FEB 2021 DIAGNOSIS LIST

21-0201: glycogen rich clear cell carcinoma (breast; breast path)
21-0202: biomarker interpretation (breast; breastpath)
21-0203: invasive lobular carcinoma with extracellular mucin (breast; breast path)
21-0204: squamous metaplasia of lactiferous duct (SMOLD) (breast; breast path)
21-0205: cystic neutrophilic granulomatous mastitis (breast; breast path)
21-0206: mucoepidermoid carcinoma (breast; breast path)
21-0207: hidroadenoma (breast; breast path)

Disclosures
February 1, 2021

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

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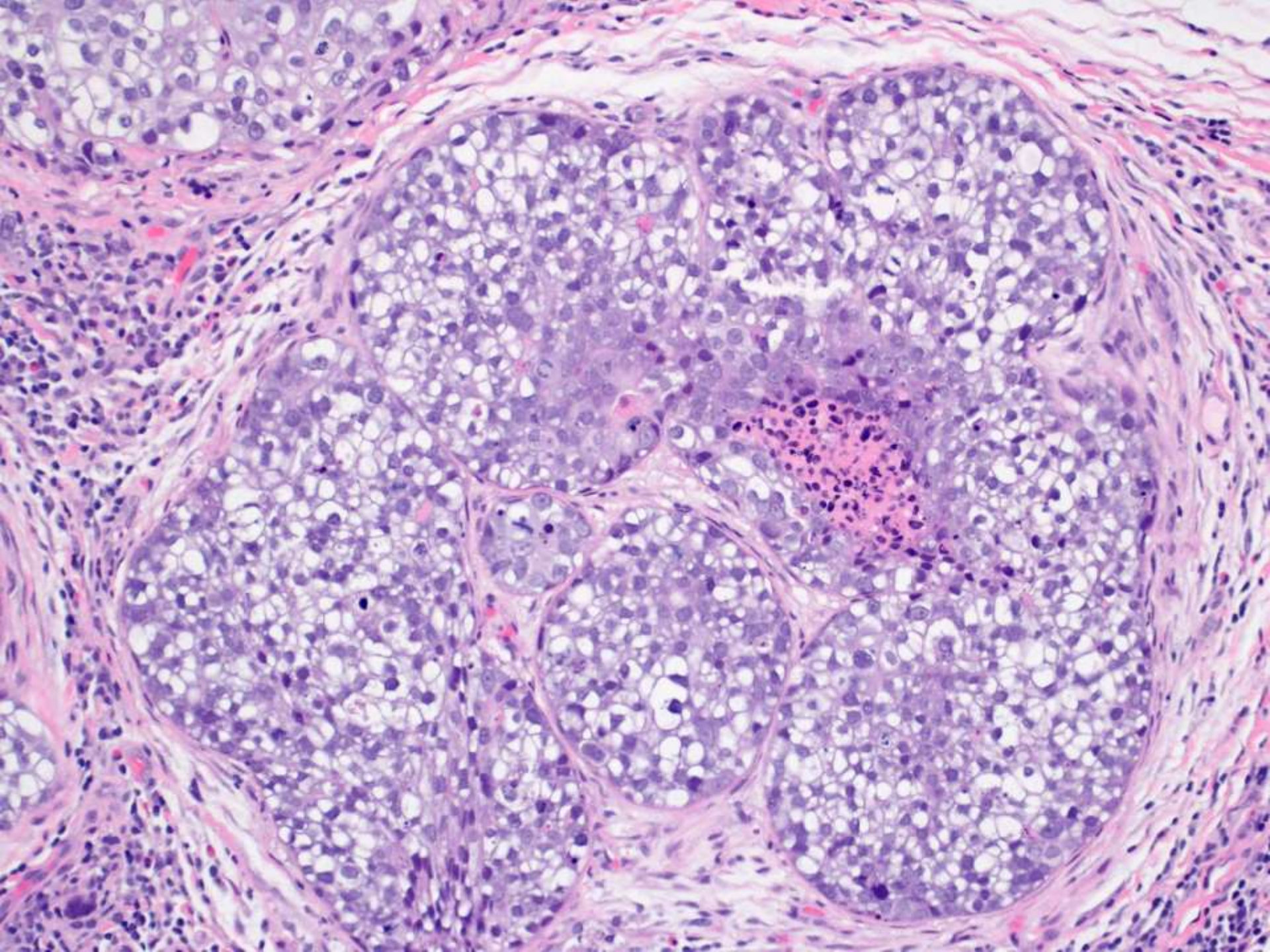
Megan Troxell, MD

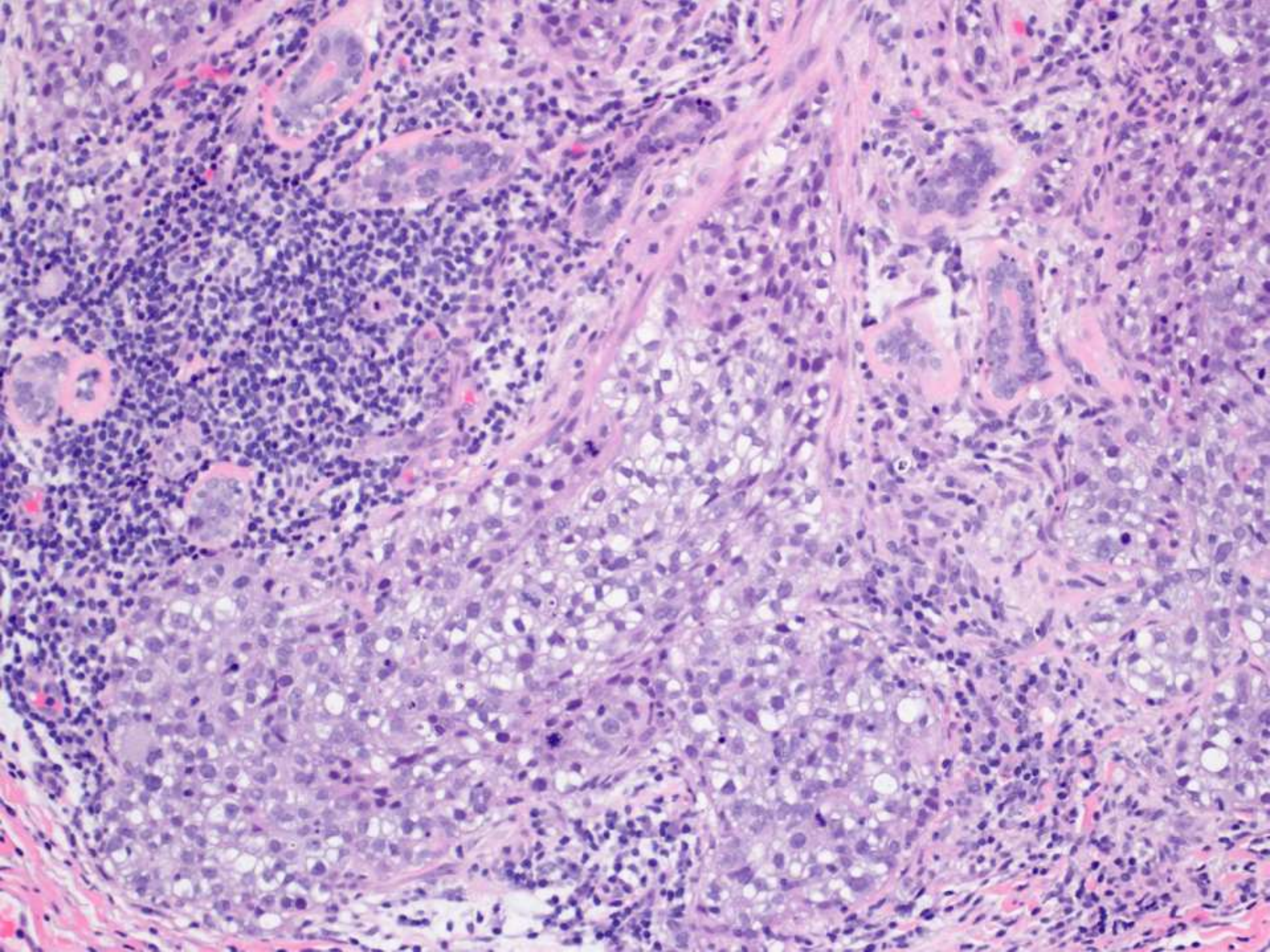
Ankur Sangoi, MD

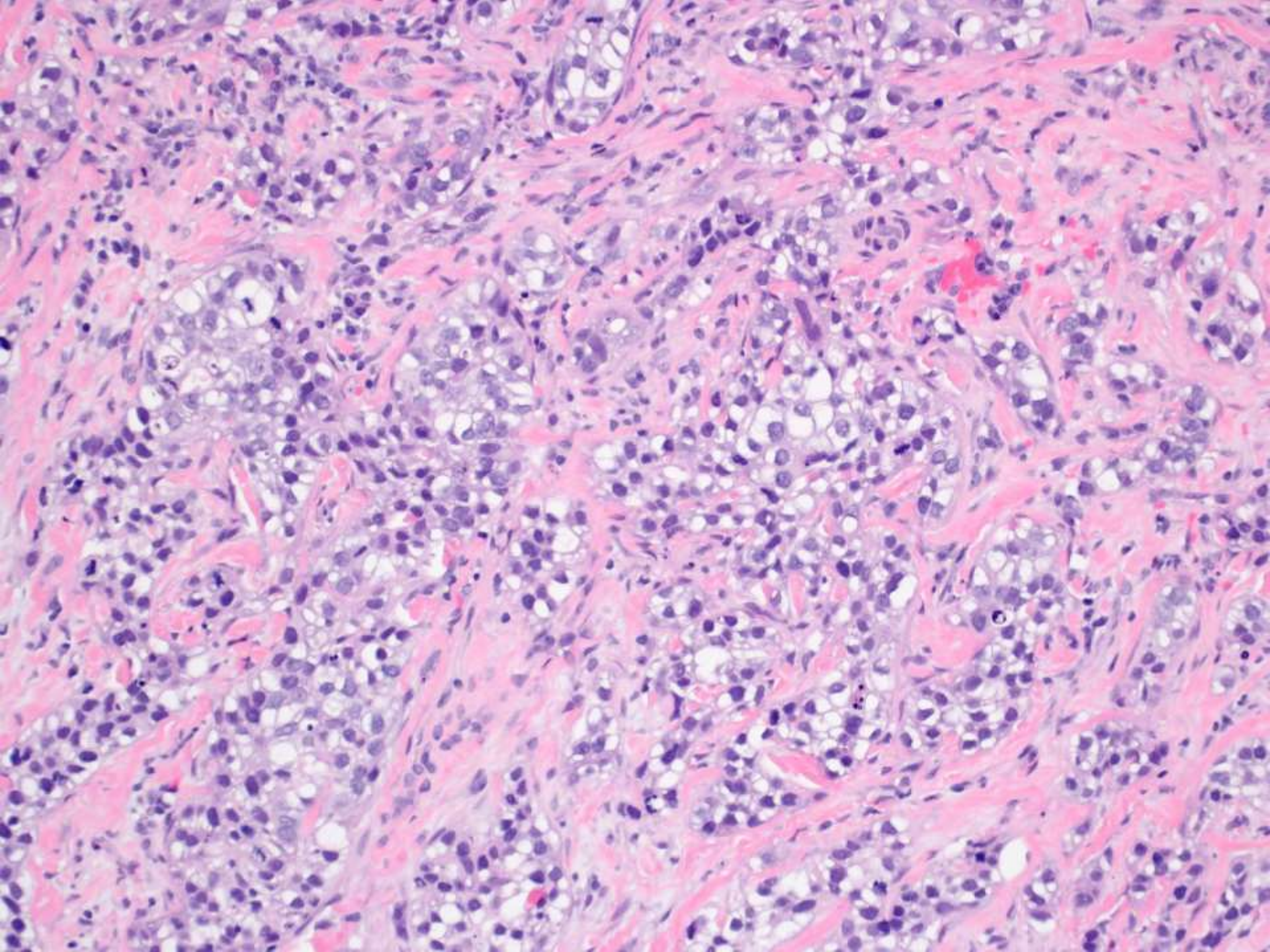
21-0201

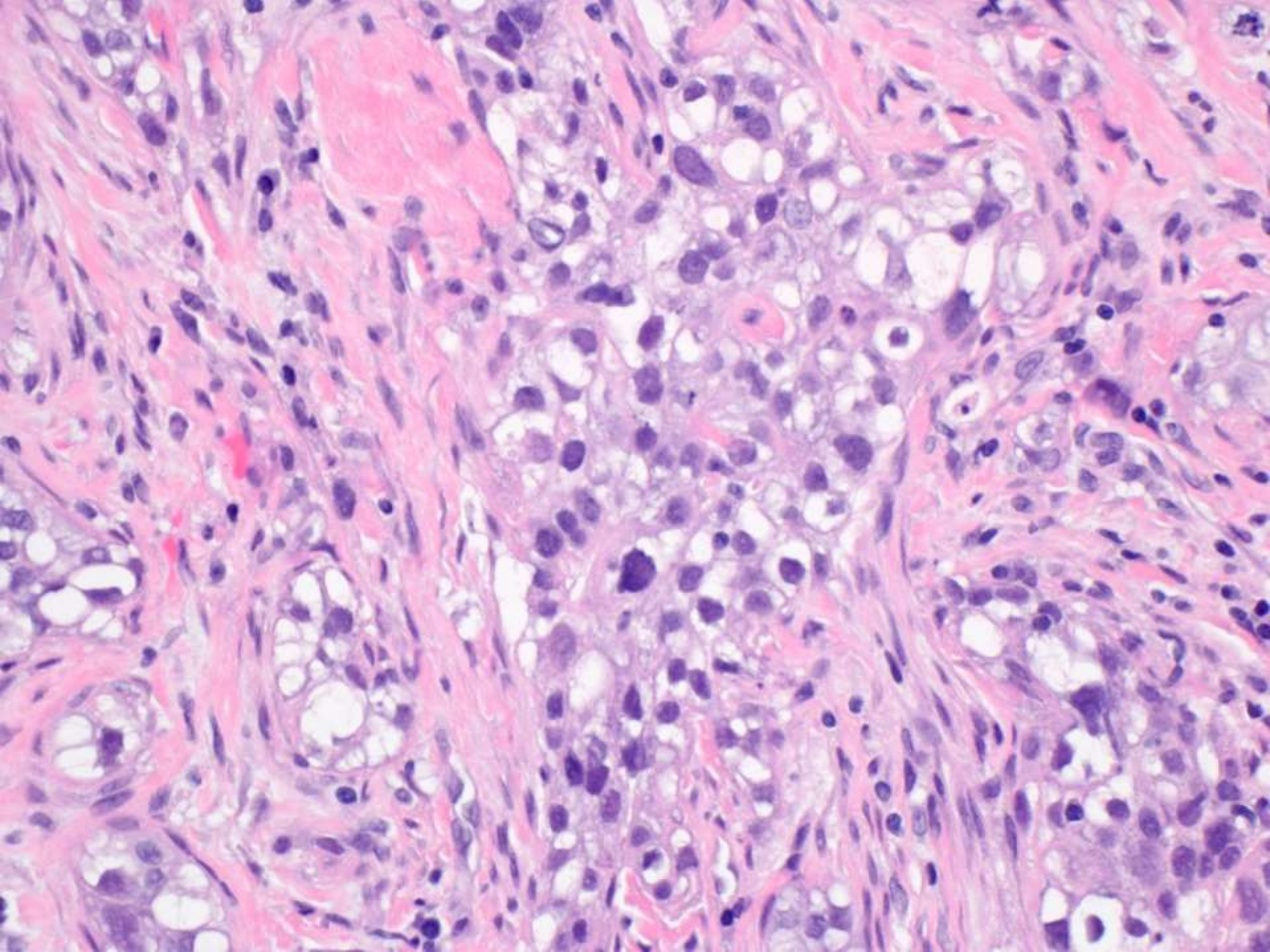
Megan Troxell; Stanford

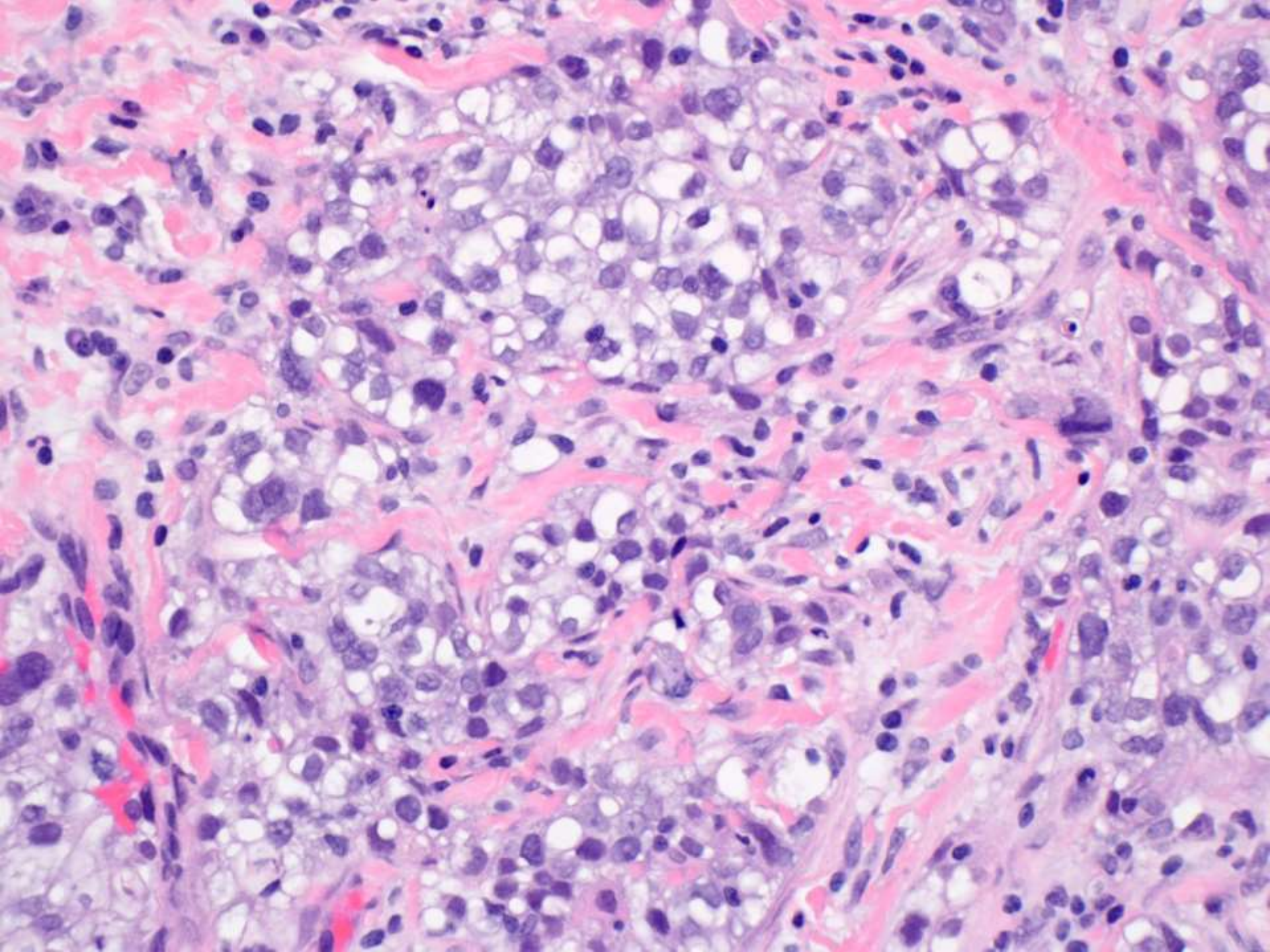
35-year-old F with breast mass.











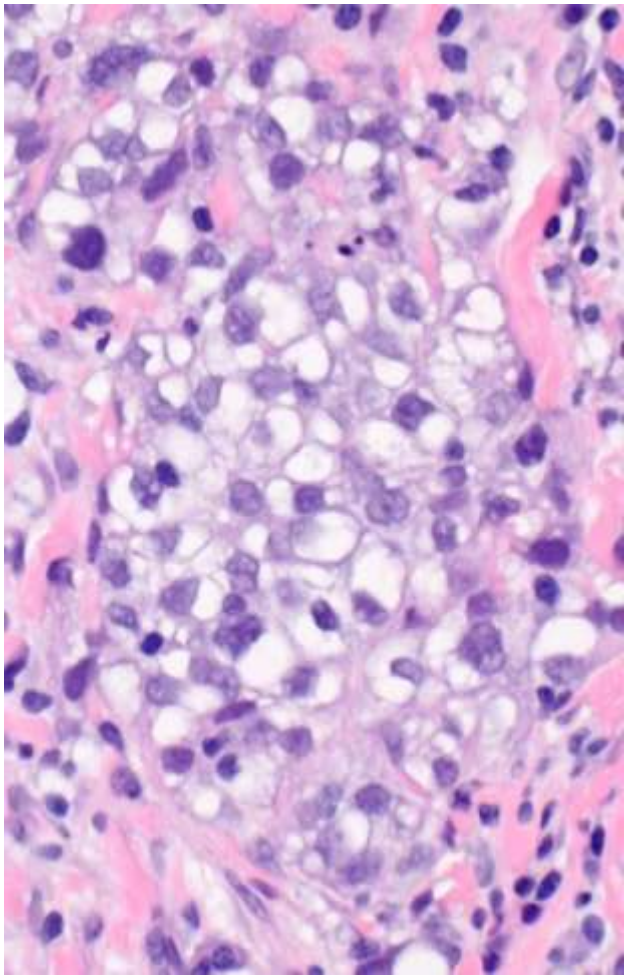
Glycogen Rich Clear Cell Carcinoma

- 0.01-3% of breast cancer
- Radiology: mass or solid/cystic mass, +/- calcification
- WHO ‘19 IBC-NST “special morphologic pattern”
  - Insufficient clinical evidence for designation as special type
- Abundant clear cytoplasm that contains glycogen
- Polygonal cells with well-defined borders
- Sheet-like, nested, corded
  - Rarely tubular, lobular (papillary)
- Prognosis?
  - Aggressive vs similar to IBC-NST of same grade/stage

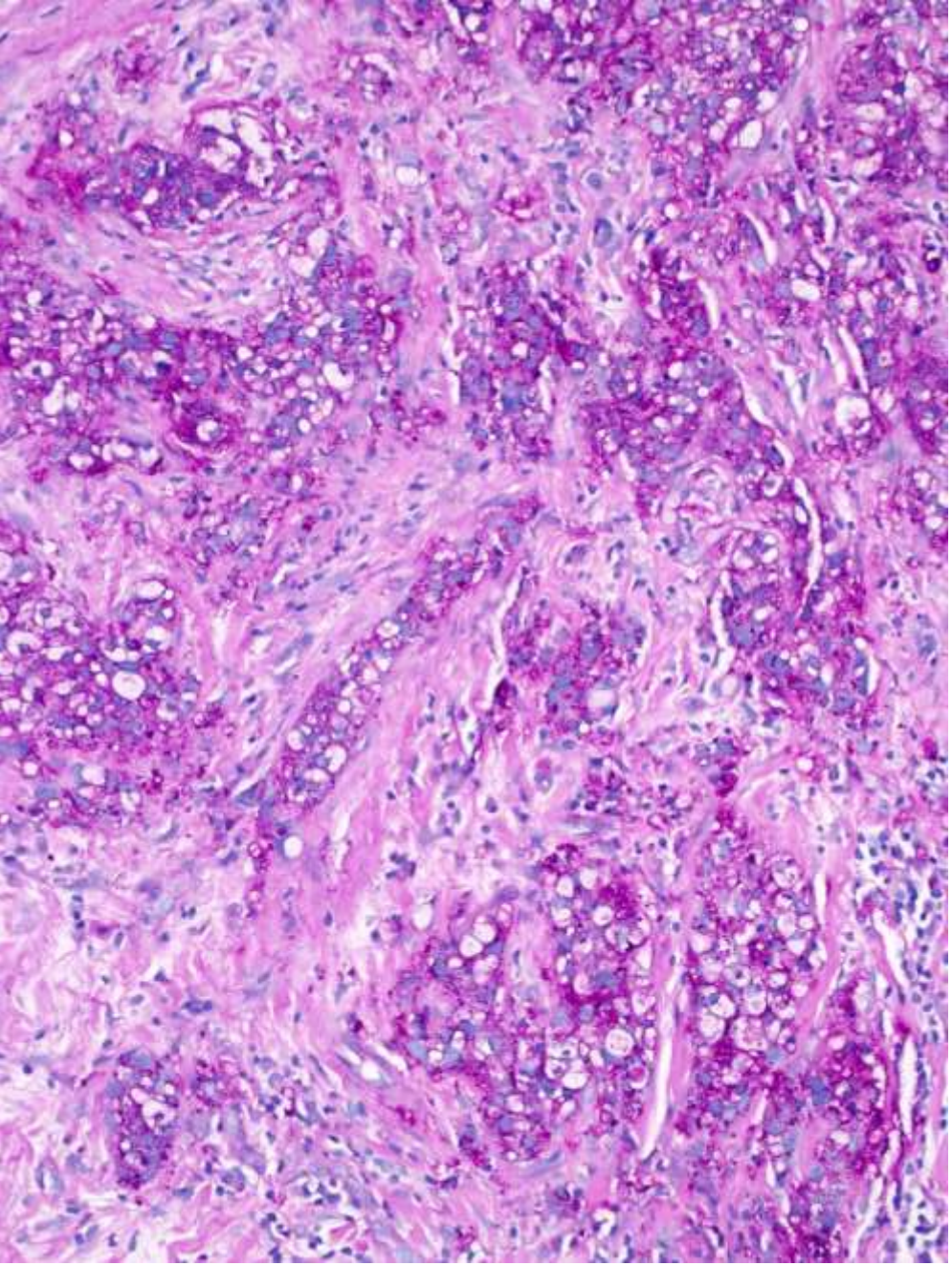
Vranic S. AIMM. 2020;28:655–60

Glycogen Rich Clear Cell Carcinoma

- Not all clear cells are glycogen-rich, ddx:
  - Lipid rich
  - Sebaceous
  - Secretory
  - Histiocytoid (apocrine)
  - Squamoid with clear cells
  - Myoepithelial
  - Metastasis
- Thus, clear cells and demonstration of glycogen required for diagnosis
  - PAS+, PASd-

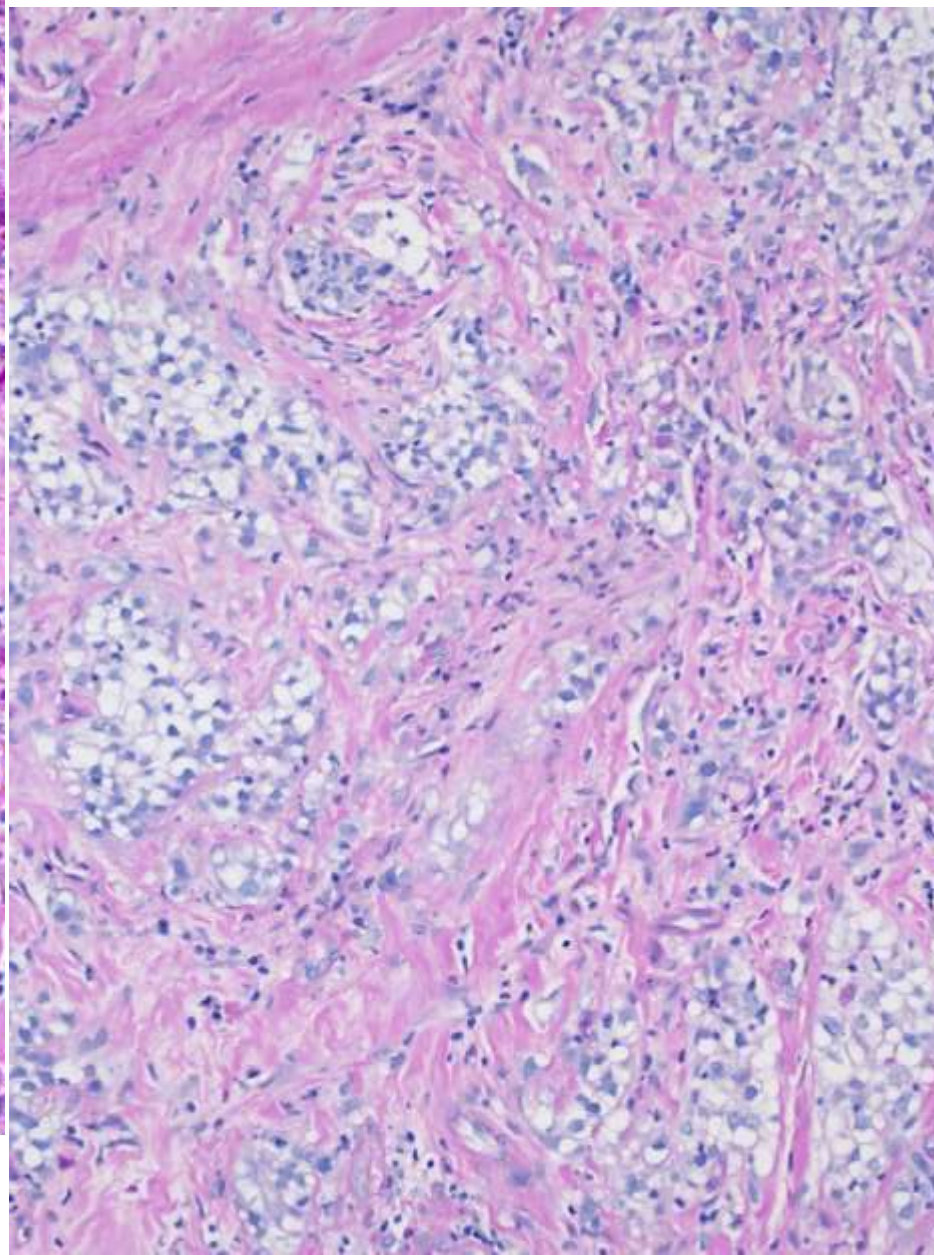


Vranic S. AIMM. 2020;28:655–60



PAS

PASd



Glycogen Rich Clear Cell Carcinoma

Phenotype	GRCC (% cases +)	This case
ER	35-50%	Negative (0)
PR	0-30%	1+ 10%
HER2	7-45% highly variable in literature	Negative (0)
Ki-67		50-60%
Other	HepPar1+	S100: Negative
Molecular (of 5 cases)	1. *BRCA2, PIK3R1, PTEN* loss *2. TP53, CDKN2A, PTEN,* *3. TP53, BCOR, PTEN* loss	

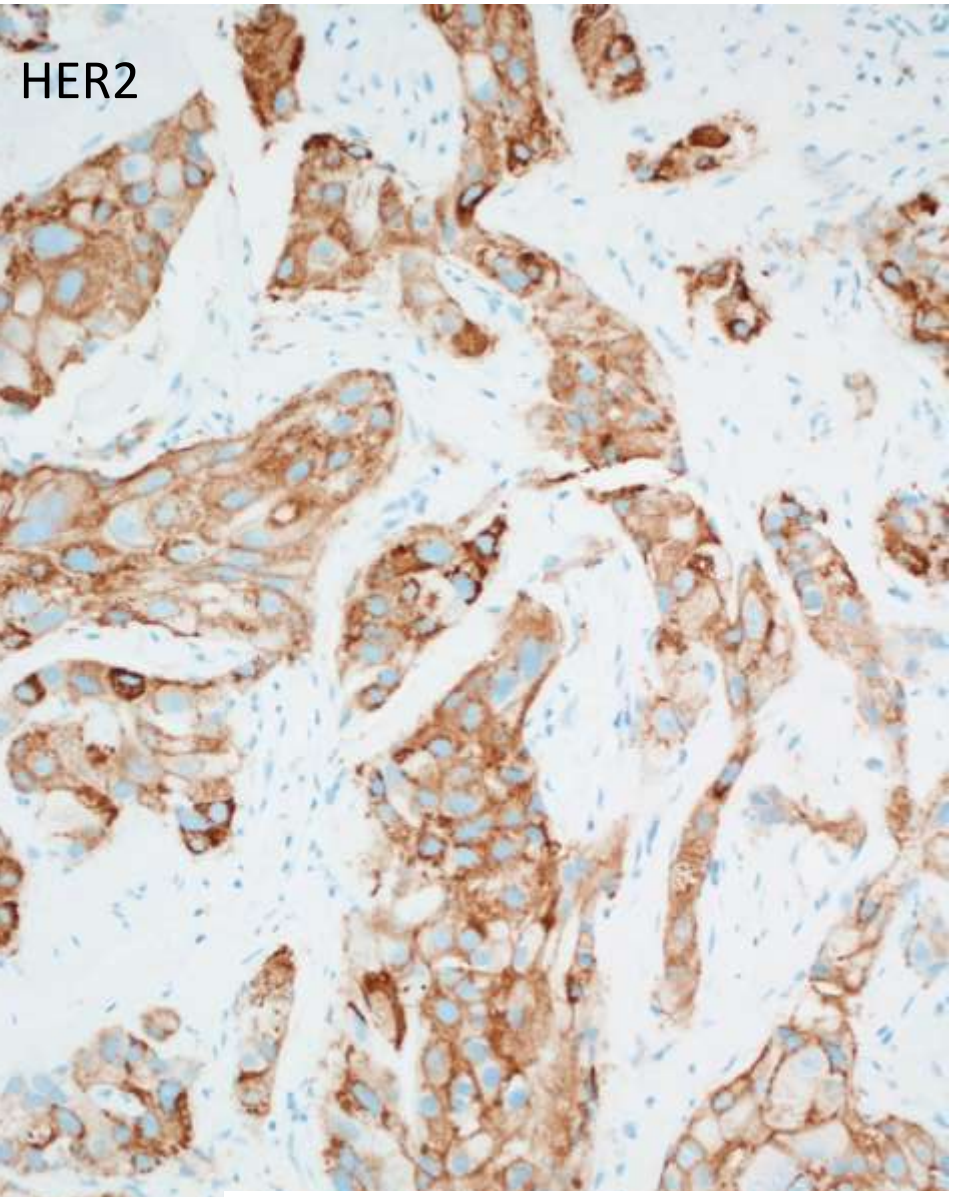
Skenderi. Breast J. 2020;26:1781–83
Vranic S. AIMM. 2020;28:655–60

21-0202

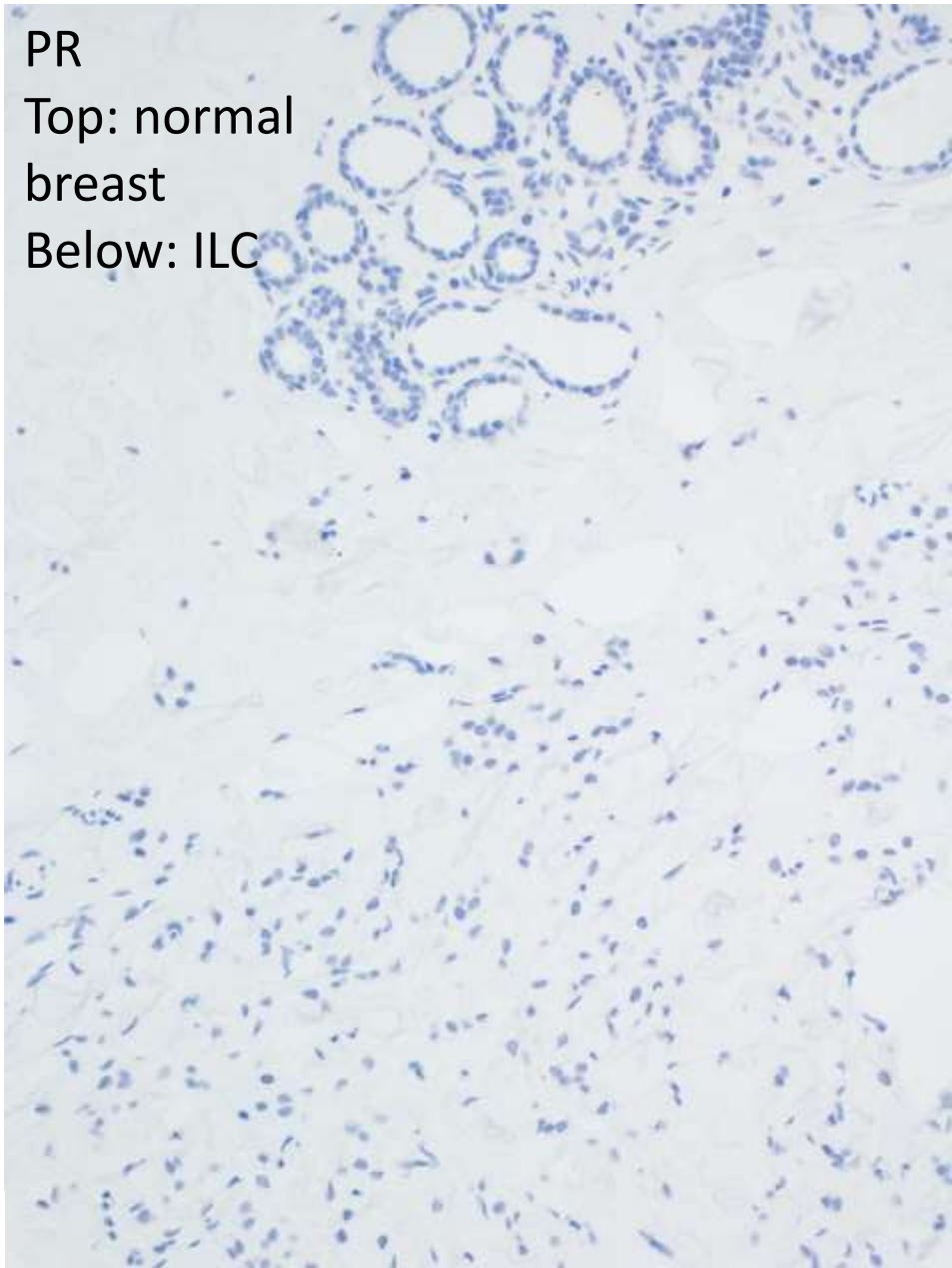
Megan Troxell; Stanford

Woman with invasive breast cancer. How to interpret biomarkers?

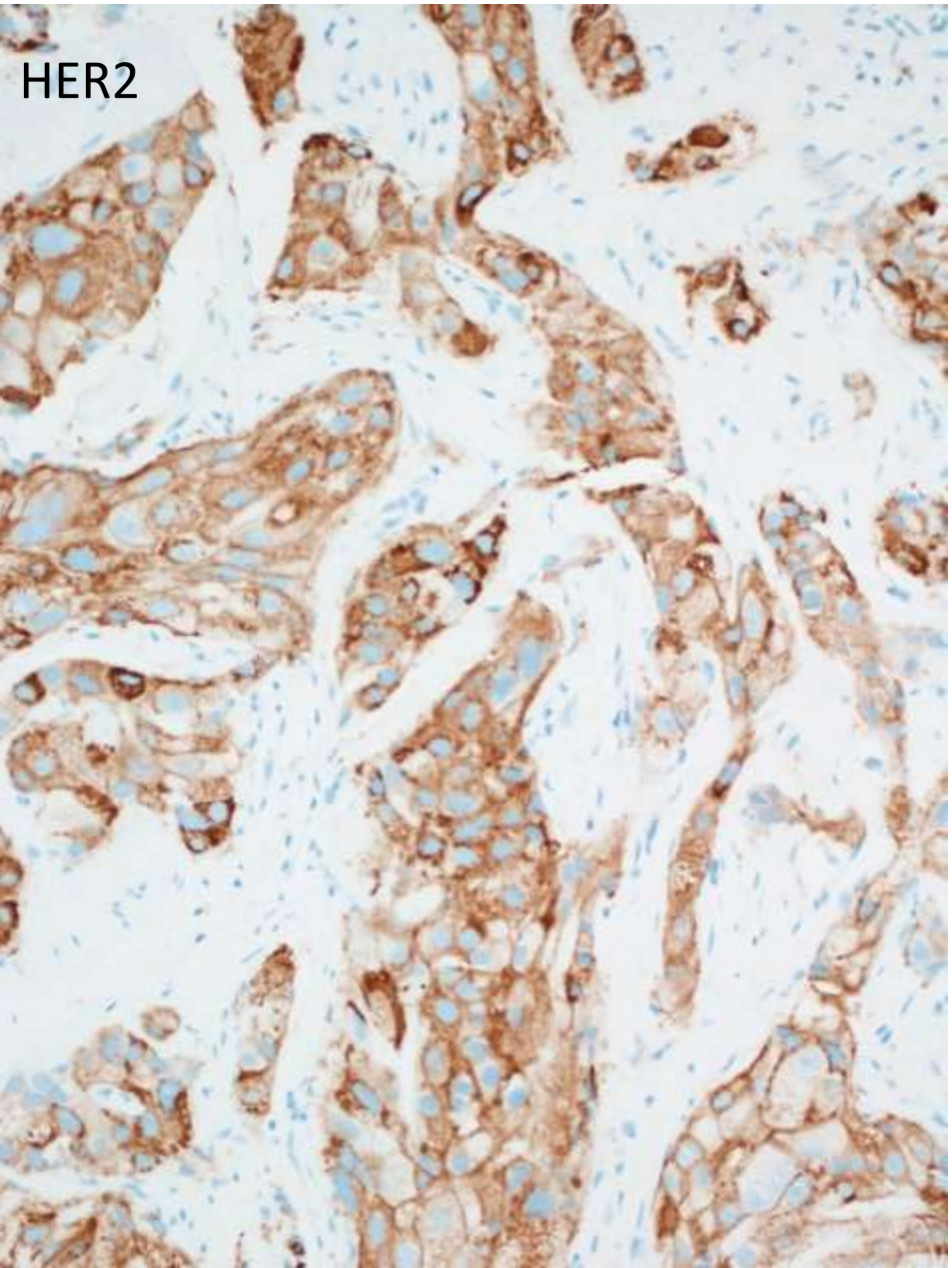
What happened to these breast biomarkers?

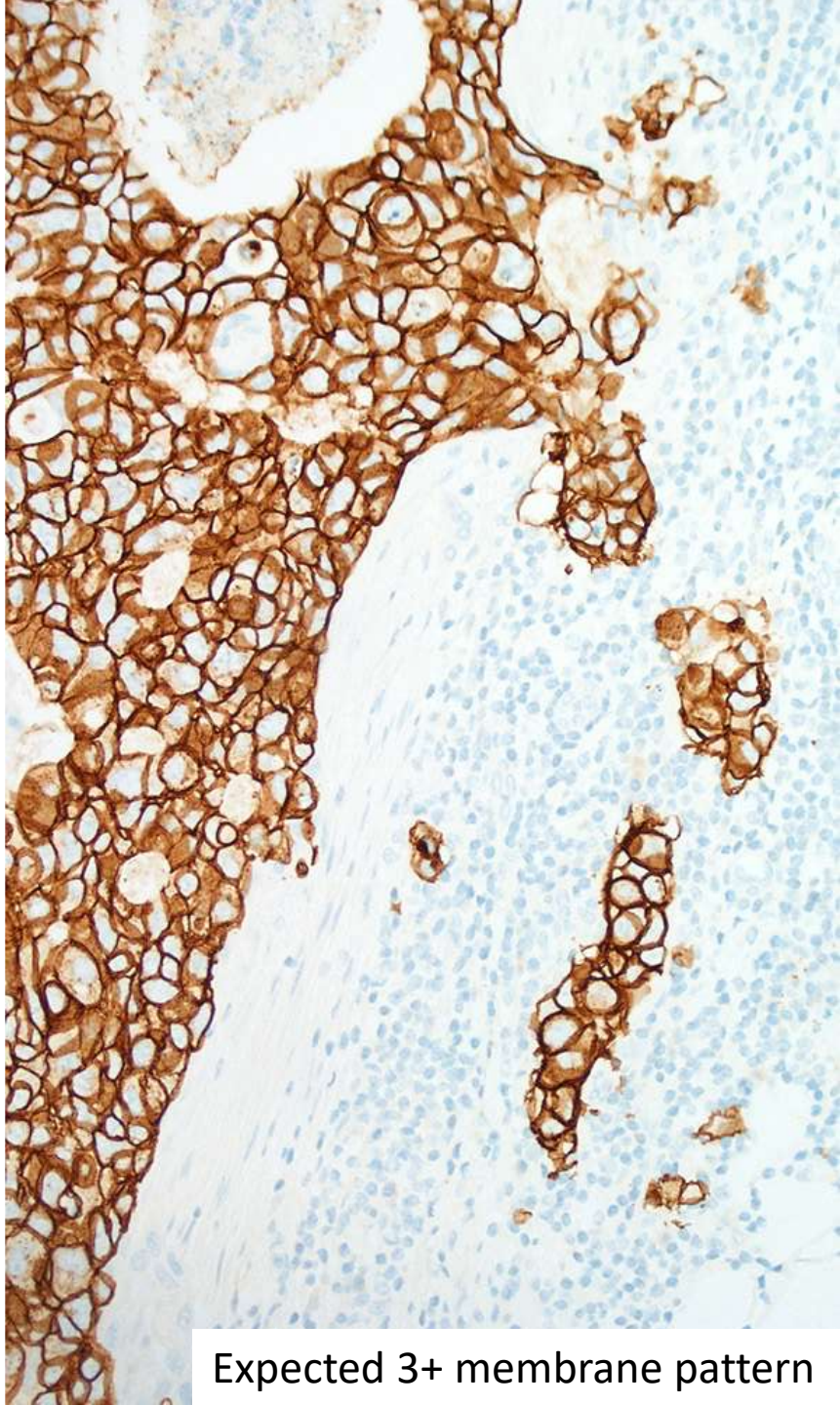


Separate cases: not the same tumor



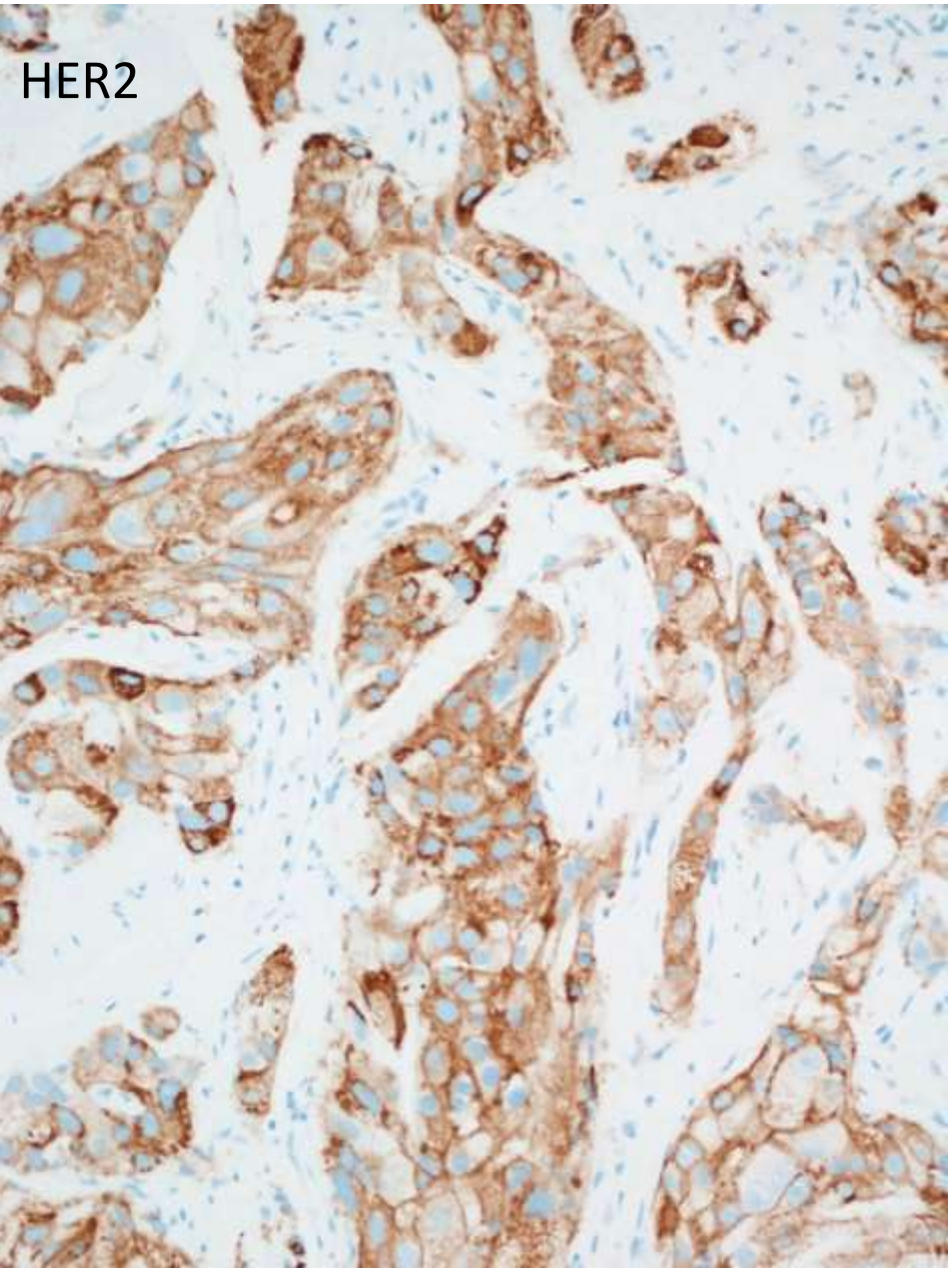
Granular cytoplasmic

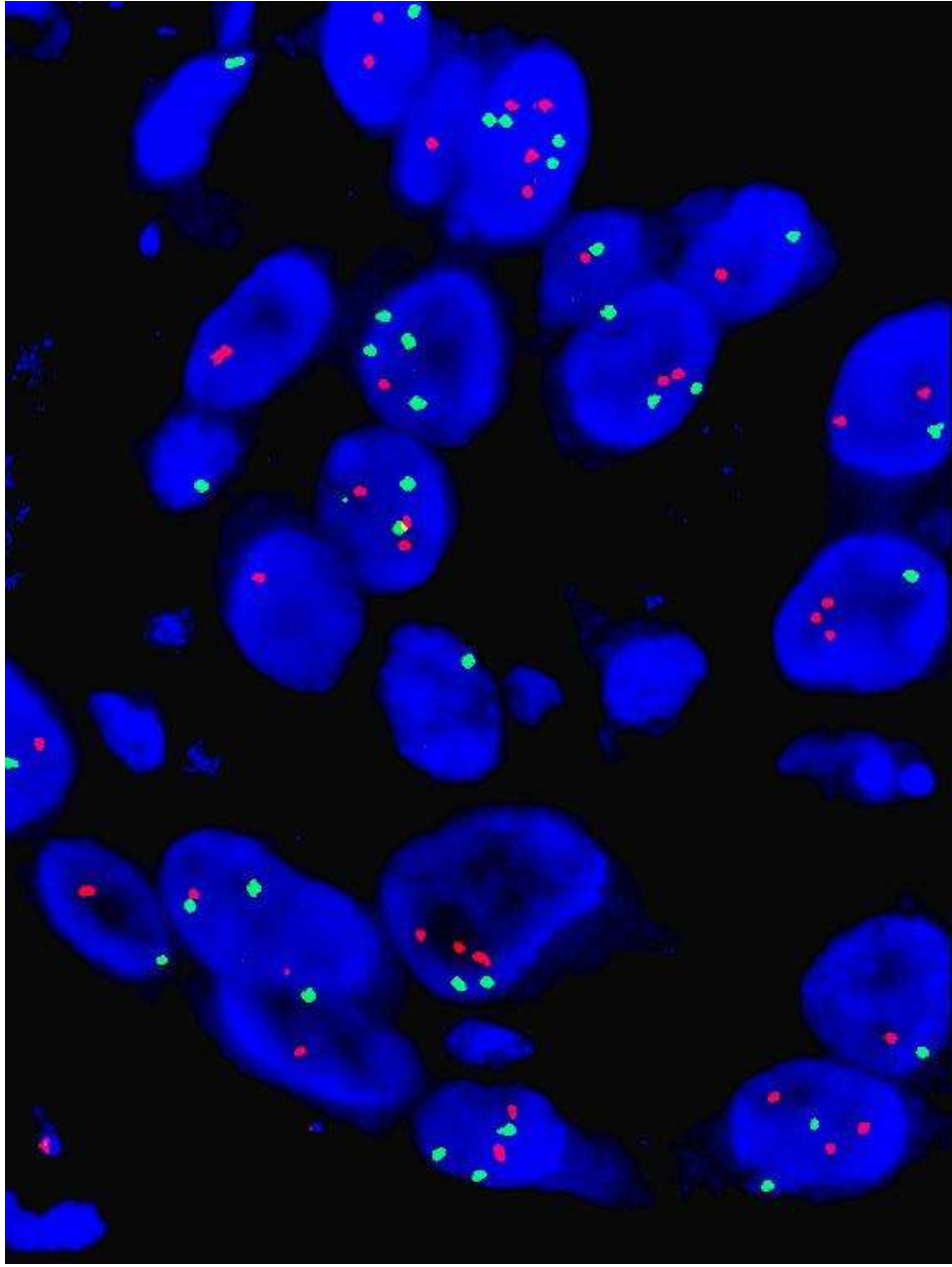




Expected 3+ membrane pattern

Granular cytoplasmic





Her2 FISH negative

HER2 cytoplasmic

- Granular cytoplasmic
  - This case with granular eosinophilic cells
  - HER2 IHC “indeterminate”
  - HER2 IHC equivocal also OK
- Also in gastric, including benign epithelium

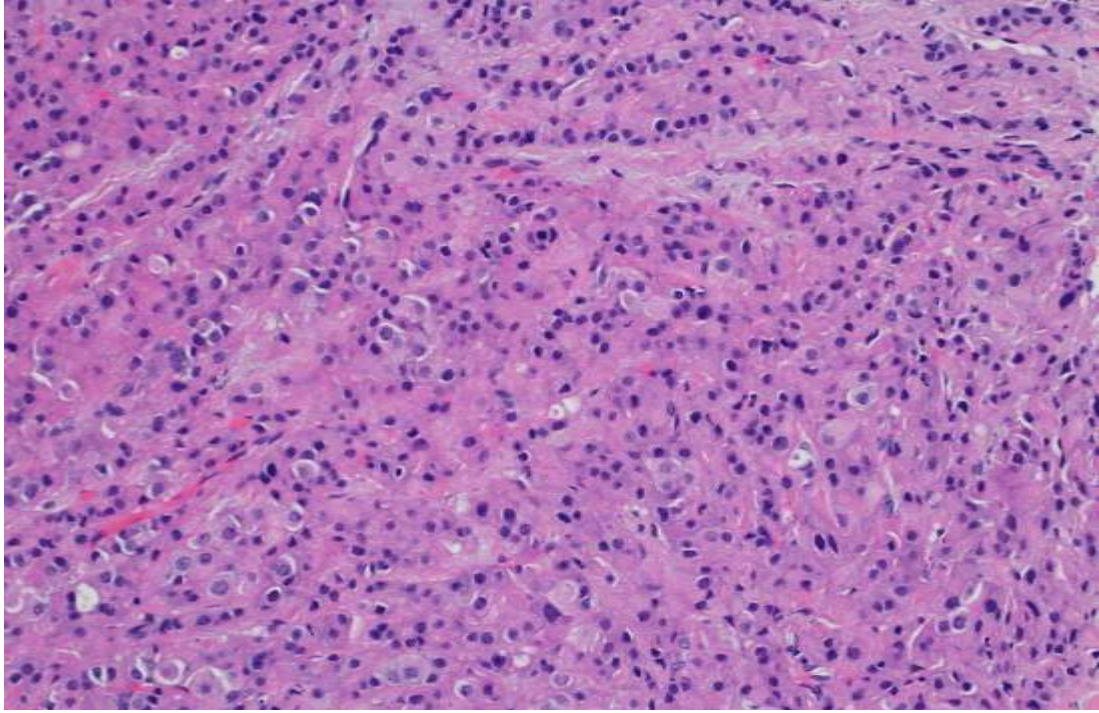
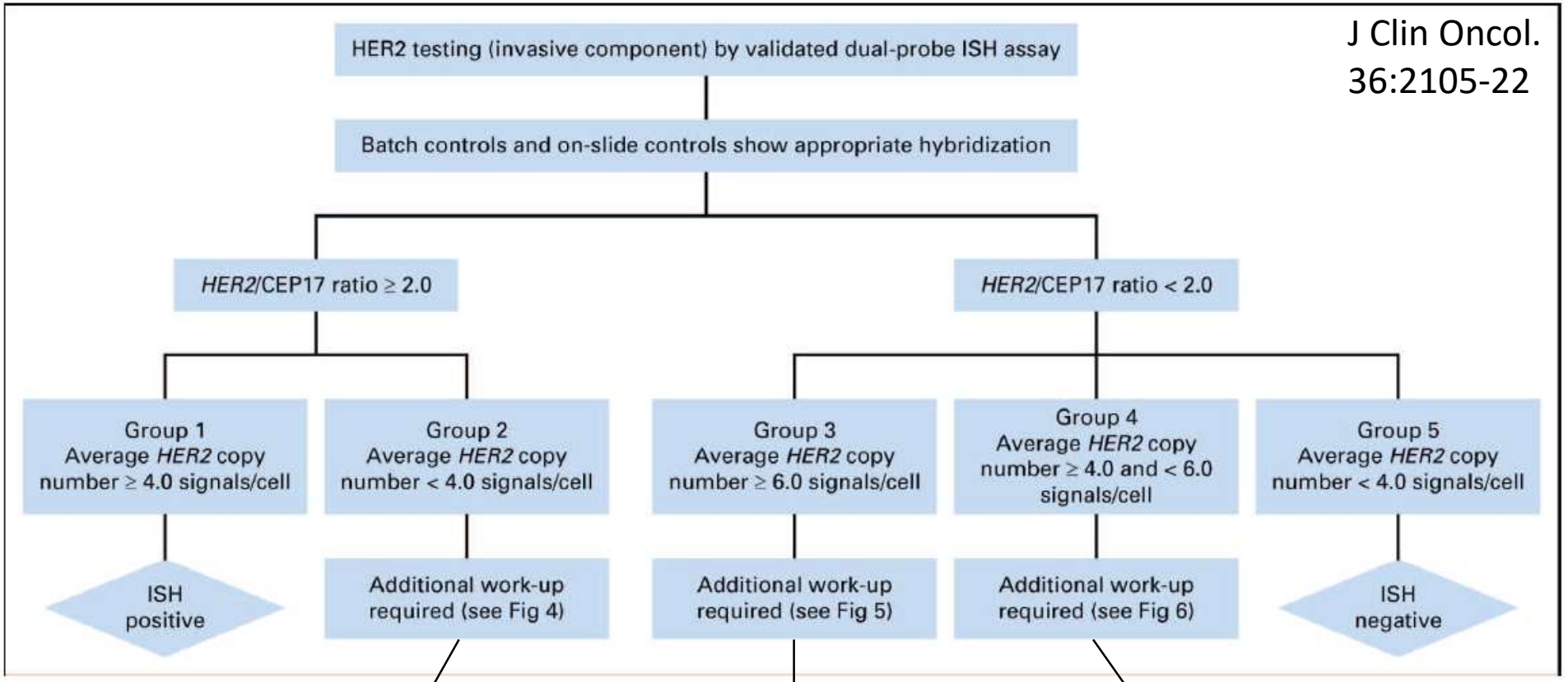


Table 7. IHC Interpretation Criteria

Review controls; if not as expected, test should be repeated
More tha 10% of tumor must show circumferential membrane staining for positive result*
Membrane staining must be intense and uniform
A homogeneous, dark circumferential (chicken wire) staining pattern should be seen
Ignore incomplete or pale membrane staining
Quantitative image analysis is encouraged for cases with weak membrane staining (1-2+) to improve consistency of interpretation
If cytoplasmic staining obscures membrane staining, repeat assay or do FISH
Reject sample if normal ducts and lobules show obvious staining
Reject sample if there are obscuring artifacts
Avoid scoring DCIS; score only infiltrating ductal carcinoma

CAP 2006 Her2 breast guidelines

2018 Her2 breast FISH simplified



J Clin Oncol. 36:2105-22

Require comments:

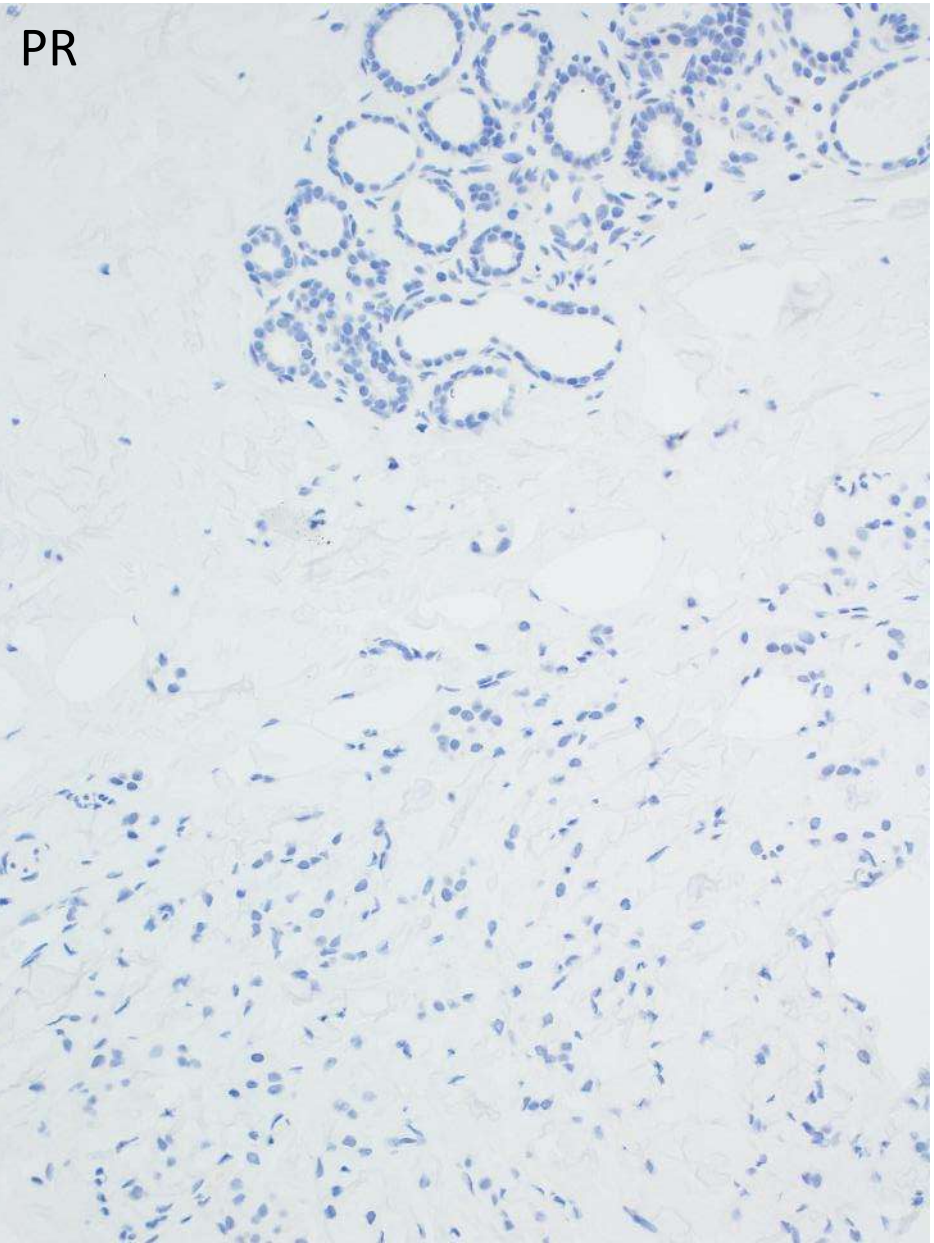
Group 2: Negative unless IHC 3+ "monosomy"

Group 3: POSITIVE unless IHC 0, 1+ "Co-amplified"

Group 4: Negative unless IHC 3+ "Equivocal"

Additional workup=IHC: 0,1+ final interpretation always negative, 3+ always POSITIVE
Groups differ in result if 2+ (count additional cells for FISH)

Top: normal breast
Below: ILC

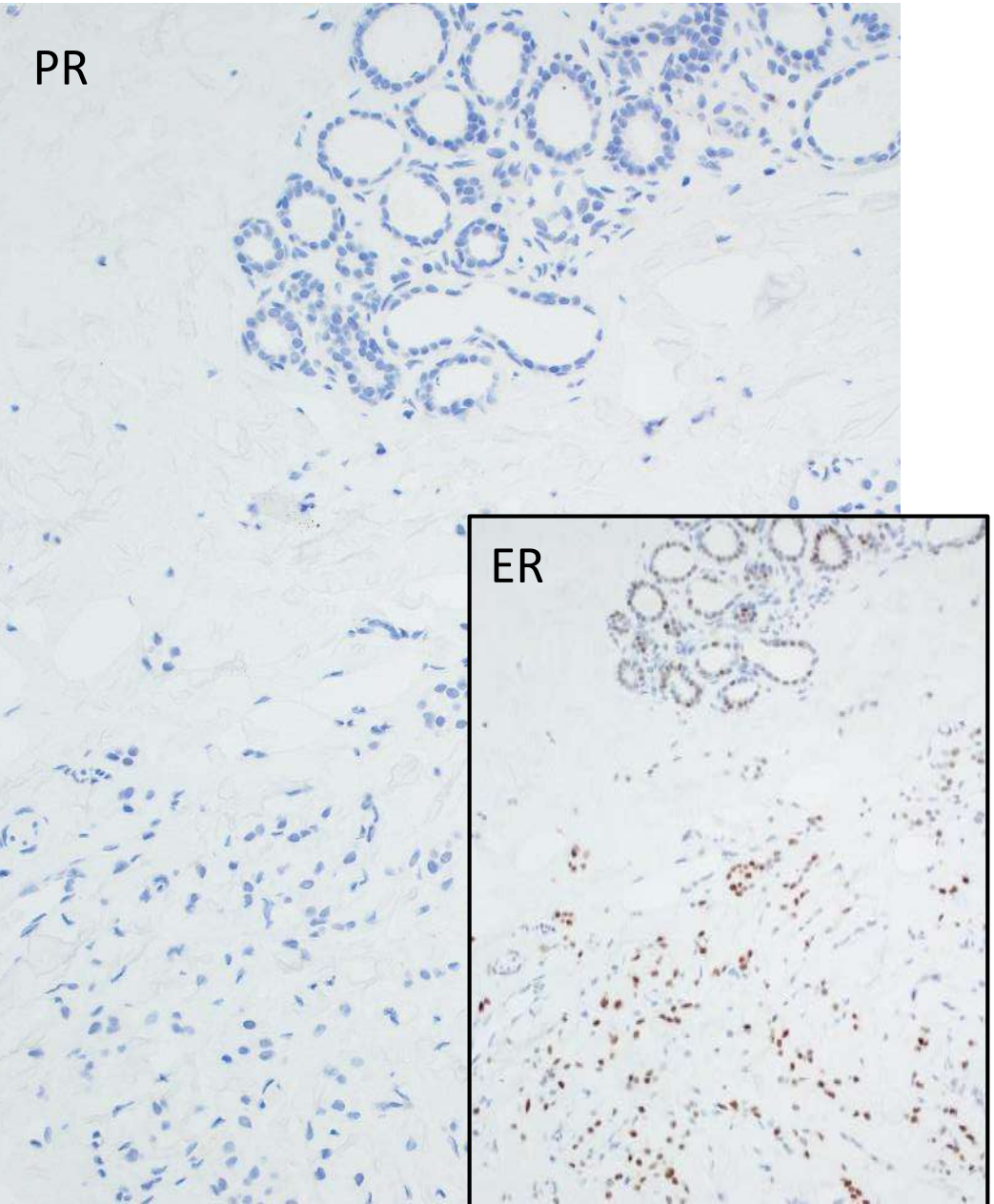


Troubleshooting

PR stain: ILC with normal breast

What happened?

Next step?



Troubleshooting

PR stain: ILC with normal breast

What happened?

Next step?

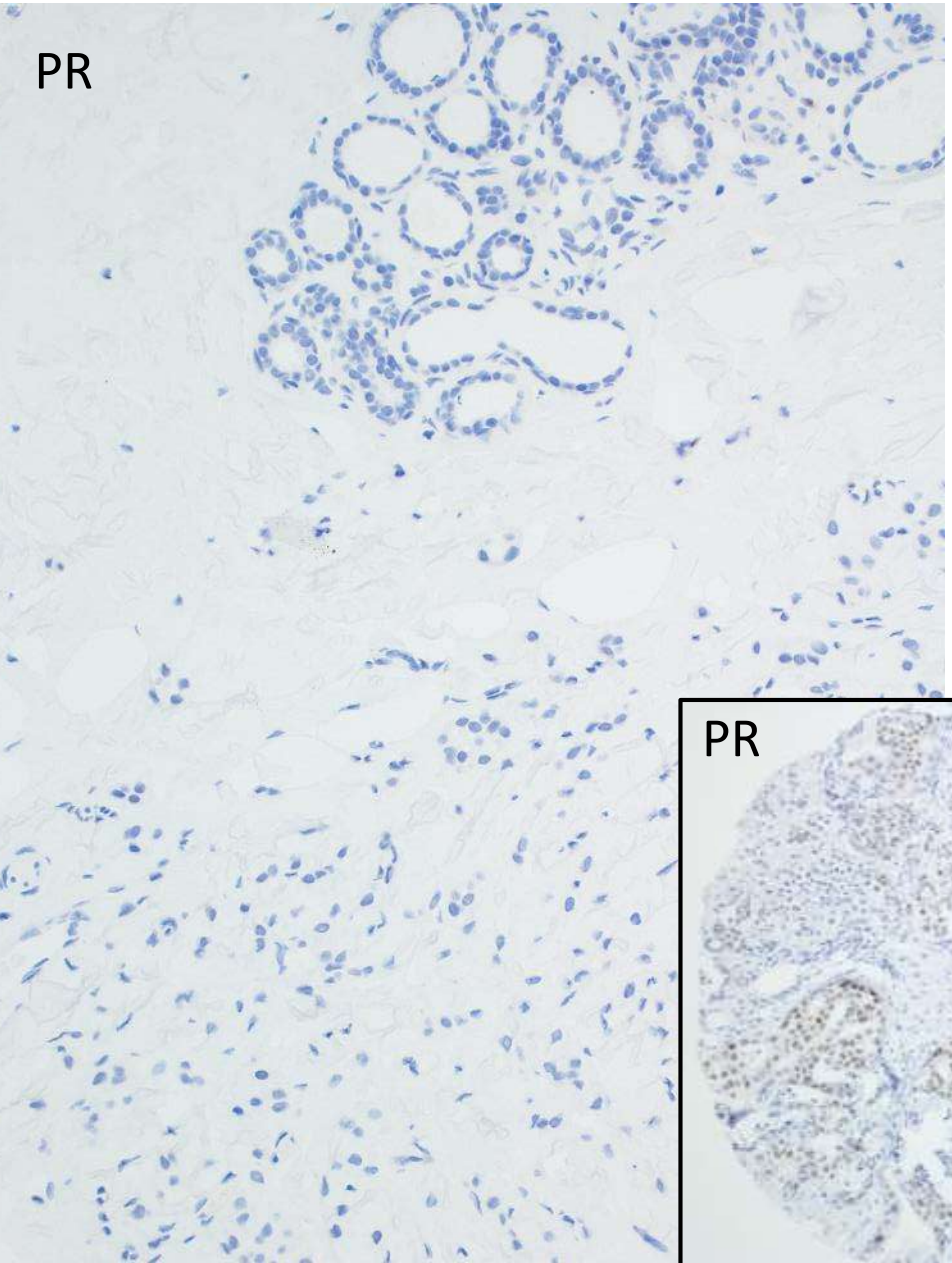
→Check ischemia/fixation

Ischemia: 1 hr

Fixation: 10 hr 10% NB formalin

ER worked!?

Allison. *Arch Pathol Lab Med*. 2020;144:545-563



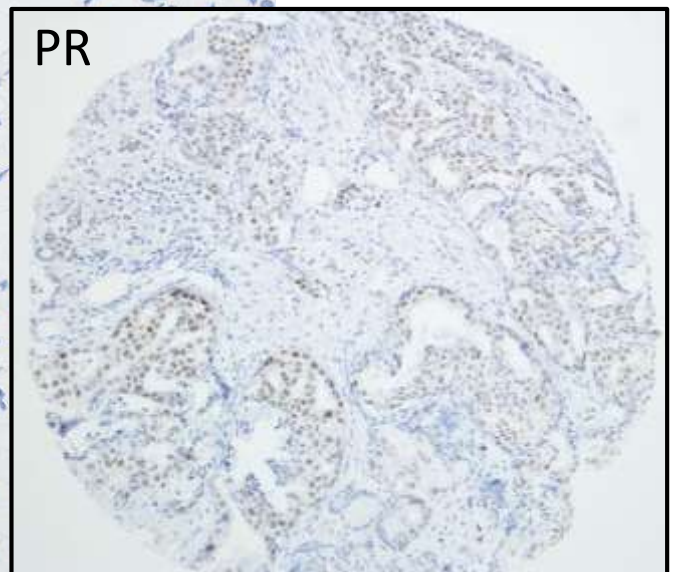
Troubleshooting

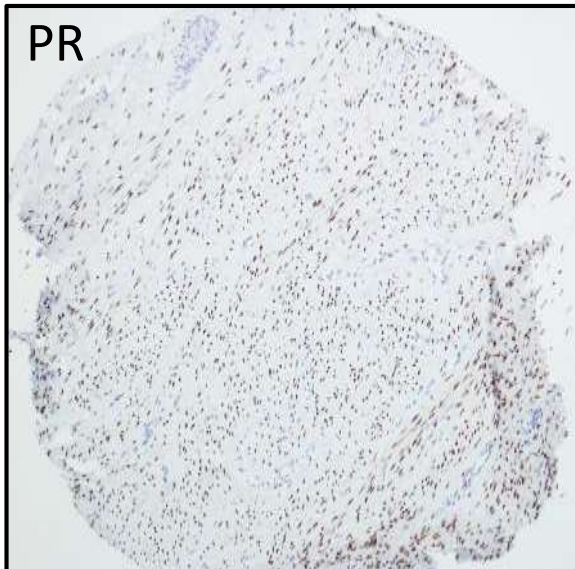
PR stain: ILC with normal breast

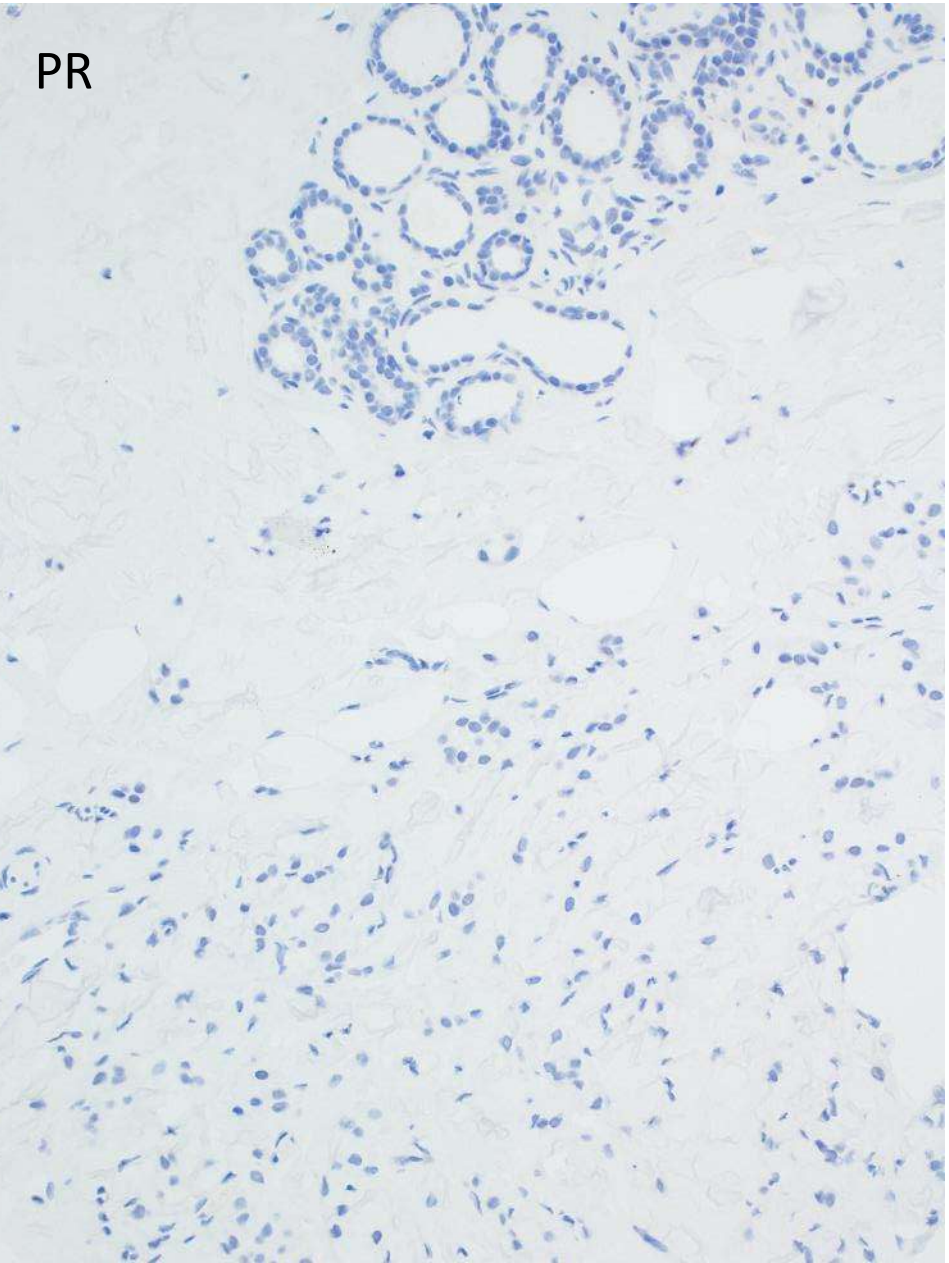
What happened?

Next step?

→Check onslide external







Troubleshooting

PR stain: ILC with normal breast

What happened?

Next step?

→Correlate with clinical history

Prior core ER+++/PR+++

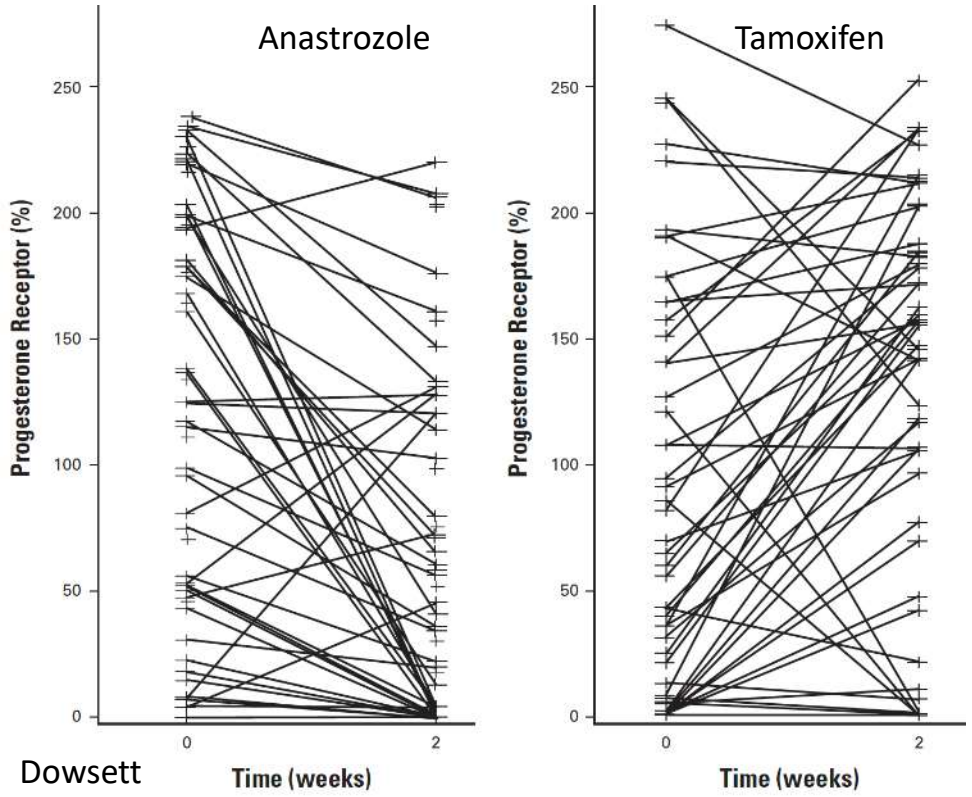
Neoadjuvant letrozole Rx

→Repeat stain? Same

Now what?

Allison. *Arch Pathol Lab Med*. 2020;144:545-563

ER PR IHC with endocrine therapy

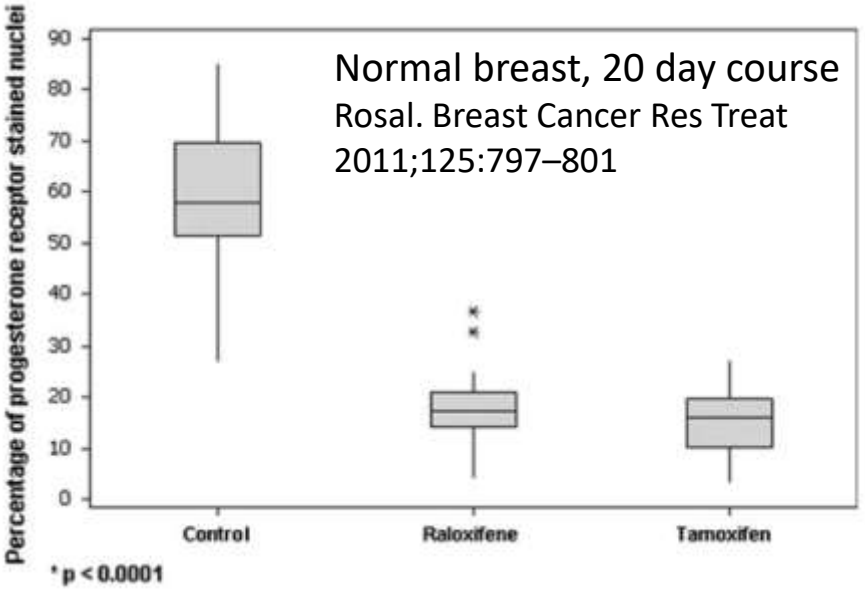


Dowsett

- Effects of tamoxifen may vary over time and differ in tumor/normal

- Profound decrease in PR with Aromatase inhibitor
  - Tumor and normal
  - Letrozole, anastrozole, exemestane

Miller. J Steroid Biochem Mol Biol. 2005;95:83-9
Dowsett. J Clin Oncol 23:2477-2492.
Kurosumi. J Cancer Res Clin Oncol.2008;134:715–22



Normal breast, 20 day course
Rosal. Breast Cancer Res Treat 2011;125:797–801

ER PR IHC with anti-endocrine therapy

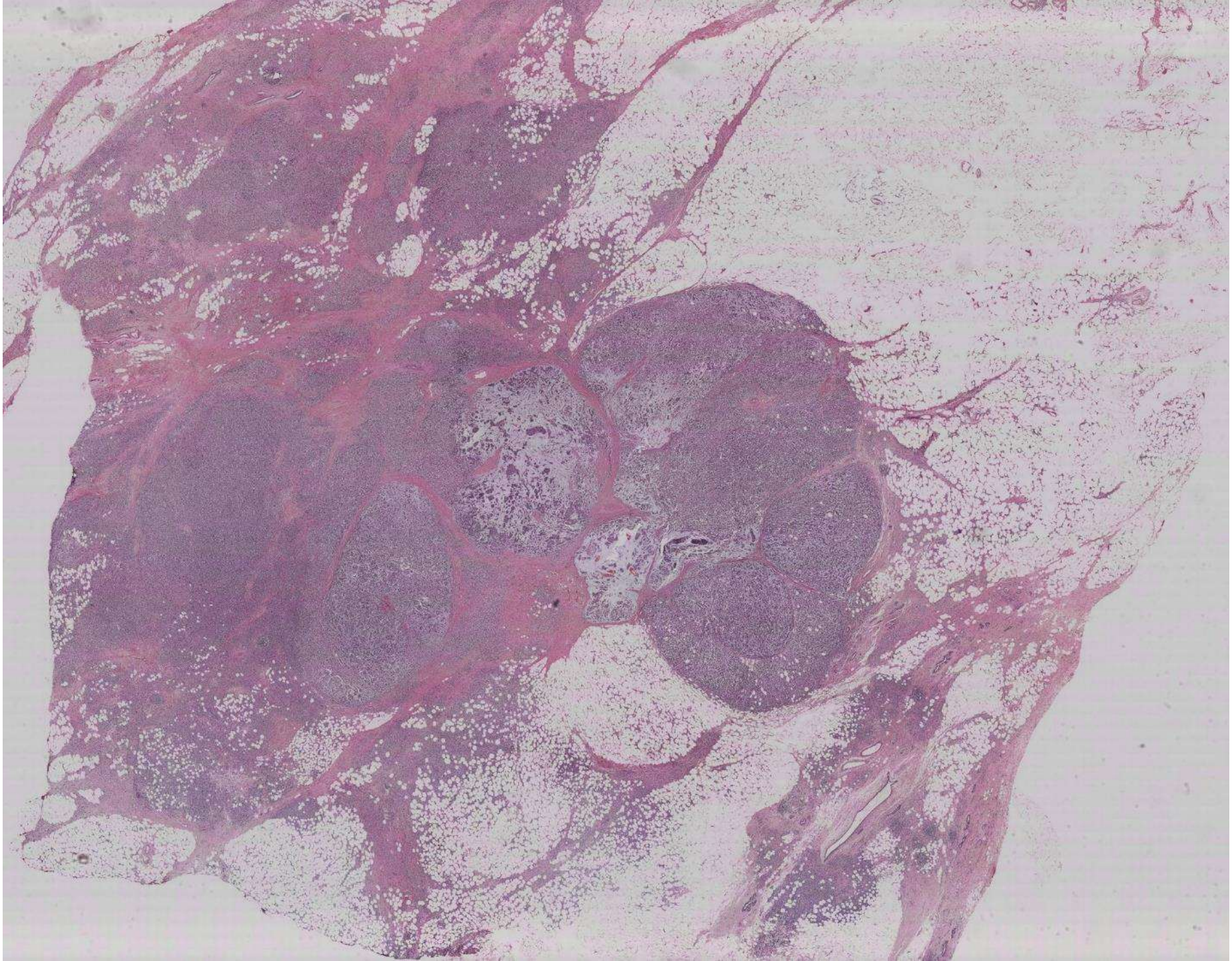
Agent	Estrogen Receptor	Progesterone Receptor
SERM Tamoxifen Raloxifene	Partial decrease	Variable
Aromatase Inhibitor Letrozole Anastrozole Exemestane	Stable or slight decrease	Decrease/negative
SERD Fulvestrant*	Decrease/negative	Decrease/negative

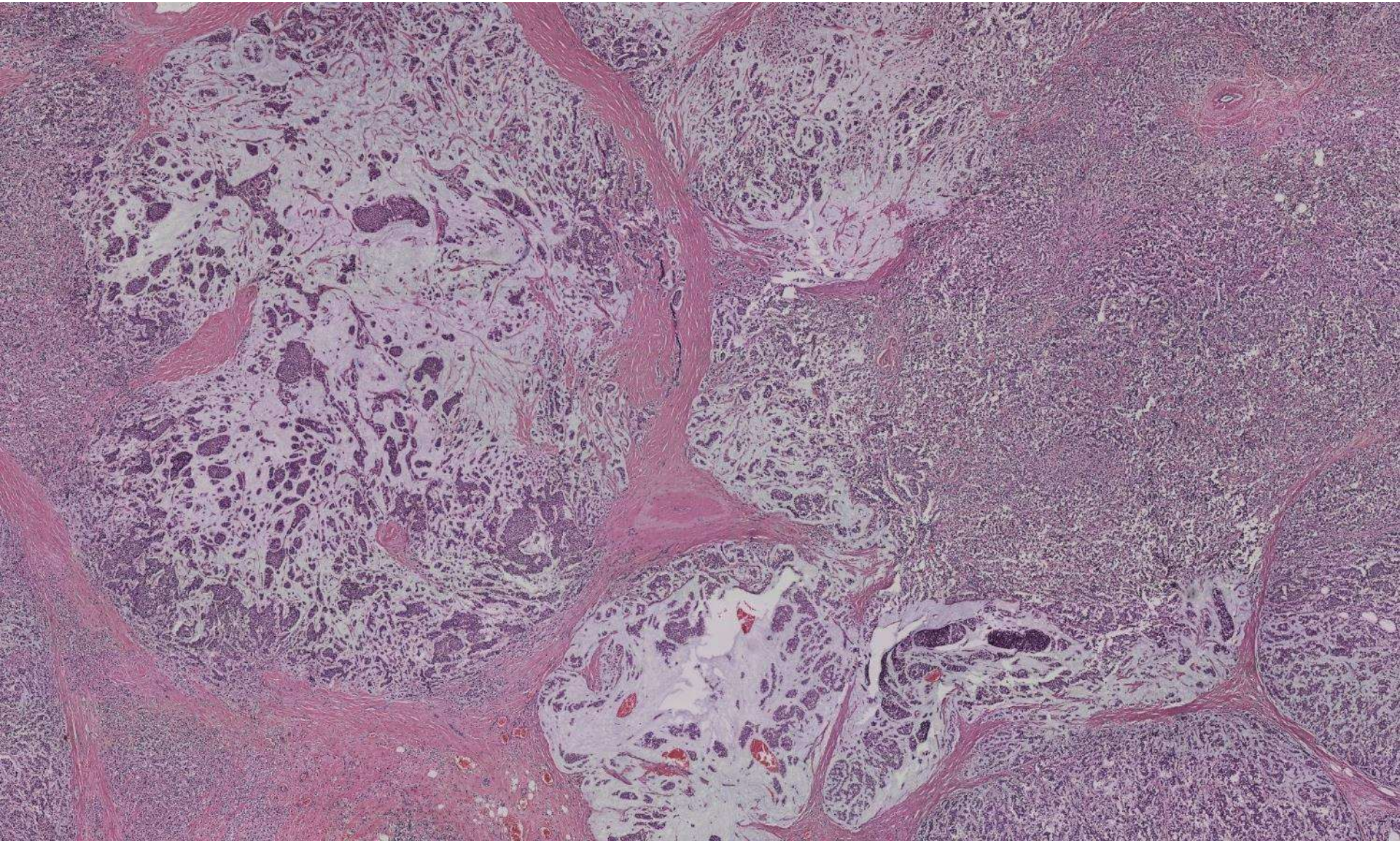
*now used in combo with PIK3 inhibitors; we may be seeing more

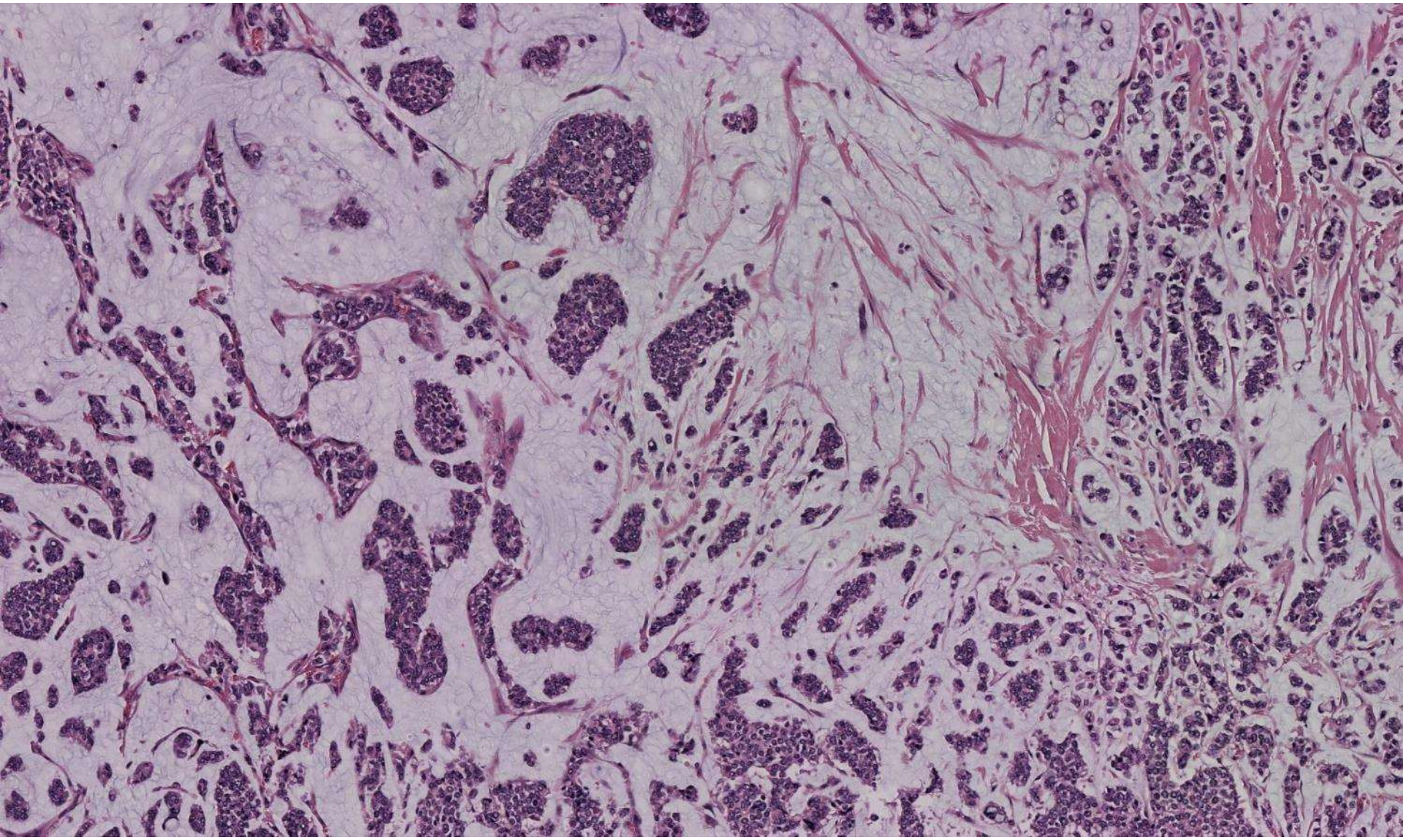
21-0203
scanned slide avail!

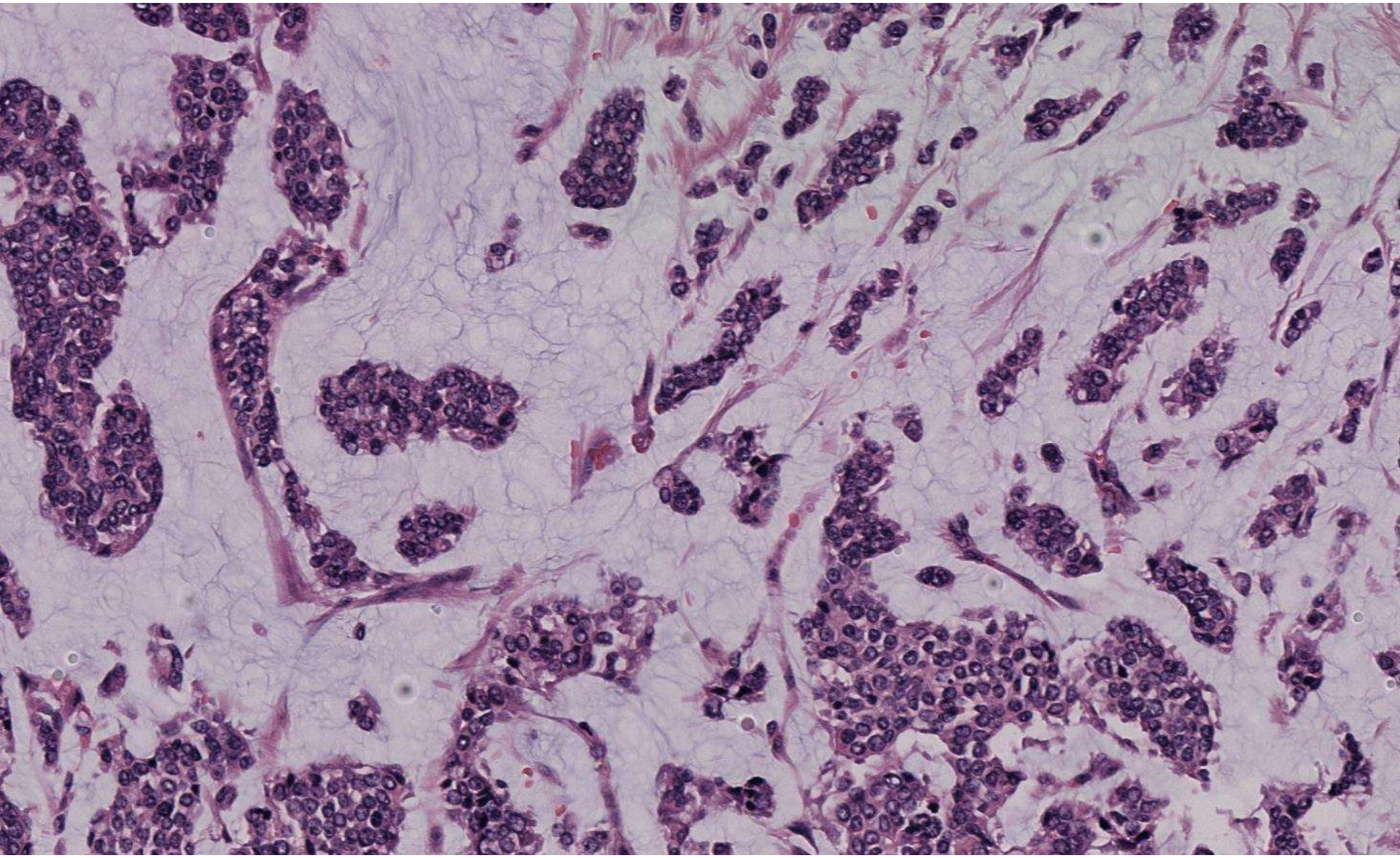
Ankur Sangoi; El Camino Hospital

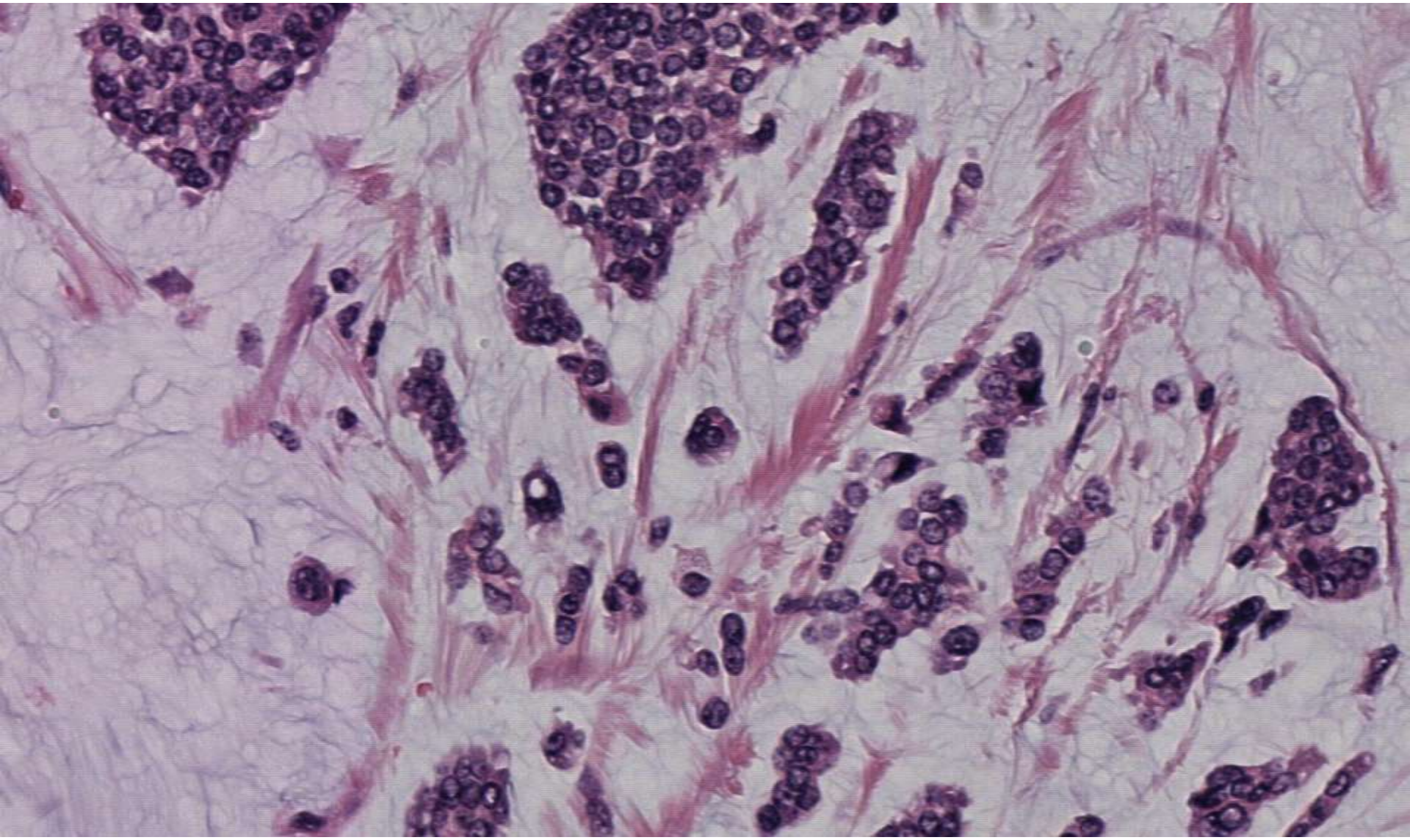
70-year-old F with large breast mass.

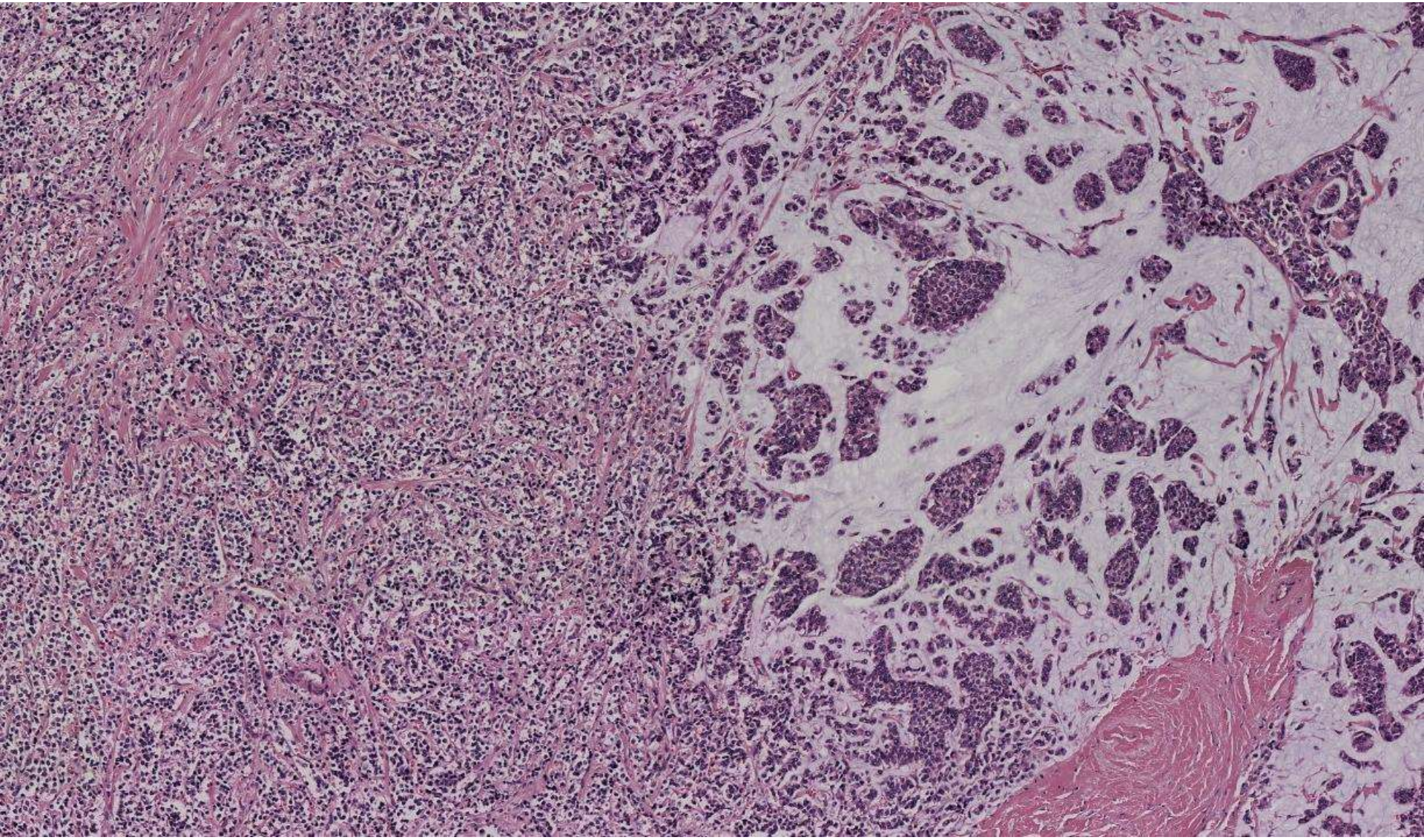


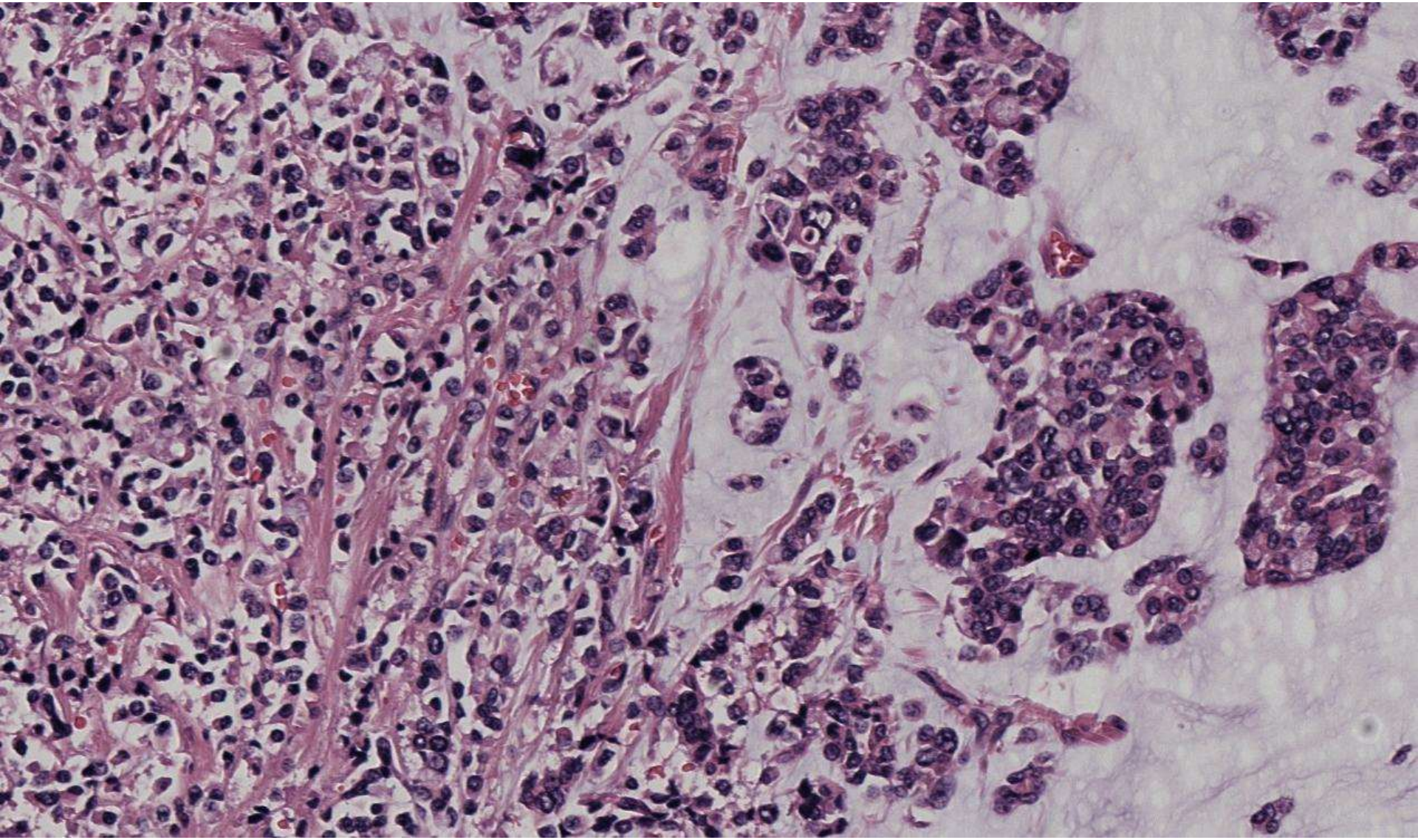


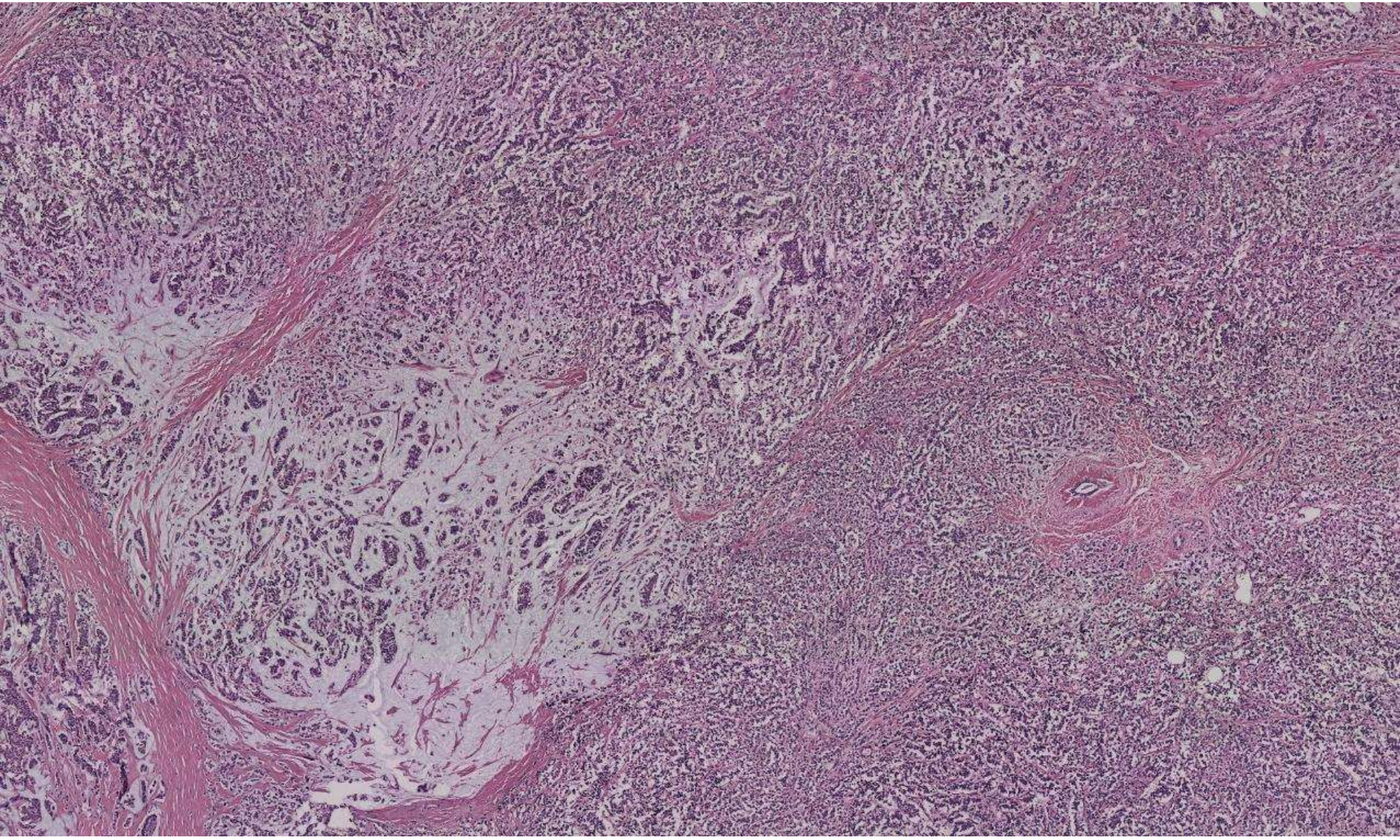


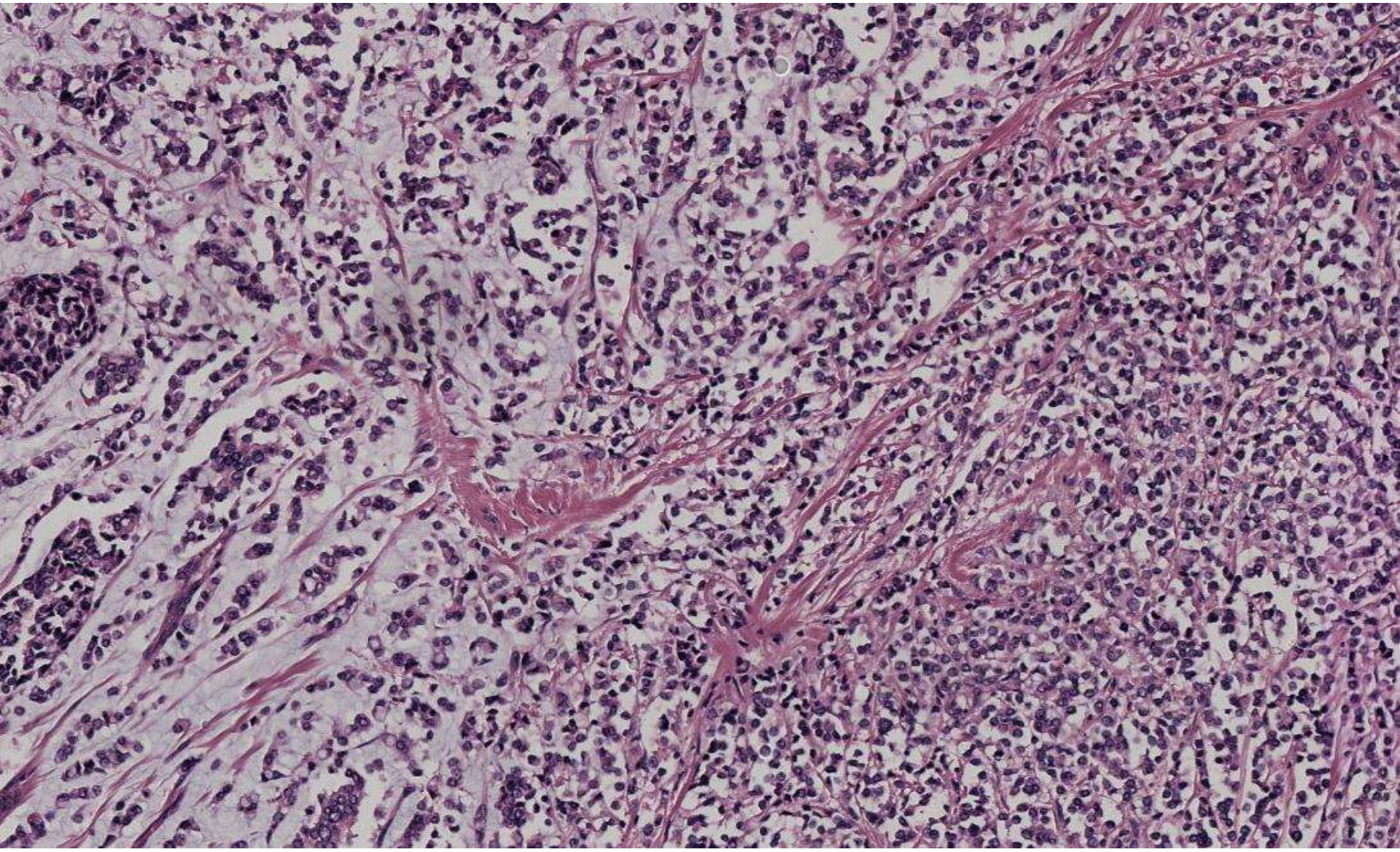


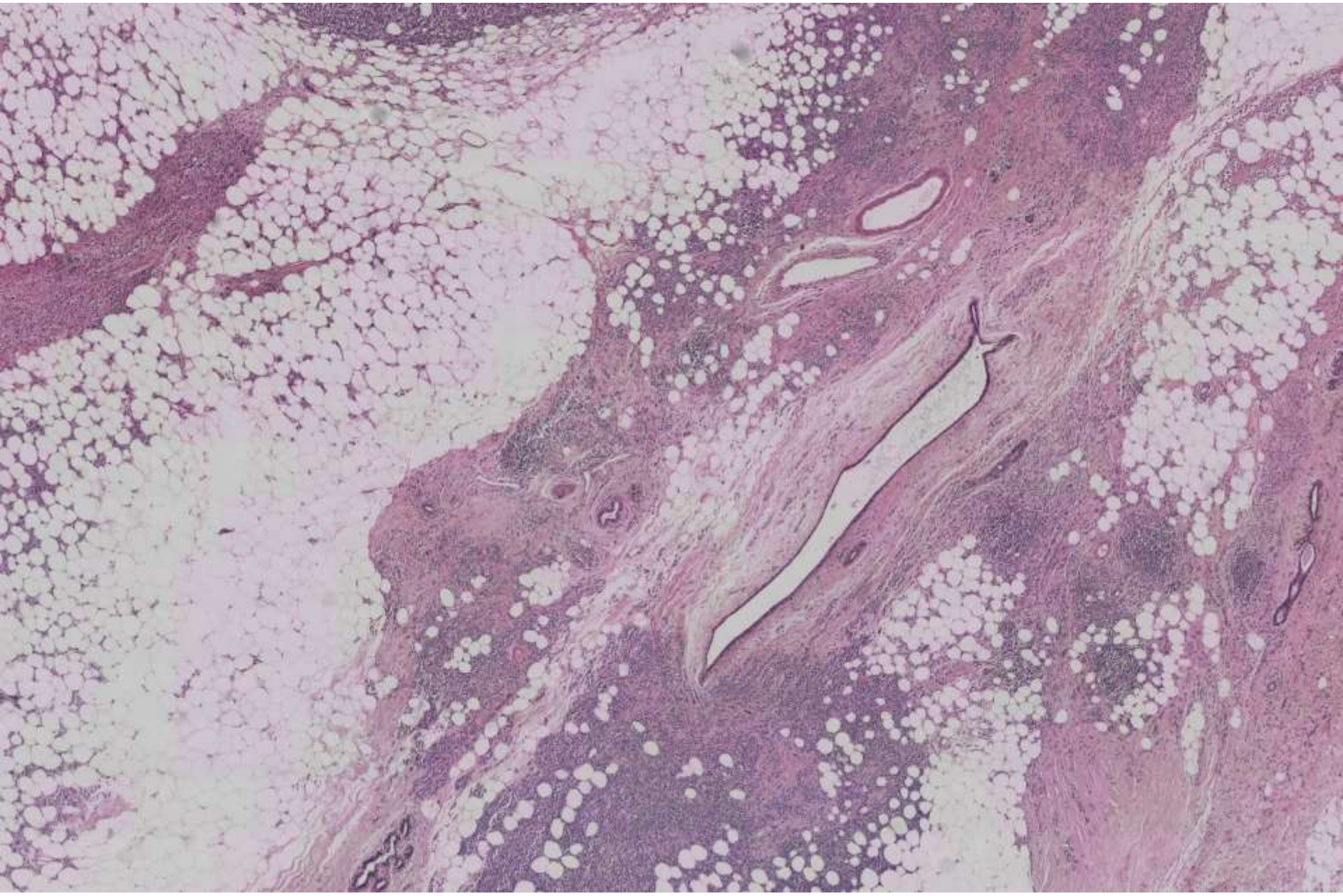


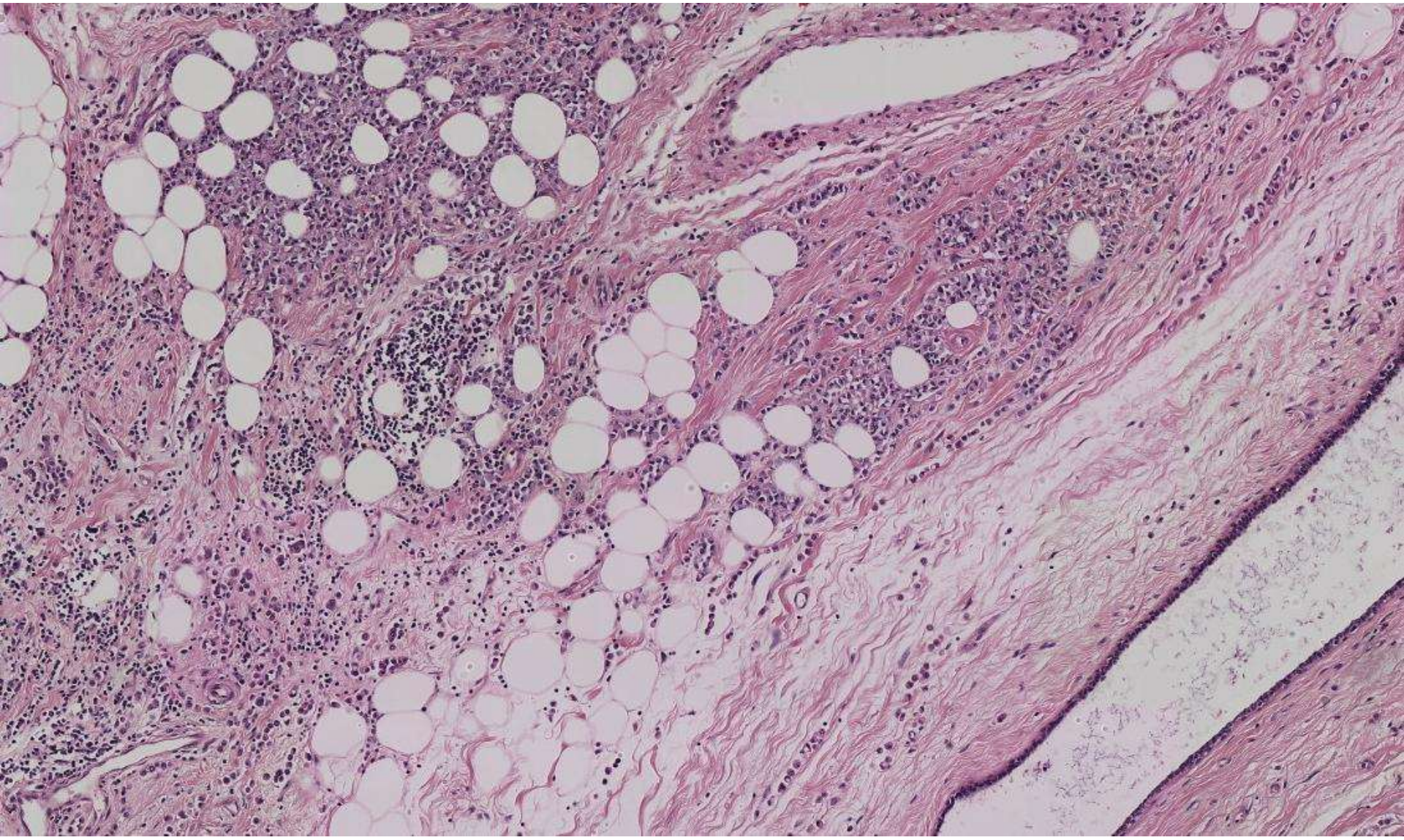


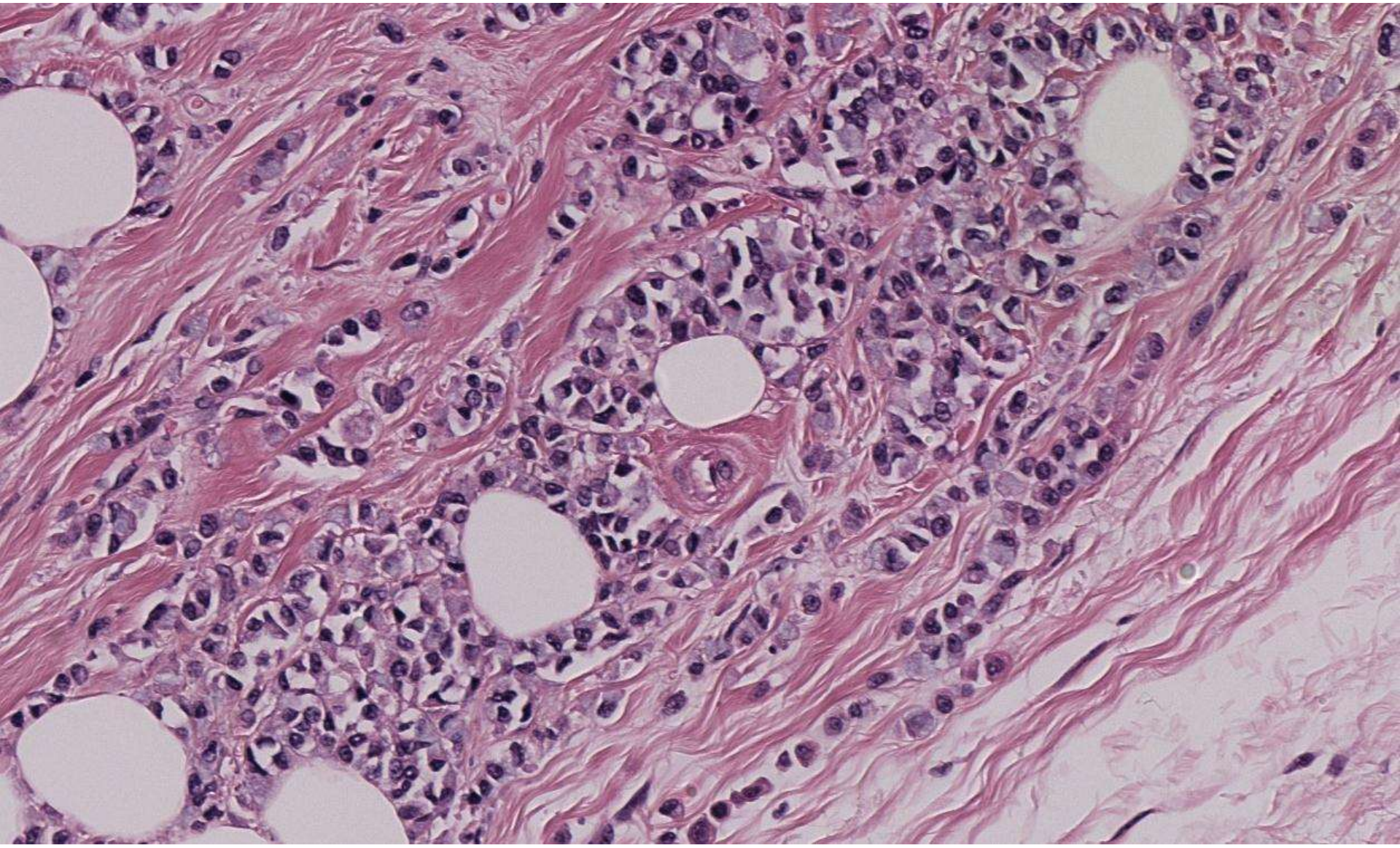










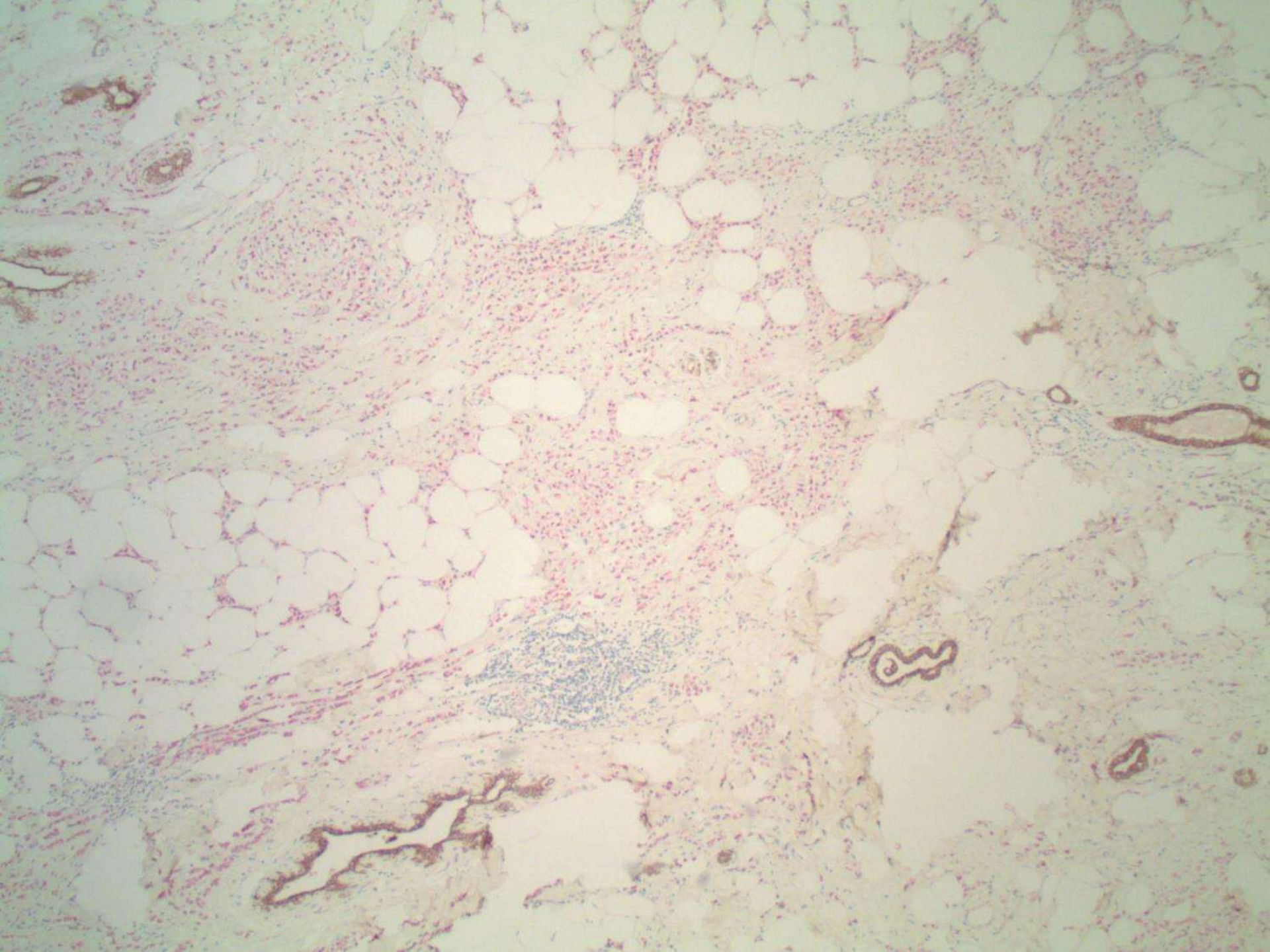


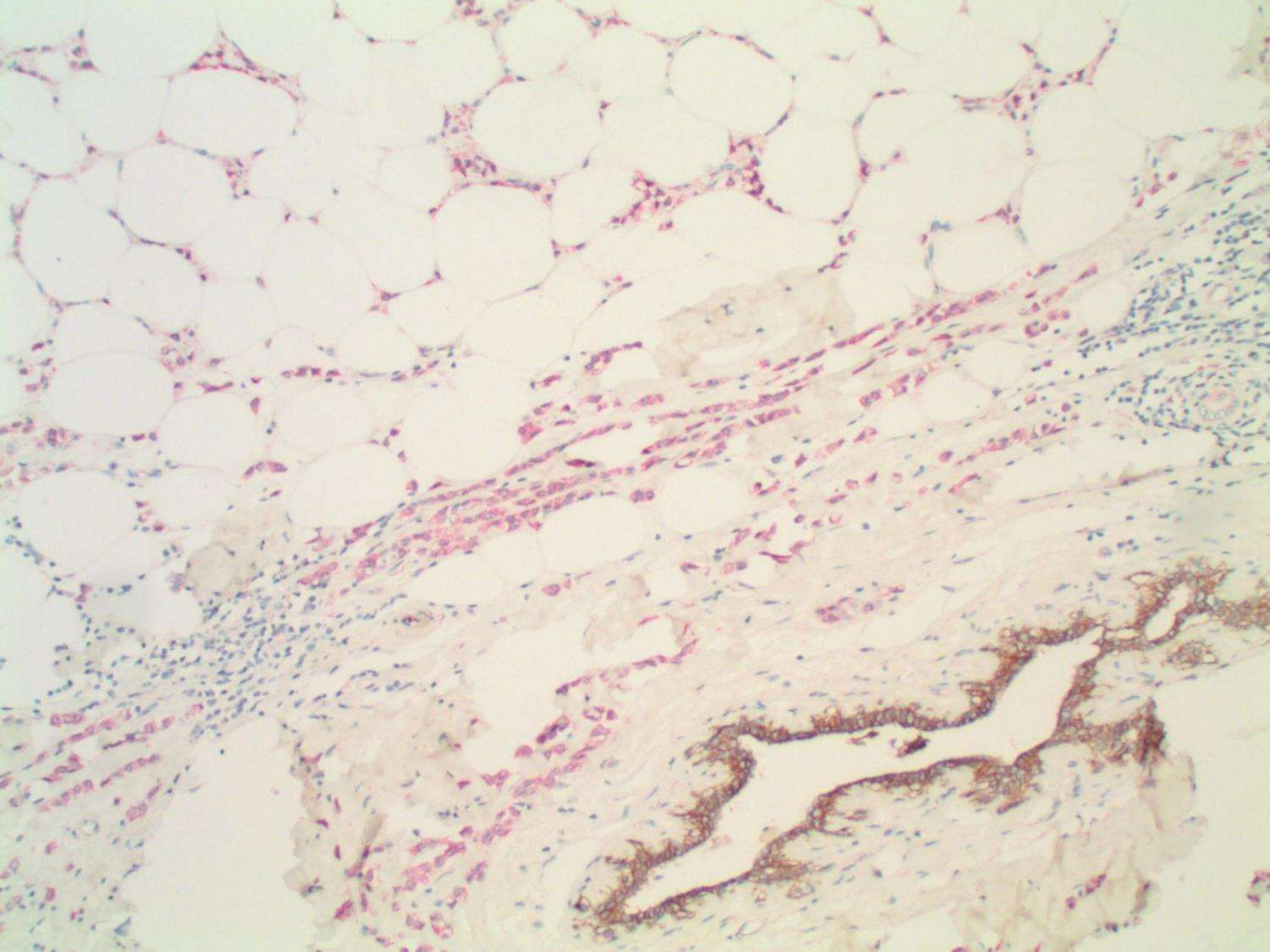
DDx

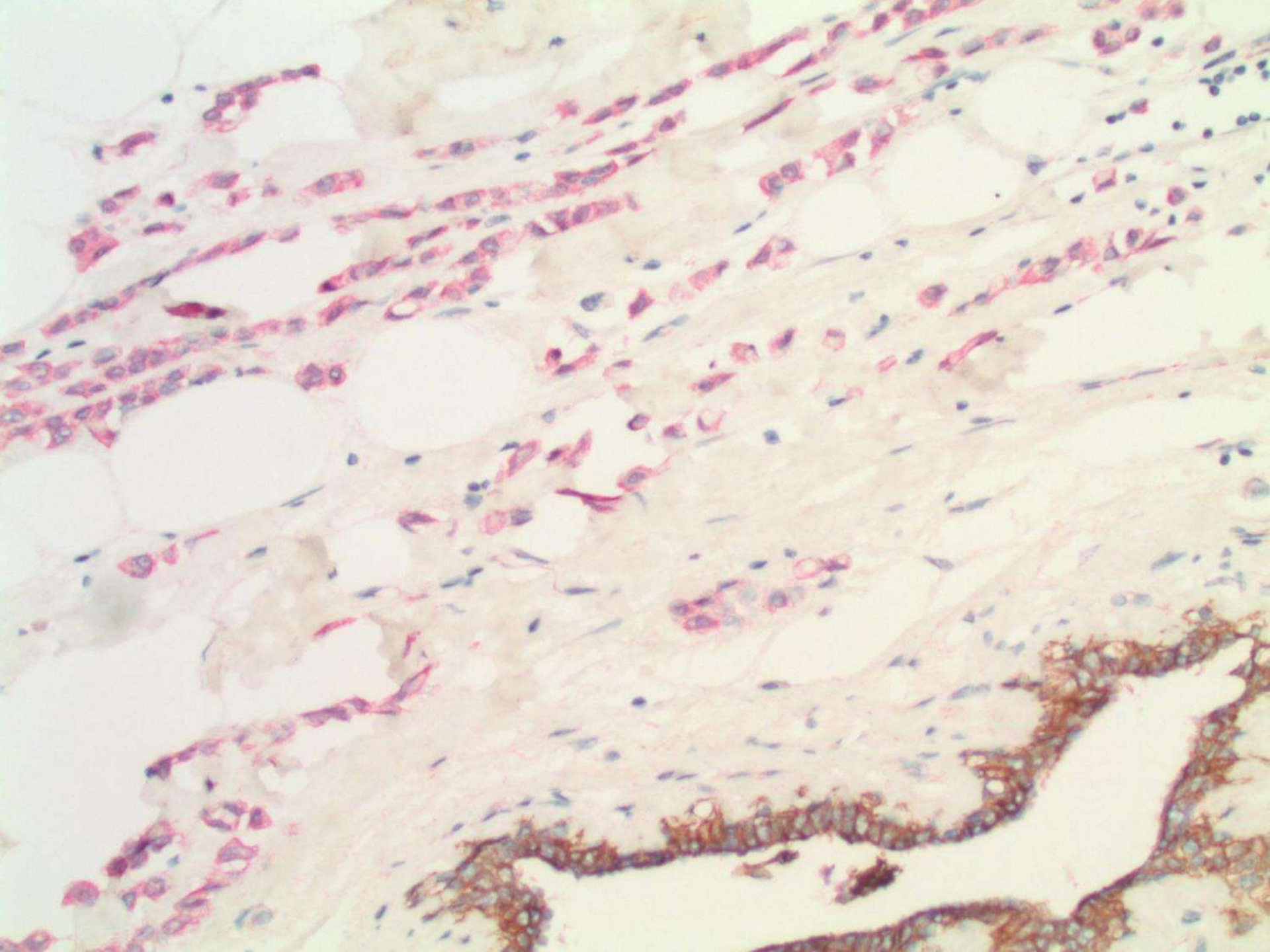
- Mixed mammary mucinous carcinoma + lobular carcinoma
- Collision lobular carcinoma + metastatic mucinous carcinoma
- Mucinous carcinoma
- Lobular carcinoma with extracellular mucin

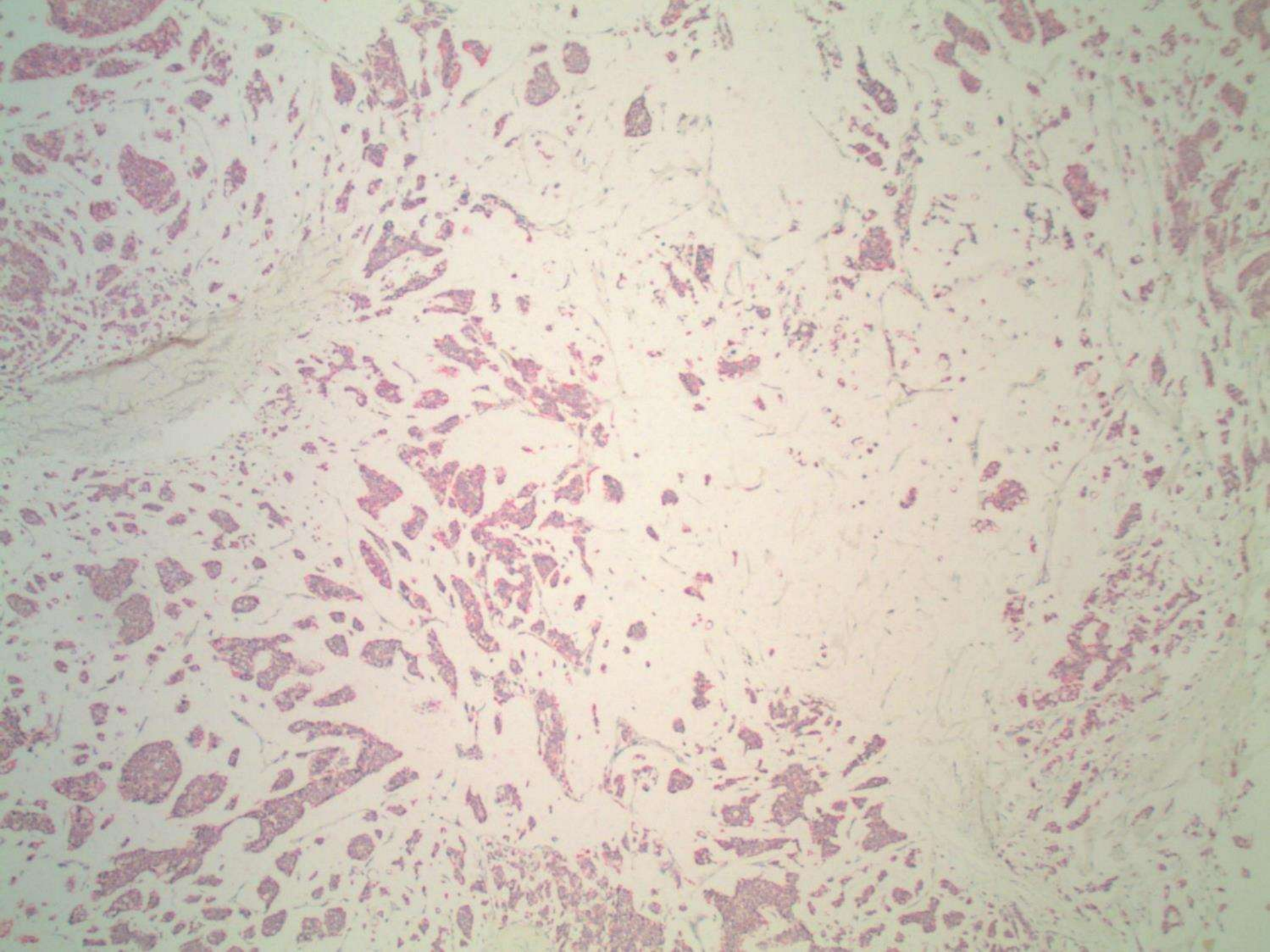
Combination IHC

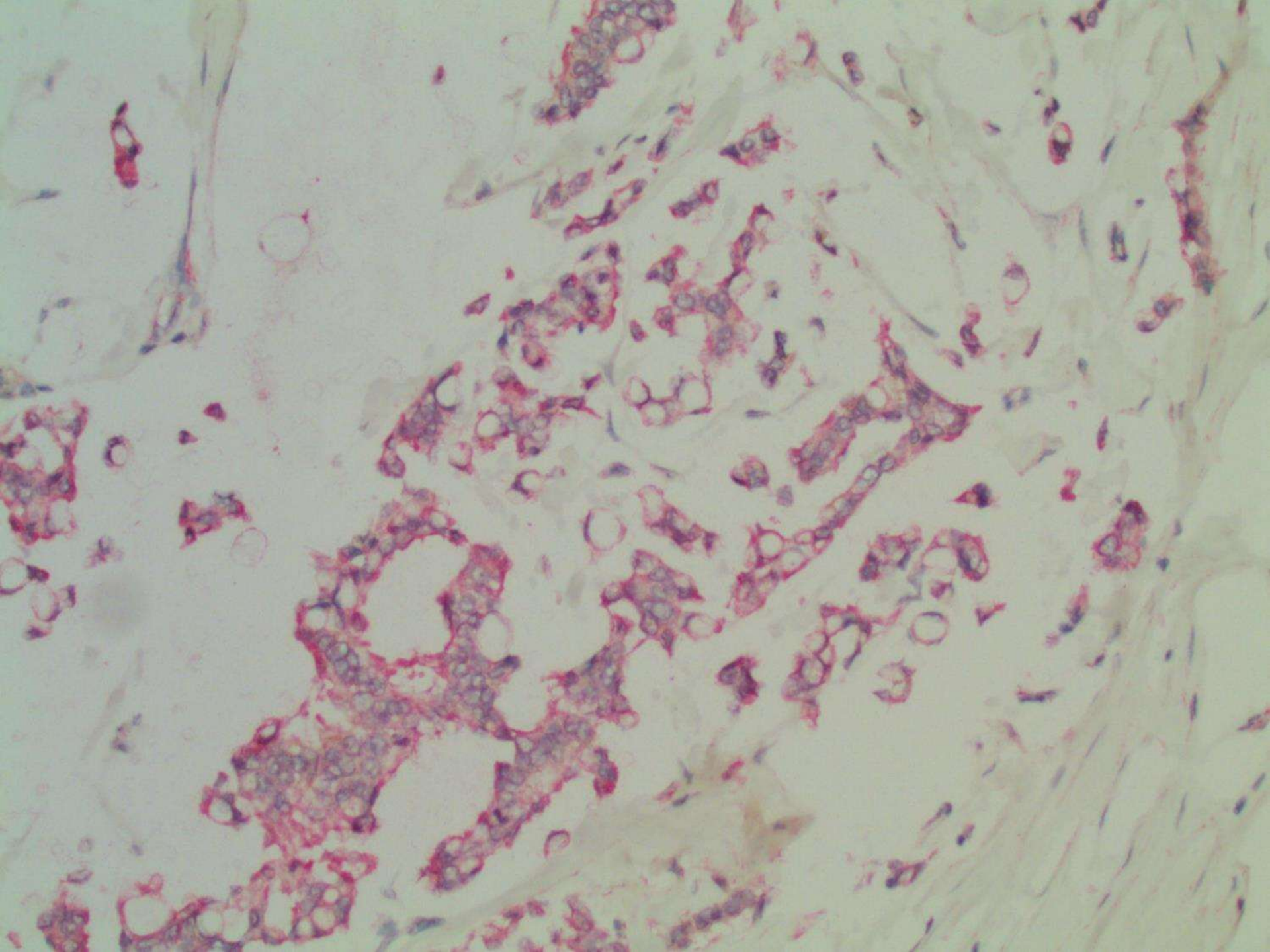
- **E-cadherin (brown)**
- **+**
- **p120 (red)**











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Invasive Lobular Carcinoma With Extracellular Mucin: Not All Mucinous Mammary Carcinomas Are Ductal!

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Abstract

Mucinous component in mammary carcinoma indicates ductal phenotype. Although intracytoplasmic mucin and signet ring cell change are frequently described with lobular carcinomas, extracellular mucin is not associated with lobular phenotype. We report 4 cases of invasive lobular carcinoma with extracellular mucin (ILCEM) and review findings of previously published cases of this rare ILC variant. Variable amount of extracellular mucin and pseudoglandular architectural pattern may lead to diagnosis of ILCEM as ductal mucinous carcinoma. Pathologists should be aware of this rare variant of ILC that will help identify more cases of this entity and clarify relevance of extracellular mucin production in ILC.

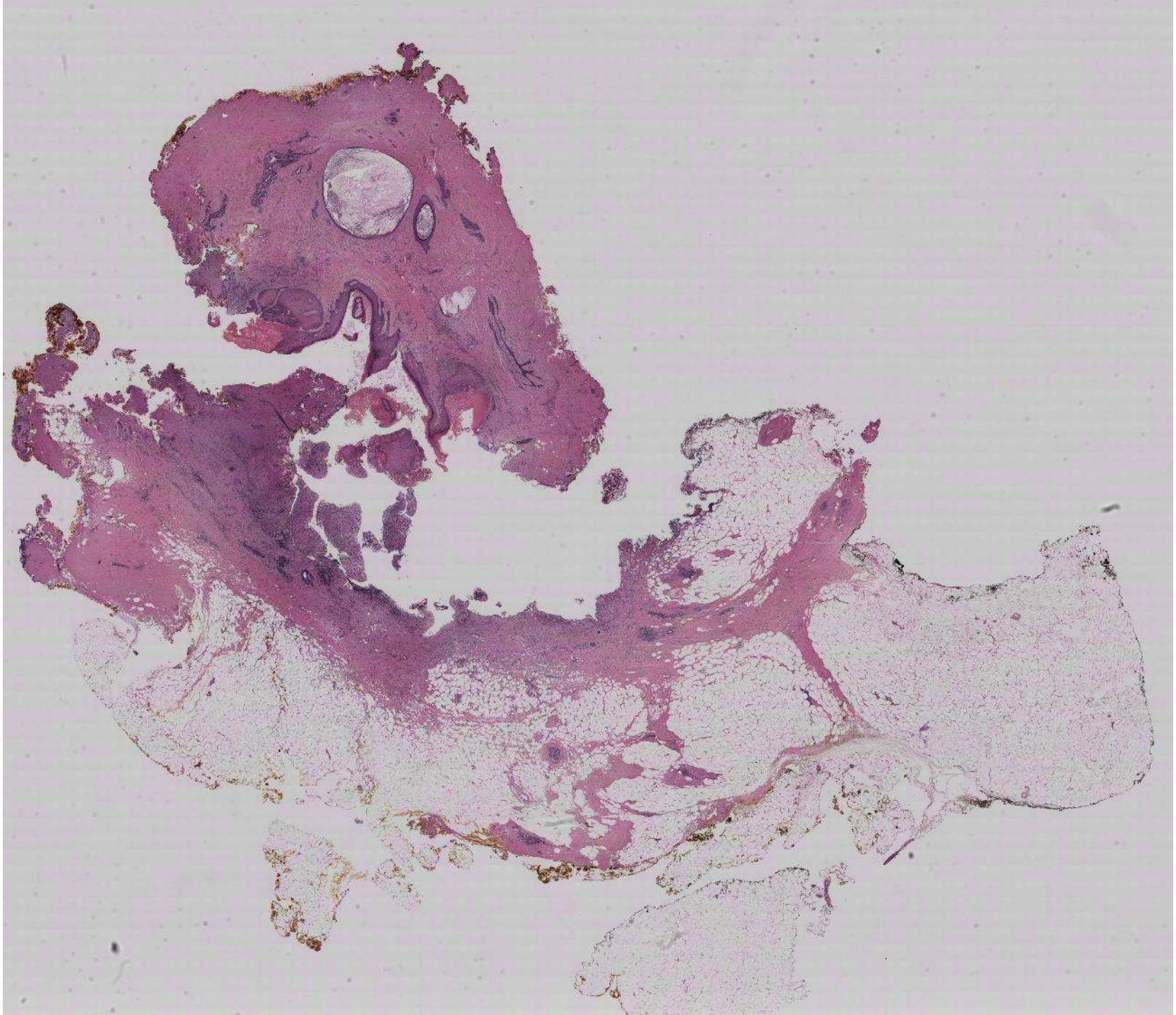
Invasive lobular carcinoma with extracellular mucin (ILCEM)

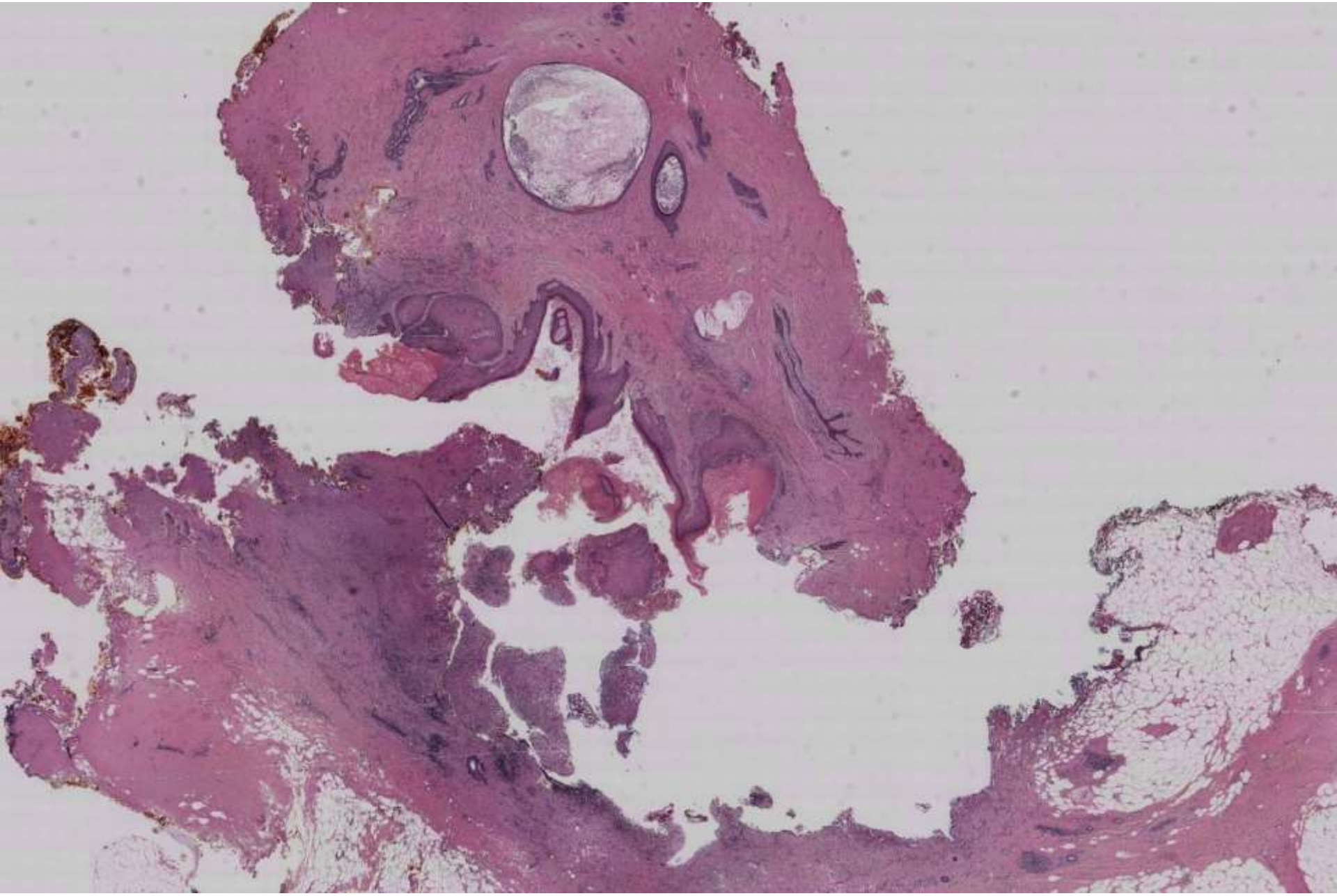
- Usually large tumors, high stage, from post-menopausal women
- Usually grade 2 of 3 (often pleomorphic ILC)
- Often HER2+
- Often have *CDH1* mutations
- 5th ed WHO: unknown whether these are subtype of mucinous carcinoma or lobular carcinoma

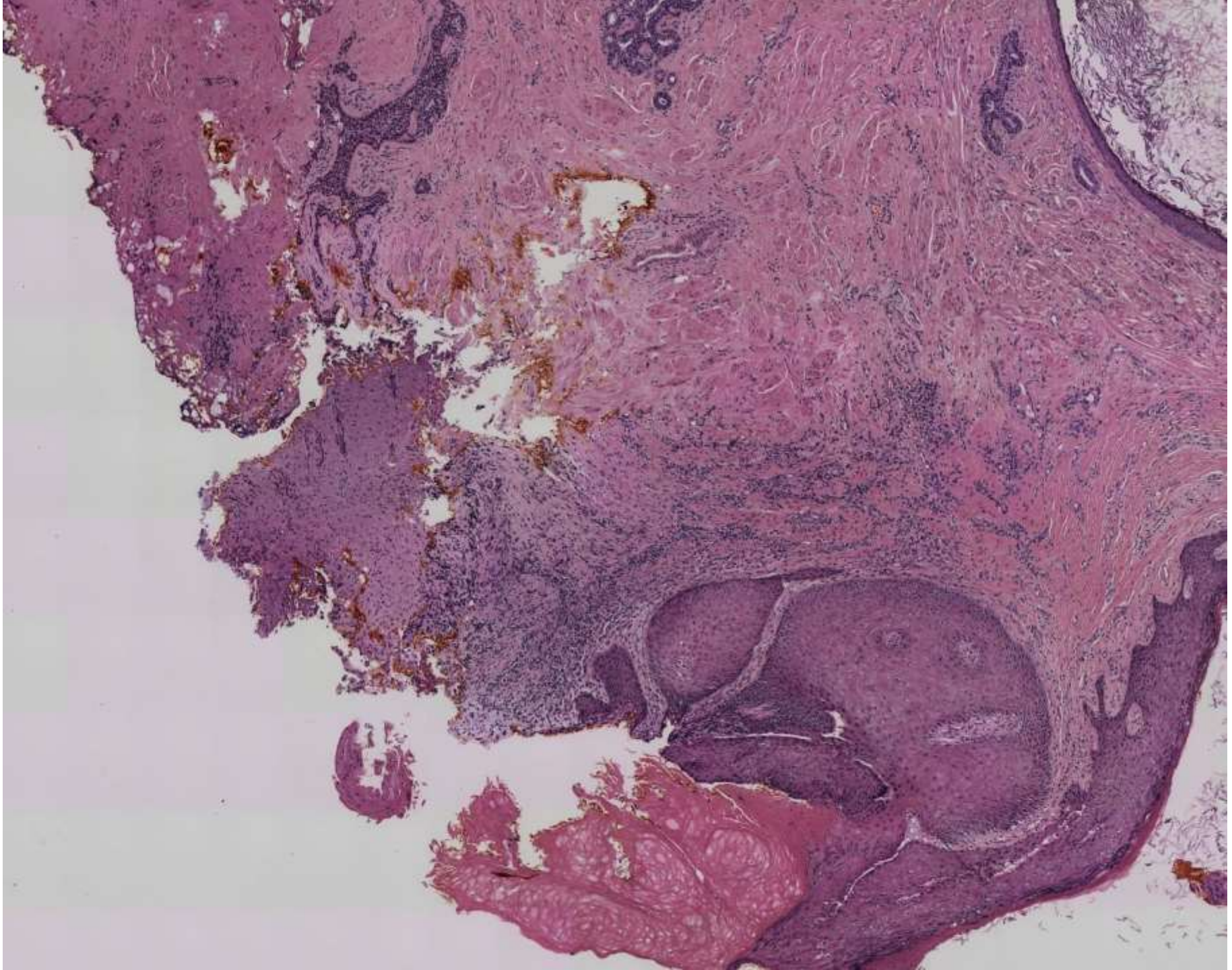
21-0204
scanned slide avail!

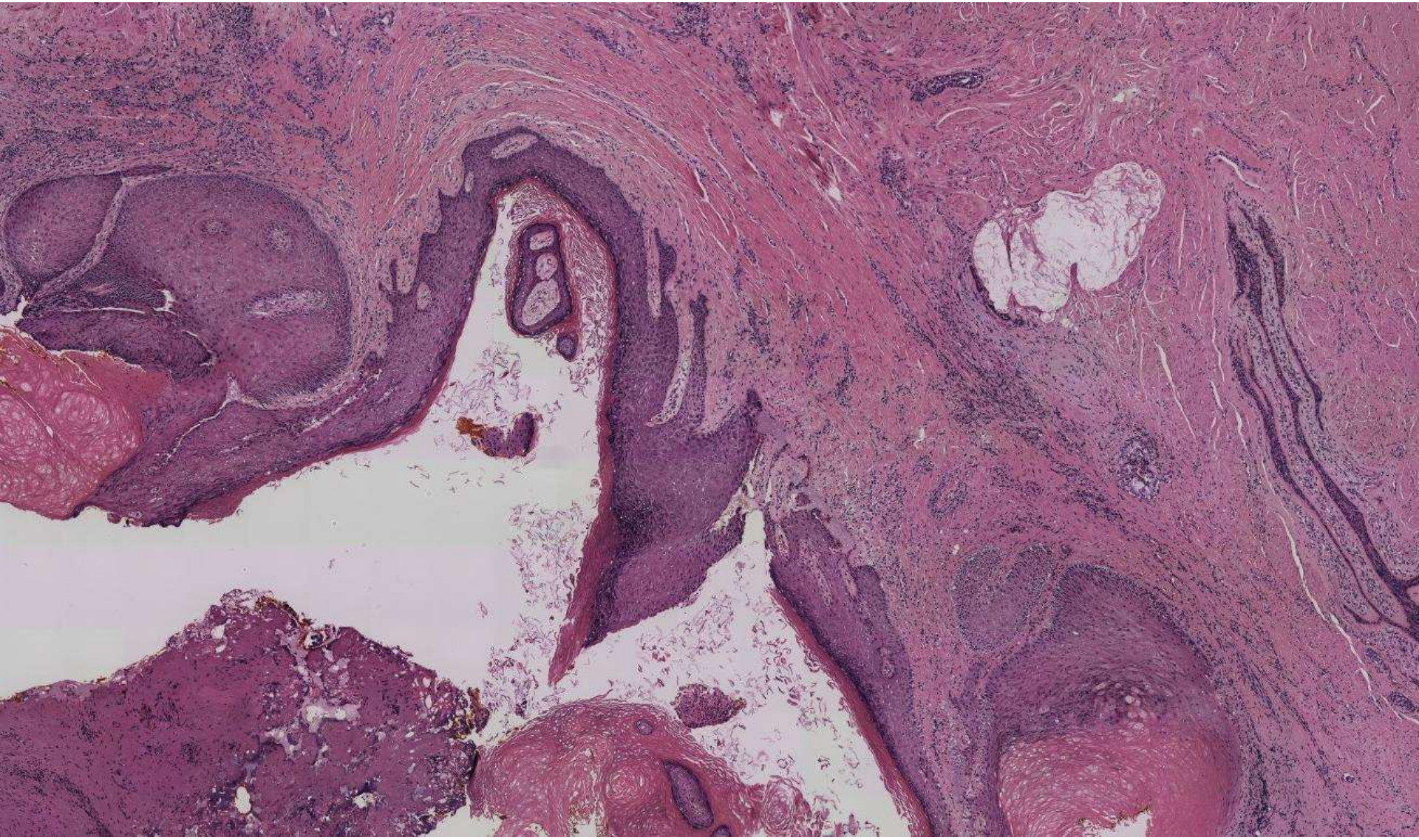
Ankur Sangoi; El Camino Hospital

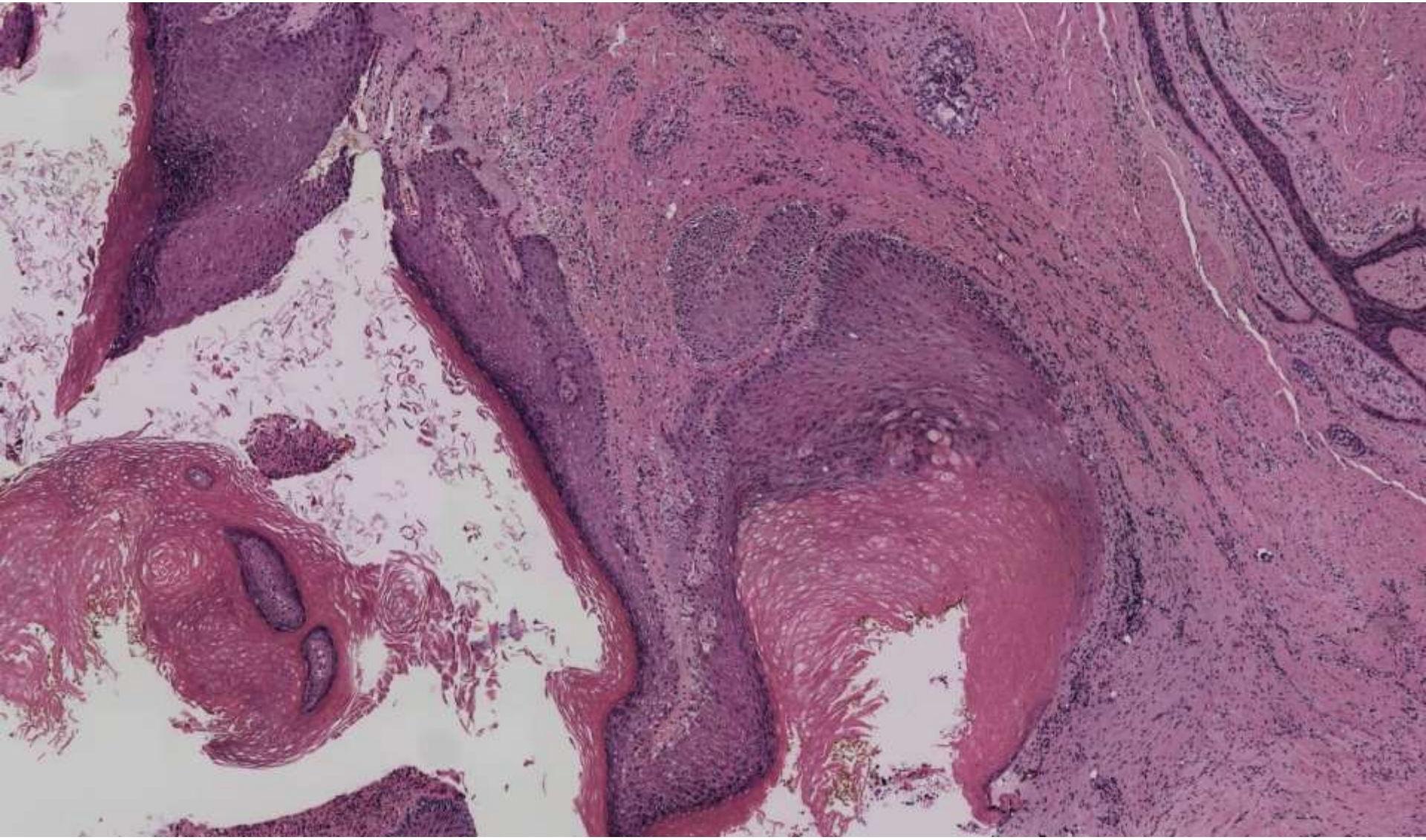
80-year-old F with painful subareolar lesion.

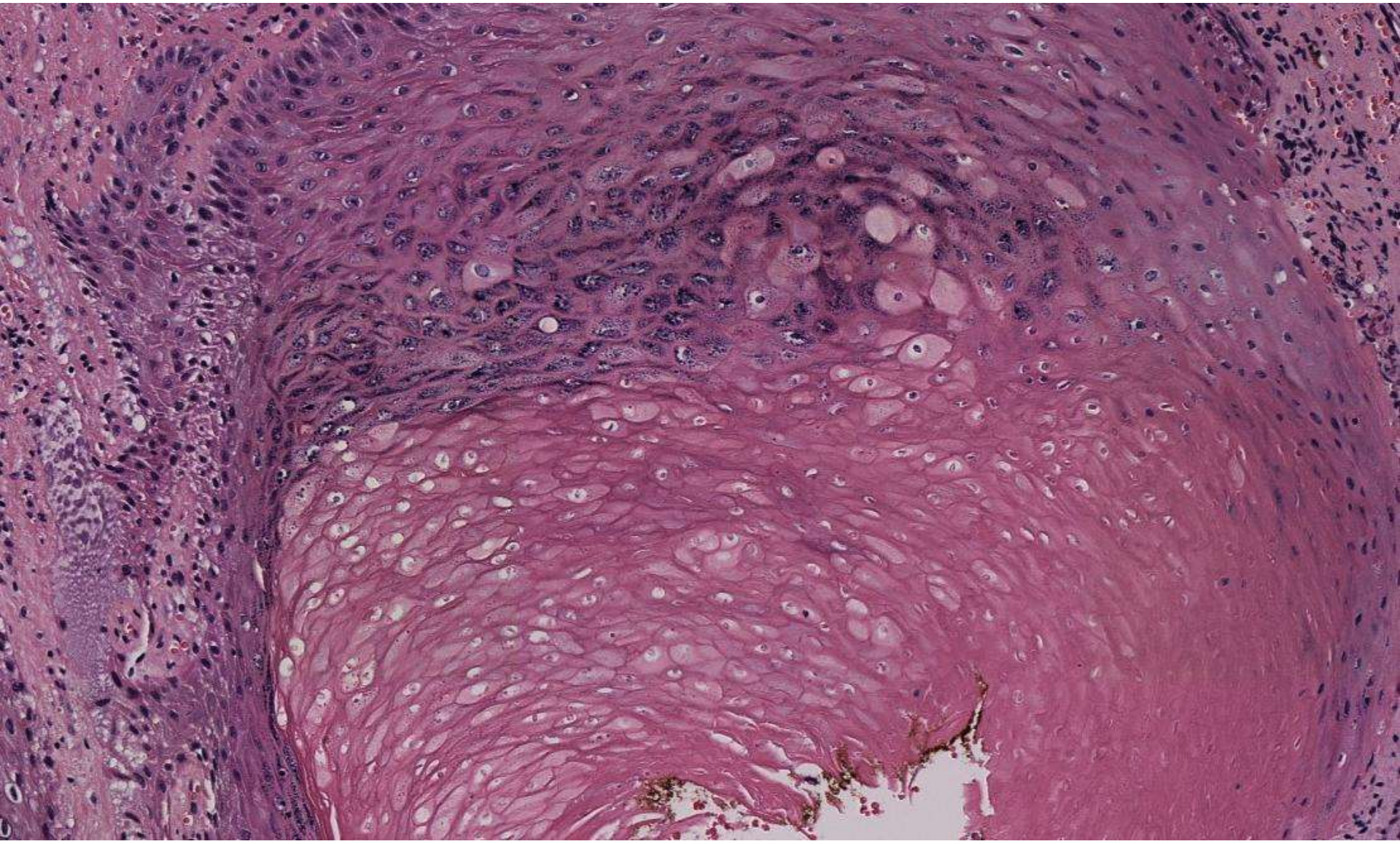


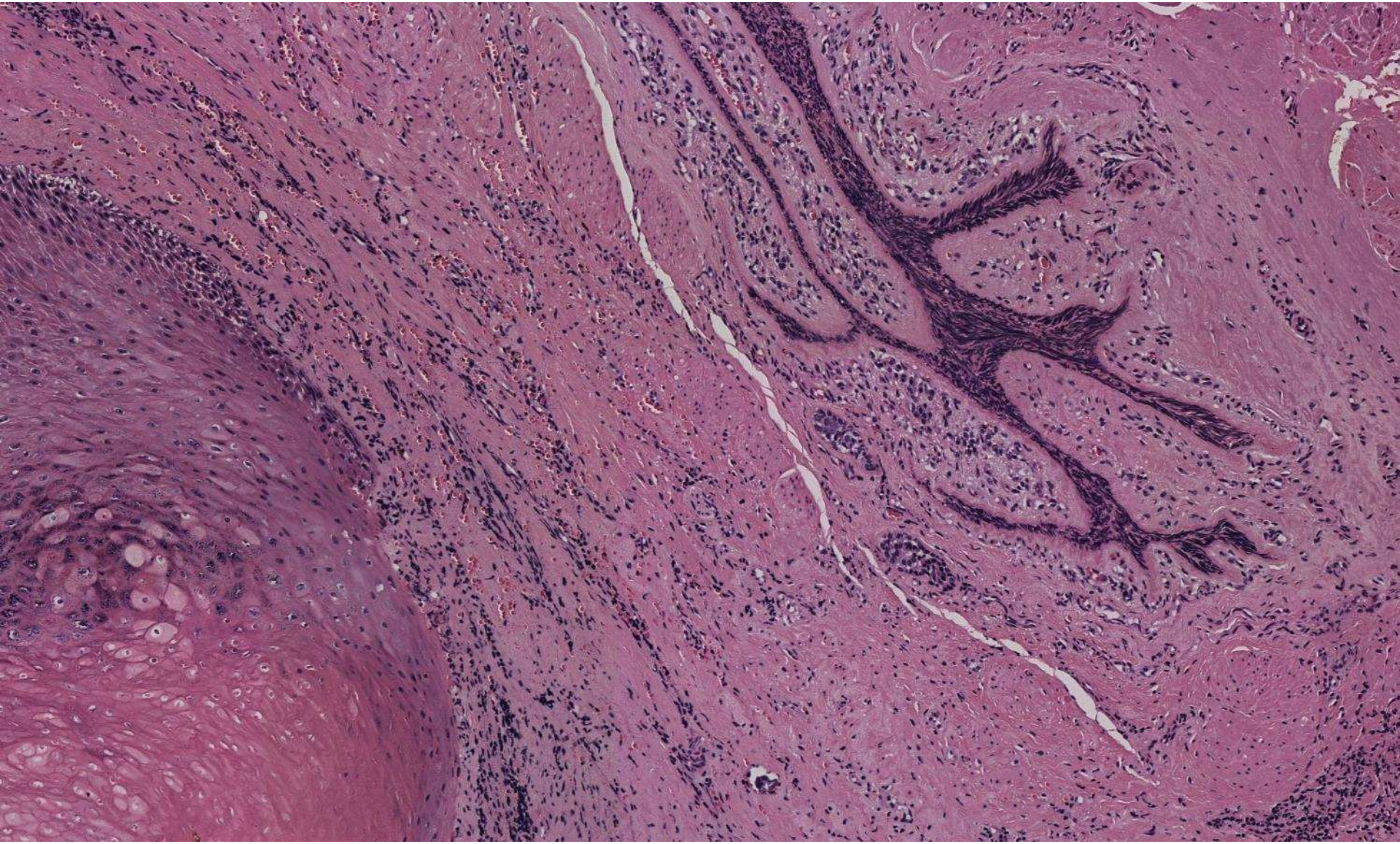


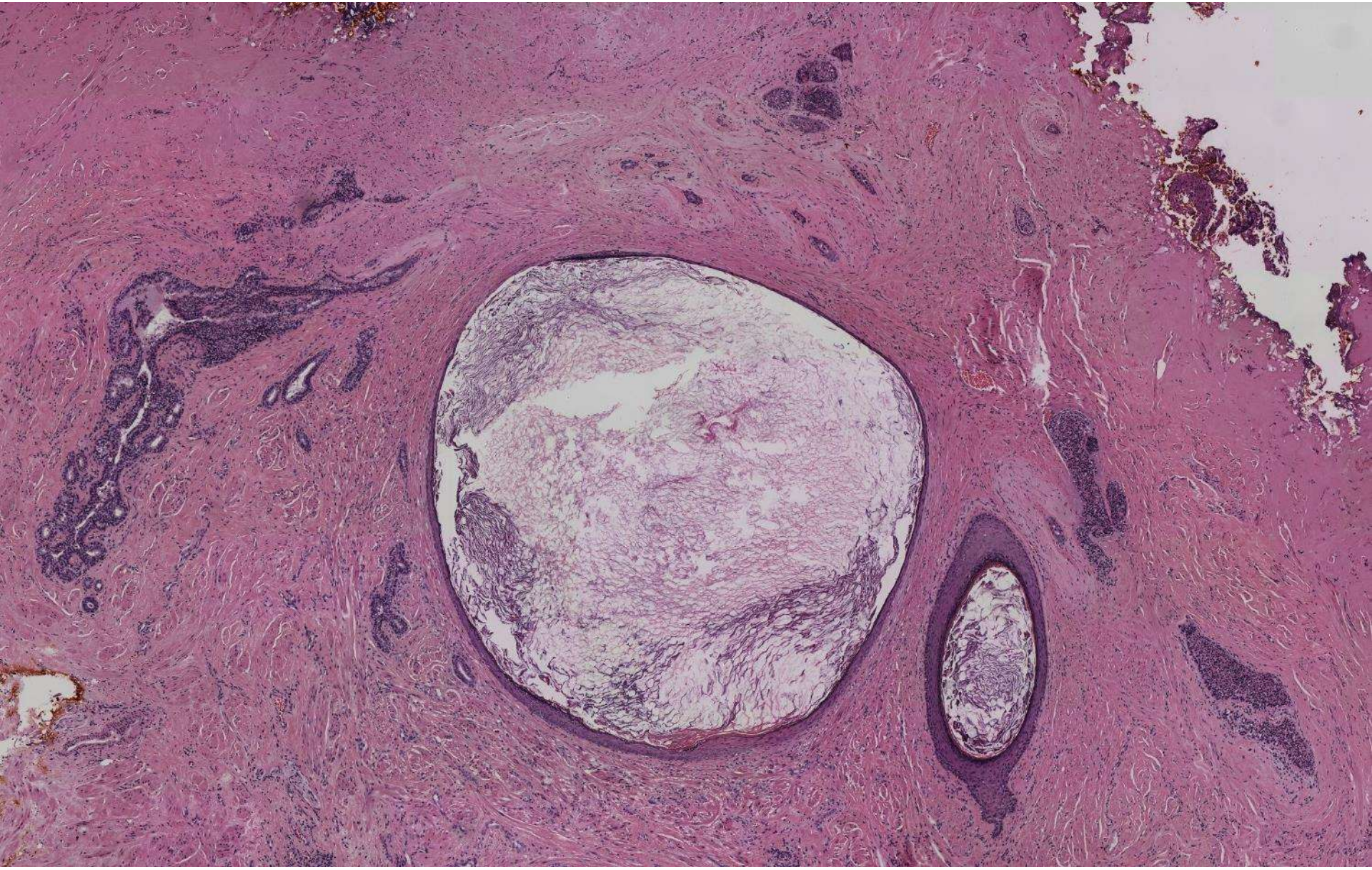


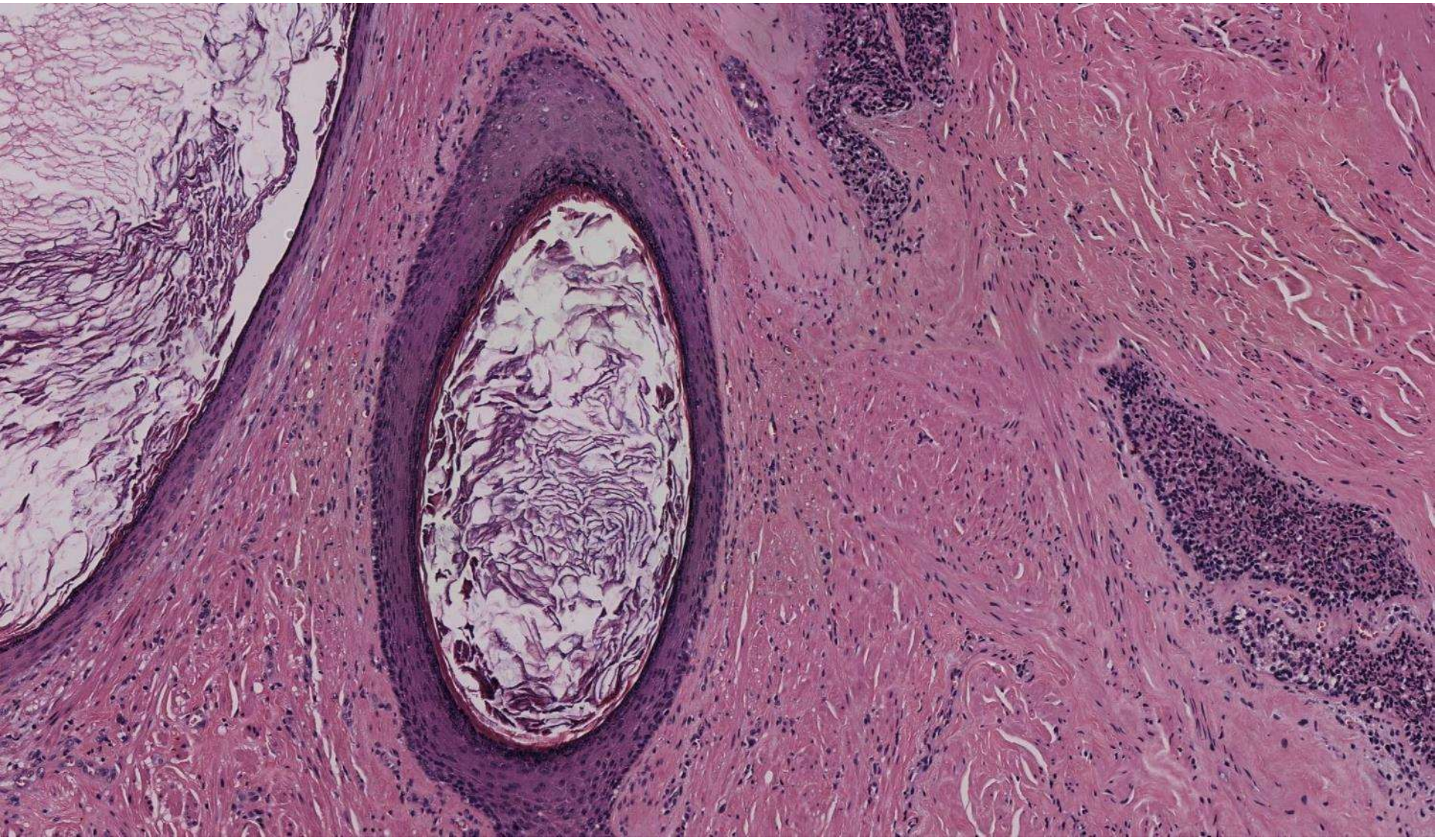


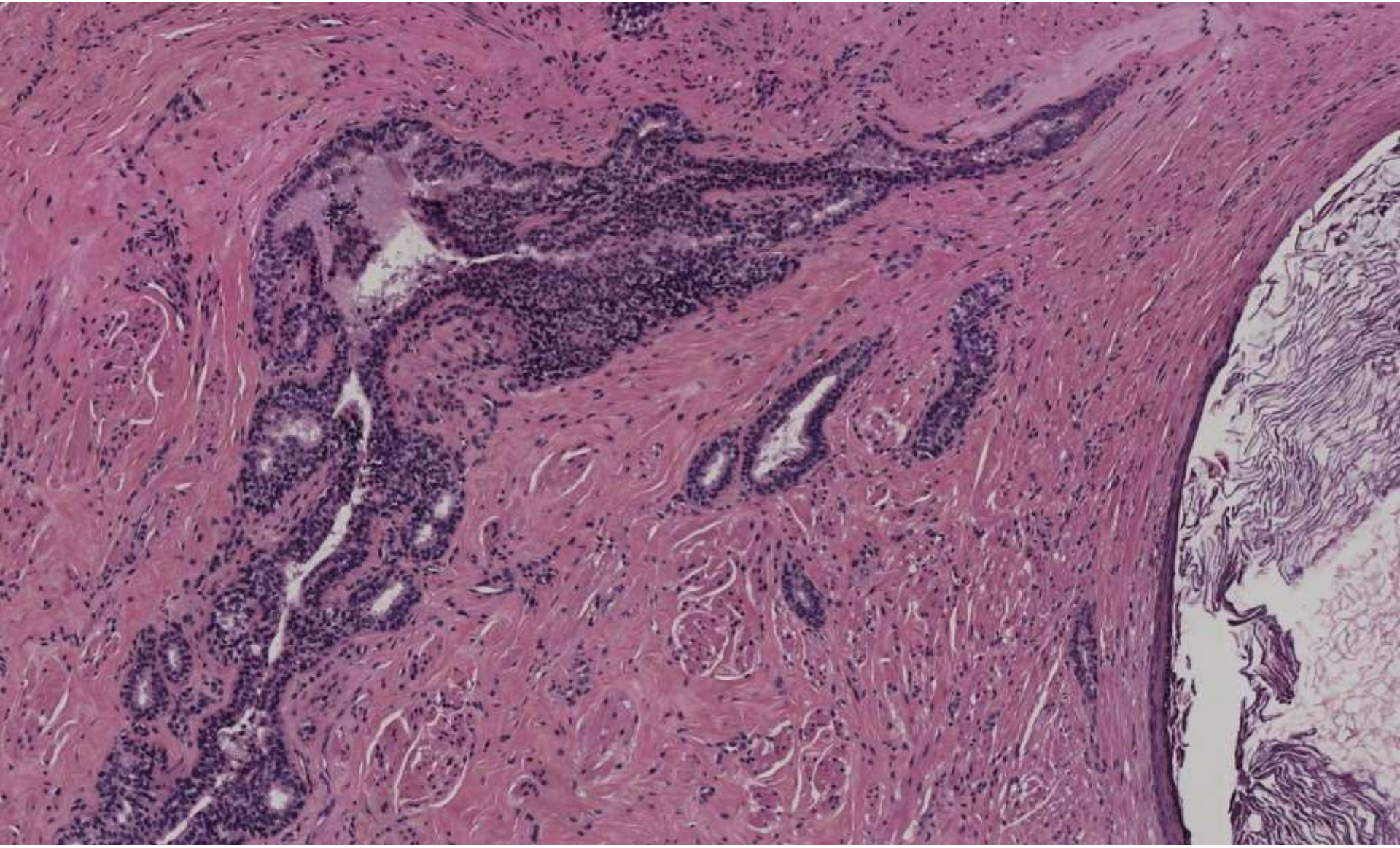


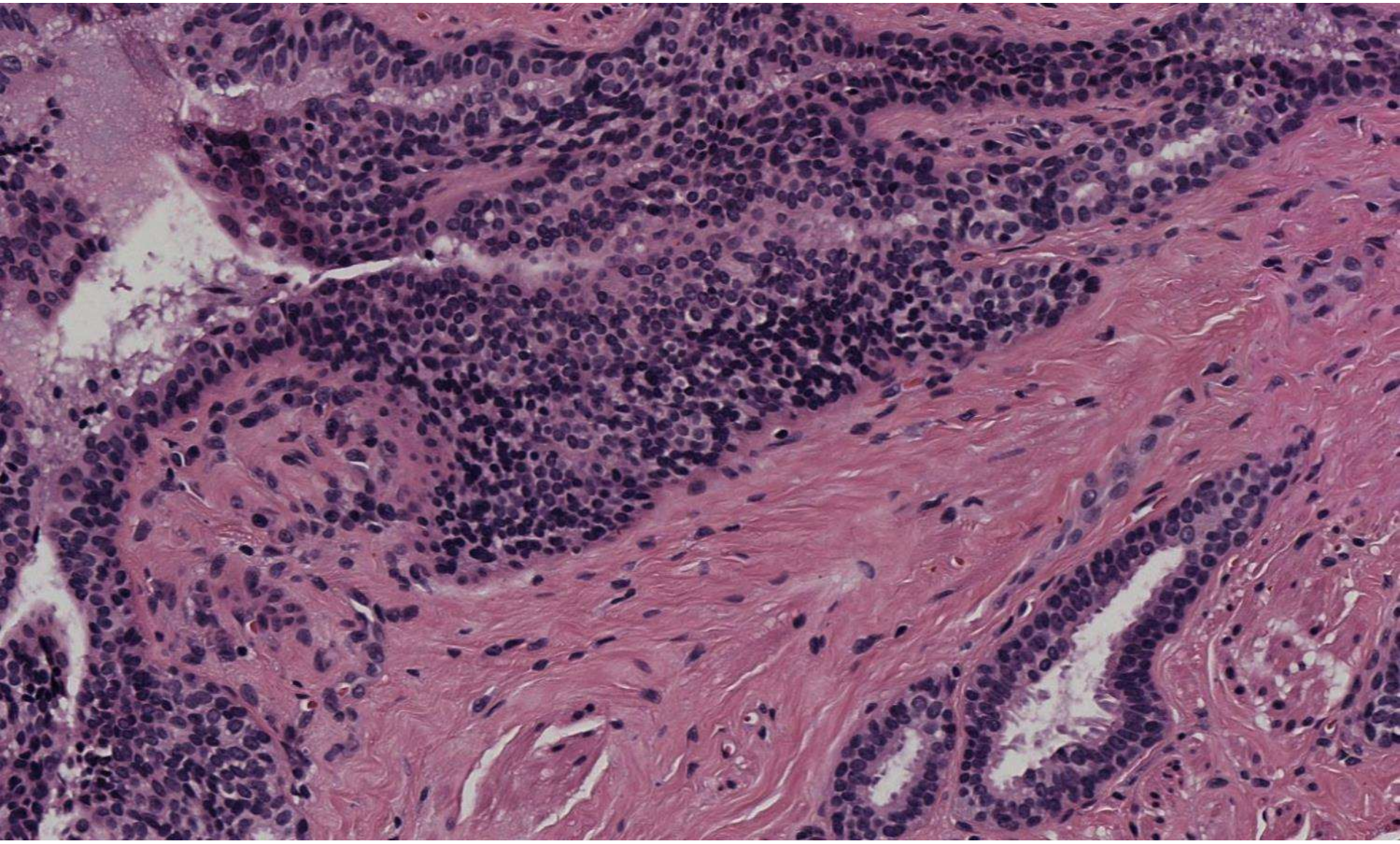












DDx

- Squamous metaplasia of lactiferous duct
- Epidermal inclusion cyst
- Infectious abscess
- Granulomatous mastitis
- Mammary duct ectasia

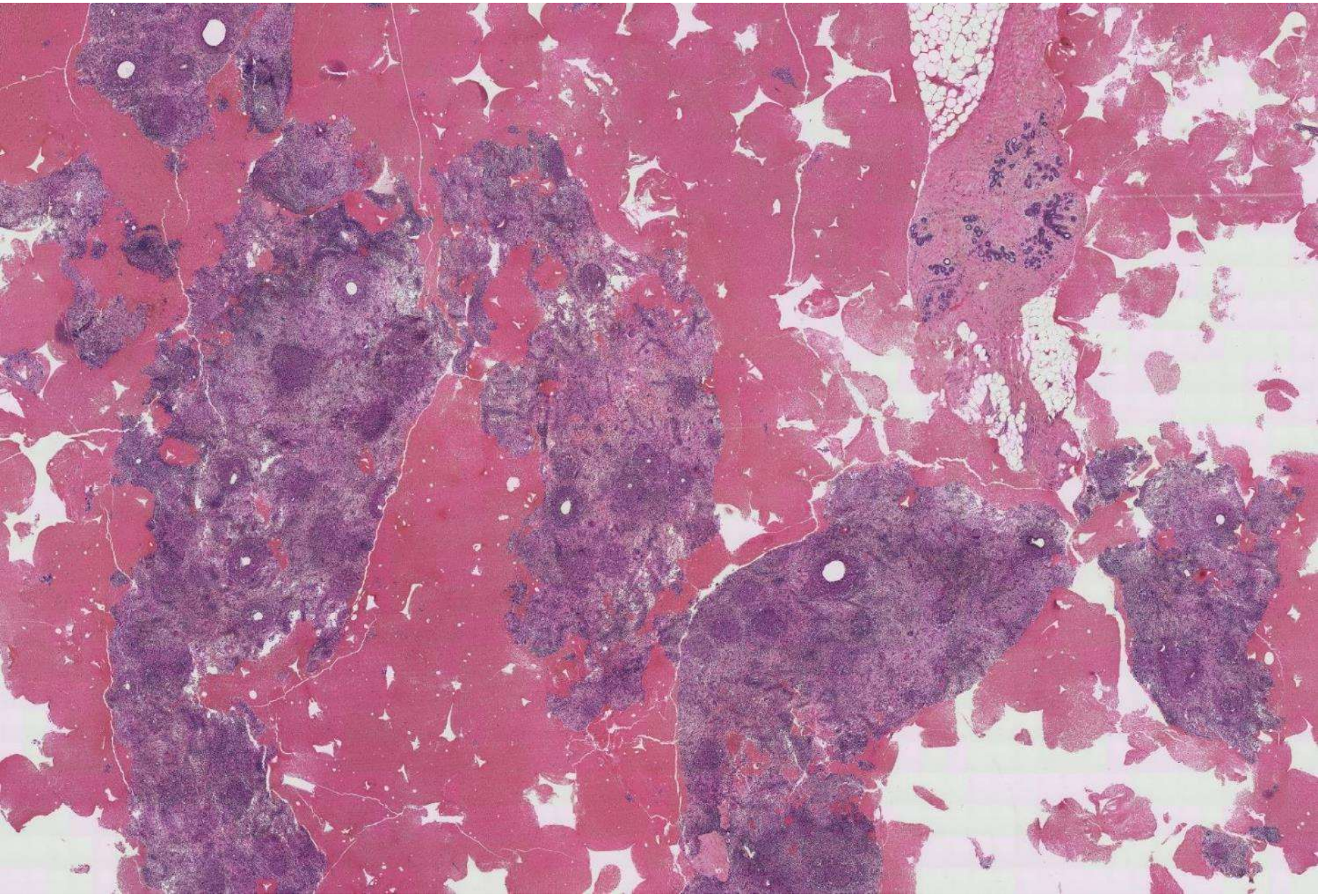
Squamous metaplasia of lactiferous duct (SMOLD)

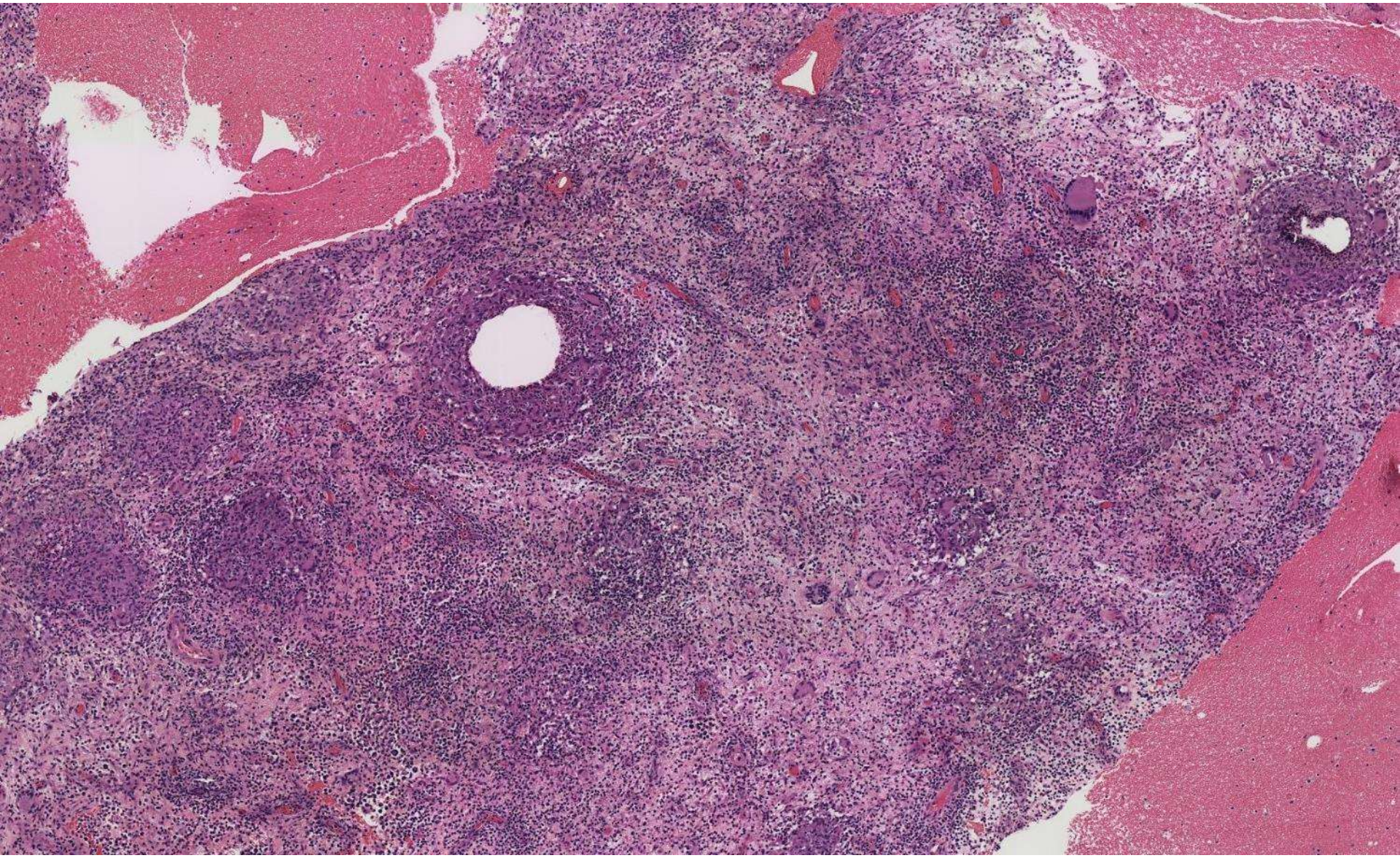
- **Nipple ducts with keratinizing squamous metaplasia w/associated chronic (+/- active) inflammatory response**
- **FNA: anucleate squamous cells & keratinous debris**
- **Clinical: smoking, recurrent subareolar abscess**
  - Often painful, red, mass
    - Mimic infection: ineffective I&D+antibiotics
- **Treatment: surgical excision**

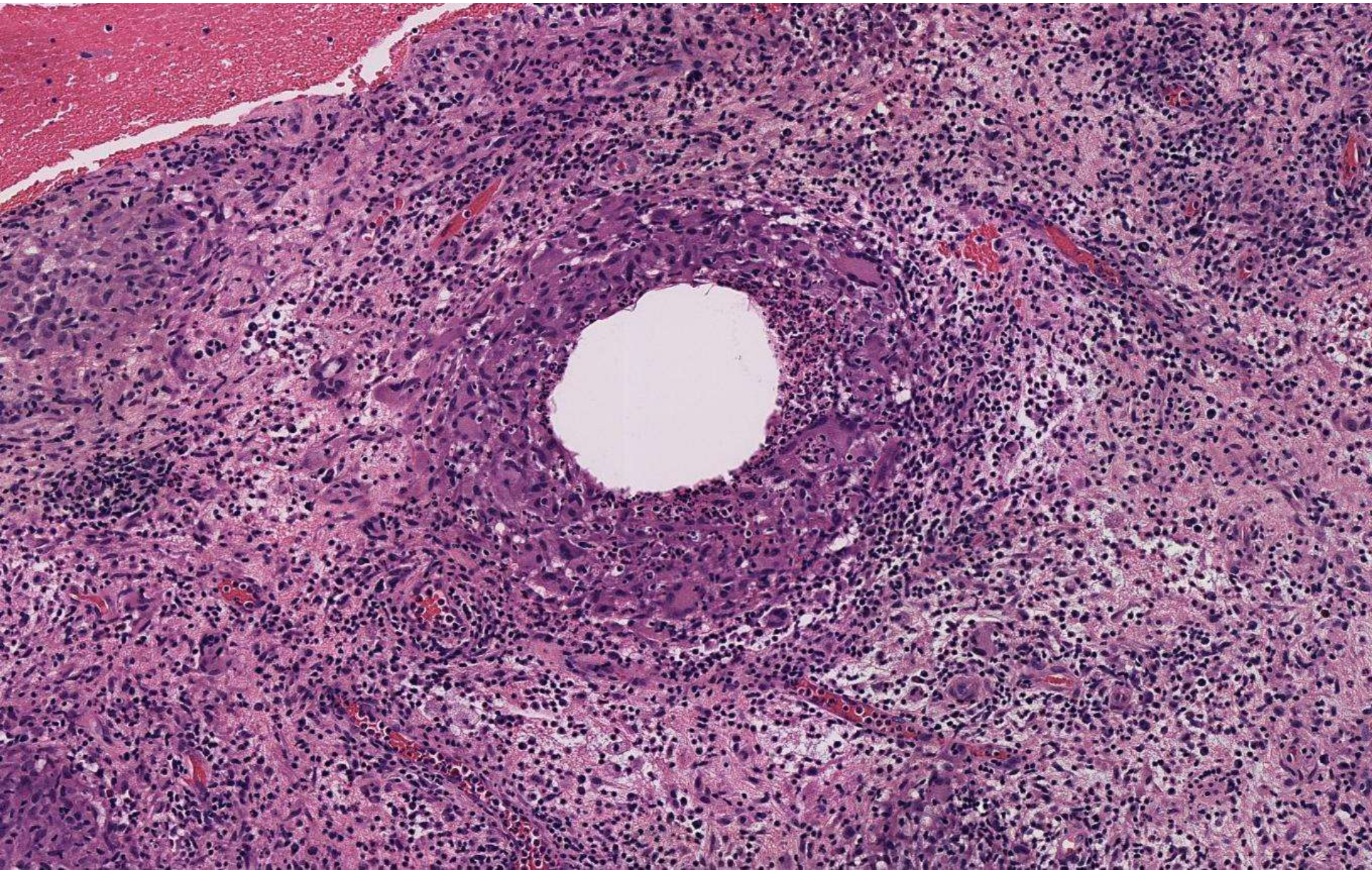
21-0205

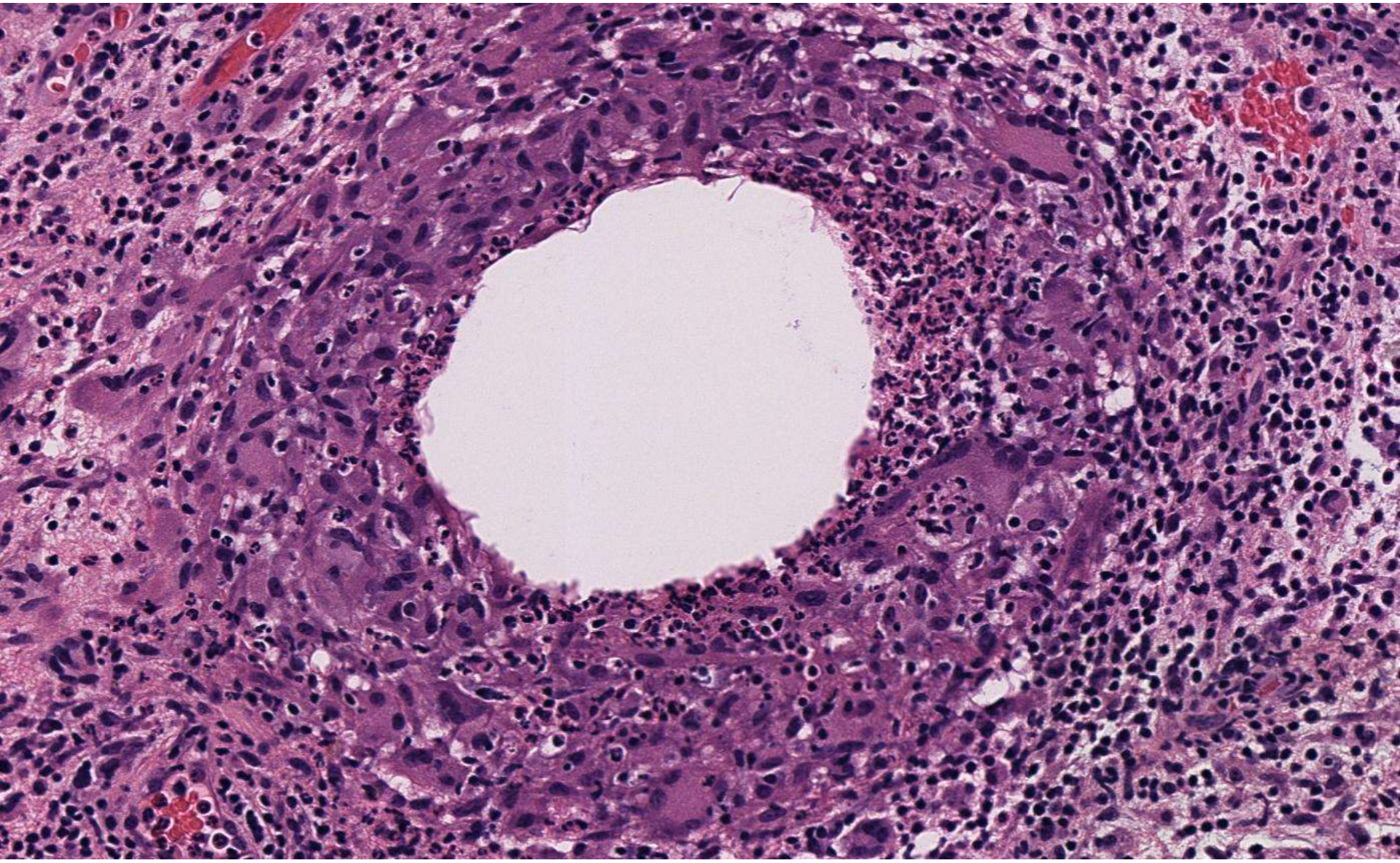
Ankur Sangoi; El Camino Hospital

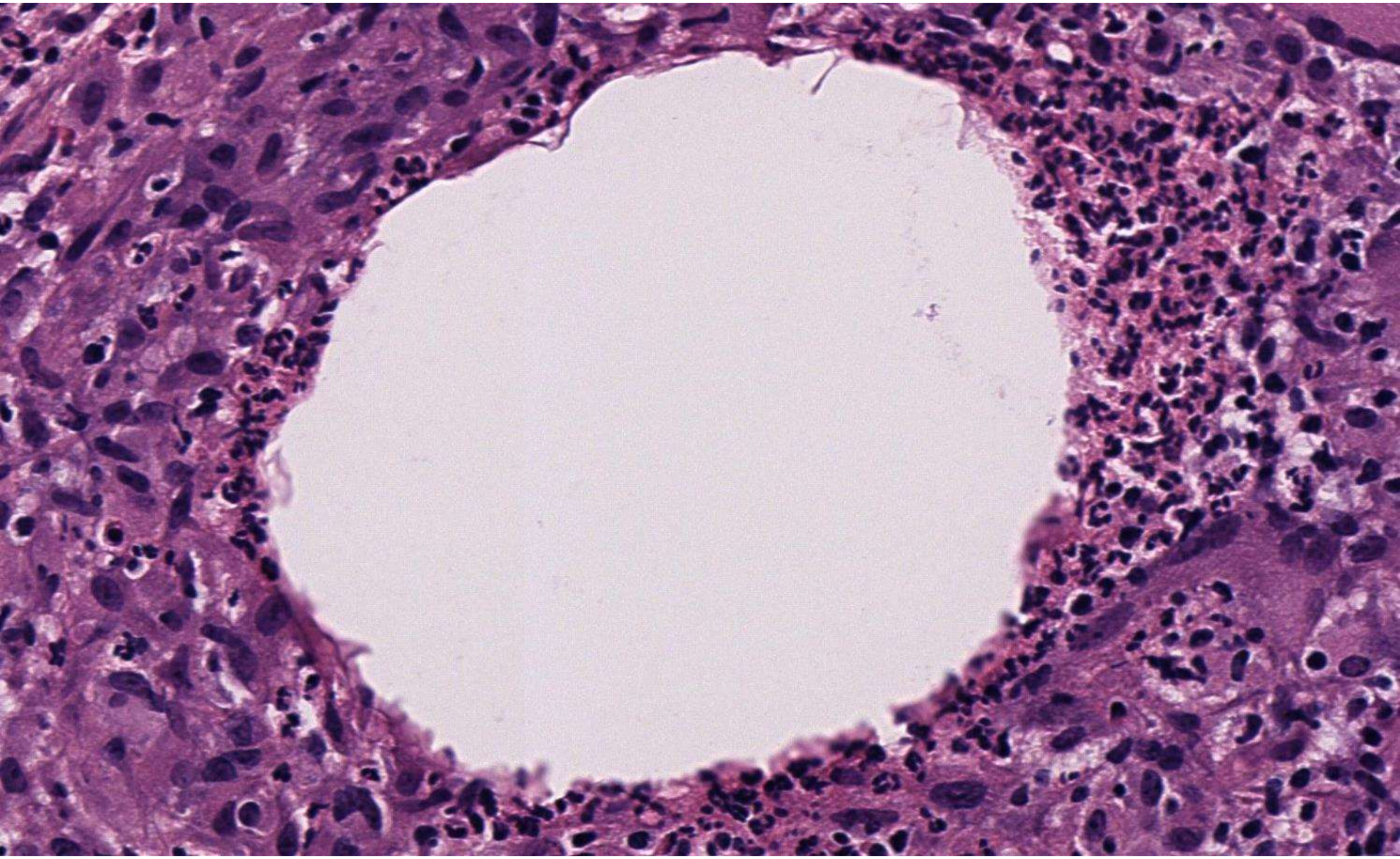
40-year-old F with clinically worrisome breast mass.

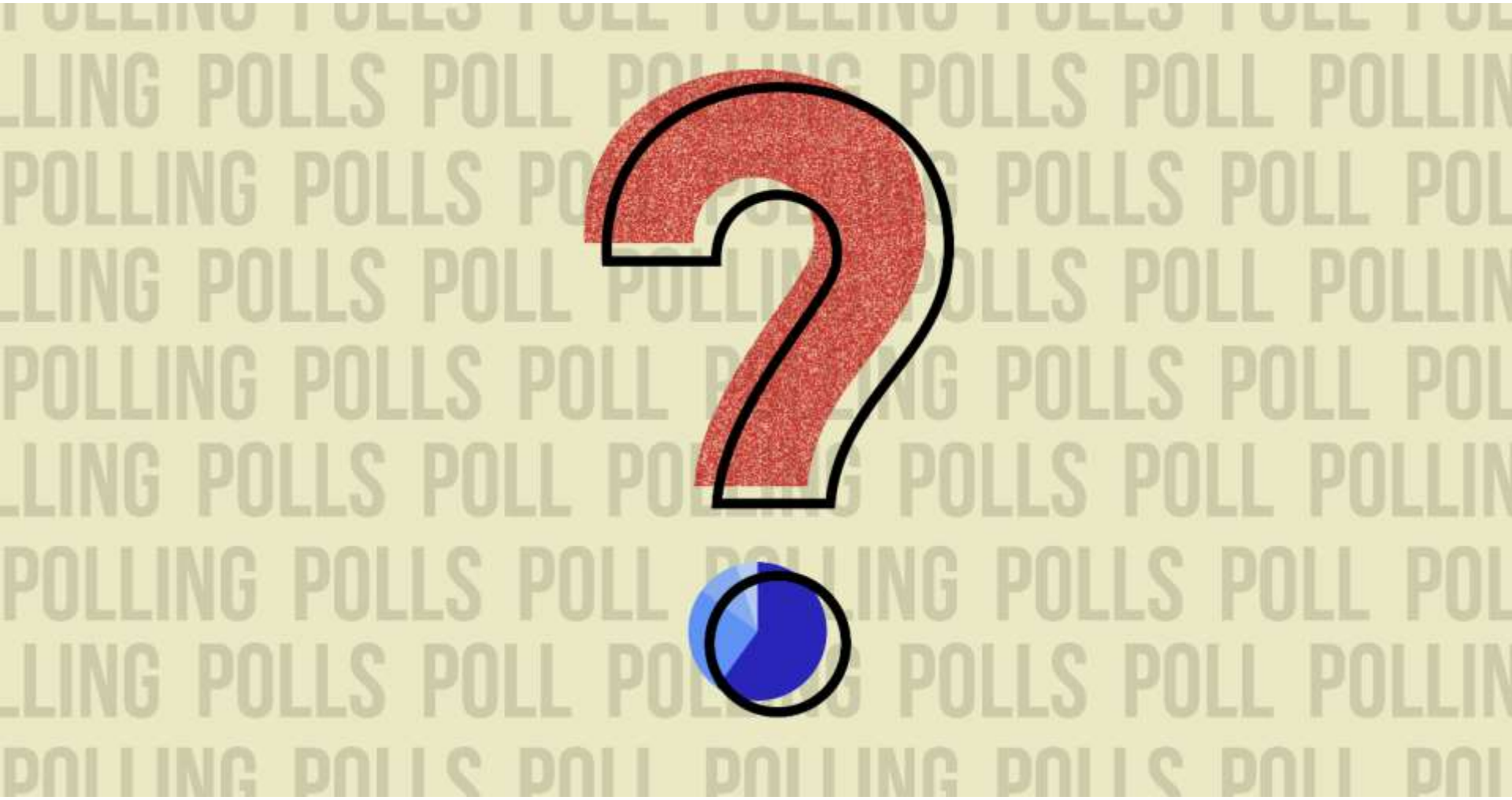






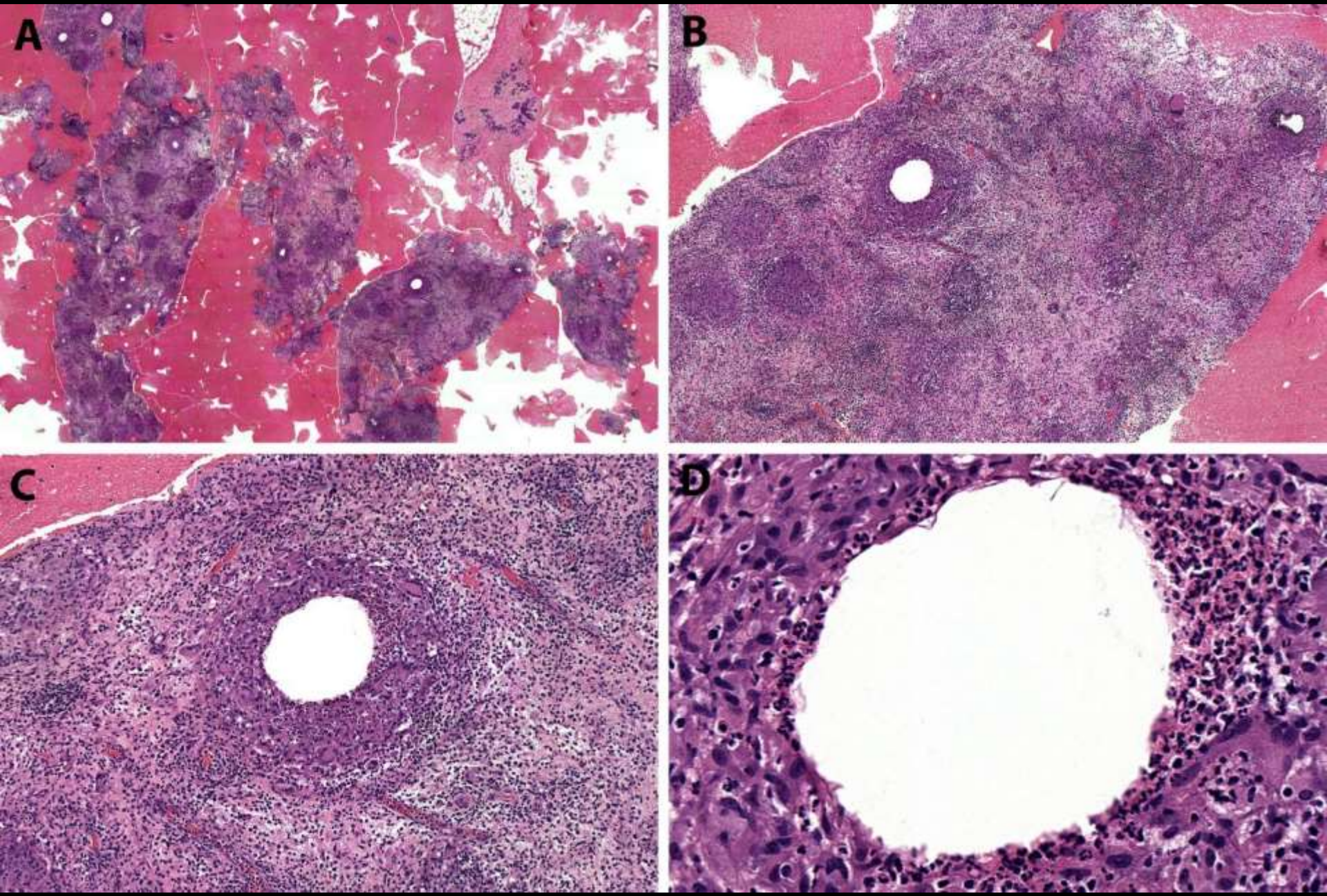


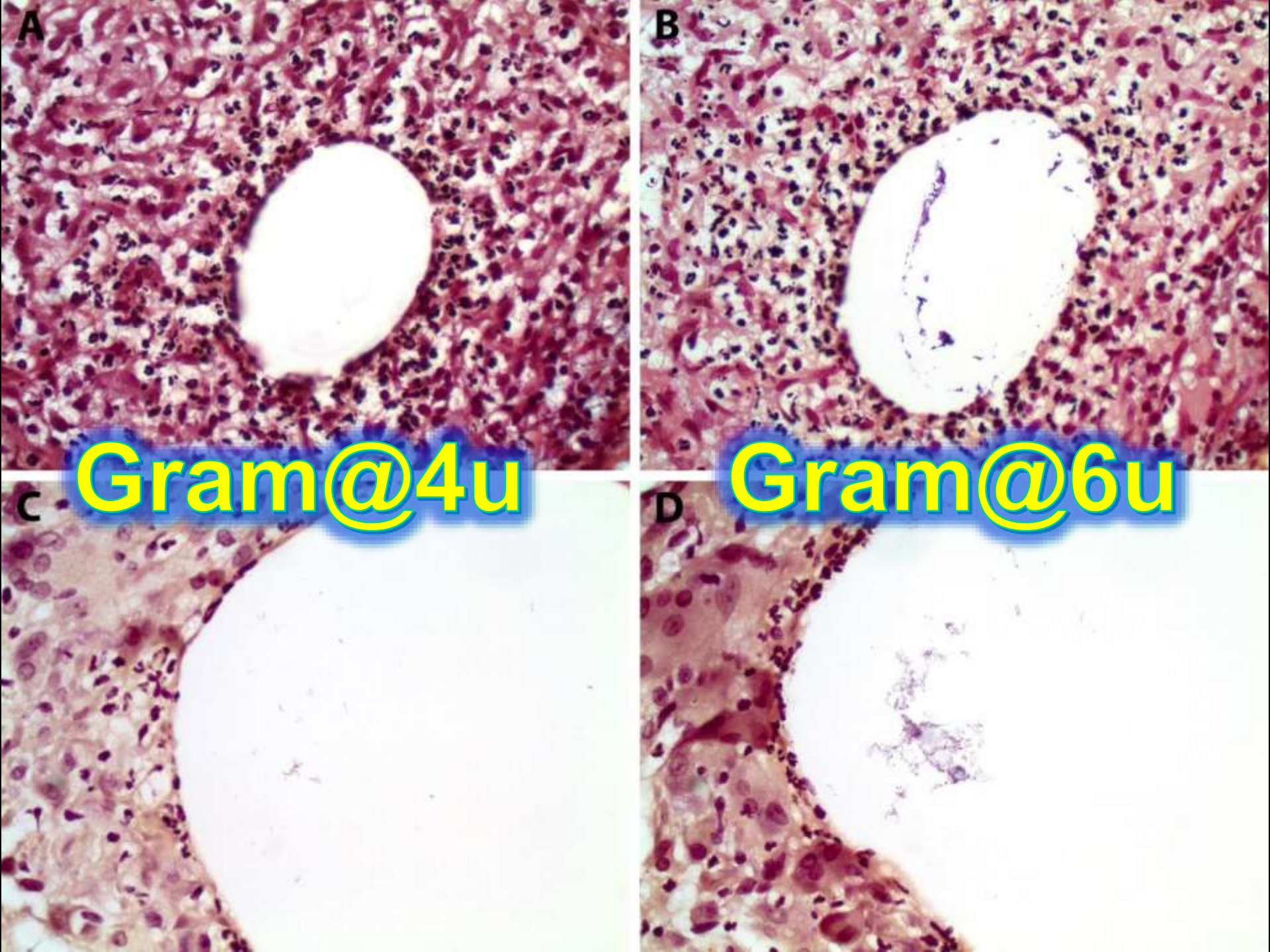



POLLING POLLS POLL

DDx

- Cystic neutrophilic granulomatous mastitis (CNGM)
- Foreign body reaction
- Fat necrosis
- Autoimmune-mediated mastitis
- Sarcoidosis
- Subareolar abscess/SMOLD


A
B
C
D


A
B
Gram@4u
Gram@6u
C
D

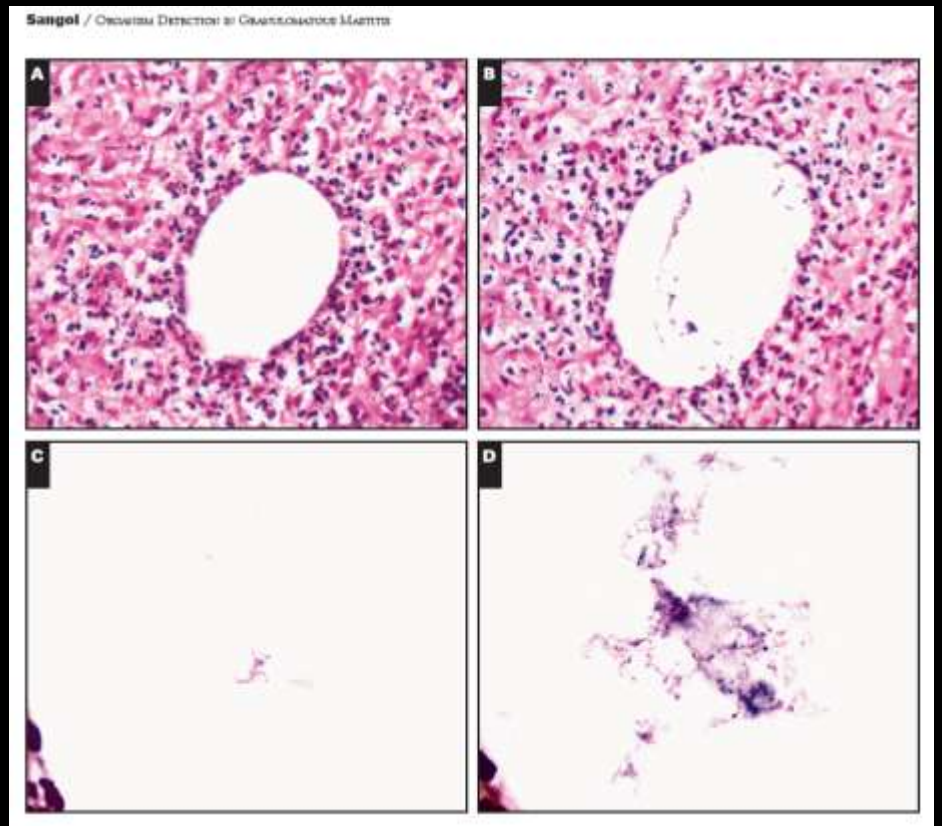
"Thick Section" Gram Stain Yields Improved Detection of Organisms in Tissue Sections of Cystic Neutrophilic Granulomatous Mastitis

Ankur R. Sangoi, MD

Form the Department of Pathology, El Camino Hospital, Mountain View, CA.

Key Words: Breast; Cystic neutrophilic; Gram stain; Granulomatous; Mastitis; Thickness

Am J Clin Pathol May 2020;153:593-597



ABSTRACT

Objectives: *Cystic neutrophilic granulomatous mastitis (CNGM) is an uncommon subtype of granulomatous mastitis featuring epithelioid histiocytes/neutrophils rimming discrete cystic spaces. When present, gram-positive bacteria (typically* Corynebacterium *species) are identified within these cystic spaces, although they can be difficult to appreciate on tissue sections.*

Methods: *Based on pilot gram-stained tissue sections of CNGM cases cut on 6 μm thickness (in which bacterial organisms were more readily identifiable) instead of the traditional 4 μm, a formal comparative analysis of 19 CNGM cases was performed on parallel 6-μm ("thick") vs 4-μm sections from one representative block per case.*

Results: *Biopsies (n = 17) and excisional specimens (n = 2) from 19 CNGM cases were included. Gram-positive palisaded rods were identified in seven cases using 4-μm sections and in 11 cases using 6-μm sections (sensitivity of 37% vs 58% in identifying organisms). Among all seven cases of organisms seen on the 4-μm section Gram stain, the paired 6-μm section Gram stain showed a higher number of and more readily identifiable bacteria.*

Conclusions: *Thick section Gram stain of representative tissue blocks performed at 6 μm improves both detection rate and ease of identification of gram-positive organisms in CNGM.*

Table 1

Clinicopathologic Features of 19 Cases of Cystic Neutrophilic Granulomatous Mastitis

Case	Procedure	Age, y	Laterality	Clinical Diagnosis	Smoker	Nulliparous	Ethnicity	Cultures	Gram Stain, 4 µm	Gram Stain, 6 µm
1	Biopsy	33	Left	Malignancy vs abscess	No	No	Asian	Not sent	Positive	Positive (more bacteria)
2	Excision	35	Left	Mass	Unknown	Unknown	Asian	Not sent	Negative	Negative
3	Biopsy	37	Left	Mass	Unknown	Unknown	Caucasian	Not sent	Negative	Positive
4	Biopsy	38	Left	Abscess	No	Yes	Asian	Negative	Negative	Negative
5	Biopsy	43	Left	Pregnant; mass	No	No	Asian	Not sent	Negative	Negative
6	Biopsy	25	Right	Mass vs mastitis	Unknown	Unknown	Unknown	Not sent	Negative	Positive
7	Biopsy	40	Right	Mastitis	No	No	Asian	Not sent	Negative	Positive
8	Biopsy	34	Right	Mass vs mastitis	No	No	Asian	Not sent	Negative	Negative
9	Biopsy	41	Right	Mass	No	No	Asian	Not sent	Negative	Negative
10	Biopsy	31	Right	Mass vs abscess	No	No	Caucasian	Not sent	Negative	Positive
11	Biopsy	41	Left	Malignancy vs mastitis	No	No	Asian	Not sent	Negative	Negative
12	Biopsy	57	Right	Fat necrosis	Unknown	Unknown	Caucasian	Not sent	Positive	Positive (more bacteria)
13	Biopsy	38	Right	Mass vs abscess	No	Yes	Asian	Negative	Negative	Negative
14	Biopsy	38	Left	Mass	Unknown	Unknown	Asian	Not sent	Positive	Positive (more bacteria)
15	Excision	45	Left	Mass	No	No	Asian	Negative	Positive	Positive (more bacteria)
16	Biopsy	38	Left	Mass	No	No	Hispanic	Negative	Negative	
17	Biopsy	34	Left	Mass vs abscess	No	No	Hispanic	Not sent	Positive	Positive (more bacteria)
18	Biopsy	33	Right	Abscess	No	No	Hispanic	Not sent[a]	Positive	Positive (more bacteria)
19	Biopsy	37	Left	Mass vs abscess	No	No	Hispanic	Not sent	Positive	Positive (more bacteria)

[a]Formalin-fixed paraffin-embedded block was sent for broad-range 16S rDNA polymerase chain reaction, which identified *Corynebacterium kroppenstedtii*.

Review

Cystic neutrophilic granulomatous mastitis: an update

Jessie M Wu, Gulisa Turashvili

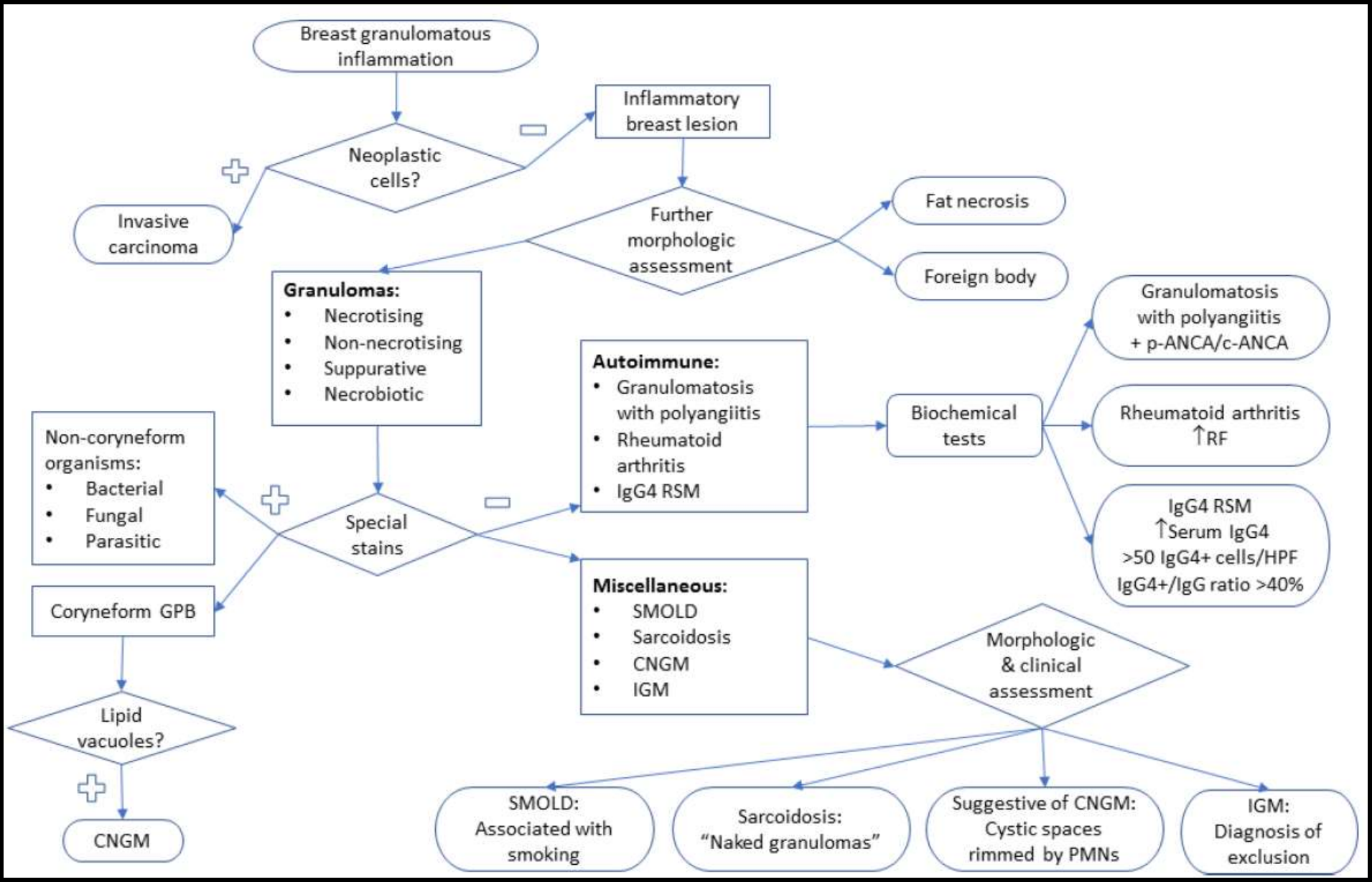
Wu JM, Turashvili G. *J Clin Pathol* 2020;**73**:445–453. doi:10.1136/jclinpath-2019-206180

Table 2 Suggested diagnostic criteria for CNGM (A) and canned comments (B) to convey degrees of diagnostic certainty in pathology reports

A

1. Histology	2. Gram stain on tissue section	3. Microbiology (culture or molecular testing)
1.1. Lobulocentric inflammation	2.1. Coryneform GPB	3.1. Positive for corynebacteria
1.2. Cystic spaces rimmed by neutrophils	2.2. Non-coryneform GPB	3.2. Positive for organisms other than corynebacteria
1.3. Granulomas	2.3. Gram negative organisms	3.3. Negative for organisms
	2.4. Mixed Gram positive and negative organisms	
	2.5. Negative for organisms	

B	Diagnostic criteria	Interpretation	Pathology report
A	(1) 2–3 of 3 features **AND** (2) 2.1 **OR** (3) 3.1	Characteristic morphology with GPB or positive culture	Diagnosis: Findings consistent with CNGM (see comment). Comment: The morphology combined with GPB on Gram stain is consistent with CNGM. Microbiological culture for corynebacteria may be considered. (include results of culture if performed)
B	(1) 2–3 of 3 features **AND** (2) 2.2 to 2.5 **OR** (3) 3.2 to 3.3	Characteristic morphology without GPB or positive culture	Diagnosis: Findings suggestive of CNGM (see comment) Comment: The morphological features are suggestive of CNGM. However, Gram stain shows no evidence of GPB indicative of *Corynebacteri*um species typically associated with CNGM. As corynebacteria are fastidious organisms, the absence of supportive microbiological evidence should not immediately exclude infection as a cause. The differential diagnosis includes other granulomatous diseases of infectious and non-infectious aetiology. Clinical and microbiological correlation is required. Microbiological culture for corynebacteria may be considered. (include results of culture if performed)
C	(1) Any of the 3 features **AND** (2) 2.1 **OR** (3) 3.1	Suspicious clinical and morphological features with GPB or positive culture (limited sample, for example, core biopsy)	Diagnosis: Granulomatous inflammation with bacterial forms (see comment) Comment: The morphological features are suggestive but not diagnostic of CNGM. Gram stain shows evidence of GPB indicative of *Corynebacteri*um species typically associated with CNGM. The differential diagnosis includes other granulomatous diseases of infectious and non-infectious aetiology. Clinical correlation is required. Microbiological culture for corynebacteria may be considered. (include results of culture if performed)
D	(1) Any of the 3 features **AND** (2) 2.2 to 2.5 **OR** (3) 3.2 to 3.3	Suspicious clinical and morphological features without GPB or positive culture (limited sample, for example, core biopsy)	Diagnosis: Granulomatous inflammation (see comment) Comment: The morphological features are those of granulomatous mastitis. Special stains (Gram, GMS, PASD, ZN) show no evidence of micro-organisms. The differential diagnosis includes CNGM and other granulomatous diseases of infectious and non-infectious aetiology. Clinical and microbiological correlation is required. Microbiological cultures, including corynebacteria, may be considered. (include results of culture if performed)


Breast granulomatous inflammation
Neoplastic cells?
+
−
Invasive carcinoma
Inflammatory breast lesion
Further morphologic assessment
Fat necrosis
Foreign body
Granulomas:
• Necrotising
• Non-necrotising
• Suppurative
• Necrobiotic
Special stains
+
−
Non-coryneform organisms:
• Bacterial
• Fungal
• Parasitic
Coryneform GPB
Lipid vacuoles?
+
CNGM
Autoimmune:
• Granulomatosis with polyangiitis
• Rheumatoid arthritis
• IgG4 RSM
Biochemical tests
Granulomatosis with polyangiitis + p-ANCA/c-ANCA
Rheumatoid arthritis ↑RF
IgG4 RSM ↑Serum IgG4 >50 IgG4+ cells/HPF IgG4+/IgG ratio >40%
Miscellaneous:
• SMOLD
• Sarcoidosis
• CNGM
• IGM
Morphologic & clinical assessment
SMOLD: Associated with smoking
Sarcoidosis: "Naked granulomas"
Suggestive of CNGM: Cystic spaces rimmed by PMNs
IGM: Diagnosis of exclusion

CNGM

- **Not all that uncommon**
- **Often parous women**
  - Indian, Hispanic > Asian, Caucasian
  - Mean age 35 y/o
- **Clinical: pain, asymmetry, or mass**

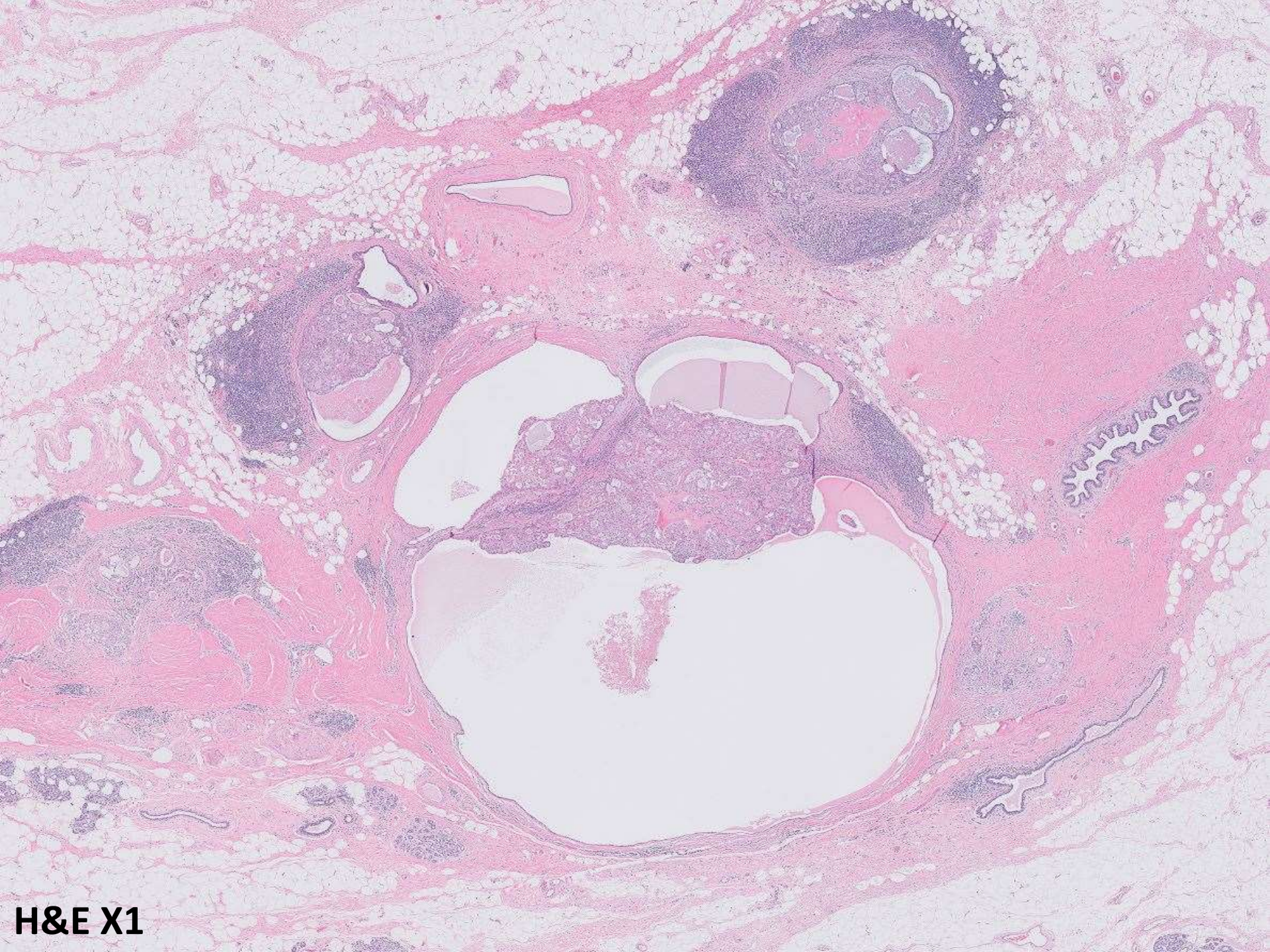
CNGM

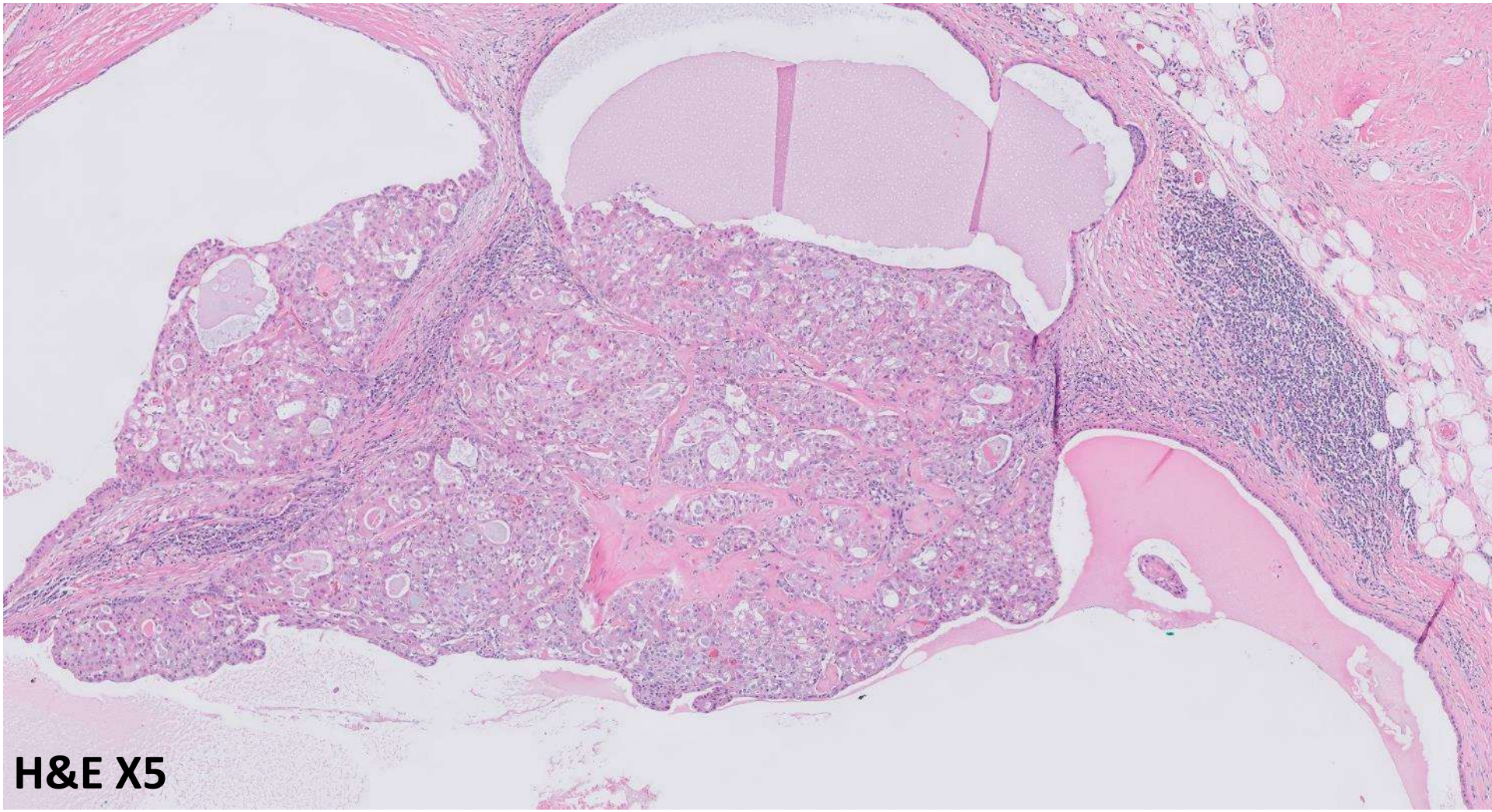
- **“thick” section (6 micron) Gram stain recommended on tissue block**
- **Routine cultures often negative**
  - Typical culprit: Corynebacterium
    - Often + on molecular testing
    - Important to suggest even in absence of + result
- **Tx: usually surgical + antibiotics**

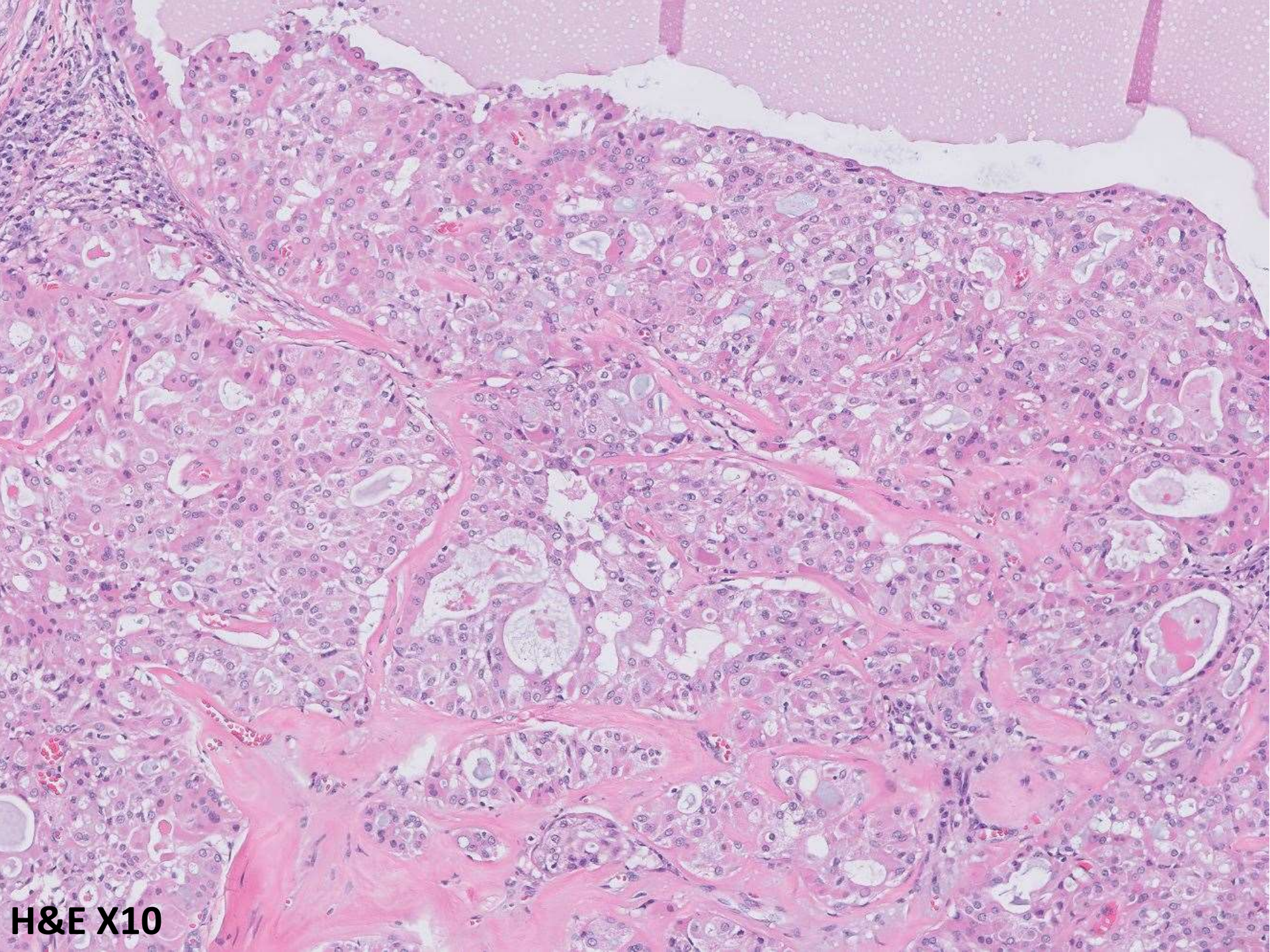
21-0206

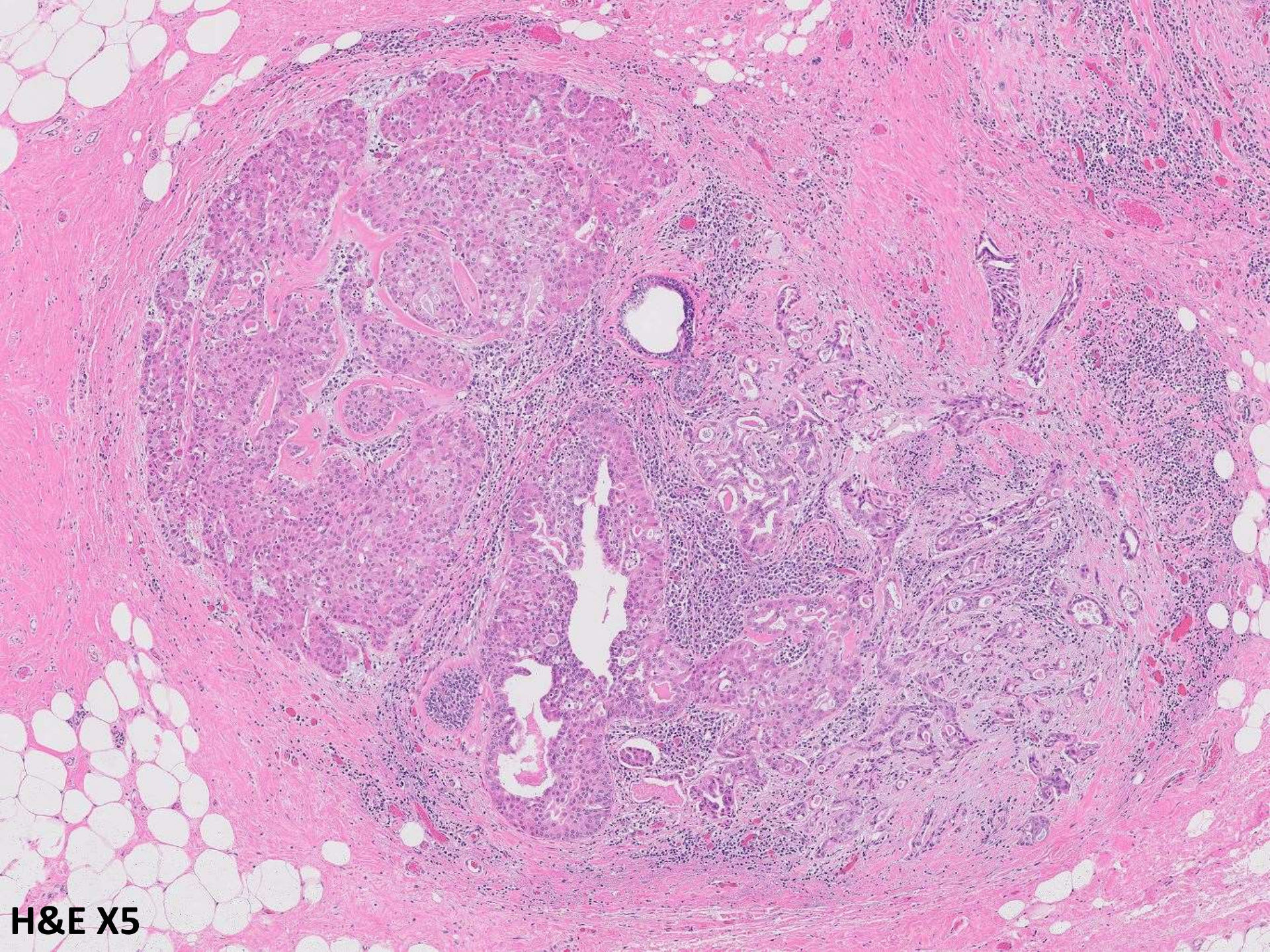
Saleh Najjar/Gregory Bean; Stanford

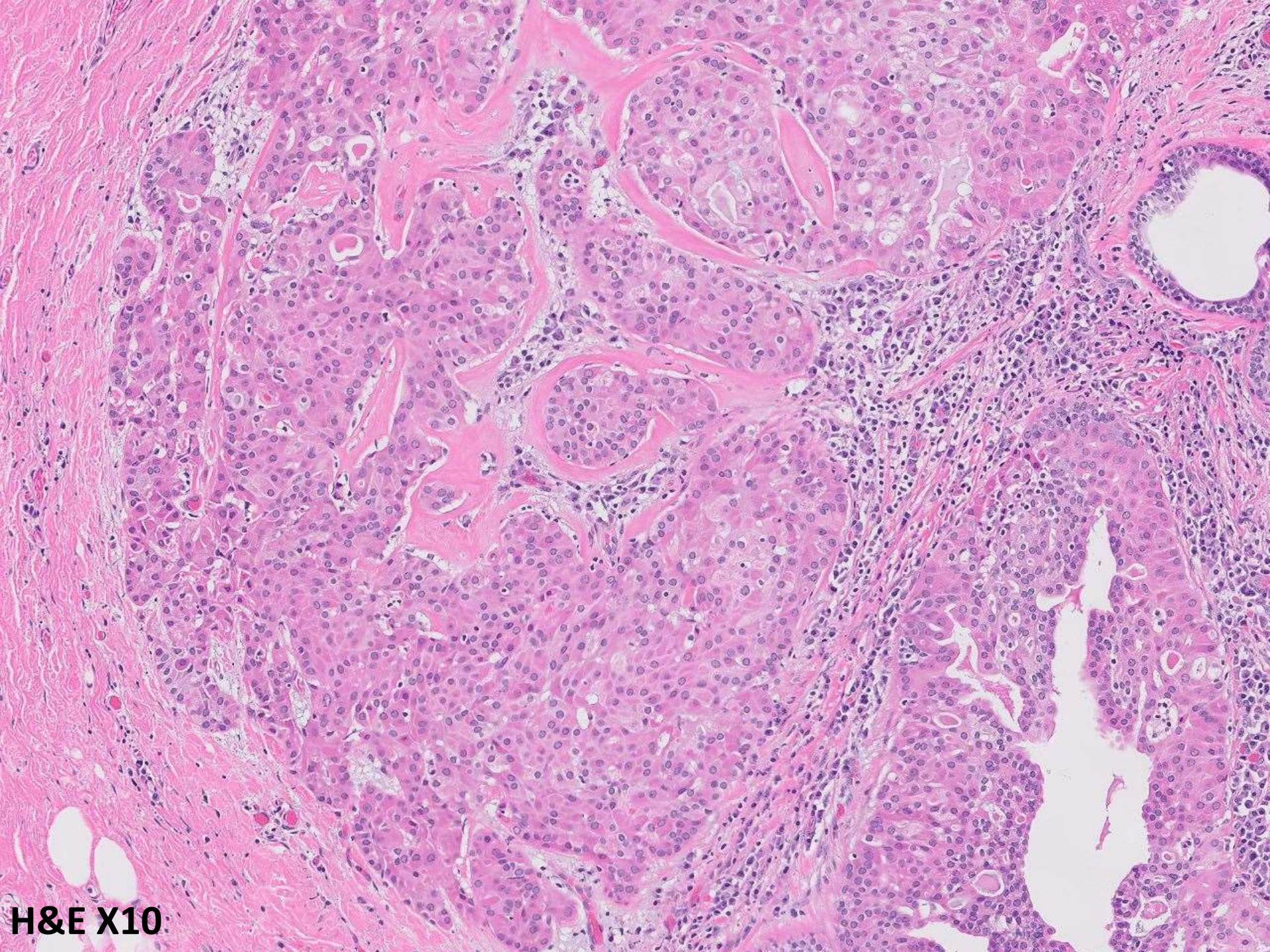
65-year-old F with asymmetry on mammogram


H&E X1


H&E X5


H&E X10


H&E X5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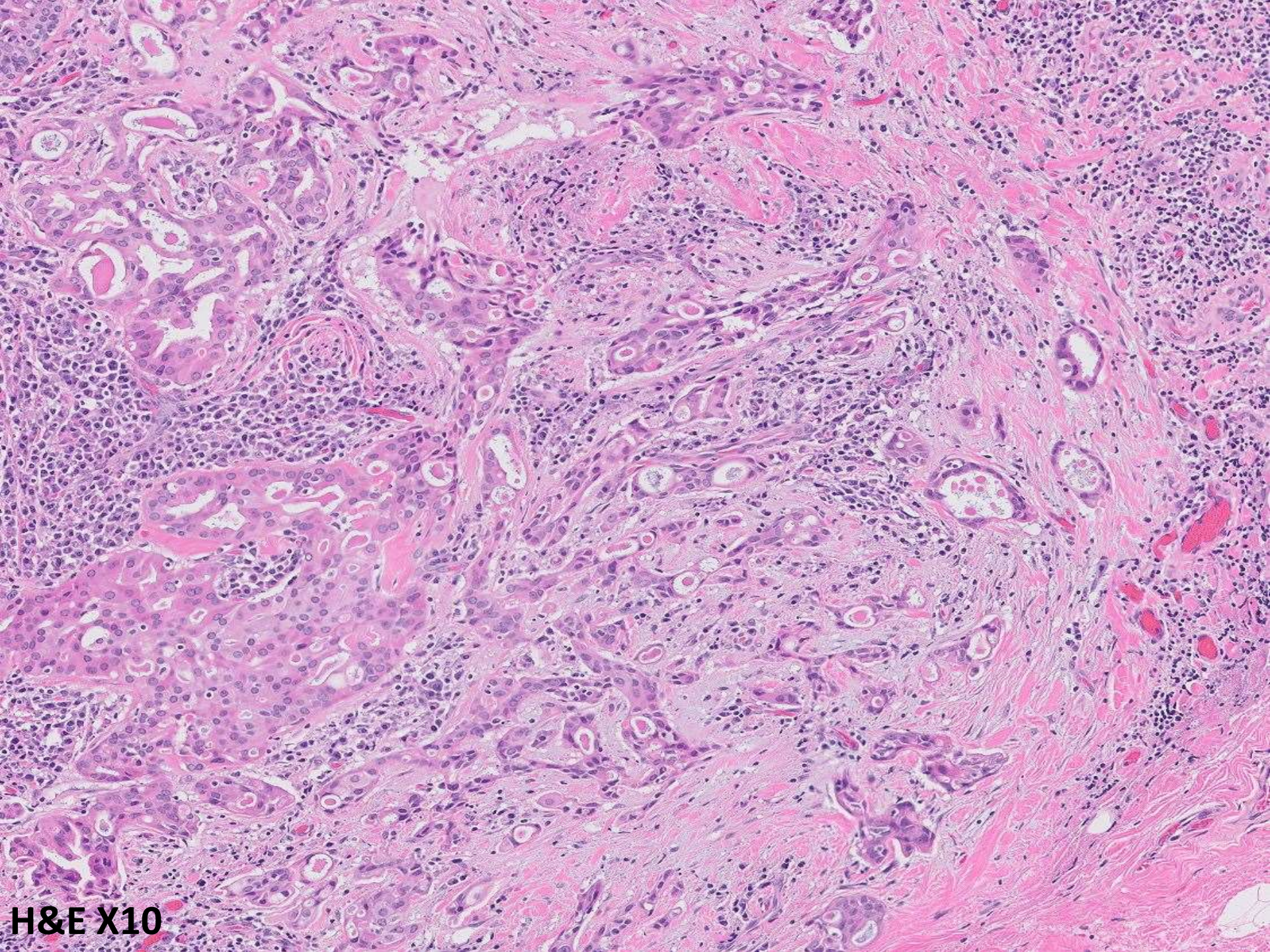
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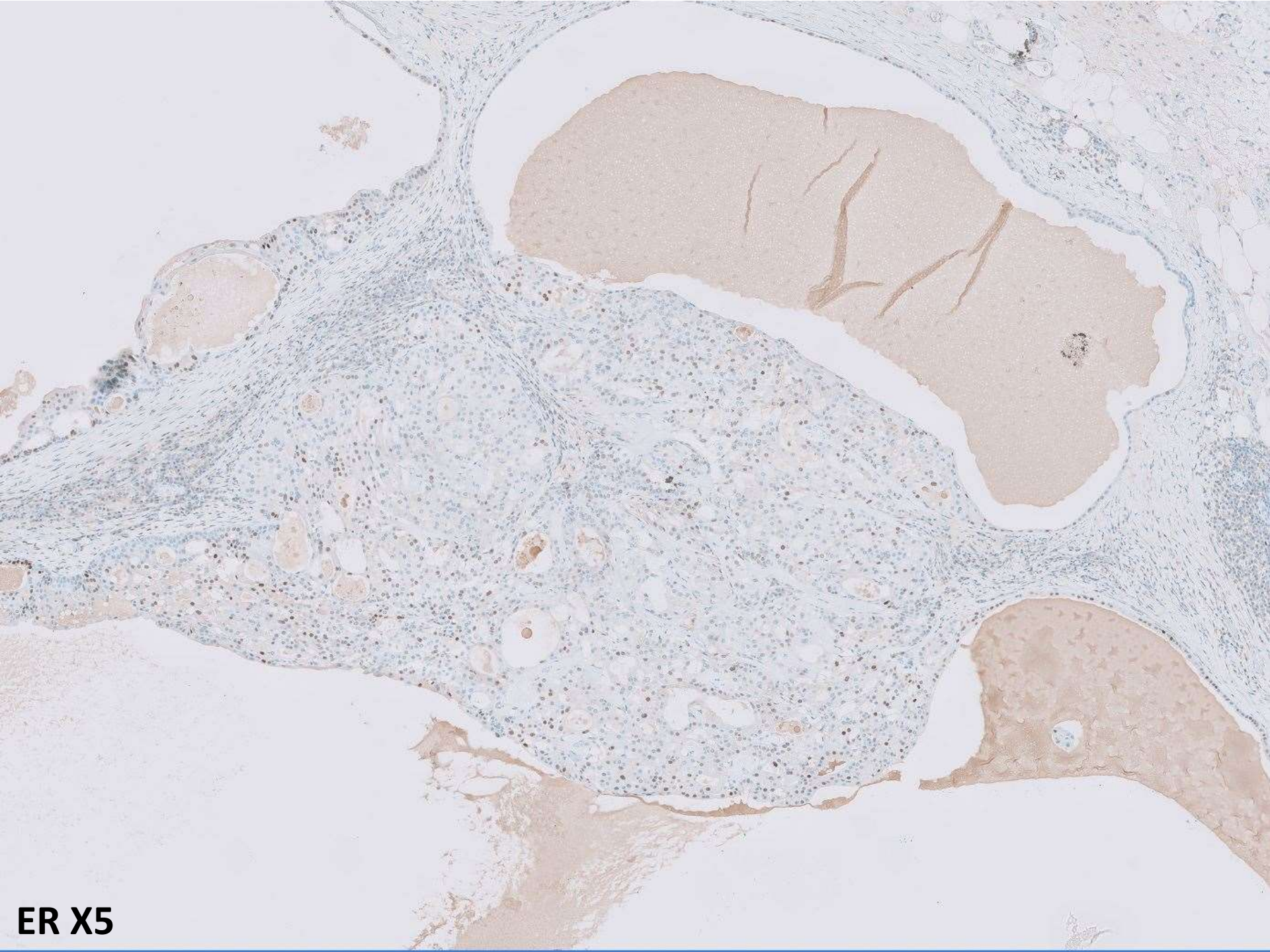
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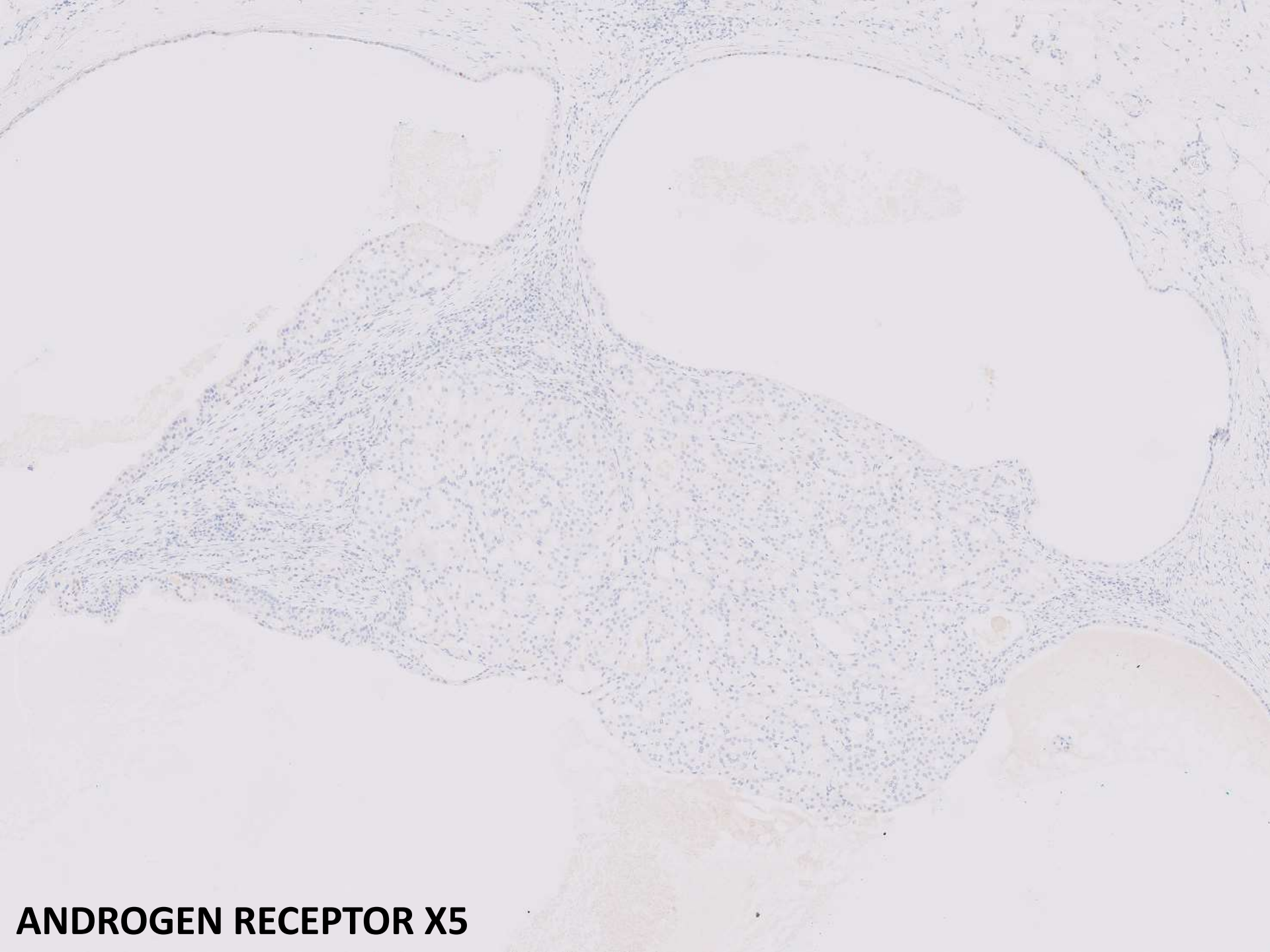
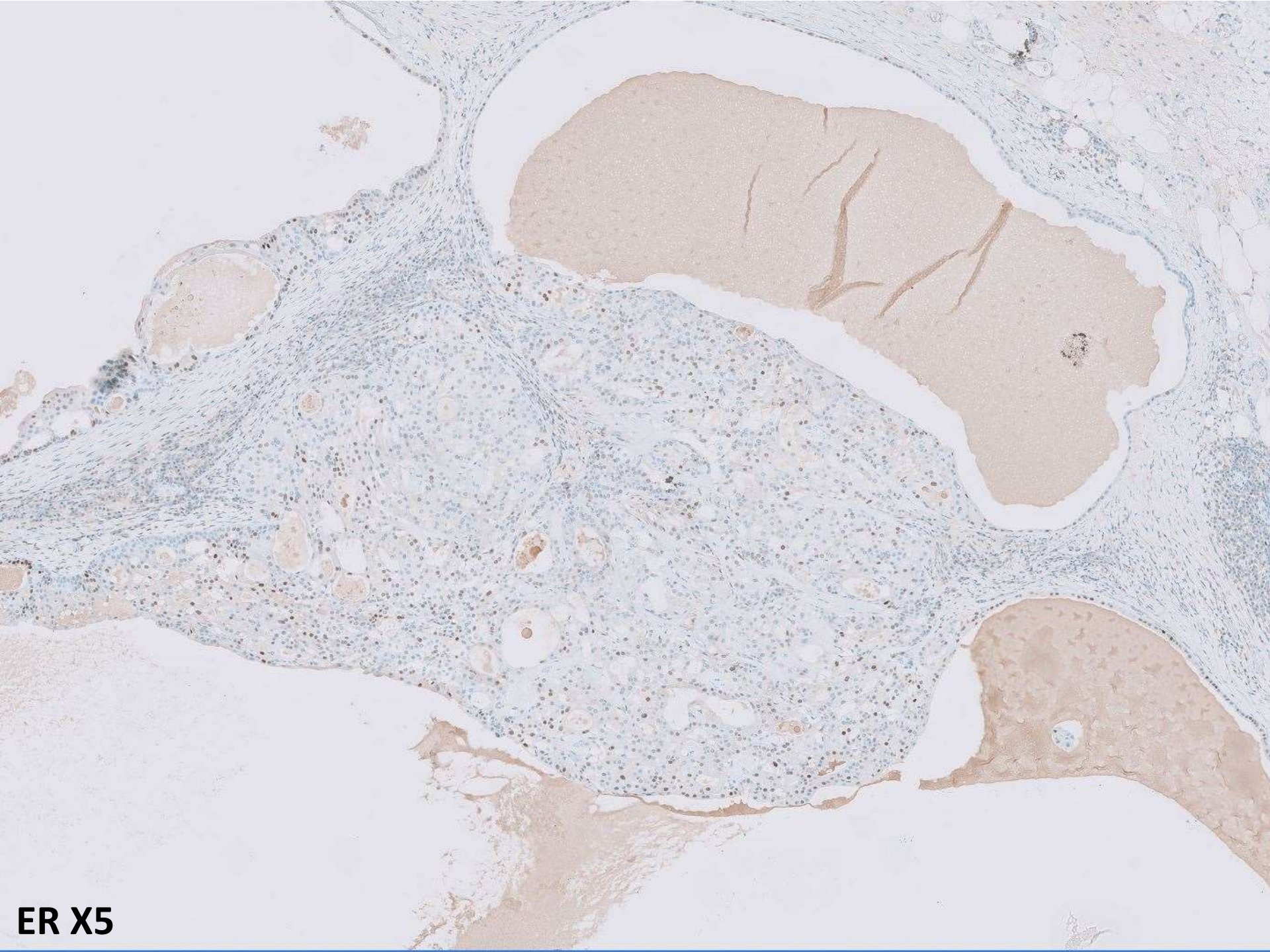
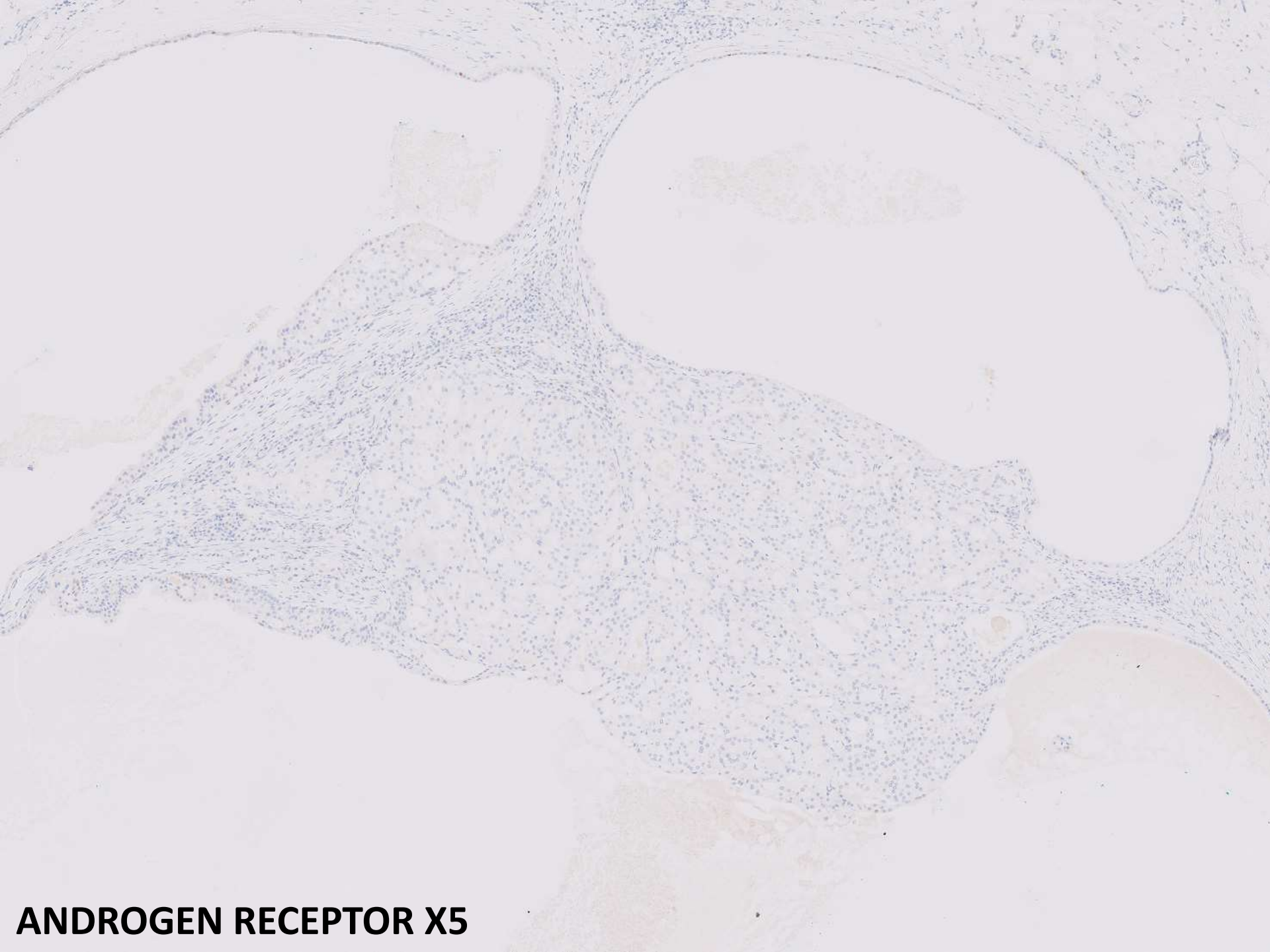


ANDROGEN RECEPTOR X5


ER X5



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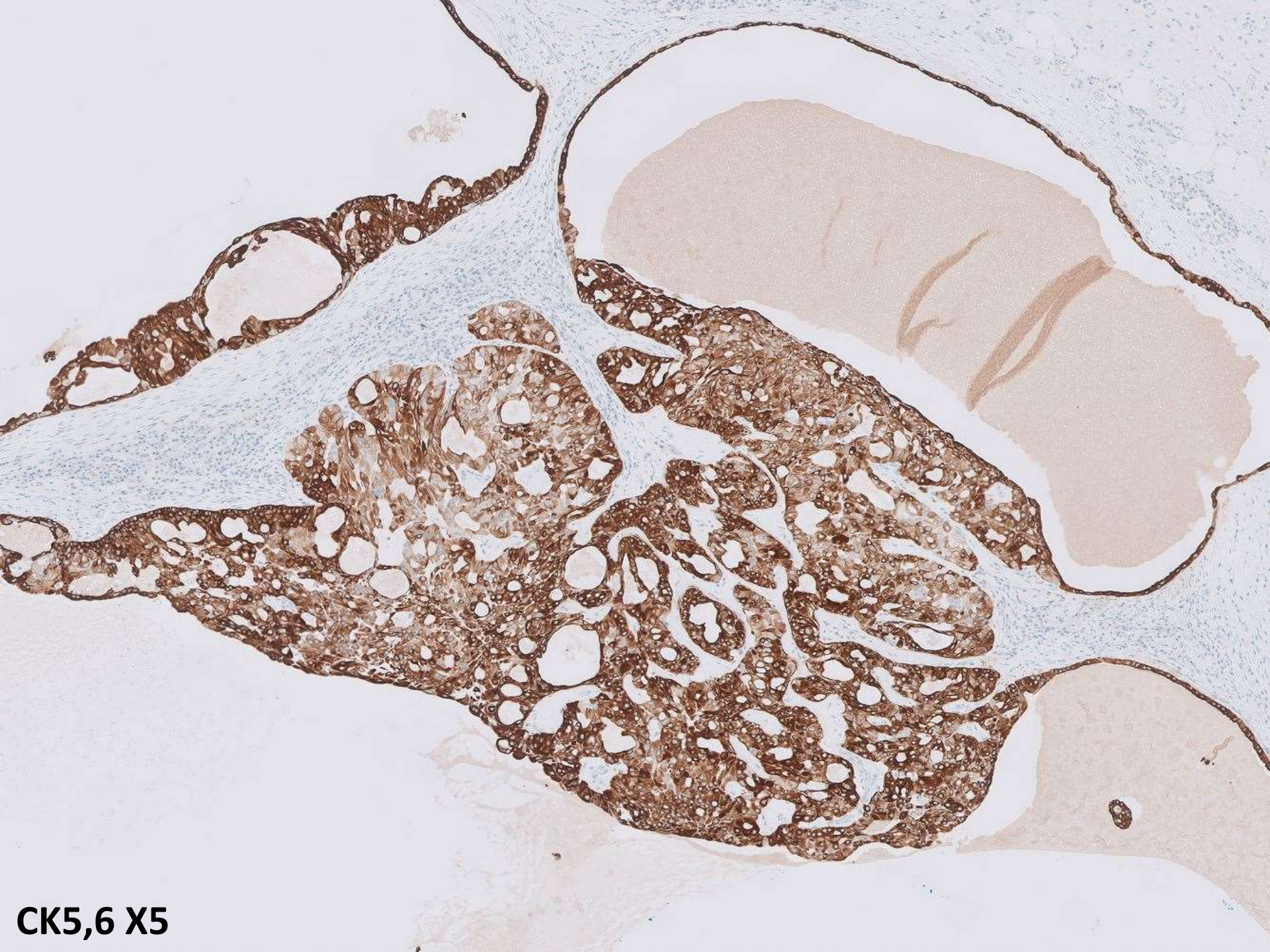
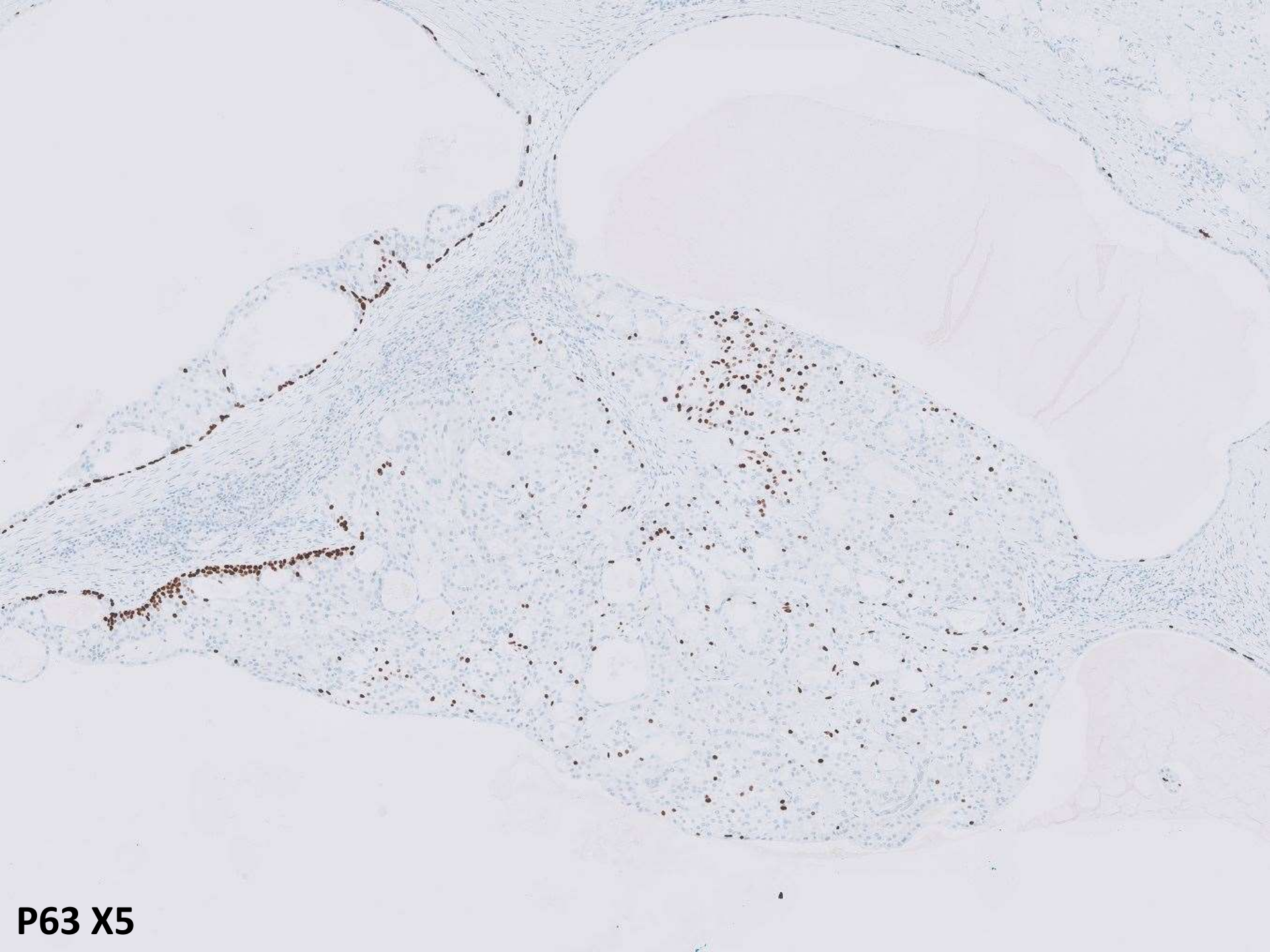
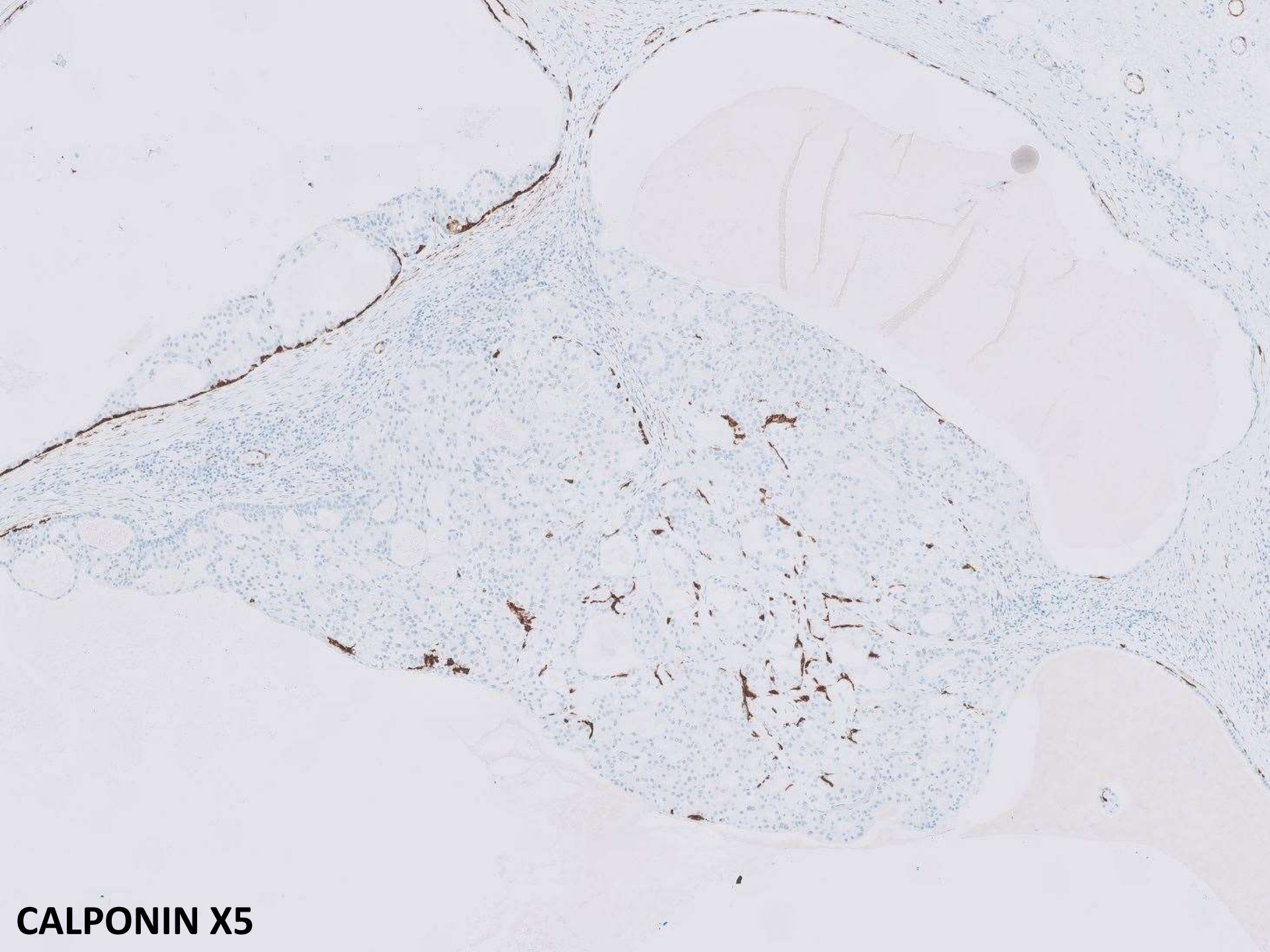


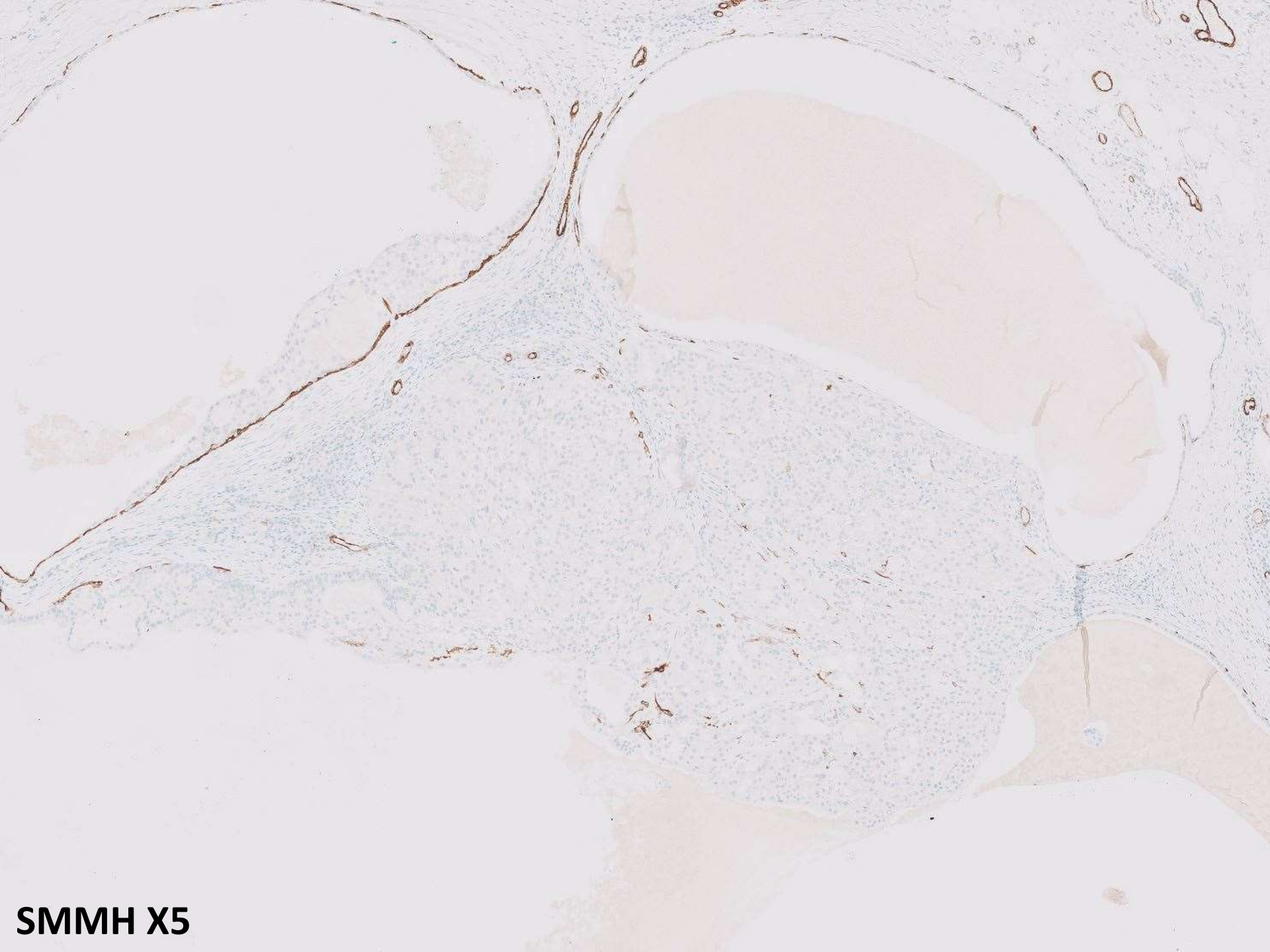
CK5,6 X5

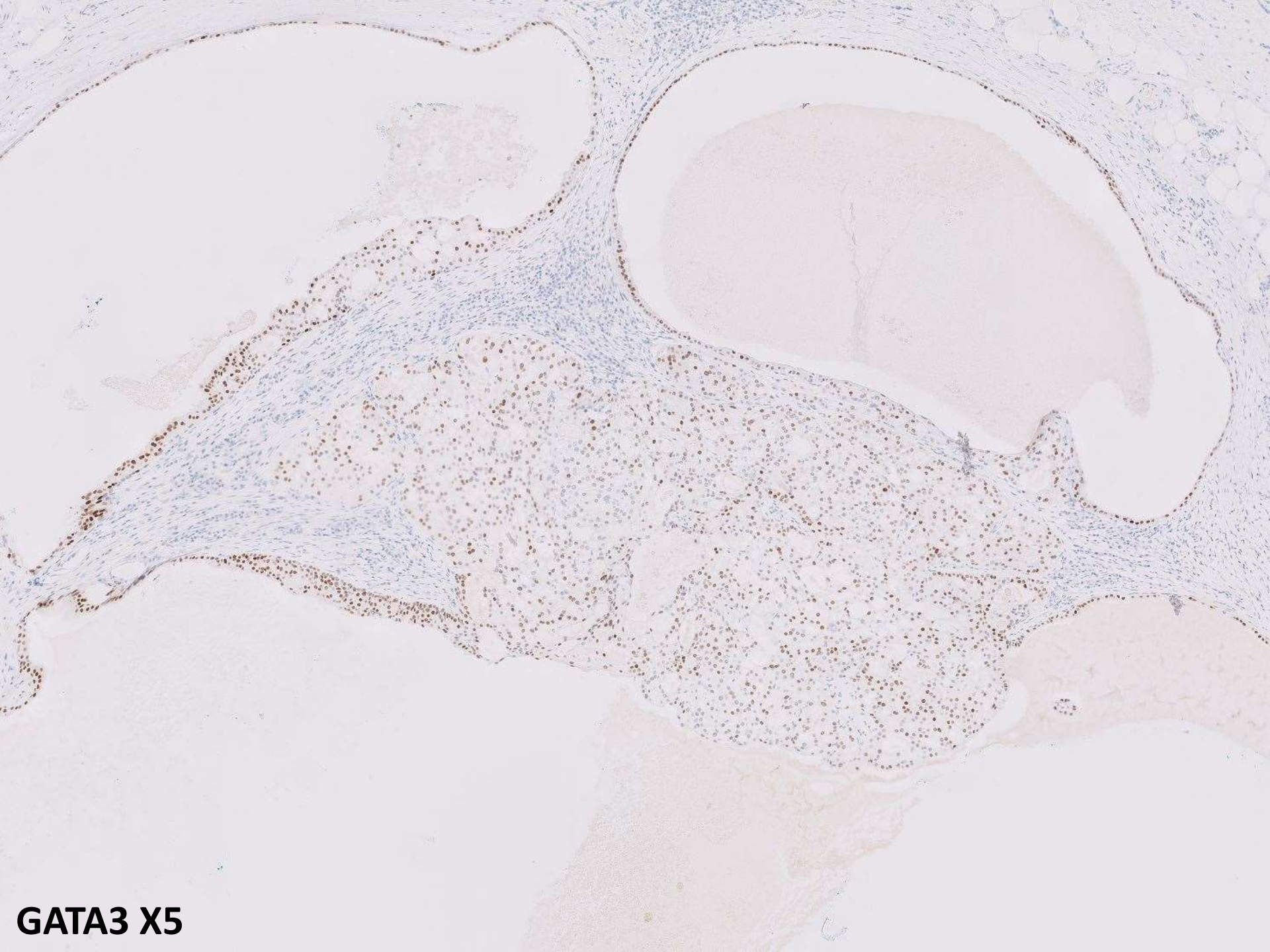


P63 X5

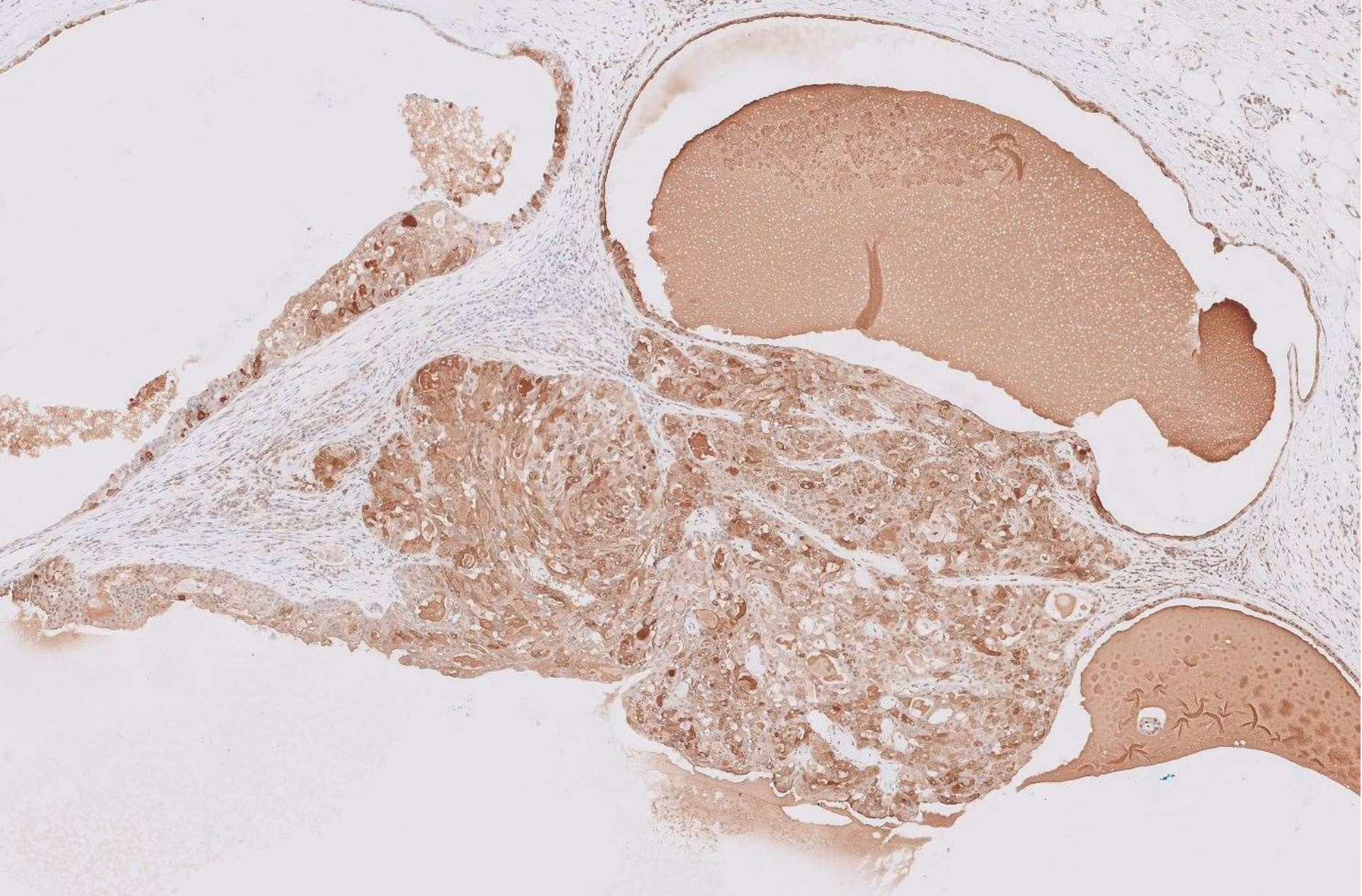


CALPONIN X5

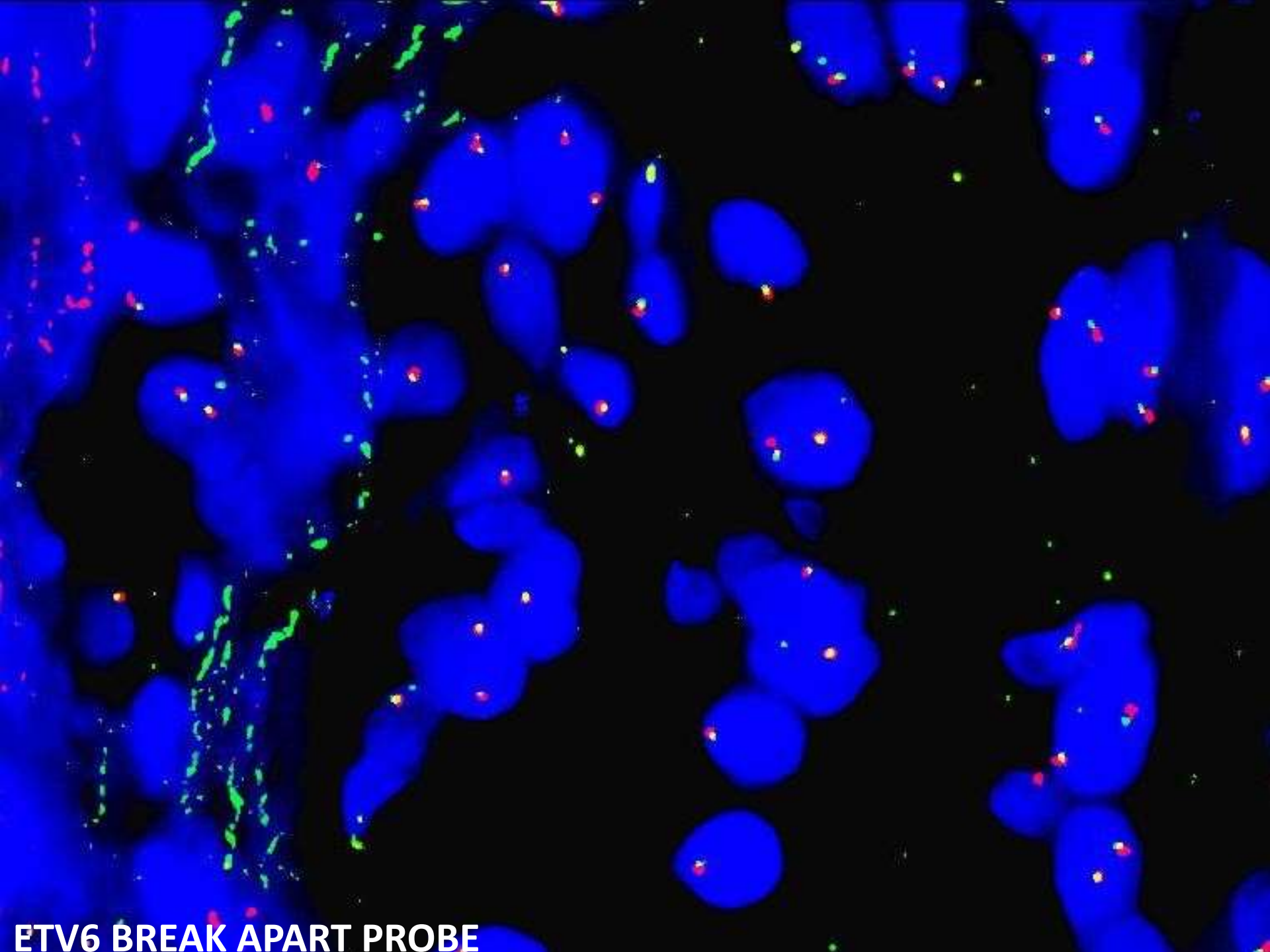

SMMH X5

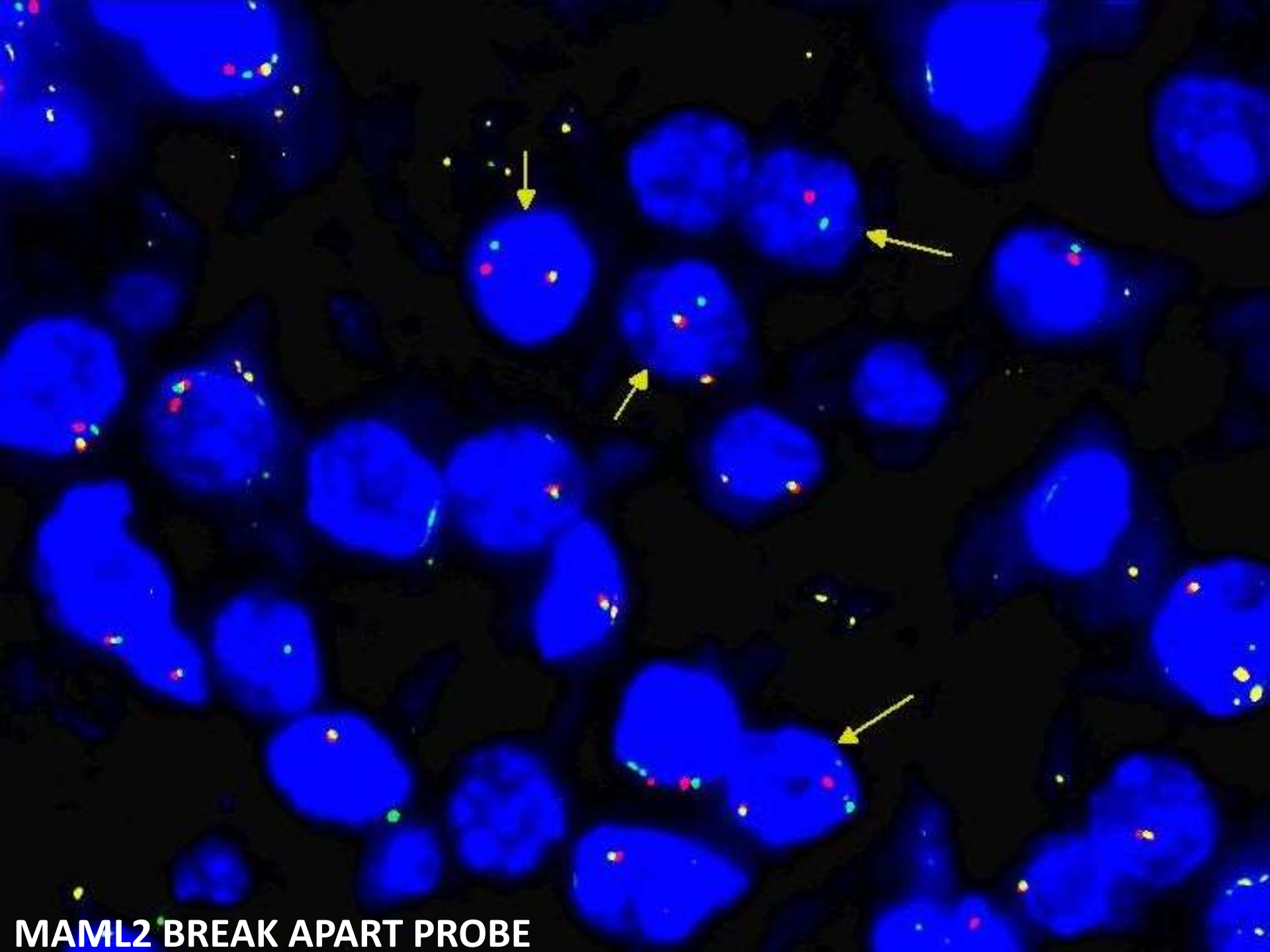


GATA3 X5



MAMMAGLOBIN X5


ETV6 BREAK APART PROBE


MAML2 BREAK APART PROBE

FINAL DIAGNOSIS

MUCOEPIDERMOID CARCINOMA OF THE BREAST

MUCOEPIDERMOID CARCINOMA OF THE BREAST

- Current WHO classification:
  - Invasive ductal carcinoma composed of mixed mucinous , intermediate (transitional) and squamoid cells arranged in cystic and solid patterns
- <40 cases reported to date

Hoon Tan P, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, et al: The 2019 WHO classification of tumours of the breast. Histopathology. Feb 13–2020

MUCOEPIDERMOID CARCINOMA OF THE BREAST

- Wide range of histomorphological patterns and grades
- Triple negative (ER-ve, PR-ve, HER2:-ve)
- IHC:
  - Epidermoid cells: CK5/6, CK14, CK7, p63
  - Intermediate cells: p63, CK5/6, CK14, CK7
  - Mucinous cells: CK7, CAM5.2, CK5/6, CK14

MUCOEPIDERMOID CARCINOMA OF THE BREAST

- Grading (interchangeable):
  - SBR
  - Auclair grading system

Histopathologic Feature	Point Value
Cystic component < 20%	2
Neural invasion	2
Necrosis	3
4 or more mitoses/10 hpf	3
Anaplasia	4
Tumor Grade	**Point Score**
Low	0 – 4
Intermediate	5 – 6
High	7 or more

Goode, R.K., Auclair, P.L. and Ellis, G.L. (1998), Mucoepidermoid carcinoma of the major salivary glands. Cancer, 82: 1217-1224.

MUCOEPIDERMOID CARCINOMA OF THE BREAST

- Molecular findings:
  - t(11;19) CRTC1-MAML2
  - t(11;15) CRTC3-MAML2

21-0207

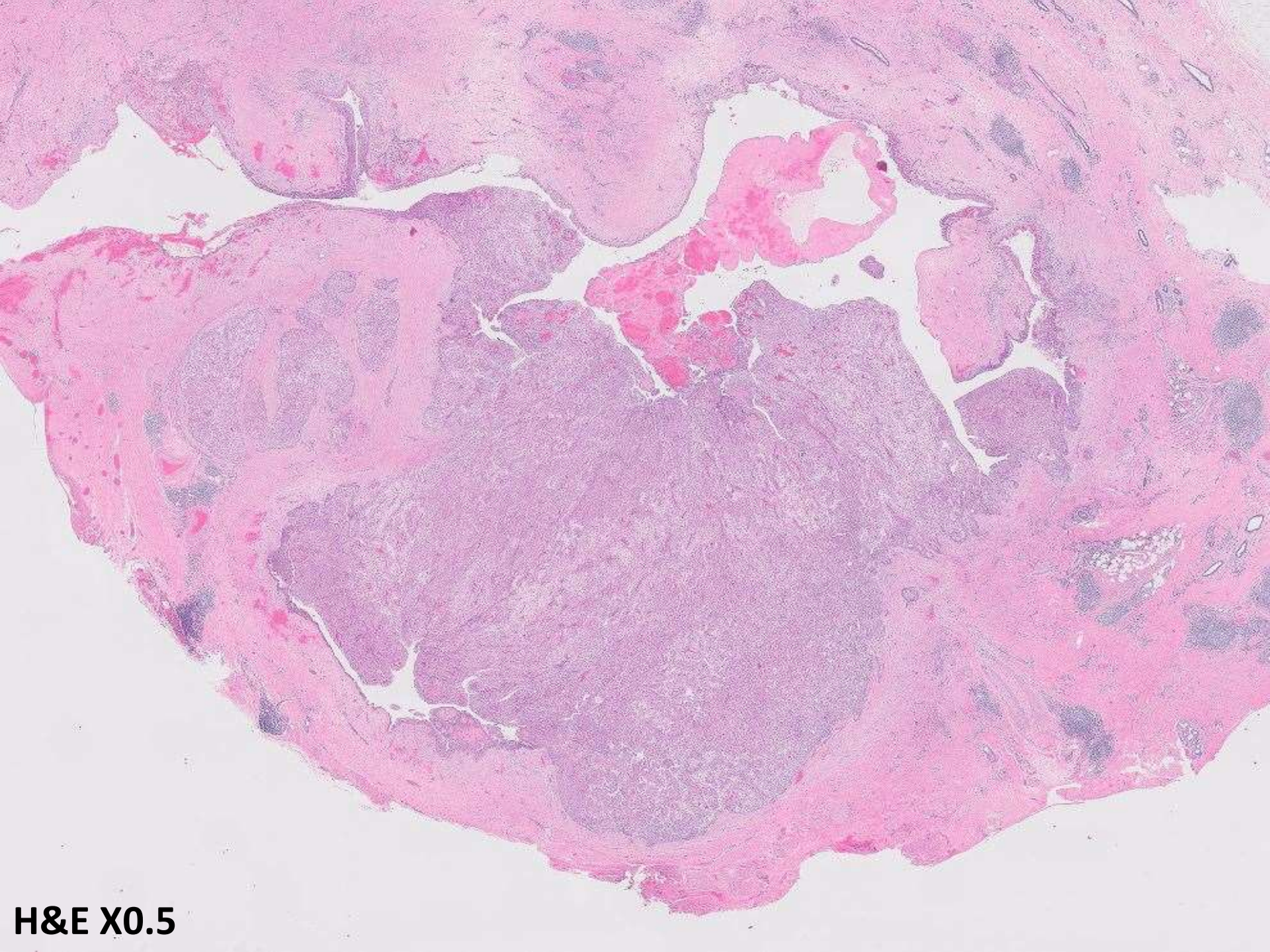
Saleh Najjar/Gregory Bean; Stanford

49-year-old M with palpable subareolar mass

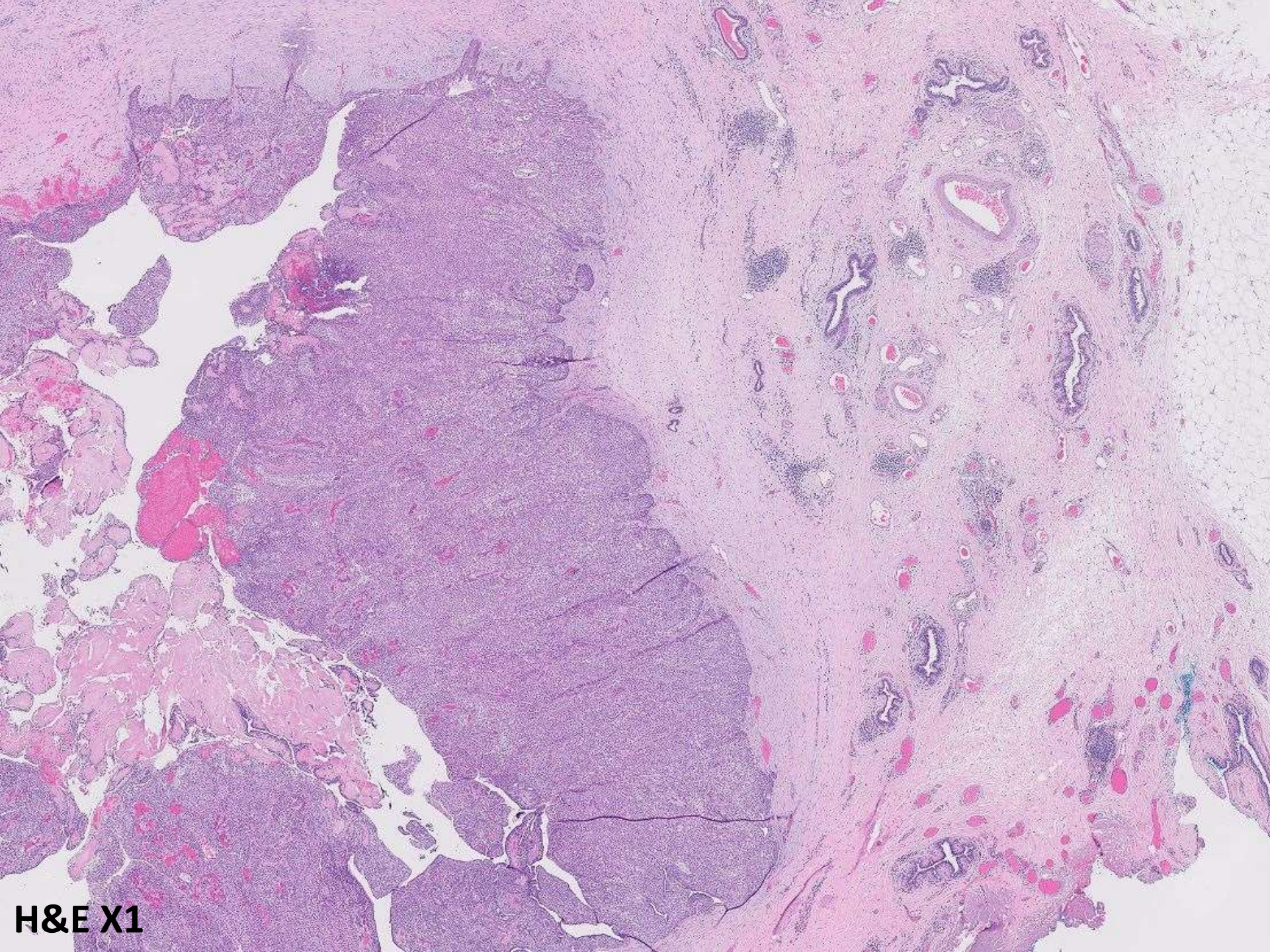
ULTRASOUND FINDINGS

- FINDINGS:
  - Large lobular mass lesion with circumscribed well-defined margins measuring 4.6 x 3.4 cm

- IMPRESSION:
  - Complex mass identified associated with palpable lesion anterior right breast . Lesion has some peripheral solid elements but appears largely cystic. Possible involvement of the deep dermis.



H&E X0.5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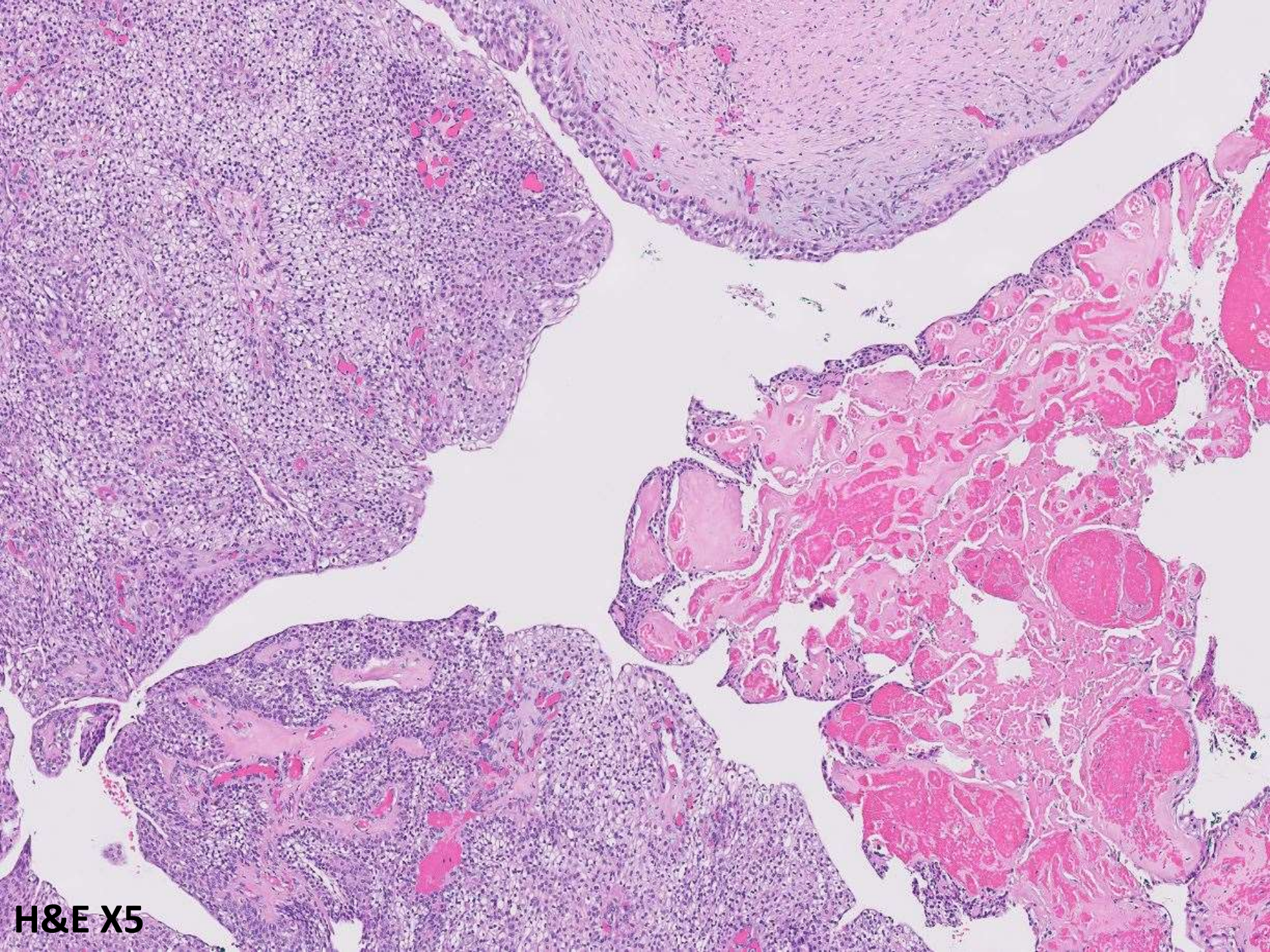
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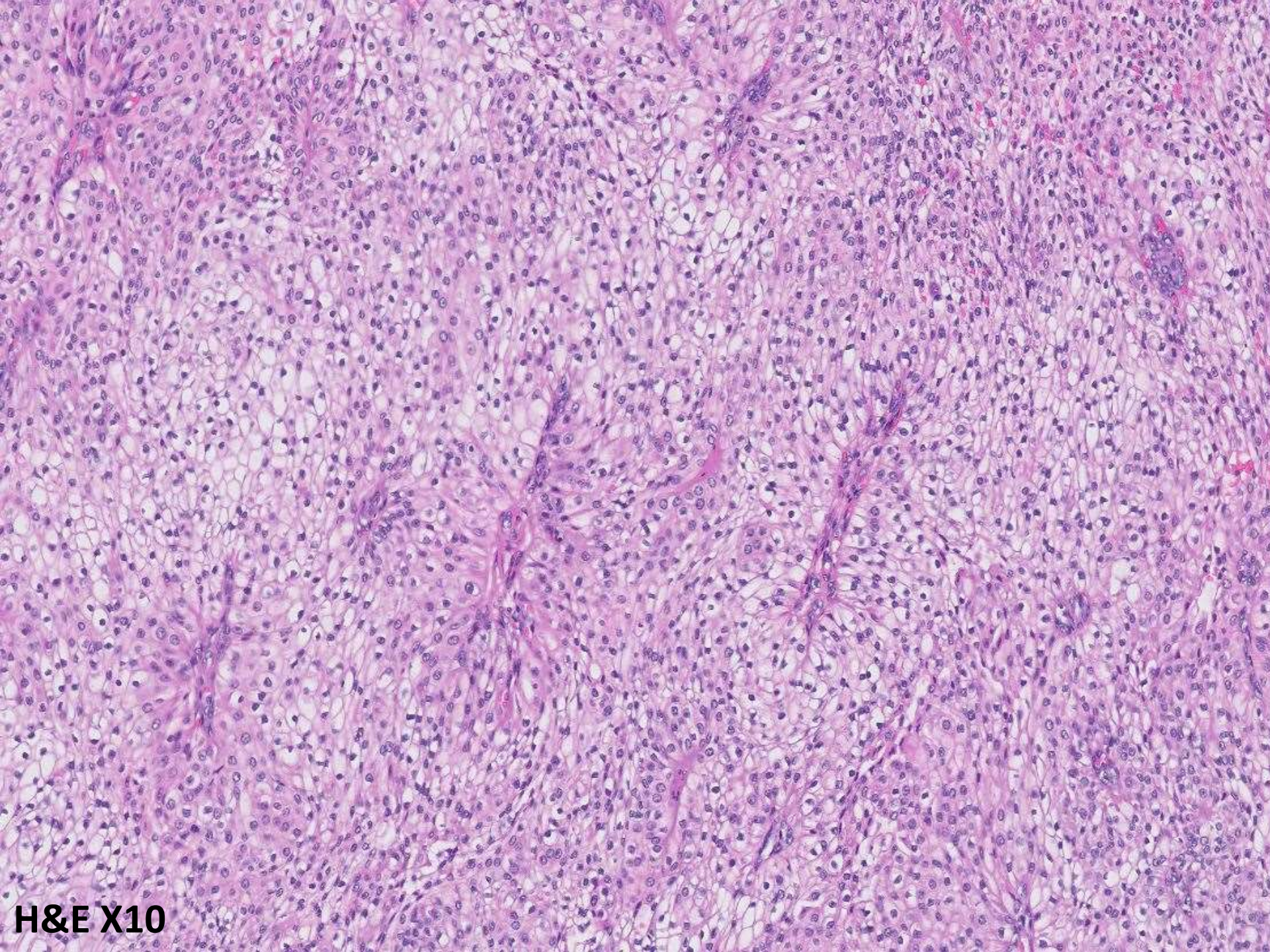
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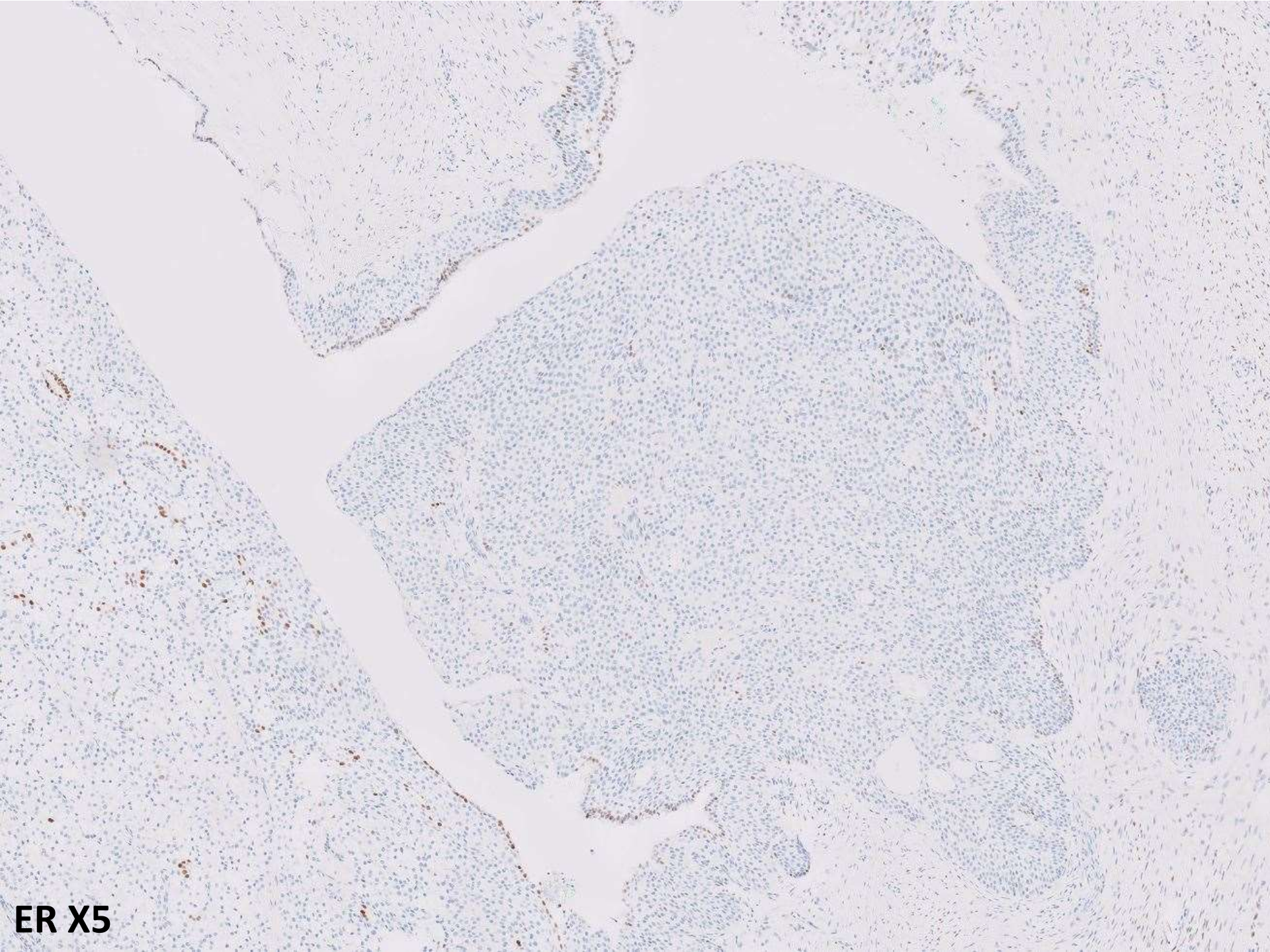
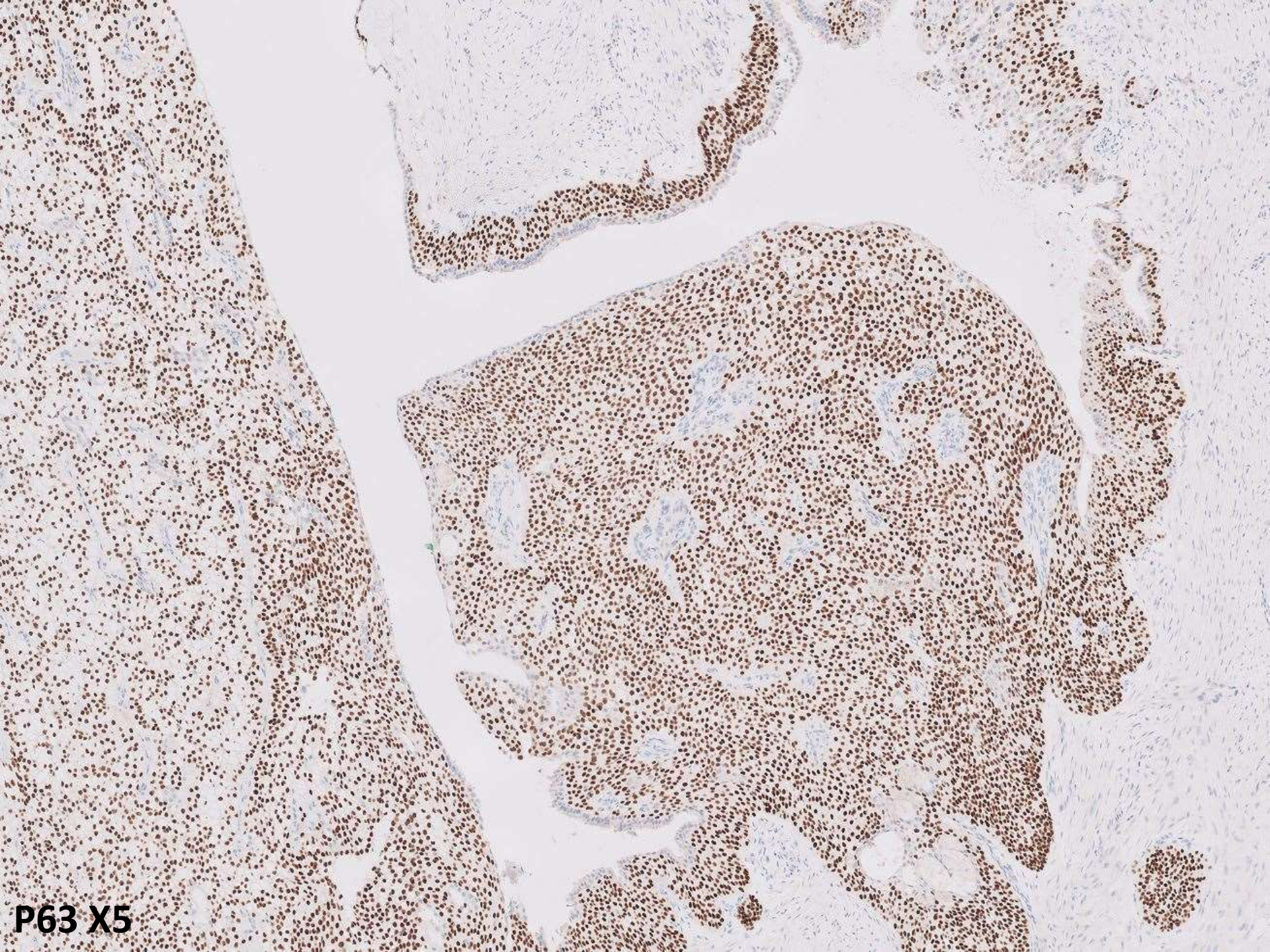

ER X5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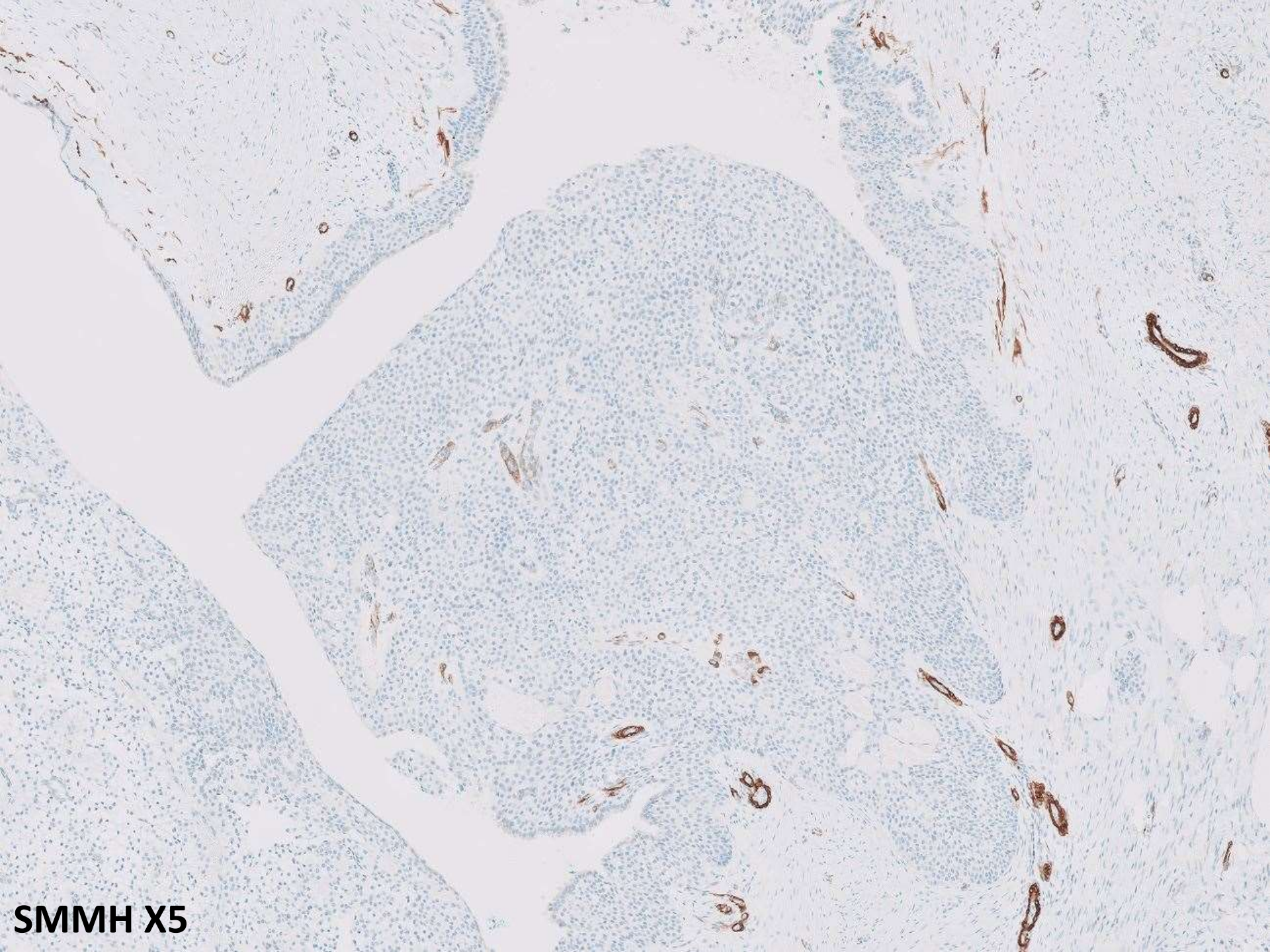
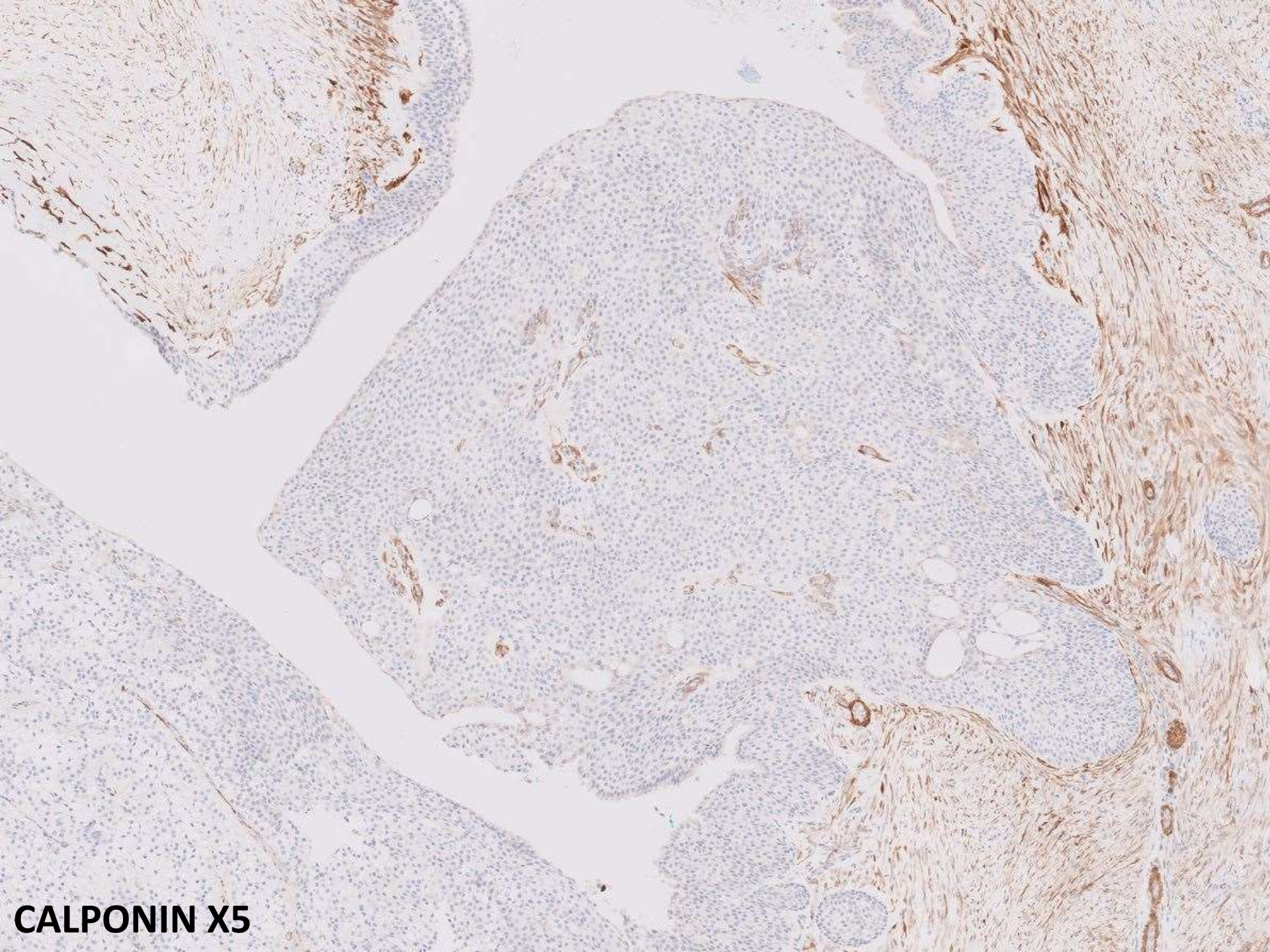
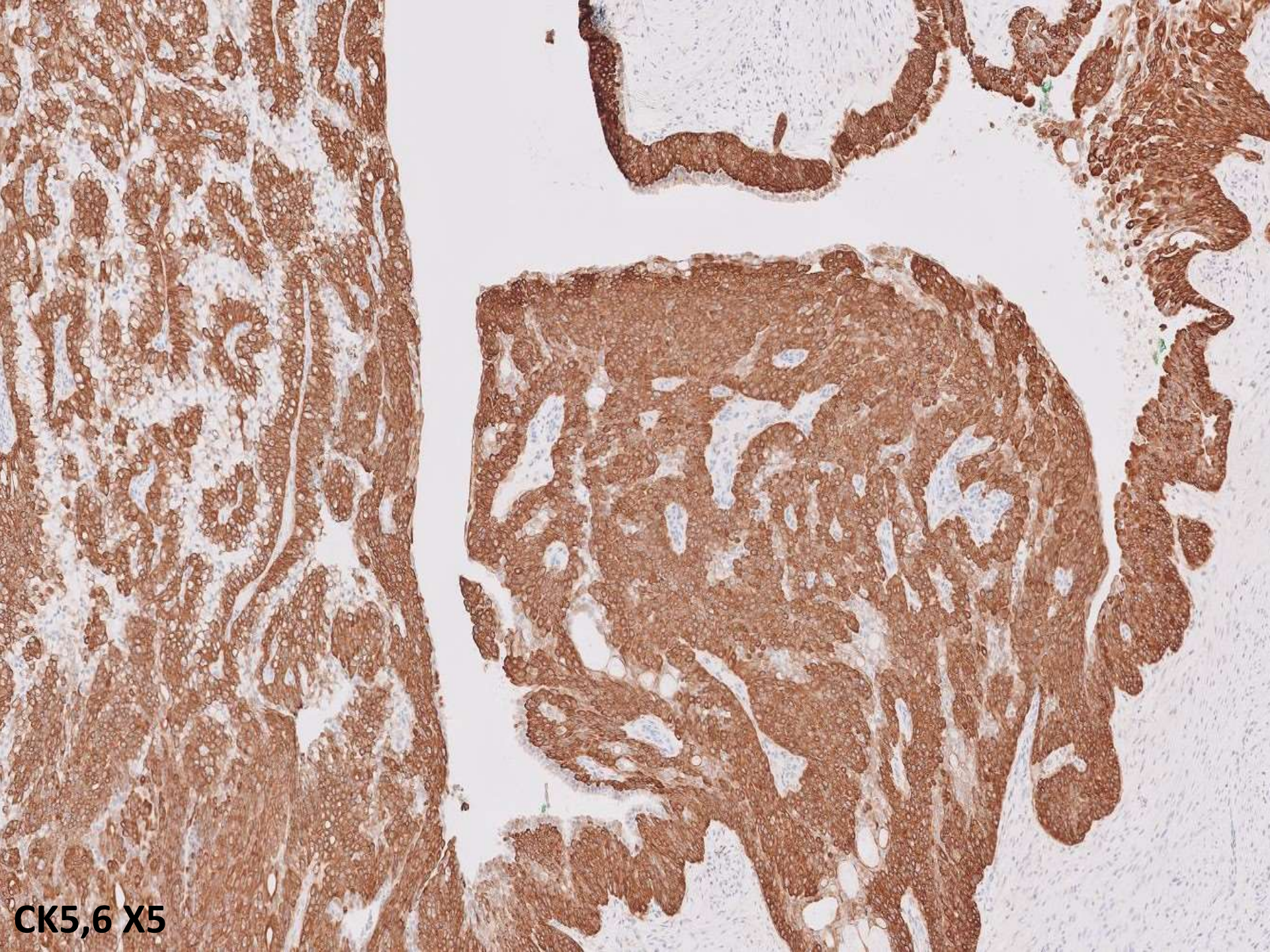

SMMH X5



CALPONIN X5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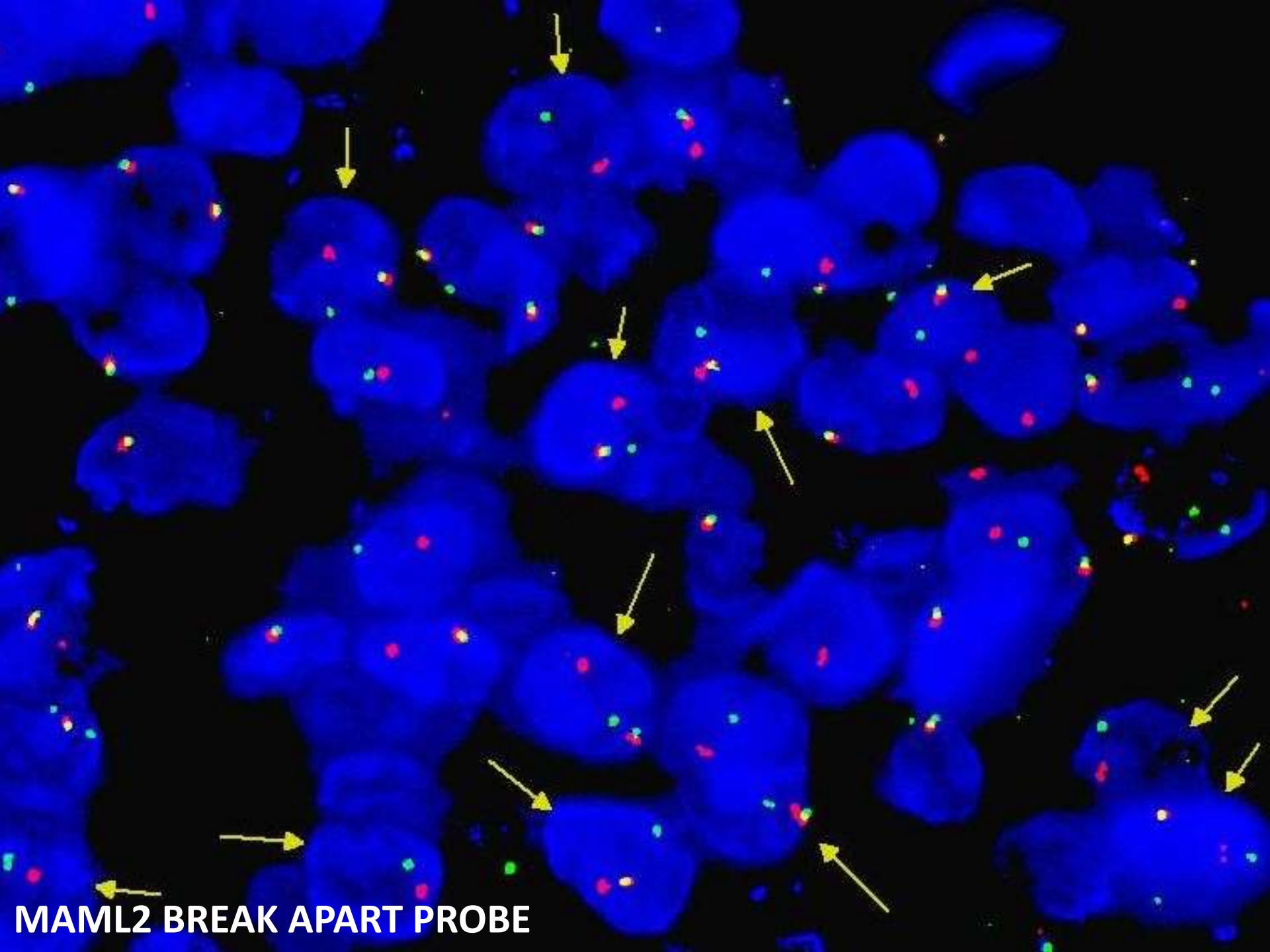
MAML2 BREAK APART PROBE

FINAL DIAGNOSIS

HIDRADENOMA OF THE BREAST

HIDRADENOMA OF THE BREAST

- Benign neoplasm originating in the skin adnexa and centered in the dermis
- Breast HA commonly affects in the nipple and areola
- Very rare tumor with few cases reported

HIDRADENOMA OF THE BREAST

- Lobulated mass
  - Solid
  - Solid and cystic components
- Composed of different types of cells: clear, polygonal, epidermoid, oncocytic, and mucinous cells.
- Harbors: t(11;19) CRTC1-MAML2

HIDRADENOMA OF THE BREAST

- Management:
  - local excision
  - Recurs very rarely, even in cases with inadequate excision

Girish G, Gopashetty M, Stewart R (2007) Reccurent clear cell hidradenoma of the breast: A case report. The Internet J Surgery 10(1):1–5