Unusual and Challenging Cases in Genitourinary Pathology

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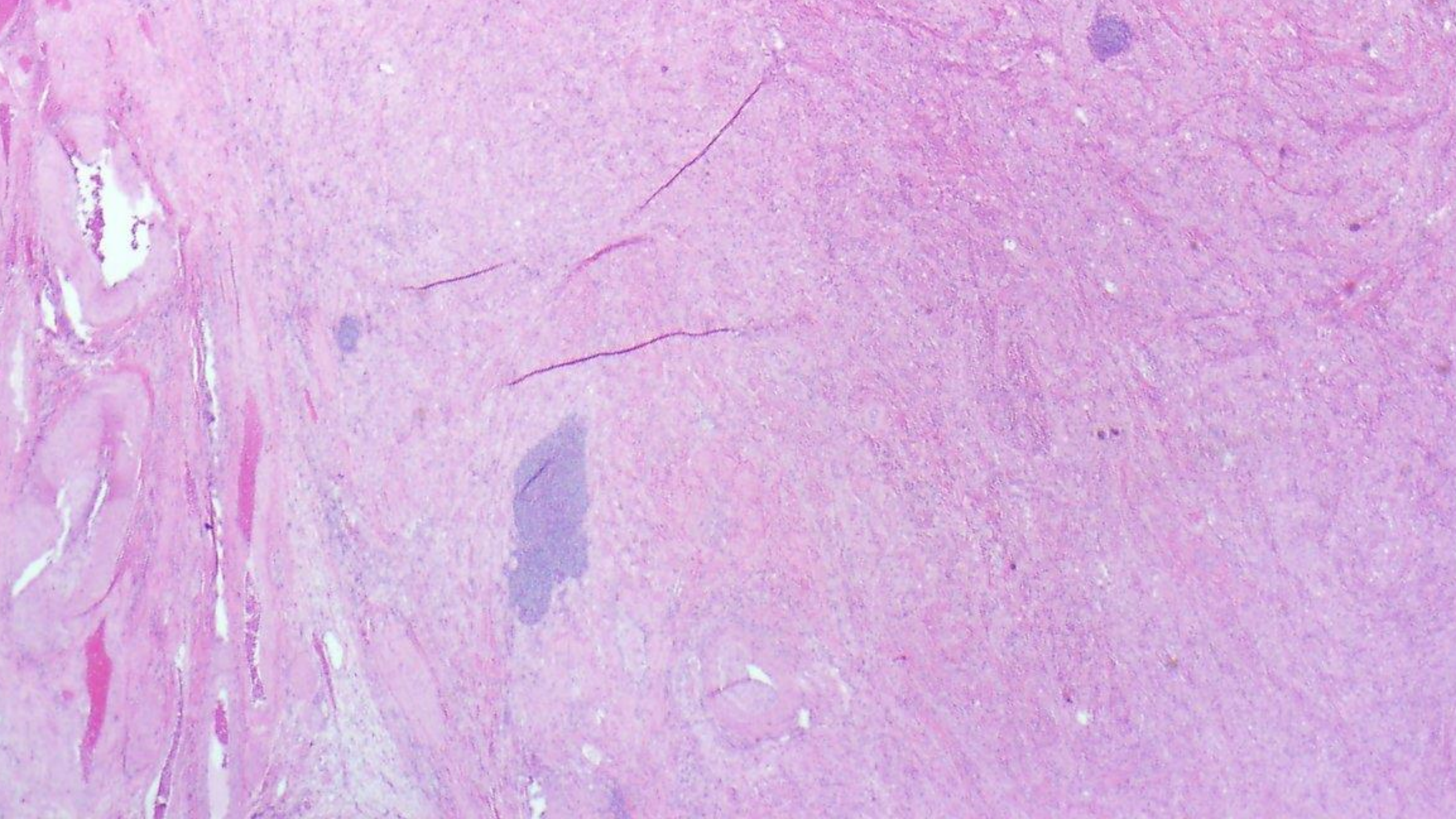
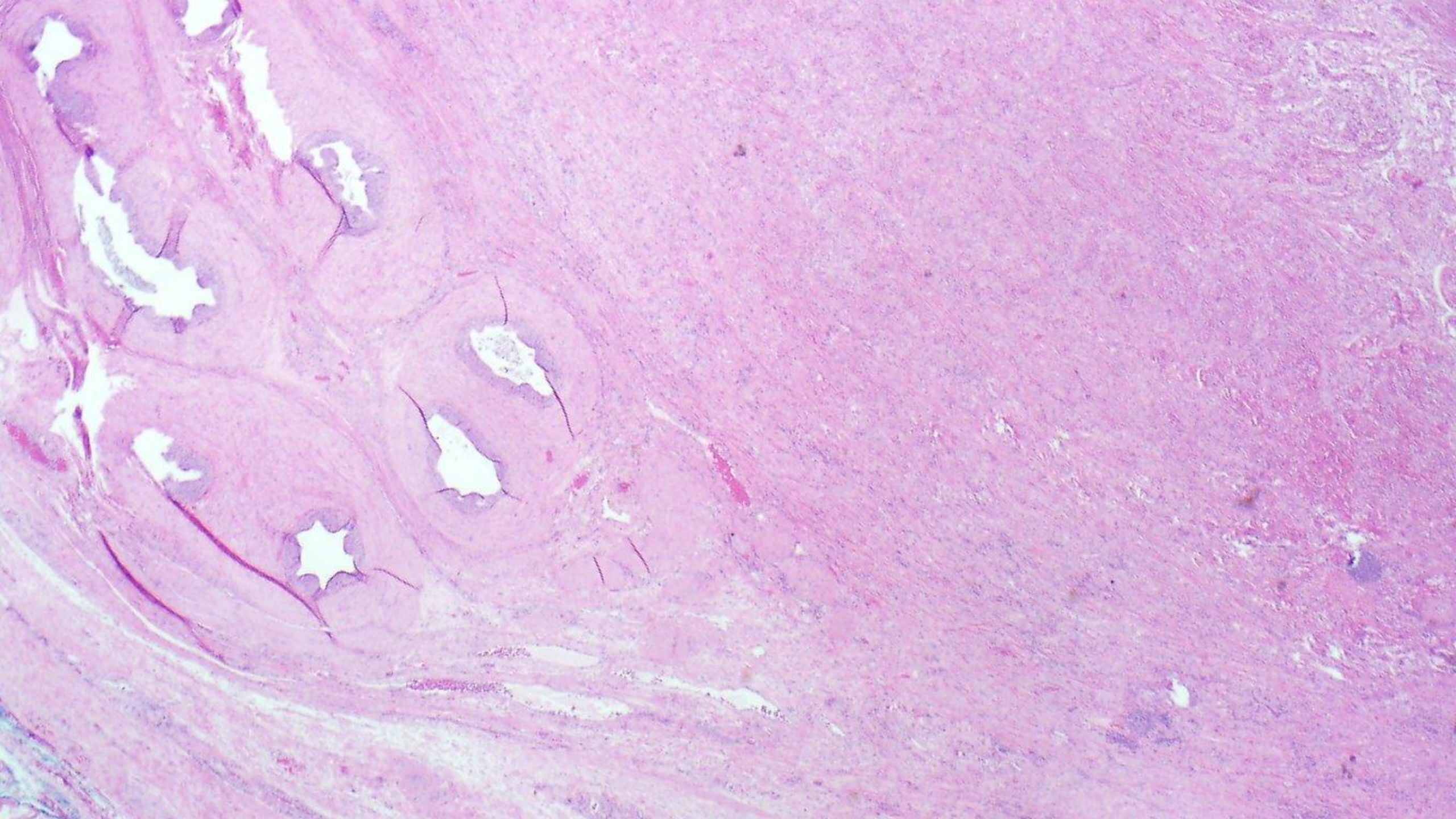
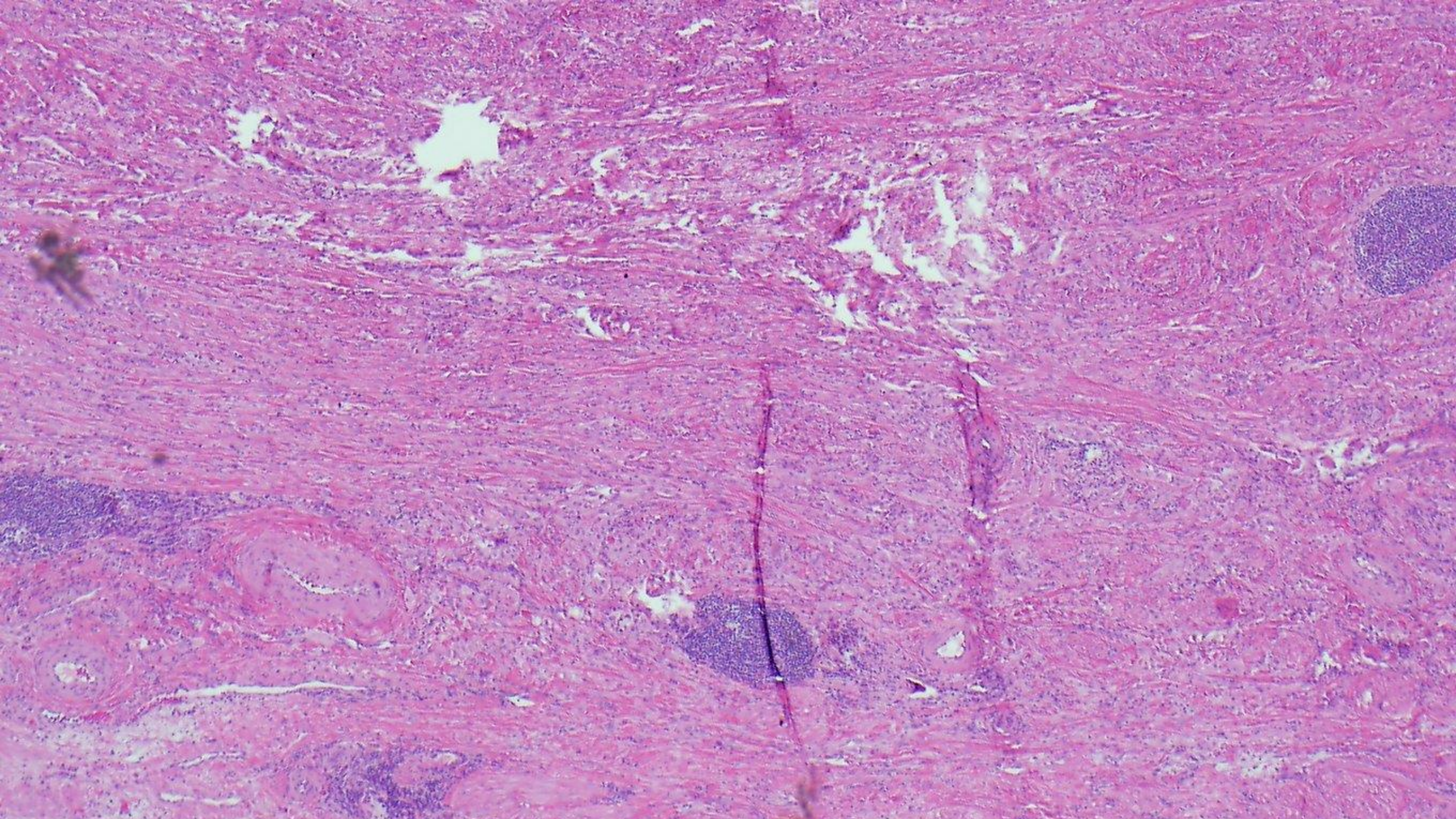
I have no conflict(s) of interest to disclose

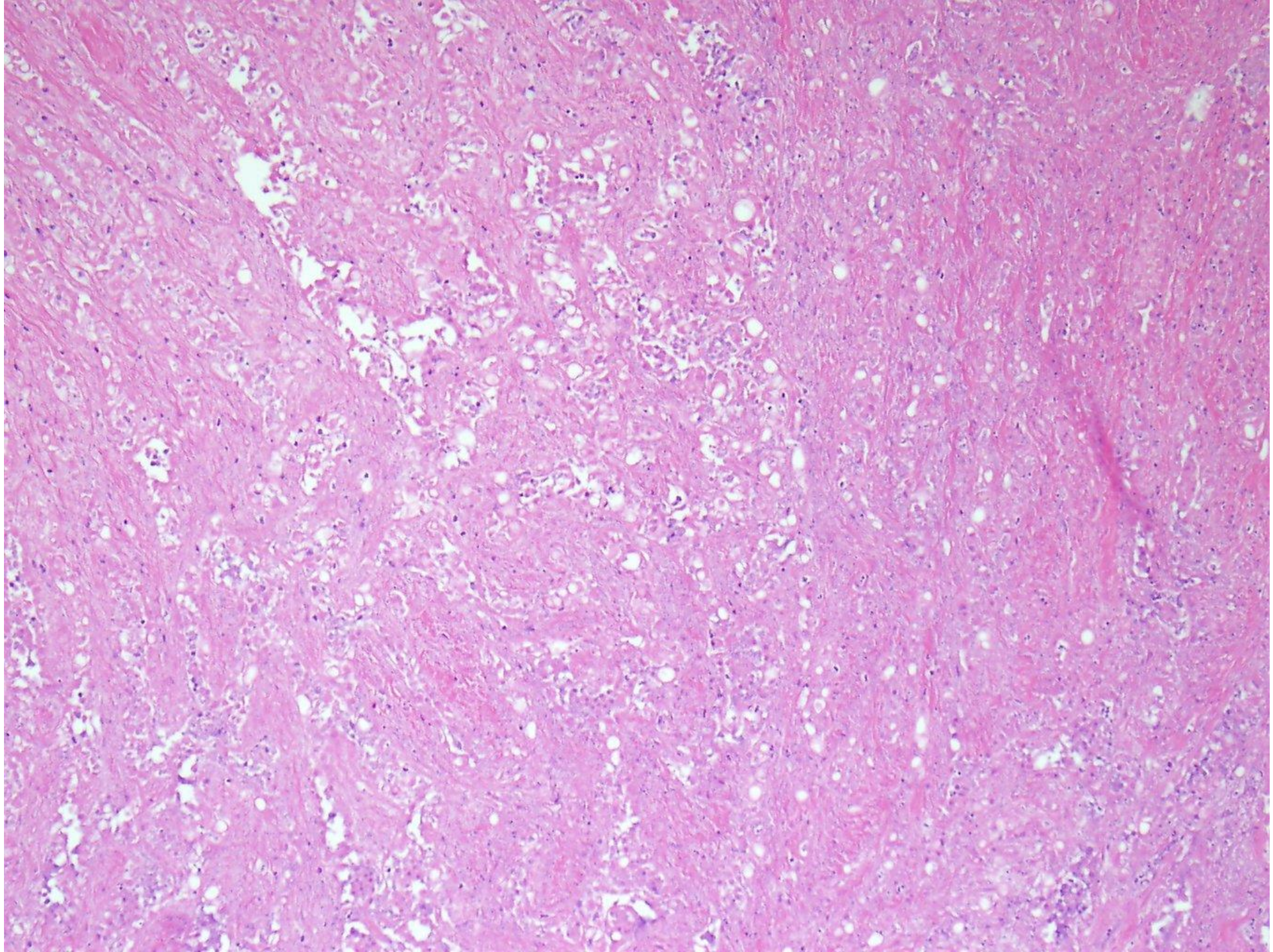
Case #1: 26 year old male with rapidly growing left paratesticular mass measuring 3.5 cm

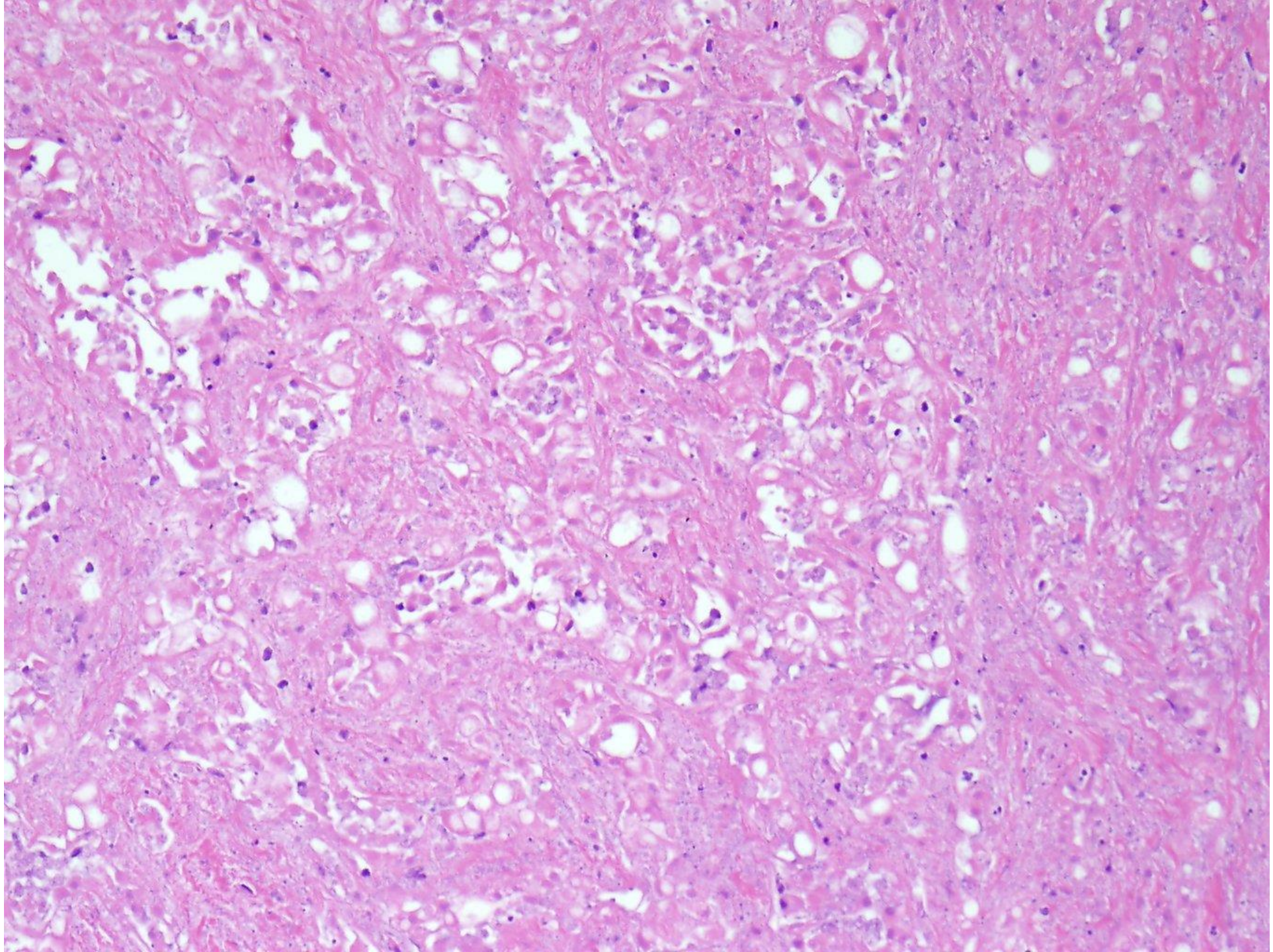
Gross Examination: 3.5 cm round firm mass with yellow center

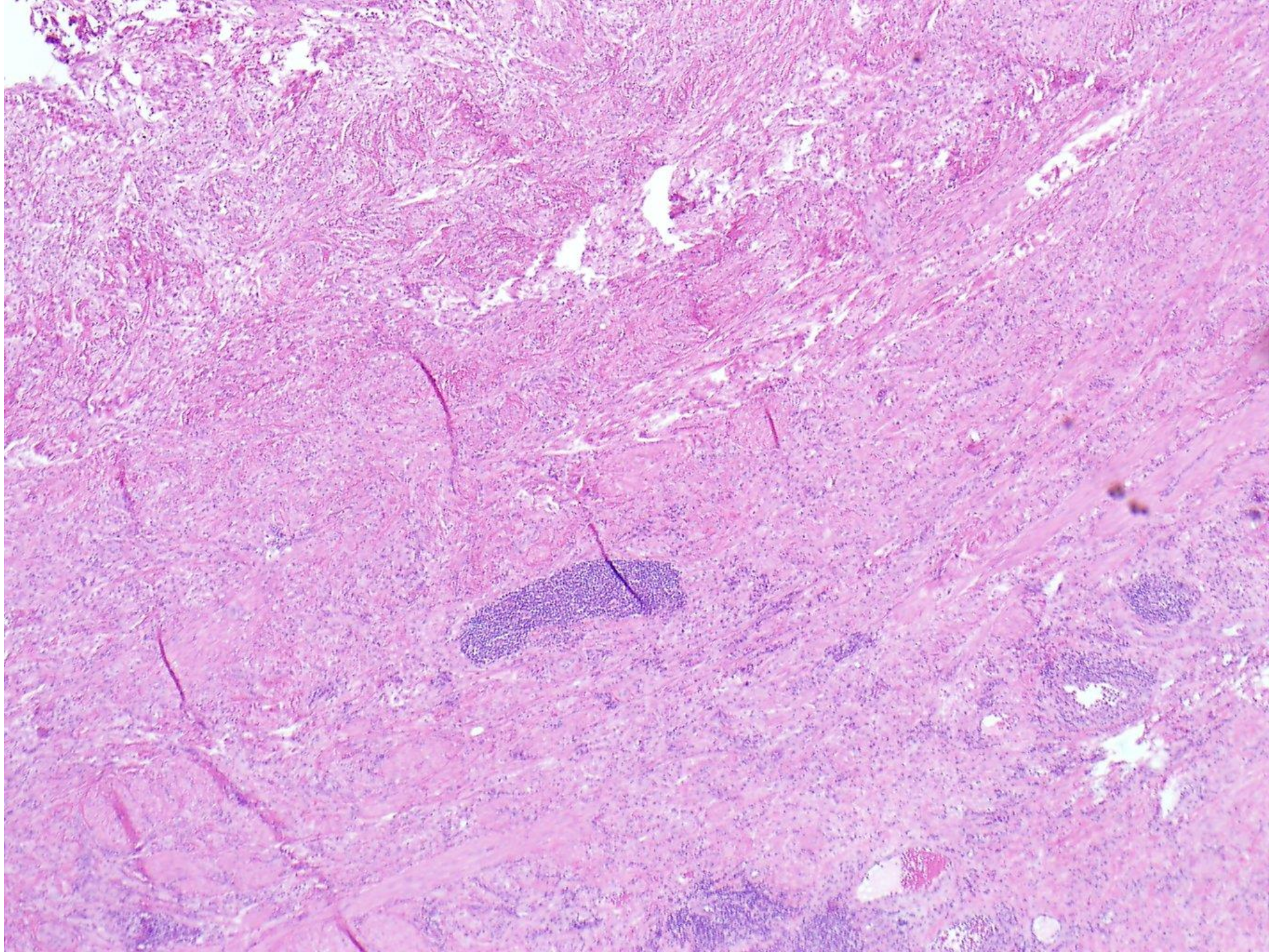


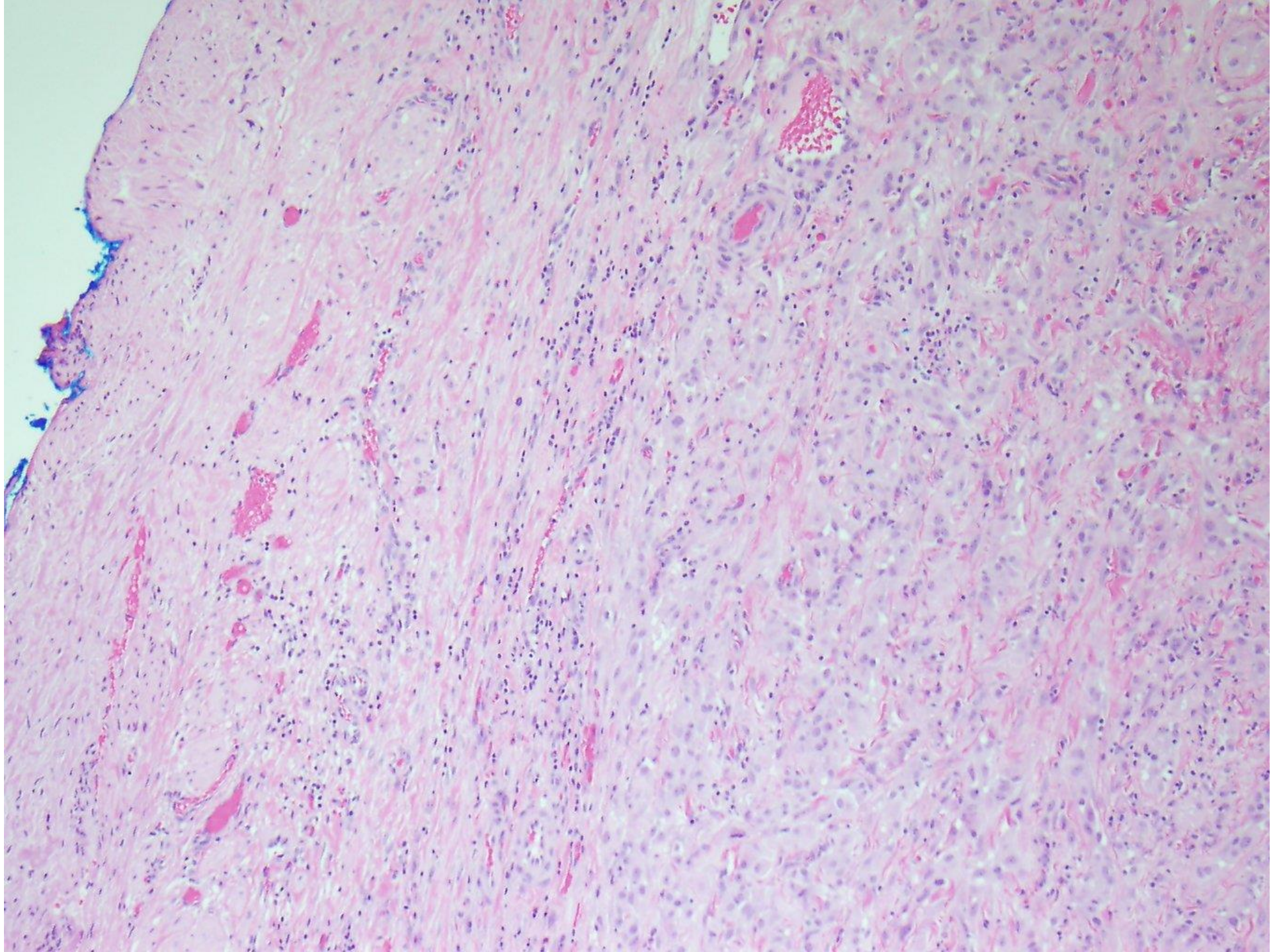


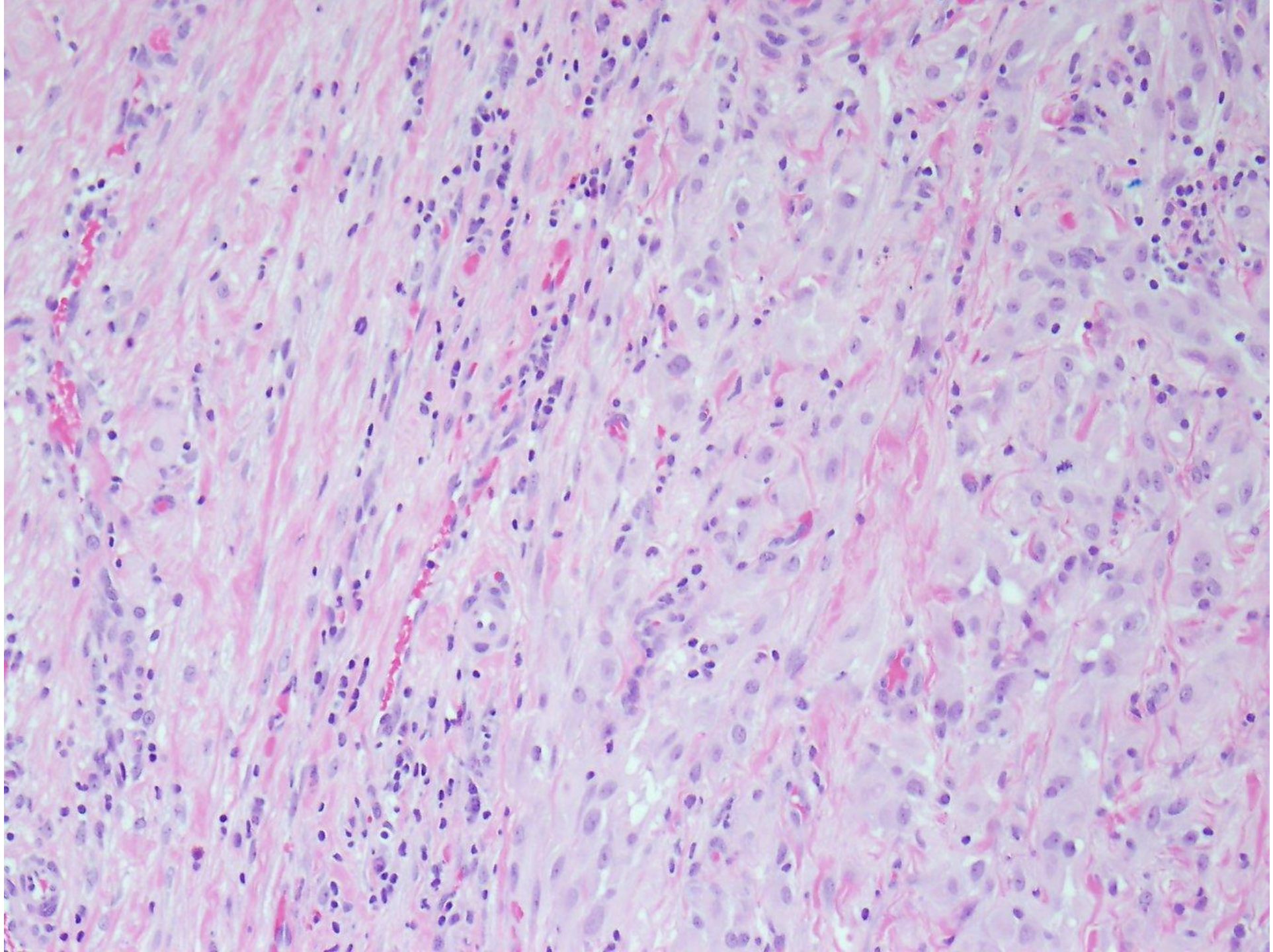


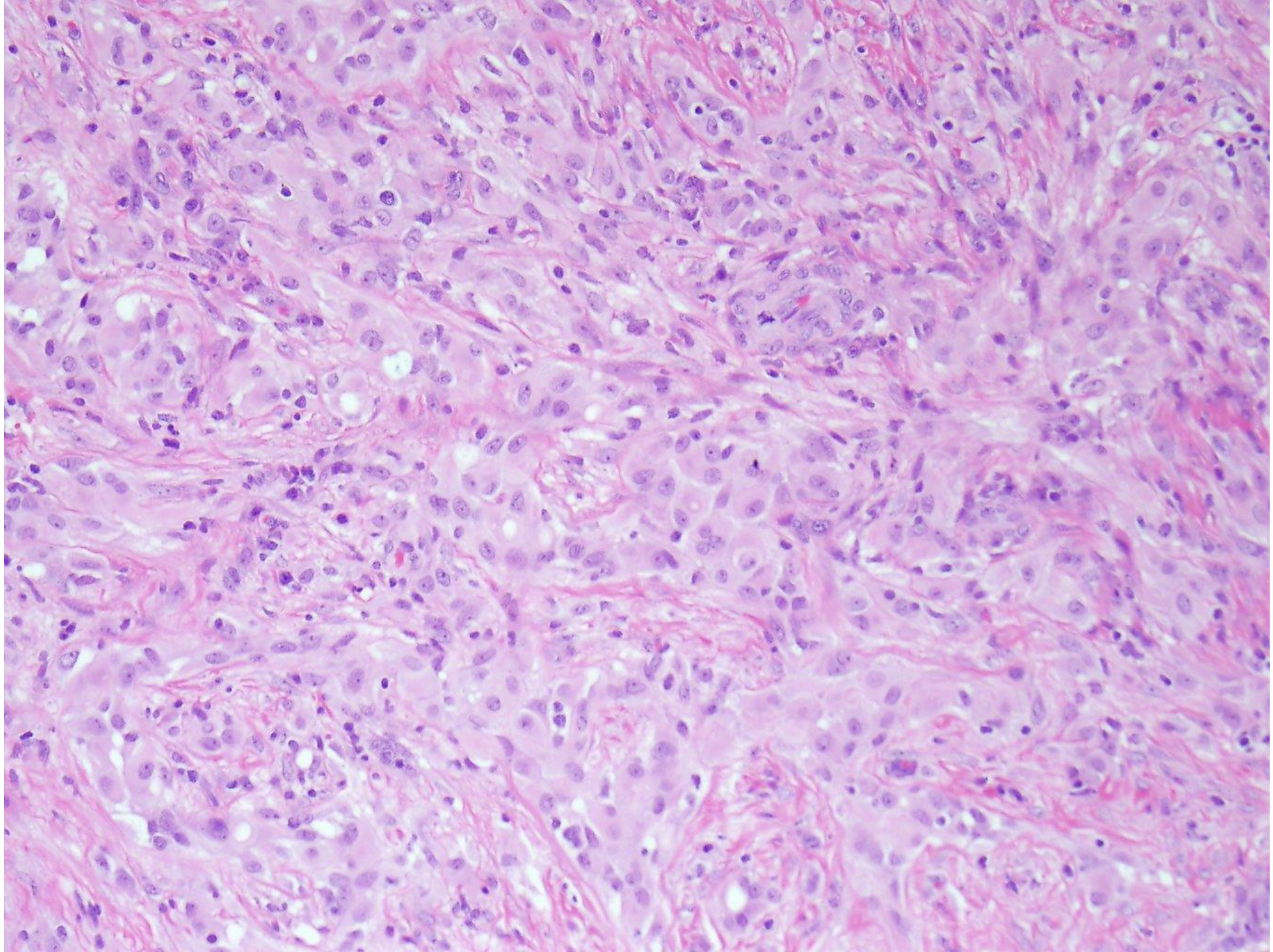


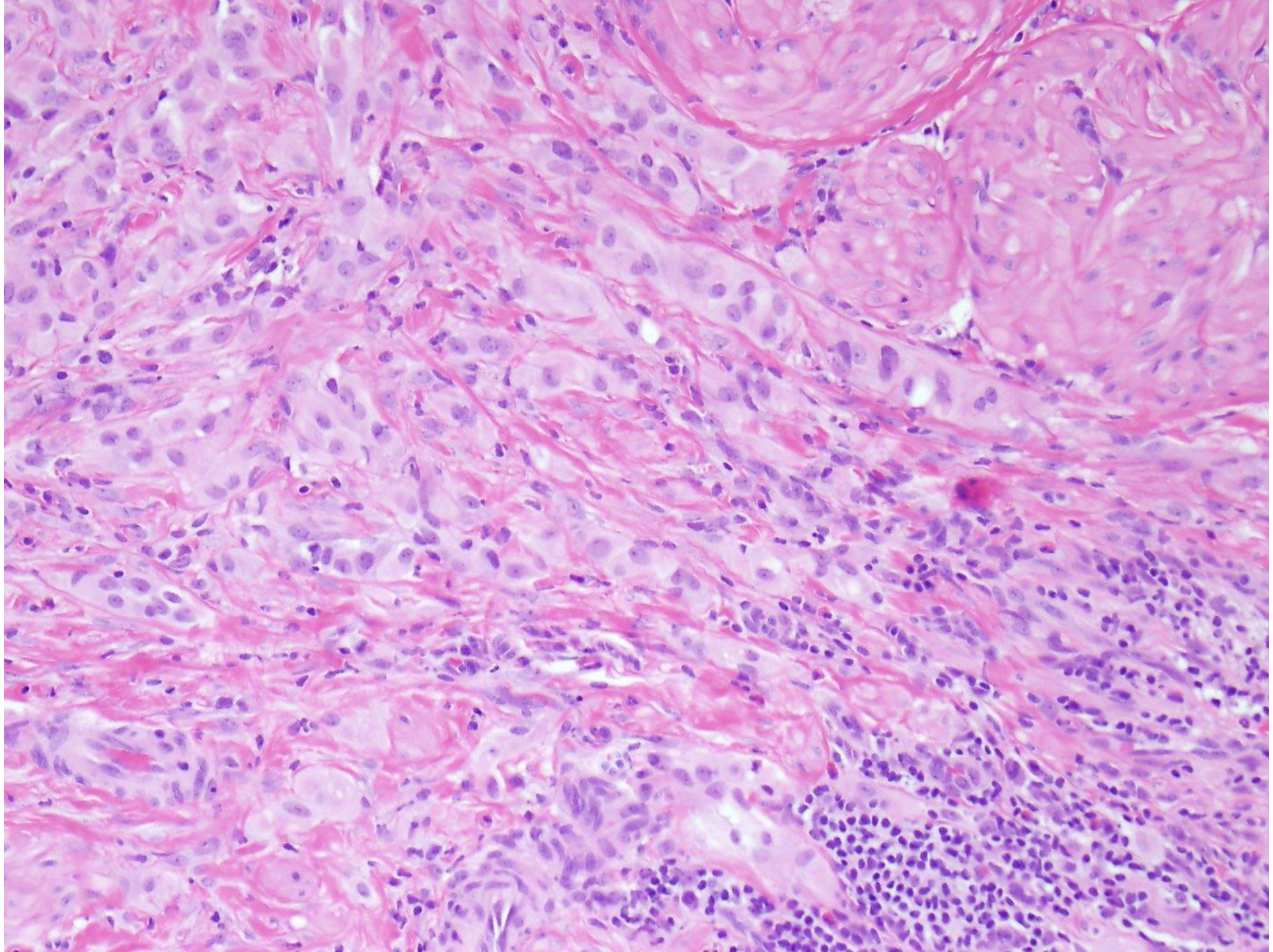












MORPHOLOGY AND IHC PROFILE

- Well Circumscribed and Non Encapsulated
- Minimal Invasion Into Surrounding Tissue
- Peripheral Lymphoid Aggregates
- Nests and Cords
- Round Nuclei and Abundant Pink Cytoplasm
- Central Necrosis
- WT-1 +
- CK7 +
- CK5 +
- CK20, HMB-45, GATA-3, SMA, INHIBIN –

DIAGNOSIS: INFARCTED ADENOMATOID TUMOR

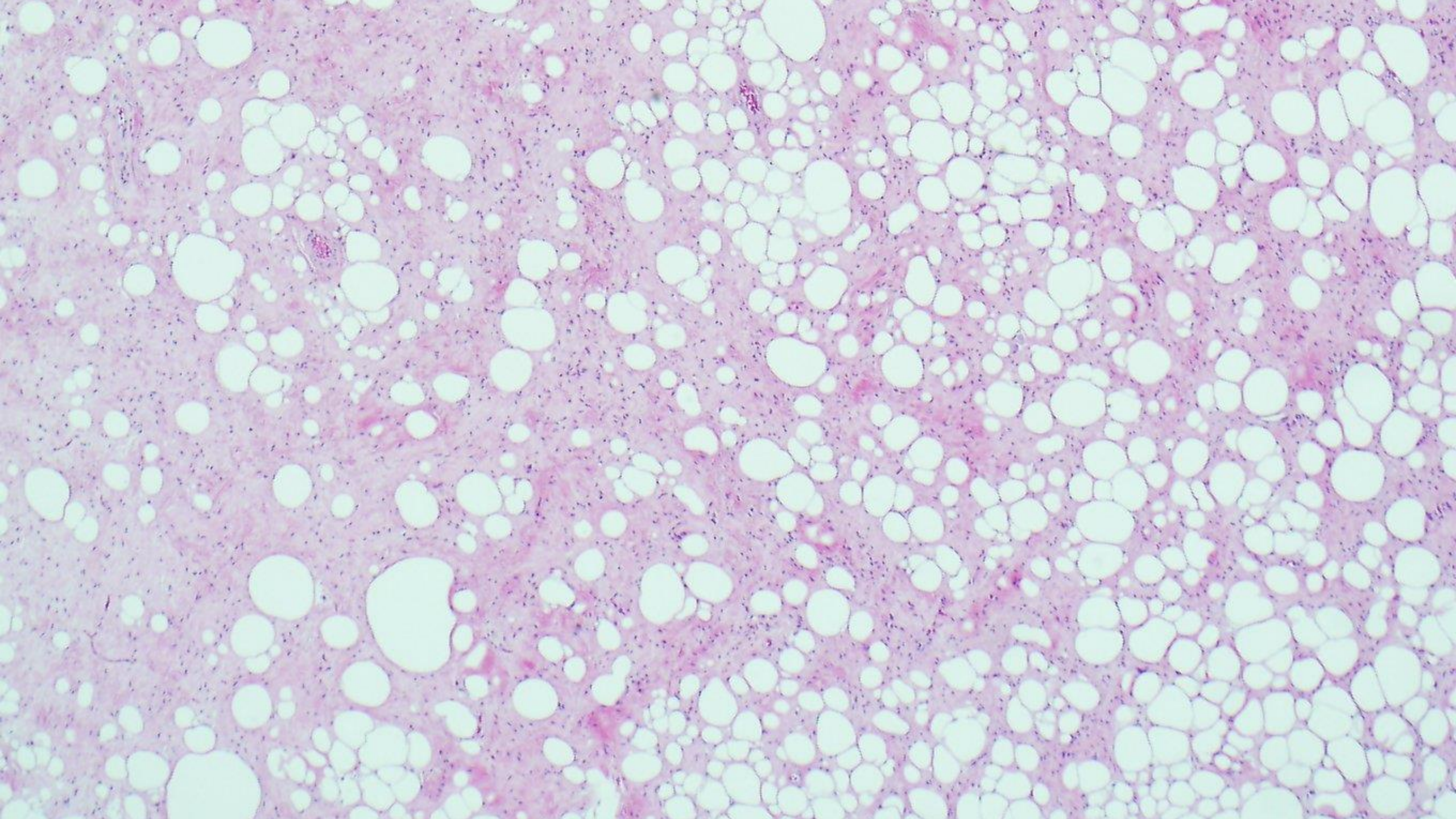
Differential Diagnosis:

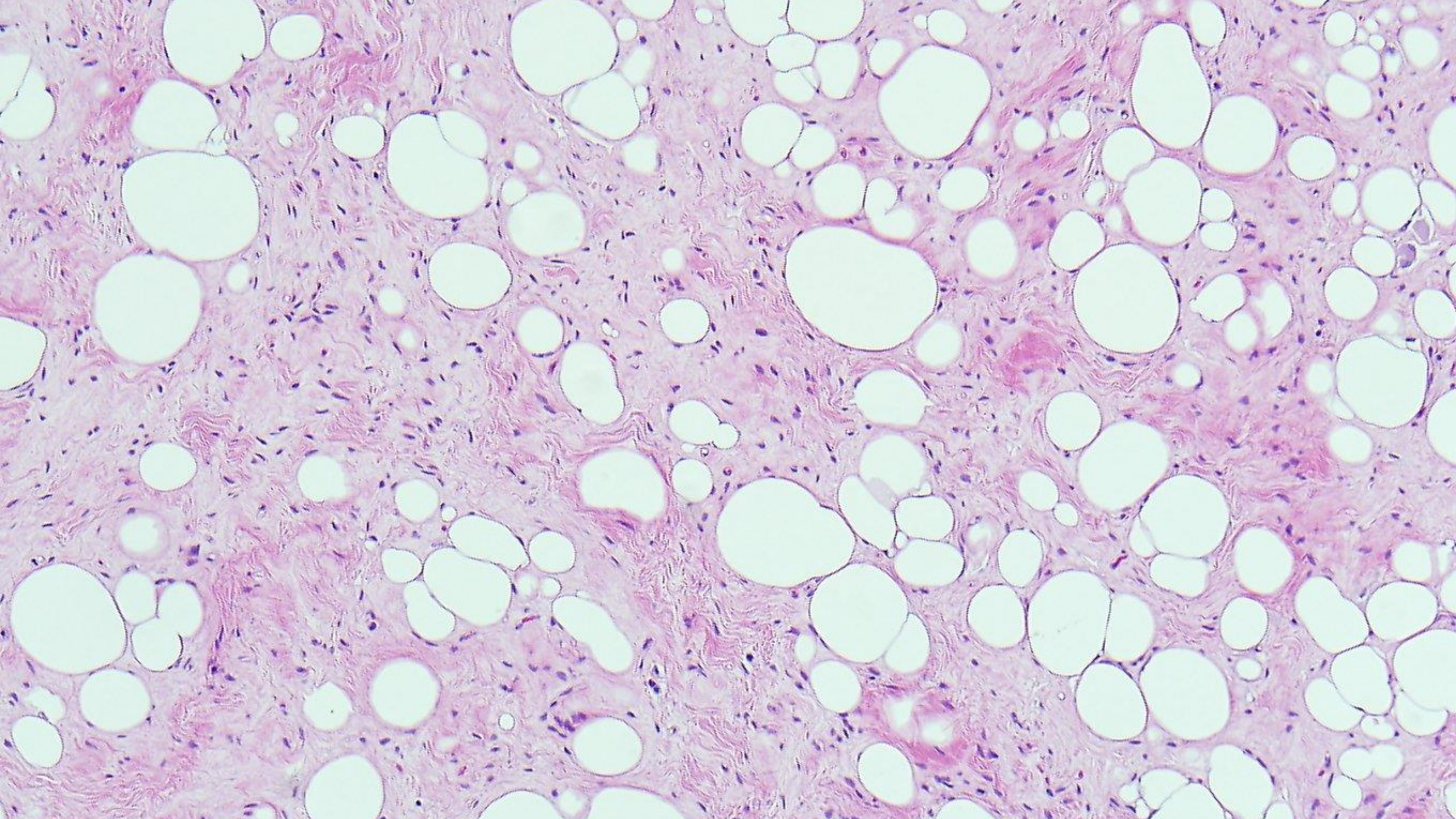
- Mesothelioma
  - Typically a gross papillary appearance with tumor studding of tunica
  - Microscopically infiltrative border and lack of circumscription and typically lacks adenomatoid-like vacuoles
  - Mitoses more common
- Leiomyoma/Leiomyosarcoma
- Vascular Lesions (Epithelioid Hemangioendothelioma/Angiosarcoma)
- Sex Cord Stromal Tumors
- Adenocarcinoma
- Epididymitis

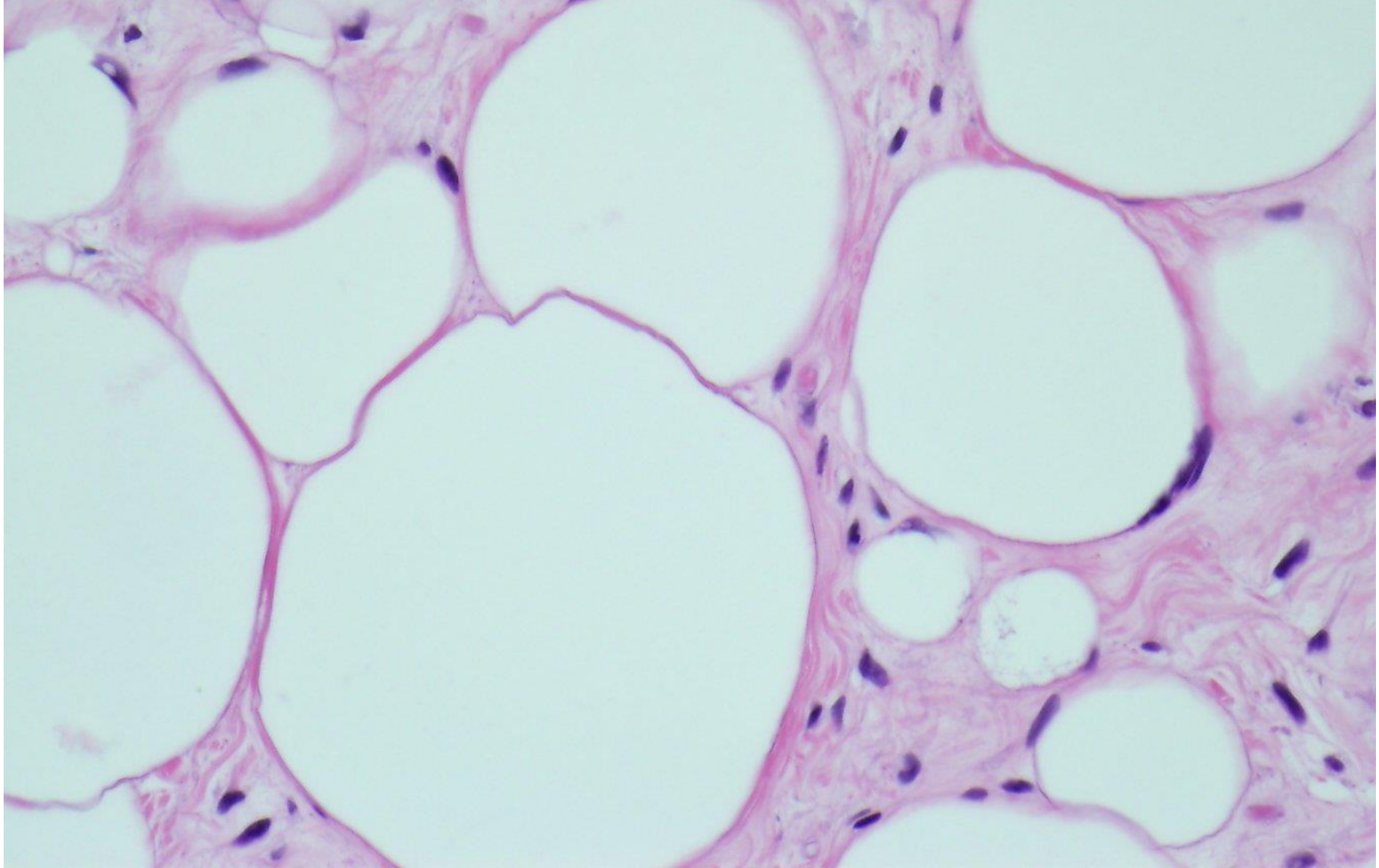
Skinnider, B. F. and R. H. Young (2004). Infarcted adenomatoid tumor: a report of five cases of a facet of a benign neoplasm that may cause diagnostic difficulty. Am J Surg Pathol **28**(1): 77-83.

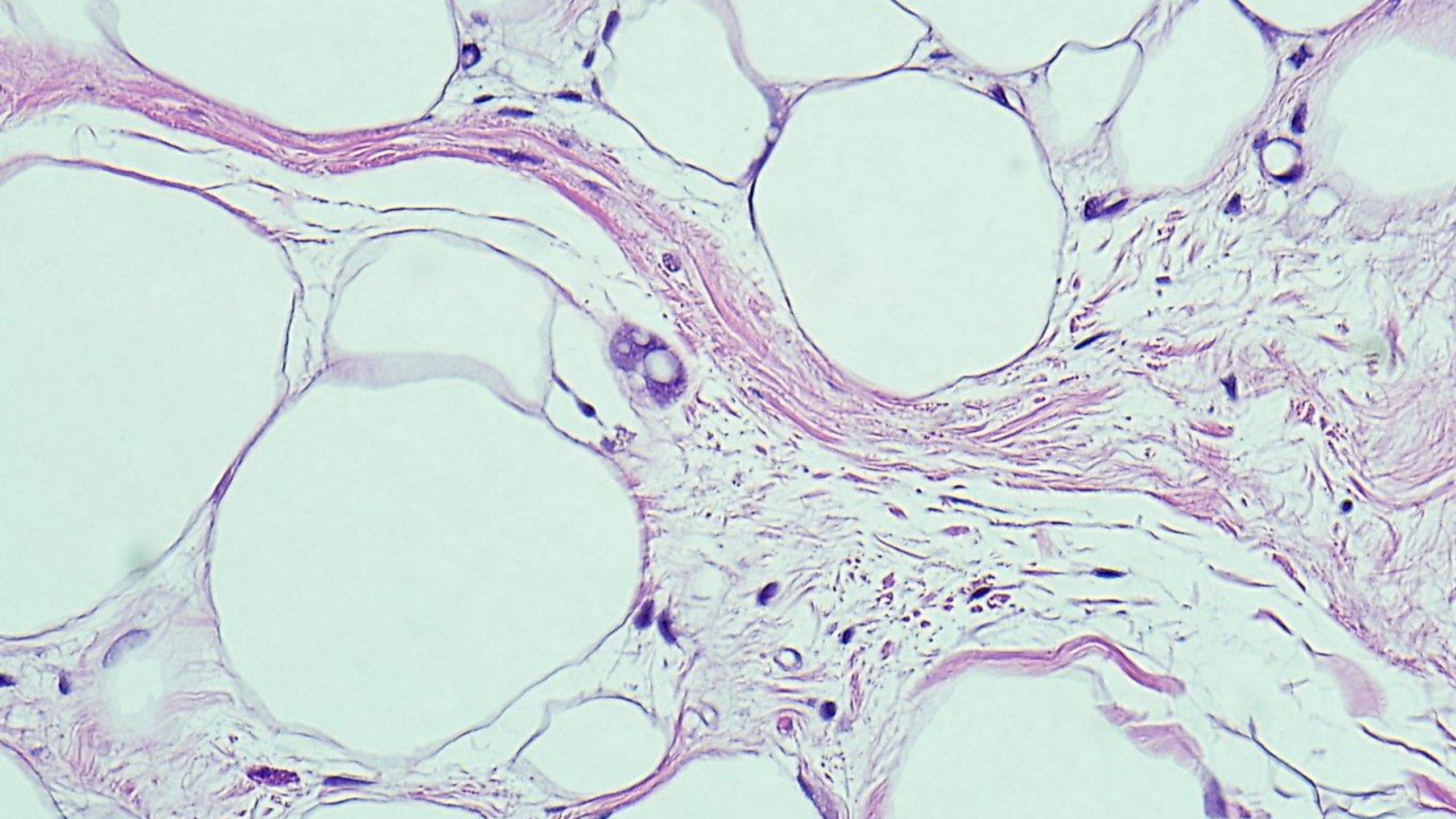
CASE #2: 46 YEAR OLD MALE WITH LONGSTANDING HISTORY OF RIGHT TESTICULAR GROWTH

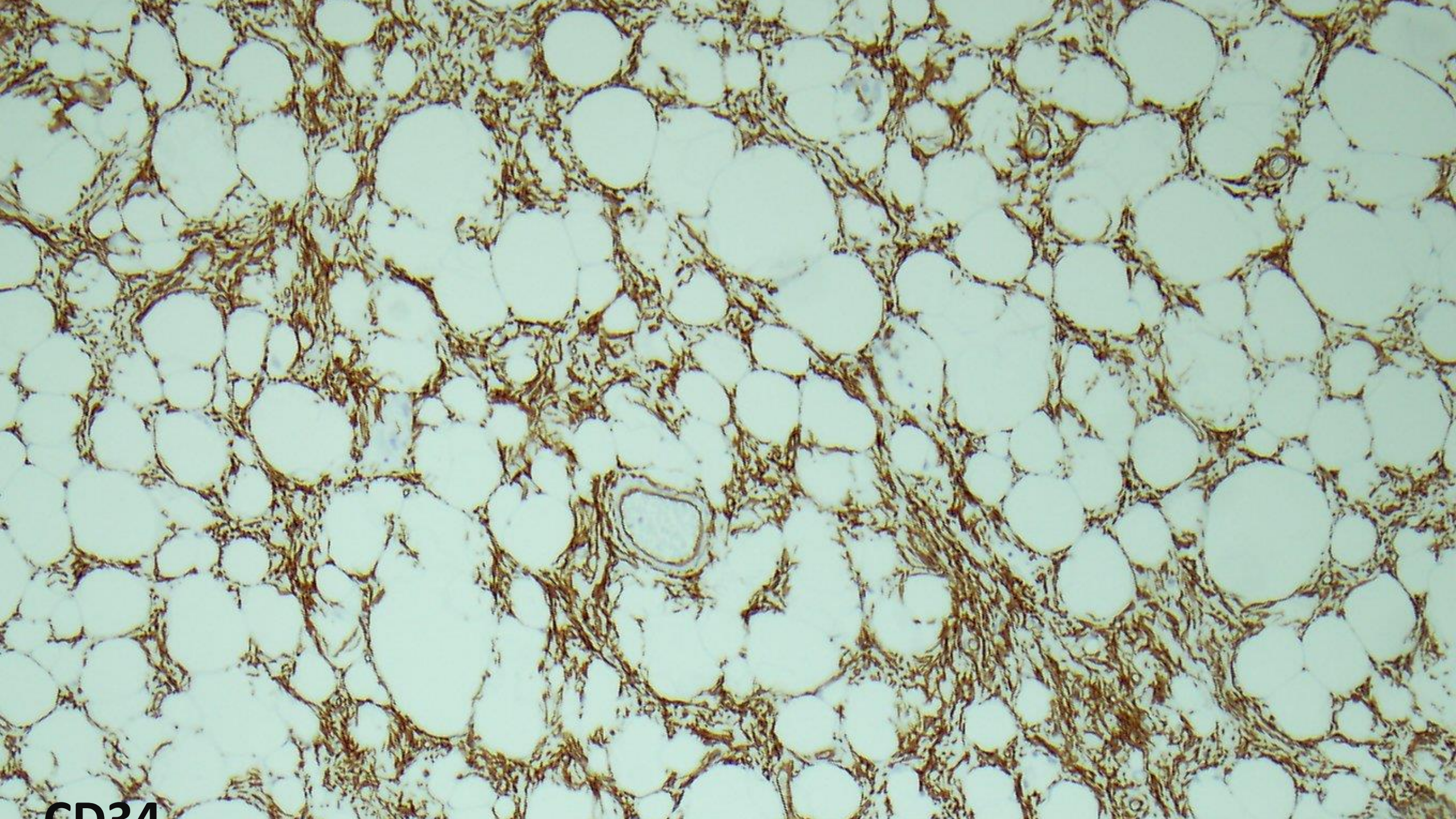
IMAGING FINDINGS: SCROTAL ULTRASOUND DEMONSTRATED A 4 X 2.4 CM HETEROGENOUS HYPERECHOIC MASS ARISING FROM THE RIGHT POSTERIOR-INFERIOR SCROTAL WALL.










CD34

MORPHOLOGY AND IHC PROFILE

- Somewhat delineated lesion with bland spindle cells, mature adipocytes, and occasional uni- and mutivacuolated lipoblasts
- Collagenous to myxoid extracellular matrix
- Mild cytologic atypia with nuclear hyperchromasia
- No obvious mitoses
- No necrosis
- CD34 (+)
- CD10, DESMIN, SMA (-)
- Negative for MDM2 Amplification (NORMAL)
  - MDM2/CEP12 Ratio: 1.0
  - Average MDM2 Signal Number per Cell: 1.8

DIAGNOSIS: ATYPICAL SPINDLE CELL LIPOMATOUS NEOPLASM

Clincial Behavior: Most cured by surgery but 10-15% may recur locally. No reported metastasis

IHC: CD34 > S100 > Desmin; Rarely MDM2 and CDK4 weakly positive (never both simultaneously); nuclear pRB may be lost

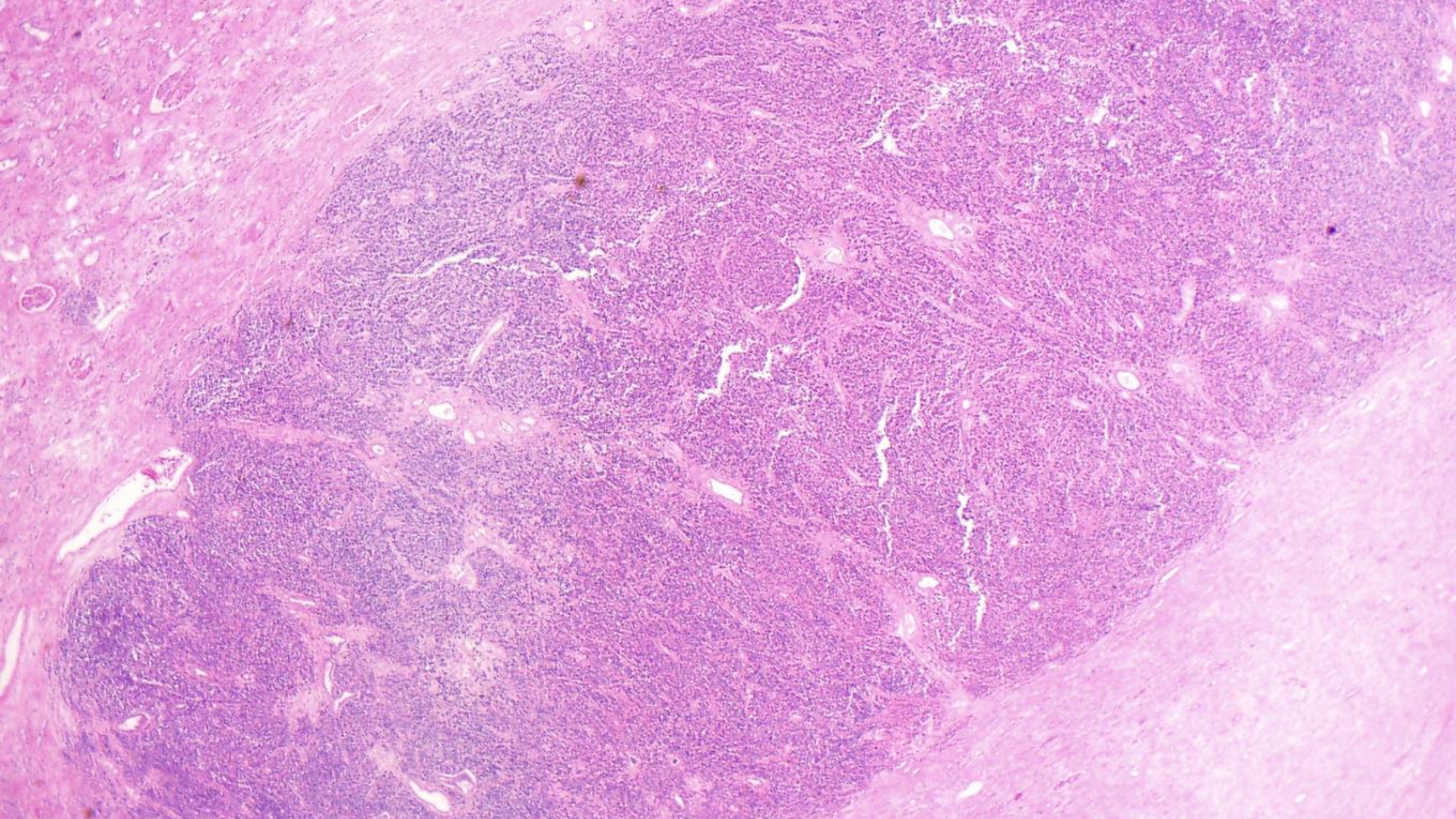
Differential Diagnosis

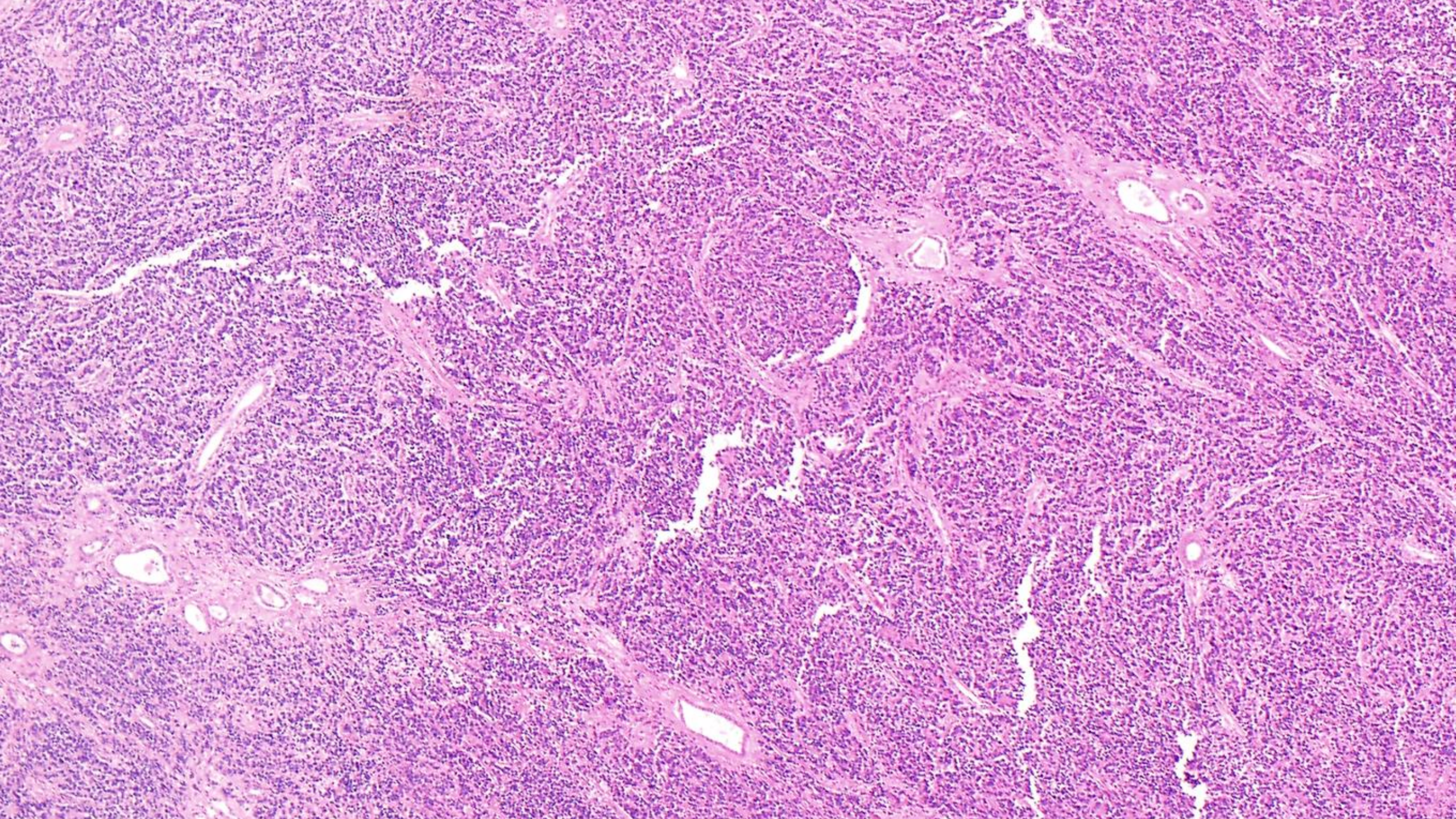
- Extramammary and Mammary Type Fibroblastoma (closely related entity)
  - Well circumscribed
  - CD34 and Desmin positive
  - Nuclear pRB may be lost
- Liposarcoma
- Spindle Cell Lipoma
- DFSP
- Neurofibroma
- Fat Forming Solitary Fibrous Tumor

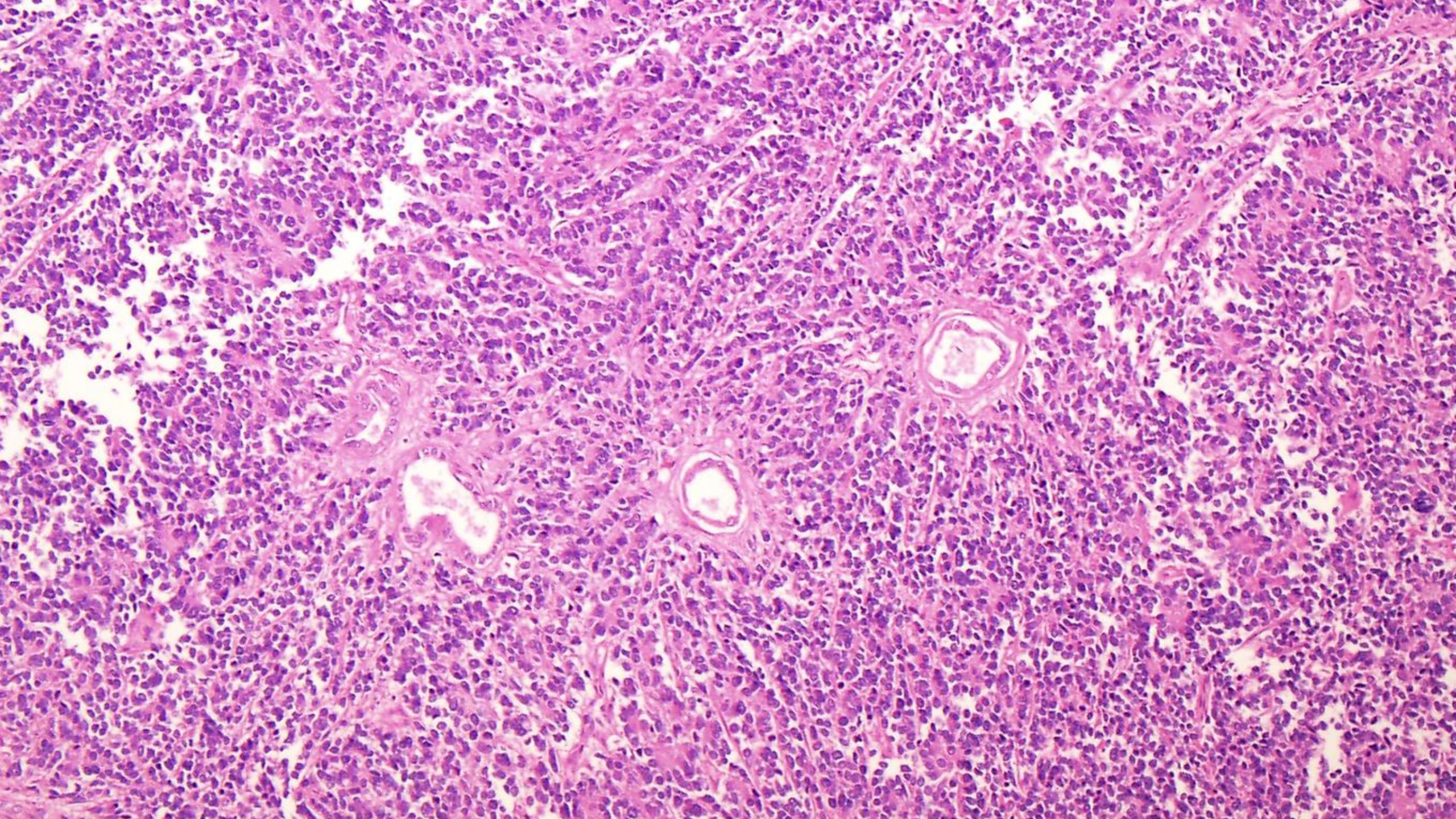
Marino-Enriquez, A., et al. (2017). "Atypical Spindle Cell Lipomatous Tumor: Clinicopathologic Characterization of 232 Cases Demonstrating a Morphologic Spectrum." Am J Surg Pathol **41**(2): 234-244.

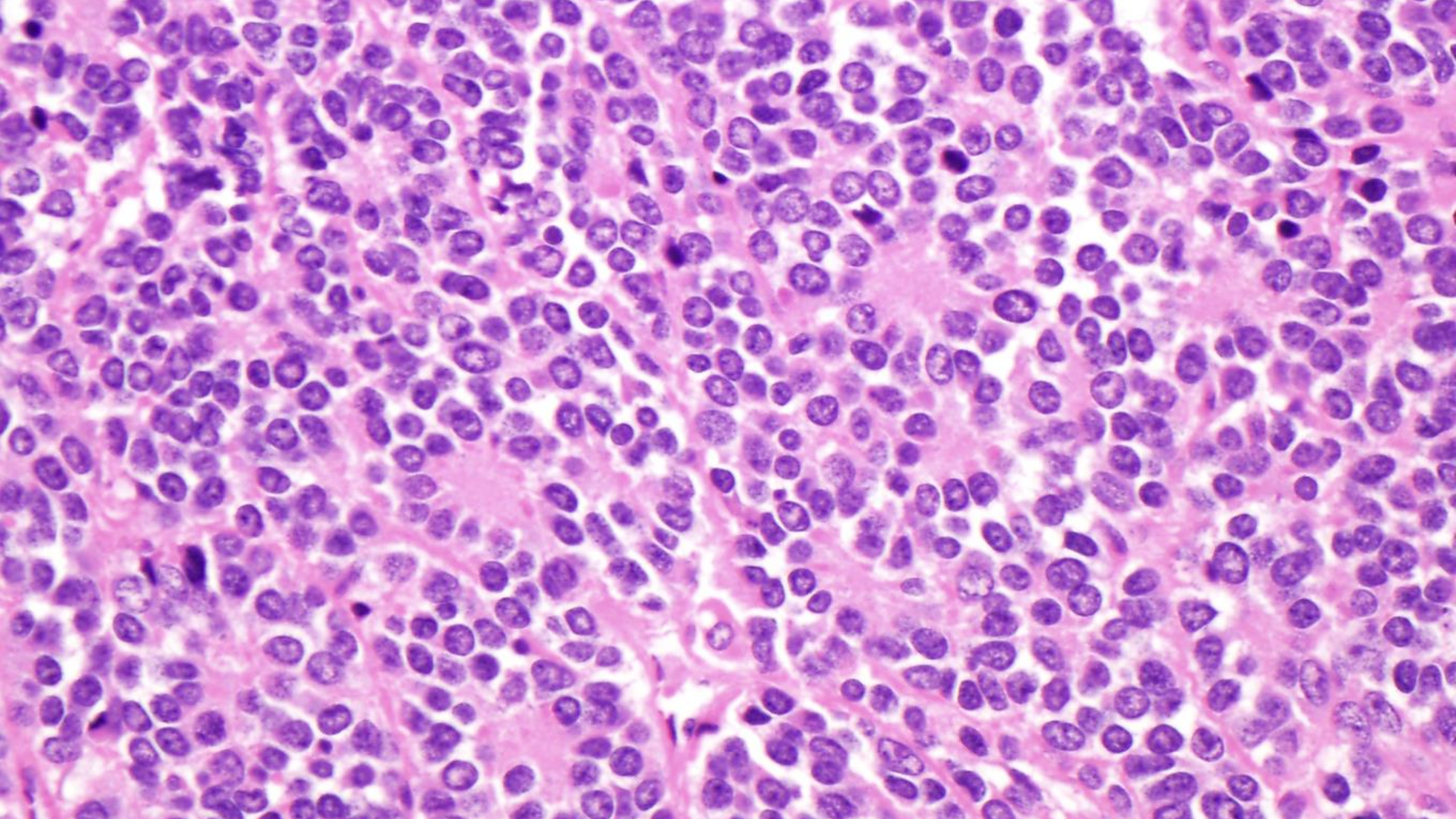
Howitt, B. E. and C. D. Fletcher (2016). "Mammary-type Myofibroblastoma: Clinicopathologic Characterization in a Series of 143 Cases." Am J Surg Pathol **40**(3): 361-367.

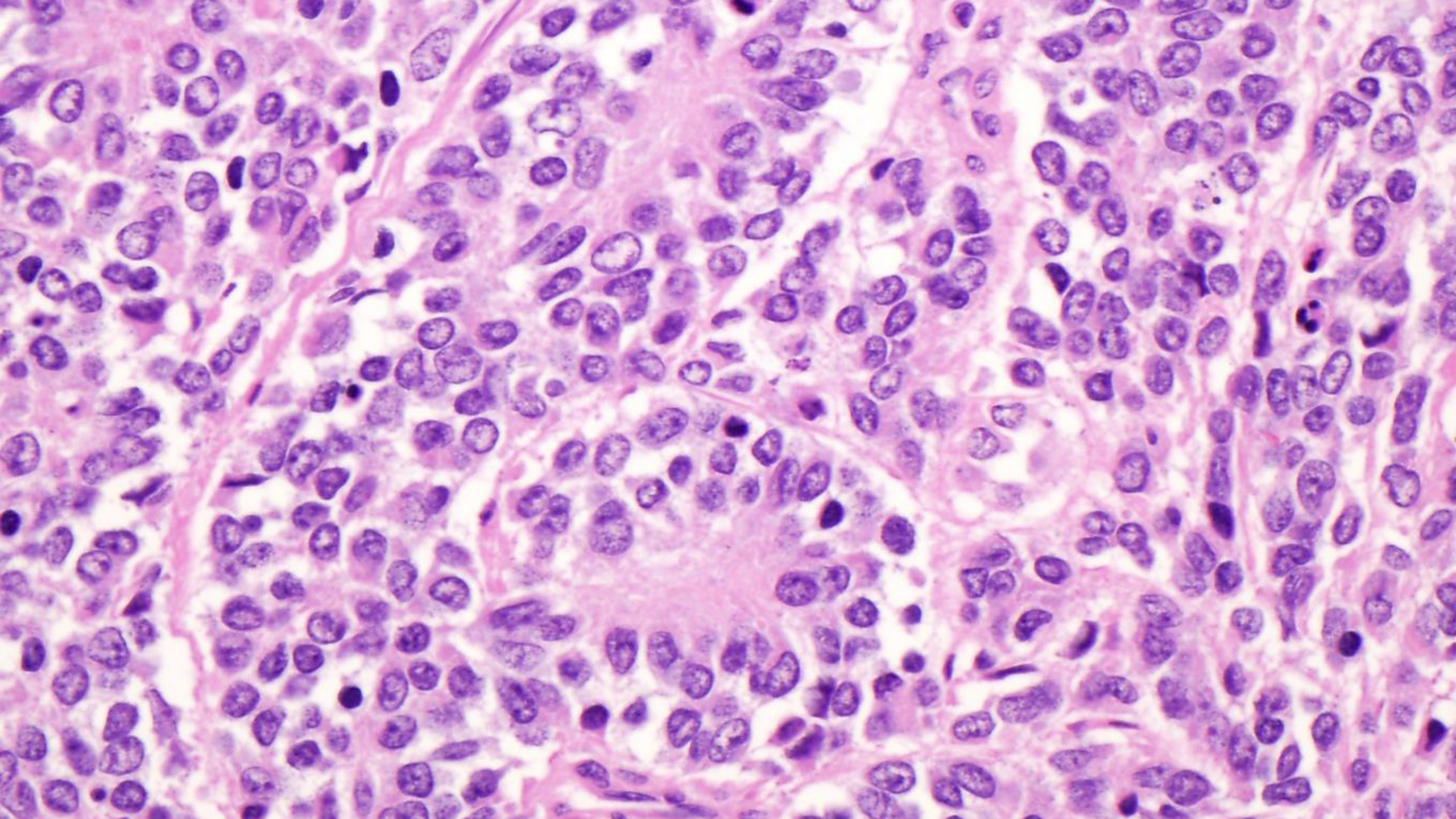
Case #3: 66 yo female with 14 cm renal mass

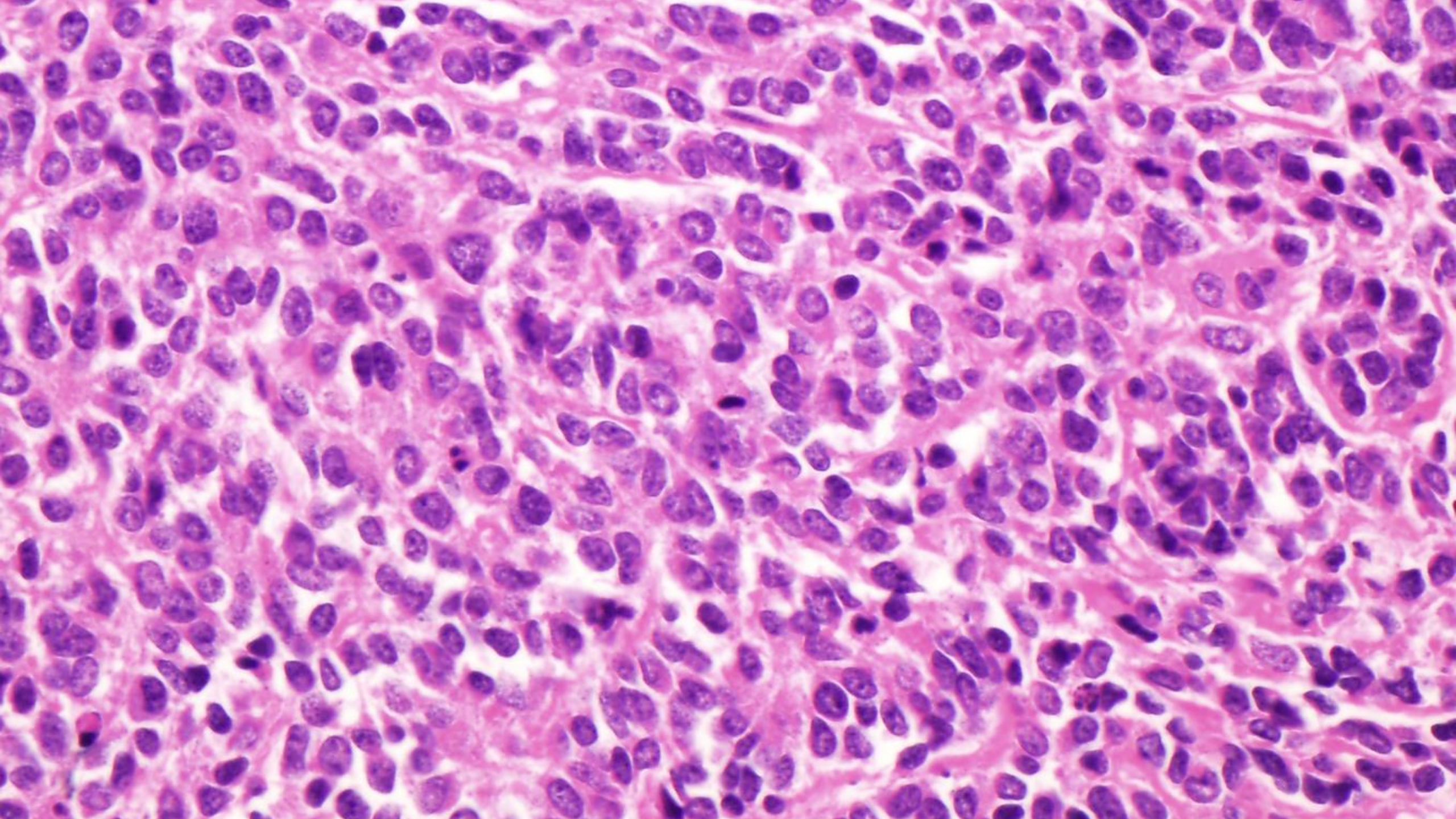


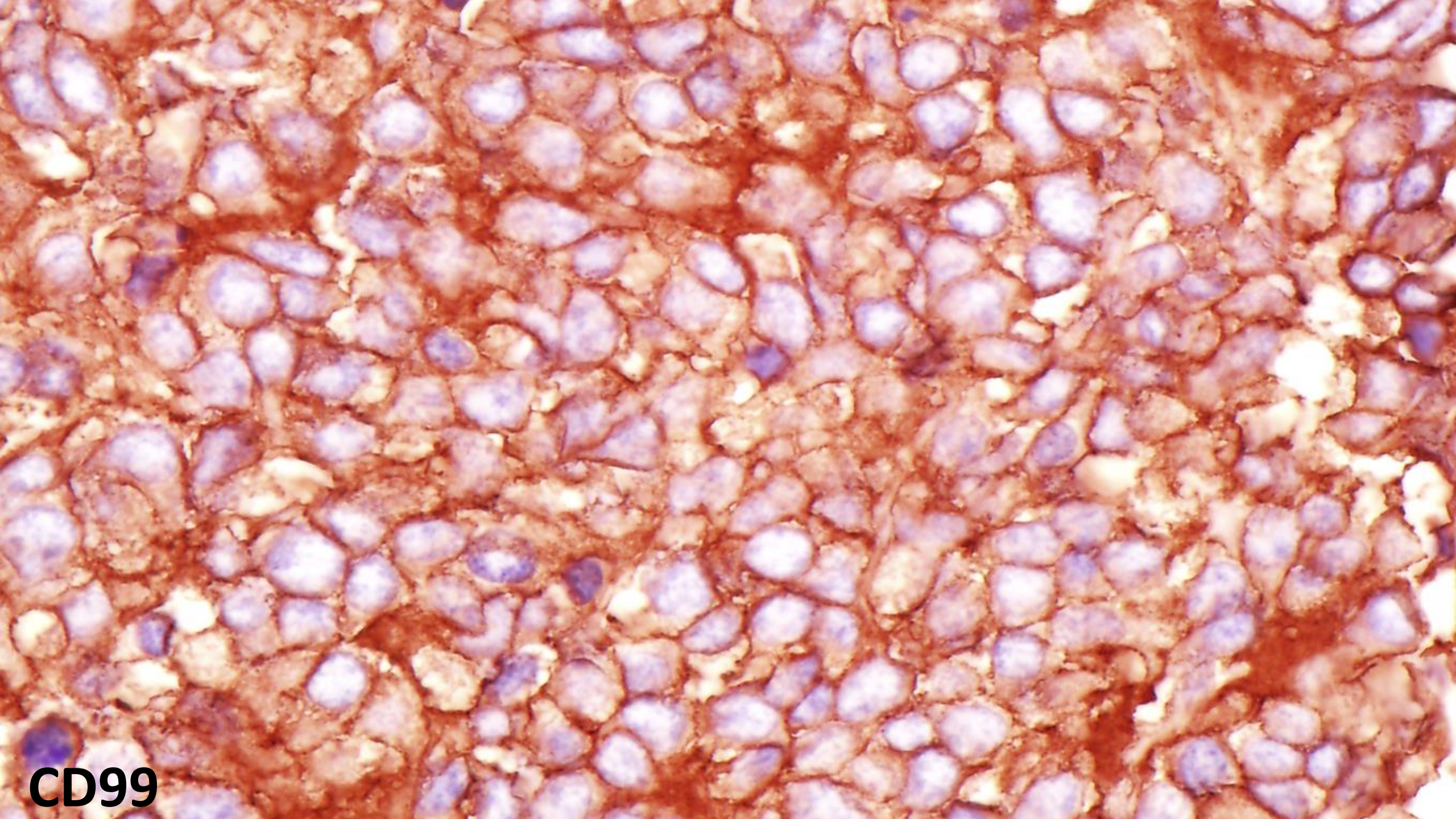


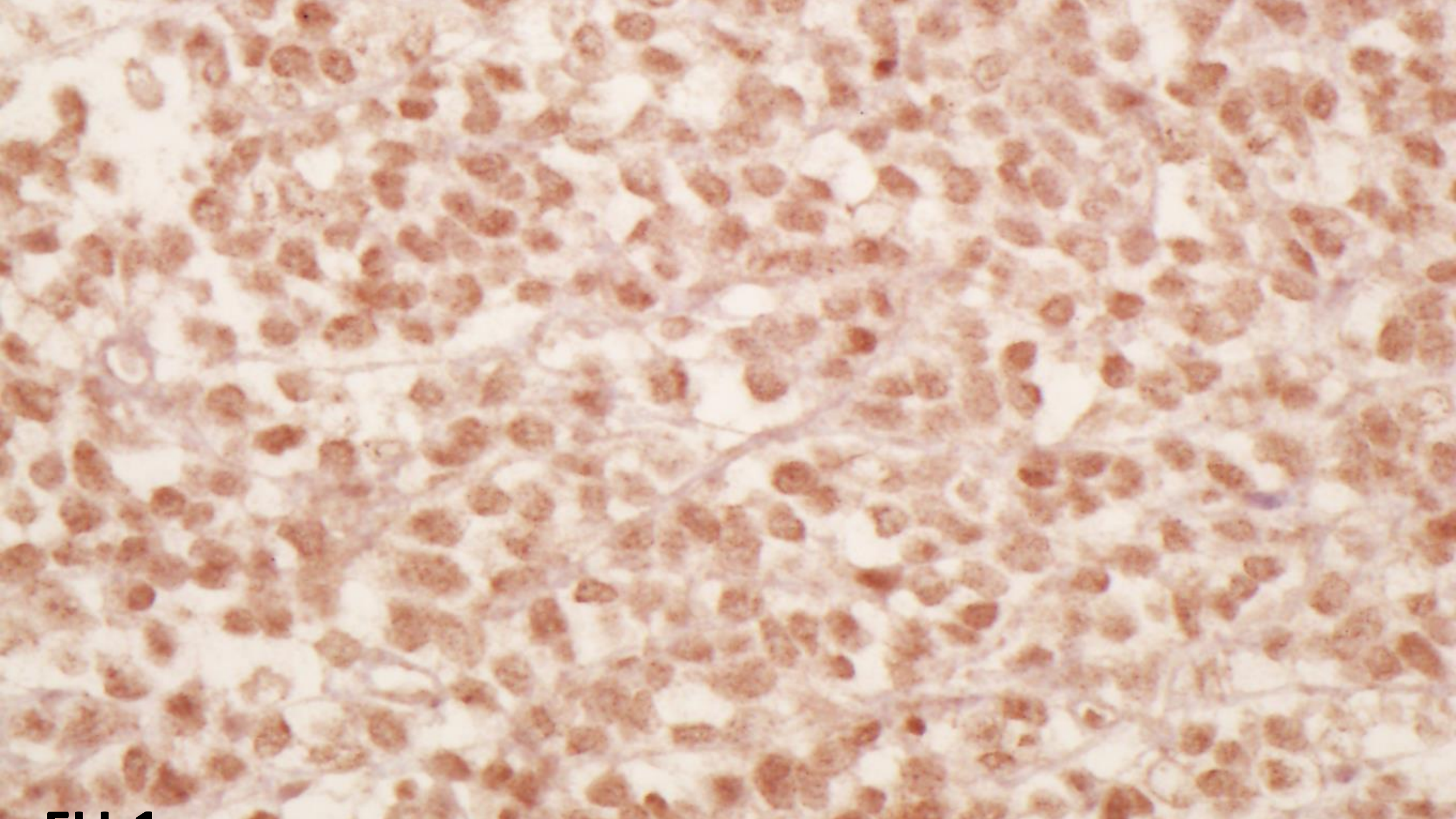


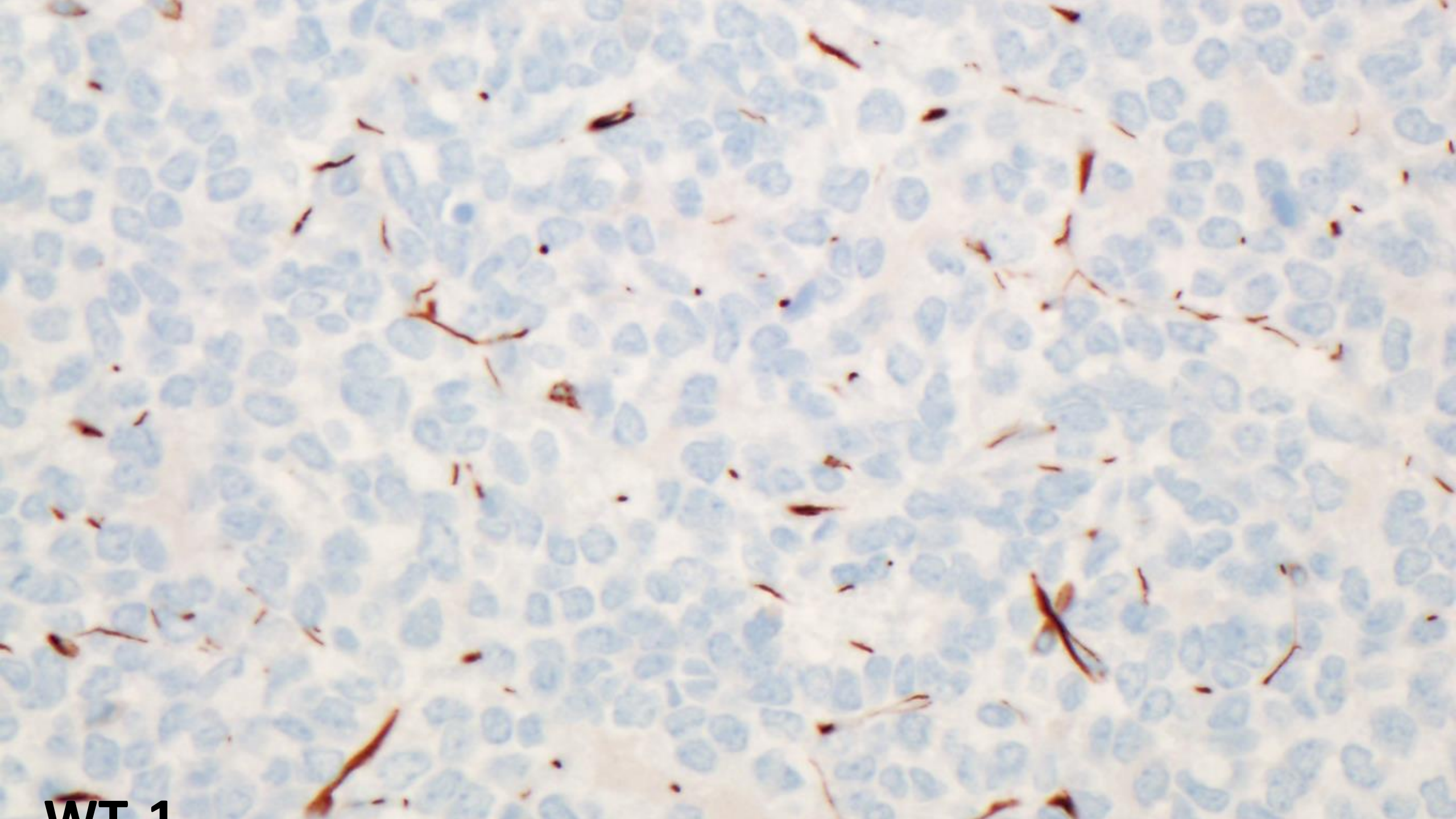


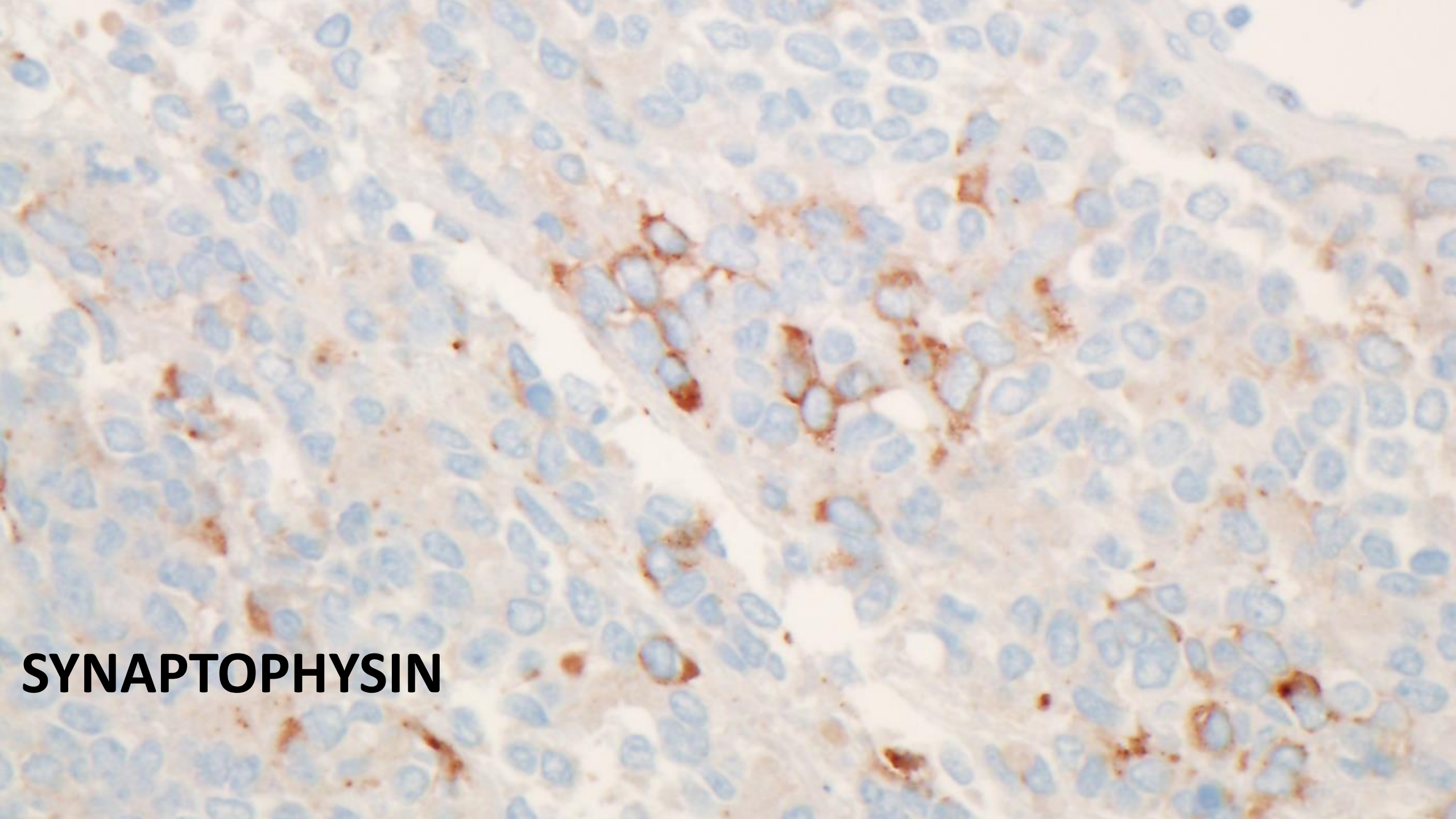





CD99




WT-1

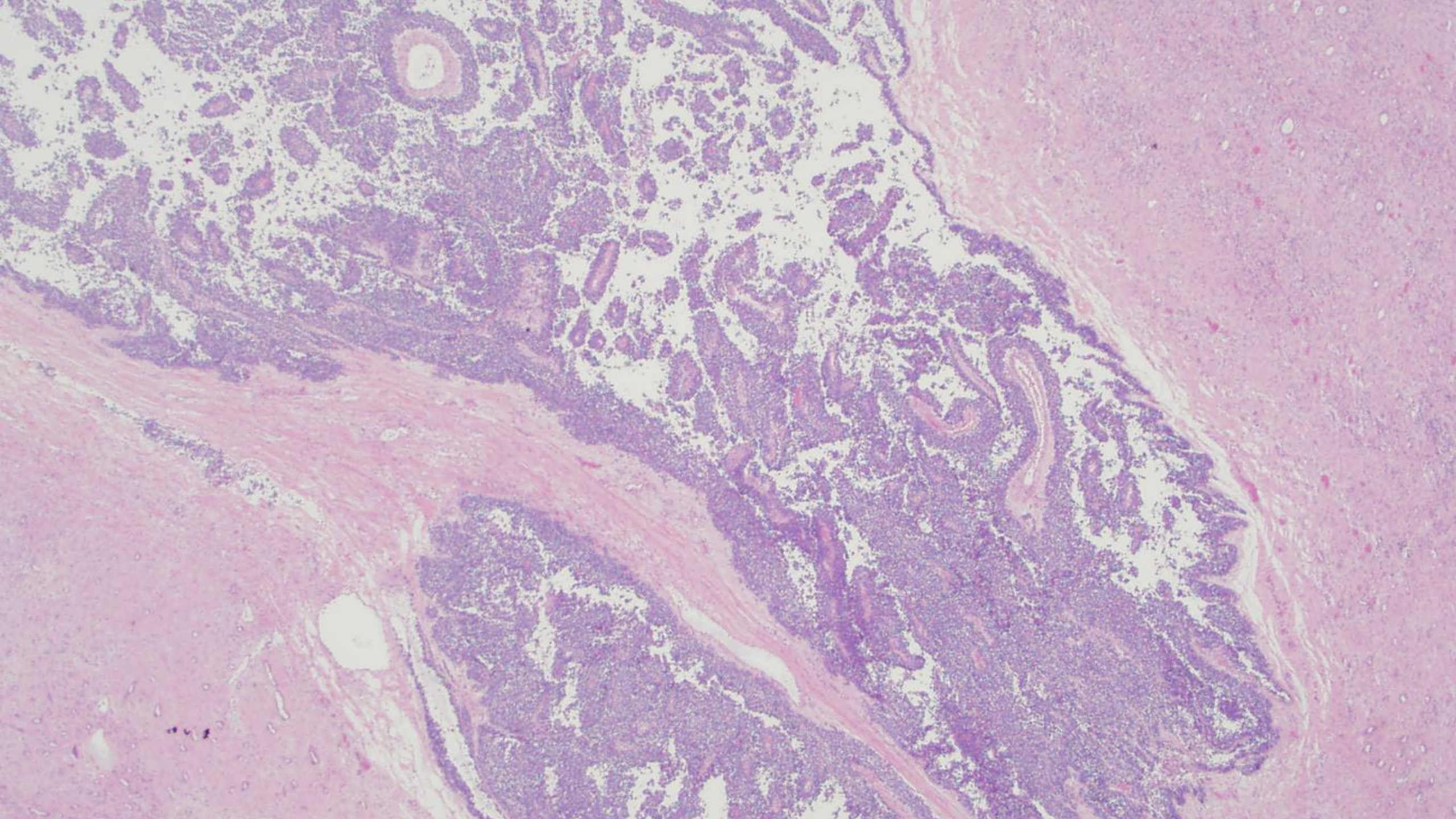

SYNAPTOPHYSIN

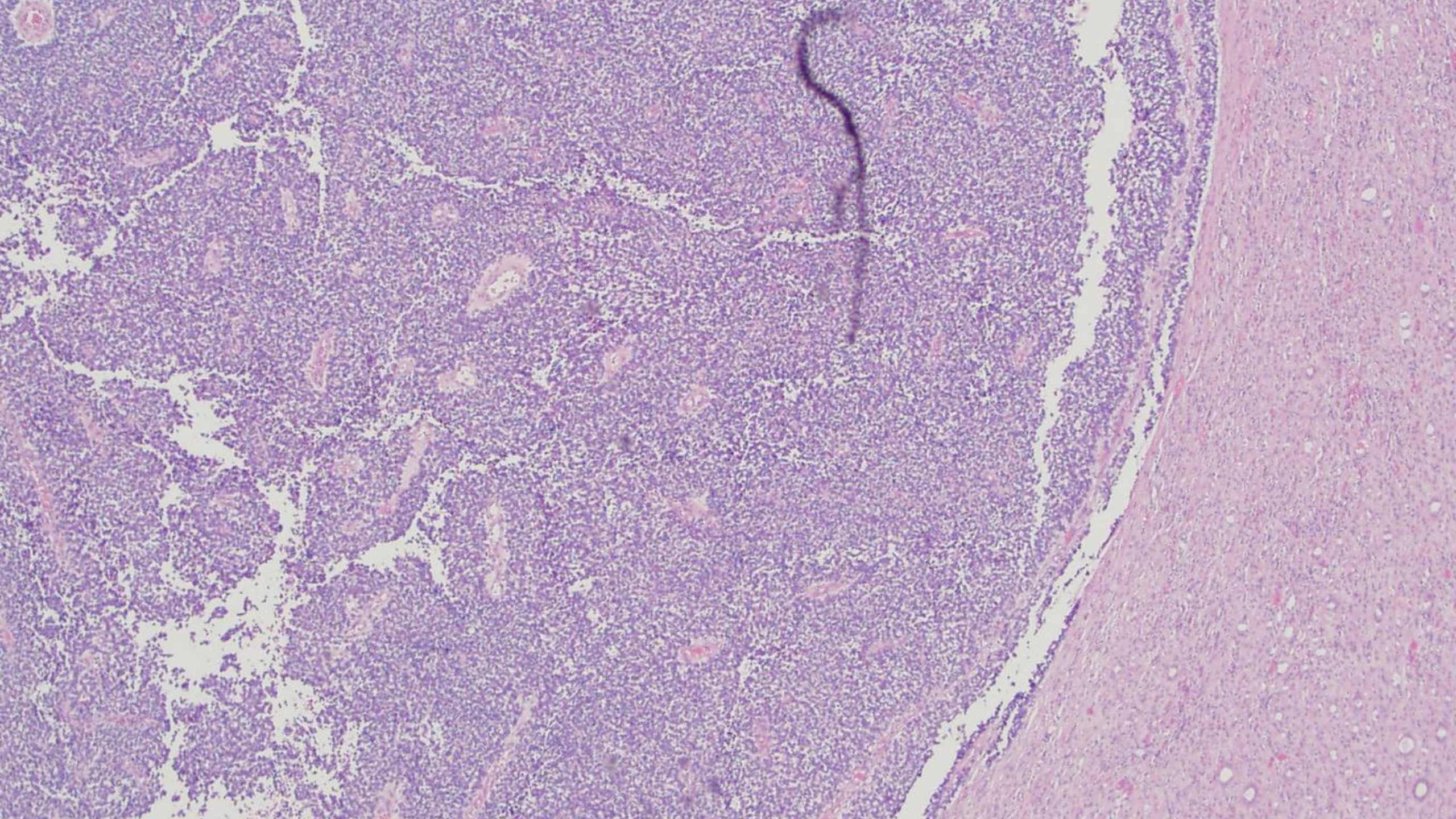
MORPHOLOGY AND IHC PROFILE:

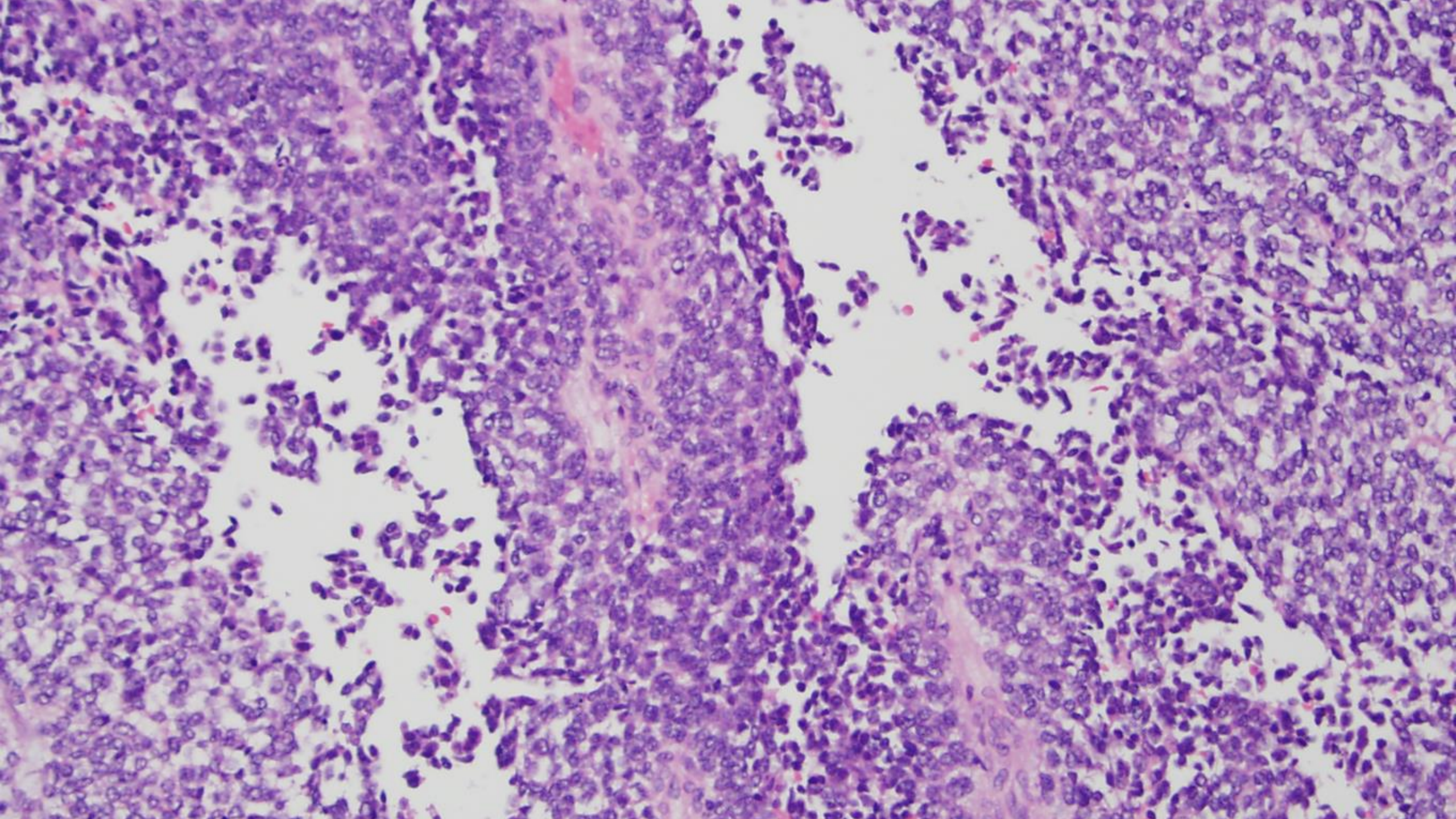
- Lobulated proliferation of primitive appearing cells
- Scant cytoplasm, vesicular nuclei, and small nucleoli
- Frequent mitotic figures and necrosis
- Homer Wright (pseudo) rosettes

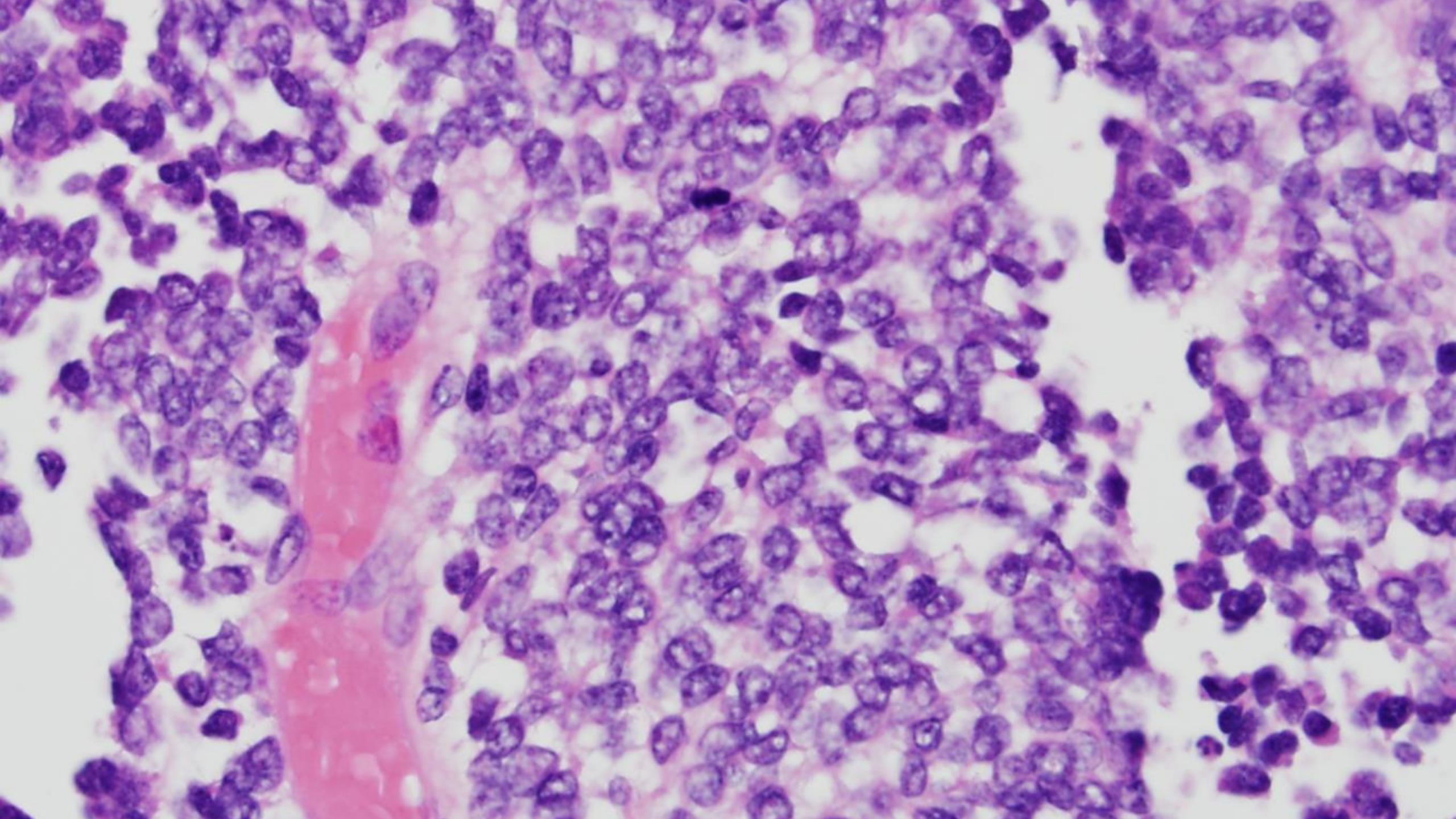
- CD99 (+)
- FLI-1 (+)
- WT-1 (-)
- Synaptophysin (focal +)
- CD45 (-)
- Desmin (-)

28 year old male with history of flank pain found to have a 10 cm renal mass.





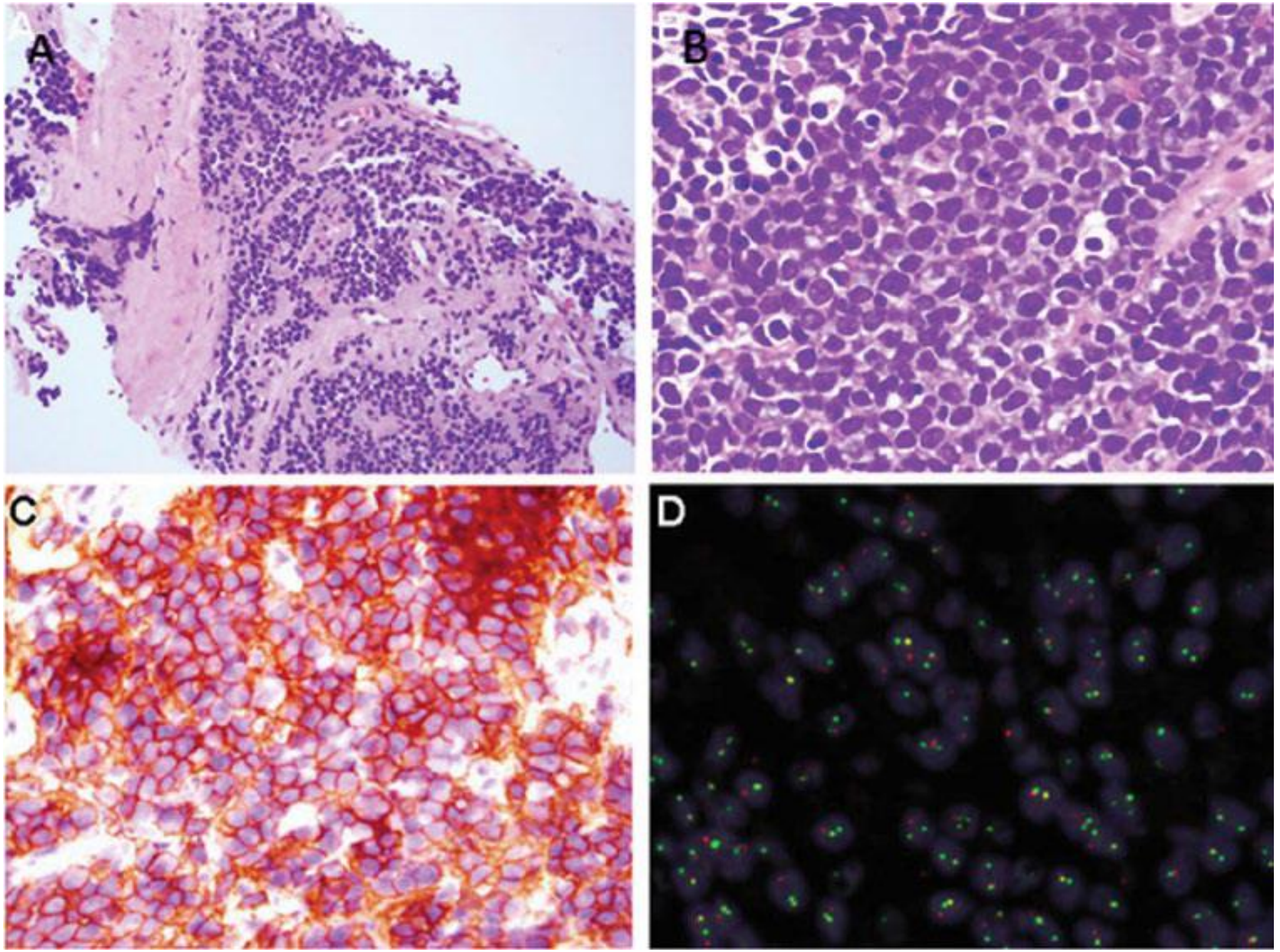




MORPHOLOGY AND IHC PROFILE:

- Lobulated proliferation of primitive appearing cells
- Scant cytoplasm, vesicular nuclei, and small nucleoli
- Frequent mitotic figures and necrosis

- CD99 (+)
- FLI-1 (+)
- Myogenin (-)
- Desmin (-)
- CD45 (-)



*Monument MJ, Grossman AH, Baker CC, Randall RL, Liu T, Albertson D. Molecular Confirmation of Ewing Sarcoma in an 85-Year-Old Woman.Int J Surg Pathol. 2015 Sep;23(6):500-4

- ADDITIONAL FISH TESTING FOR EWS PERFORMED IN BOTH CASES:
  - BOTH (+) FOR EWS REARRANGEMENT

- DIAGNOSIS:
  - PRIMITIVE NEUROECTODERMAL TUMOR (PNET/EWINGS SARCOMA)

EWINGS/PNET KIDNEY

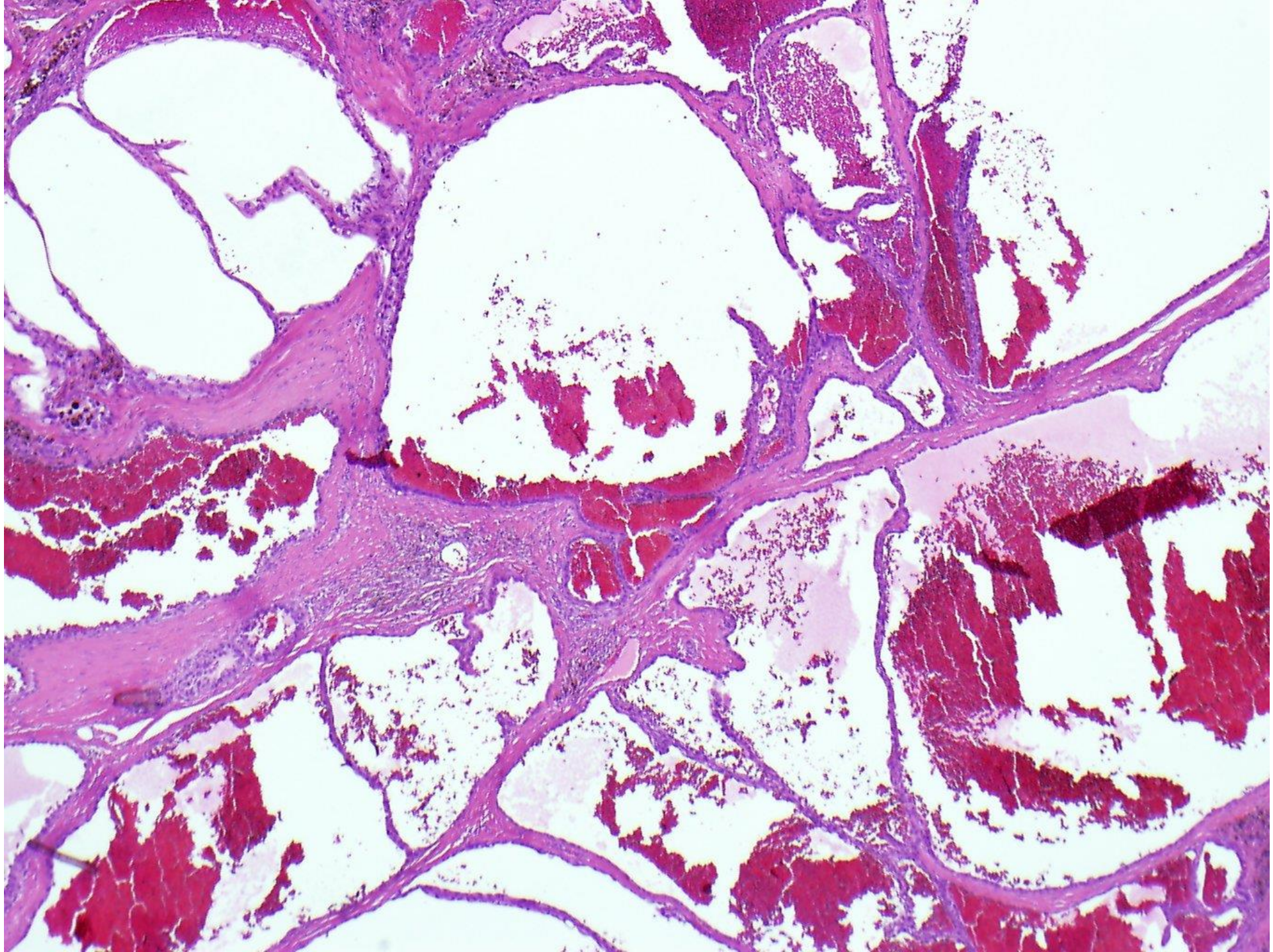
- Most common rearrangement is EWS-FLI1 translocation with gene fusion t(11;22)(q24;q12)
- Majority have strong CD99 staining and are WT-1 negative

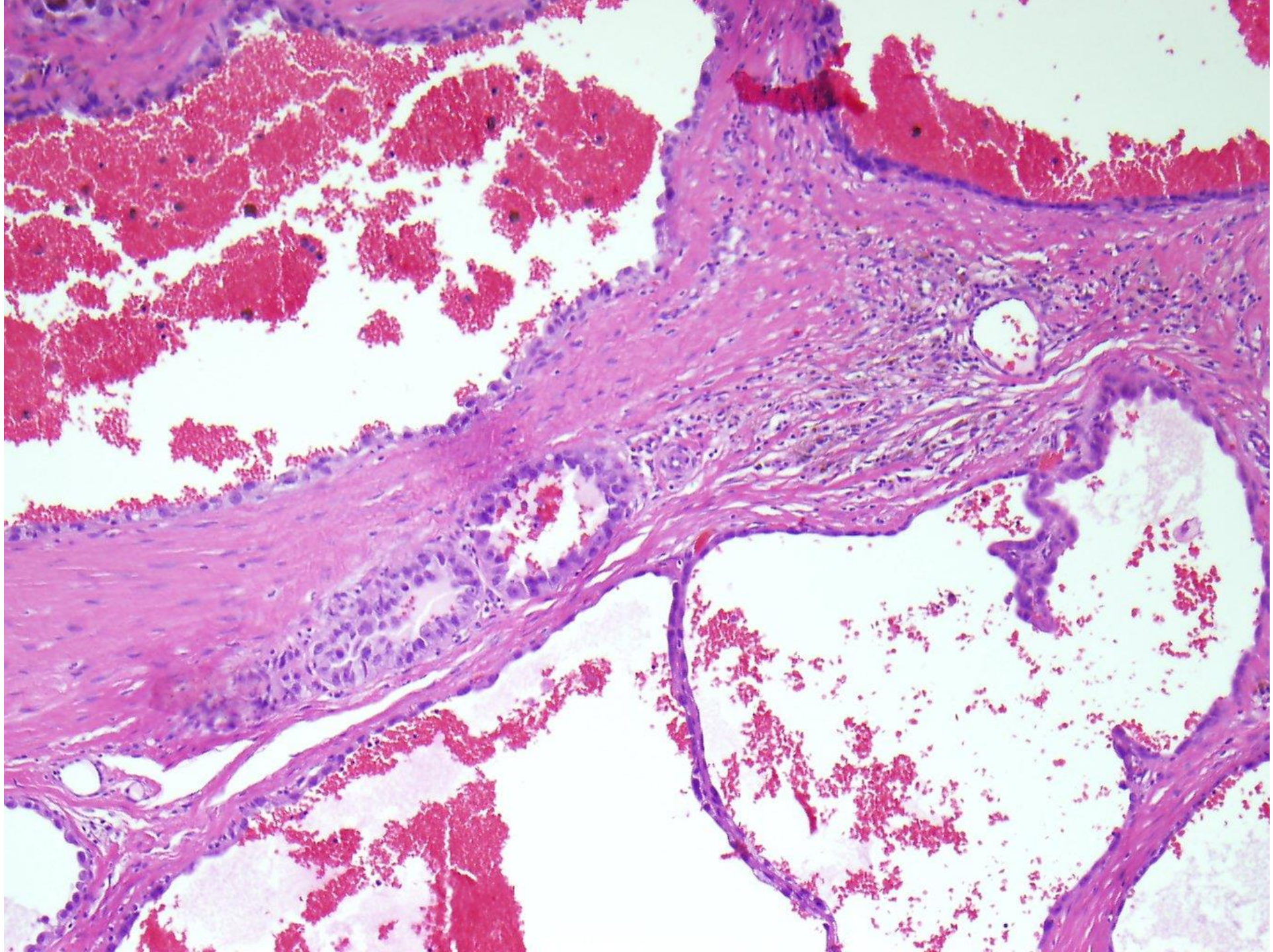
Differential Diagnosis

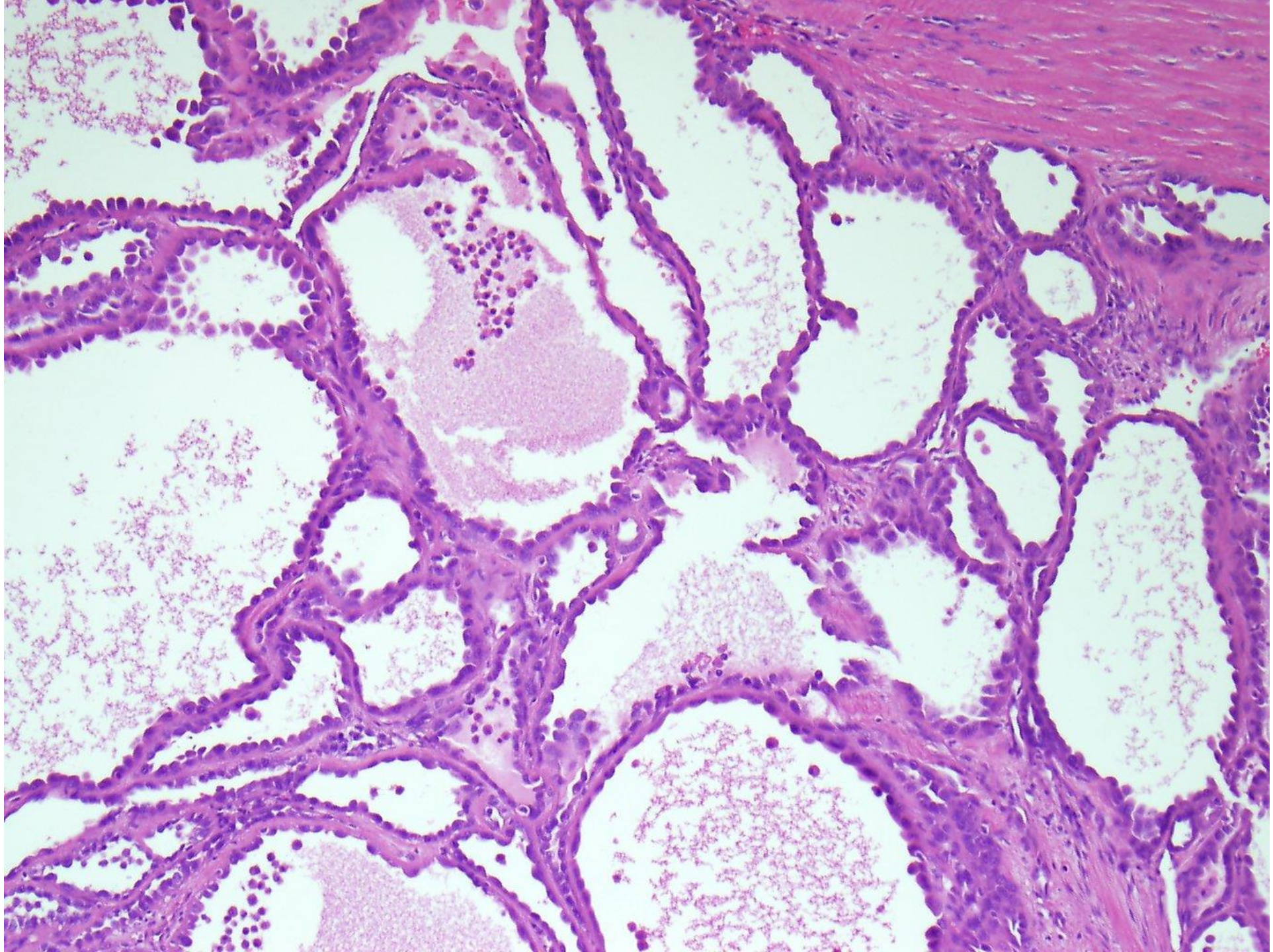
- Blastemal Predominant Wilms Tumor
- Rhabdomyosarcoma
- Small Cell Carcinoma
- Lymphoma
- Desmoplastic Small Round Cell Sarcoma
- Poorly Differentiated Synovial Sarcoma
- CIC rearranged Small Round Blue Cell Tumors
- Clear Cell Sarcoma

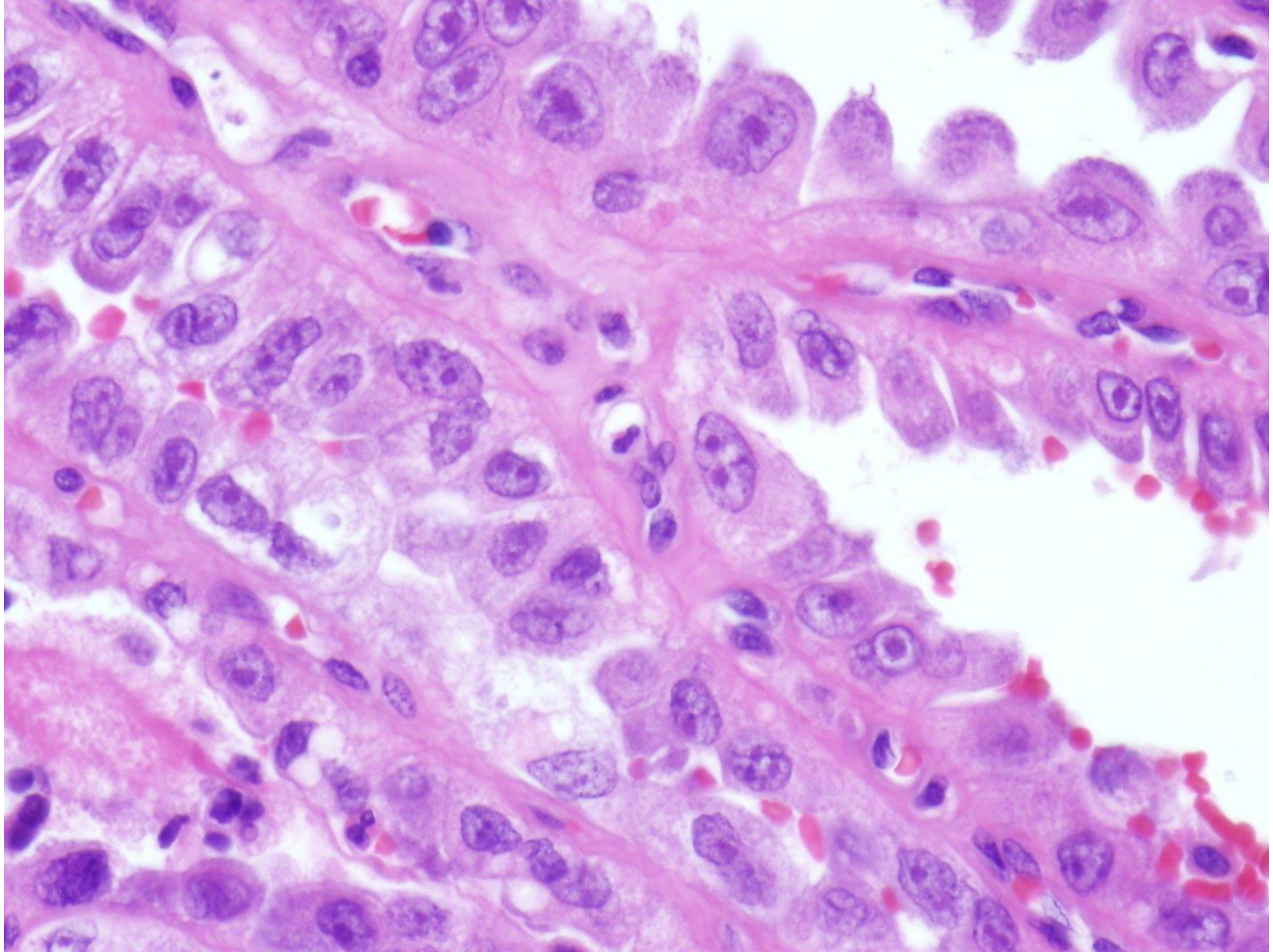
*Amin et al. Diagnostic Pathology Genitourinary Second Edition. Amirsys 2016
*Ellison et al. Immunohistochemistry of primary malignant neuroepithelial tumors of the kidney: a potential source of confusion? A study of 30 cases from the National Wilms Tumor Study Pathology Center. Hum Pathol. 2007 Feb;38(2):205-11.
*Murugan et al. Primary Ewing sarcoma/primitive neuroectodermal tumor of the kidney: a clinicopathologic study of 23 cases. Pathol Oncol Res. 2018 Jan;24(1):153-159
*Mangray et al. Clinicopathologic fetures of a series of primary renal CIC-rearranged sarcomas with comprehensive molecular analysis. Am J Surg Pathol. 2018 Oct;42(10):1360-1369.

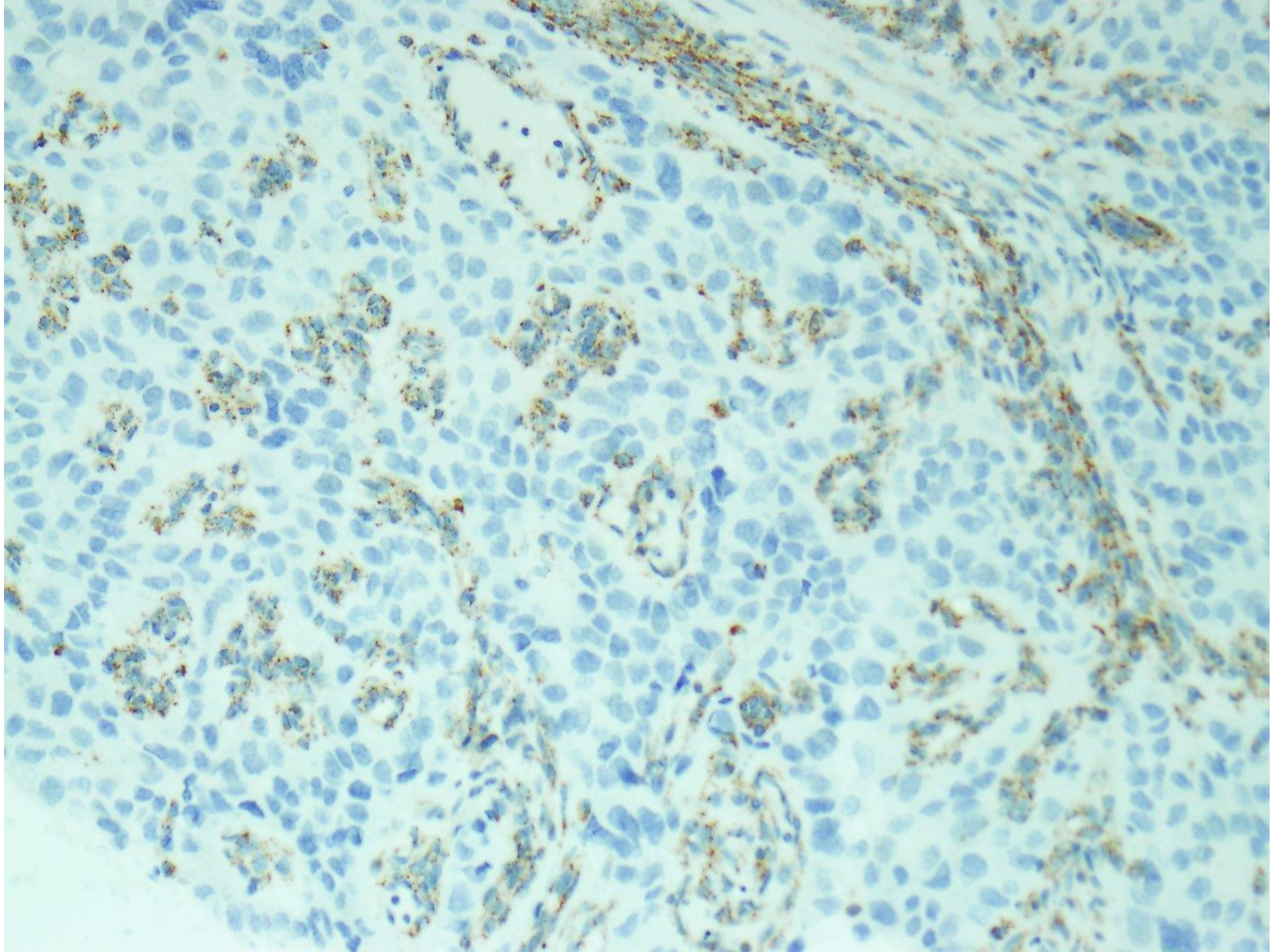
Case #7: 55 yo female renal mass with multiple local recurrences and distant metastasis to CNS

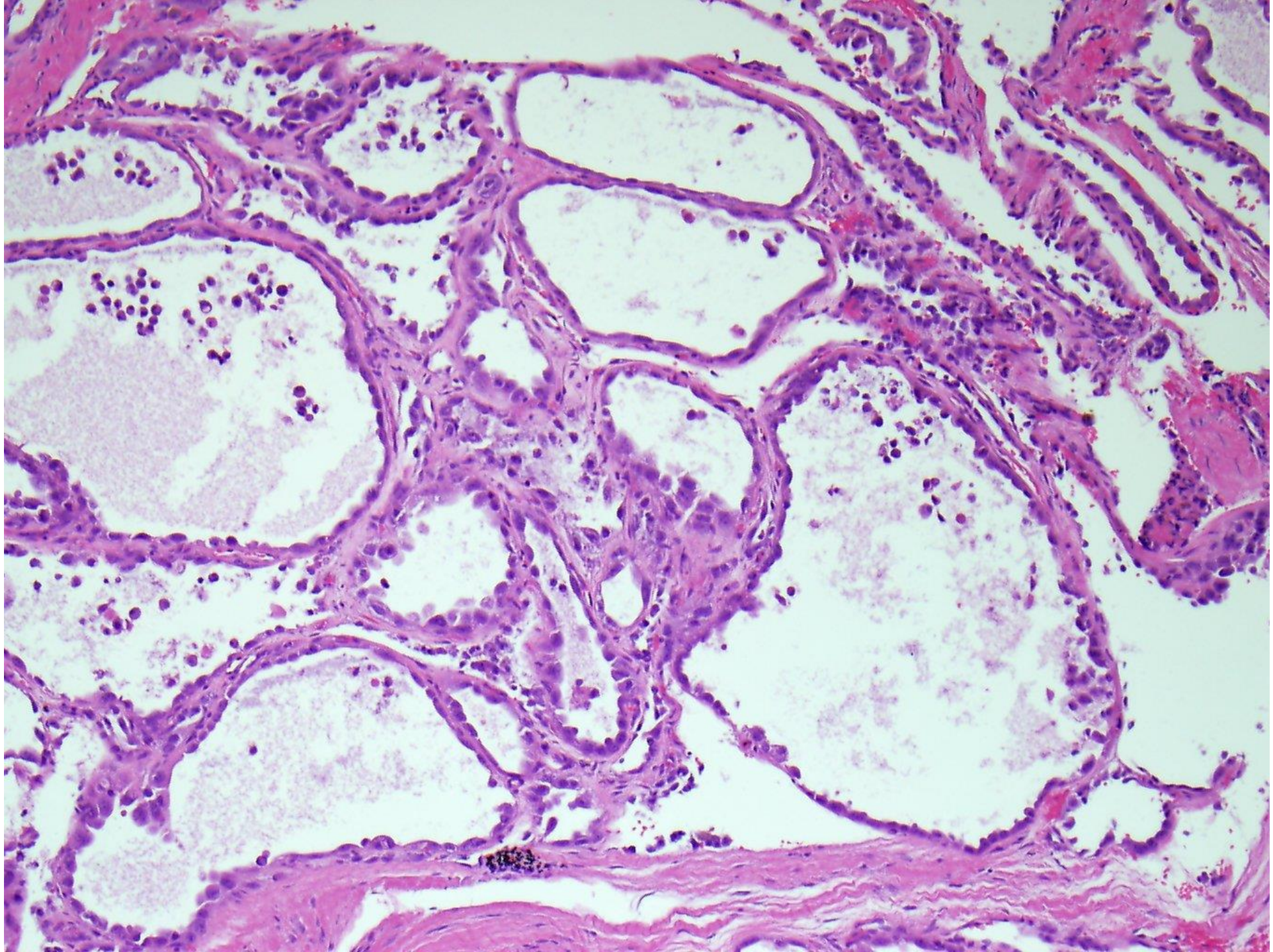












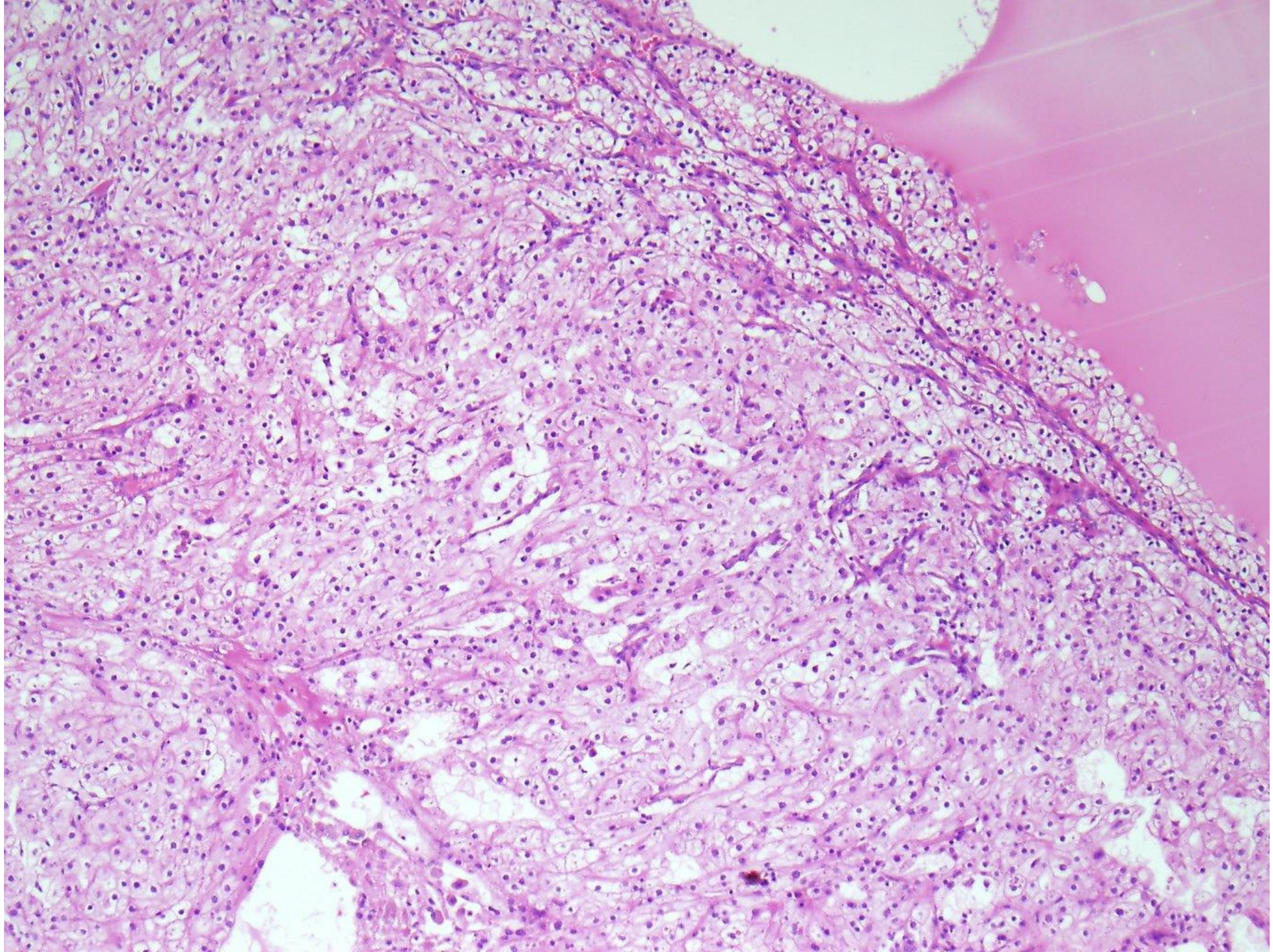
Morphology

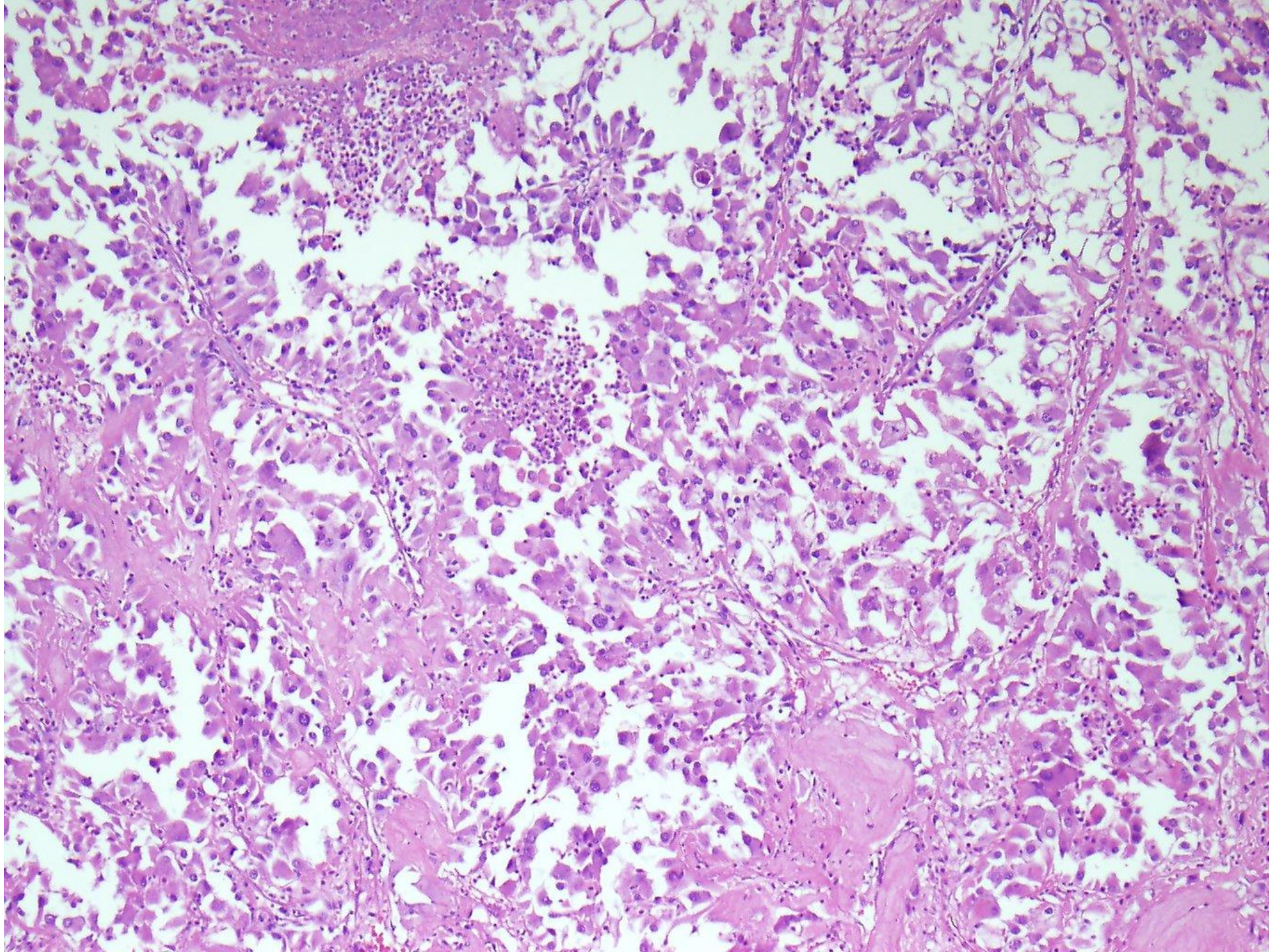
- Tubulocystic architecture
- Variable degrees of cytologic atypia
    - Areas with marked pleomorphism, macronucleoli and perinucleolar clearing

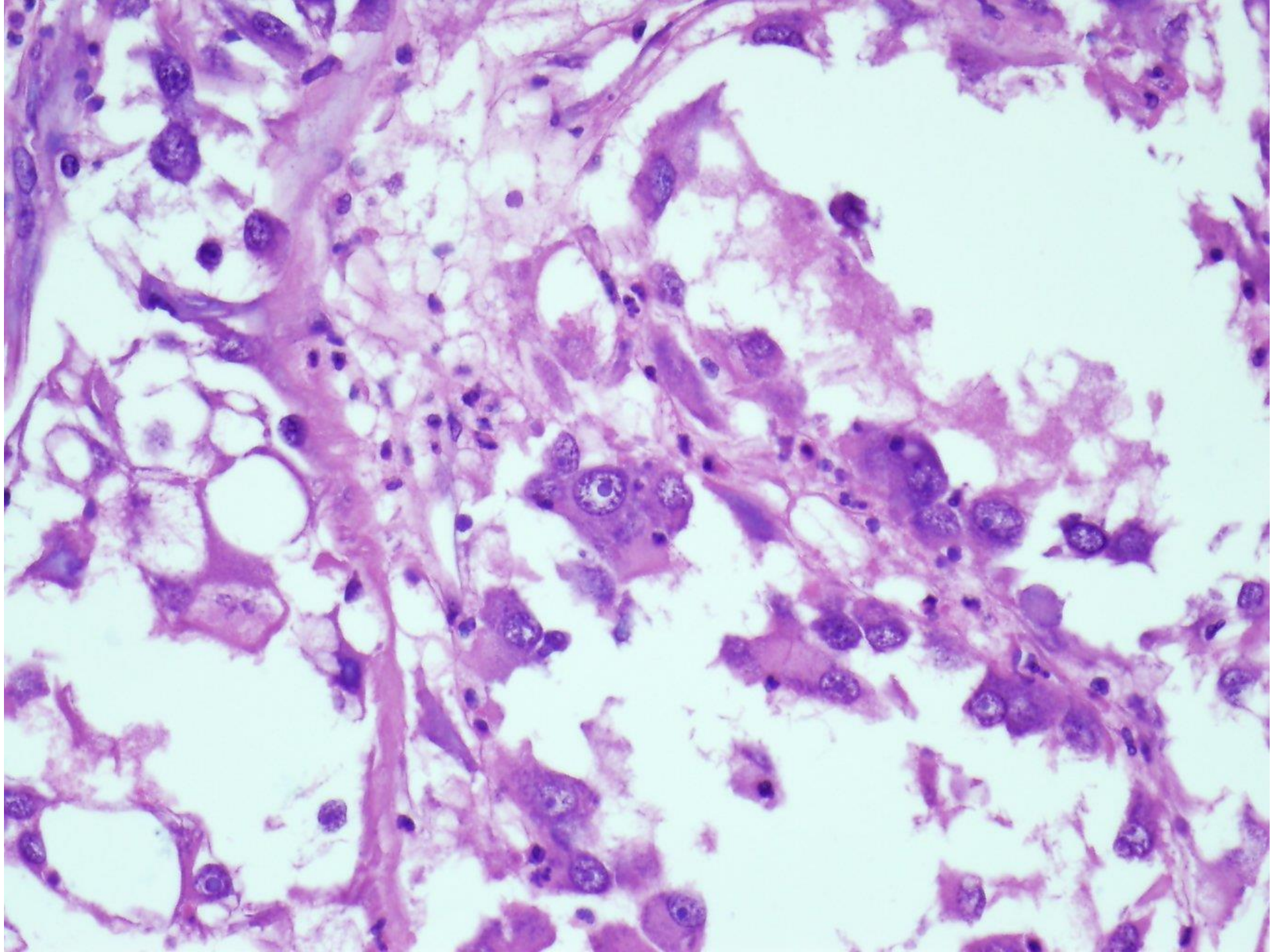
Key IHC

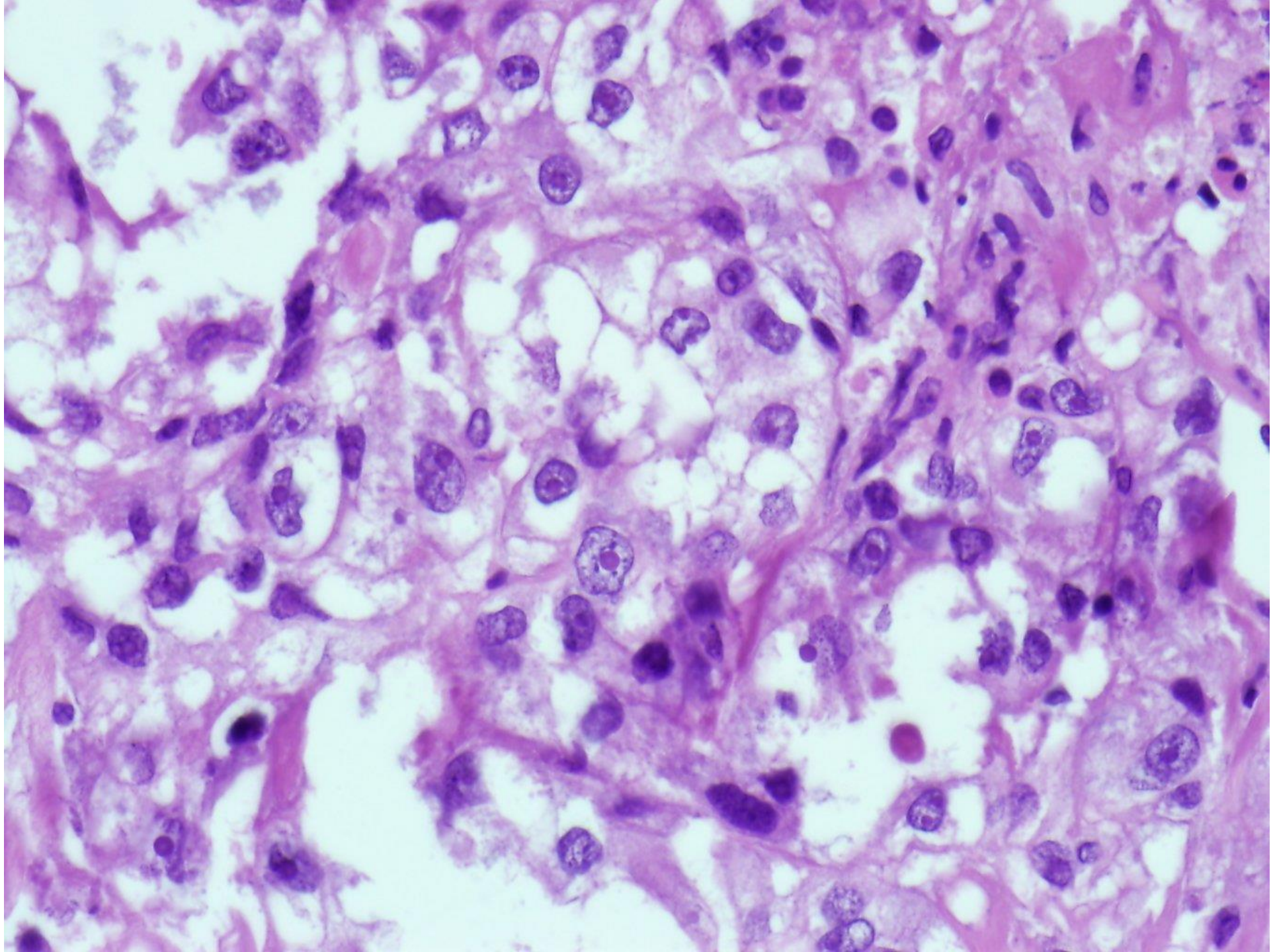
- Complete loss of fumarate hydratase (FH) staining within carcinoma

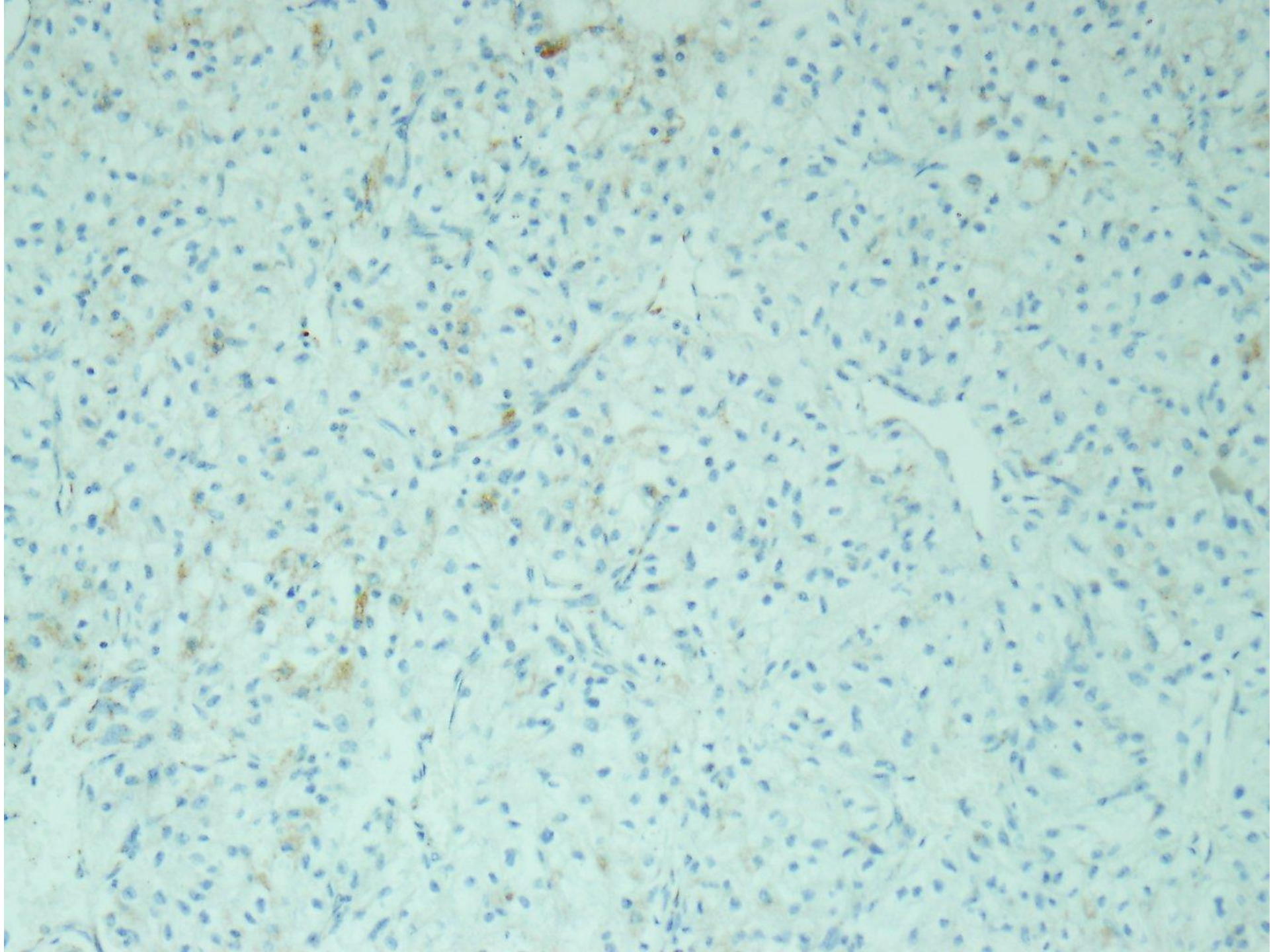
Case #8: 60 yo male renal mass with metastases to CNS

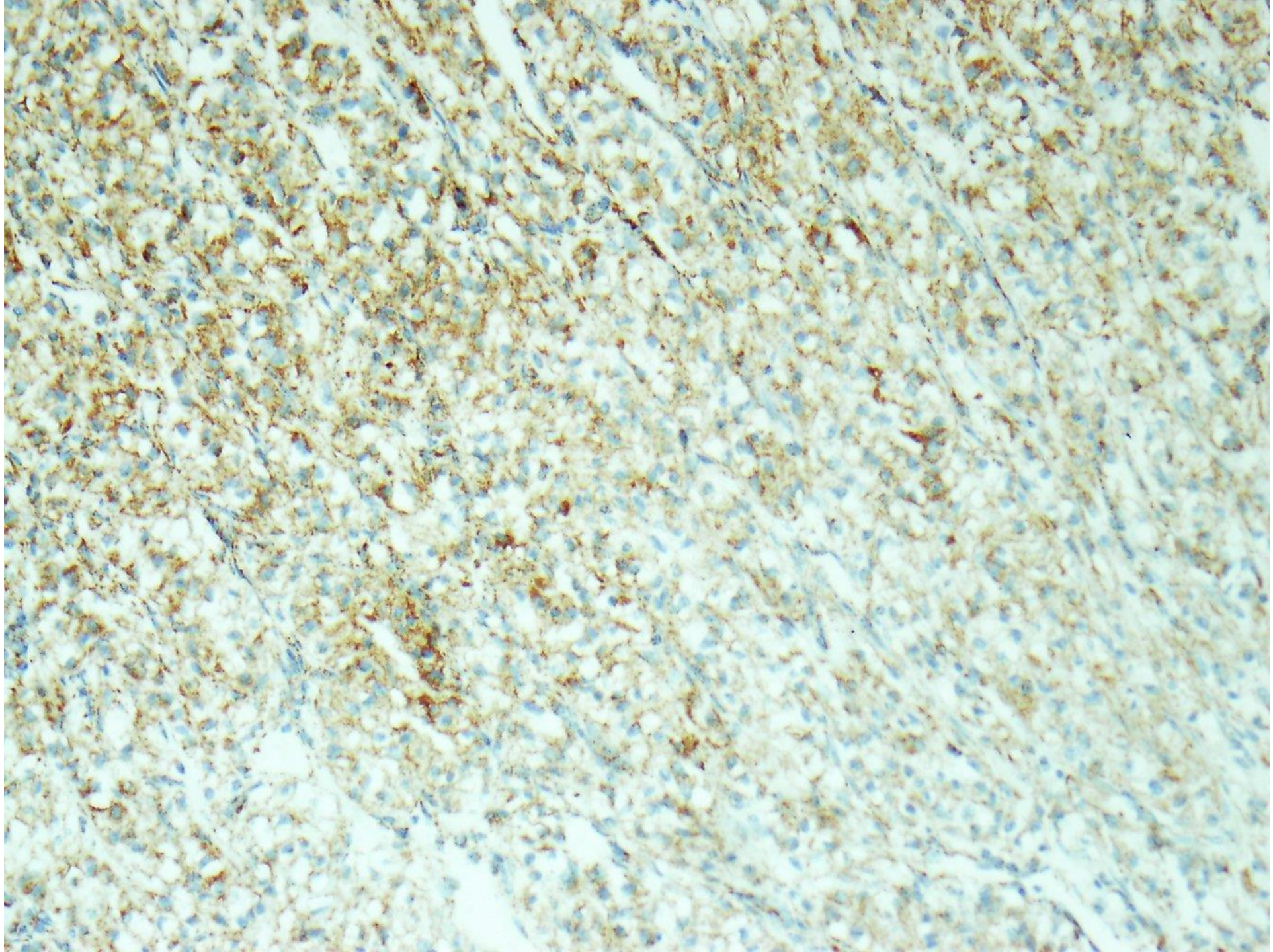


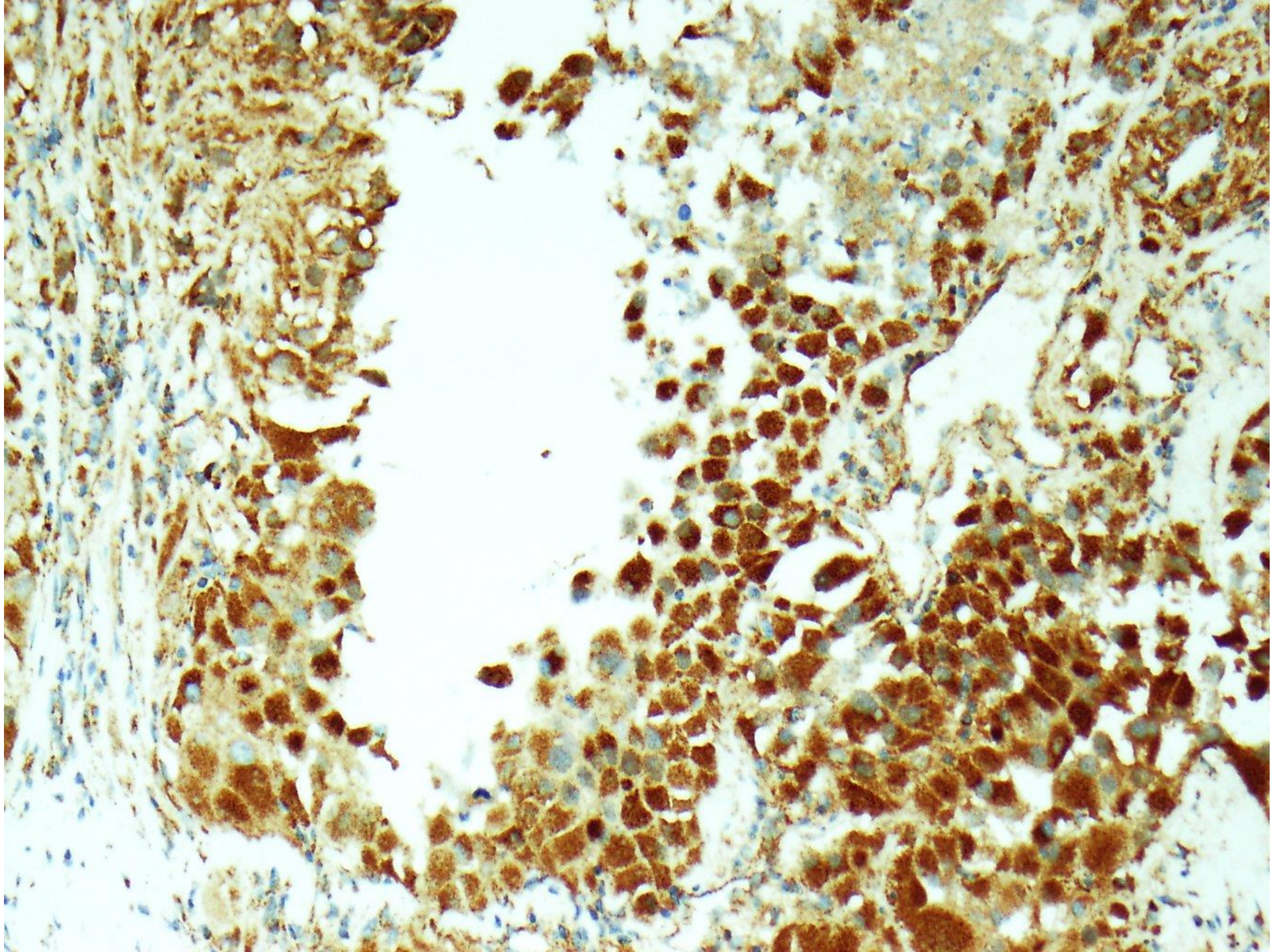












Morphology

- Variable cystic, papillary, solid morphology with clear to eosinophilic cytoplasm
- Variable degrees of cytologic atypia
    - Areas with marked pleomorphism, macronucleoli and perinucleolar clearing

Key IHC

- Indeterminate fumarate hydratase (FH) staining within carcinoma
    - Note: initial staining at an outside institution reported to be negative (different clone).

Additional Molecular Testing: Both patients with FH mutations (splice site point mutation and insertion)

Diagnosis: FH Deficient Renal Cell Carcinoma / Hereditary leiomyomatosis associated renal cell carcinoma (HLRCC)

- Germline mutational analysis required for diagnosis of HLRCC
  - Clinical and/or family history of uterine leiomyomas, cutaneous leiomyomas, renal cysts
- FH deficient tumors with somatic mutations can be indistinguishable

HLRCC and FH deficient RCC

- Variable architecture: Papillary, Solid, Tubulocystic, Cystic, Sarcomatoid

- High grade with macronuclei, inclusion like nucleoli with perinucleolar clearing

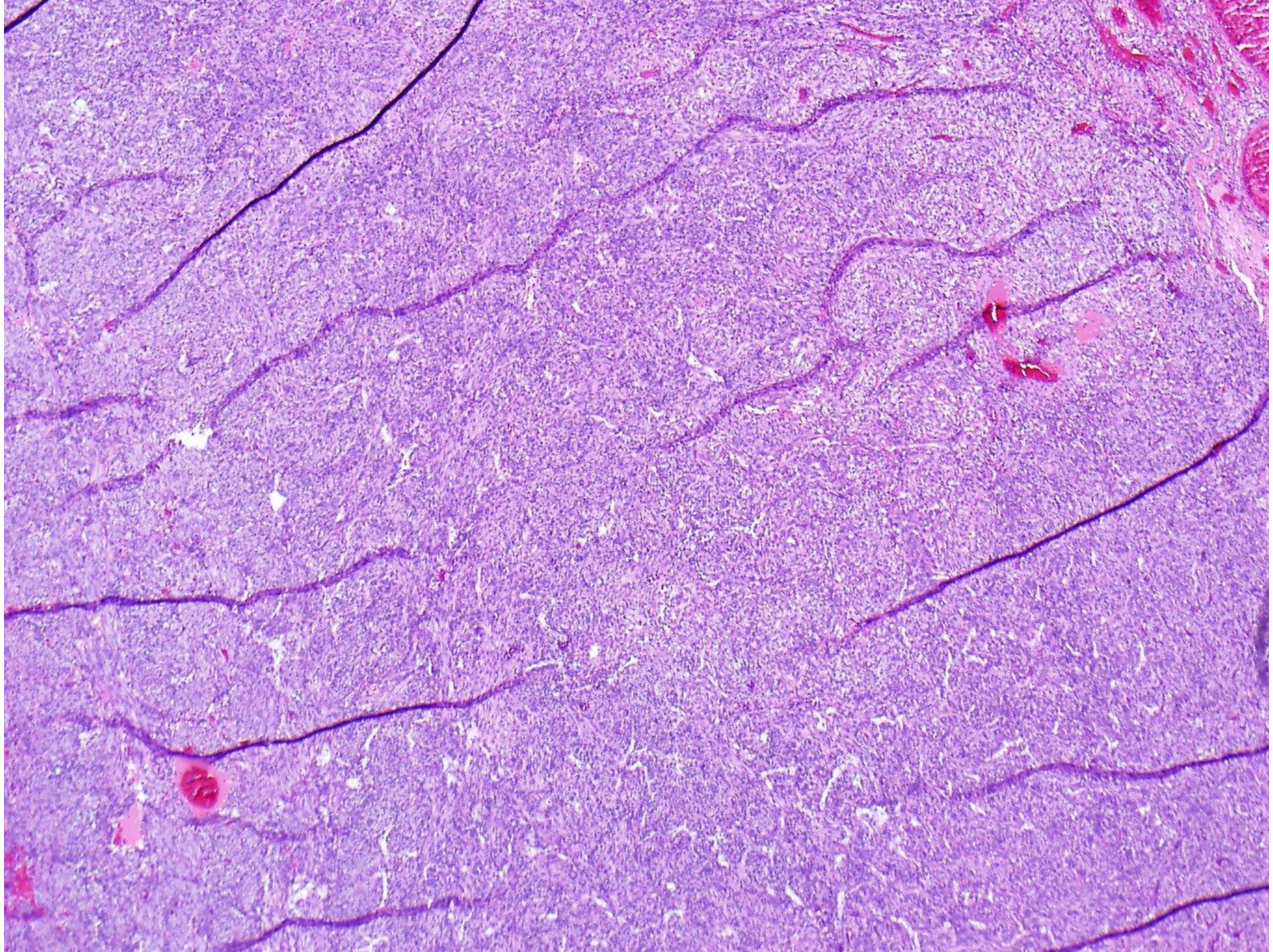
- Immunohistochemistry
  - 2SC (2-succinocysteine) overexpression
  - FH (fumarate hydratase) loss
  - Pax8 usually retained

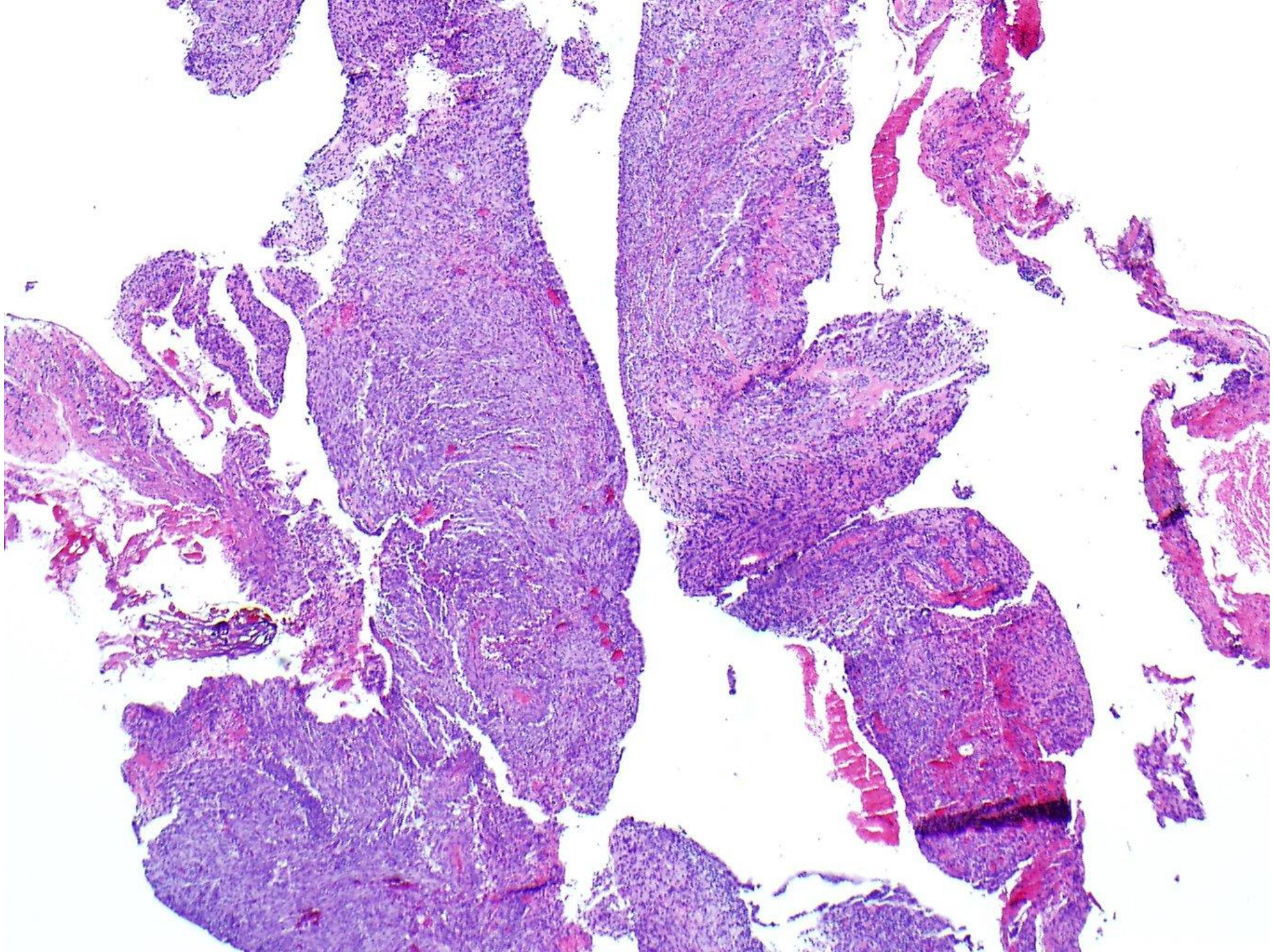
Differential Diagnosis of HLRCC

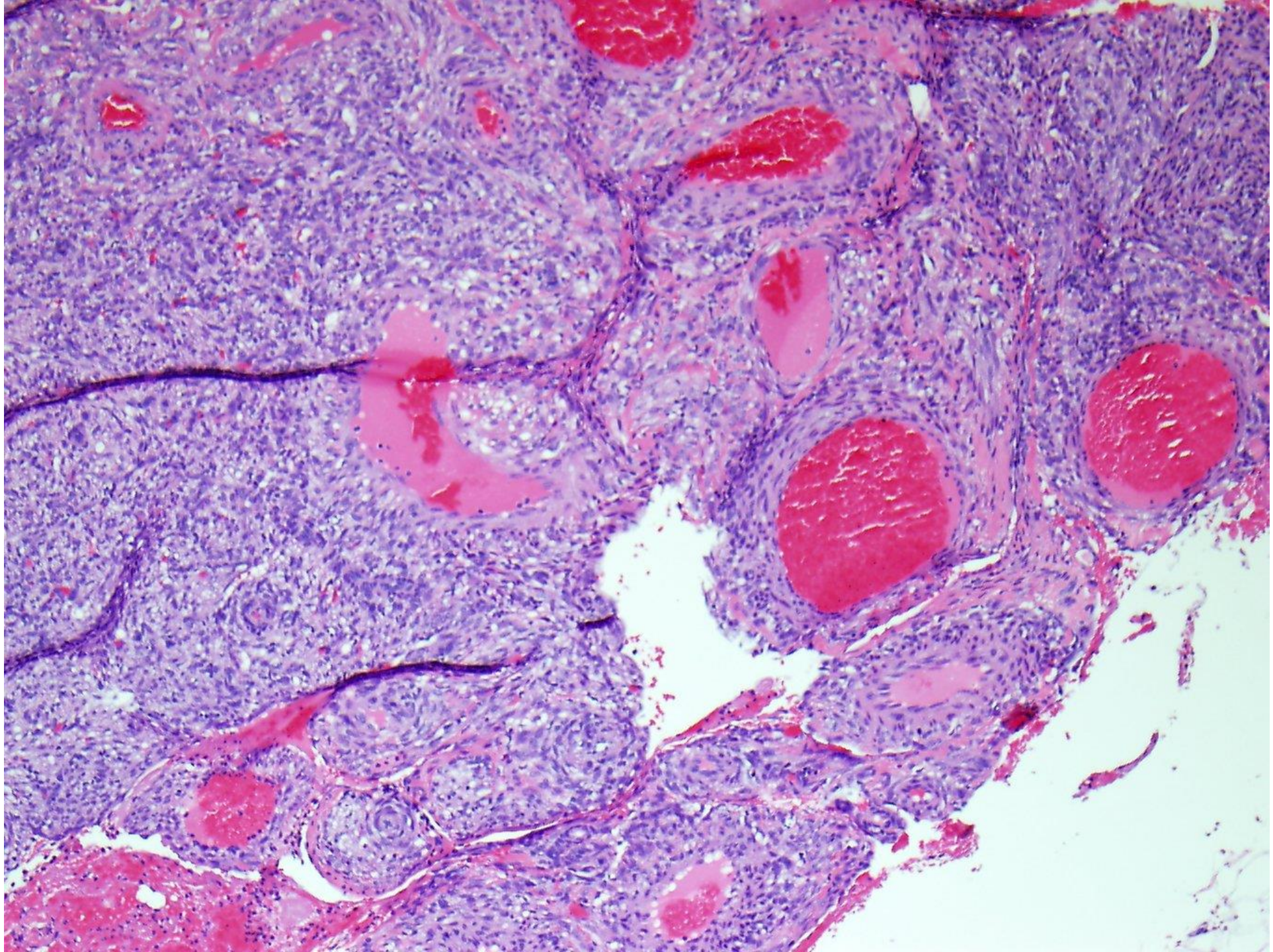
- FH Deficient Renal Cell Carcinoma
- Collecting Duct Carcinoma
- High Grade Clear Cell Renal Cell Carcinoma
- Translocation Associated Renal Cell Carcinoma (Especially TFE3)
- Type II Papillary Renal Cell Carcinoma / Unclassified Renal Cell Carcinoma

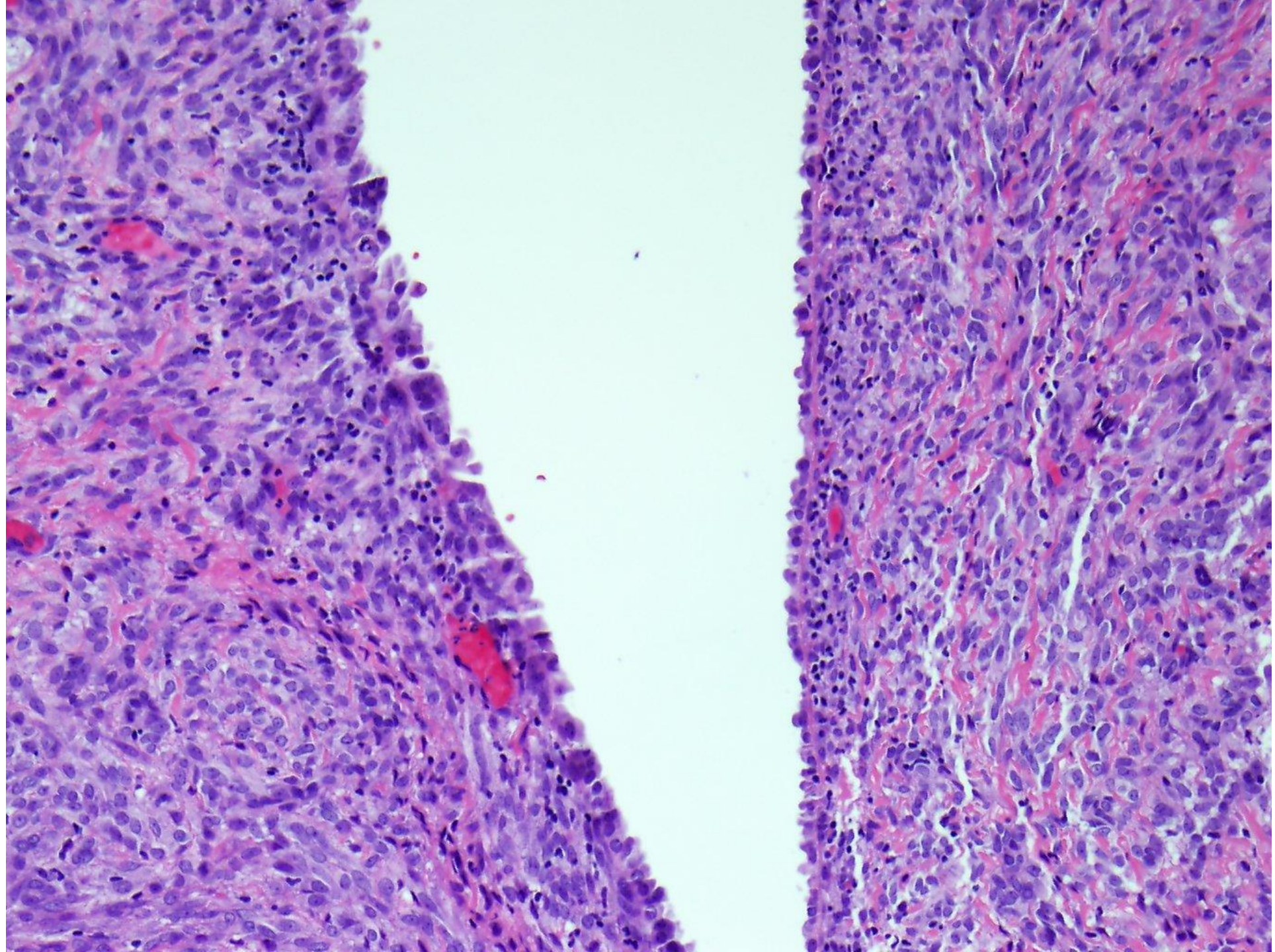
*Trpkov et al. Fumarate hydratase-deficient renal cell carcinoma is strongly correlated with fumarate hydratase mutation and hereditary leiomyomatosis and renal cell carcinoma syndrome. Am J Surg Pathol. 2016 Jul;40(7):865-75
*Sanz-Ortega et al. Morphologic and molecular characteristics of uterine leiomyomas in hereditary leiomyomatosis and renal cancer (HLRCC) syndrome. Am J Surg Pathol 2013.37(1):74-80

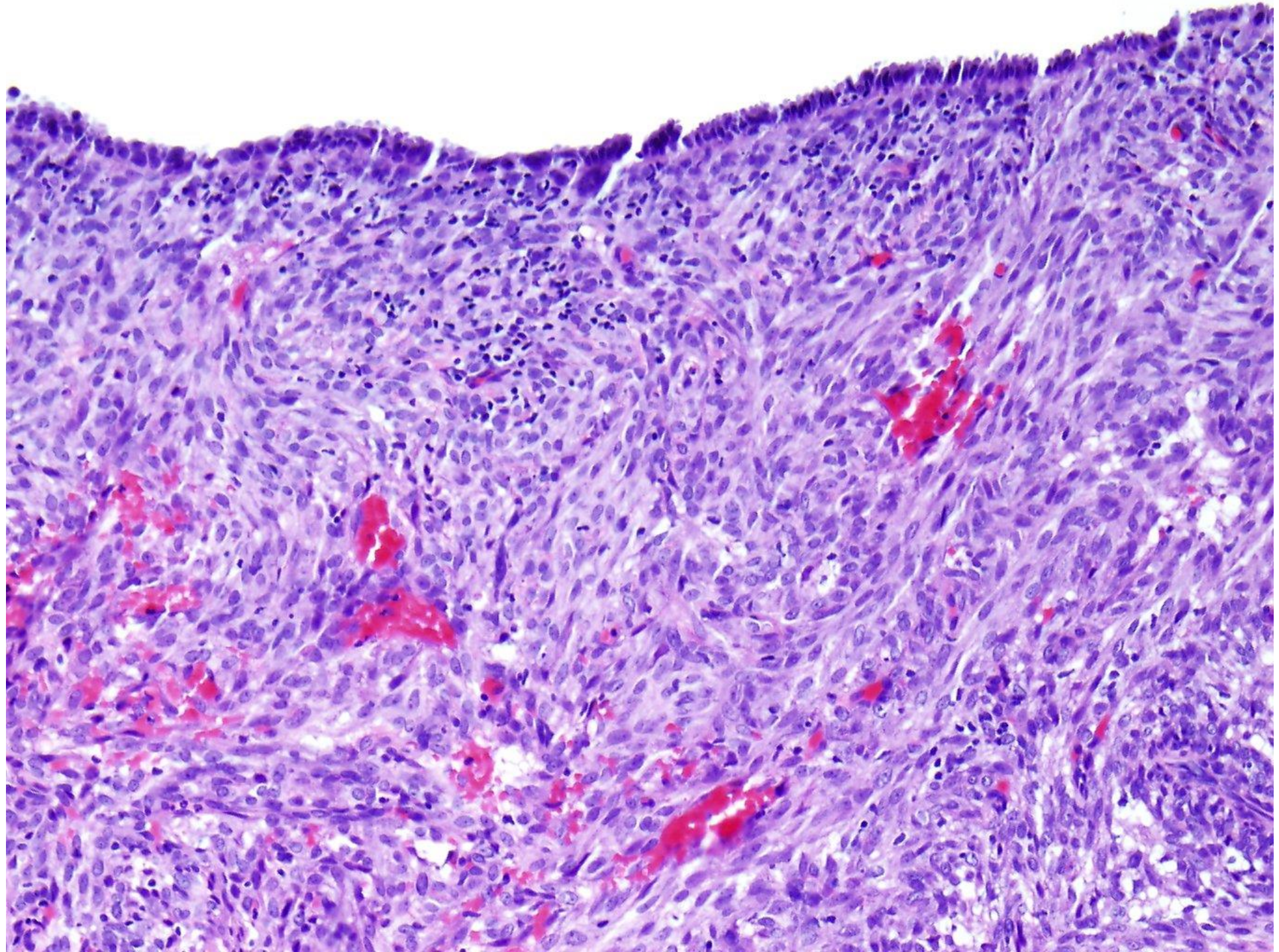
33 year old female with 2 cm solid and cystic renal mass

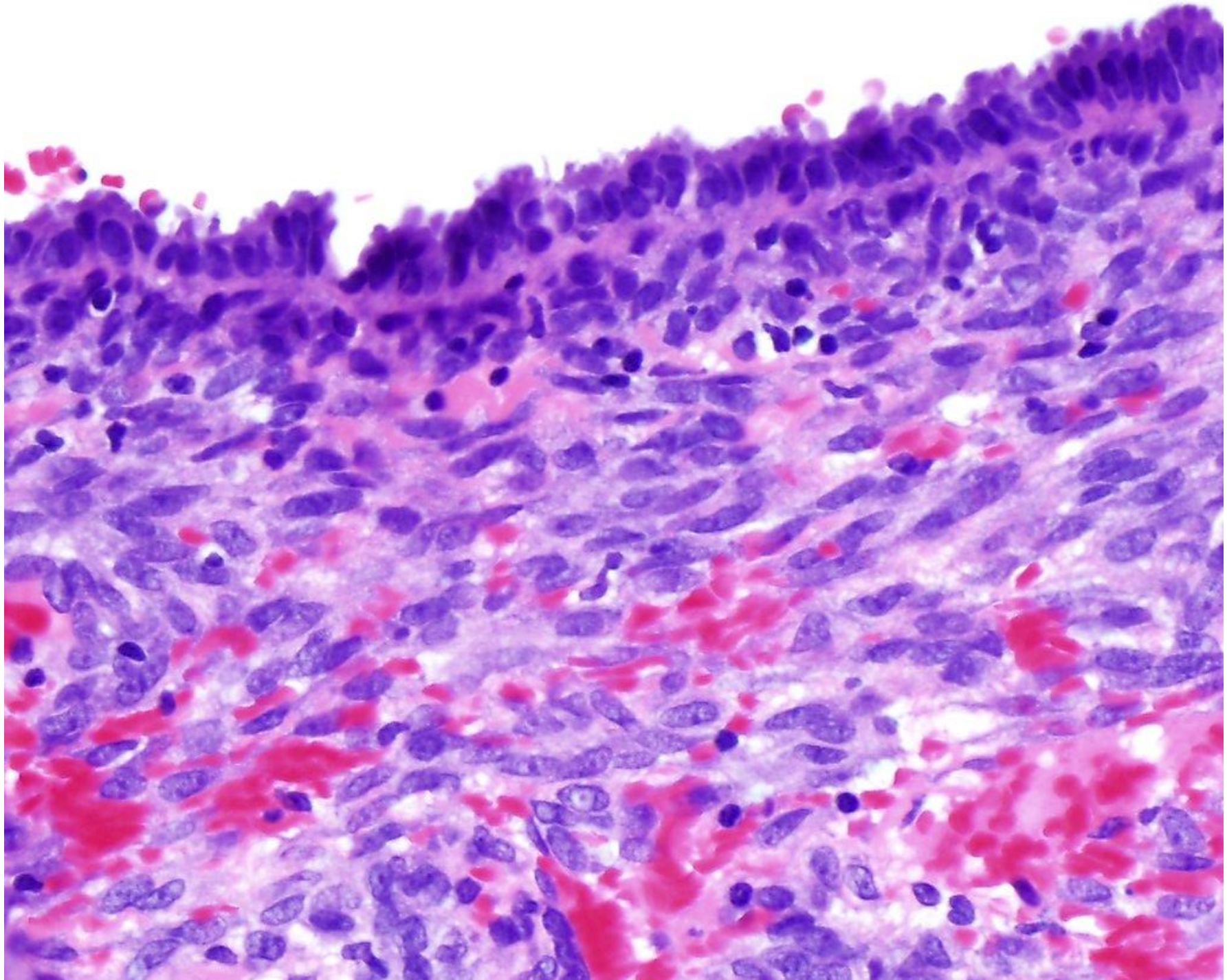


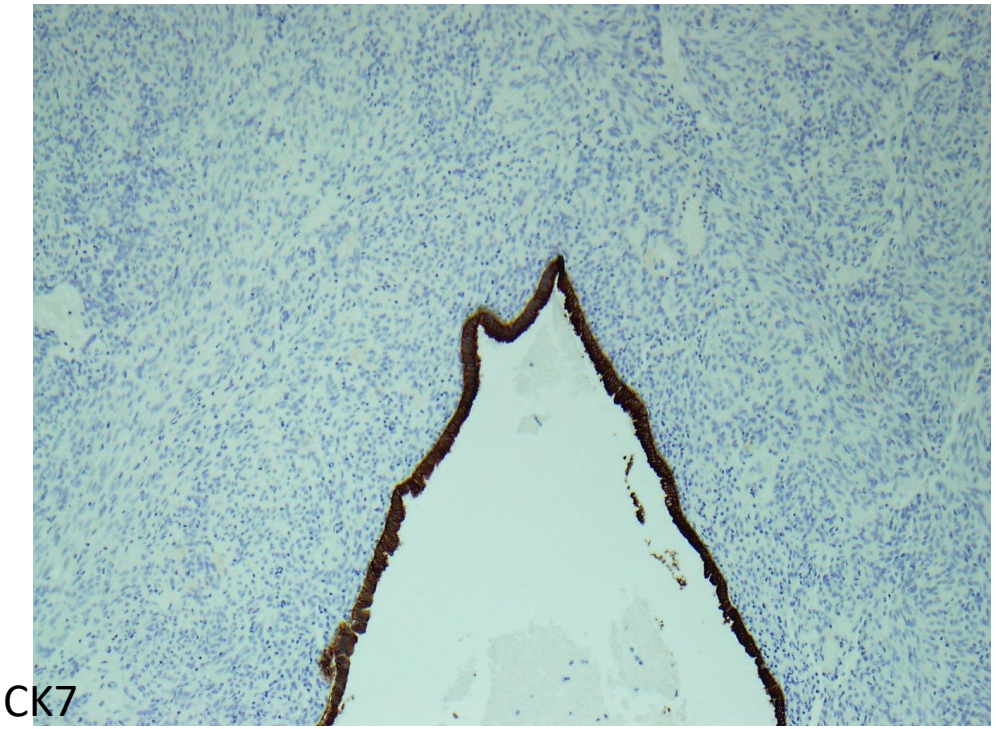




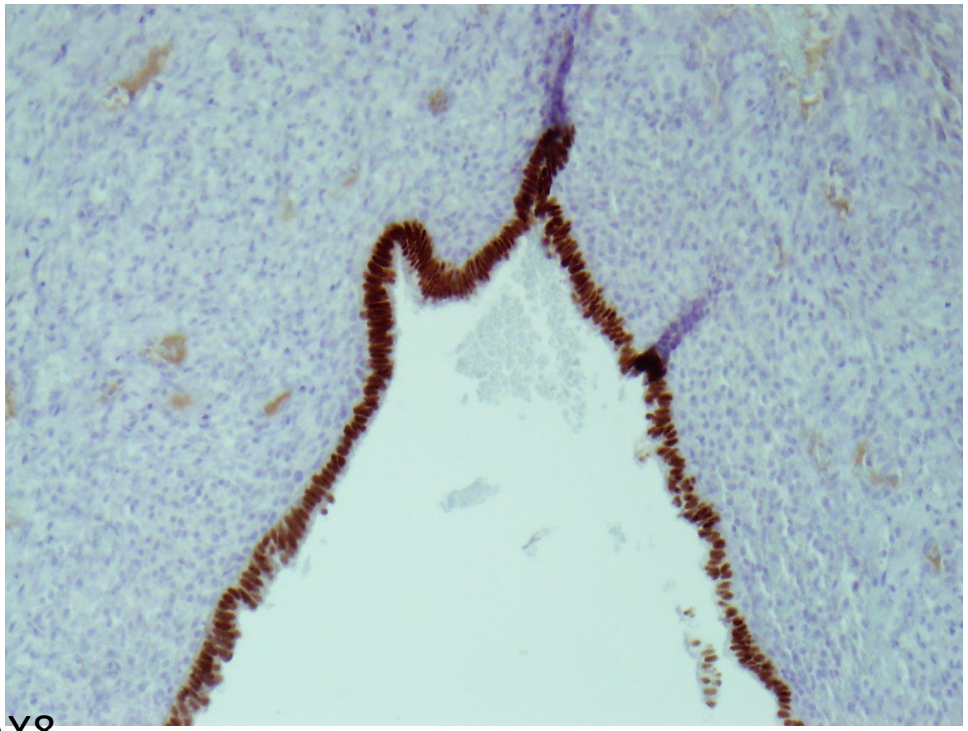




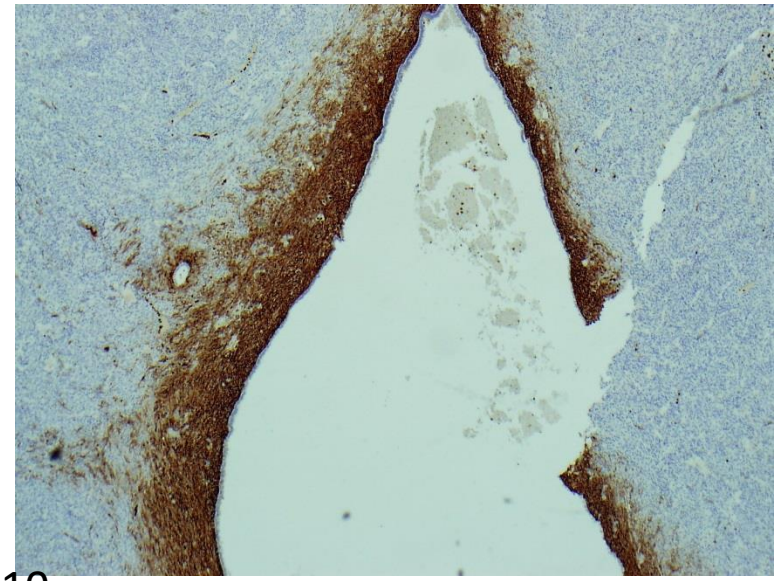




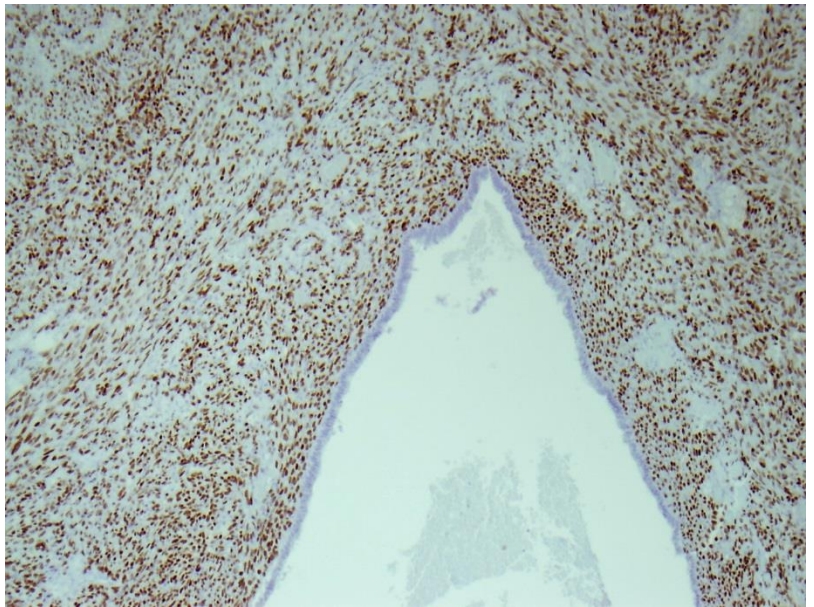
CK7



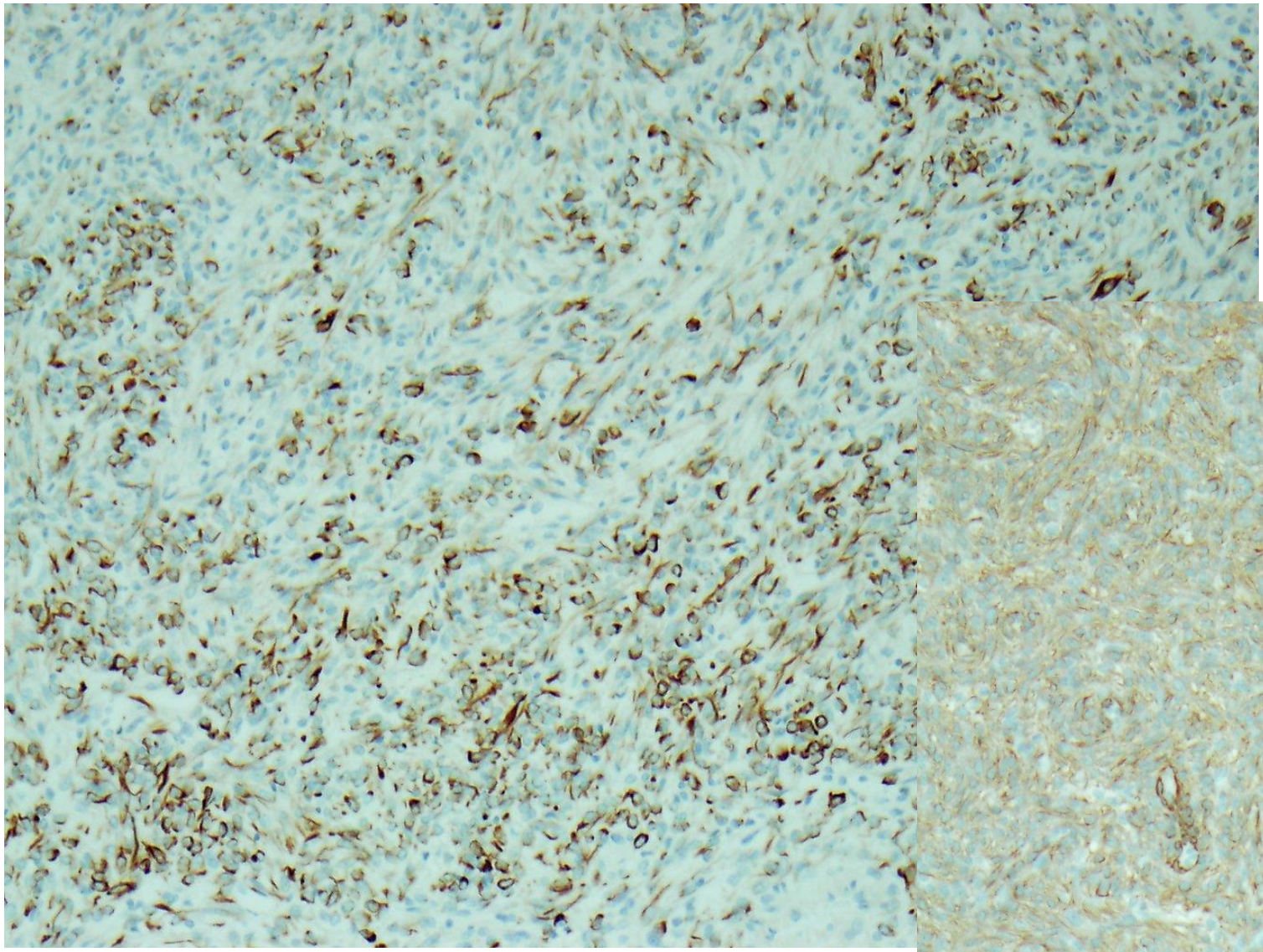
PAX8



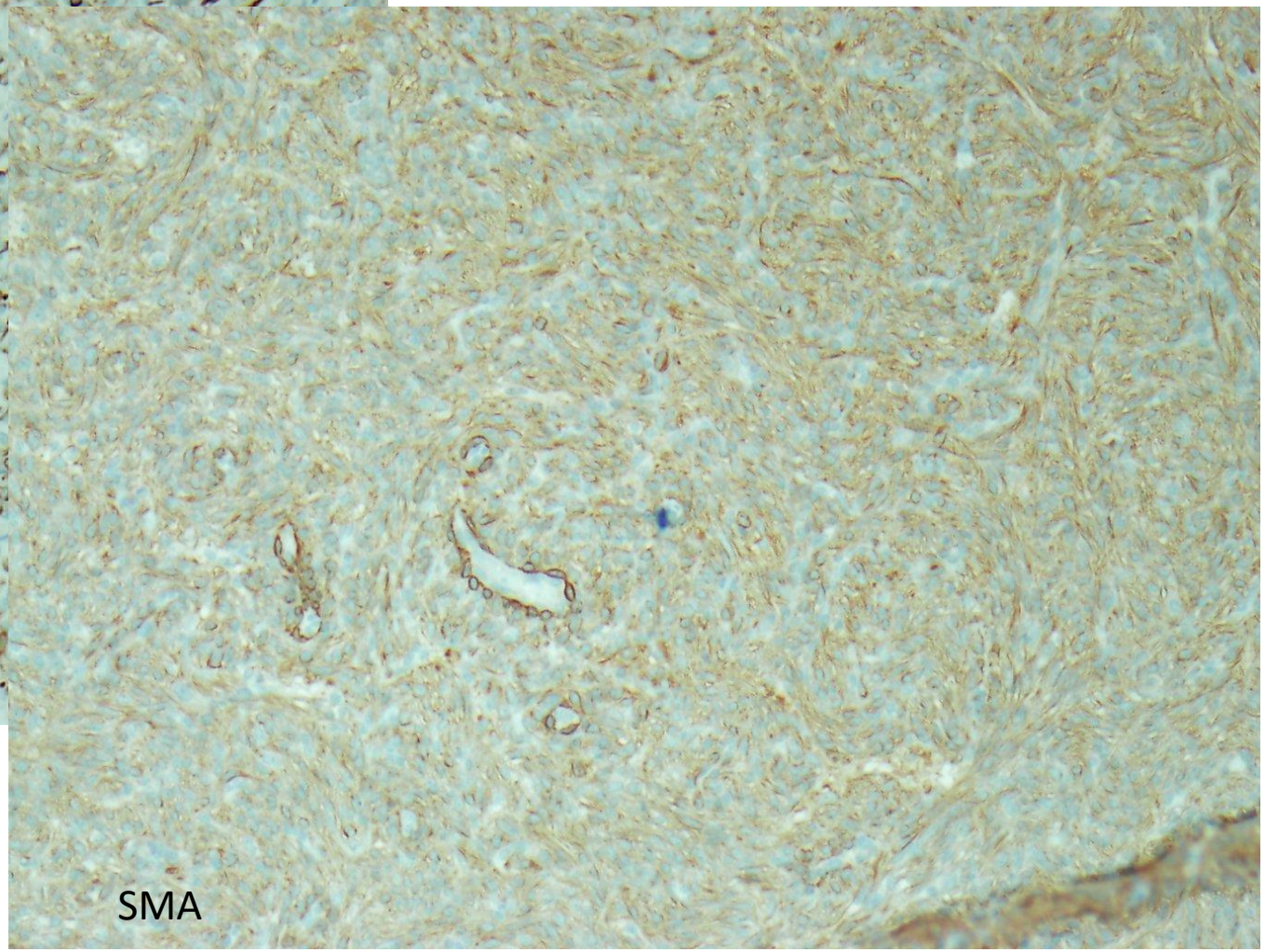
CD10



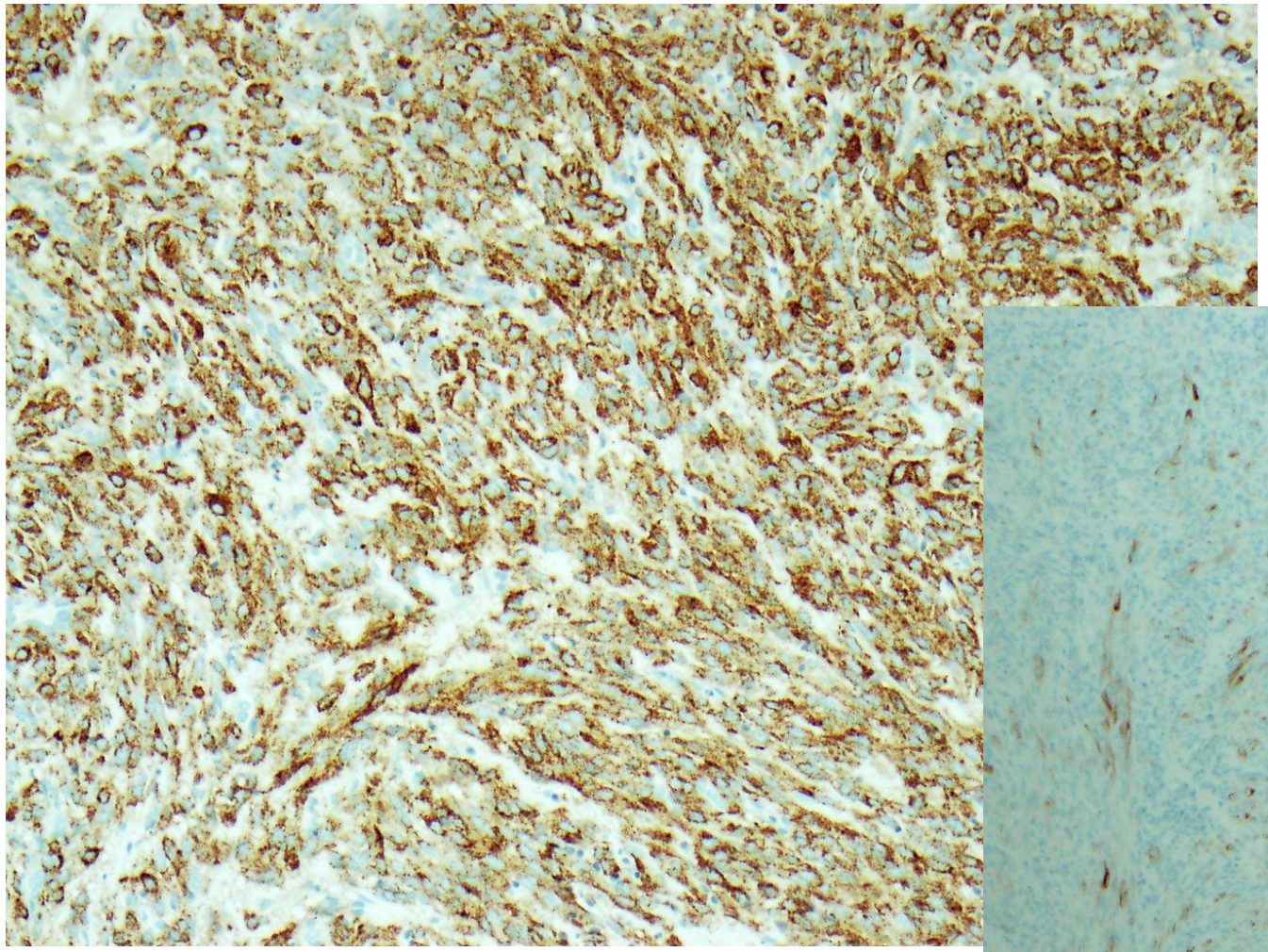
ER



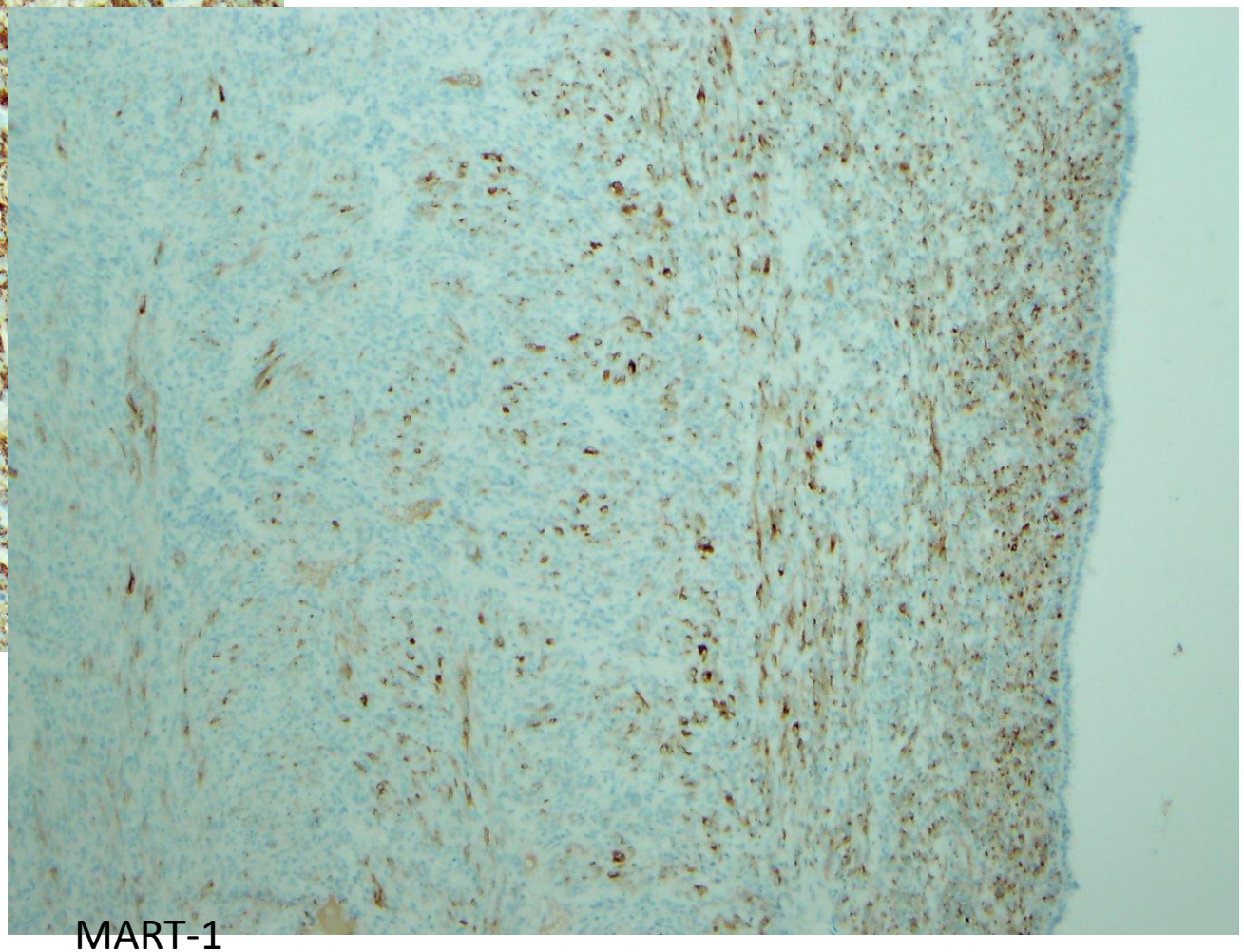
DESMIN



SMA



HMB45



MART-1

MORPHOLOGY AND IHC PROFILE

- CYSTIC TUMOR WITH EPITHELIAL LINED CYSTS COMPOSED OF COLUMNAR TO CUBOIDAL EPITHELIUM WITH PERIEPITHELIAL CELLULAR STROMA AND DYSPLASTIC BLOOD VESSELS

- STROMA
  - CD10, ER, DESMIN, SMA, HMB45 AND MART-1 POSITIVE

- EPITHELIUM
  - PAX8 AND CK7 POSITIVE

DIAGNOSIS: ANGIOMYOLIPOMA WITH EPITHELIAL CYSTS (AMLEC)

- Uncommon variant of Angiomyolipoma with cystic spaces lined by variable hobnail, cuboidal, or columnar epithelium.
- Typical cases show a hypercellular periepithelial Mullerian stroma that stains positive for ER, PR, CD10.
- Variable amounts of other components typical of AML's (adipose tissue, smooth muscle, dysplastic vessels).
- HMB45 and other melanocytic markers positive in non-epithelial components.

DIFFERENTIAL DIAGNOSIS

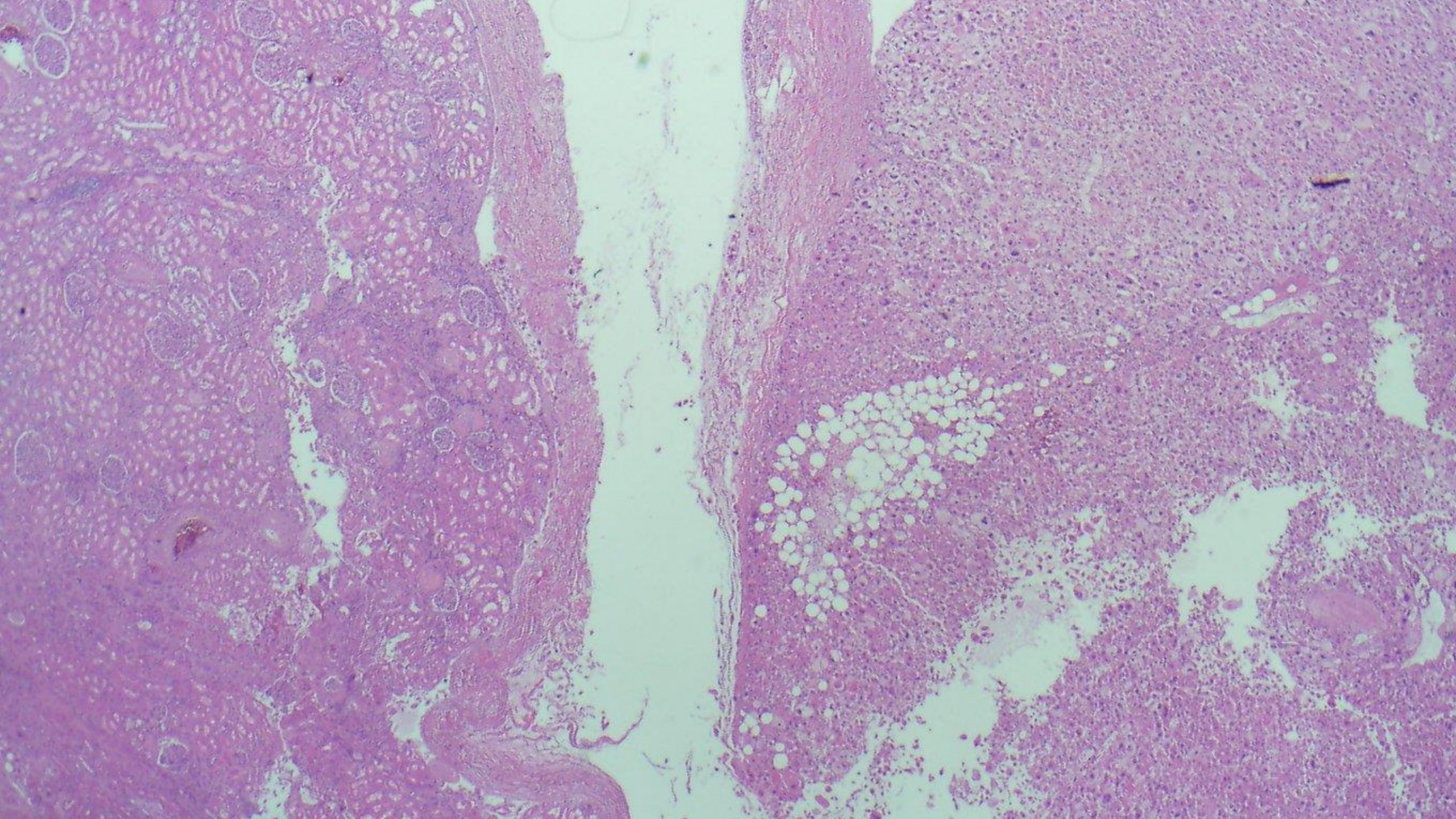
- Mixed epithelial and stromal tumor / Adult cystic nephroma
  - More common in females
  - May have long standing history of hormone therapy
- Cystic variants of renal cell carcinoma
- Benign renal cysts

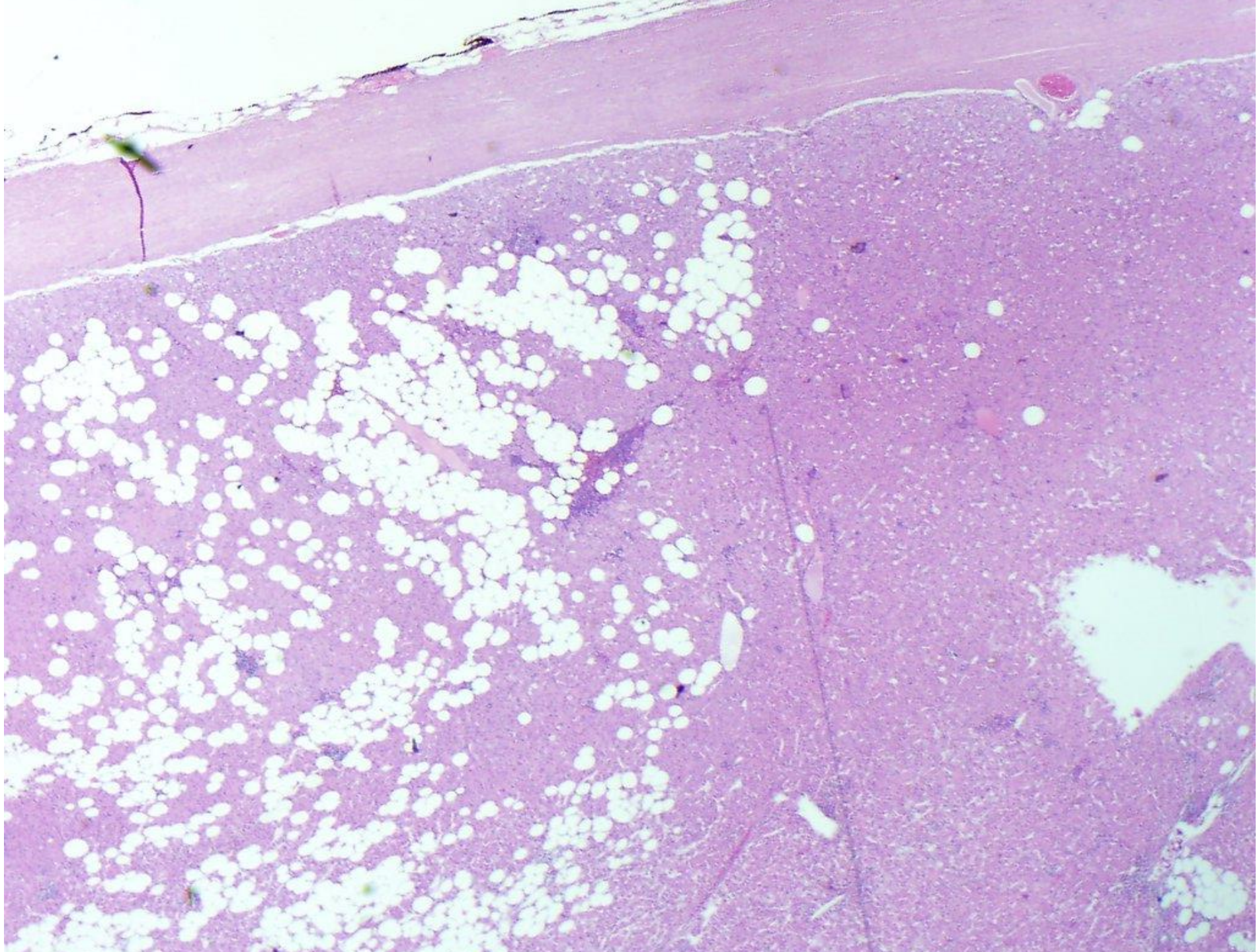
Aydin, H. et al. Renal angiomyolipoma: clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association. Am J Surg Pathol 2009. 33 (2):289–297.

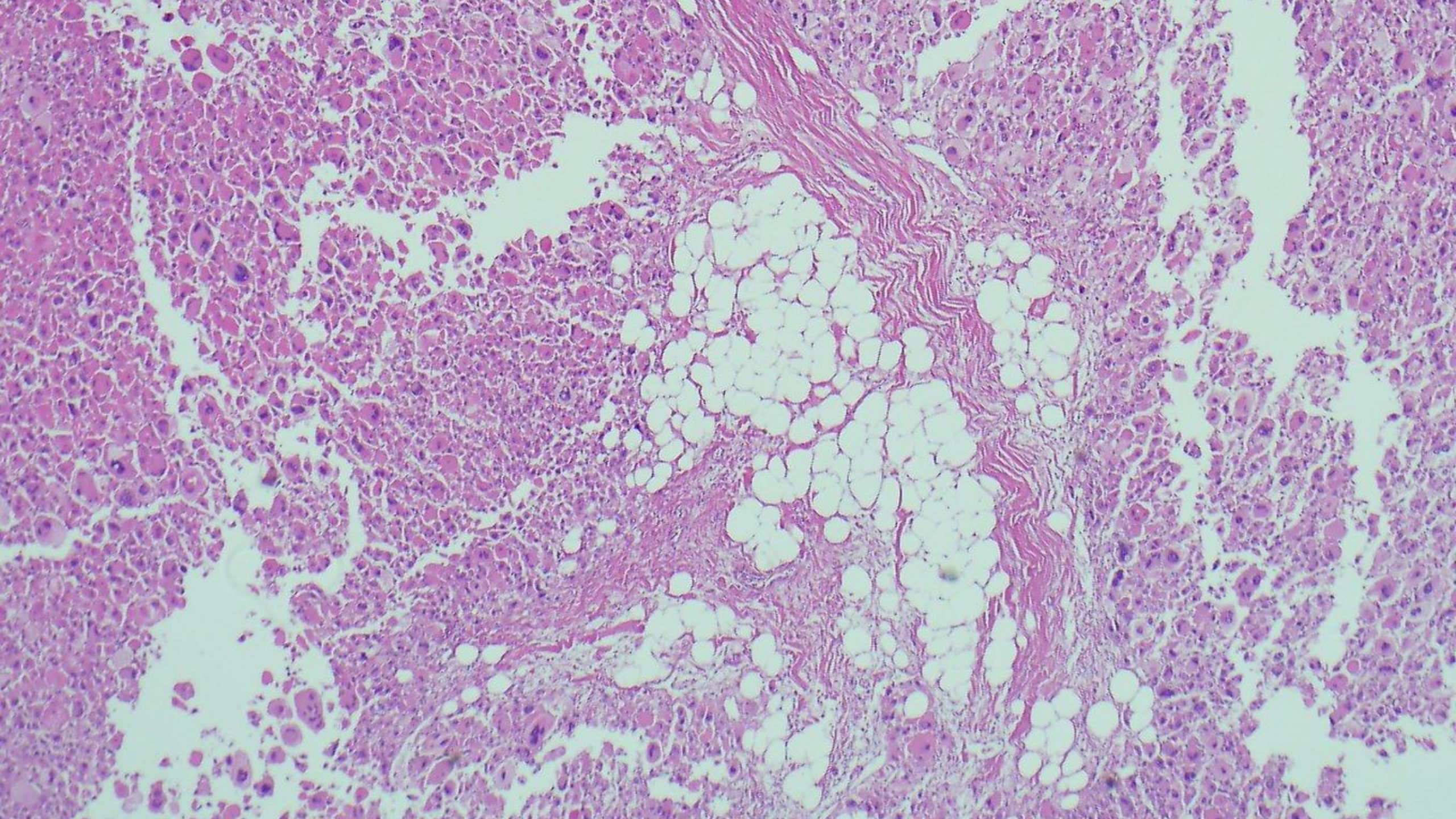
Fine, SW et al. Angiomyolipoma with epithelial cysts (AMLEC): a distinct cystic variant of angiomyolipoma. Am J Surg Pathol 2006. May;30(5):593-9.

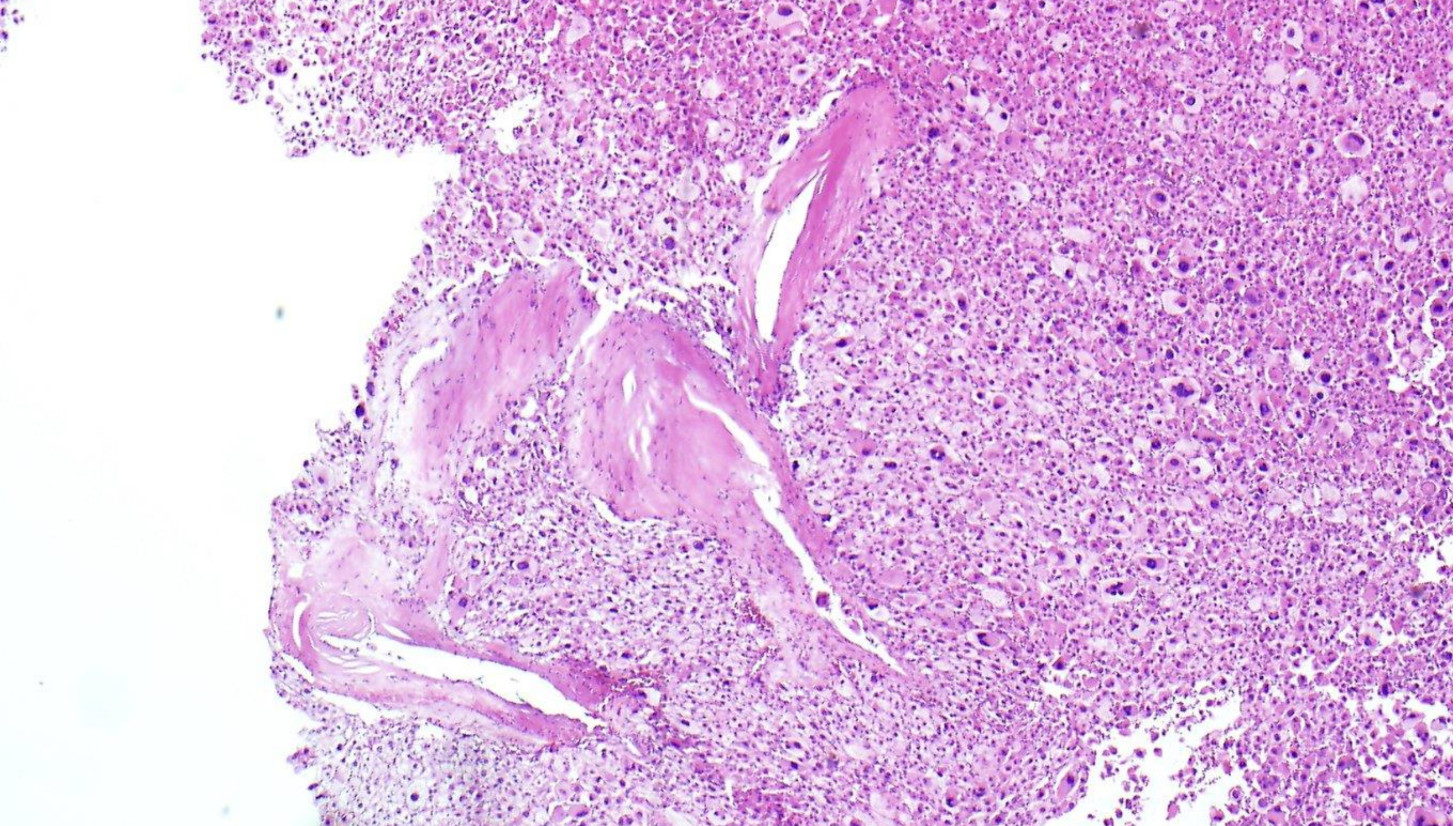
70 year old male found to have colonic adenocarcinoma (pT2N1M0). Upon staging workup the patient was found to concurrently have a large retroperitoneal mass

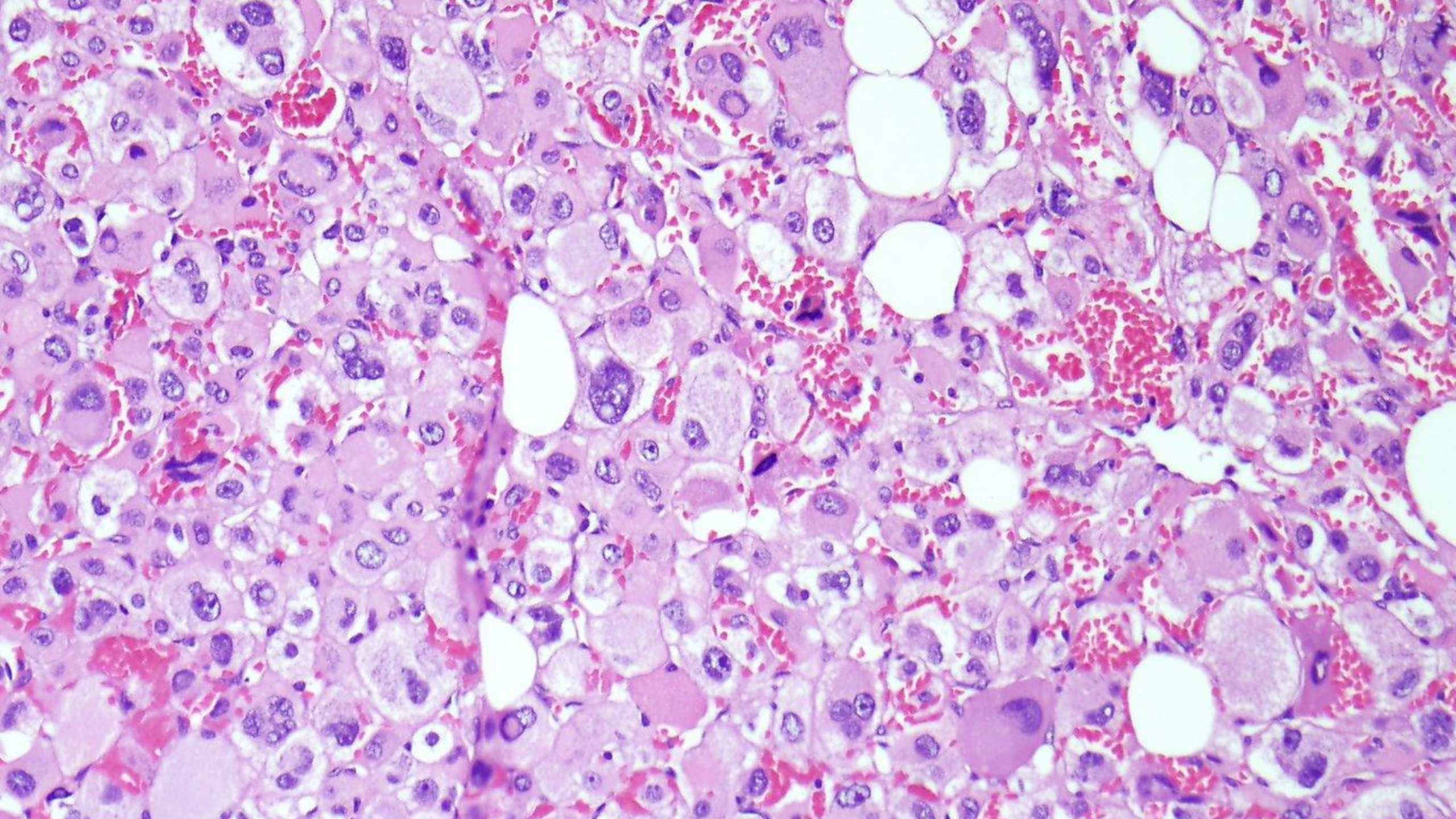
Gross Exam: 26 cm well defined mass which abuts kidney but does not invade and contains cystic and necrotic areas.

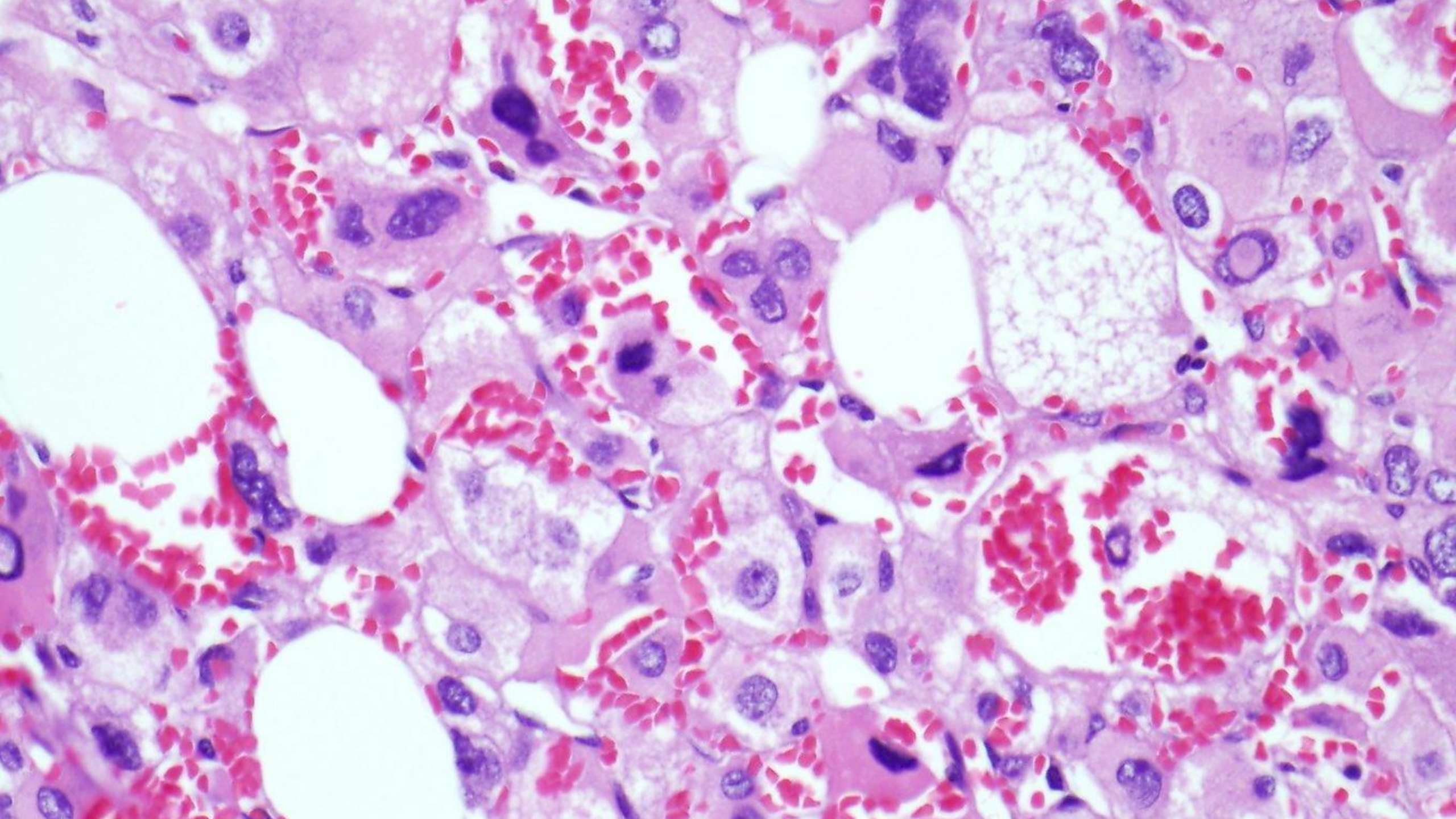


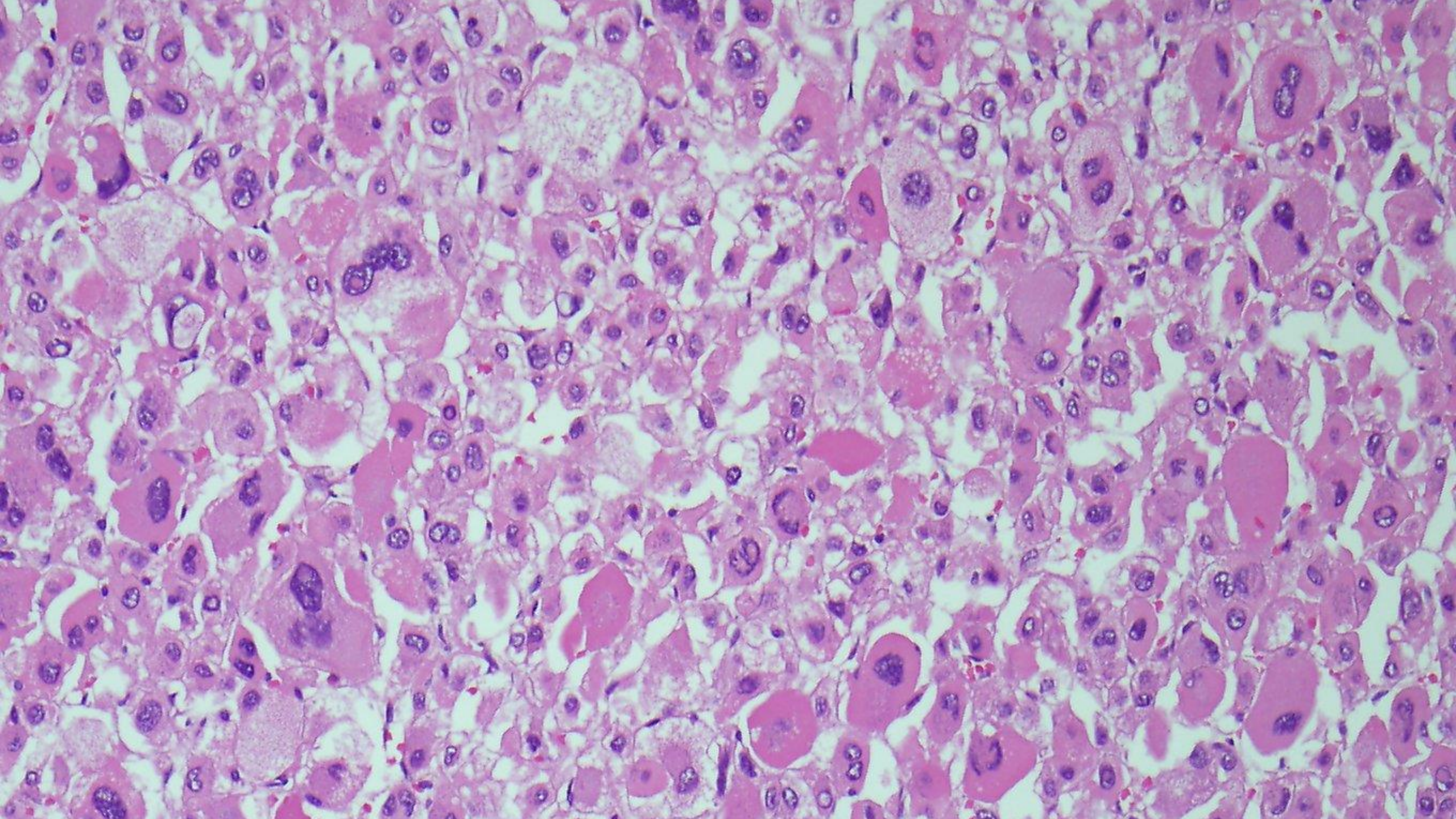


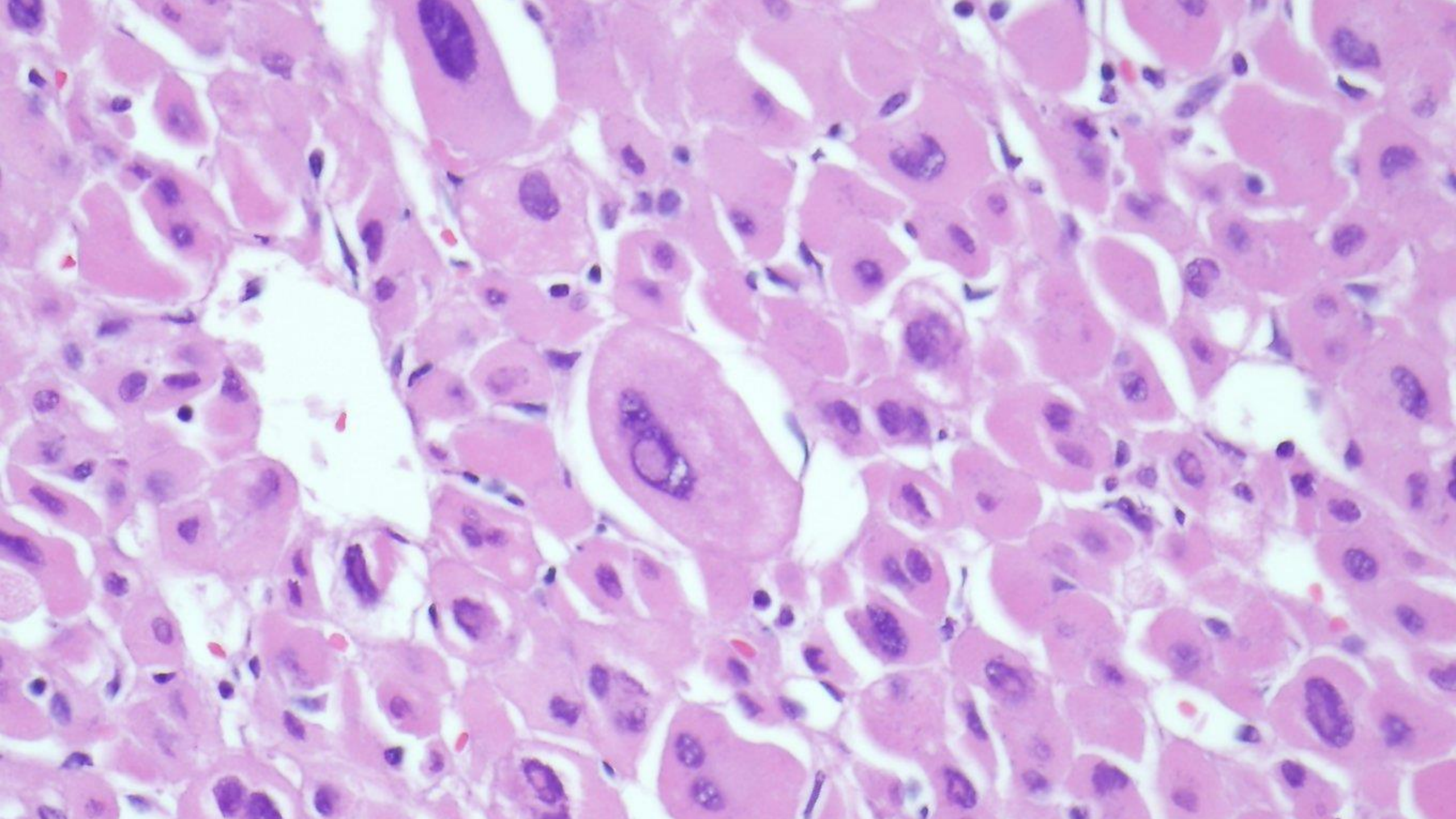


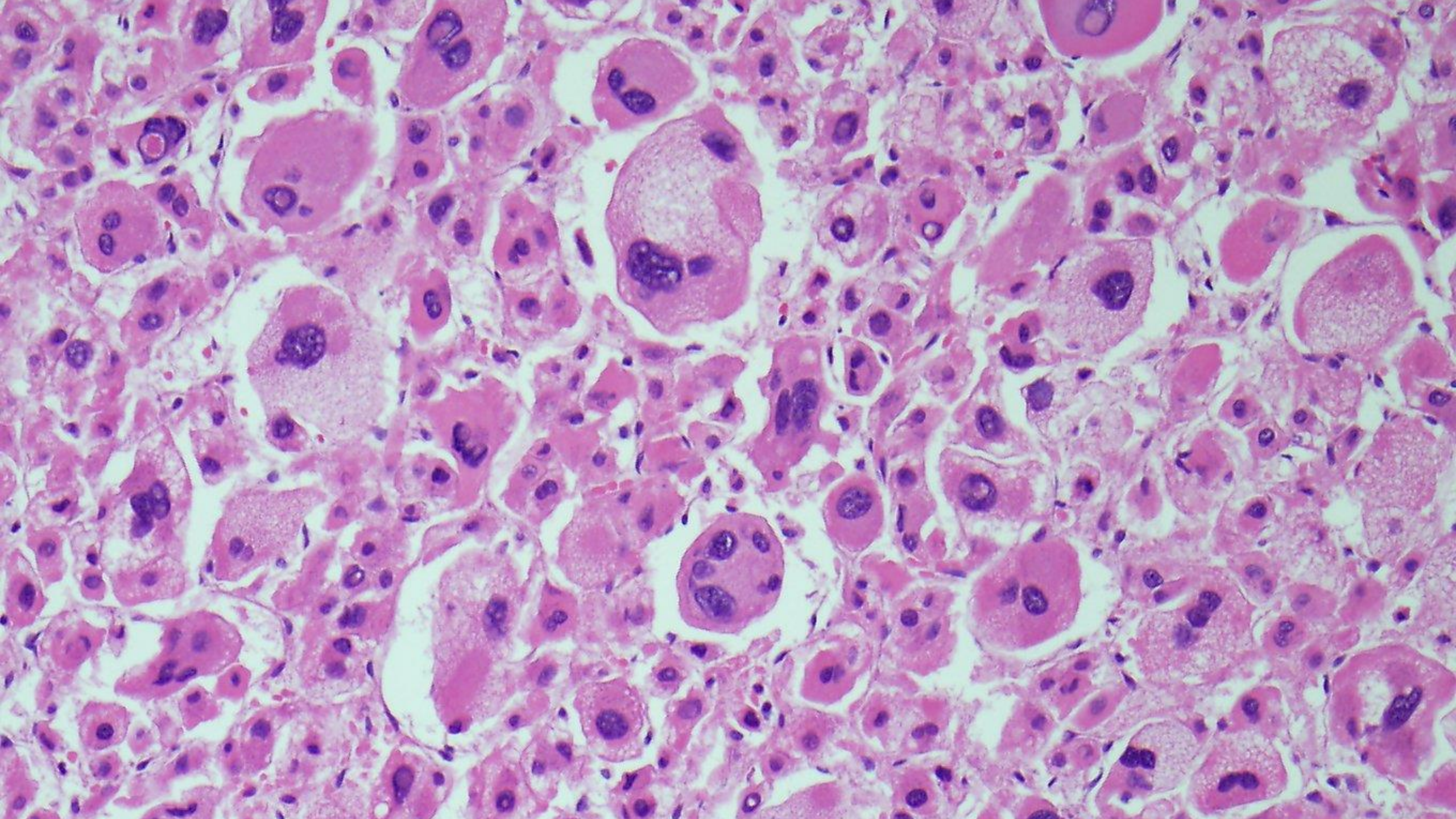


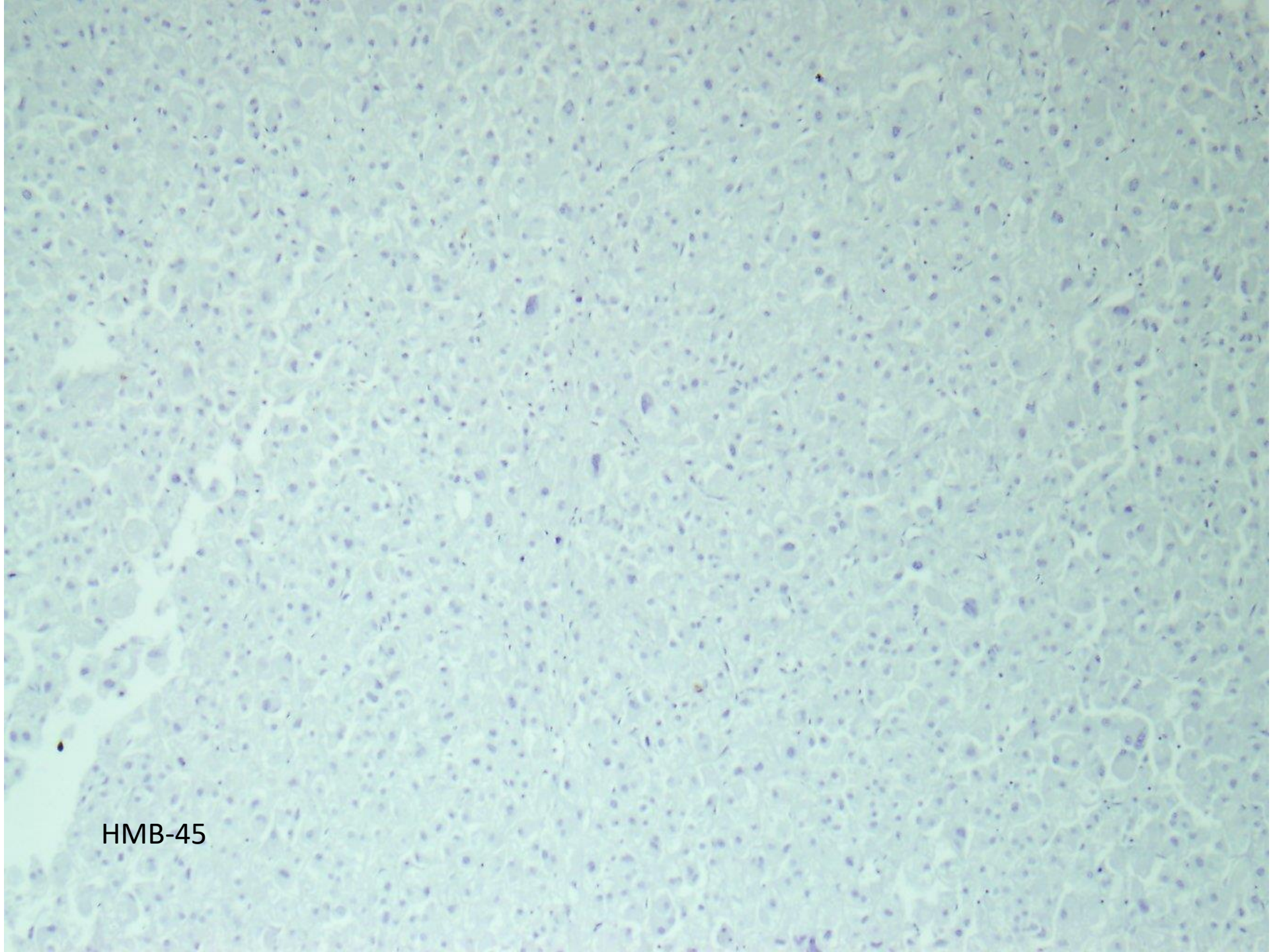


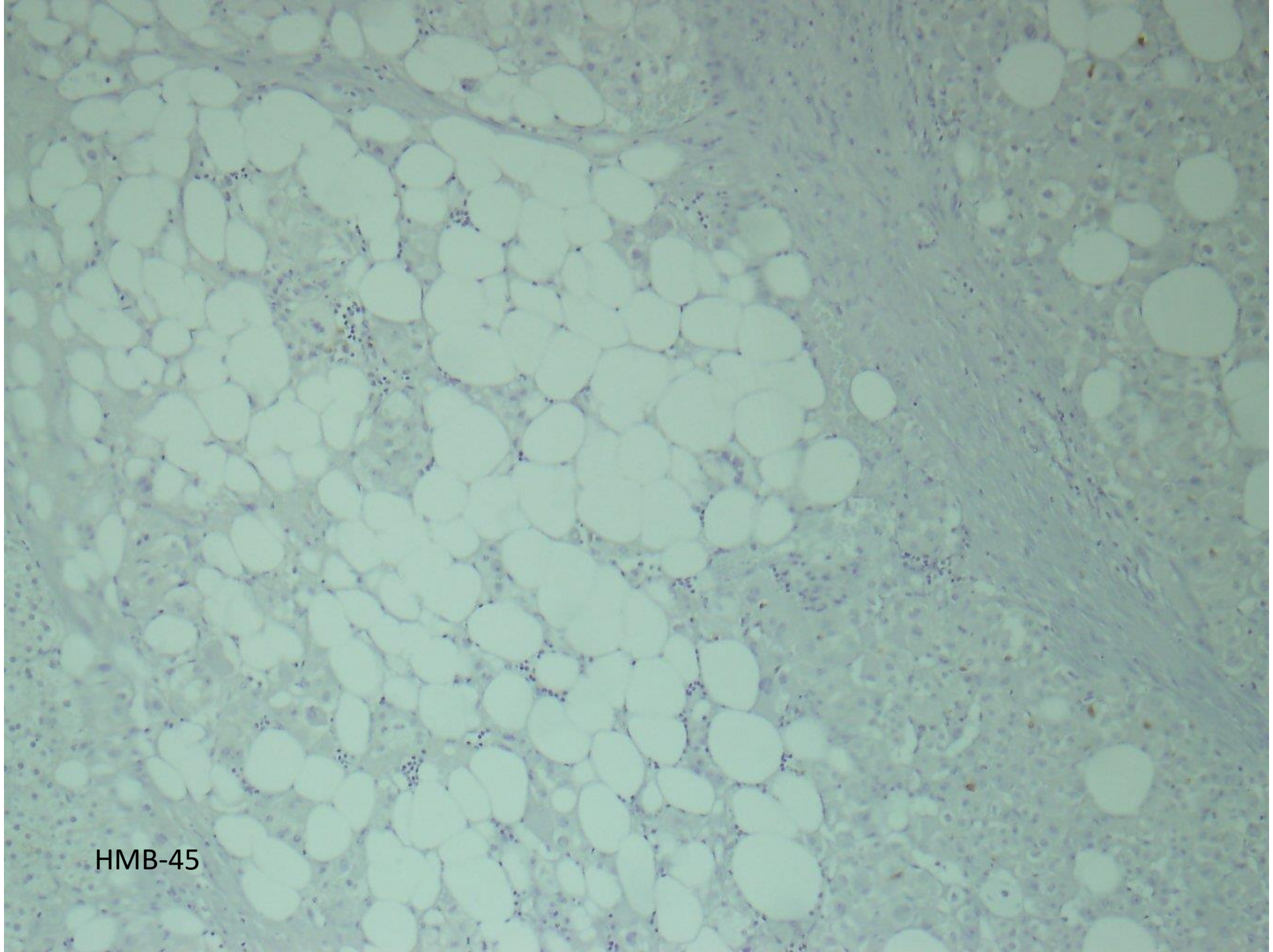


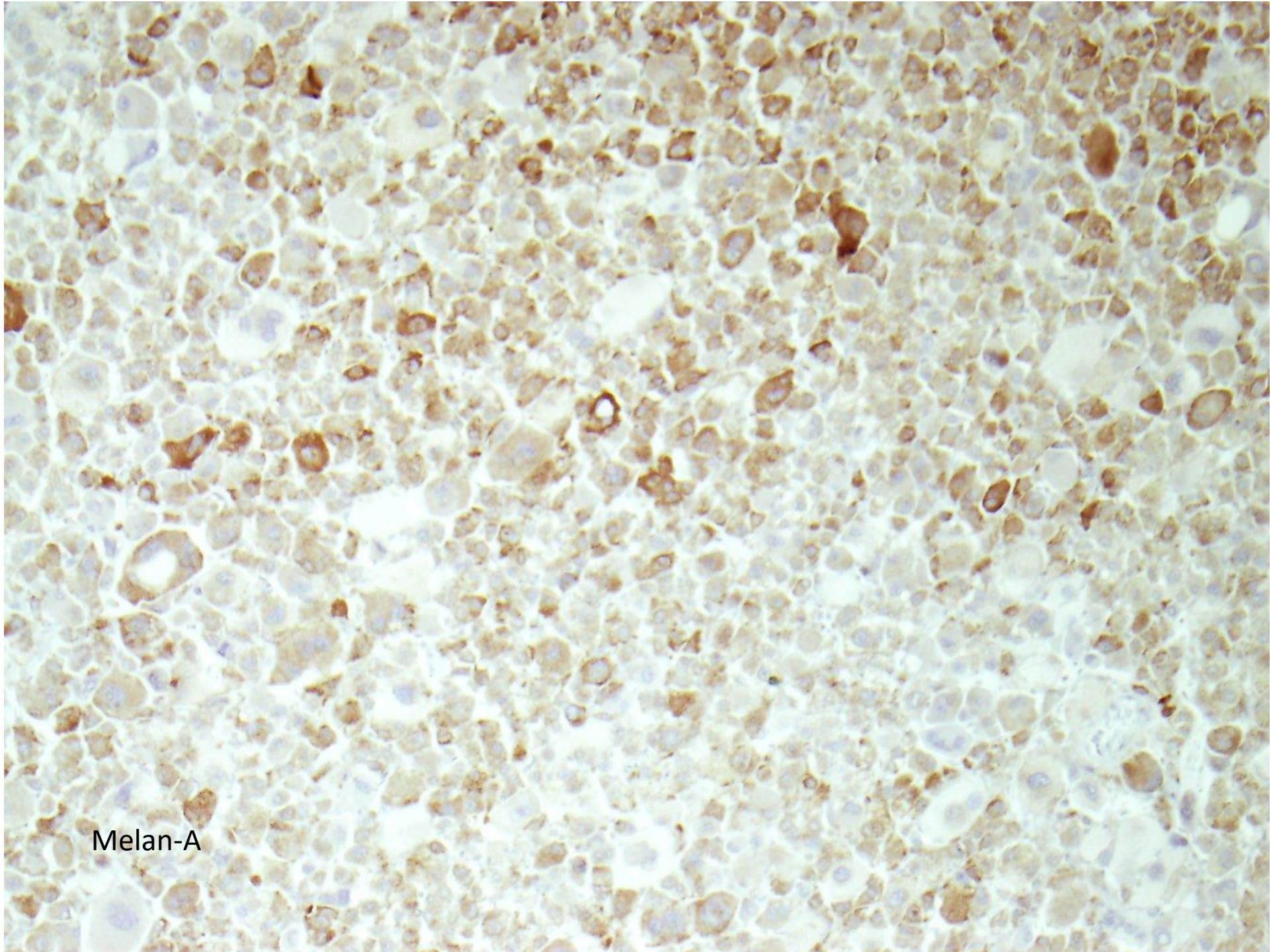


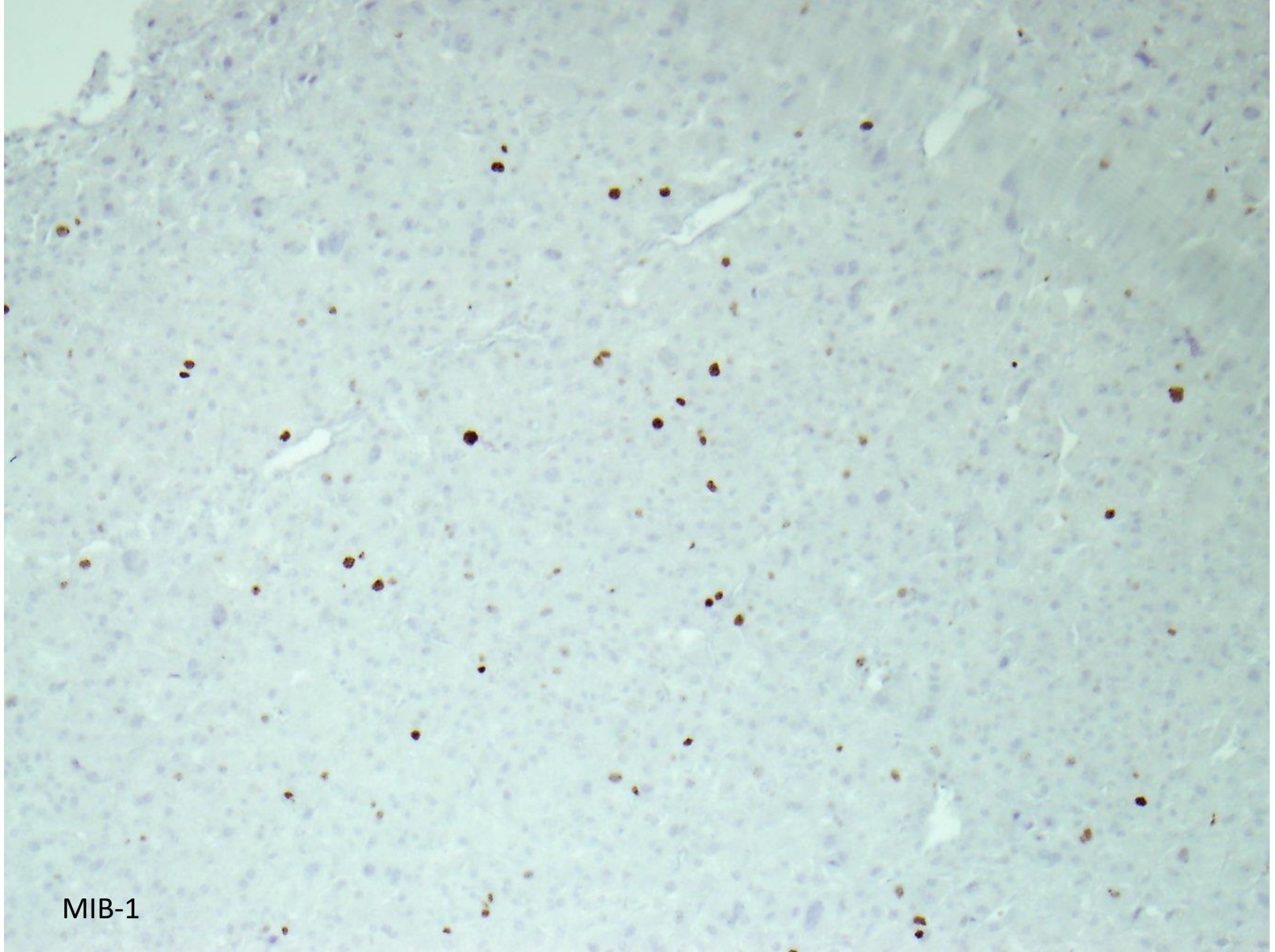


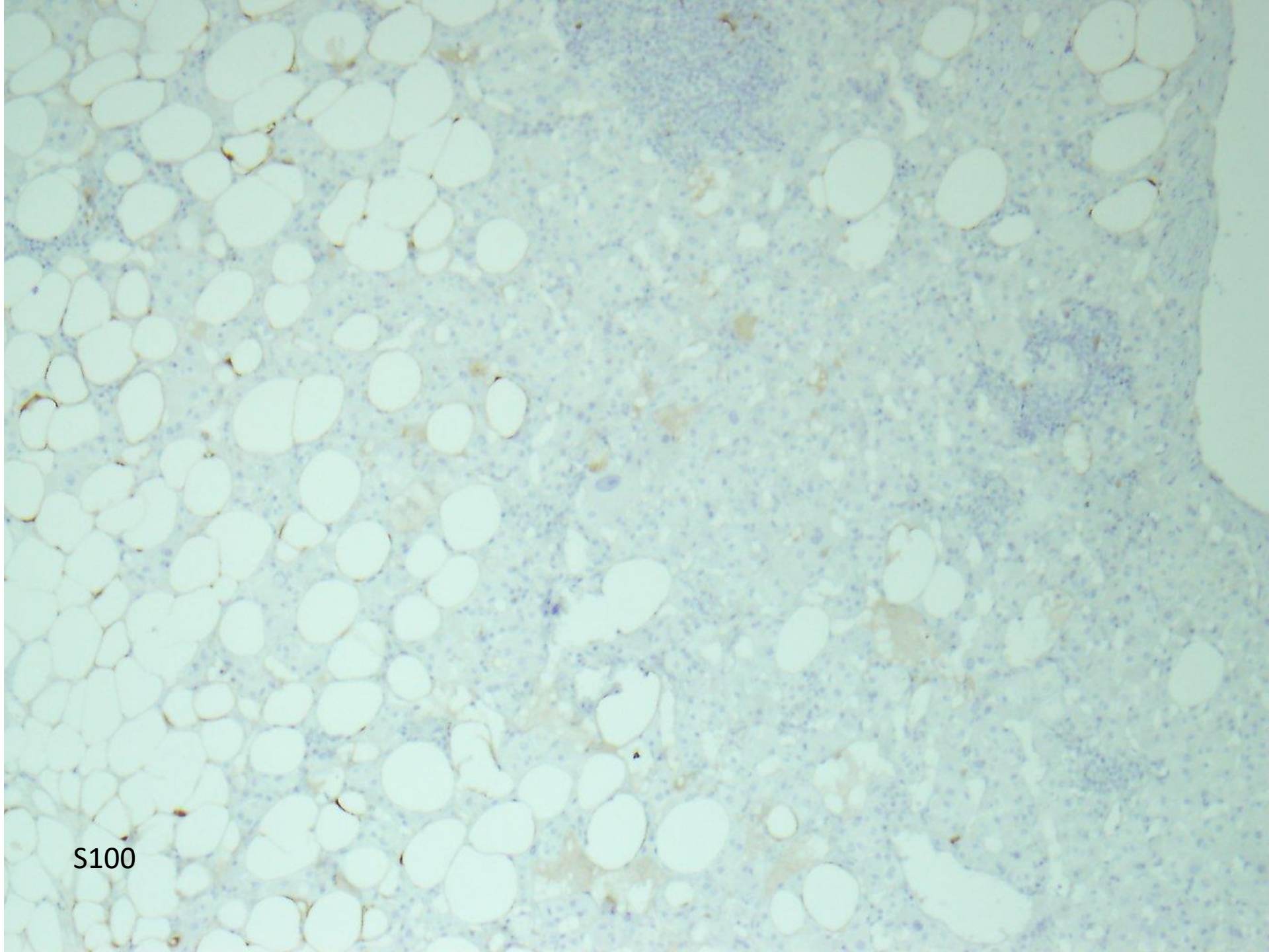


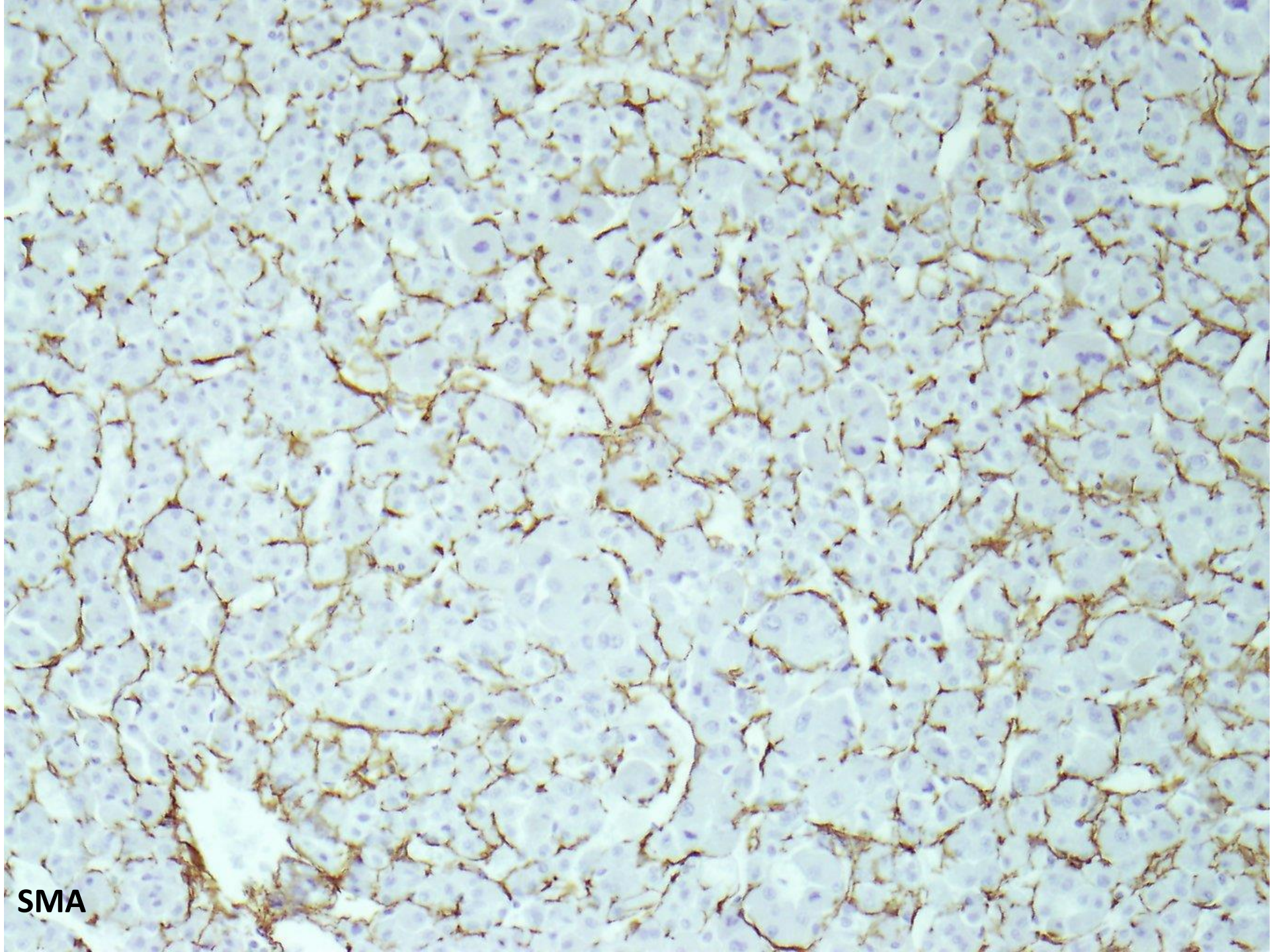

HMB-45


HMB-45


Melan-A


MIB-1


S100


SMA

Morphologic Findings:

- Solid “carcinoma like” pattern of growth
- Large pleomorphic cells with occasional multinucleated tumor giant cells, prominent nucleoli, intranuclear inclusions
- Rich vascular supporting stroma
- Rare mitotic figures
- Necrosis
- Areas with adipose tissue and large dysplastic vessels

Immunohistochemistry and FISH Testing

- HMB45 (-)
- Desmin/SMA (+ in large vessels and capillaries)
- Pax8 (-)
- Melan-A (+)
- Ki-67 (overall 2%)
- Inhibin (rare minimal + staining)
- S100 (focal + staining in fat)
- Cam 5.2 (scattered + staining in minority of cells)
- MDM2 FISH: negative for MDM2 amplification

FAVORED DIAGNOSIS: EPITHELIOID ANGIOMYOLIPOMA

- Oncocytic variant of adrenal adenoma in the limited differential for this case.

Differential Diagnosis of Epithelioid AML

- Adrenal adenoma (oncocytic variant)
- Renal cell carcinoma (clear cell, chromophobe, unclassified)
- Metastatic melanoma

*Ozgur Mete and Theodorus H. van der Kwast (2011) Epithelioid Angiomyolipoma: A Morphologically Distinct Variant That Mimics a Variety of Intra-abdominal Neoplasms. Archives of Pathology & Laboratory Medicine: May 2011, Vol. 135, No. 5, pp. 665-670.

*Aydin, H. , C. Magi-Galluzzi , B. R. Lane , et al. Renal angiomyolipoma: clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association. Am J Surg Pathol 2009. 33 (2):289–297.

QUESTIONS?