JUNE 2023 DIAGNOSIS LIST

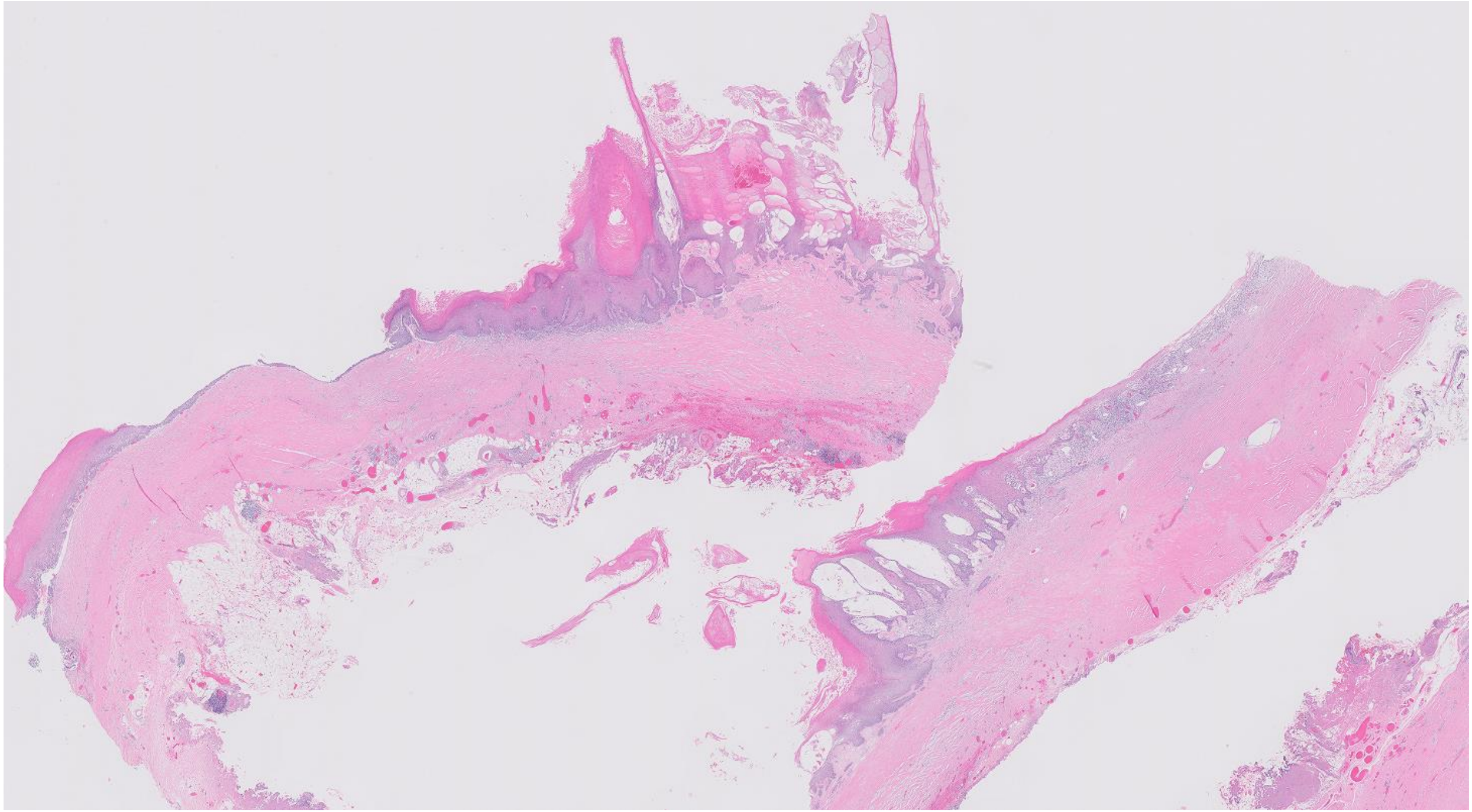
23-0601: Invasive squamous cell carcinoma of breast capsule
23-0602: Benign biphasic neoplasm, favor mucous gland adenoma
23-0603: AD-PKD, Xanthogranulomatous pyelonephritis- Liesegang Rings
23-0604: EBV positive plasmacytoma
23-0605: Atypical apocrine adenosis
23-0606: Pagetoid DCIS
23-0607: Pancreatic intraductal oncocytic papillary neoplasm with high-grade dysplasia
23-0608: Mixed papillary and squamoid/mucinous tumor, favor arising in benign epithelial inclusion

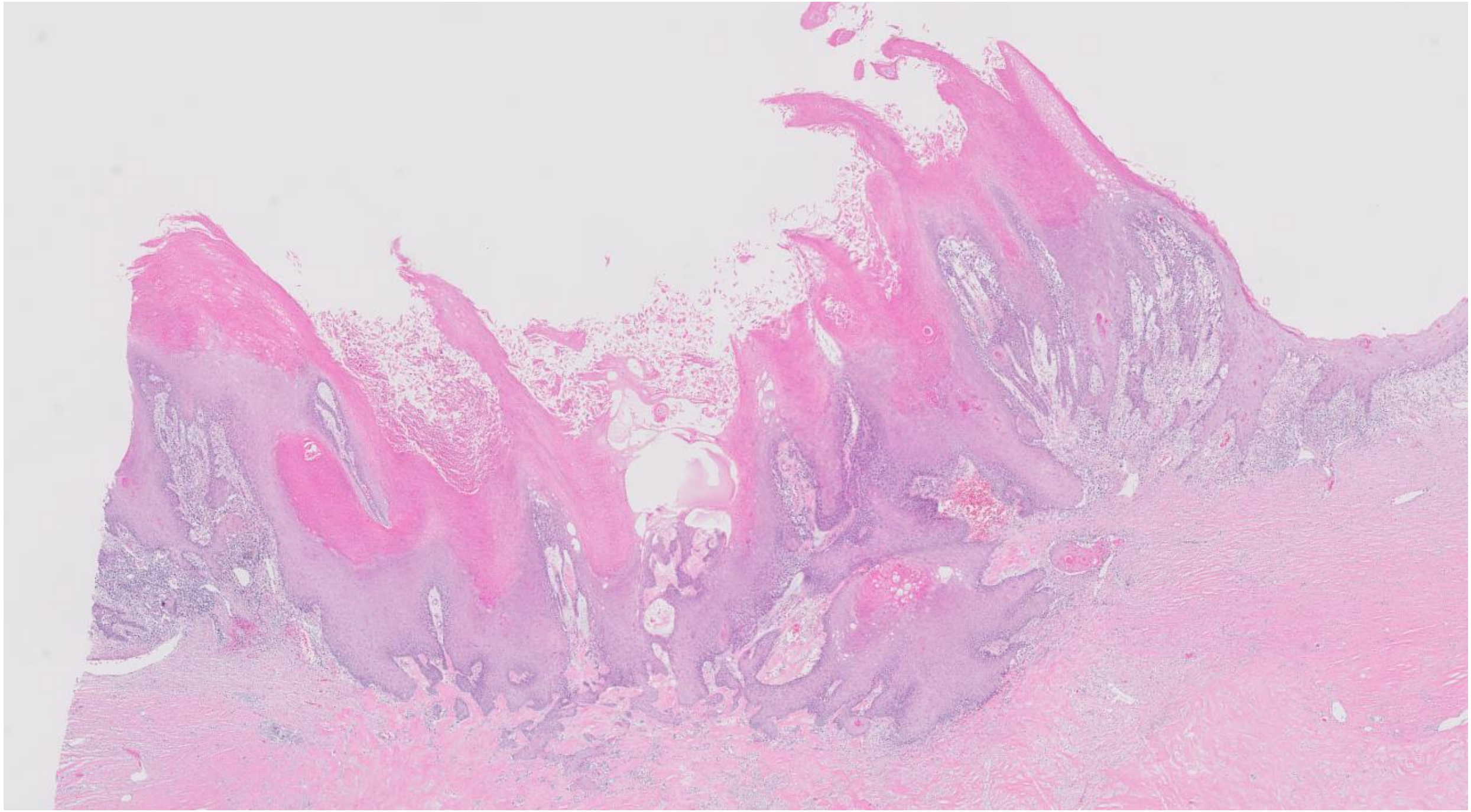
23-0601

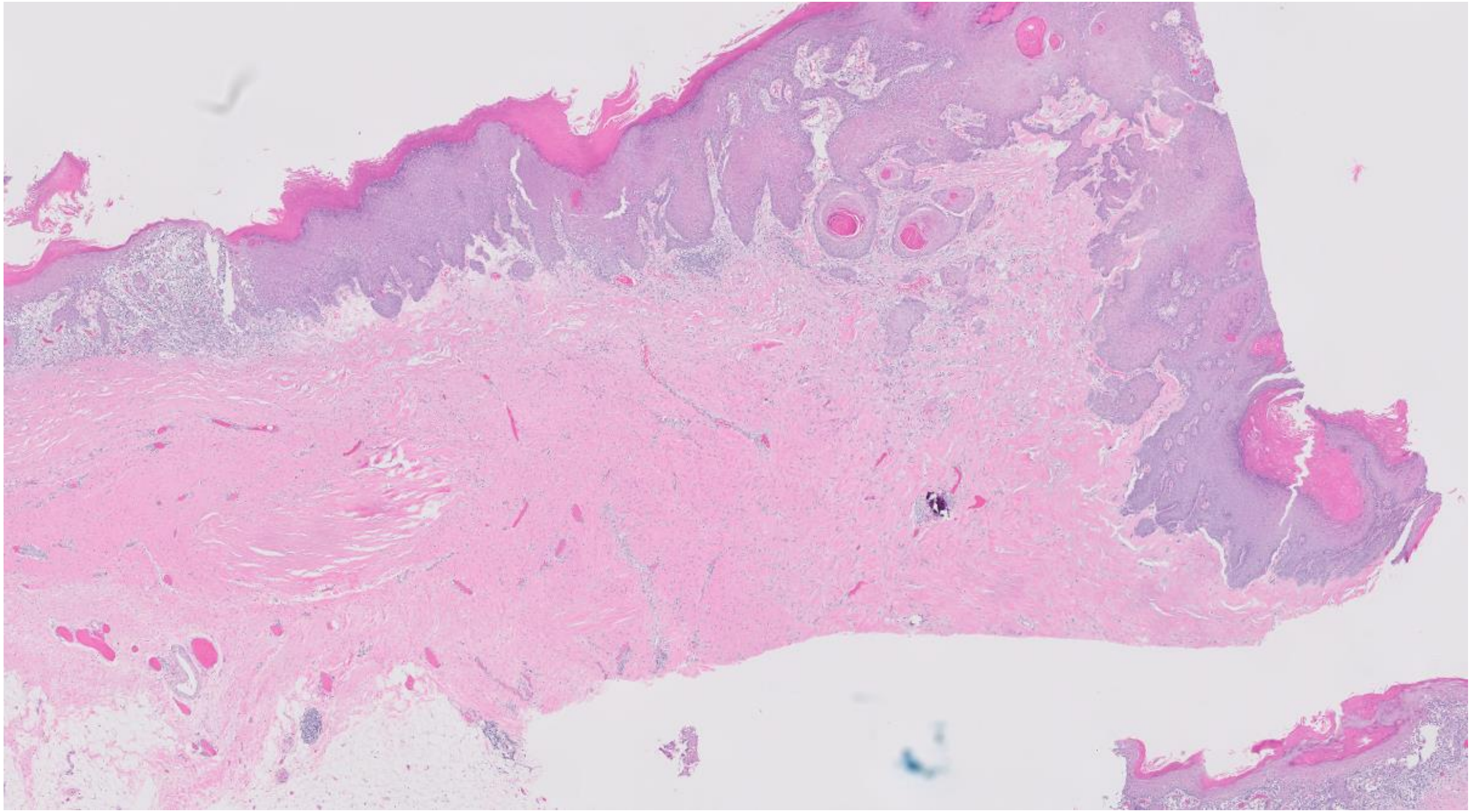
Ying Liu/Gregory Bean; Stanford

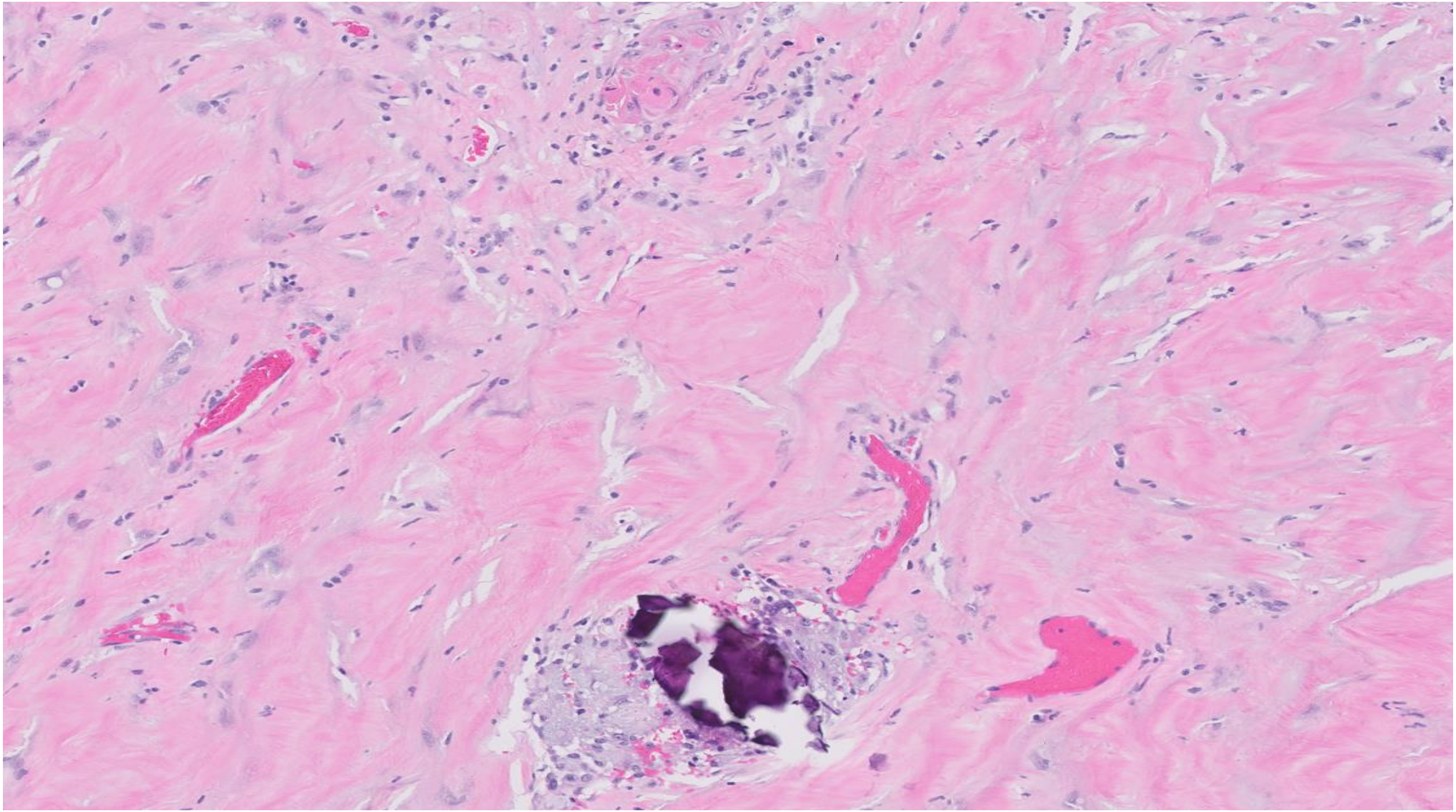
72-year-old woman with a history of implants for augmentation in 2005, right side implant revision in 2017, and right implant exchange with concern for purulence and capsular contracture in 2021. The patient recently underwent right capsulectomy.

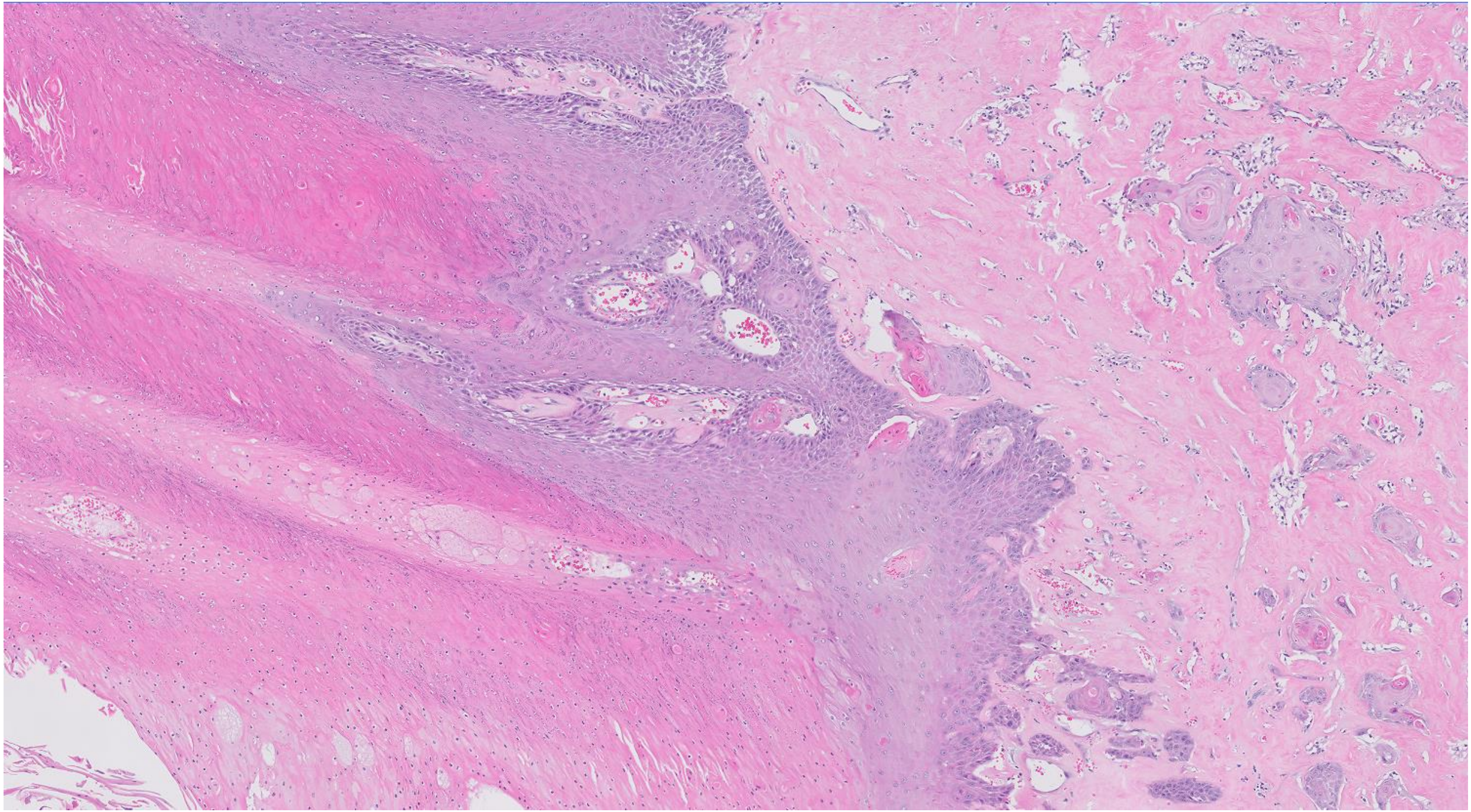
(consult case provided courtesy of Dr. John Moretto of California Pacific Medical Center, San Francisco, CA)

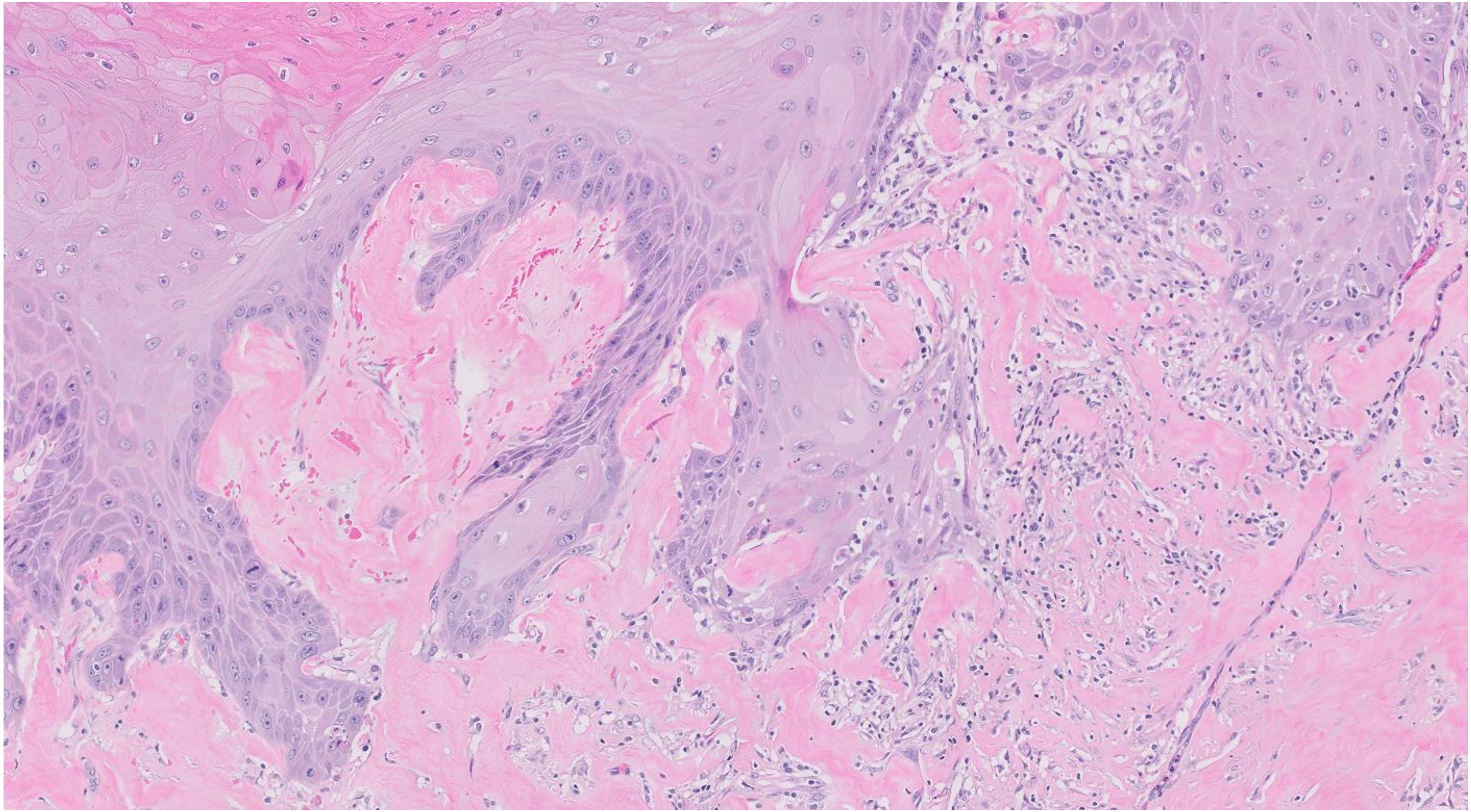


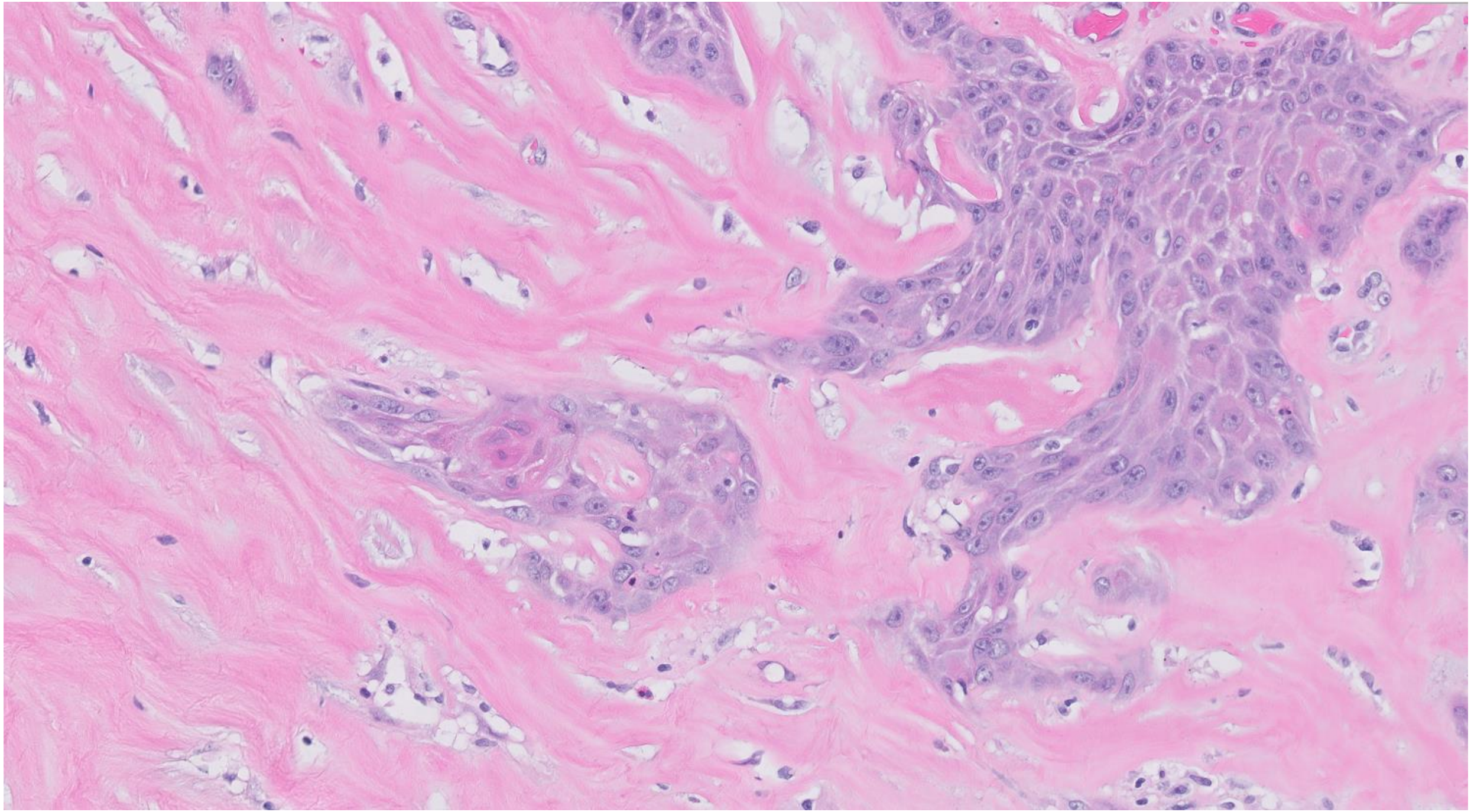












Differential Diagnosis

- Pseudoepitheliomatous hyperplasia (PEH)
- Invasive squamous carcinoma (SCC)
- Breast Implant-Associated Anaplastic Large Cell Lymphoma (BI-ALCL)
- Epstein-Barr Virus(+) Large B-Cell Lymphoma Associated With Breast Implants (EBV+ LBCL-BI)
- ……

Pseudoepitheliomatous hyperplasia (PEH)

- Can mimic SCC, especially SCC in situ, but does not show infiltrative features or high-grade cytologic atypia
- Mitotic figures can be numerous but should be in basilar keratinocytes and not atypical
- Well-differentiated SCC generally shows malignant features not commonly seen in PEH, including
  - Infiltrative areas
  - Cytologic atypia, atypical mitoses
  - Squamous pearls

Squamous Cell Carcinoma Arising in Breast Implant Capsules

Mytien Thi Goldberg, MD,[a] Jason Llaneras, MD,[b] Thomas D. Willson, MD,[a] John Brain Boyd, MD,[a] Rose J. Venegas, MD,[c] Christine Dauphine, MD,[d] and Babak N. Kalantari, MD[e]

TABLE 1. Review of the Literature Detailing 8 Reported Cases of SCC Associated With Breast Implant Capsule

Study	No. Patients	Age at Diagnosis	History of Cancer	Reason for Implantation	Type of Implant	Time Until Diagnosis, y	Therapeutic Treatment	Follow-up
Paletta et al[9]	1	52	Not Reported	Cosmetic	Silicone implant (Heyer Schulte)	16	Radical mastectomy	Disease free at 12-month follow-up
Zomerle et ali[10]	1	58	Not reported	Cosmetic	Smooth Silicone Implant	15	Radical Mastectomy	Not Reported
Oslen et al[11]	2	56	Not Reported	Cosmetic	Textured Saline implant	18	Mastectomy with postoperative chemotherapy	Palliative care at 1-month follow-up
		81	Not reported	Breast reconstruction status post benign lesion excision	Unknown Silicone implant	42	Mastectomy	Distant metastases at 5-month follow-up
Kitchen et al[12]	1	52	Not Reported	Cosmetic	Silicone Implant (Heyer Schulte)	25	Modified radical mastectomy	Not reported
Buchanan et al[13]	1	65	Not reported	Cosmetic	Foam-Covered silastic (Heyer Schulte)	35	Radical Mastectomy, medial chest wall resection and postoperative radiation	Disease free at 8-year follow-up
Goldberg et al (Current Study)	2	40	No personal or family history	Cosmetic	Smooth Saline Implants	11	Neoadjuvant chemotherapy, Patient expired before` chest wall resection	Expired from malignant pleural effusions at 3-month follow-up
		62	No personal or family history	Breast reconstruction status post benign lesion excision	Silicone implants	32	Chemoradiation	Lost to follow-up

Included are the 6 previously published cases and the 2 reviewed in this study.

Case Report

Primary Squamous Cell Carcinoma Arising From a Breast Implant Capsule: A Case Report and Review of the Literature

Aesthetic Surgery Journal
2018, Vol 38(7) NP97–NP102

DOI: 10.1093/asj/sjy092
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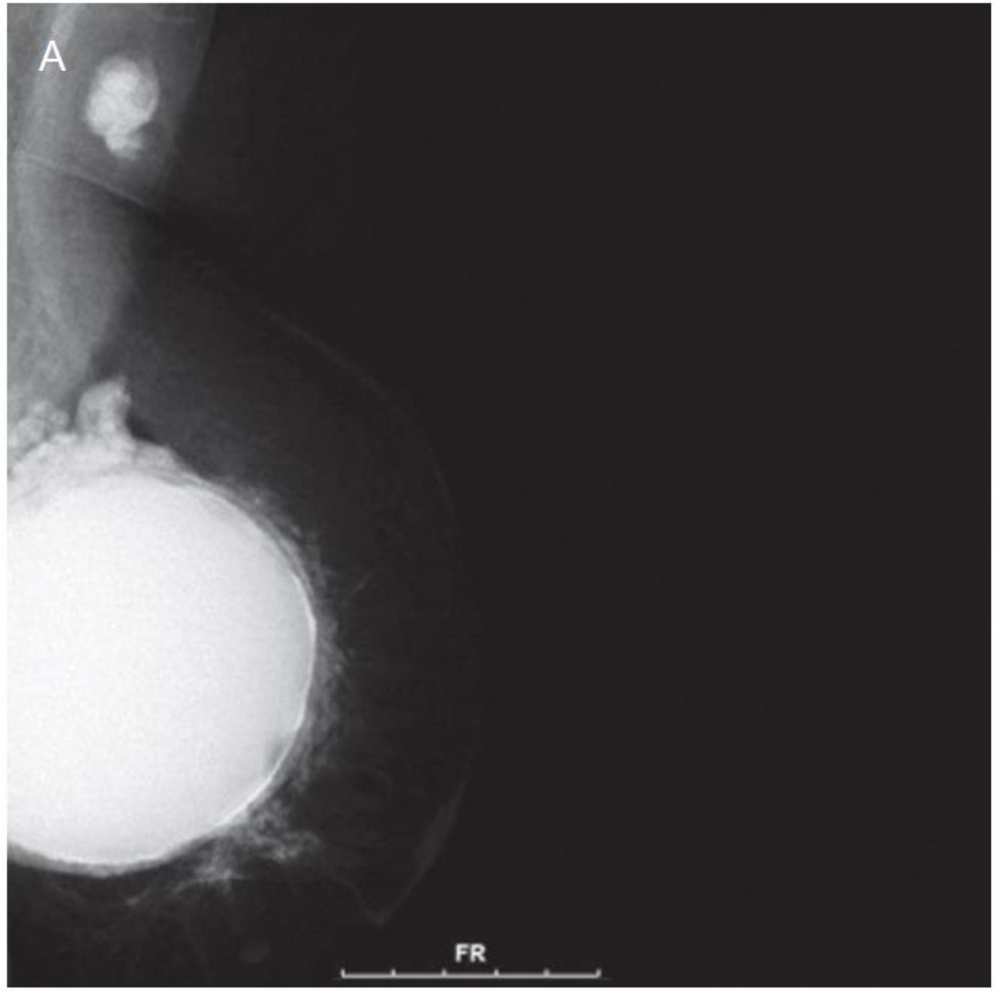

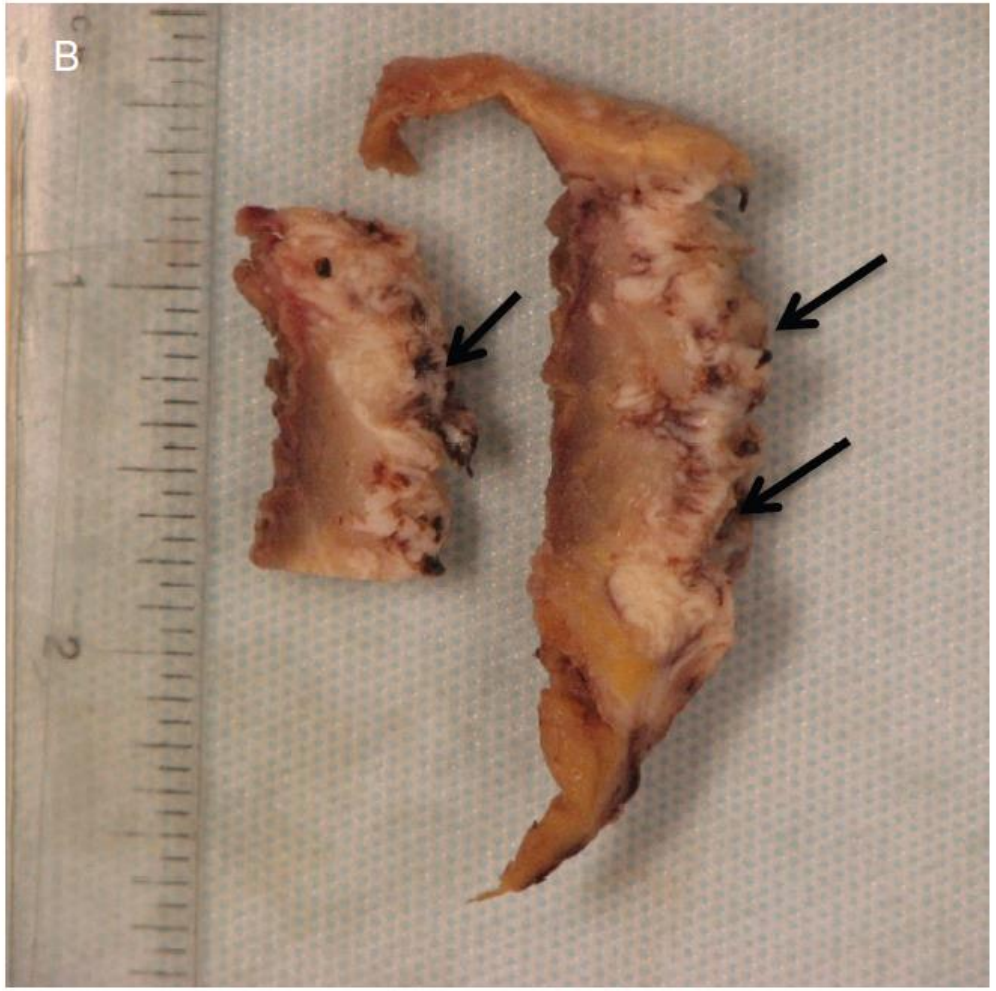

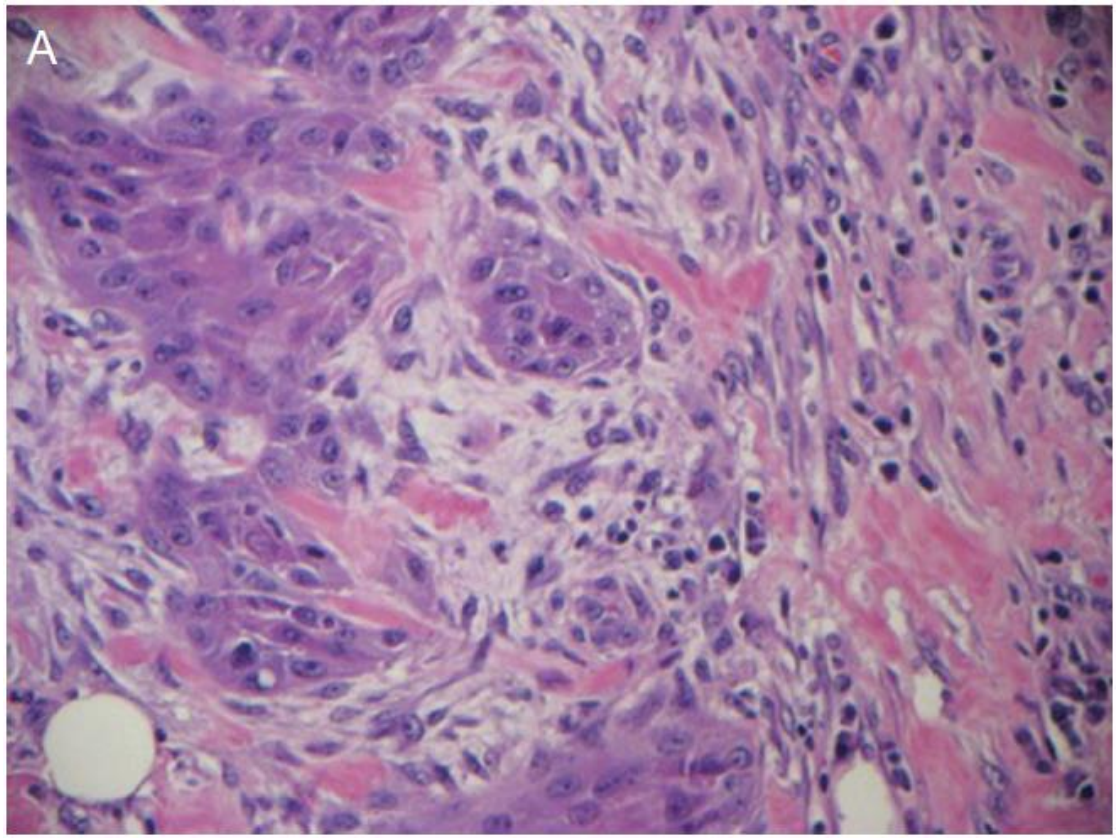
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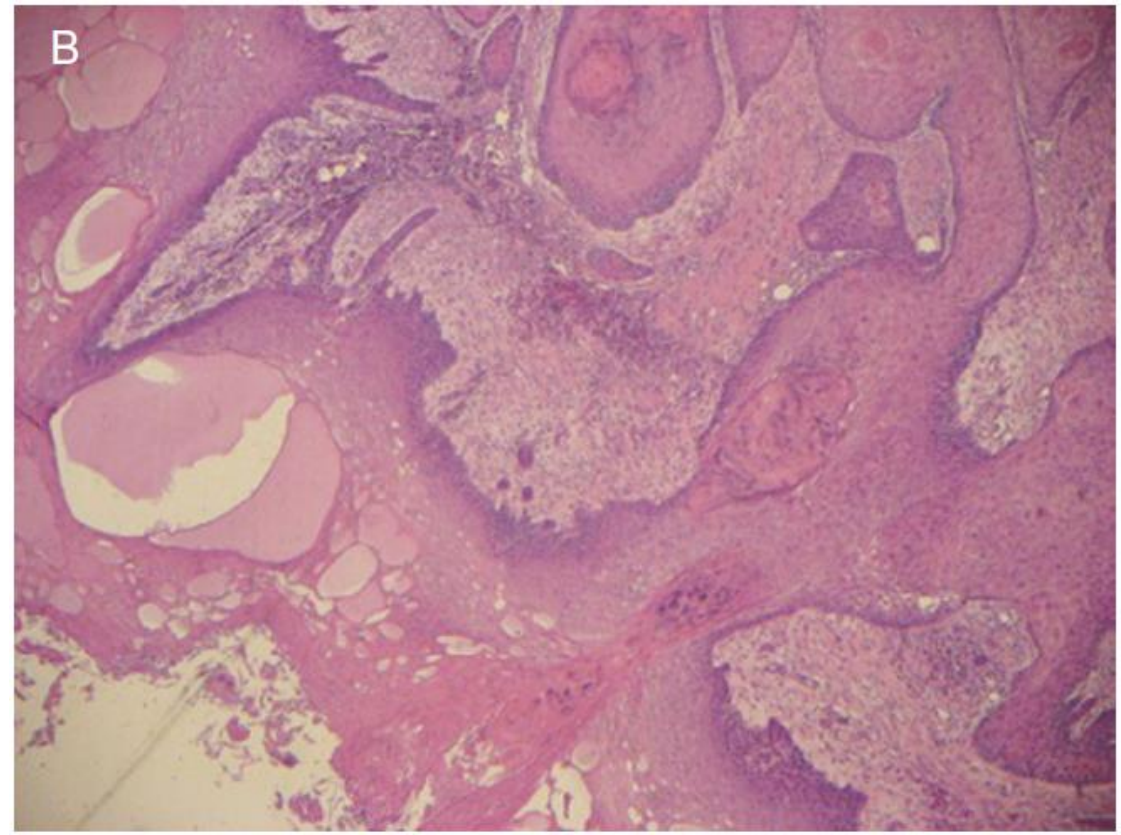
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Human Pathology (2017) 67, 94–100

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Original contribution

Breast implant capsule–associated squamous cell carcinoma: a report of 2 cases☆

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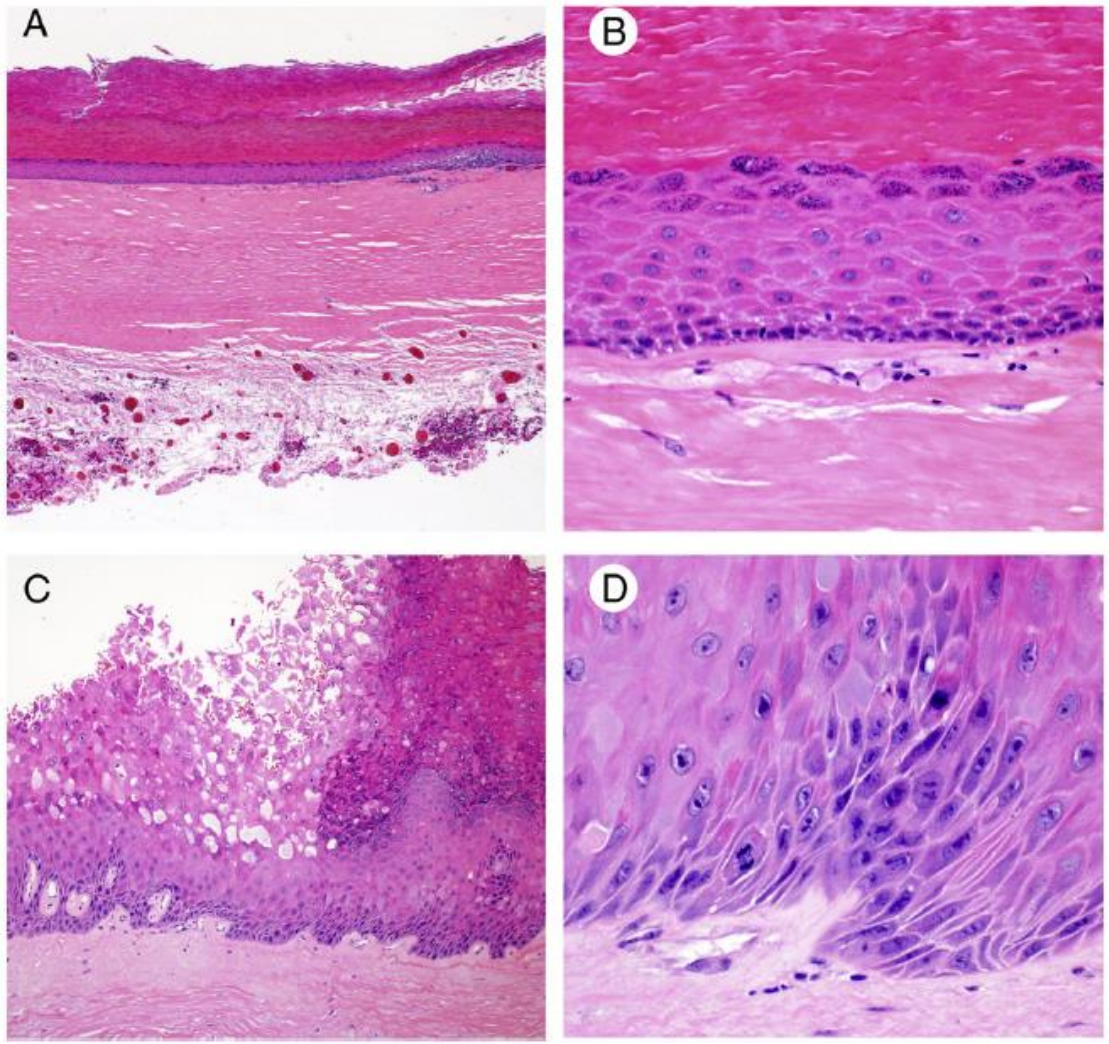

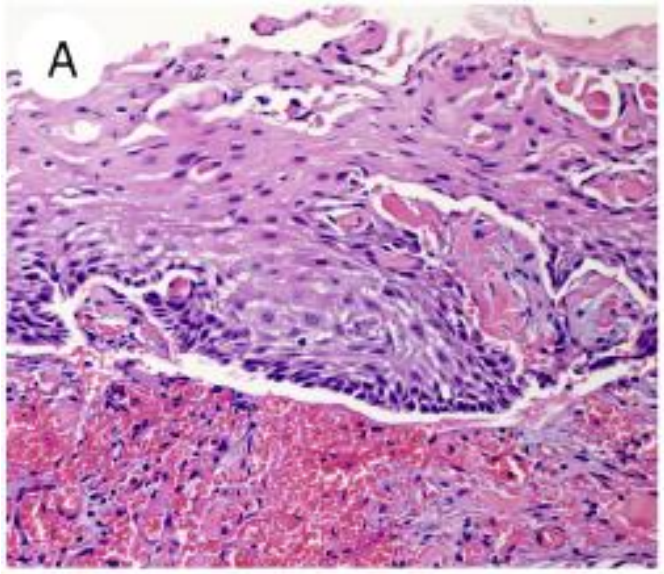
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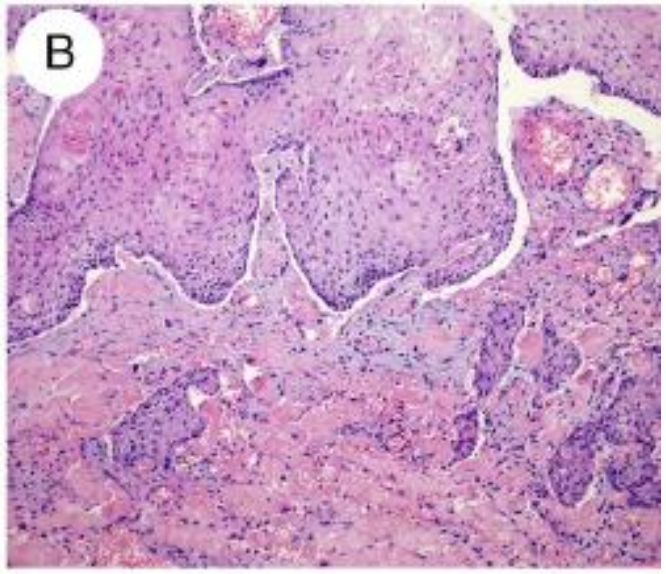
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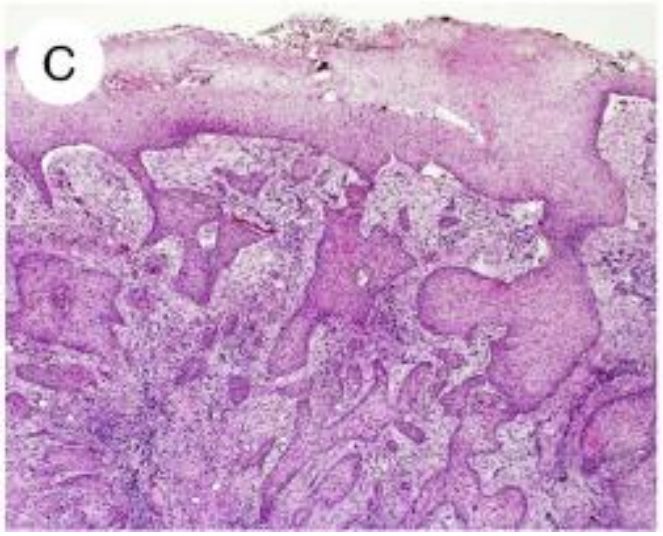
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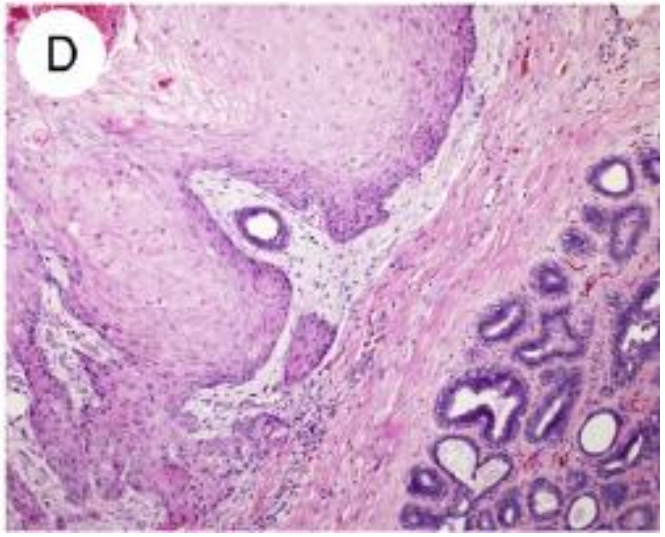
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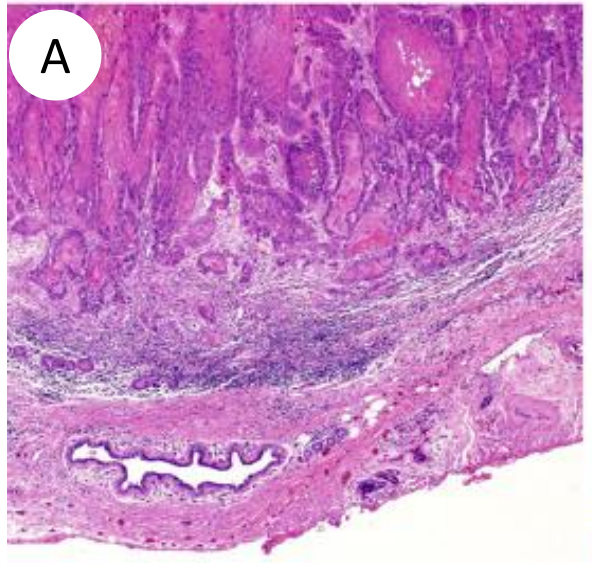
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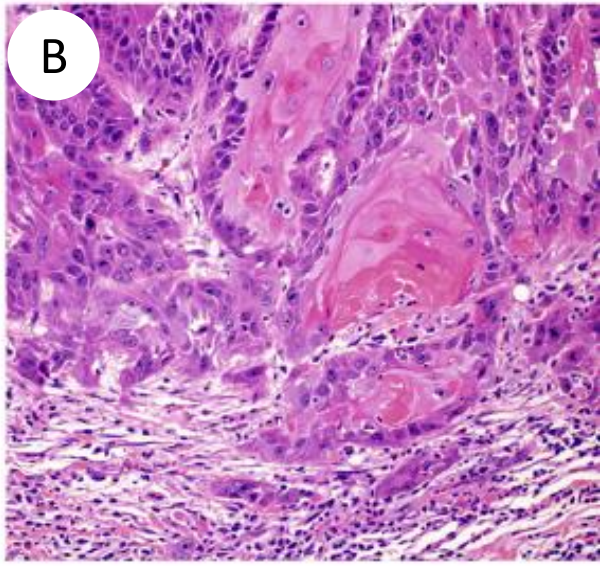
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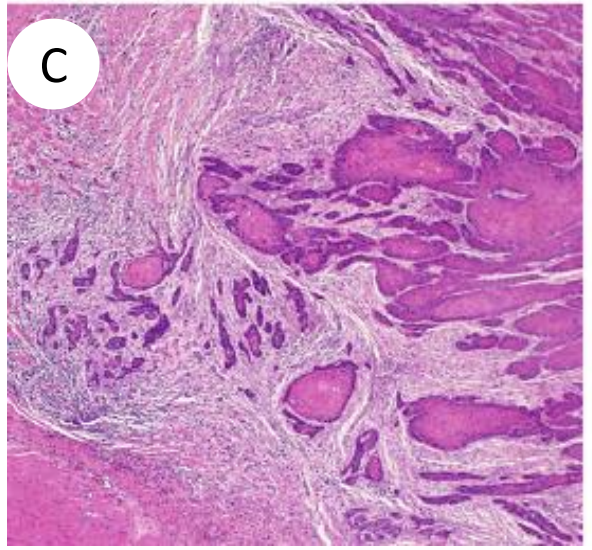
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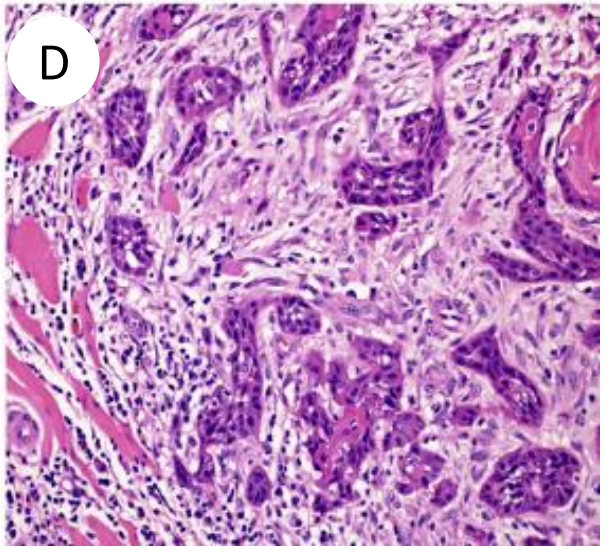
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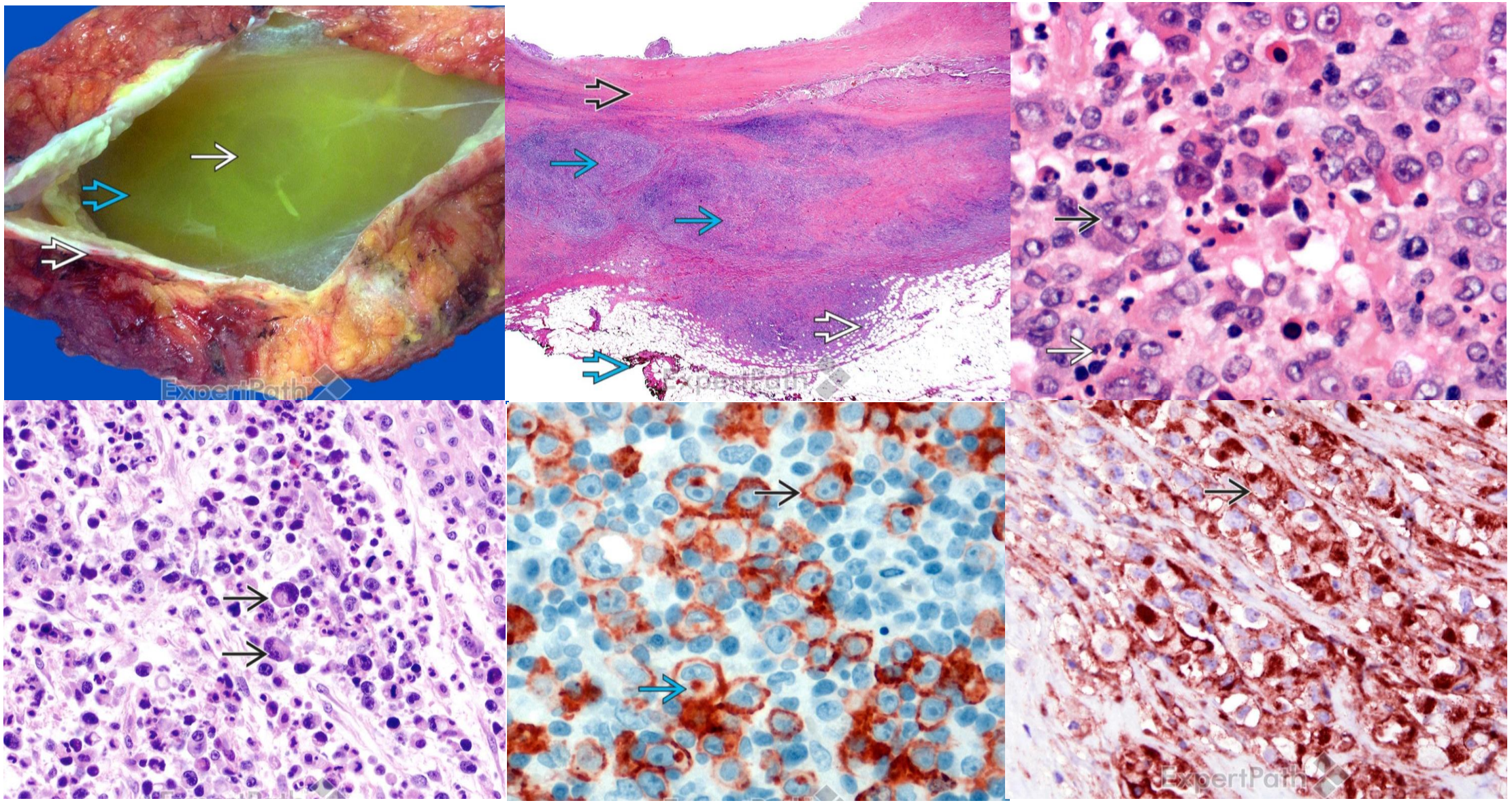
Breast Implant-Associated Anaplastic Large Cell Lymphoma (BI-ALCL)

- High frequency of peri-implant effusion
- Large lymphoma cells (Hallmark cells); morphologic features overlap with EBV+ LBCL-BI
- Morphologic differences between BI-ALCL and EBV+ LBCL-BI
  - Hallmark cells only in BI-ALCL
  - Eosinophils only in BI-ALCL
  - Many free-floating cells in peri-implant fluid only in BI-ALCL
  - Synovium-like lining layer on luminal side of capsule only in BI-ALCL
- Ancillary studies:
  - T-cell antigens (+); Strong and uniform CD30(+) in all cases
  - No evidence of EBV infection in BI-ALCL
  - Clonality studies: Monoclonal *TRG* and/or *TRB* rearrangements

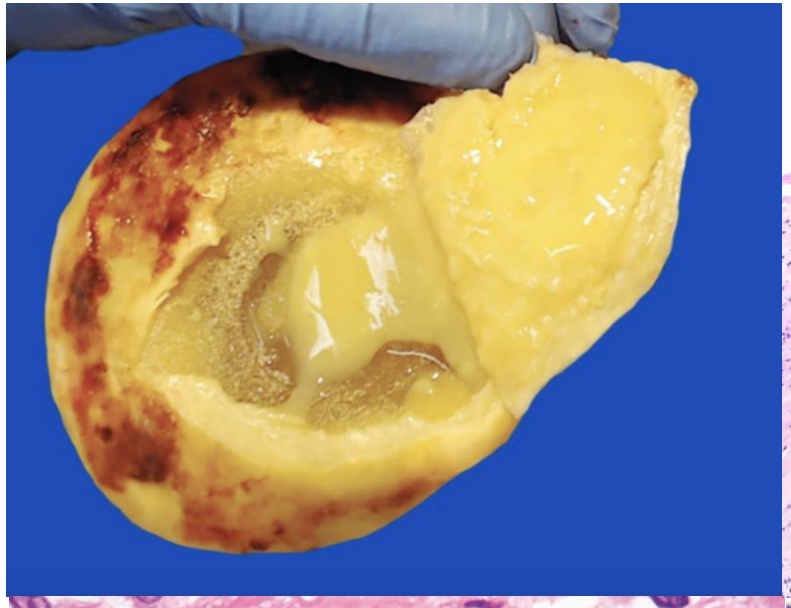
Breast Implant-Associated Anaplastic Large Cell Lymphoma

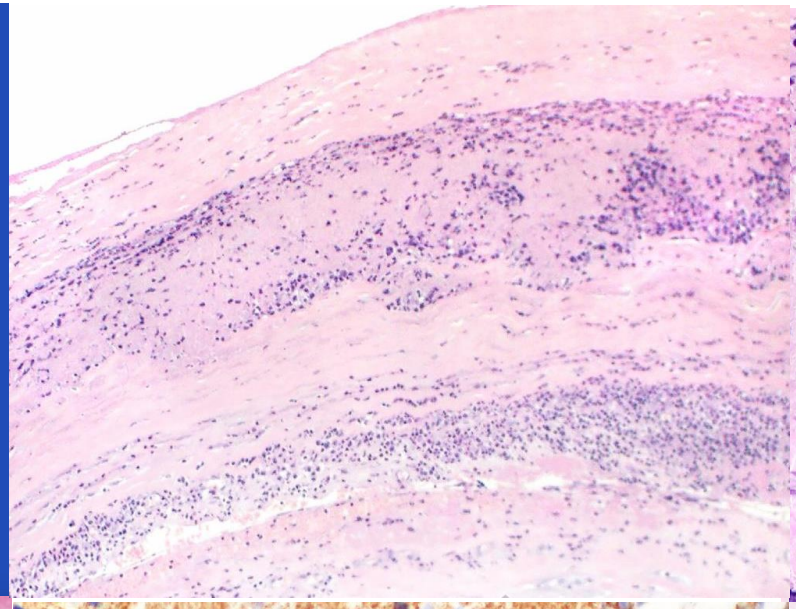


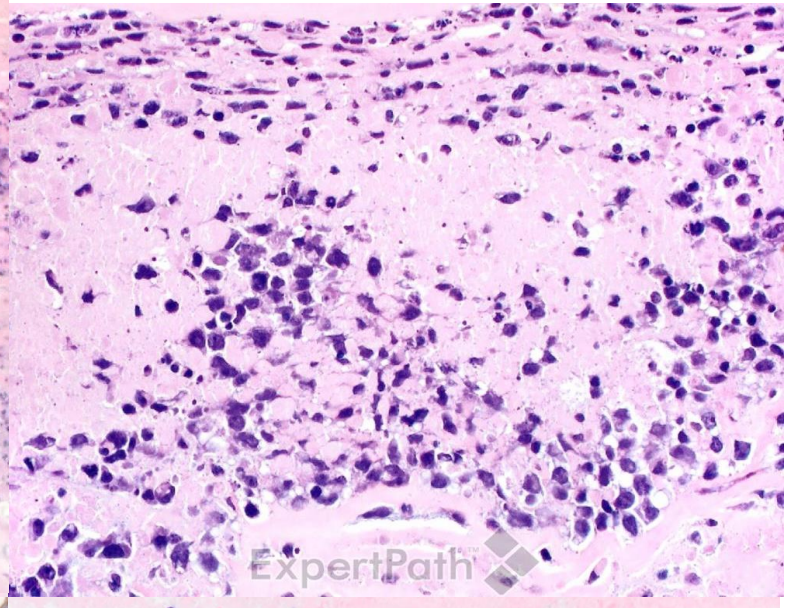
EBV+ Large B-Cell Lymphoma Associated With Breast Implants (EBV+ LBCL-BI)

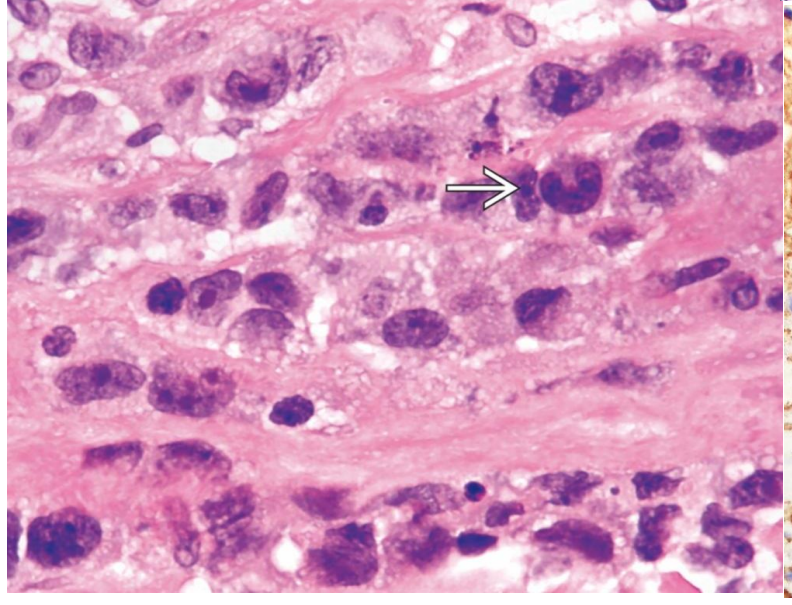
- Has many similarities with BI-ALCL
- Neoplastic cells are large with oval or lobated nuclei with prominent nucleolus (no "hallmark" cells); Extensive necrosis and karyorrhexis in background
- Morphologic features of EBV+ LBCL-BI compared to BI-ALCL
  - Thicker capsule and less effusion
  - Lymphoplasmacytic aggregates in outer capsule
  - Dystrophic calcification on luminal side of capsule
  - Lipid-laden (foamy) histiocytes
  - Layering of lymphoma cells
- Ancillary studies:
  - Express B-cell markers: CD20, CD79, and pax-5
  - EBV latency pattern type III: EBER(+), LMP1(+), and EBNA2(+)
  - Monoclonal *IGH* gene rearrangement
- Natural history still not well defined due to recent recognition and limited follow-up

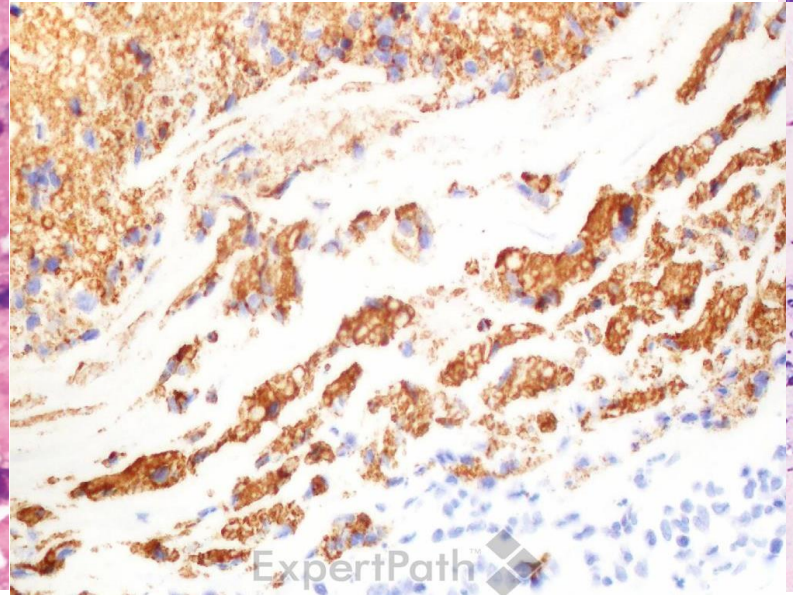
EBV+ Large B-Cell Lymphoma Associated With Breast Implants

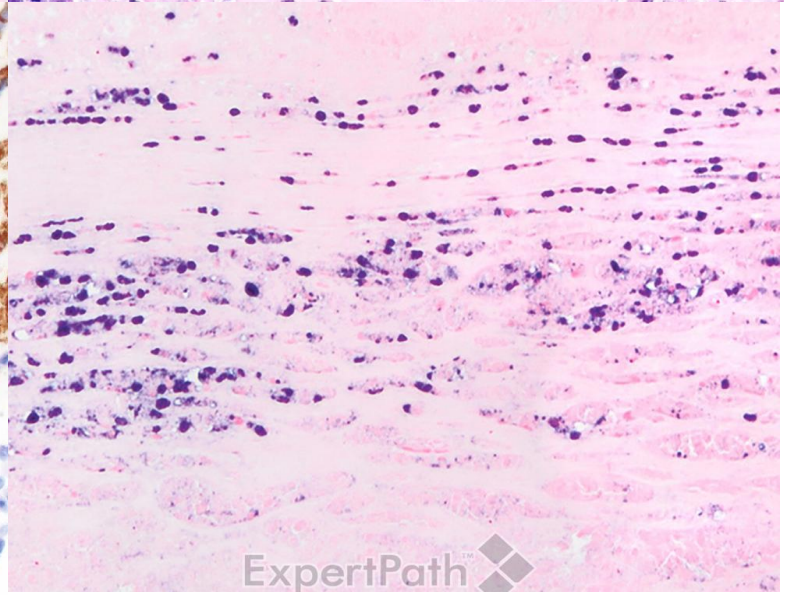












Summary

- Modern breast implants are widely acknowledged as a safe and effective
- Breast implant-associated ALCL is the only well-recognized periprosthetic malignancy
- SCC clearly differs from ALCL, theories on the etiology of both infer a chronic inflammatory state within the capsule
- ALCL and SCC related to breast implant capsules into a single entity known as “chronic inflammatory capsular malignancies”
- Epithelialization of the breast implant capsule secondary either to the migration of ductal cells or the induction of squamous metaplasia in the mesodermal lining; malignant transformation occurred in a chronic inflammatory environment, ultimately leading to the development of invasive SCC

Take Home Points

- SCC arising from periprosthetic capsule is a distinct and possibly underreported entity of which plastic surgeons should be aware
- Pathologic examination of the capsules is crucial in patients with suspicious clinical presentations and intraoperative findings
- Increased awareness of this entity may allow for earlier diagnosis, and management

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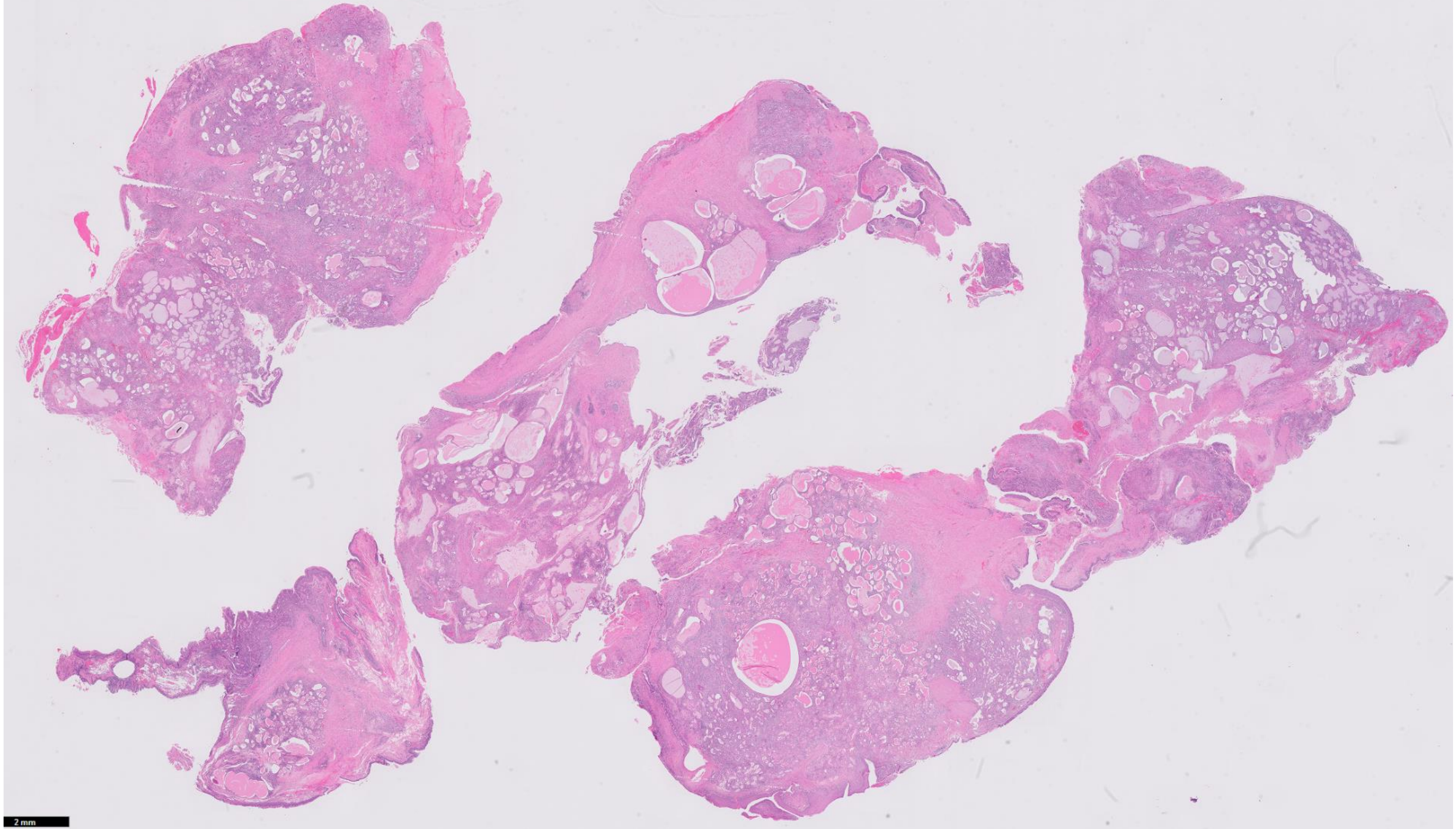
- Expertpath

23-0602

Eric Ollila and Brittany Holmes; Stanford

41-year-old female with a 2 cm tracheal mass located 2 cm below the glottic free edge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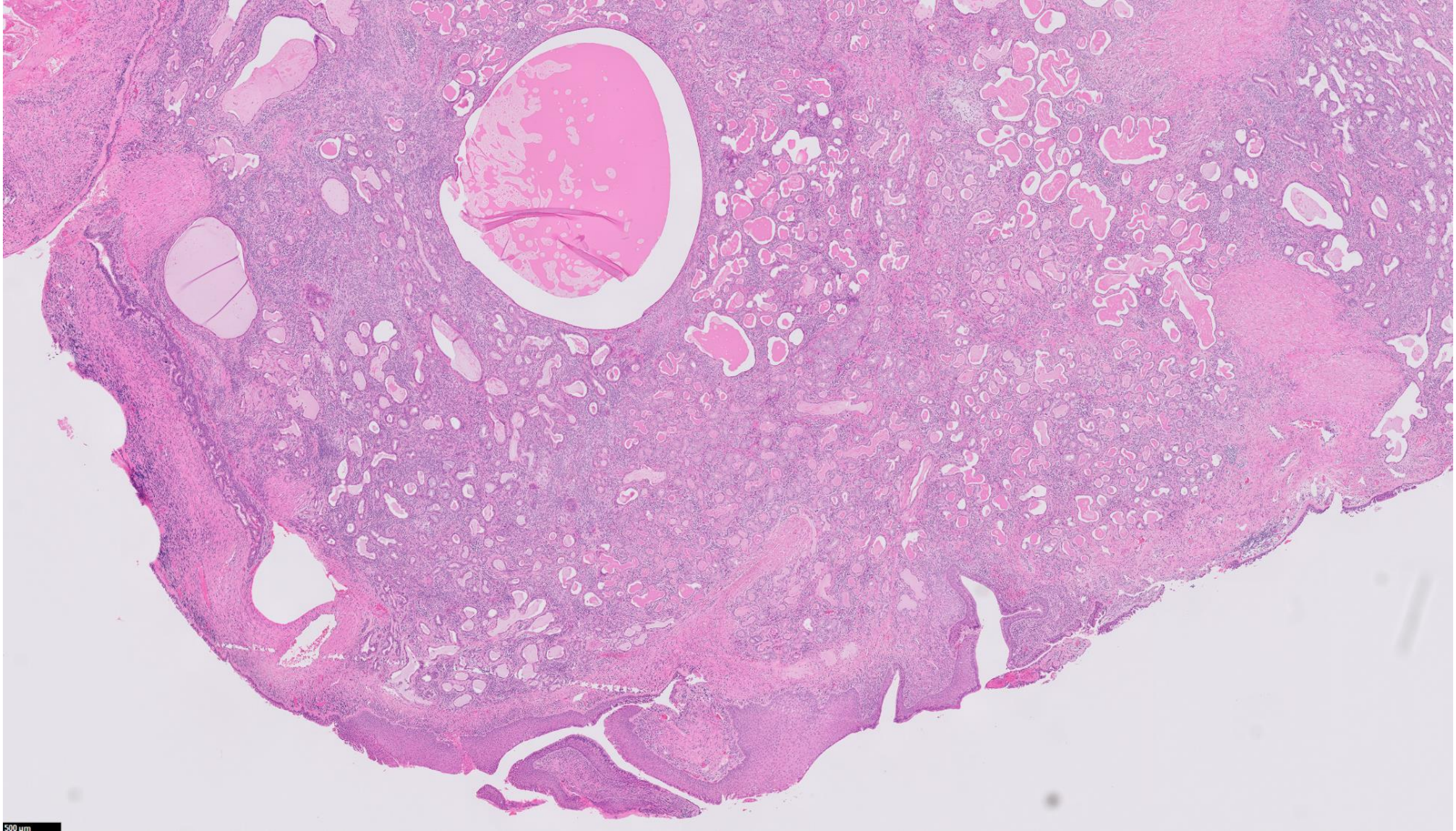
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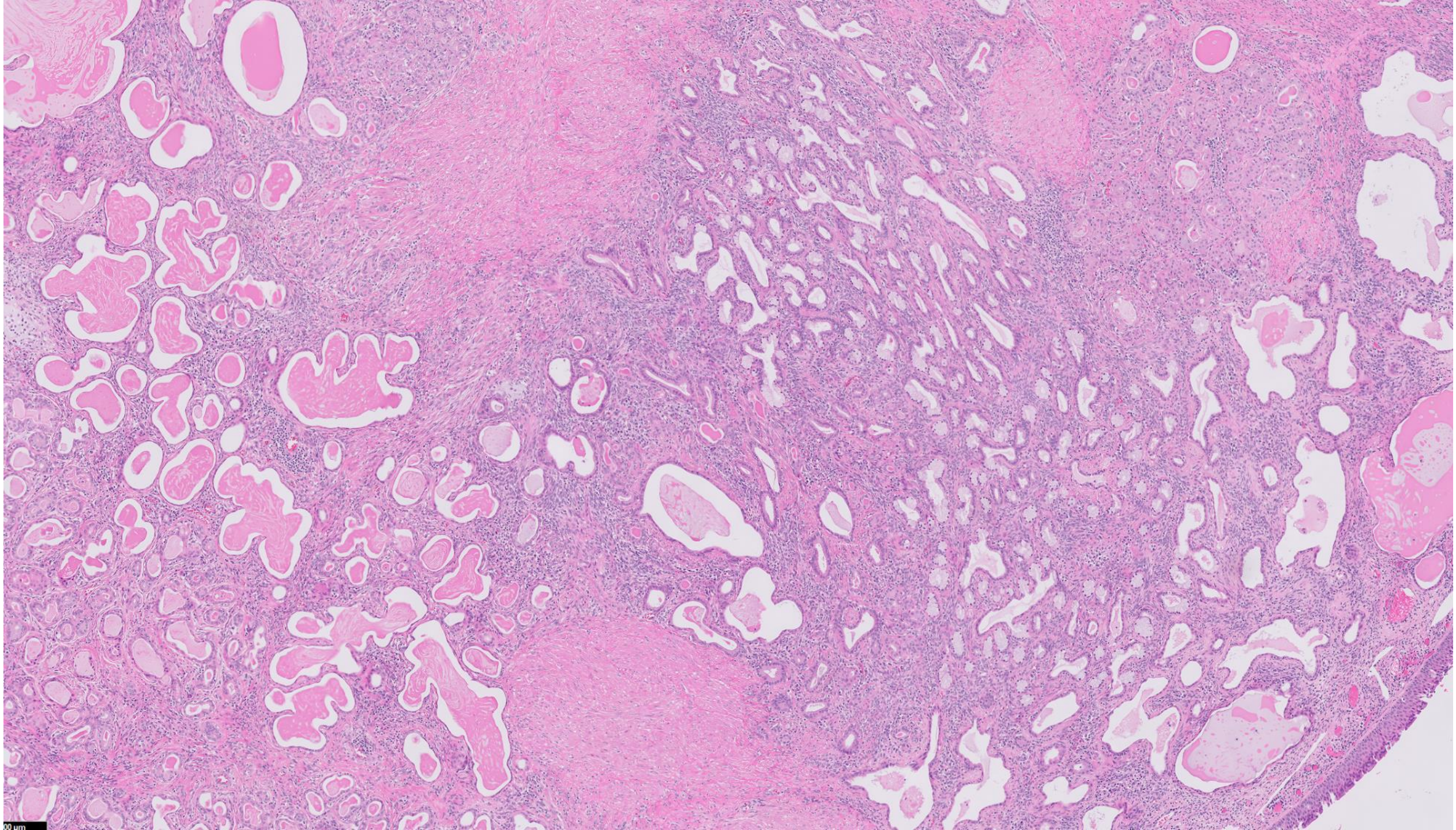
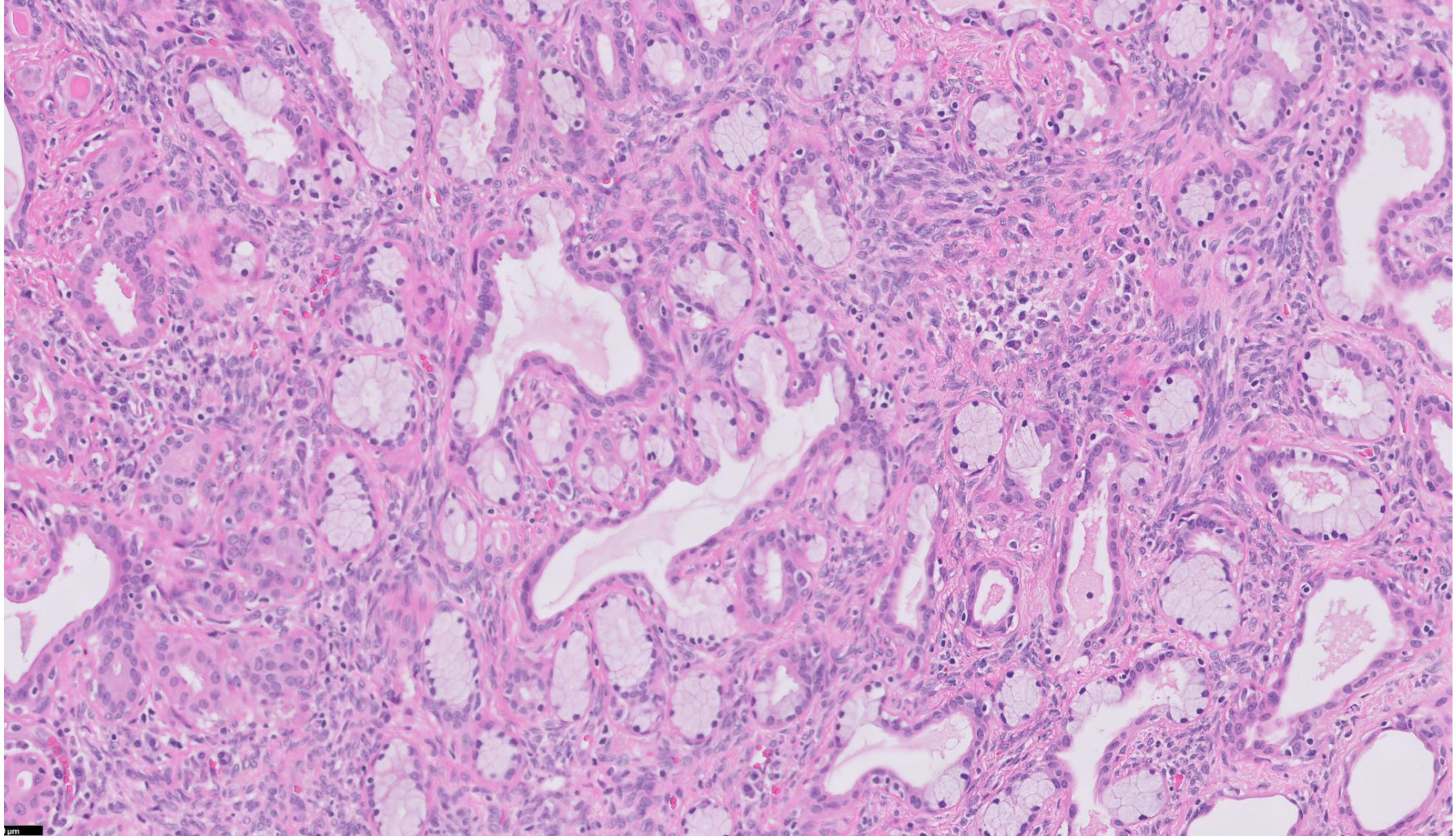
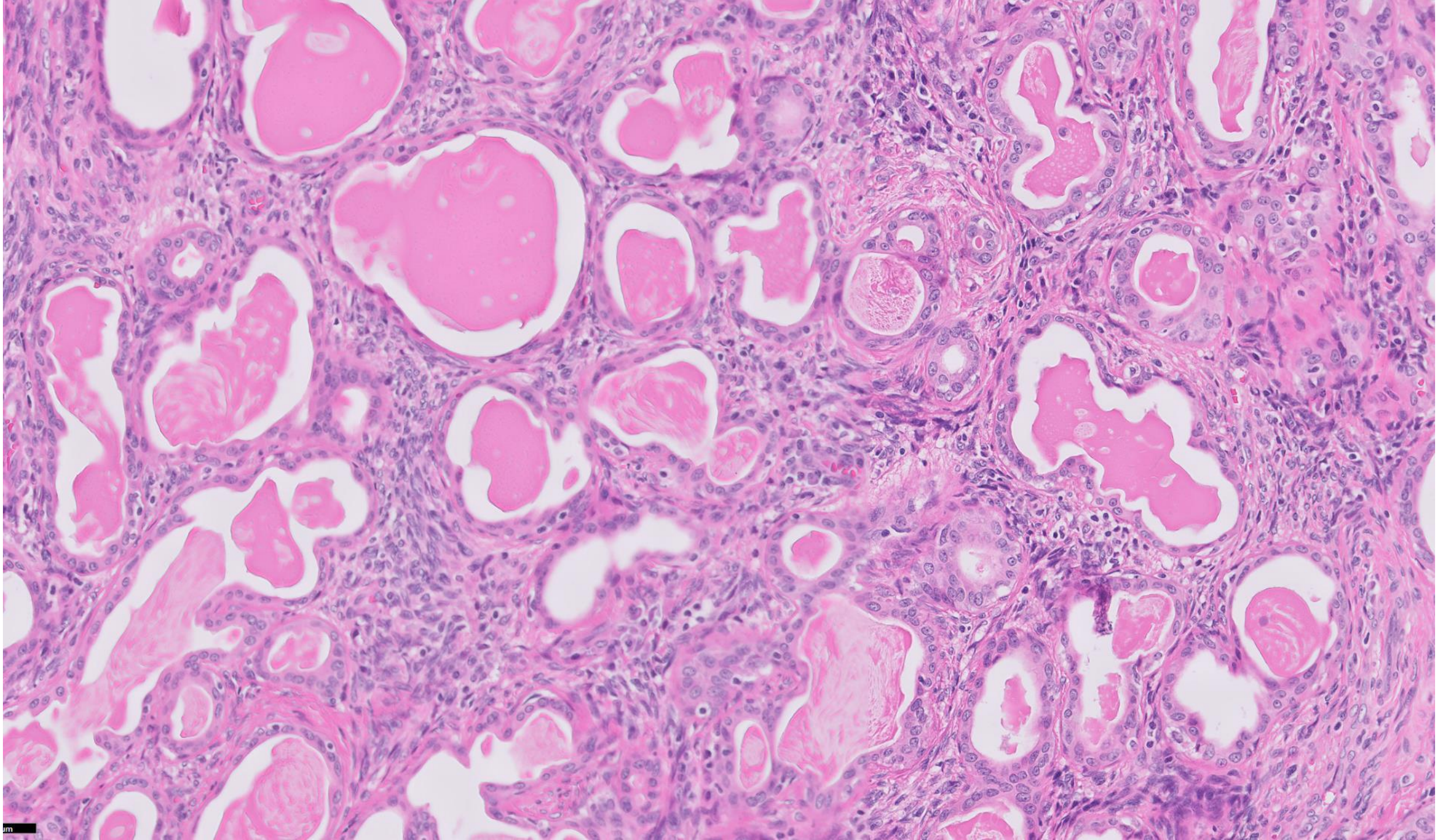
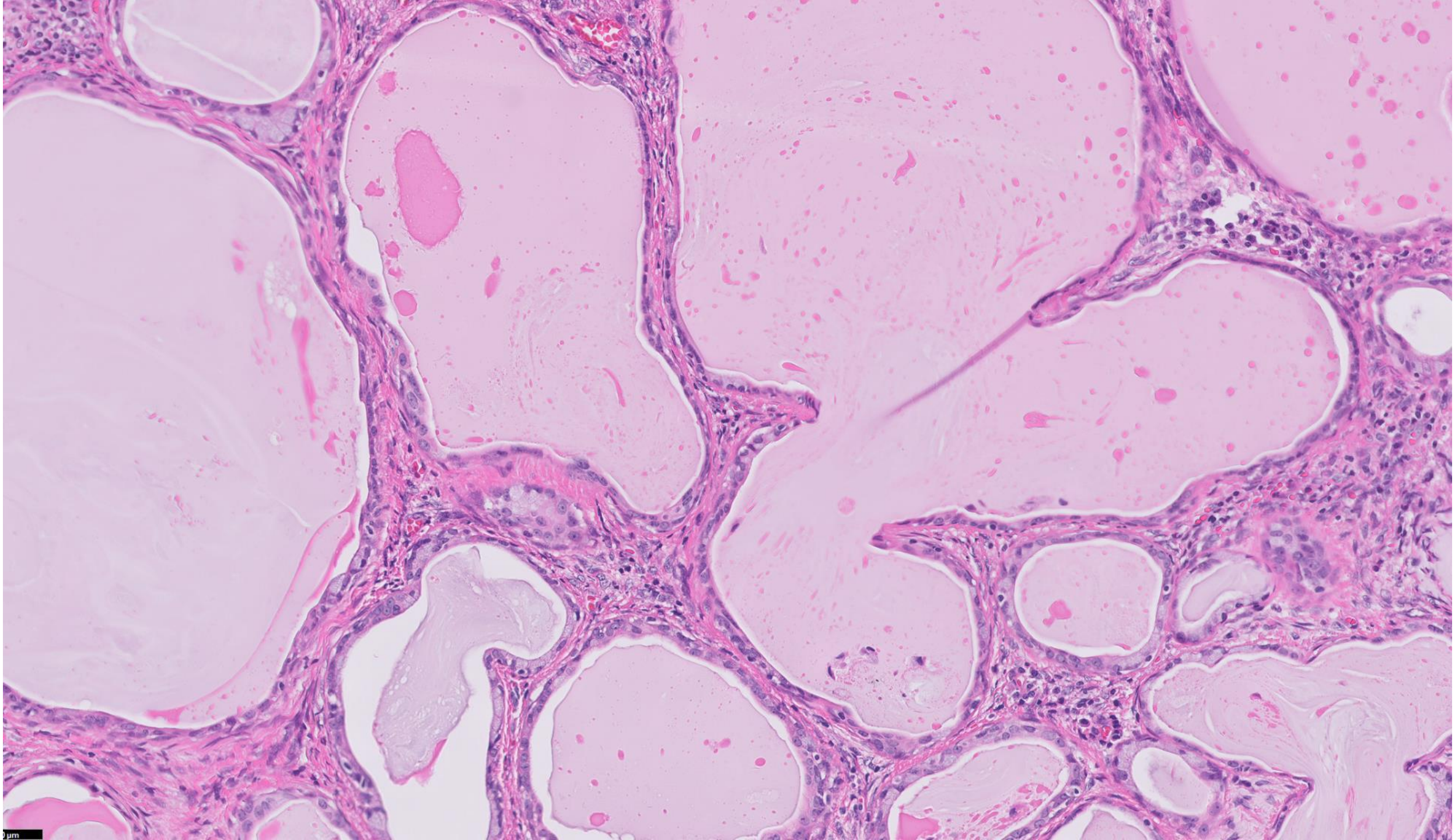
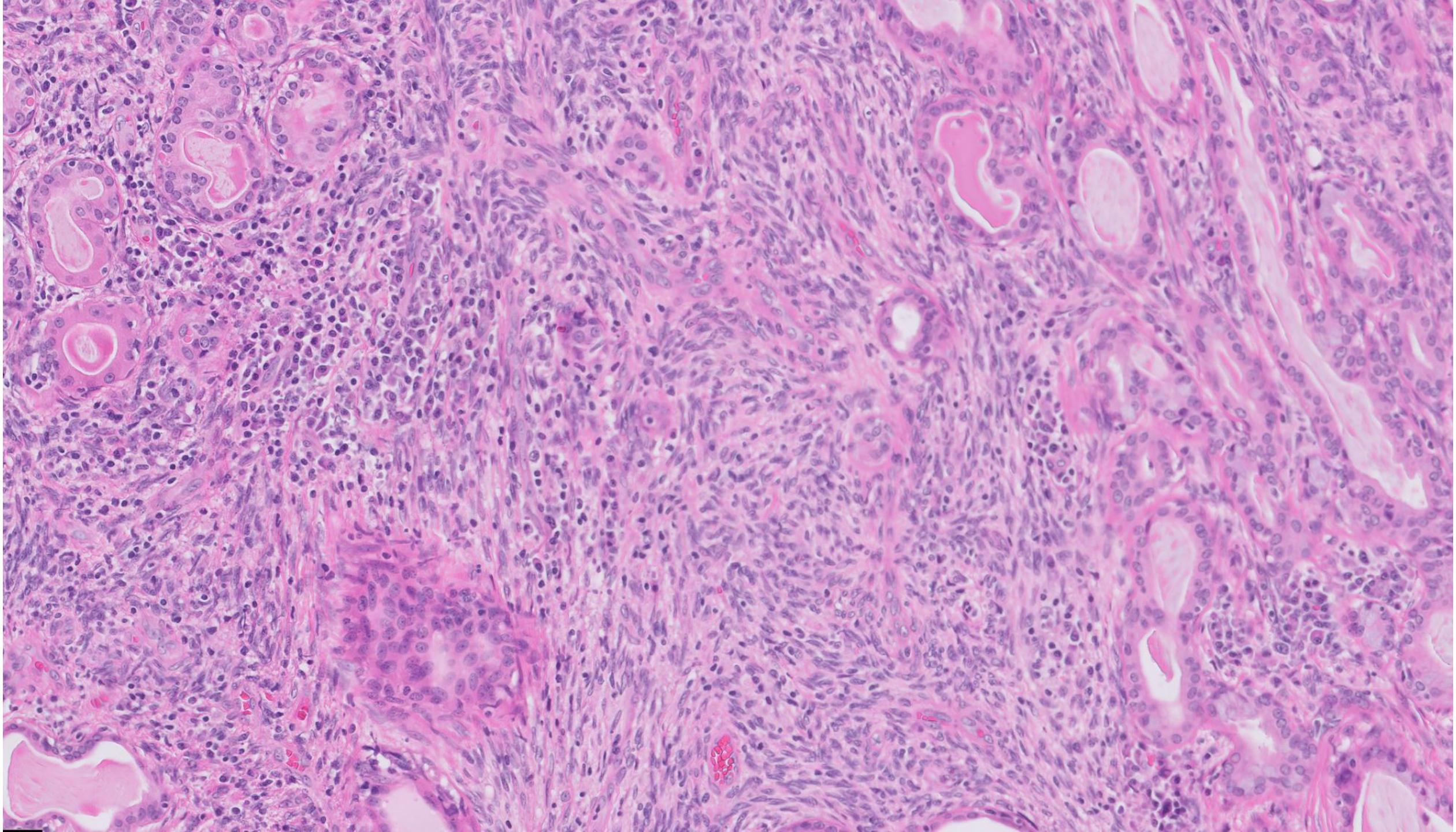
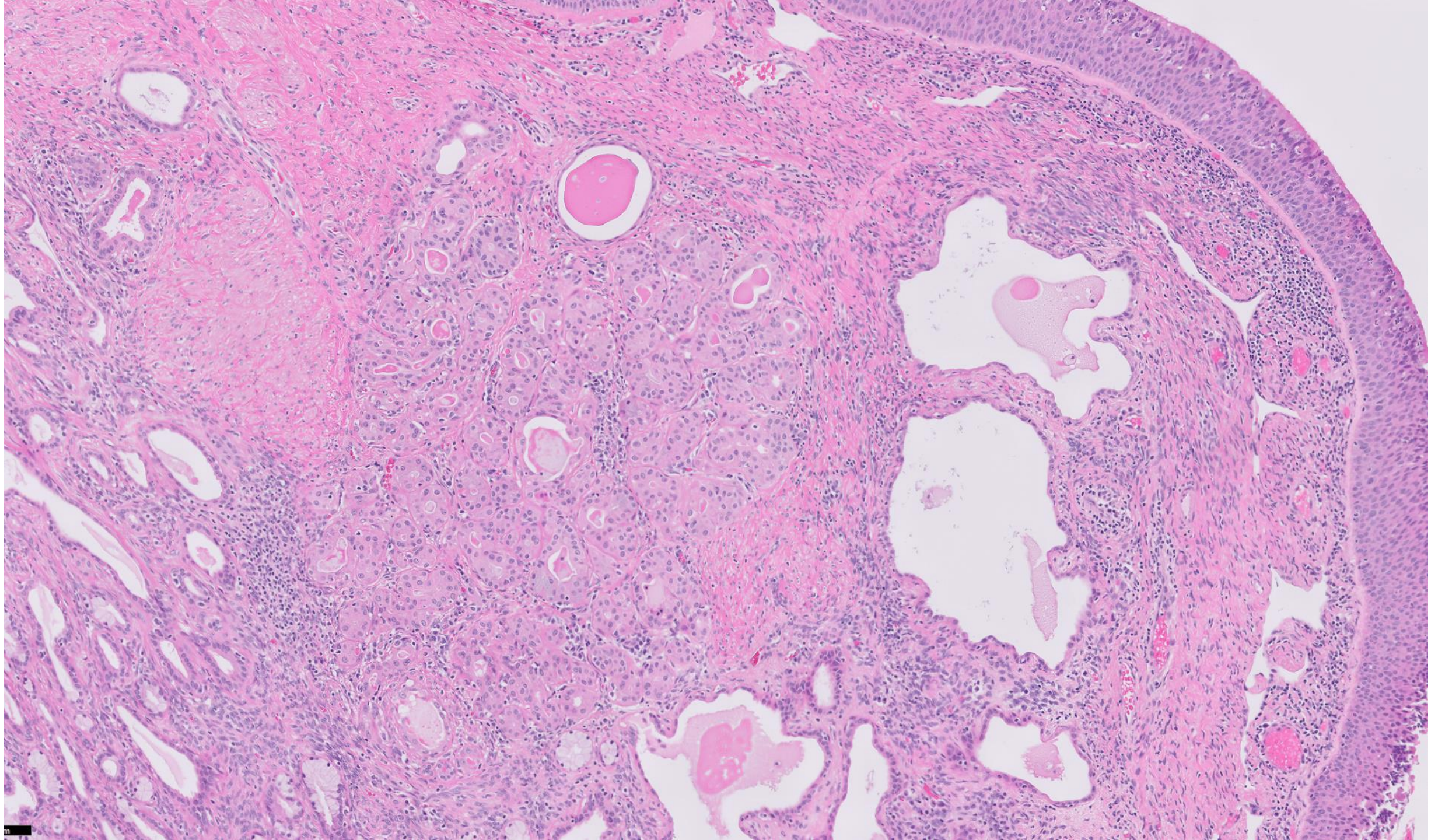


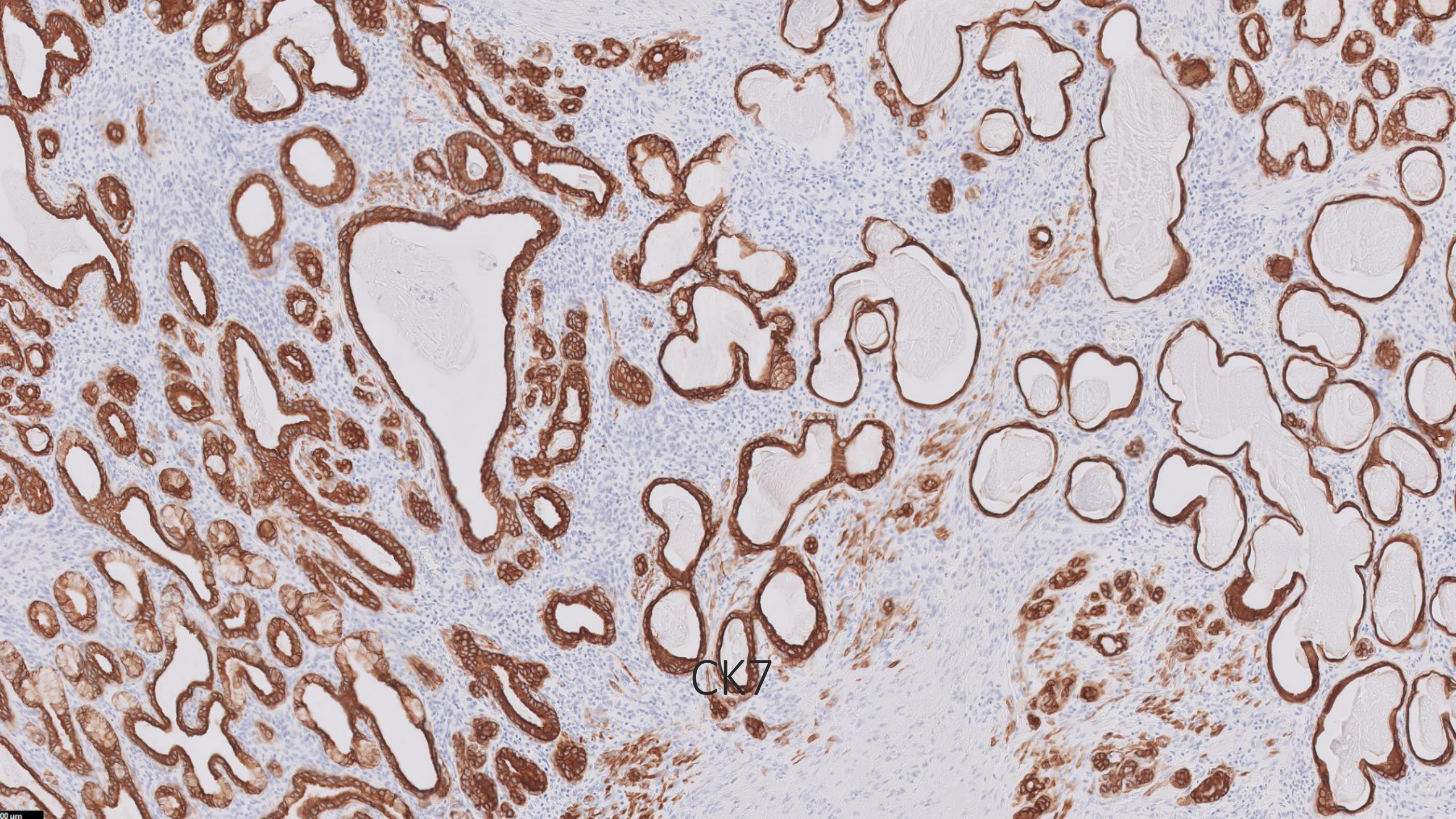


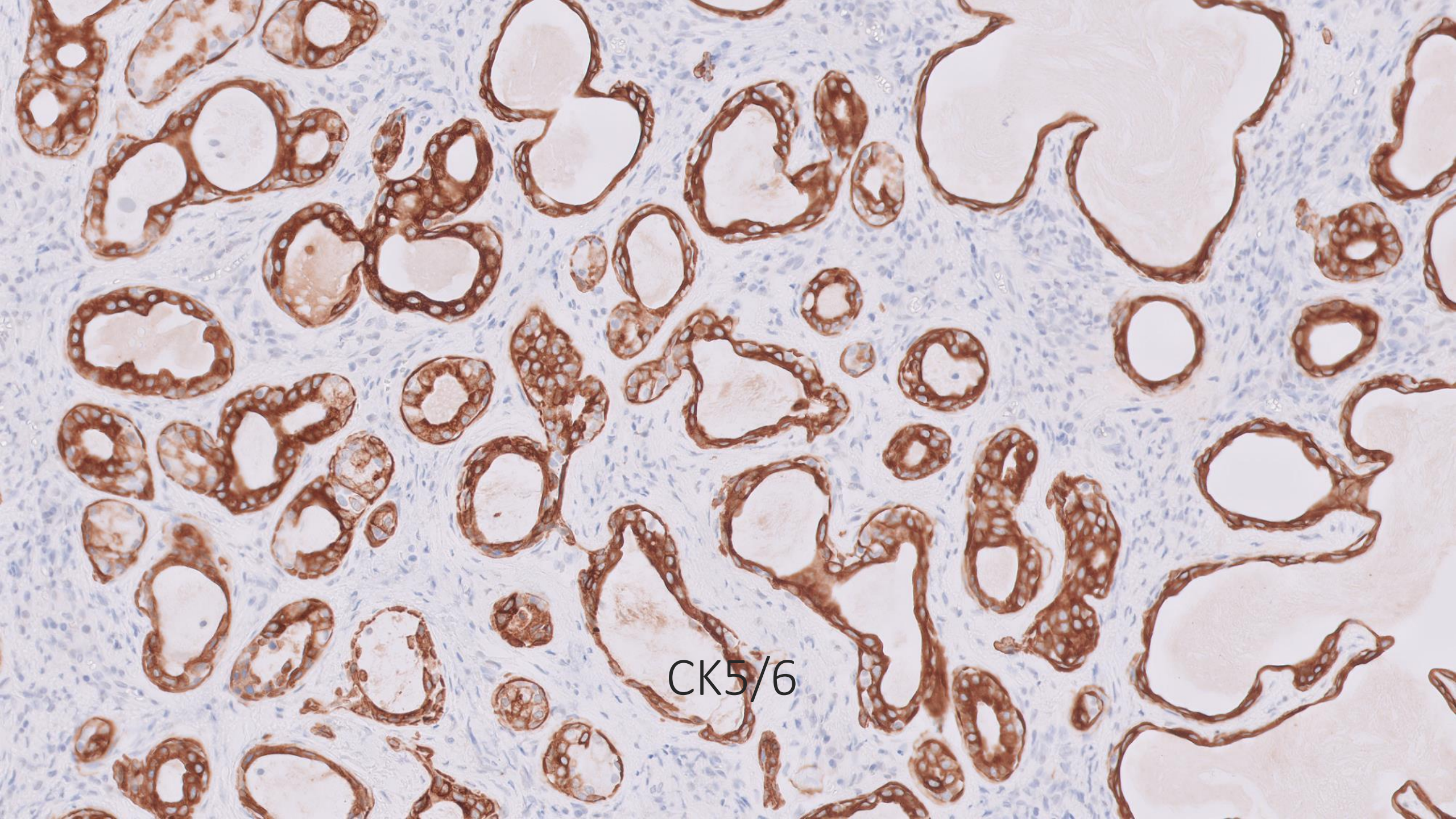


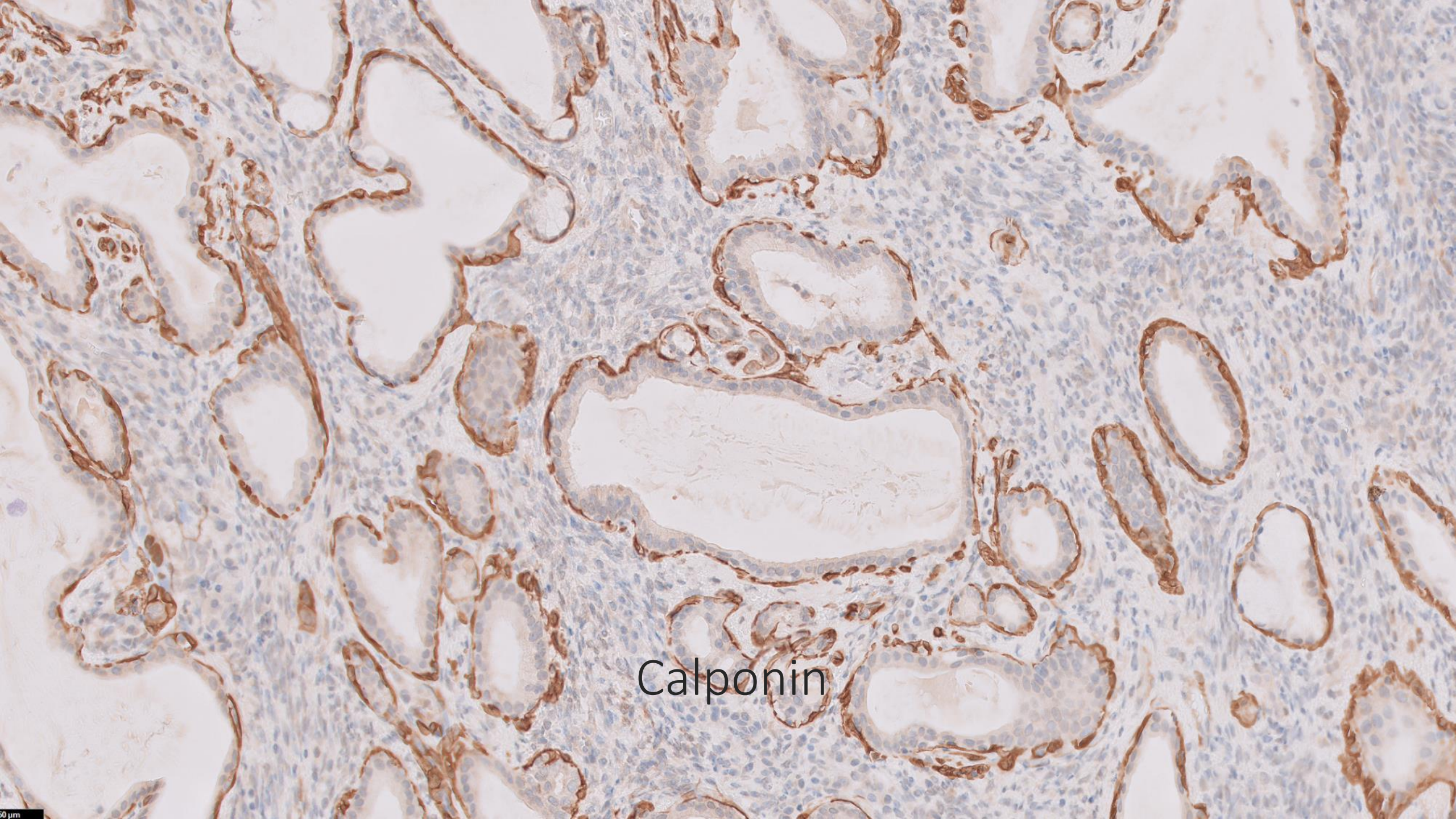







CK7


CK5/6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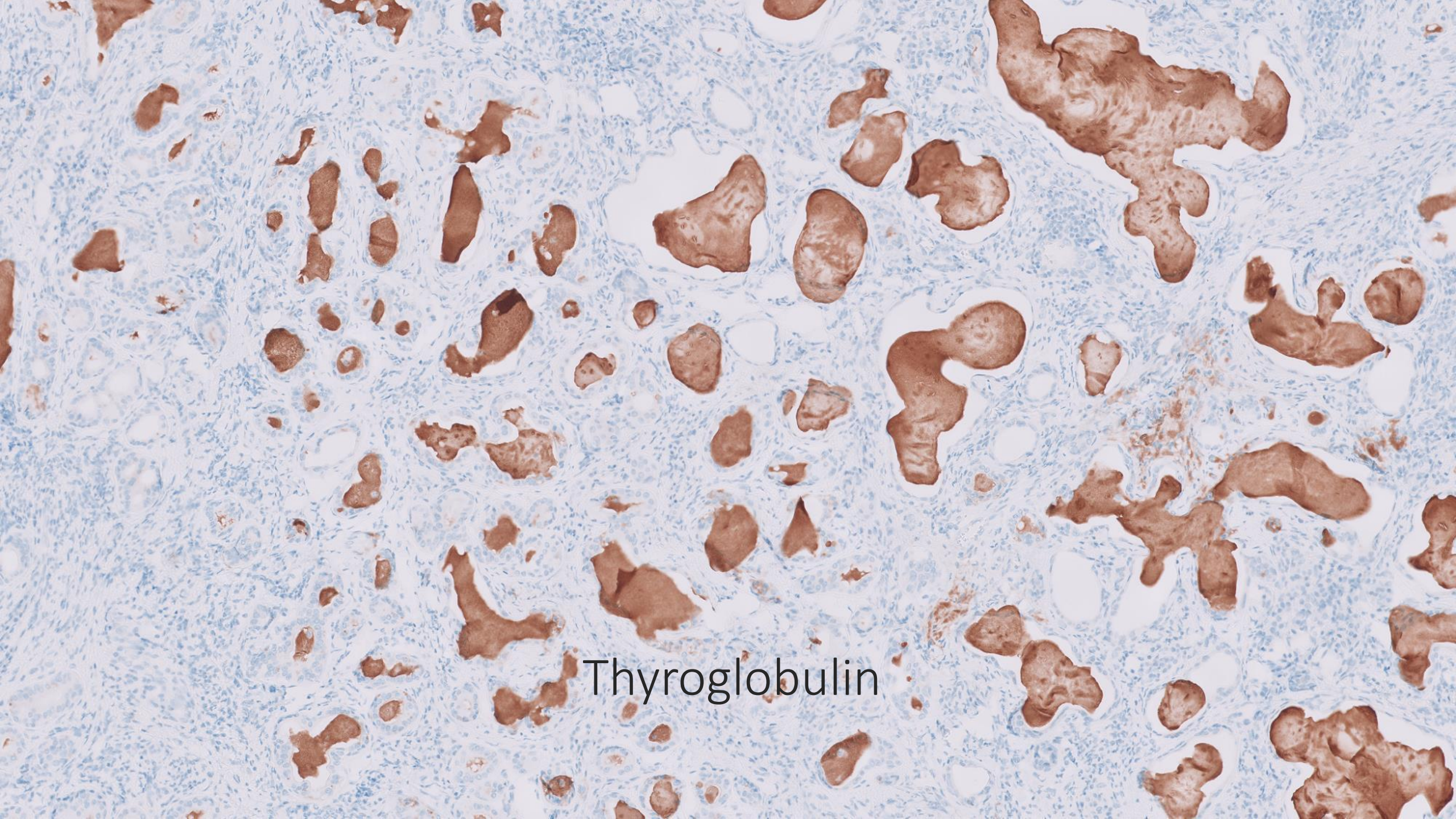
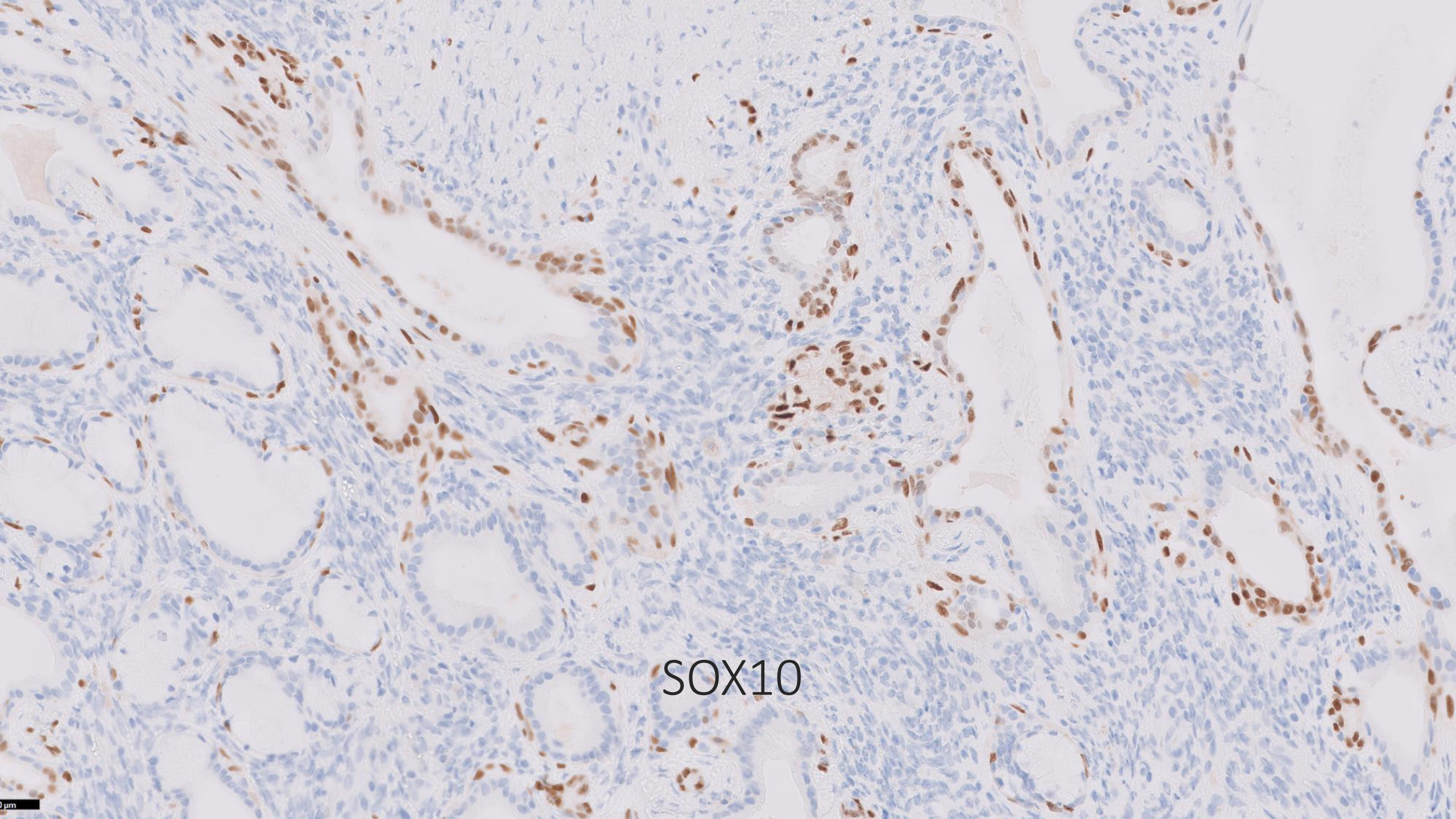
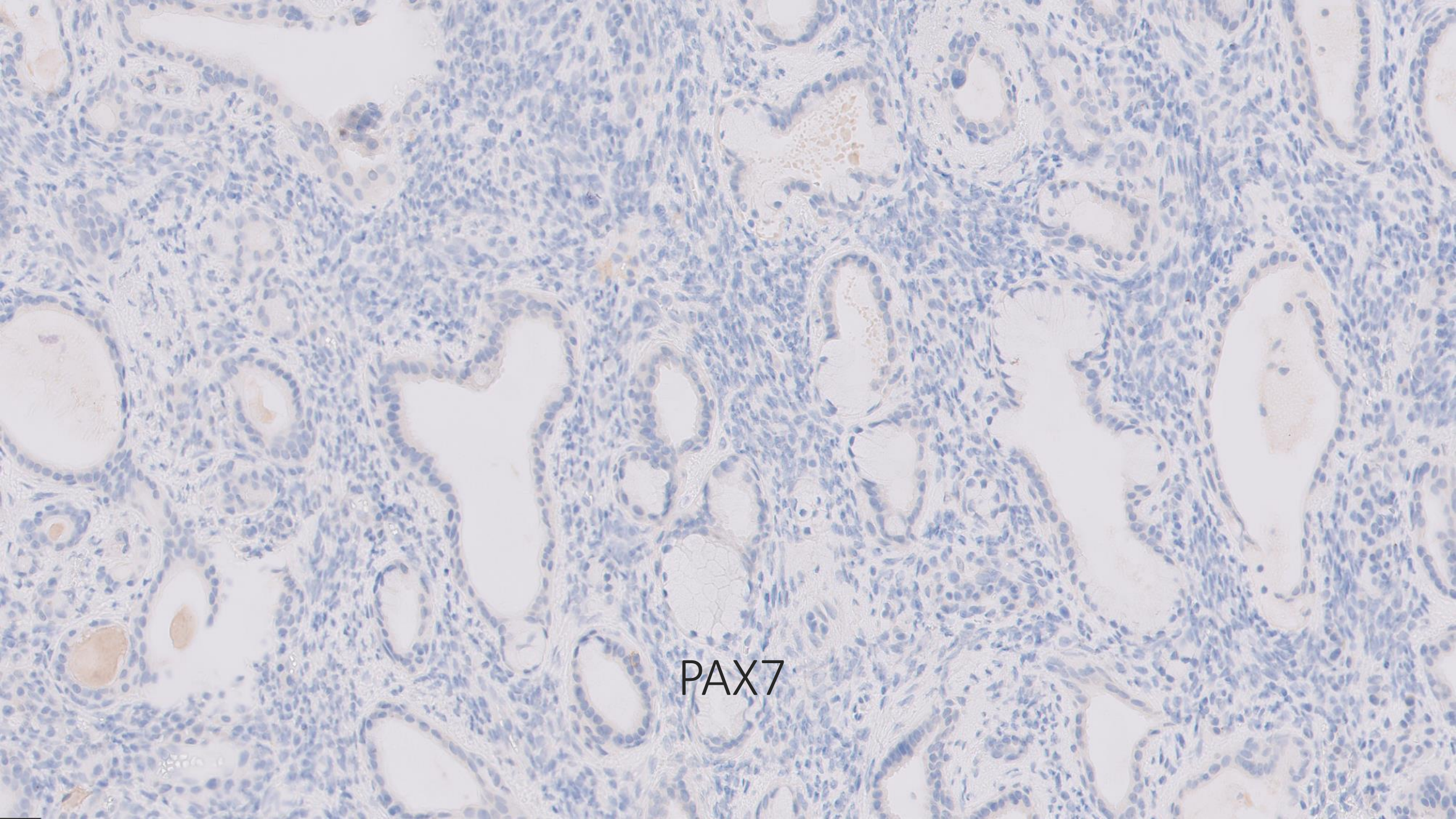
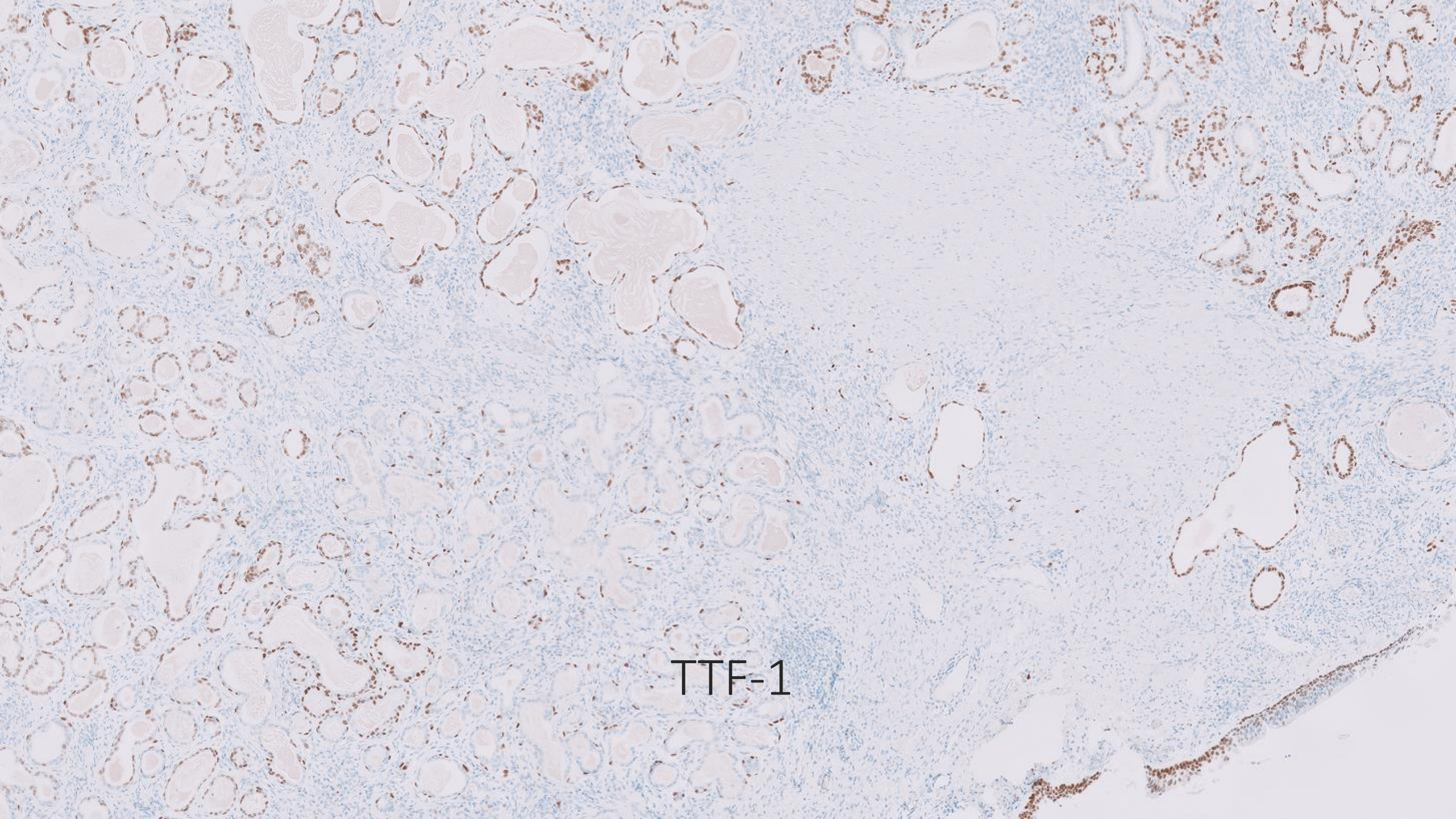

Thyroglobulin


SOX10


PAX7



TTF-1

Summary

41-year-old female

Tracheal mass (2 cm)

Histology

- Lobular architecture
- Biphasic proliferation of seromucinous glands
- Spindled stroma
- No atypia

Ancillary studies

- IHC
  - Glands
    - Positive for TTF-1 (patchy) and SOX10 (patchy)
      - Luminal cells - CK7 and CK5/6 +
      - Myoepithelial cells - calponin and CK5/6 +
    - Negative for thyroglobulin
  - Stroma
    - Rare myogenin
    - Negative PAX7
- MAML2 FISH negative

Mucous gland adenoma

Histology

- **Proximal airways**
- Well-circumscribed
- **Seromucinous glands with cystic dilation**
  - Flattened to columnar cells
  - Oncocytic, clear, ciliated cells variable
- No atypia
- **Spindled stroma variable**

IHC

- Epithelial cells
  - **Negative for TTF1**
- Stromal cells
  - Variable keratins, SMA, and S100

Sclerosing polycystic adenoma

Histology

- Rare **salivary gland** neoplasm
  - Parotid gland
  - Sinonasal, submandibular, and lacrimal gland
- Cystic and multilobular growth
- Large **acinar cells** with brightly **eosinophilic intracytoplasmic granules**
- **Biphasic ductal process**
  - Variable foamy, vacuolated, and apocrine cells
  - May resemble low-grade DCIS
- Sclerotic stroma

IHC

- SOX10 + in all cell types
- PTEN loss – ductal and acinar

Mucoepidermoid carcinoma

Histology

- Circumscribed to infiltrative
- Not biphasic
- **Three cell types**
  - Mucous, intermediate, and squamoid
- Variable atypia
- No stromal component

IHC/Molecular

- P63/p40 +
- S100, SOX10, TTF-1 -
- **MAML2 translocation**

Direct extension or metastasis

- Less likely due to
  - Lack of atypia
  - Lobular growth
  - Biphasic process
- Lung primary
  - No lung lesion
- Thyroid
  - Colloid-like intraluminal material
  - Thyroglobulin negative

Respiratory adenomas

- General features
  - Circumscribed
  - Peripheral
  - Usually TTF1 +

Respiratory adenomas

- Sclerosing pneumocytoma
  - **Dual population of surface and round cells**
  - Mixture of papillary, sclerotic, solid, and hemorrhagic growth patterns
    - **Solid pattern may have tubular structures**

- Alveolar adenoma
  - **Cystic alveolar-like spaces** lined by type II pneumocytes
  - **Spindle-rich stroma**
  - Rarely hilar

Respiratory adenomas

- Bronchiolar adenoma / ciliated muconodular papillary tumor
  - **Biphasic** papillary and/or flat glandular epithelium
    - Luminal cells
      - Mucous and ciliated cells (proximal-type areas) – TTF1 negative
      - Type II pneumocytes and club cells (distal-type areas) – TTF1 positive
    - Basal cells – CK5/6 and p40 positive
    - BRAF positive
  - **Middle-aged to elderly patients**

Finalized report

- **Benign biphasic neoplasm (see comment)**
  - Although mucous gland adenomas are reportedly TTF-1 negative, the morphology and overall staining pattern leads us to favor a diagnosis of mucous gland adenoma
  - Sclerosing polycystic adenoma was also considered, but the presence of spindled stroma and absence of epithelial cells with prominent eosinophilic cytoplasmic granules is more in keeping with a mucous gland adenoma

Follow up

- None – consult case

- **Proximal airways**
- Extremely **rare**
- Clinical presentation
  - Symptoms of obstruction
    - Cough, hemoptysis, dyspnea, and recurrent pneumonia
- Histology
  - **Seromucinous glands with cystic dilation**
    - Oncocytic, clear, ciliated cells variable
  - **Spindled stroma** variable
  - **TTF-1 negative**
- Cured by resection

23-0603

Alexander Craig, AP/CP PGY-2; UCSF Pathology

59ish-year-old female

History of GERD, CAD, dyslipidemia, viral thyroiditis

End-stage renal disease due to autosomal-dominant polycystic kidney disease (AD-PKD)

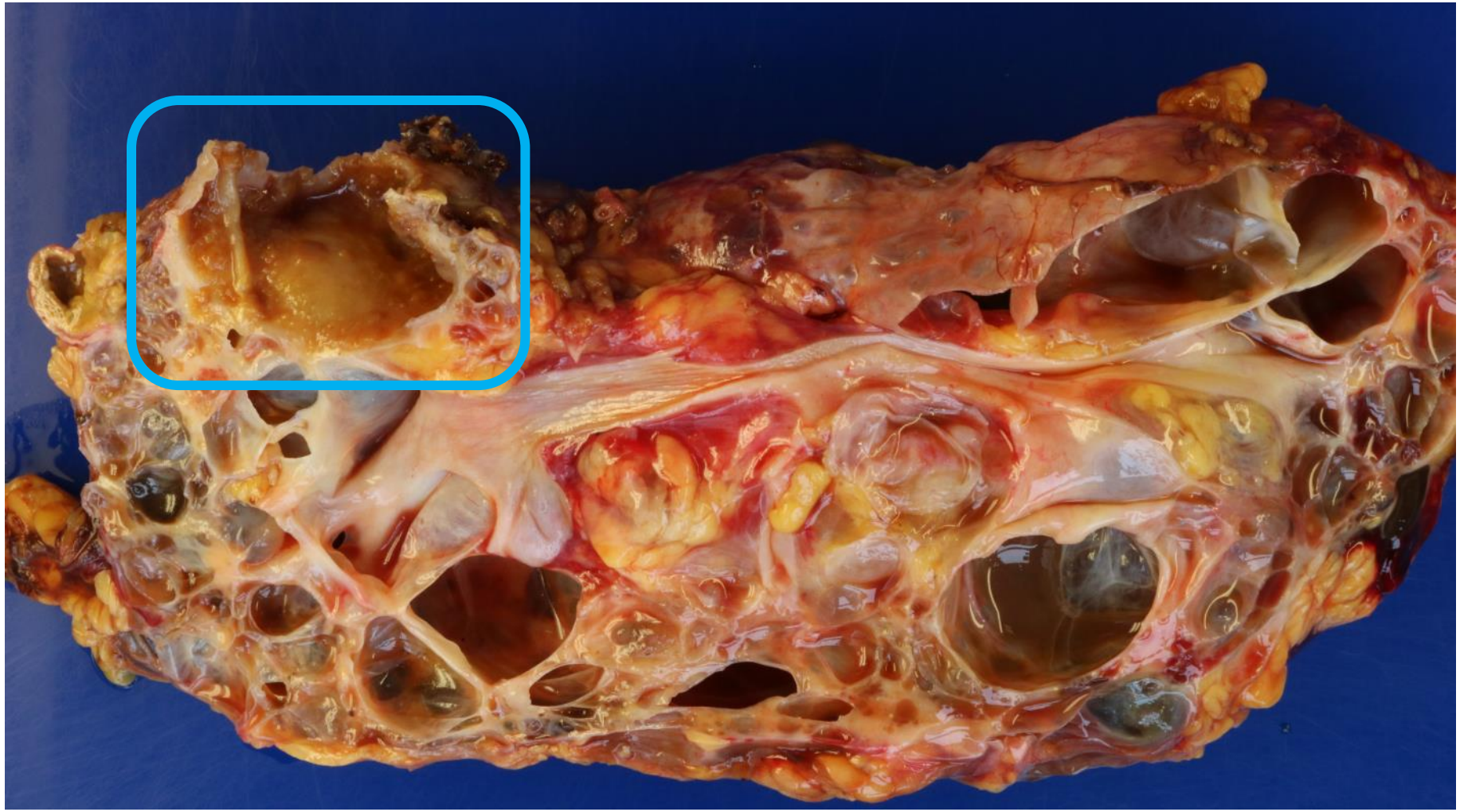
Undergoes bilateral native nephrectomies followed by living-unrelated kidney transplant

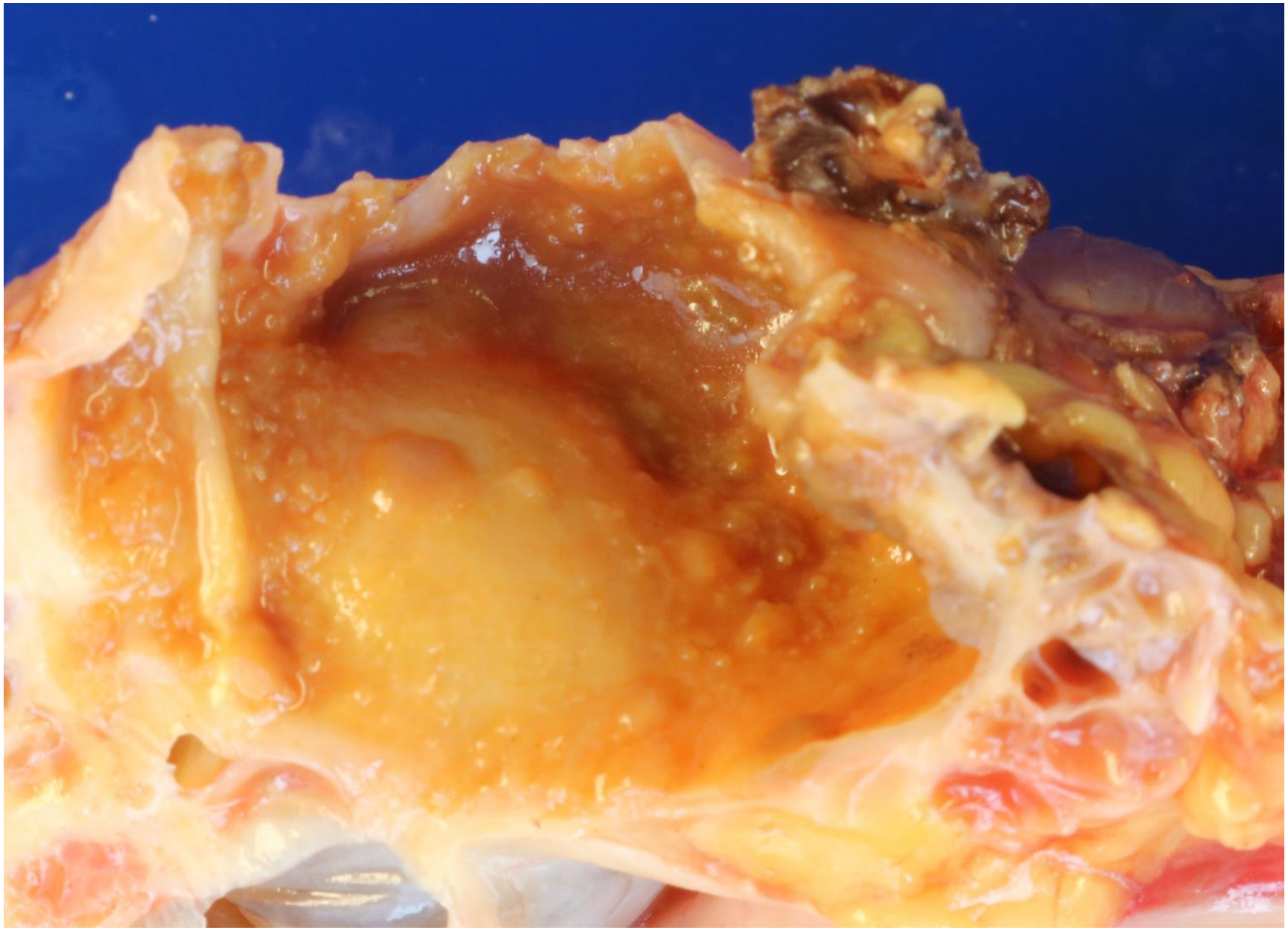
Case

- Immunosuppressed with thymoglobulin induction, belatacept, mycophenolate
- COVID negative
- No recent travel
- No unusual exposures
- Labs significant for:
  - WBC 11.5
  - sCr 2.75
  - eGFR 19

Left Kidney: Gross Findings

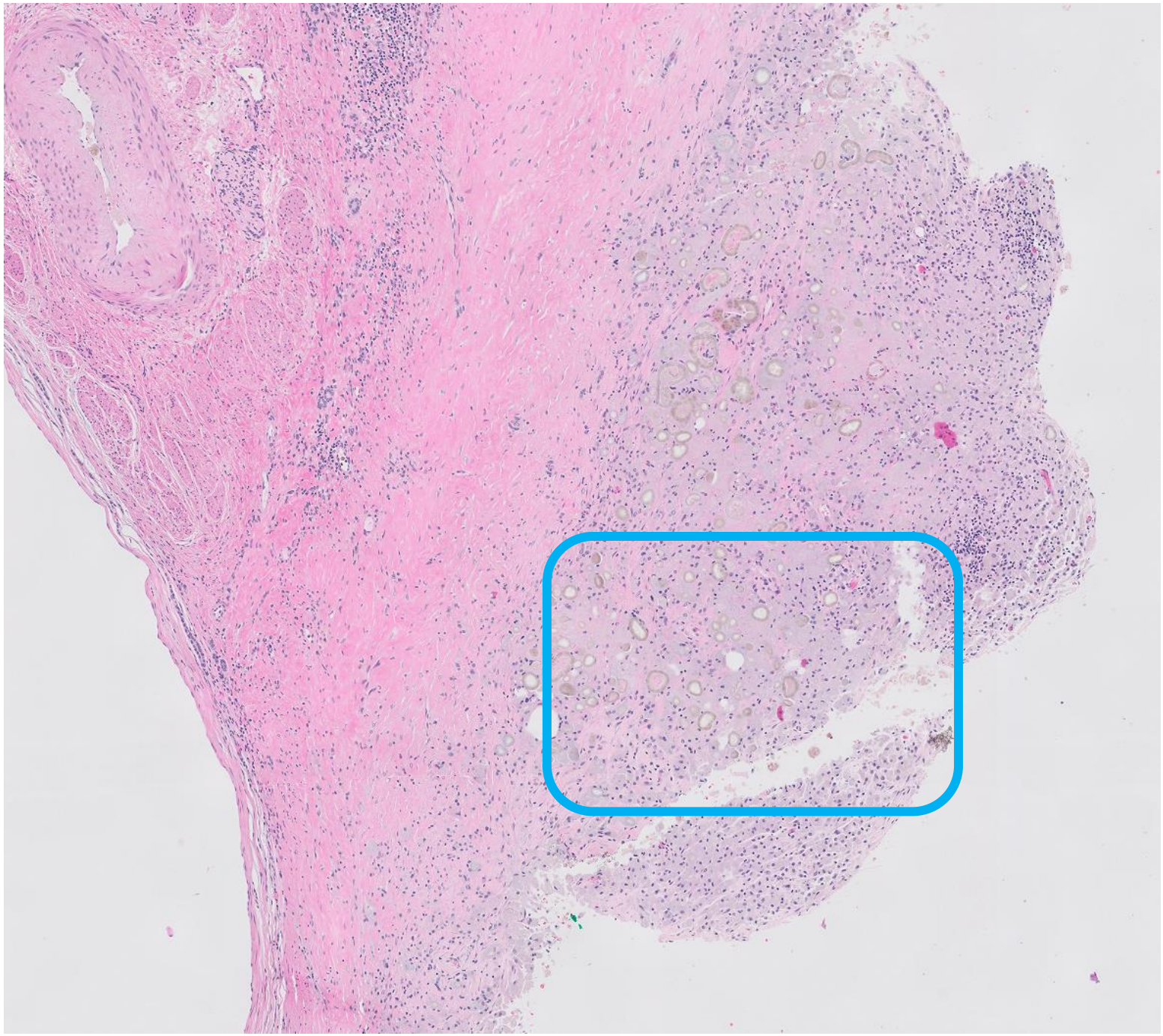
- Minimal normal parenchyma identified
- Parenchyma replaced by innumerable cysts (up to 7 cm) filled w/ thin, cloudy red-brown fluid and soft brown debris
- Cysts lined by smooth, glistening tan-pink mucosa – except for a single large cyst, which is lined by nodular brown tissue

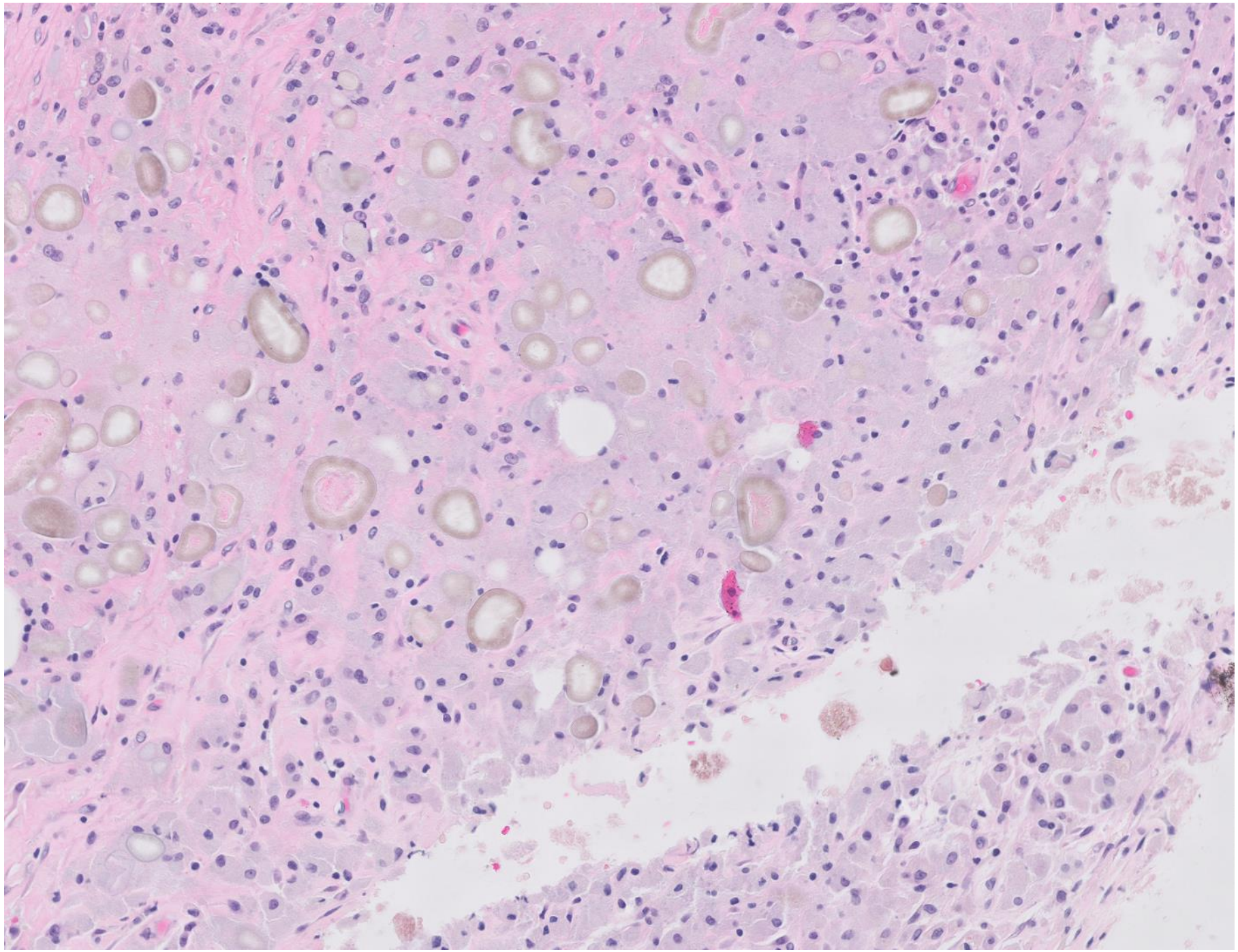


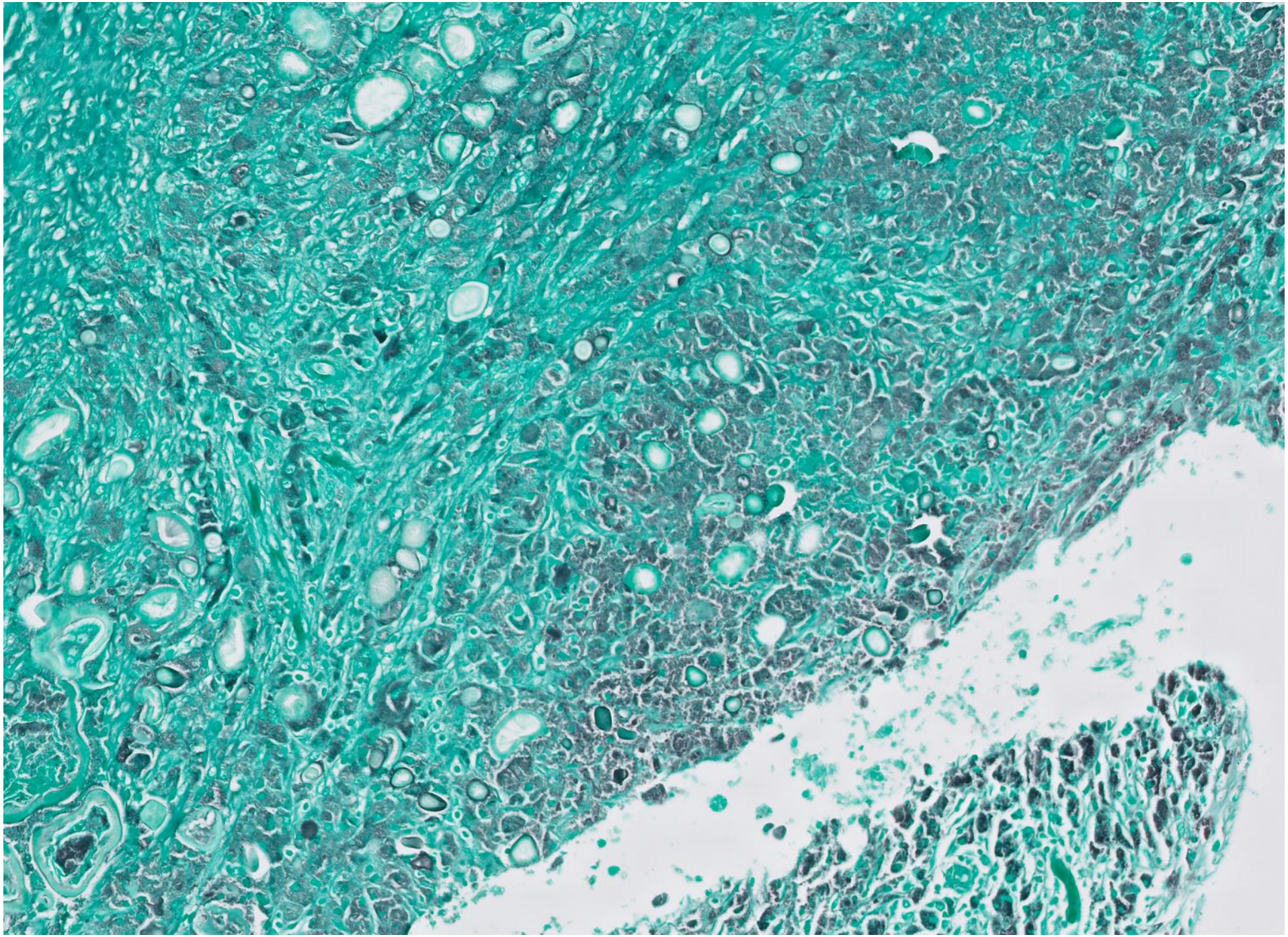


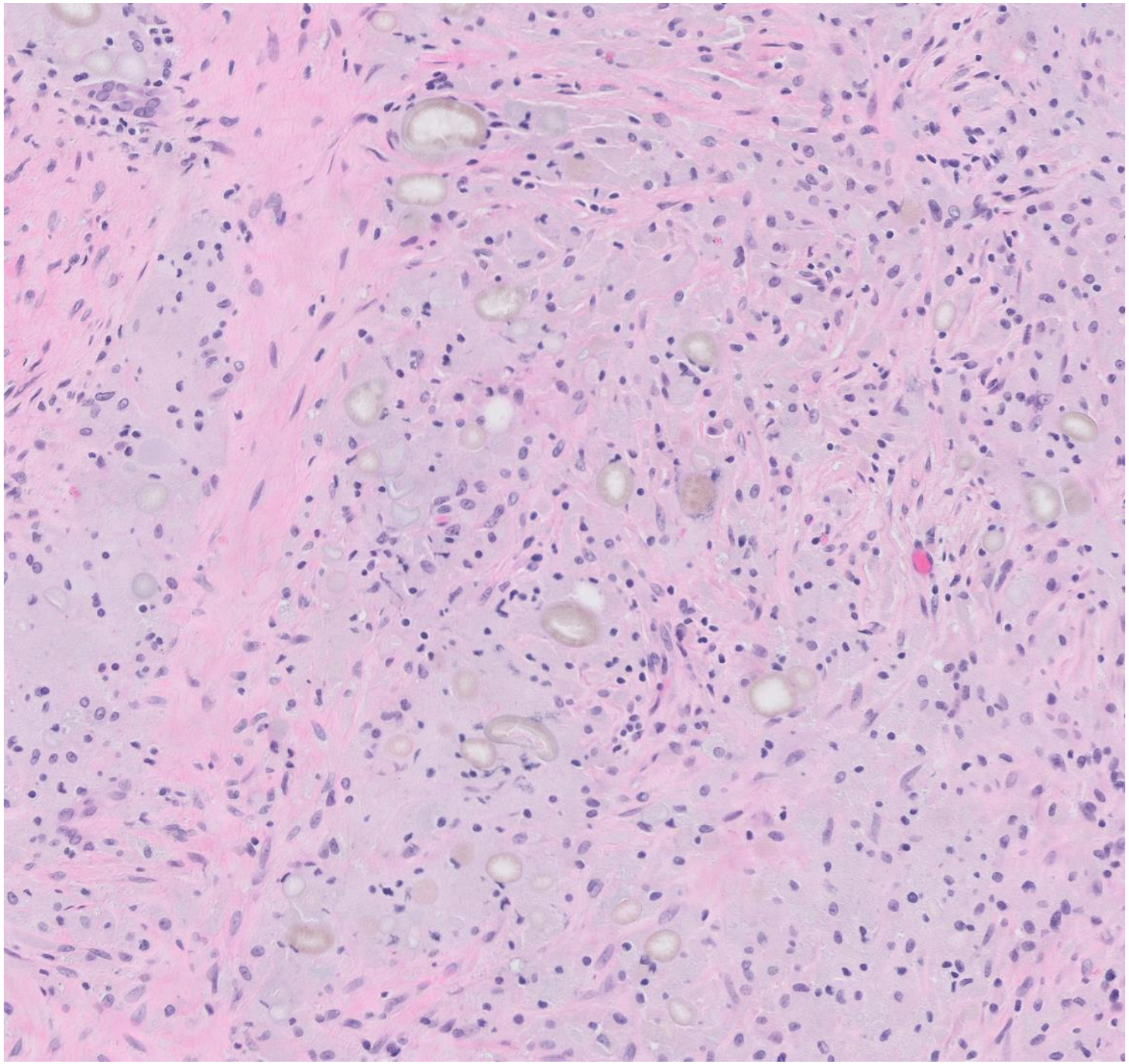
Left Kidney: Microscopic Findings

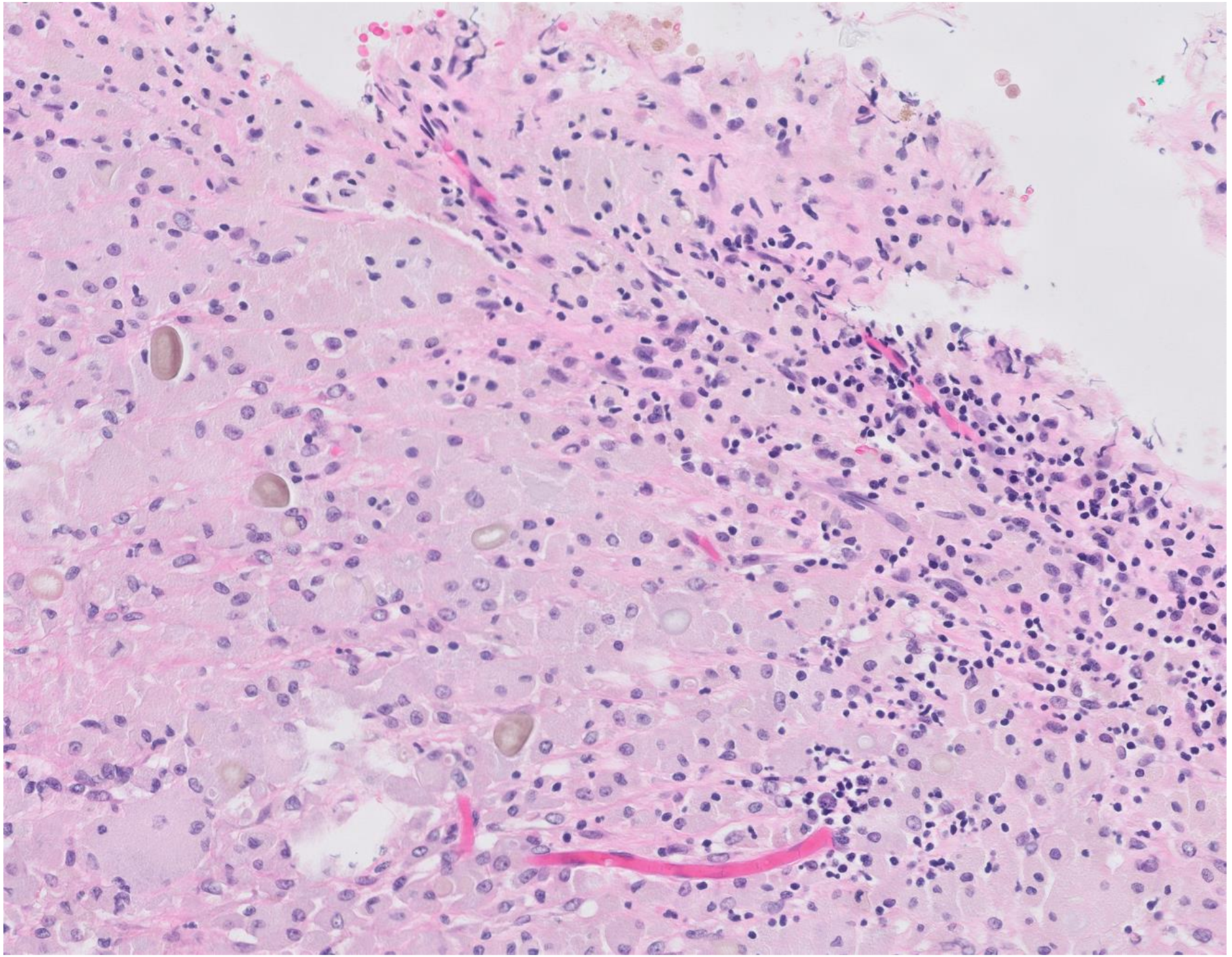
- Advanced cystic degenerative changes of AD-PKD

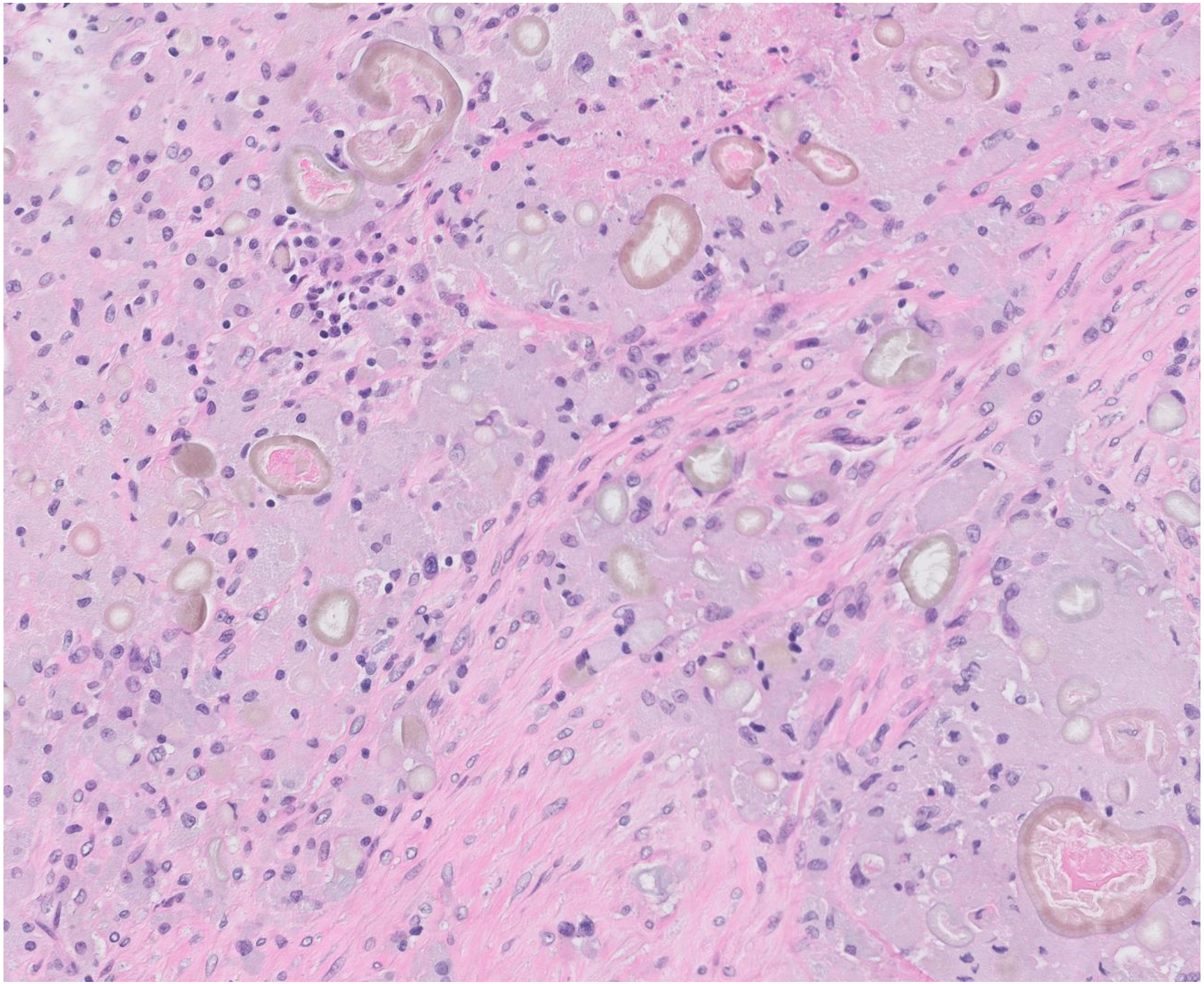












Left Kidney: Microscopic Findings

- Advanced cystic degenerative changes of AD-PKD
- **Liesegang Rings**
- Numerous tan-brown, lamellar structures of variable size (10-100 um) with amorphous central cores
  - Rings may contain multinucleated giant cells
- Associated with cystic and inflammatory conditions
- Few case reports describe this in kidneys, synovium, conjunctivae, eyelids

Pathophysiology and Chemistry

- Exact process of formation in vivo is unclear
- Apparently related to supersaturated colloid solutions
- Can see glycoprotein rings in pulmonary corpora amylacea
- Chemical composition: mixed
  - Fe, S, Si, Ca

Left Kidney: Microscopic Findings

- Advanced cystic degenerative changes of AD-PKD
- **Liesegang Rings**
- Numerous tan-brown, lamellar structures of variable size (10-100 um) with amorphous central cores
  - Rings may contain multinucleated giant cells
- Associated with cystic and inflammatory conditions
- Few case reports describe this in kidneys, synovium, conjunctivae, eyelids
- May be mistaken for other histologic findings...

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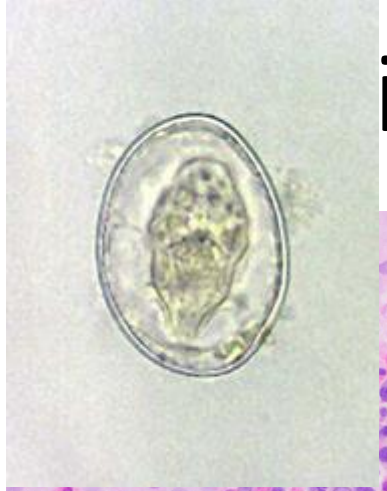
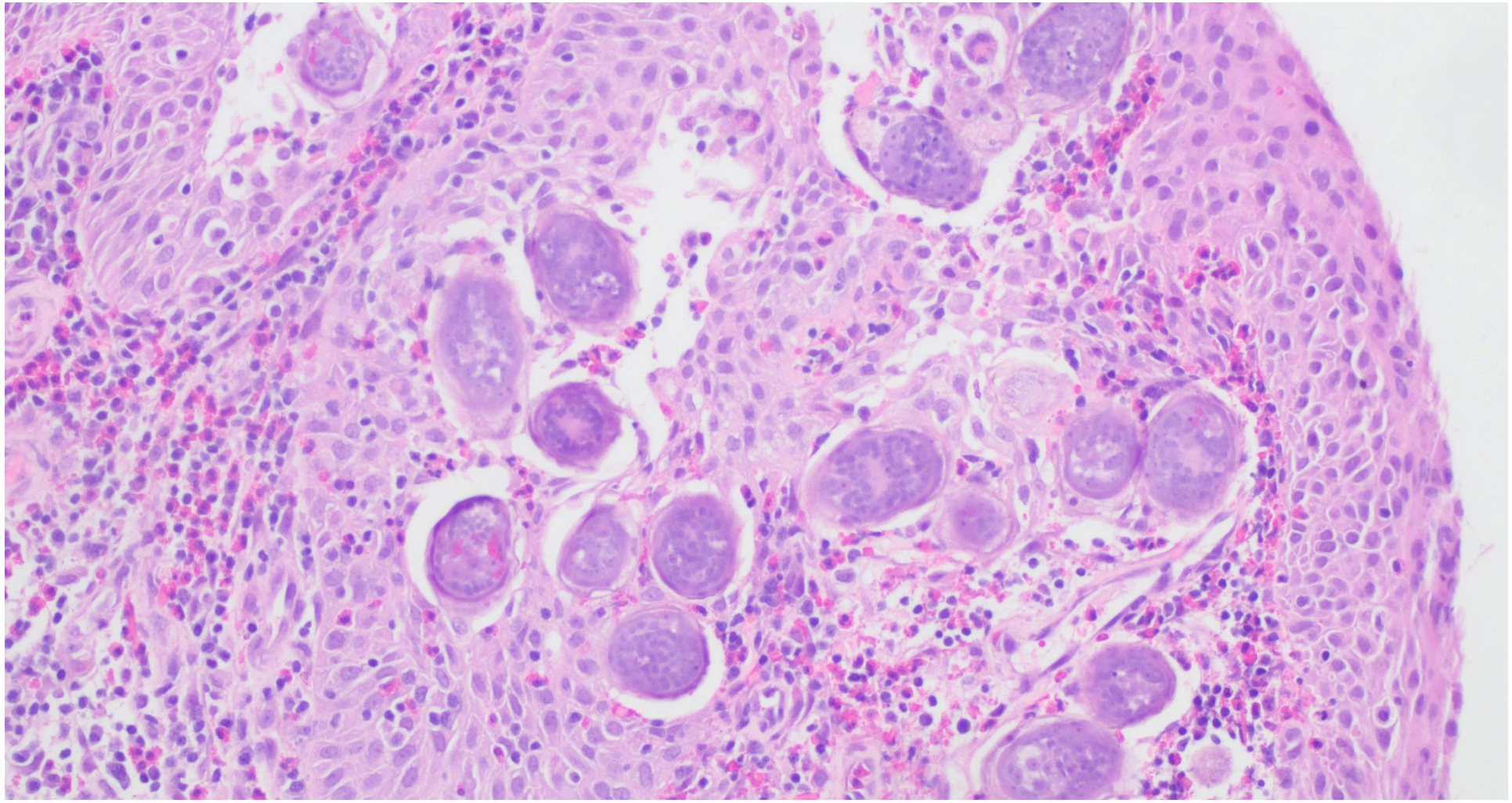
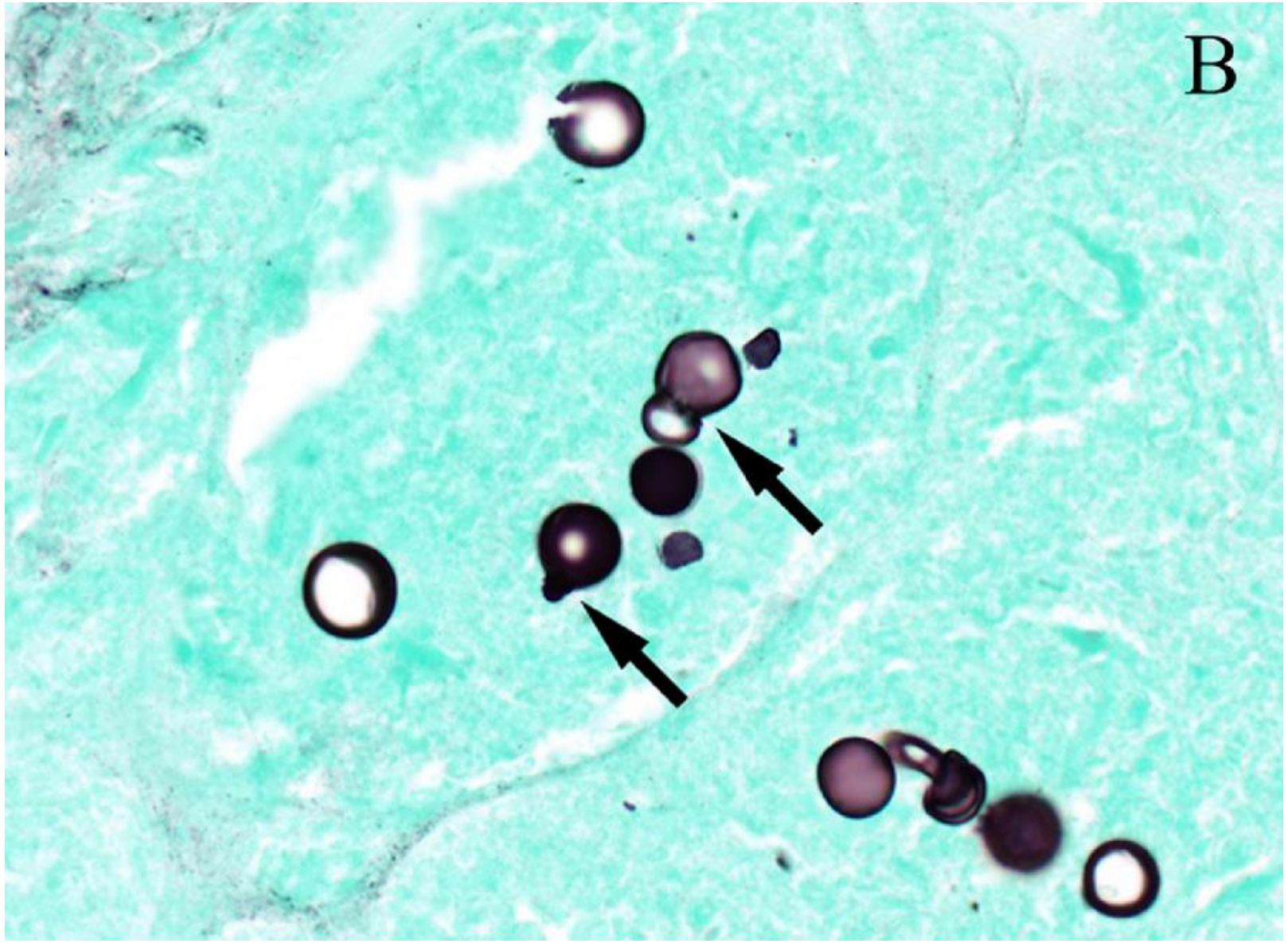


Upper left:
Kansas State University Parasitology.
Photos by S.J. Upton.

Parasites



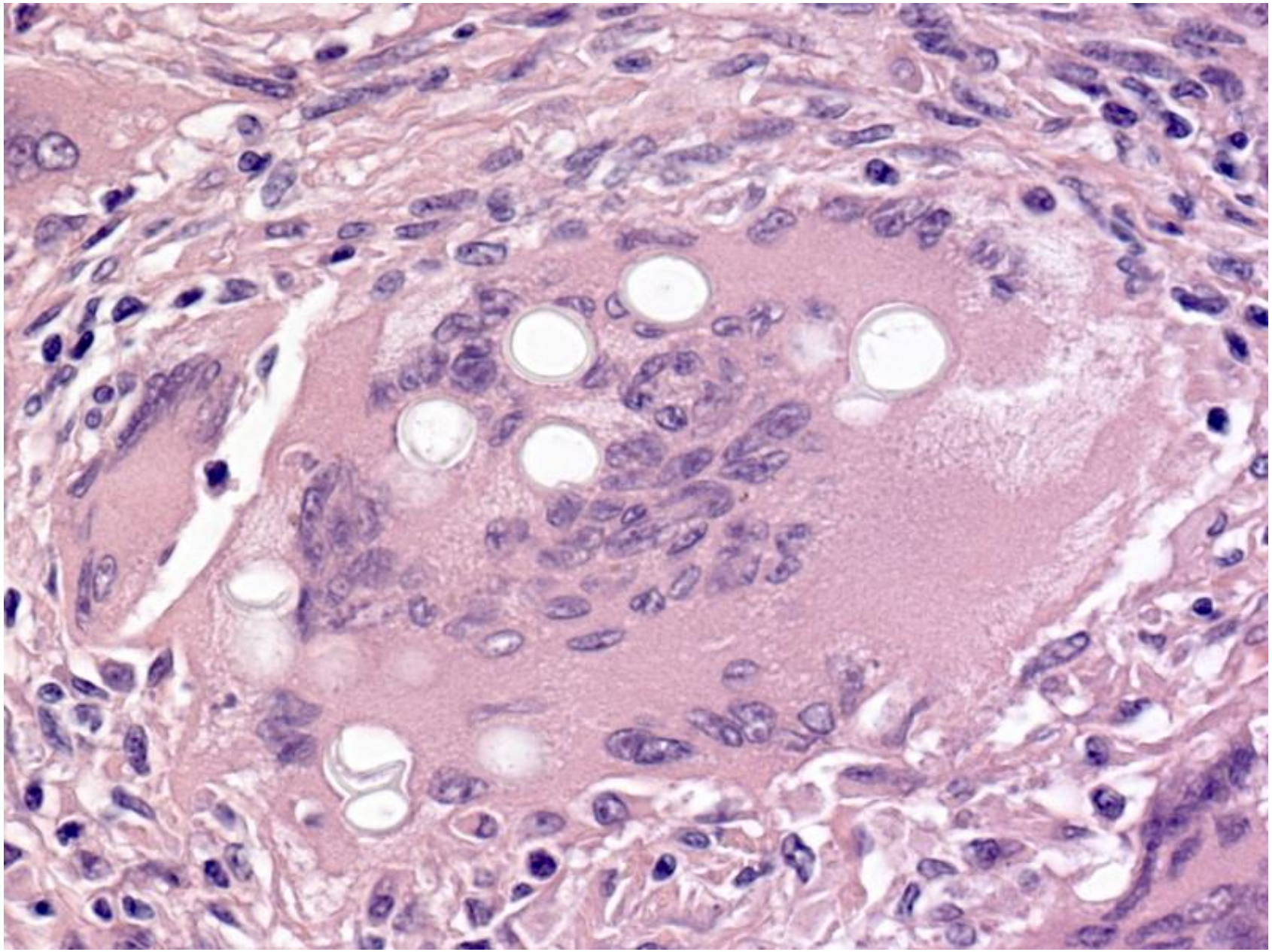
Fungi

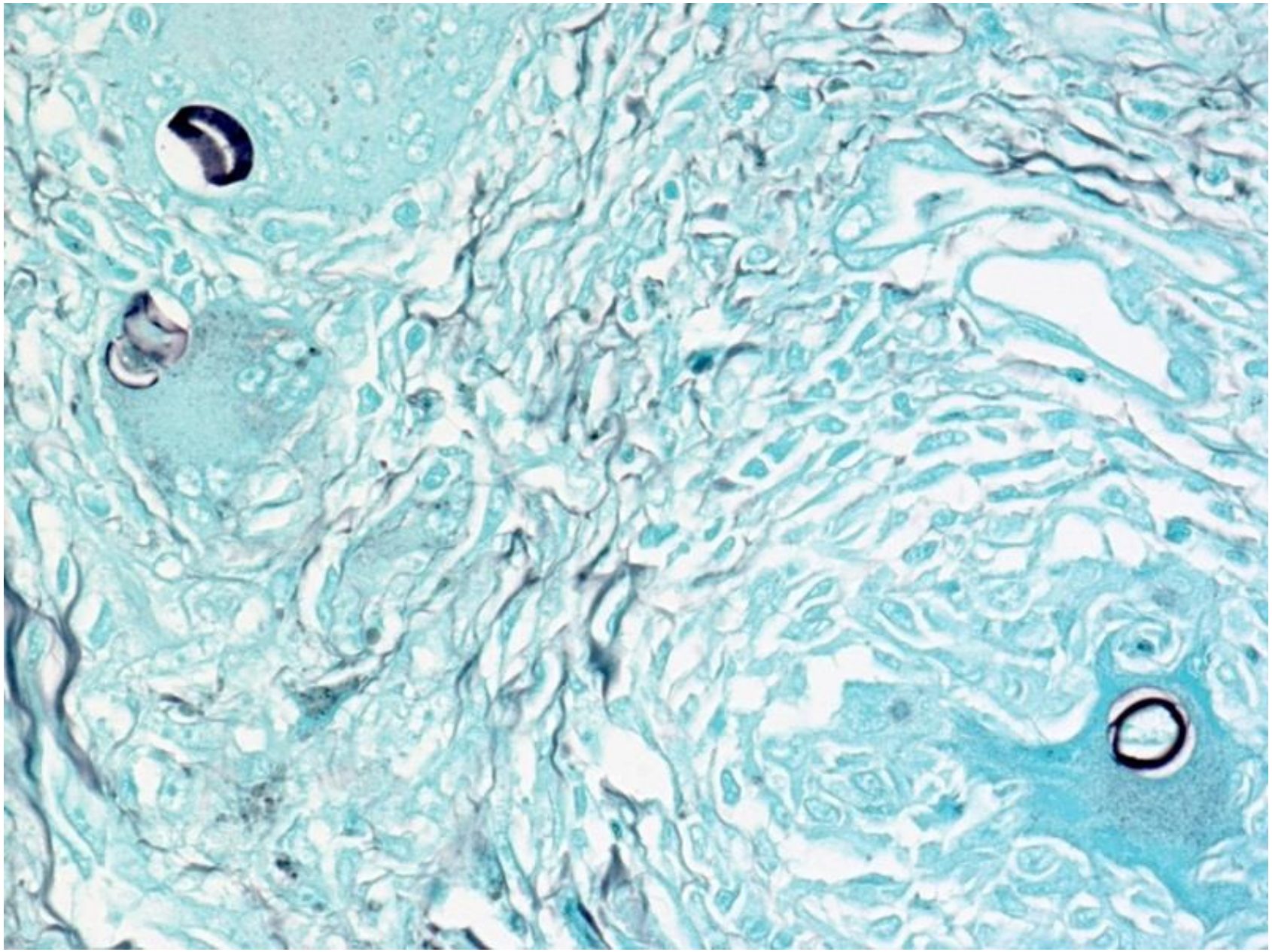


Yemar et al. Am J Med 2020.

Pulmonary blastomycosis

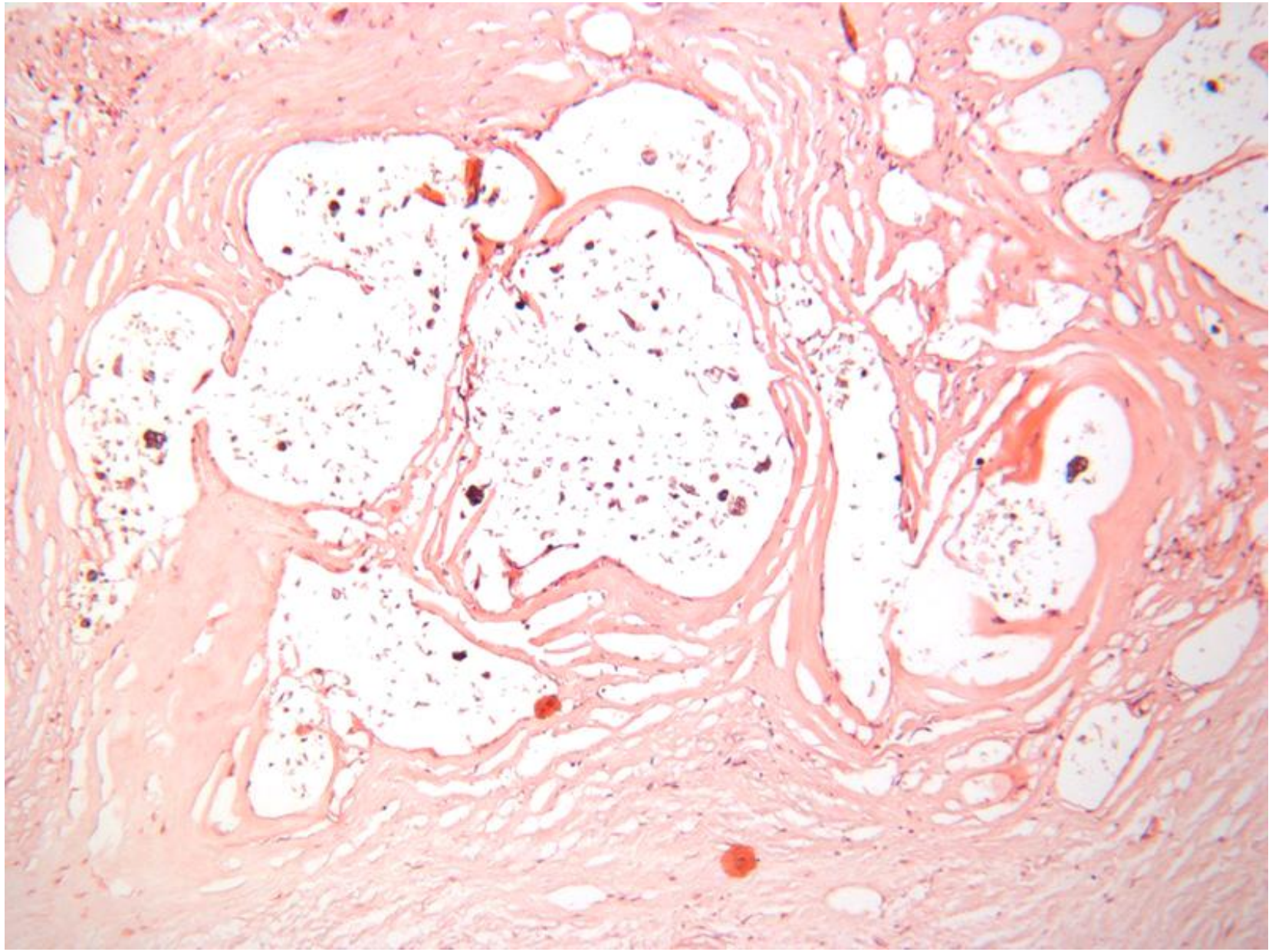
- From a man in his 20s with pneumonia that is not getting better after 1 month of antibiotics

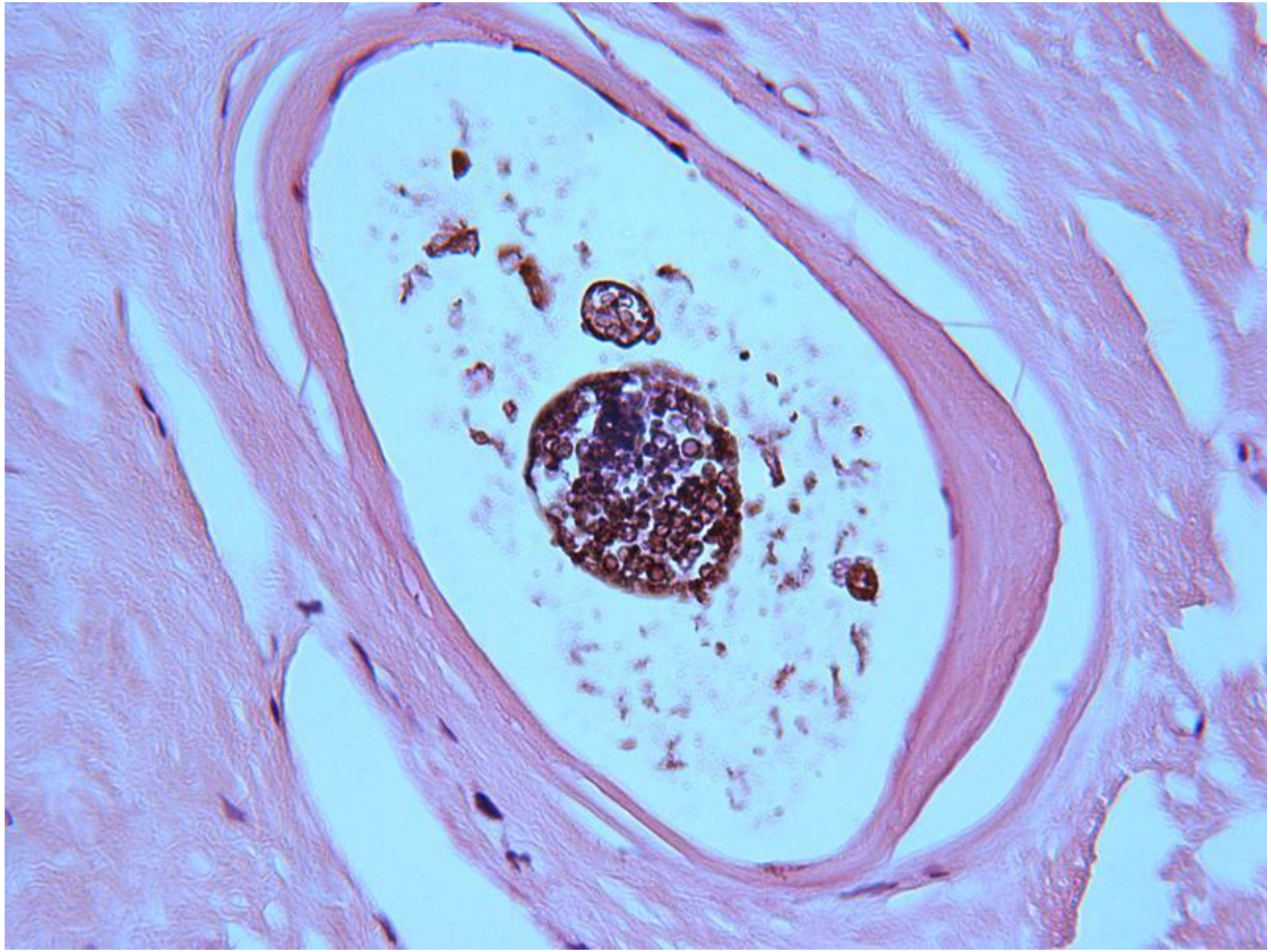


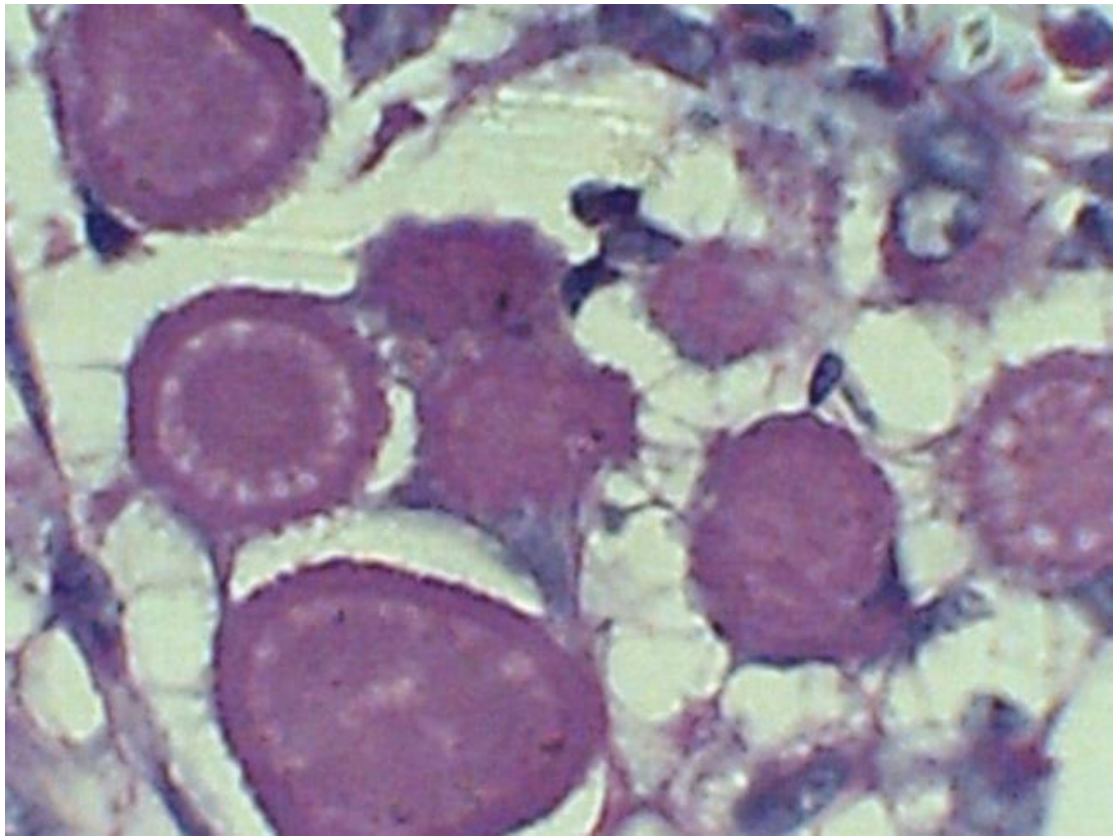


Myospherulosis

- From a woman in her 30s with history of nasal curettage and packing with petrolatum gauze







PAS, 200x

Pegas et al. Patholog Res Int 2010.

Final Pathologic Diagnosis

- Left Kidney:
  1. End-stage renal disease with gross and microscopic findings consistent with AD-PKD.
  2. Xanthogranulomatous pyelonephritis.

Liesegang Rings

- Benign finding
- May be mistaken for parasites, fungi, or other organisms
- Pathologists should be aware of these in the context of cystic/inflammatory diseases

References

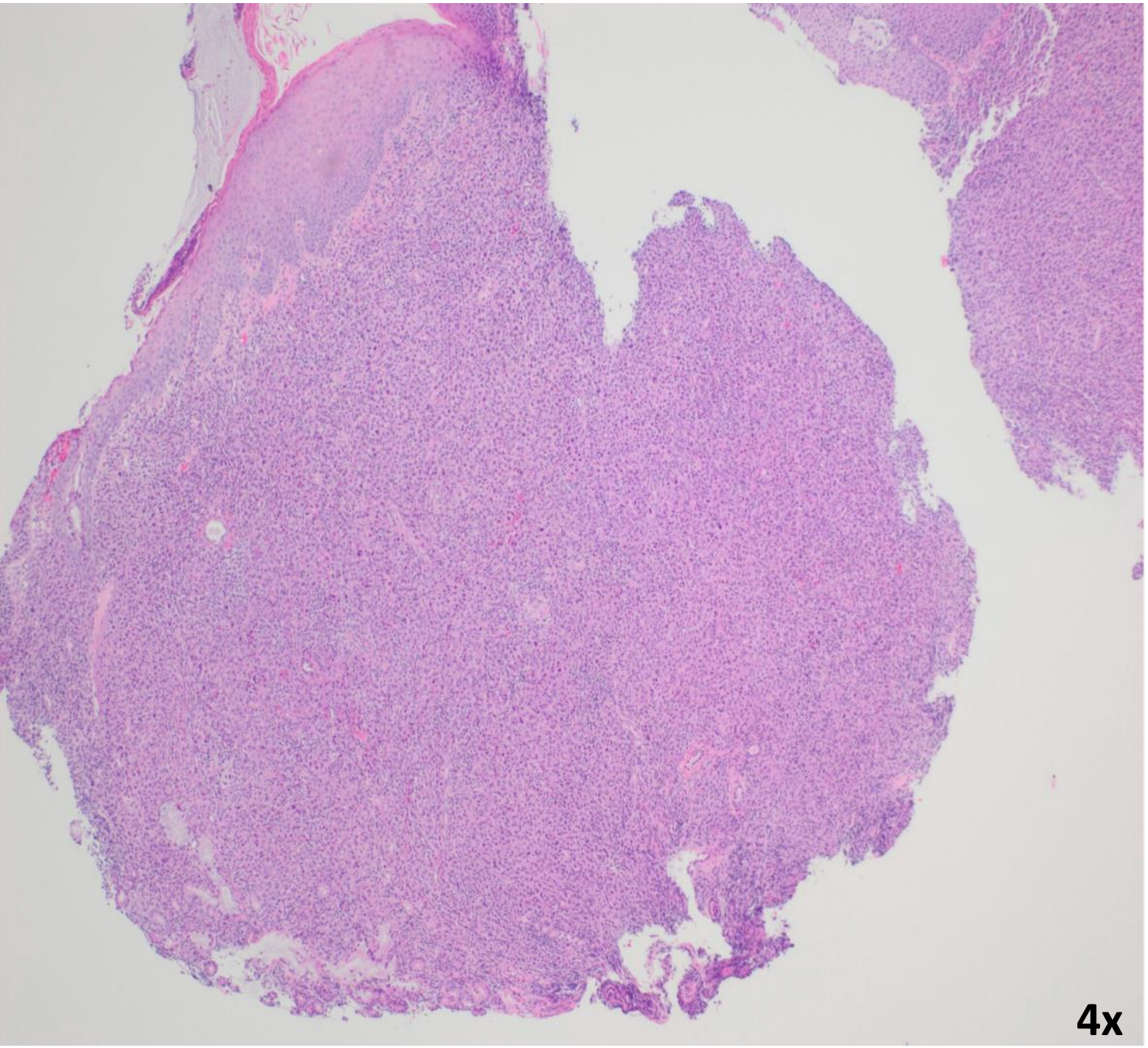
1. Pegas KL, Edelweiss MI, Cambruzzi E, Zettler CG. Liesegang rings in xanthogranulomatous pyelonephritis: a case report. Patholog Res Int. 2010 Jan 4;2010:602523. doi: 10.4061/2010/602523. PMID: 21151725; PMCID: PMC2990386.

2. Yetmar ZA, Cano Cevallos E, Pritt B, DeSimone DC. Disseminated Blastomycosis Presenting as Obstructive Renal Mass Treated With Fluconazole. Am J Med. 2020 Jul;133(7):e378-e379. doi: 10.1016/j.amjmed.2019.12.004. Epub 2020 Jan 8. PMID: 31926139.

23-0604

Anjanaa Vijayanarayanan, Sonam Prakash; UCSF

67-year-old man with an 8mm lesion on the left anterior nasal septum, undergoing a biopsy. Additionally, the patient is noted to have a small IgM kappa paraprotein.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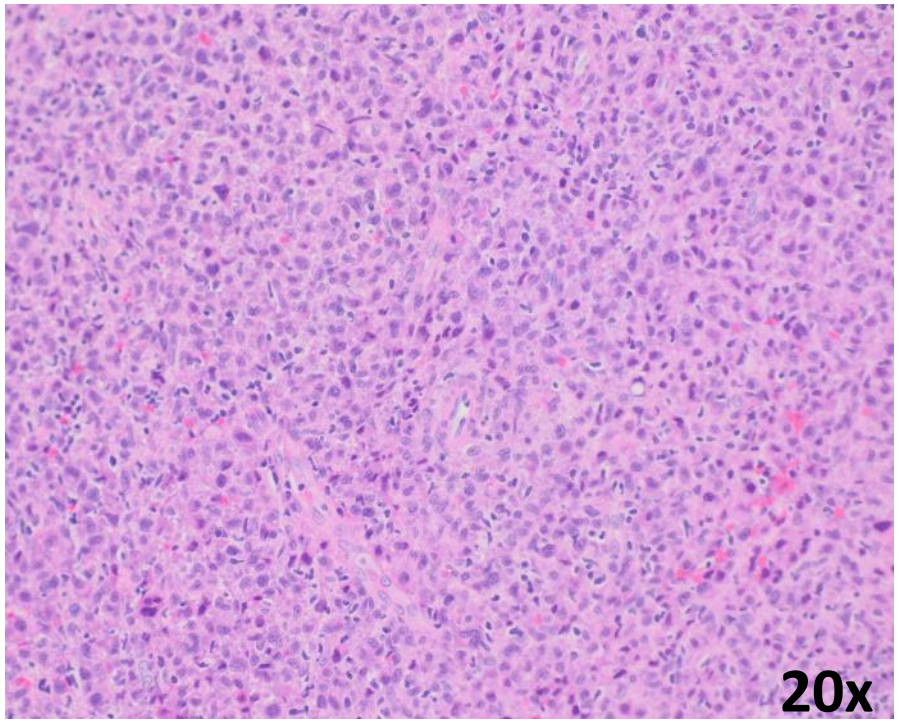
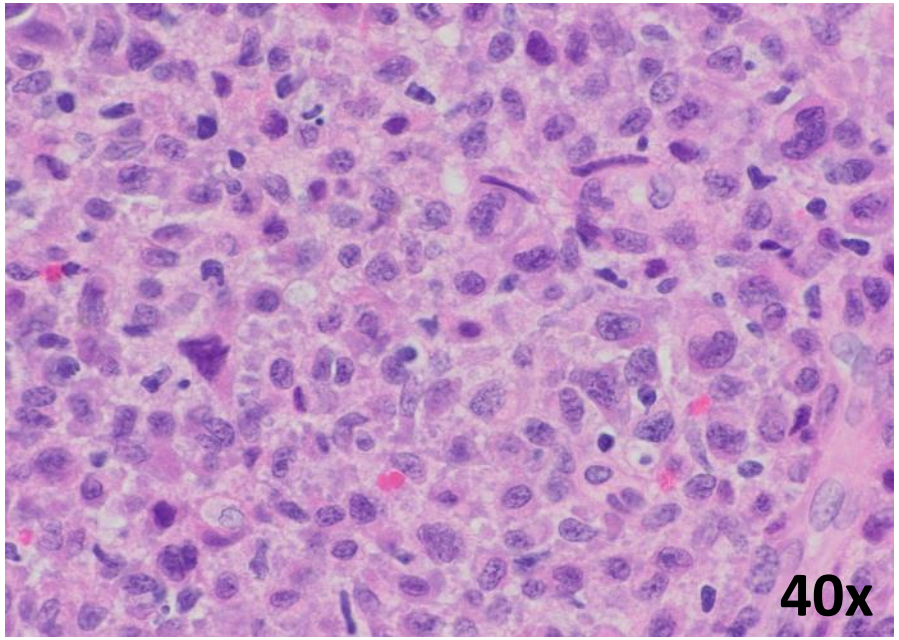

20x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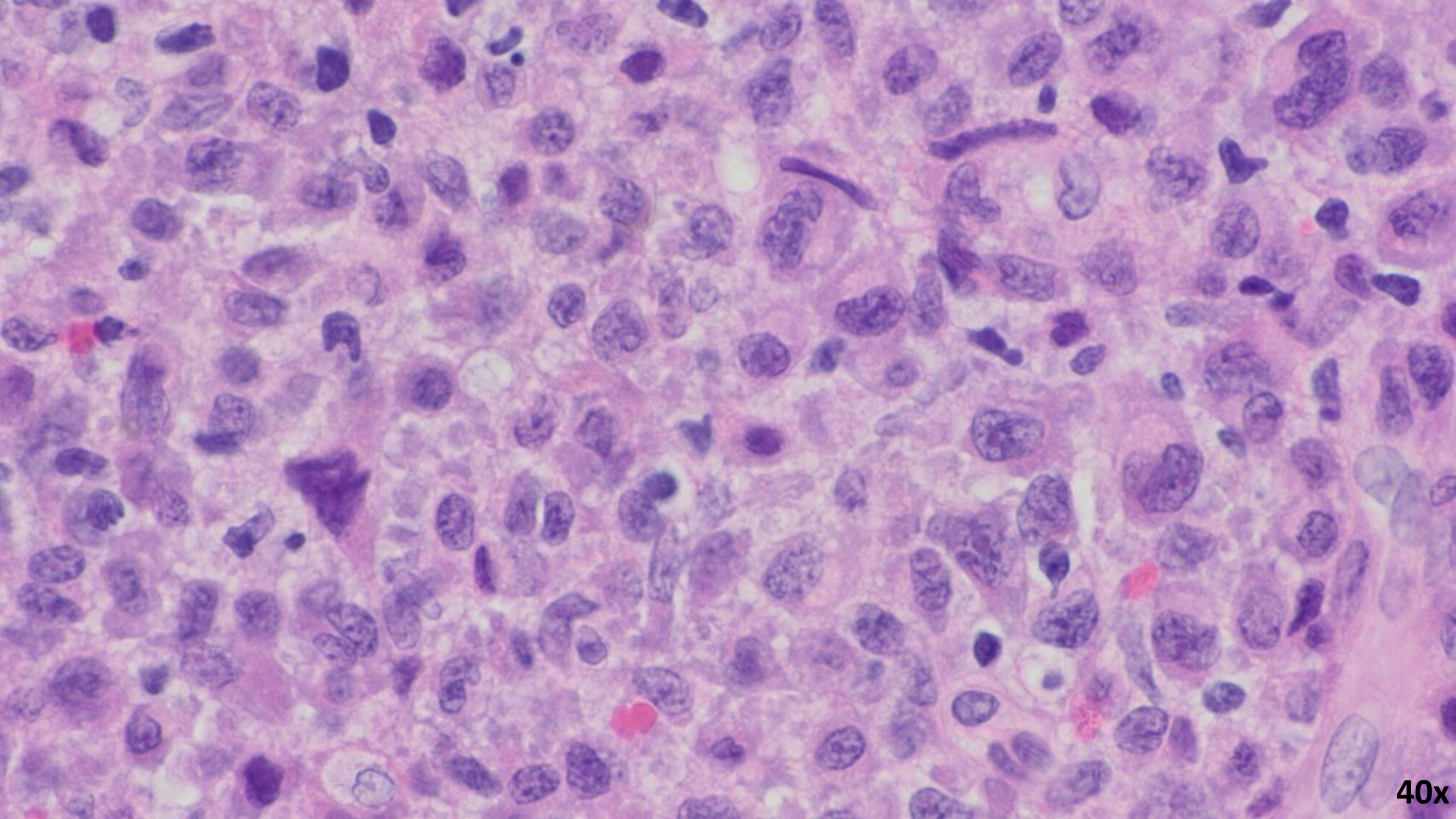
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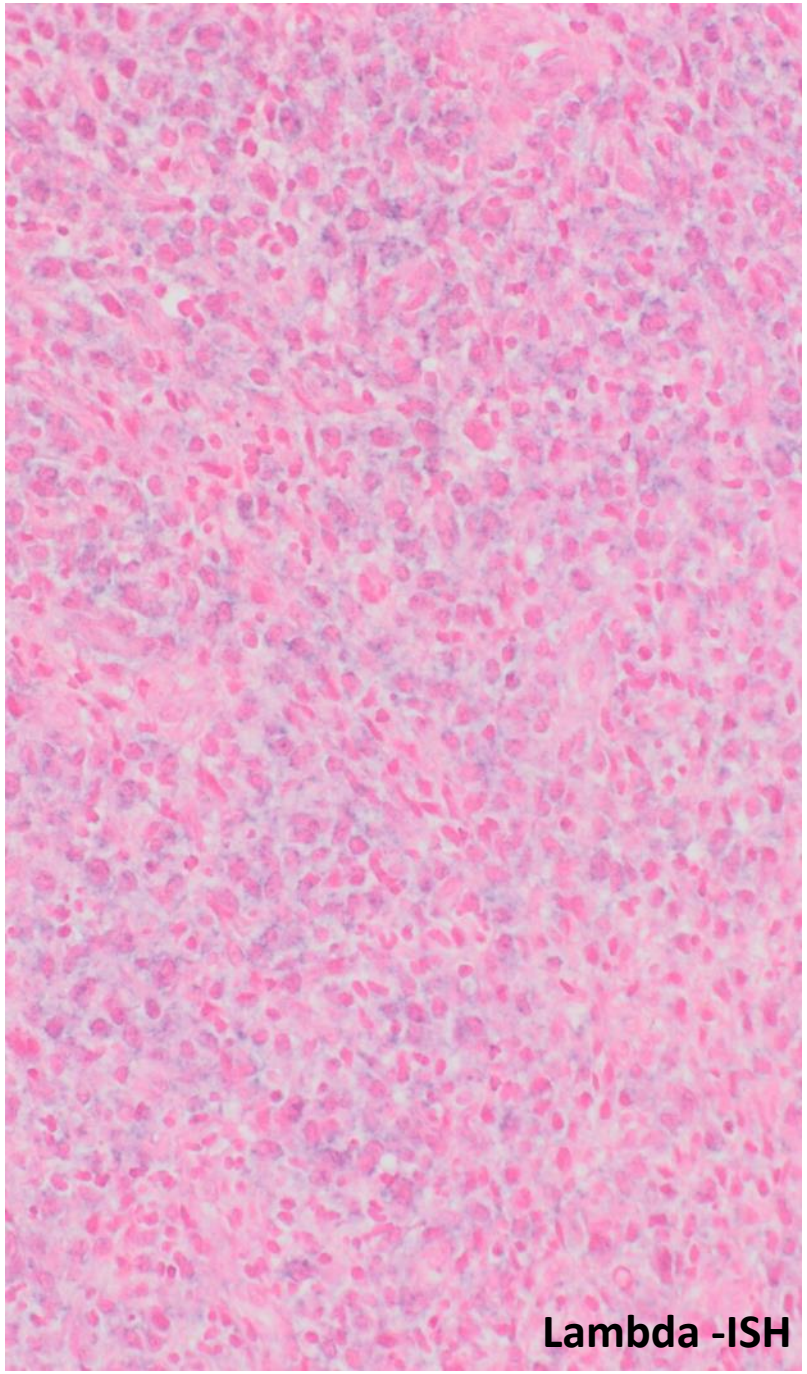
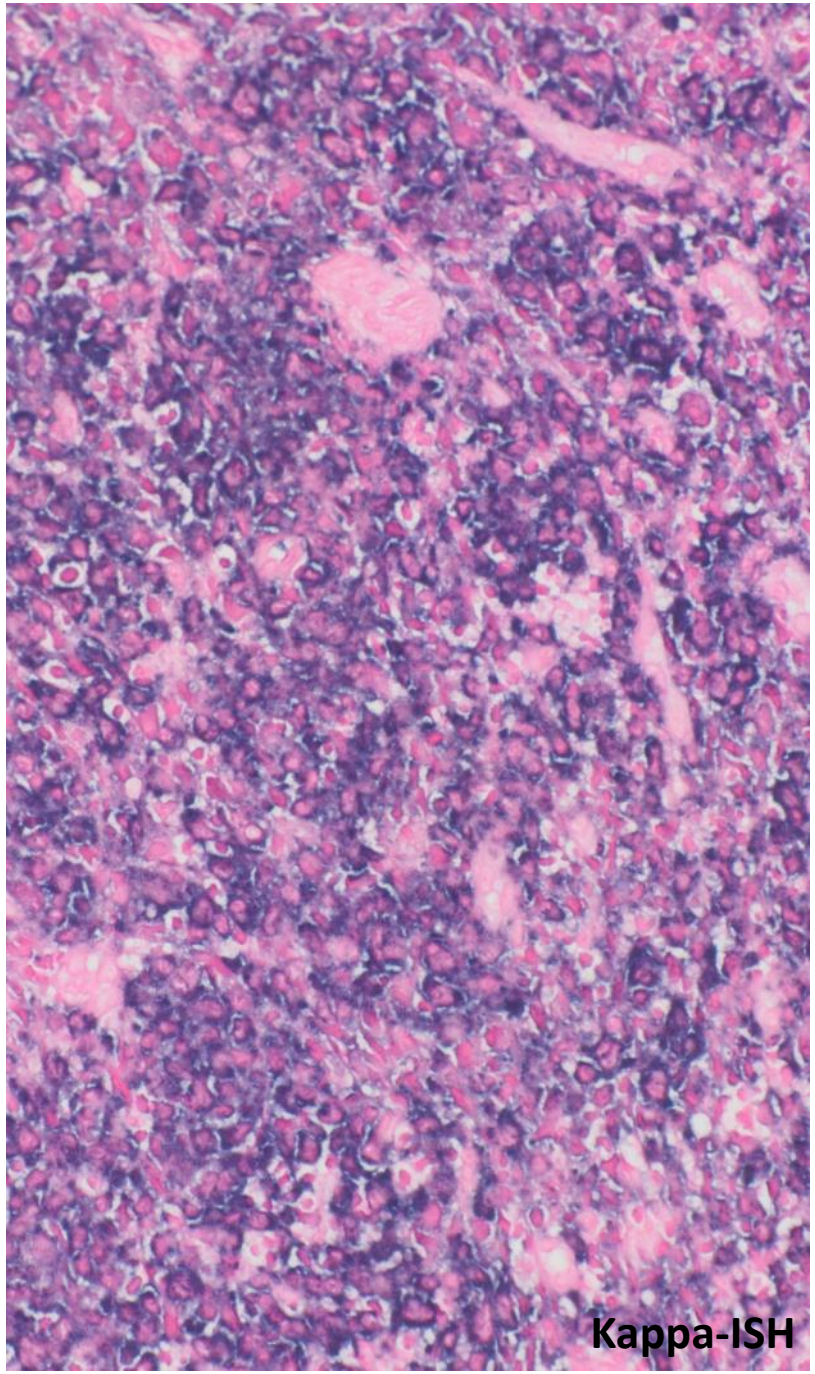
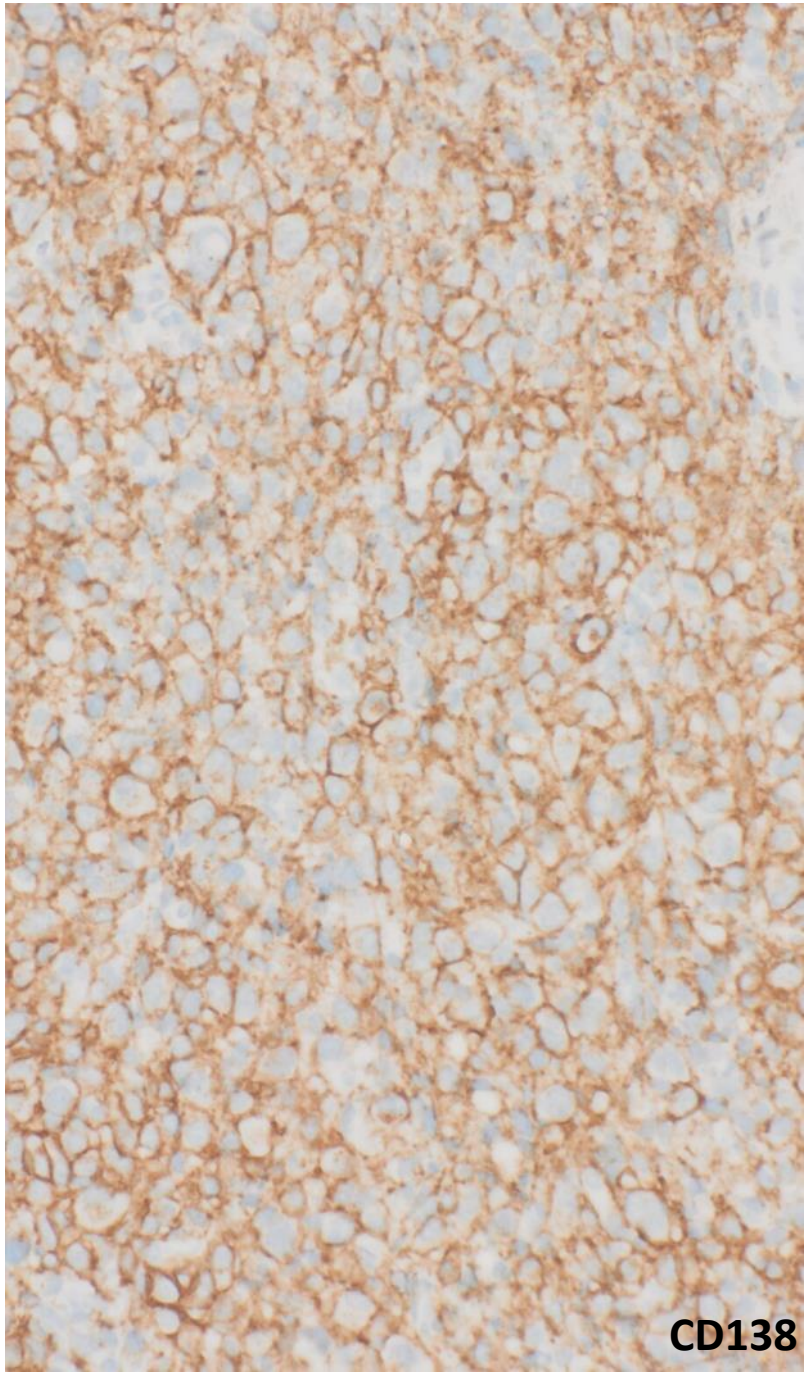
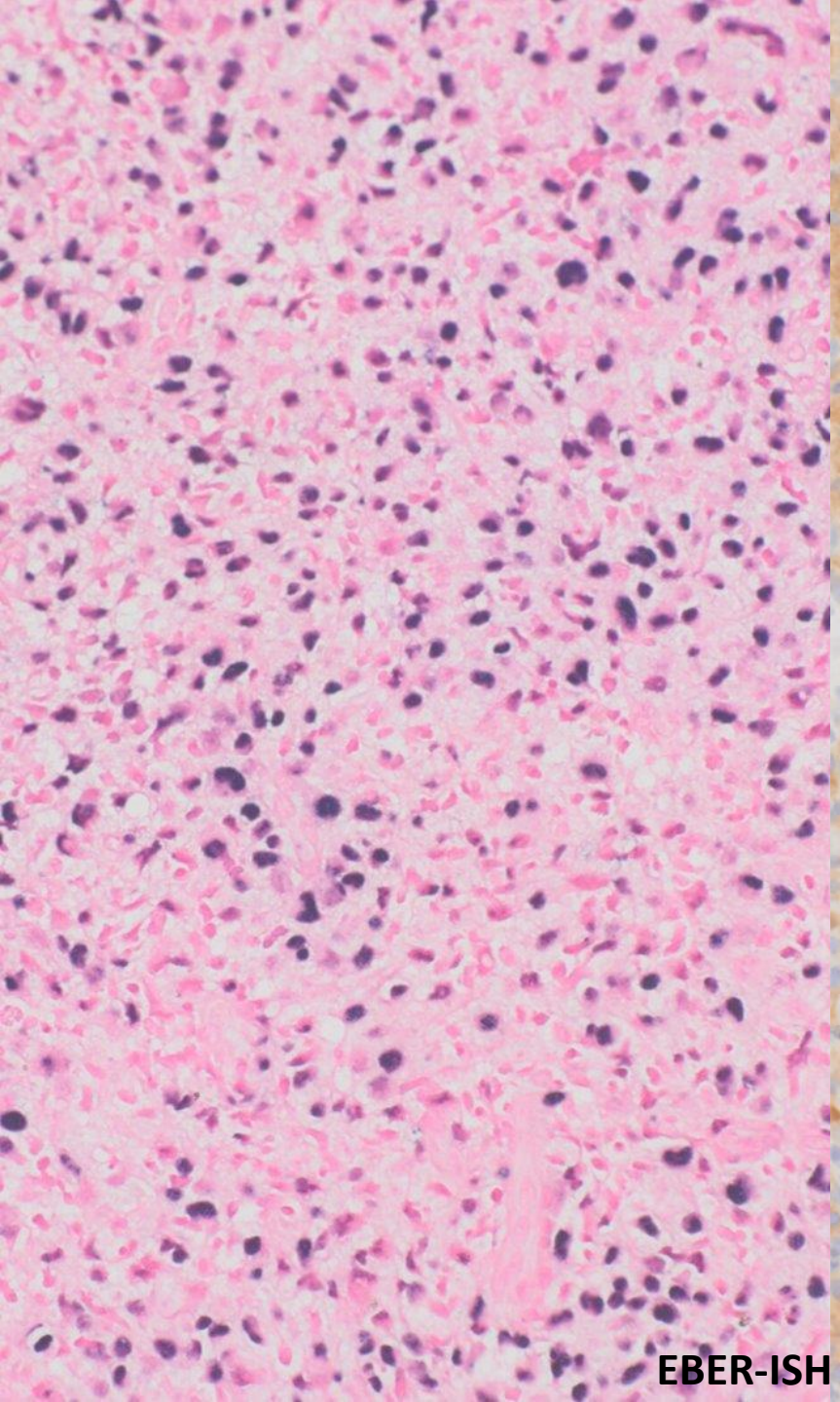

Lambda -ISH


Kappa-ISH


CD138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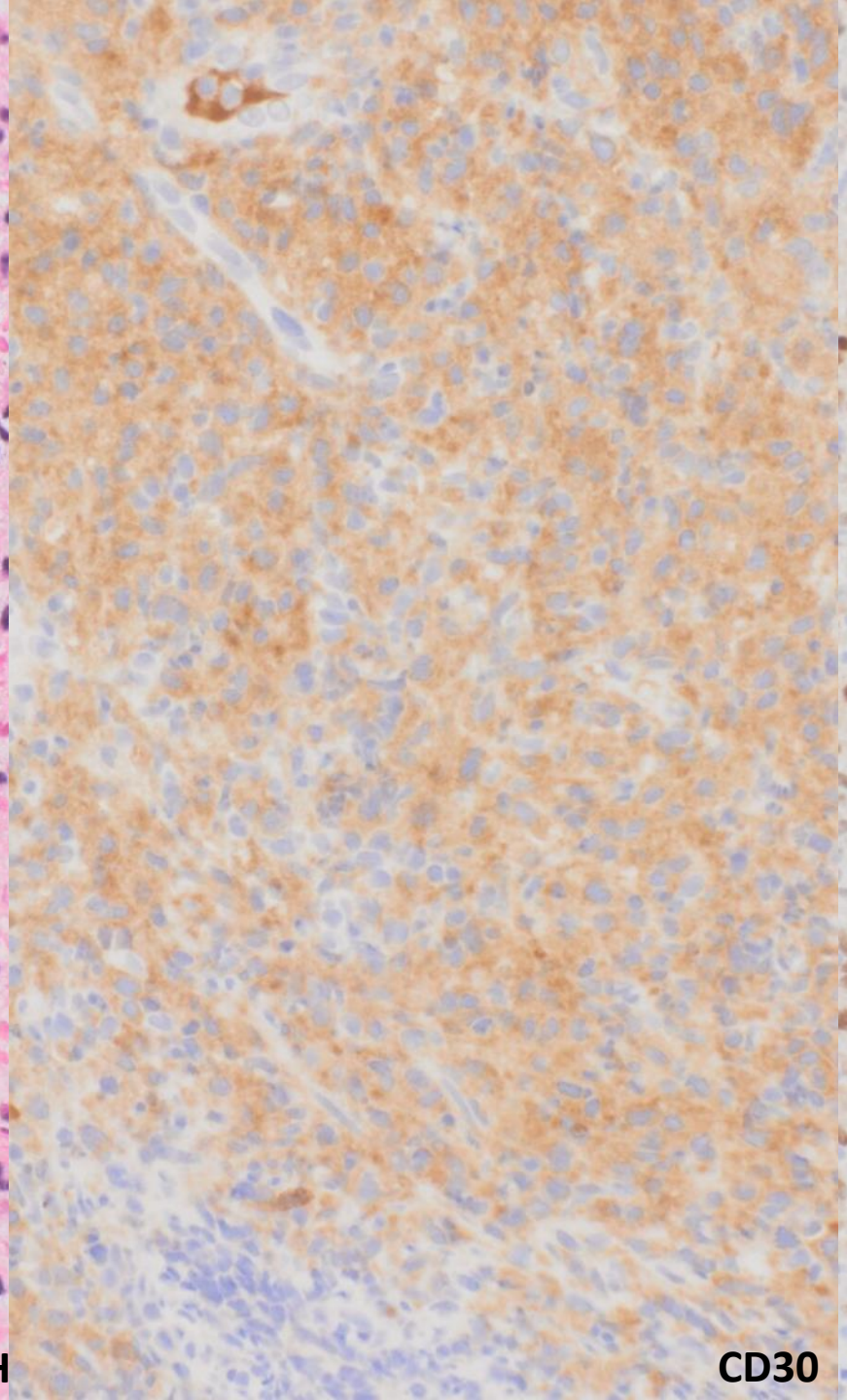
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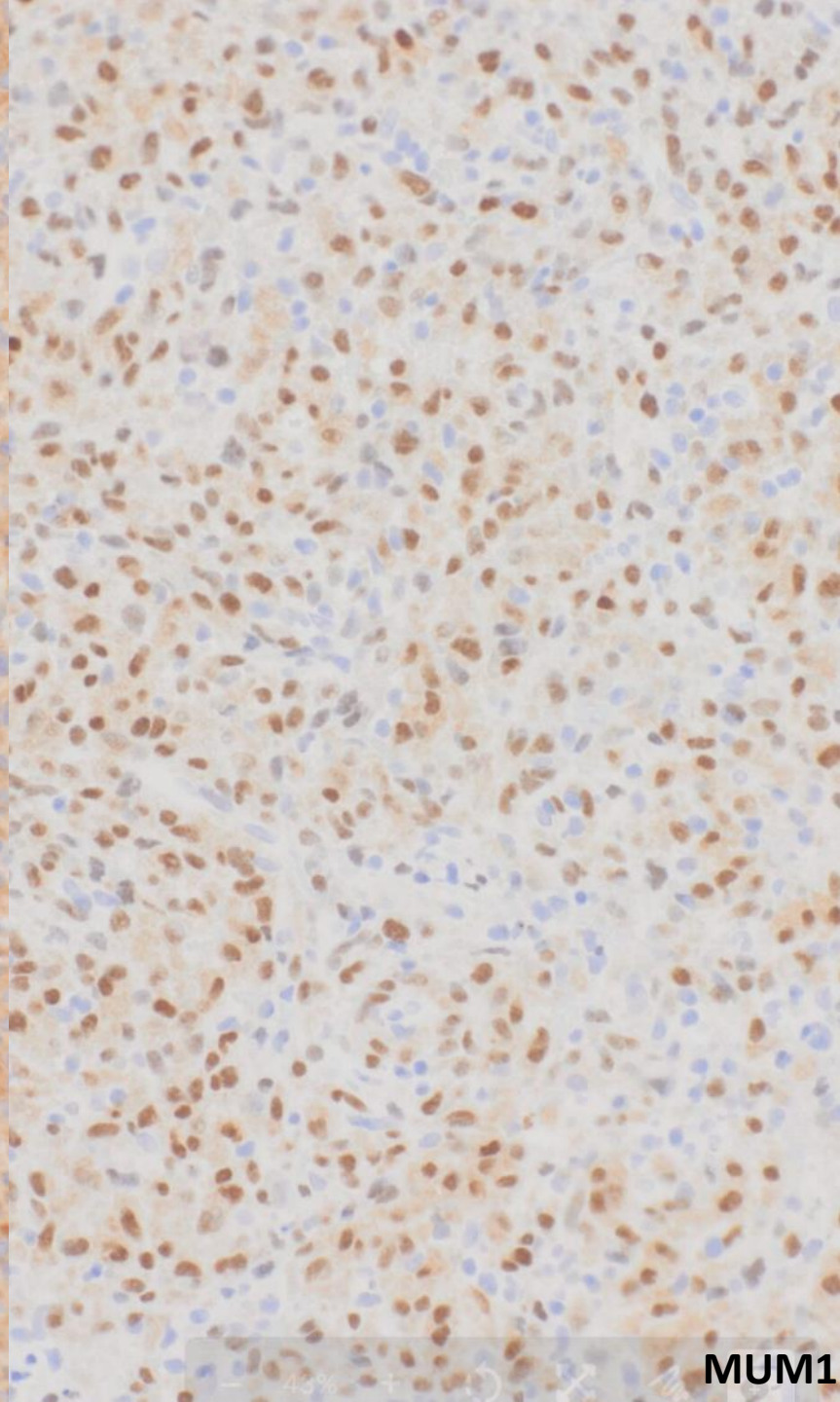
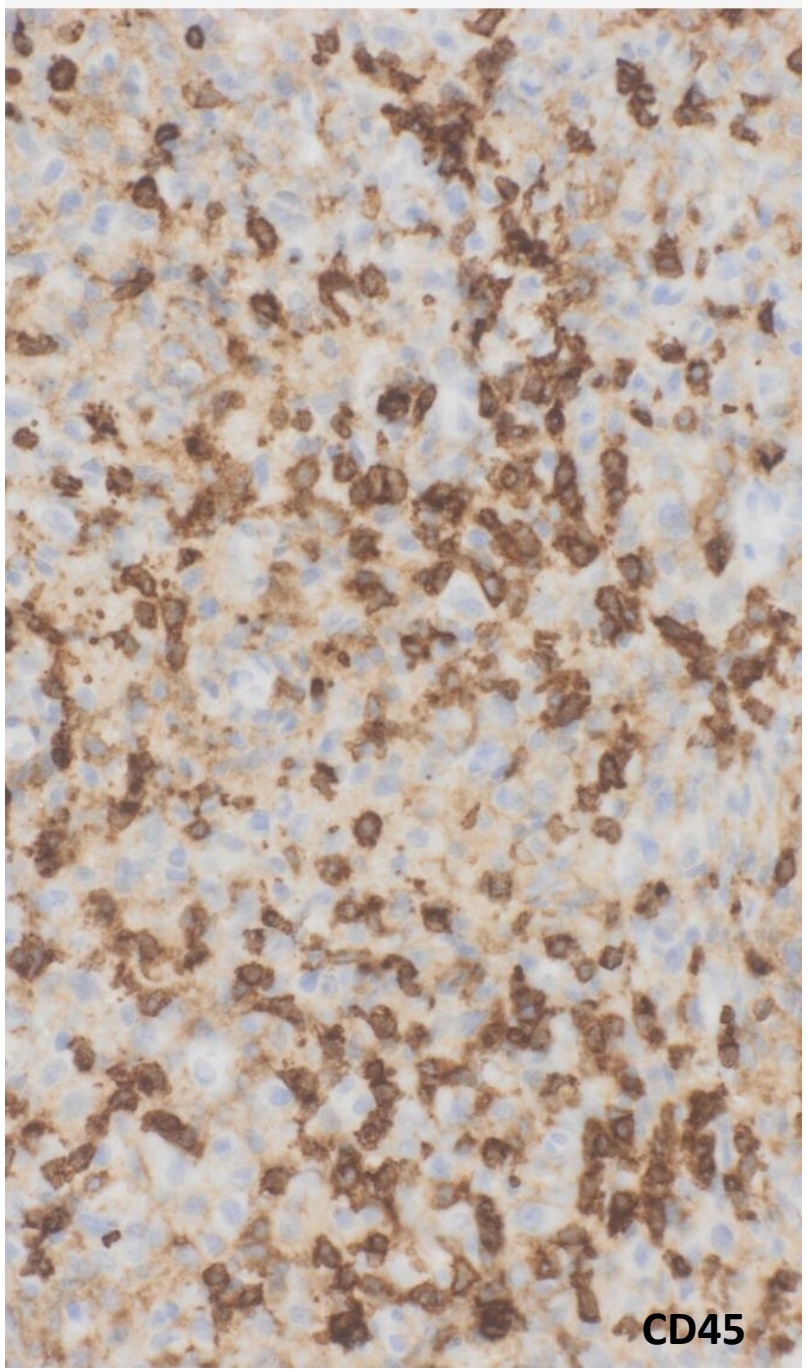

MUM1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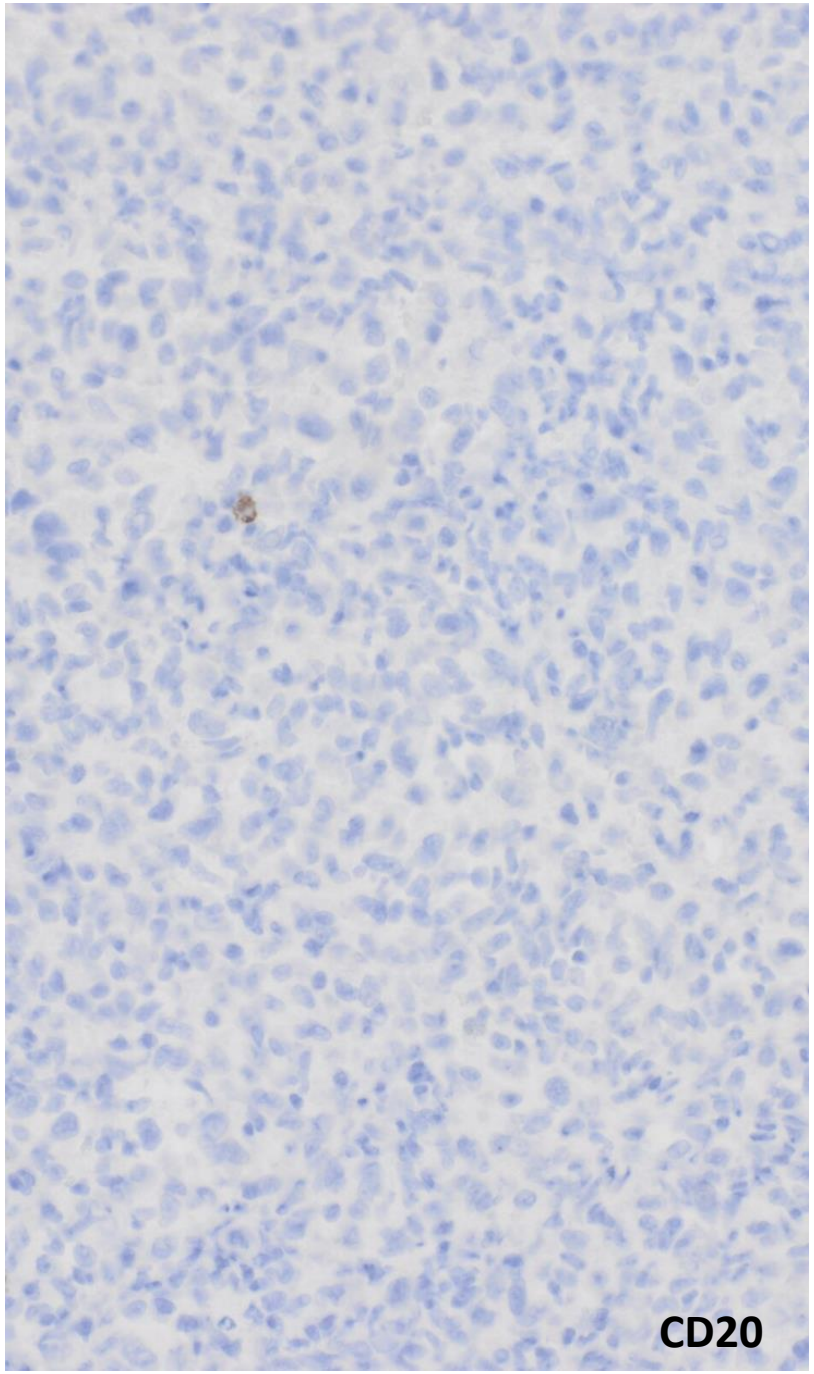
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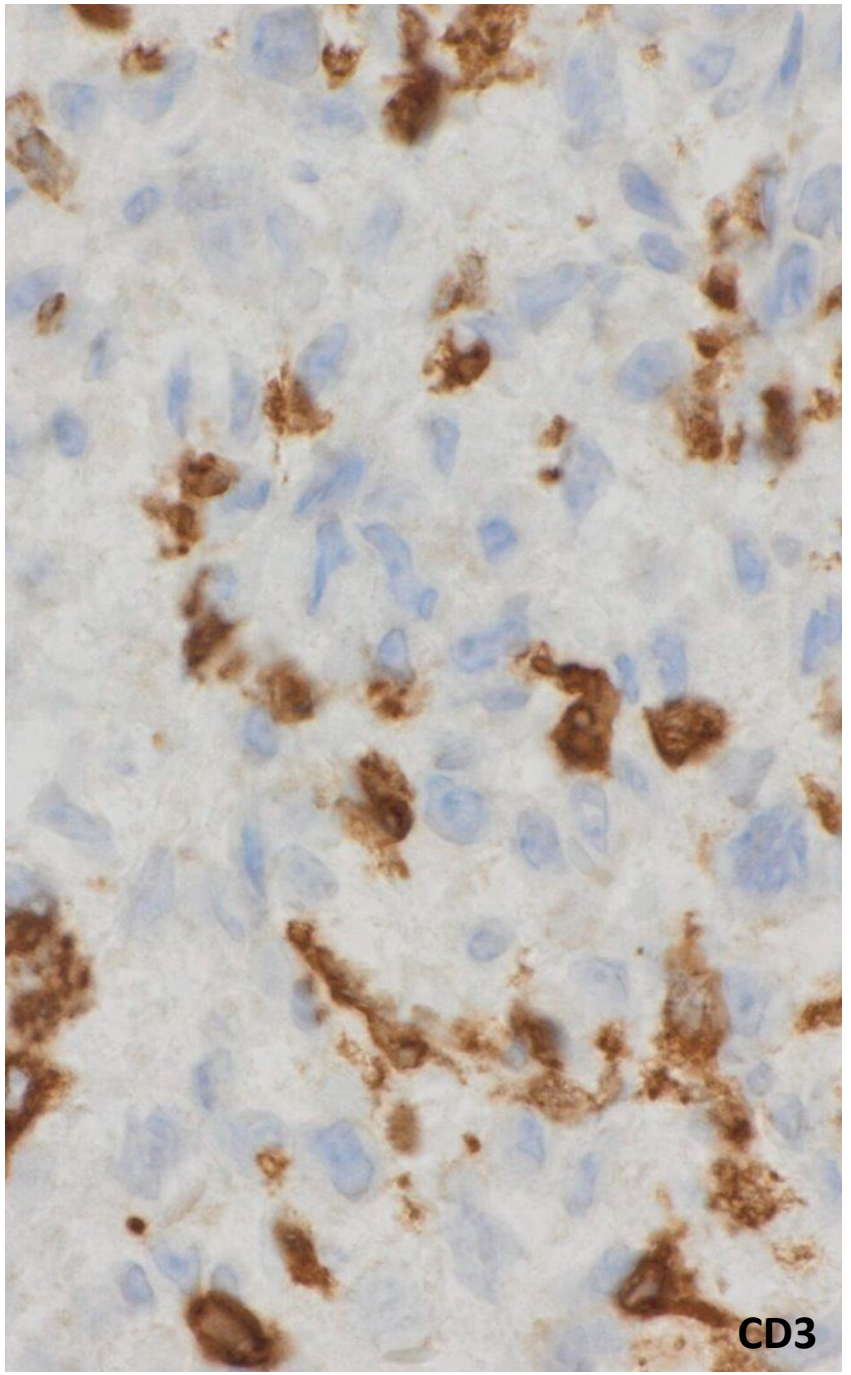
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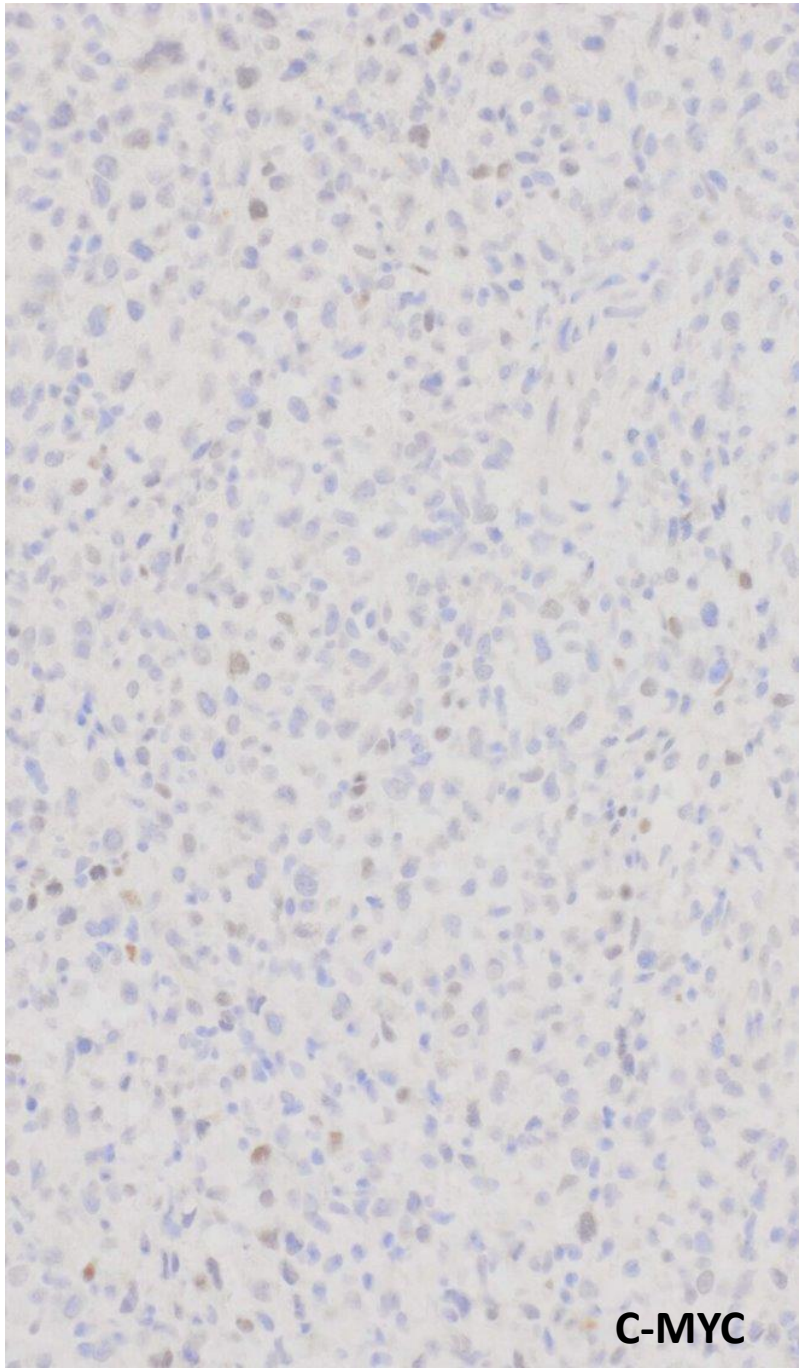
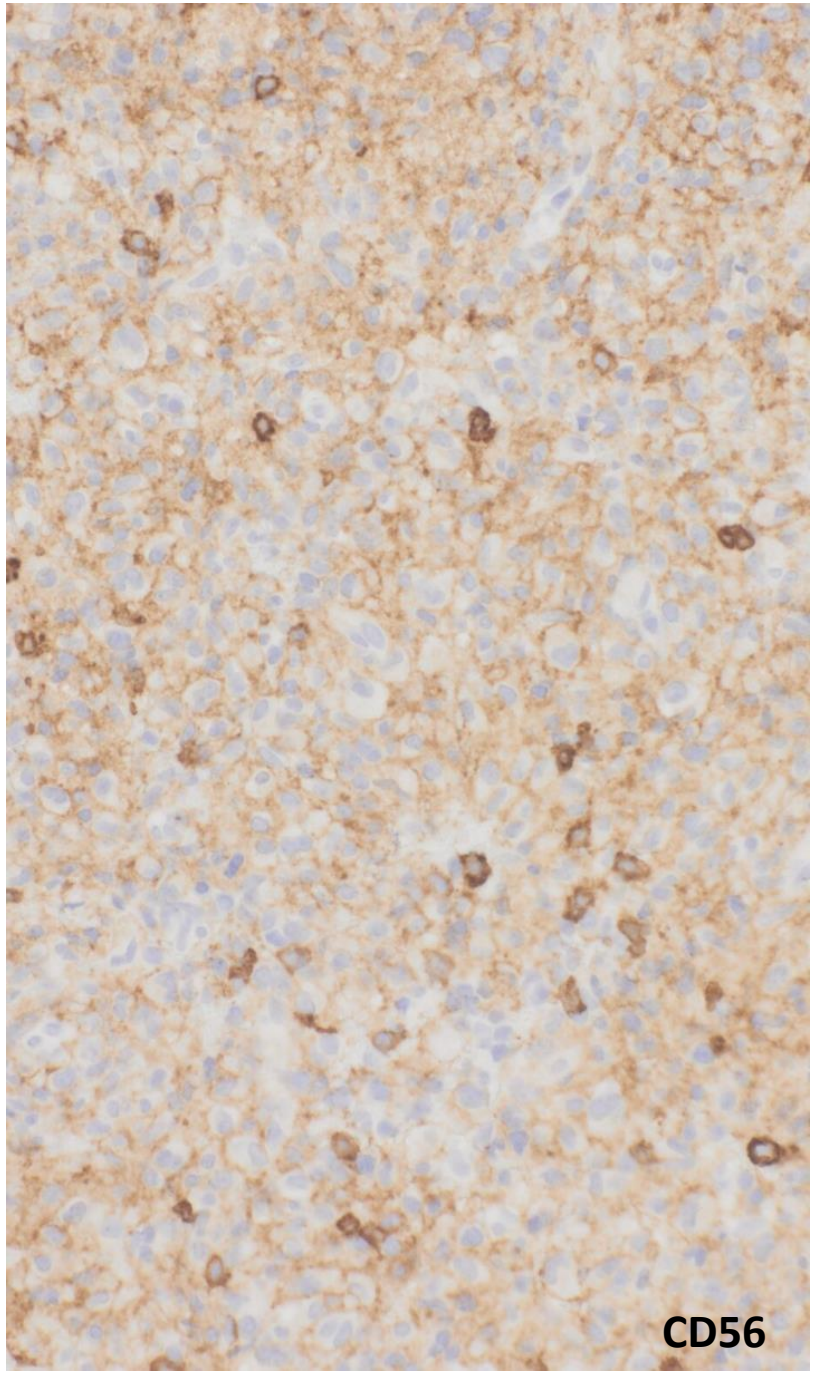

C-MYC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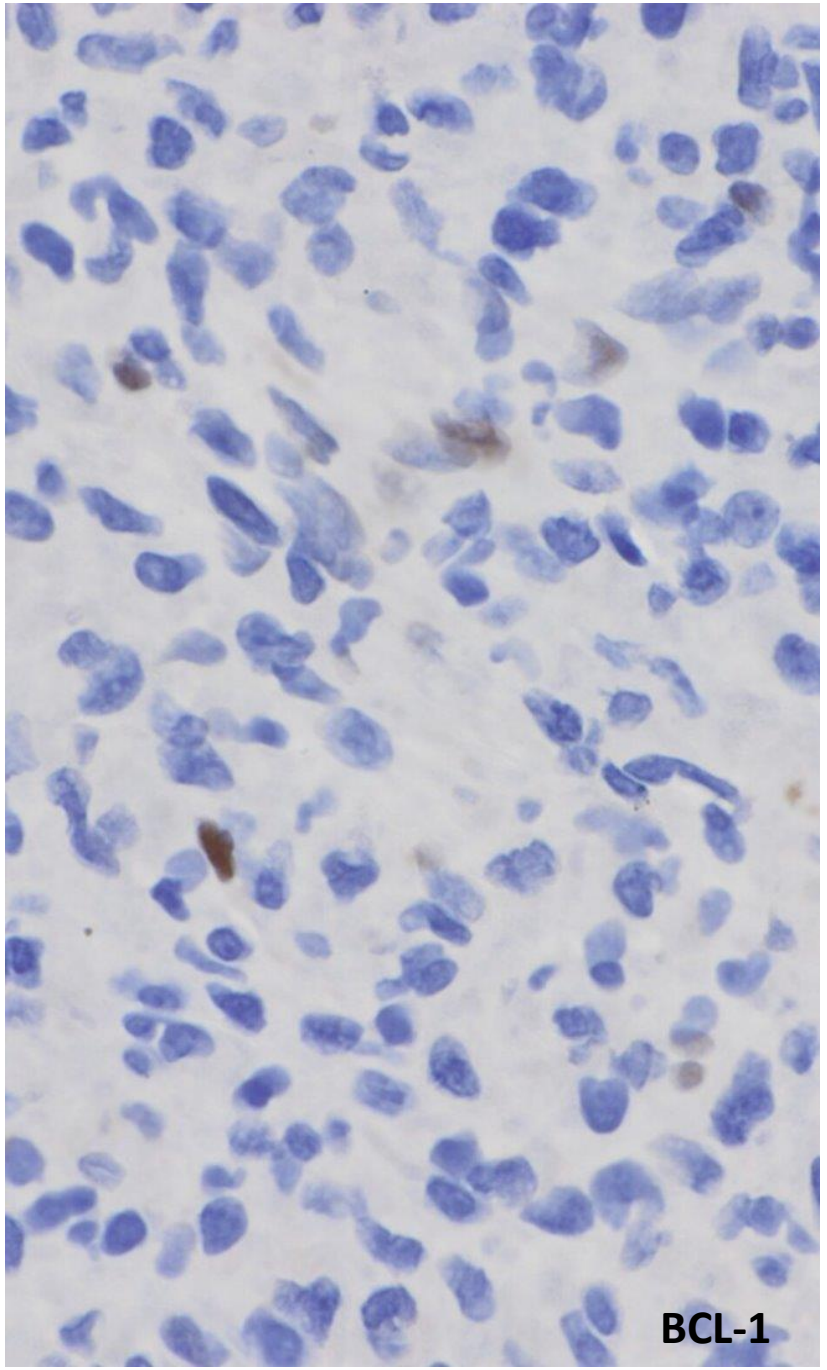
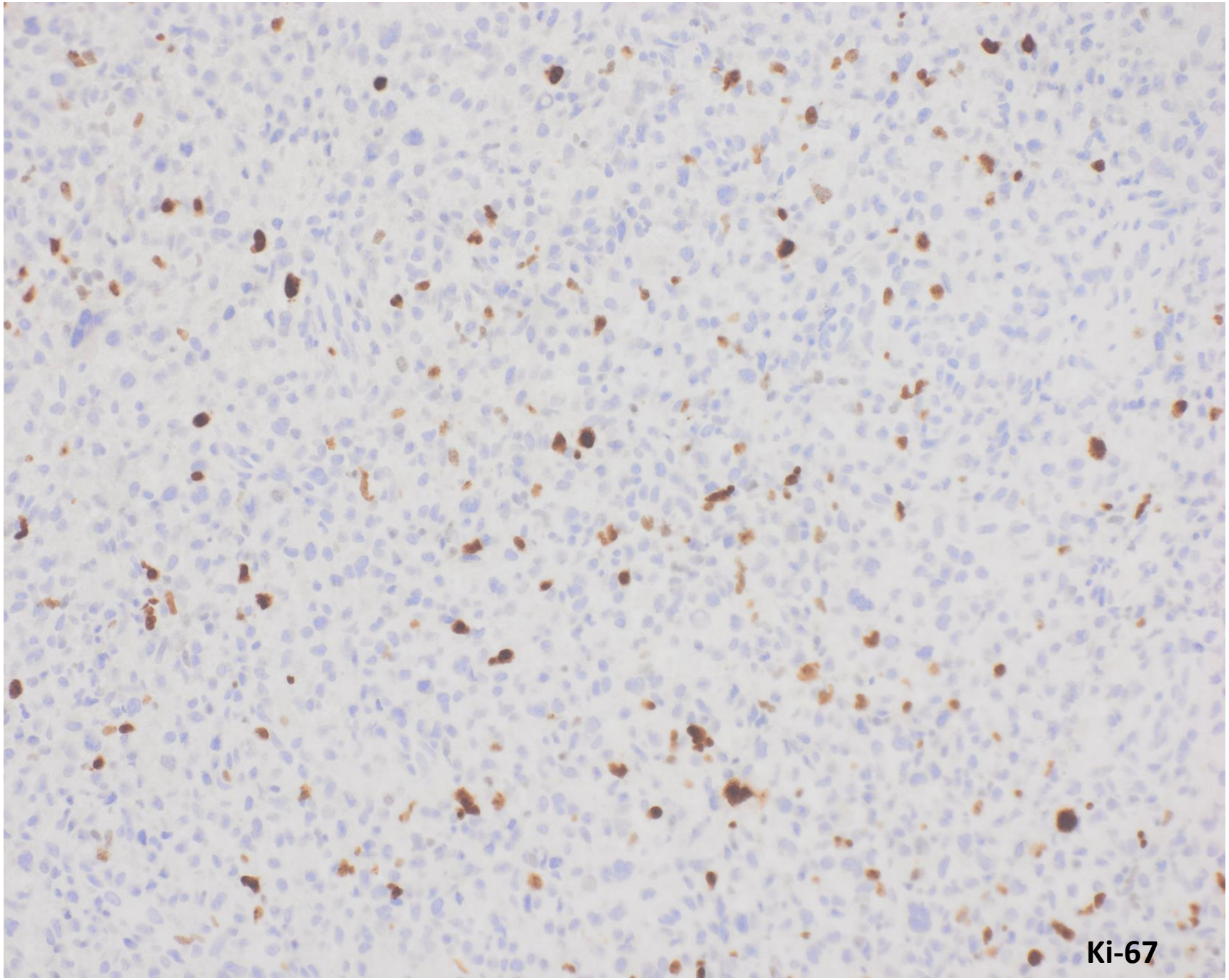

BCL-1


Ki-67

Additional history

- Bone marrow was normal and did not show abnormal plasma cells.
- HHV8 negative by IHC
- The lesion had been present since 2017 without much change. The pt reported occasional nasal fullness
- PET-CT: No appreciable uptake
- The patient reported 30 lbs weight loss but no other B symptoms and was doing well, essentially asymptomatic

EBV-Positive plasmacytoma

- The morphologic and immunophenotypic features of this lesion raise two diagnostic considerations: EBV-positive plasmacytoma or plasmablastic lymphoma.
- The low proliferation index, anaplastic morphology without mitotic figures or necrosis, and the indolent clinical behavior of this lesion do not support a high-grade process such as plasmablastic lymphoma.
- The overall findings are most in keeping with an EBV positive plasmacytoma, an uncommon but reported entity.

Reference:

Zhou T, Cheng J, Karrs J, Davies-Hill T, Pack SD, Xi L, Tyagi M, Kim J, Jaffe ES, Raffeld M, Pittaluga S. Clinicopathologic and Molecular Characterization of Epstein-Barr Virus-positive Plasmacytoma. Am J Surg Pathol. 2022 Oct 1;46(10):1364-1379. doi: 10.1097/PAS.0000000000001923. Epub 2022 Jun 1. PMID: 35650679; PMCID: PMC9481705.

Clinicopathologic and Molecular Characterization of Epstein-Barr Virus–positive Plasmacytoma

Ting Zhou, MD, PhD, Jinjun Cheng, MD, PhD,* Jeremiah Karrs, DO,* Theresa Davies-Hill, BS,* Svetlana D. Pack, PhD,† Liqiang Xi, MD,† Manoj Tyagi, PhD,† Jung Kim, PhD,† Elaine S. Jaffe, MD,* Mark Raffeld, MD,† and Stefania Pittaluga, MD, PhD**

Abstract: Epstein-Barr virus (EBV)-positive plasmacytoma is a rare plasma cell neoplasm. It remains unclear whether EBV-positive plasmacytoma represents a distinct entity or a variant of plasmacytoma. It shares morphologic features with plasmablastic lymphoma (PBL) and may cause diagnostic uncertainty. To better understand EBV-positive plasmacytoma and explore diagnostic criteria, this study describes 19 cases of EBV-positive plasmacytoma, compared with 27 cases of EBV-negative plasmacytoma and 48 cases of EBV-positive PBL. We reviewed the clin-

biological variant of plasmacytoma. Thorough morphologic examination remains the cornerstone for distinguishing EBV-positive plasmacytoma and PBL, and molecular studies can be a valuable complementary tool.

Key Words: Epstein-Barr virus, plasmacytoma, plasmablastic lymphoma

(*Am J Surg Pathol* 2022;46:1364–1379)

EBV+ Plasmacytoma (19)
EBV- Plasmacytoma (27)
EBV+ Plasmablastic Lymphoma (48)

- Both can show MYC expression by IHC and MYC rearrangement; more common in PBL
- Favorable outcome in plasmacytomas: excision +/- radiation

	EBV+ plasmacytoma (n=19)	**EBV+ Plasmablastic lymphoma (PBL) (n=48)**
Cytomorphology	Anaplastic	Plasmablastic
Mitotic figures, starry sky, necrosis	Absent	Common
Light chain restriction	Present	Loss of light chain expression in ~50% cases
Proliferation rate	Low	High
Sites of involvement	Upper resp tract (nasal cavity), bone	Skin, soft tissue, GI tract
Mutational profile	Lack mutations seen in PBL	*STAT3, JAK1, SOCS1, JAK2, PIM1, PRDM1, NRAS, TP53, TET2,* and *CARD11*

Summary

- EBV-positive plasmacytoma is a rare plasma cell neoplasm and should be regarded as a biological variant of plasmacytoma.

- It shares morphologic features with plasmablastic lymphoma (PBL) and may cause diagnostic uncertainty.

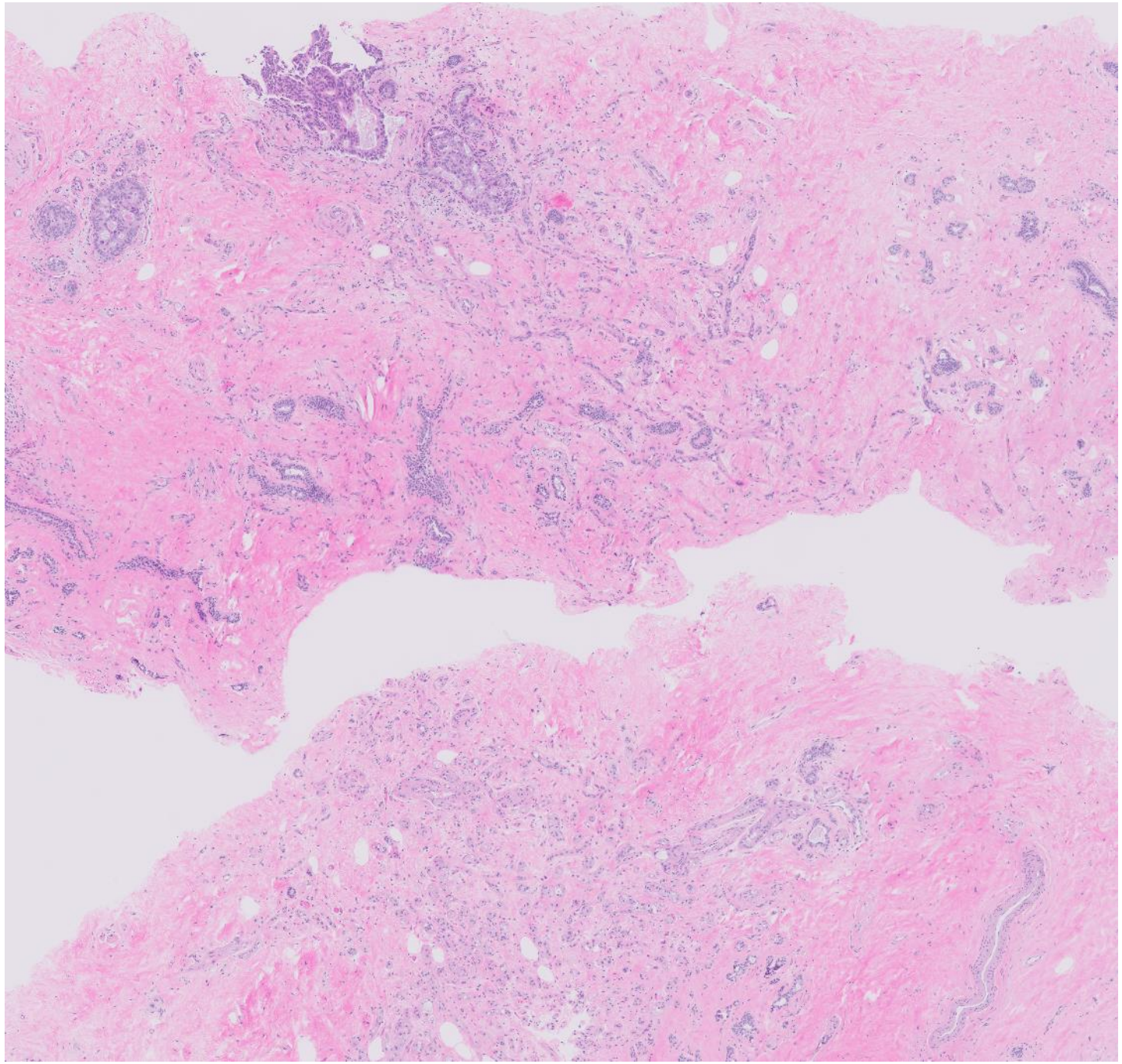
- Thorough morphologic examination with ancillary testing remains the cornerstone for distinguishing EBV-positive plasmacytoma and PBL.

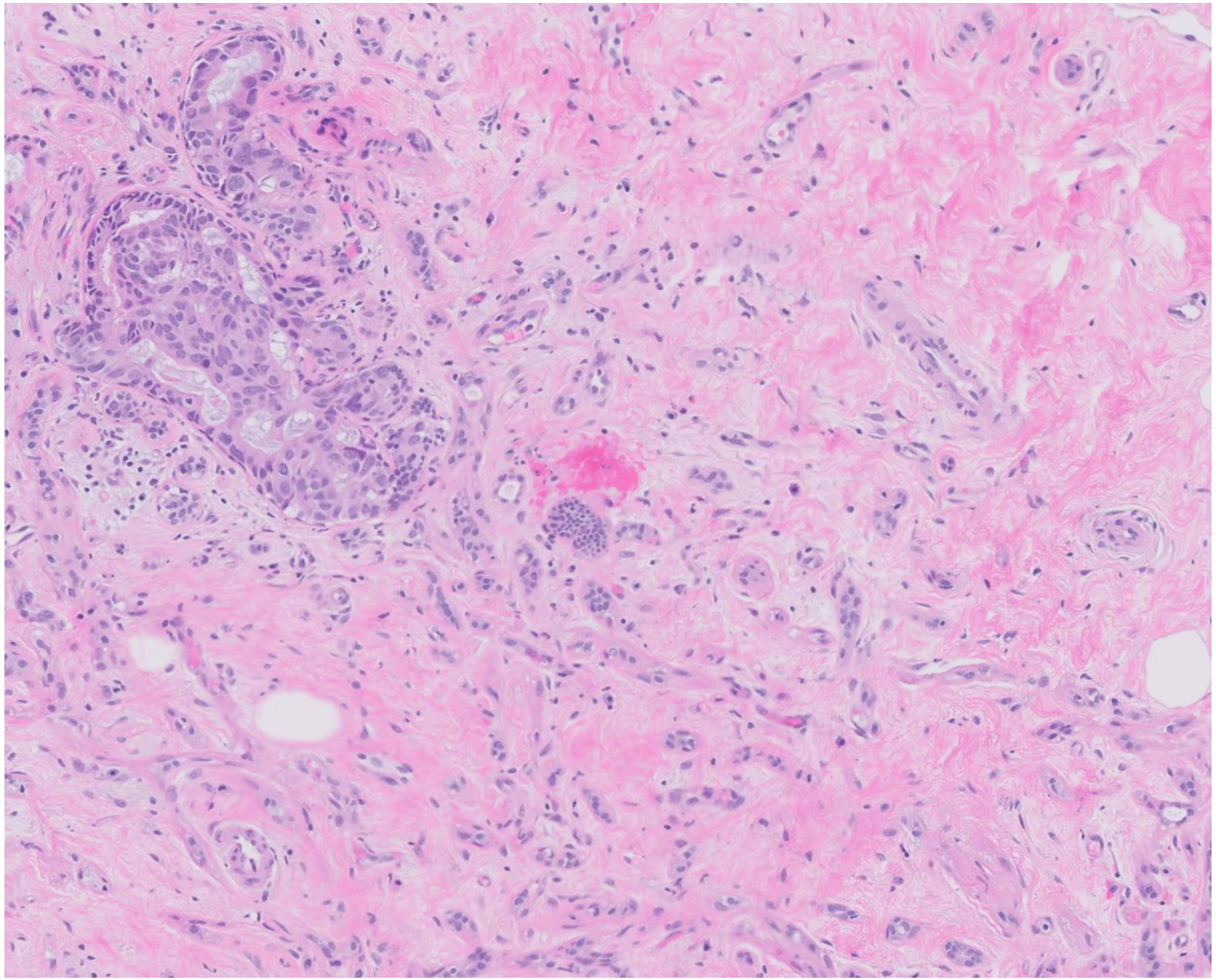
- Clinical findings, including the patient's presentation, imaging, bone marrow findings, SPEP and UPEP findings, and overall behavior of the lesion are crucial to distinguish between PBL,EBV-positive plasmacytoma, and EBV-positive plasma cell myeloma.

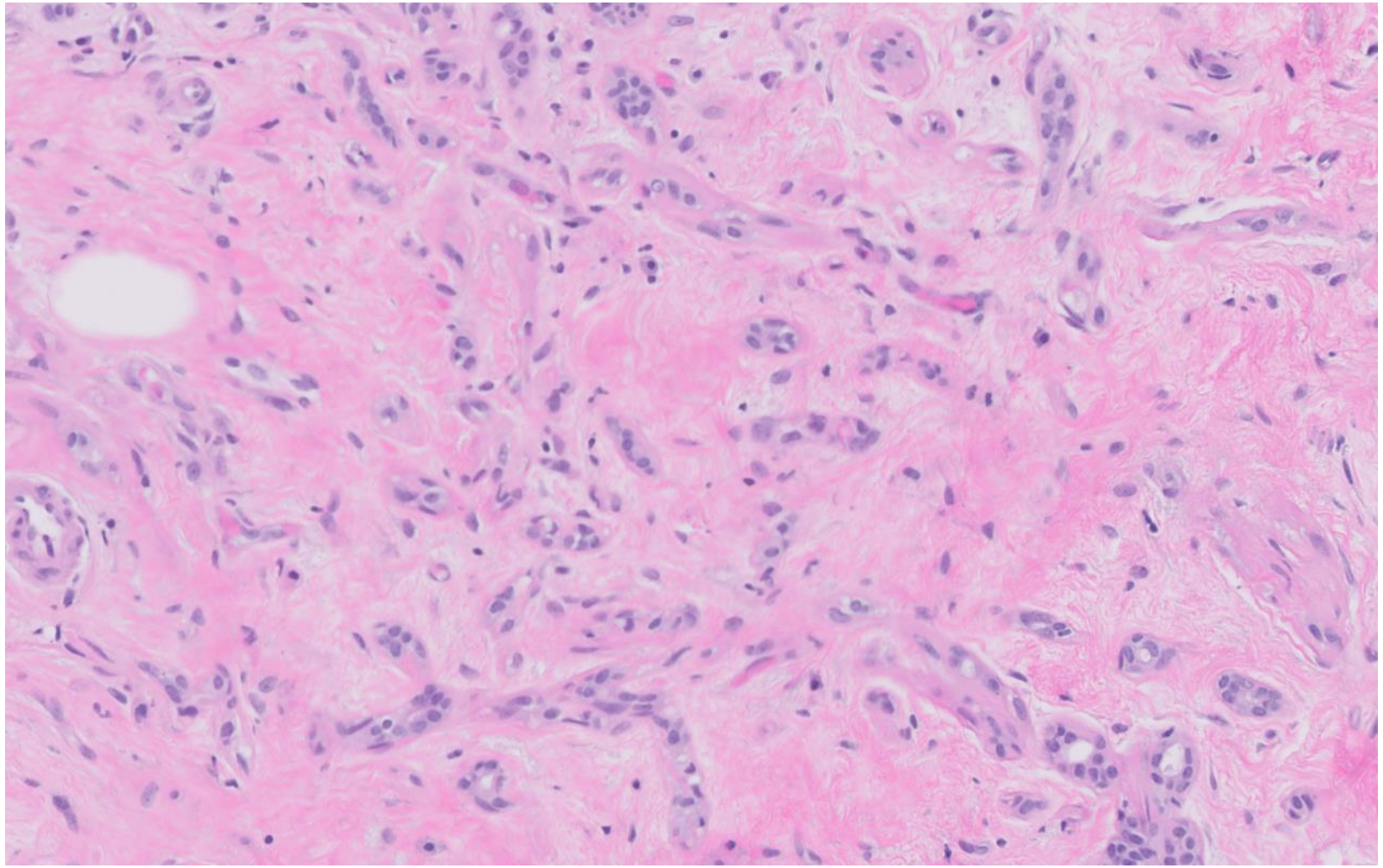
23-0605

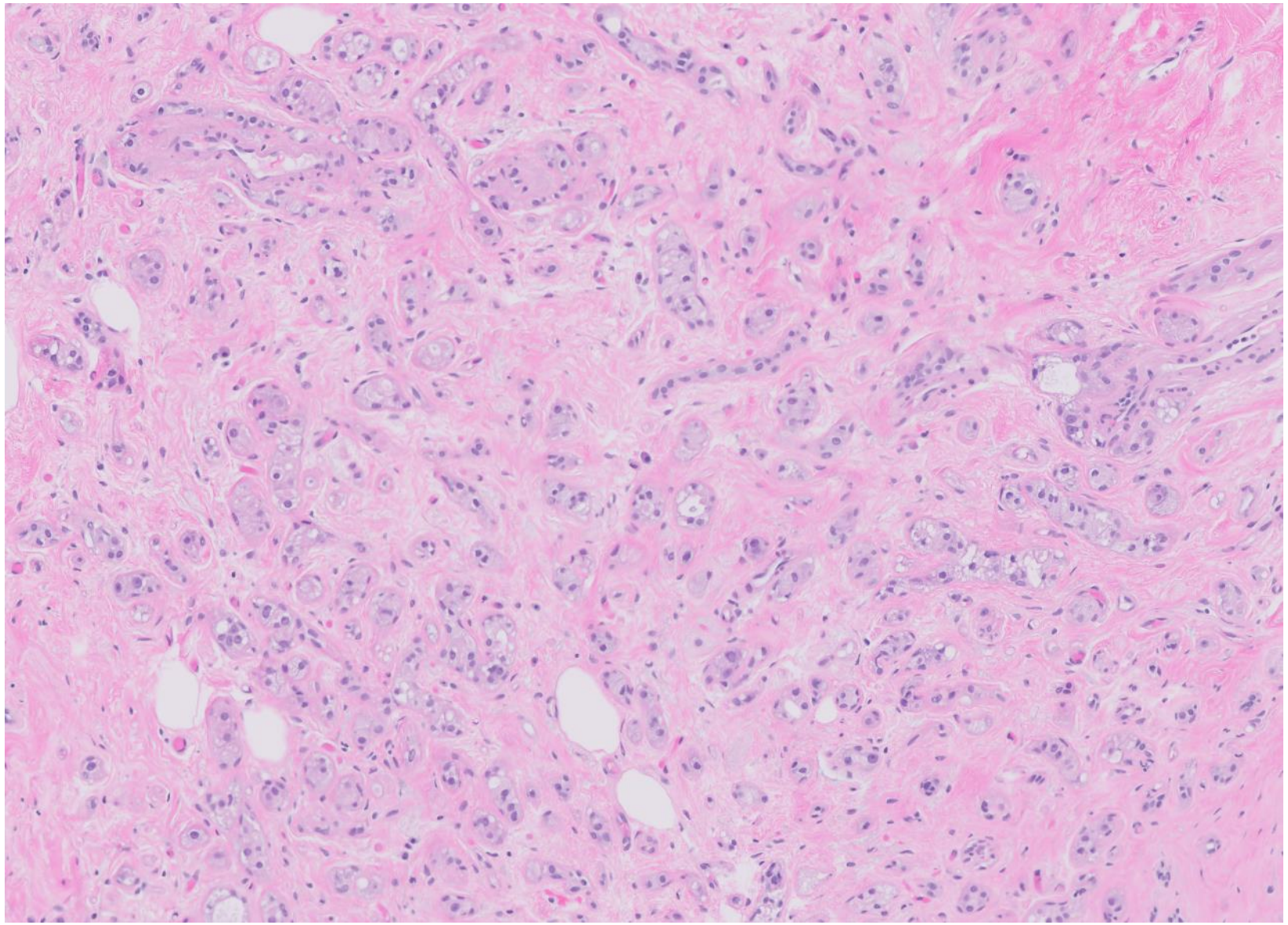
Ragini Phansalkar (post soph fellow)/ Megan Troxell; Stanford

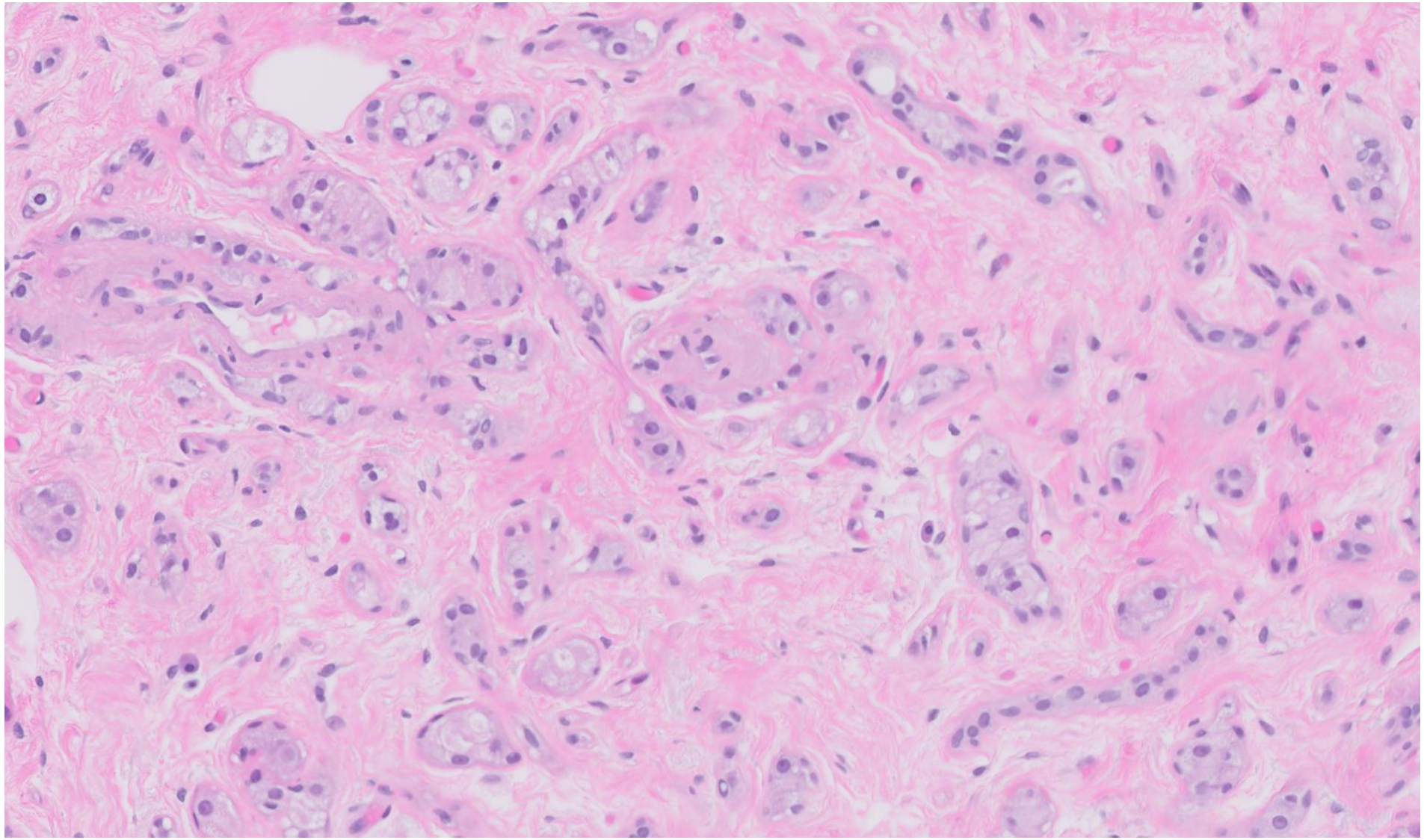
80s F undergoing left breast core biopsy for calcifications





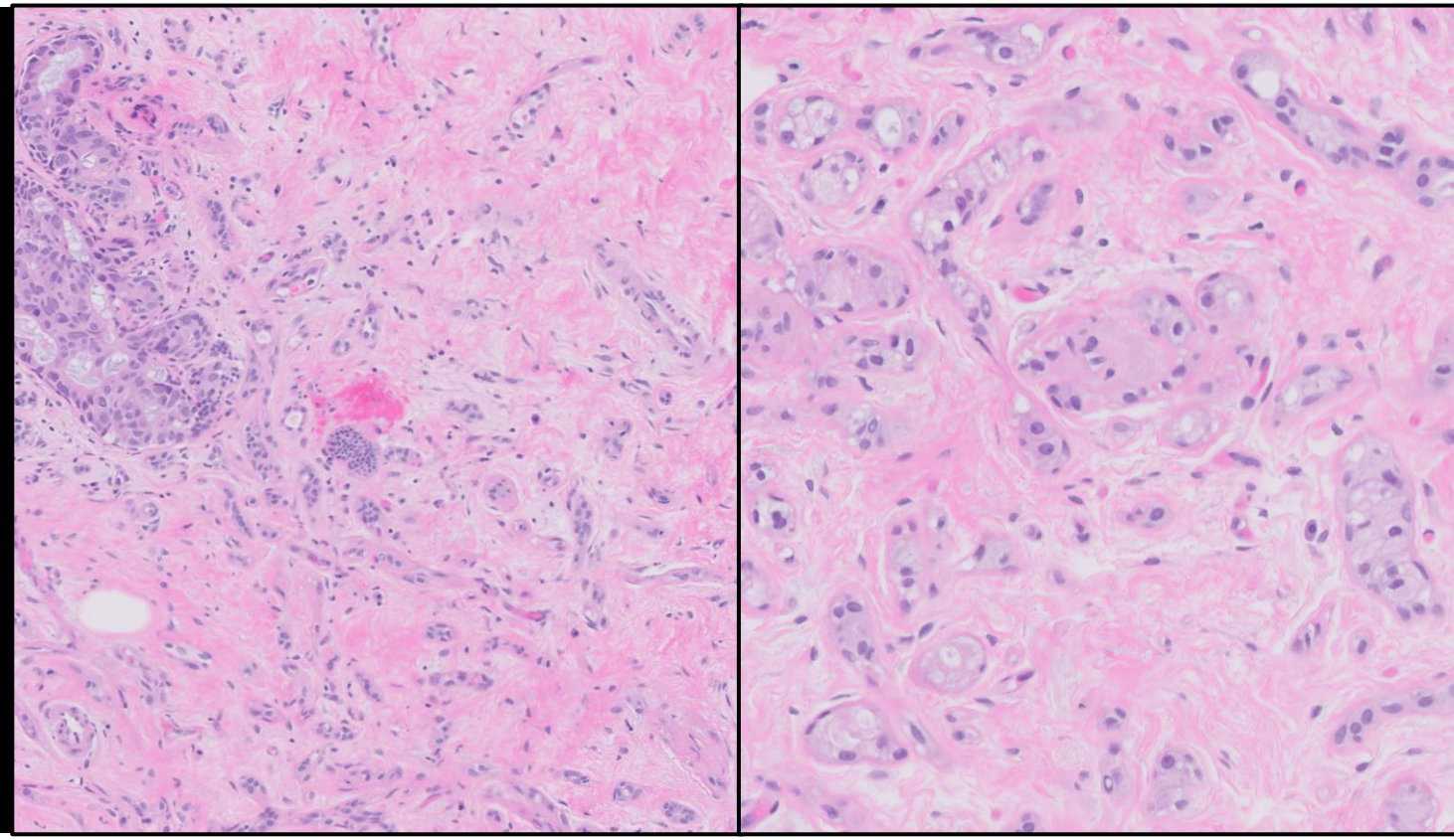




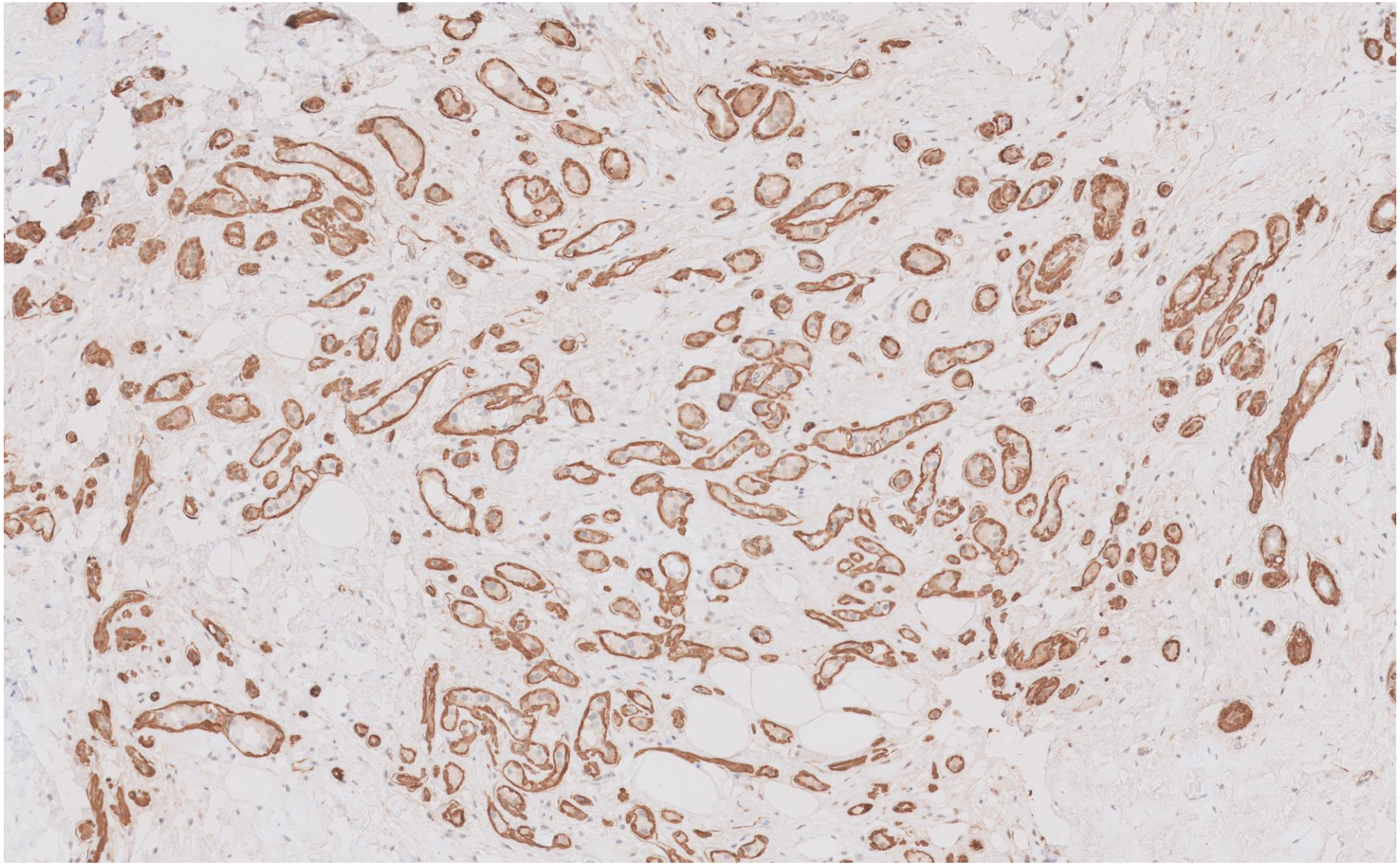


Differential Diagnosis

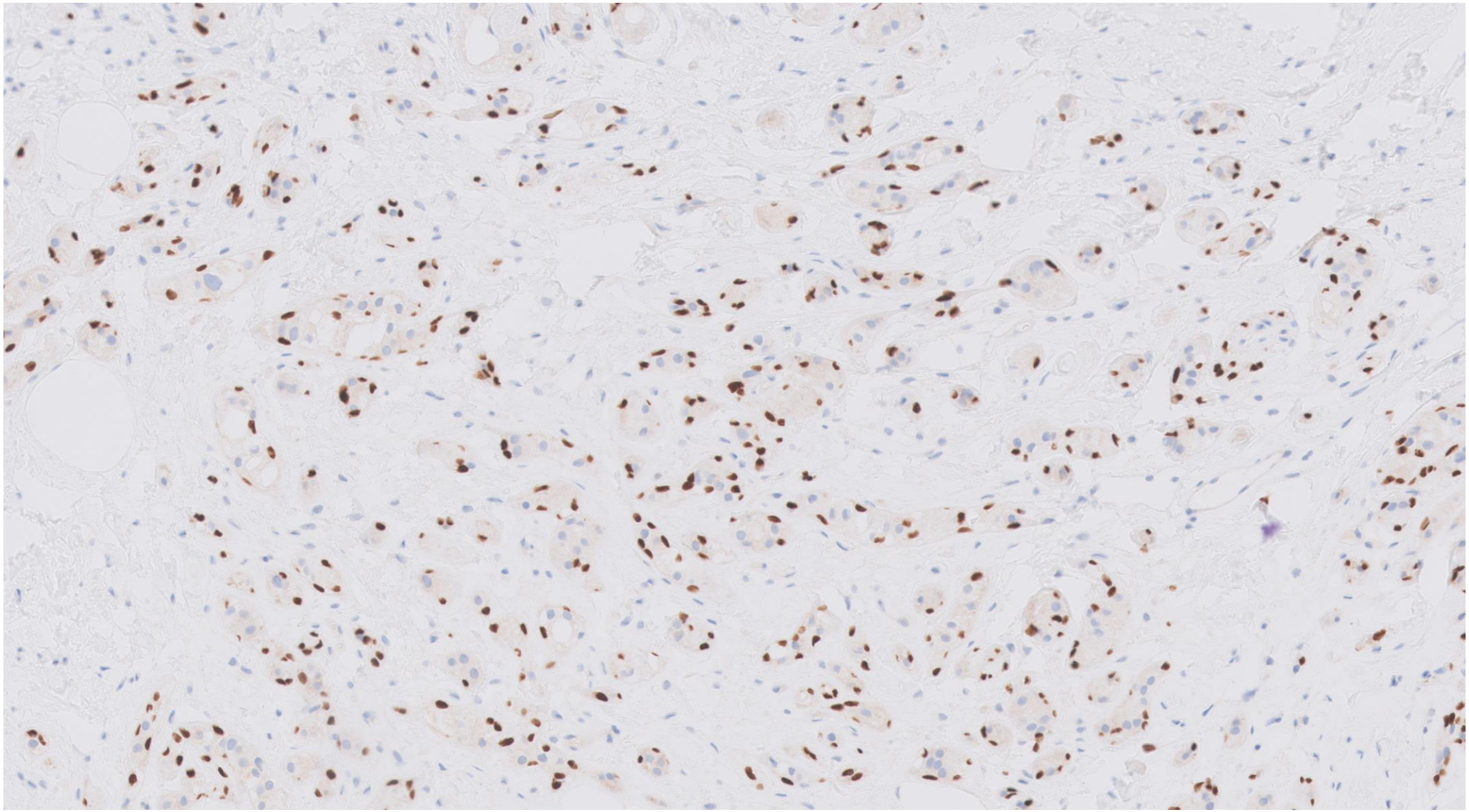
- DCIS with:
- Invasive carcinoma
- Sclerosing adenosis
- +/- atypia
- +/- DCIS



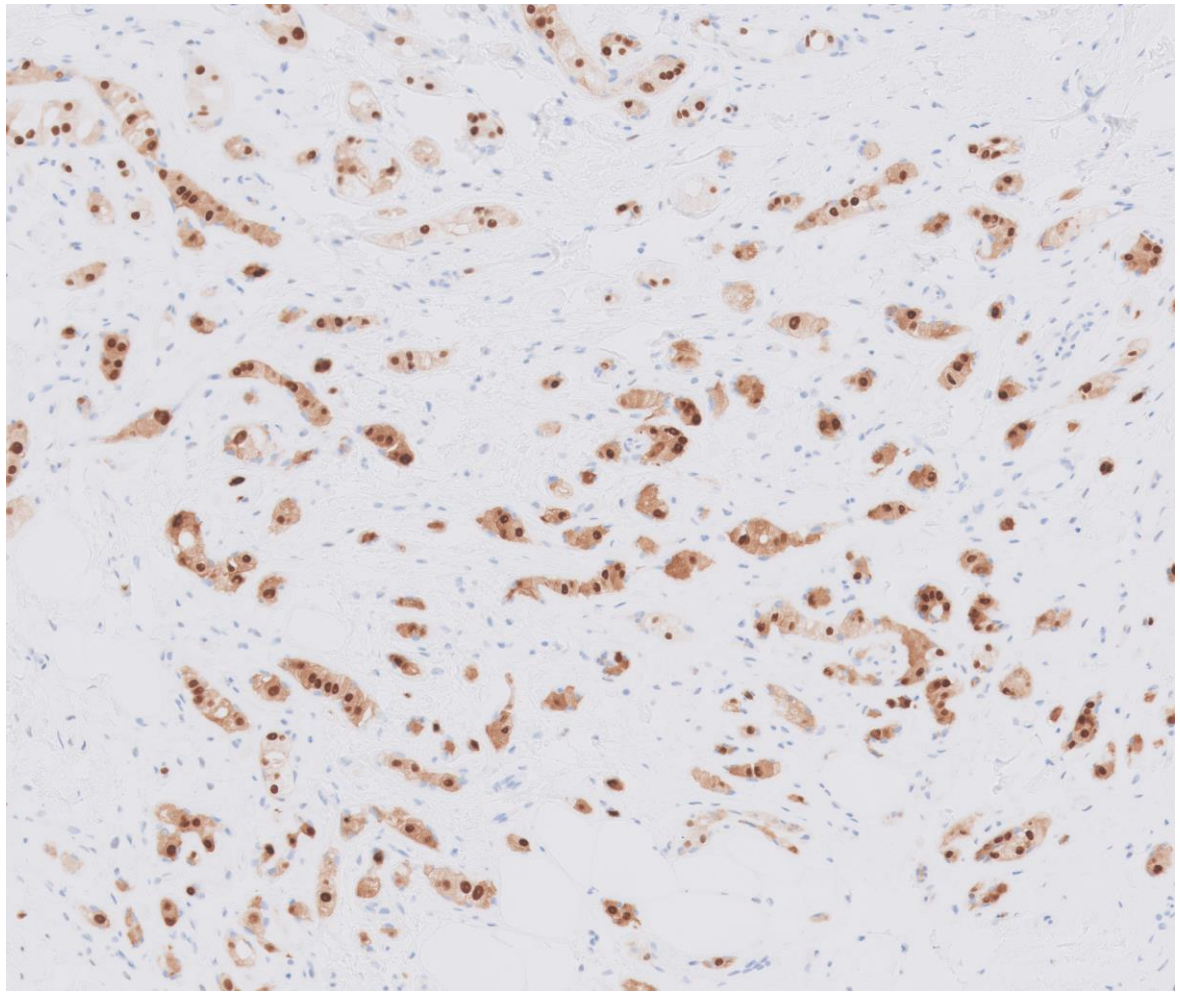
Calponin



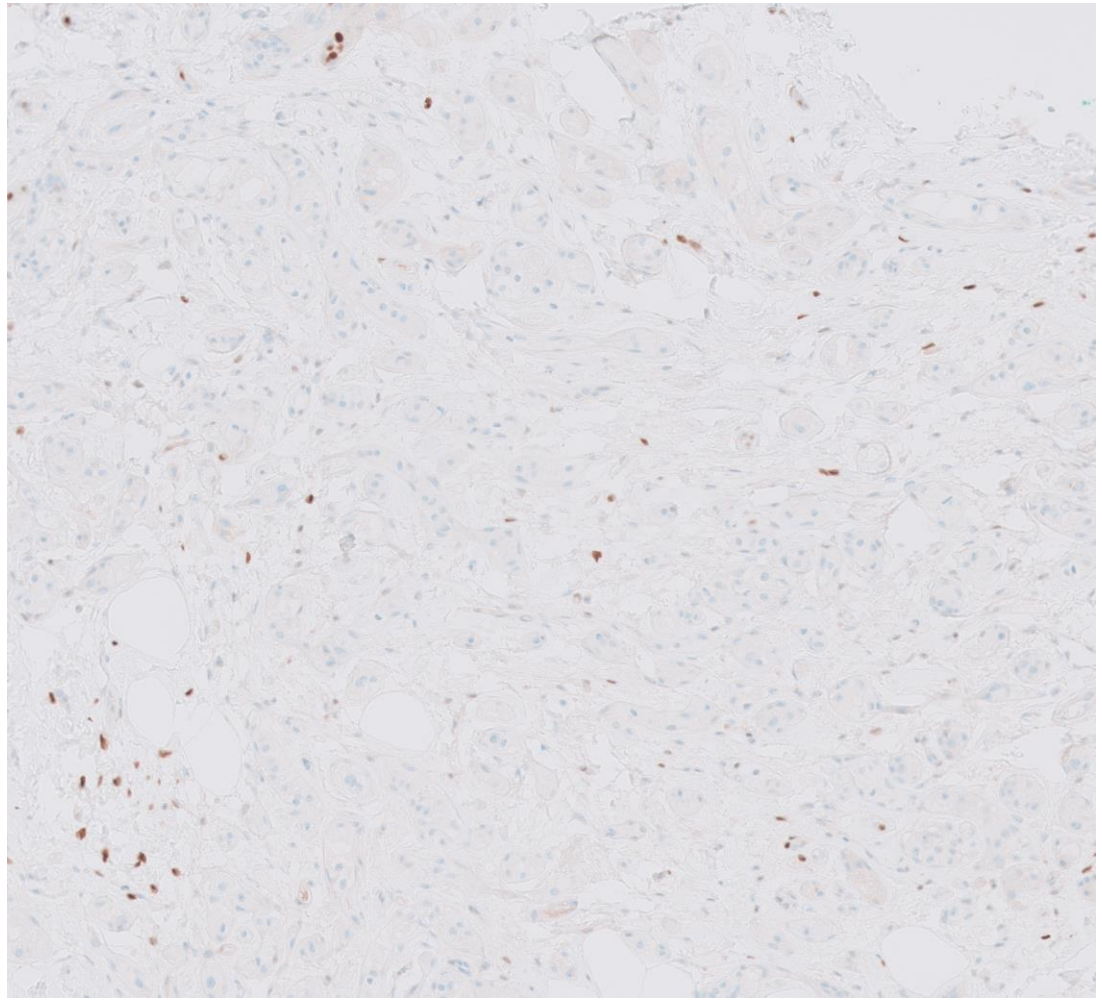
P63



AR



ER



Atypical apocrine adenosis

Histologic features

- Sclerosing adenosis with apocrine change AND cytologic atypia (3x variation in nuclear size)
- When superimposed on sclerosing adenosis, apocrine cells may lose some characteristic features such as eosinophilic cytoplasm
- Atypical apocrine adenosis can mimic invasive carcinoma- myoepithelial cells can help differentiate

Epidemiology

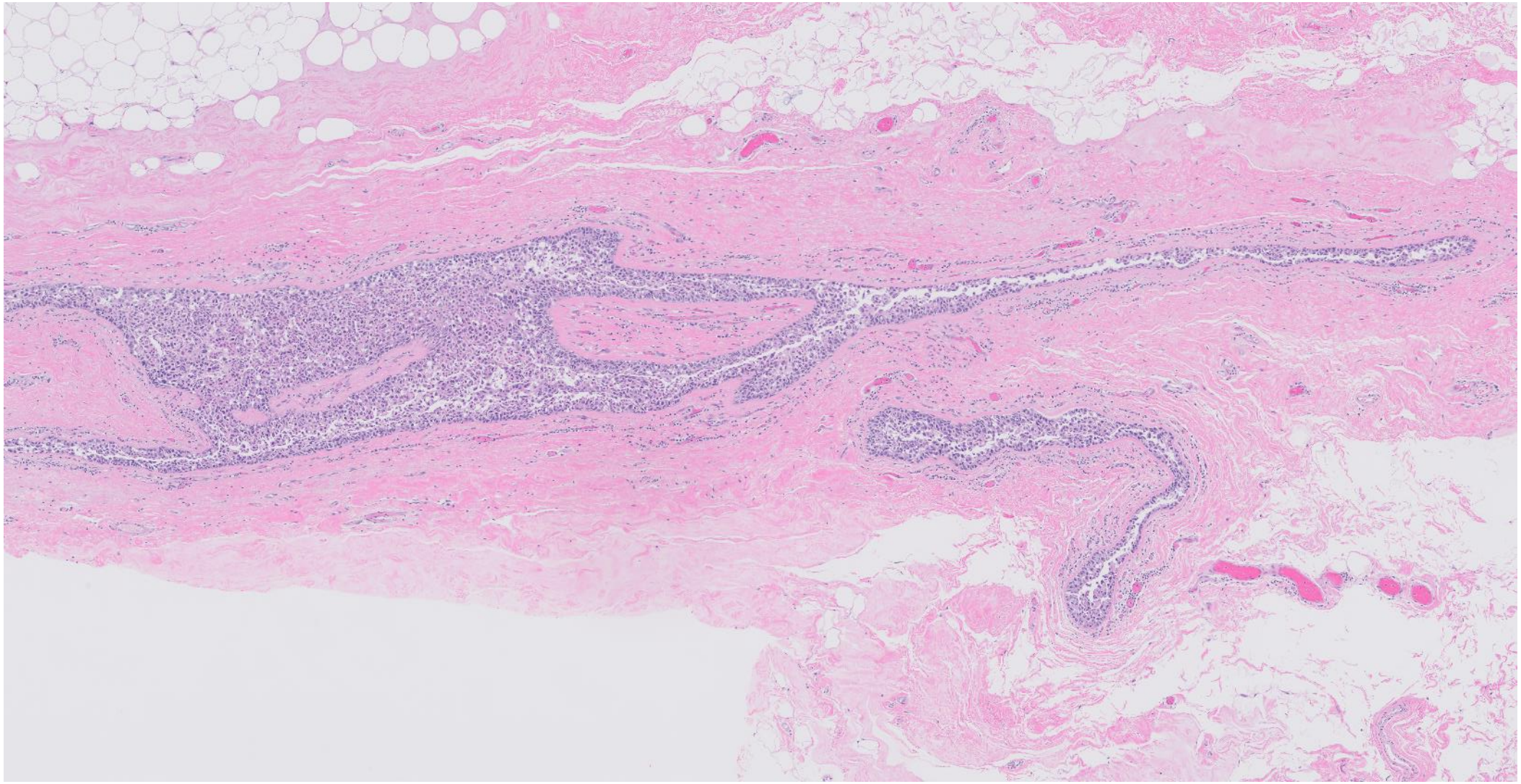
- Rare- 0.4% of cases in the Mayo Benign Breast Disease cohort
- In 4 studies following a total of 128 patients, no increased risk of carcinoma

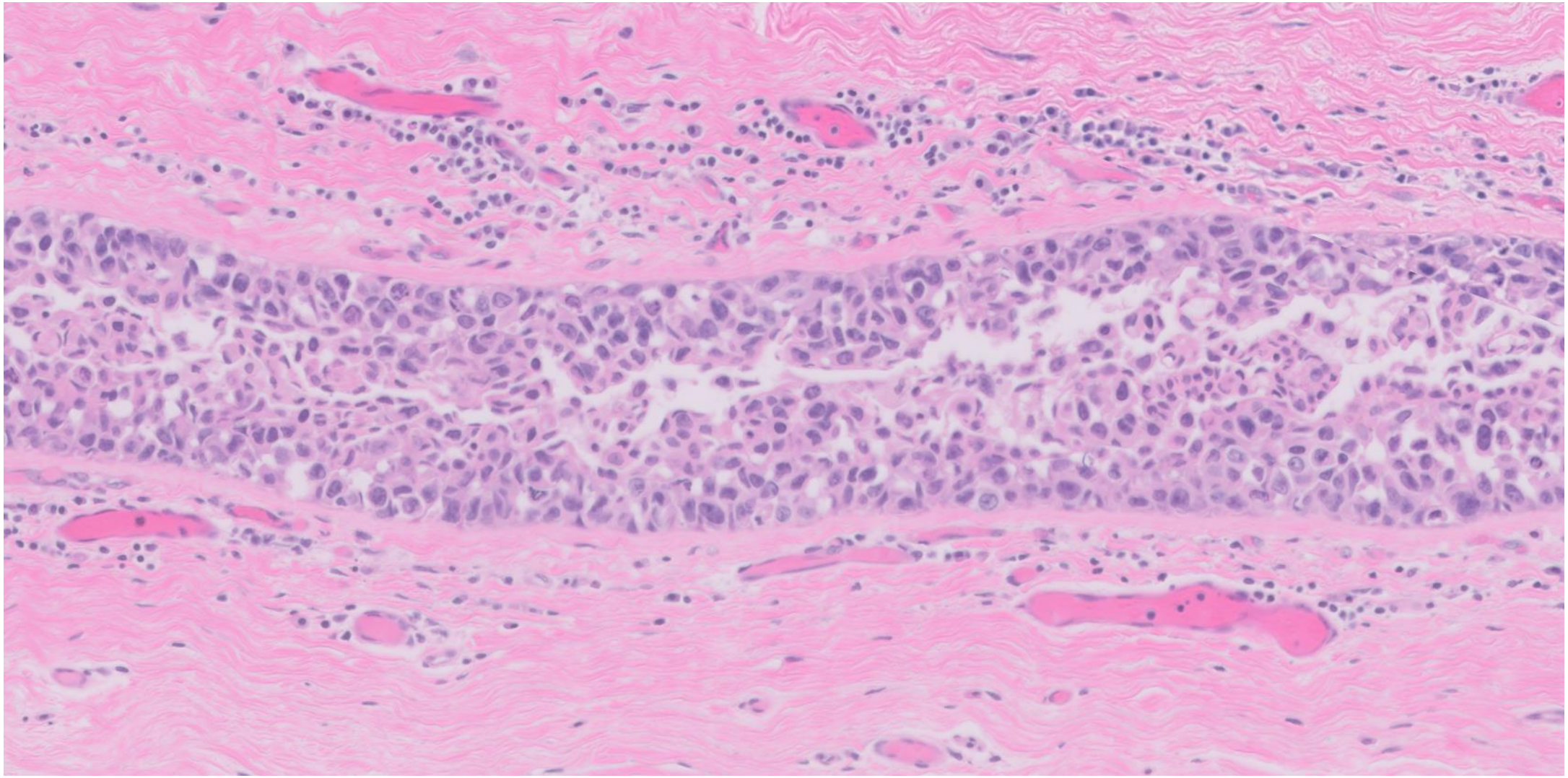
Asirvatham et al, Arch Pathol Lab Med, 2016

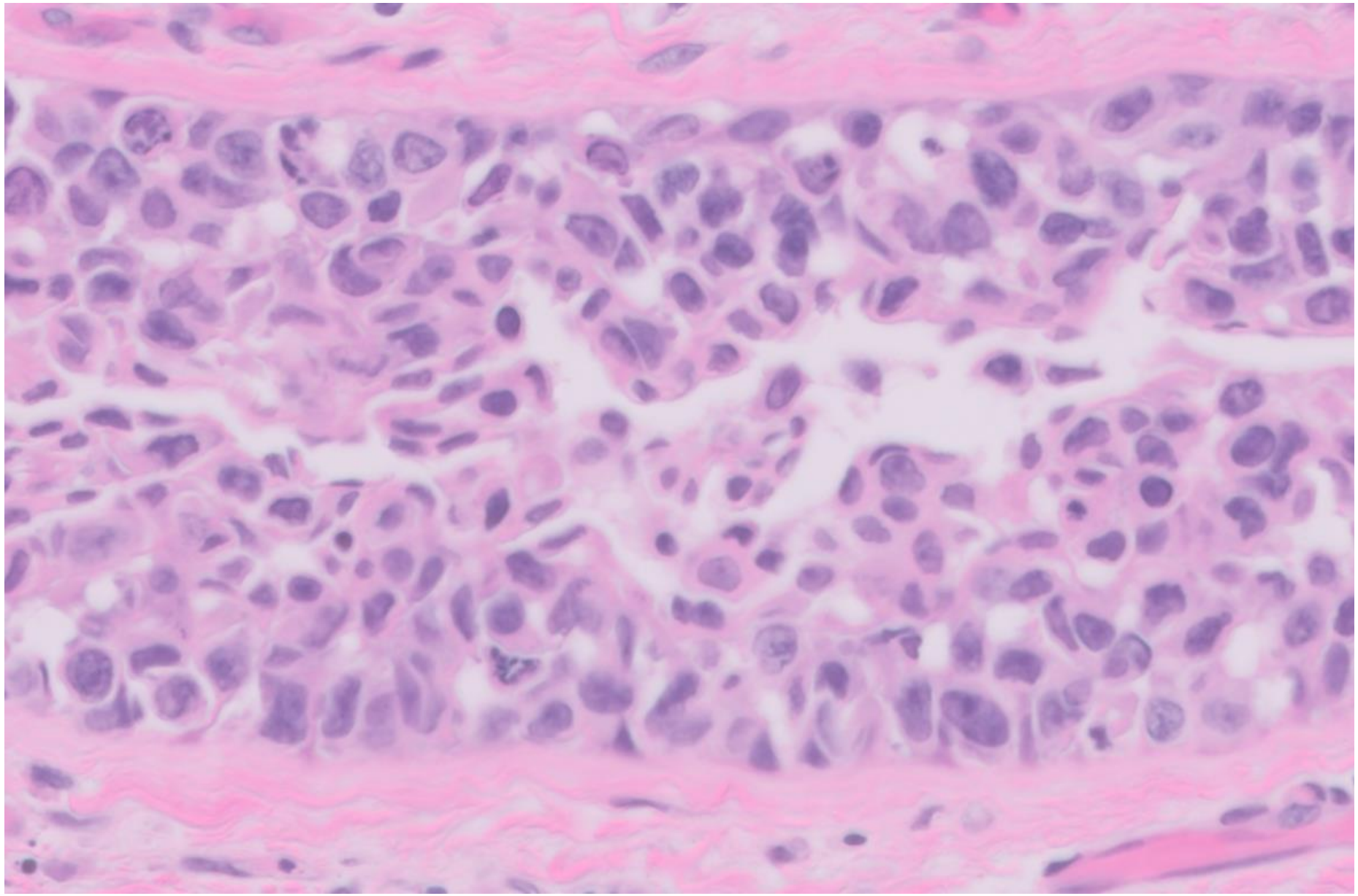
23-0606

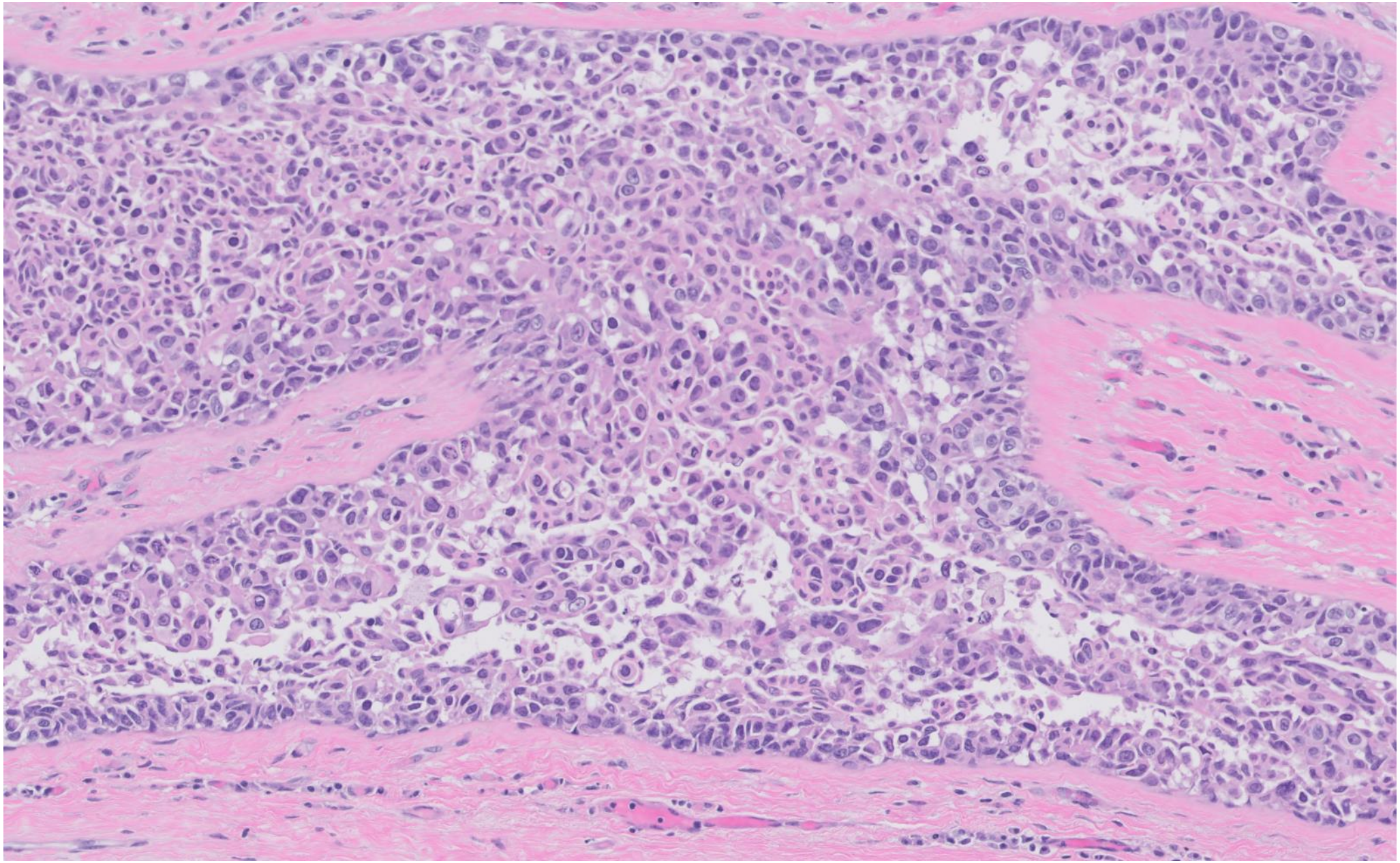
Ragini Phansalkar (post soph fellow)/ Megan Troxell; Stanford

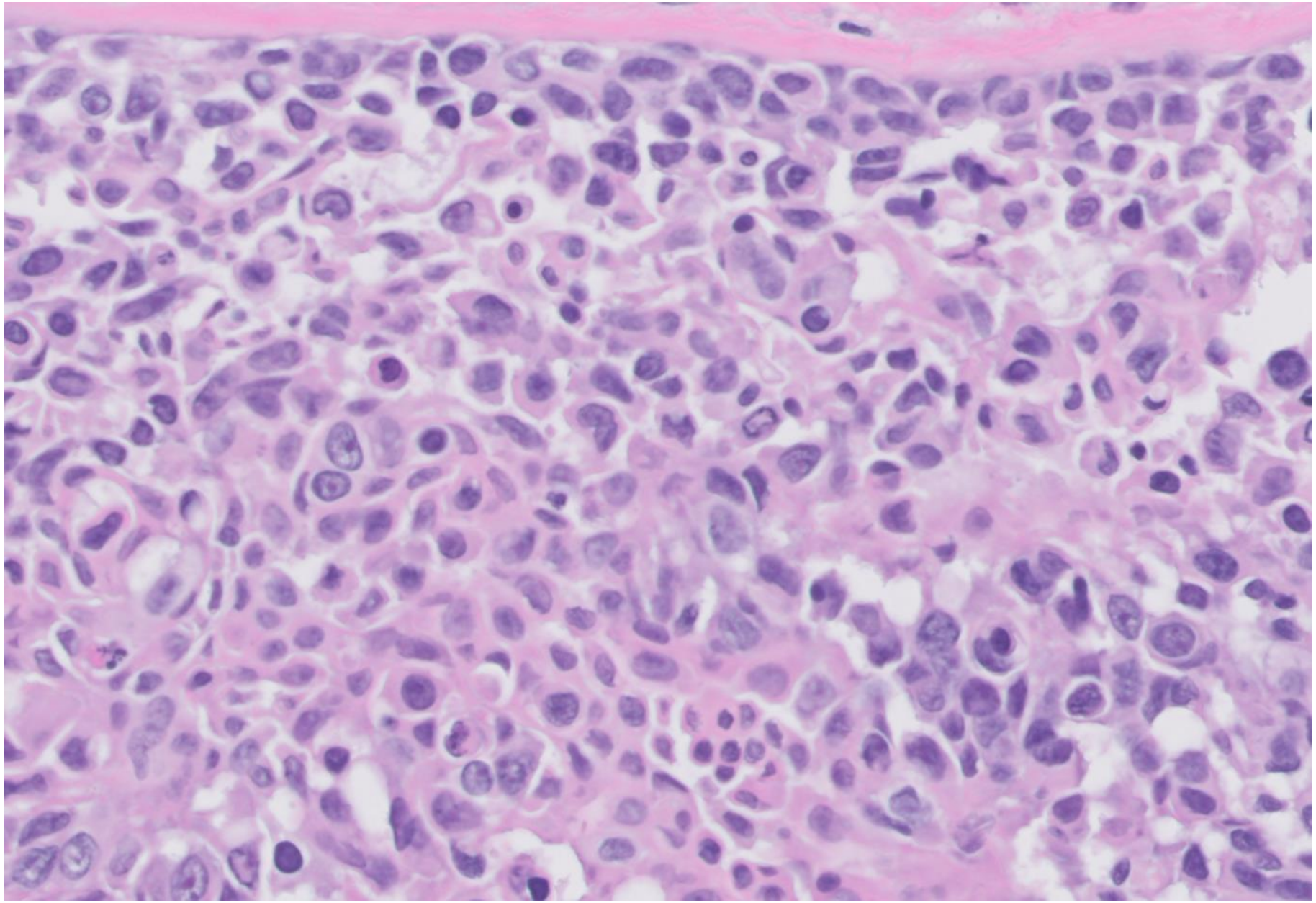
40s F undergoing bilateral breast reduction/mastopexy





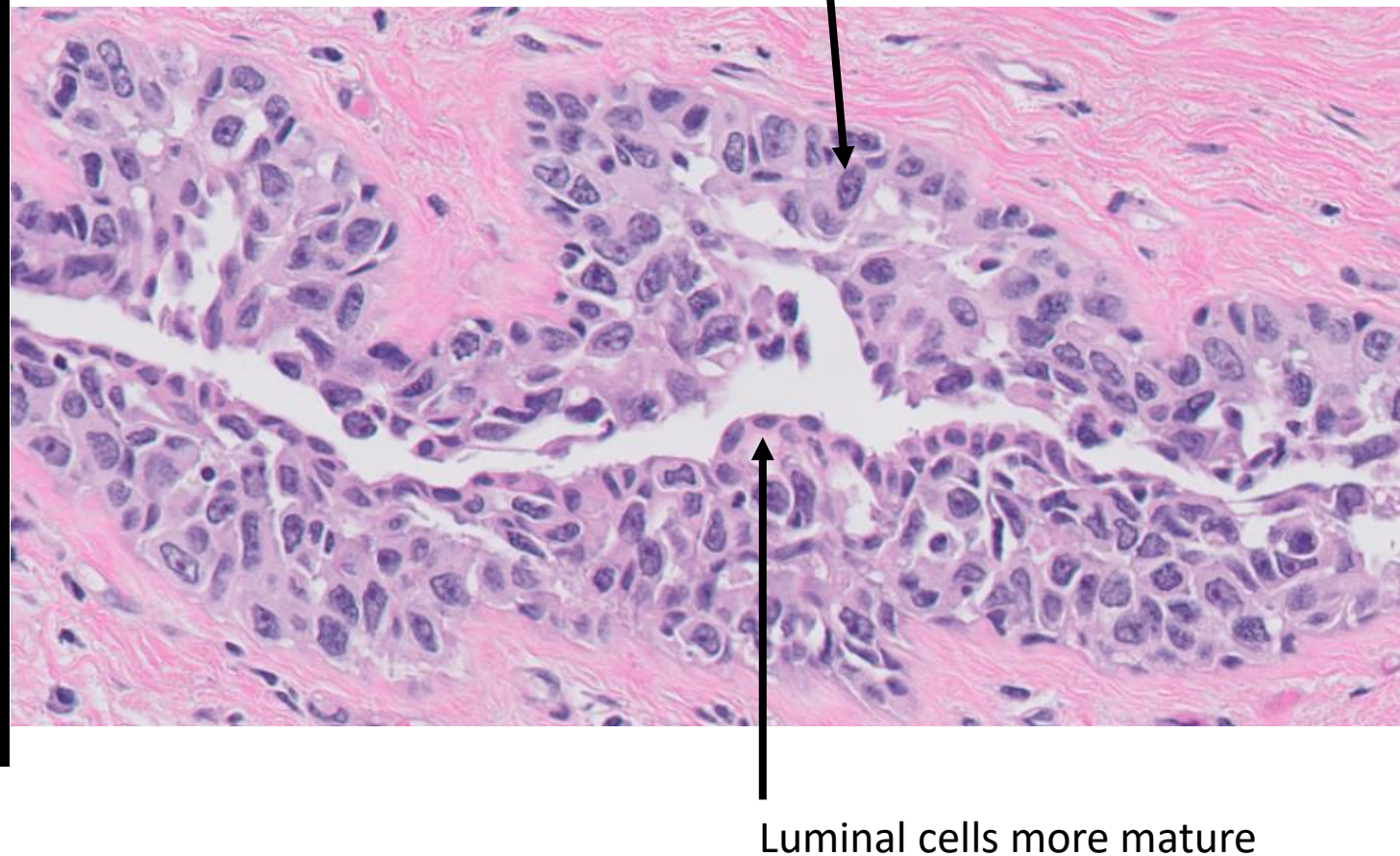




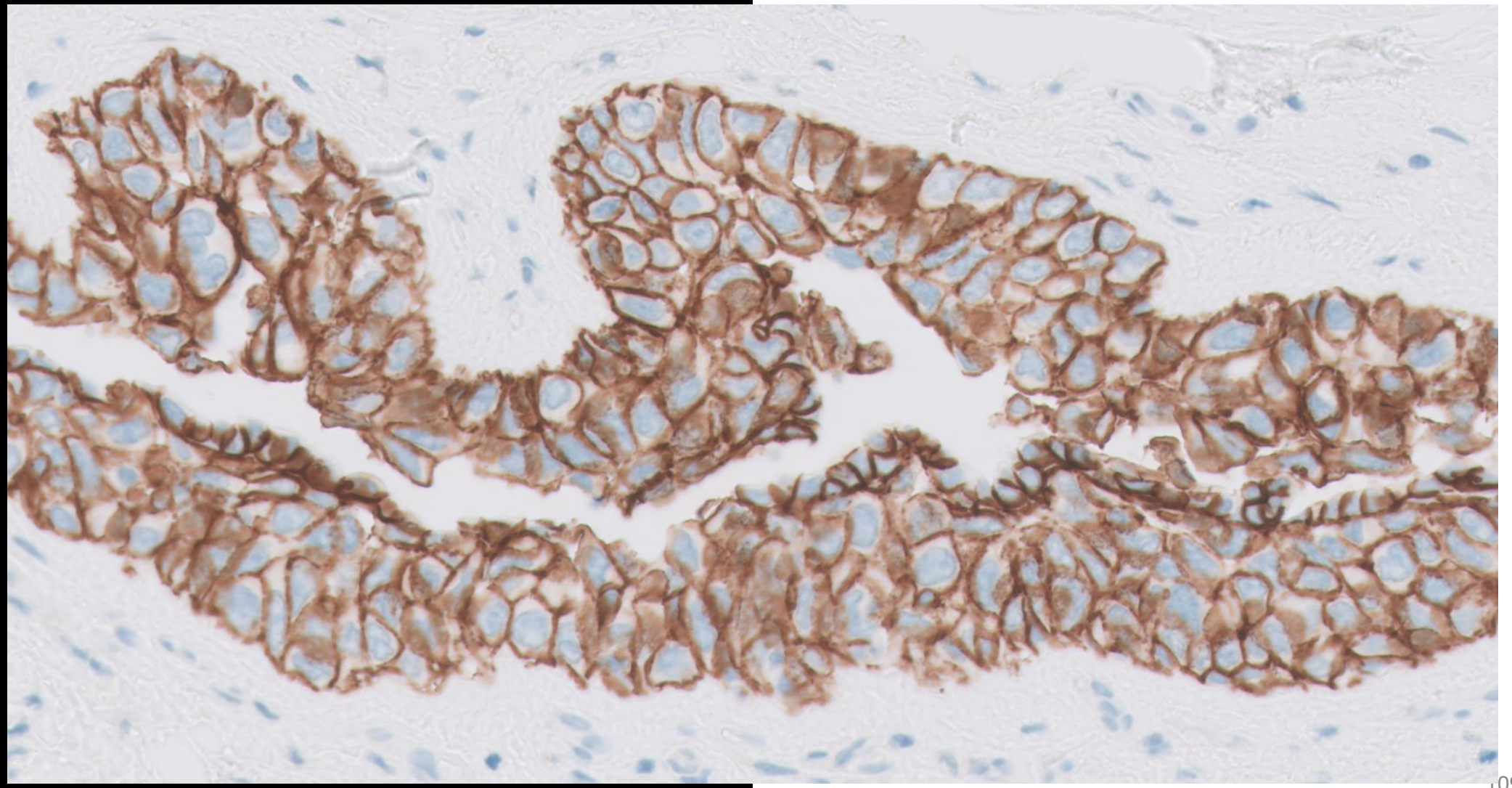


Differential Diagnosis

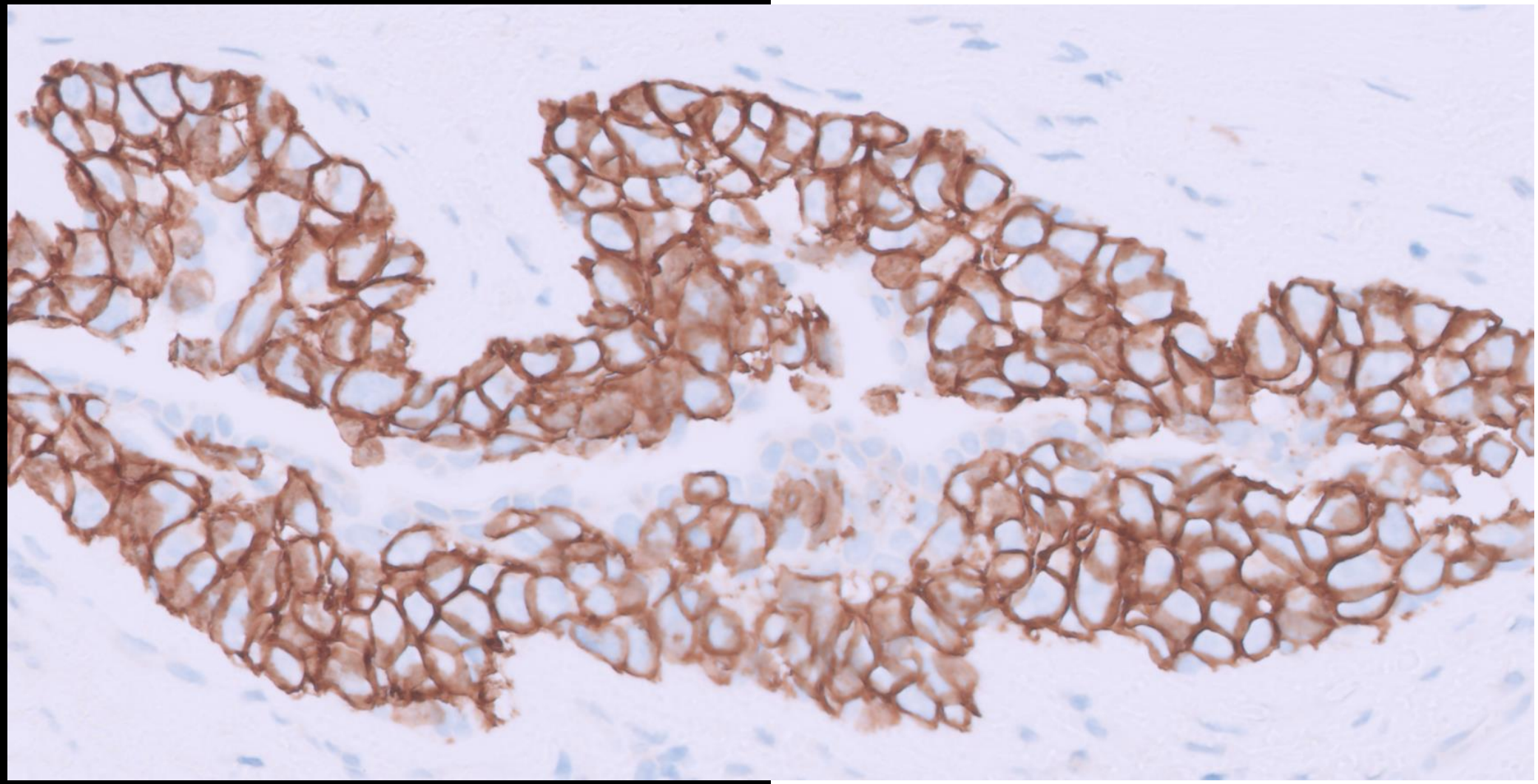
- DCIS
- LCIS (pleomorphic)
- Myoepithelial proliferation



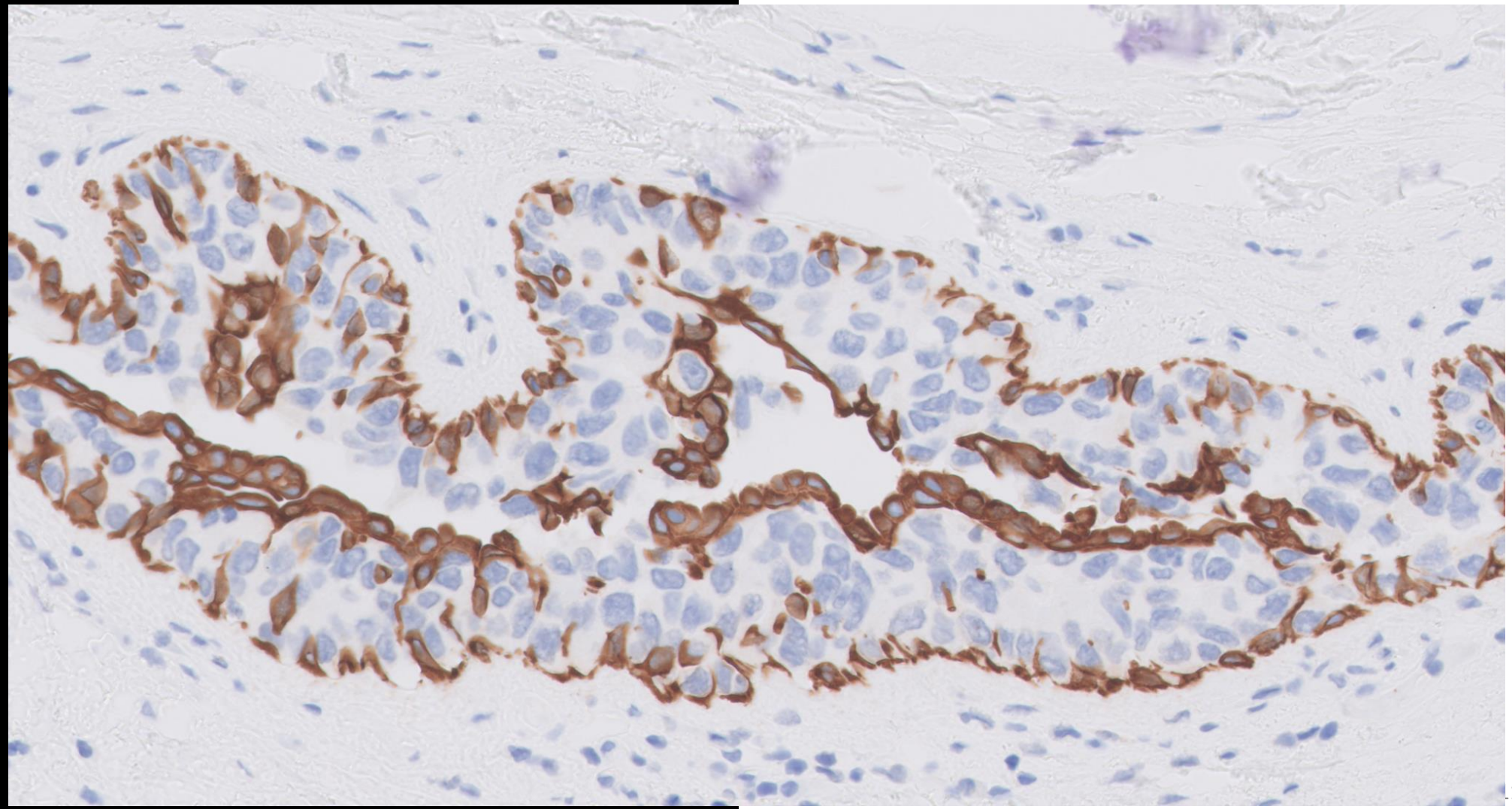
Atypical cells are E-cadherin positive (ductal)



Atypical cells are Her2 positive (high-grade)



Highlights myoepithelial and luminal cells
Atypical cells are CK5/6 negative



Pagetoid spread of high-grade dCIs

HISTOLOGIC FEATURES

- Malignant cells extending between luminal and myoepithelial layers
- Pagetoid spread in ducts often seen in LCIS
- Single-cell necrosis may be present

Incidence of carcinoma in breast reductions

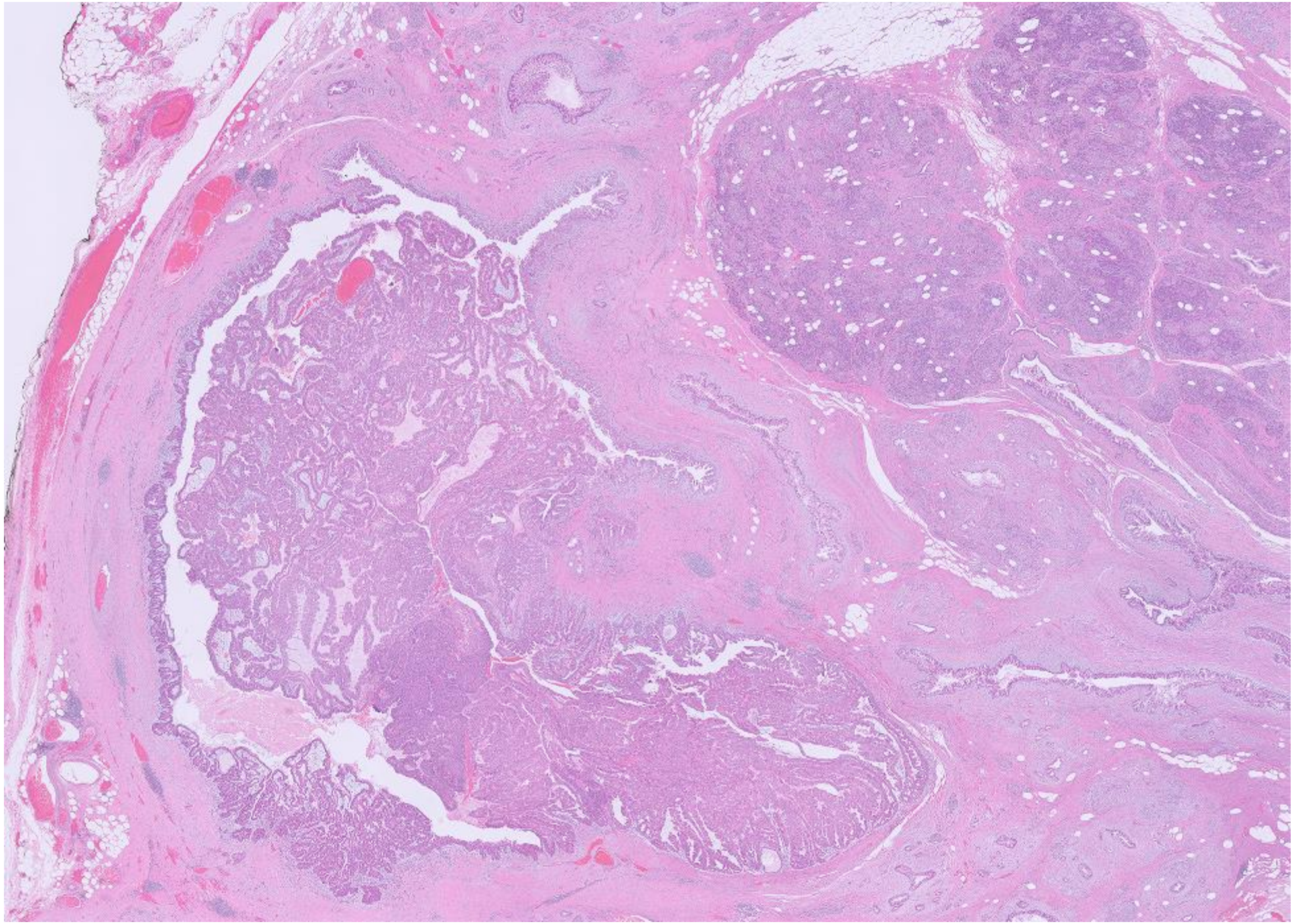
- In one study of 18k+ women undergoing reduction mammoplasty
  - 0.27% had incidental carcinoma in situ
  - 0.71% had incidental invasive carcinoma

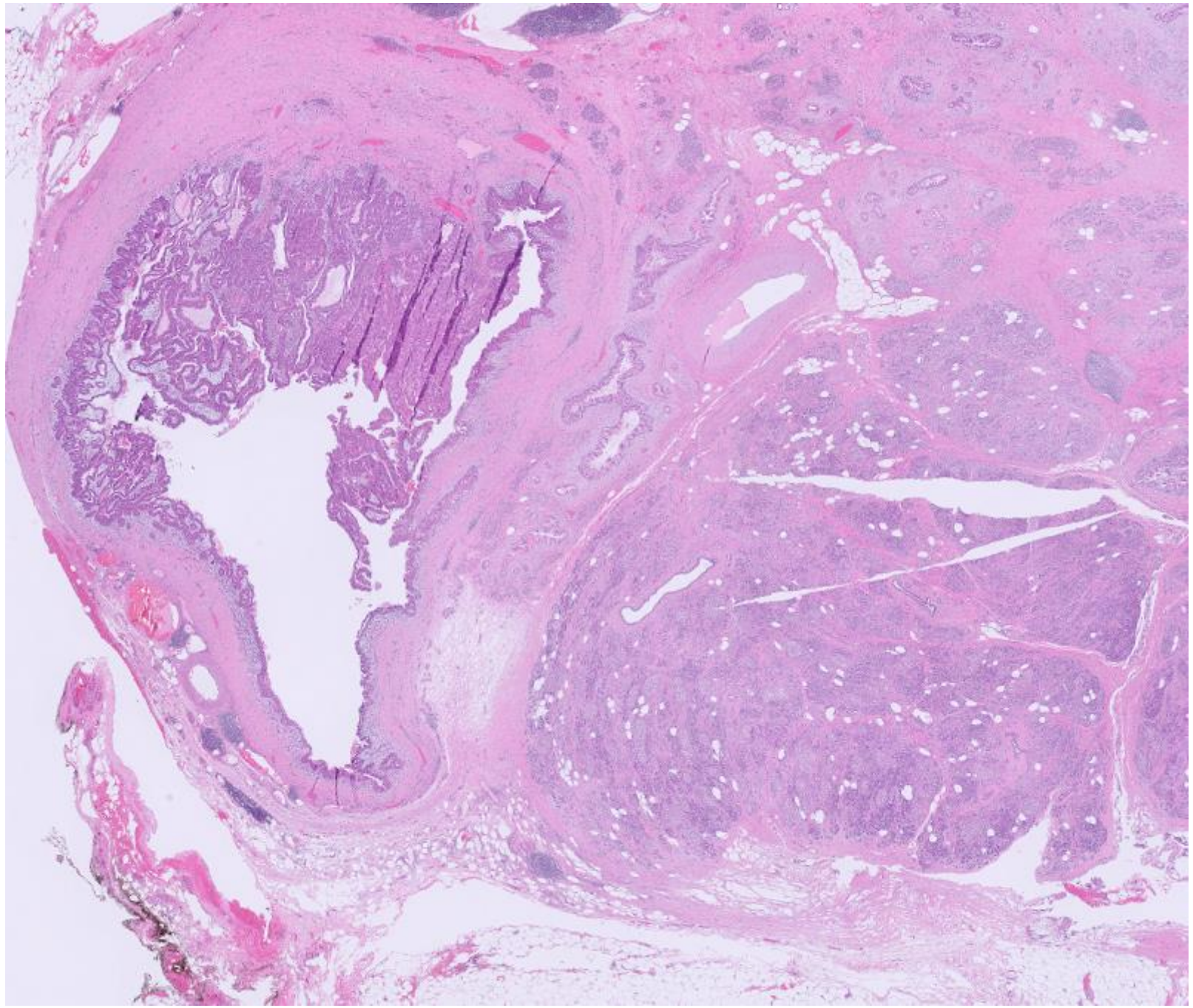
Walle et al, Ann Surg Oncol, 2019

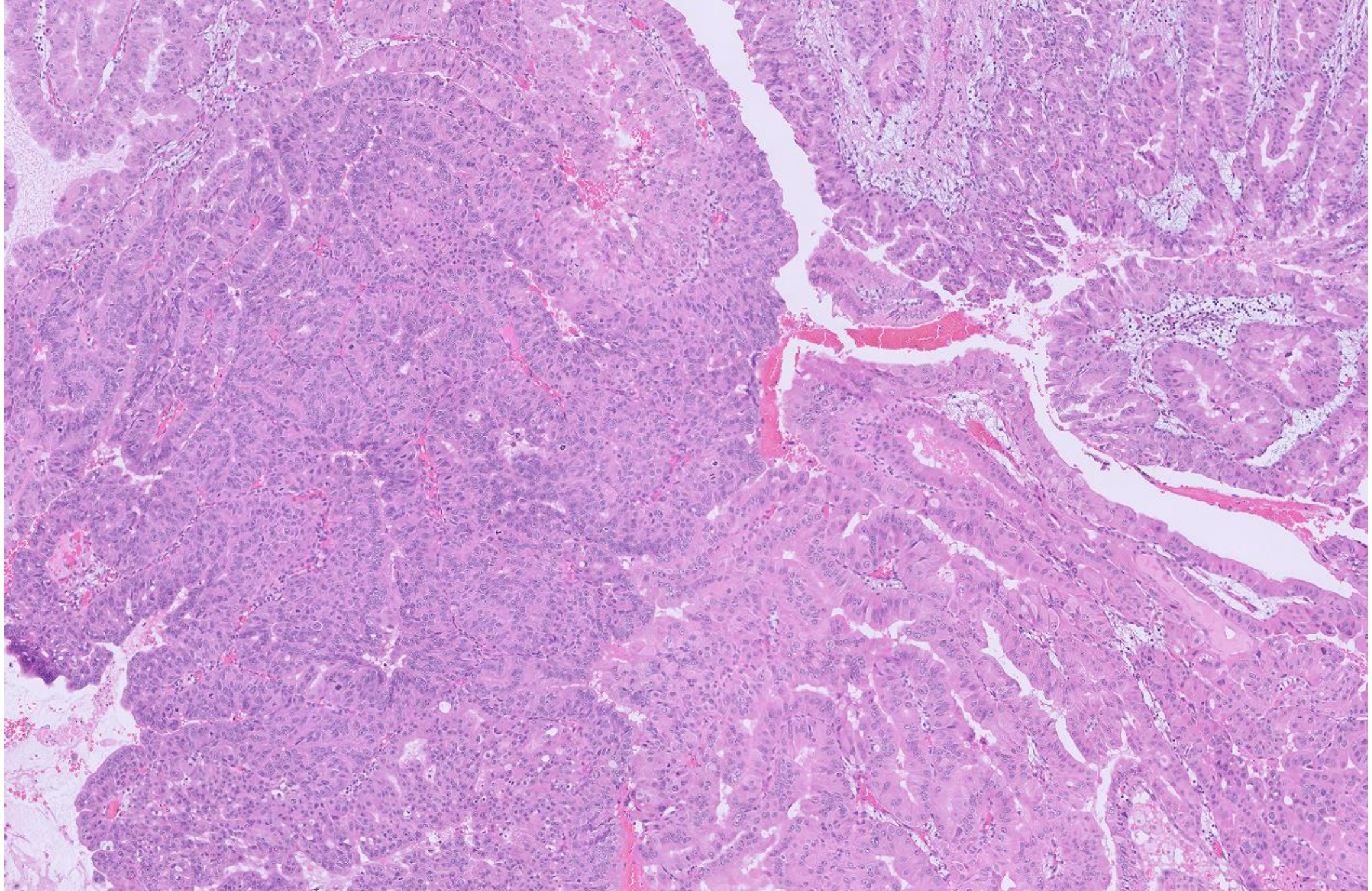
23-0607

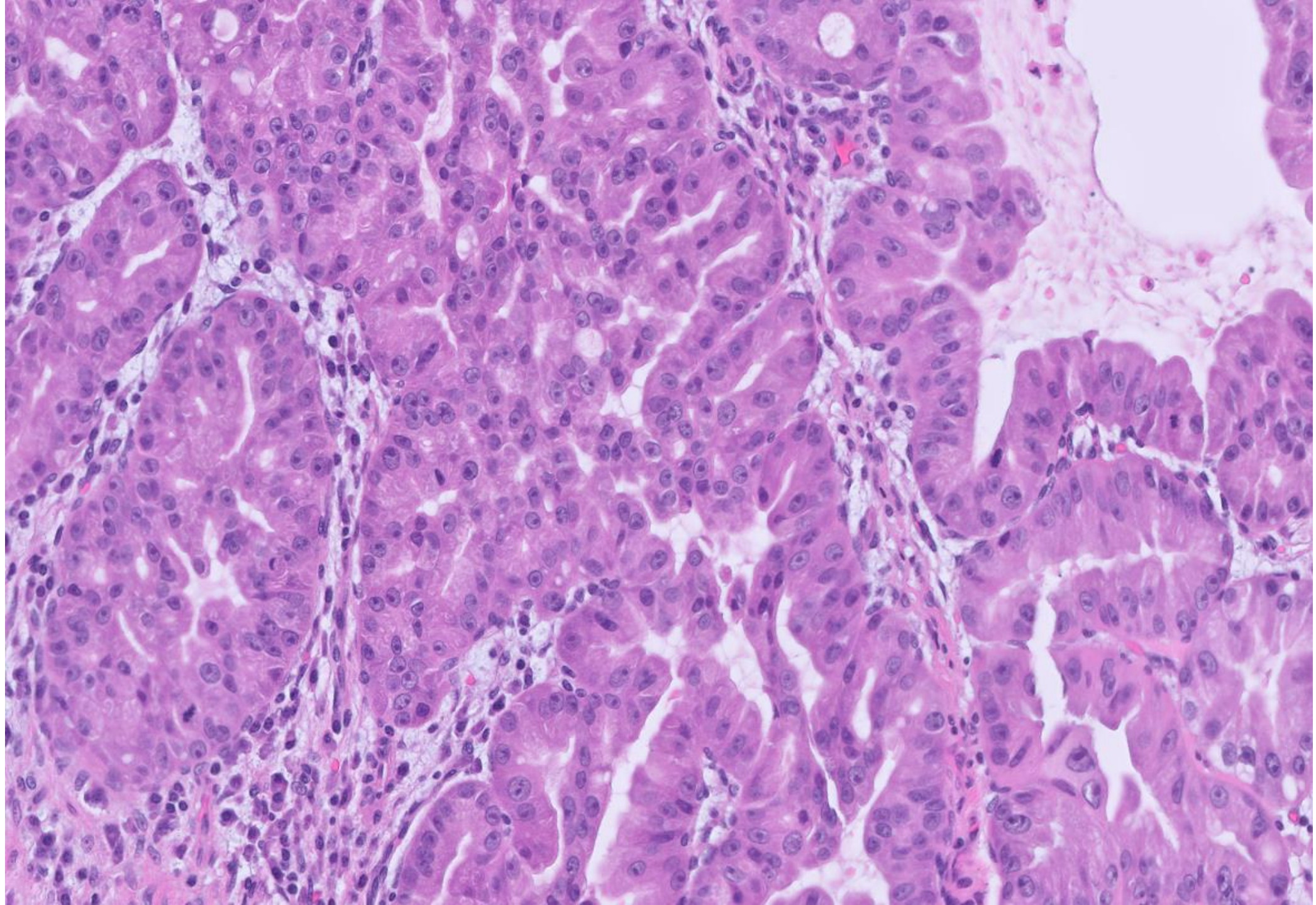
Marietya Lauw, MD/John Higgins, MD/Gregory Charville, MD, PhD; Stanford

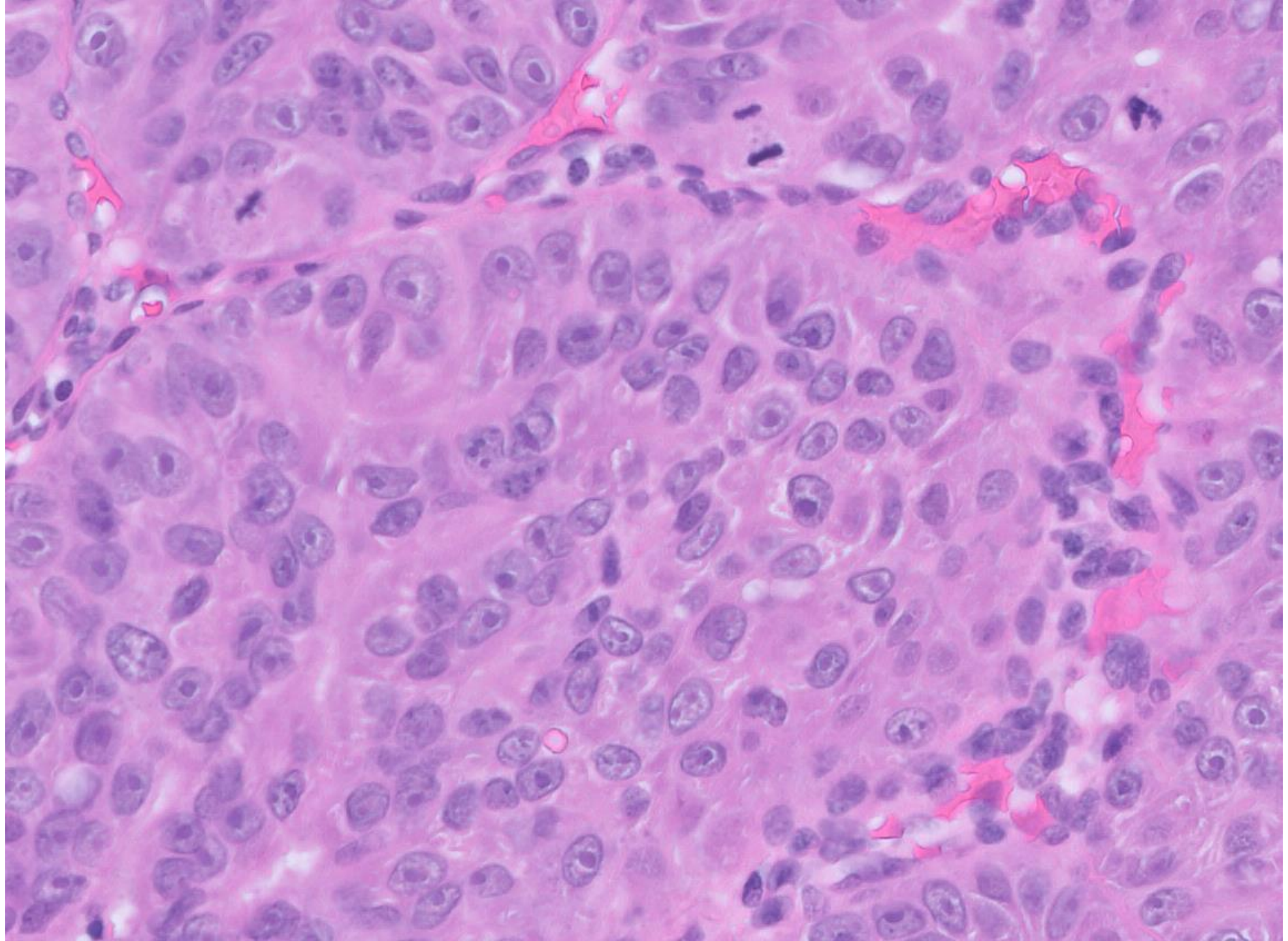
50s M with a multiseptated cystic lesion in the tail of the pancreas with dilation of the pancreatic duct. The distal pancreatectomy specimen shows a 2.1-cm mixed cystic and solid lesion.

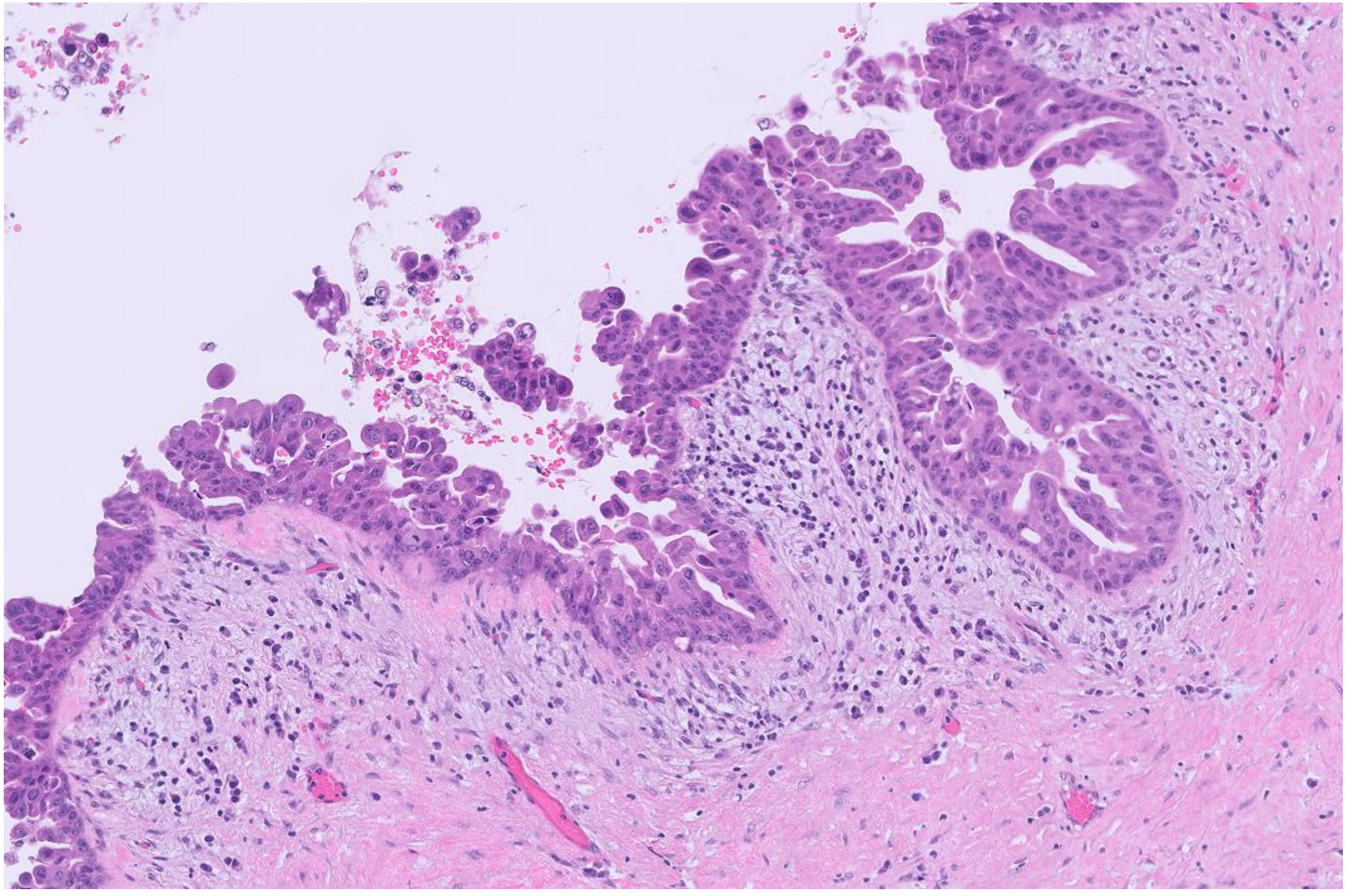


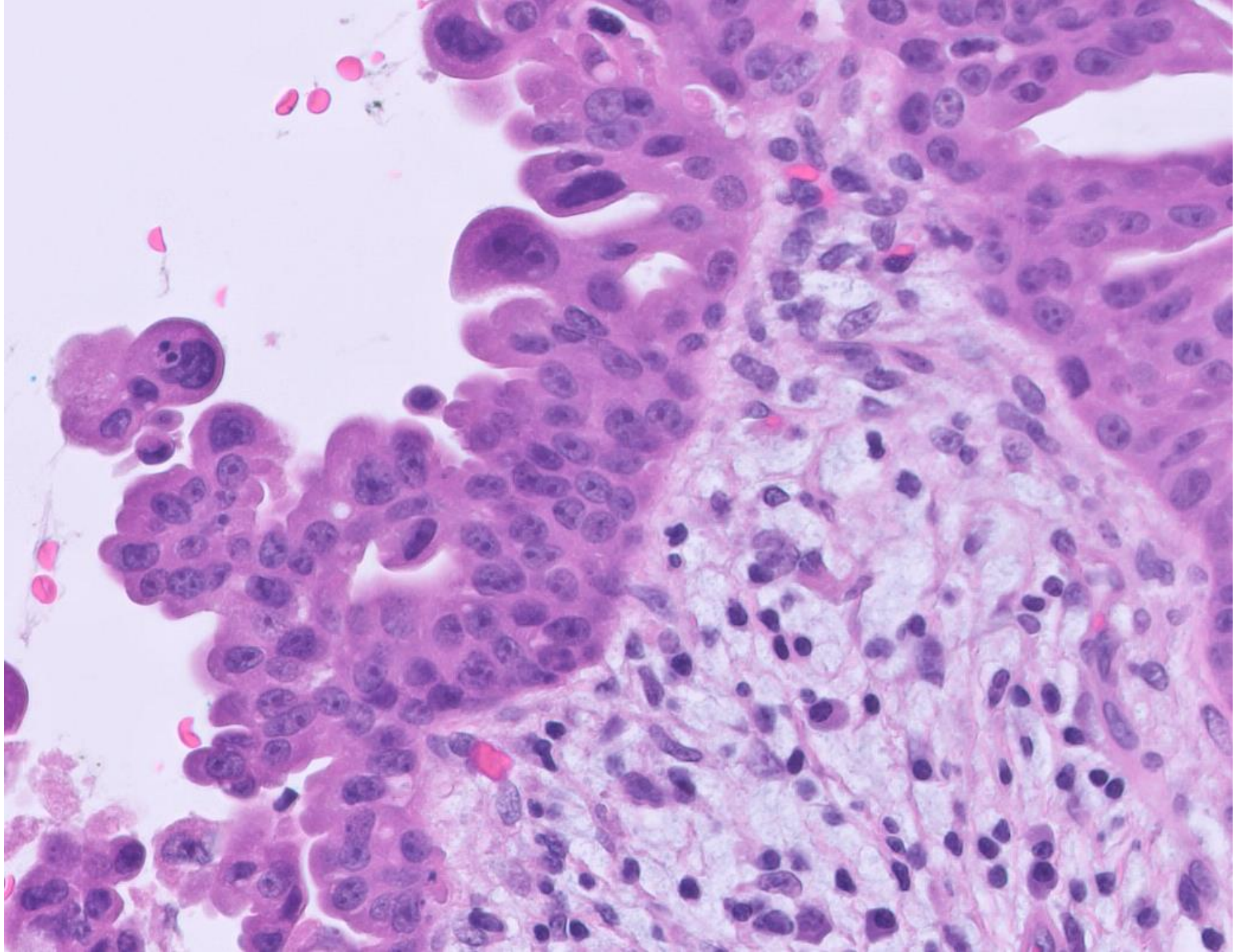


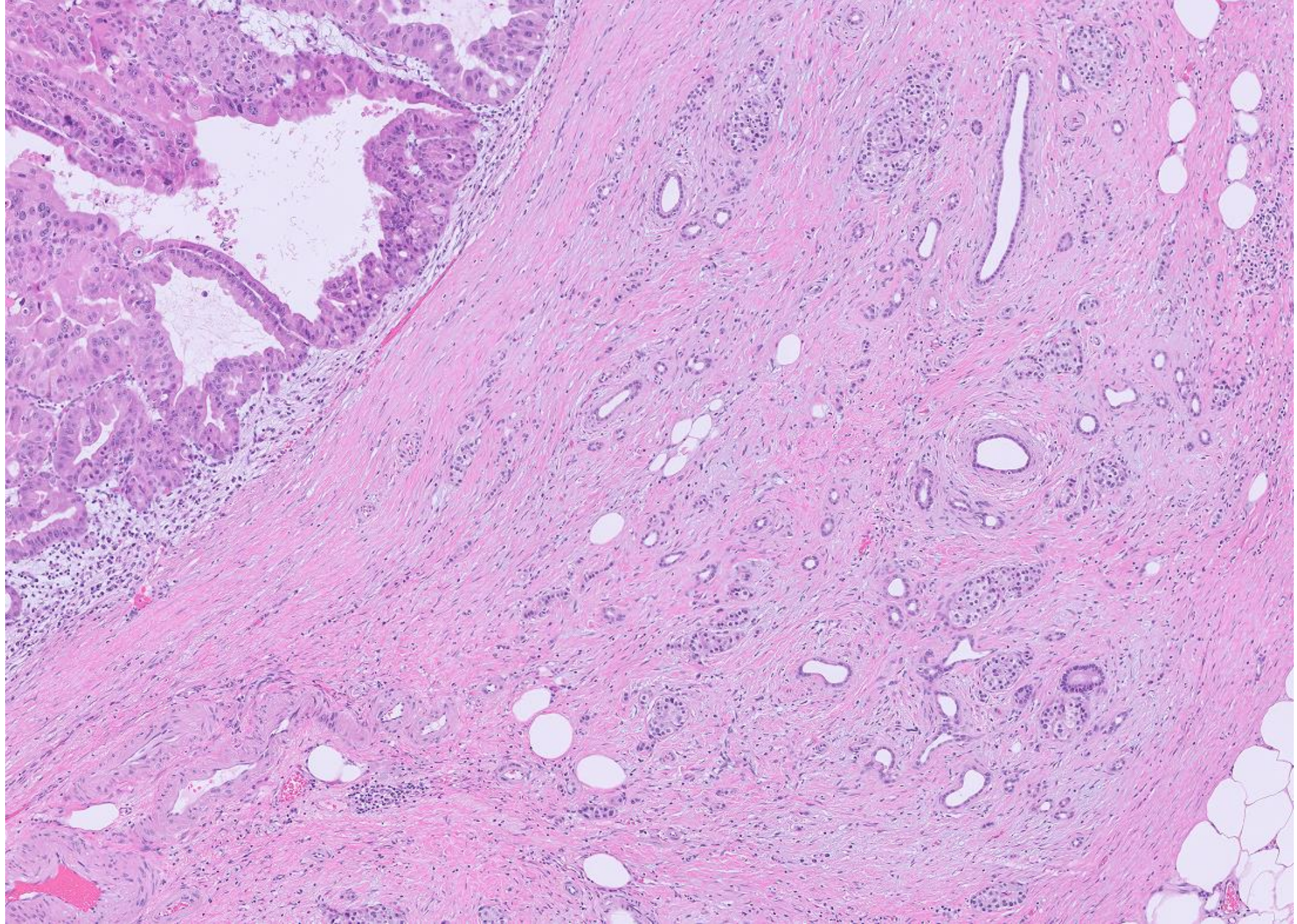












Final diagnosis

Distal pancreas, Subtotal pancreatectomy

- Pancreatic intraductal oncocytic papillary neoplasm with high-grade dysplasia, 2.1 cm
- No definitive invasive carcinoma is identified

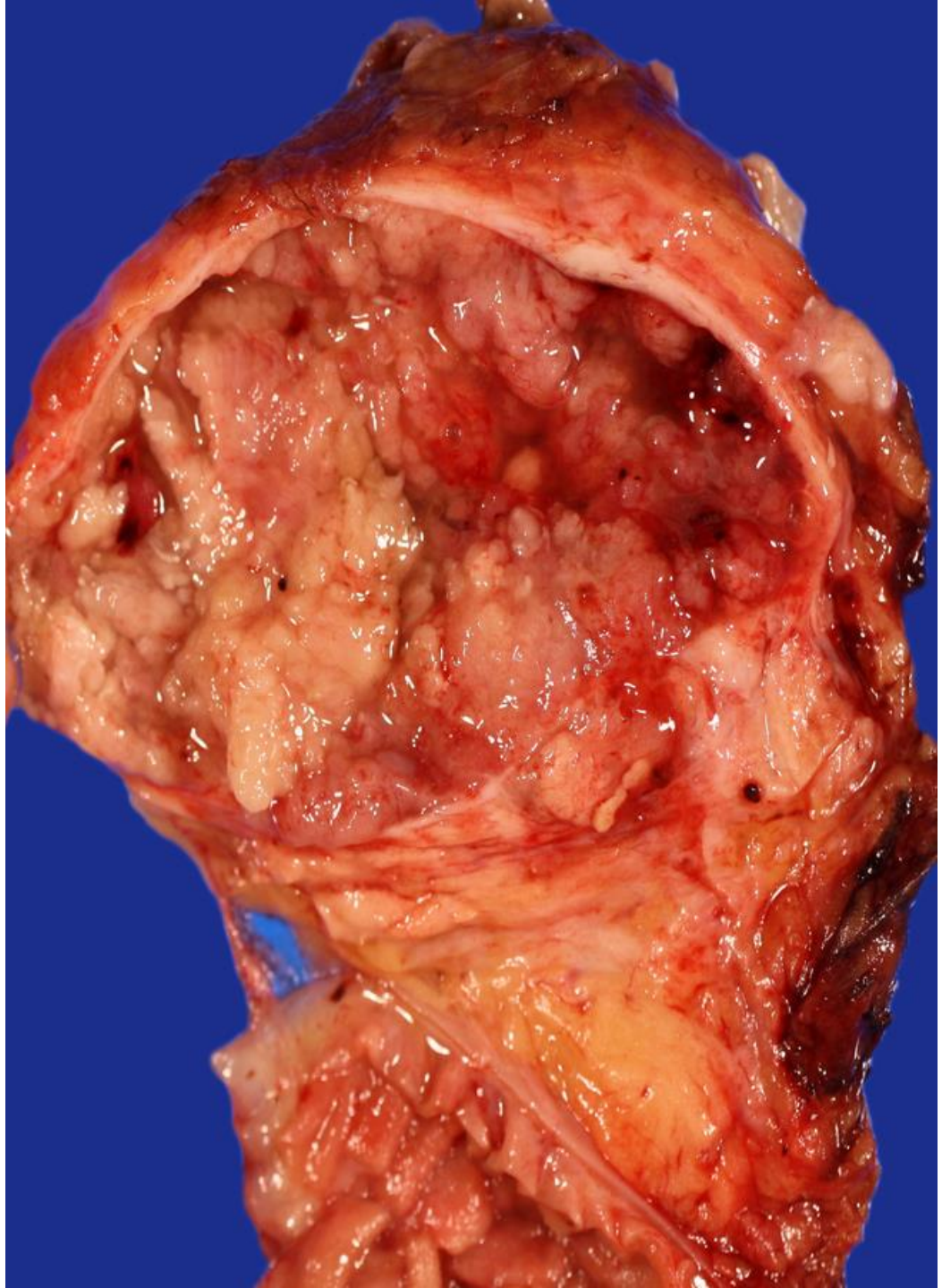
Intraductal oncocytic papillary neoplasm (IOPN)

- First described as a distinct entity in a report of 11 cases in 1996
- In 2010, the World Health Organization (WHO) classified IOPN as a subtype of intraductal papillary mucinous neoplasm (IPMN), since both IOPN and IPMN present similarly as a cystic pancreatic lesion due to dilation of the native ducts by the intraductal neoplasm
- More recent studies have illustrated differences between these entities, warranting revisions in classification:
  - Mucin production is minimal in IOPNs
  - IOPNs are genetically distinct as they generally lack the alterations commonly found in the other subtypes of IPMN, including mutations in *KRAS* and *GNAS*
- *Acceptable terminology:* Oncocytic subtype of intraductal papillary mucinous neoplasm

Epidemiology

- Accounts for 4.5% of all intraductal neoplasms of the pancreas
- More common in females
- Patient age ranges from 36 to 87 years (mean: 59 years)
- 67% in the head of the pancreas, 28% in the body/tail, and 5% diffusely involved the gland
- Almost half (44%) of the lesions were discovered incidentally during work-up for other intra-abdominal pathologies such as bladder neoplasm or polycystic ovarian cysts
- Presenting symptoms included abdominal or back pain, nausea, hematochezia, and weight loss
- None of the patients presented with jaundice

Wang et al. Am J Surg Pathol. 2019 May;43(5):656-661.



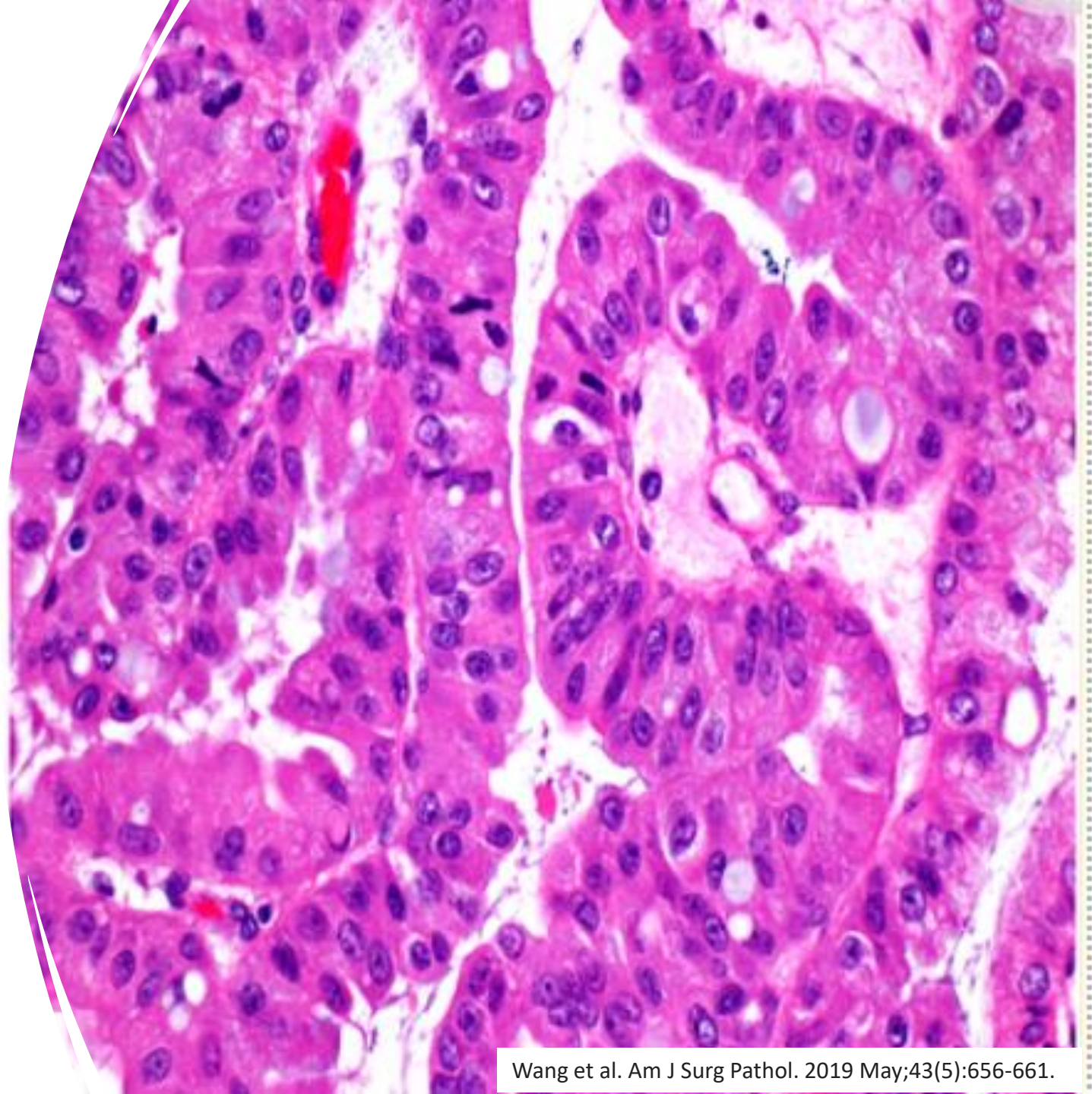
Gross appearance

- Typically large (ranged from 1 to 14 cm (median=4.5 cm) in greatest dimension)
- Tan-brown, friable papillary projections or solid nodules within cystically dilated pancreatic ducts, with little intraductal mucin accumulation
- Lesion needs to be entirely submitted to rule out invasive carcinoma

Wang et al. Am J Surg Pathol. 2019 May;43(5):656-661.

Microscopy

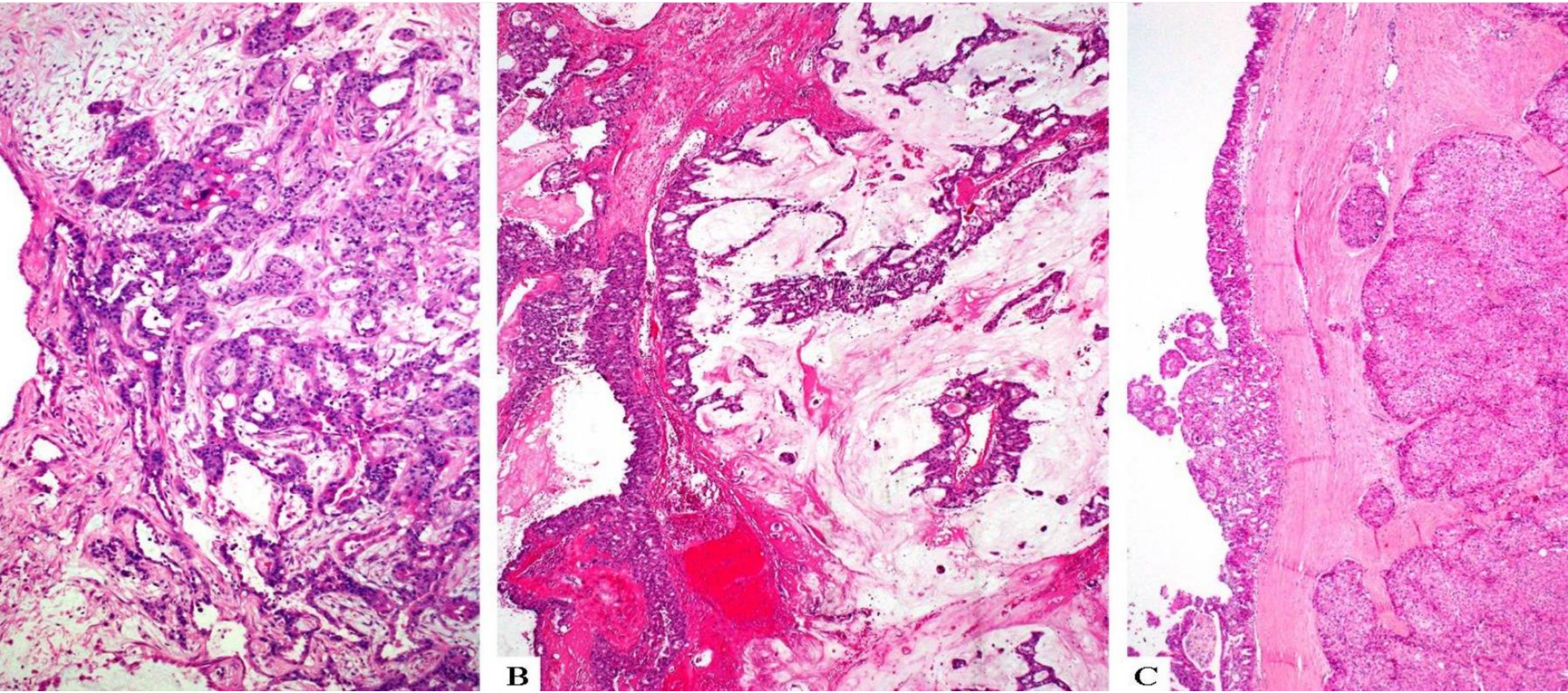
- Multilocular or unilocular cysts
- Form complex and arborizing papillae with delicate fibrovascular cores
- The papillae are lined by 2–5 layers of cuboidal to columnar cells with mitochondrion-rich eosinophilic granular cytoplasm that contains a large, round nucleus with a prominent nucleolus
- These cells form cribriformed structures, with mucin-containing intraepithelial lumina. Interspersed goblet cells are also common
- In some cases, the epithelium of adjacent papillae may fuse, producing a solid growth pattern
- Based on both the architectural complexity and the degree of nuclear atypia, **essentially all IOPNs have high-grade dysplasia**



Wang et al. Am J Surg Pathol. 2019 May;43(5):656-661.

Associated invasive carcinoma

- Occurs in about 30% of IOPNs and is usually limited in extent
- The invasive component is mostly composed of small infiltrating tubules or solid nests composed of oncocytic cells
- In rare cases, the invasive component has abundant stromal mucin accumulation

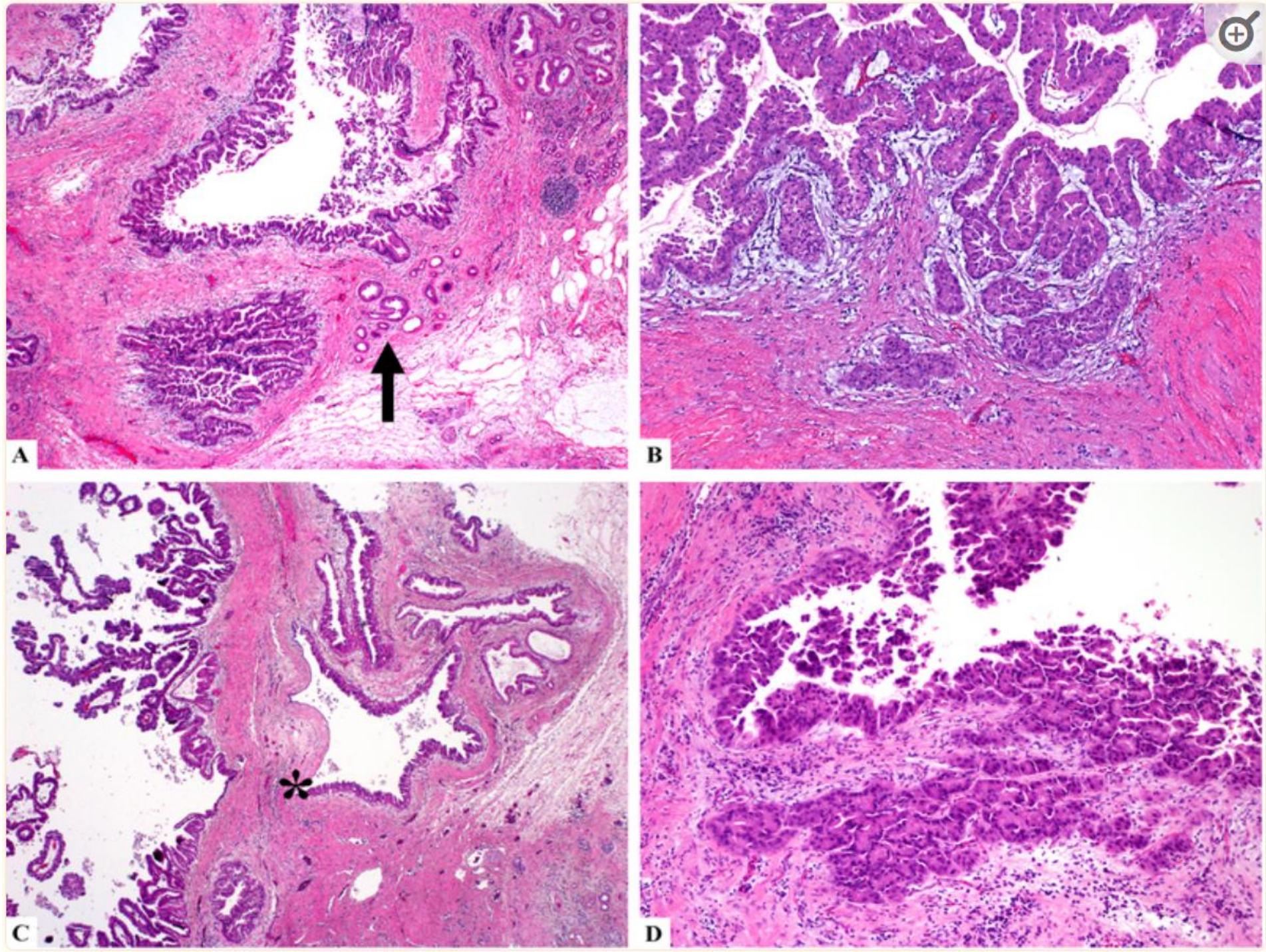


Wang et al. Am J Surg Pathol. 2019 May;43(5):656-661.

Pitfalls: Pseudoinvasion

- Many IOPNs reveal morphologic features mimicking invasive carcinoma
- The neoplasms often grow along adjacent benign ducts, which mimic invasion especially because of the more dispersed appearance of the atrophic glands
- Myxoid or edematous stroma surrounding the massively dilated ducts involved by IOPN also sometimes simulates desmoplastic stroma, which could be misinterpreted as invasion when it is associated with involved smaller ductules
- If present, abrupt transition from a morphologically normal epithelium to oncocytic epithelium within the same duct is helpful in recognizing intraductal extension into small ducts
- The overall lobulated architecture, presence of the same stroma surrounding adjacent ducts, as well as maintained luminal connections on deeper sections favor pseudo-invasion
- Tangential sectioning also mimics invasion by creating a complex appearance

Wang et al. Am J Surg Pathol. 2019 May;43(5):656-661.


A
B
C
D

Immunohistochemistry

- Mostly H&E diagnosis
- IOPNs diffusely label for EMA (MUC1) and MUC6, whereas MUC2 and MUC5AC expression is largely restricted to goblet cells
- There is consistent immunolabelling with Hep Par-1; however, in situ hybridization for albumin is negative

Prognosis

- Although IOPNs are associated with invasive carcinoma in about 30% of cases, patients' 5-year disease-specific survival rate approaches 100%
- Local recurrences, which are seen in as many as 45% of cases and may occur > 10 years after the initial resection, can often be successfully treated with additional resection

Take Home Messages

- IOPN is a distinct entity in the WHO classification of tumors
- It is a cystic epithelial neoplasm composed of exophytic nodular projections lined by oncocytic glandular epithelium, which grows within dilated pancreatic ducts
- The entire lesion needs to be submitted to evaluate for possible invasion
- Based on both the architectural complexity and the degree of nuclear atypia, **essentially all IOPNs have high-grade dysplasia**
- Many IOPNs reveal morphologic features mimicking invasive carcinoma

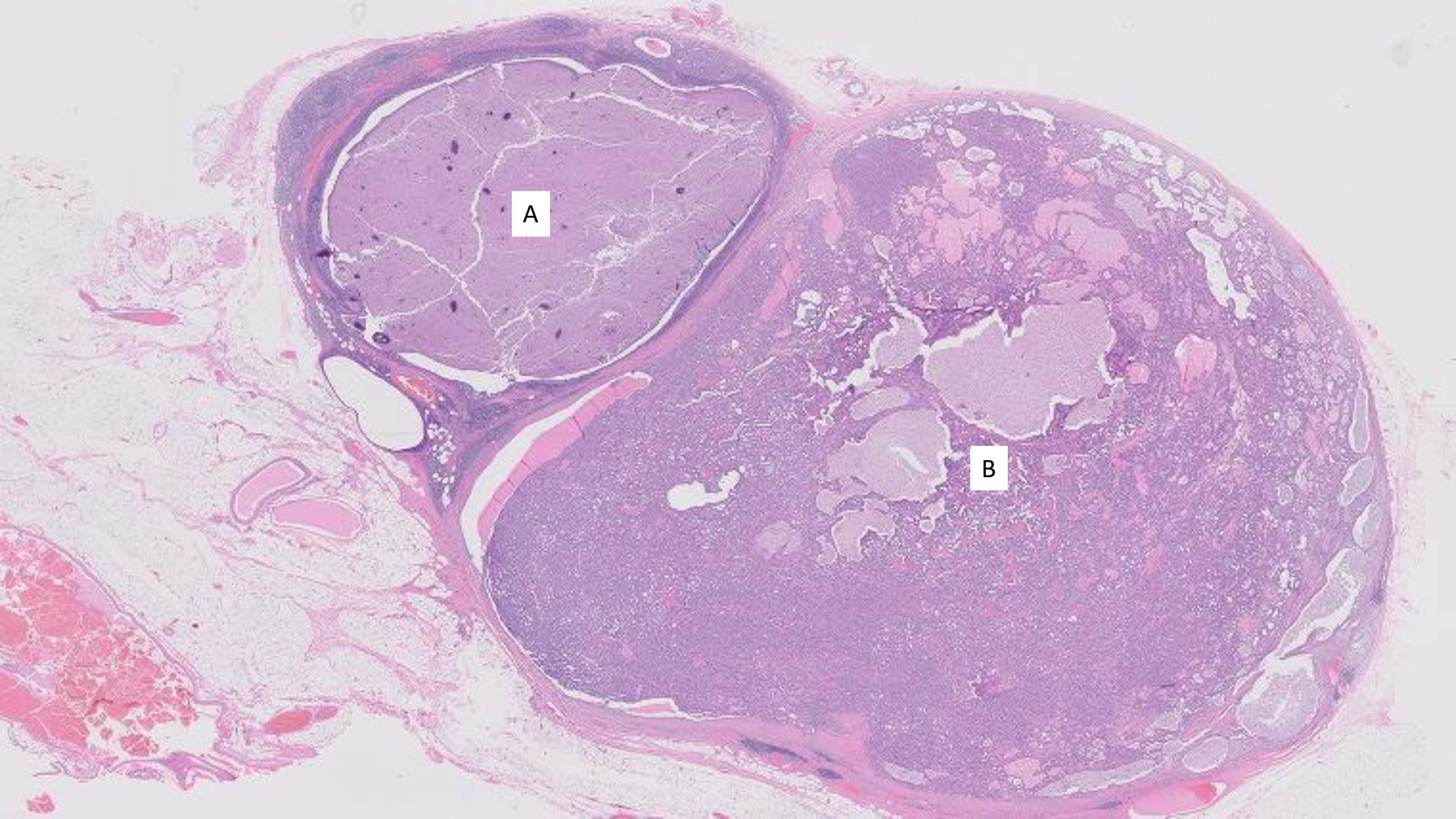
References

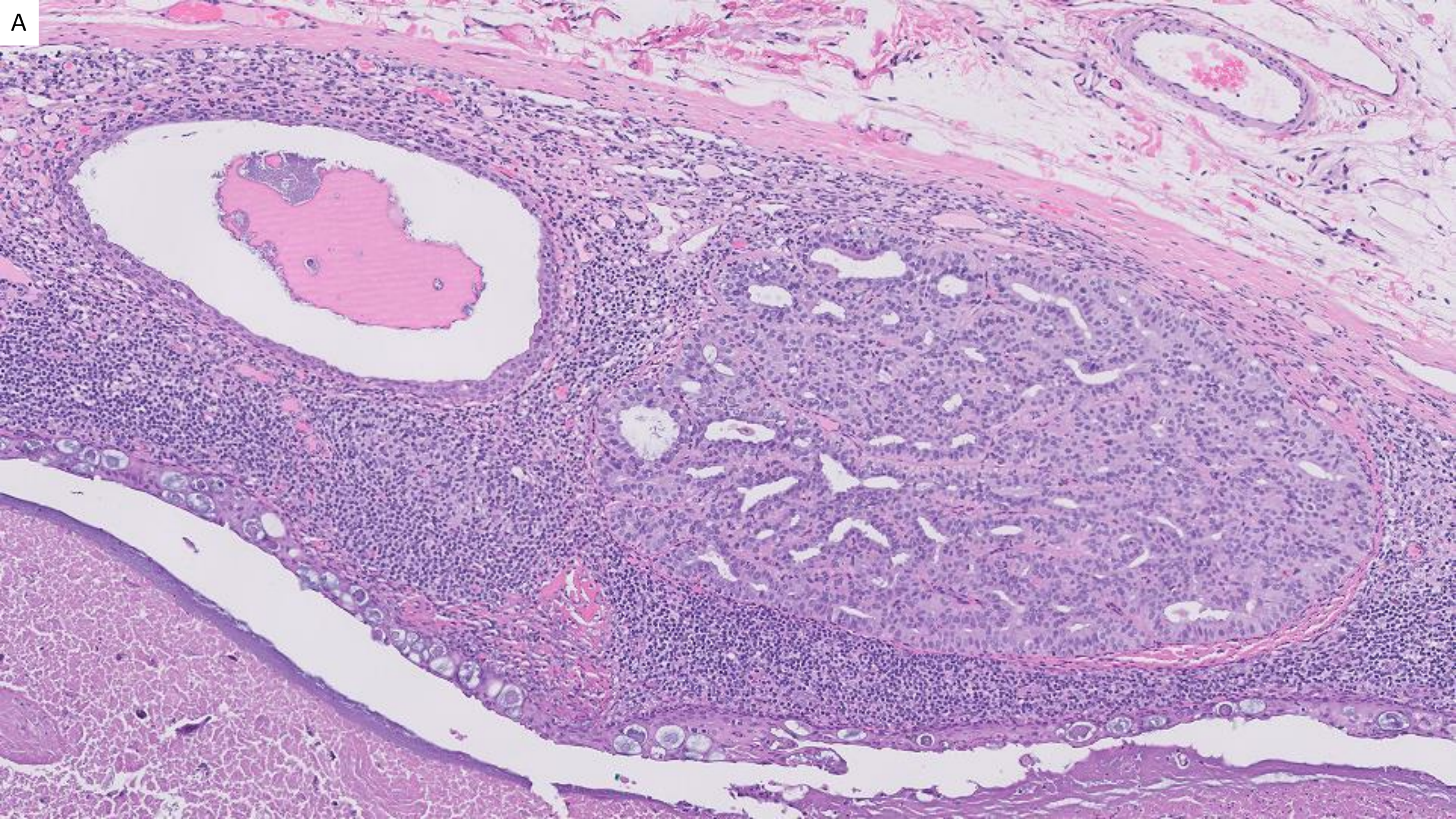
- WHO Classification of Tumours Editorial Board. Digestive system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2019
- Wang T, Askan G, Adsay V, Allen P, Jarnagin WR, Memis B, Sigel C, Seven IE, Klimstra DS, Basturk O. Intraductal Oncocytic Papillary Neoplasms: Clinical-Pathologic Characterization of 24 Cases, With An Emphasis on Associated Invasive Carcinomas. Am J Surg Pathol. 2019 May;43(5):656-661. doi: 10.1097/PAS.0000000000001226. PMID: 30986801; PMCID: PMC6467507.

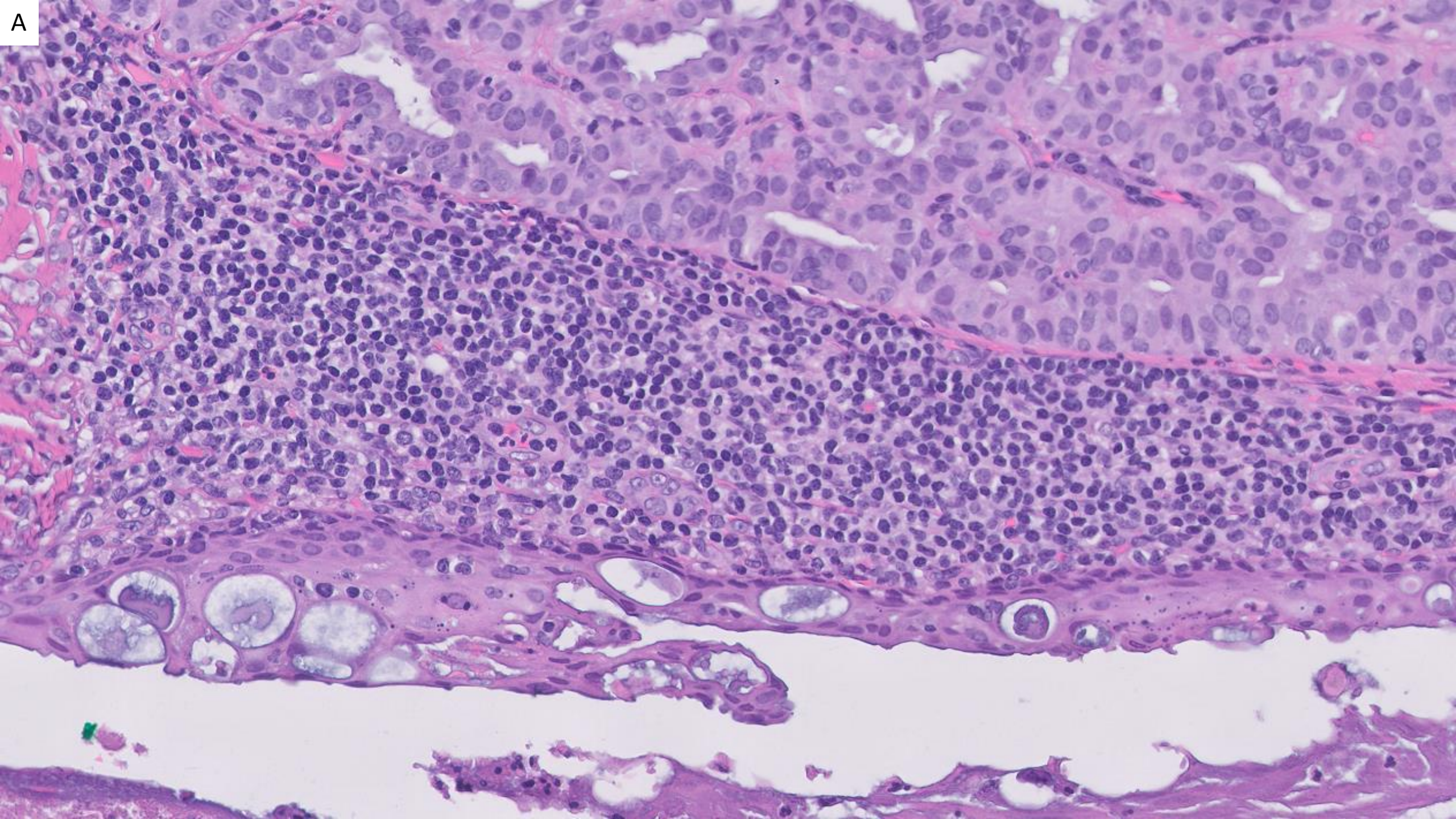
23-0608

Marietya Lauw, MD/Gregory Bean, MD, PhD; Stanford

Woman in her 50s with an enlarged (~ 2 cm) left axillary lymph node


A
B


A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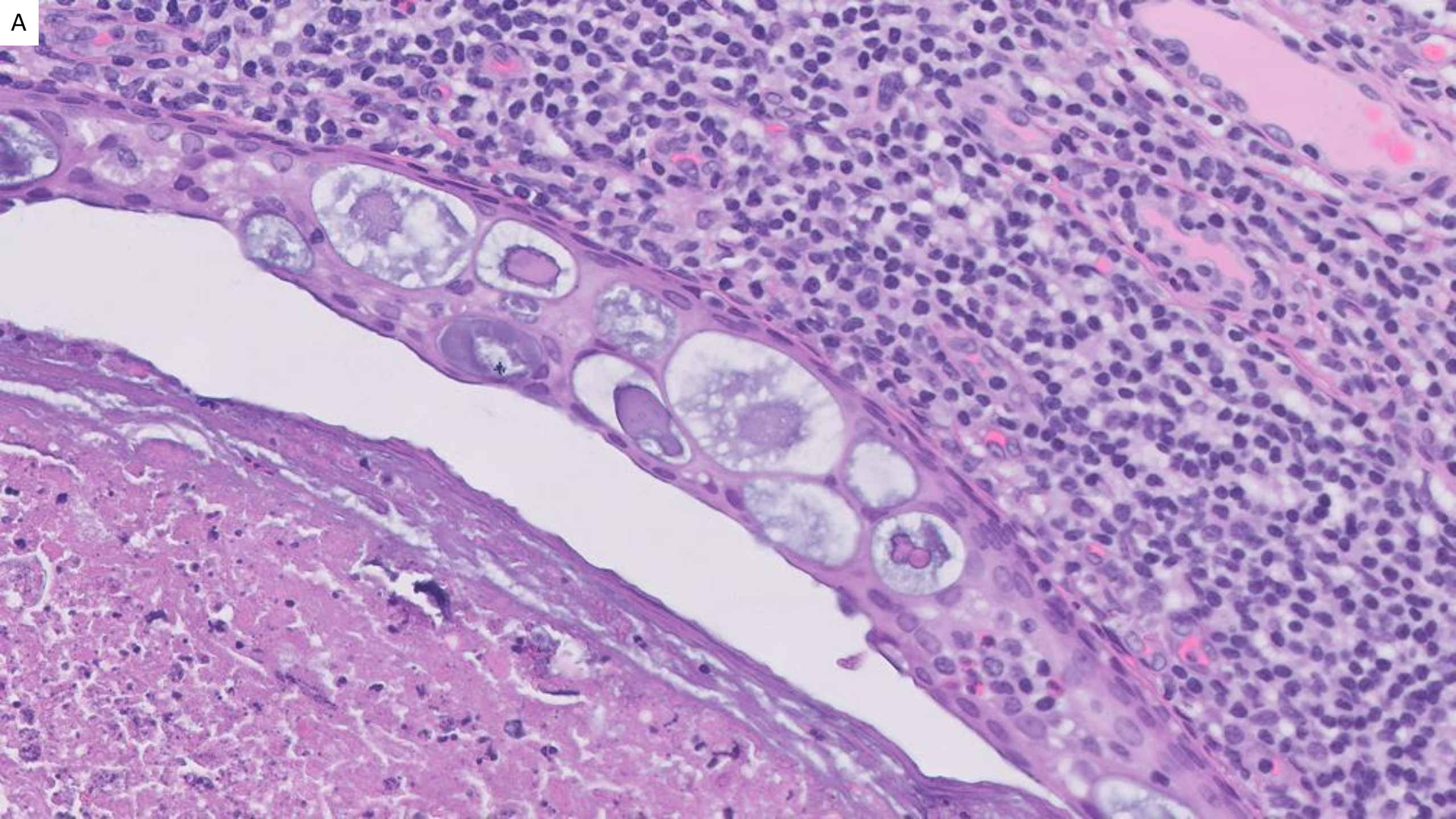
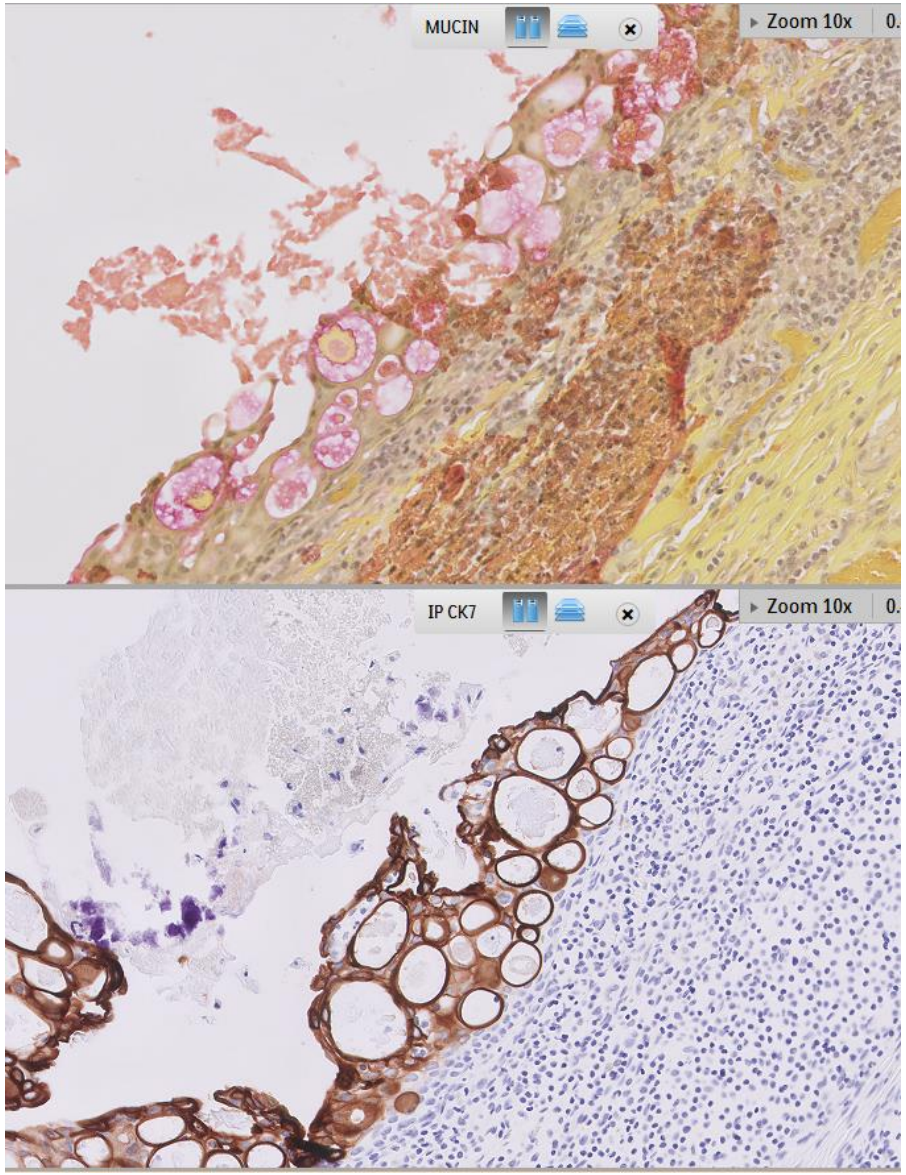
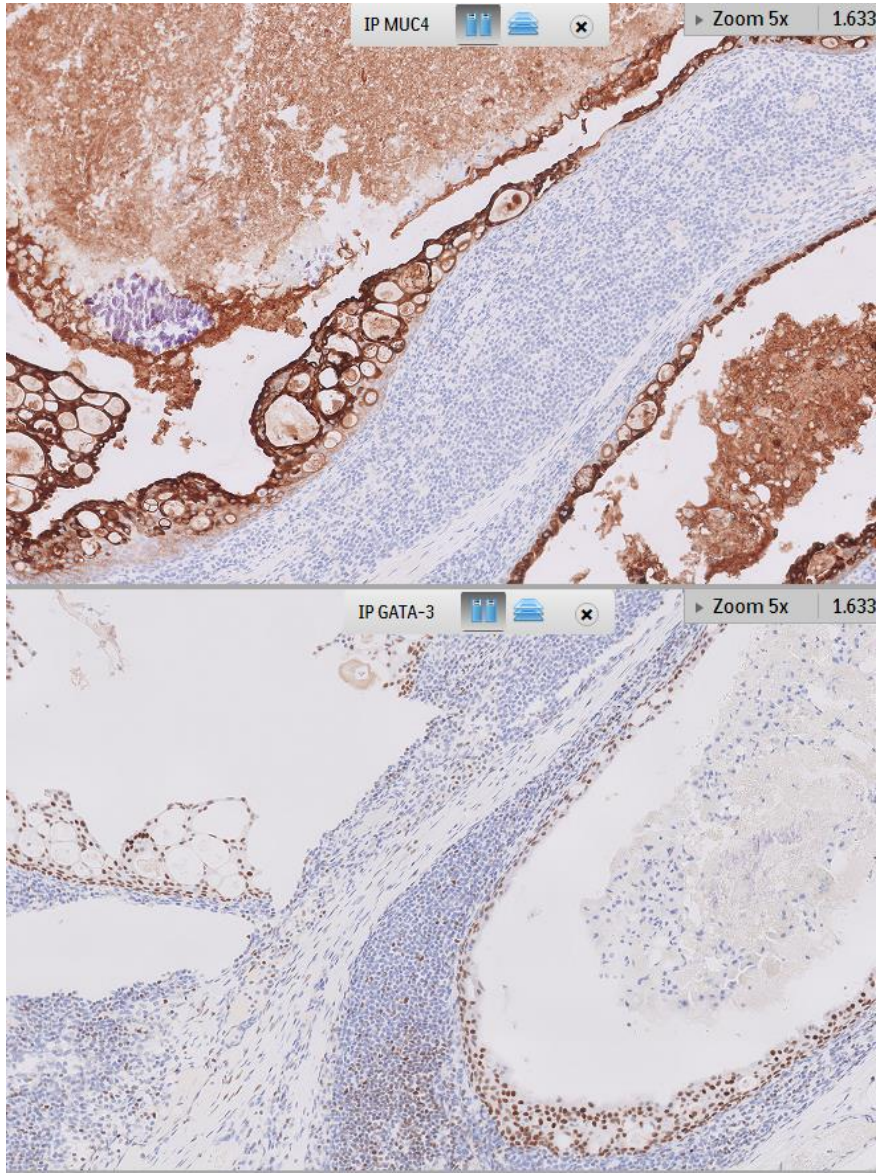
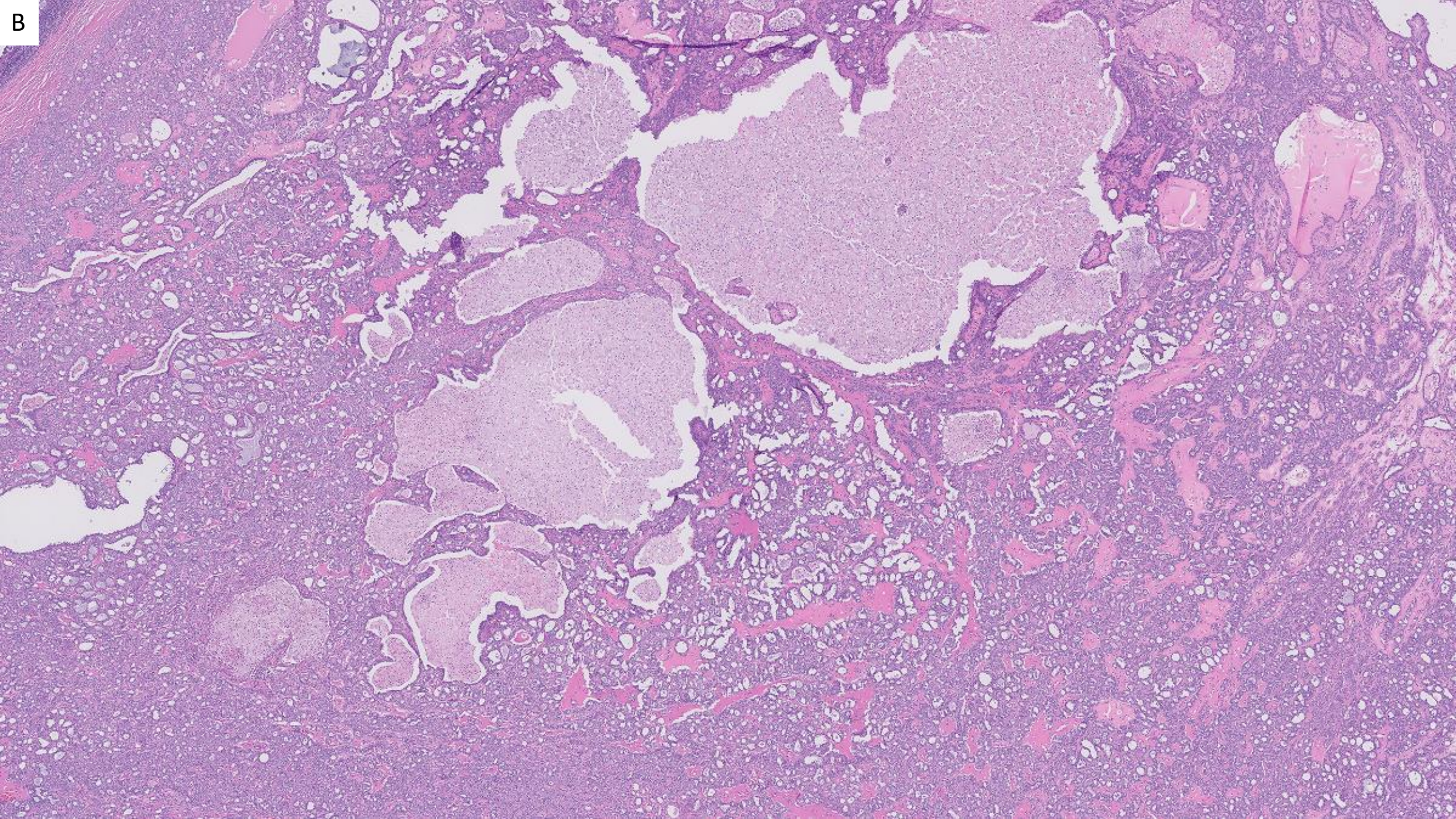

A

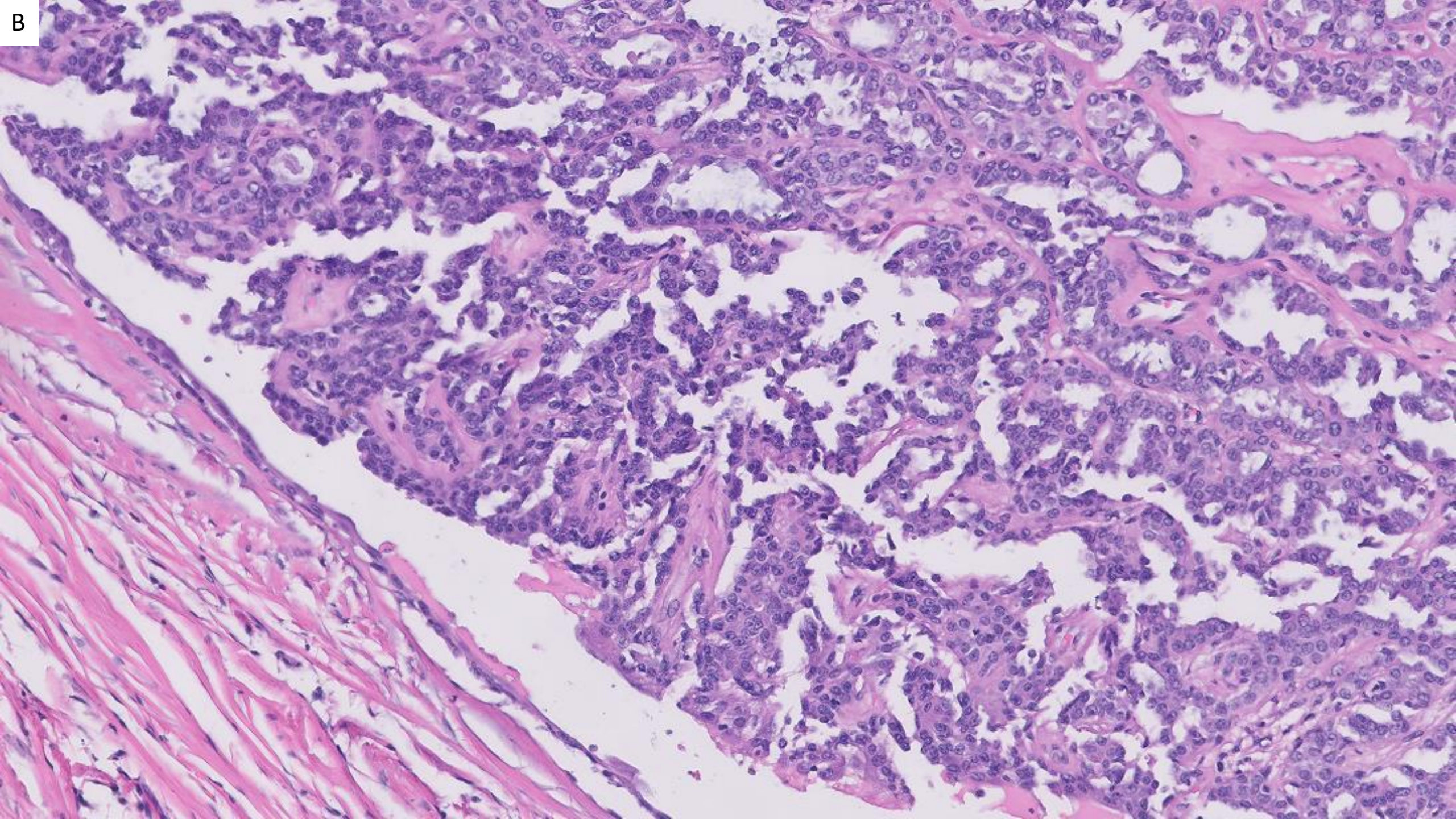
Immunophenotype component A

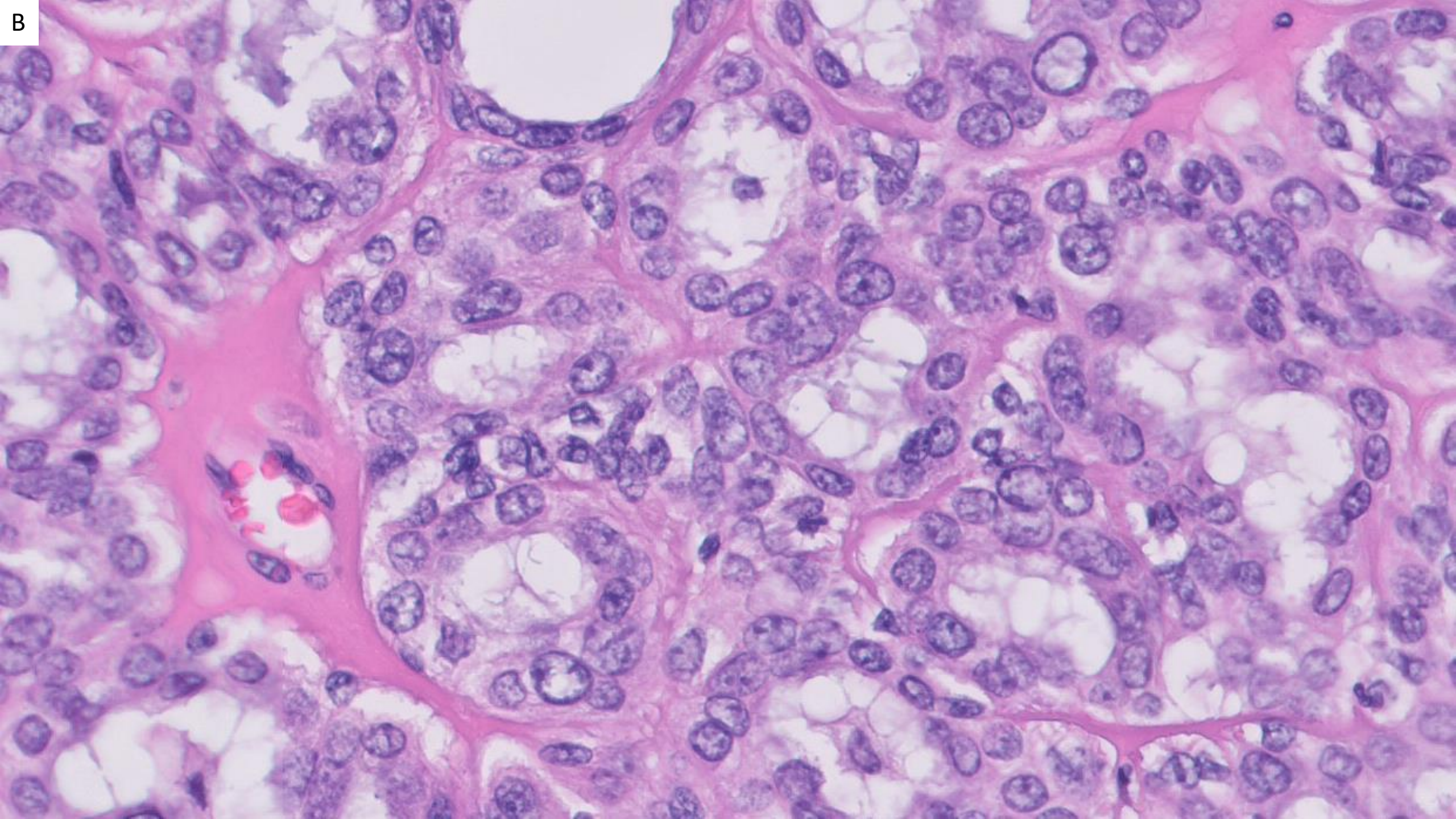
- Mucicarmine highlights extracellular material of the glandular lumen
- Lesional cells are diffusely positive for CK5/6, CK7, GATA3 and MUC4, patchy positive for Cam5.2, TRPS1 and GCDFP15
- They are negative for SMM, calponin, AR, ER, HER2, S100, SOX10 and mammaglobin
- p63 expression is limited to the basal layer

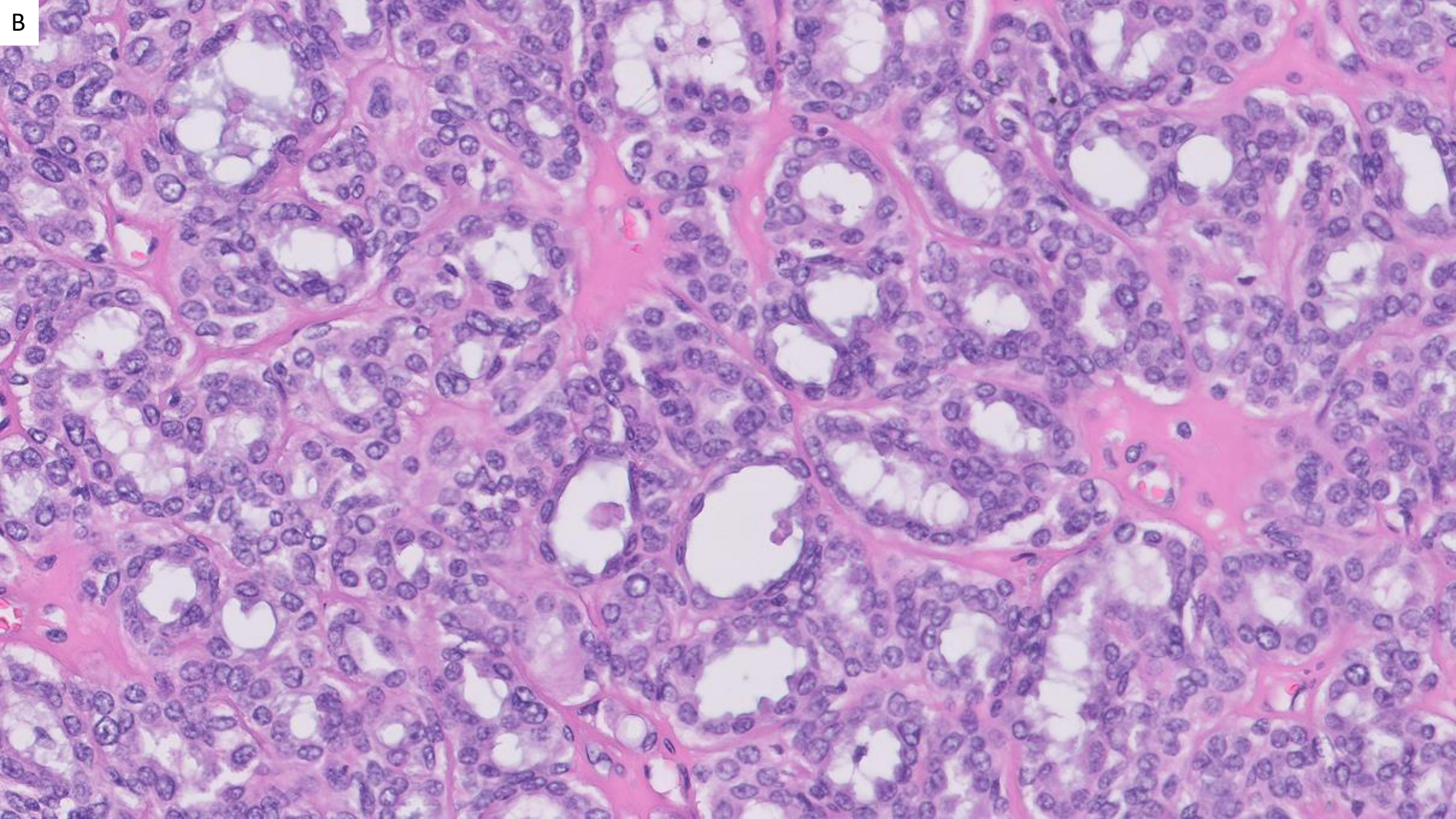

MUCIN
Zoom 10x
IP CK7
Zoom 10x


IP MUC4
Zoom 5x
IP GATA-3
Zoom 5x


B

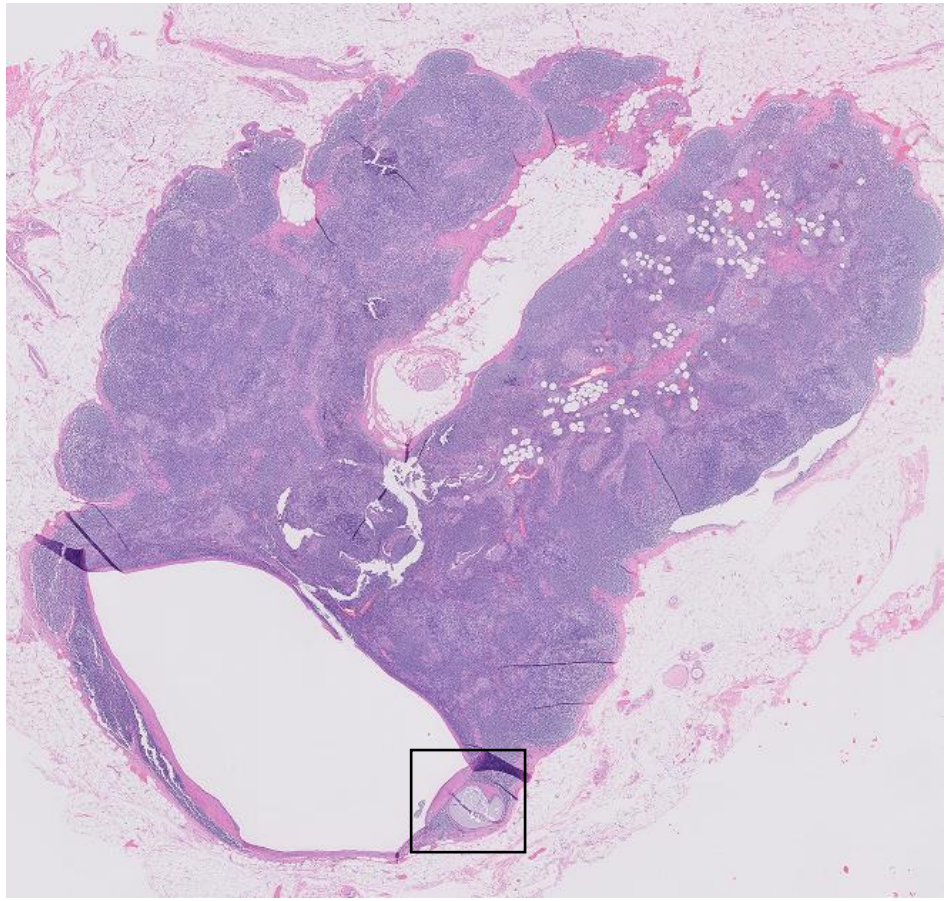

B

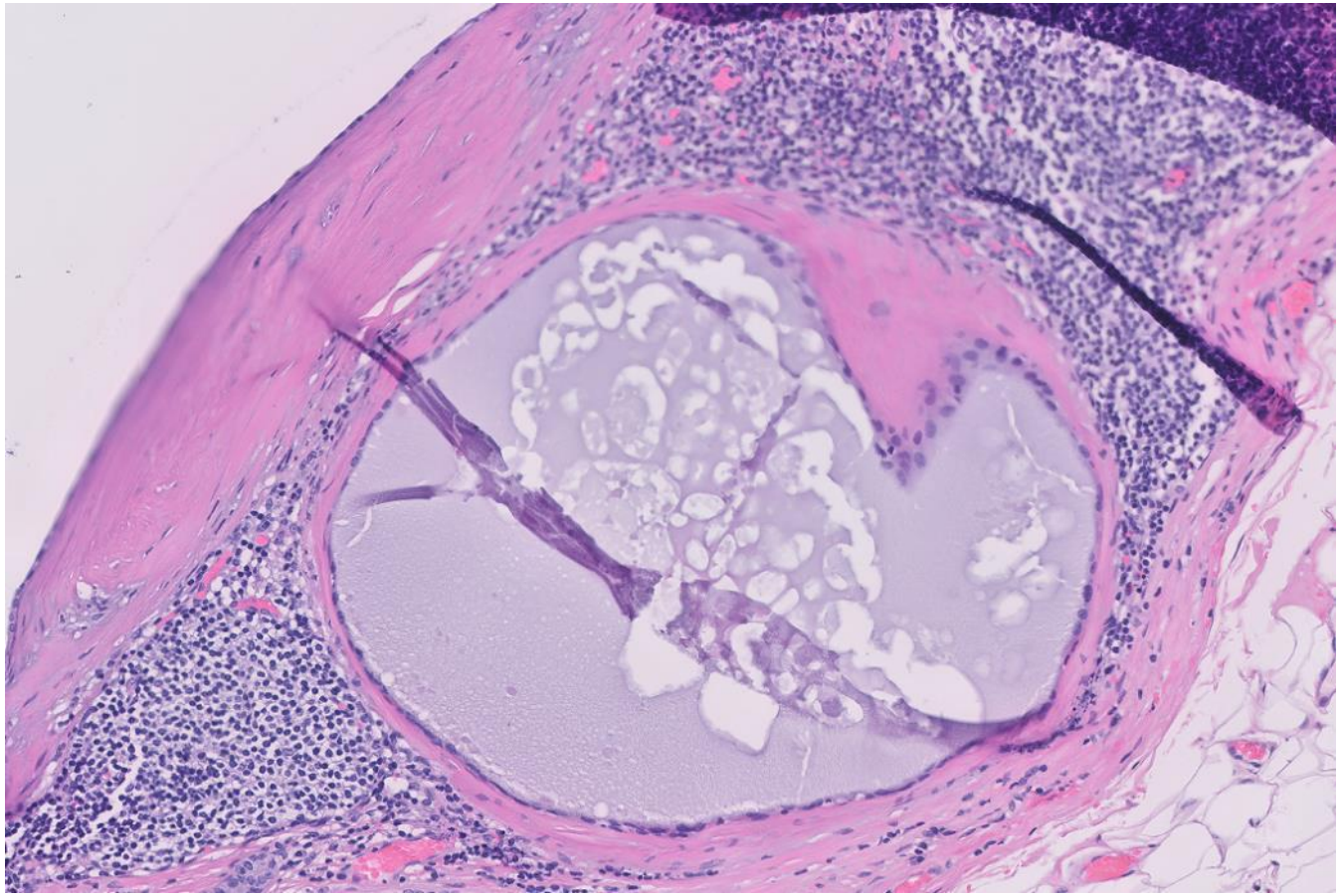

B


B

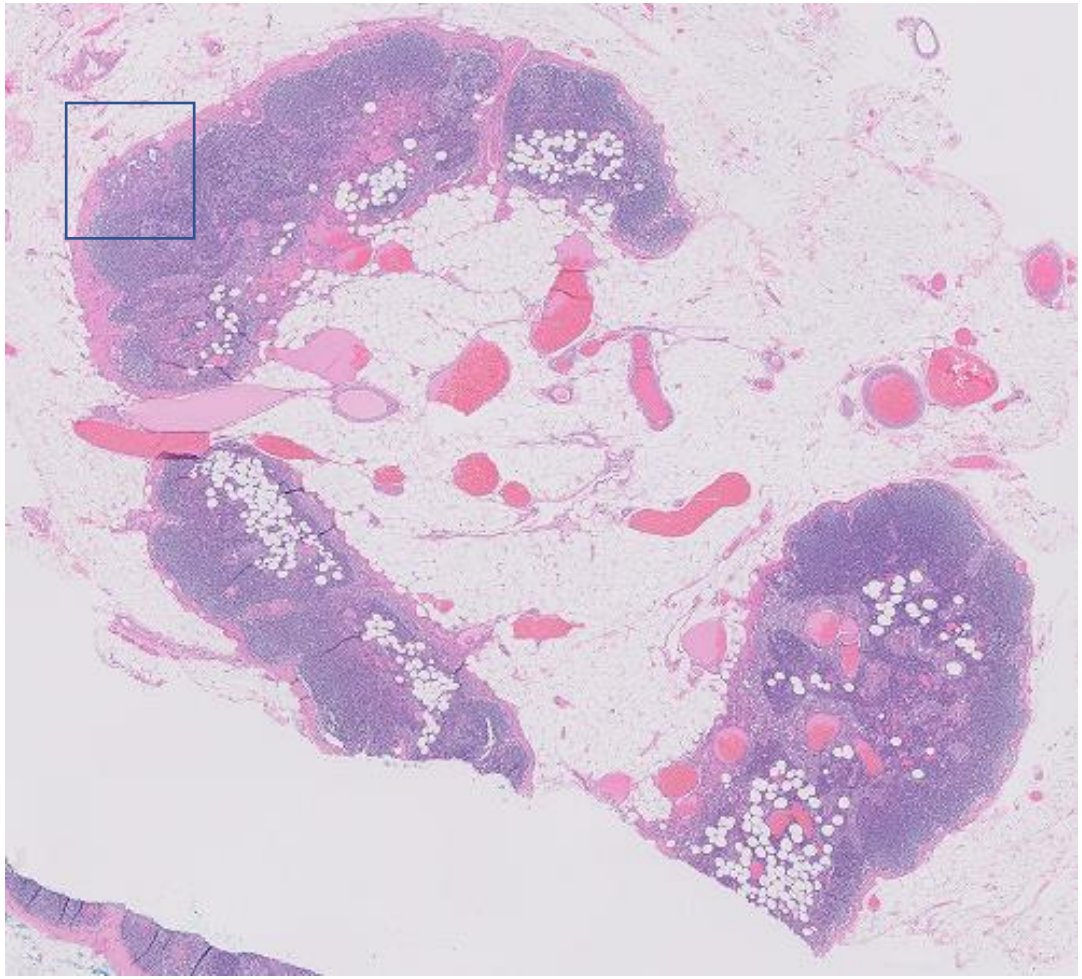
Immunophenotype component B

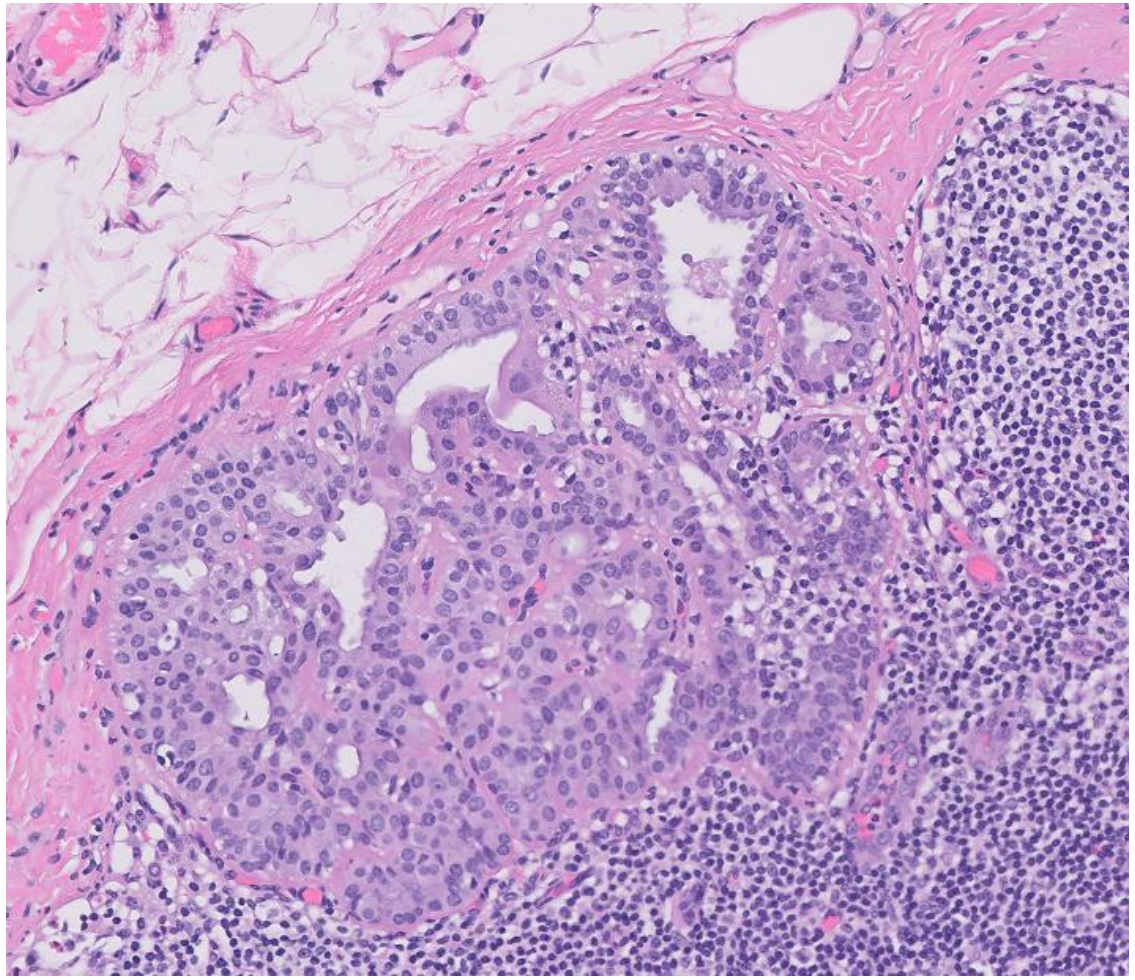
- p63, SMM and calponin highlight intact myoepithelial cell layers around the periphery of the lesion and along papillary fibrovascular cores; no proliferative expansion of myoepithelial cells is seen
- ER shows patchy positive staining
- HER2 is not overexpressed (1+)
- CK5/6 variably stains myoepithelial cells and epithelial cells, providing no support for conventional low-grade ductal atypia





Smaller lymph nodes





Smaller lymph nodes

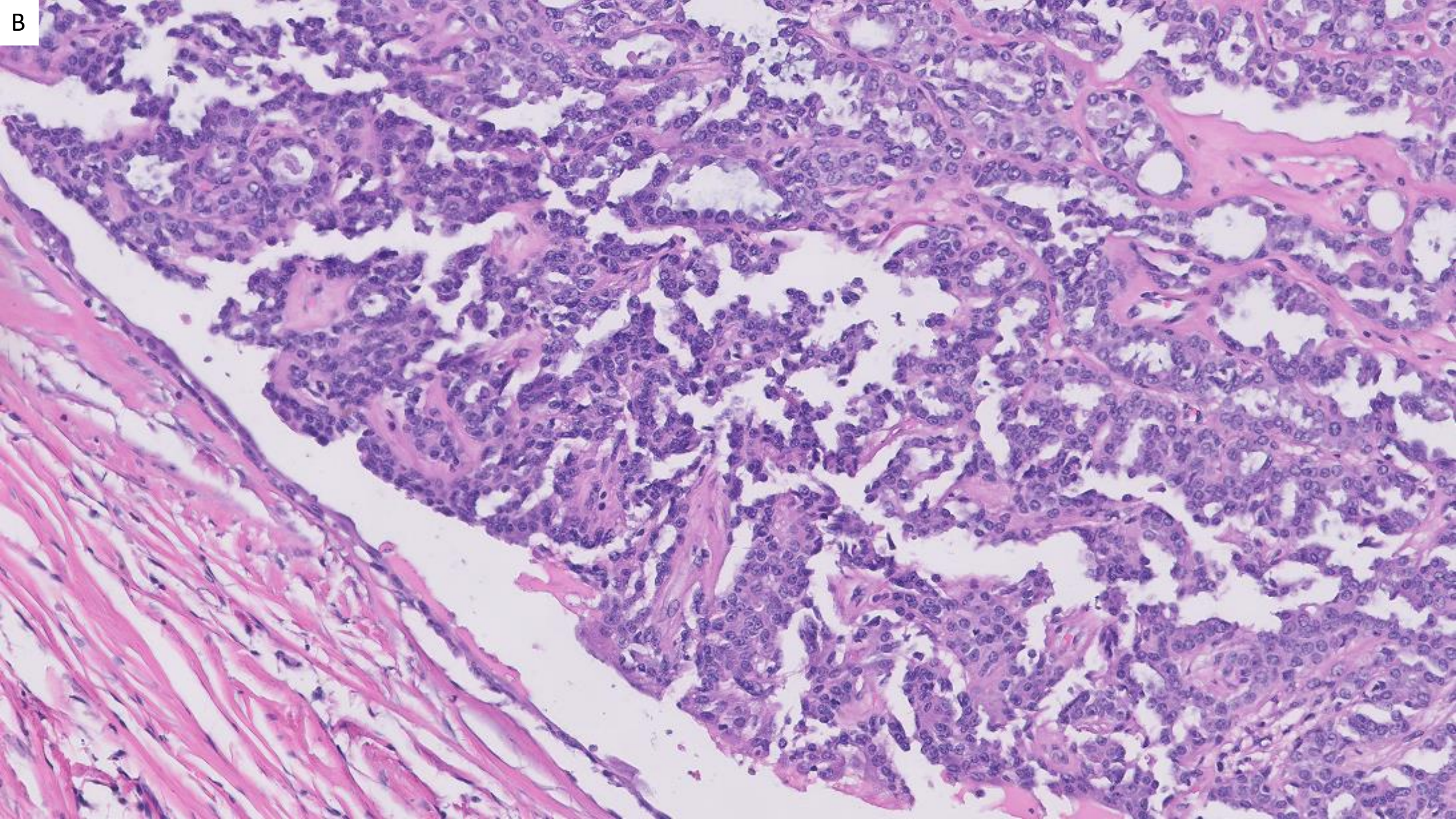
Differential diagnosis

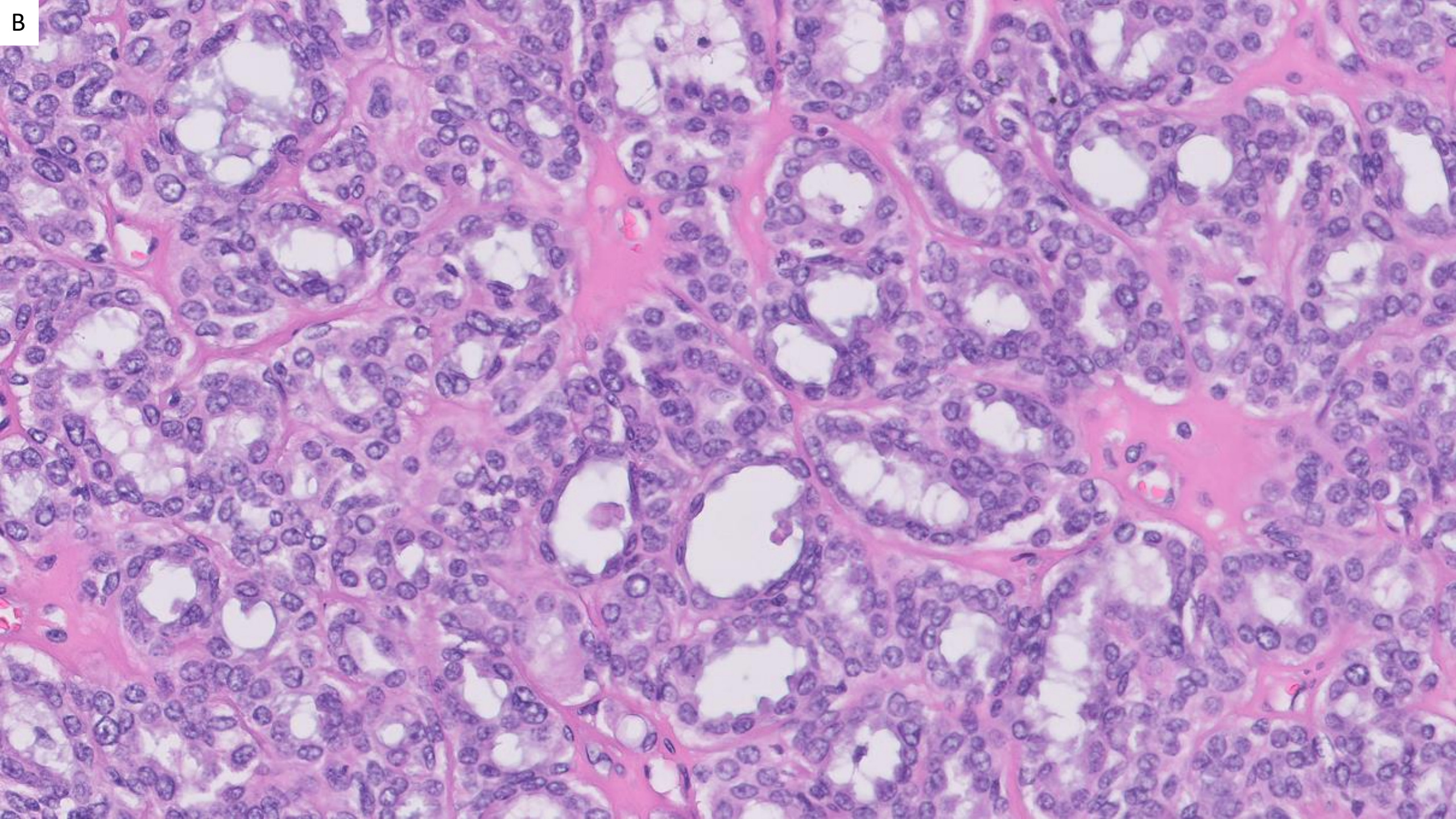
- Hidradenoma vs mucoepidermoid carcinoma

- Ancillary studies

  Fluorescence in situ hybridization for MAML2 rearrangement: Negative

  RNA-based next-generation sequencing for fusion testing (Fusion-STAMP): Negative for gene rearrangements


B


B

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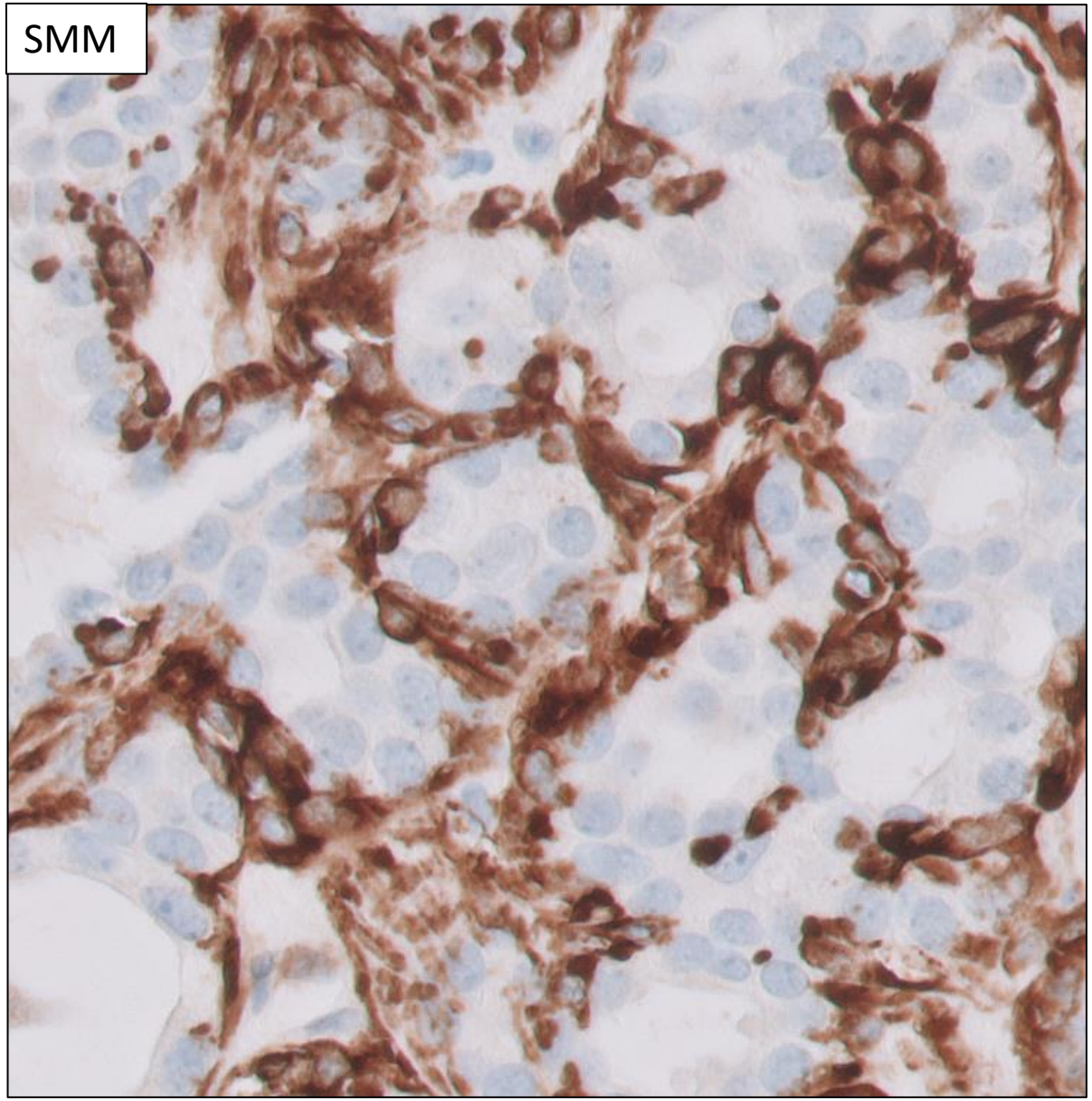
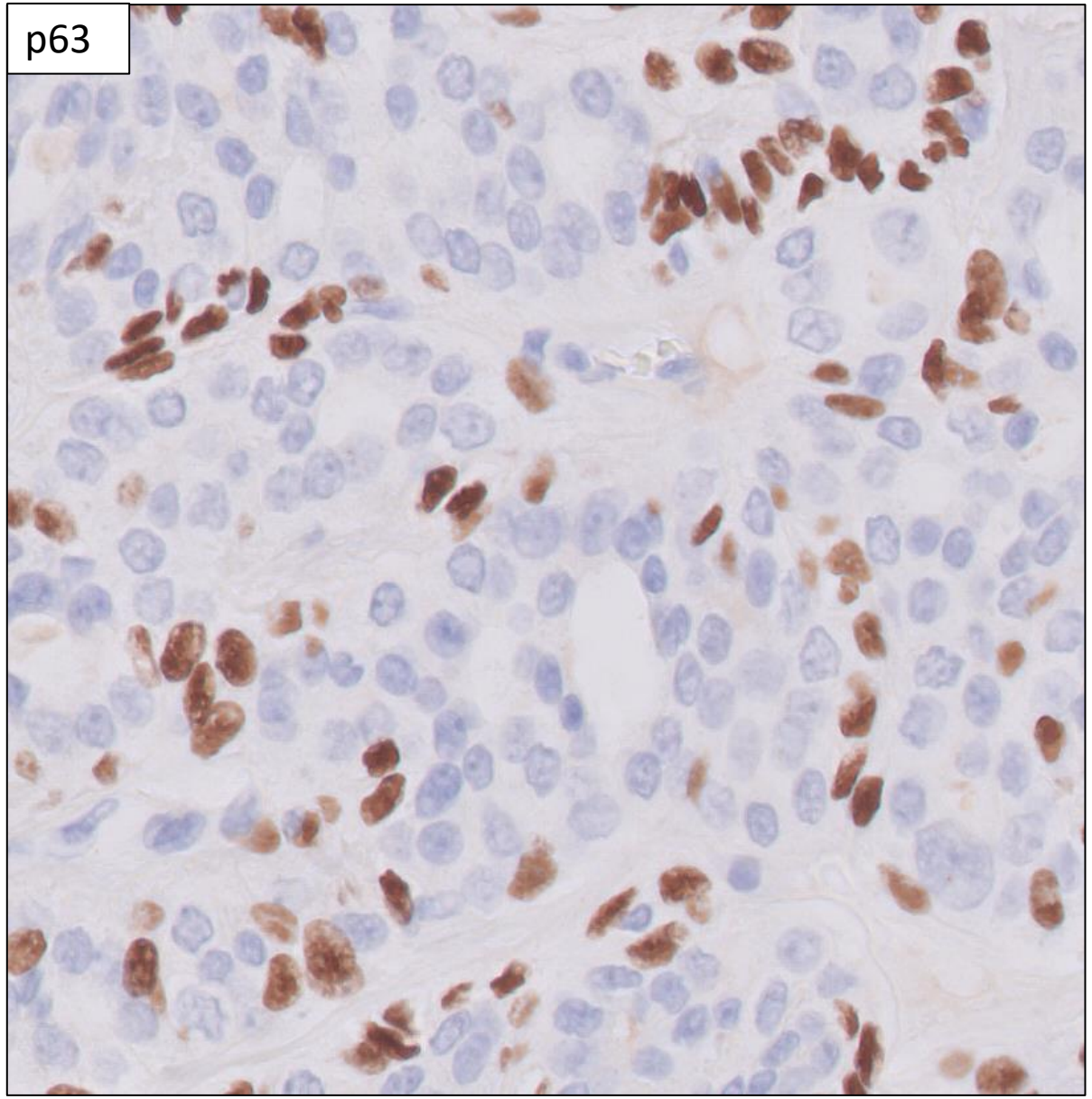
SMM



p63

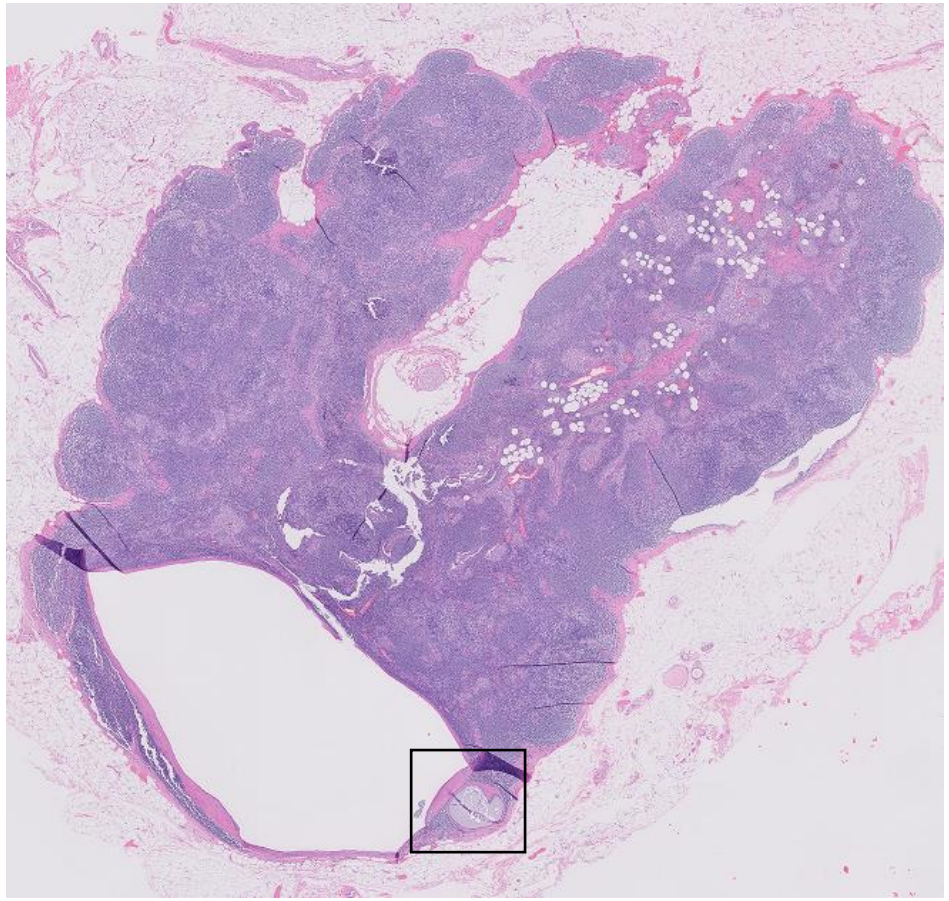


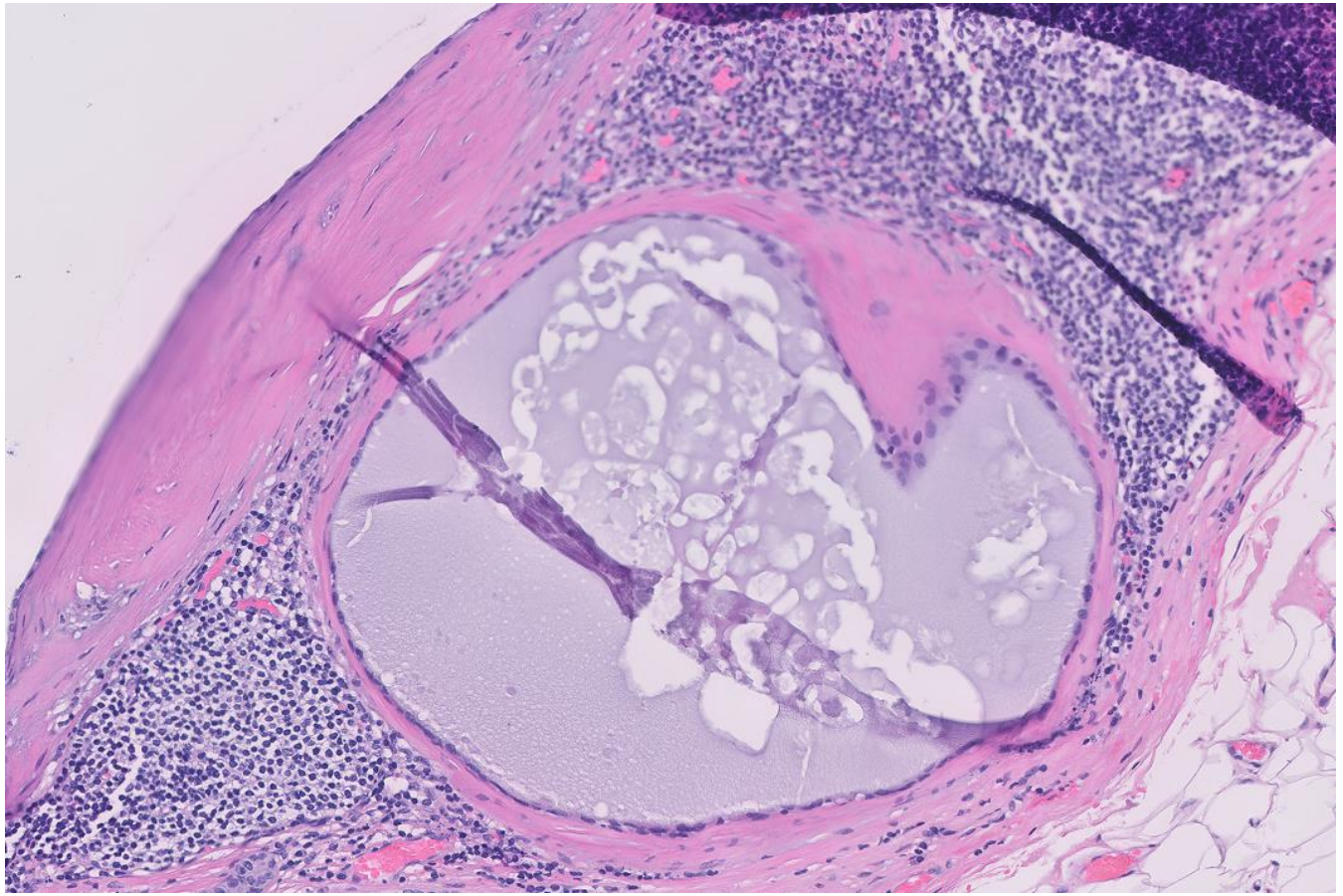
Diagnosis

- Intranodal papilloma arising from benign mammary-type glandular inclusions in axillary lymph node

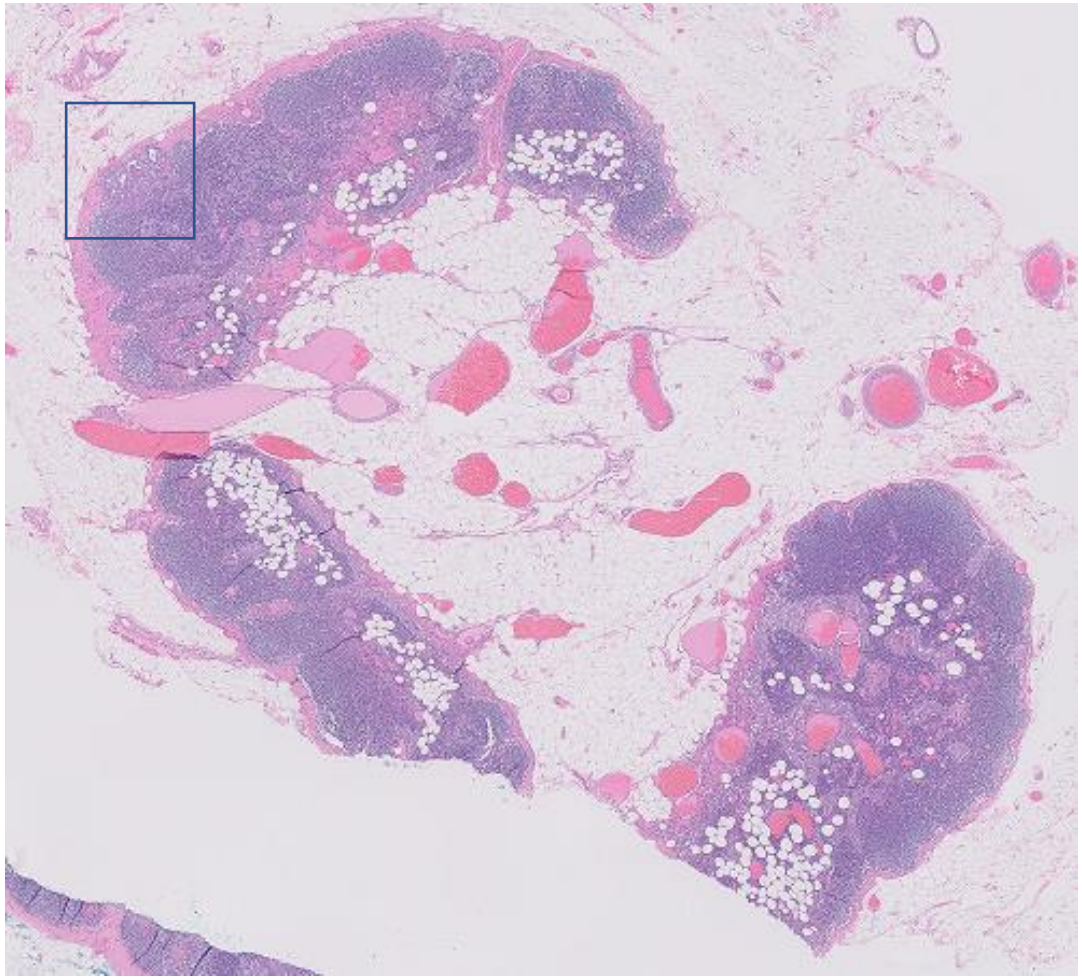
Final diagnosis

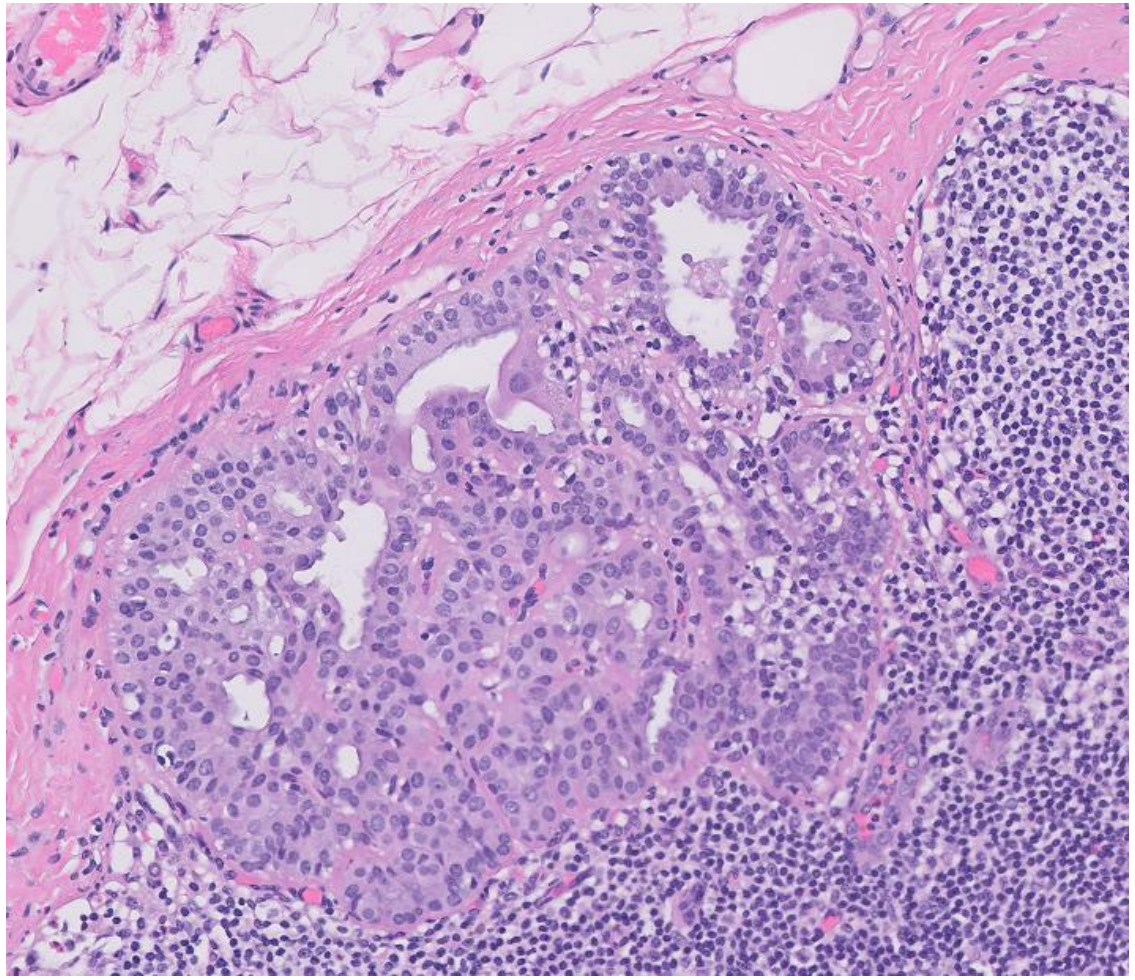
- Mixed papillary and squamoid/mucinous tumor, favor arising in benign epithelial inclusion (see comment)





Smaller lymph nodes





Smaller lymph nodes

Lymph node inclusions

- Epithelial inclusions
  - Mammary-type glandular inclusions
  - Mullerian-type glandular inclusions
  - Squamous inclusions
  - Mixed glandular-squamous inclusions.

  Diagnostic pitfalls: metastatic mammary carcinoma, or metastatic adenocarcinoma of another site, such as the gynecologic tract.

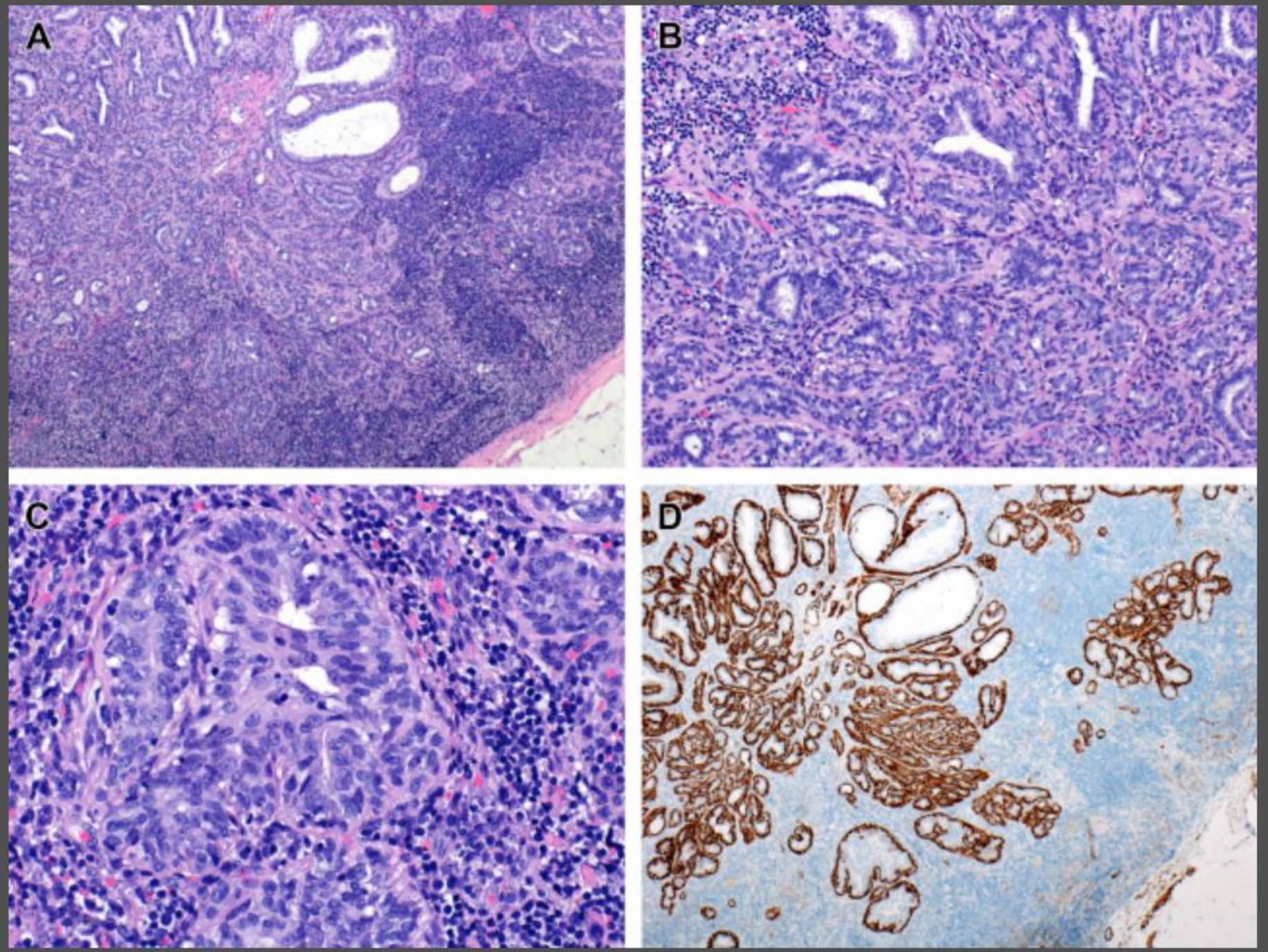
- Non-epithelial inclusions: Nevi

  Diagnostic pitfalls: metastatic melanoma or less commonly metastatic spindle cell (sarcomatoid) mammary carcinoma

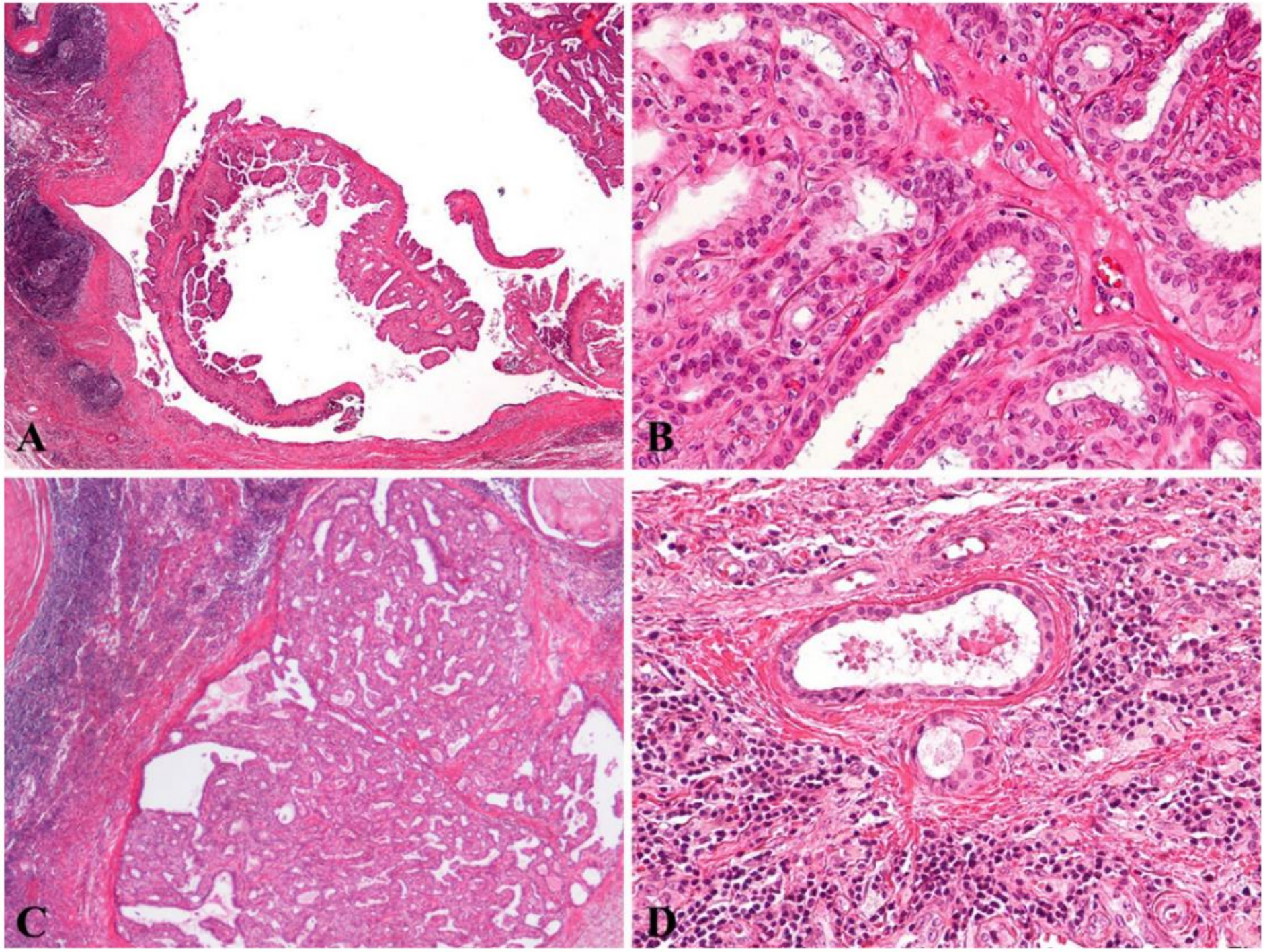
Cimino-Mathews A. Surg Pathol Clin. 2018 Mar;11(1):43-59.

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

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



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



Dzodic R, et al. Diagn Pathol. 2010 Mar; 5:17.

Nodal hidradenoma?

- Nodal hidradenomas without a cutaneous or other primary have been rarely reported in the literature and shown a benign clinical course
- Theorized to arise from benign lymph node inclusions
- The lack of detectable MAML2 translocation may disfavor the diagnosis of hidradenoma. However, it is uncertain whether a hidradenoma arising in this unusual context would share the pathogenesis of other reported tumors
- Other less likely possibilities: Metastasis from an undetected primary, either breast or elsewhere
- Given the association with the papilloma component in the same node, it is favored that the two components are related, with one population arising from the other or both arising from the same origin. Both components show bland cytomorphology; no high-grade features are identified.

Take Home Messages

- Epithelial inclusions with associated florid proliferation can occur in a lymph node
- These cases should be evaluated with cautions, not to mistake the findings as metastatic carcinoma, especially in a core biopsy
- Perform myoepithelial markers if the findings could represent mammary-type glandular inclusions
- If the findings are inconclusive, we could recommend obtaining a bigger sample (e.g. excisional biopsy)
- Mammary-type glandular inclusions can be involved by DCIS and this possibility should be excluded

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