April 2019 DIAGNOSIS LIST

19-0401: Placental site trophoblastic tumor (uterus; GYN pathology)
19-0402: Epithelial-myoepithelial carcinoma (salivary gland; head&neck pathology)
19-0403: Recurrent granulosa cell tumor (soft tissue; GYN pathology)
19-0404: Embryonal tumor with multilayred rosettes (brain; neuropathology)
19-0405: Acellular dermal matrix with intralymphatic histiocytosis (breast; breast pathology)
19-0406: Reticulohistiocytoma (skin; dermatopathology&soft tissue pathology)
19-0407: ALK+ anaplastic large cell lymphoma (pancreas; hematopathology)
19-0408: ALK- anaplastic large cell lymphoma (lung; hematopathology)
19-0409: Epstein-Barr virus-associated Inflammatory Pseudotumor-like Follicular Dendritic Cell Tumor
19-0410: Malakoplakia (small bowel; GI pathology)

Disclosures
April 8, 2019

Dr. Ankur Sangoi has disclosed a financial relationship with Google (consultant). Dr. Roberto Novoa has disclosed financial relationships with Enspectra Health (consultant), Novartis Argentina (speaker honorarium), and HealthCert (speaker honorarium). Dr. Keith Dunchan has disclosed a financial relationship with ABBVie (consultant). South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented.

The following planners and faculty had no financial relationships with commercial interests to disclose:

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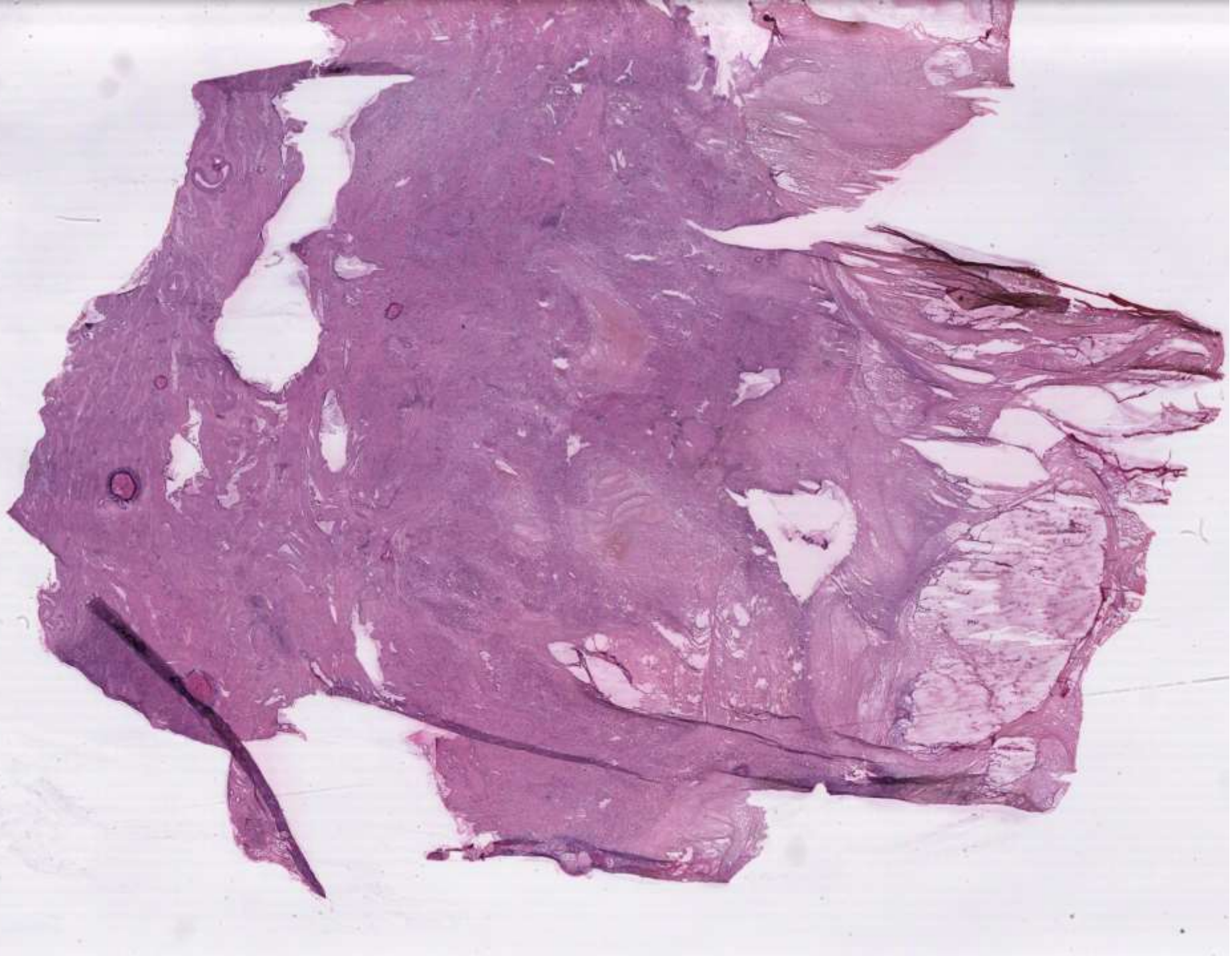
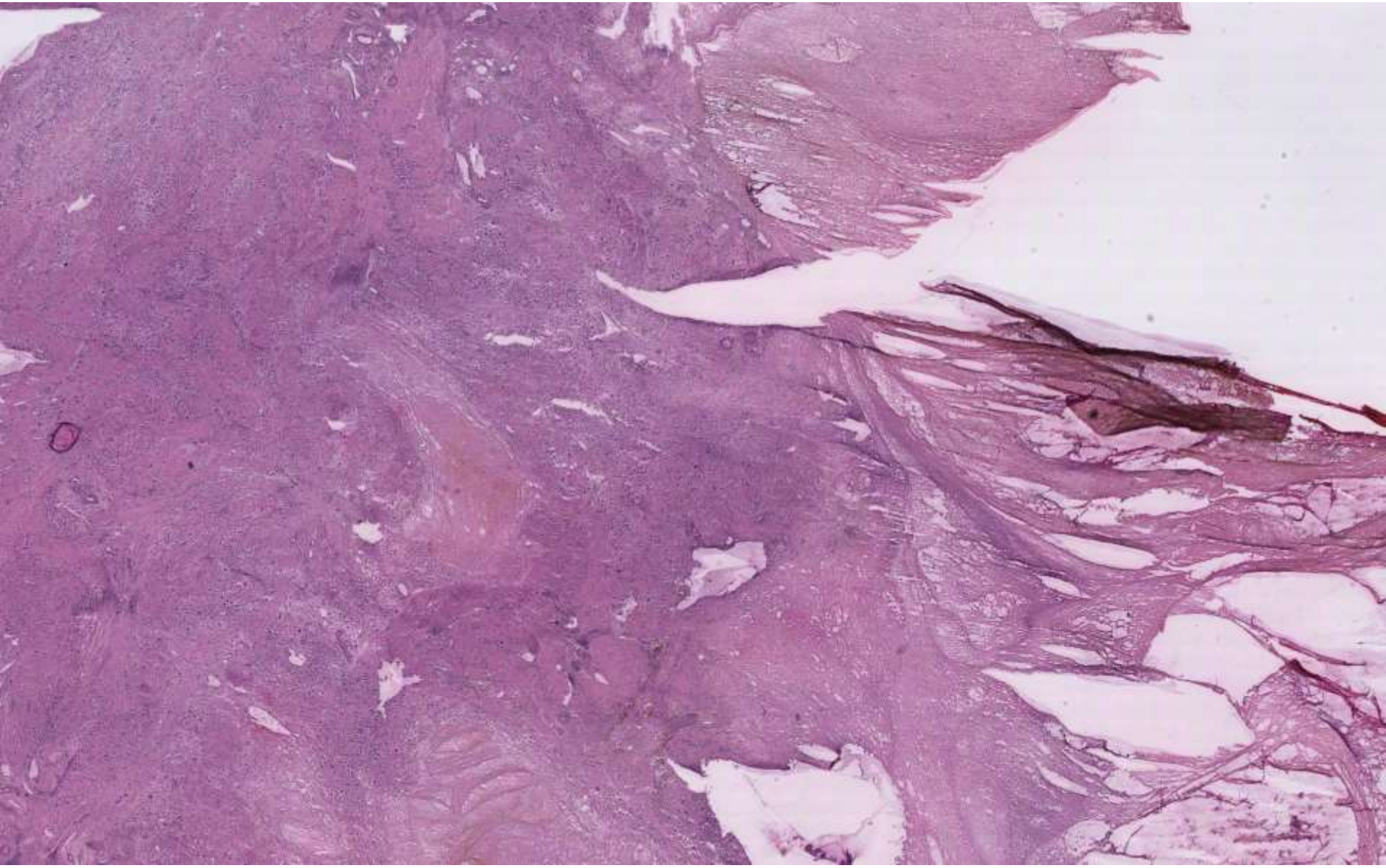
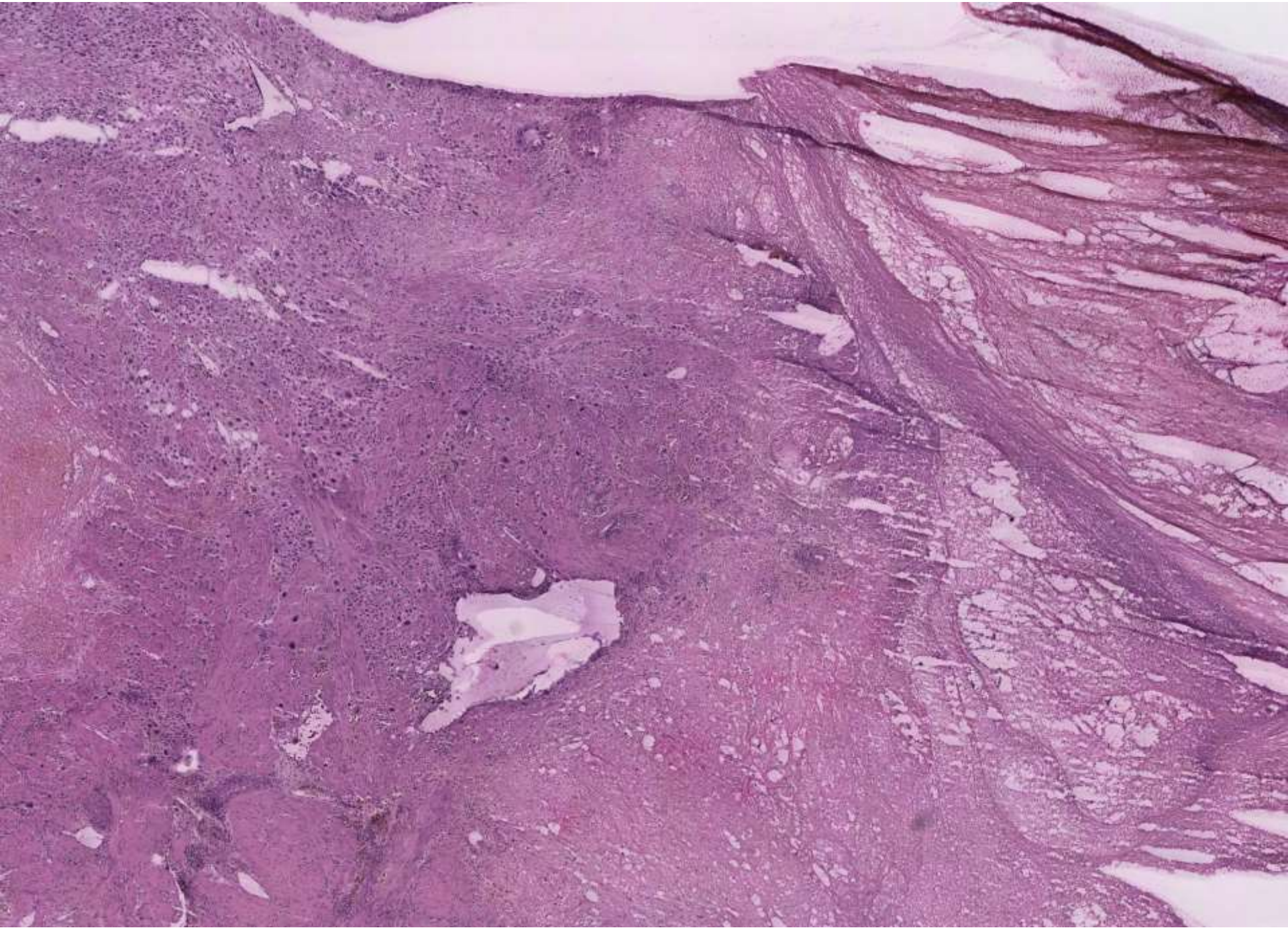
19-0401
(scanned slide available)

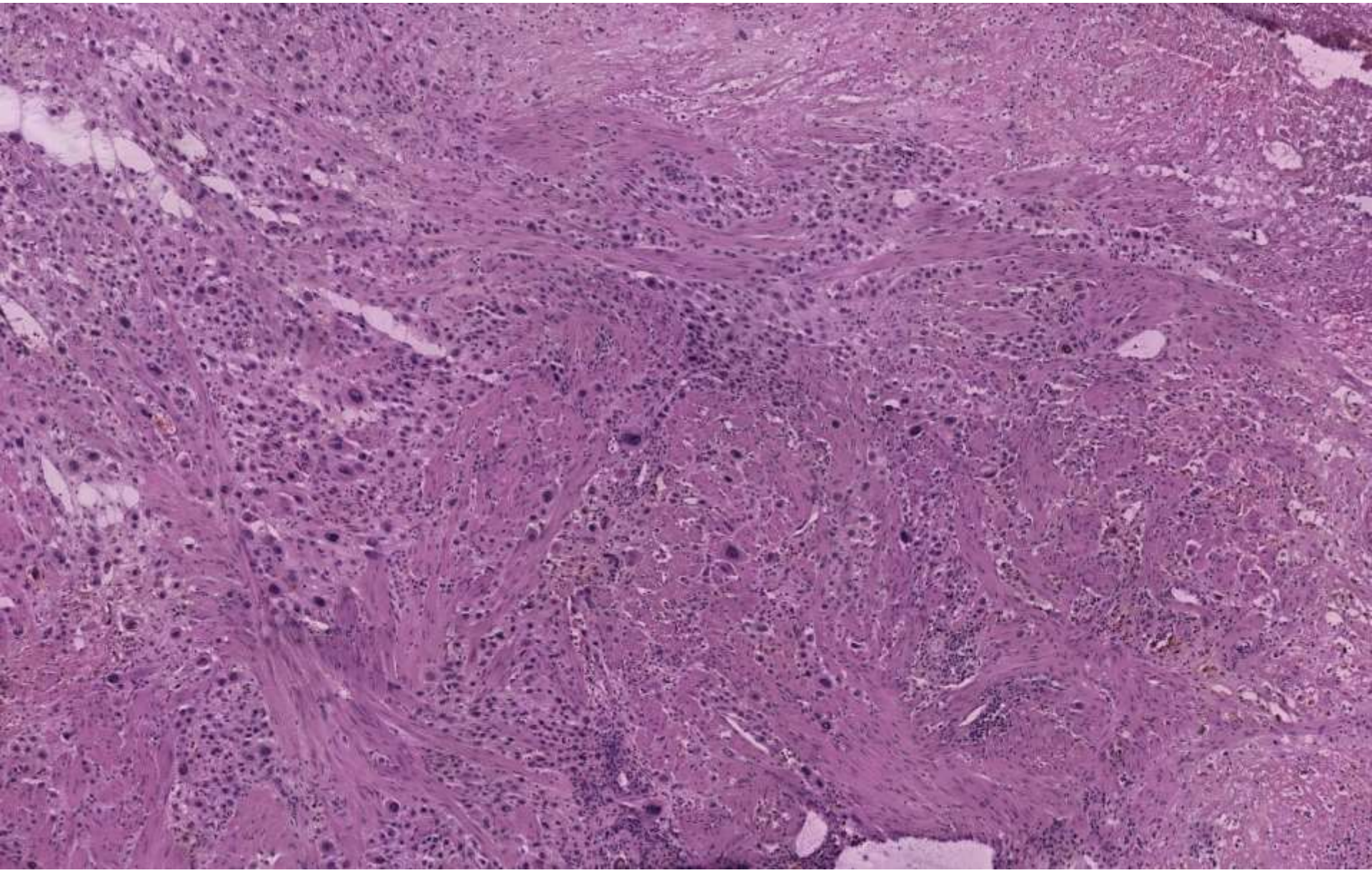
Charles Lombard; El Camino Hospital

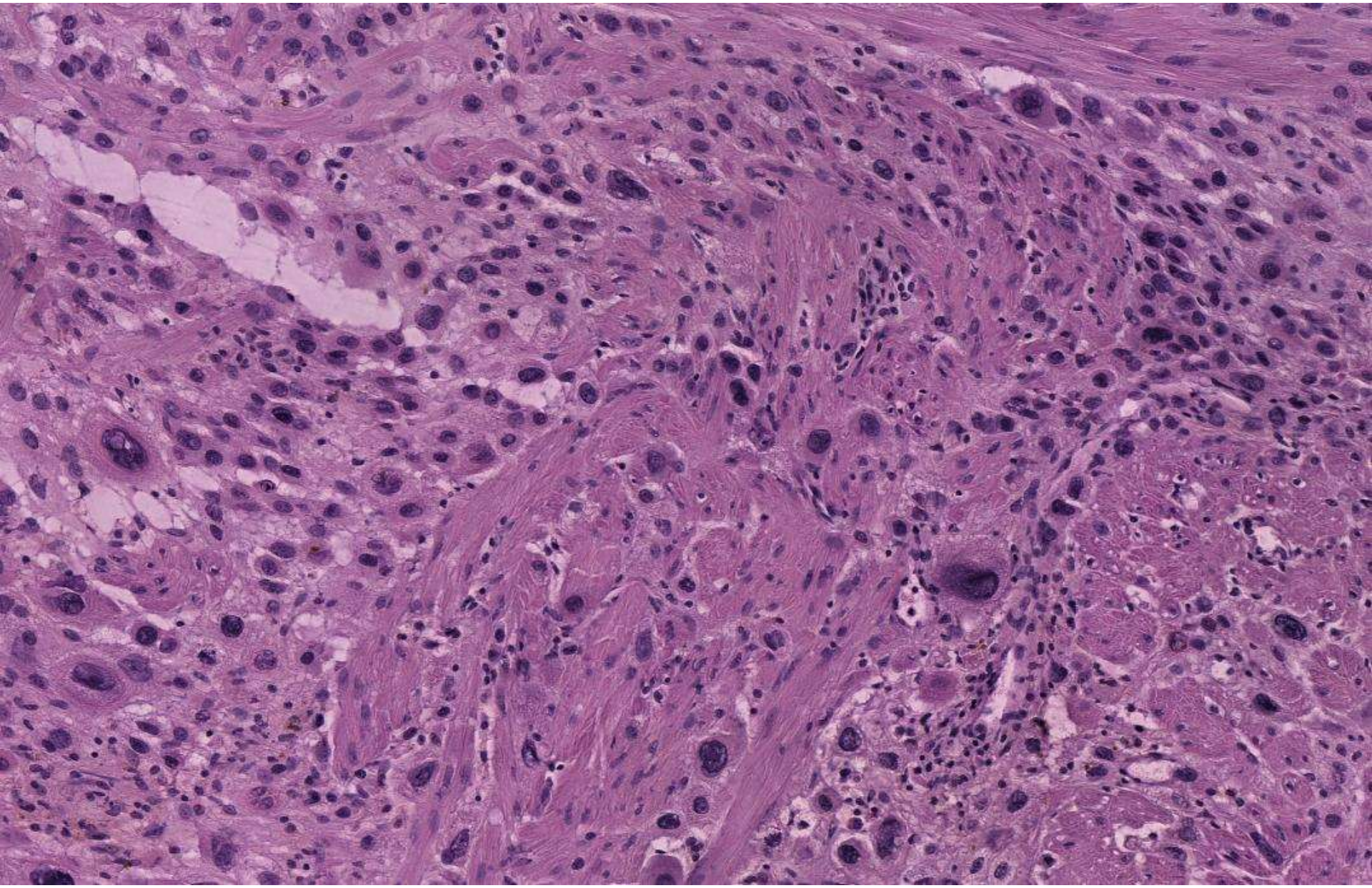
37-year-old female undergoes total hystrectomy for thickened endometrium. Intraoperative frozen section performed.

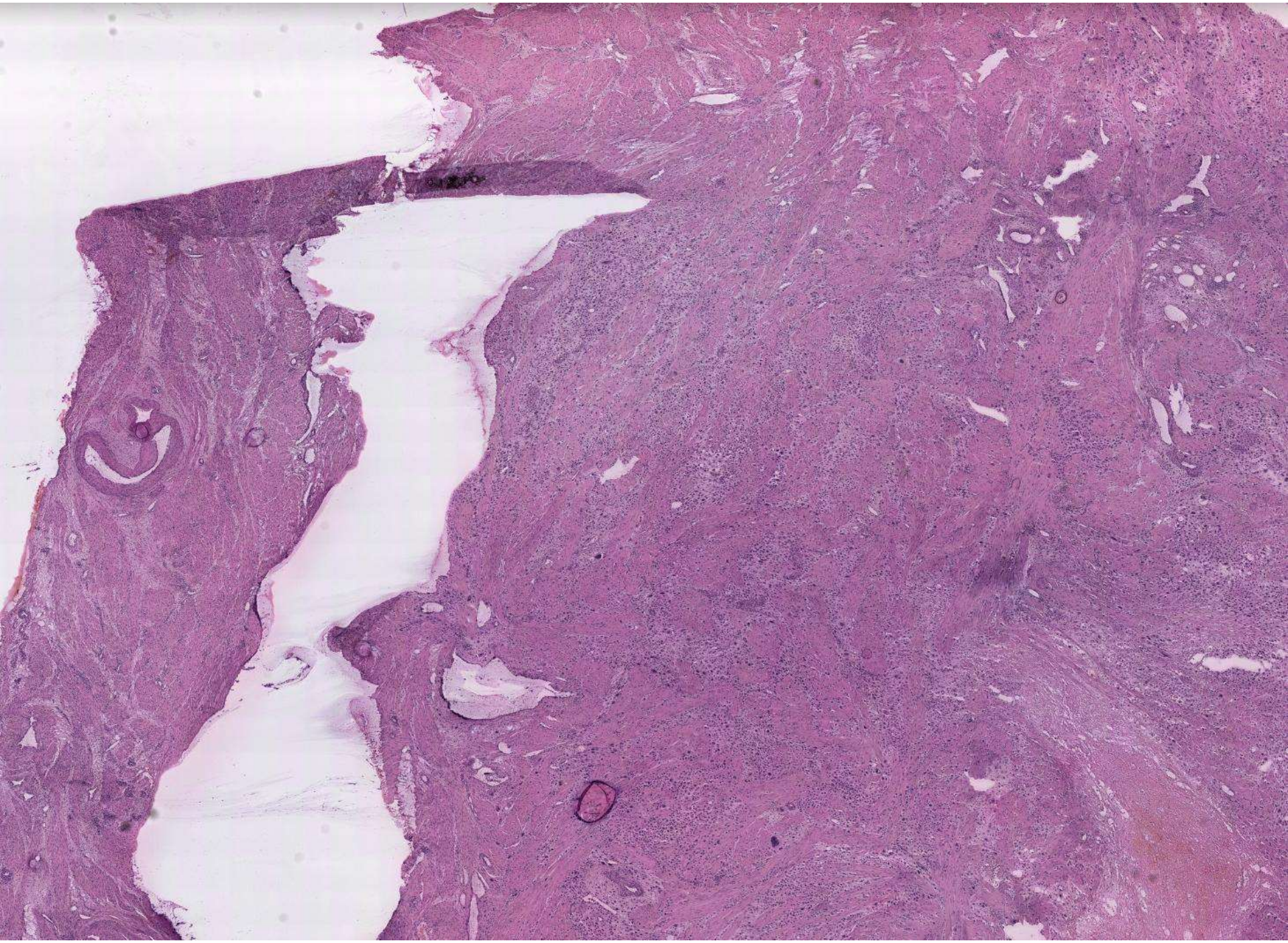


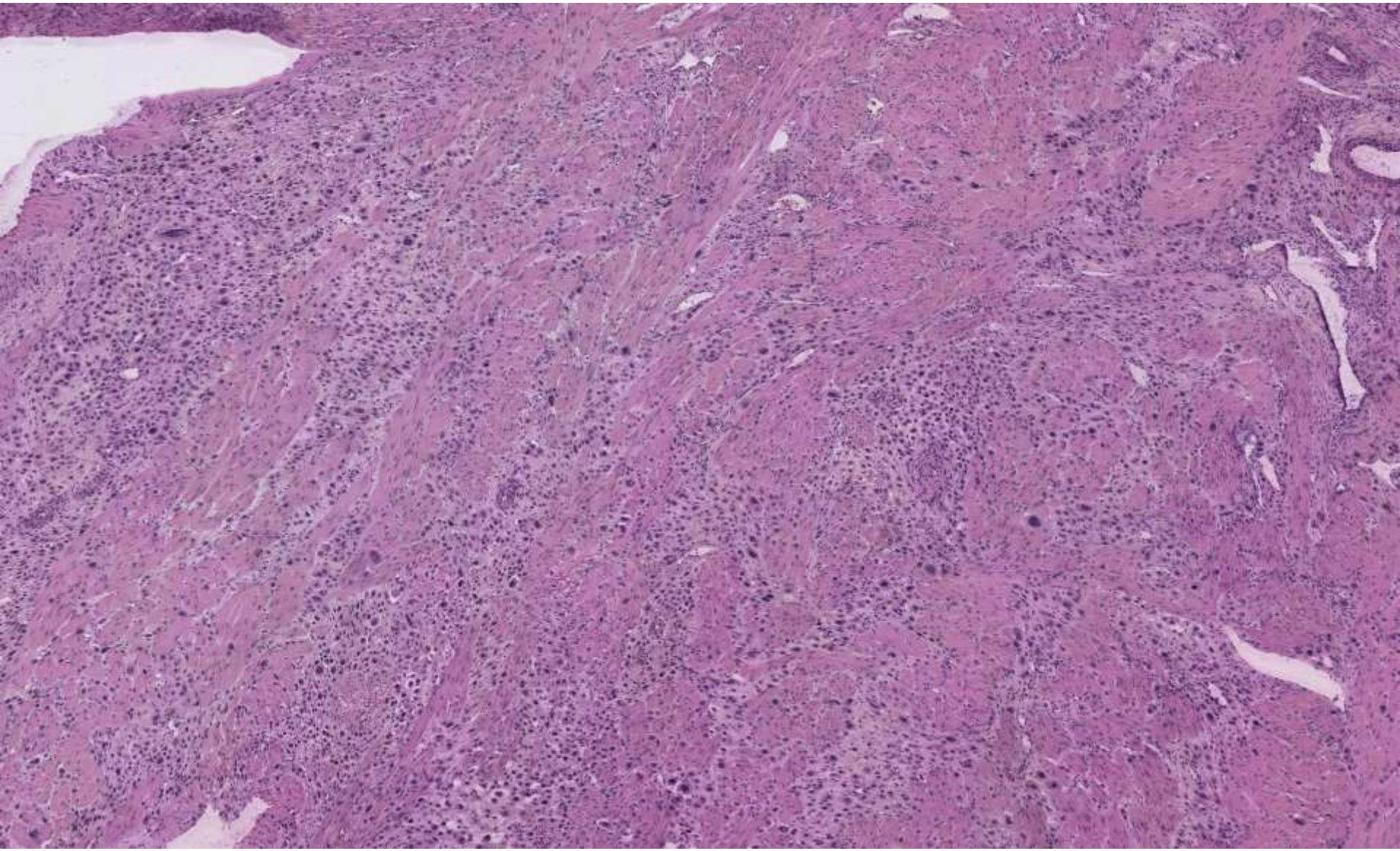


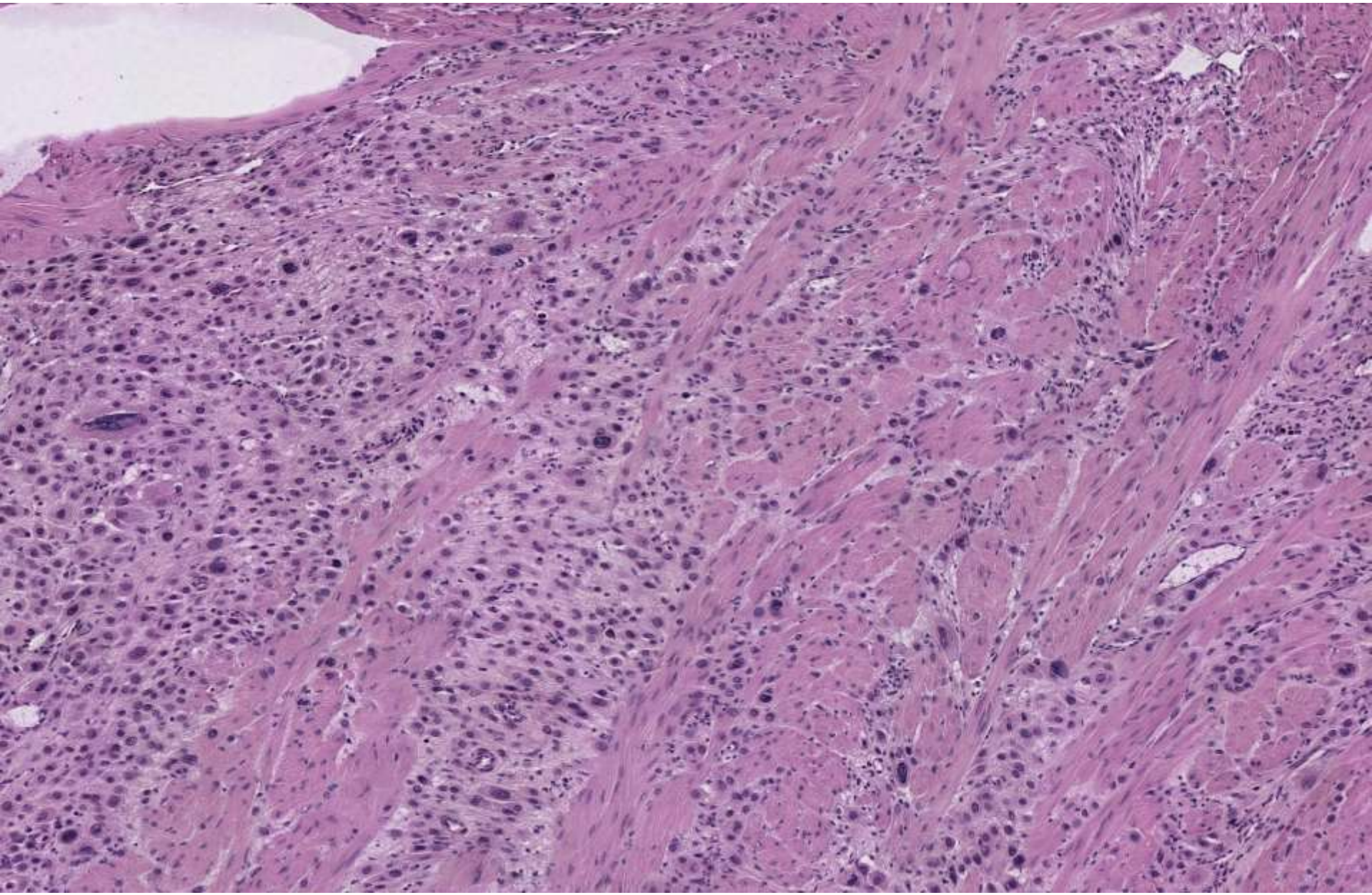


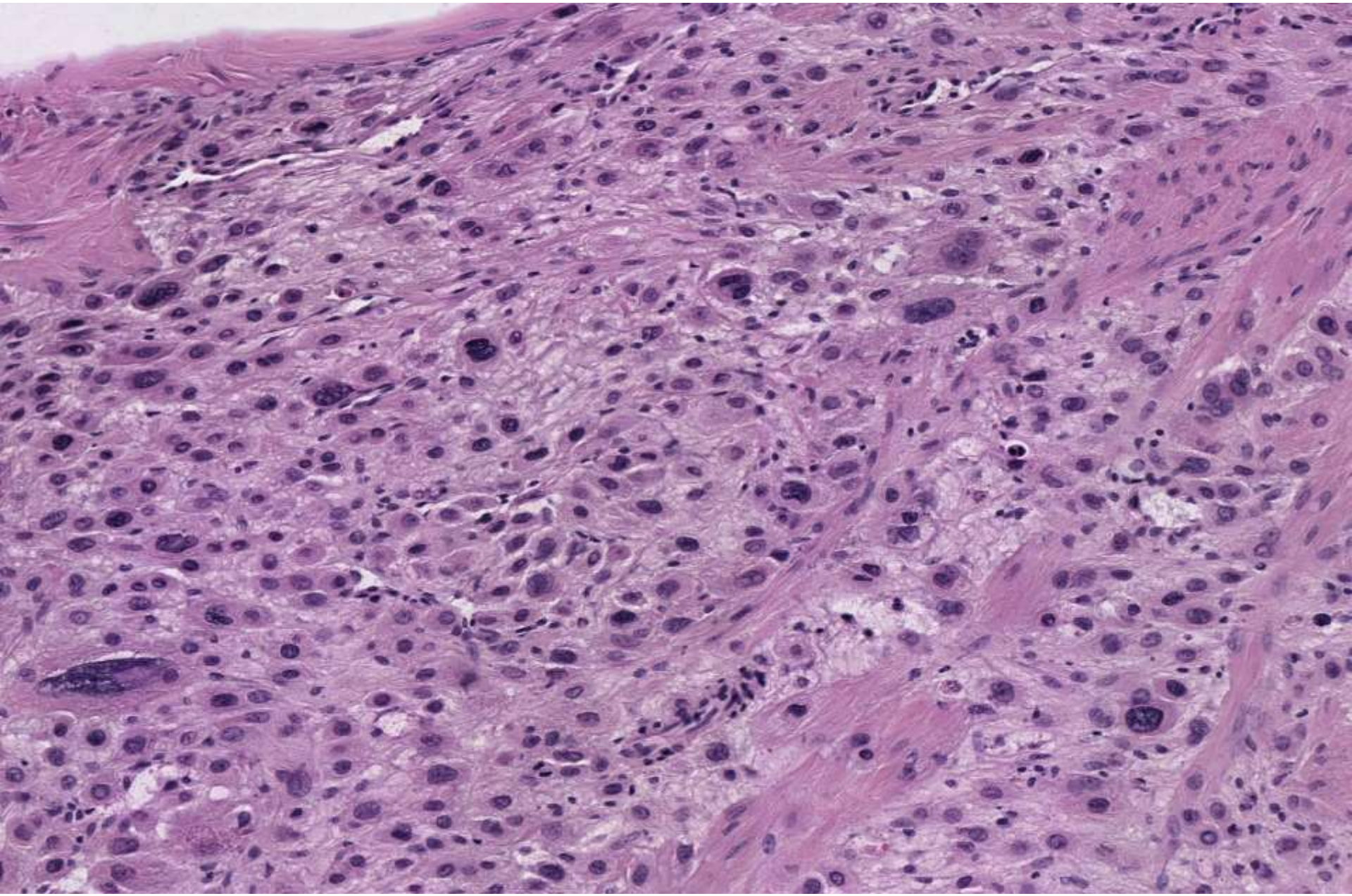


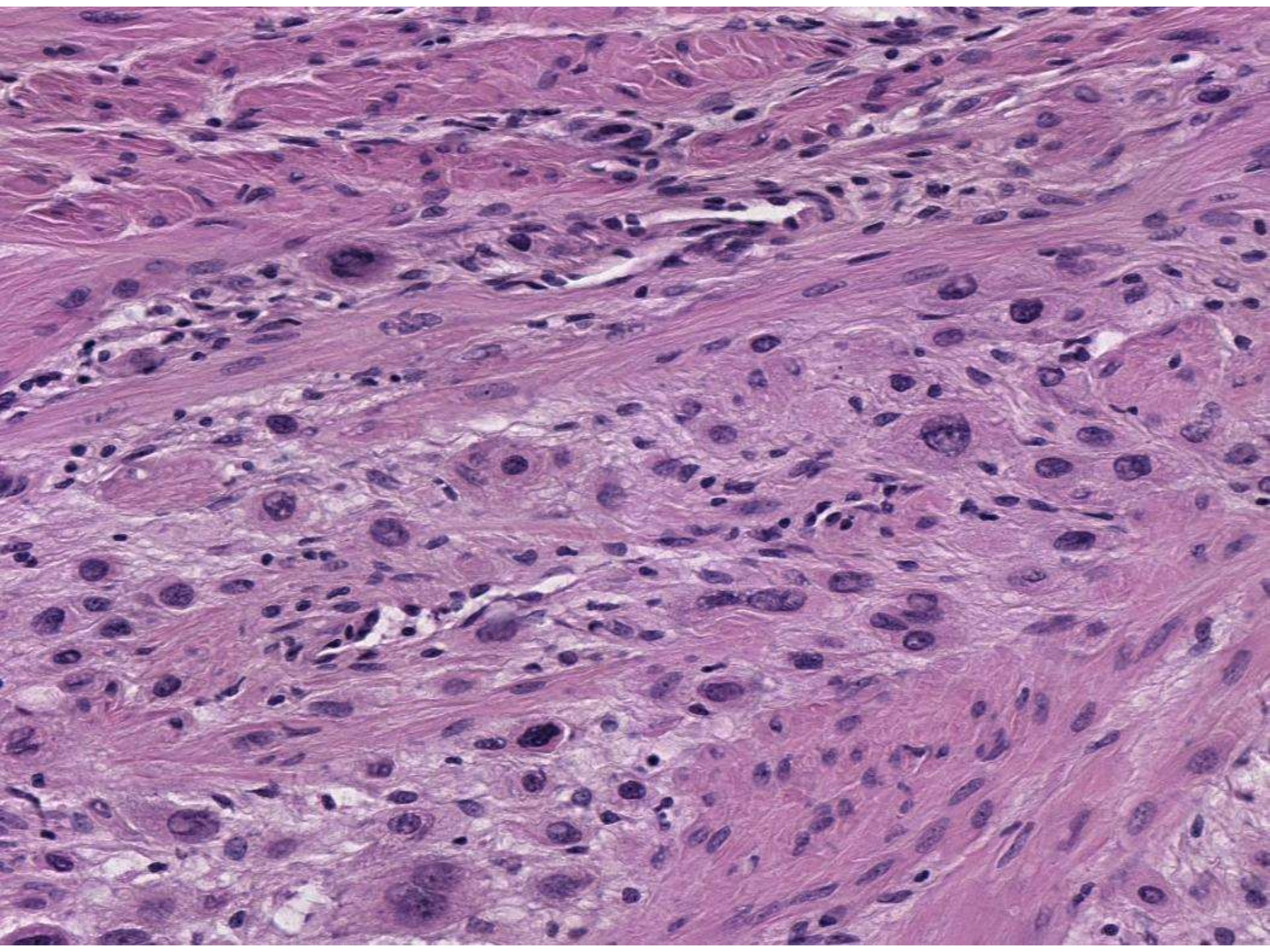






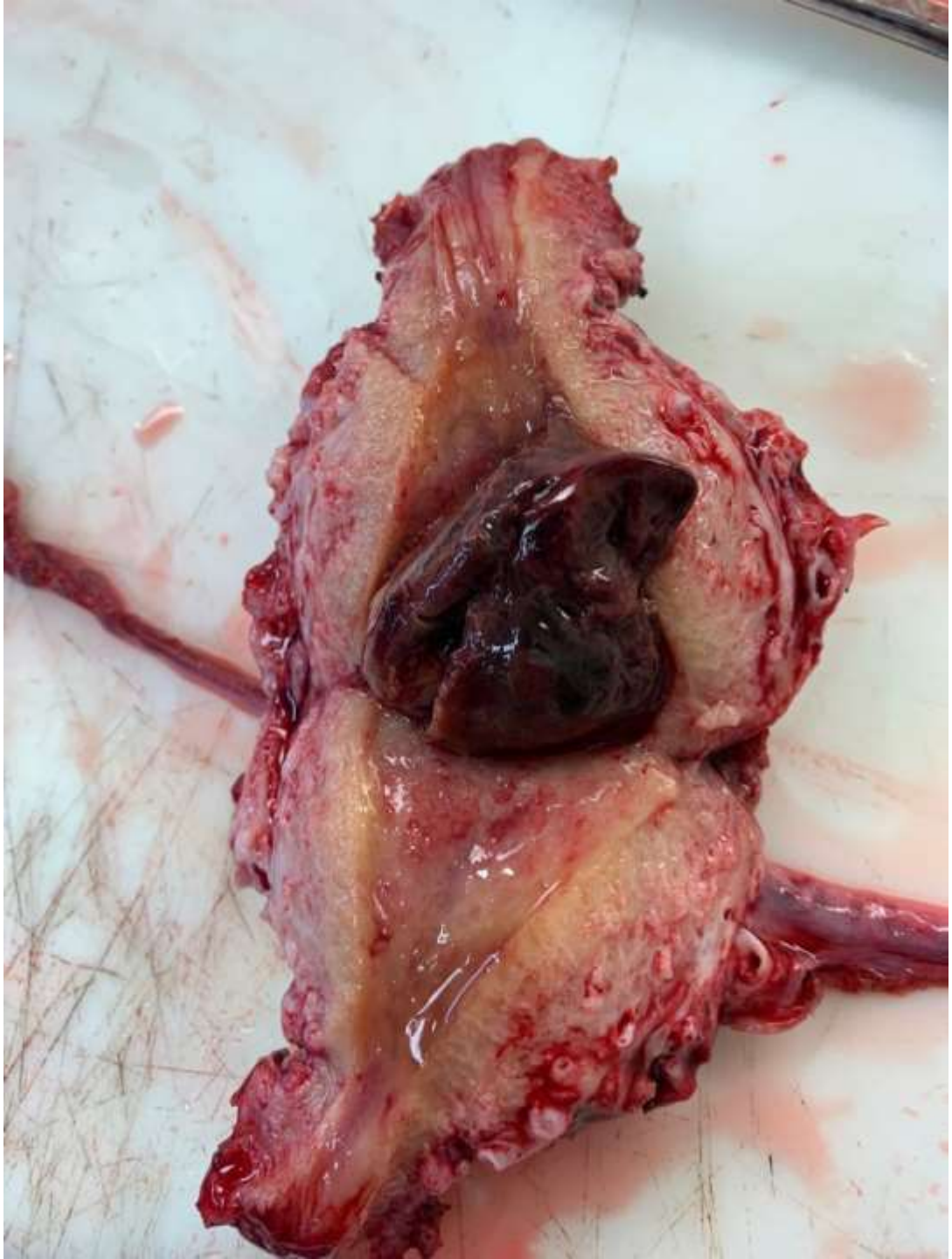


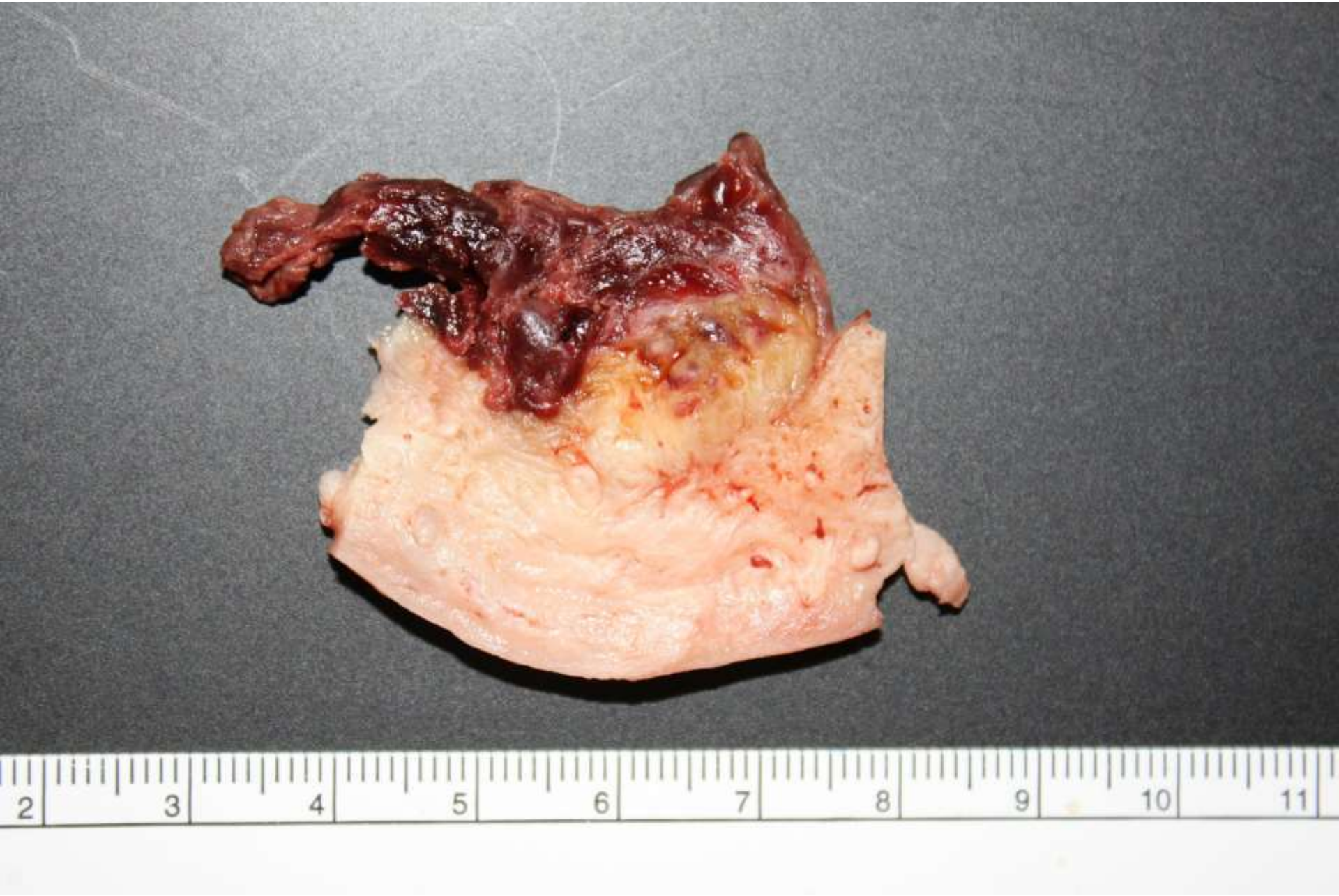




Clinical History

- Pt had NSVD 8 months previously
- Has vaginal discharge starting 4 months post delivery (?? BV clinical dx)
- Resumed menstuation 4-5 months pp
- D/C for ?? Retained placental tissue just prior to hysterectomy at which time PSTT was diagnosed

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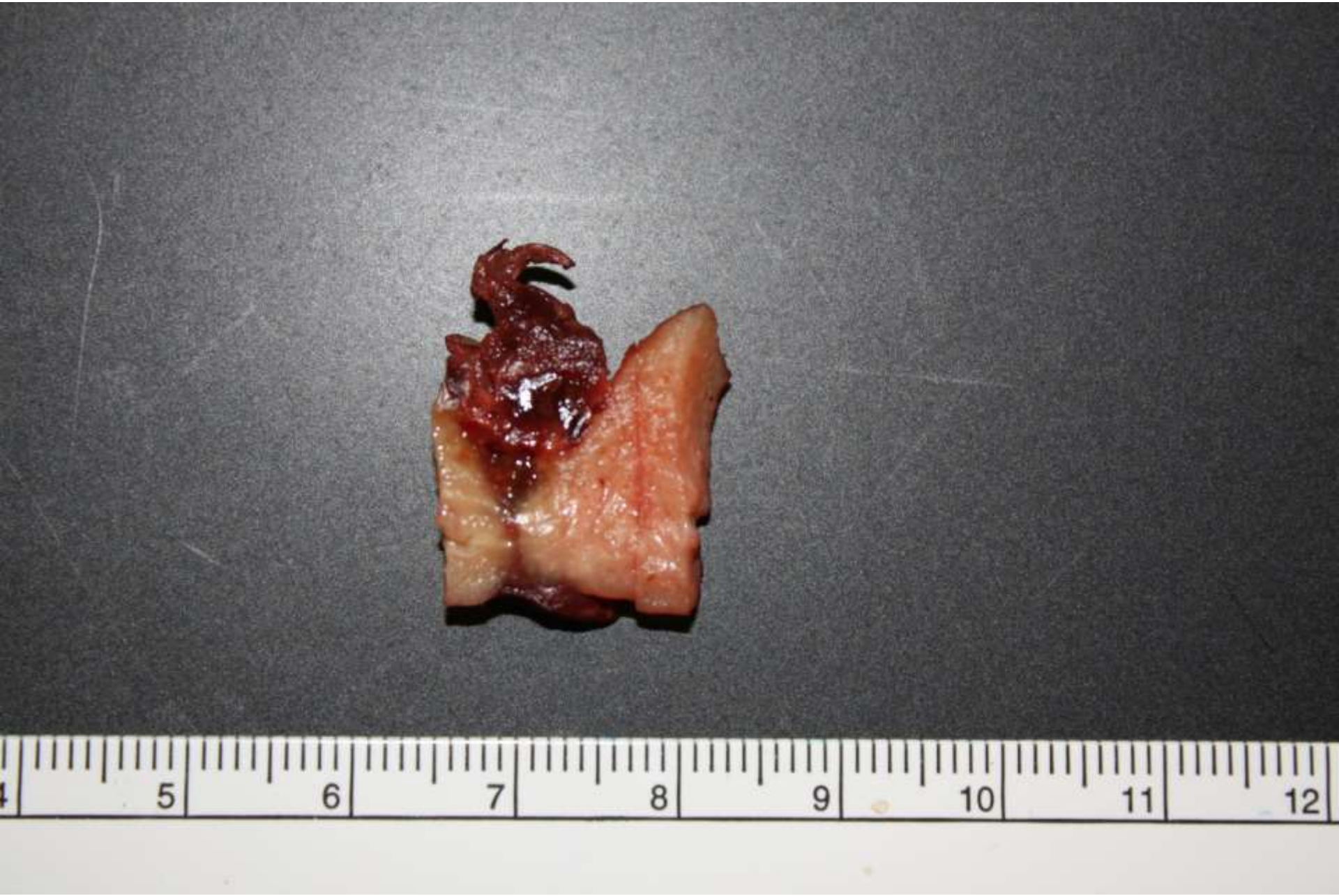
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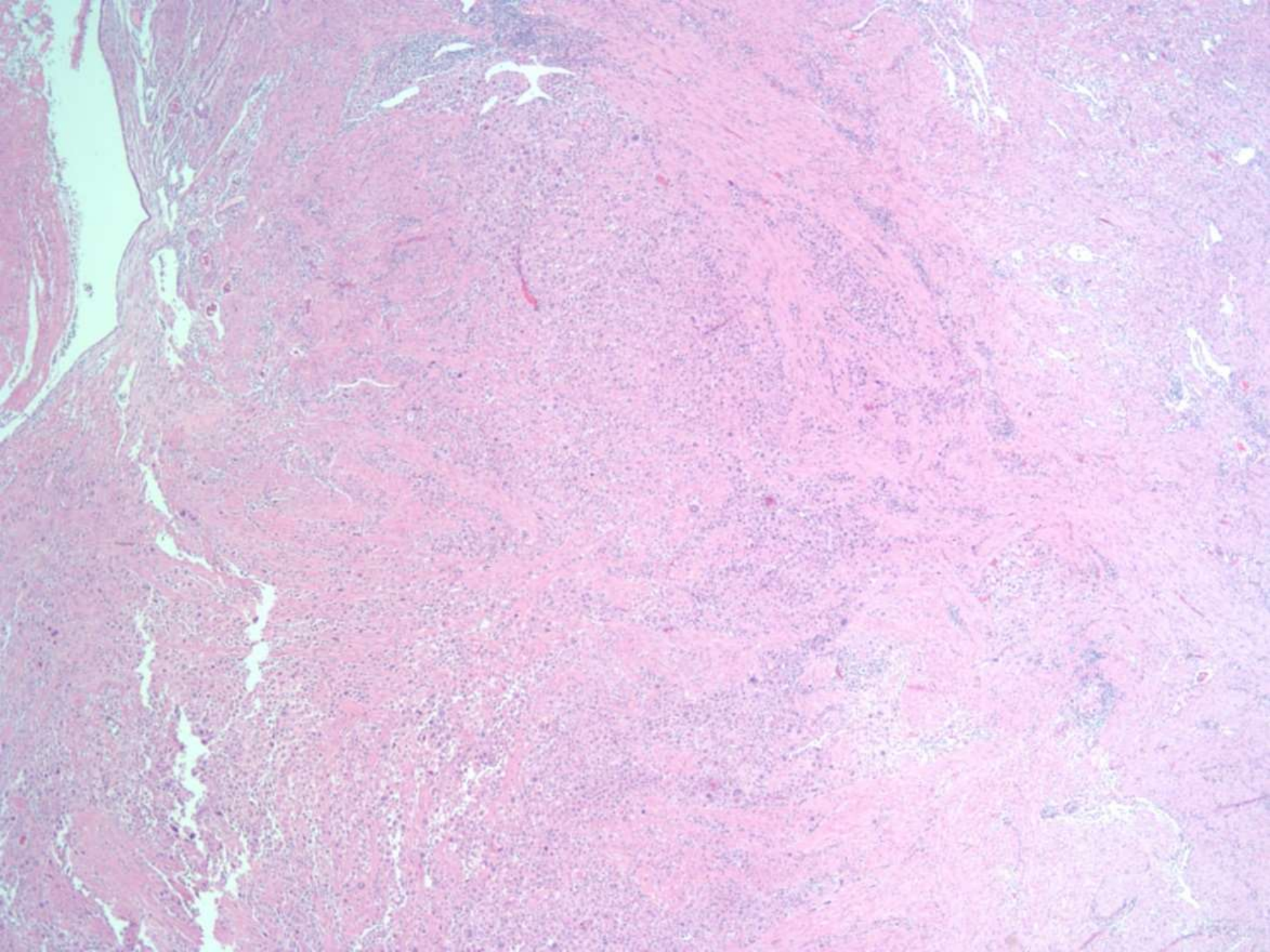
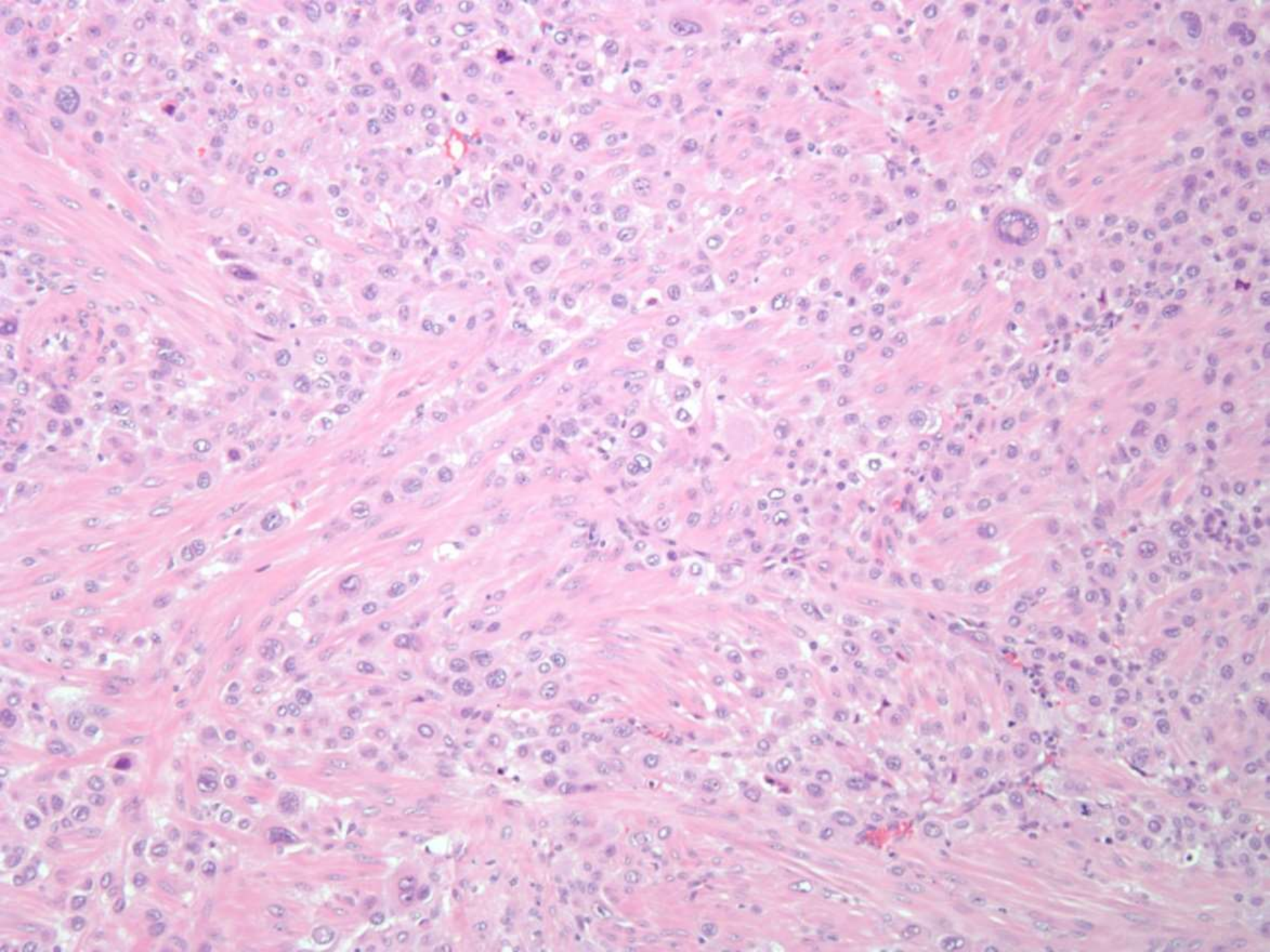
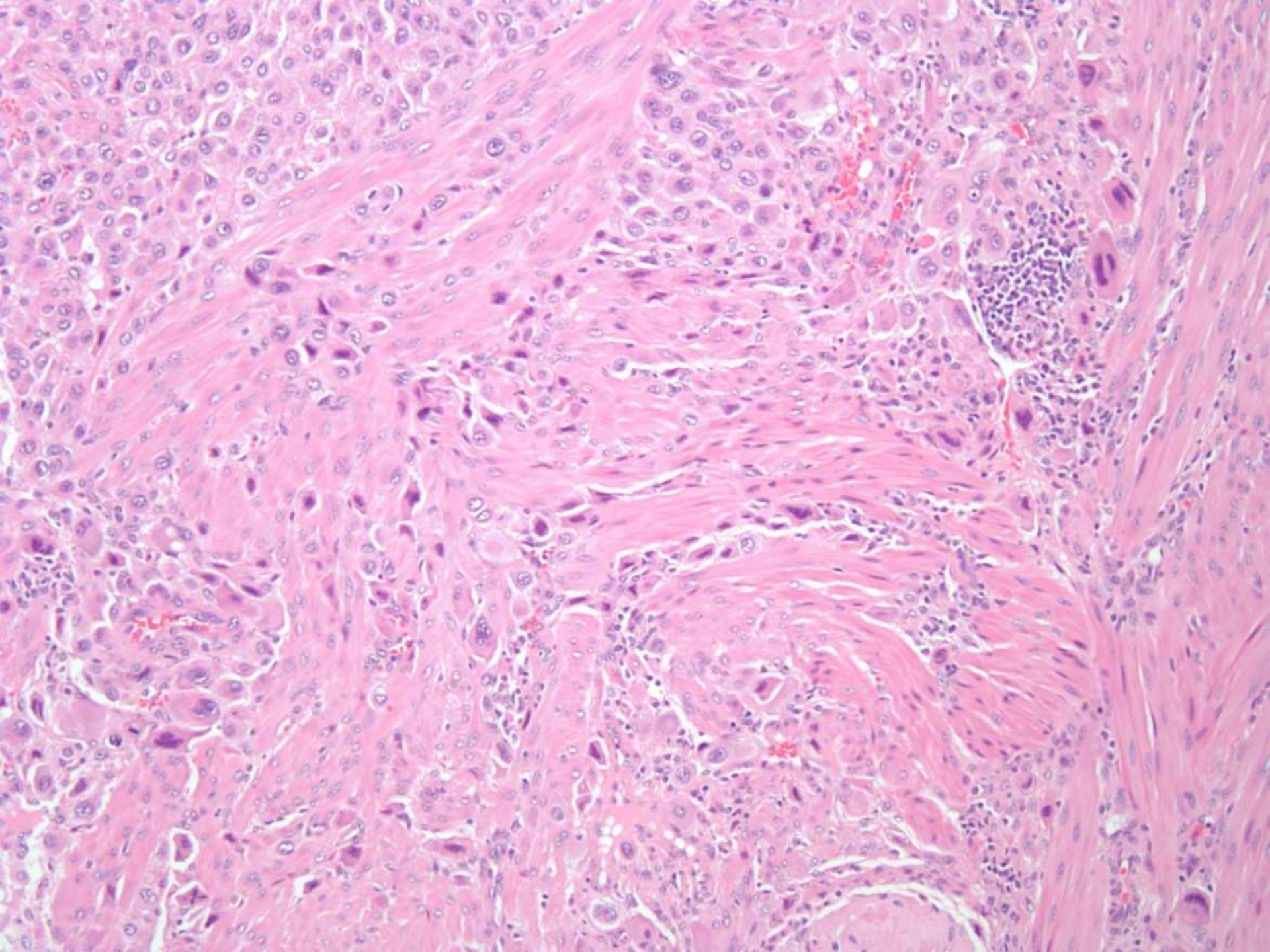
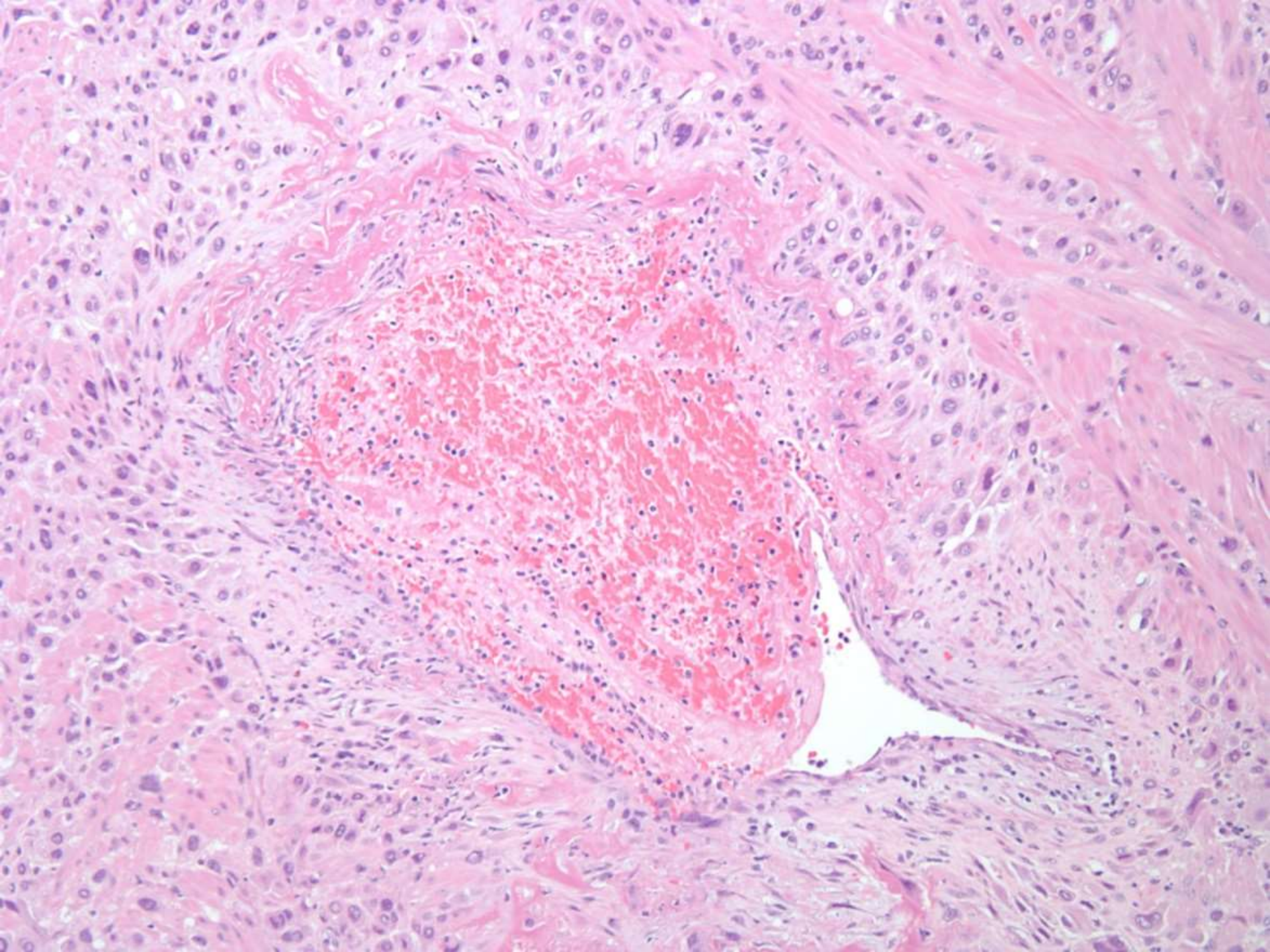
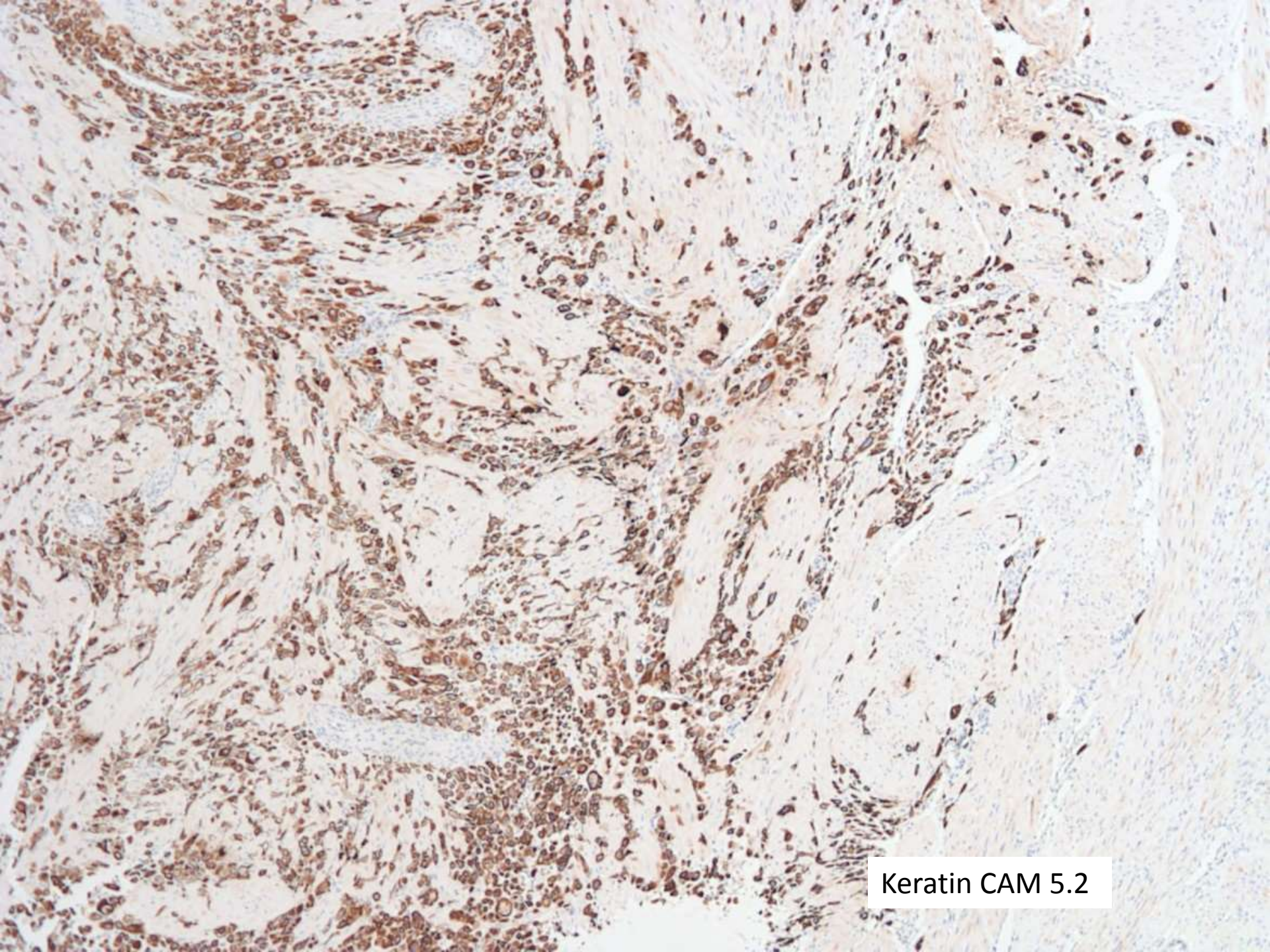
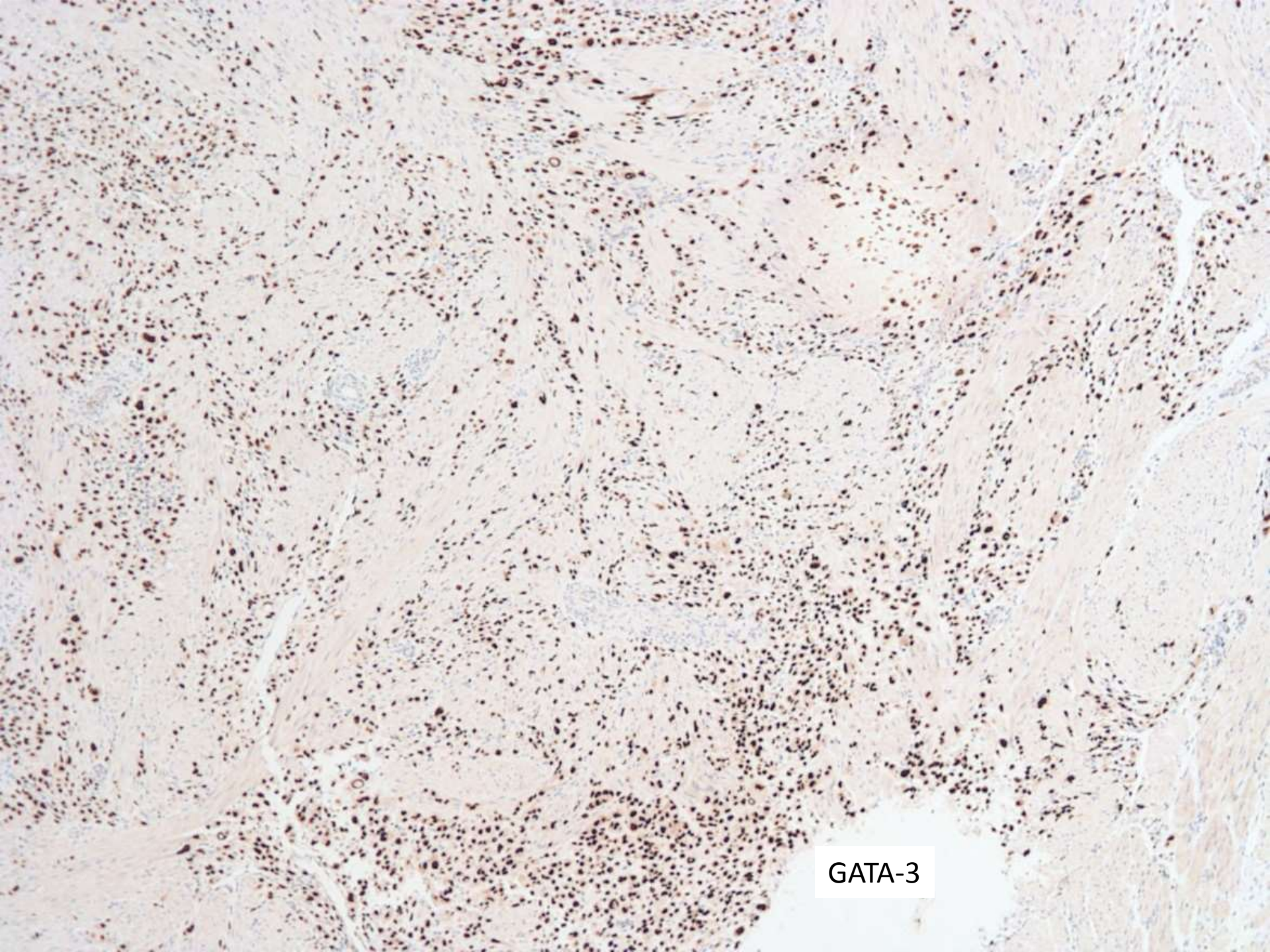


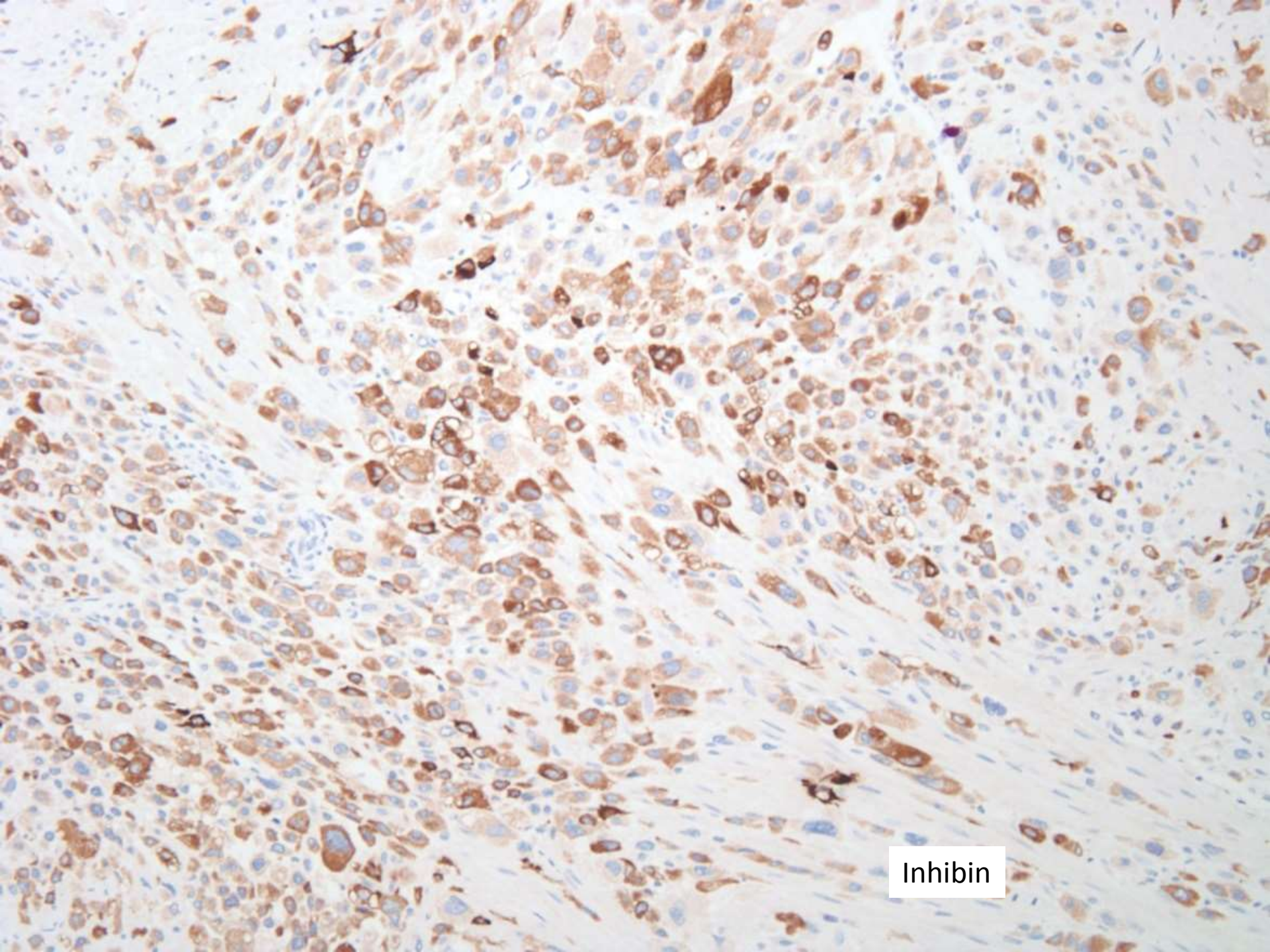







Keratin CAM 5.2


GATA-3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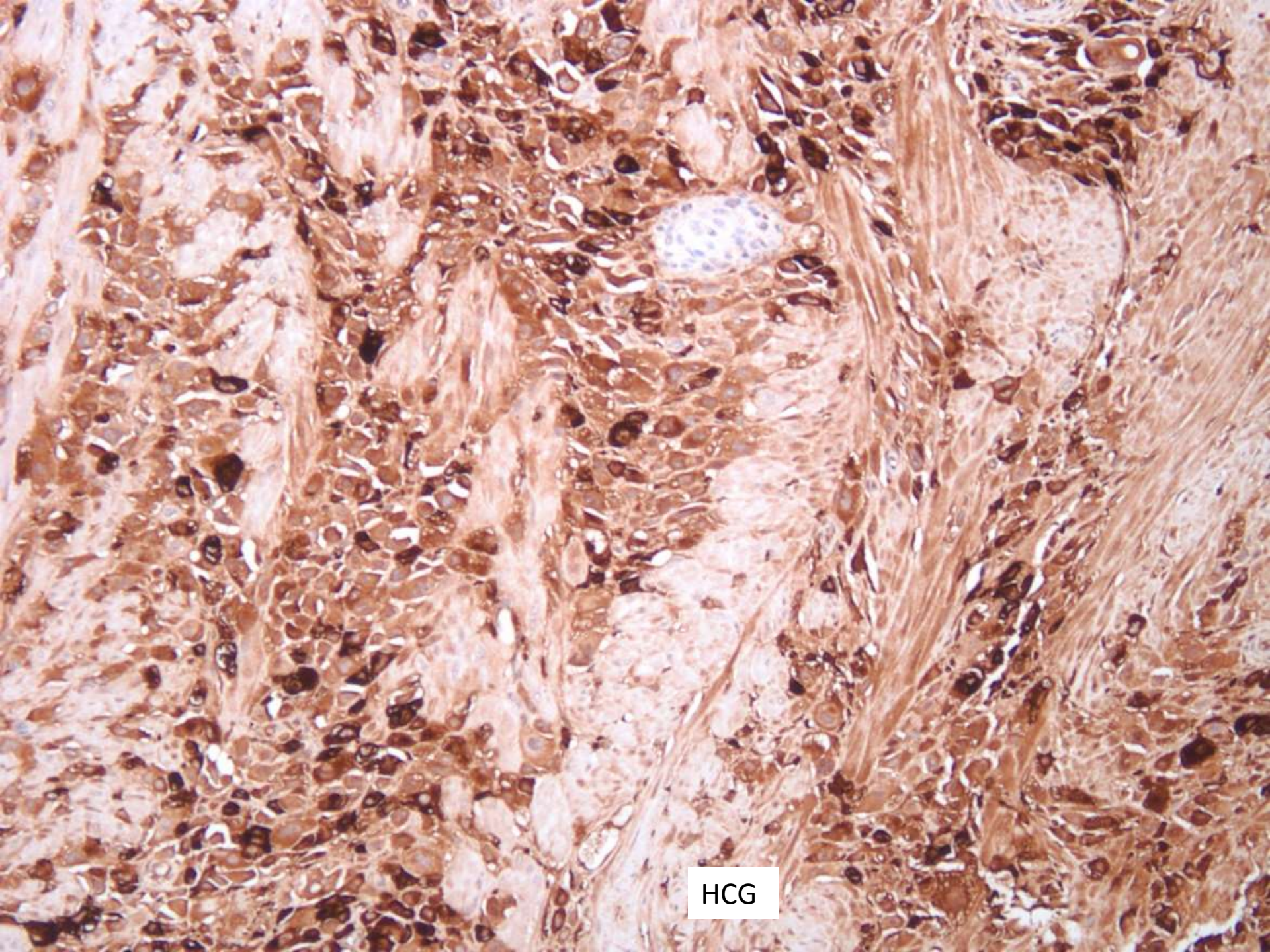
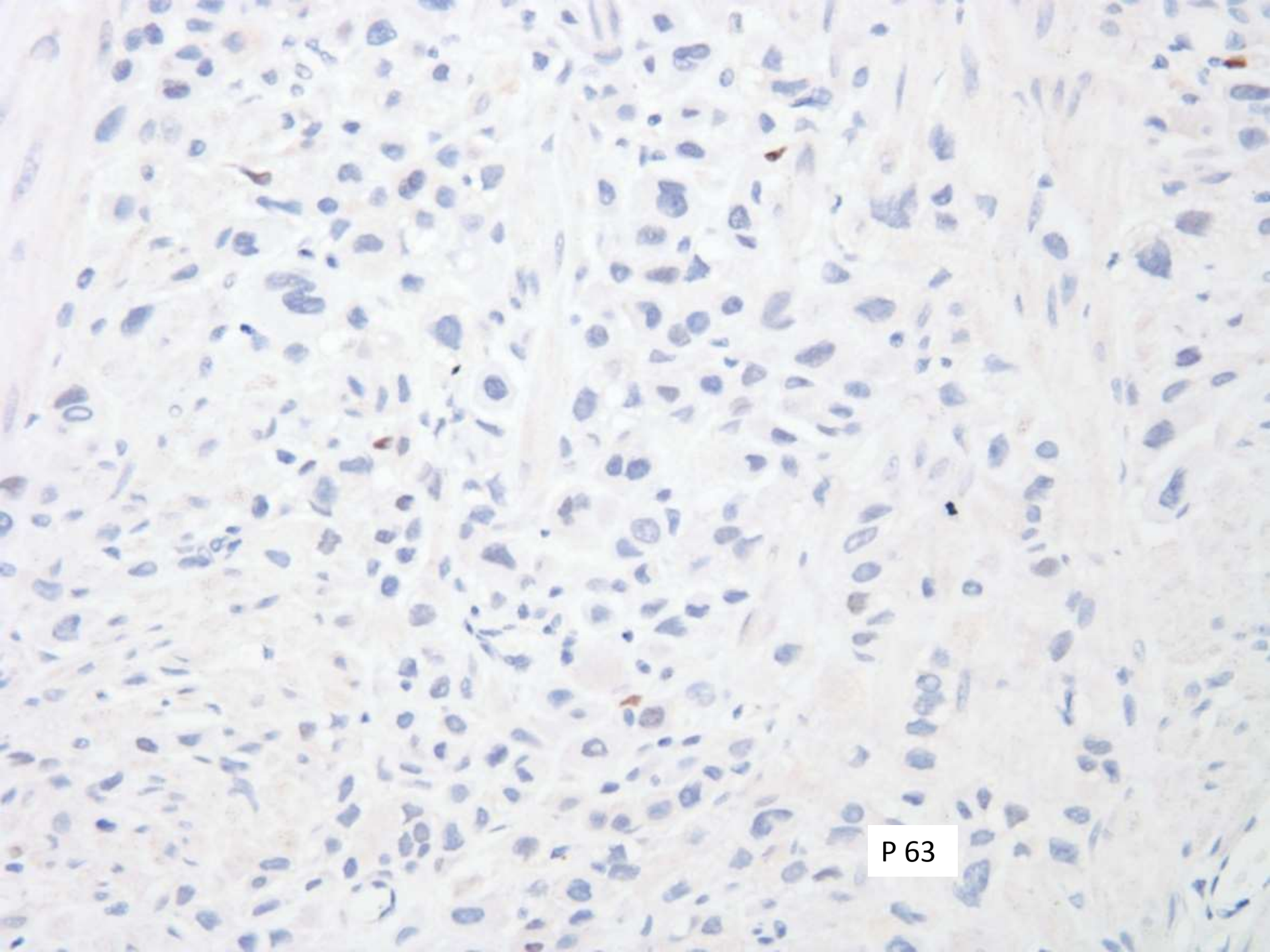

HCG


P 63

PSTT

- A neoplasm of implantation site intermediate trophoblasts.
- Rare; < 3% of gestational trophoblastic disease cases.
- Can occur after normal pregnancy, spontaneous abortion, or molar pregnancy
- B-HCG levels are typically < 1,000
- Interval from gestation: 2 weeks-17 years (median 12-18 months)

PSTT– Gross features

- Tumor invades myometrium and may have a polypoid intralumenal growth pattern
- Hemorrhage and necrosis are common
- May extend through myometrium to the serosa and invade the adnexal tissues

PSTT– microscopic features

- Sheets of polygonal to spindle shaped intermediate trophoblast
  - Cells may exhibit marked atypia with large convoluted hyperchromatic nuclei and eosinophilic to clear cytoplasm
  - Infiltrate and splay myometrial fibers
  - Chorionic villi are not usually identified
    - Recent pregnancy within weeks
    - Need to exclude exaggerated implantation site and invasive mole

PSTT-- IHC

- Positive for: hPL, MUC4, CD 146
- Postive for: Gata-3, Inhibin
- HCG can show focal positive staining
- P63: Negative
- PLAP: Negative
- Ki-67: 10-30%

PSTT– molecular/cytogenetics

- Complex karyotype with lack of recurrent molecular aberrations
- Lack of Y-chromosome suggests preferential requirement of the paternaly derived X chromosome in the pathogenesis of PSTT

PSTT-- DDX

- Choriocarcinoma
  - Biphasic cyto/syncytiotrophoblastic proliferation
  - Strong diffuse HCG staining
- Epithelioid Trophoblastic Tumor
  - Nodular expansile growth
  - Geographic necrosis, ca++, hyaline change
  - P63 positive
- Exaggerated placental site nodule
  - Recent pregnancy
  - Absence vascular invasion, necrosis, mitosis
  - Absence of confluent trophoblastic growth
- Epithelioid SMT, Poorly differentiated carcinoma, Melanoma
  - Differential morphologies and distinct IHC staining patterns

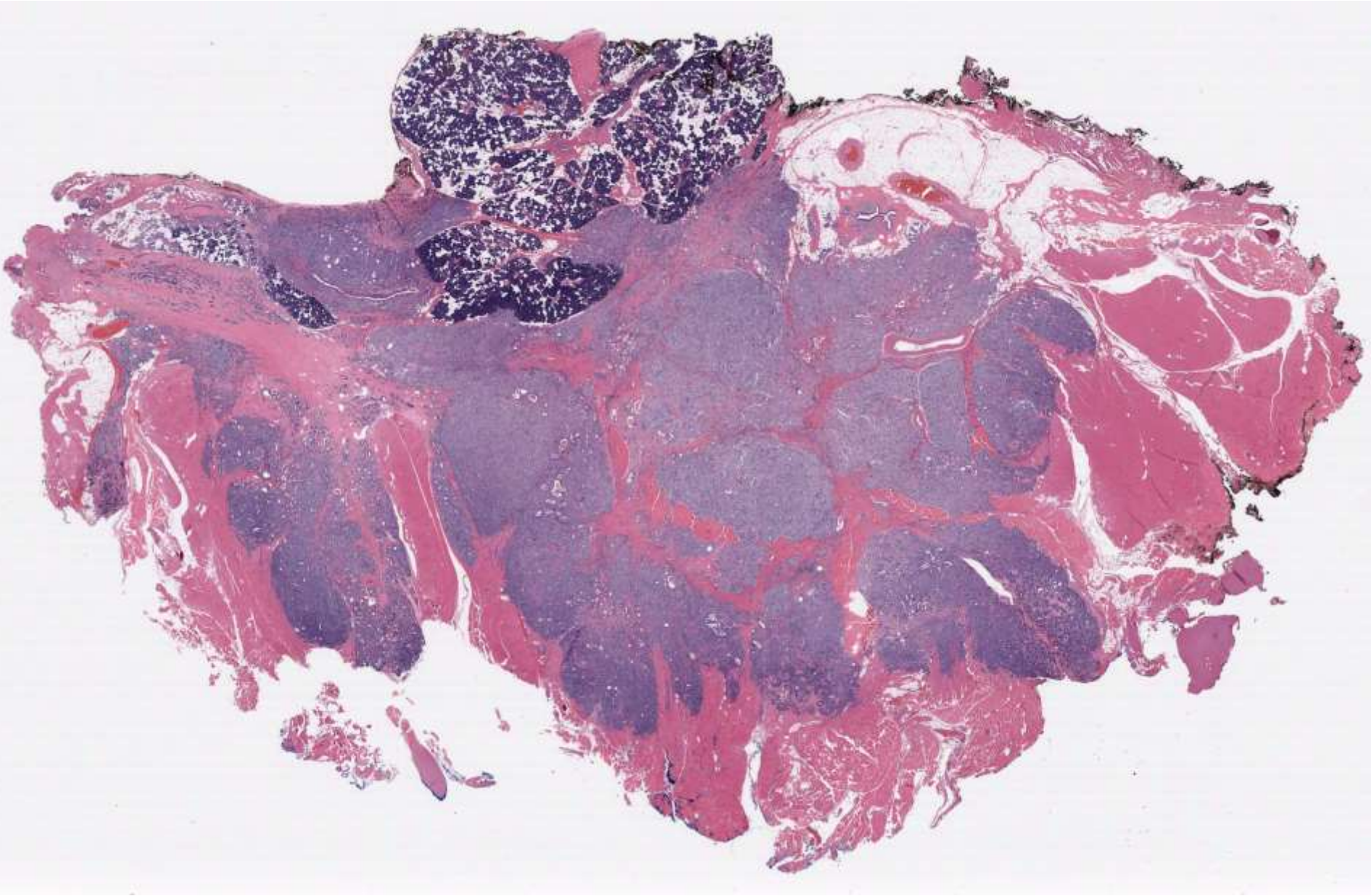
PSTT—treatment/prognosis

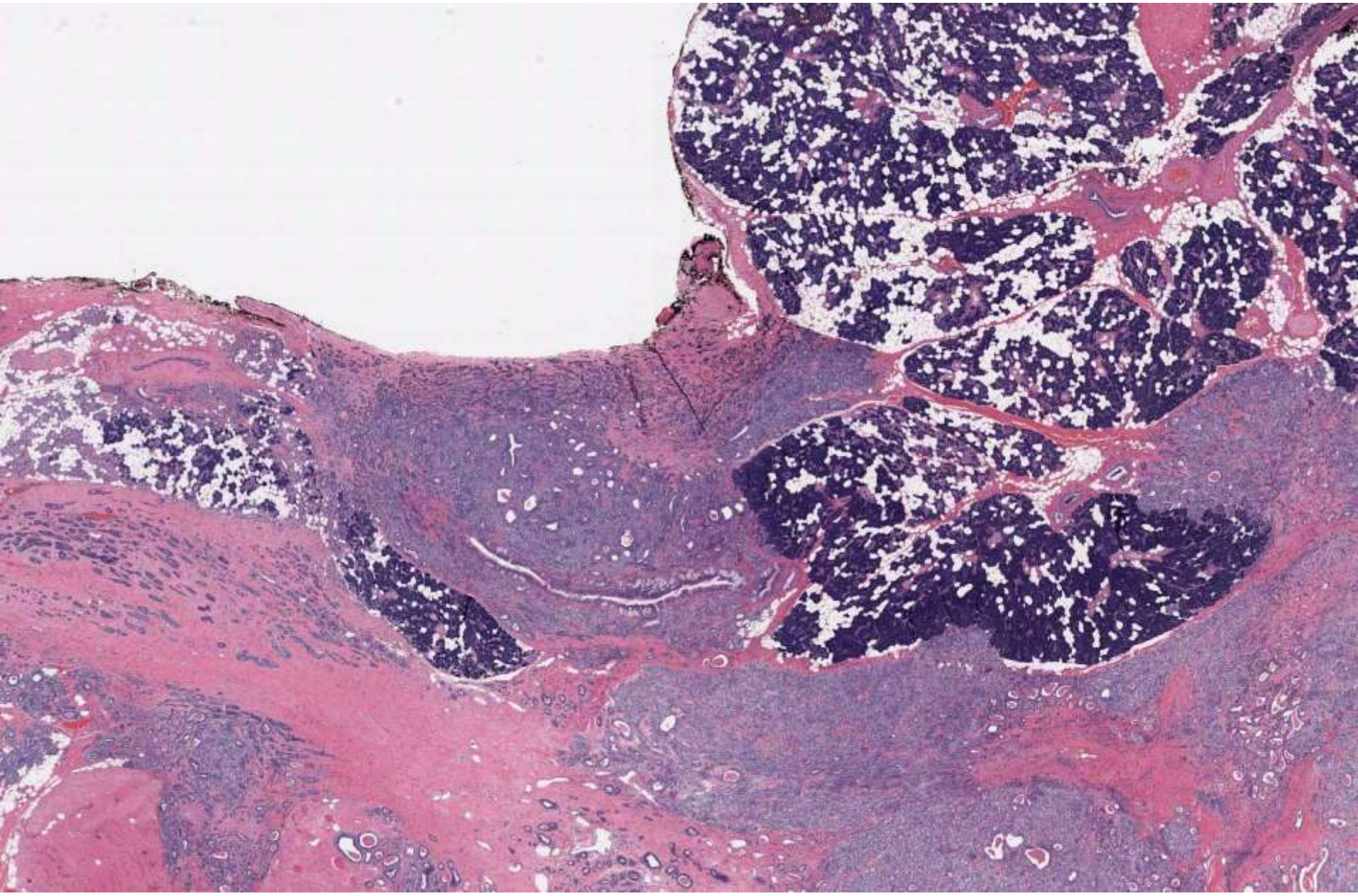
- Hysterectomy is curative in most patients
  - Chemotherapy for metastasis/recurrences
- 25% may develop recurrence
- 15% die of disease
- 10-15% are clinically malignant and fail to respond to intensive chemotherapy
- Adverse prognostic features:
  - Advanced FIGO stage
  - Tumor size > 3 cm
  - Invasion > 50% through myometrium
  - Antecedent pregnancy of 48 months or more
  - Tumor cells with clear cytoplasm
  - High mitotic rate(> 5/10 hpf)
  - Extensive necrosis
  - P53 expression

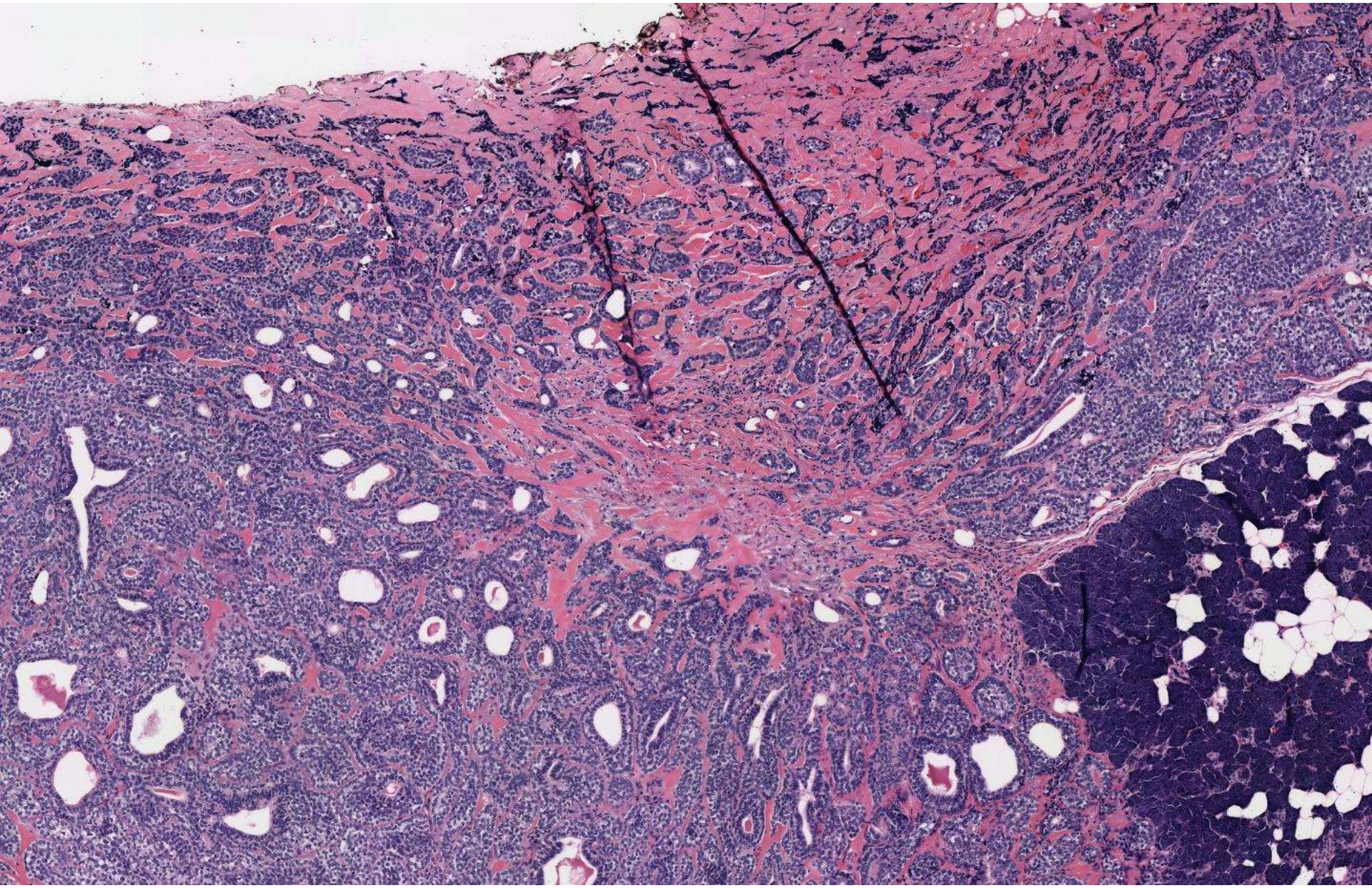
19-0402
(scanned slide available)

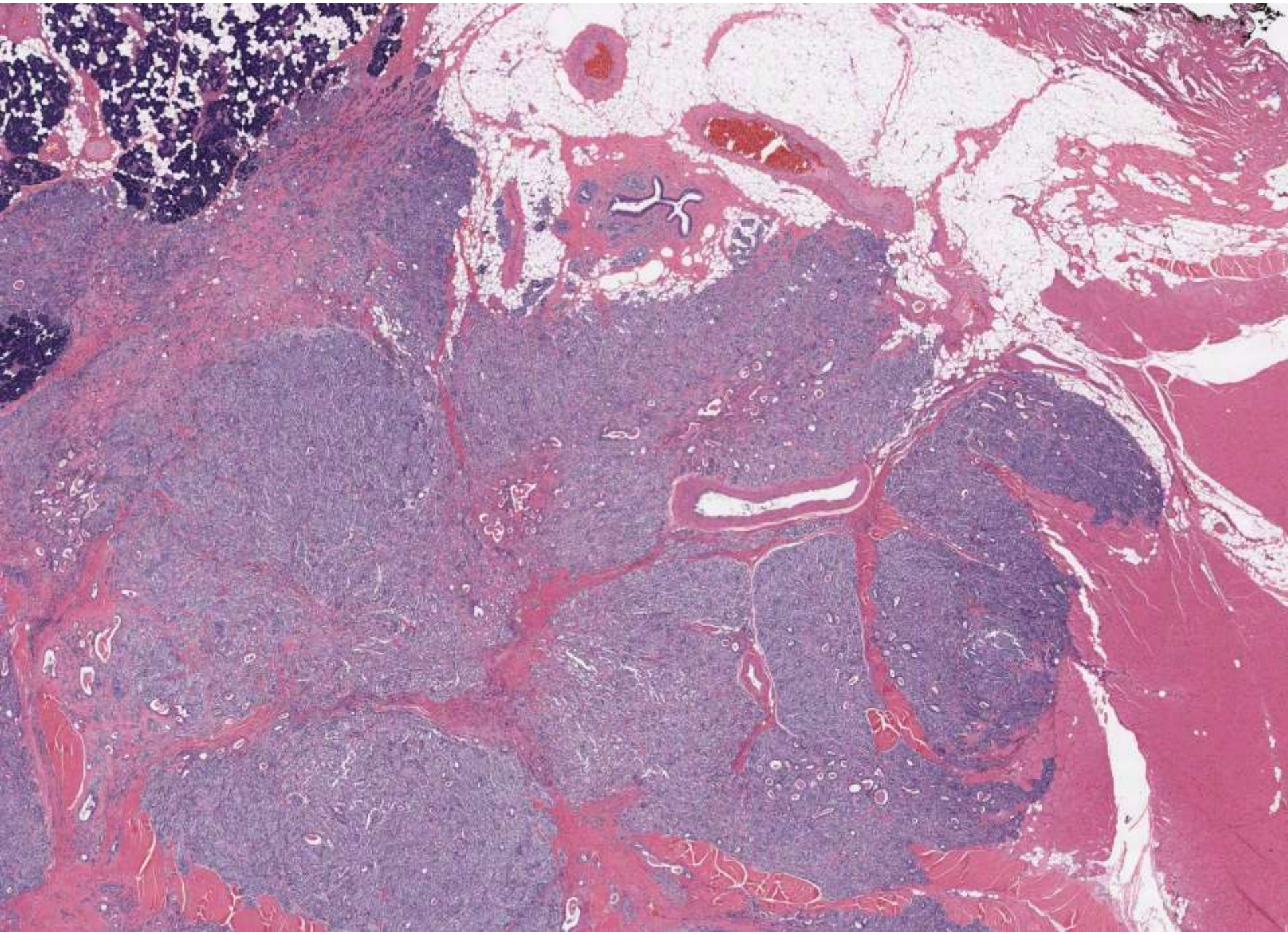
Balaram Puligandlia; Kaiser Oakland

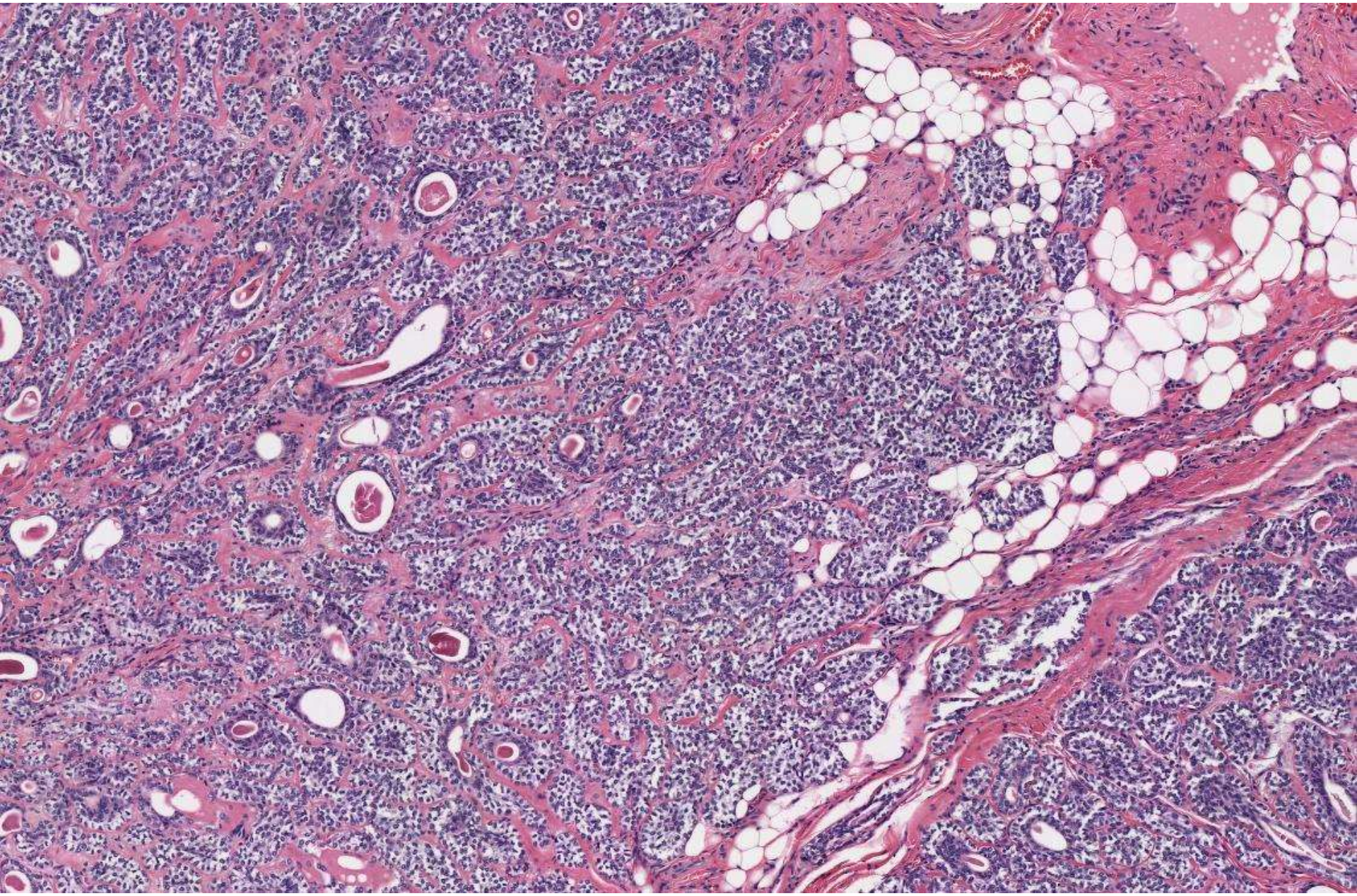
62-year-old male with right parotid mass.

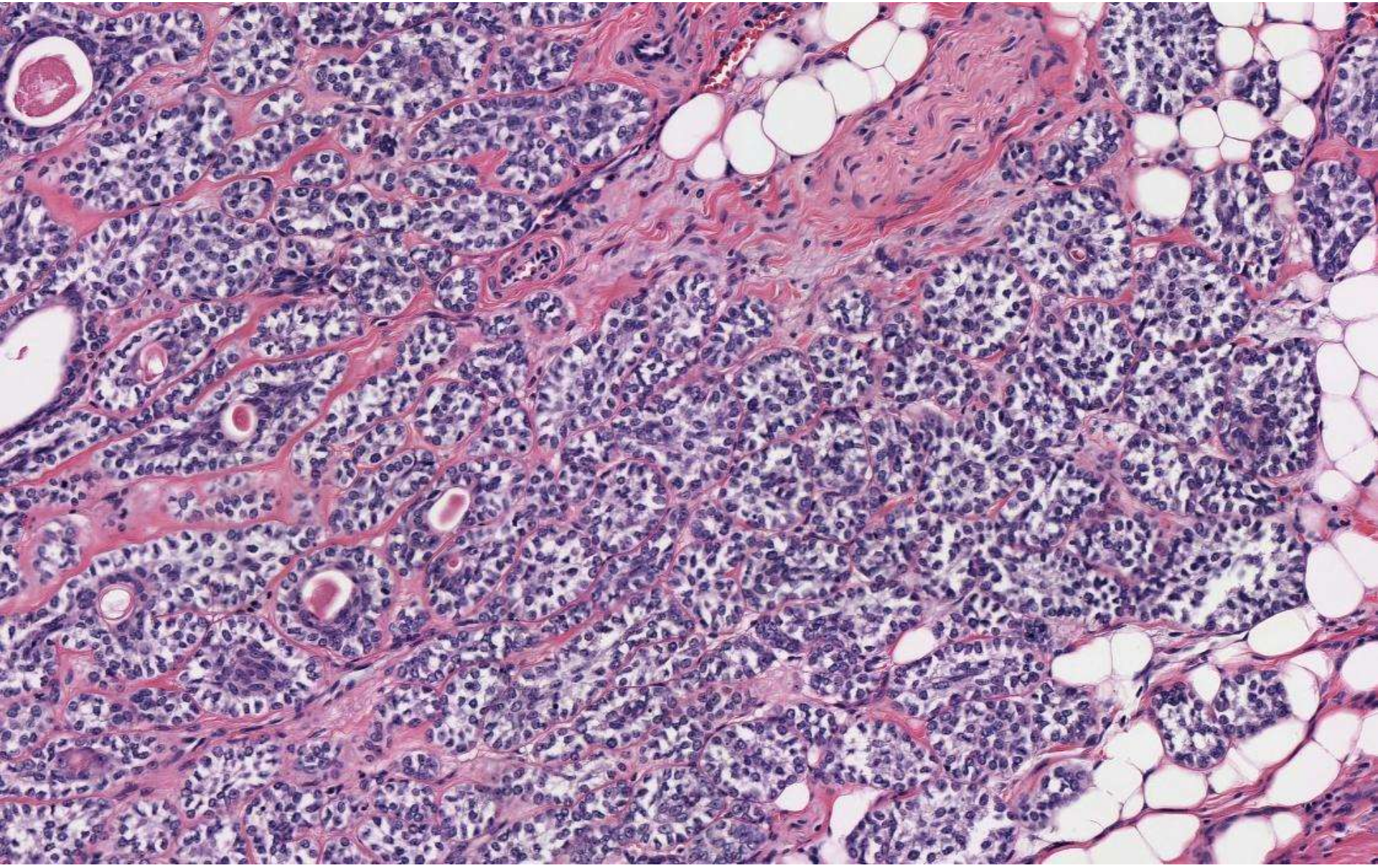


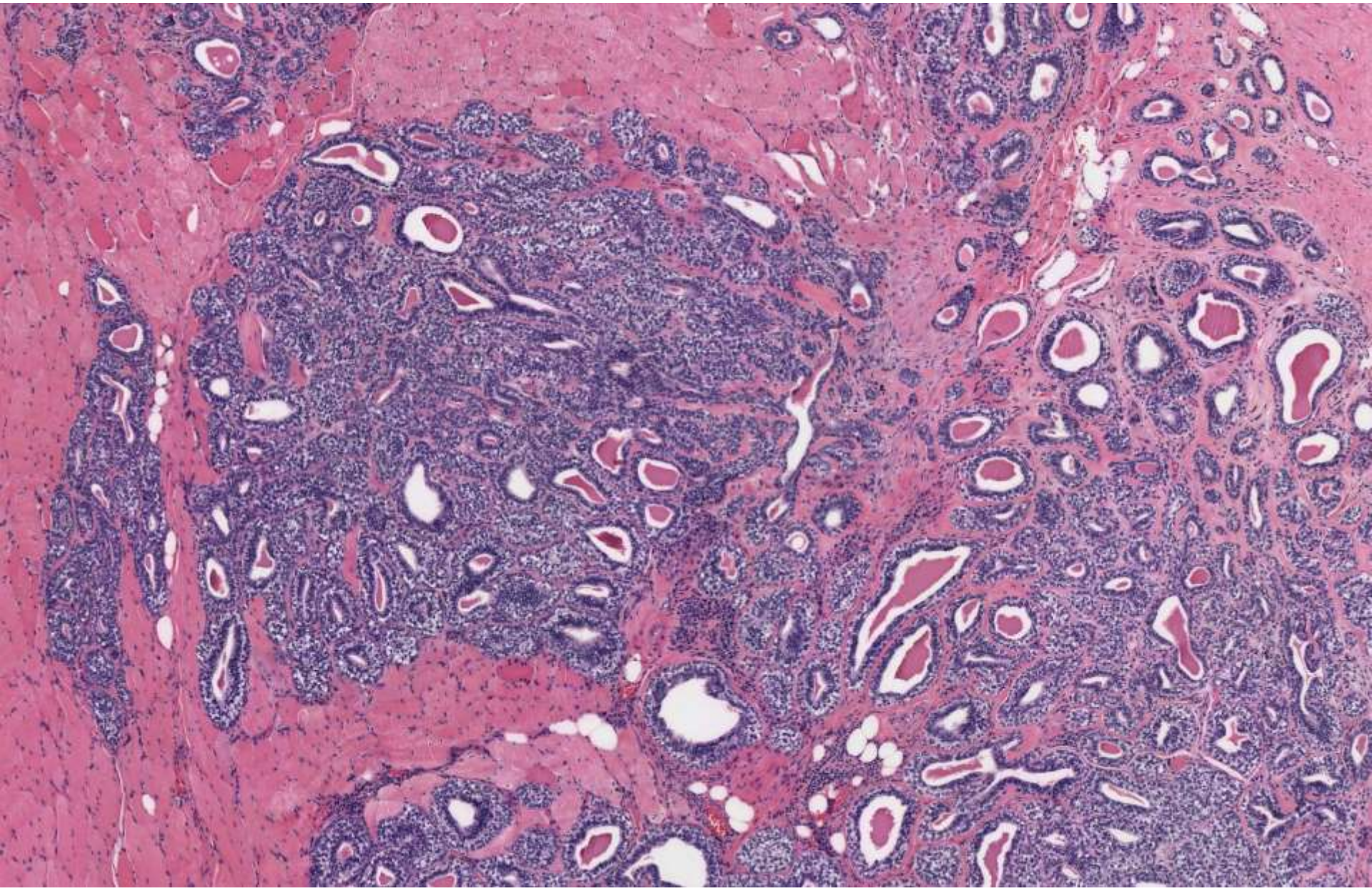


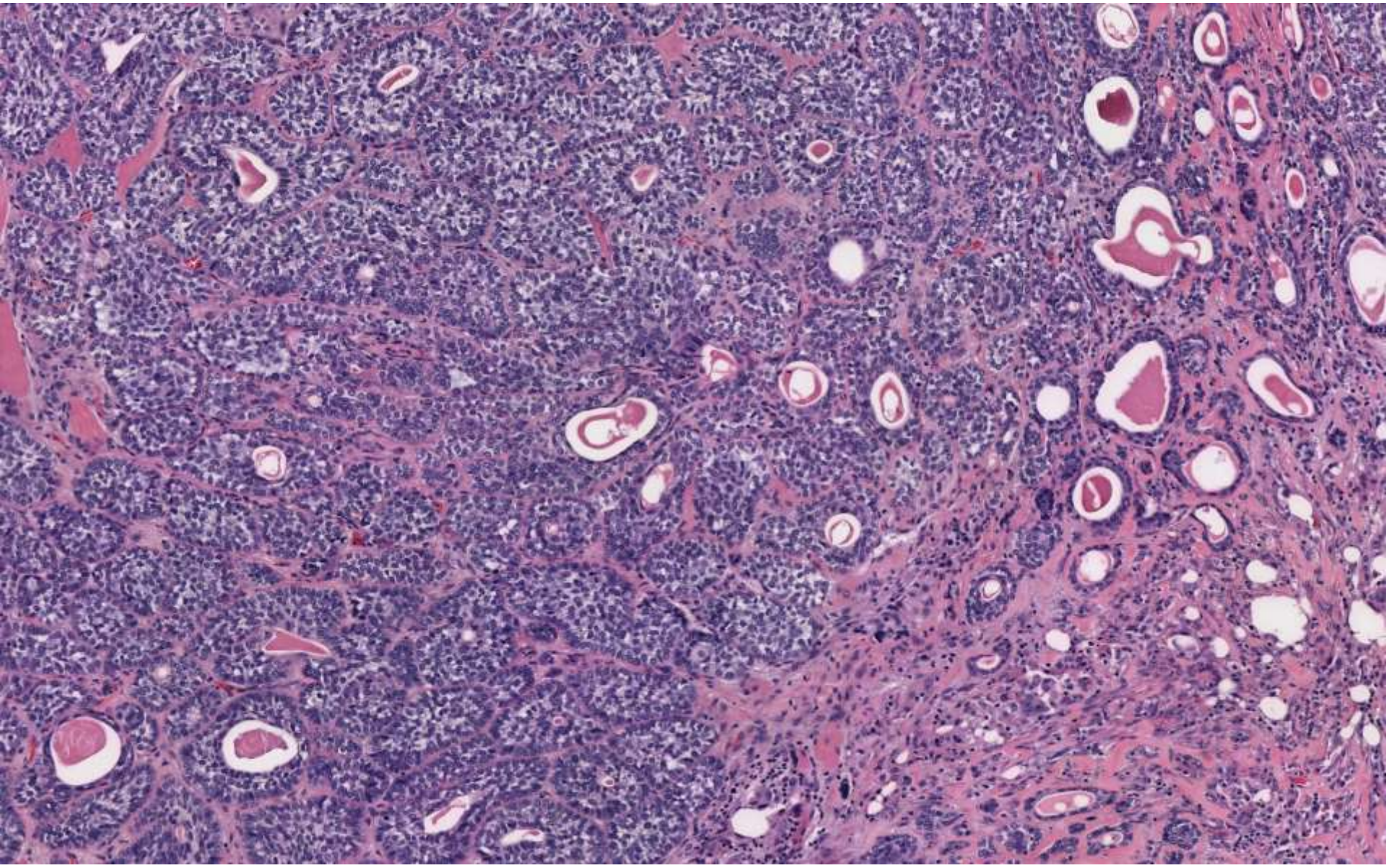


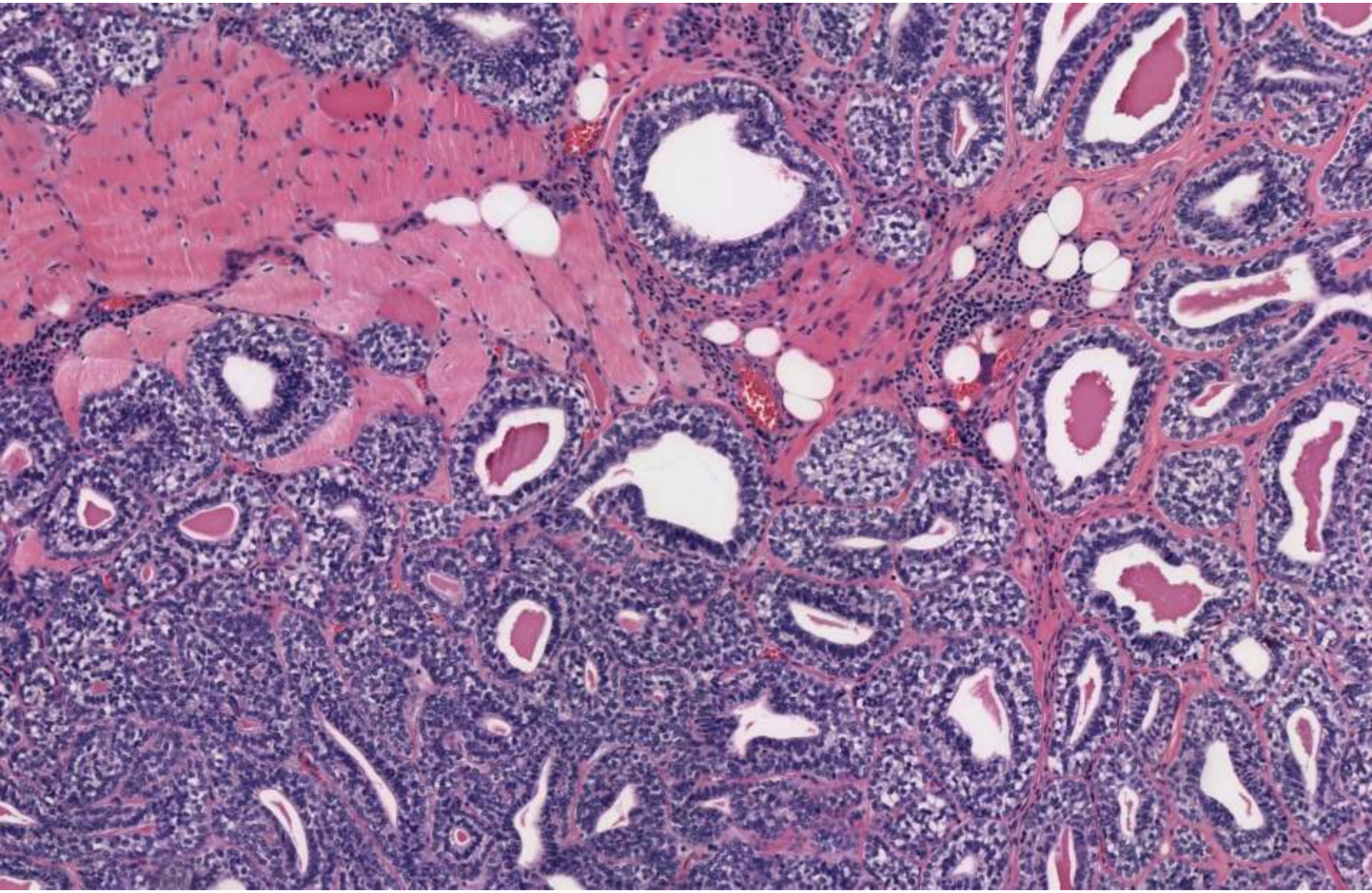


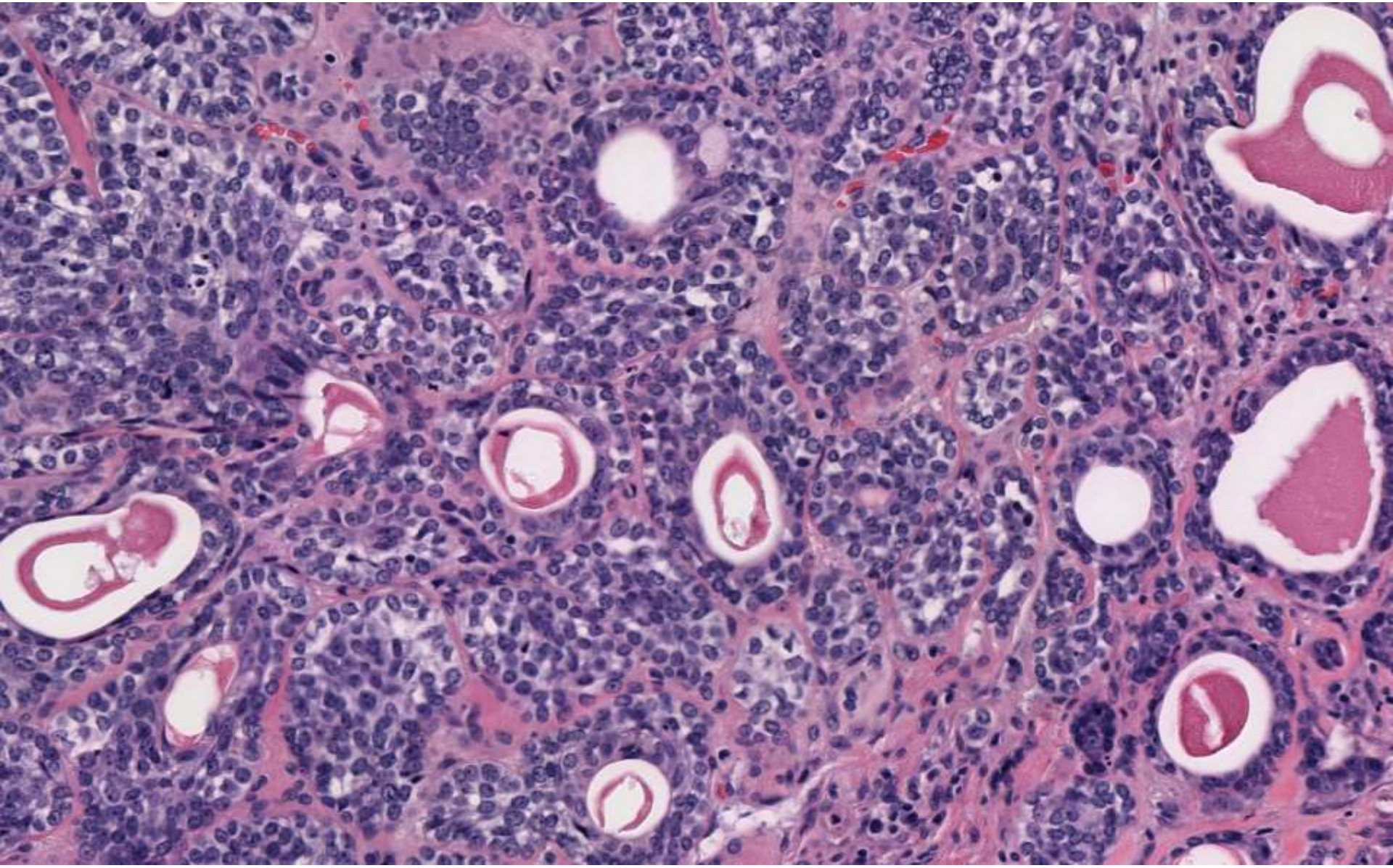


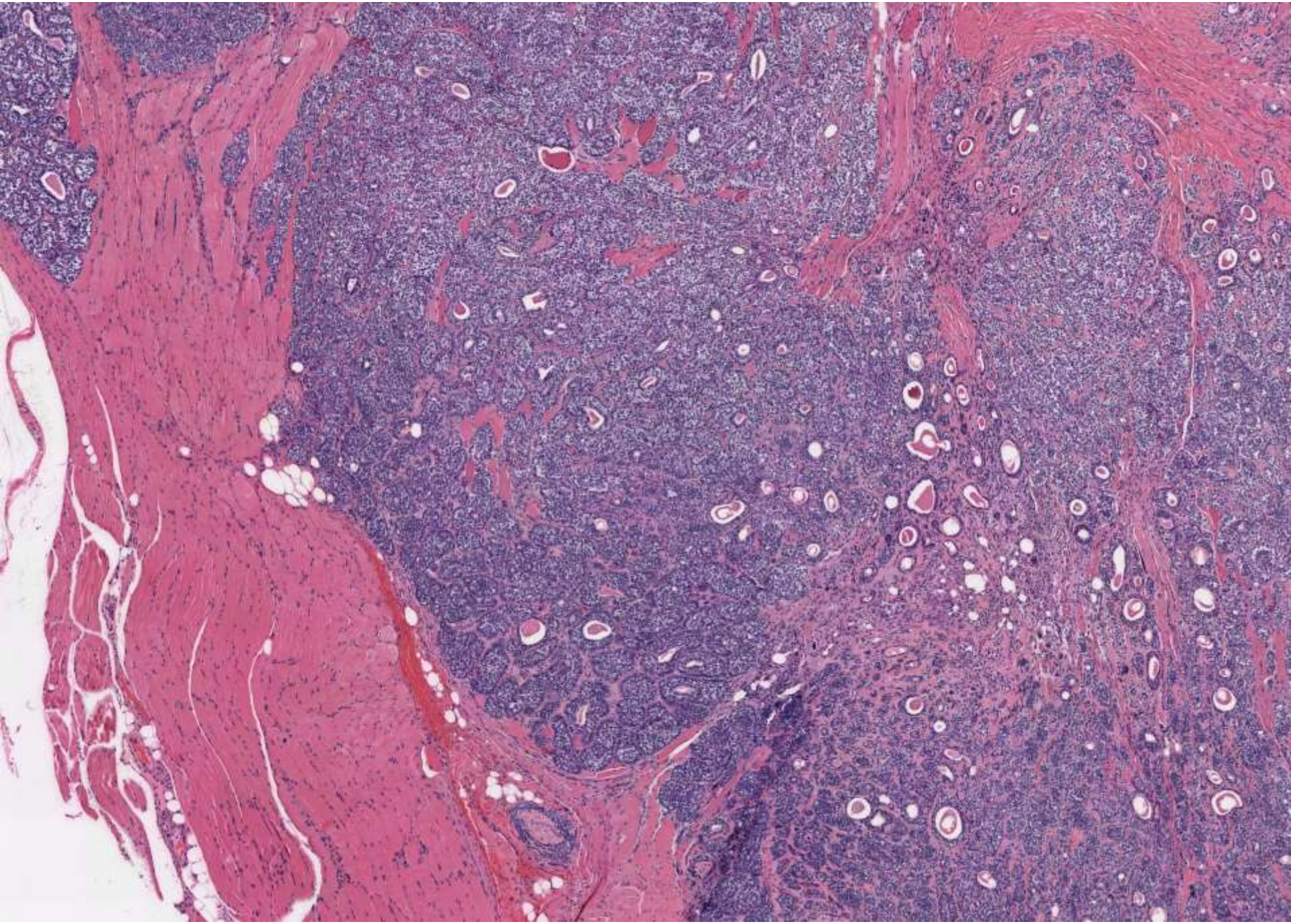


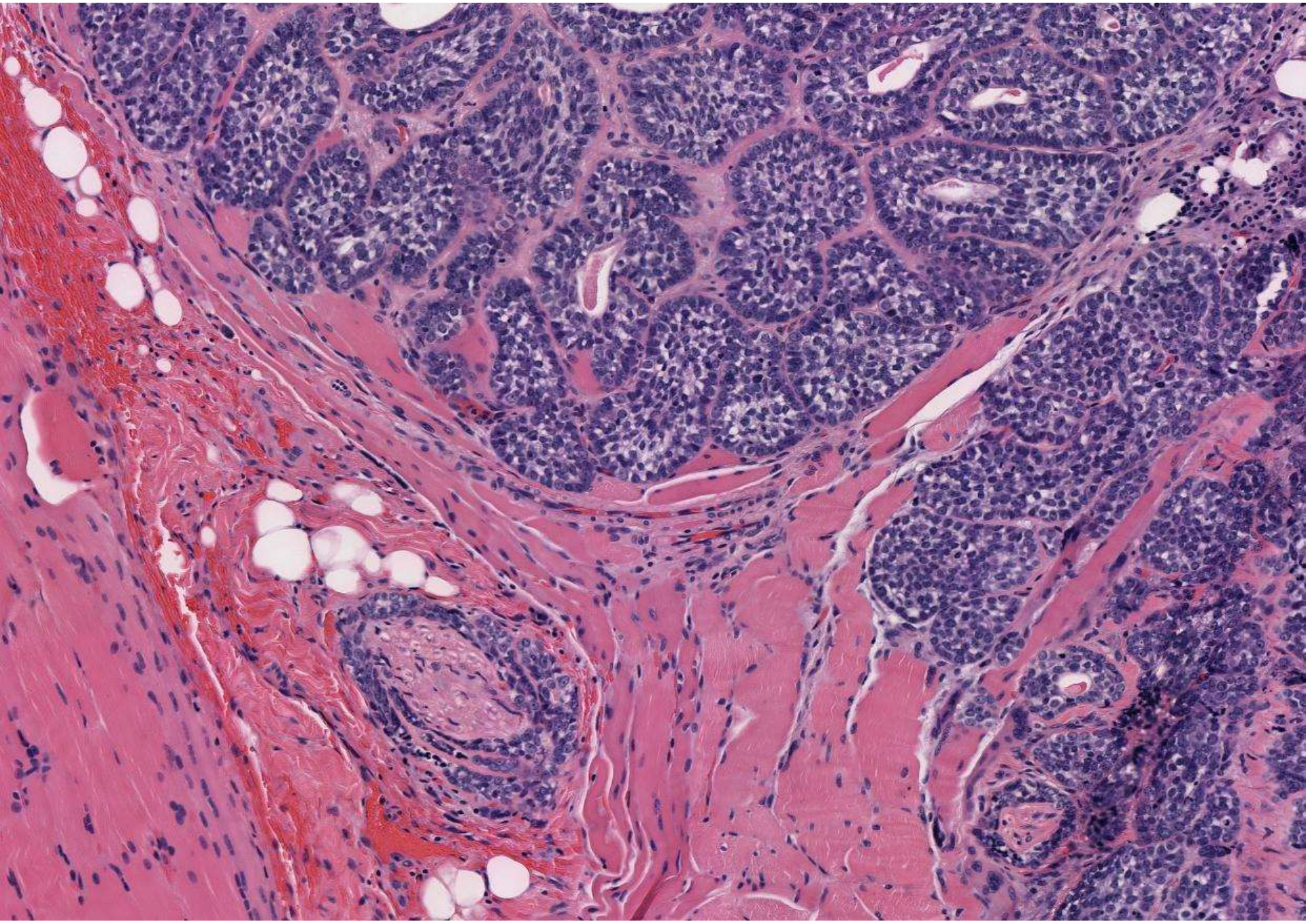












EPITHELIAL-MYOEPITHELIAL CARCINOMA

EMCA

- Low grade biphasic tumor
- 2% of malignant salivary gland tumors
- 70% in the parotid gland
- Oncocytic, Apocrine, Dedifferentiated
- Broad DDx (ACC, Clear Cell Acinic)
- *RAS* mutations in 20-25%

Am J Surg Pathol 31(1): 44-57, 2007

EMCA

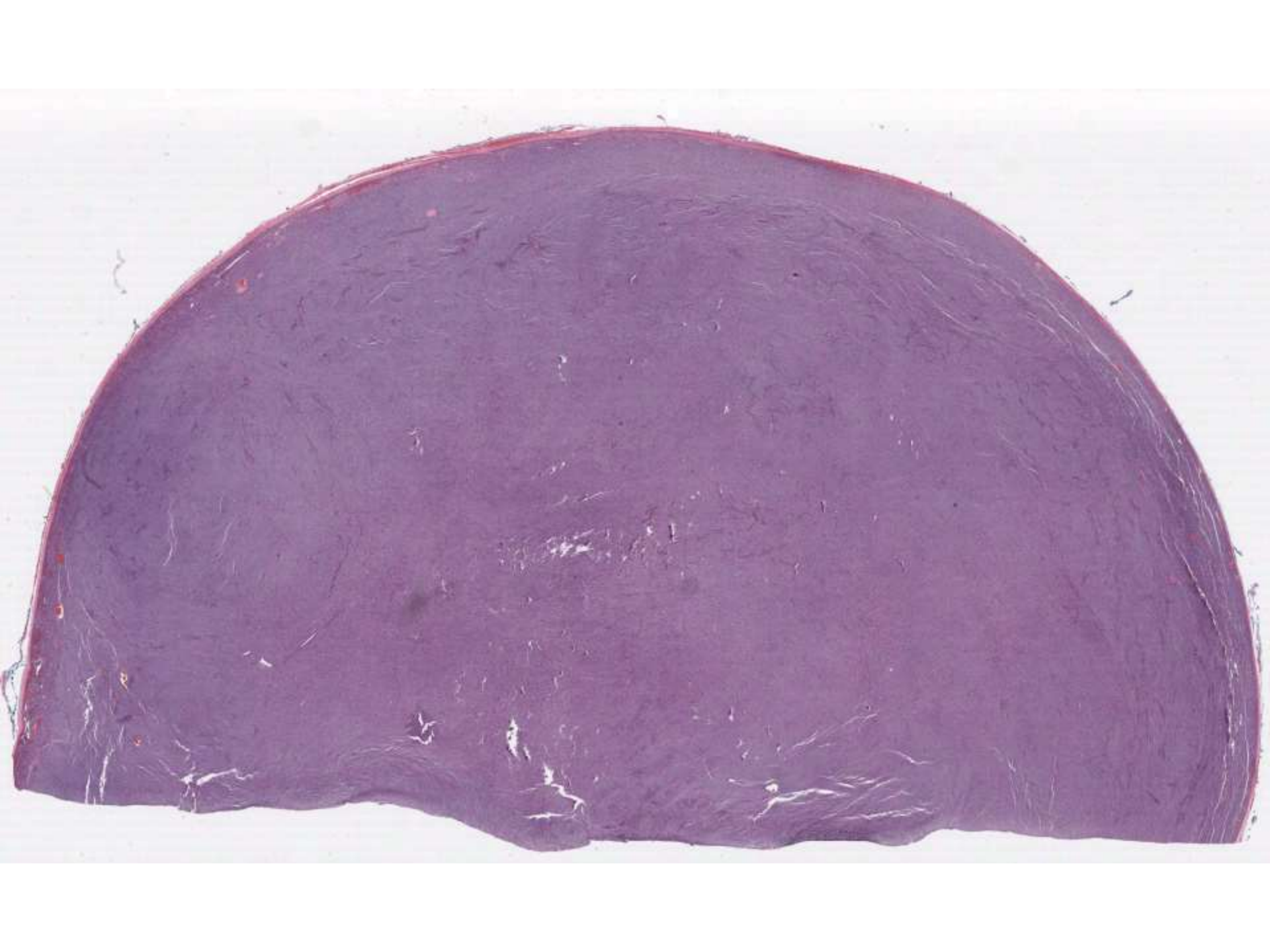
- Prognostic factors: Margin status, vascular invasion, necrosis & high grade cytology
- 5 Year DFE: 90-95%, 10 Year DFE: 80-90%
- Median DFS 11 Years
- Can have late recurrences in about 30-50%
- Distant metastases in 10-20%

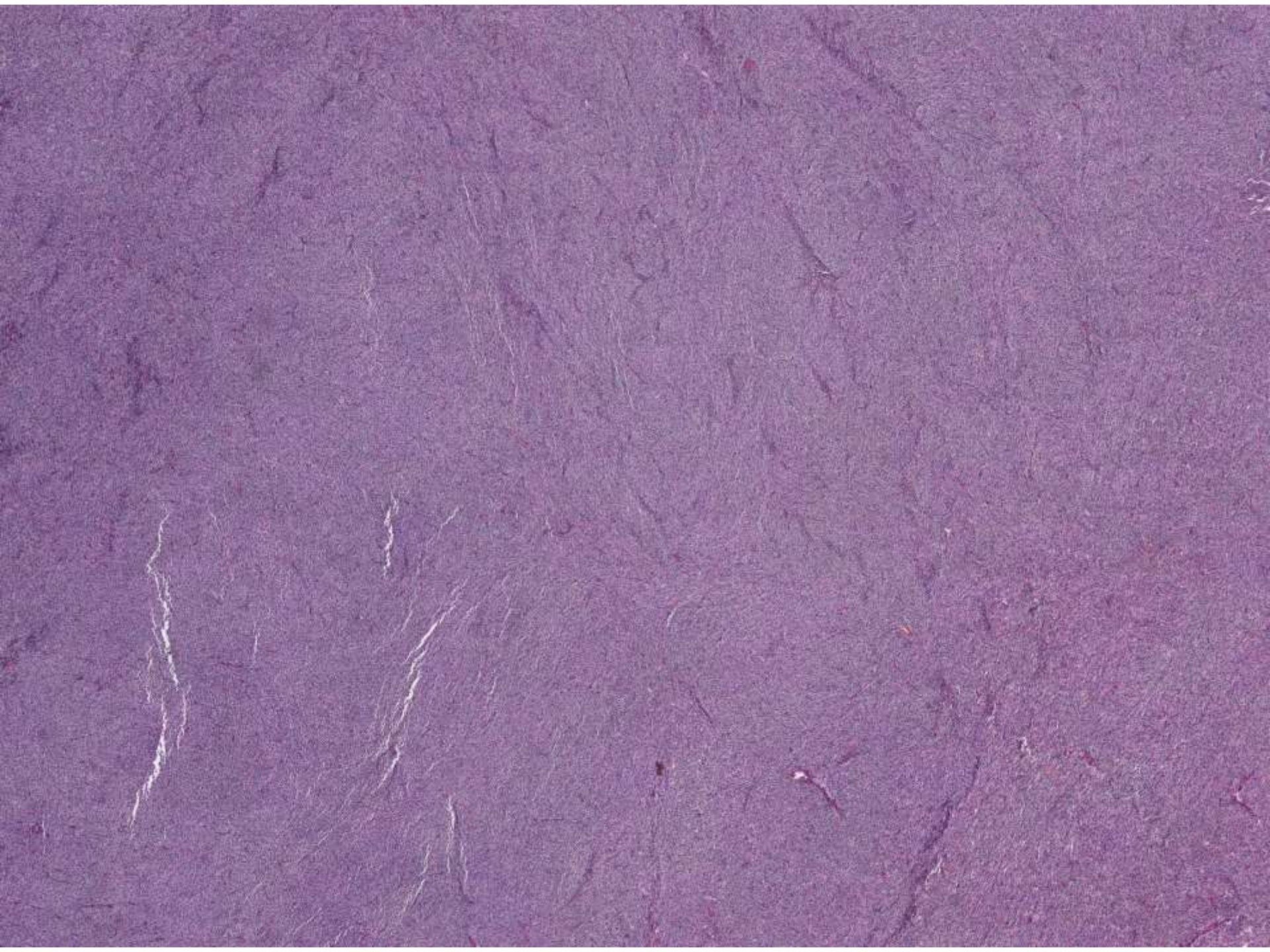
Surgical Pathology 10: 155-76, 2017

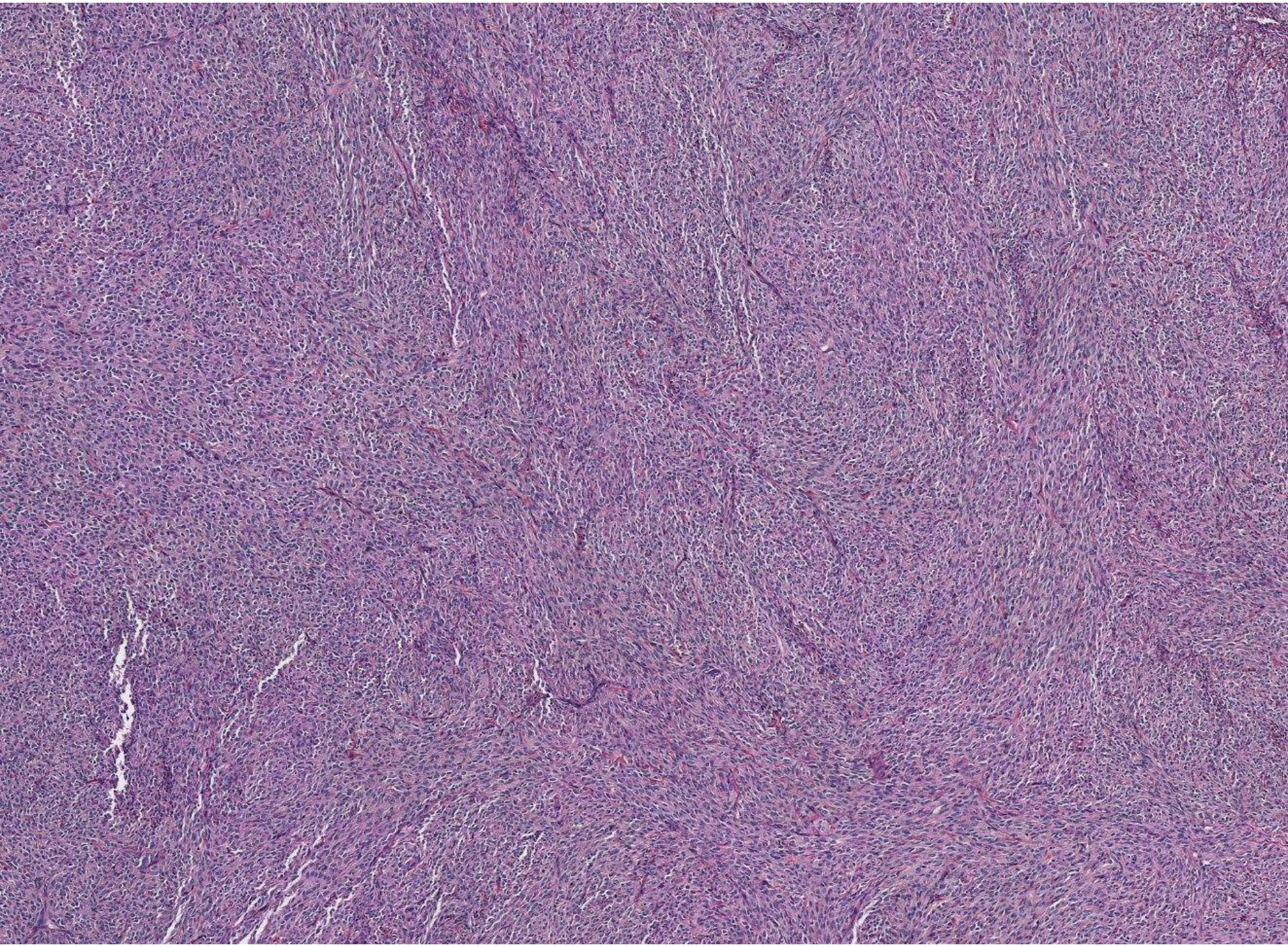
19-0403
(scanned slide available)

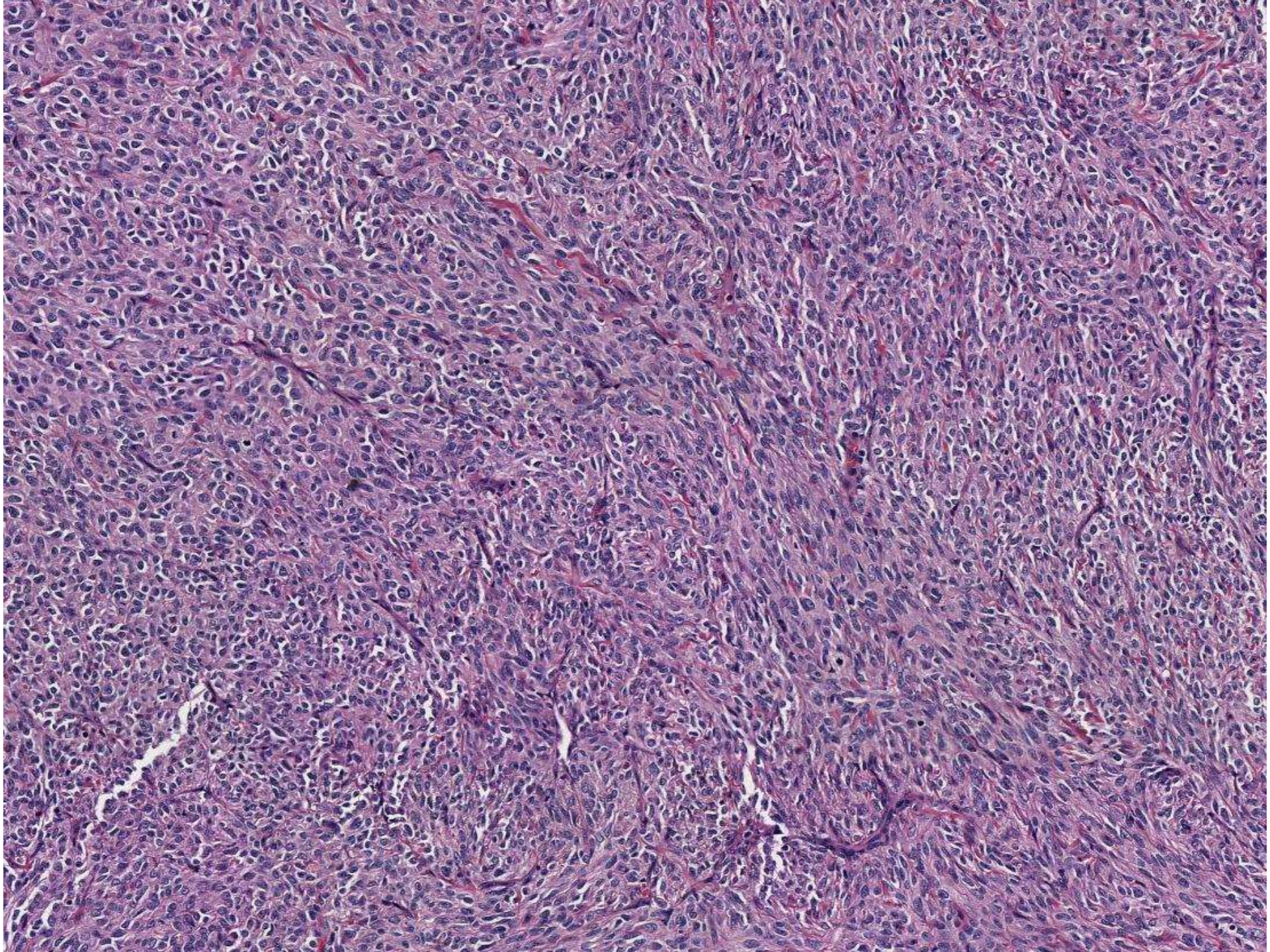
Keith Duncan; Mills Peninsula

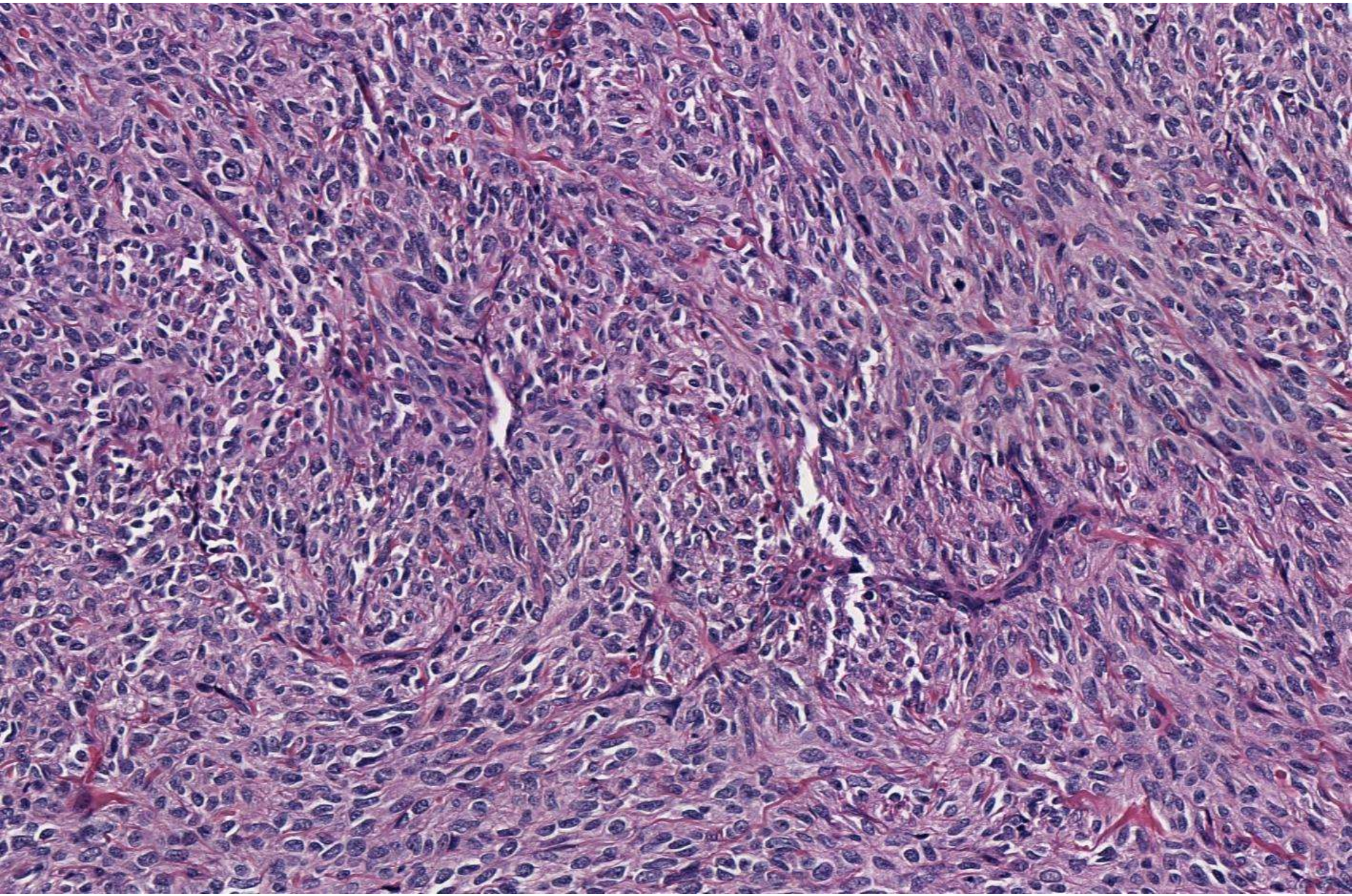
66-year-old female with recurrent left pelvic tumor that first began in 1984 with a left ovarian mass.

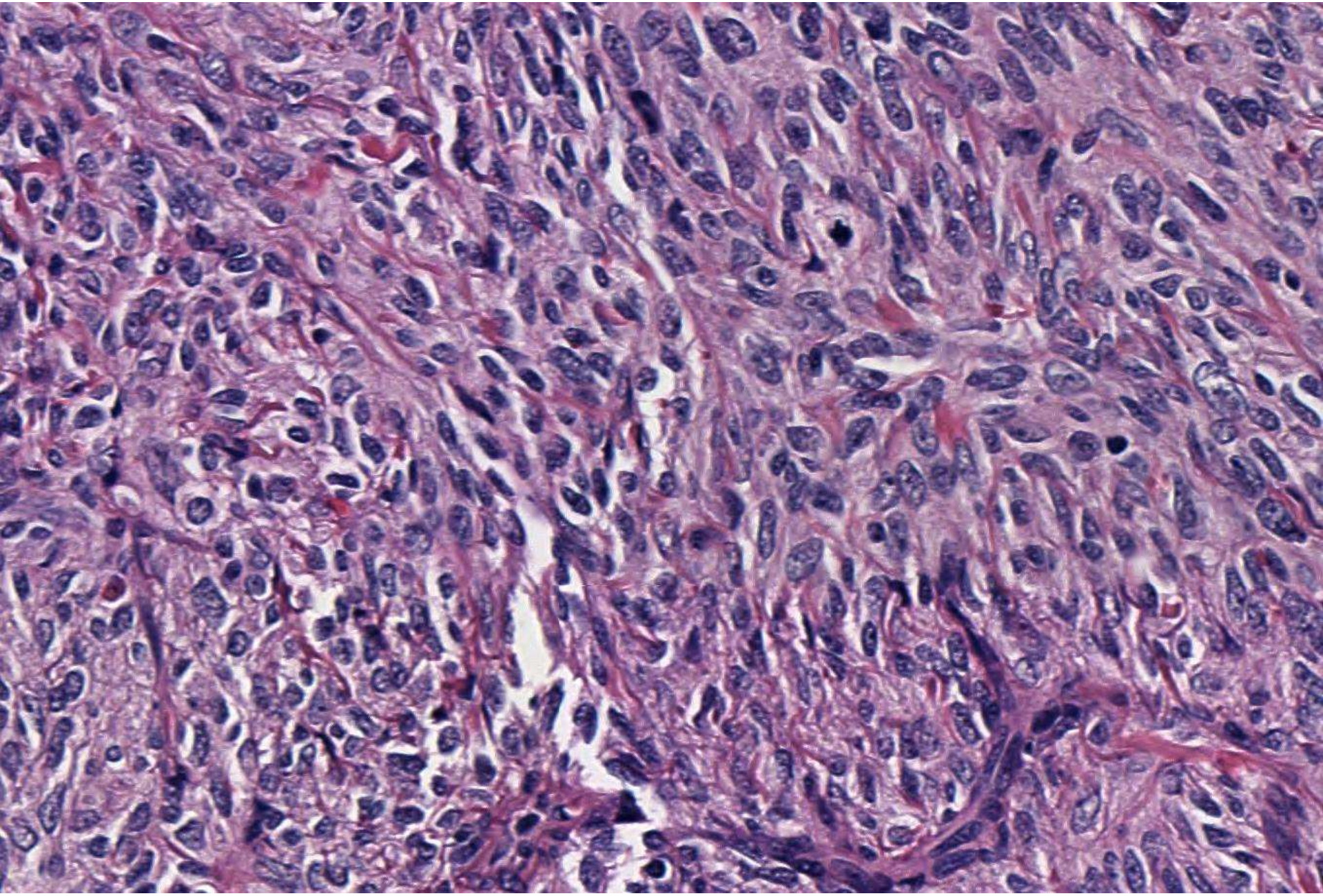












RECURRENT TUMOR SEEN BY MANY EXPERTS BEFORE THE TURN OF THE CENTURY

- LONG HISTORY DATING BACK TO 1984
- DR. ROBERT YOUNG: FIBROSARCOMA.
- STANFORD: LOW GRADE FIBROSARCOMA
- DR. FLETCHER RENDERED A DIAGNOSIS OF MITOTICALLY ACTIVE CELLULAR FIBROMA.

AND THEN THERE WAS NEXT GENERATION SEQUENCE TESTING

- CLINICIAN ASKED FOR FOUNDATION ONE MEDICINE EVALUATION
- FOXL2 C134W MUTATION DISCOVERED!
- 52 OF THE 56 ADULT GRANULOSA CELL TUMORS HARBOR THE MUTATION, OF WHICH 3 WERE HEMI/HOMOZYGOUS

GRANULOSA CELL TUMOR DEFINITION / GENERAL

- DIFFERENTIATION TOWARDS FOLLICULAR GRANULOSA CELLS
- USUALLY WOMEN AGE 15+ YEARS; 75% ASSOCIATED WITH HYPERESTROGENISM METRORRHAGIA, ENDOMETRIAL HYPERPLASIA / CARCINOMA
- 10 YEAR SURVIVAL > 90%; TENDS TO RECUR LOCALLY, UP TO 20 YEARS LATER
- 5 - 25% RISK OF MALIGNANCY, CANNOT PREDICT FROM HISTOLOGY

MICROSCOPIC DESCRIPTION

- SMALL, BLAND, CUBOIDAL TO POLYGONAL CELLS IN VARIOUS PATTERNS, INCLUDING CALL-EXNER BODIES, MACROFOLLICULAR, TRABECULAR, SOLID AND INSULAR PATTERNS
- CELLS MAY BE LUTEINIZED; MAY HAVE THECA CELL COMPONENT
- CELLS HAVE COFFEE BEAN NUCLEI
- CENTRAL ROUND NUCLEI WITH SINGLE PROMINENT NUCLEOLI

IPOX STAINS

- **POSITIVE STAINS**
- INHIBIN, VIMENTIN, SMOOTH MUSCLE ACTIN, S100 (50%), KERATIN (DOT-LIKE IN 30-50%), DESMIN
- **NEGATIVE STAINS**
- EMA

DIFFERENTIAL DIAGNOSIS

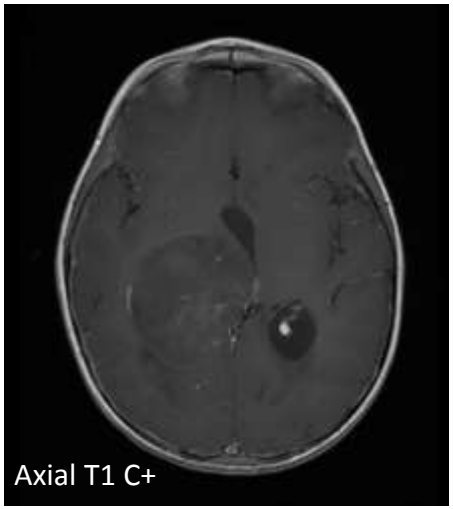
- CARCINOID TUMOR
- ENDOMETRIOID CARCINOMA
- ENDOMETRIAL STROMAL SARCOMA
- POORLY DIFFERENTIATED OVARIAN SURFACE EPITHELIAL CARCINOMA:
- SMALL CELL CARCINOMA OF HYPERCALCEMIC TYPE

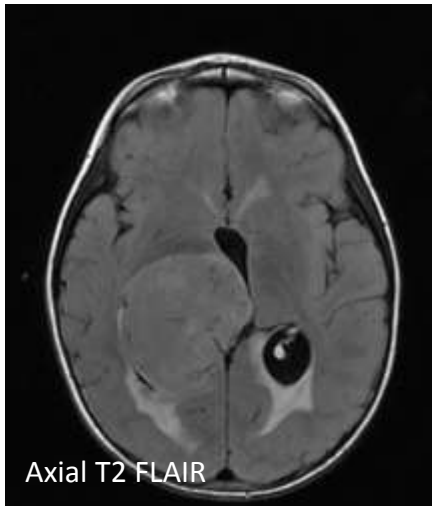
19-0404

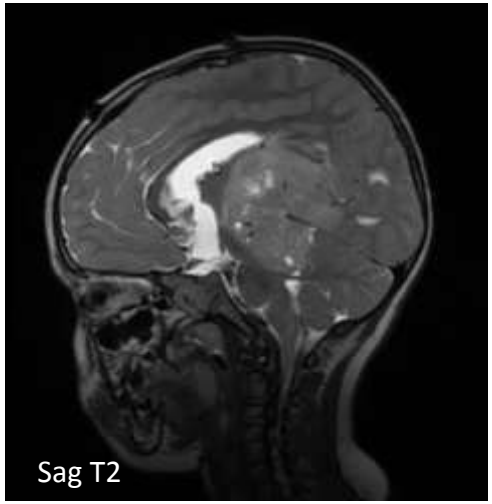
Romain Cayrol/Hannes Vogel; Stanford

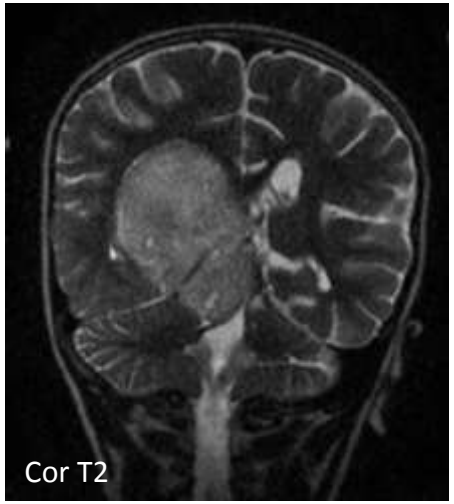
2-year-old female with newly diagnosed thalamic lesion and hydrocephalus, initially presented with headache, nausea, and vomiting.

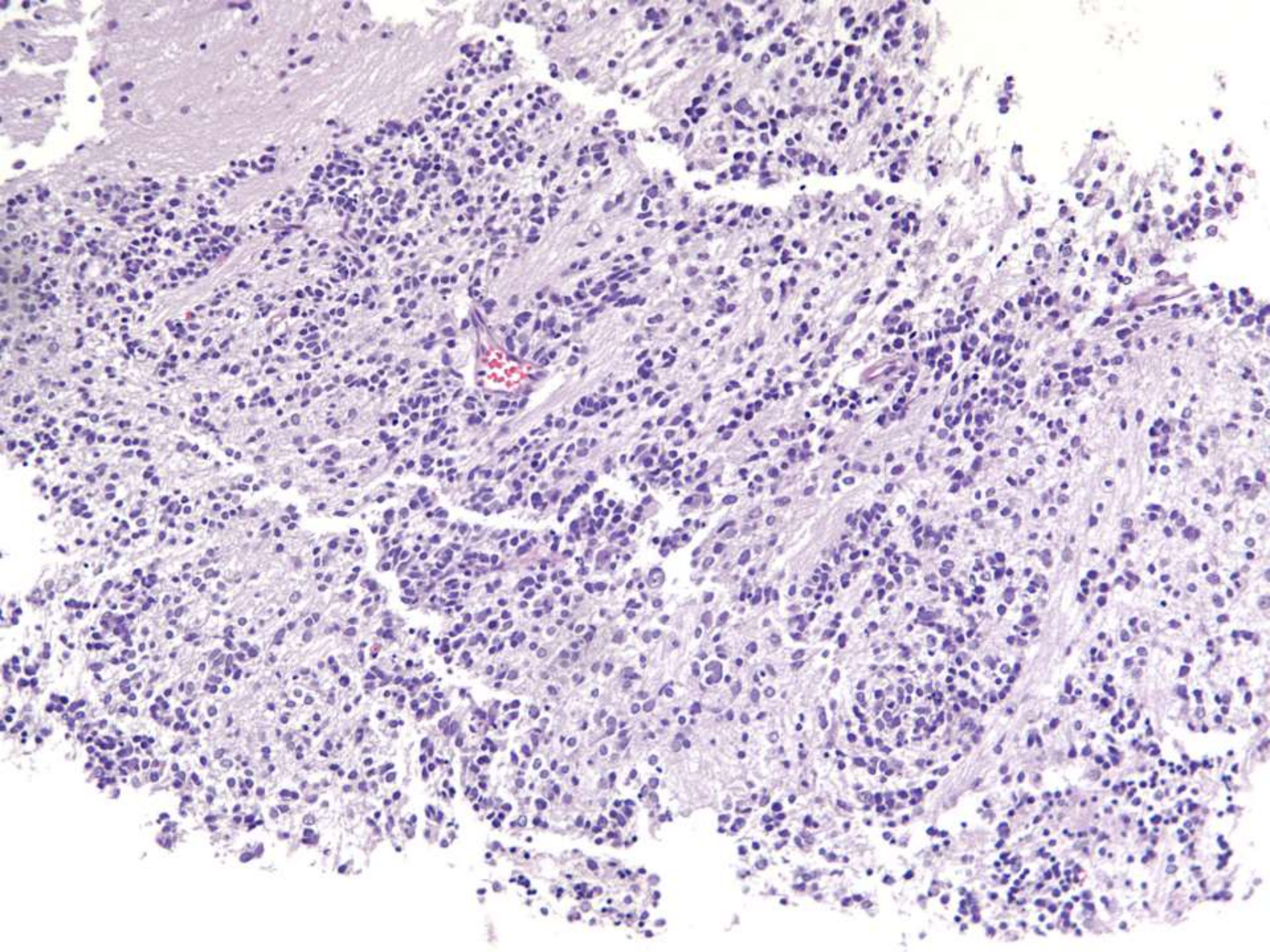
Imaging

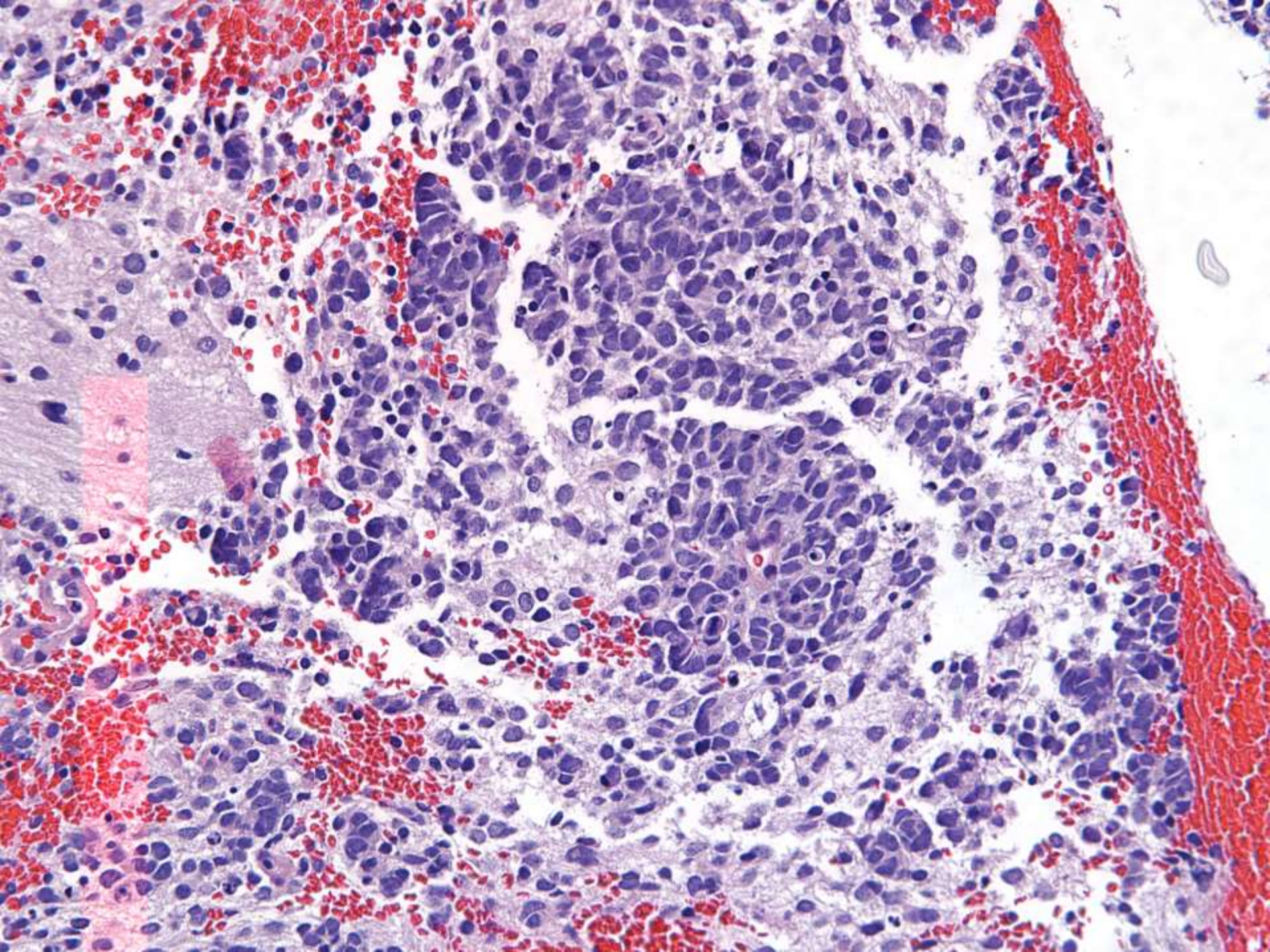


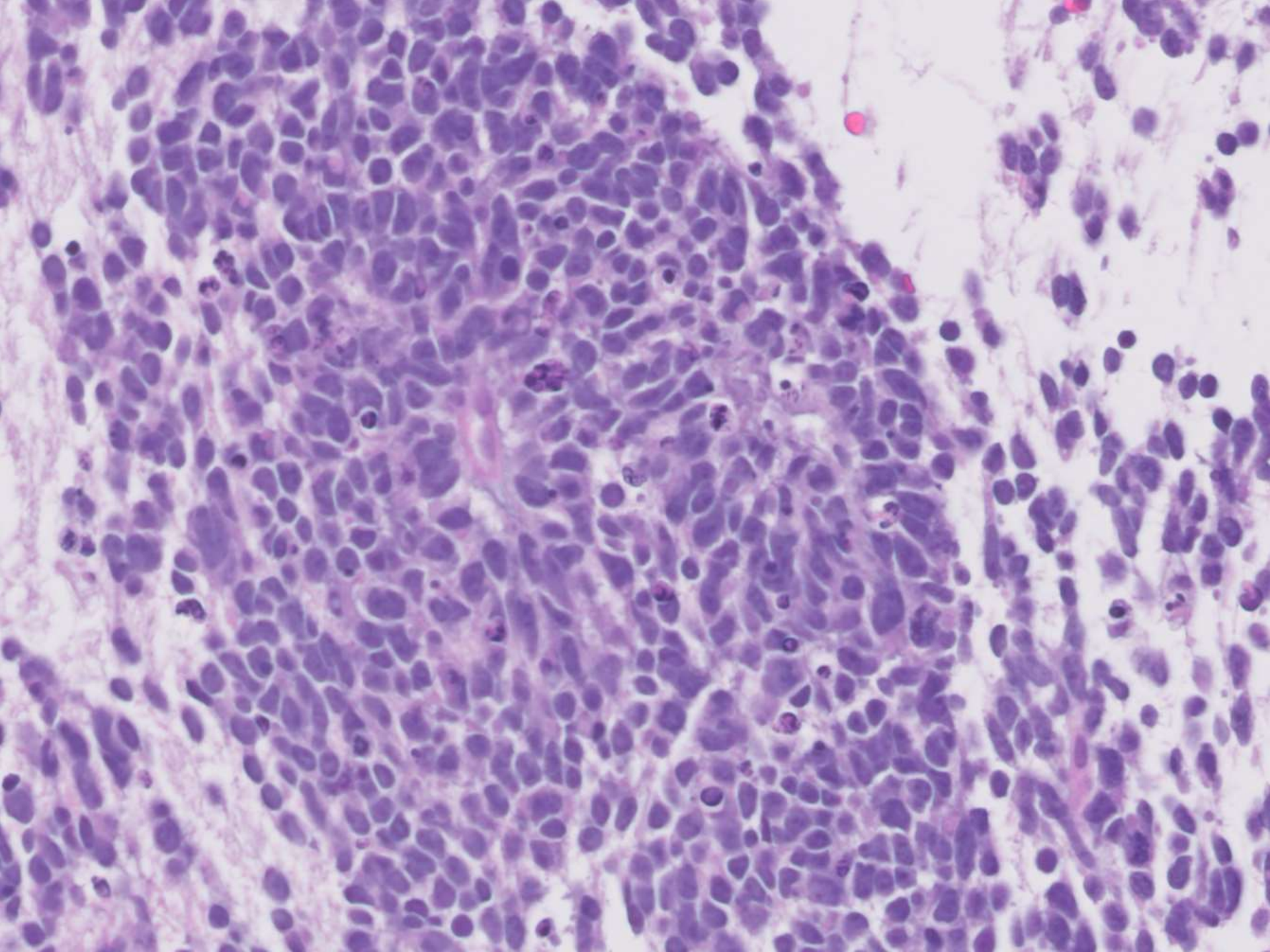












- Immunohistochemistry
  - Synaptophysin +, INI +
  - H3K27M -, H3K27me3 partial loss

Diagnosis

- **BRAIN, RIGHT PARIETAL LESION, BIOPSY**
- **-- HIGH GRADE NEUROEPITHELIAL TUMOR, FAVOR EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES (ETMR)**

- Molecular testing of the miRNA cluster at chromosome 19q13.4 was performed at St-Judes and amplification of 19q13.4 is detected, confirming the diagnosis of ETMR

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]

Embryonal tumours
Medulloblastomas, genetically defined
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH
- *Medulloblastoma, group 3*
- *Medulloblastoma, group 4*

Medulloblastomas, histologically defined
- Medulloblastoma, classic
- Medulloblastoma, desmoplastic/nodular
- Medulloblastoma with extensive nodularity
- Medulloblastoma, large cell / anaplastic

Medulloblastoma, NOS

Embryonal tumour with multilayered rosettes, C19MC-altered
Embryonal tumour with multilayered rosettes, NOS
Medulloepithelioma
CNS neuroblastoma
CNS ganglioneuroblastoma
CNS embryonal tumour, NOS
Atypical teratoid/rhabdoid tumour
CNS embryonal tumour with rhabdoid features





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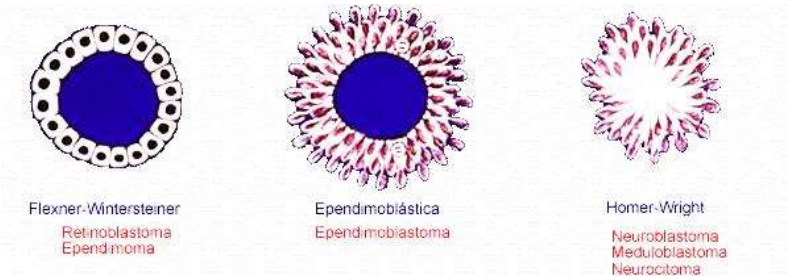
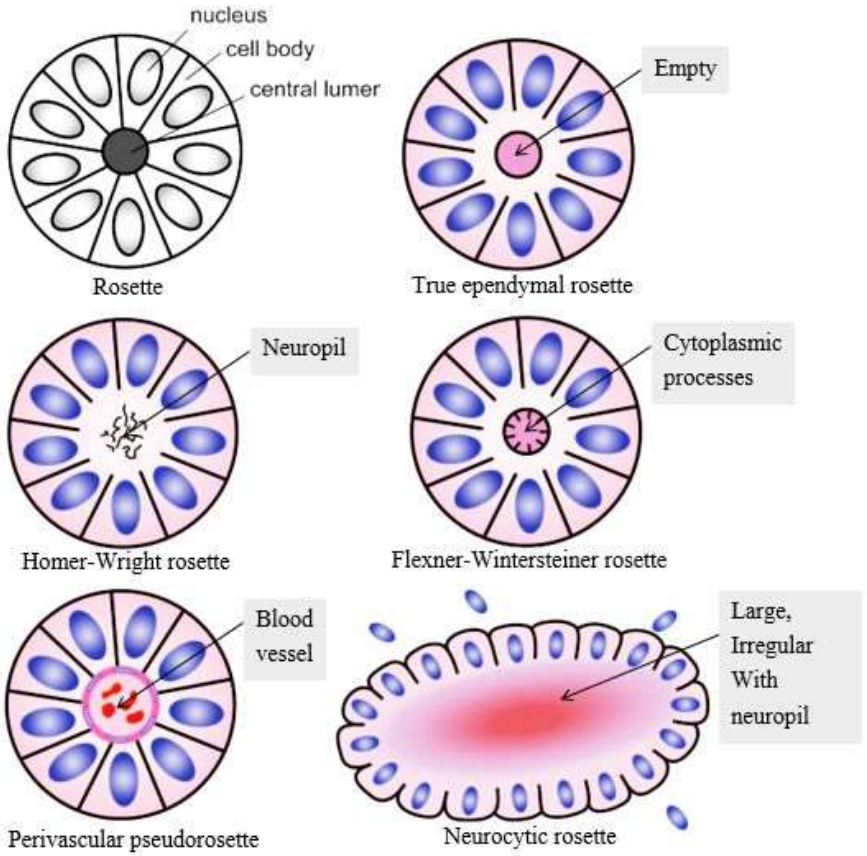
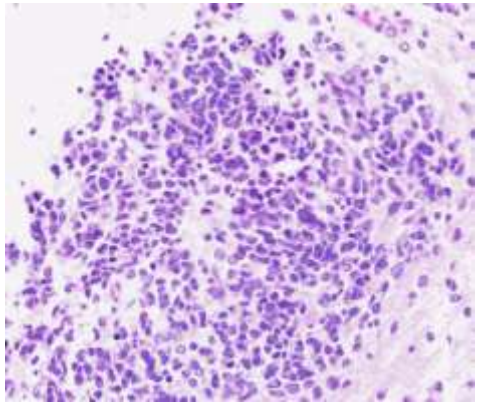




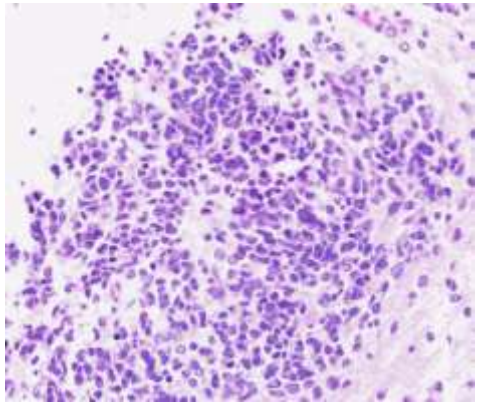
Rosettes are little round groupings of cells found in tumors. They usually consist of cells in a spoke-wheel or halo arrangement surrounding a central, acellular region.

ETMR

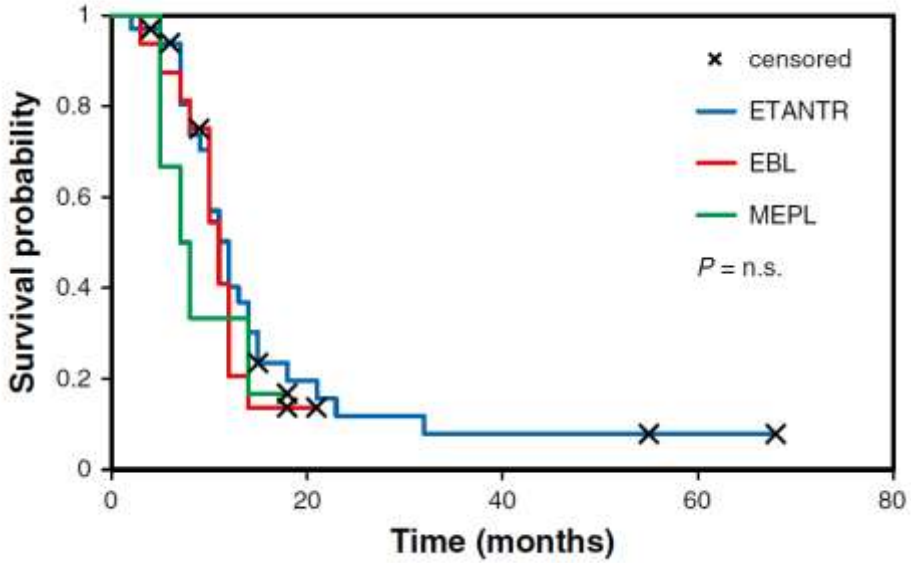


- Epidemiology
  - Pediatric (< 4 years old, often < 2 year old), M=F
- Location
  - Supratentorial (hemispheres in 70% of cases), infratentorial (cerebellum or brainstem)
- Clinical manifestations include increased intracranial pressure (headaches, nausea, vomiting, visual disturbances)
- Imaging minimal to marked contrast enhancement, +/- calcification, +/- cysts

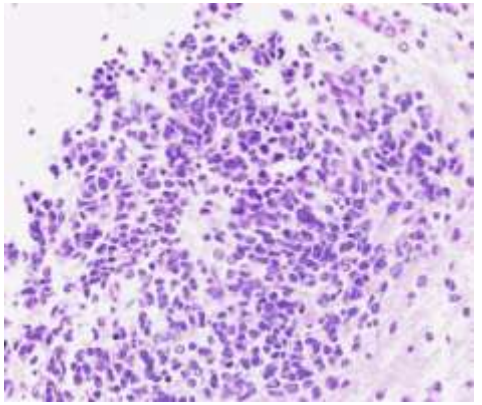
ETMR



- Prognosis
  - Aggressive clinical course, 12 month survival
  - Leptomeningial dissemination has been described as well as soft tissue infiltration and extracranial metastasis

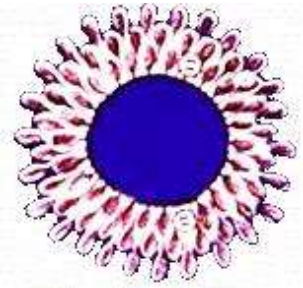


ETMR



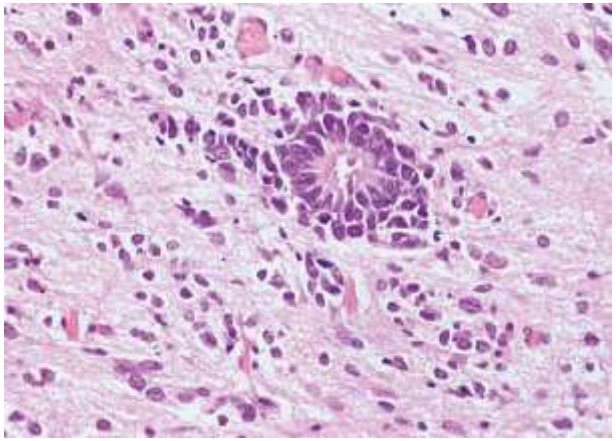
- Gross
  - Grey-pink, circumscribed, with necrosis and hemorrhage

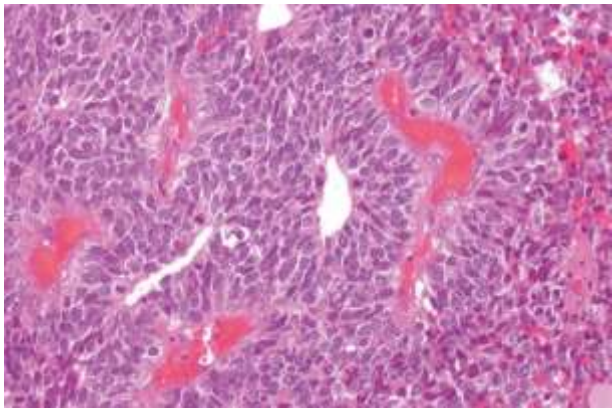
- Microscopy
  - Historically many names: ependymoblastoma, medulloepithelioma, embryonal tumor with abundant neuropil and true rosette (ETANTR)
  - Multilayered rosettes with mitotically active pseudostratified neuroepithelium around a central lumen
    - Nuclei tend to be pushed away from the central lumen
    - Three recognized histological patterns

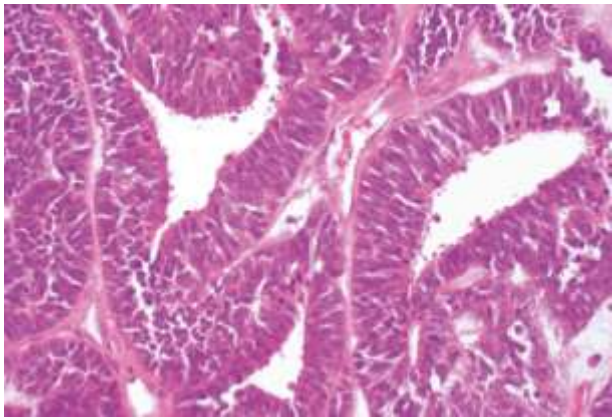


Histology

- Embryonal tumor with abundant neuropil and true rosettes (ETANR)
  - Biphasic architecture with dense clusters of small cells (with occasional rosettes) and paucicellular neuropil rich areas +/- ganglion cells
- Ependymoblastoma
  - Sheets and clusters of poorly differentiated cells, numerous rosettes
- Medulloepithelioma
  - Young children, papillary-tubular-trabecular arrangement of pseudostratified neuroepithelium, external limiting membrane reminiscent of a primitive neural tube, mitosis near the luminal surface, mature neurons and glial cells can be seen, rare cases with mesenchymal differentiation

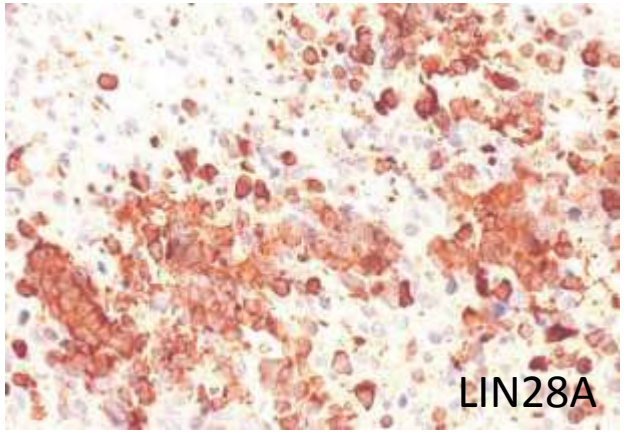


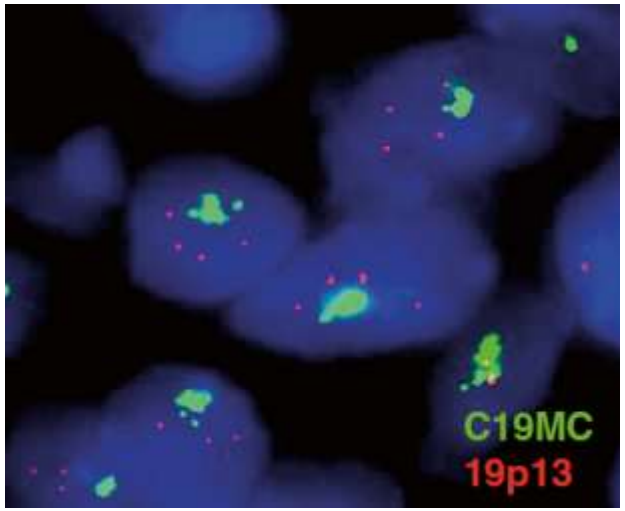




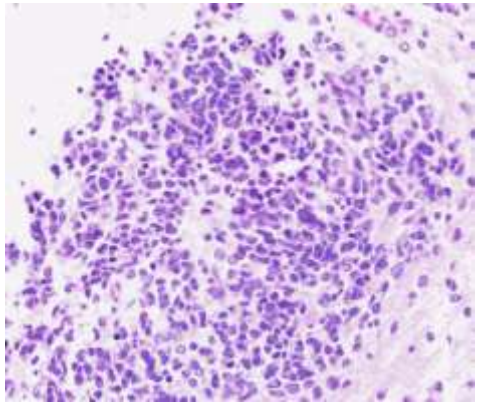
Additional studies

- Immunophenotype
  - Nestin, vimentin, synaptophysin, LIN28A, INI
  - Focal cytokeratins, CD99 and EMA in small cell component
- EM
  - High n/c, few organelles, abortive cilia, amorphous surface coating on the luminal side with no true membrane
  - Extensive lateral junctions in the medulloepithelioma
- Genetics
  - Amplicon of 19q13.42 (0.89 Mb), specific and sensitive marker, microRNA cluster named C19MC, C19MC-TTYH1 fusion
    - Detected by FISH
  - Recurrent copy loss chromosomes 2, 7q, 11q and loss of 6q
  - Methylation and gene expression array demonstrate this tumor is distinct from other pediatric tumors





ETMR



- Cell of origin: sub-ventricular zone stem cell ?

- Treatment
  - Gross total resection
  - Post-treatment neuronal differentiation has been associated with better outcome
- Patient follow up
  - VP shunt
  - Cytoreductive chemotherapy for easier resection, cycle 1 completed
  - Imaging reveals an unchanged size of the right brainstem mass extending supratentorially with similar associated mass effect, increased signal and cystic changes within the mass may represent post-treatment effects.

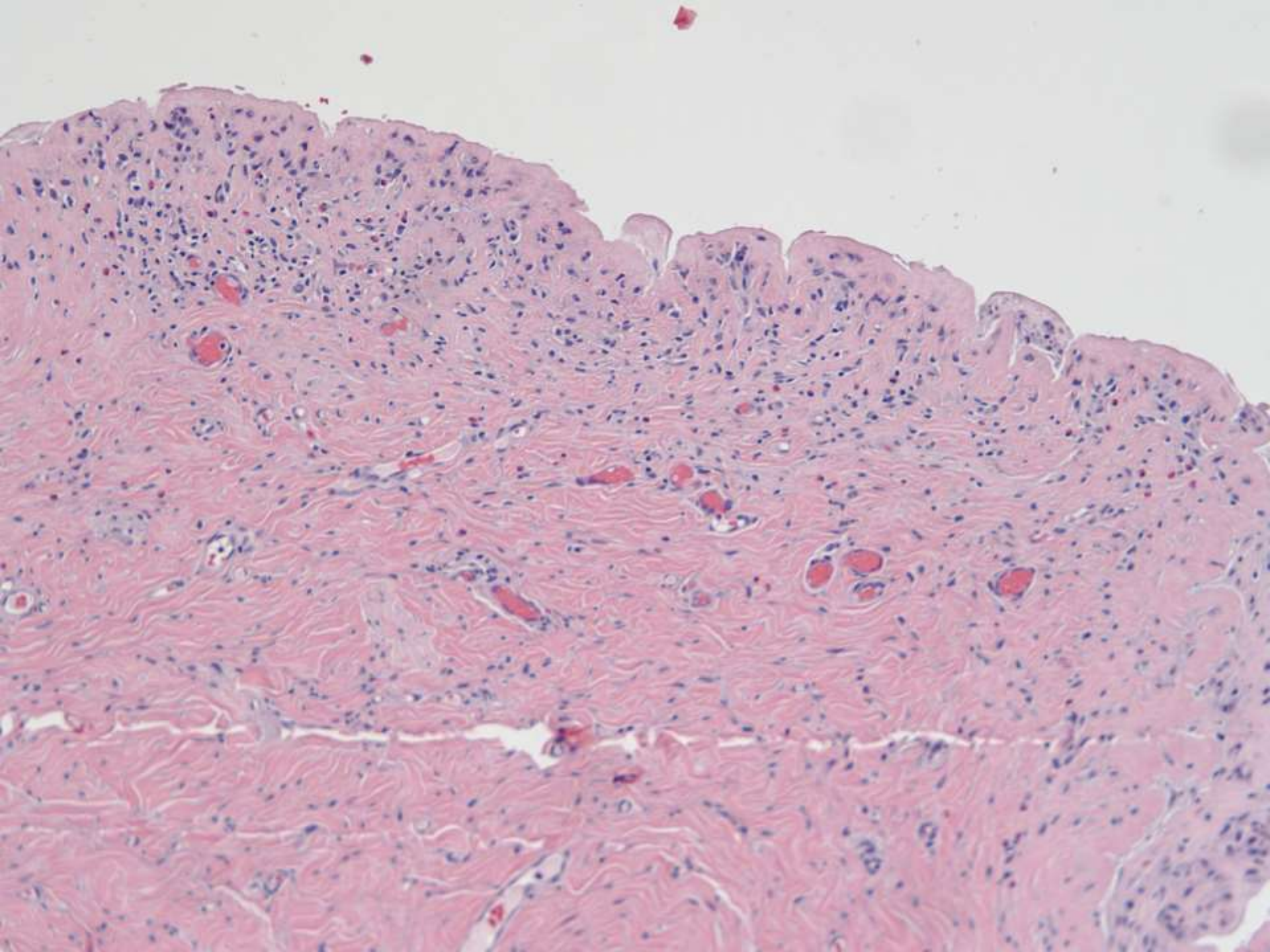
References

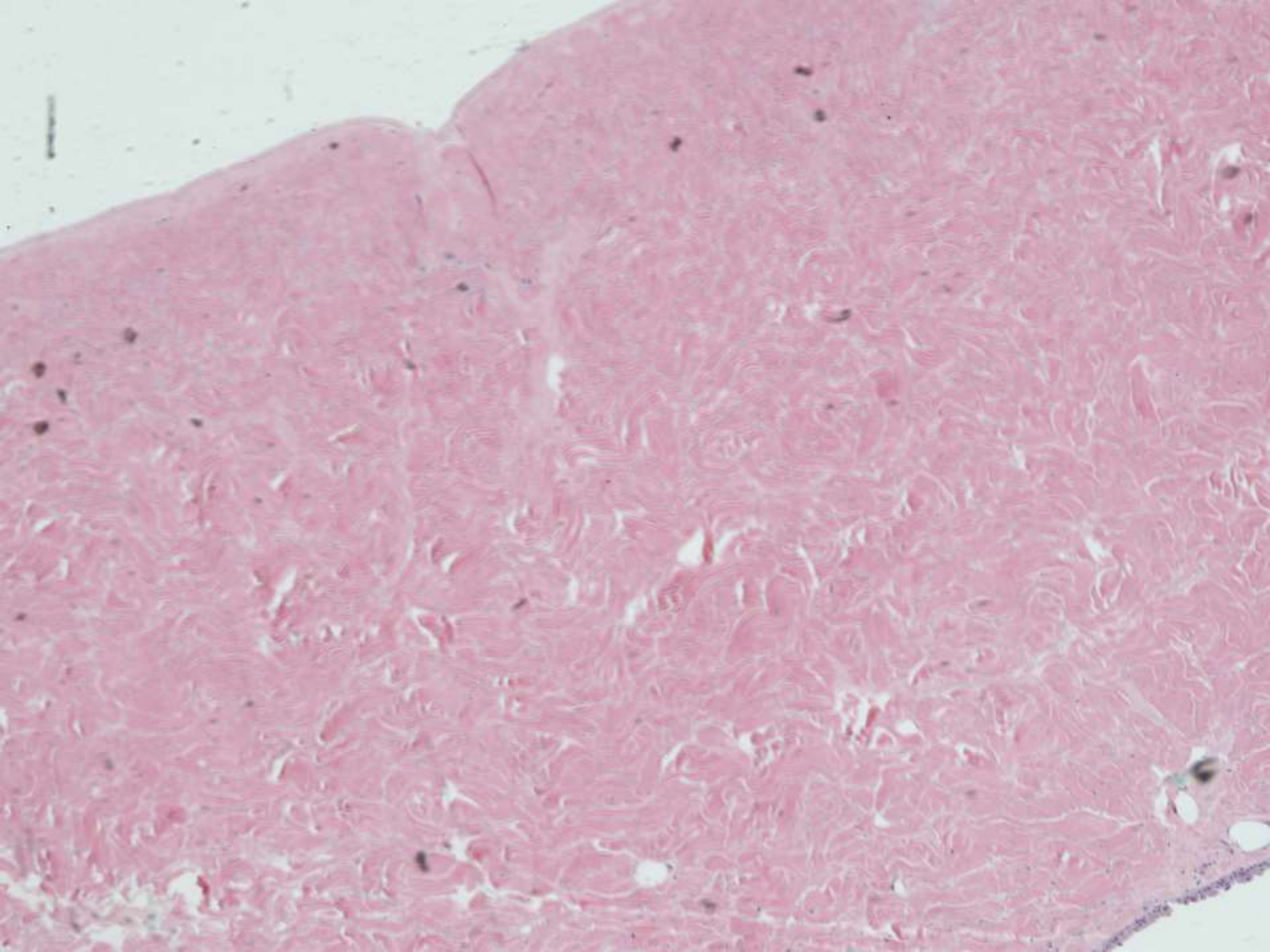
- WHO classification of tumors, Revised 4th edition, 2016
- Embryonal tumor with multilayered rosettes (ETMR): signed, sealed, delivered. Wesseling P . Acta Neuropathol. 2014 Aug;128(2):305-8.
- Embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma share molecular similarity and comprise a single clinicopathological entity. Korshunov A et al. Acta Neuropathol. 2014 Aug;128(2):279-89.
- CNS-PNETs with C19MC amplification and/or LIN28 expression comprise a distinct histogenetic diagnostic and therapeutic entity. Spence T et al. Acta Neuropathol. 2014 Aug;128(2):291-303
- Embryonal Tumor with Multilayered Rosettes, C19MC-Altered: Clinical, Pathological, and Neuroimaging Findings. Wang B et al. J Neuroimaging. 2018 Sep;28(5):483-489.

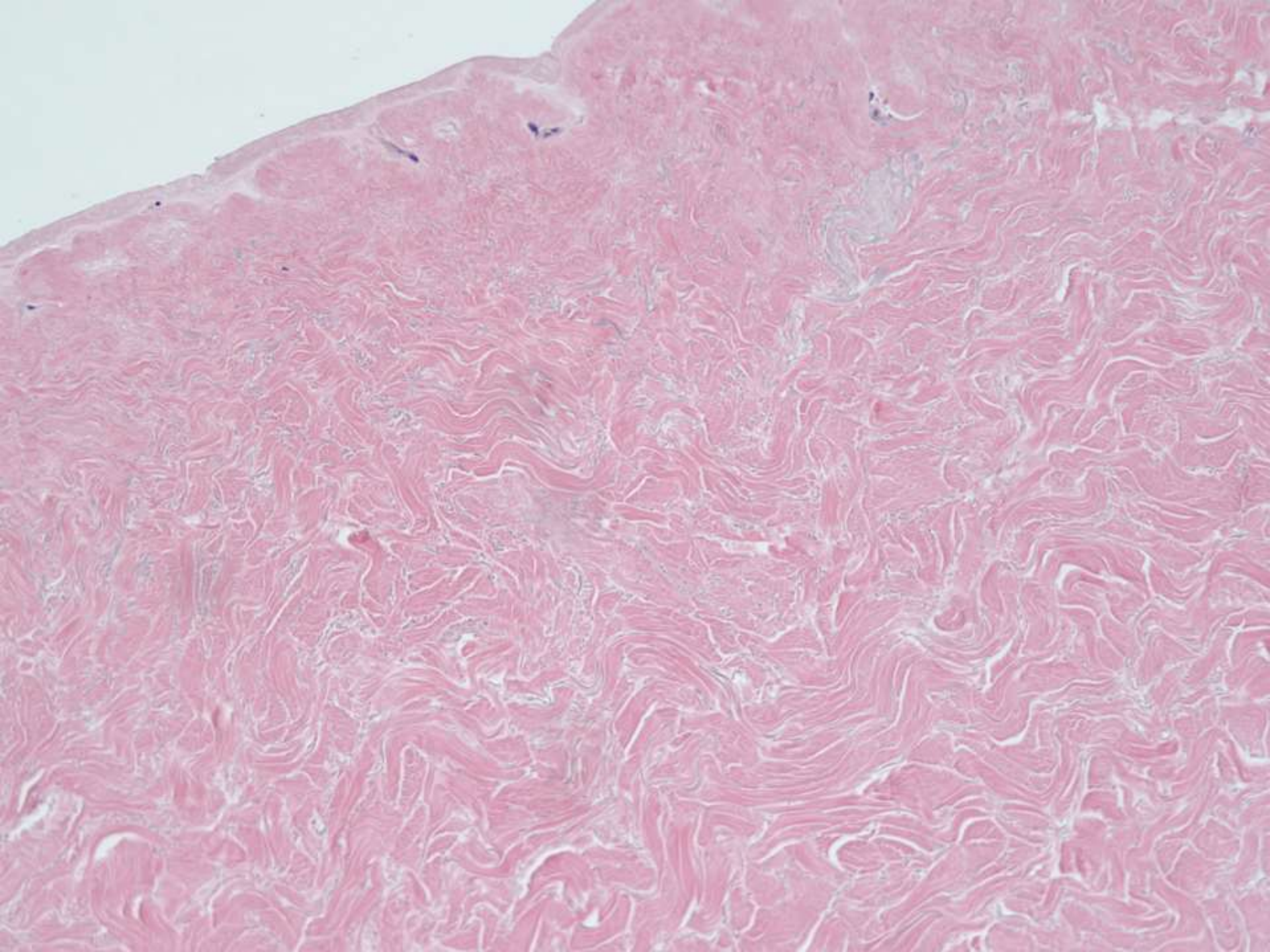
19-0405

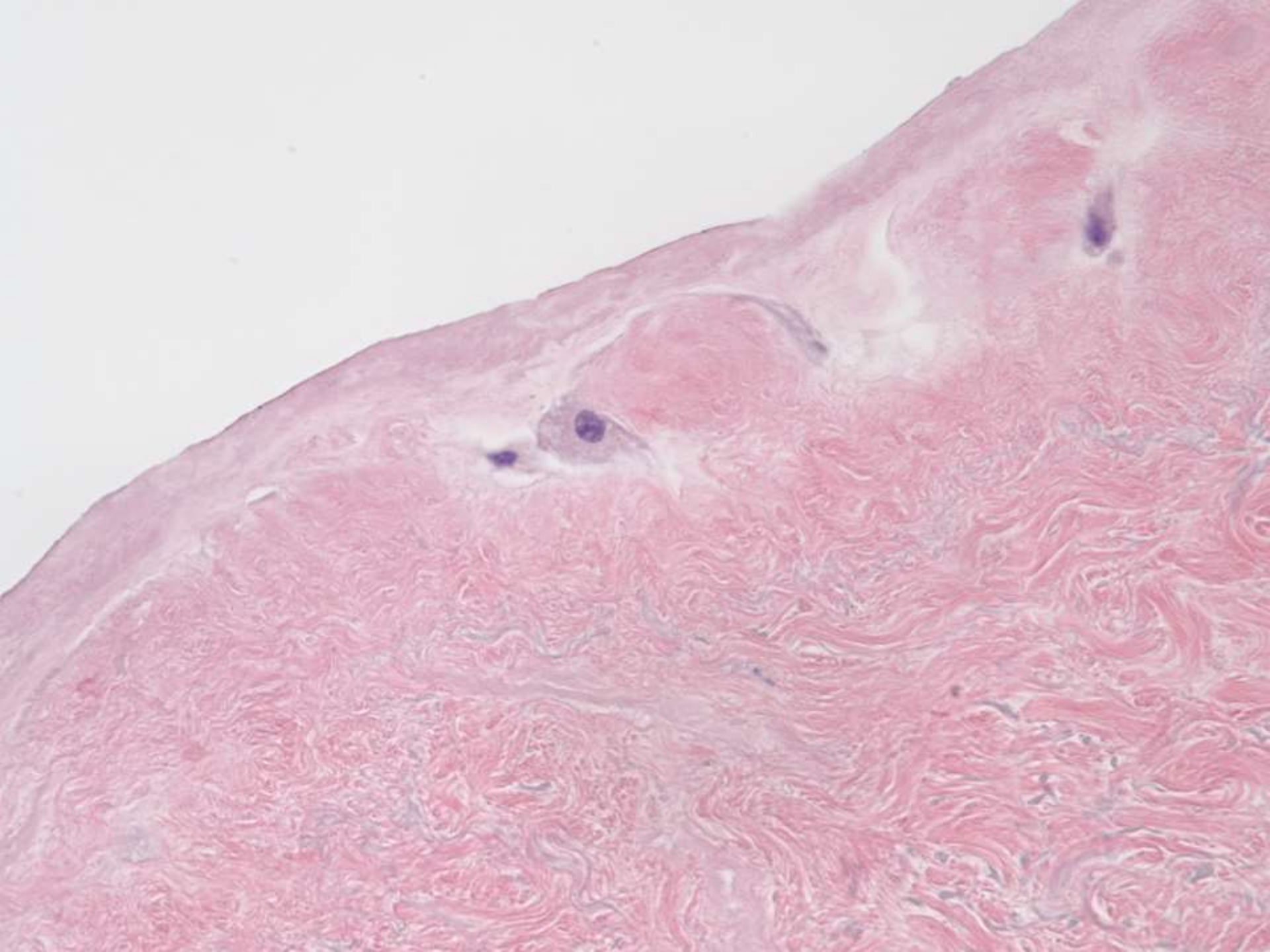
Megan Troxell; Stanford

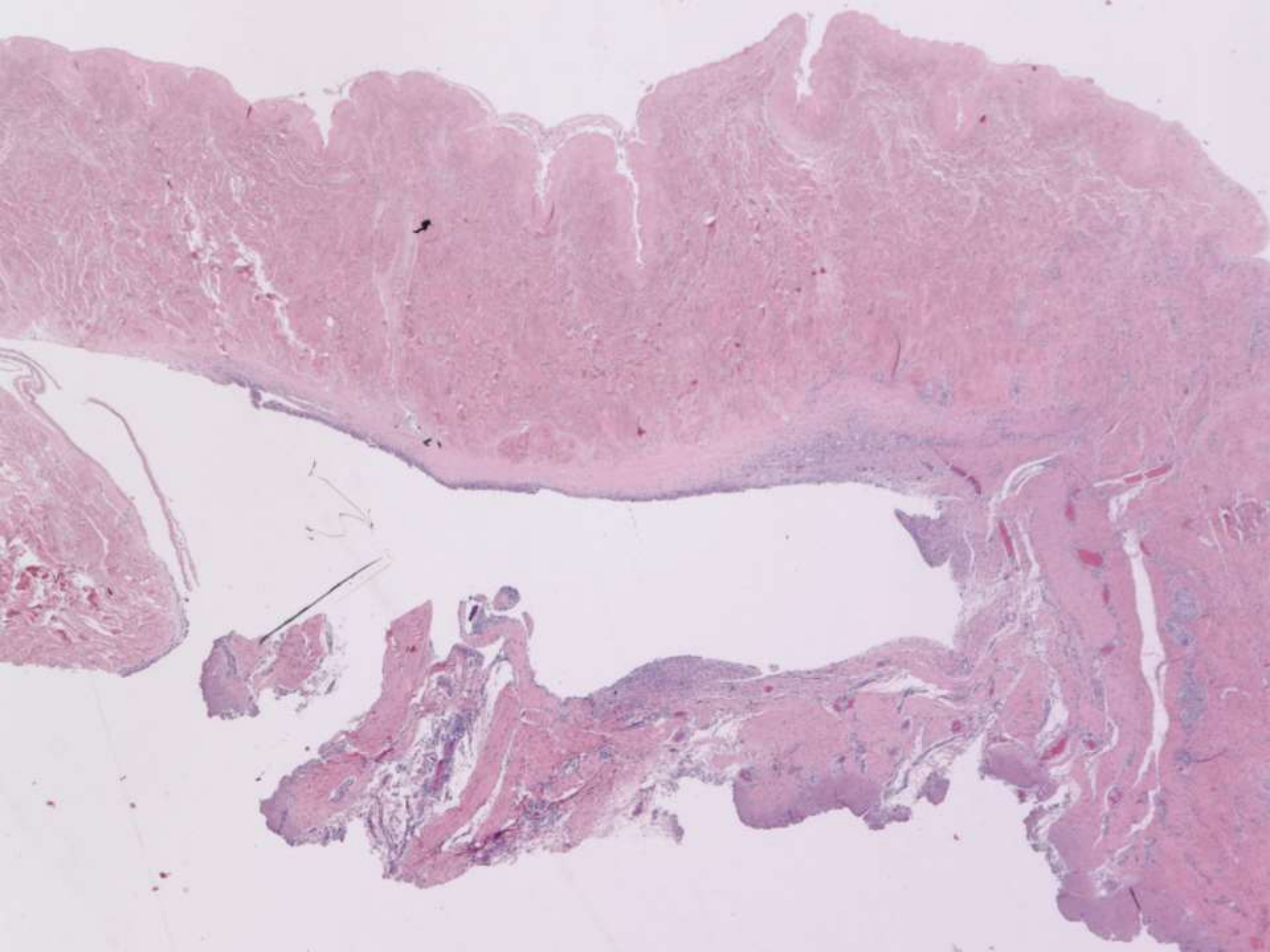
39-year-old female s/p bilateral mastectomy for extensive DCIS of left breast with bilateral breast reconstruction and tissue expander placement. She returns for capsulectomy and bilateral breast reconstruction revision and tissue expander removal.

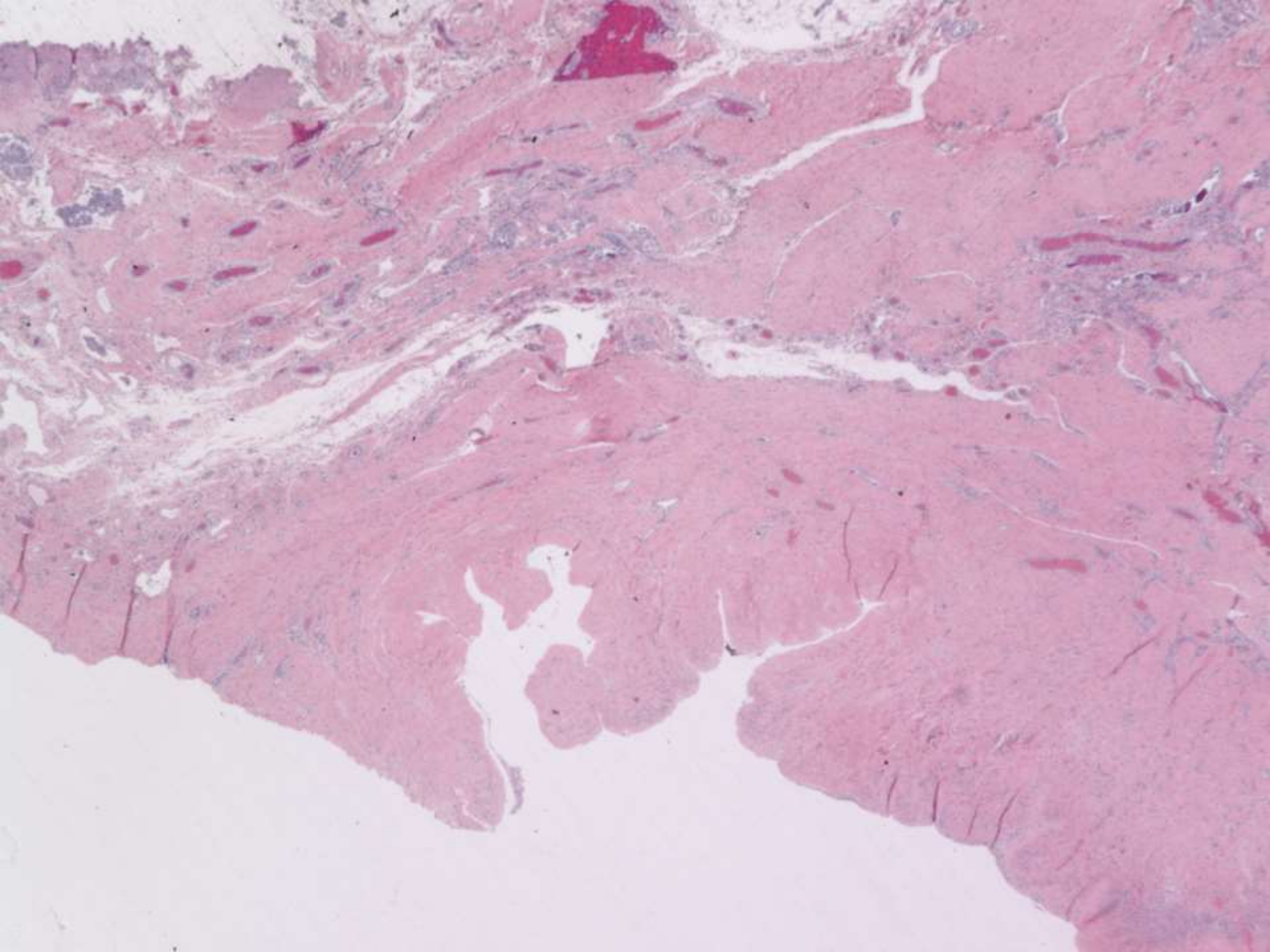


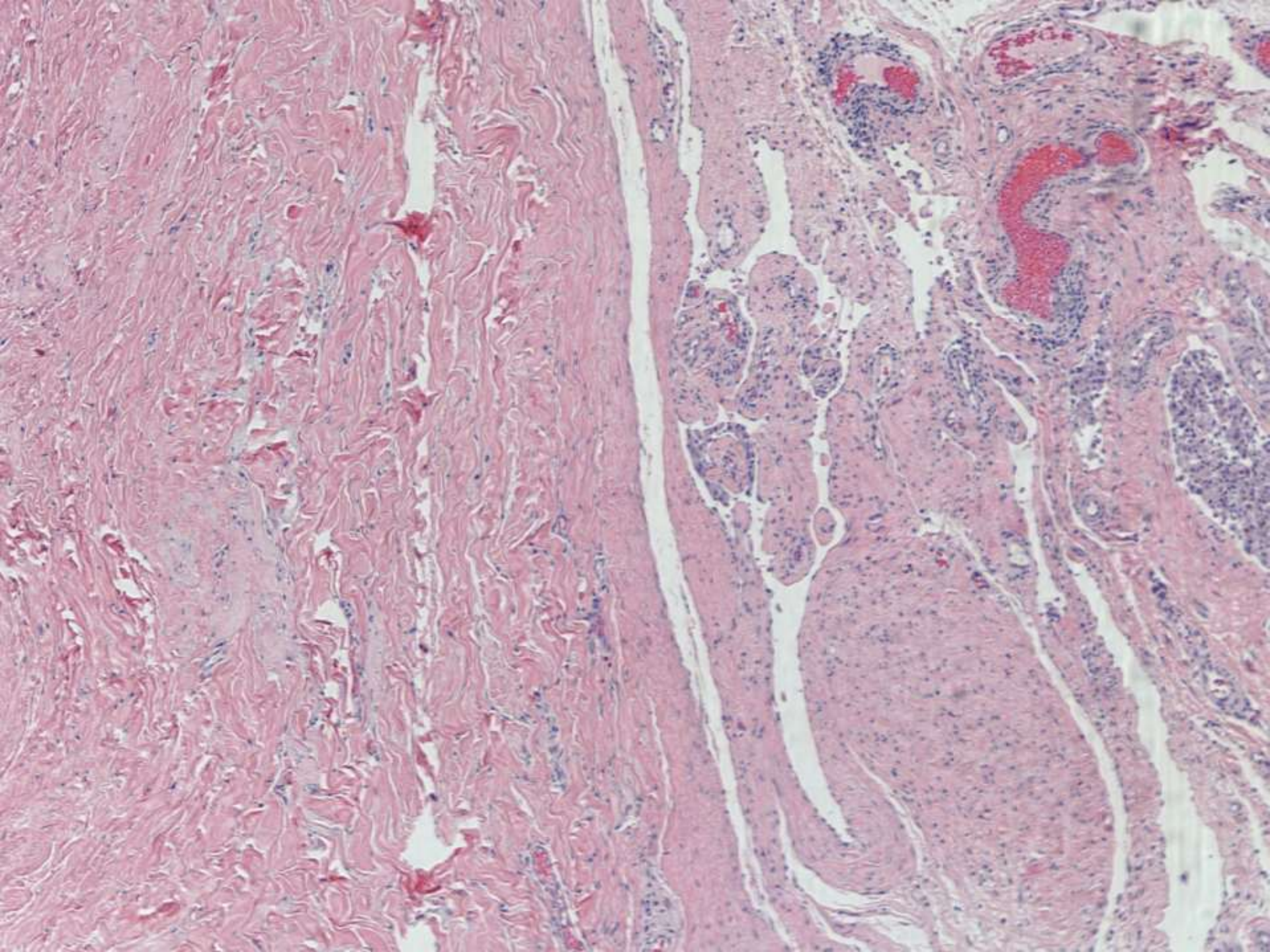


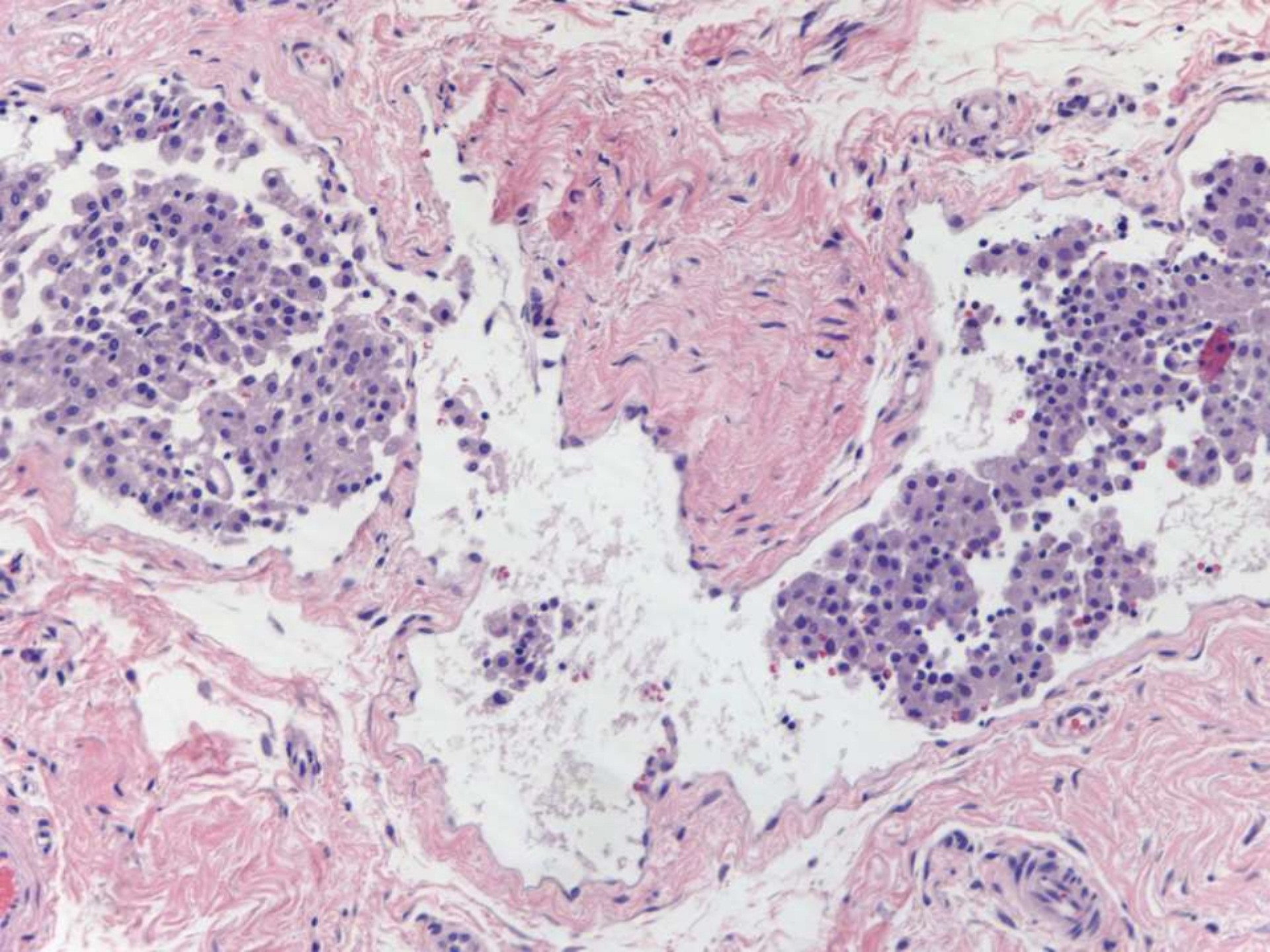


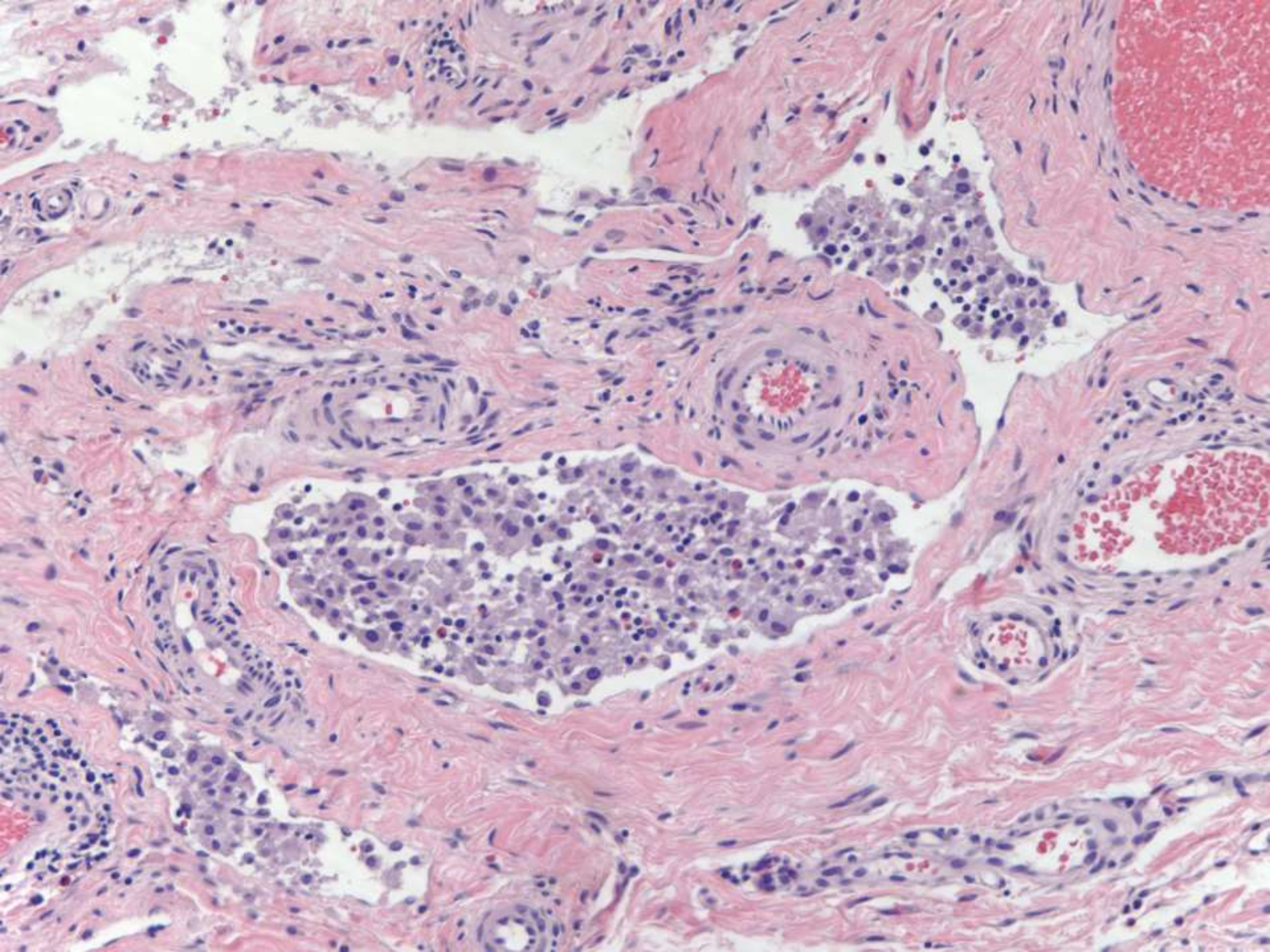


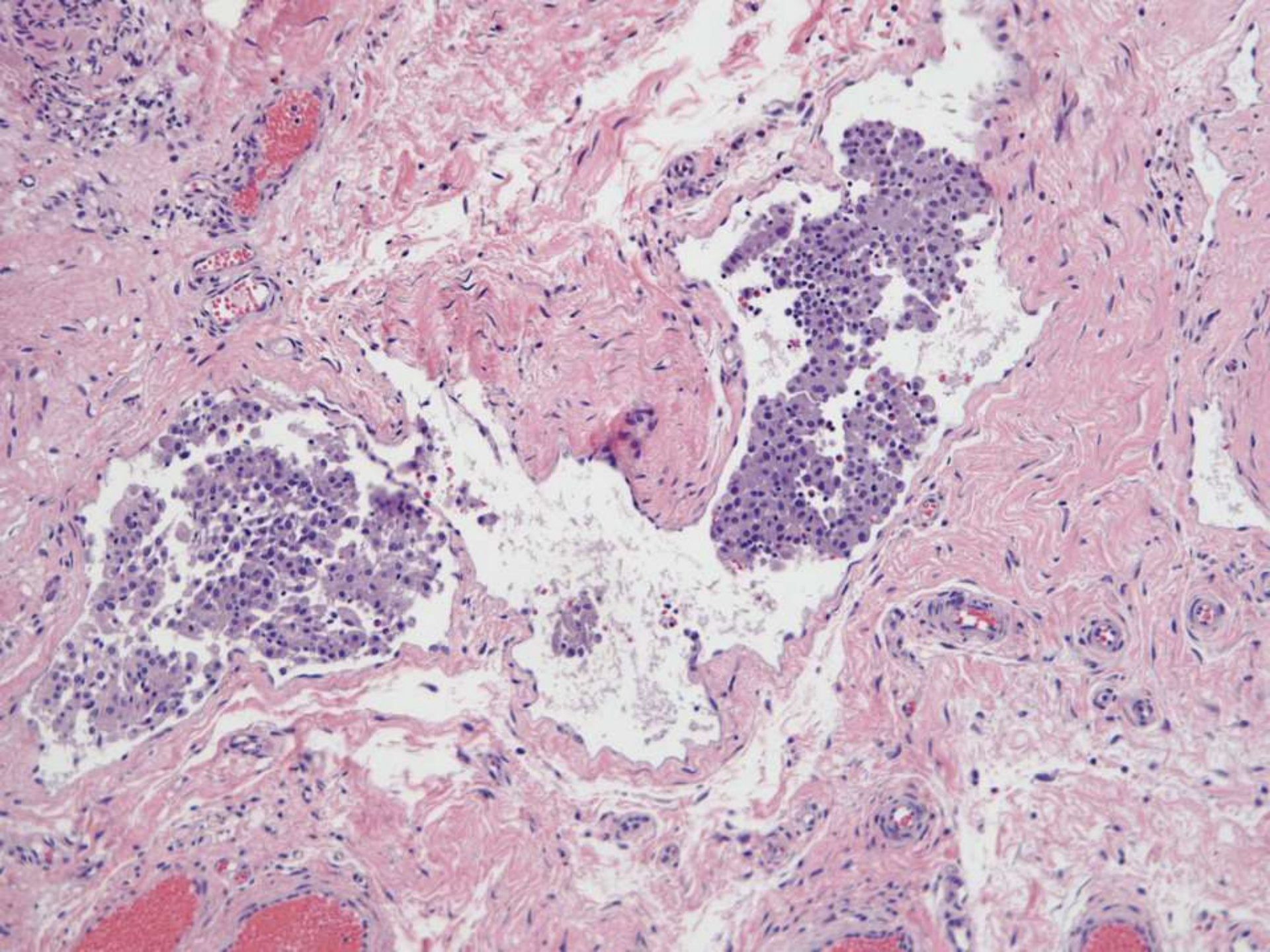








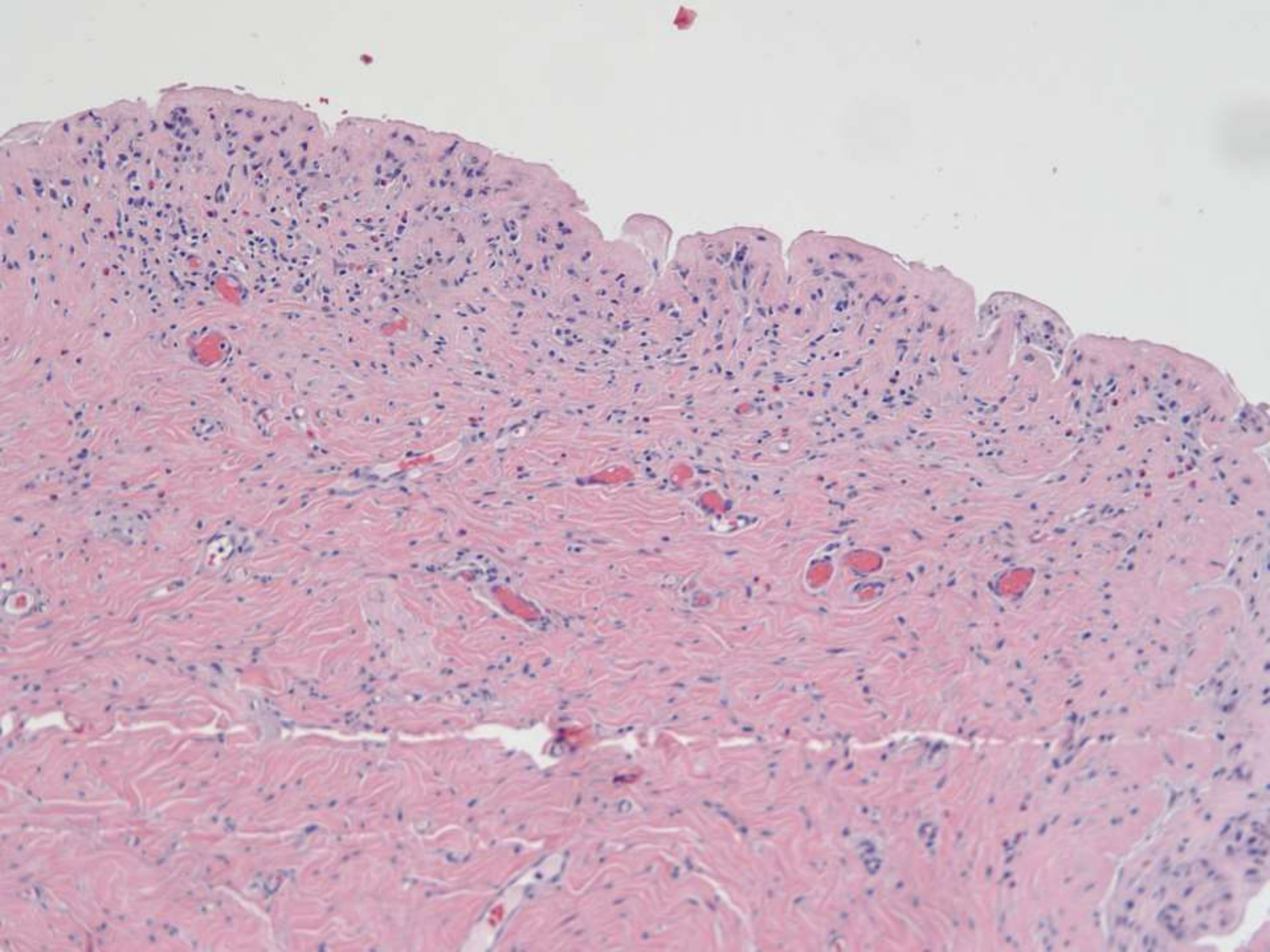


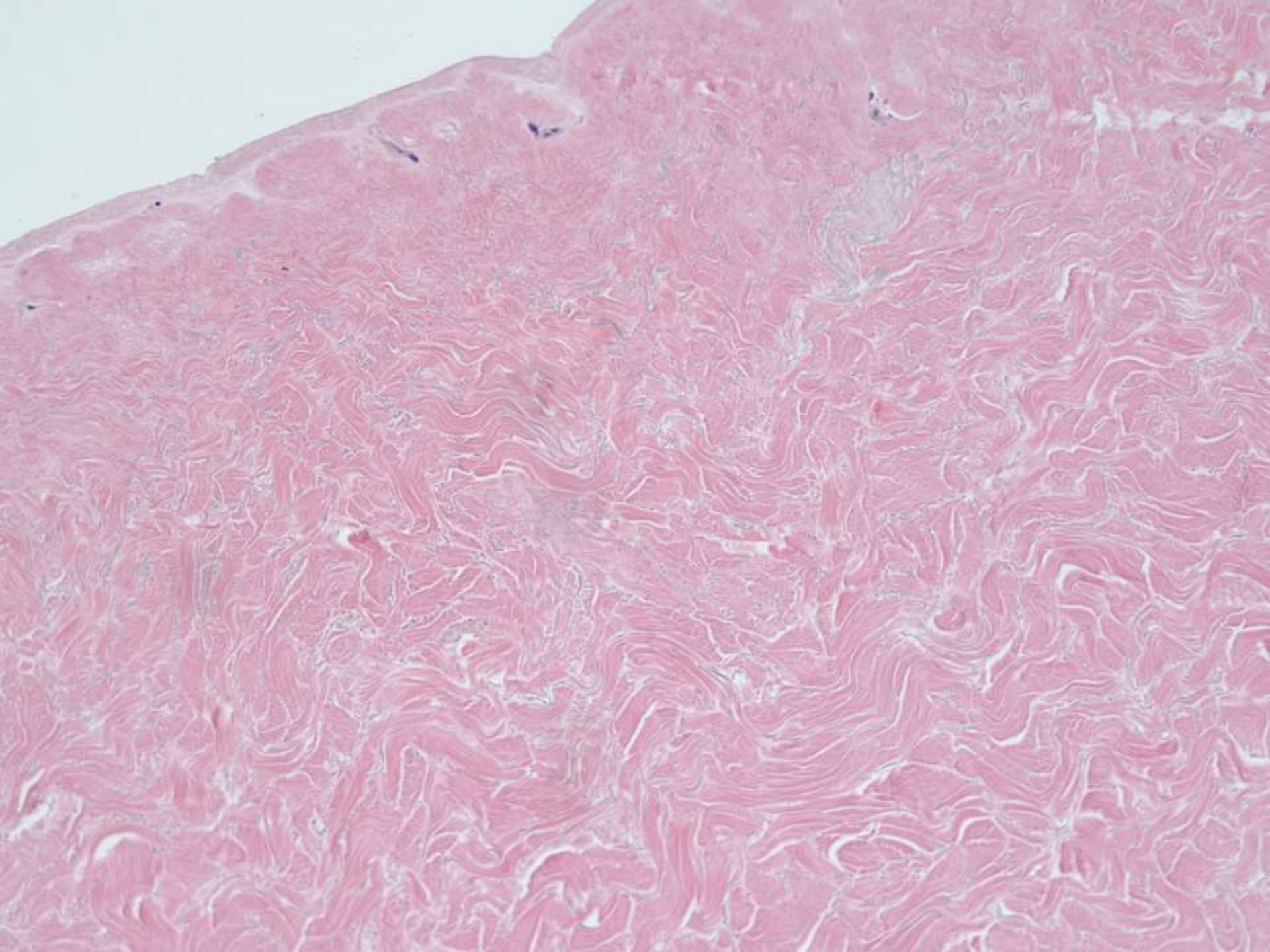


History:

38 year old BRCA2 positive woman

- Lumpectomy: Extensive Int/HG DCIS
- Bilateral Mastectomy and Reconstruction using tissue expander and acellular dermal matrix
- Capsulectomy of acellular dermal matrix and placement of silicone implant
- Patient is “happy with cosmetic results”

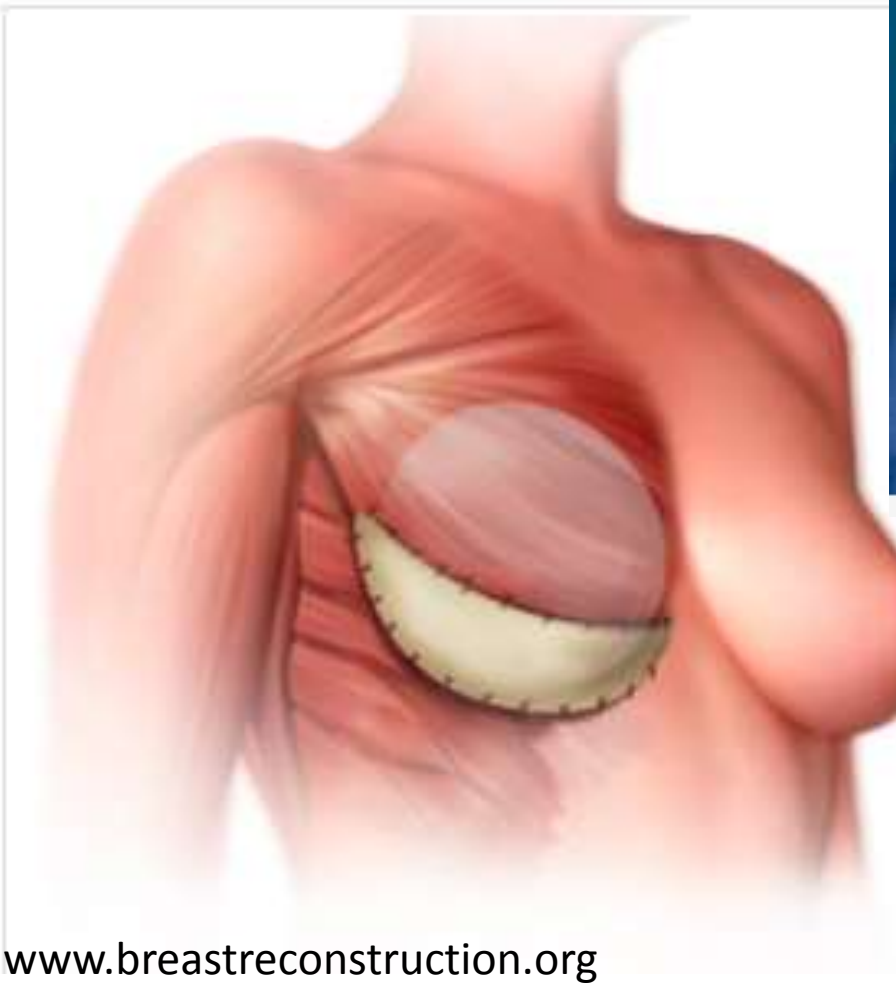




Acellular Dermal Matrix (ADM)

- Derived from donated (cadaveric) human skin
- “Multi-step process” that removes all the cells
- Essentially acts as a scaffold
- Over time, recipient cells grow into it
- U.S. Tissue Bank screens donors
  - Syphilis, Hepatitis B and C, and HIV 1 and 2
- Cost $5-7K/sheet

https://prma-enhance.com/breast-reconstruction-blog/what-is-alloderm-breast-reconstruction/



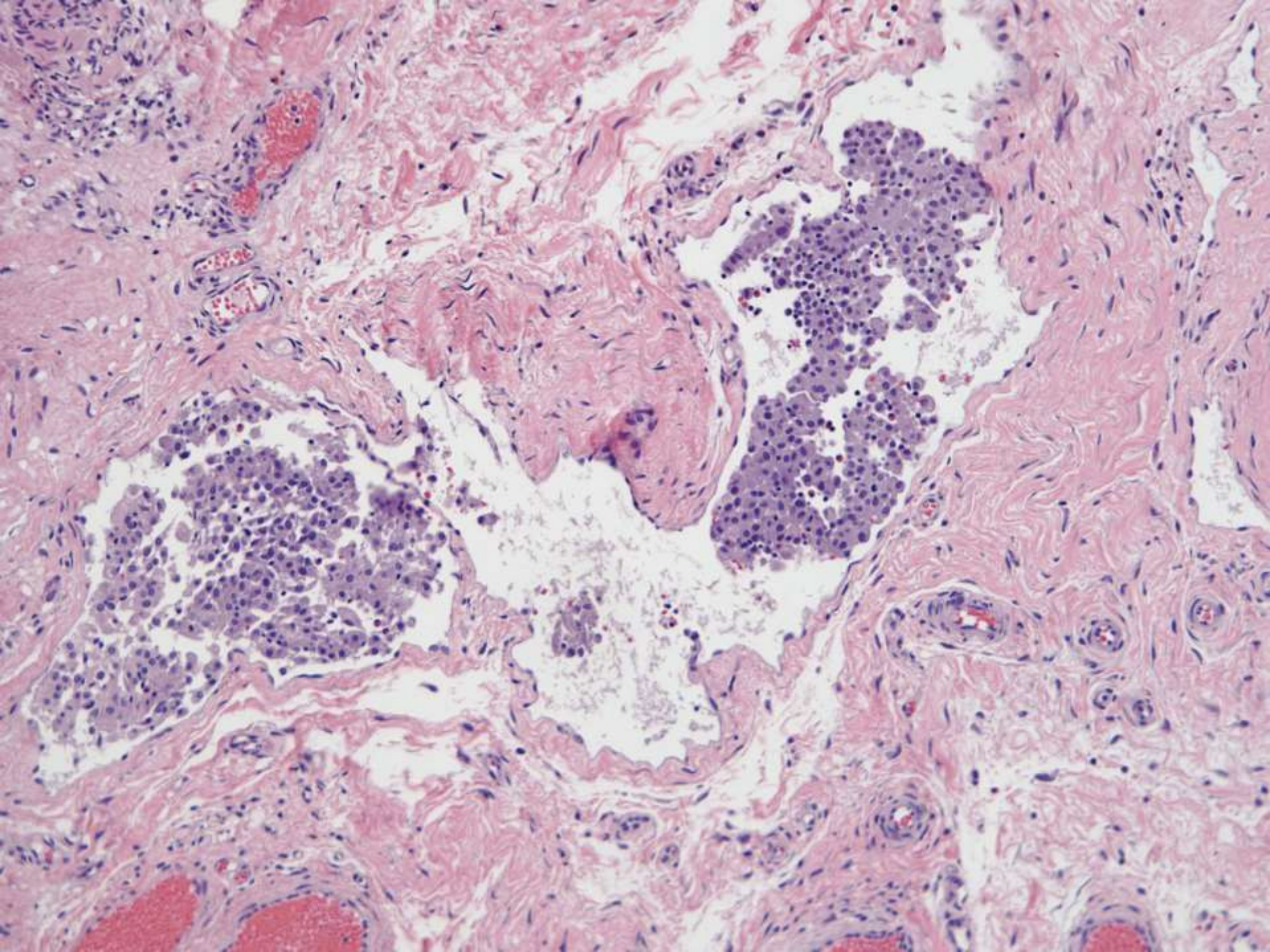
www.breastreconstruction.org

http://hcp.alloderm.com/

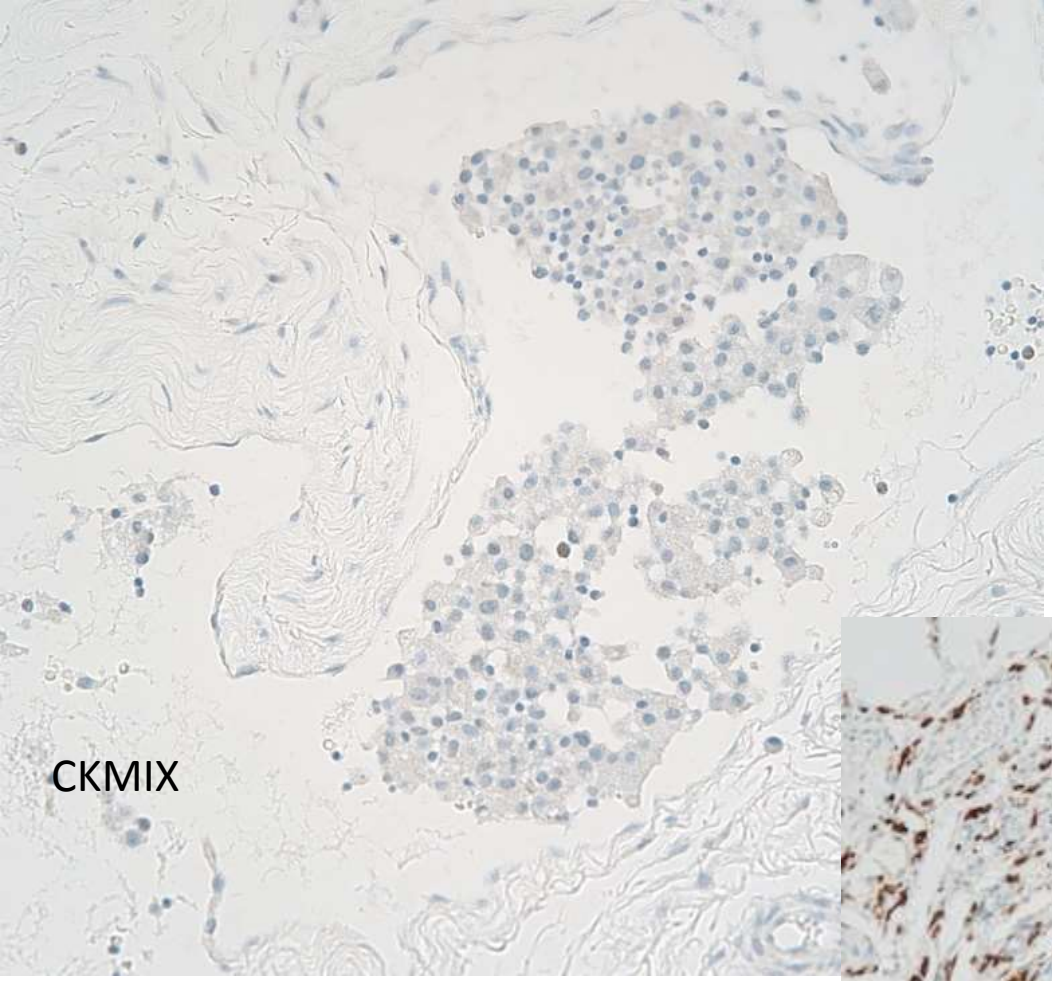
ADM	Source	Aseptic/sterile
AlloDerm (LifeCell Corp, Branchburg, NJ)	Human	Aseptic
AlloDerm RTU (LifeCell Corp, Branchburg, NJ)	Human	Sterile (SAL 10^{-3})
AlloMax (Davol Inc, Murray Hill, NJ)	Human	Sterile (SAL 10^{-6})
FlexHD (Ethicon Inc, Somerville, NJ)	Human	Aseptic
DermaMatrix (MTF/Synthes CMF, West Chester, Pa)	Human	Sterile (SAL 10^{-6})
DermACELL (LifeNet Health, Virginia Beach, Va)	Human	Sterile (SAL 10^{-6})
NeoForm (Mentor, Santa Barbara, Calif)	Human	Sterile (SAL 10^{-6})
Strattice (LifeCell Corp, Branchburg, NJ)	Porcine	Sterile (SAL 10^{-3})
Permacol (Covidien, Boulder, Colo)	Porcine	Sterile (SAL 10^{-6})
SurgiMend PRS (TEI Biosciences Inc, Boston, Mass)	Bovine	Sterile (SAL 10^{-6})

Zenn et al Eplasty. 2017 Jun 12;17:e18

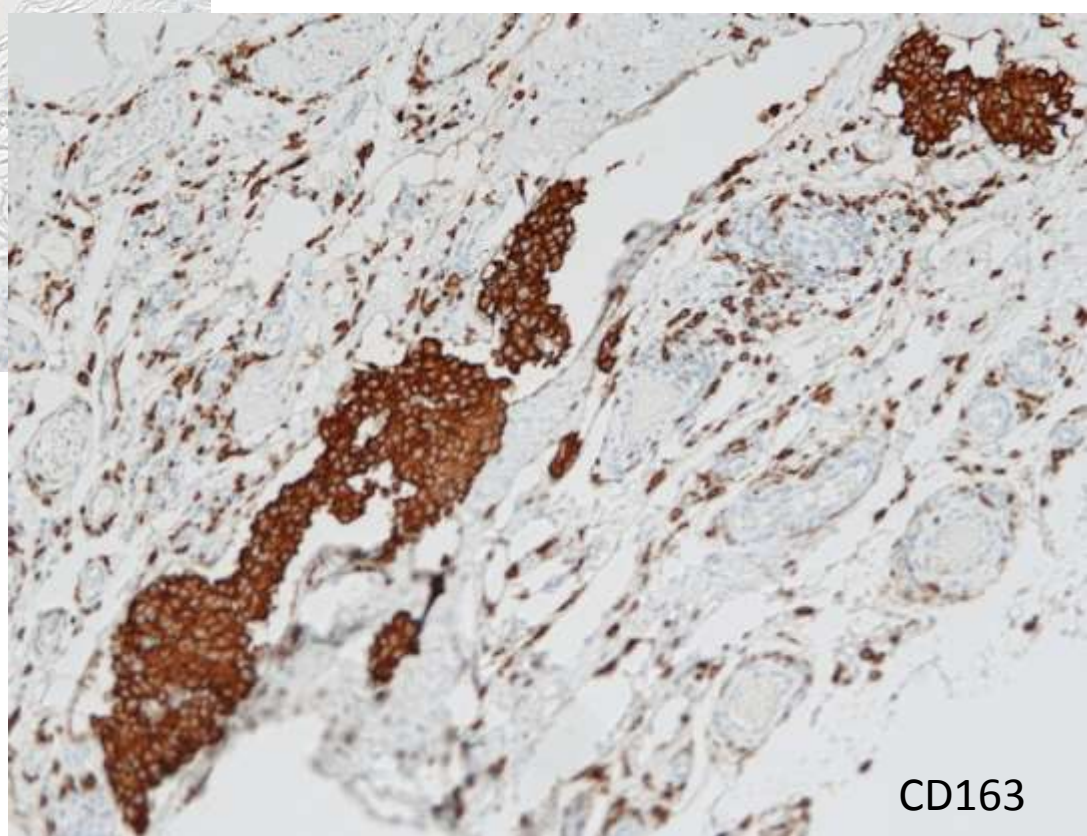
- Various tissue sources
  - human, bovine, porcine
- Methods of decellularization and Ag removal
- Use of supplemental crosslinking
- Final preparation (aseptic vs sterile).



Intravascular histiocytosis



CKMIX



CD163

Also negative:
S100, CD2, CD7, CD30, CD34
Scattered Ki-67+

Intralymphatic histiocytosis

- Usually skin
- Rash, erythema
- Ddx:
  - Reactive endotheliomatosis
  - intravascular lymphoma
  - Rosai-Dorfman

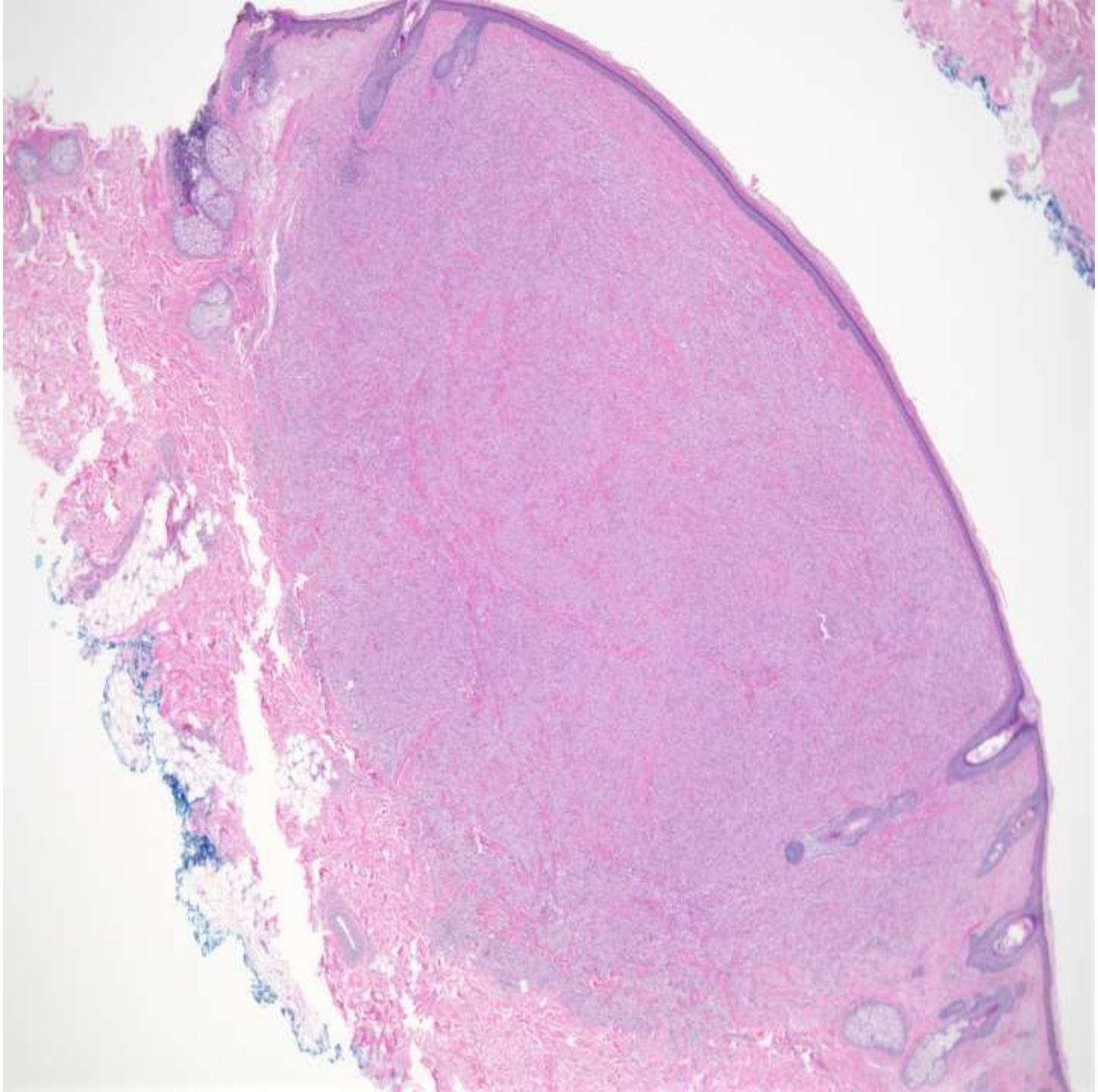
Associated disease
RA (16)
RA, breast carcinoma
RA, fibromyalgia
RA, lymphedema
RA, Klippel-Trenaunay syndrome
RA, Merkel cell carcinoma
RA, malignant melanoma
Rheumatic fever
Myocardial infarct, diabetes mellitus
Tonsillitis
Orthopedic metal implant
Breast carcinoma (2)
Post-metal prosthesis (3)
Melanoma in situ
Vulval necrosis
Colonic carcinoma, tuberculosis, and vasculitis

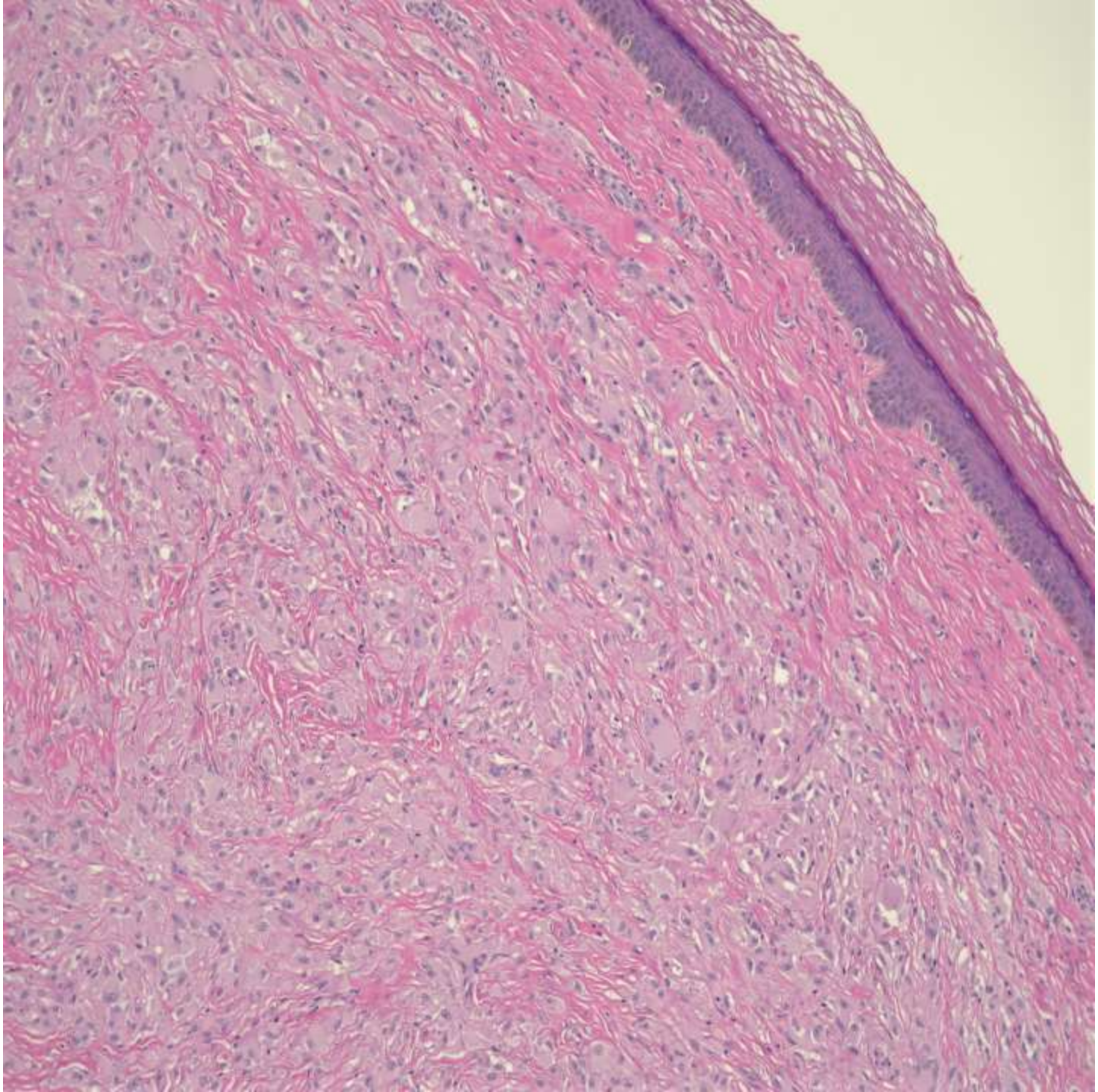
Bakr. J Am Acad Dermatol 2014;70:927-33

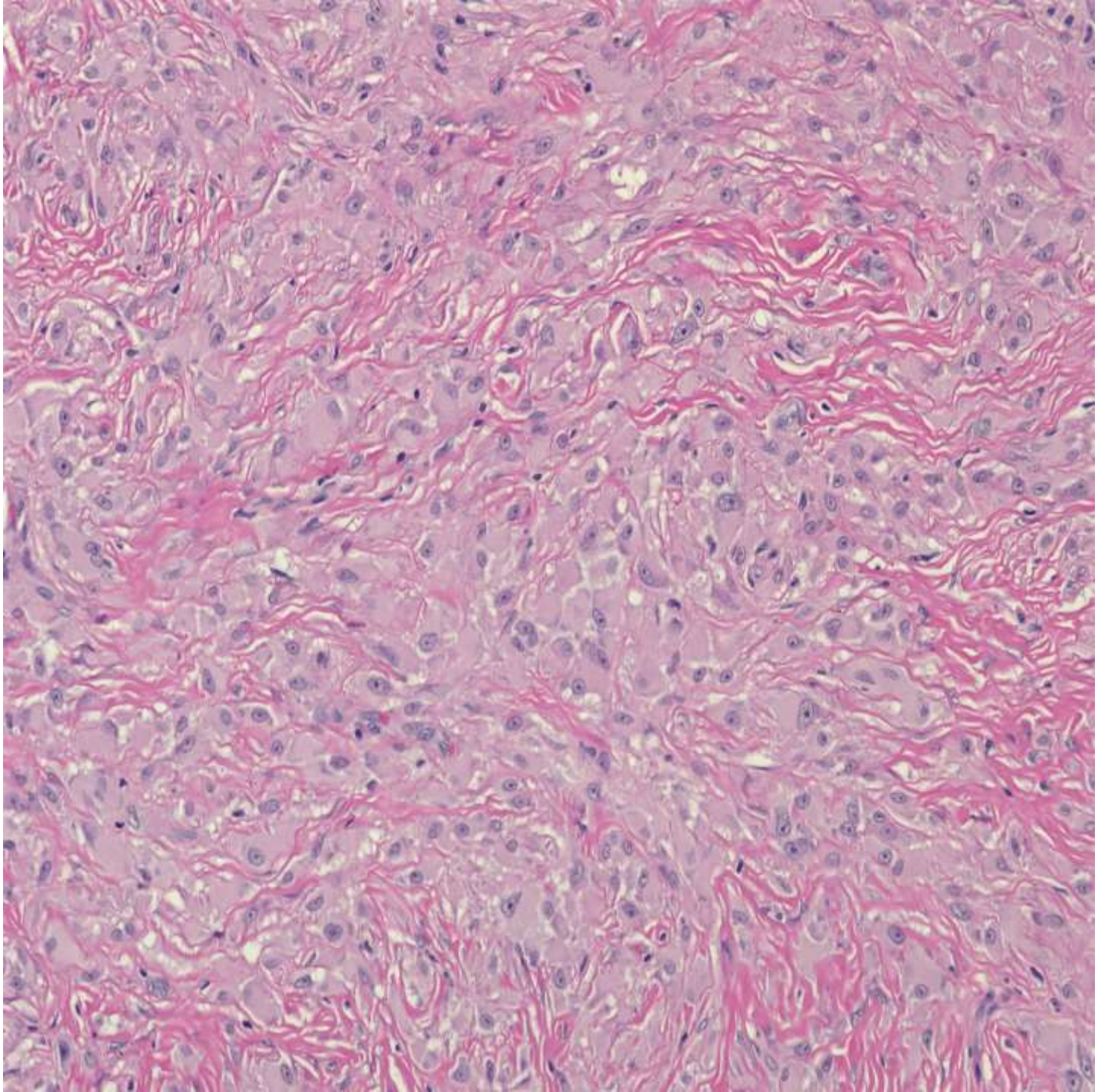
19-0406

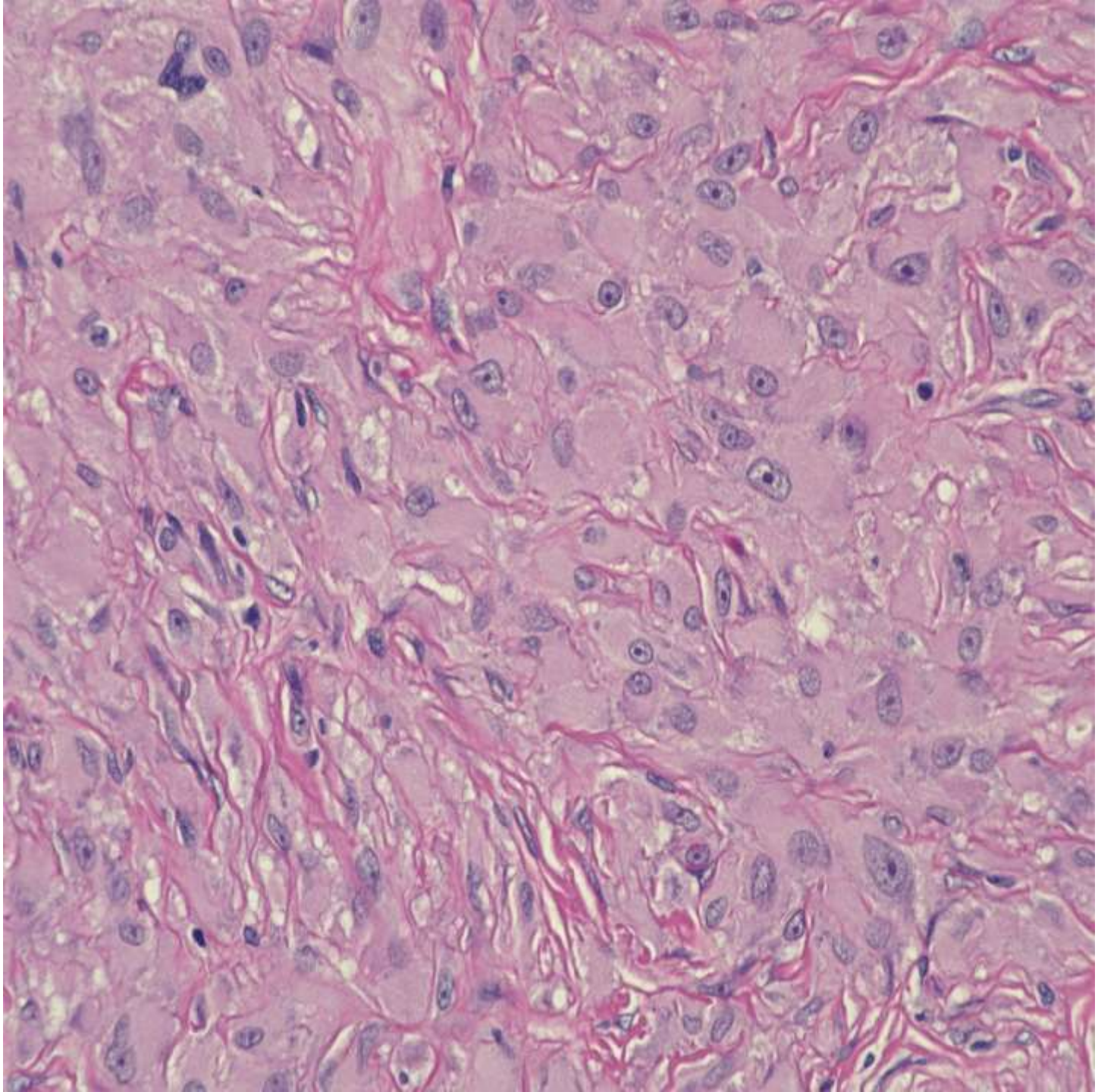
Sebastian Fernandez-Pol/Robero Novoa; Stanford

71-year-old male with a soft, palpable nodule on the left cheek, favor cyst.



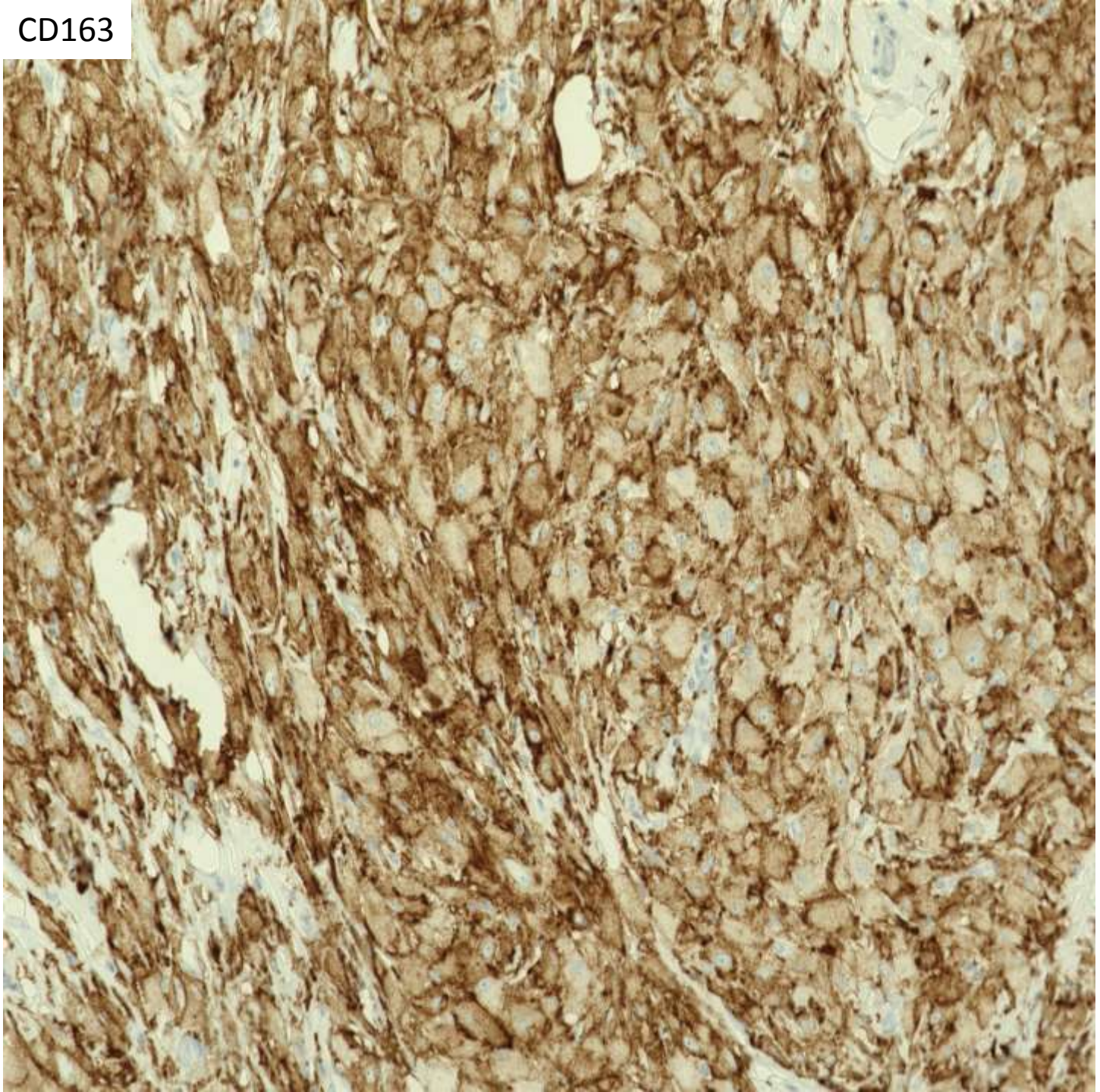


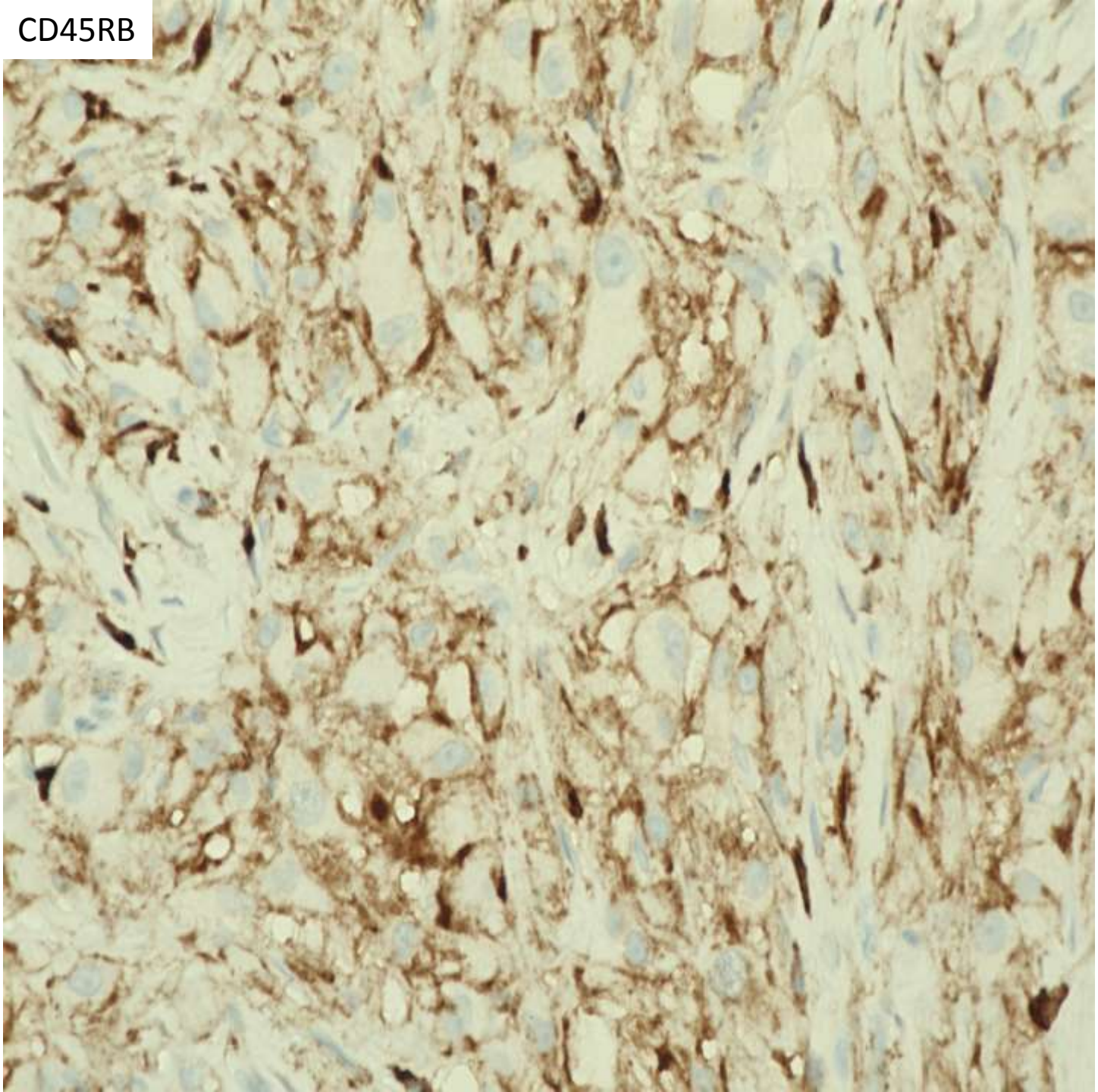




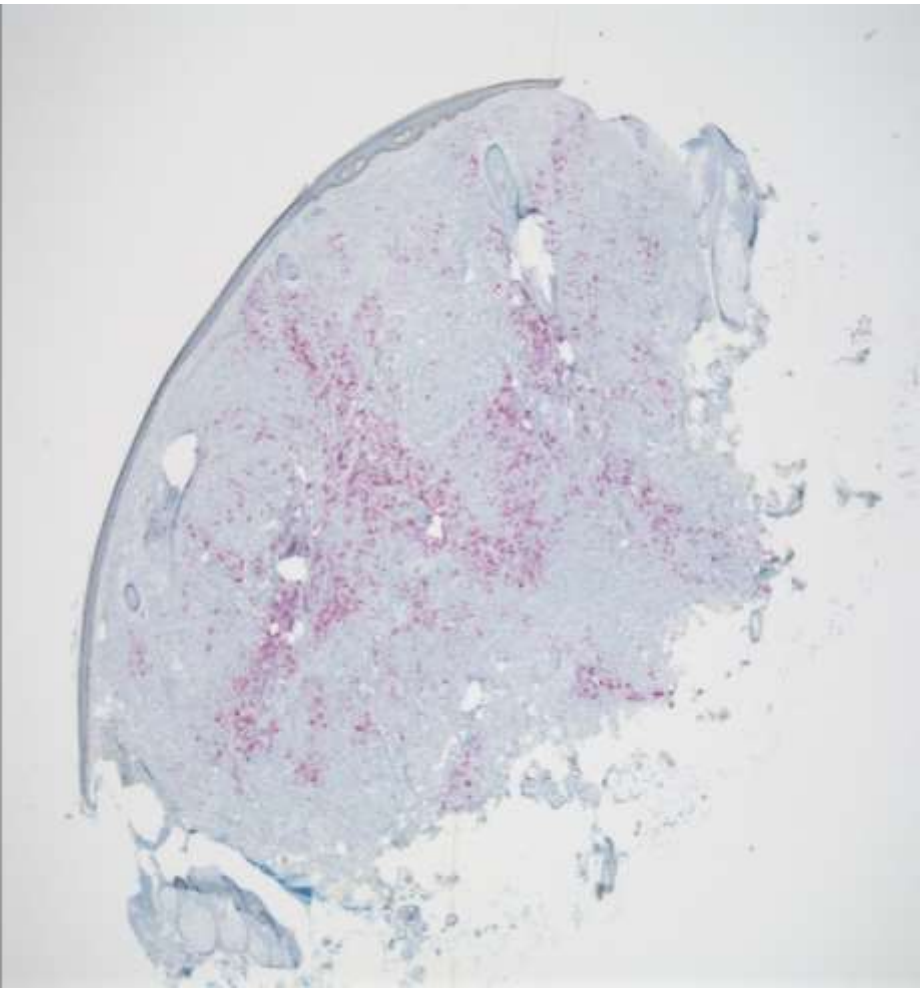
Differential diagnosis

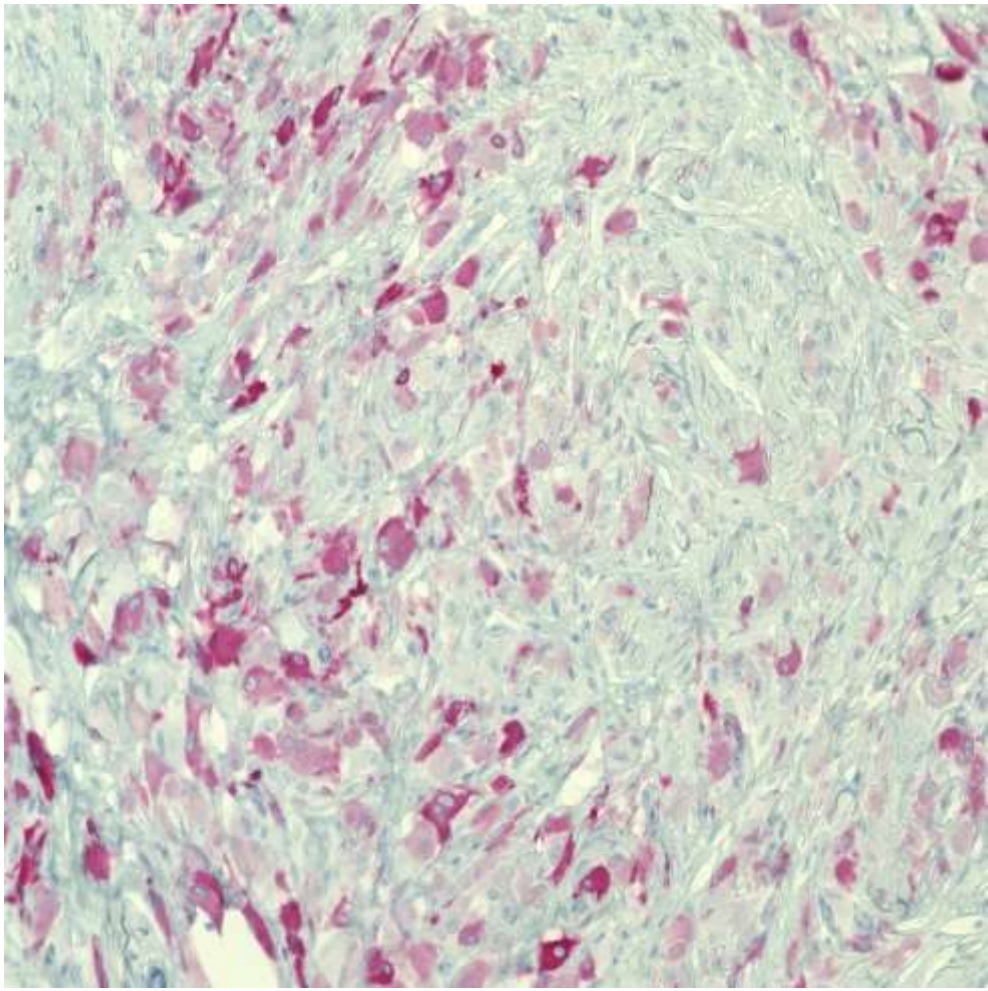
- **Reticulohistiocytoma (Solitary epithelioid histiocytoma) – CD163+, CD68+**
- Granular cell tumor – S100+, Inhibin+, SF1+, CD68+
- Cutaneous non-neural granular cell tumor – S100-, NKI-C3+, ALK+ (44%)
- Epithelioid fibrous histiocytoma – S100+/-, EMA+/-, Factor 13a, ALK+

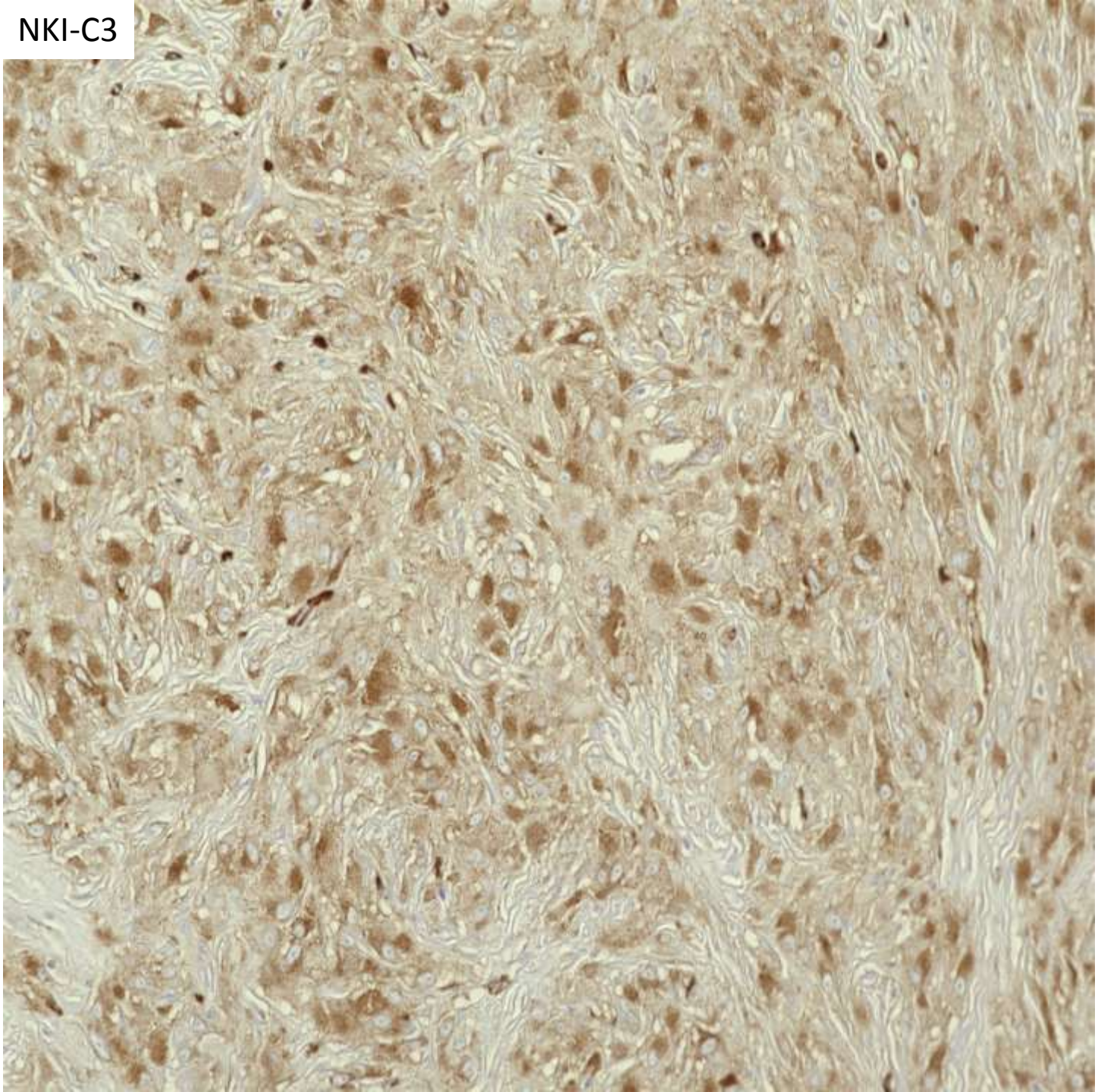

CD163

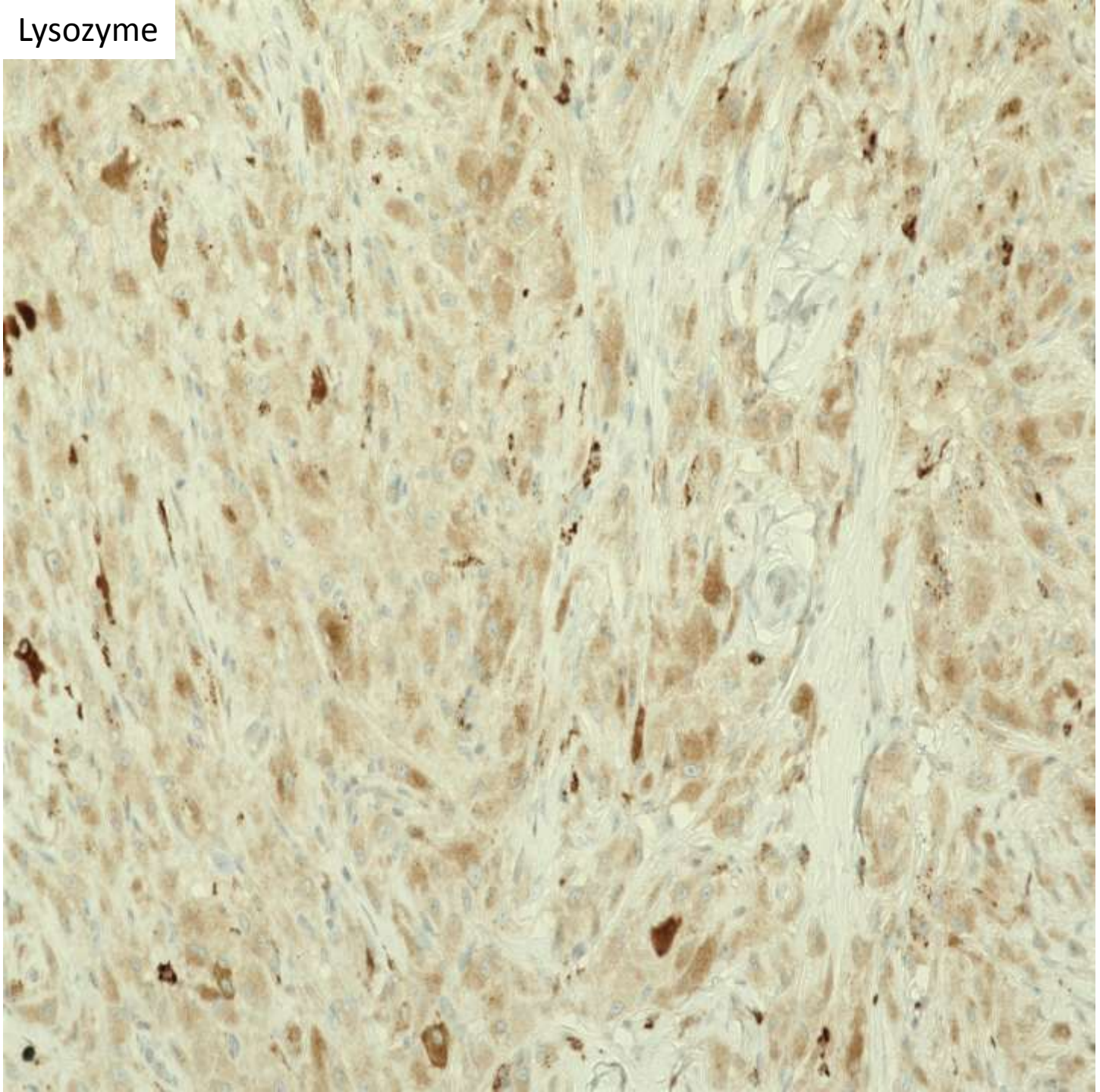

CD45RB

Melan A






NKI-C3


Lysozyme

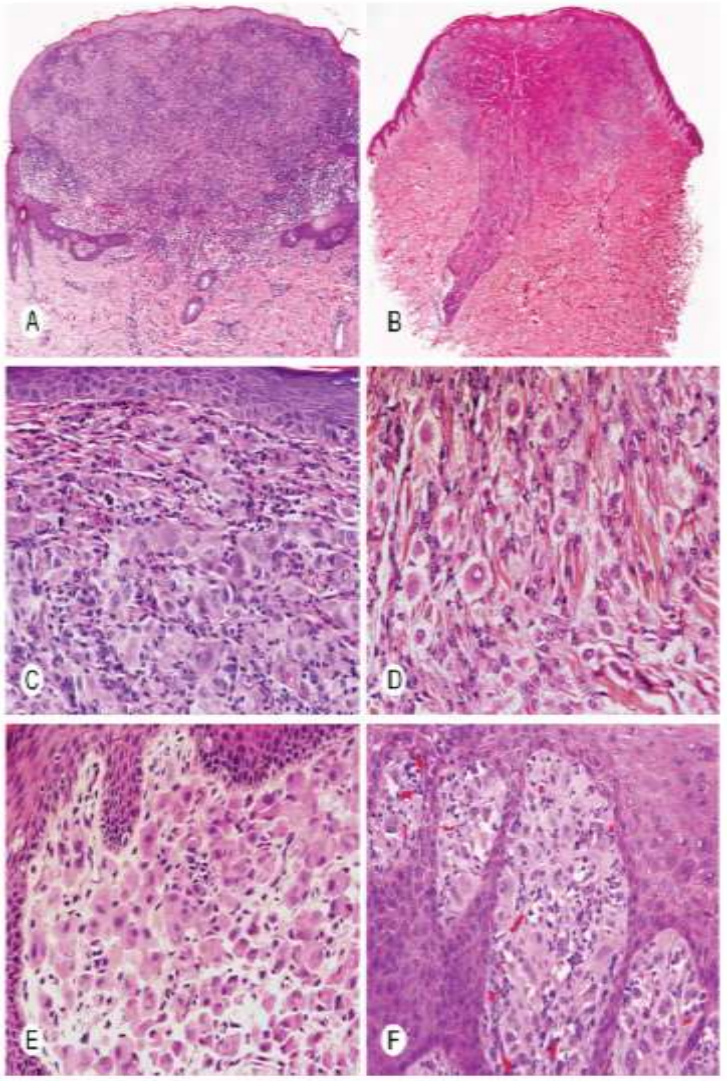
Reticulohistiocytoma

- Can exist as:
  - **Solitary nodule**
  - Multiple or generalized cutaneous nodules
  - “Multicentric reticulohistiocytosis”

Solitary epithelioid histiocytoma (reticulohistiocytoma)

- Benign dermal lesion composed of epithelioid histiocytes with eosinophilic “ground glass” cytoplasm that express histiocyte markers

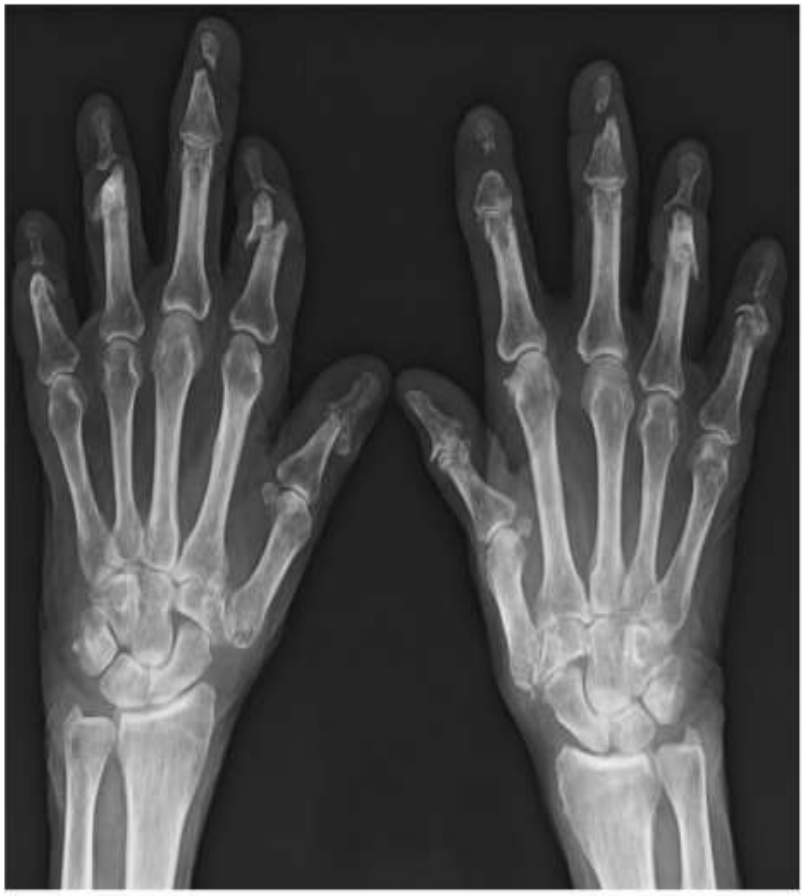
- **Typically does not recur following local excision**



Miettinen M, Fetsch JF: Reticulohistiocytoma (solitary epithelioid histiocytoma). A clinicopathologic and immunohistiochemical study of 44

Multicentric reticulohistiocytosis

- Symmetric erosive polyarthritis mimicking rheumatoid arthritis
- Subsequent appearance of typical papulonodular skin lesions
- Generally remits spontaneously in 10 years
- Frequent coexistence of neoplasms or autoimmune diseases warrant a careful evaluation of suspected cases

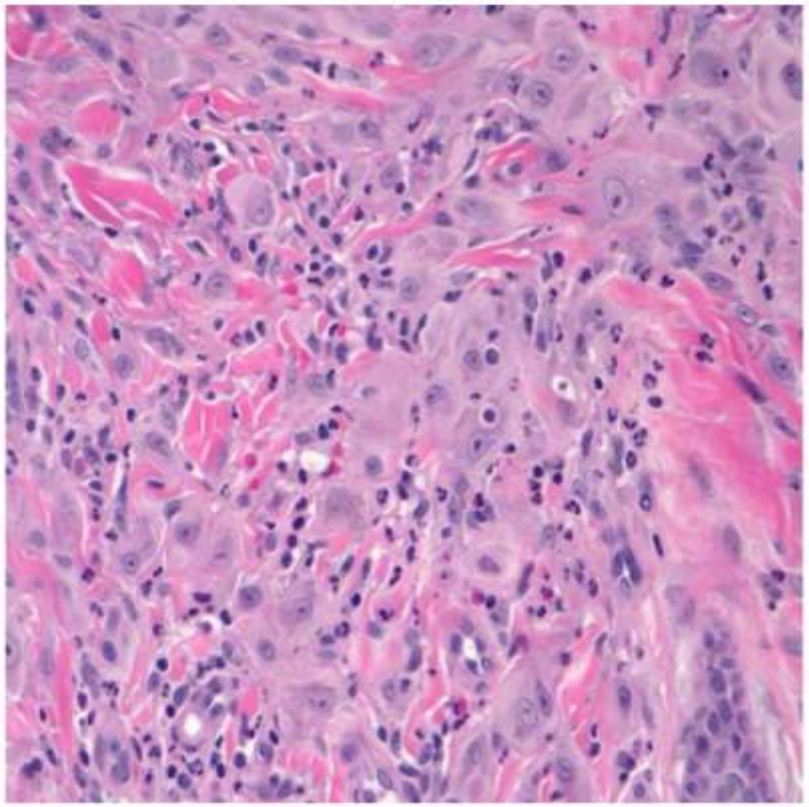


Selmi C, Greenspan A, Huntley A, Gershwin ME. Multicentric reticulohistiocytosis: a critical review. Curr Rheumatol Rep. 2015 Jun;17(6):511. doi:

Reticulohistiocytoma (solitary epitheloid histiocytoma)

Table 2. Immunohistochemistry profile of reticulohistiocytoma

Immunoperoxidase stain expression
Consistent positive expression [a]
CD68
CD163
Vimentin
Variable positive expression [b]
MITF
S100 protein
No expression [c]
CD1a
Cytokeratin
HMB-45
Melan-A/MART-1
Tyrosine

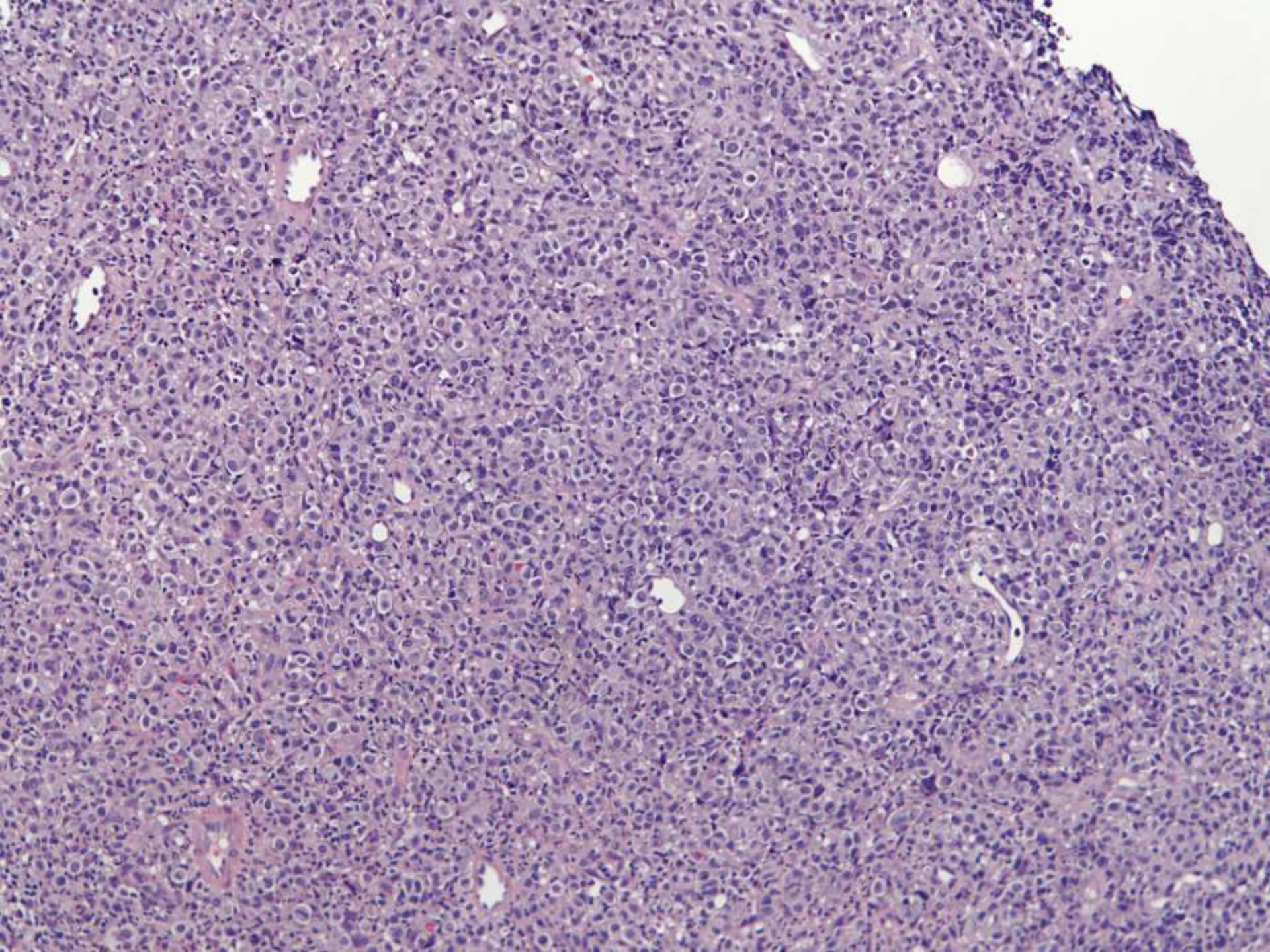


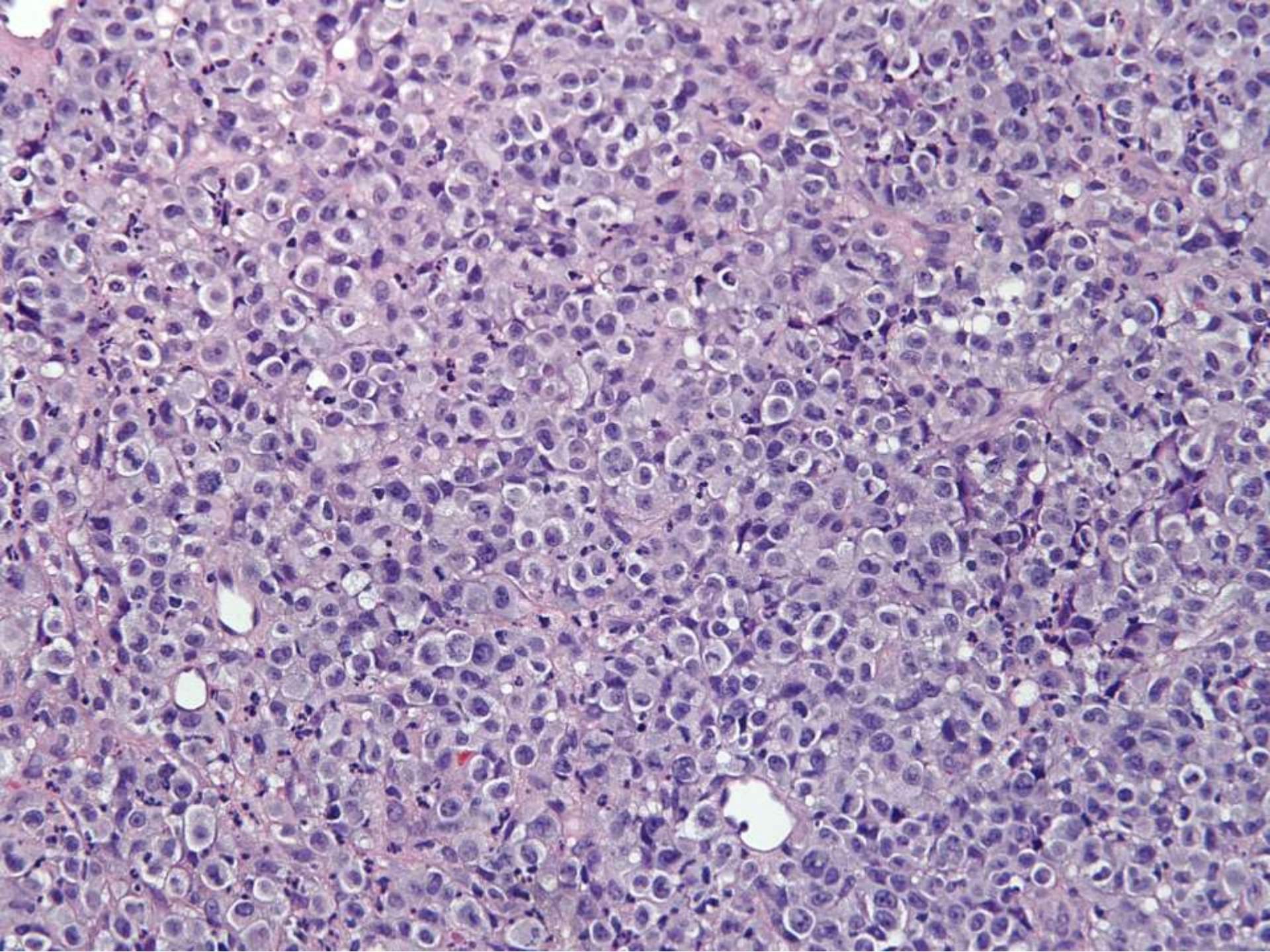
Cohen PR, Lee RA. Adult-onset reticulohistiocytoma presenting as a solitary asymptomatic red knee nodule: report and review of clinical presentations and immunohistochemistry staining features of reticulohistiocytosis. Dermatol Online J. 2014 Mar 17;20(3).

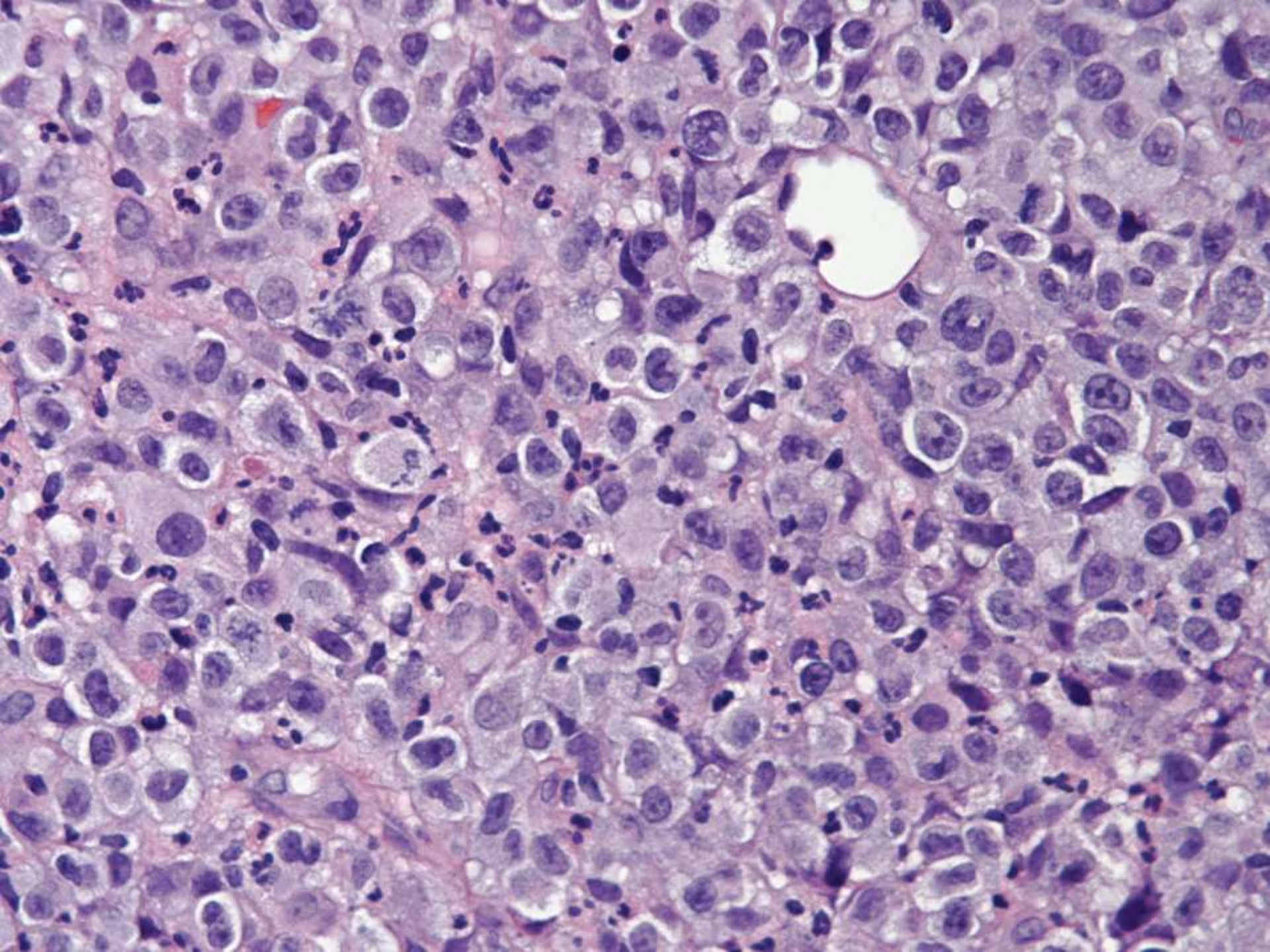
19-0407

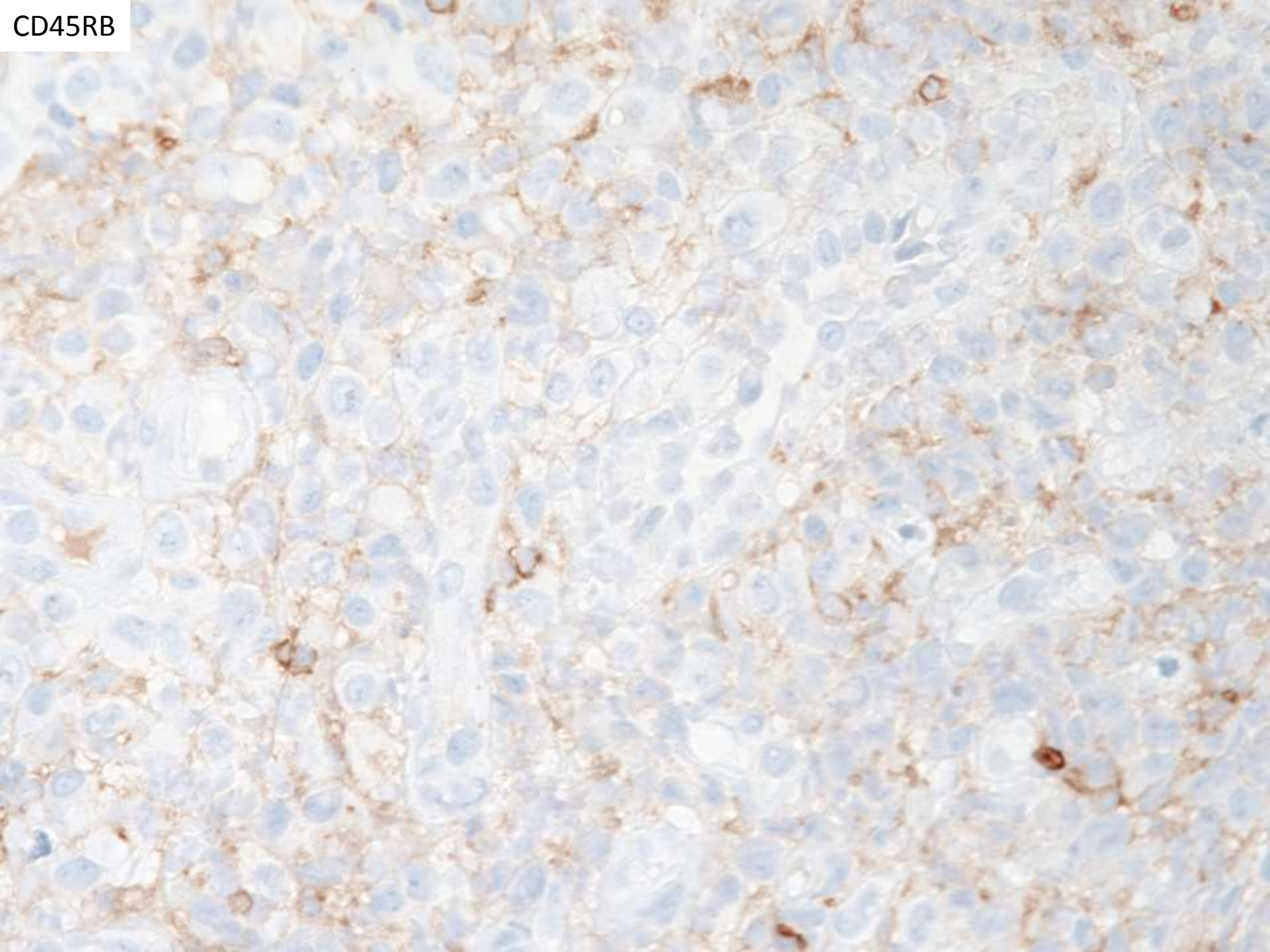
Sebastian Fernandez-Pol/Yaso Natkunam; Stanford

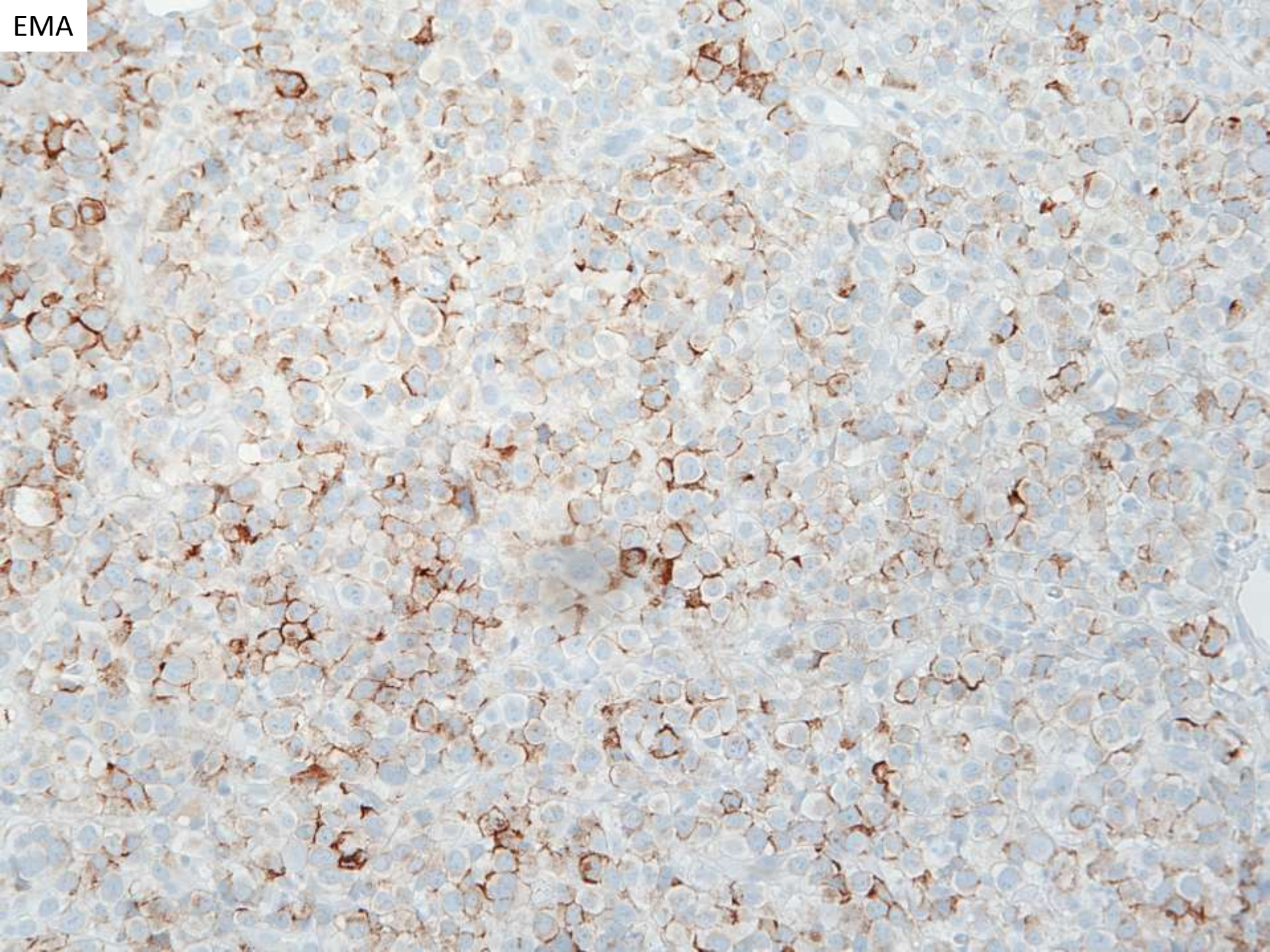
64-year-old female with a 2cm pancreatic head mass.



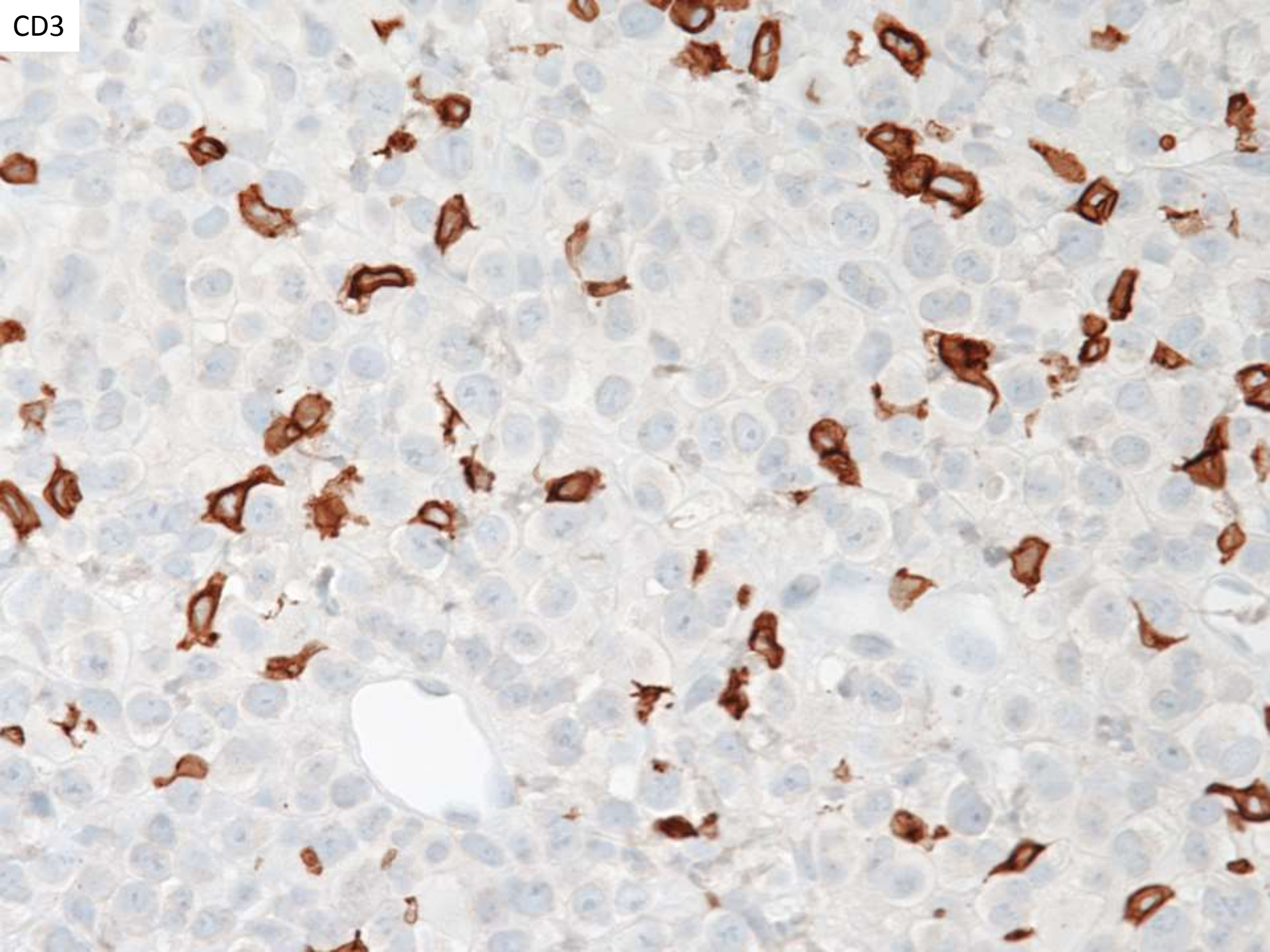


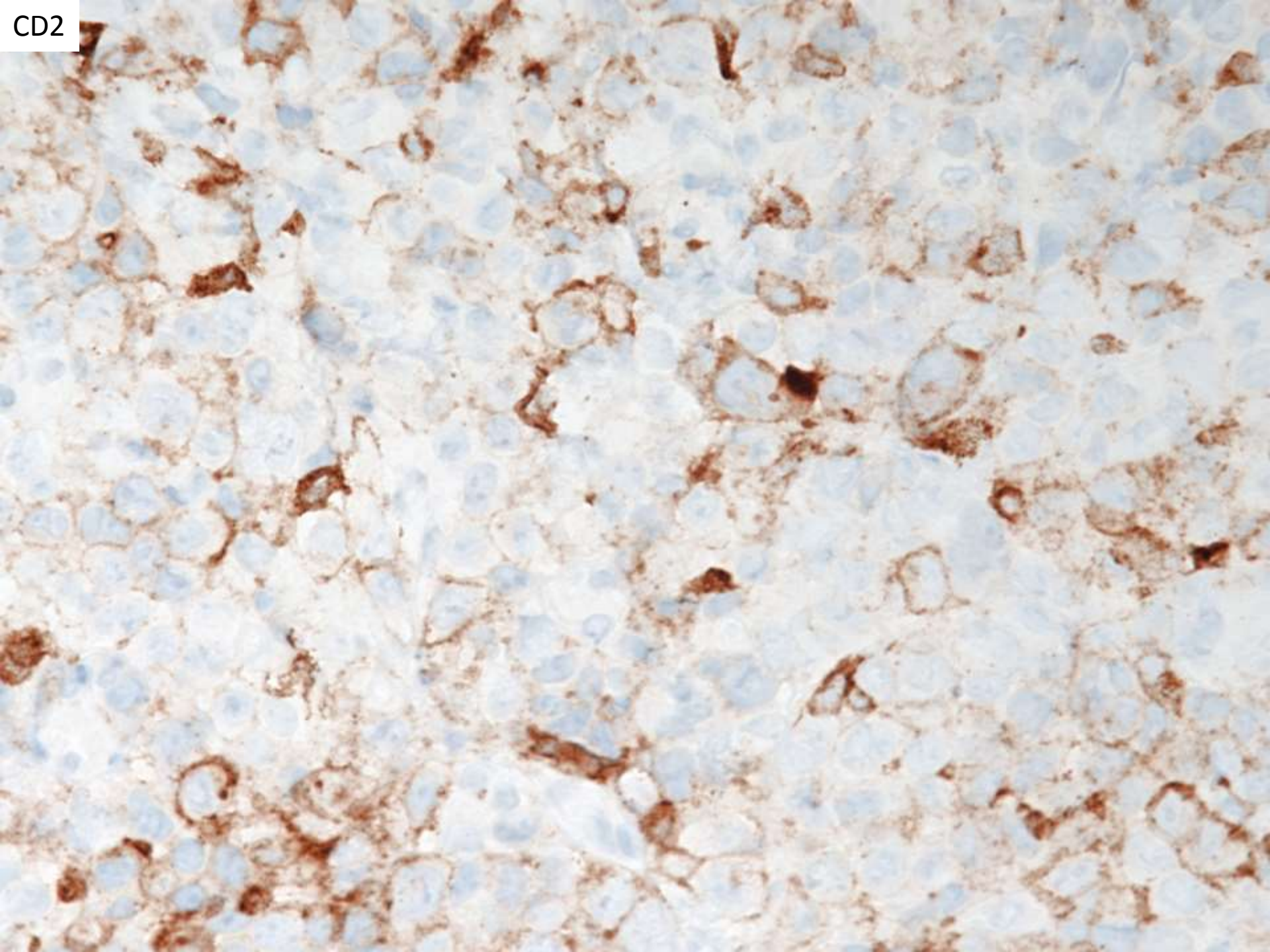


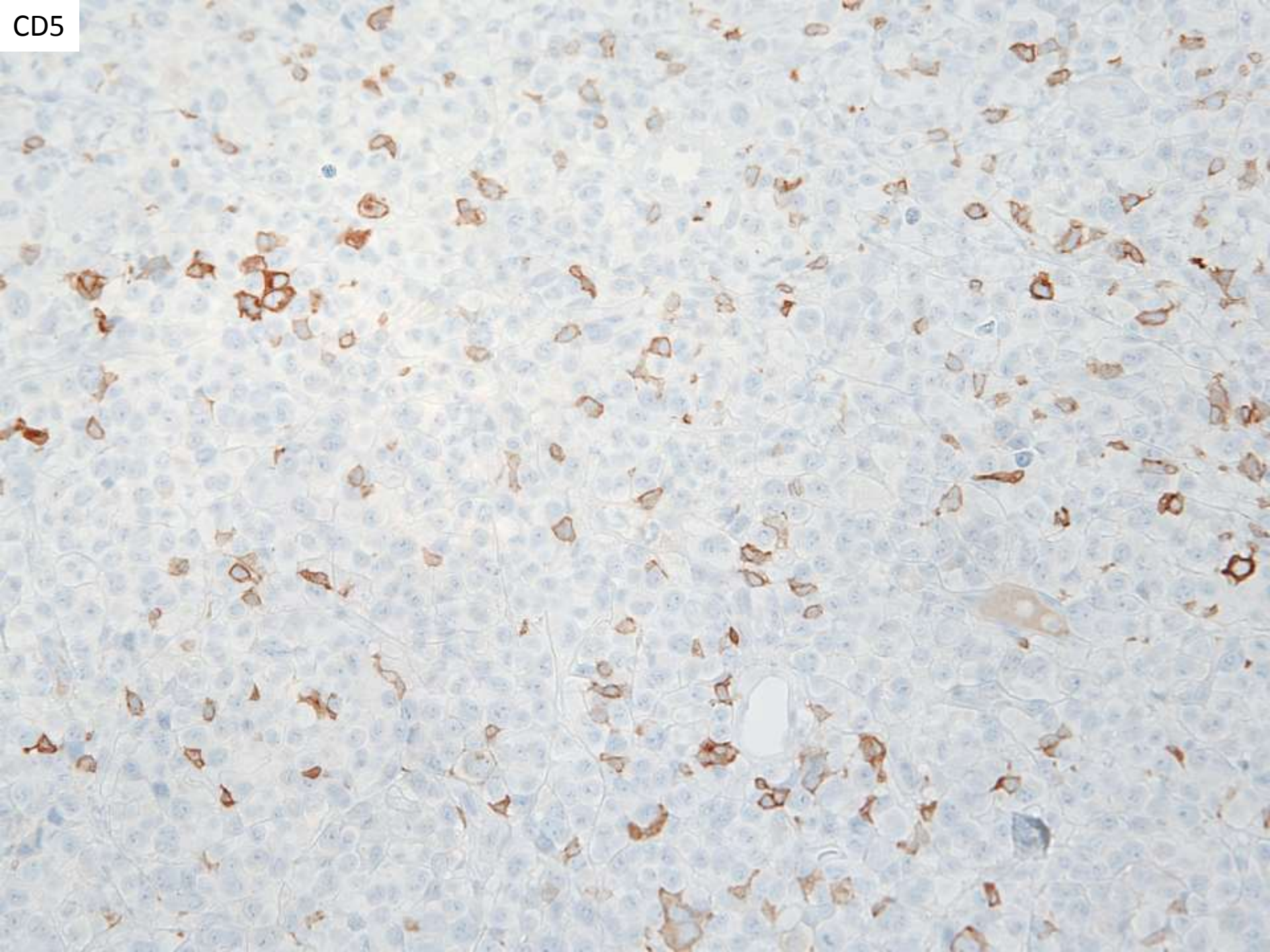

CD45RB

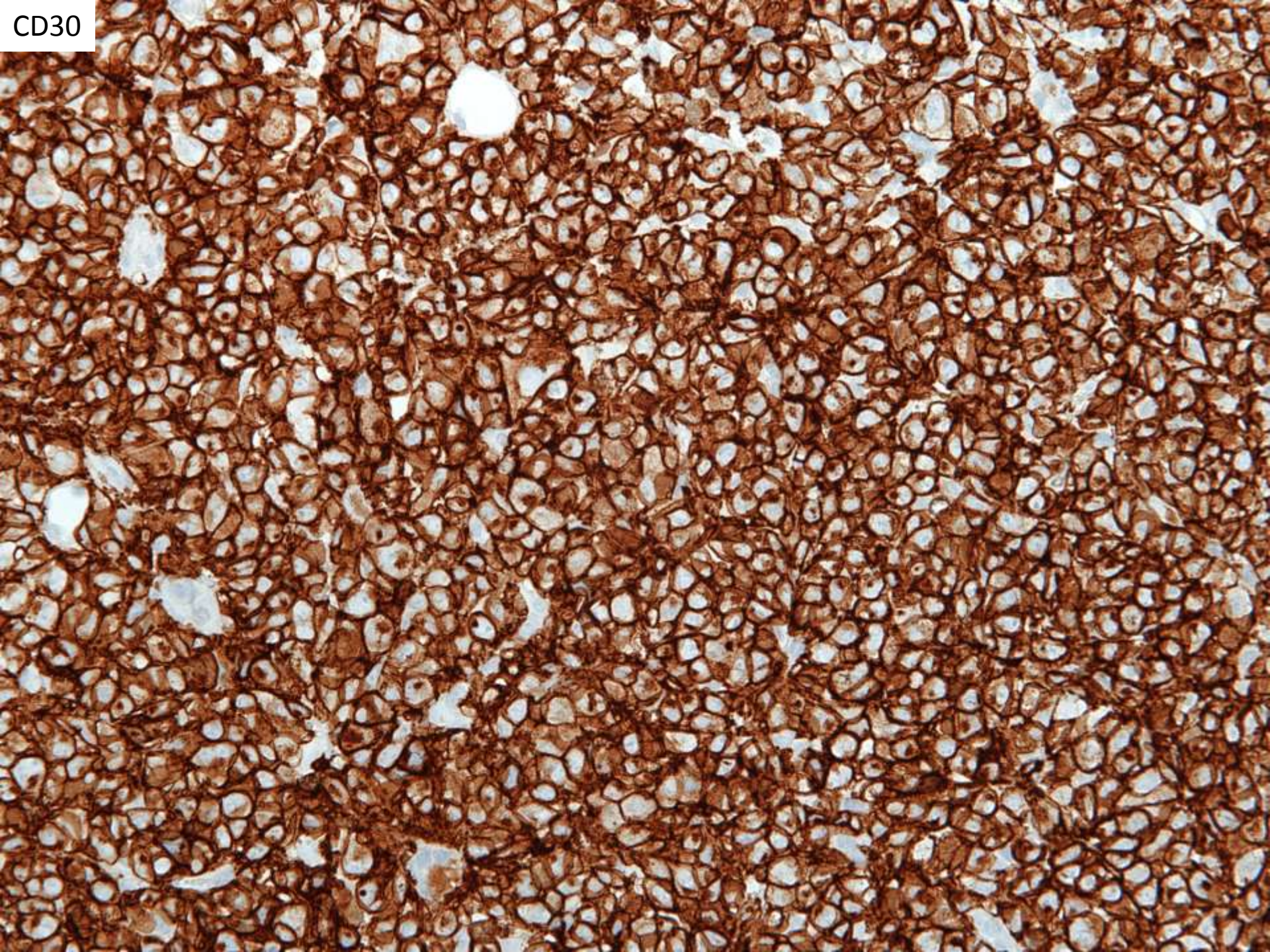

EMA

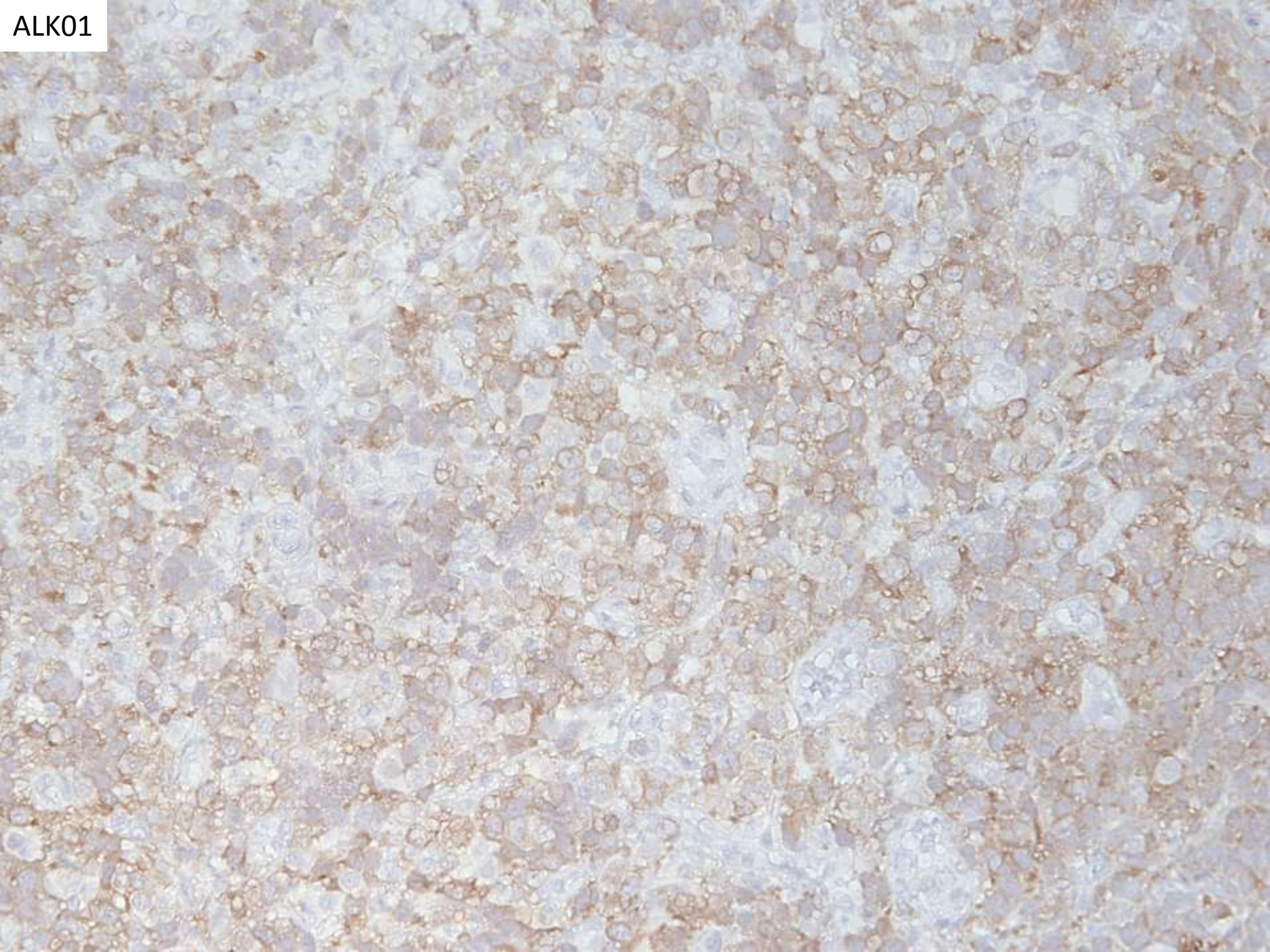

CD20

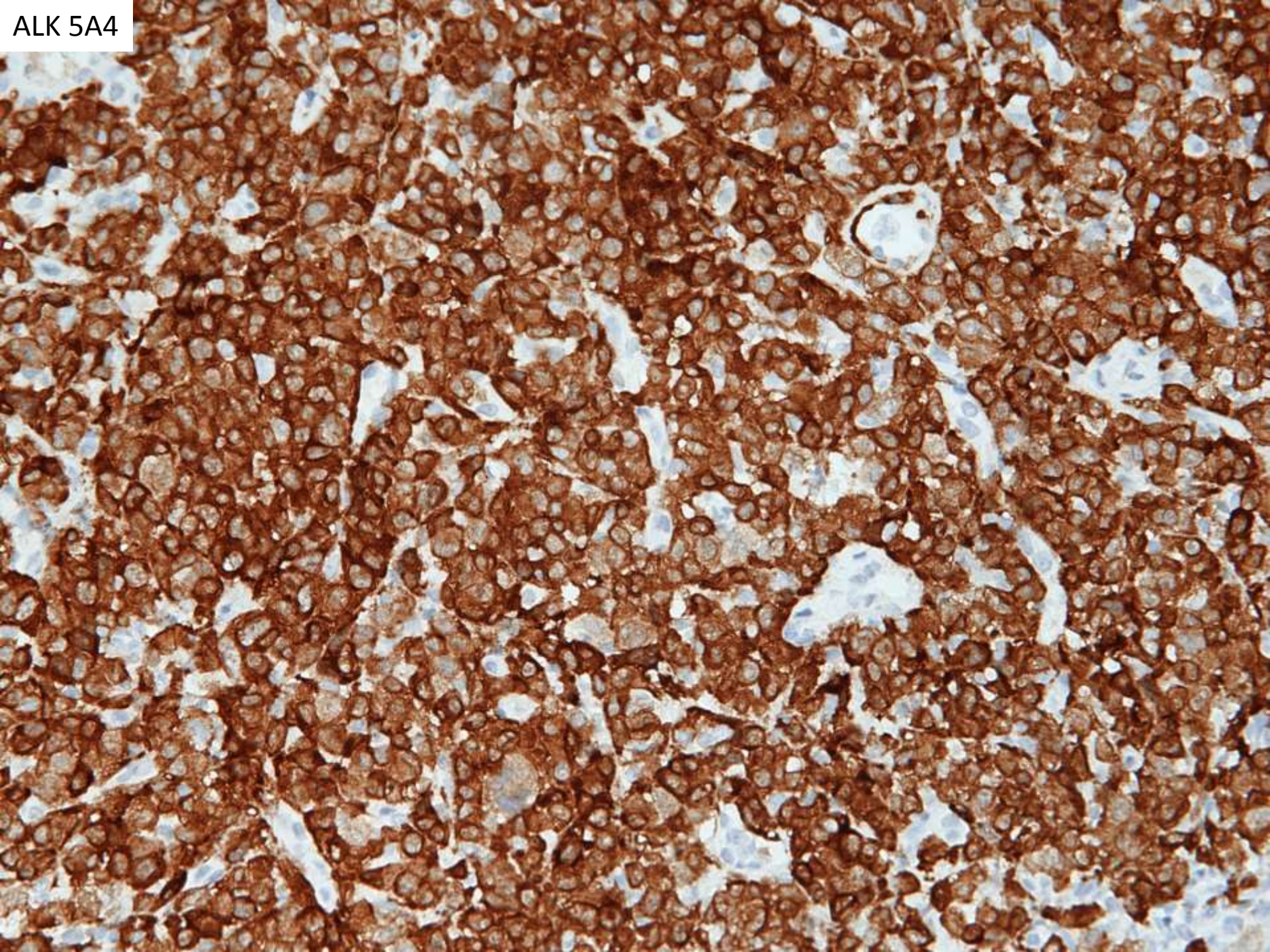

CD3


CD2


CD5


CD30


ALK01


ALK 5A4

ALK-positive anaplastic large cell lymphoma (ALCL)

- CD30+ T-cell lymphoma with ALK gene rearrangement
- ALK immunohistochemistry is routinely used to detect ALK expression to establish the diagnosis
- ALK01 antibody clone in routine use lacks sensitivity for soft tissue tumors and may also miss some ALK+ ALCLs
  - We now use 5A4 antibody clone to detect ALK expression in both soft tissue tumors and ALK+ ALCL

Anaplastic large cell lymphoma (ALCL) subtypes

Molecular subtype	5 year overall survival
ALK+	85%
DUSP22-rearranged	90%
Triple negative	42%
TP63-rearranged	17%

Parrilla et al (2014). ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood, 124(9), 1473-1480.

Take home points

- When ruling out hematolymphoid, consider doing CD45RB, CD43, and CD30

- ALK01 antibody is commonly used but may lack sensitivity for ALK expression in hematolymphoid tumors
  - Known to be less sensitive than other clones in soft tissue tumors
  - Also variable results in lung adenocarcinoma

1. Taheri D, Zahavi DJ, Del Carmen Rodriguez M, Meliti A, Rezaee N, Yonescu R, et al. For staining of ALK protein, the novel D5F3 antibody demonstrates superior overall performance in terms of intensity and extent of staining in comparison to the currently used ALK1 antibody. Virchows Arch. 2016;469:345–50.
2. Jung-Soo P, Guhyun K, Jin Hee S. ALK immunohistochemistry for ALK gene rear-rangement screening in non–small cell lung cancer: a systematic review and meta-analysis. J Biol Markers. 2016;31(4):e413–e421.

19-0408

Marietya Law/Soon-Ryum Yang/Joshua Menke; UCSF

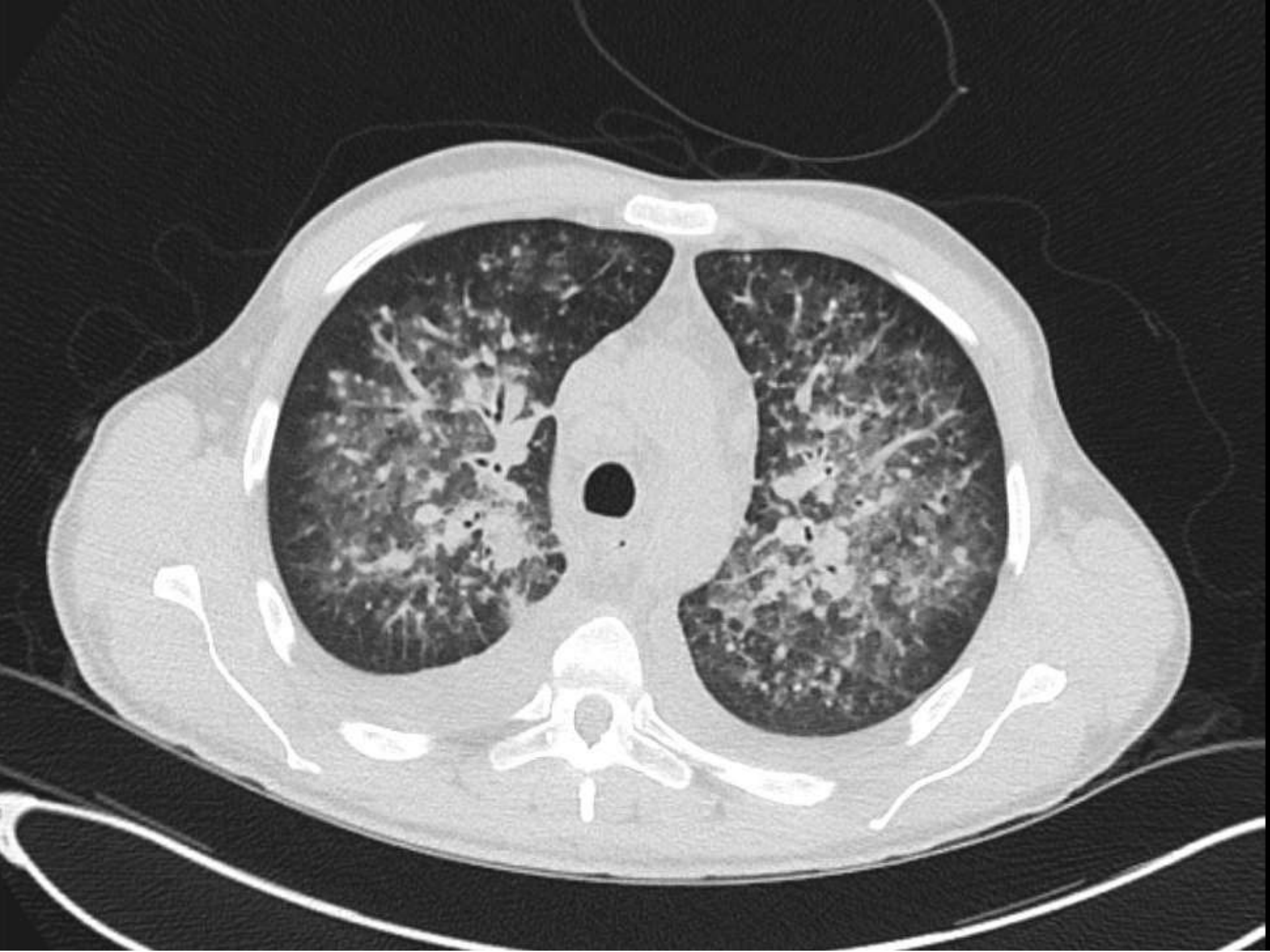
A 45-year-old immigrant presented with shortness of breath, fatigue, cough, and fever. His condition was worsening rapidly and his chest X-ray and CT-scan showed bilateral pleural effusions with diffuse bilateral ground glass opacities, nodules, and nodular consolidation pattern. Despite antibiotics, he developed respiratory failure. An FNA and core biopsy of the dominant lung nodule were performed.

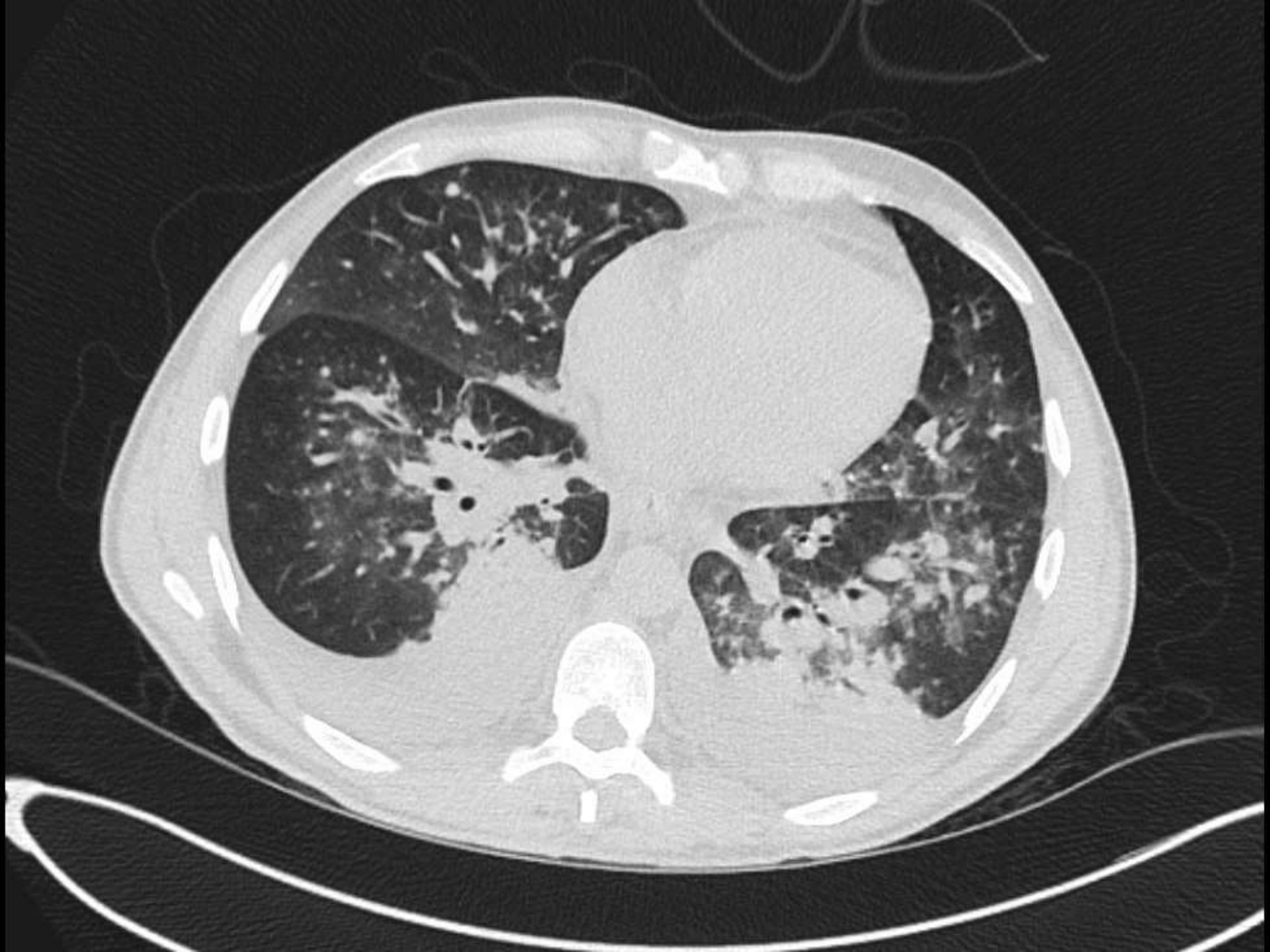
Clinical presentation

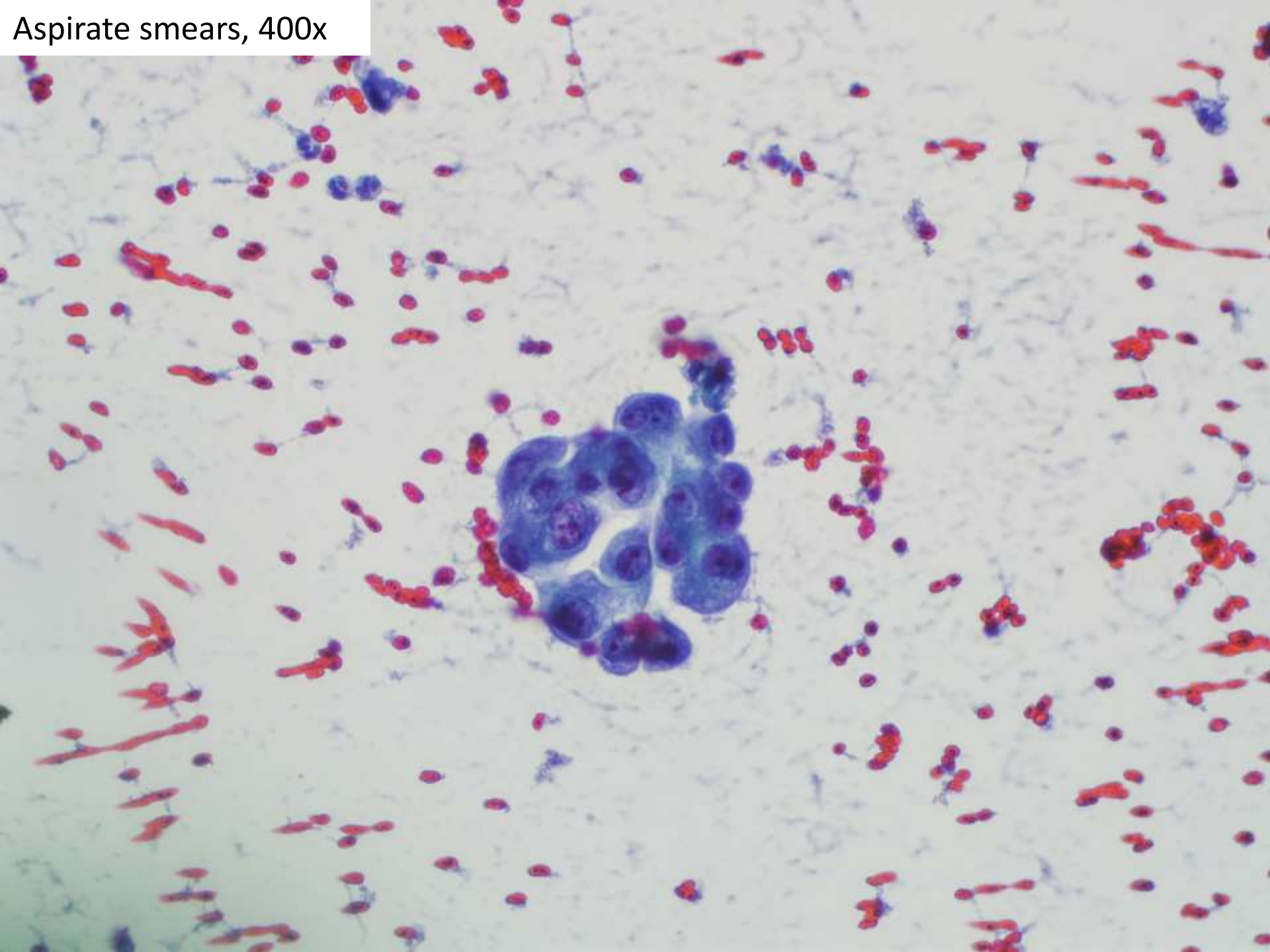
- 45-year-old man
- No significant past medical history
- Immigrated from Algeria in 2009
- Presented in ED with worsening shortness of breath since 2 weeks, fatigue, productive cough, subjective fever → Dx: viral pneumonia and discharged

Follow up

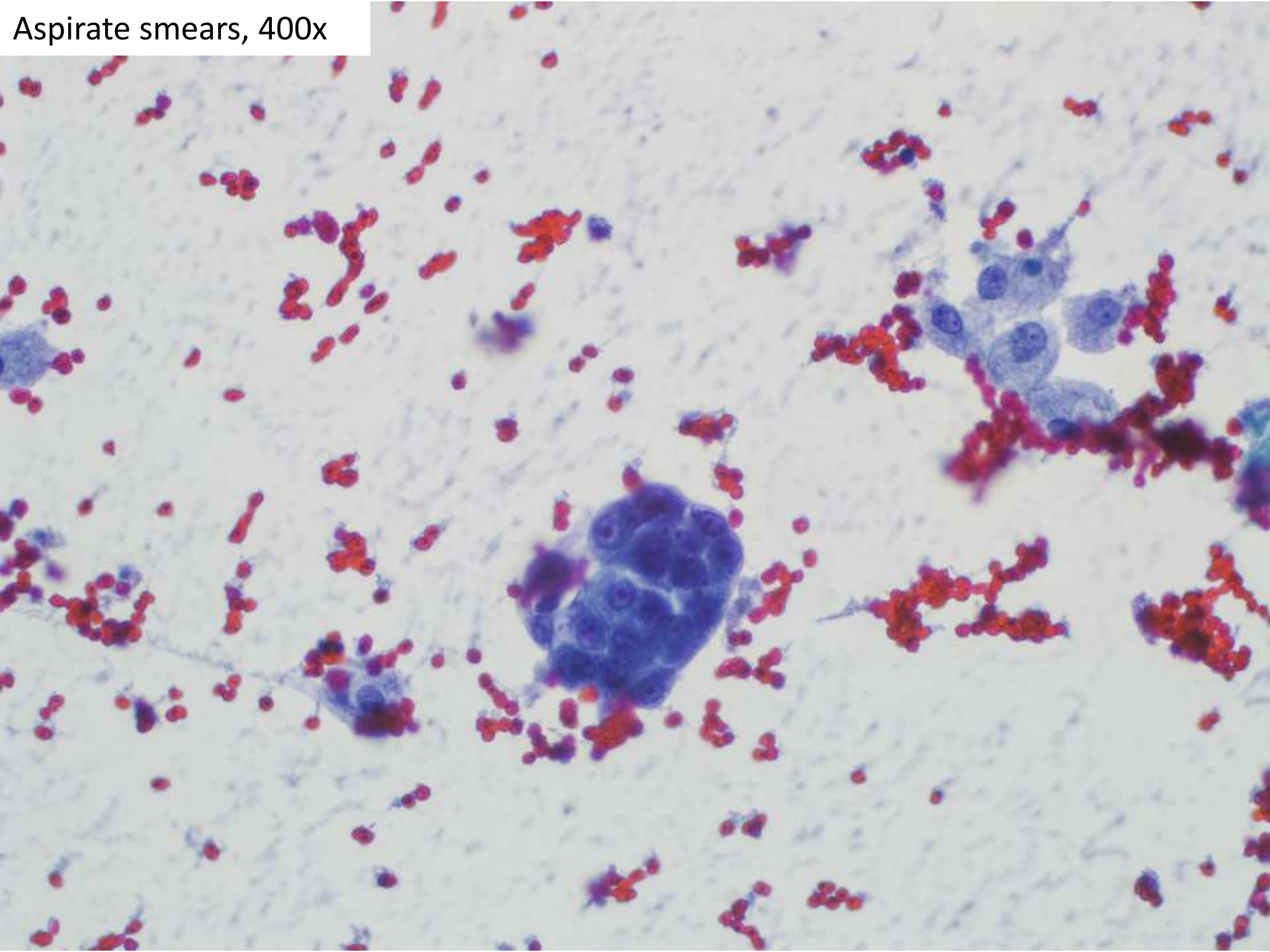
- Patient came back to ED with profound fatigue and was confined to bed for 5 days
- Chest X-ray and CT chest: bilateral pleural effusions with diffuse bilateral ground glass opacities, nodules, and nodular consolidation pattern → admission, started on antibiotics
- Patient developed rapidly worsening hypoxemic respiratory failure → CT-guided FNA and core biopsy of dominant lung nodule



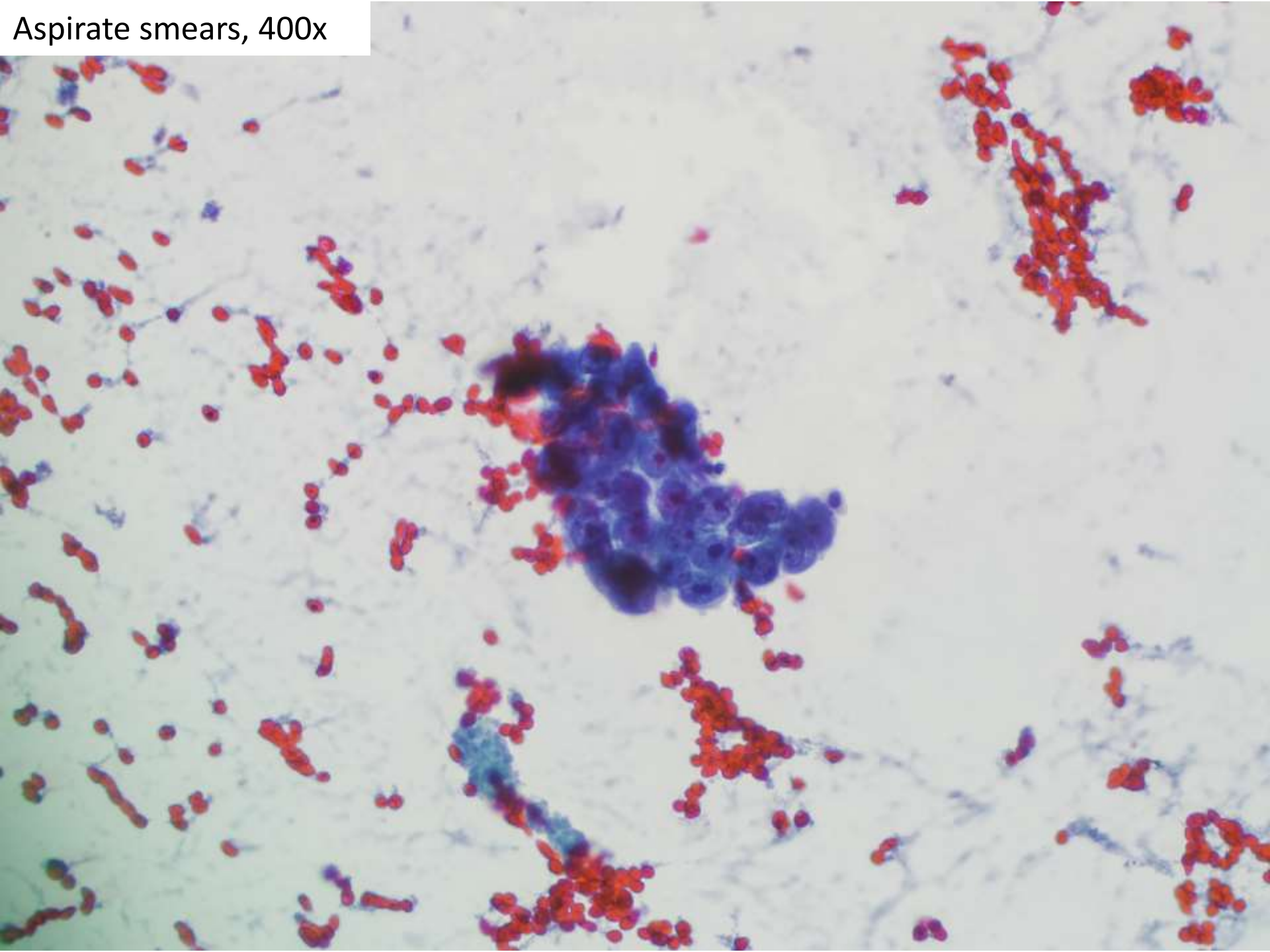


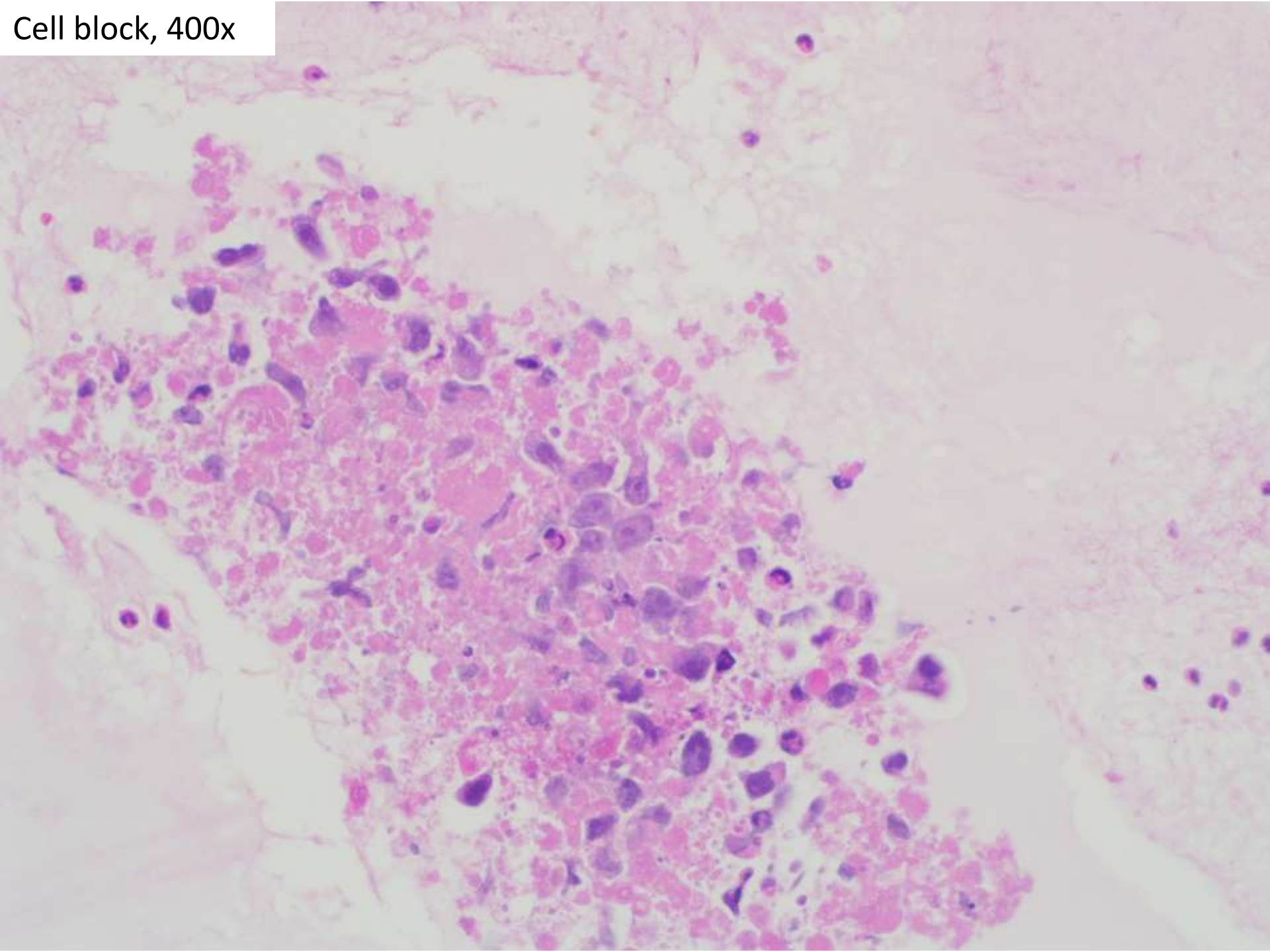

Aspirate smears, 400x

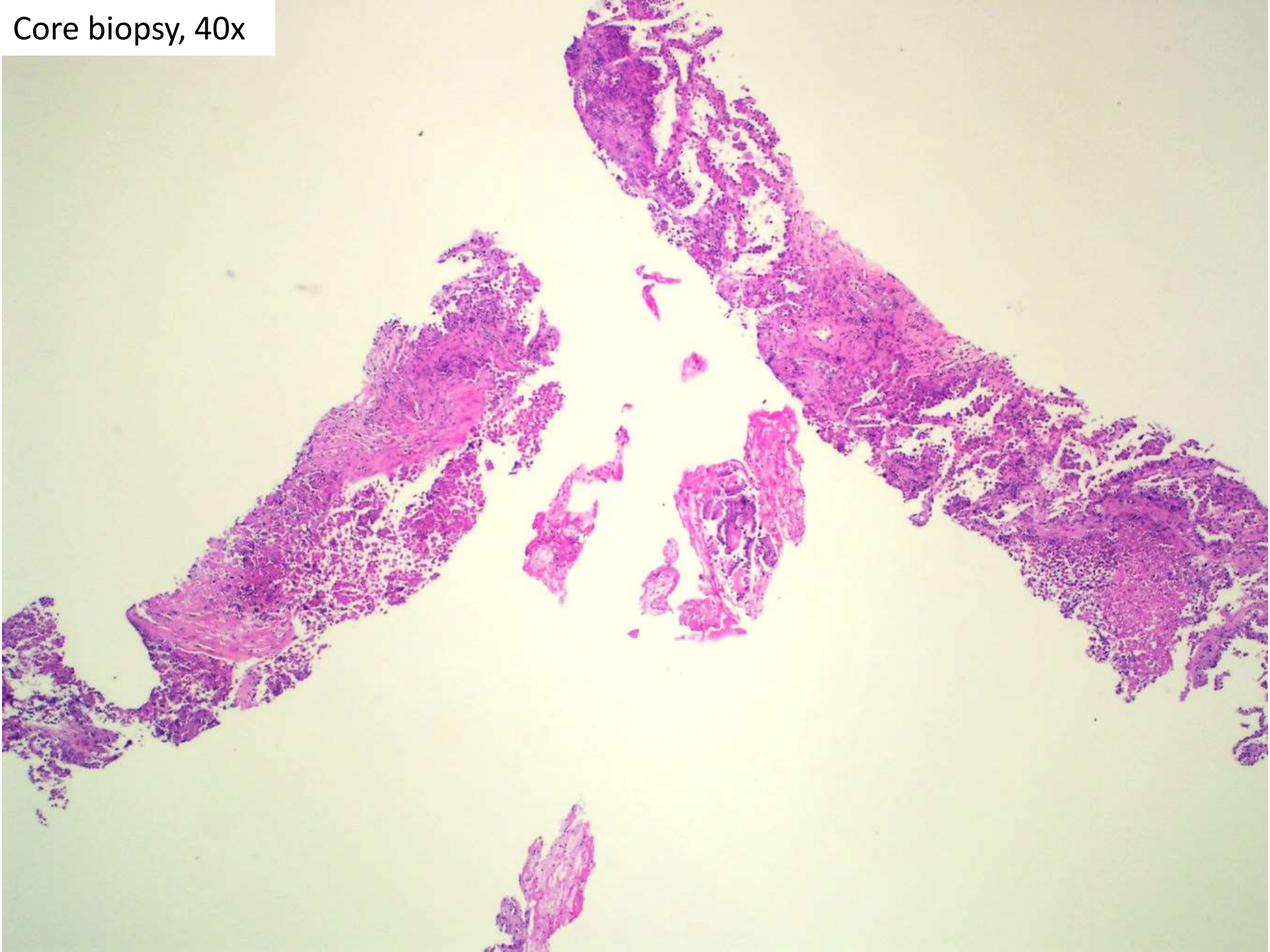
Aspirate smears, 400x

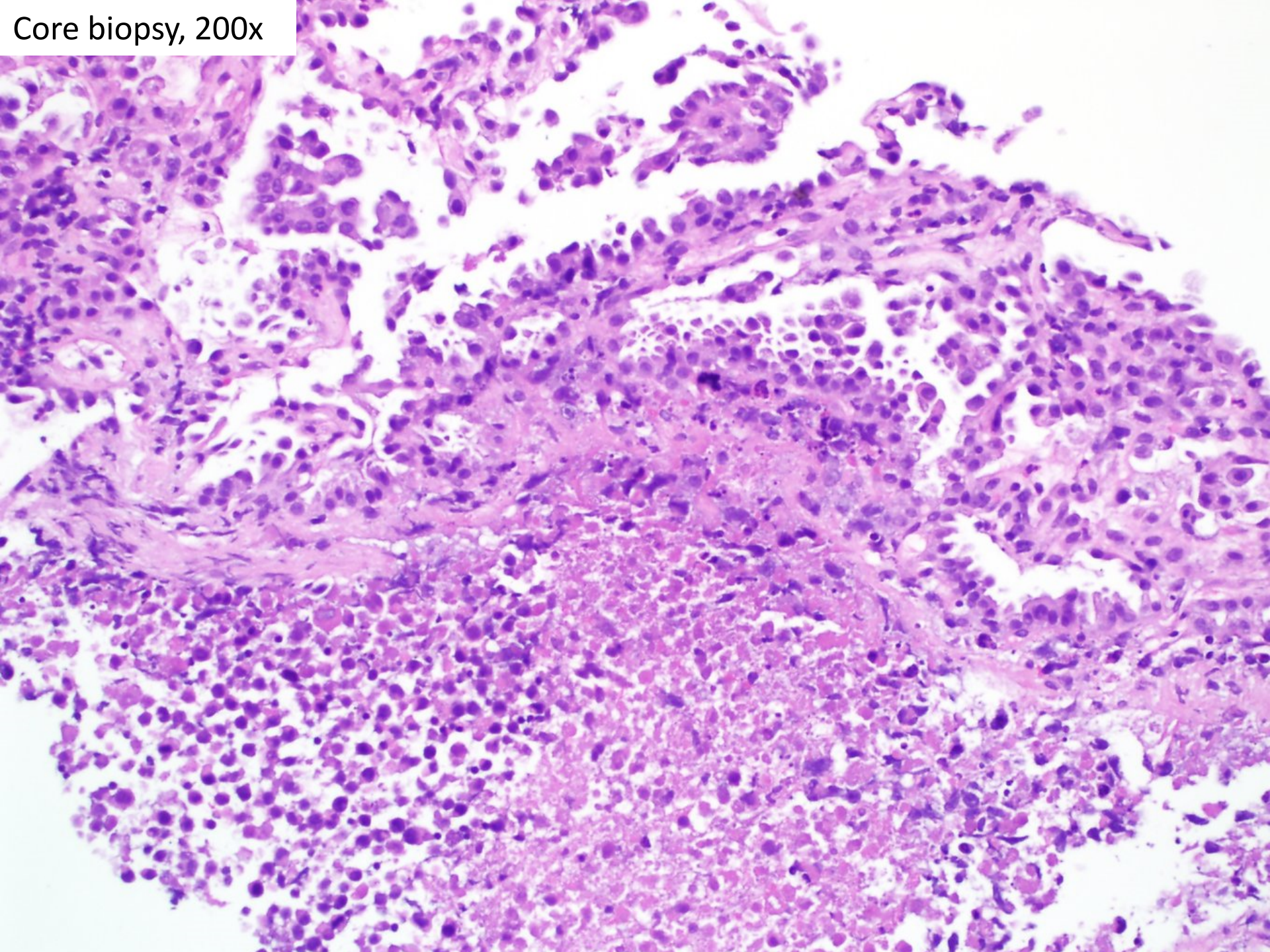


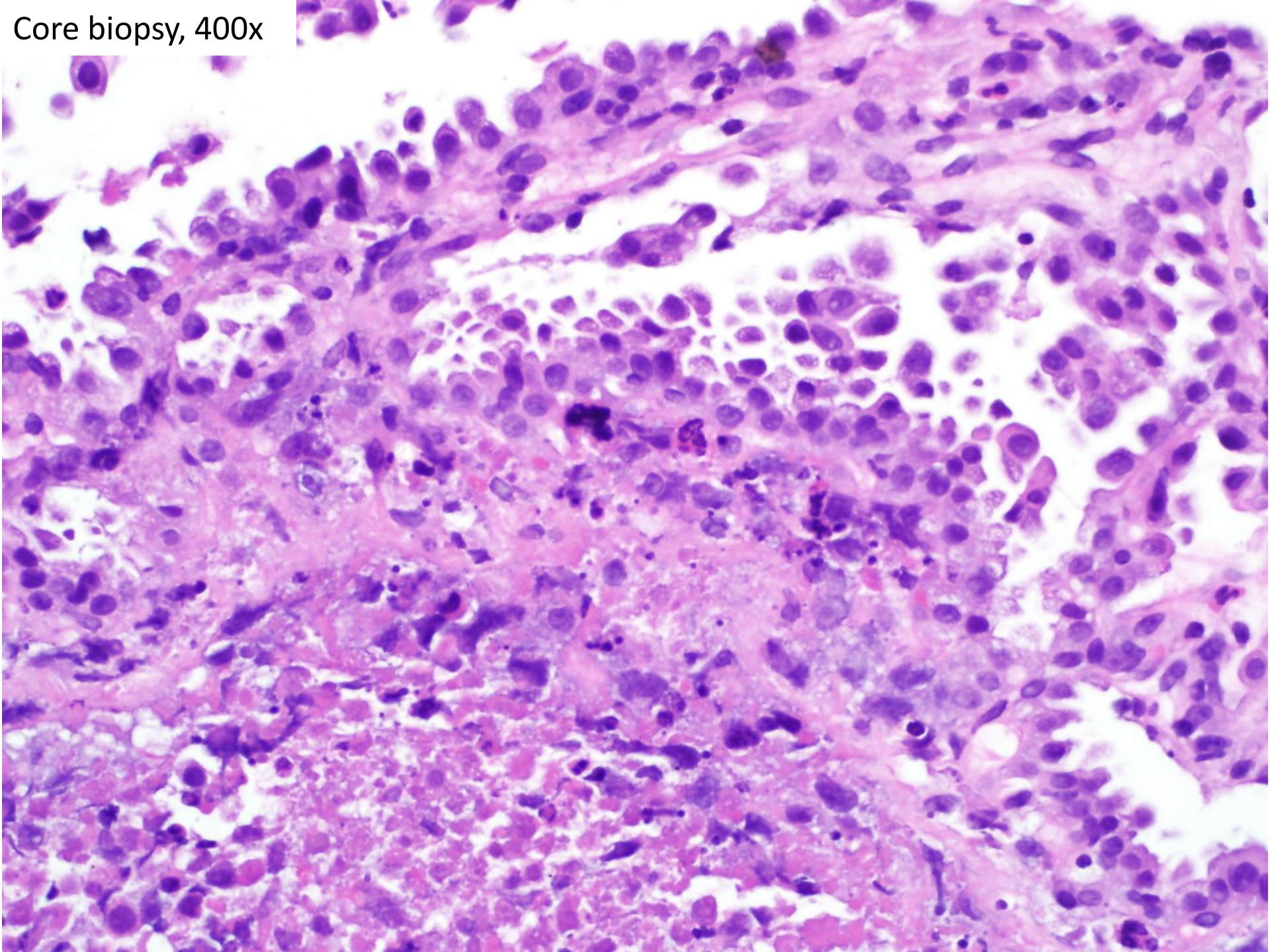
Aspirate smears, 400x



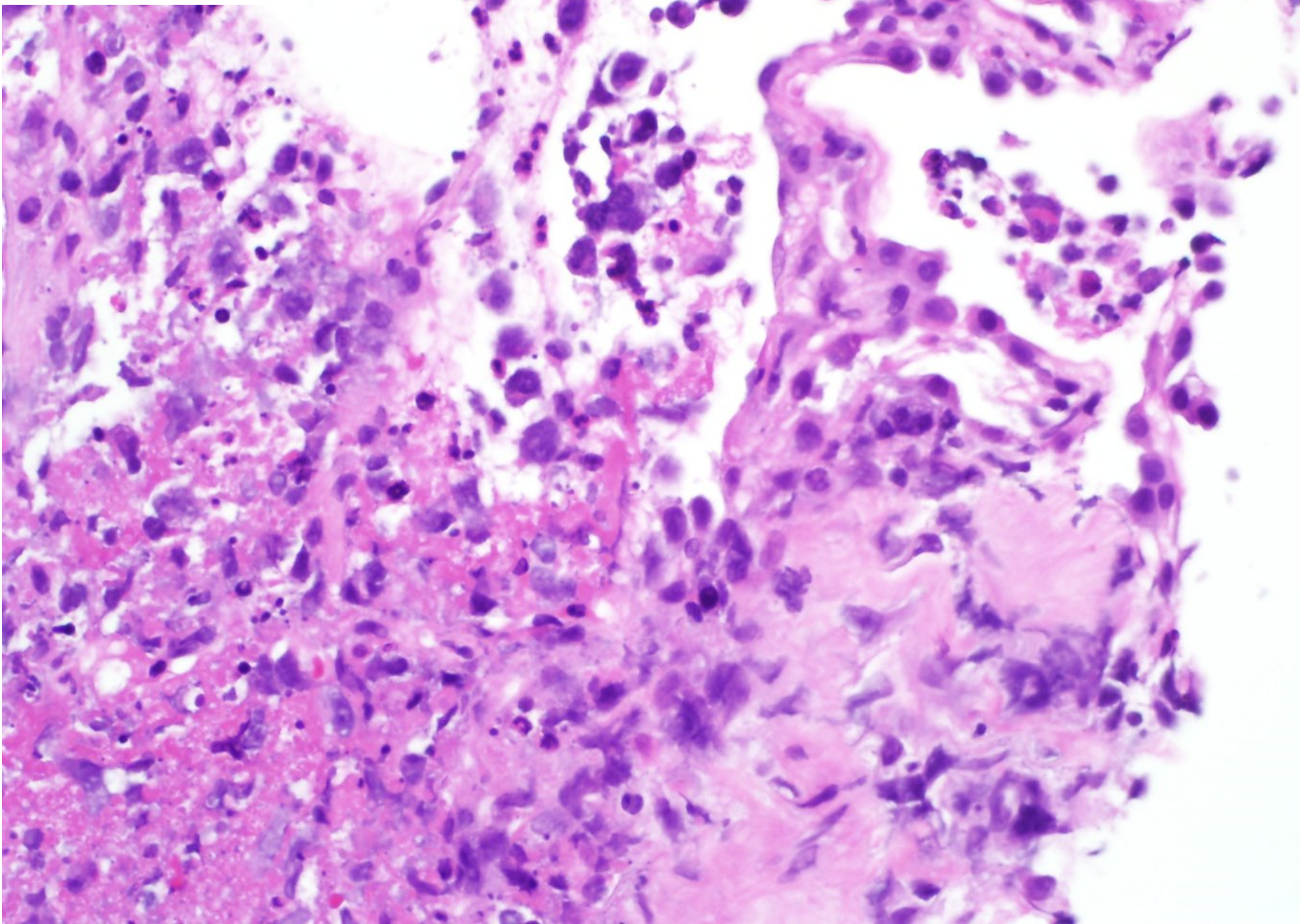

Cell block, 400x


Core biopsy, 40x

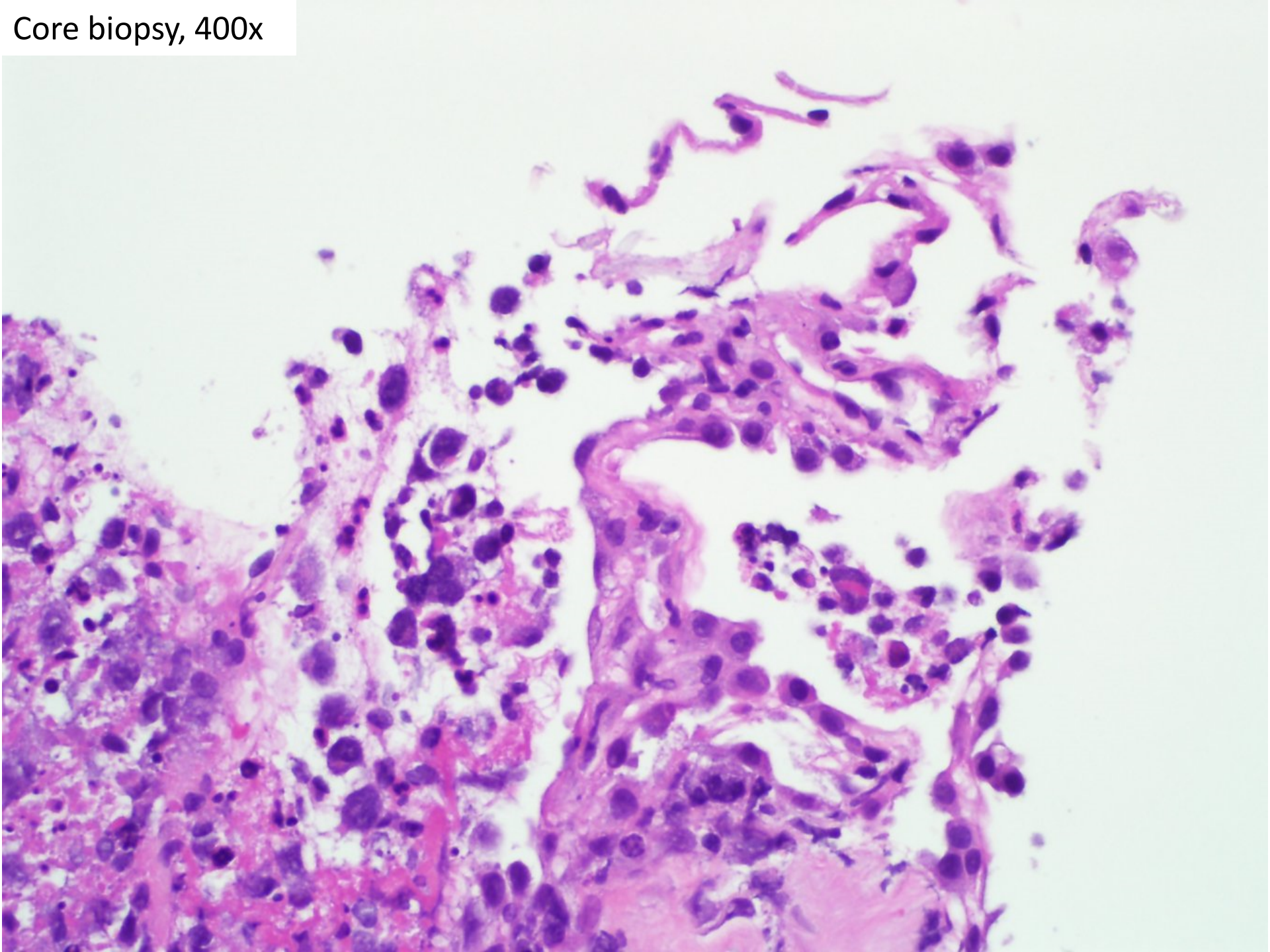

Core biopsy, 200x


Core biopsy, 400x

Core biopsy, 400x

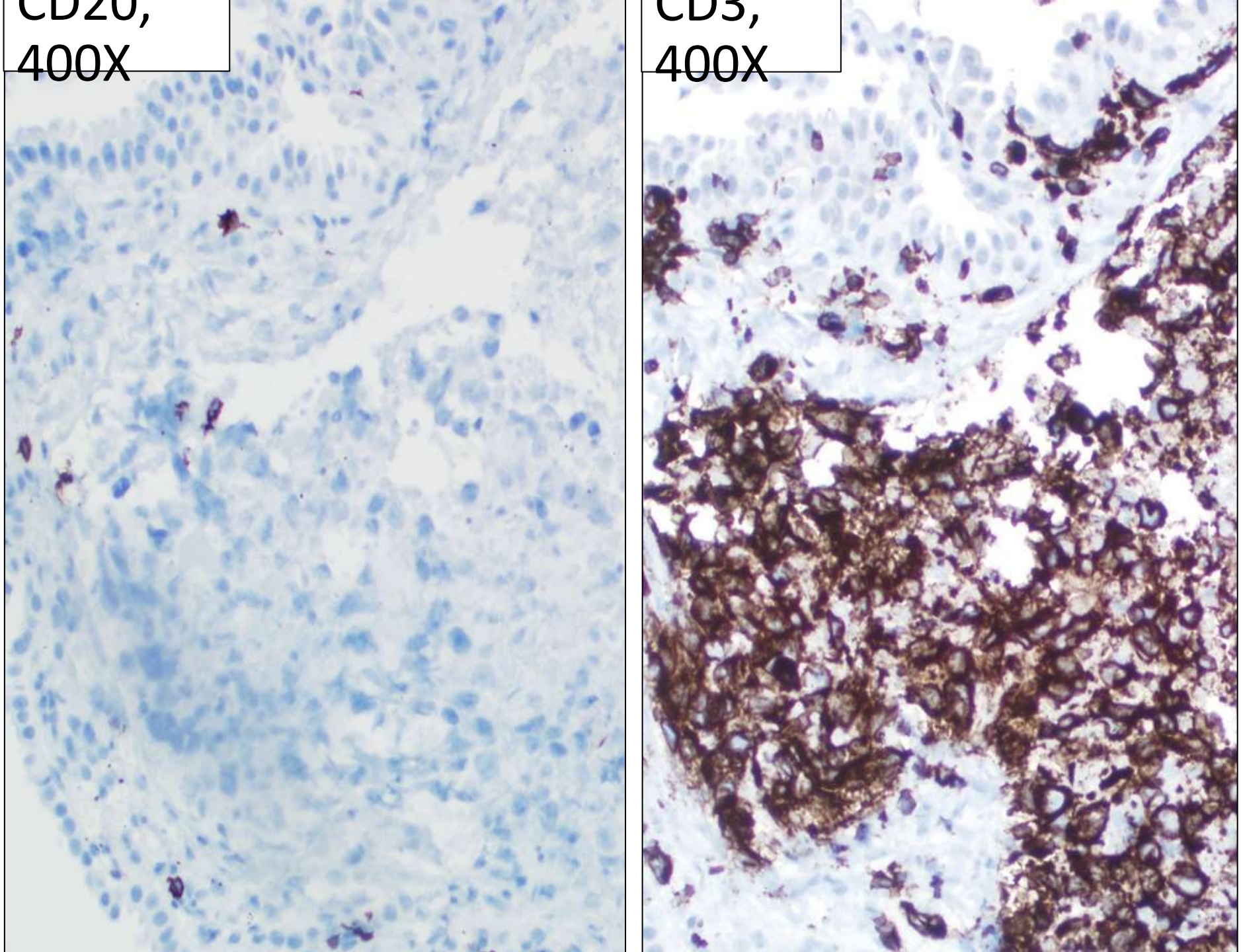


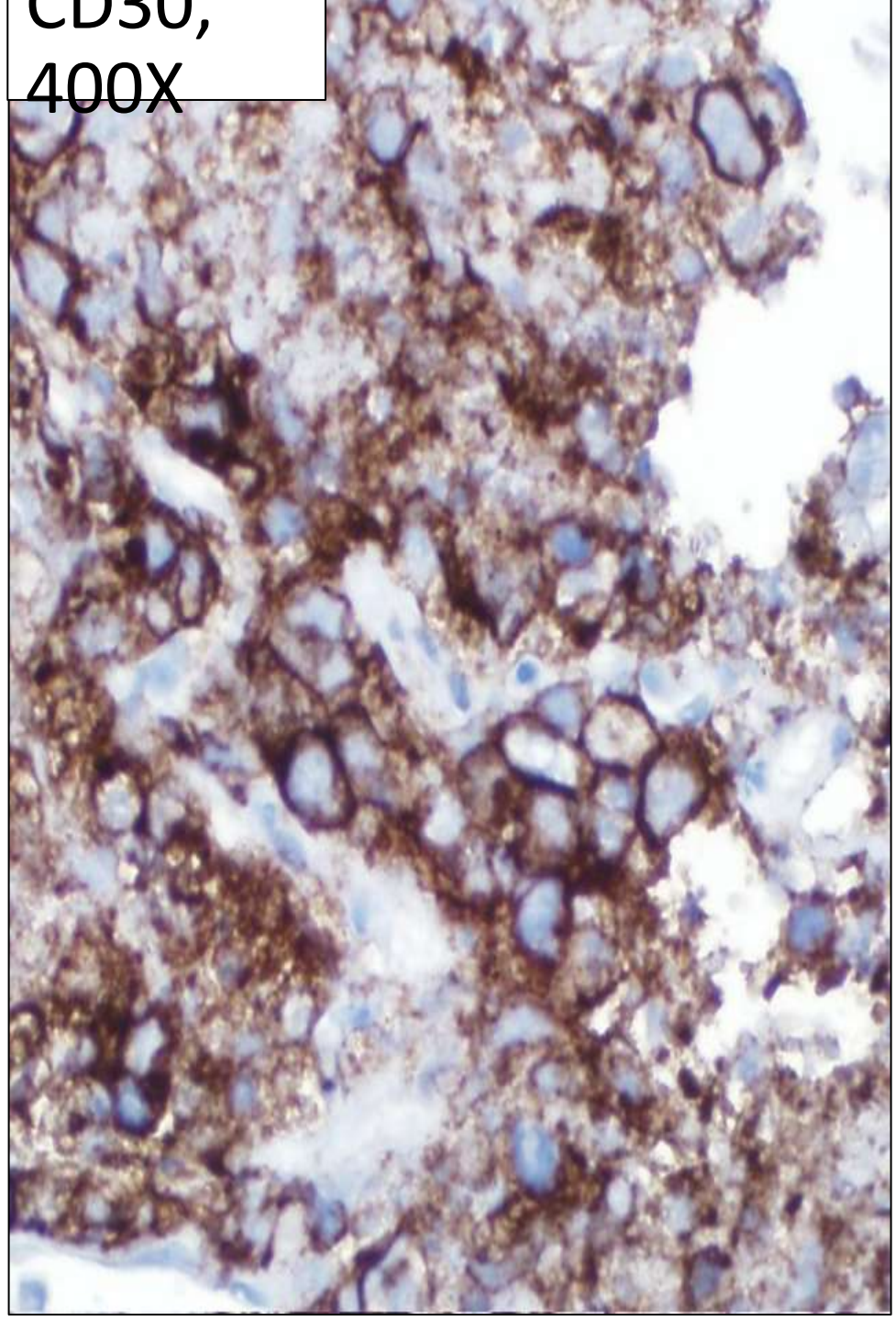
Core biopsy, 400x

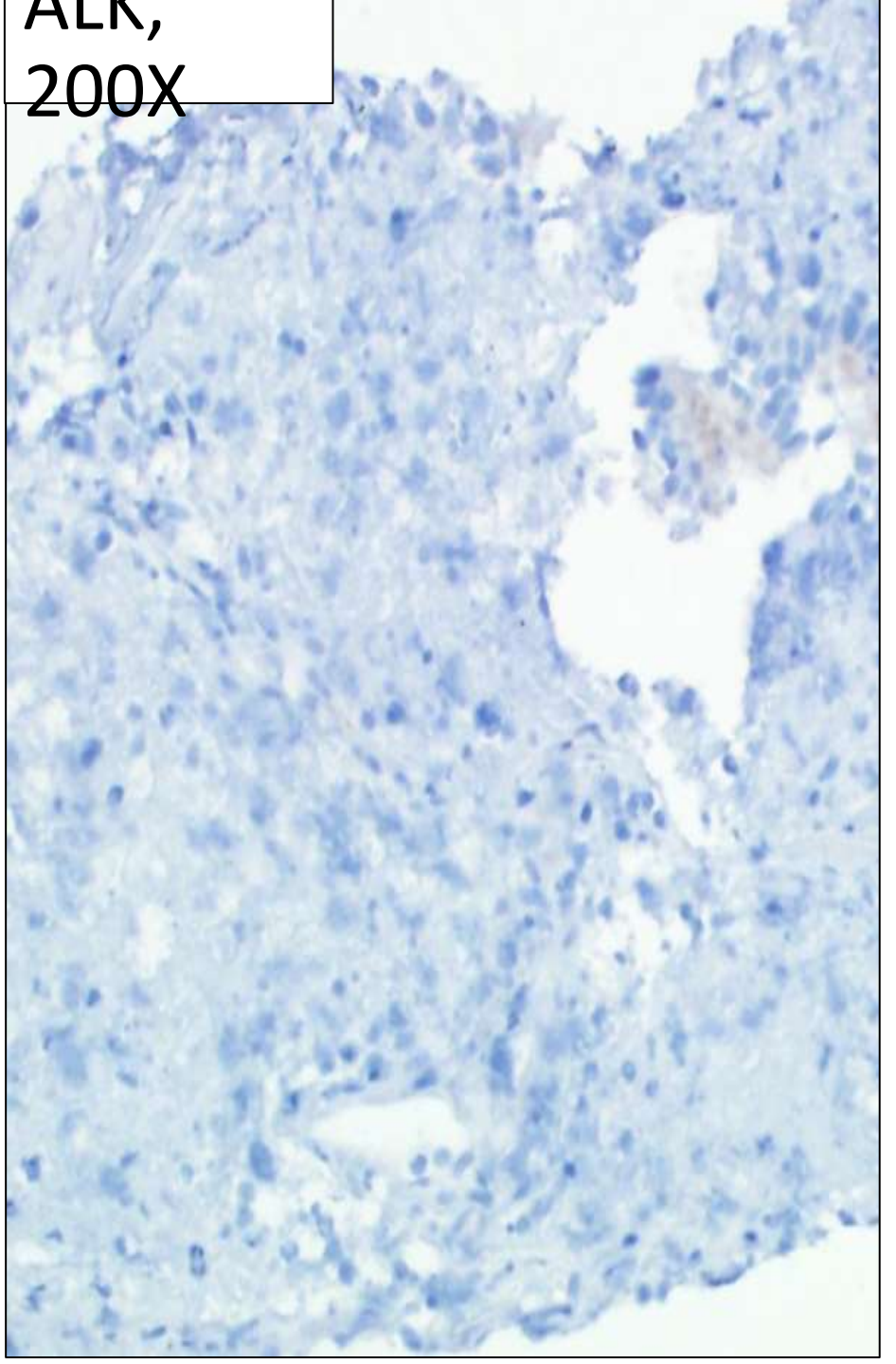


Stains

- Pankeratin negative
- S100 negative
- Synaptophysin negative
- Chromogranin negative
- AFB, GMS, HSV, and CMV all negative


CD20,
400X
CD3,
400X


CD30,
400X

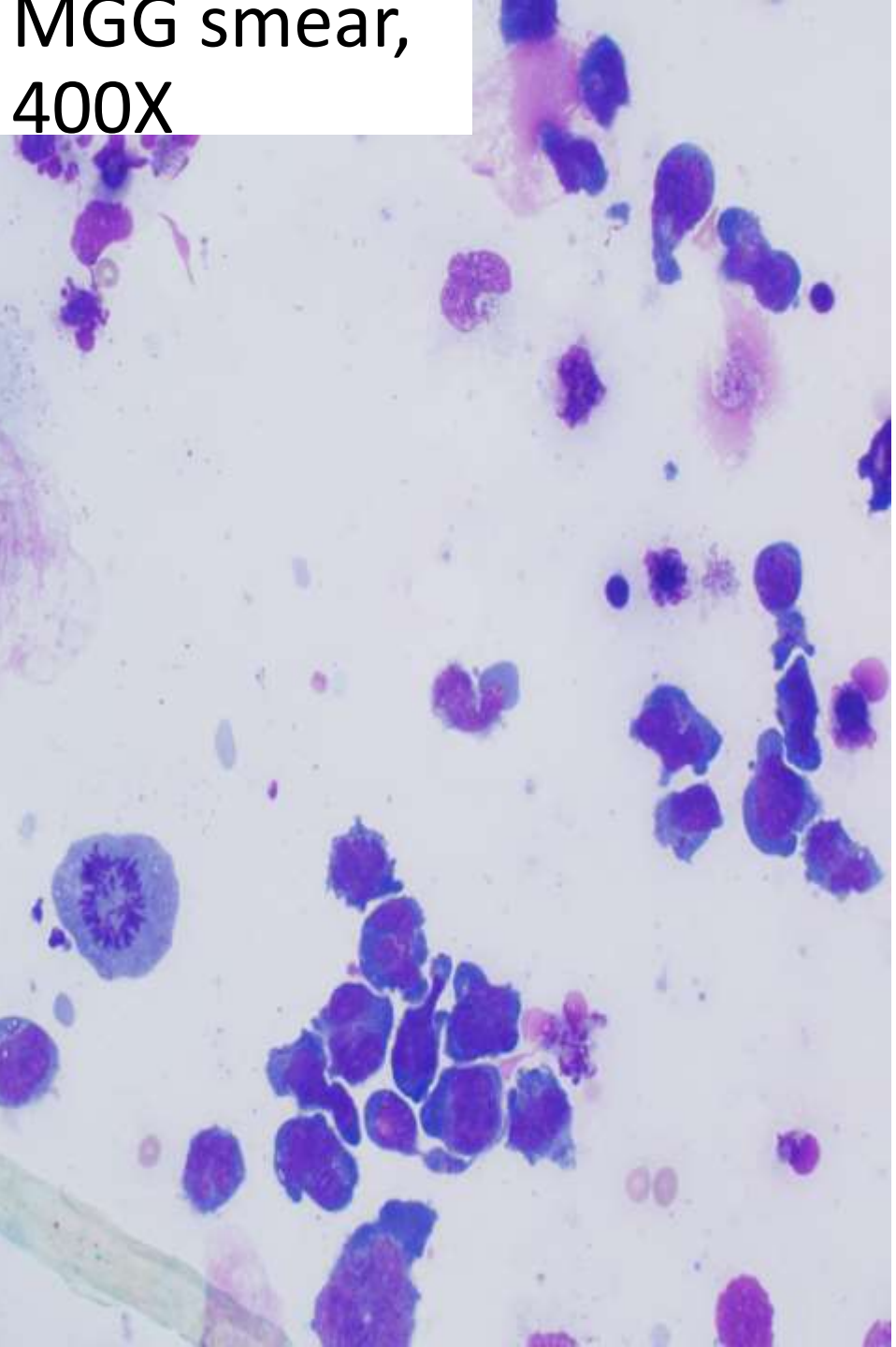

ALK,
200X

Diagnosis:

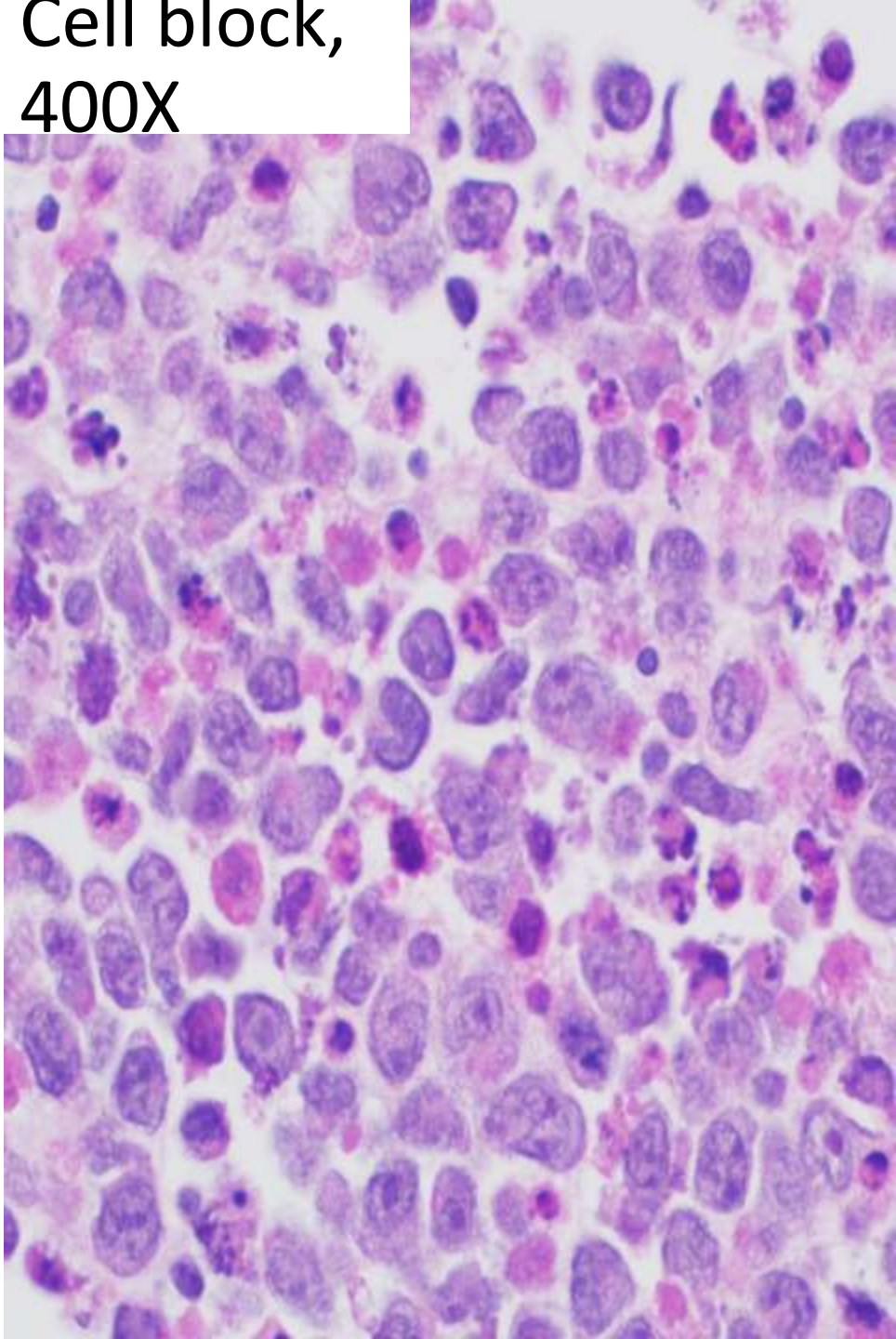
Anaplastic large cell lymphoma, ALK-negative

While working up the initial specimens, pleural fluid was submitted

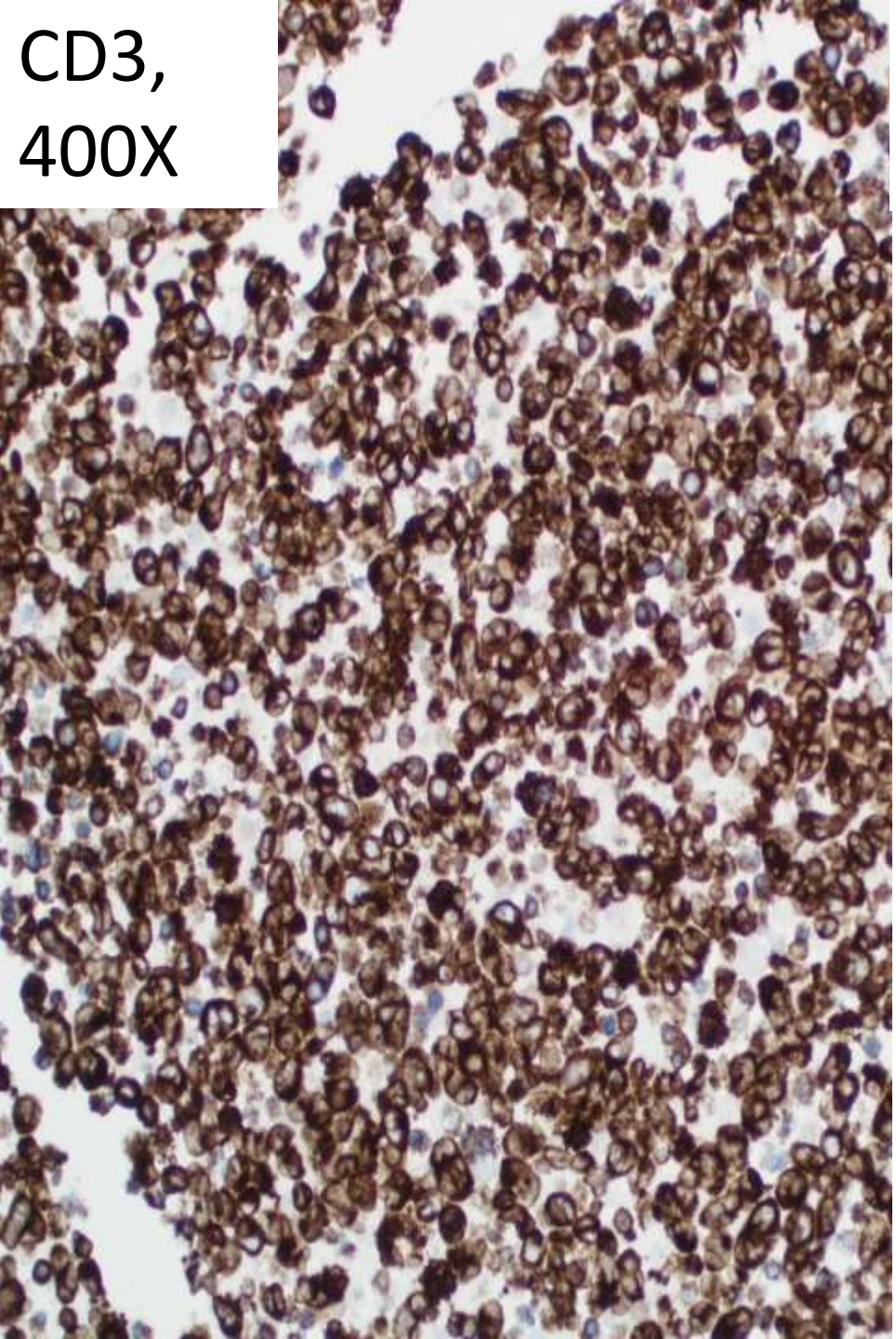
MGG smear, 400X



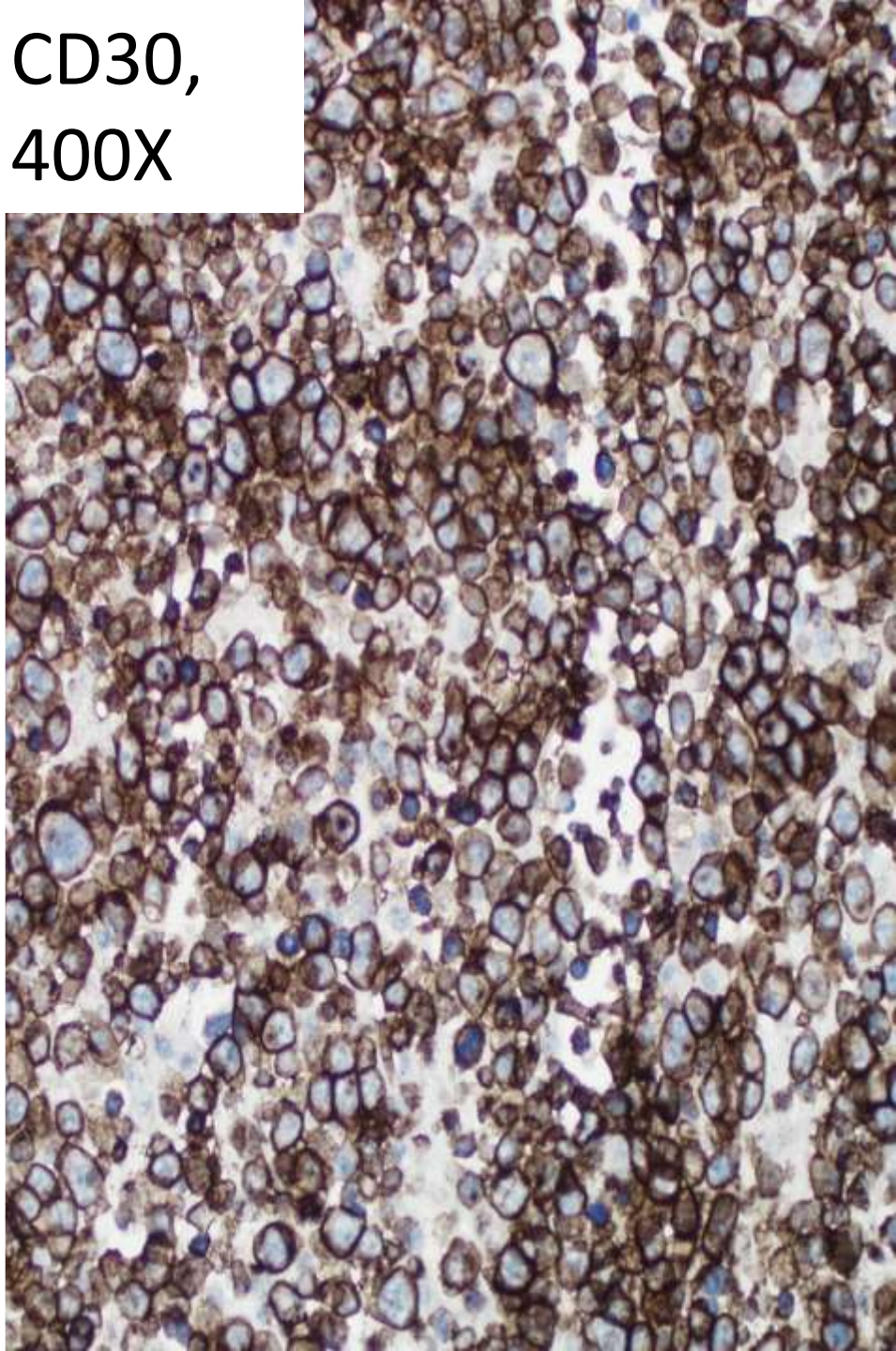
Cell block, 400X



CD3, 400X



CD30, 400X



Additional testing of pleural fluid specimen

- **IHC/ISH**: Negative for ALK, HHV-8, and EBV by ISH (EBER)

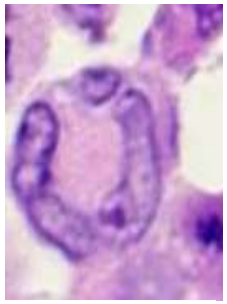
- **Flow cytometry:** Atypical T-cell population (71% of leukocytes) that expresses CD2, CD7, cCD3, partial weak CD30, and CD38, but not ALK, sCD3, CD4, or CD8

- **FISH**: Negative for *DUSP22* (*IRF4*) and *TP63* rearrangements

- **FoundationOne Heme**: *STAT3* Y640F, *DNMT3A* splice site 639+1 G>T, and *DDX3X* splice site 1497+1 G>A mutations

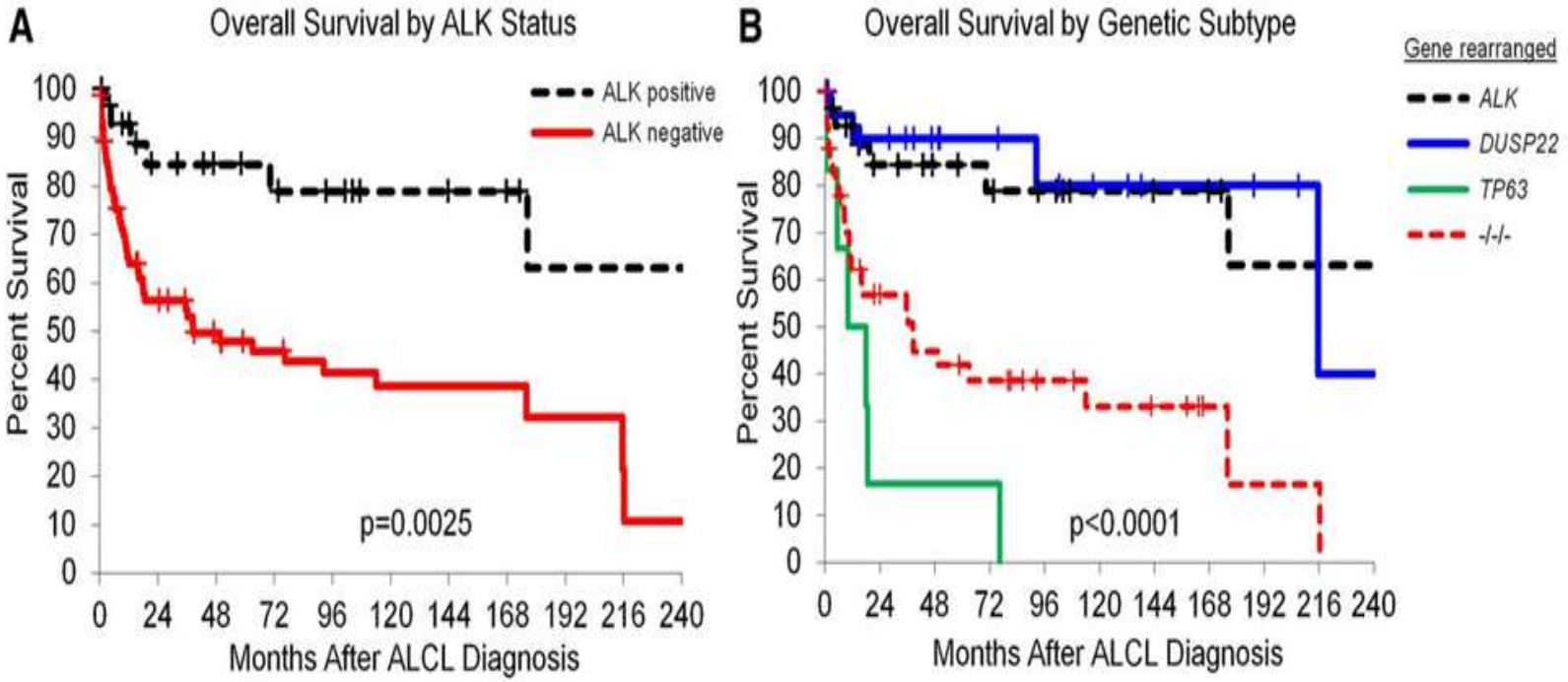
Comparison of systemic ALCL subtypes

	ALK-negative ALCL	ALK-positive ALCL
Site	Lymph nodes > extranodal	Lymph nodes < extranodal
Age at presentation	Median 58 years, 40-65 years	First 3 decades of life
5-year failure free and overall survival	49% and 36%	70% and 60%
Morphology	Hallmark cells	Hallmark cells; small cell and lymphohistiocytic patterns
CD30	Strong diffuse positive	Strong diffuse positive
ALK	Positive	Negative
T-cell antigens	Frequent loss (e.g. null cell phenotype)	Frequent loss
Cytotoxic markers	Positive	Positive
Genetics	*JAK1* and *STAT3* mutations; translocations of tyrosine	*ALK* translocations (e.g. *NPM1-ALK*)



Hallmark cell

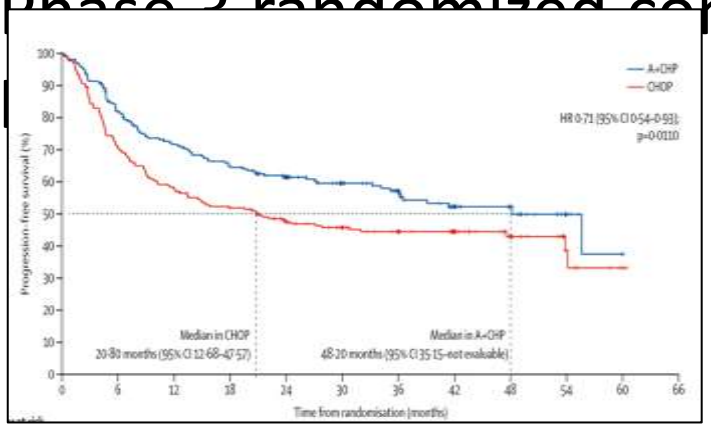
Prognostic differences in ALCL by genotype



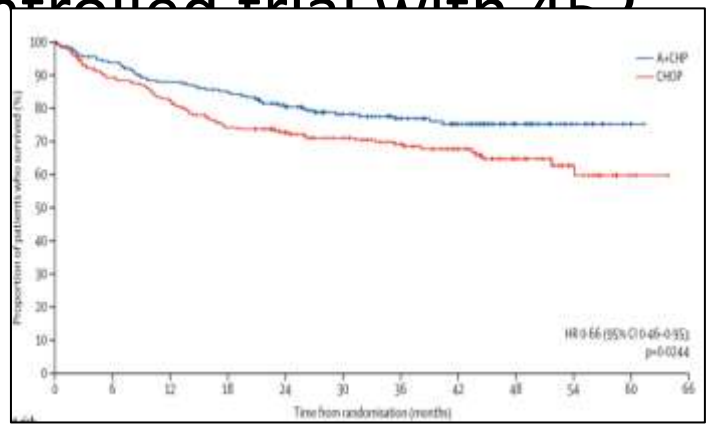
Parilla Castellar, et al. Blood. 2014.

ECHELON-2 Study

- Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone **(A+CHP) versus** cyclophosphamide, doxorubicin, vincristine, and prednisone **(CHOP)** for treatment of CD30-positive peripheral T-cell lymphomas
- Phase 3 randomized controlled trial with 452



Progression free survival



Overall survival

Horwitz et al.

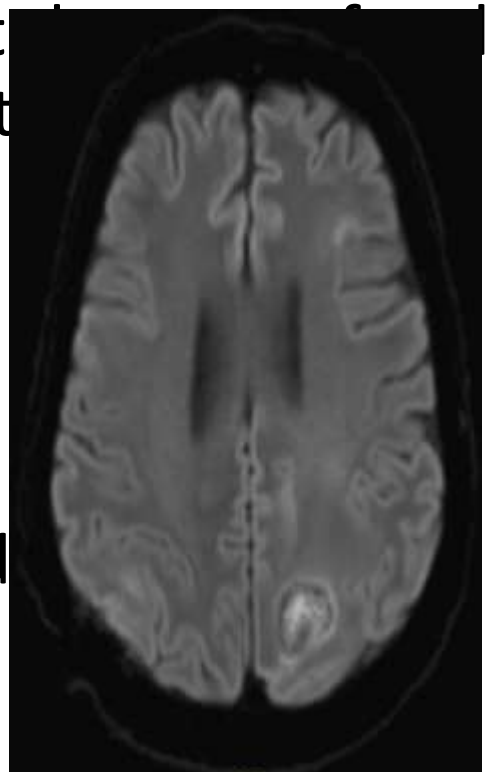
Summary

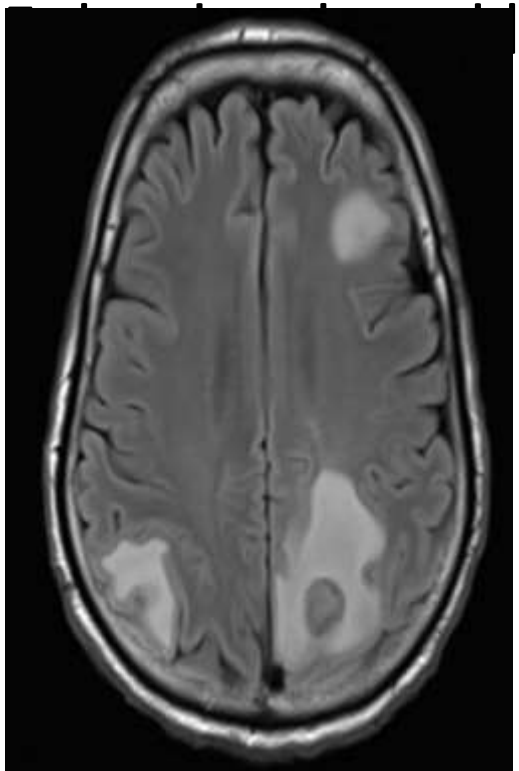
- ALK-negative ALCL can manifest in extranodal sites
- ALK-negative ALCL has similar morphology and immunophenotype to ALK-positive ALCL but different clinical and genetic findings
- *ALK* and *DUSP22* rearrangements are associated with good prognosis and *TP63* rearrangement is associated with poor prognosis in ALCL
- Improved survival of mature CD30-positive T-cell lymphomas such as ALCL with A+CHP (ECHELON-2 trial)

Patient follow up

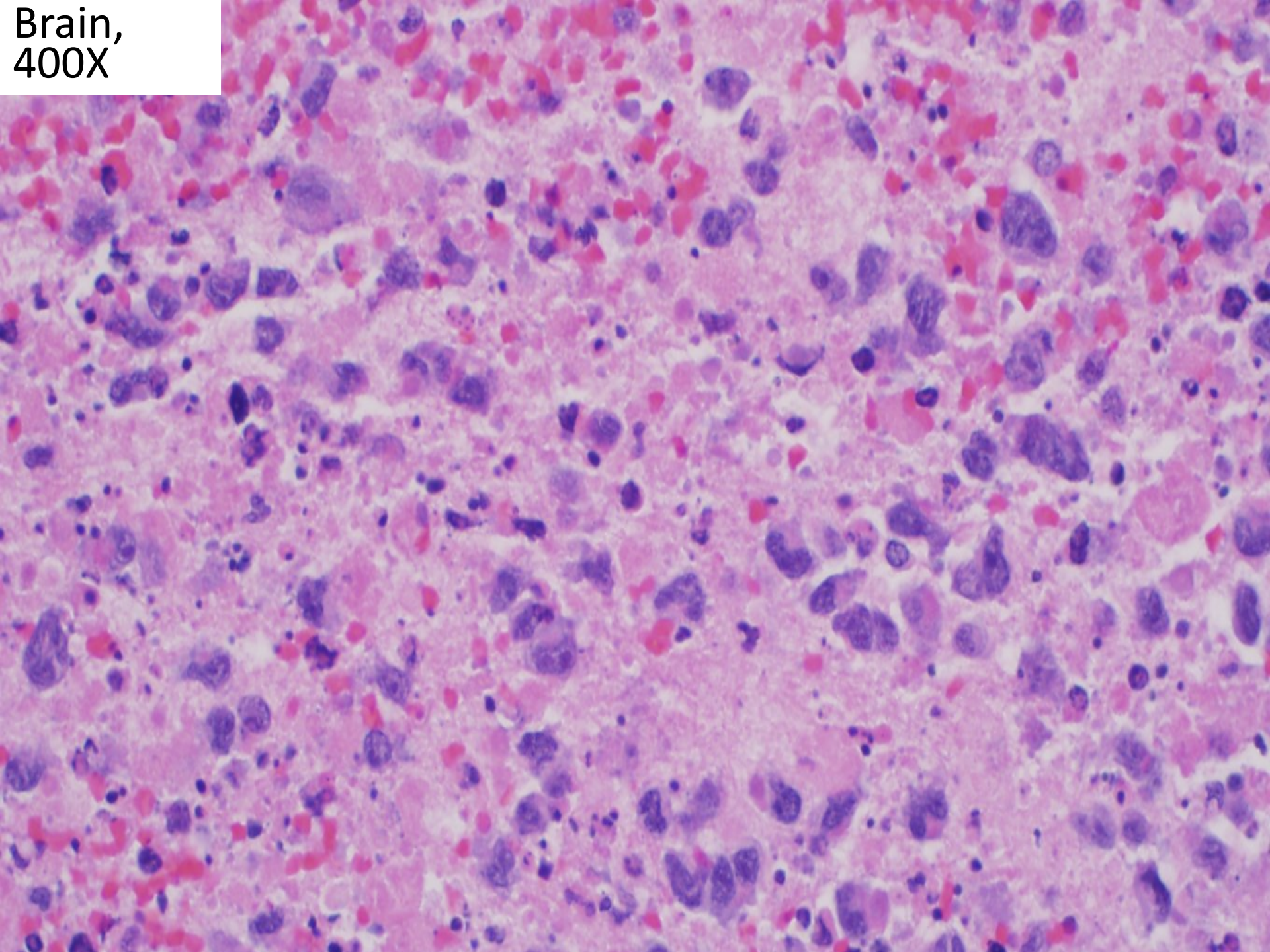
- Patient showed great systemic response after 1 cycle A+CHP and was extubated and discharged 2 weeks later
- However, at [illegible] left sided parest
- MRI Brain:

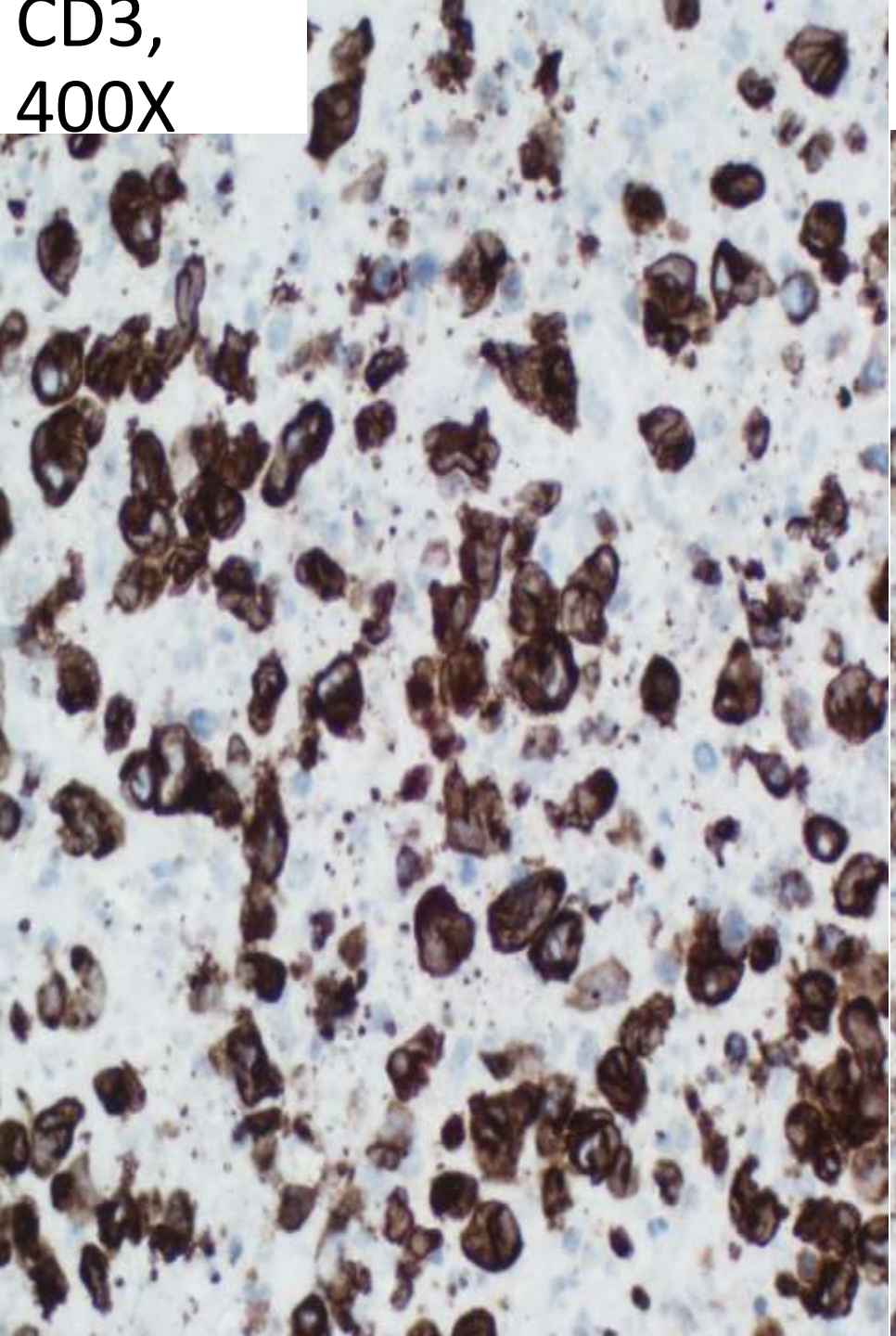
Diffusion weighted image

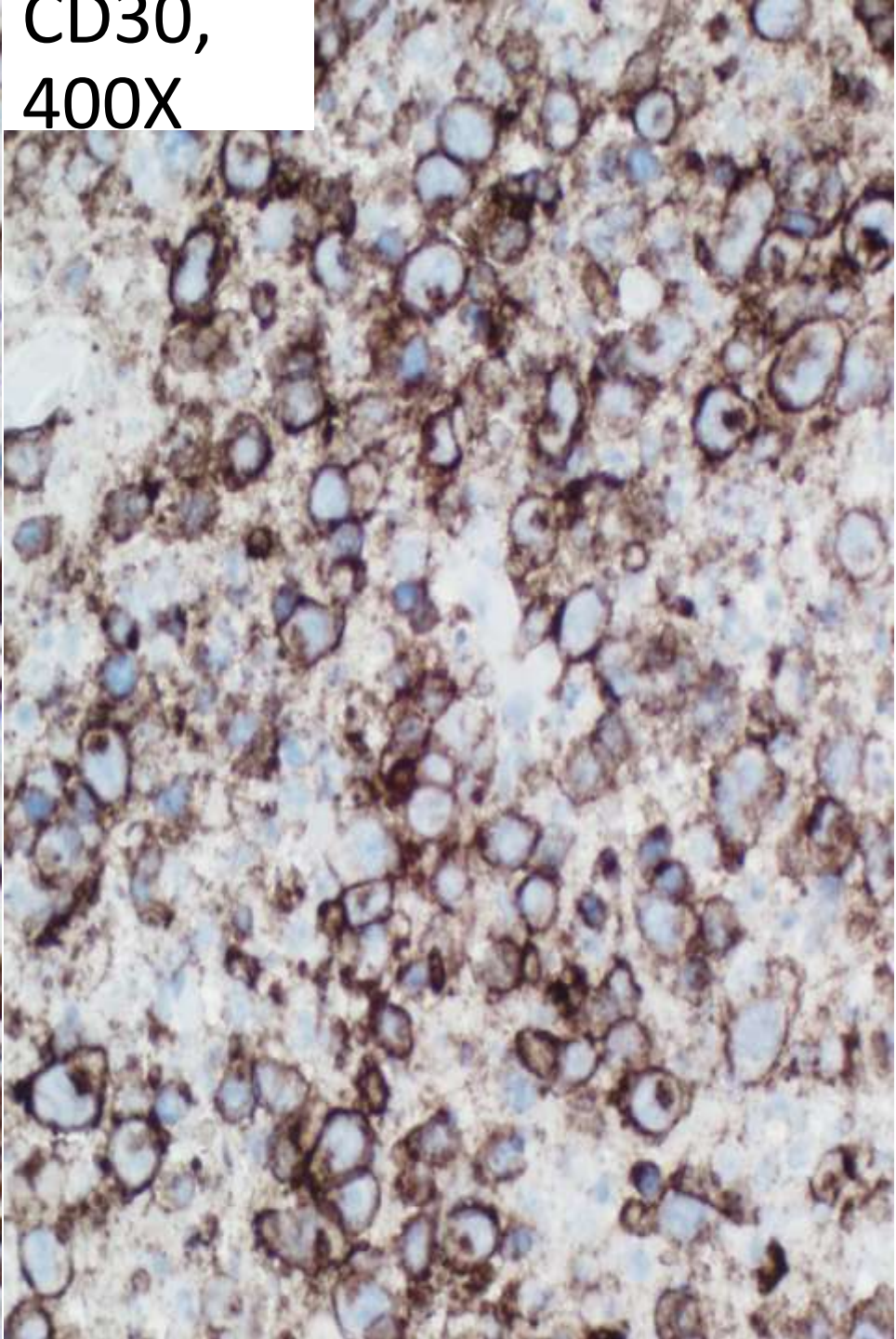




FLAIR


Brain,
400X


CD3,
400X

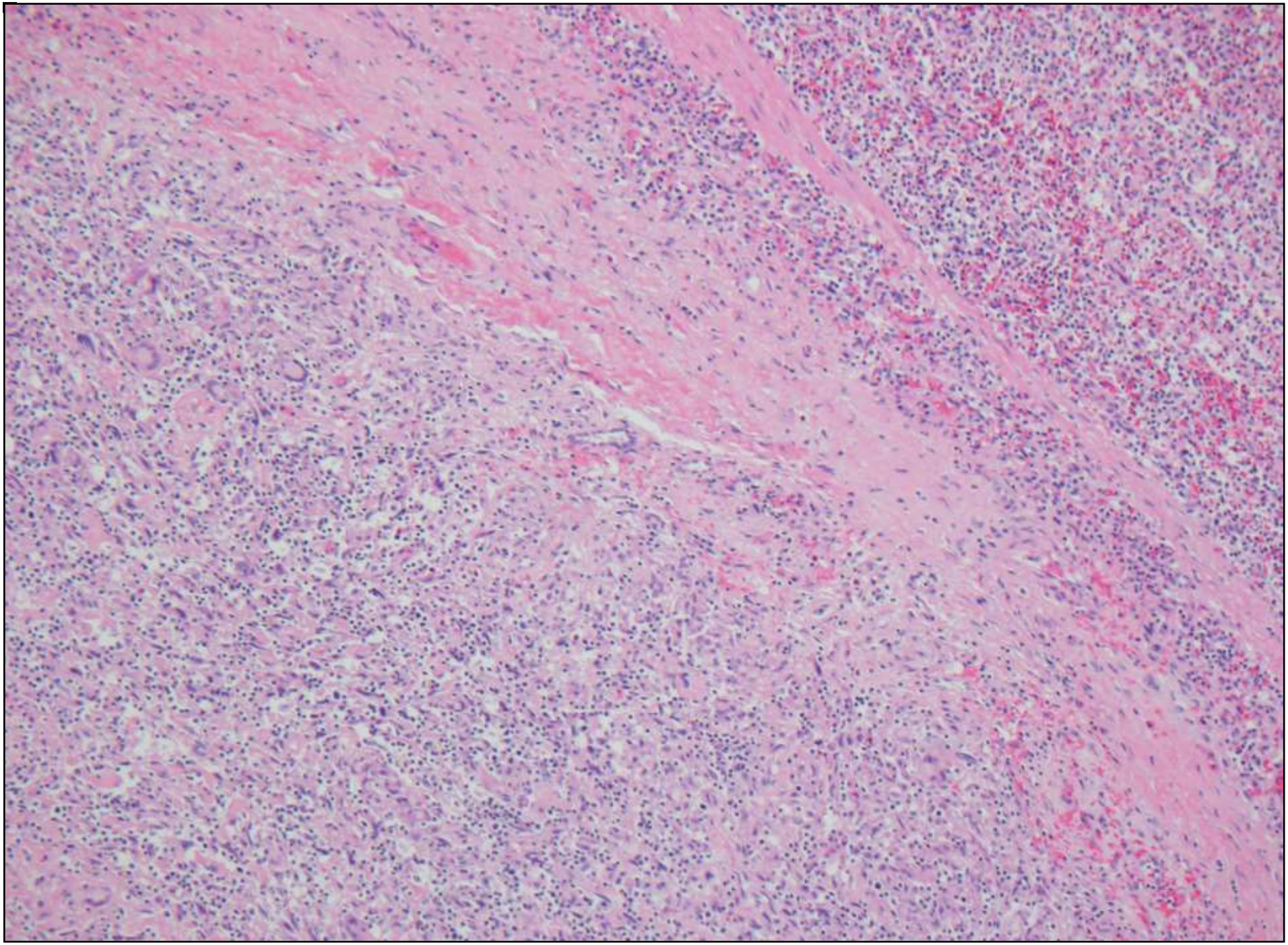

CD30,
400X

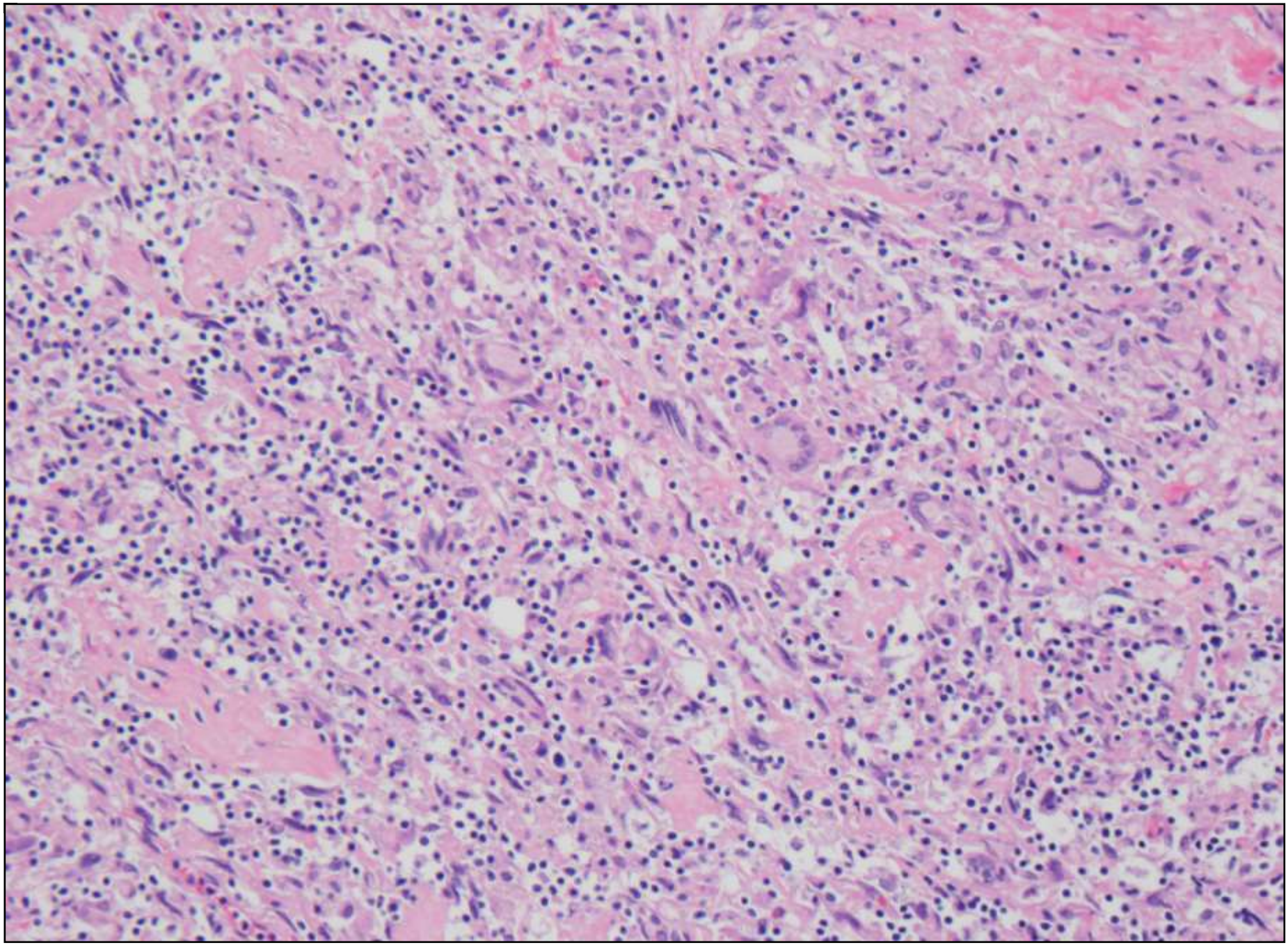
The patient was started on dexamethasone and high dose intrathecal methotrexate. Unfortunately, he has not shown any improvement.

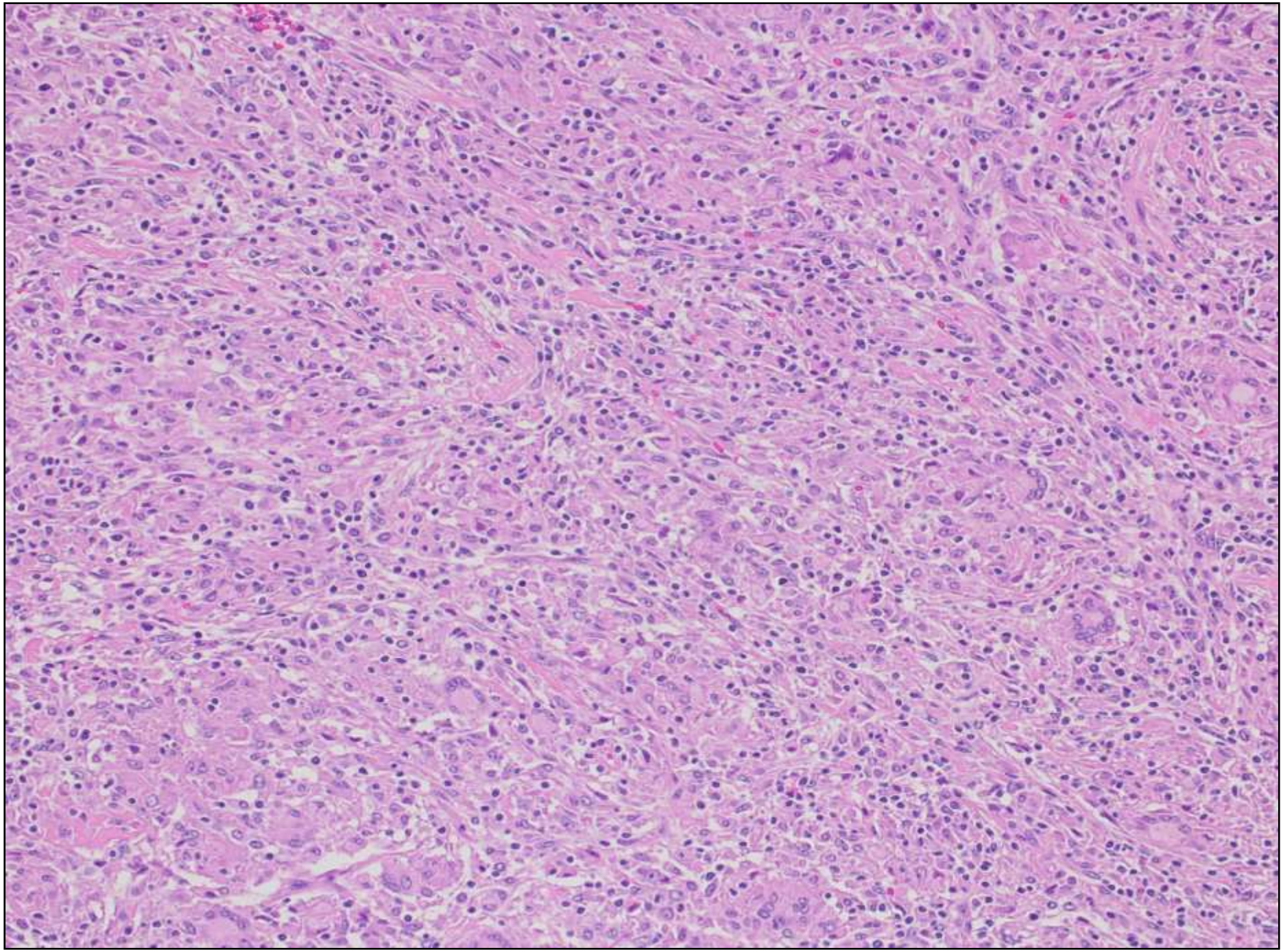
19-0309

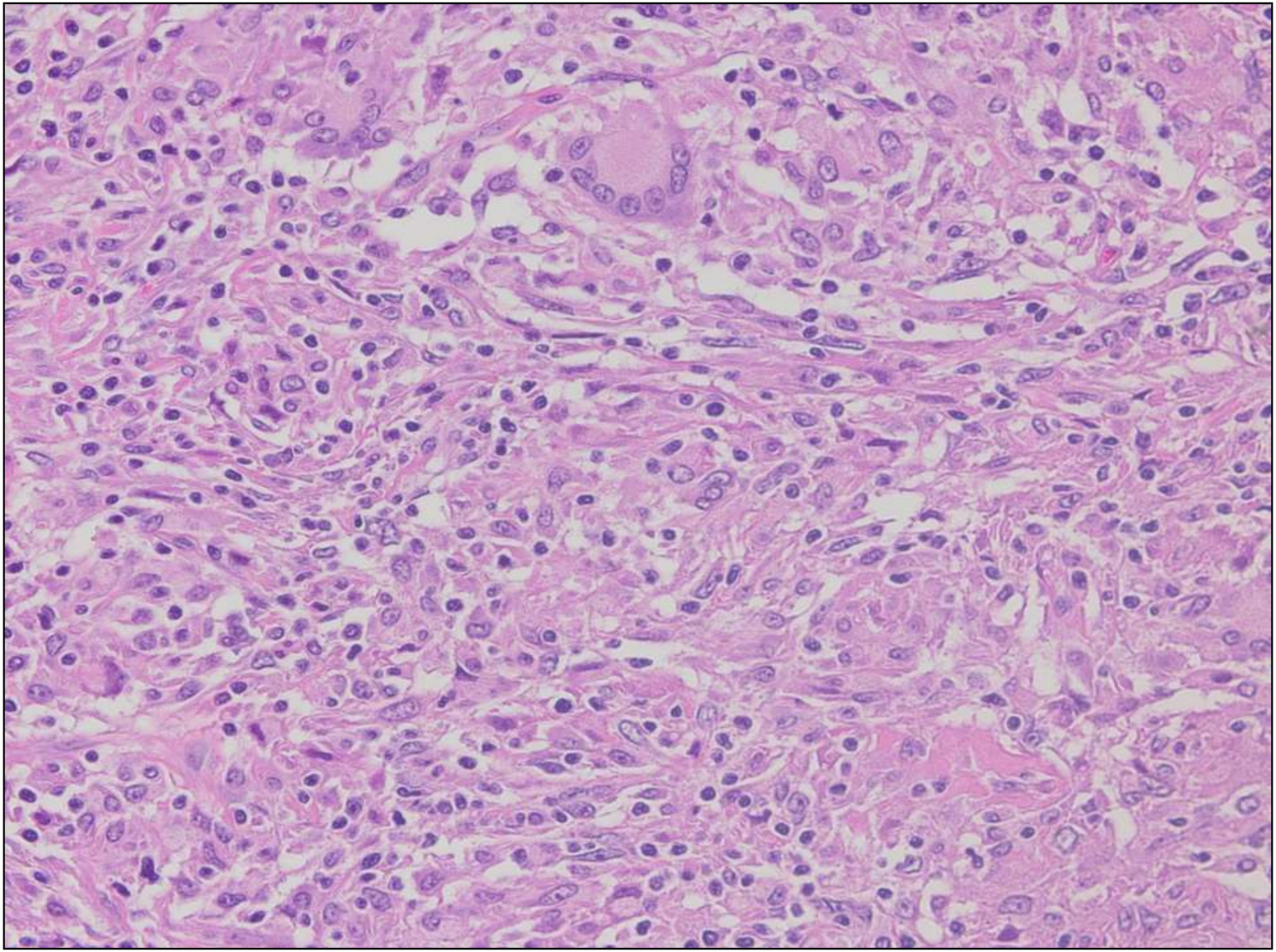
Neda Mirzamani/Sonam Prakash/Yi Xie; UCSF

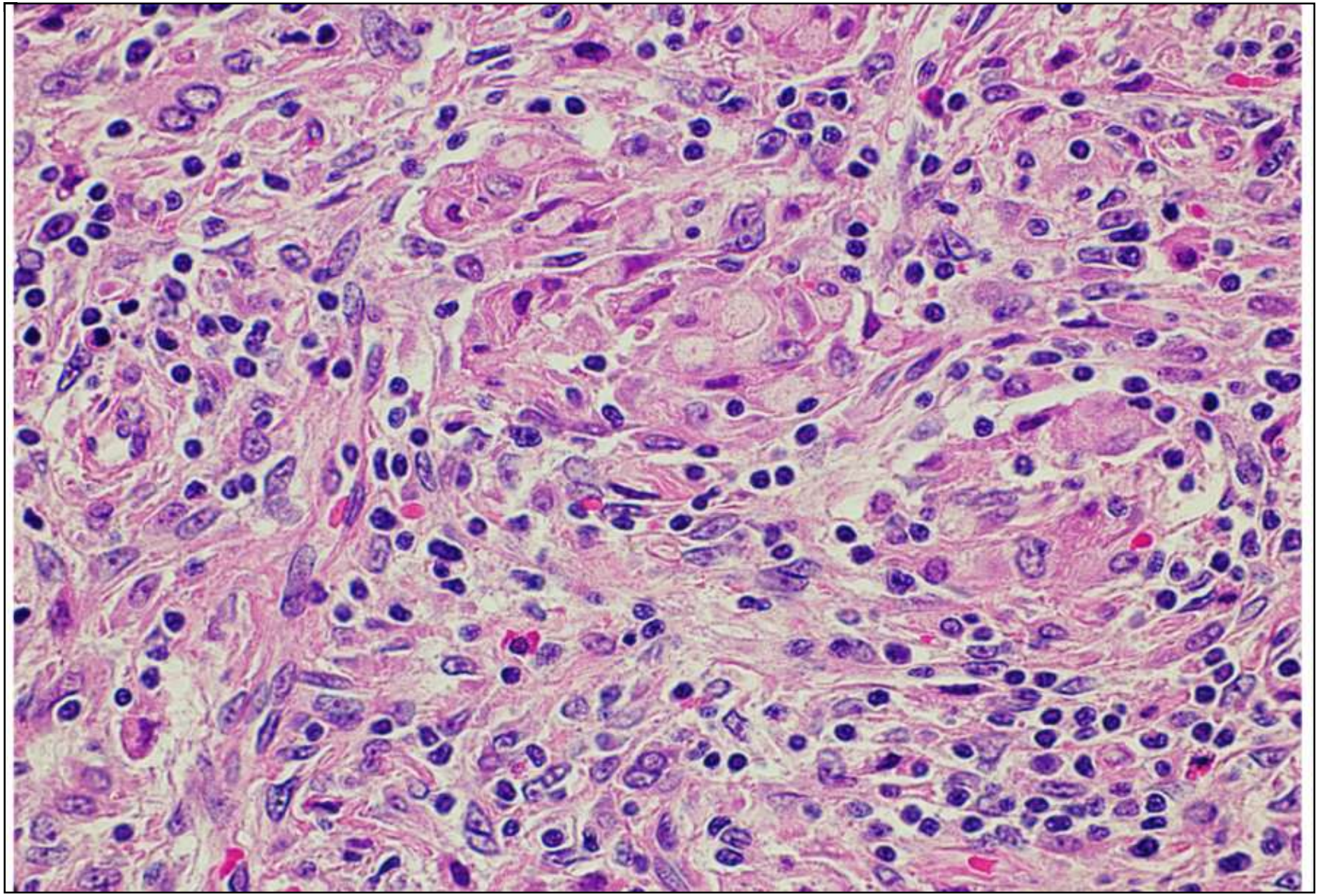
A 79-year-old woman with history of diffuse large B-cell lymphoma status post chemotherapy and recently diagnosed colon cancer status post colectomy. She was found to have splenomegaly with a bulging mass measuring 10 x 8.5 x 8 cm with no extracapsular extension. Splenectomy was performed.

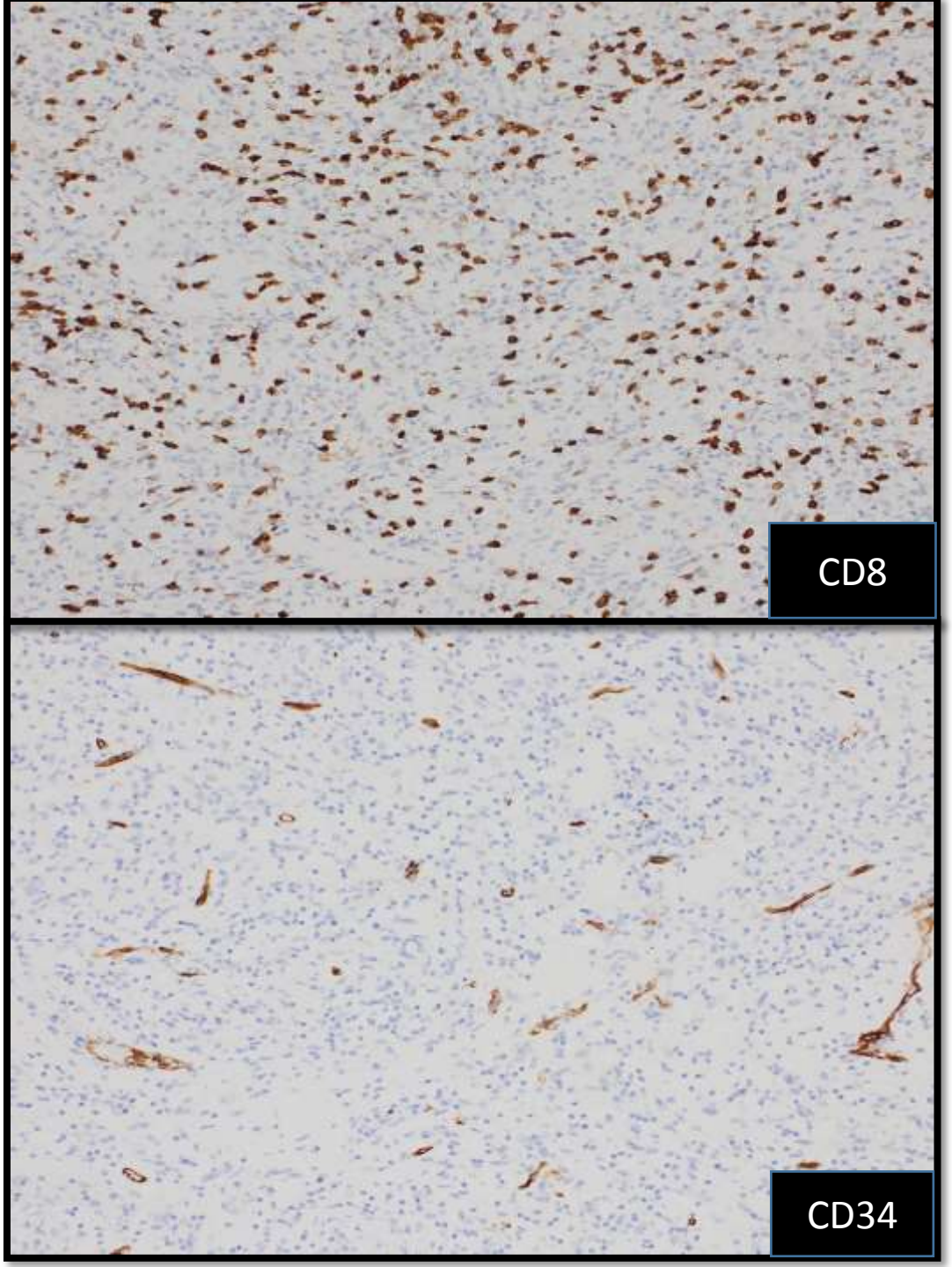


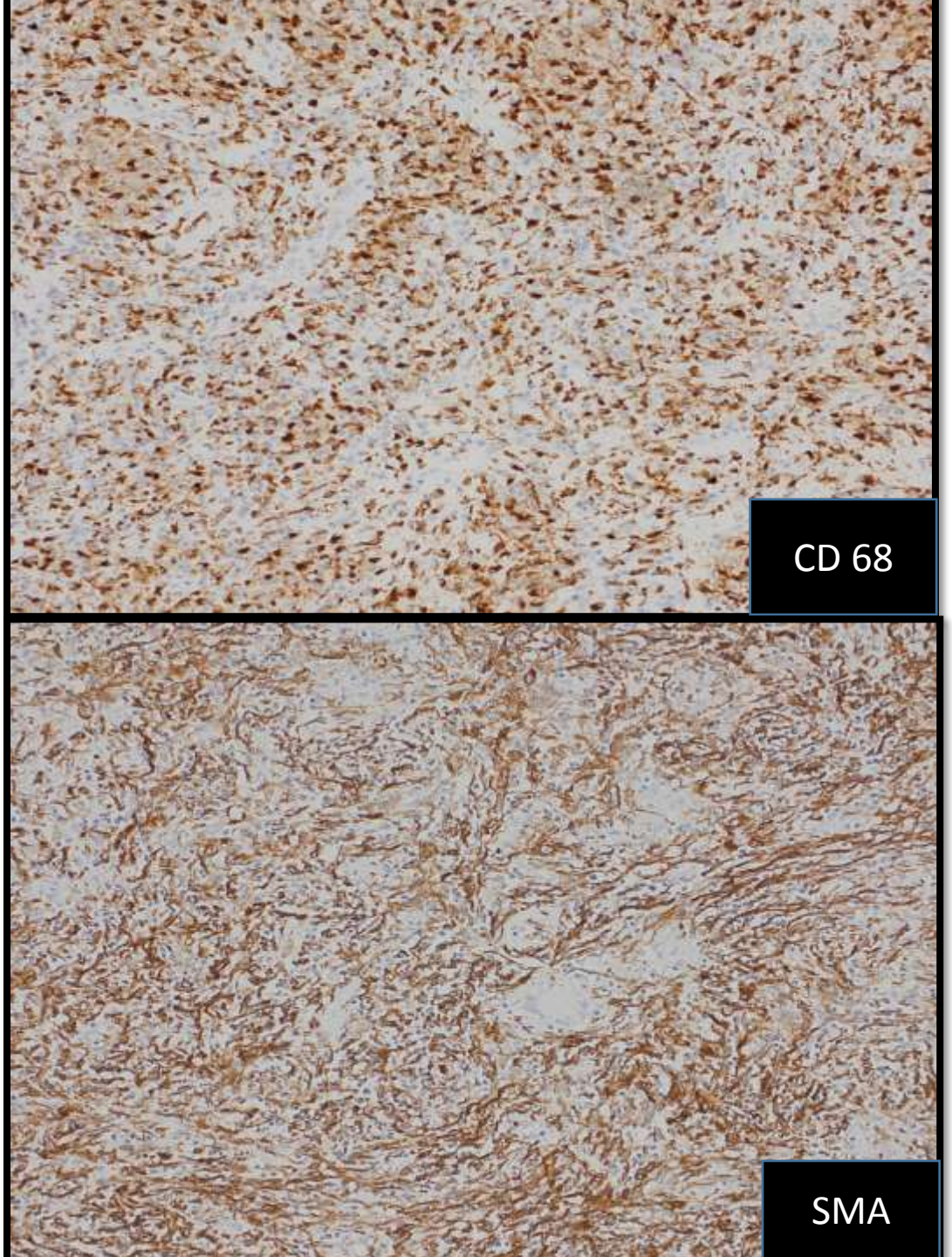


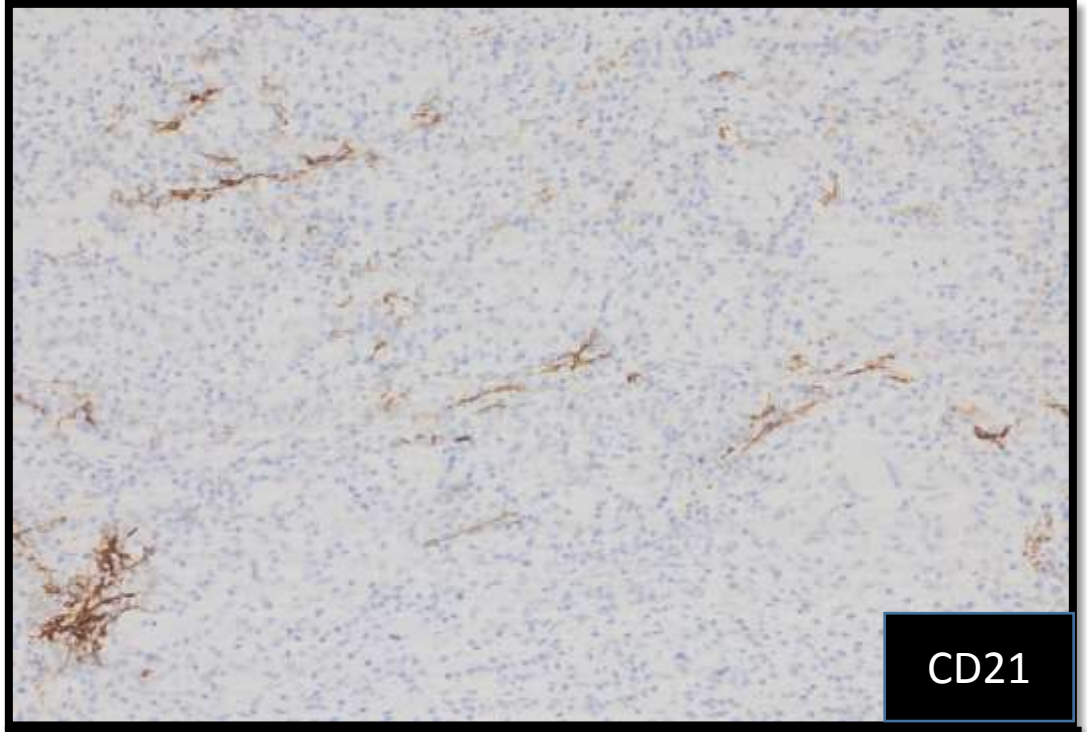


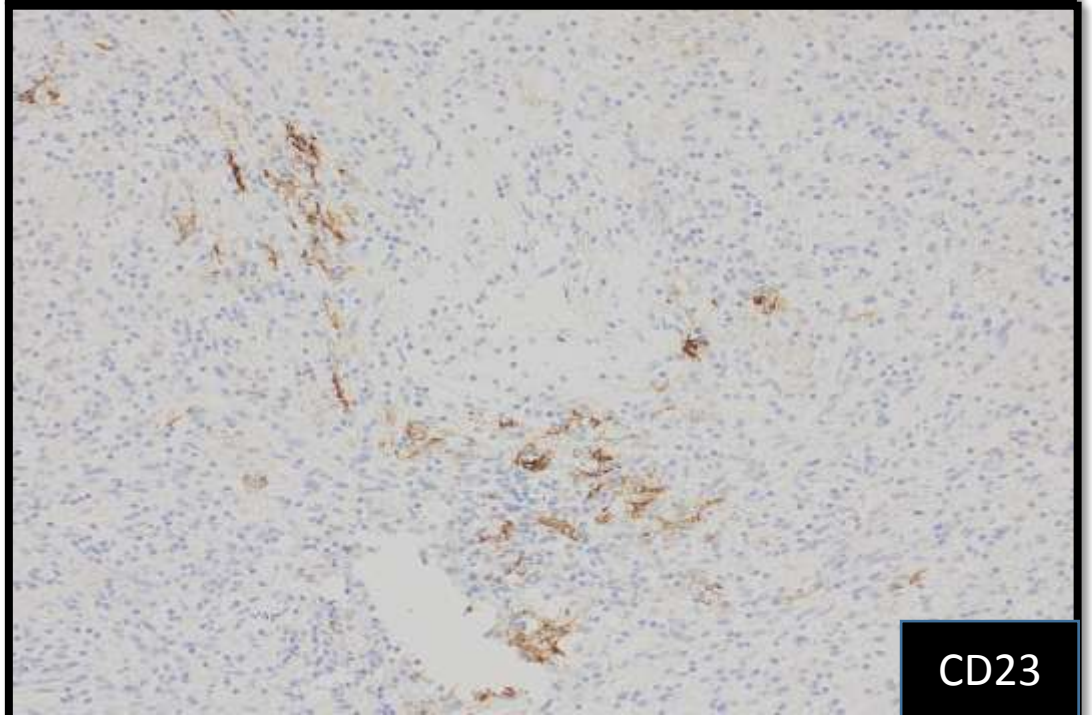


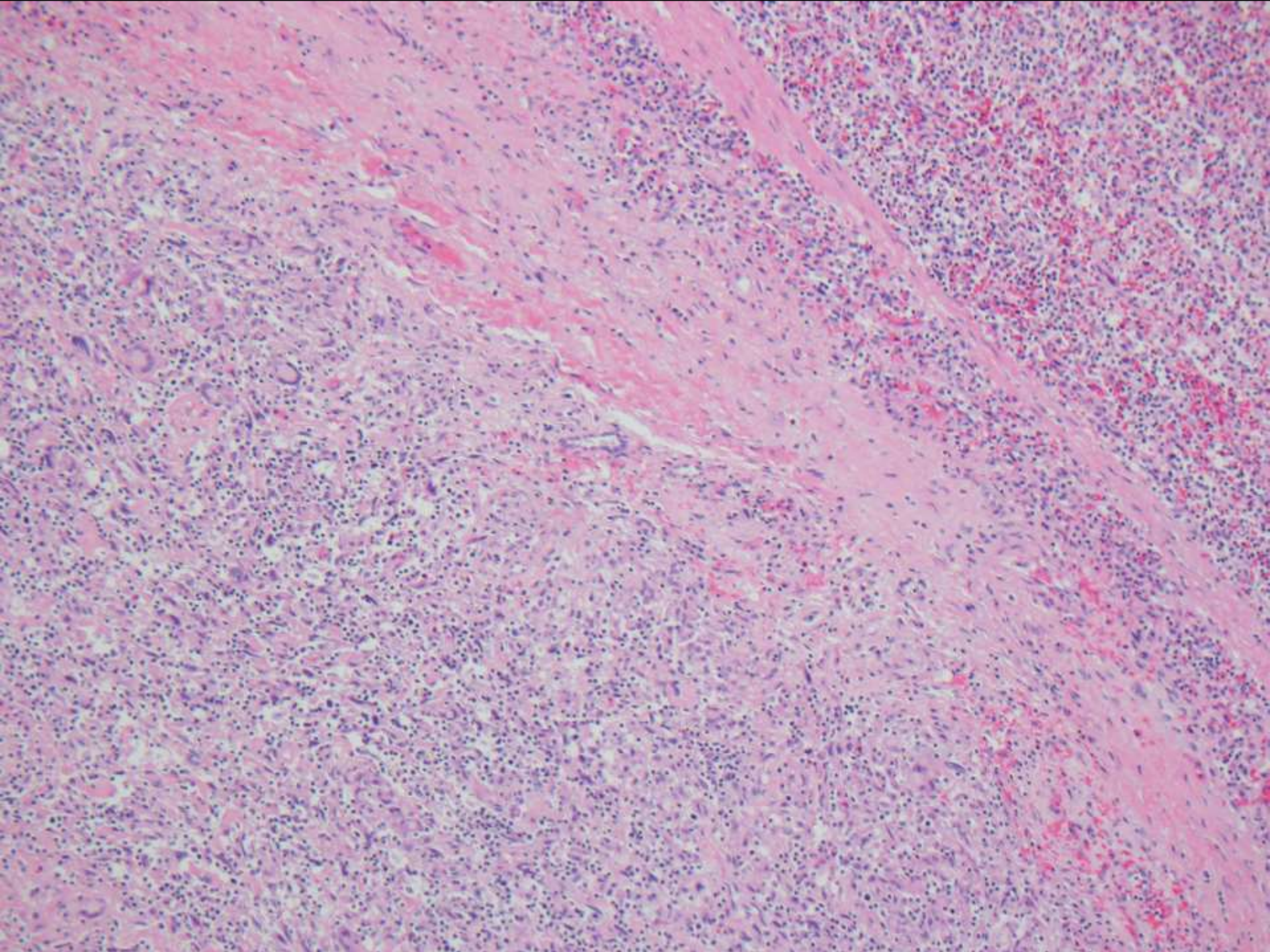


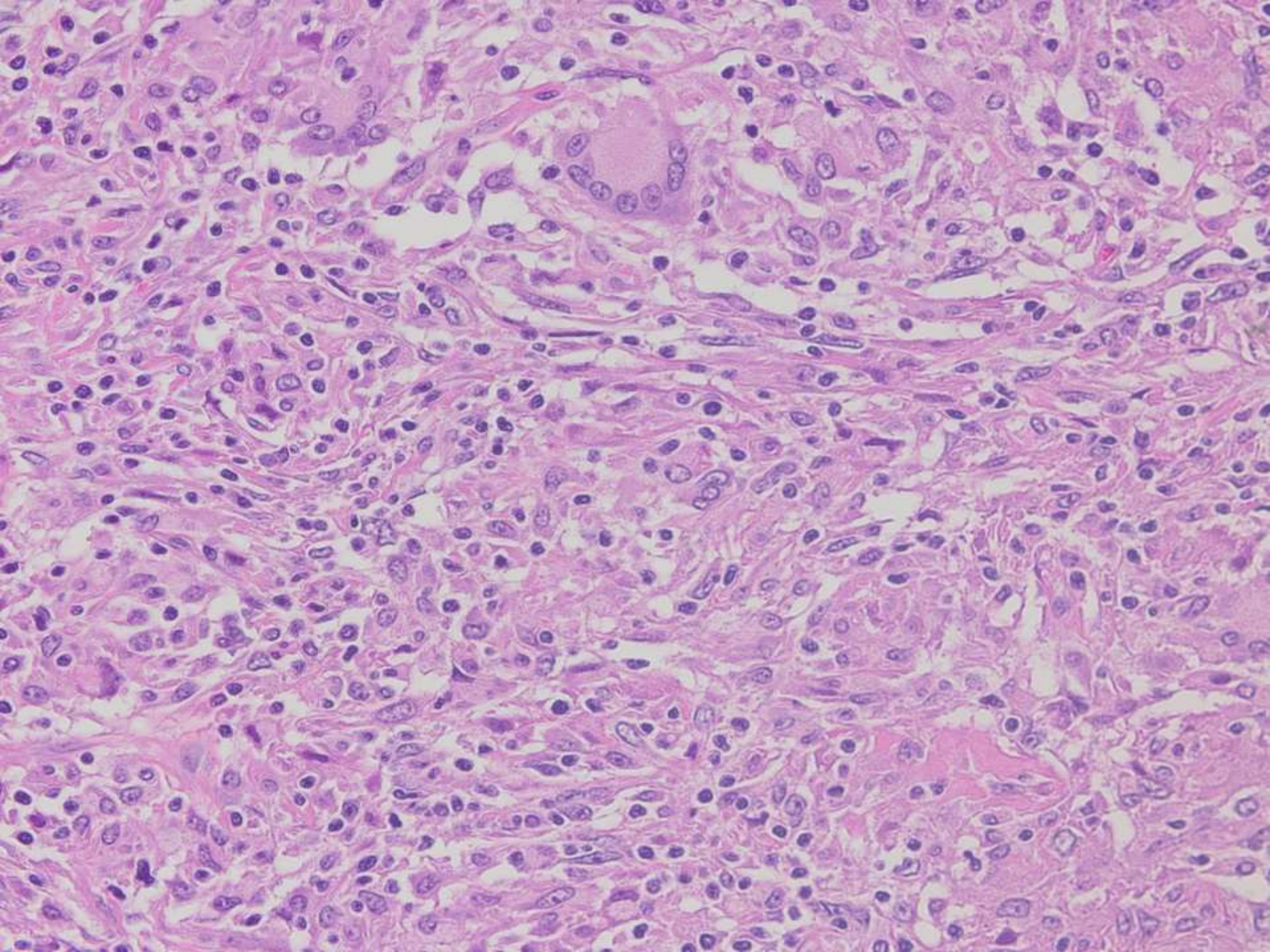

CD8
CD34

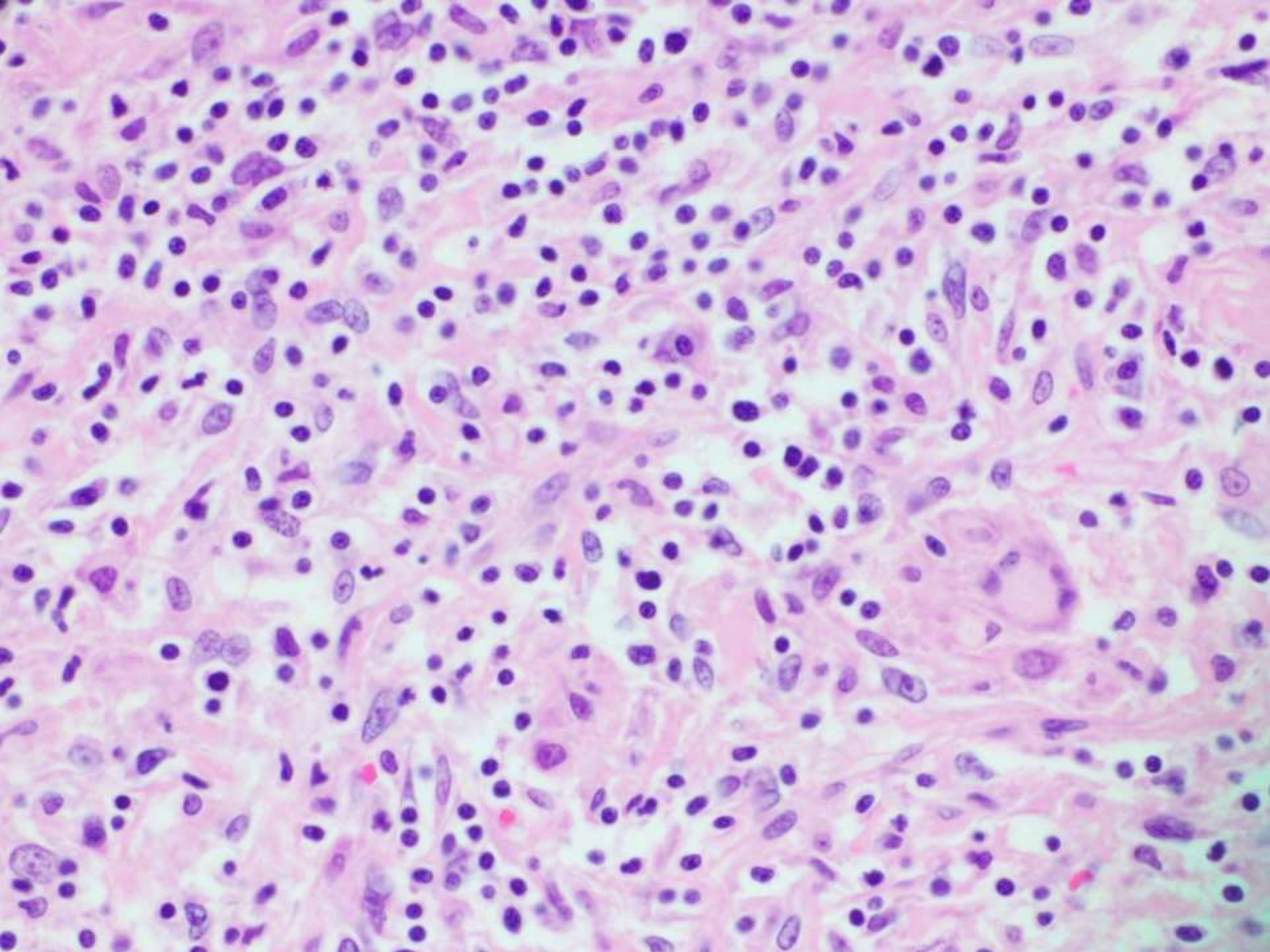

CD 68
SMA


CD21


CD23







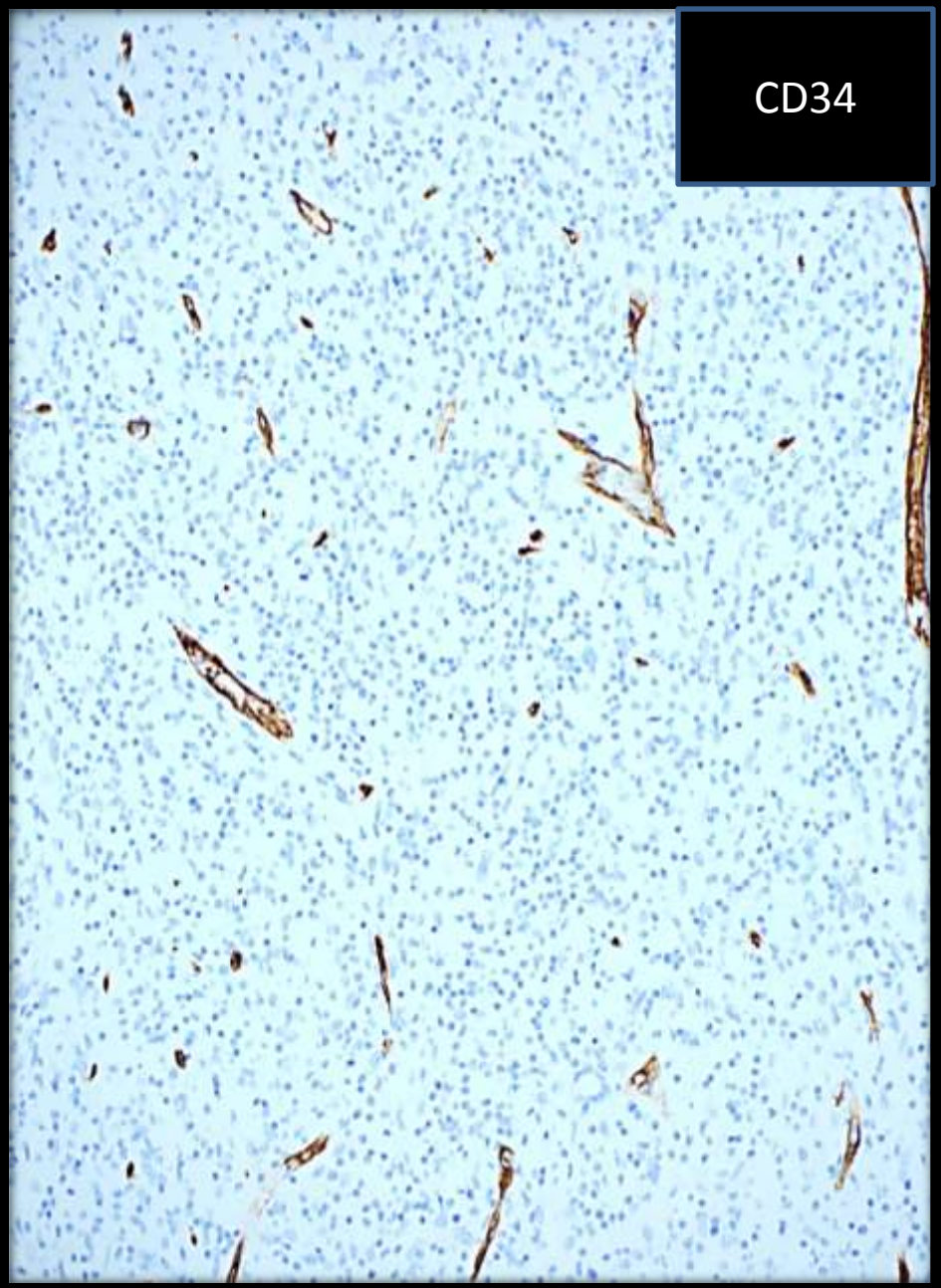
Morphologic Features	Differential Diagnosis
Multinucleated giant cells and epithelioid histiocytes	• Granulomatous inflammation ▪ Sarcoidosis ▪ Infection
Well circumscribed mass	• Sclerosing Angiomatoid Nodular Transformation of the Spleen (SANT)
Inflammatory spindle cell proliferation	• Inflammatory pseudotumor • IgG4-related disease • Inflammatory myofibroblastic tumor • Kaposi sarcoma • Interdigitating dendritic cell tumor • Follicular dendritic cell tumor

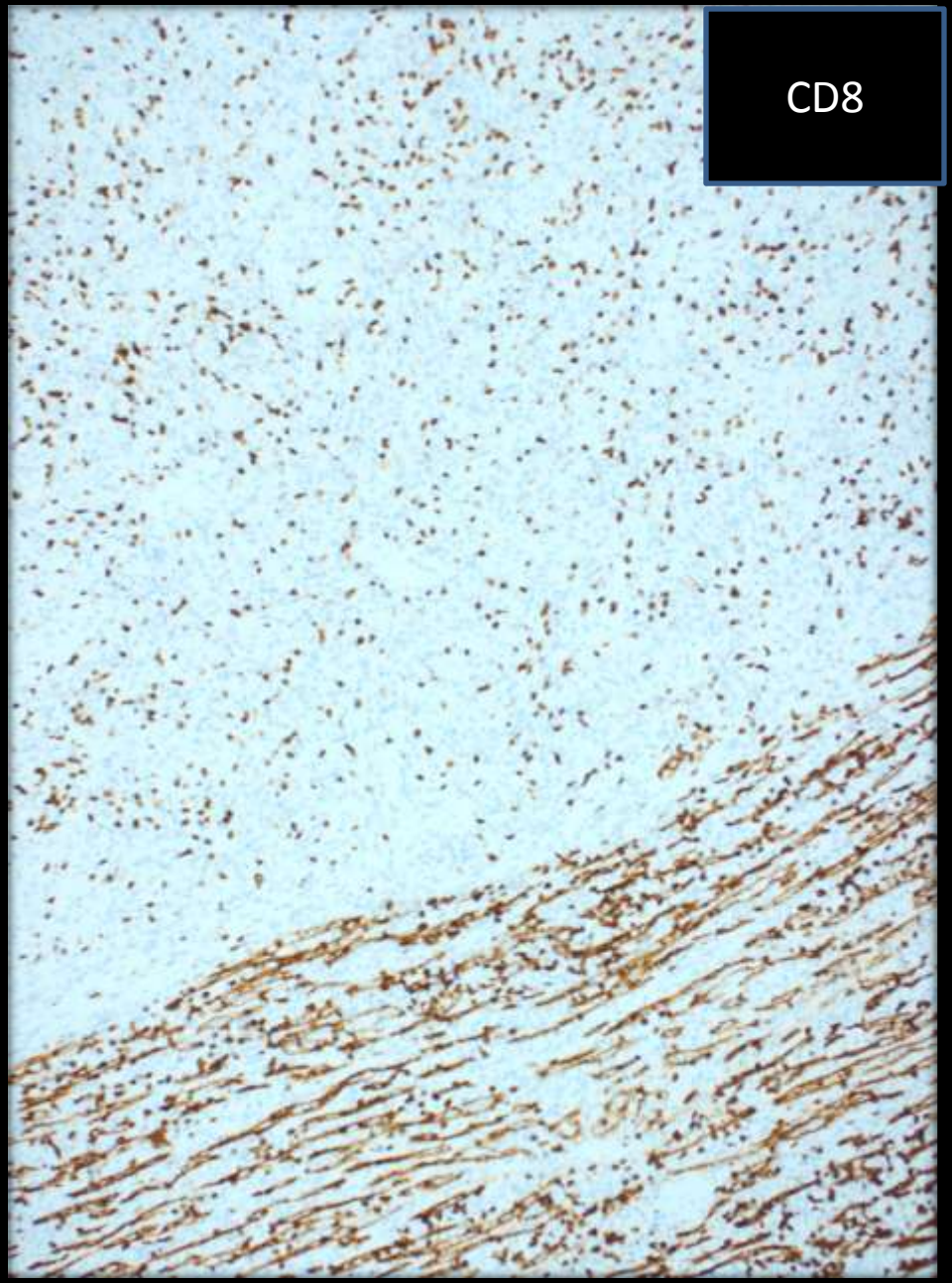
Work Up

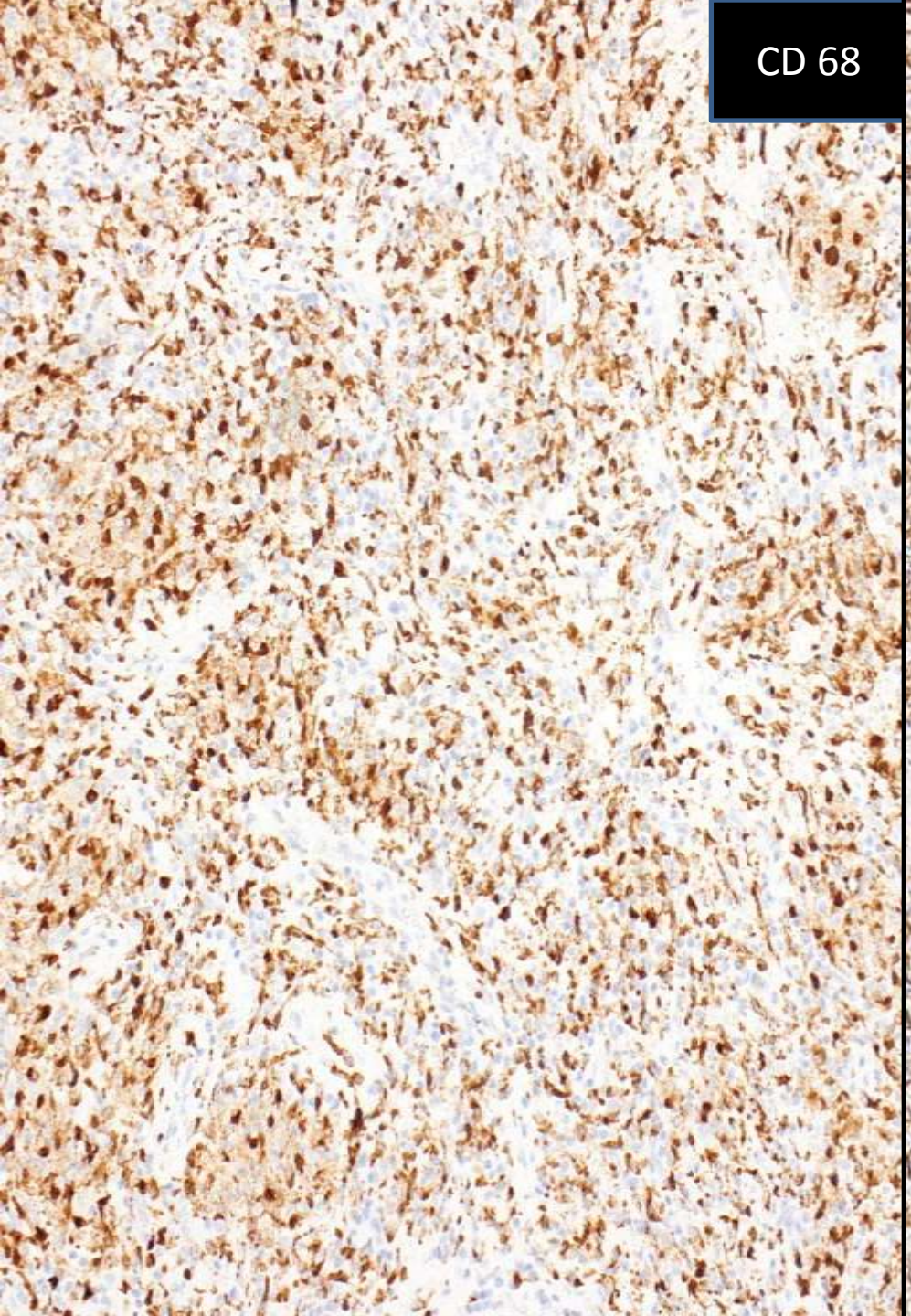
Special stains	AFB
Vascular marker	CD31, CD34, CD8
Spindle cell proliferation	
Fibrohistiocytic markers	CD68, SMA
Neural markers	S100
Follicular dendritic cell markers	CD21, CD23, D2-40, CXCL13

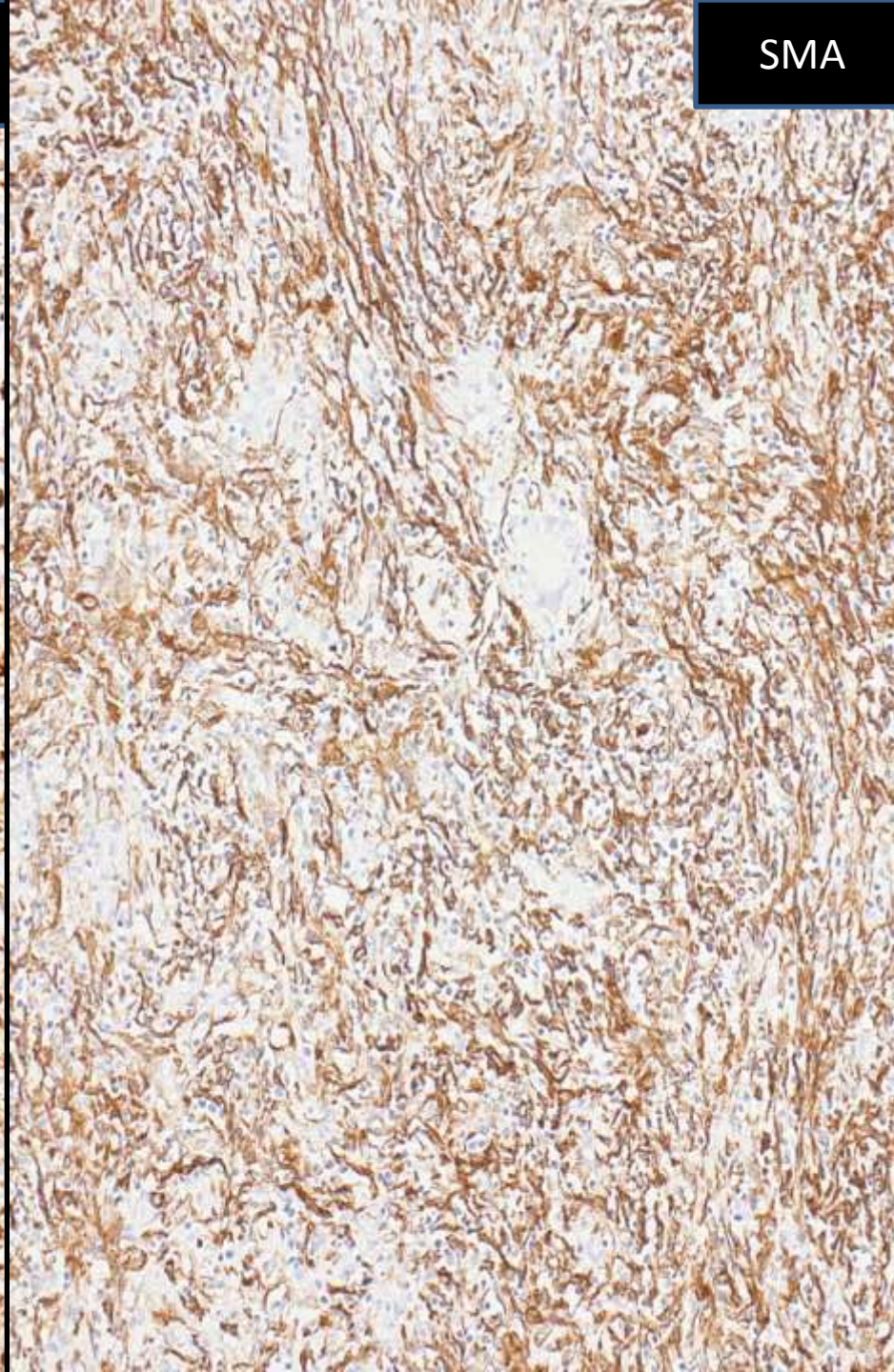
Results

- **AFB** Negative
- **CD8, CD31, CD34** No proliferation of blood vessels or sinusoids
- **CD68** Positive in histiocytes & subset of spindle cells
- **SMA** Positive in spindle cells
- **CD21, CD23** Focally positive
- **S100** Negative


CD34

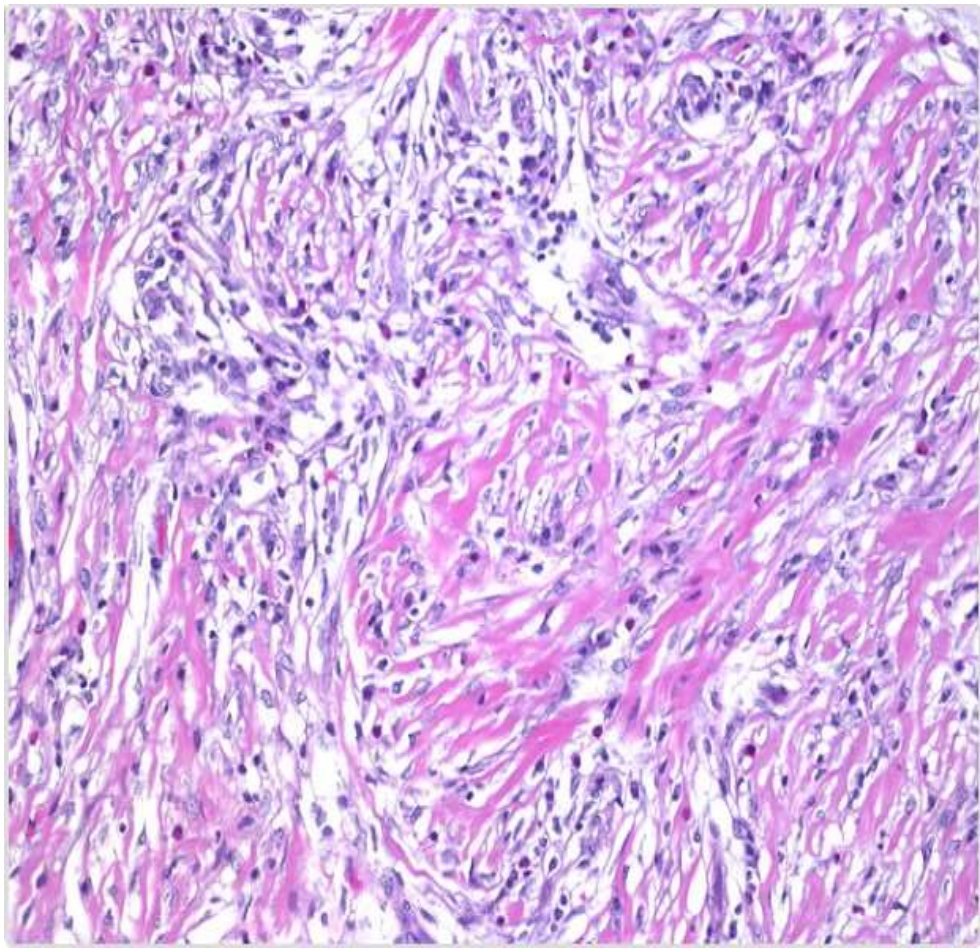

CD8


CD 68


SMA

Inflammatory pseudotumor

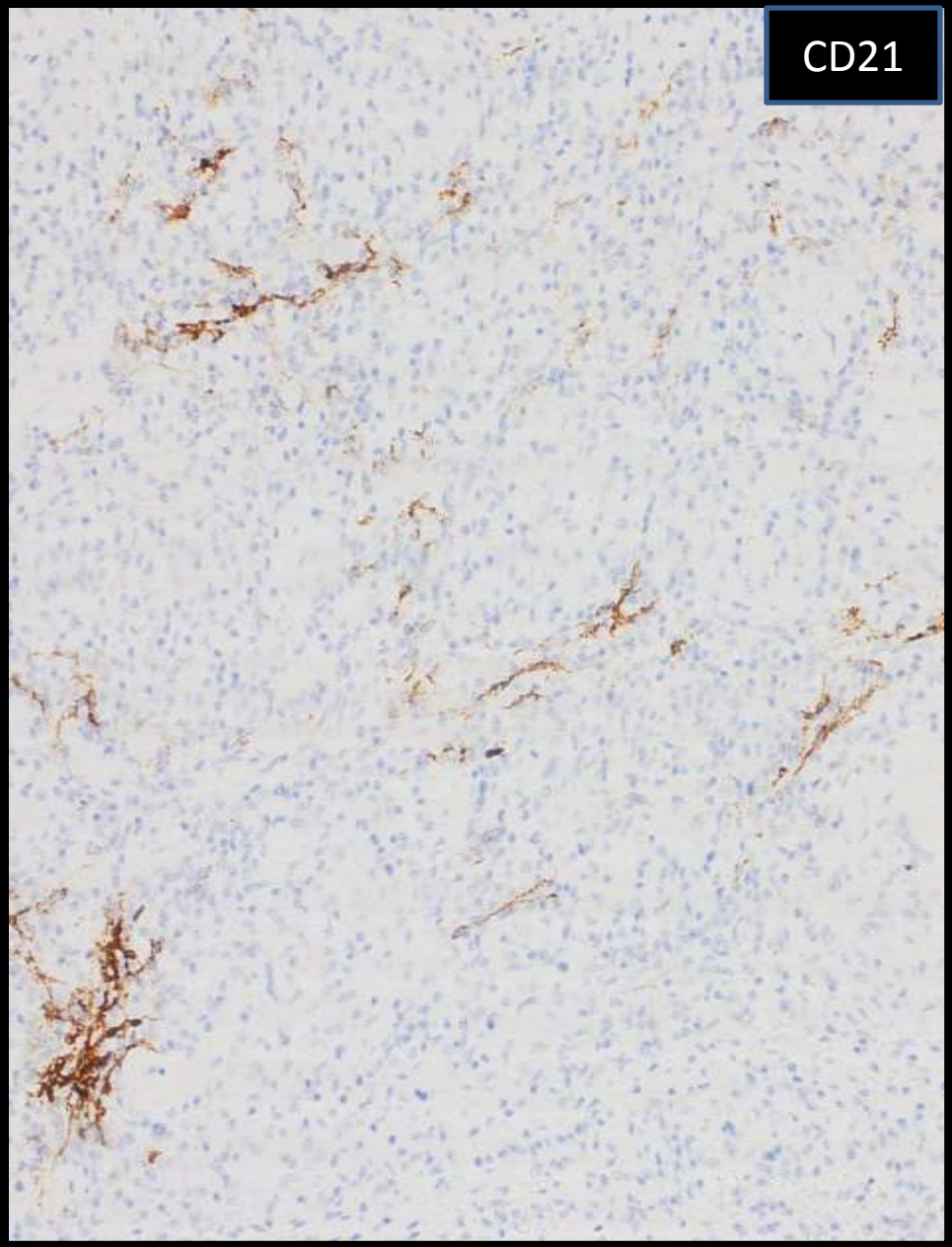
- Benign – non neoplastic
- Unknown etiology
- Infections-autoimmune-reactive-neoplastic
- Middle-aged to older persons
- Female > male in splenic type 5:3
- Single mass or multiple masses

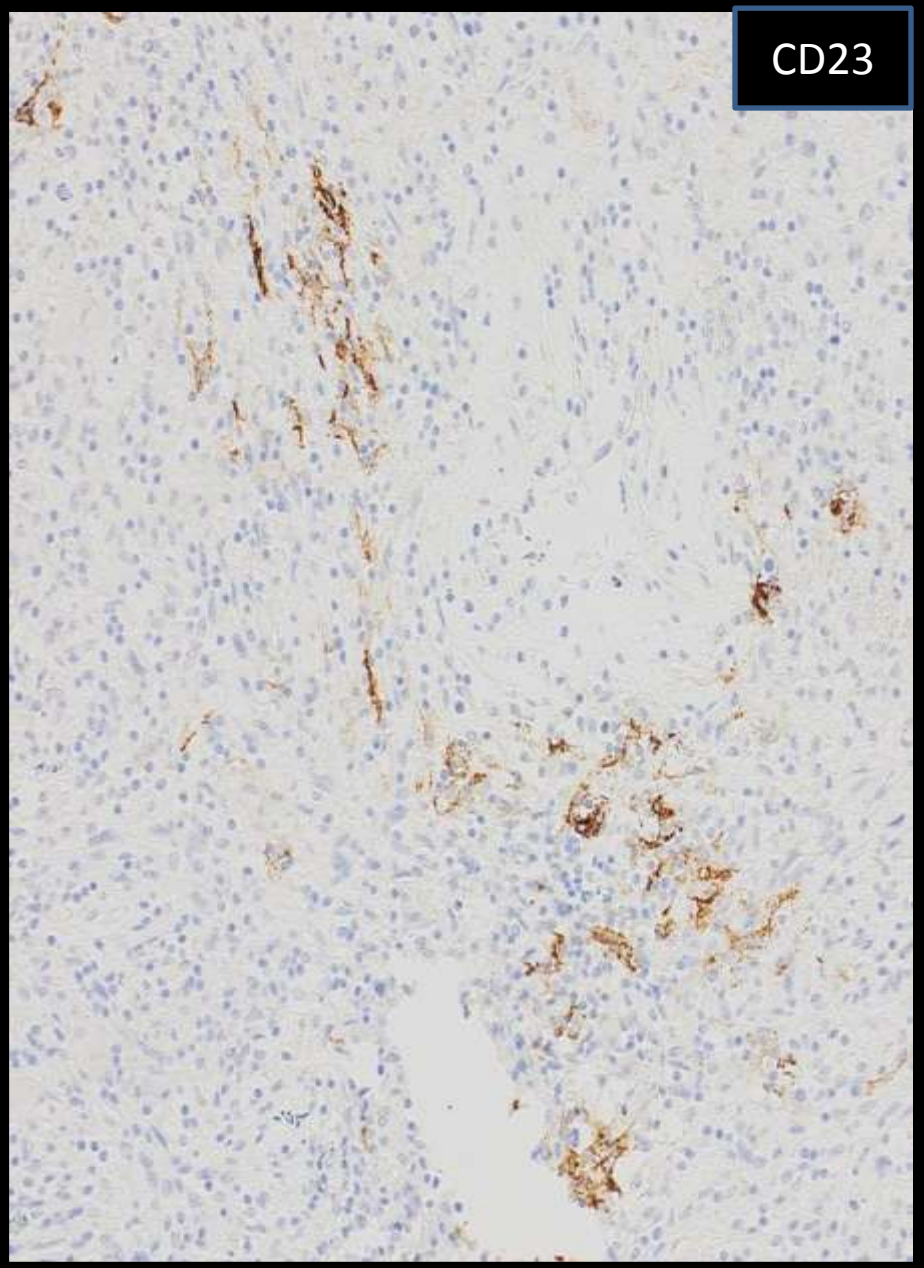


Web pathology
Dharam Ramnani, MD

Inflammatory myofibroblastic tumor

- Children and adolescent
- Clonal, neoplastic of intermediate biologic potential
- Abdomen and pelvis- Lymph nodes (uncommon)
- Myofibroblastic spindle cells associated with inflammatory cells
- Cytoplasmic ALK1(+) ~ 60%, particularly pediatric cases
- Multiple recurrences – Metastasis


CD21


CD23

Follicular dendritic cell tumor

- Synonyms: FDC tumor-Dendritic reticulum cell sarcoma
- Origin: Mesenchymal stem cells
- Rare neoplasm
- Adult predominance, median 50, F=M
- Arise in the setting of hyaline-vascular Castleman (10-20%)
- Asymptomatic

Follicular dendritic cell tumor (FDCS)

- Nodal (common): cervical and axillary
- Extranodal (30%): Waldeyer ring is most common- GI-soft tissue-thyroid-mediastinum-liver- spleen
- Adults; median age: 50 years, M=F
- Rare systemic symptoms
- Most cases behave like low- to intermediate-grade soft tissue sarcoma

Inflammatory Pseudotumor-Like follicular/fibroblastic dendritic cell tumor

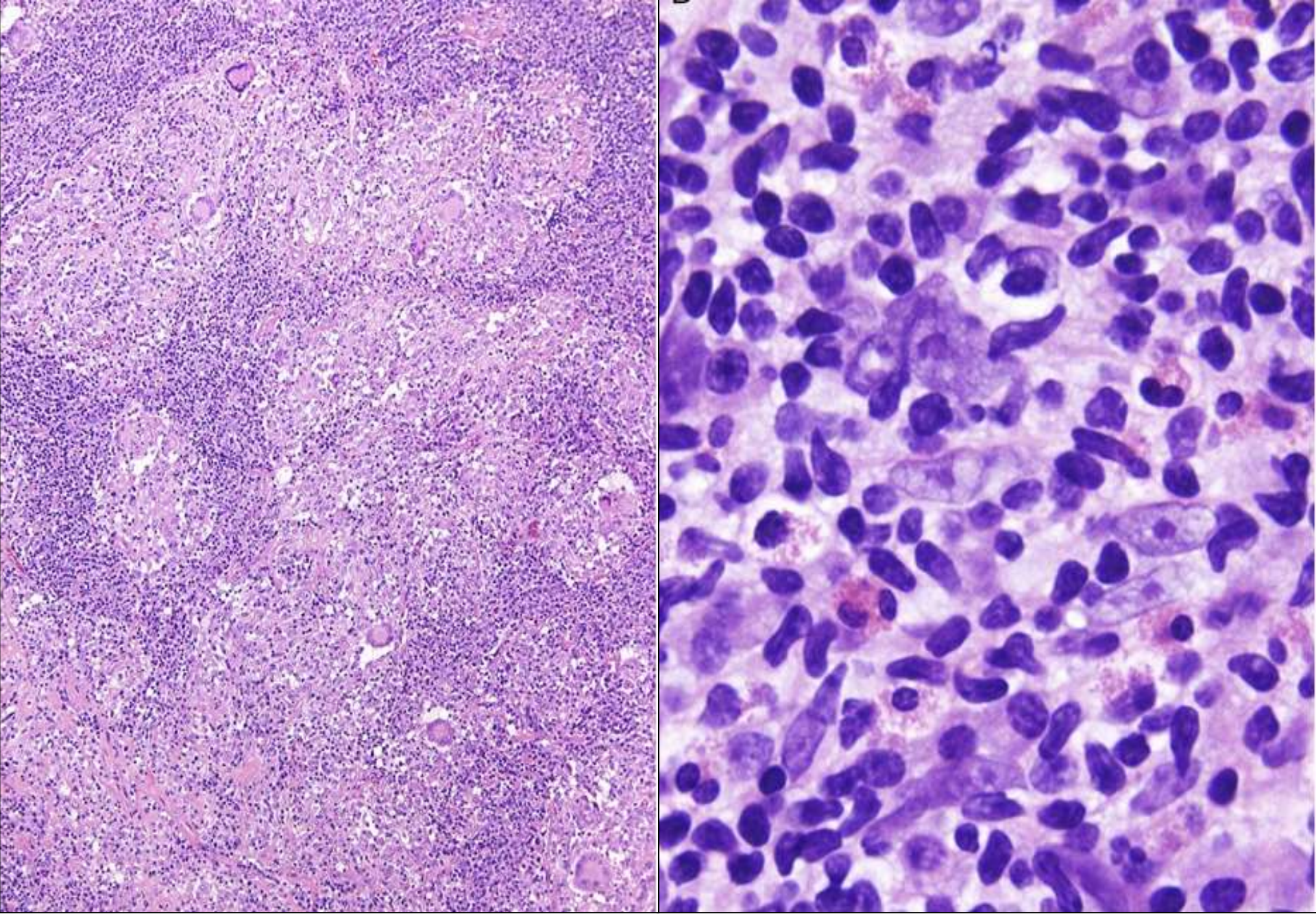
- More prevalent in Asia, M:F ratio 1:3
- Often arises in liver and spleen
- Median age: 56 years
- Systemic symptoms: Weight loss and fever
- Paraneoplastic pemphigus can occur rarely
- 50% found incidentally

Inflammatory Pseudotumor-Like follicular/fibroblastic dendritic cell tumor

- Subset associated with a concomitant malignancy
  - Breast cancer
  - Gastric cancer
  - EBV-positive gastric cancer
  - DLBCL

Pathology

- Well demarcated from surrounding parenchyma
- Size range: 1.5 to 22.3 cm
- Striking resemblance to inflammatory pseudotumor or inflammatory myofibroblastic tumor
- Two morphological variants: Granulomatous and eosinophil-rich (Am J Surg Pathol. 2014;38:646–53).



Am J Surg Pathol. 2014;38:646–53

Immunohistochemistry

- One or more FDC-associated markers:

  CD21, CD23, CD35, Ki-M4p, and CNA.42,

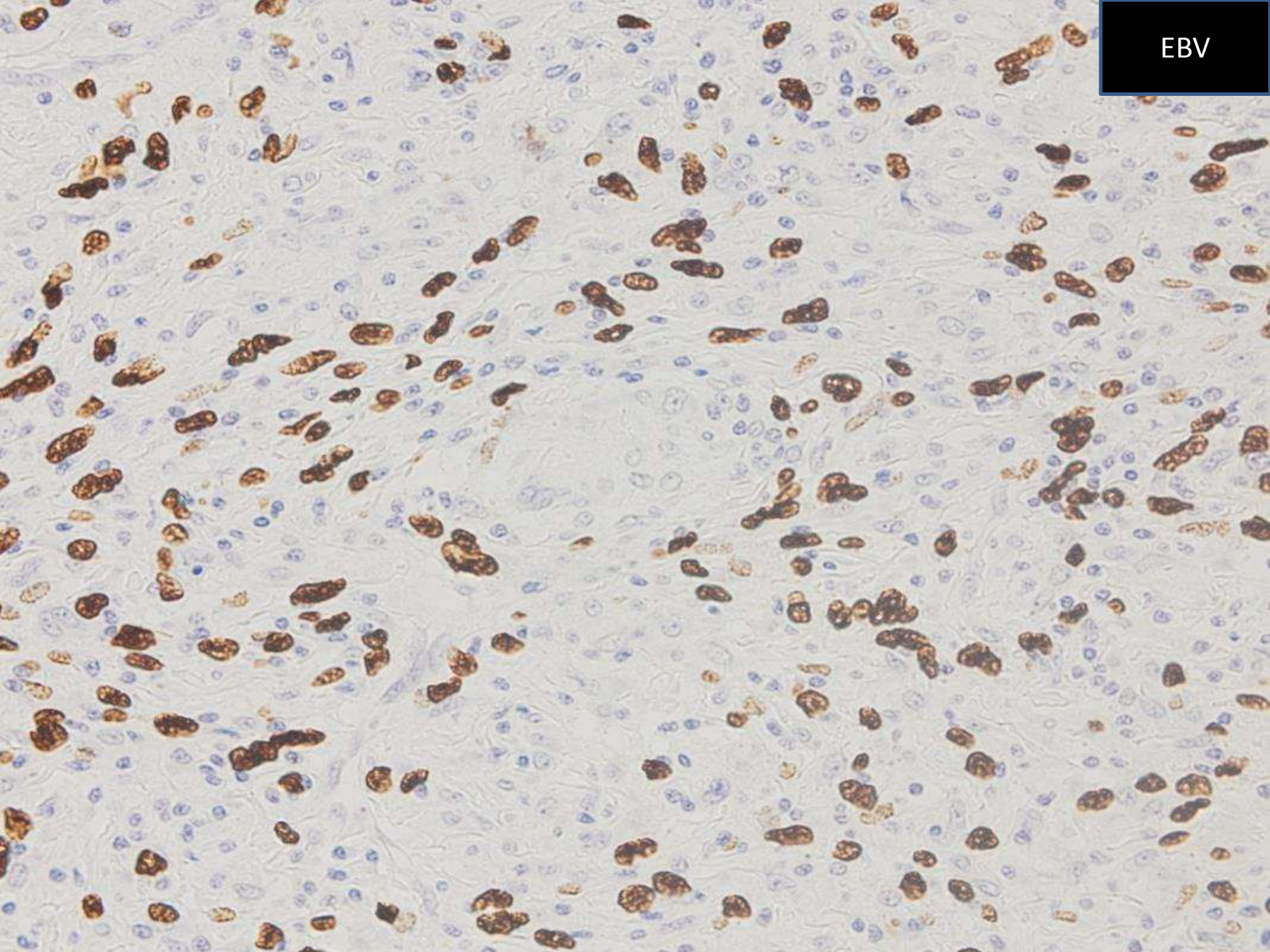
  clusterin, D2-40, CXCL13

  (extensive or very focal or negative)

  CD35 the most sensitive and reliable marker
- Often express vimentin and SMA, and /or CD68
- EBV
- CD31(-), ALK-1(-), CD34(-), CD8(-), Desmin (-), Caldesmon(-)

Pathogenesis

- Consistently associated with Epstein-Barr virus
- Strong expression of EBER in the spindle cells but not in the inflammatory cells
- Monoclonal EBV


EBV

Prognosis

- More indolent than conventional FDC sarcoma (Am J Surg Pathol. 2001;25:721–31)

- Splenic origin:
  - Indolent clinical course
  - Cured with resection
  - Relapse is rare

- Liver:
  - Tend to recur

Take home message

- The diagnosis of fibroinflammatory tumor of spleen may be difficult.
- A large immunohistochemical panel is required in combination with other clinicopathologic information.
- FDC markers and EBER useful in diagnosis of IPT-like FDC tumor

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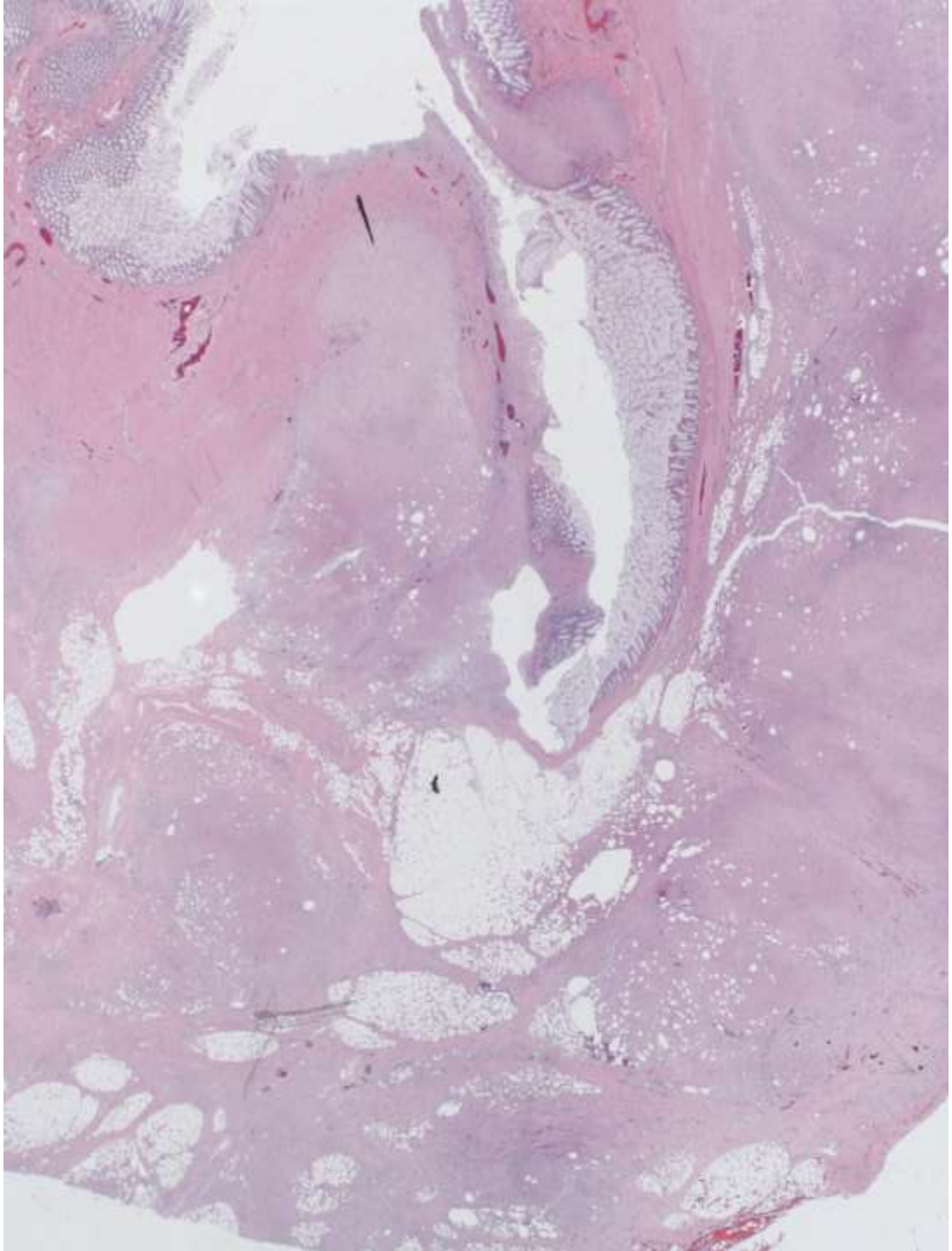
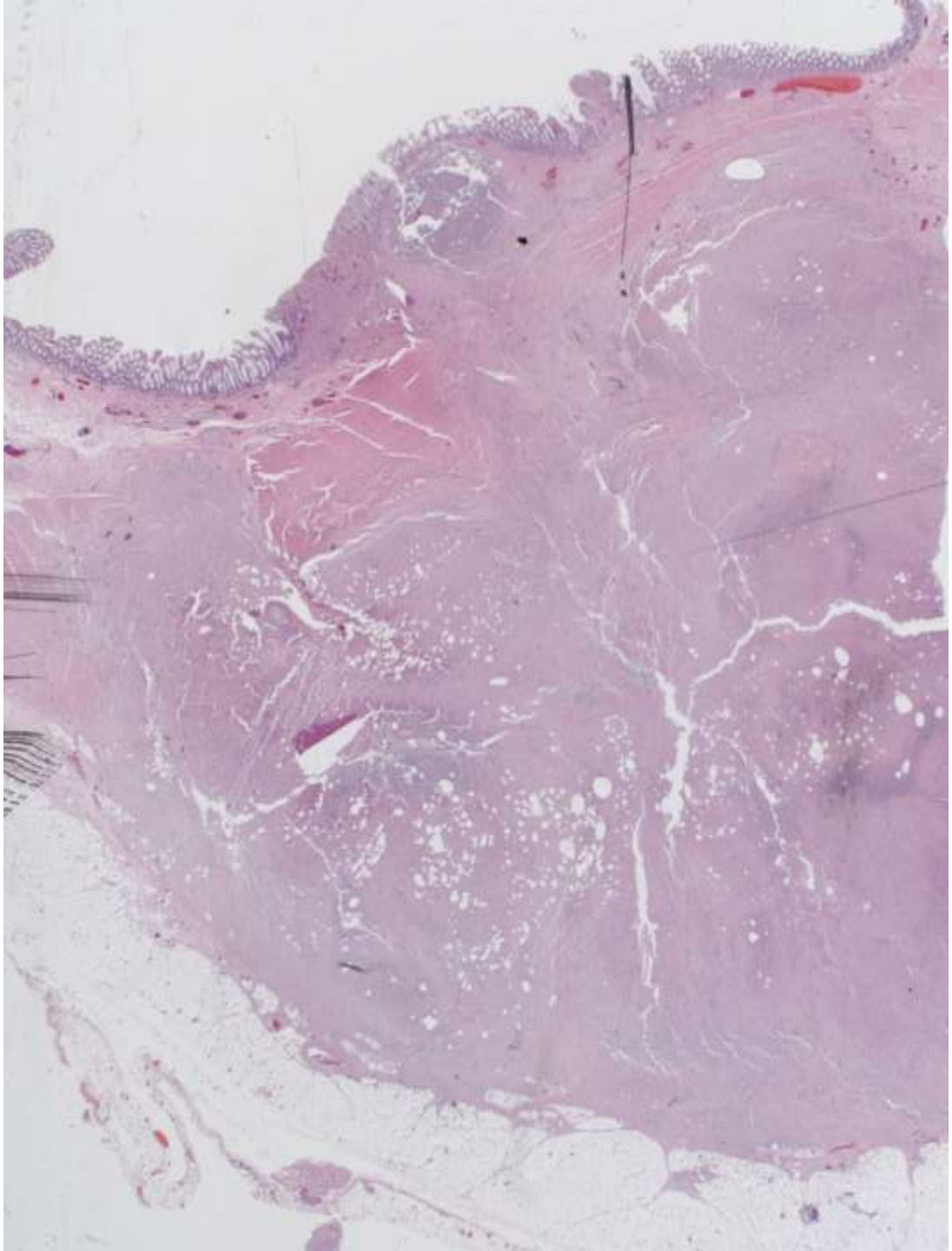
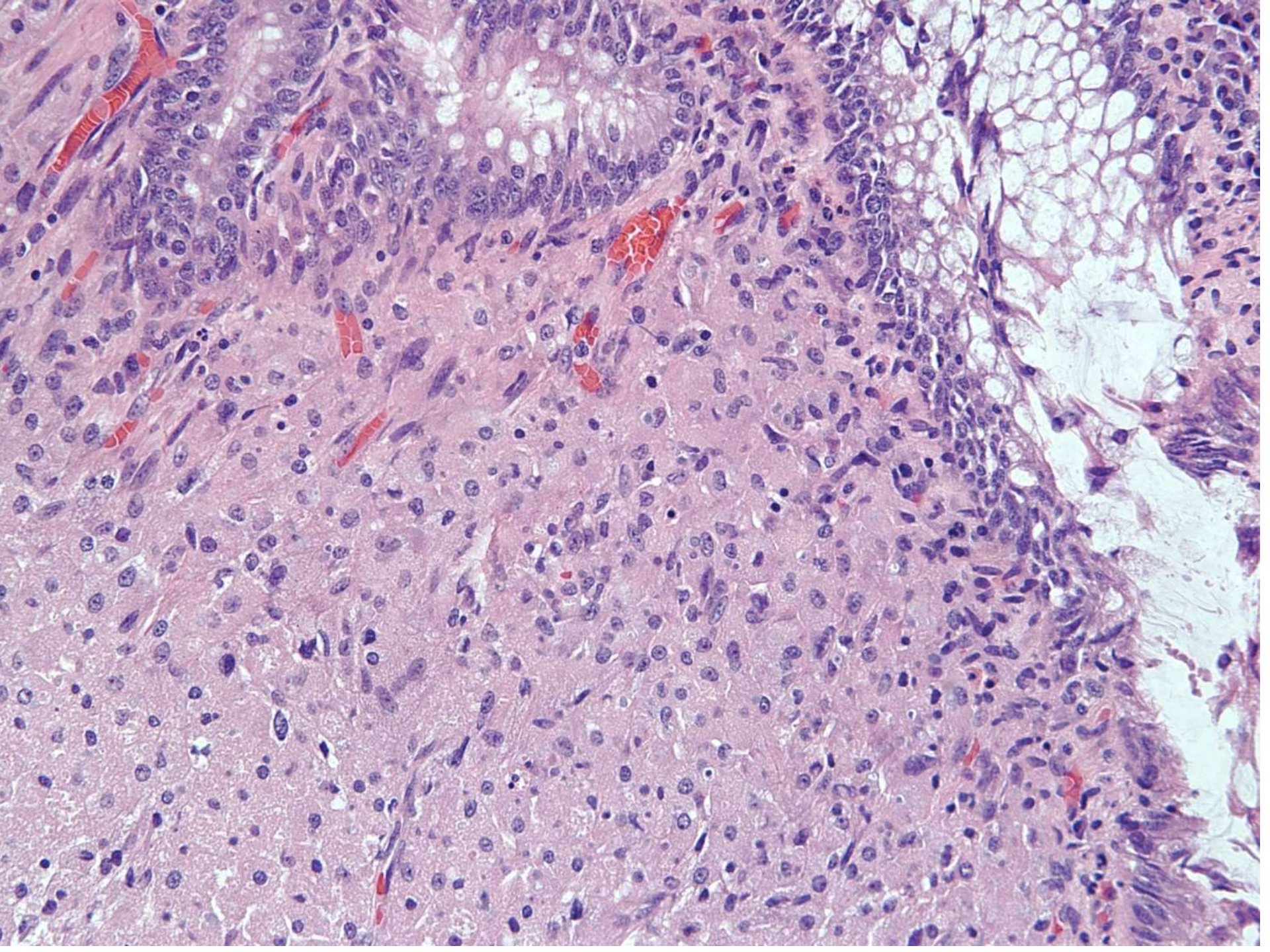
19-0410

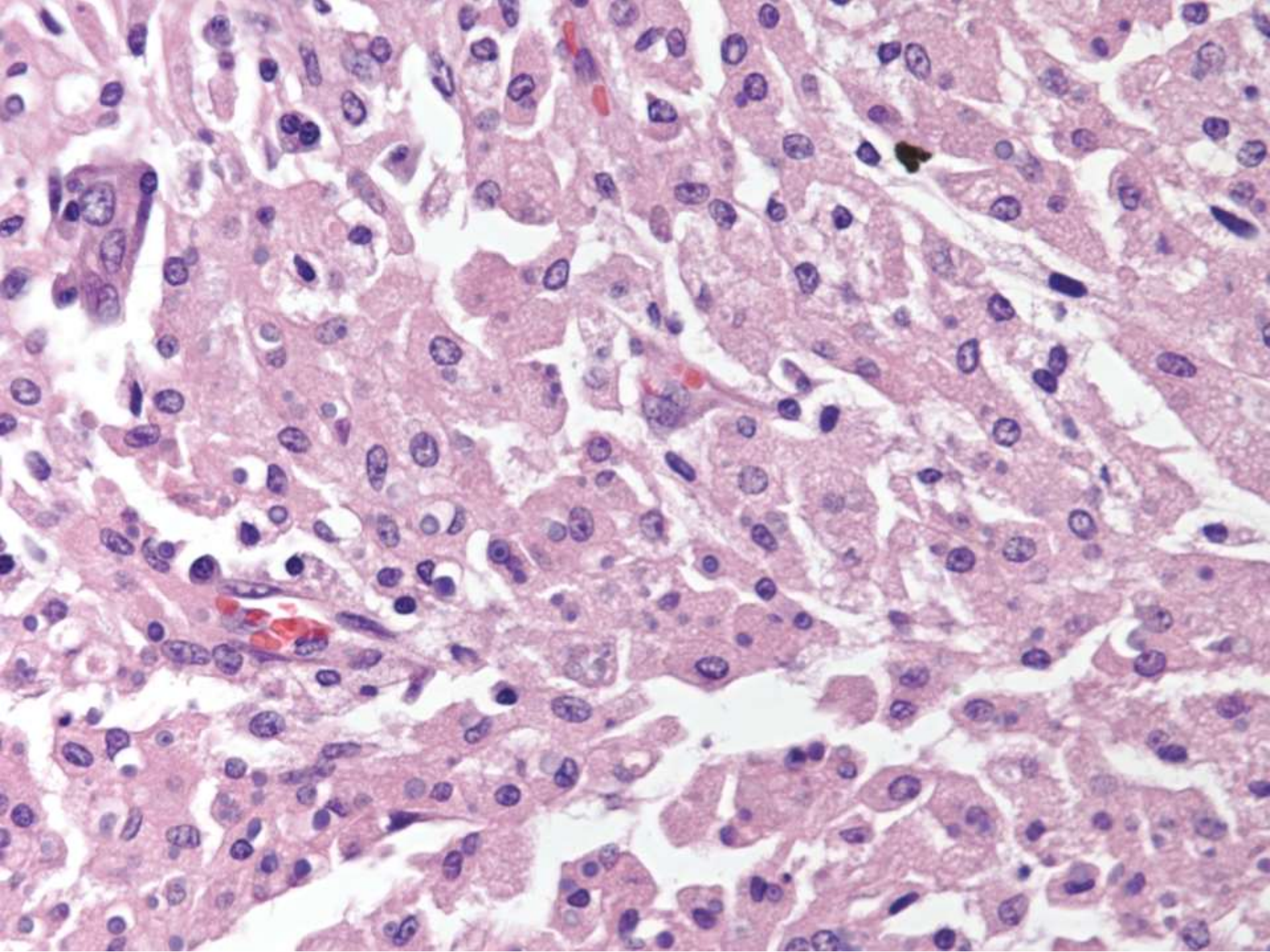
Jing Zhang/David Bingham; Stanford

60-year-old female s/p bilateral lung transplant now presents with mass encasing sigmoid colon and adherent to uterus, small bowel, and abdominal wall.

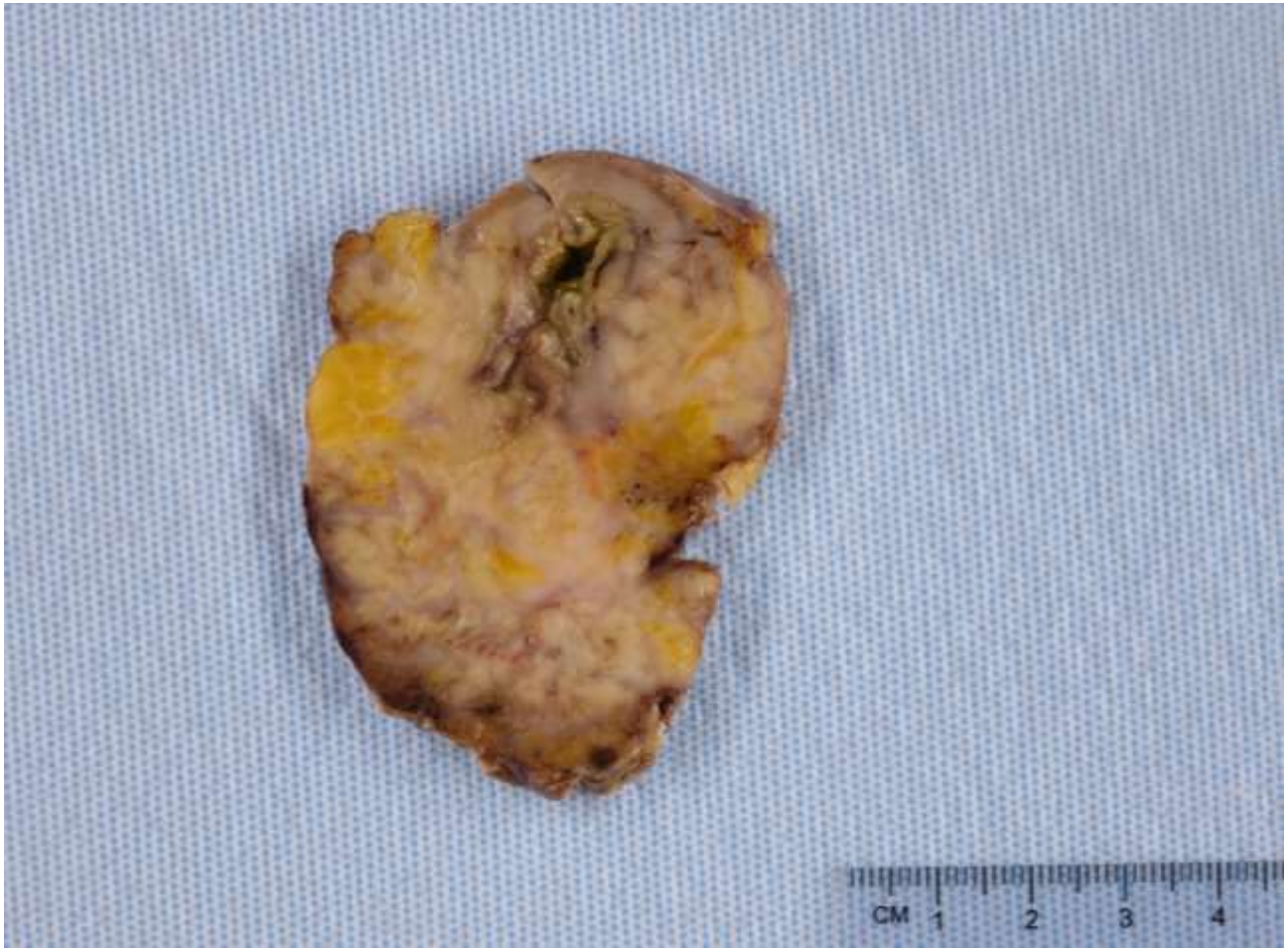






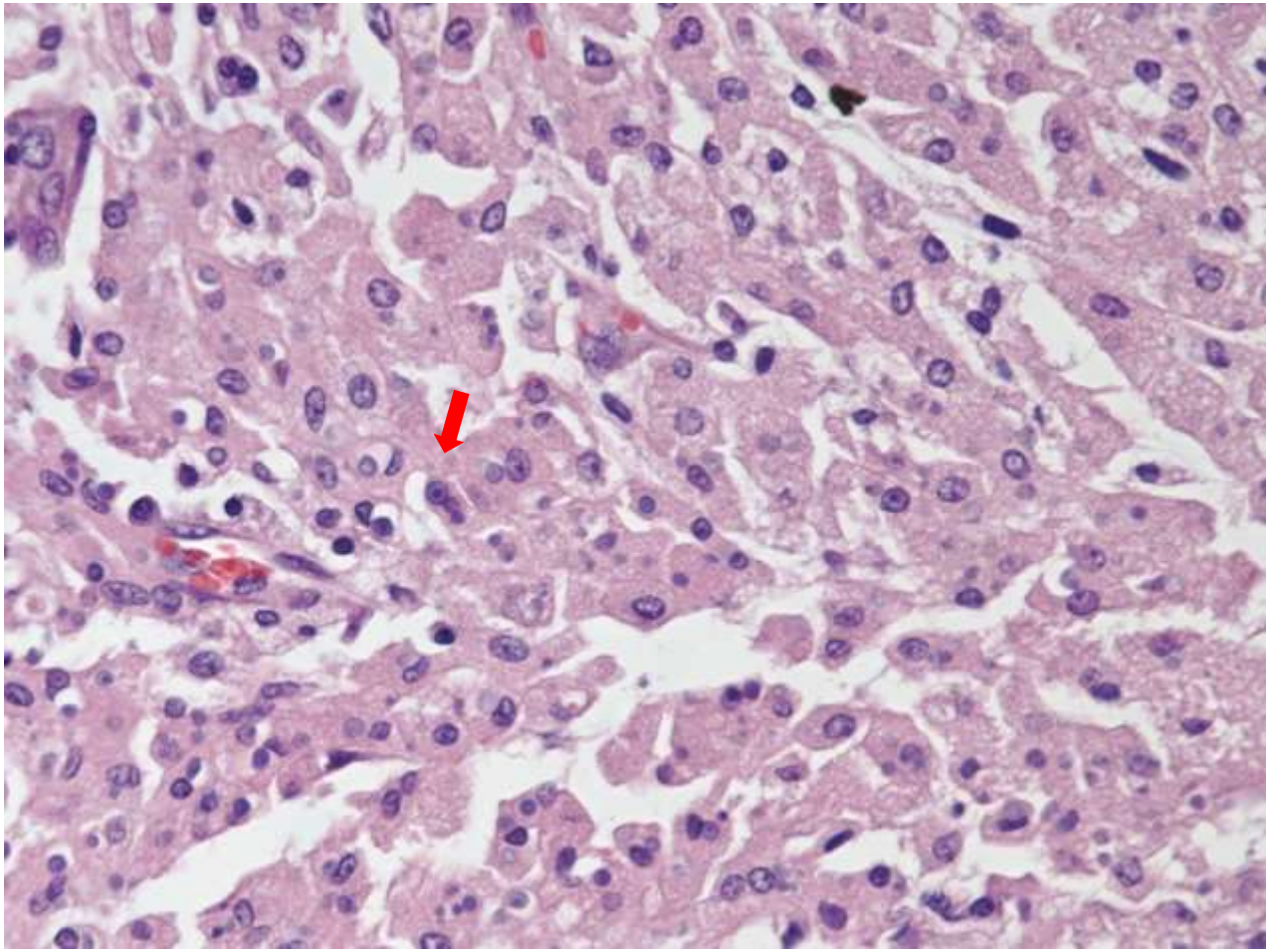


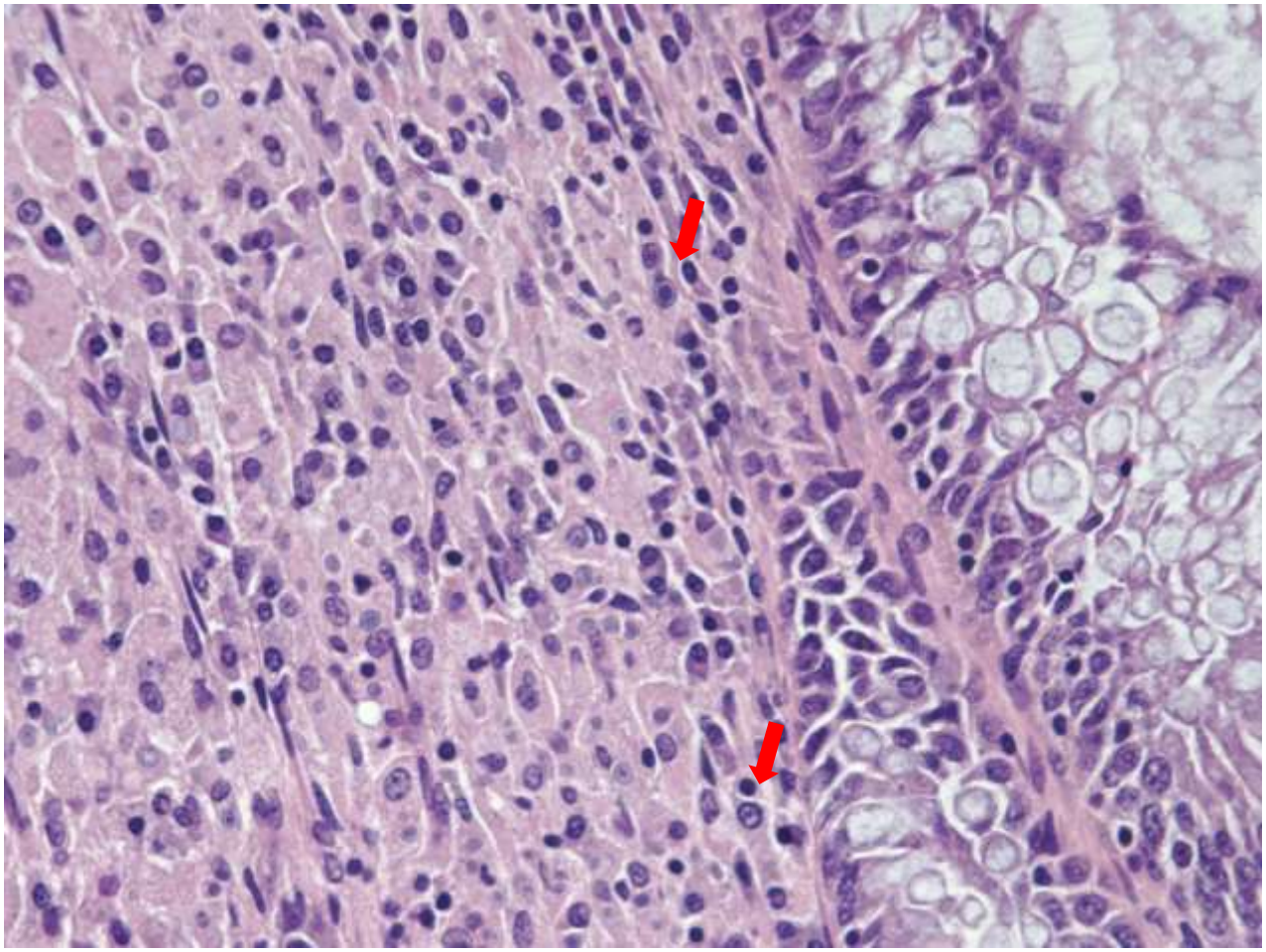
Colon Cross Section



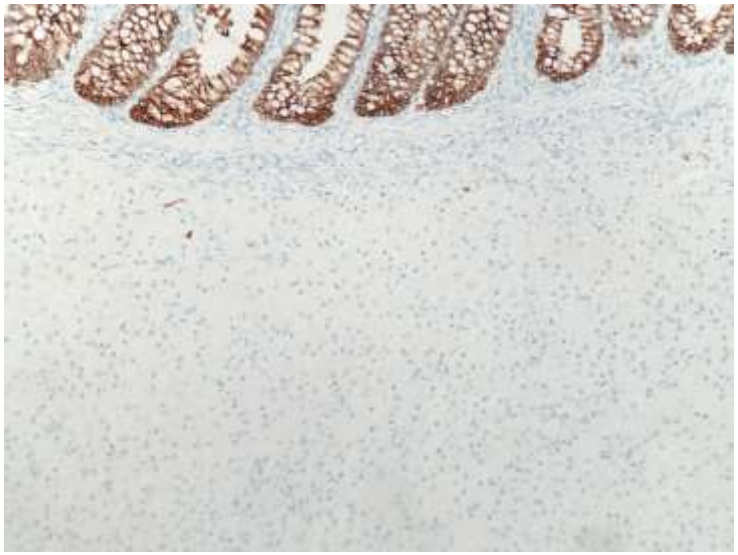
Differential Diagnosis

- Malakoplakia
- Whipple disease
- Poorly differentiated carcinoma
- Granular cell tumor

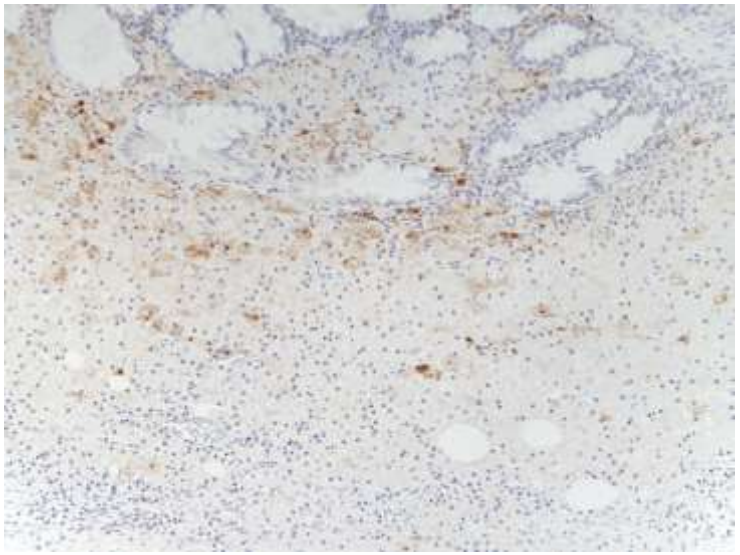




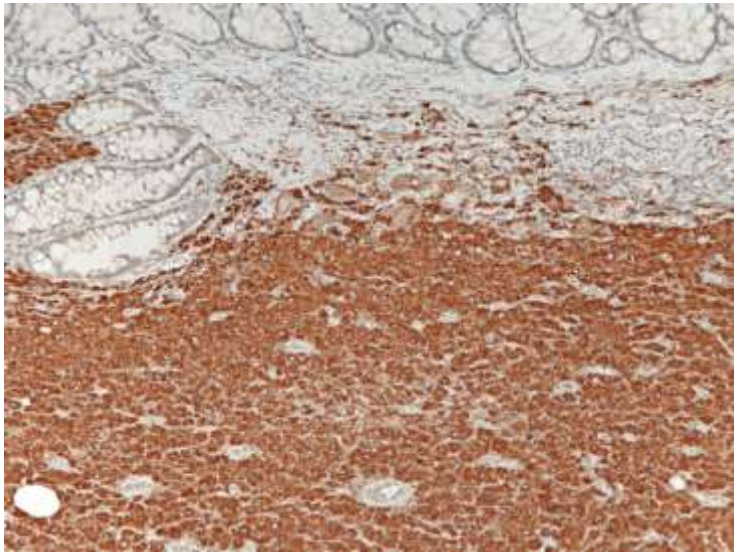
CK Mix



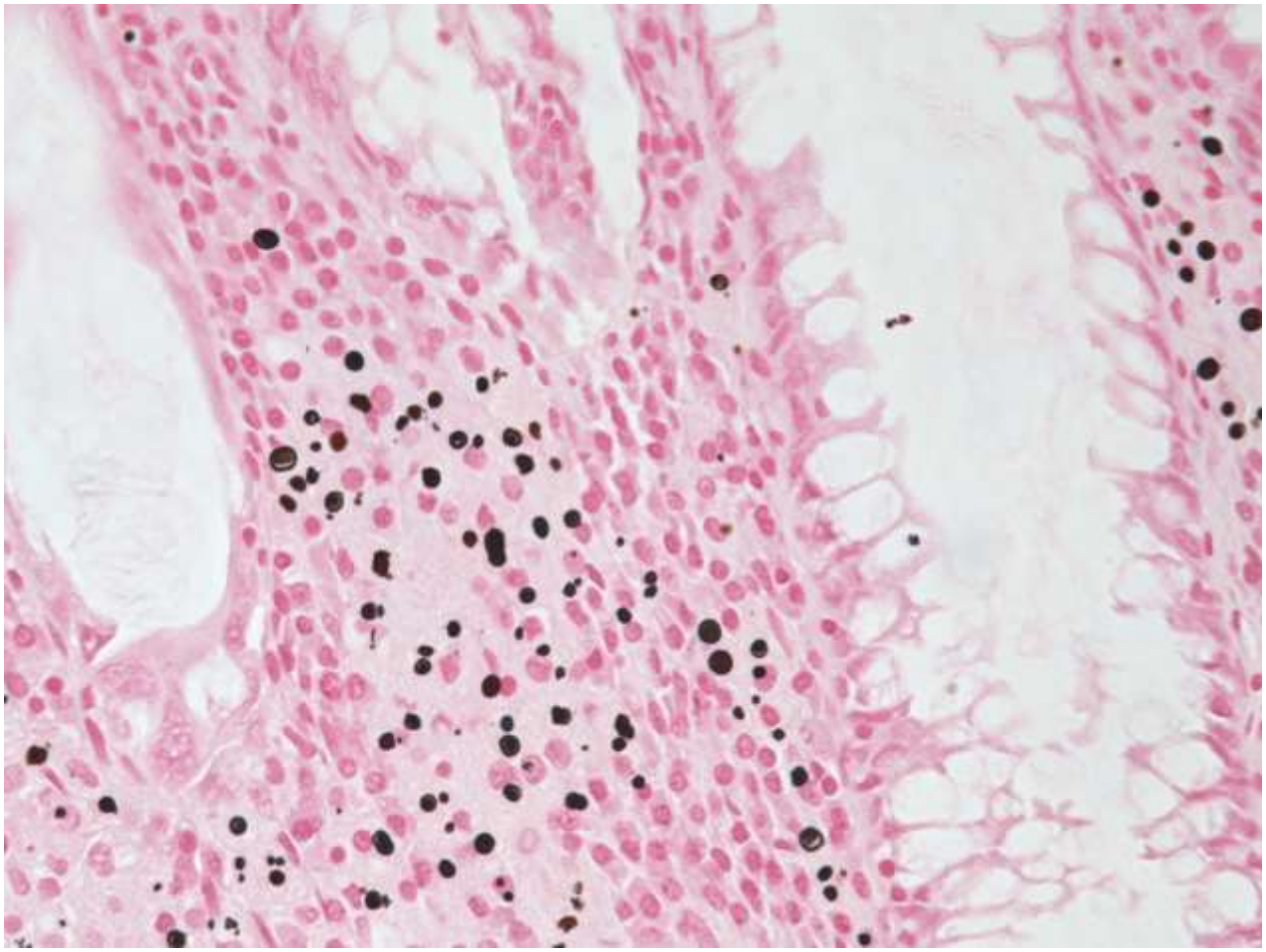
S100



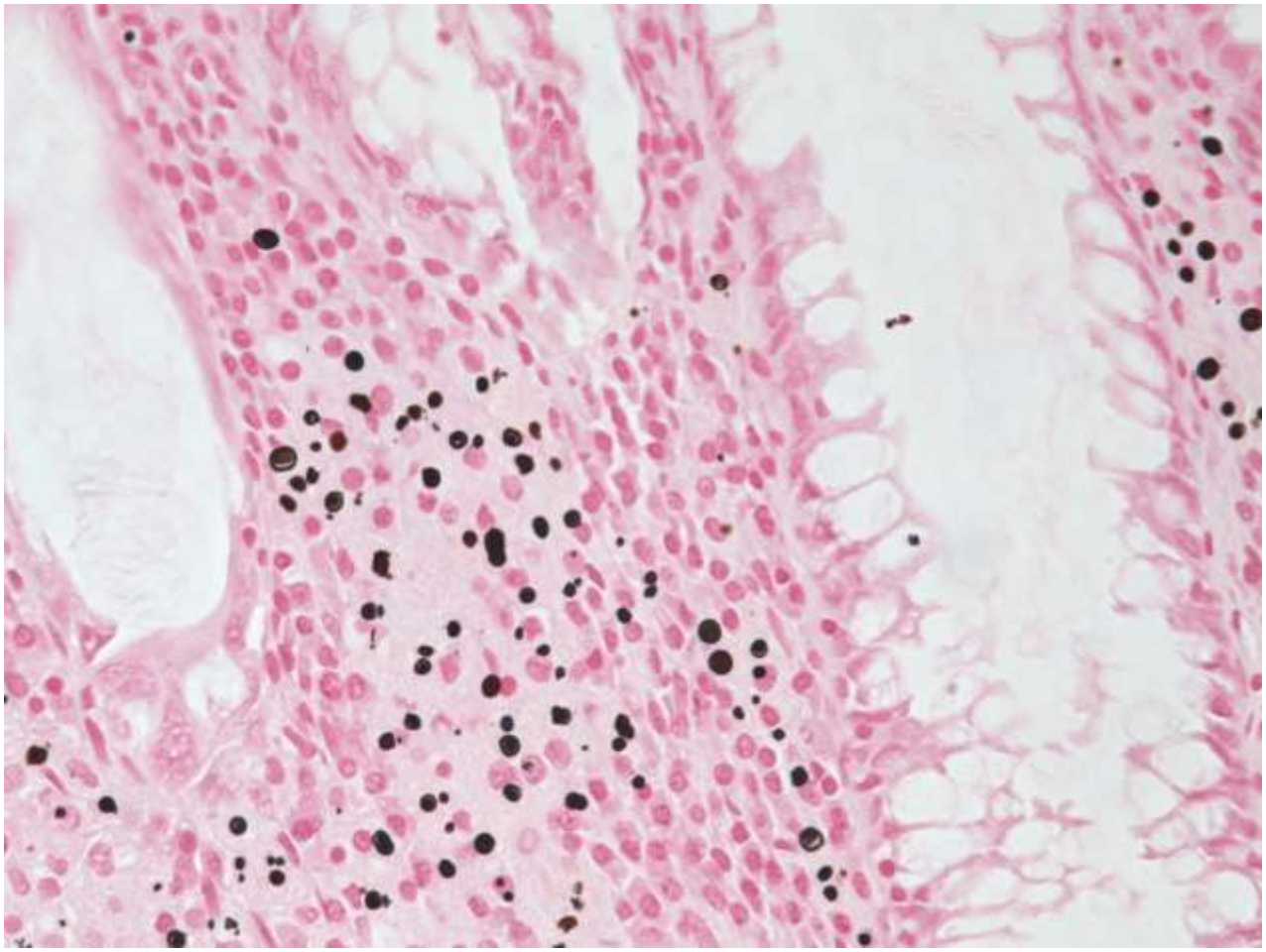
CD68



Von Kossa

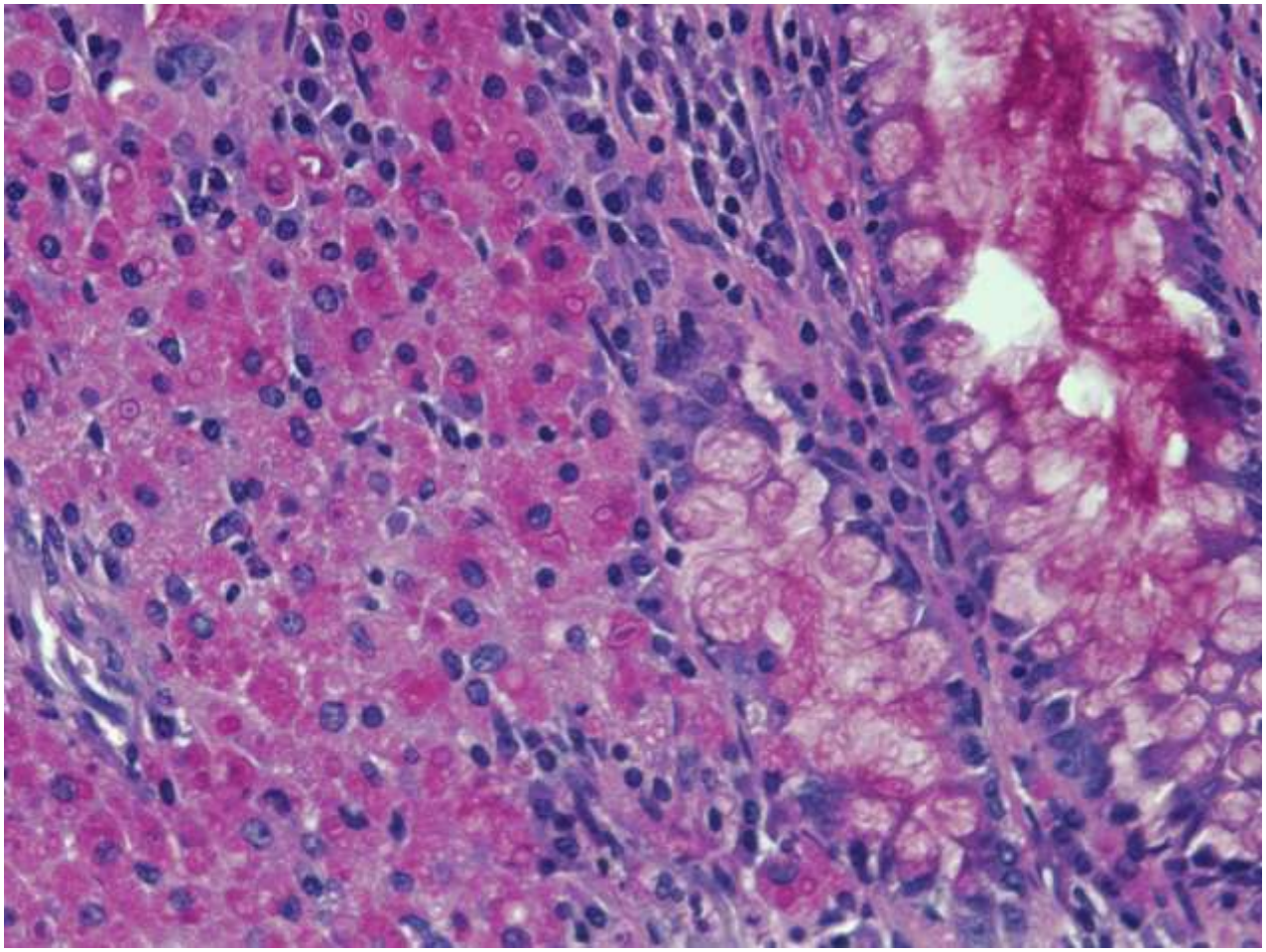


Von Kossa



Highlights **Michaelis-Guttman** bodies the concentrically layered intracytoplasmic inclusions thought to be remnants of phagosomes mineralized by iron and calcium

PAS



Final Diagnosis

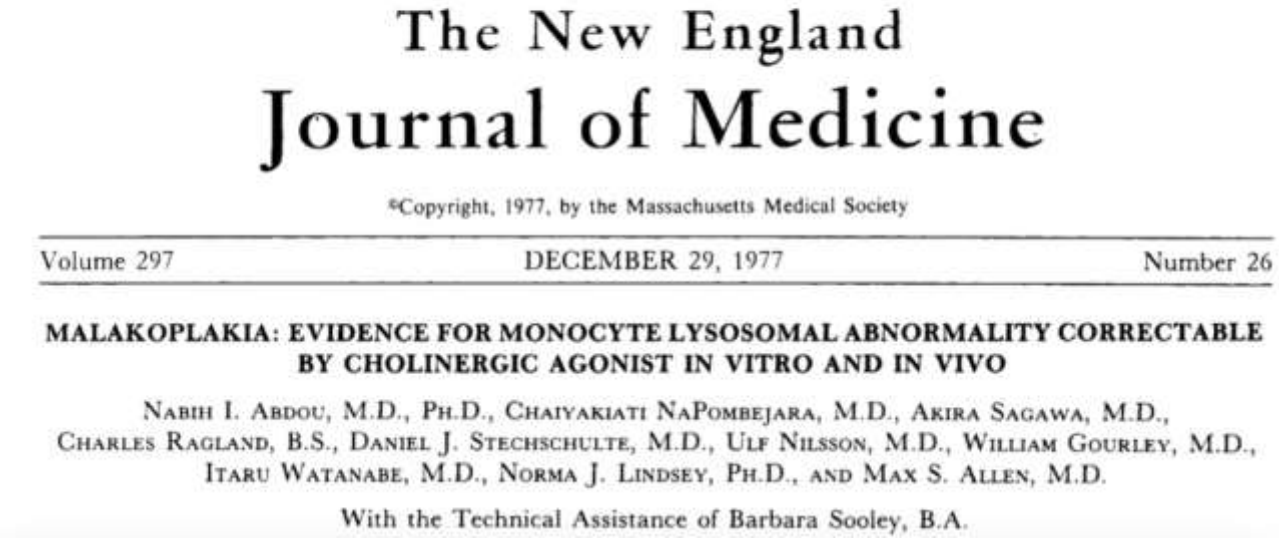
MALAKOPLAKIA

Malakoplakia

- Greek name “soft plaque”
- Discovered by Michaelis and Gutmann in early 1900s
- Can affect multiple organ systems: GU system most often, then GI, others
- Can present as incidental findings such as on endoscopy, or as a mass forming lesion, causing strictures or obstruction

Etiology?

Generally accepted to be a defect in macrophages phagocytosis leading to impaired bactericidal activities



The New England
Journal of Medicine

Volume 297 DECEMBER 29, 1977 Number 26

MALAKOPLAKIA: EVIDENCE FOR MONOCYTE LYSOSOMAL ABNORMALITY CORRECTABLE BY CHOLINERGIC AGONIST IN VITRO AND IN VIVO

NABIH I. ABDOU, M.D., PH.D., CHAIYAKIATI NAPOMBEJARA, M.D., AKIRA SAGAWA, M.D., CHARLES RAGLAND, B.S., DANIEL J. STECHSCHULTE, M.D., ULF NILSSON, M.D., WILLIAM GOURLEY, M.D., ITARU WATANABE, M.D., NORMA J. LINDSEY, PH.D., AND MAX S. ALLEN, M.D.

With the Technical Assistance of Barbara Sooley, B.A.

Often occurs in association with an immunocompromised state

- 5/6 Stanford in house cases in the last 20 years have been transplant patients, including this patient

- And in the setting of chronic infection
  - Association with gram negative bacteria:
  - Escherichia coli
  - Klebsiella
  - Yersinia
  - Proteus

Treatments:

- Empiric therapy with antibiotics
- Supportive care
- Surgical intervention or treatment of other underlying condition

Citations

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