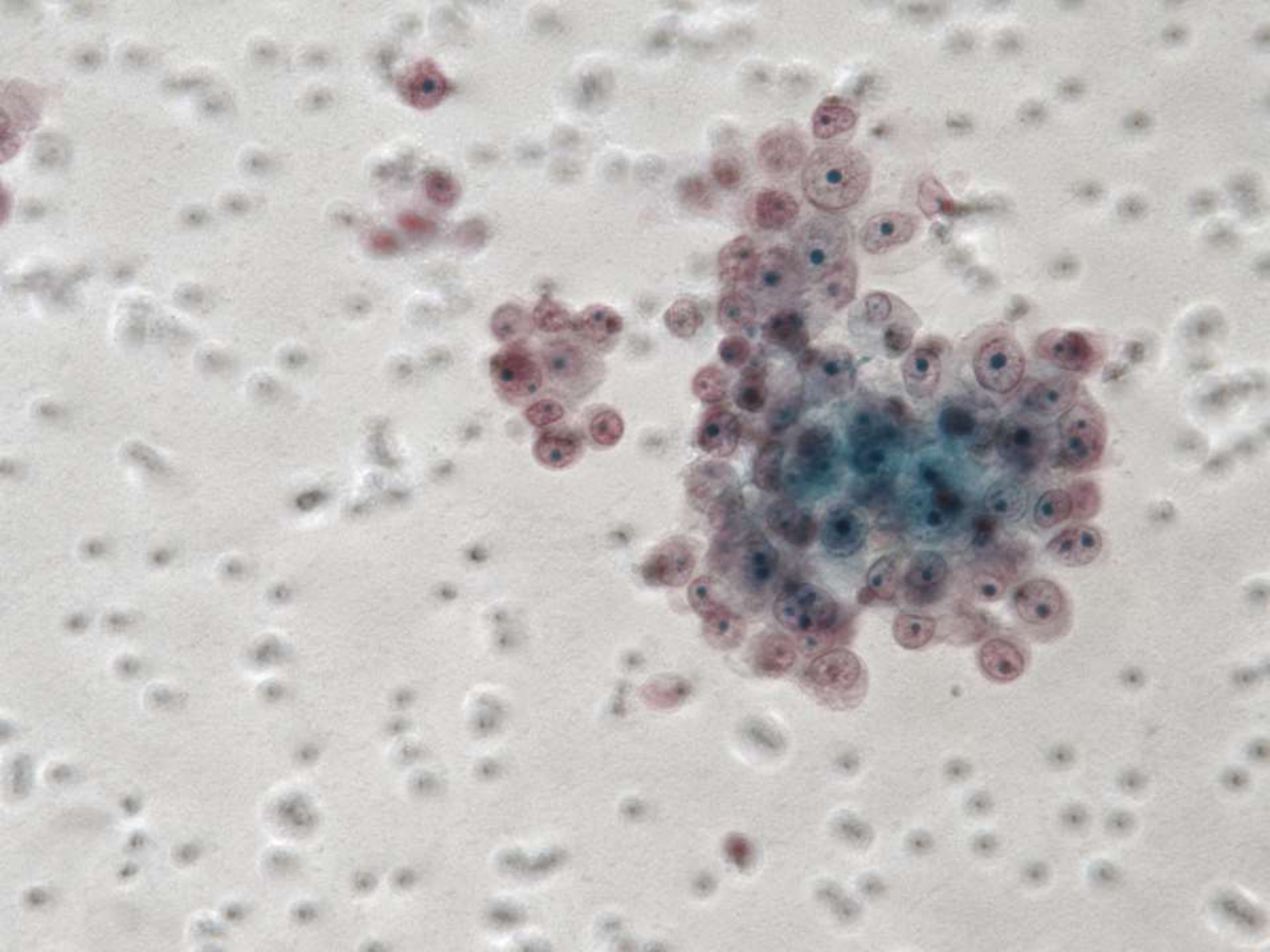
SB 6357

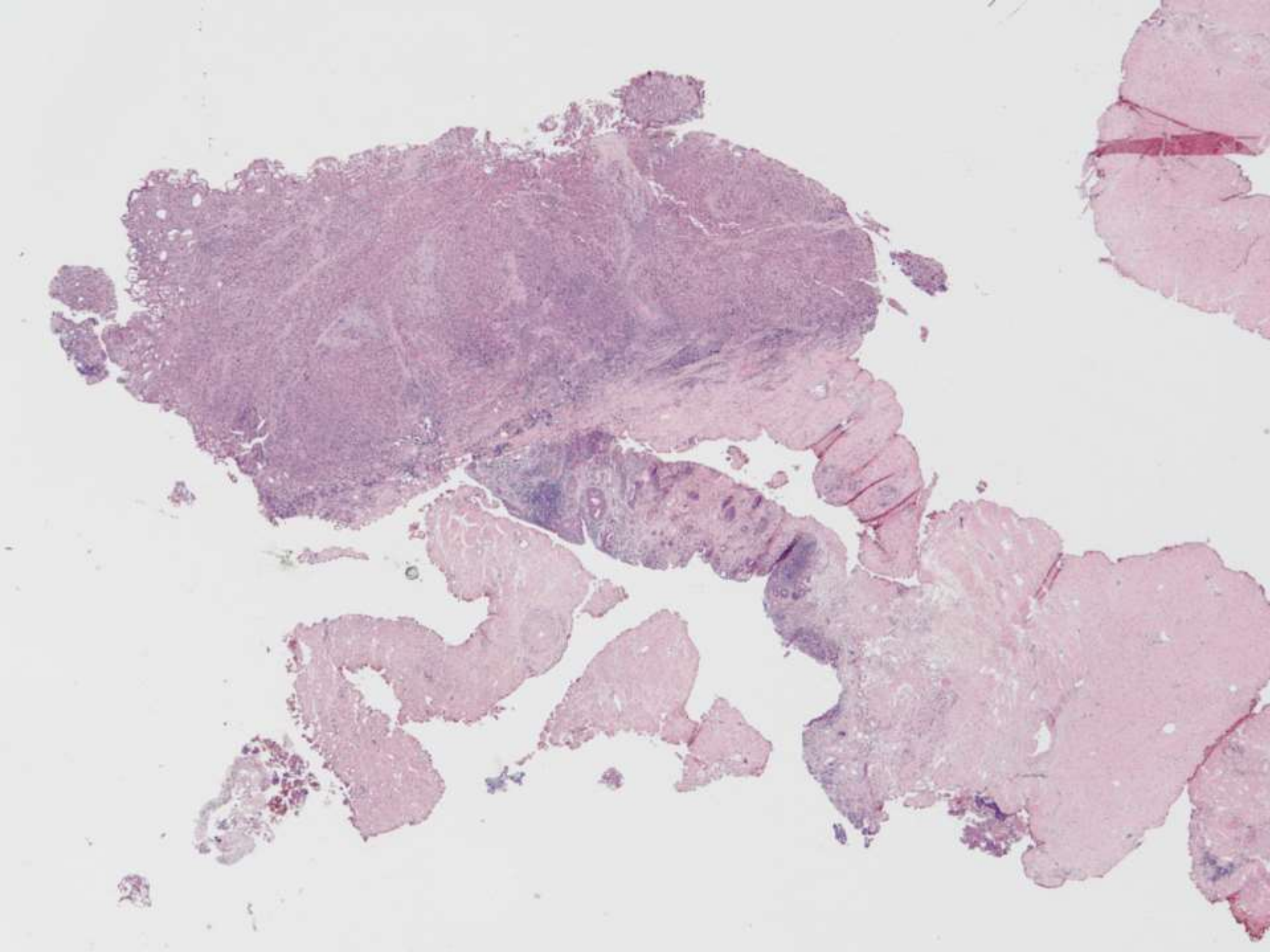
Erna Forgo/Christine Louie; Stanford/Palo Alto VA

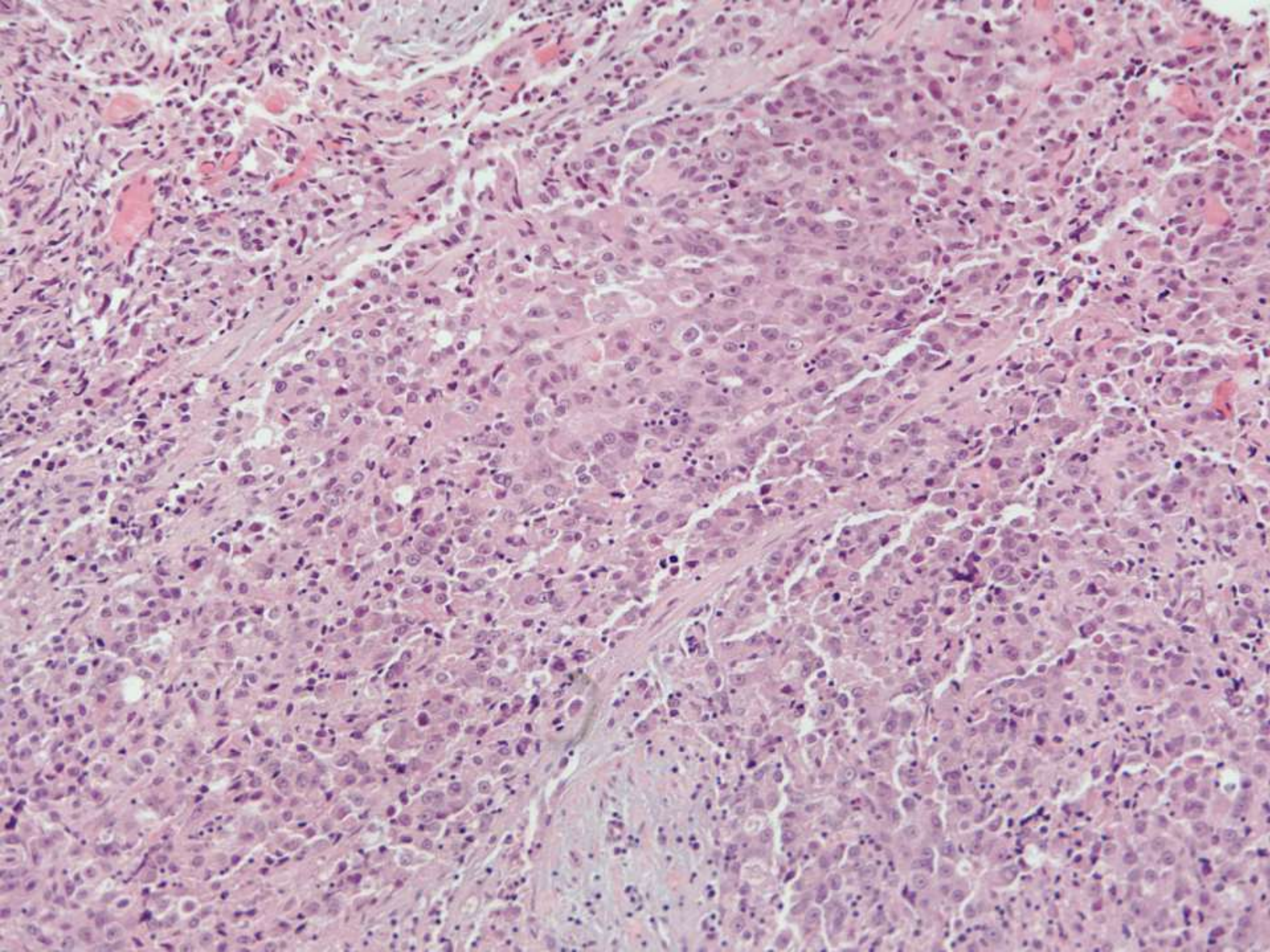
75-year-old male with hematuria and no significant past medical history. Urine cytology specimen and TURBT submitted.

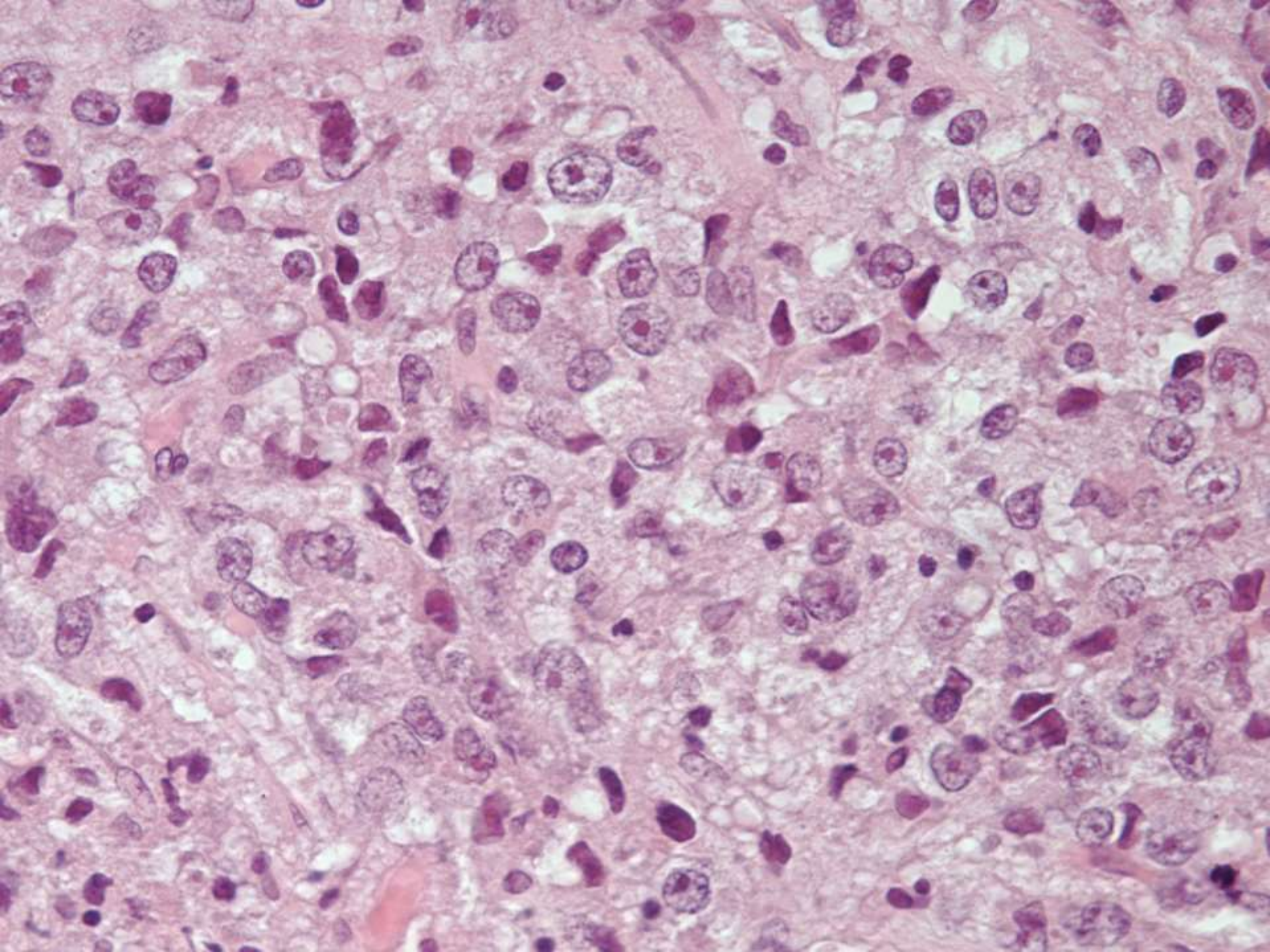










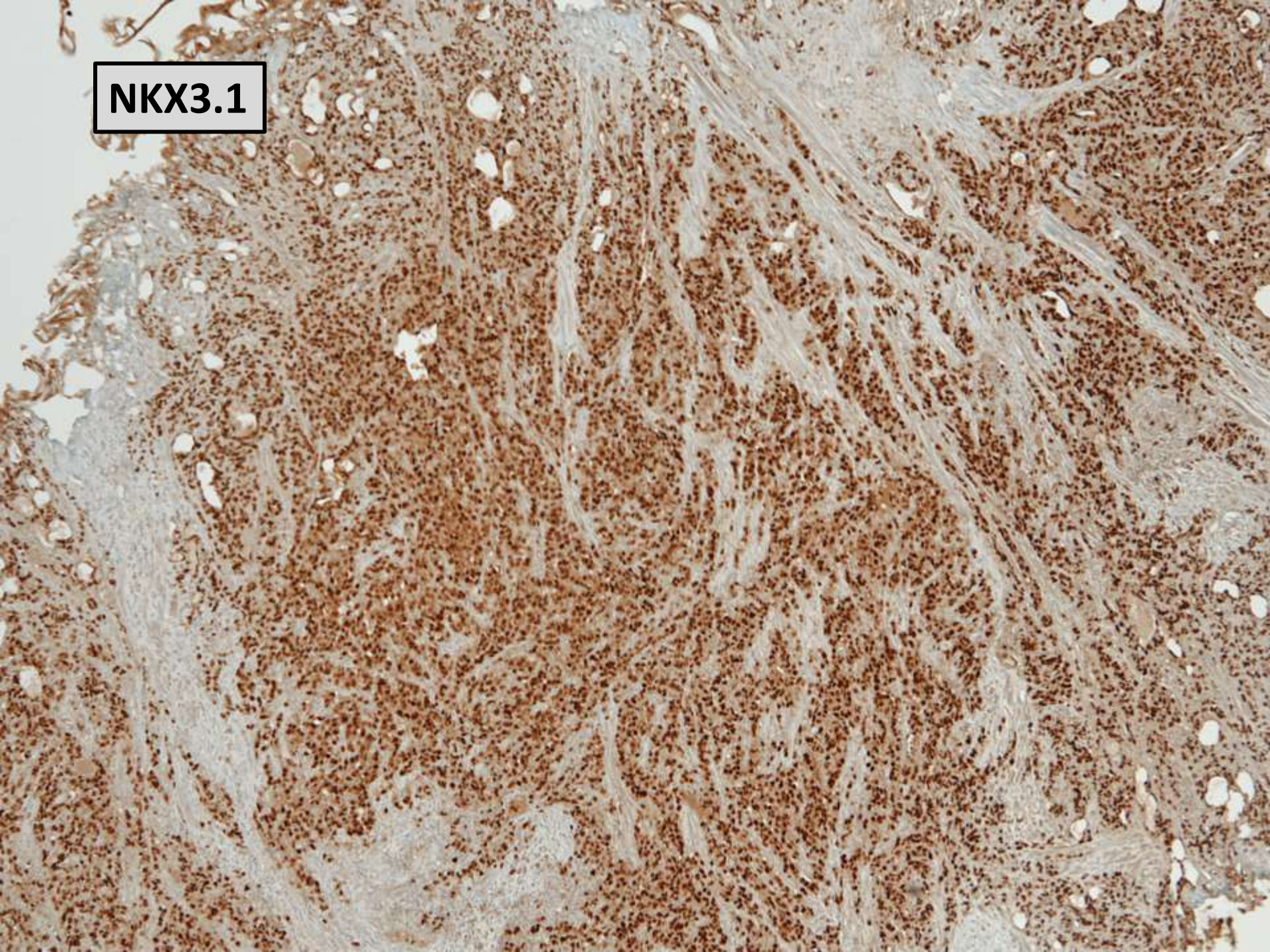


Diagnosis?

Differential Diagnosis

- Urothelial carcinoma
- Urothelial carcinoma
- Urothelial carcinoma

- Prostatic adenocarcinoma
- Metastatic adenocarcinoma


NKX3.1

Diagn Cytopathol. 1988;4(4):300-5.

Cytologic features of prostatic adenocarcinoma in urine: a clinicopathologic and immunocytochemical study.

Varma VA[1], Fekete PS, Franks MJ, Walther MM.

Author information

1 Department of Pathology, Atlanta Veterans Administration Medical Center, Decatur 30033.

- 22 patients with prostatic adenocarcinoma and tumor cells in urine
- Hematuria (59%) and/or obstruction (50%)
- Prostatic palpation/instrumentation preceded collection (68%)
- High grade (Gleason's Grade 7-10), extensive (urethral involvement 23%)

Cytopathology. 1994 Jun;5(3):164-70.

Prostatic carcinoma cells in urine specimens.

Rupp M[1], O'Hara B, McCullough L, Saxena S, Olchiewski J.

Author information

1 Department of Pathology and Cell Biology, Thomas Jefferson University Hospital, Philadelphia, PA 19107-5244.

- 4 patients with prostatic adenocarcinoma with cytologic preparations between 1985-1990
- Urinary tract symptoms
- All high grade (Gleason's Grade 8-10)
- Cytologic features:
  - Large
  - Often multiple nucleoli

Immunocytochemical study of urine cytological preparations from secondary prostatic adenocarcinoma involving the urinary bladder.

Mai KT[1], Ahmed I, Robertson SJ, Belanger EC, Veinot JP, Islam S.

Author information

1 Division of Anatomical Pathology, Department of Laboratory Medicine, Hospital and Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, Ontario, Canada. ktmai@ottawahospital.on.ca

Table I. Summary of Findings of the 15 Study Cases

		Original Dx							
Cases	*Ages*	*Neg*	*Atyp*	*UC*	*PCA*	*PSA*	*HMW*	*P63*	*CK20 neg*
1	69				1	+	–	–	–
2	78				1	+	–	–	–
3	81				1	–	–	–	–
4	74				1	–	–	NA	NA
5	77				1	+	–	–	NA
6	70			1		+	NA	NA	NA
7	67			1		–	NA	NA	NA
8	70		1			+	NA	NA	NA
9	85		1			–	–	NA	NA
10	84		1			–	–	–	NA
11	75		1			+w	–	NA	NA
12	82		1			+w	NA	NA	NA
13	66	1				+	NA	NA	NA
14	70	1				+	NA	NA	NA
15	72	1				–	–	NA	NA
Total: 15		3/15	5/15	2/15	5/15	9 pos/15	10 neg/10	5 neg/5	

PSA, prostatic-specific antigen; Dx, diagnosis; Neg, negative; Atp, Atypia; PCA, prostatic adenocarcinoma; UC, urothelial carcinoma; HMWCK, high-molecular-weight cytokeratin, CK20, cytokeratin 20; NA, not available; +w, weakly positive.

Diagn Cytopathol. 2011 Feb;39(

Morphologic featu

Tyler KL[1], Selvaggi SM

Author informat

1 Departmen
Madison, W

Table I. Patient De

Case no(s)	*Age (y*
1	80
2	58
3	93
4	72

BW, bladder washing

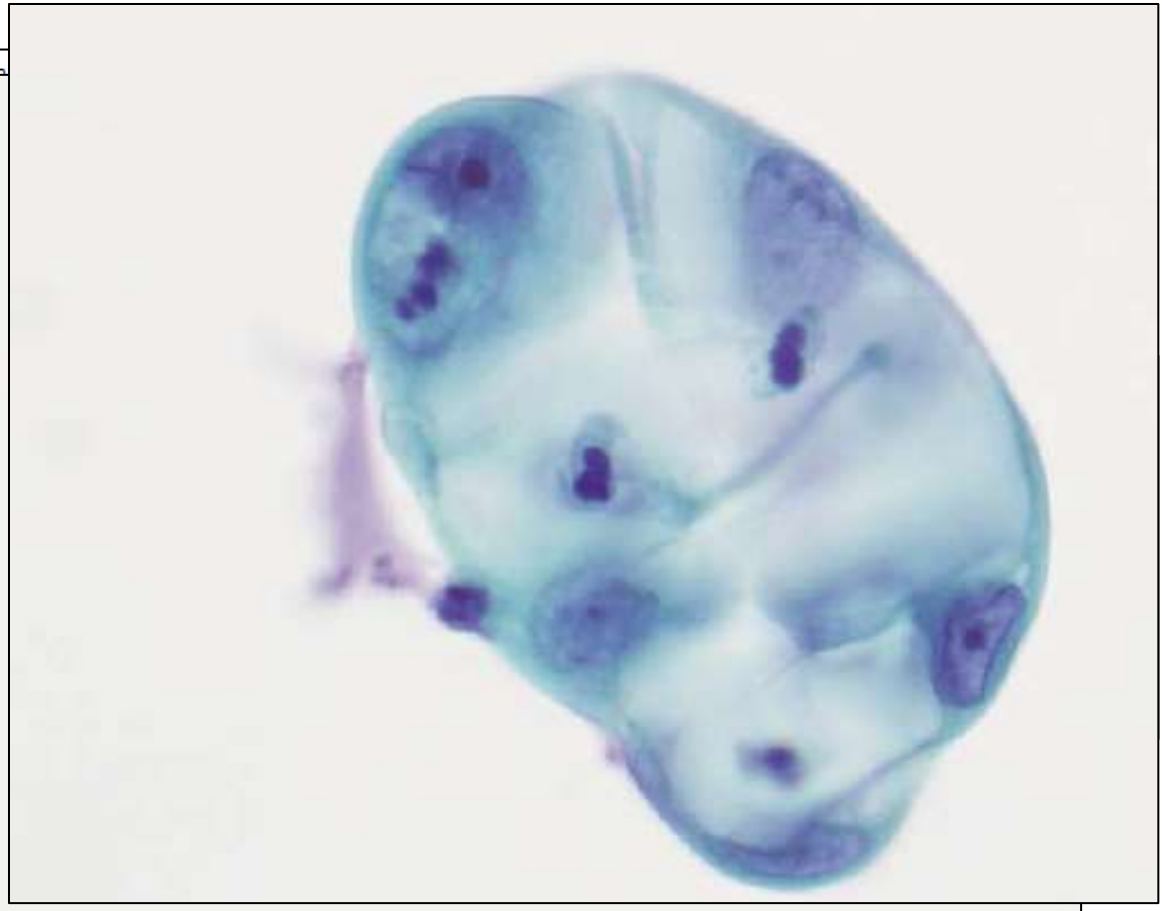


Table II. Cytologic Features of Prostatic Adenocarcinoma in Urine

Case no(s)	*Clustered*	*Nuclear shape*	*N:C*	*Nucleoli*	*Chromatin*	*Cytoplasm*	*Vacuoles*
1	Yes	Round	Increased	Present	Fine	Pale blue	None
2	Yes	Irregular	Decreased	Present	Course	Pale blue	Large
3	Yes	Oval	Increased	Present	Fine	Pale blue	None
4	Yes	Round	Increased	Present	Fine	Pale blue	None

Acta Cytol. 2013;57(2):184-8. doi: 10.1159/000345693. Epub 2013 Feb 28.

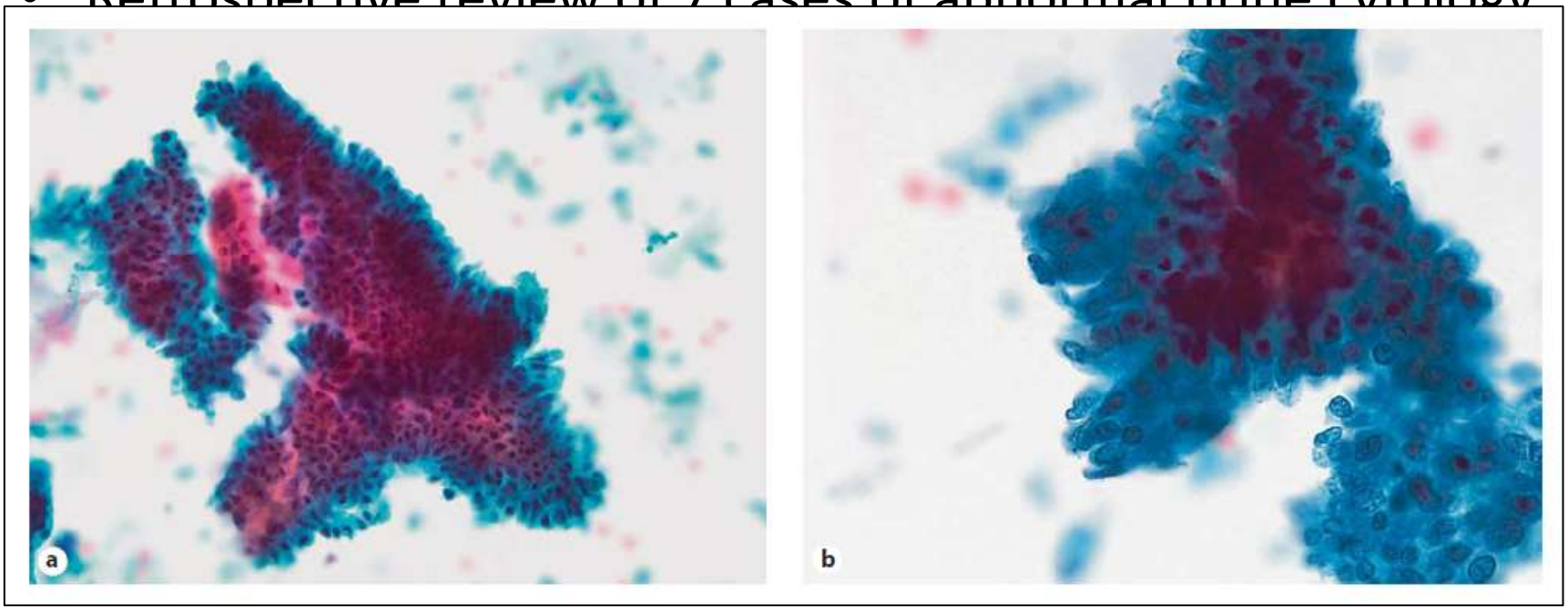
Urinary cytology of prostatic duct adenocarcinoma - a clinicopathologic analysis.

Sathiyamoorthy S[1], Ali SZ.

Author information

1 Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD, USA.

- Retrospective review of 7 cases of abnormal urine cytology



- Hematuria (n=5), bladder obstruction (n=1), perineal mass (n=1), elevated PSA (n=6)

Take home points

- Prostatic adenocarcinoma is common
- Involvement of the urinary bladder by prostatic adenocarcinoma occasionally occurs
- Malignant cells are rarely identified in urine
  - Clusters of large atypical cells with prominent nucleoli

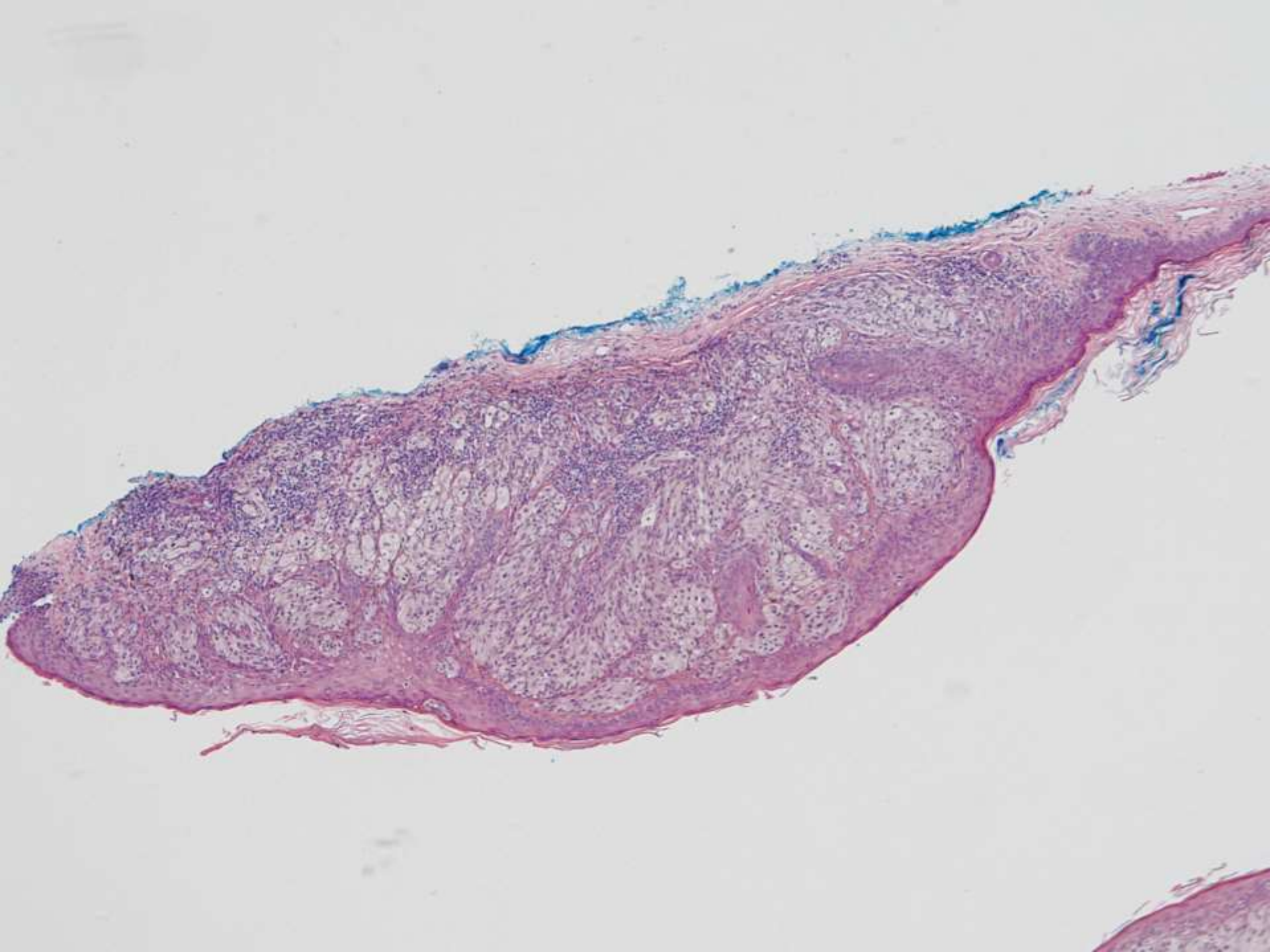
SB 6358

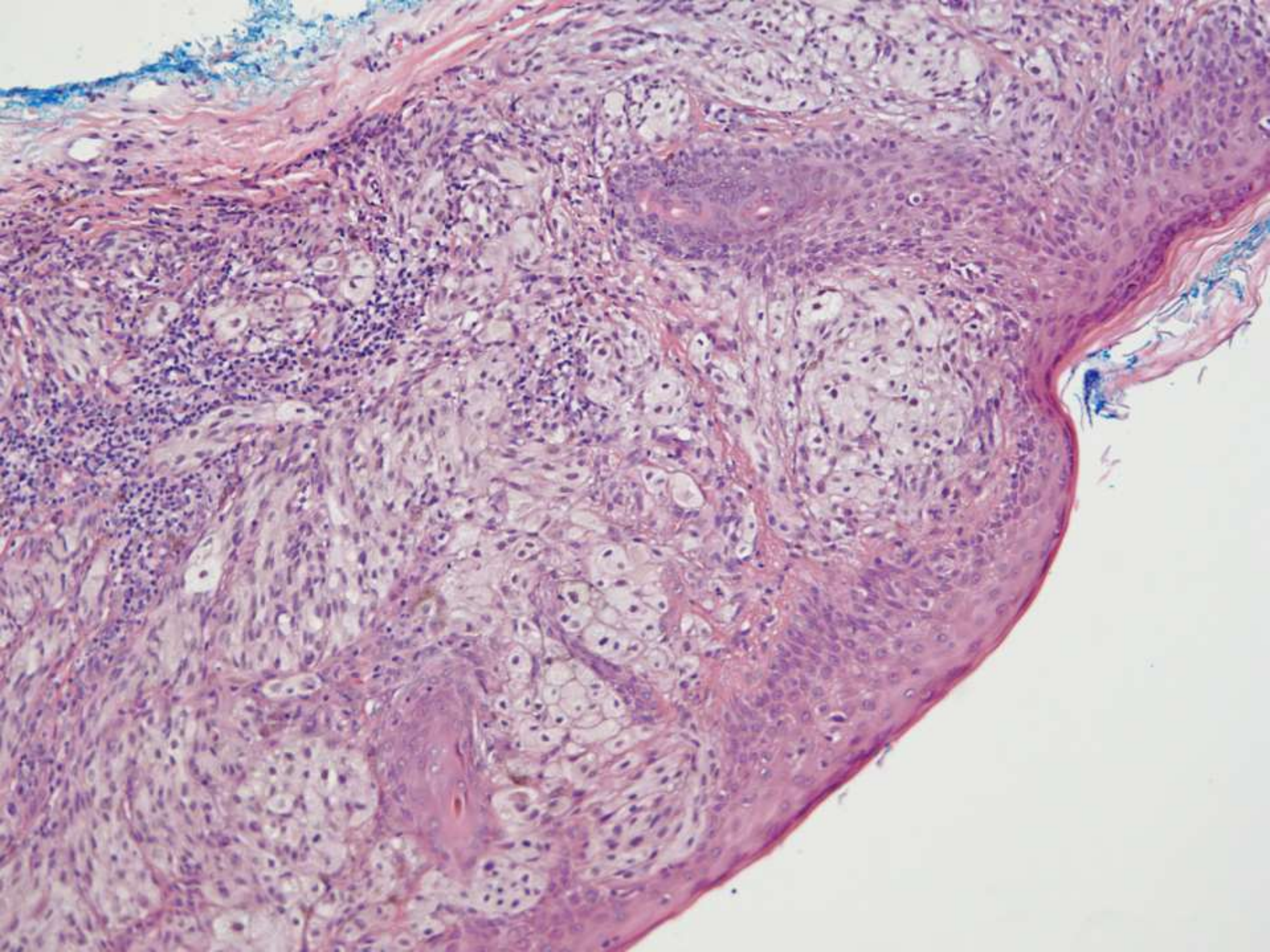
Rebekah Wieland/Ryanne Brown/Christine Louie; Stanford/Palo Alto VA

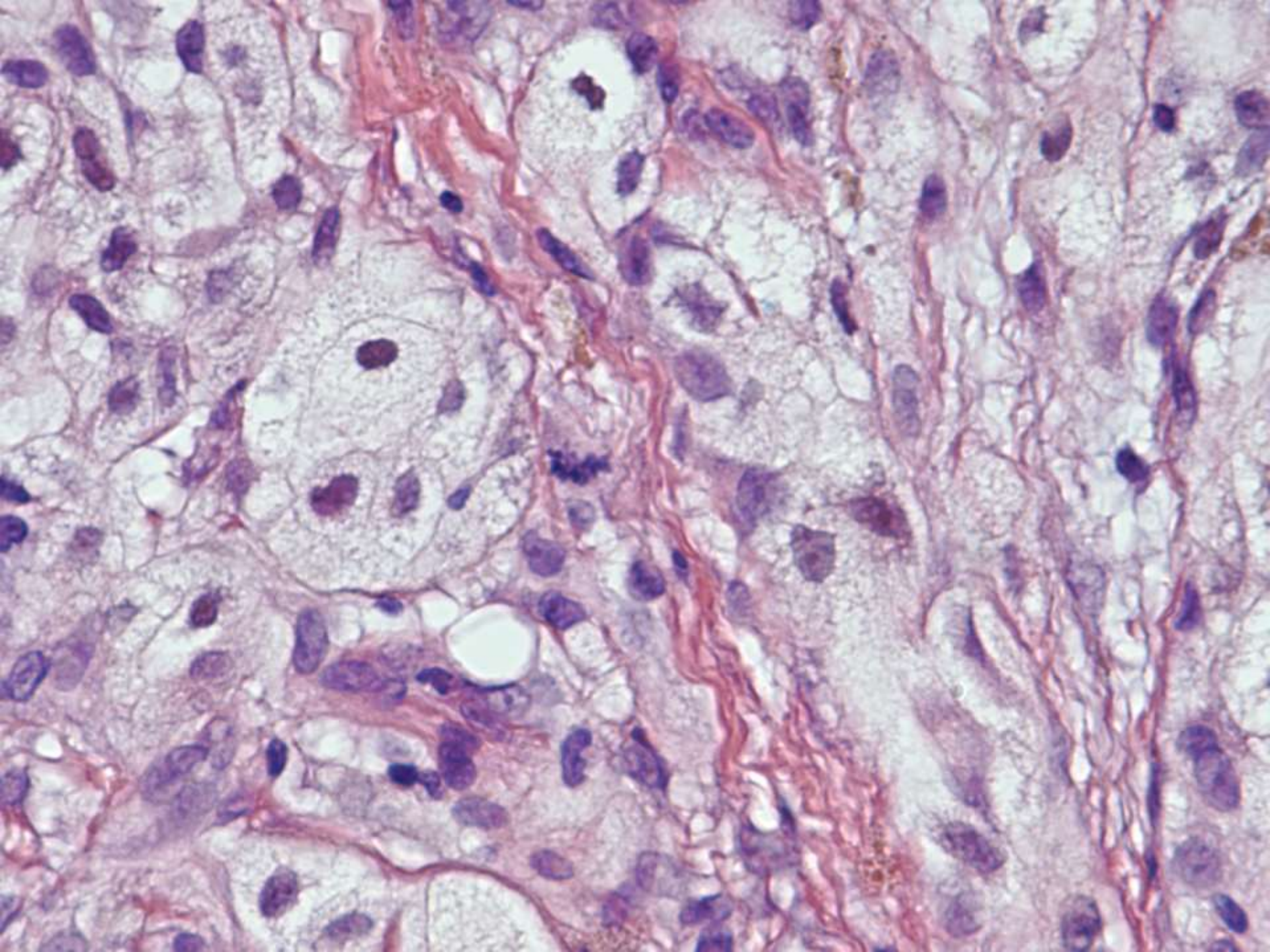
90-year-old male presenting with 3mm brown papule with slightly waxy appearance on left arm for past several months without change.

Case Presentation

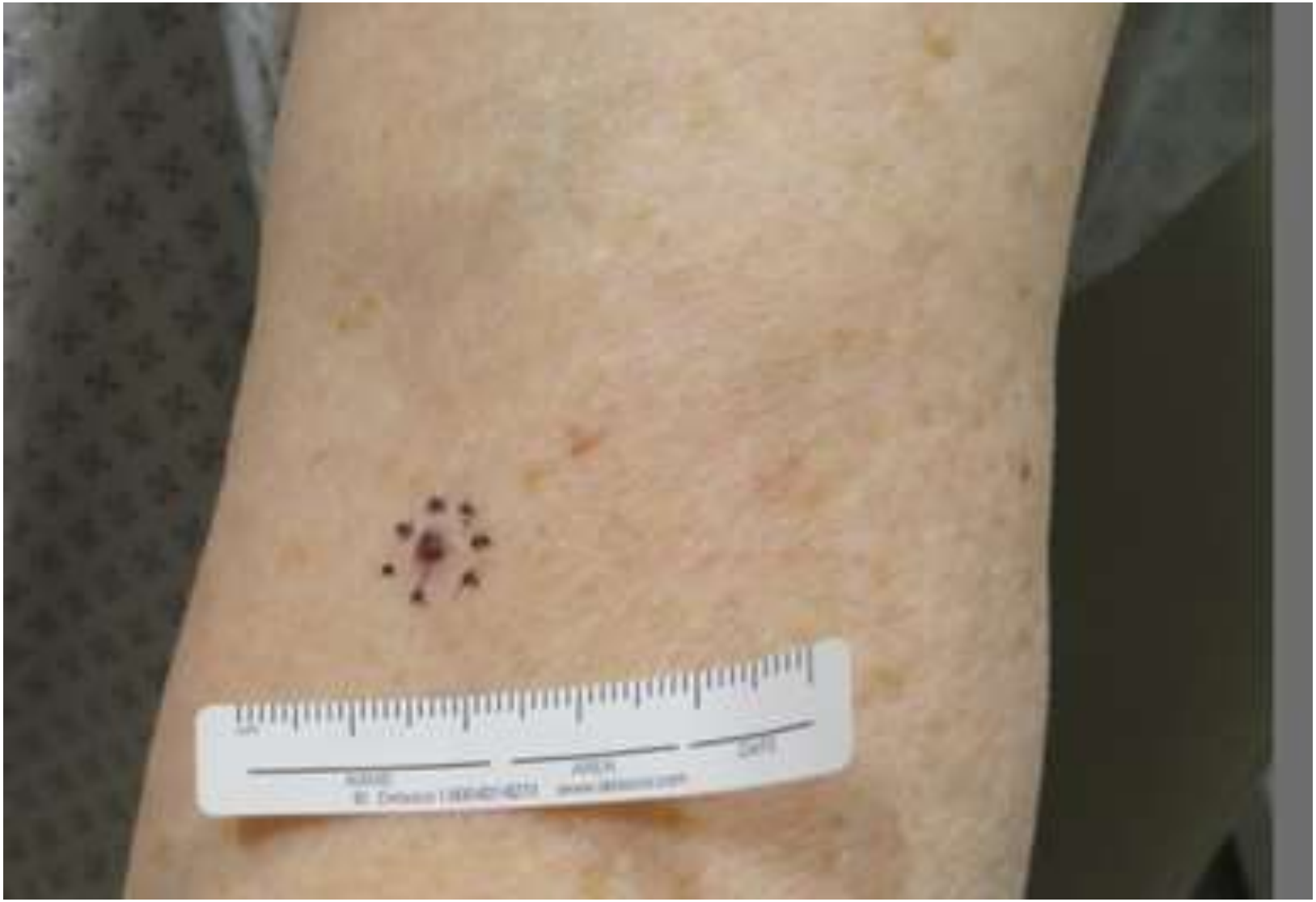
- 90 y.o. male presenting with a 3 mm brown papule with a slightly waxy appearance on the left arm for past several years without change.

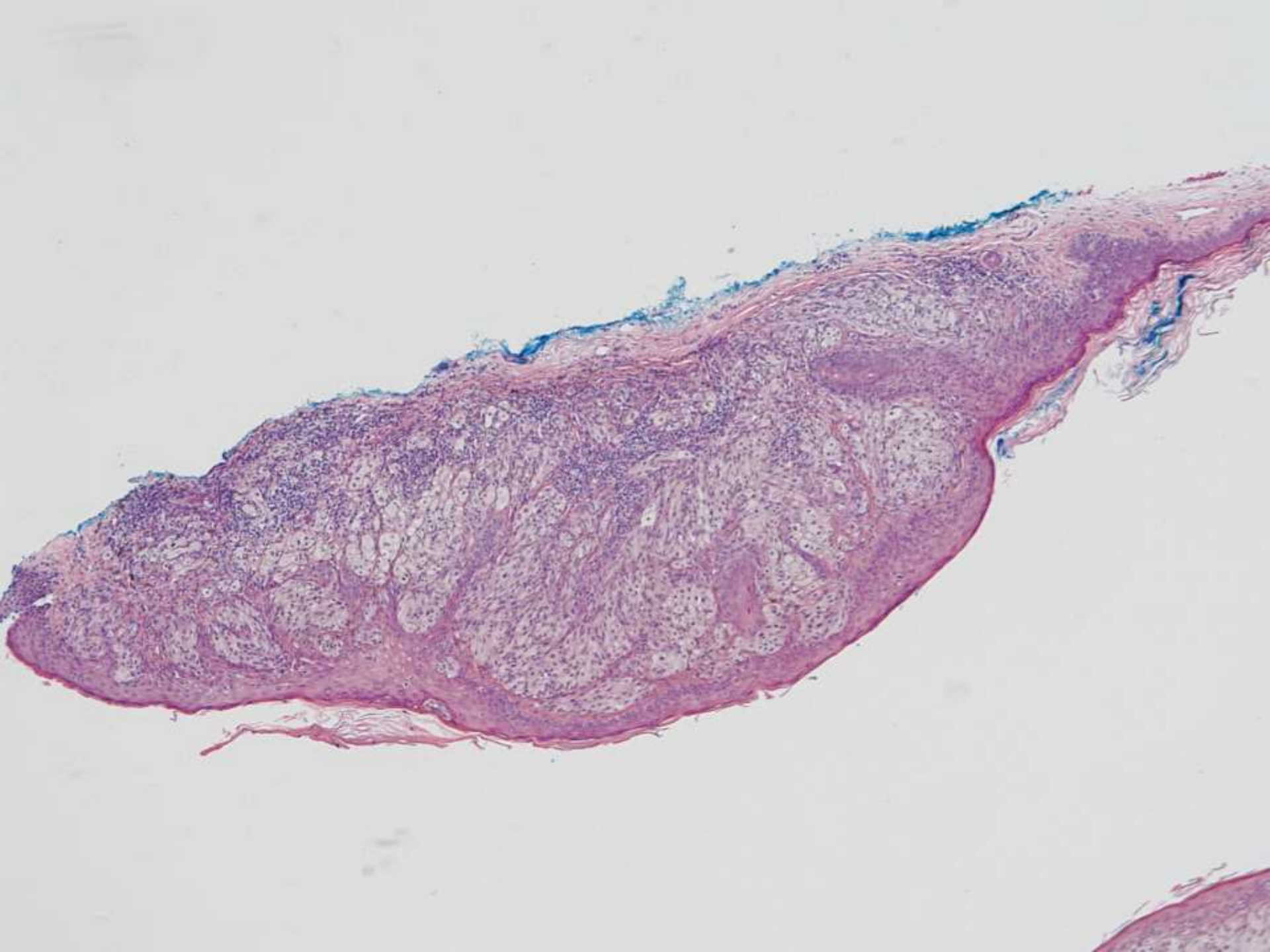


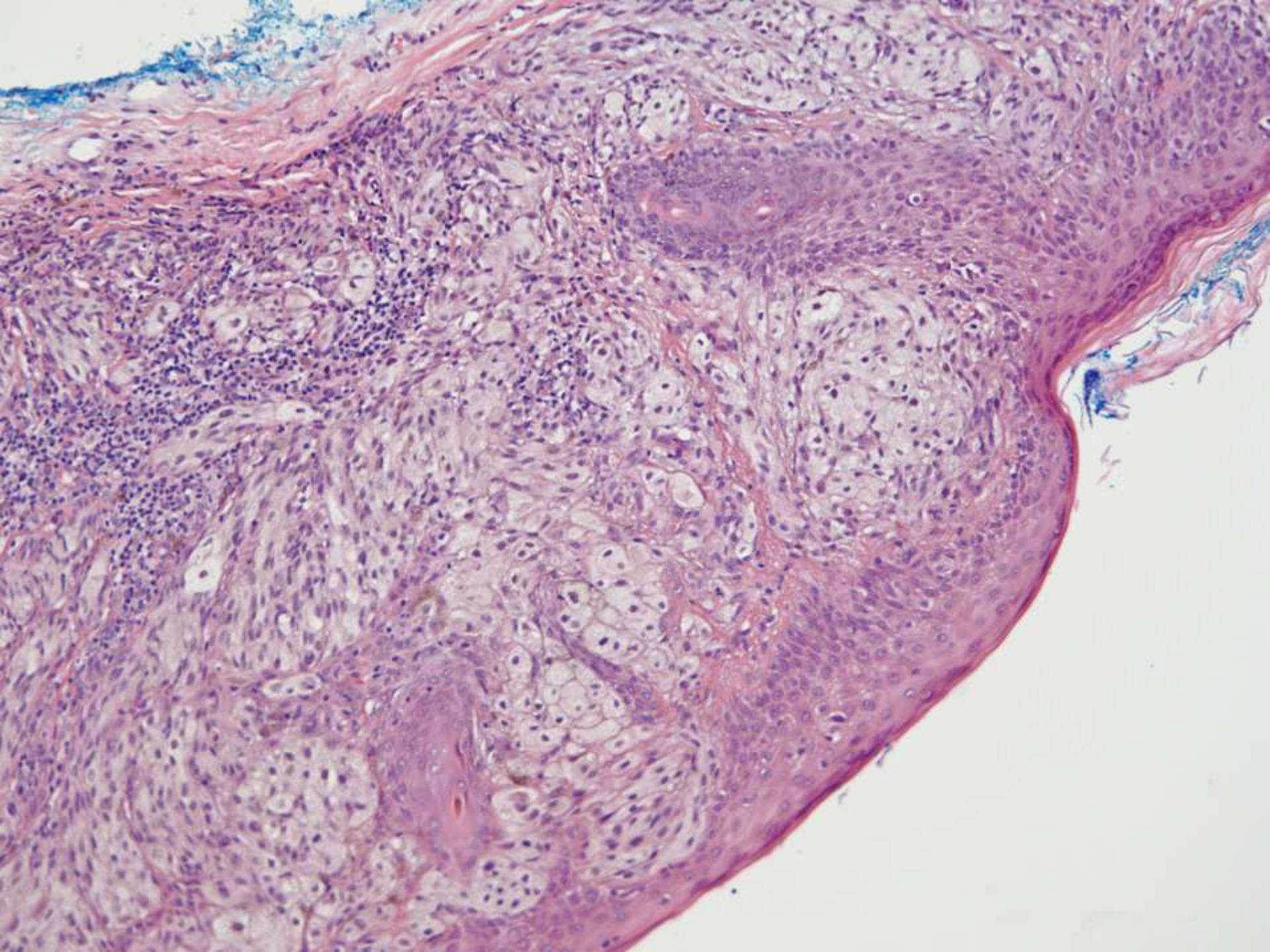


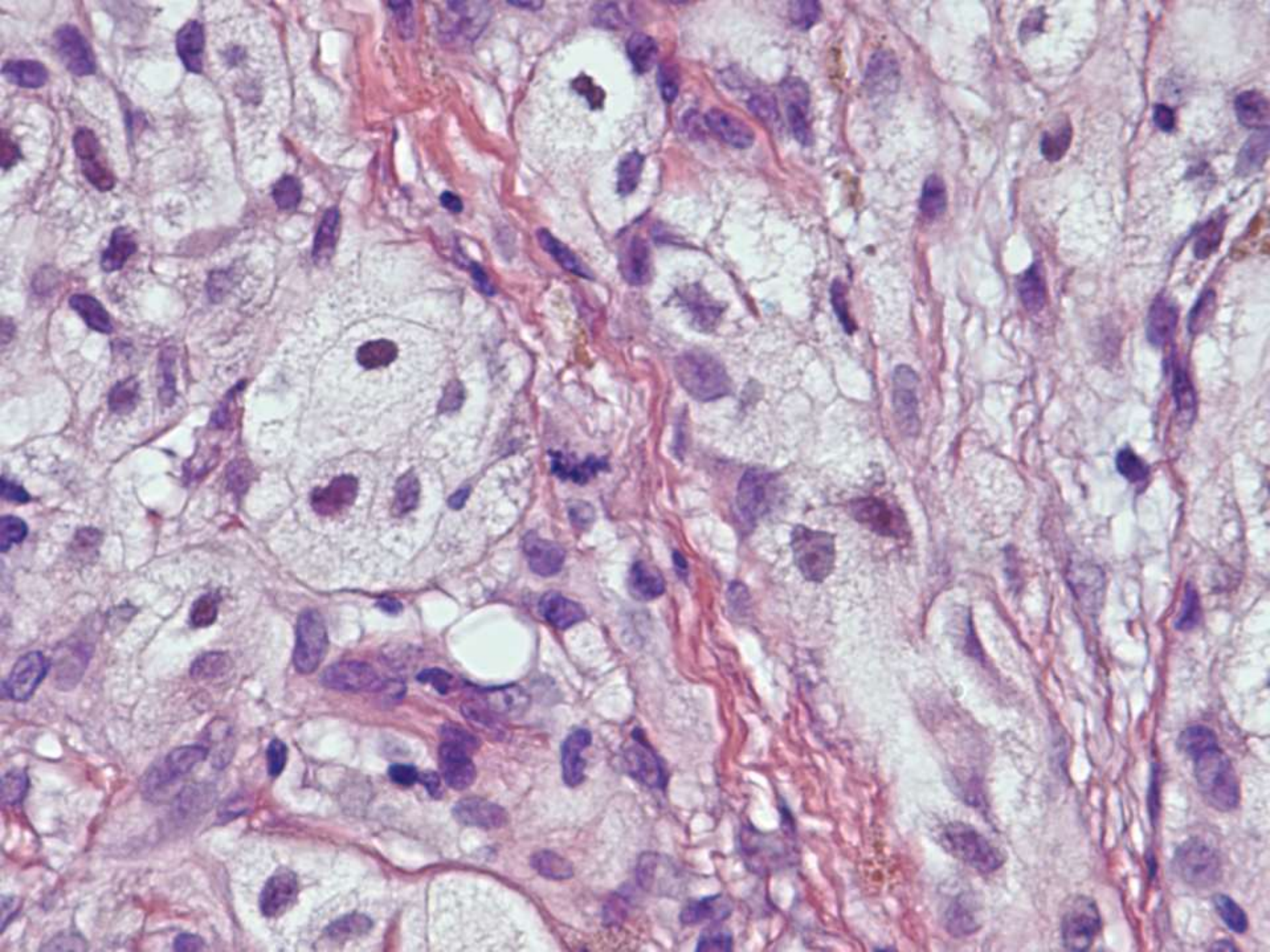


Diagnosis?





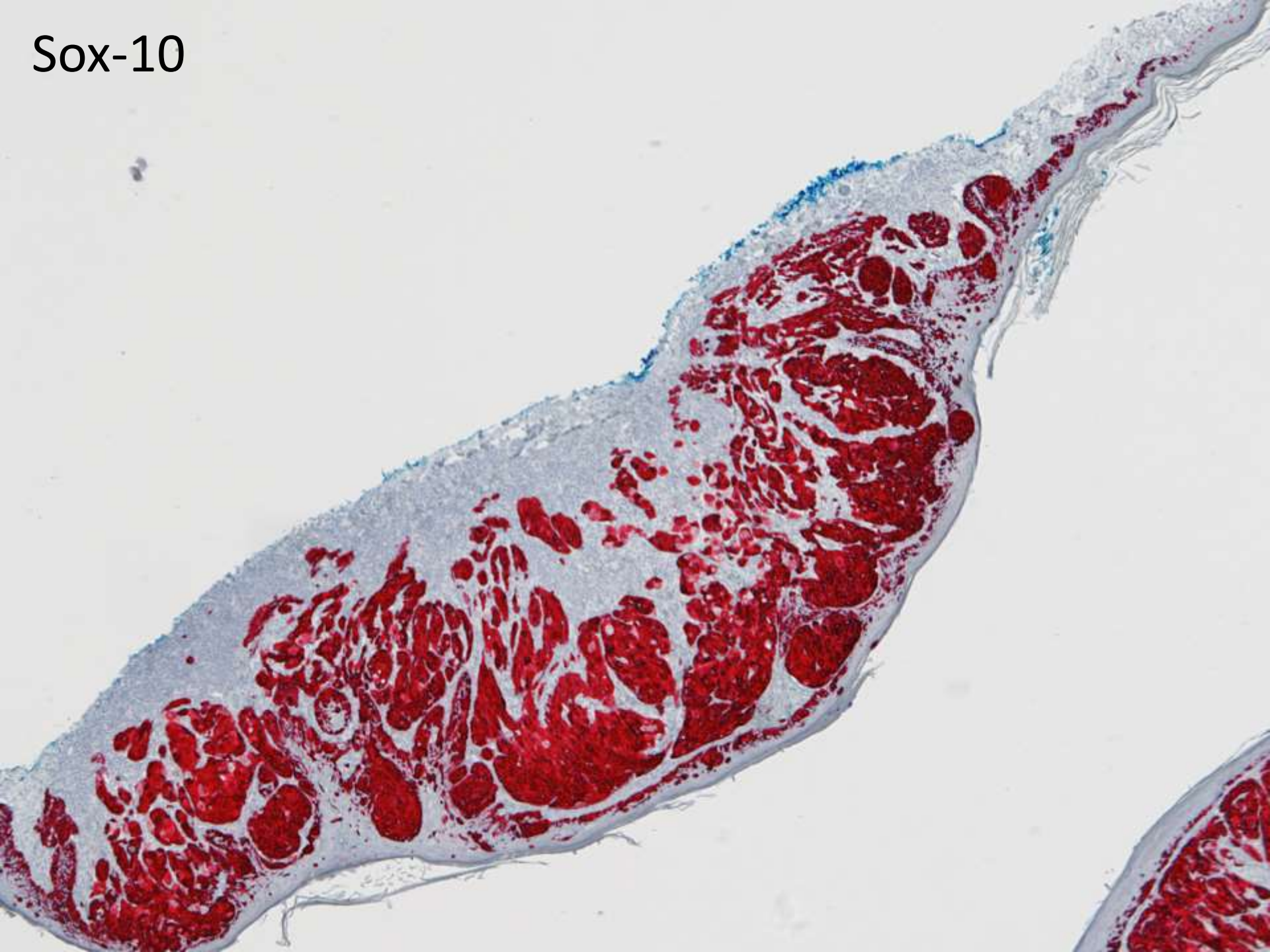




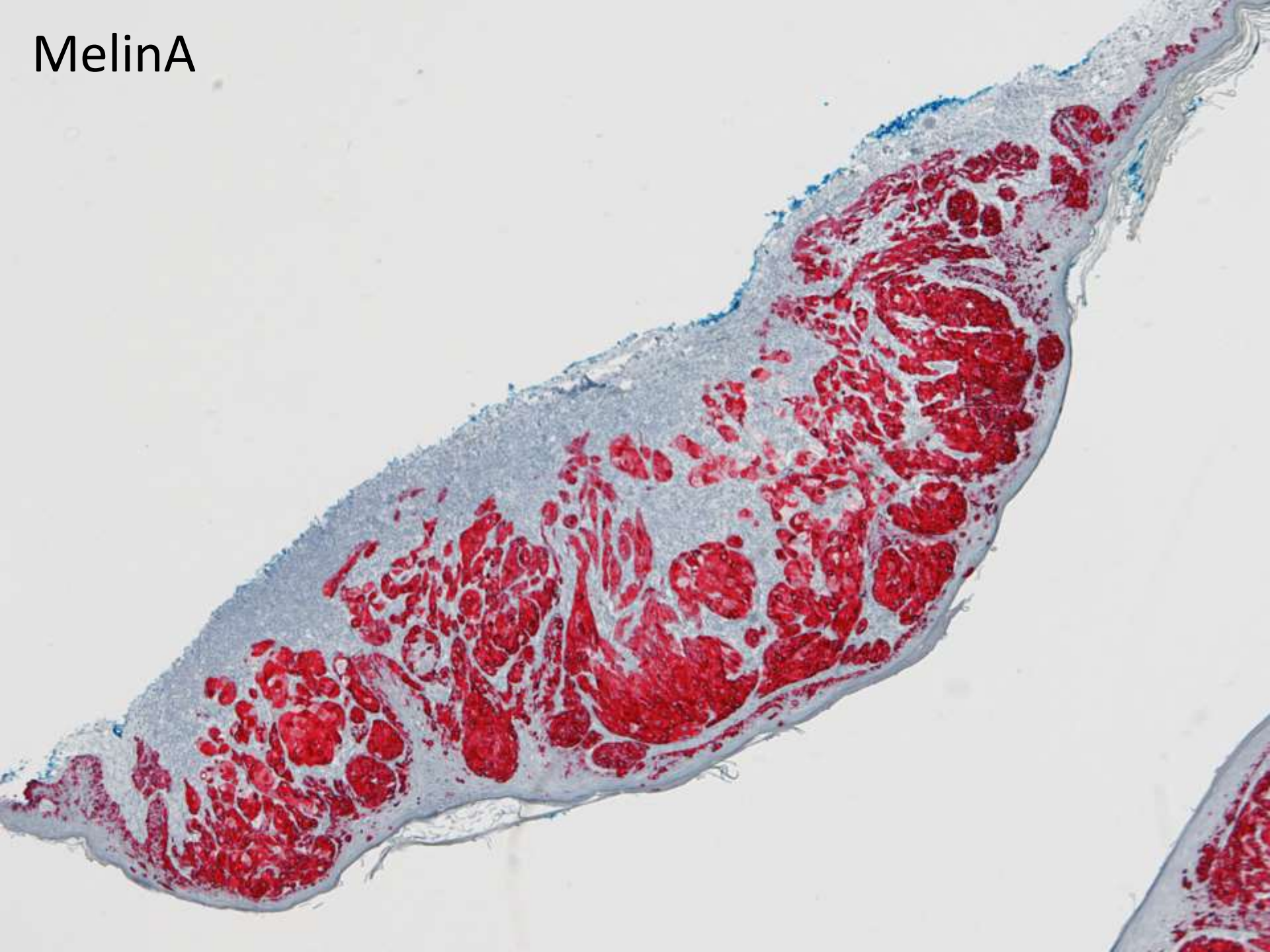
Differential Diagnosis

- Balloon cell nevus
- Sebaceous neoplasm
- Xanthoma
- Hibernoma
- Melanoma, pseudolipoblastic type
- Melanoma, balloon cell type
- Metastatic clear cell renal cell carcinoma

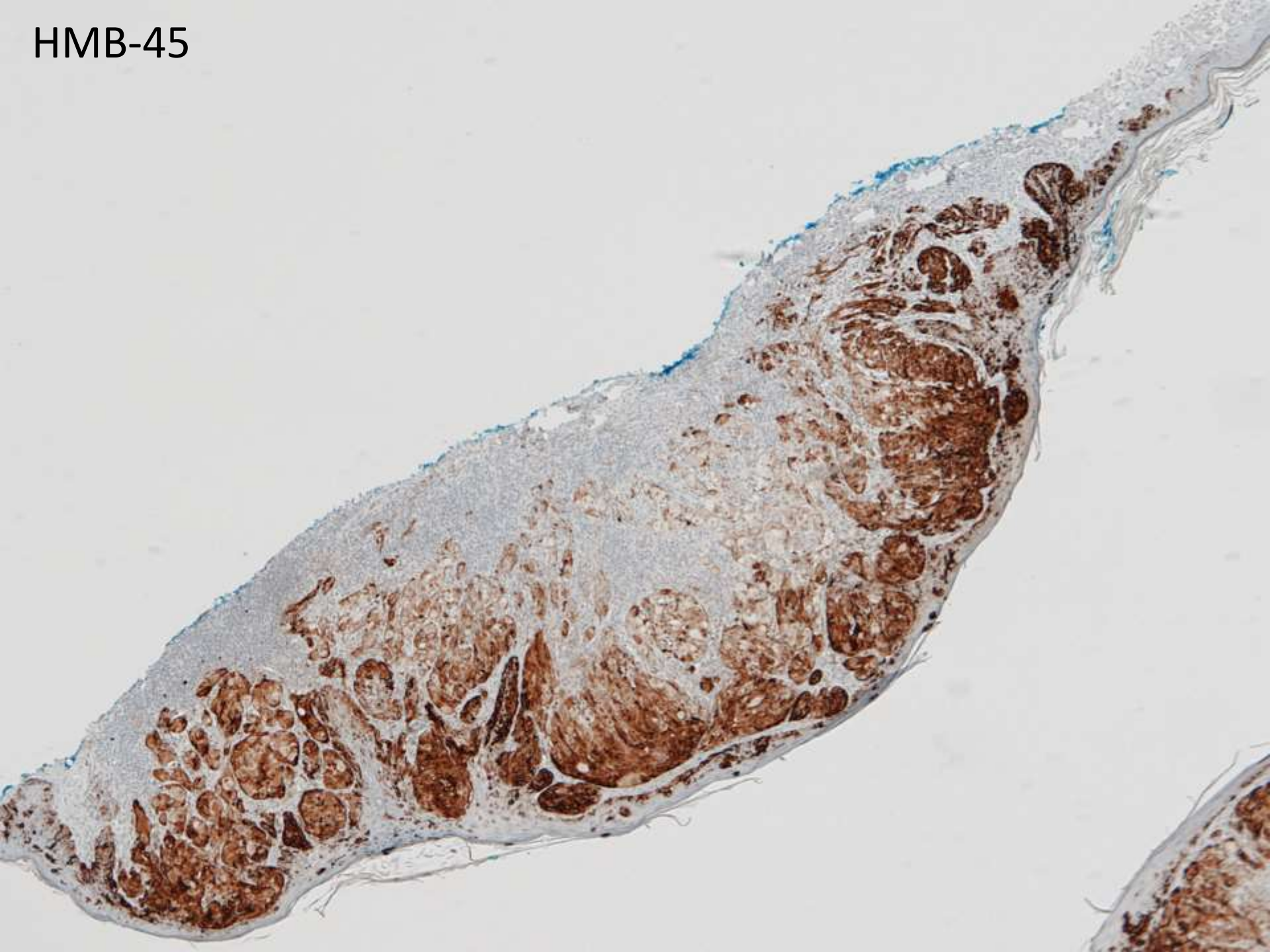
Sox-10



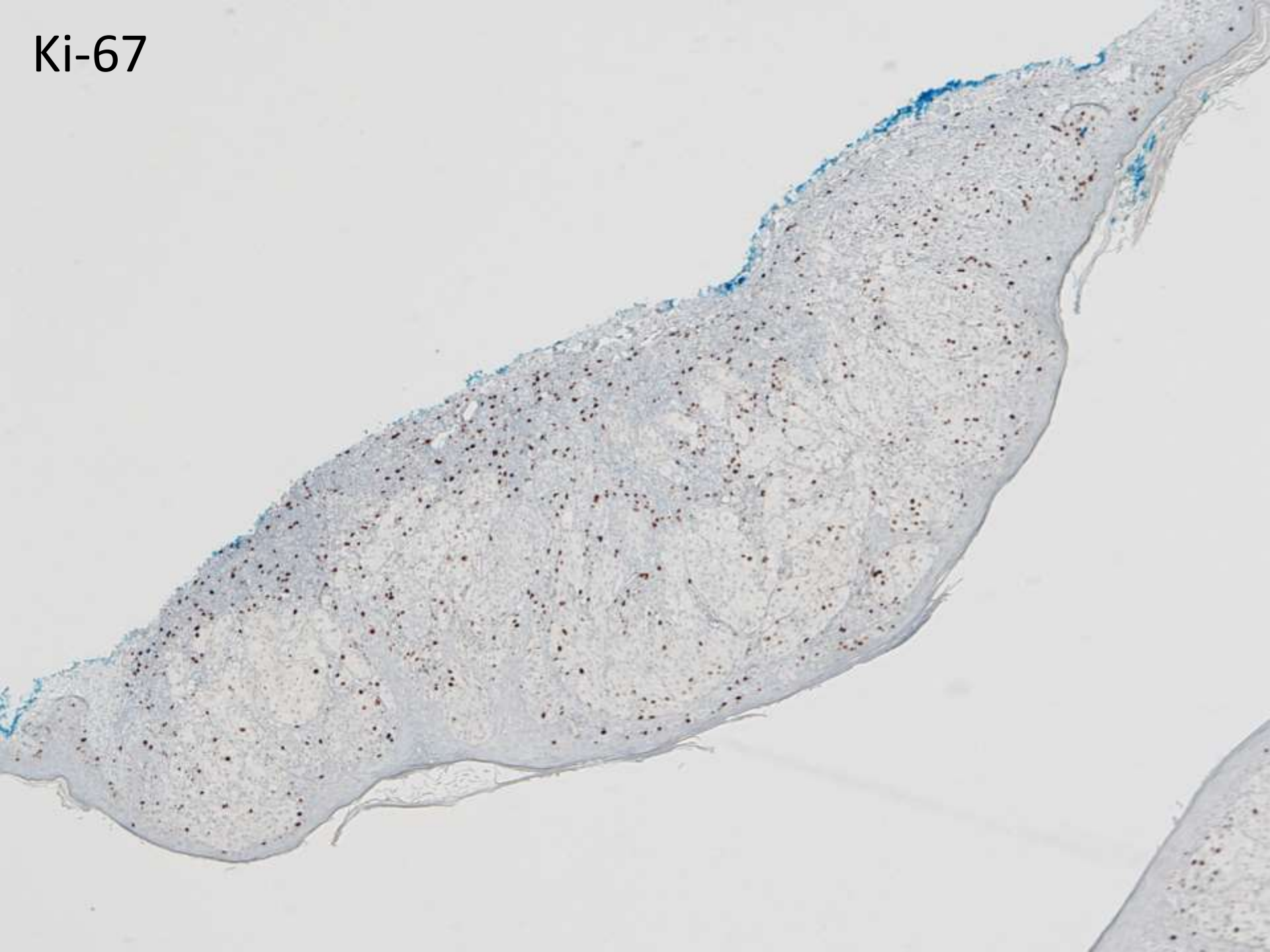
MelinA



HMB-45



Ki-67



Final Diagnosis:

Invasive melanoma, Balloon cell type

Invasive melanoma, Balloon cell type

- Rarest histological type of primary cutaneous melanoma
- Clinical appearance varies
  - Nodular, ulcerated, polypoid, pigmented and non-pigmented
- Clinical differential diagnoses of basal cell carcinoma, dysplastic nevus, malignant melanoma, seborrheic keratosis, and cutaneous adnexal tumors

Invasive melanoma, Balloon cell type

- Balloon cell change can occur in conventional melanomas
  - Commonly in metastasis or recurring lesion
- Defined as greater than 50% foamy balloon cells
- Presence of nuclear pleomorphism, mitosis, cytologic atypia, and lack of maturation with descent help distinguish from balloon cell nevus

Invasive melanoma, Balloon cell type

- Express usual melanocytic markers of a malignant melanoma
- Prognosis correlates with tumor thickness
- Etiology of clear cell change is unclear; held to represent degenerating melanosomes

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- Kao, G. F., Helwig, E. B., & Graham, J. H. (1992). Balloon cell malignant melanoma of the skin. A clinicopathologic study of 34 cases with histochemical, immunohistochemical, and ultrastructural observations. *Cancer, 69*(12), 2942-2952.
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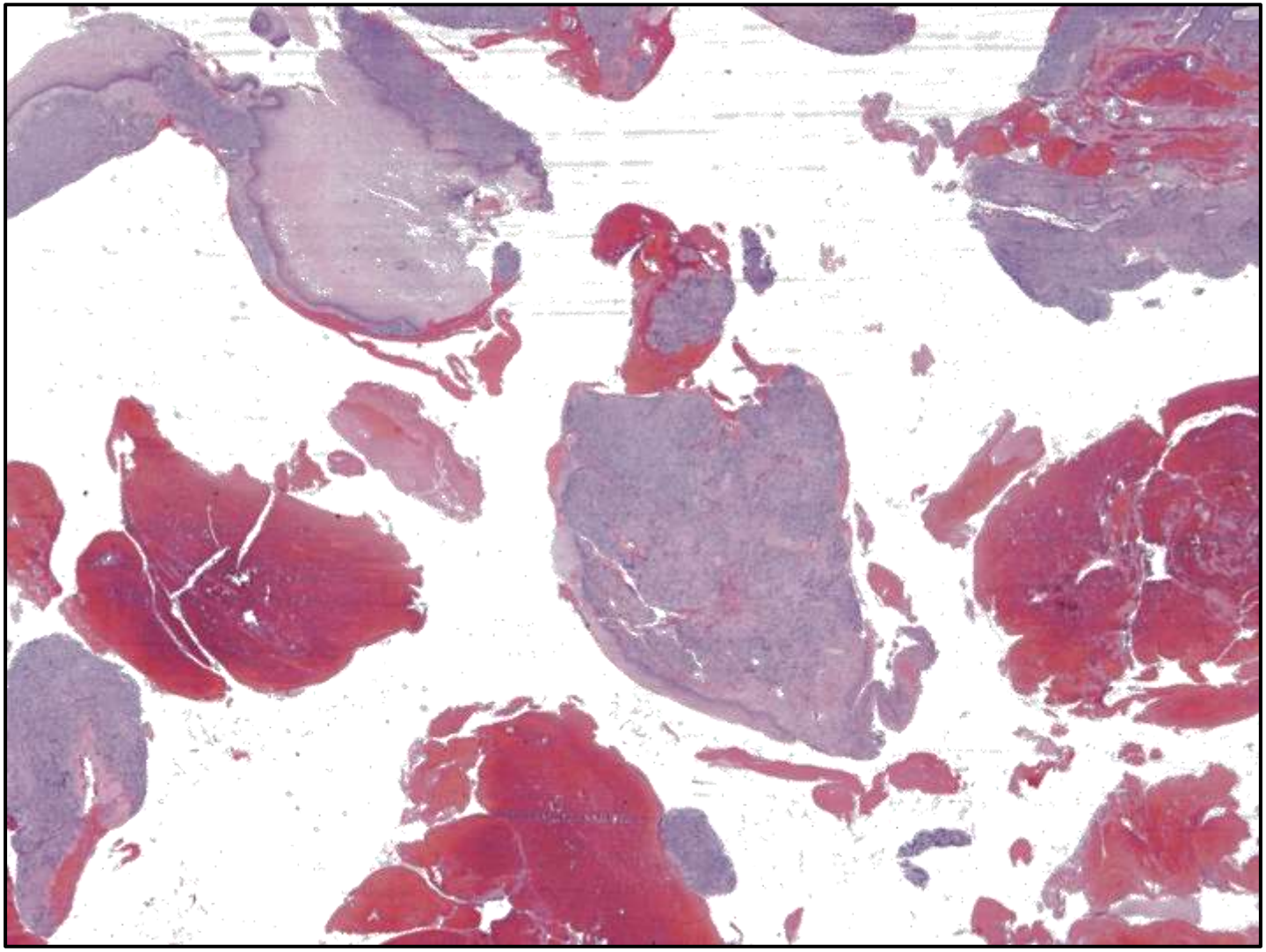
SB 6359

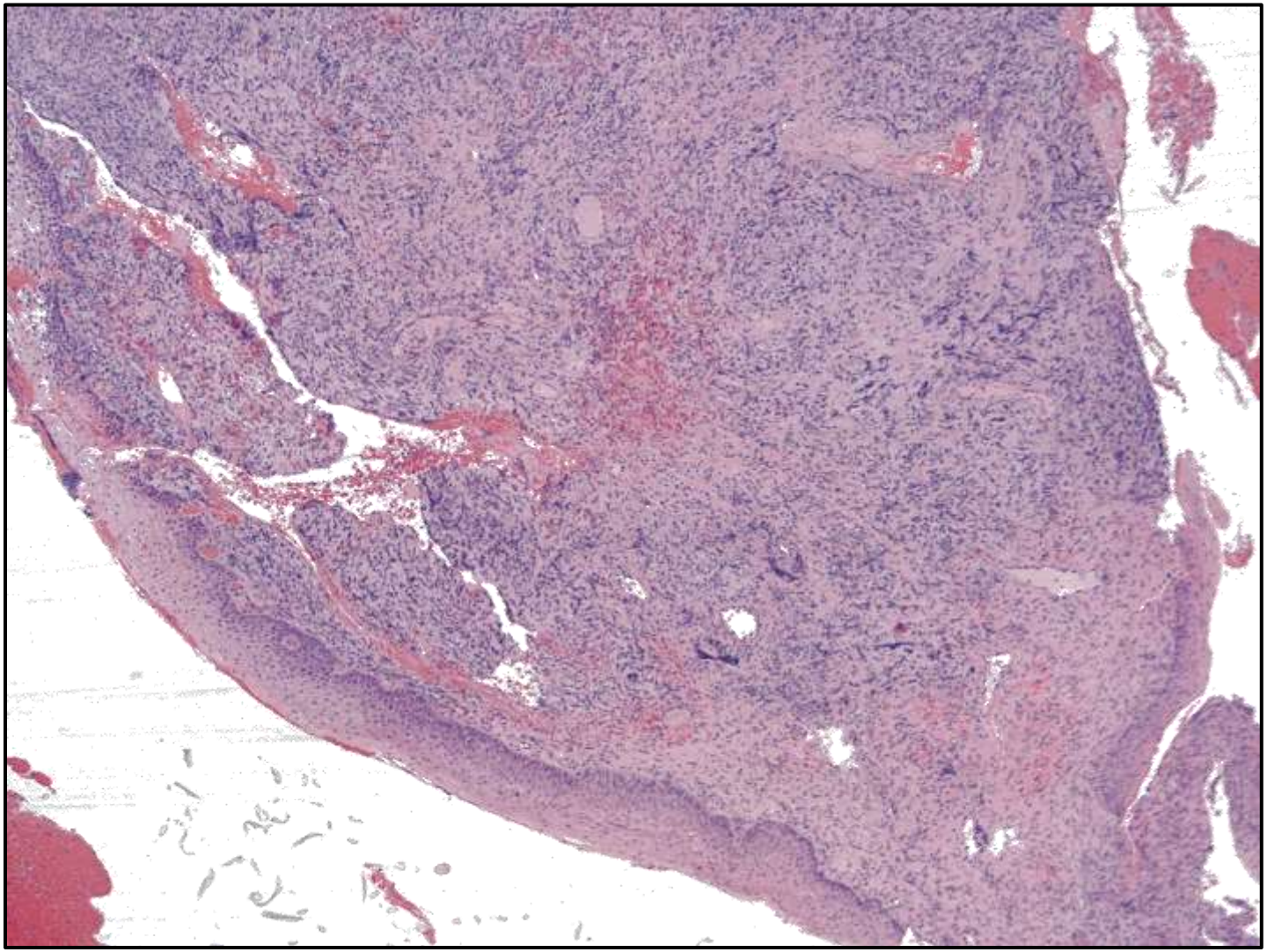
Francisco Beca/Brooke Howitt; Stanford

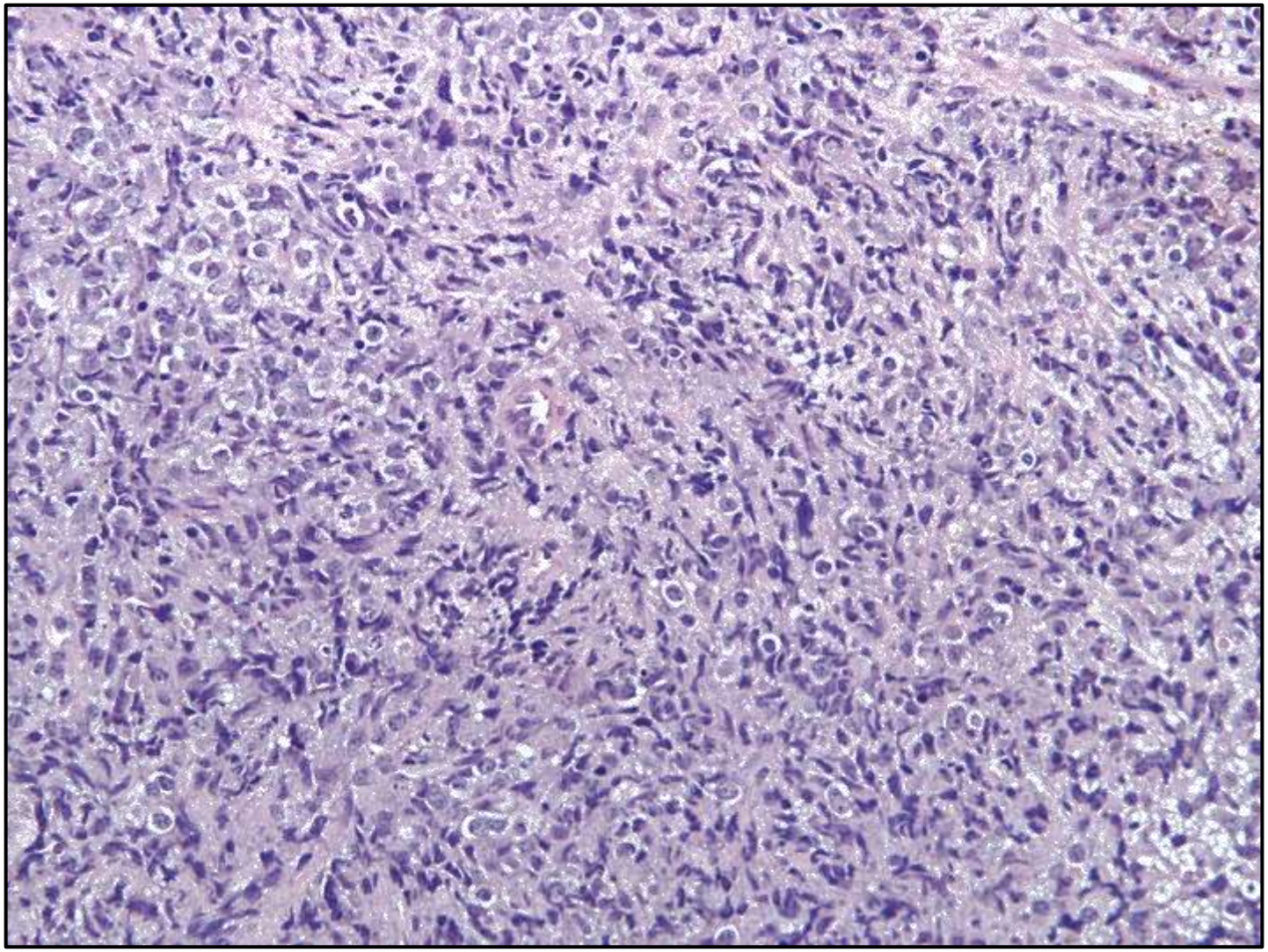
28-year-old female, G0P0, with vaginal bleeding and pain.

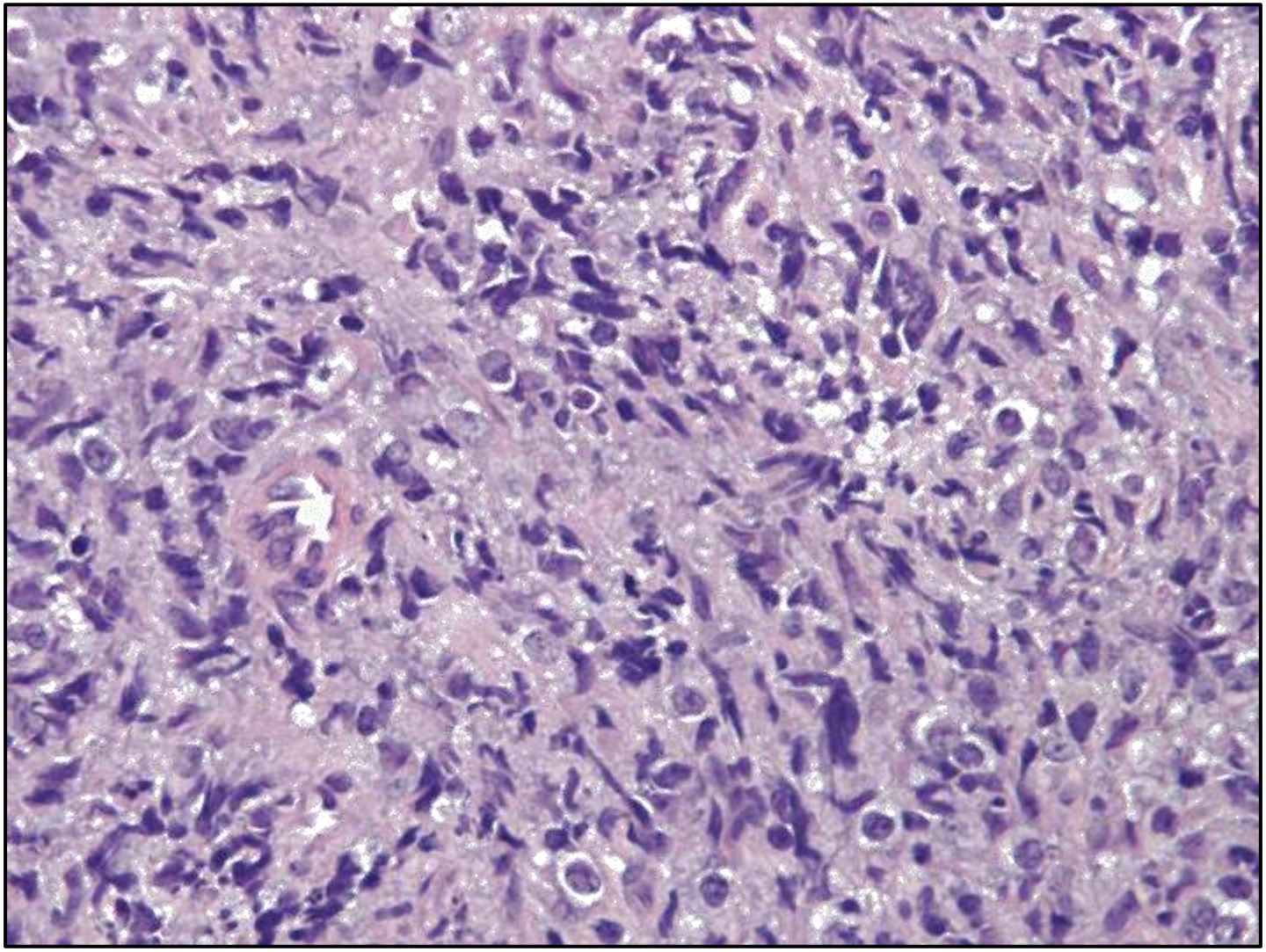
Clinical History

- 28 year-old female, G0P0
- Healthy until February 2018
- Vaginal bleeding and pain
- Saw a gynecologist at Sutter and had a pelvic ultrasound at this time showing a heterogeneous focus in endometrium with cystic spaces
- Later, the patient is transferred to Stanford and has a cervical biopsy performed









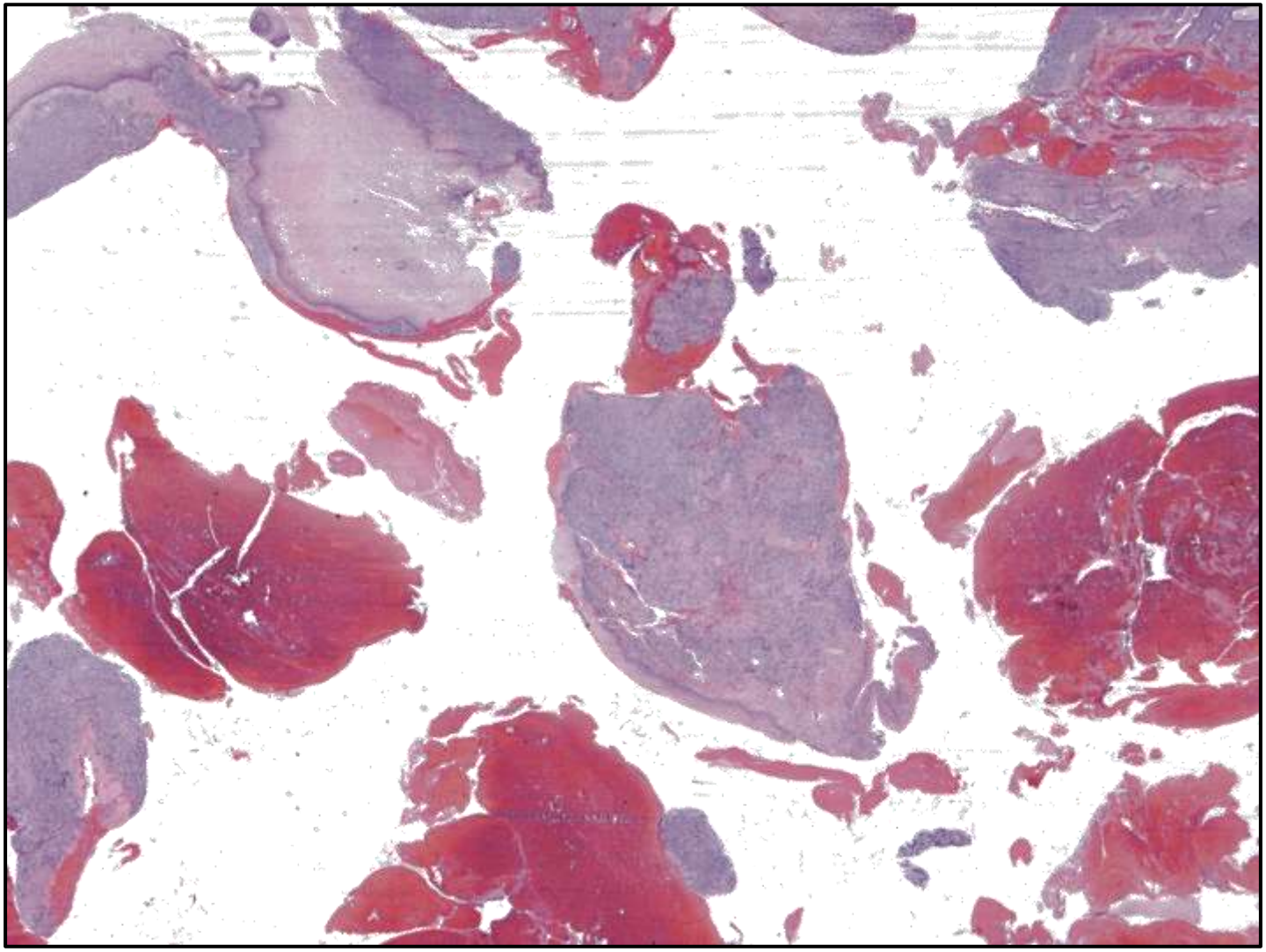
South Bay Society of Pathology

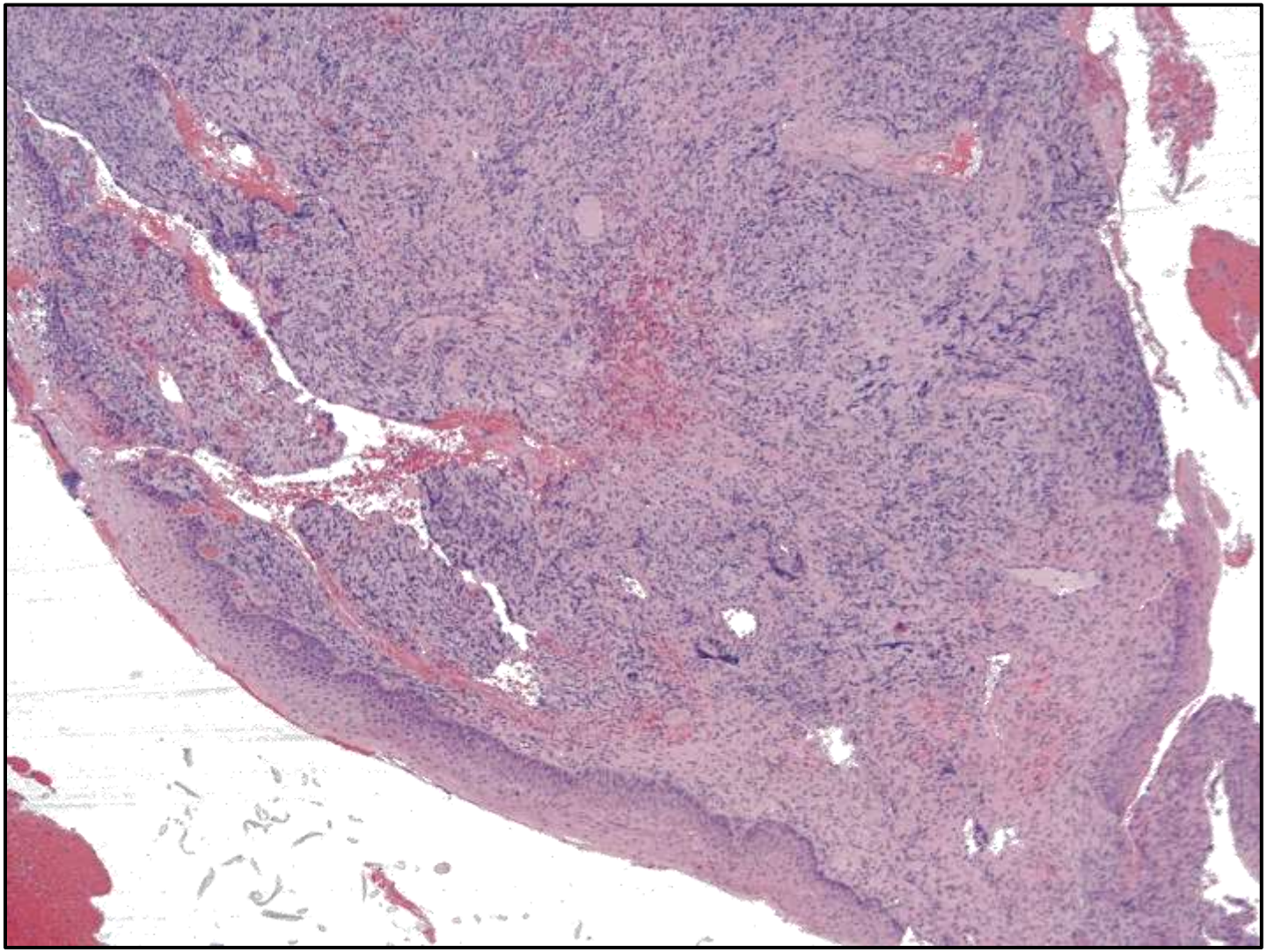
Francisco Beca

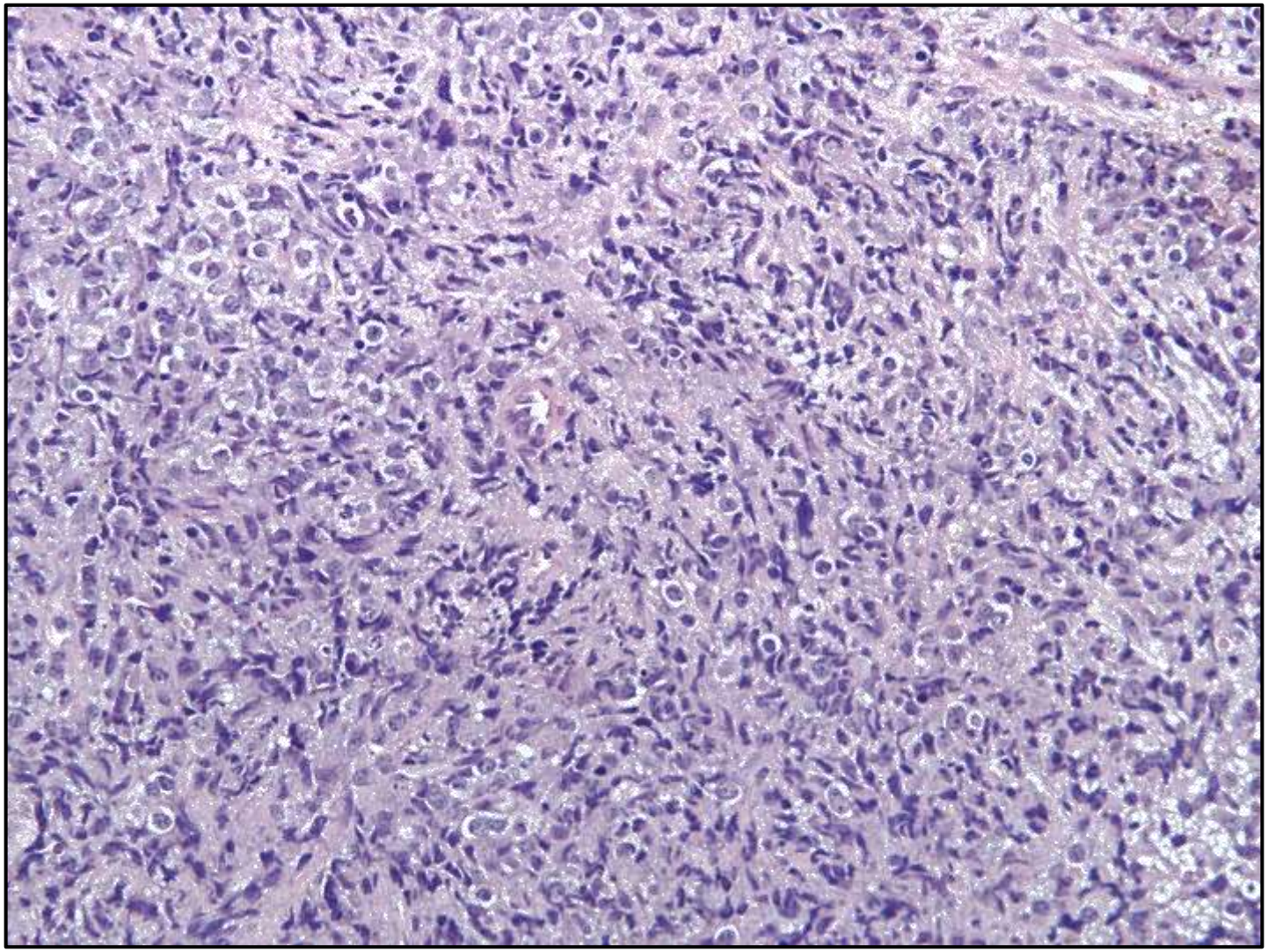
February 2019

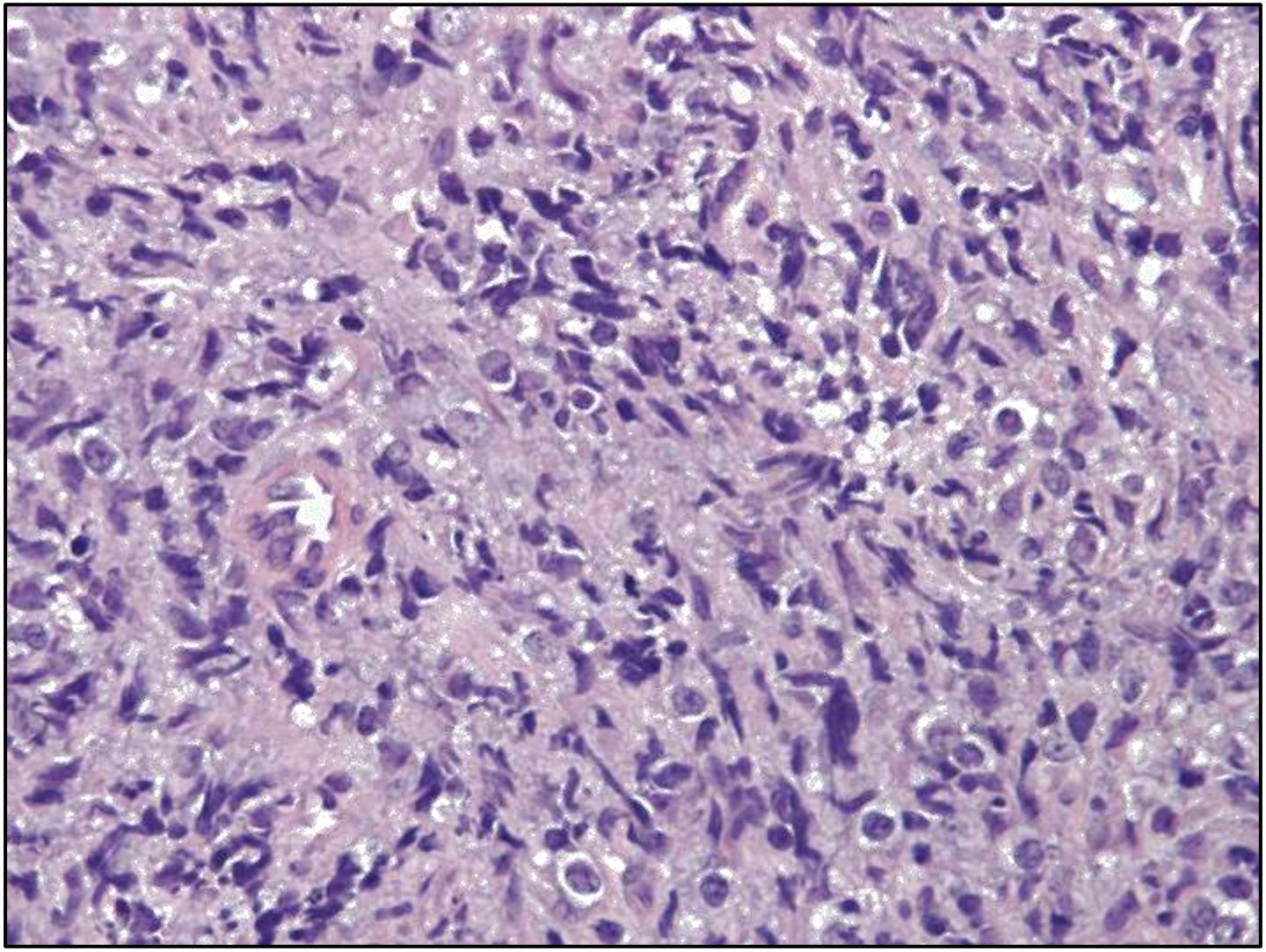
Clinical History

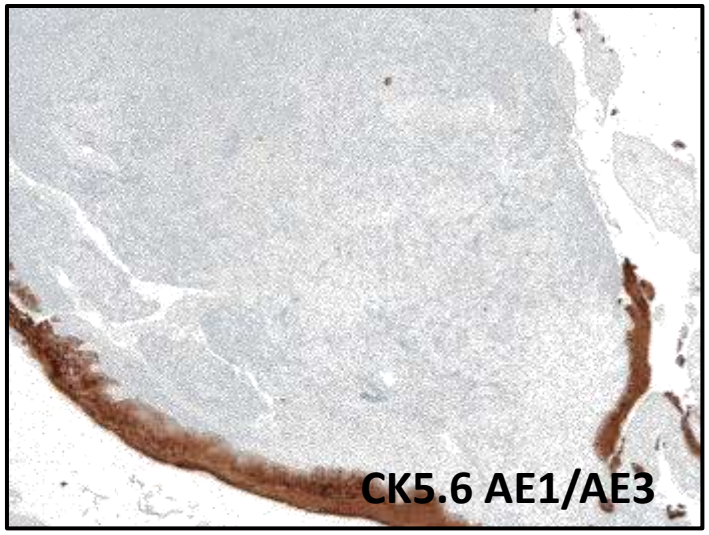
- 28 year-old female, G0P0
- Healthy until February 2018
- Vaginal bleeding and pain
- Heterogeneous focus in endometrium with cystic spaces in US
- A cervical biopsy is performed at Stanford

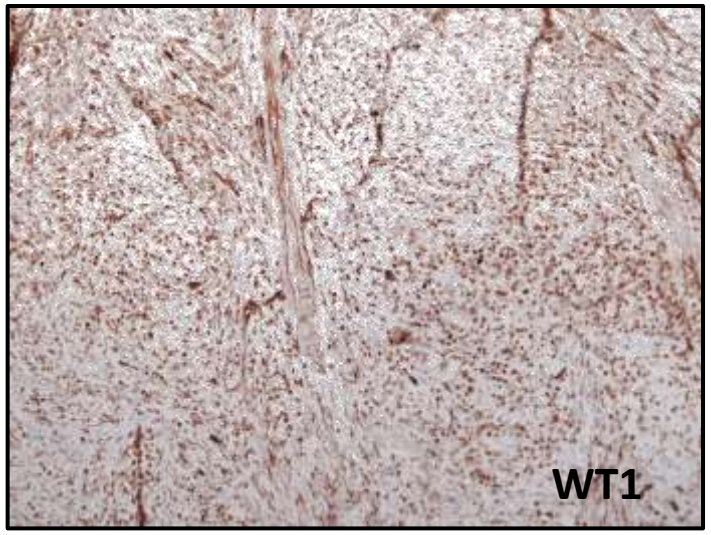


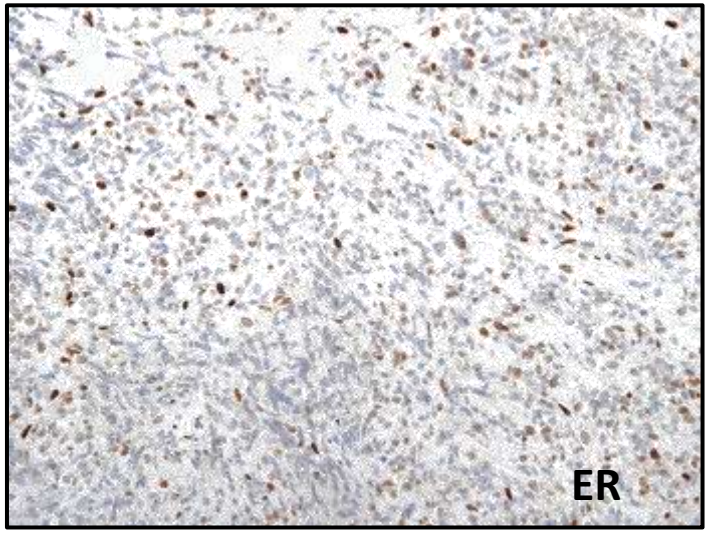







CK5.6 AE1/AE3


WT1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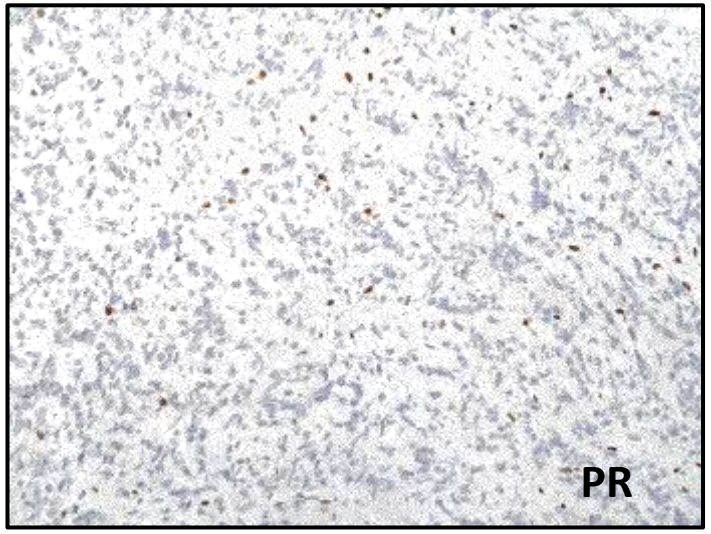

PR

Differential Diagnoses

- Undifferentiated carcinoma
- Undifferentiated sarcoma

- Small cell carcinoma of the ovary, hypercalcemic type

- SMARCA4-deficient undifferentiated uterine sarcoma

Modern Pathology
https://doi.org/10.1038/s41379-018-0049-z

USCAP

ARTICLE

SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

David L. Kolin[1] · Fei Dong[2] · Michele Baltay[2] · Neal Lindeman[2] · Laura MacConaill[2] · Marisa R. Nucci[1] · Christopher P. Crum[1] · Brooke E. Howitt[1,3]

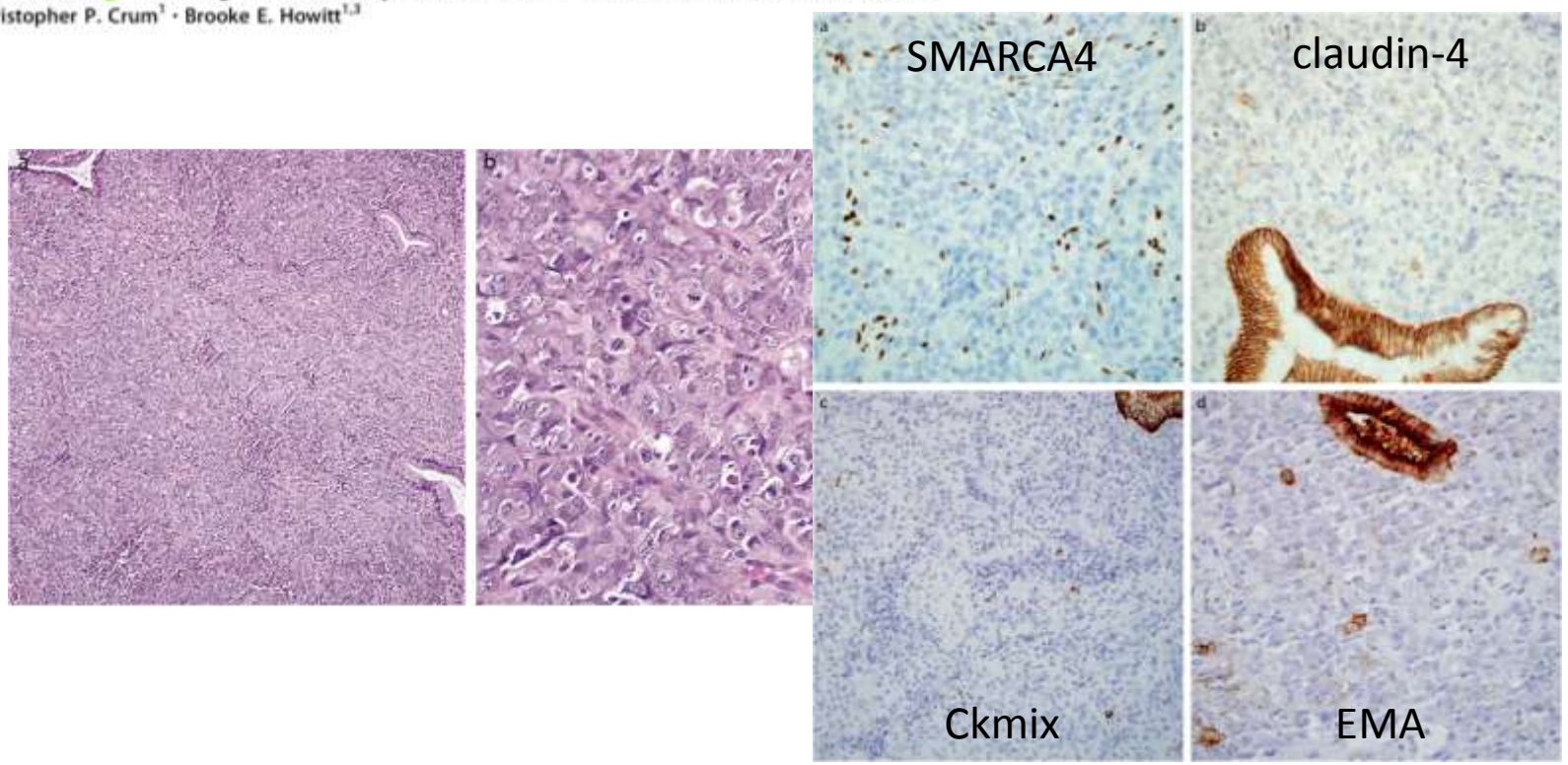


Table 2 Clinicopathologic features of cases of SMARCA4-deficient undifferentiated uterine sarcoma/malignant rhabdoid tumor of the uterus

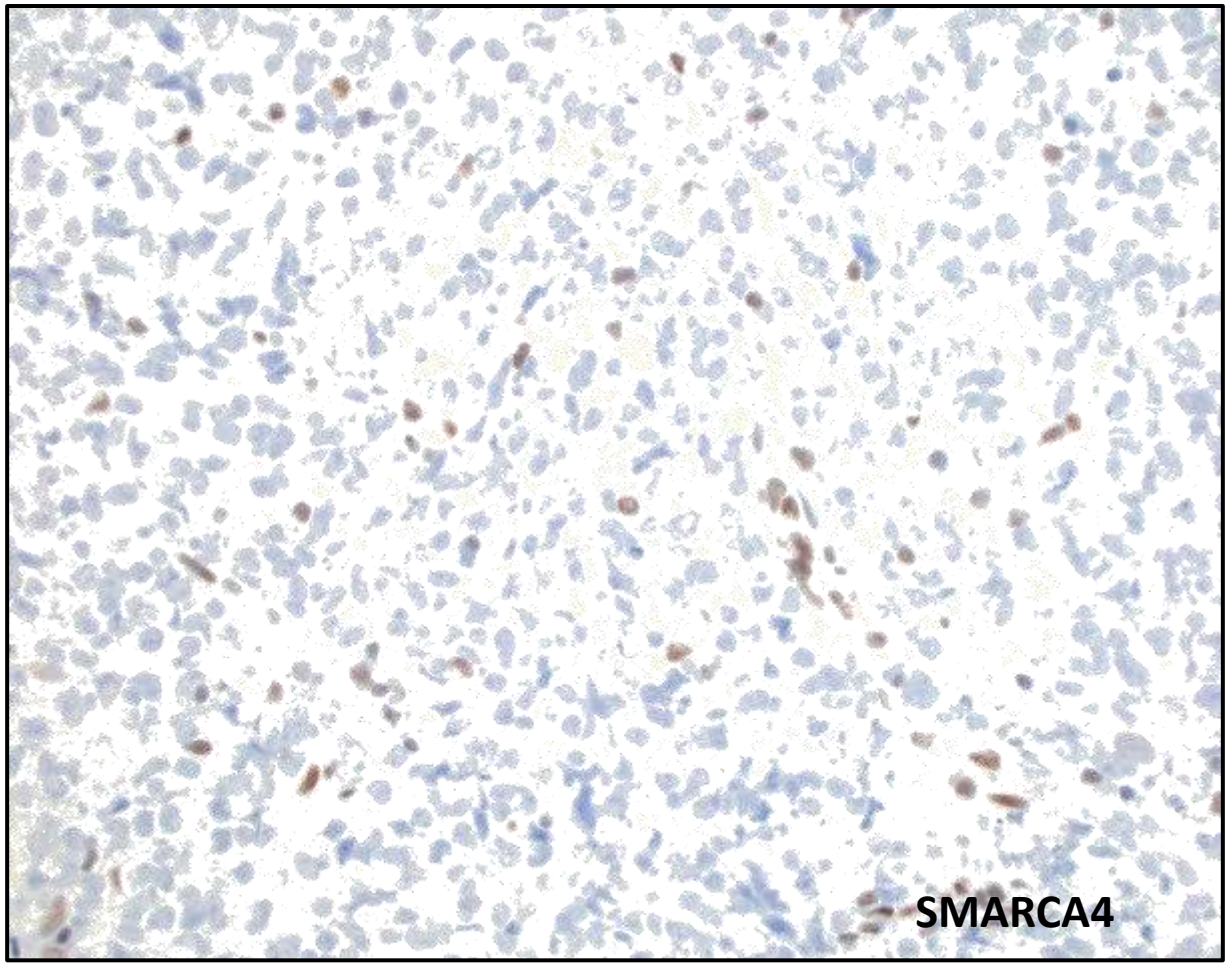
Case	Age (years)	Follow-up	MMR IHC	SMARCA4 IHC	Claudin-4 IHC	SMARCB1 IHC	WT-1 IHC	HMB-45 IHC	Genomic alterations
1	25	DOD at 7 months	Intact	Lost	Negative	Intact	Negative	Negative	Failed MPS
2	33	DOD at 9 months	Intact	Lost	Negative	Intact	Negative	Negative	*SMARCA4* c.3426delC frameshift *SMARCA4* c.4759G>T nonsense *TERT* promoter mutation
3	34	DOD at 1 month	Intact	Lost	Rare cells	Intact	Positive	ND	*SMARCA4* c.2554A>T nonsense *ASXL1* c.1205G>A, p.R402Q missense
4	29	DOD at 4 months	ND	Lost	Negative	ND	ND	Negative	*SMARCA4-PSG8* inversion *ARID1B* c.5687G>A, p.R1896Q missense
5	58	DOD at 43 months	ND	ND	ND	Intact	ND	Negative	*SMARCA4* c.582_587GCCCCT>G frameshift *NPRL2* c.428G>A *SH2B3* c.1666G>A *SMARCA4* c.598C>G, p.L200V (VUS) *ZNF217* c.2061_2061A>TTA frameshift

MMR mismatch repair, *DOD* dead of disease, *VUS* variant of uncertain significance, *ND* not done

SMARCA4-deficient undifferentiated uterine sarcoma

- Clinical presentation
- Morphology
- Immunophenotype (excluding SMARCA4 Or SMARCB1)
- MMR status
- SMARCA4 or SMARCB1 expression status 
- SMARCA4 mutation status 

SMARCA4 shows loss in tumor cell



SMARCA4 is mutated

SB 6360

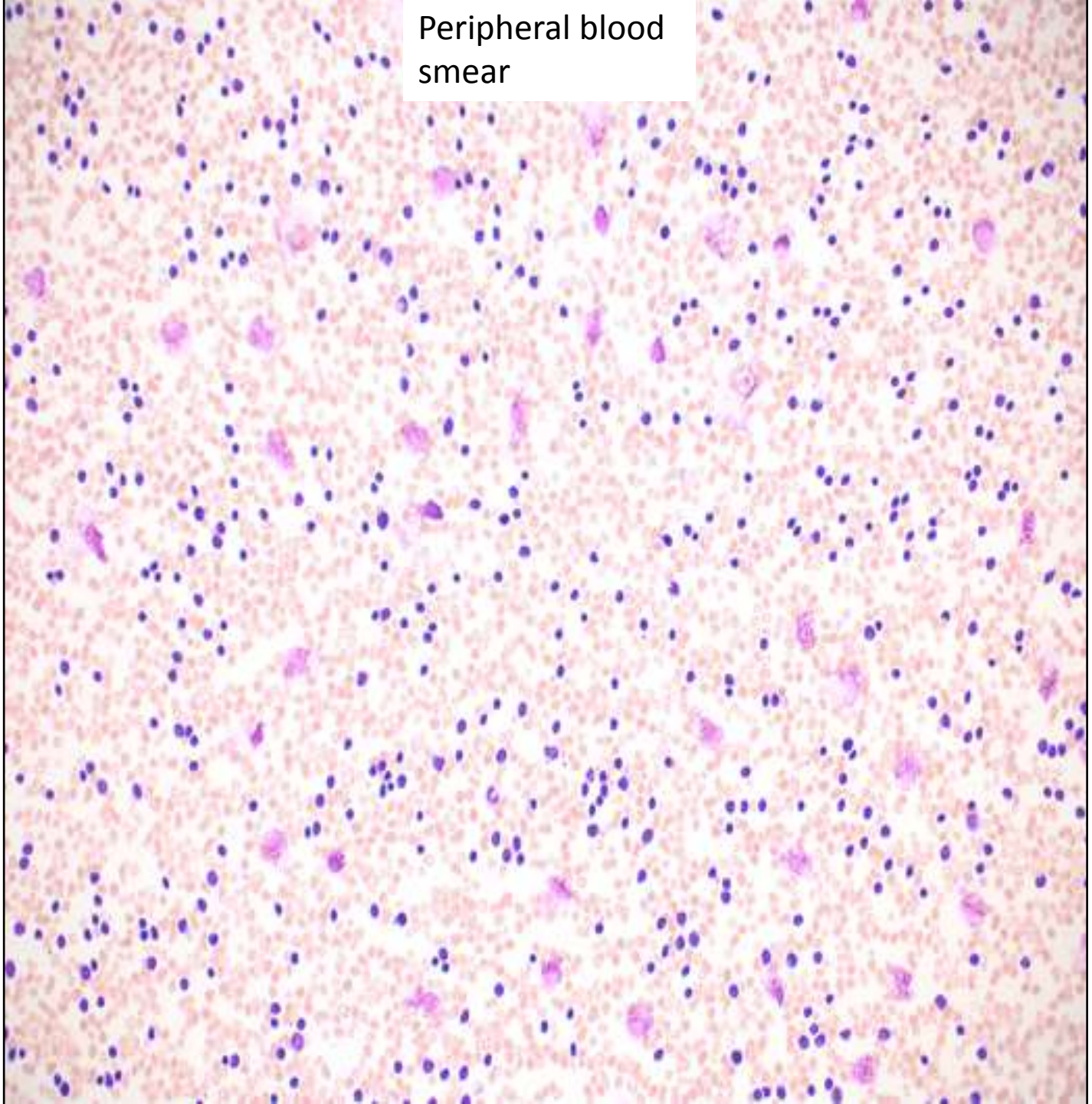
Neda Mirzamani/Linlin Wang/Sonam Prakash; UCSF

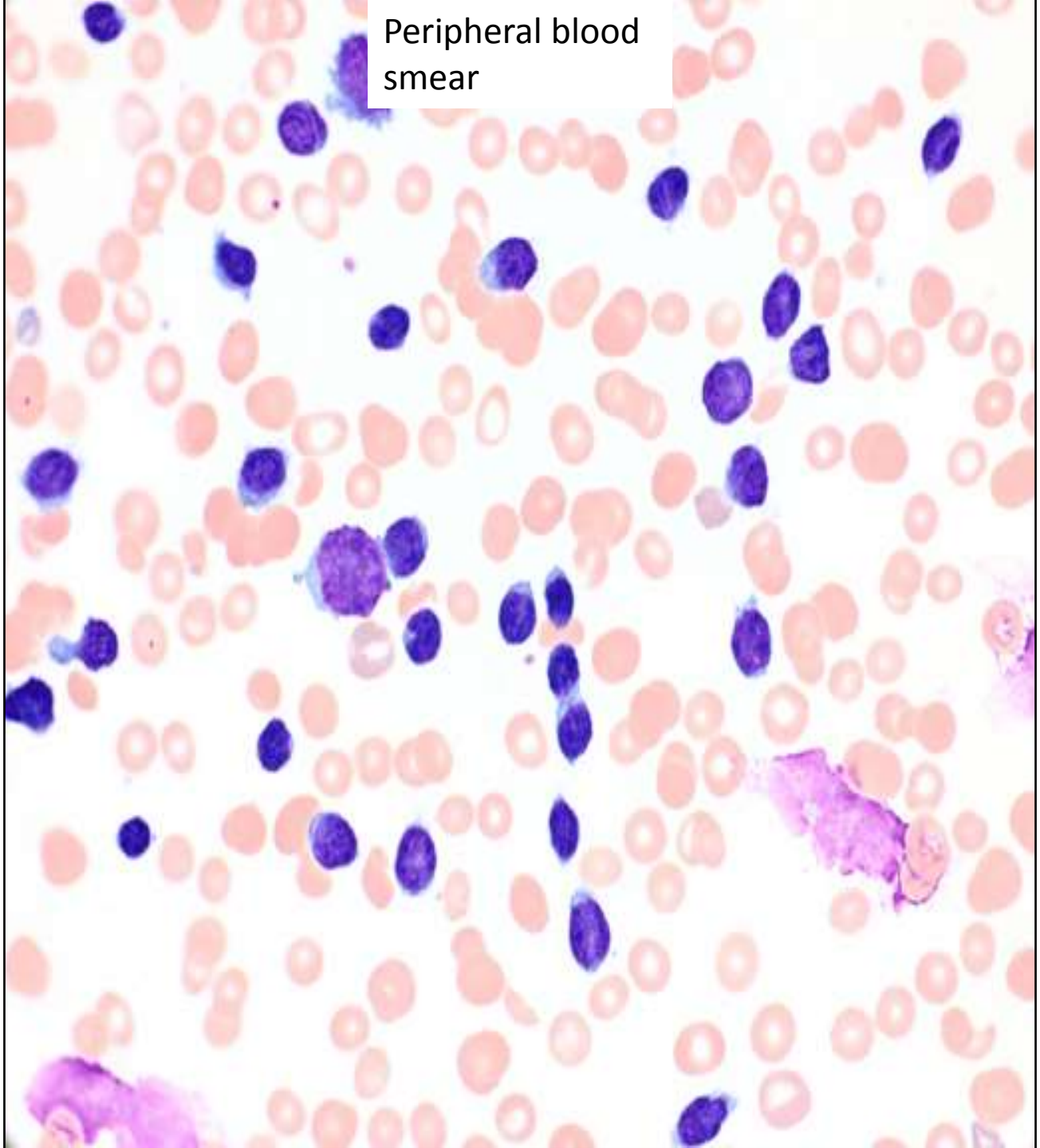
45-year-old male presented with weakness in upper extremity and aphasia. During imaging studies CT of brain shows left basal ganglia hemorrhage (5.7 cm). Patient also has massive splenomegaly (34 cm in diameter). No significant adenopathy identified.

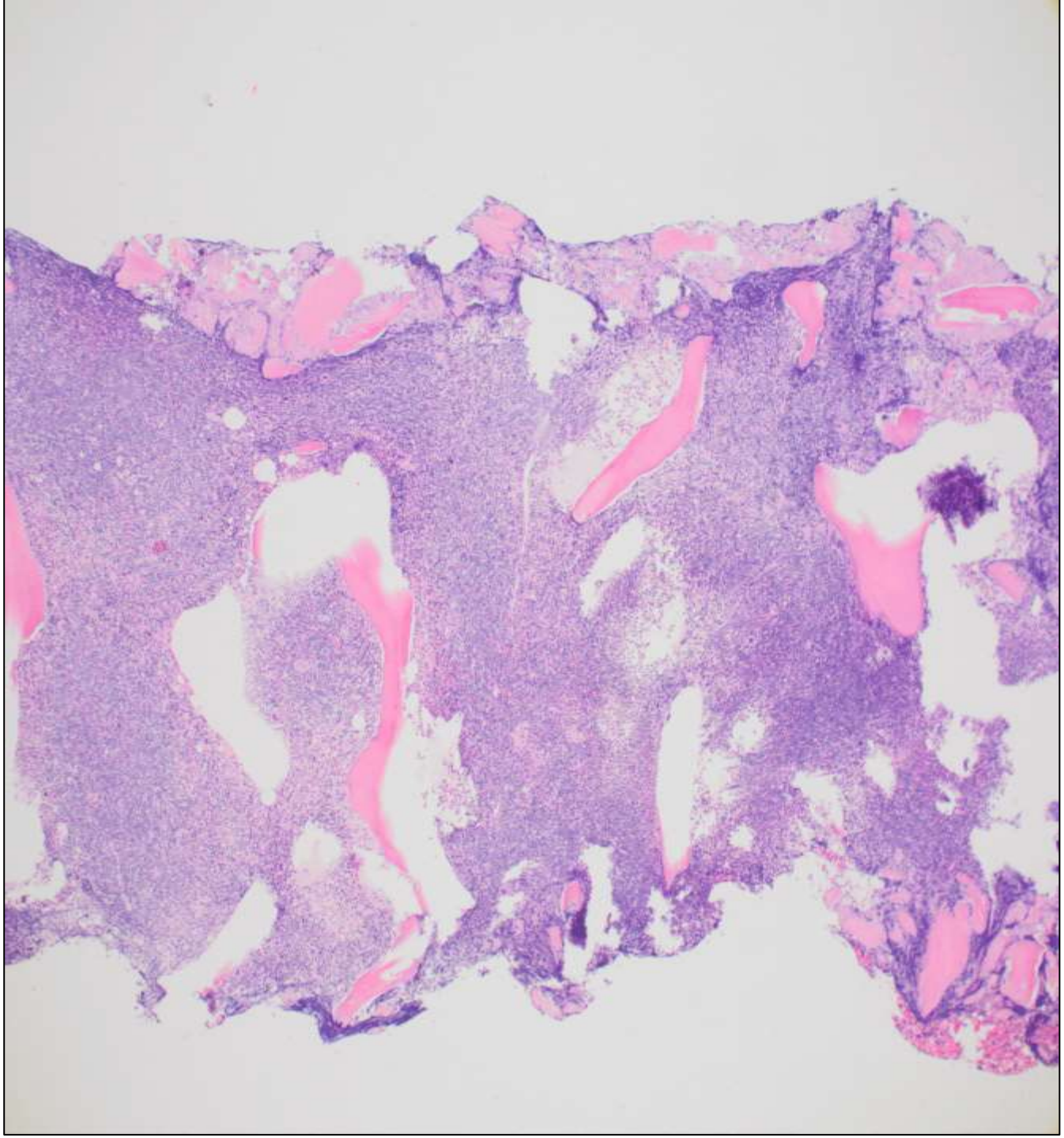
Case presentation

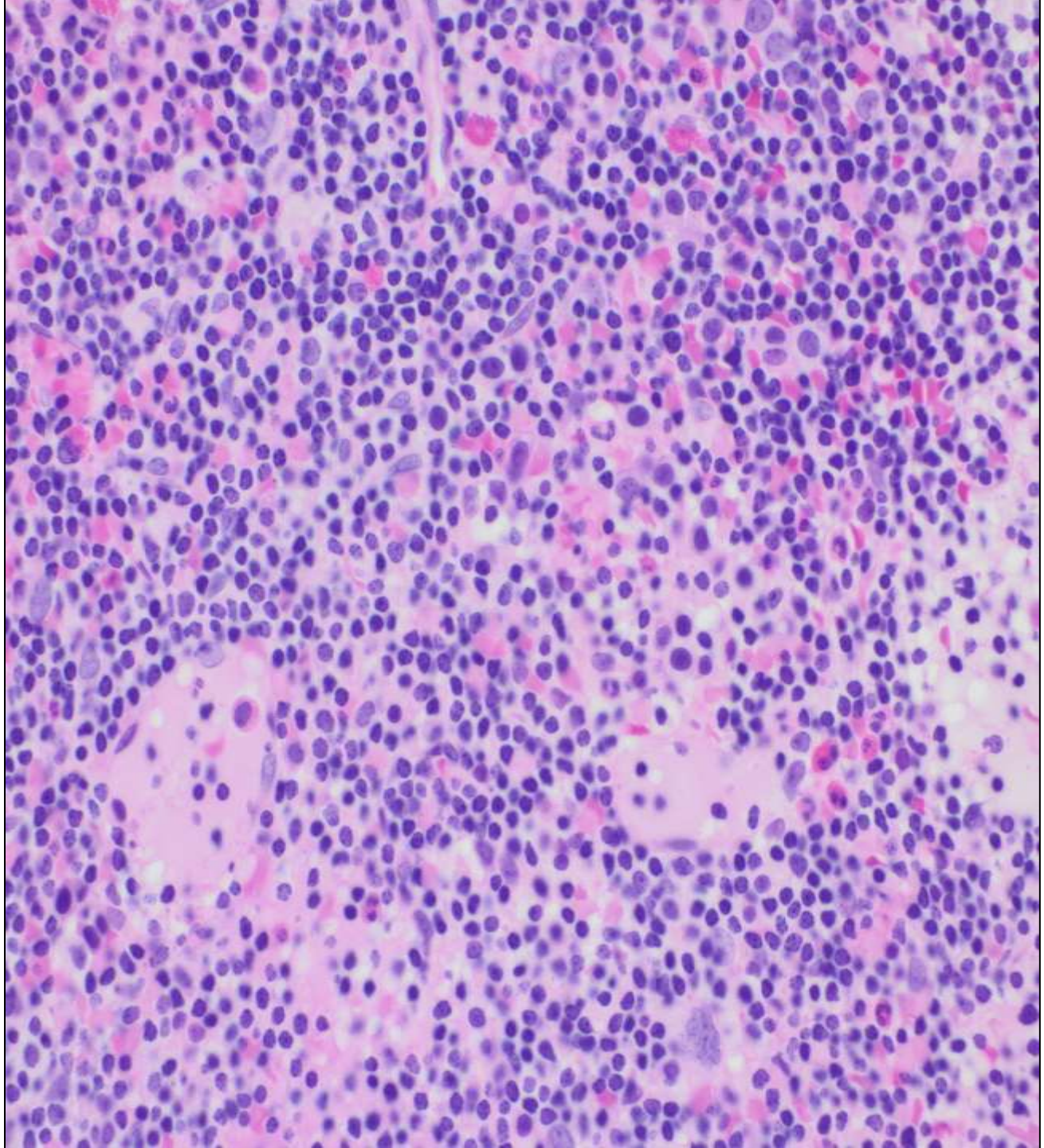
- 45-year-old man
- Weakness in upper extremity and aphasia
- No significant lymphadenopathy
- CT brain: Left basal ganglia hemorrhage (5.7 cm)
- Massive splenomegaly (34 cm in diameter)

- CBC: WBC: 323 x10E9/L (Absolute lymphocyte count: 313 x10E9/L)
- Hb: 5 g/dL
- Platelet: 17 x10E9/L

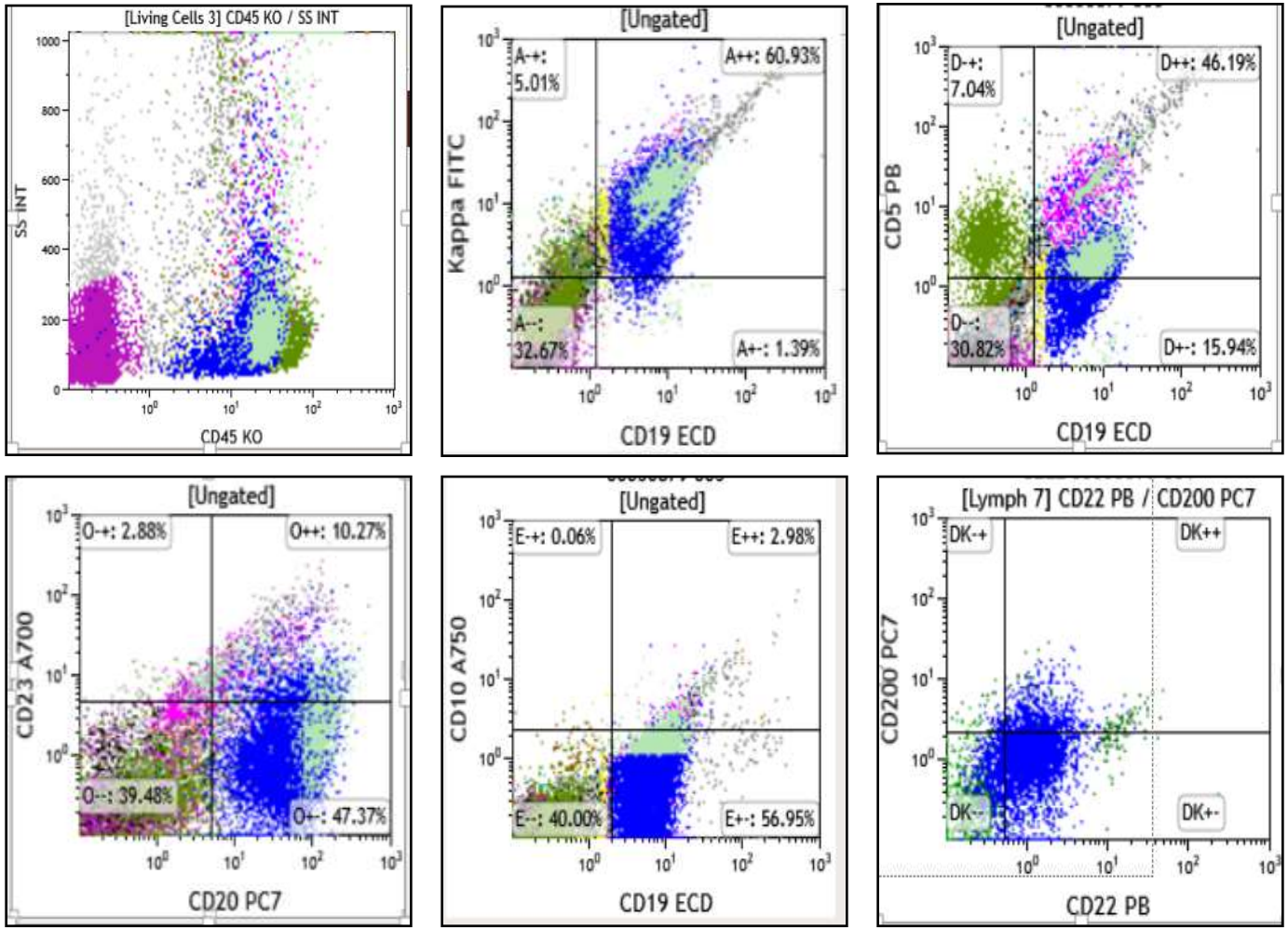

Peripheral blood
smear

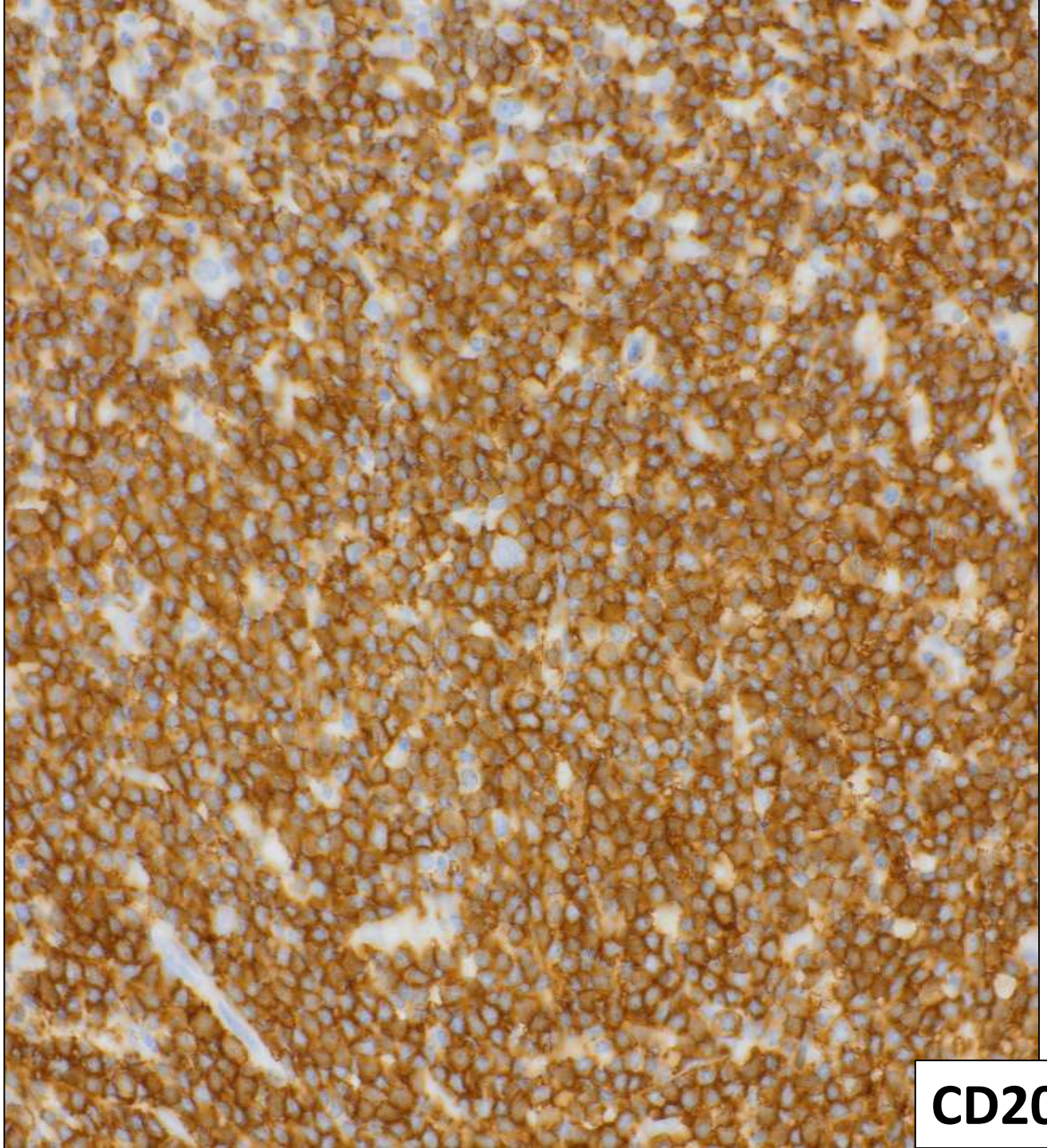

Peripheral blood
smear

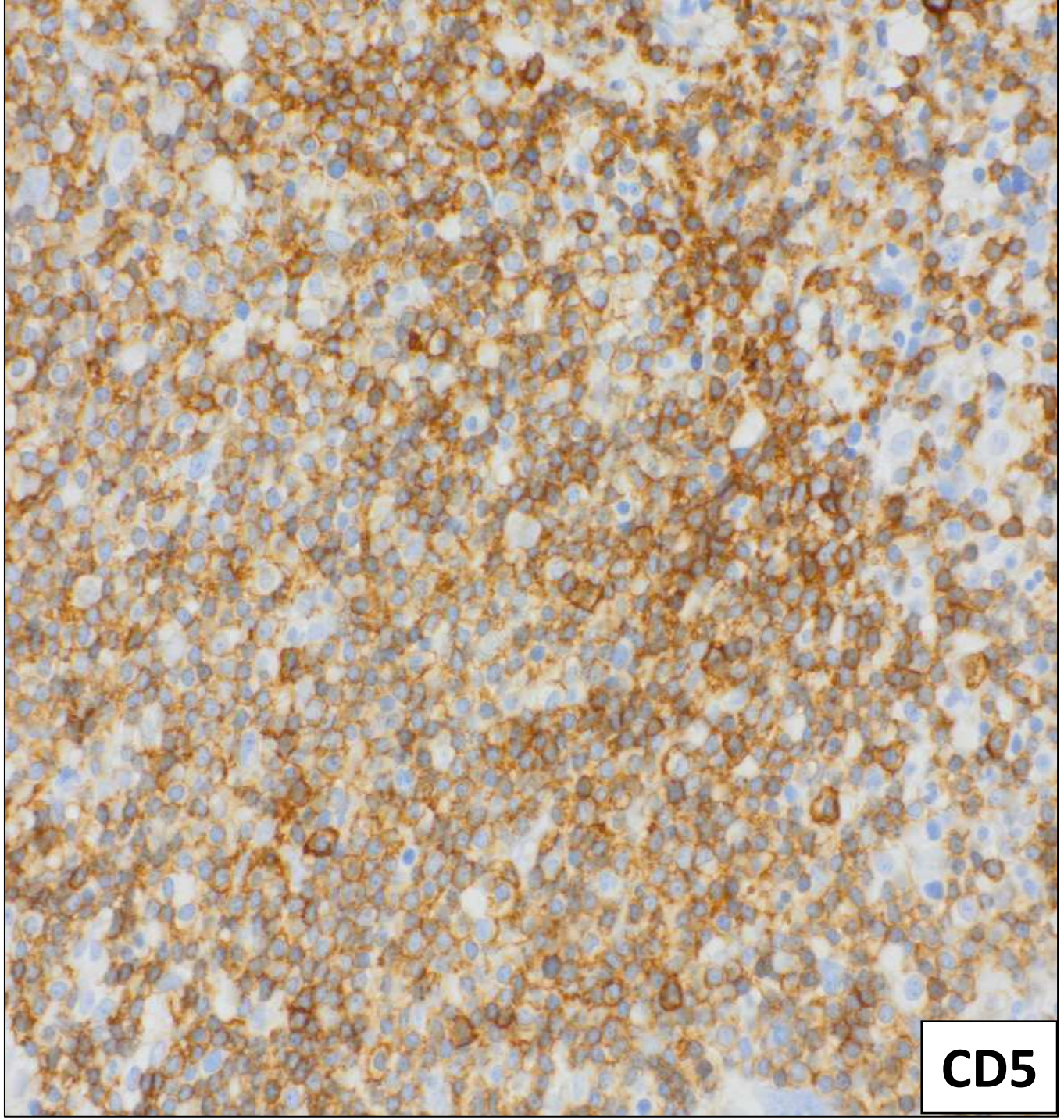


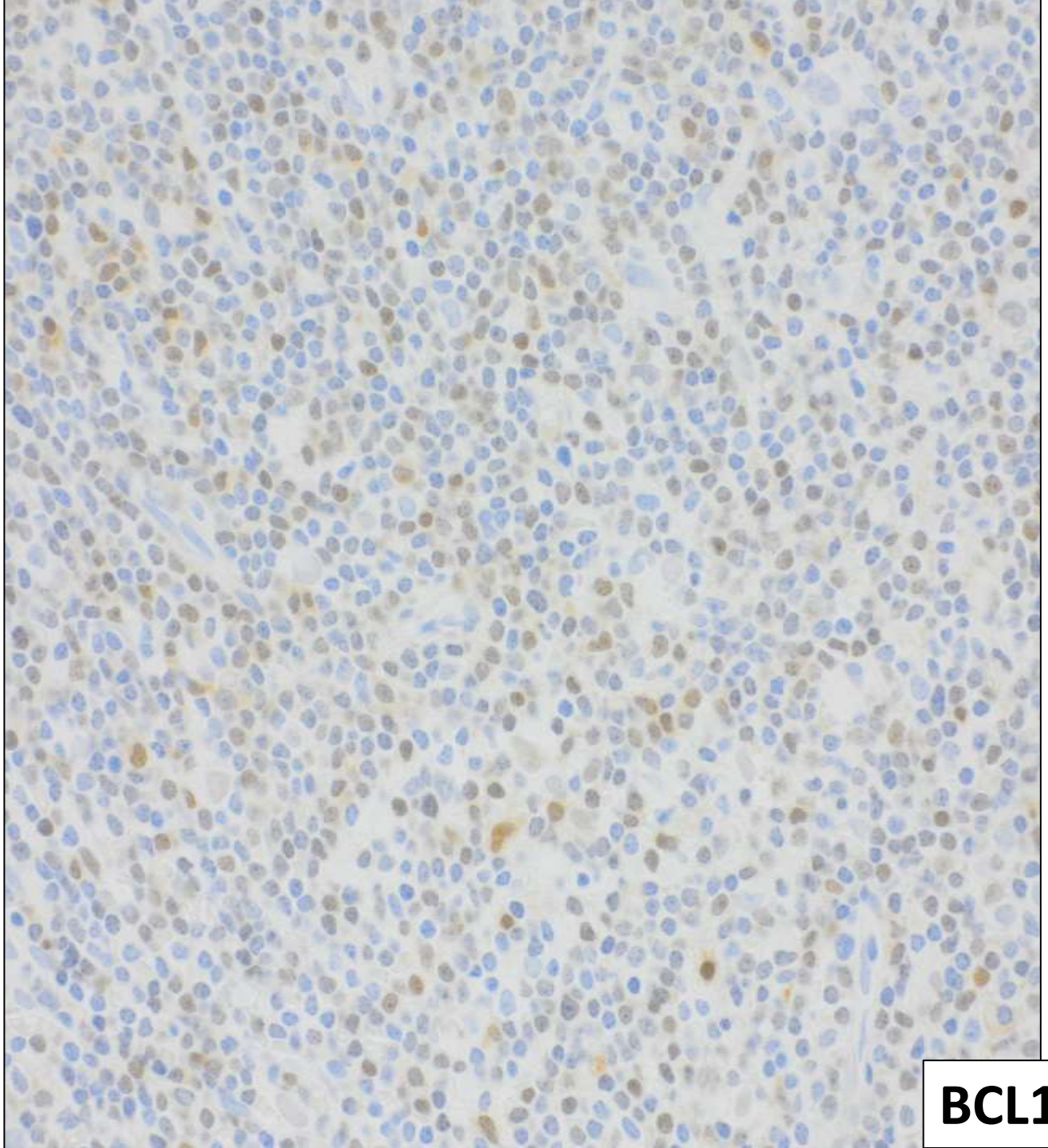


Flow cytometry




CD20


CD5


BCL1

Diagnosis?

Neda Mirzamani

Hematopathology fellow

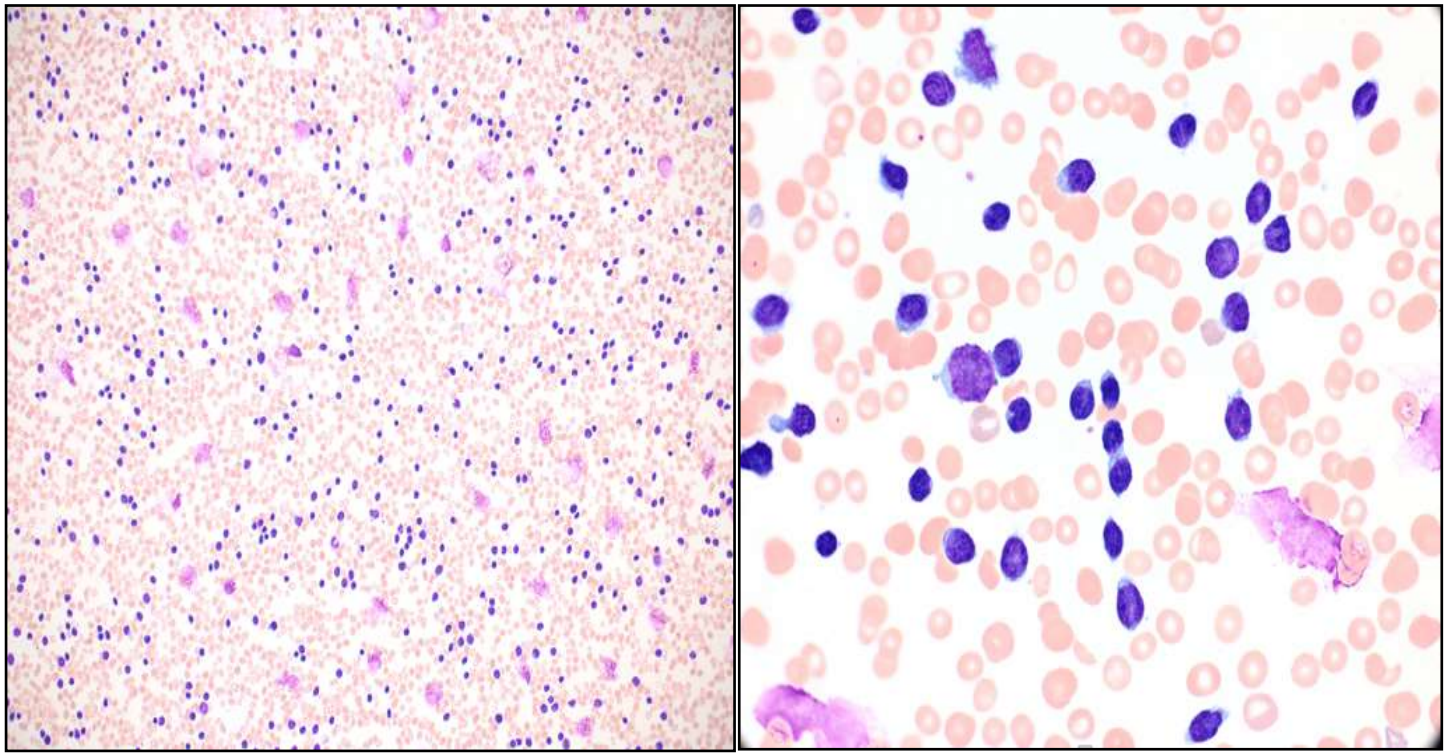
UCSF

Peripheral blood

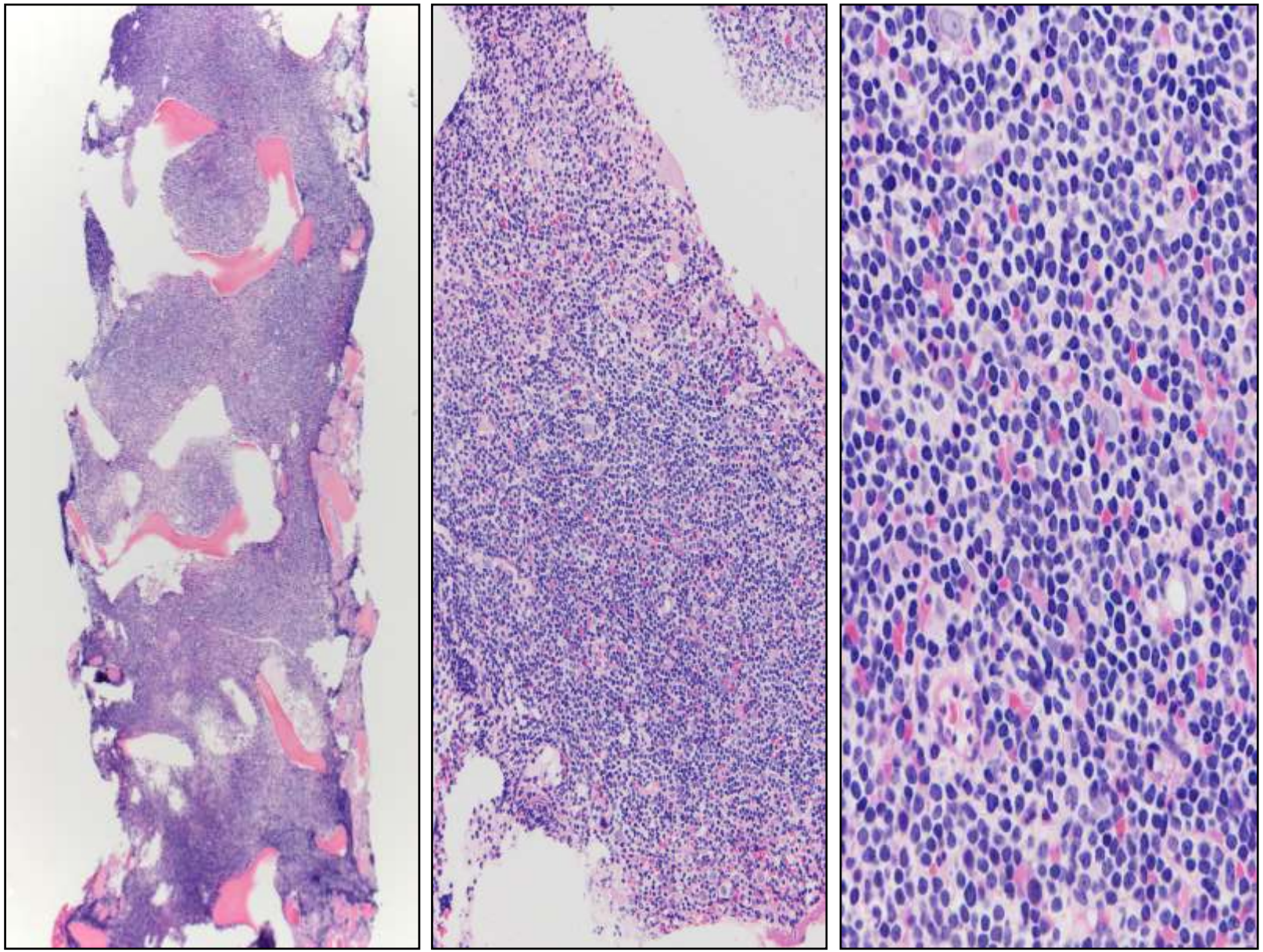
WBC: 323 x10 E9/L (Absolute lymphocyte count: 313 x 10 E9/L)

Hb: 5 g/dL

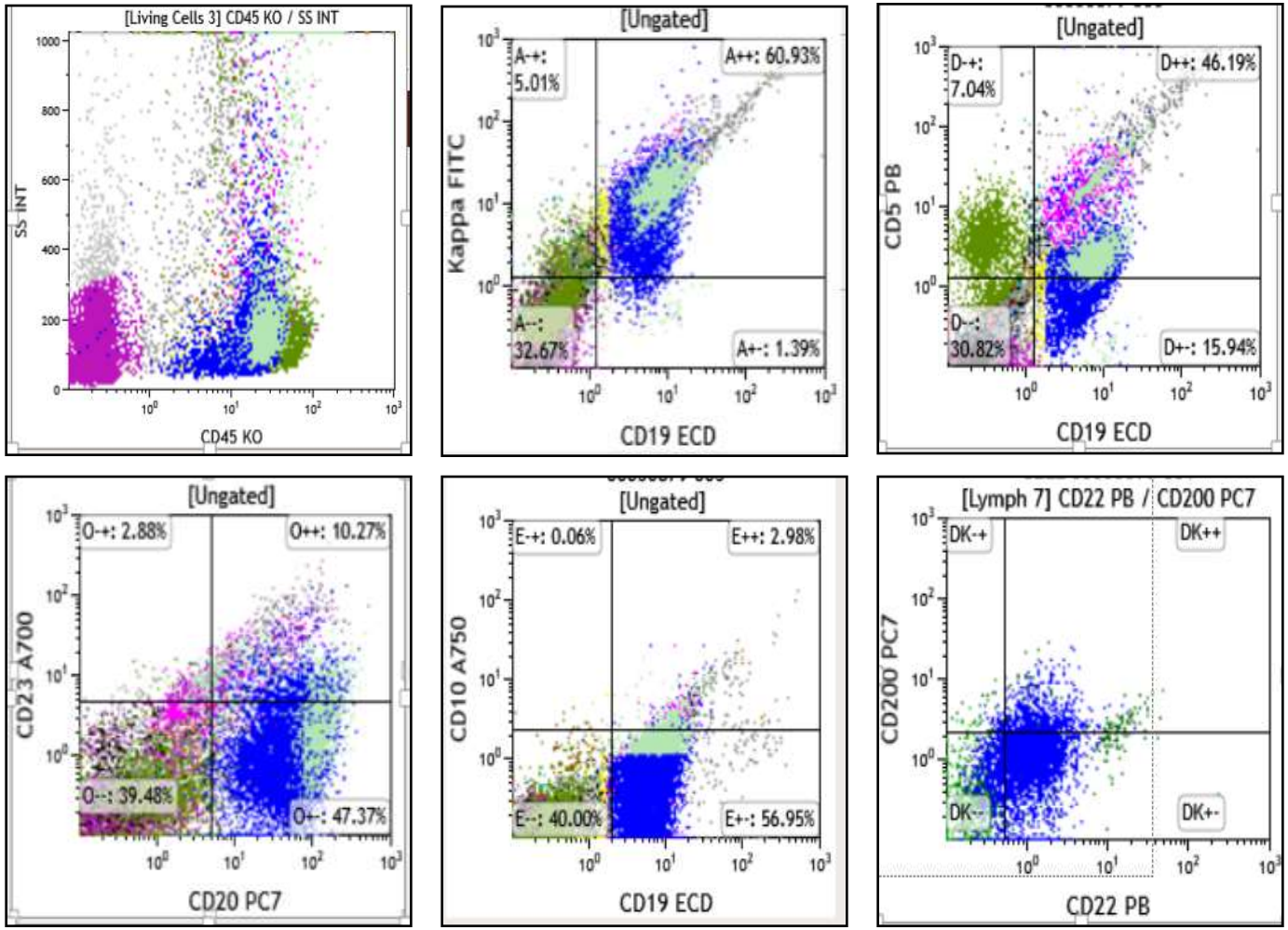
Platelet: 17 x10 E9/L



Bone marrow biopsy



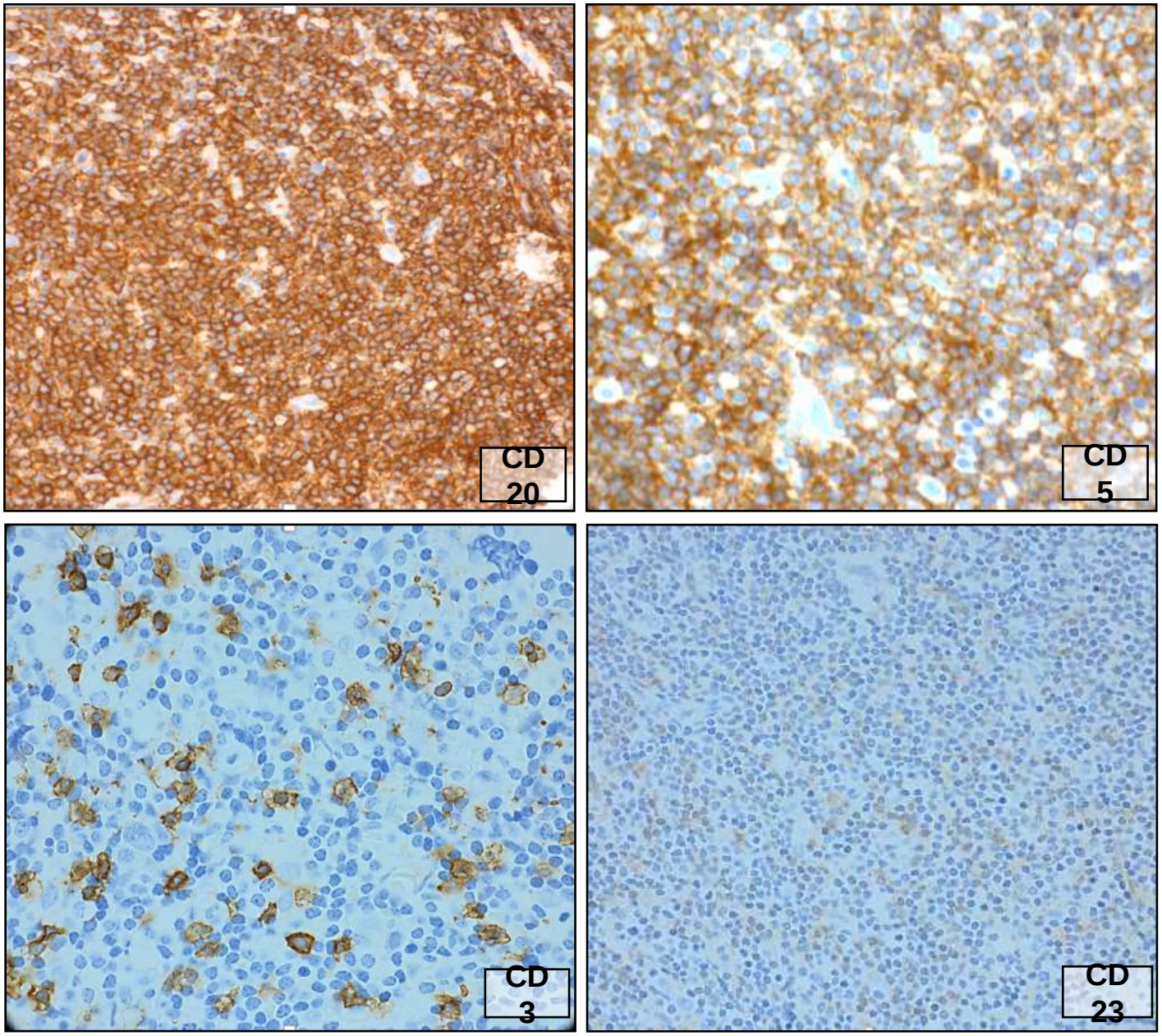
Flow cytometry



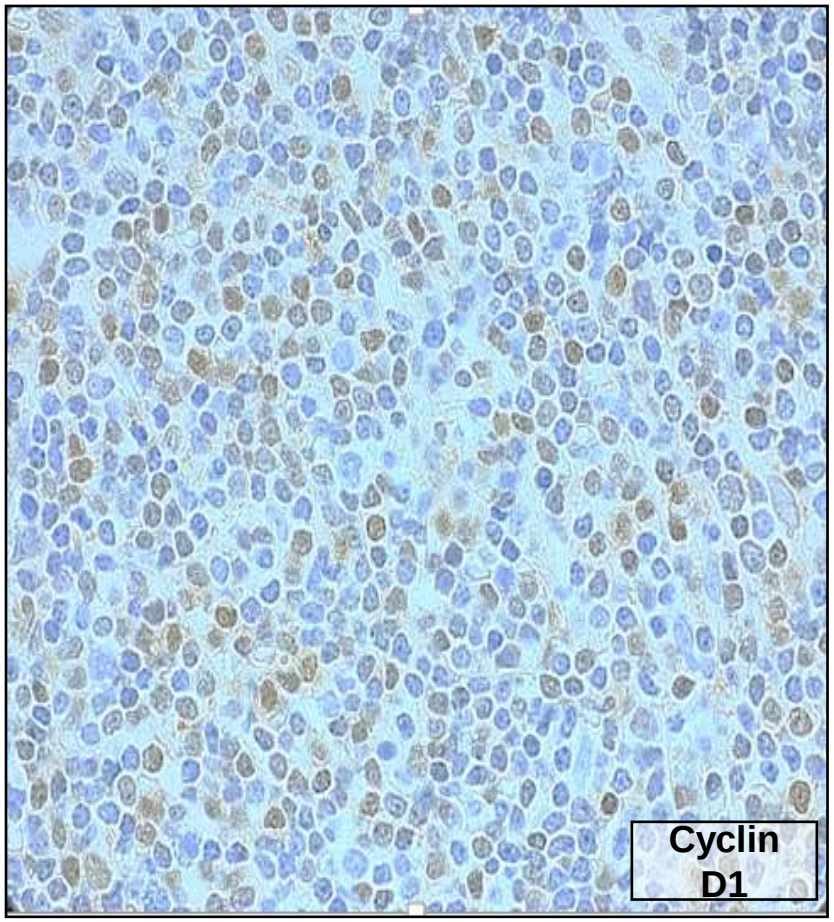
Positive: Weak CD5, weak CD19, variable CD20, variable CD22, weak absent CD23, variable CD79b, and HLA DR

Negative: CD10, CD34, CD103, CD123, CD200

Immunohistochemistry



Immunohistochemistry



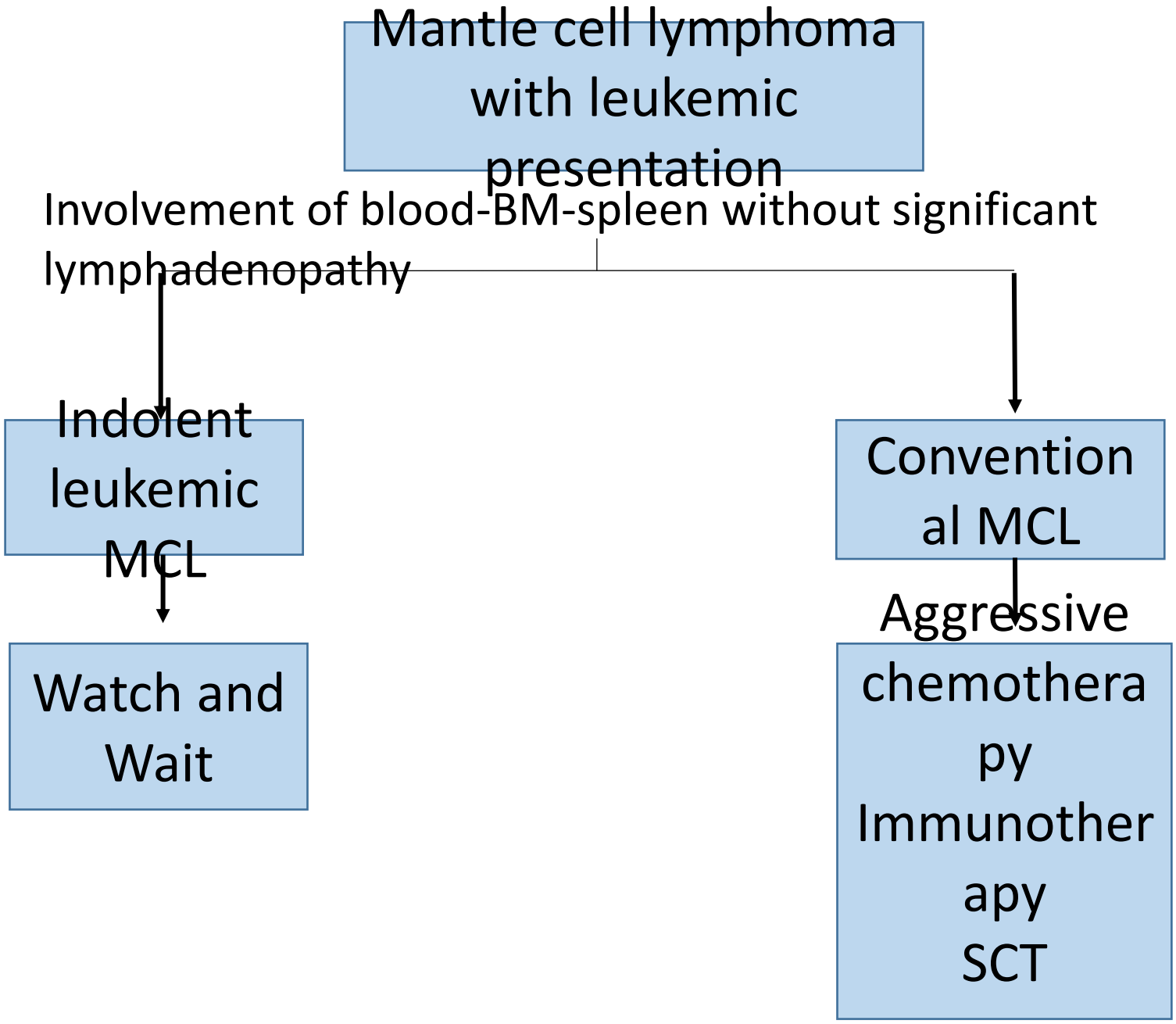
Fluorescence in situ hybridization (FISH)

POSITIVE for IGH/CCND1

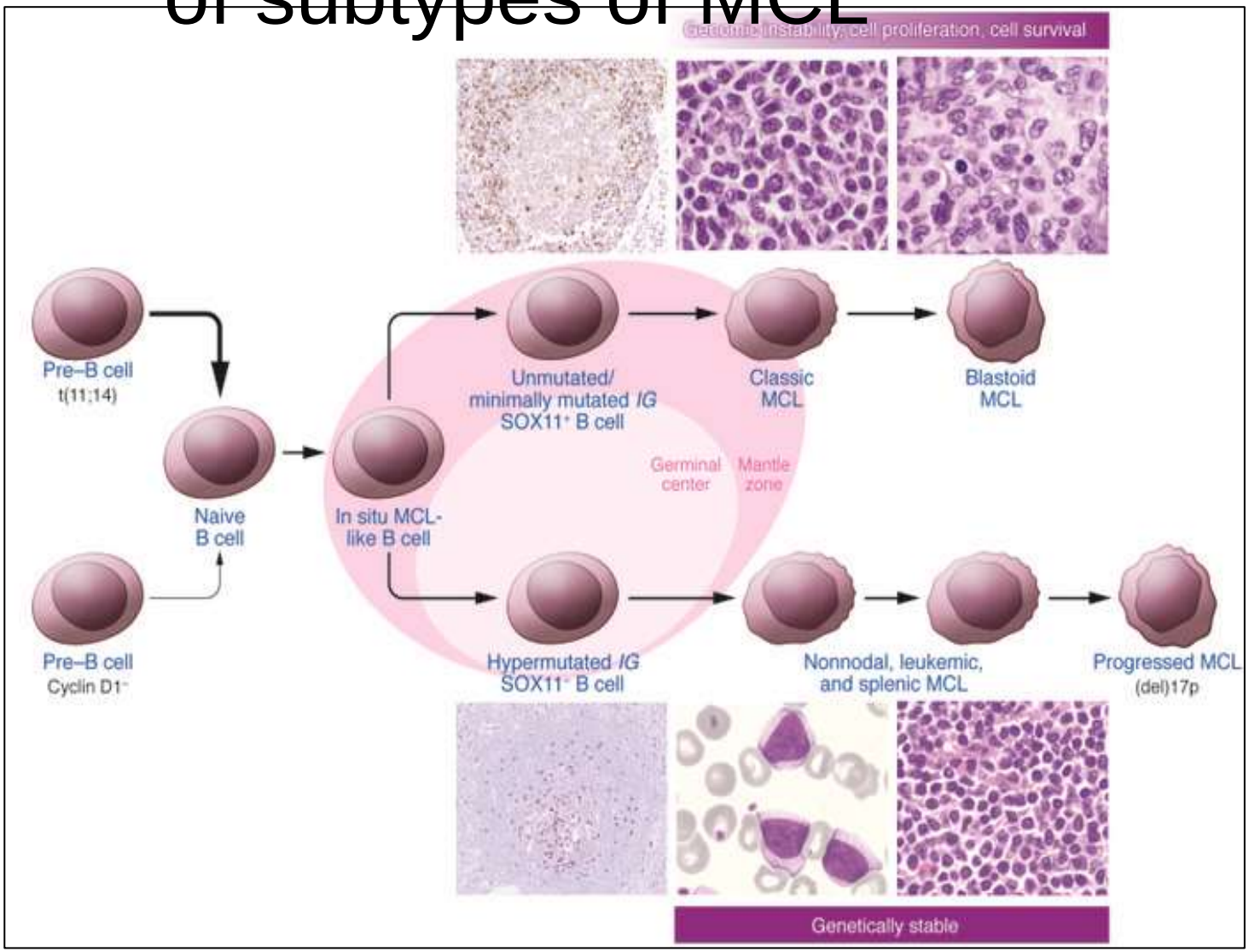
Diagnosis

Mantle cell lymphoma

(leukemic presentation)


Mantle cell lymphoma with leukemic presentation
Involvement of blood-BM-spleen without significant lymphadenopathy
Indolent leukemic MCL
Watch and Wait
Convention al MCL
Aggressive
chemothera py
Immunother apy
SCT

Proposed model of molecular pathogenesis of subtypes of MCL



Pedro Jares, et al. *J Clin Invest.* 2012;122(10):3416-3423.

Biomarkers for diagnosis of MCL subtypes

Conventional MCL	Indolent leukemic non nodal MCL
SOX11+	SOX11-
Complex karyotype	Simple karyotype with t(11;14)
Unmutated IGHV	Hypermutated IGHV

Overlapping features

Mutations in TP53

Deletions in ATM

Deletions of 13q14

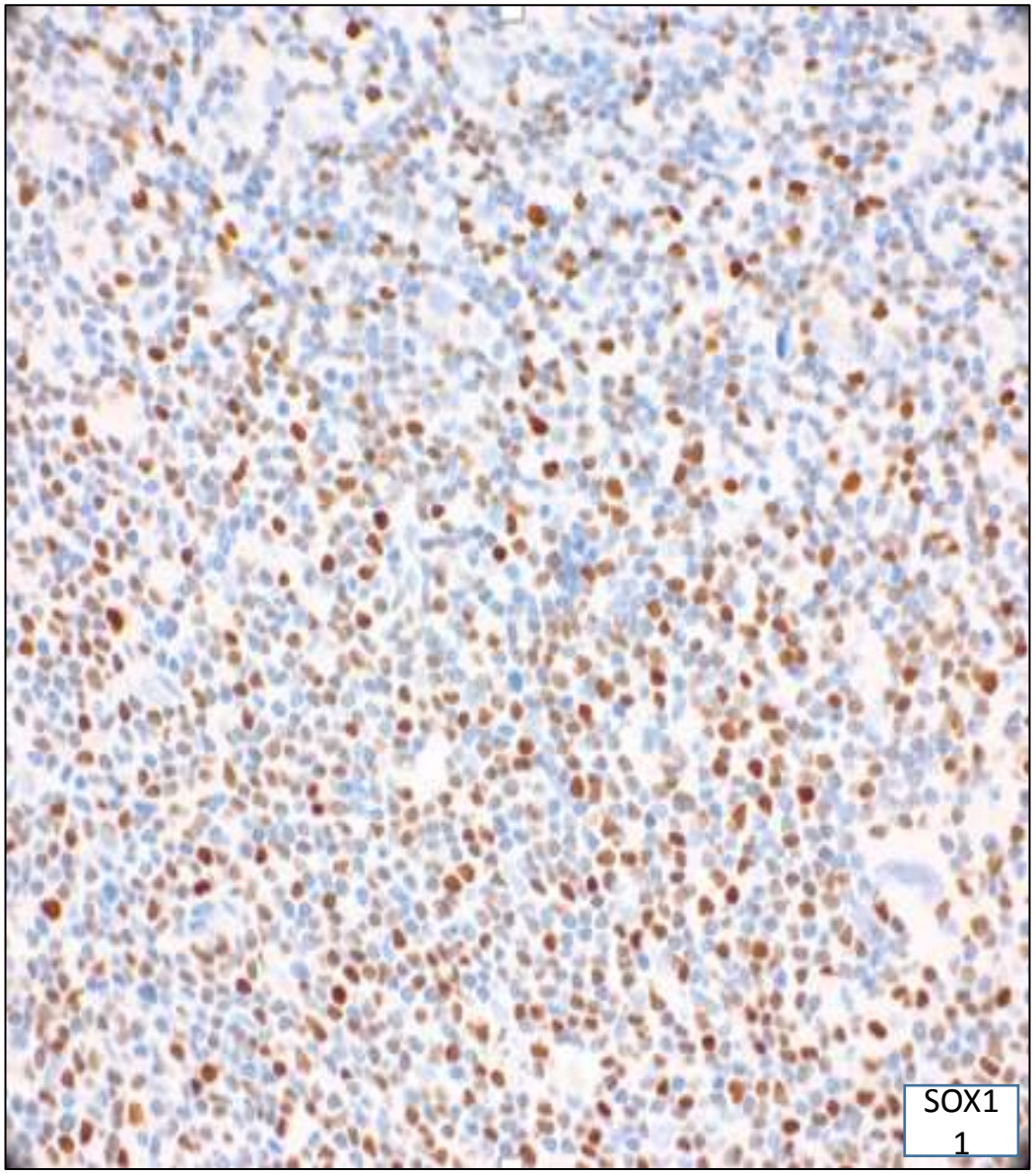
SOX11 as a discriminatory or prognostic biomarker**?**

- Borderline SOX11 expression
- Technical difficulties
- The lack of defined cut-off levels of SOX11 expression

Coming back to our case

- What do you predict?
- Leukemic presentation
- No significant lymphadenopathy
- CyclinD1 positive

SOX 11



Cytogenetics & molecular testing

- Complex cytogenetics including t(5;8) and t(11;14), in 20 of 21 cells analyzed
- Unmutated IGVH
- FISH analysis:
  - POSITIVE for CCND1/IGH gene fusion (90.5%)
  - POSITIVE for deletion of 11q22.3 (ATM) (83.5%)
  - Negative for trisomy 12
  - Negative for deletion of 13q14.3

Final diagnosis

Conventional mantle cell lymphoma with leukemic presentation

Management

- Clinically diagnosed with indolent non-nodal leukemic mantle cell lymphoma and treated with bendamustine.

- Switched to conventional MCL regimen: R-maxiCHOP alternating with high-dose cytarabine (followed by consolidation autologous stem cell transplant).

Take home message

- Mantle cell lymphoma is a heterogeneous disease with variable presentations.

- Conventional MCL: aggressive clinical course, unmutated IGHV, SOX11 positive, complex karyotype.

- Indolent leukemic non-nodal MCL: indolent clinical course, mutated IGHV, SOX11 negative, simple karyotype
  - Cases with additional cytogenetic abnormalities: more aggressive

- Not all leukemic MCL are indolent non-nodal MCL