# JAN 2019 DIAGNOSIS LIST

6341: epithelioid hemangioendothelioma [lung/neoplastic lung pathology]
6342: Langerhans cell histiocytosis [large bowel; hematopathology]
6343: breast hamartoma [breast/breast pathology]
6344: primary adenosquamous carcinoma [tonsil/head&neck pathology]
6345: consistent with histiocytic sarcoma [lymph node/bone&soft tissue pathology]
6346: metastatic epithelioid hemangioendothelioma [lung/neoplastic lung pathology]
6347: astroblastoma [brain/neuropathology]
6348: Metastatic acinar cell carcinoma of pancreatic origin [liver/GI pathology]
6349: thrombotic microangiopathy [kidney/non-neoplastic kidney]
6350: tissue floater from lobular breast carcinoma [prostate/GU pathology]

# Disclosures
# January 14, 2019

Dr. Ankur Sangoi has disclosed a financial relationship with Google (consultant). South Bay Pathology Society has determined that this relationship is not relevant to his role as planner and moderator of the clinical cases being presented.

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

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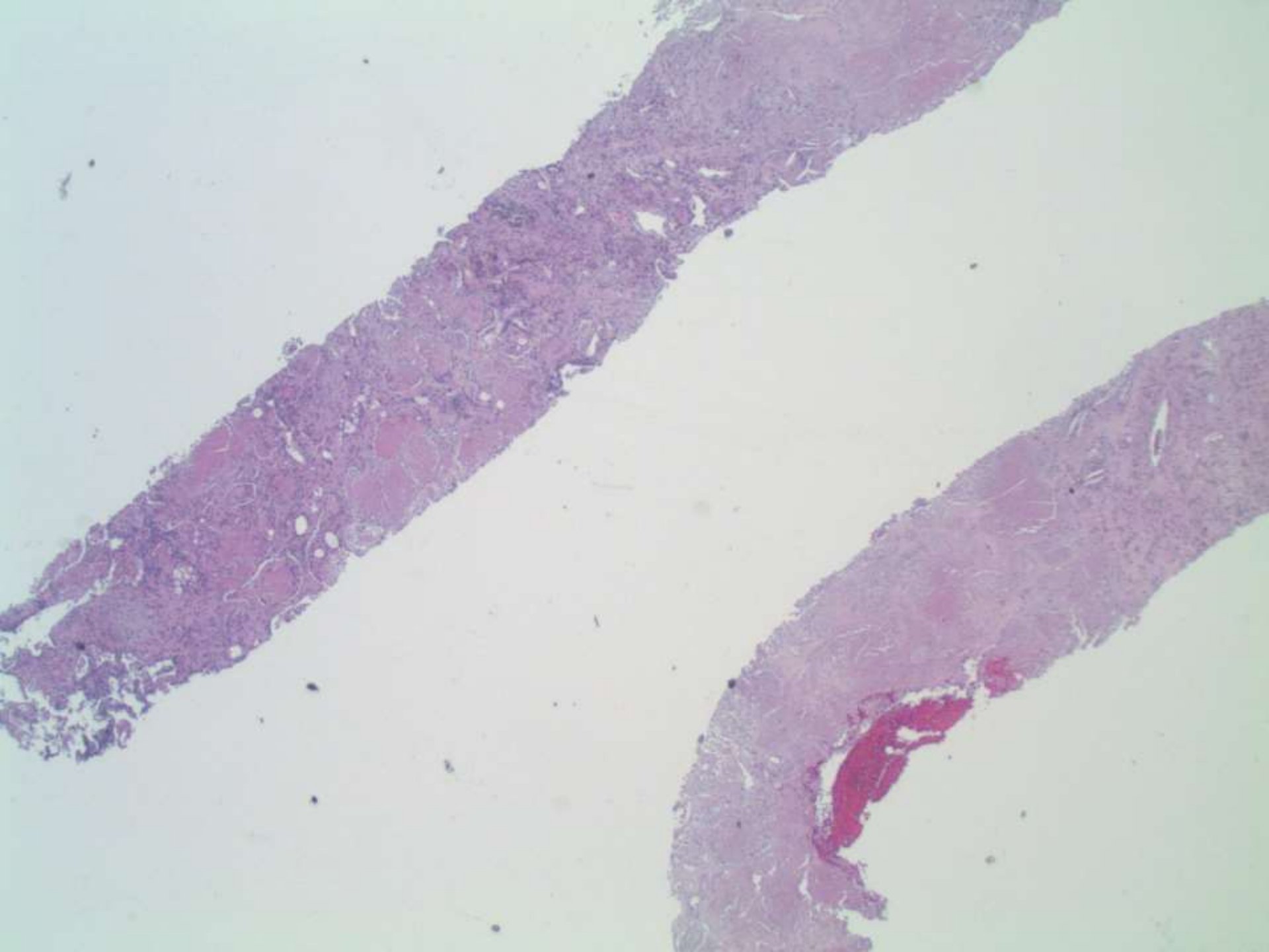
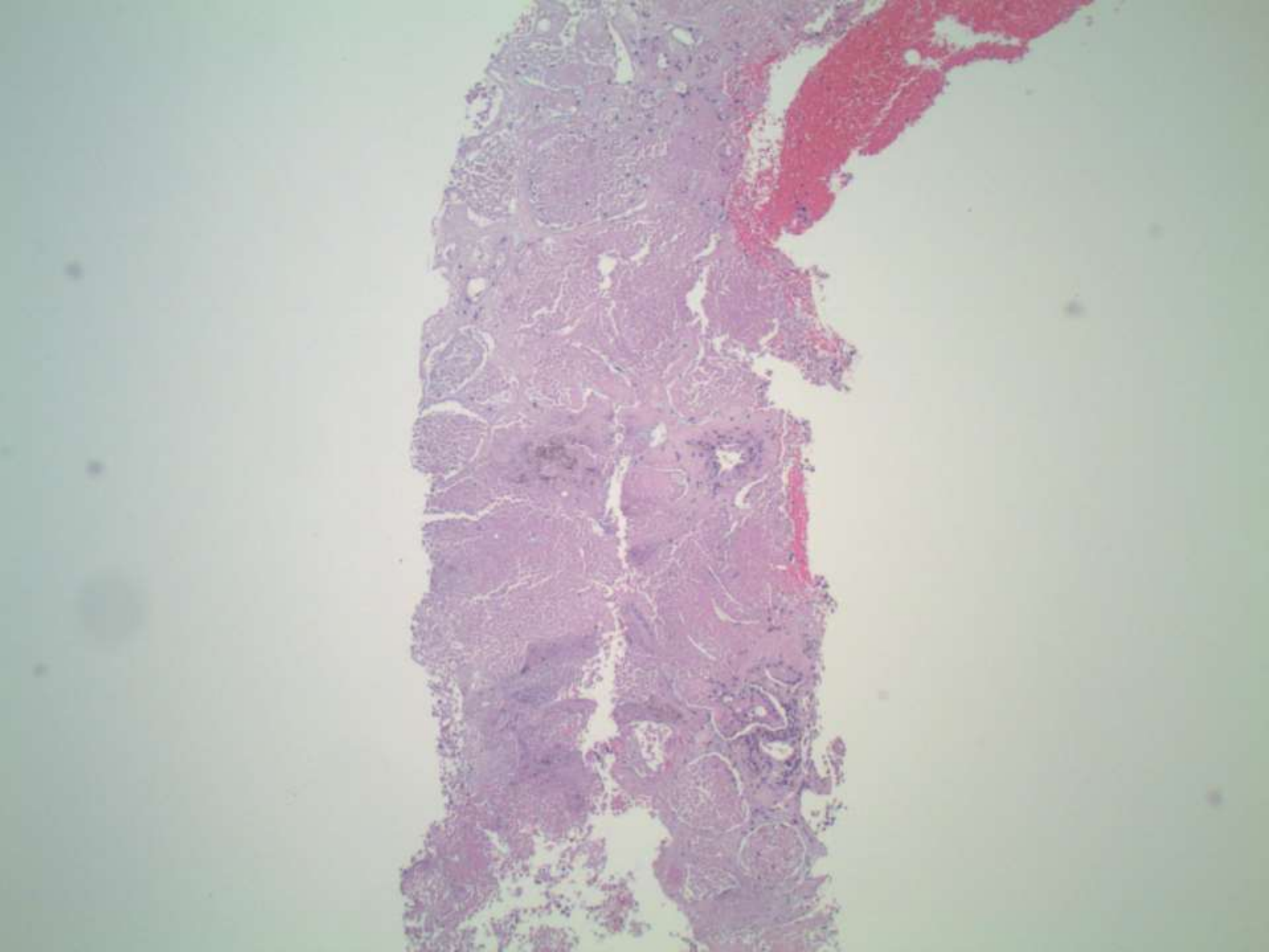
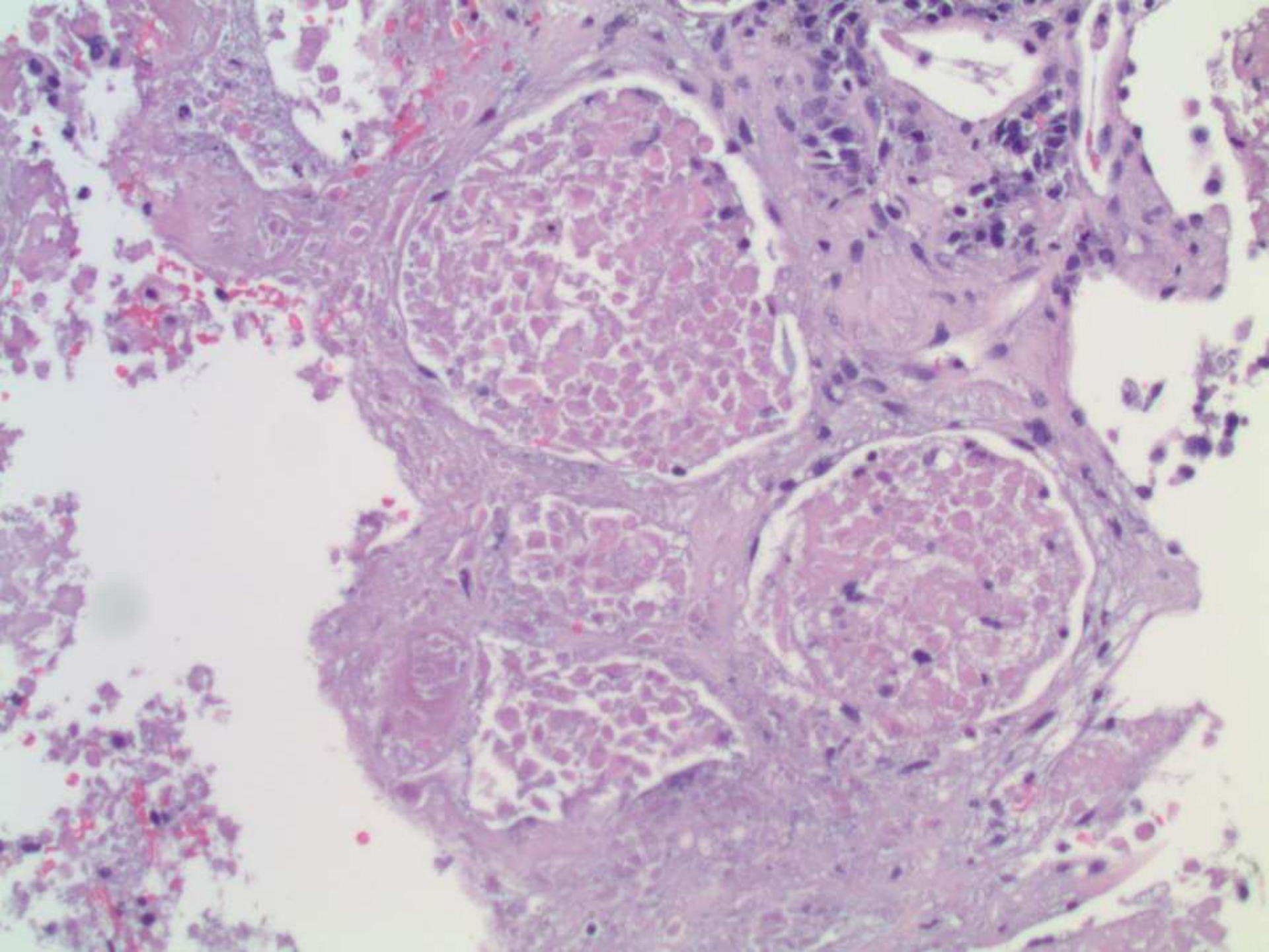
# SB 6341

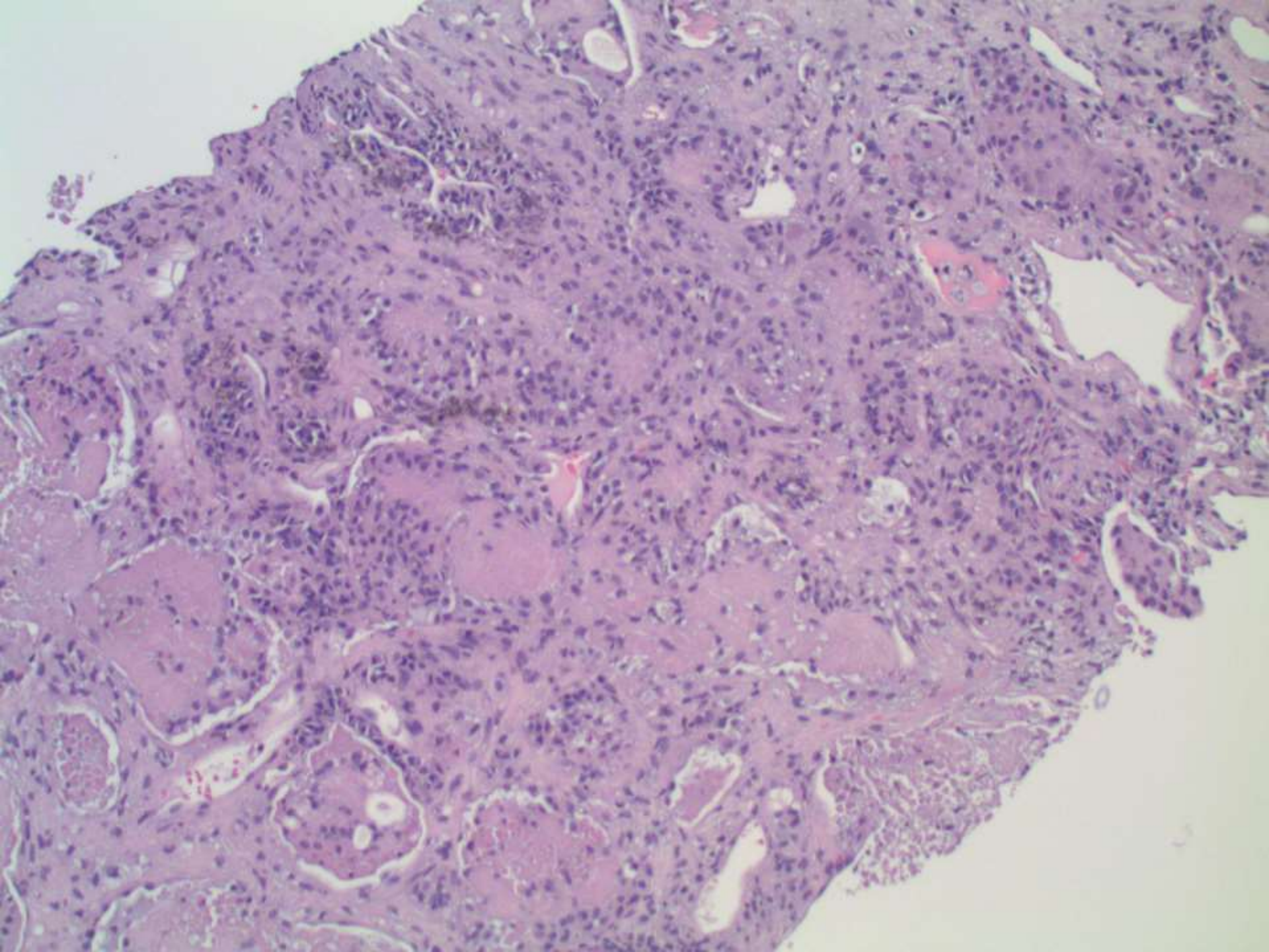
**Mahendra Ranchod; Good Samaritan Hospital**

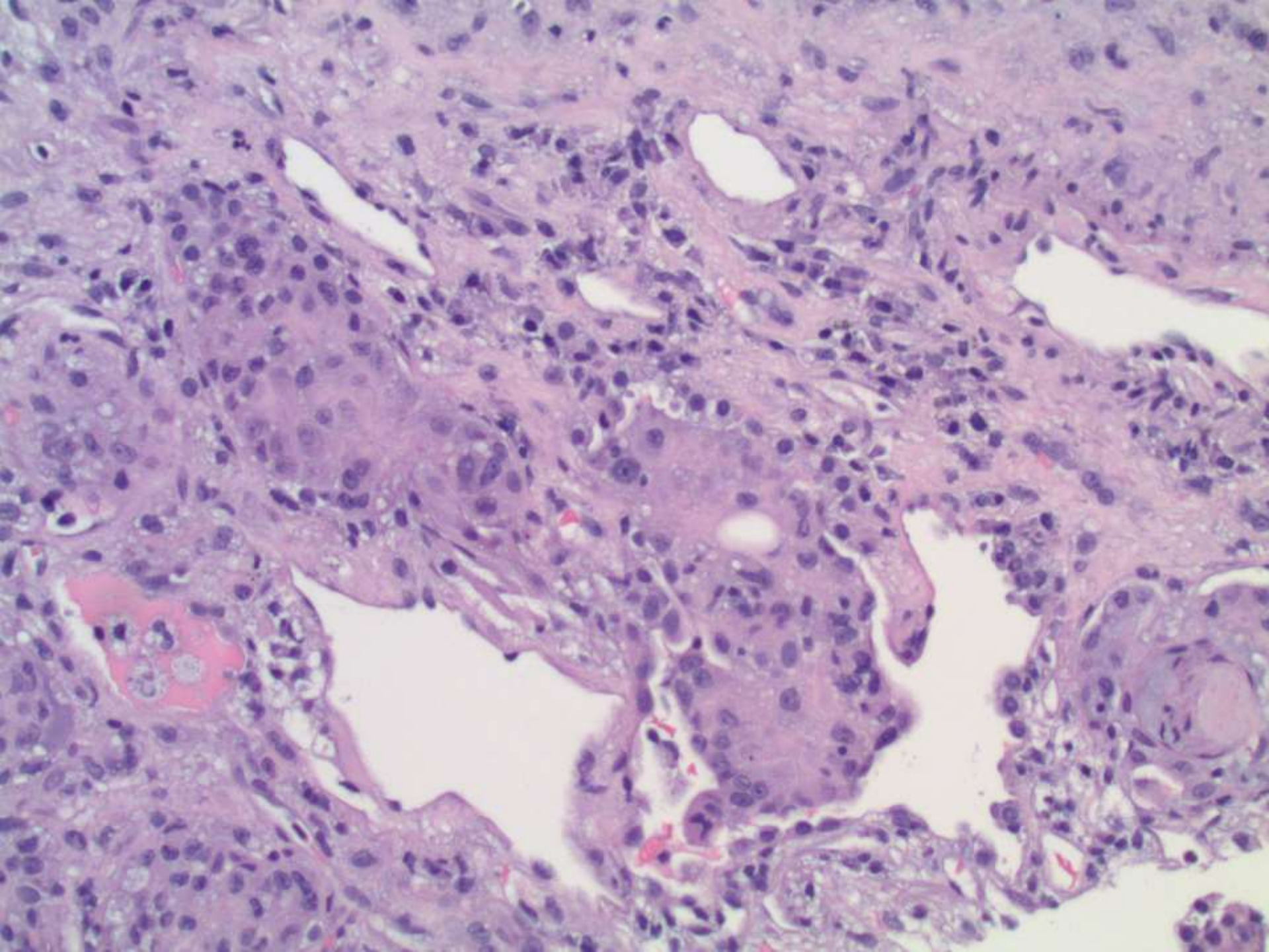
38-year-old male (recent immigrant from Mexico), presents with back pain. CT scan shows destructive lesions of T12, L2, L3. Biopsy of bone was non-diagnostic. Biopsy of right lung infiltrate performed.

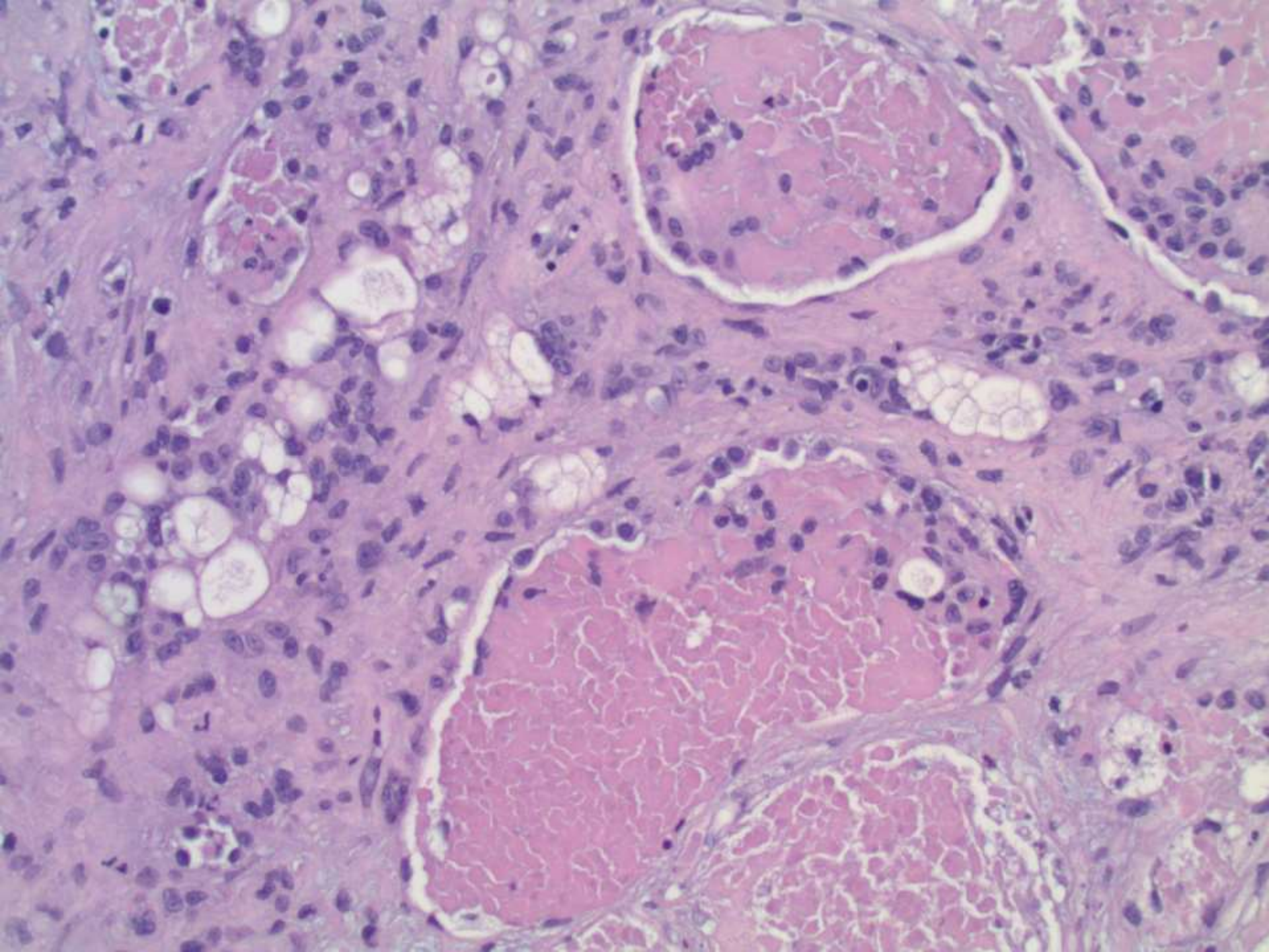


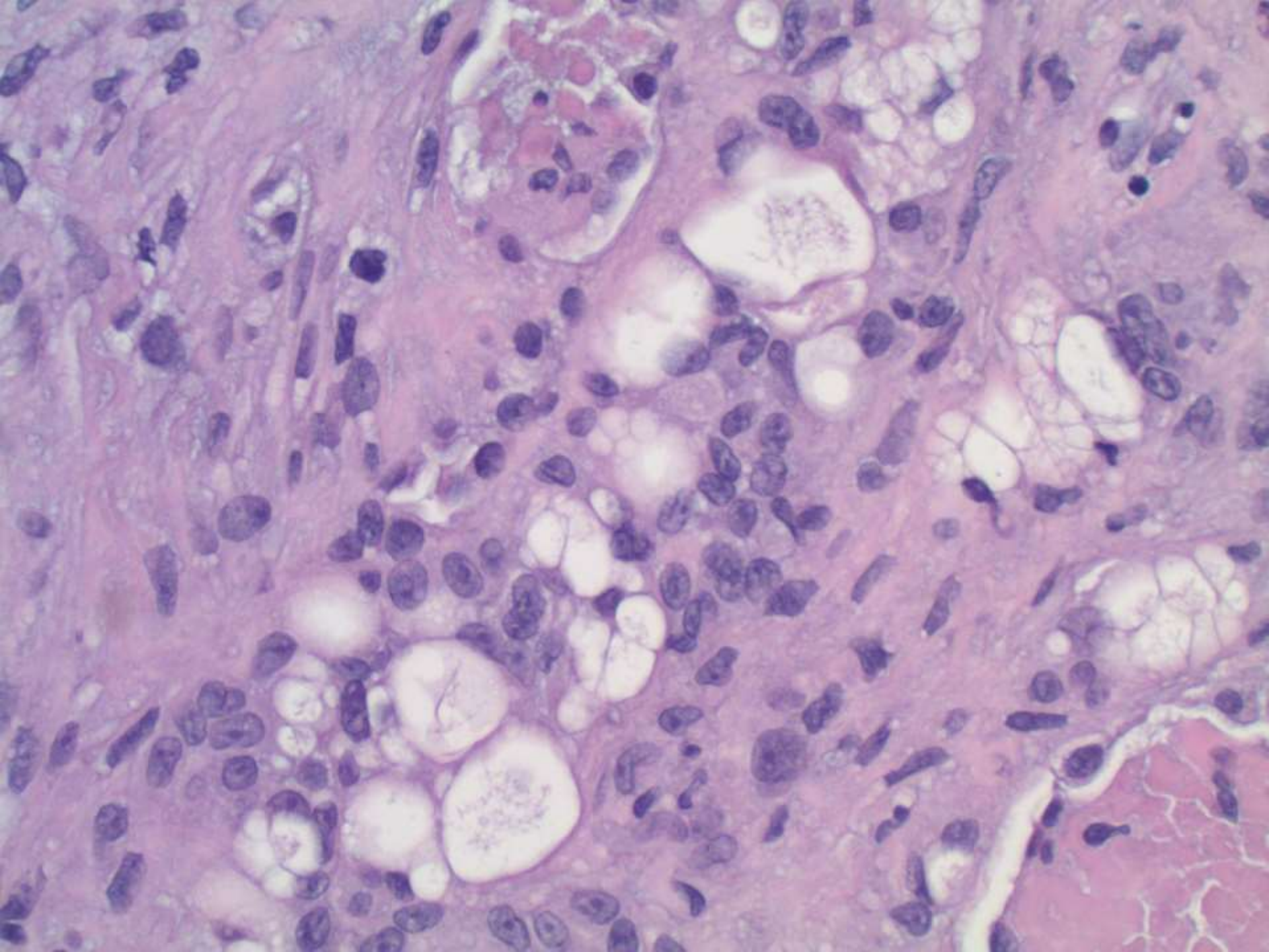


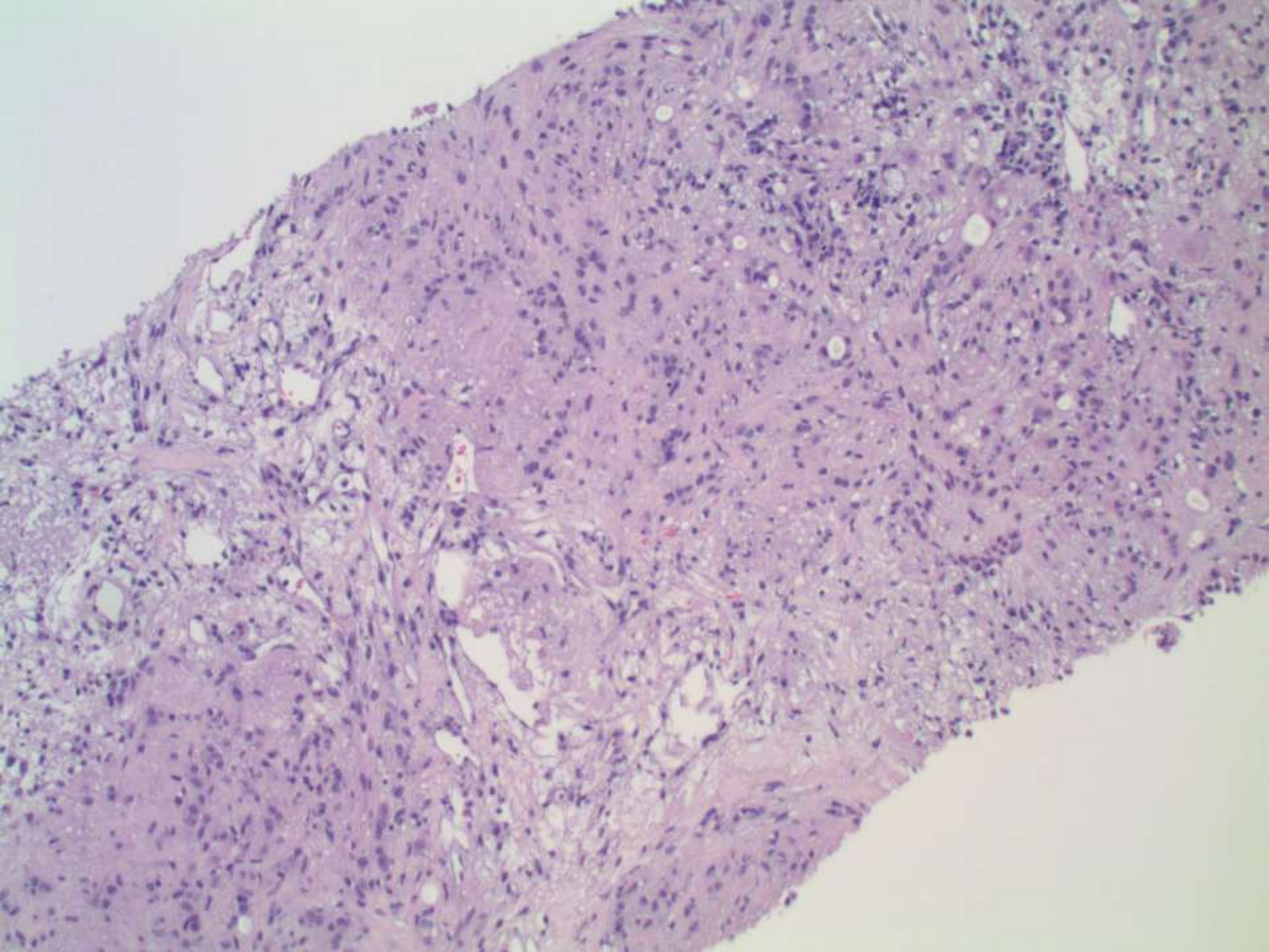


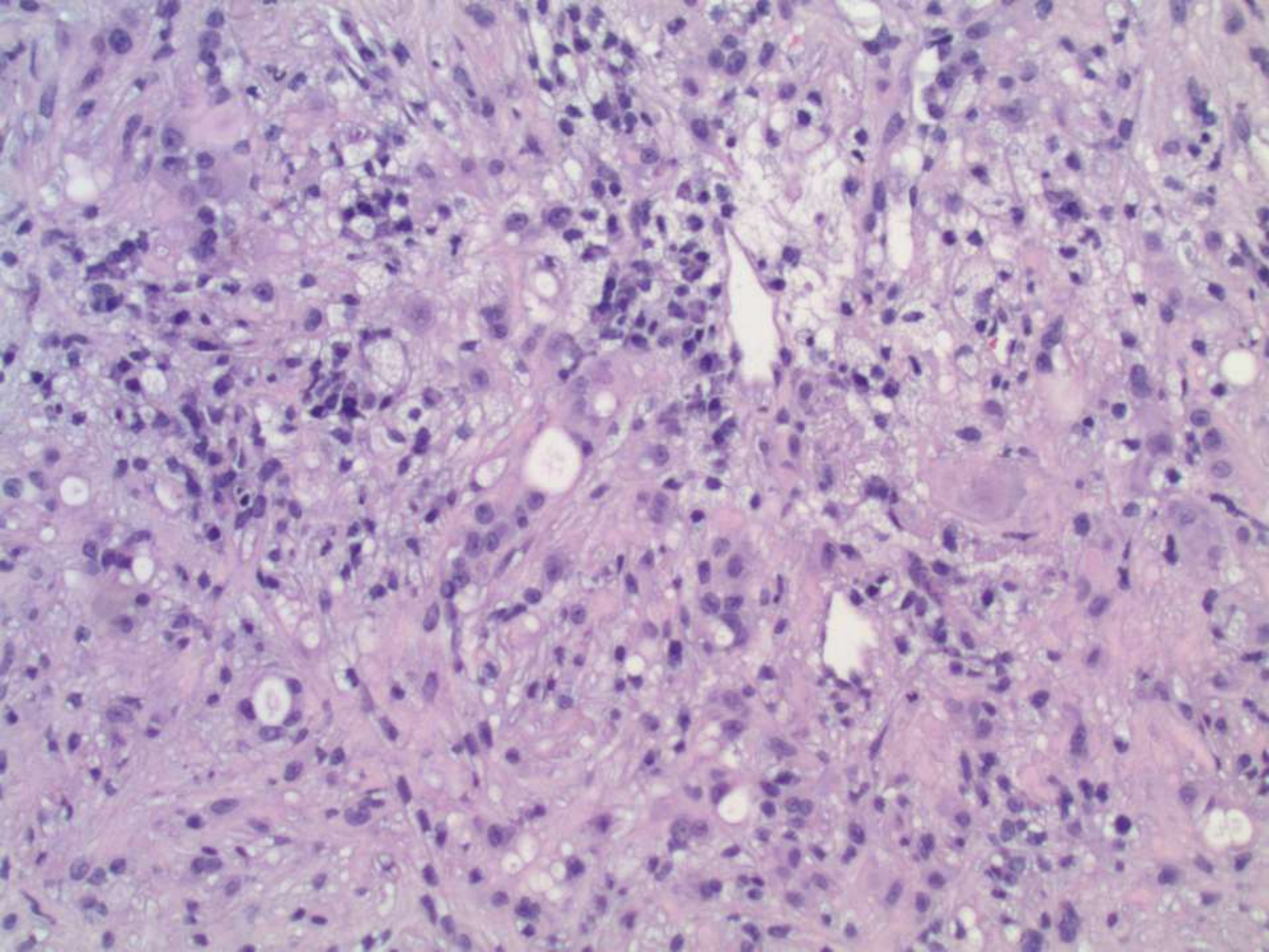


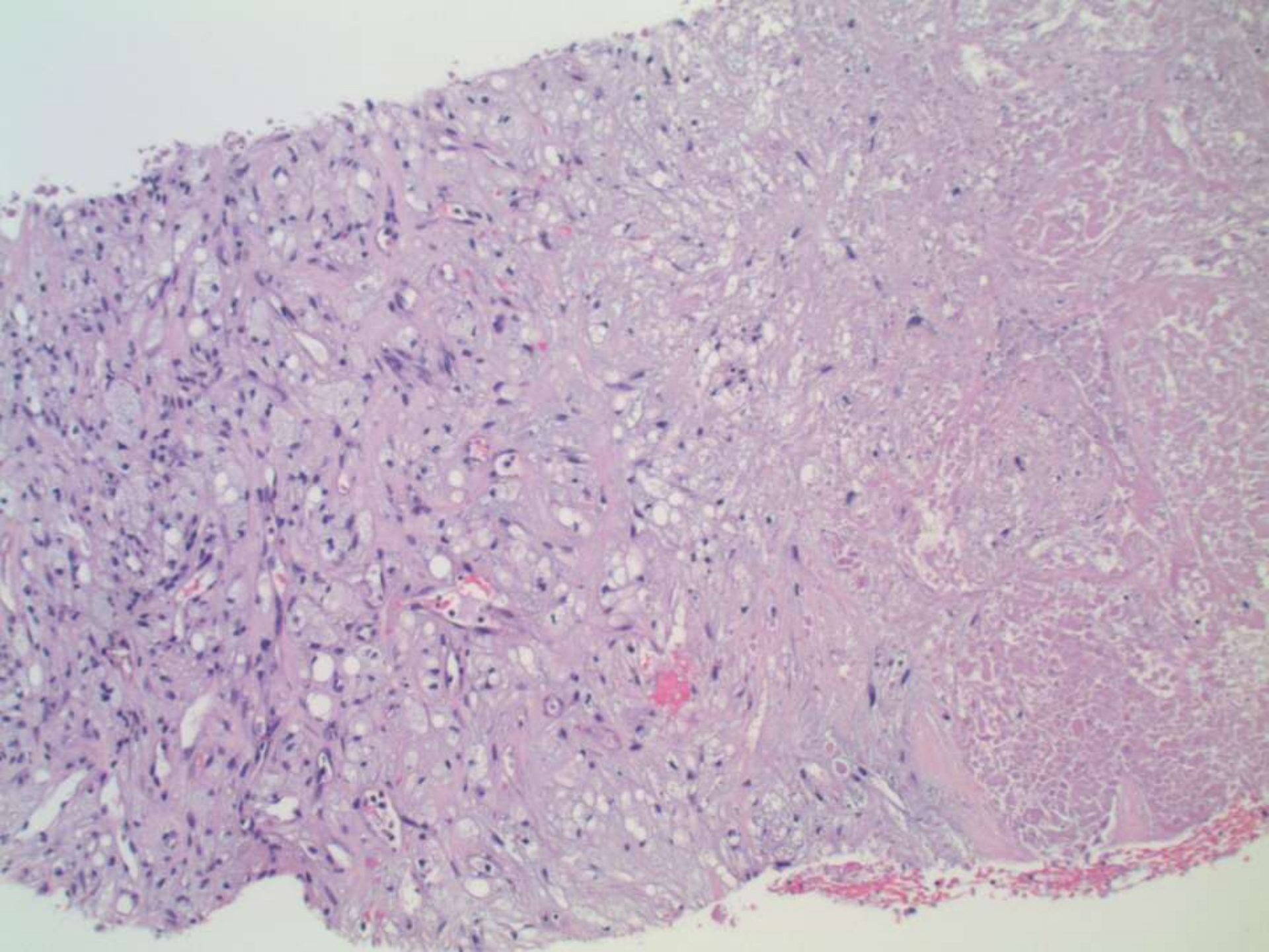


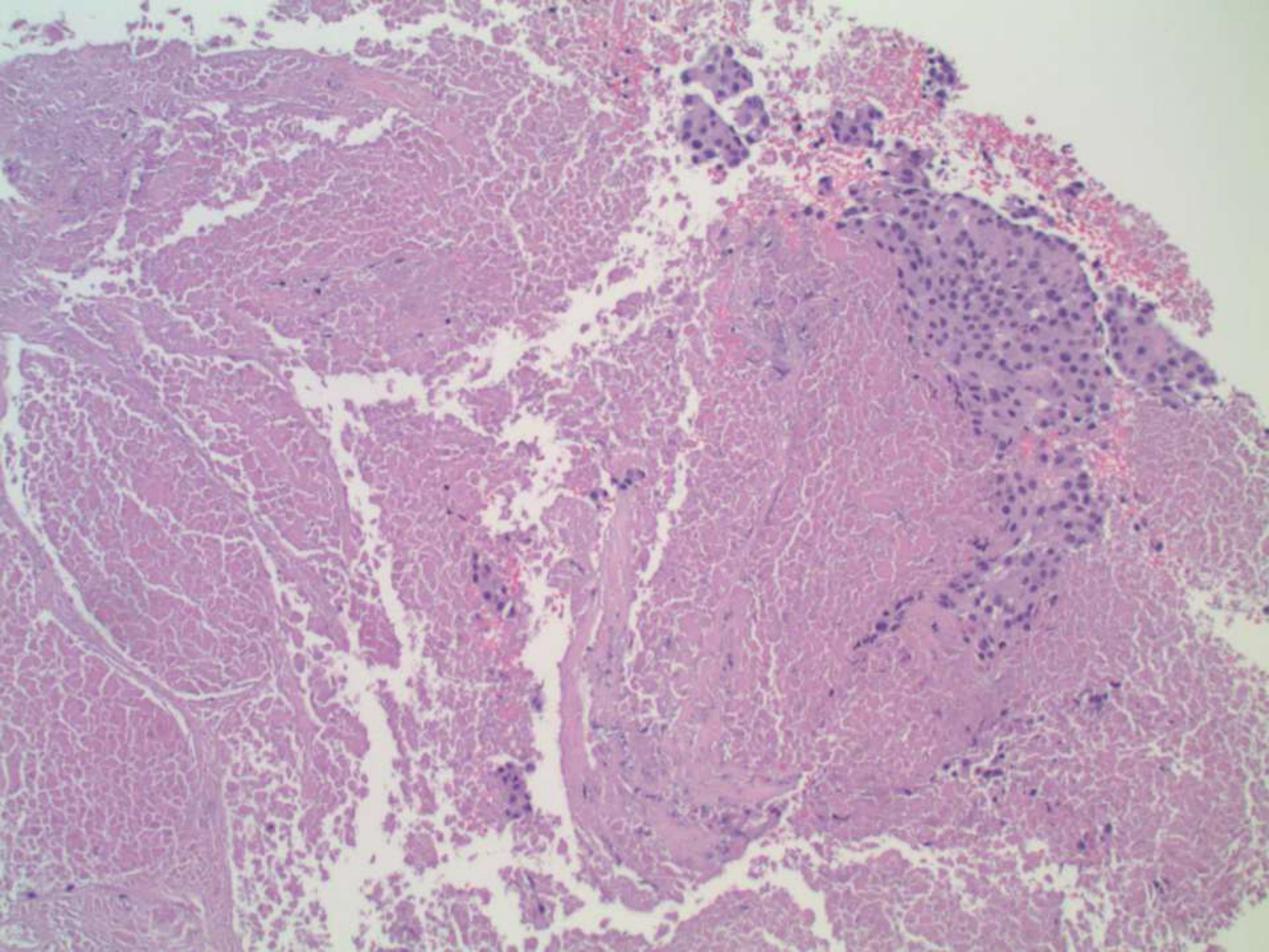


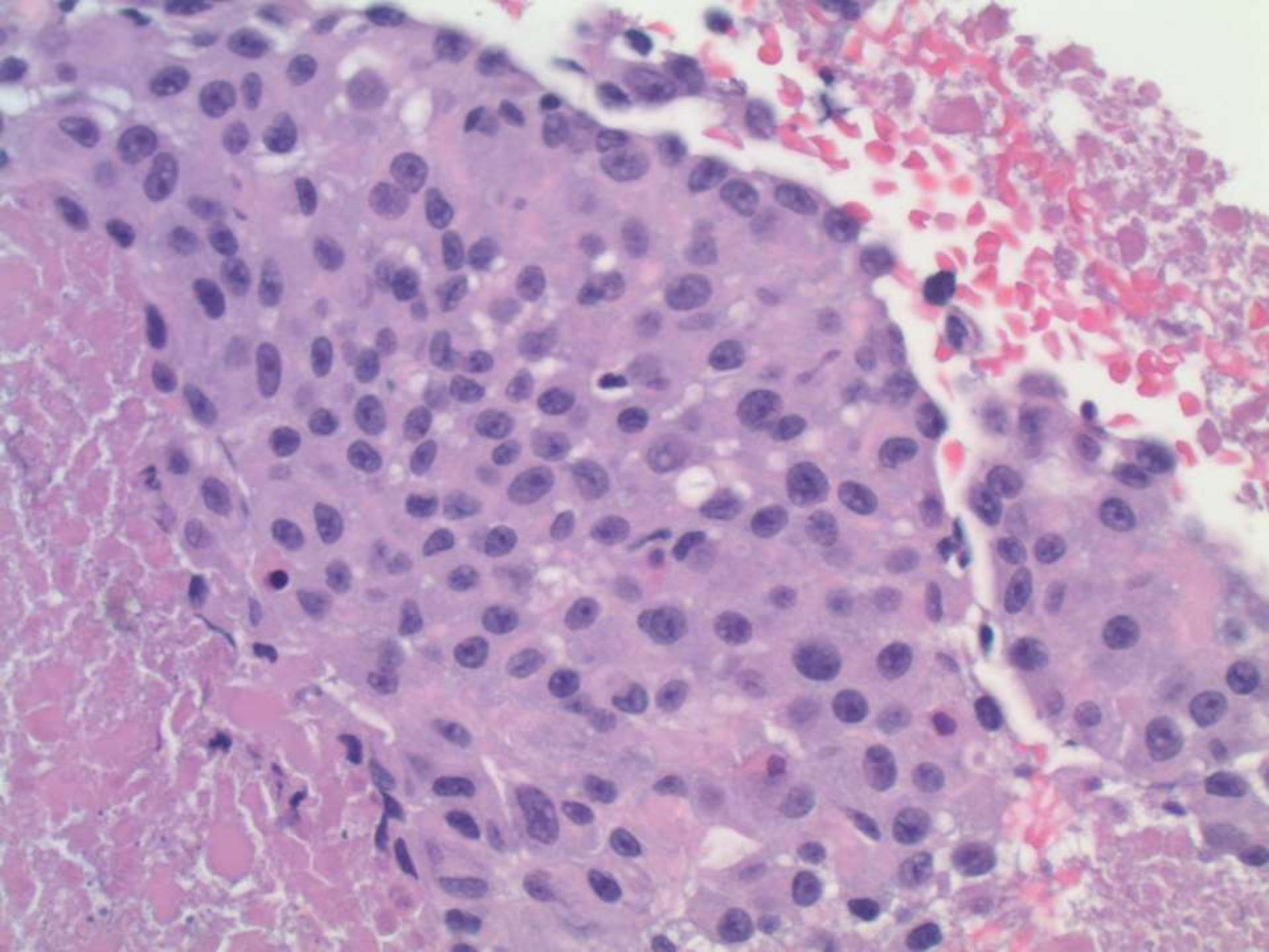


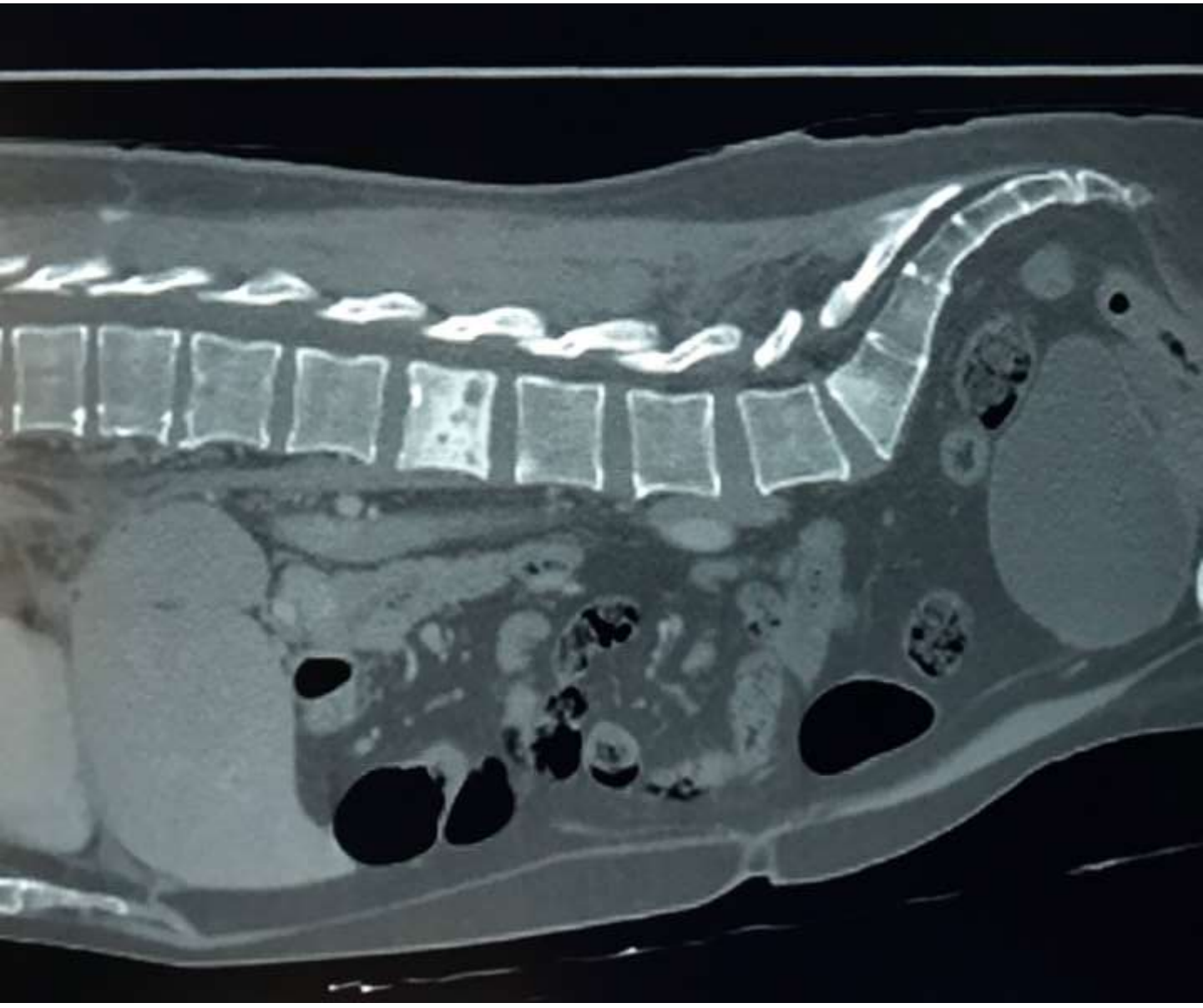


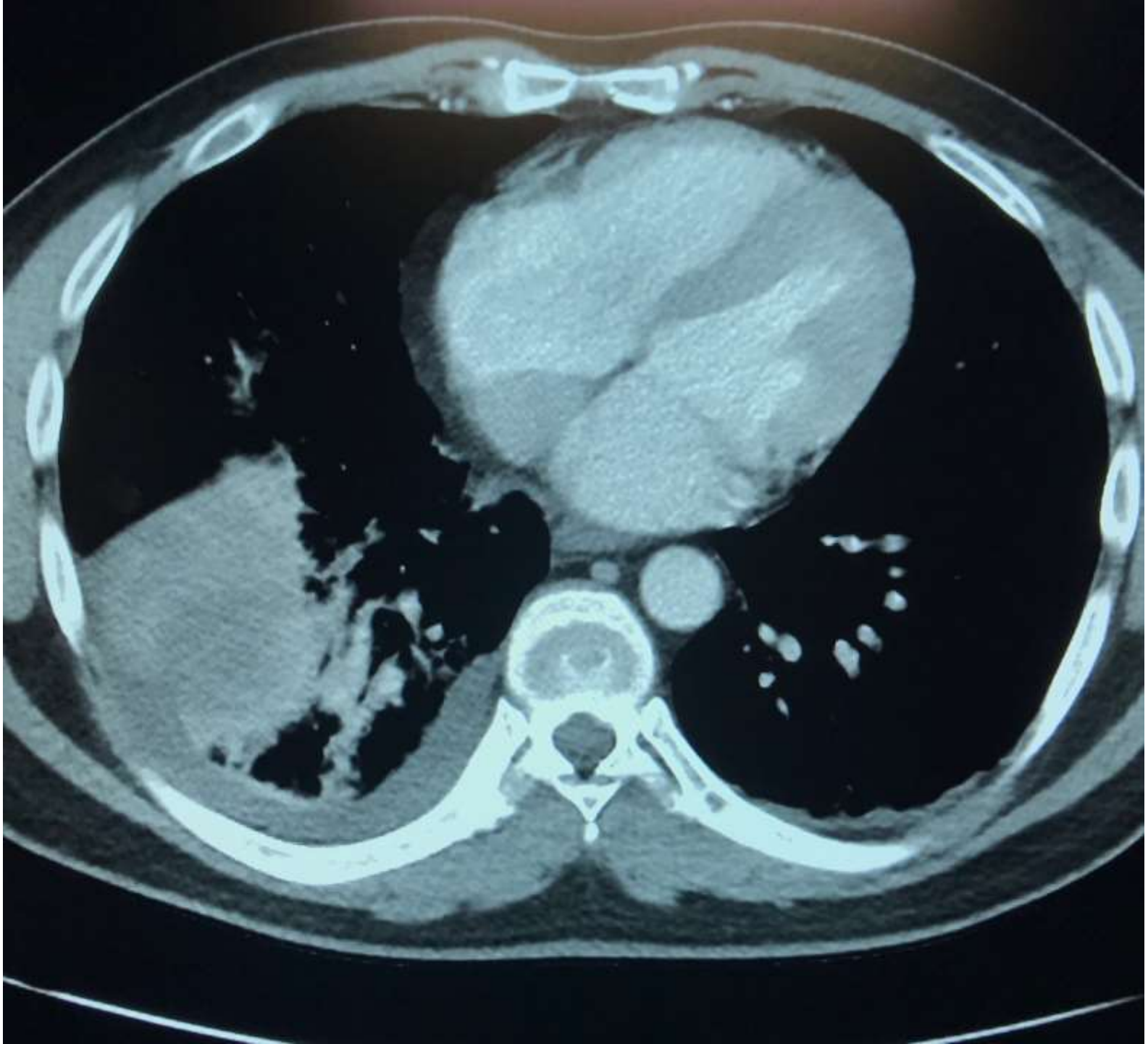












# Epithelioid Hemangioendothelioma (slide 3)

- Low to intermediate grade malignancy
- 5 year survival 60% (20%)
- Multiple pulmonary nodules
- Diffuse pleural involvement
- Multiple organs, especially liver and bone

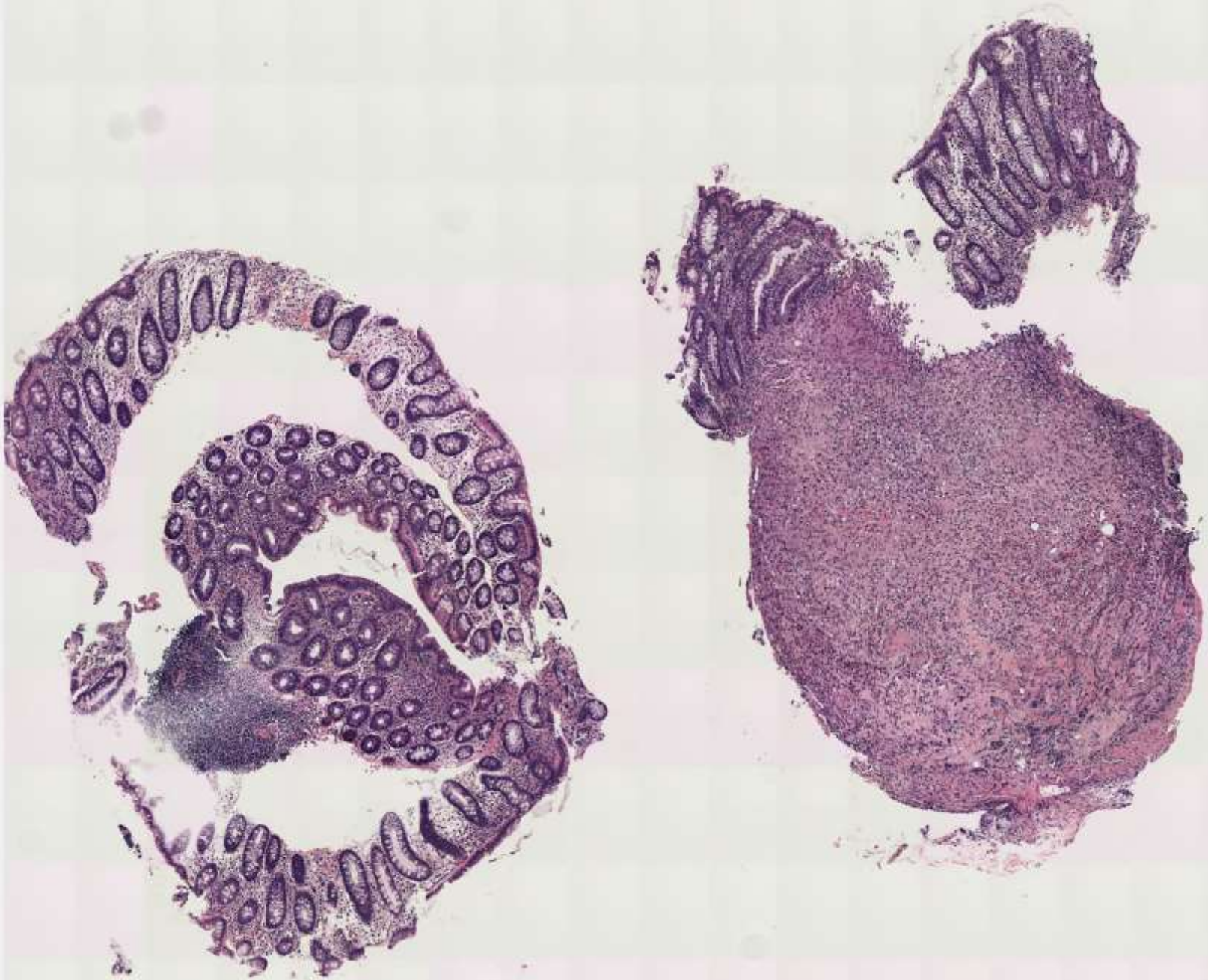
# Epithelioid Hemangioendothelioma (slide 4)

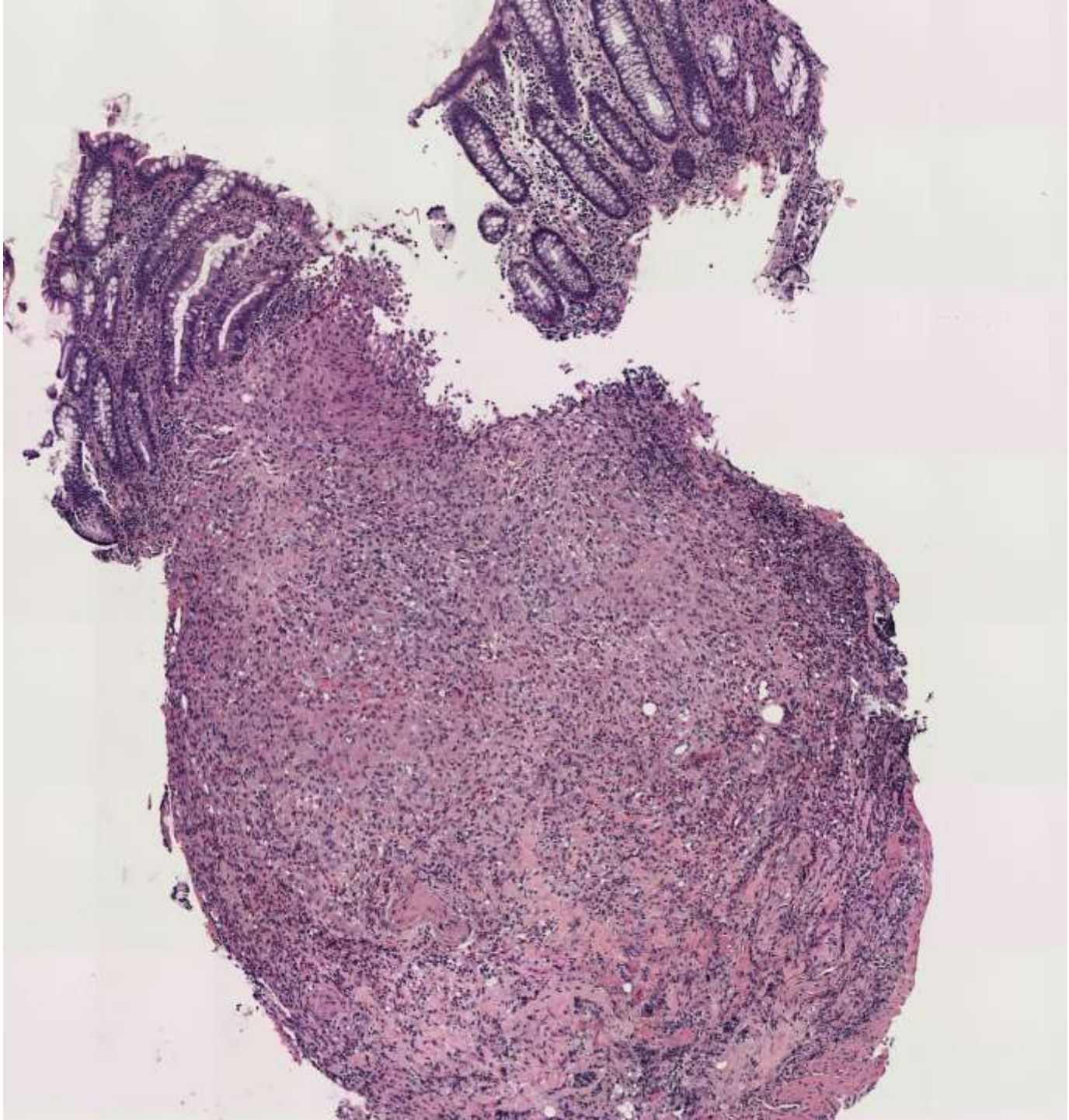
- Nodules have peripheral cellularity and central sclerosis/myxoid stroma with necrosis
- Intra-alveolar growth (IVBAT)
- Epithelioid cells with intracytoplasmic lumina
- Can be mistaken for benign process in needle biopsy:
  - Young age
  - Bland histiocytoid cells
  - Sclerotic/myxoid center with necrosis
- Positive for CD31, CD34 and Fli-1
- Caution: May be positive for cytokeratins, including CK7

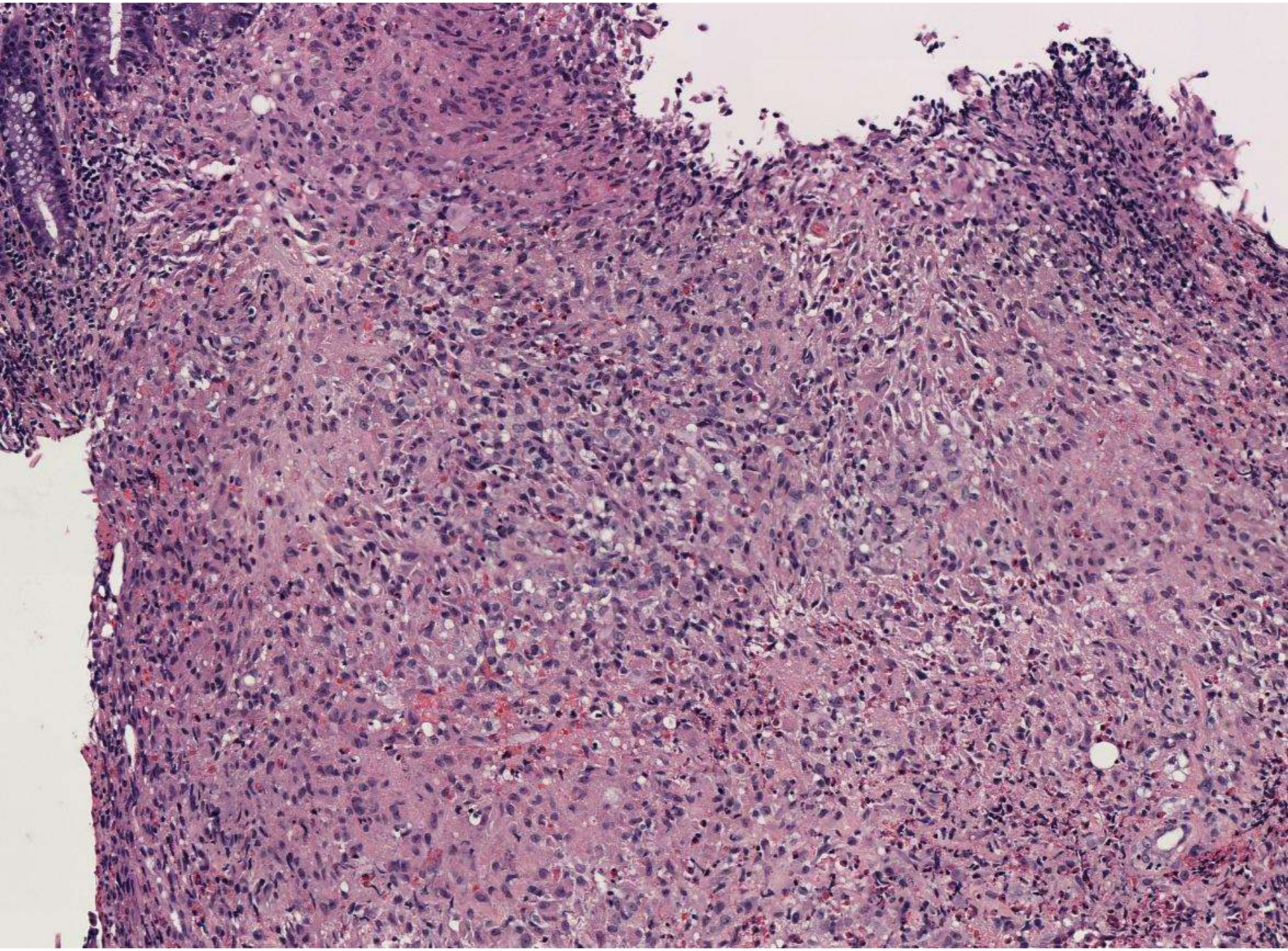
# SB 6342

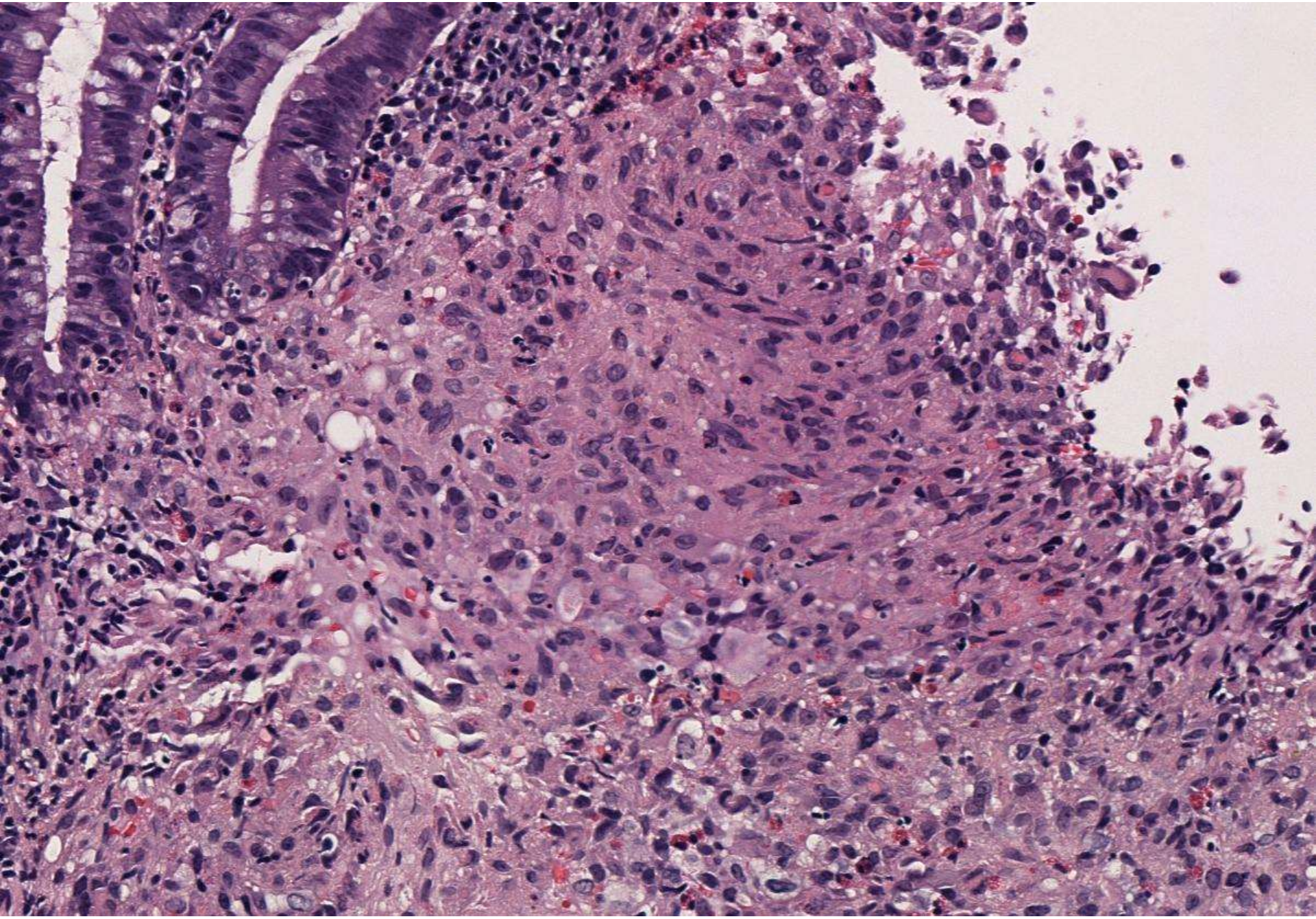
**Thuy Nguyen; Mills-Peninsula Health Services**

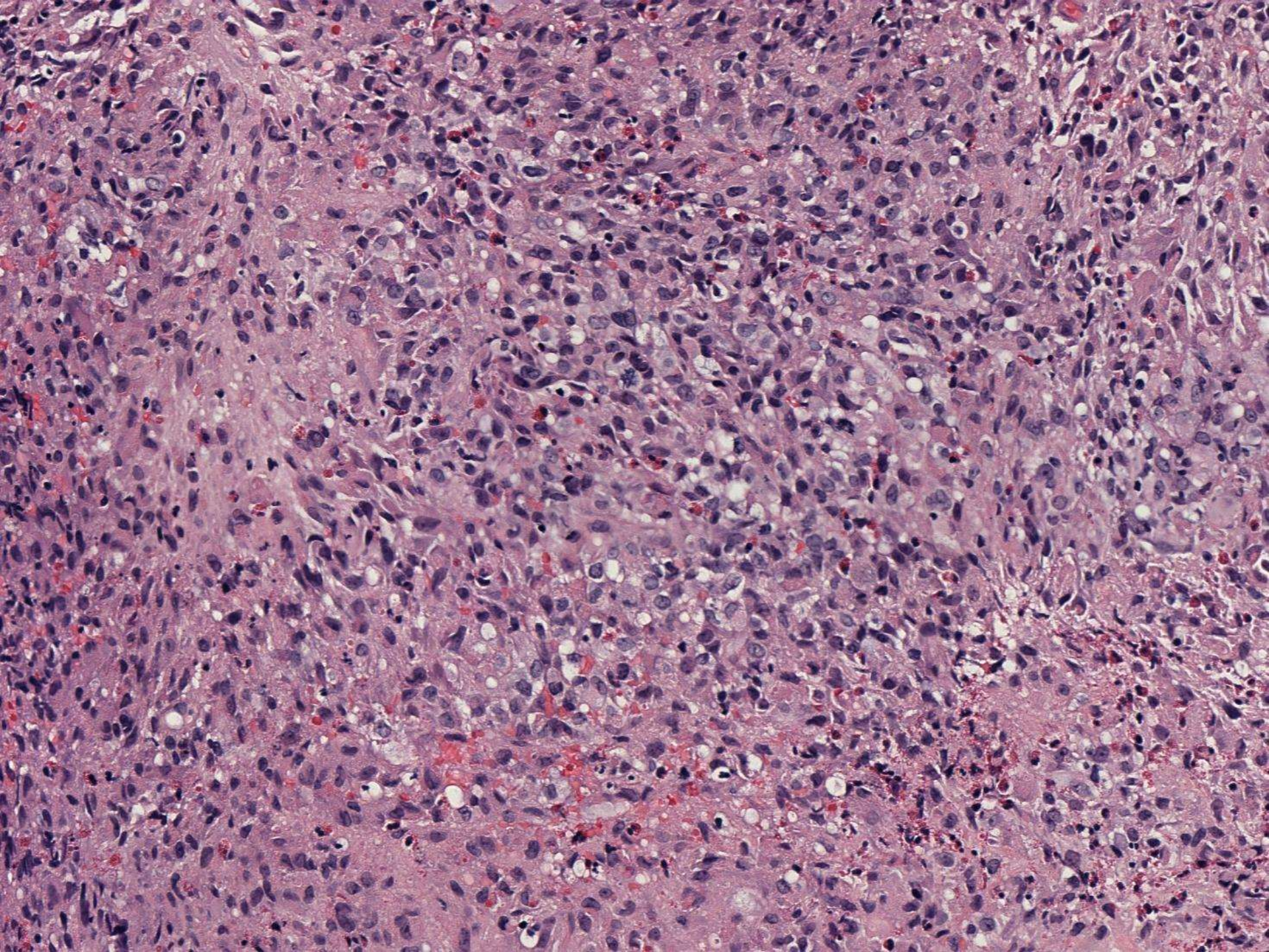
75-year-old female with colon polyps seen in routine colonoscopy.

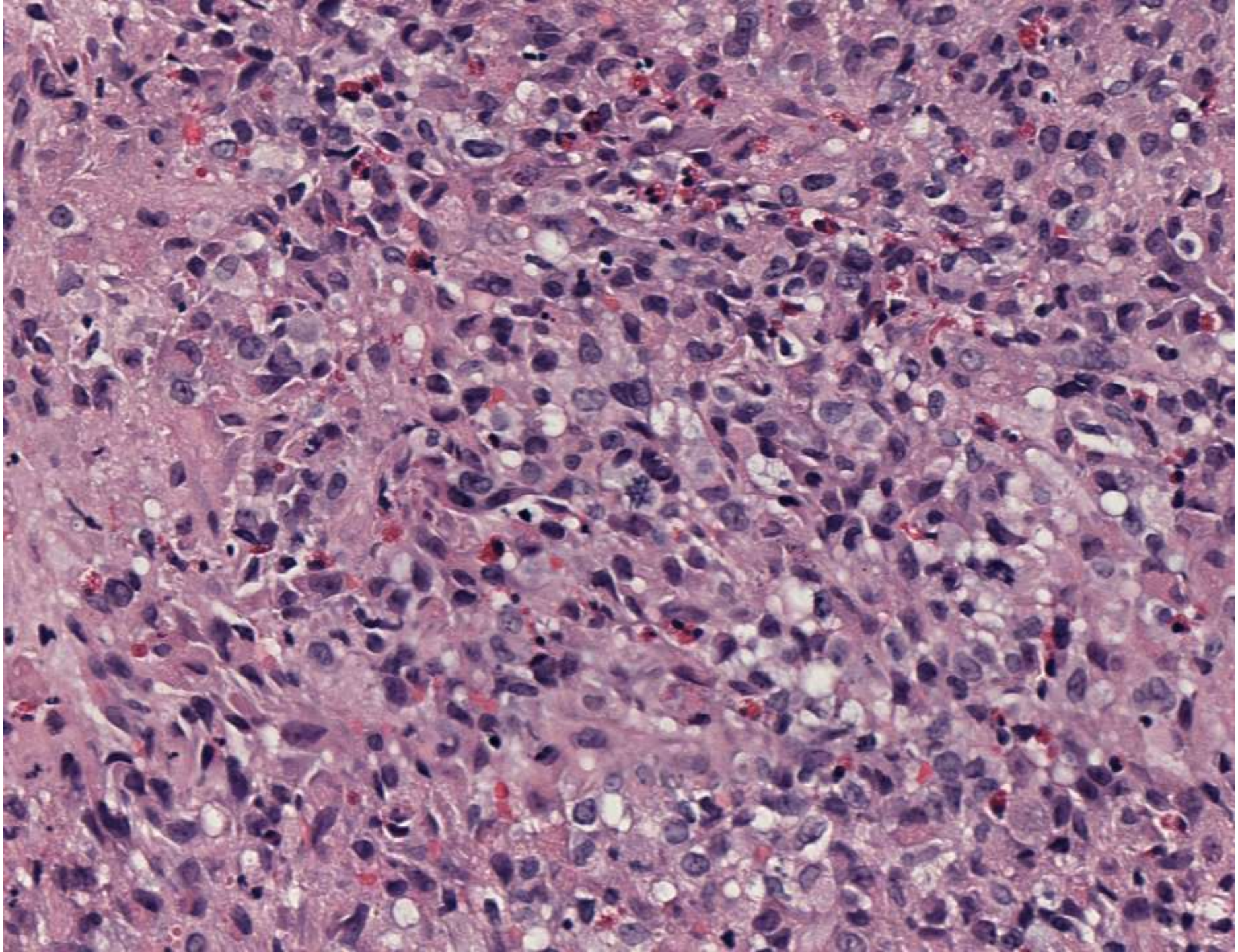


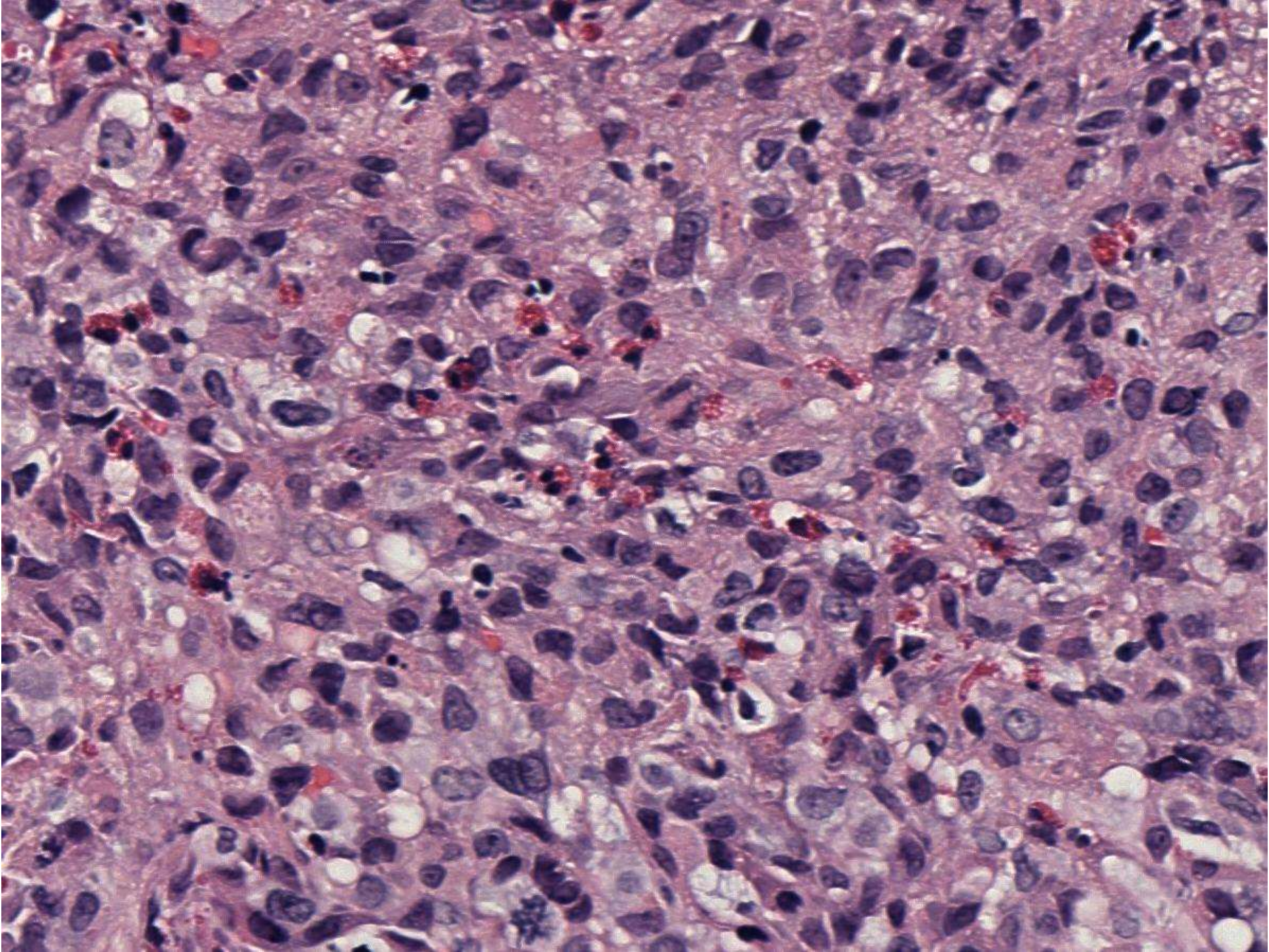




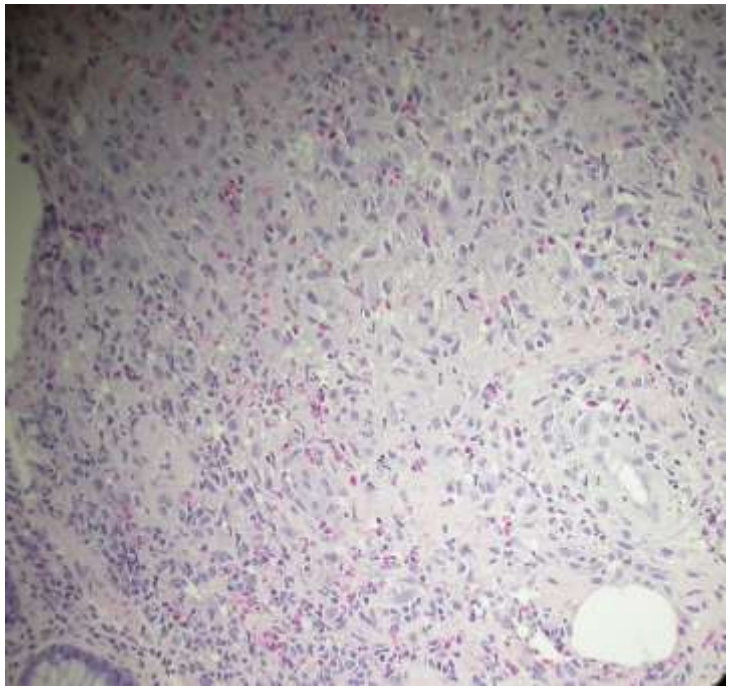








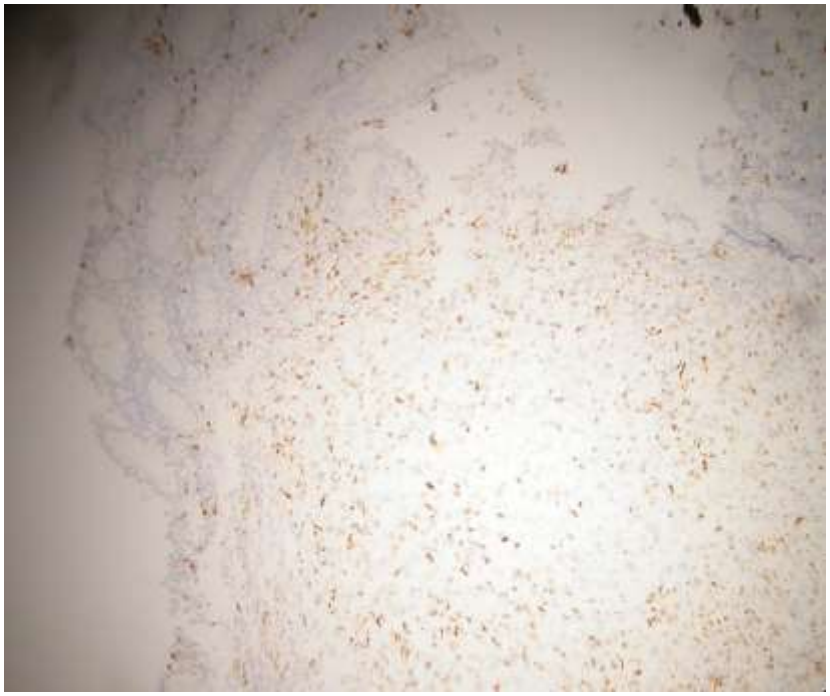
# Differential Diagnosis



**Infectious - granuloma**
**Neoplastic - lymphoproliferative disorder**

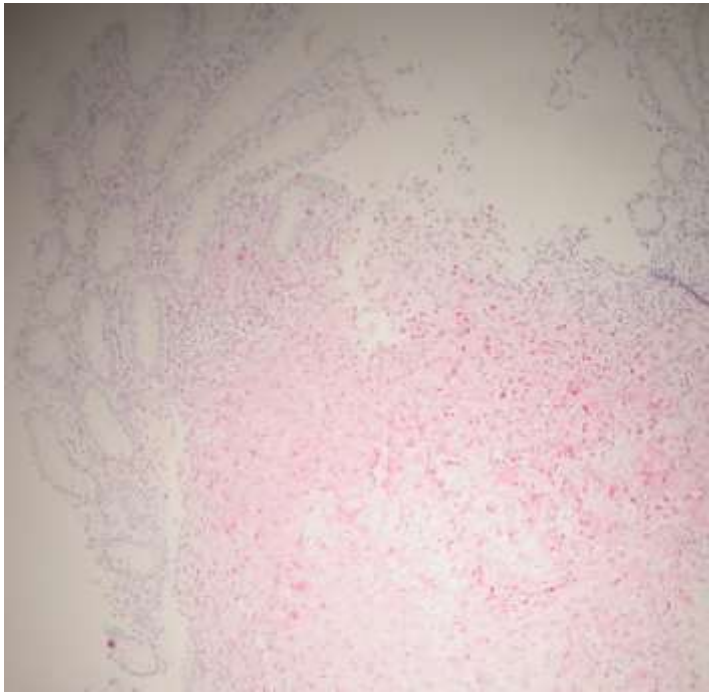
- **Langerhans cell histiocytosis**
- **Lymphoma**
- **Mastocytosis**

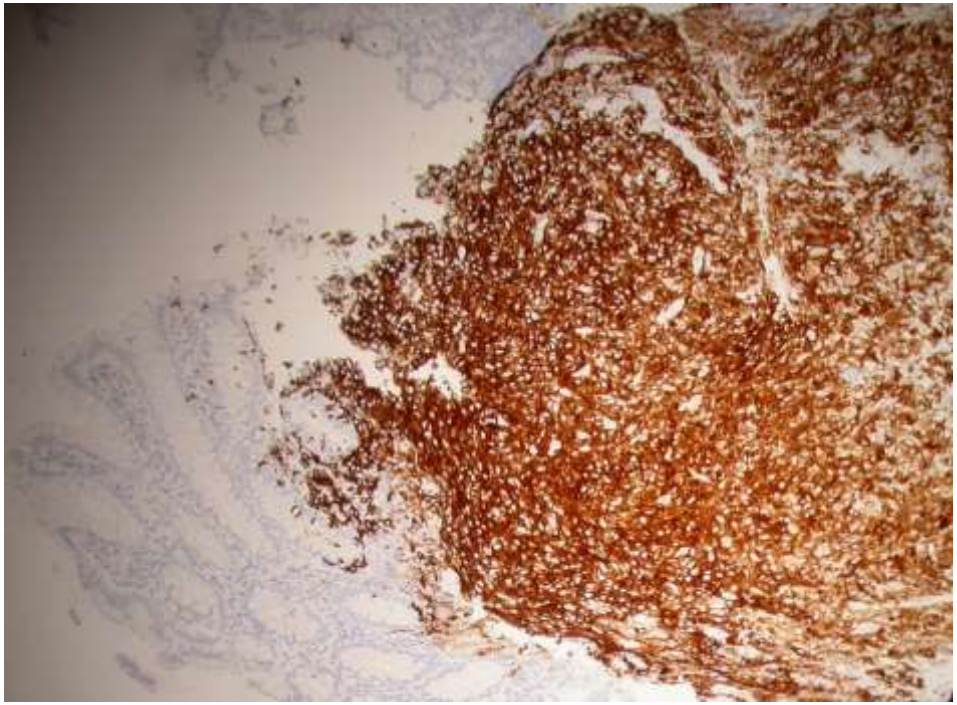
**No parasites**
**AFB & GMS stains are negative**



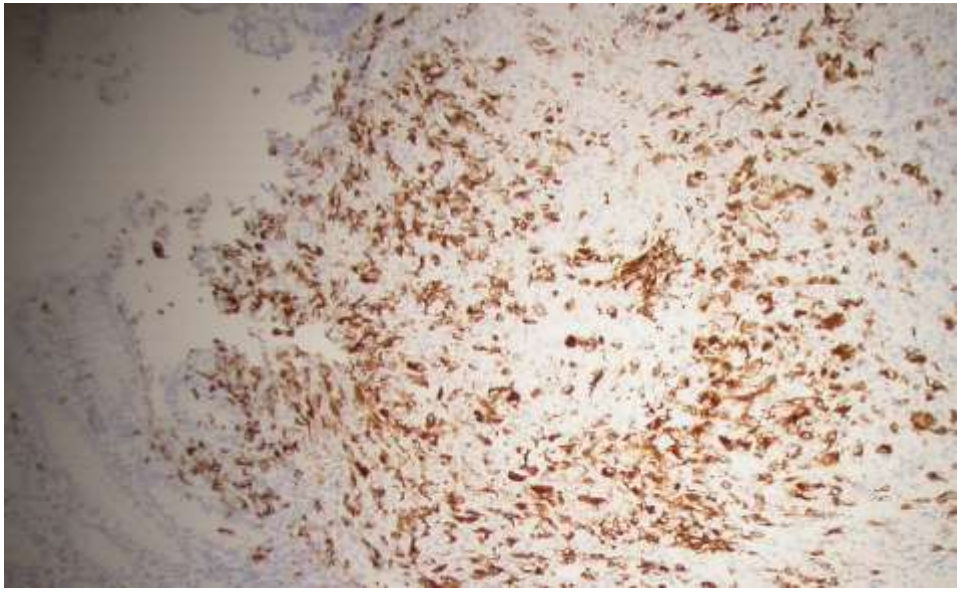
**CD68**

**S100**





**CD1a**



**Langherin**

# Diagnosis

**Langerhans cell histiocytosis involving GI tract**

**- Systemic disease**

**- Typically in children**

**- Sporadic single lesion limited to GI tract**

**- Adults**

**- Predominantly female**

**- Encounter incidentally as a solitary polyp**

**- No symptoms**

**- Rare cases may develop multifocal and systemic disease**

**- Close follow up is advised**

# Follow up

**- Bone scans and MRI are negative for evidence of systemic disease**
**- No clinical symptoms**
**- Advised to have a follow up colonoscopy in 6 months**

# References

**Singhi AD, Montgomery EA. Gastrointestinal tract langerhans cell histiocytosis: A clinicopathologic study of 12 patients. Am J Sure Pathol. 2011; 35(2):305-10.**

**Kibria R, Gibbs PM, Novick DM. Adult Langerhans cell histiocytosis: a rare cause of colon polyp. Endoscopy. 2009; Suppl 2:E160-1.**

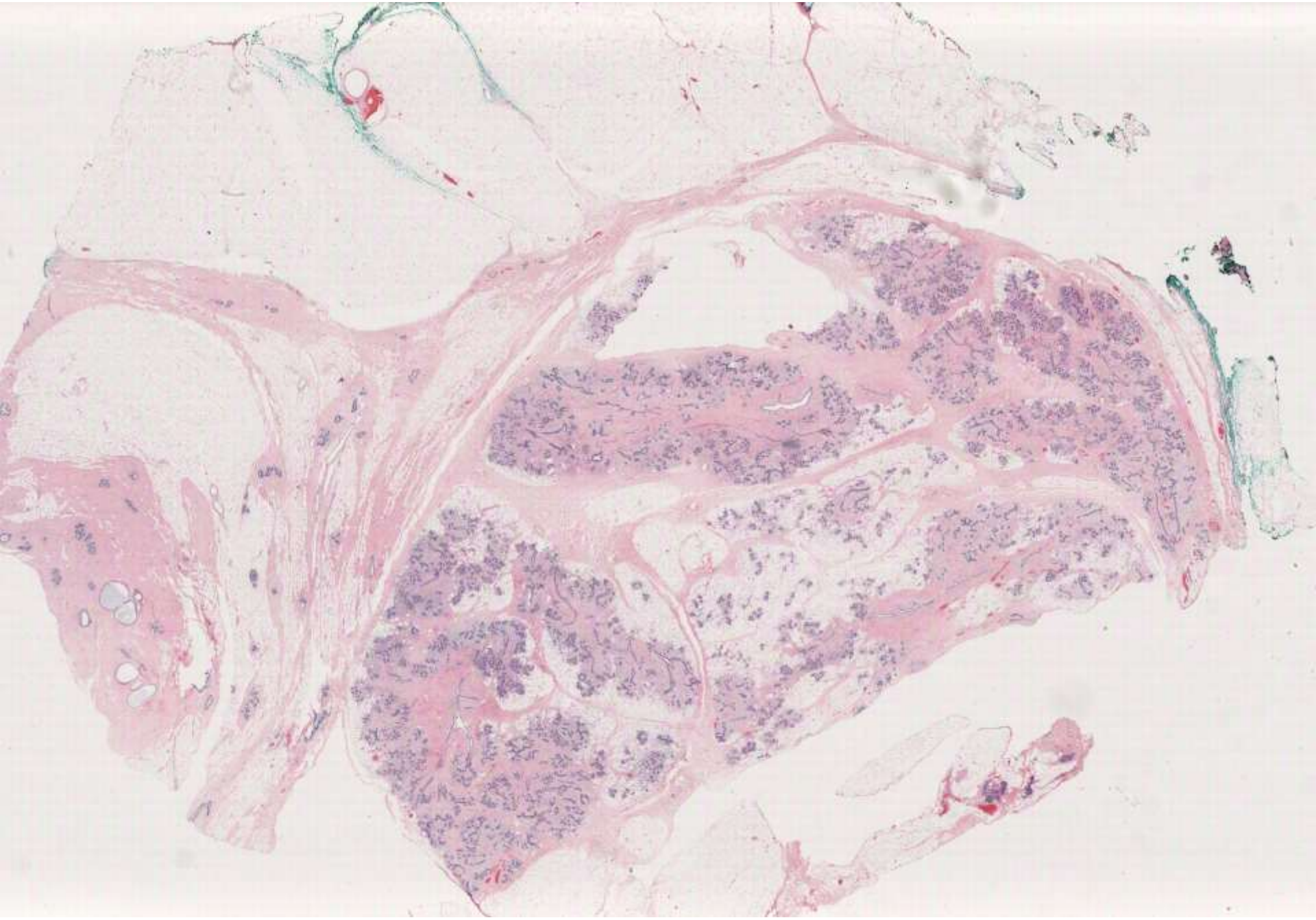
**Shankar U, Prasad M, Chaurasia OP. A rare case of langerhans cell histiocytosis of the gastrointestinal tract. World J Gastroenterol. 2012; 18(12):1410-3.**

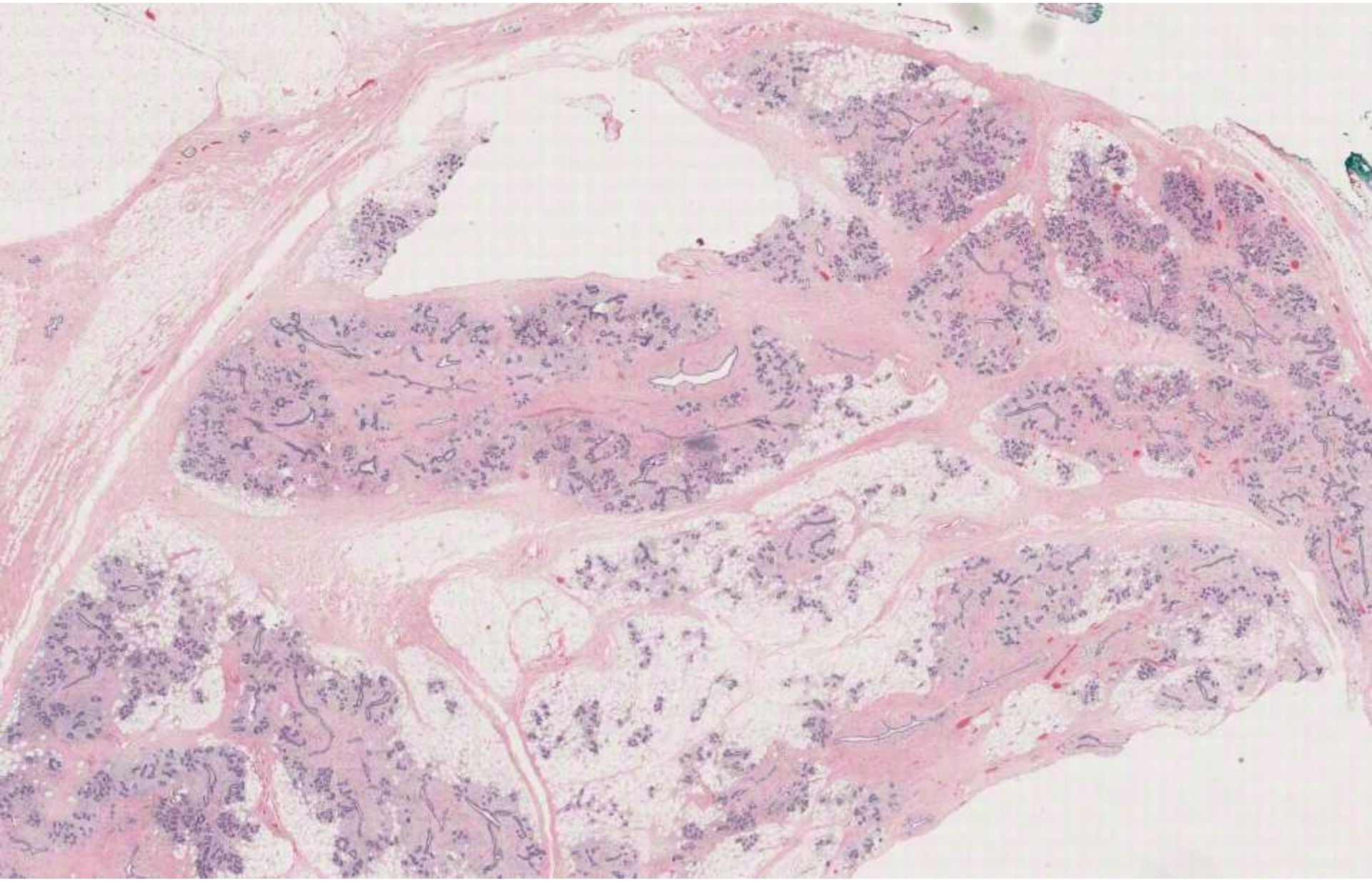
# SB 6343

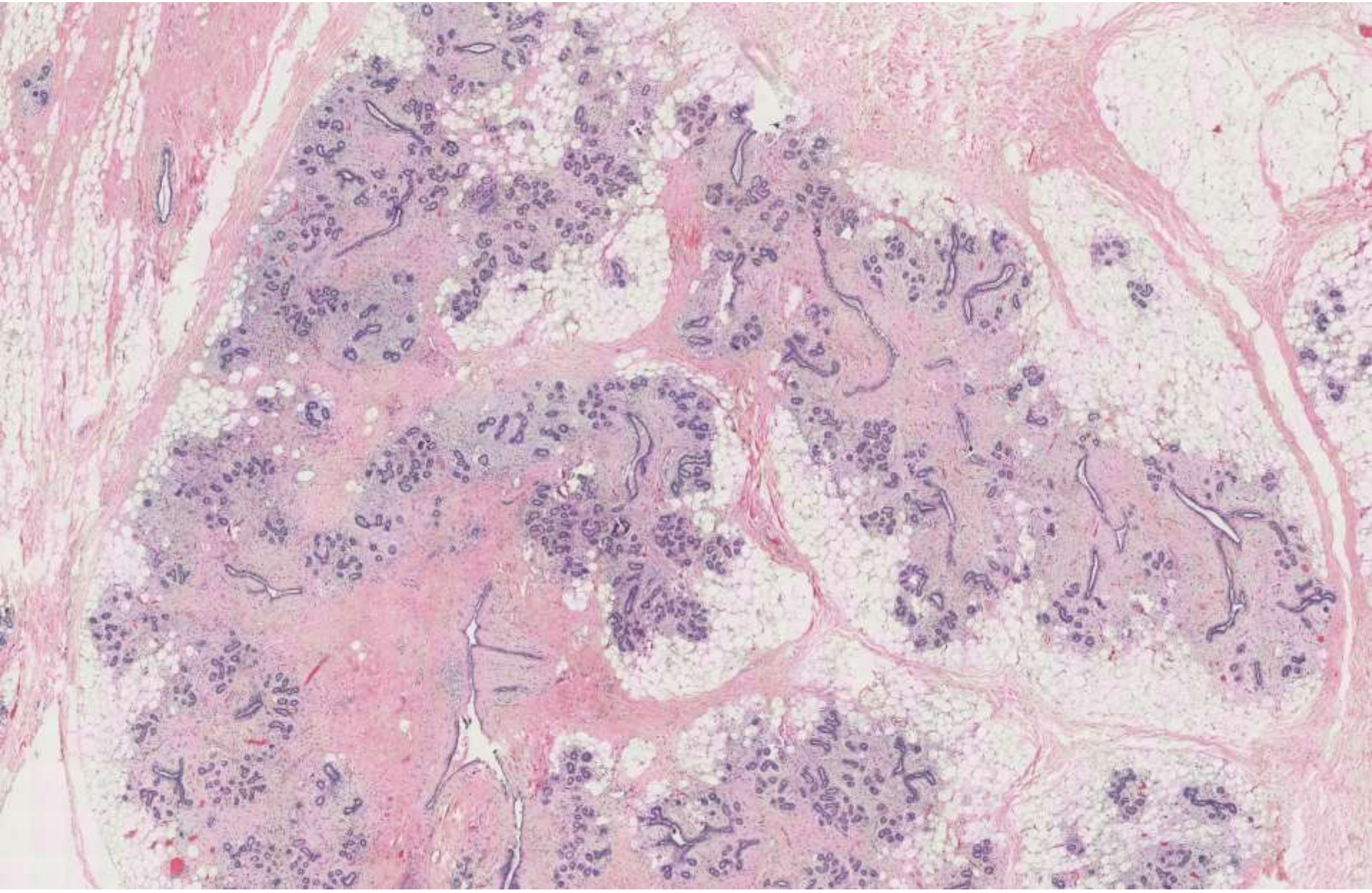
**Kelly Mooney/Megan Troxell; Stanford**

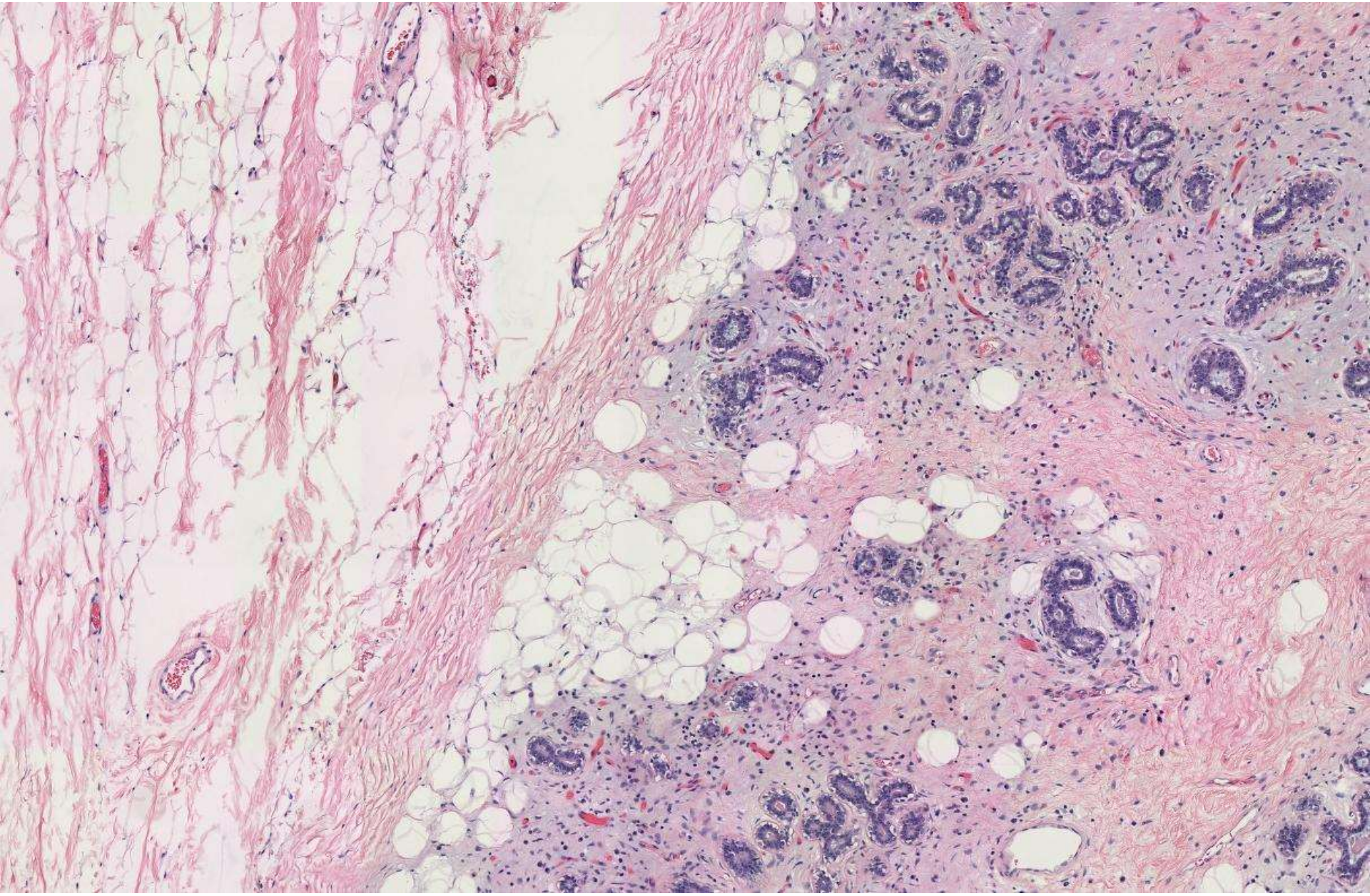
30-year-old BRCA positive female with left breast invasive ductal carcinoma, with contralateral breast ultrasound revealing 3.5cm oval mass with circumscribed margins with mixed echogenicity including hypo/hyper-echoic areas. Bilateral mastectomy performed.

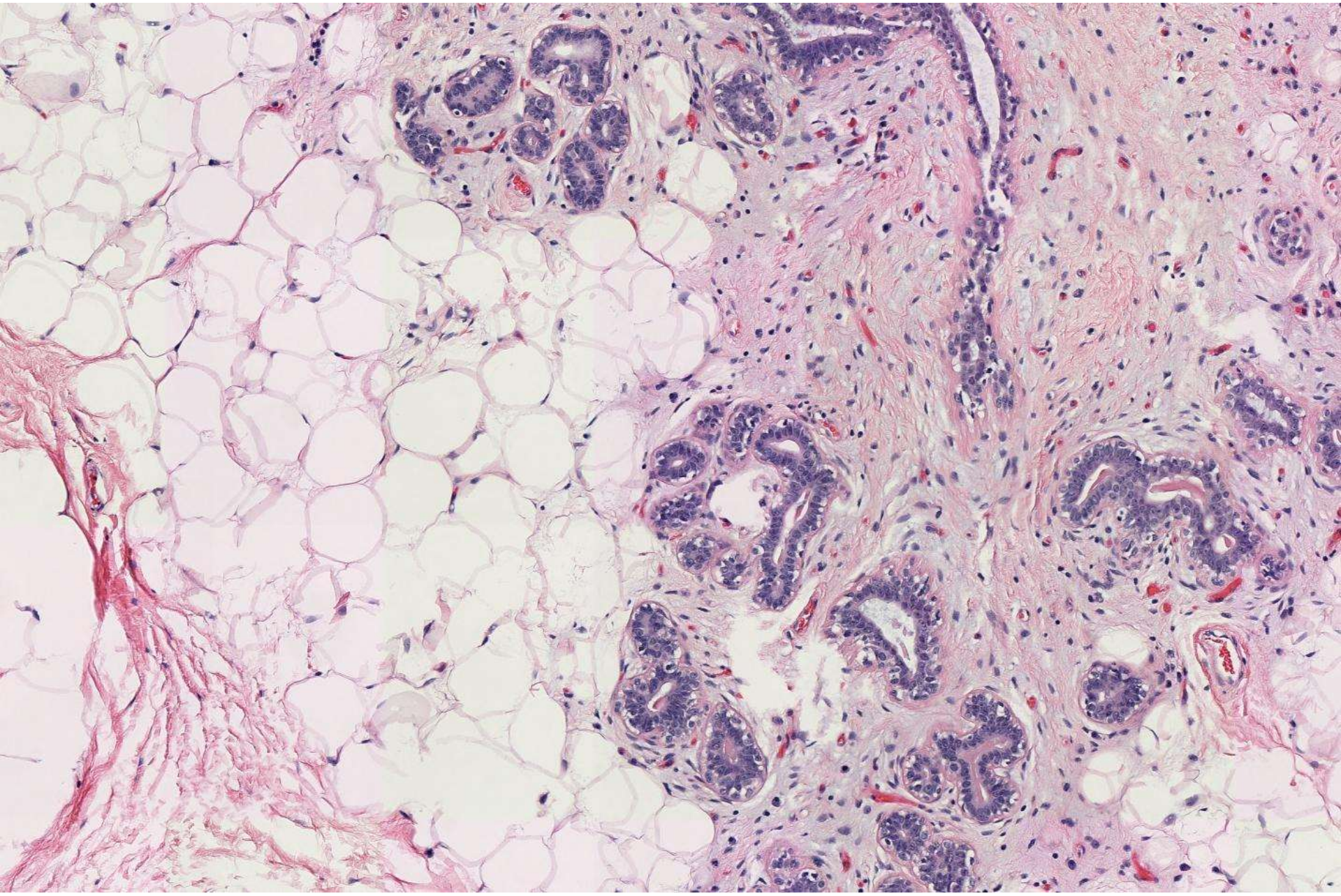

LOGIQ
S8
2
3
RIGHT BREAST 4 O'CLOCK 6 CM FN RAD AREA OF PALP
S
1 L 3.09 cm

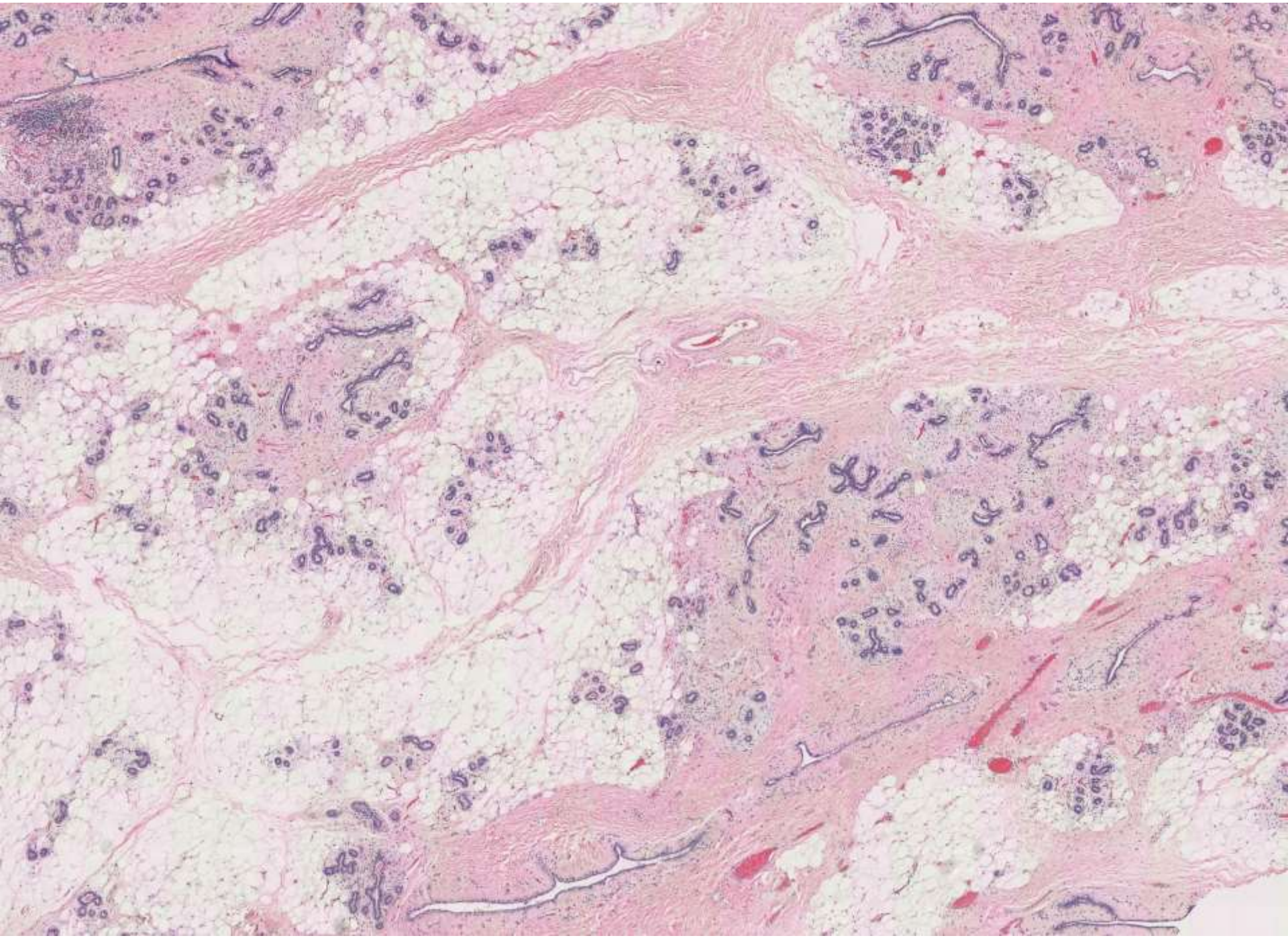


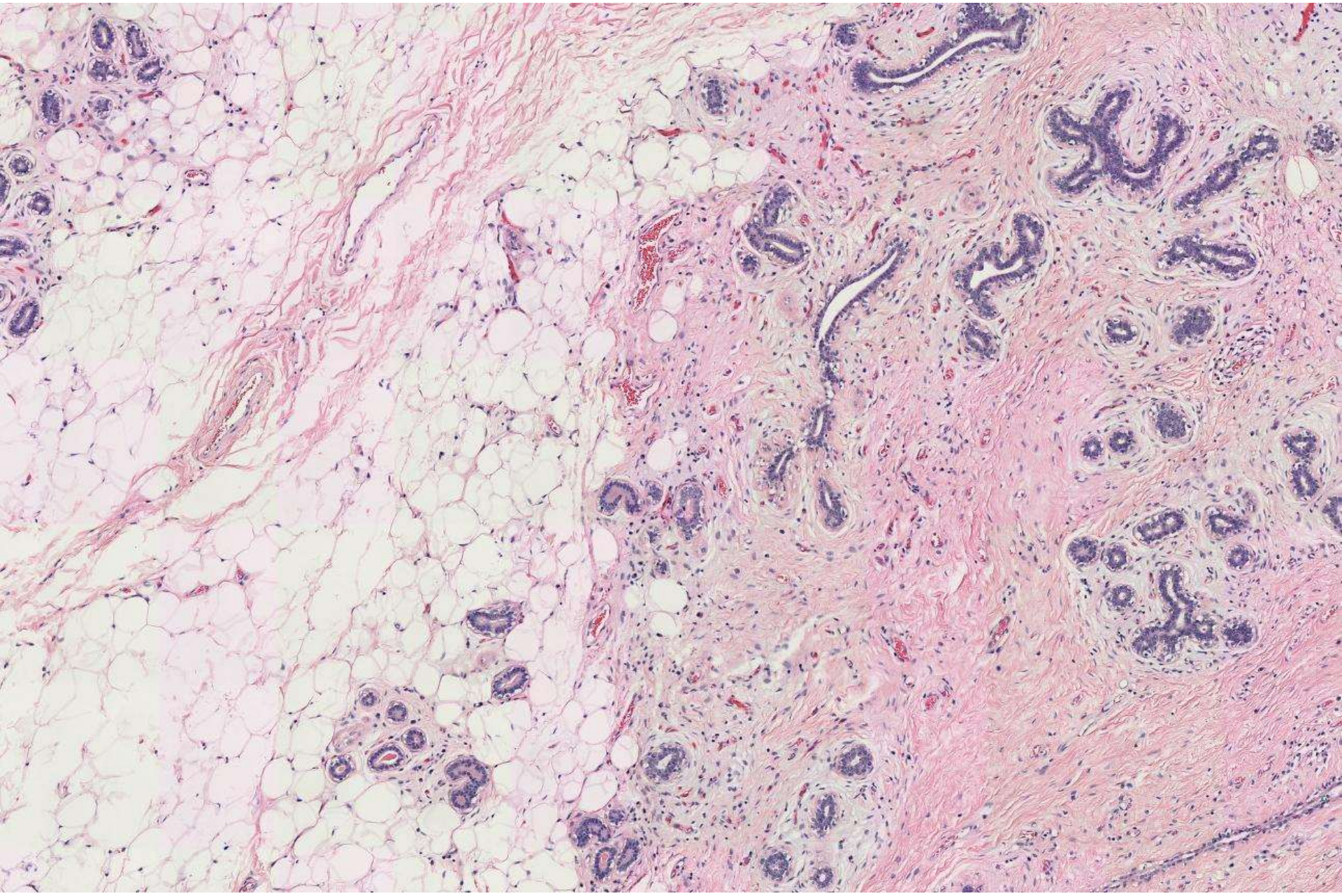












*Answer:*
# Mammary Hamartoma

Other names: fibroadenolipoma, adenolipofibroma, chondrolipoma
"Mastoma" (1968)

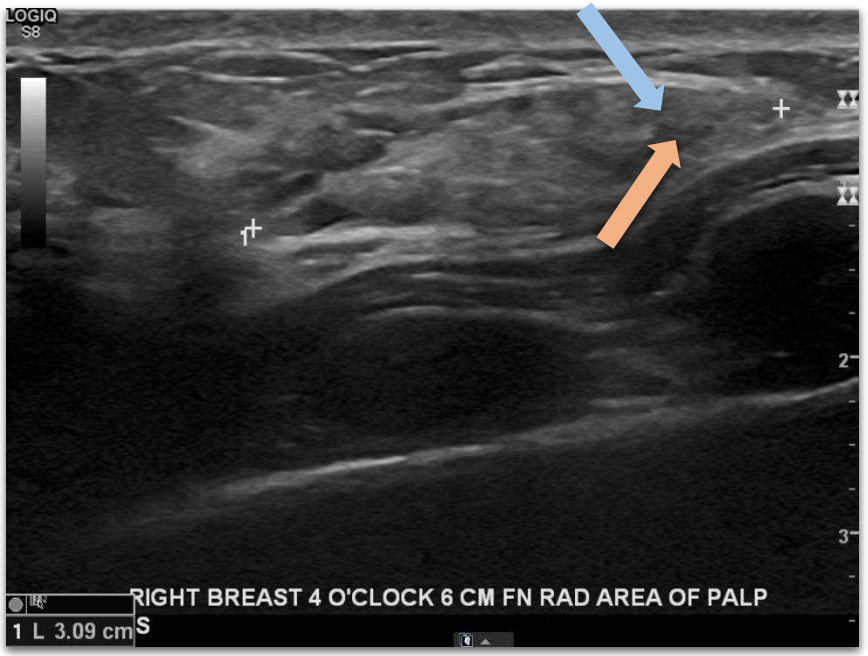
# Mammary Hamartoma

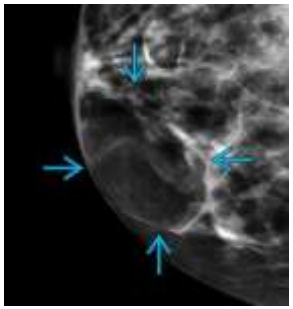
- 1-5% of benign breast tumors (incidence 1%)
- Women, age 20-80 (mean 45)
- Chromosome 12 breakpoints
- 50-75% of women with Cowden Syndrome (*PTEN*)
- No treatment needed for most cases; may excise large symptomatic masses or those with atypical imaging appearance
  - Rare recurrence
  - Rare likely coincidental IDC, LCIS

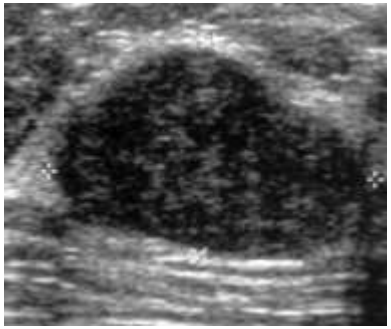
# Characteristic imaging

<u>Mixed echogenicity</u>
hyperechoic
fibroglandular tissue
interspersed with
hypoechoic fat

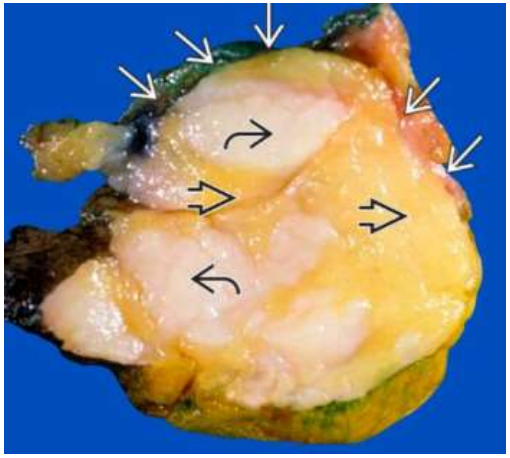
*"slice of salami"*
*"breast within a breast"*





# Macroscopic findings

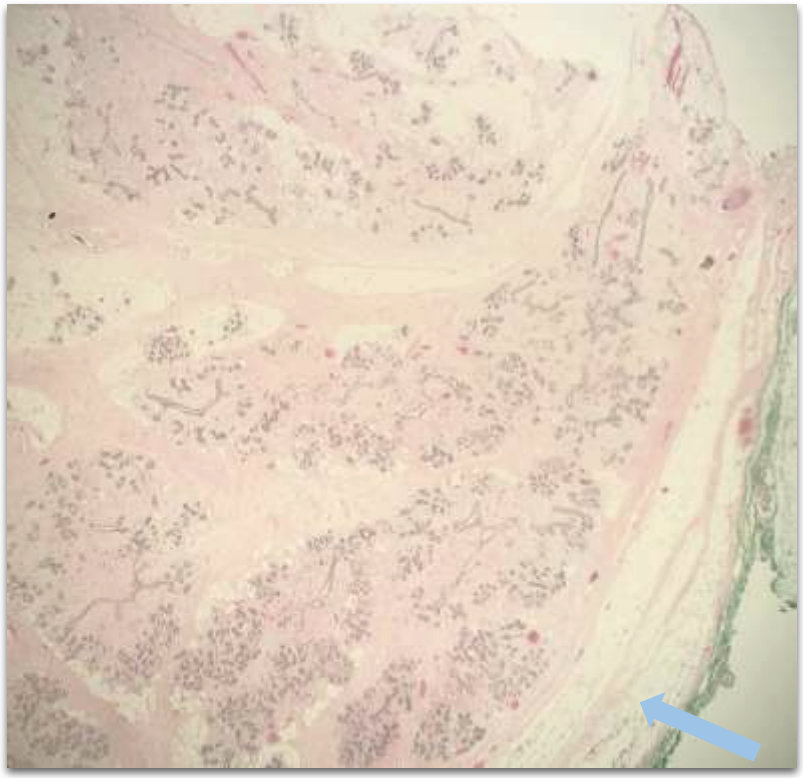


# Microscopic findings

Well-circumscribed mass
Thin capsule

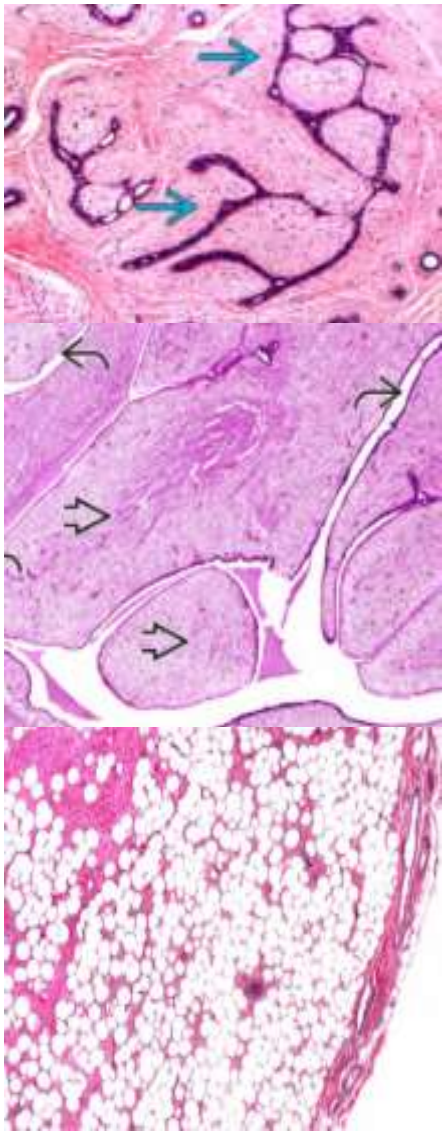
Normal-appearing ducts and lobules with a minor component of adipose

May see:
Stromal hyalinization
Fibrocystic change
Giant stromal cells
Cartilaginous stromal metaplasia
Smooth muscle (myoid hamartoma)



# Admixed stromal and epithelial elements forming a mass

| | |
|---|---|
| **Fibro-adenoma** | Stromal proliferation<br>**Distortion of epithelial component**<br>**Rarely include adipose** |
| **Phyllodes tumor** | **Distortion of epithelial component**<br>**Nuclear atypia**, **mitoses**<br>Larger, cellular<br>May contain malignant adipose tissue (liposarcoma) |
| Spindle cell lipoma /Lipomatous variant of myofibroblastoma | (-) epithelial component<br>More evenly distributed adipose |



# References

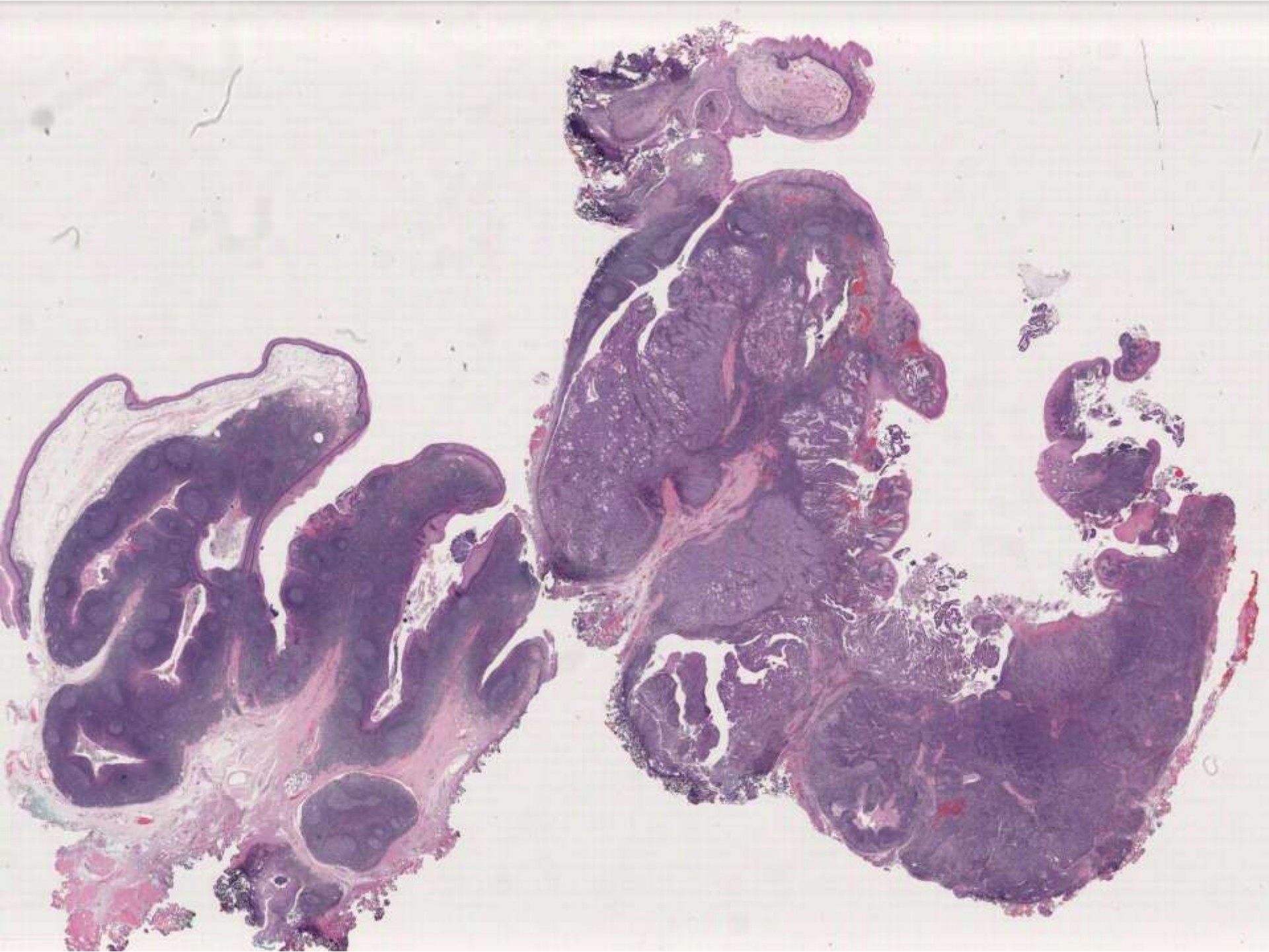

1. Hoda, S.A., P.P. Rosen, E. Brogi, and F.C. Koerner. *Rosen's Breast Pathology*. Wolters Kluwer Health, 2014.
2. Amir, R. A. & Sheikh, S. S. Breast hamartoma: A report of 14 cases of an under-recognized and under-reported entity. Int J Surg Case Rep 22, 1–4 (2016).
3. Sevim, Y. et al. Breast hamartoma: a clinicopathologic analysis of 27 cases and a literature review. Clinics (Sao Paulo) 69, 515–523 (2014).
4. Tse, G. M. K. et al. Hamartoma of the breast: a clinicopathological review. J. Clin. Pathol. 55, 951–954 (2002).

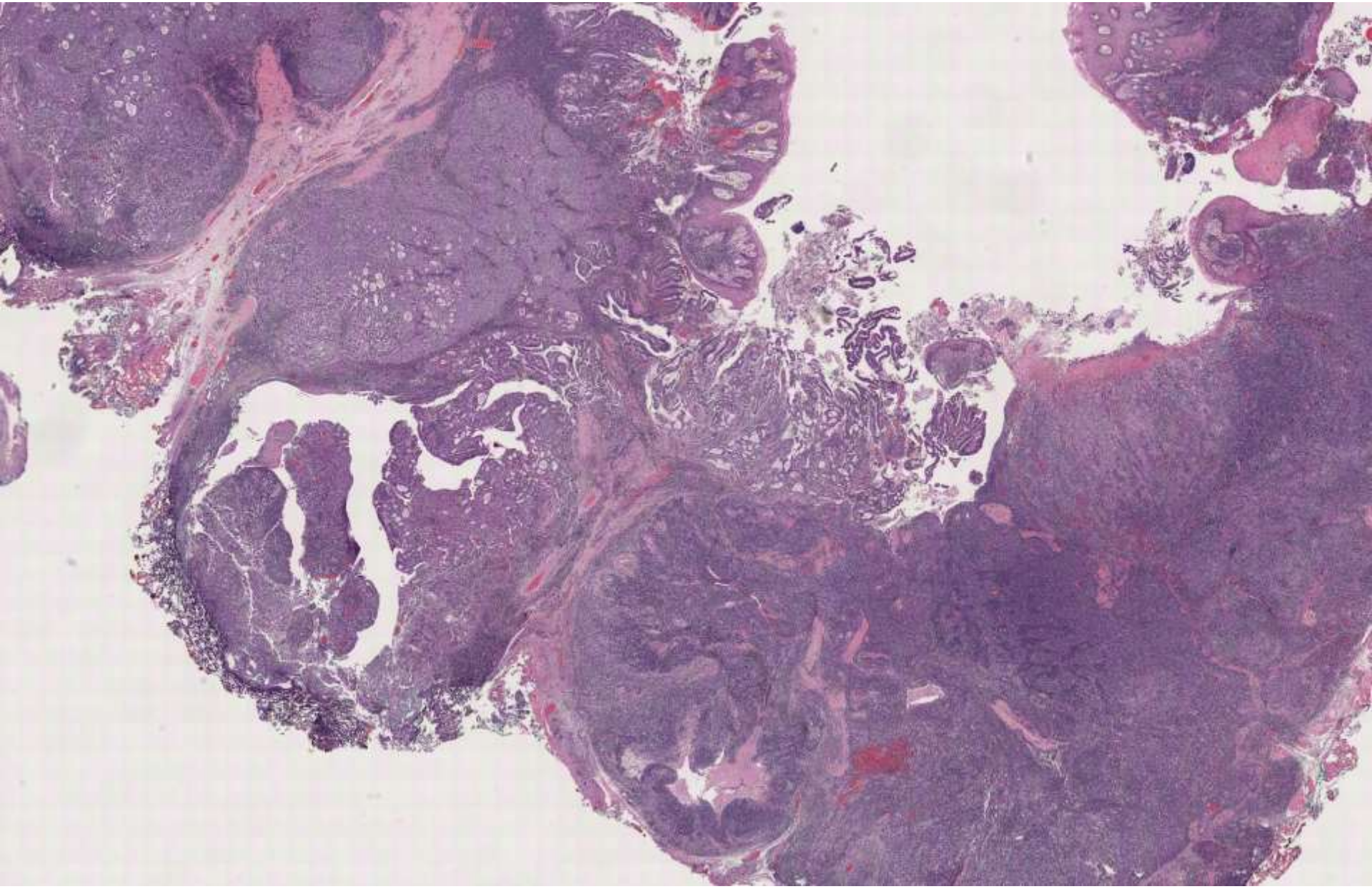

Images: from ExpertPath.com

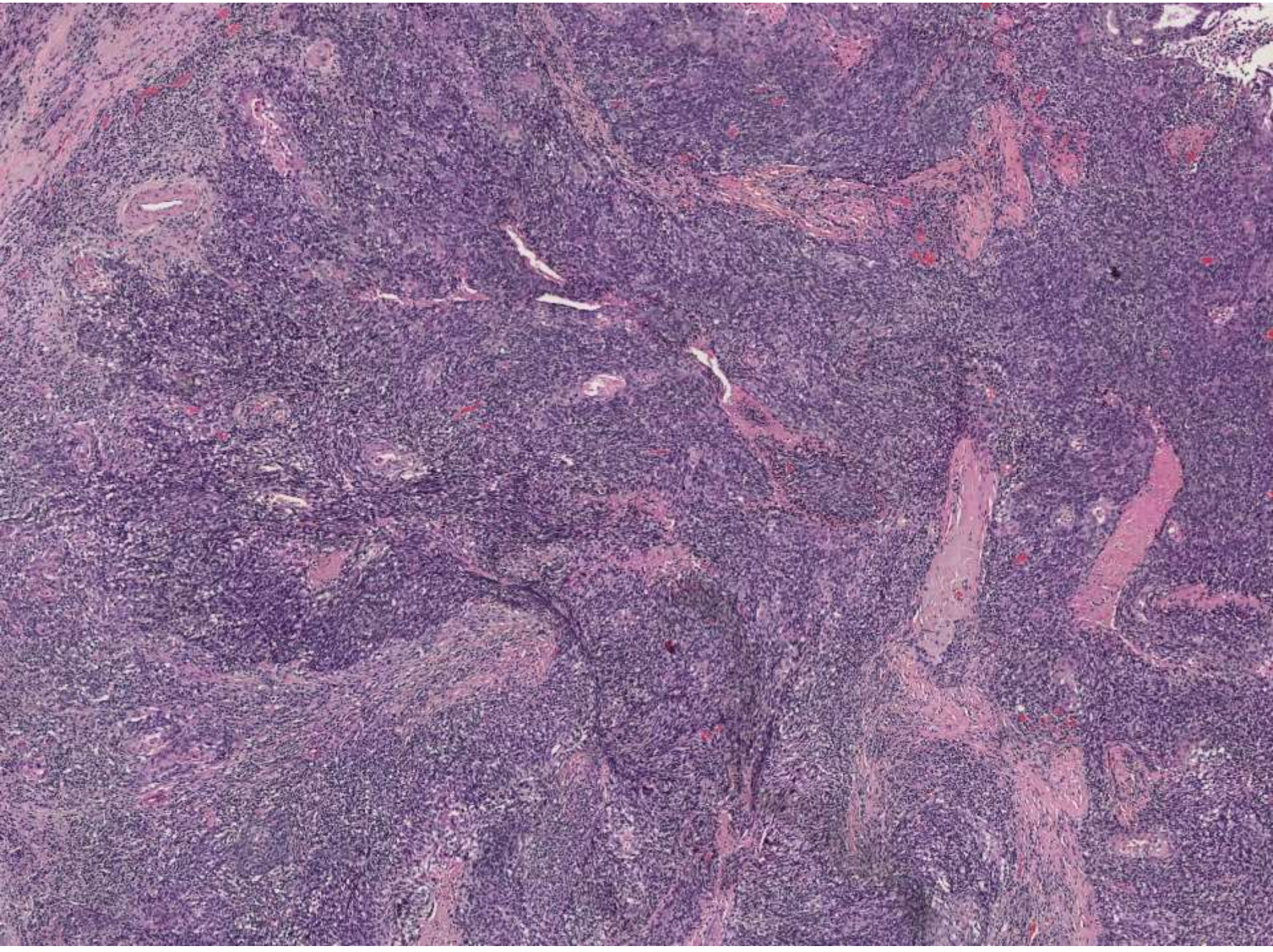
# SB 6344
# (scanned slide available)

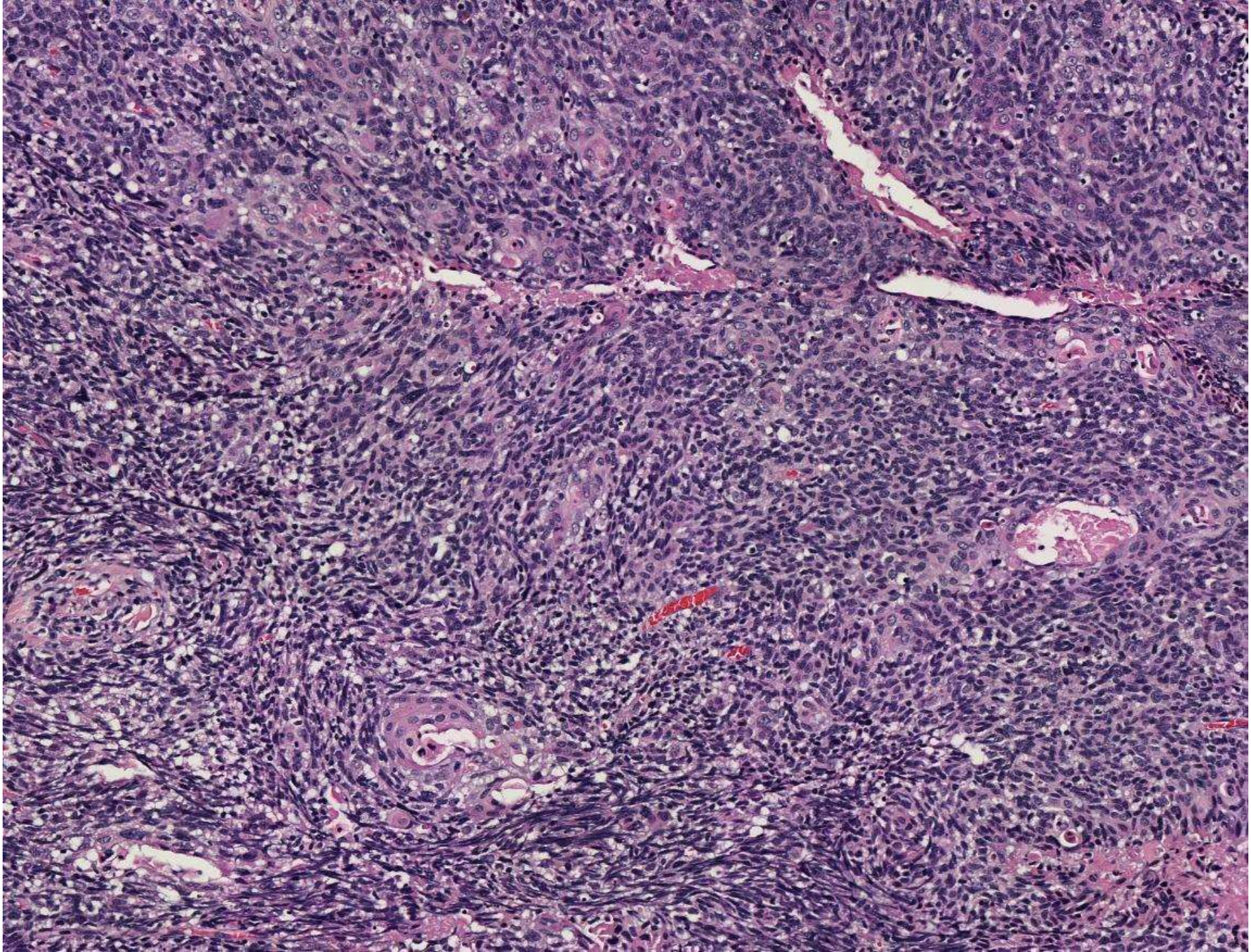
**Ankur Sangoi; El Camino Hospital**

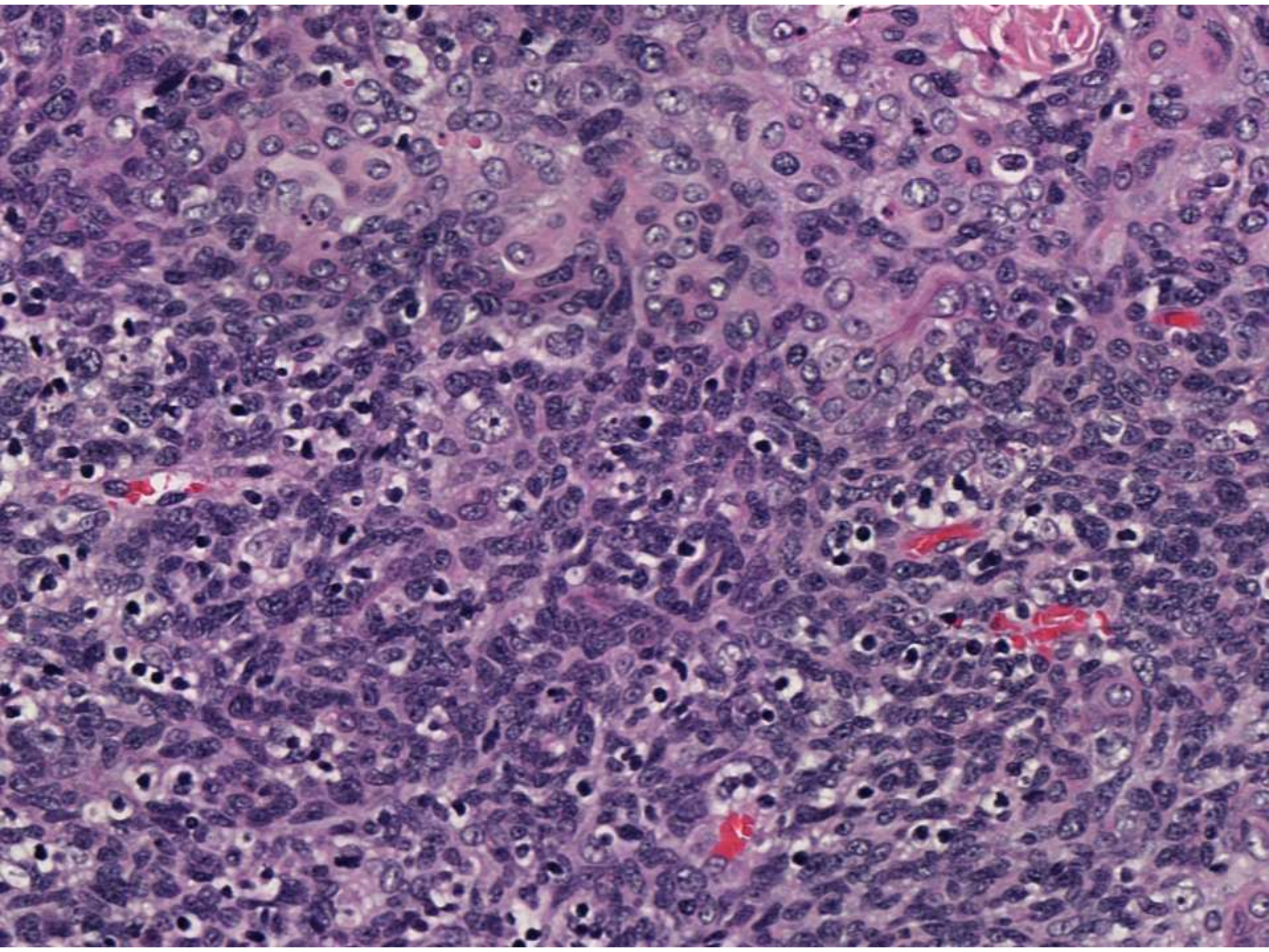
57-year-old male with h/o prostate cancer s/p prostatectomy (Gleason grade 3+4 with tertiary pattern 5, mixed acinar/ductal adenocarcinoma, pT3aN0). Now presents with cystic neck mass diagnosed as metastatic squamous cell carcinoma by FNA. Work-up revealed tonsillar mass identified. Tonsillectomy performed at time of oropharyngeal mapping.

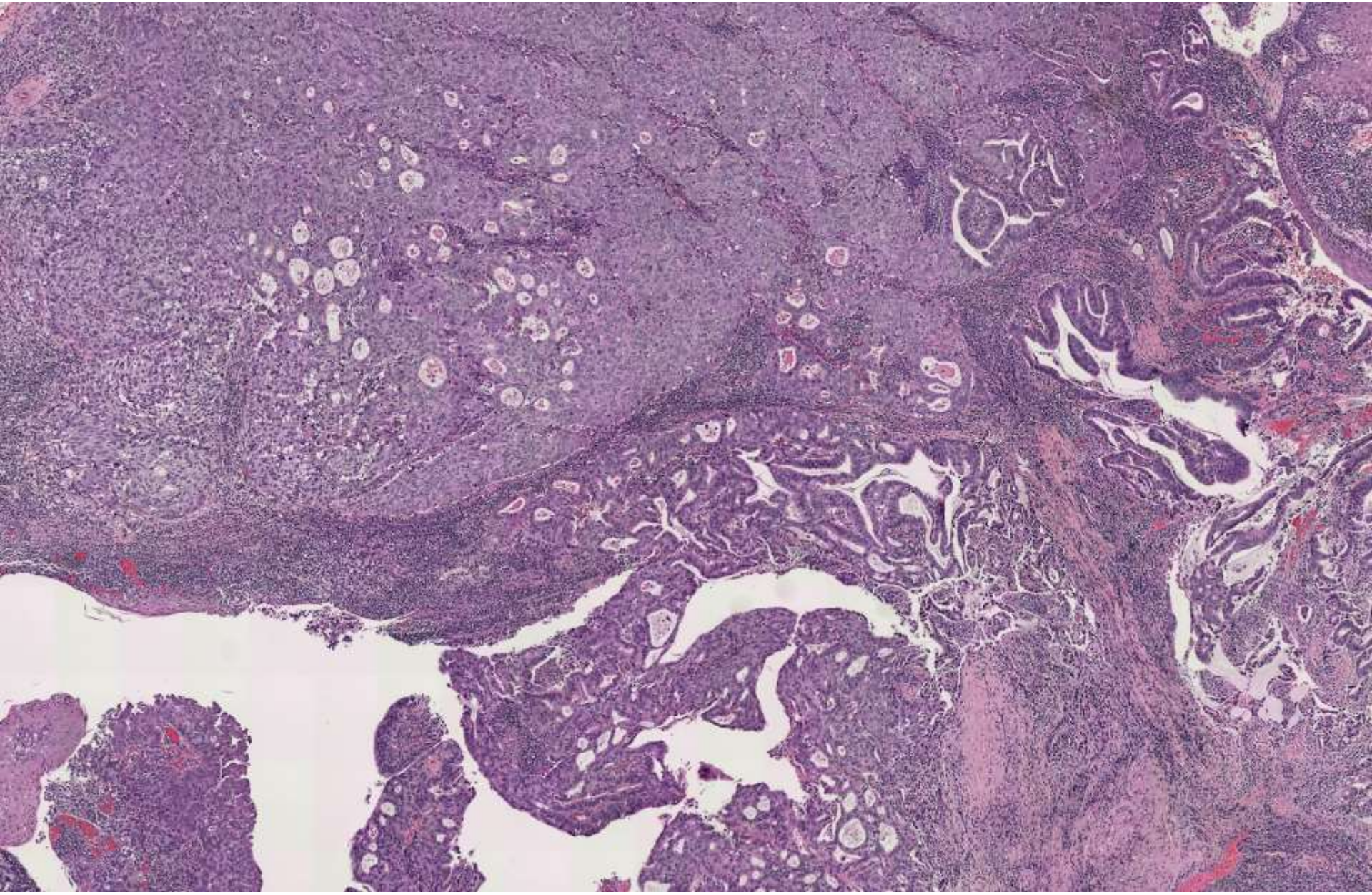


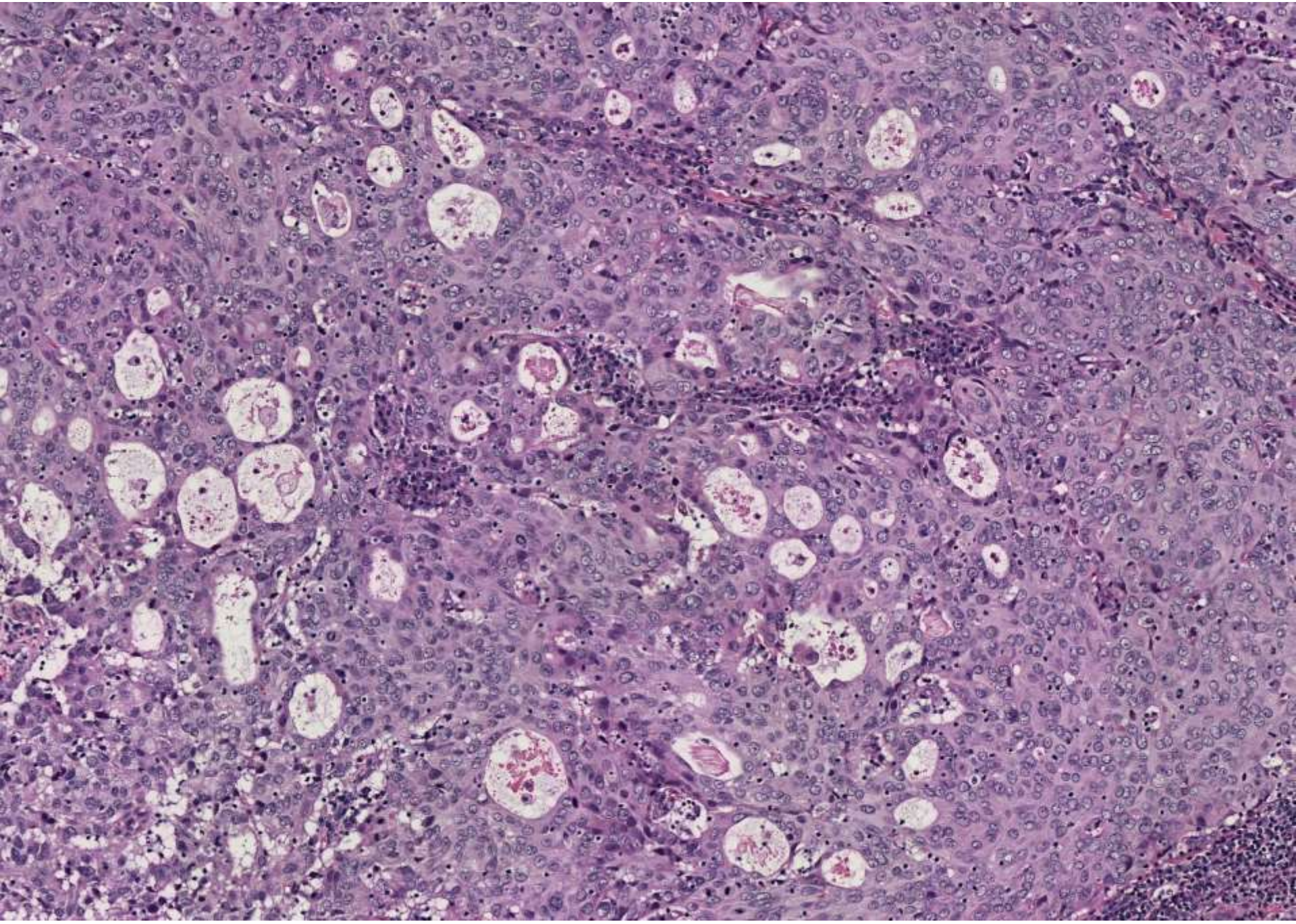


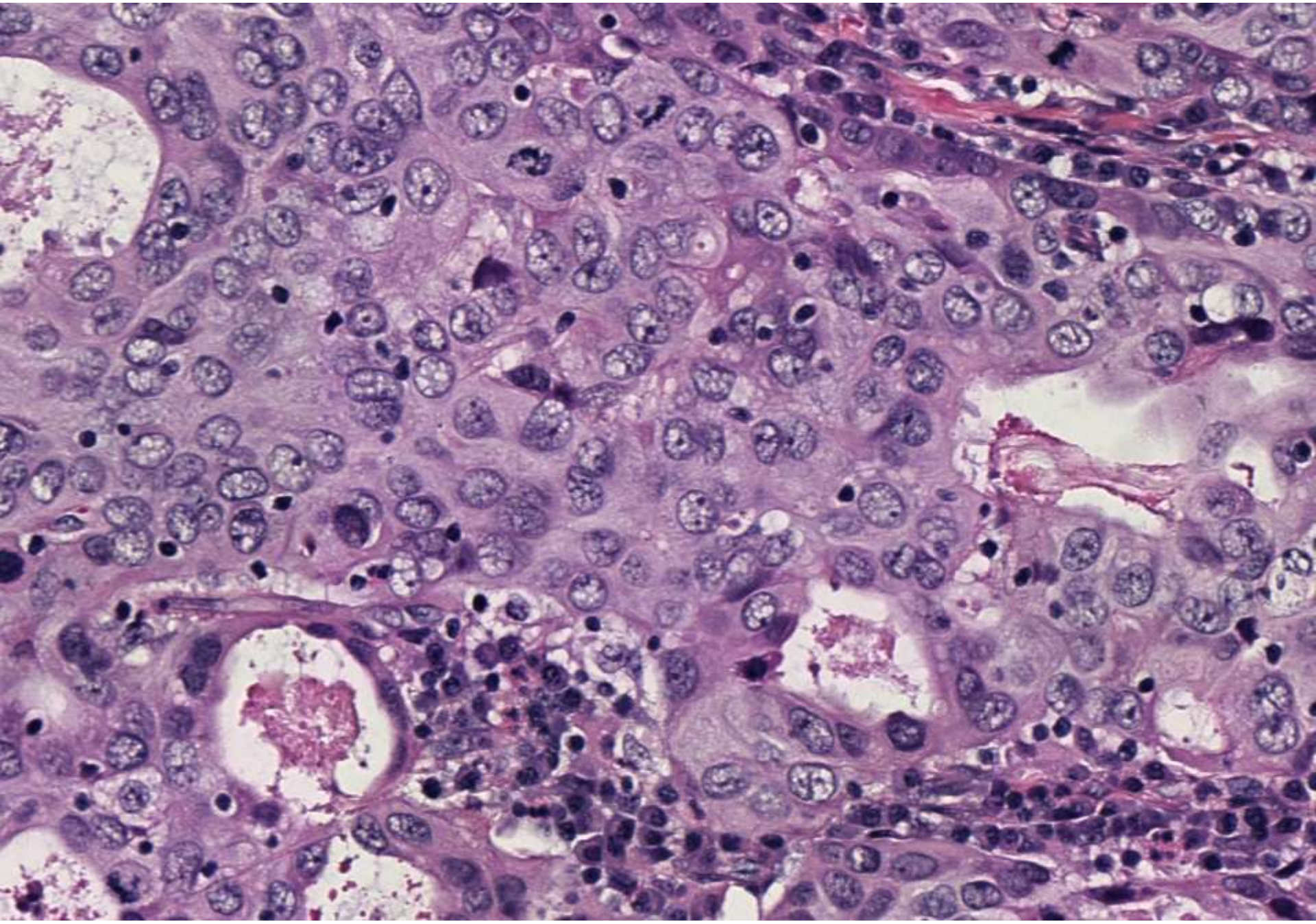


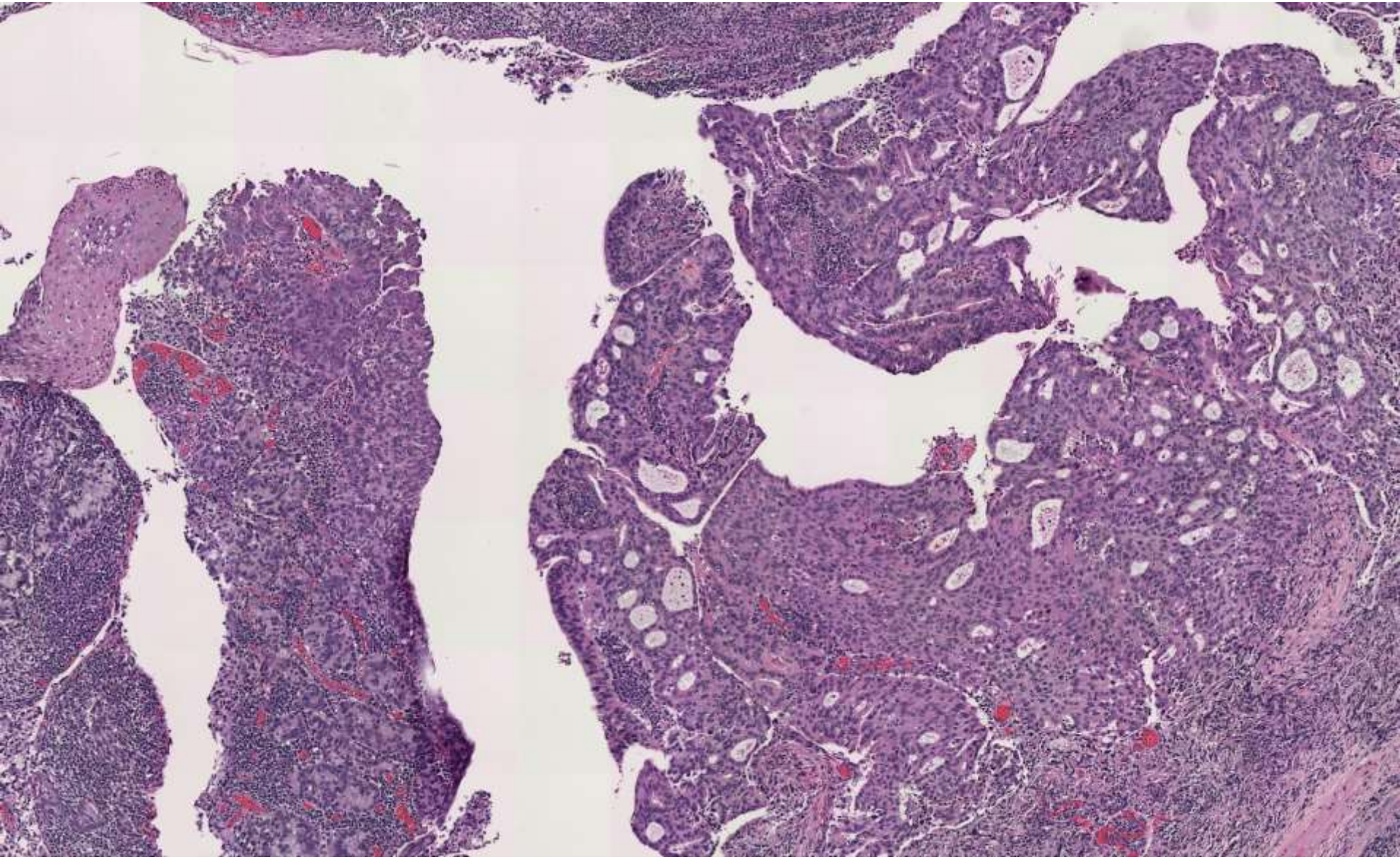


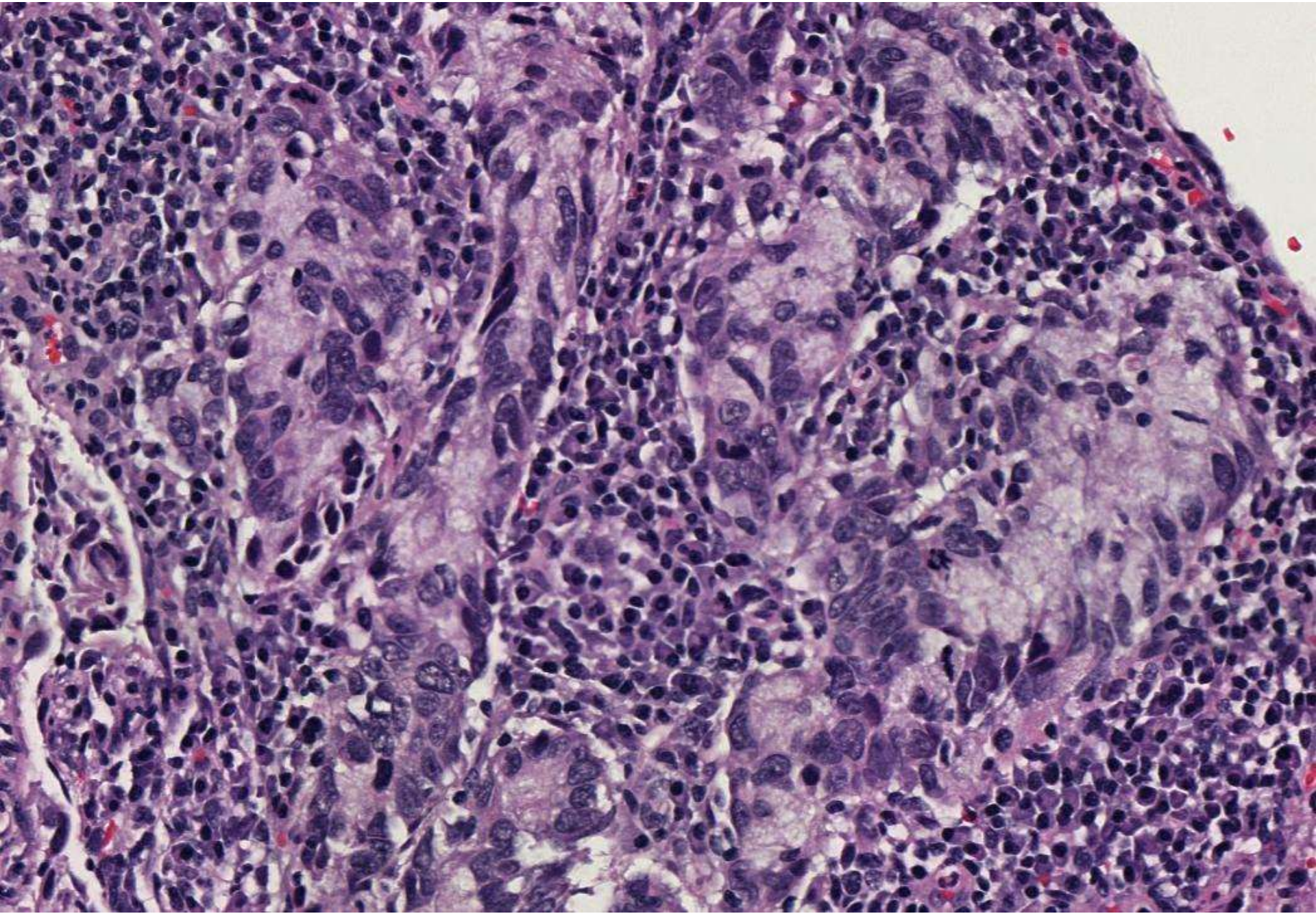


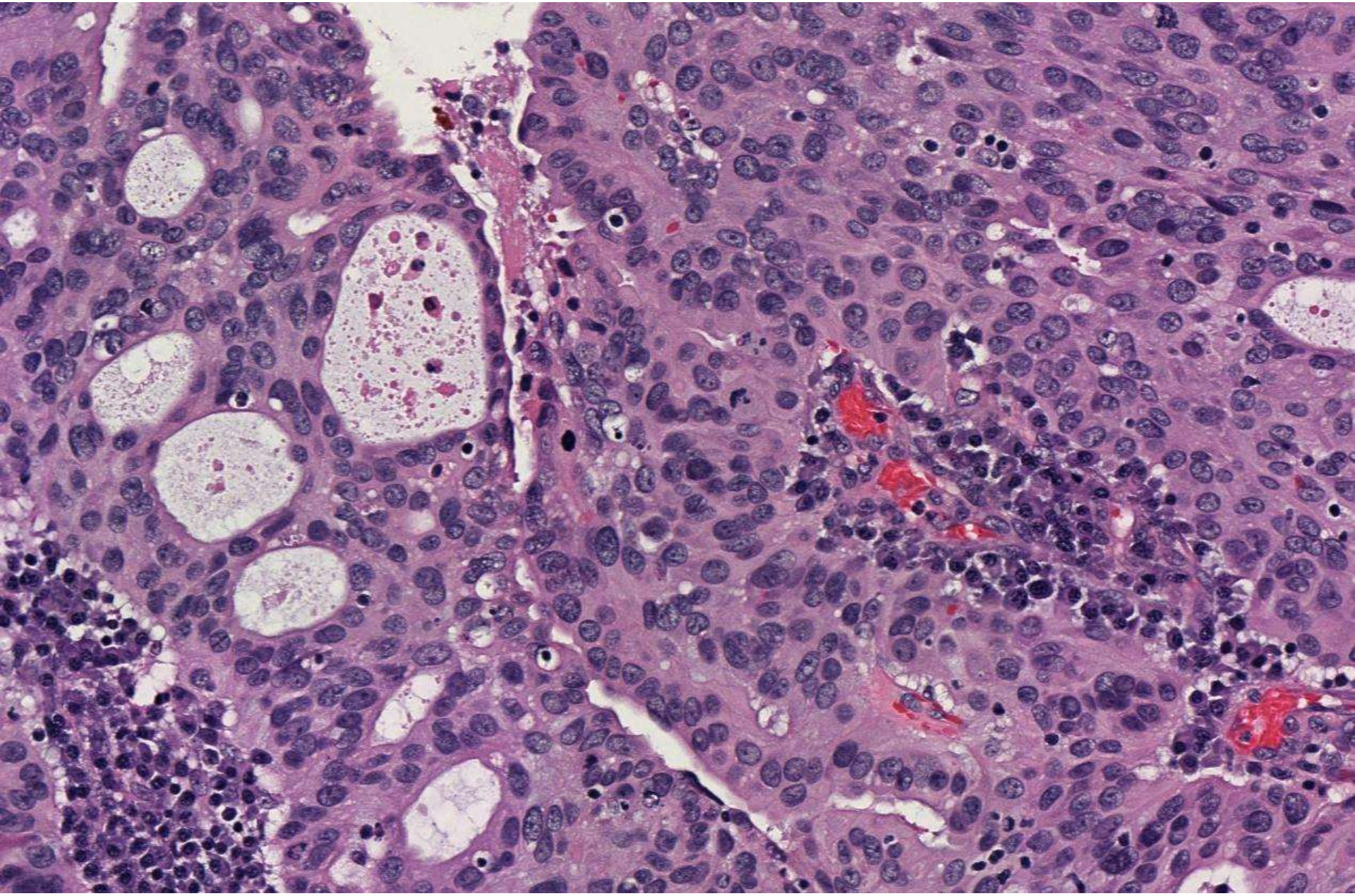


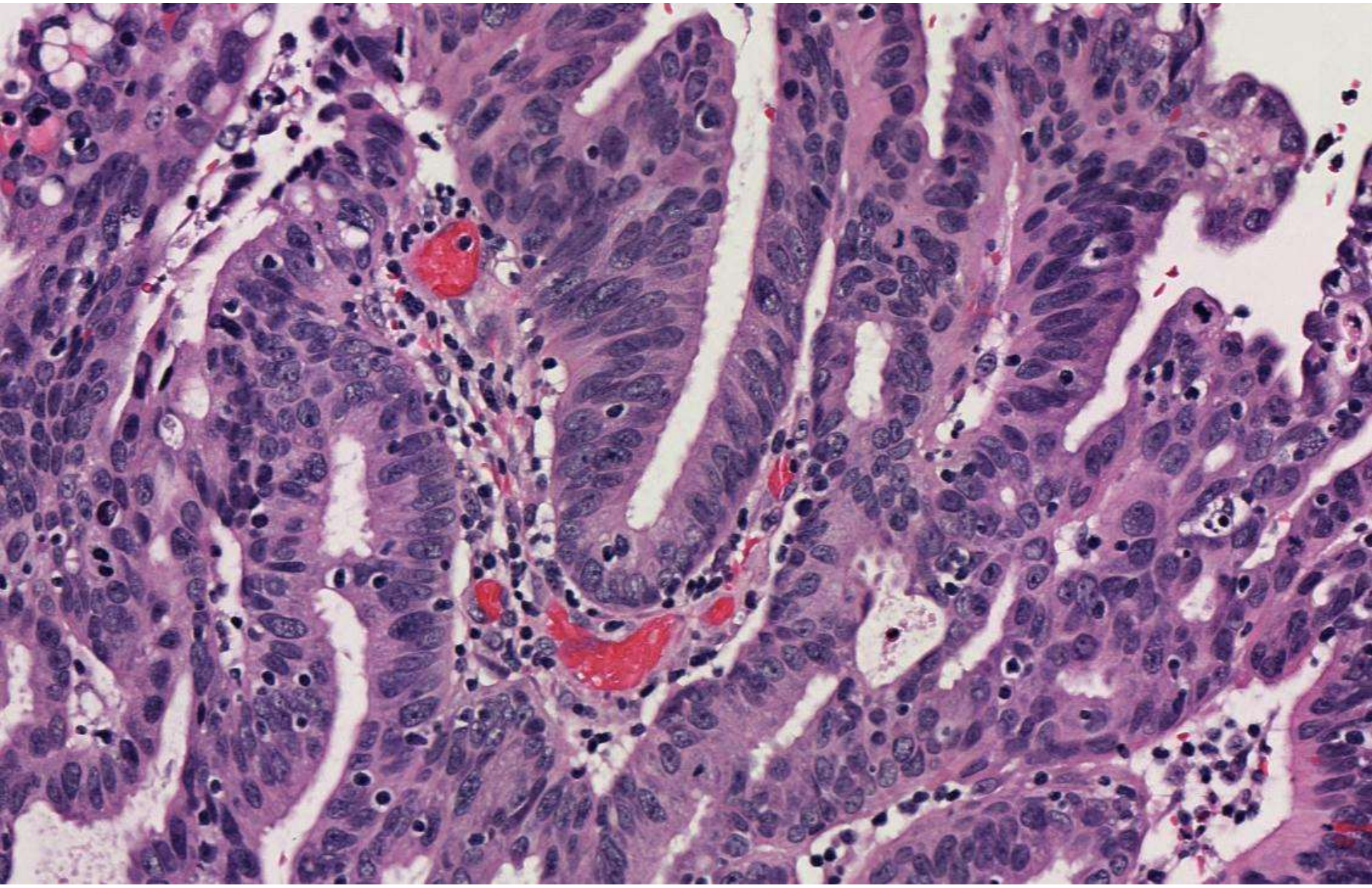






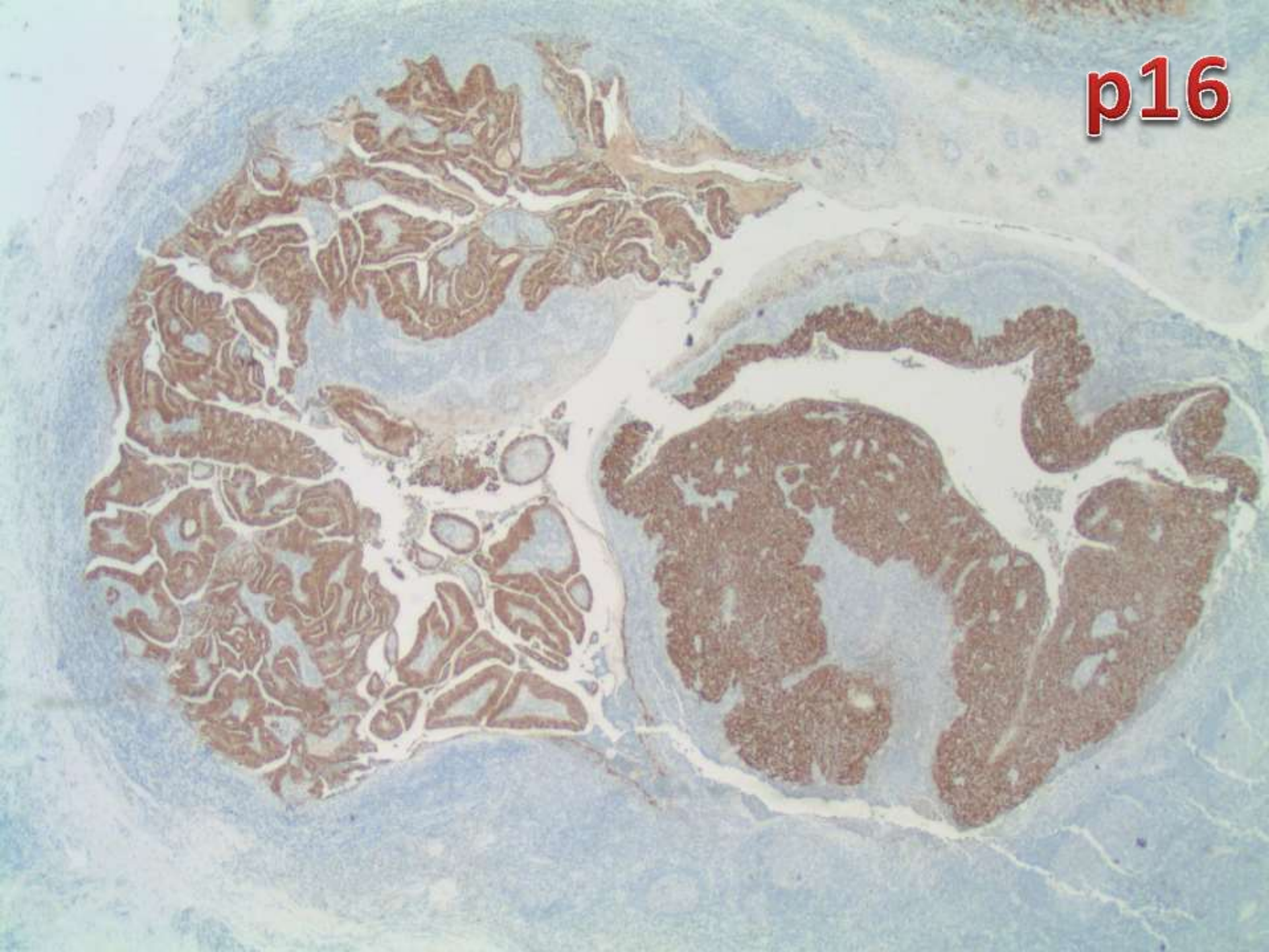


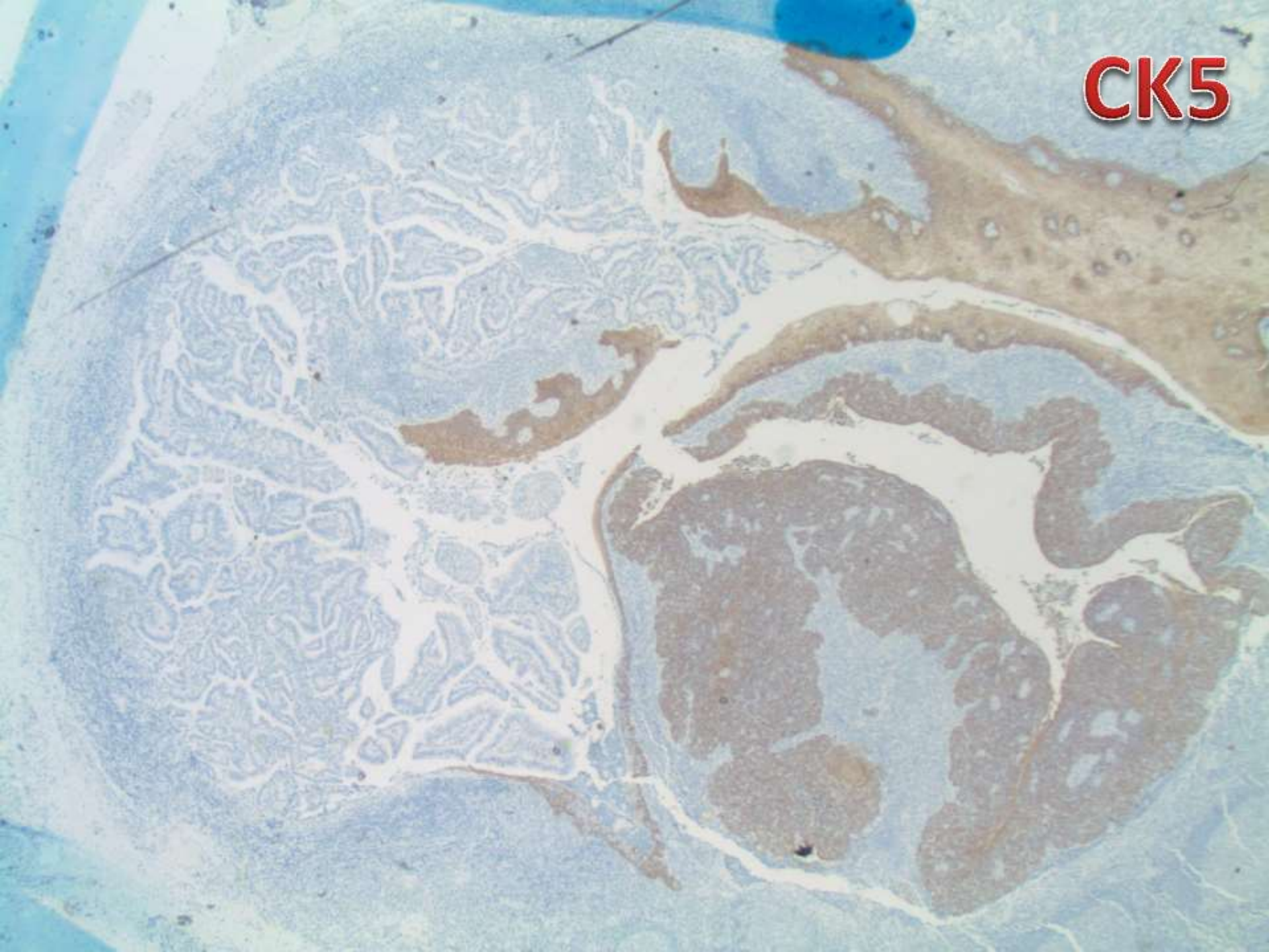


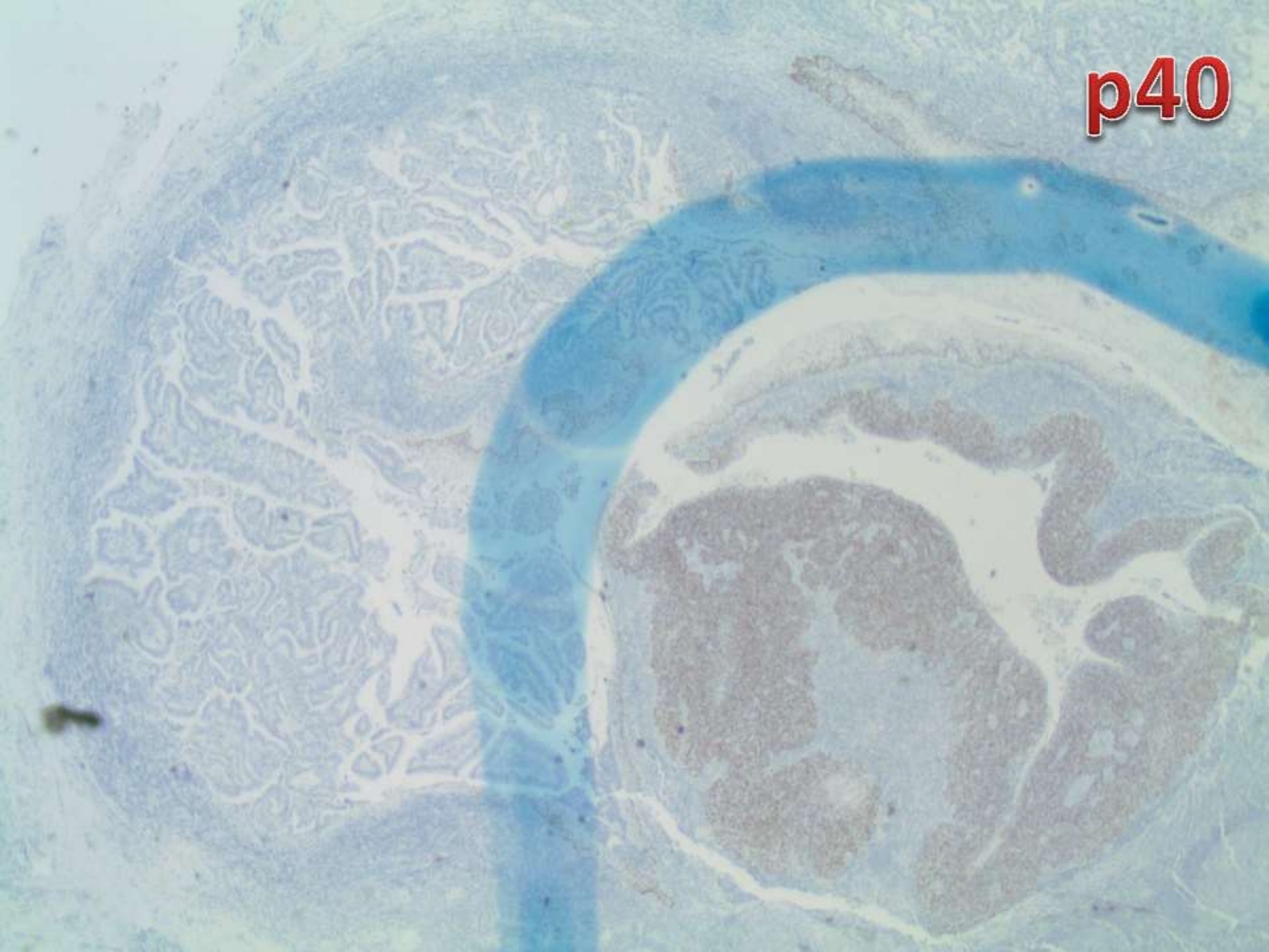


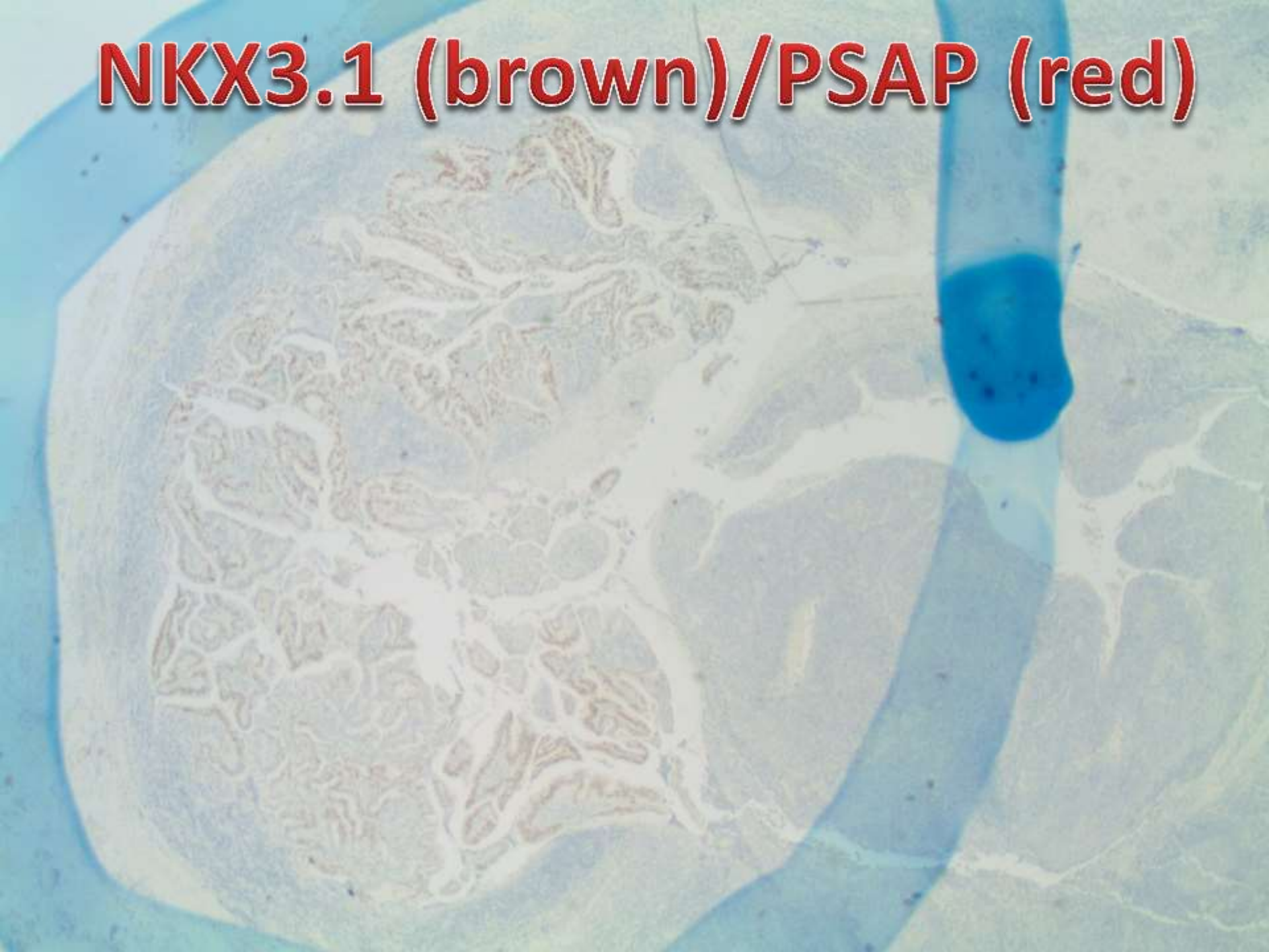
# DDx

- **Pseudoglandular squamous cell carcinoma**
- **Adenosquamous carcinoma**
- **Mucoepidermoid carcinoma**
- **Collision tumor**
  - Primary tonsillar squamous cell carcinoma + metastatic prostatic adenocarcinoma

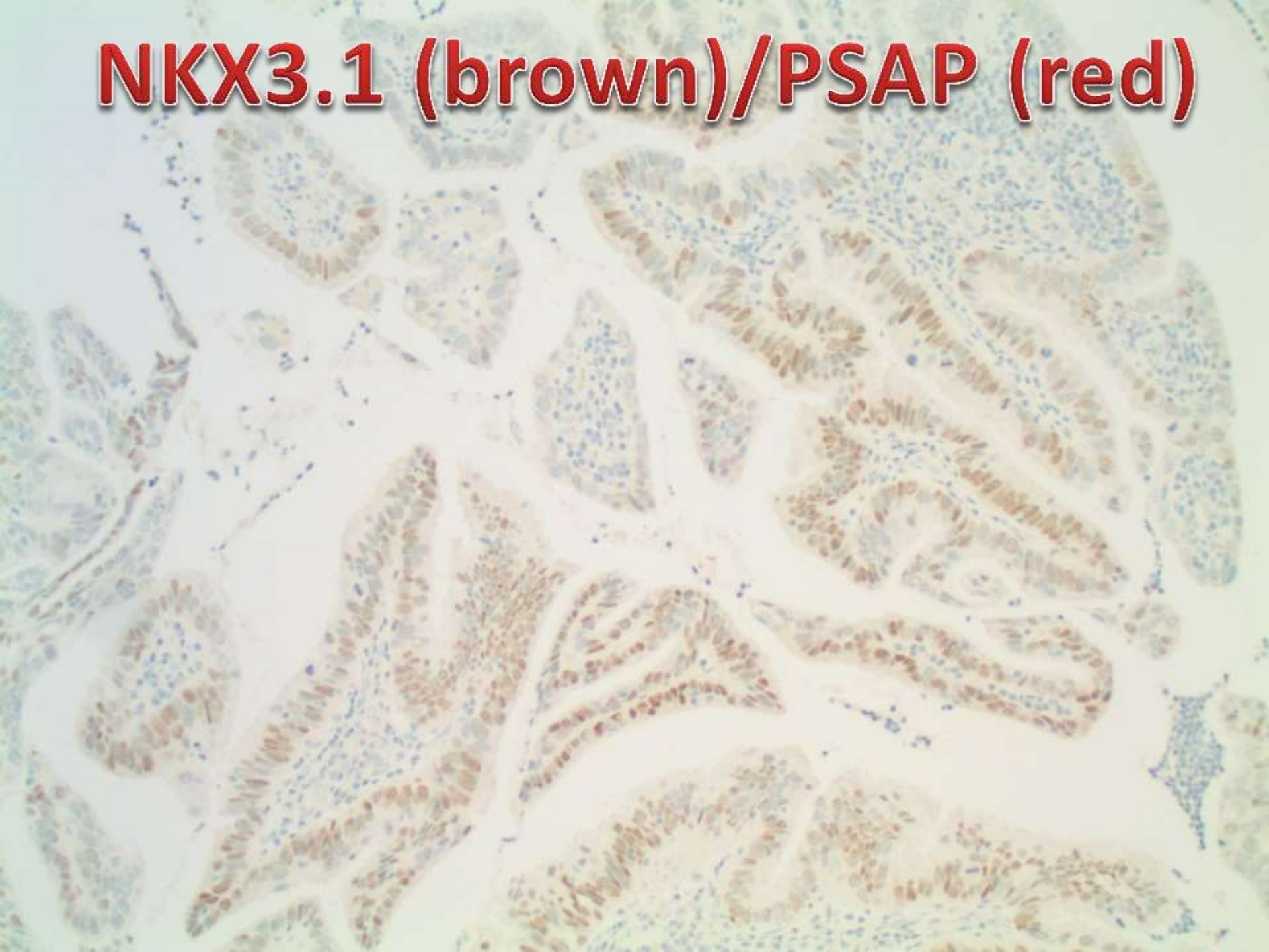

p16


CK5


p40


NKX3.1 (brown)/PSAP (red)

# NKX3.1 (brown)/PSAP (red)



# NKX3.1 as a Marker of Prostatic Origin in Metastatic Tumors

*Bora Gurel, MD,* Tehmina Z. Ali, MD,† Elizabeth A. Montgomery, MD,* Shahnaz Begum, PhD,* Jessica Hicks, BA,* Michael Goggins, MD,*‡ Charles G. Eberhart, MD, PhD,*‡ Douglas P. Clark, MD,*‡ Charles J. Bieberich, PhD,§ Jonathan I. Epstein, MD,*‡‖ and Angelo M. De Marzo, MD, PhD*‡‖*

*Am J Surg Pathol* • Volume 34, Number 8, August 2010

**Of 383 non-prostatic tumors tested, only 1 was NKX3.1+ (invasive lobular carcinoma)**

TABLE 3. The Average Percentage of Positively Stained Cells and the Calculated Staining Scores of NKX3.1, PSA and PSAP for Normal Prostate, Primary and Metastatic Prostate Carcinoma

| | NKX3.1 | | PSA‘ | | PSAP | |
|---|---|---|---|---|---|---|
| | % Positive (Range) | Staining Score(SD) | % Positive (Range) | Staining Score(SD) | % Positive (Range) | Staining Score(SD) |
| Normal Prostate | 92.0 (38.3-100) | 218.3 (85.22) | 965.0 (0-100) | 241.7 (76.88) | 97.6 (0-100) | 287.8 (50.96) |
| Primary Ca | 84.7 (25-100) | 179.1 (77.84) | 87.3 (10-100) | 180.7 (91.36) | 98.6 (85-100) | 249.2 (64.35) |
| Lymph Node Met | 74.2 (0-100) | 155.4 (84.78) | 80.1 (0-100) | 1743.0 (99.14) | 94.4 (0-100) | 235.6 (78.24) |
| Distant Site Met | 54.0 (0-88.3) | 111.4 (85.36) | 30.8 (0-100) | 50.8 (92.83) | 74.2 (0-100) | 162.0 (116.49) |
| Average | 80.5 | 175.9 (87.83) | 83.1 | 186.0 (101.29) | 95.0 | 248.5 (77.32) |

# DDx

- Pseudoglandular squamous cell carcinoma
- Adenosquamous carcinoma
- Mucoepidermoid carcinoma
- **Collision tumor???**
  - Primary tonsillar squamous cell carcinoma + metastatic prostatic adenocarcinoma

# NKX3.1

**Positive staining - normal**

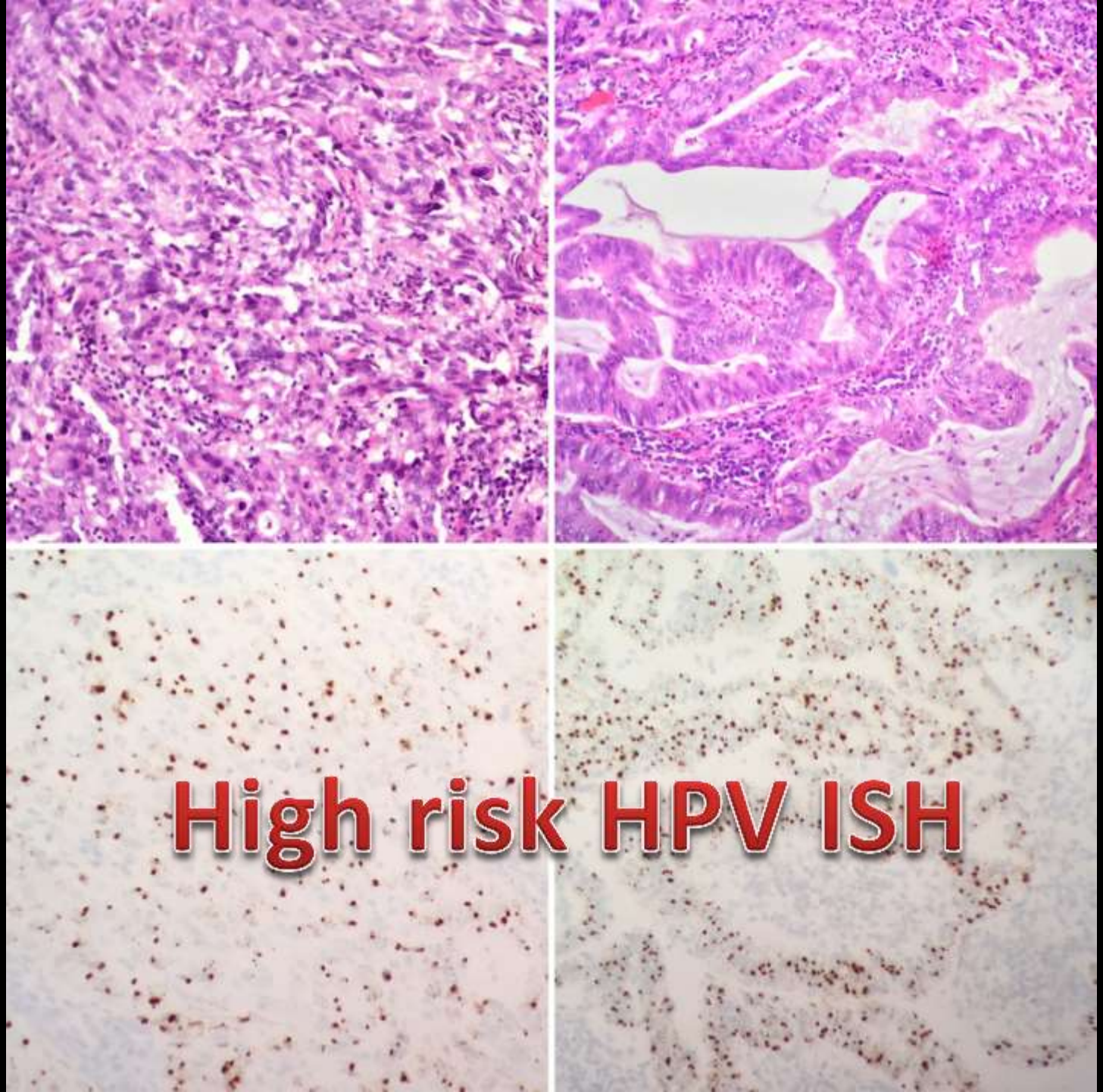
Highly expressed in the prostate and at a lower level in the testis

Salivary gland tissue; bronchial submucosal glands; isolated regions of transitional epithelium in the ureter

**USCAP Vancouver 2018**

**Perjar I, Tang S, Wobker S, Greene K. "NKX3.1 expression in salivary gland neoplasms (a potential diagnostic pitfall)"**

**→ subset of salivary duct carcinomas**


High risk HPV ISH

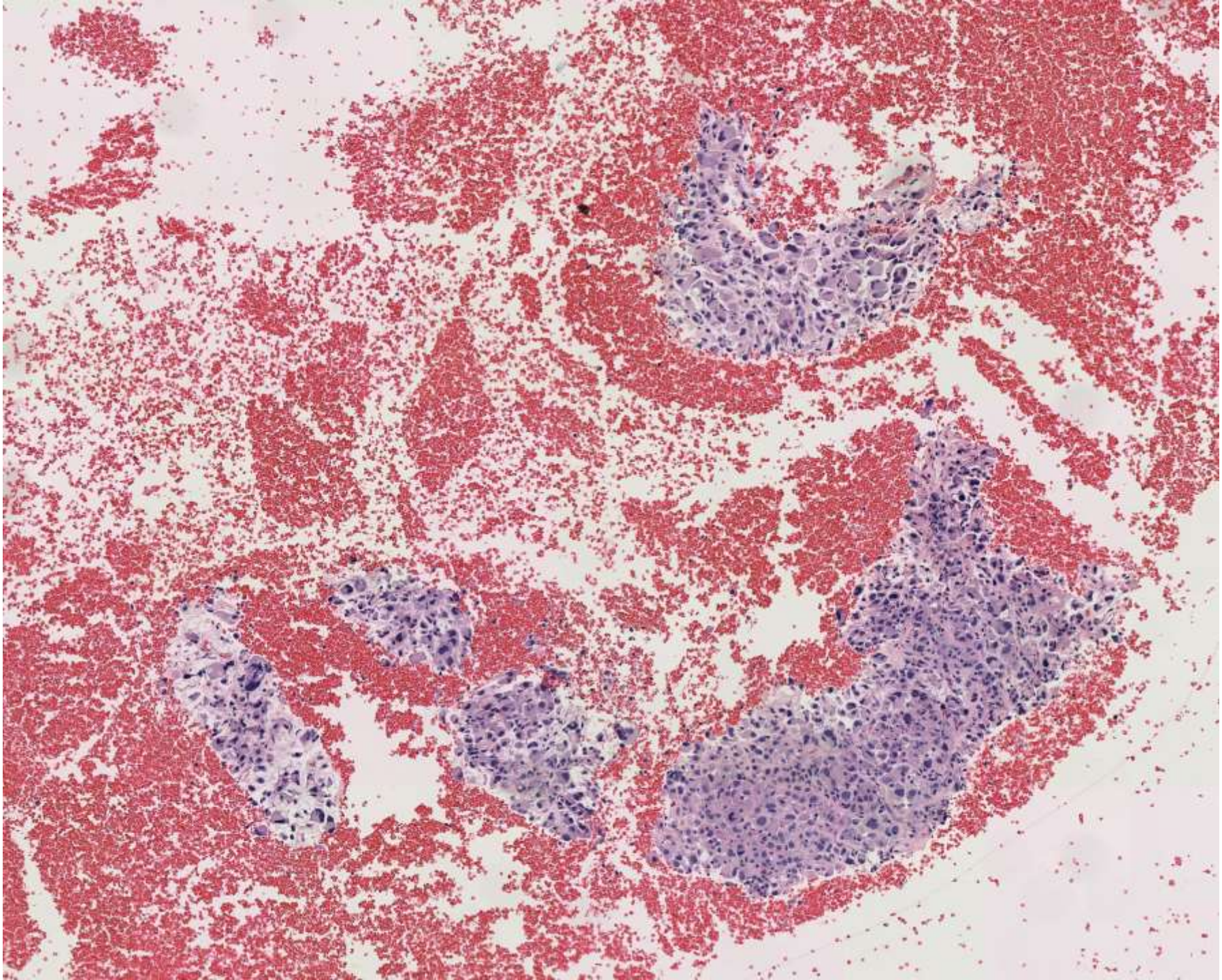
# Final Dx

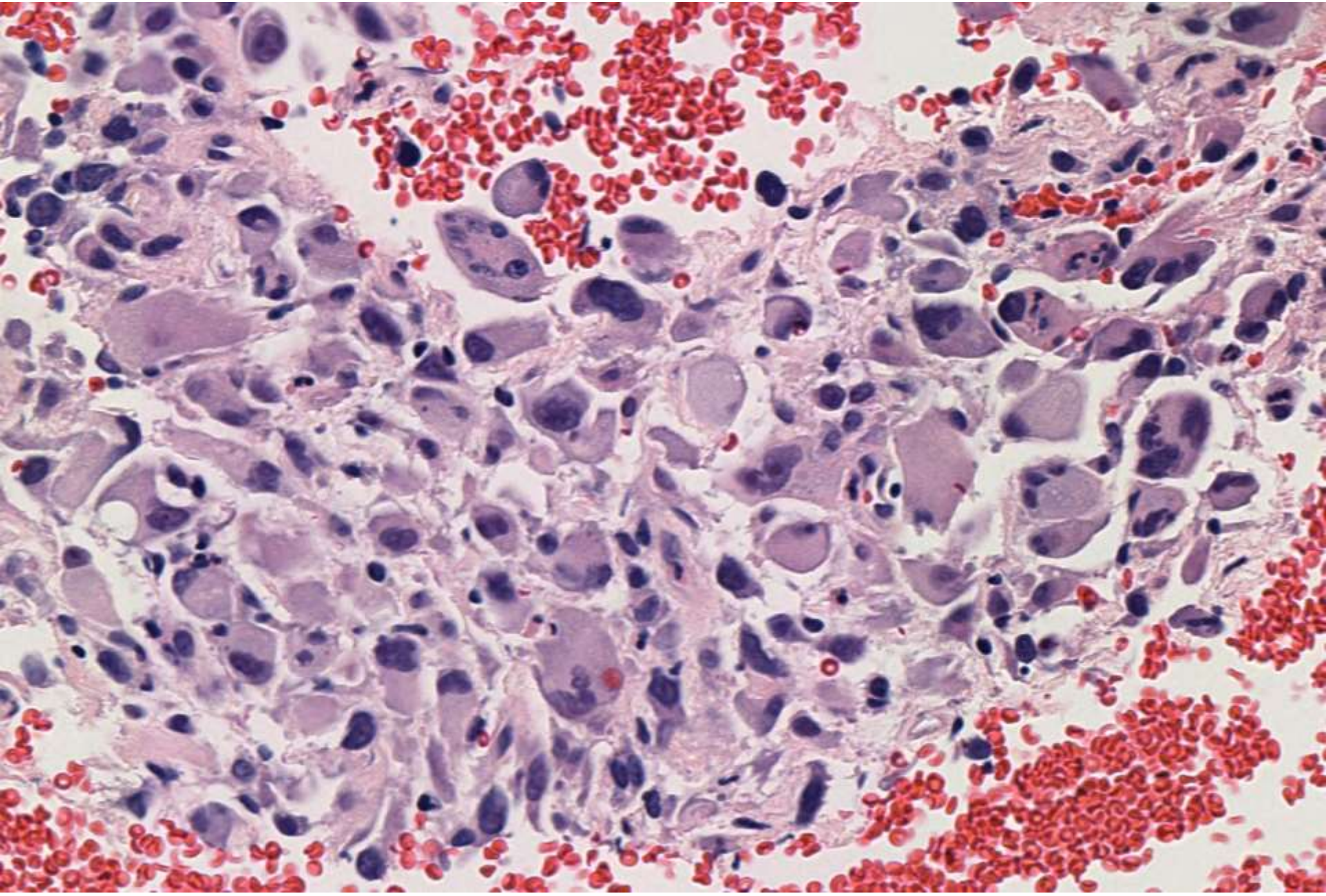
- p16+ adenosquamous carcinoma

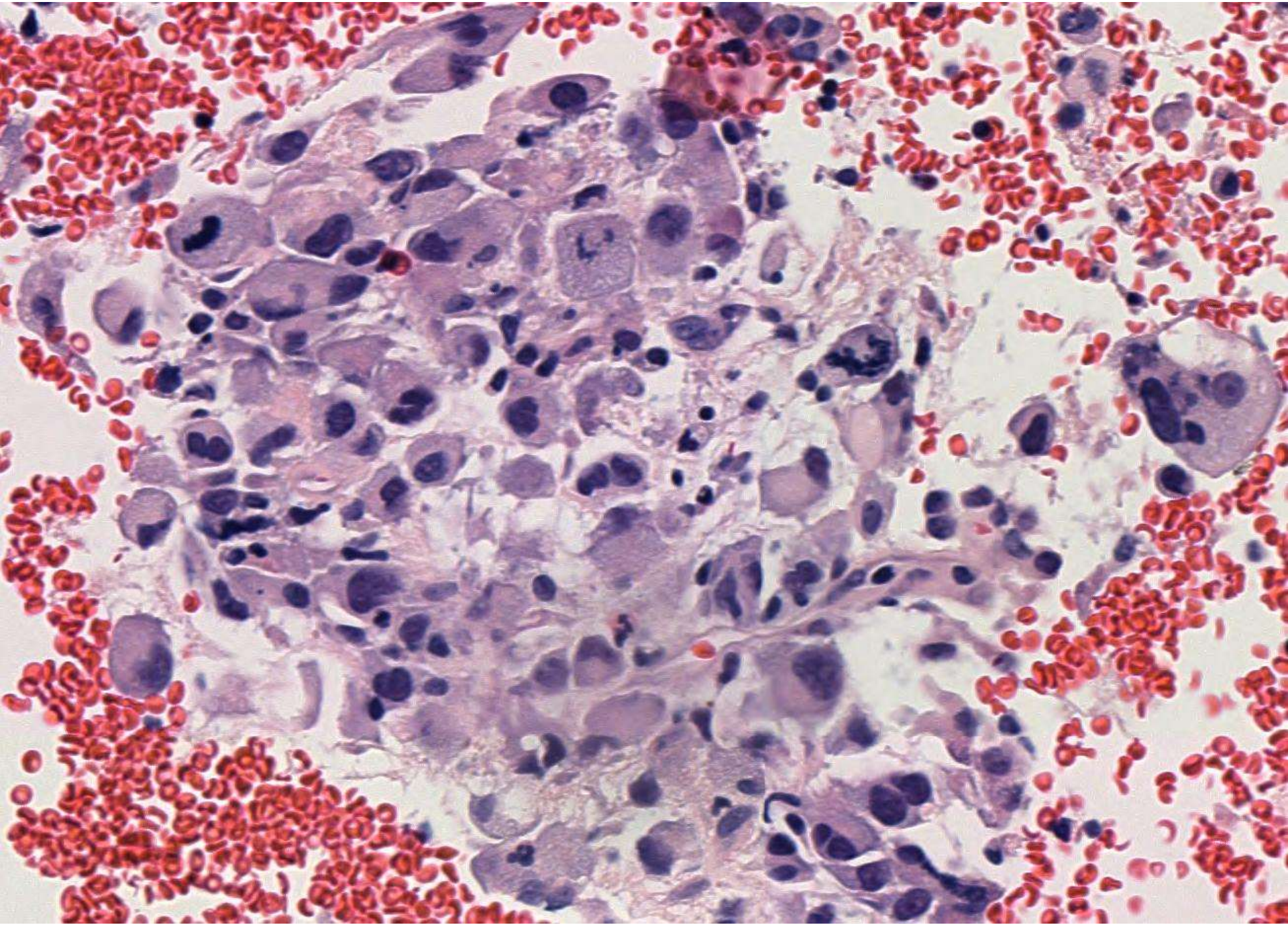
# SB 6345
# (scanned slide available)

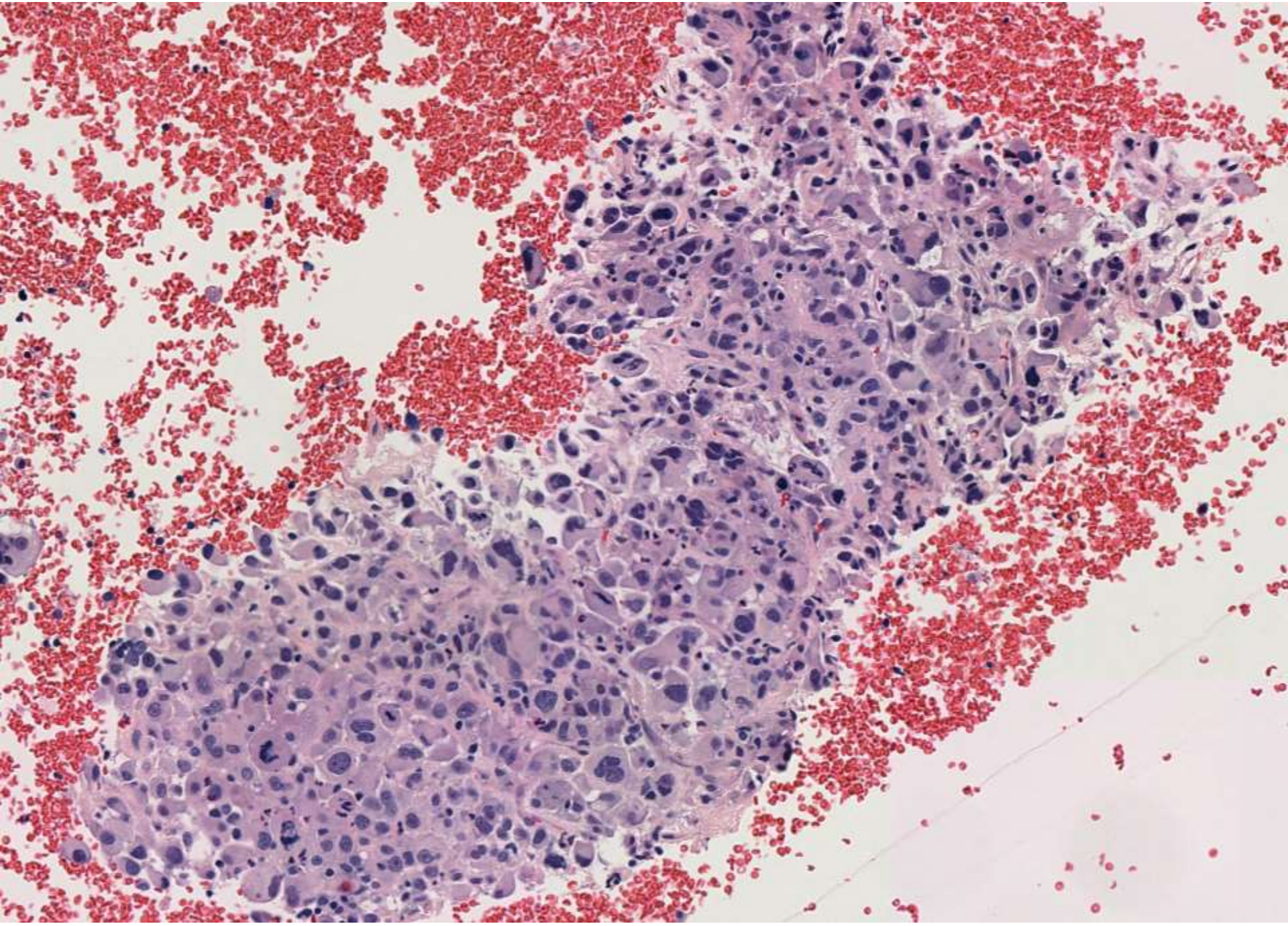
**Yue Peng/Cathryn Cadwell/Mark Lu; SF VA Medical Center**

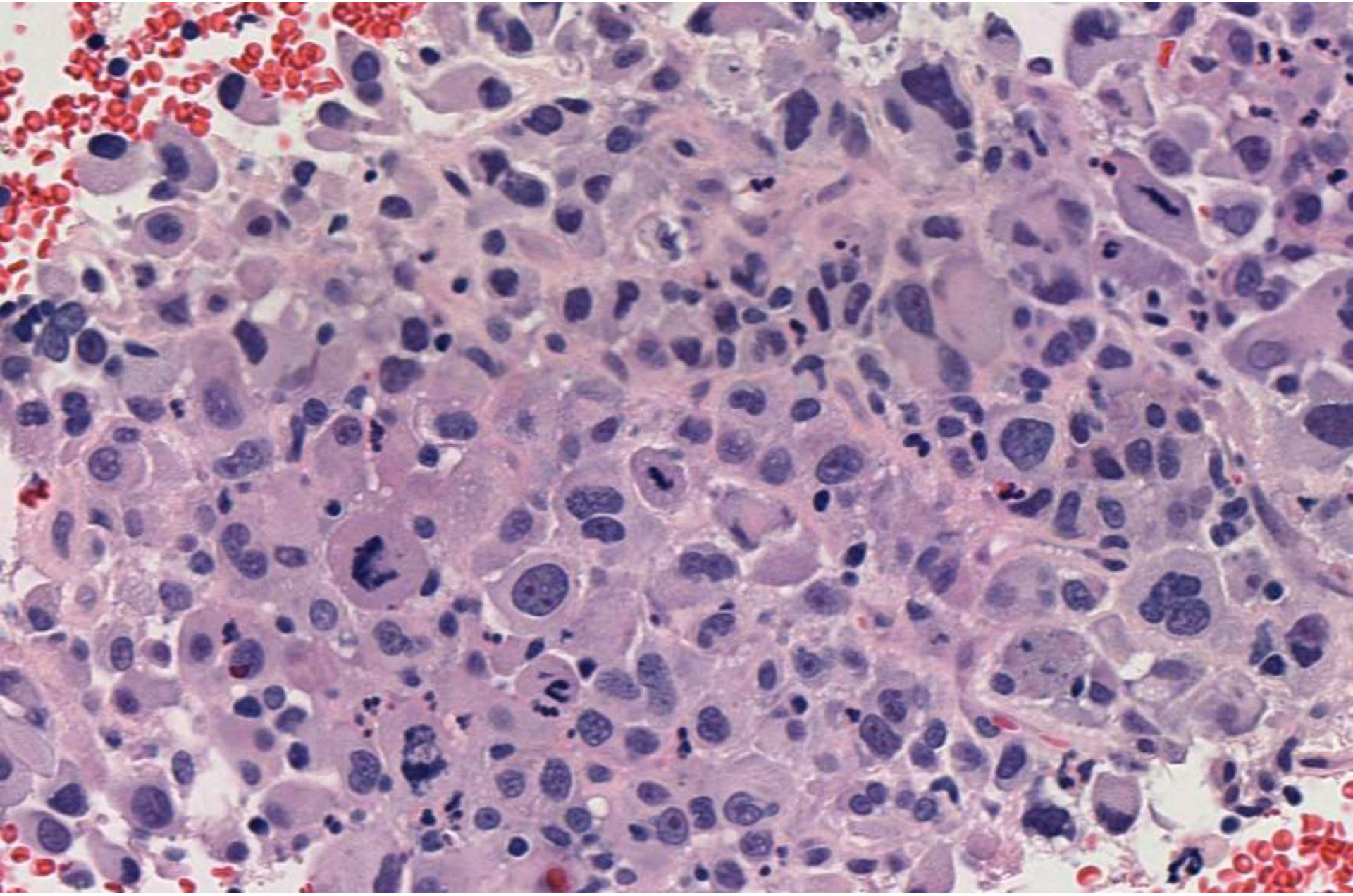
76-year-old female with COPD, recurrent pneumonia who presents with hypermetabolic 3.6cm right RLL lung mass with endobronchial extension and ipsilateral hilar and subcarinal lymph node FDG uptake compatible with nodal metastasis. FNA subcarinal lymph node performed.

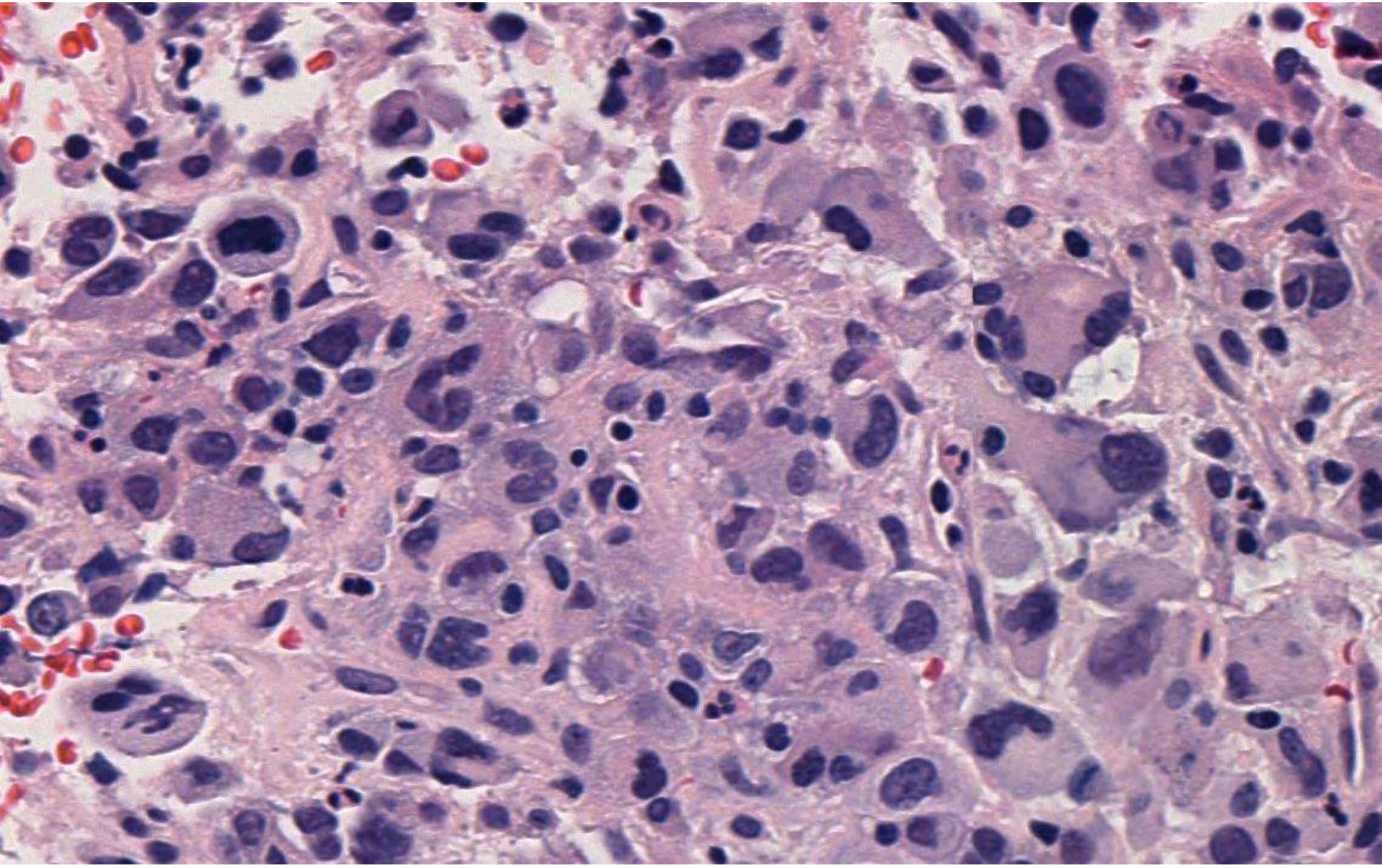












# Summary of IHCs and DDx:

- Metastatic poorly/undifferentiated carcinoma:

  Pan-CK, CK7, CK8/18, CK20, P40, CK5/6, TTF-1, synaptophysin, chromogranin, Pax8: **Negative**

  EMA: **Equivocal**

- Metastatic melanoma:

  S100, SOX10: **Negative**

- Mesenchymal malignancy:

  Desmin, Caldesmon, ERG, CD34, HMB45: **Negative**

- Hematolymphoid malignancy:

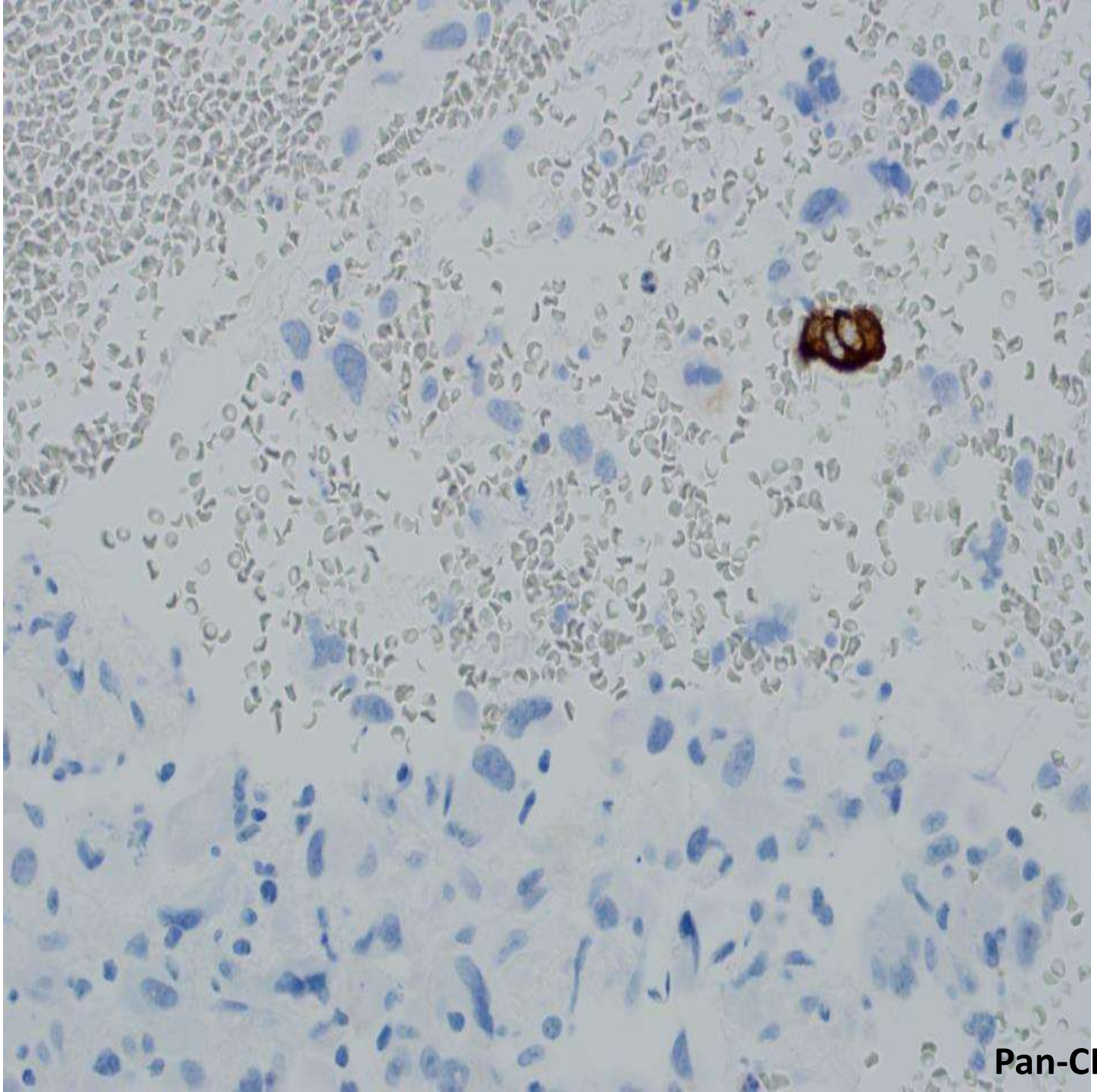
  CD79a, Pax5; CD3, CD5, CD30, ALK, vWF, MPO, CD34, CD1a, CD21: **Negative**

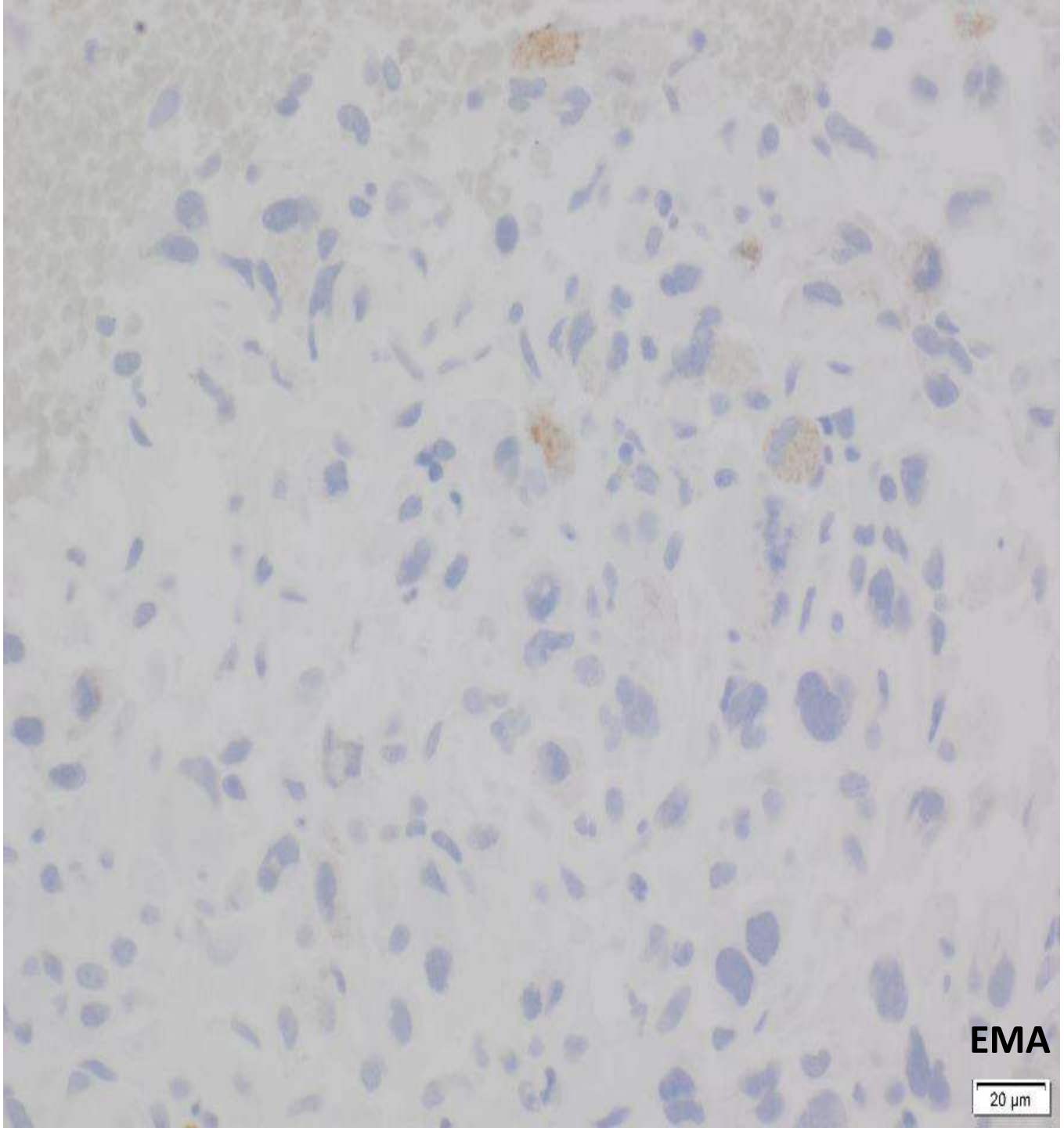
  CD4, CD45, Lysozyme: **Negative**

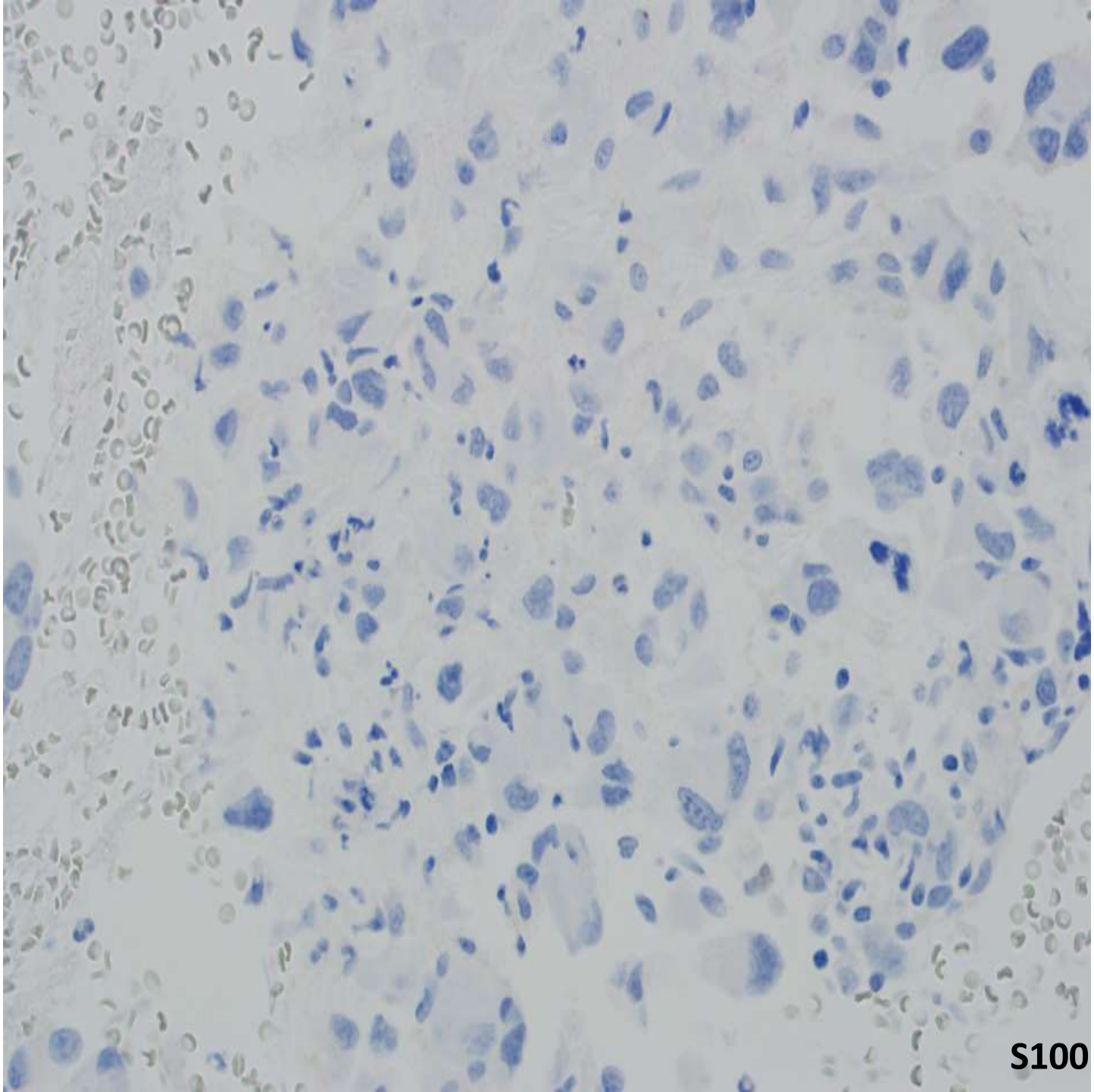
  CD45RO: **Positive**

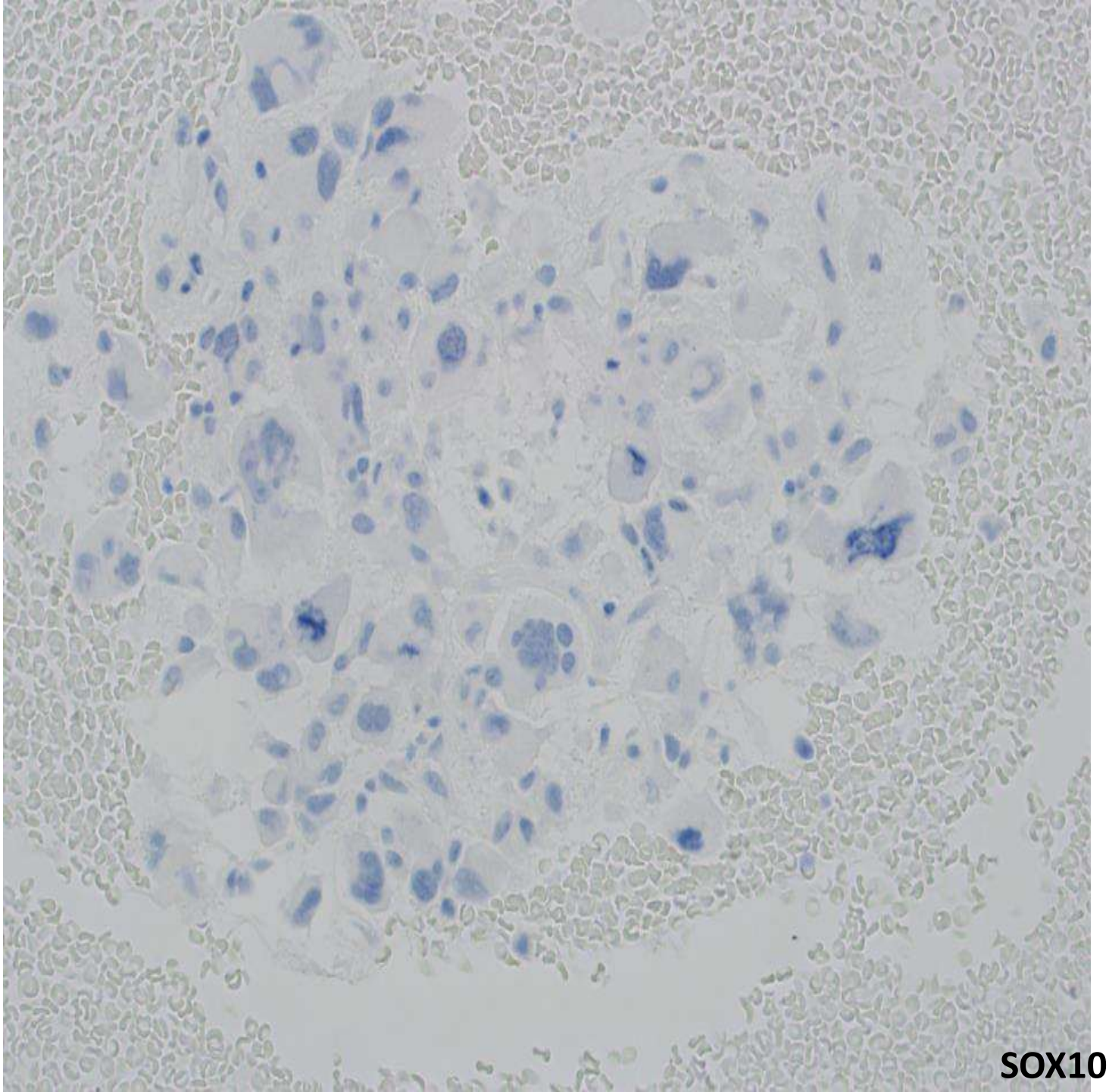
  **CD68**: **Positive**, granular cytoplasmic staining

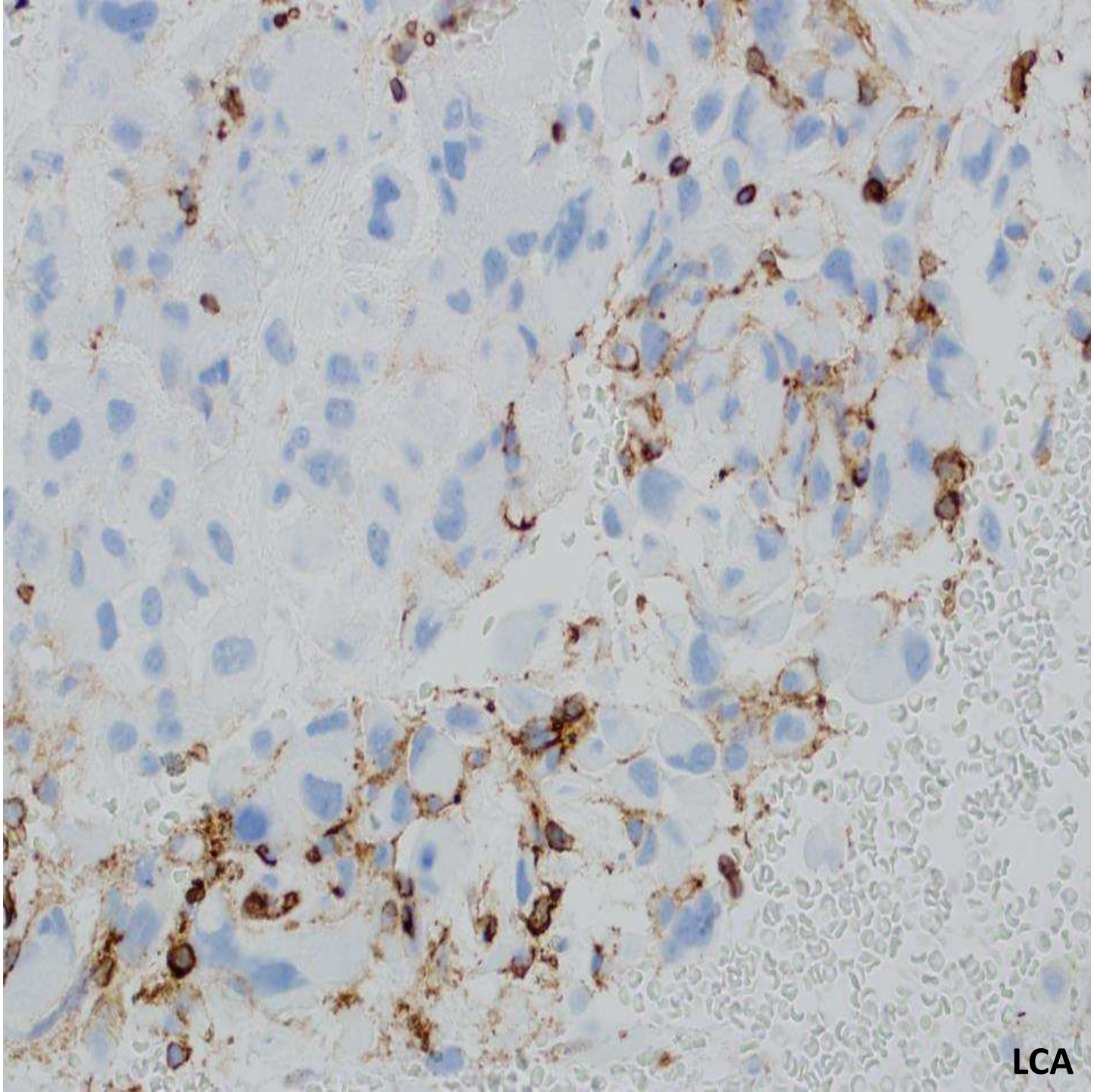
  **CD163**: **Positive**, membrane and cytoplasmic staining

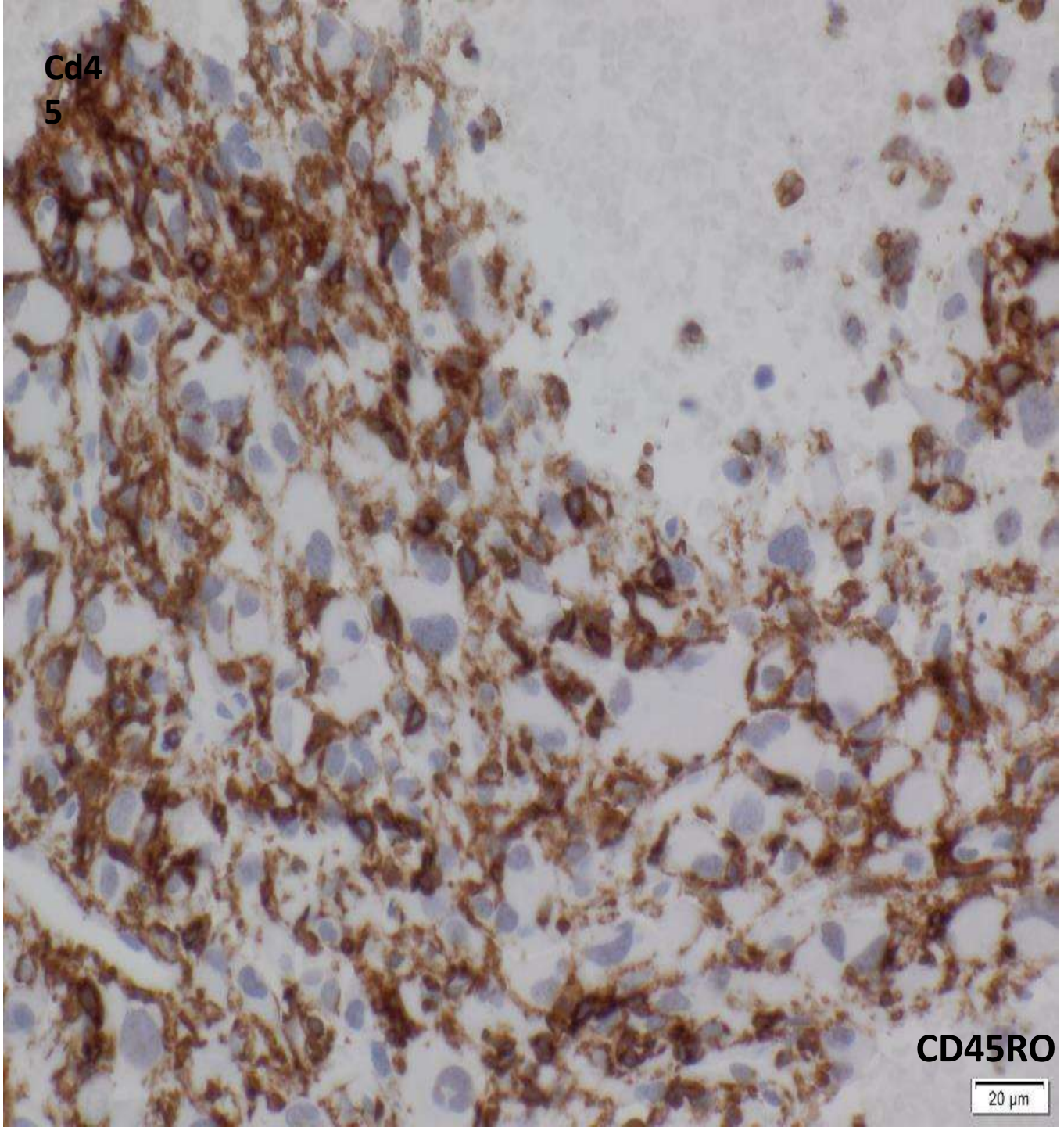

Pan-CK

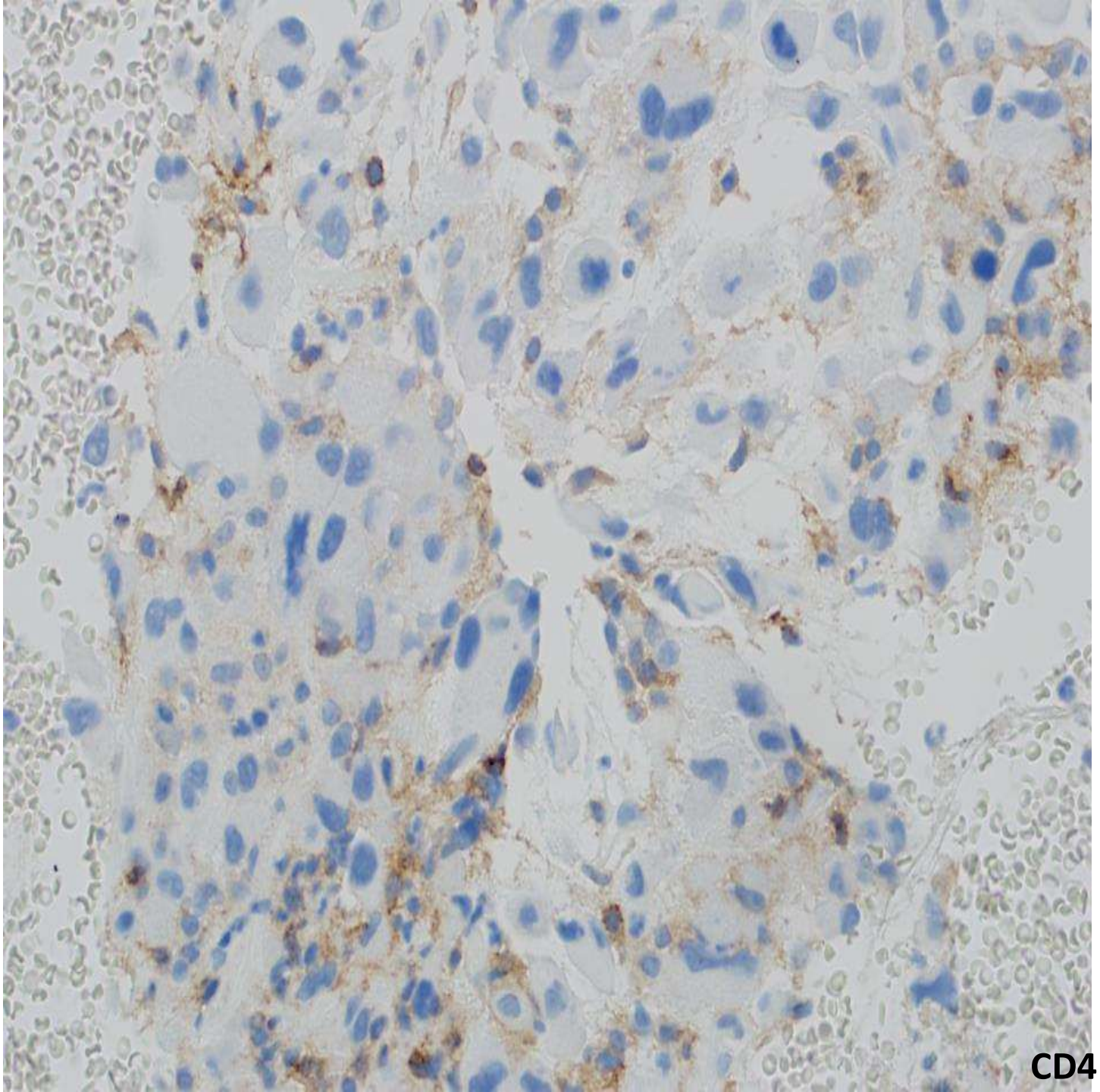

EMA
20 µm

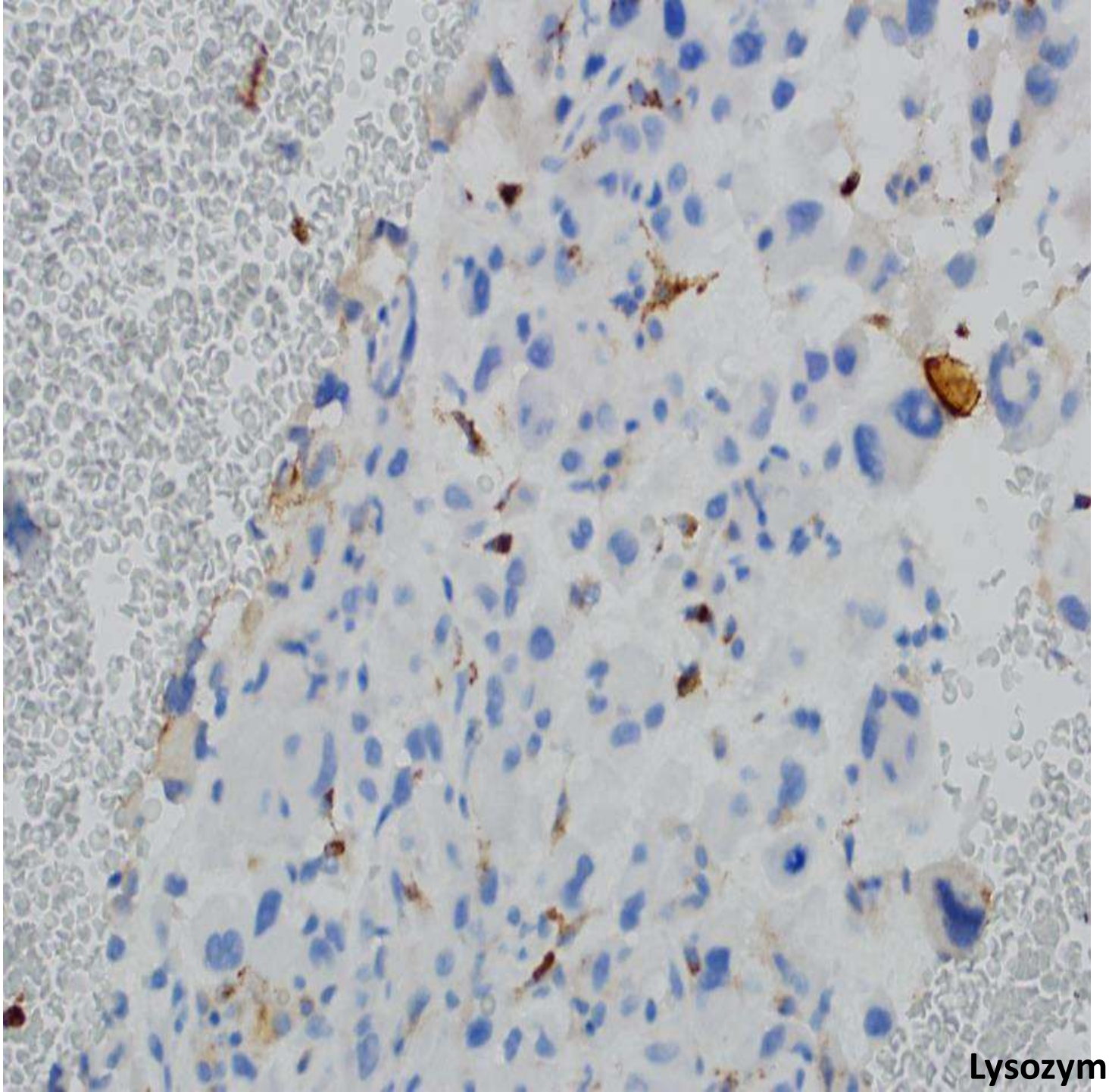

S100


SOX10

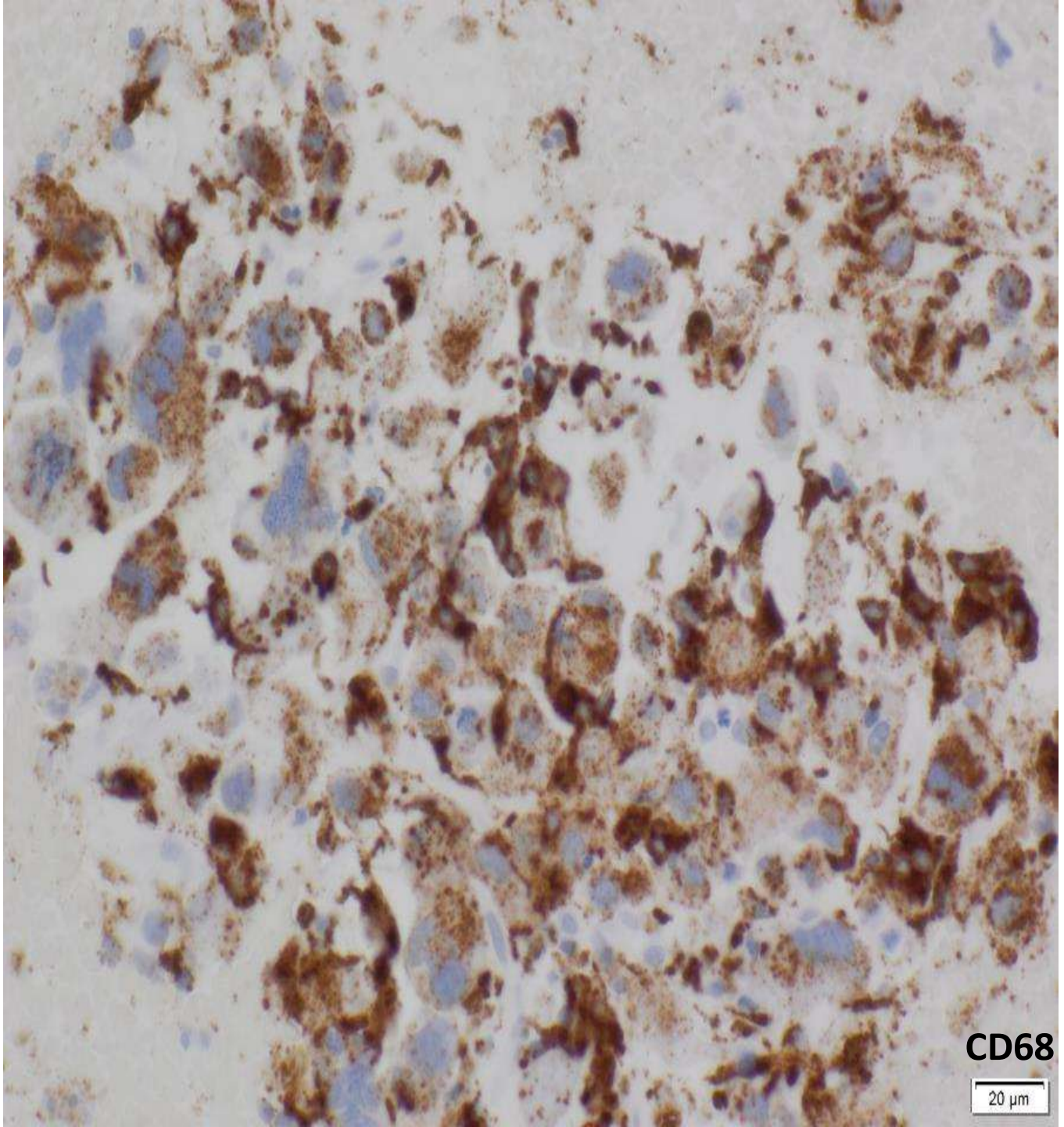

LCA

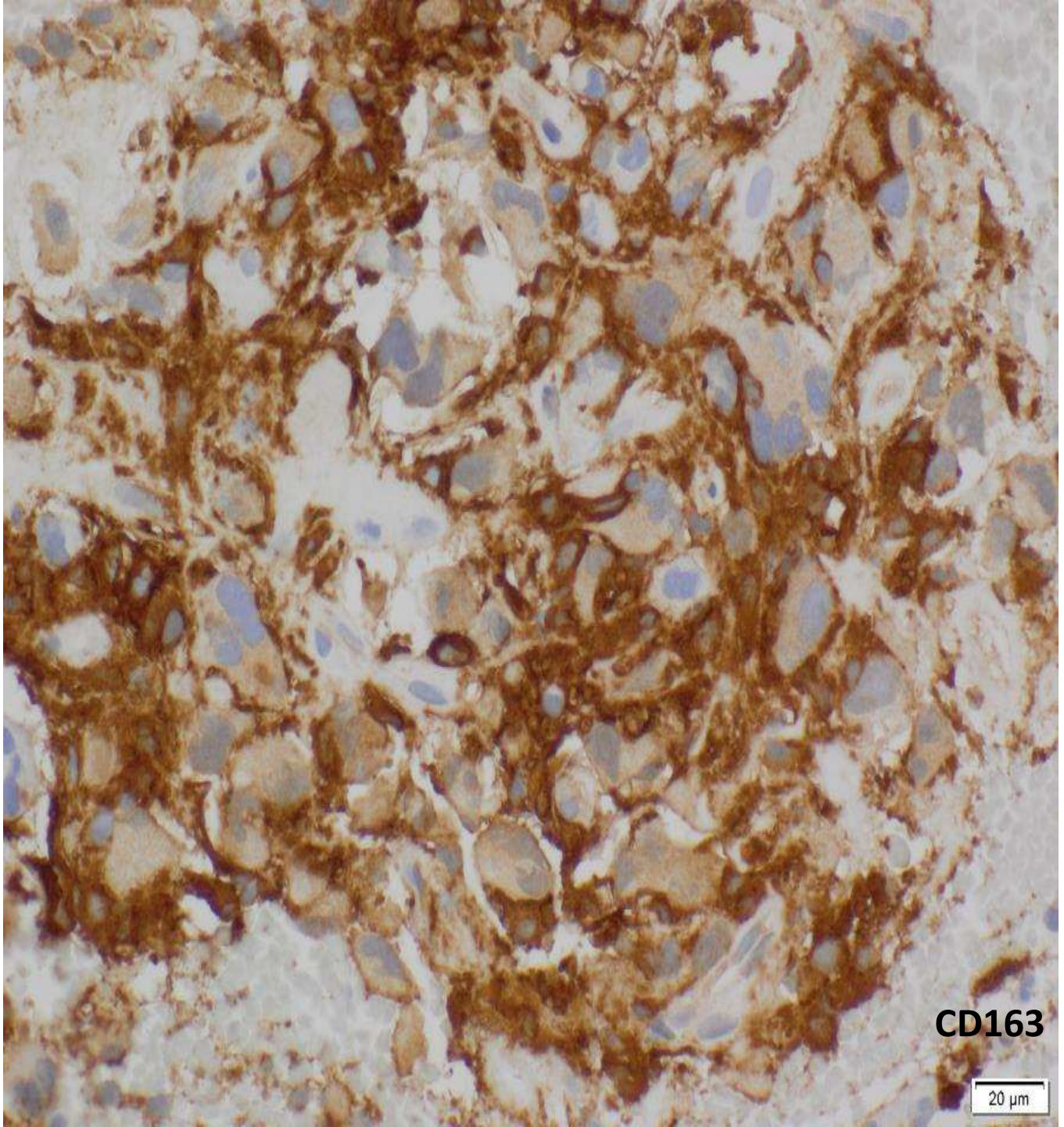

Cd4
5
CD45RO
20 µm

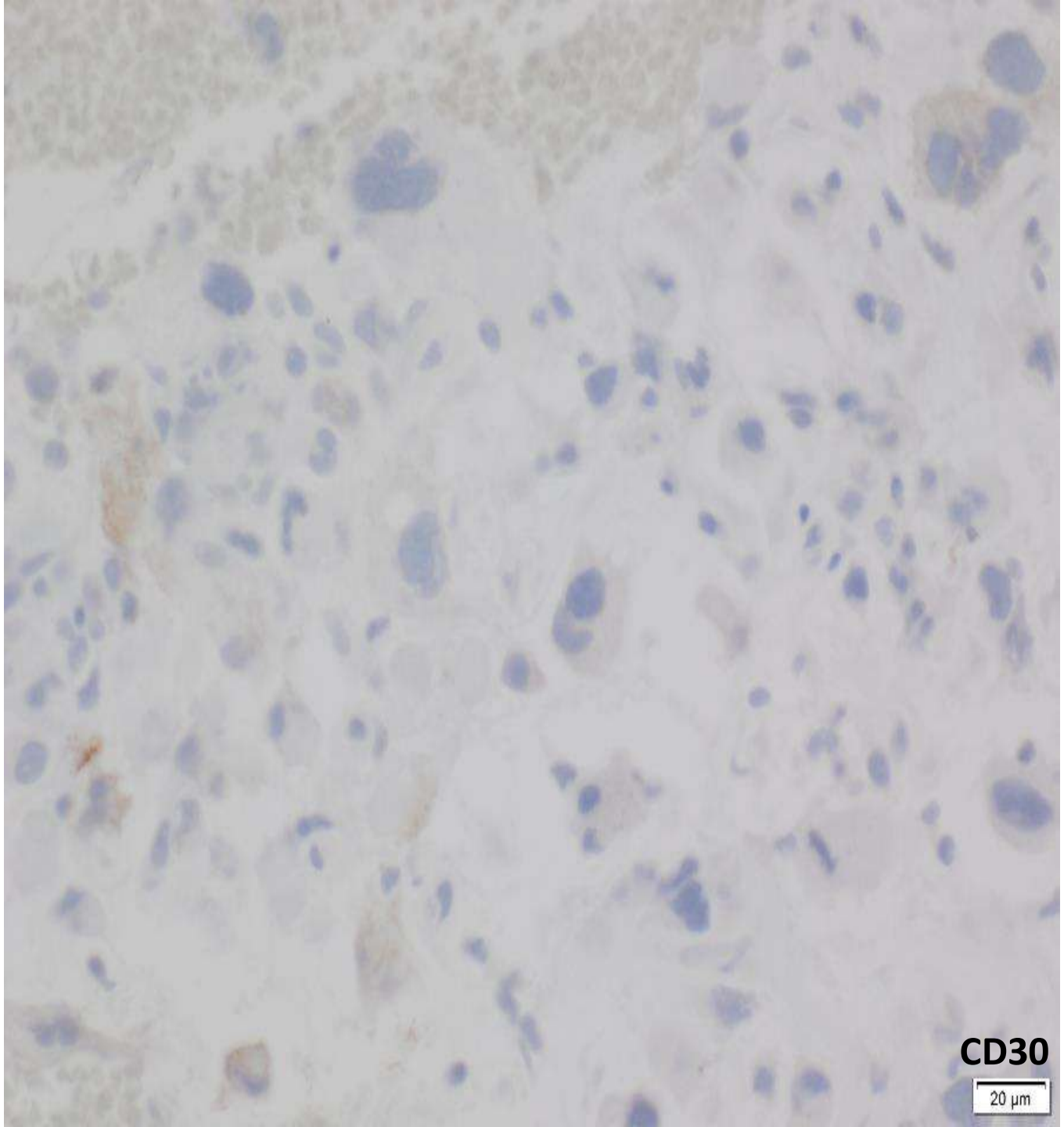

CD4

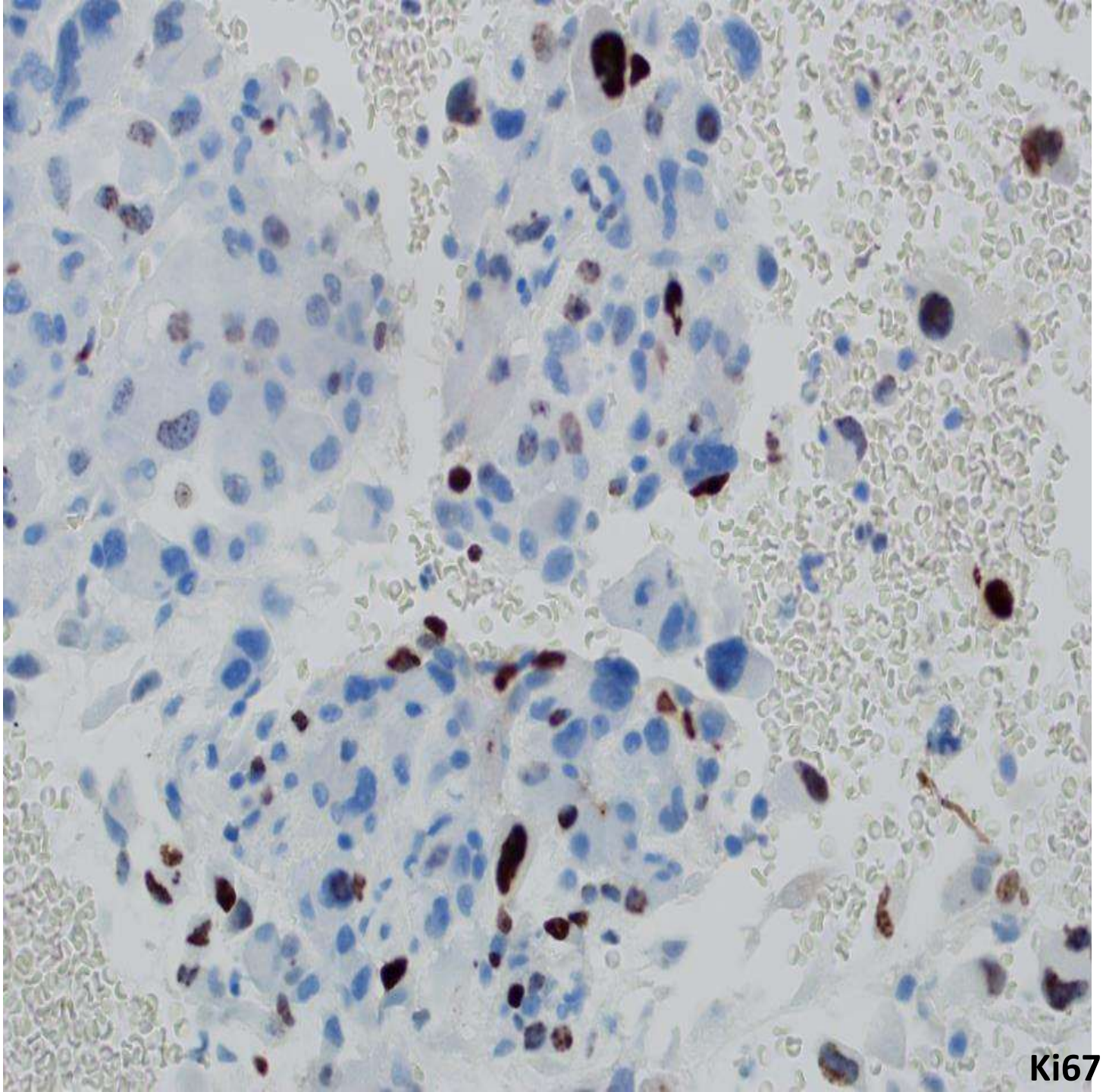


Lysozyme


CD68
20 µm


CD163
20 µm


CD30
20 µm


Ki67

# Histiocytic and Dendritic Cell Neoplasm (WHO Classification)

- Histiocytic sarcoma
- Tumors derived from Langerhans cells
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

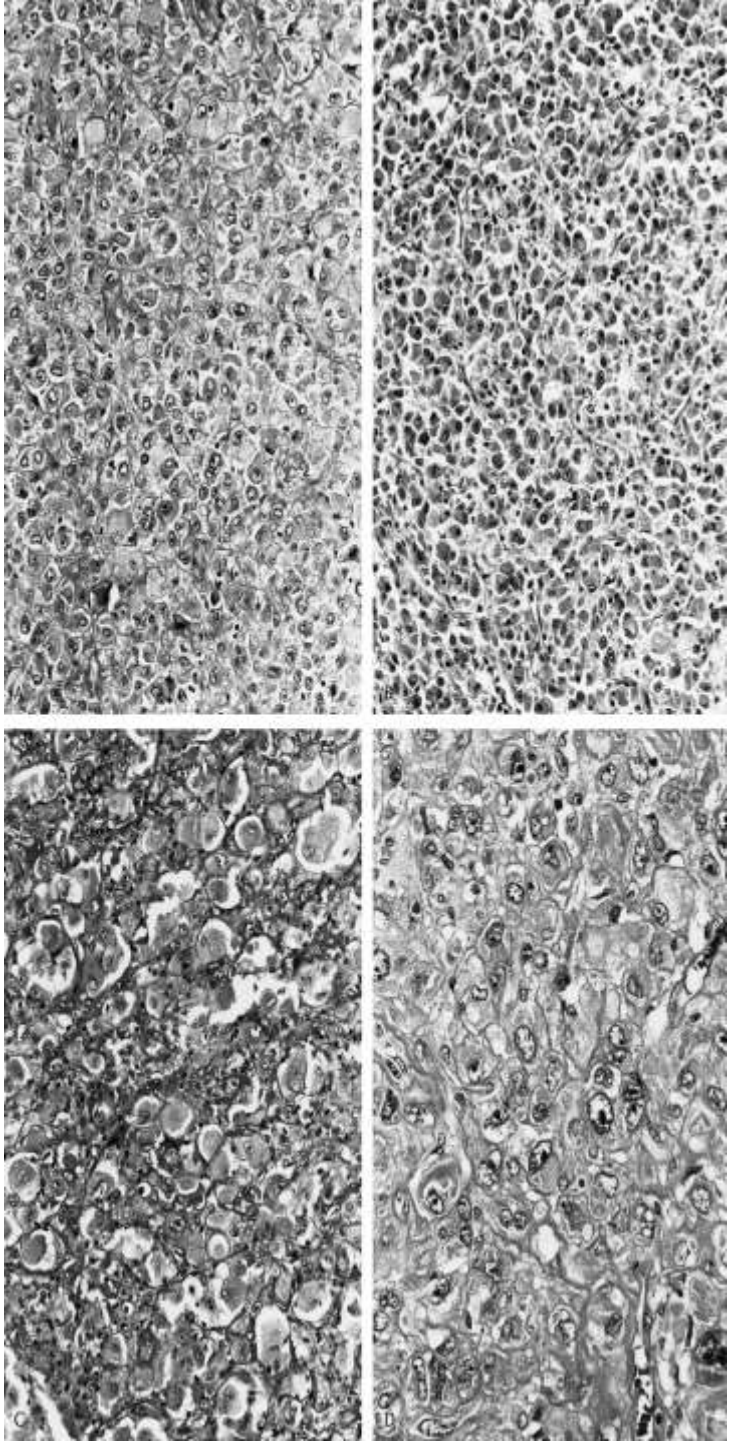
# Histiocytic and dendritic cell neoplasms

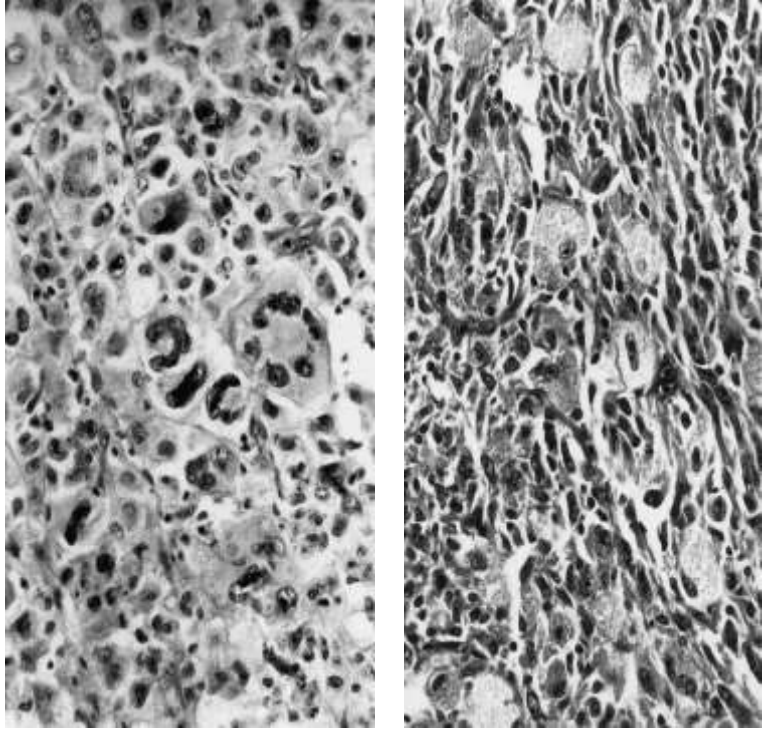
| Marker | Langerhans cell | Interdigitating dendritic cell | Follicular dendritic cell | Plasmacytoid dendritic cell | Dermal/interstitial dendritic cell | Macrophages |
|---|---|---|---|---|---|---|
| CD1a | ++ | - | - | - | - | - |
| CD4 | + | + | + | + | +/- | + |
| CD21 | - | - | ++ | - | - | - |
| CD68 | +/- | +/- | - | ++ | + | ++ |
| CD123 | - | - | - | ++ | - | - |
| CD163 | - | - | - | - | - | ++ |
| Langerin | ++ | - | - | - | - | - |
| Lysozyme | +/- | - | - | - | - | + |
| Factor XIIIa | - | - | +/- | - | ++ | -/+ |
| S100 | ++ | ++ | +/- | - | +/- | +/- |

# Histiocytic Sarcoma

(Hornick JL, Jaffe ES, Fletcher CD. 2004. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. )

- Rare neoplasm
- Etiology unknown
- The most common primary sites appear to be LN, skin, GI; spleen, CNS, or other extranodal sites
- Microscopy: diffuse non-cohesive proliferation of large cells (>20 µm)
- Immunophenotype: By definition, expression of one or more histiocytic markers (CD163, CD68, lysozyme) with absence of Langerhans cell (CD1a, langerin), follicular dendritic cell (CD21, CD35) and myeloid cell (CD13, MPO) markers. Exclusion of metastatic undifferentiated large cell carcinoma, melanoma, DLBCL, ALCL, etc.





(Hornick JL, Jaffe ES, Fletcher CD. 2004. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. )

- Large epithelioid cells with abundant eosinophilic well-defined cell borders, and oval to irregular nuclei vesicular chromatin and usually large eosinophilic nu
- Binucleated cells, pleomorphism with tumor giant
- Focally clear or foamy cytoplasm
- Focally sarcomatoid (spindle cell) features
- Cytophagocytosis was evident in some cases
- Mitotic figures median: 11 per 10 HPF
- Stromal inflammatory infiltrate, most often of neu

# Histiocytic sarcoma (cont.)

- Genetic profile: high frequency of clonal Ig receptor gene rearrangements in sporadic H/DC sarcomas, particularly when there is an association with low-grade B cell lymphoma-transdifferntiation; BRAF V600E mutation; stepwise inactivation of PTEN, $p16^{INK4A}$, and $p14^{ARF}$
- Aggressive neoplasm, poor response to therapy
- No standard treatment regimen
- For patients with multifocal disease, suggest aggressive multiagent chemotherapy with six cycles of ifosfamide, mesna, carboplatin, and etoposide (ICE) or Cyclophosphamide, doxorubicin, vincristine, prednis one (CHOP)

# Other differential diagnoses

- Large cell carcinoma of lung

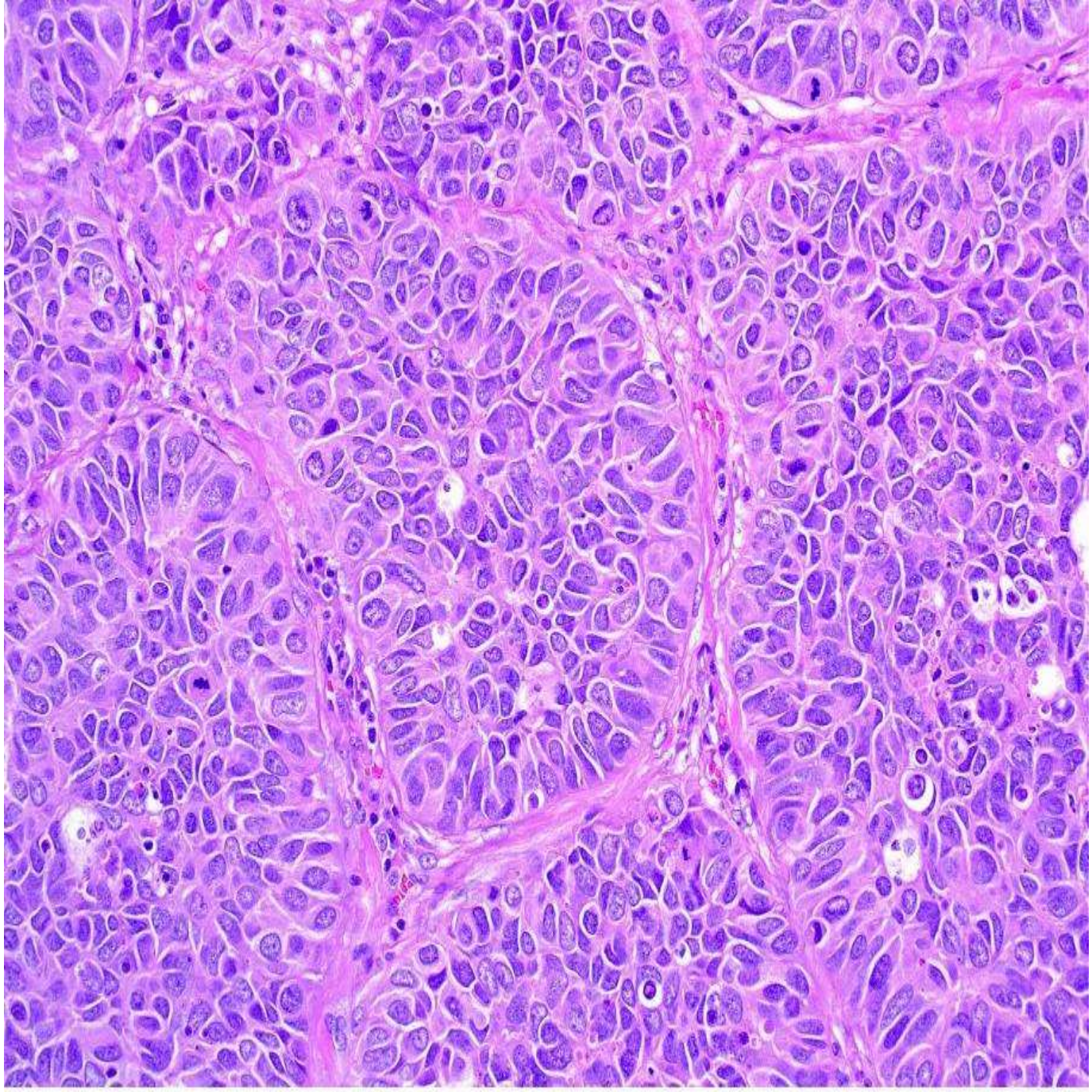
  Undifferentiated non-small cell carcinoma that lacks the cytological, architectural, and immunohistochemical features of small cell carcinoma, adenocarcinoma, or SCC

- Pleomorphic/giant cell carcinoma of lung

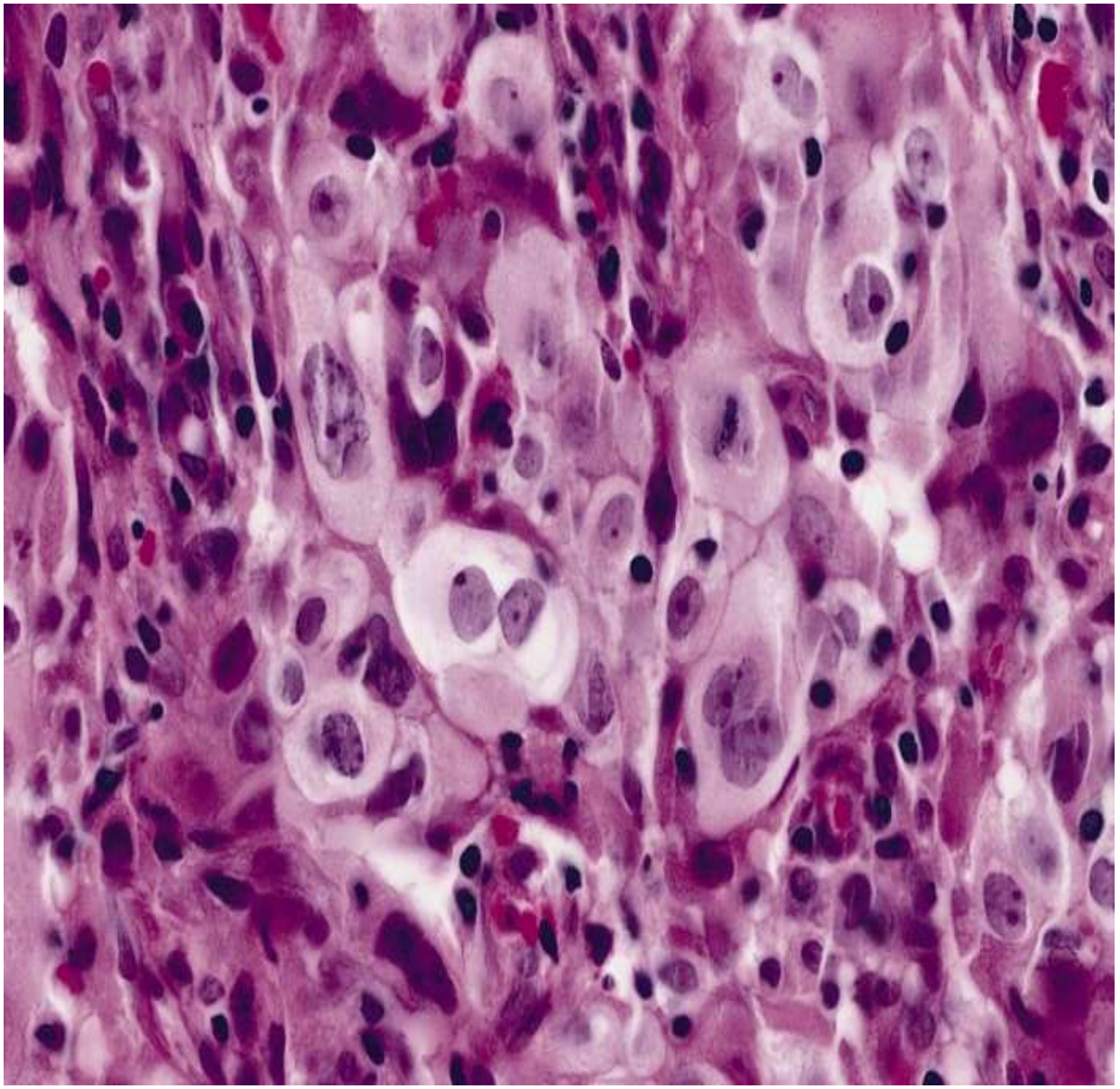
  Poorly differentiated non-small cell lung carcinoma namely a SCC, adenocarcinoma, or undifferentiated NSCC that contains at least 10% spindle and/or giant cells

  Giant cell carcinoma consists almost entirely of tumor giant cells with no differentiated carcinomatous elements

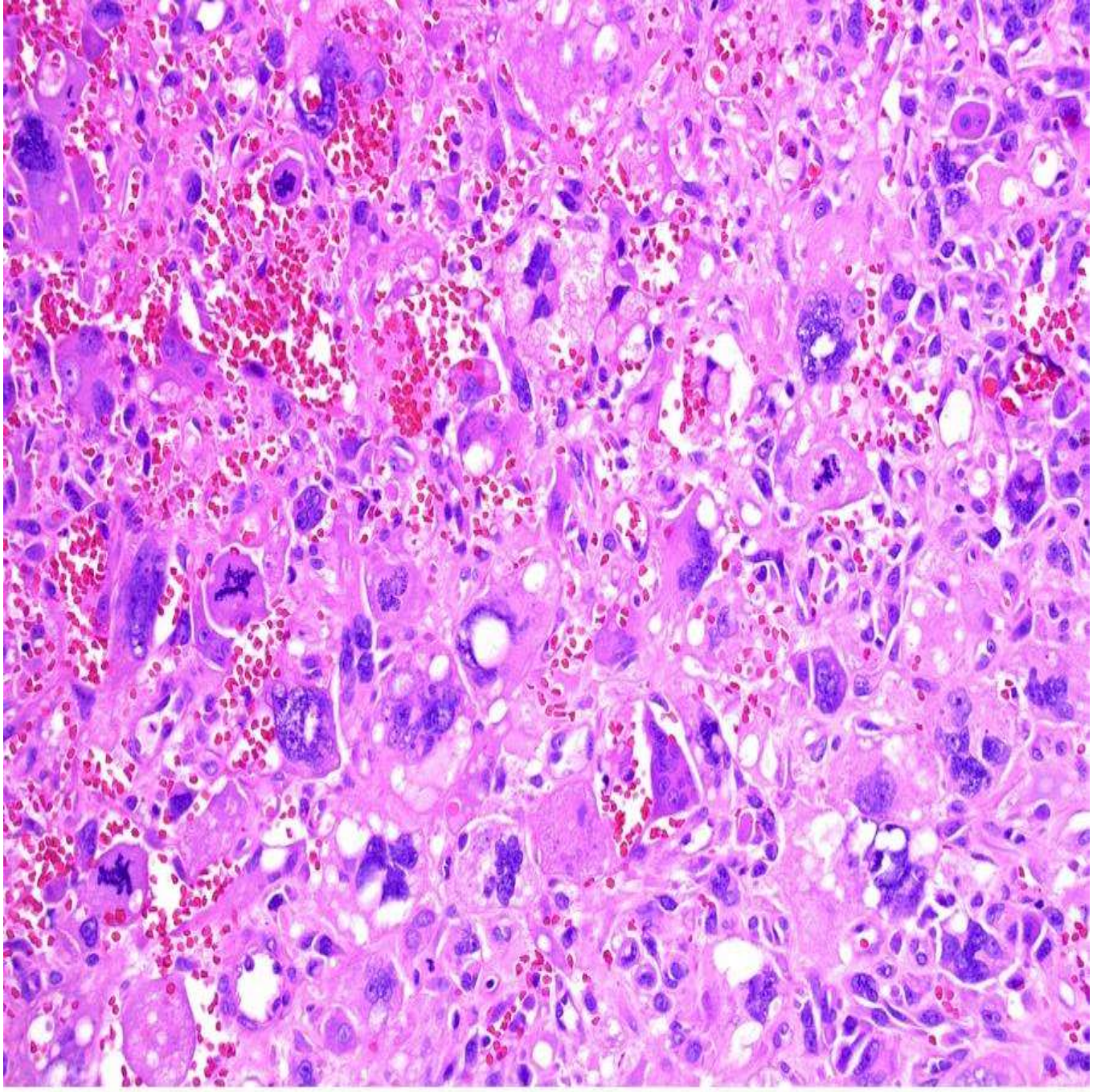
**Keratin expression is not required in the spindle/giant cell component if non-pleomorphic carcinomatous elements are clearly present**



Large cell carcinoma H&E 200X



Large cell carcinoma of the lung



Giant cell CA lung HE 200Xb

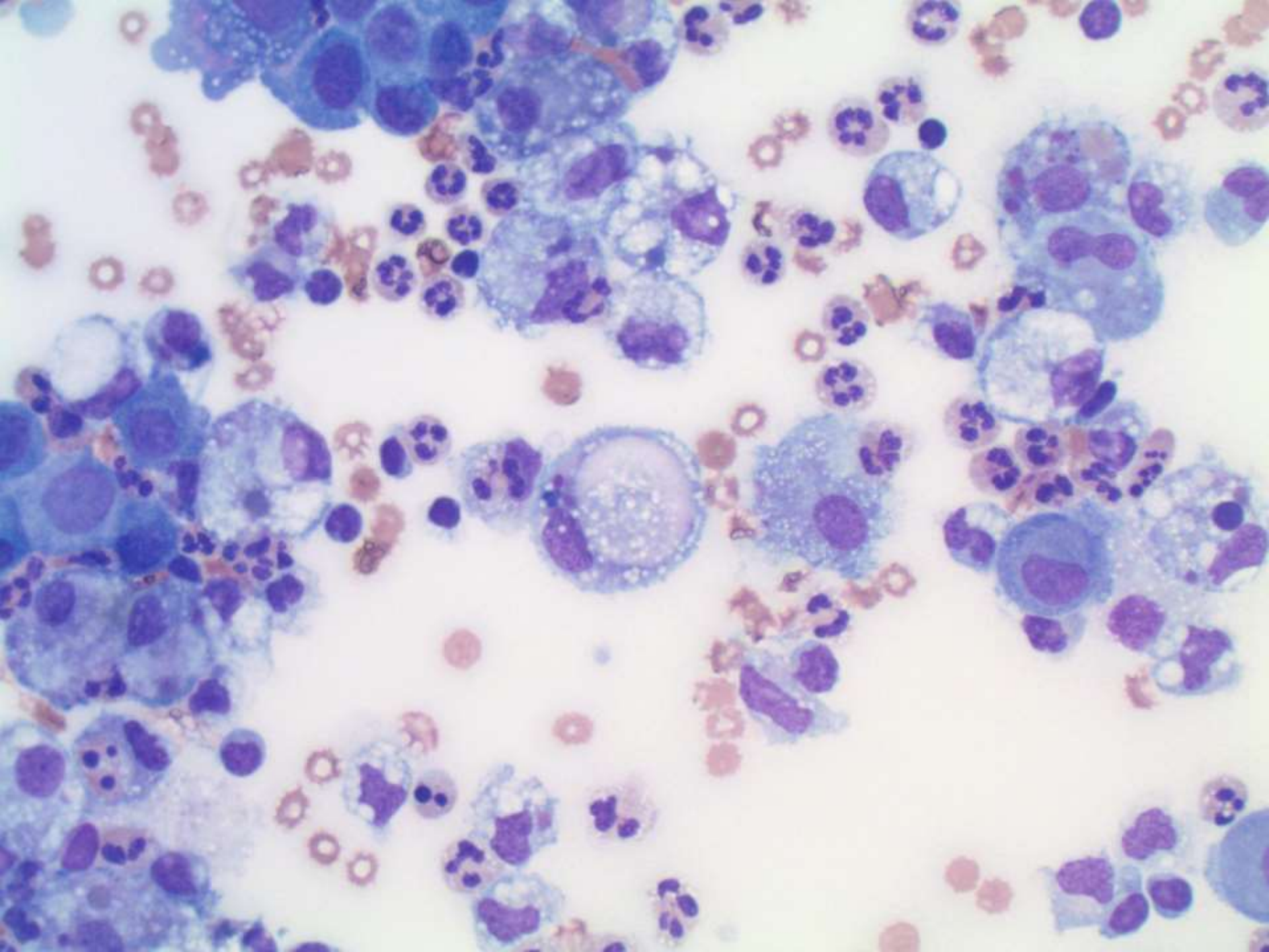
# Reference

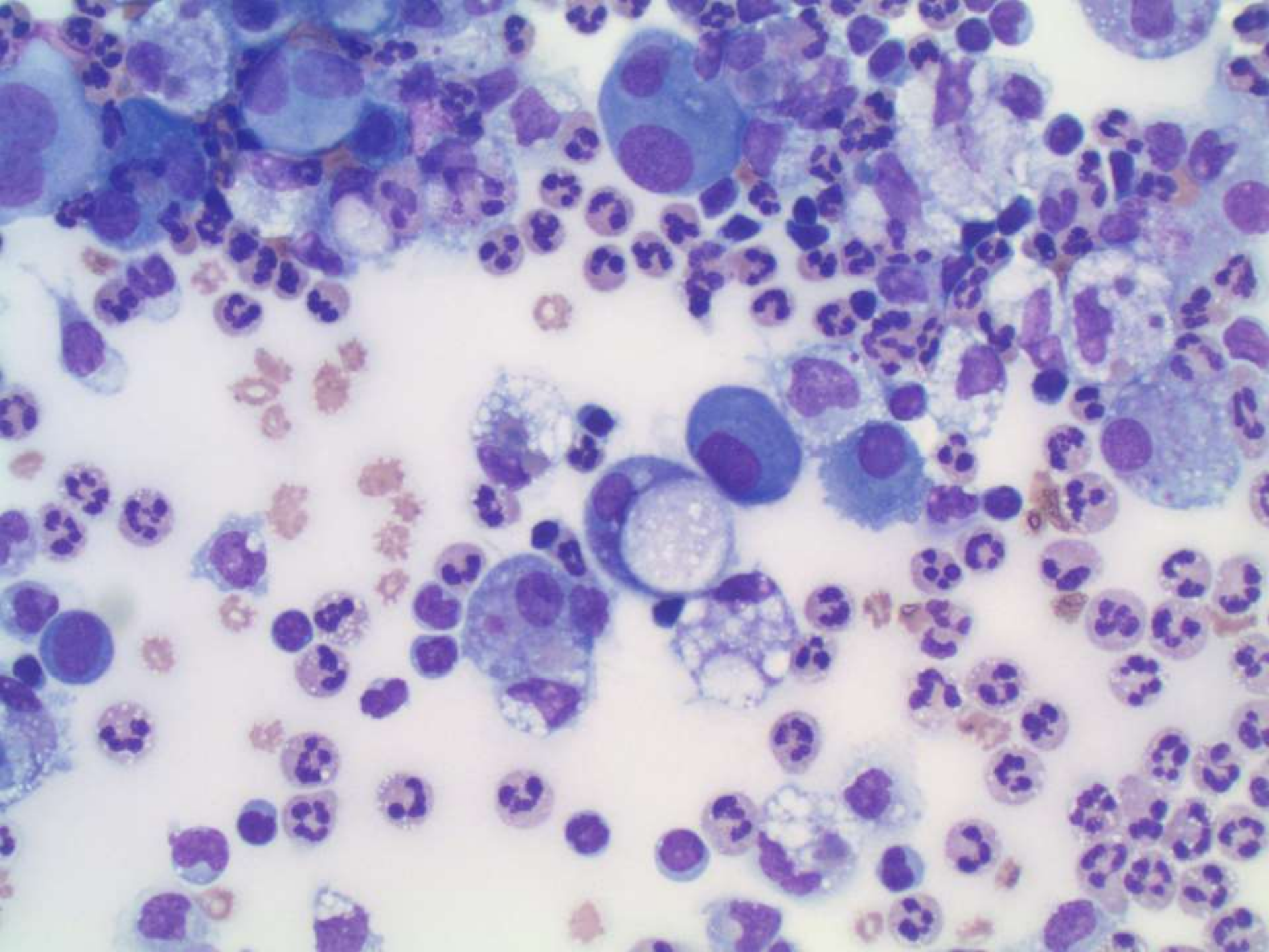

- Buonocore S, Valente AF, Nightingale D, Bogart J, Souid AK: Histiocytic sarcoma in a 3-year-old male: a case report. Pediatrics 116:e322-325, 2005
- Carrasco DR, Fenton T, Sukhdeo K, Protopopova M, Enos M, You MJ, Di Vizio D, Nogueira C, Stommel J, Pinkus GS, Fletcher C, Hornick JL, Cavenee WK, Furnari FB, Depinho RA. The PTEN and INK4A/ARF tumor suppressors maintain myelolymphoid homeostasis and cooperate to constrain histiocytic sarcoma development in humans. Cancer Cell. 2006 May;9(5):379-90.
- Chen W, Lau SK, Fong D, Wang J, Wang E, Arber DA, Weiss LM, Huang Q. High frequency of clonal immunoglobulin receptor gene rearrangements in sporadic histiocytic/dendritic cell sarcomas. Am J Surg Pathol. 2009 Jun;33(6):863-73.
- Feldman AL, Arber DA, Pittaluga S, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. Blood 2008; 111:5433.
- Go H, Jeon YK, Huh J, Choi SJ, Choi YD, Cha HJ, Kim HJ, Park G, Min S, Kim JE. Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology. 2014 Aug;65(2):261-72.
- Hornick JL, Jaffe ES, Fletcher CD. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. Am J Surg Pathol 2004; 28:1133.
- Stacher E, Beham-Schmid C, Terpe HJ, Simiantonaki N, Popper HH: Pulmonary histiocytic sarcoma mimicking pulmonary Langerhans cell histiocytosis in a young adult presenting with spontaneous pneumothorax: a potential diagnostic pitfall. Virchows Arch 455:187-190, 2009
- Tomita S, Ogura G, Inomoto C, Kajiwara H, Masuda R, Iwazaki M, Kojima M, Nakamura N. Histiocytic Sarcoma Originating in the Lung in a 16-Year-Old Male. J Clin Exp Hematop. 2015;55(1):45-9

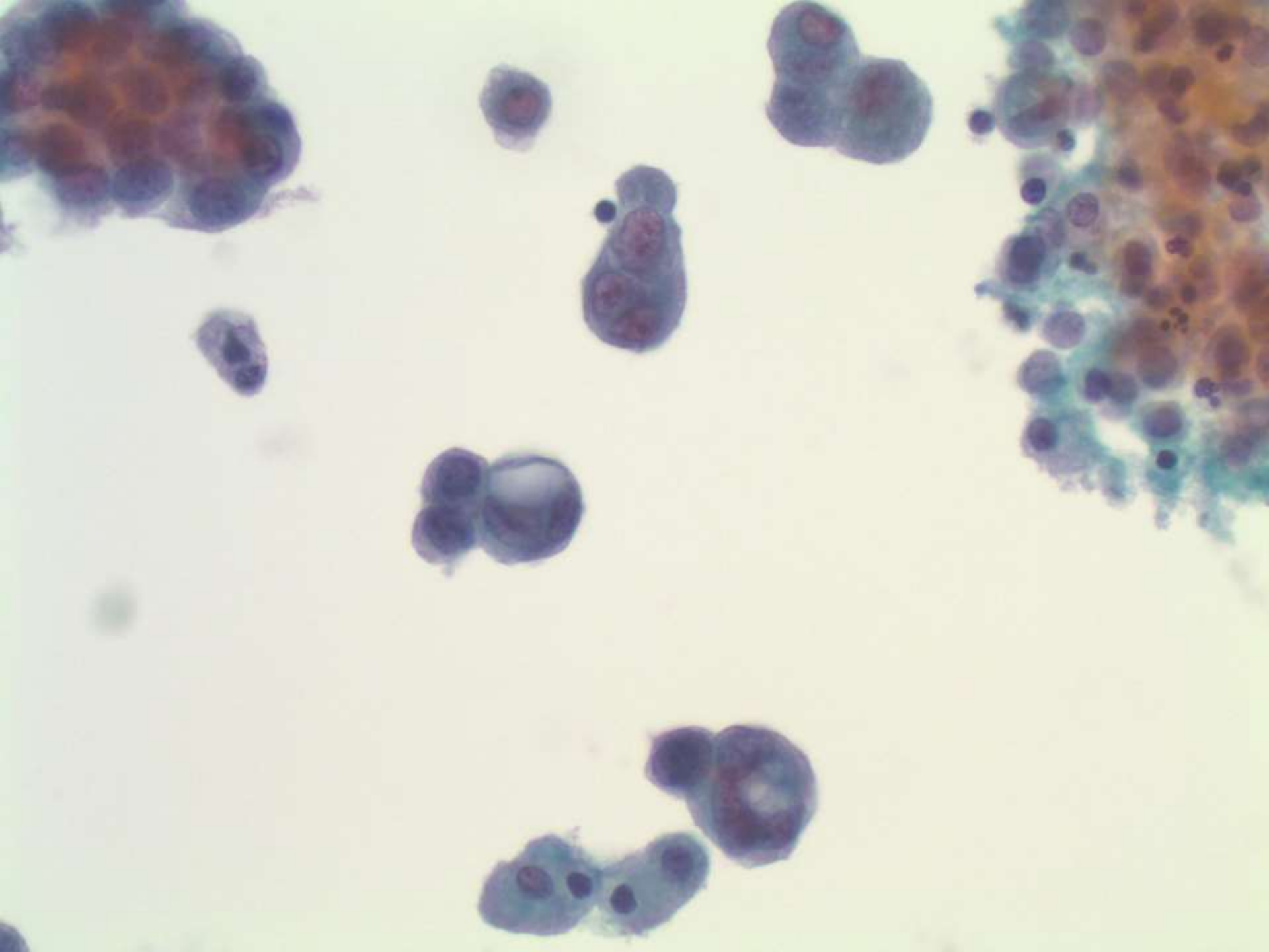
# SB 6346

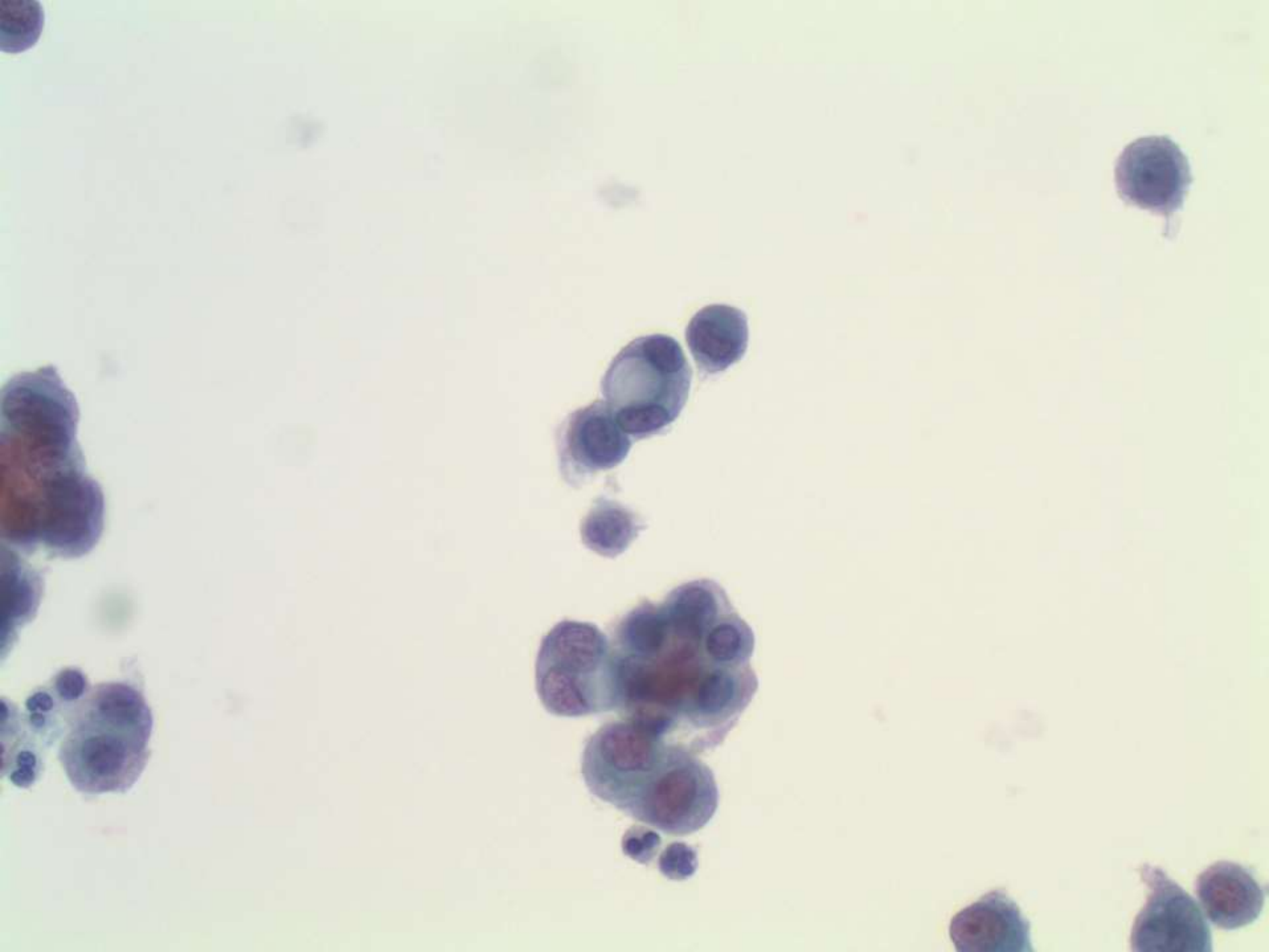
**Sharon Wu; El Camino Hospital**

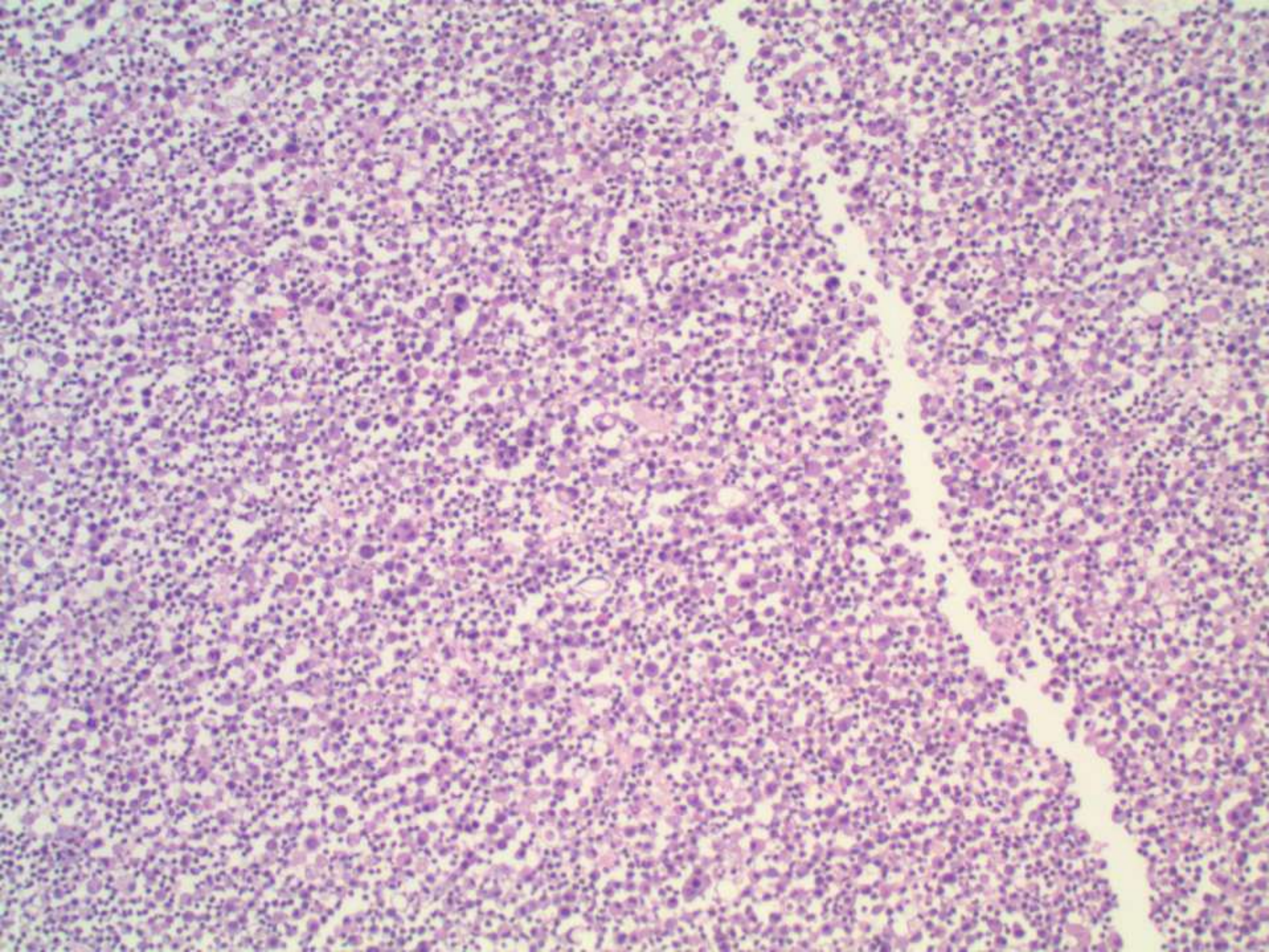
68-year-old male heavy smoker with right pleural effusion.

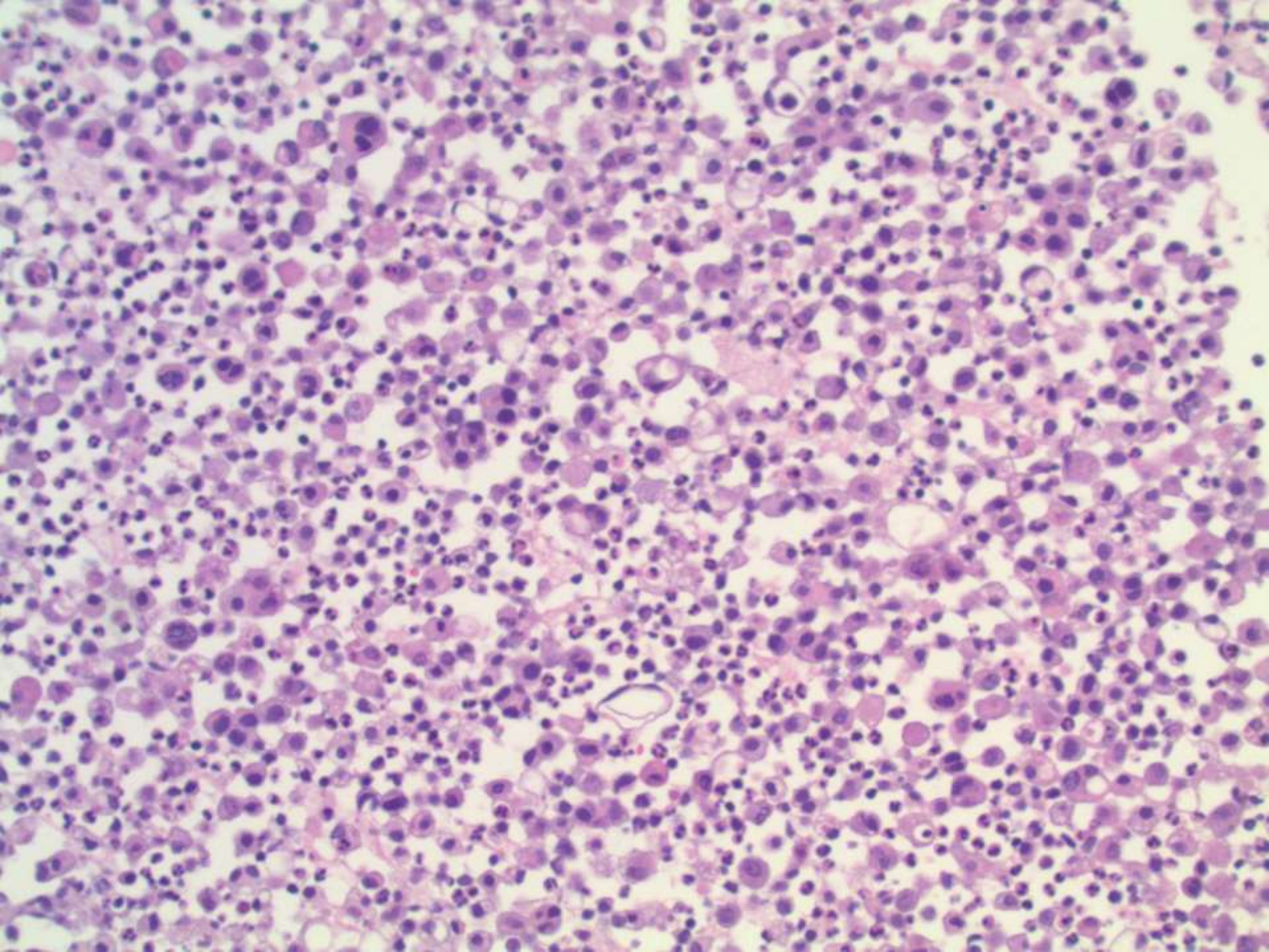


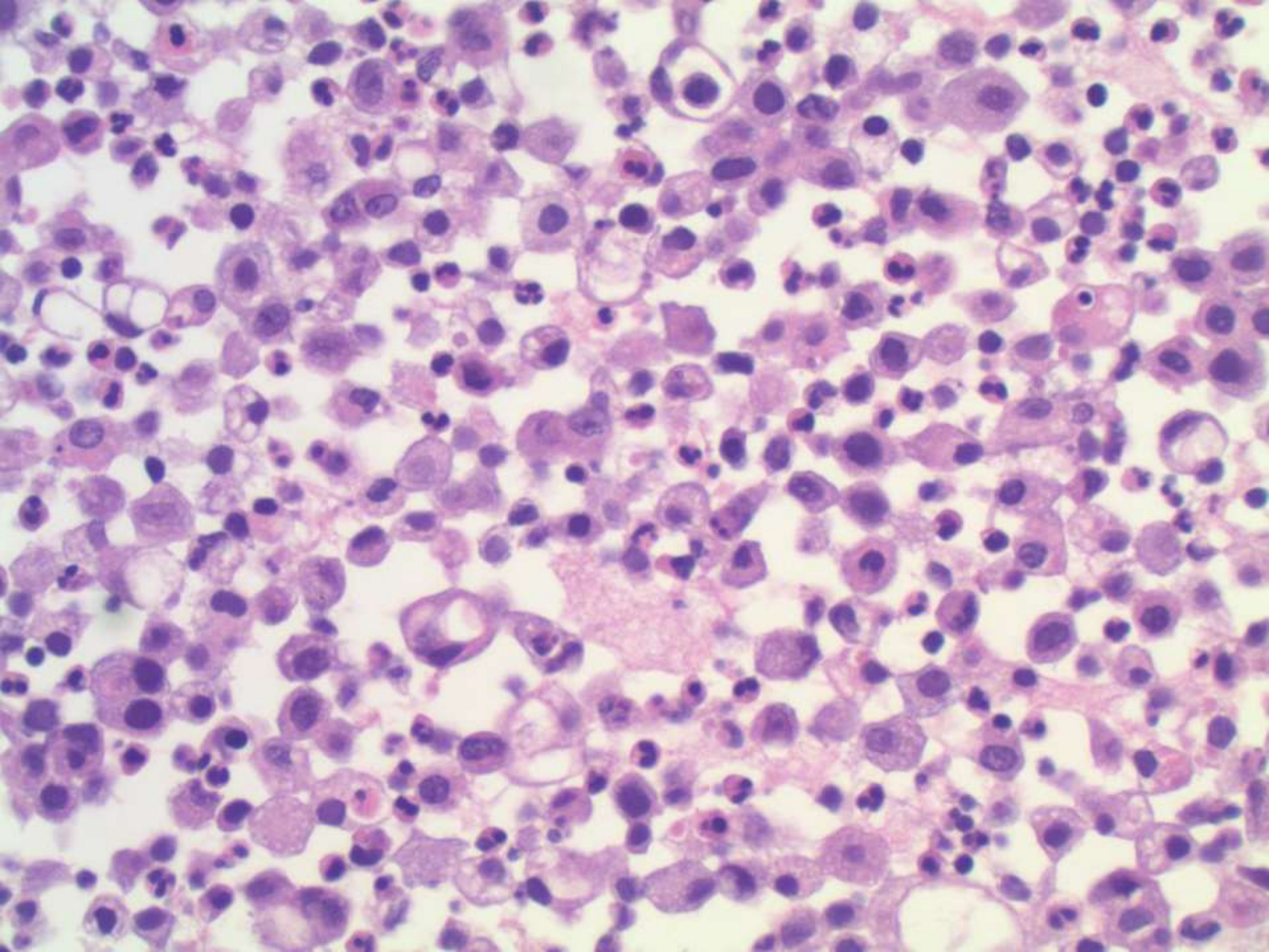












# Clinical History

- Multiple lung and liver masses of variable size
- Malignant pleural effusion?

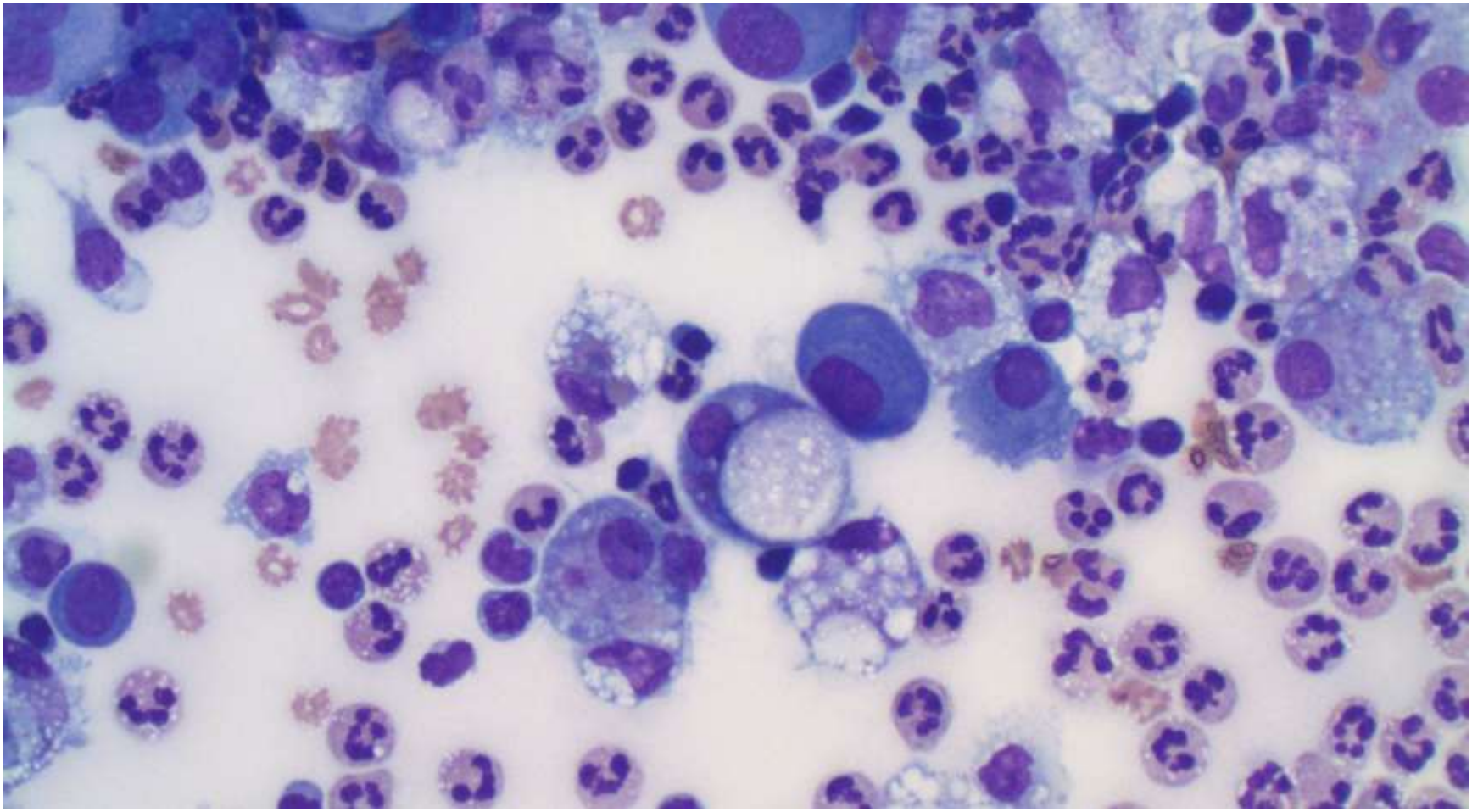
# Practical Challenges in Fluid Cytology

- Common case in your work list
- Limited look at a few diagnostic cells
- Obscuring background of reactive/inflammatory cells
- Little to no architecture
- Tolerance of uncertainty, (dis)comfort
- Personal preference
- Descriptive or definitive

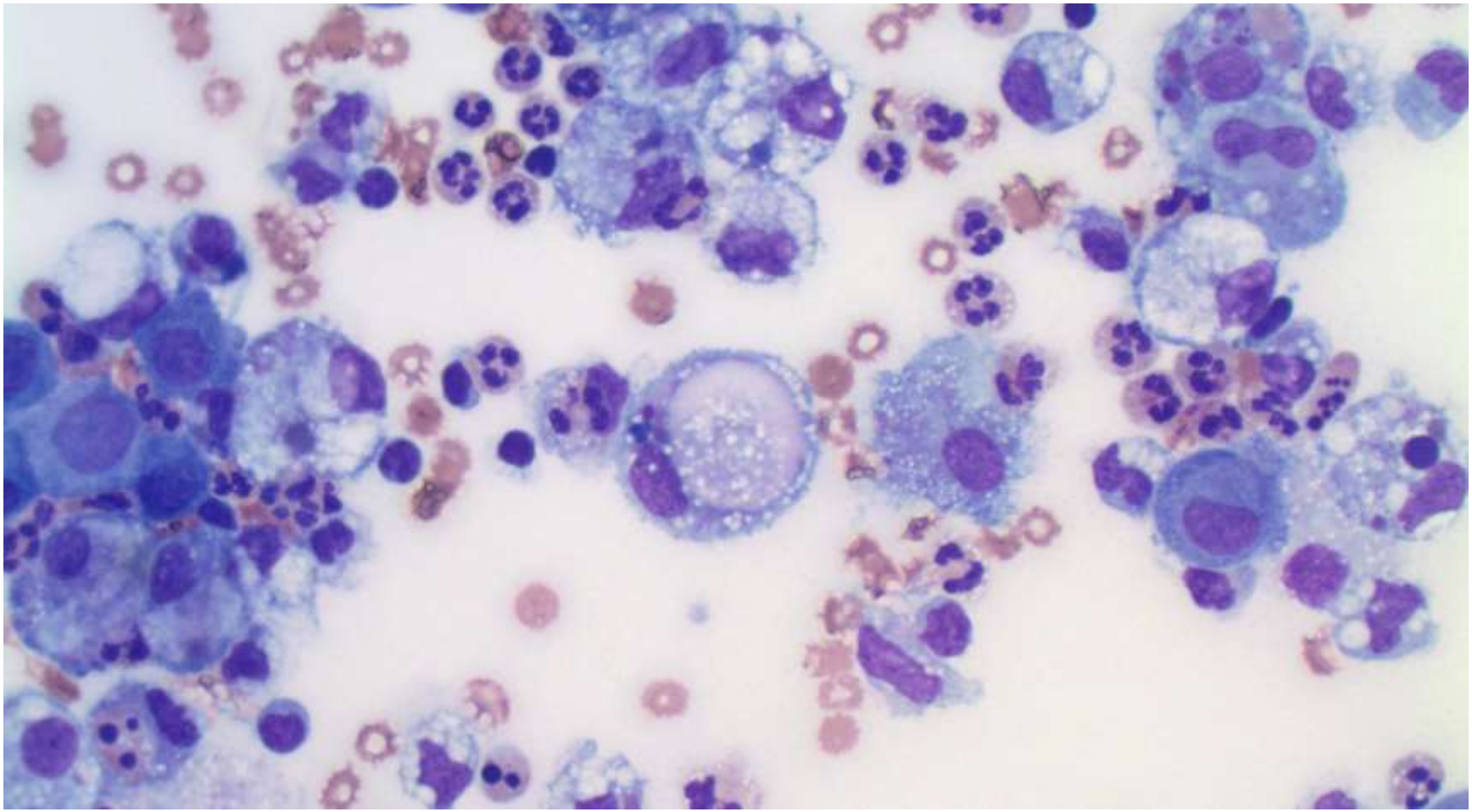
# Clinical Issues in Fluid Cytology

- Clinical history
- What will happen next?
- Time of presentation?
- Have they gone for the actual lesion?
- Will they?
- Adequate cells for ancillary testing?
- Conversation with clinician

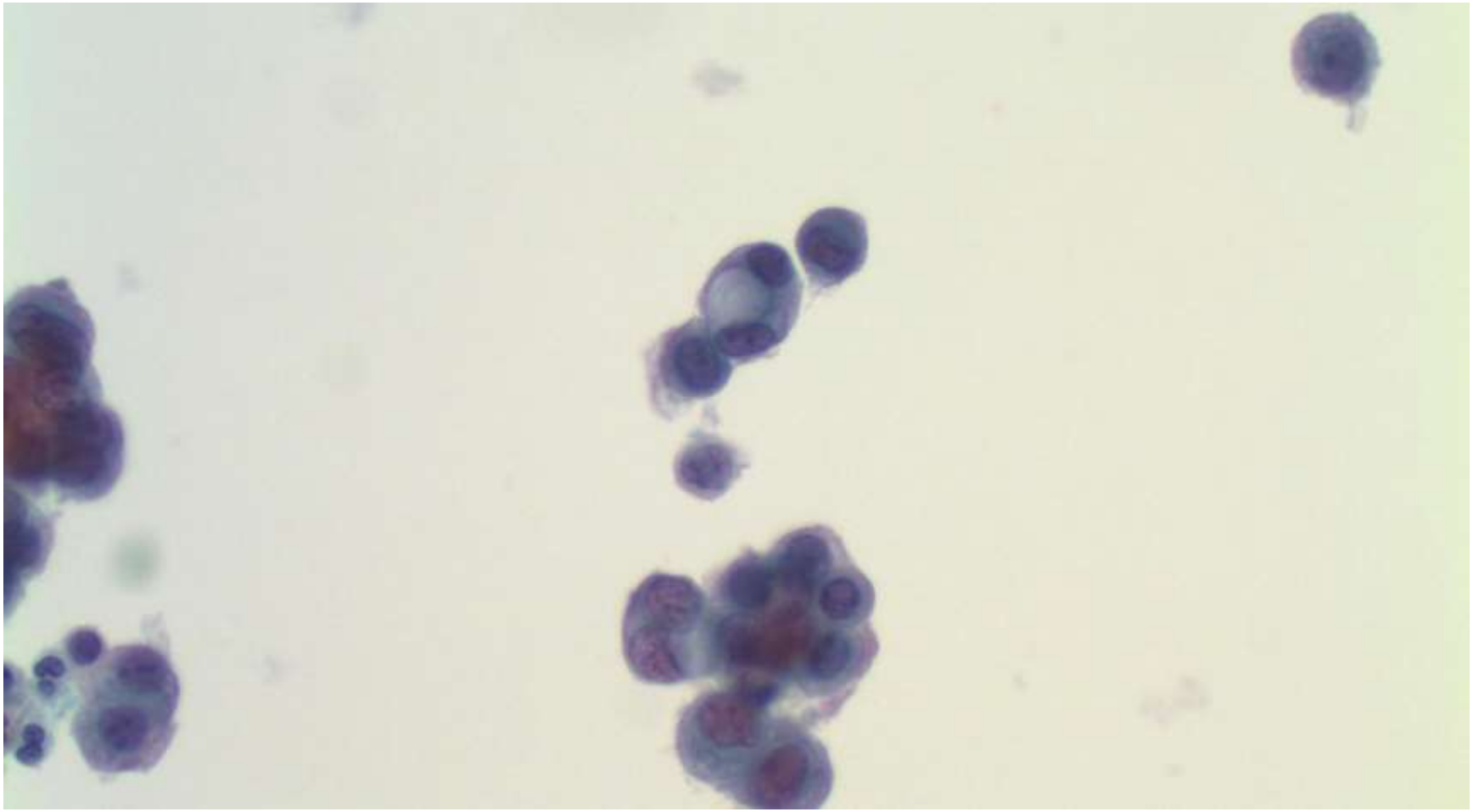
# How concerned am I?



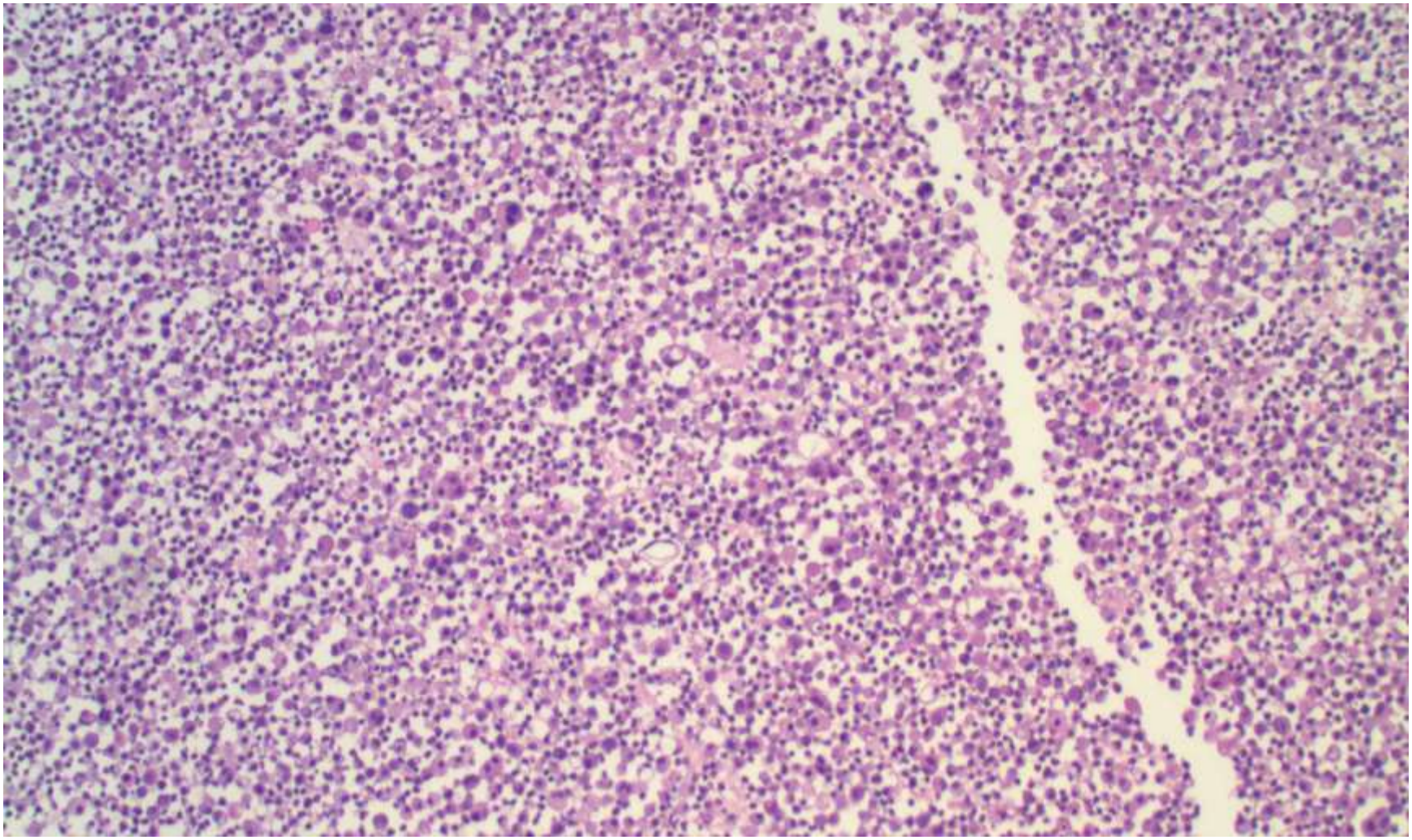
# Histiocytes? Mesos? Carcinoma?



# “Unimpressive”… “It’s not killing me”



# Ok it’s cellular, but it’s a pleural fluid.



Histiocytes, mesos, inflammatory
Should I stain it though?
What time is it? What day is it?
I'm tired and paranoid so I'll just stain it for everything.
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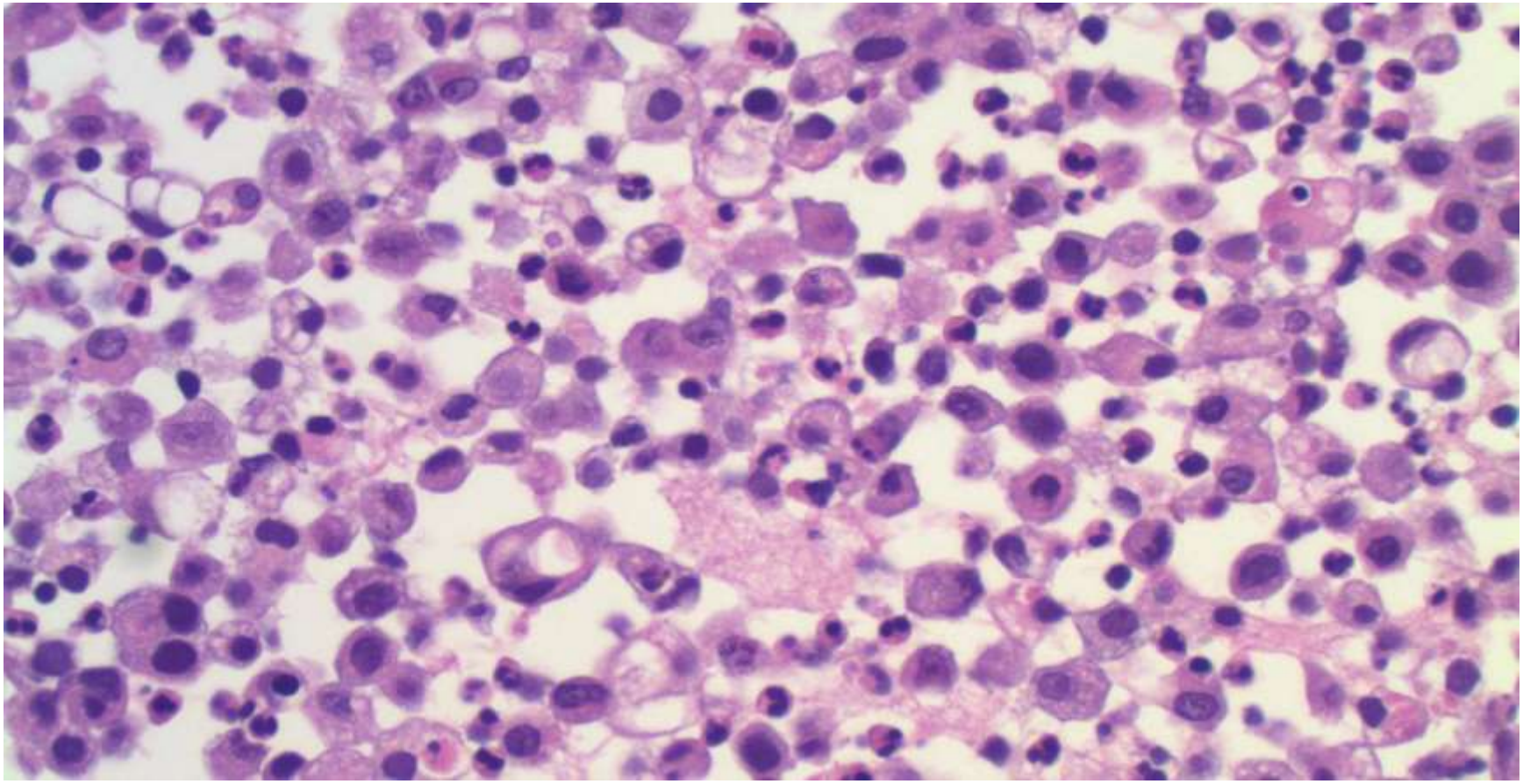


# Decision making

Education in Pathology and Laboratory Medicine

## How Does a Pathologist Make a Diagnosis?

*Gil Patrus Pena, MD; José de Souza Andrade-Filho, MD*

Arch Pathol Lab Med. 2009;133:124–132

# Decision making domains

- Cognitive
- Communicative
- Normative
- Medical Conduct

# Cognitive

- Perception, attention, memory and search
- A diagnostic strategy or approach
  - Pattern recognition, algorithms, exhaustive strategy, hypothetical and deductive reasoning
- Collect data
- Make observations and check hypotheses against the data
- The Work-Up

# Communicative

- Description, interpretation and diagnosis
- Constructing an argument: warrants and backings
- Weighing evidence with experience
- Qualifiers
- Written documentation
- Talking to clinicians
- The most important part of the job

# Normative

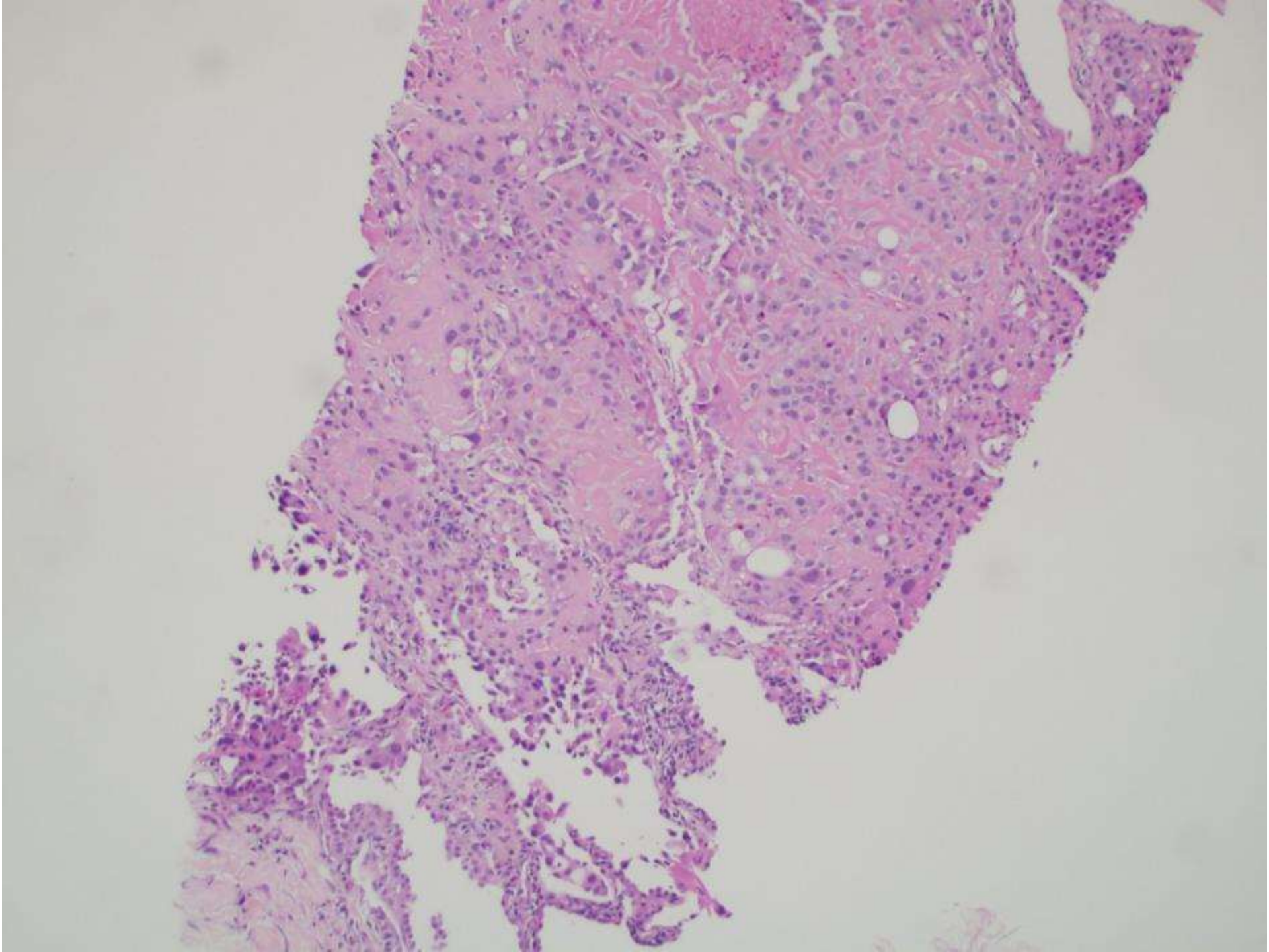
- Follow the rules of classification and reporting
- Social norms
- Respect for patient, clinician and fellow pathologist
- Ethical conduct
- The stuff that comes with the job

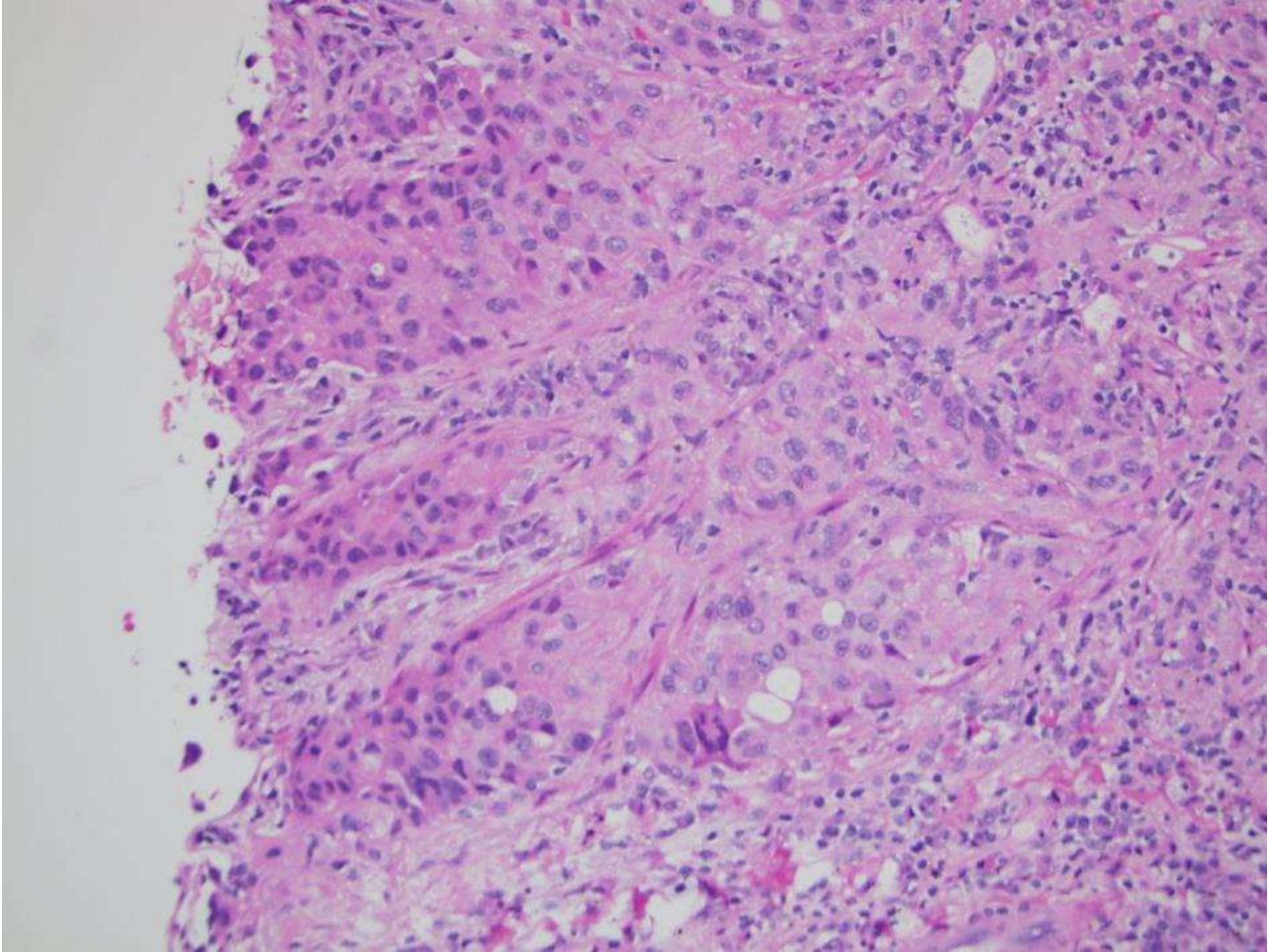
# Medical conduct

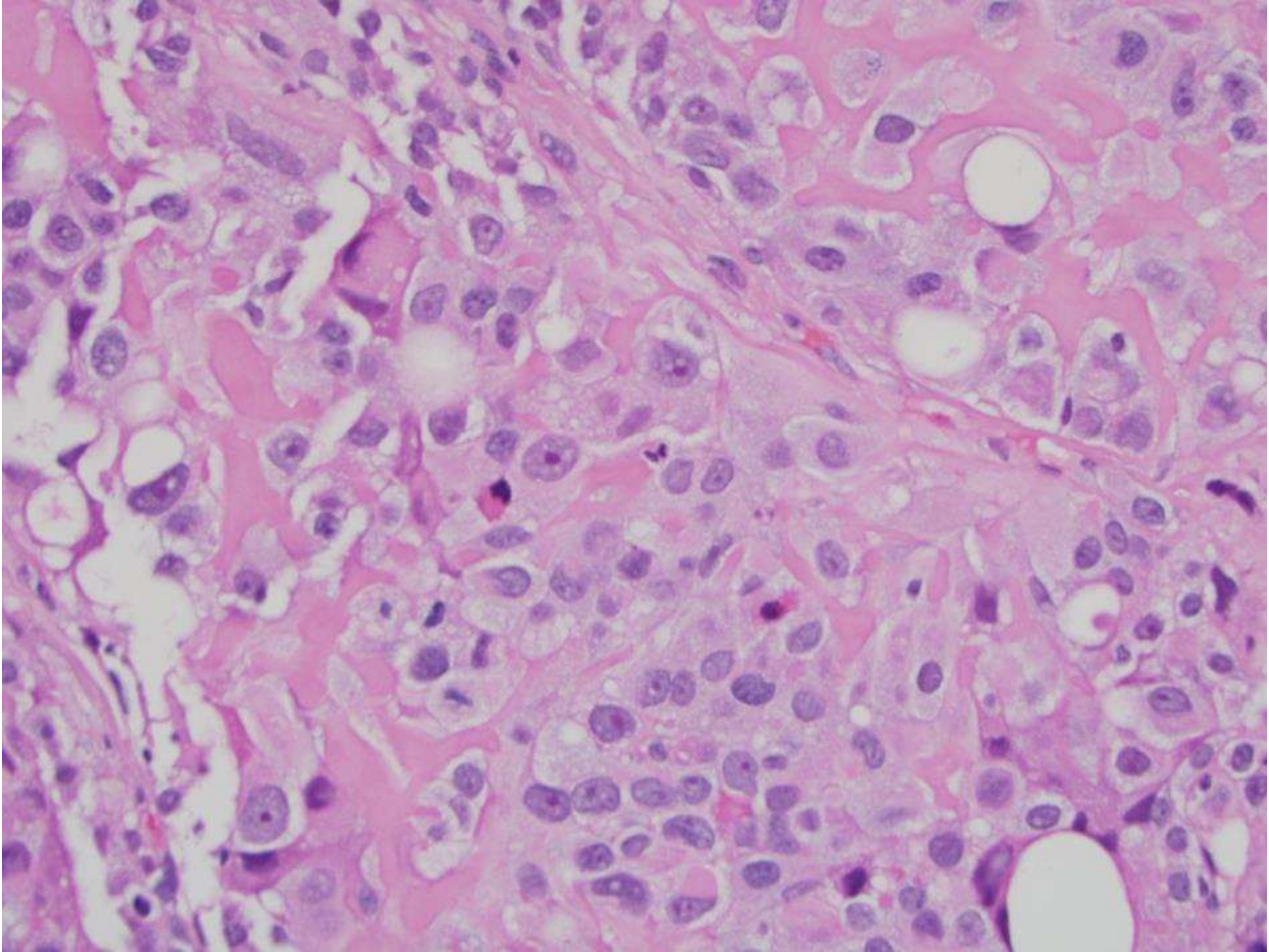
- Consequences of the diagnosis
- Is the diagnosis clear regarding the expected conduct?
- Am I ok to assume all the responsibility for the diagnosis, or should I show it to another pathologist?
- Should I do more (stains, ancillary, another sample, consultation?) or “let it go”?
- The stuff that keeps you up at night

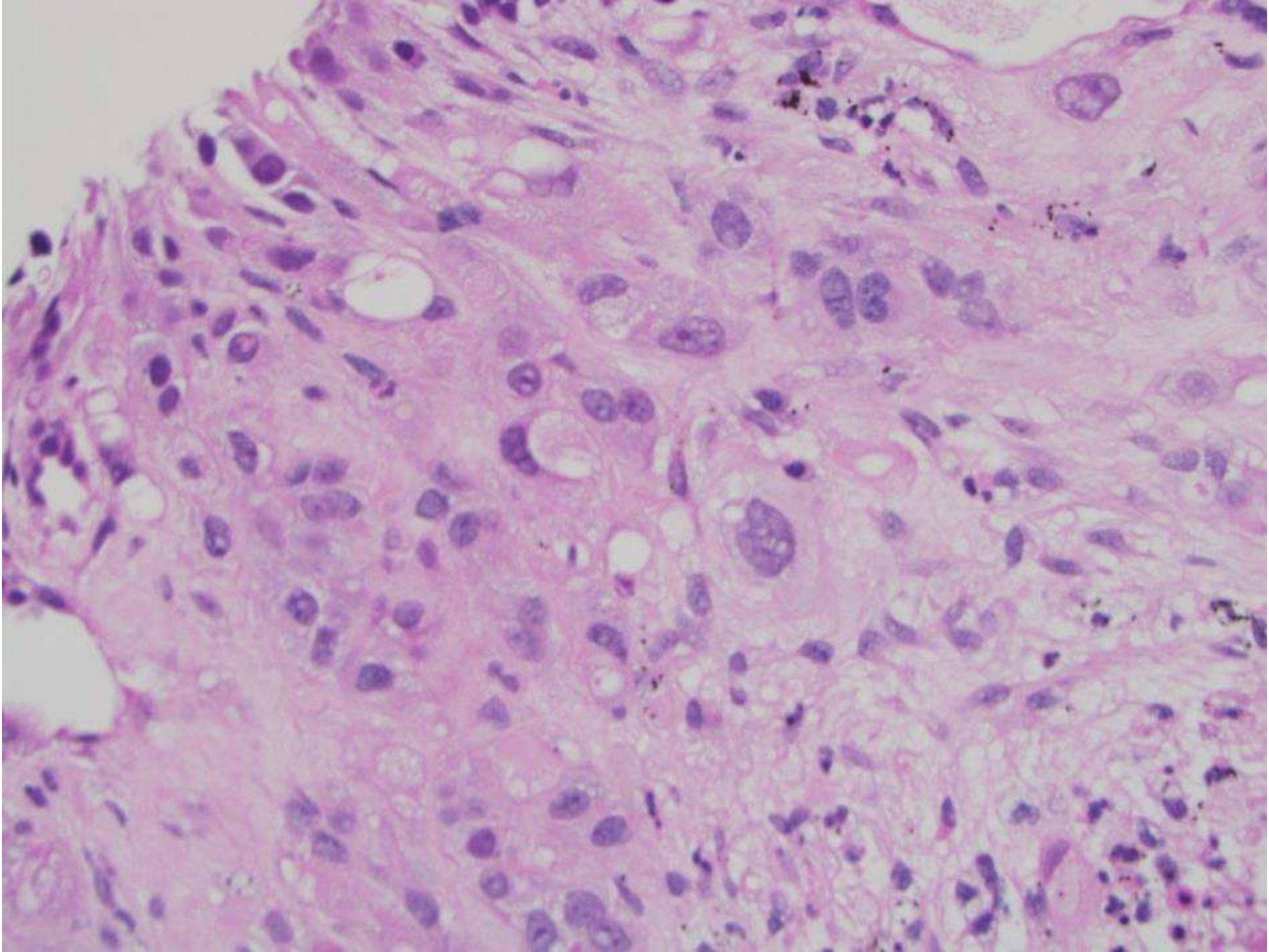
# Back to our patient's pleural fluid:

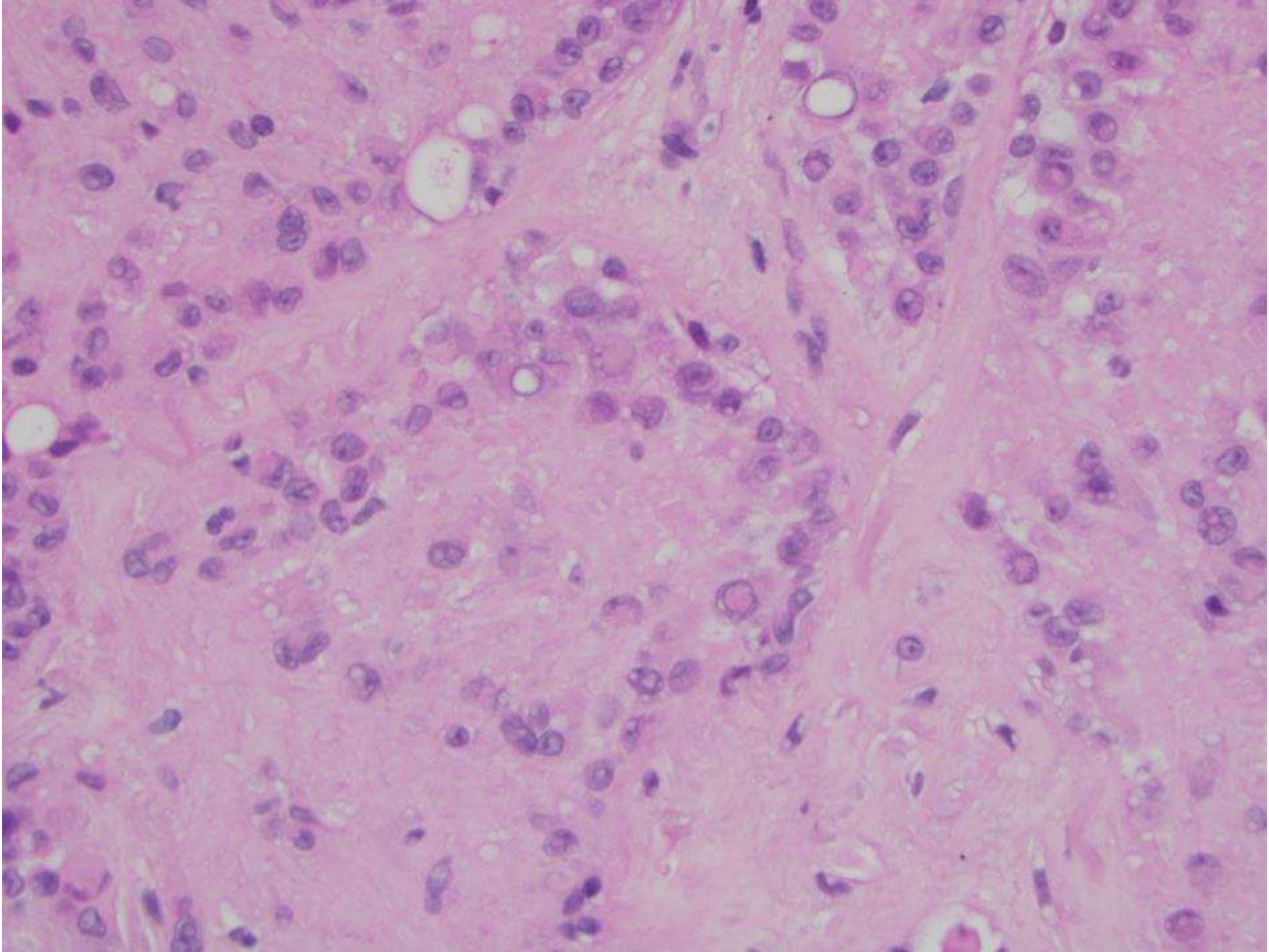
- The work-up
  - Clinical history
  - Immunohistochemistry
- The most important part of the job
  - What I need to make a diagnosis
  - What I tell the oncologist when he/she calls
- The stuff that comes with the job
  - How my practice practices
- The stuff that keeps you up at night
  - If I call this, something will happen to the patient
  - If I call this, nothing will happen to the patient

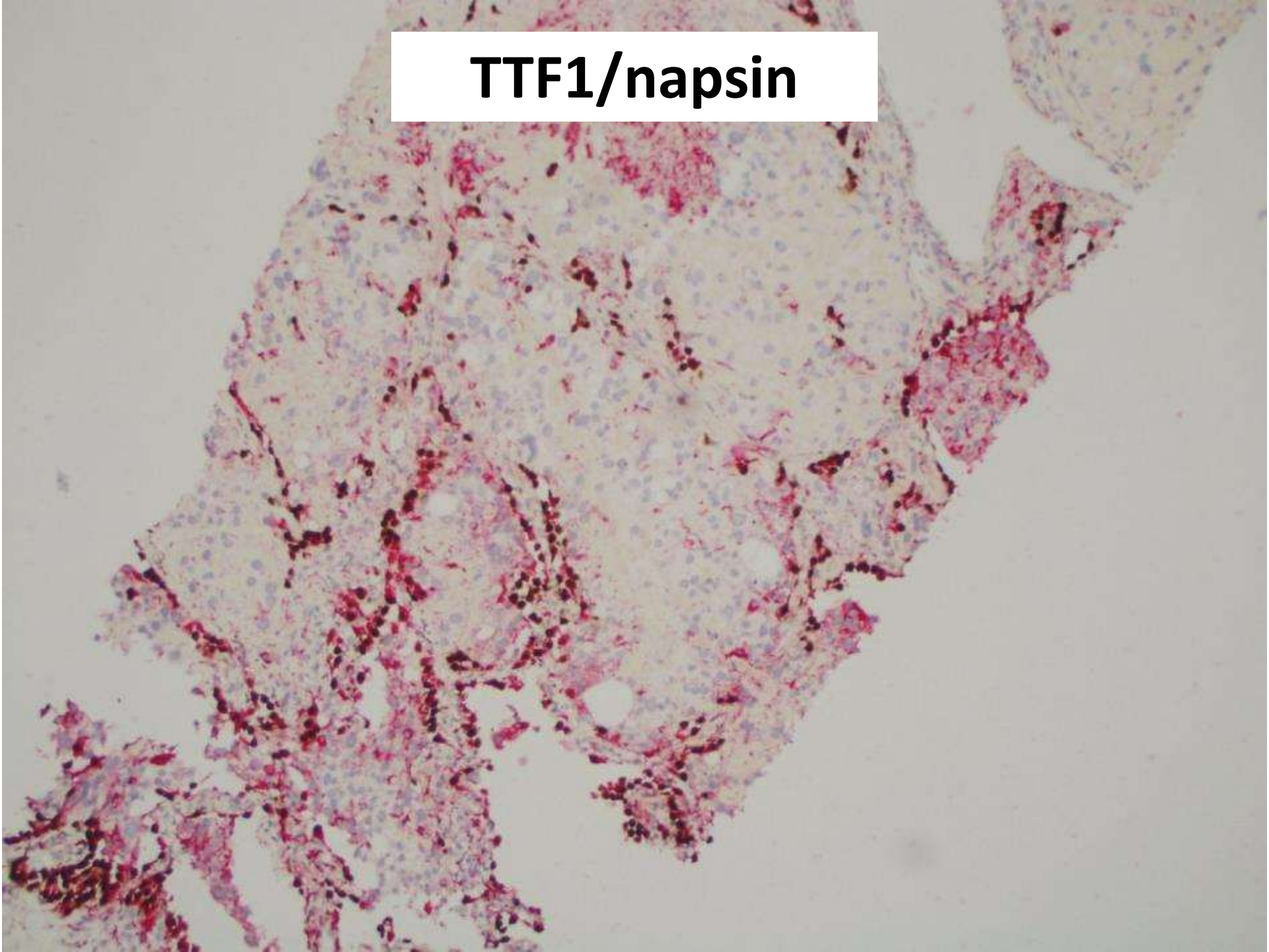


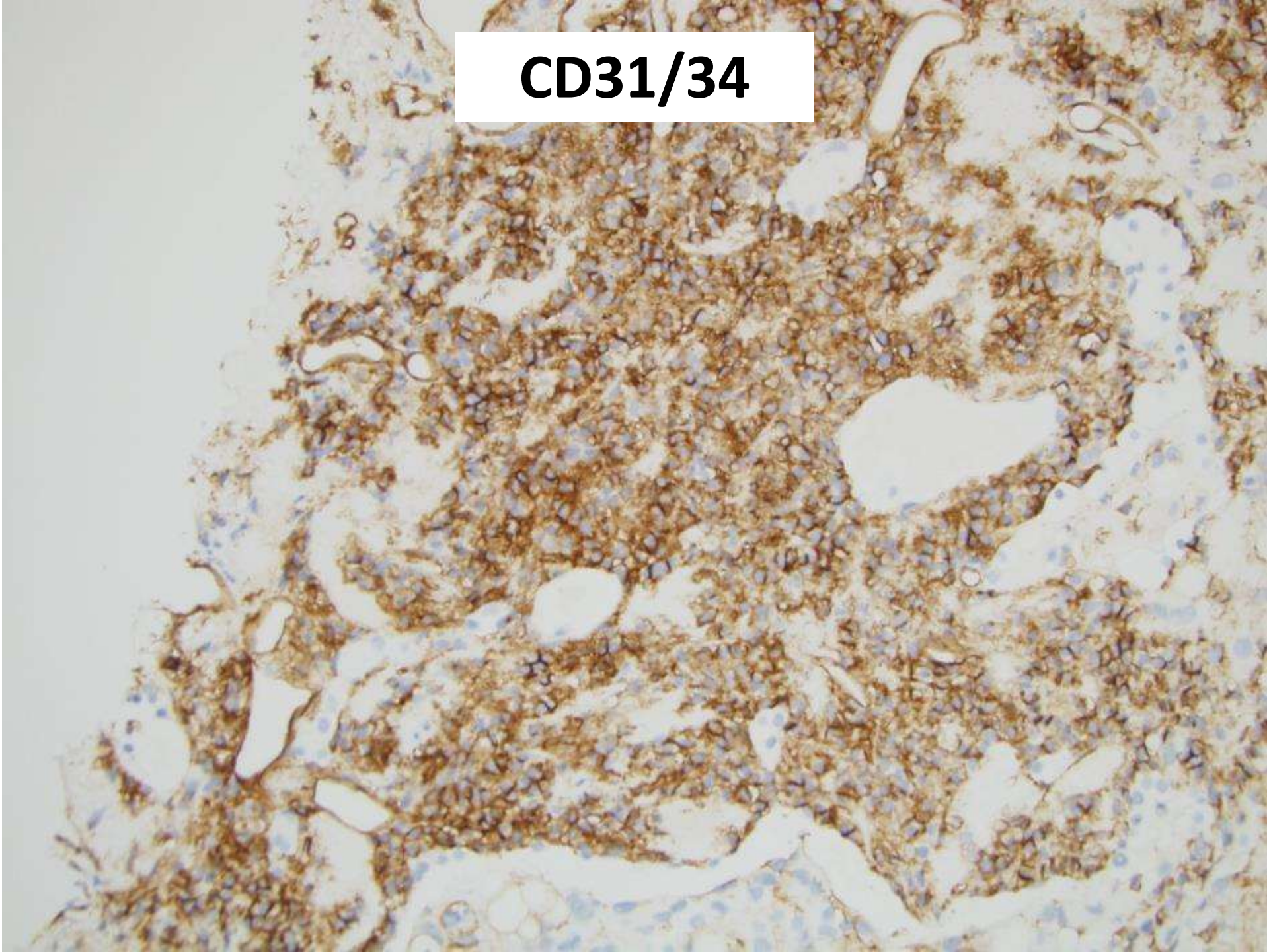


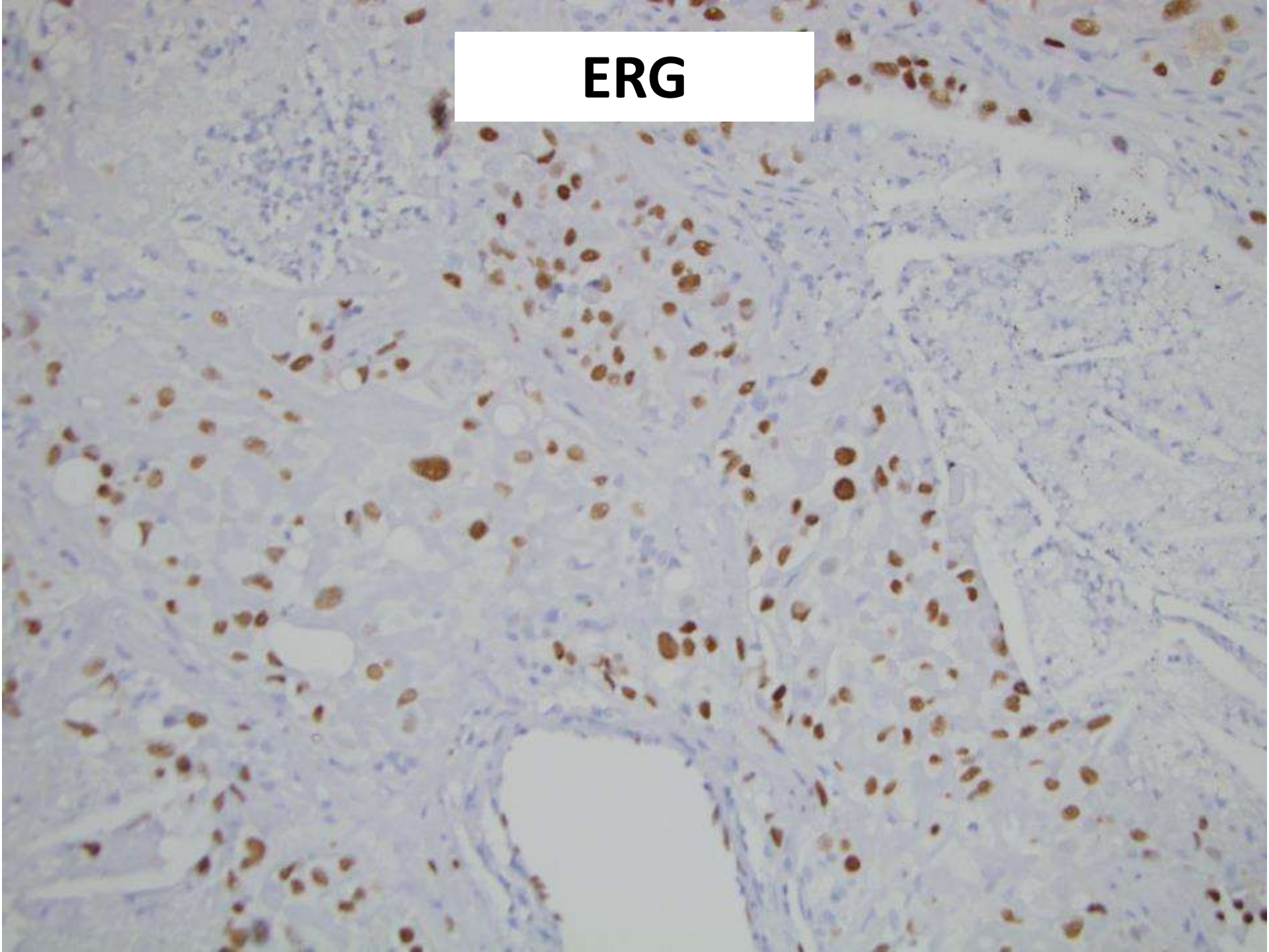


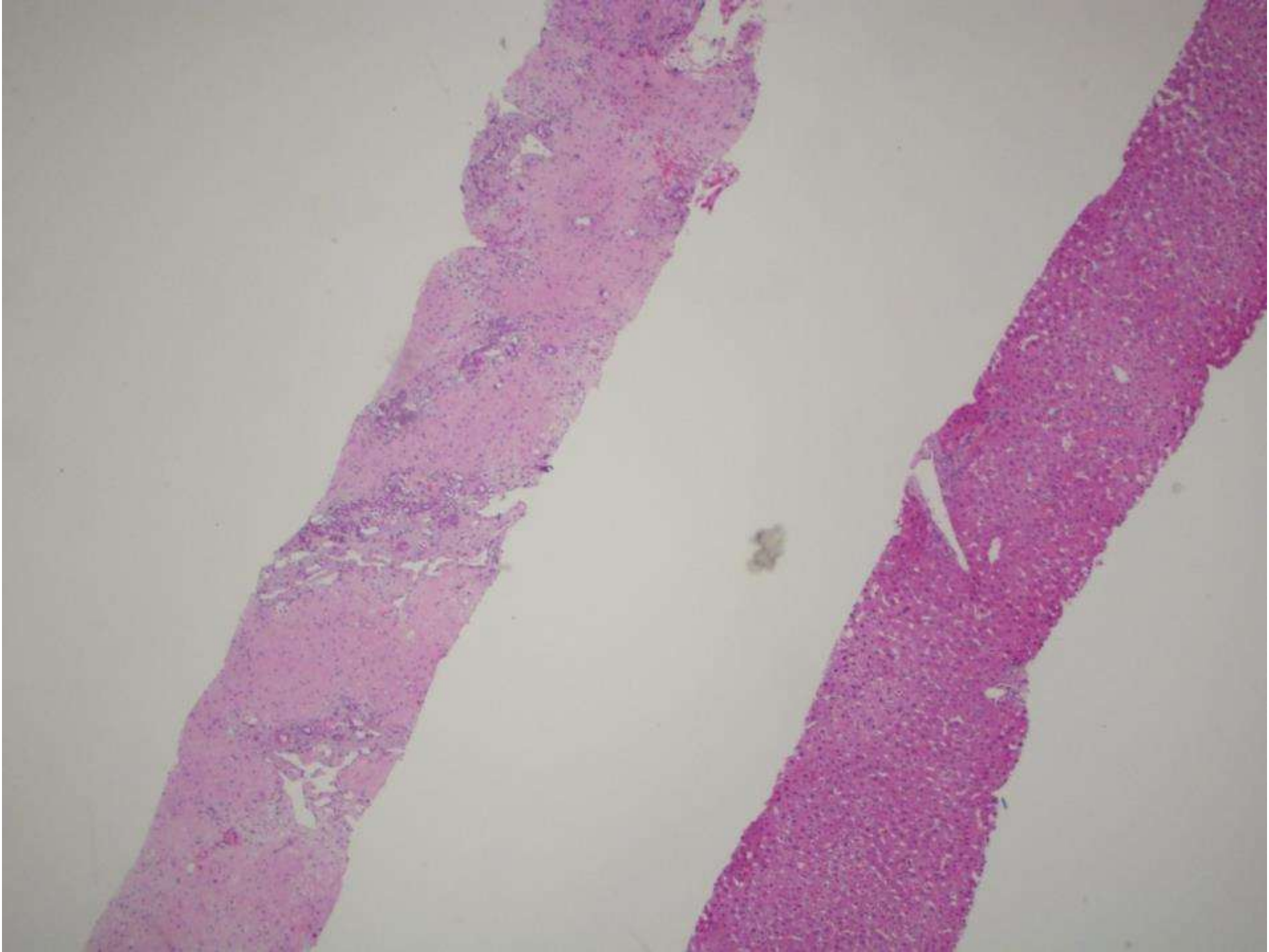


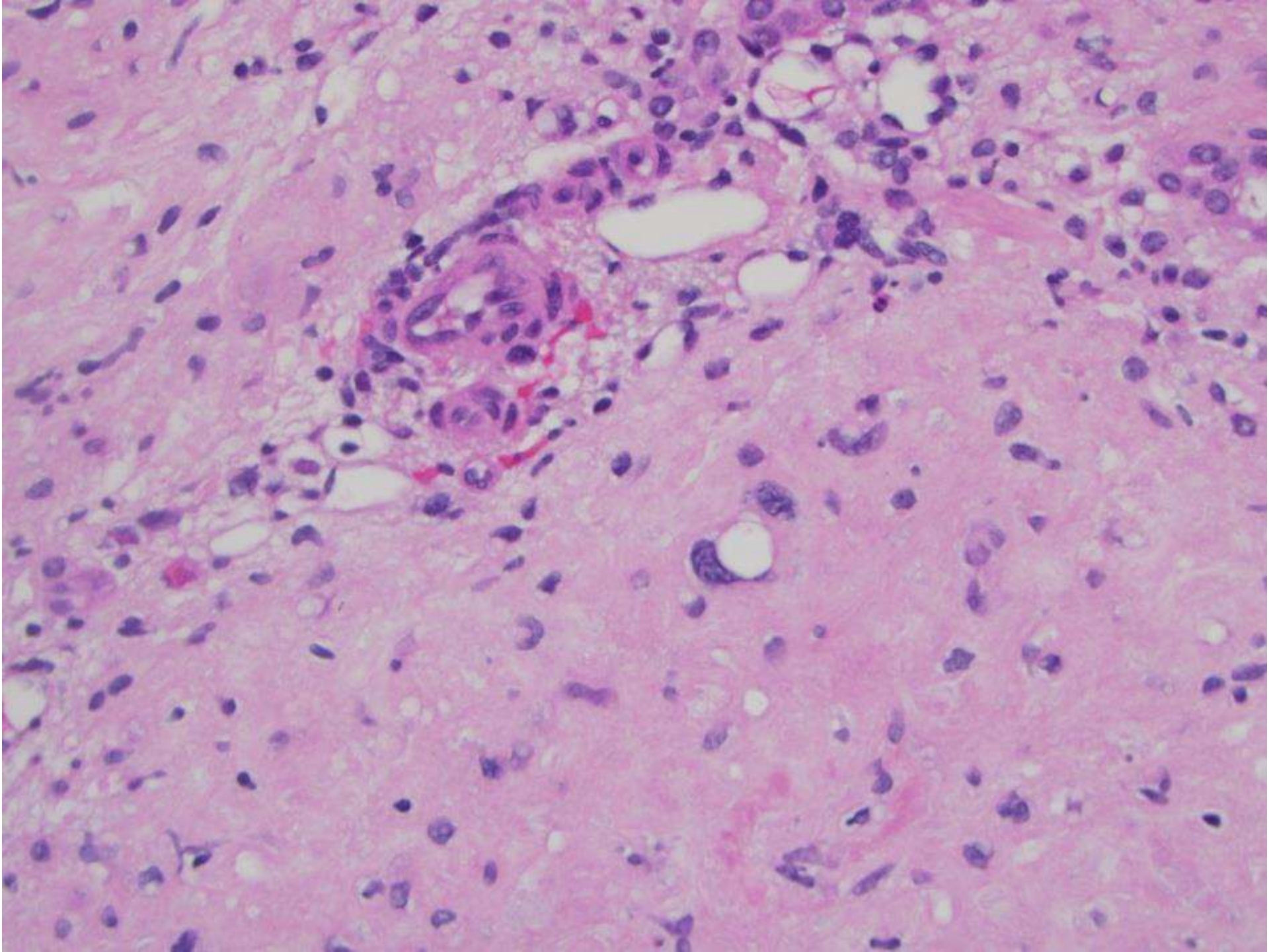



TTF1/napsin


CD31/34


ERG

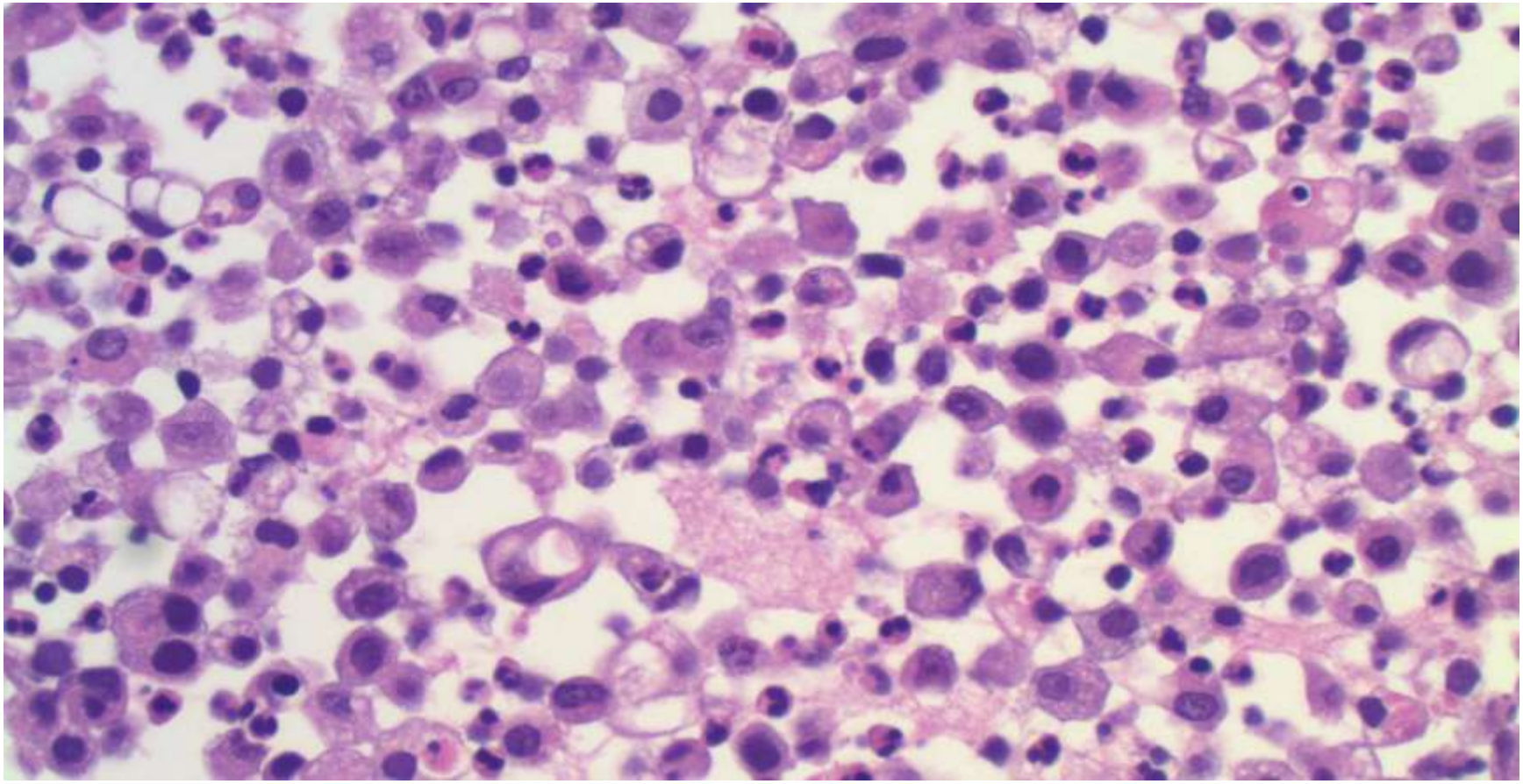




# Diagnosis

- Epithelioid hemangioendothelioma

Histiocytes, mesos, inflammatory
Should I stain it though?
What time is it? What day is it?
I'm tired and don't want to think so I'll just stain it for everything.
It's Friday and I'm leaving town tomorrow so I'll just sign it out.
Mesos and histiocytes can have vacuoles.
But could they be signet ring cells?



Histiocytes, mesos, inflammatory

Should I stain it though?

What time is it? What day is it?

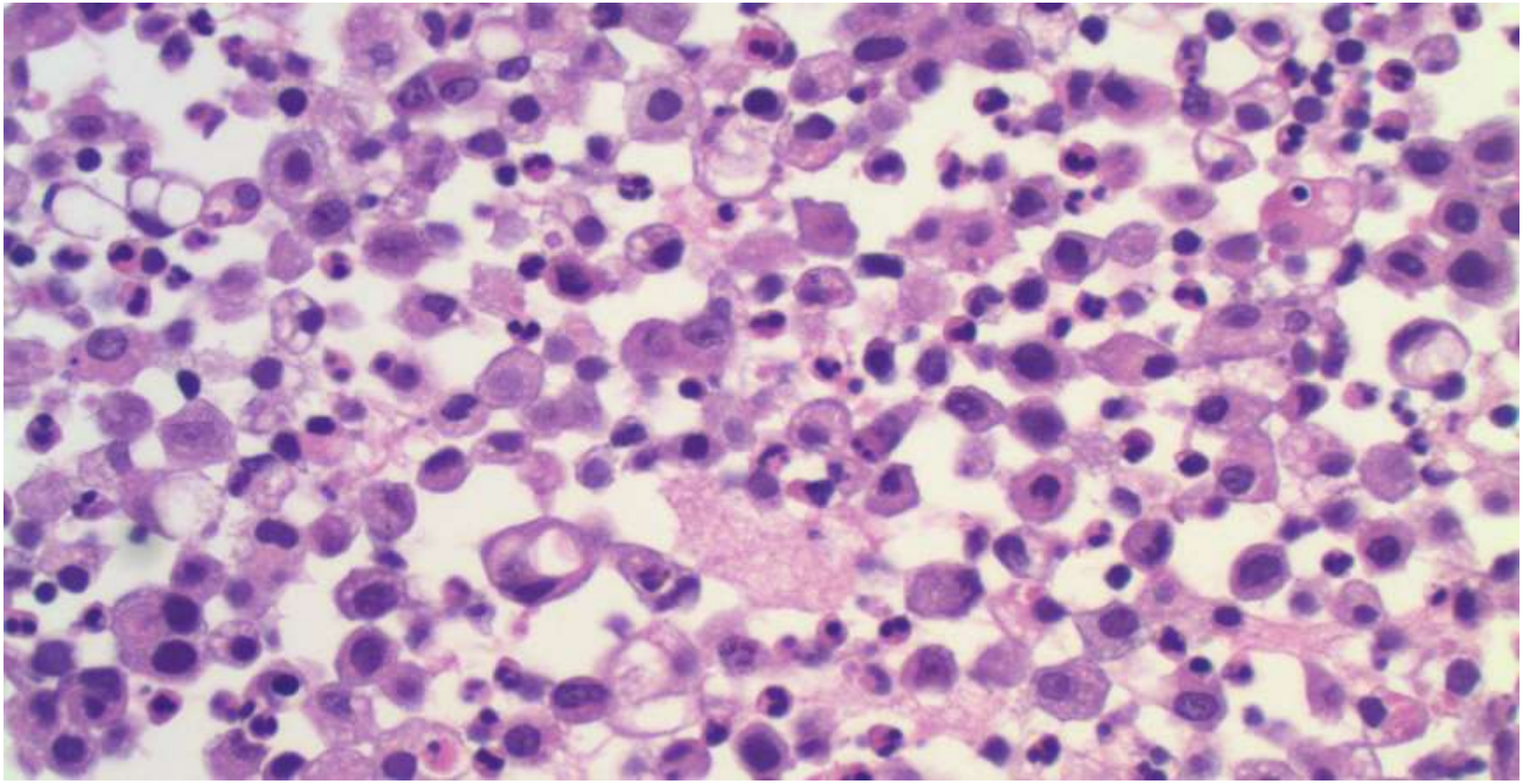
I'm tired and don't want to think so I'll just stain it for everything.

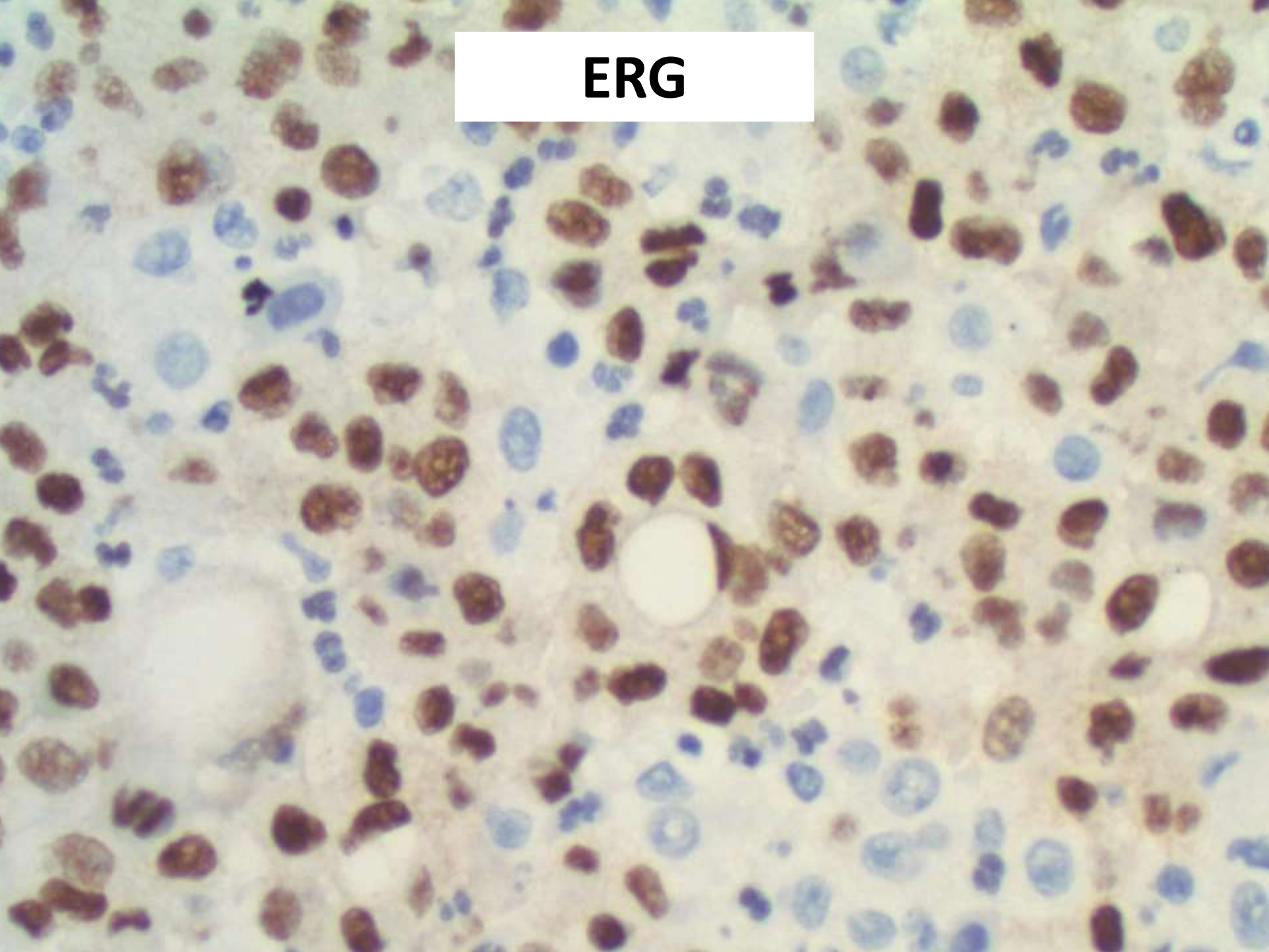
It's Friday and I'm leaving town tomorrow so I'll just sign it out.

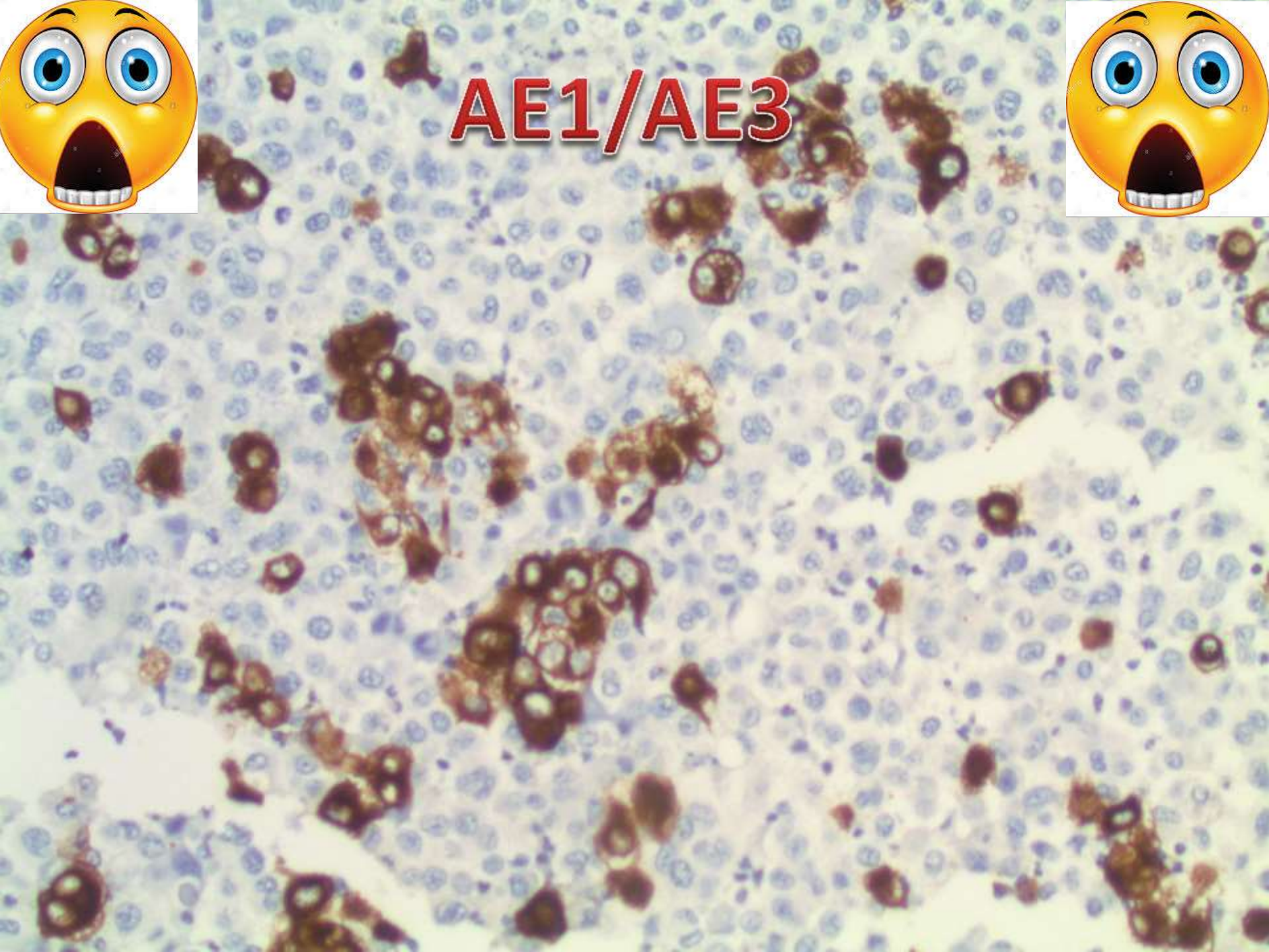
Mesos and histiocytes can have vacuoles.

But could they be signet ring cells?

# ORDER ERG STAIN




ERG


AE1/AE3

# “But can you call it?”

- Pleural fluid, cytology:
  - Involved by metastatic epithelioid hemangioendothelioma

# Conclusion

- The work-up
  - ✓Clinical history
  - ✓Immunohistochemistry
- The most important part of the job
  - ✓The diagnostic stain is positive and I ruled out other things so I'm good
  - ✓It's positive with what they had before
- The stuff that comes with the job
  - ✓I did what my colleagues would have done
  - ✓Consensus agreement
- The stuff that keeps you up at night
  - – Time will tell

# Immunohistochemistry

- **Positive**
  - CD31
  - CD34
  - ERG
  - FLI1
  - Factor VIII
- Podoplanin/D2-40
- AE1/AE3 (up to 38%)
- SMA

- **Negative**
  - Calretinin
  - WT1
  - TTF1/napsin
  - MOC31
  - BerEP4
  - CD68
  - P40
  - CK5/6
  - EMA

# Immunohistochemistry

**Table 2. Summary of Immunohistochemical Results for Epithelioid Hemangioendothelioma and Metastatic Carcinoma***

| | Fli-1 | Cytokeratin | CD34 | CD31 | Podoplanin |
|---|---|---|---|---|---|
| *P* | <.001 | .01 | .005 | .01 | >.99 |
| EHE (n = 13), % | 100 | 38 | 85 | 100 | 54 |
| MCA (n = 13), % | 15 | 100 | 15 | 38 | 31 |
| Lung (n = 5), % | 20 | 100 | 0 | 80 | 40 |
| Breast (n = 4), % | 0 | 100 | 25 | 0 | 50 |
| Kidney (n = 3), % | 0 | 100 | 33 | 33 | 0 |
| Bladder (n = 1), % | 100 | 100 | 0 | 0 | 0 |

* Positive cytokeratin staining reflects cellular expression of cytokeratins recognized by a cocktail of monoclonal antibodies (AE1, AE3, and 5D3). EHE indicates epithelioid hemangioendothelioma; MCA, metastatic carcinoma.

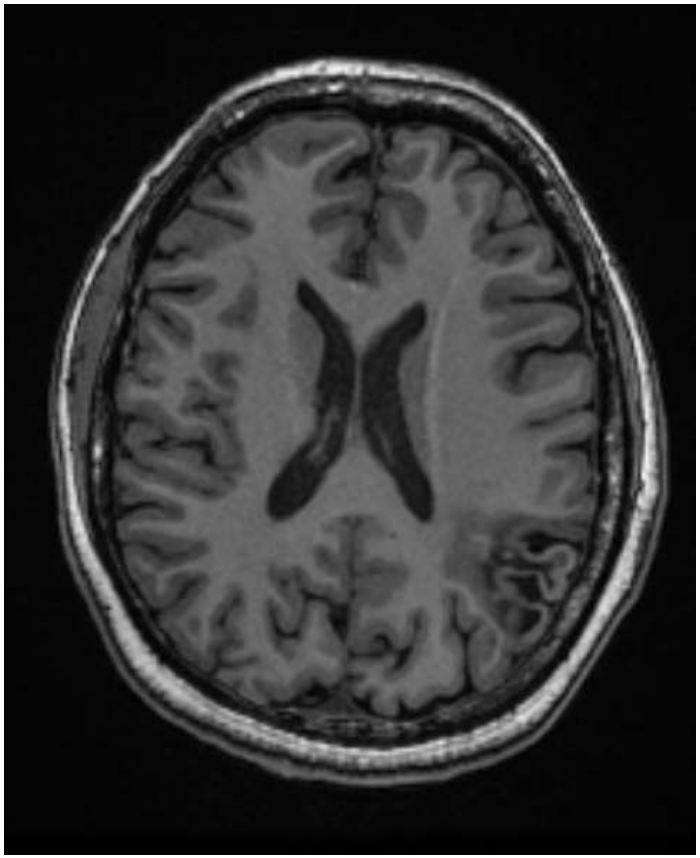
Gill, R. Archives of Pathology and Laboratory Medicine, June 2009, vol 133, no 6.

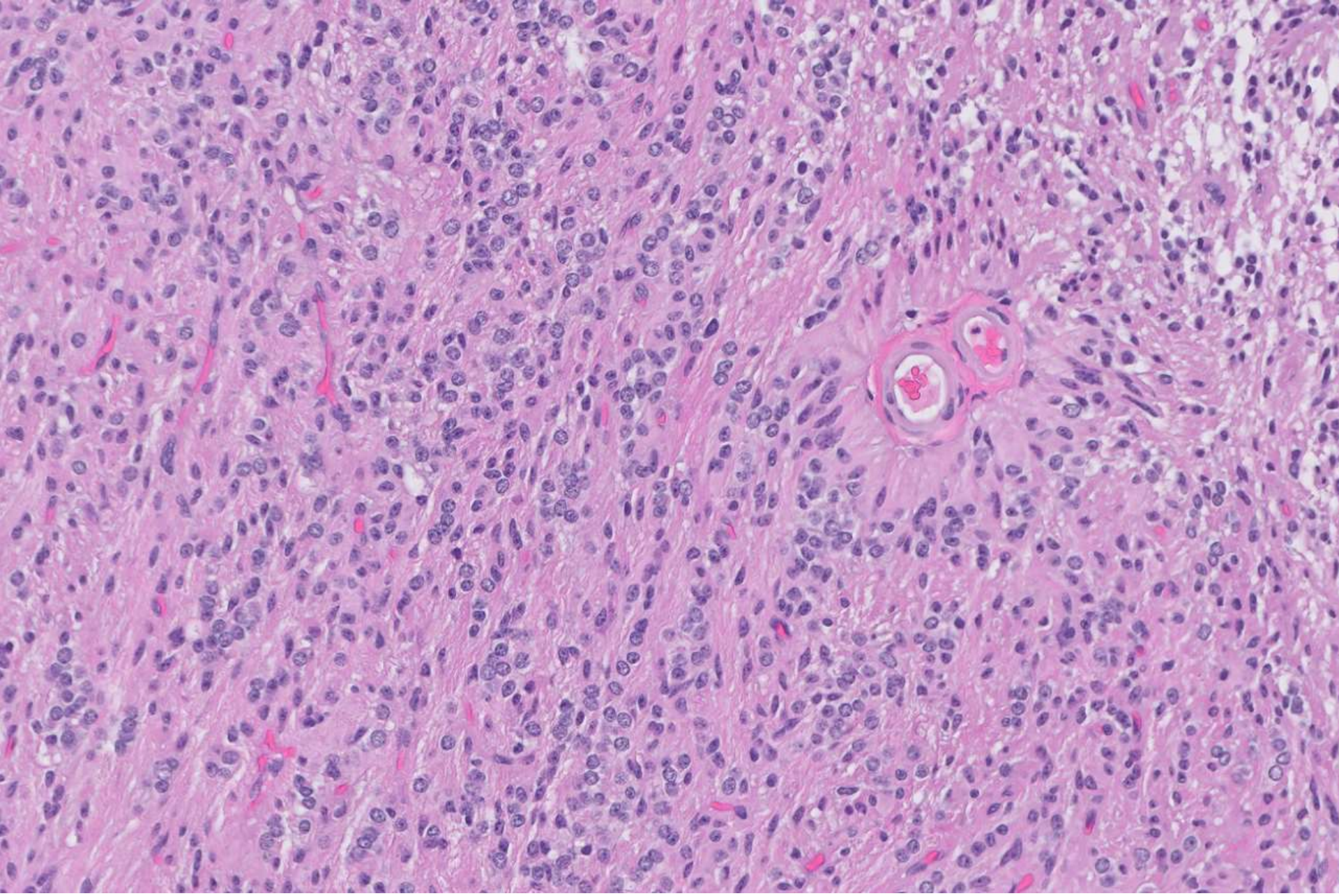
# SB 6347

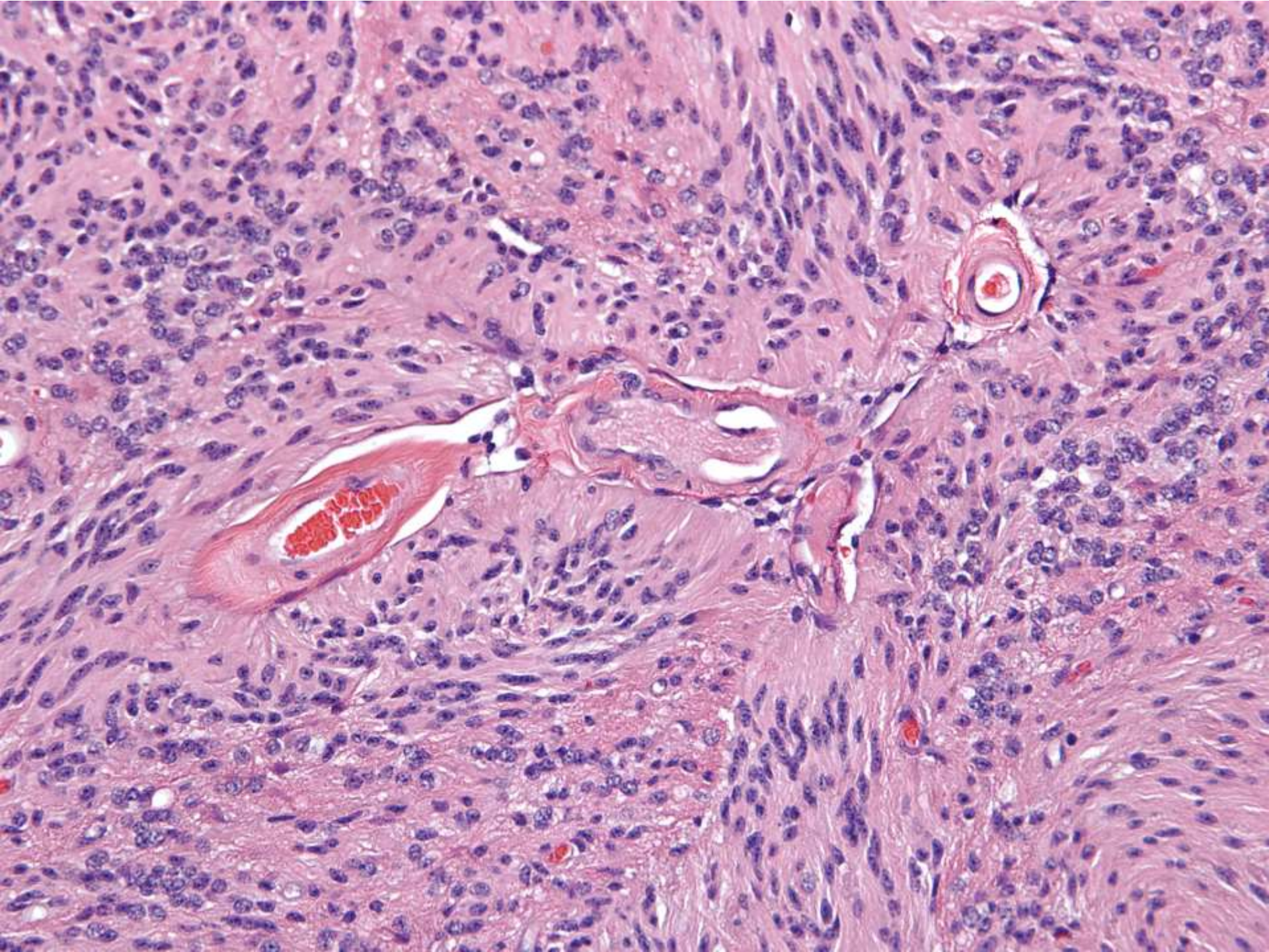
**Hannes Vogel; Stanford**

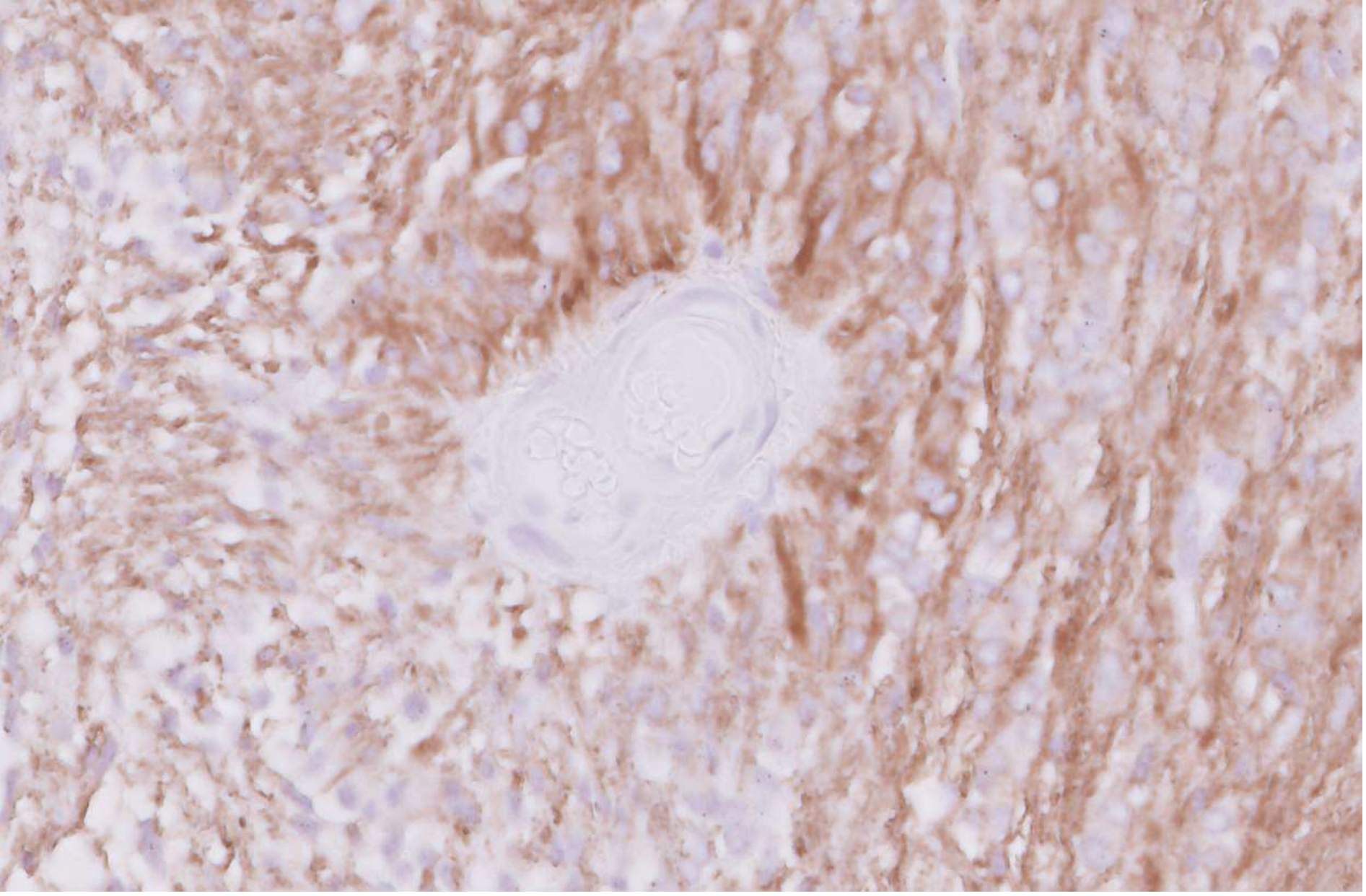
39-year-old female with a history of seizures dating back to age 15, possibly related to head trauma in her youth. An MRI from 2016 demonstrates encephalomalacia in the left parietal lobe.

39-year-old female with a history of seizures dating back to age 15, possibly related to head trauma in her youth.  An MRI from 2016 demonstrates encephalomalacia in the left parietal lobe.

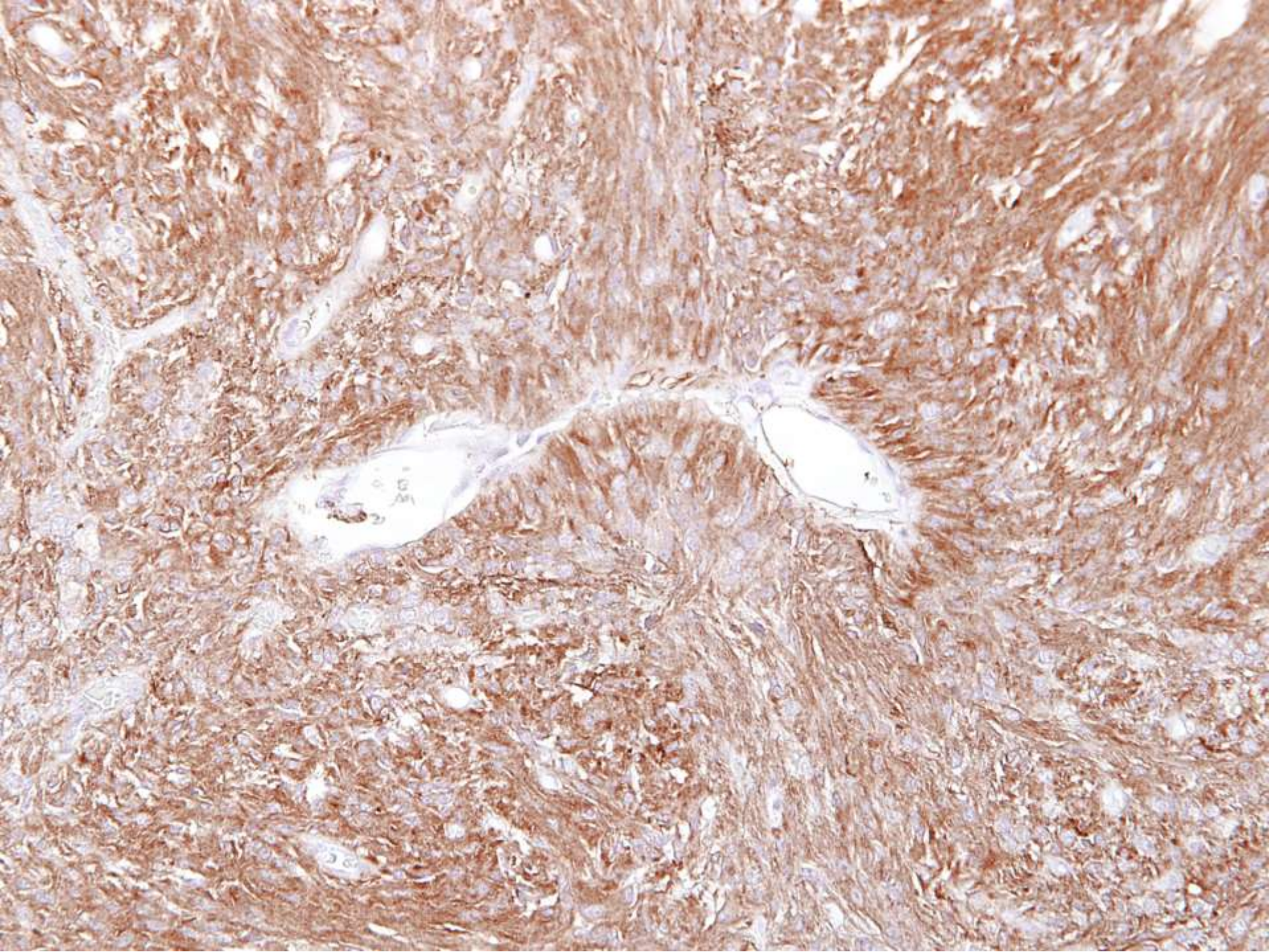


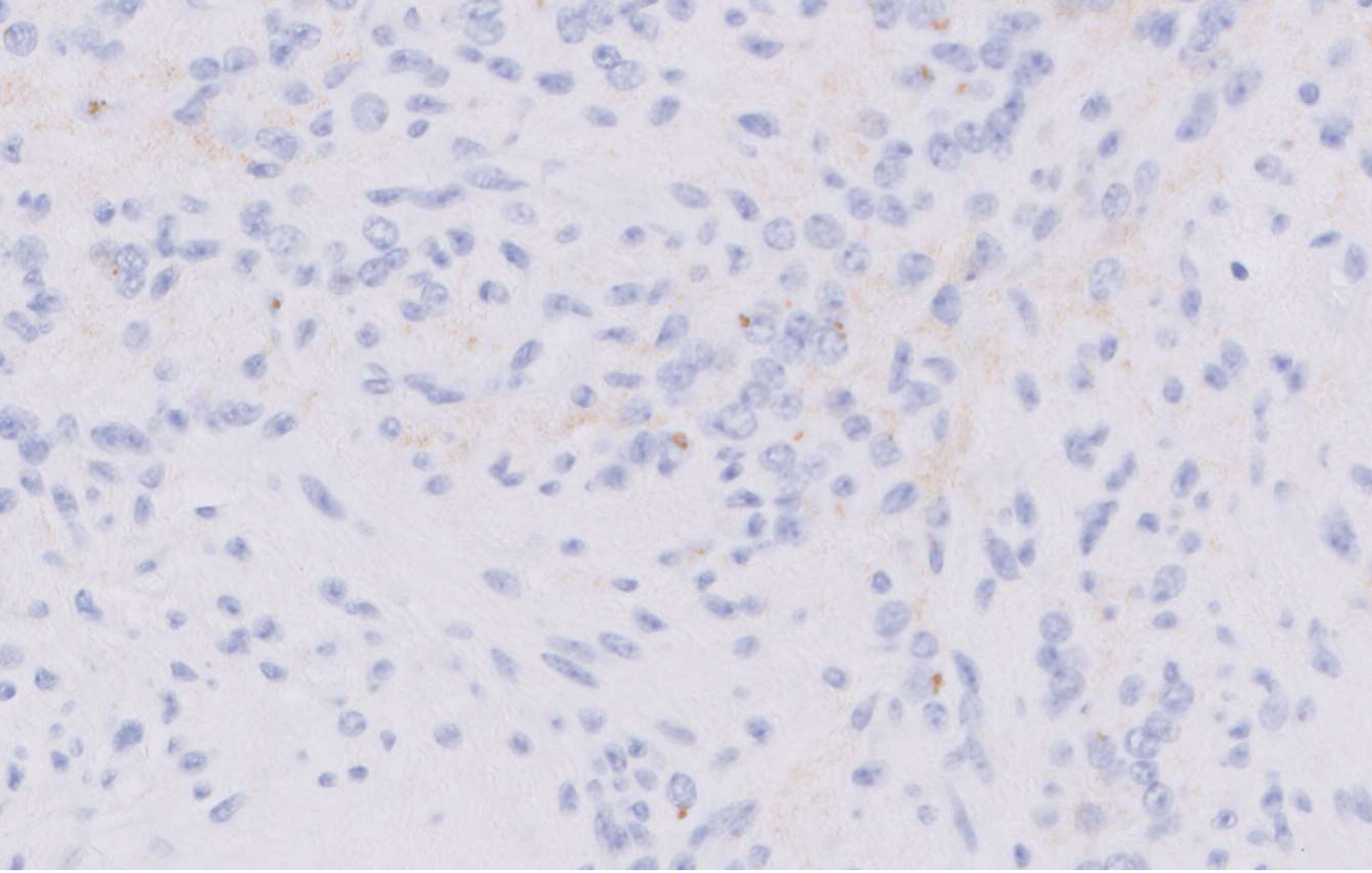




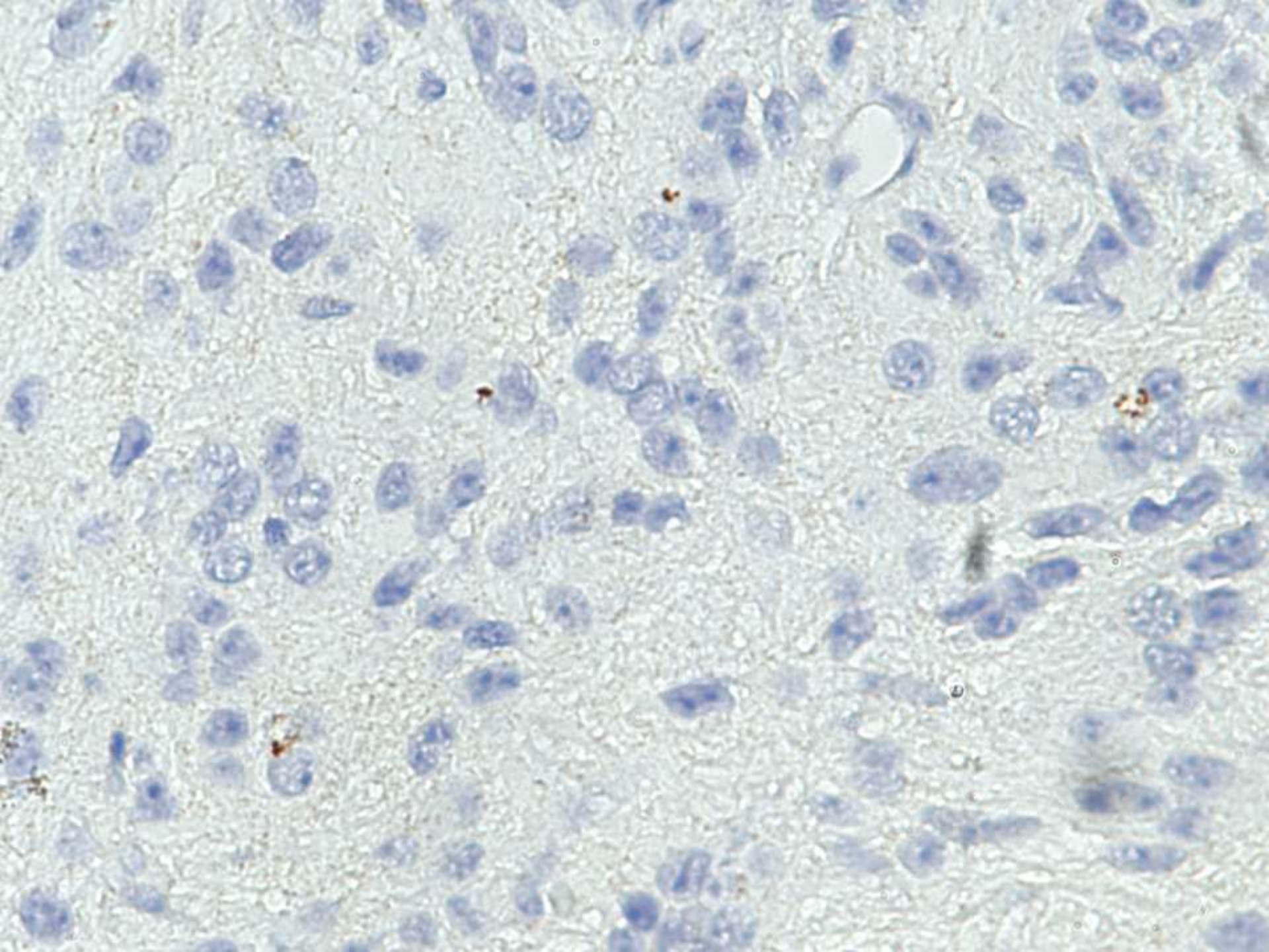


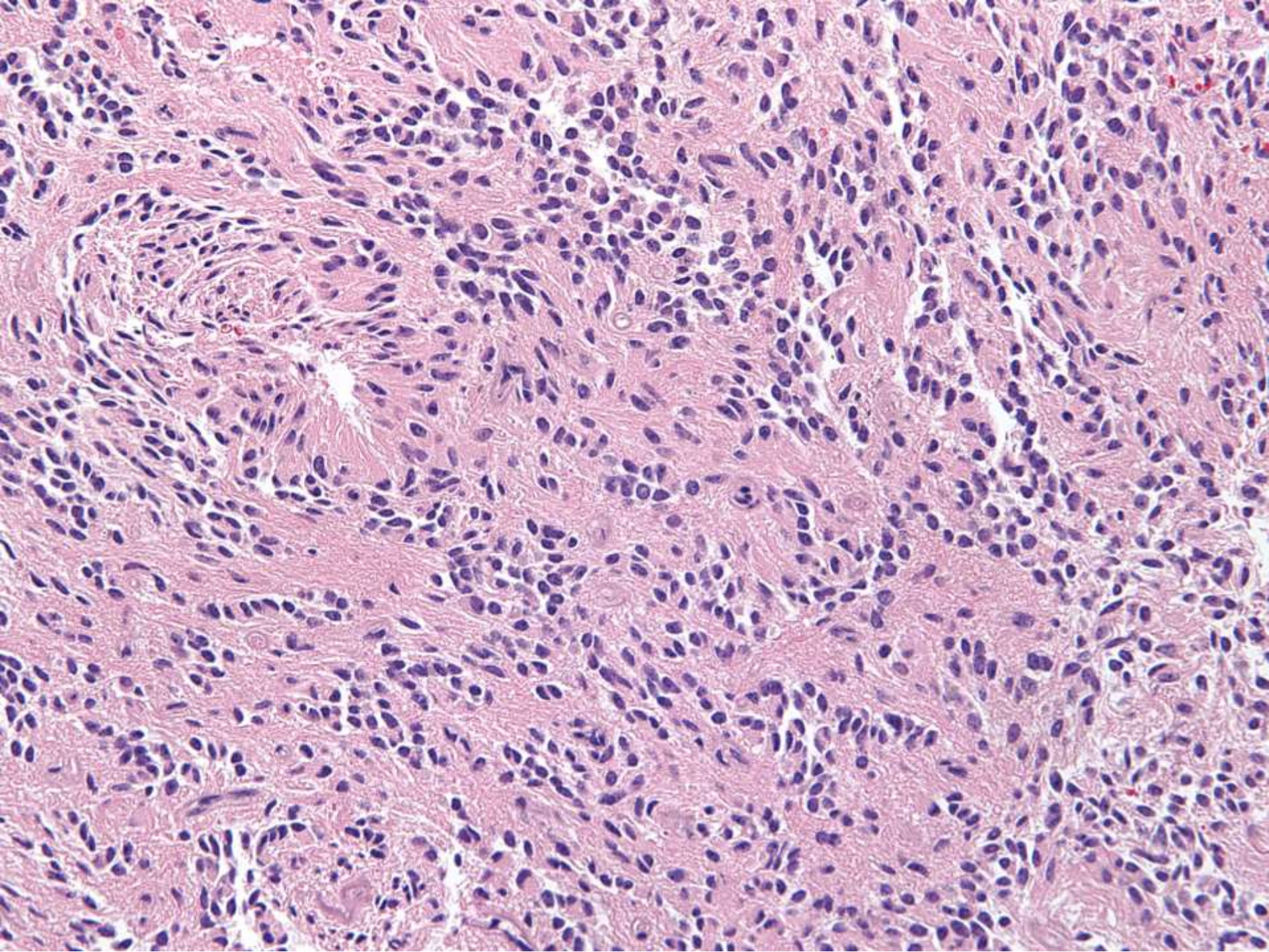
GFAP

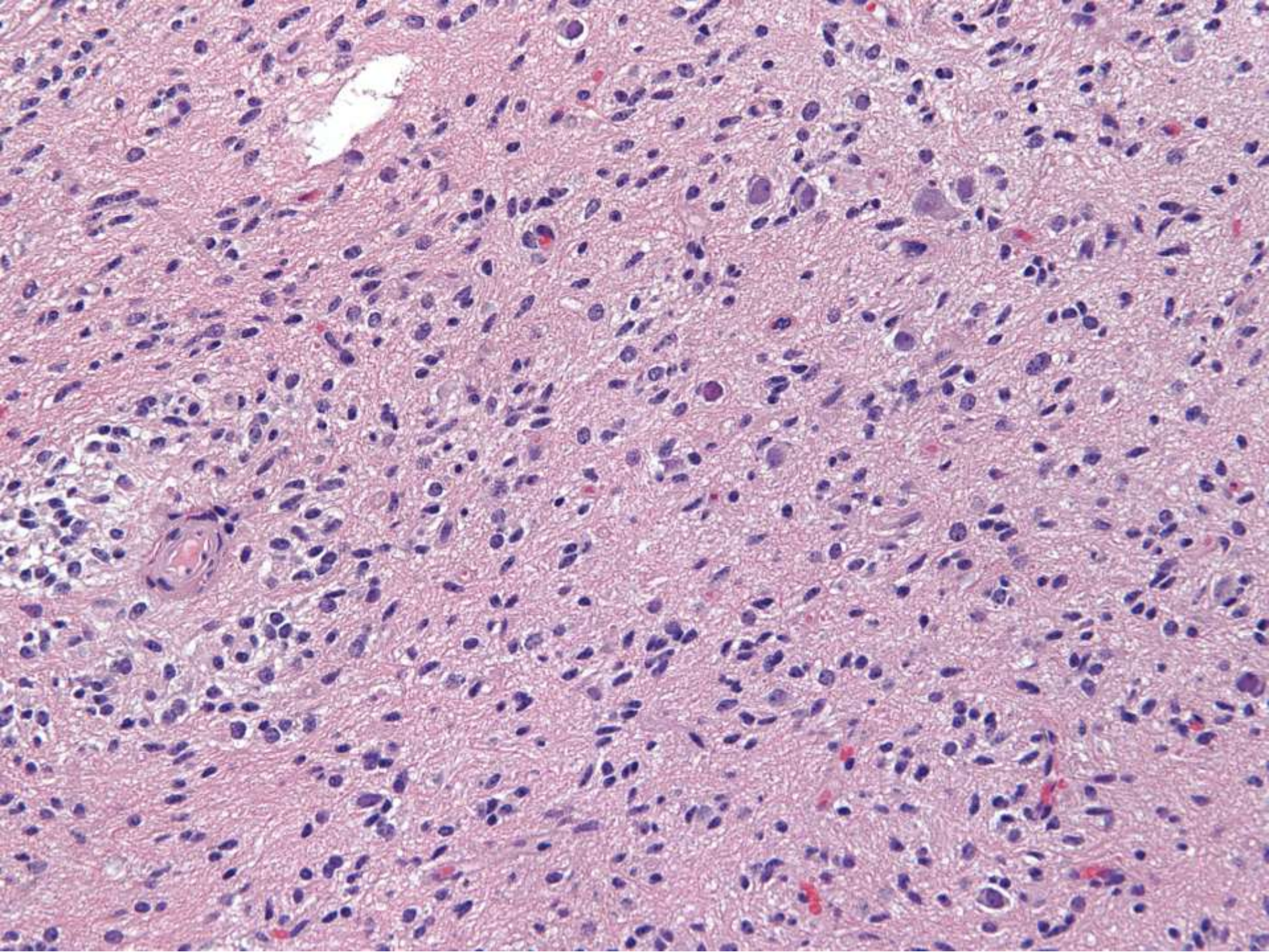


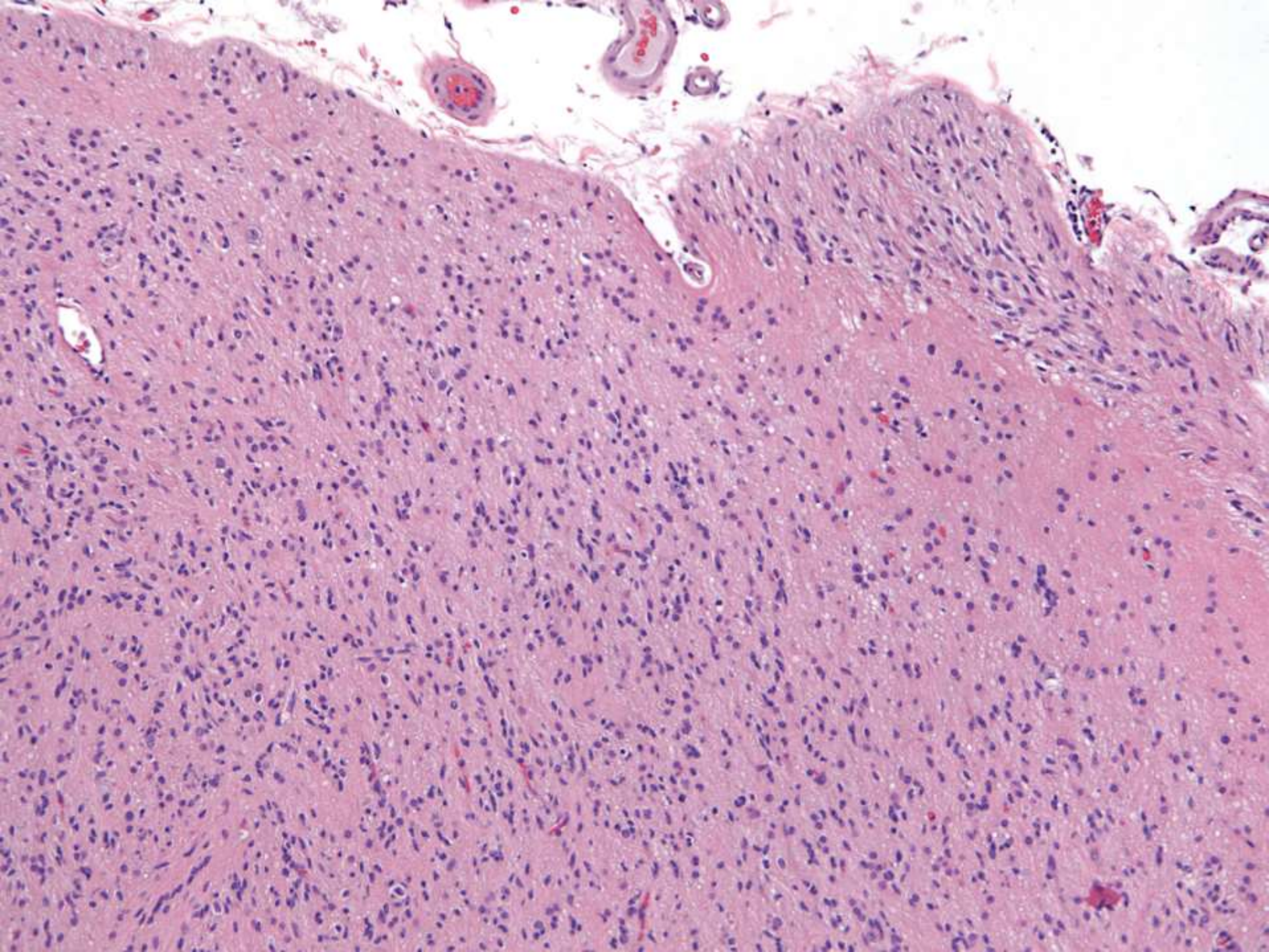


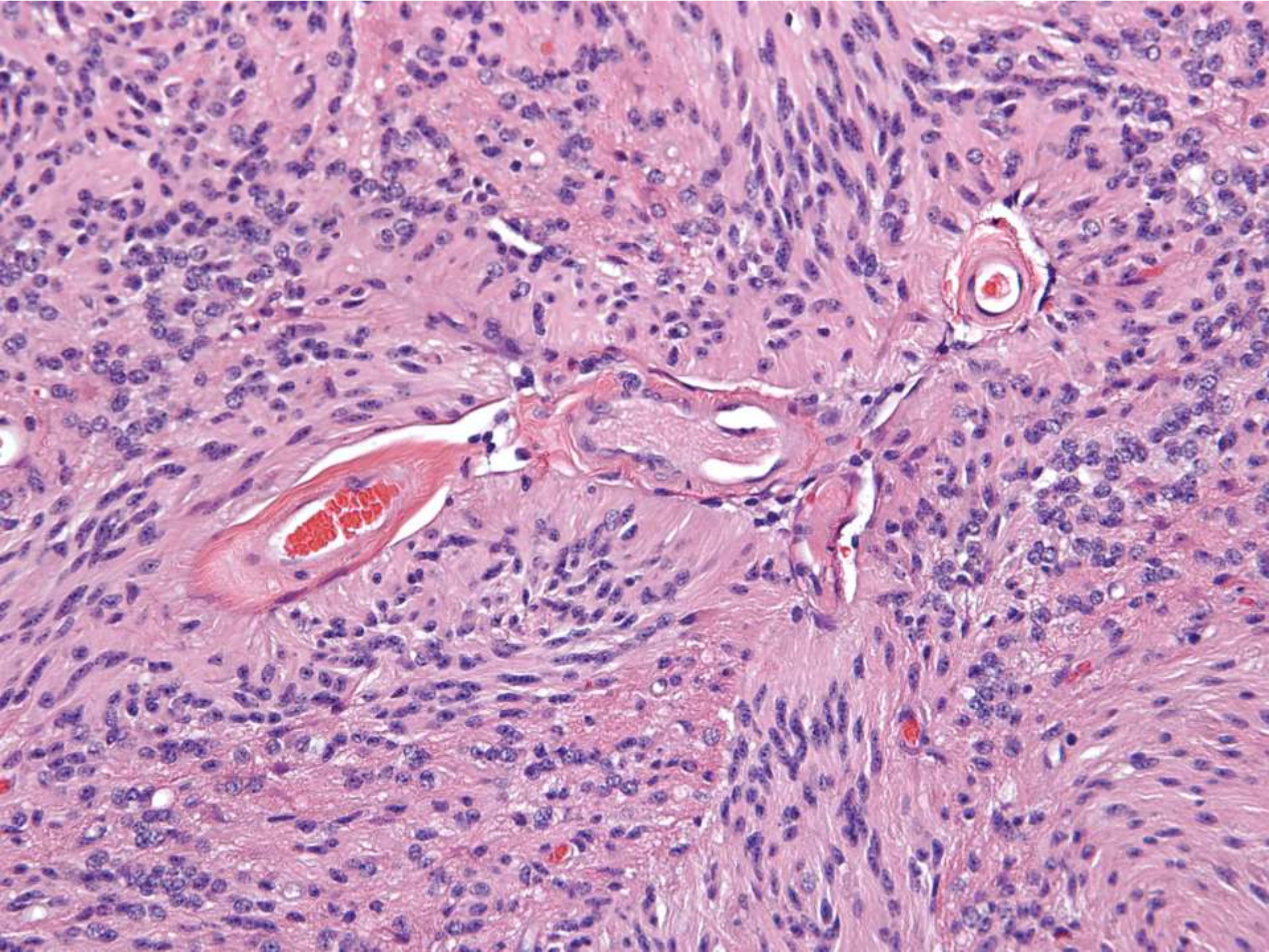
EMA

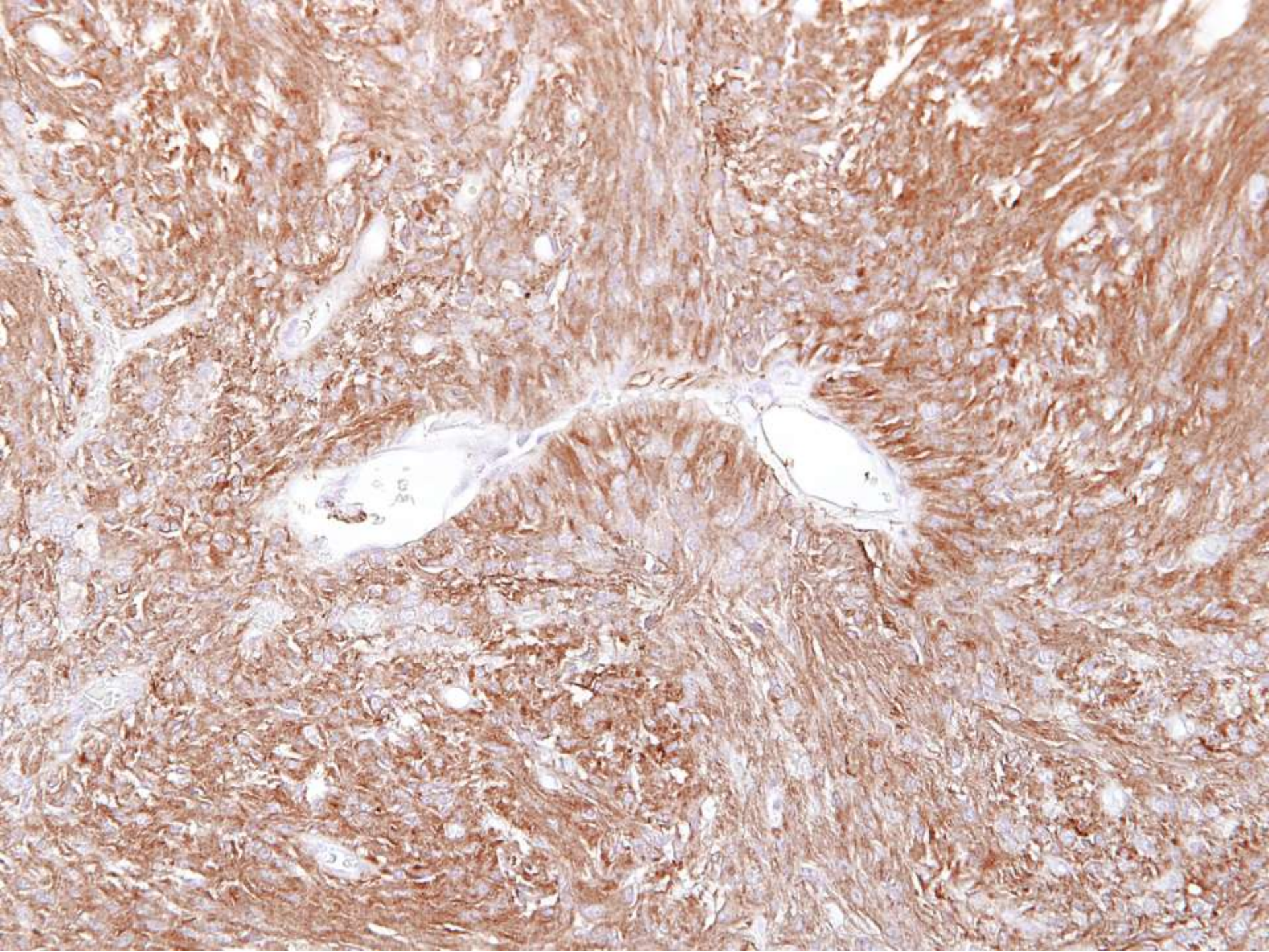


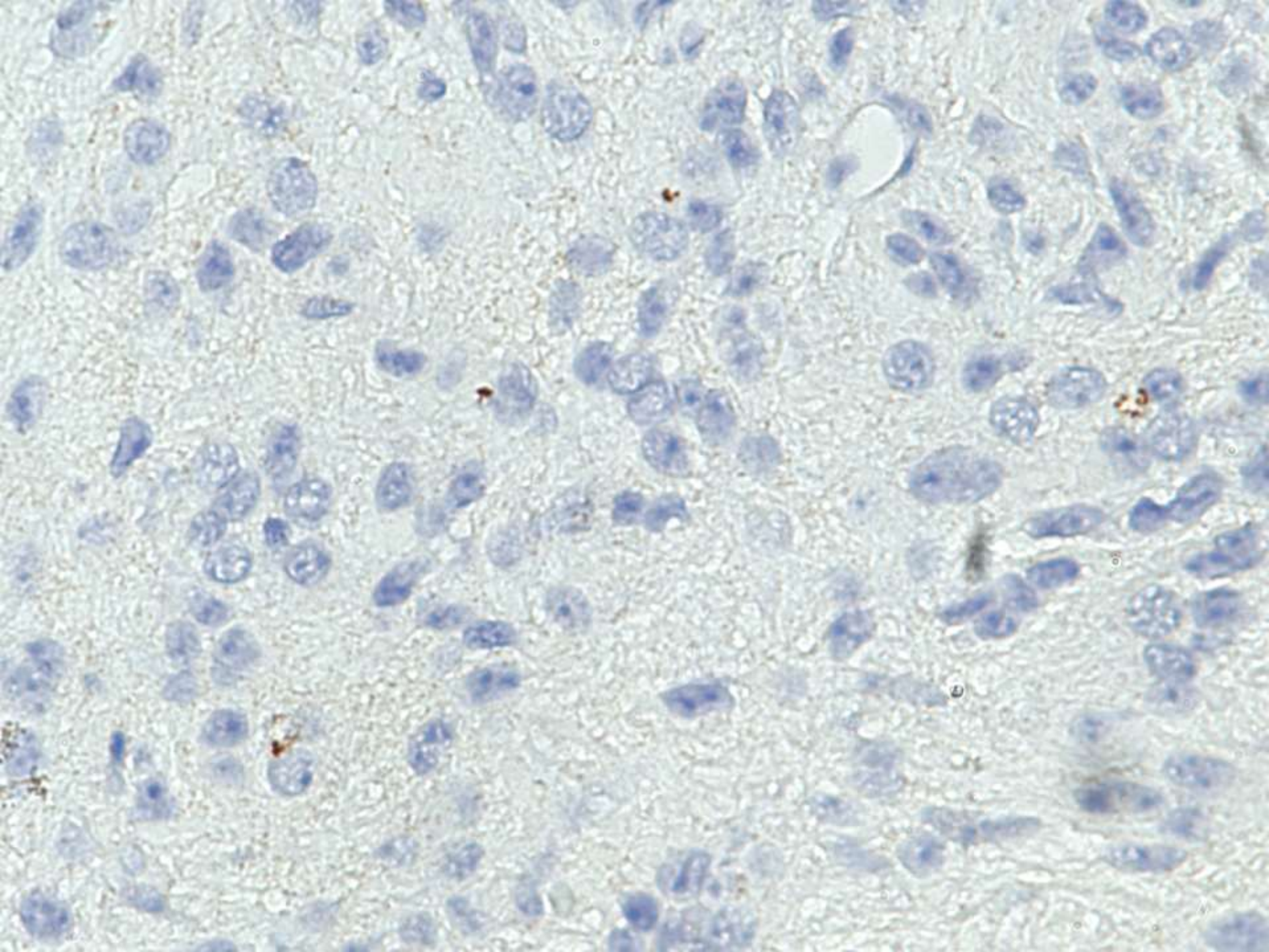












**Epileptogenic tumors**

Usually involve the cortex
Pilocytic astrocytoma
Astrocytoma WHO grade II-IV
Oligodendrogliomas
Ganglioglioma, other ganglion cell tumors
Other glioneuronal tumors (papillary, etc.)
Dysembryoplastic neuroepithelial tumor (DNET)
Angiocentric glioma
PXA
Astroblastoma
Meningiomas

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Angiocentric glioma
PXA
Astroblastoma
Meningiomas

**Astroblastoma**

WHO definition: *" A rare glial neoplasm composed of cells that are positive for GFAP and have broad, non- or slightly tapering processes radiating towards central blood vessels (astroblastic pseudorosettes) that often demonstrate sclerosis."*

Affect children to young adults; ?female predominance
Biological behavior varies; no WHO grade assigned
Well-differentiated (1 mitosis/10hpf) versus malignant (>5 mitoses/hpf)
Majority are supratentorial
Cell of origin most closely akin to astrocytic precursors, possibly tanycytes

# Multimodal molecular analysis of astroblastoma enables reclassification of most cases into more specific molecular entities

Matthew D. Wood [1]; Tarik Tihan[1]; Arie Perry[1,2]; Geeta Chacko[3]; Clinton Turner[4]; Cunfeng Pu[5]; Christopher Payne[6]; Alexander Yu[6]; Serguei I. Bannykh[7]; David A. Solomon [1]

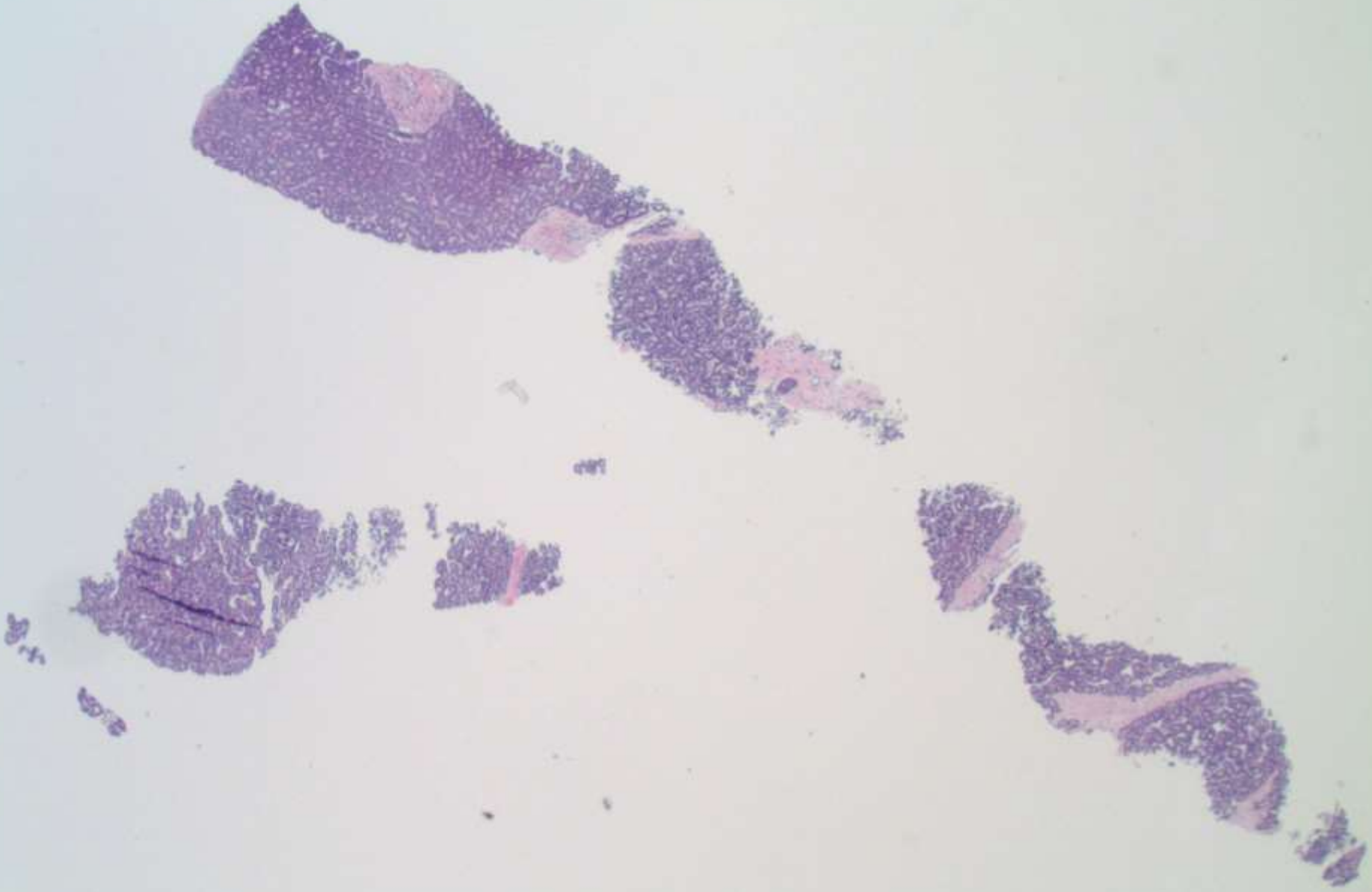
- Recent genomic profiling identified a subset of CNS embryonal tumors with astroblastoma-like morphology that harbored MN1 gene fusions, termed “CNS high-grade neuroepithelial tumors with MN1 alteration” (CNSHGNET-MN1
- NGS of 500 cancer-associated genes in a series of eight cases. FISH analysis of the MN1 locus and genome-wide DNA methylation profiling
- Four cases showed MN1 alteration by FISH
- Two adult cases harbored other cancer-associated gene mutations or copy number
- Three of these cases grouped with the CNS-HGNETMN1 entity by methylation profiling
- Two of four MN1 intact cases by FISH showed genetic features of either anaplastic PXA or IDH-wildtype GBM
- Two clinically indolent cases remained unclassifiable despite multimodal molecular analysis
- Astroblastoma histology is not specific for any entity and additional genetic characterization should be considered for astroblastomas

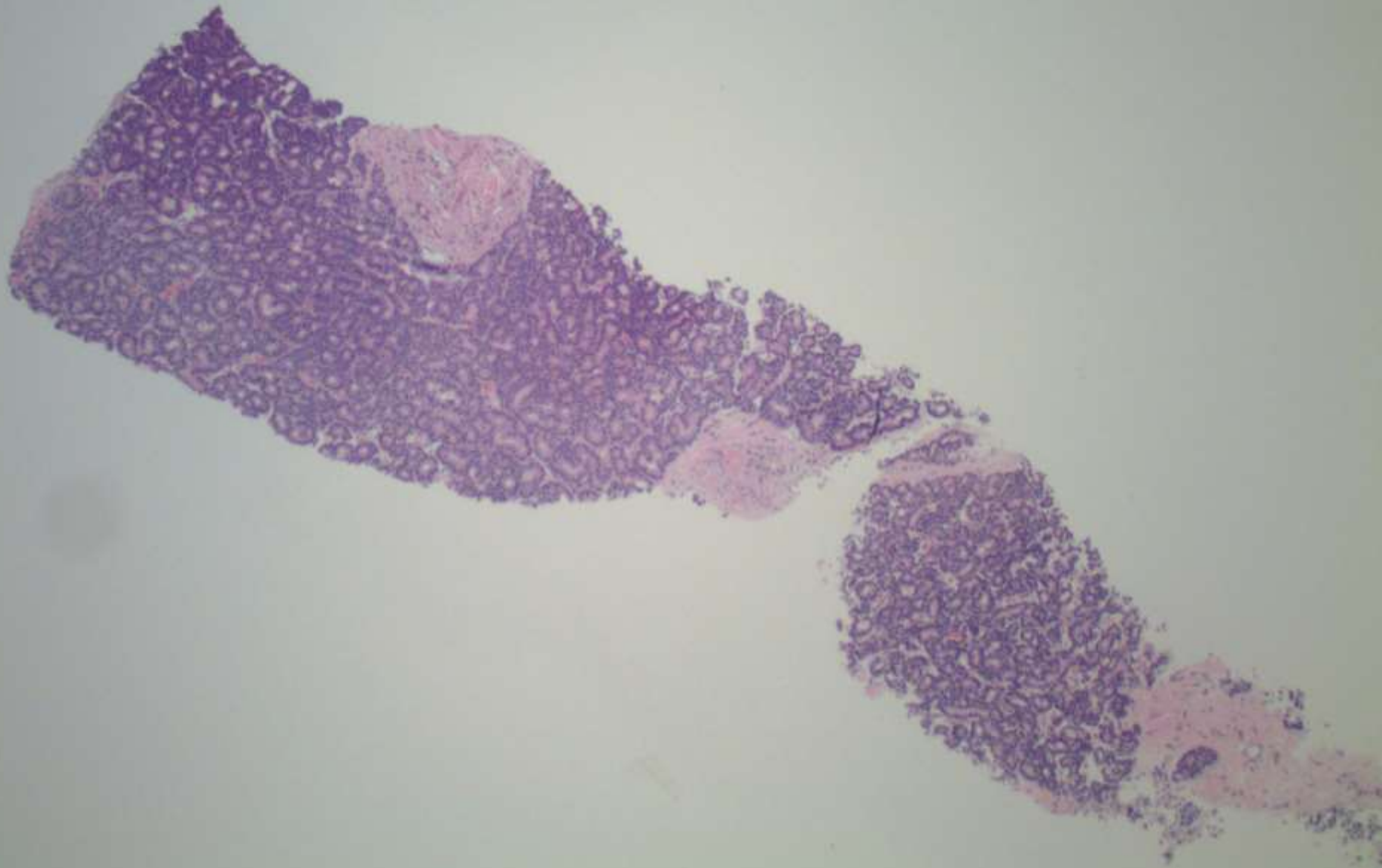
Brain Pathology 28 (2018) 192–202

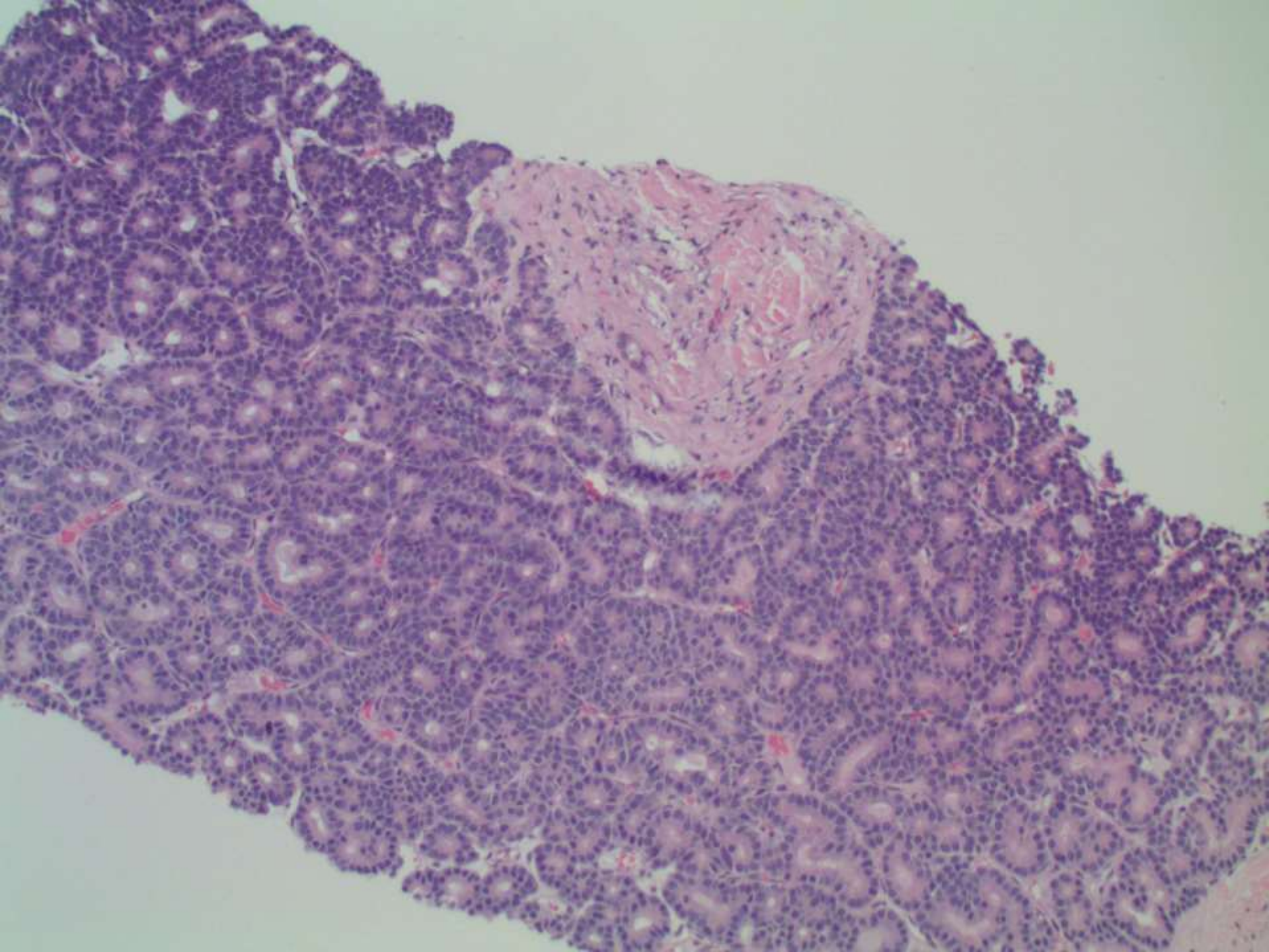
# SB 6348

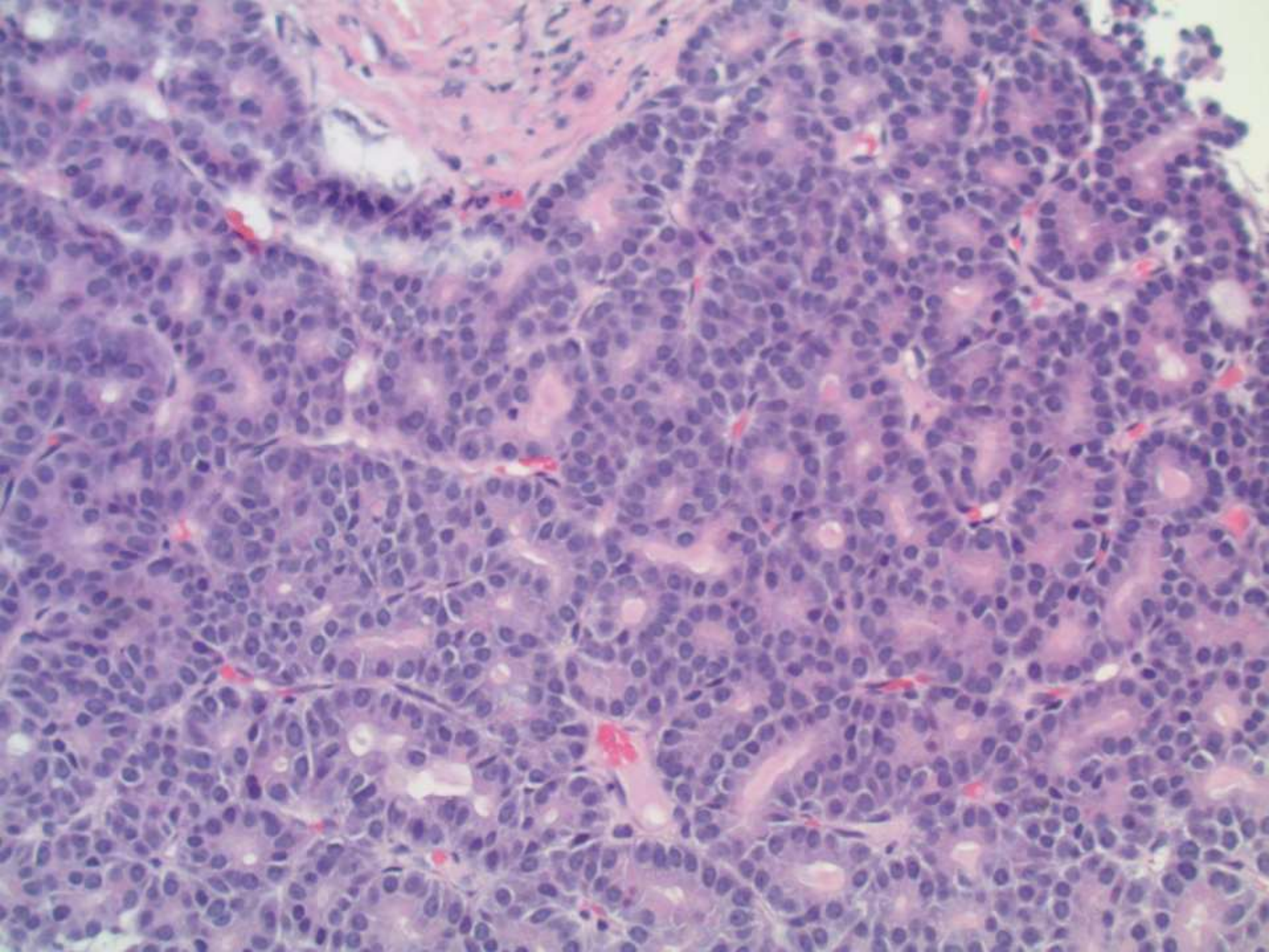
**Mahendra Ranchod; Good Samaritan Hospital**

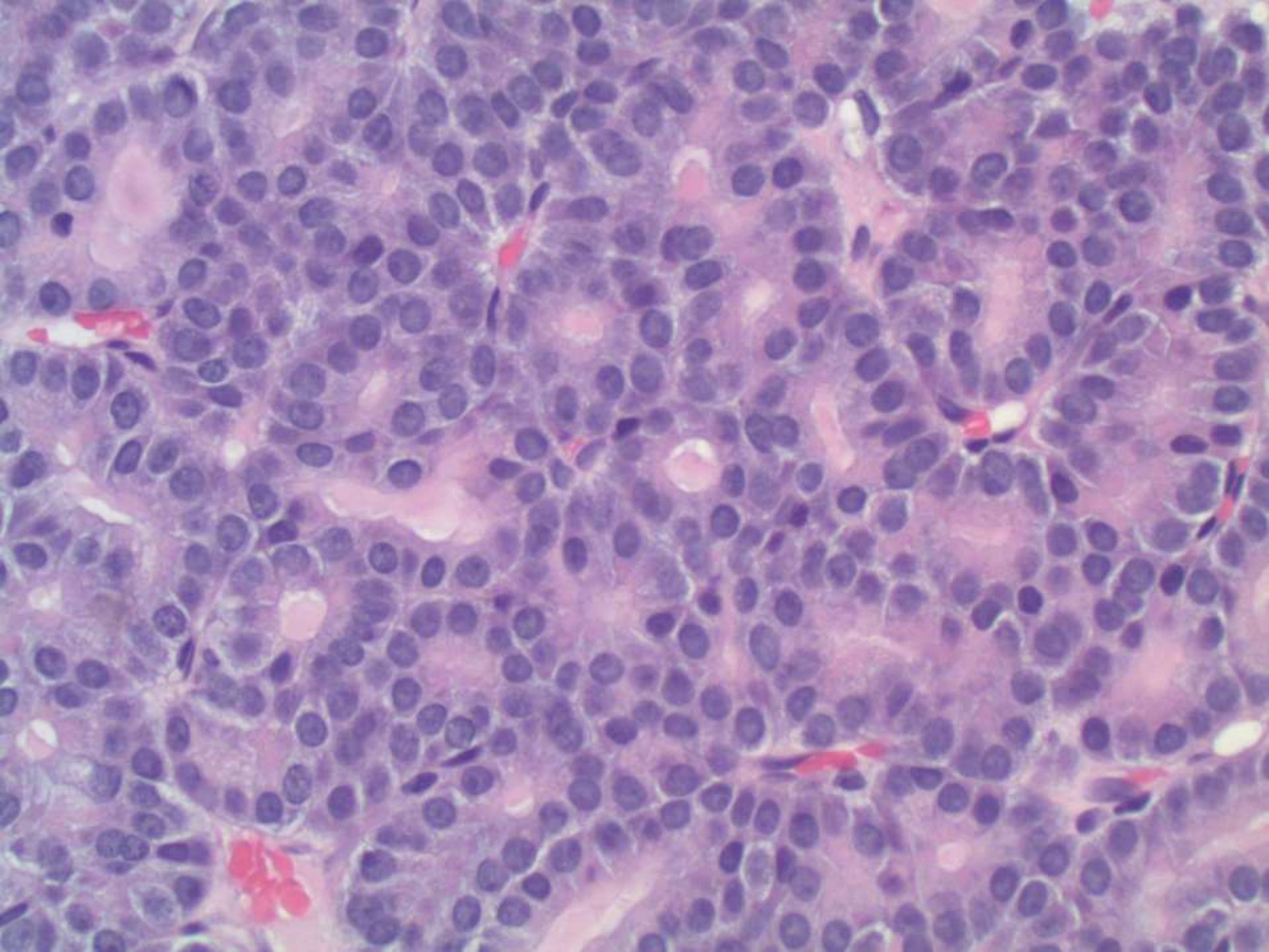
72-year-old male with multiple liver lesions and a pancreatic mass. Liver biopsy performed.











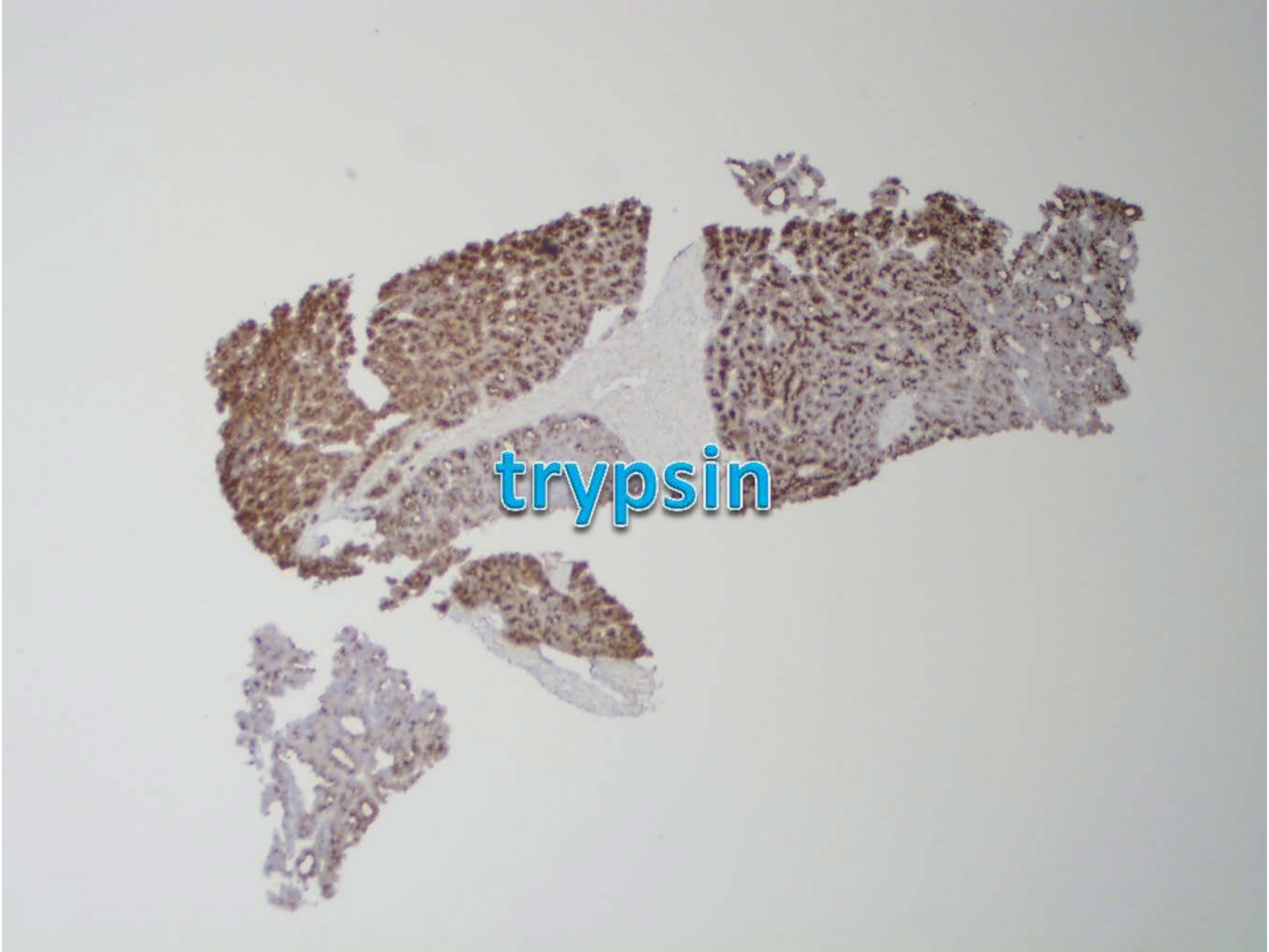
# SBPS 6348 (slide 1)

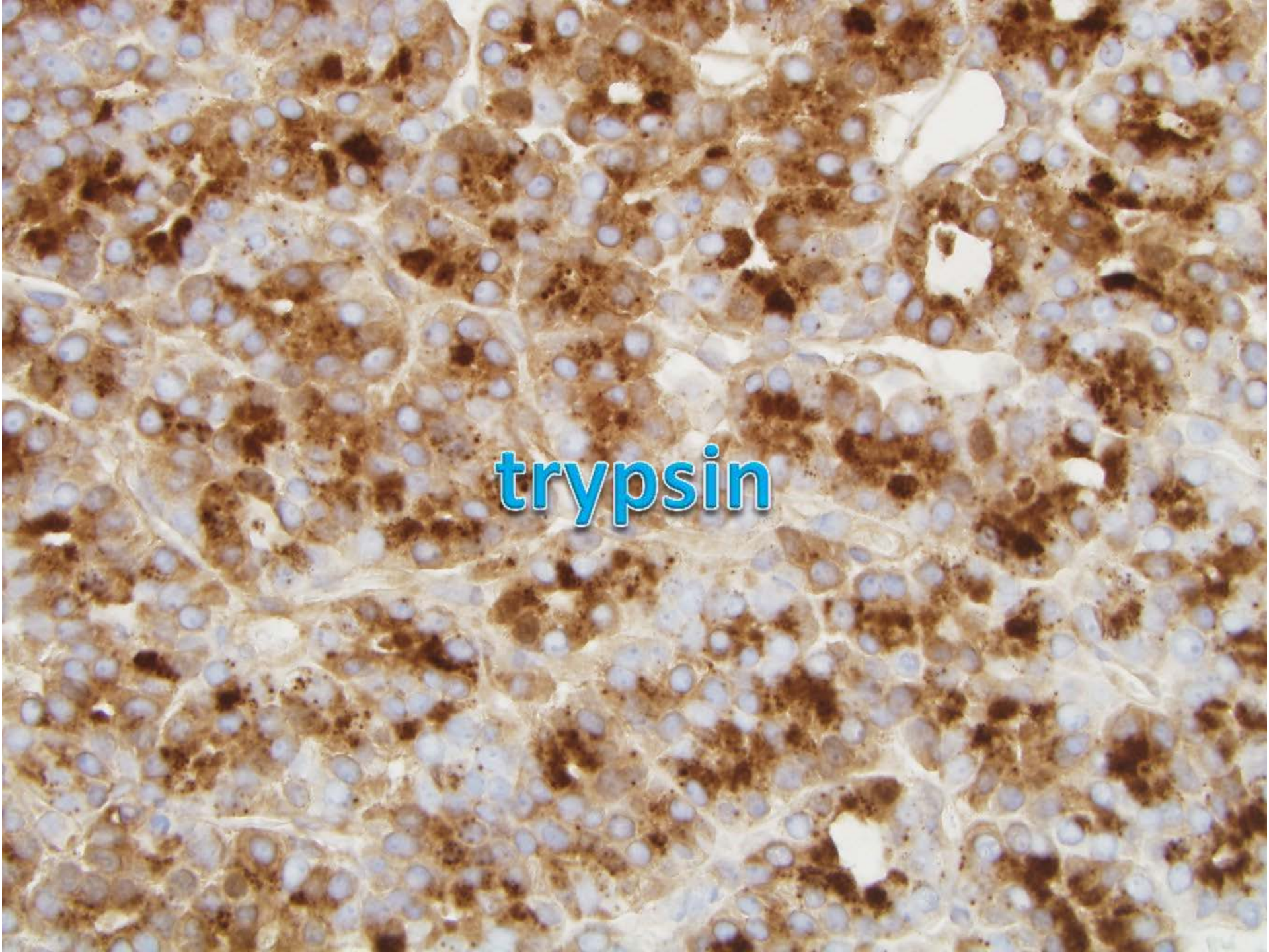
## Initial impression: metastatic well diff NET

- GI bleeding, gastric and duodenal ulcers
- H&E appearance
- ? Gastrin-producing NET

**BUT…….**

- Synapto, chromo, CD56 & PDX-1 stains were negative
- Ki-67 : 80%
- Serum gastrin normal


trypsin


trypsin

# Acinar cell carcinoma of pancreas (slide 3)

- **Lab**
  - **Trypsin IHC : positive**
  - **Lipase IHC : weak positive**
  - **Serum lipase 19,700 u/L**

- **Clinical**
  - **Multiple subcut. nodules**
    **(10% lipase hypersecretory syndrome)**
  - **50% have metastases at time of diagnosis**
  - **5 year survival 10%**

# Acinar cell carcinoma (slide 4)

- **Histology of pure ACC**
  - **Lobular with acinar structures**
  - **Trabecular, glandular, oncocytic, pleomorphic**

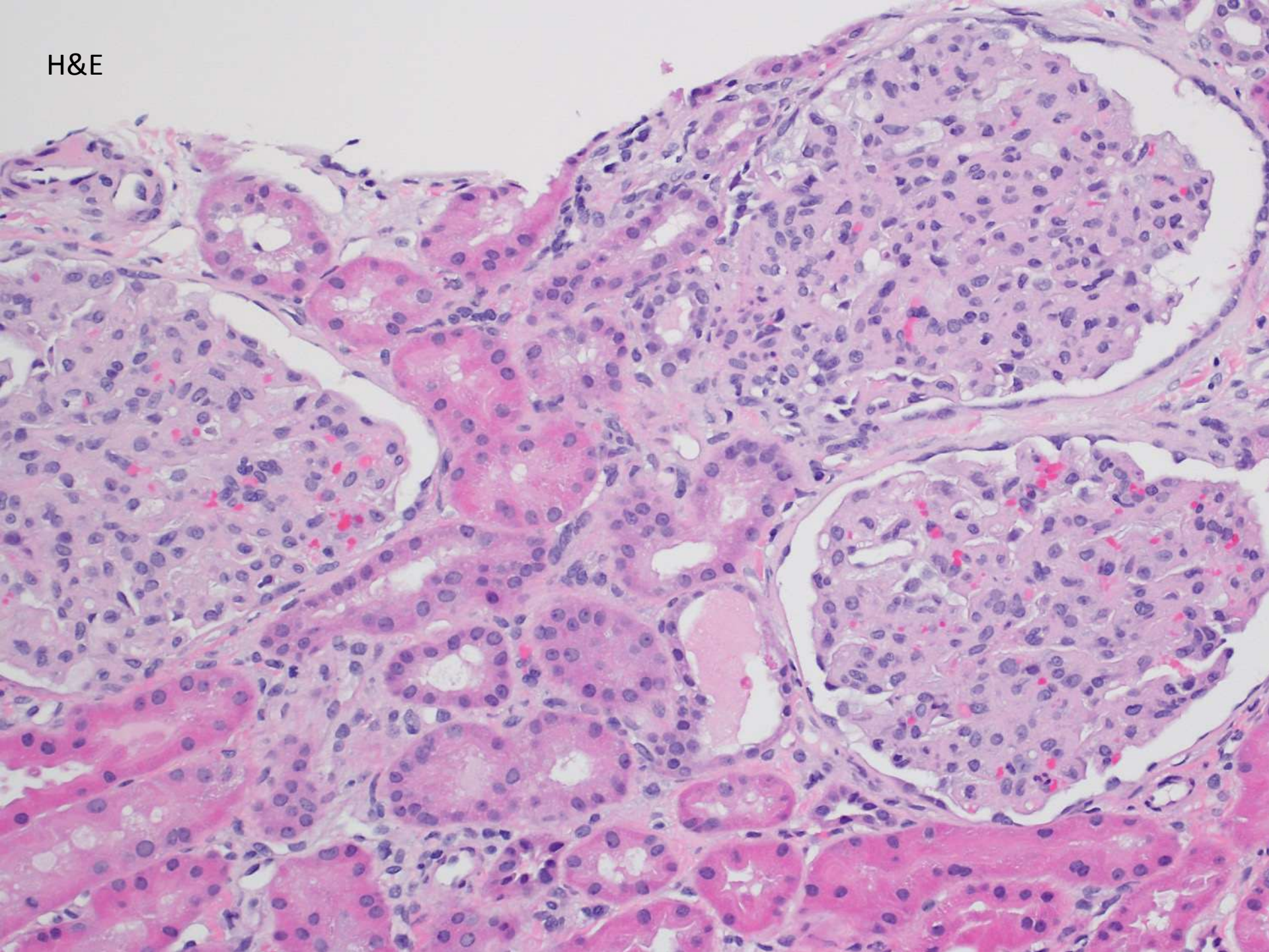
- **Variants**
  - **ACC with scattered endocrine cells**
  - **Mixed acinar-neuroendocrine CA (MANEC)**
  - **Mixed acinar-ductal CA**

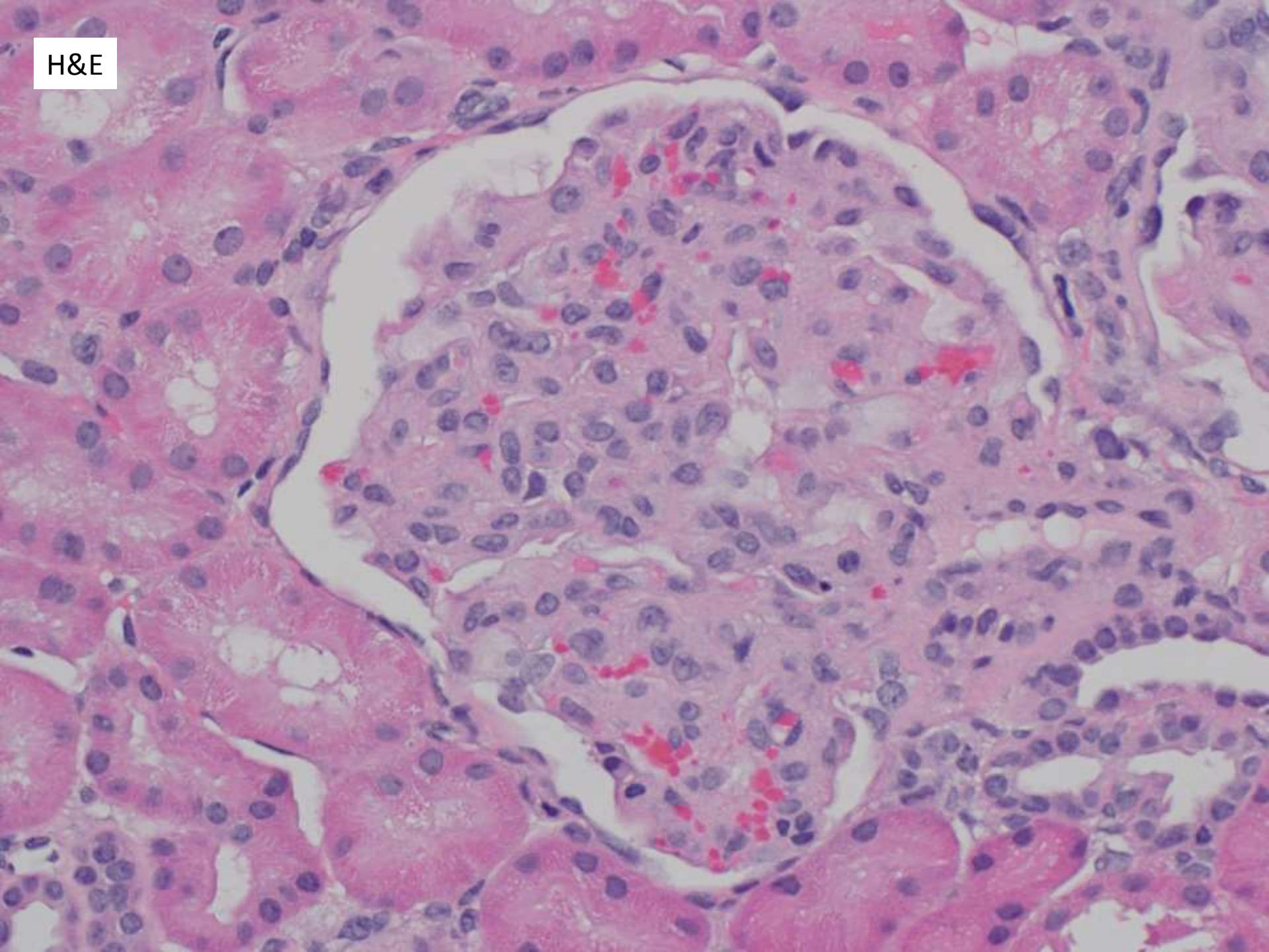
- **About IHC**
  - **Be cautious about positive synapto and chromo stains**
  - **Trypsin + BCL10 best combination for ACC**
  - **Lipase and amylase not sensitive**

# SB 6349

**Megan Troxell/Dean Fong; Stanford/Kaiser SF**

19-year-old female with nausea, vomiting, abdominal pain, edema. Upper endoscopy demonstrated mild gastritis. Found to have proteinuria (4.4g), normal serum creatine (0.7mg/dl). Kidney biopsy performed.


H&E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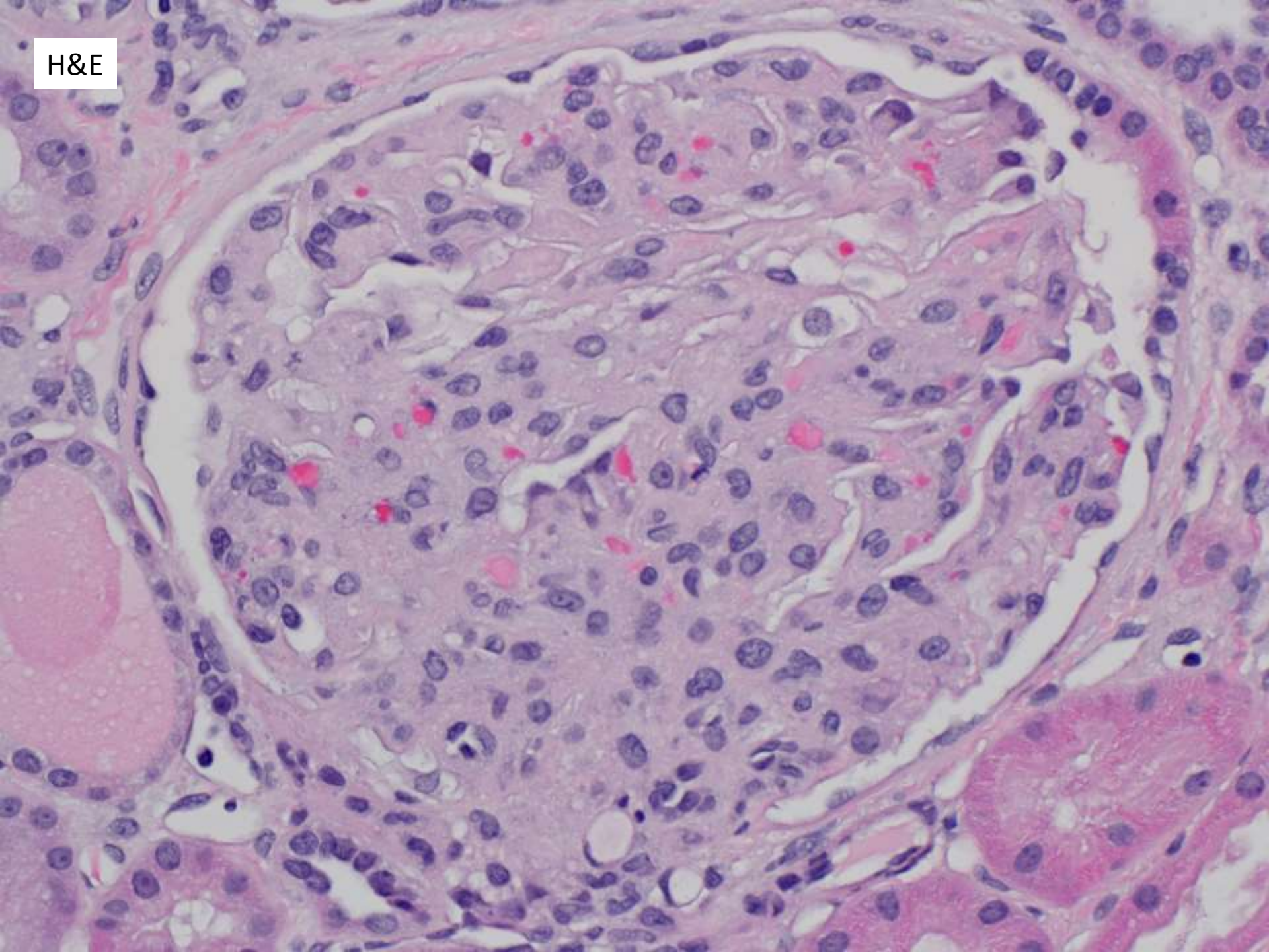
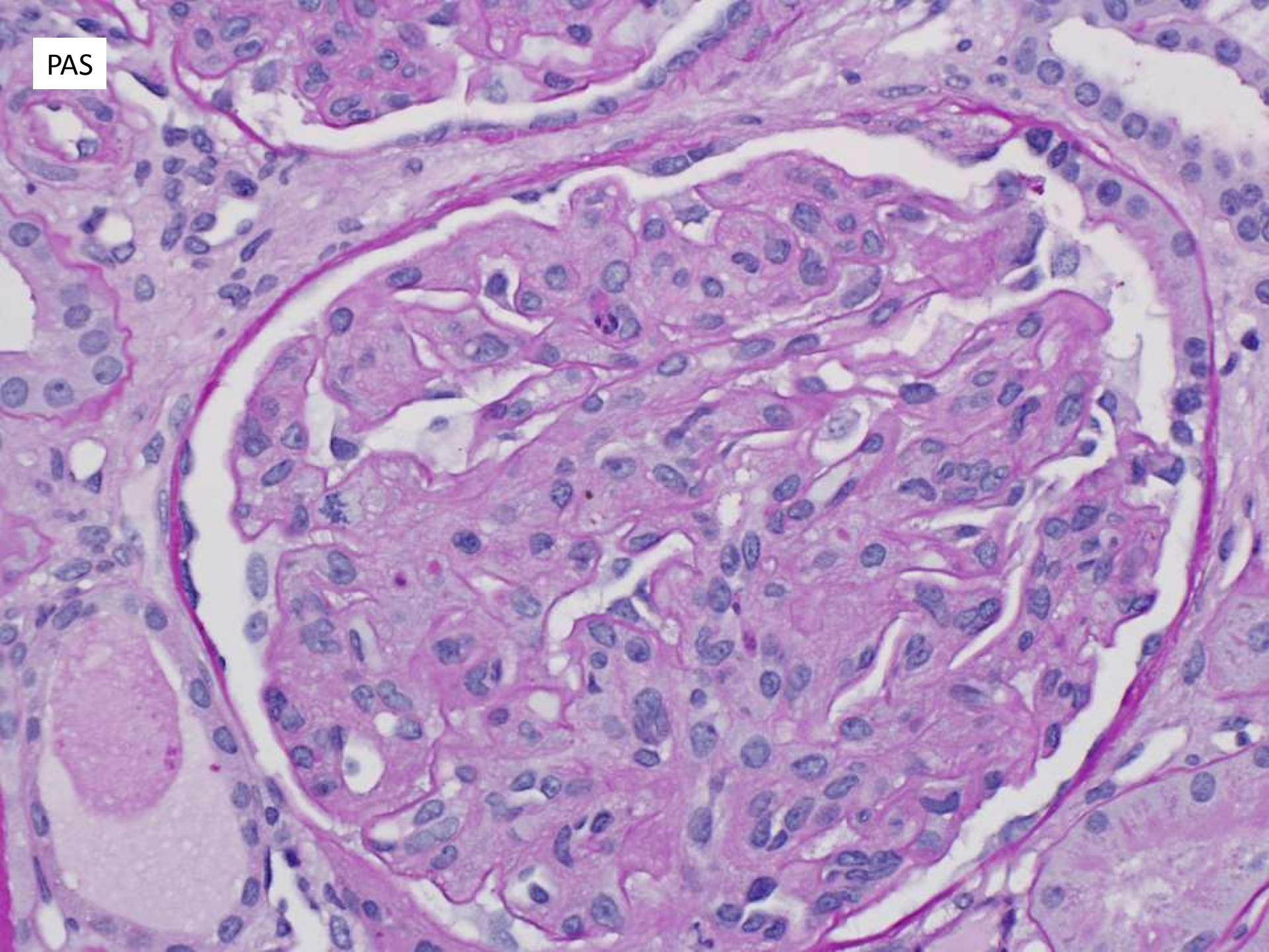
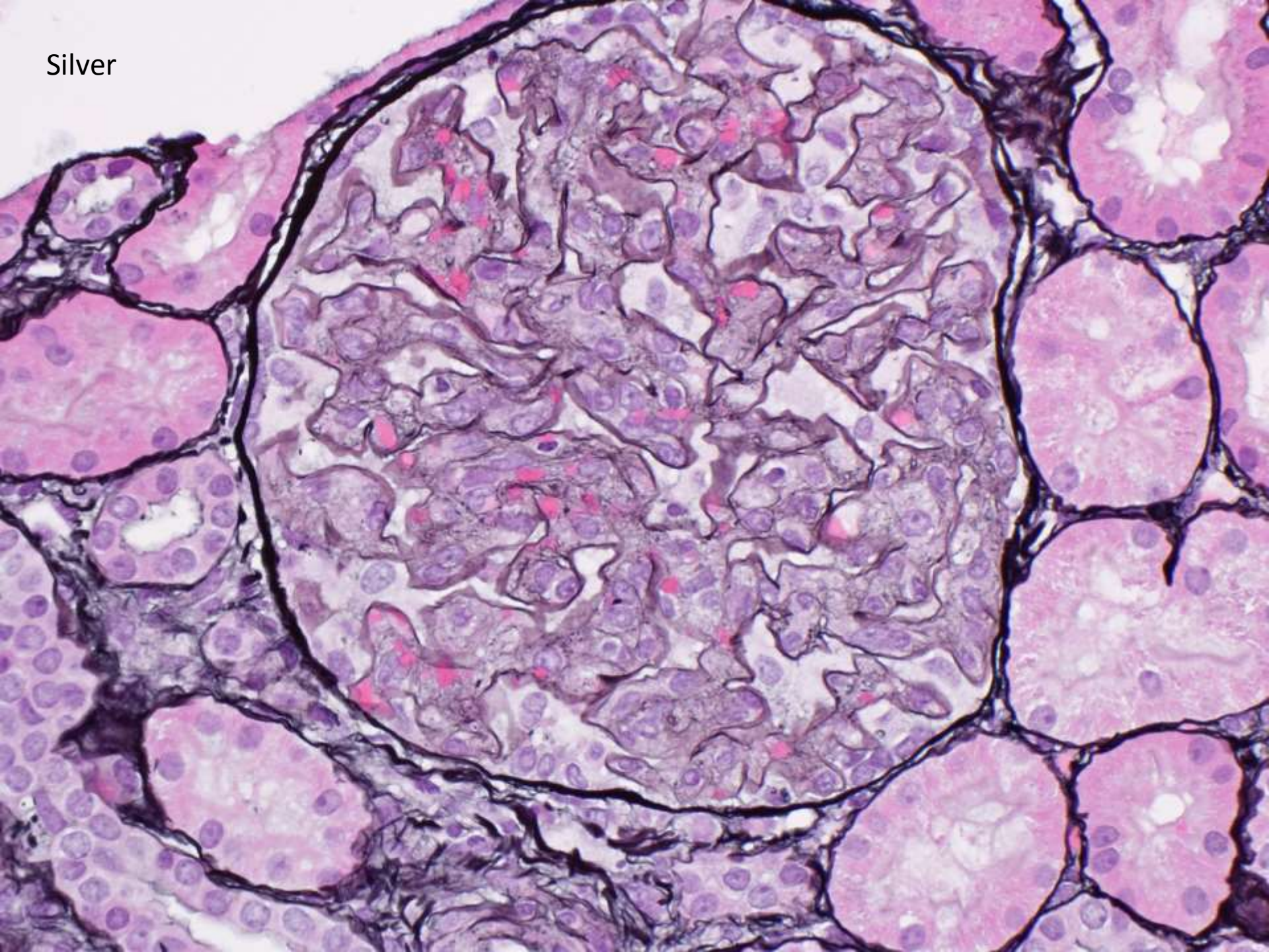
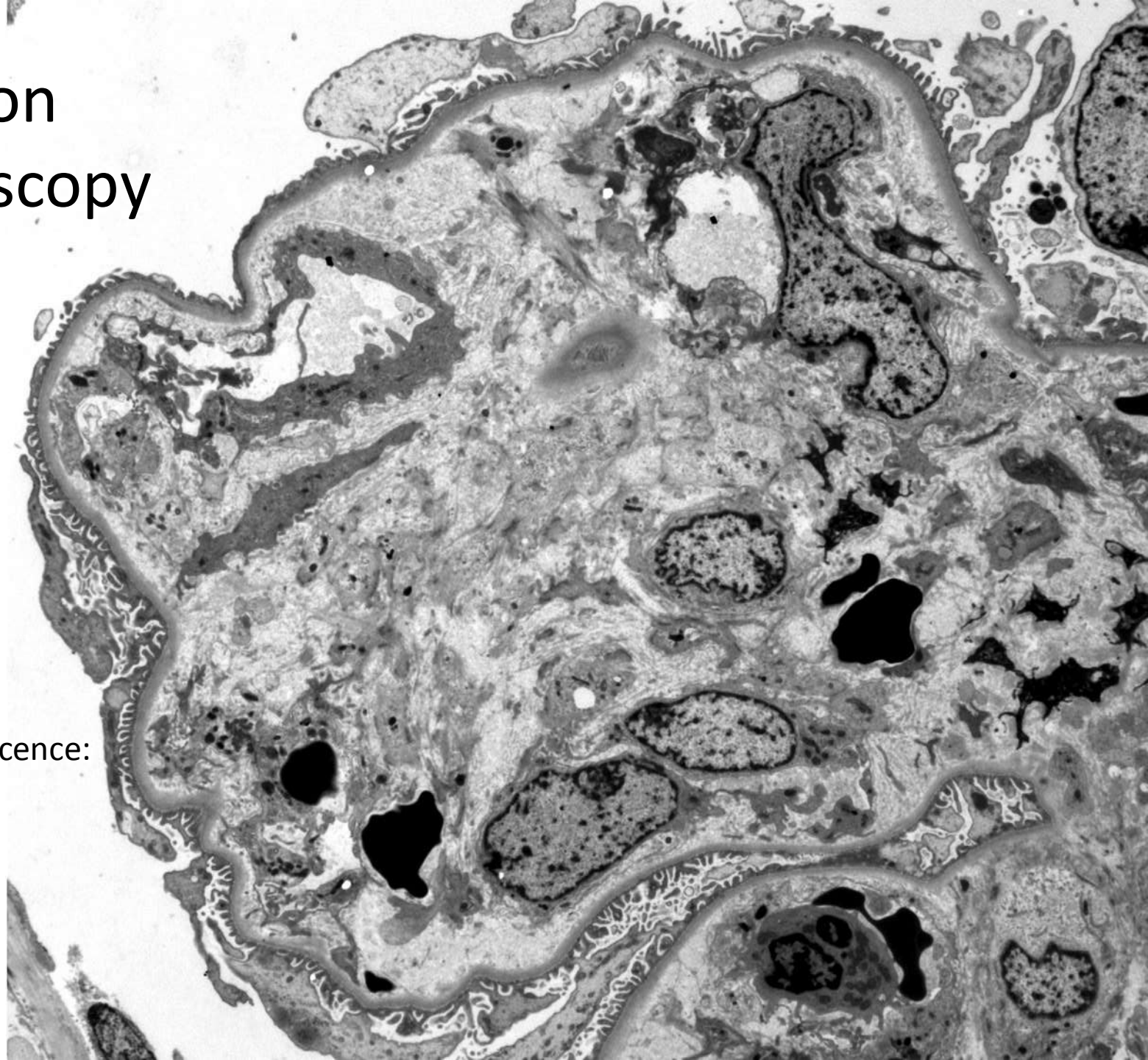

H&E


PAS


Silver

# Electron Microscopy

3000x



Immunofluorescence: negative

# Thrombotic Microangiopathy

- Infectious/epidemic
  - Shiga/verotoxin
  - Strep pneumonia, Salmonella typhi
  - HIV, H1N1
  - Other
- Alternate complement pathway 'Atypical HUS'
  - Hereditary
  - Acquired (Autoantibody-MGUS)
- Other genetic (DGKE, PLG, THBD)
- Deficient ADAMTS13 (TTP)
  - Hereditary, acquired
- Cobalamin metabolic deficiency
- Autoimmune
  - Lupus (anti-phospholipid)
  - Scleroderma
- Malignant hypertension
- Drug
  - Illicit
  - Immunosuppressives
    - Calcineurin inhibitors, sirolimus
  - Platelet agents
  - Cancer chemo
    - Gemcitibine, mitomycin C
    - Anti-VEGF
  - Other (quinine)
- Radiation
- Transplantation (esp stem cell)
- Malignancy
- Pancreatitis
- Pregnancy (pre-eclampsia)

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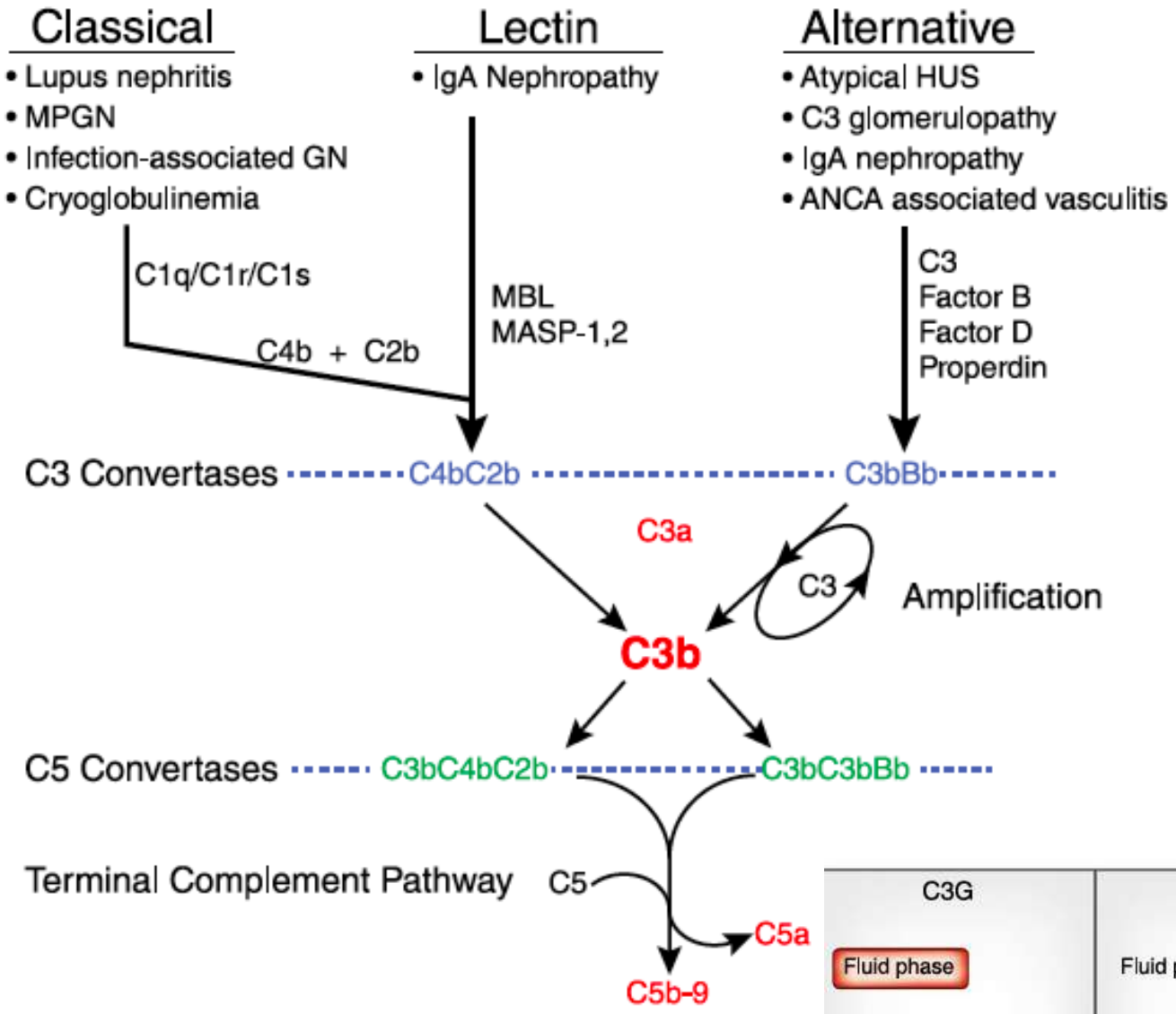
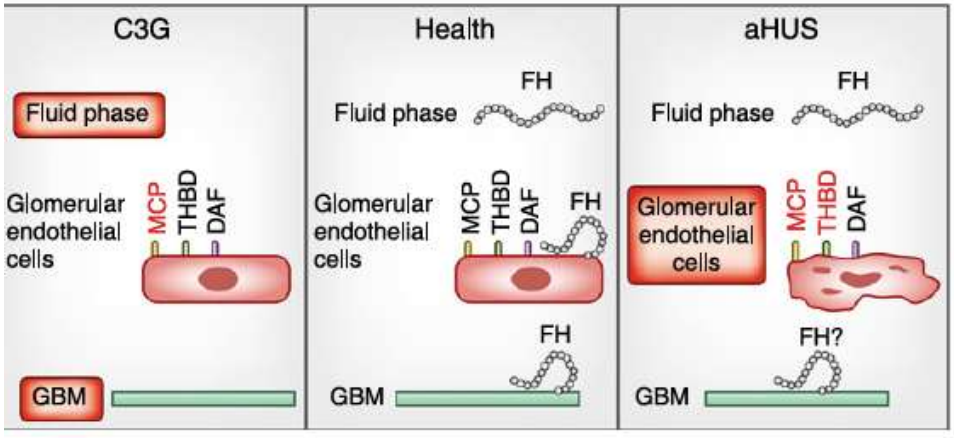


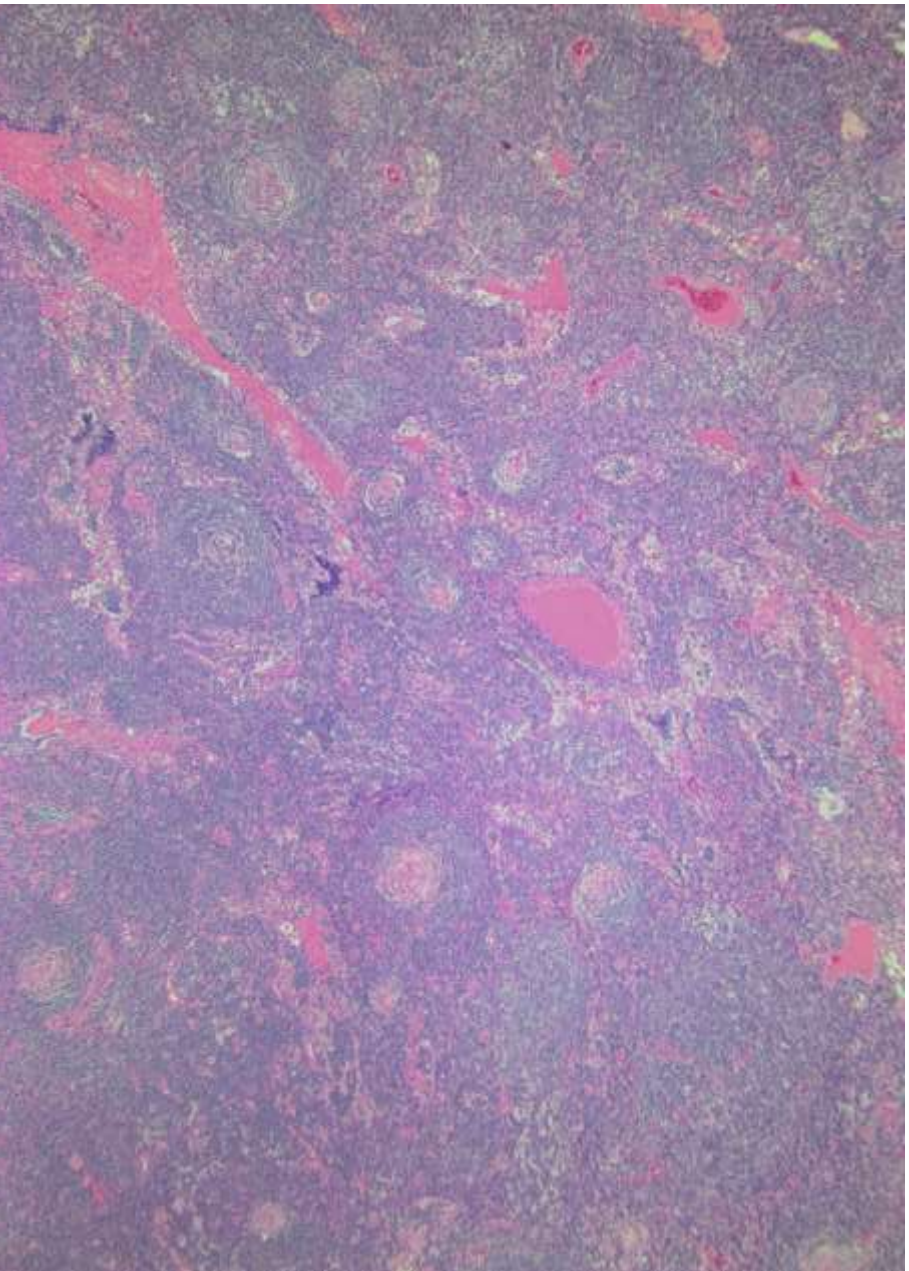



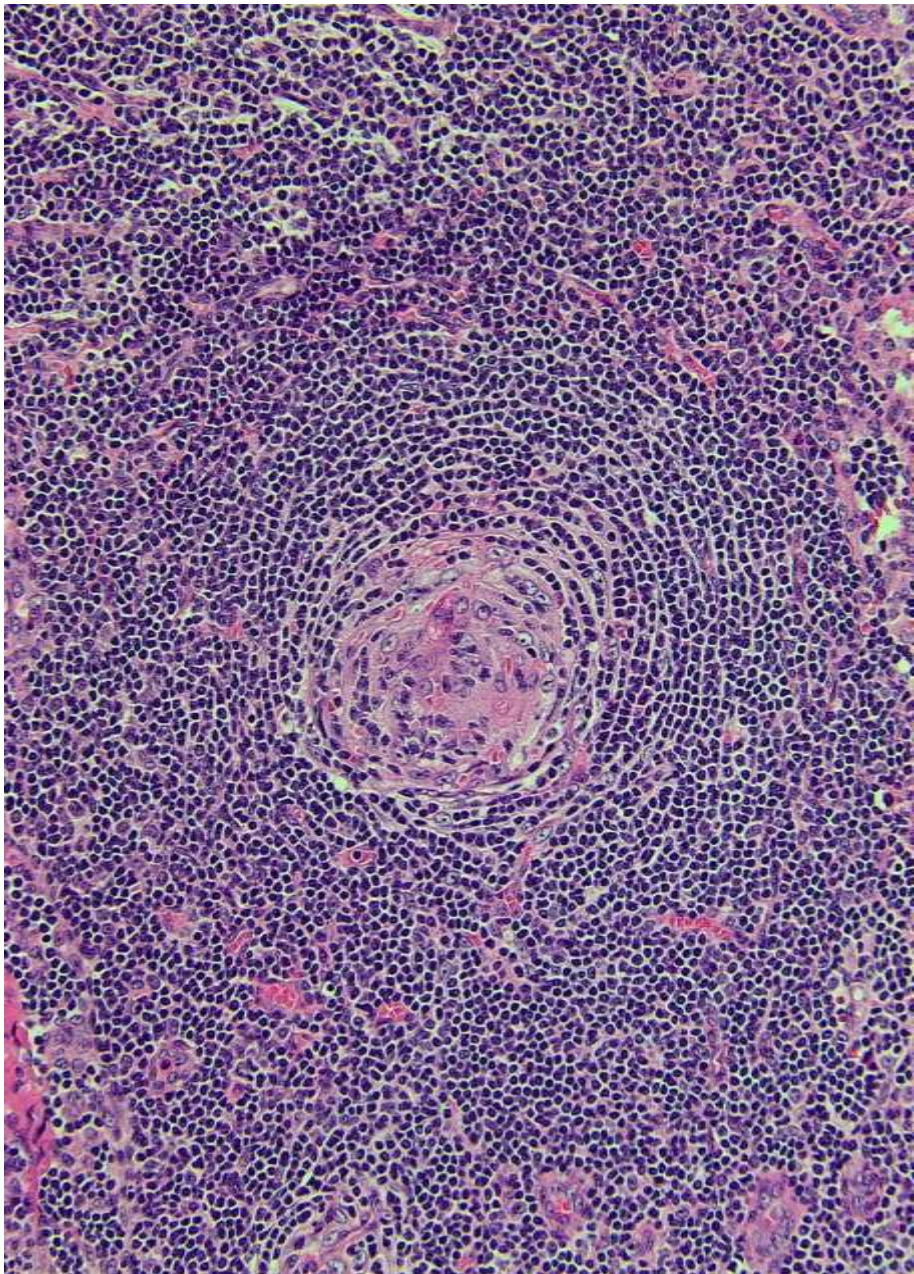

Thurman, Nester. Clin J Am Soc Nephrol 11: 1856–66, 2016.

# Additional studies reveal…

- Many possibilities ruled out
- Complement genetic studies:
  - CFI: VUS in upstream non-coding region
  - CFH: 3 polymorphisms, present in 23% normal patients, but enriched in patients with aHUS
  - ?mild susceptibility to other inciting factors?
- Proteinuria resolved, treated conservatively

# But within a few months, lymphadenopathy



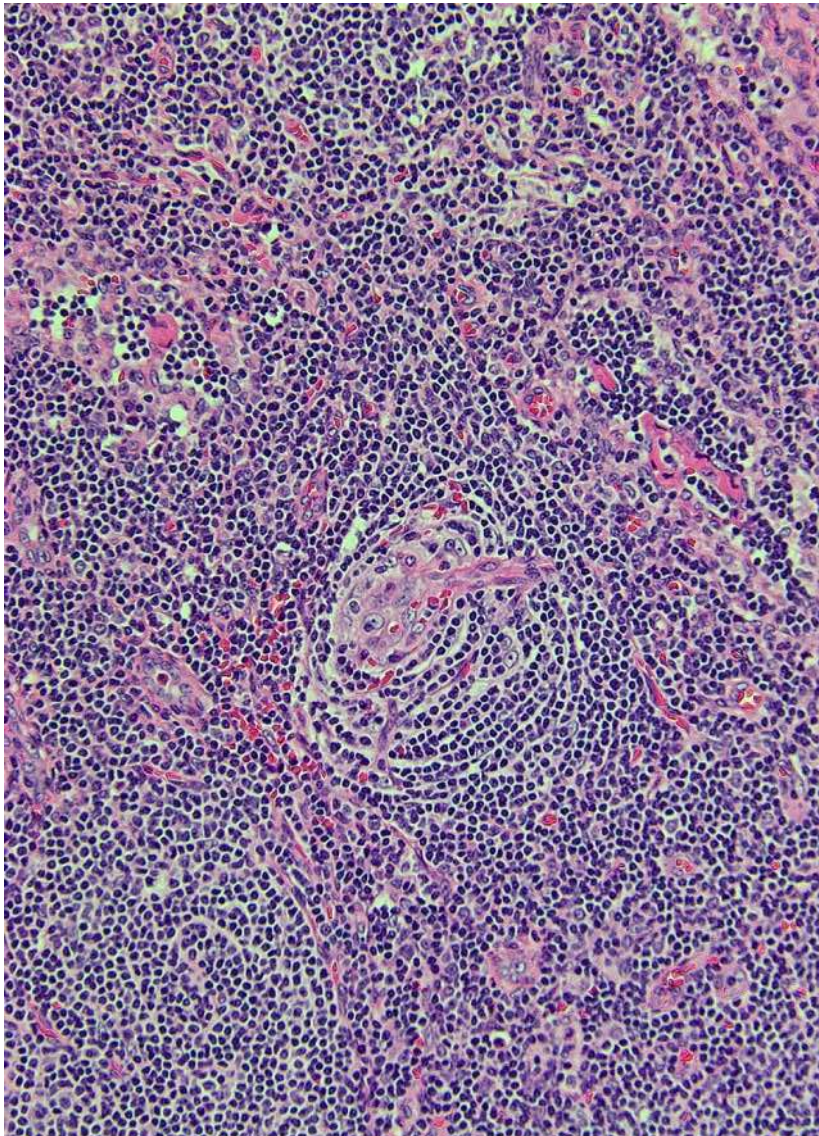


## Kidney Involvement in Multicentric Castleman Disease

*Sumeet Suneja, MD,[1] Mala Chidambaram, MD,[1] Andrew M. Herzenberg, MD,[2] and Joanne M. Bargman, MD[1]*

AJKD. 2009;53: 550-4

- Renal pathology in Castleman?
  - **Amyloid**
  - **TMA**
  - AIN, FSGS, other
- Pathophysiology?
  - Castleman usually elevated IL-6, VEGF
  - Glomerular TMA known with VEGF **inhibitors** (!)



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    - Anti-VEGF
  - Other (quinine)
- Radiation
- Transplantation (esp stem cell)
- Malignancy
- Pancreatitis
- Pregnancy (pre-eclampsia)
- **Castleman/TAFRO**

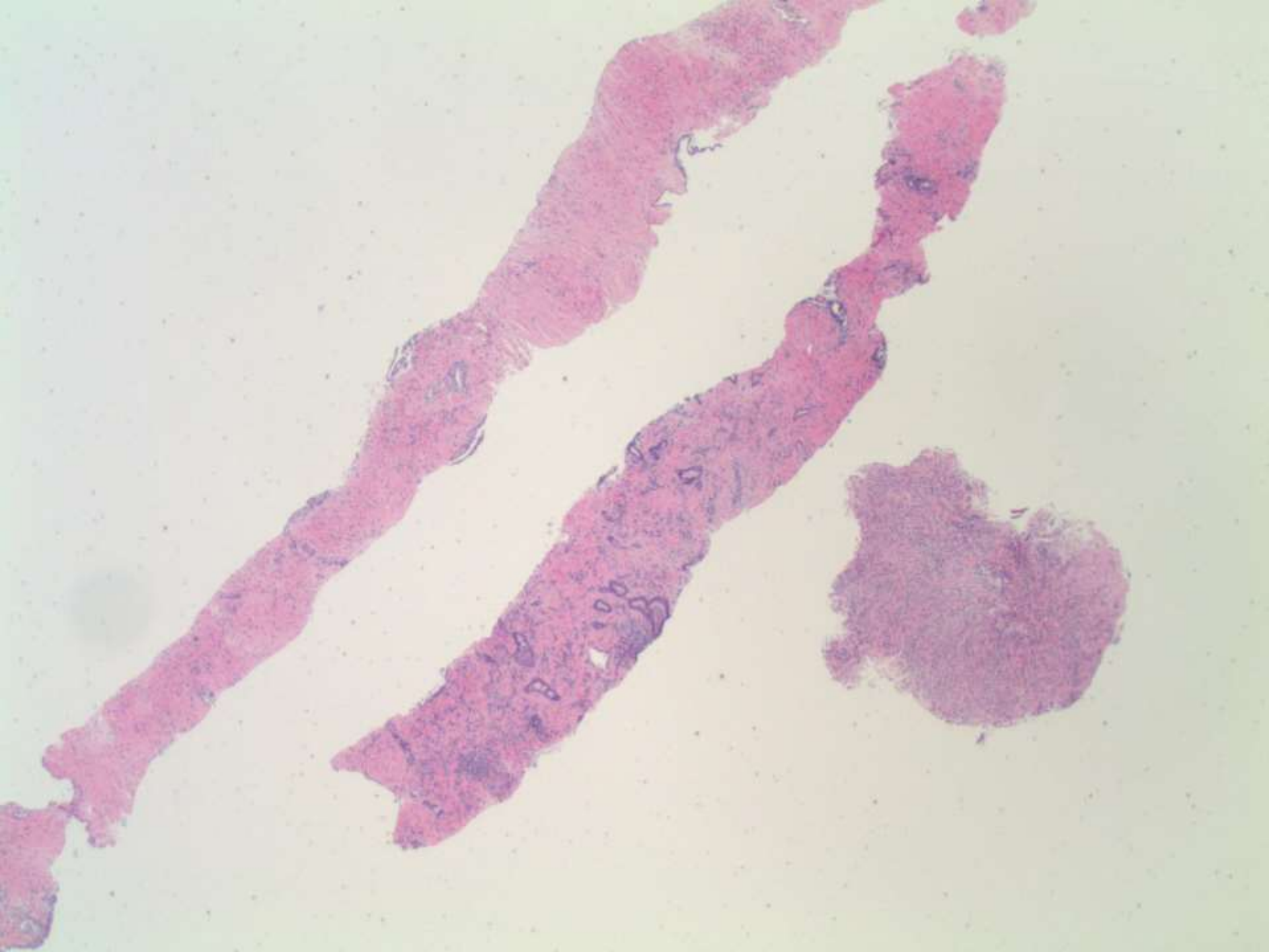
# Take homes

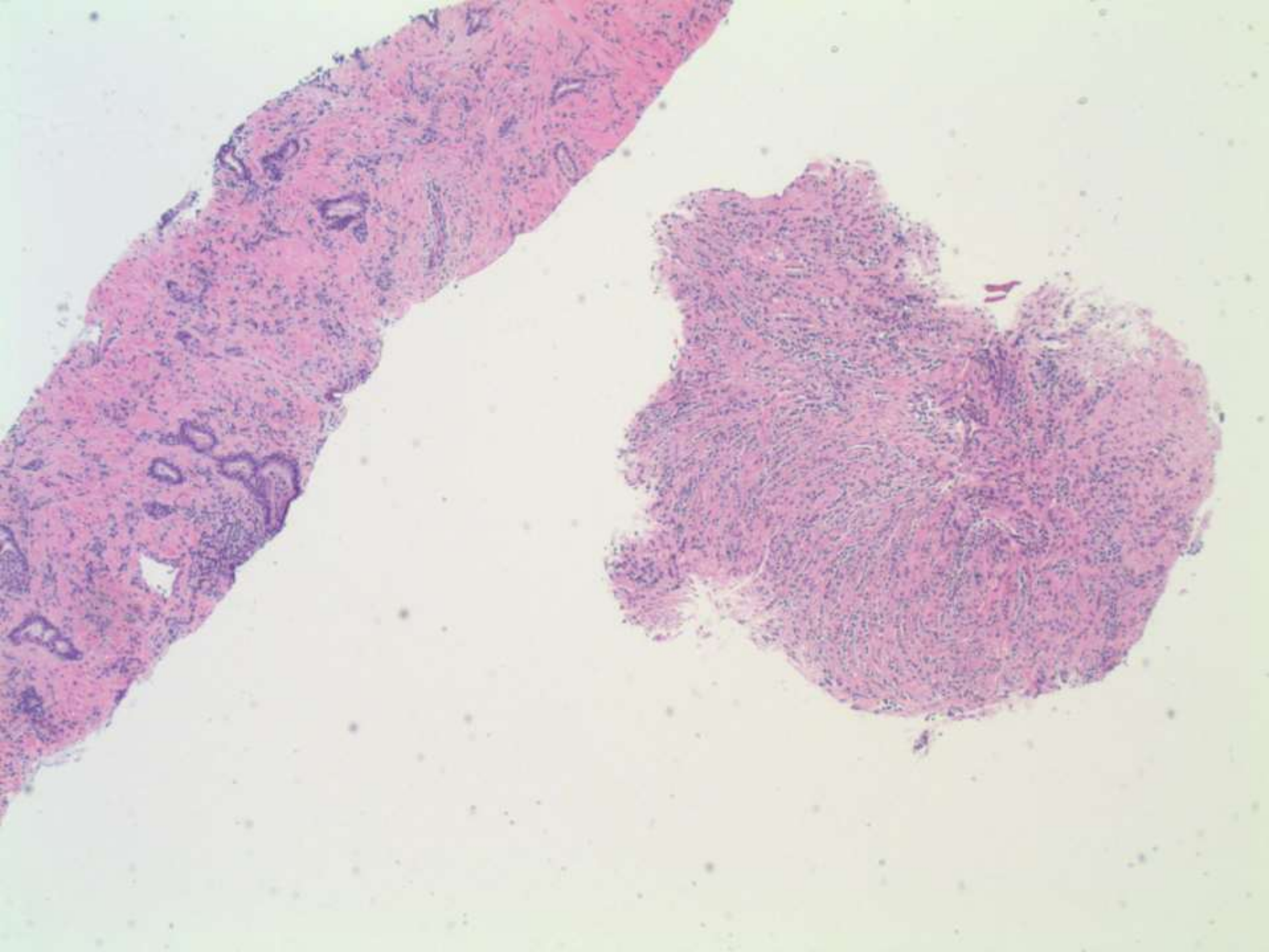
- Alternate complement abnormalities in atypical HUS, esp. in young patients
- The list of TMA associations is long and growing
  - Castleman
  - TAFRO
    - Thrombocytopenia, Anasarca, MyeloFibrosis, Renal dysfunction, and Organomegaly (serum IL-6, VEGF elevated)
  - POEMS
    - Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, skin changes
  - MGUS

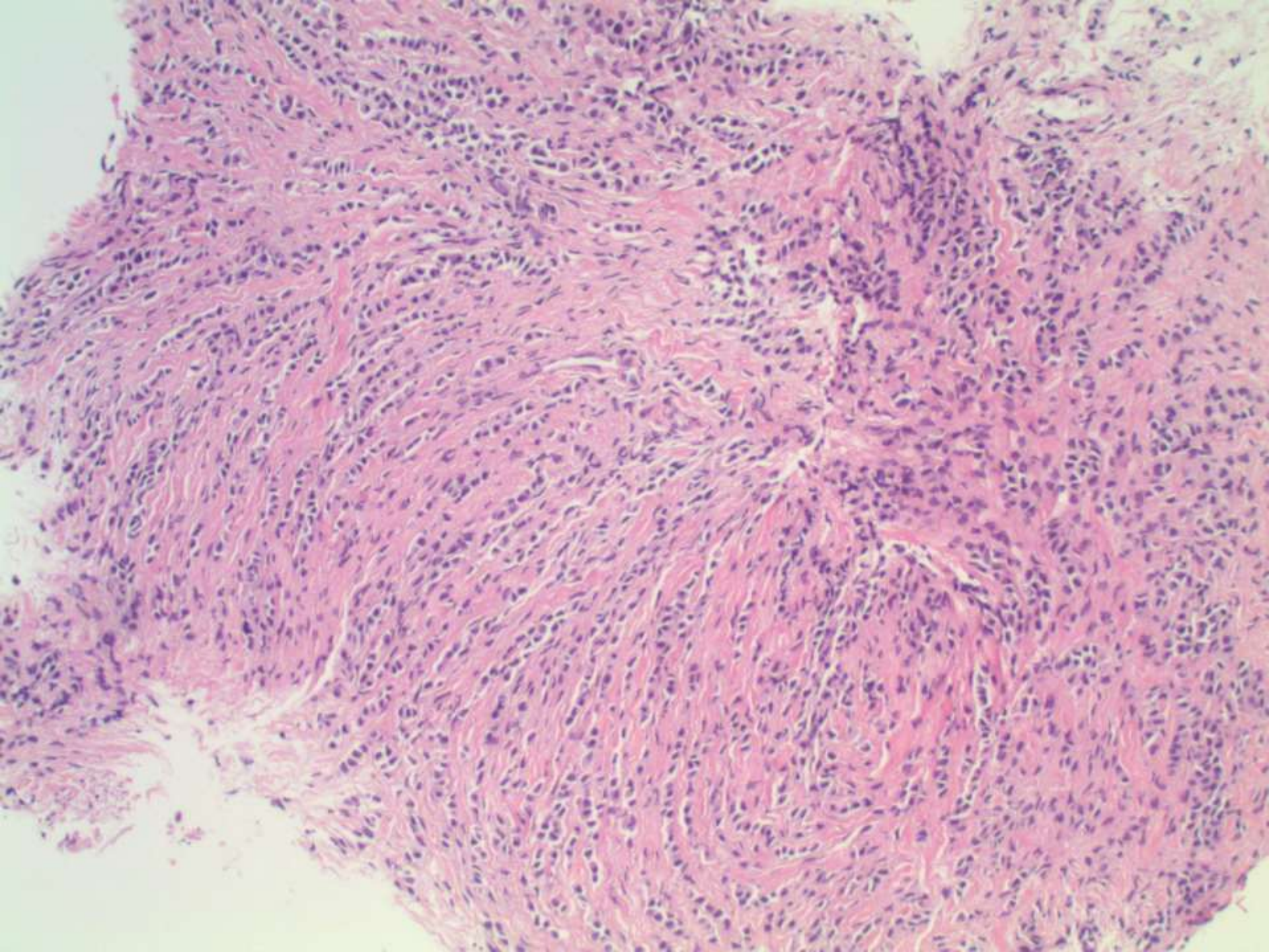
# SB 6350

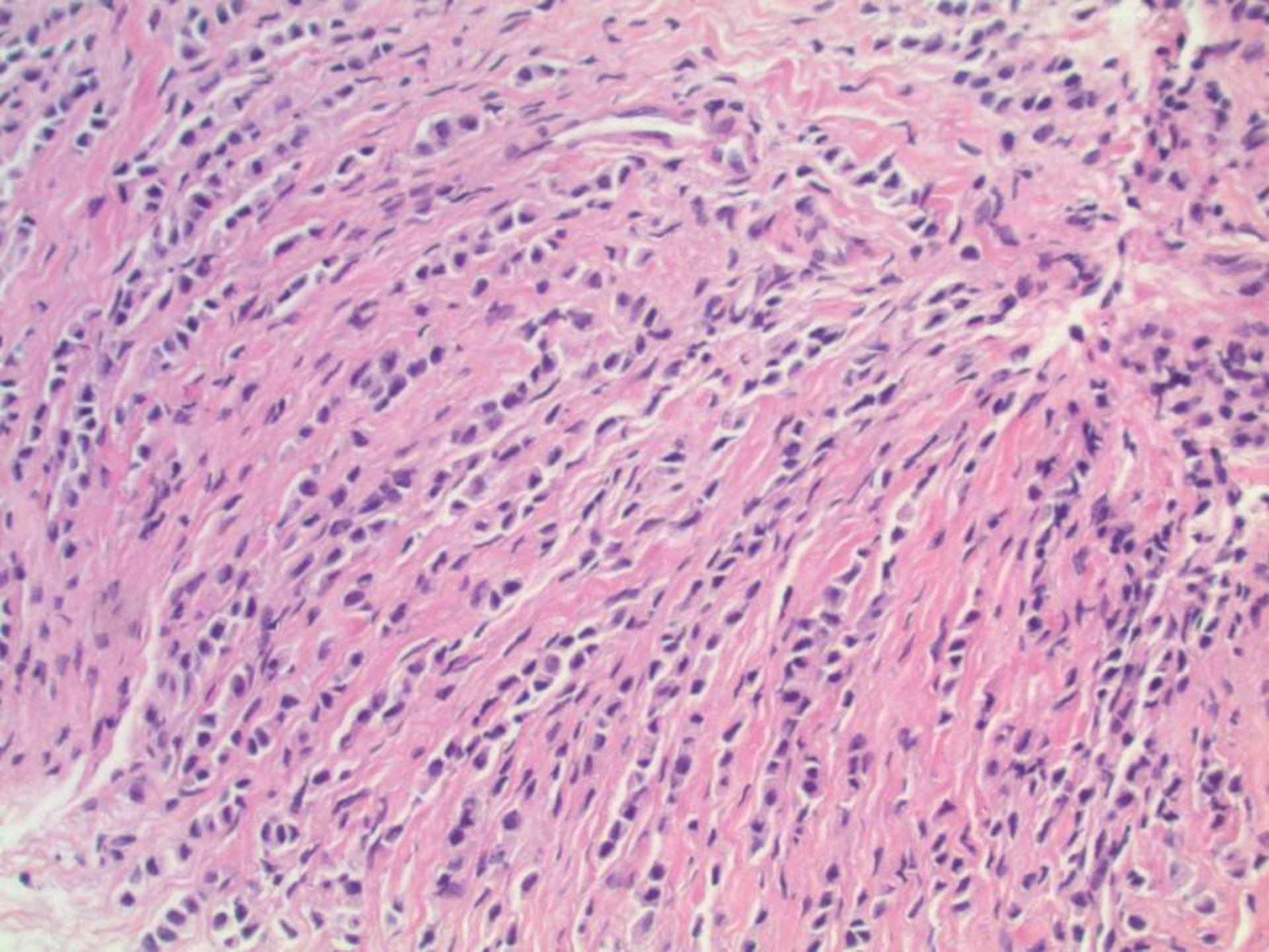
**Ankur Sangoi; El Camino Hospital**

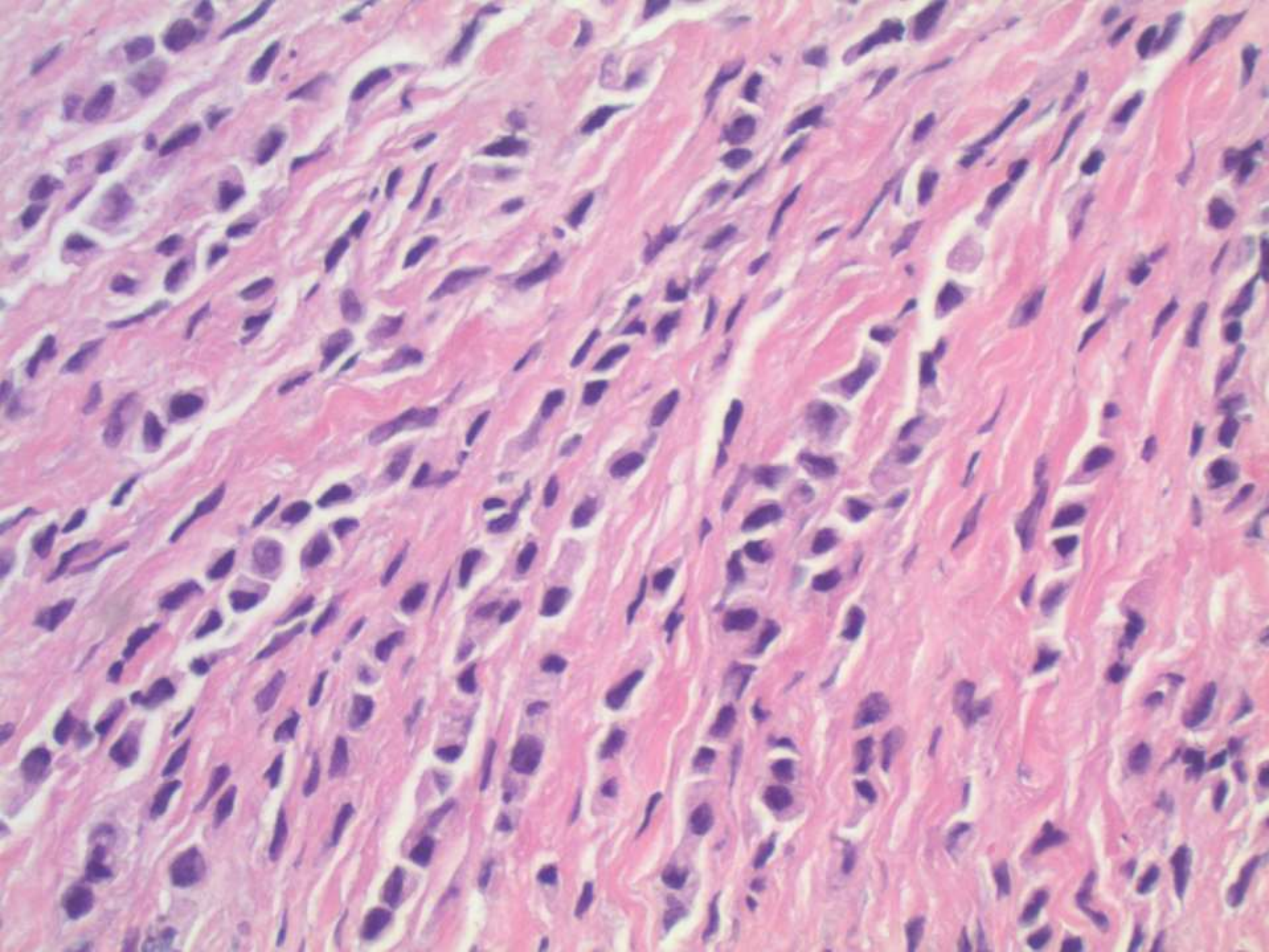
52-year-old male found to have bilateral breast enlargement. Upon work-up, elevated serum PSA discovered. MRI-guided prostate biopsy performed of abnormal area seen on imaging.







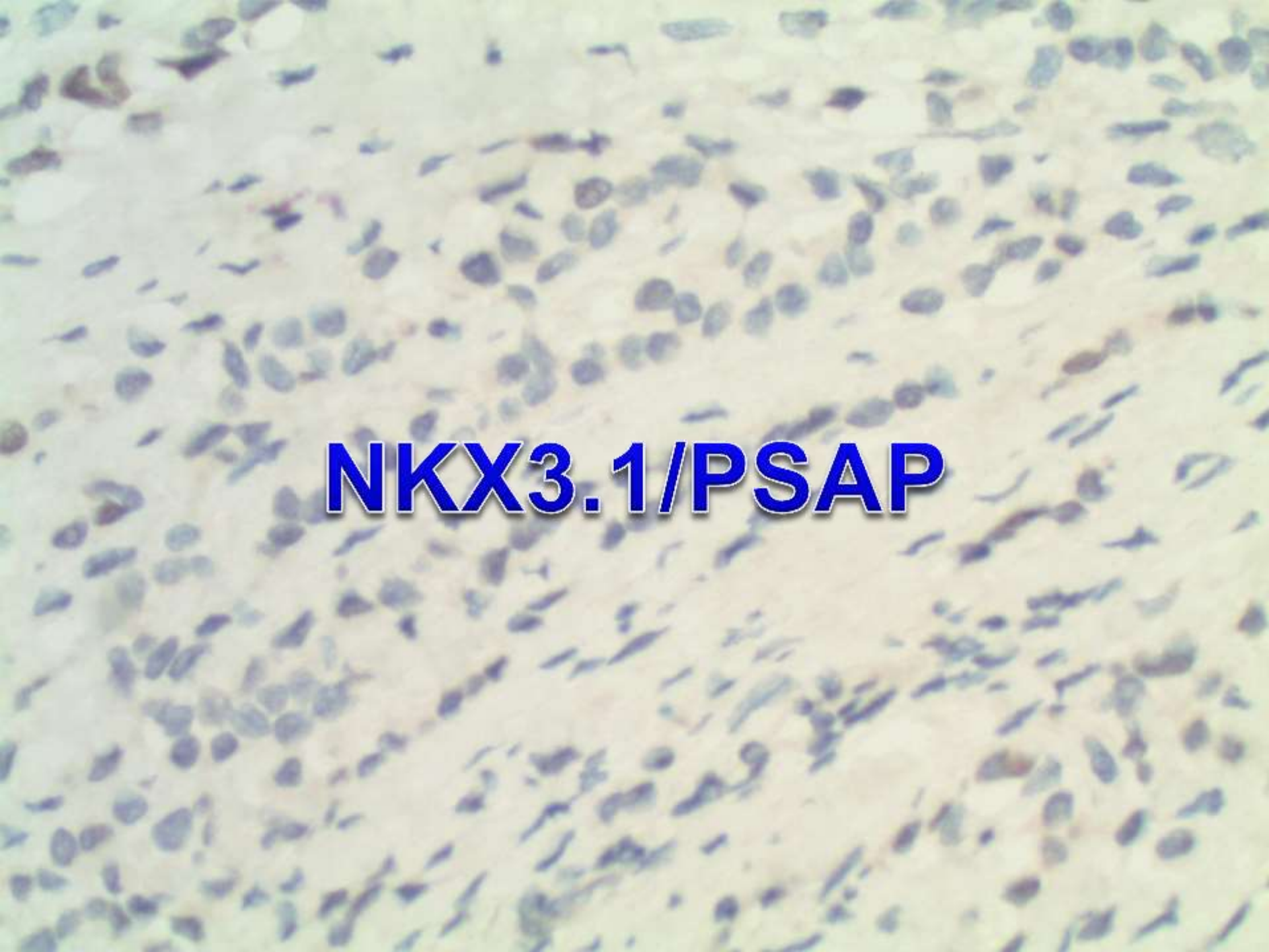


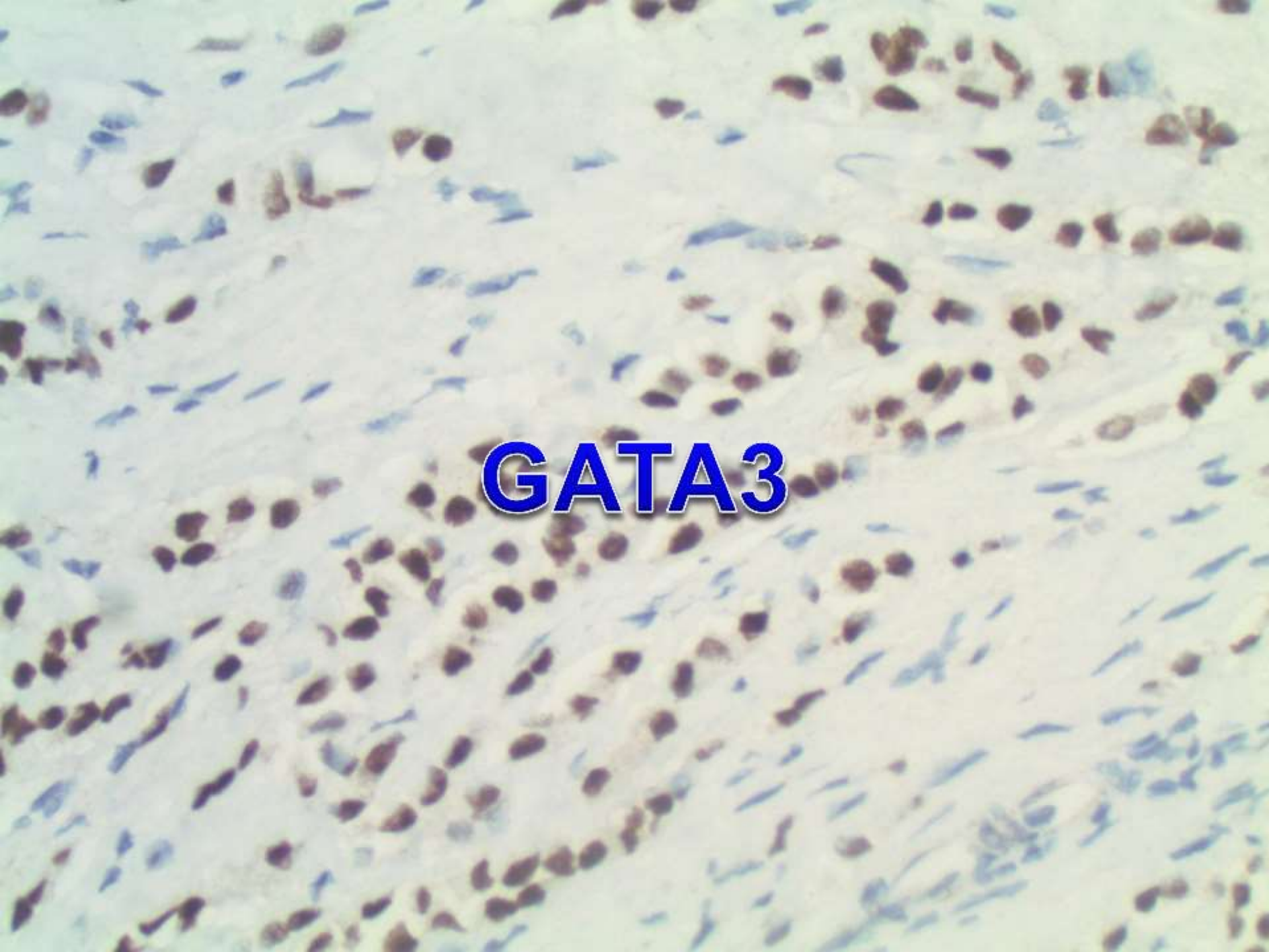


# DDx

- Gleason 5+5 prostatic adenocarcinoma
- Plasmacytoid urothelial carcinoma
- Signet ring GI tract adenocarcinoma
- Metastatic lobular carcinoma
- something else…

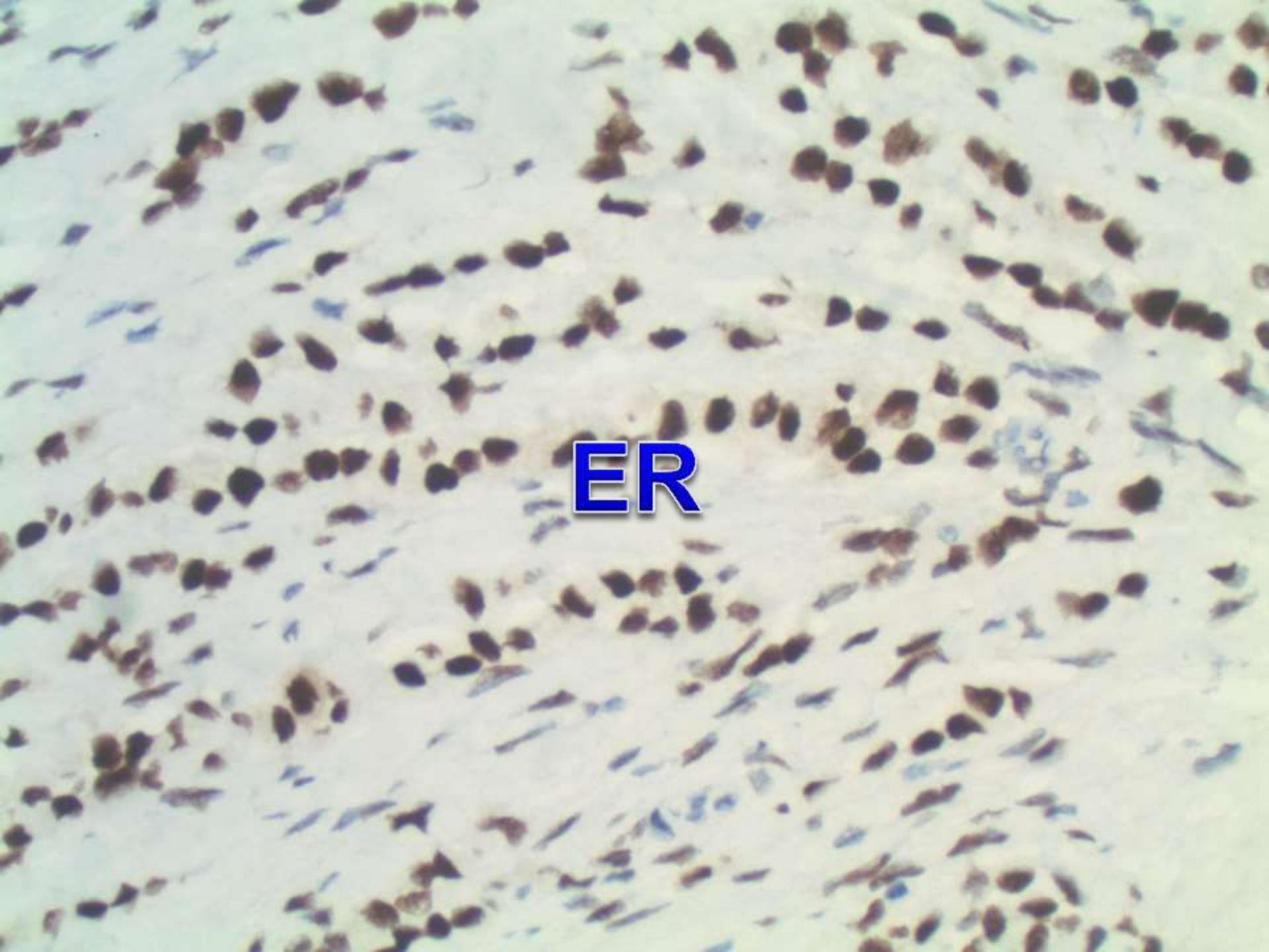

PIN3

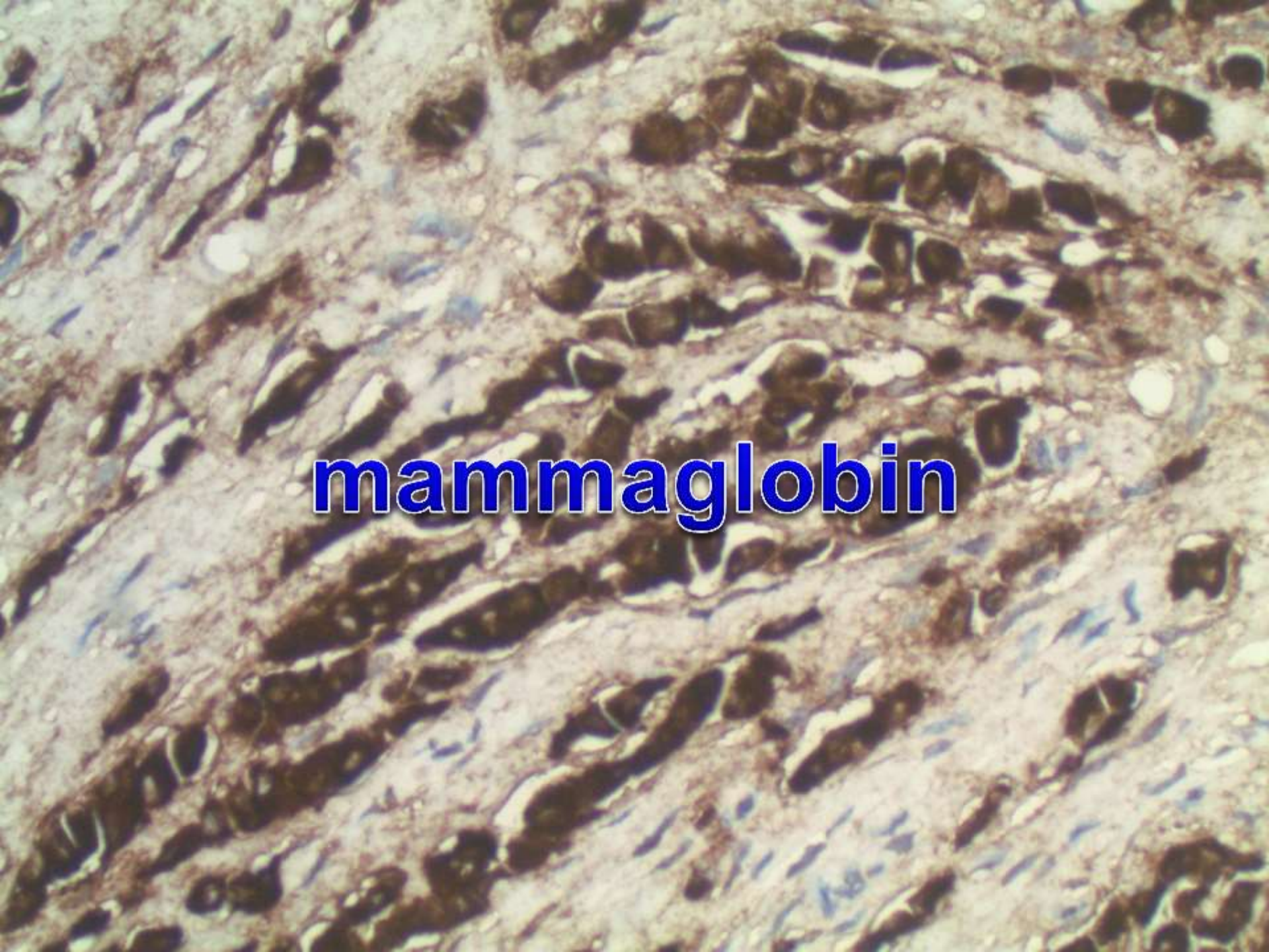

NKX3.1/PSAP

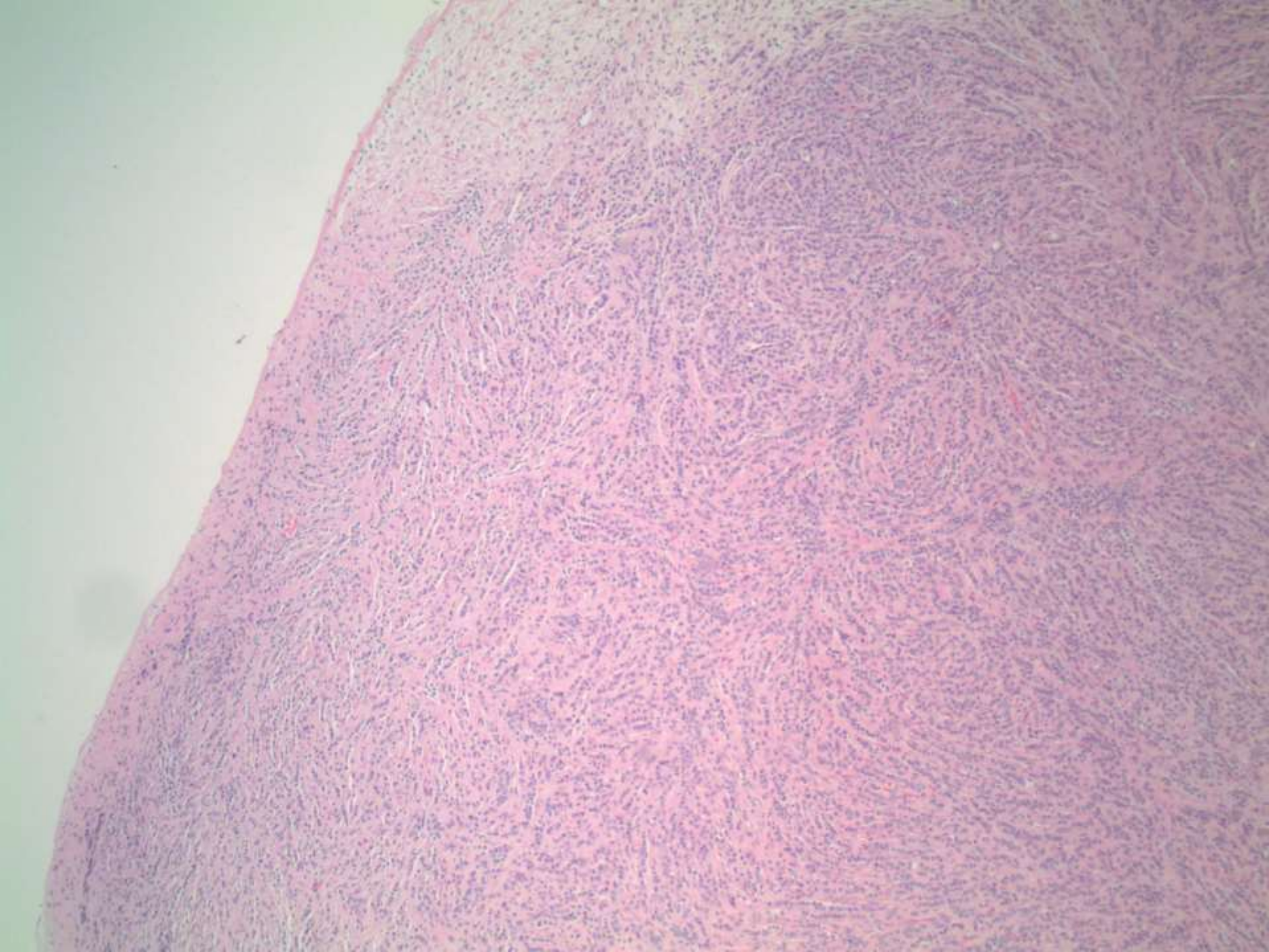

GATA3

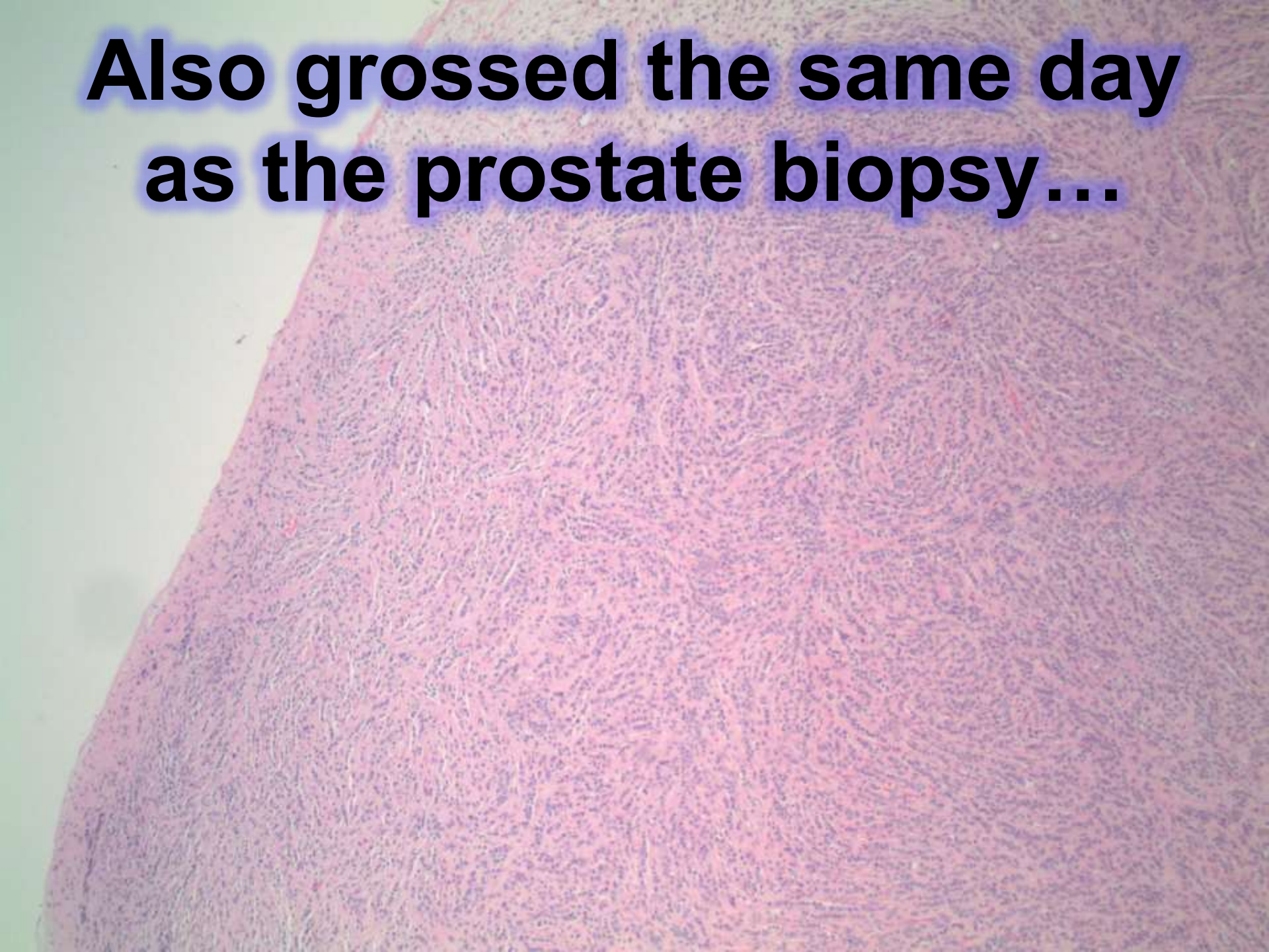

uroplakin2


CK20

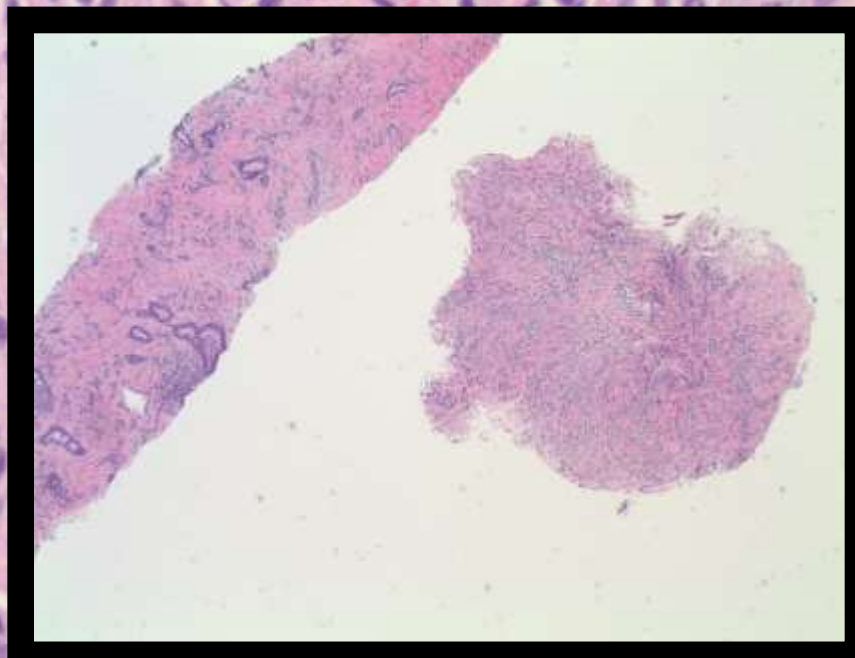

ER


mammaglobin




Also grossed the same day as the prostate biopsy…

# Oophorectomy with metastatic lobular carcinoma



# DDx

- Gleason 5+5 prostatic adenocarcinoma
- Plasmacytoid urothelial carcinoma
- Signet ring colorectal adenocarcinoma
- Metastatic lobular carcinoma
- something else…

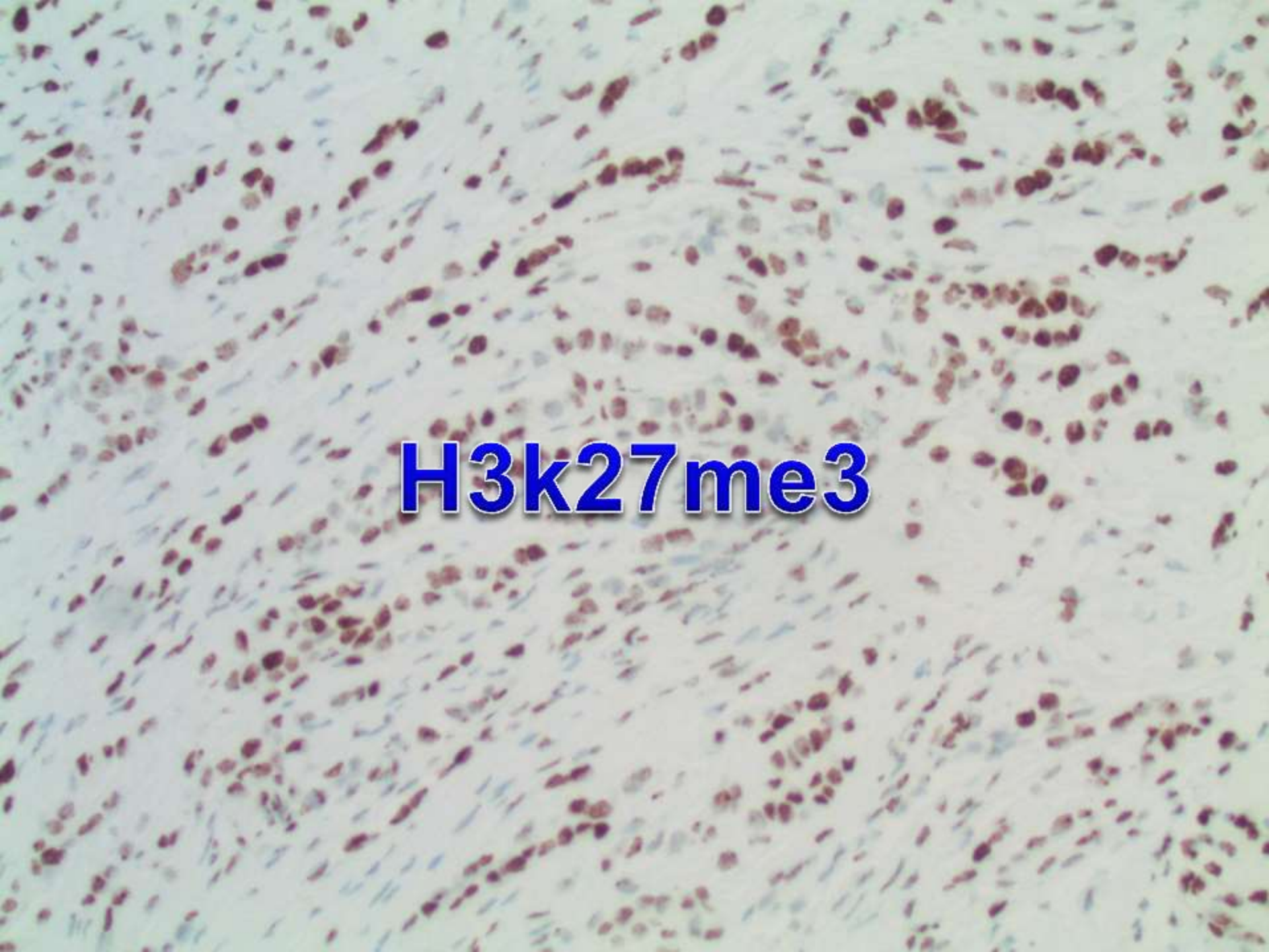
# Final Dx

- **Benign prostatic glands/stroma**
  - Tissue floater from metastatic ILC

# novel antibody: H3k27me3

- **Alternate Test Names:**
  anti-Tri-Methyl-Histone-H3 (Lys27)

- **Loss of expression sensitive for sporadic & radiation-induced MPNST**


H3k27me3


It's a Girl!
H3k27me3
It's a Girl!

# H3k27me3

- **Alternate Test Names:** anti-Tri-Methyl-Histone-H3 (Lys27)
- **Loss of expression sensitive for sporadic & radiation-induced MPNST**
- **H3K27me3 immunohistochemistry highlights the inactivated X chromosome (Xi) and predicts sex in non-neoplastic tissues**
  - Histopathology. 2016 Oct;69(4):702-4