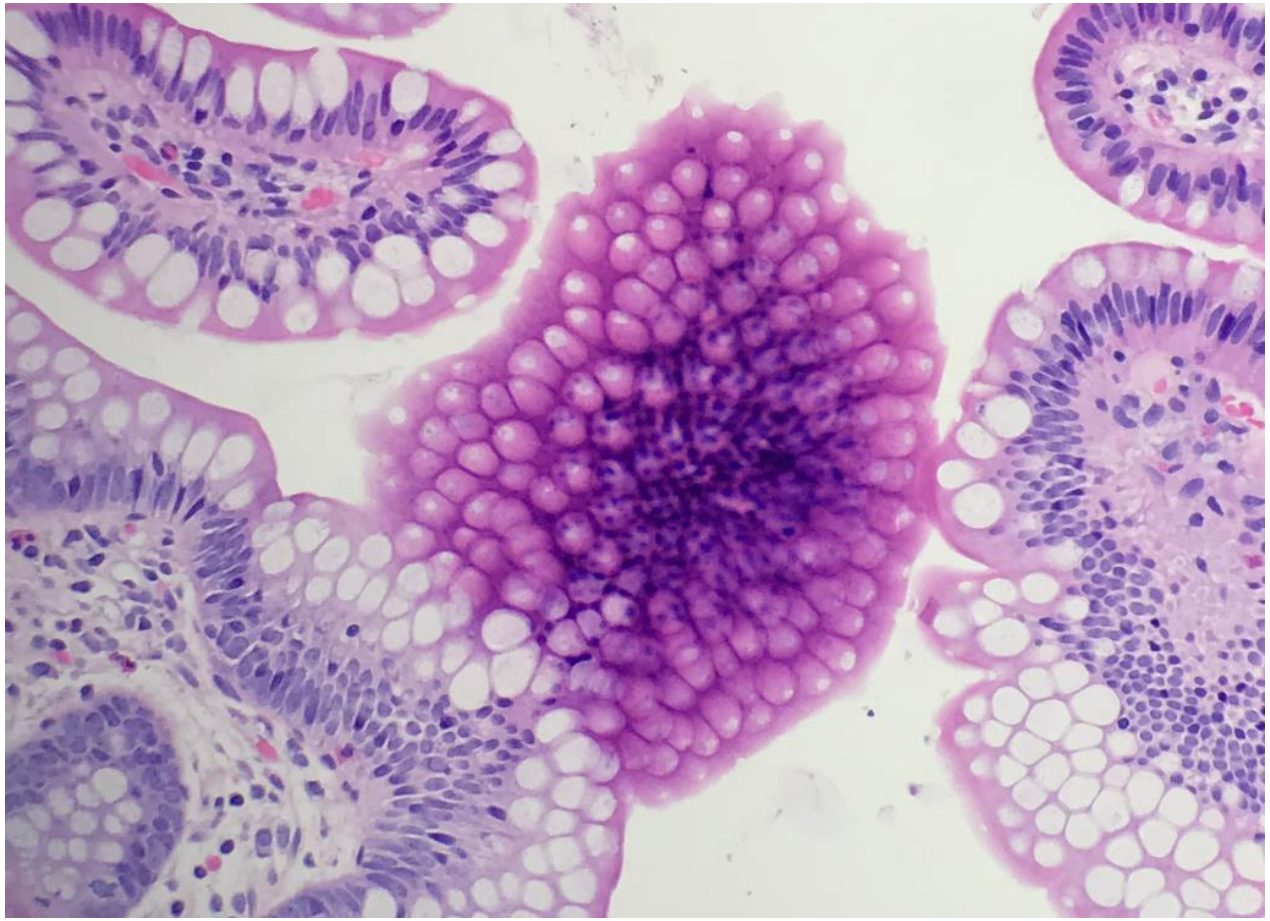
South Bay Pathology Society

December 2025



South Bay Pathology Society December 2025

Disclosures
December 1, 2025

Dr. G. Charville has disclosed a financial relationship with Cartography Biosciences (consultant). Dr. D. Twa has disclosed a financial relationship with Bristol-Myers-Squibb (grant). Dr. Y. Chen has disclosed a financial relationship with Astra Zeneca (honorarium). South Bay Pathology Society has determined that none of these relationships are relevant to the clinical diagnostic cases being discussed; all relationships are therefore mitigated. The activity planners and faculty listed below have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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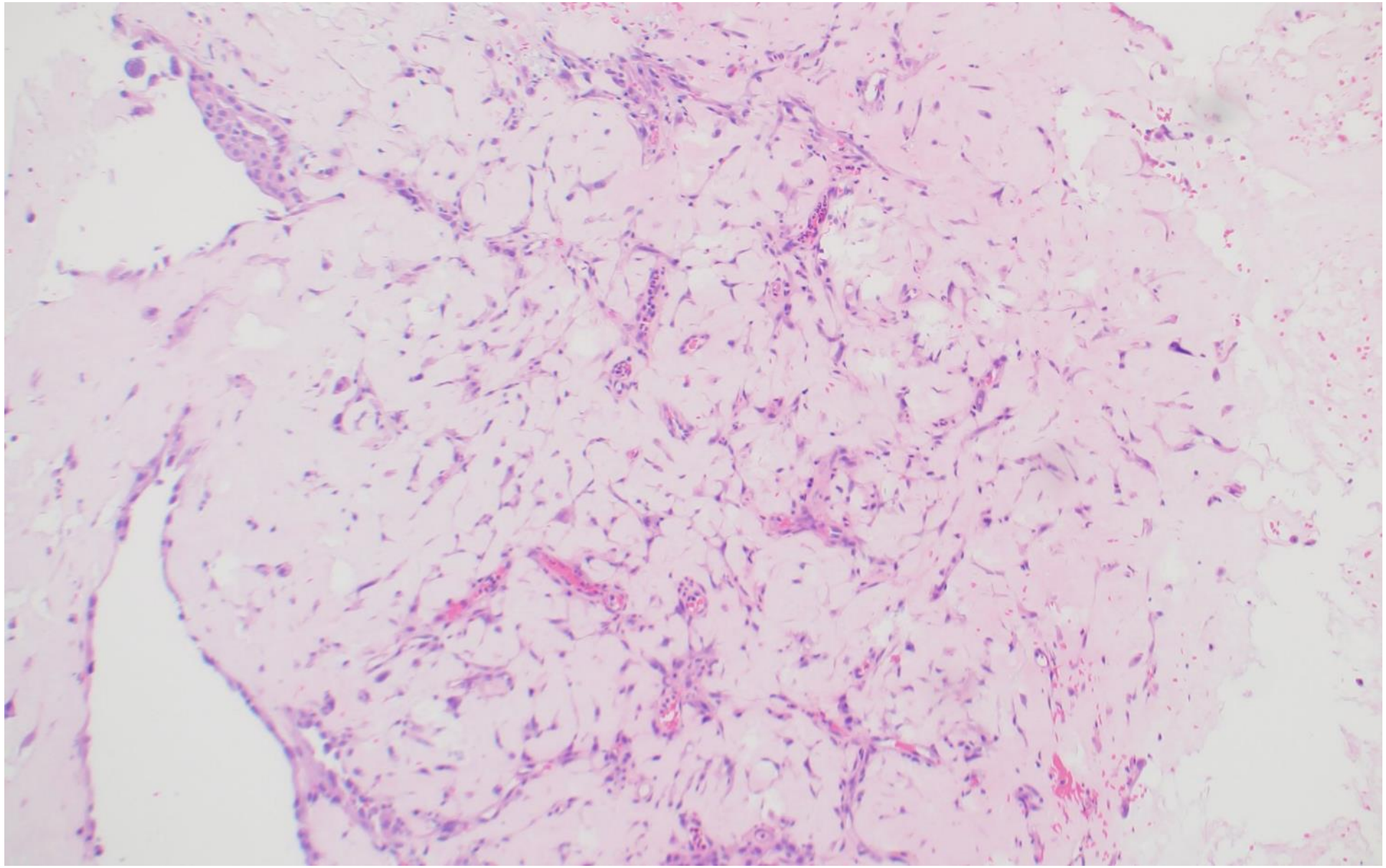
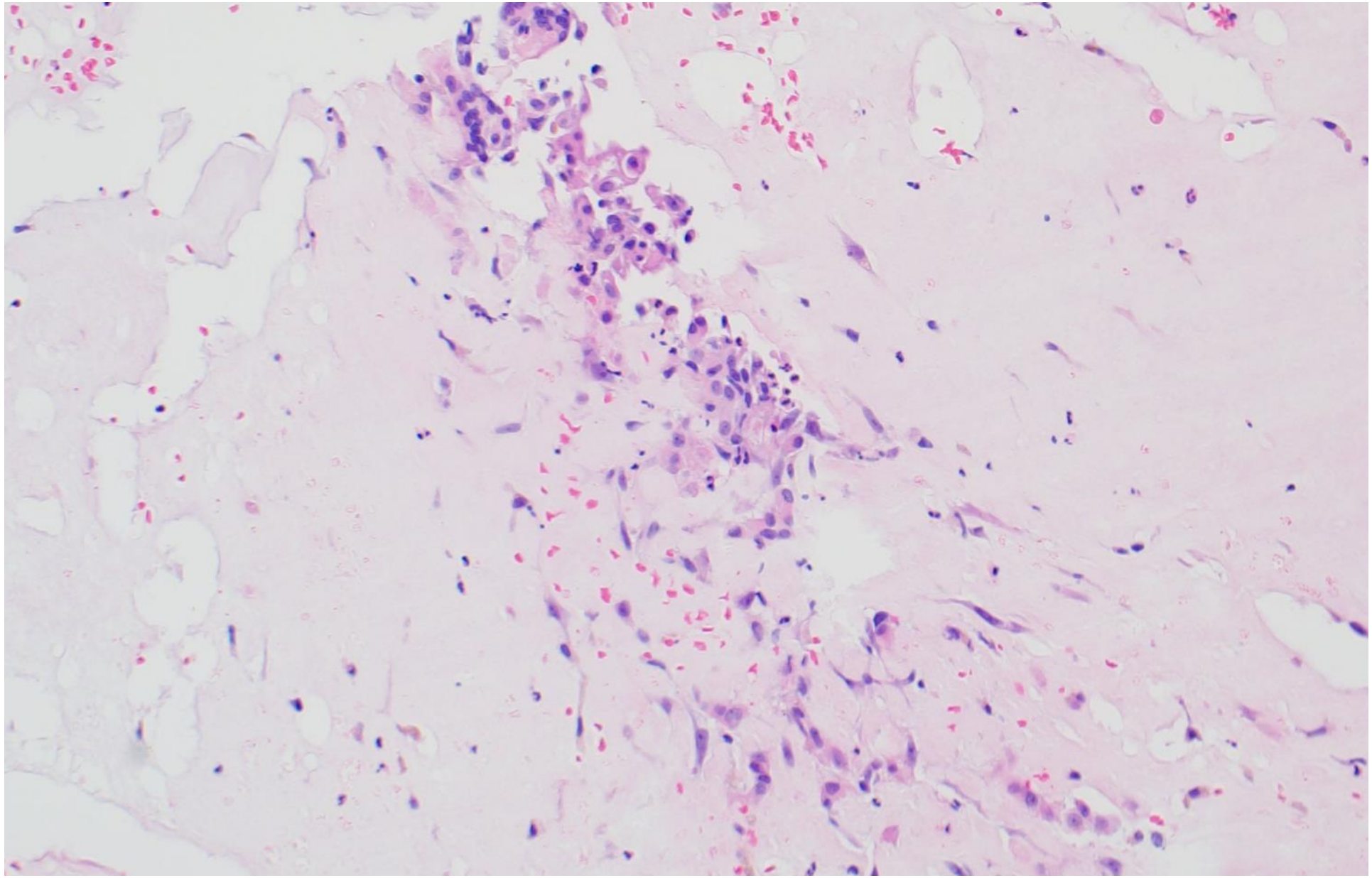
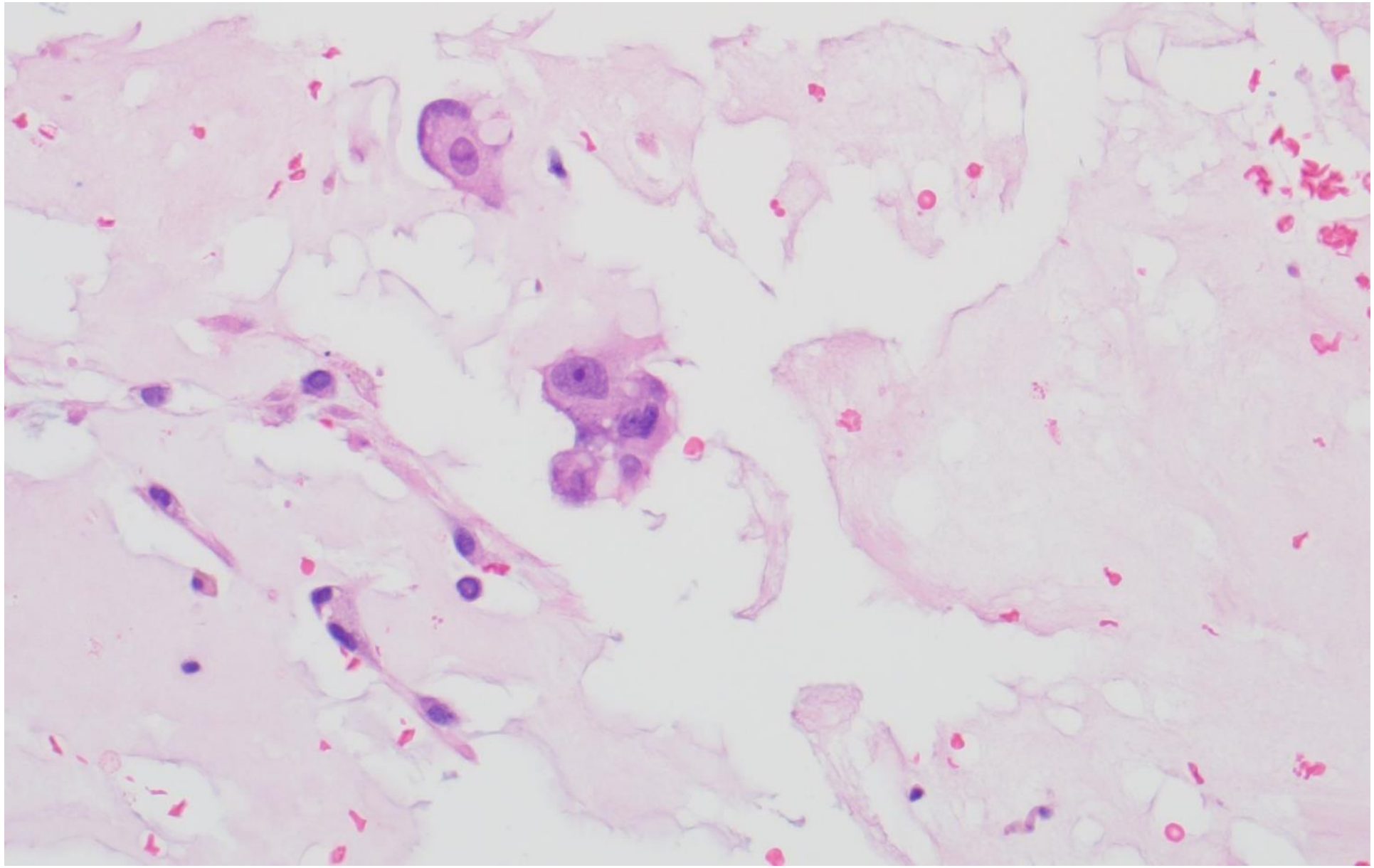
25-1201

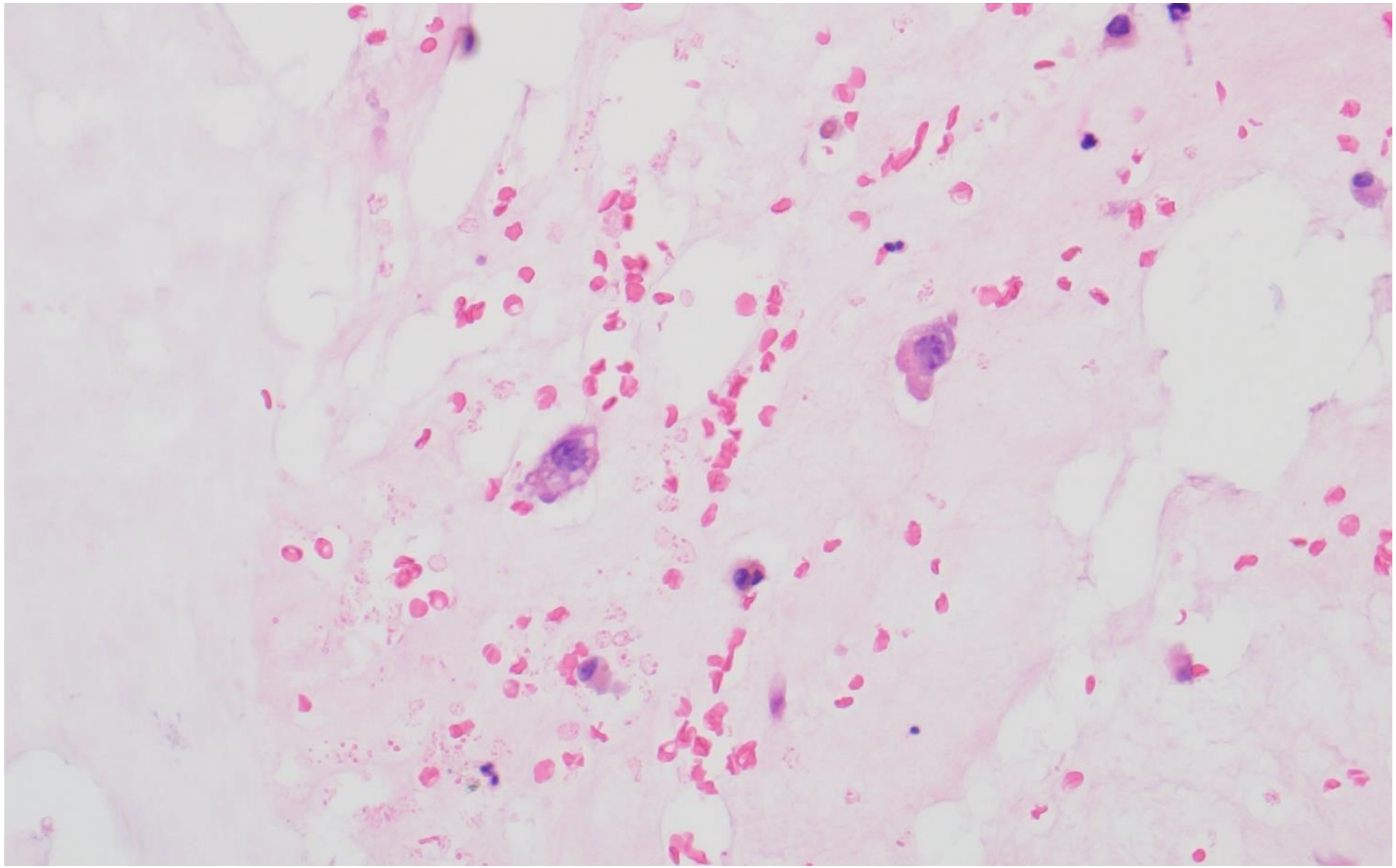
Adebola Adeniyi, Jodi Gedallovich, Emily Chan, Kelly Ernst; Stanford

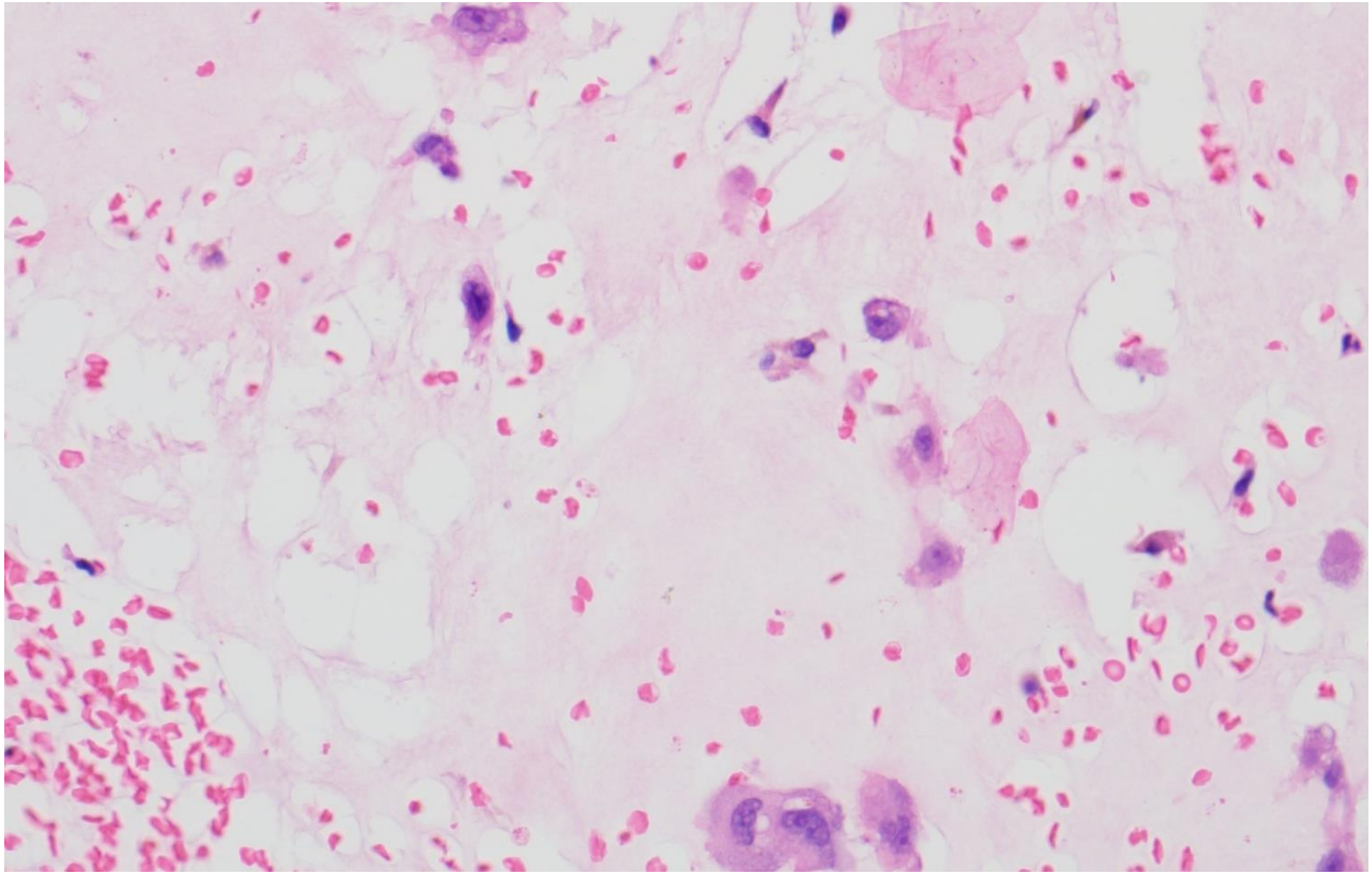
70s year-old man with bilateral stones and cysts, now with a 4.2 cm right kidney midpole nodule, protruding into and abutting the renal sinus without invasion of the main renal vein on the IVC, previously corresponding to a simple cyst. FNA was performed.

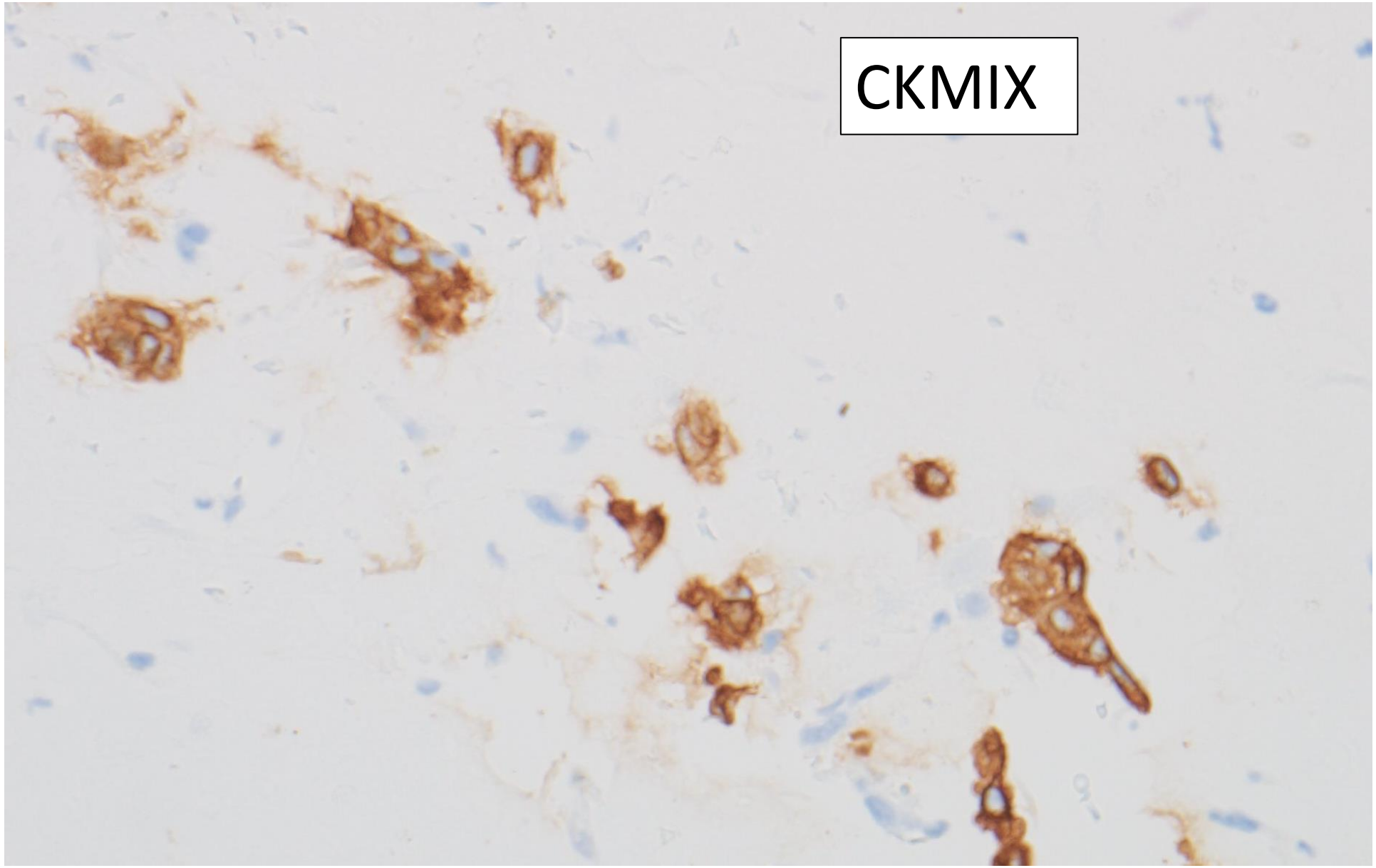


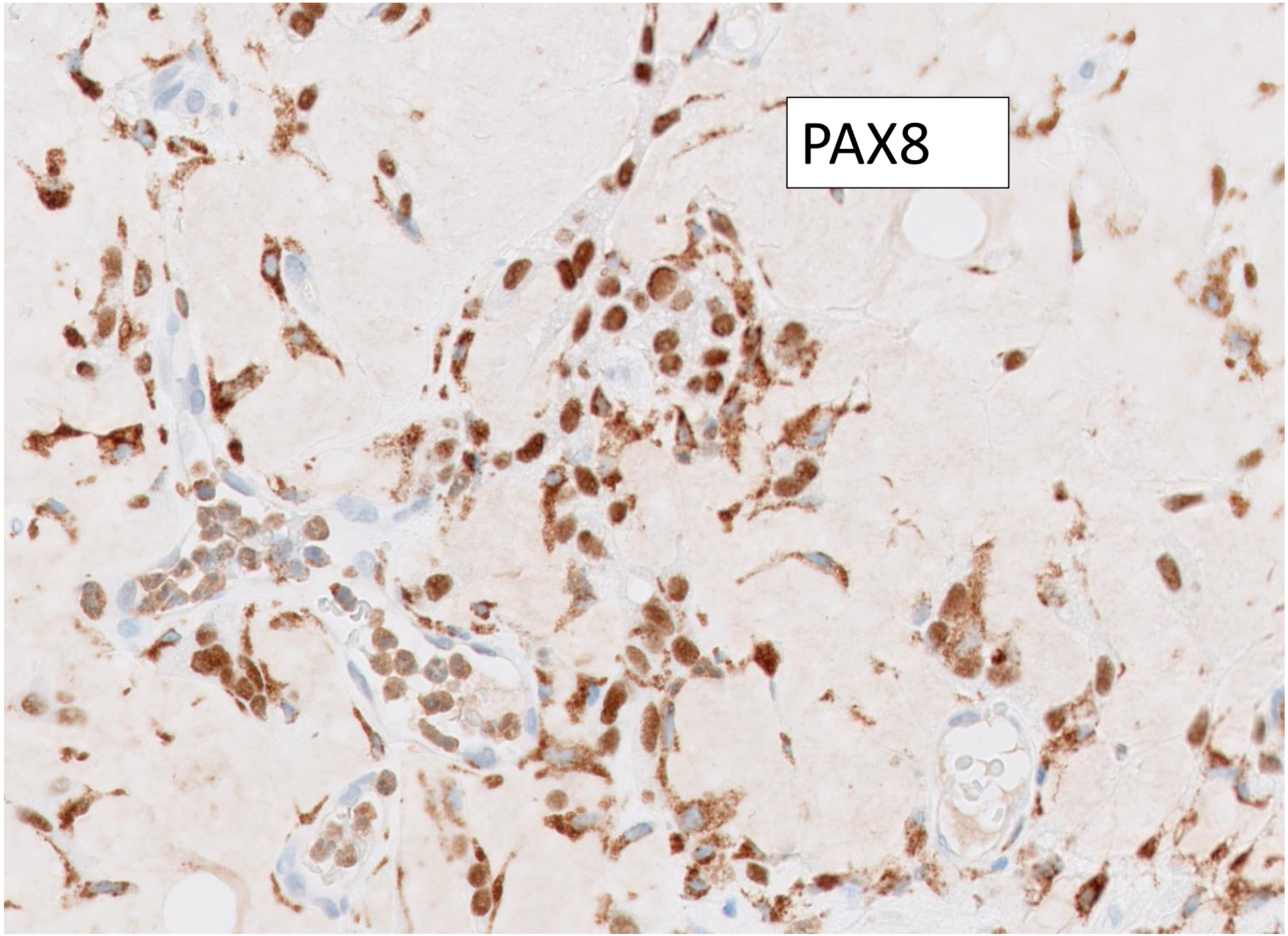


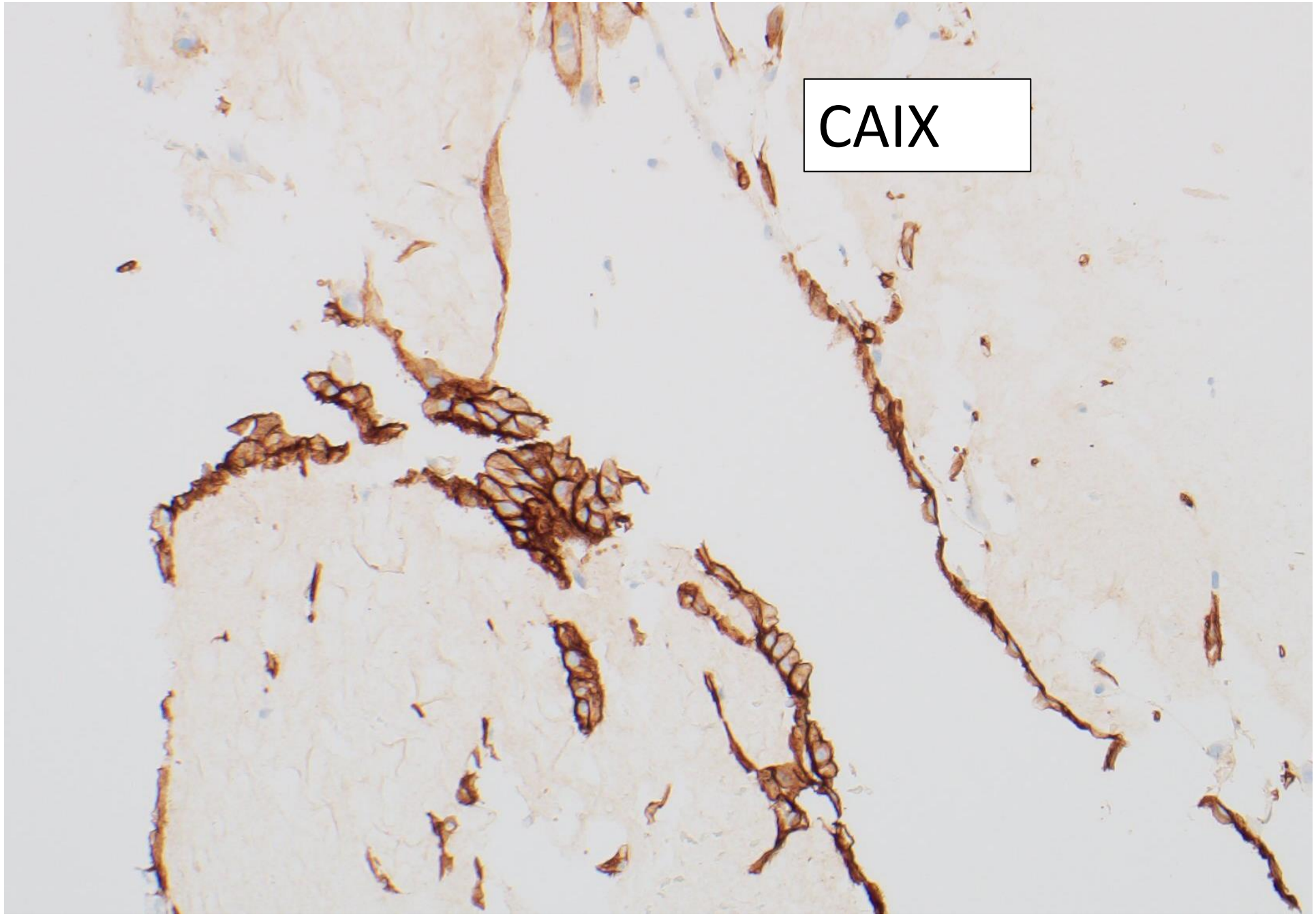







CKMIX

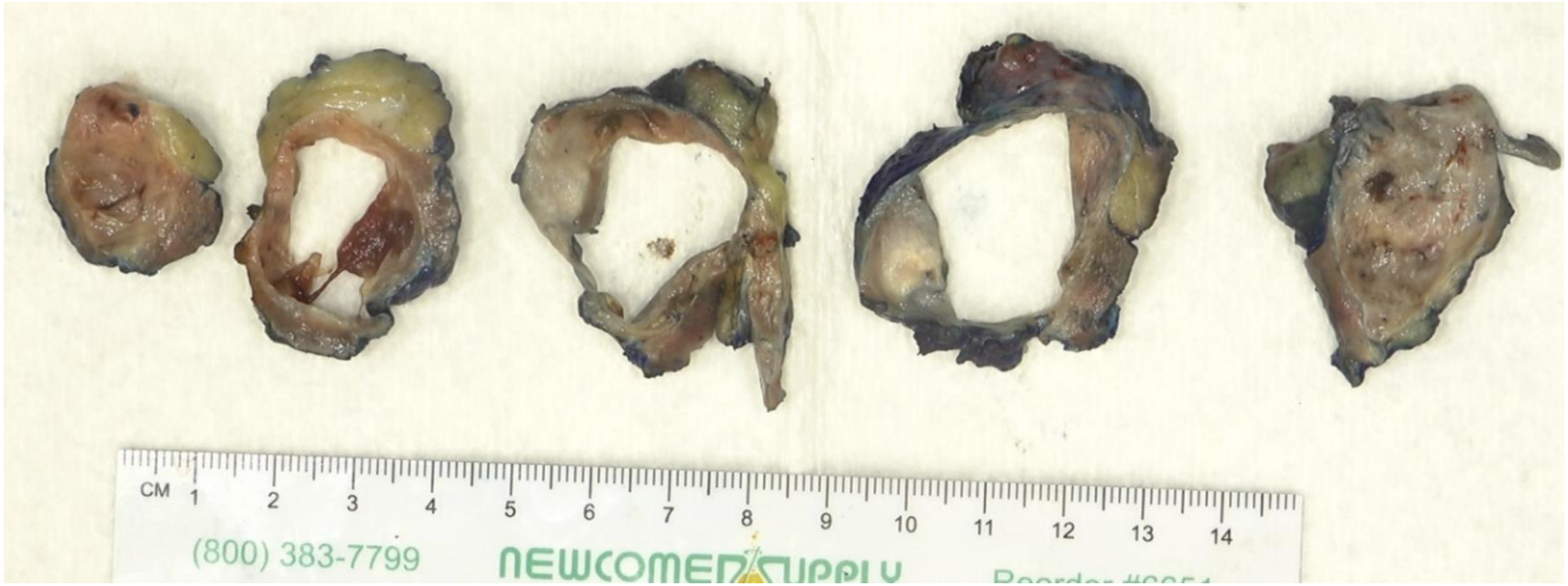

PAX8

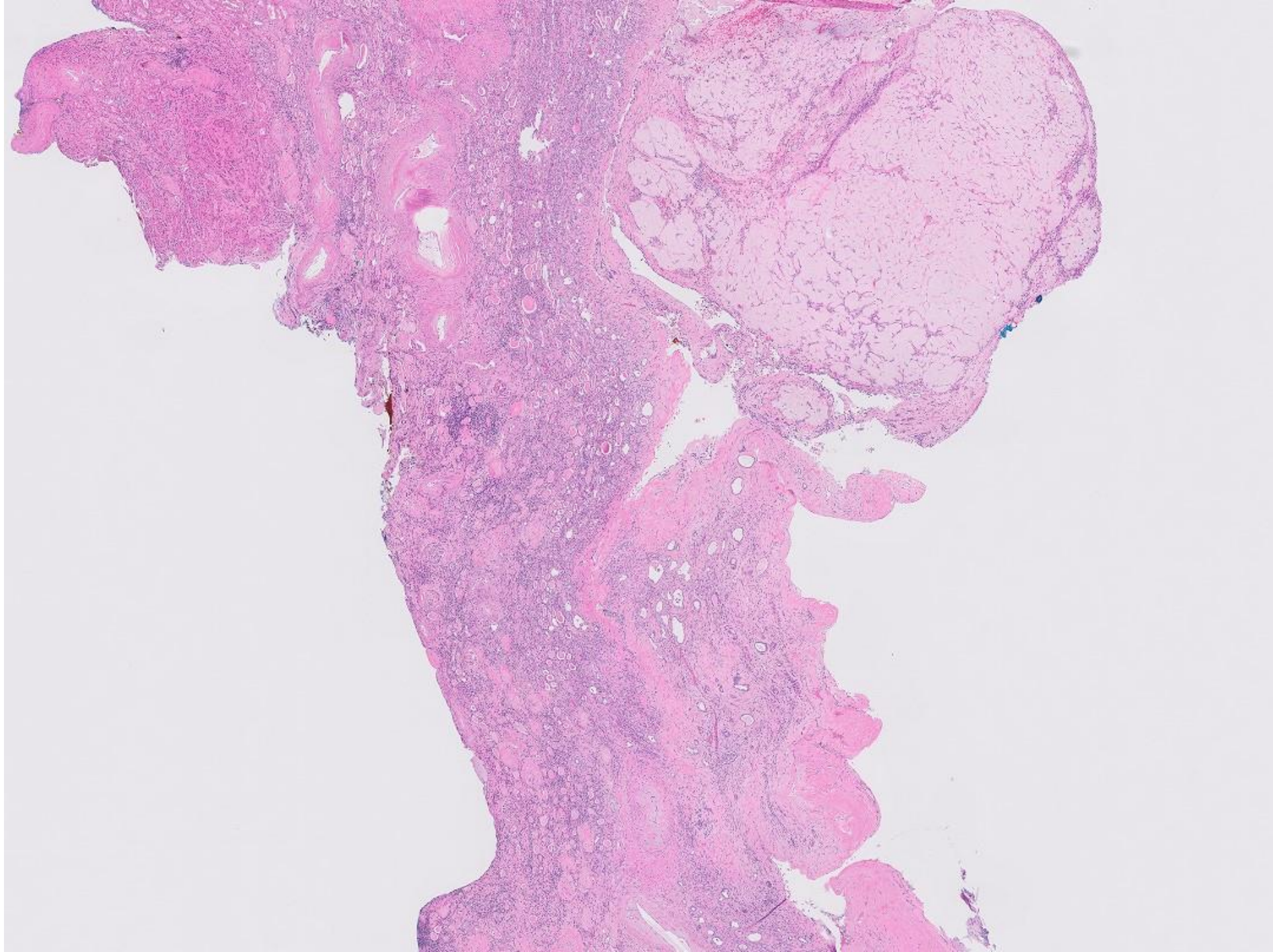

CAIX

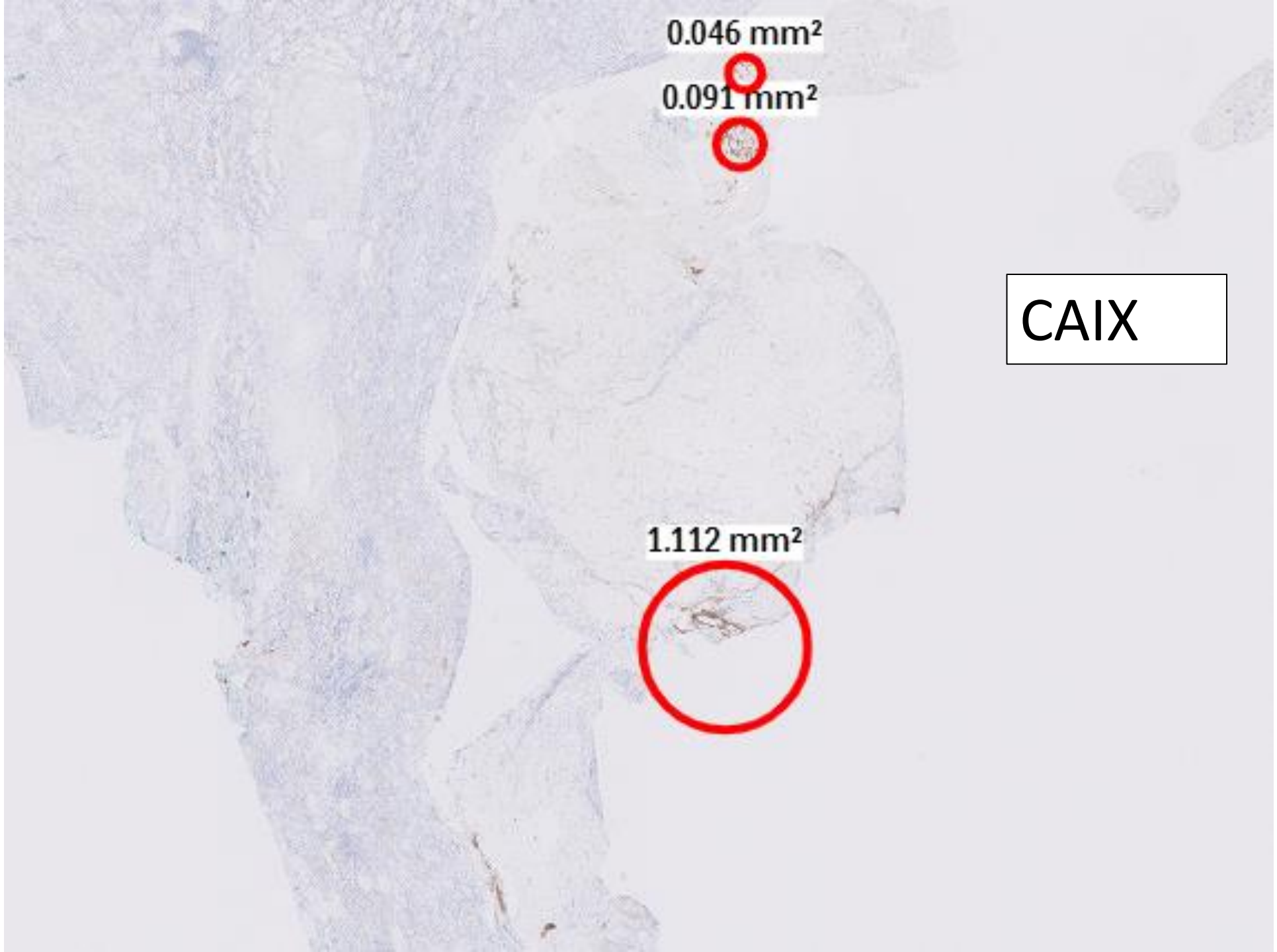
DIAGNOSIS?

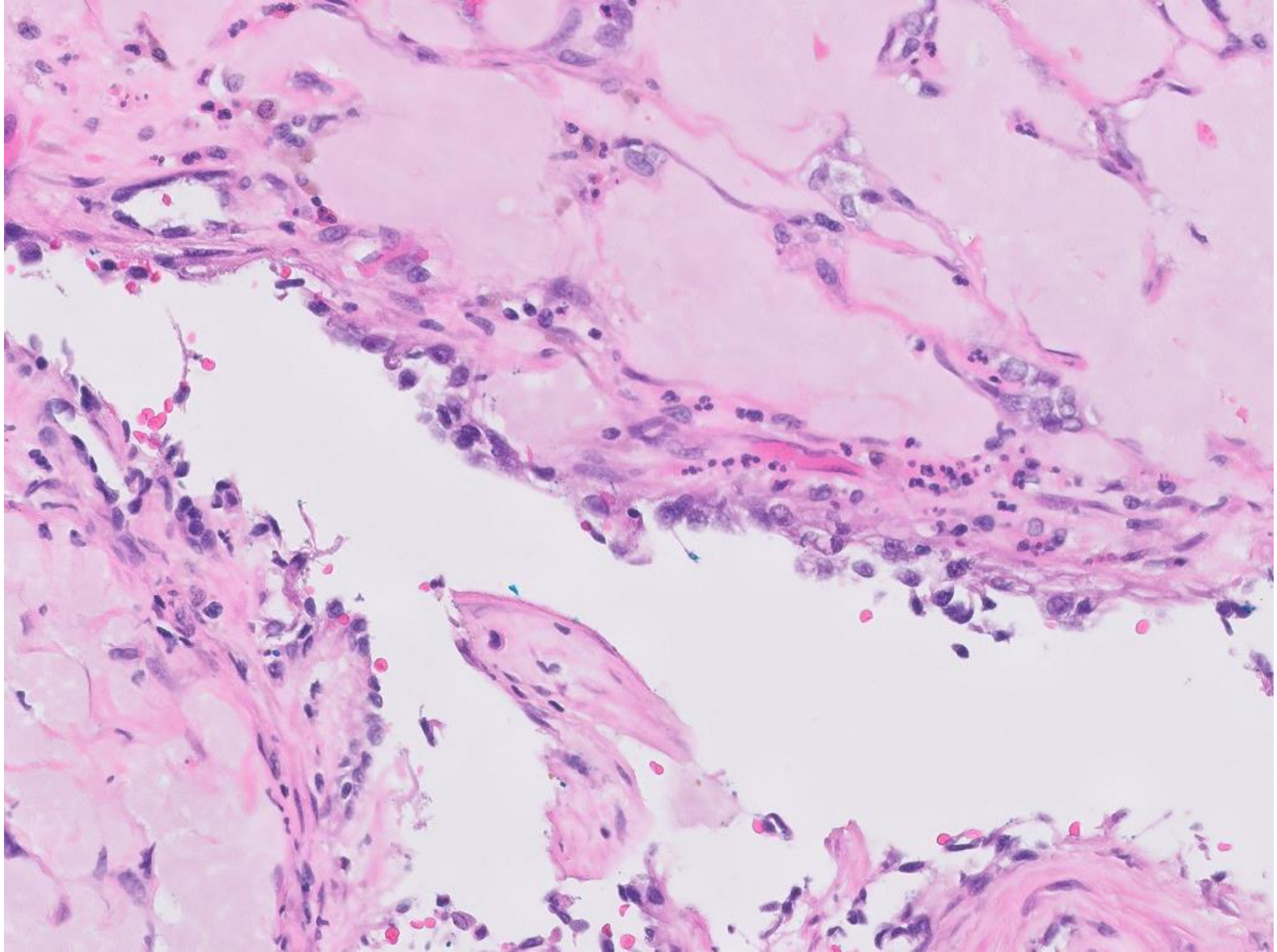
Renal Cell Carcinoma?

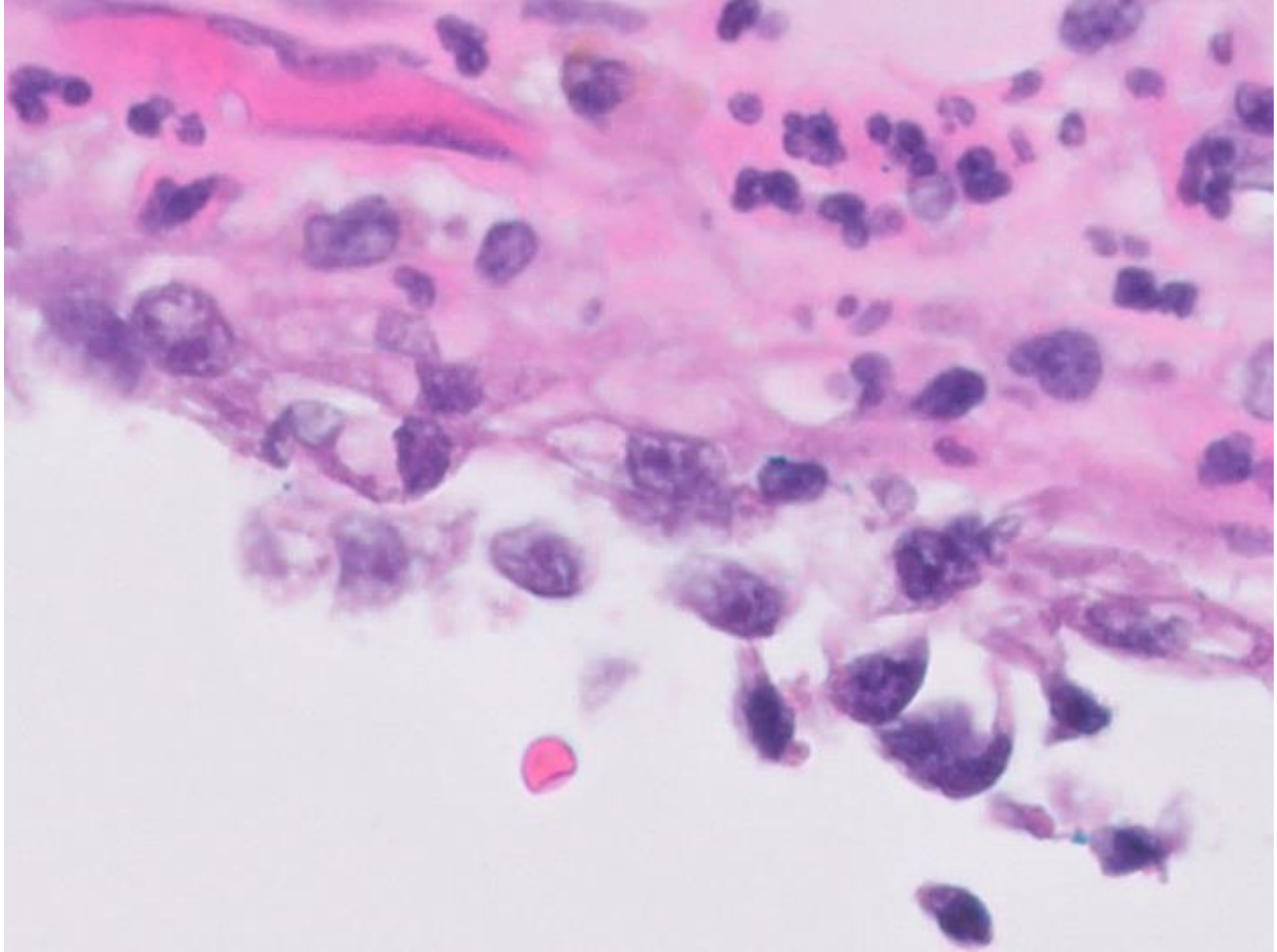
Right Partial Nephrectomy Resection






0.046 mm²
0.091 mm²
1.112 mm²
CAIX





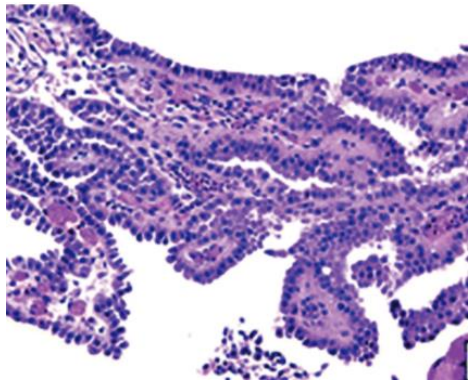
Nephrogenic Adenoma (NA)

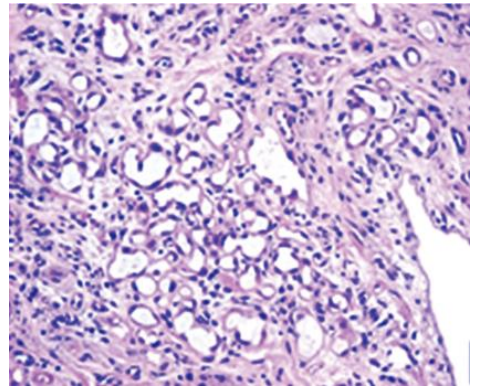
- Benign lesion of the genitourinary tract thought to arise from exfoliated renal tubular cells often in the setting of prior injury
- Male adults are the most common demographic
- Causes nonspecific symptoms with histopathology that can closely mimic multiple malignant lesions of the urinary tract

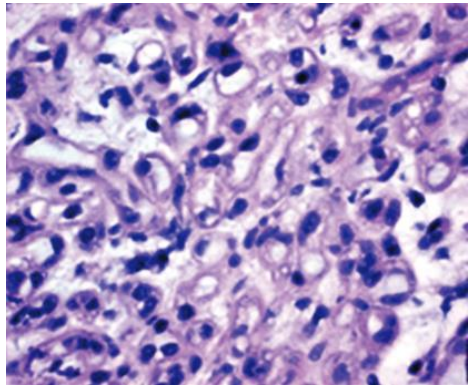
Venyo, A. K.-G. (2015). Nephrogenic adenoma of the urinary bladder: A review of the literature. *International Scholarly Research Notices*, *2015*, 1–15. https://doi.org/10.1155/2015/704982

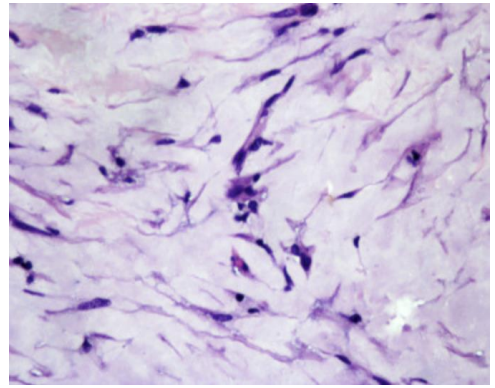
Nephrogenic Adenoma Variants/Histologic Spectrum

- Tubule
- Papillary
- Signet ring-like
- Vessel-like formations
- Flat
- Fibromyxoid









Venyo, A. K.-G. (2015). Nephrogenic adenoma of the urinary bladder: A review of the literature. *International Scholarly Research Notices*, *2015*, 1–15. https://doi.org/10.1155/2015/704982

Khedaoui, R., Encabo, B., & Tardío, J. C. (2016). Fibromyxoid nephrogenic adenoma protruding in a renal cortical cyst. A rare morphological variant in an outstanding location. *Pathology - Research and Practice*, *212*(2), 135–138. https://doi.org/10.1016/j.prp.2015.09.013

Nephrogenic Adenoma: Fibromyxoid Variant

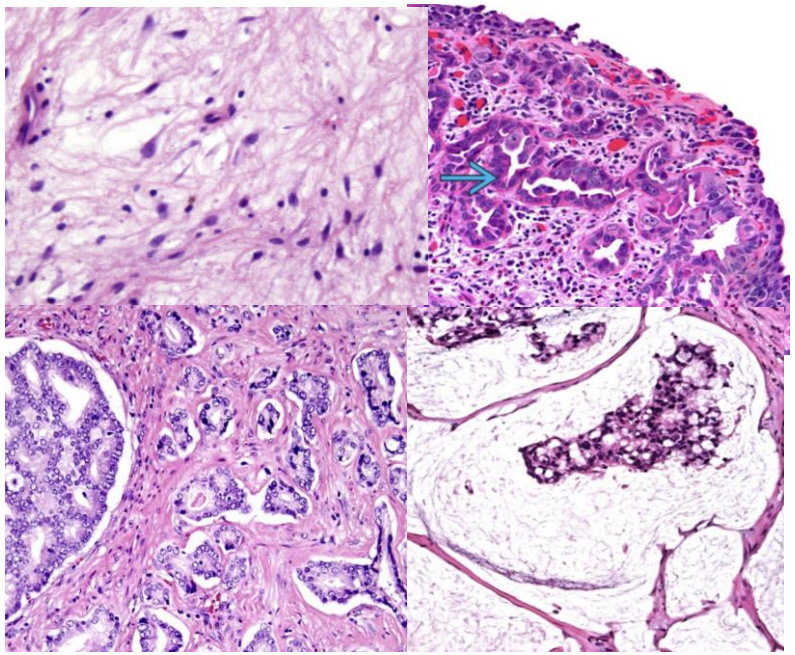
- Rare variant that had first been reported in 2007 by Hansel et al. and it has been described as spindle-shaped renal epithelial cells within a fibromxyoid background
- The largest case series of fibromyxoid nephrogenic adenoma had been published by Li et al. who had identified 43 lesions predominately in the bladder, prostate, and upper urinary tract of elderly men

Hansel, D.E., Nadasdy T., and Epstein J.I. “Fibromyxoid Nephrogenic Adenoma: A Newly Recognized Variant Mimicking Mucinous Adenocarcinoma.” *The American Journal of Surgical Pathology* 31, no. 8 (2007): 1231–37.

Li L., Williamson S.R., Castillo R.P., et al. “Fibromyxoid Nephrogenic Adenoma: A Series of 43 Cases Reassessing Predisposing Conditions, Clinical Presentation, and Morphology.” *The American Journal of Surgical Pathology* 47, no. 1 (2023): 37–46.

Differential Diagnosis

- Perinephric myxoid pseudotumor of fat
- Prostatic adenocarcinoma
- Urothelial Carcinoma
  - Tubular variant
  - Nested variant
  - Glandular differentiation
  - Papillary urothelial carcinoma
- Adenocarcinoma of bladder
  - Mucinous



Expertpath. (n.d.). http://expertpath.com

Dashti, N. K., Fritchie, K. J., & Folpe, A. L. (2019). Perinephric Myxoid Pseudotumor of fat: A distinctive pseudoneoplasm most often associated with non-neoplastic renal disease. *Human Pathology*, *87*, 37–43. https://doi.org/10.1016/j.humpath.2019.02.005

Immunohistochemical Pitfalls/Overlap with Nephrogenic Adenoma

- Can see significant immunohistochemical overlap with other renal neoplasms, such as renal cell carcinoma as demonstrated by this case
  - PAX 8 & CK7
- Variable alpha-methylacyl-CoA racemase (AMCR) expression
- No current literature describing CA-IX immunoreactivity for nephrogenic adenoma
  - For this current case, CA-IX staining was observed in the initial fine-needle aspiration sample but not in the resection sample
  - This may be attributable to tissue hypoxia rather than neoplastic expression
  - Given this information, however, one should try to avoid using CA-IX when considering pathologies outside of RCC as this stain can become a pitfall.

Potter C., and Harris A.L. "Hypoxia Inducible Carbonic Anhydrase IX, Marker of Tumour Hypoxia, Survival Pathway and Therapy Target." *Cell Cycle* 3, no. 2 (2004): 164–67.

Skinnider B.F., Oliva E., Young R.H., et al. "Expression of Alpha-Methylacyl-CoA Racemase (P504S) in Nephrogenic Adenoma: A Significant Immunohistochemical Pitfall Compounding the Differential Diagnosis with Prostatic Adenocarcinoma." *The American Journal of Surgical Pathology* 28, no. 6 (2004): 701–5.

Take Away Points

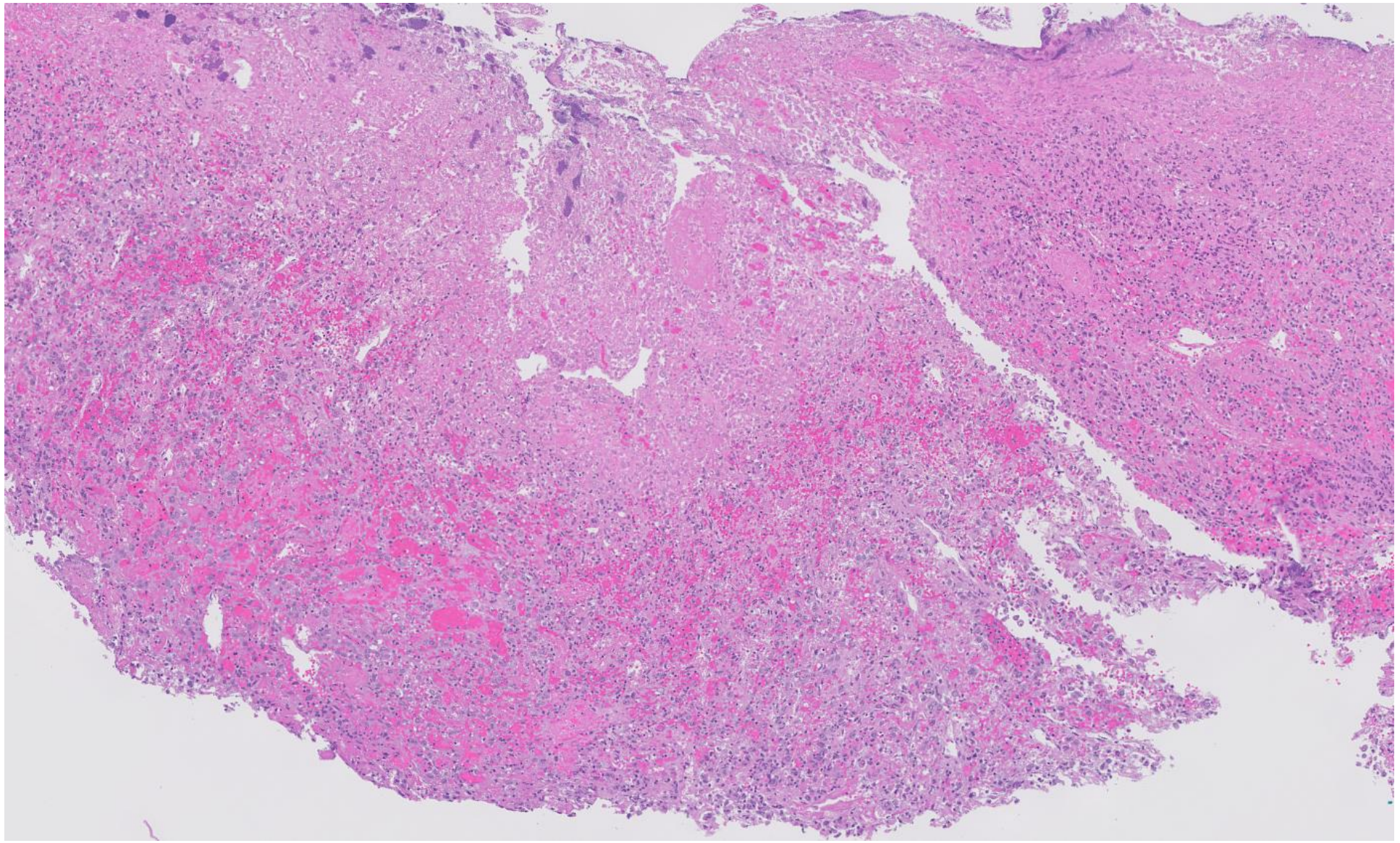
- Fibromyxoid nephrogenic adenoma is a rare benign entity that has the potential to mimic various malignant pathologies
- Small kidney biopsies/fine needle aspiration can be a very useful diagnostic tool when the sample is adequate, however, when the sample is very limited, one should keep benign mimics within their differential
- There is significant immunohistochemical overlap between nephrogenic adenoma and other renal neoplasms, such as renal cell carcinoma. Thus, caution is advised regarding the interpretation of stains in limited preparations.
  - In particular, CA-IX should be avoided (if possible) when there are pathologies you are considering outside of RCC
- Awareness of the fibromyxoid variant of NA and its cytologic features is critical for pathologists to avoid misdiagnosis and ensure the appropriate management of this benign process.

25-1202

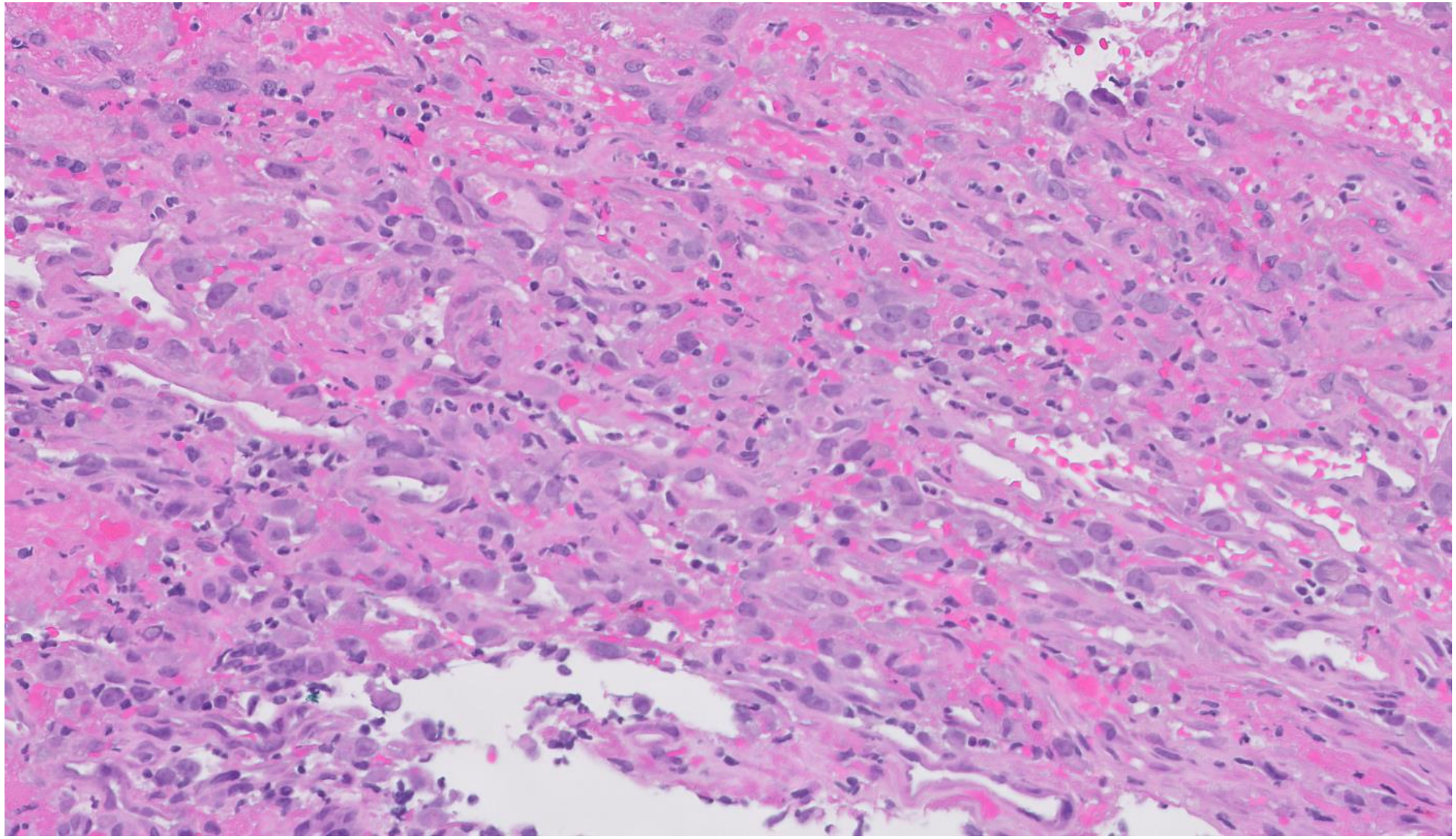
Christine Heisen, Xiaohua Qian; Stanford

68-year-old woman presenting with upper gastrointestinal bleeding. 3.6 cm polypoid mass from the greater curvature of the stomach and three lung nodules identified on imaging.

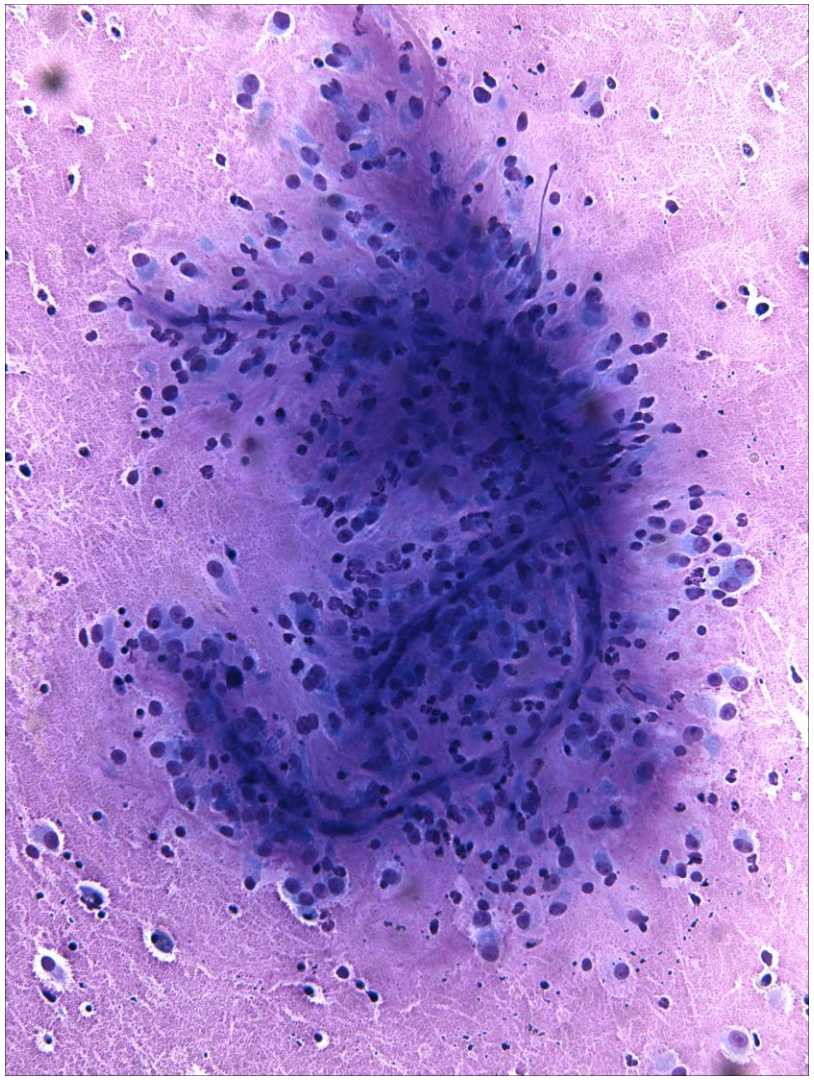
Gastric mass biopsy

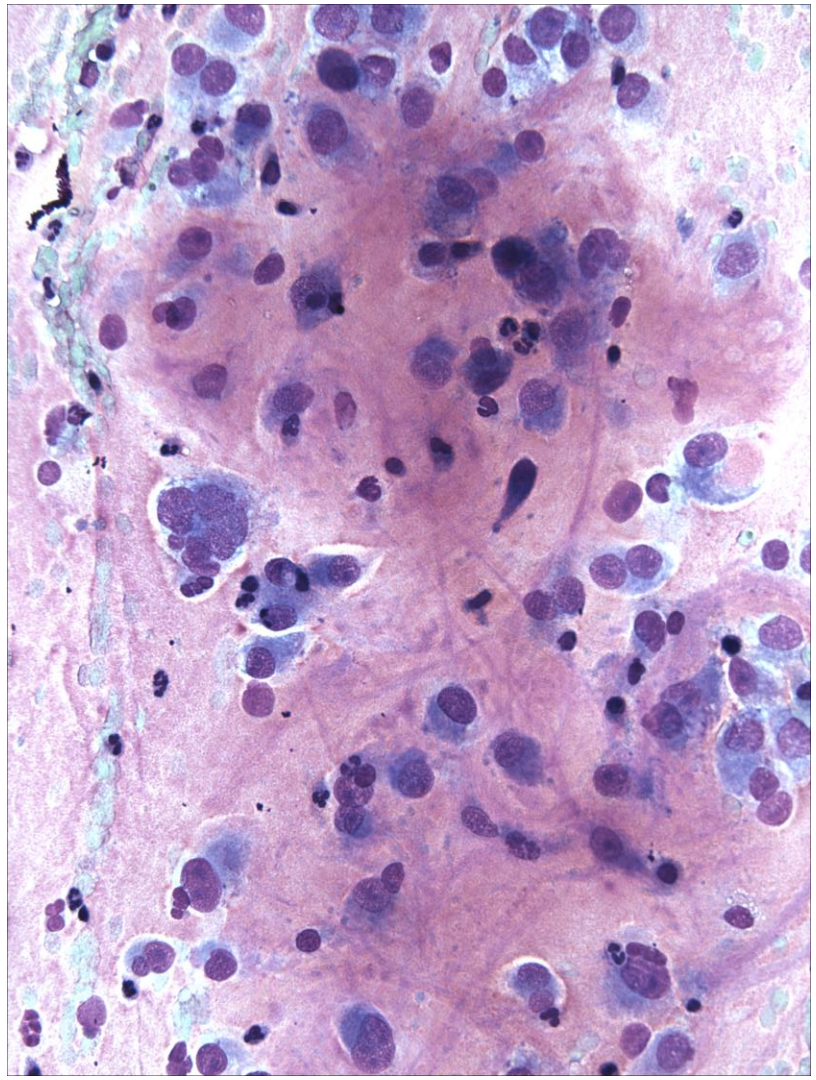


Gastric mass biopsy

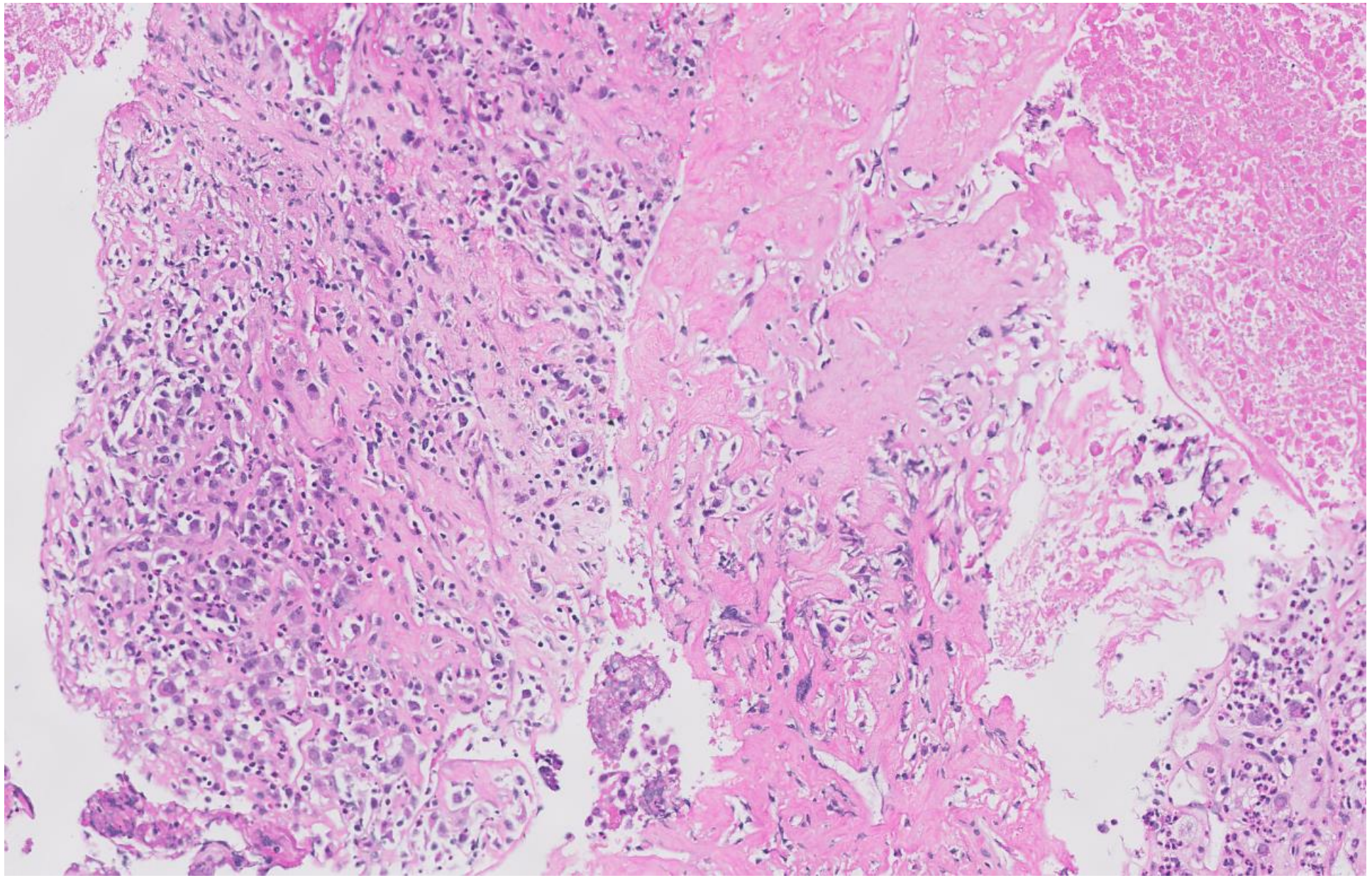


FNA/core lung

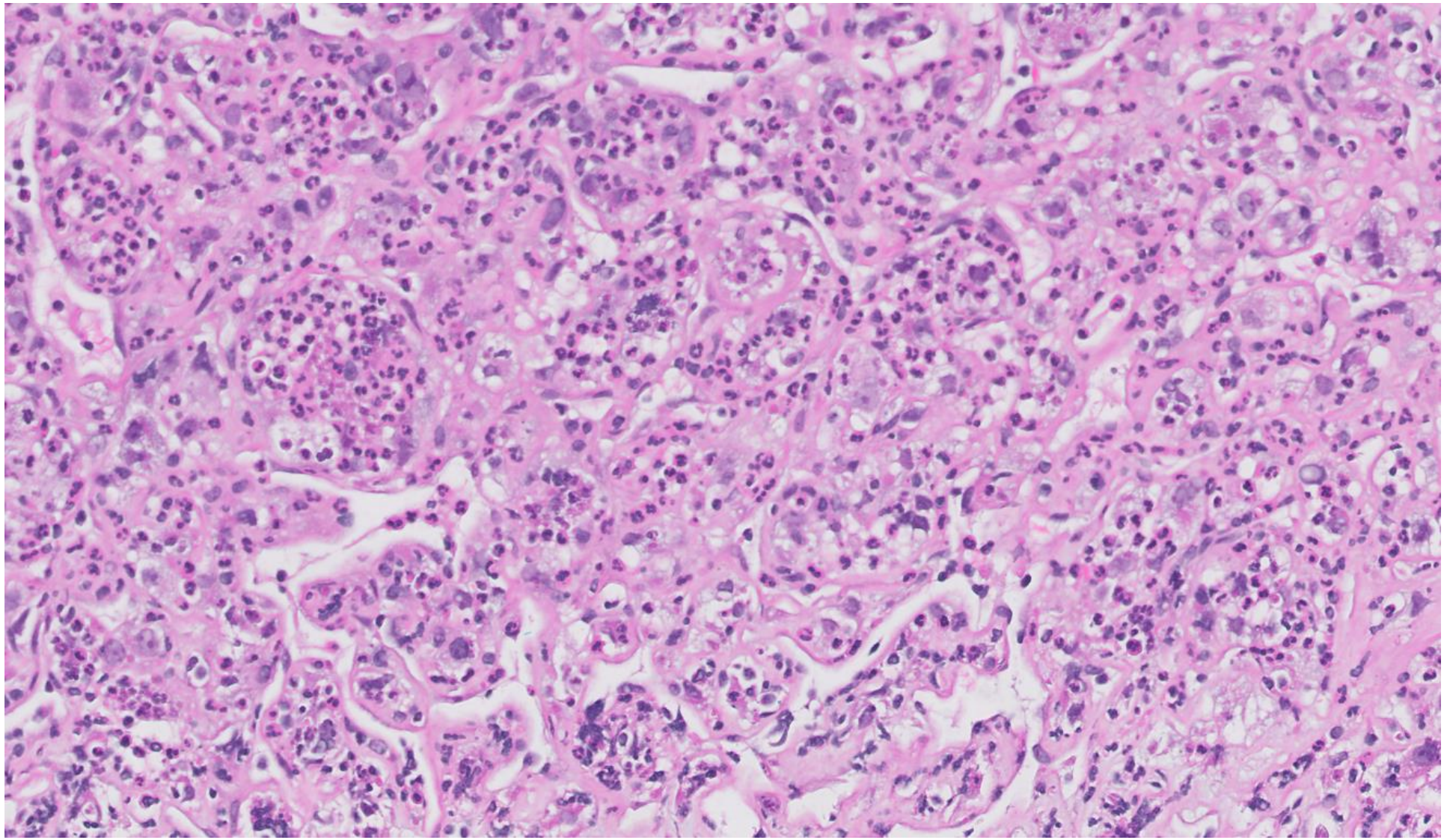




FNA/core lung

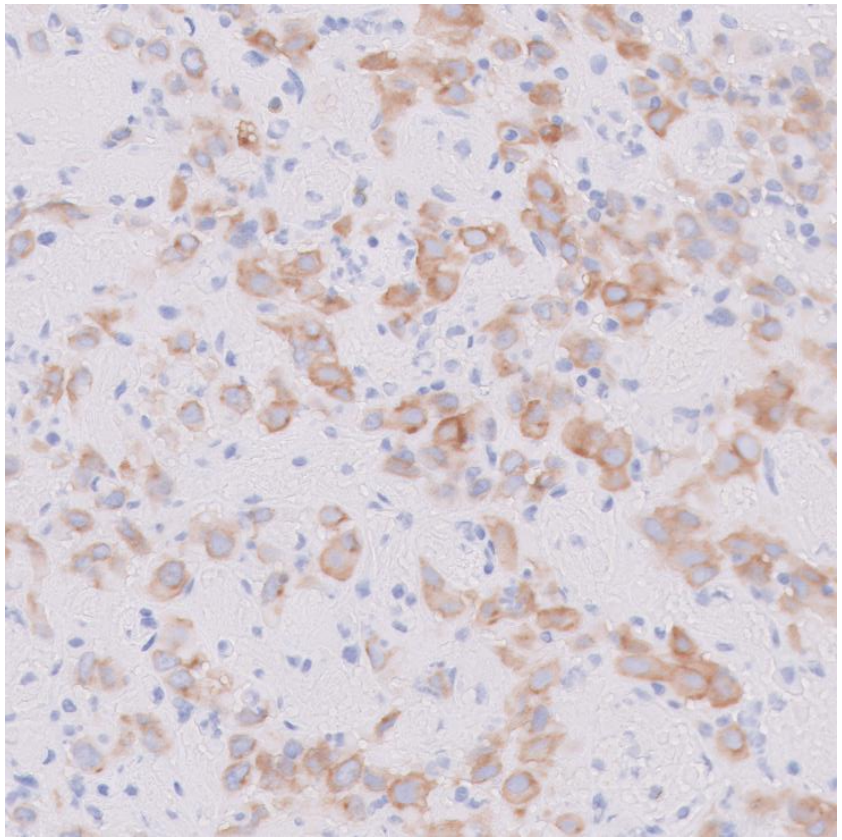


FNA/core lung

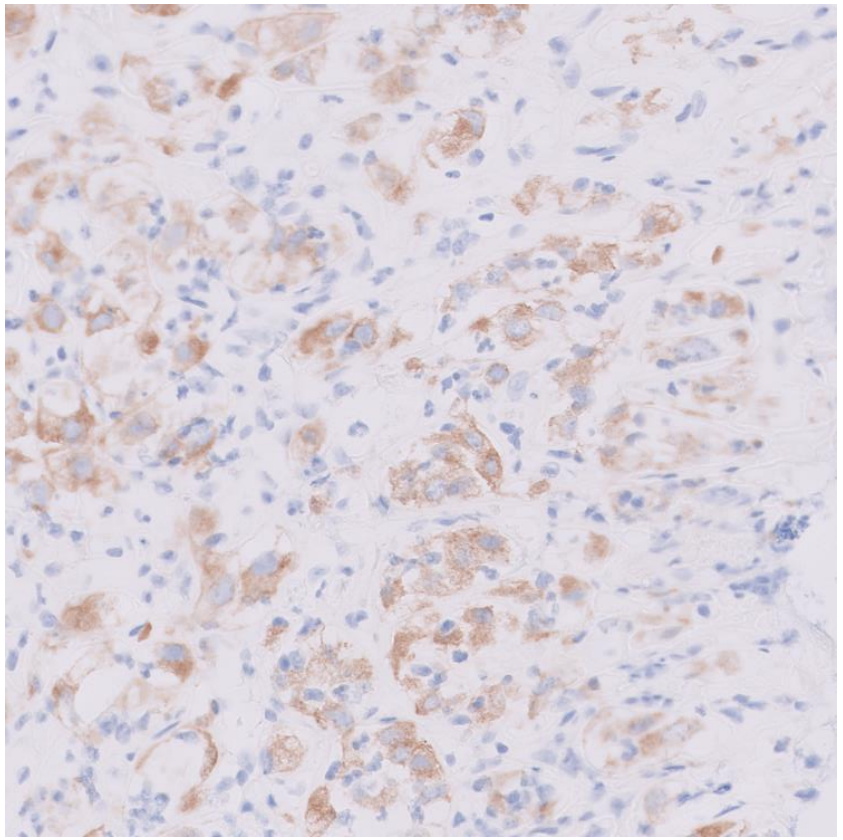


DIAGNOSIS?

ALK immunostain



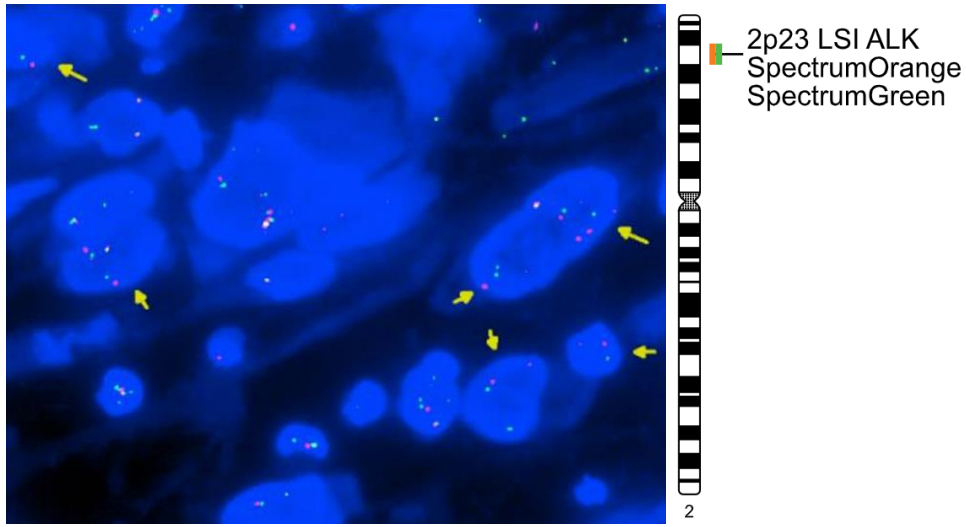
stomach



lung

Molecular Studies

- ALK rearrangement confirmed by FISH
- EML4:: ALK rearrangement by NGS



SUMMARY OF FINDINGS

EML4::ALK rearrangement

The following variants are not known to be clinically relevant at this time:

BRCA2 P59A (Unknown significance)

EGFR A1201T (Unknown significance)

Final Diagnosis

Lung and stomach biopsies:

ALK-positive epithelioid neoplasm (see comment)

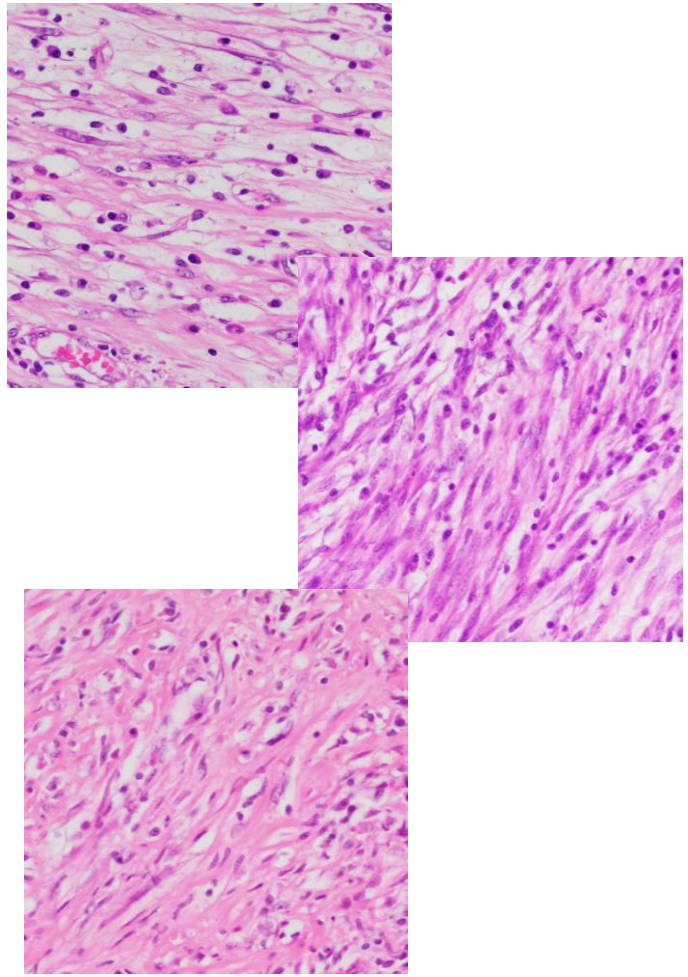
> "The findings in the gastric mass and lung biopsies raise consideration for an **epithelioid inflammatory myofibroblastic sarcoma (E-IMS)**."

Differential Diagnoses

- Gastrointestinal stromal tumor (epithelioid variant)
- Inflammatory leiomyosarcoma
- Poorly differentiated carcinoma (e.g. SMARCA4, SMARCB1-deficient)
- Anaplastic large cell lymphoma
- Inflammatory myofibroblastic tumor/epithelioid inflammatory myofibroblastic sarcoma

Inflammatory Myofibroblastic Tumor (IMT)

	Classic IMT
Demographics	Younger; ♀>♂
Anatomic site	Lung, mesentery, GU, GYN, other
Survival	Indolent
Cytomorphology	Plump spindle cells in background of lymphoplasmacytic infiltrate
Histologic Features	spindled fibroblastic-myofibroblastic cells and inflammatory cells in myxoid, hypercellular or hypocellular fibrous pattern; +/- dystrophic calcs and osseous metaplasia; necrosis uncommon
ALK immunostaining	Present in 50-60% of cases; usually cytoplasmic
ALK fusion partner	TPM3, TPM4, CLTC, CARS, …
IHC	variable SMA, MSA, calponin, desmin; 30% with focal keratin



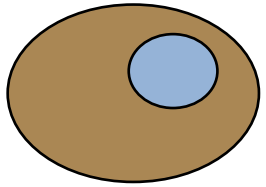
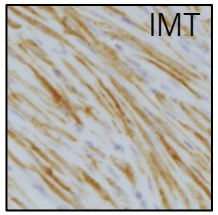
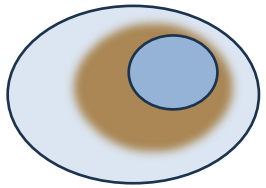
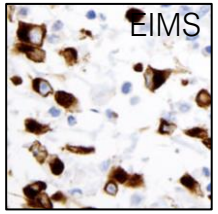
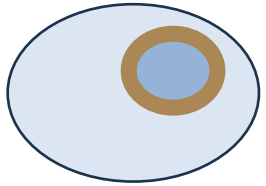
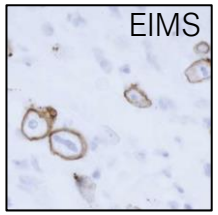
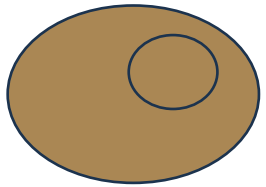
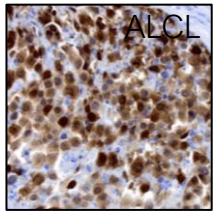
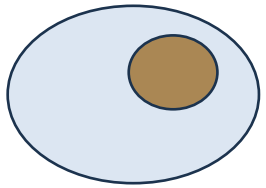
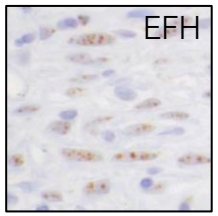
Images: WHO Blue Books
Modified from Lee et. al. 2015

Epithelioid Inflammatory Myofibroblastic Sarcoma (EIMS)

	Classic IMT	Epithelioid IMS
Demographics	Younger; ♀>♂	Young to middle age; ♂>♀
Anatomic site	Lung, mesentery, GU, GYN, other	Intraabdominal
Survival	Indolent	Aggressive
Cytomorphology	Plump spindle cells in background of lymphoplasmacytic infiltrate	Large epithelioid cells in background of myxoid stroma, neutrophil-rich, vascular network
Histologic Features	spindled fibroblastic-myofibroblastic cells and inflammatory cells in myxoid, hypercellular or hypocellular fibrous pattern; +/- dystrophic calcs and osseous metaplasia; necrosis uncommon	plump epithelioid or histiocytoid tumor cells with admixed with neutrophils in an abundant myxoid stroma
ALK immunostaining	Present in 50-60% of cases; usually cytoplasmic	Nearly 100%; often nuclear membranous
ALK fusion partner	TPM3, TPM4, CLTC, CARS, …	RANBP2, RRBP1, EML4
IHC	variable SMA, MSA, calponin, desmin; 30% with focal keratin	

Modified from Lee et. al. 2015

ALK Staining Pattern and Fusion Partners

diffuse cytoplasmic			TPM3, TPM4, NPM1, **EML4**, ATIC, TFG, LMNA, FN1, PPFIBP2, DCTN1, others; CLTC (granular)
perinuclear accentuated cytoplasmic			**RRBP1, EML4**[1]
nuclear membranous			**RANBP2**
nuclear and cytoplasmic			NPM1
nuclear			SP100 (dot-like)[2]

Images: WHO Blue Books, Marino-Enriquez et al 2011, Pan et al 2016, Lee et al 2016; Ref 1. Jiang et al 2017; Ref 2. Agaimy 2025

ALK Inhibitors

- Tissue agnostic target -> Confers eligibility for ALK inhibitor treatment
  - Classically associated with ALK rearrangements: ALCL, NSCLC, DLBCL, other carcinomas, alveolar rhabdomyosarcoma, …

- EIMS/IMT: Crizotinib used as targeted treatment +/- radiation, chemotherapy[1, 2]
  - Long-term effectiveness of ALK inhibitors can be limited by resistance mutations

(1) Butrynski et al 2010; (2) Gros et al 2022

Patient Update

- Oral crizotinib started
- Excellent treatment response
  - resolution of the gastric mass
  - pleural masses are stable in size, although without enhancement suggesting that this just may be scar tissue
- Repeat CT CAP every three months
- Stable disease 2 years since diagnosis

Sources

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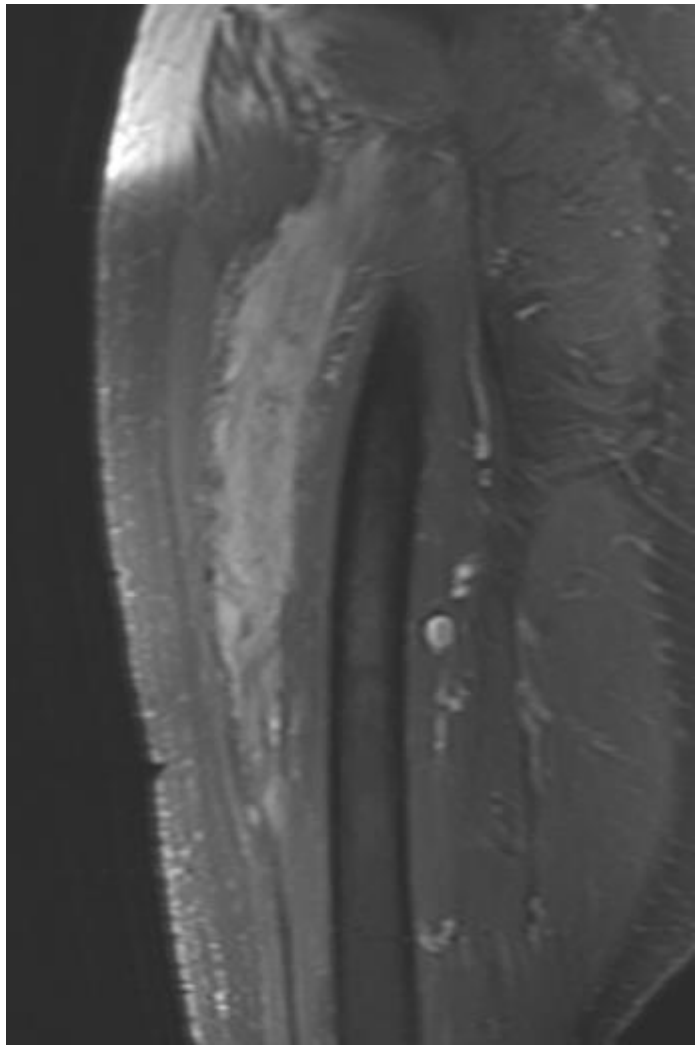
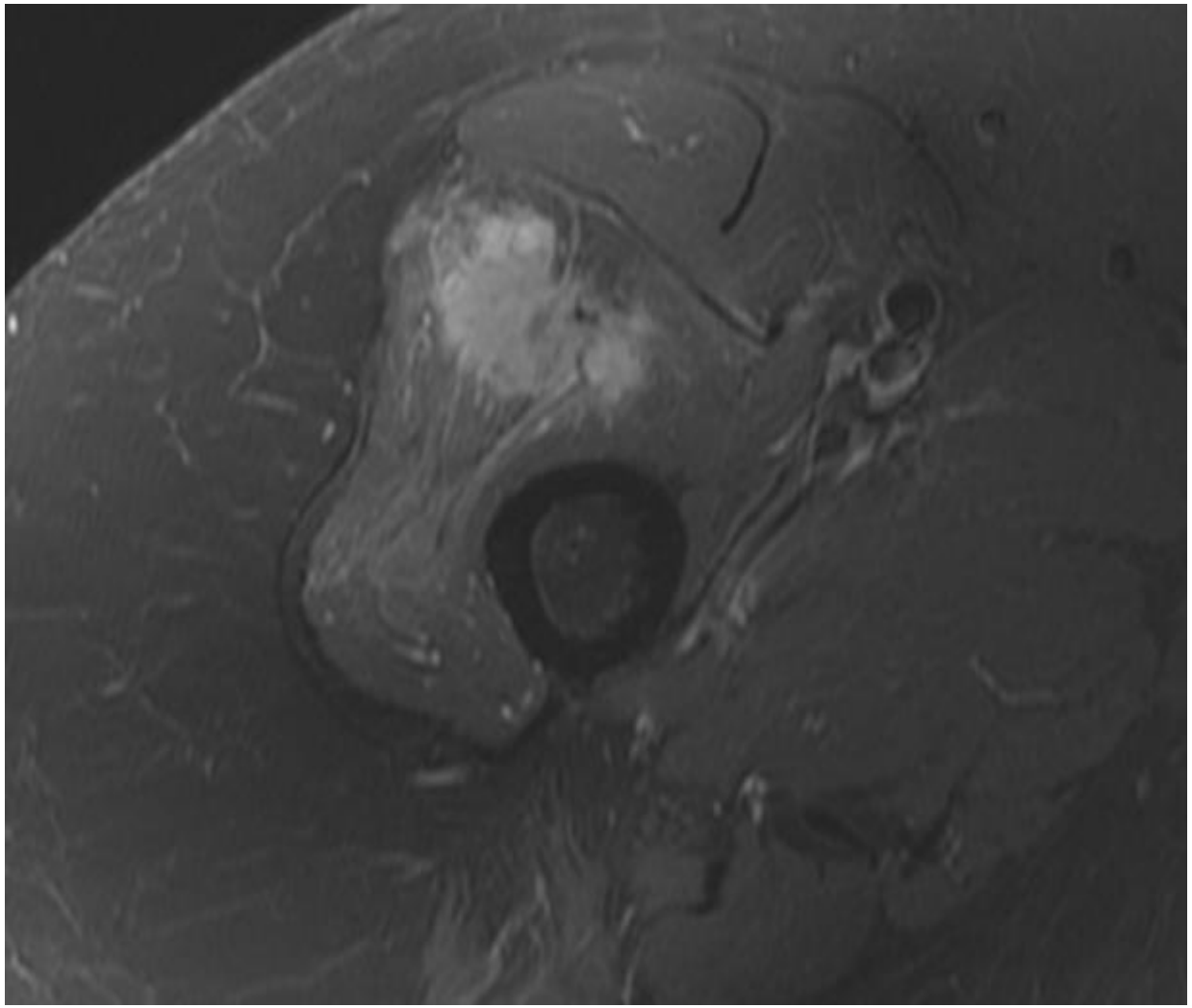
25-1203

David Twa, Greg Charville, Stanford

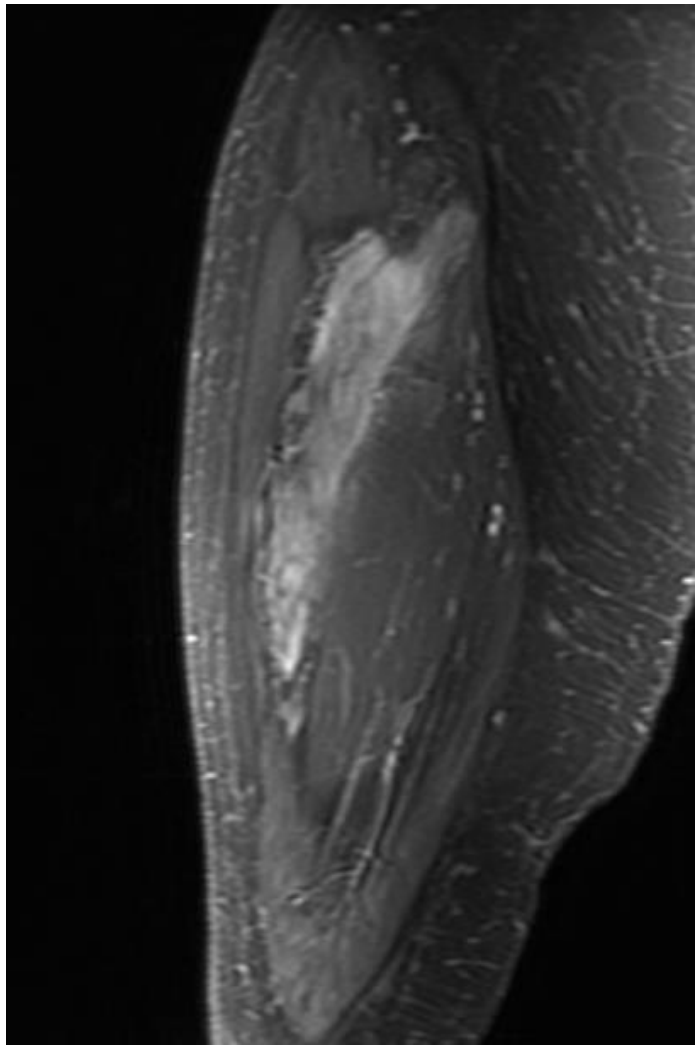
65F with hereditary hemochromatosis and right hip pain

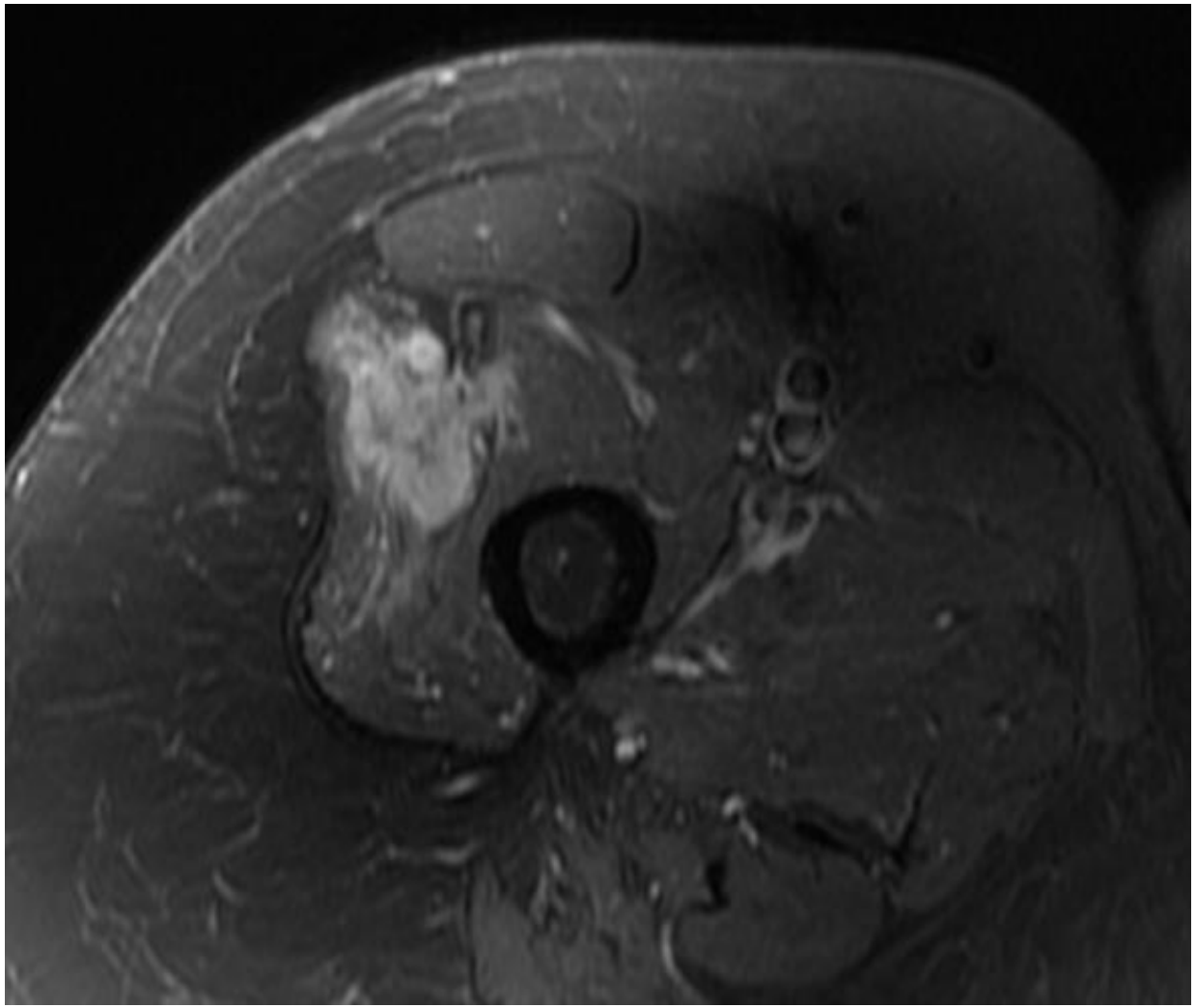
2016 MRI, T1 fat sat with contrast



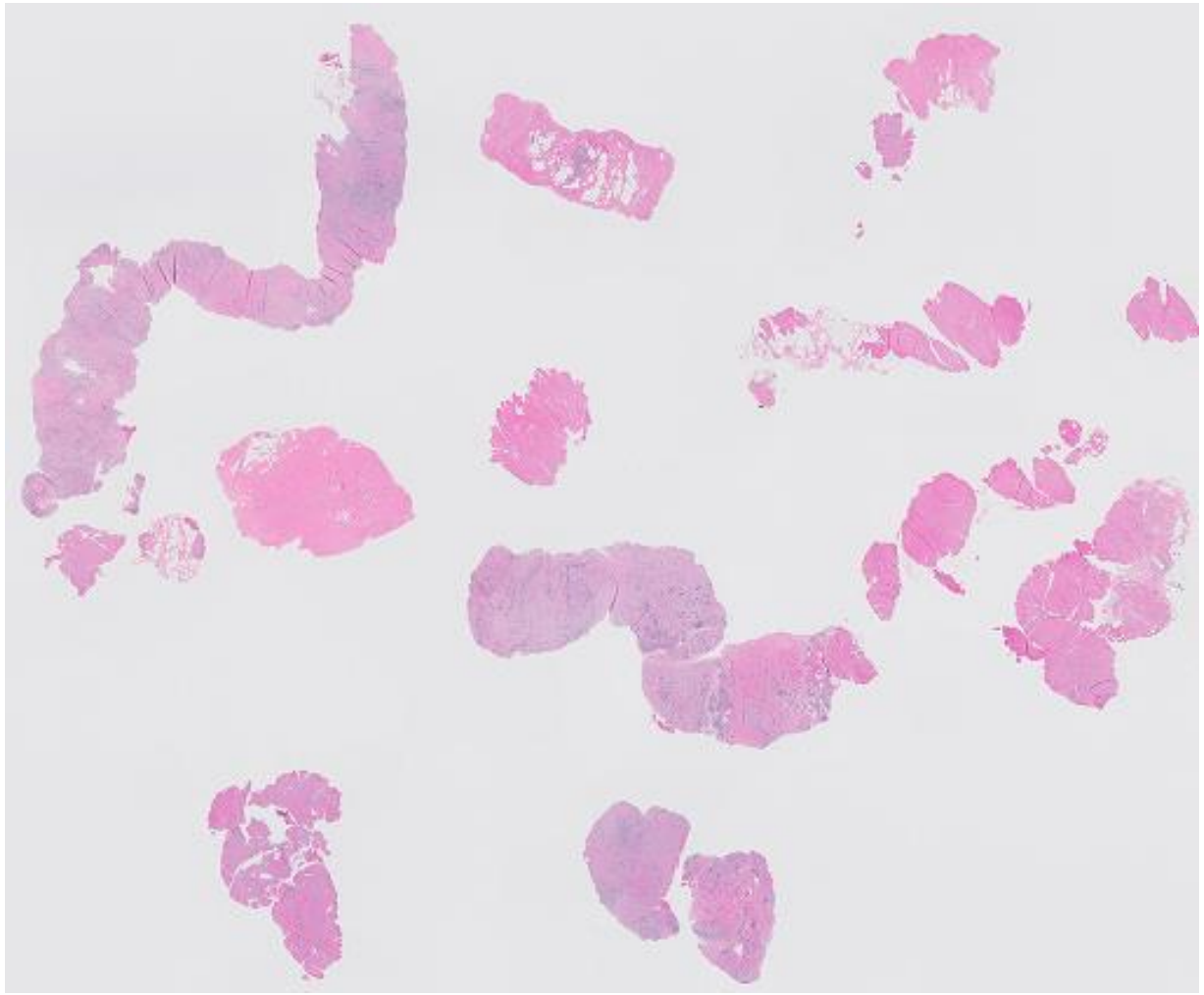


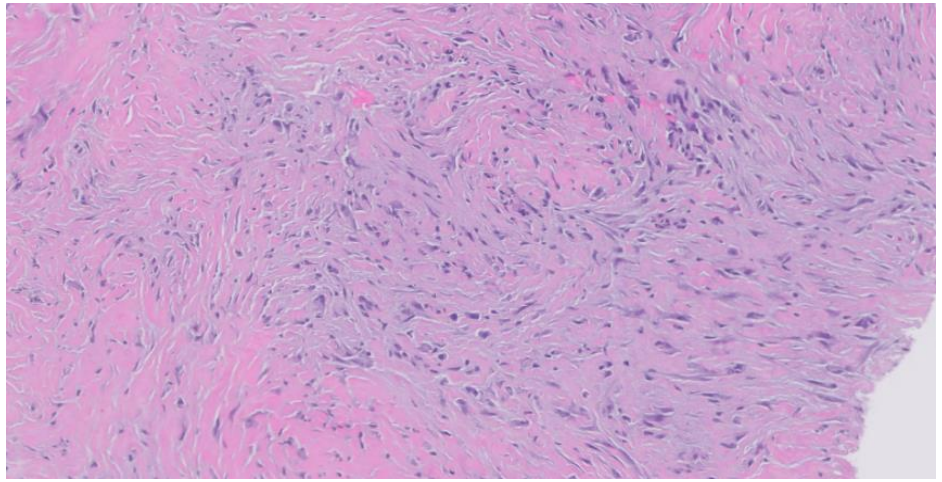
2018 MRI, T1 fat sat with contrast

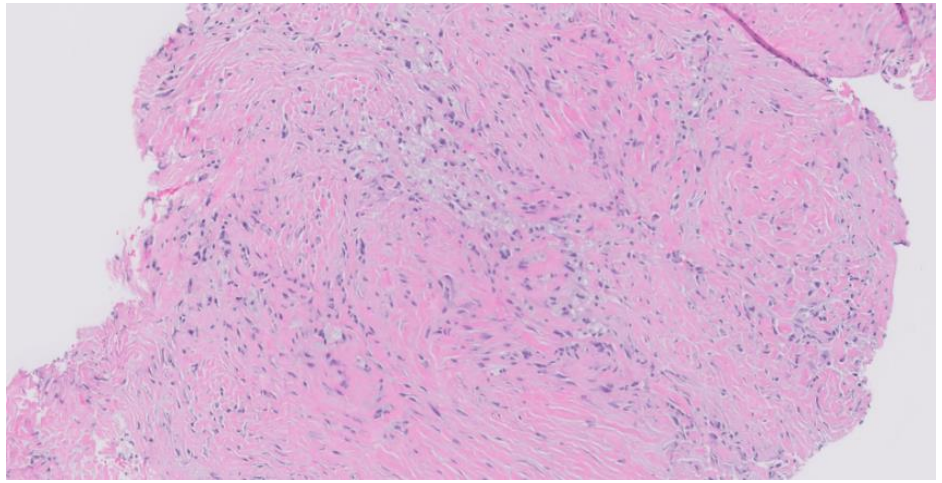




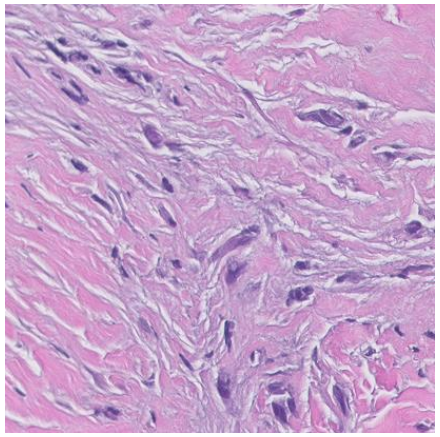
core biopsy

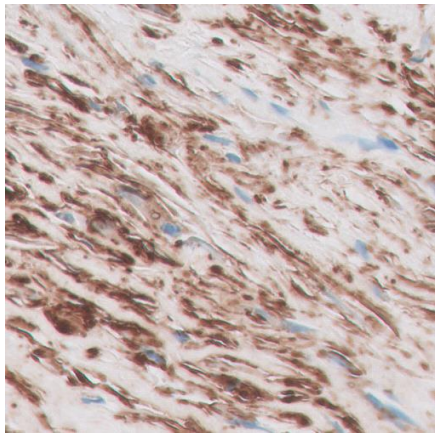




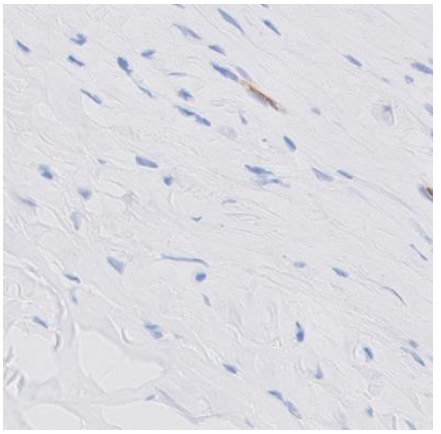


core biopsy

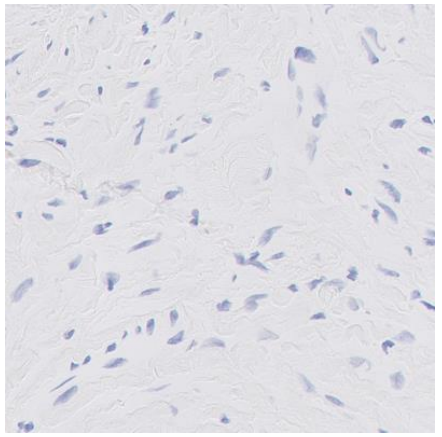




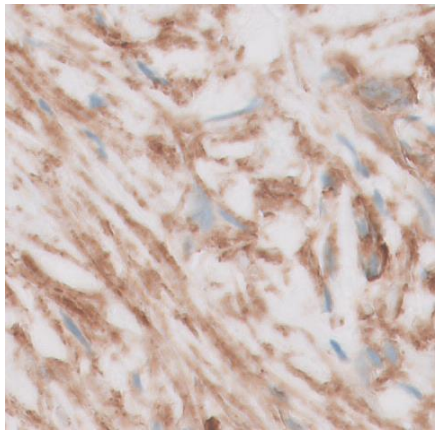
SMA



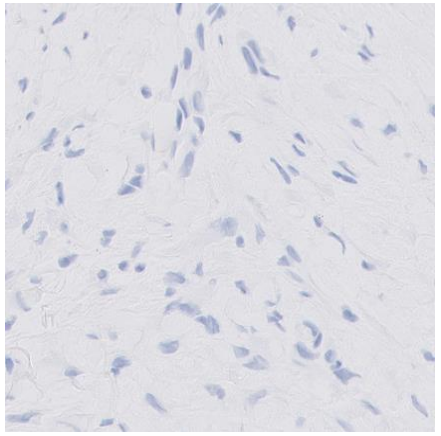
Desmin



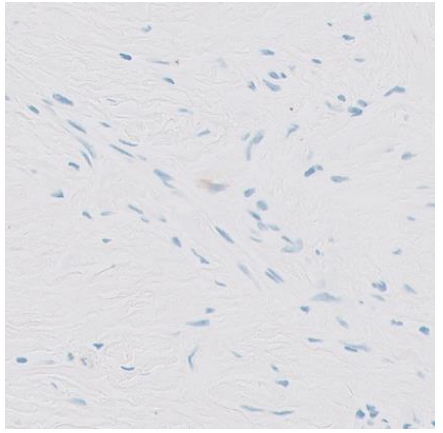
CD34



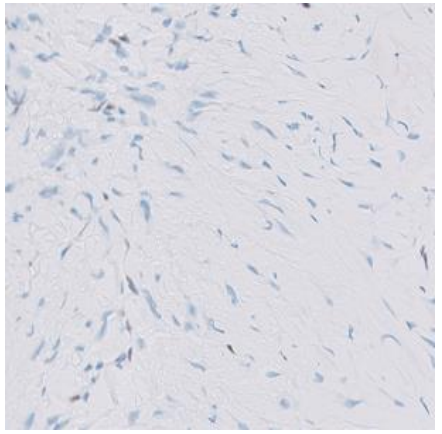
B-Cat



MUC4



S100



ERG

DIAGNOSIS?

Conflicts of interest disclosure – Dave Twa

- Relationships with commercial interests:
  - Clinical practice committee member: Association for Molecular Pathology
  - Grant and information sharing: Bristol Myers Squibb
  - Regular shares: Apple, Bausch Health, Johnson & Johnson, Merck, Microsoft, Procter & Gamble, Telus, Google
- **No applicability** here

Self test

Myofibroblastic tumors:

A. Generally express SMA, PAX11, and CD117, with rare desmin positivity
B. Molecular profiling has limited prognostic and theranostic utility
C. Are not associated with constitutional diseases
D. Are the second most diverse category of soft tissue tumors, per the WHO
E. Cannot be malignant in *absence* of an elevated mitotic index
F. None of the above
G. Two of the above

Self test

Myofibroblastic tumors:

A. Generally express SMA, PAX11, and CD117, with rare desmin positivity
   - PAX11 does not exist, CD117 is common to GISTs, PMID: 31100836

B. Molecular profiling has limited prognostic and theranostic utility
   - Genomic underpinnings portend unfavorable prognosis, PMID:31538390

C. Are not associated with constitutional diseases
   - Gardner syndrome, PMID: 11342777

D. Are the second most diverse category of soft tissue tumors, per the WHO
   - They are the first, second are tumors of uncertain diff, WHO 5th ed

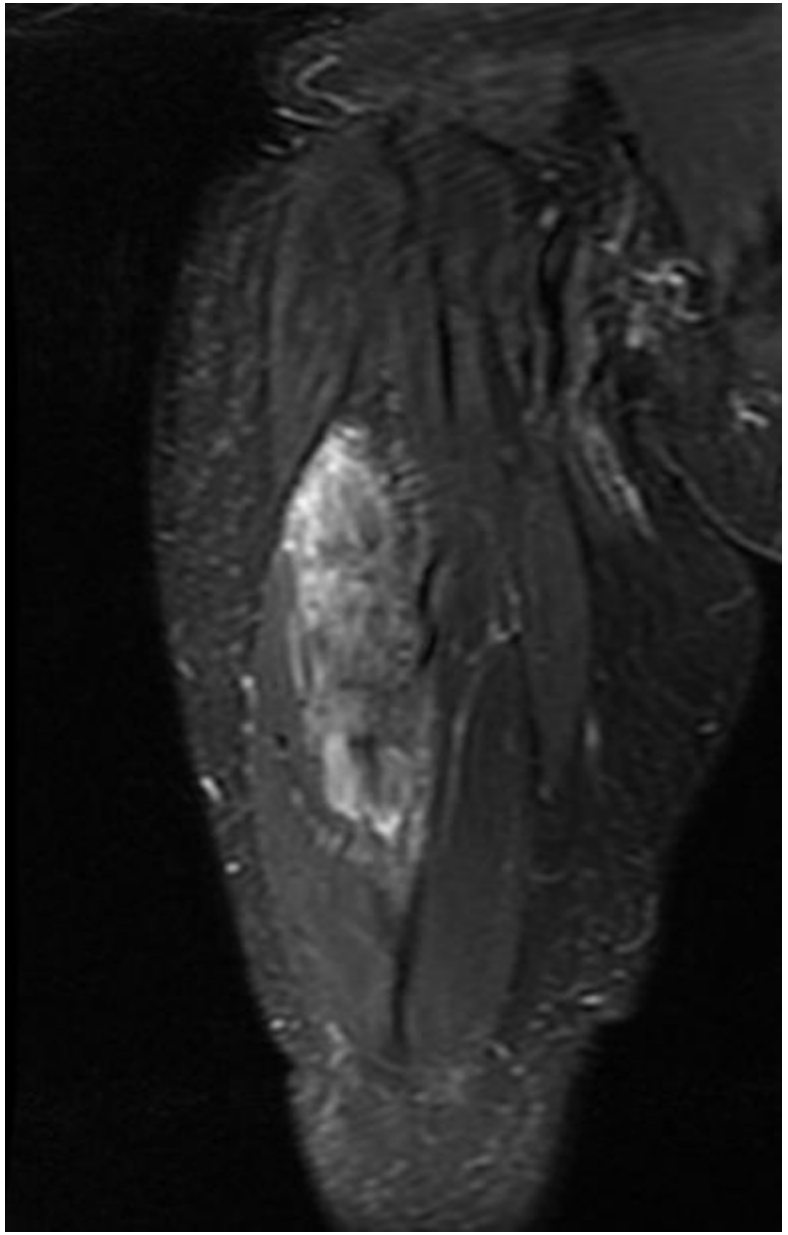
E. Cannot be malignant in *absence* of an elevated mitotic index
   - Many malignant processes can lack mitotic activity, WHO 5th ed

F. None of the above

G. Two of the above

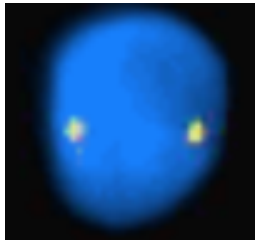
Clinical presentation

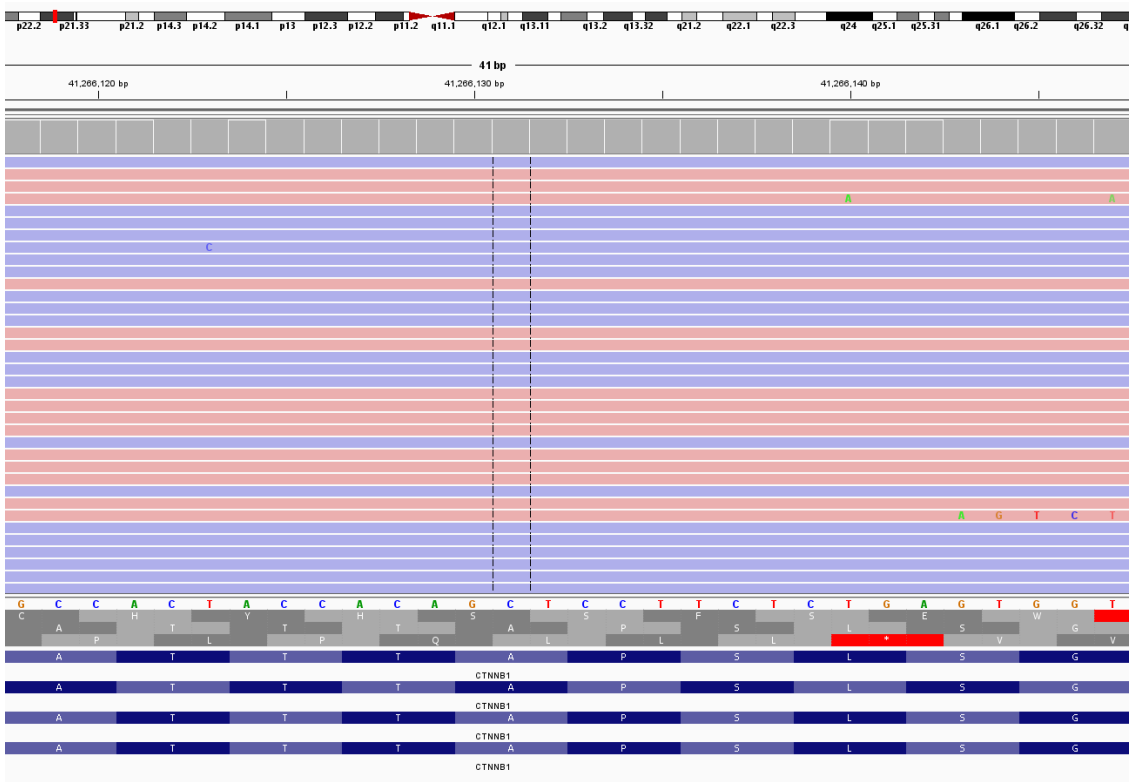
- 65F
- Hemochromatosis
- Right sided hip pain dating to 2013
- Large enhancing lesion (16 x 5 x 3 cm)



Initial core biopsy 2014 – outside institution (no slides)

- Bland spindle cell proliferation with a myxoid background
- **Positive**: MSA
- **Negative**: desmin, S100, CD34, caldesmon, MUC4, ALK1, keratin
- **Equivocal**: B-cat
- FISH for *FUS* break apart: **negative**
- Targeted *CTNNB1* exon 3 sequencing: **negative**





Features to exclude differential diagnoses

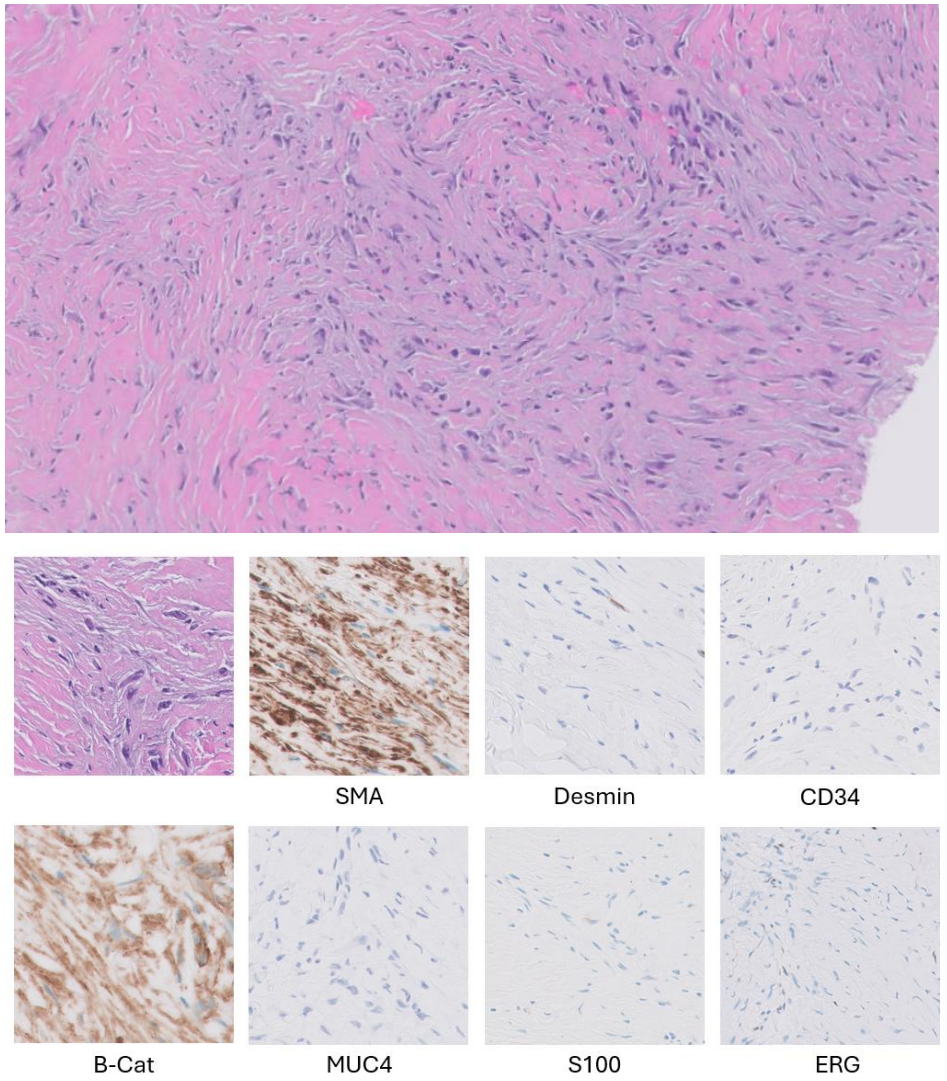
- **Clinical history**:
  - Nodular fasciitis (large, deep, demographics)
  - Trauma (histomorphology)
- **Histomorphology**:
  - Inflammatory myofibroblastic tumor (inflammatory constituents, ALK)
  - Low grade myxofibrosarcoma (extracellular matrix, cytology)
- **IHC**:
  - Solitary fibrous tumor (CD34)
  - Spindle cell carcinoma (keratin)
  - Low grade leiomyosarcoma (desmin, caldesmon)
  - Spindle cell/sclerosing rhabdomyosarcoma (desmin, location)
  - Melanoma (S100, clinical history, cytology)
  - Peripheral nerve sheath tumor (S100, imaging features)
- **FISH for structural rearrangements**:
  - Low grade fibromyxoid sarcoma (*FUS* break apart, MUC4 IHC)
- **Targeted sequencing for SNV/INDELs**:
  - Fibromatosis (*CTNNB1* ex3 status, patient demographics for *APC*)

Disease progression

- Further lesional growth with intralesional necrosis
- Frank erosion into femoral neck and trochanter
- Satellite nodules within adjacent muscle groups
- Multiple biopsies redemonstrating same pathology
- Patient remains untreated but in considerable pain
- **Clinical course pointing away from a benign process**

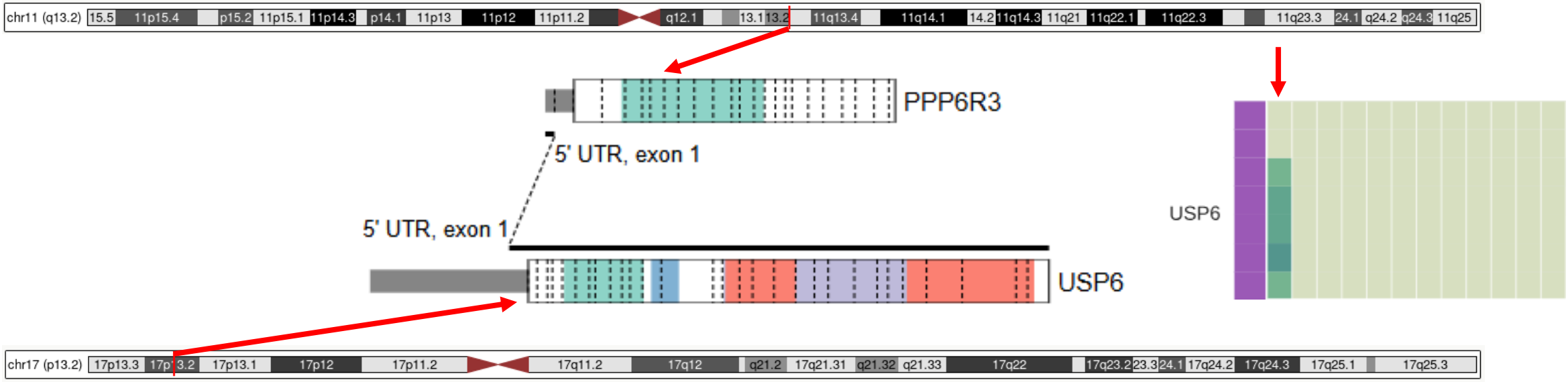
Rebiopsy 2022 –

- Bland myofibroblastic proliferation with mild cytologic atypia
- Minimal mitoses and necrosis
- **Positive**: actin
- **Focal positive**: desmin
- **Negative**: MUC4, S100, CD34, B-cat, ERG
- Fusion-STAMP ordered (UC500 demonstrated signature compatible with USP6 rearrangement; exon imbalance?)



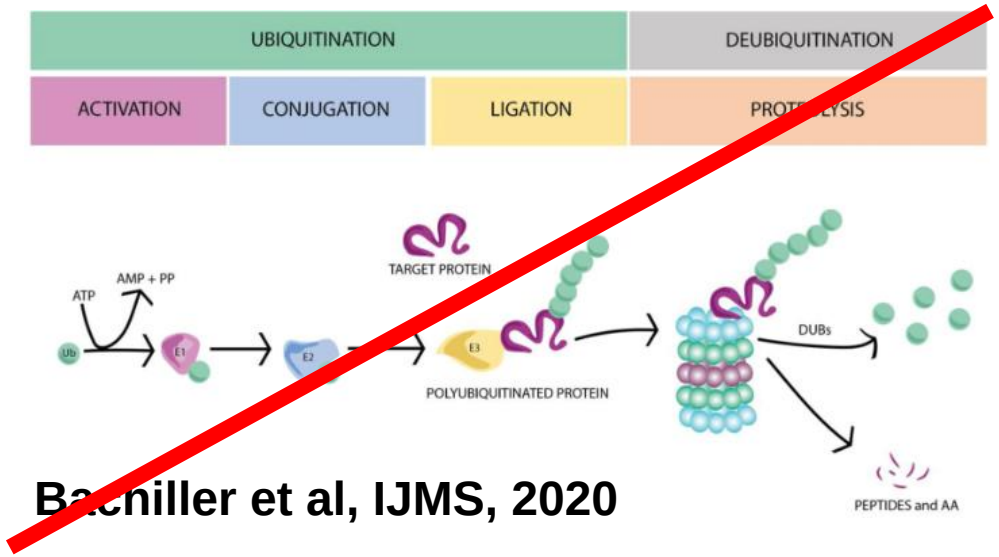
Fusion-STAMP findings

- Complex rearrangement involving chromosomes 11 and 17
- Promoter swap of *PPP6R3*; start codon of *USP6* preserved with all domains
- Highly expressed *USP6* compared to other cases on same run

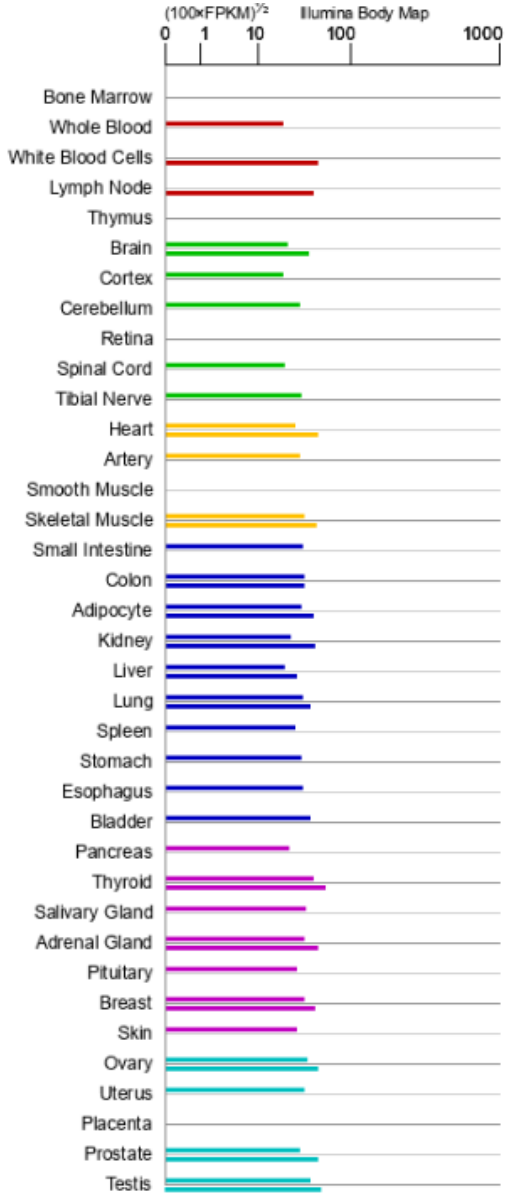


PPP6R3::USP6 fusion

- *PPP6R3* widely expressed across most tissue types, including soft tissues, analogous to *MYH9*
- USP6 protein involved in de-ubiquitination and increased Wnt signaling (PMID: 27162353)



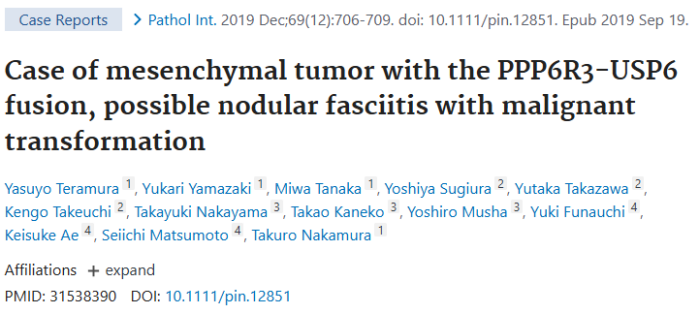
Bachiller et al, IJMS, 2020



Genecards

PPP6R3::USP6 fusion

- *USP6* rearrangements are present in ~90% nodular fasciitis cases (PMID: 28752842)
- *MYH9* is the most frequent partner, but many others have been described: *CDH11*, *COL1A1*, *COL1A2*, *COL3A1*, *CTNNB1*, *EIF5A*, *OMD*, *TRAP150*, *SERPINH1*, *SPARC*, and *ZNF9* (PMID: 36828621)
- The partner does matter; *PPP6R3* rearrangements have an aggressive clinical course, though this is a **rare** rearrangement in the literature (n=3)



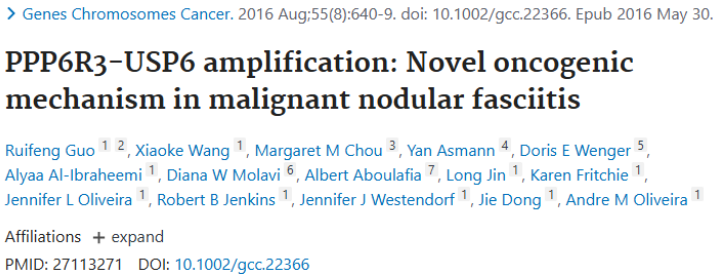
Case Reports › Pathol Int. 2019 Dec;69(12):706-709. doi: 10.1111/pin.12851. Epub 2019 Sep 19.

Case of mesenchymal tumor with the PPP6R3-USP6 fusion, possible nodular fasciitis with malignant transformation

Yasuyo Teramura [1], Yukari Yamazaki [1], Miwa Tanaka [1], Yoshiya Sugiura [2], Yutaka Takazawa [2], Kengo Takeuchi [2], Takayuki Nakayama [3], Takao Kaneko [3], Yoshiro Musha [3], Yuki Funauchi [4], Keisuke Ae [4], Seiichi Matsumoto [4], Takuro Nakamura [1]

Affiliations + expand

PMID: 31538390 DOI: 10.1111/pin.12851



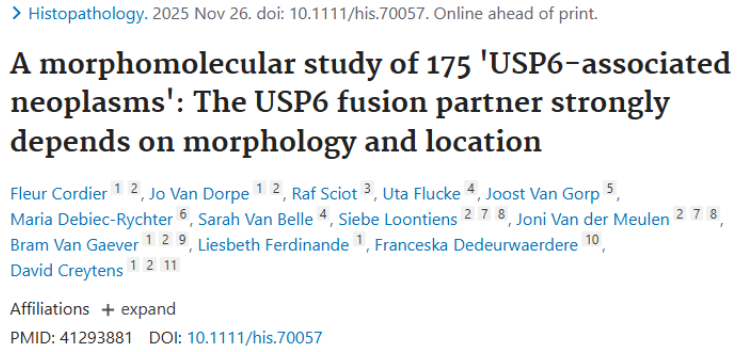
› Genes Chromosomes Cancer. 2016 Aug;55(8):640-9. doi: 10.1002/gcc.22366. Epub 2016 May 30.

PPP6R3-USP6 amplification: Novel oncogenic mechanism in malignant nodular fasciitis

Ruifeng Guo [1 2], Xiaoke Wang [1], Margaret M Chou [3], Yan Asmann [4], Doris E Wenger [5], Alyaa Al-Ibraheemi [1], Diana W Molavi [6], Albert Aboulafia [7], Long Jin [1], Karen Fritchie [1], Jennifer L Oliveira [1], Robert B Jenkins [1], Jennifer J Westendorf [1], Jie Dong [1], Andre M Oliveira [1]

Affiliations + expand

PMID: 27113271 DOI: 10.1002/gcc.22366



› Histopathology. 2025 Nov 26. doi: 10.1111/his.70057. Online ahead of print.

A morphomolecular study of 175 'USP6-associated neoplasms': The USP6 fusion partner strongly depends on morphology and location

Fleur Cordier [1 2], Jo Van Dorpe [1 2], Raf Sciot [3], Uta Flucke [4], Joost Van Gorp [5], Maria Debiec-Rychter [6], Sarah Van Belle [4], Siebe Loontiens [2 7 8], Joni Van der Meulen [2 7 8], Bram Van Gaever [1 2 9], Liesbeth Ferdinande [1], Franceska Dedeurwaerdere [10], David Creytens [1 2 11]

Affiliations + expand

PMID: 41293881 DOI: 10.1111/his.70057

Take home points

- Rare forms of malignant nodular fasciitis exist
- Molecular testing can be useful to confirm diagnosis and prognosticate clinical course
- Review of clinical history and imaging help solidify the aggressive nature of the disease process

Questions

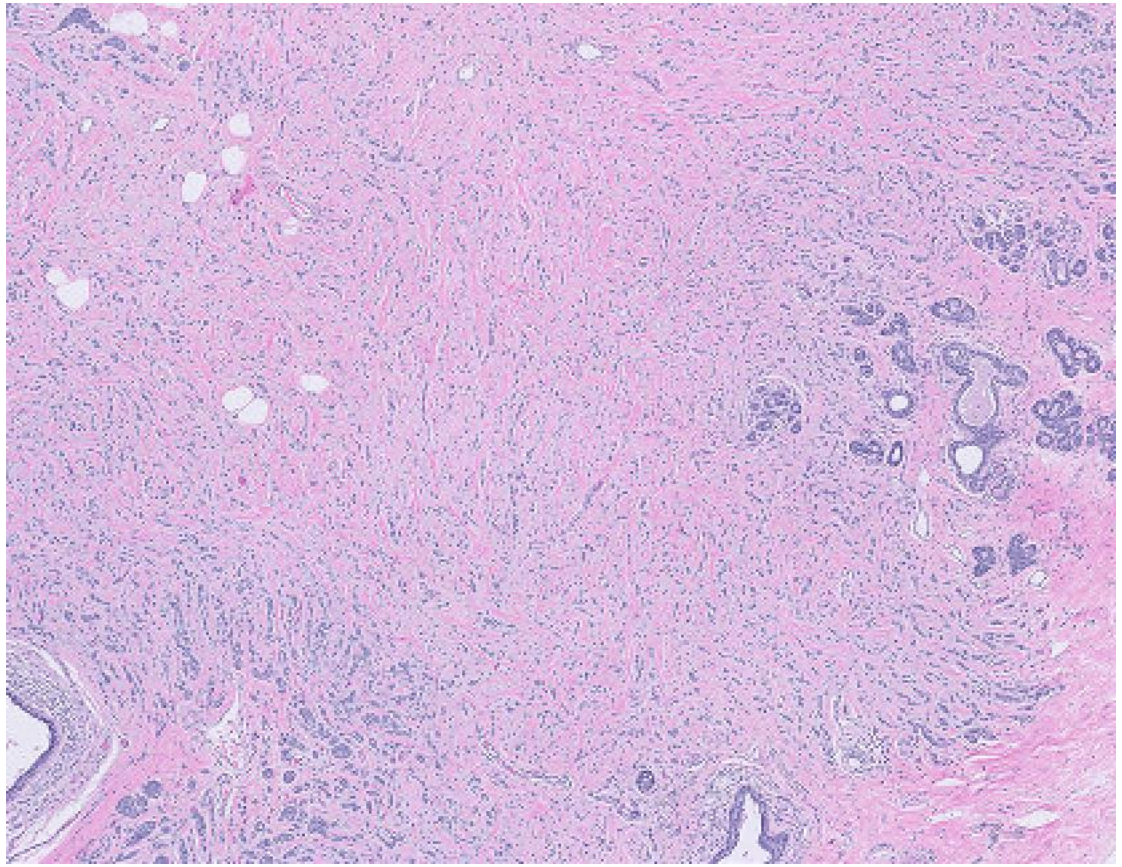
25-1204

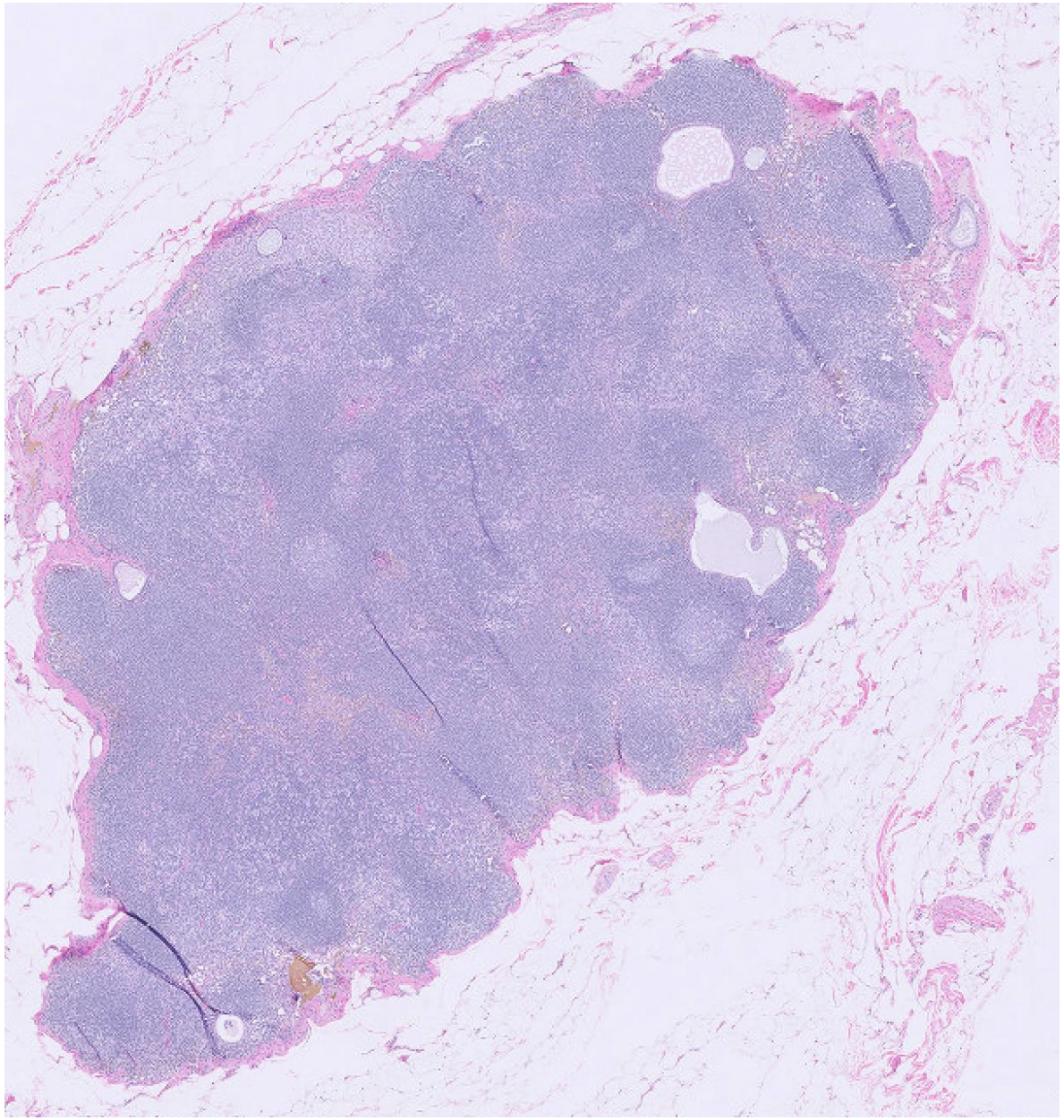
Hamideh Doozandeh, Yunn-Yi Chen; UCSF

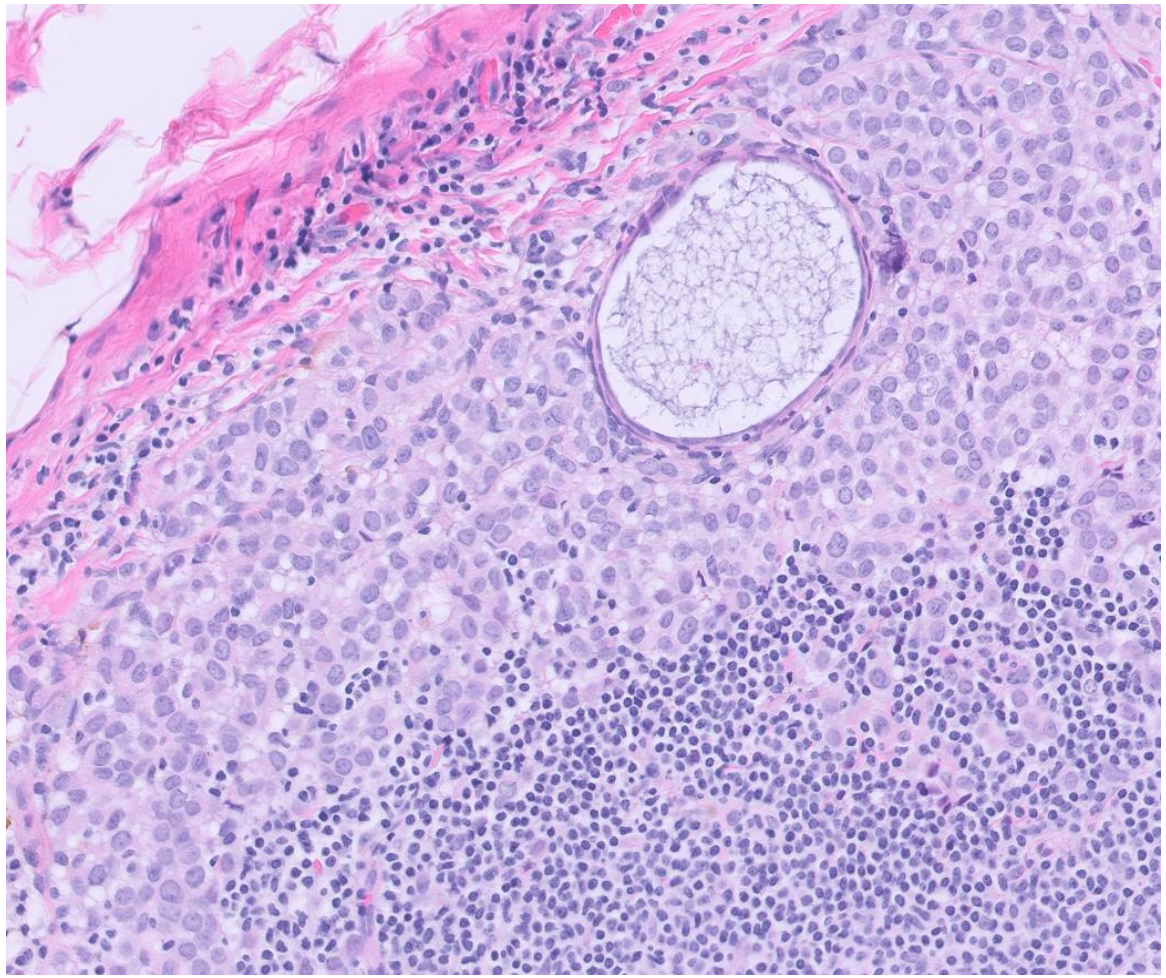
A) 49-year-old woman with screen detected left breast invasive lobular carcinoma, grade 1, who underwent left mastectomy and axillary sentinel lymph node biopsy.

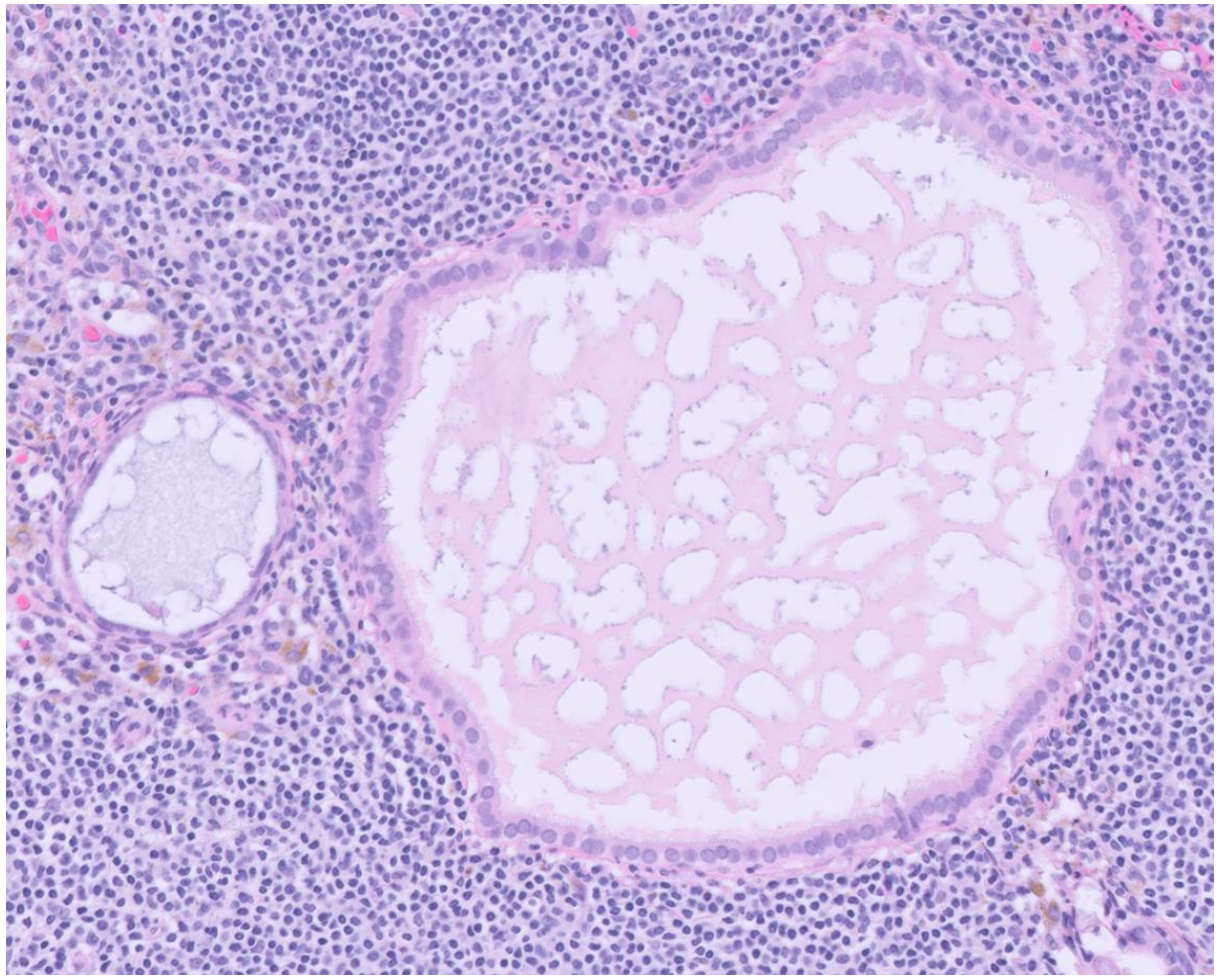
Left breast, mastectomy: Multifocal invasive lobular carcinoma, 8.9 cm

Left axillary sentinel lymph node?





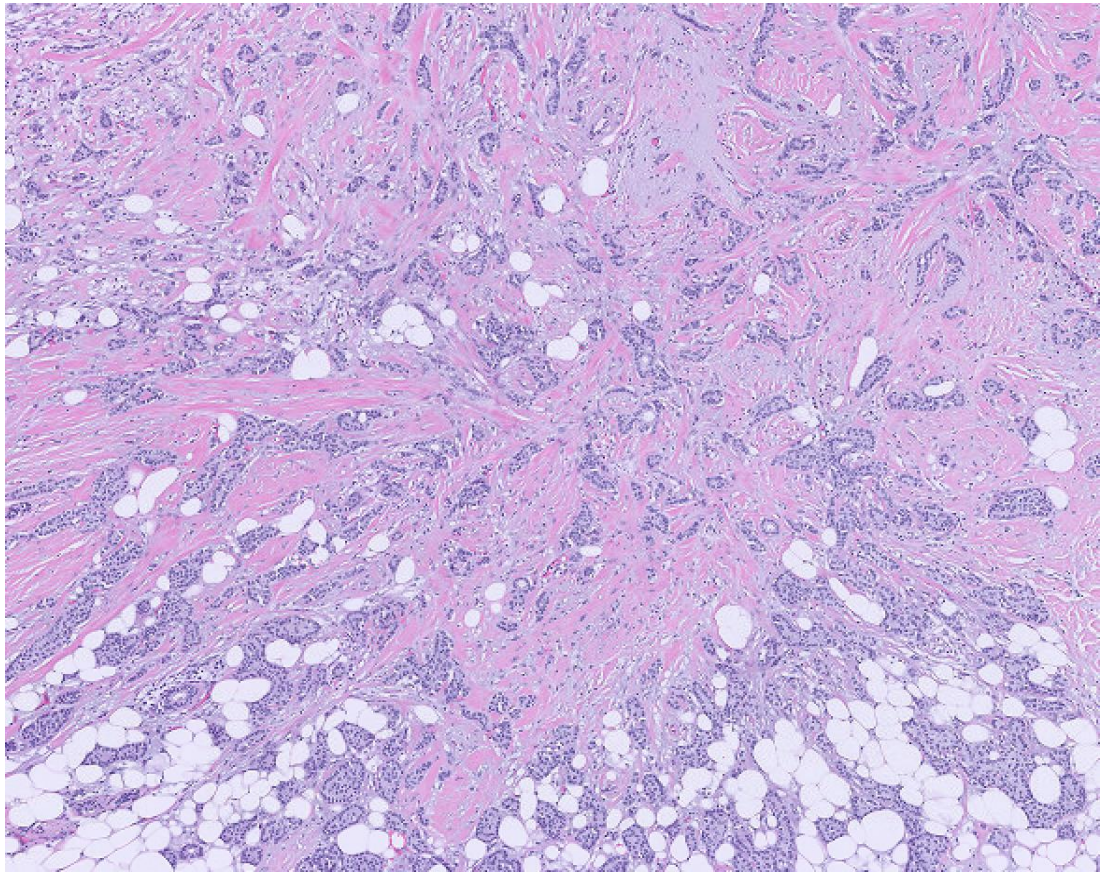


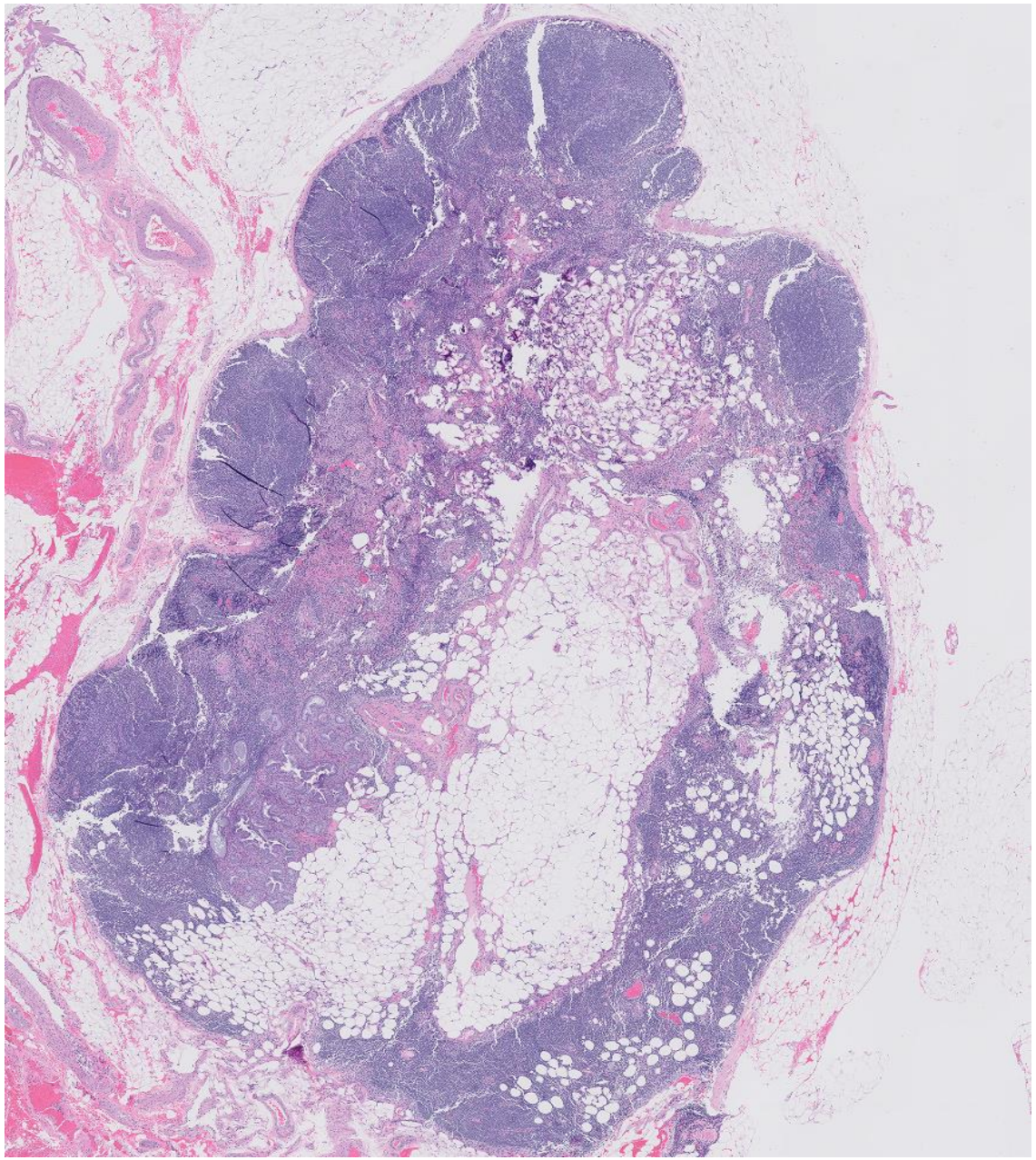


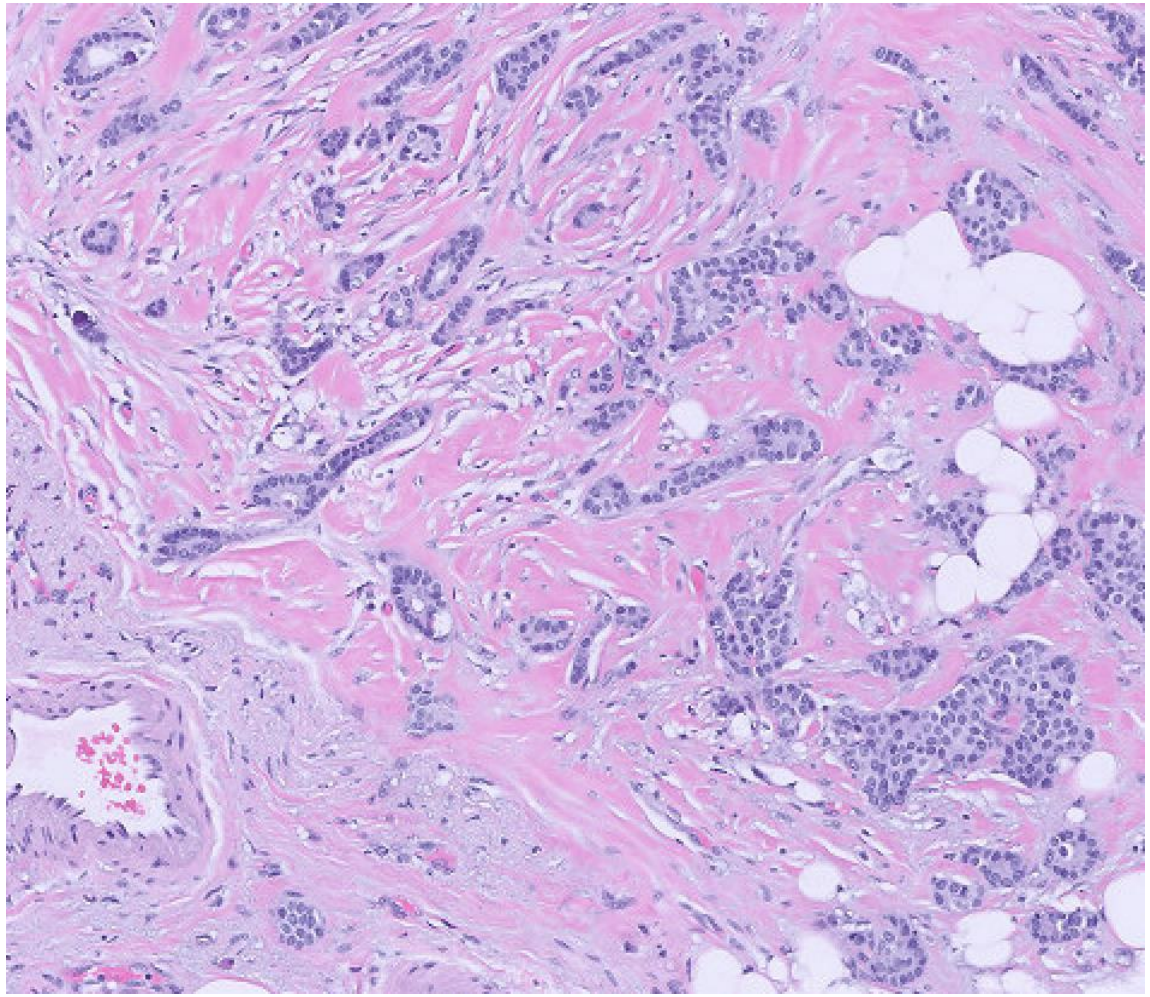
B)76-year-old woman with invasive ductal carcinoma of right breast, who underwent right partial mastectomy and sentinel lymph node biopsy.

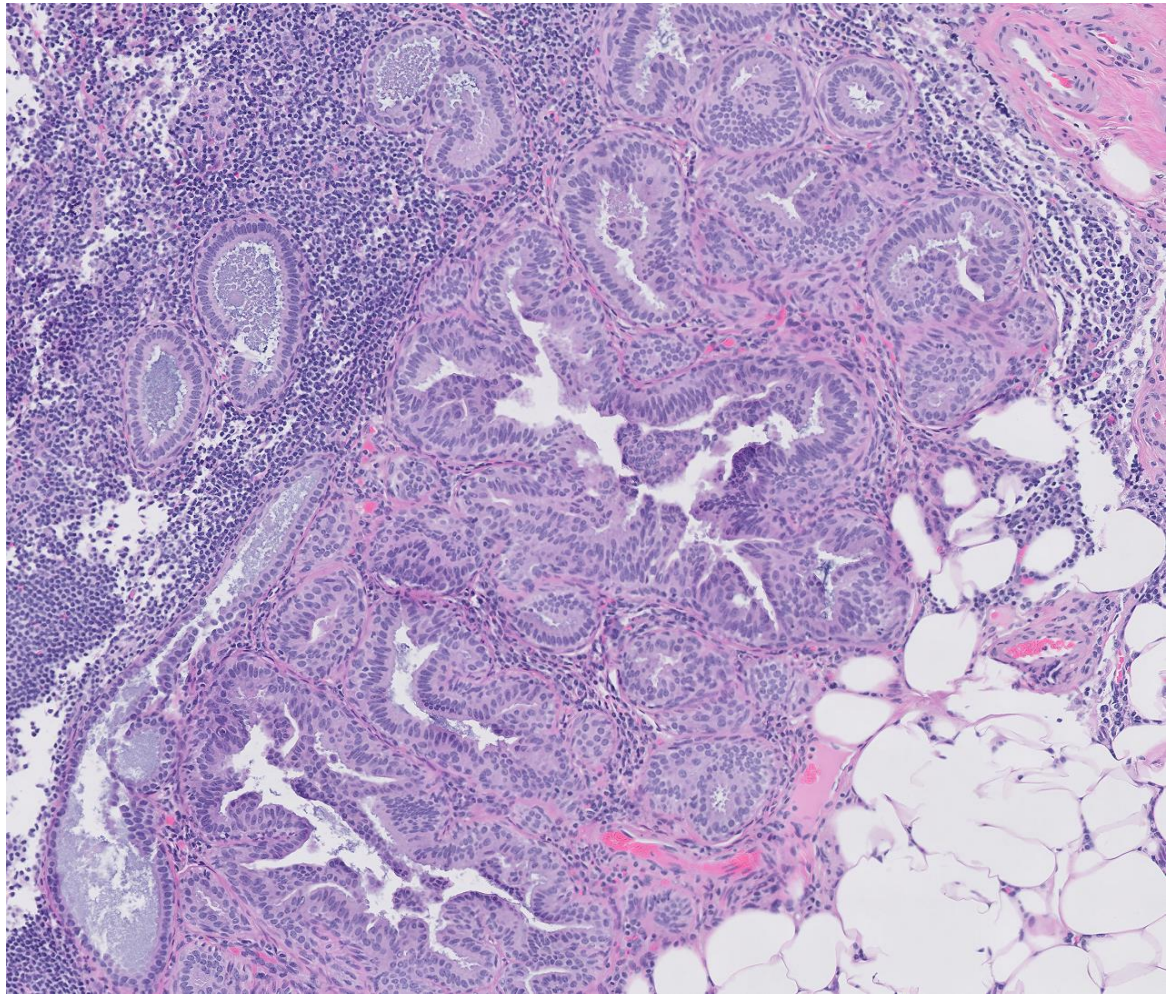
Right breast, partial mastectomy: Invasive ductal carcinoma, 9 mm, Nottingham grade 1

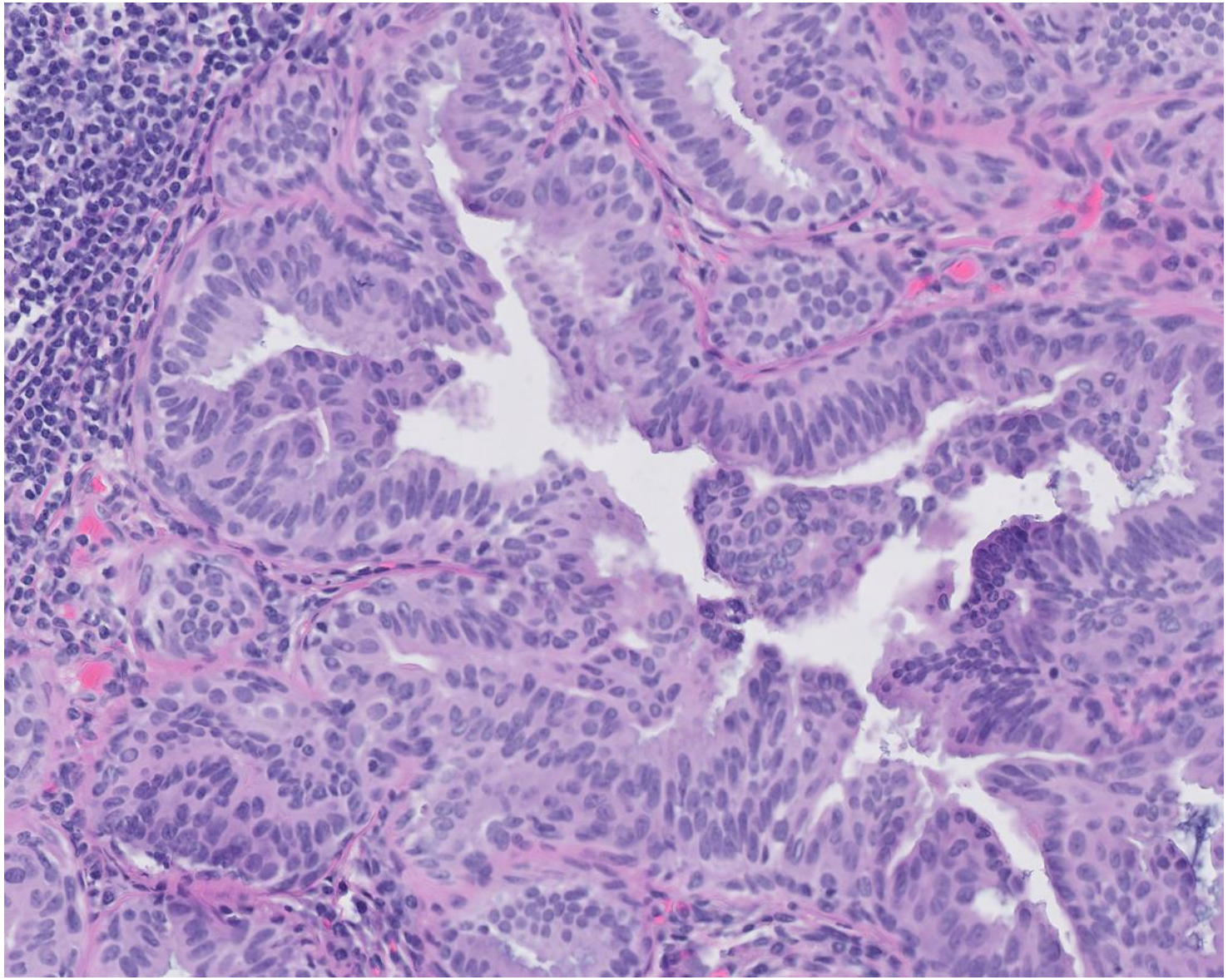
Right axillary sentinel lymph node, biopsy?





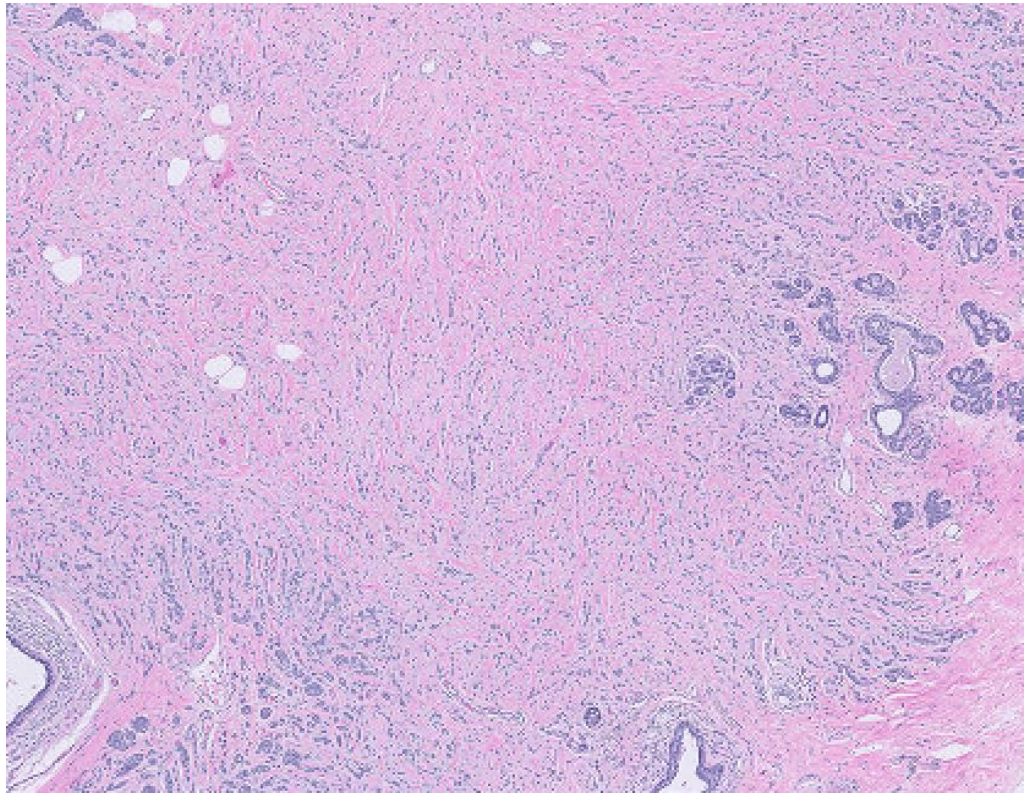


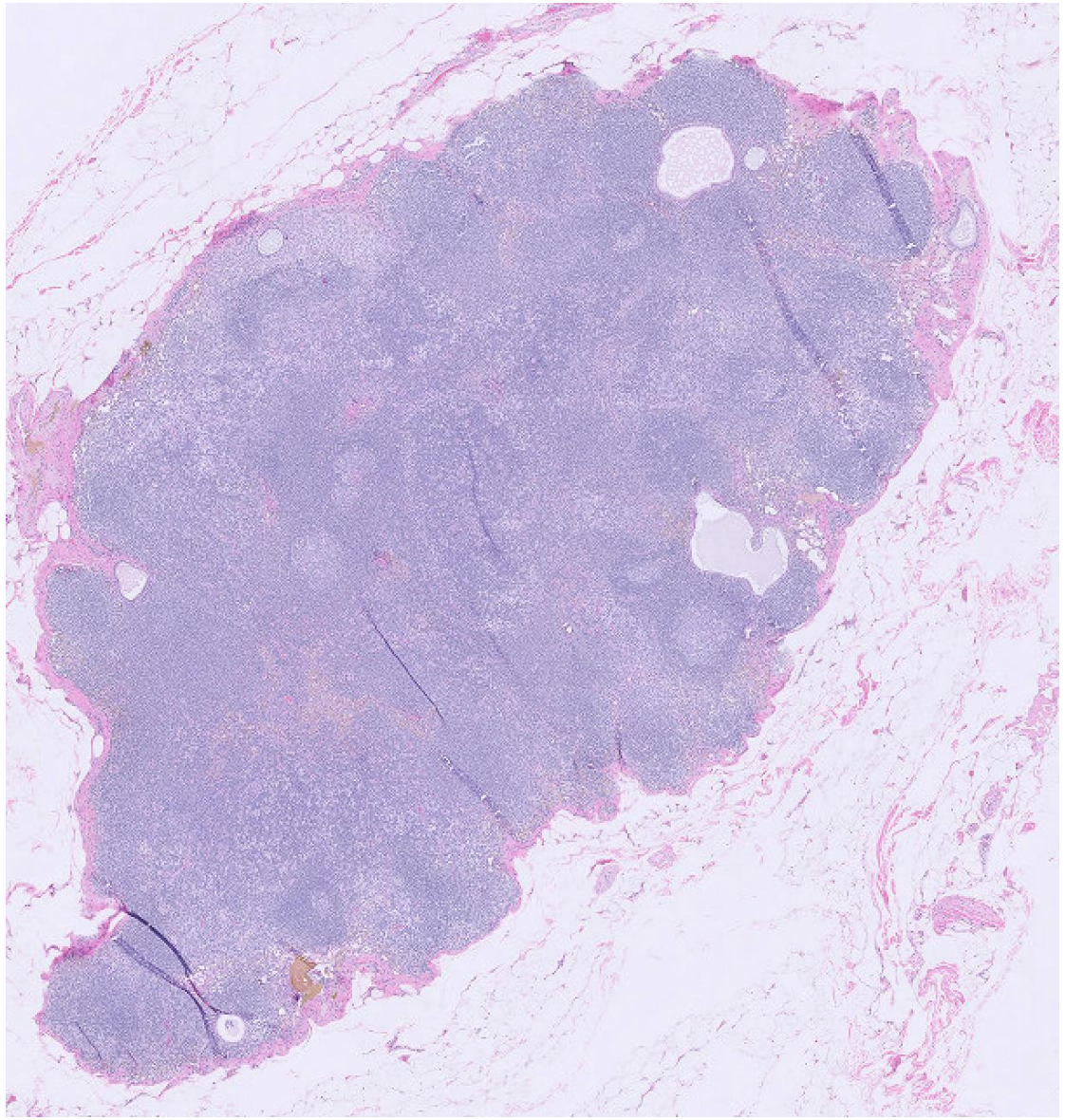




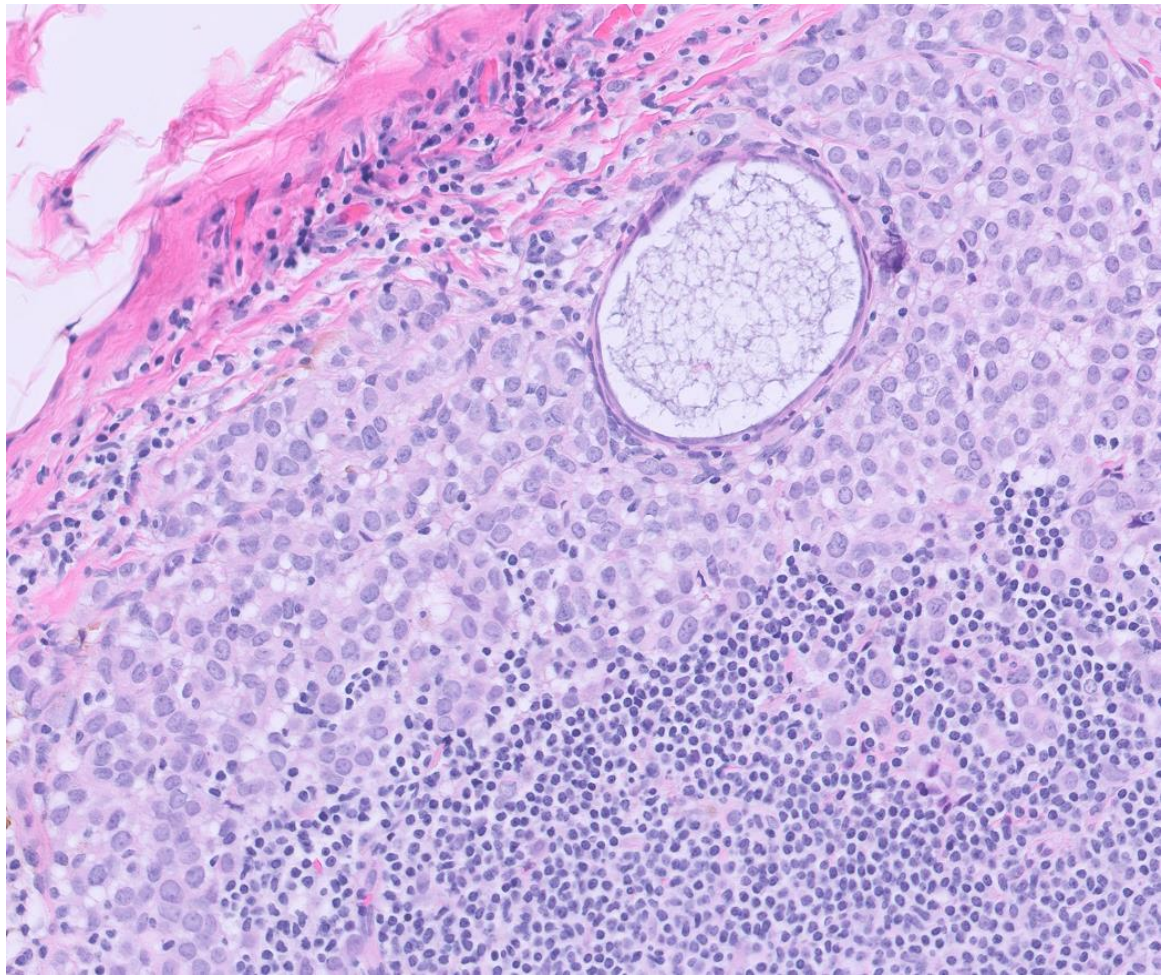
DIAGNOSIS?

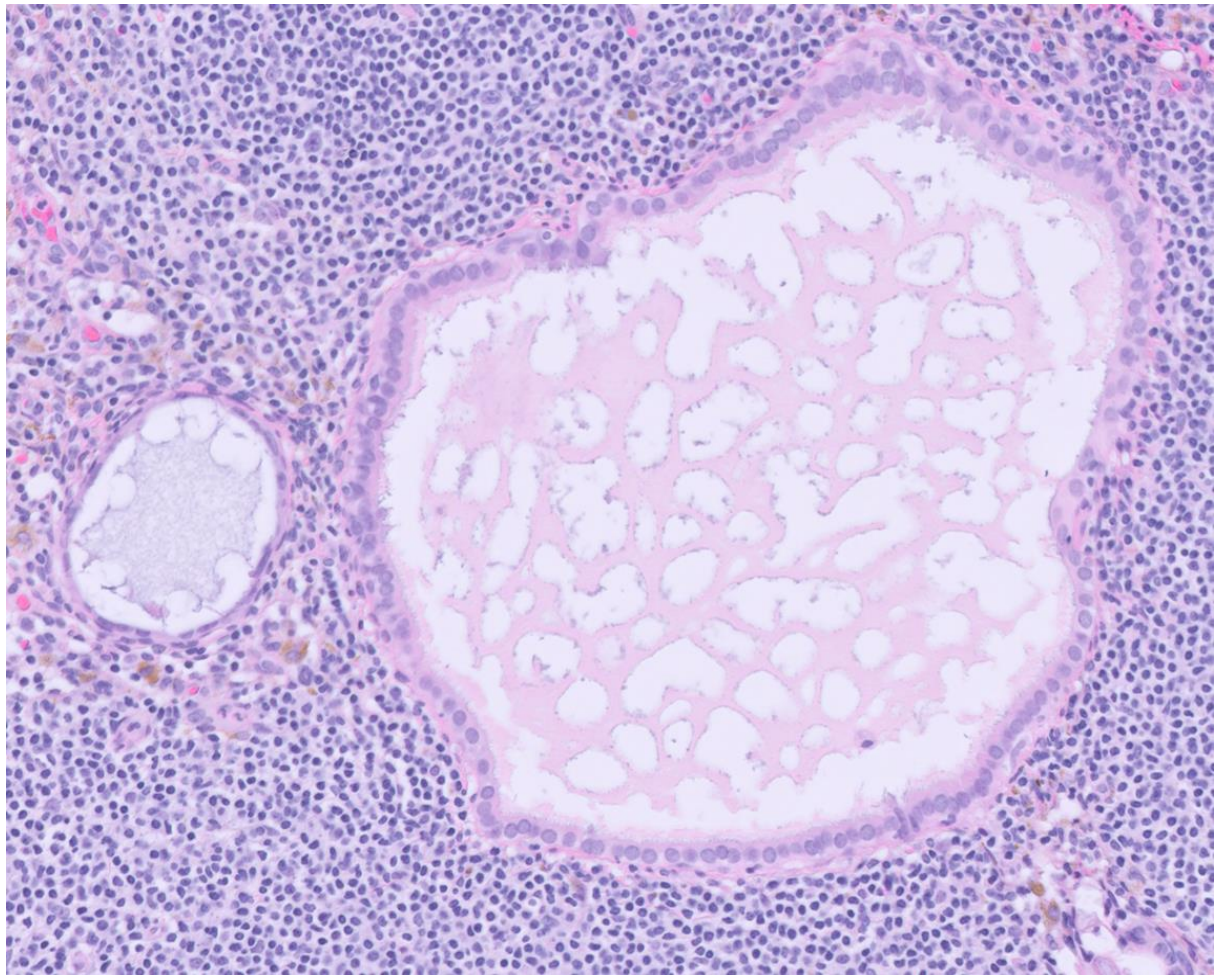
49-years-old woman with screen detected left breast invasive lobular carcinoma, grade 1, who undergoes left mastectomy and axillary sentinel lymph node biopsy.
Pathology:
A. Left breast, mastectomy: Multifocal invasive lobular carcinoma, 8.9 cm, margins
negative.
B. Left axillary sentinel lymph node?





UCSF





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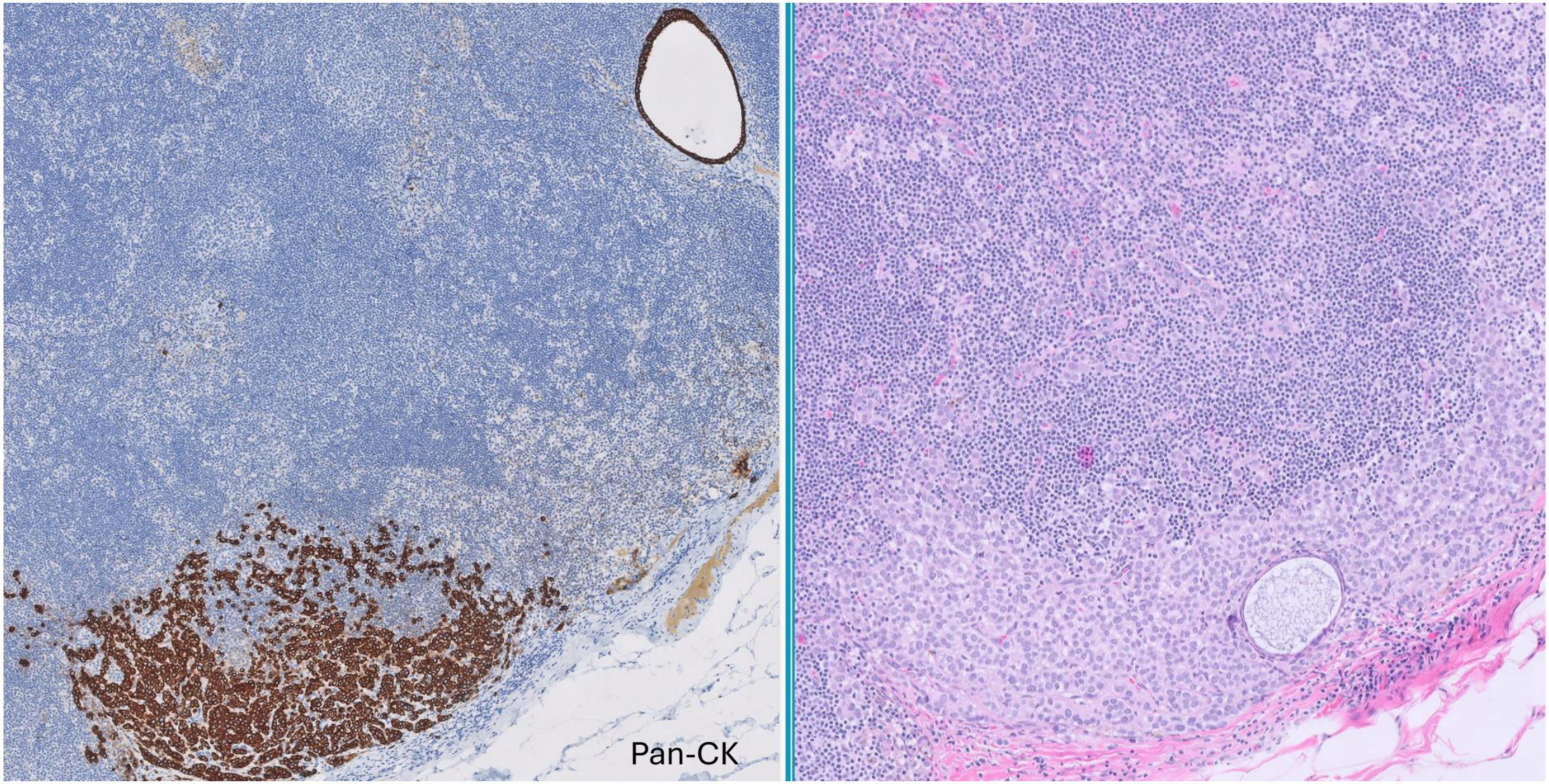

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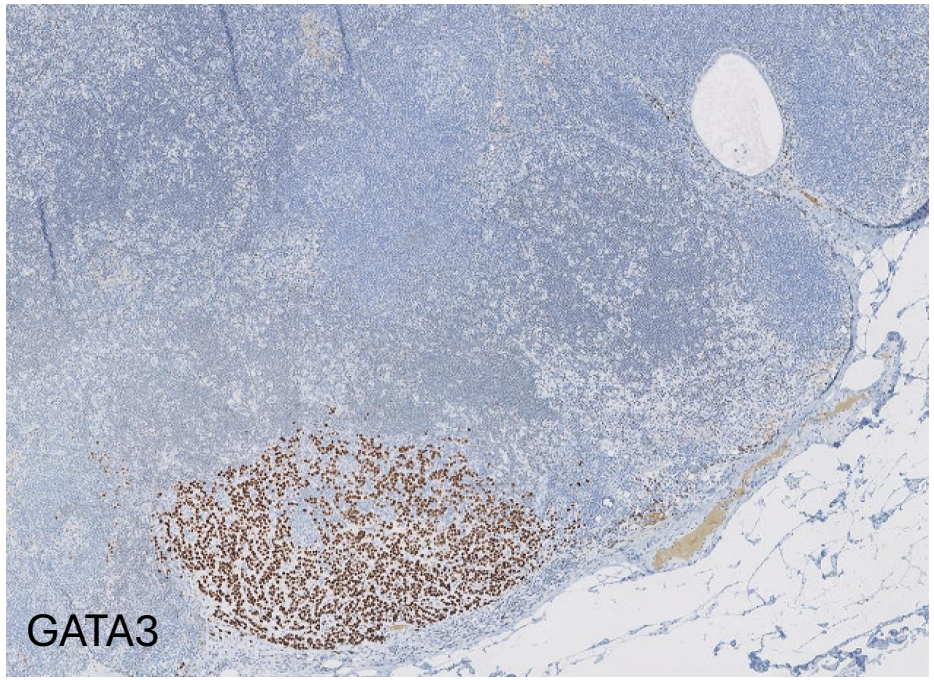

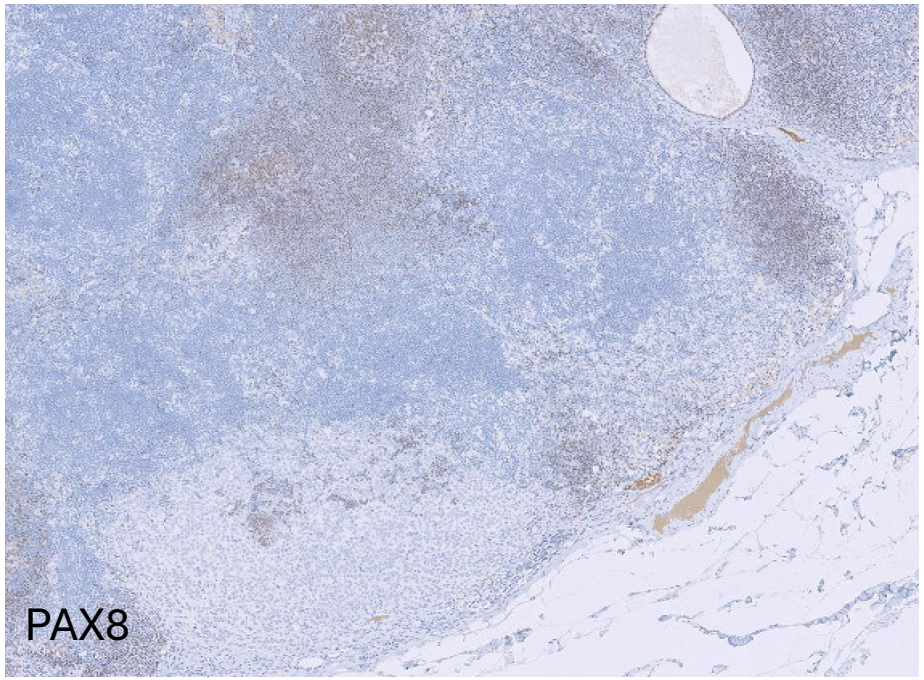

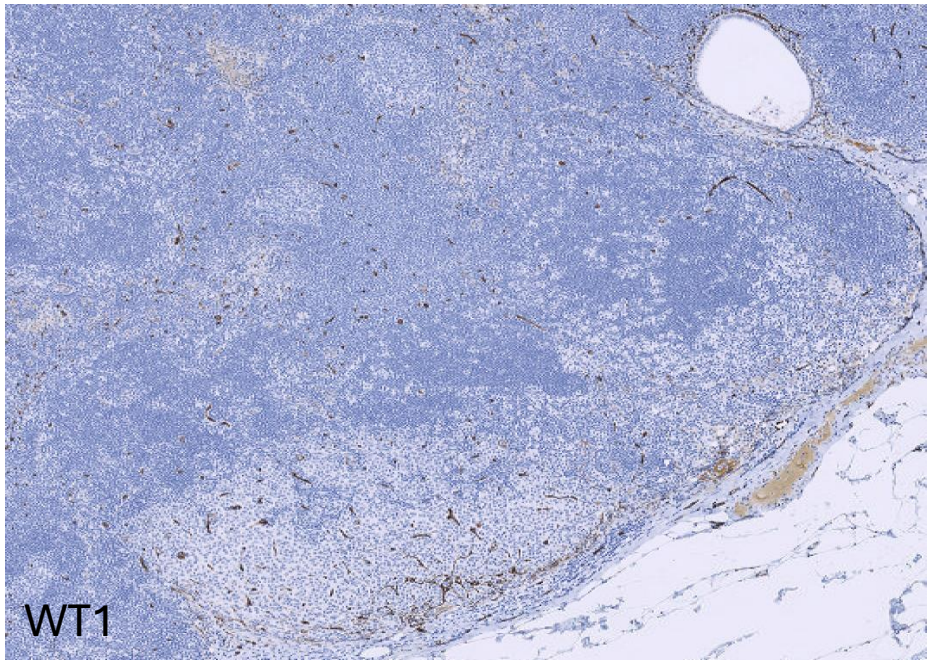

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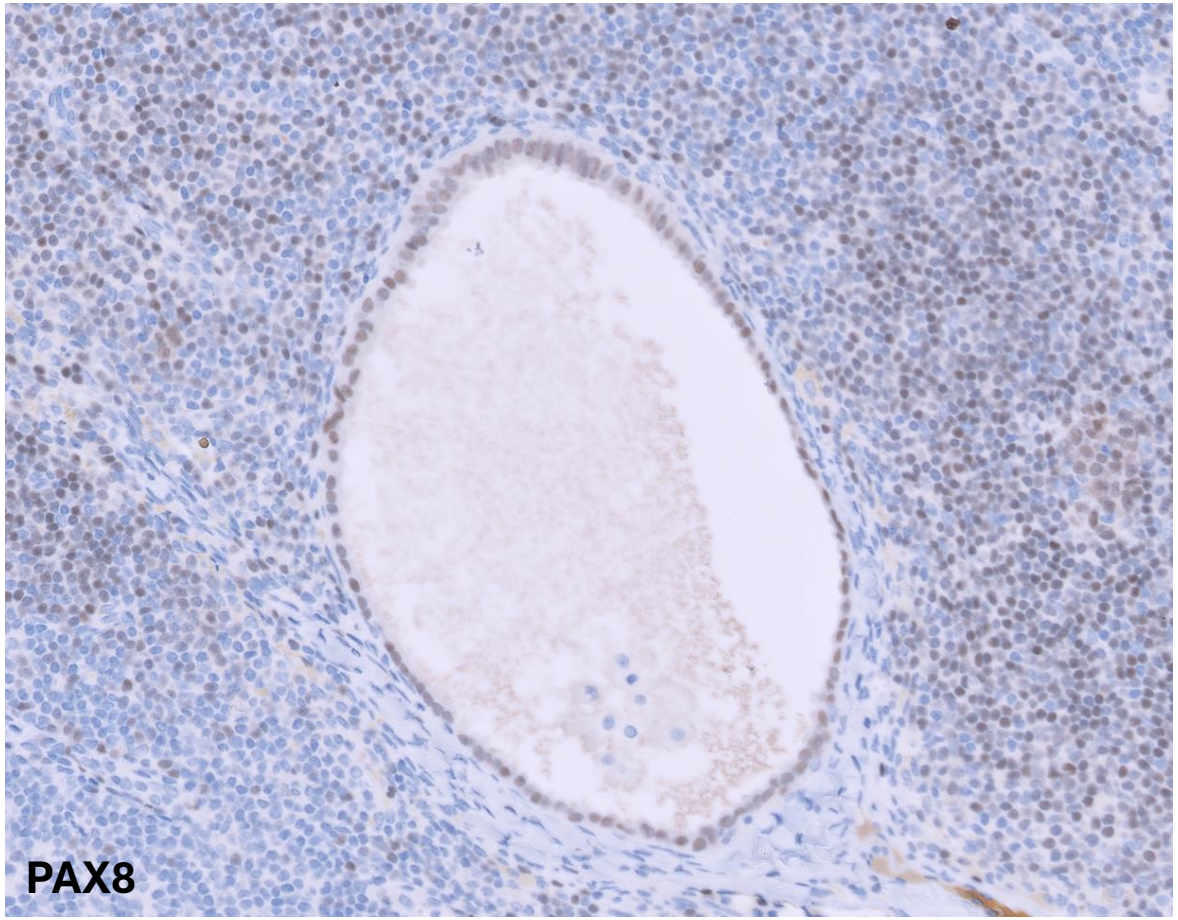

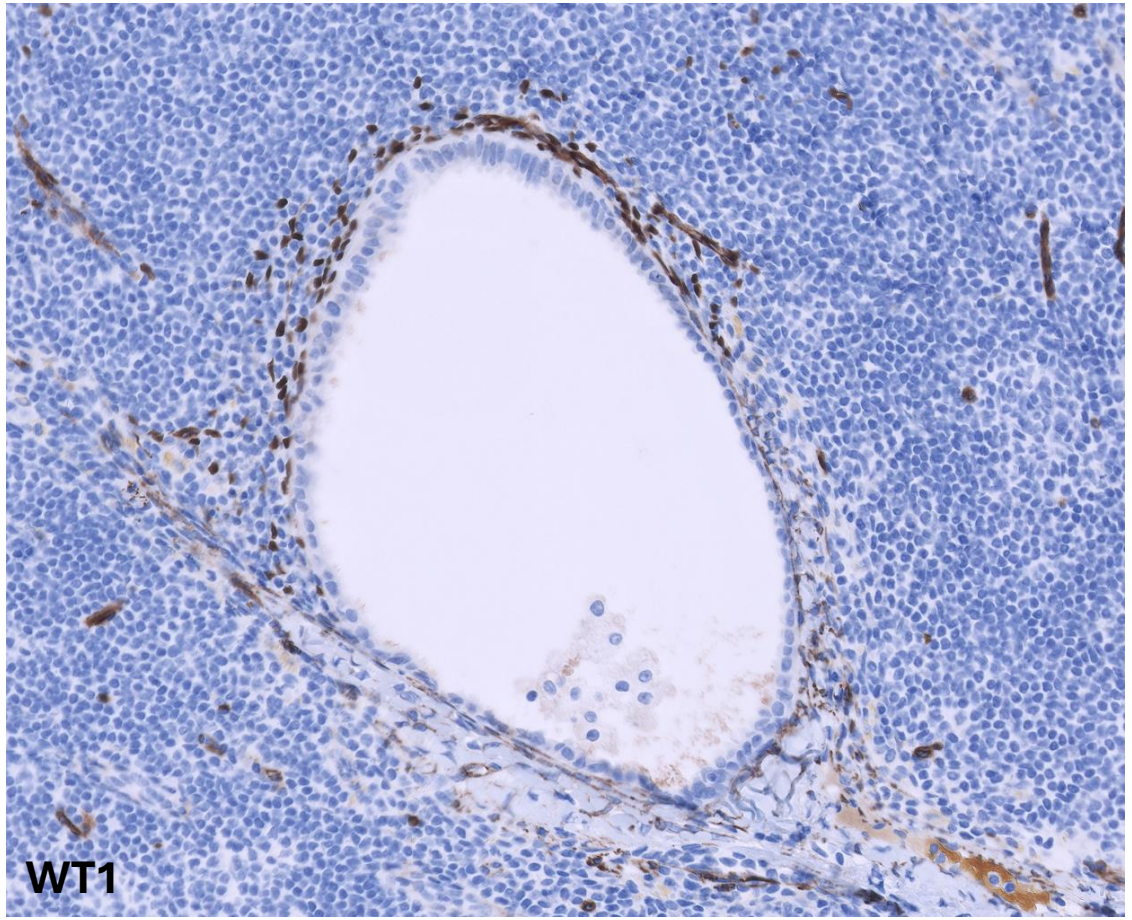

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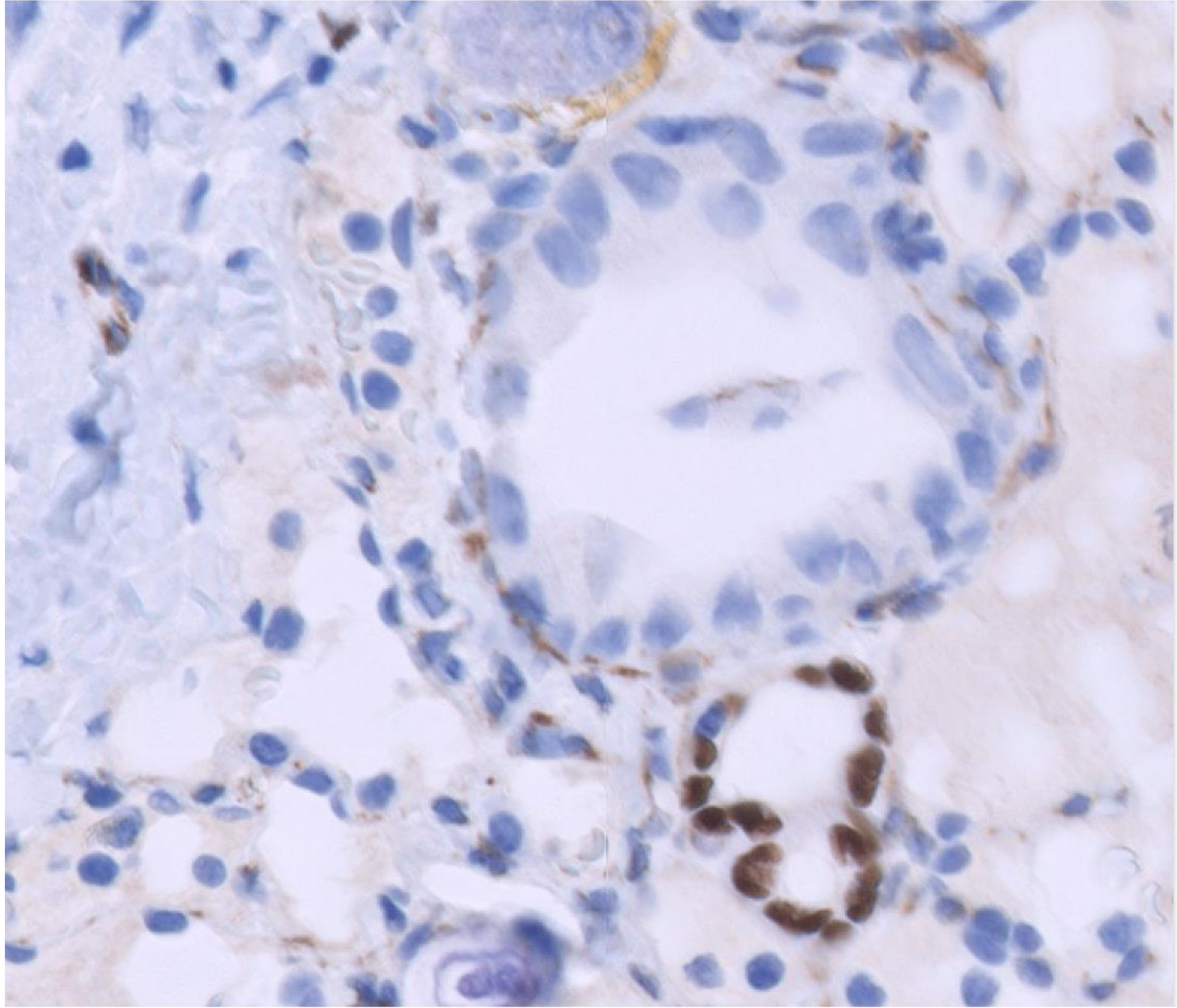
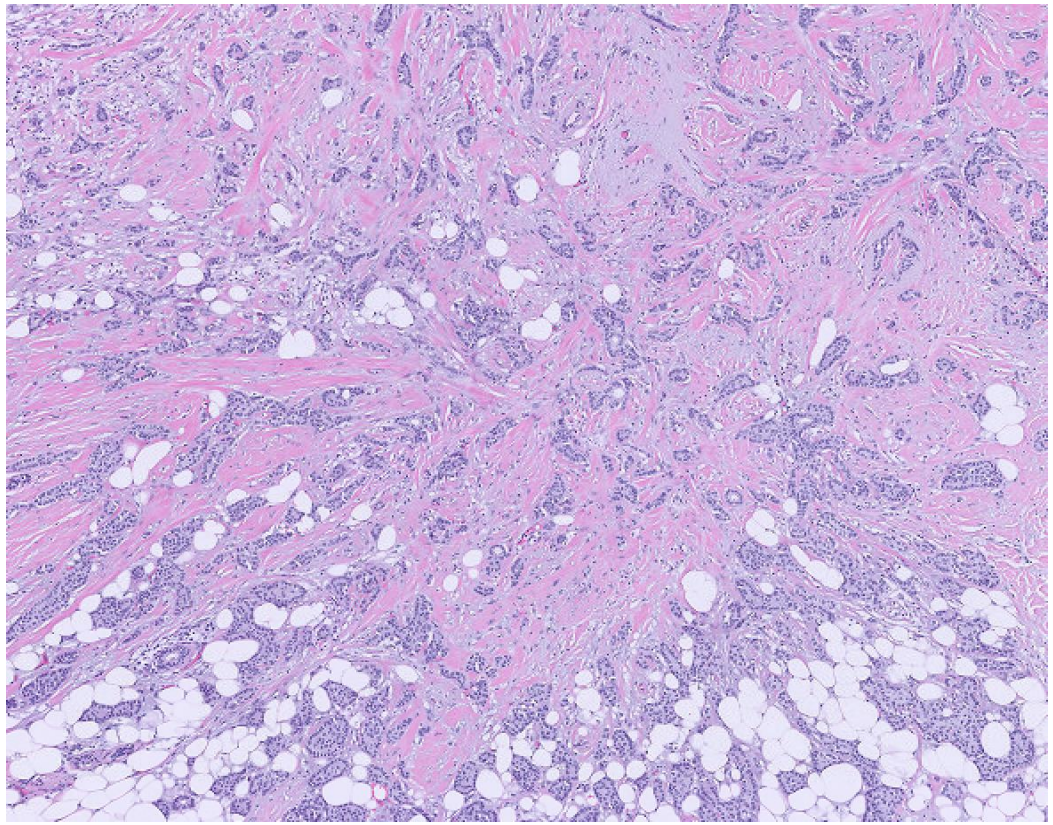


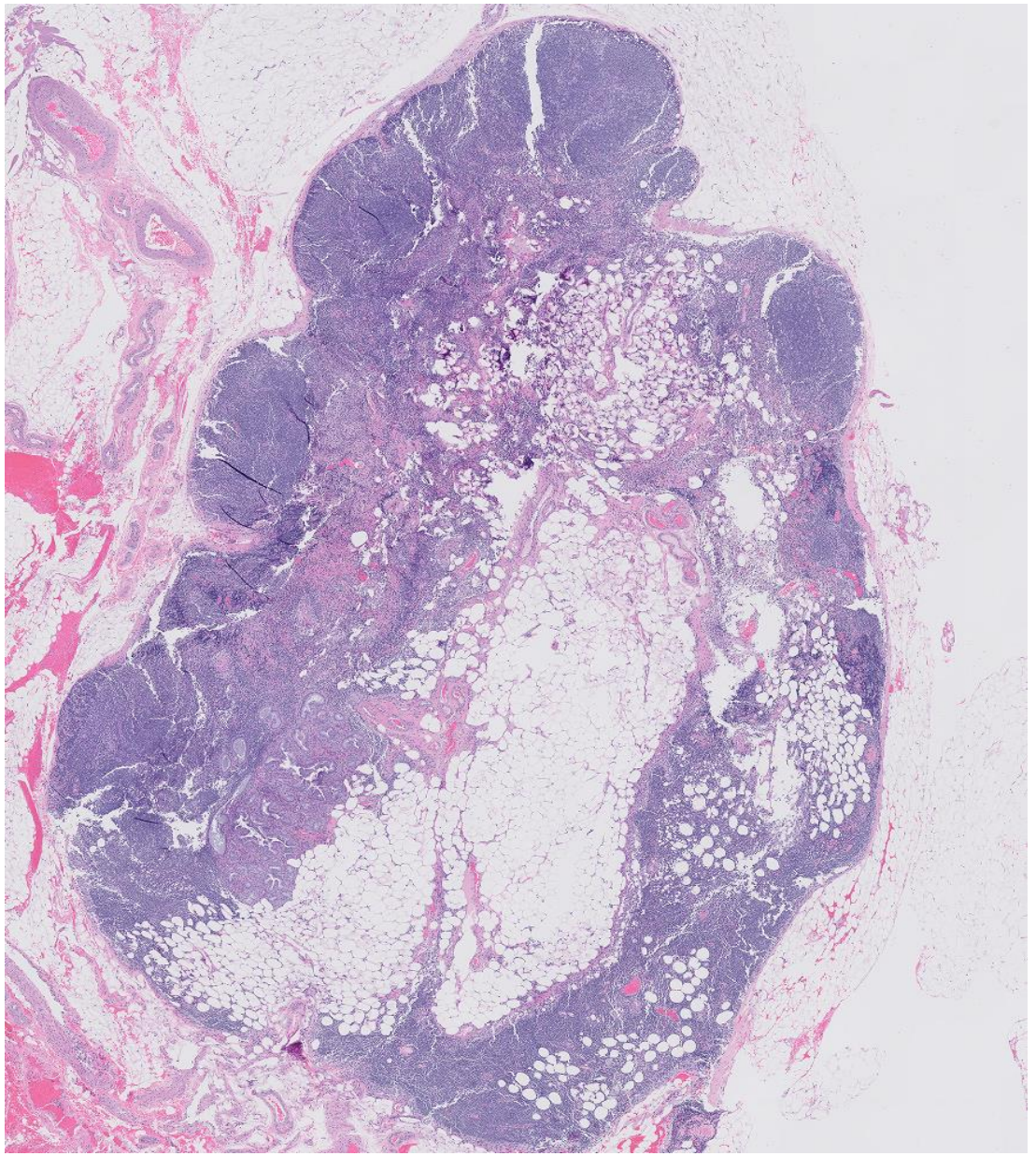
76-year-old woman with biopsy proven invasive ductal carcinoma of right breast, who underwent right partial mastectomy and sentinel lymph node biopsy.

Pathology:

A. Right breast, partial mastectomy: Invasive ductal carcinoma, 9 mm, Nottingham grade 1, negative margins.

B. Right axillary sentinel lymph node, biopsy?





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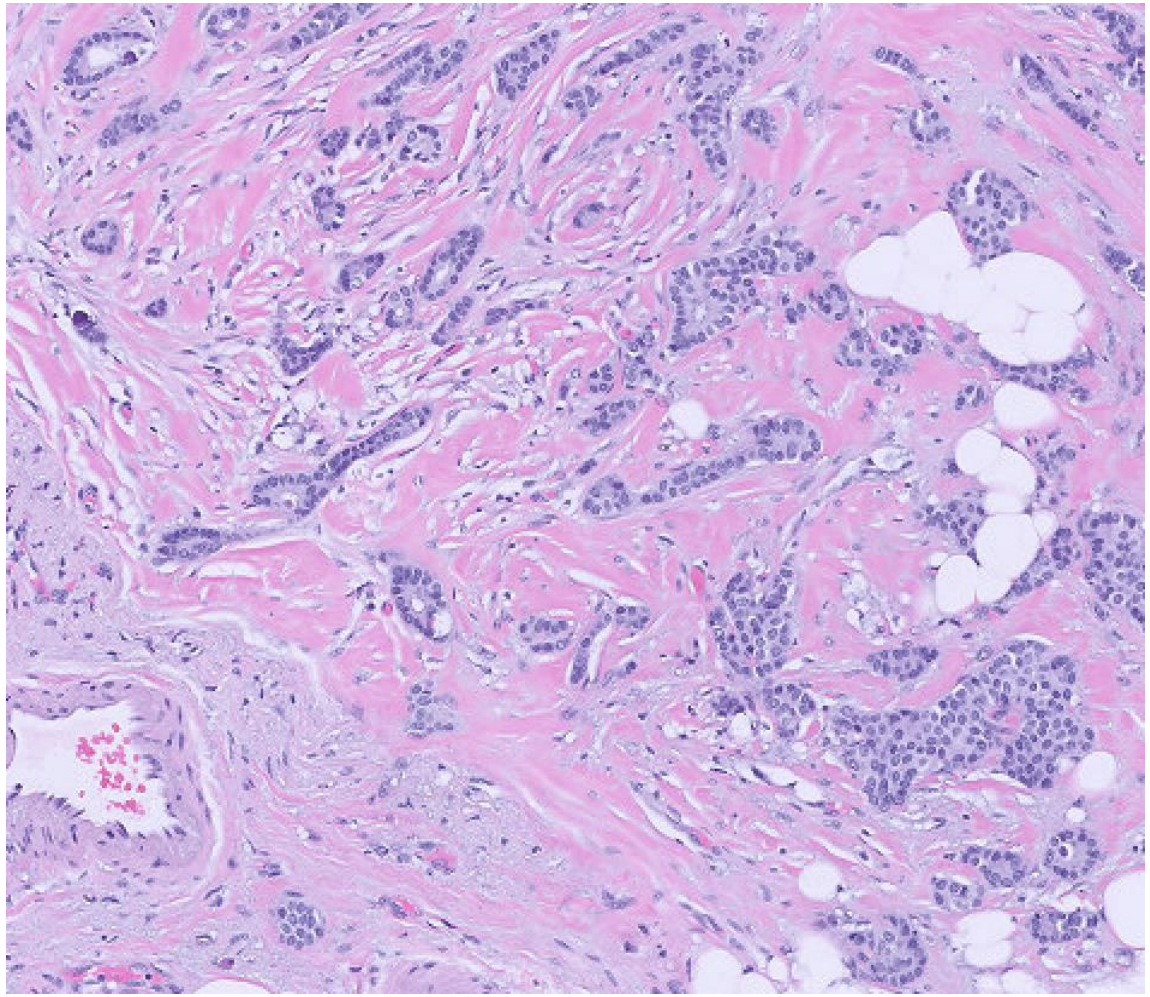

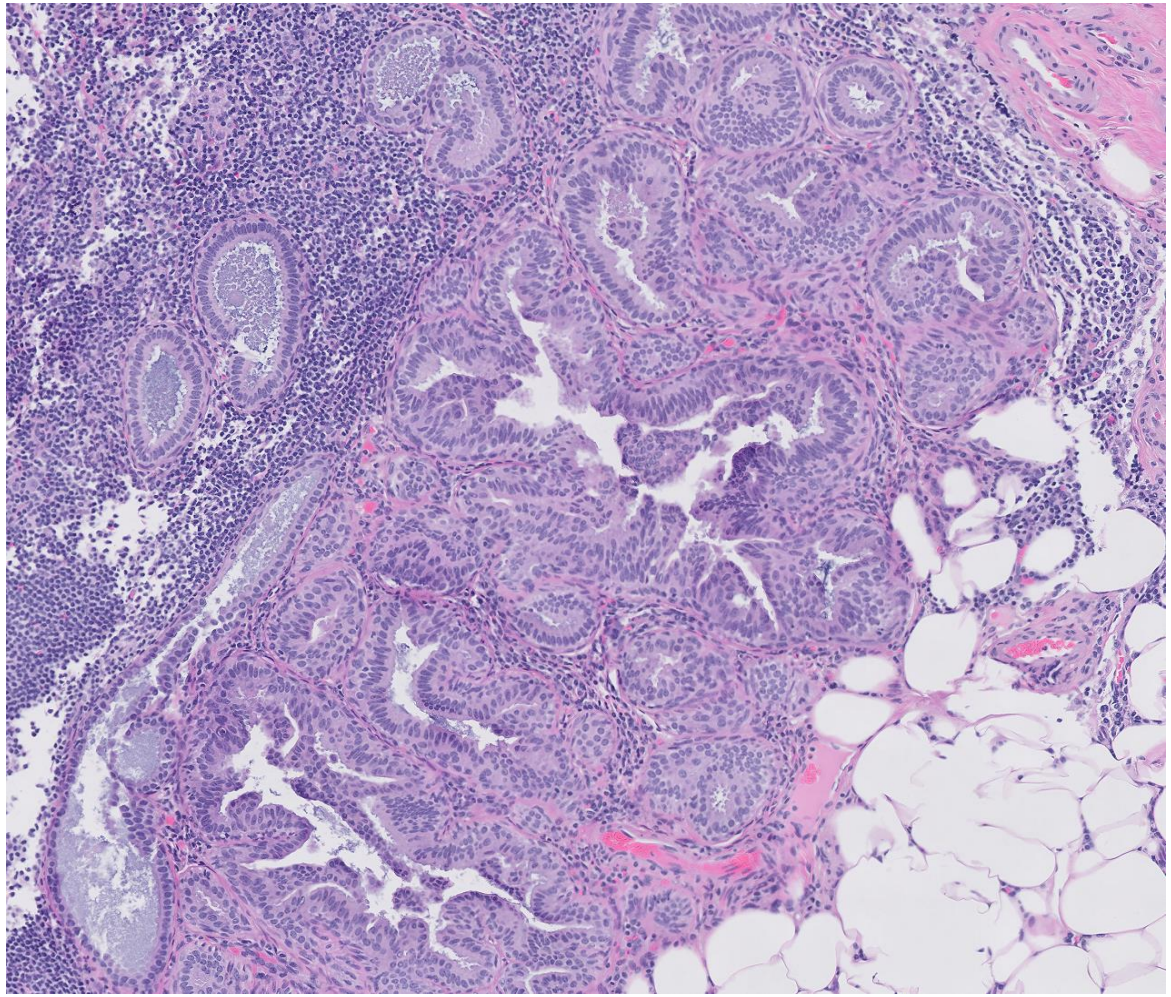

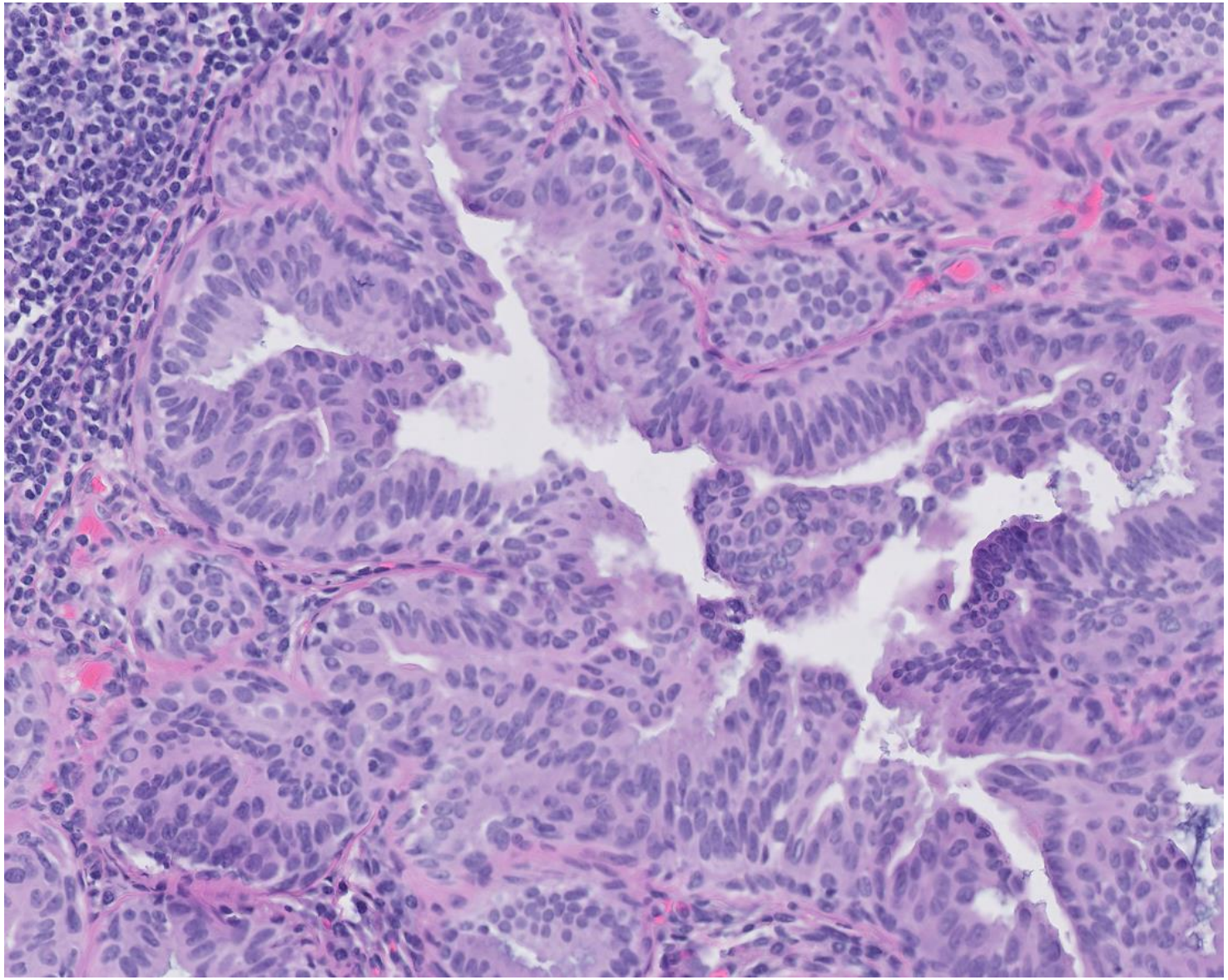

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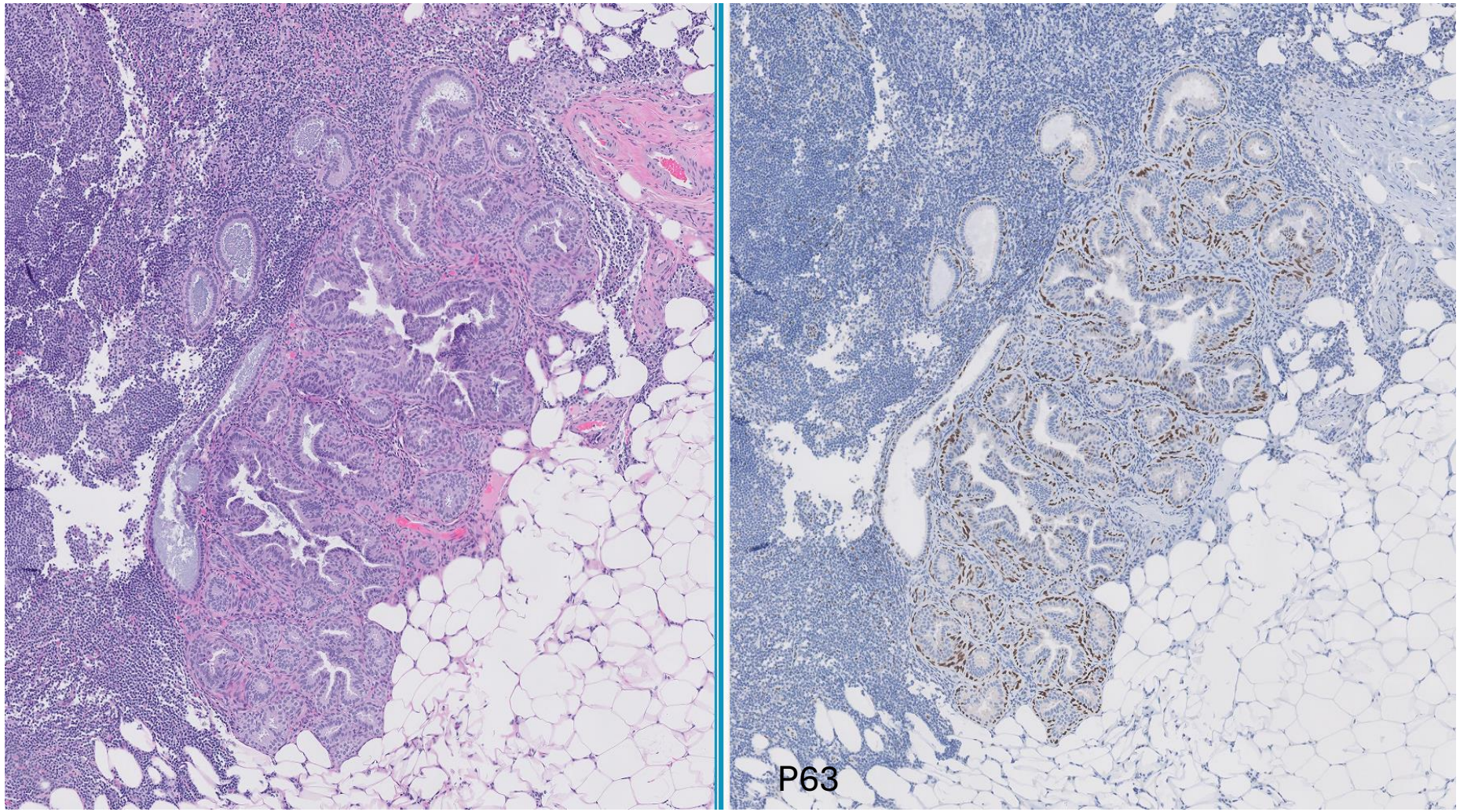

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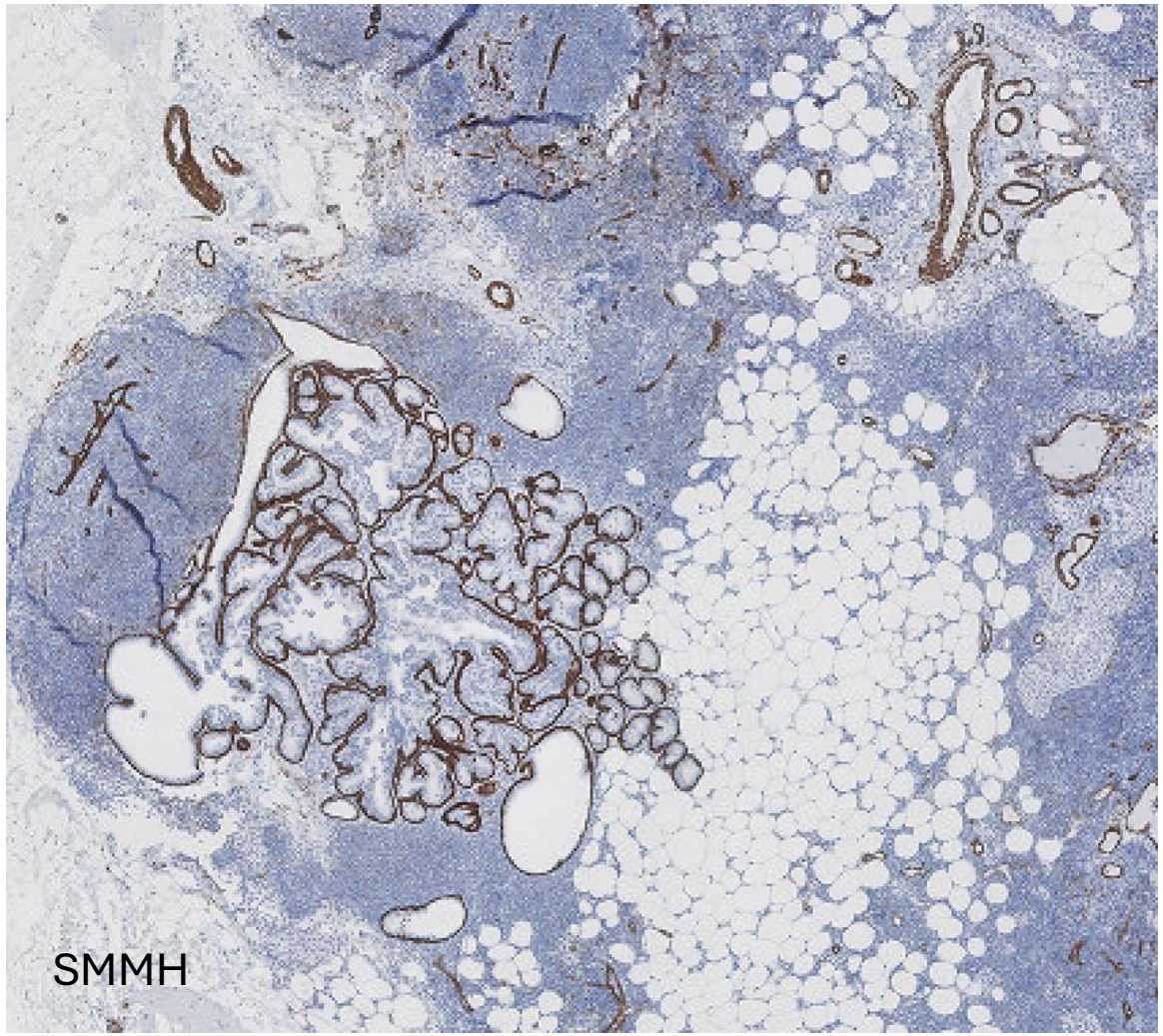

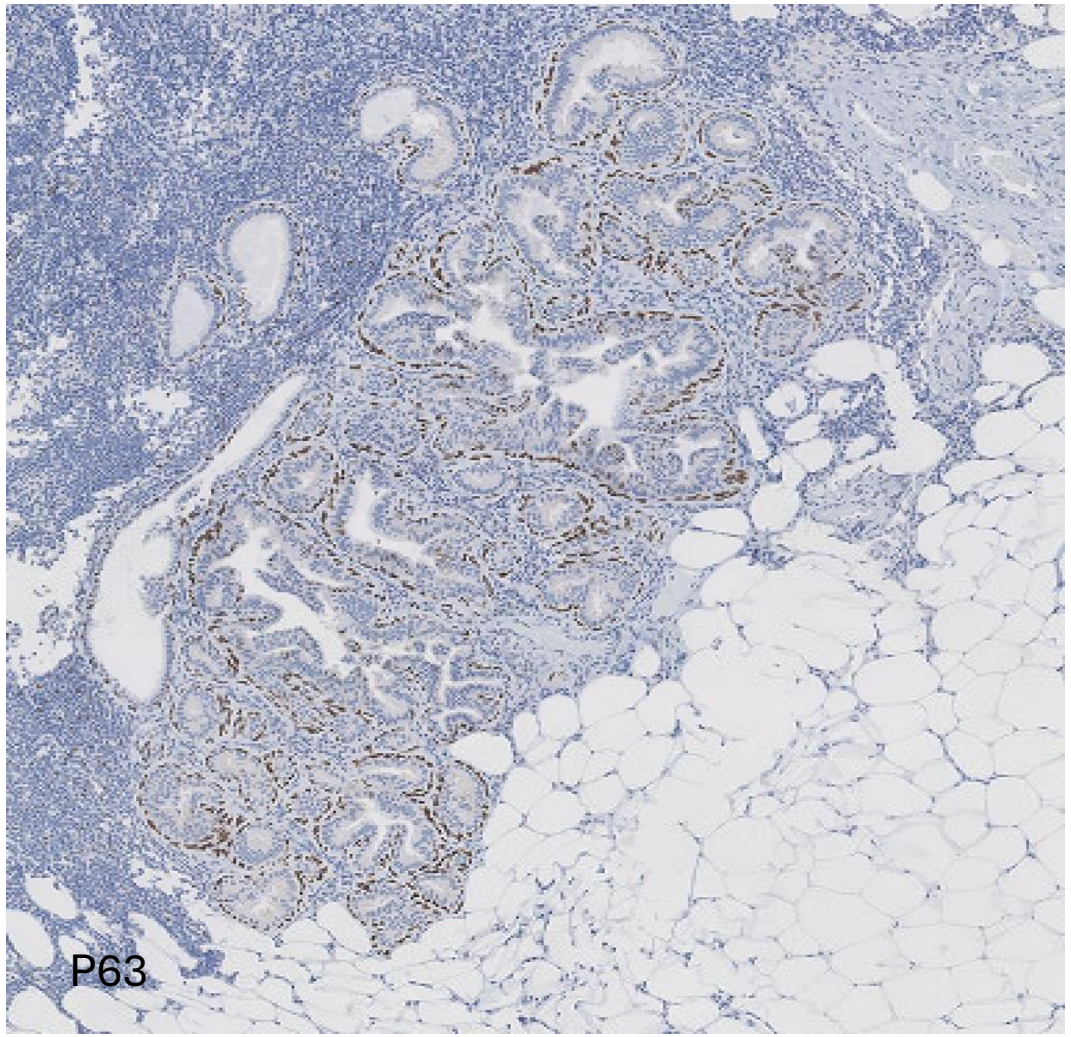

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Lymph nodes inclusions

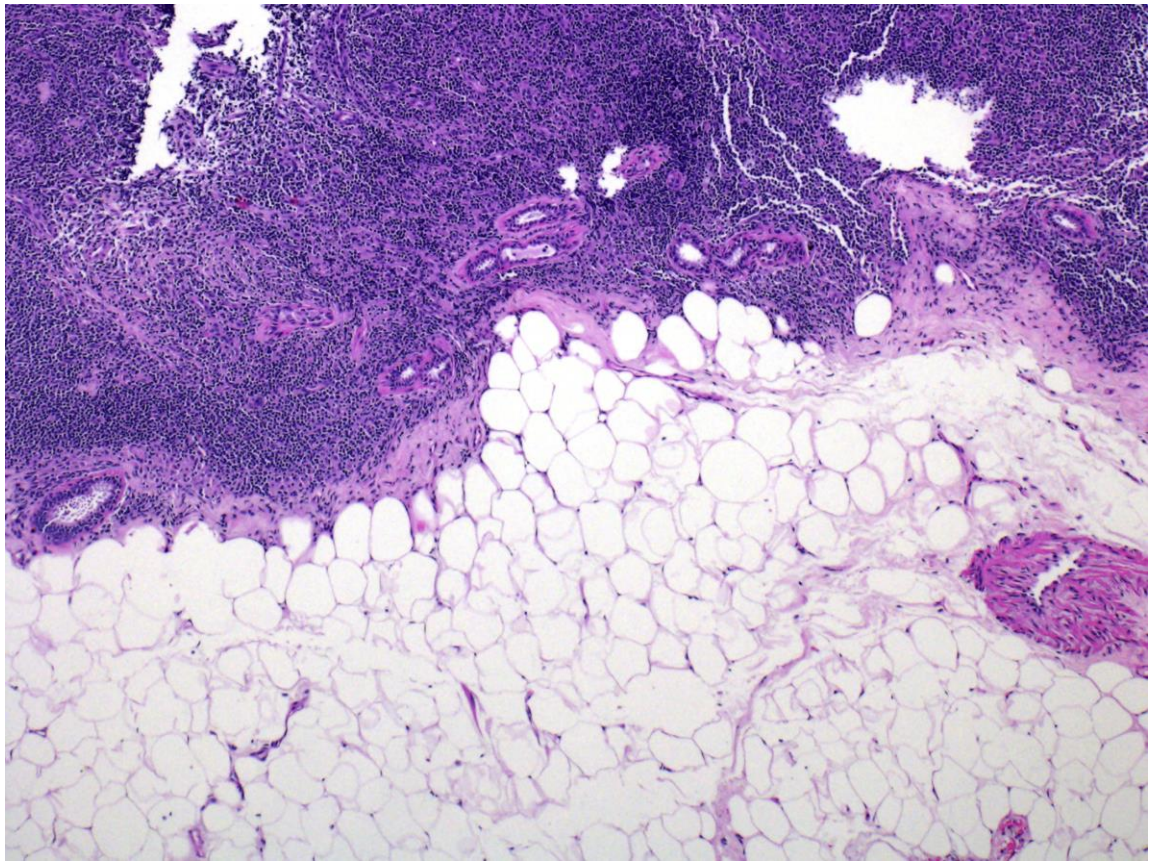
- **Epithelial Inclusions**
  - Mammary-type glandular inclusions (heterotopic breast tissue)
  - Müllerian-type glandular inclusions (endosalpingiosis, endometriosis, endocervicosis)
  - Squamous inclusions
  - Mixed glandular–squamous inclusions
- **Non-epithelial Inclusions**
  - Nodal nevi (benign melanocytic nests)

Mammary-Type Glandular Inclusions

Mechanism
- Benign displacement or mechanical transport
- Ectopic mammary tissue

Pathologic features
- Lack gross pathologic findings
- Microscopic: Most commonly located within the lymph node capsule

Bland glands with two cell layers (luminal & myoepithelial)



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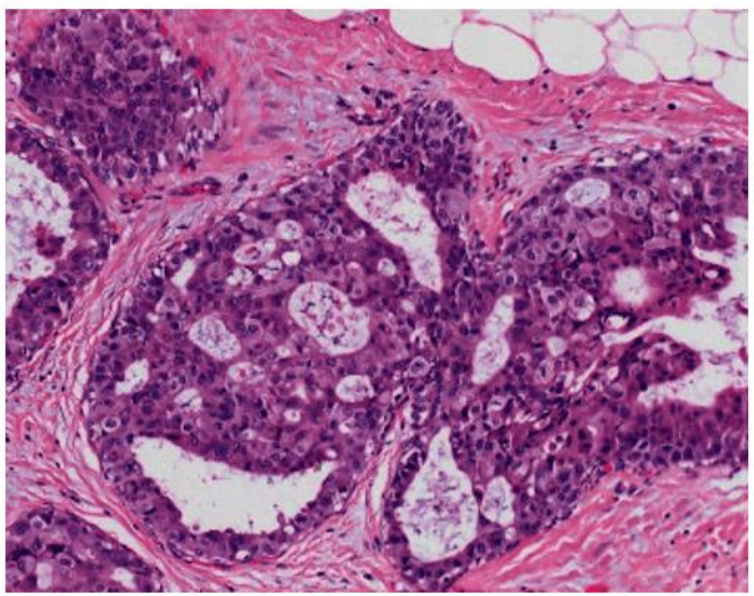
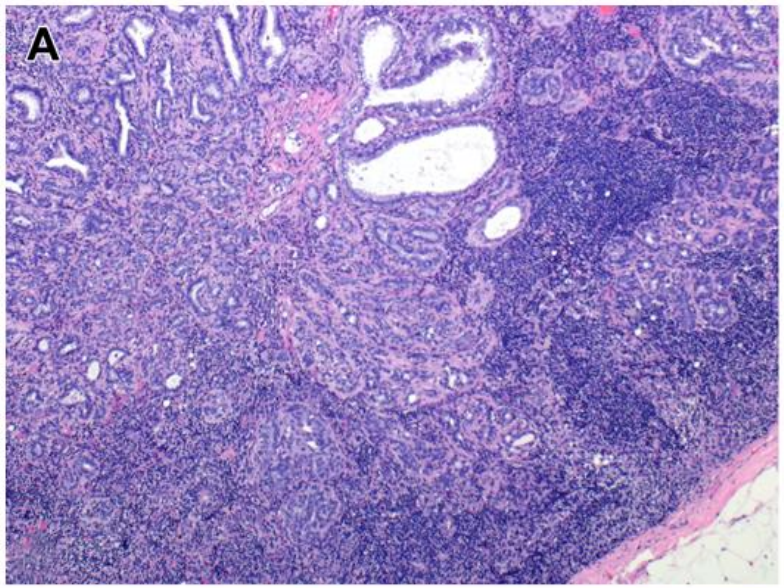
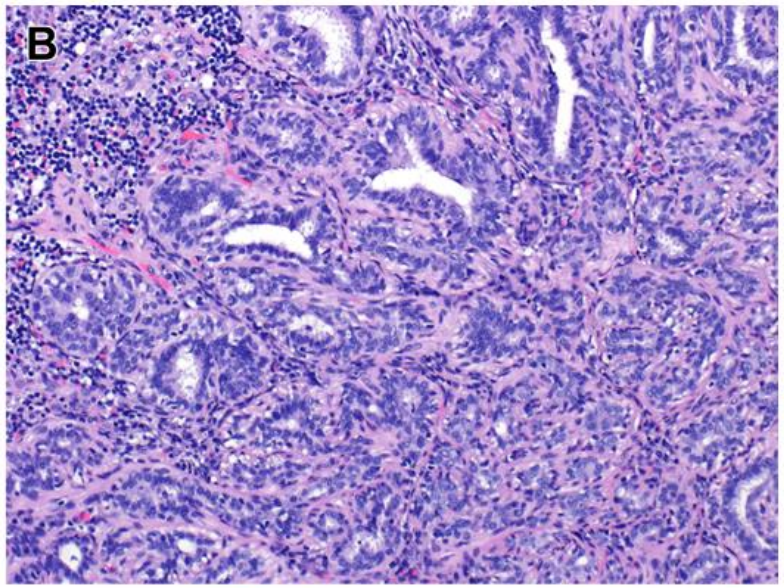
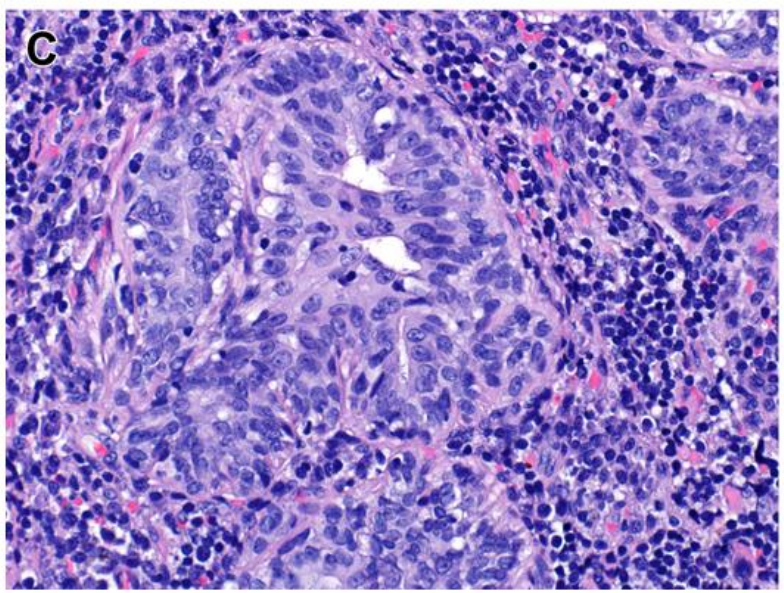
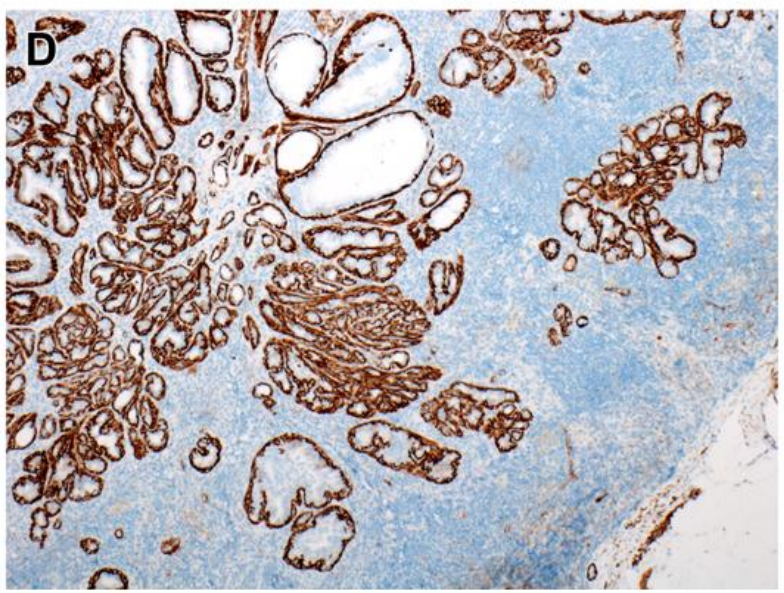
- Range of histologic appearances; benign or atypical proliferative changes
- Frozen section challenges











Nielson KJ, Guo R, Solanki MH, Sturgis CD. Ductal Carcinoma Arising in a Squamous Epithelial Inclusion Cyst within an Axillary Lymph Node: A Challenging Nodal Metastasis. Case Rep Pathol. 2023 Oct 31;2023:9979532.

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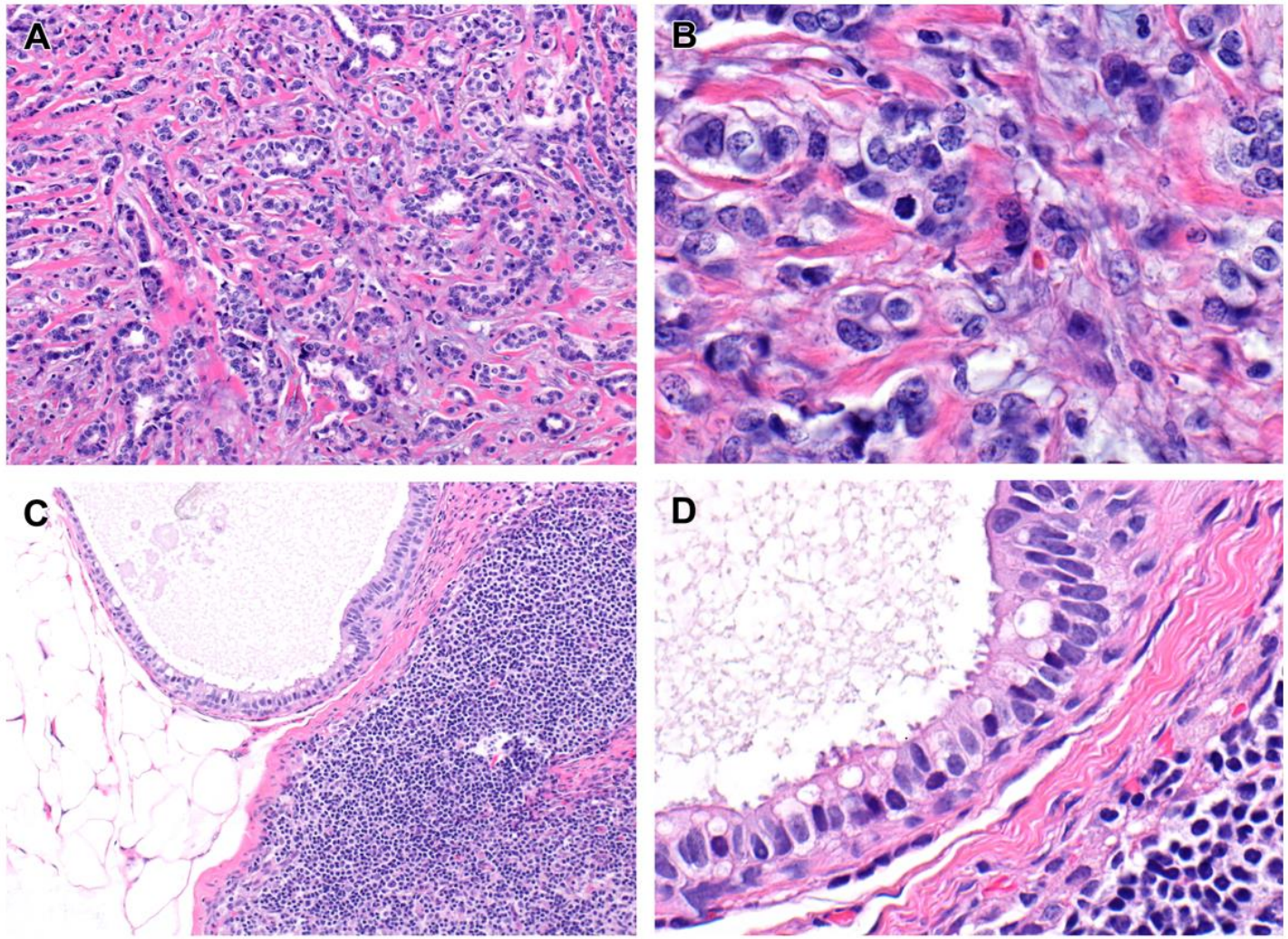
Differential Diagnosis

- Metastatic ductal carcinoma
- Metastatic well-differentiated adenocarcinoma of another primary site (eg; lung or upper gastrointestinal tract)
- Other benign inclusions, specifically Mullerian-type glandular inclusions



Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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Diagnosis

- Histology
- IHC: Luminal cells stains with CK7, GCDFP-15, Mammaglobin and GATA3 which can also be positive in metastatic breast carcinoma. Therefore, IHC for myoepithelial cells is helpful for differentiating mammary-type glandular inclusions from metastatic breast carcinoma.

Müllerian-Type Glandular Inclusions

- Abdominal and pelvic sites
- Supra-diaphragmatic

Mechanism

Supradiaphragmatic: not clear

Subdiaphragmatic:

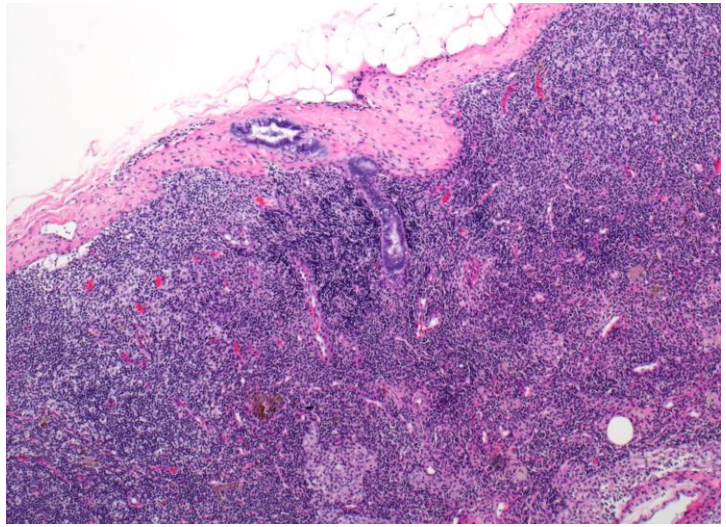
- Tubal cells implantation from unsampled serous borderline tumors
- Metaplasia

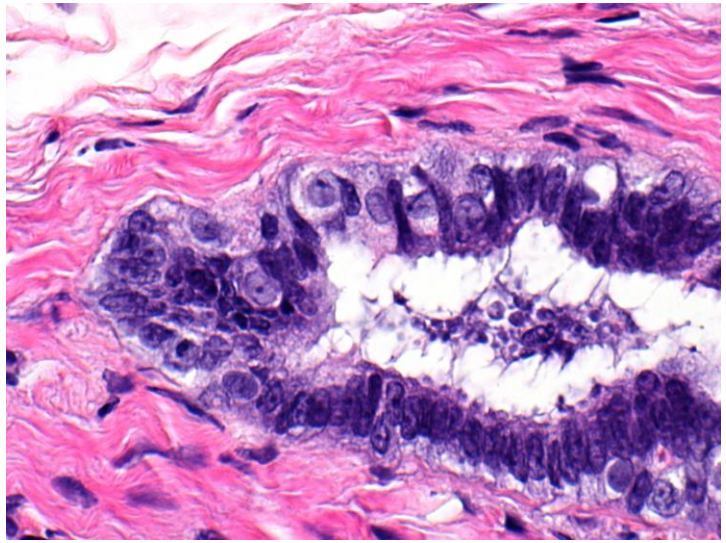
Pathologic features

- Lack gross pathologic findings
- Microscopic

Usually located within the lymph node capsule

Endosalpingiosis, endometriosis or endocervicosis lined by bland columnar cells with cilia, with interspersed intercalated cells





Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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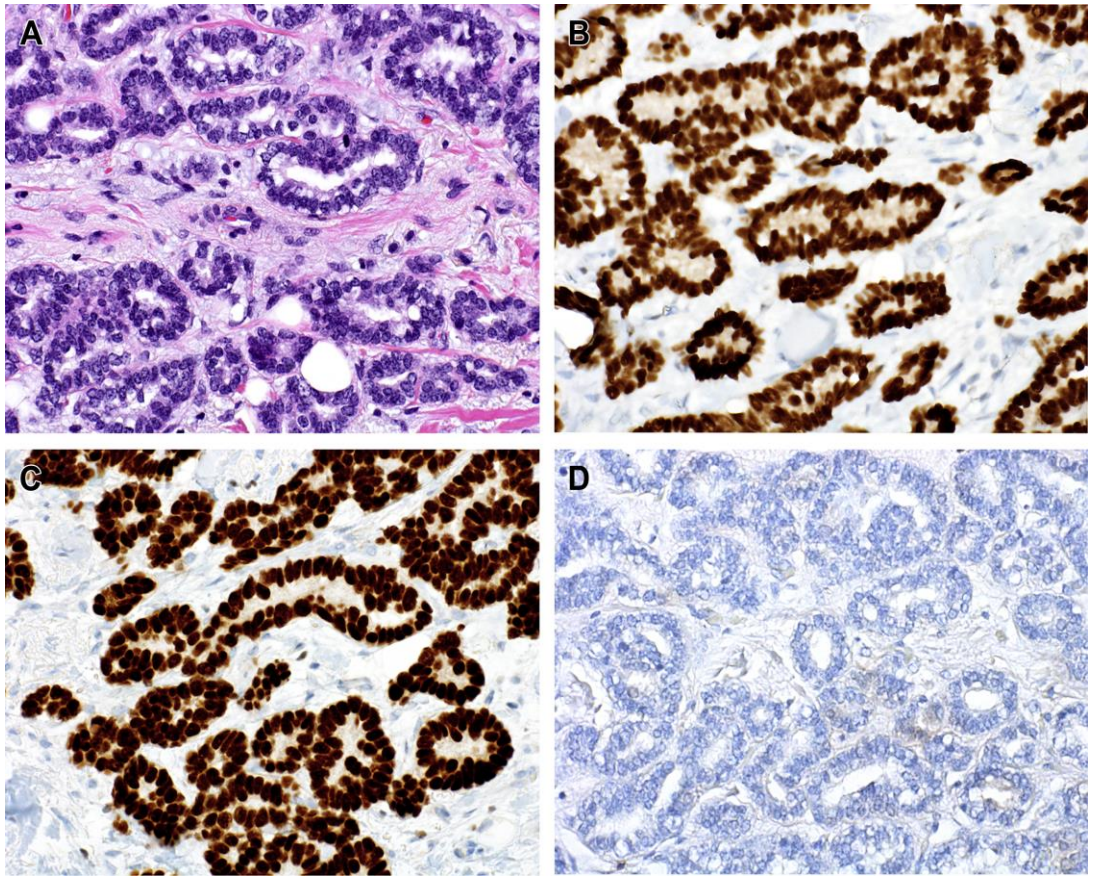
Differential Diagnosis

- Benign mammary-type glandular inclusions
- Metastatic mammary carcinoma
- Metastatic gynecologic tract adenocarcinoma
- Metastatic adenocarcinoma of other sites, such as lung or upper gastrointestinal tract



Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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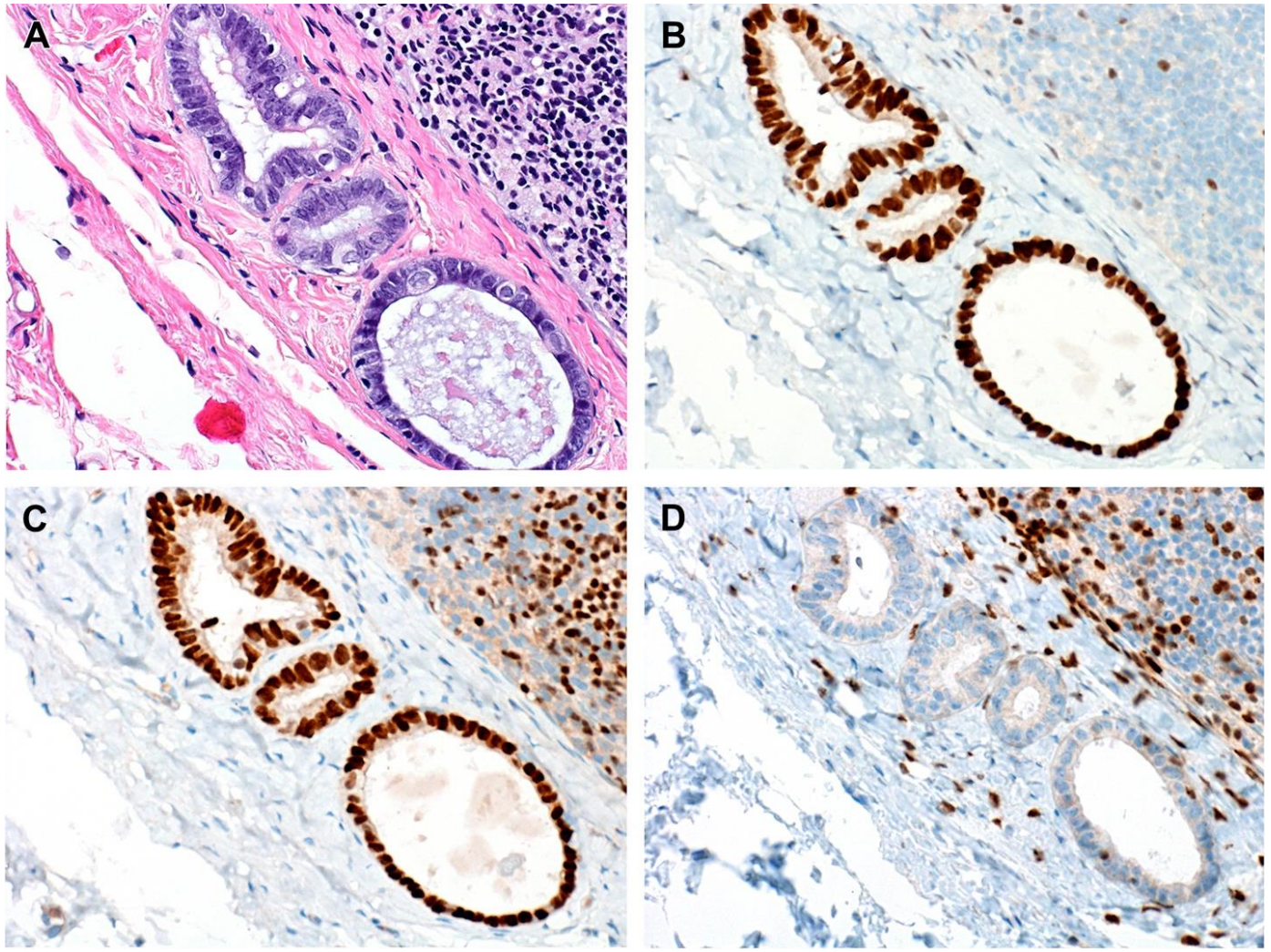
Diagnosis

- Histology
- IHC:

+ CK7, PAX8, WT1, and ER
- GATA3, GCDFP, and mammaglobin

Prognosis

- Occult gynecologic primary malignancy can arise from these inclusions



Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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Squamous Inclusions

Mechanisms: Unclear

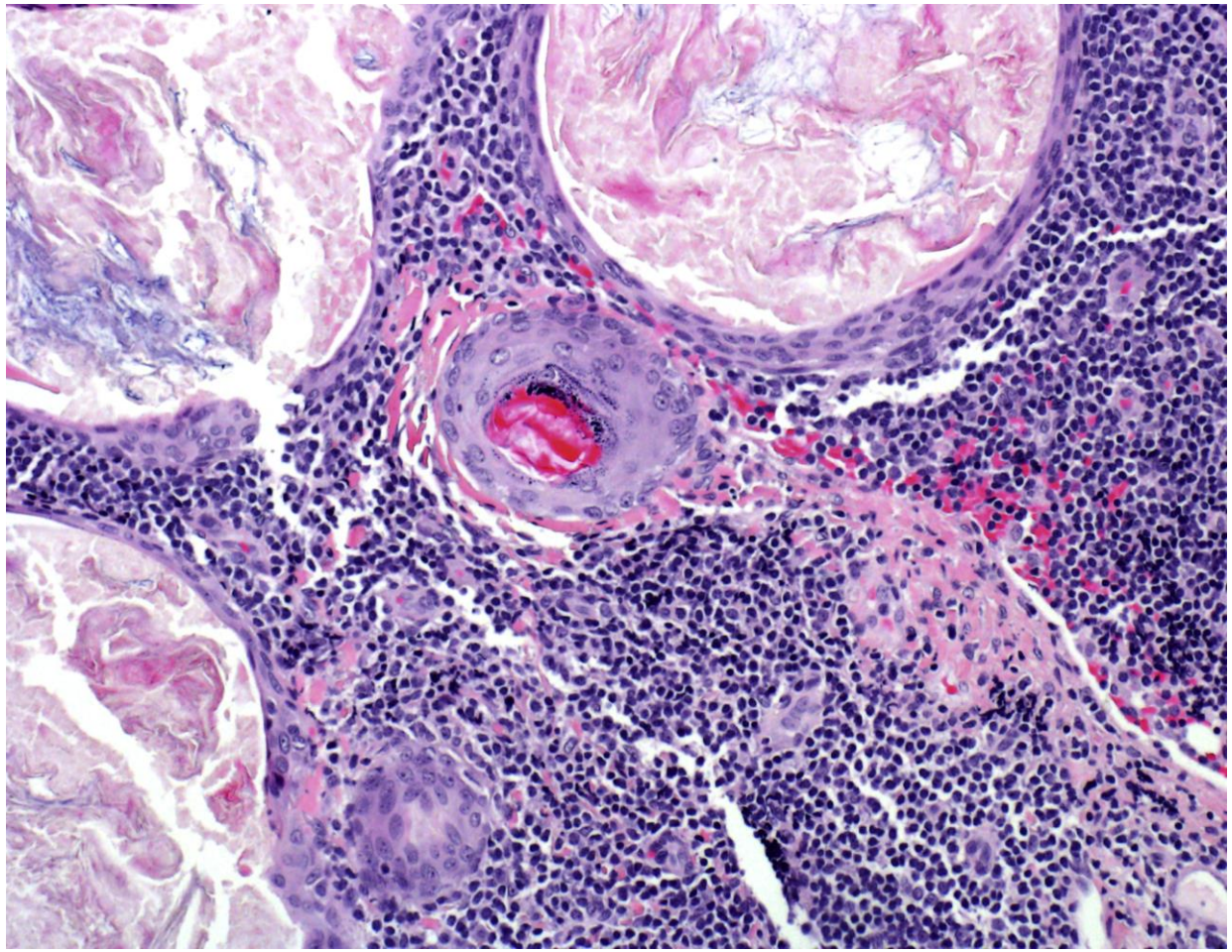
Pathologic features

- Lack gross pathologic findings
- Microscopic

Located within the lymph node parenchyma or capsule, and can be multiple or individual

Squamous-lined cysts with central keratinaceous debris or individual squamous nests

The cells lack atypia or mitotic activity



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Differential Diagnosis

- Metastatic squamous cell carcinoma

Uncommon H&N primary

Cutaneous squamous cell carcinoma of the upper extremities or trunk is unlikely to be an occult primary

- Sarcomatoid (metaplastic) breast carcinoma with a squamous component

Diagnosis

- Histology
- IHC: Not helpful unless it is (HPV)-related squamous cell carcinoma of the head and neck or anogenital region

Prognosis

- Lymph node squamous inclusions are benign. There have been no reports of malignancy arising from in axillary nodal squamous inclusion
- No additional treatment is required

Mixed Glandular-Squamous Inclusions

Pathologic Features

- Gross: Lack gross findings unless is florid or cystic
- Microscopically: Varying degrees of benign glands with benign squamous nests or squamous-lined cysts

Differential Diagnosis

- Metastatic breast adenosquamous carcinoma (very low risk of metastatic spread)

Diagnosis

- Histology
- IHC: Myoepithelial cell layer in the glandular component excludes the diagnosis of metastatic adenocarcinoma

Prognosis

- Mixed glandular-squamous inclusions are benign incidental findings in lymph nodes excised for other reasons
- There have been no reported instances of malignancy
- No treatment required

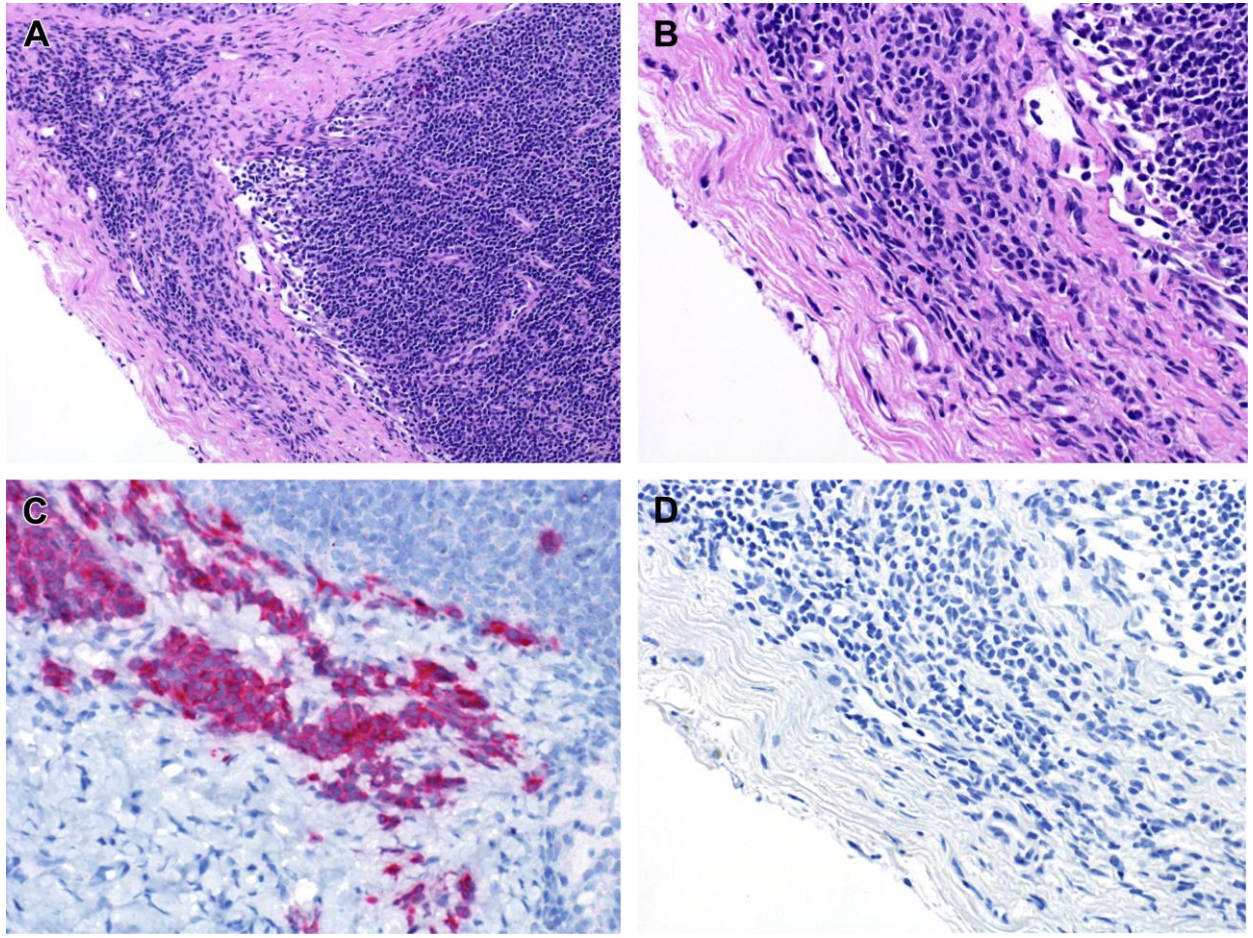
Non-Epithelial Inclusions: Nodal Nevi

Mechanism

- Mechanical transport of nevocytes
- Lymphatic drainage of nevocytes from the skin
- Aberrant embryogenesis

Pathologic Features

- Lack gross pathologic findings
- Microscopically, nodal nevi are located in the lymph node capsule and may extend into the lymph node fibrous trabeculae nodal nevi consist of bland, spindled nevocytes



Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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Differential Diagnosis

- Metastatic melanoma: This is particularly an issue because nodal nevi can occur in the sentinel nodes or regional lymph nodes excised as part of a melanoma staging procedure
- Metastatic spindle cell (sarcomatoid) carcinoma

Diagnosis

- Histologic features
- IHC

Nodal nevi: + Melan A, SOX10, and S100

- HMB45

Metastatic melanoma: + Melan A, SOX10, and S100 and HMB45

Metastatic desmoplastic melanomas: + SOX10, and S100

Mammary carcinomas can label for S100 and SOX10

Prognosis

Benign incidental findings. No additional treatment is necessary

Diagnosis	Histologic Features	Immunohistochemical Features	Differential Diagnosis
Mammary-type glandular inclusions	Bland mammary glands with associated myoepithelial layer	+ ER, GATA3, GCDFP, mammaglobin +/– S100 + p63, SMMHC (myoepithelial cells) - PAX8, WT1	Metastatic mammary carcinoma
Mullerian-type glandular inclusions	Bland glands with ciliated cells admixed with intercalated (peg) cells	+ ER, PAX8, WT1 - GATA3, GCDFP, mammaglobin, S100 - p63, SMMHC (myoepithelial cells)	Metastatic mammary or gynecologic carcinoma
Squamous inclusions	Bland squamous nests or squamous-lined cysts	+ p63, CK5/6 +/– GATA3 - ER, GCDFP, mammaglobin, PAX8, WT1, S100, SMMHC	Metastatic squamous cell carcinoma, or metastatic metaplastic/sarcomatoid mammary carcinoma
Nodal nevi	Bland, spindled nevocytes located within lymph node capsule	+ Melan A, SOX10, S100, MITF - HMB45, cytokeratins, ER, GATA3, GCDFP, mammaglobin, PAX8, WT1	Metastatic melanoma, or metastatic spindle cell (sarcomatoid) carcinoma

Take home point

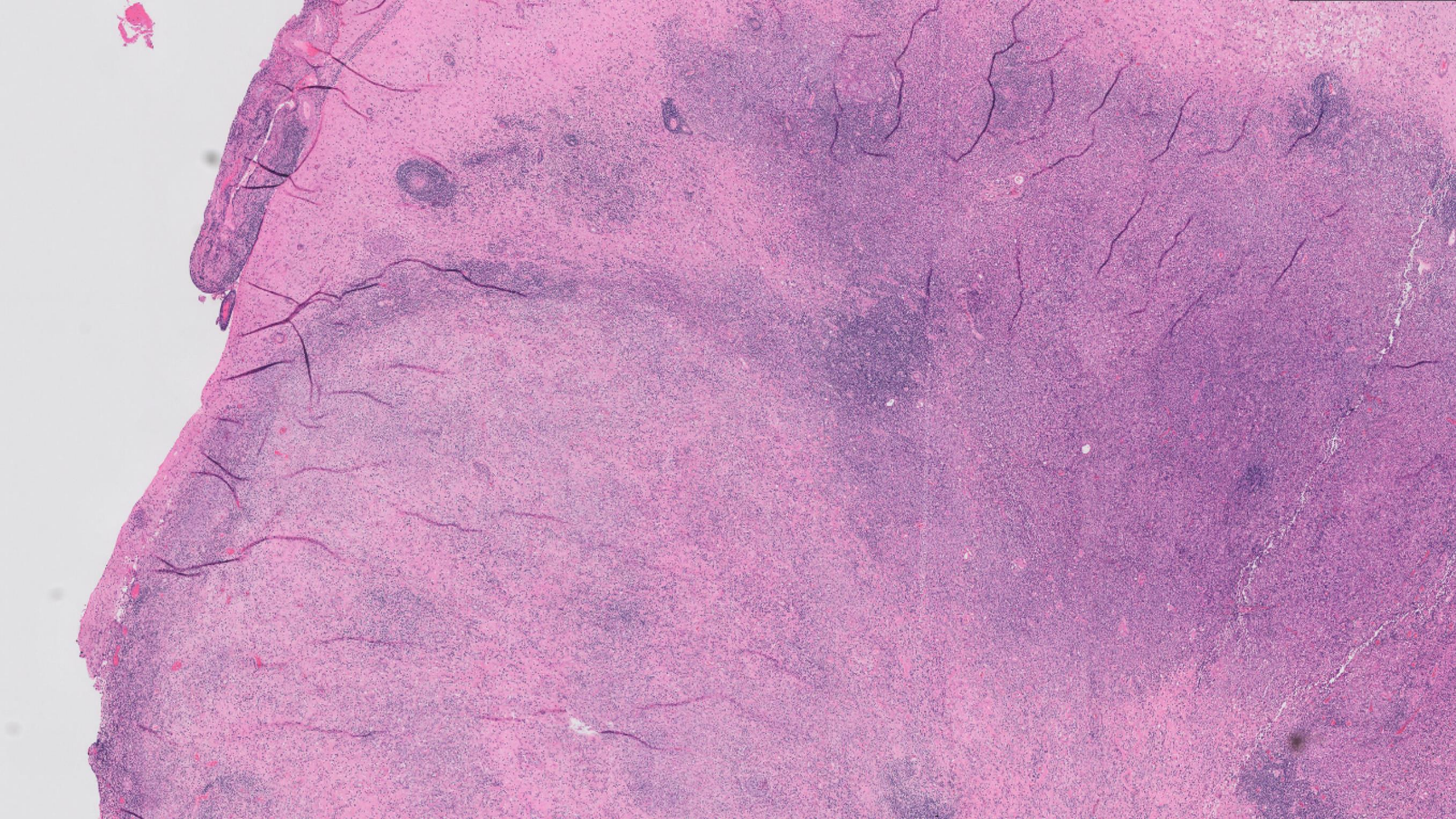
- Important **diagnostic pitfall** in breast cancer staging
- **Awareness and proper IHC use** prevent misclassification as metastatic carcinoma
- These inclusions are **benign, incidental findings** with no prognostic or therapeutic consequence

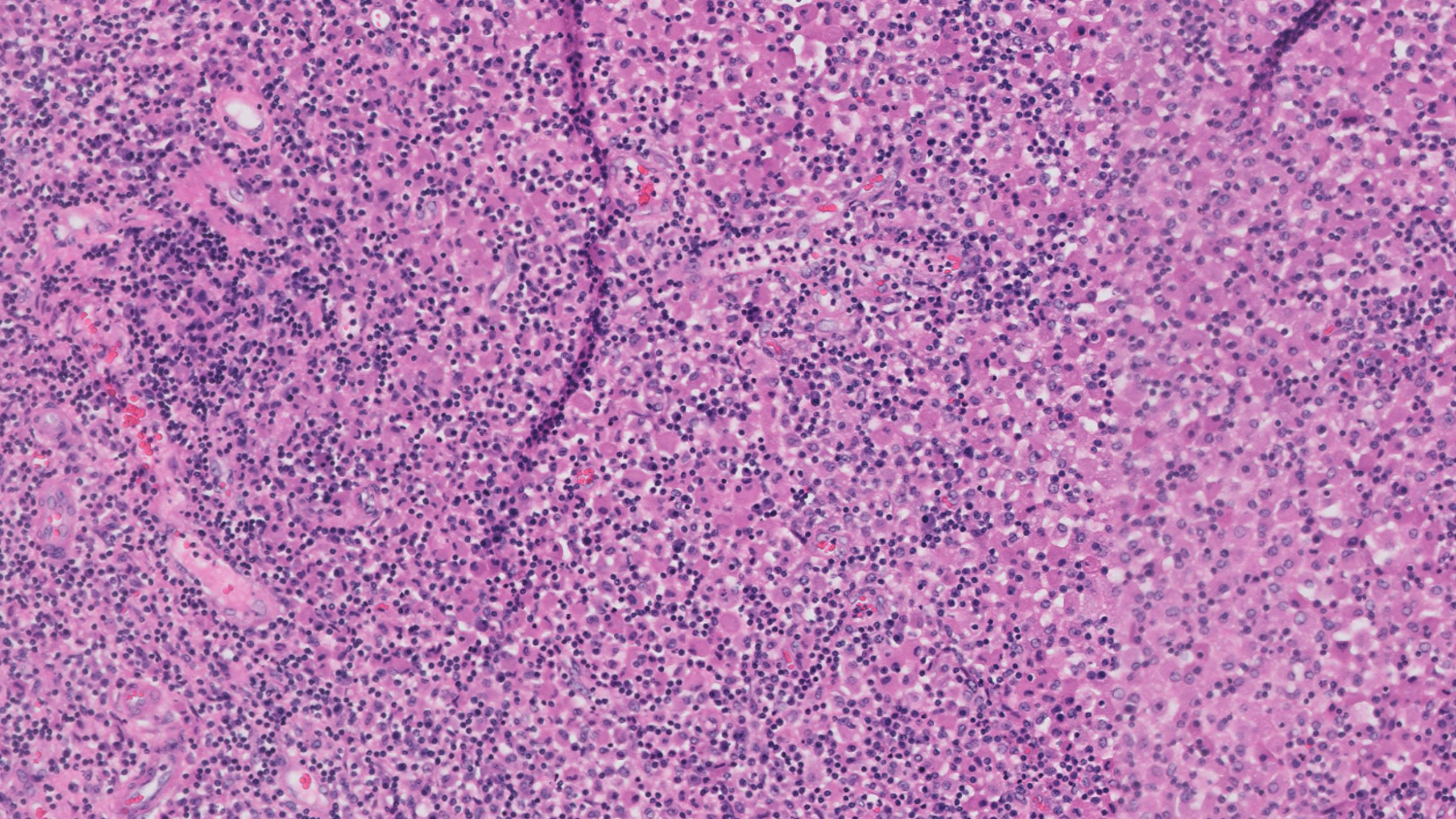
- Cimino-Mathews A. Axillary Lymph Node Inclusions. Surg Pathol Clin. 2018 Mar;11(1):43-59. doi: 10.1016/j.path.2017.09.004. Epub 2017 Nov 29. PMID: 29413659.
- Commander LA, Ollila DW, O'Connor SM, Hertel JD, Calhoun BC. Ductal Carcinoma In Situ Simultaneously Involving the Breast and Epithelial Inclusions in an Ipsilateral Axillary Lymph Node. Int J Surg Pathol. 2018 Sep;26(6):564-568. doi: 10.1177/1066896918763899. Epub 2018 Mar 21. PMID: 29560779.
- Nielson KJ, Guo R, Solanki MH, Sturgis CD. Ductal Carcinoma Arising in a Squamous Epithelial Inclusion Cyst within an Axillary Lymph Node: A Challenging Nodal Metastasis. Case Rep Pathol. 2023 Oct 31;2023:9979532. doi: 10.1155/2023/9979532. PMID: 37942426; PMCID: PMC10630003.

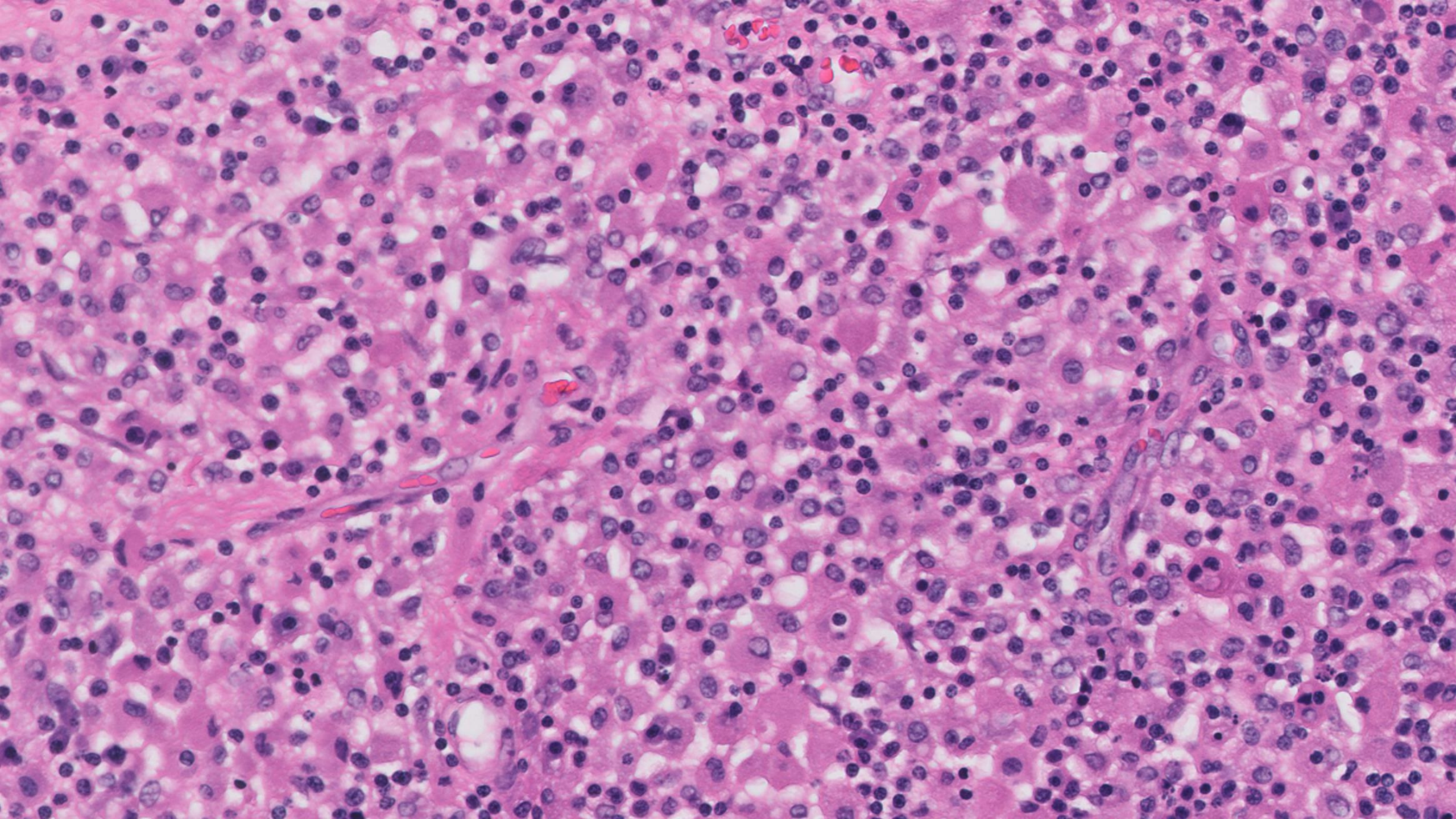
25-1205

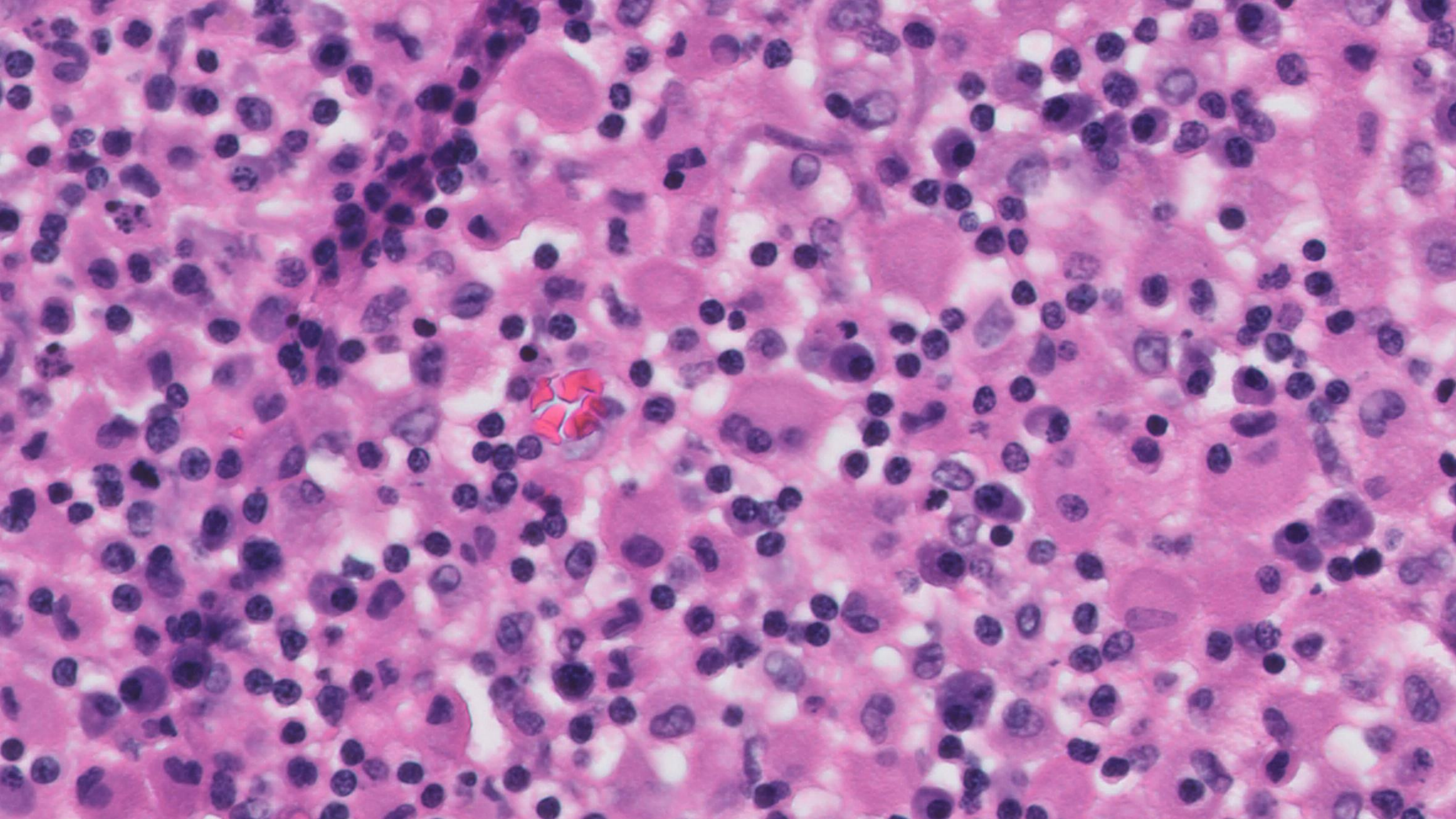
George de Castro and Anjanaa Vijayanarayana; UCSF

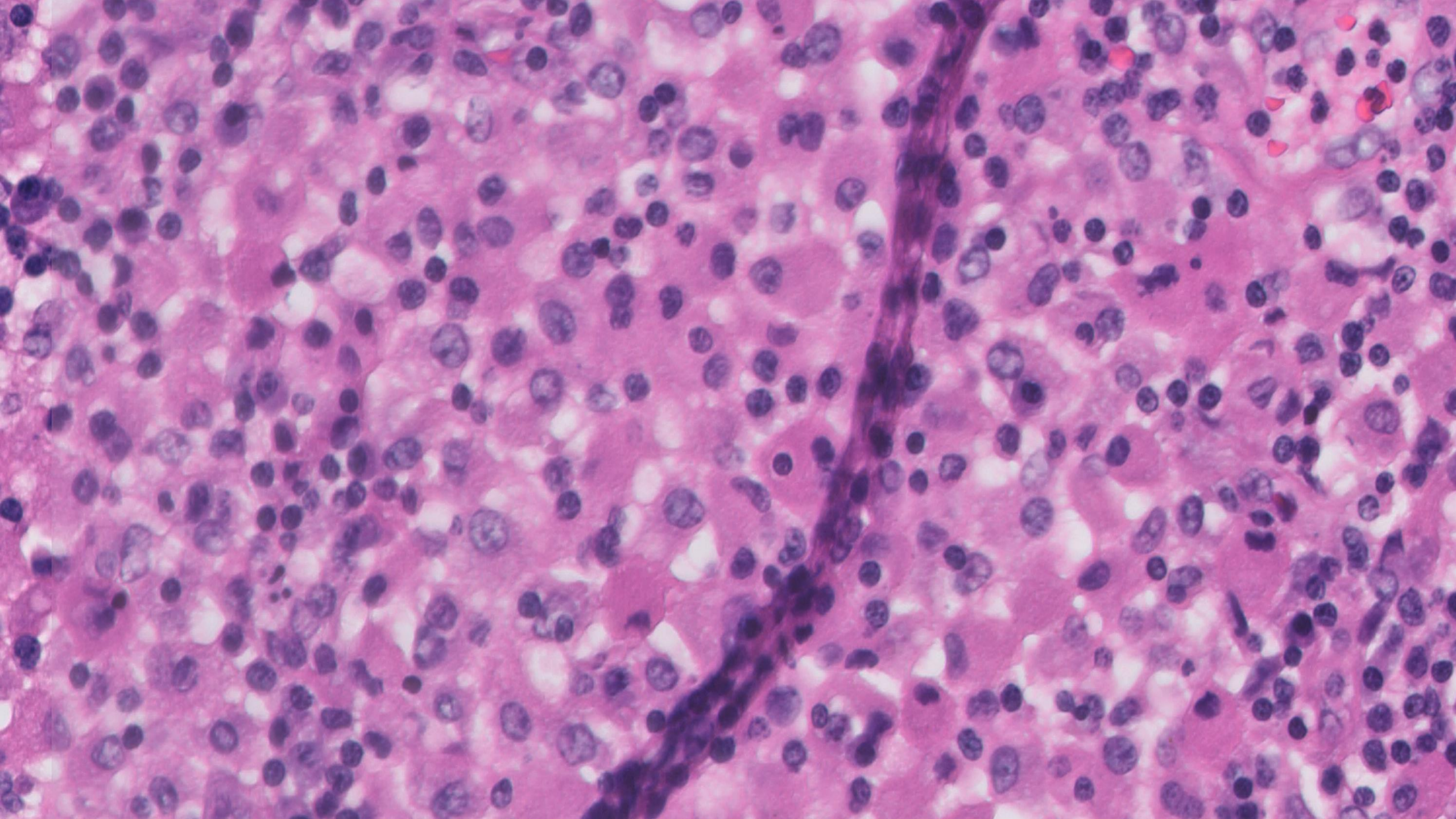
The patient is a 26-year-old woman with a right frontal lobe tumor.

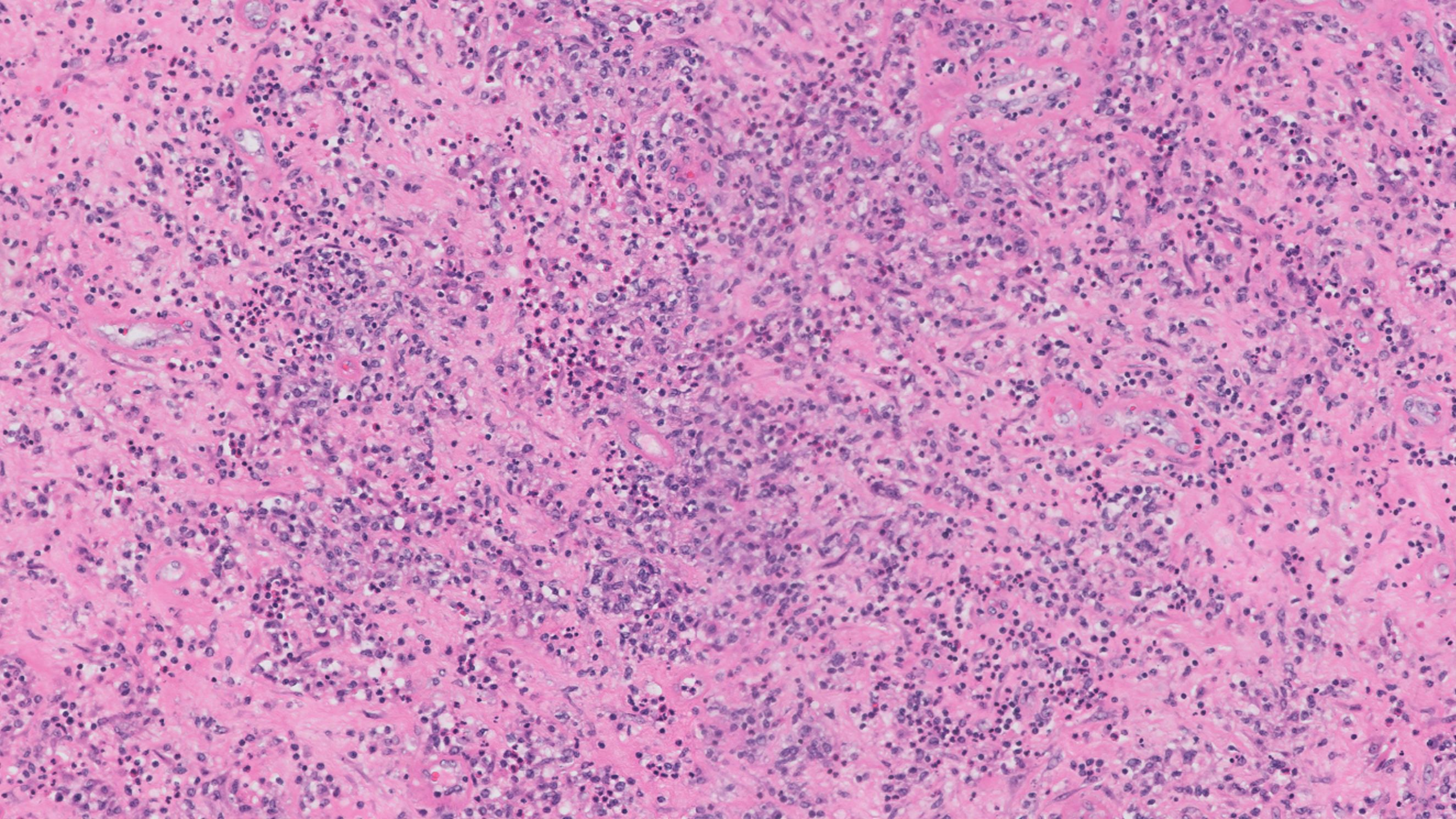


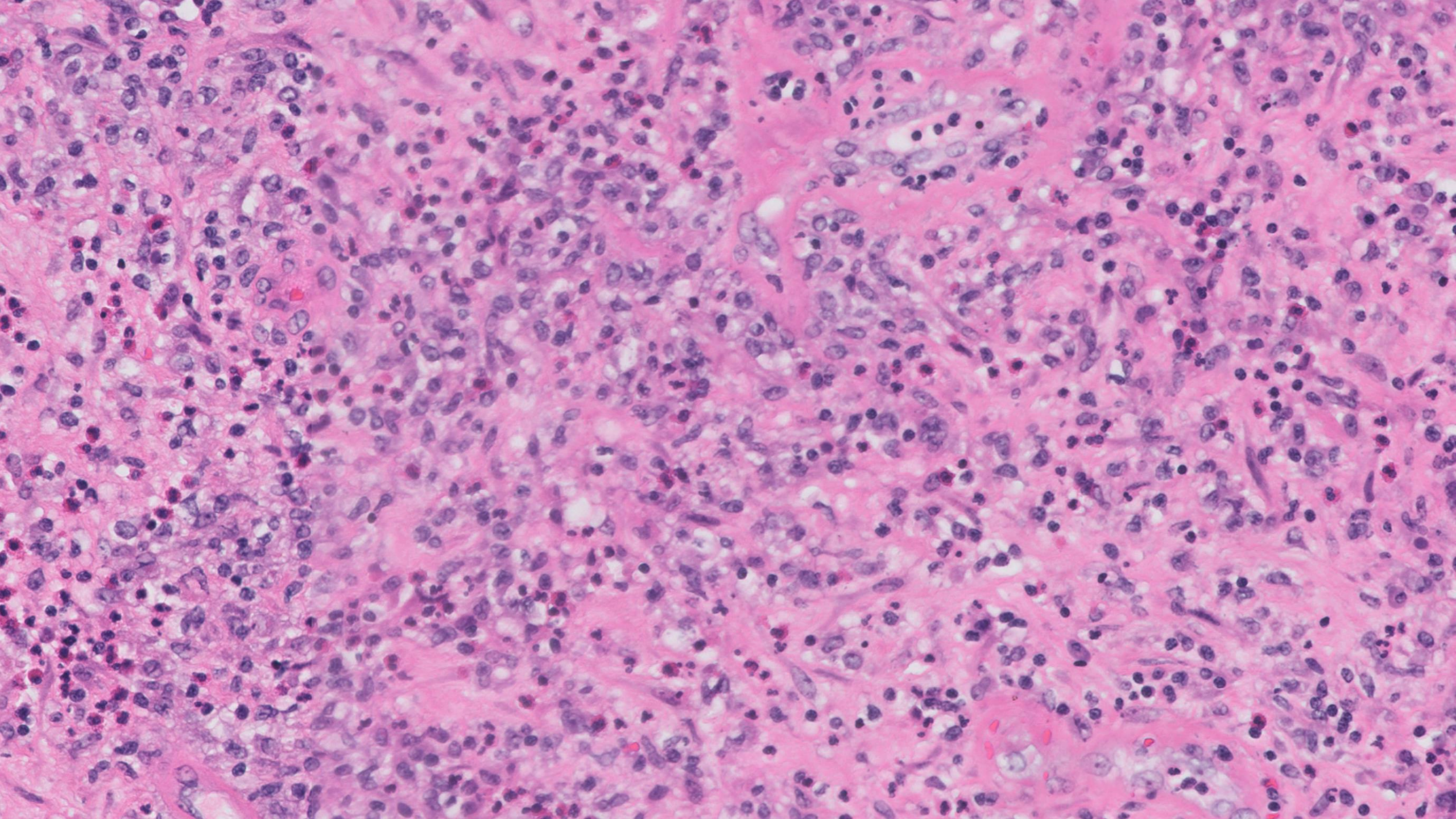


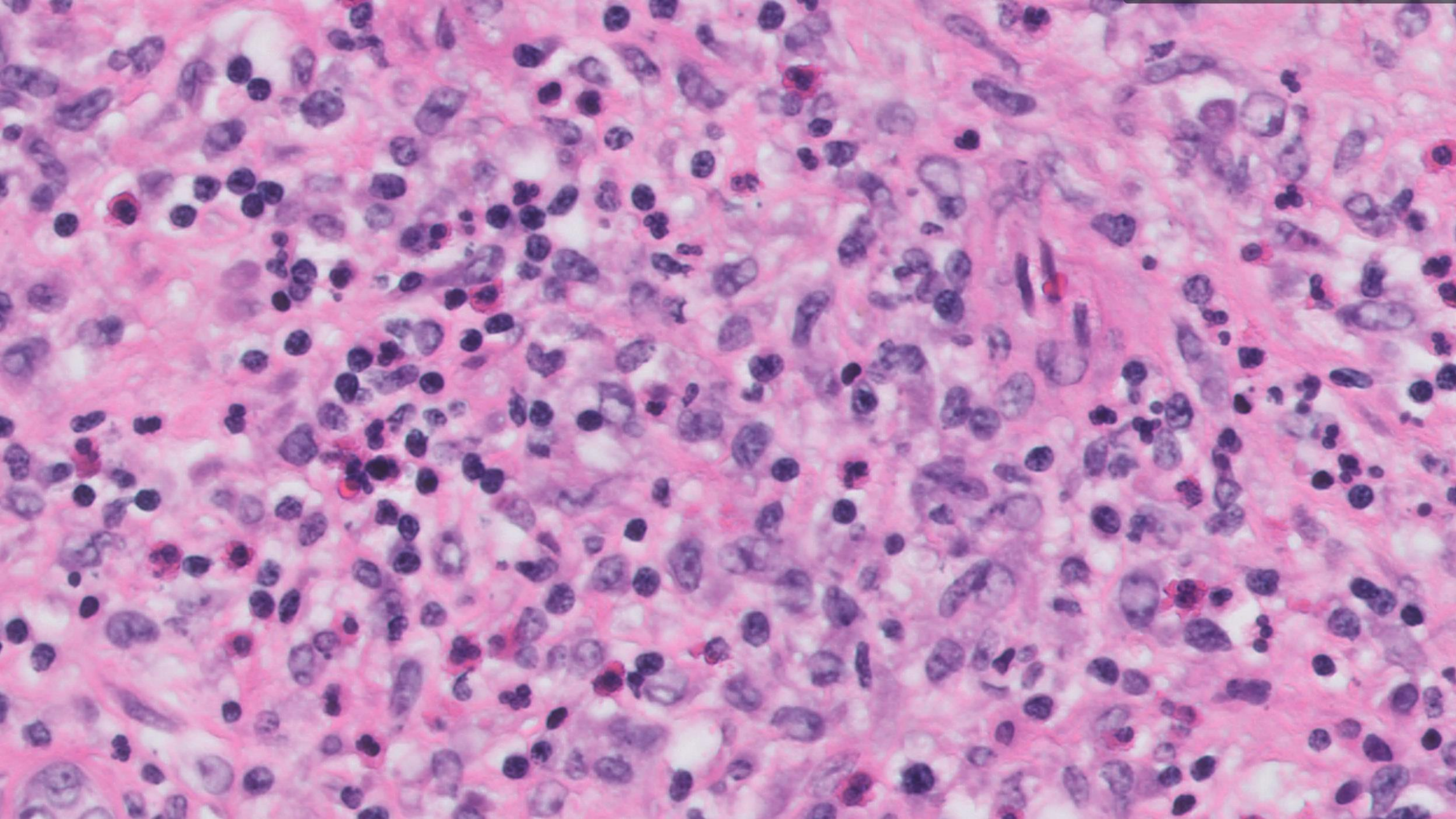


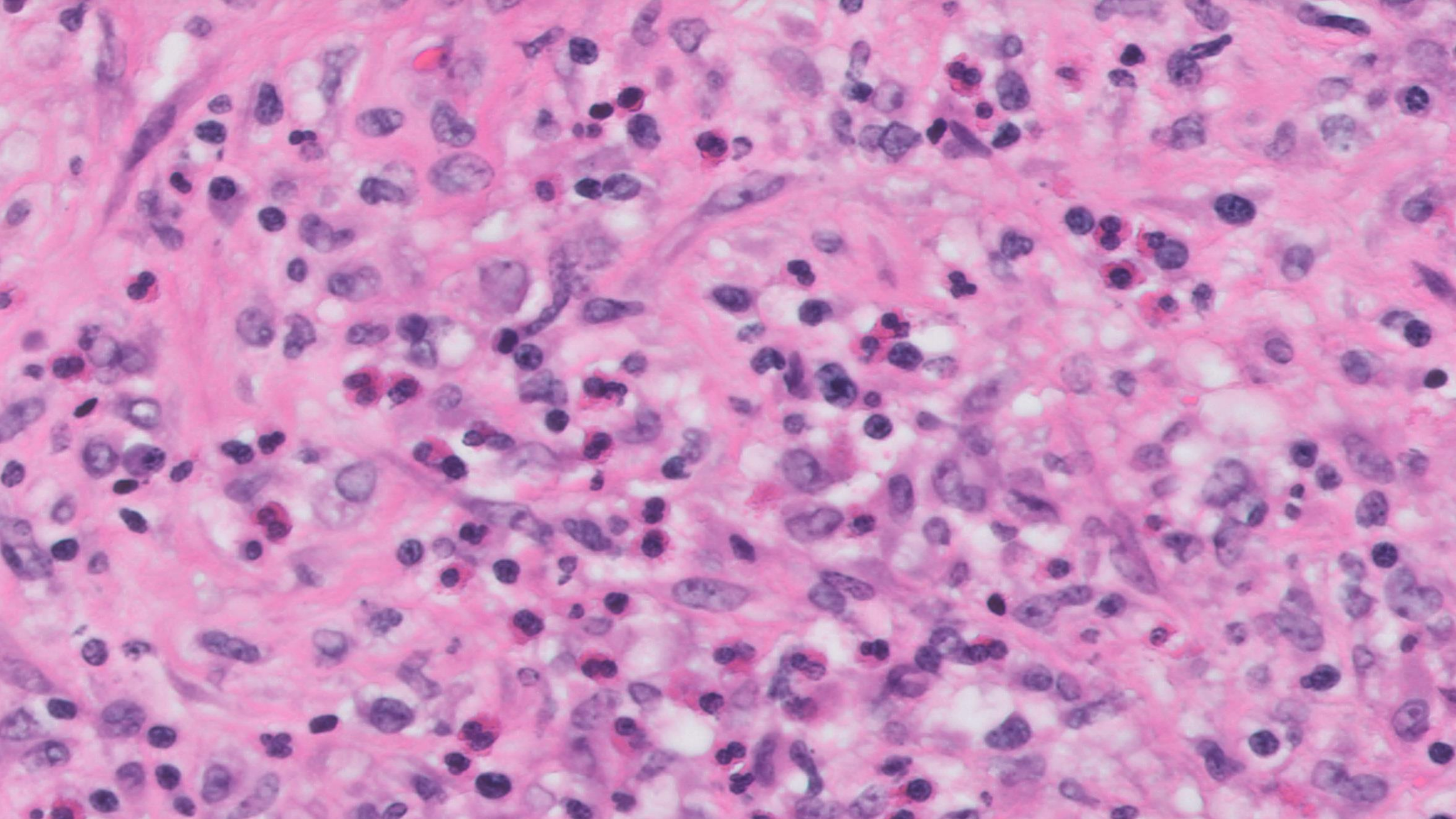




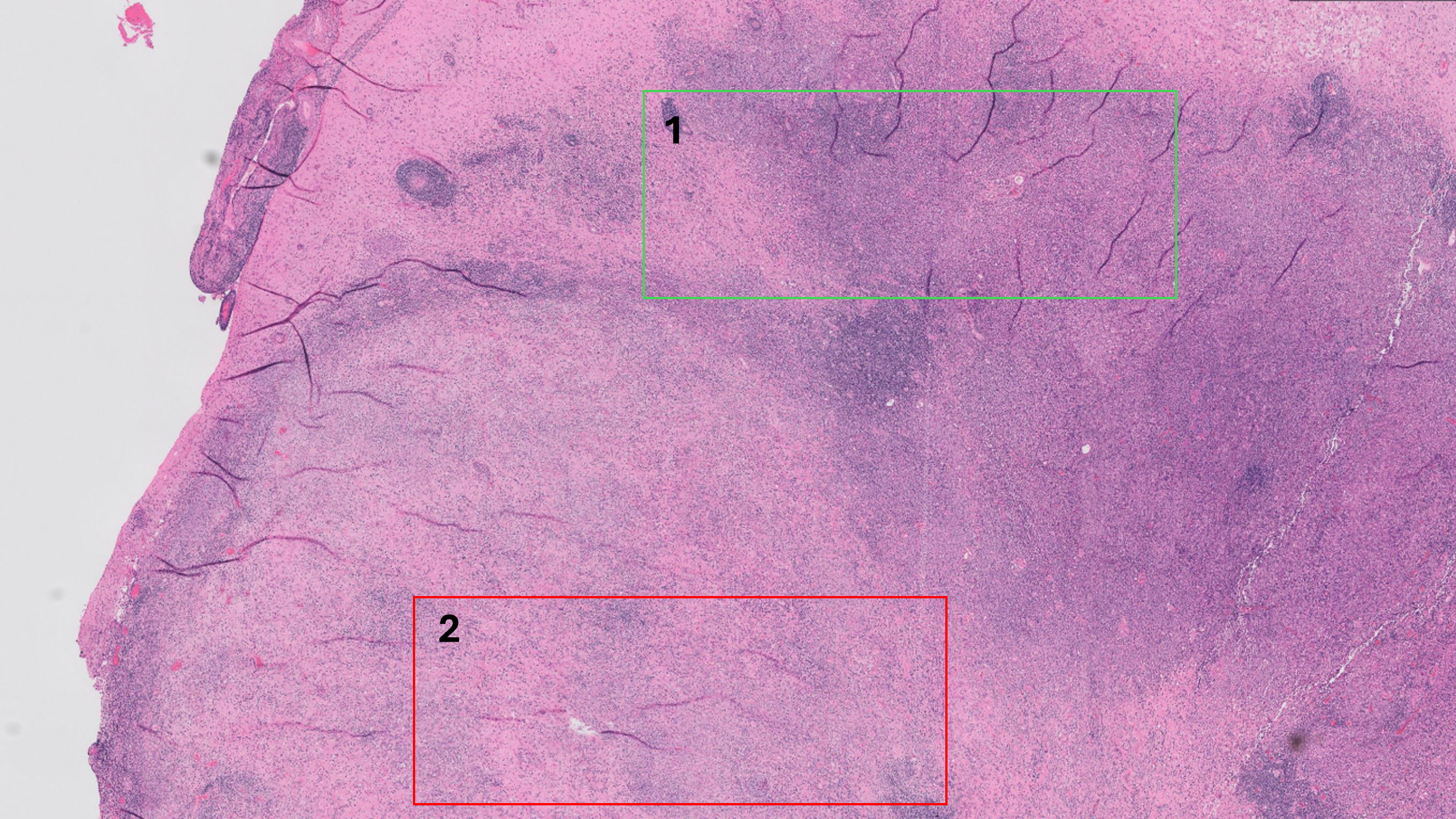








DIAGNOSIS?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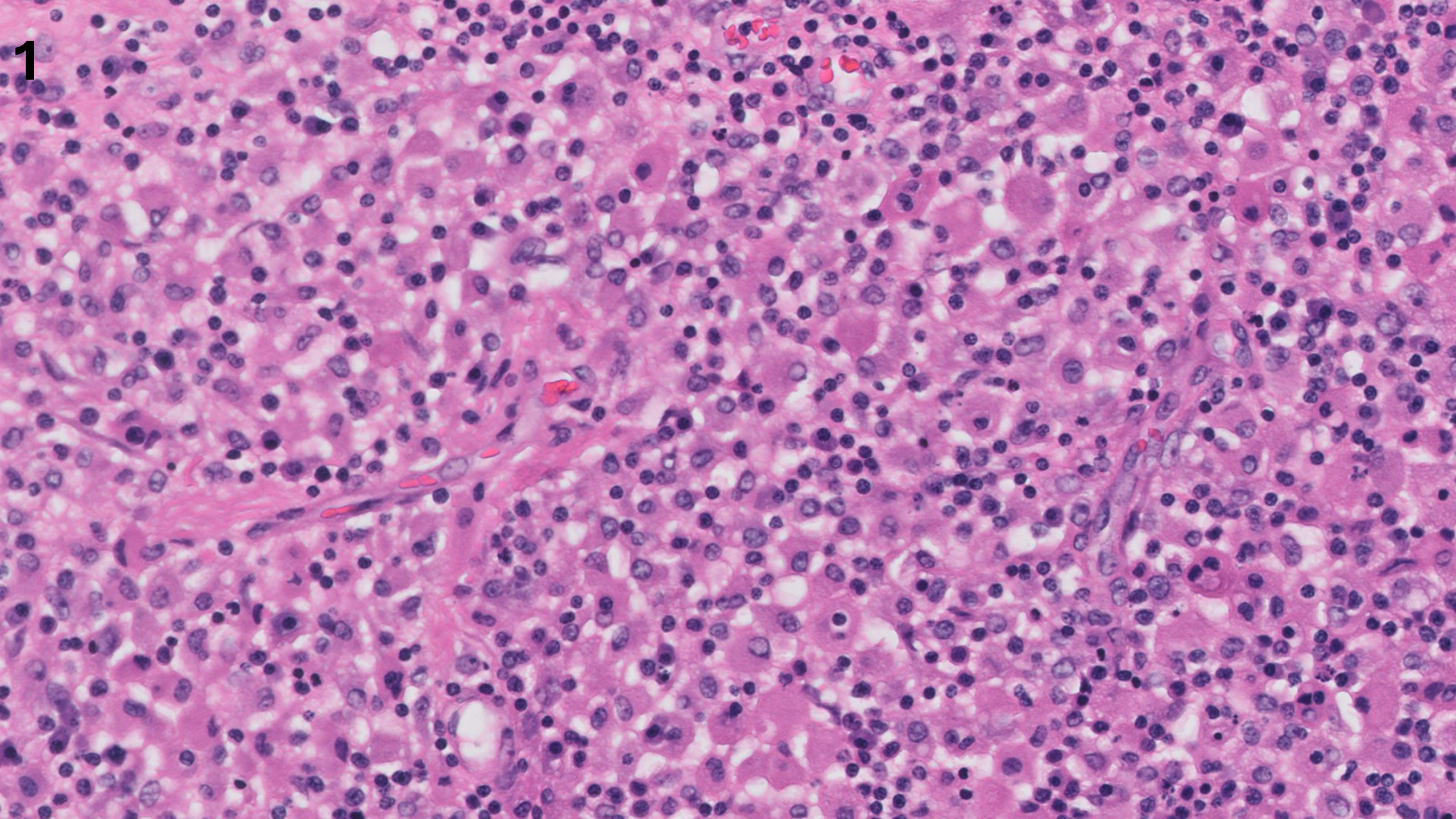
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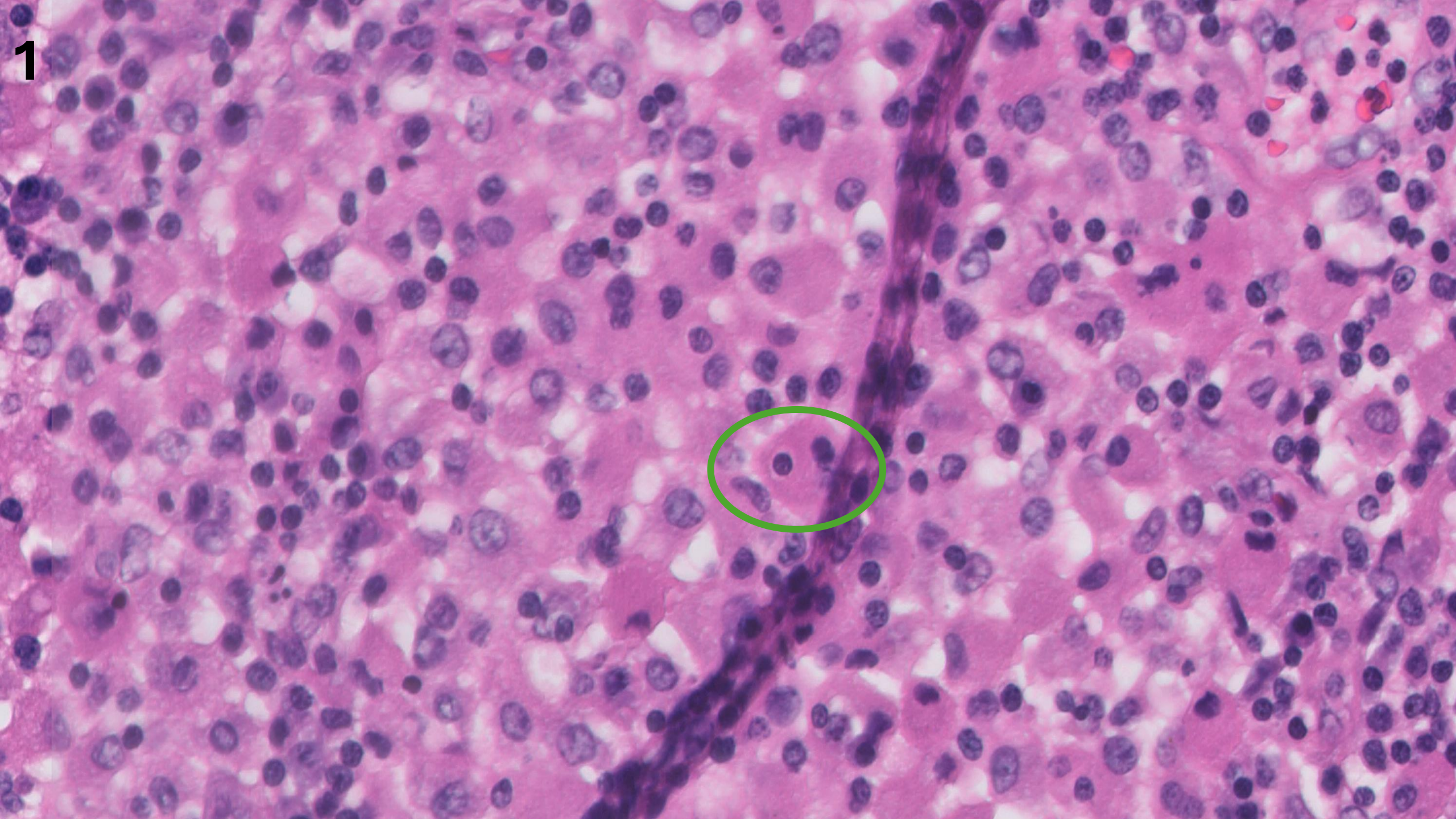
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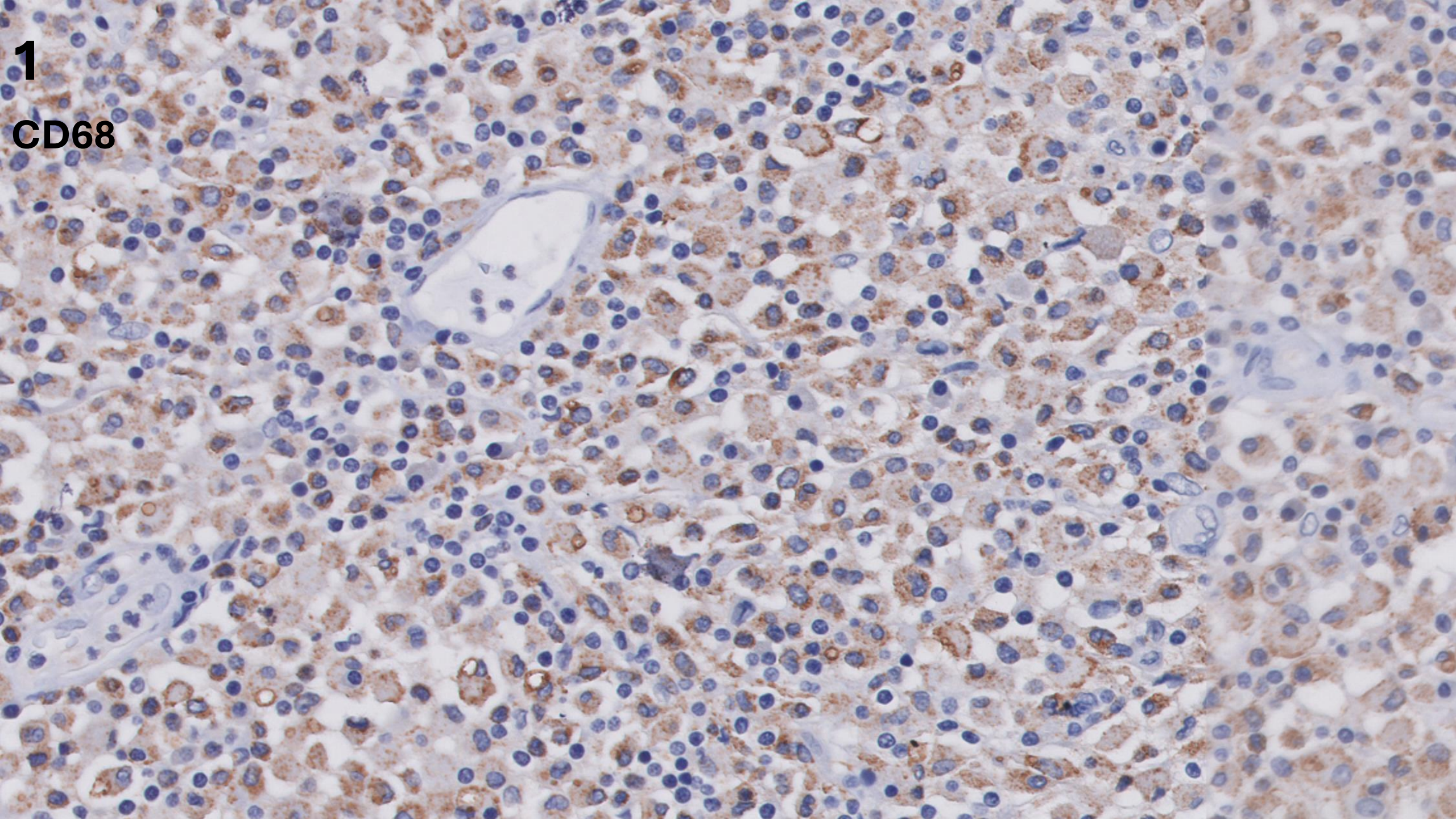
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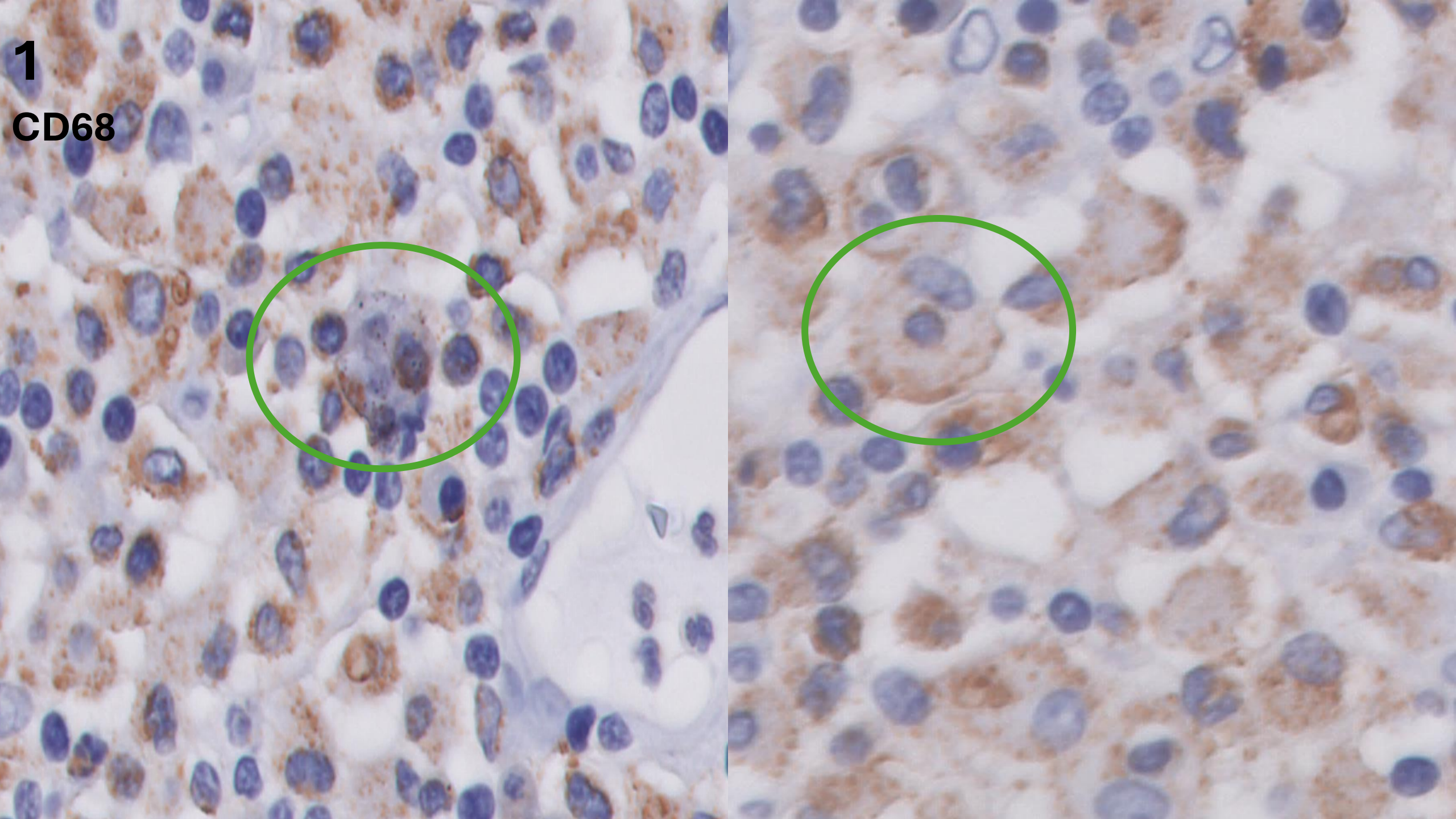
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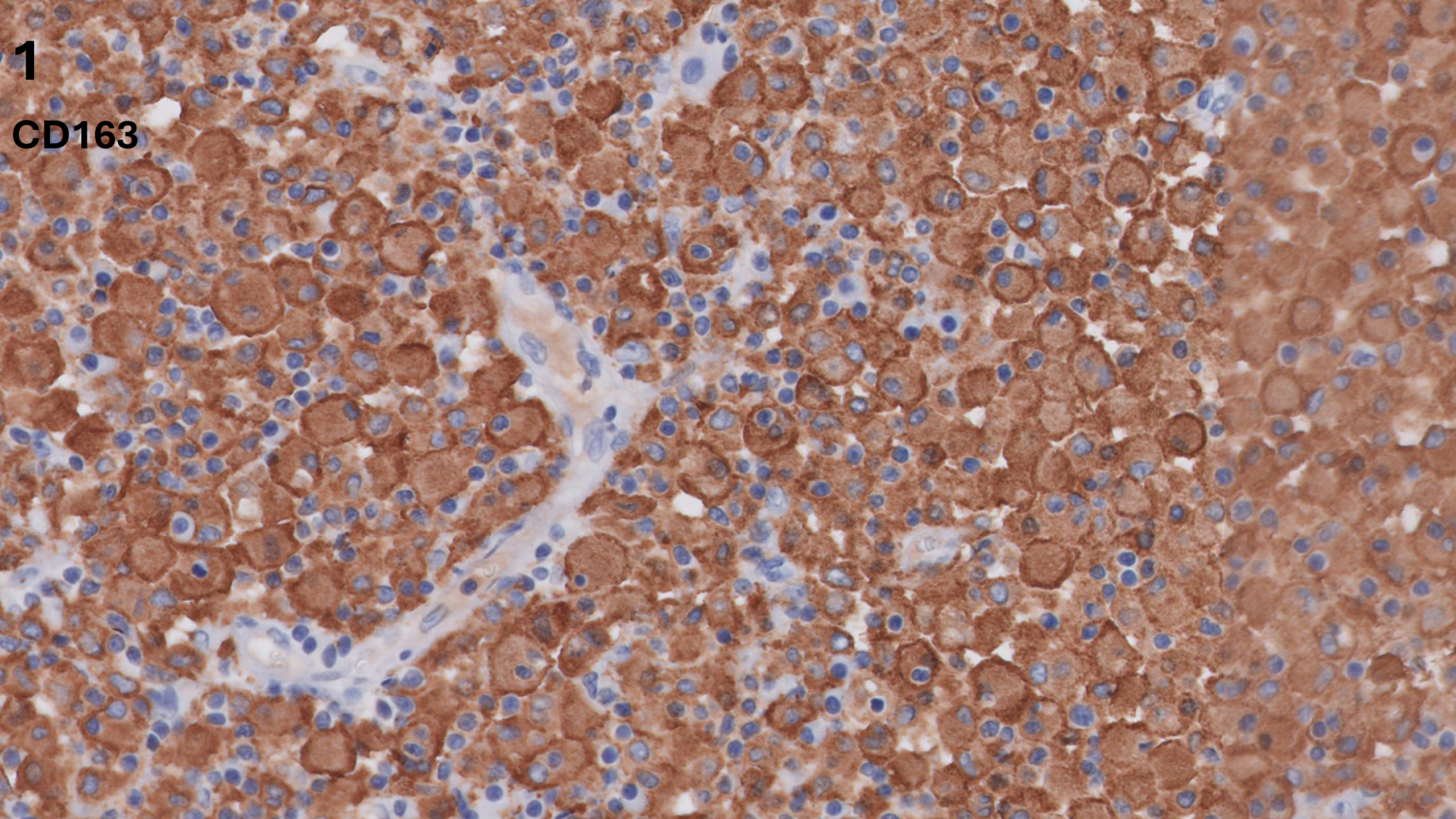
CD68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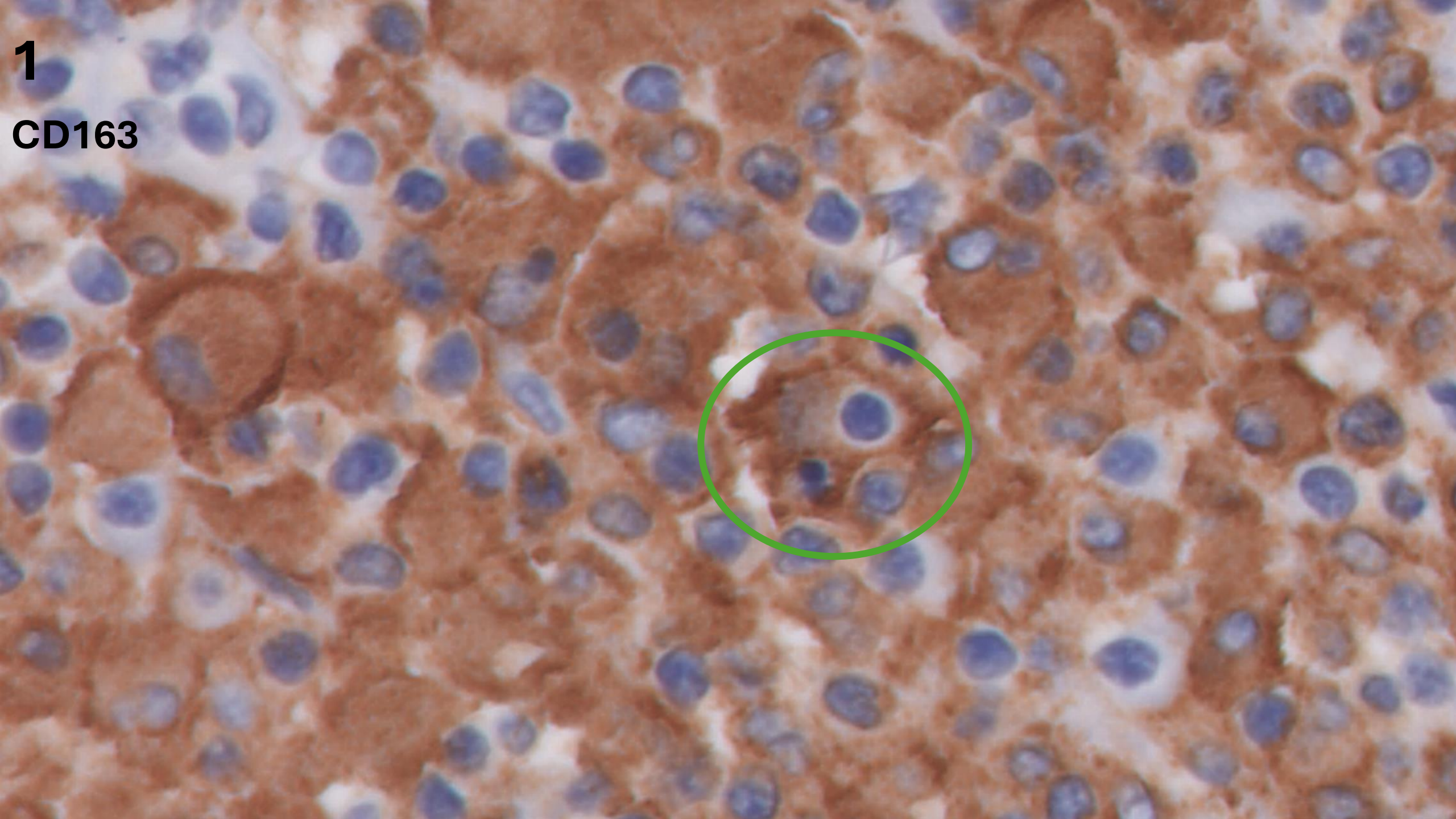
CD163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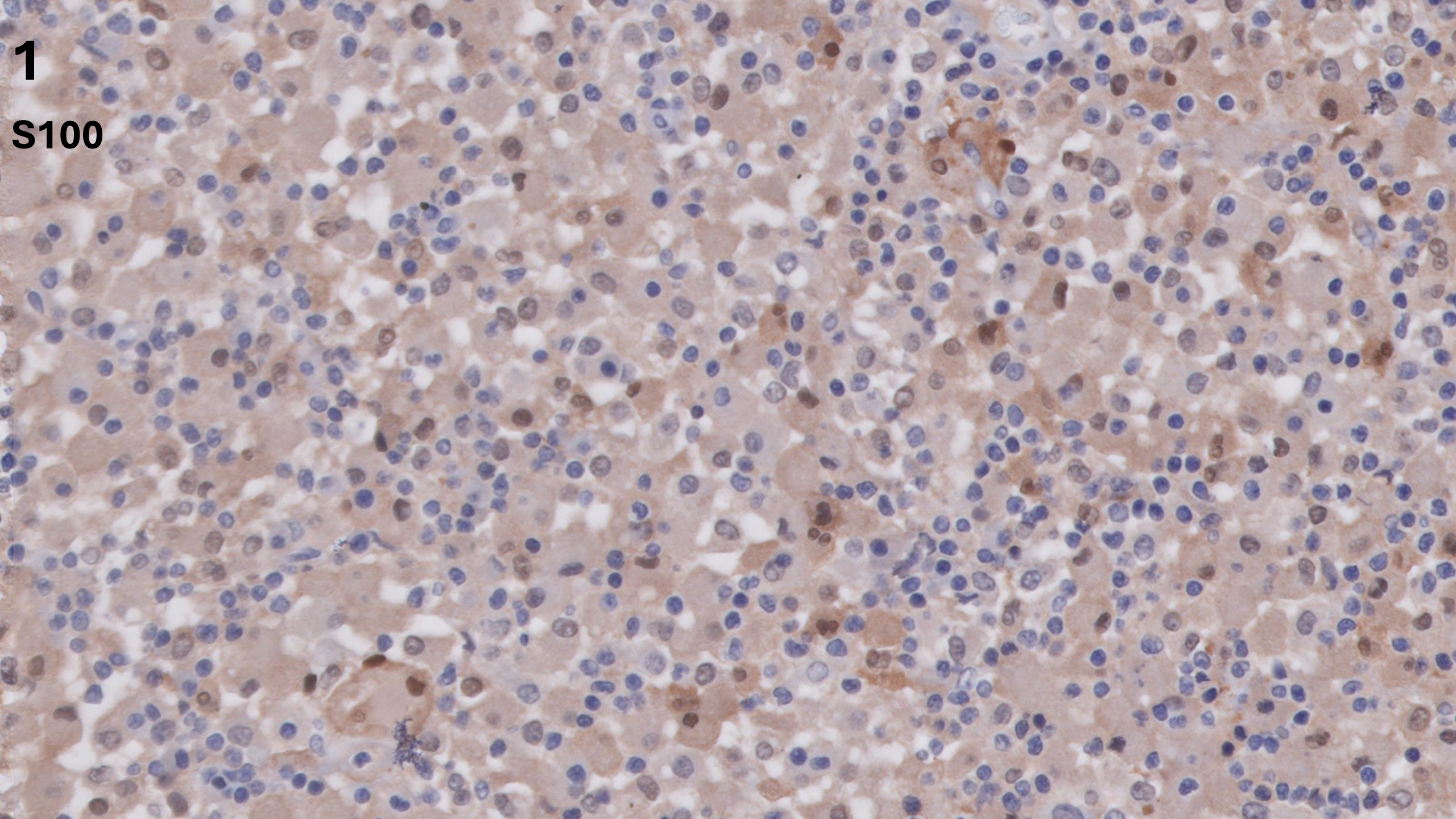
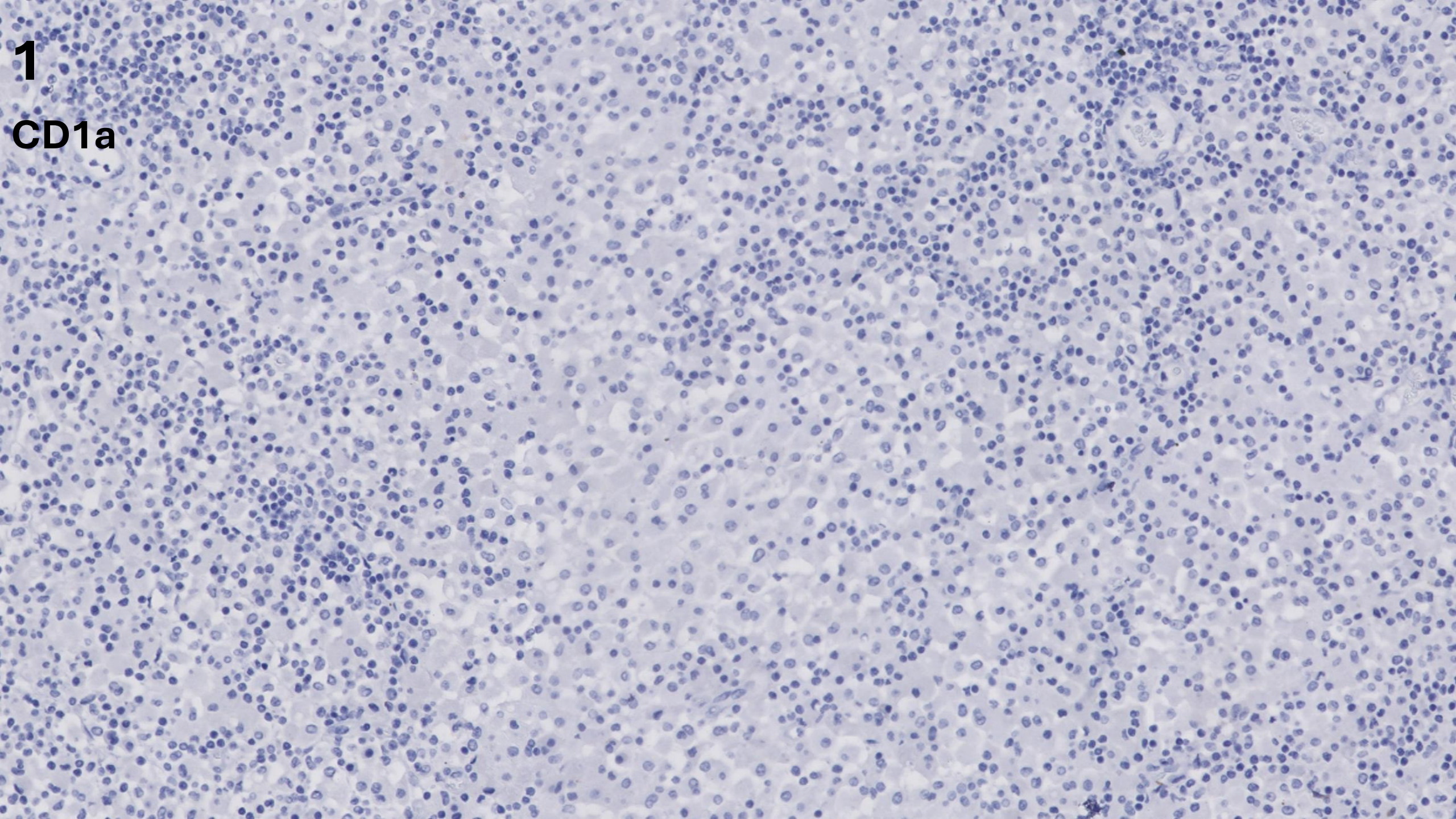
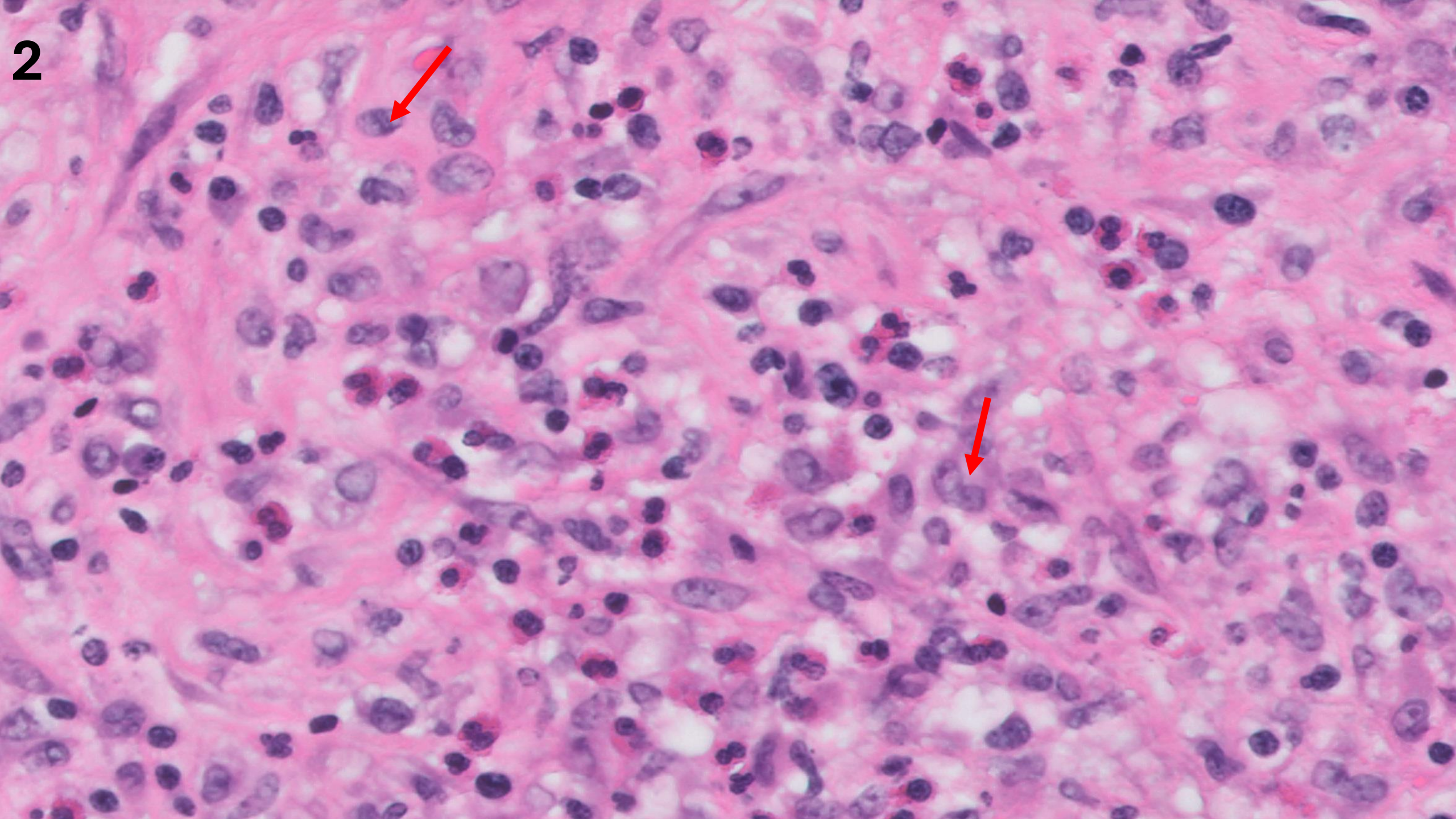
CD163


1
S100


1
CD1a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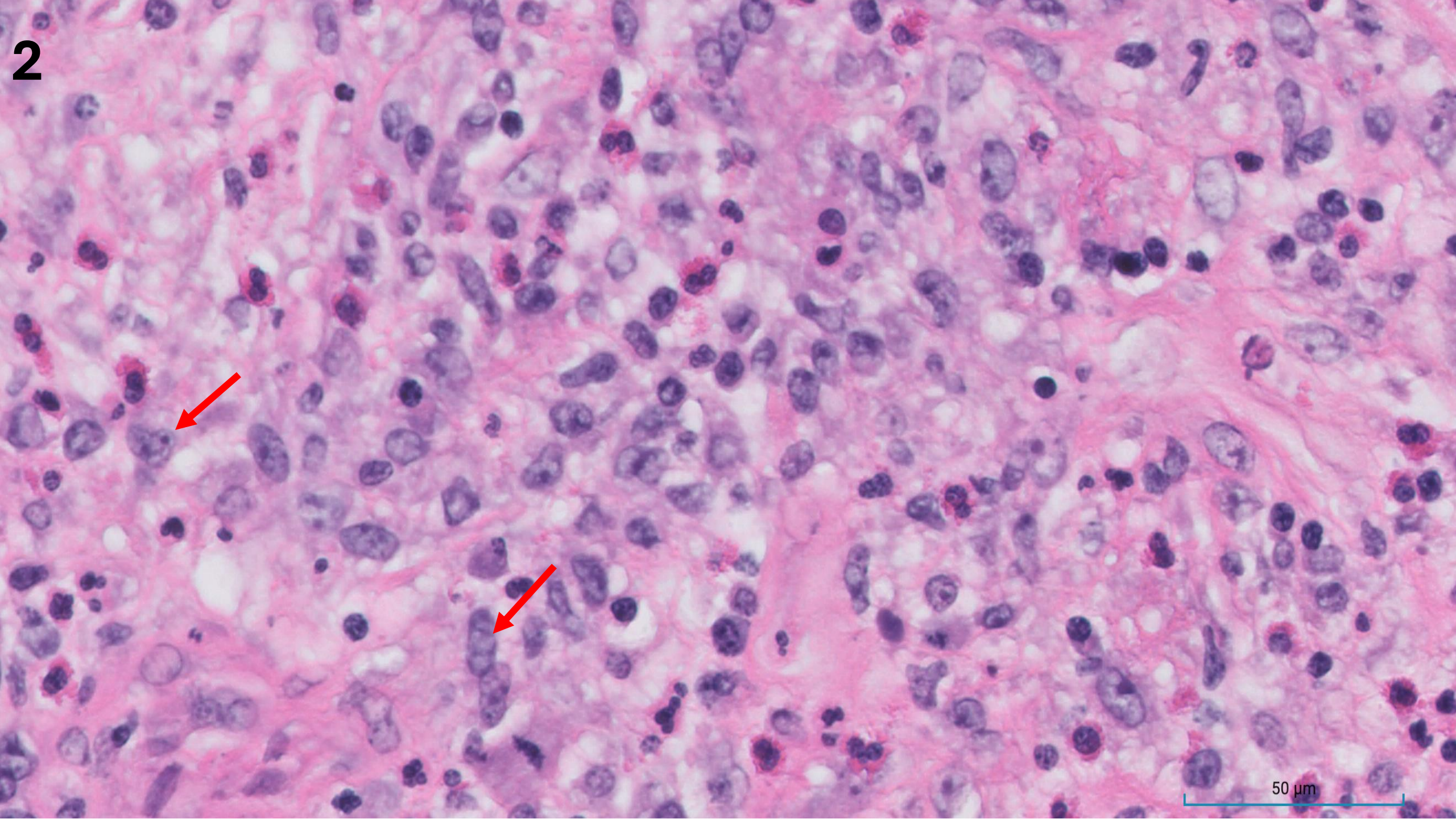
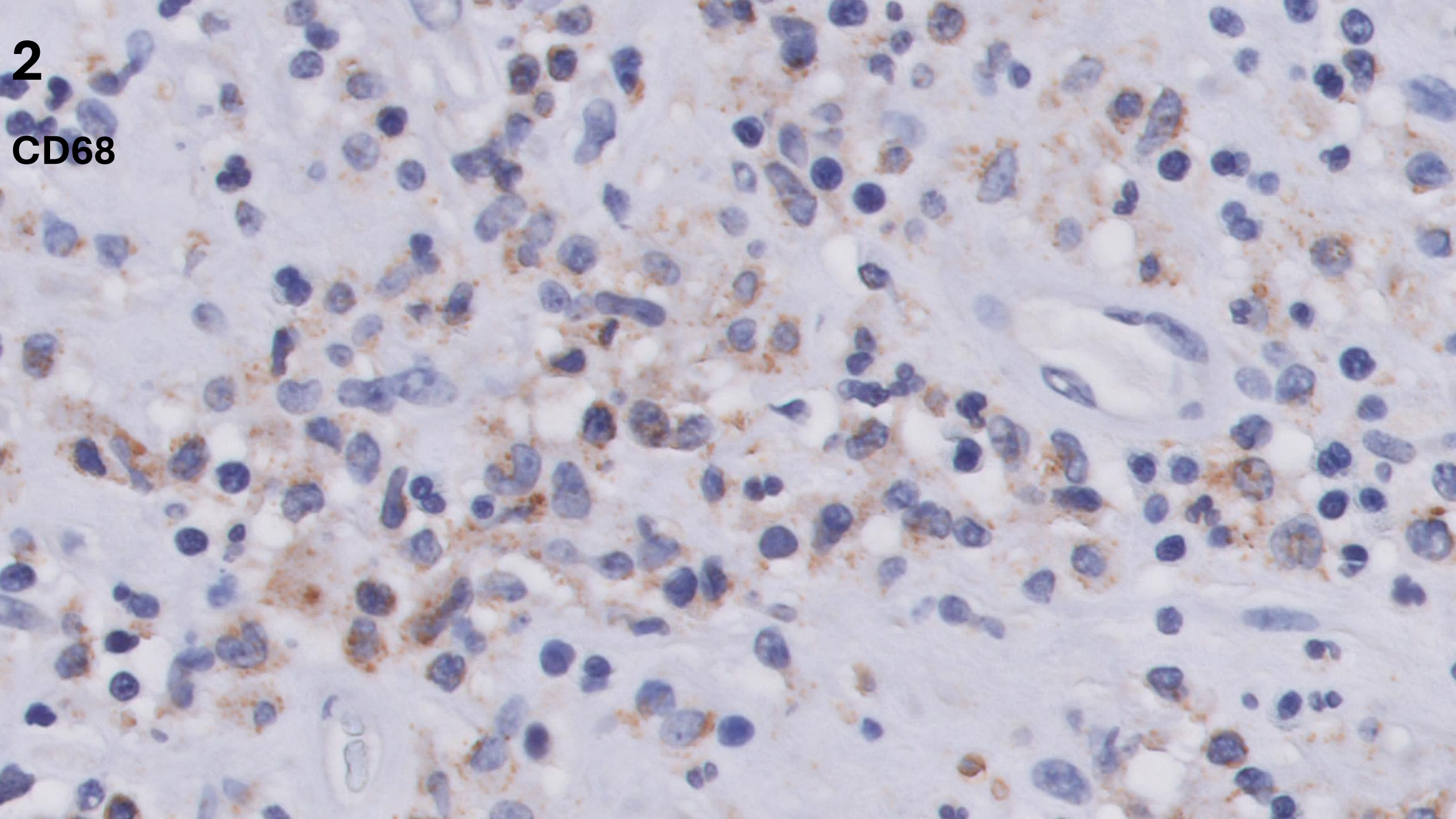

2
50 µm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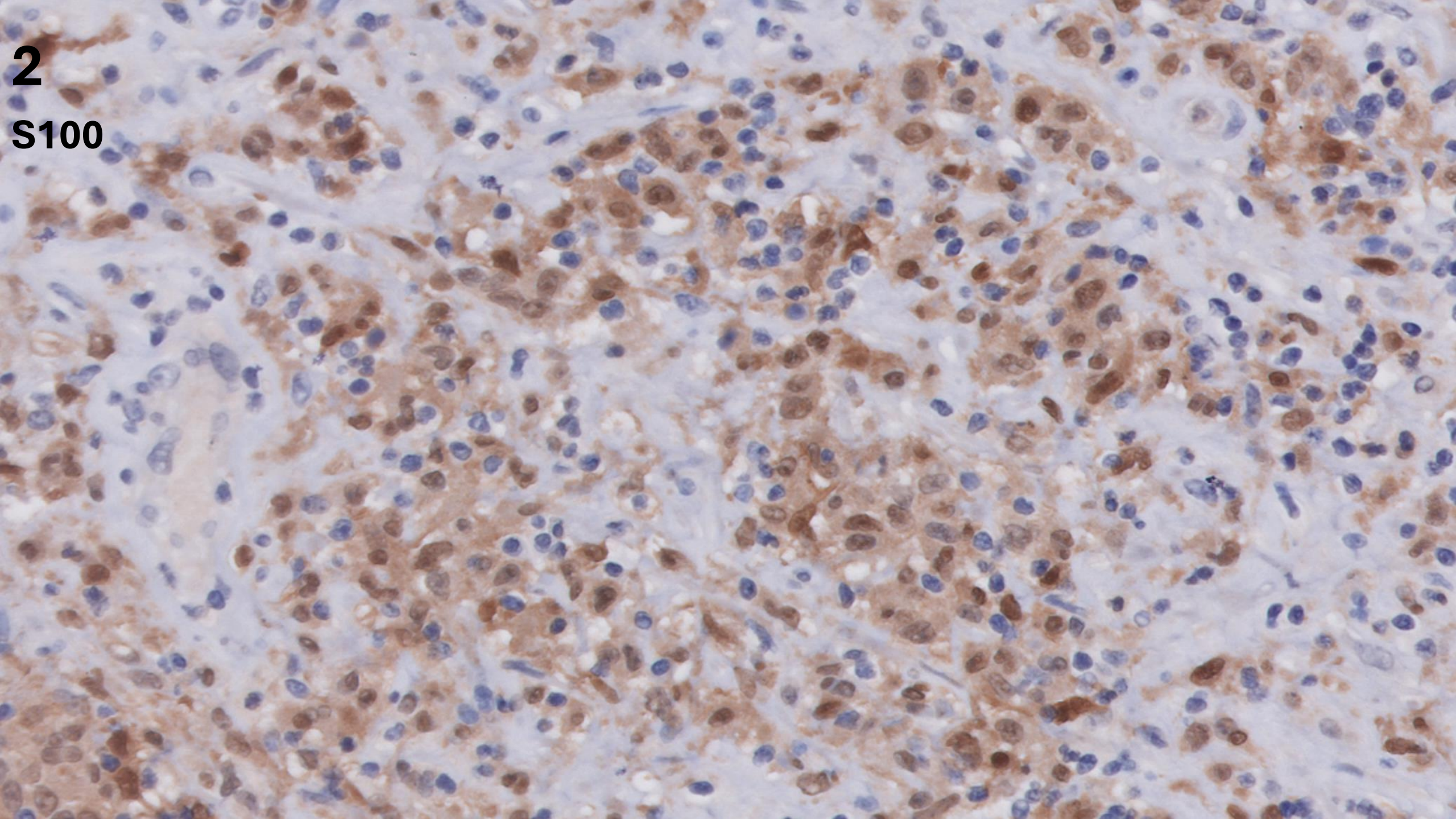
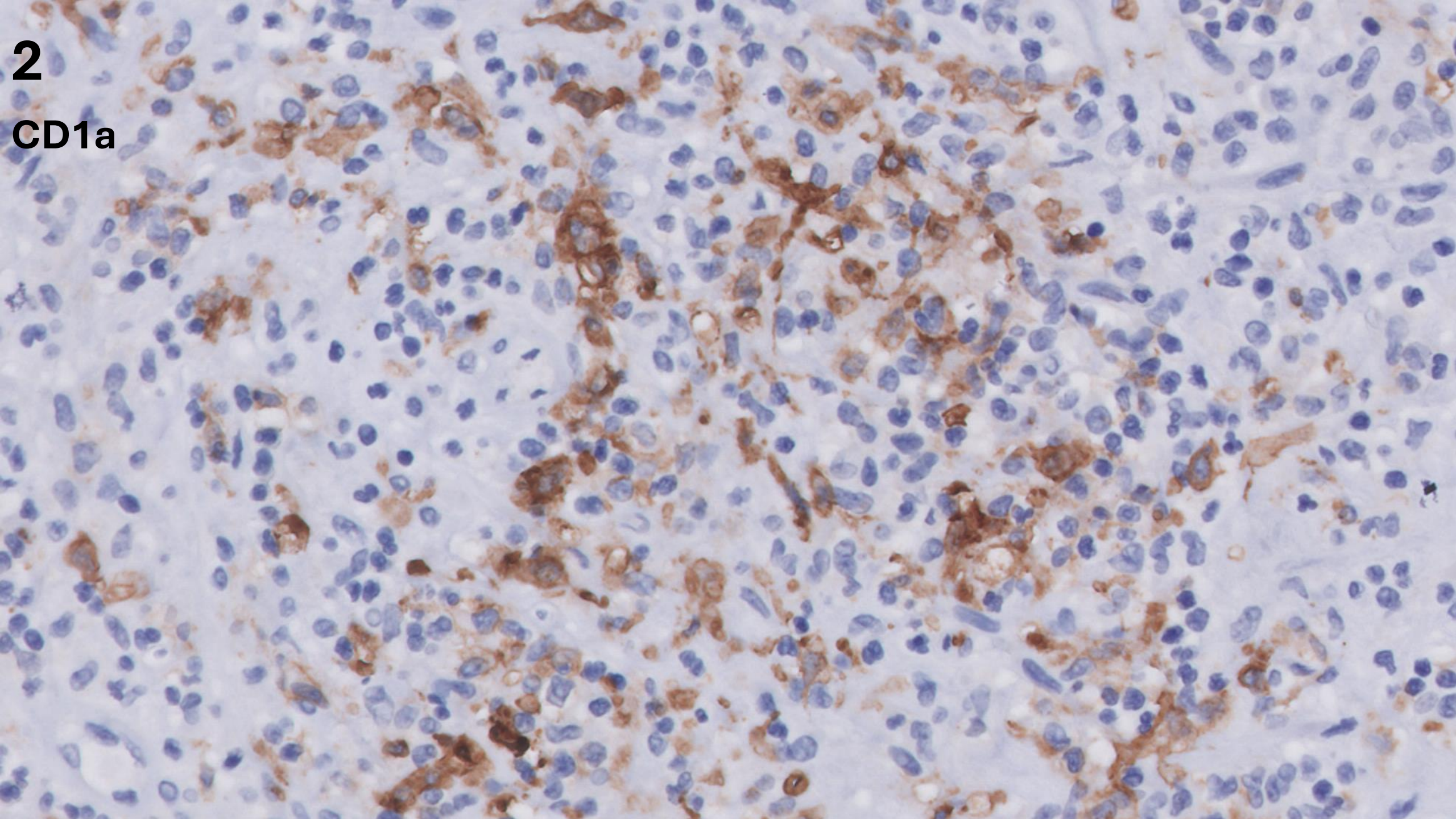
CD68


2
S100


2
CD1a

Brain, right frontal tumor:

Mixed histiocytic disorder with focal features of Rosai-Dorfman Disease (RDD) and Langerhans cell histiocytosis (LCH).

Case Discussion

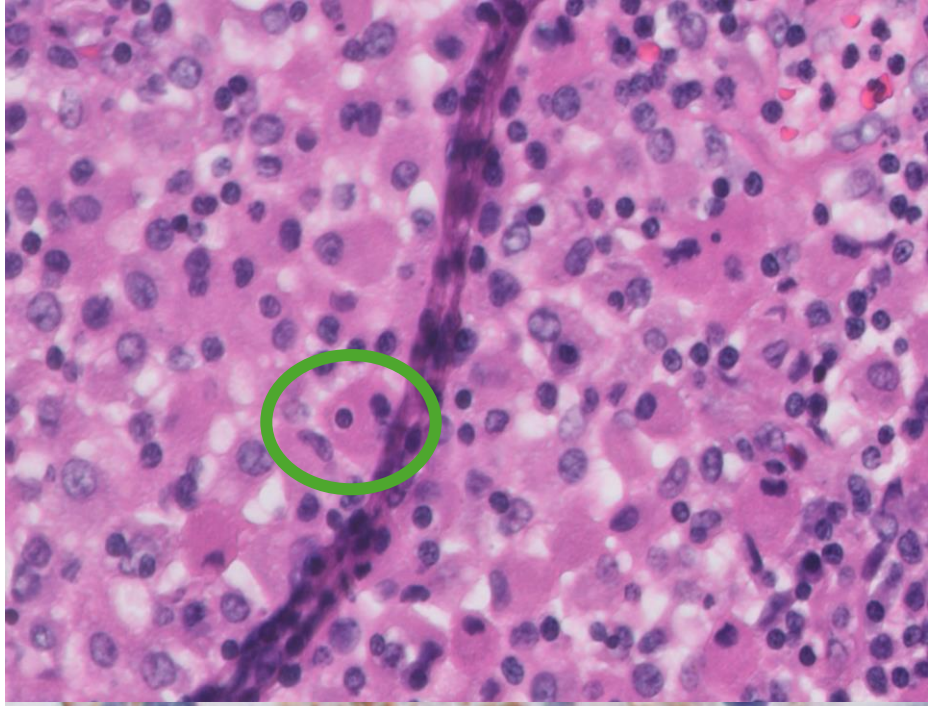
Rosai–Dorfman disease (RDD): Rare histiocytic neoplasm characterized the accumulation of large, S100-positive histiocytes with emperipolesis.

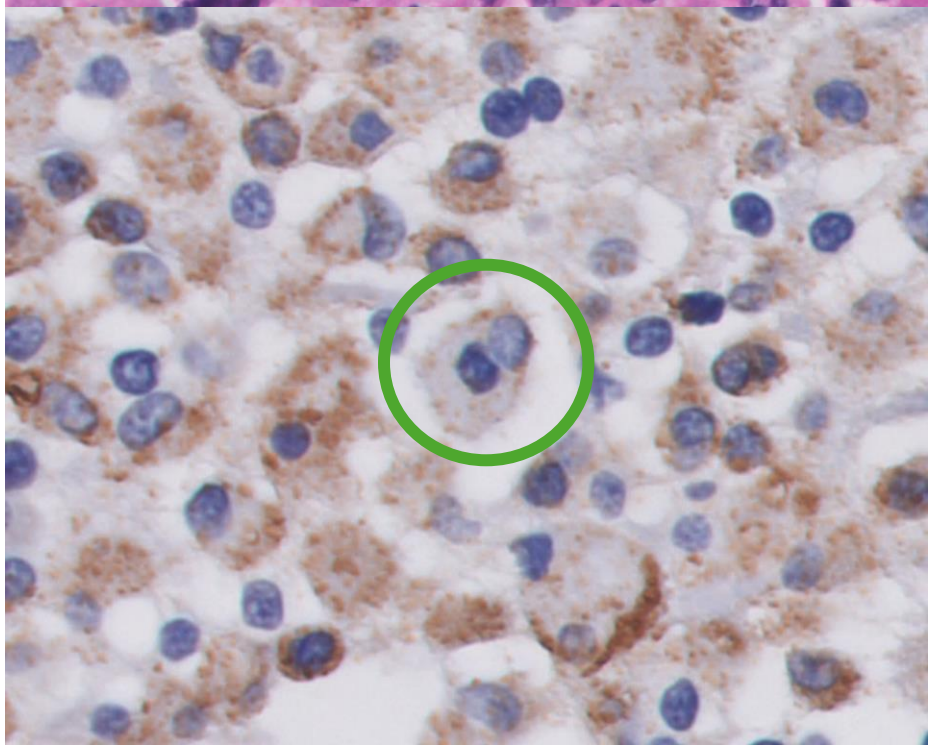
- Nodal RDD:
  - Younger patients (infants – 20 years old)
  - Commonly presents as slow-growing painless lymphadenopathy with B-symptoms
  - Lymph nodes can be huge, matted.
- Extranodal RDD: 43% of cases
  - Skin, head and neck, and CNS
  - Slightly older population (30-50 years old)
- Disease is often self-limited and resolves spontaneously
  - More aggressive clinical course associated with multifocal involvement

Case Discussion

RDD: Histopathology

- **Accumulation of large histiocytes with round nuclei and abundant eosinophilic-pale cytoplasm.**
- **Emperipolesis** (engulfment of intact hematopoietic cells, typically lymphocytes, within histiocyte cytoplasm)
- Cytological atypia and mitoses infrequent
- **Background with abundant plasma cells** along with lymphocytes
- **Capsular and stromal fibrosis may be prominent**
- Advanced cases may show nodal effacement
- **Extranodal RDD lesions may show more fibrosis and less frequent emperipolesis**, making histopathologic diagnosis more challenging.





Case Discussion

RDD: Immunohistochemistry

- **Histiocytes positive for CD68, CD163 and S100**
  - Can help highlight emperipoiesis
- **Negative for CD1a and CD207 (Langerin)**
- Positive for OCT2 and Cyclin D1

RDD: Molecular

- Pathogenesis unclear
- ~50% of cases carry gain-of-function mutations in MAPK/ERK pathway genes (including *KRAS*, *NRAS*, *MAP2K1*
  - ***BRAF* V600E rare**

Case Discussion

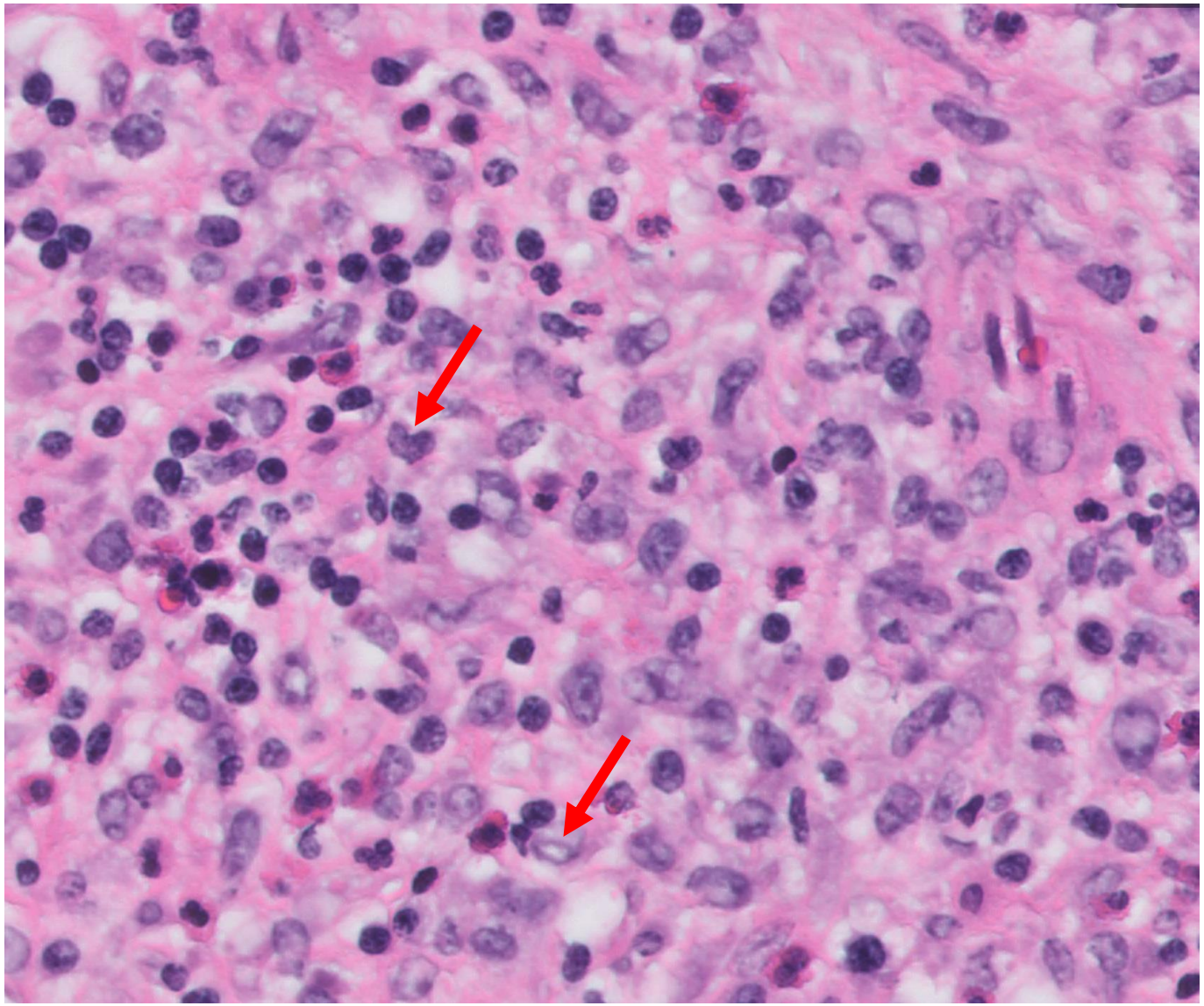
Langerhans Cell Histiocytosis (LCH): **Rare clonal neoplasm with accumulation of CD1a+, CD207/Langerin+ myeloid dendritic cells.**

- More common in childhood (1-3 years old)
- Single system (SS-LCH) or multi-system involvement (MS-LCH)
- May arise in virtually any organ system, commonly bone (79%), skin (36%) and pituitary gland (25%)
  - MS-LCH with involvement of liver, spleen, or bone marrow (cytopenias) is considered higher-risk disease
  - Pulmonary LCH significantly associated with smoking
- Favorable prognosis for SS-LCH, significant morbidity in MS-LCH

Case Discussion

LCH Histopathology:

- **Sheets of large, round-oval histiocytes with irregular, elongated nuclei with prominent nuclear grooves and folds**
  - **Coffee bean nuclei**
  - Minimal nuclear atypia and variable mitotic activity. May see necrotic foci
- **Prominent eosinophil-rich inflammatory background**
  - **Lymphocytes and occasional multinucleated histiocytes** (both LCH-type and osteoclastic-type, especially in bone).
- Late lesions: Diagnostic cells are decreased and fibrosis is increased.



Case Discussion

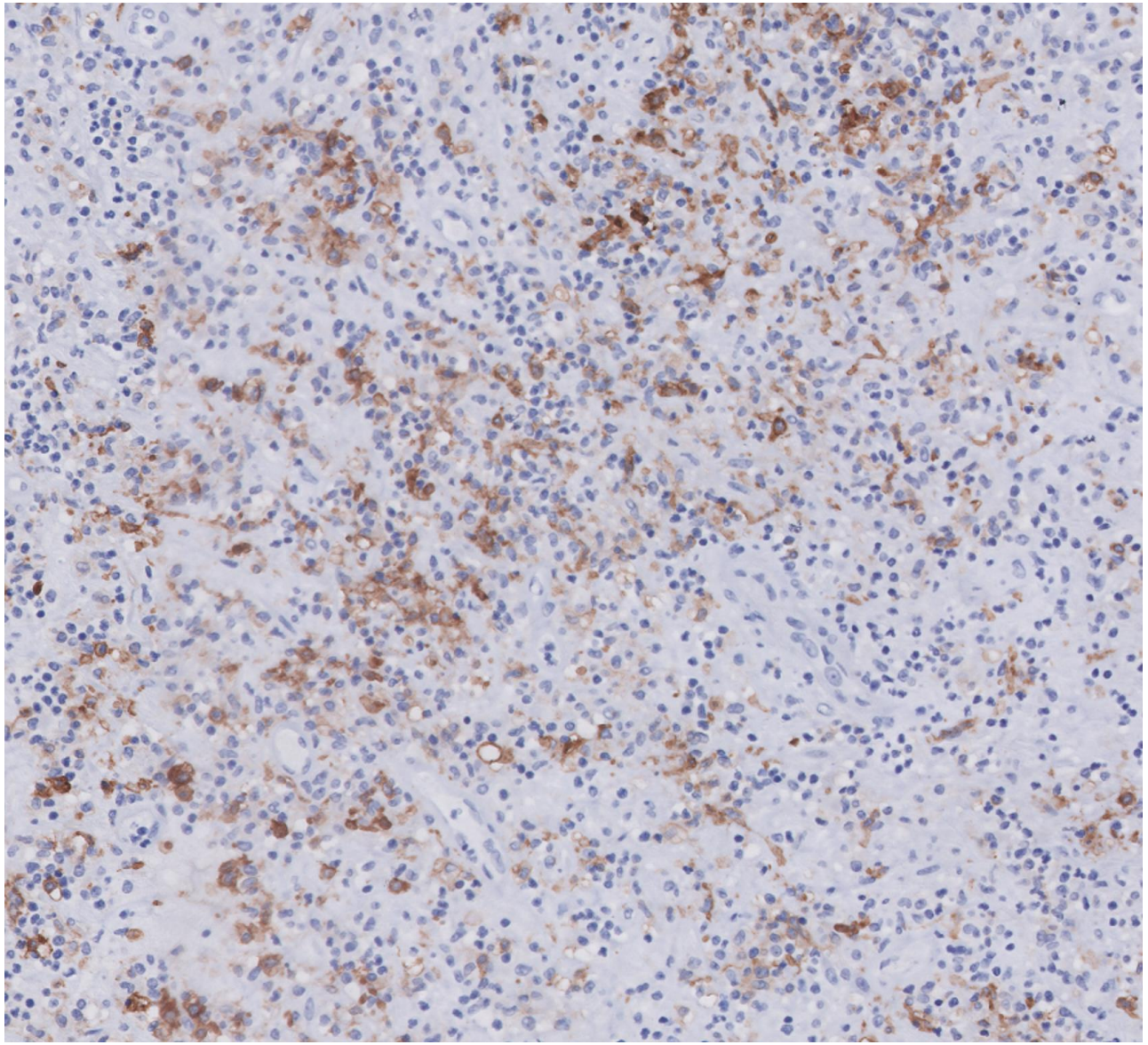
LCH: Immunohistochemistry

- **LCH cells positive for CD1a, CD207 (Langerin), S100,** Cyclin D1.
  - Langerin: surrogate for Birbeck granules.
- **Majority CD68+**
- OCT2 negative.

LCH: Molecular

- **Commonly driven by activating mutations in MAP-K pathway (most commonly BRAFV600E, 50-60%).**
- BRAF V600E is highly associated with an increased risk of relapse and development of MS-LCH.

CD1a

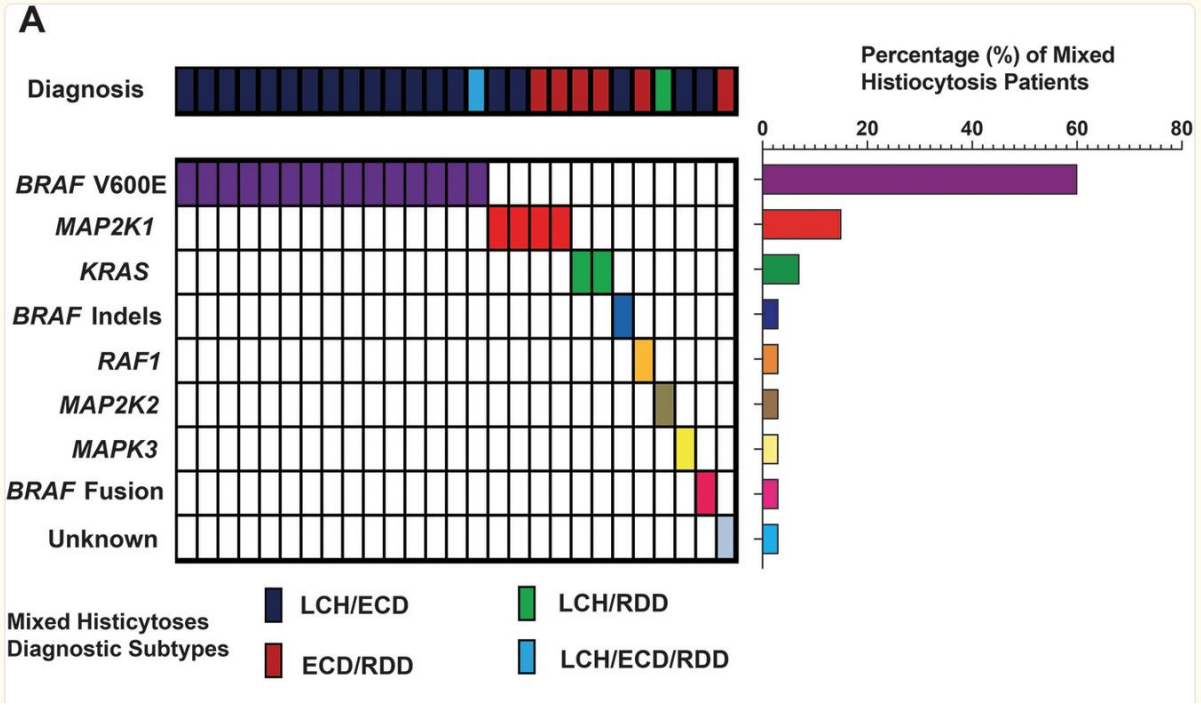


Case Discussion

Mixed Histiocytosis:

- Very rare emerging group defined by overlap of histocytic neoplasms (RDD, LCH, Erdheim-Chester).
- Co-occurrence of histiocyte neoplasms is very rare but has been reported in the literature in case reports.
- Described as either involvement of disease at different sites simultaneously, or presence of combined-features (biphenotypic) within same lesion.
- Frequently demonstrate oncogenic driver mutations

Figure 3: Molecular profiling of patients with mixed histiocytic neoplasms:



Friedman JS, Durham BH, Reiner AS, et al. Mixed histiocytic neoplasms: A multicentre series revealing diverse somatic mutations and responses to targeted therapy. *Br J Haematol*. 2024;205(1):127-137. doi:10.1111/bjh.19462

Thanks for listening!

Credit:

- Dr. Anjanaa Vijayanarayanan
- UCSF Hematopathology and Neuropathology

Resources:

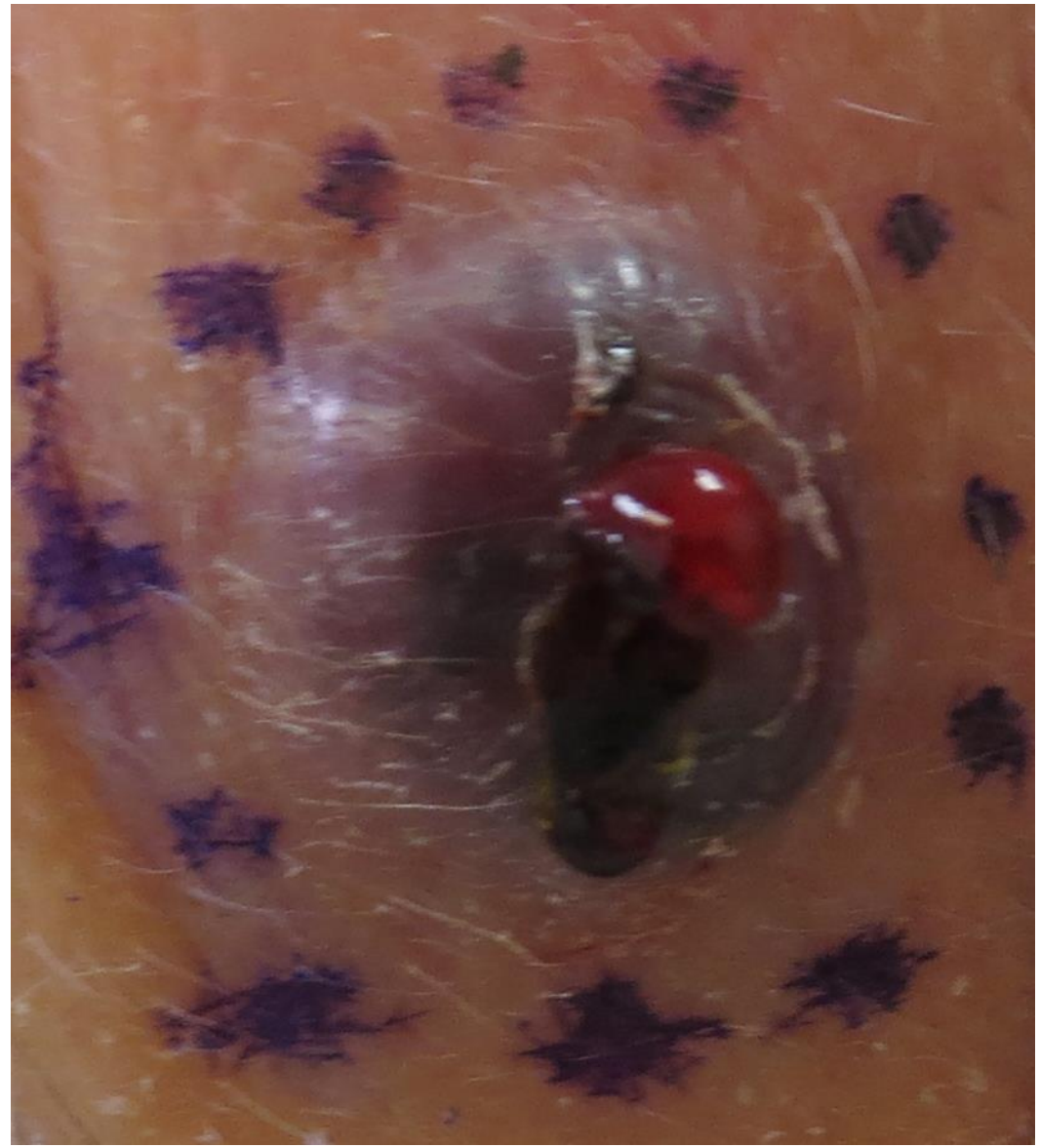
- World Health Organization Classification of Tumours Editorial Board. *Haematolymphoid Tumours*. 5th ed. Vol 2. Lyon, France: International Agency for Research on Cancer; 2022.

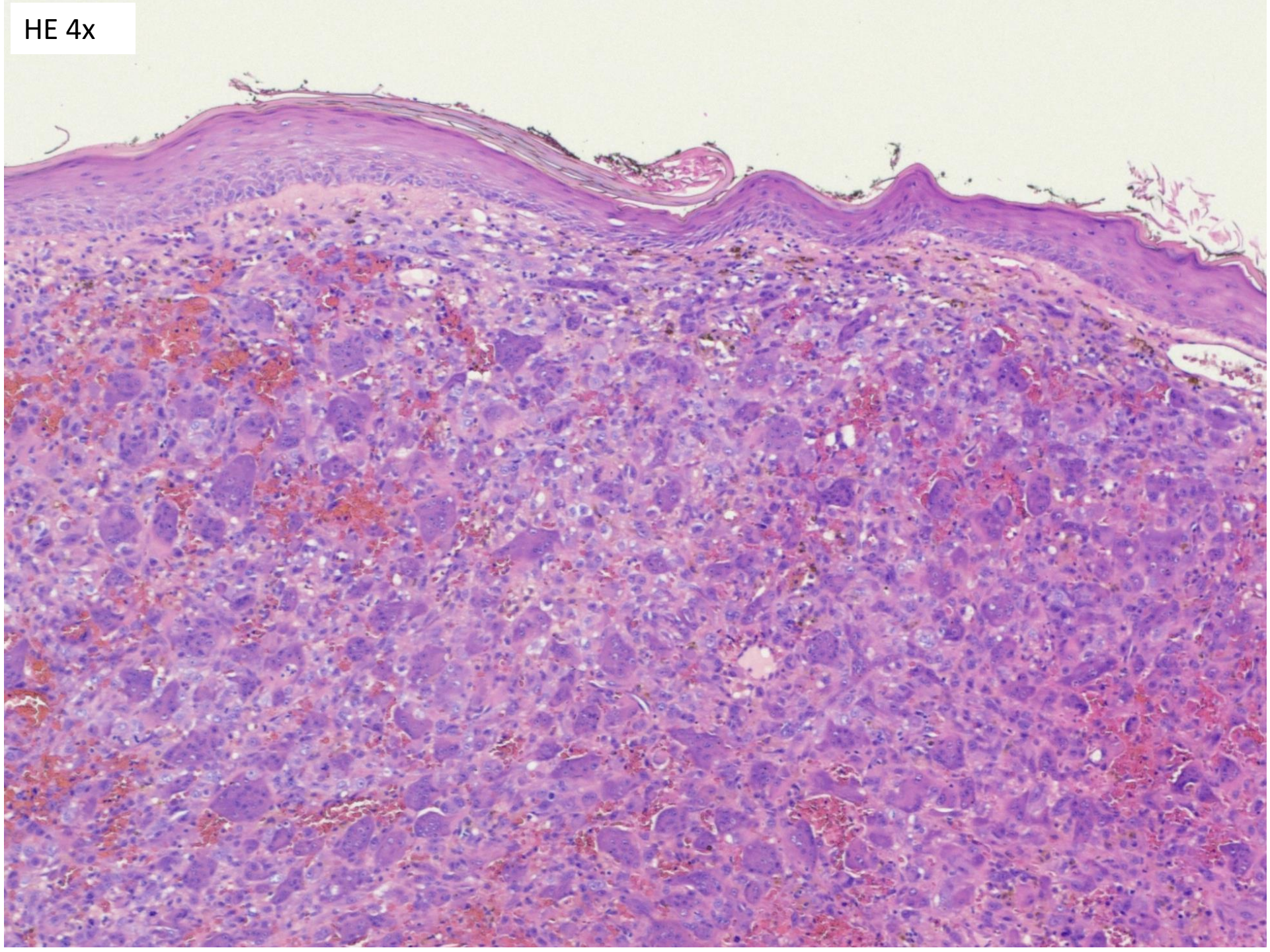
- Friedman JS, Durham BH, Reiner AS, et al. Mixed histiocytic neoplasms: A multicentre series revealing diverse somatic mutations and responses to targeted therapy. *Br J Haematol*. 2024;205(1):127-137. doi:10.1111/bjh.19462

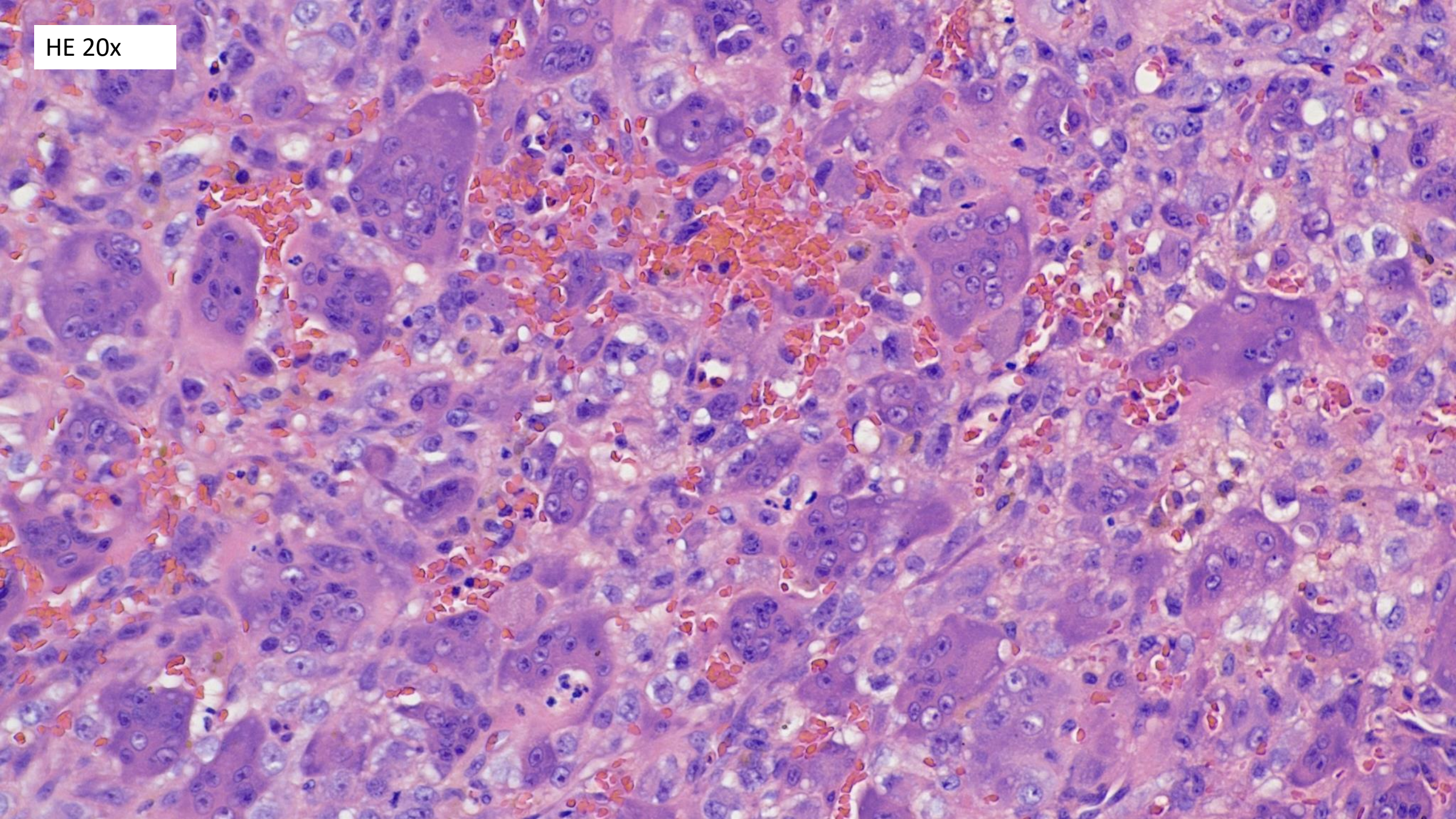
25-1206

Margarita Munoz de Toro, Hubert Lau, and Ryanne Brown; Stanford, VA hospital

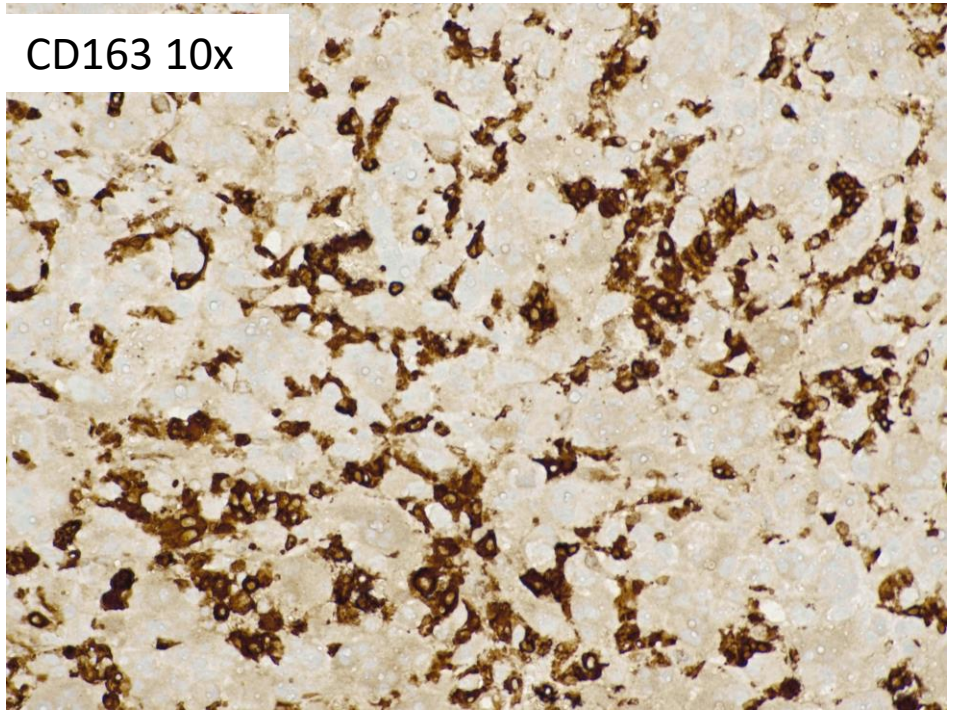
77-year-old man with history of invasive melanoma of the left frontal scalp status post resection in 2016 and local recurrence treated with wide local excision with negative margins in 2021. He presented in 2024 with a new 1.2 cm nodule with central crust on the left temple, clinically concerning for recurrent melanoma.



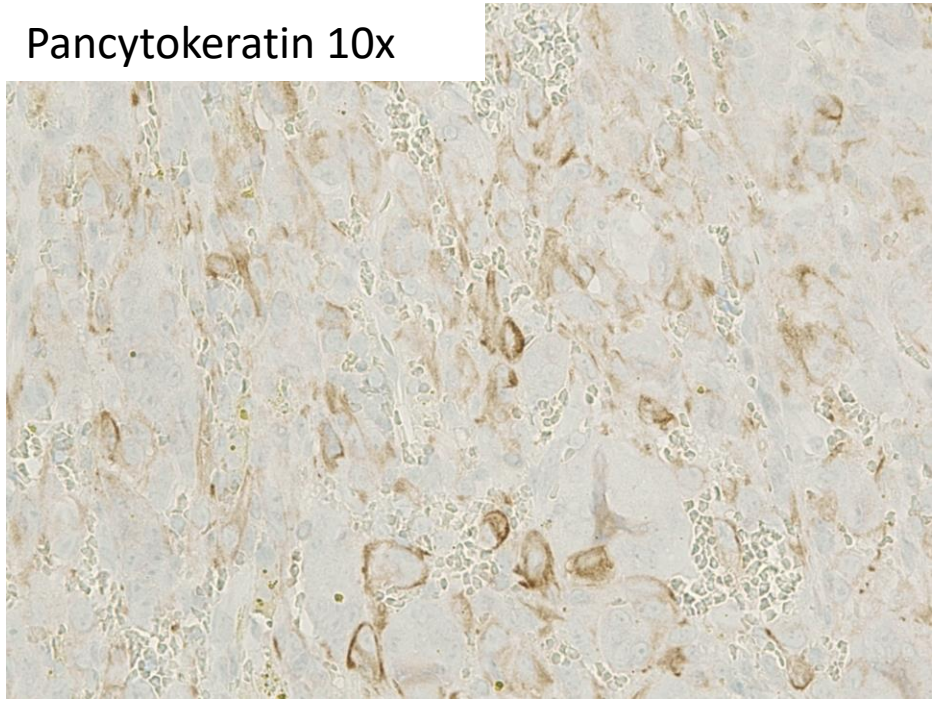

HE 4x


HE 20x

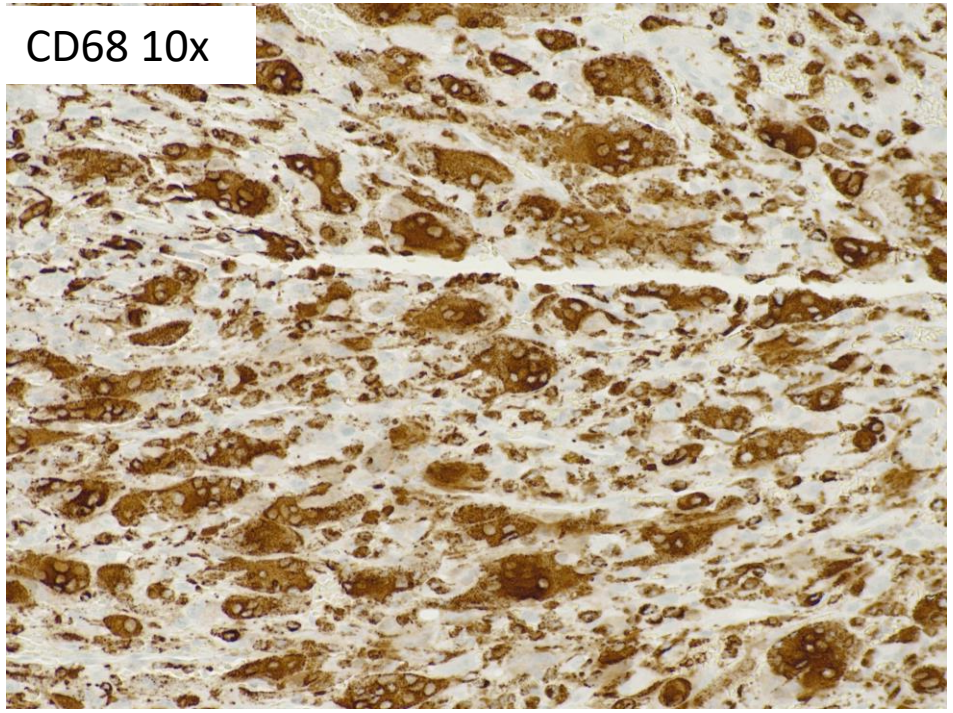
CD163 10x



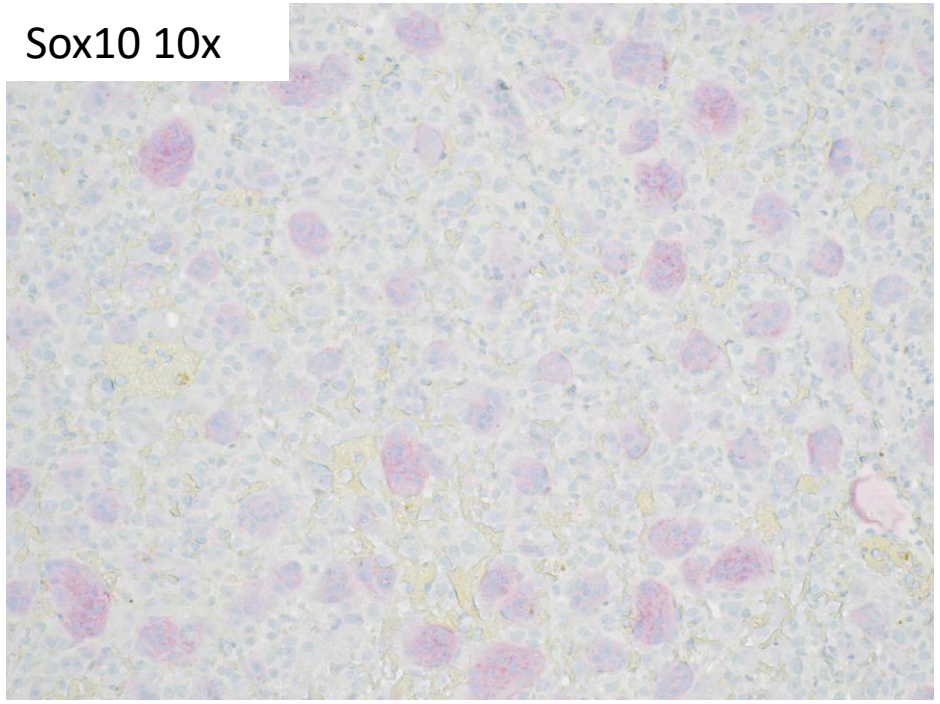
Pancytokeratin 10x



CD68 10x



Sox10 10x



Other negative IHC stains:

- S100
- Mart-1/MelanA
- ERG

DIAGNOSIS?

South Bay Pathology Society Meeting

Dec-2025

Margarita Munoz de Toro, Hubert Lau and Ryanne Brown

Palo Alto Veteran Affairs Medical Center
Stanford University

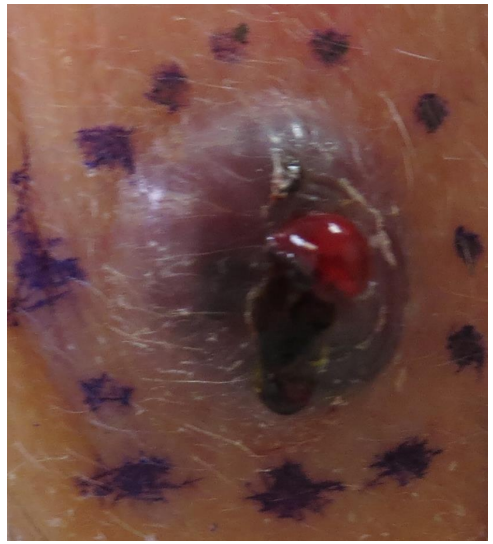
Case presentation

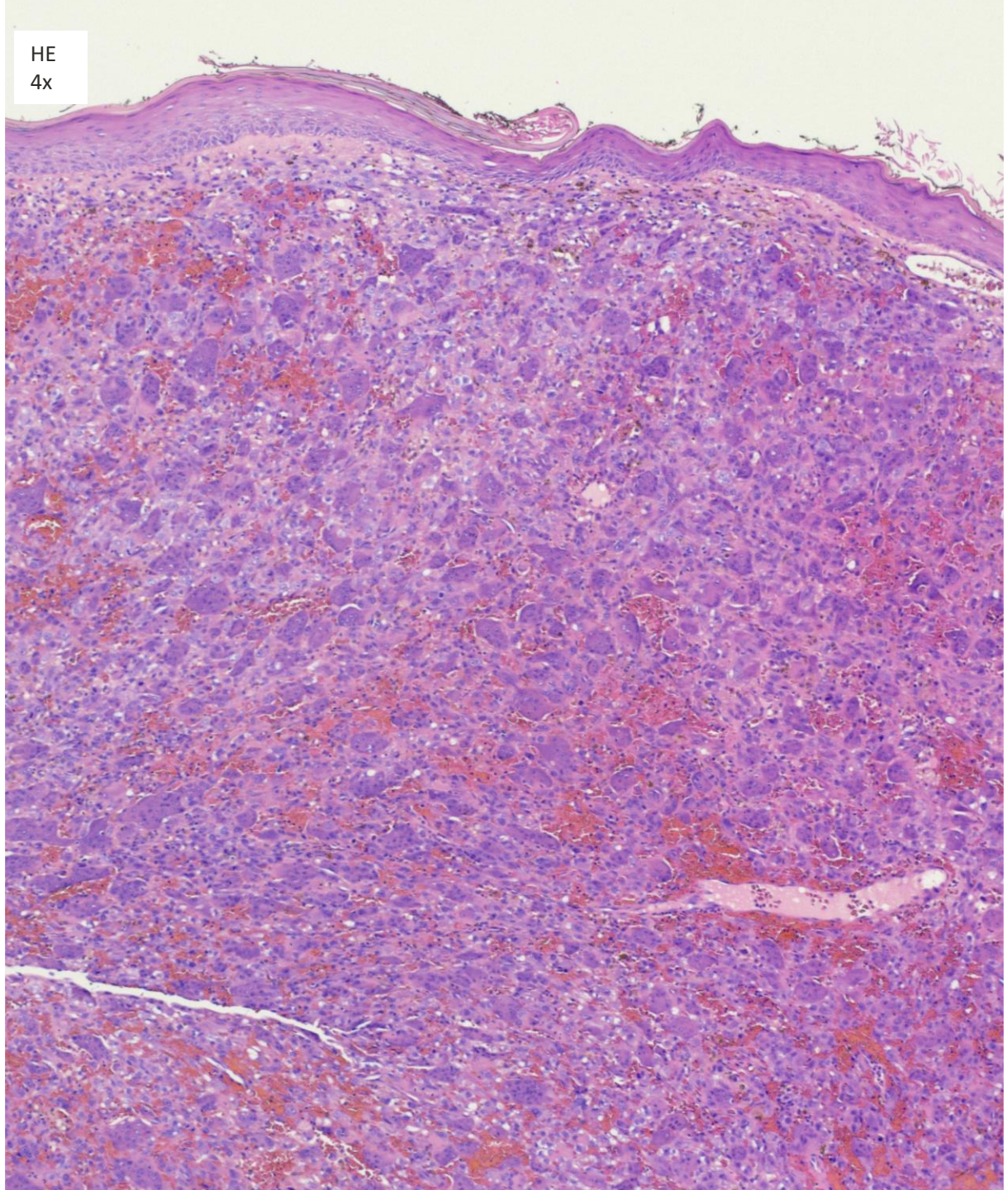
77-year-old man

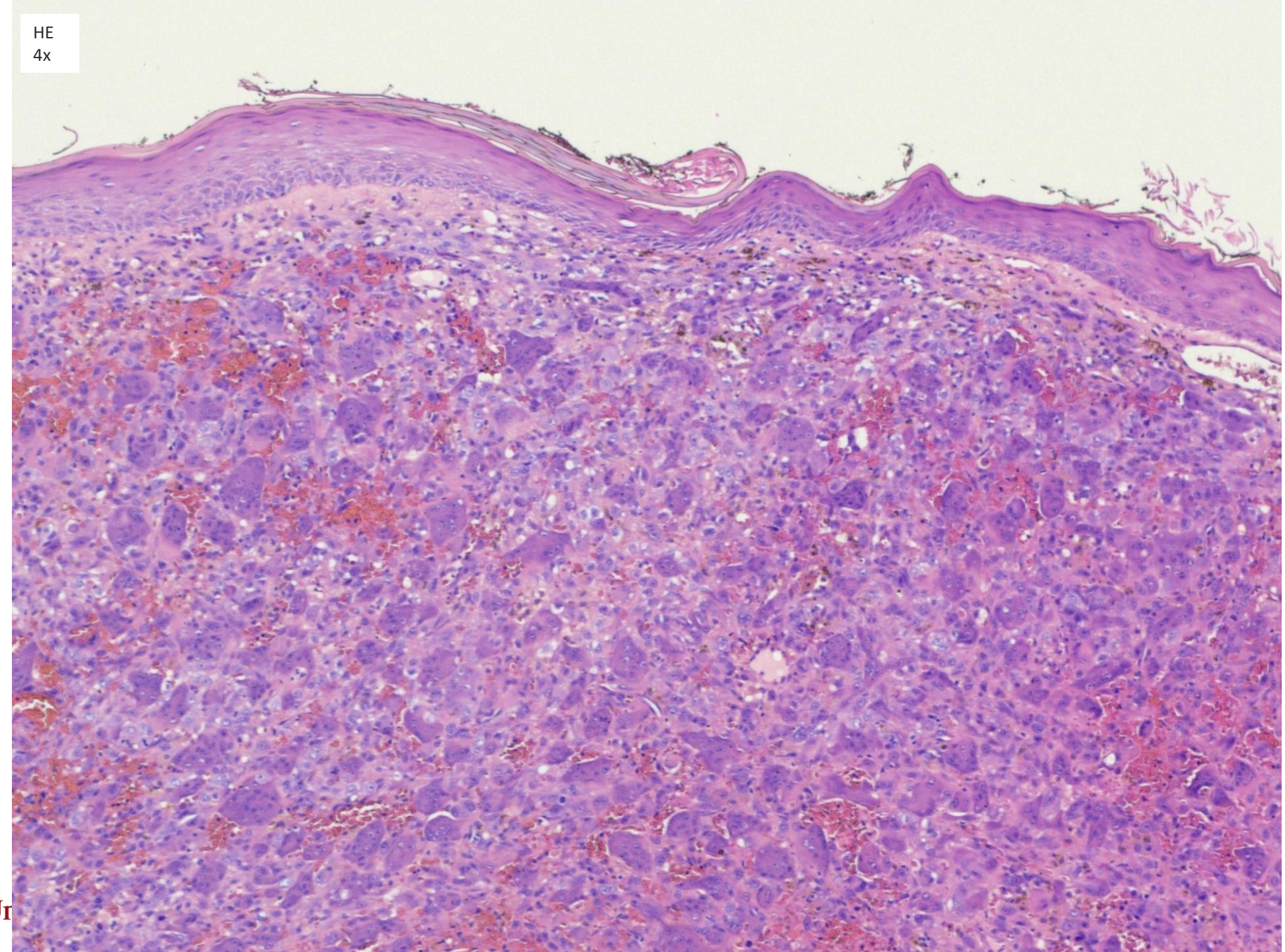
2016 → invasive melanoma of the left frontal scalp

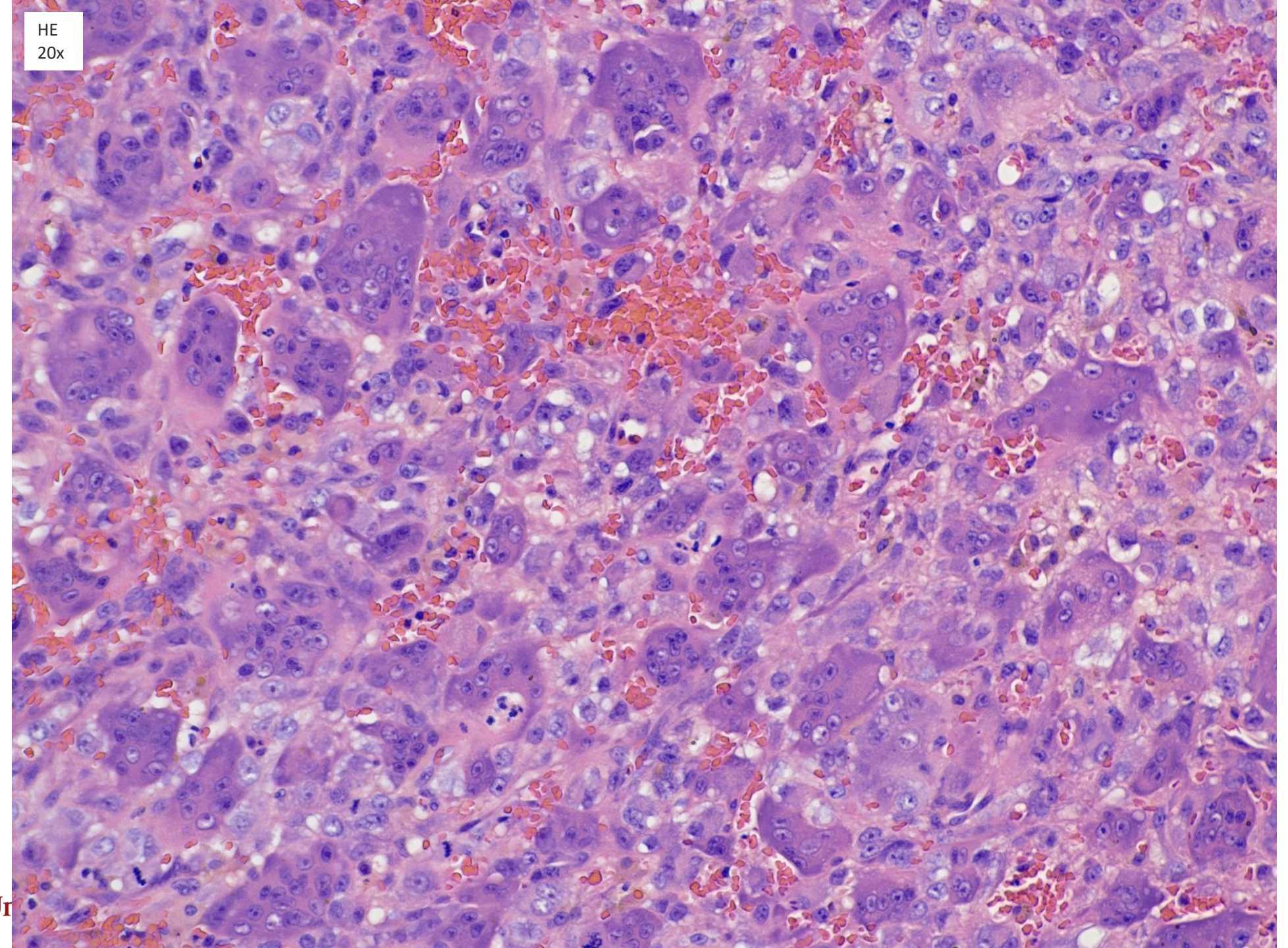
2021 → local recurrence treated with wide-local excision with negative margins

2024 → New 1.2 cm nodule with central crust on the left temple, clinically concerning for recurrent melanoma



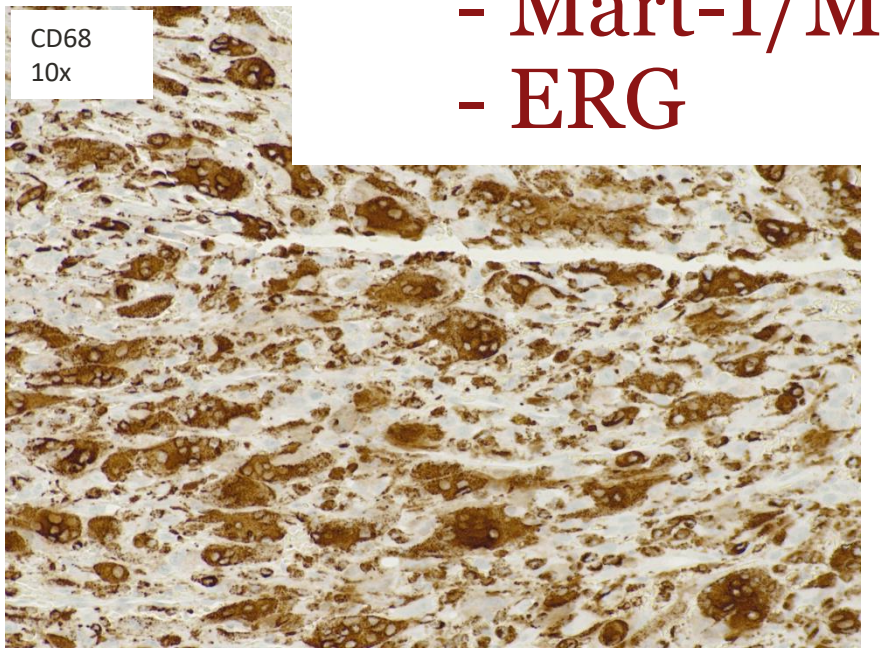

HE
4x

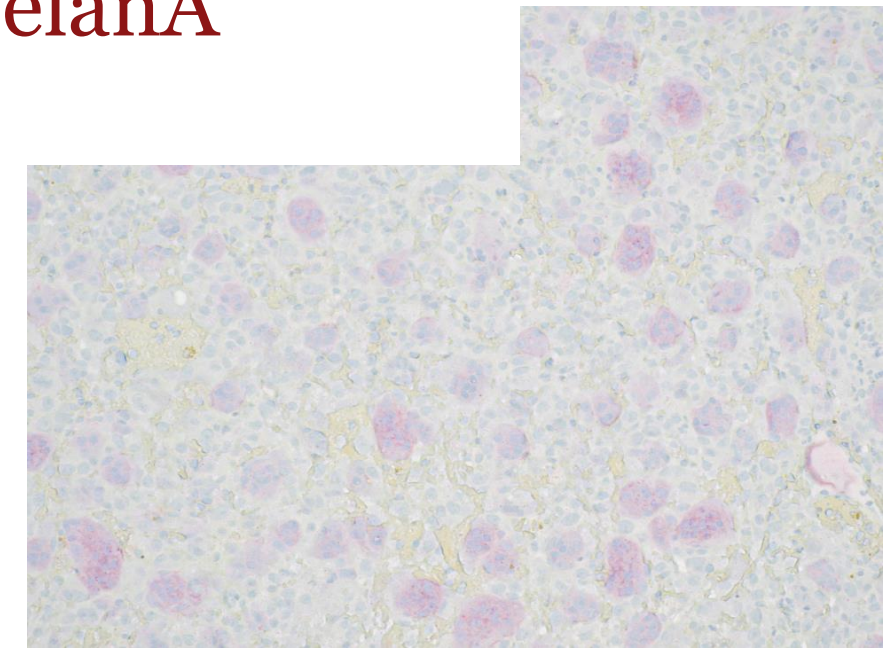



HE
20x

Other negative IHC stains:

- S100
- Mart-1/MelanA
- ERG



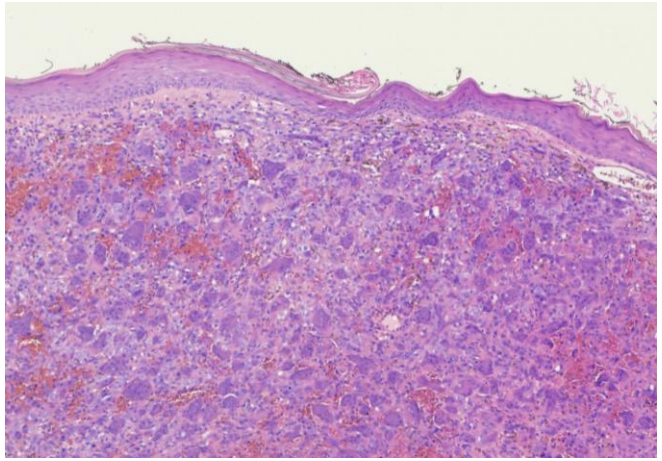


Differential diagnosis:

- Undifferentiated/dedifferentiated melanoma with osteoclast-like giant cells
- Giant cell tumor of soft tissue
- Giant cell-rich atypical fibroxanthoma
- Keratin-positive giant cell tumor (*HMGA2*::*NCOR2* fusion positive)
- Poorly differentiated carcinoma with osteoclast-like giant cells


WHAT'S
NEXT?

Targeted NGS

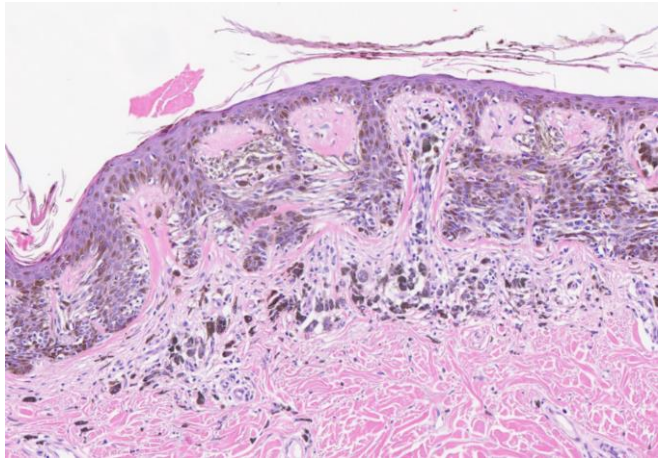


2024 giant-cell rich tumor biopsy specimen

Tumor mutation burden of 20.8 mutations per megabase

<u>Pathogenic or likely pathogenic variants</u>
NRAS Q61R
RAC1 P29S
TP53 V147D
TP53 V173G

≠



2021 melanoma excision specimen

Tumor burden mutation of 7.0 mutations per megabase

BRAF K601E mutation

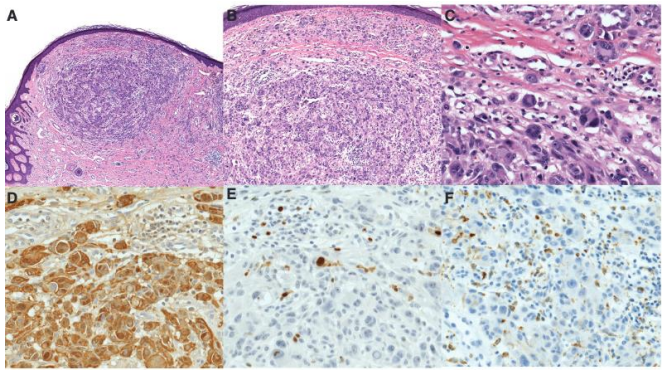
Melanoma with giant multinucleated cells

J Cutan Pathol 2016: 43: 821–829
doi: 10.1111/cup.12750
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

Intratumoral multinucleated giant cells are not a prognostic pathologic feature in cutaneous melanoma

- 562 cases of primary cutaneous melanoma
- 37 (6.58%) with multinucleated giant cells
- Distribution very similar to melanomas without multinucleated giant cells cases
- Head and neck
- Not prognostic factor
- 16 cases IHC → + S100, -CD68



International Journal of Surgical Pathology
Volume 23, Issue 6, September 2015, Pages 478-482

https://doi-org.laneproxy.stanford.edu/10.1177/1066896915592016

SAGE journals

Case Reports

Malignant Melanoma With Osteoclast-Like Differentiation

Jason K. Wasserman, MD, PhD, Harmanjatinder S. Sekhon, MD, PhD, and Yasmine Ayroud, MD

- Neoplastic melanocytes and giant cells co-expressed: HMB-45, Melan-A, and S100
- Multinucleated giant cells positive CD68 and CD163

ORIGINAL ARTICLE

Malignant Melanoma with Osteoclast-Like Giant Cells: An Unusual Host Response

Immunohistochemical and Ultrastructural Study of Three Cases and Literature Review

Al-Brahim, Nabeel MD; Salama, Samih MD, FRCP(C)

- Neoplastic melanocytes + S100, Melan A, HMB45
- Multinucleated giant cells + CD68

Li, Xiaoxiao. DOI: 10.1097/DAD.0000000000000860
Wasserman JK, DOI:10.1177/1066896915592016
Srisuttiyakorn C. PMID: 27246995

Melanoma

Low-cumulative sun damage

Superficial spreading melanomas
Trunk and extremities

***BRAF*V600E**

TERT promoter

CDKN2A

PTEN

TP53

High-cumulative sun damage

Melanoma lentigo maligna
Desmoplastic melanoma
Older individuals

High mutation burden

NRAS

BRAF non-V600E

NF1

TERT promoter

CDKN2A

KIT (occasional)

Non-cumulative sun damage

Spitz melanomas
- **Tyrosine kinase fusion**
- **Serine-threonine kinase fusion**

Acral melanomas

Mucosal melanomas

Melanomas arising from congenital or blue nevi
- ***GNA11* or *GNAQ* mutations**

Uveal melanomas
- ***GNA11* or *GNAQ* mutations**

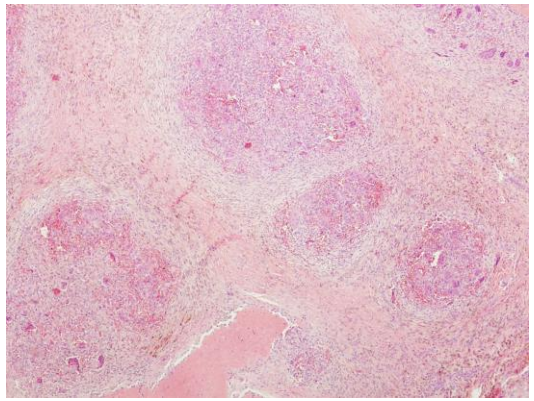
No *BRAF*, *NRAS* or *NF1* mutations (triple wild-type)

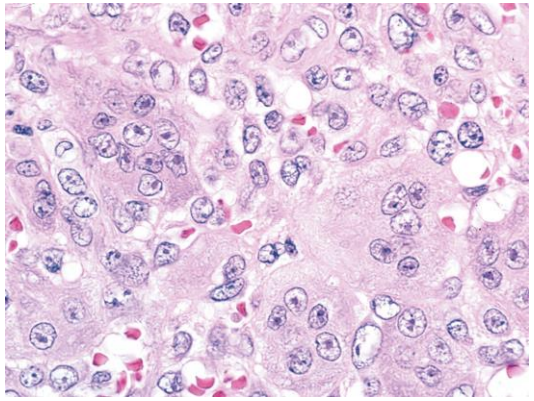
KIT mutations
Gene amplifications
Structural rearrangements (*CCND1* gene and *SF3B1)*

Kim HJ et al. PMCID: PMC10931637

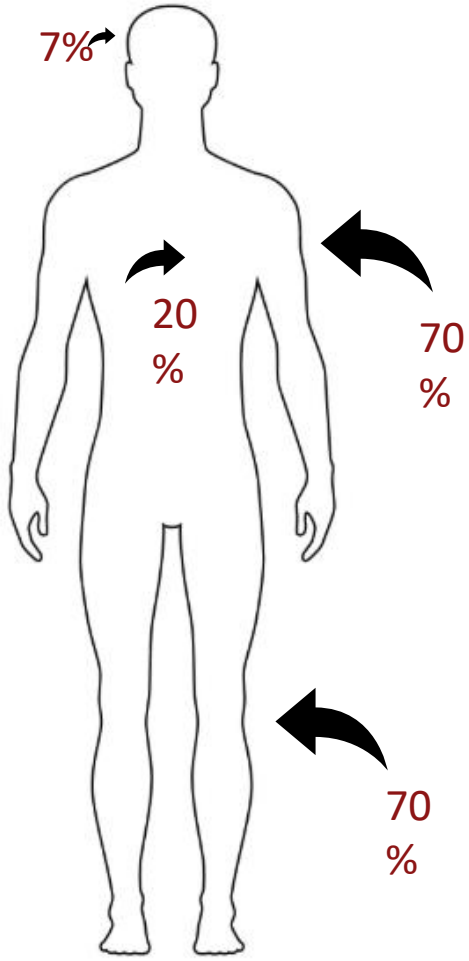
Giant cell tumor of soft tissue

- M=F 50 years of age
- Superficial soft tissue (70%)
- Deep fascia (30%)
- Lacks mutations in the *H3F3A* gene (present in giant cell tumor of bone)





Multinodular architecture
Stromal hemorrhage 50%
Metaplastic bone formation 50%
LVI 30%

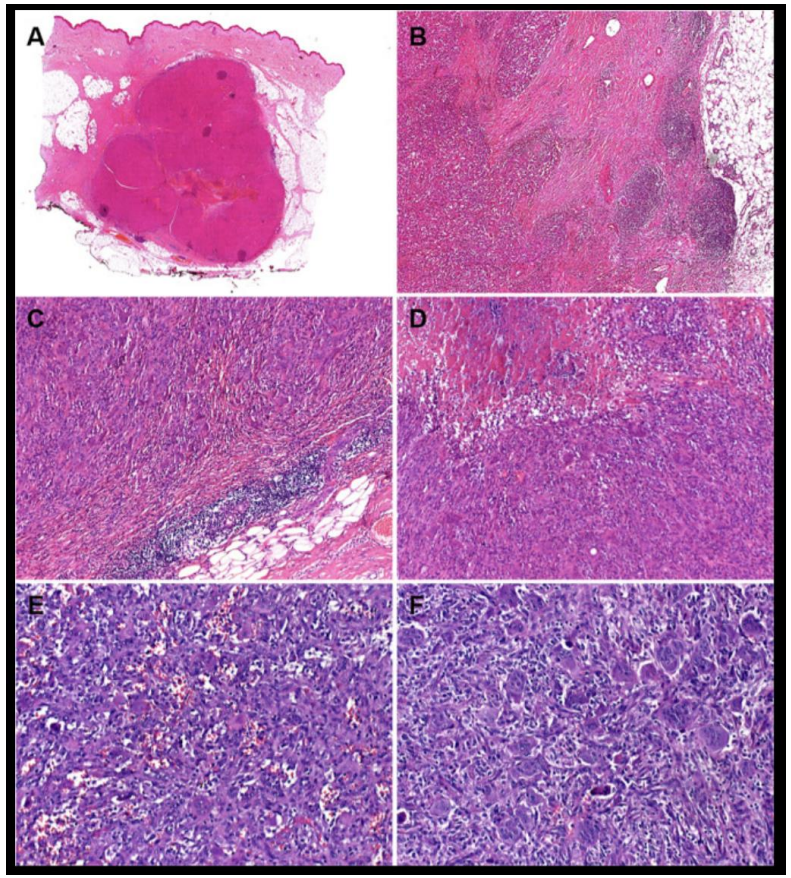


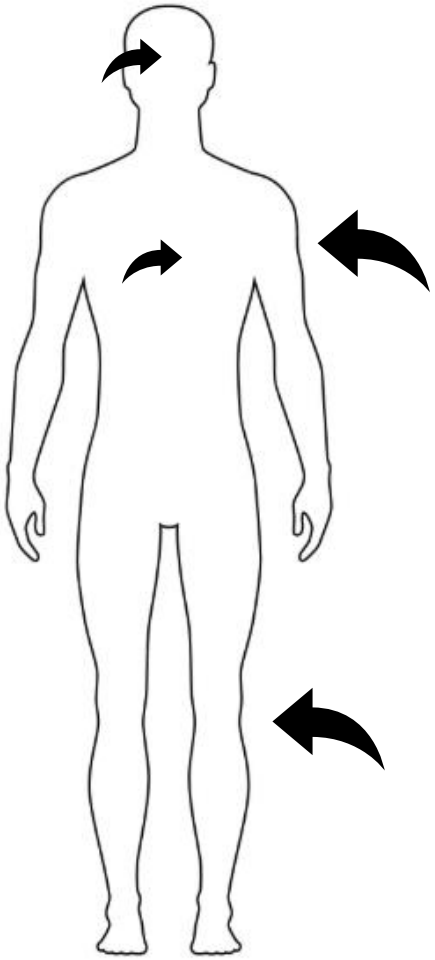
van der Linde RM. PMID: 41082975

Keratin-positive giant cell tumor (*HMGA2::NCOR2* fusion positive)

- Emerging entity <40 cases reported with uncertain biologic potential
- F 20-30 years of age
- Subcutaneous tissue
- Bone (vertebral bodies)
- *HMGA2::NCOR2* fusion

- Lobulated (uni/multi)
- Peritumoral lymphoid aggregates
- Stromal hemorrhage/hemosiderin
- Low mitotic activity
- Necrosis, LVI infrequent
- No metaplastic bone formation



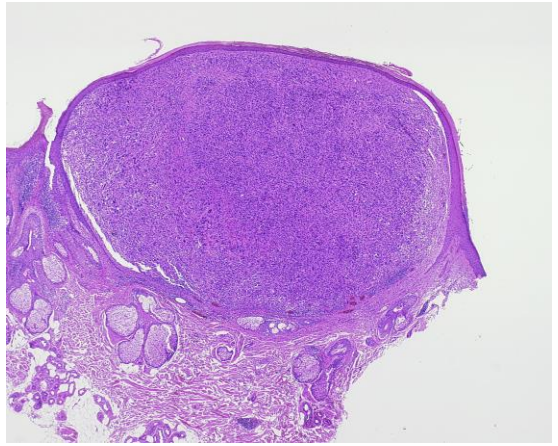


Agaimy A. PMCID: PMC8295036

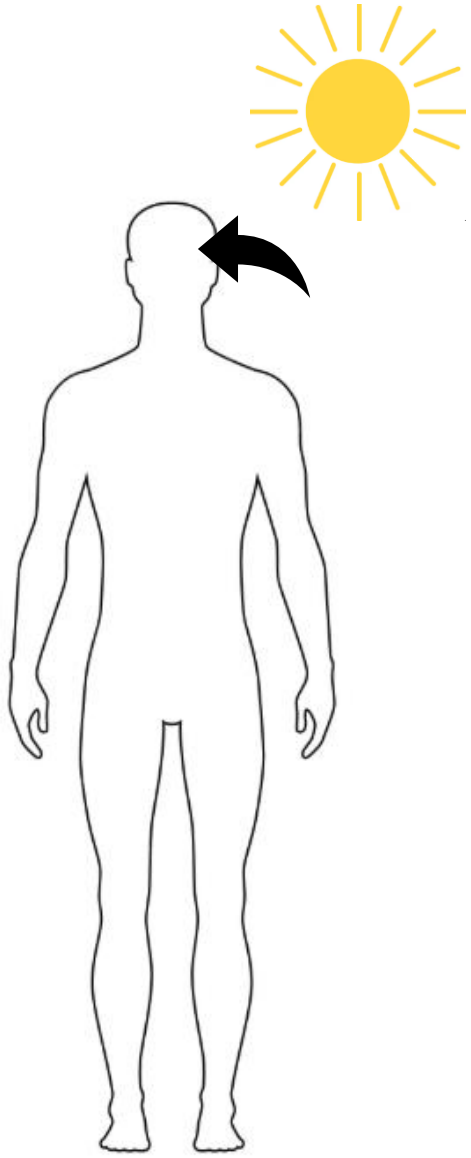
Atypical fibroxanthoma

- M, elderly
- Sun exposed areas
- Diagnosis of exclusion
- DERMAL based
- Etiology:
  - UV radiation exposure with UV-signature mutations in *TP53*
  - Radiotherapy
  - Immunosuppression

PLEOMPRPHIC DERMAL SARCOMA
- Size
- Hypodermis involvement
- PNI
- LVI
- Necrosis



Well circumscribed
Pleomorphic, spindled to epithelioid cells
Irregularly arranged
Numerous mitotic figures



Anderson JD. PMID: 35301743

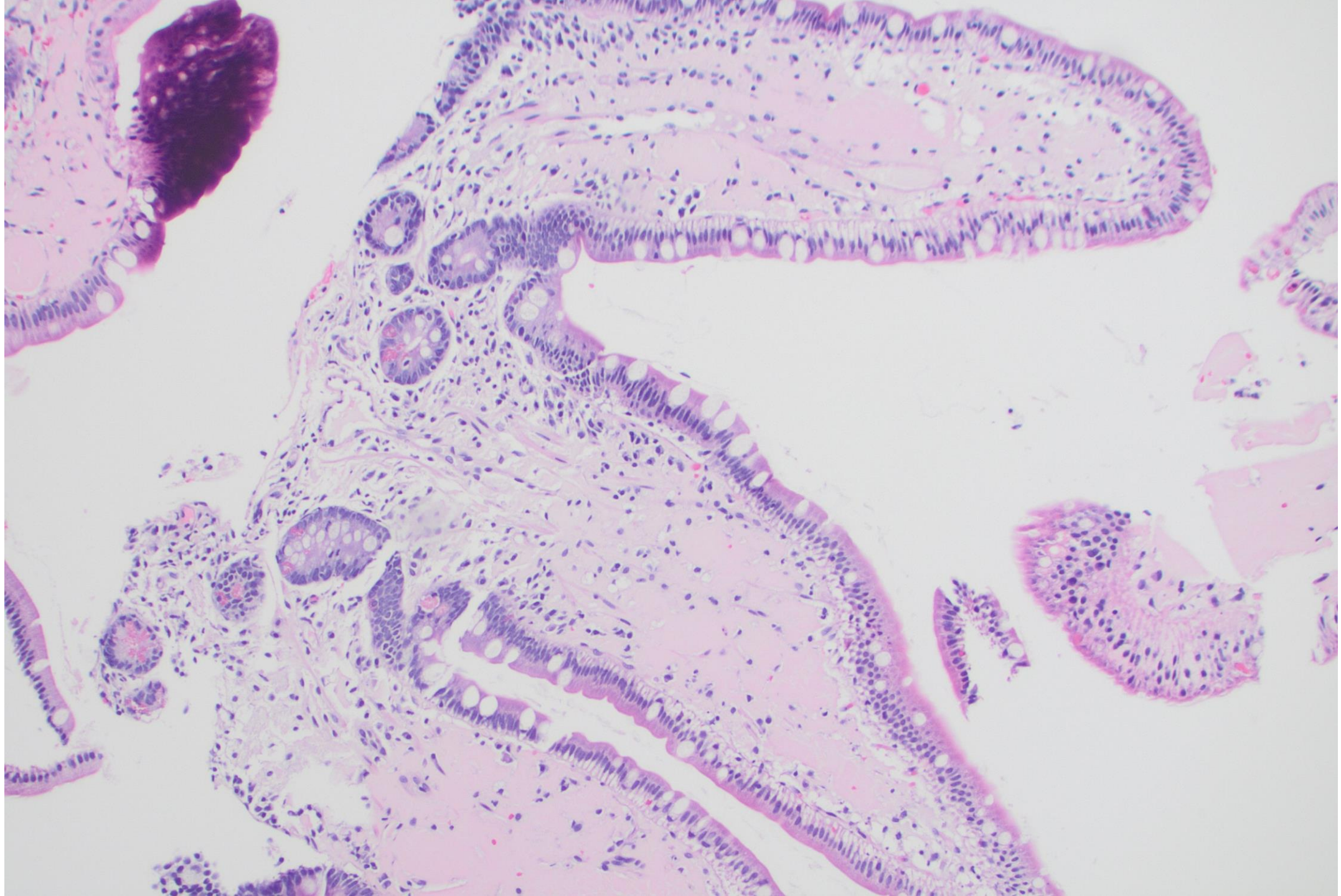
Summary

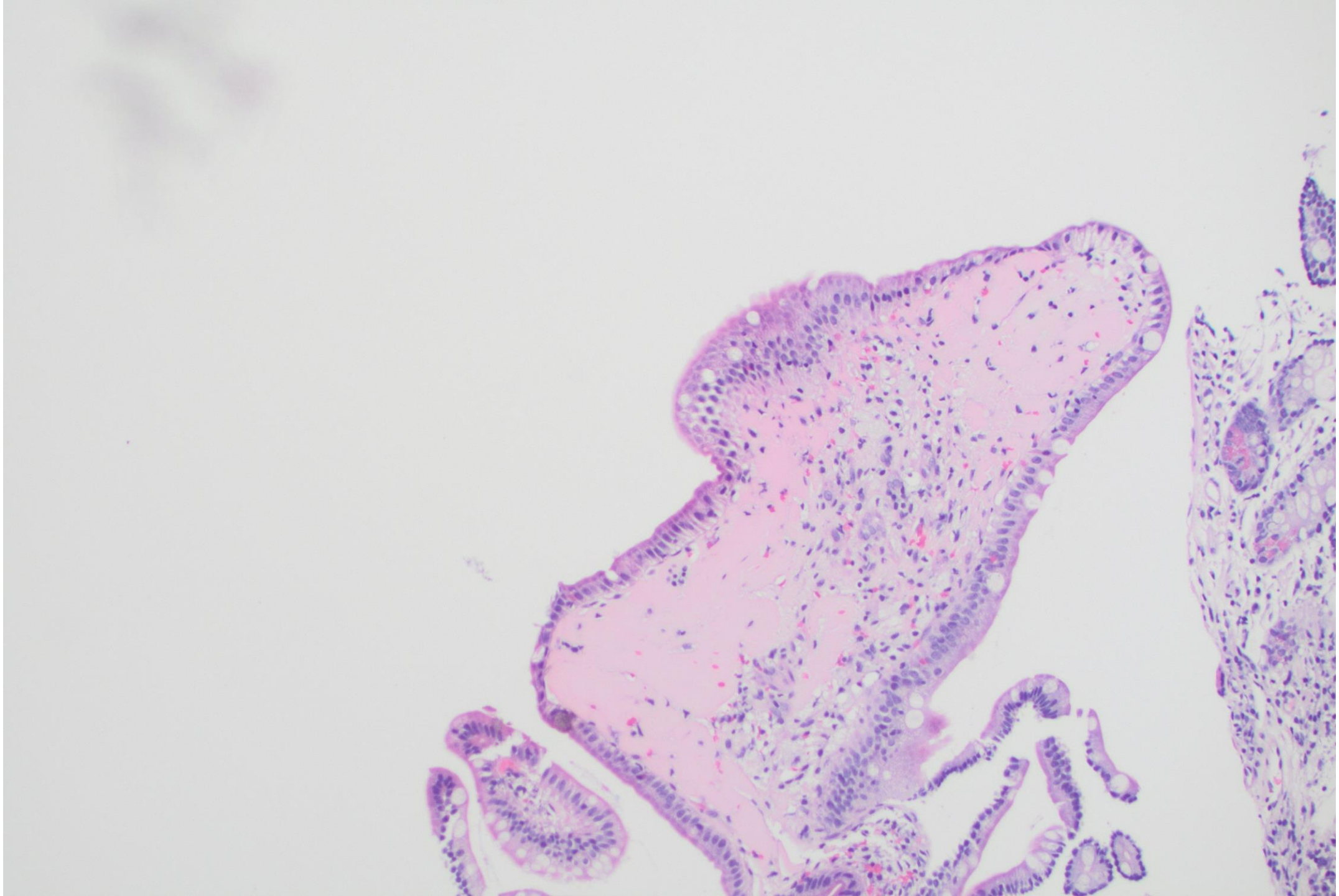
- Multinucleated giant cells can be present in a variety of neoplastic including cutaneous and soft tissue tumors
- Careful attention to the clinical and histologic features, along with immunohistochemical and/or molecular analysis, will permit the correct diagnosis to be established in most cases.

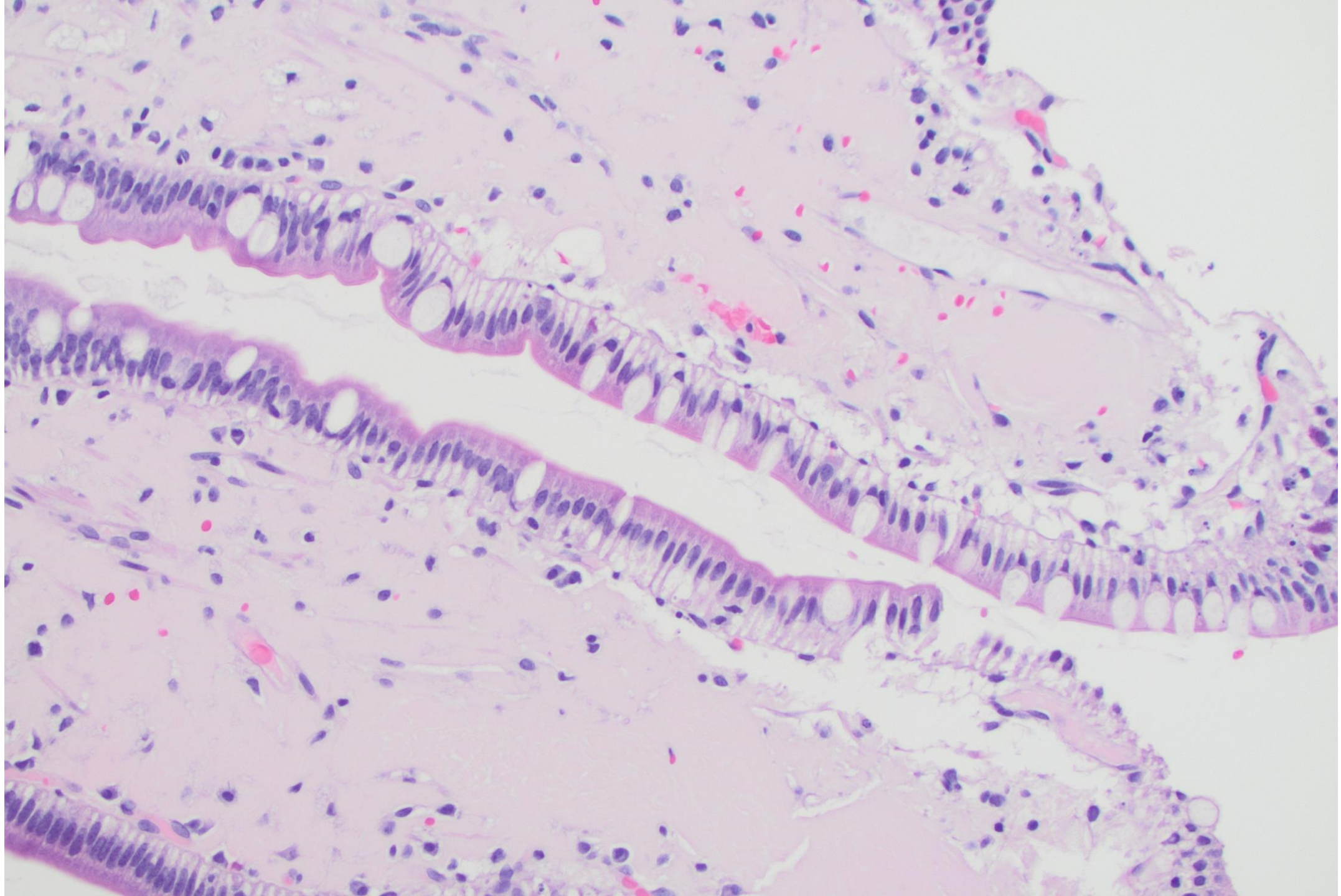
25-1207

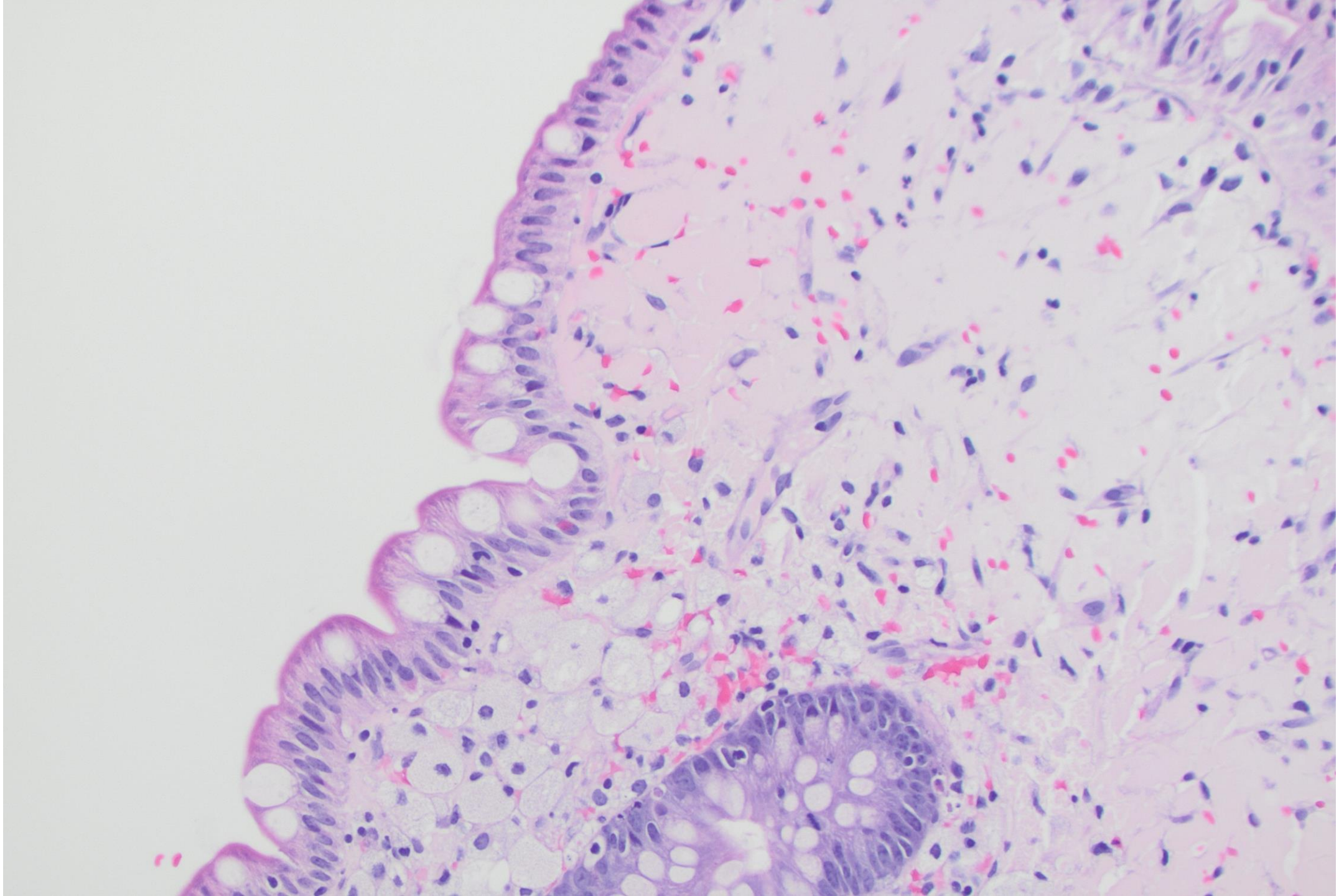
Greg Rumore; Kaiser Permanente

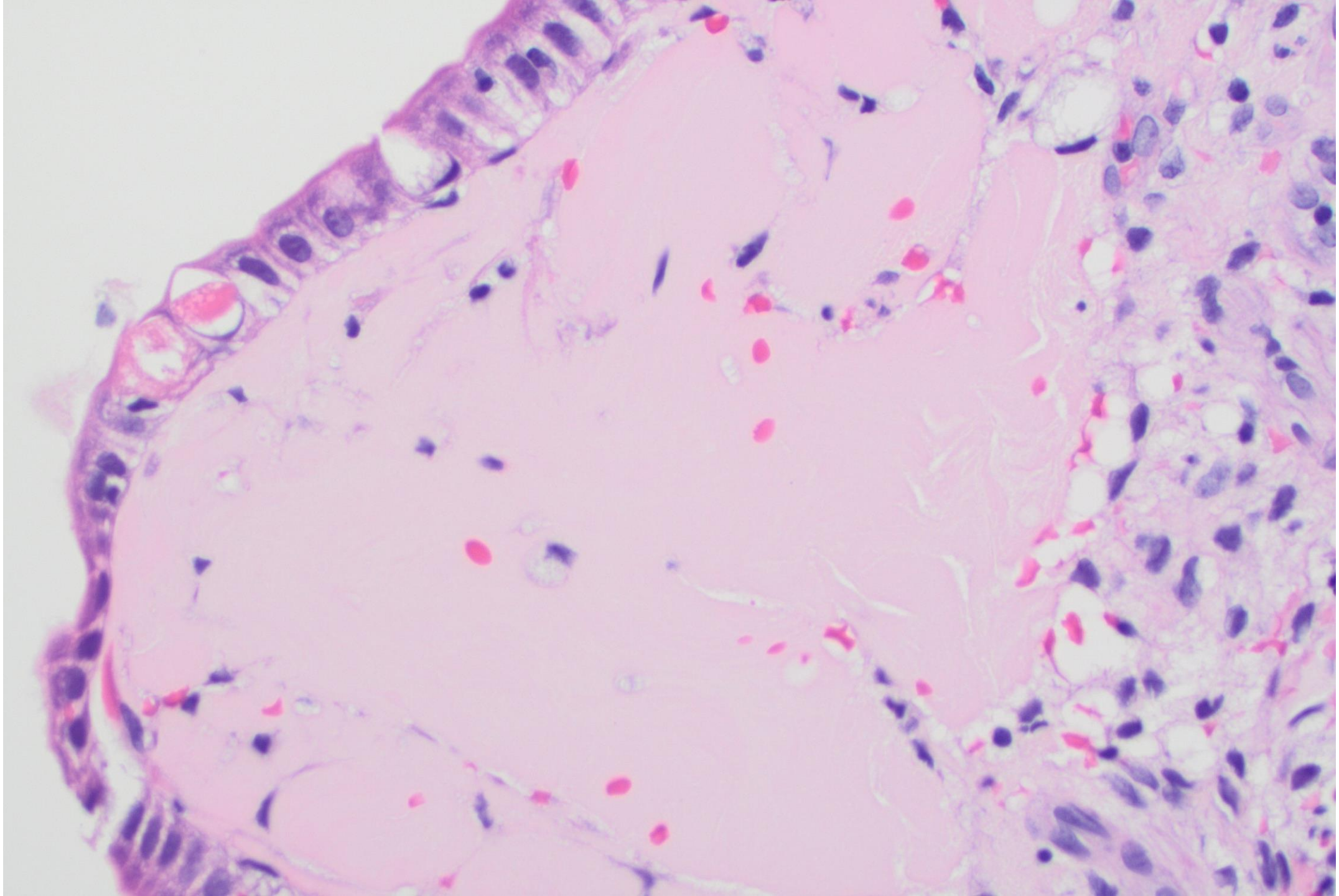
Duodenal Biopsy in 70’s female with UGI hemorrhage



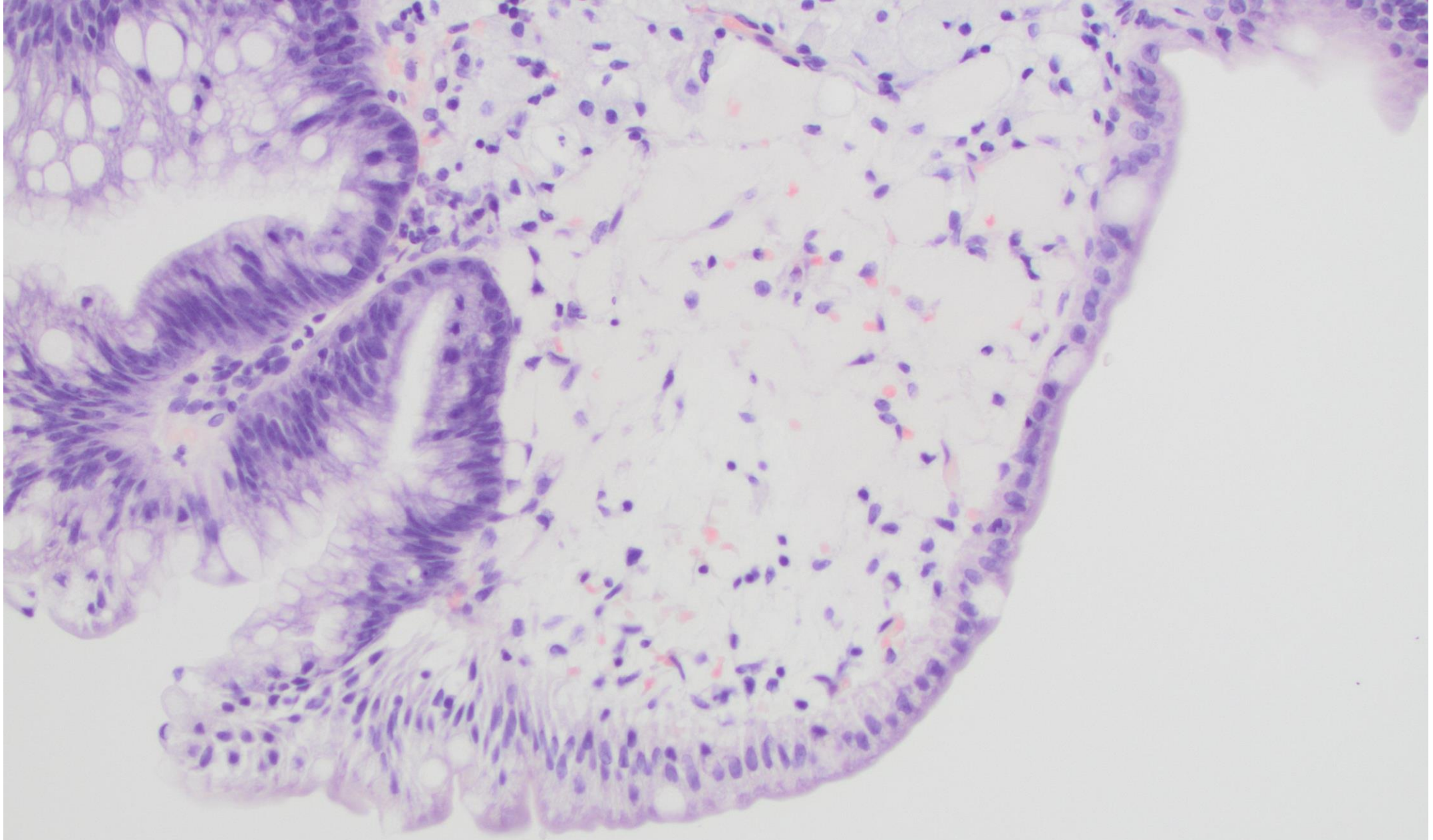








DIAGNOSIS?



Congo Red

Pt. has history of Waldenstrom Macroglobulinemia

- Endoscopy-”proliferative lymphangiectasia” in duodenum
- Dilated villi containing homogeneous eosinophilic material, foamy histiocytes
- Congo red negative
- LC/MS-predominance of peptides associated with kappa immunoglobulin light chains and Mu immunoglobulin heavy chains
- Comment: No support for amyloidosis. In the appropriate clinical context these results are c/w monoclonal IgM kappa deposits associated with Waldenstrom Macroglobulinemia

Waldenstrom Macroglobulinemia

- Uncommon B cell lymphoproliferative disorder
- Lymphadenopathy, organomegaly, circulating monoclonal IgM paraprotein (hyperviscosity)
- Gastrointestinal involvement is rare

GASTROENTEROLOGY 65:308-315, 1973

Vol. 65, No. 2
Printed in U.S.A.

INTESTINAL INVOLVEMENT IN WALDENSTROM'S MACROGLOBULINEMIA

MARSHALL S. BEDINE, M.D., JOHN H. YARDLEY, M.D., HERBERT L. ELLIOTT, M.D., JOHN G. BANWELL, M.D., AND THOMAS R. HENDRIX, M.D.

Departments of Medicine and Pathology, The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland

A patient with Waldenstrom's macroglobulinemia is described in whom malabsorption and weight loss were the chief clinical manifestations. Deposits of hyaline material in the lamina propria of the small intestine produced bizarre, clubbed villi and were associated with large foamy macrophages of uncertain origin. There were also various lymphoid cells in the lamina propria that included plasma and plasmacytoid cells having amorphous intranuclear inclusions of the type often found in Waldenstrom's macroglobulinemia. The hyaline material deposited in the villi was thought to be macroglobulin. Local production of macroglobulin by abnormal lymphoid cells in the villi may have contributed to its deposition there. The deposits were probably a major factor causing malabsorption.

Waldenstrom's macroglobulinemia is a quently include edema, dyspnea, retinal

Mechanisms of GI involvement by WM

- Deposition of immunoglobulin light chain fragments as amyloid
- Infiltration of wall of GI tract by lymphoplasmacytic cells with local production of monoclonal IgM-lymphatic dilatation and obstruction with secondary lymphangiectasia-not necessarily related to IgM levels
- Infiltration of mesenteric lymph nodes-distortion of anatomy also leading to lymphangiectasia

Clinical manifestations

- Protein losing enteropathy with diarrhea and malabsorption syndrome
- Arterial or venous thrombosis

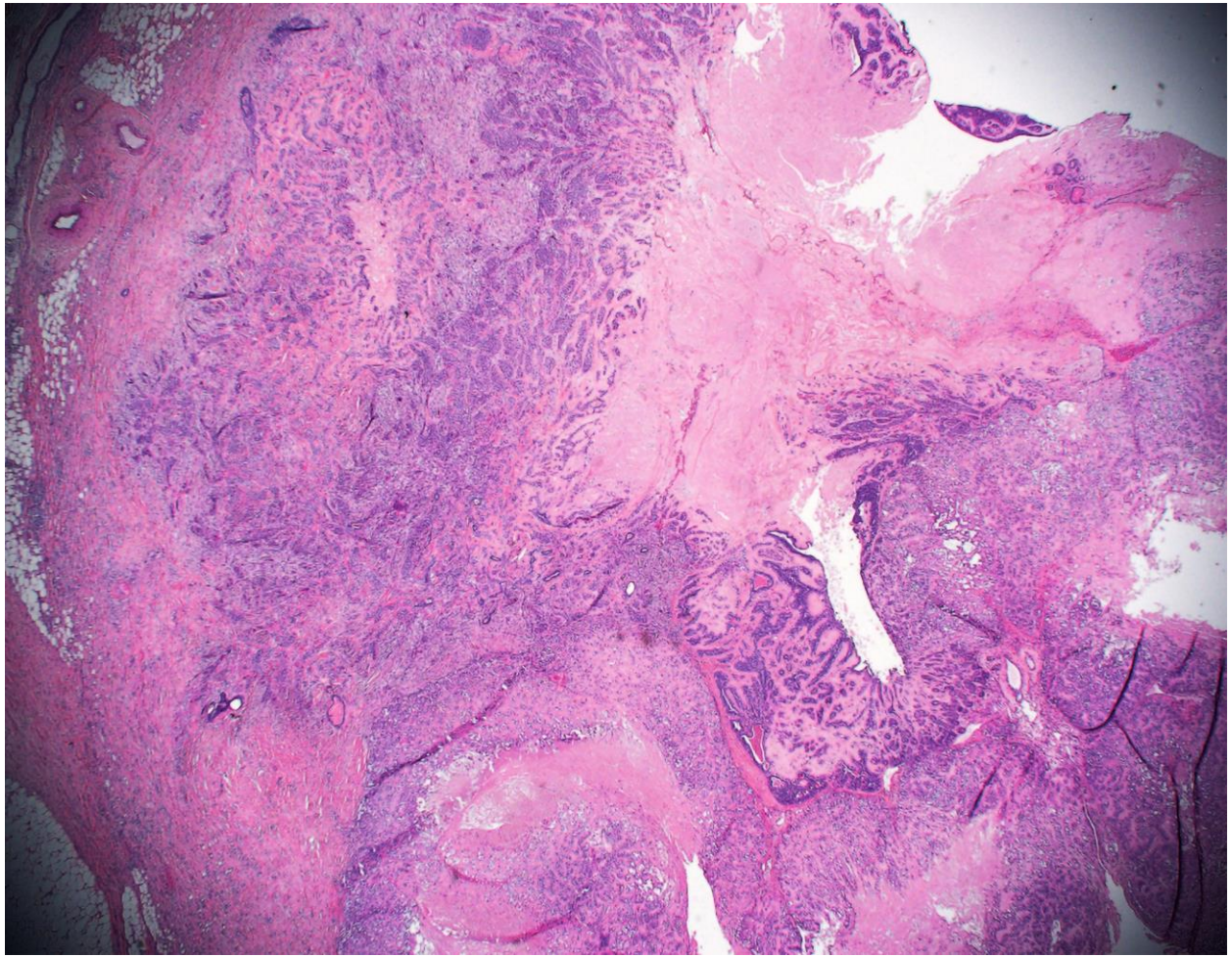
References

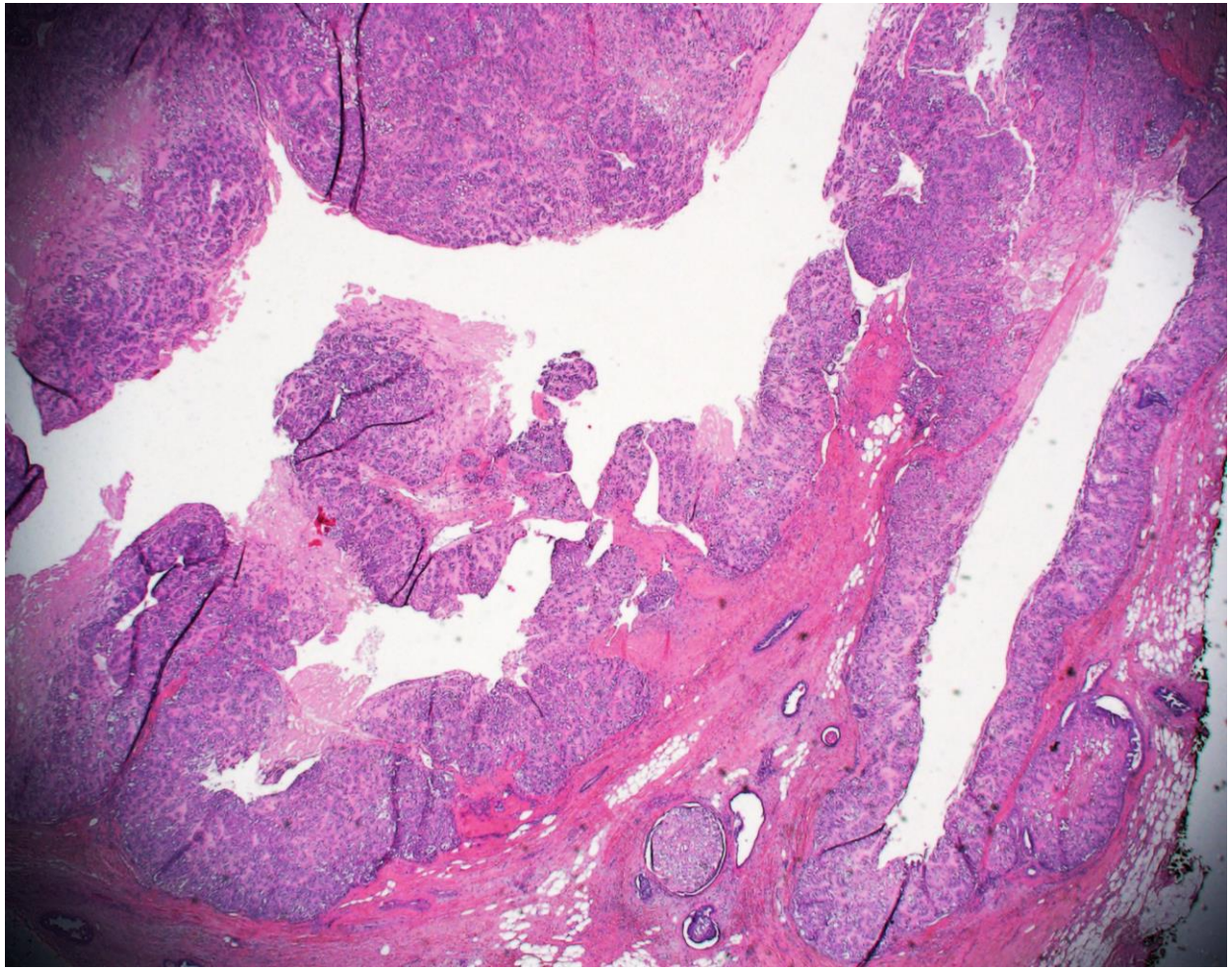
- Bedine, M.S., Yardley, J.H., et al, Intestinal Involvement in Waldenstrom's Macroglobulinemia, Gastroenterology 65:308-315, 1973
- Pratz, K.W, Dingli, D., et al, Intestinal Lymphangiectasia With Protein-losing Enteropathy in Waldenstrom Macroglobulinemia, Medicine 86(4), p210-214, July 2007

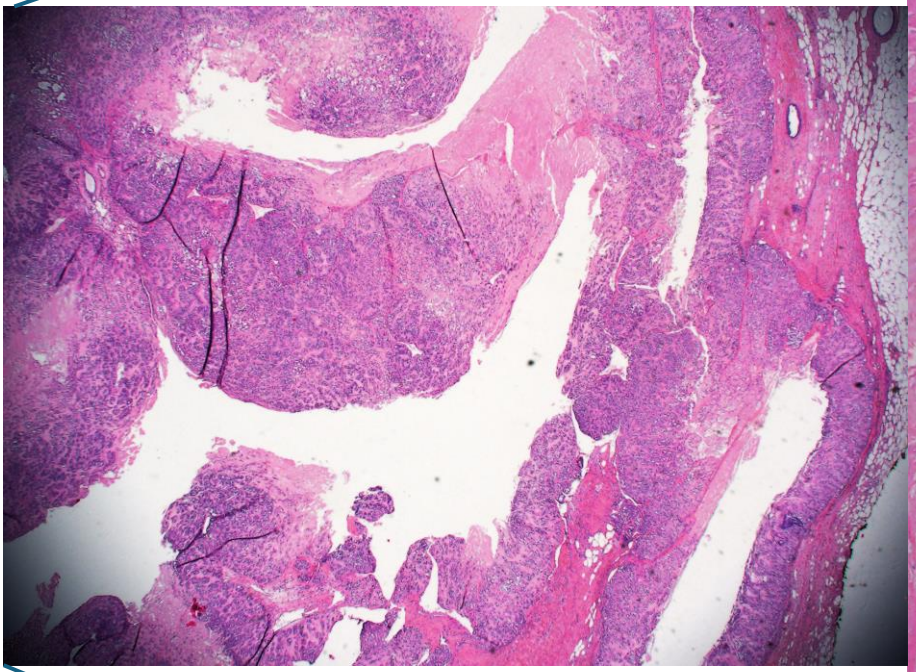
25-1208

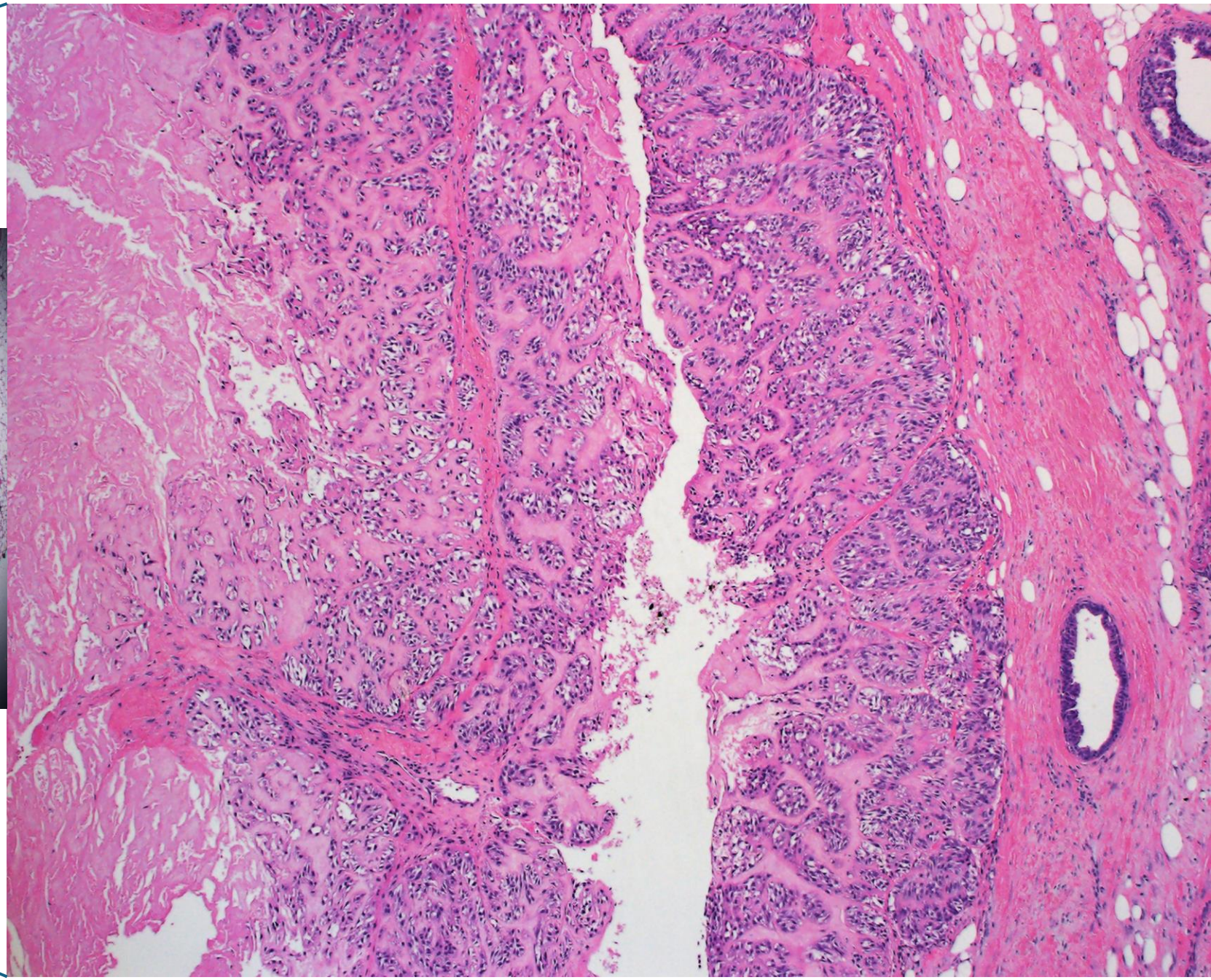
Cansu Karakas; Stanford

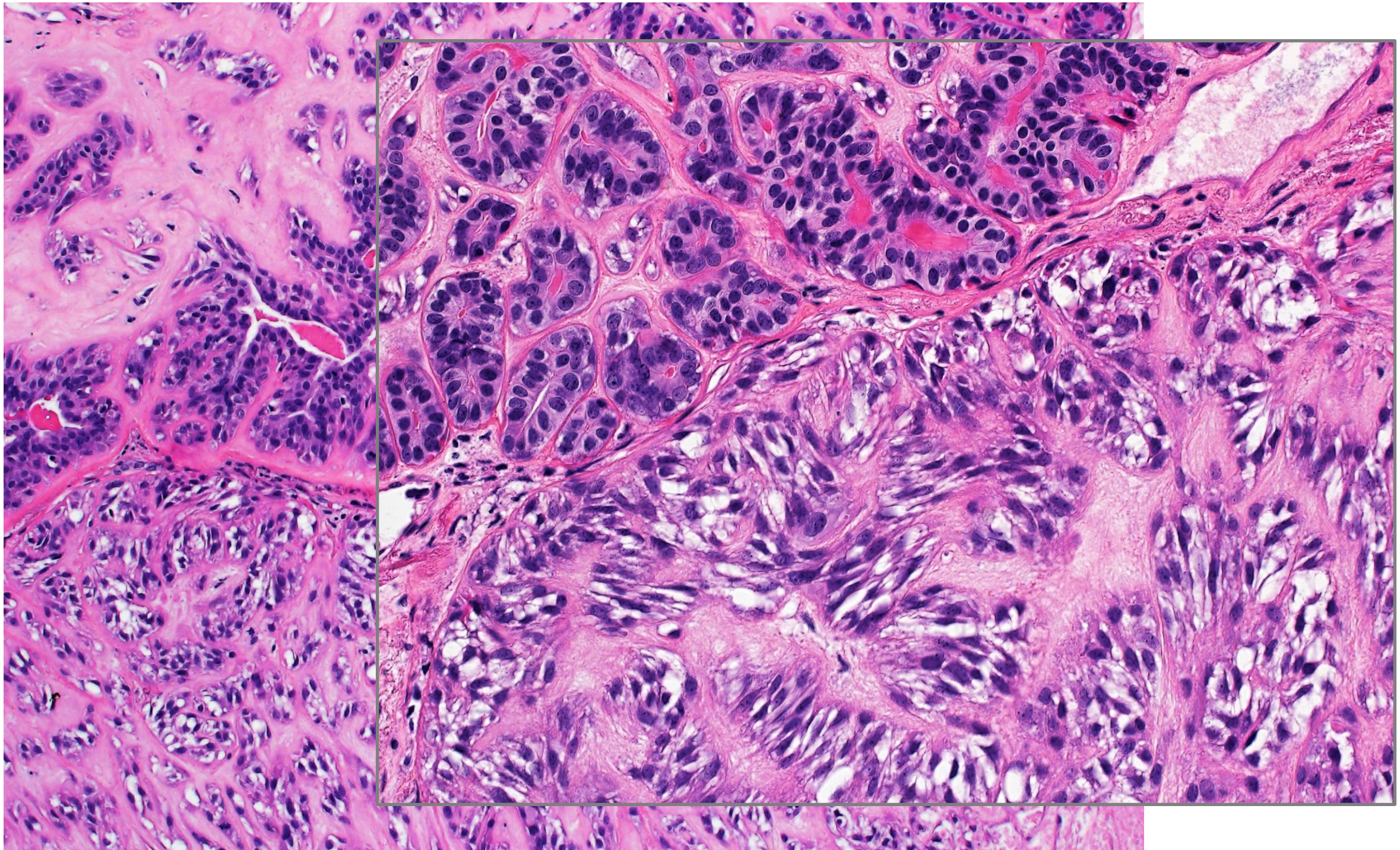
58 yo woman with 5.5 cm cystic breast mass

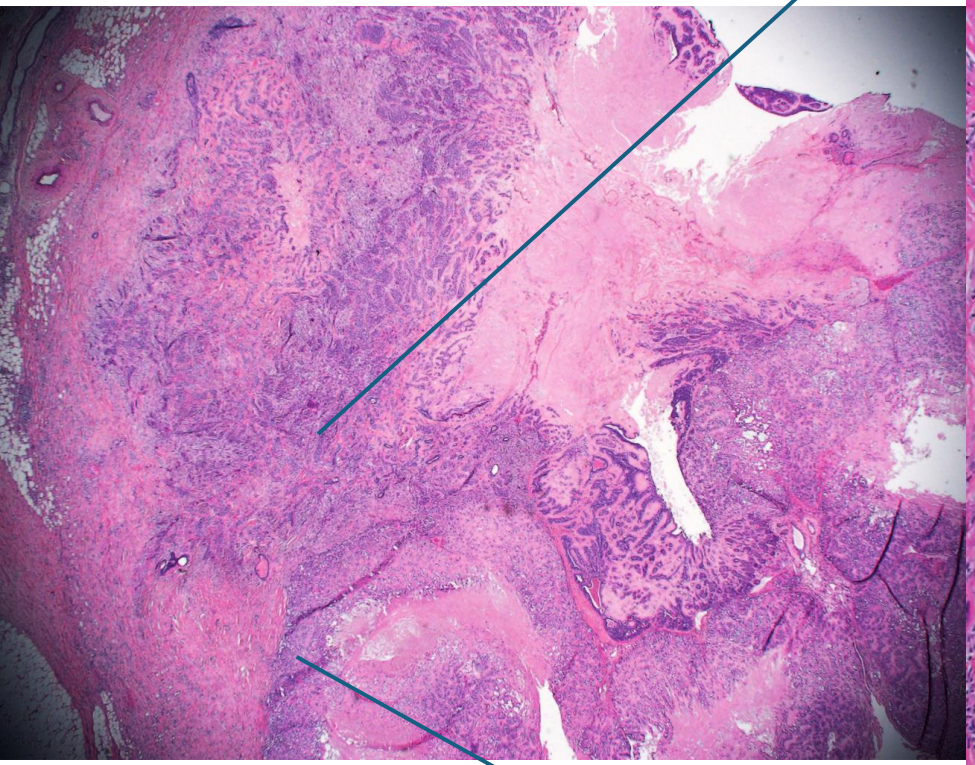


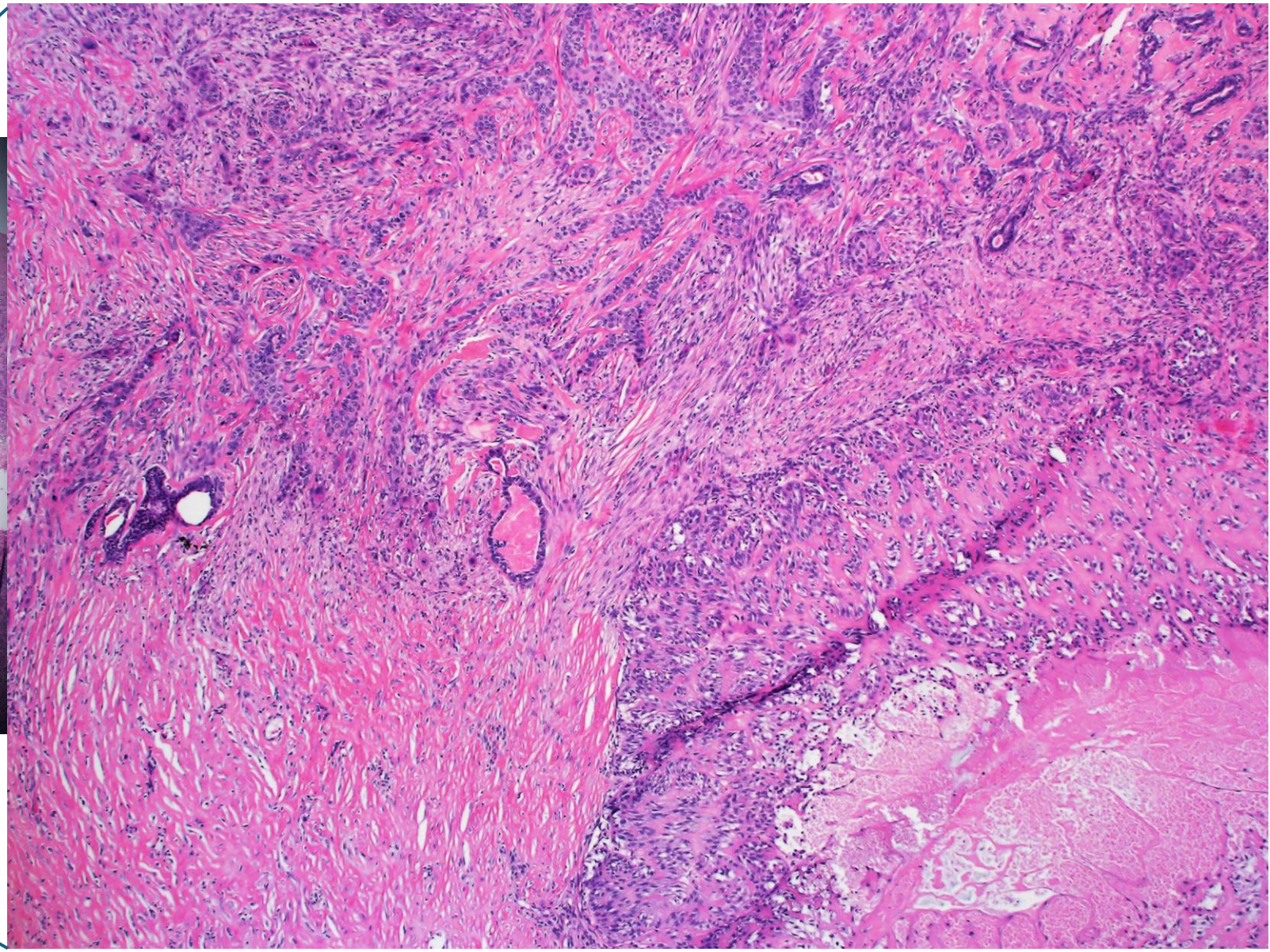


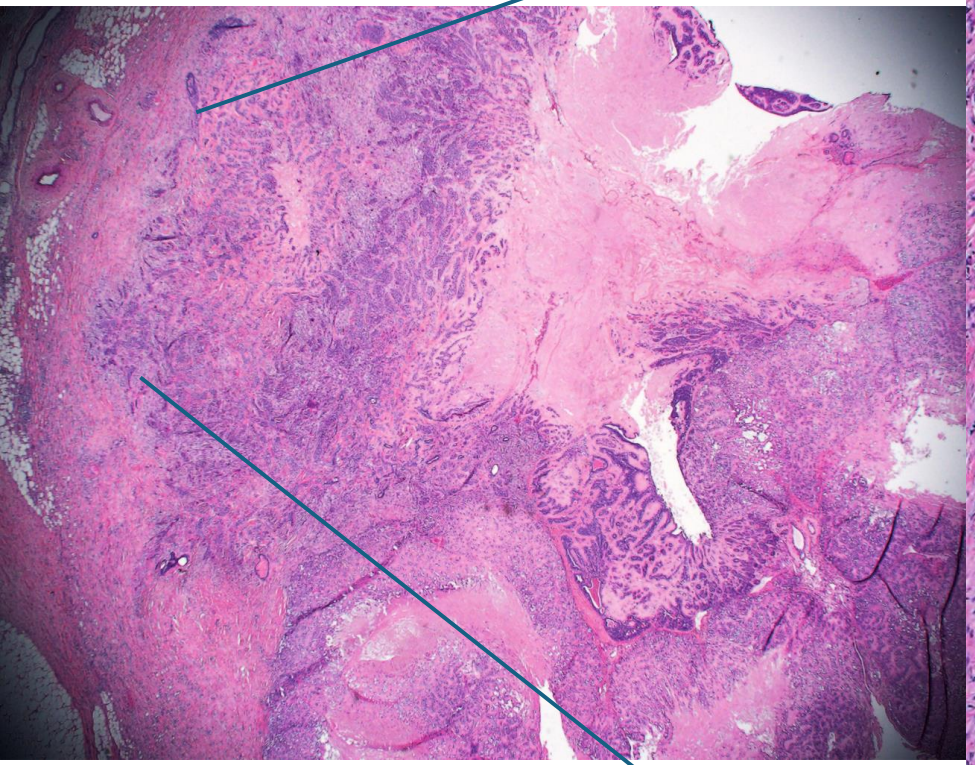


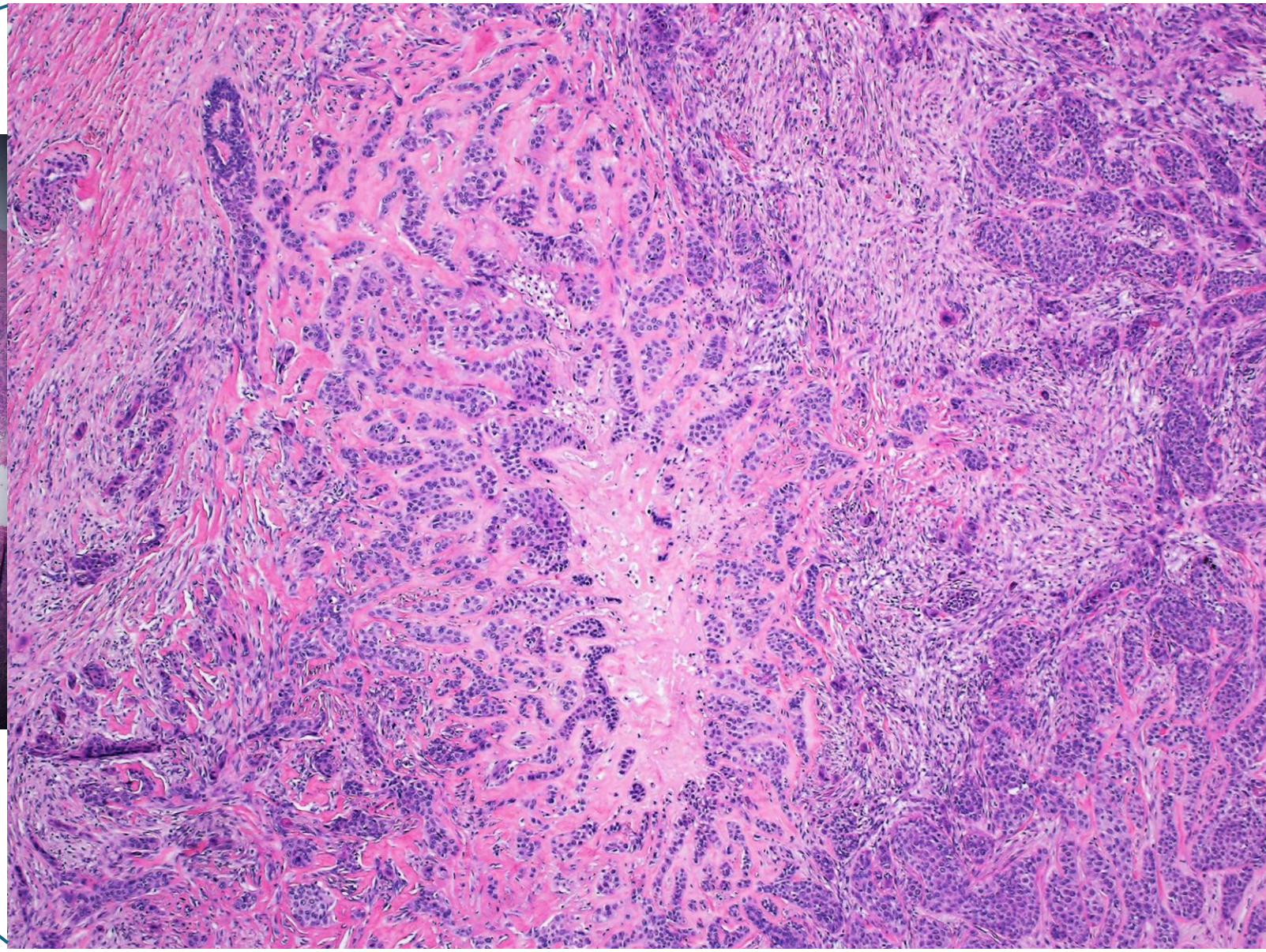


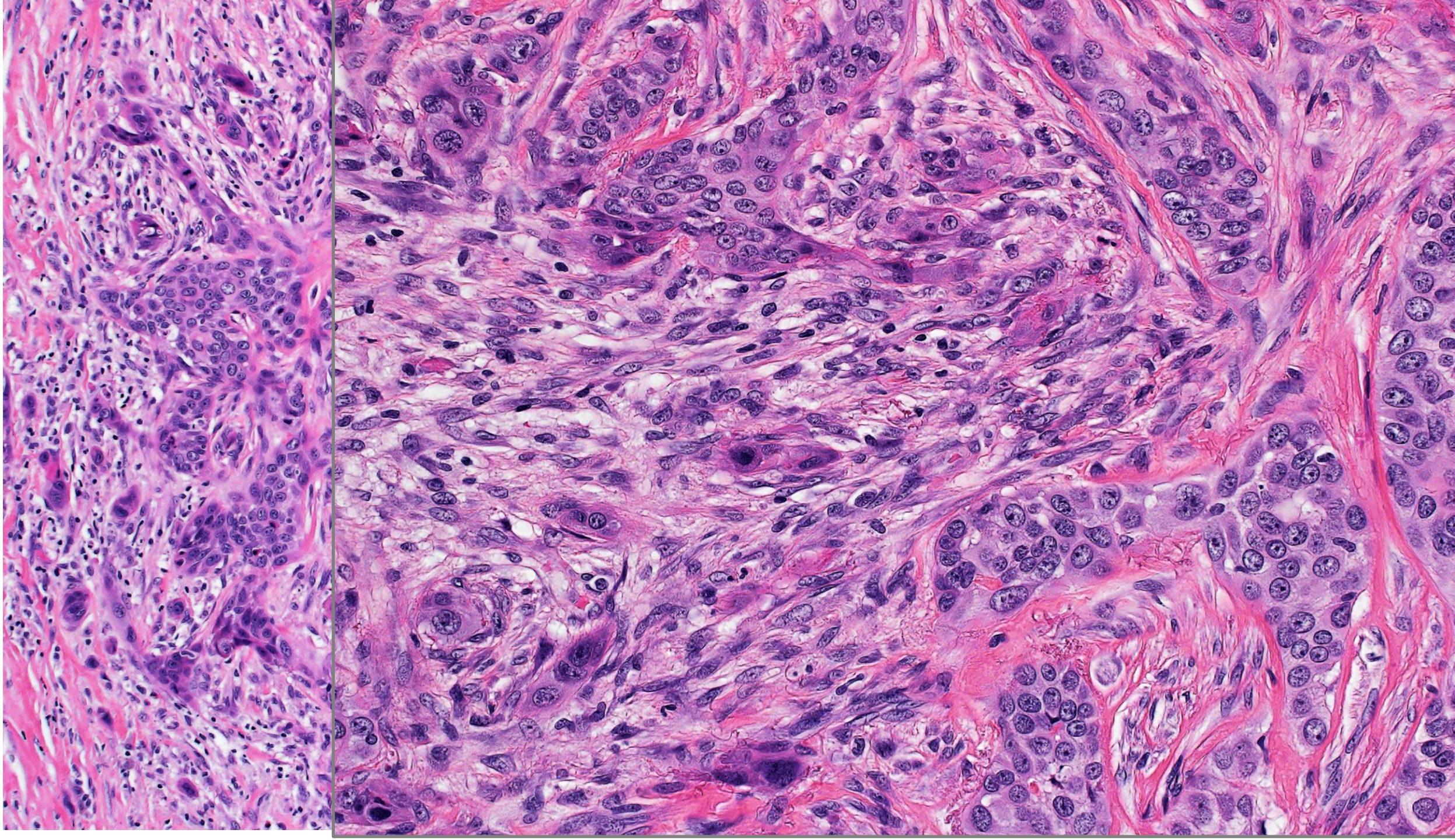










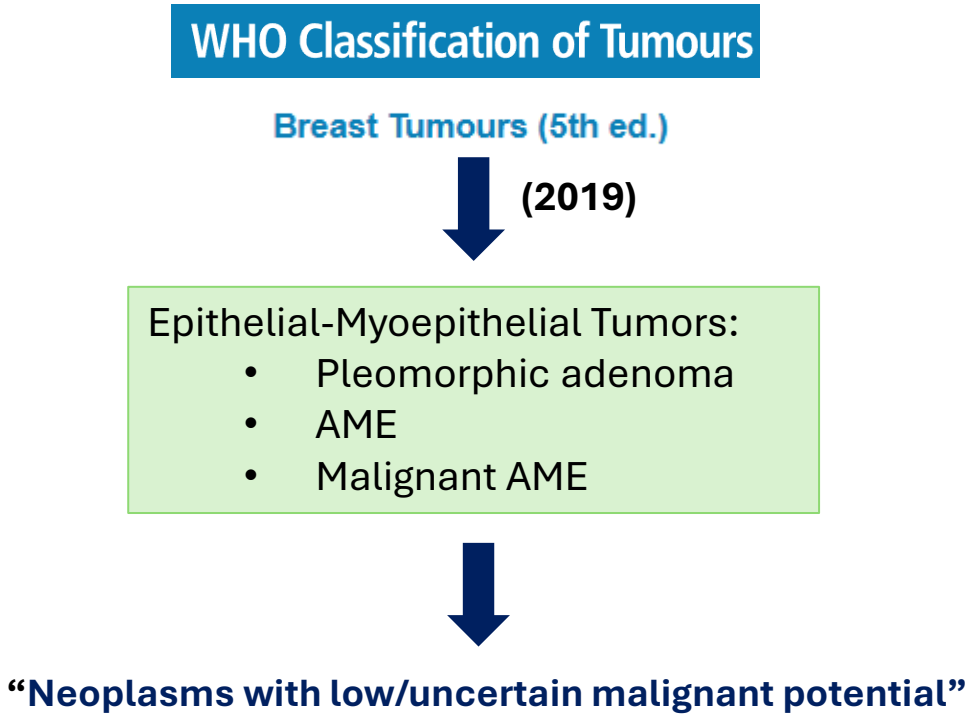


DIAGNOSIS?

Adenomyoepithelioma (AME)

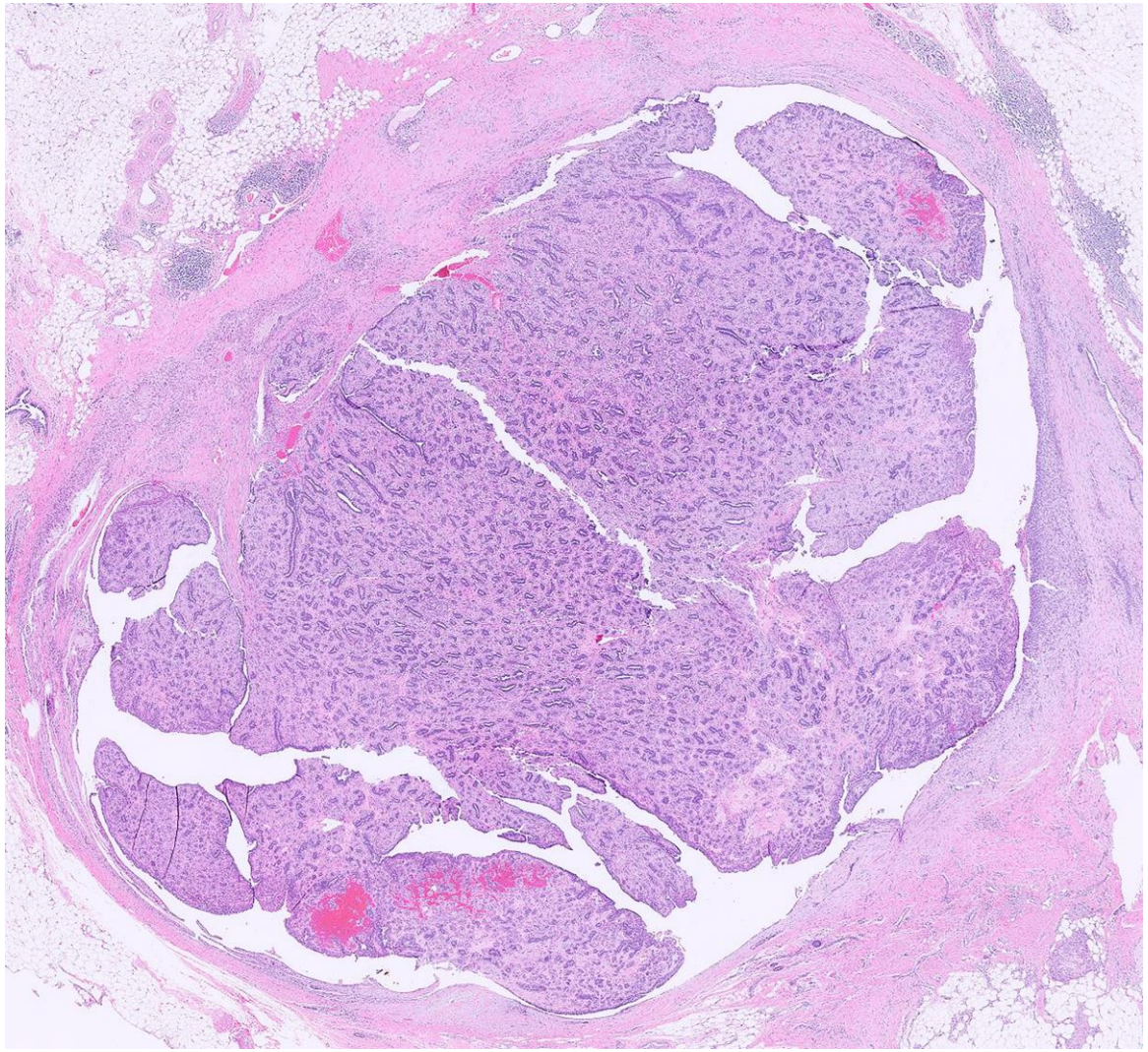
- Biphasic neoplasm characterized by small epithelium-lined spaces with inner luminal epithelial cells and proliferation of variably enlarged and clearly noticeable luminal ME cels. Malignant transformation can occur from either components.

WHO (5th Edition)



Benign AME

- No/Minimal cytological atypia
- Low mitotic rate (≤3 mitoses per 10HPF)
- No necrosis
- Sclerosis or intervening fibrosis frequently present
- ER/PR usually weakly positive/patchy
- HER2 negative



Atypical AME

- Some, but not all of the features of M–AME

- The criteria for “atypical AME” have not been well-established **(defined in the new 6th WHO edition)**

- Histologic features:
  - Overgrowth of epithelial/myoepithelial component
  - Moderately increased mitoses (>3 , ≤5 mitoses per 10 HPFs) in ME/LE cells
  - Mild to moderate nuclear atypia in either component
  - With/without mildly infiltrative pattern and +/- focal necrosis

✓ Atypical mitotic figures, Ki-67 index of > 10% in the MEC component favors malignant transformation (Rakha et al.)

Zhang et al. Breast J. 2004;10:154–155.
Wiens et al. Am J Surg. 2020;219:651–654

Malignant AME

Malignant AME

(Essential: Background recognizable AME architecture)

Luminal Component:

- Invasive ductal ca
- Invasive lobular ca
- Metaplastic ca
  - SCC
  - LGASC
  - Matrix-producing ca
- AdCC

Myoepithelial component:

- Metaplastic ca, spindle cell type
- Myoepithelial carcinoma

Luminal/Myoepithelial Component

- Biphasic carcinomas
- Often ME cells predominant cell type

Epithelial-Myoepithelial carcinoma:
Malignant transformation in both components, irrespective of the presence of AME component

Malignant AME

- Rare (single cell reports or case series)
- Older women (65 years; range 40-93)
- Larger mass than AME (1-17 cm; median 4 cm), rapid size increase
- Usually occurs in peripheral portion
- Multilobulated, well-defined mass to a poorly defined mass with infiltrative borders (reported in >50% of the cases)
- Shares some histologic/genetic overlap with AME → derives from malignant transformation of a classic AME

Malignant AME

- Features that are highly suggestive for a diagnosis of malignancy:
  - ✓ Moderate to marked nuclear atypia
  - ✓ Infiltrative margins (at least focally irregular)
  - ✓ High mitotic activity (>10 per 10 HPF)
  - ✓ Necrosis (>50% of cases)
- Mostly ER/PR/HER2 negative
- Wide spectrum of architectures (solid, tubular/glandular, cystic and papillary etc.)
- **Loss of ME markers/Aberrant ME marker expression**

AME- Immunohistochemistry

Luminal cells
IHC:
LMWCK (CK7, 8, 18, 19)
EMA

Myoepithelial cells
IHC:
HMWCK (CK 5/6, 14, 17),
SMA, calponin, SMM-HC, p63, S100

PANEL APPROACH!

cytologic atypia ↑ → ↑ aberrant expression

- p63, p40 and basal CKs expression in ductal epithelium with squamous metaplasia
- Cross reactivities with stromal myofibroblasts or endothelial cells

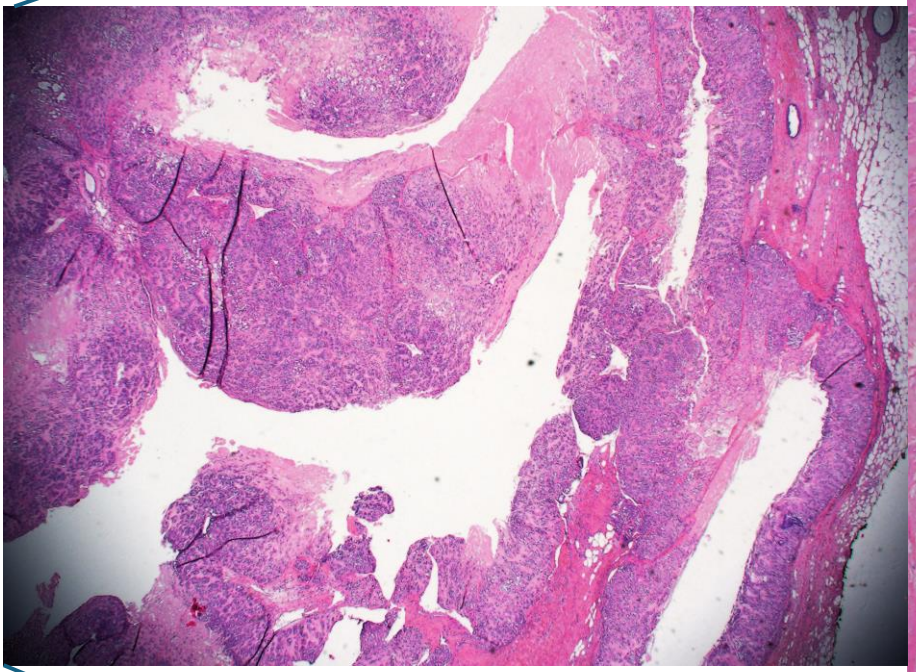
Malignant AME- Differential Diagnosis

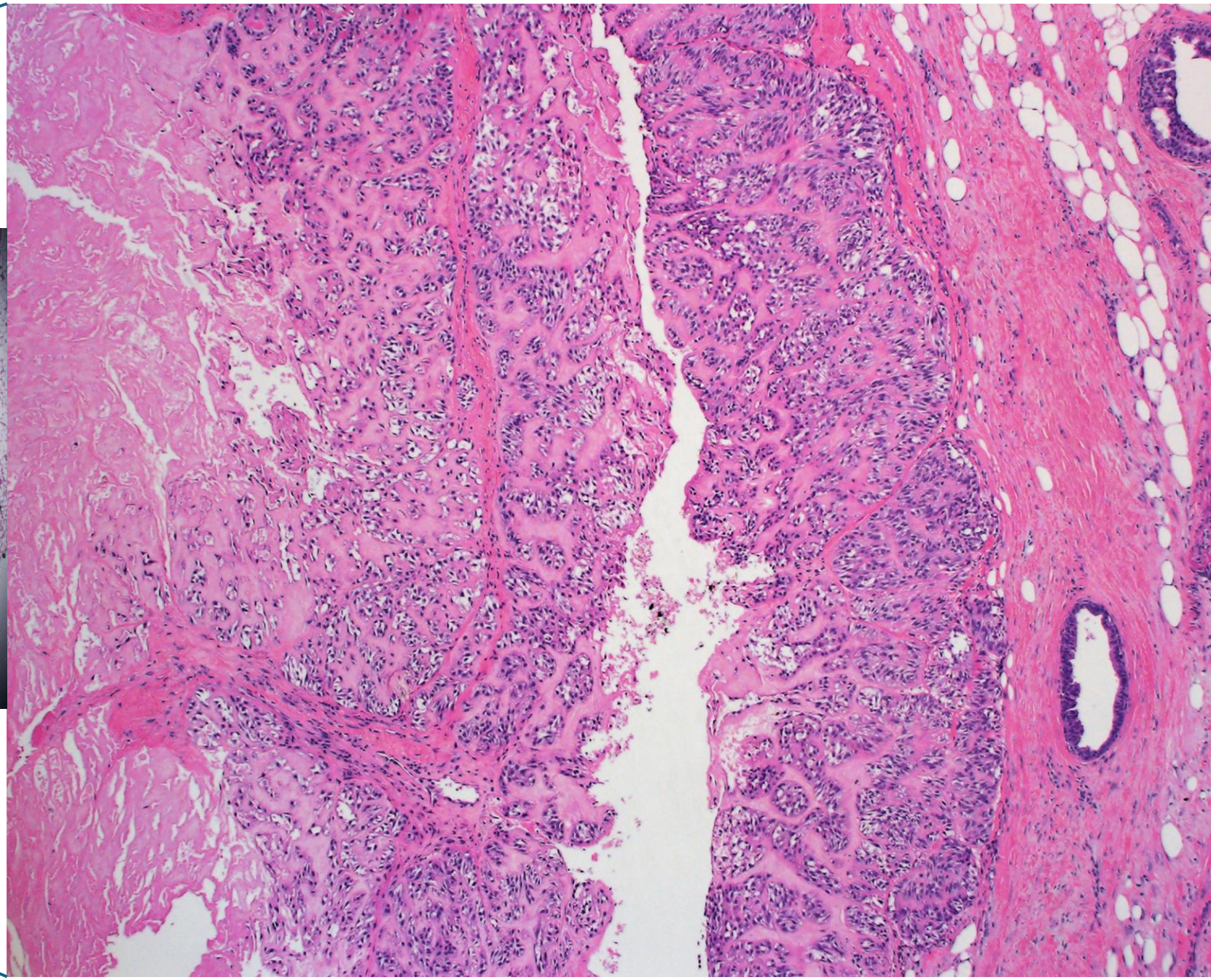
- Metaplastic carcinoma
- Adenoid cystic carcinoma:
  - Adenomyoepitheliomatous component within ADCC
  - OR
  - ADCC with coexisting AME

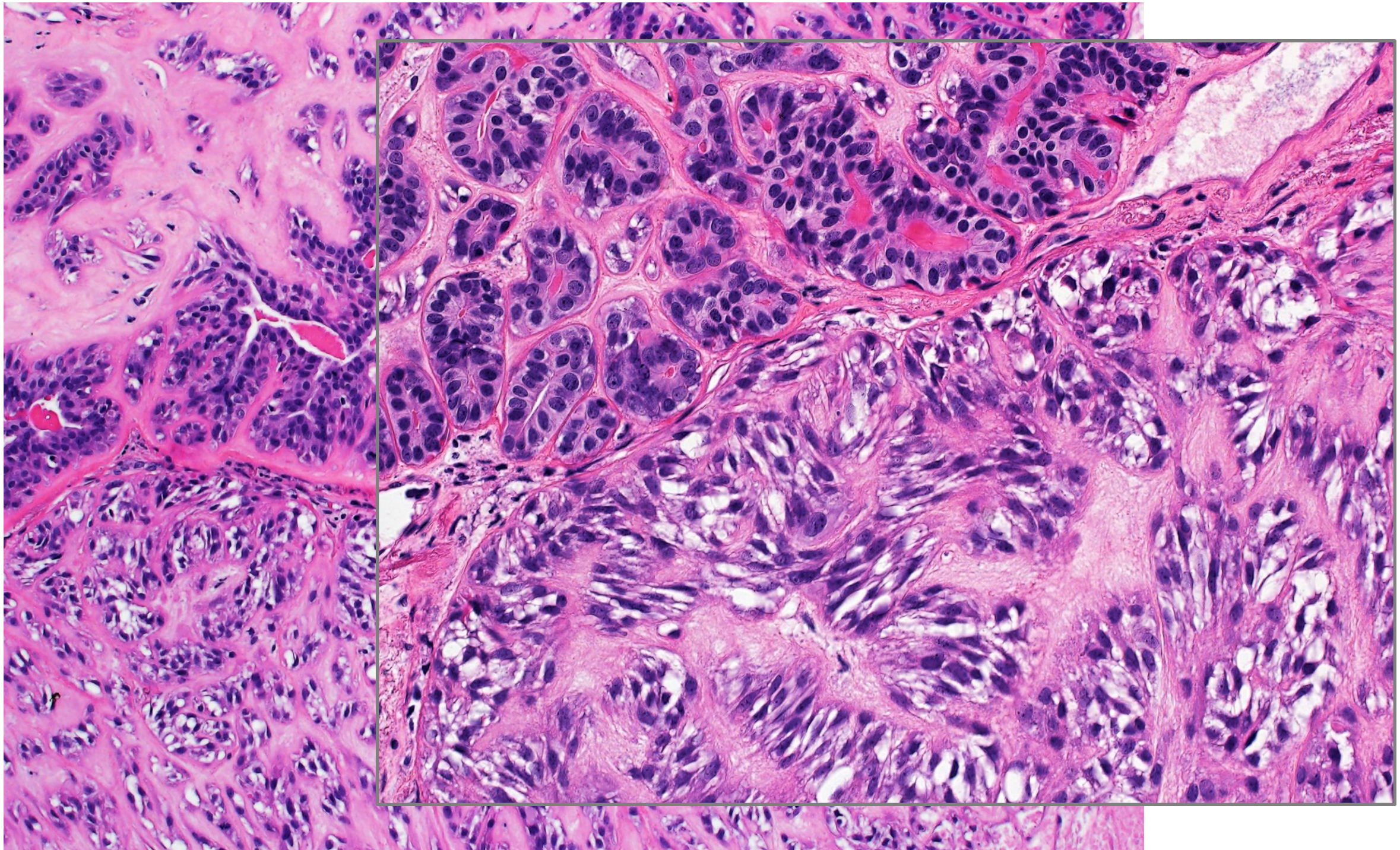
- ✓ The association with C-AME or A-AME
- ✓ HRAS Q61R mutation in ER(-) AME

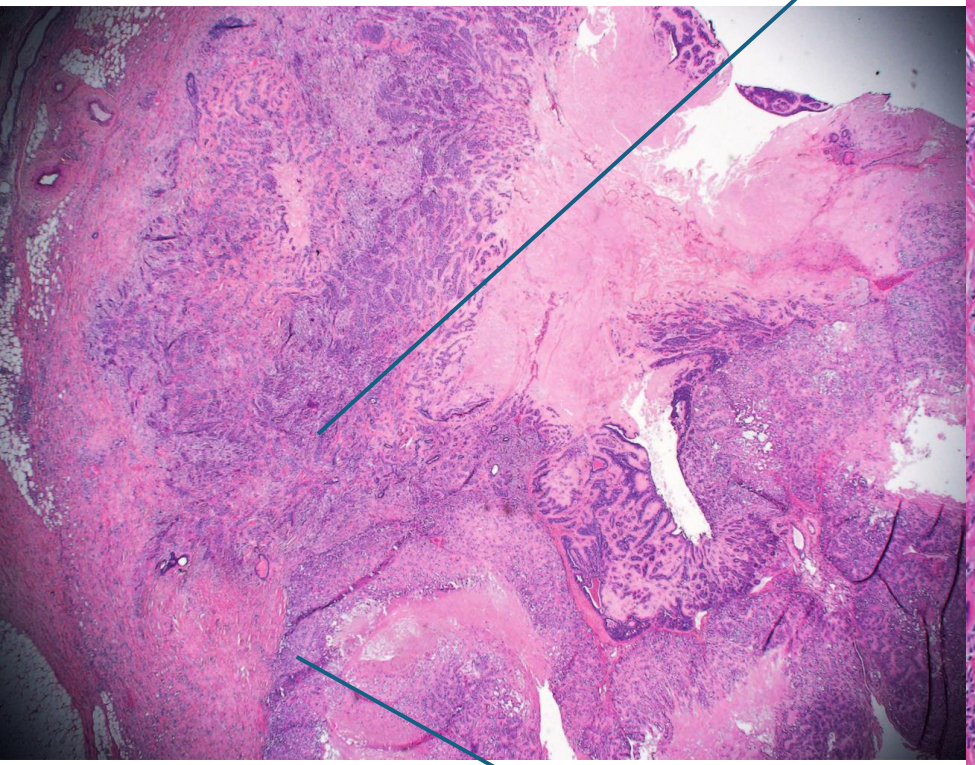
- **Nevertheless, all these tumours are part of the spectrum of breast tumours composed of epithelial and myoepithelial cells; therefore, their features can merge.**

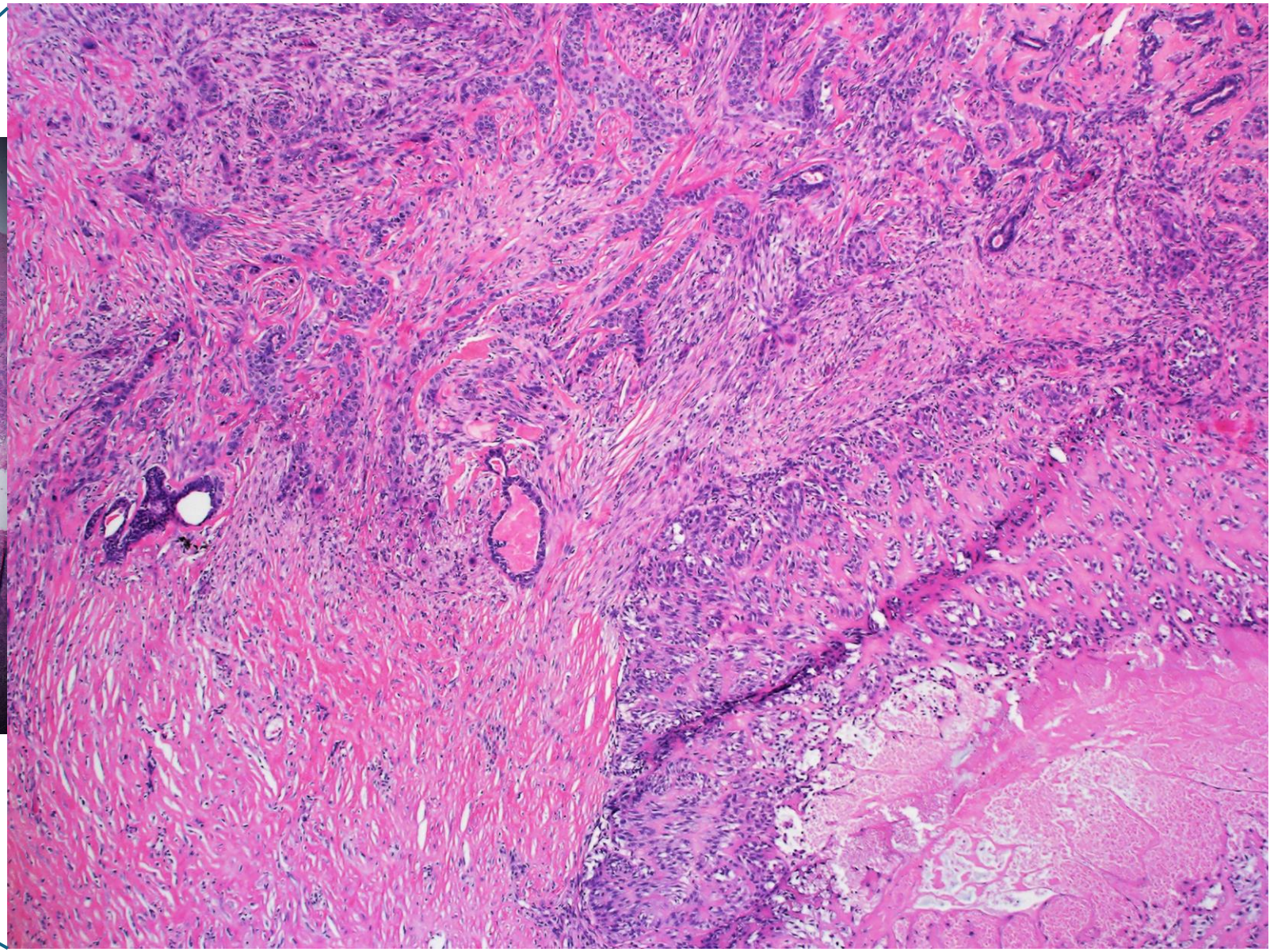
Arch Pathol Lab Med—Vol 146, August 2022
J Pathol 2018; 245: 373–383

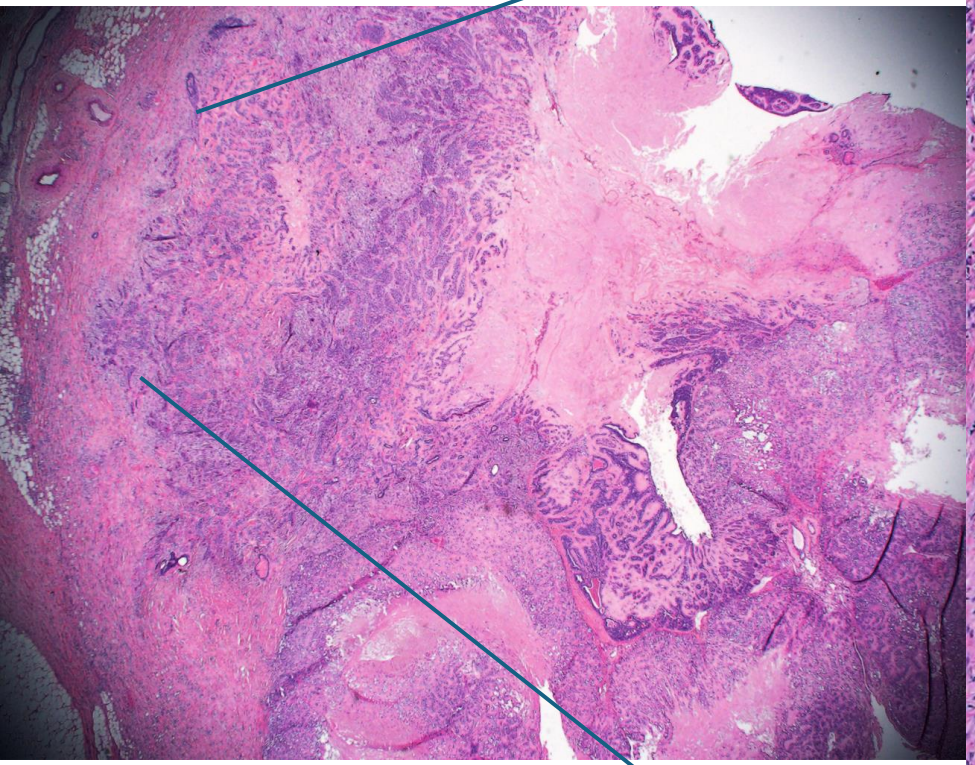


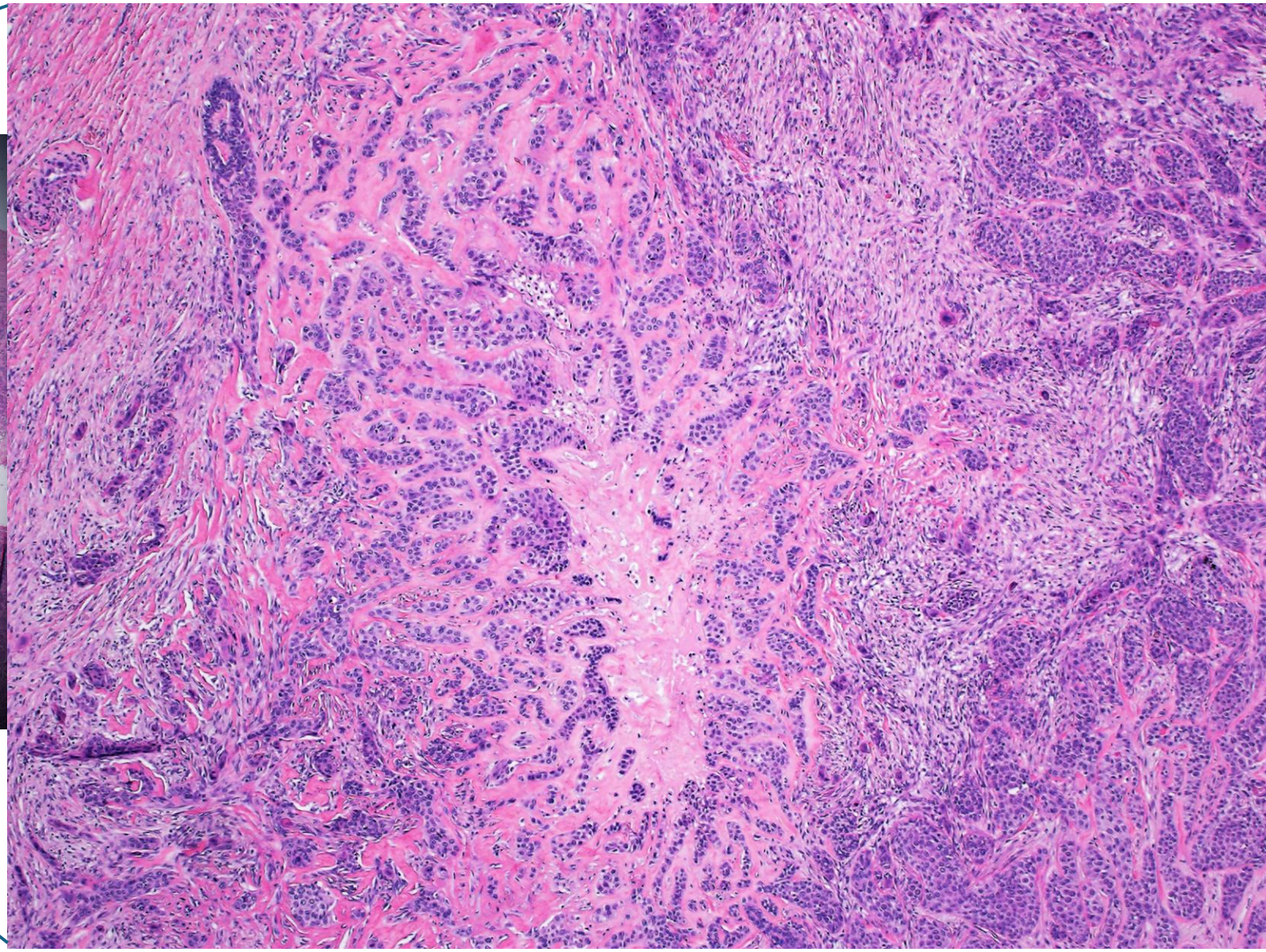


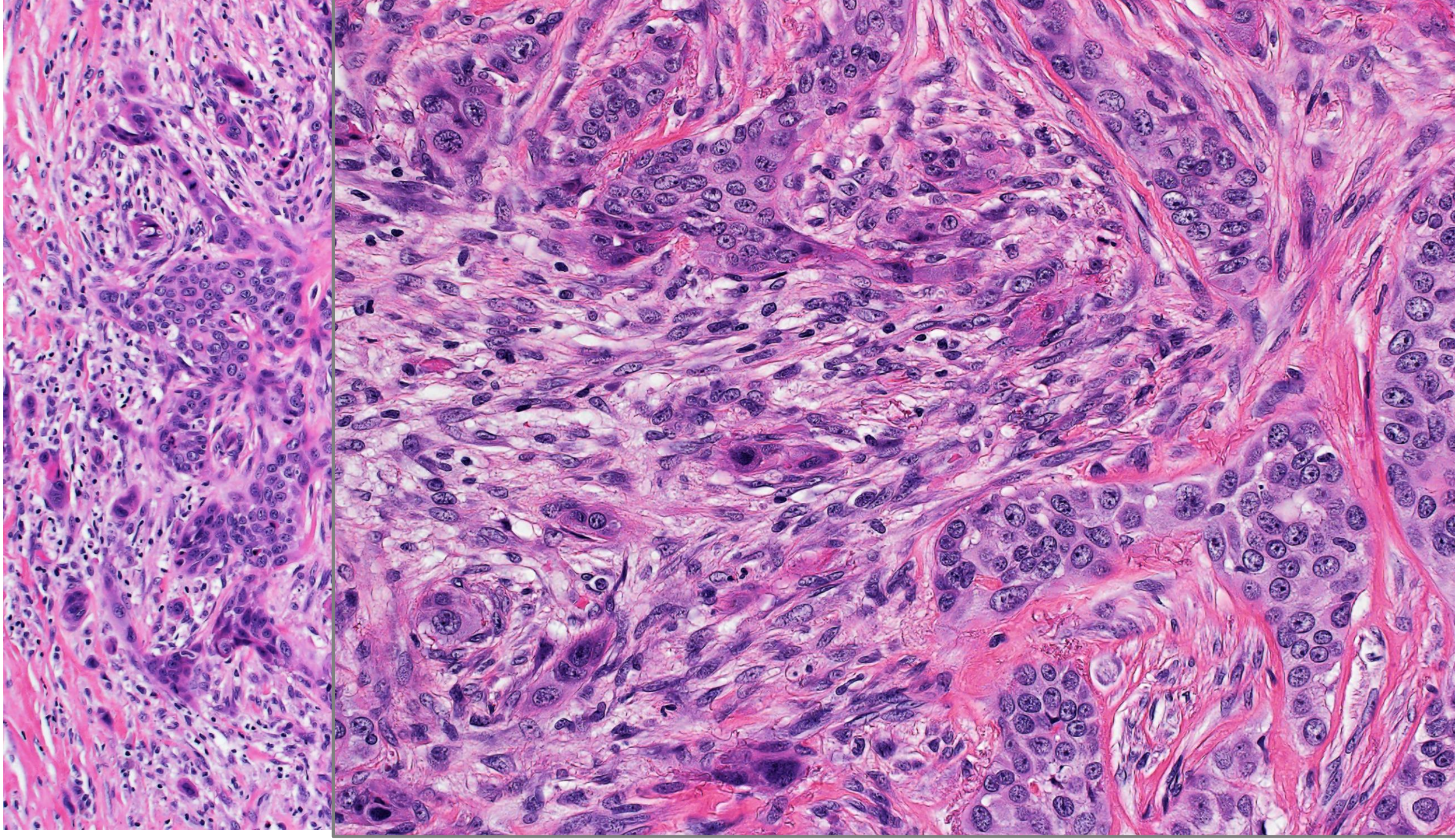












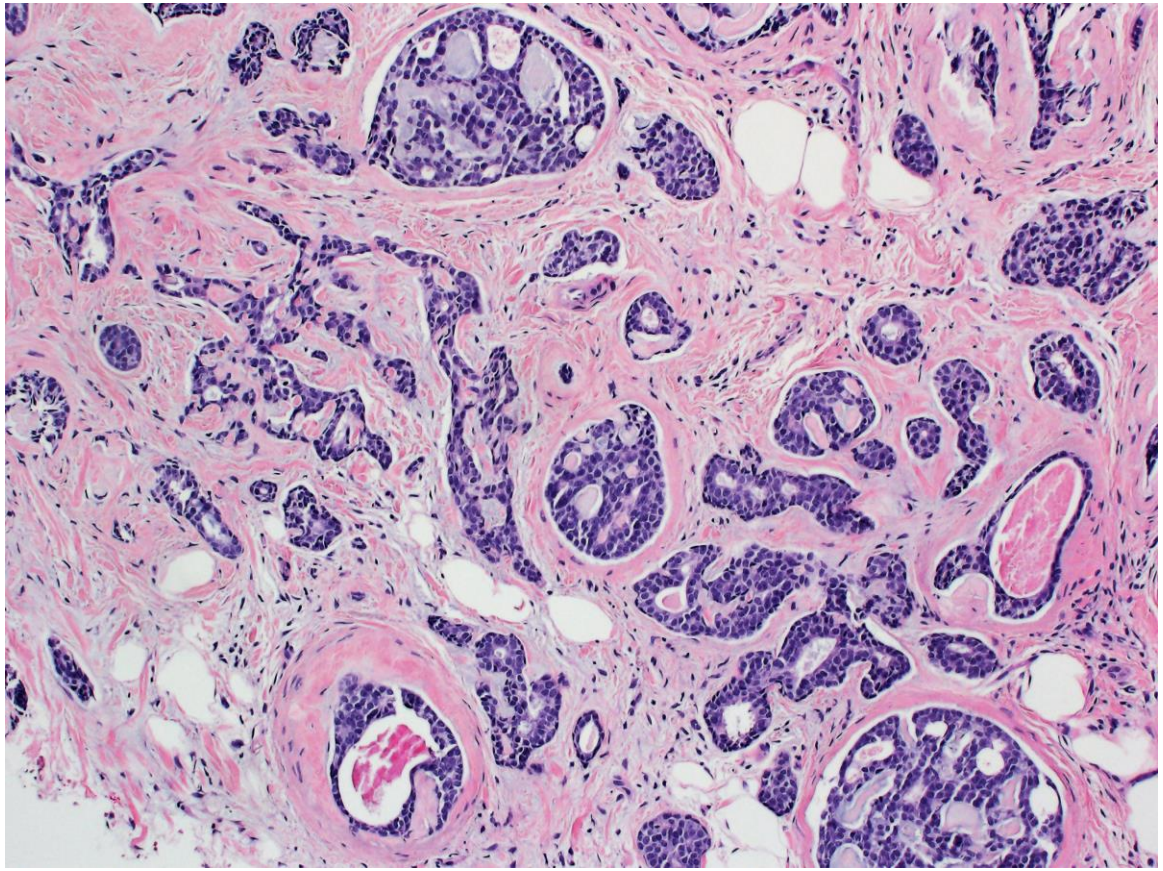
Differential Diagnosis- AdCC

- Translocation: t(6;9)(q22-23;p23-24) creates MYB-NFIB fusion
  - (≥50 % of breast AdCC and **0 % of breast AME**)

- c-MYB IHC:
  - AdCC: c-MYB expression in both MYB rearrangement-positive and -negative cases
  - AME: 27 % with weak-to-moderate c-Myb expression

- HRAS Q61R mutation in ER-negative AME

AdCC



Baraban et al. Histopathology 2018

Molecular Alterations in AME (cont.)

Filho et al. Nat Commun. 2018;9(1):1816

- 43 AME cases
  - 18 (42%) displayed atypical histologic features
  - 16 (37%) lacked ER expression (associated with nuclear pleomorphism, high mitotic rate, and higher Ki-67 proliferation index)

Whole-exome and targeted sequencing analysis

- Different signaling pathways; associated with ER status
  - **ER-positive AMEs**: *PIK3CA* or *AKT1* E17K mutations
  - **ER-negative AMEs**: *HRAS Q61* and G12/G13 hotspot mutations with *PIK3CA*/*PIK3R1*mutations

Molecular Alterations in AME (cont.)

- Fewer copy number alterations and lower TMB in AMEs than conventional breast carcinoma, ductal phenotype

- Frequent copy number alterations:
  - Losses of 6p22 (19%), 9p21 (*CDKN2A*, 13%), and 4q31 (*INPP4B*, 6%), and gains of 12p12.3 (*ETV6*, 16%) and 5p15 (*TERT*, 13%)

- Malignant transformation has been associated with homozygous deletion of *CDKN2A* or somatic mutations in *TERT* and amplification of c-Myc gene

- Rare reported mutations: *APC, STK11, ATM, EGFR, FGFR3* and *GNAS*, with or without concurrent *AKT1*

Molecular Alterations in AME (cont.)

Comparison of AME with salivary gland tumors

- *HMGA2-WIF1* fusion in one ER (+) AME (1/13 cases)
  - Associated with tubular and papillary growth pattern and no cellular atypia
  - Lacked HRAS, PIK3CA or AKT1 somatic mutations

- PLAG1 rearrangement (2/7 AME cases, CTNNB1:PLAG1, TRPS1:PLAG1)

- Different from salivary gland tumors where HMGA2 rearrangement is linked to progression of pleomorphic adenoma ➡ epithelial-myoepithelial carcinoma

- *MYB-NFIB*, *MYB-MYBL1*(AdCC) not detected in AMEs

Pareja et al. NPJ Breast Cancer 2019
Ma et al. Histopathology 2021

M-AME-Prognosis and Treatment

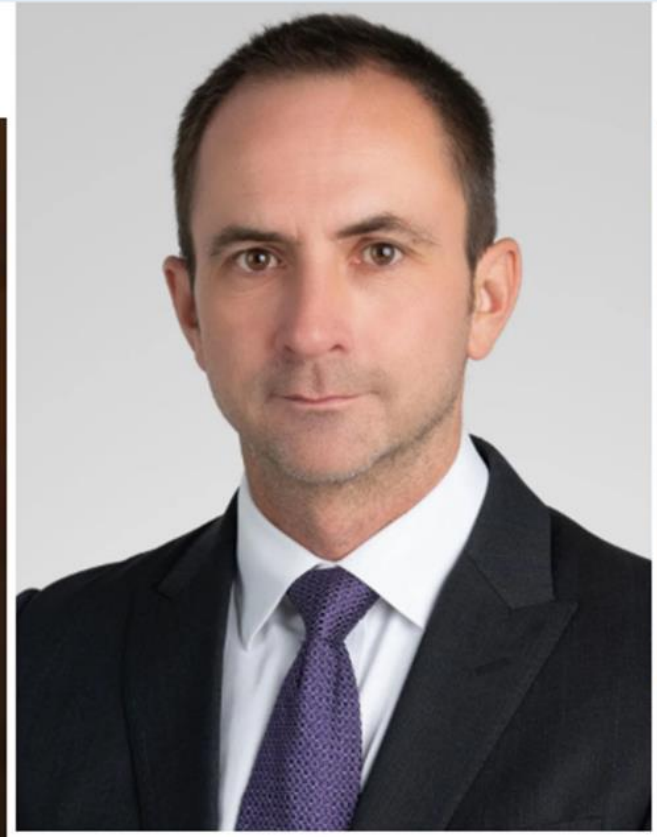
- Large size may be associated with metastatic potential
- Distant metastatic sites: lung/brain (most) and others (thyroid, bone, brain, liver, kidney, skin, soft tissue, and thoracic wall)
  - Can appear after several years
  - Local recurrences 8 months to 5 years after initial excision
- Surgical excision with negative surgical margins +/- ALND
- Prognosis of malignant AME with invasive carcinoma depends on the histological subtype of the invasive disease
- The role of chemotherapy in M–AME is not clear
  - Benefit of eribulin reported in a patient with stage 4 M–AME

67th ANNUAL SOUTH BAY PATHOLOGY SOCIETY SPRING MEETING

SELECTED ISSUES IN BREAST PATHOLOGY

SATURDAY, MAY 9, 2026

Gregory Bean, MD
Stanford University



Gregor Krings, MD, PhD
Cleveland Clinic
Keynote Speaker

Yunn-Yi Chen, MD, PhD
UCSF

In person meeting at (space will be limited!):

Sheraton Palo Alto Hotel
625 El Camino Real
Palo Alto, CA 94301