Disclosures
December 4, 2017

Dr. Jeffrey Simko has disclosed that he has financial relationships with the following commercial interests: 3D biopsy (stock ownership), 3scan (stock ownership), and GenomeDX (consultant). South Bay Pathology Society has determined that these relationships are not relevant to the clinical case being presented.

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

Presenters:

Charles Lombard, MD
Greg Rumore, MD
Bernadette DeRussy, MD
Megan Troxell, MD, PhD
Jonathan Lavezo, MD
Hannes Vogel, MD
Eliah Shamir, MD
Jessica Davis, MD
Sebastian Fernandez-Pol, MD
Dita Gratzinger, MD, PhD
Brent Tan, MD, PhD
Serena Tan, MD
Eduardo Zambrano, MD
Ankur Sangoi, MD

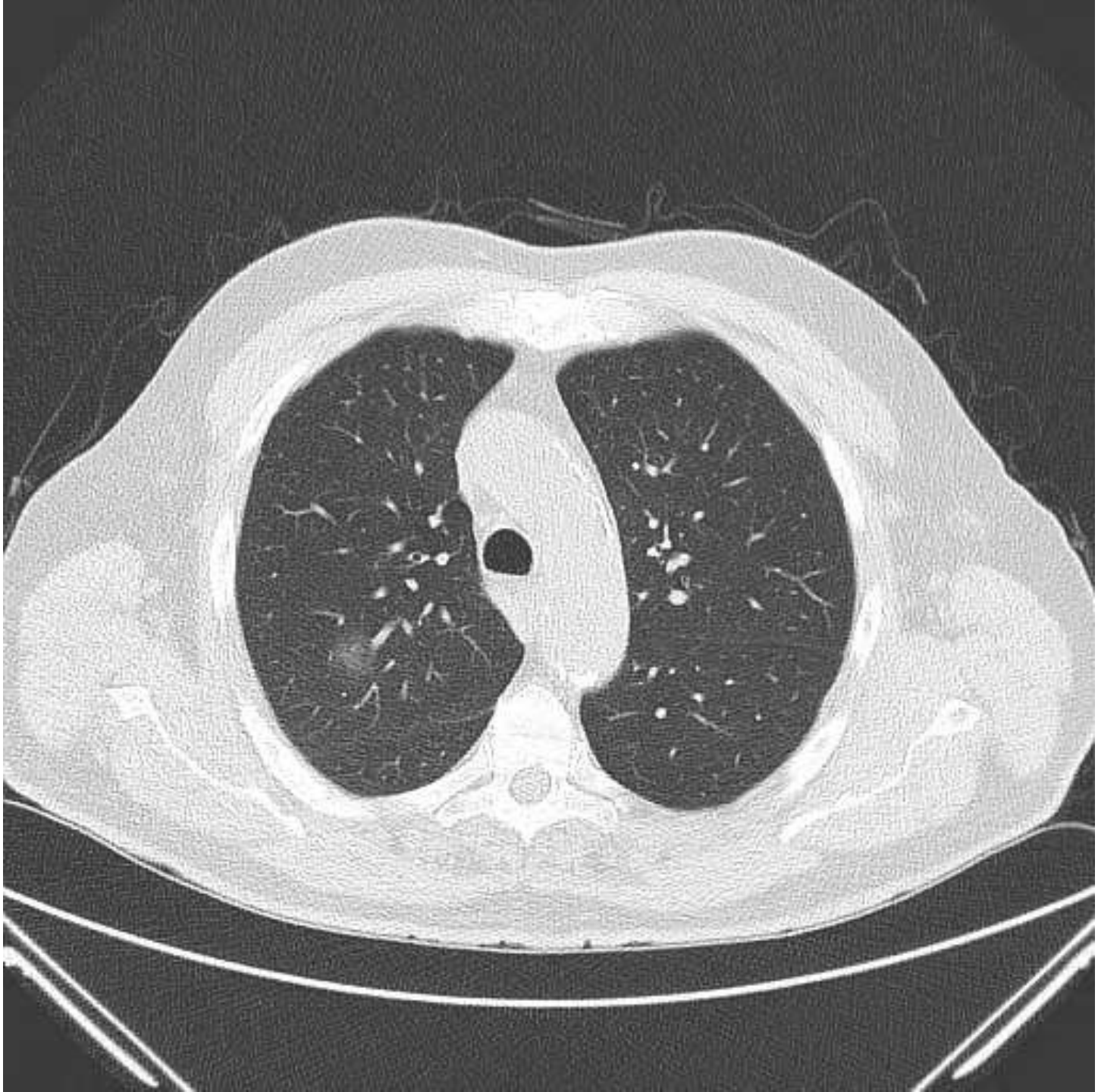
Activity Planners/Moderator:

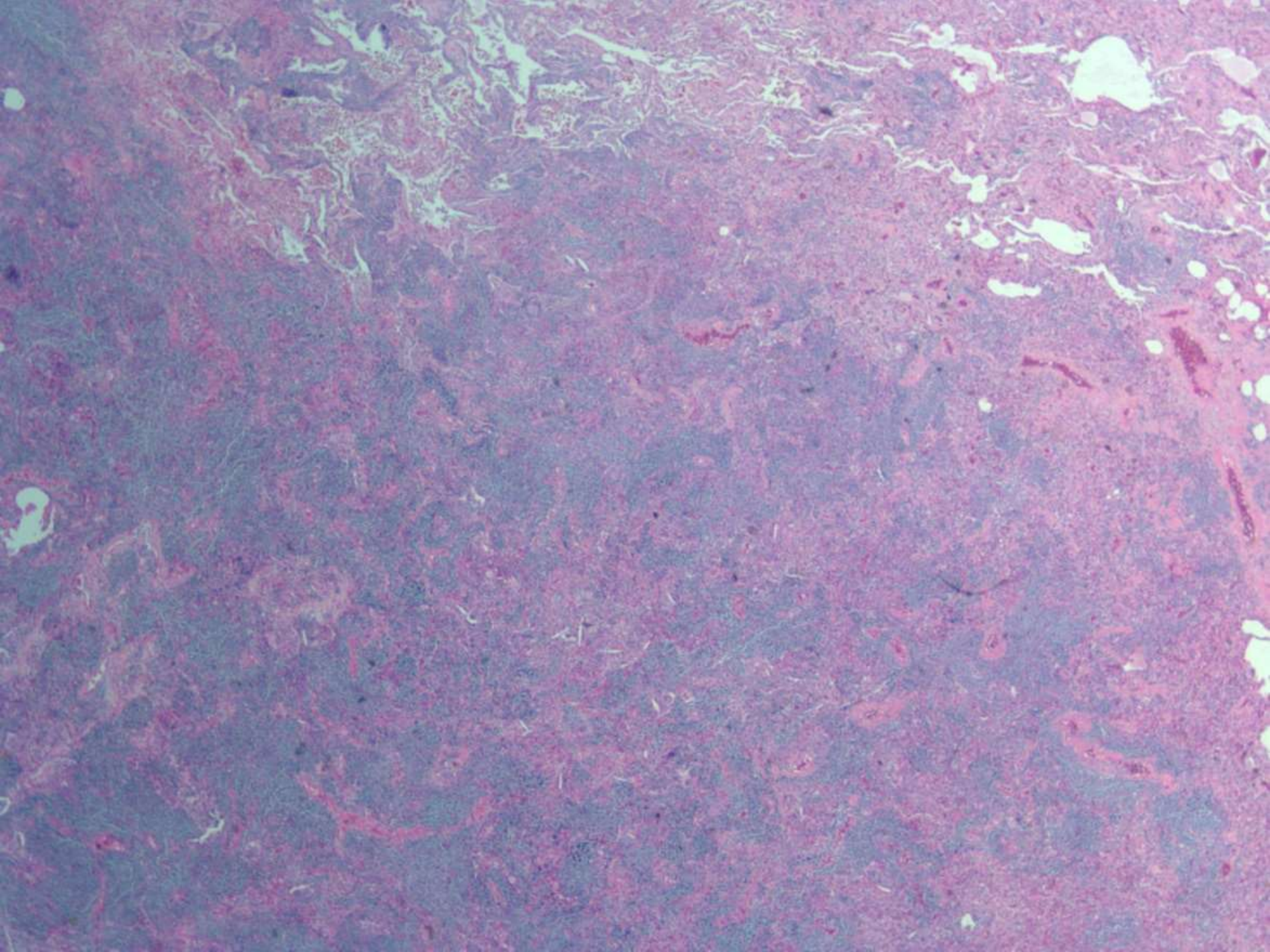
Kristin Jensen, MD
Ankur Sangoi, MD

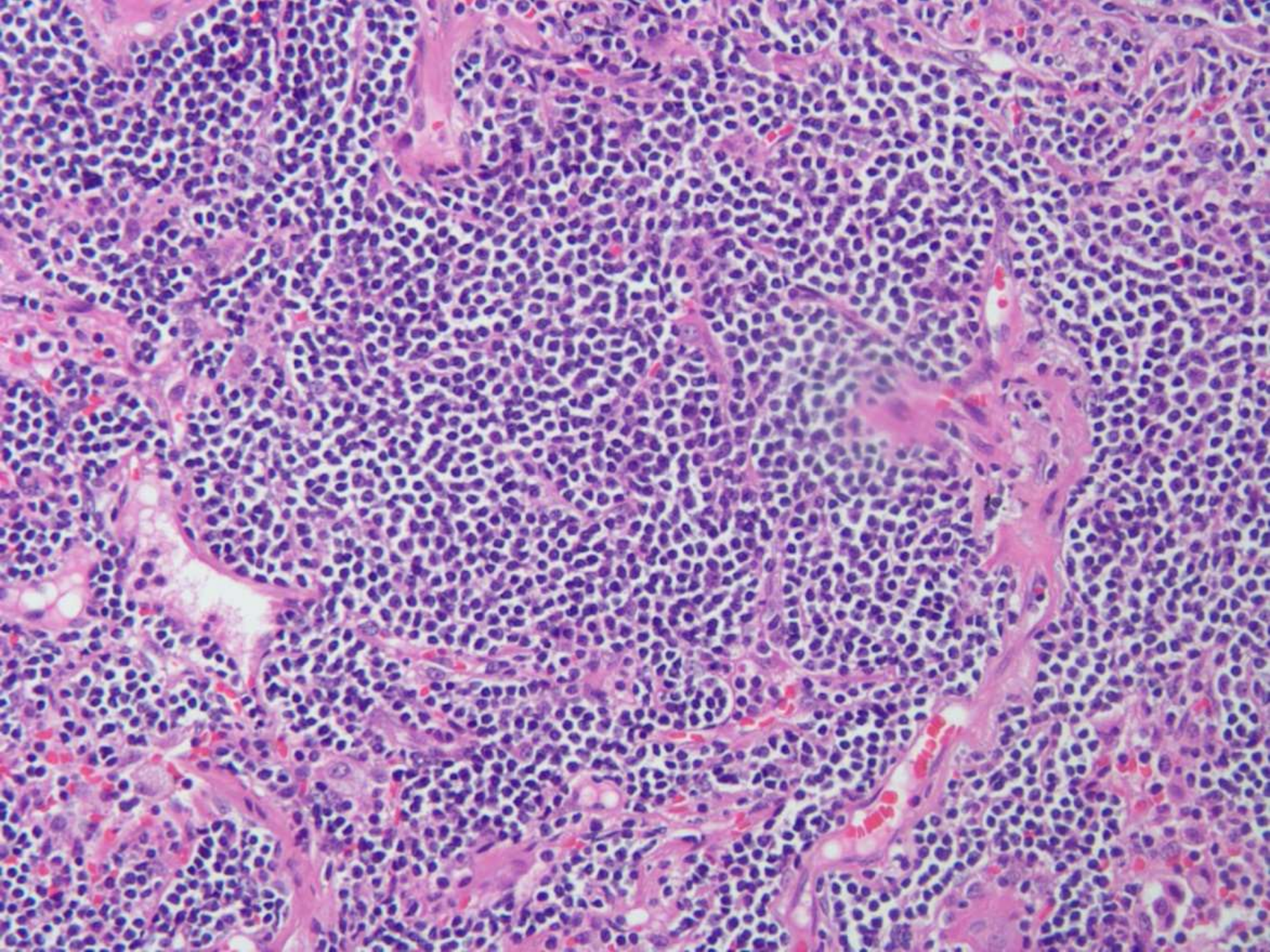
SB 6193 – case from Sept 2017 (scanned slide available)

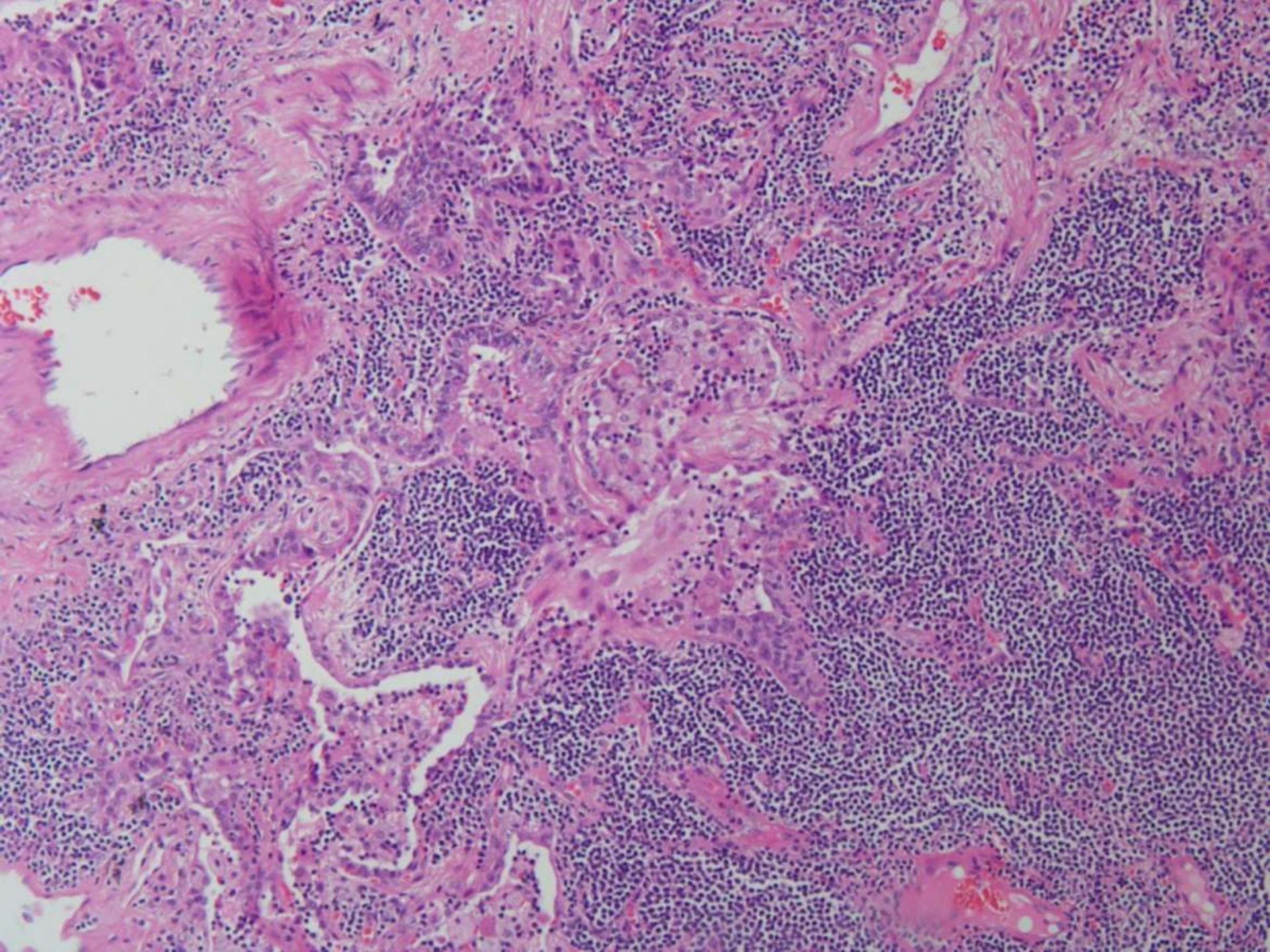
Charles Lombard; El Camino Hospital

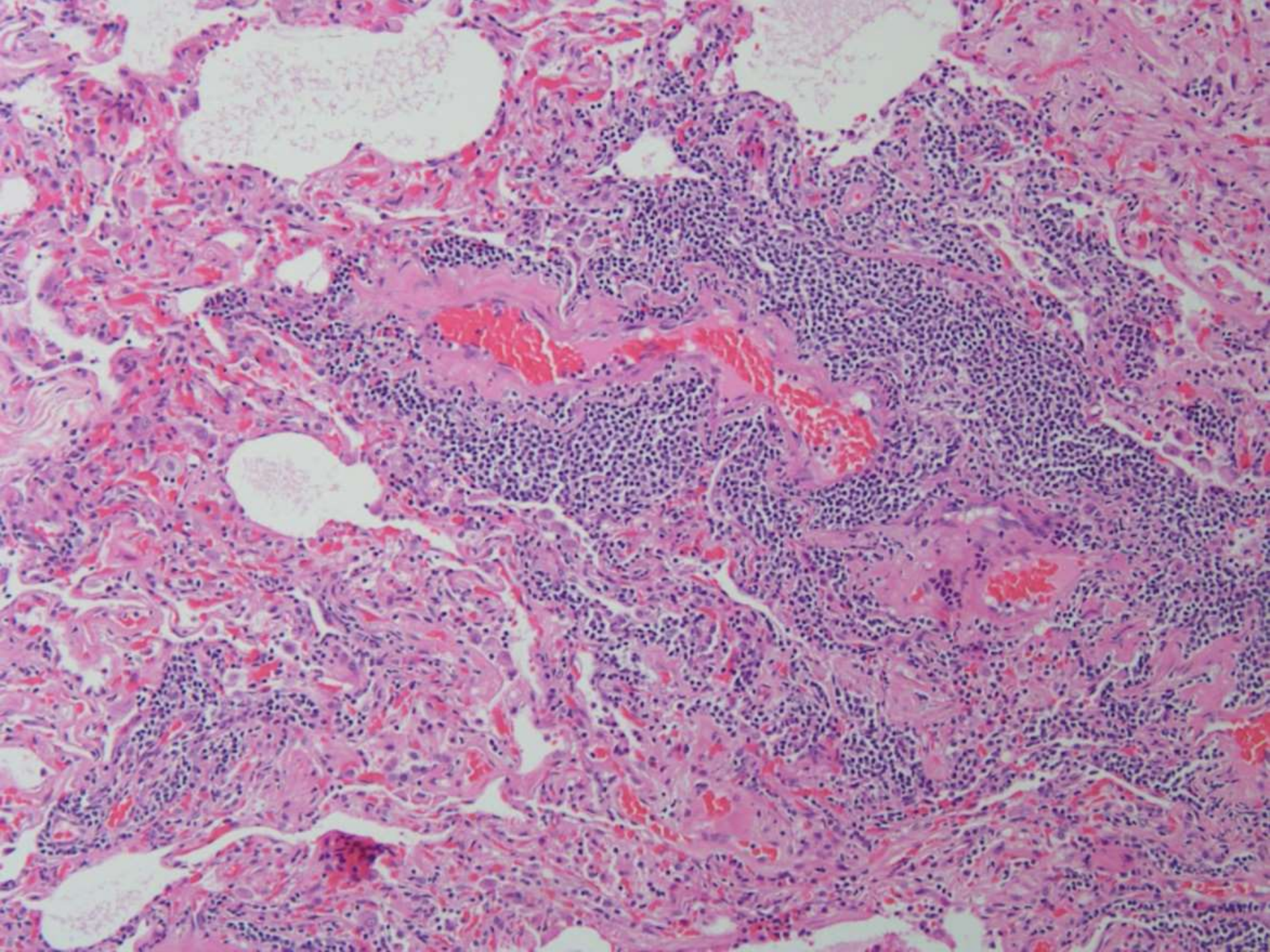
82-year-old man with pulmonary nodule; also has hilar/mediastinal lymphadenopathy.

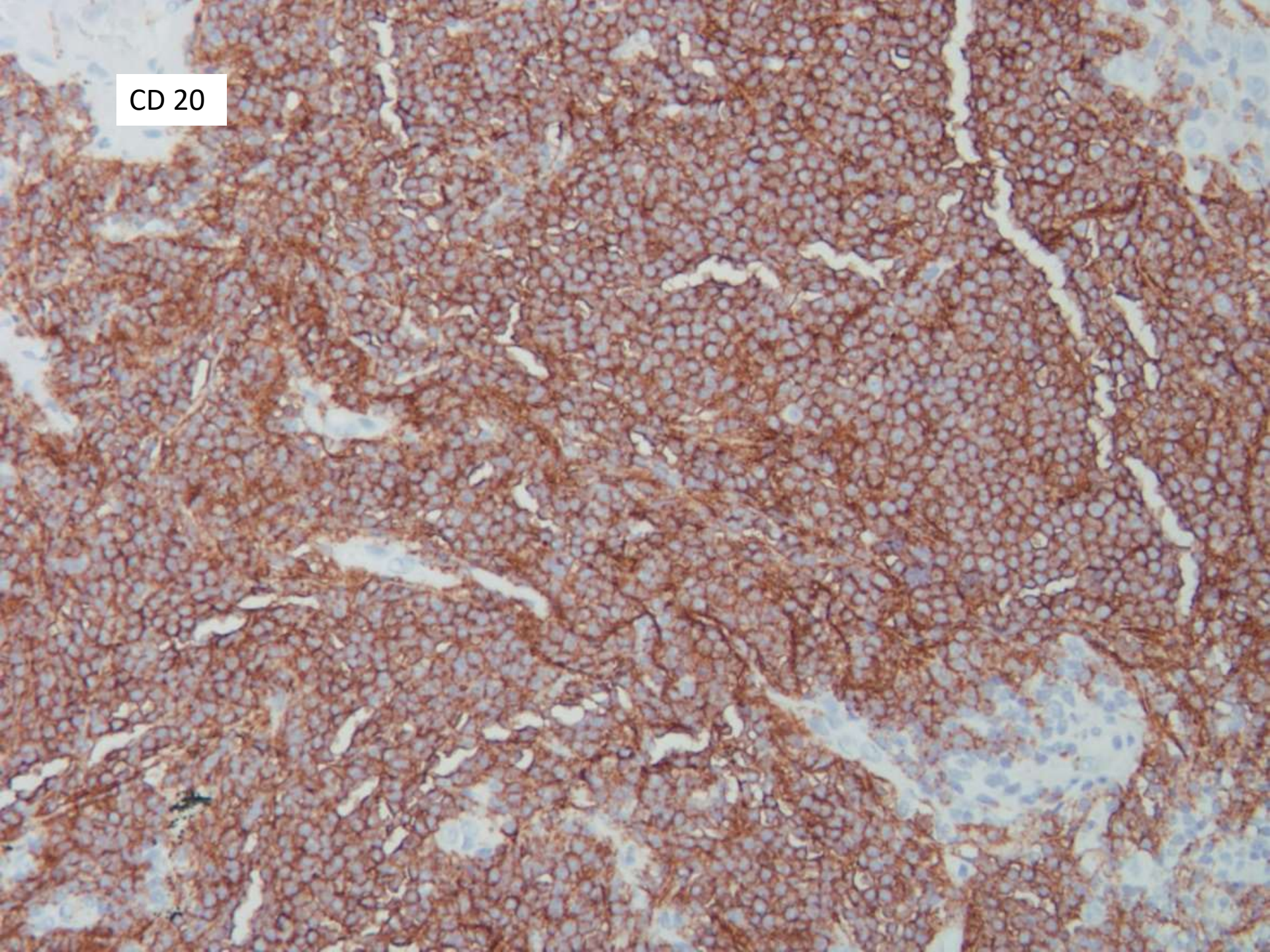


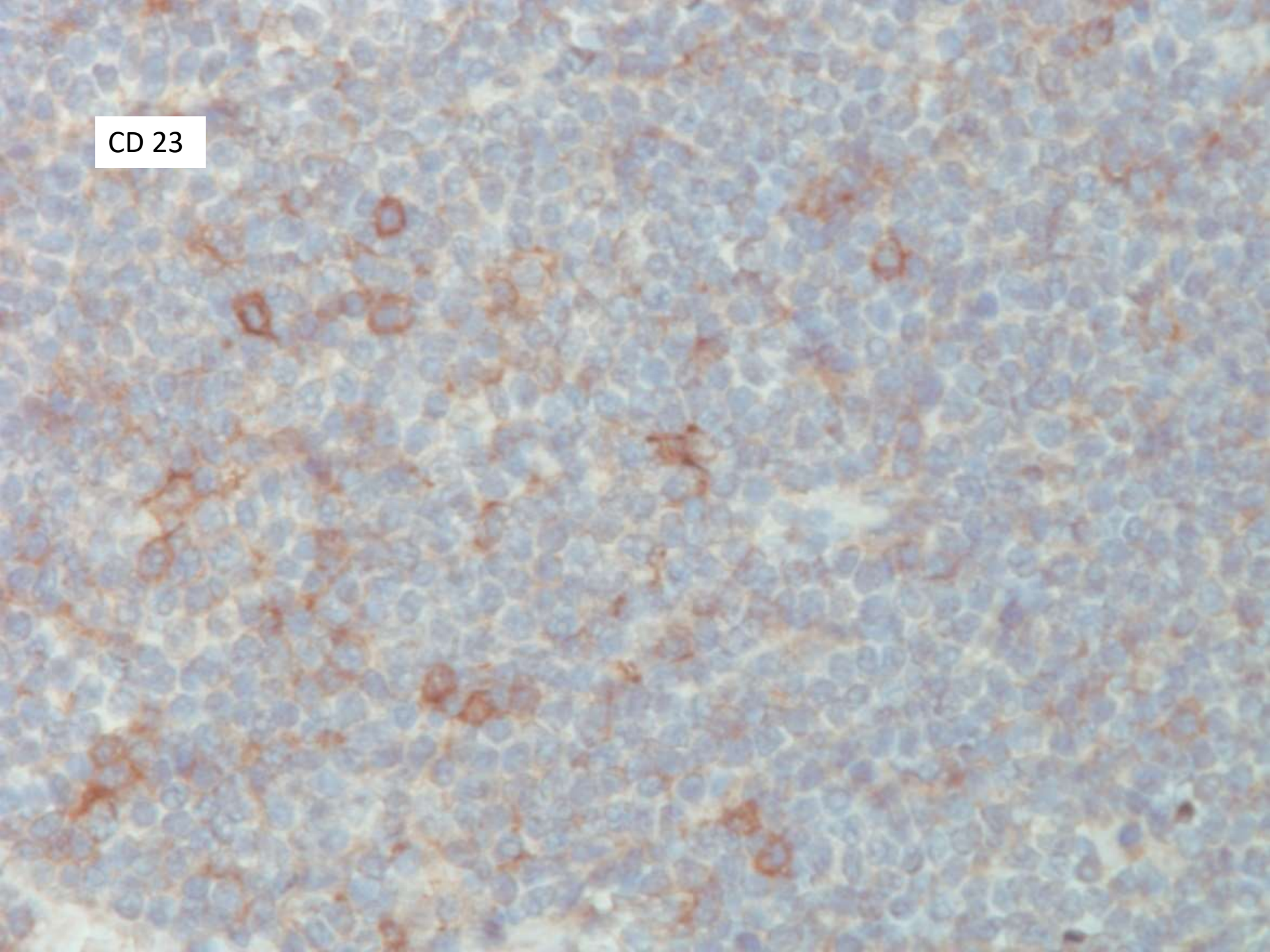


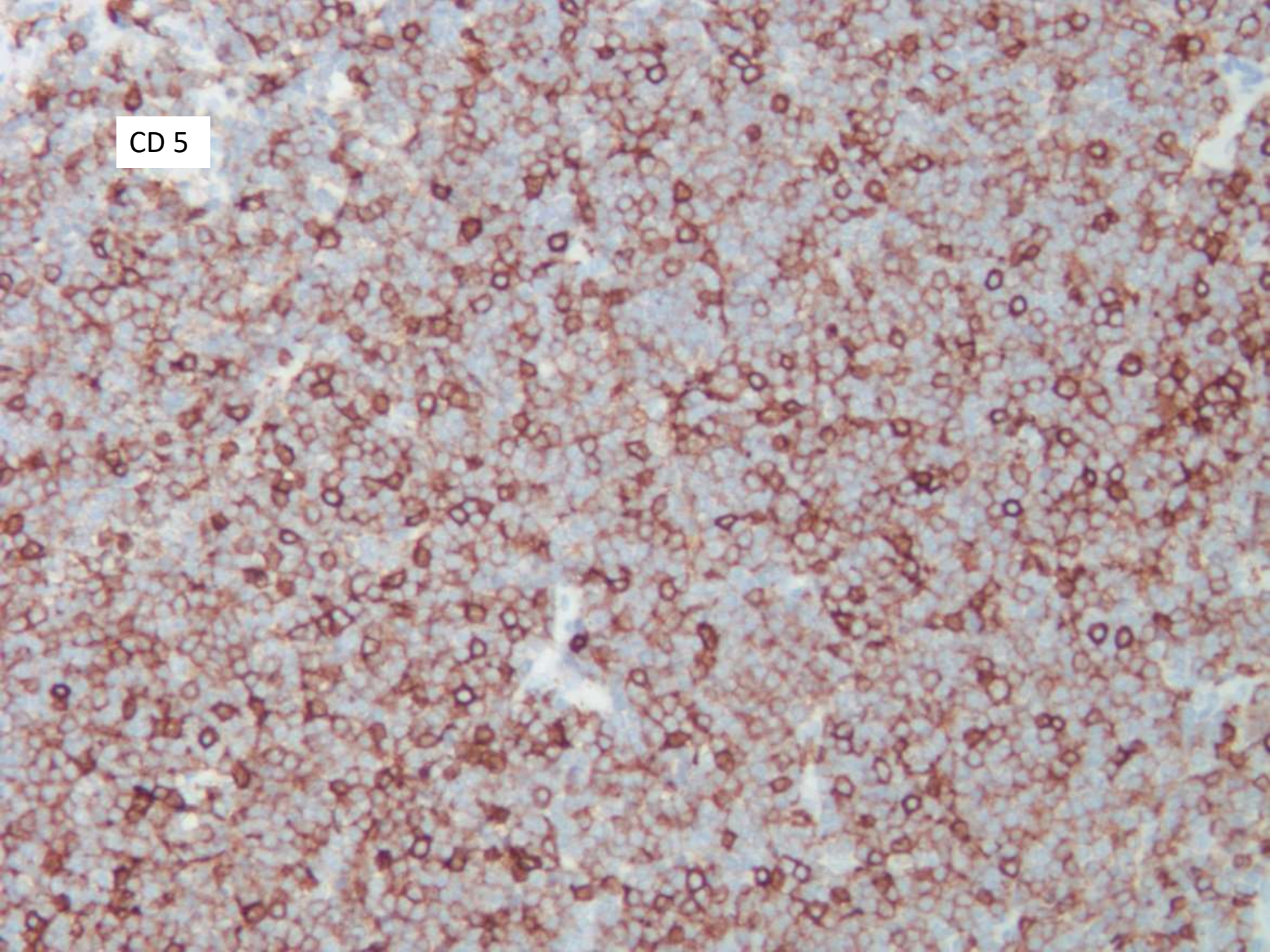


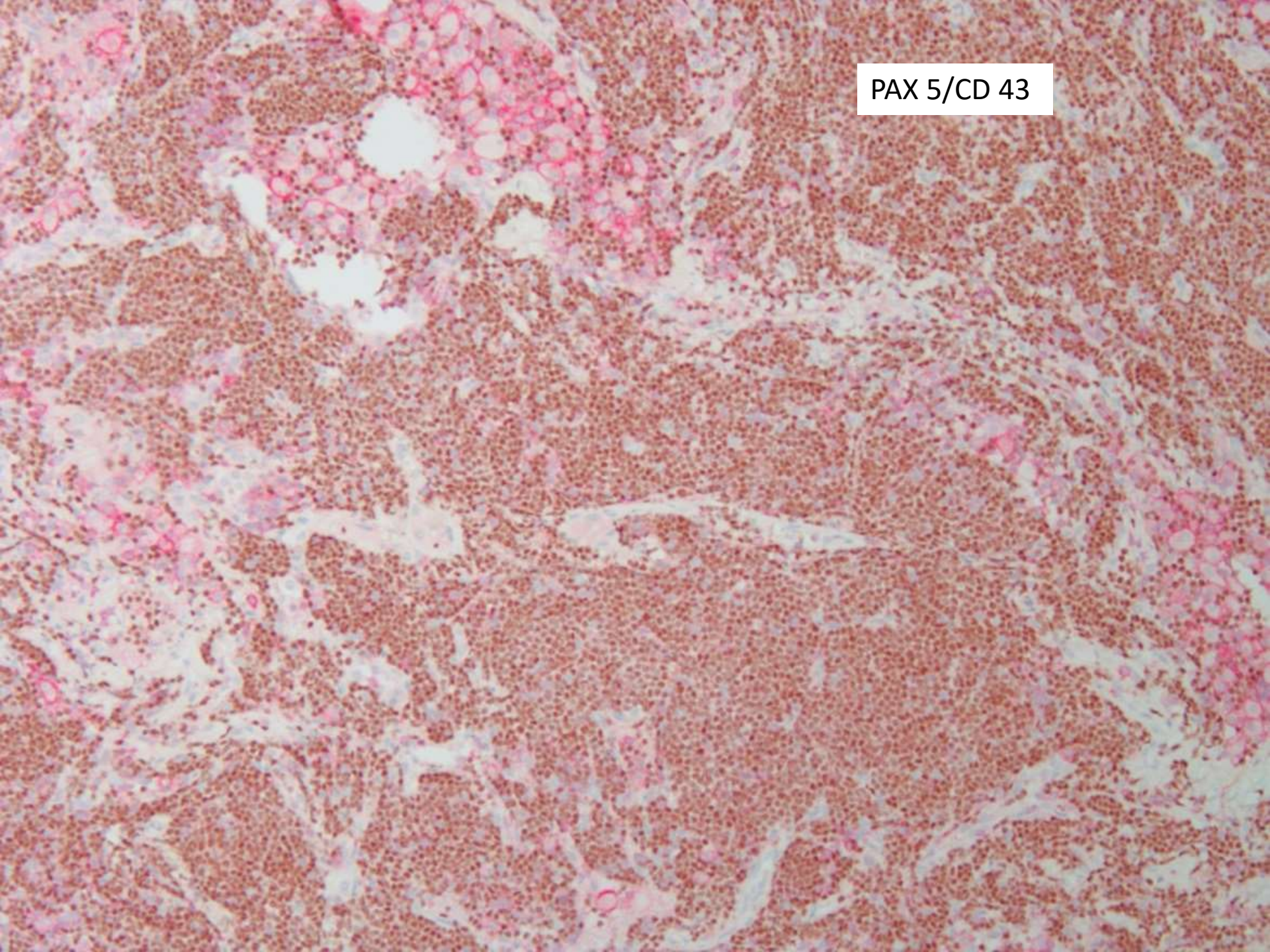





CD 20


CD 23


CD 5


PAX 5/CD 43

Chronic lymphocytic leukemia

Patient with known CLL

- WBC 28,500
  - 78% lymphocytes
- Hg/Hct: 9.6/28.9
- Platelets: 135,000
- Increasing nodule identified on CT scan
- Asymptomatic

Pulmonary parenchymal involvement in CLL

- Pulmonary infiltrates identified in 25-40% of patients
- < 20% of these are due to leukemic infiltrates
- Most commonly infiltrates are related to infectious etiologies
- Majority of patients are known to have an advanced stage (Rai 3-4)
- In one study involvement of the lung was independent of the absolute lymphocyte count although there was a statistical trend towards a higher count in cases with lung involvement

Pulmonary parenchymal involvement in chronic lymphocytic leukemia

- Prior extranodal involvement was strongly associated with leukemic pulmonary infiltrates
  - Skin
  - Sinuses
  - Stomach
  - Prostate
  - Other

Radiographic appearance

- Centrilobular micronodules with “tree in bud” appearance
- Ground glass opacities with a centrilobular distribution
- Homogeneous areas of consolidation
- Bronchiectasis may ensue

Pulmonary parenchymal involvement in chronic lymphocytic leukemia

- Infectious etiologies must be rigorously excluded
- Leukemic pulmonary involvement can't be established by transbronchial biopsy
- When identified, particularly with an inflammatory infiltrate the differential diagnosis includes:
  - A pathologic infiltrate
  - A non-specific host response ("passenger effect")
- One studies suggest that when identified on transbronchial biopsy that this represents true extranodal involvement rather than a bystander phenomenon.

References:

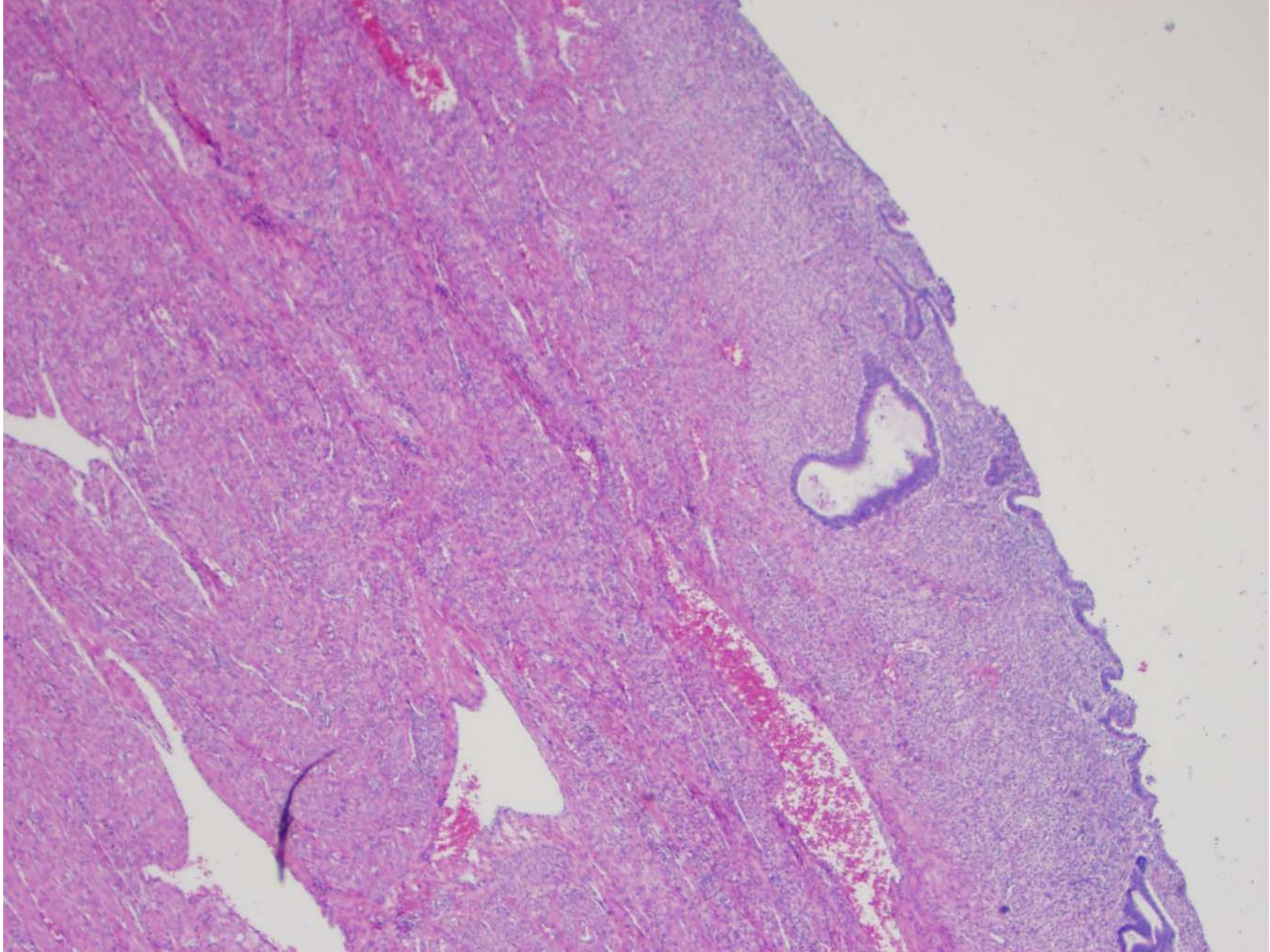
- Hill et al: “Pulmonary involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma is a specific pathologic finding independent of inflammatory infiltration”. Leukemia and Lymphoma 2012; 53 (4): 589-595.

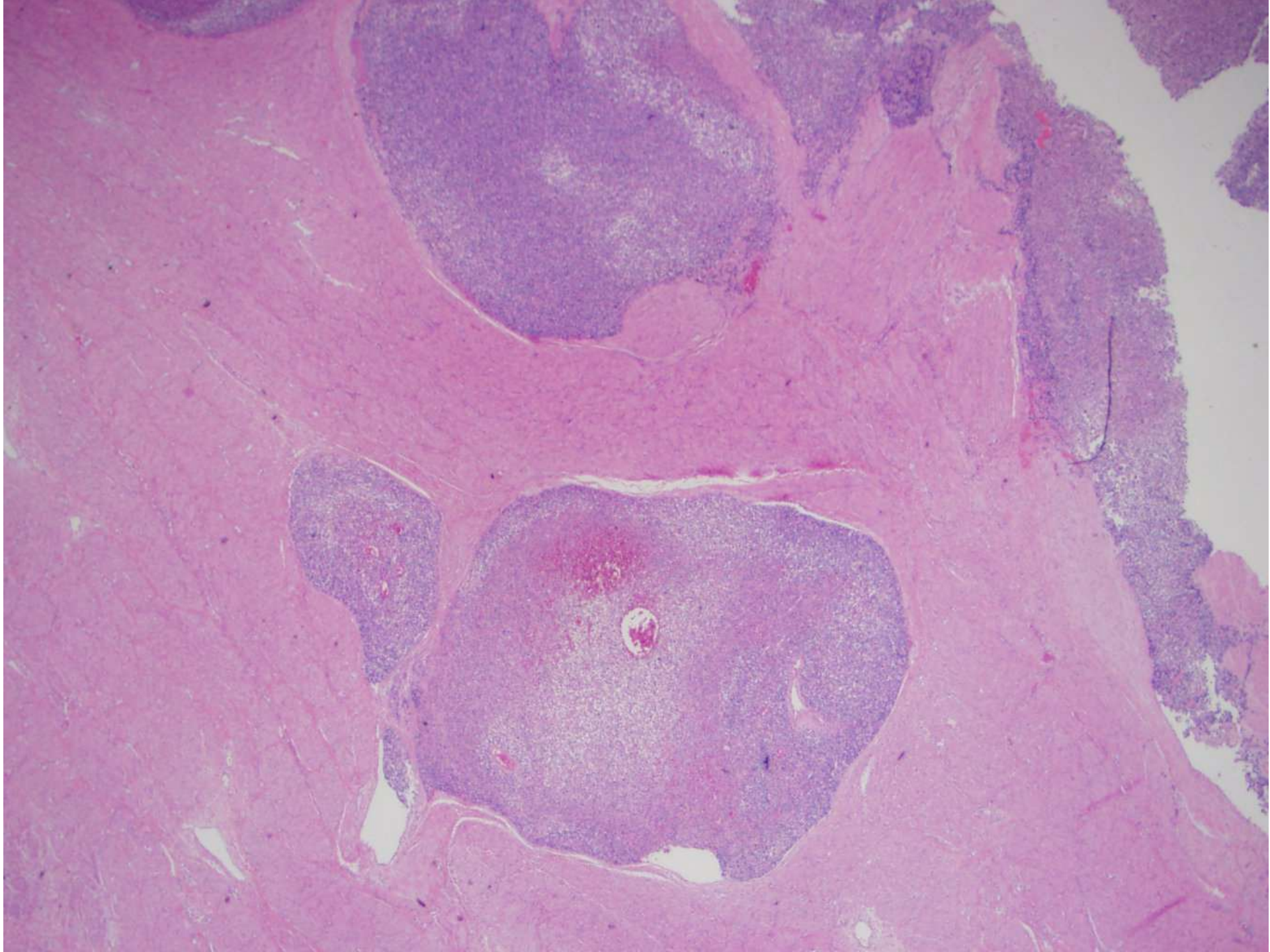
- Carmier et al: “Serious bronchopulmonary involvement due to chronic lymphocytic leukemia”. European Respiratory Reviews 2013; 22: 416-419.

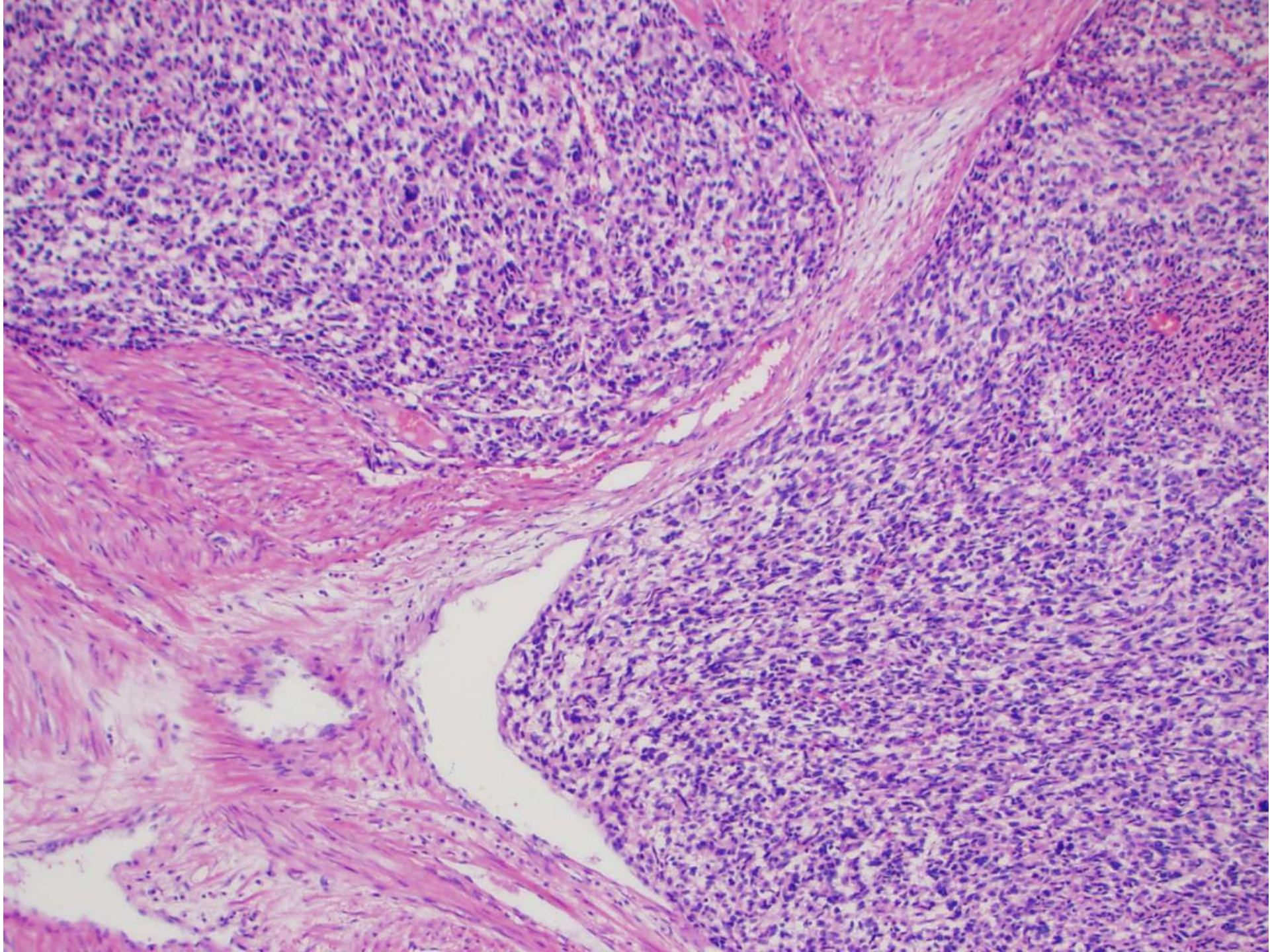
SB 6222

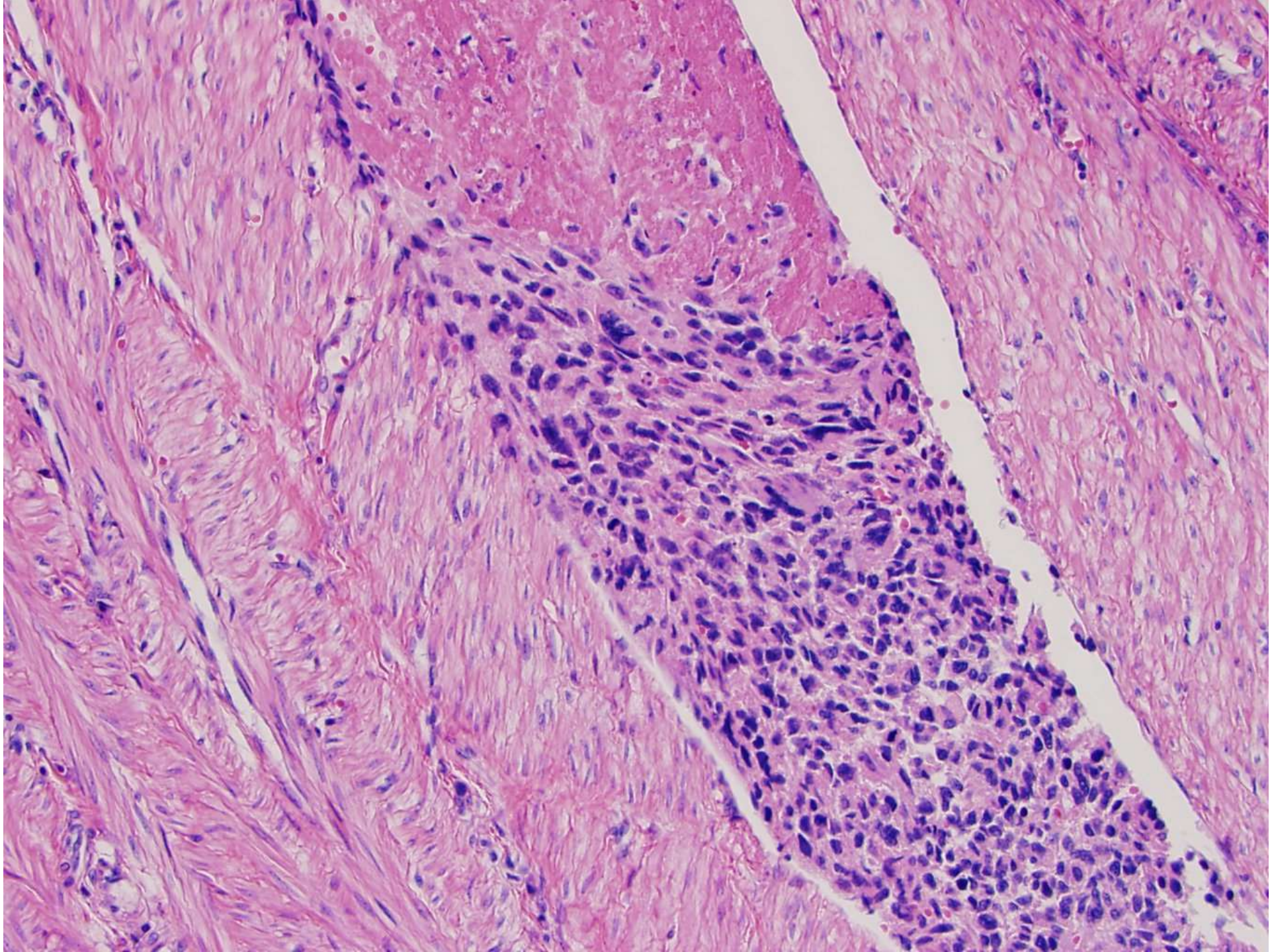
Greg Rumore; Kaiser Walnut Creek

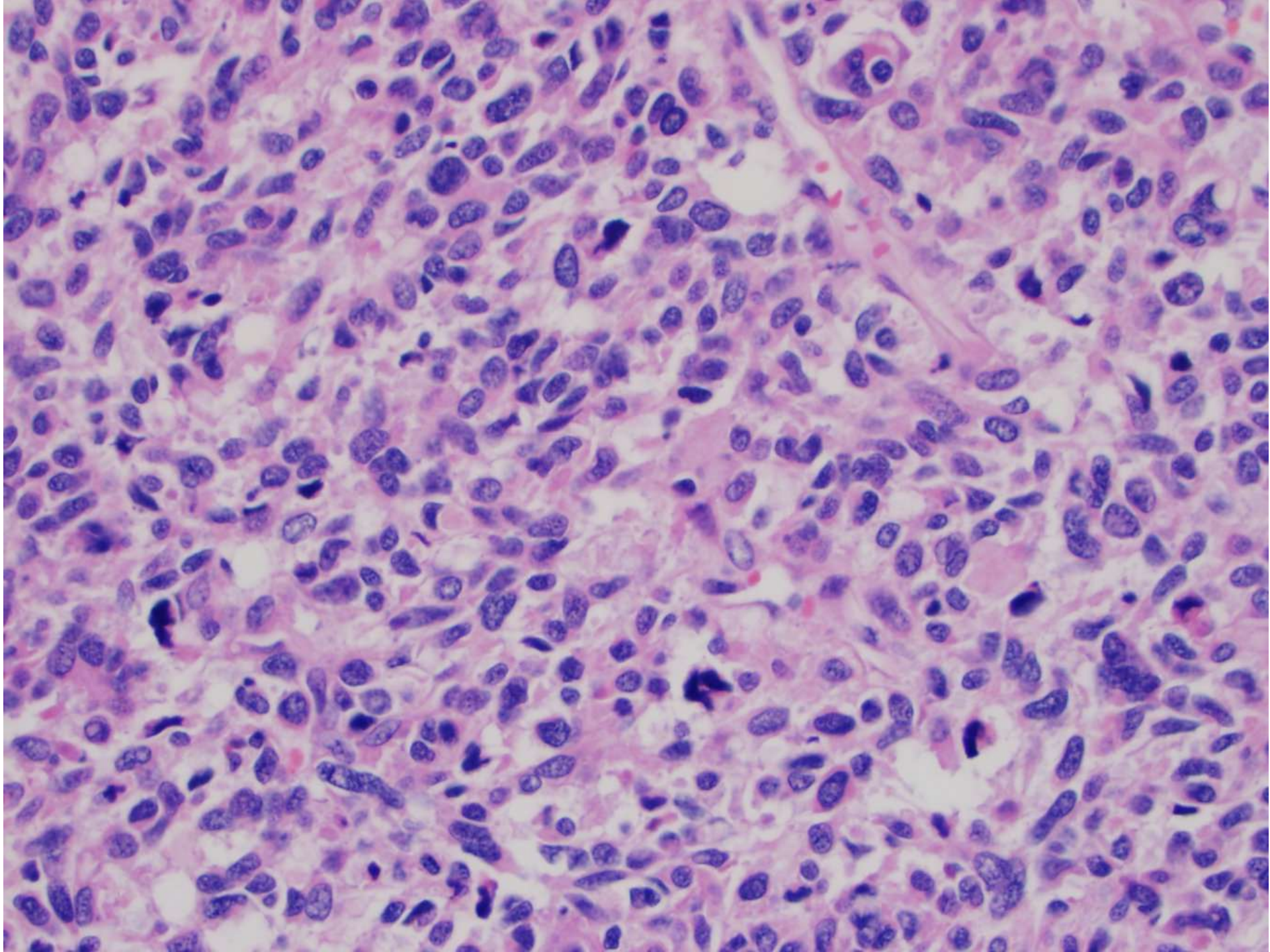
58-year-old woman with vaginal bleeding and uterine mass.

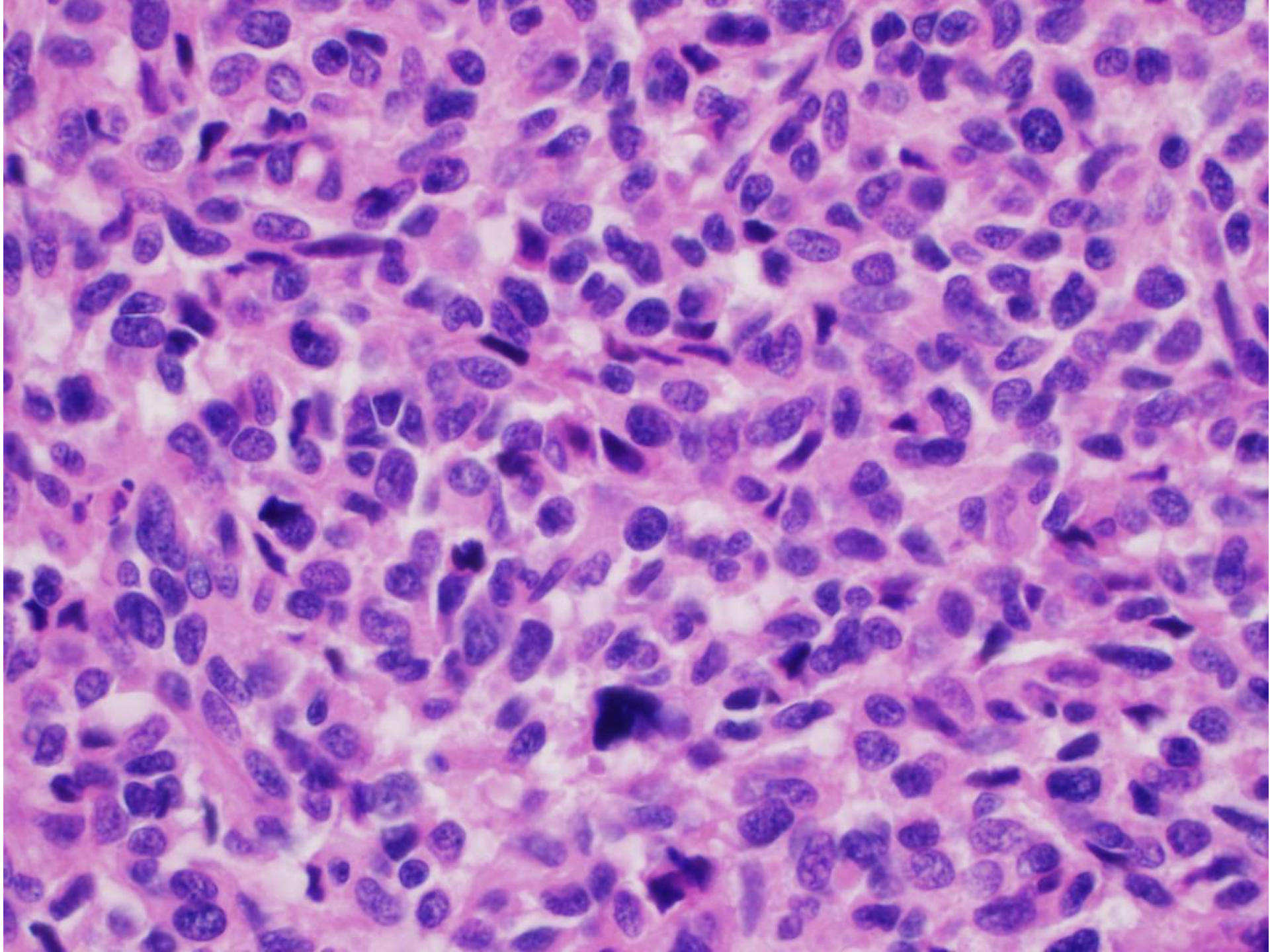


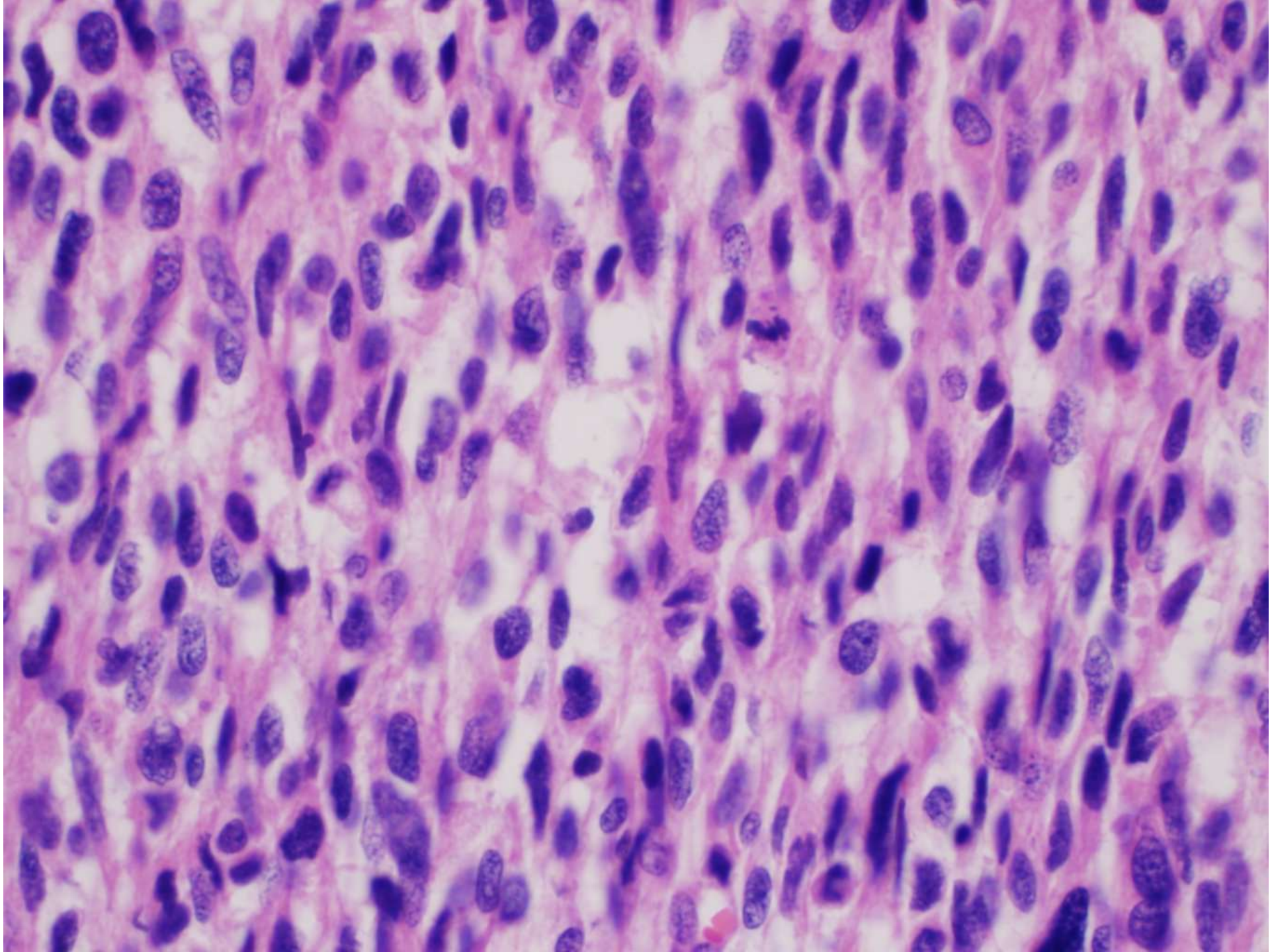


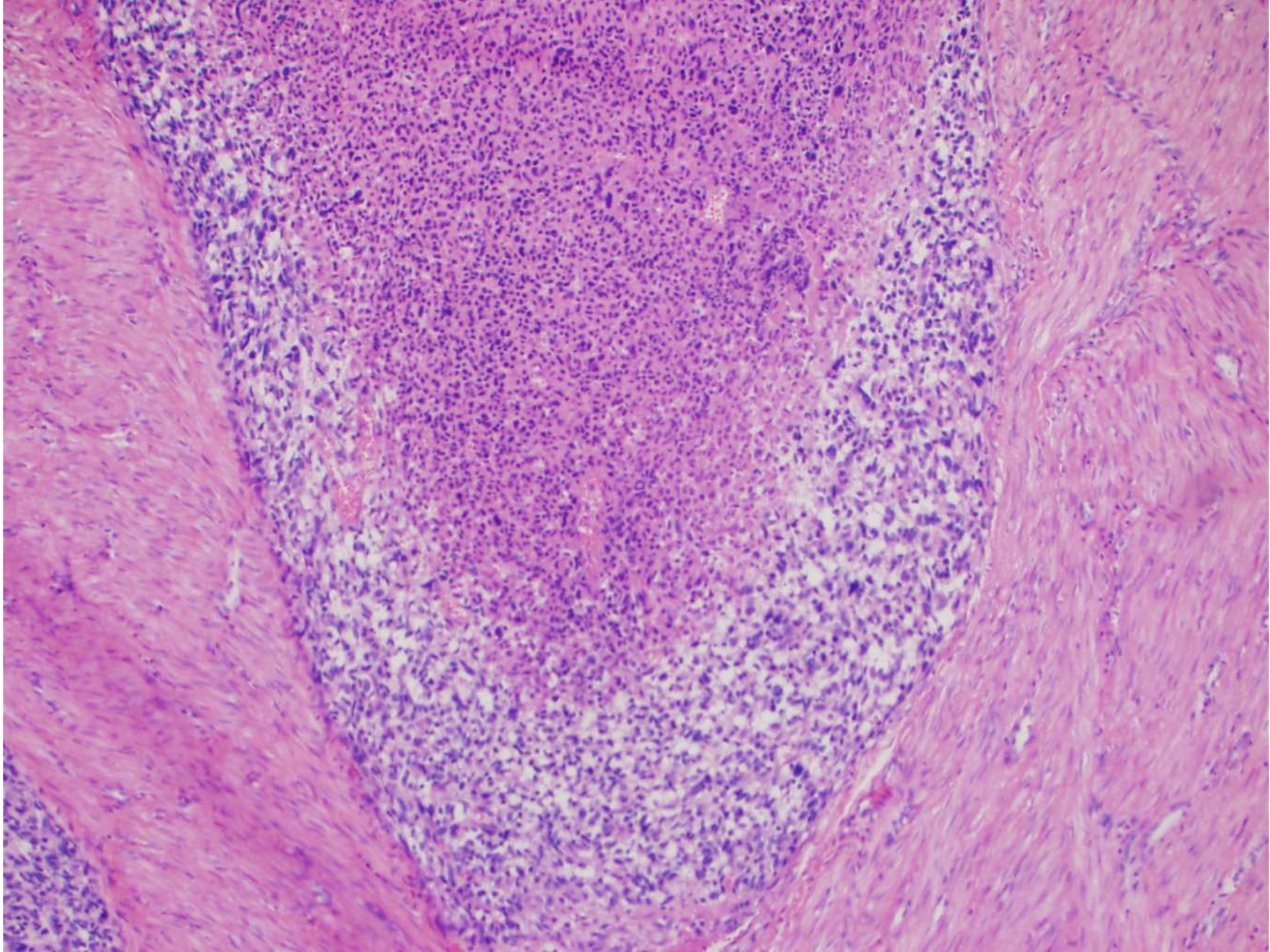












Immunohistochemistry

- Desmin-positive
- Caldesmon-positive
- HMB-45-positive (focal)
- Melan A-positive (rare cells)
- **Diagnosis: Malignant Perivascular Epithelioid Cell Tumor (PECOMA)**
- Ref: Perivascular Epithelioid Cell Neoplasm of Gynecologic Tract; Clinicopathologic and Immunohistochemical Characterization of 16 Cases.
- Schoolmeester,J.K. et al; AJSP Feb;38(2):176-188

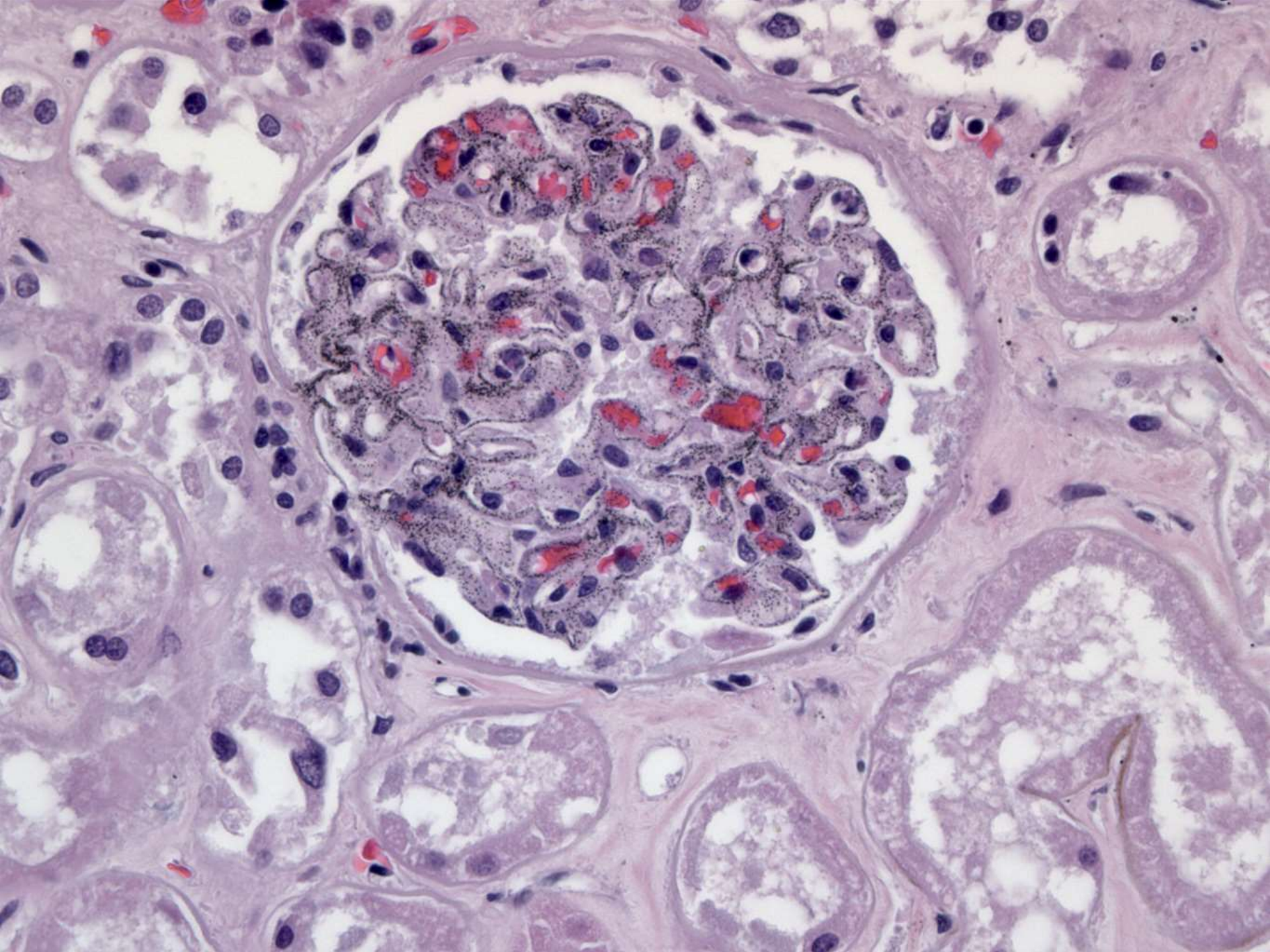
Malignant Potential in PECOMAs of Female Genital Tract

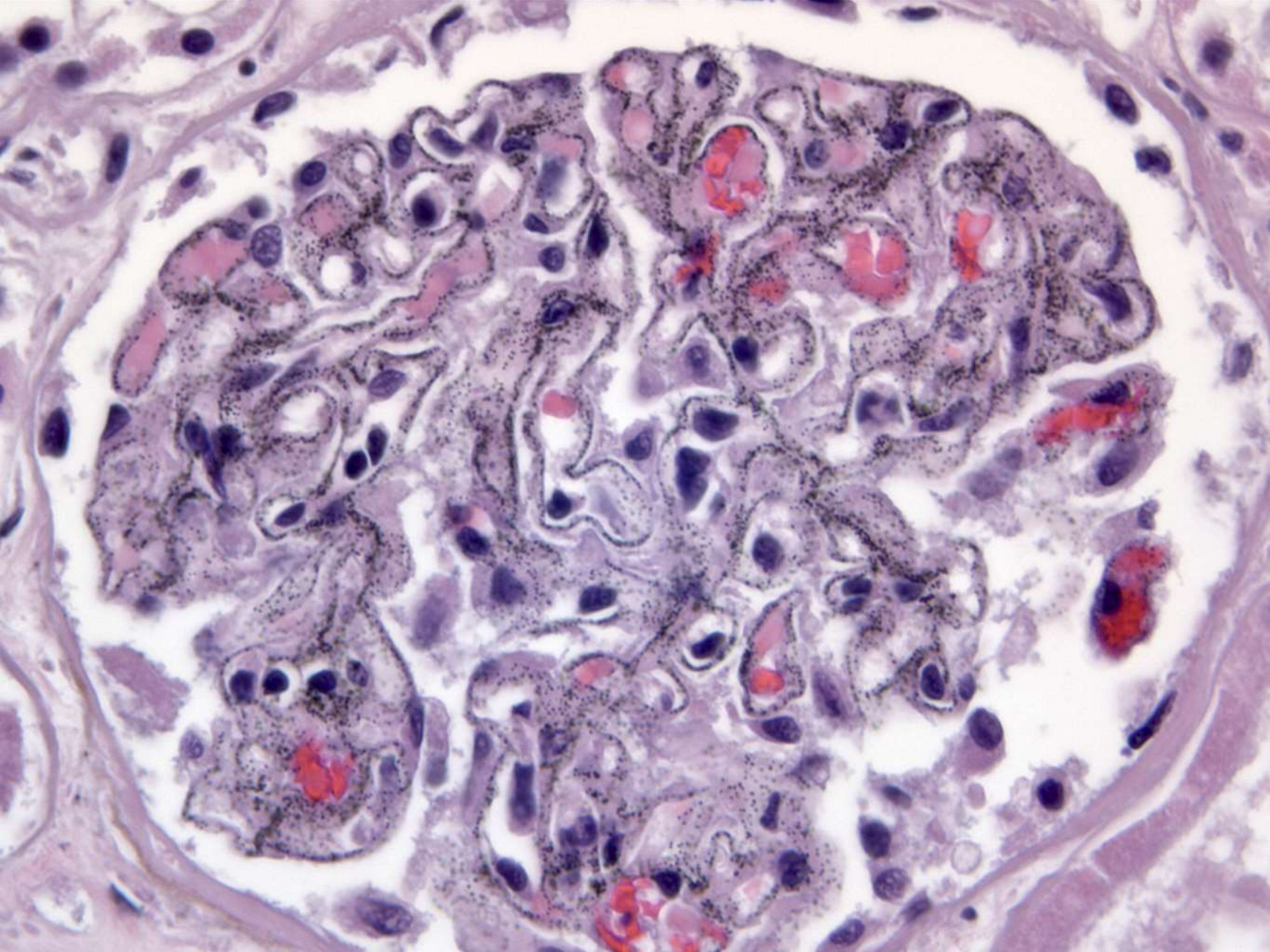
- **4 or more of the following:**
- Size> 5cm.
- Infiltrative growth pattern
- High grade nuclei
- Necrosis
- Vascular invasion
- Mitotic index of 1 per 50 HPF

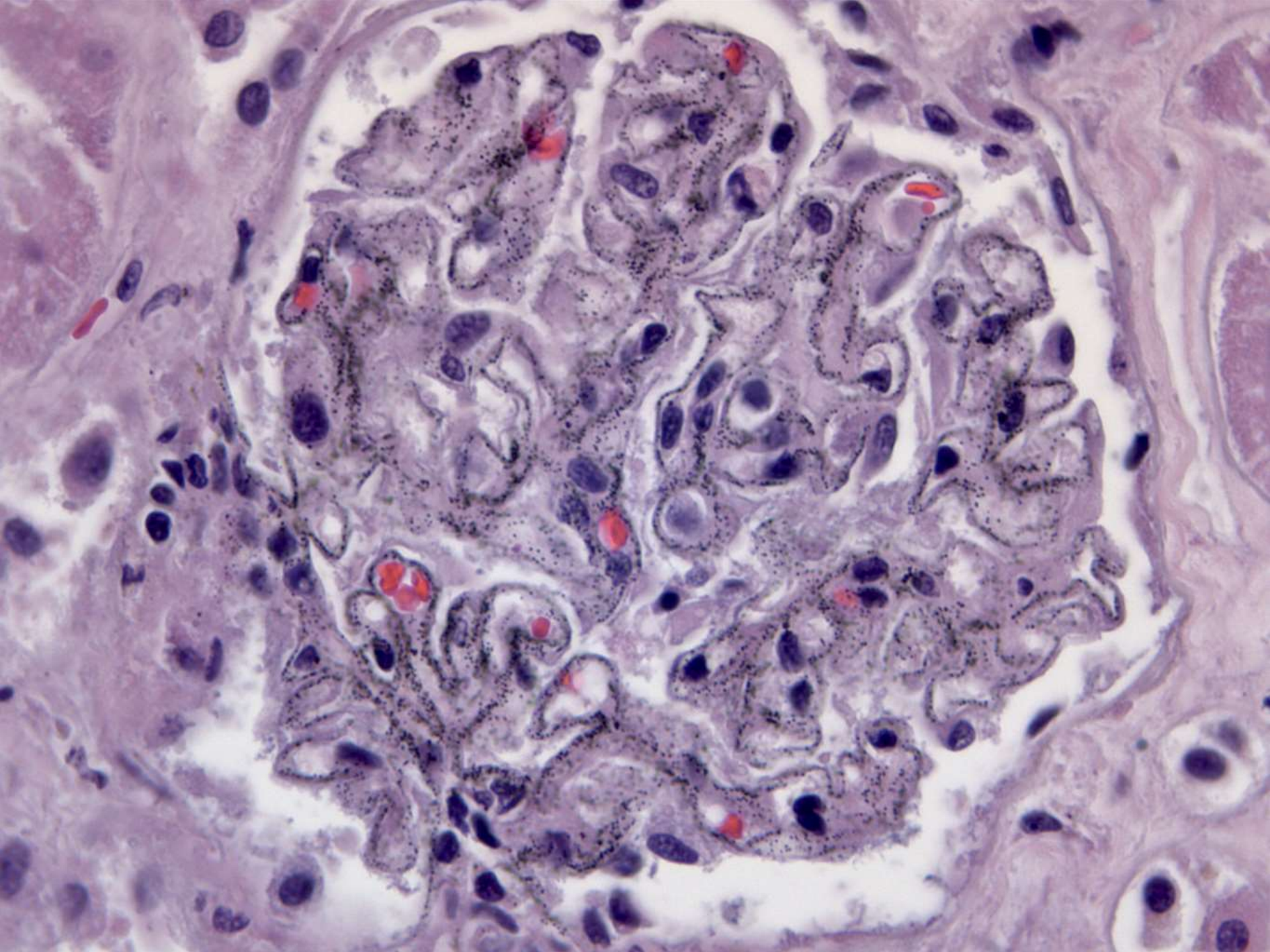
SB 6223
(scanned slide available)

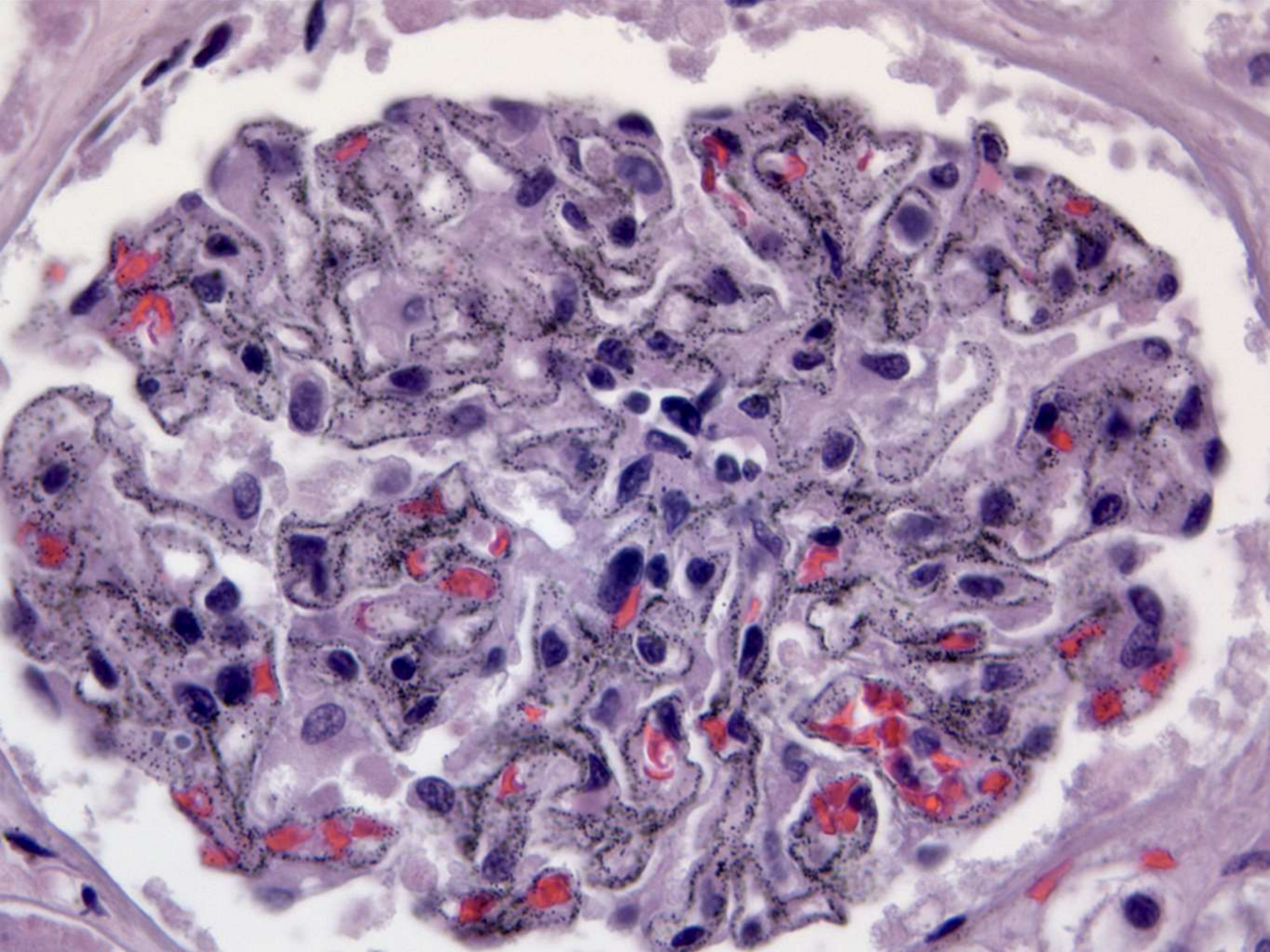
Bernadette DeRussy/Megan Troxell; Stanford

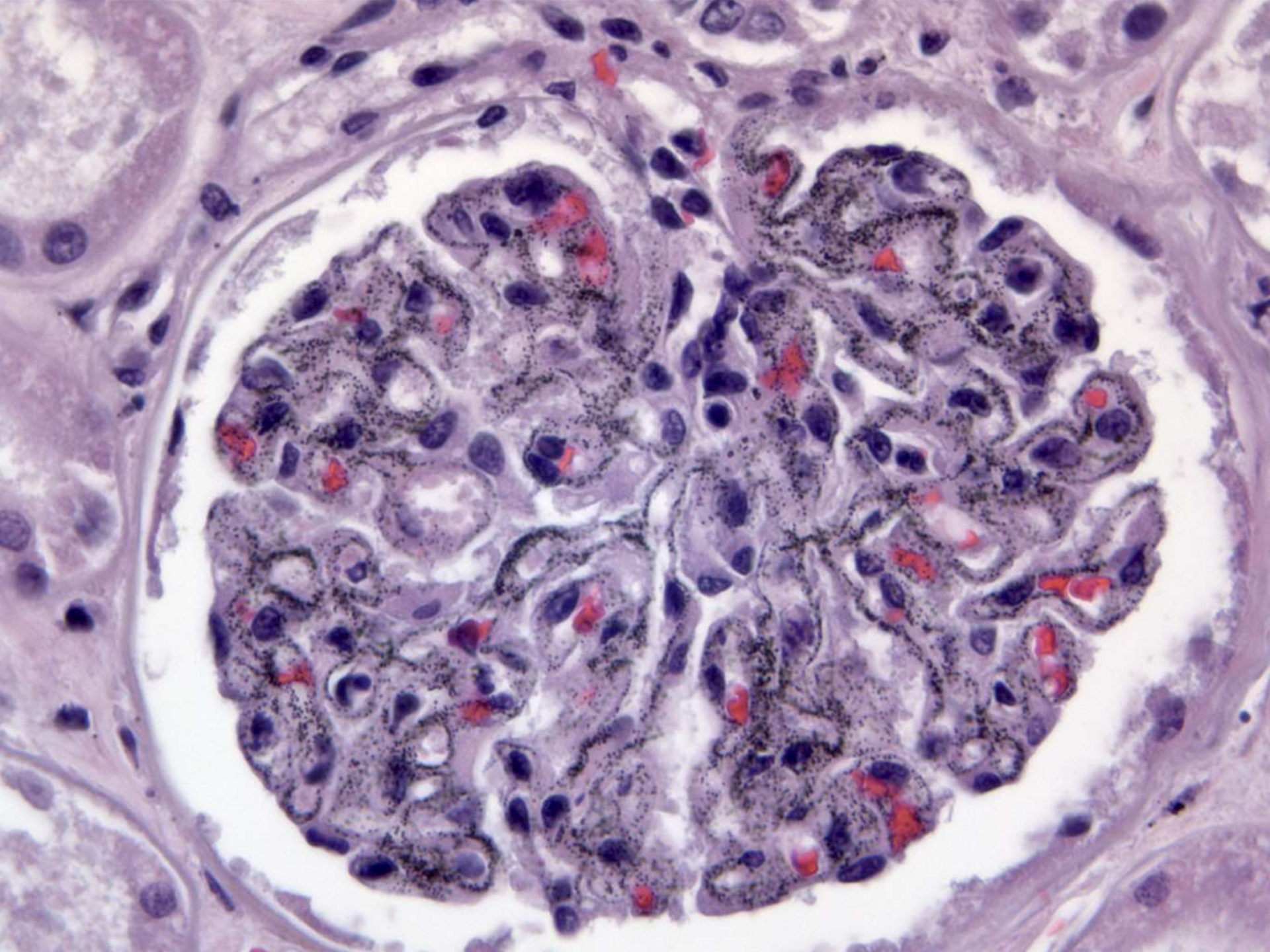
54-year-old male 7 months post stem cell transplant for MDS. Autopsy findings included subdural hematoma, pleural effusion, GVHD. Section of kidney provided.

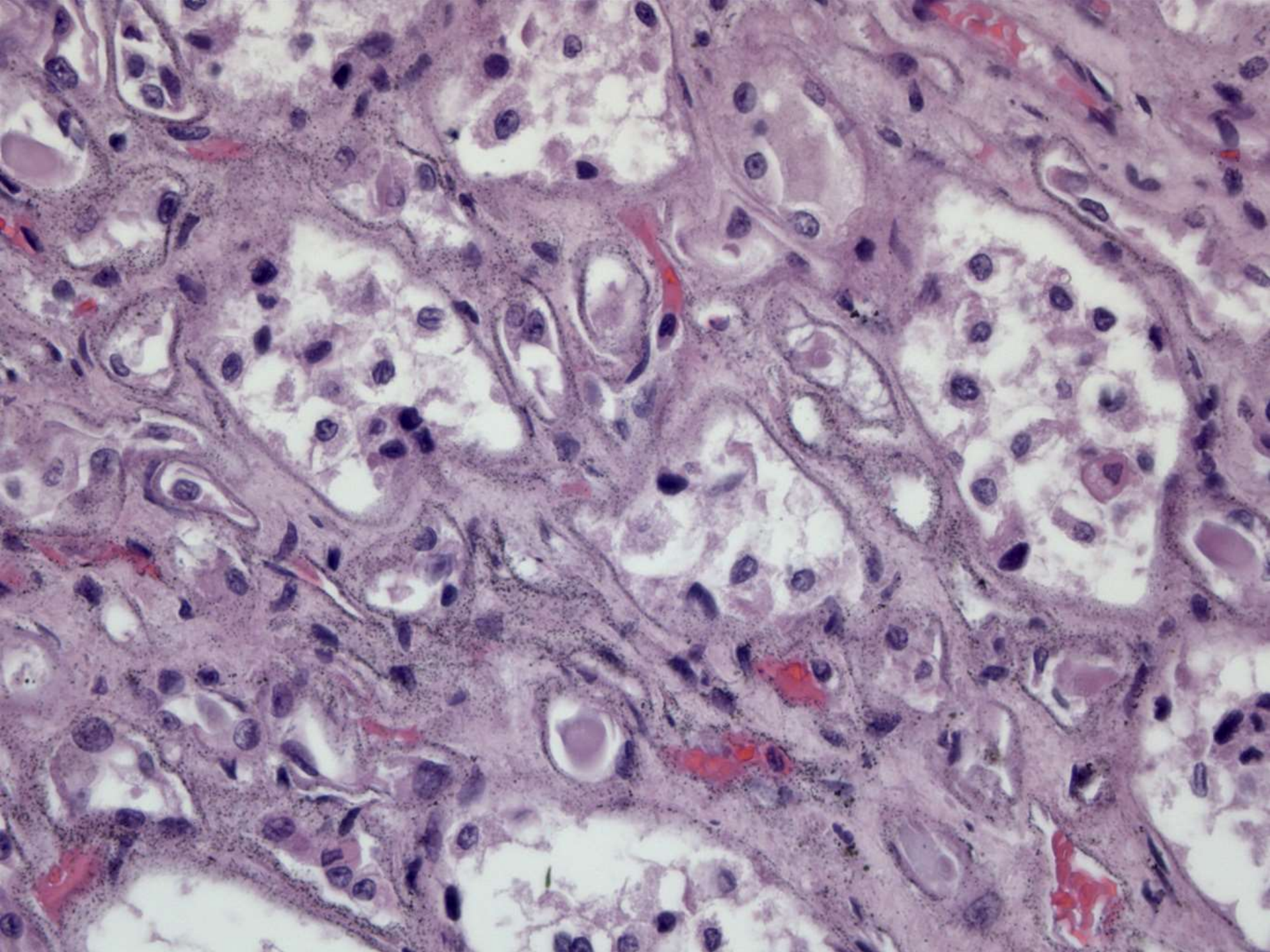


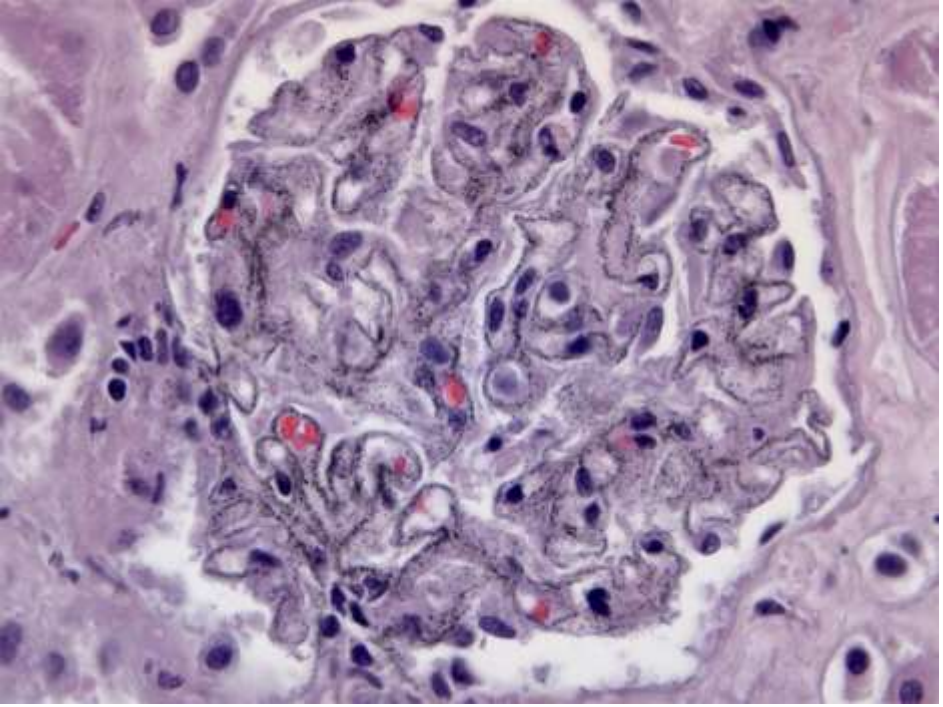
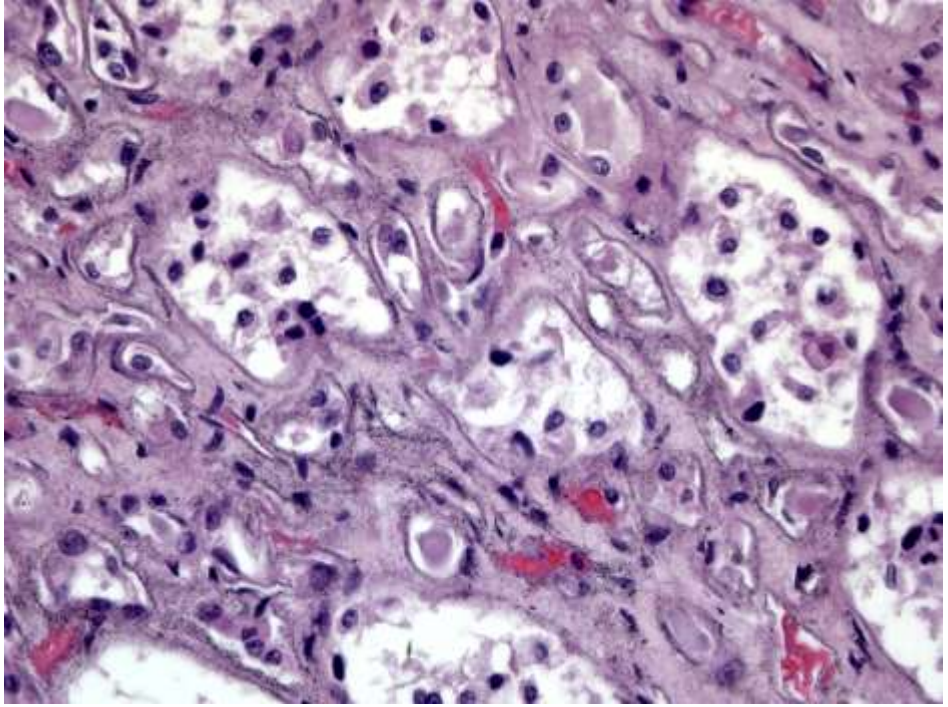
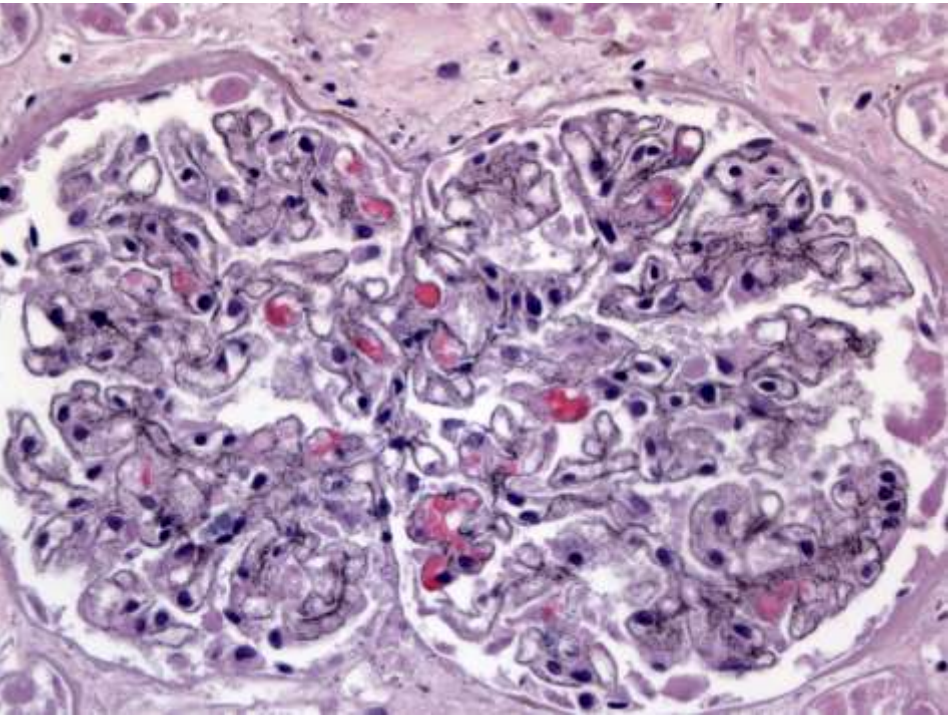
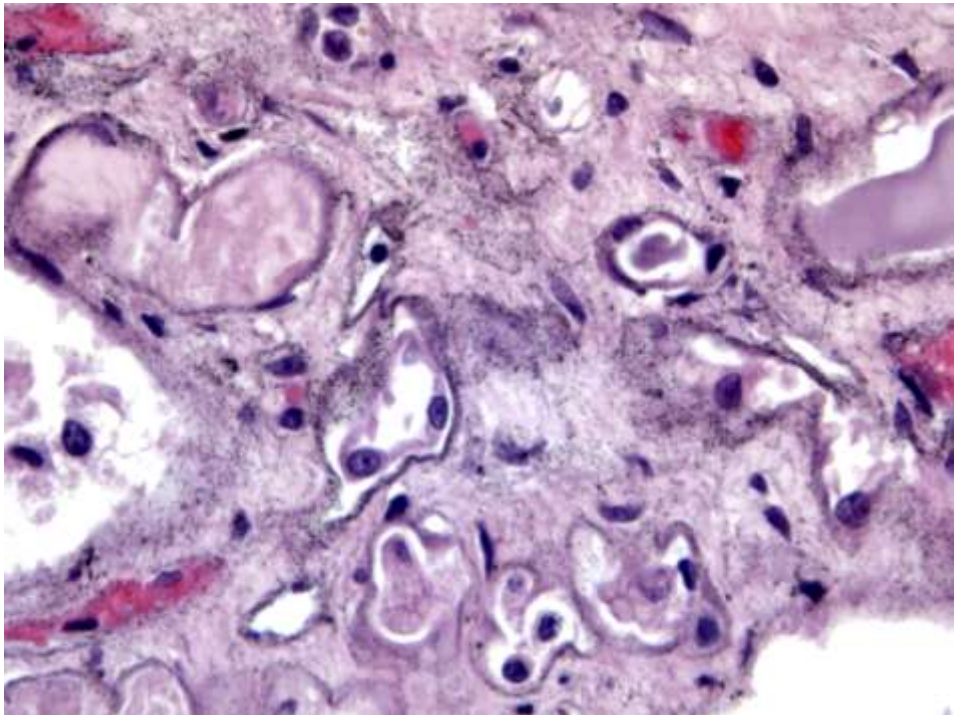










Black Kidney: Differential Diagnosis

Ochronosis
- Deposits of homogentisic acid in tubules/casts, not glomeruli

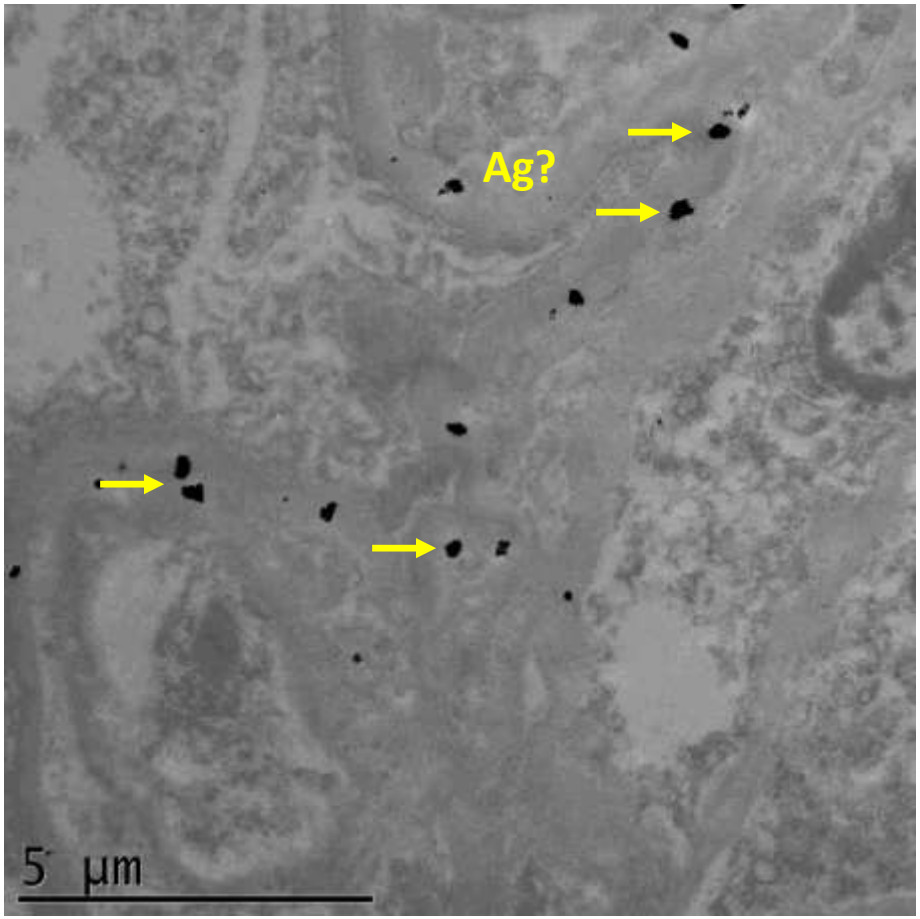
Lecithin-Cholesterol Acyltransferase Deficiency
- Osmophilic lipid deposits in glomerular basement membrane, may be confused with silver deposits by electron microscopy
- No pigment on light microscopy

Metallosis/metal deposition of sorts

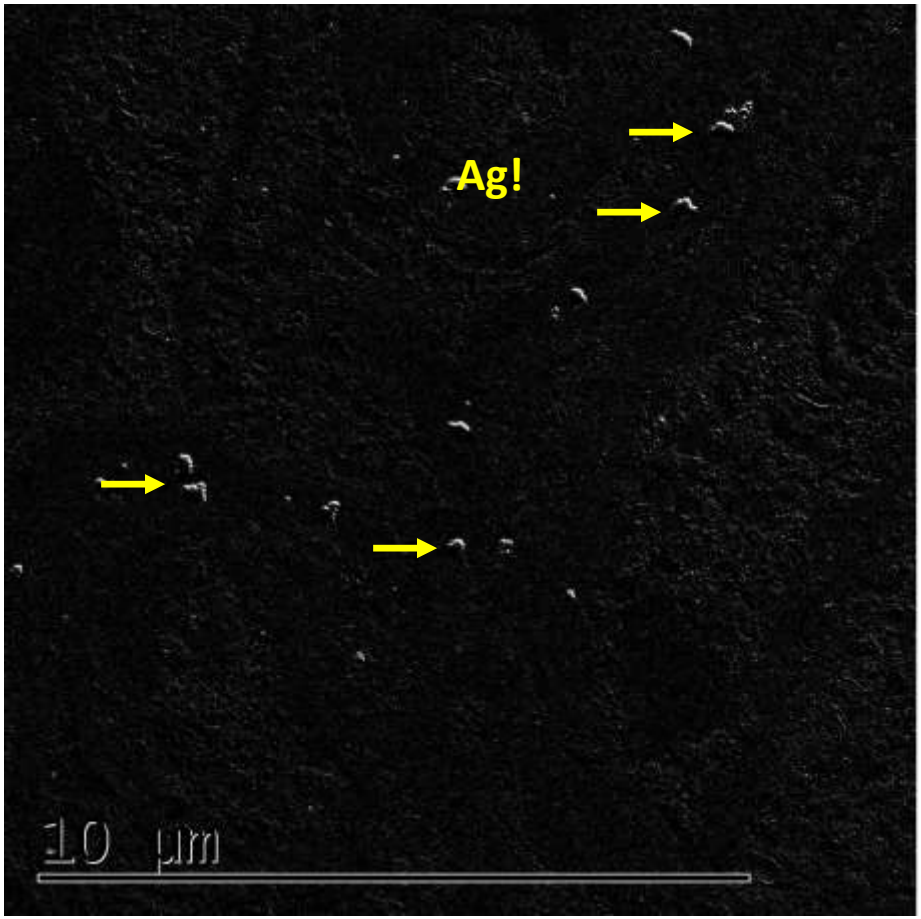
Additional History

Took over the counter colloidal silver for years for “health reasons”

Wife started noticing change in skin tone about two years prior to death



TEM image of sample section

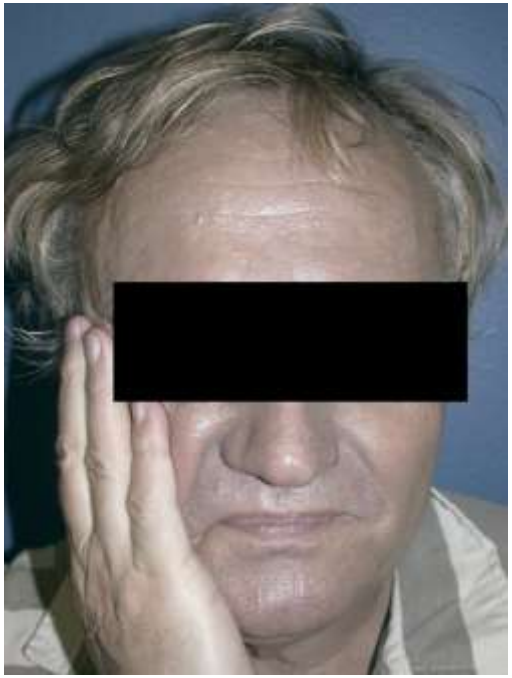


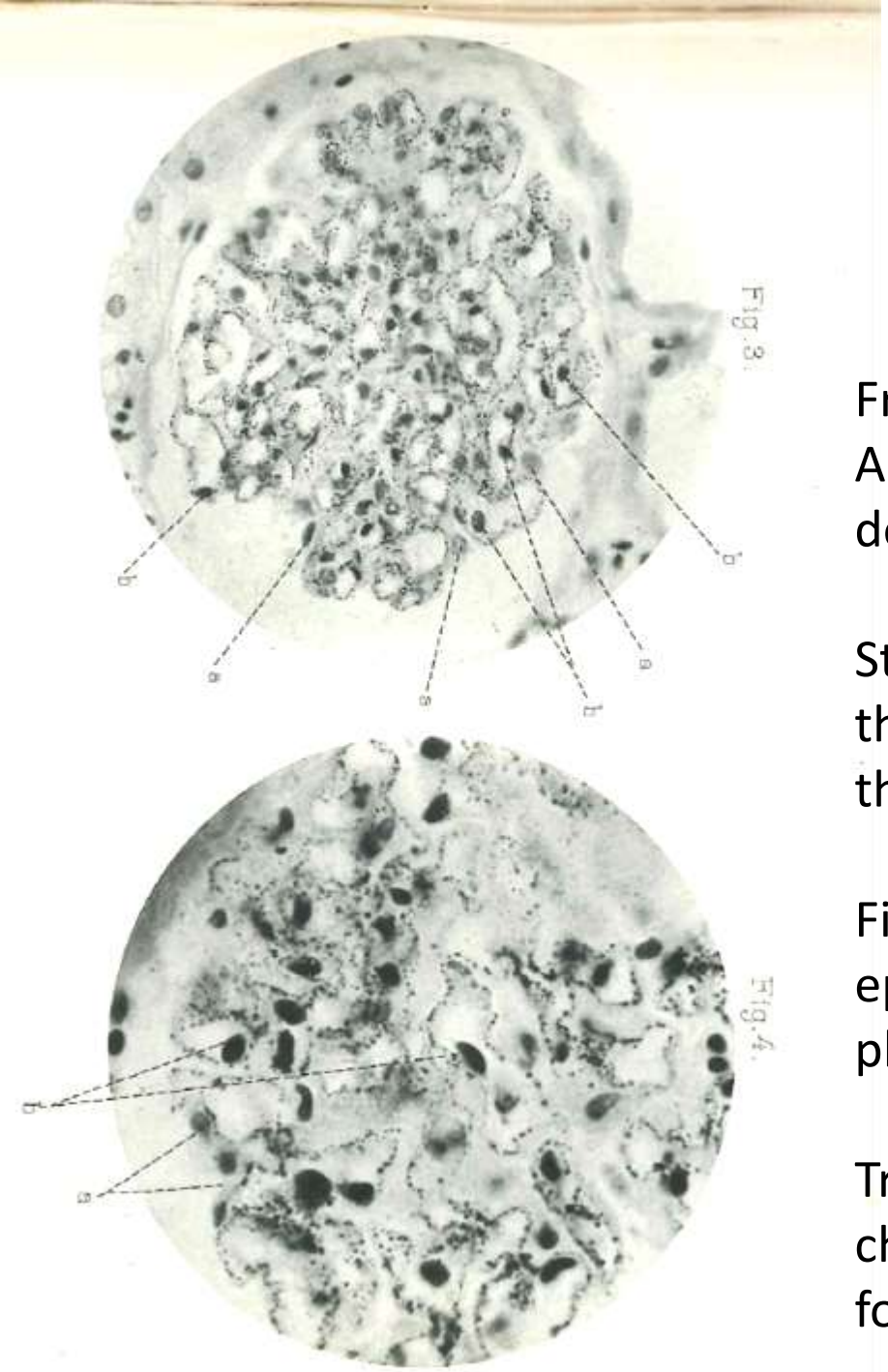
Electron Energy Loss Difference image of same sample section, at an energy range specific to silver. Bright areas correspond to silver.

Argyria

Irreversible deposition of silver in skin, mucous membranes, eyes and internal organs

First known description in 980 AD by Avicenna:
- Used silver filings as a blood purifier, for offensive breath, and for palpitations of the heart
- Pathology text describes a patient with bluish discoloration of the eyes associated with ingestion of silver





X.

Ueber Argyrie.

Von

Dr. Jahn.

Assistent am pathol. Institut d. Universität Leipzig.

From 1894:
Autopsy of a 58 year old tailor with tabes dorsalis

Studies localization of silver deposits throughout body (mostly in kidney, thyroid, choroid plexus)

Finds them in basement membranes not epithelium has some claimed (takes photograms to prove the point)

Tries to feed three mice with flour/silver chloride but they wouldn't eat it and he found nothing on sacrificing them

Beitr Path Anat 16:218-239, 1894

XIII.

Ueber die Ablagerung des Silbers in den Nieren.

Von

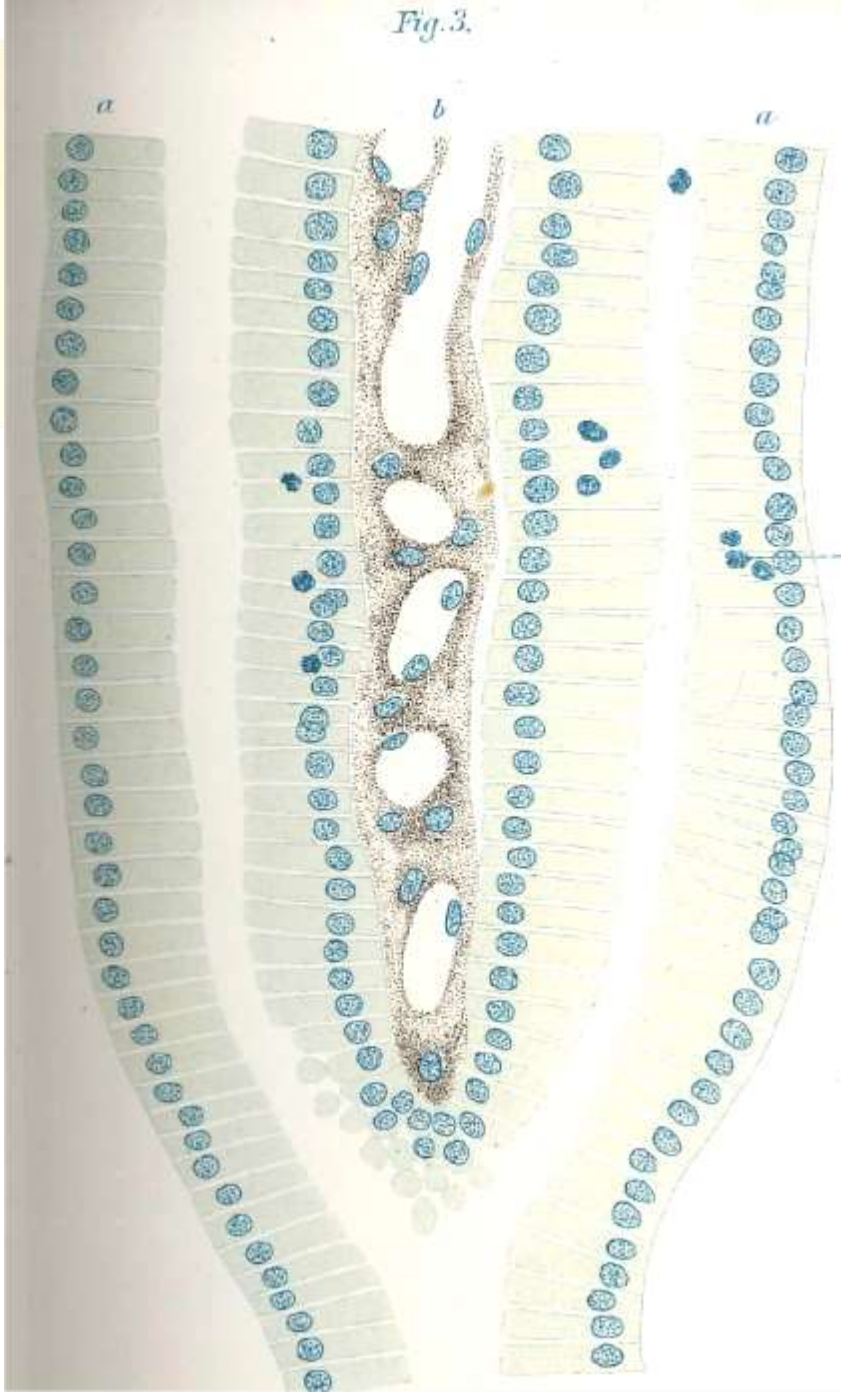
C. v. Kahlden.

(Aus dem Pathologisch-anatomischen Institut der Universität Freiburg i. B.)

Kidneys of young girl who had been treated for long time with silver nitrate: tubulitis and interstitial fibrosis – speculates nephrotoxicity

Feeds bunnies silver to see if he can reproduce nephrotoxicity: gives pills with a bunch of silver nitrate, pushes pill in with a little piece of turnip. After 109 days he sacrificed an animal that had lost a lot of weight.

Necropsy: kidneys rich with blood showed marked brown coloration of the medulla. More intense towards papillae. No chronic injury.



Beitr Path Anat 15:611-625, 1894

Argyria: Long and Short

Potential exposures: Occupational, Health care (antibiotic), Over the counter colloidal silver (promoted as "cure-all")

Not thought to be toxic -- question of nephrotoxicity but not proven

Psychosocial effects:
"Permanent discoloration of the skin is often a serious cosmetic problem and may result in psychological stress and social isolation."

Captures the pathologist's imagination:
"Cases of argyria seem to have an intrinsic appeal to pathologists, for though reports can be traced in the files, slides and blocks seem to disappear."

J Pathol. 1972 Jun;107(2):123-5.

8 *proven* COLLOIDAL SILVER BENEFITS

1

ANTIBACTERIAL

Not only is colloidal silver super effective at eliminating bacterial infections, but it also is equally effective at resistant strains of bacteria and it does not cause any further mutations — which is great news for its long-term use as an antibiotic treatment.

2

WOUND CARE/ SKIN HEALTH

Colloidal silver preparations can be used for topical use to treat burns, thrush, periodontitis, and even skin conditions such as psoriasis and eczema.

3

PINK EYE/ EAR INFECTIONS

Colloidal silver can be used for prompt action against the highly infectious pink eye condition whether it is caused by a virus or a bacteria. It also helps heal ear infection even if it is caused by a fungus.

4

ANTIVIRAL

Colloidal silver benefits can be experienced as an anti-viral for HIV/AIDS, pneumonia, herpes, shingles and warts. Dr. Martin Hum, from the Institute for Optimum Nutrition, lists colloidal silver as one of the natural remedies to stop viruses fast.

5

ANTI-INFLAMMATORY

Colloidal silver is a natural anti-inflammatory that works fast to reduce swelling, repair inflammation in the skin or in the body.

6

SINUSITIS

Colloidal silver can benefit people as a nasal spray that kills Staph aureus and Pseudomonas aeruginosa infections that could directly cause sinusitis and allergies.

7

COLD/FLU

Speed recovery to the common cold and flu bug with colloidal silver's immune-boosting benefits.

8

PNEUMONIA

Whether ingested or used in a breathing treatment, colloidal silver succeeds when antibiotics just don't cut it. It even holds up against viral strains of pneumonia!

Dr. Axe
FOOD + MEDICINE

References

1. Jahn: Ueber Argyrie*. Beitr Path Anat* 16:218-239, 1894

2. Kahlden: Ueber die Ablagerung des Silbers in den Nieren. *Beitr Path Anat* 15:611-625, 1894

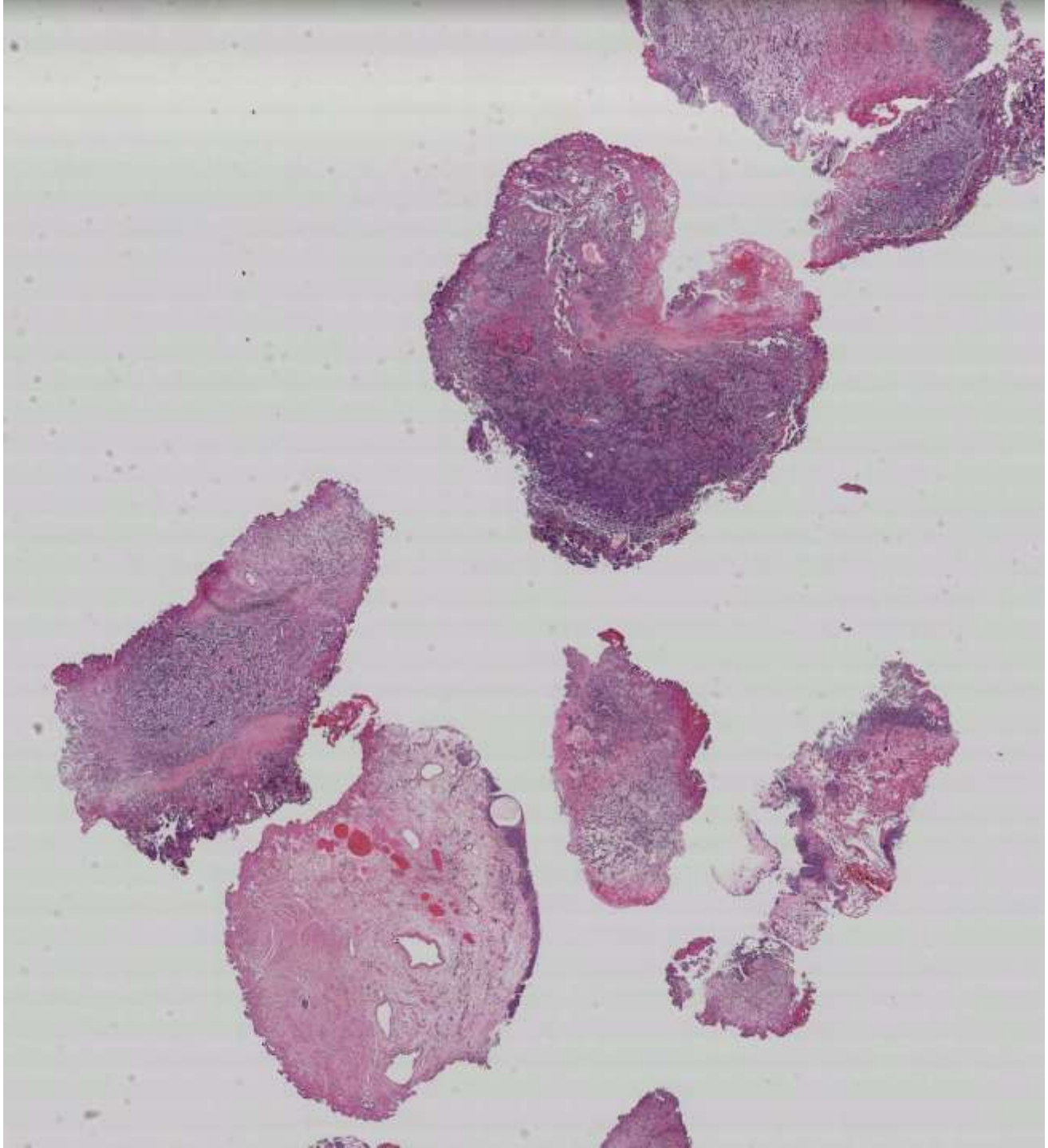
3. Mayr M, Kim MJ, Wanner D, Helmut H, Schroeder J, Mihatsch MJ. Argyria and decreased kidney function: are silver compounds toxic to the kidney? Am J Kidney Dis. 2009 May;53(5):890-4.

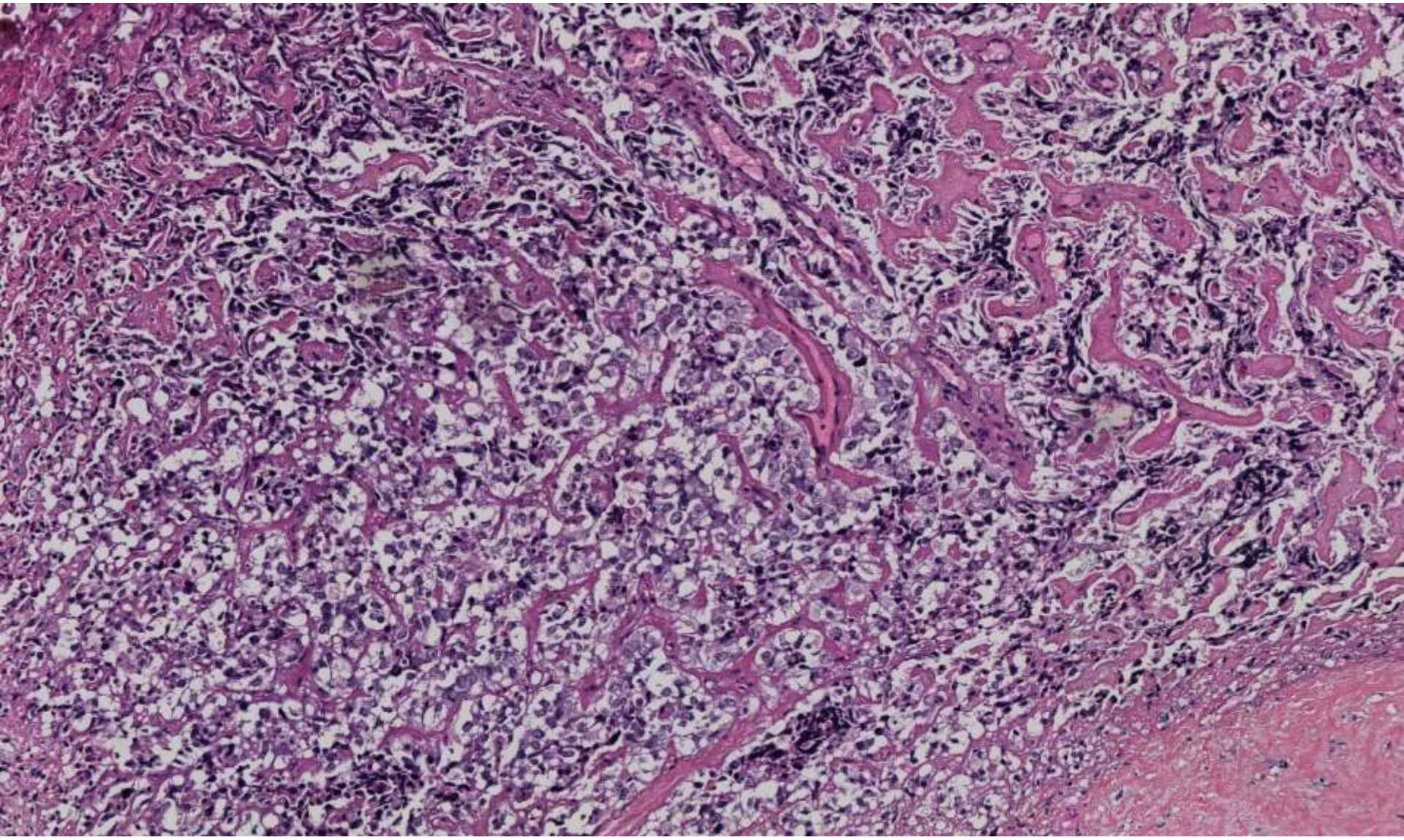
4. Walker F. Basement-membrane turnover in man. *J Pathol.* 1972 Jun;107(2):123-5.

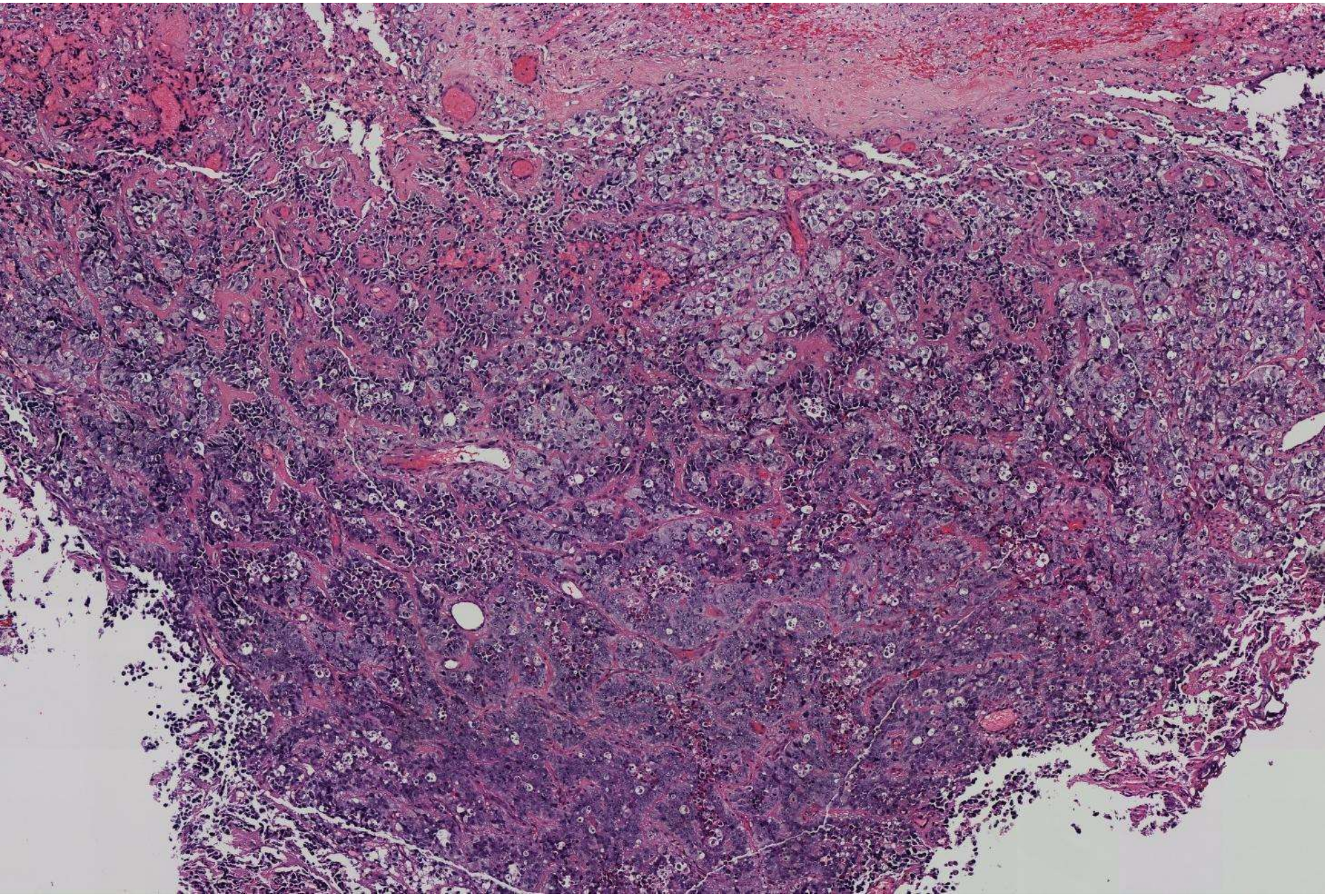
SB 6224
(scanned slide available)

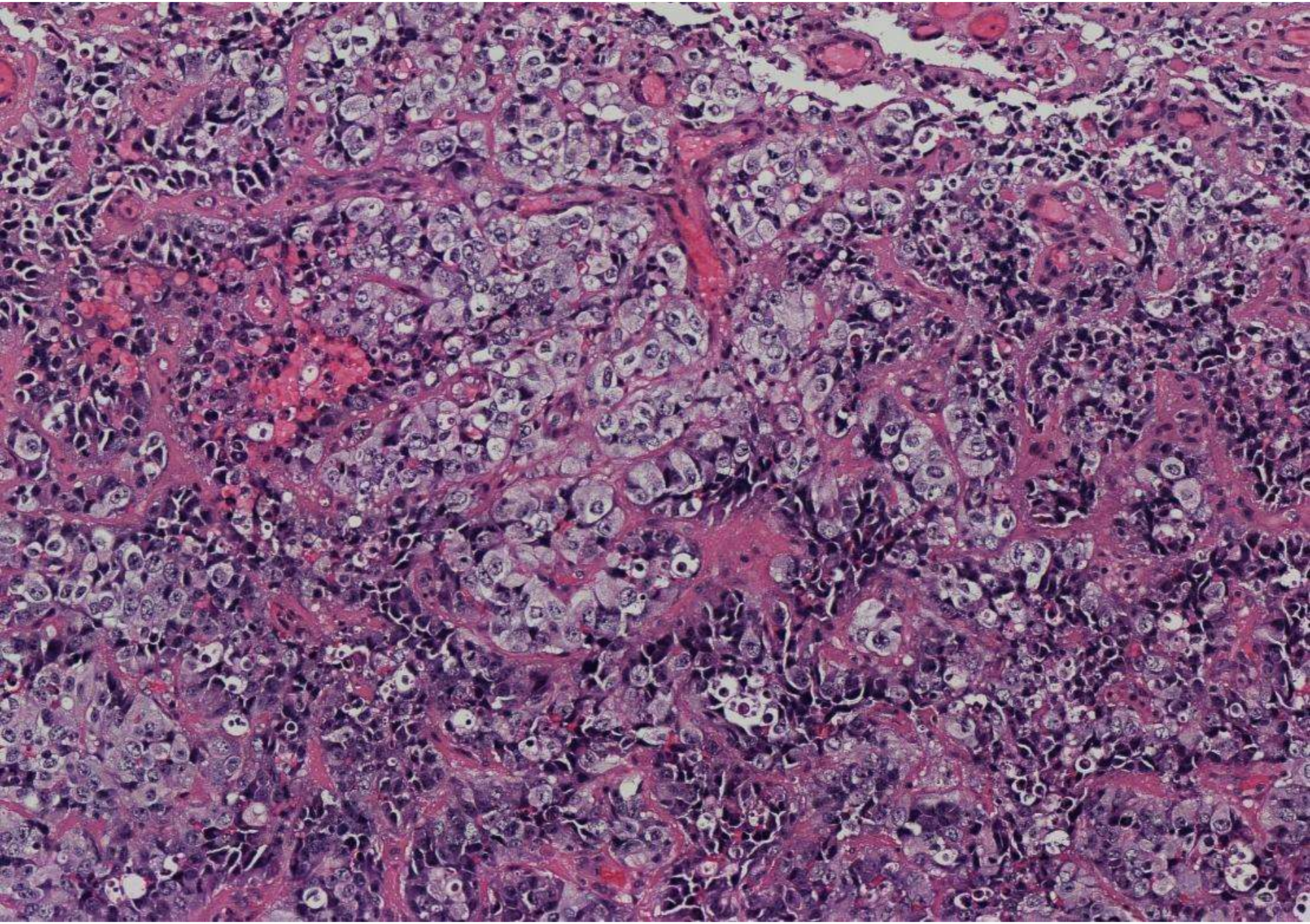
Jeff Simko; UCSF

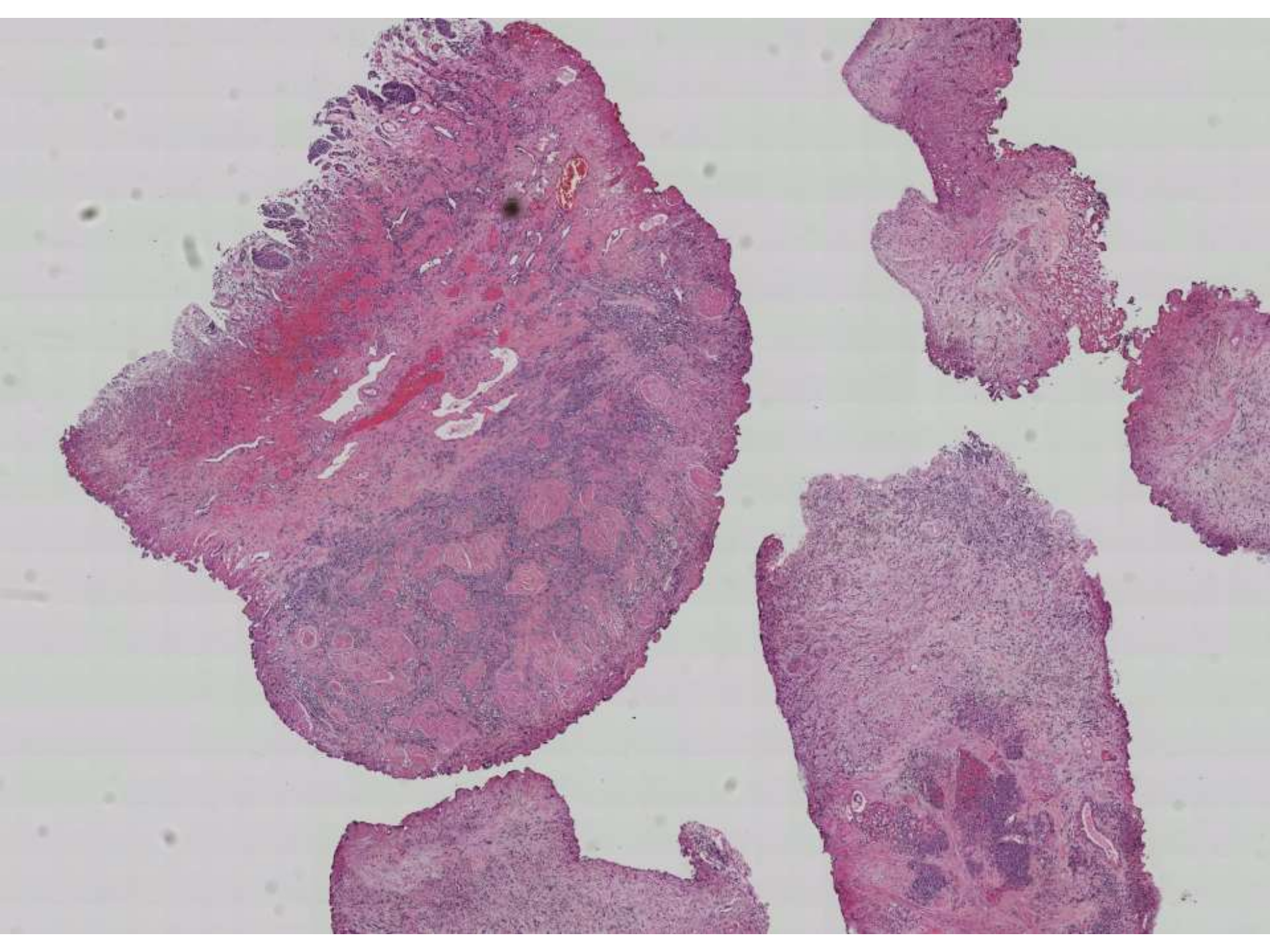
Adult male with TURBT for area irradiated
5 years earlier for prostate cancer.

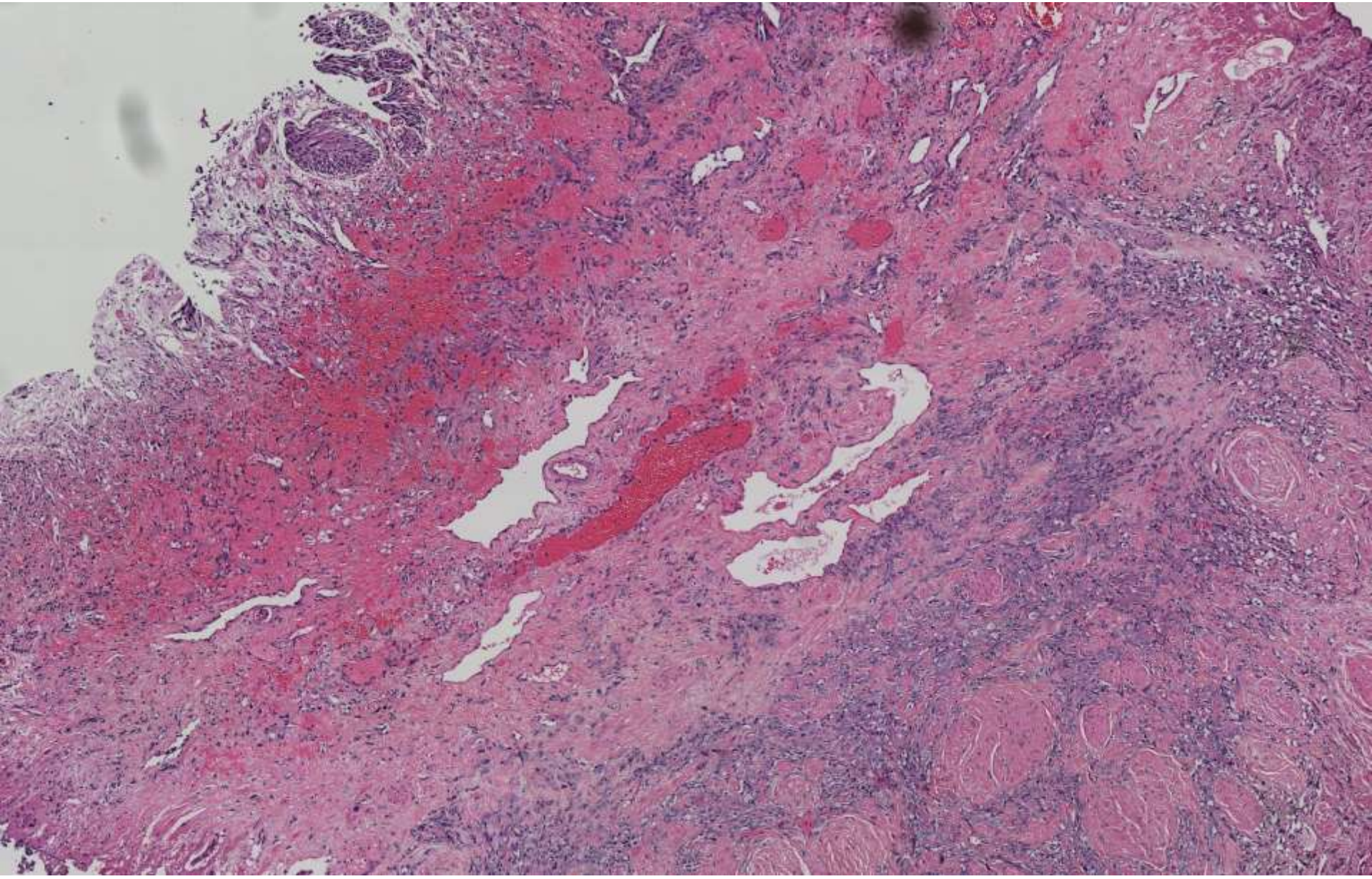


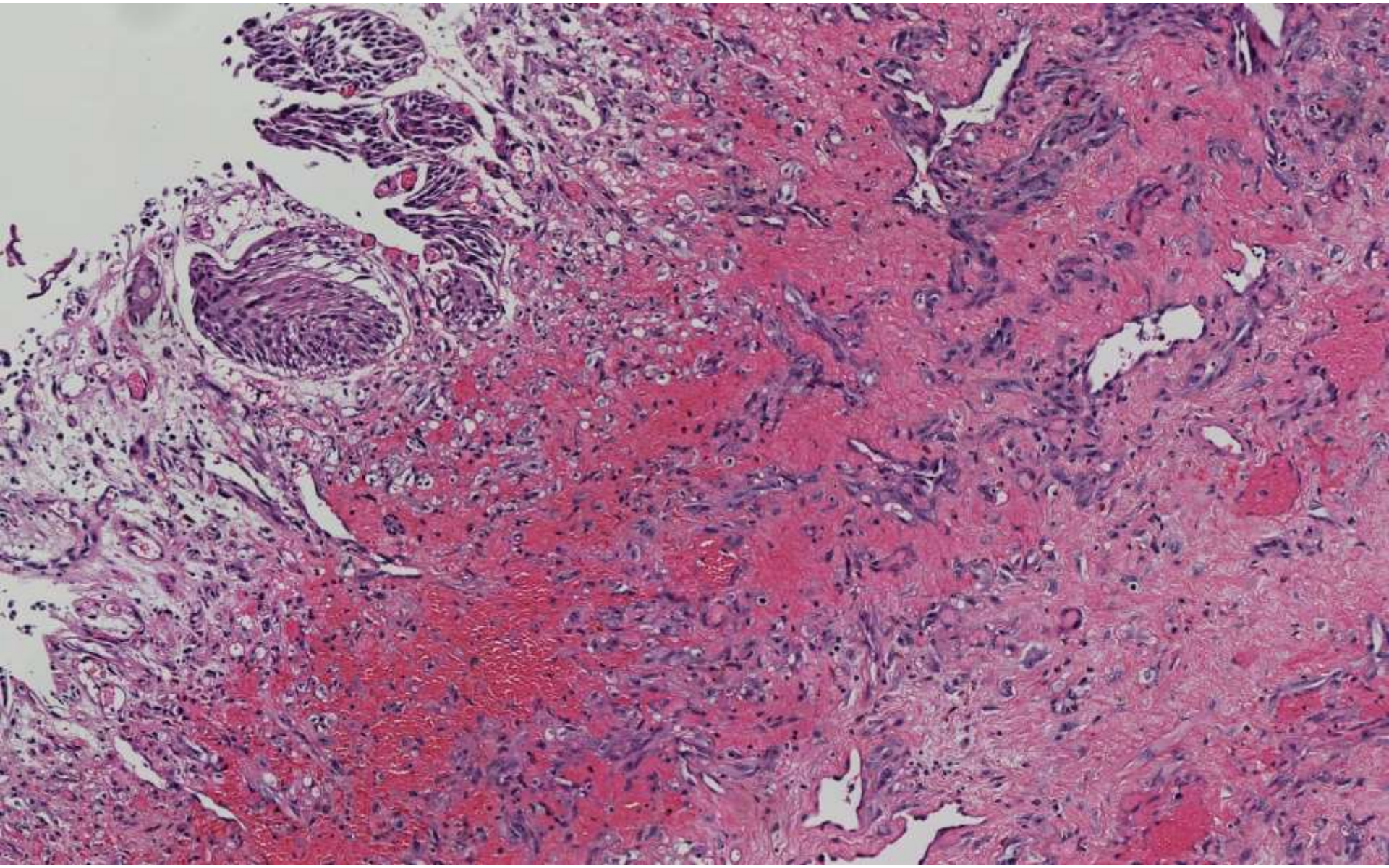


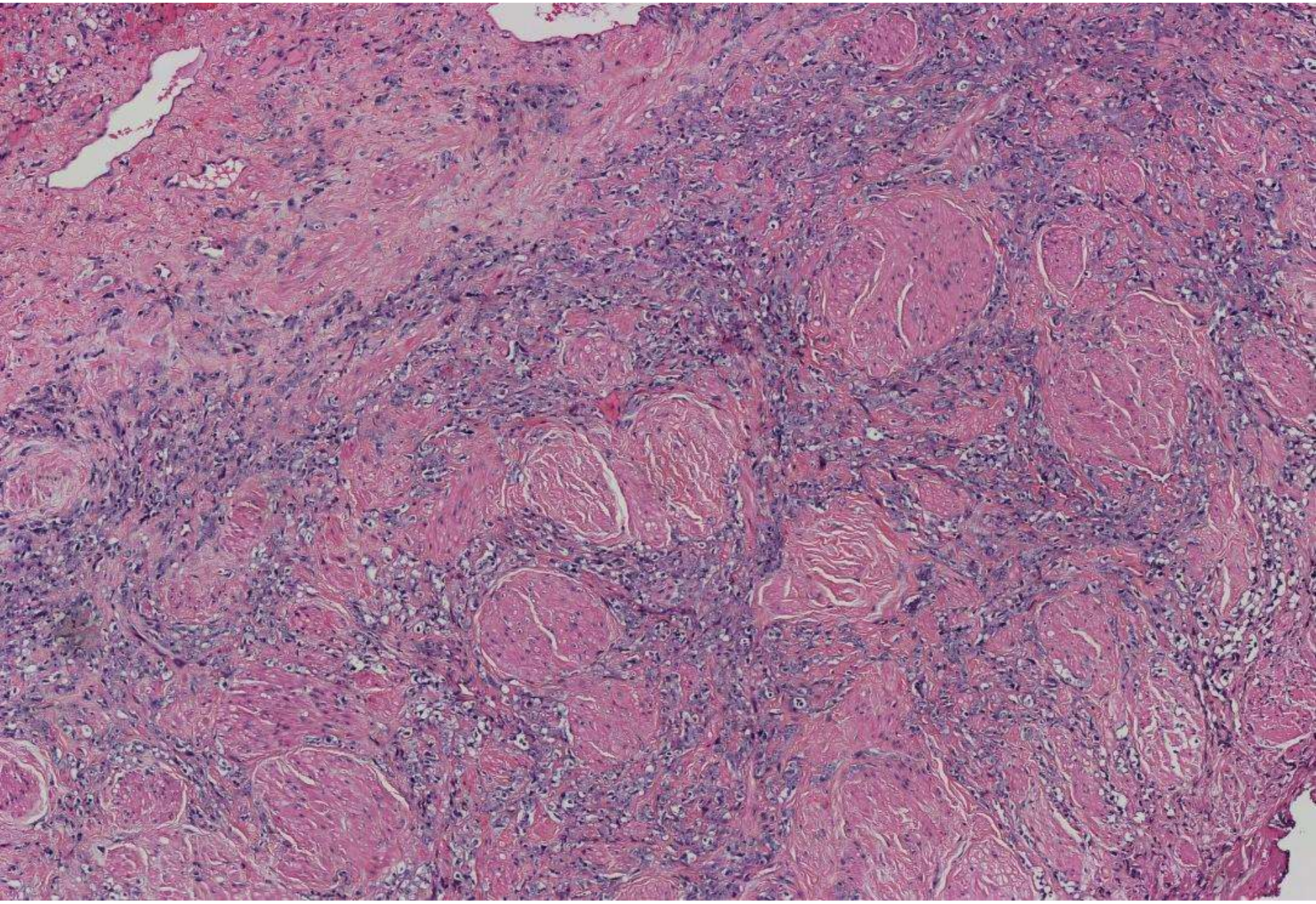


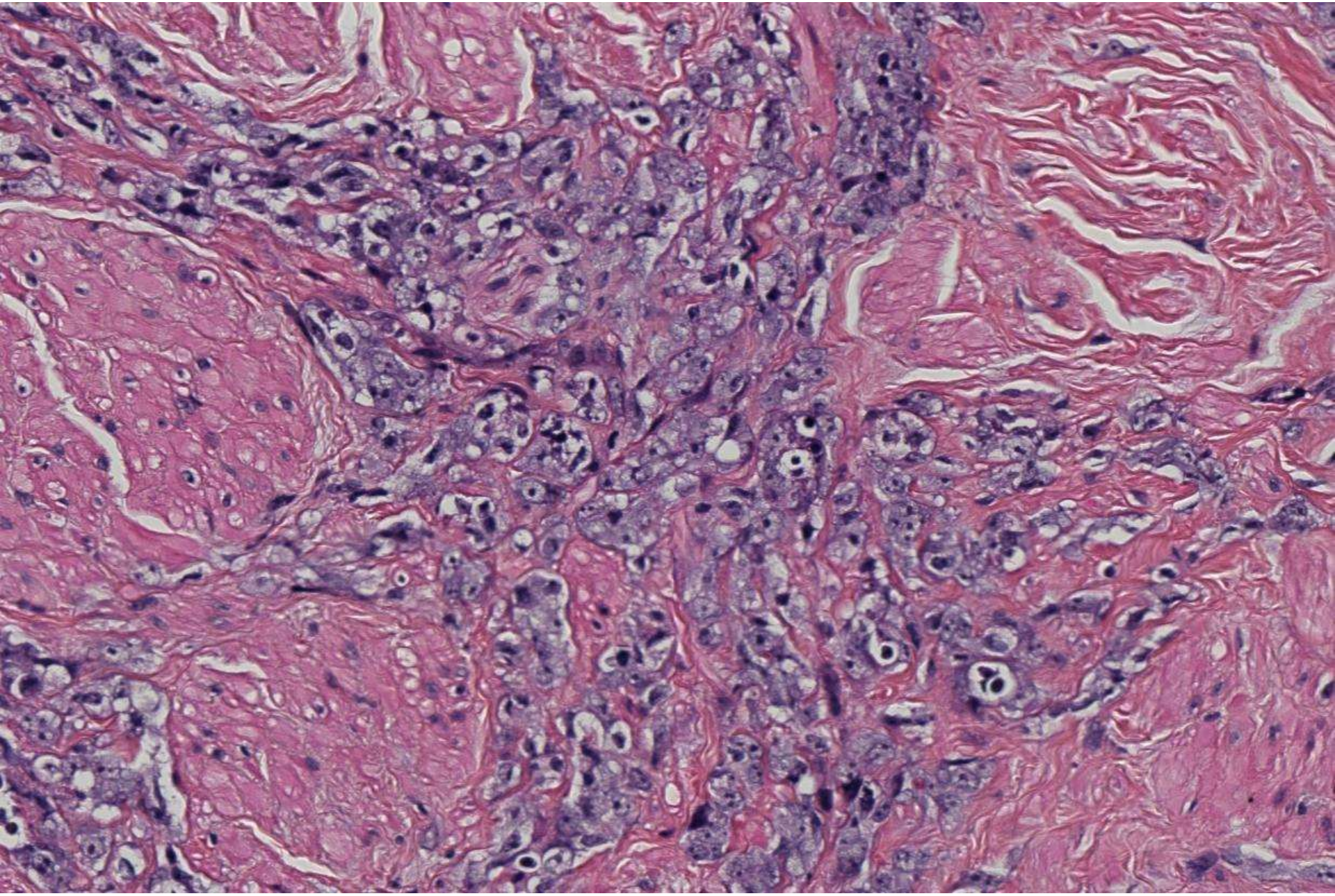


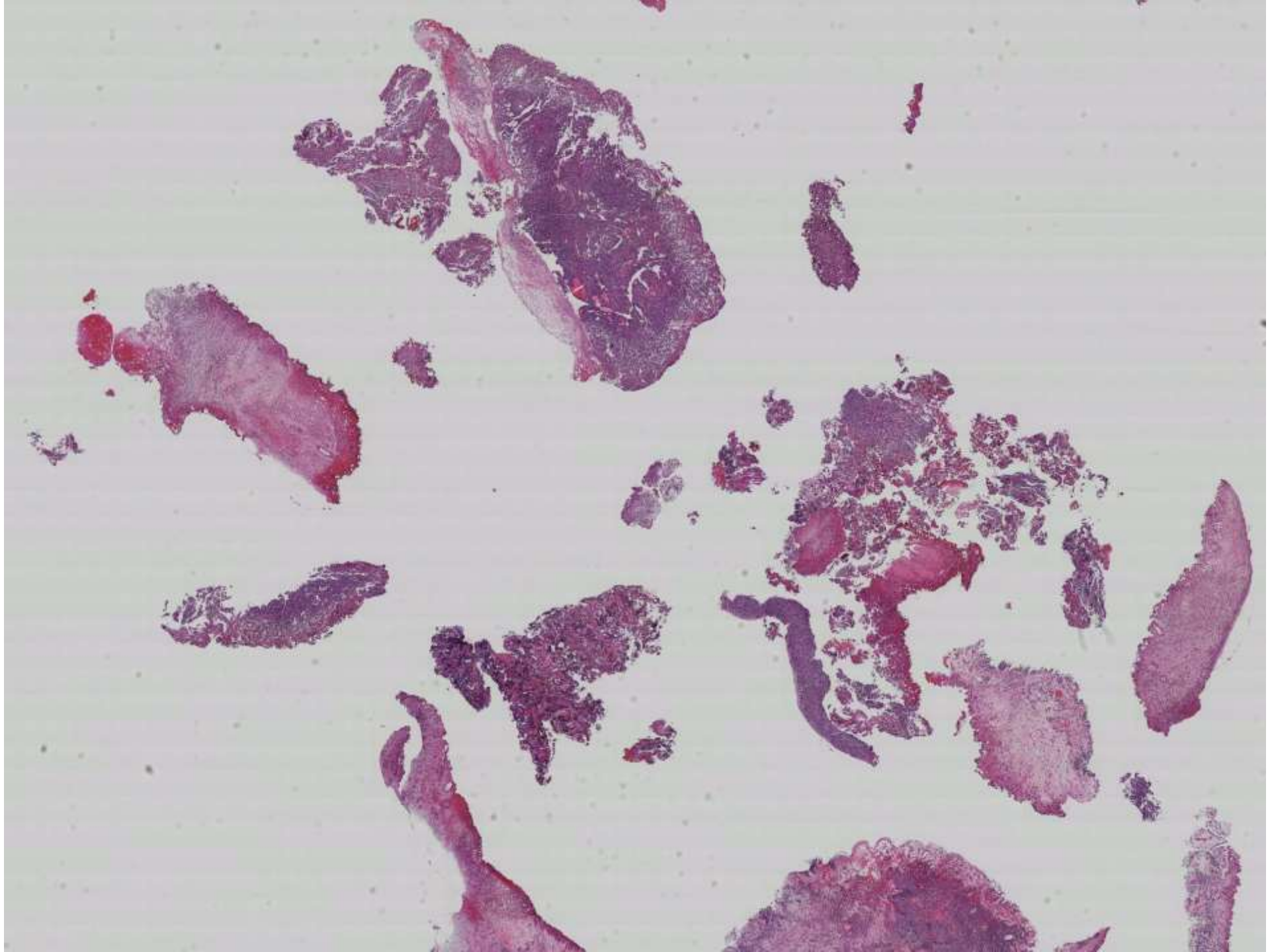


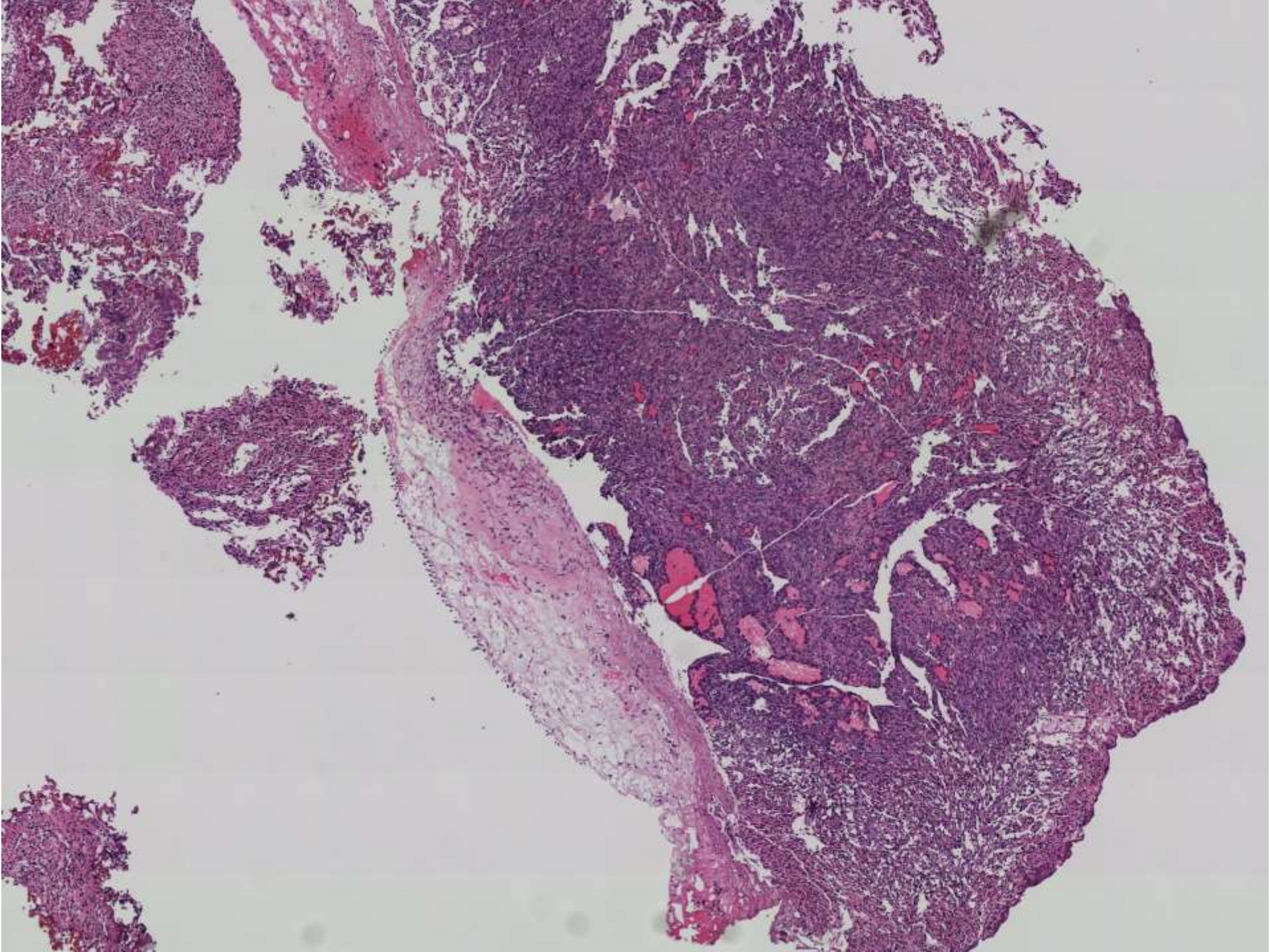


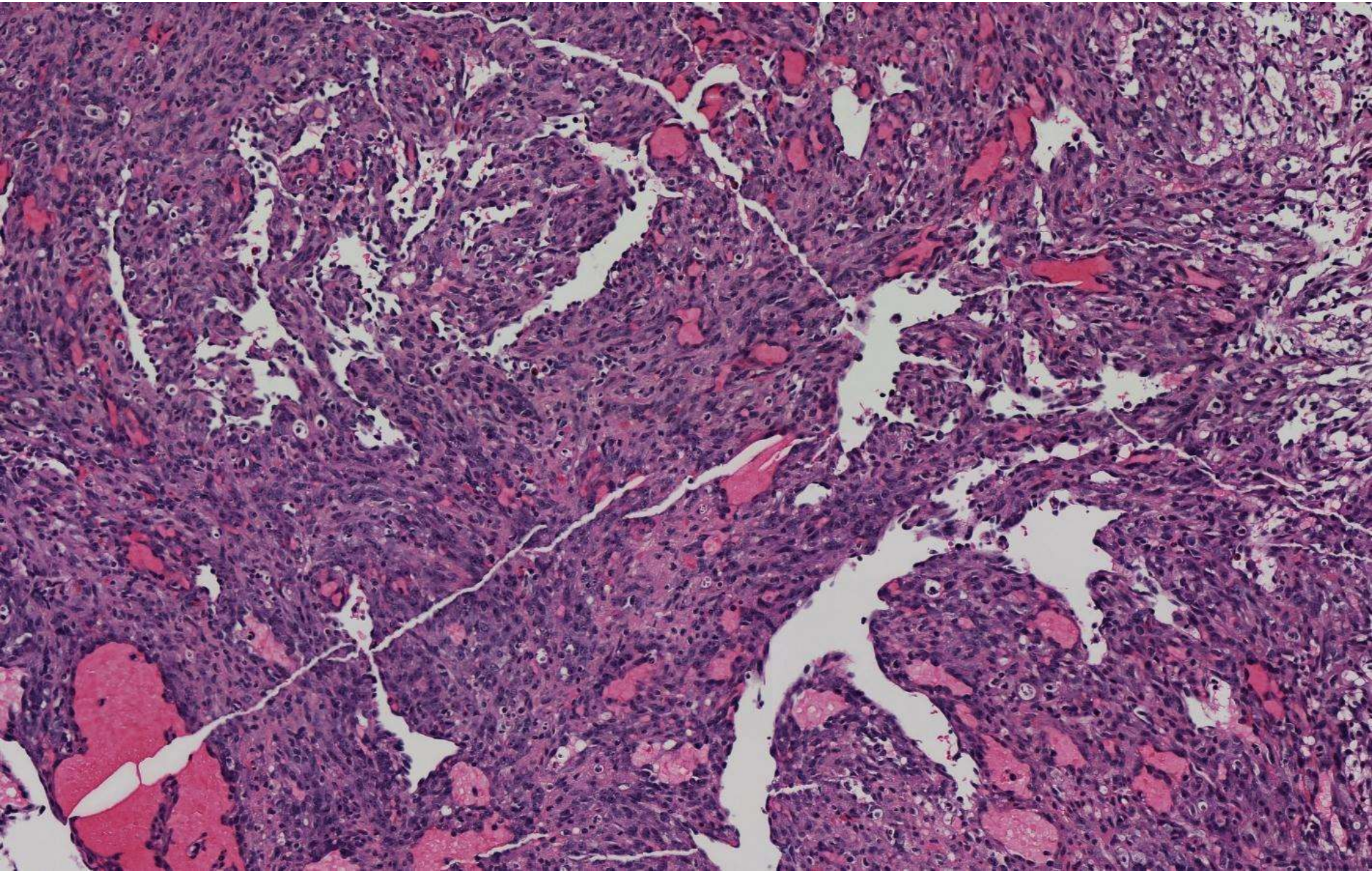


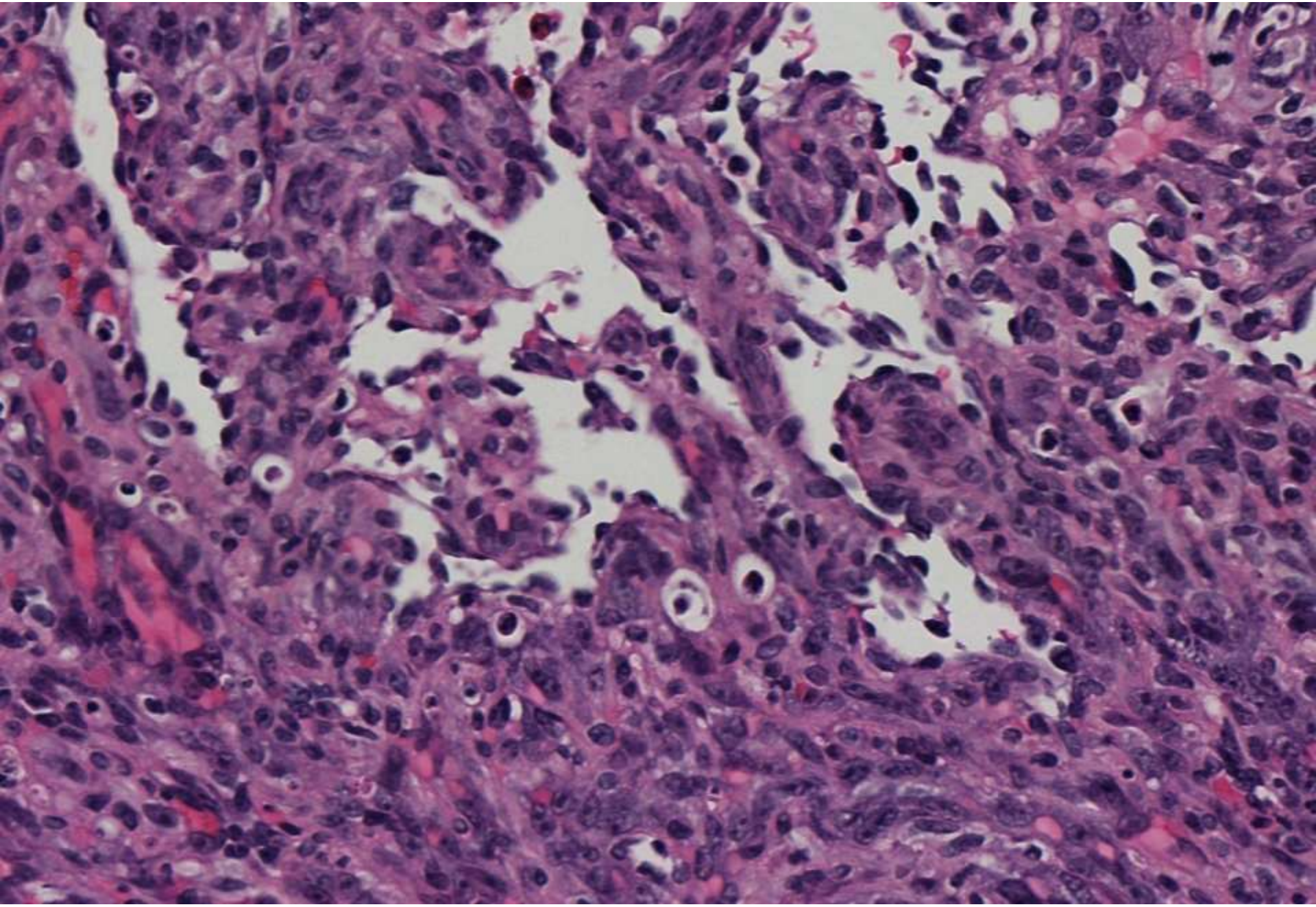












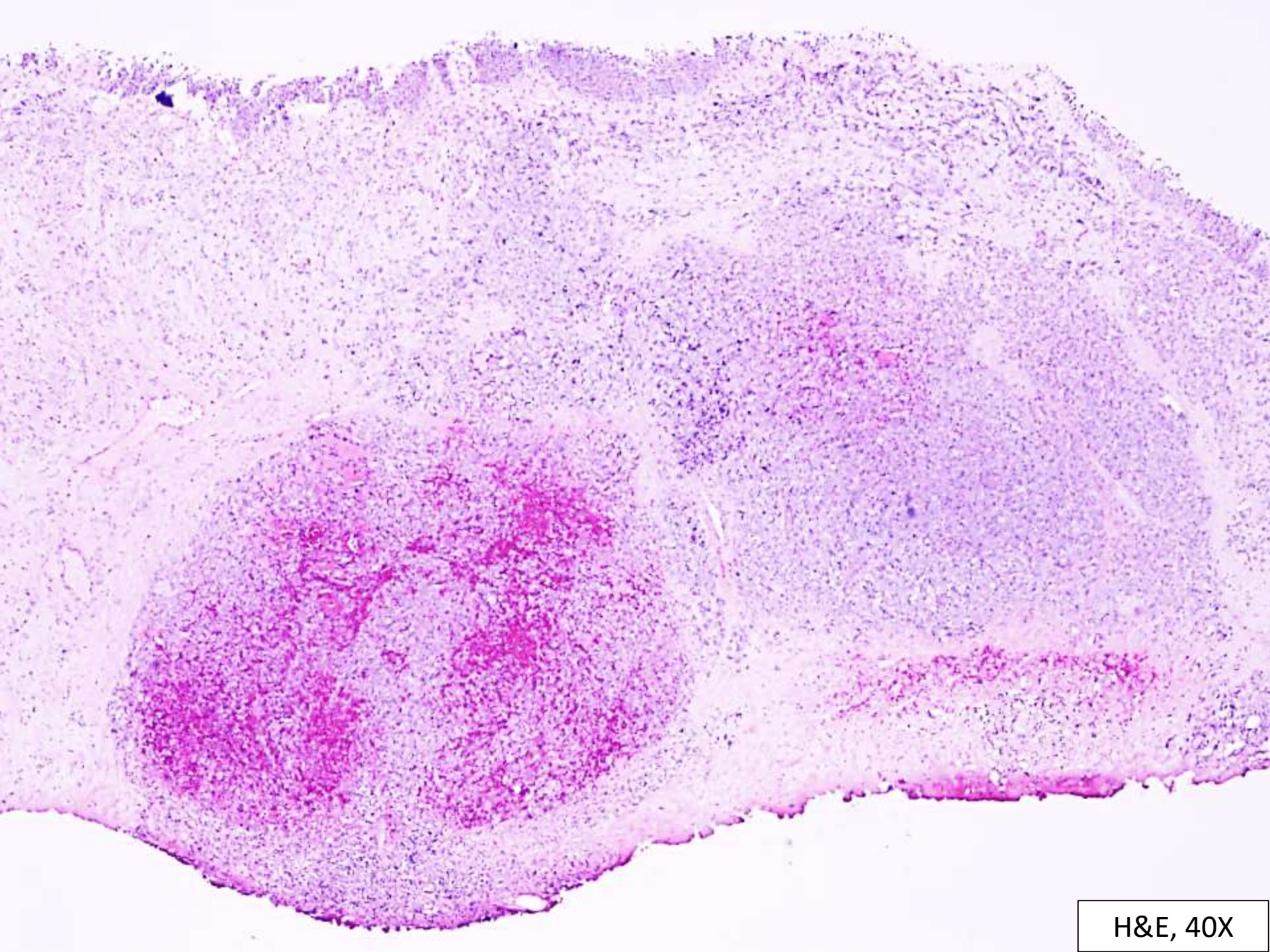
Clinical History

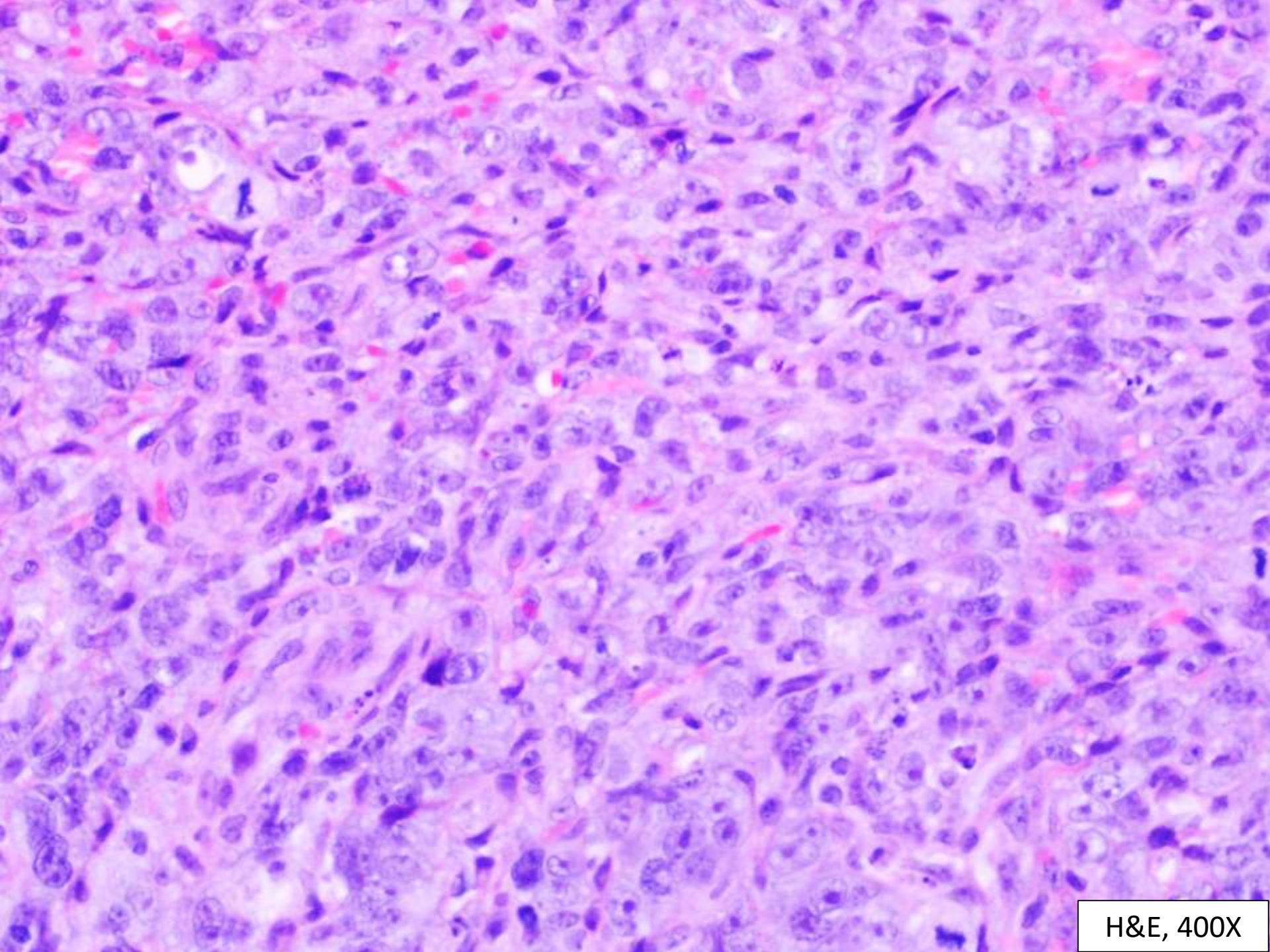
- Prostatic adenocarcinoma, Gleason score 4+4=8
- Treatment (2004):
  - Neoadjuvant and hormone therapy
  - External beam radiation to whole pelvis and brachytherapy
  - Received permanent prostate implant
- CT scan (8/2010) showed a mass involving the urinary bladder neck representing either prostate cancer recurrence or primary bladder tumor

Diagnosis:

Angiosarcoma with invasion into muscularis propria

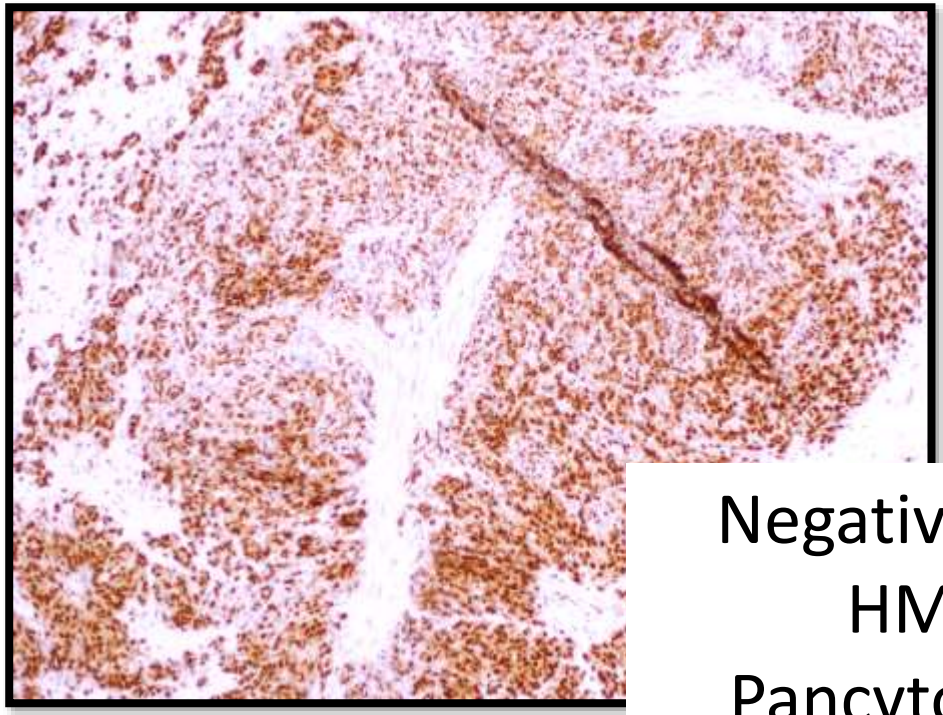
- Vascular proliferation with areas of solid growth
- Spindled and large pleomorphic cells with significant nuclear atypia, prominent nucleoli
- 1-2 mitoses per HPF

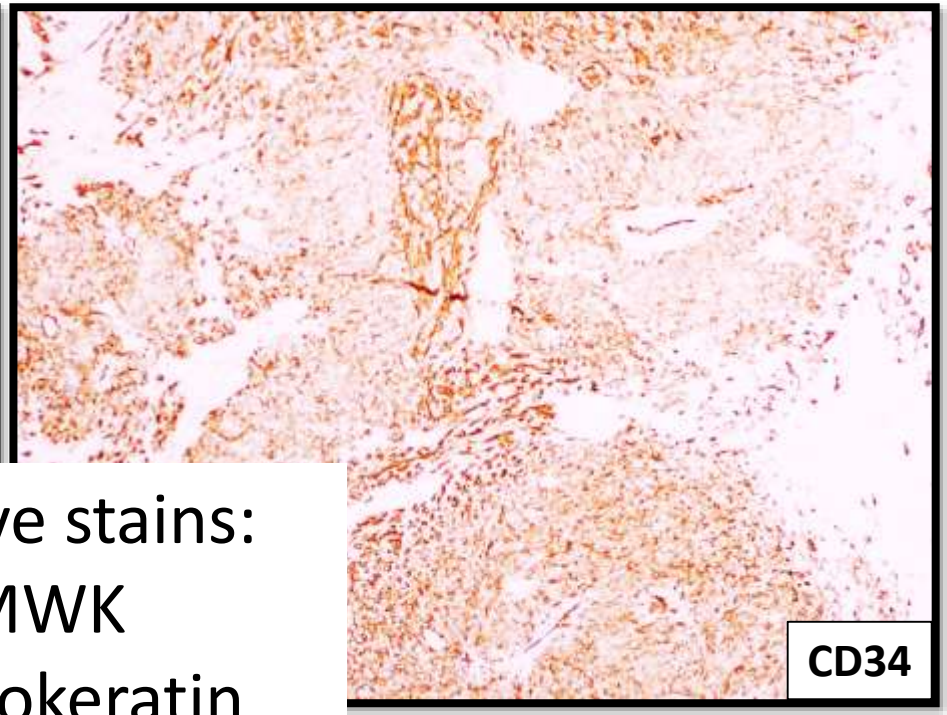

H&E, 40X


H&E, 400X

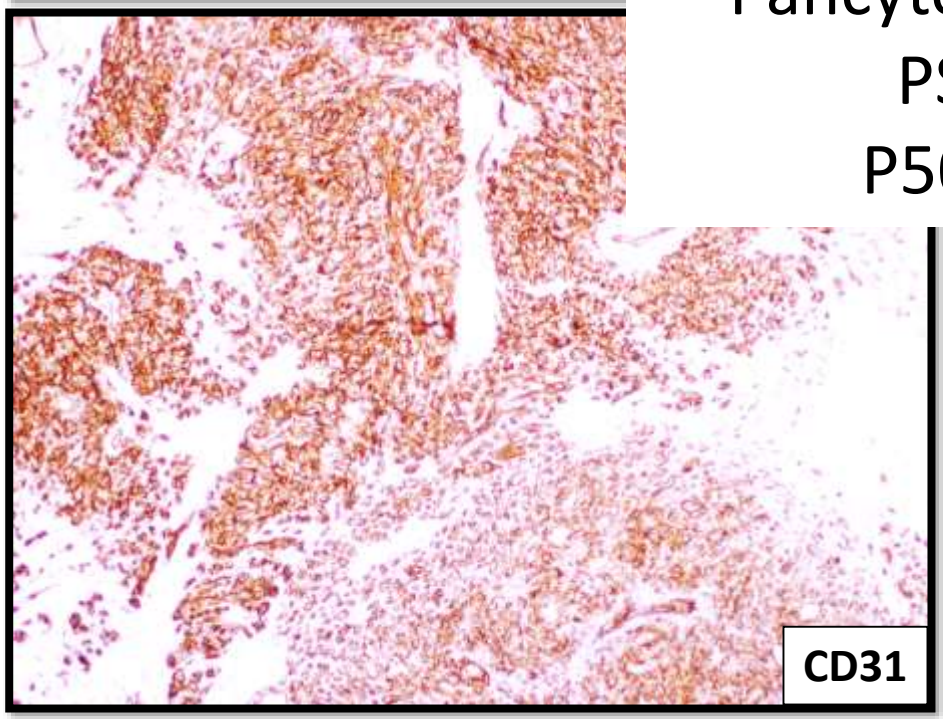
Differential Diagnosis

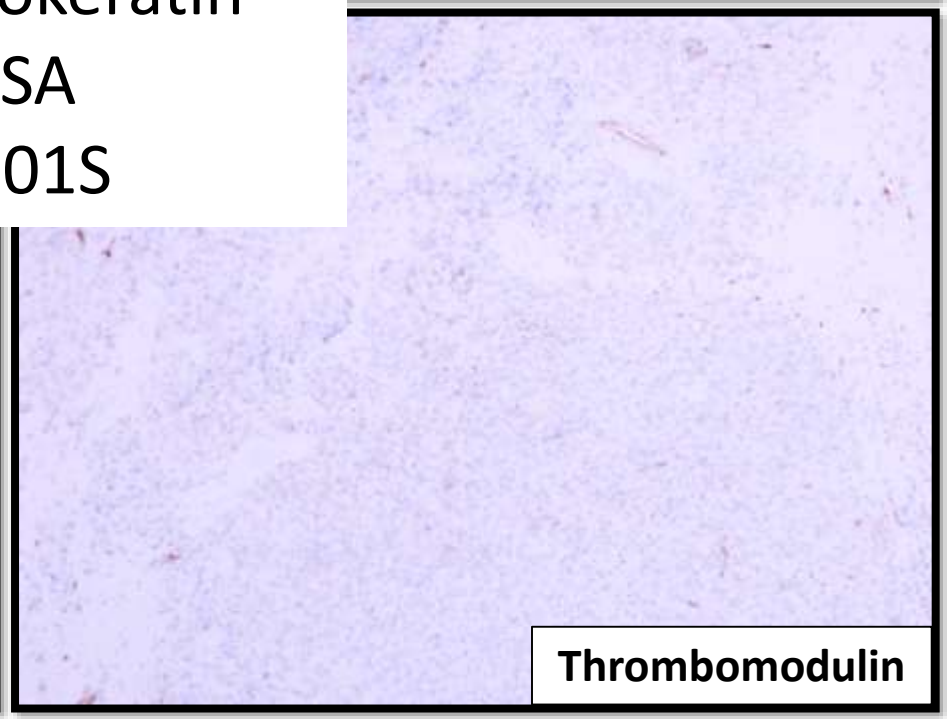
- Prostatic adenocarcinoma
- Angiosarcoma
- Epithelioid sarcoma
- Urothelial carcinoma
- Other malignancies





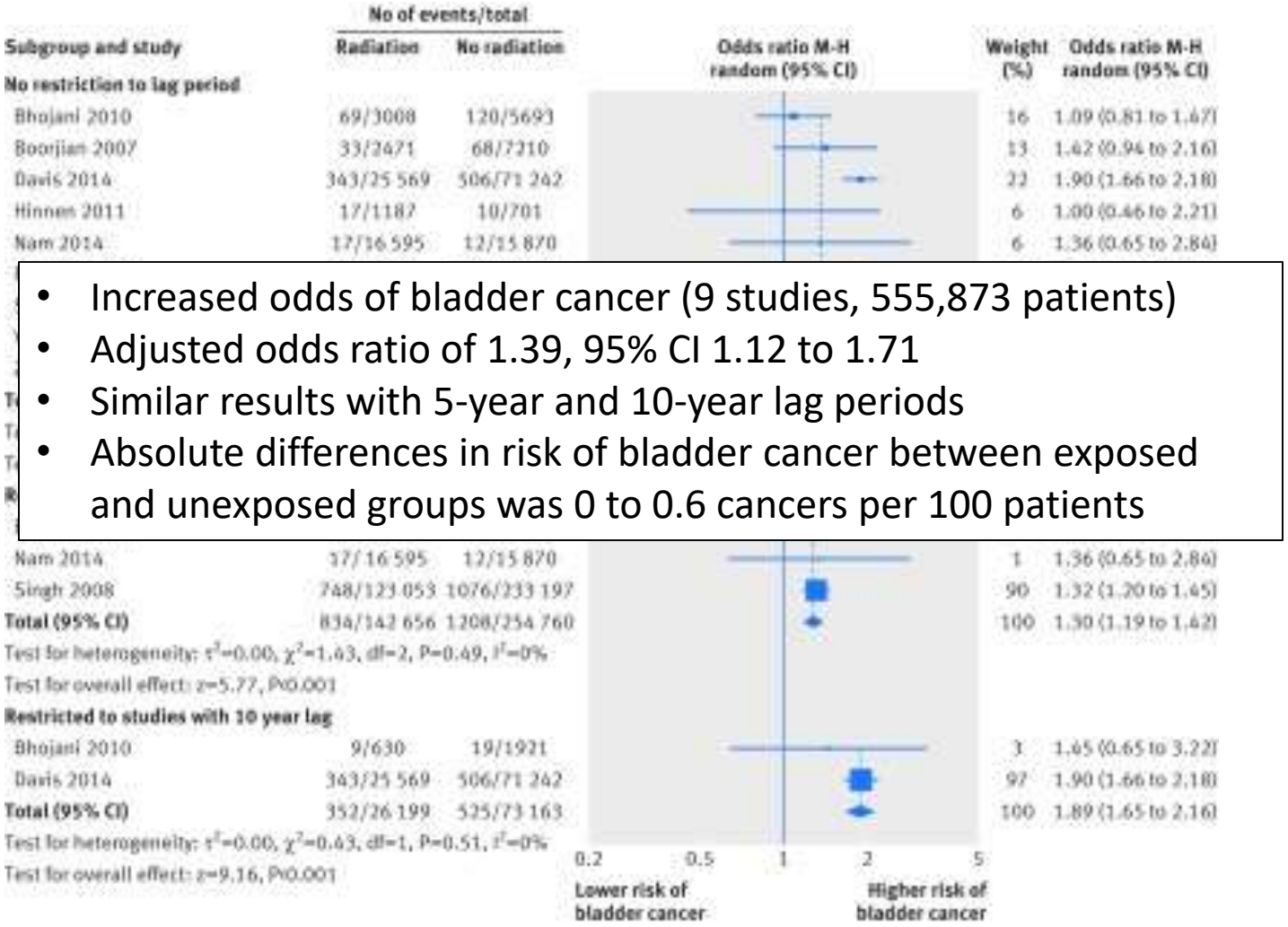
Negative stains:
HMWK
Pancytokeratin
PSA
P501S





- 1-3% of all sarcomas are radiation-associated
- In pediatric oncology patients, radiation is the strongest treatment-related contributor to development of solid tumors, including soft tissue tumors (linear dose-response relationship)
- Median latency period between radiation and sarcoma is ~12 years
- Most common types:
  - Undifferentiated pleomorphic sarcoma
  - Osteosarcoma
  - Angiosarcoma
    - Most often cutaneous site following breast RT
    - 0.1%-0.3% of post-radiation breast cancer patients develop angiosarcoma
- Most post-radiation sarcomas are high grade
- Nearly all post-radiation angiosarcomas demonstrate *MYC* amplification, but this may not be entirely specific for this entity
- Worse outcomes for radiation-induced UPS versus sporadic

Risk of bladder cancer following radiation for prostate cancer



- Increased odds of bladder cancer (9 studies, 555,873 patients)
- Adjusted odds ratio of 1.39, 95% CI 1.12 to 1.71
- Similar results with 5-year and 10-year lag periods
- Absolute differences in risk of bladder cancer between exposed and unexposed groups was 0 to 0.6 cancers per 100 patients

Wallis et al. BMJ vol 352; 2016.

	No lag restriction		
	Studies	No of patients	OR (95% CI)
Bladder cancer			
Versus no radiotherapy:			
Any radiotherapy	9	555 873	1.39 (1.12 to 1.71)*
EBRT	6	186 854	1.37 (1.05 to 1.77)*
Brachytherapy	3	161 889	1.25 (1.10 to 1.42)*

Wallis et al. BMJ vol 352; 2016.

Angiosarcoma of the bladder

- ~20 cases of angiosarcoma of the bladder have been reported
- 9 occurred after pelvic radiation
- One series showed 69% of cases were men

Ojerholm et al. The American Journal of Medicine, Vol 128, No 5, May 2015
Warne et al. BMJ Case Reports, 2011

Summary of findings in 9 bladder angiosarcoma cases arising after radiation

Age range / median (years)	47 - 83 / 71
Gender	5 males 4 females
Original tumor	Prostate cancer (N=4) Endometrial carcinoma (N=3) Ovarian dysgerminoma (N=1)
Range / median interval since radiotherapy / Type of radiation	Range: 8 months - 16 years / Median: 9 years / External beam (N=4); Intraperitoneal (N=1)
Clinical presentation	Gross painless hematuria (N=4) Painless microhematuria (N=1) Intermittent painless vaginal bleeding and hematuria (N=1) Perforated distal ileum (N=1)
Cytologic features	Epithelioid morphology (N=2)
Immunophenotype	4 cases had IHC data All were positive for at least one vascular marker None were positive for cytokeratins
Treatment	Cystoprostatectomy only (N=2) Cystoprostatectomy + chemotherapy (N=1) Cystoprostatectomy + referred for chemotherapy and radiation (N=1) Transurethral resection (N=1) Unresectable, palliative radiation administered (N=1)
Outcome	5 patients died of disease 2-14 months following diagnosis or surgery 2 patients alive after 19 months and 2.5 years

Our Case

- Treatment:
  - Radical cystoprostatectomy with bilateral pelvic lymph node dissection (10/15/2010)
  - Chemotherapy (through 3/2011)
- Developed diffuse osseous metastases (2/2011)
- Palliative care begun (3/2011); patient refused radiation
- Hospice (3/29/2011)

References

1. Keehn, A., Ludmir, E., Taylor, J., & Rabbani, F. (2017). Incidence of bladder cancer after radiation for prostate cancer as a function of time and radiation modality. *World J Urol, 35*(5), 713-720.
2. Morgan, M. A., Moutos, D. M., Pippitt, C. H., Jr., Suda, R. R., Smith, J. J., & Thurnau, G. R. (1989). Vaginal and bladder angiosarcoma after therapeutic irradiation. *South Med J, 82*(11), 1434-1436.
3. Nanus, D. M., Kelsen, D., & Clark, D. G. (1987). Radiation-induced angiosarcoma. *Cancer, 60*(4), 777-779.
4. Navon, J. D., Rahimzadeh, M., Wong, A. K., Carpenter, P. M., & Ahlering, T. E. (1997). Angiosarcoma of the bladder after therapeutic irradiation for prostate cancer. *J Urol, 157*(4), 1359-1360.
5. Ojerholm, E., Stripp, D., Mamtani, R., Van Arsdalen, K., & Tripp, P. (2015). Angiosarcoma of the bladder following prostate radiotherapy. *Am J Med, 128*(5), e11-12.
6. Seethala, R. R., Gomez, J. A., & Vakar-Lopez, F. (2006). Primary angiosarcoma of the bladder. *Arch Pathol Lab Med, 130*(10), 1543-1547. d
7. Sholl, L. M., Barletta, J. A., & Hornick, J. L. (2017). Radiation-associated neoplasia: clinical, pathological and genomic correlates. *Histopathology, 70*(1), 70-80.
8. Tavora, F., Montgomery, E., & Epstein, J. I. (2008). A series of vascular tumors and tumorlike lesions of the bladder. *Am J Surg Pathol, 32*(8), 1213-1219.
9. Wallis, C. J., Mahar, A. L., Choo, R., Herschorn, S., Kodama, R. T., Shah, P. S., . . . Nam, R. K. (2016). Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ, 352*, i851.
10. Warne, R. R., Ong, J. S., Snowball, B., & Vivian, J. B. (2011). Primary angiosarcoma of the bladder in a young female. *BMJ Case Rep, 2011*.
11. Williams, S., Romaguera, R., & Kava, B. (2008). Angiosarcoma of the bladder: case report and review of the literature. *ScientificWorldJournal, 8*, 508-511.

Angiosarcomas of the bladder arising after radiation

Source	Age/ sex	Original tumor	Interval since radiotx/type tx	Clinical Presentation
Seethala et al. Arch Pathol Lab Med, Vol 130, Oct 2006	66/M		4 years	Gross painless hematuria
Navon et al. The Journal of Urology, Vol 157, April 1997	78/M	Prostatic adenocarcinoma	13 years/External beam radiation	Gross painless hematuria
Morgan et al. South Med J, Vol 82, Nov 1989	72/F	Endometrial adenocarcinoma	9 years/Intraperitoneal radium	Intermittent painless vaginal bleeding and hematuria
Ojerholm et al. The American Journal of Medicine, Nov 2014	61/M	Prostate cancer Gleason 4+3	7 years	Gross hematuria
Tavora et al. AM J Surg Pathol, Vol 32, Aug 2008	73/F	Endometrial carcinoma	17 months	
Tavora et al. AM J Surg Pathol, Vol 32, Aug 2008	71/M	Prostatic adenocarcinoma	8 months	
Williams et al. Scientific World Journal, Vol 8, 2008	71/M	Prostate cancer	10 years/external beam radiation	Gross painless hematuria
Nanus et al. Cancer, Vol 60, 1997	47/F	Ovarian dysgerminoma	16 years/30 treatments of 250 KV x-ray to a total of 4800 rad to the lower abdomen	Perforated distal ileum
Kuluga et al. Virchows Arch, Vol 450, 2007	83/F	Endometrioid adenocarcinoma	14 years/external beam radiation	Painless microhematuria

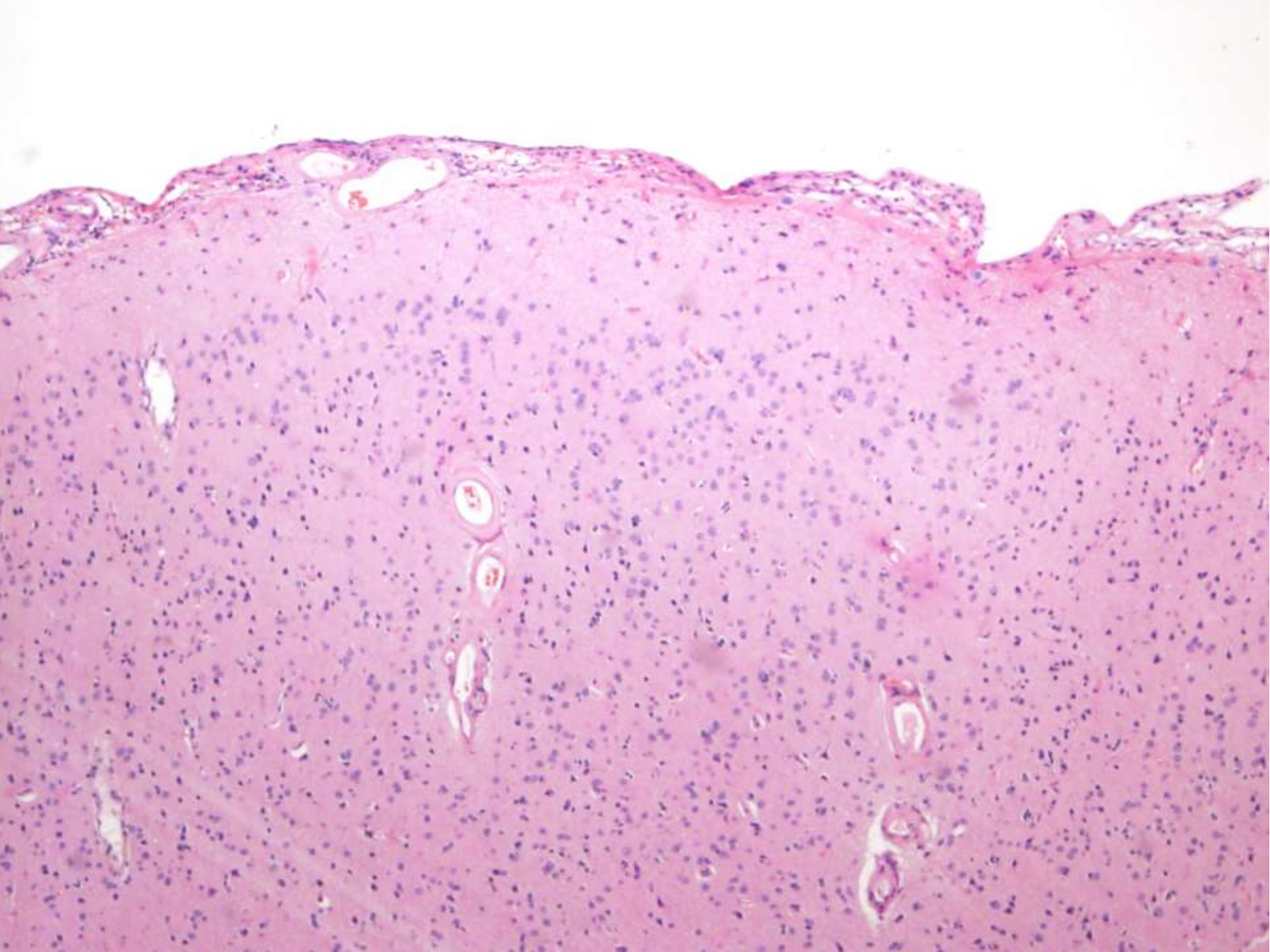
Angiosarcomas of the bladder arising after radiation

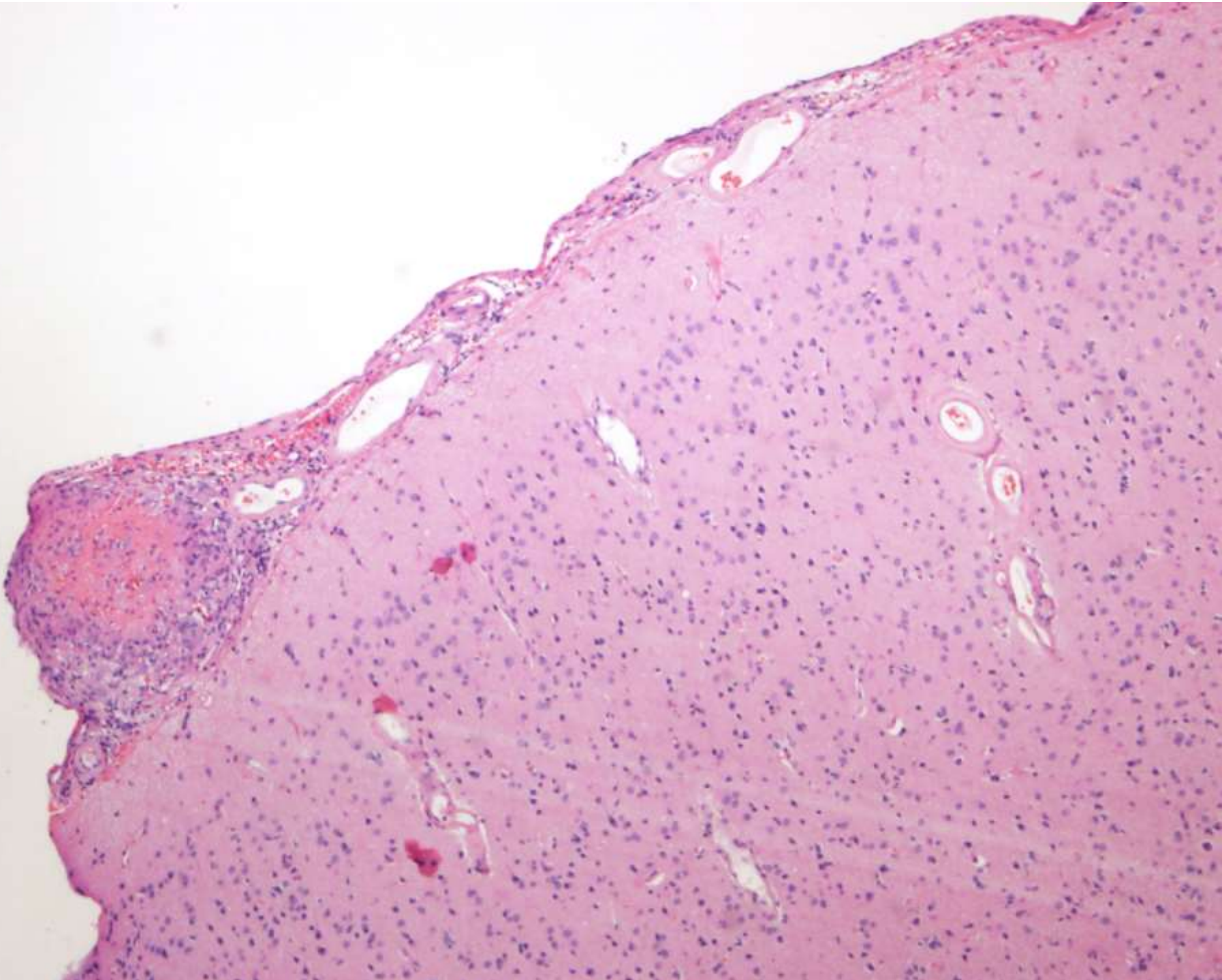
Source	Architecture/Cytologic Features	IHC	Treatment	Outcome
Seethala et al. Arch Pathol Lab Med Vol 130, Oct 2006	Solid, focally primitive/Epithelioid and spindled	CD31+ CD34+ CK-	Cystoprostatectomy, chemo	Alive and well after 19 months
Navon et al. The Journal of Urology, Vol 157, April 1997	Anastomosing vascular spaces/atypical endothelial cells, rare mitoses	F. VIII+ CD34+ Ulex europaeus lectin-	Cystoprostatectomy	Disease free after 2.5 years
Ojerholm et al. The American Journal of Medicine, Nov 2014			Cystoprostatectomy	No disease after 4 months
Tavora et al. AM J Surg Pathol, Vol 32, Aug 2008	Anastomosing vascular spaces, necrosis, invading MP/atypical endothelial cells			Died of disease after 2 months
Tavora et al. AM J Surg Pathol, Vol 32, Aug 2008	Anastomosing vascular spaces, necrosis, invading MP/atypical endothelial cells			Died of disease after 4 months
Williams et al. Scientific World Journal, Vol 8, 2008	Anastomosing vascular spaces/Epithelioid cells	CD31+ CD34+ F. VIII+	Cystoprostatectomy, pelvic lymph node dissection, referred for chemoradiation	Died of disease 3 months after surgery
Nanus, et al. Cancer, Vol 60, 1997			Unresectable, palliative radiation given	Died of disease 14 months following bladder dx
Kuluga et al. Virchows Arch, Vol 450, 2007	Sheet-like growth, necrosis/epithelioid cells	CD31+ F. VIII- CD34-CK-	Transurethral resection	Died of disease after 3 months

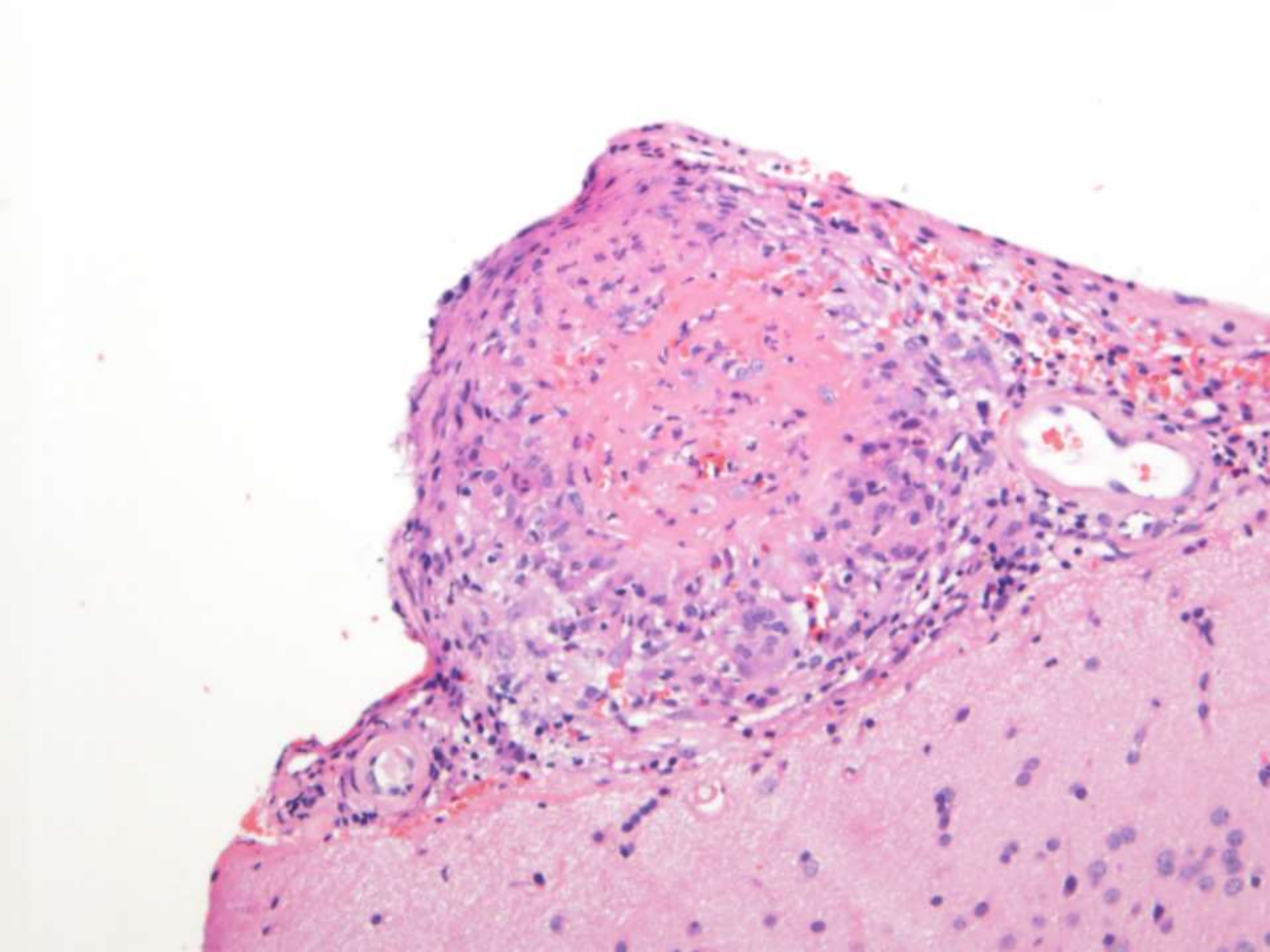
SB 6225

Jonathan Lavezo/Hannes Vogel; Stanford

69-year-old female with a nine year history of MS currently treated with teriflunomide, 10 months of cough and shortness of breath with CT findings concerning for ILD and lung biopsy showing non-necrotizing granulomas, possible organizing pneumonia, and scattered eosinophils, is admitted to the hospital with confusion, motor disturbance and hallucinations.

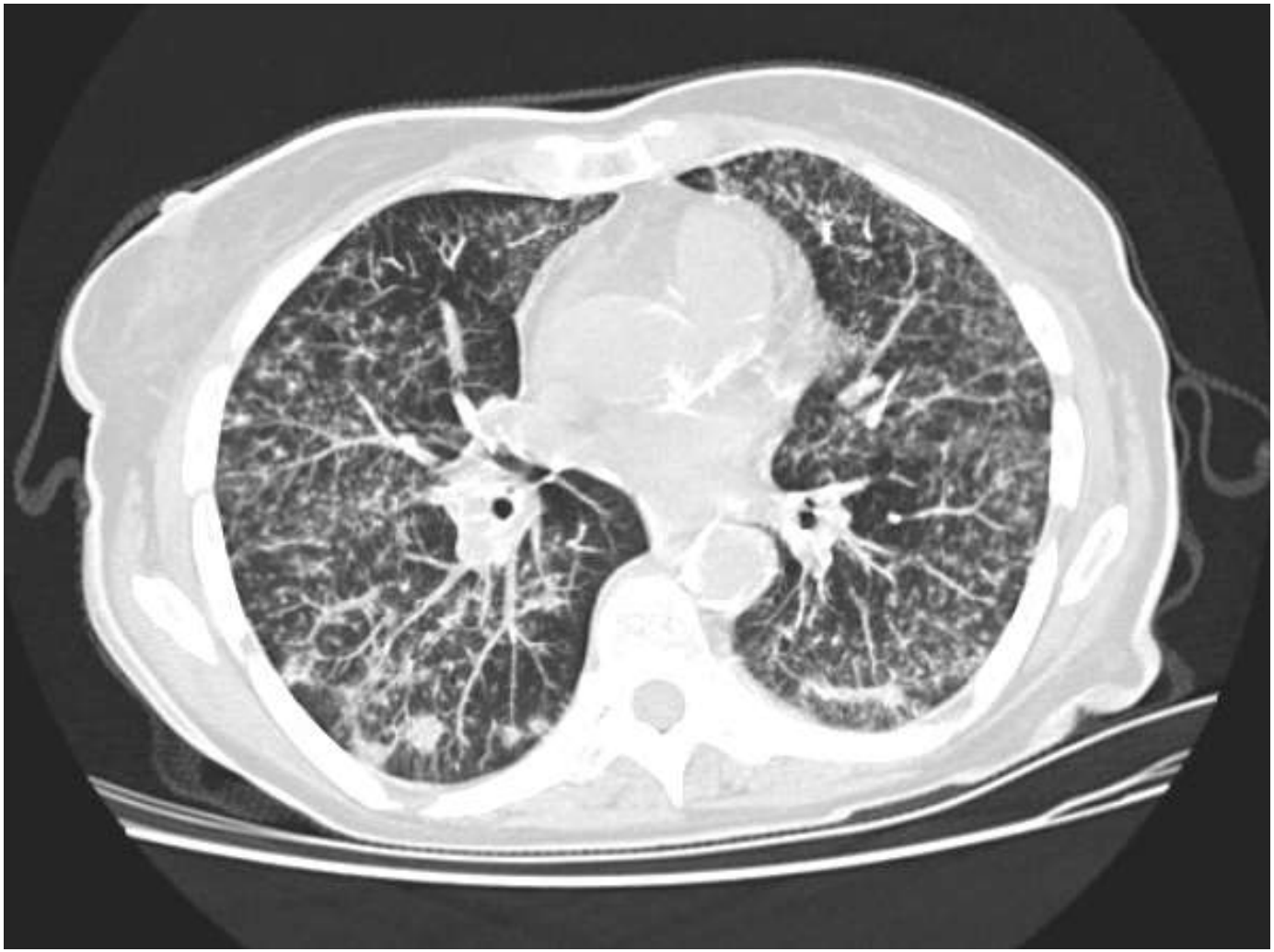






Clinical History

- 2008: Diagnosed with multiple sclerosis
- 2016: Transitioned care to SUH neurology
- January 2017: Developed a persistent dry cough and shortness of breath
- April 2017: Evaluated by PCP for symptoms
  - Chest X-ray/CT



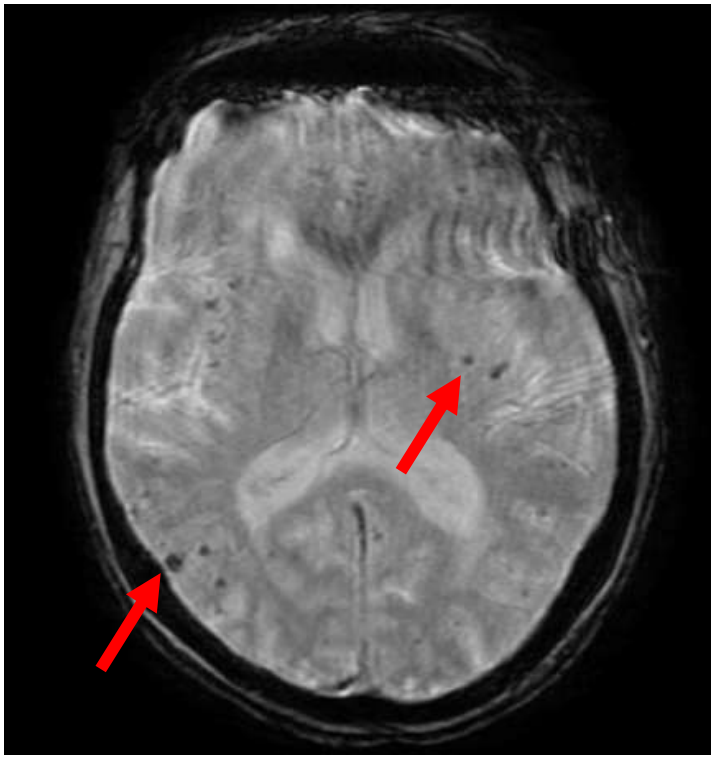
Clinical History

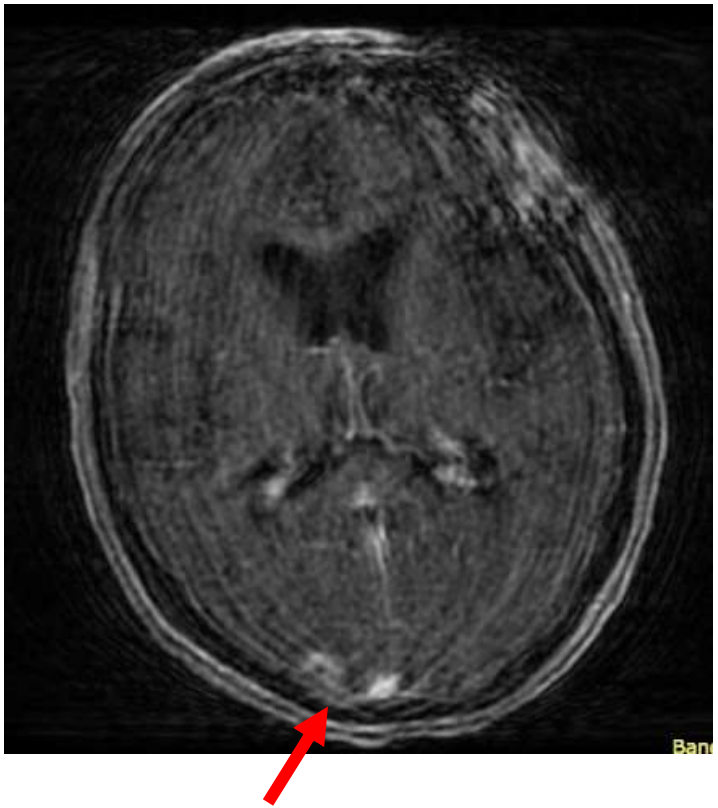
- Referred to pulmonology
- June 2017: Video Assisted Thorascopic Surgery (VATS) lung biopsy preformed
- July 2017: Biopsy sent to Stanford for pathology consultation

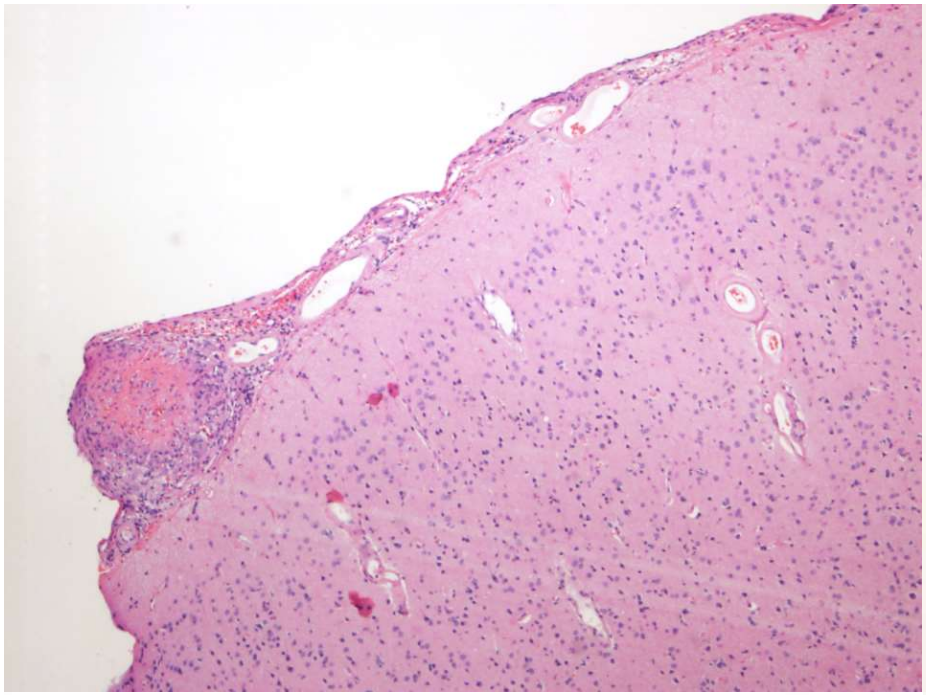
Case Presentation

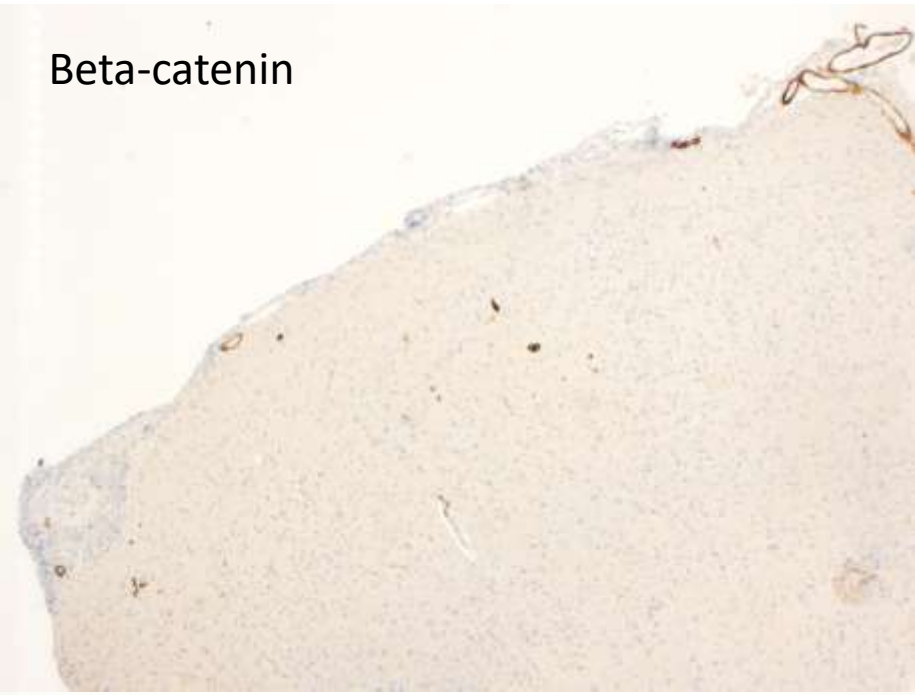
- Received several courses of clarithromycin and azithromycin without improvement and ultimately diagnosed with ILD
- Mid September 2017: had colonoscopy for work up of positive stool occult blood test, no malignancy found
- Family notes precipitous cognitive decline after colonoscopy
- September 28, 2017: presented to her PCP with several weeks of increasing confusion, difficulty walking, and visual hallucinations with continued shortness of breath
- Sent to the ER at Good Samaritan Hospital where she was admitted
- Brain biopsy at Good Samaritan Hospital performed

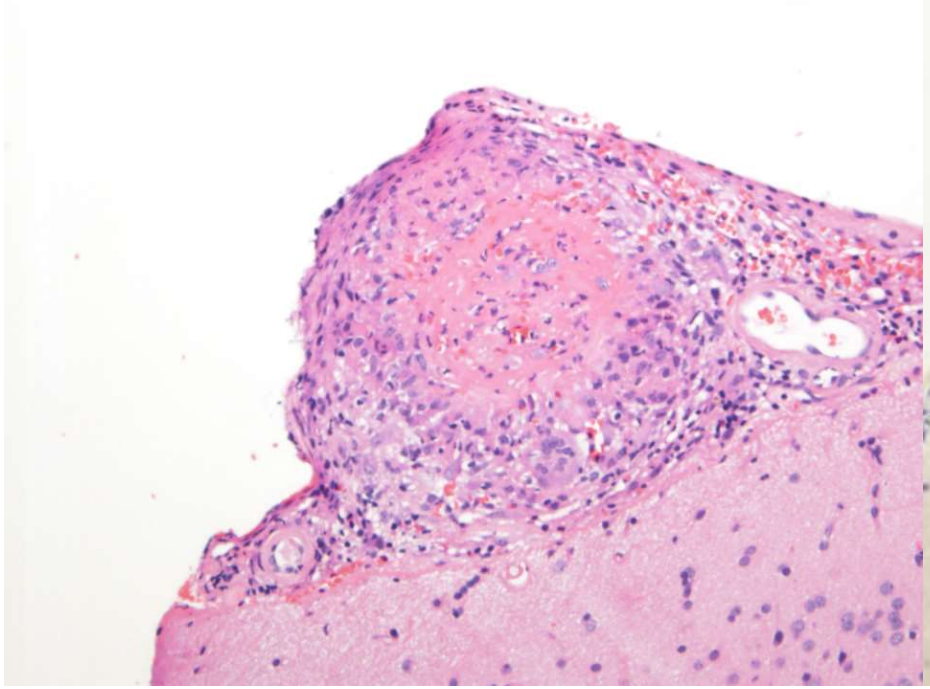
Stanford Imaging

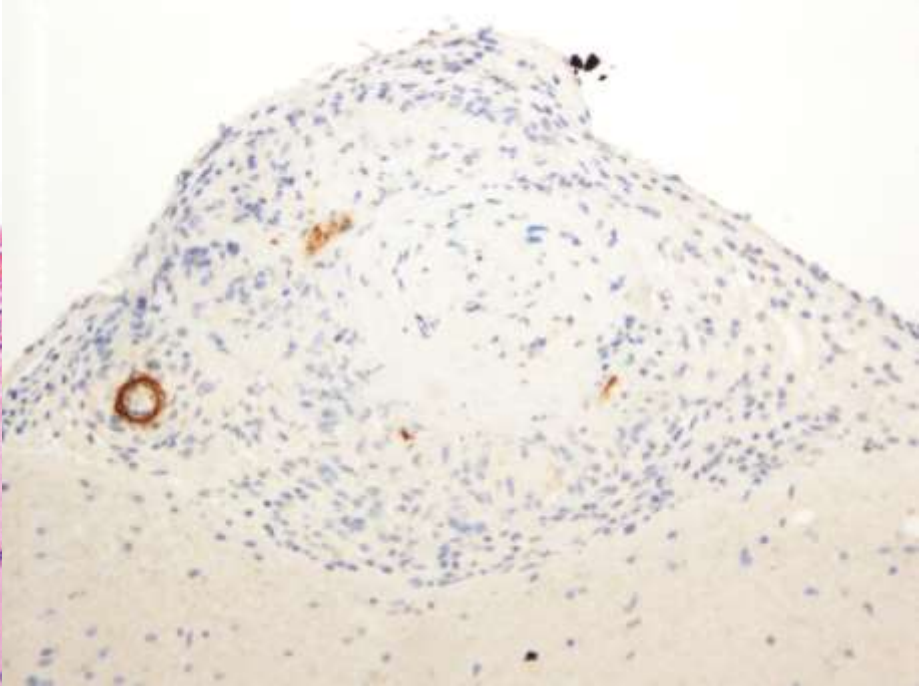







Beta-catenin





Diagnosis

- GRANULOMATOUS ANGIITIS
- CEREBRAL AMYLOID ANGIOPATHY

Inflammatory Cerebral Amyloid Angiopathy, Amyloid-β–Related Angiitis, and Primary Angiitis of the Central Nervous System

Similarities and Differences

Aimen Moussaddy, MD; Ariel Levy, MD, FRCP; Daniel Strbian, MD, PhD; Sophia Sundararajan, MD, PhD; France Berthelet, MD, FRCP; Sylvain Lanthier, MD, OD, CSPQ

Review

International Journal of Stroke WSO

Cerebral amyloid angiopathy associated with inflammation: A systematic review of clinical and imaging features and outcome

Andrej Corovic[1], Siobhan Kelly[1] and Hugh S Markus[2]

International Journal of Stroke
0(0) 1–11

DOI: 10.1177/1747493017741569
journals.sagepub.com/home/wso
SAGE

Cerebral amyloid angiopathy (CAA)

Deposition of amyloid-beta (AB) in walls of small/medium blood vessels, mostly in arteries of leptomeninges and cerebral cortex

- Architectural disruption of AB laden vessels leads to vascular rupture and lobar hemorrhage or microbleeds.
- Accumulation of AB causes vessel occlusion, leading to ischemic leukoencephalopathy and cerebral infarction

CAA associated with inflammation (CAA-I)

Inflammatory response to the vascular deposits of AB in the brain with two variants:

1. Predominantly perivascular inflammatory infiltrates (cerebral amyloid angiopathy-related inflammation – **CAARI**)
2. Transmural vasculitis process with or without granuloma formation (A-beta related angiitis – **ABRA**)

Inflammatory Cerebral Amyloid Angiopathy, Amyloid-β–Related Angiitis, and Primary Angiitis of the Central Nervous System

Similarities and Differences

Aimen Moussaddy, MD; Ariel Levy, MD, FRCP; Daniel Strbian, MD, PhD; Sophia Sundararajan, MD, PhD; France Berthelet, MD, FRCP; Sylvain Lanthier, MD, OD, CSPQ

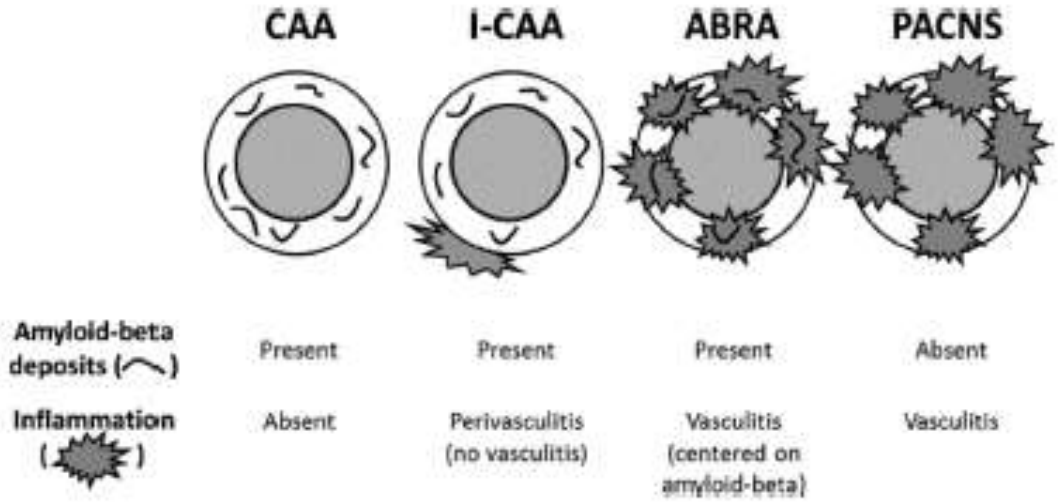


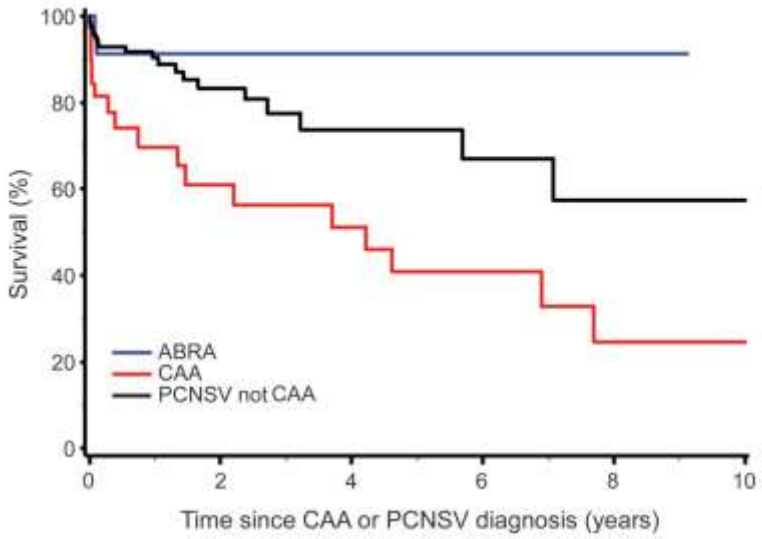
Figure 3. Distinctive histopathologic changes of cerebral amyloid angiopathy (CAA), inflammatory CAA (I-CAA), amyloid-β-related angiitis (ABRA), and primary angiitis of the central nervous system (PACNS).

Aβ-related angiitis

Comparison with CAA without inflammation and primary CNS vasculitis

Carlo Salvarani, MD
Gene G. Hunder, MD
Jonathan M. Morris, MD
Robert D. Brown, Jr., MD, MPH
Teresa Christianson
Caterina Giannini, MD, PhD

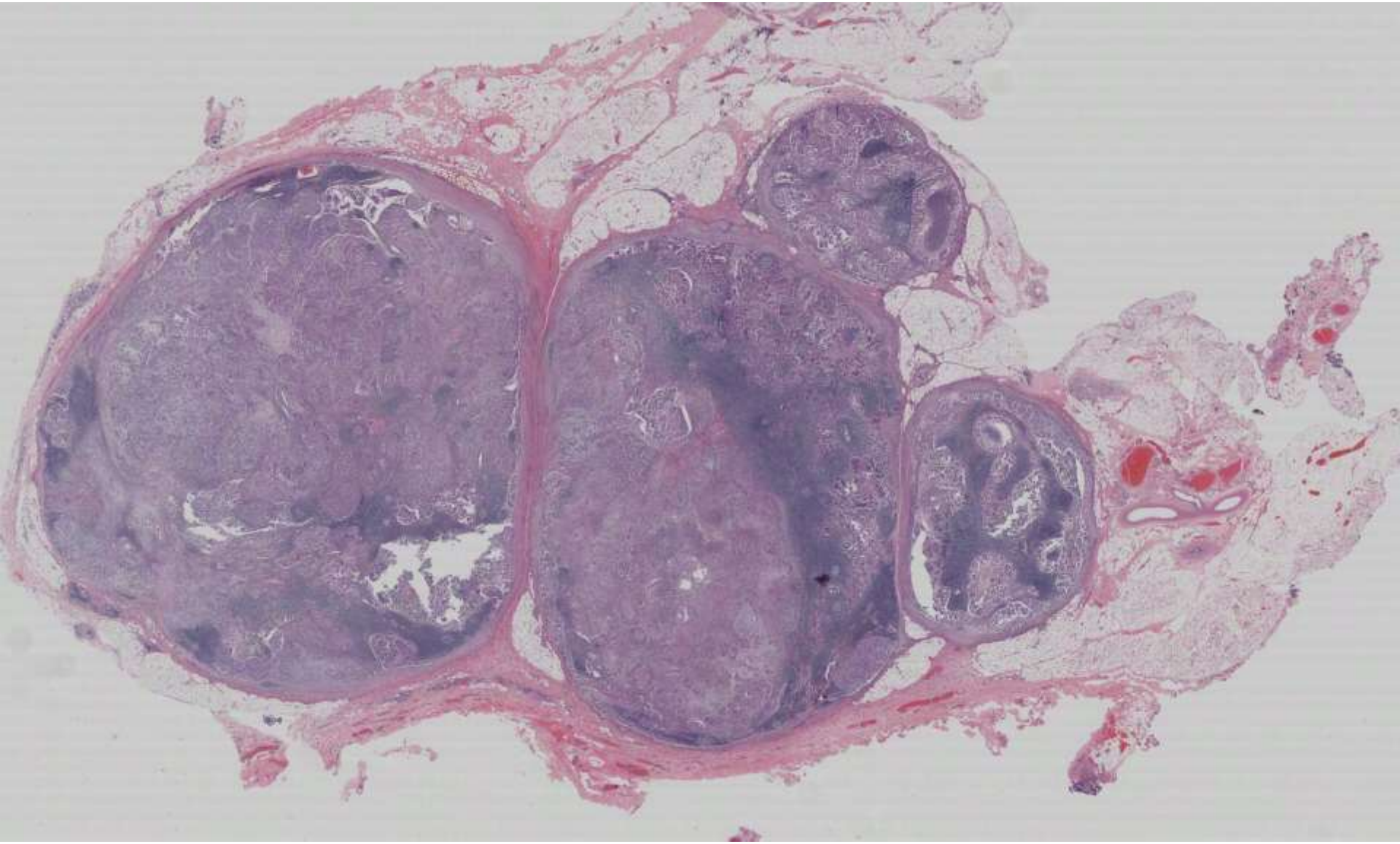
Figure 2 Survival curves of patients with ABRA, CAA, and PCNSV

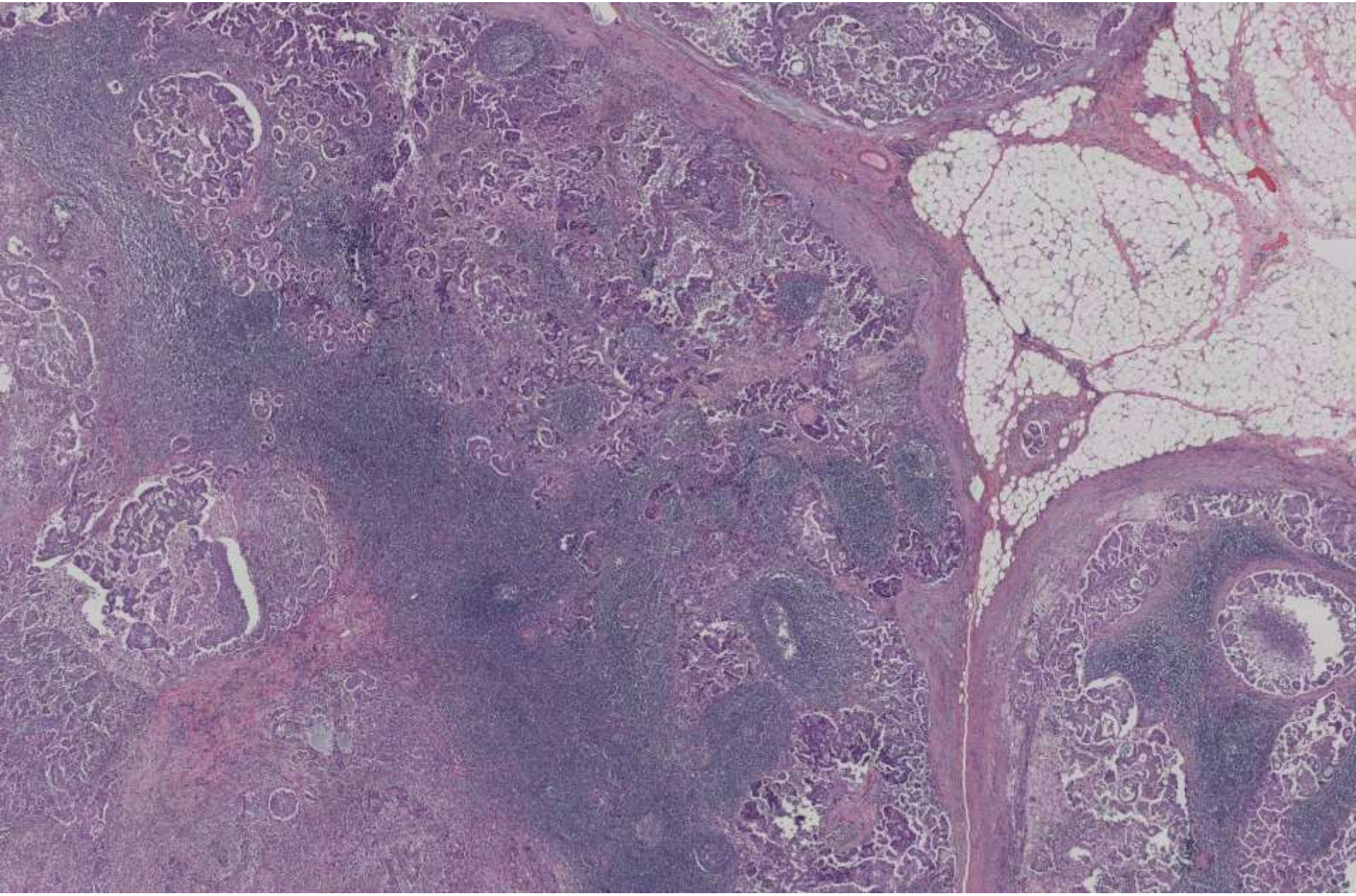


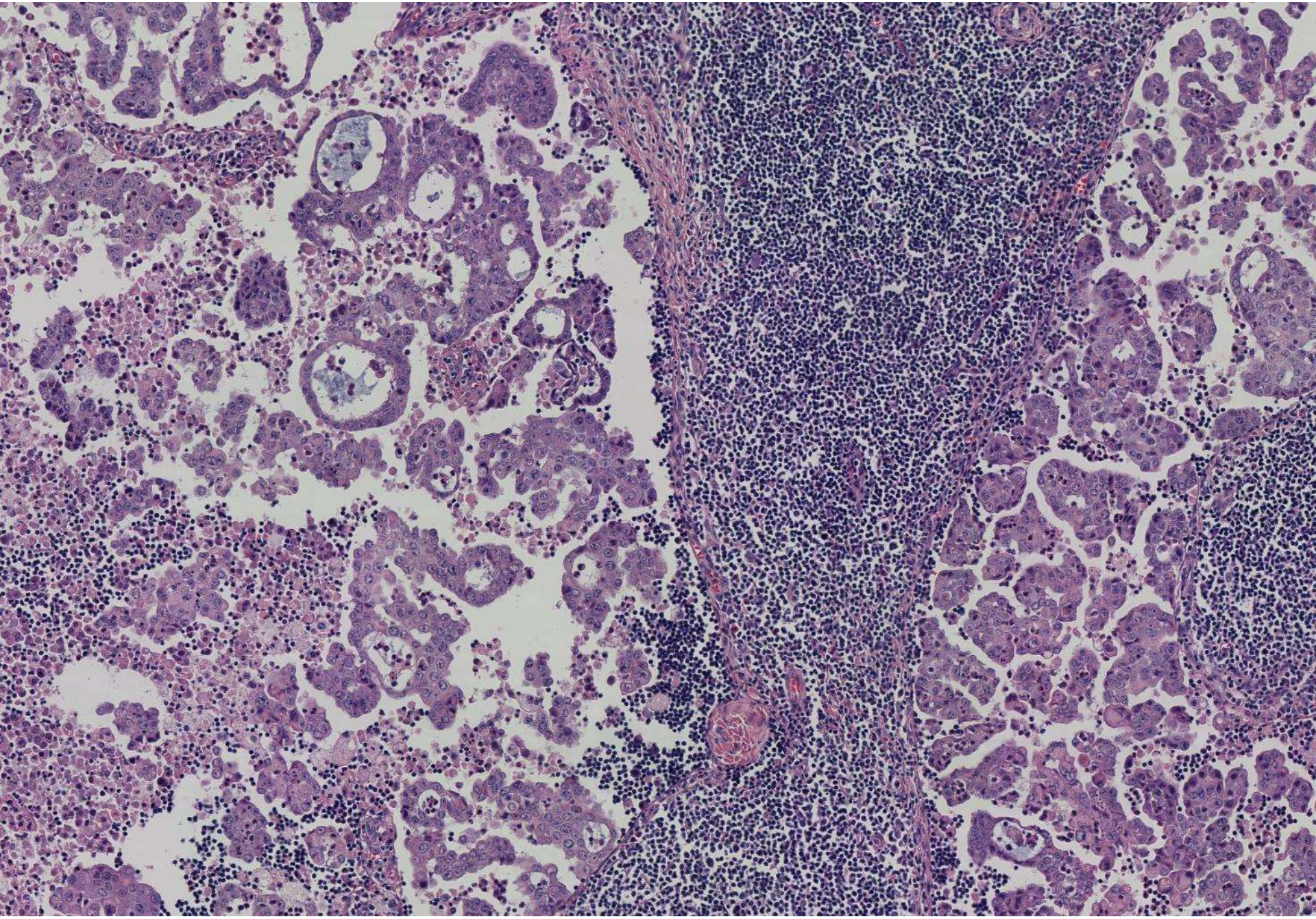
SB 6226
(scanned slide available)

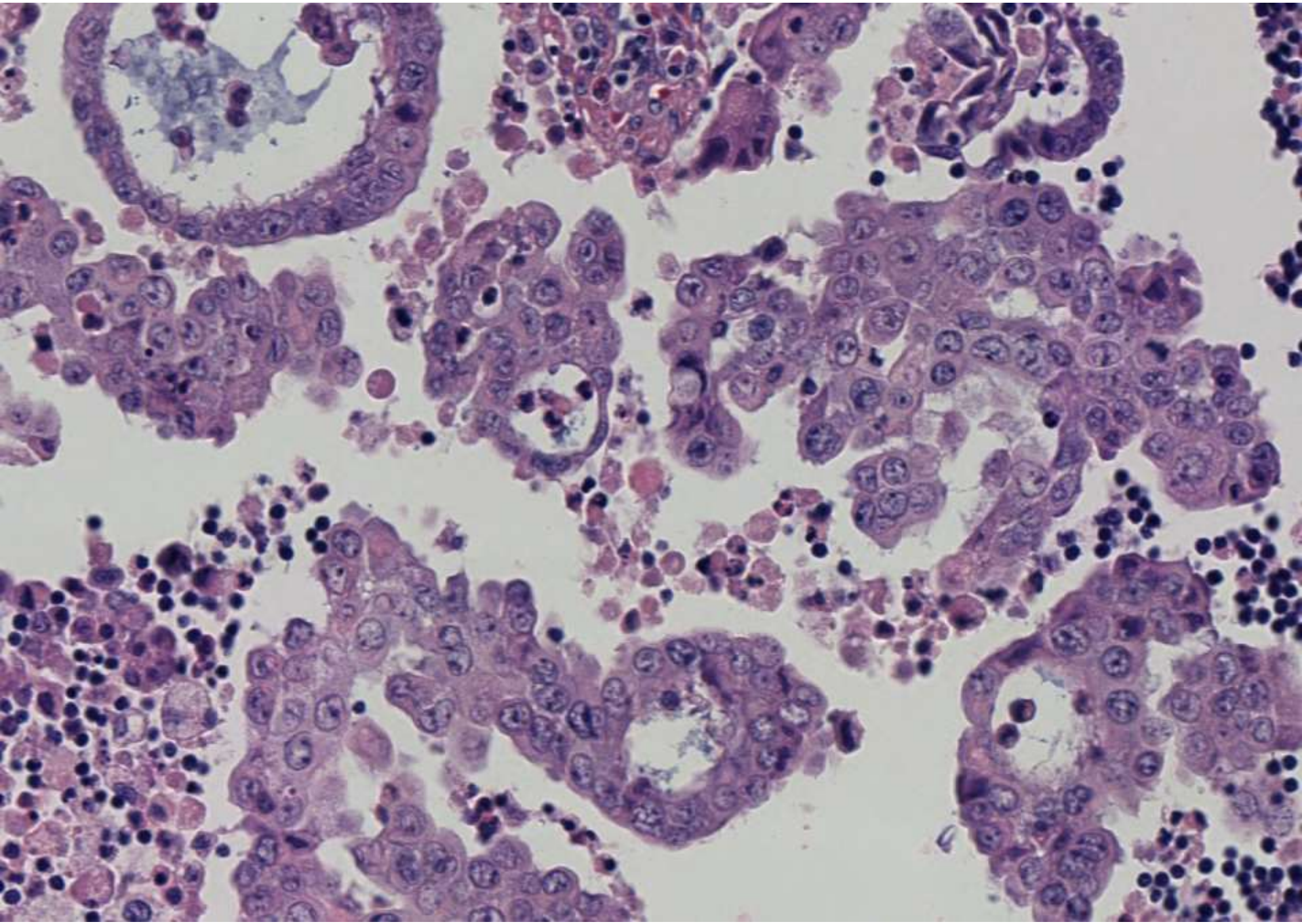
Eliah Shamir/Jessica Davis: UCSF

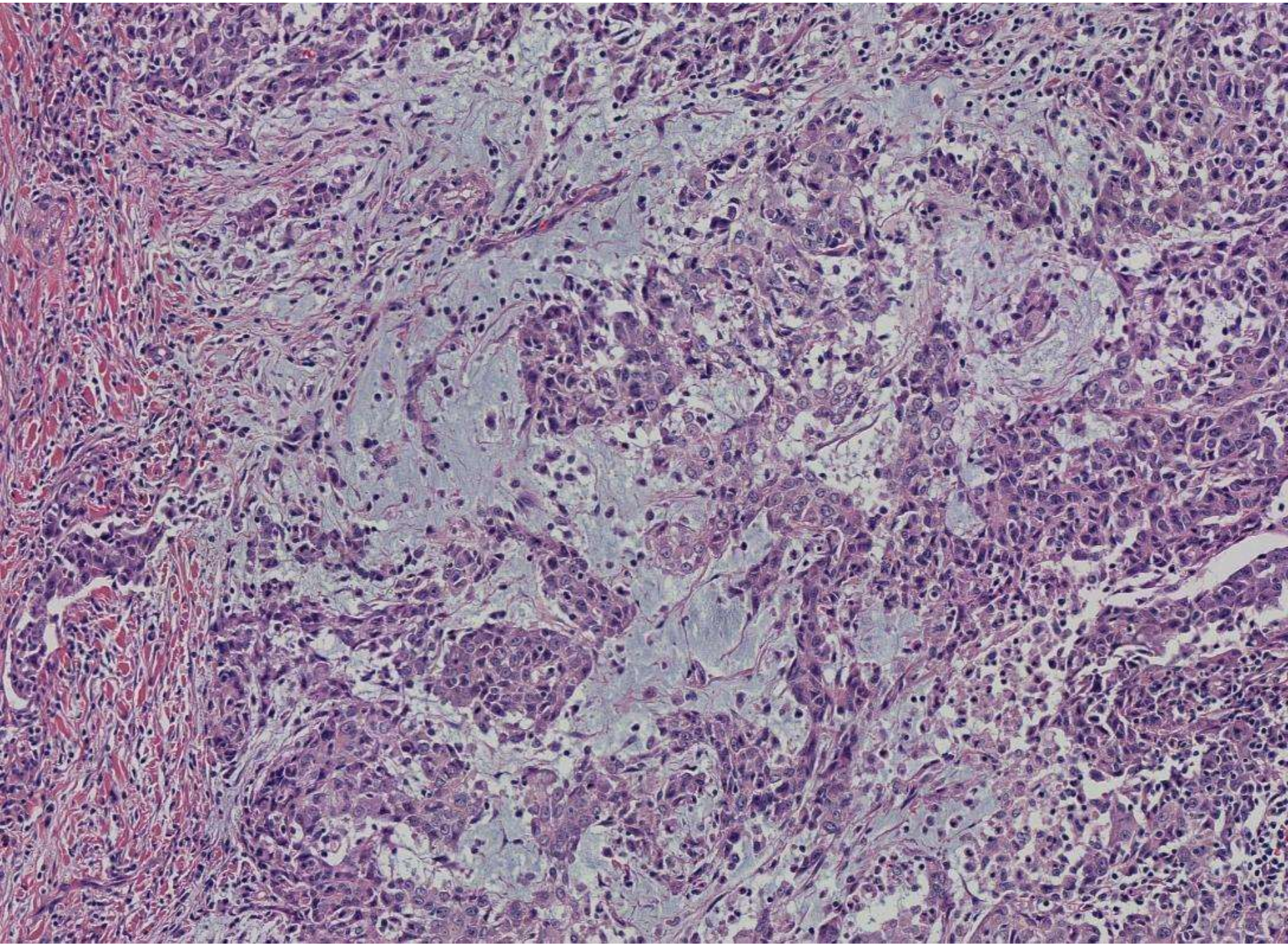
26-year-old female presented with 3-month h/o bilateral cervical lymphadenopathy, dysphagia, night sweats, and SOB. CT neck showed bilateral level 2-5 lymphadenopathy and a mediastinal/ thymic mass. FNA of right supraclavicular LN was diagnosed as poorly differentiated

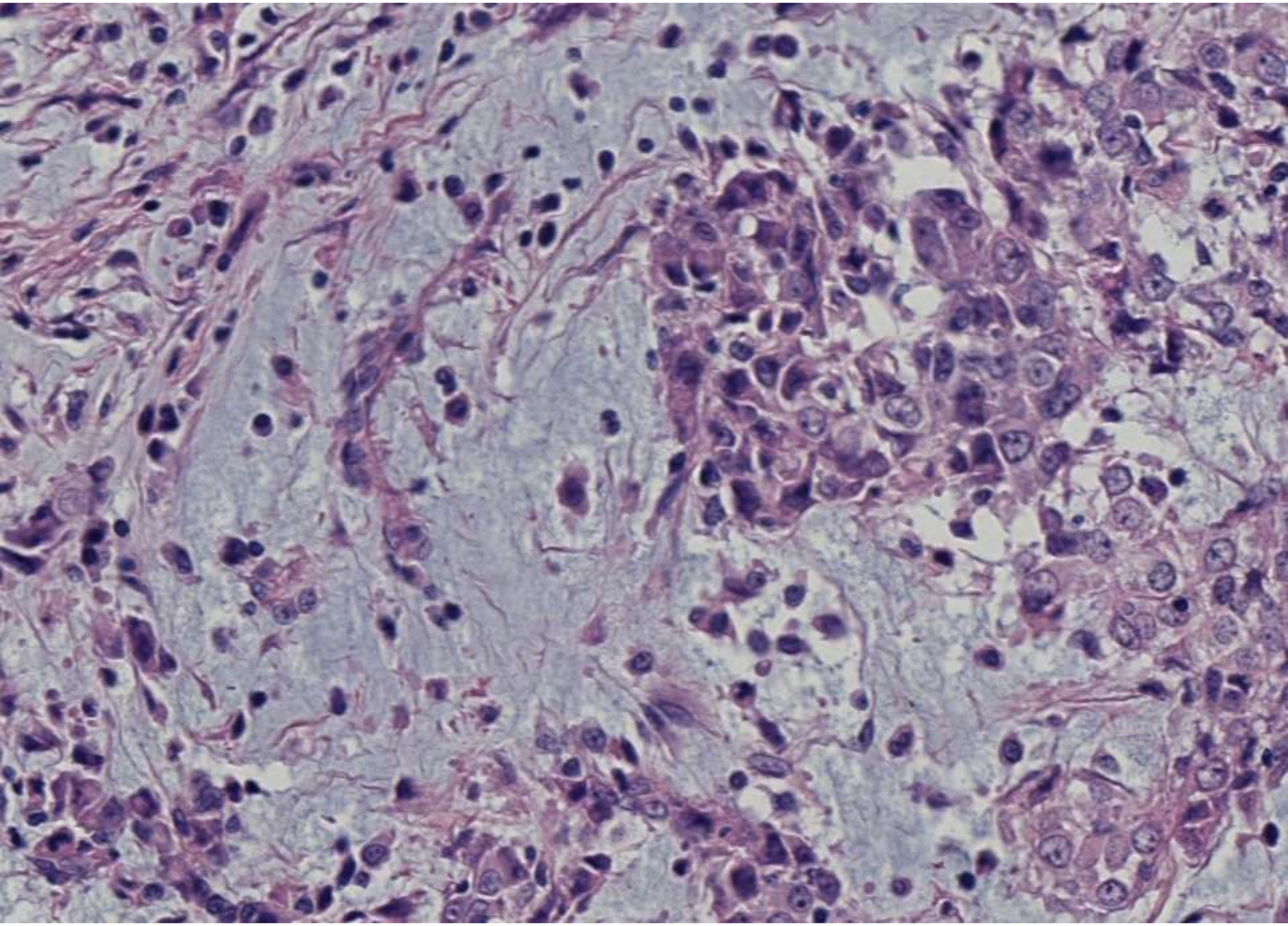


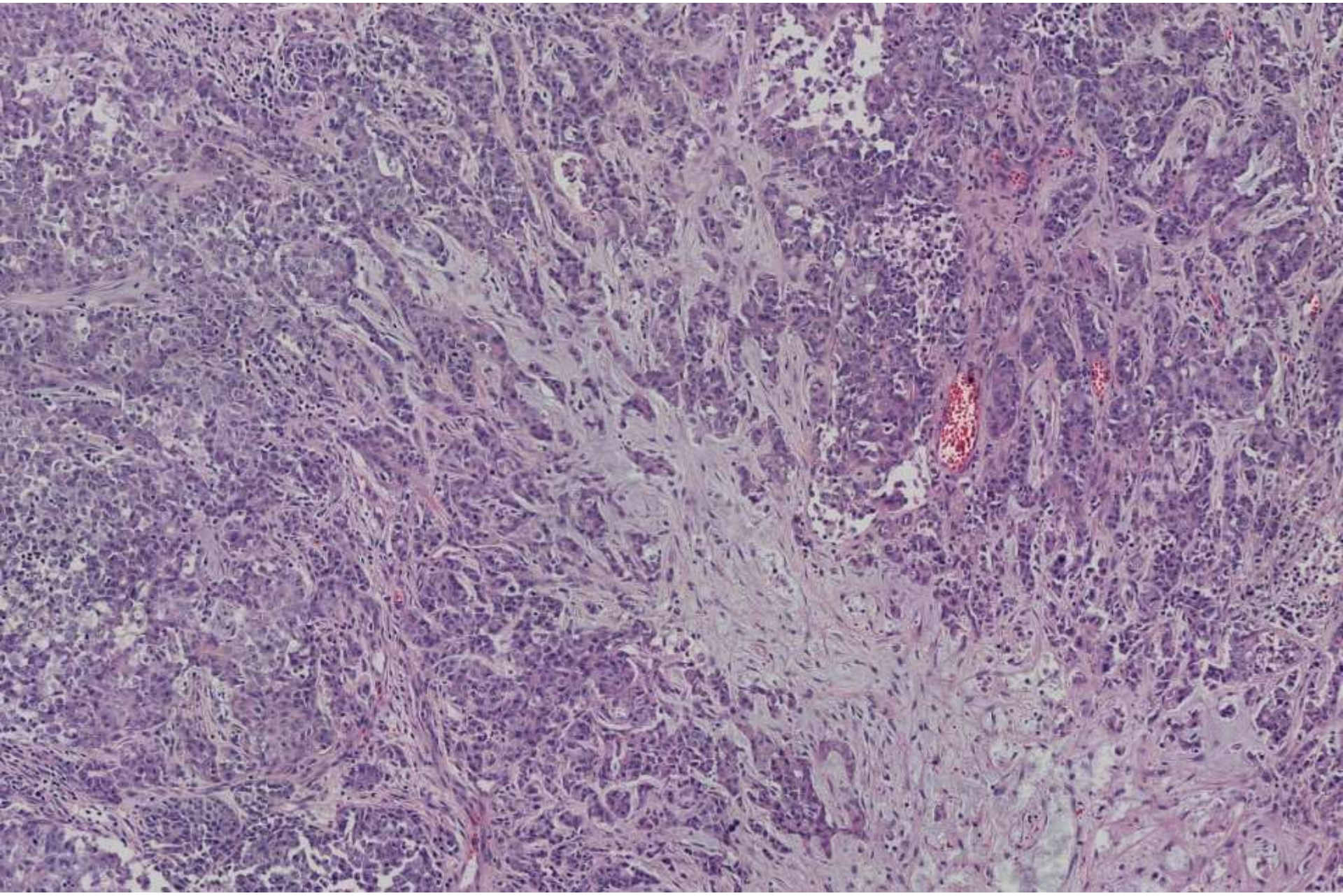


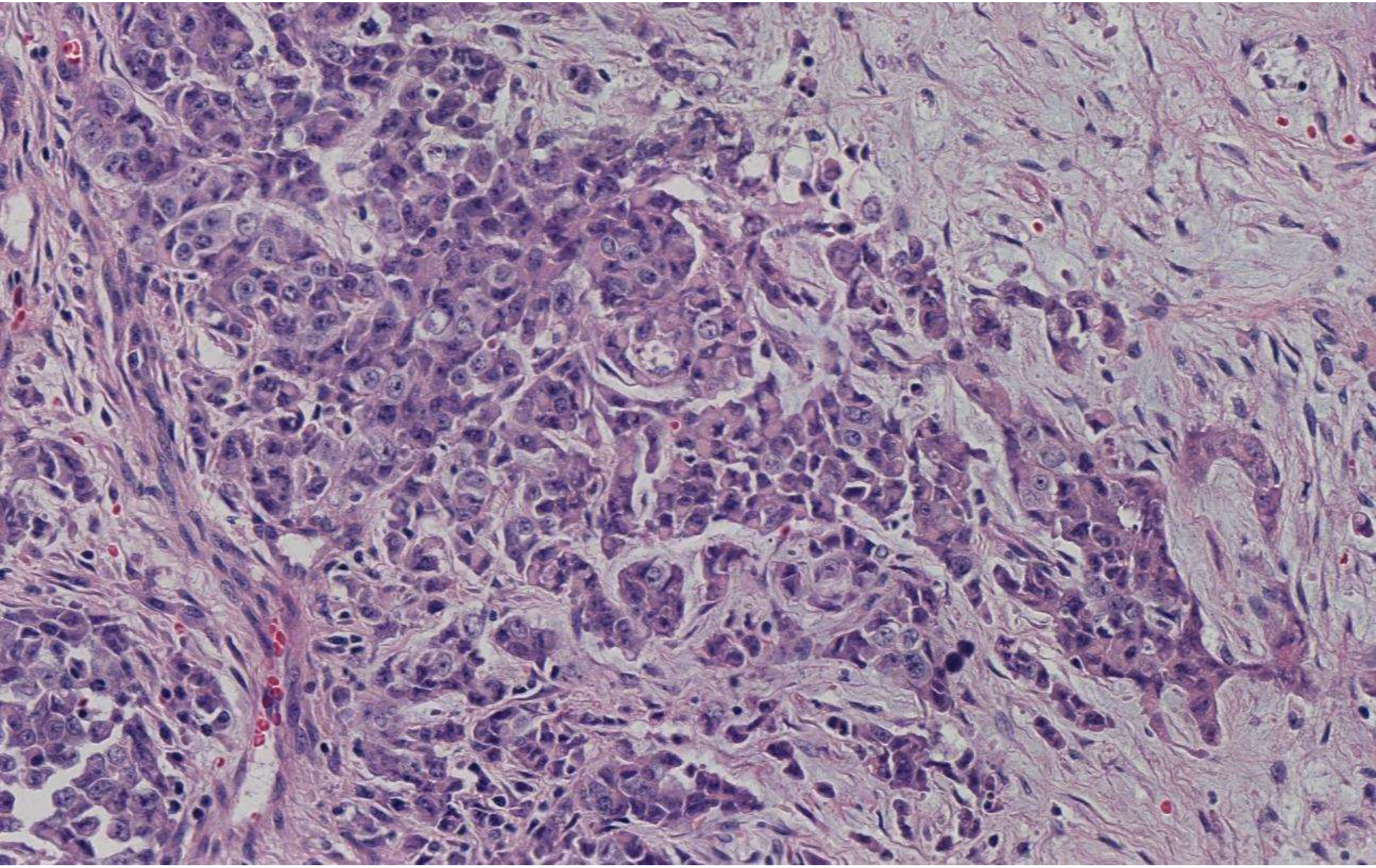


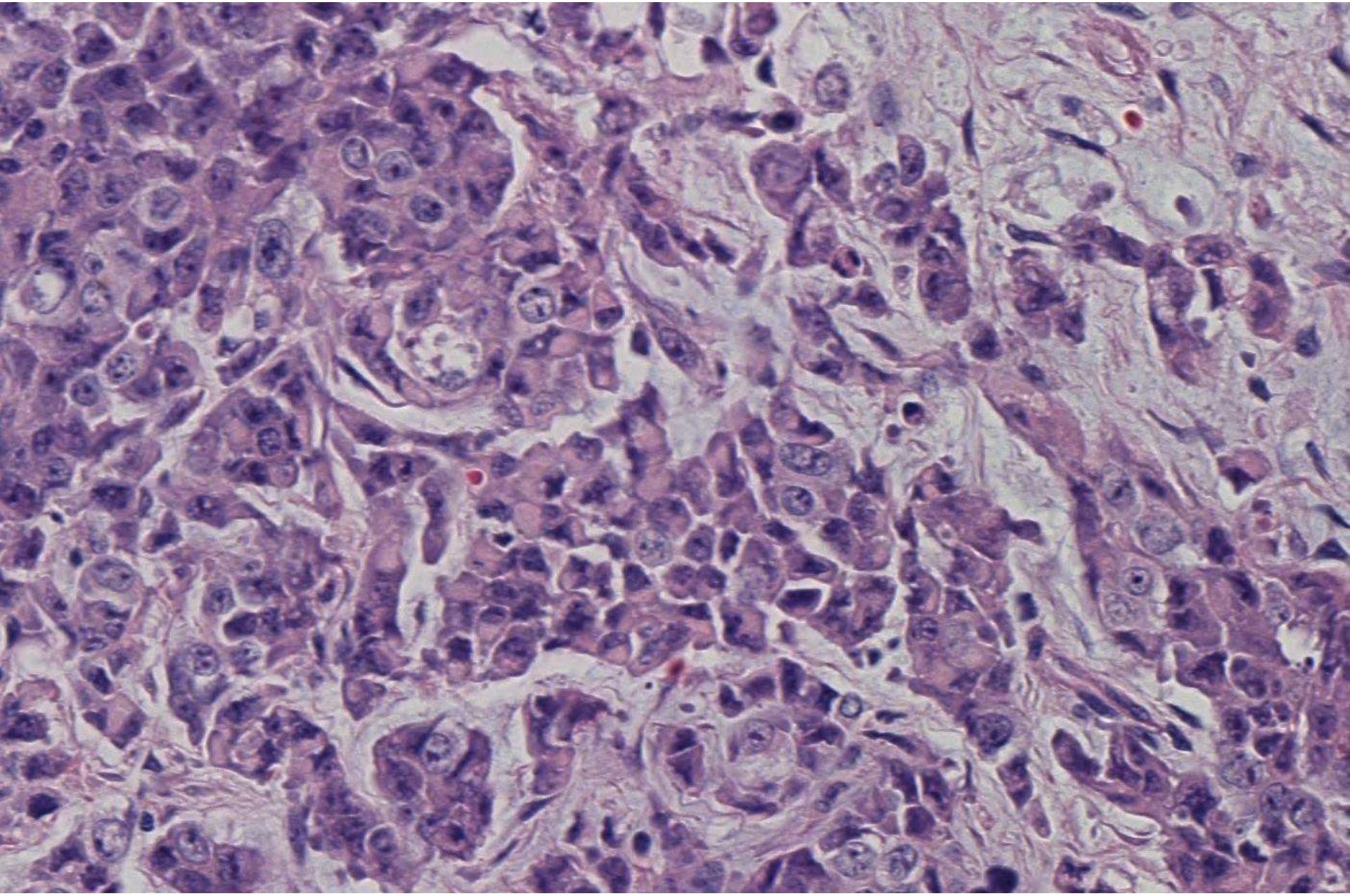












26-year-old woman with bilateral cervical lymphadenopathy and a mediastinal/thymic mass

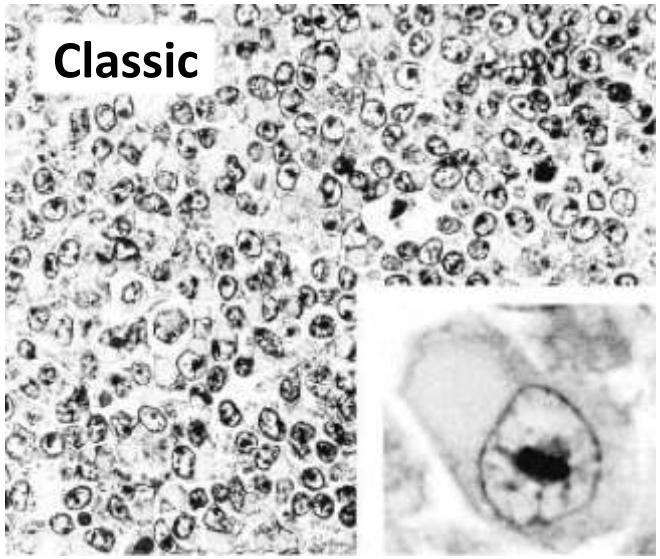
Dr. Eliah Shamir, PGY-2
Dr. Jessica Davis, Assistant Professor
Department of Pathology, UCSF
South Bay Meeting
December 4, 2017

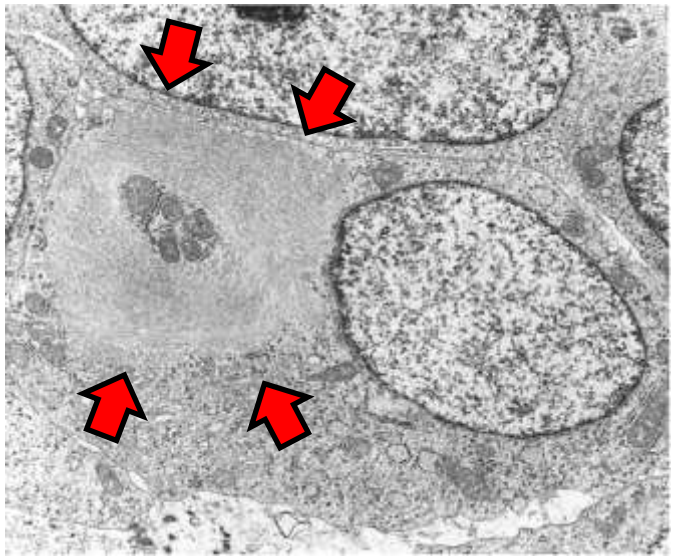
Diagnosis:

Extrarenal rhabdoid tumor

Rhabdoid tumors
(renal rhabdoid, ATRT, extrarenal rhabdoid)

- First definitively characterized in kidney in 1989:
  1. Highly malignant
  2. Predominantly in infants and young children (<3 yo)
  3. ***Wide spectrum of histologic findings:*** 8 major patterns (classic, sclerosing, epithelioid, spindled, lymphomatoid, vascular, pseudopapillary, cystic)



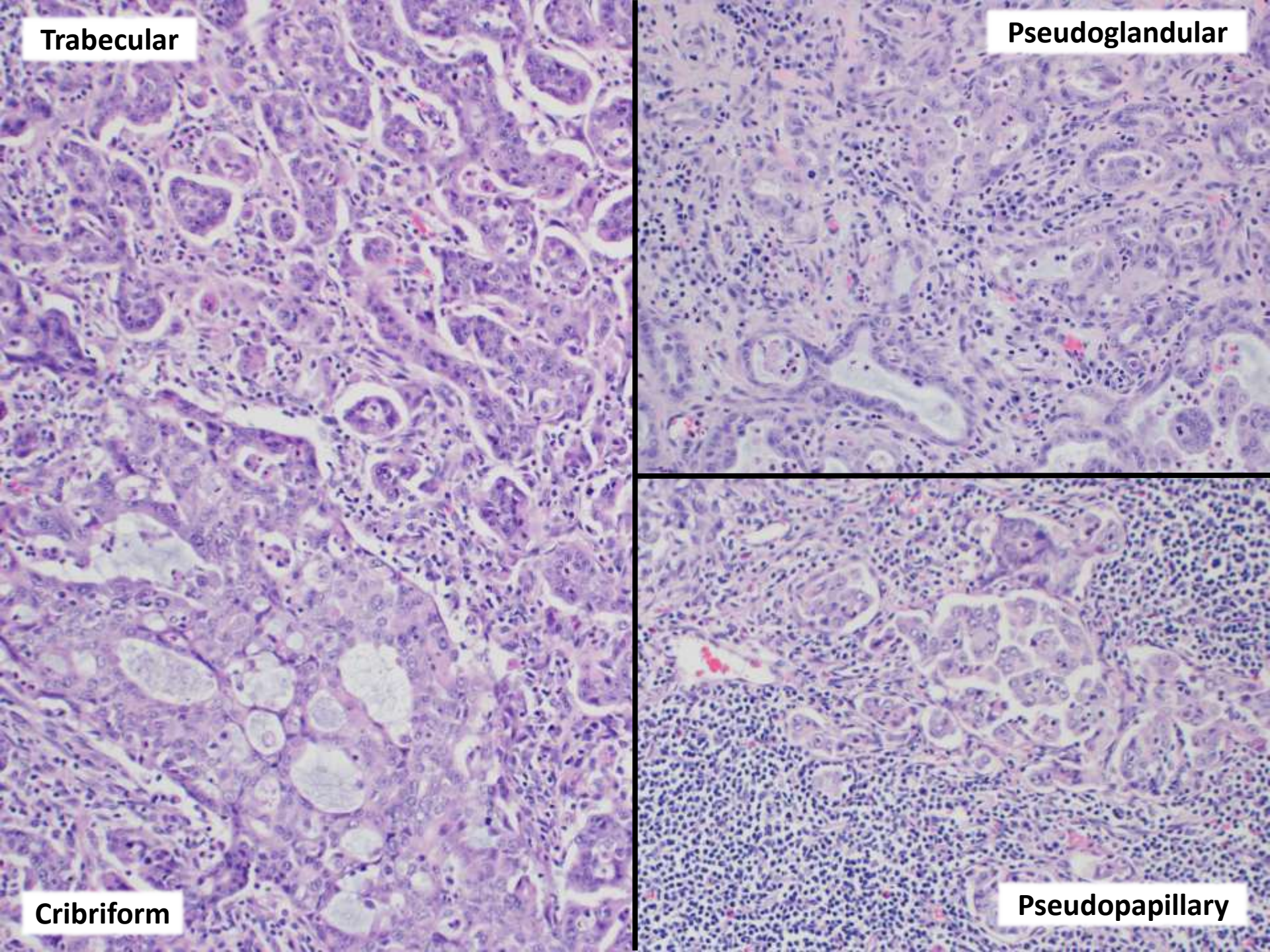


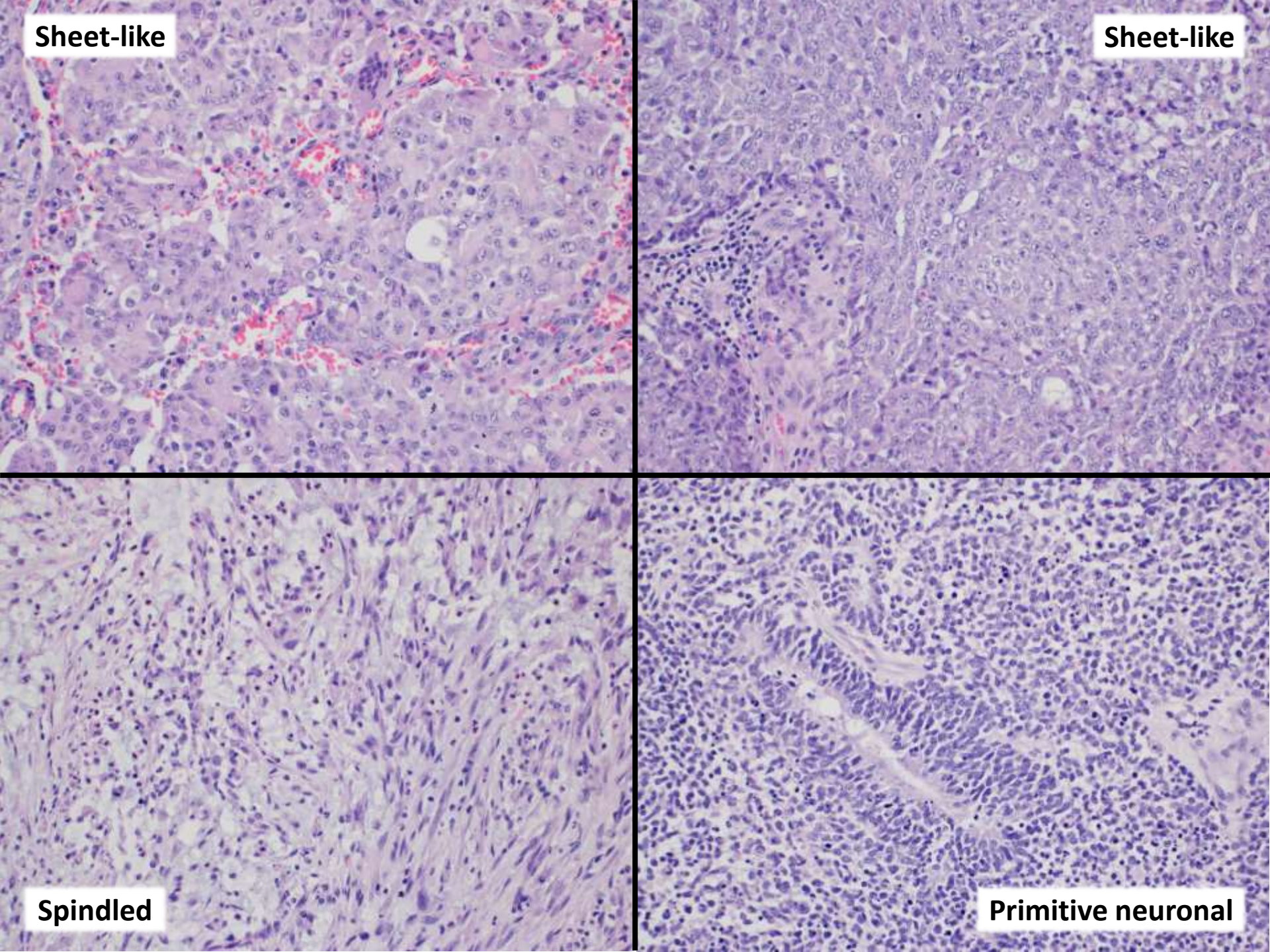
Weeks et al, *AJSP* 1989;13(6).
Margol and Judkins, *Cancer Genetics* 2014;207.

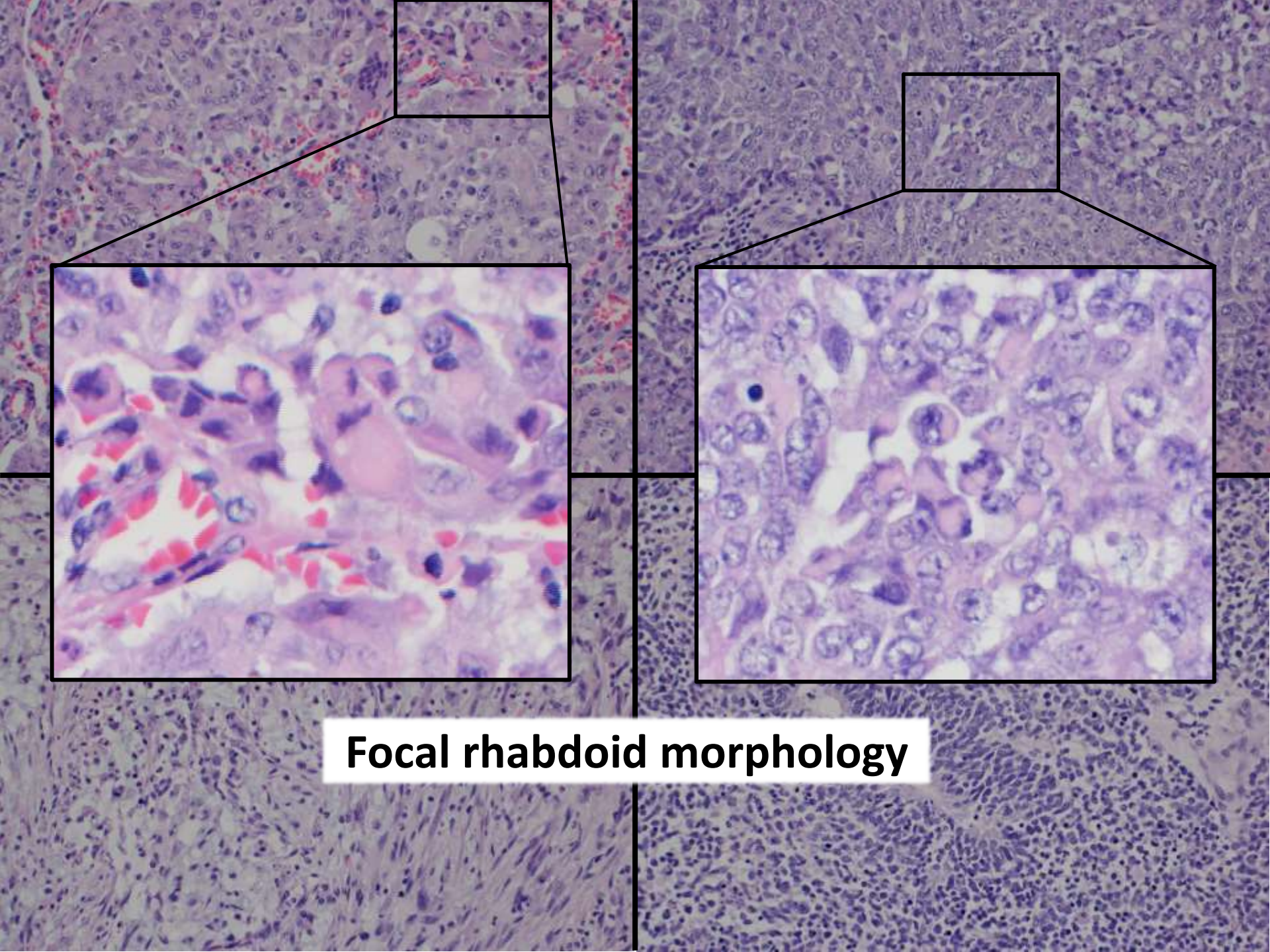
A diagnostic challenge

- Rare
- Divergent differentiation along epithelial, mesenchymal, and neuroepithelial lines
- Limited utility of many IHC markers
- Classic rhabdoid features may be minimal

Weeks et al, *AJSP* 1989;13(6).
Margol and Judkins, *Cancer Genetics* 2014;207.

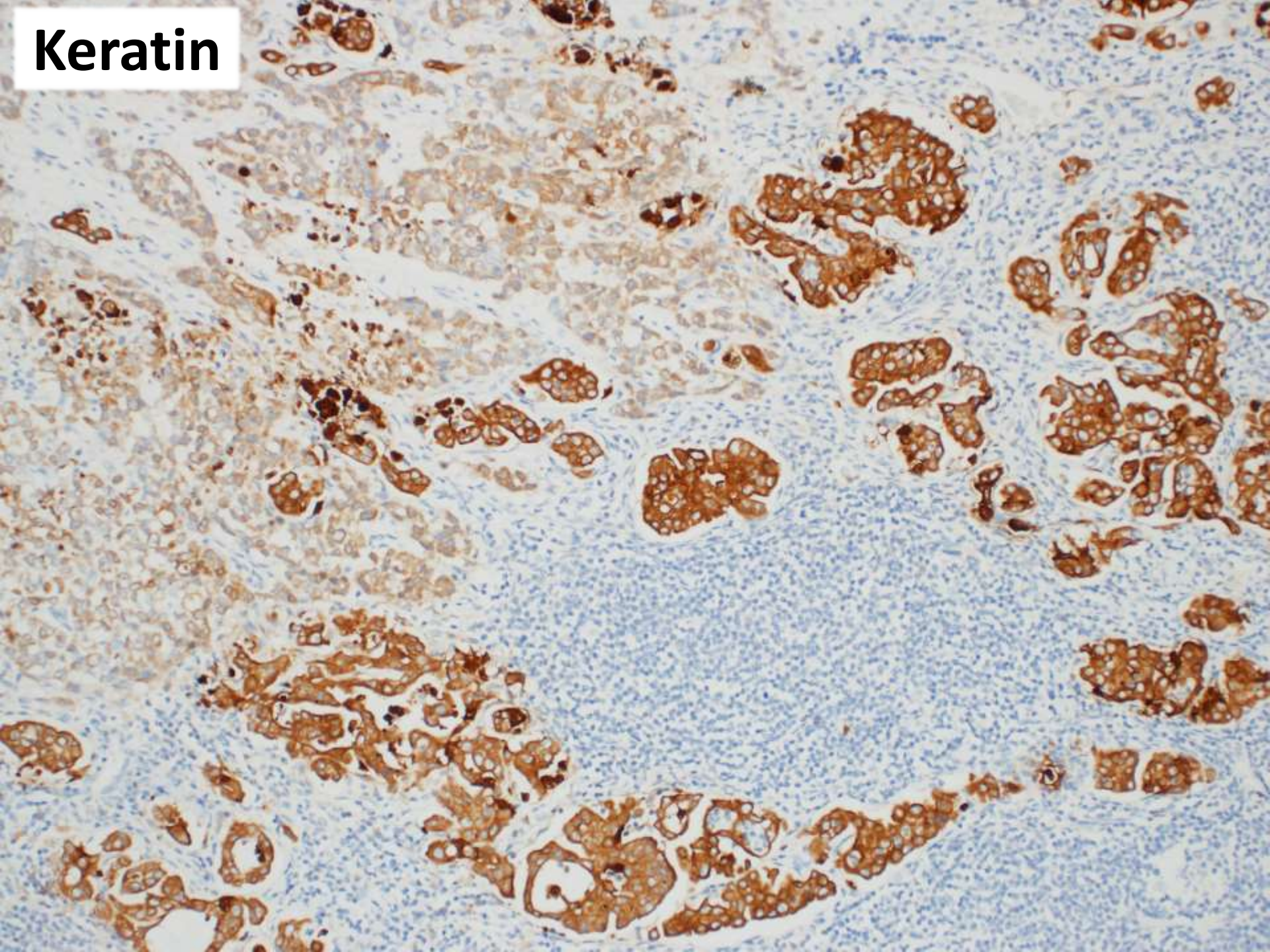

Trabecular
Pseudoglandular
Cribriform
Pseudopapillary


Sheet-like
Sheet-like
Spindled
Primitive neuronal


Focal rhabdoid morphology

Differential diagnosis

- Mixed germ cell tumor
- Thyroid carcinoma
- Thymic carcinoma
- NUT midline carcinoma
- Metastatic carcinoma


Keratin

Tumor staining pattern

Positive:

- Keratin
- EMA
- SOX2
- PAX8 (weak)

} Non-specific

Negative:

- OCT4
- SALL4
- CD30
- Glypican 3

} Against mixed germ cell tumor

- CD5
- EBV ISH
- p63

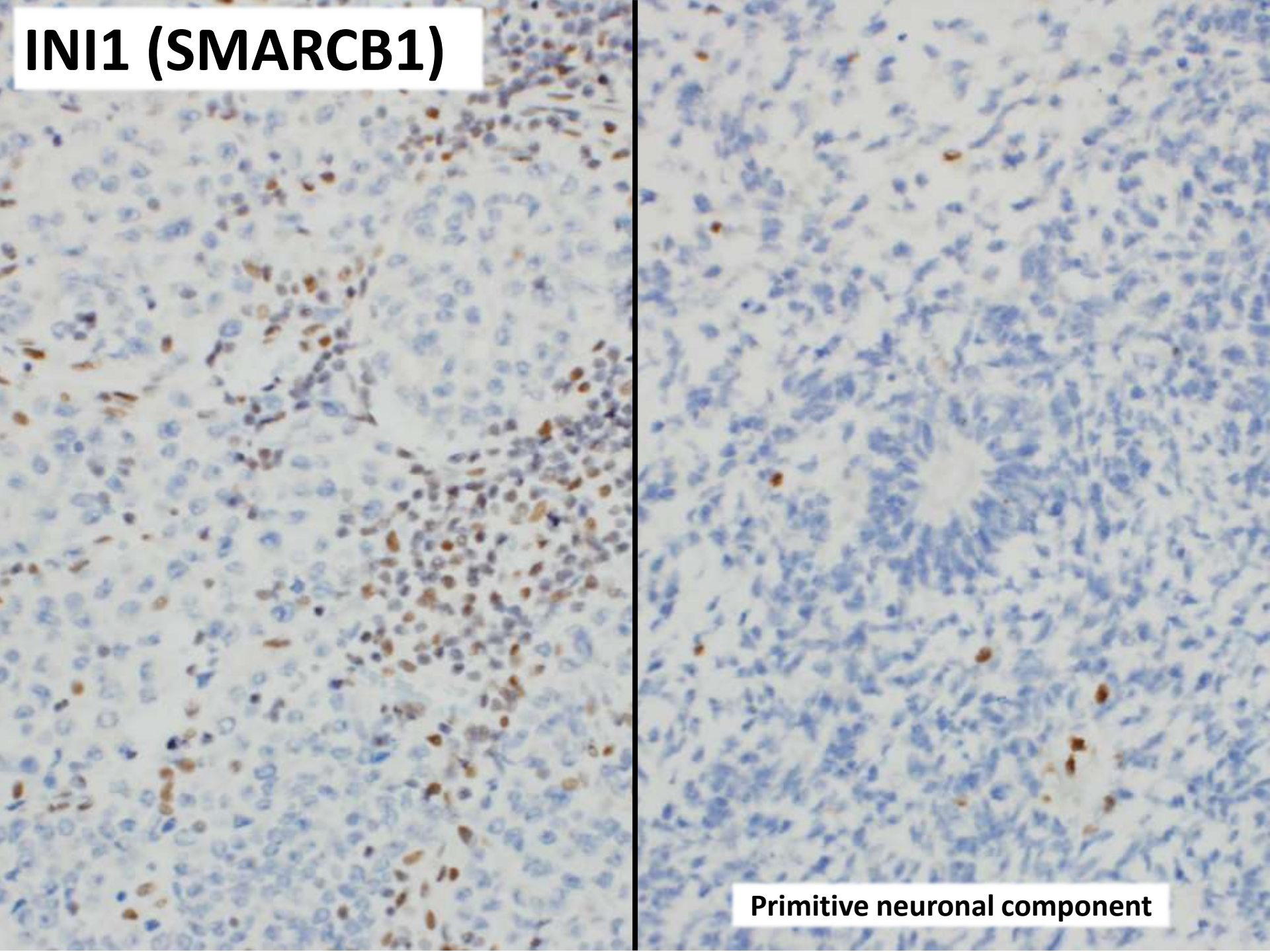
} Against thymic / lymphoepithelioma-like carcinoma

- TTF1

} Against thyroid carcinoma

- Desmin
- WT1
- GATA3
- NUT

} Against NUT carcinoma


INI1 (SMARCB1)
Primitive neuronal component

Integrase interactor 1 (INI1) aka SMARCB1

- Core subunit of the SWI/SNF chromatin remodeling complex
- Biallelic inactivation of *INI1* is the primary oncogenic event in rhabdoid tumors
  - Loss of INI1 by IHC in 98% (soft tissue, kidney, and CNS)
  - ~75% due to *INI1* gene mutations and/or deletions
  - First hit germline *INI1* mutation in up to 35%
- Patients with INI1-deficient tumors are now eligible for EZH2-targeted therapy

Hollman and Hornick, *Am J Surg Pathol* 2011;35.

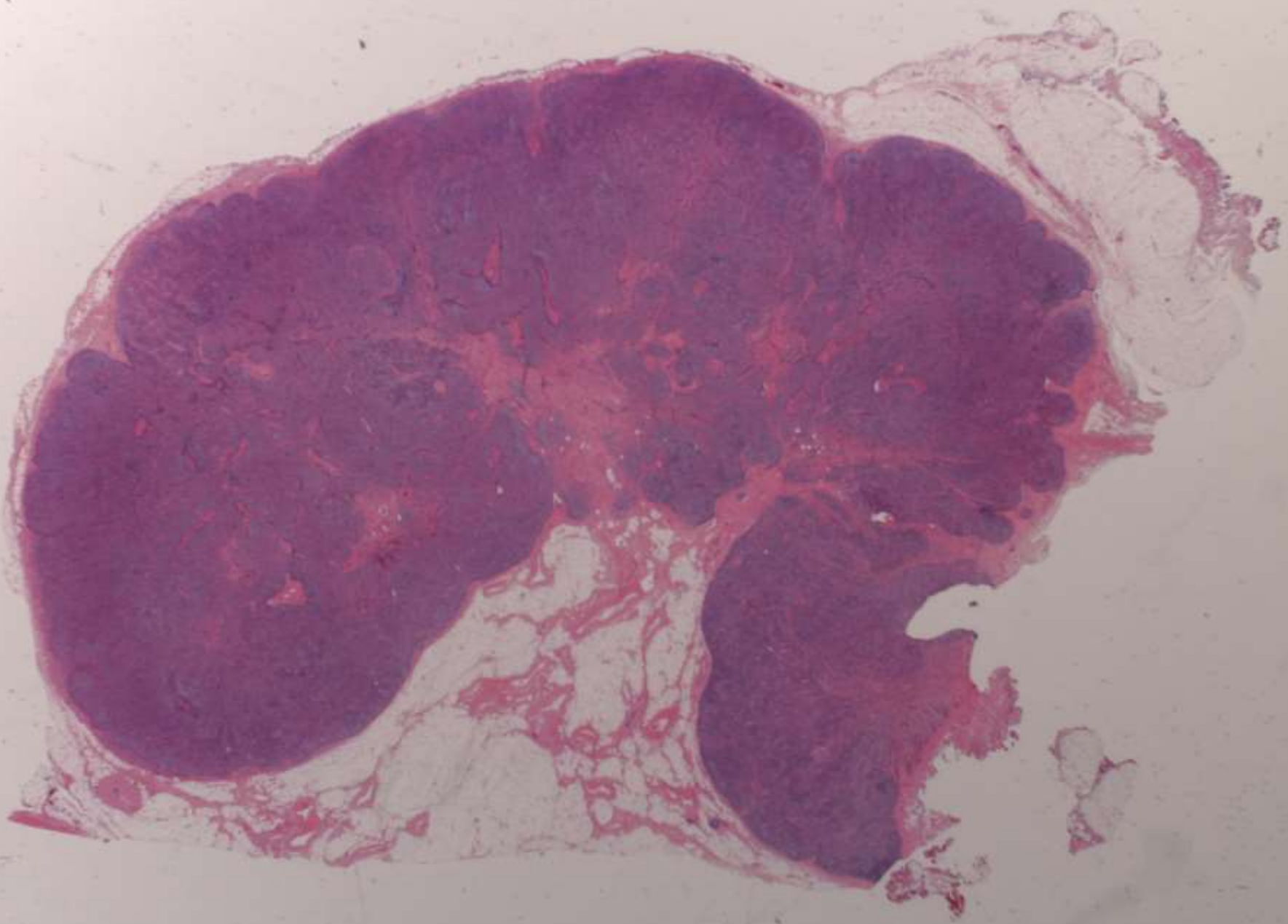
Take Home Points

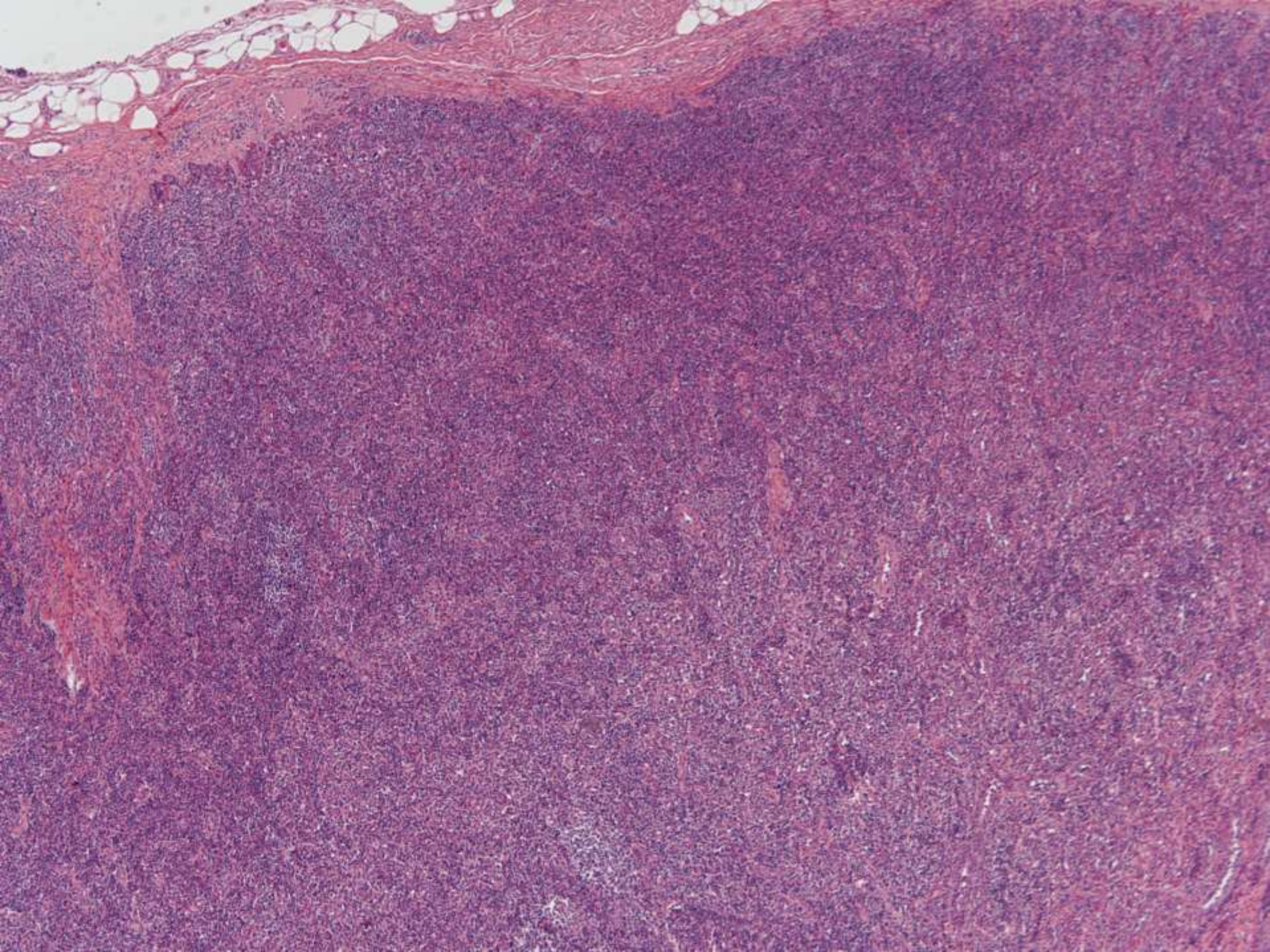
- Diverse histologic patterns + rhabdoid morphology → ***Perform INI1 immunostain***
- Rhabdoid tumors can present at any location (trunk/neck relatively common extrarenal site)
- Extrarenal rhabdoid tumors occur in a wider age range, including adults

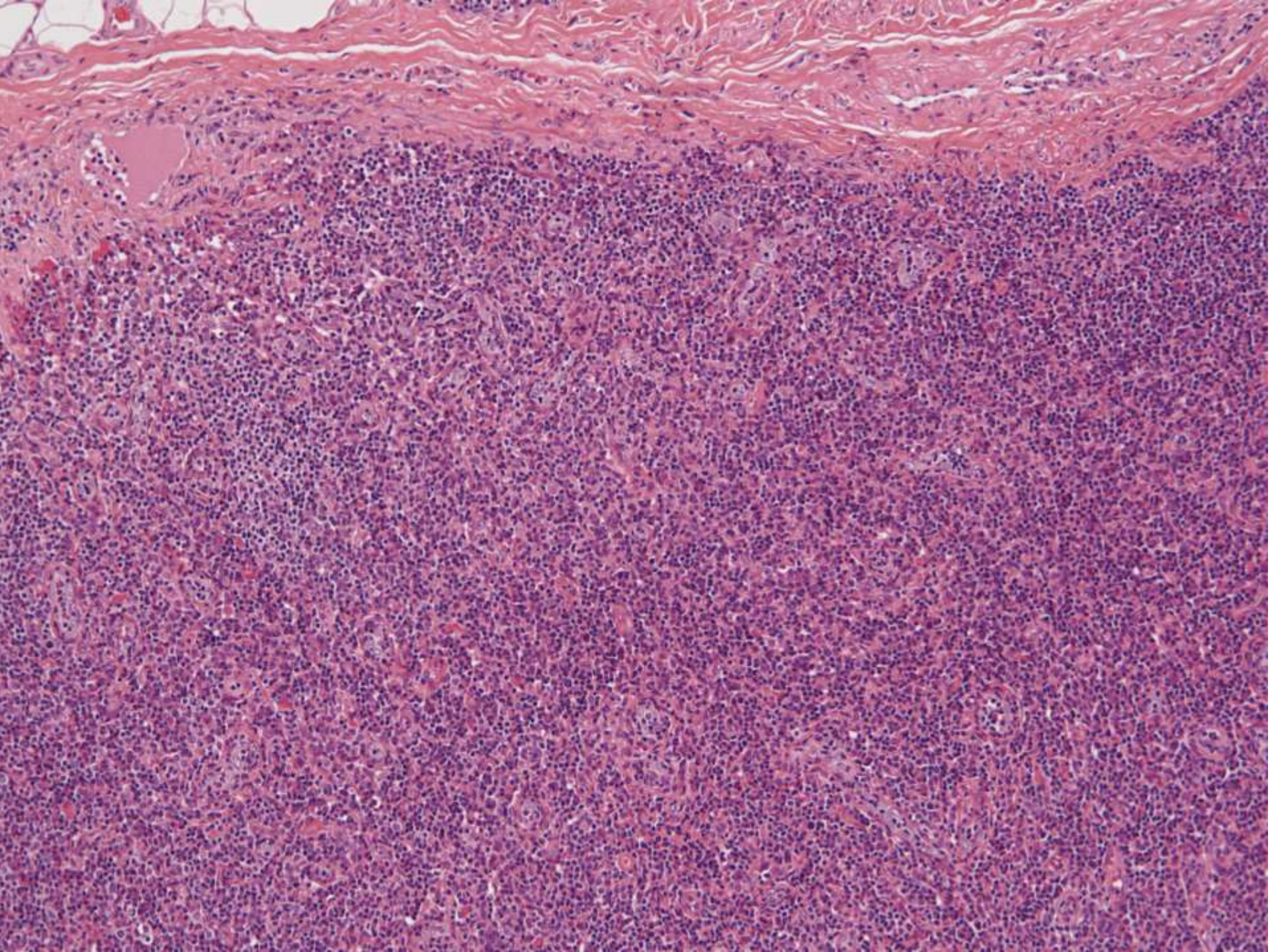
SB 6227

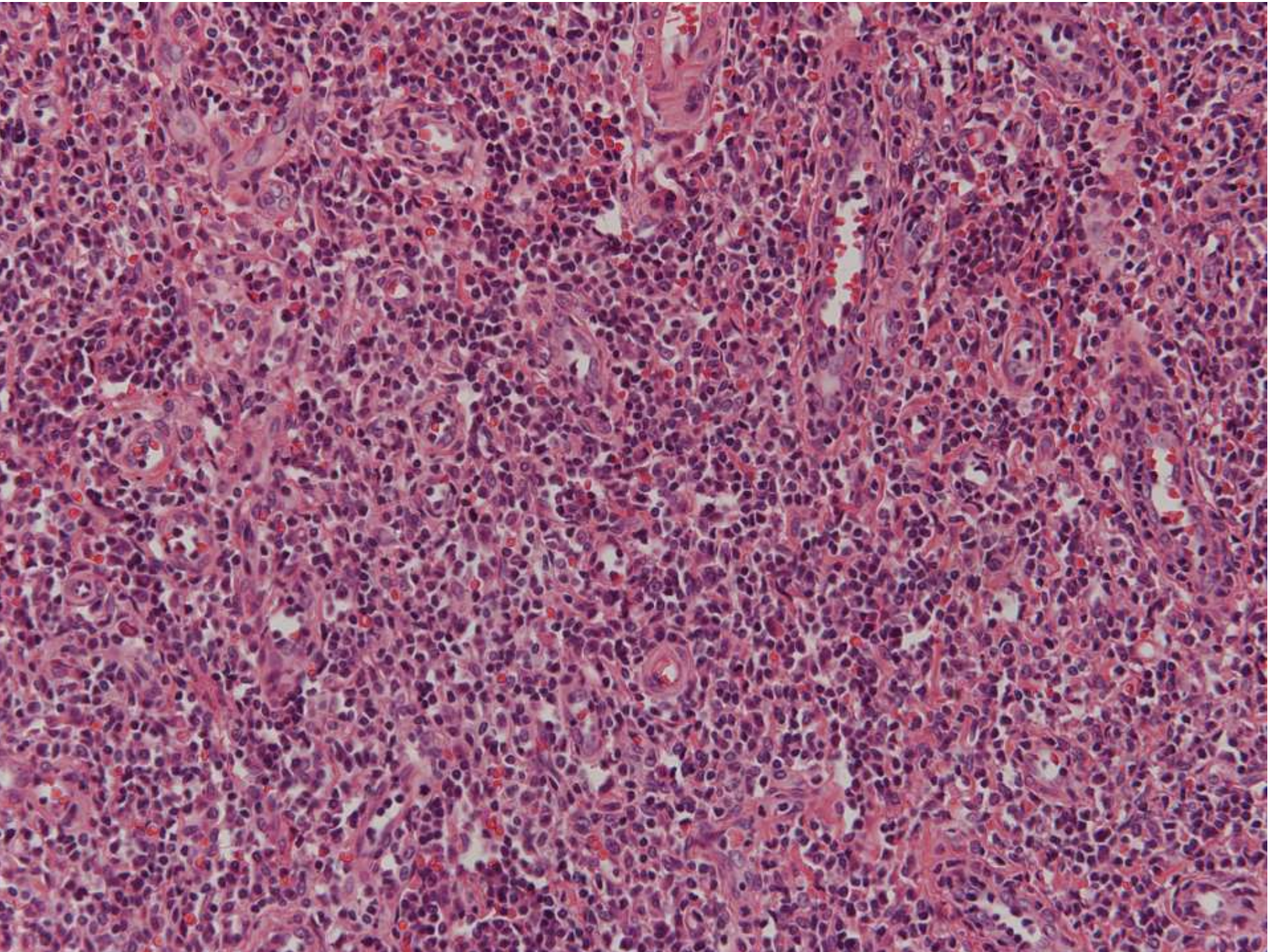
Sebastian Fernandez-Pol/Dita Gratzinger/Brent Tan; Stanford

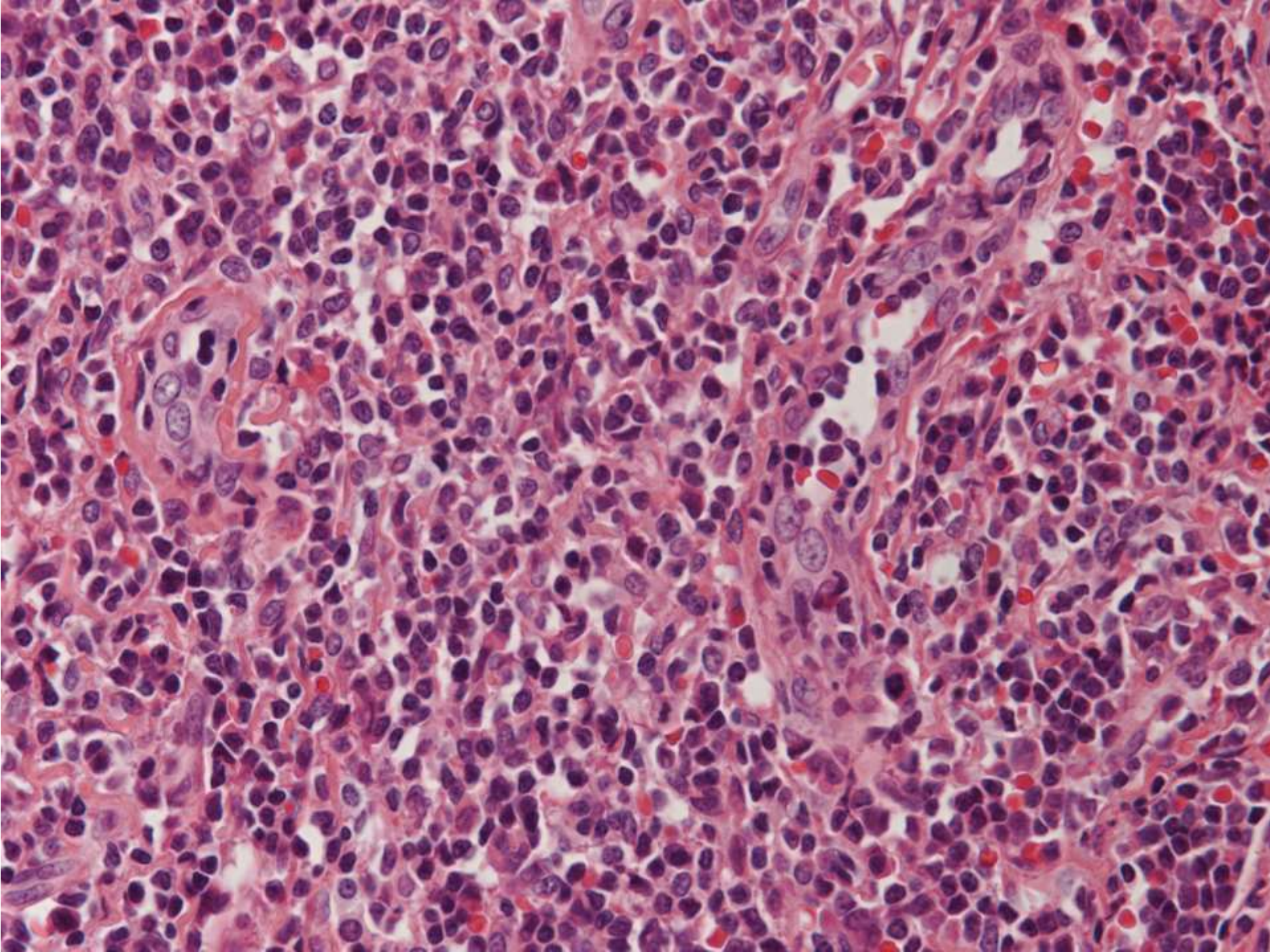
54-year-old male presenting with widespread lymphadenopathy.

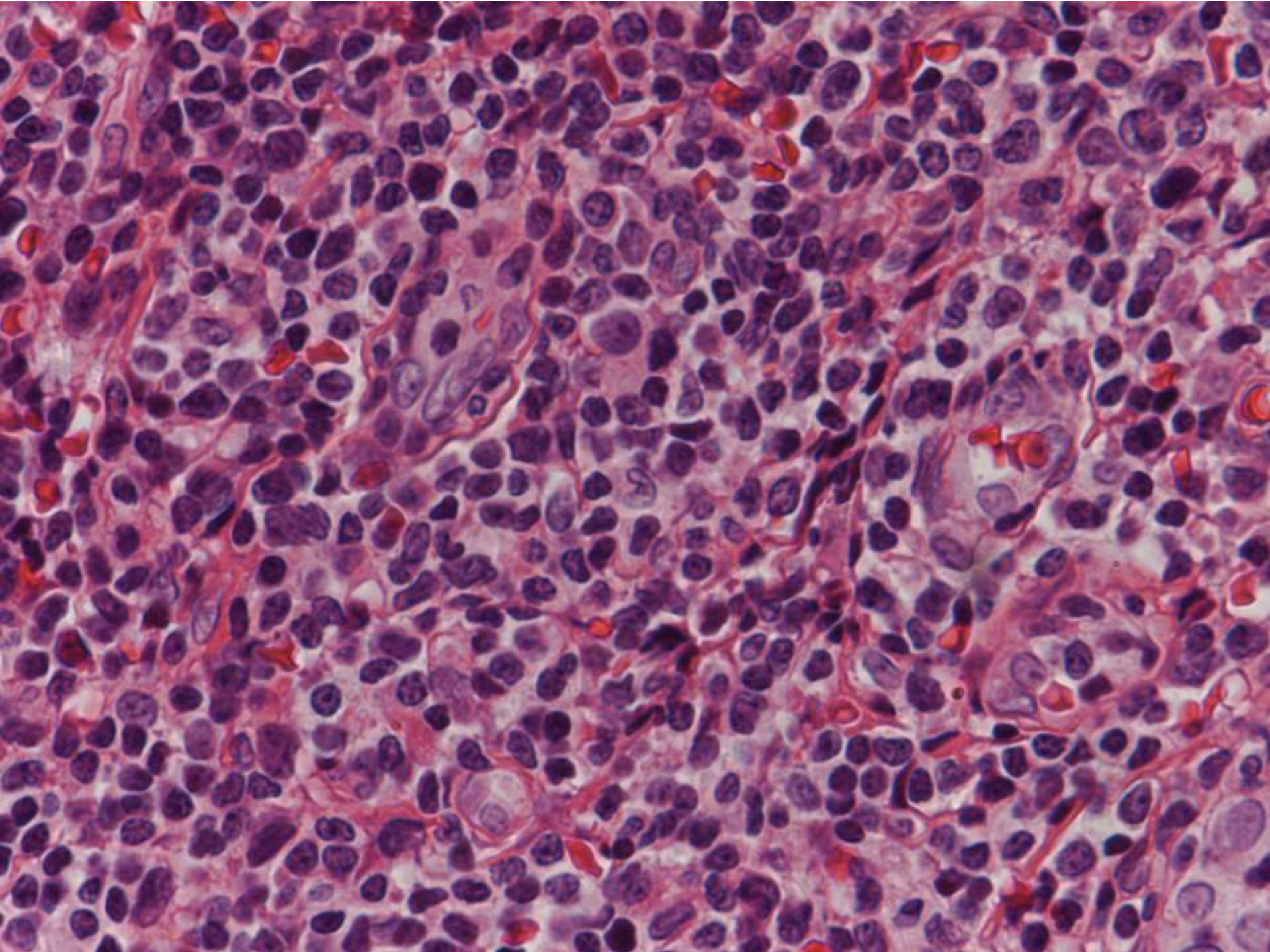


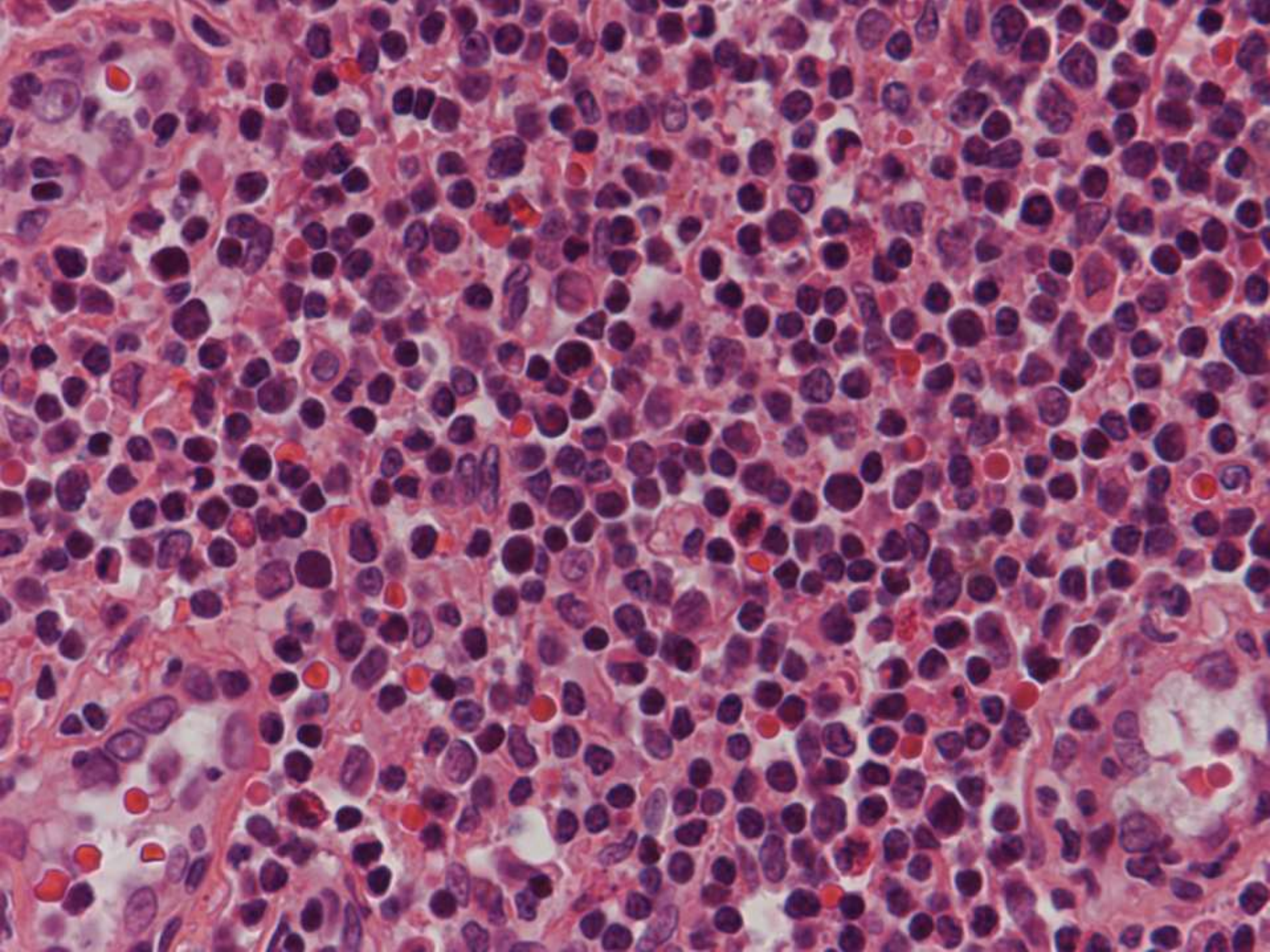


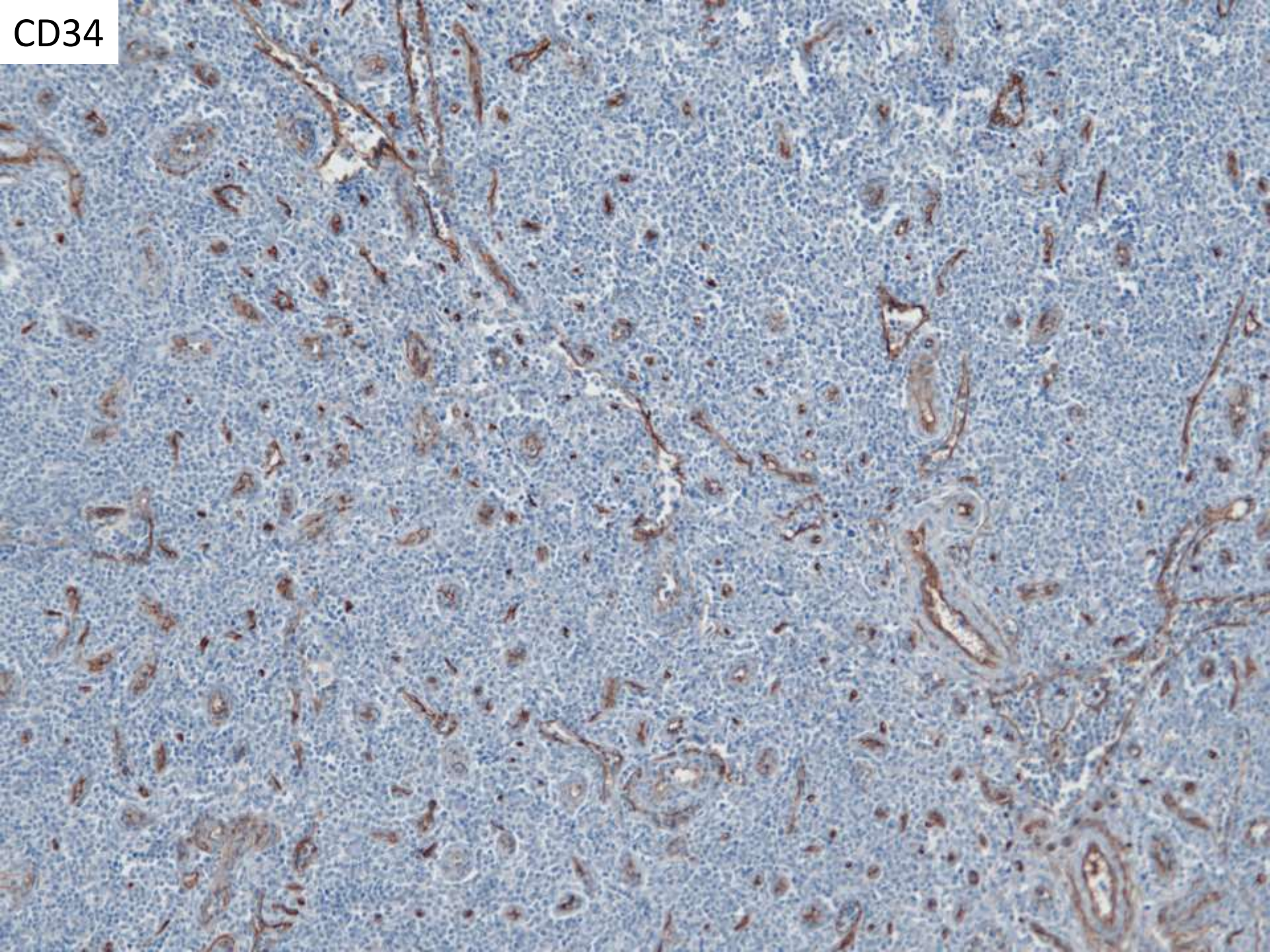




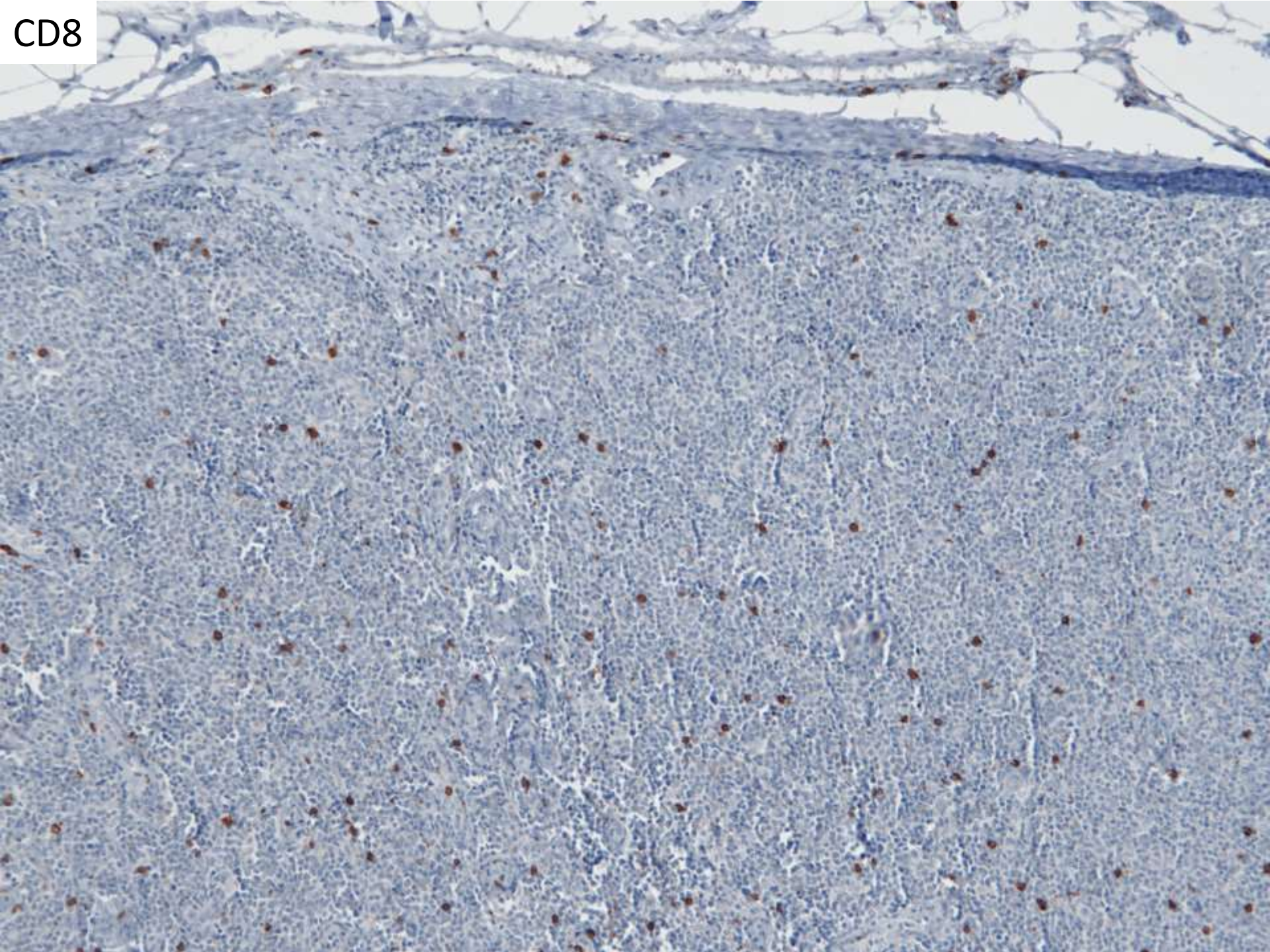


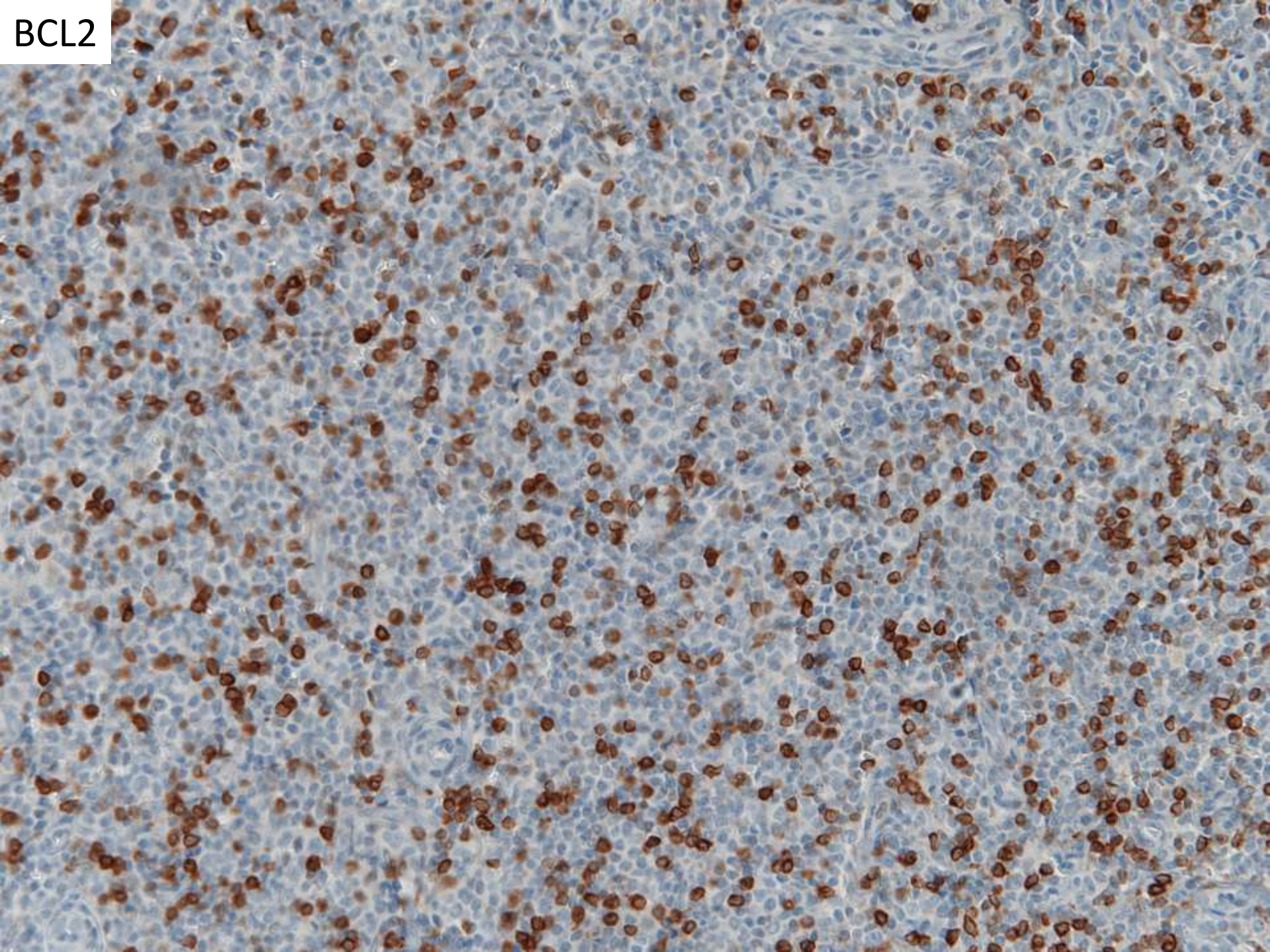


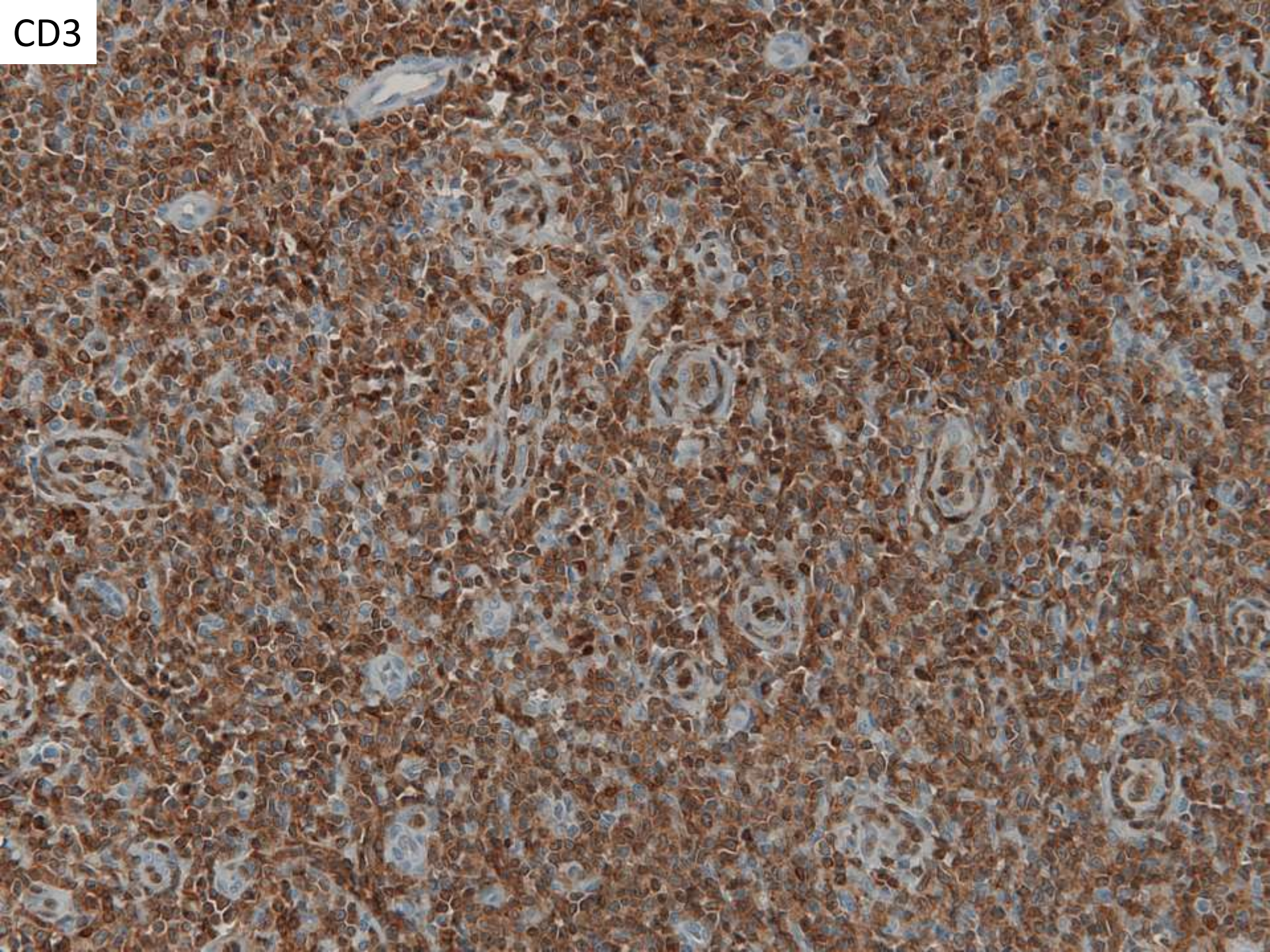


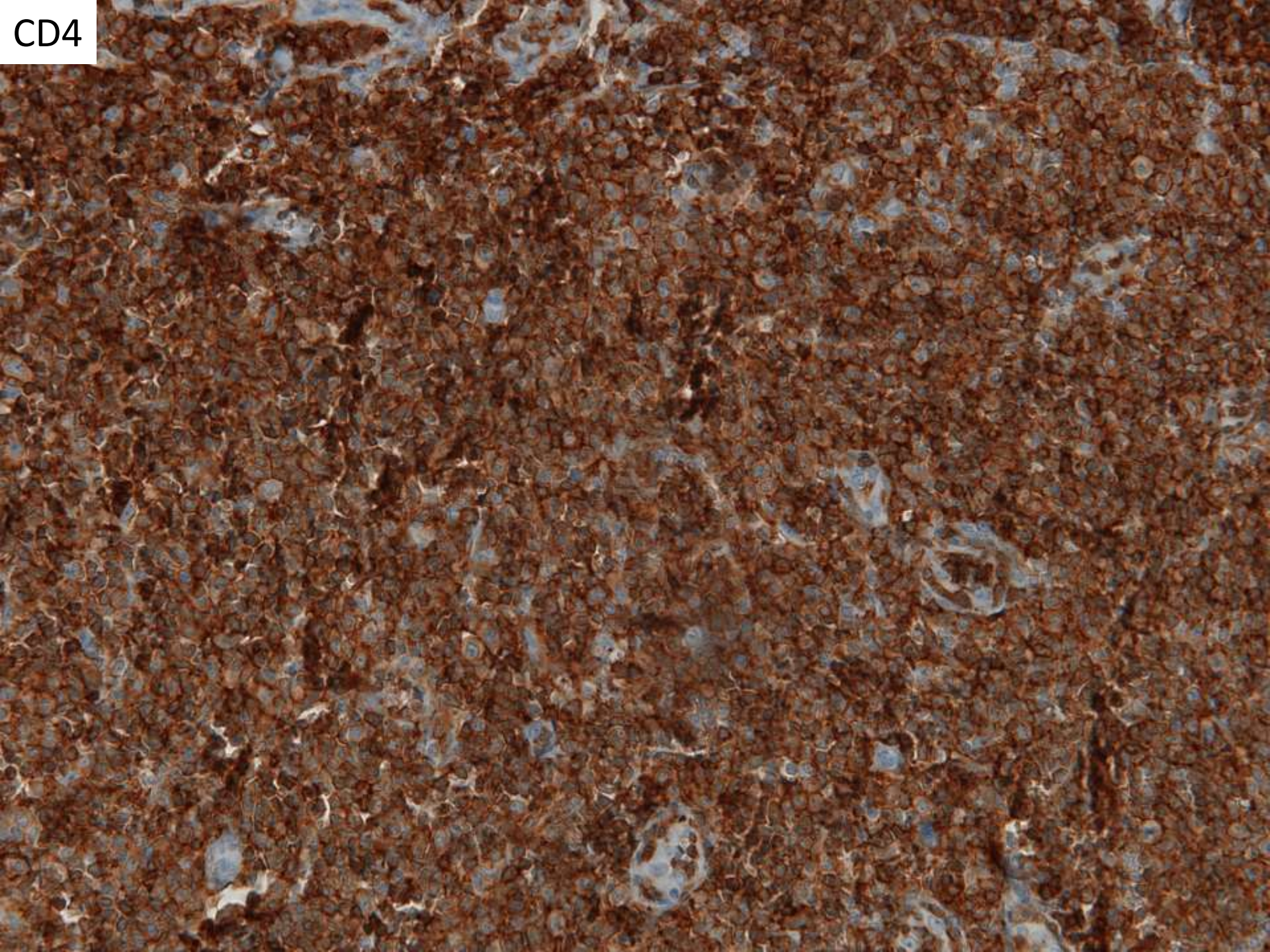

CD34

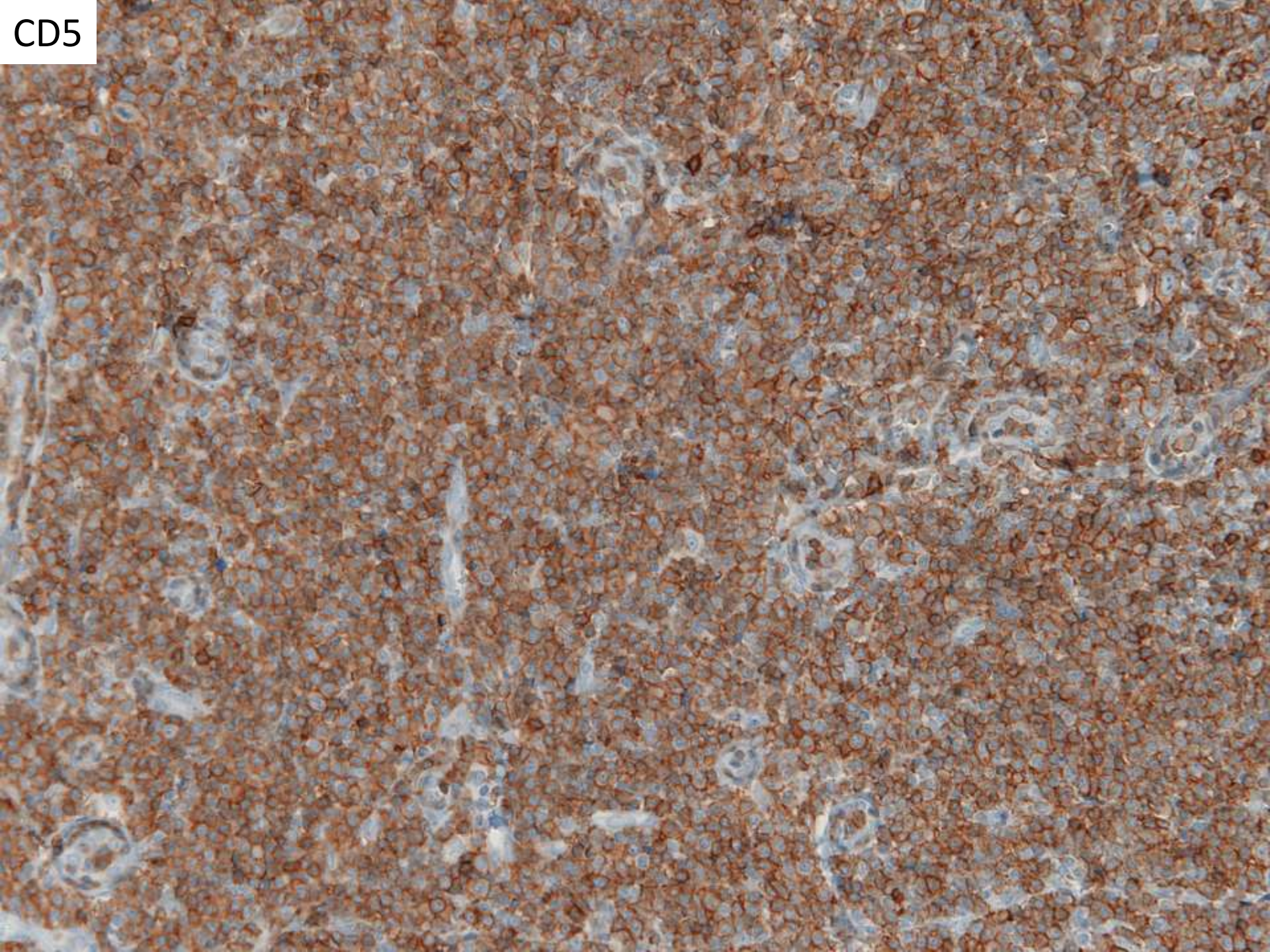

CD21

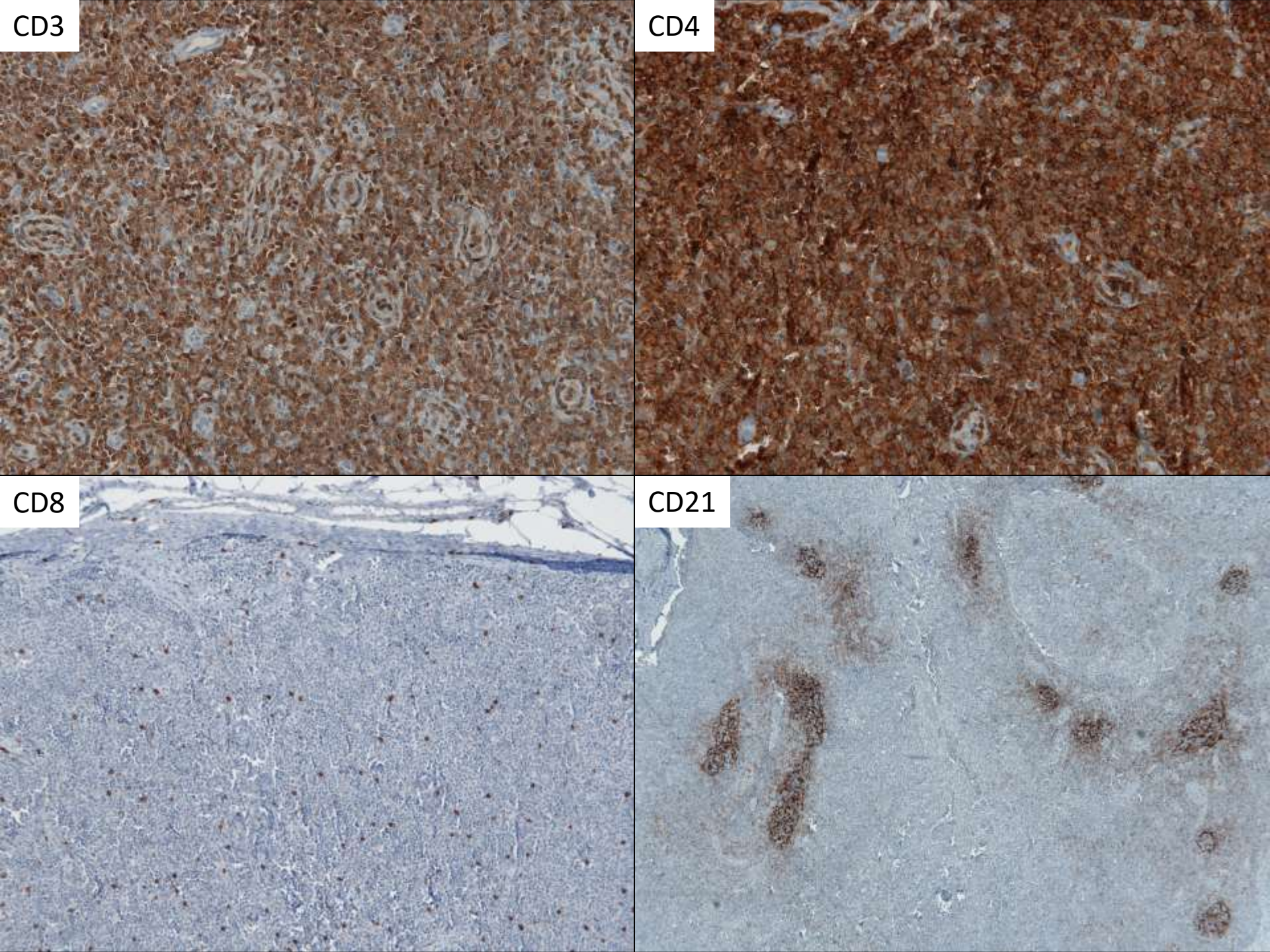

CD8

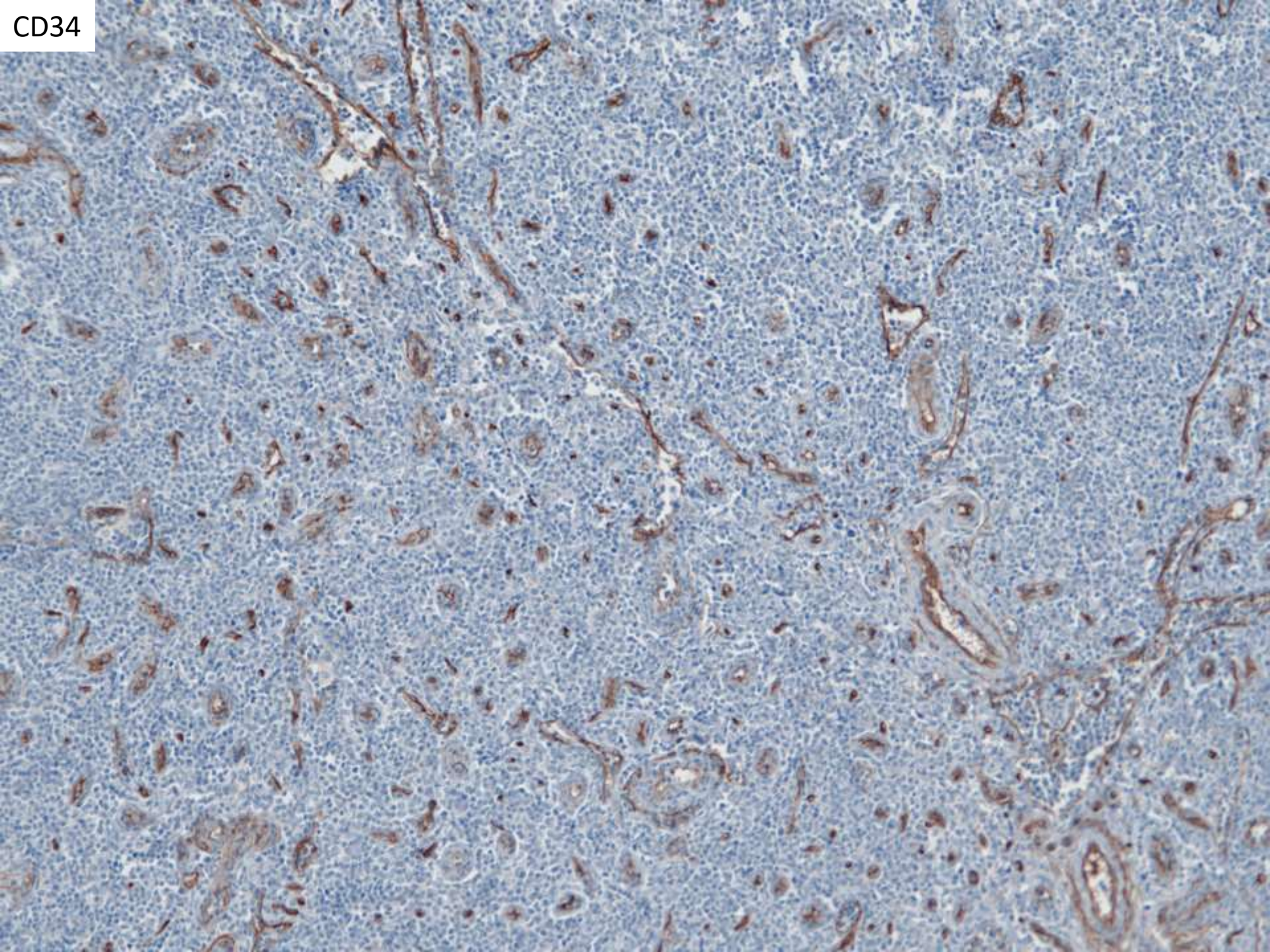

BCL2


CD3


CD4


CD5


CD3
CD4
CD8
CD21


CD34

Differential diagnosis

- Mature CD4+ T-cell lymphoma
  - Angioimmunoblastic T-cell lymphoma
  - Cutaneous T-cell lymphoma/Mycosis fungoides
- Diffuse paracortical proliferation
  - EBV/Infectious mononucleosis
    - Architecture of the lymph node or tonsil may be distorted, but is not effaced
  - CMV
  - HSV
  - Dilantin (phenytoin)

Additional clinical history

- The patient has a history of mycosis fungoides and Sézary syndrome

Human Pathology (2015) 46, 1382–1389

ELSEVIER

Human
PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

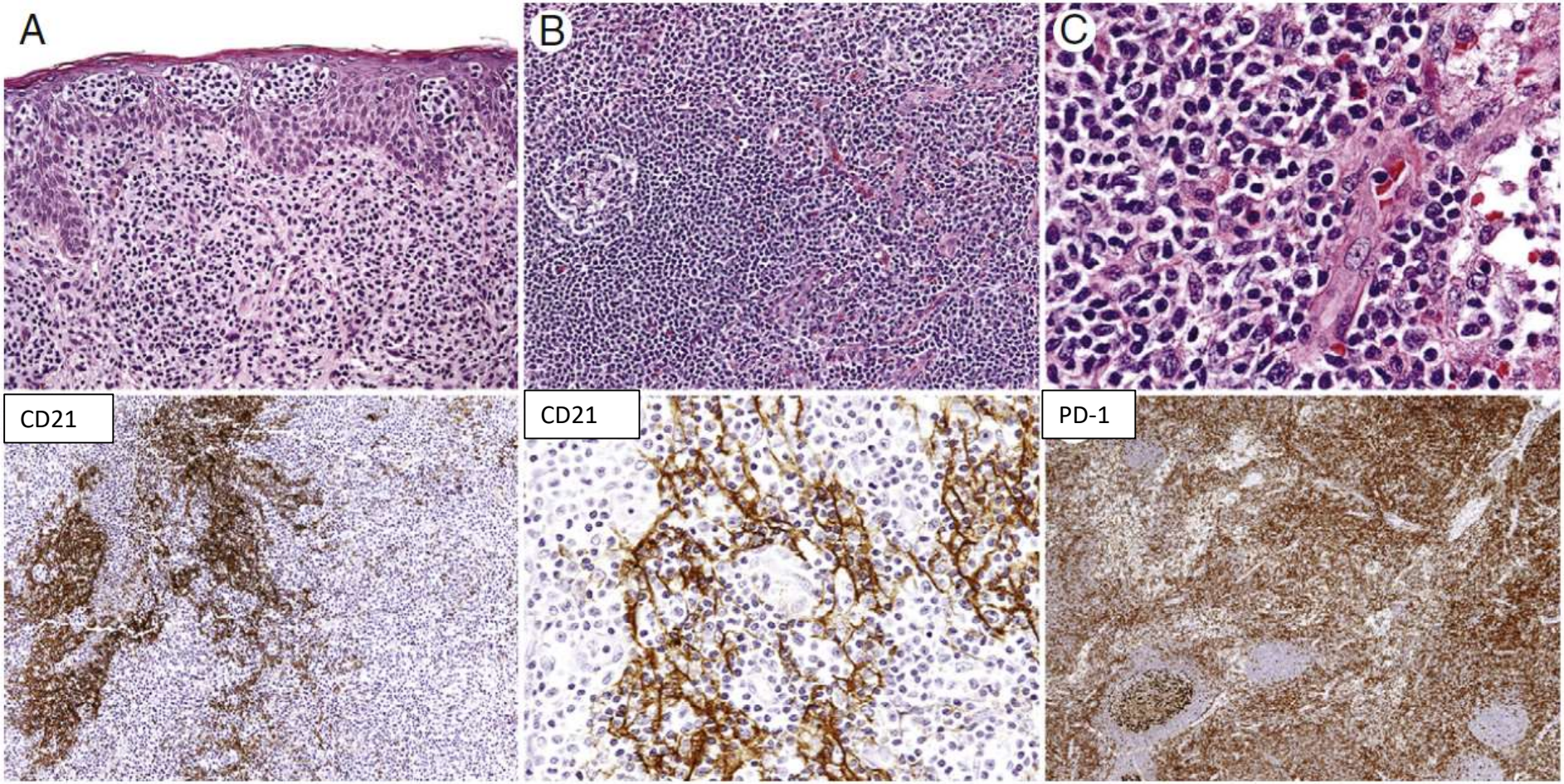
Lymph node involvement by mycosis fungoides and Sézary syndrome mimicking angioimmunoblastic T-cell lymphoma☆

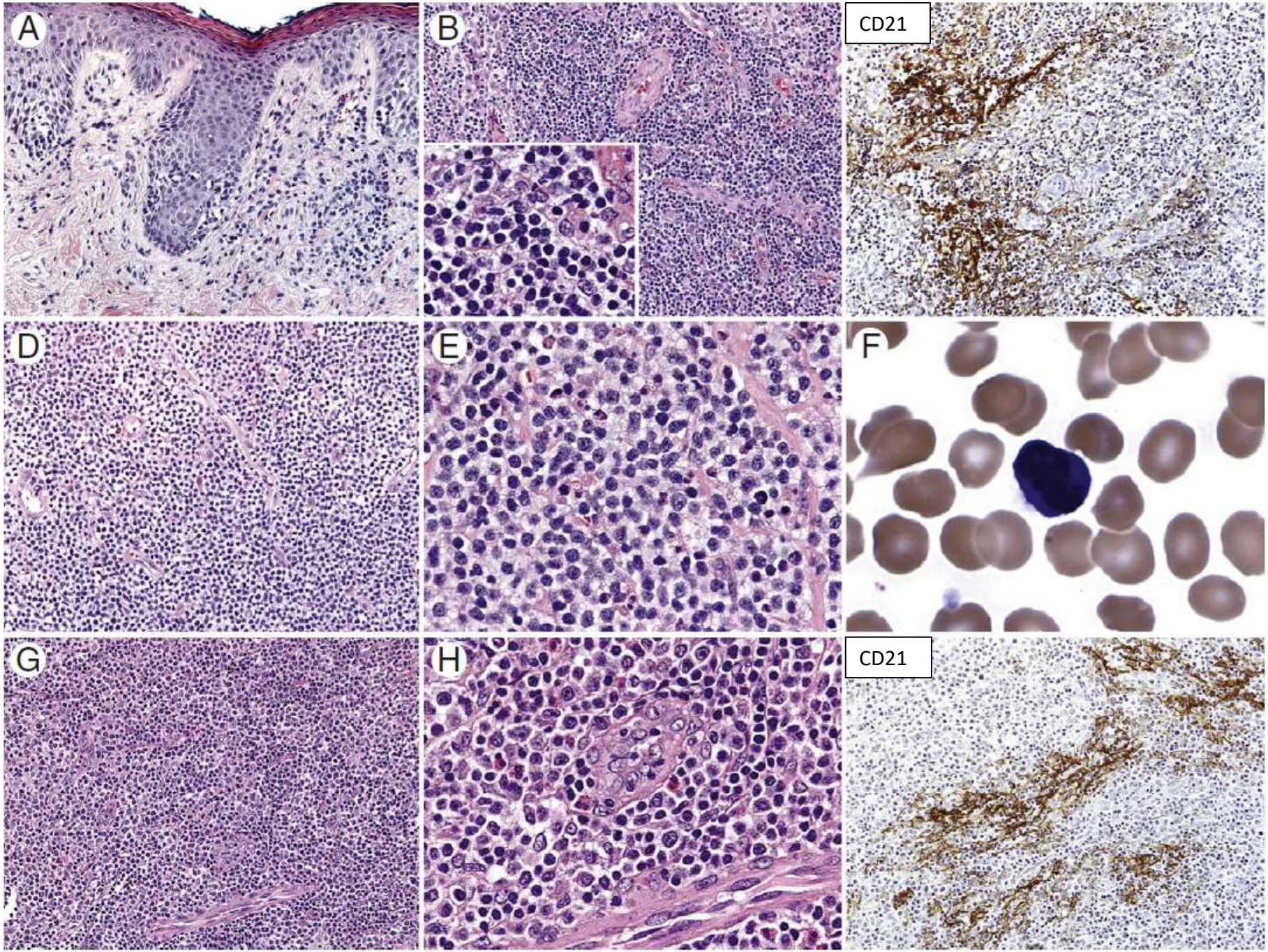
Robert E. LeBlanc MD[a], Martina I. Lefterova MD, PhD[a], Carlos J. Suarez MD[a], Mahkam Tavallaee MD, MPH[b], Youn H. Kim MD[b], Iris Schrijver MD[a], Jinah Kim MD, PhD[a], Dita Gratzinger MD, PhD[a,*]

[a]Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305
[b]Department of Dermatology, Stanford University School of Medicine, Stanford, CA 94305

Received 16 March 2015; revised 28 May 2015; accepted 29 May 2015

- 4 patients with mycosis fungoides or Sézary syndrome whose nodal disease mimicked angioimmunoblastic T-cell lymphoma
- "Lymph node biopsies revealed dense CD4+ T-cell infiltrates that **coexpressed follicular helper T-cell** markers and were accompanied by **proliferations of high endothelial venules** and **arborizing CD21+ follicular dendritic cell networks**"


A
B
C
CD21
CD21
PD-1


A
B
CD21
D
E
F
G
H
CD21

Immunophenotype of MF and AITL overlap

Table 2 Lymph node immunohistochemistry and flow cytometry results

Patient	CD2	CD3	CD4	CD7	CD26	CD10	PD1	BCL-6	CXCL13	CD21 [a]	CD30	EBER
1	+	+	+	−	−	+	+	−	−	+	−	−
2	NA	+	+	NA	NA	+	+	+	+	+	−	NA
3	NA	+	+	Dim	Dim	−	+	−	−	−	−	−
4	NA	+	+	−	Dim	+	−	−	+	+	−	−

Abbreviation: NA, not available.

[a] CD21 considered positive if it elucidated arborizing dendritic cell networks.

Take home points

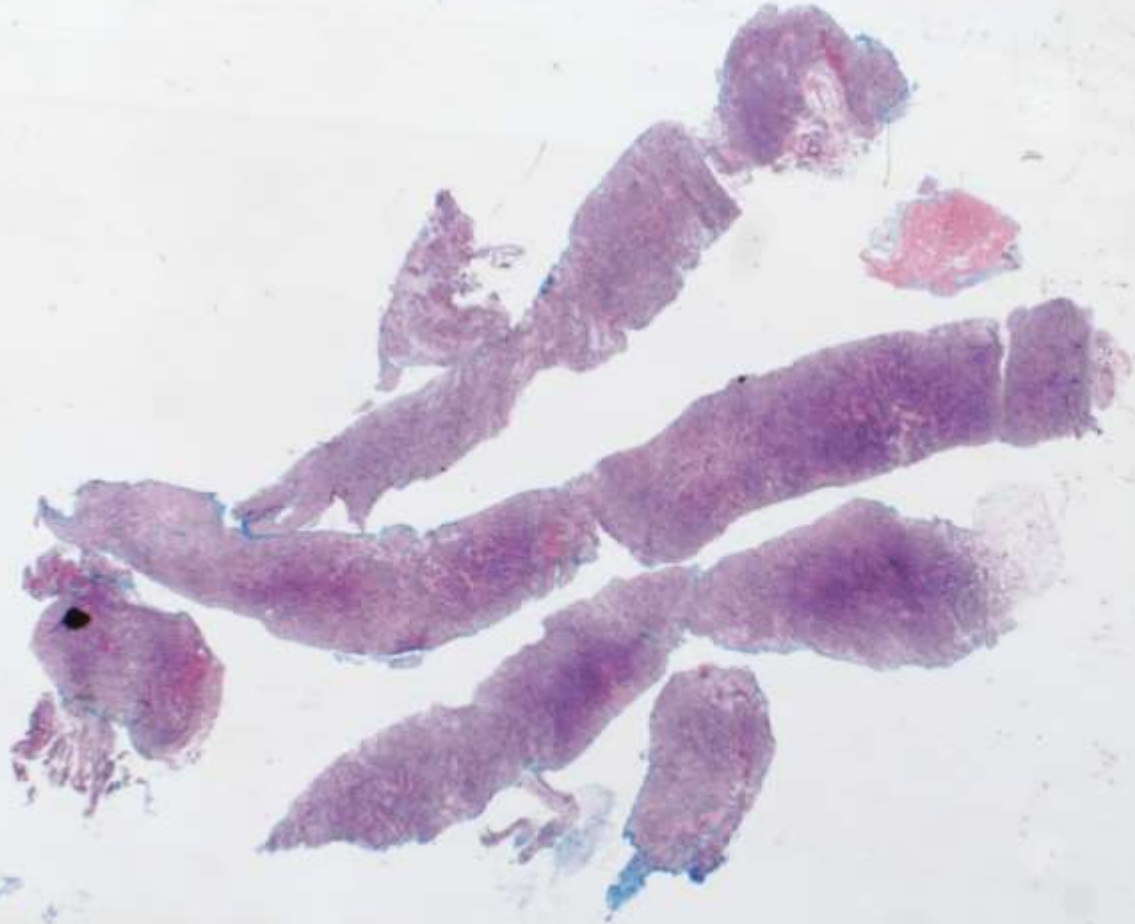
- Lymph nodes involved by MF/CTCL can morphologically and immunophenotypically mimic AITL

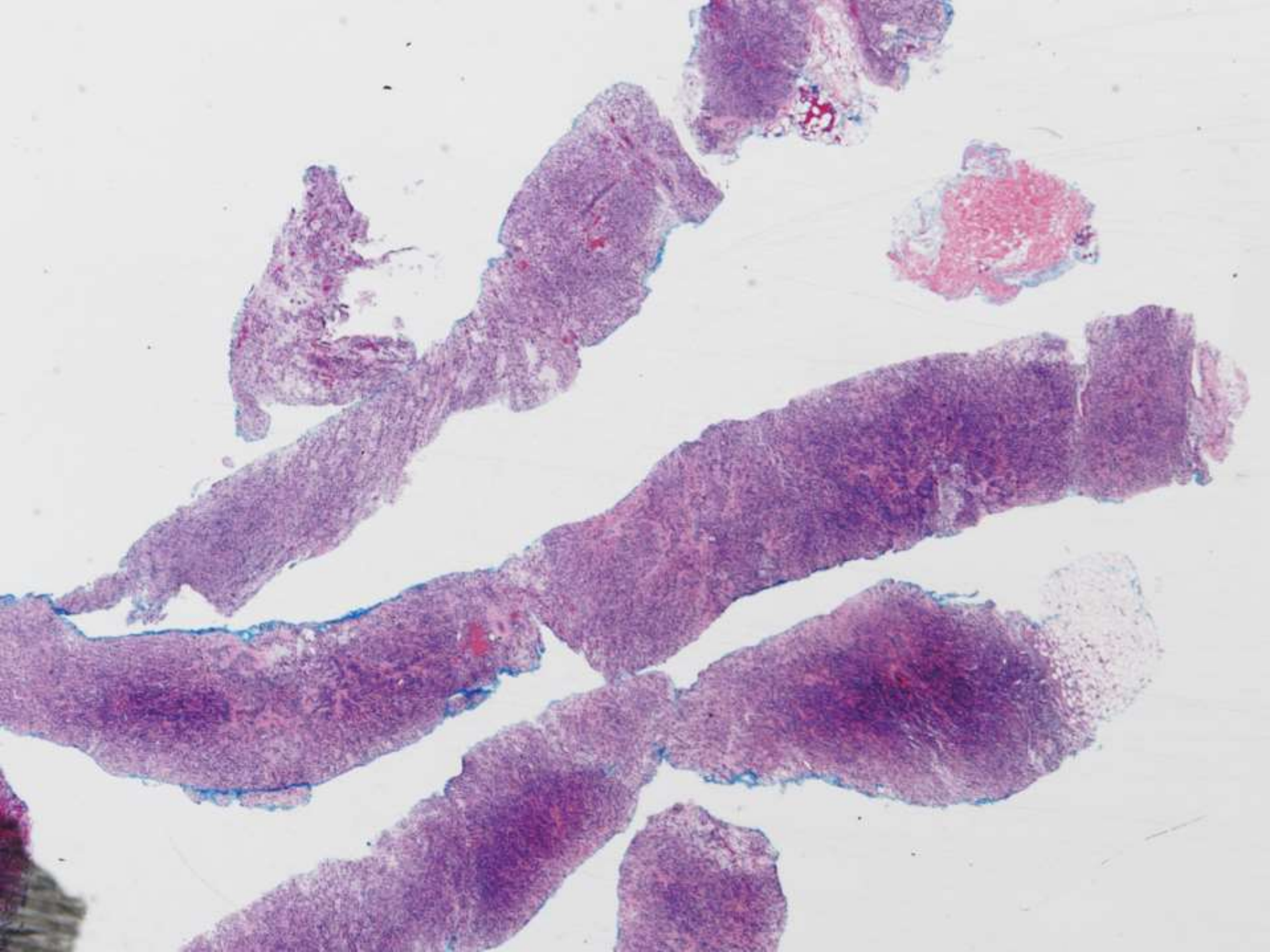
- The only way to distinguish the two is to known the clinical history

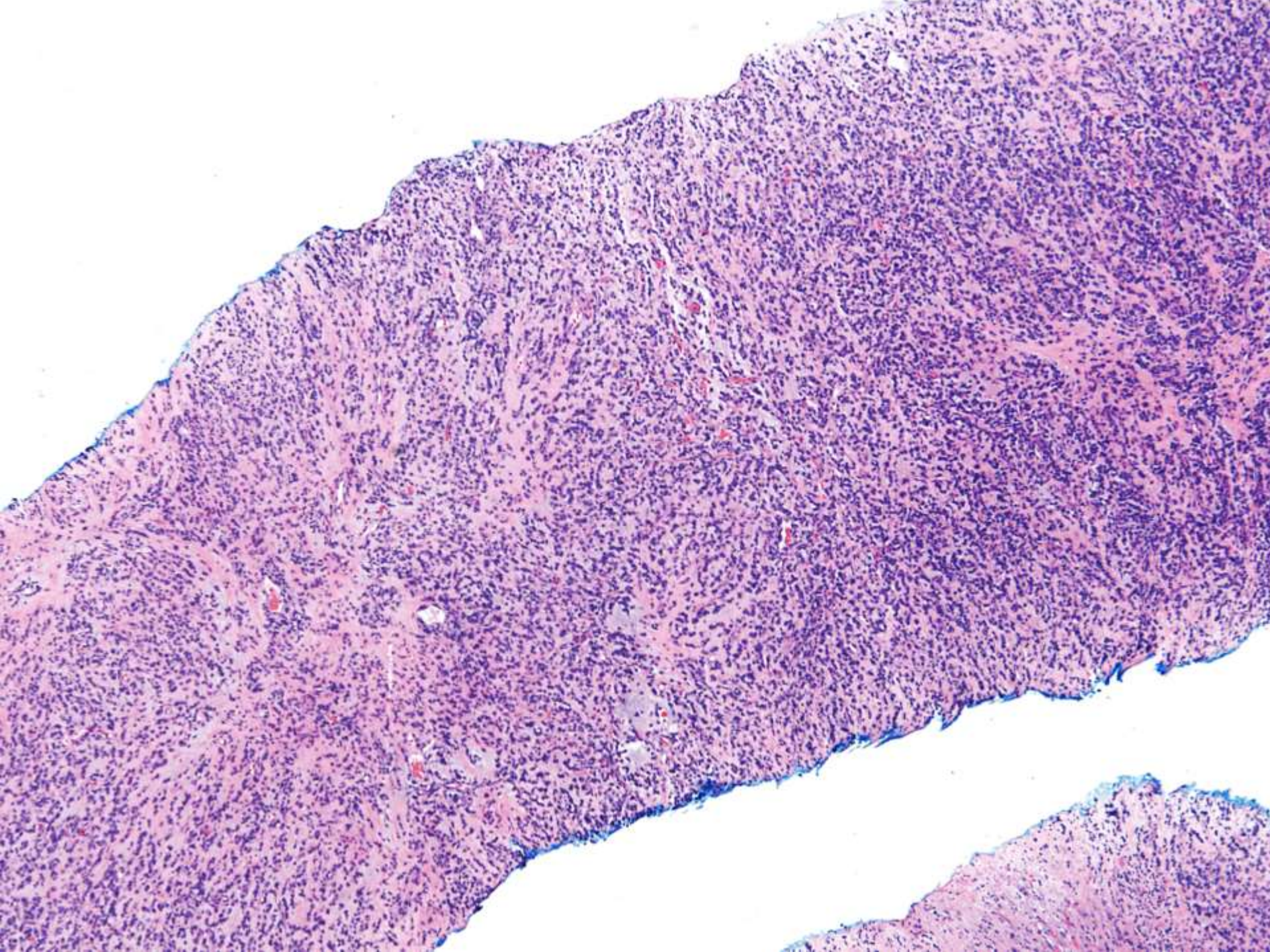
SB 6228

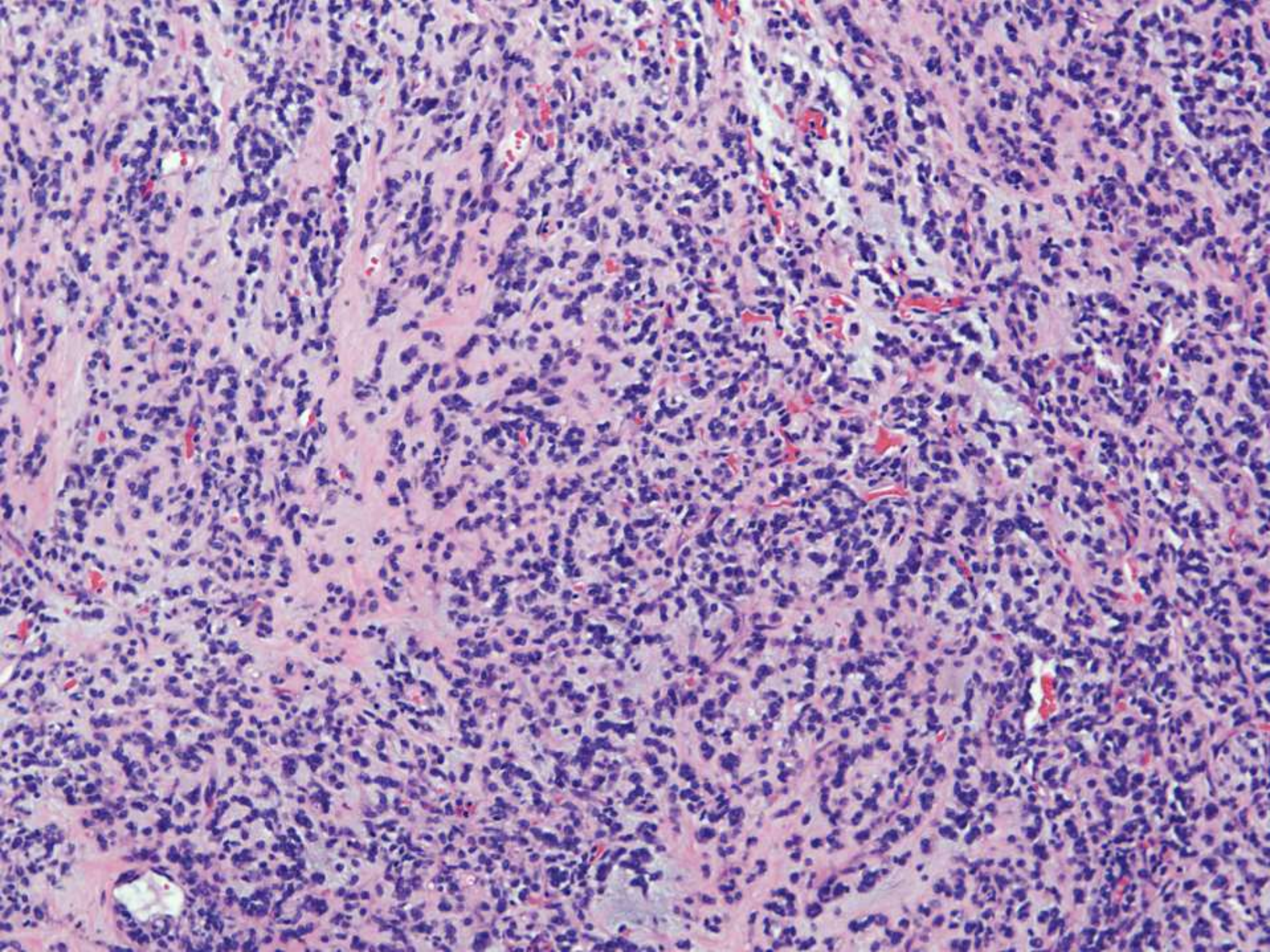
Serena Tan/Eduardo Zambrano; Stanford

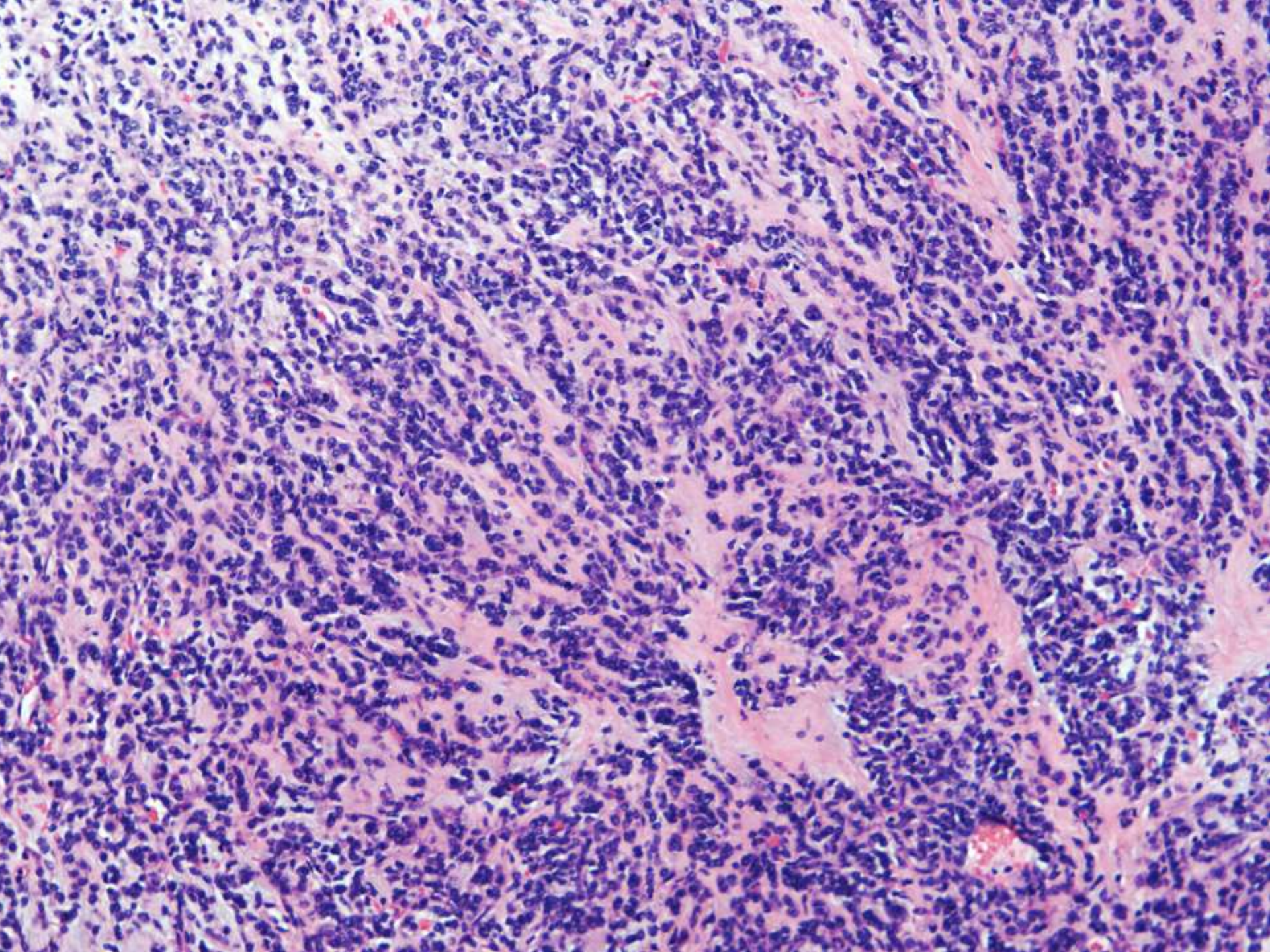
68-year-old female with lesions in the right breast/axilla, liver, lung, and left calf. Right breast biopsy submitted.

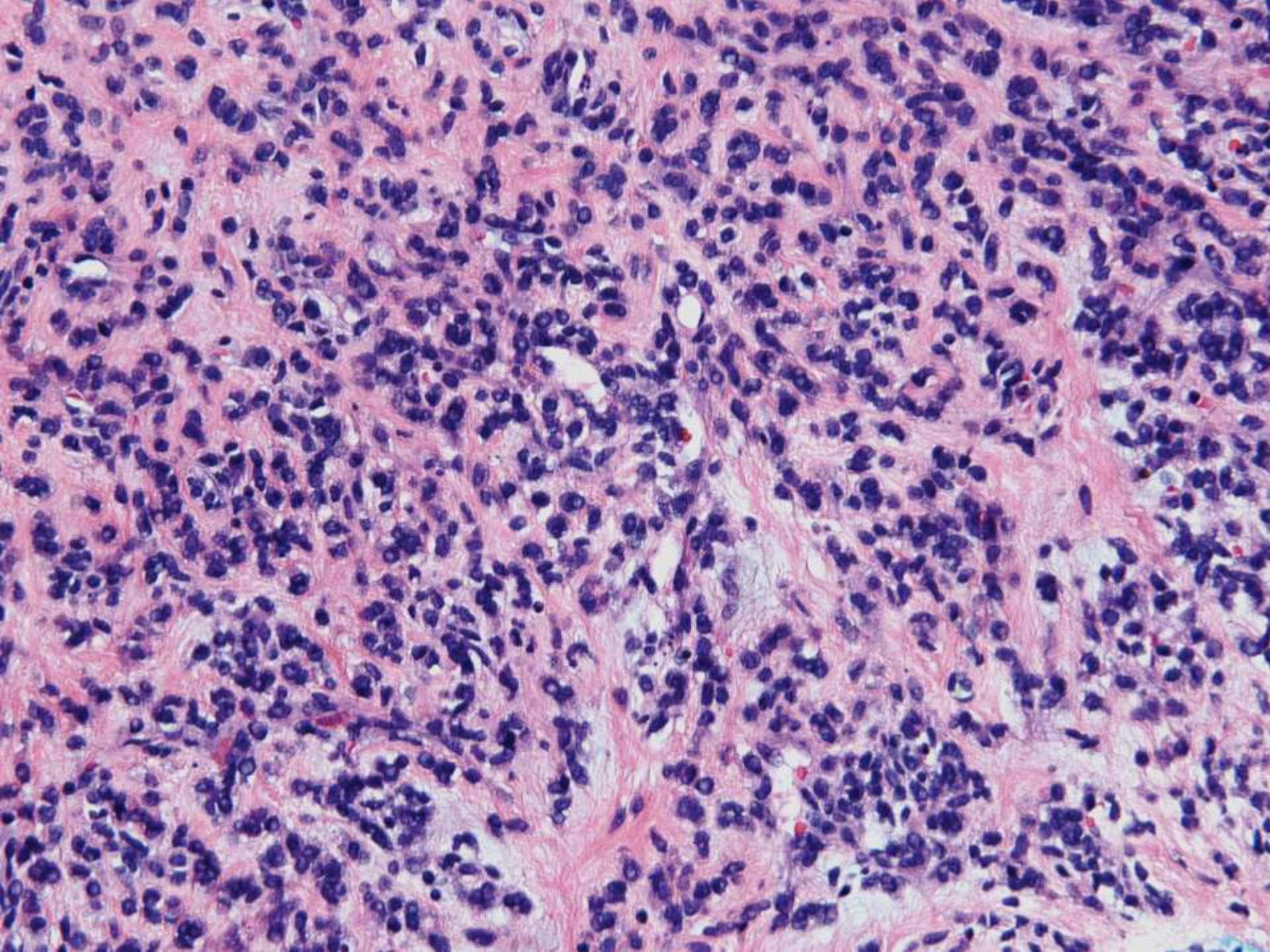


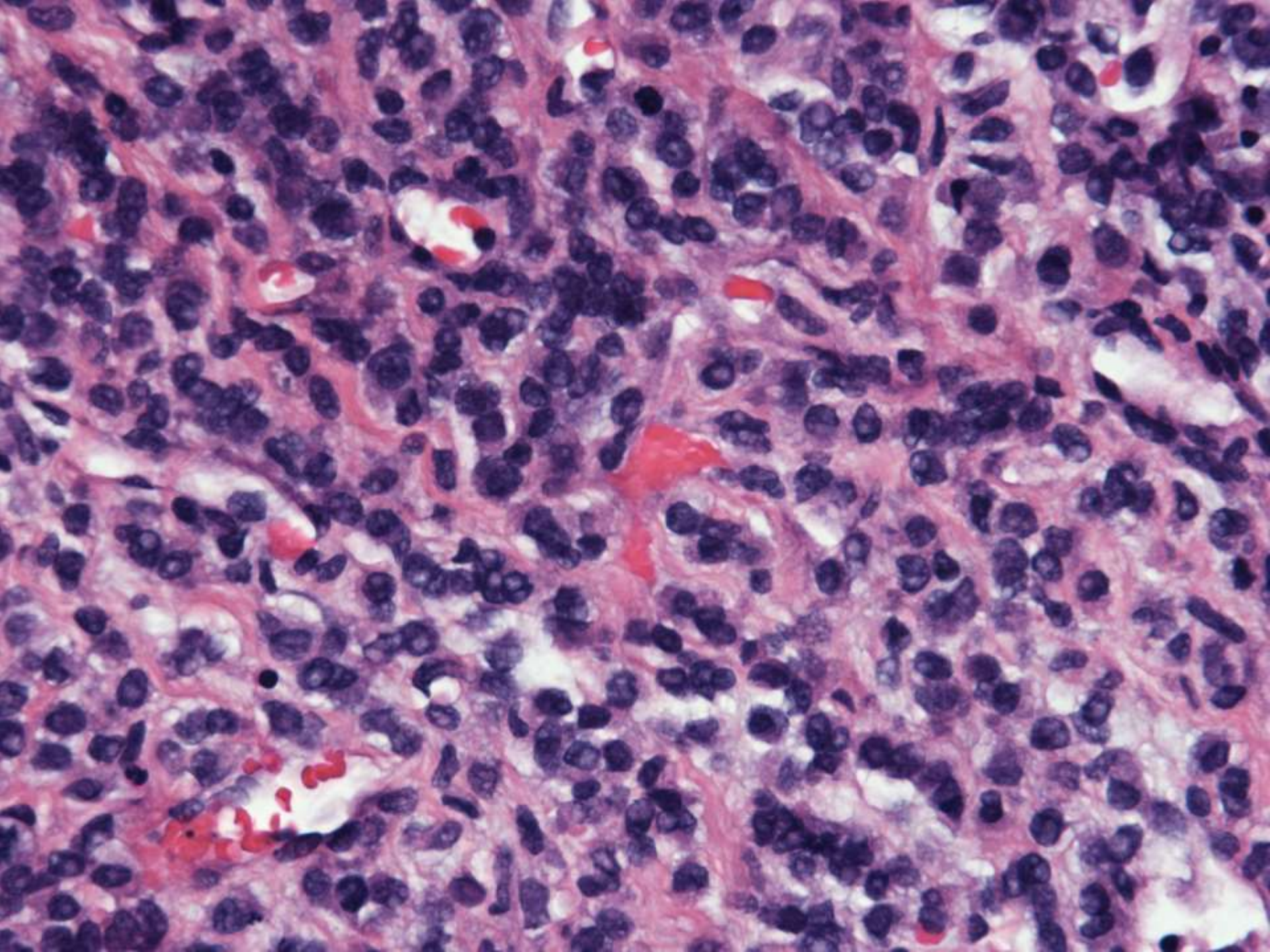


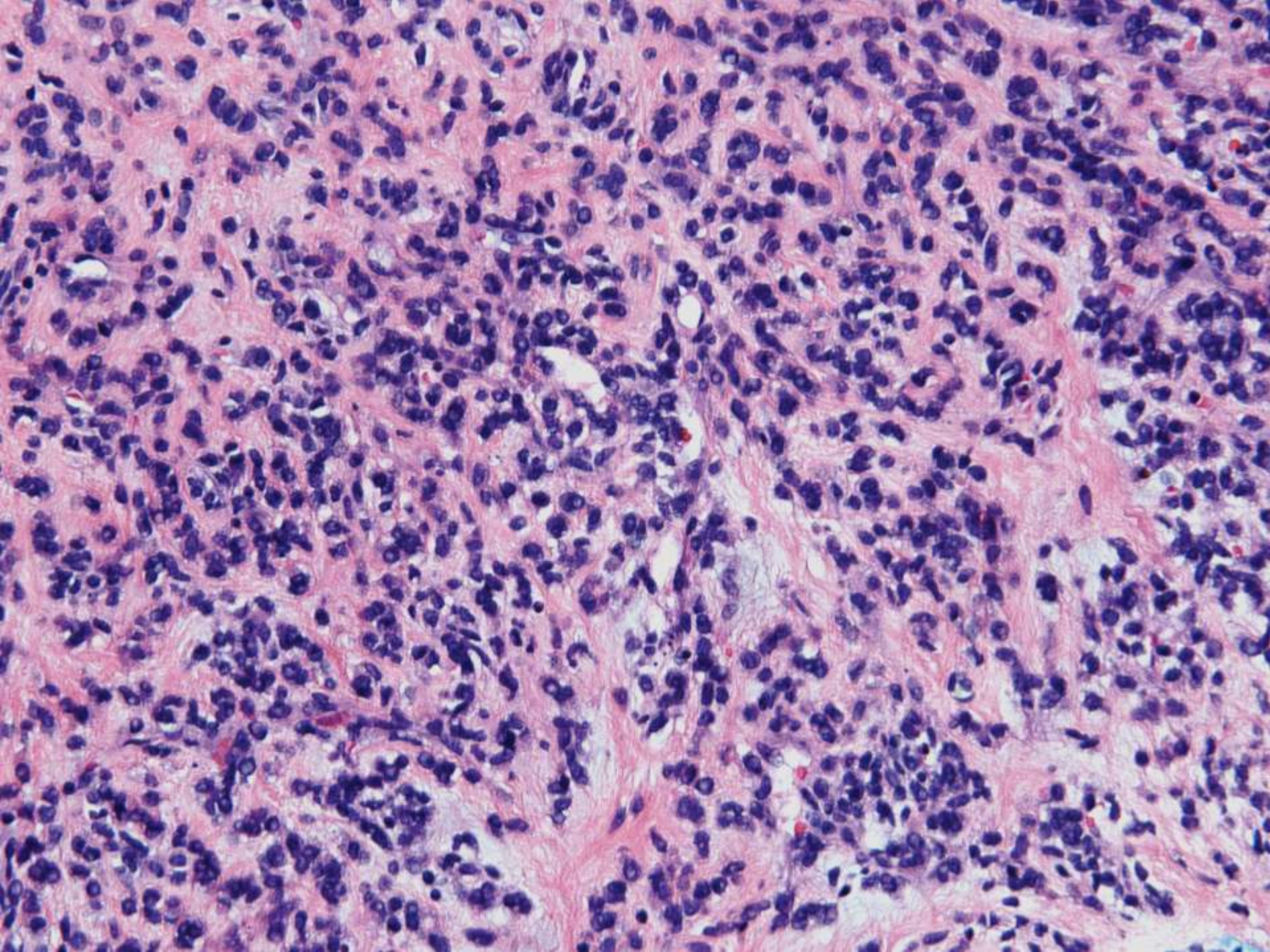












“SRBCT” of Breast: Differential Diagnosis

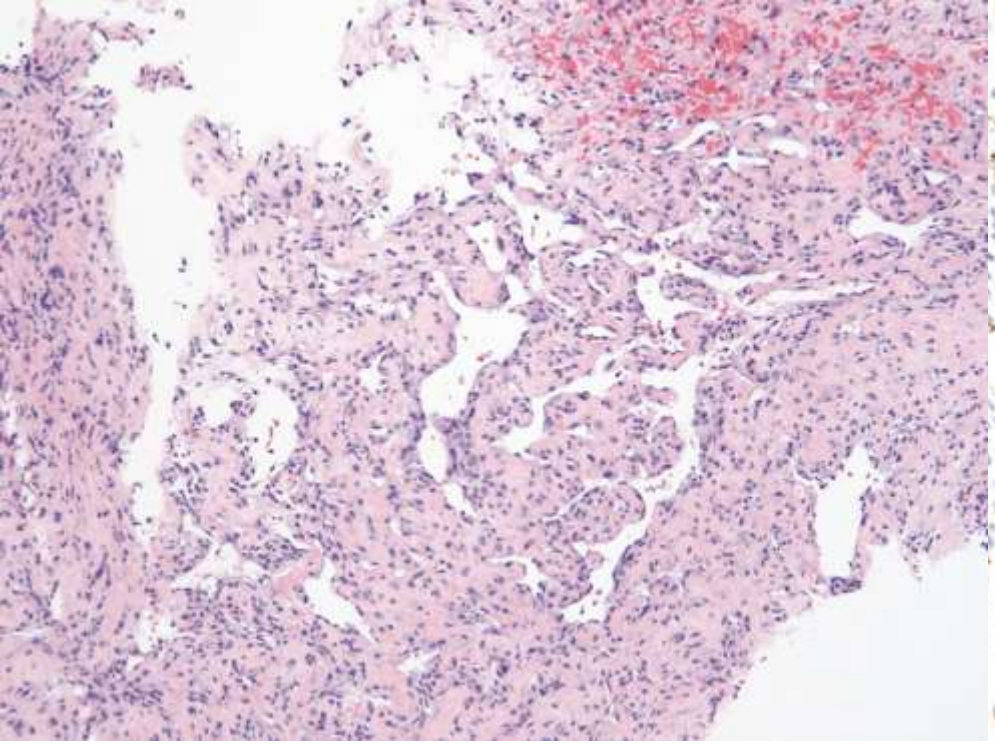
Poorly differentiated/small cell/neuroendocrine carcinoma

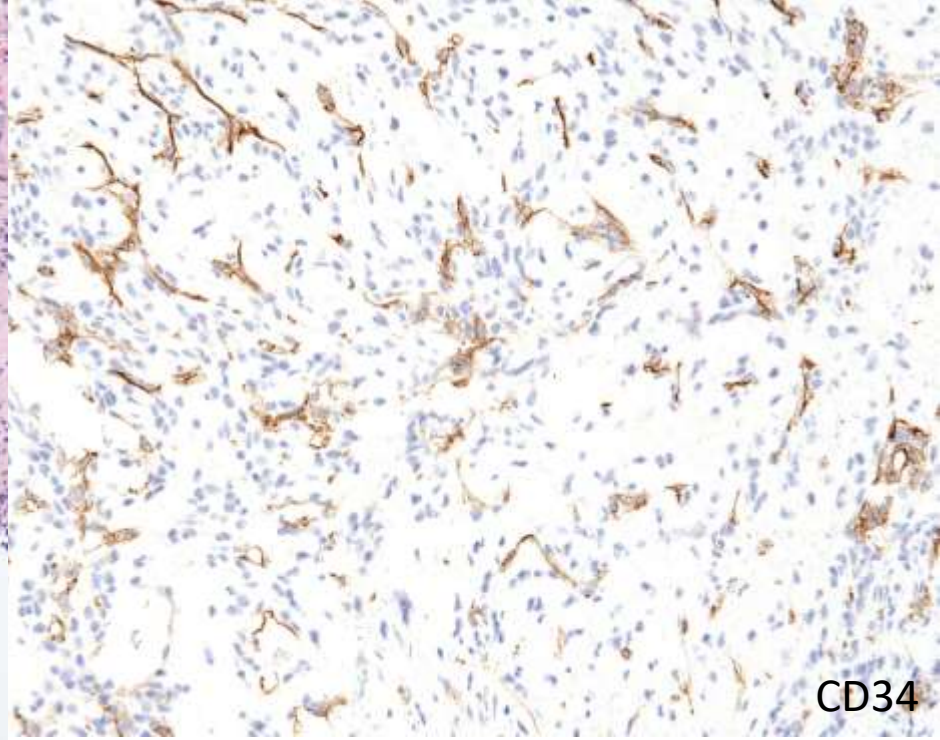
Myofibroblastoma

Lymphoma

Other SRBCT (Ewing, Rhabdomyosarcoma, etc.)

Metastasis





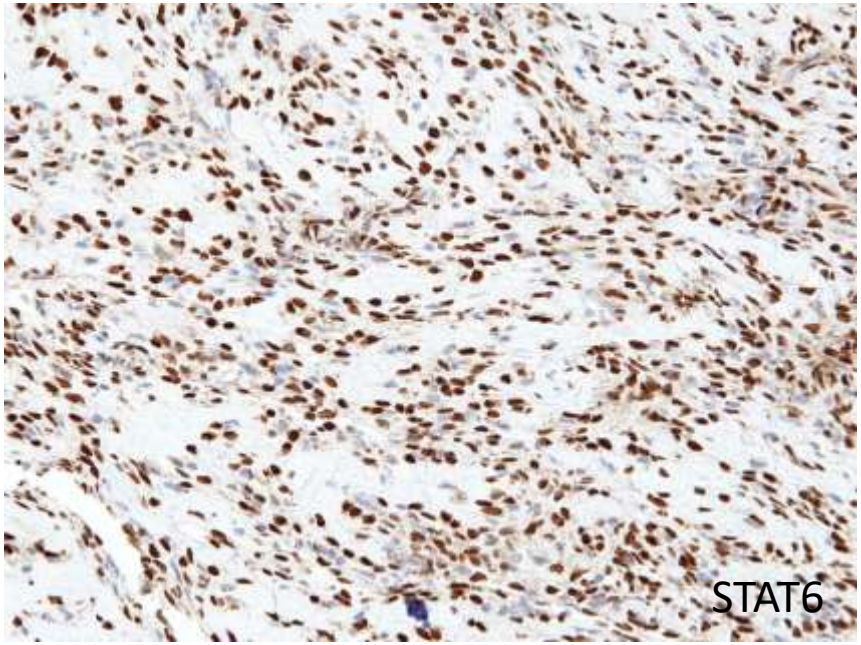
Calf

Negative: CD34, SMA, desmin, S100, ERG, CKmix

INI retained

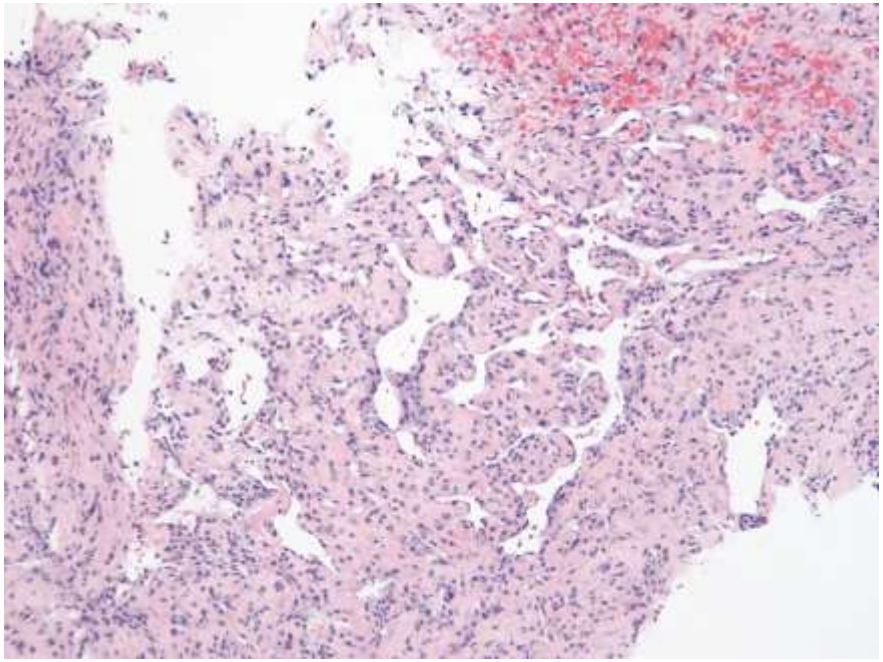
STAT6 positive

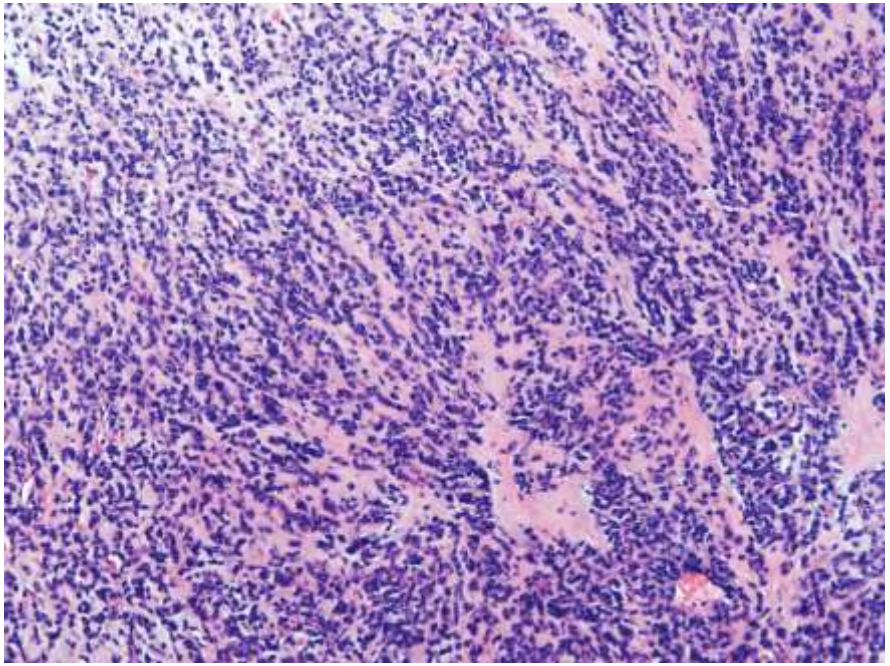
FISH *MDM2* negative

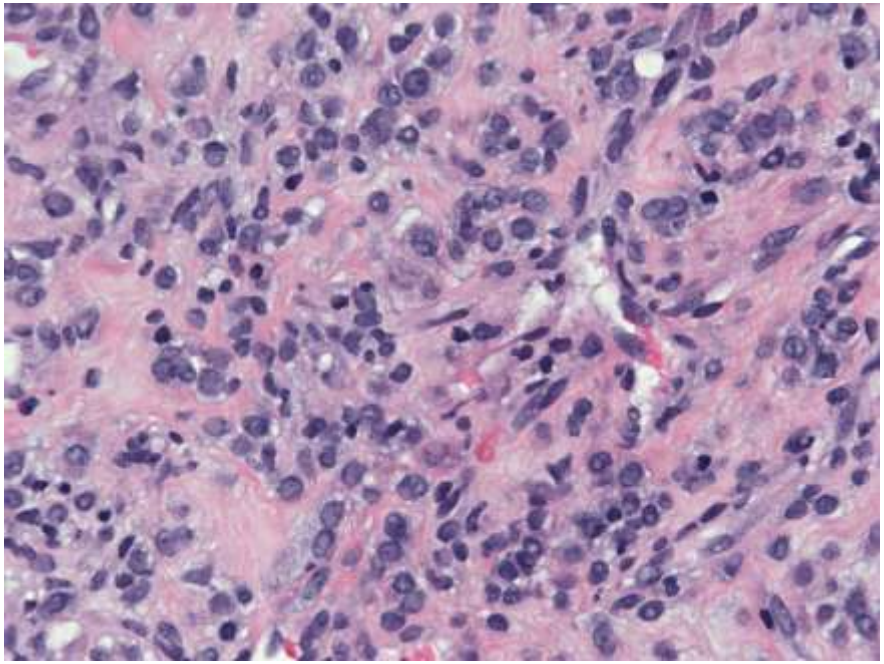


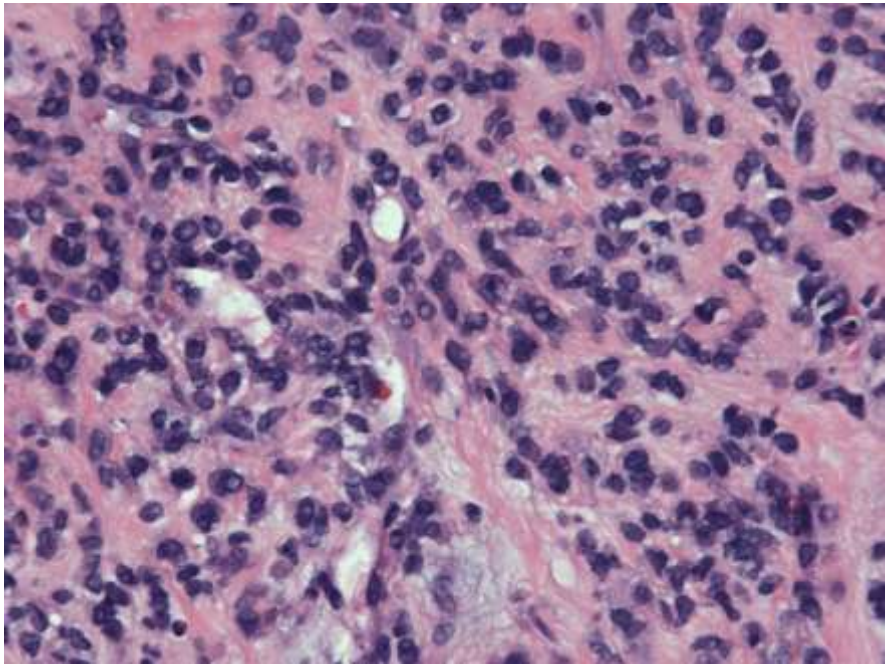
Calf

Breast



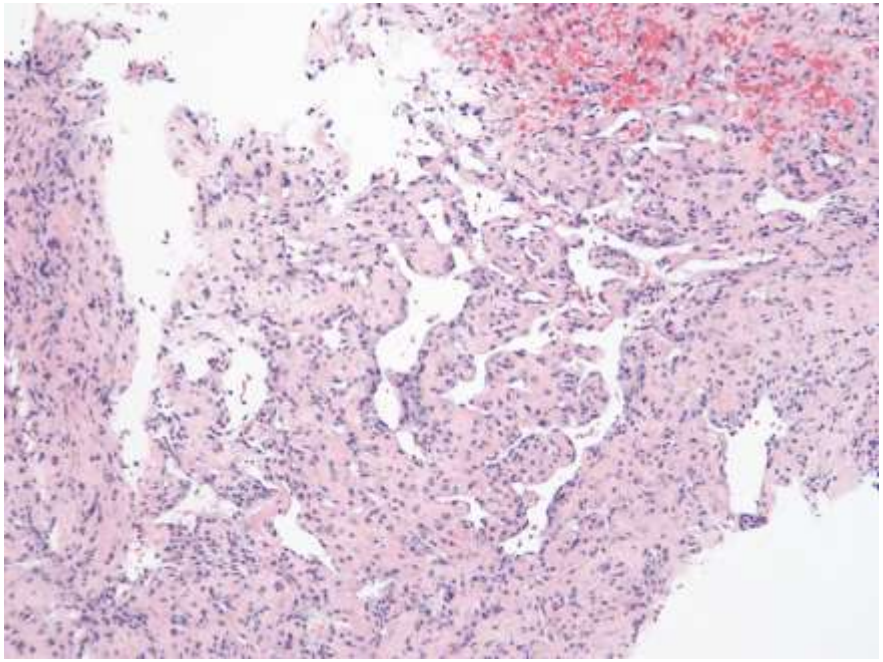


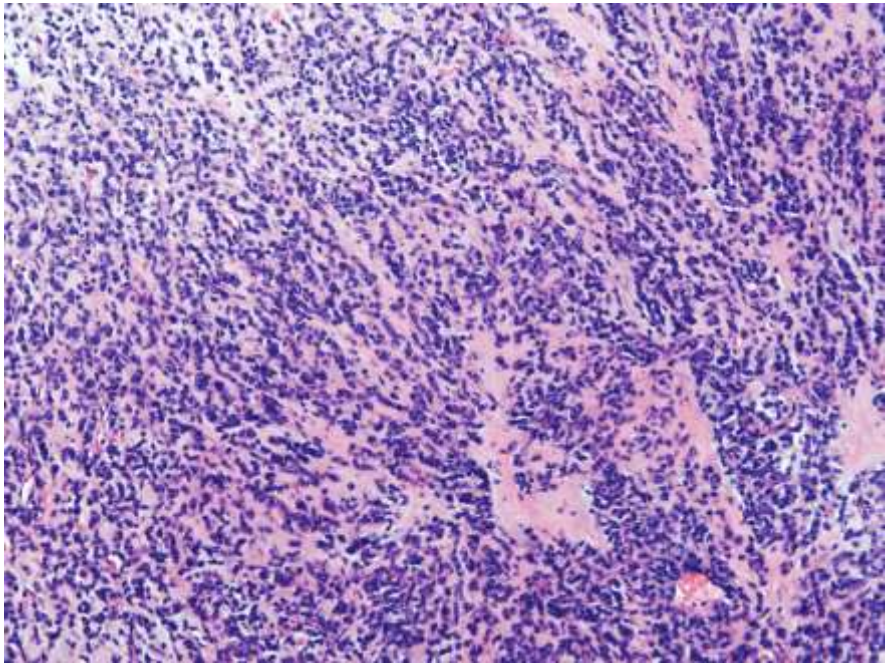


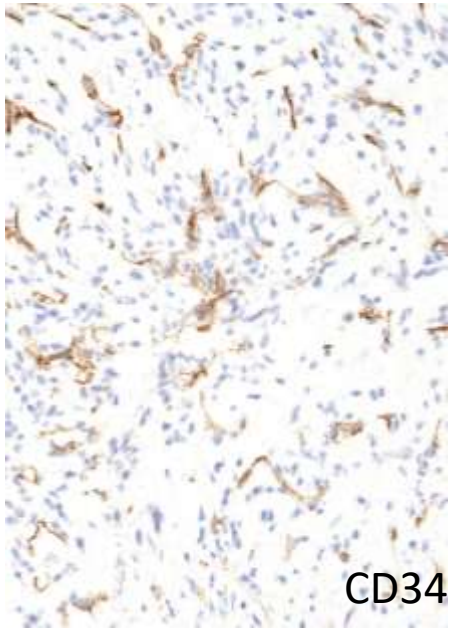


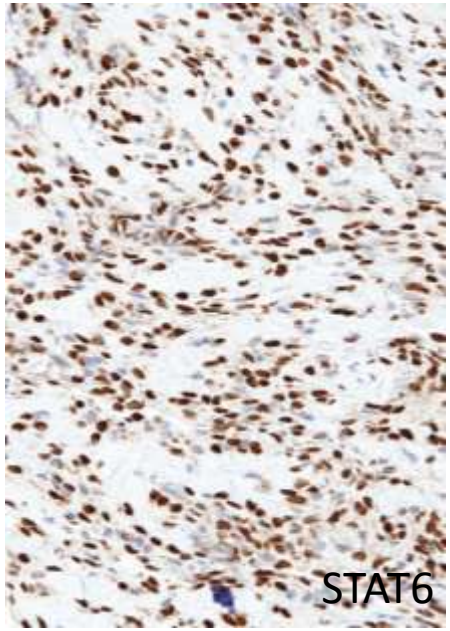
Calf

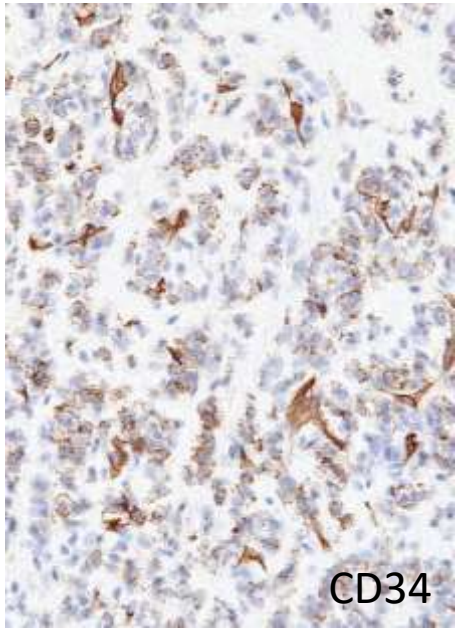
Breast

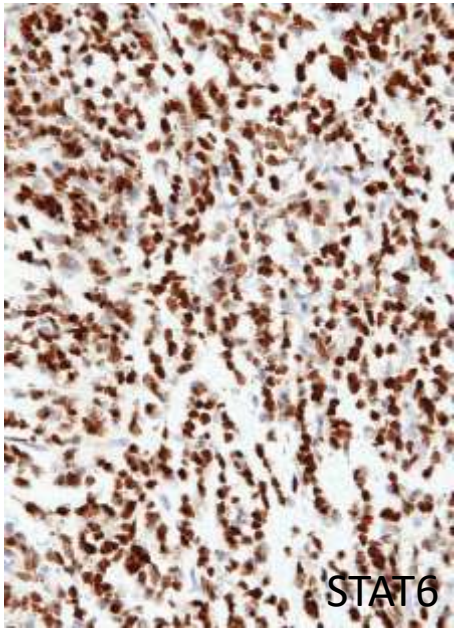




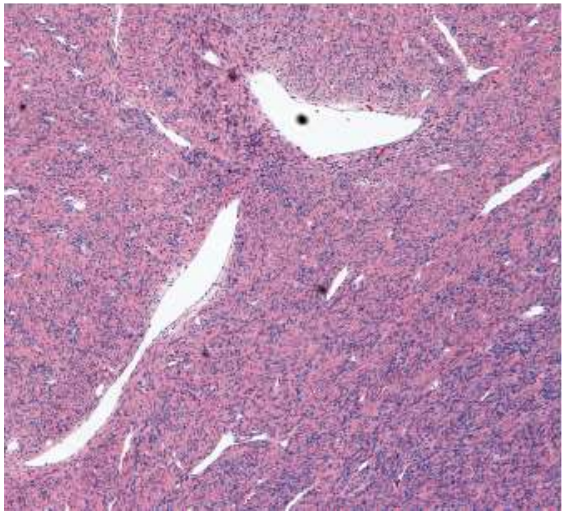


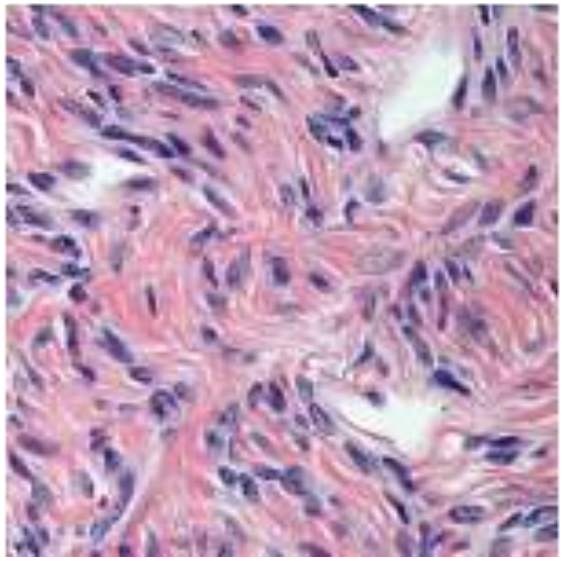






Solitary Fibrous Tumors



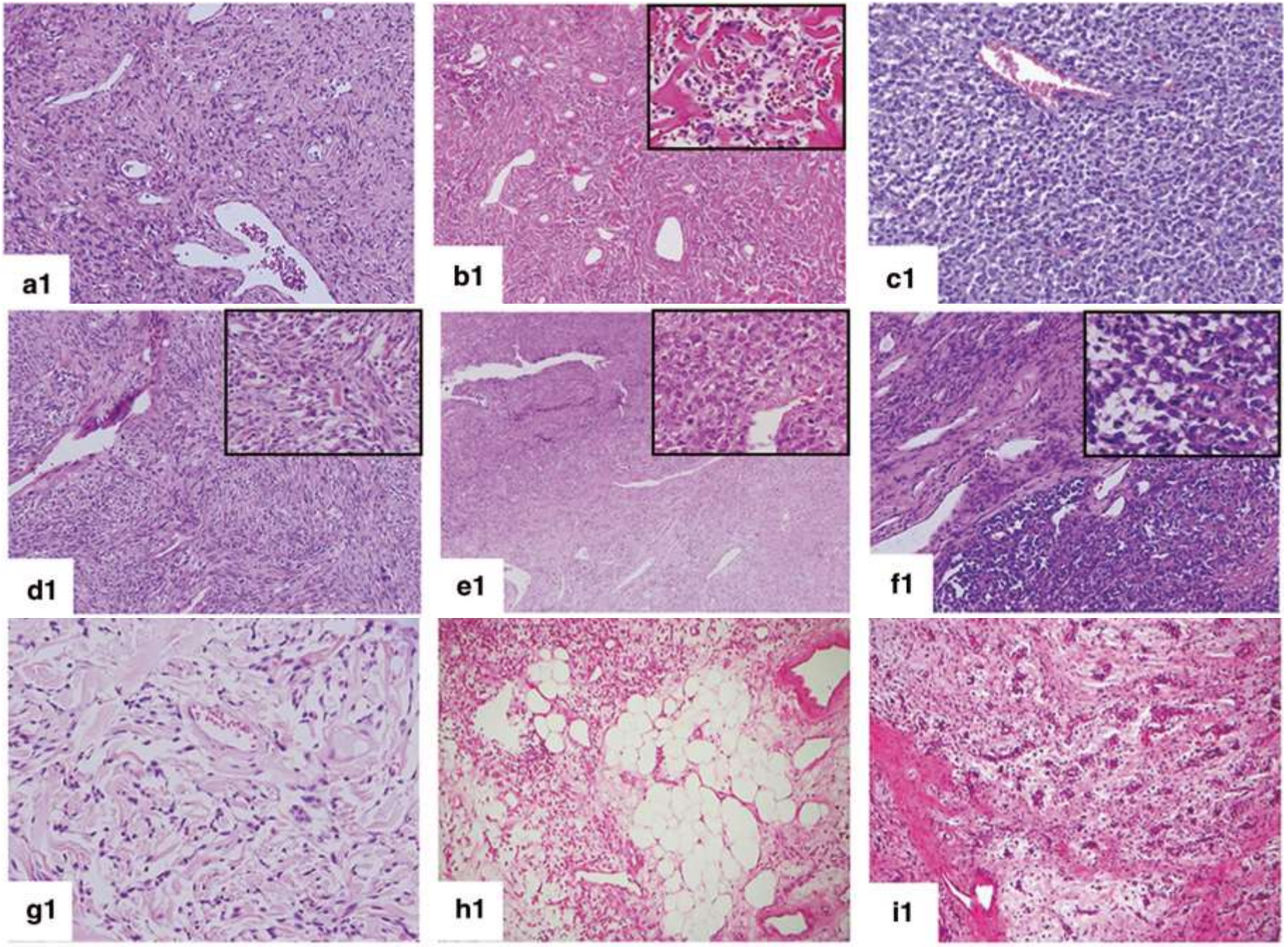


Fibroblastic neoplasm featuring prominent branching (staghorn) vessels, “patternless pattern” and classically fibrous stroma

Can arise virtually anywhere

Behavior can be unpredictable; distant metastases can arise years after initial presentation

CD34+ STAT6+; Characteristic *NAB2-STAT6* fusion



Mod Pathol. 2015 Oct;28(10):1324-35.

Solitary Fibrous Tumors - Quirks

Can be histologically varied (in spite of “classic” look)

Histology not always predictive of behavior
- Hypercellularity, pleomorphism, high mitotic activity, necrosis and infiltrative margins suggestive aggression
- Benign appearing SFTs can rarely recur/metastasize
- Size and location most important predictors

IHC Pitfalls:
Malignant SFTs can lose CD34 expression
Dedifferentiated SFTs can lose STAT6 expression
Beta-catenin can be rarely positive

References

Dagrada GP, Spagnuolo RD, Mauro V, Tamborini E, Cesana L, Gronchi A, Stacchiotti S, Pierotti MA, Negri T, Pilotti S. Solitary fibrous tumors: loss of chimeric protein expression and genomic instability mark dedifferentiation. *Mod Pathol.* 2015 Aug;28(8):1074-83.

Gholami S, Cassidy MR, Kirane A, Kuk D, Zanchelli B, Antonescu CR, Singer S, Brennan M. Size and Location are the Most Important Risk Factors for Malignant Behavior in Resected Solitary Fibrous Tumors. *Ann Surg Oncol.* 2017 Dec;24(13):3865-3871.

Hajdu M, Singer S, Maki RG, Schwartz GK, Keohan ML, Antonescu CR. IGF2 Overexpression in Solitary Fibrous Tumors is Independent of Anatomic Location and is Related to Loss of Imprinting. *The Journal of Pathology.* 2010;221(3):300-307.

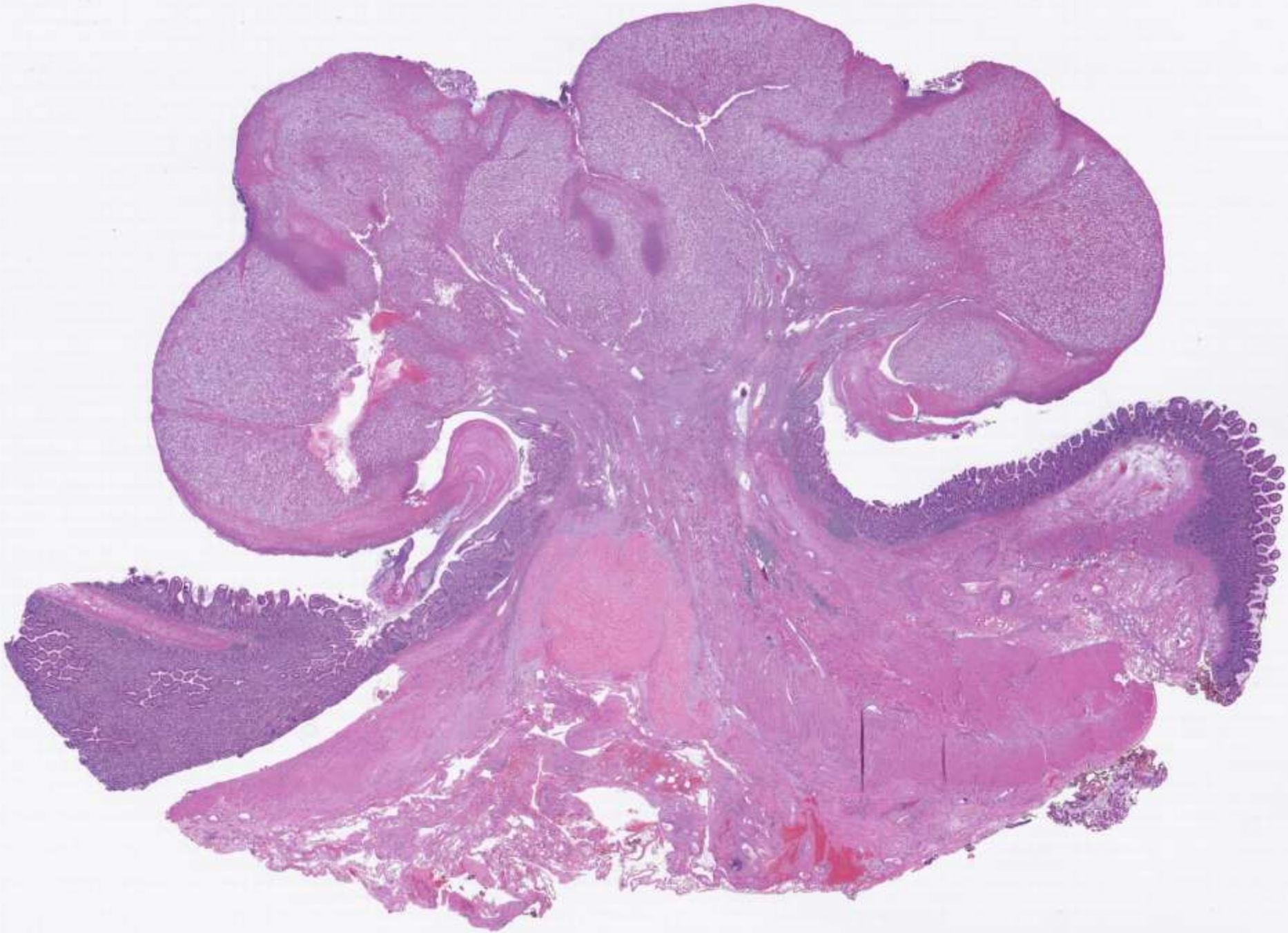
Tai HC, Chuang IC, Chen TC, Li CF, Huang SC, Kao YC, Lin PC, Tsai JW, Lan J, Yu SC, Yen SL, Jung SM, Liao KC, Fang FM, Huang HY. NAB2-STAT6 fusion types account for clinicopathological variations in solitary fibrous tumors. *Mod Pathol.* 2015 Oct;28(10):1324-35.

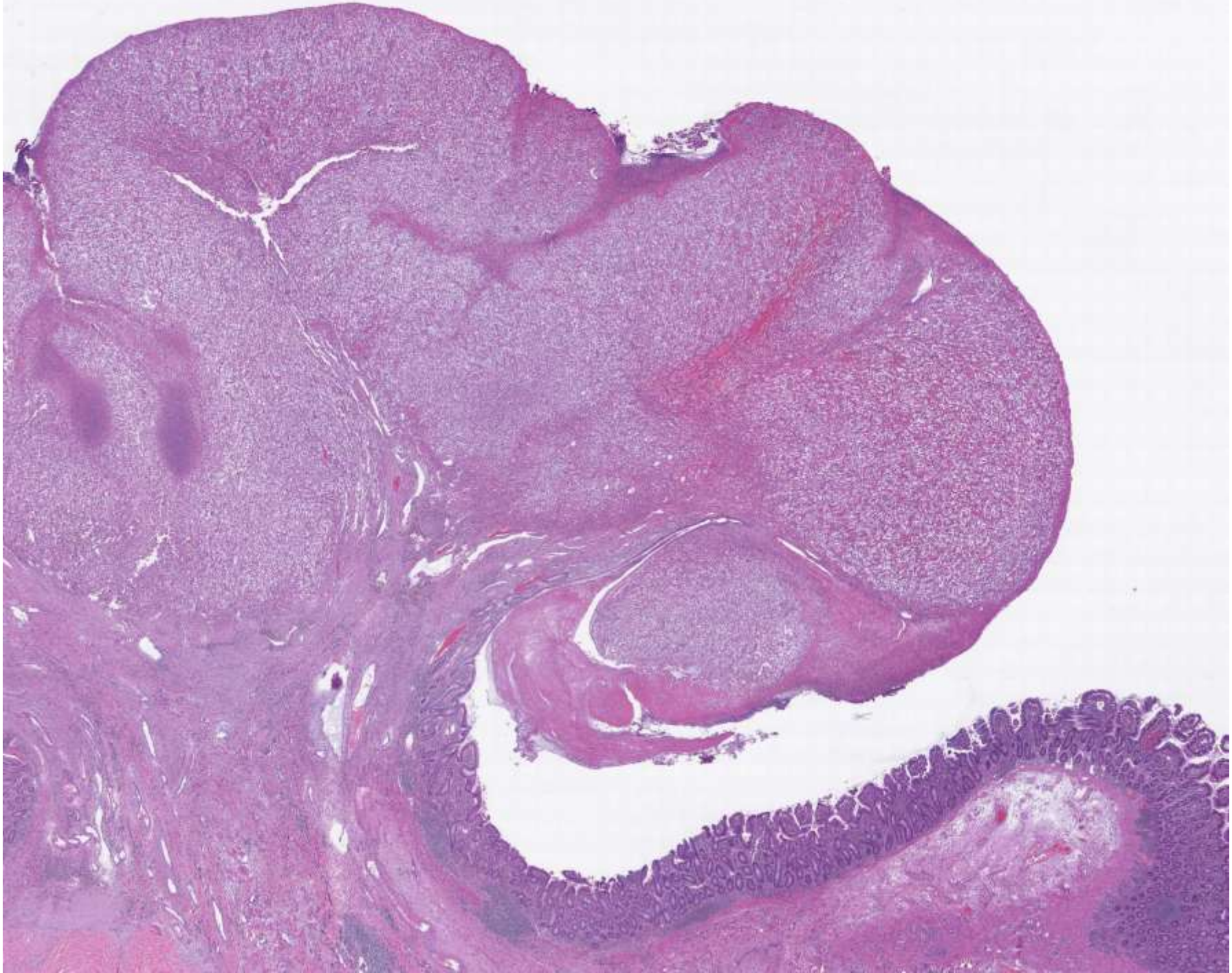
Vogels RJ, Vlenterie M, Versleijen-Jonkers YM, et al. Solitary fibrous tumor – clinicopathologic, immunohistochemical and molecular analysis of 28 cases. *Diagnostic Pathology*. 2014;9:224.

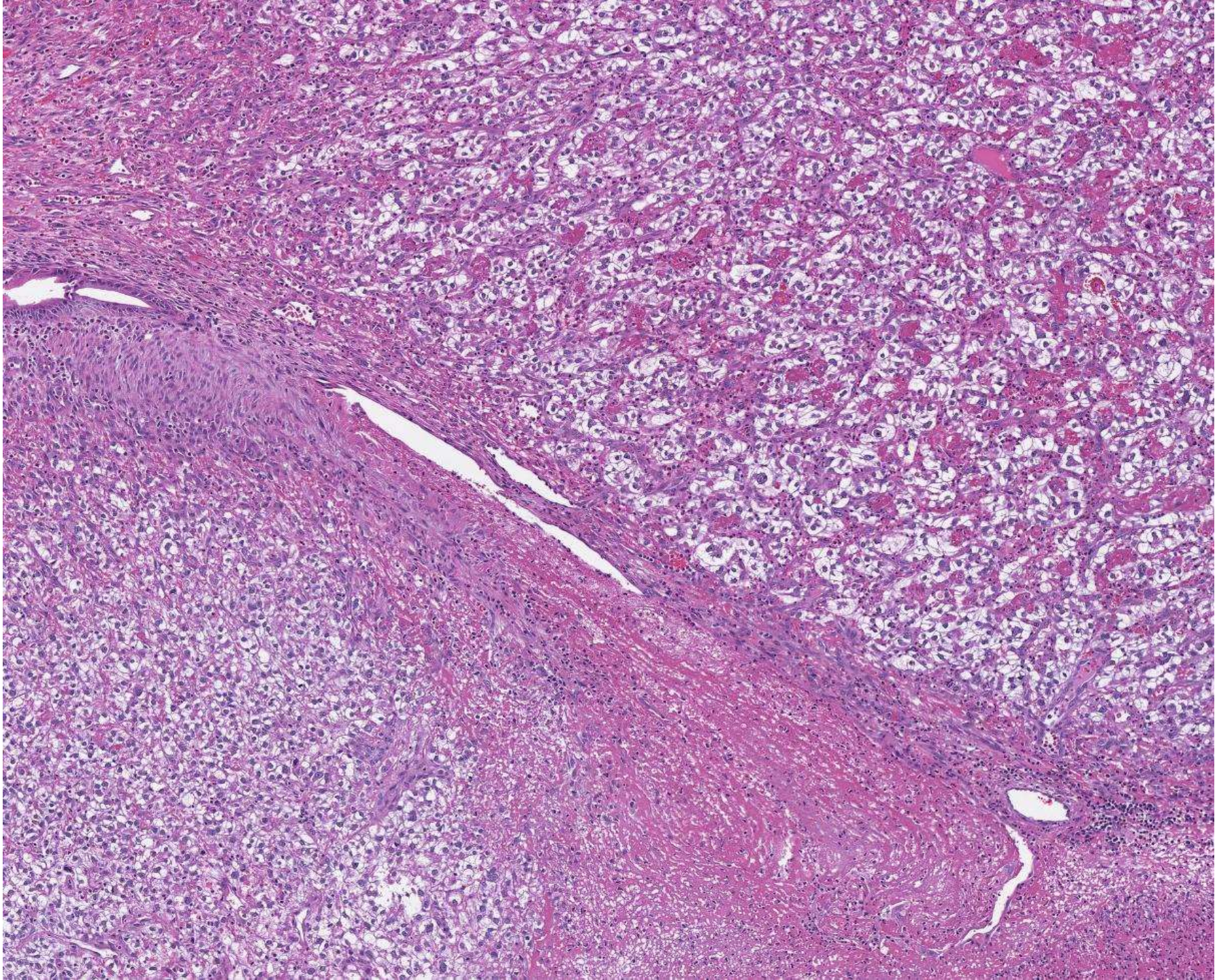
SB 6229

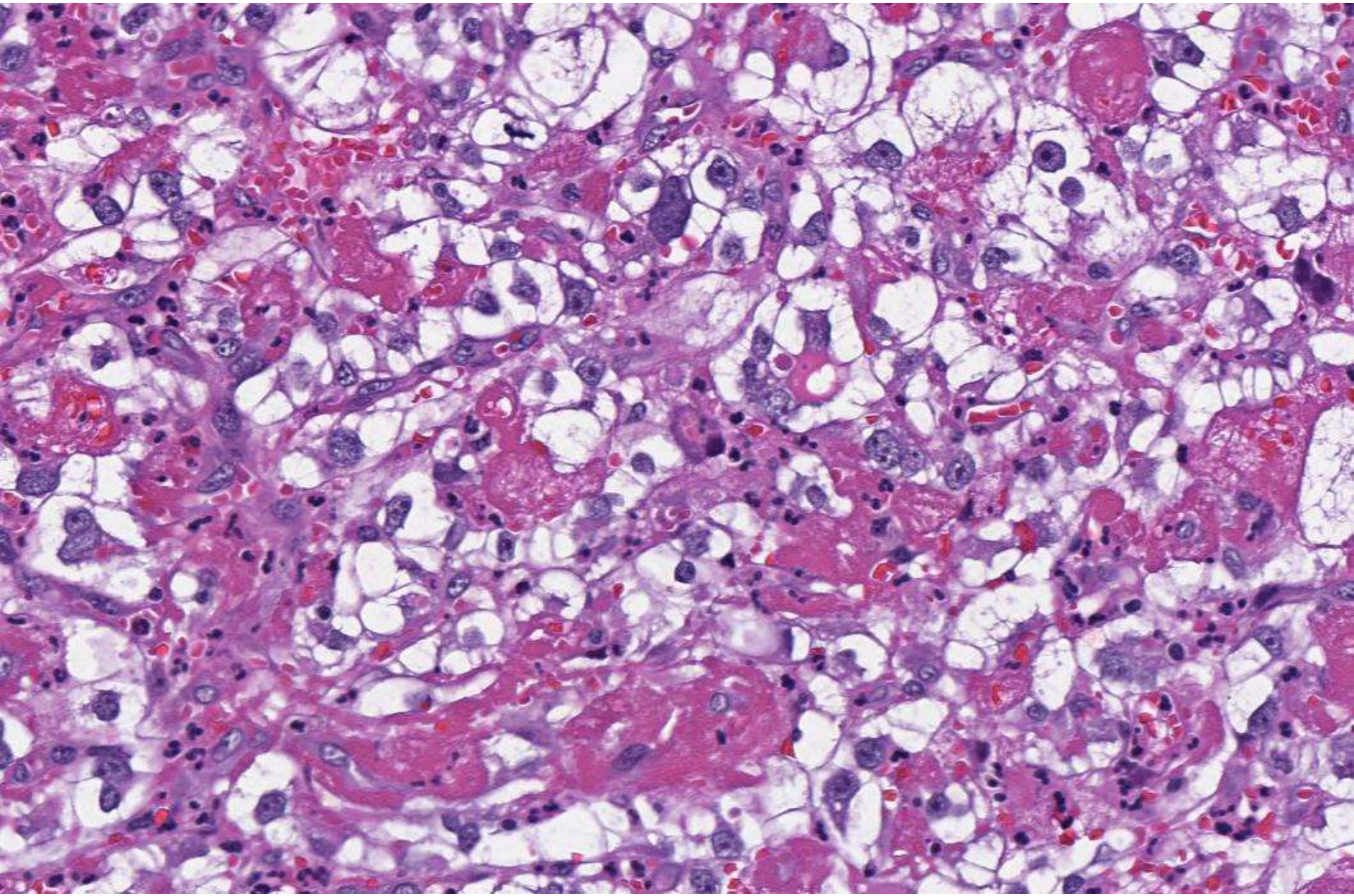
Ankur Sangoi; El Camino Hospital

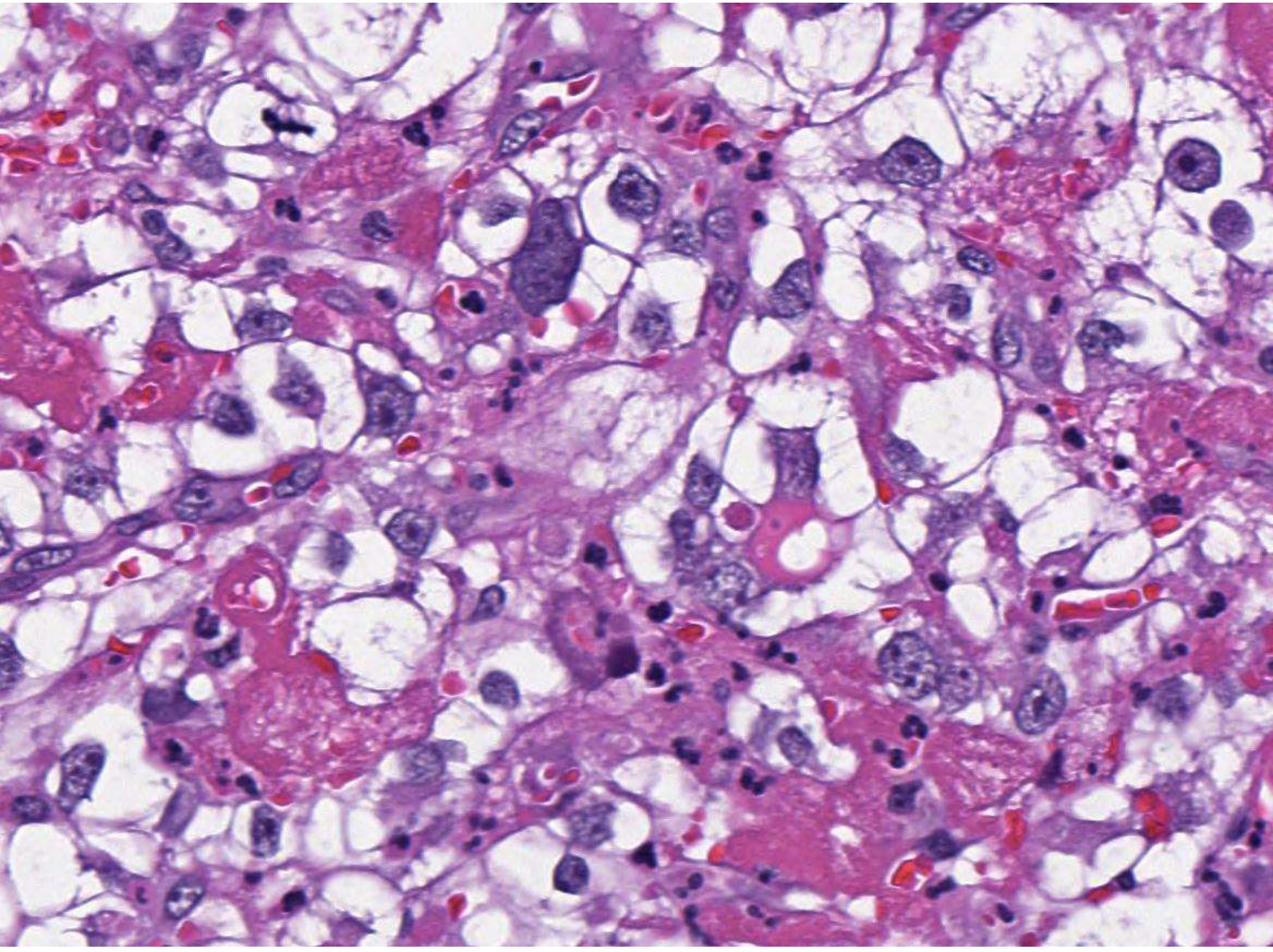
59-year-old male presenting with symptoms of small bowel obstruction. Resection submitted.











DDx

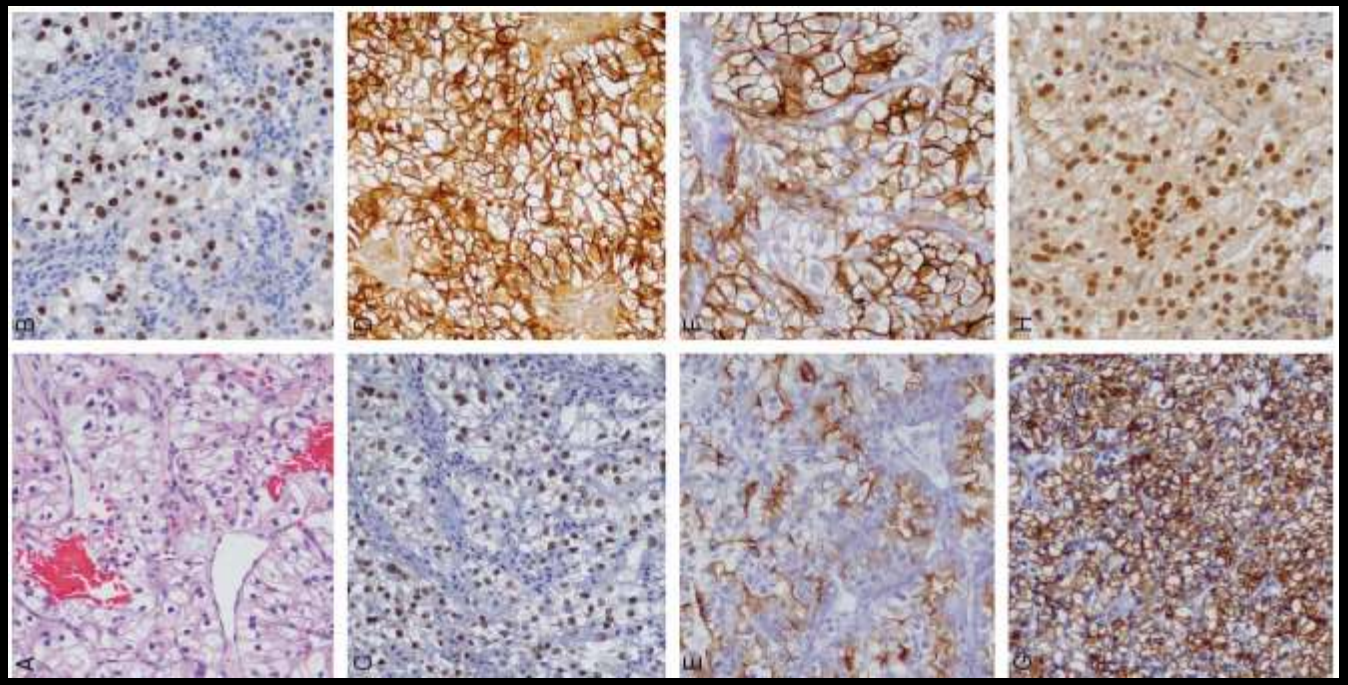
- **Small bowel adenocarcinoma**
- **Clear cell sarcoma-like tumor of GI tract**
- **Malignant GI neuroectodermal tumor**
- **Melanoma**
- **Epithelioid GIST**
- **Epithelioid leiomyosarcoma**
- **PEComa**
- **Paraganglioma**
- **Metastasis**
  - Metastatic RCC

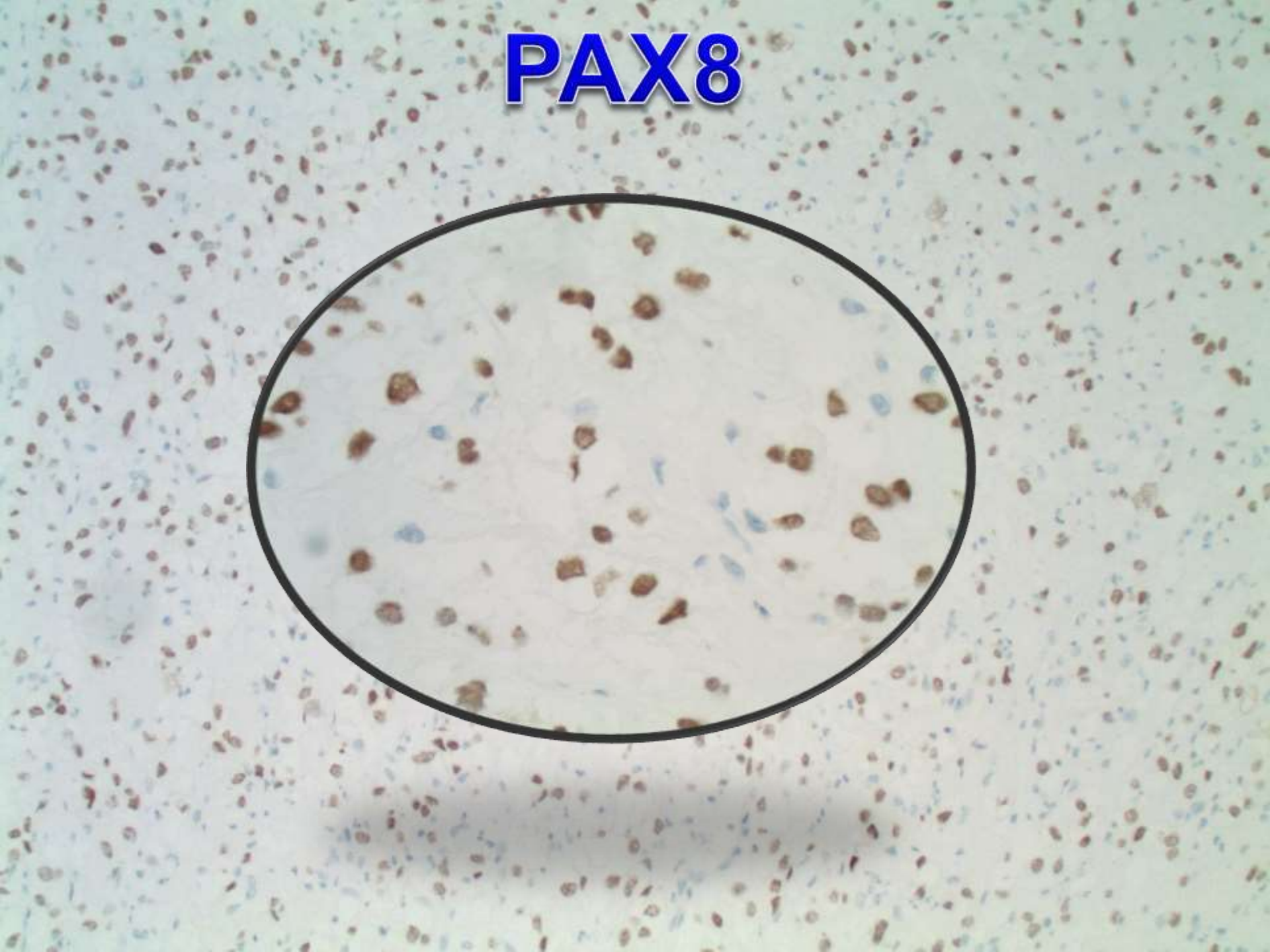
The Use of Immunohistochemistry in the Diagnosis of Metastatic Clear Cell Renal Cell Carcinoma

A Review of PAX-8, PAX-2, hKIM-1, RCCma, and CD10

Ankur R. Sangoi, MD,† Jason Karamchandani, MD,* Jinah Kim, MD, PhD,*
Reetesh K. Pai, MD,* and Jesse K. McKenney, MD**

Adv Anat Pathol • Volume 17, Number 6, November 2010




PAX8

DIAGNOSIS: metastatic RCC

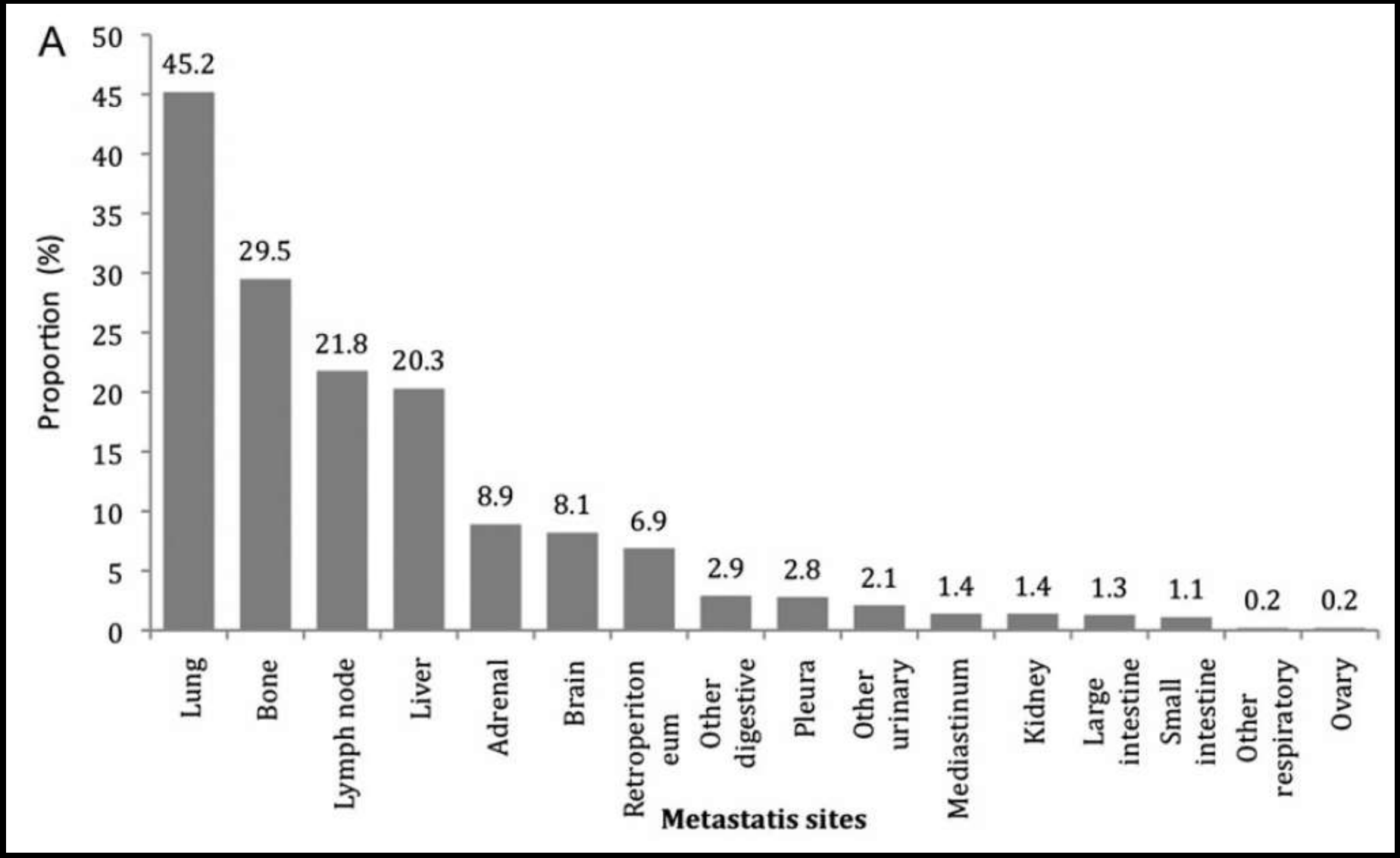
Distribution of metastatic sites in renal cell carcinoma: a population-based analysis

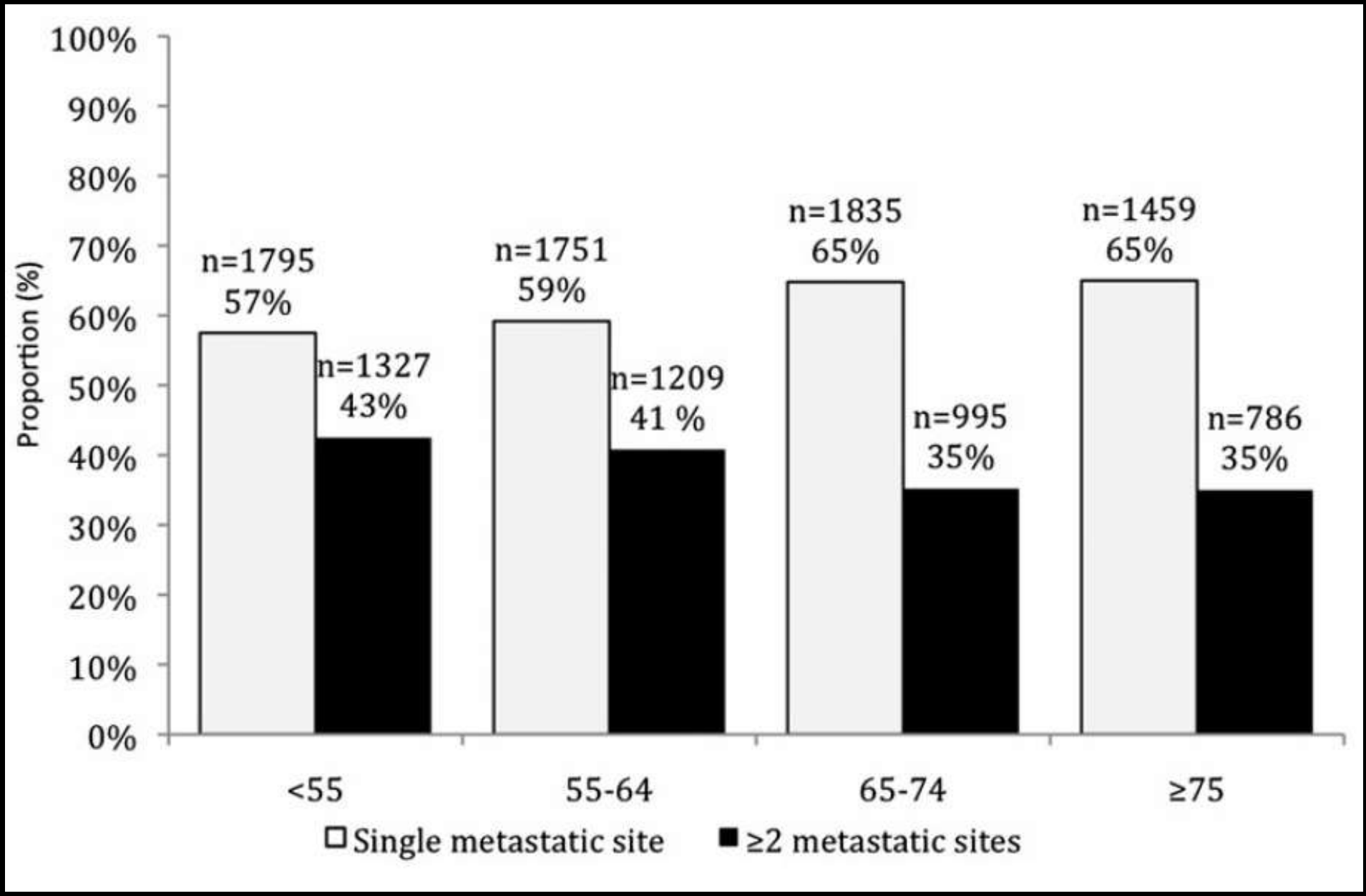
M. Bianchi[1,2*†], M. Sun[2†], C. Jeldres[2,3], S. F. Shariat[4], Q.-D. Trinh[2,5], A. Briganti[1], Z. Tian[2], J. Schmitges[2,6], M. Graefen[6], P. Perrotte[3], M. Menon[5], F. Montorsi[1] & P. I. Karakiewicz[2,3]

Annals of Oncology 23: 973–980, 2012

Table 1. Descriptive characteristics of patients diagnosed with metastatic renal cell carcinoma, Nationwide Inpatient Sample, 1998–2007

	Overall	<55 years	55–64 years	65–74 years	≥75 years	*P*-value
No. of patients	11 157	3122 (28.0)	2960 (26.5)	2830 (25.4)	2245 (20.1)	—
Site of metastases						
Lung	5039 (45.2)	1417 (45.4)	1419 (47.9)	1232 (43.5)	971 (43.3)	<0.01
Bone	3268 (29.5)	922 (29.5)	910 (30.7)	820 (29.0)	616 (27.4)	0.07
Lymph node	2451 (21.8)	816 (26.1)	638 (21.6)	590 (20.8)	407 (18.1)	<0.001
Liver	2267 (20.3)	648 (20.8)	569 (19.2)	507 (17.9)	543 (24.2)	<0.001
Adrenal	991 (8.9)	306 (9.8)	268 (9.1)	255 (9.0)	162 (7.2)	0.01
Brain	904 (8.1)	291 (9.3)	279 (9.4)	212 (7.5)	122 (5.4)	<0.001
Other[a]	2027 (18.2)	551 (17.6)	520 (17.6)	526 (18.6)	430 (19.2)	0.4
No. of metastatic sites						<0.001
1	6840 (61.3)	1795 (57.5)	1751 (59.2)	1835 (64.8)	1459 (65.0)	
≥2	4317 (38.3)	1327 (42.5)	1209 (40.8)	995 (35.2)	786 (35.0)	
Sex						<0.001
Male	7113 (63.8)	2170 (69.6)	2046 (69.1)	1747 (61.7)	1150 (51.2)	
Female	4040 (36.2)	949 (30.4)	914 (30.9)	1083 (38.3)	1094 (48.8)	
Race						<0.001
Caucasian	6358 (57.0)	1625 (52.0)	1654 (55.9)	1682 (59.4)	1397 (62.2)	
African-American	775 (6.9)	289 (9.3)	200 (6.8)	176 (6.2)	110 (4.9)	
Hispanic	787 (7.1)	275 (8.8)	228 (7.7)	174 (6.1)	110 (4.9)	
Other[b]	335 (3.0)	108 (3.5)	96 (3.2)	74 (2.6)	57 (2.5)	
Unknown	2902 (26.0)	825 (26.4)	782 (26.4)	724 (25.6)	571 (25.4)	

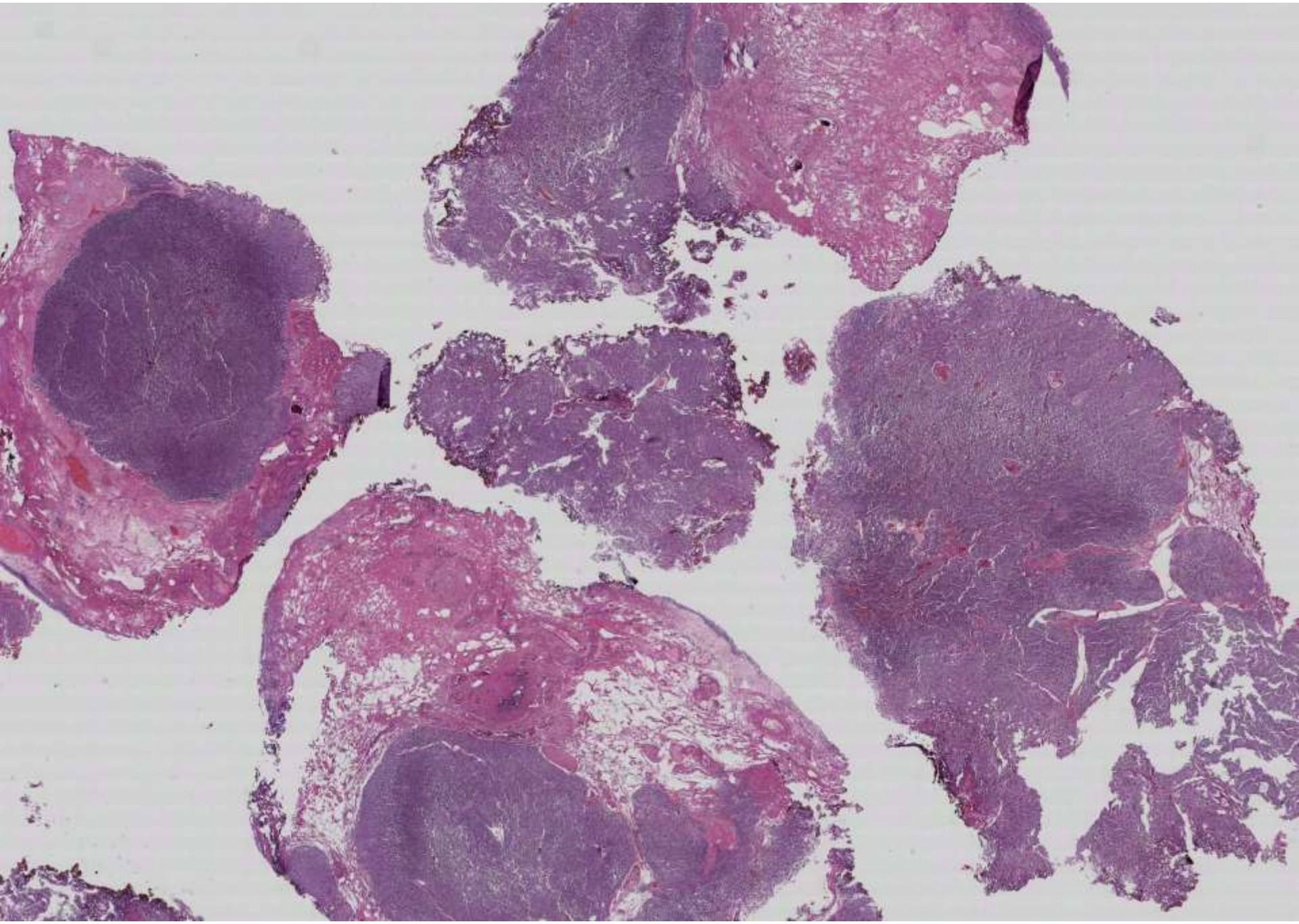

A
Proportion (%)
50
45
40
35
30
25
20
15
10
5
0
45.2
29.5
21.8
20.3
8.9
8.1
6.9
2.9
2.8
2.1
1.4
1.4
1.3
1.1
0.2
0.2
Lung
Bone
Lymph node
Liver
Adrenal
Brain
Retroperiton eum
Other digestive
Pleura
Other urinary
Mediastinum
Kidney
Large intestine
Small intestine
Other respiratory
Ovary
Metastatis sites

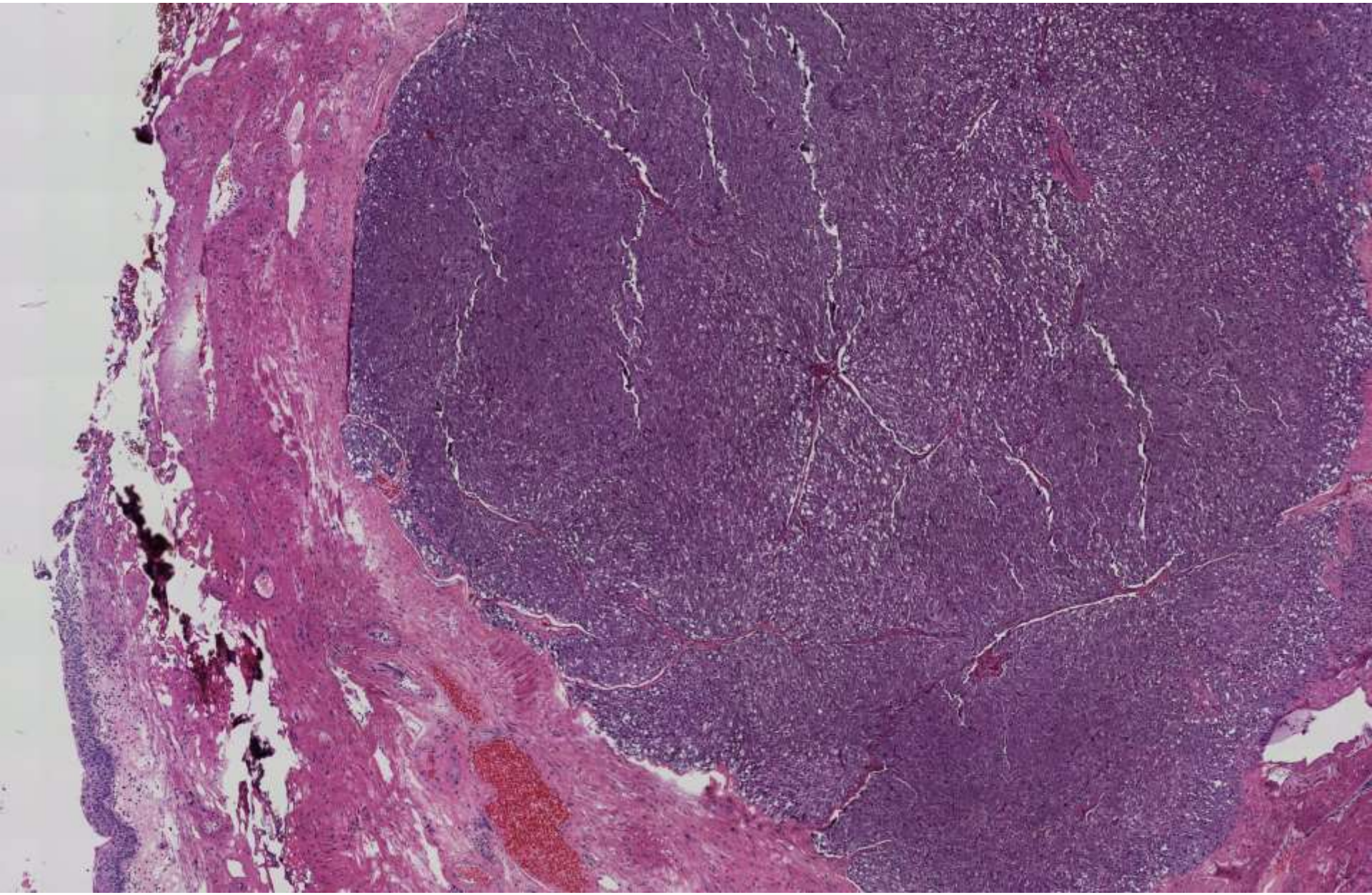

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion (%)
n=1795
57%
n=1327
43%
n=1751
59%
n=1209
41 %
n=1835
65%
n=995
35%
n=1459
65%
n=786
35%
<55
55-64
65-74
≥75
Single metastatic site
≥2 metastatic sites

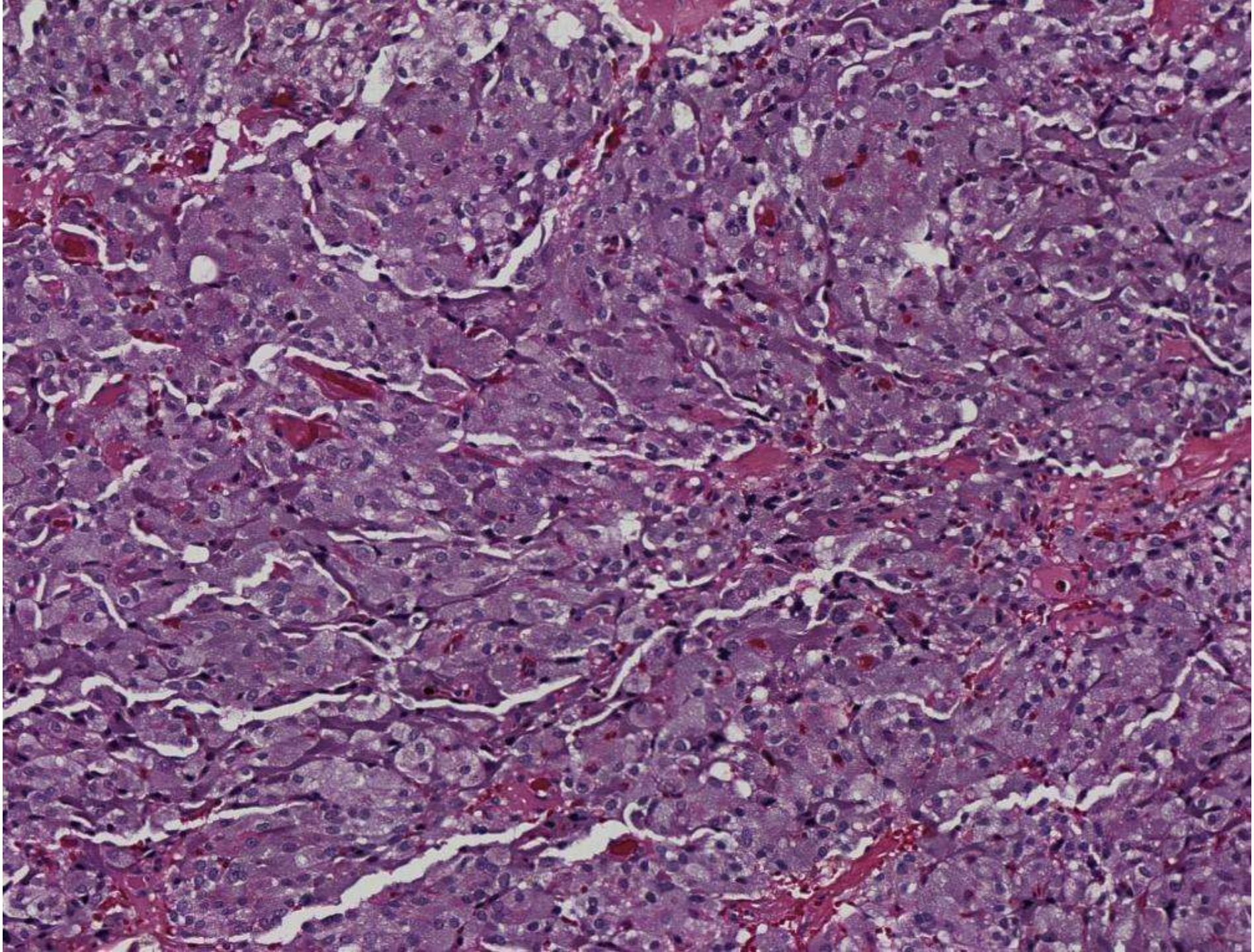
SB 6230
(scanned slide available)

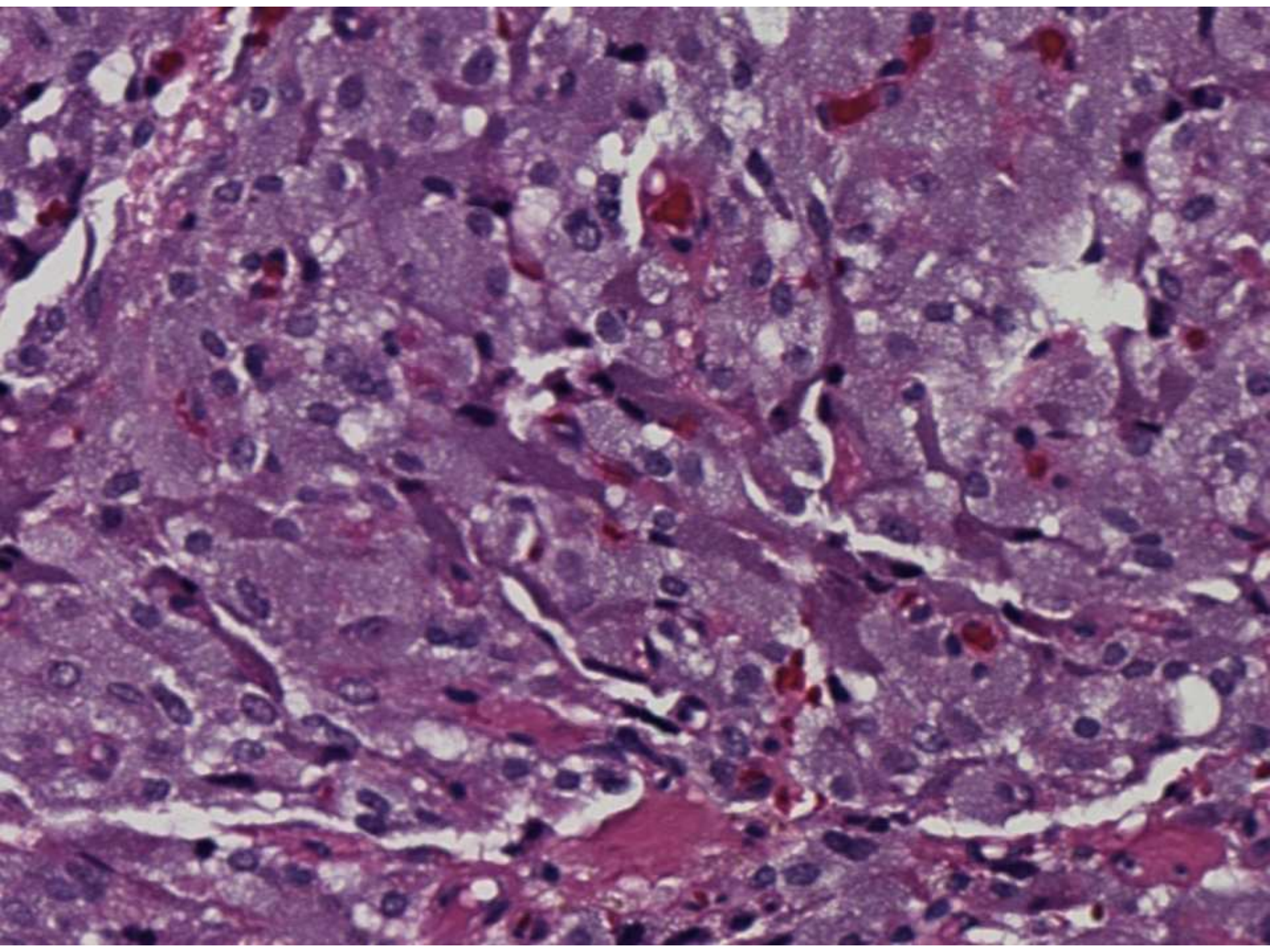
Ankur Sangoi; El Camino Hospital

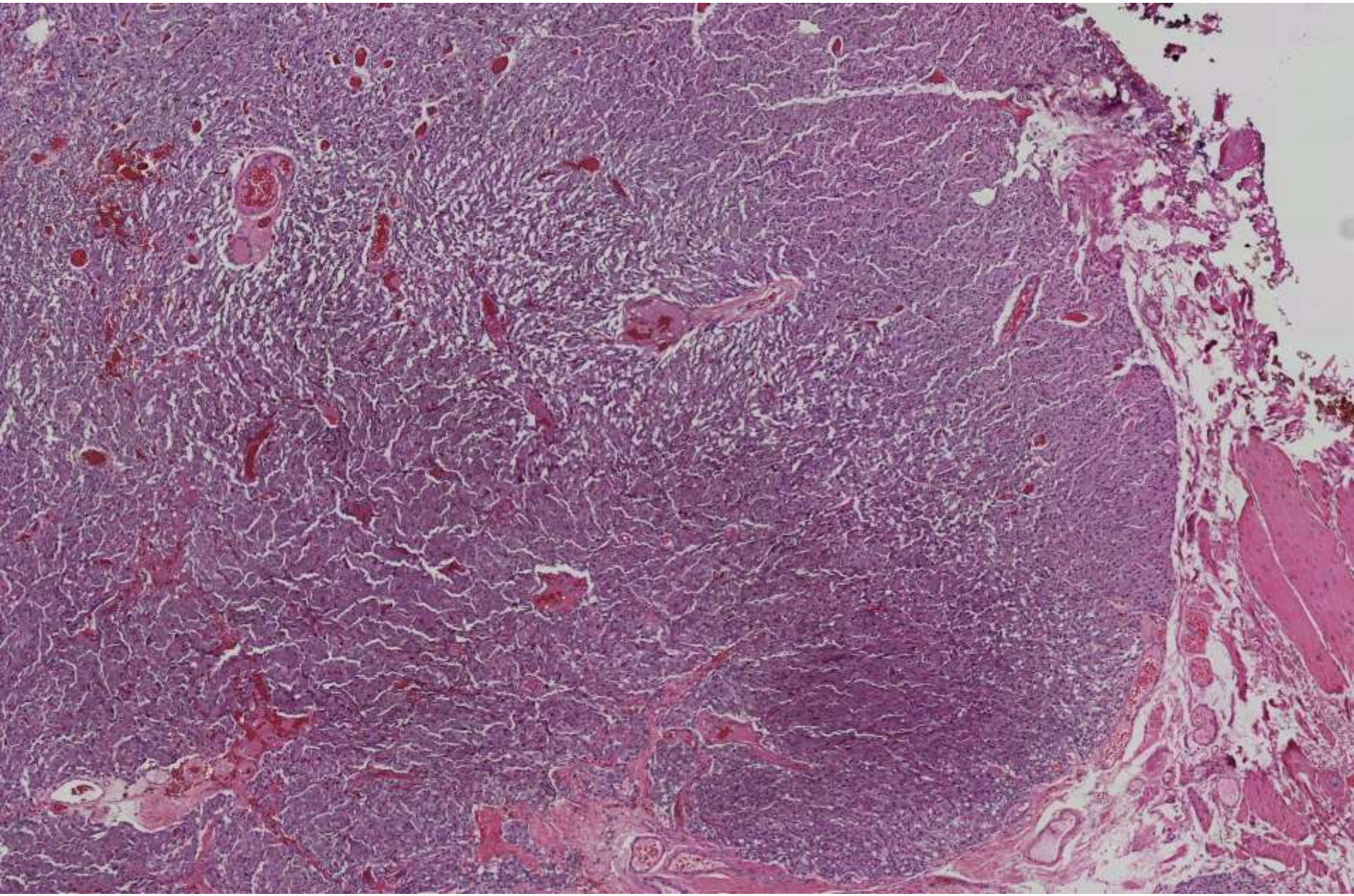
88-year-old male with remote history of prostate cancer and recently lung biopsy showing lung primary adenocarcinoma. On imaging, a bladder dome tumor was identified and resected.

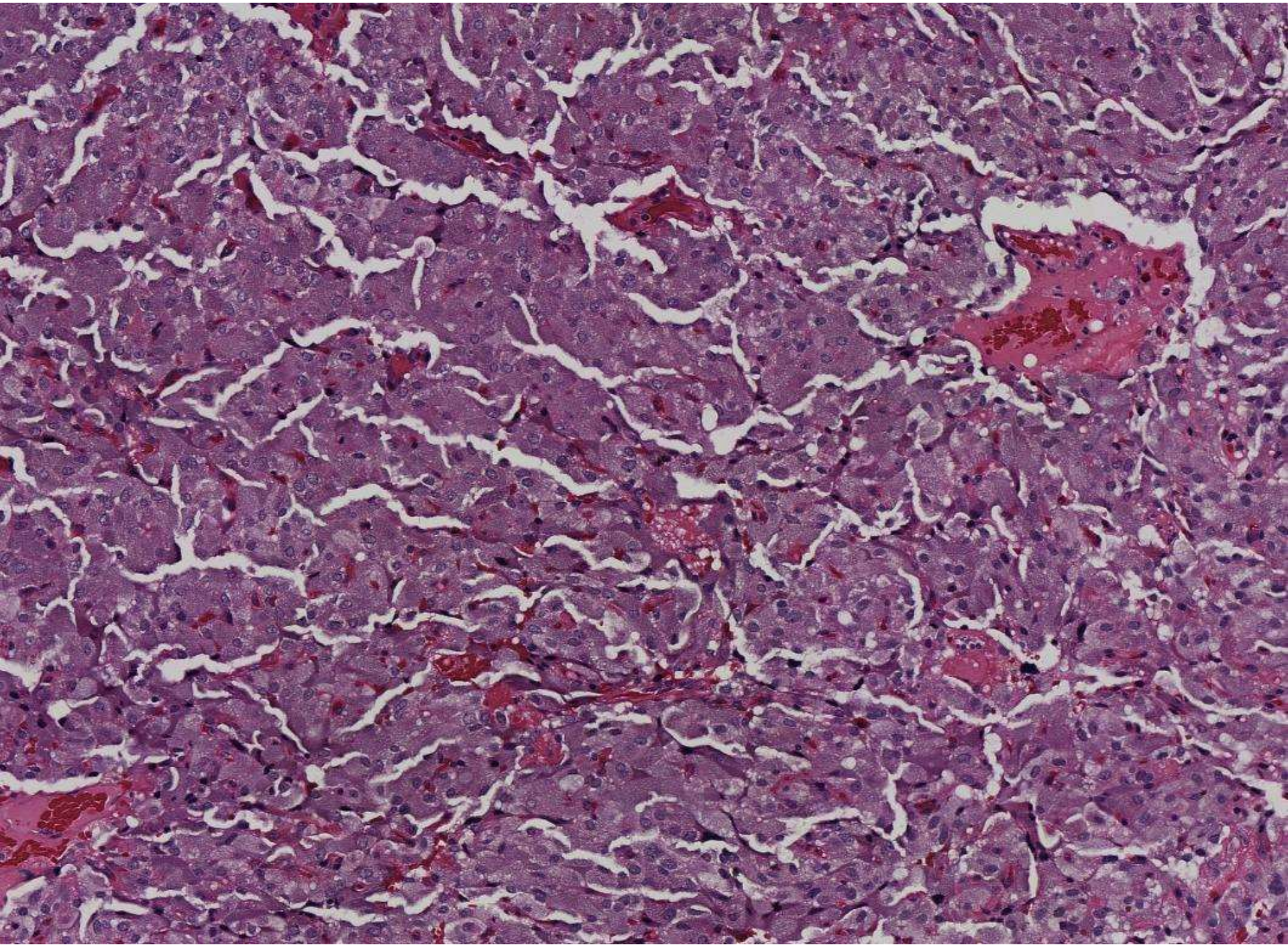


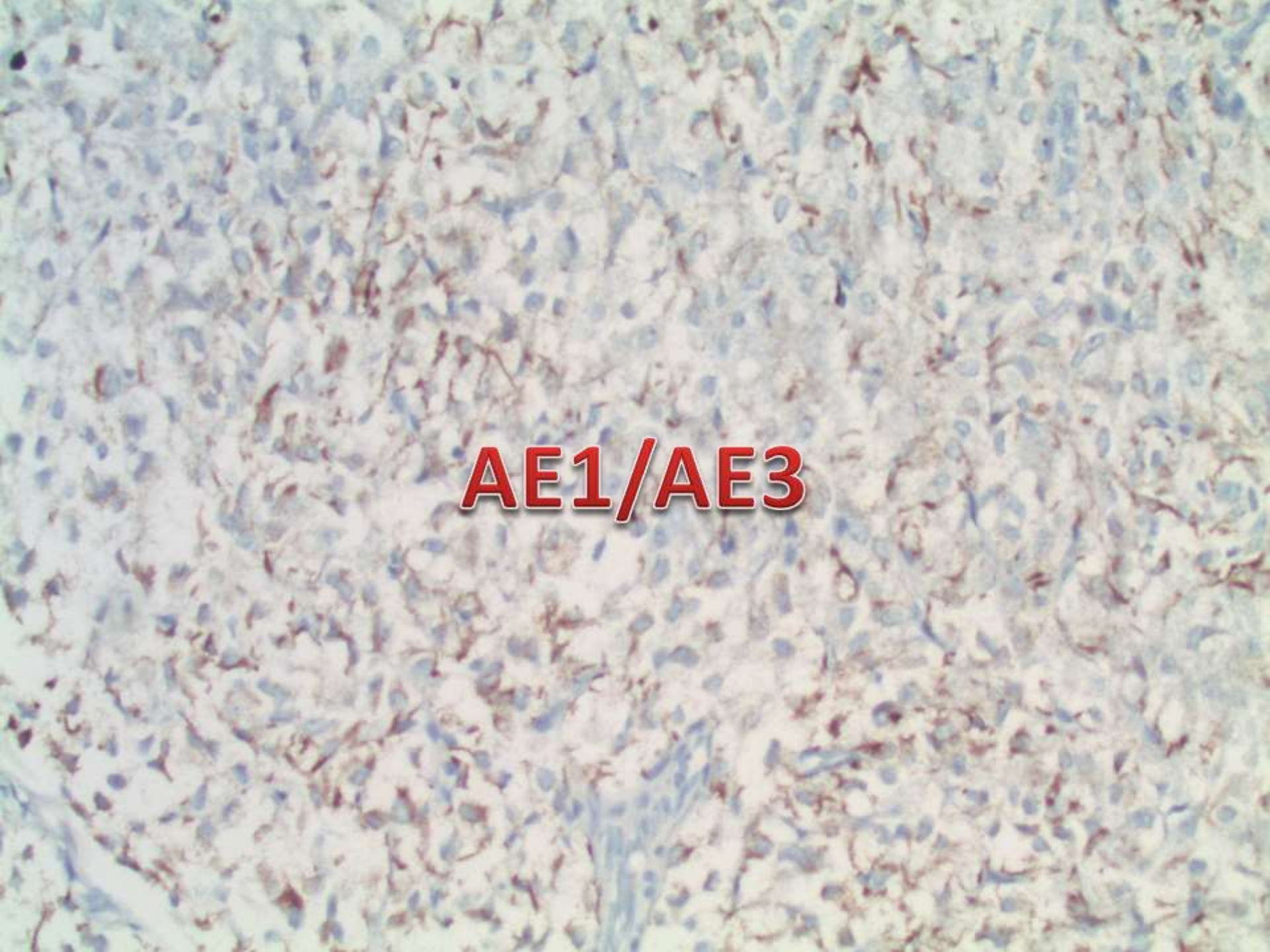






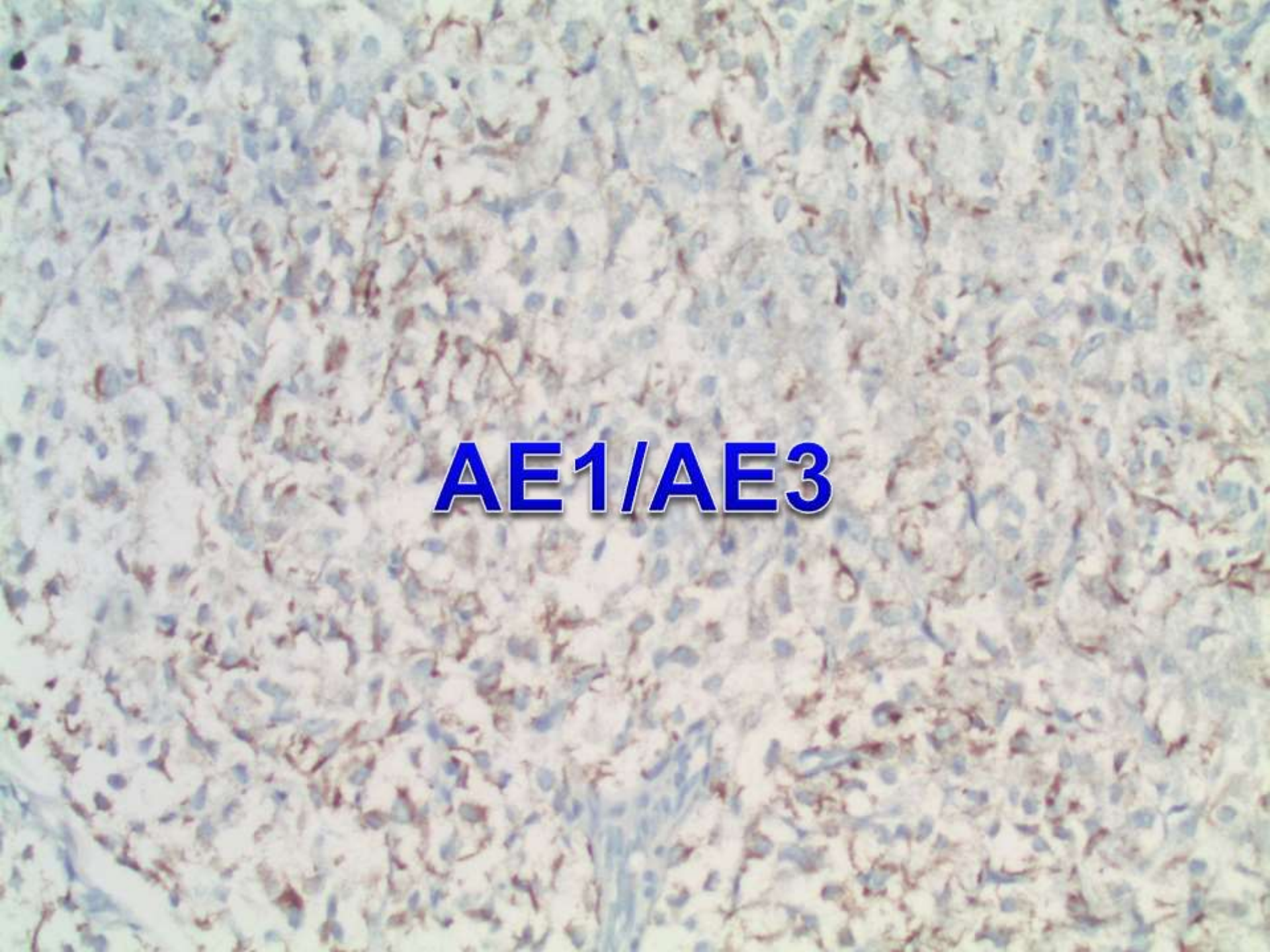


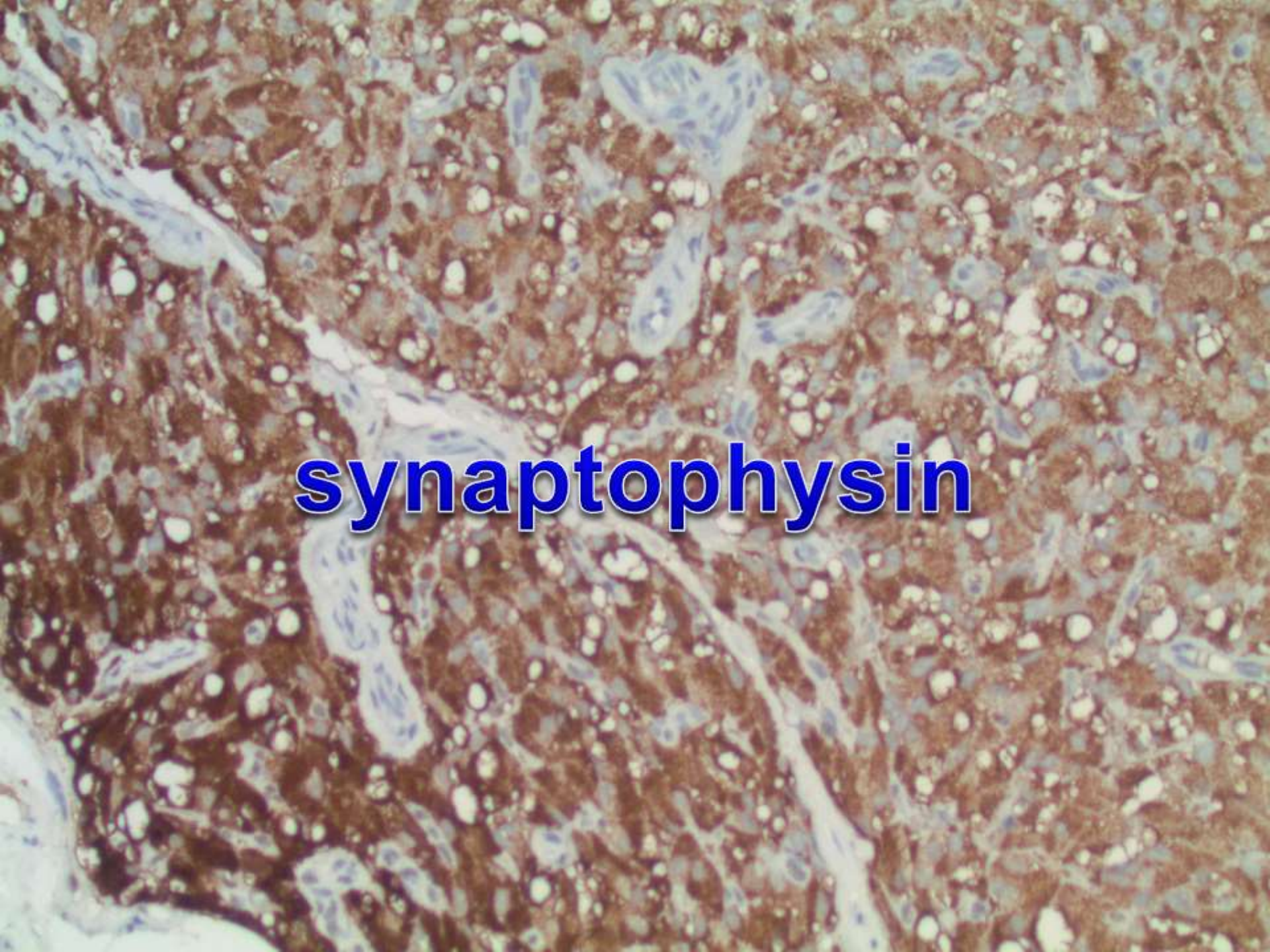


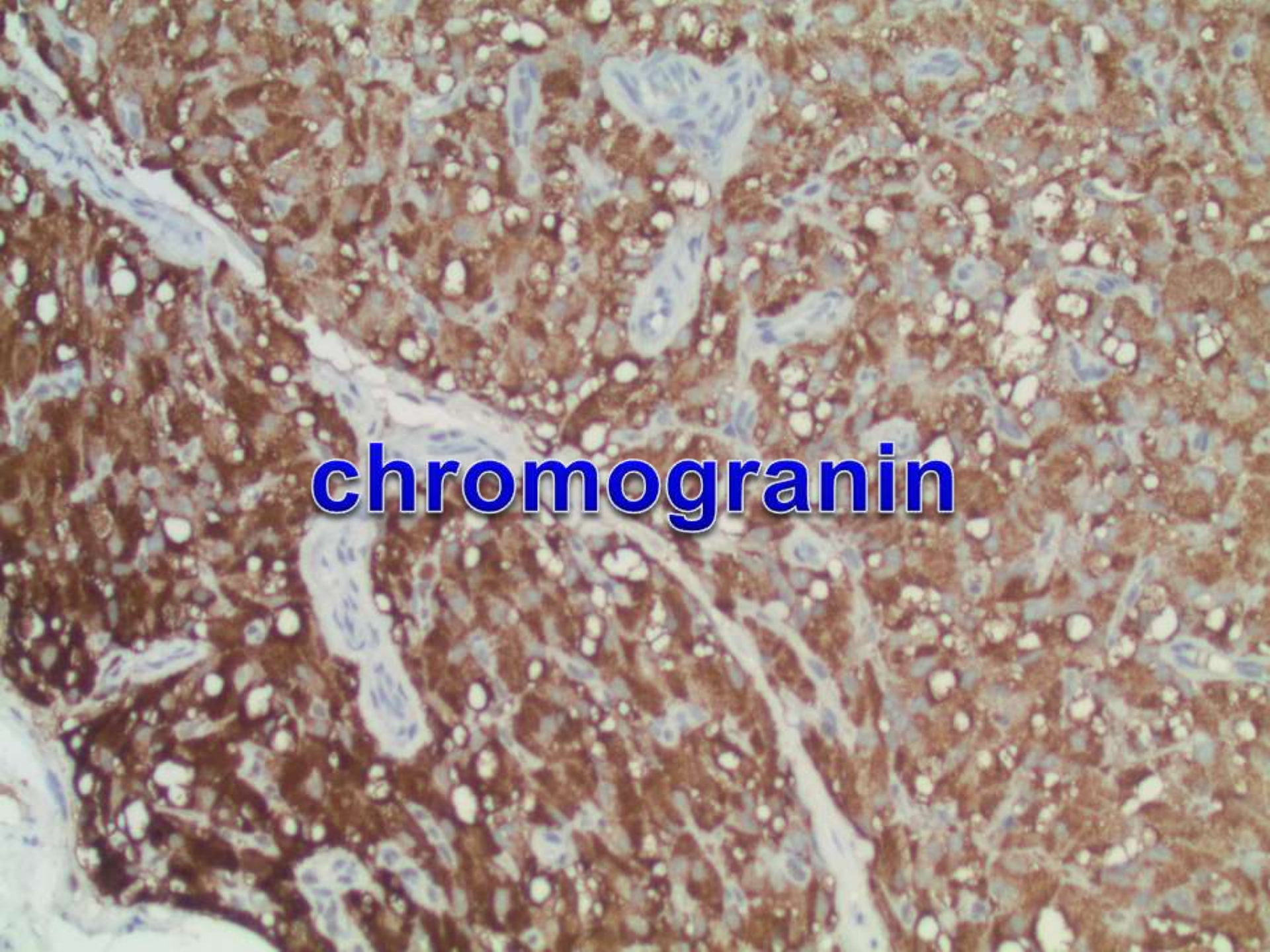

AE1/AE3

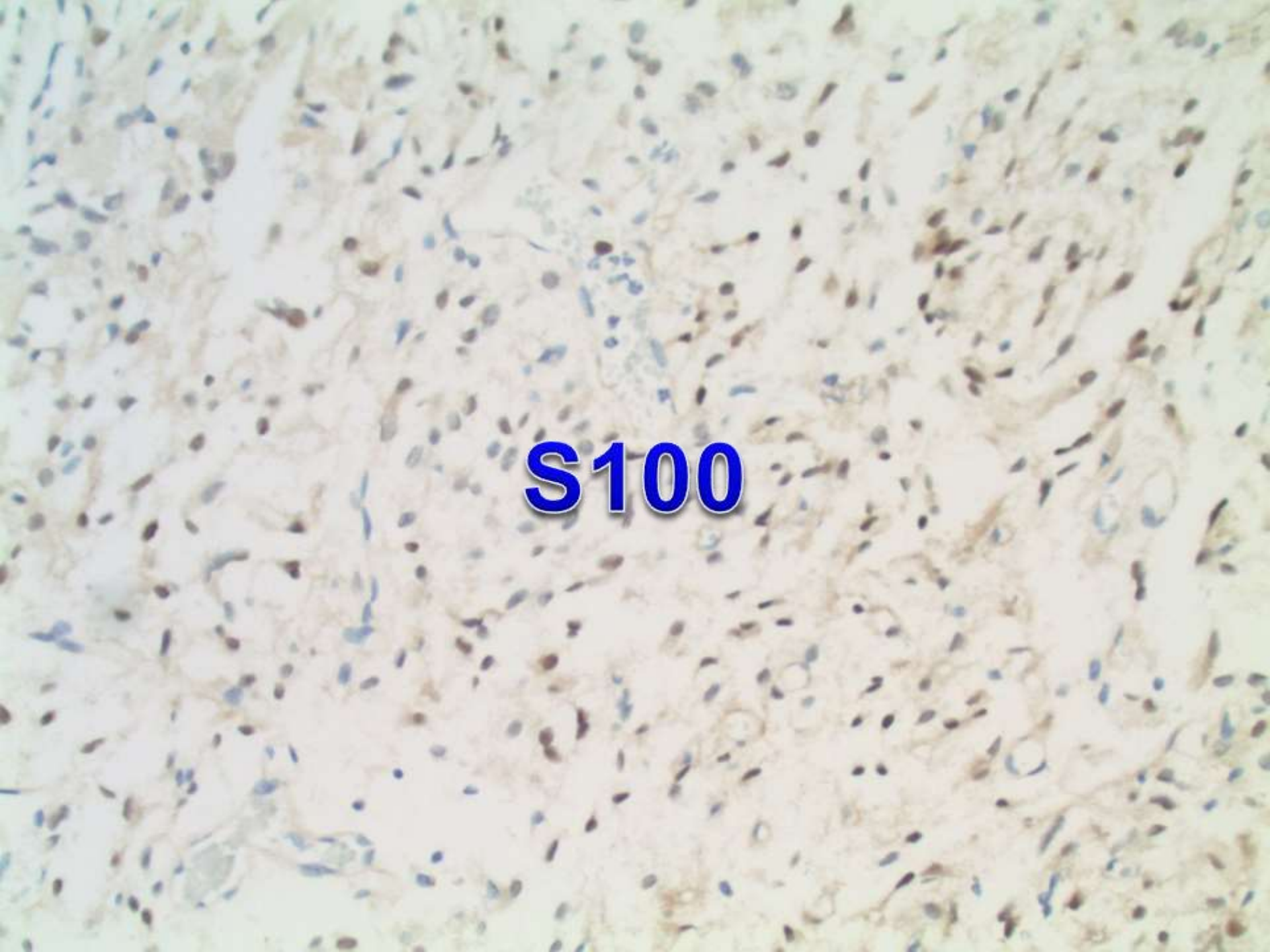
DDx

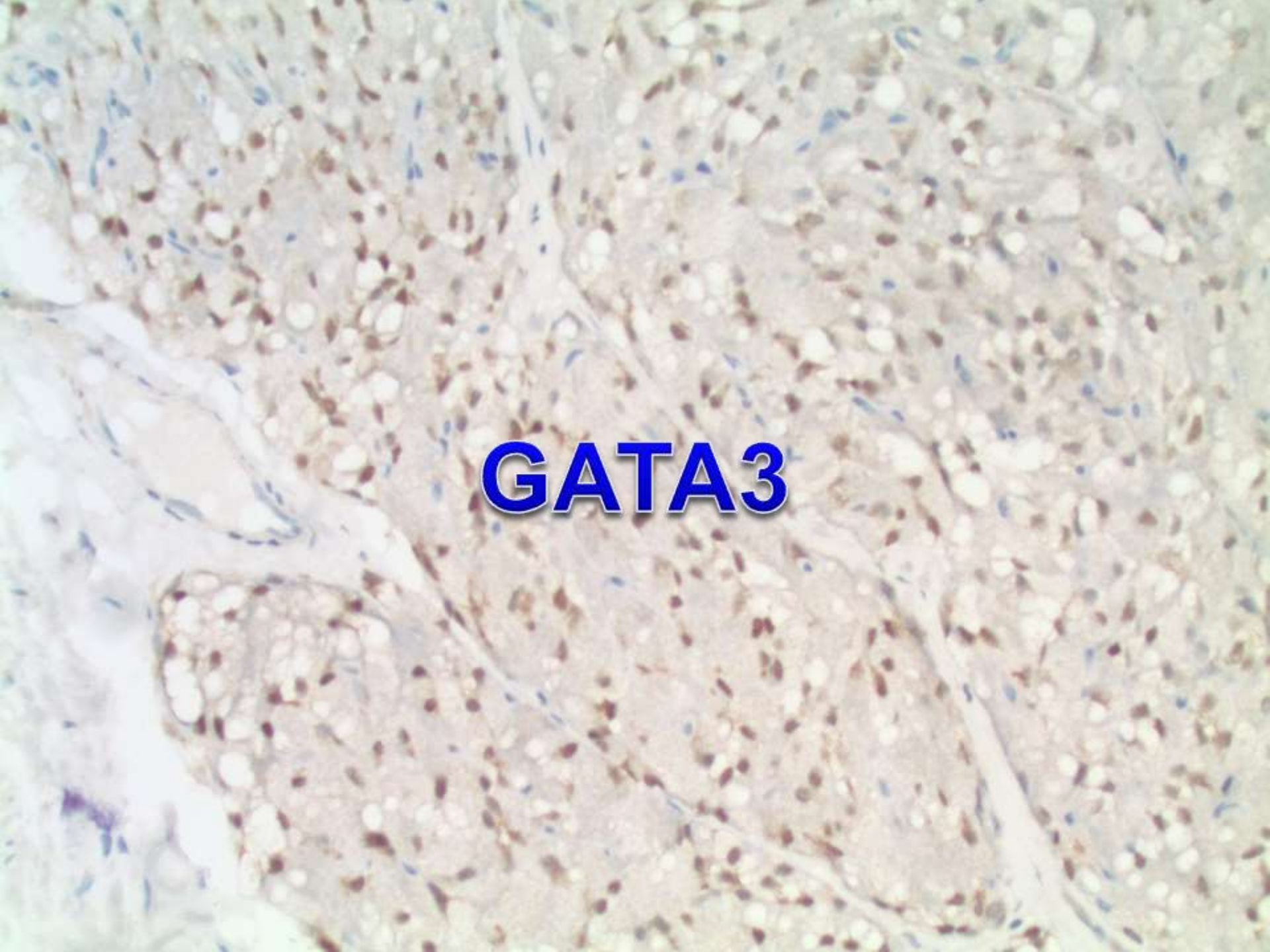
- Urothelial carcinoma
- Prostatic carcinoma
- Carcinoid tumor
- Paraganglioma
- Granular cell tumor
- Melanoma
- Leiomyoma
- PEComa


AE1/AE3


synaptophysin


chromogranin


S100


GATA3

RELEVANT IHC

- **positive: synaptophysin, chromogranin, S100, GATA3**

- **negative: p63/CK5, CAM5.2, SOX10, melanA, HMB45, cathepsinK, desmin**

DIAGNOSIS: paraganglioma

- **Infrequent, age range 10-88 y/o**
- **Often young women**
- 50% have positive urinary VMA
- Many cases are hereditary and associated with familial paraganglioma, neurofibromatosis Type 1, vHL disease, Carney triad or rarely MEN2
- 50% have “micturition attack” during urination with full bladder, consisting of bursting headache, pounding sensation, anxiety, sweating, syncope, hypertension or hematuria

Bladder paraganglioma

- Most T1 & T2 tumors typically behave in a benign fashion
  - T3 and T4 stage tumors having a risk of recurrence or metastasis
- criteria for malignancy (estimated at 5-15%), are metastases and/or extensive local disease
  - tumors associated with *SDHB* mutations have an increased association with metastases

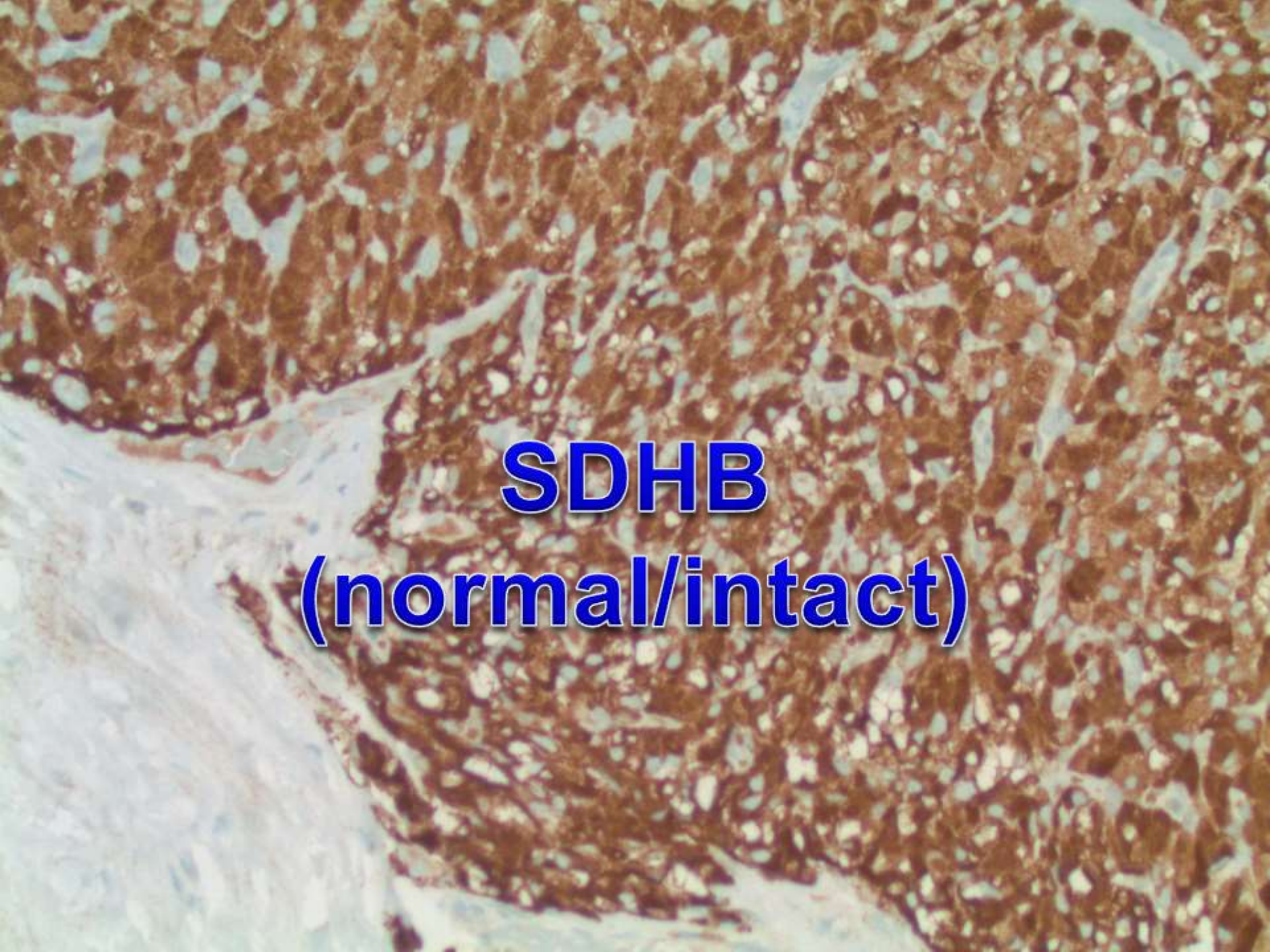
Clinicopathologic Characteristics and Mutational Status of Succinate Dehydrogenase Genes in Paraganglioma of the Urinary Bladder

A Multi-Institutional Korean Study

Sanghui Park, MD; So Young Kang, PhD; Chee Young Kwon, MD; Ji Eun Kwon, MD; Sang Kyum Kim, MD; Ji Yeon Kim, MD; Chul Hwan Kim, MD; Hyun-Jung Kim, MD; Kyung Chul Moon, MD; Ju Yeon Pyo, MD; Won Young Park, MD; Eun Su Park, MD; Ji-Youn Sung, MD; Sun Hee Sung, MD; Young-Ha Oh, MD; Seung Eun Lee, MD; Wonae Lee, MD; Jong Im Lee, MD; Nam Hoon Cho, MD; Soo Jin Jung, MD; Min-Sun Cho, MD; Yong Mee Cho, MD; Hyun Yee Cho, MD; Eun Jung Cha, MD; Yang-Seok Chae, MD; Cheeyoung Choe, MD; Yeong Jin Choi, MD; Jooryung Huh, MD; Jae Y. Ro, MD

Arch Pathol Lab Med—Vol 141, May 2017

In conclusion, PBPG is a very rare bladder tumor with 17% (9 of 52) incidence of SDH deficiency and 5.8% (3 of 52) incidence of malignancy. Younger age of the patient, large tumor size, higher number of mitoses, and presence of LVI and *SDHB* mutations are potential criteria to predict the malignant behavior of PBPGs.


SDHB
(normal/intact)