AUGUST 2020 DIAGNOSIS LIST

20-0801: eosinophilic solid and cystic renal cell carcinoma (kidney/GU pathology)
20-0802: SDH-mutated renal cell carcinoma (kidney/GU pathology)
20-0803: intraosseous hibernoma (bone/BST pathology)
20-0804: astrocytoma, IDH1 mutant, cIMPACT-NOW Grade 4 (brain/neuropathology)
20-0805: endolymphatic sac tumor (mastoid/H&N pathology)
20-0806: neuroendocrine tumor grade 2 (arytenoid/H&N pathology)
20-0807: non-invasive papillary urothelial carcinoma with “micropapillary” features (bladder/GU pathology)
20-0808: malakoplakia (bladder/GU pathology)

Disclosures
August 4, 2020

The following planners and presenters had disclosures:

Ankur Sangoi: Google-consultant

Jeff Simko: Equity and Scientific Advisory Board-3D Biopsy, 3Scan; Equity-Lightspeed microscopy, Inc.; Research support-Intuitive Surgical Inc, Progenics Inc; Stockholder-Gilead Corp, ABBIVE Corp; consultant for research-Proscia Inc.

South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented. The presentation slides have been reviewed for potential bias and found to contain none.

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

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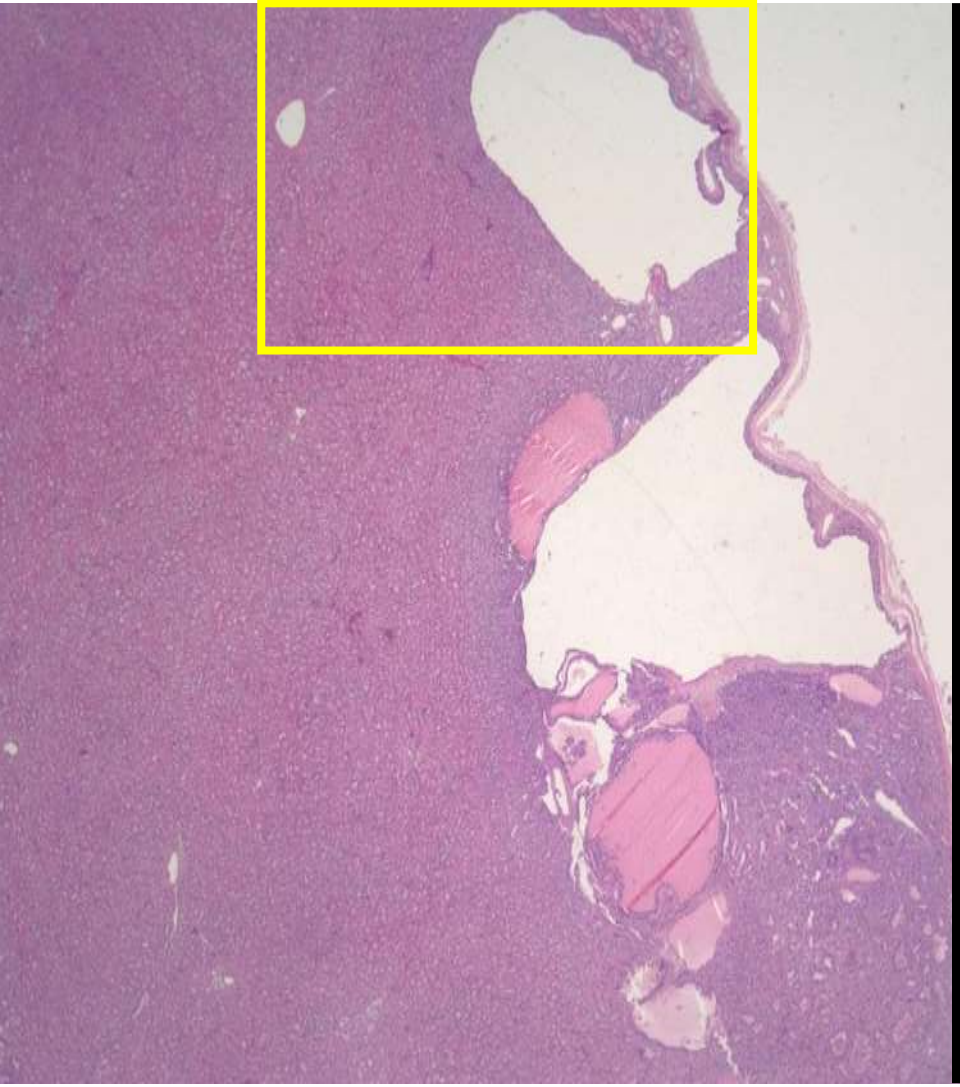
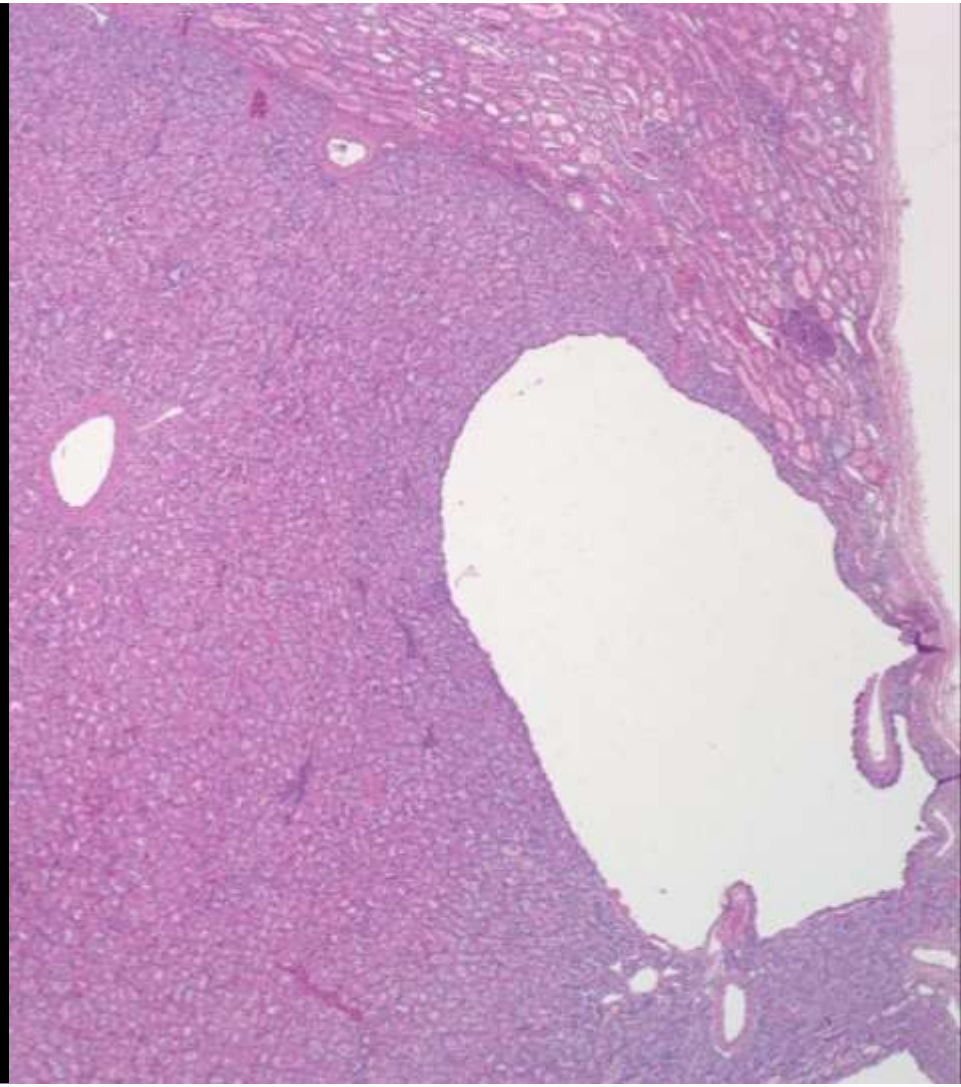
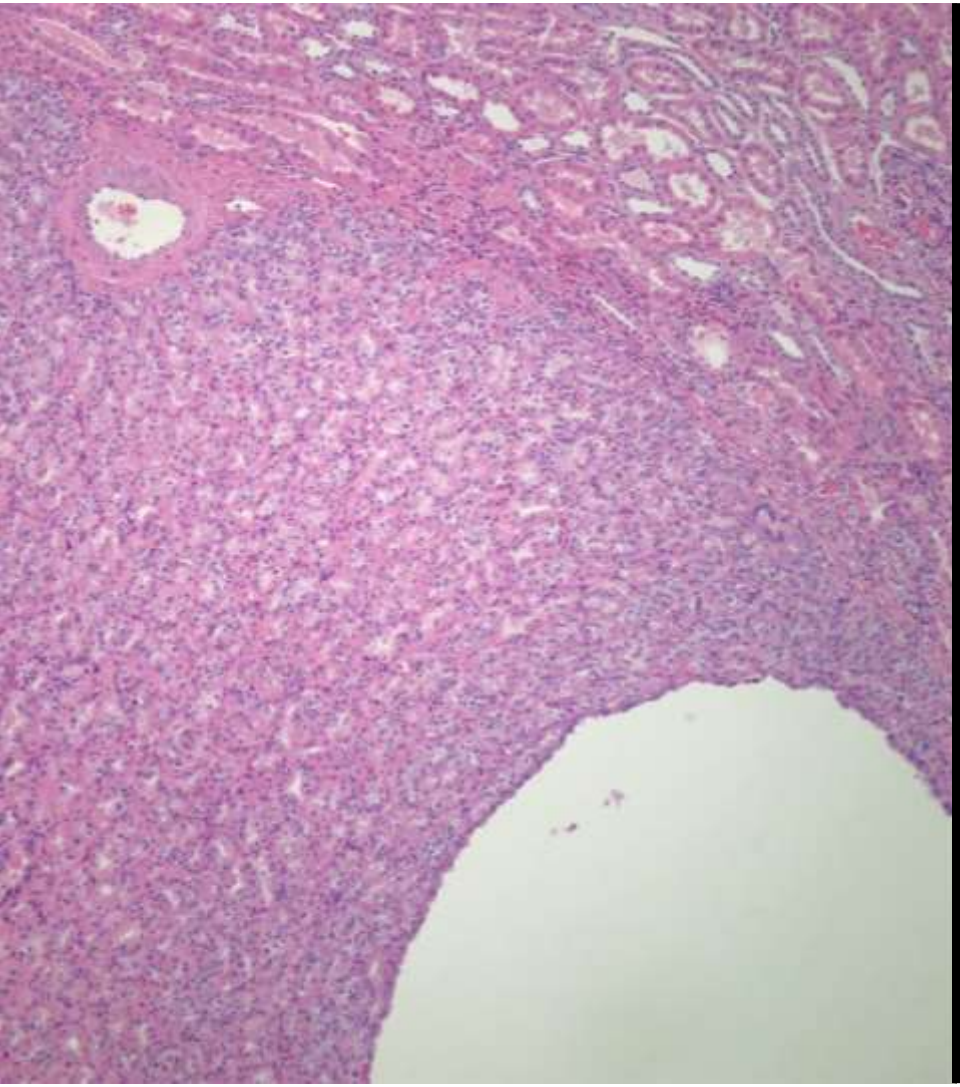
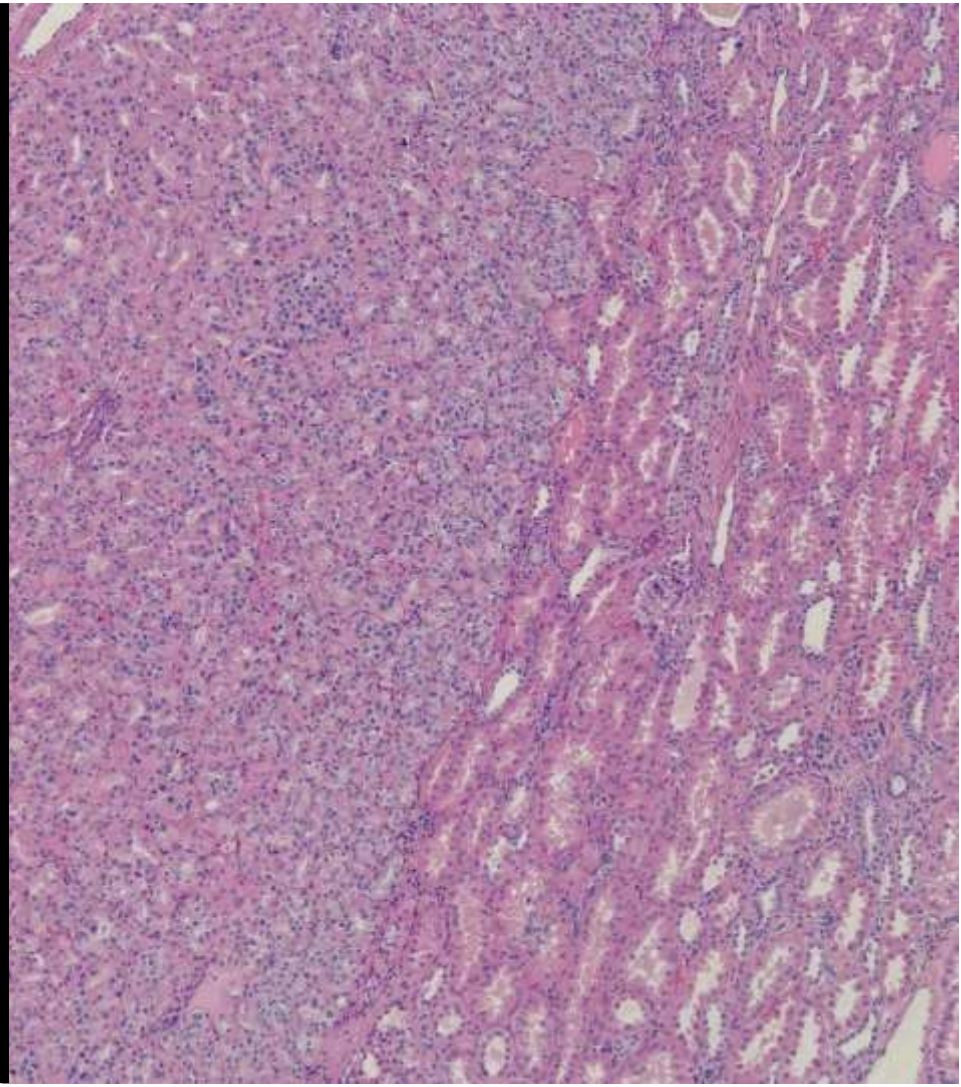
20-0801

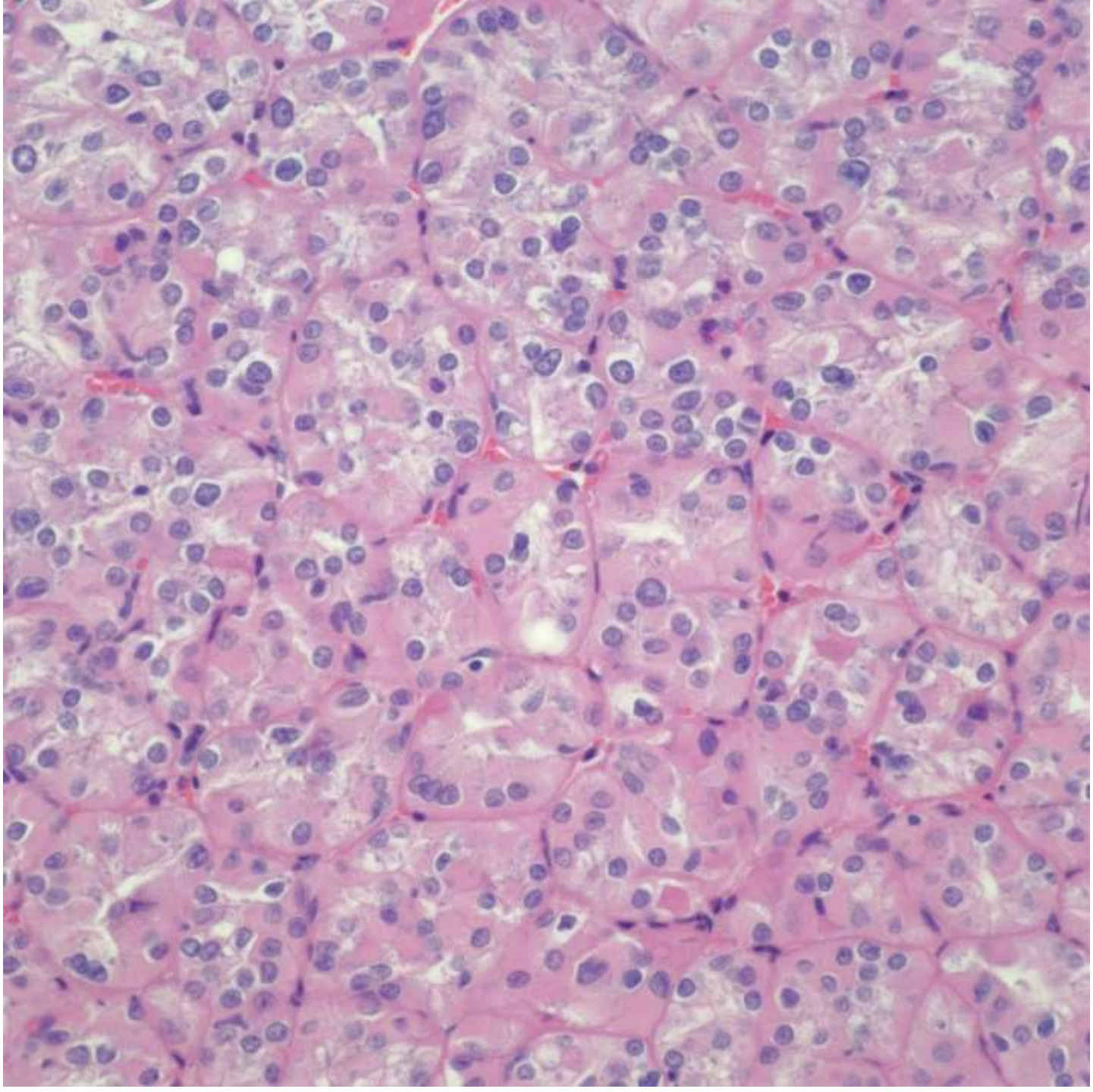
Iny Jhun/Christine Louie; Palo Alto VA

49-year-old F with 3cm renal mass.





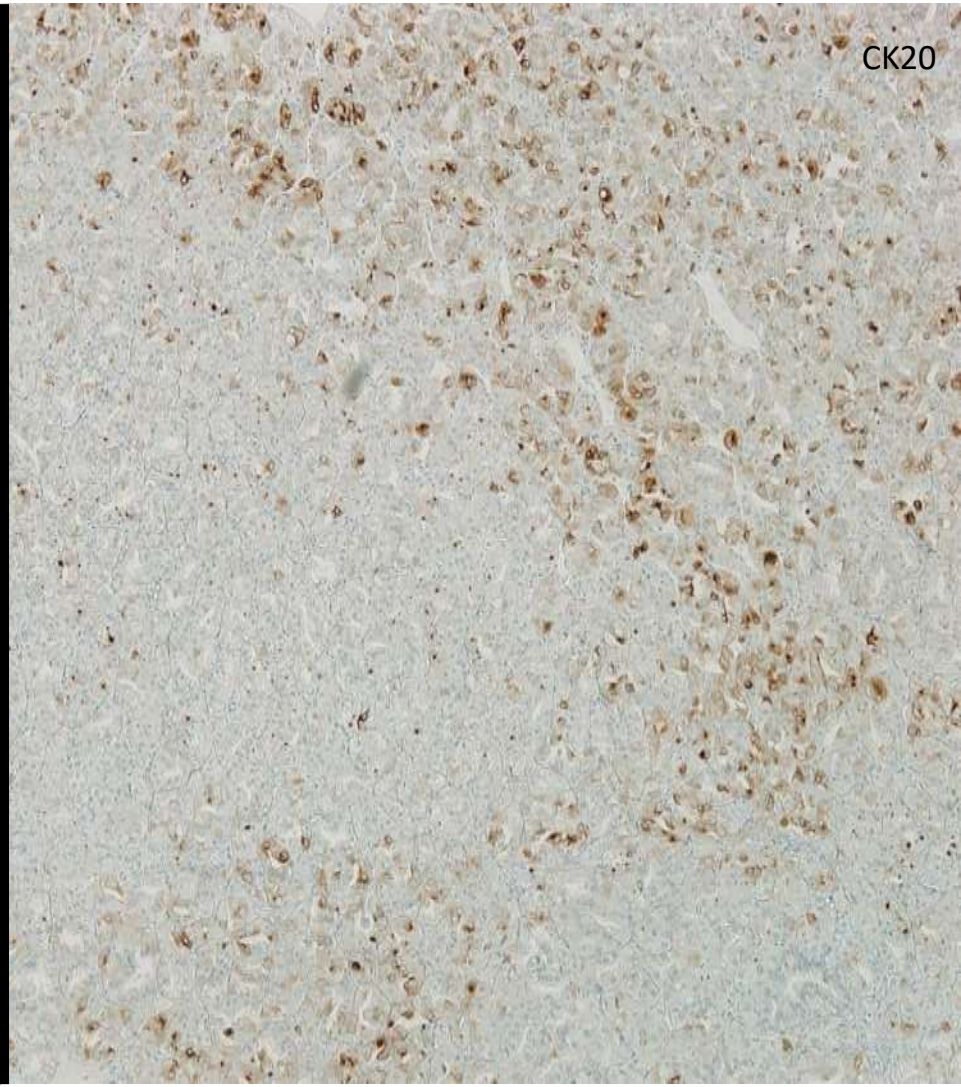






CAIX


CD117


CK7


CK20

Eosinophilic solid and cystic renal cell carcinoma (ESC RCC): Case Summary

- Clinical history: 49 female with 3 cm exophytic left upper pole renal mass, stable in size since 12/2015
- Gross: 2.6 cm homogenous, pale-tan, well-circumscribed tumor contained 3 cysts (0.3-0.5 cm)
- Micro:
  - Architecture:
    - Eosinophilic cells arranged in nests and tubular architecture
    - Variably sized cystic spaces
  - Cytology:
    - Moderate eosinophilic cytoplasm with coarse cytoplasmic granules
    - Some with perinuclear halos/clearing
- Differential dx: chromophobe RCC (CK7/CD117+), oncocytoma (CD117+)
- IHC:
  - Positive: CK20 (patchy), CK7 (rare)
  - Negative: CAIX, CD117, cathepsin K
  - Retained: SDHB and FH

ESC RCC: Clinical

- Occurs predominantly in female individuals, associated with tuberous sclerosis complex (TSC)[a]
- Median age: 55 years (32-79)[b]
- Incidence: 0.2% (2 in 1000) (likely underestimate)
- Clinical course: indolent, but has metastatic potential (2 of 60; 3%)[c]

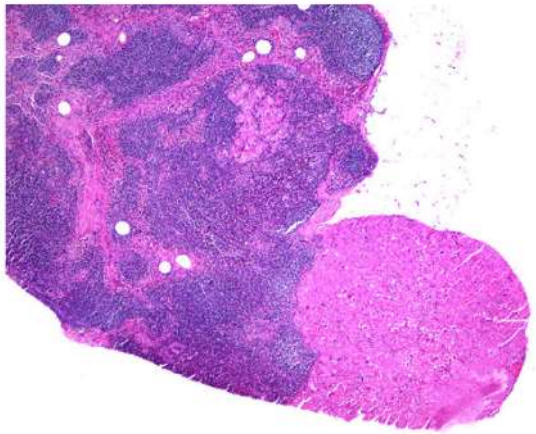
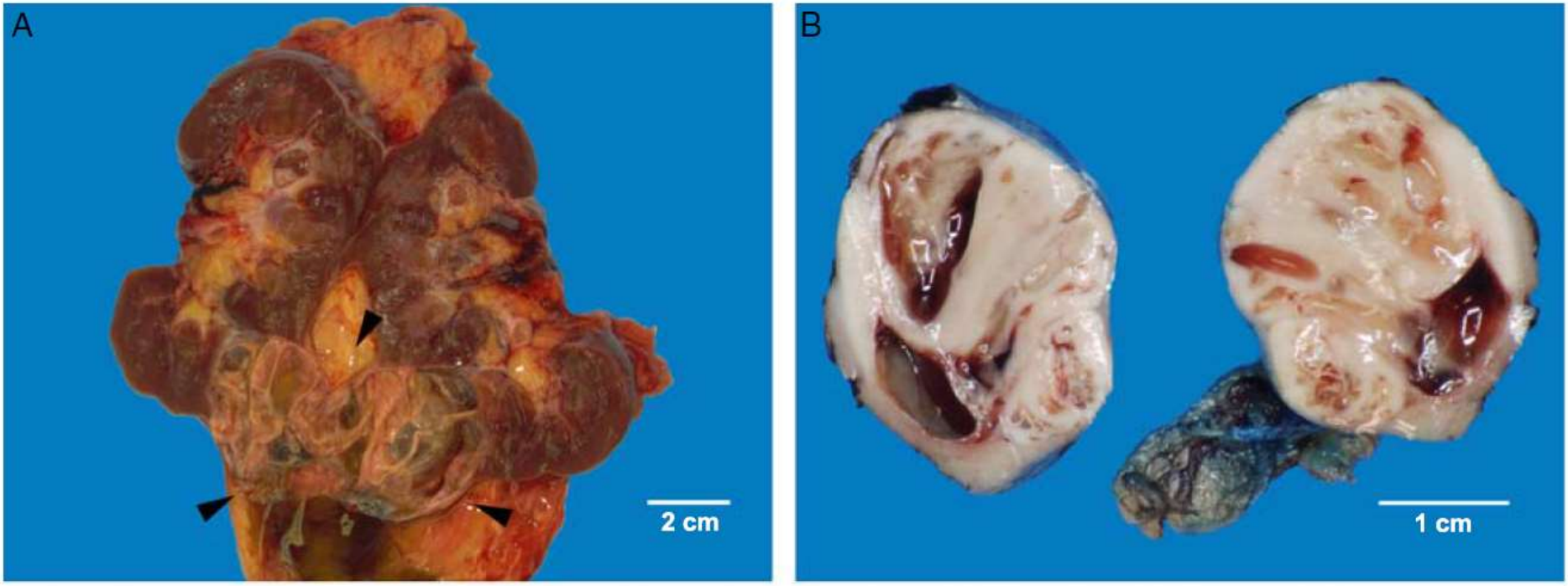


Figure 2. Metastatic renal cell carcinoma. Solid nodules of the eosinophilic solid and cystic (ESC) renal cell carcinoma were present in a hilar lymph node.

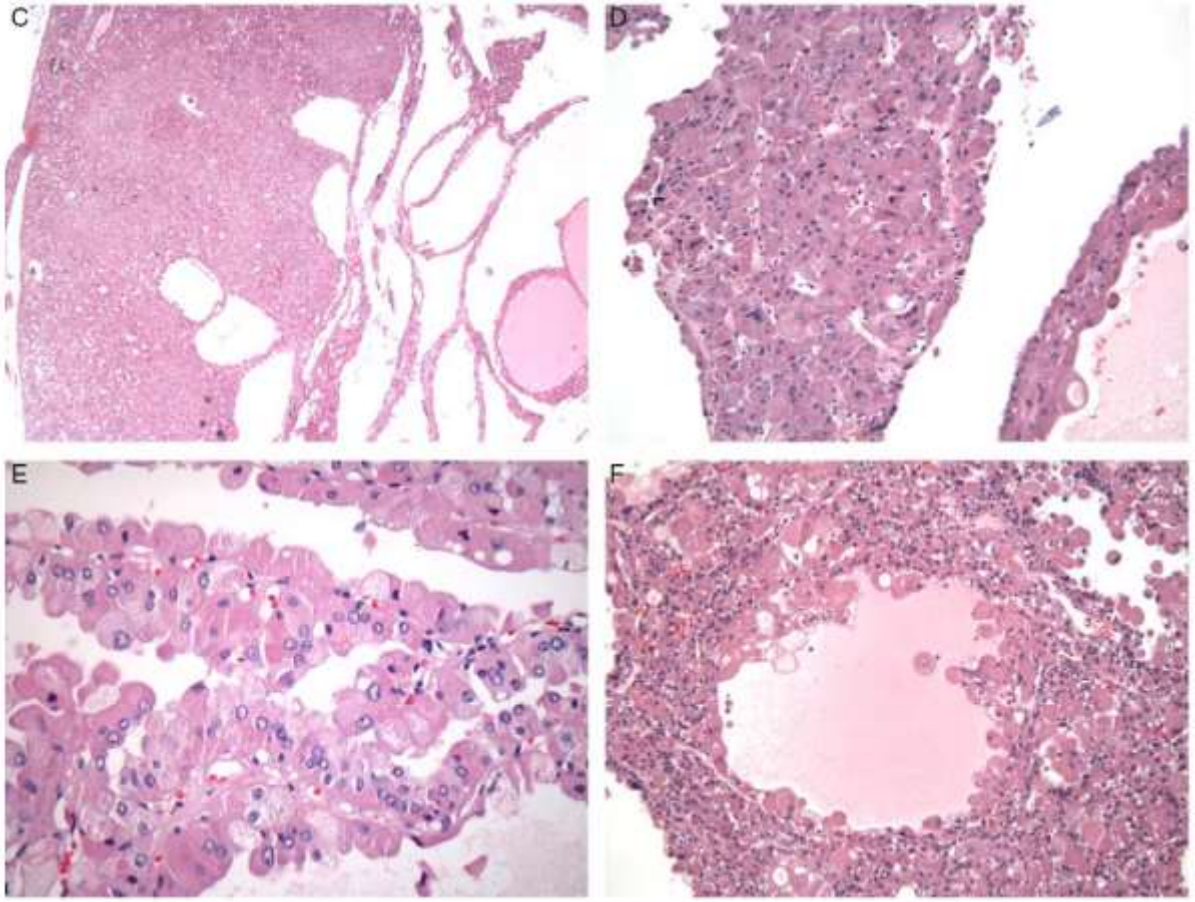
[a] cultural and linguistic elements for CME accreditation
[b] case series of 19 patients without TSC (Trpkov 2017)
[c] McKenney 2018

ESC RCC: Gross

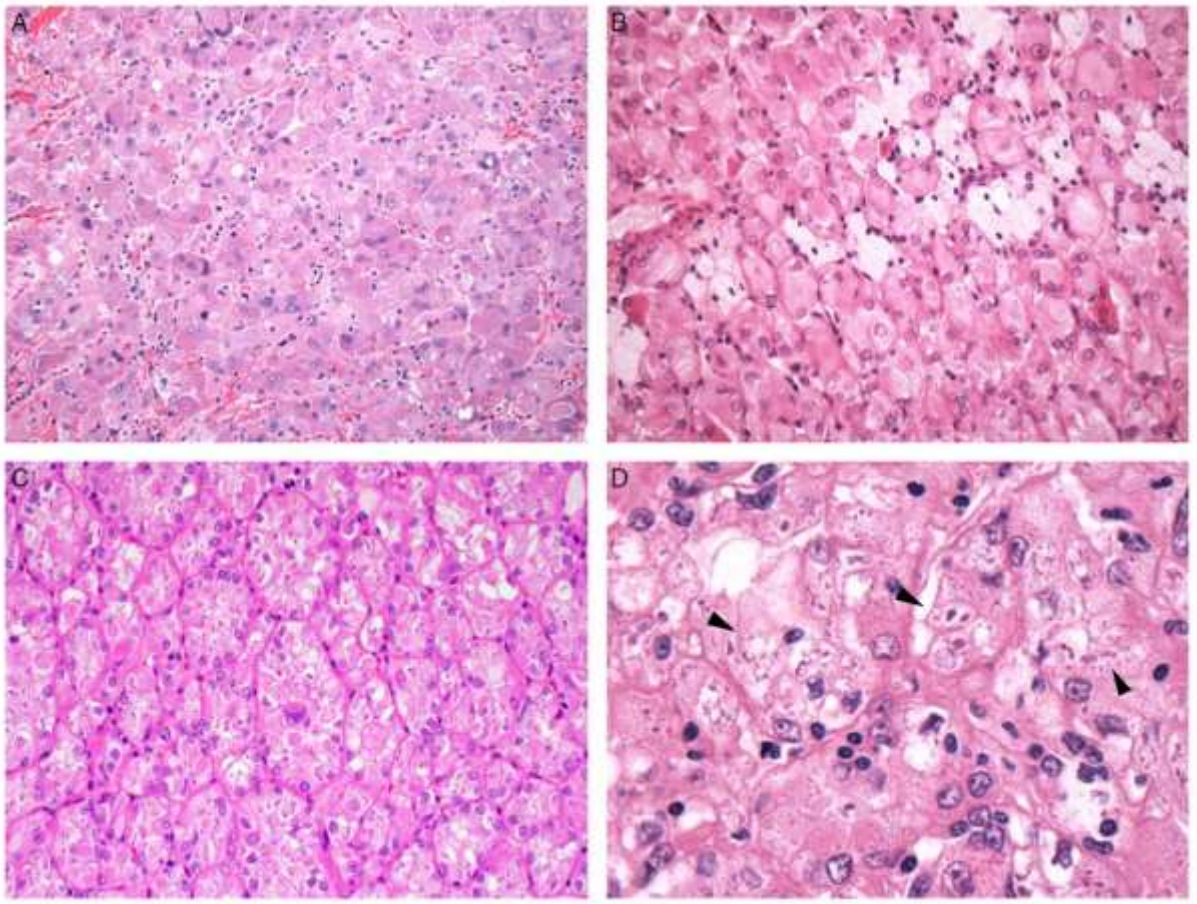


- Median size: 3.1 cm (1.2-13.5 cm); 80% < 5 cm
- Mixed solid & cystic (macroscopic or microscopic)

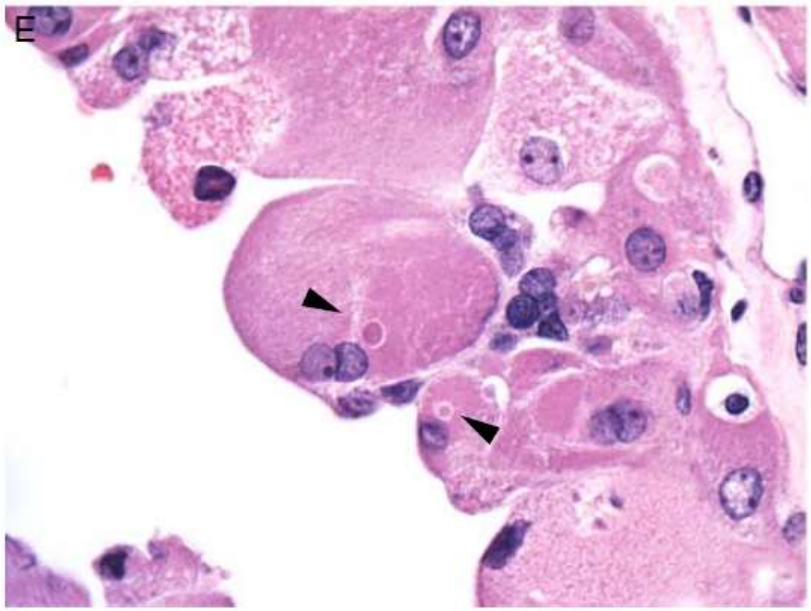
ESC RCC: Micro, Architecture

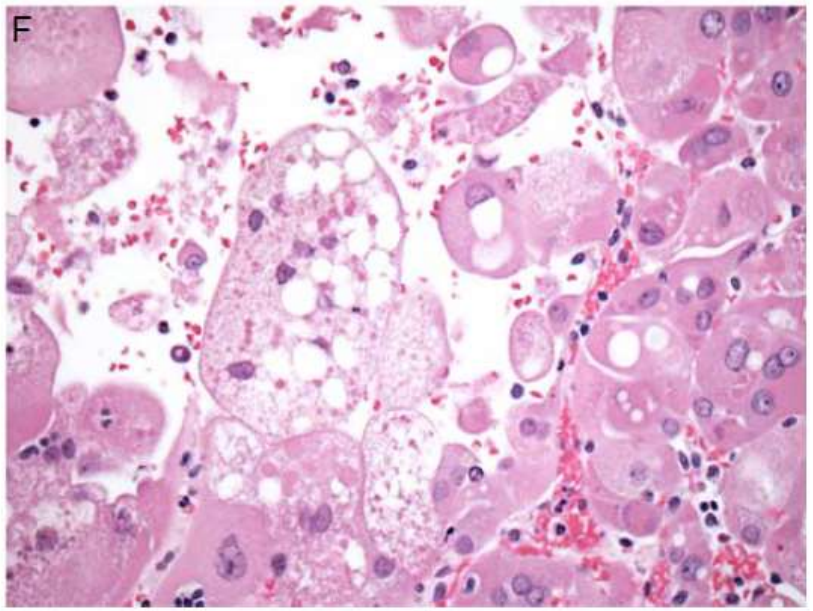


ESC RCC: Micro, Cytologic Features

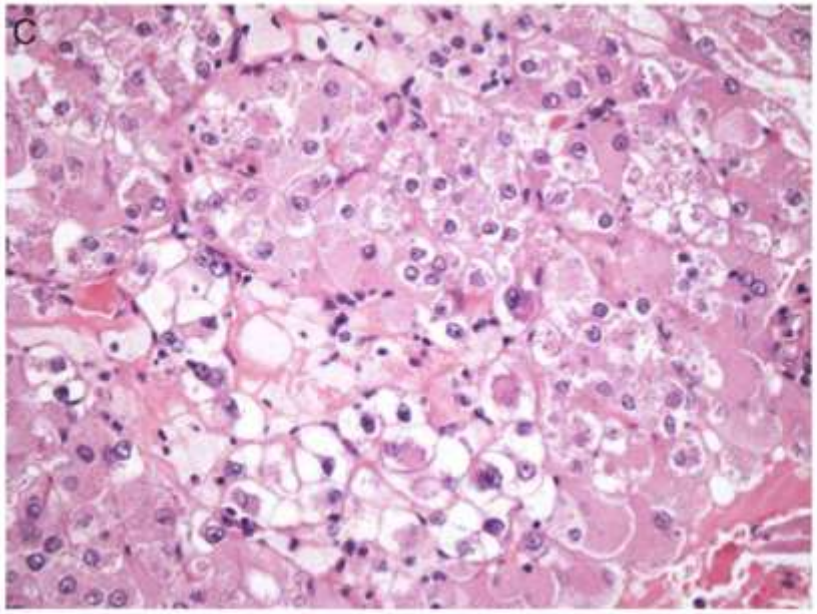


ESC RCC: Micro, Cytologic Features (cont'd)

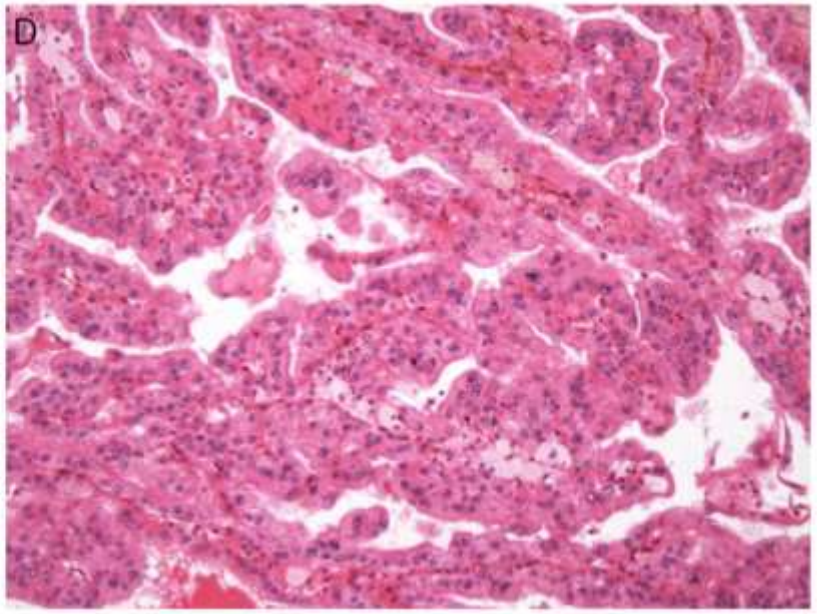




ESC RCC: Micro, Variations



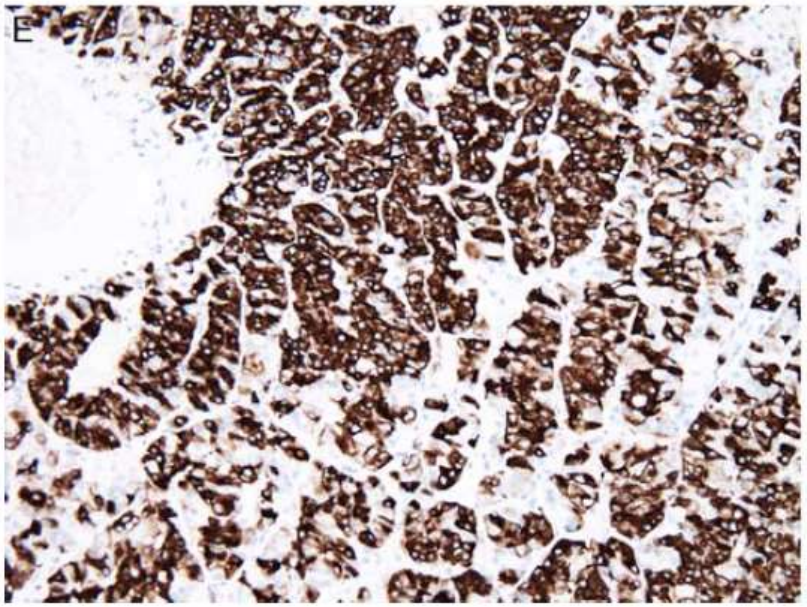
chromophobe-like morphology
clear cell change



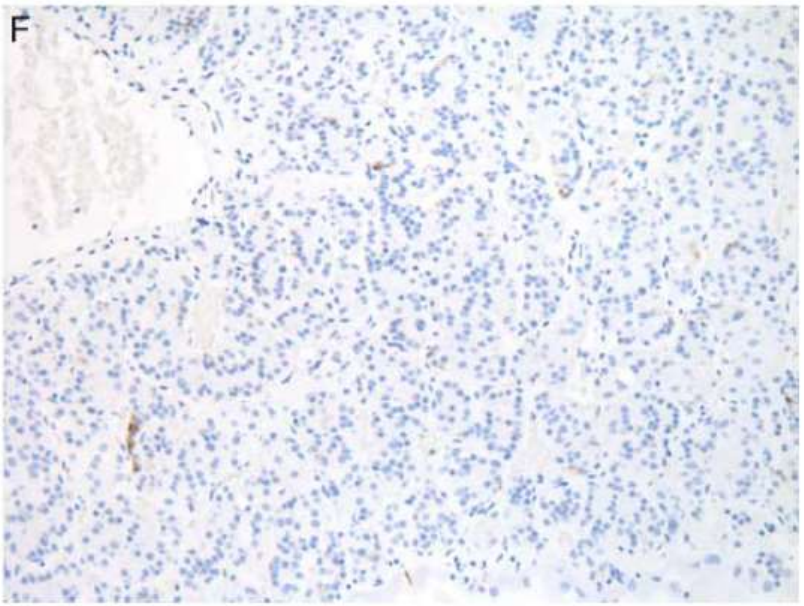
papillary arrangement

ESC RCC: IHC

CK20 positive



CK7 negative



- **CK20+/CK7-**
- CA9 (-)
- AE1/AE3 (+)
- PAX-8 (+)
- Vimentin (+)
- AMACR (patchy)
- CD117 (-)
- CD10 (+ or focal)

TABLE 1. IHC Results for ESC RCC

Patient	PAX8	AMACR	CD10	CD117	EMA	CK7	CK20	CA9	AE1/AE3	CK8/18	Vimentin	Hamartin	Tuberin
1	+	+/–	–	–	+/–	–	+	NA	+/–	+	–	–	+
2	+	+	+	–	+/–	–	+/–	NA	+/–	+	+	–	+
3	+	–	–	NA	NA	+/–	+	+	–	+	–	NA	NA
4	NA	+/–	NA	NA	–	–	+	–	–	+	+/–	–	+
5	+	NA	NA	NA	NA	–	+	NA	NA	NA	NA	–	+
6	+	+/–	NA	NA	NA	+/–	+	–	NA	NA	NA	–	+
7	+	+/–	+	–	–	–	+/–	+	+/–	+	–	–	+
8	+	+/–	+/–	–	–	–	+	–	+/–	+	+	–	+
9	+	–	+	–	–	–	+	–	–	+/–	+	NA	NA
10	+	–	+	–	+/–	–	–	–	+/–	+	+	NA	NA
11	+	+/–	–	+/–	–	–	–	–	+/–	+/–	+	–	+/–
12	+	+/–	+/–	–	+/–	+/–	+	NA	+/–	+/–	+	–	+
13	+	+/–	+/–	–	–	–	+	–	+	+	+	–	+
14	+	+	+/–	–	–	–	+/–	NA	+	+	+	NA	NA
15	+	+/–	+	–	–	+/–	+	–	+	+	+	NA	NA
16	+	+	+/–	–	NA	–	+	NA	NA	NA	NA	NA	NA
Percent pos* (%)	100	80	77	8	33	25	88	20	77	100	77	0	100

*Percent positive includes both focal and diffuse positive cases, excluding cases with unavailable result.
+ indicates positive; –, negative; +/–, focal; NA, not available.

ESC RCC: Differential Diagnosis

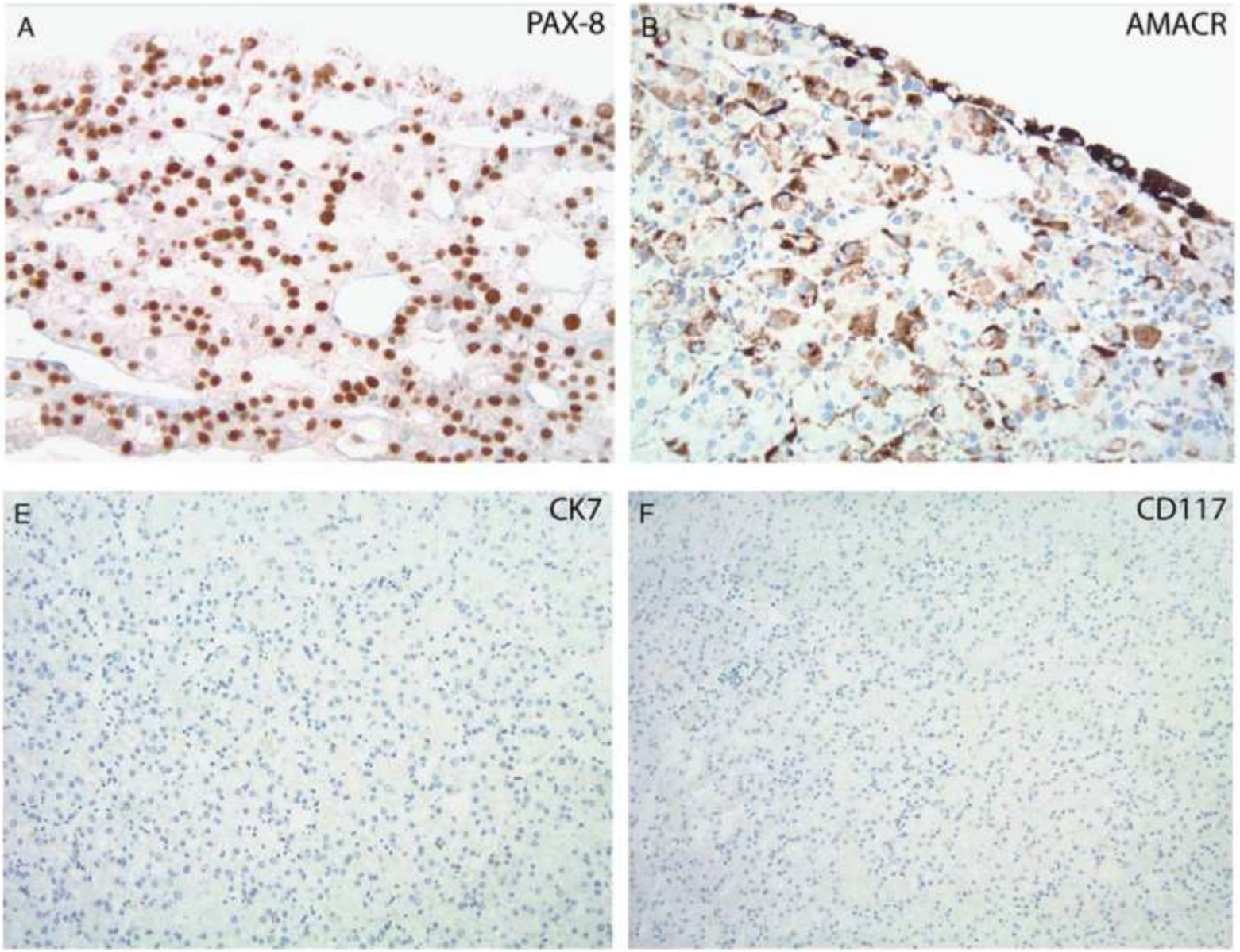
- Other renal tumors w/eosinophilic cytoplasm
  - Oncocytoma (CK20-)
  - eosinophilic variant of chromophobe RCC (CD117+, CK20-, CK7++)
  - SDH-deficient RCC (SDHB loss)
  - MiT translocation-type RCC (TFE3)
  - epithelioid AML (PAX8 neg)
- Other common RCCs
  - Clear cell RCC, high grade (CK20-, CK7+ cystic epithelium, CA9 strong membranous, delicate vascular pattern)
  - Oncocytic papillary RCC, with solid pattern (CK20-/CK7+)

Characteristic features of ESC RCC (vs other renal neoplasms):

- cytoplasmic stippling
- striking female predominance

TABLE 3. Key Features and Immunostains Helpful in Distinguishing ESC RCC From Other Renal Tumors

Diagnosis	Key Distinguishing Features	IHC
ESC RCC	Female individuals, solid and cystic growth, voluminous eosinophilic cytoplasm, granular cytoplasmic stippling, usually low stage	$CK20^+/CK7^-$, $CD117^-$, $PAX8^+$, $PanCK^+$, $HMB45^-$, $CA9^-$ (no membranous reactivity)
Chromophobe RCC, eosinophilic	Solid and uniform architecture, irregular nuclear membranes, perinuclear halos	$CD117^+$, $CK7^+$, $CK20^-$
Oncocytoma	Uniform cytology, lacks macrocysts	$CD117^+$, $CK7^{-/+}$, $CK20^-$
Epithelioid angiomyolipoma	Epithelioid cells that may be pleomorphic, lacks macrocysts	$PAX8^-$, $HMB45^+$, $PanCK^-$, $CK7^-$, $CK20^-$
Papillary RCC, oncocytic	Papillary formations (at least focal), uniform cytology	$CK7^+$, $CK20^-$
Clear cell RCC, eosinophilic morphology	Focal clear cell areas, delicate vasculature, may contain macrocysts	$CA9^+$, $CK20^-$
MiT translocation RCC	Large cells with clear (or eosinophilic) morphology, focal papillary and nested growth, lack cysts (usually)	$TFE3^+$, $TFEB^+$, $HMB45^+$, $PanCK^-$
SDH-deficient RCC	Lacks macrocysts, uniform low-grade oncocytic cells with flocculent to densely eosinophilic cytoplasmic vacuoles	$CD117^-$, $SDHB^-$, $SDHA^+$, $CK20^-$



IGURE 3. Typical immunophenotypic features of eosinophilic, solid and cystic solid RCC. A, Nuclear PAX8 reactivity. B, Patchy ytoplasmic AMACR staining. C, Diffuse or (D) patchy CK20 immunoreactivity. No staining with (E) CK7 or (F) CD117.

ESC RCC: Molecular Karyotyping

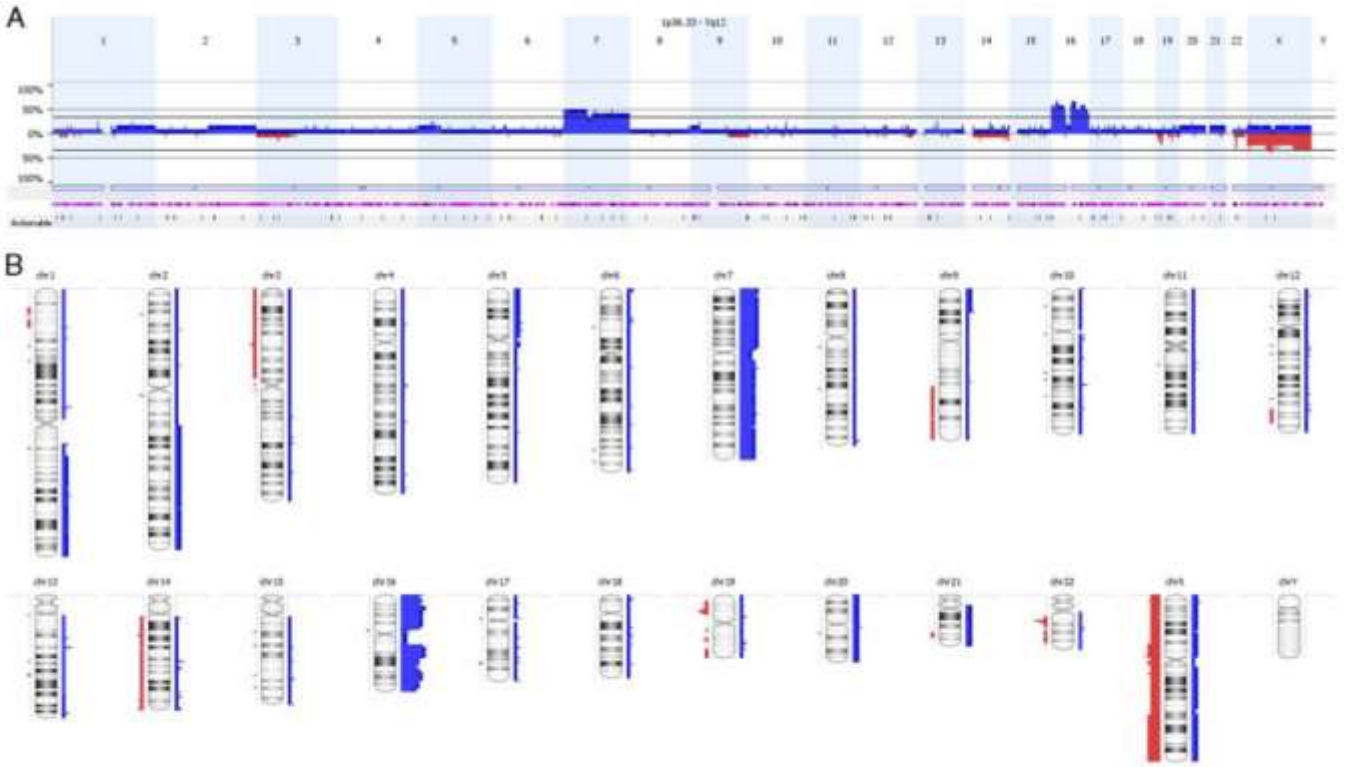


FIGURE 5. A, Molecular karyotyping profiles of eosinophilic solid and cystic renal cell carcinoma (ESC RCC) demonstrated frequent genomic alterations consisting of copy number gains on chromosomes 7 and 16 and copy number losses on chromosome X (blue = copy number gains; red = copy number loses). B, The corresponding idiogram shows the copy number–altered chromosomal regions.

ESC RCC: Molecular

TABLE 1. Copy Number Alterations in ESC RCC

Chromosomes	Cytoband	No. Genes	Frequency (%)*	No. Selected Genes	Selected Genes†
Gain					
7	p21.2-q36.2	1995	42-50	42	HIPK2, TRIM24, CARD11, BRAF, EZH2, CASP2, STYXL1, SERPINE1, CLDN3, CDK6, AKAP9, ELN, CLIP2, ABCB1, PIK3CG, RAC1, PPP1R3A, PPP1R9A, SMO, KIAA1549, PDGFA, PILRB, PMS2, CREB3L2, FLNC, RHEB, LMTK2, BHLHA15, UBE2H, BAIAP2L1, TECPR1, KLHDC10, ZC3HC1, MOSPD3, GRM8, SBDS, YWHAG, EPHB6, MET, STAG3, ETV1, HIP1
13	q14.2	73	33	3	RB1, LPAR6, RCBTB2
16	p13.3-q23.1	1218	33-67	16	PHLPP2, WWOX, CYLD, HERPUD1, NQO1, BCAR1, ADAMTS18, TSC2, MLST8, PDPK1, RBFOX1, CDH1, CREBBP, SIAH1, CDH11, CBFB
19	19p12	192	33	2	ZNF486, MIR1270
Loss					
22	q11.23	112	33	1	GSTT1
x	p11.21	56	42	5	RRAGB, SPIN2B, SPIN2A, FAAH2, ZXDB
LOH					
9	q21.1-22.2	358	33	3	NTRK2, GNAQ, SYK
9	q33.1	34	33	1	TLR4
11	p11.2-11.11	209	33	1	DDB2
16	p11.2-11.1	461	75	1	FUS
X	q11.1-13.1	173	75	5	AR, MSN, FOXO4, NONO, ERCC6L
X	q13.1-21.1	272	33	4	XIST, FOXO4, NONO, ERCC6L

*Frequency or frequency ranges of copy number alteration in evaluated cases.
†Selected genes based on their relevance to biological pathways.

TABLE 2. Enriched Gene Sets and Pathways in Genomic Altered Regions in ESC RCC

Enrichment Score	Pathway Term	Genes	*P*	FDR (%)
25.9	Regulation of TOR signaling pathway	AKT1S1, MLST8, TSC1, TSC2	< 0.001	0.7
15.6	Tyrosine-specific protein kinase	AXL, TEK, EGFR, INSR, MET, NTRK2, ROR2, SYK	< 0.001	< 0.001
15.1	Cell cycle control	CCNE1, CDK6, CDKN2A, CDKN2B, RB1	< 0.001	0.4
14.98	Smoothened signaling pathway	GLI3, HIPK2, PTCH1, SMO	0.002	3.76
9.2	Induction of apoptosis by intracellular signals	BCL3, BBC3, BAX, JAK2, ABL1, HIPK2, XPA	< 0.001	0.17

FDR indicates false-discovery rate.

Summary: ESC RCC

- Rare renal neoplasm predominantly found in females
- Solid & (micro)cystic; characteristic cytoplasmic stippling
- CK20+/CK7-
- Indolent clinical behavior with metastatic potential

References

K. Trpkov, O. Hes, M. Bonert, *et al.* Eosinophilic, solid, and cystic renal cell carcinoma: clinicopathologic study of 16 unique, sporadic neoplasms occurring in women Am J Surg Pathol, 2016(40):60-71.

K. Trpkov, H. Abou-Ouf, O. Hes, *et al.* Eosinophilic solid and cystic renal cell carcinoma (ESC RCC): further morphologic and molecular characterization of ESC RCC as a distinct entity Am J Surg Pathol, 2017(41):1299-1308.

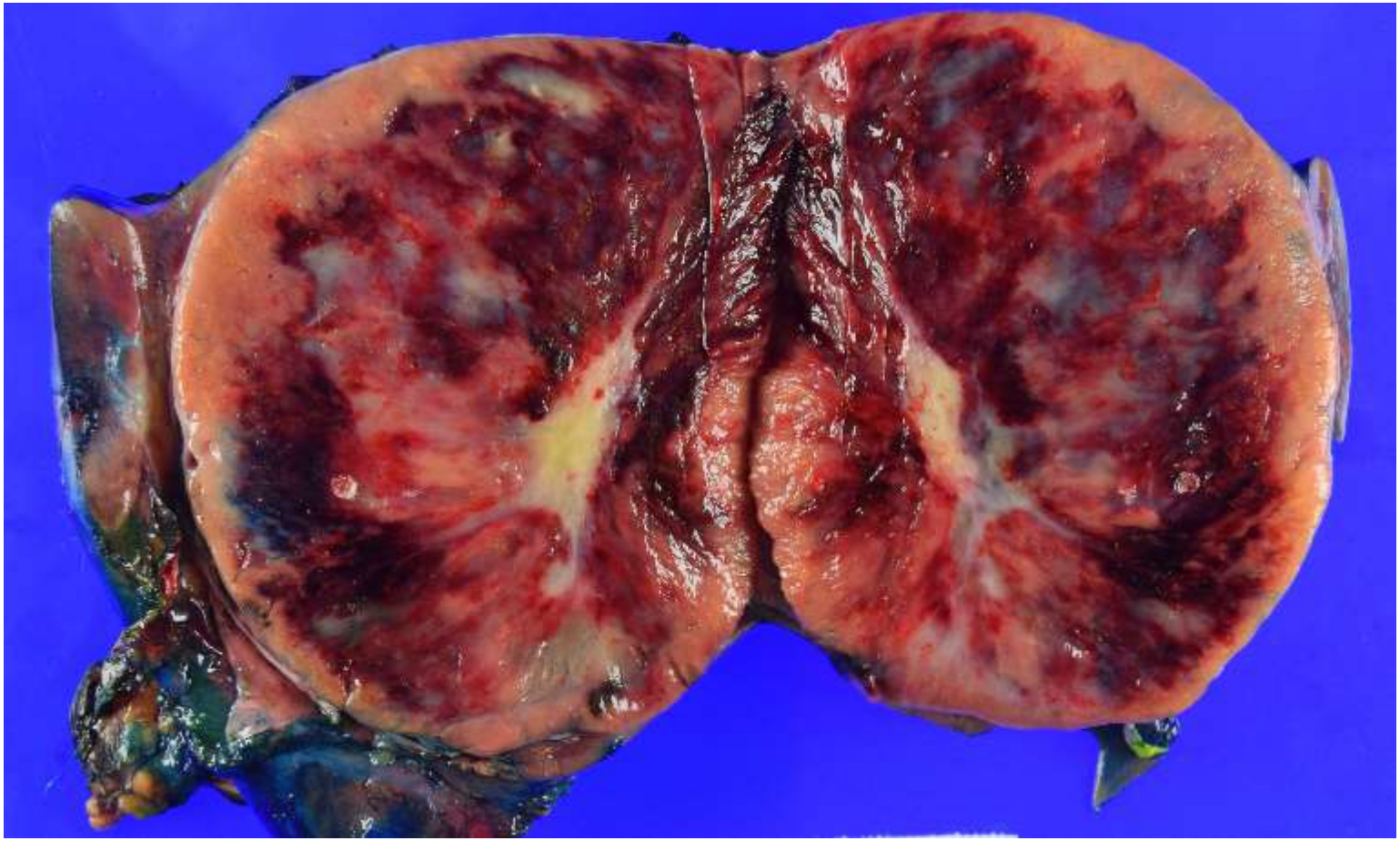
Siadat F, Trpkov K. ESC, ALK, HOT and LOT: Three Letter Acronyms of Emerging Renal Entities Knocking on the Door of the WHO Classification. *Cancers (Basel)*. 2020;12(1):168.

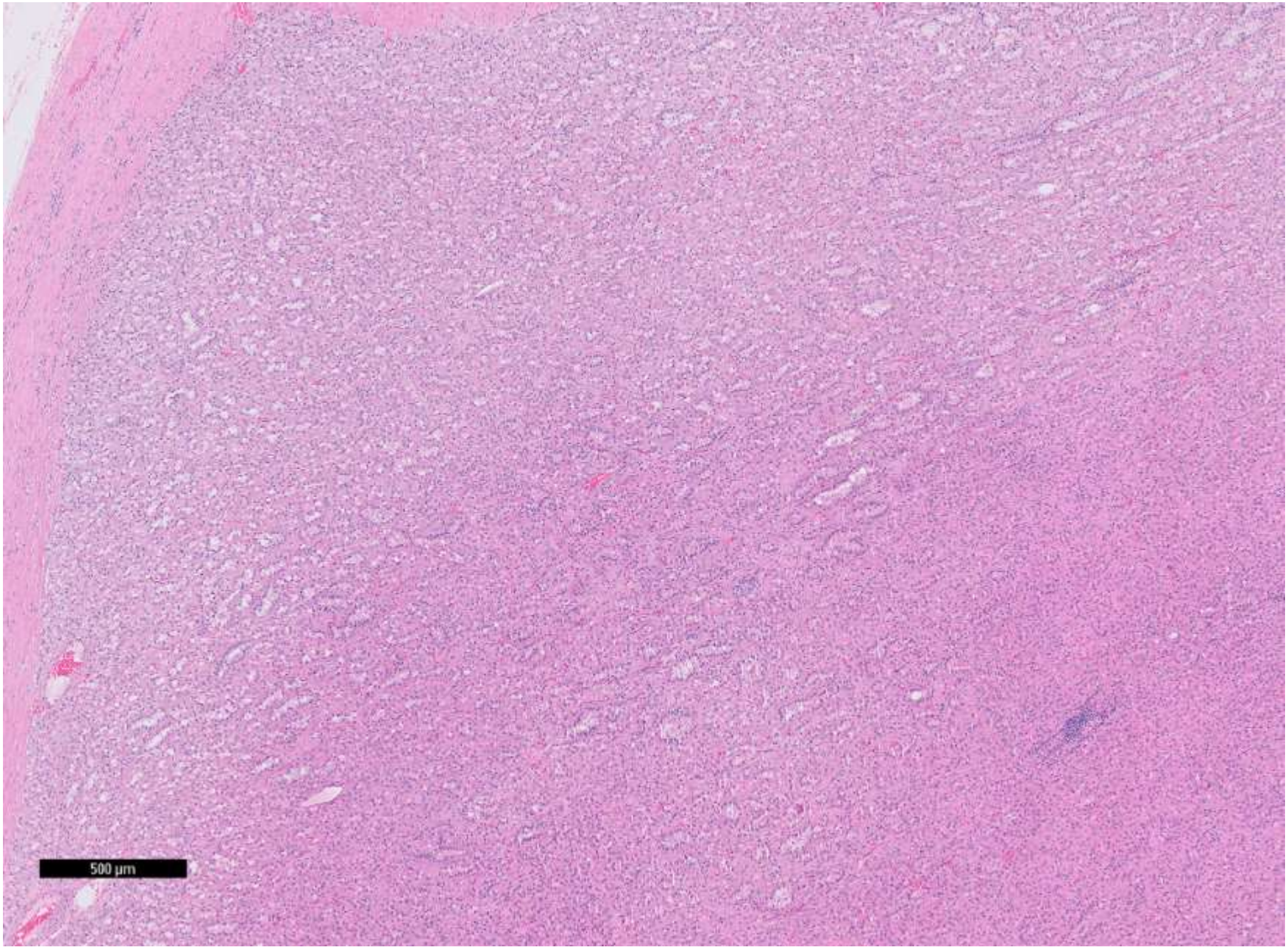
McKenney JK, Przybycin CG, Trpkov K, Magi-Galluzzi C. Eosinophilic solid and cystic renal cell carcinomas have metastatic potential. *Histopathology*. 2018;72(6):1066-1067.

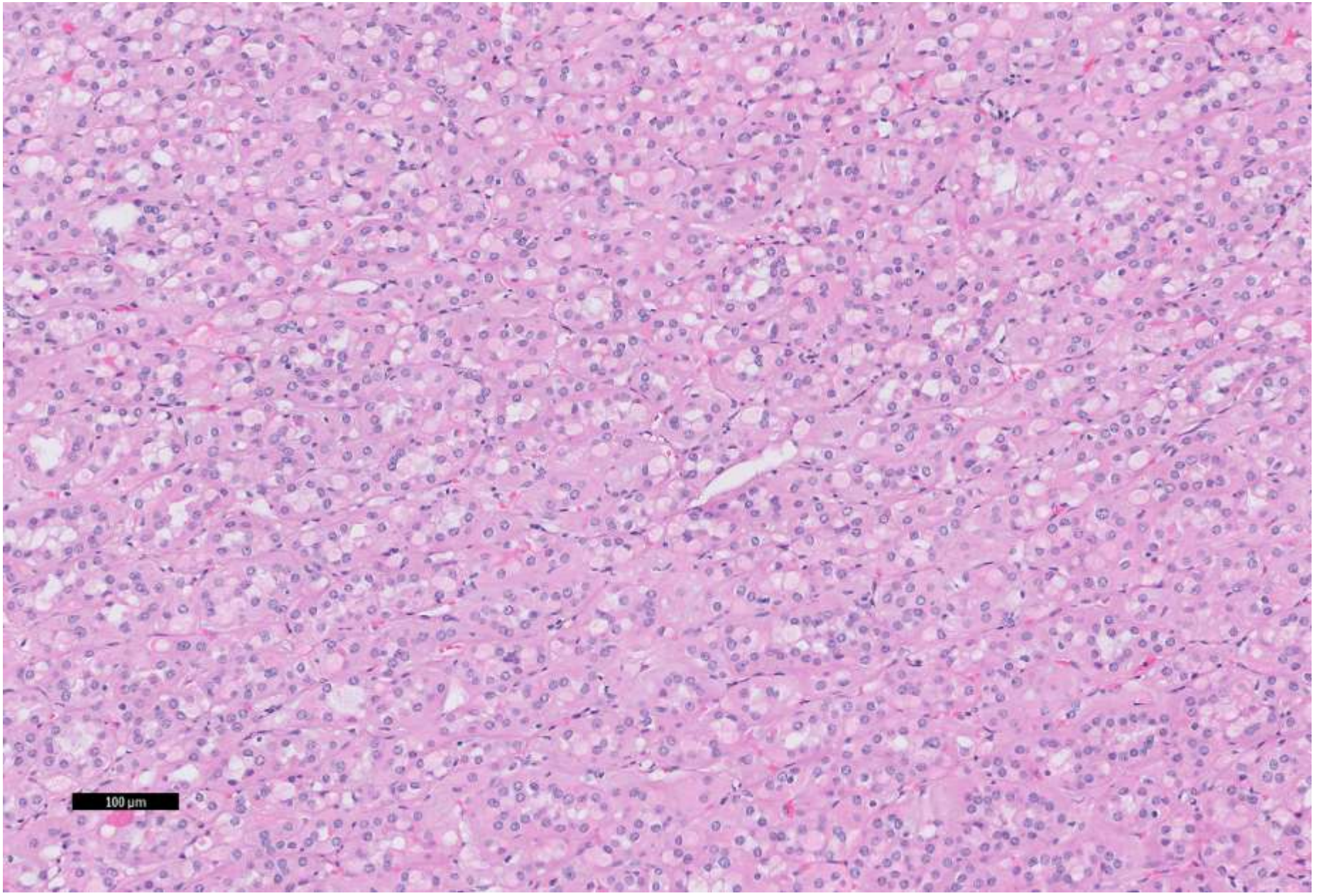
20-0802

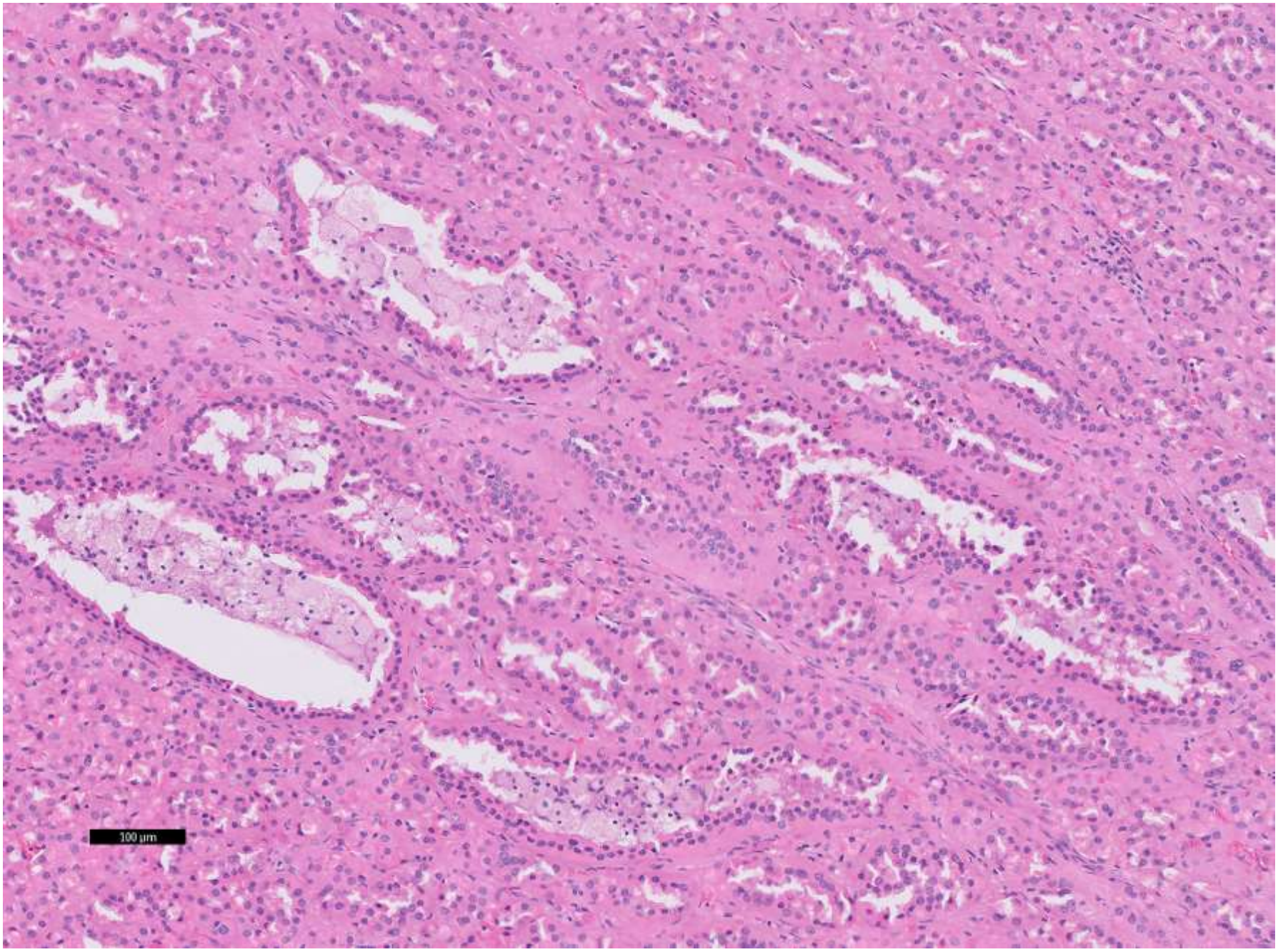
Cornelia Ding/Jeff Simko/Emily Chan; UCSF

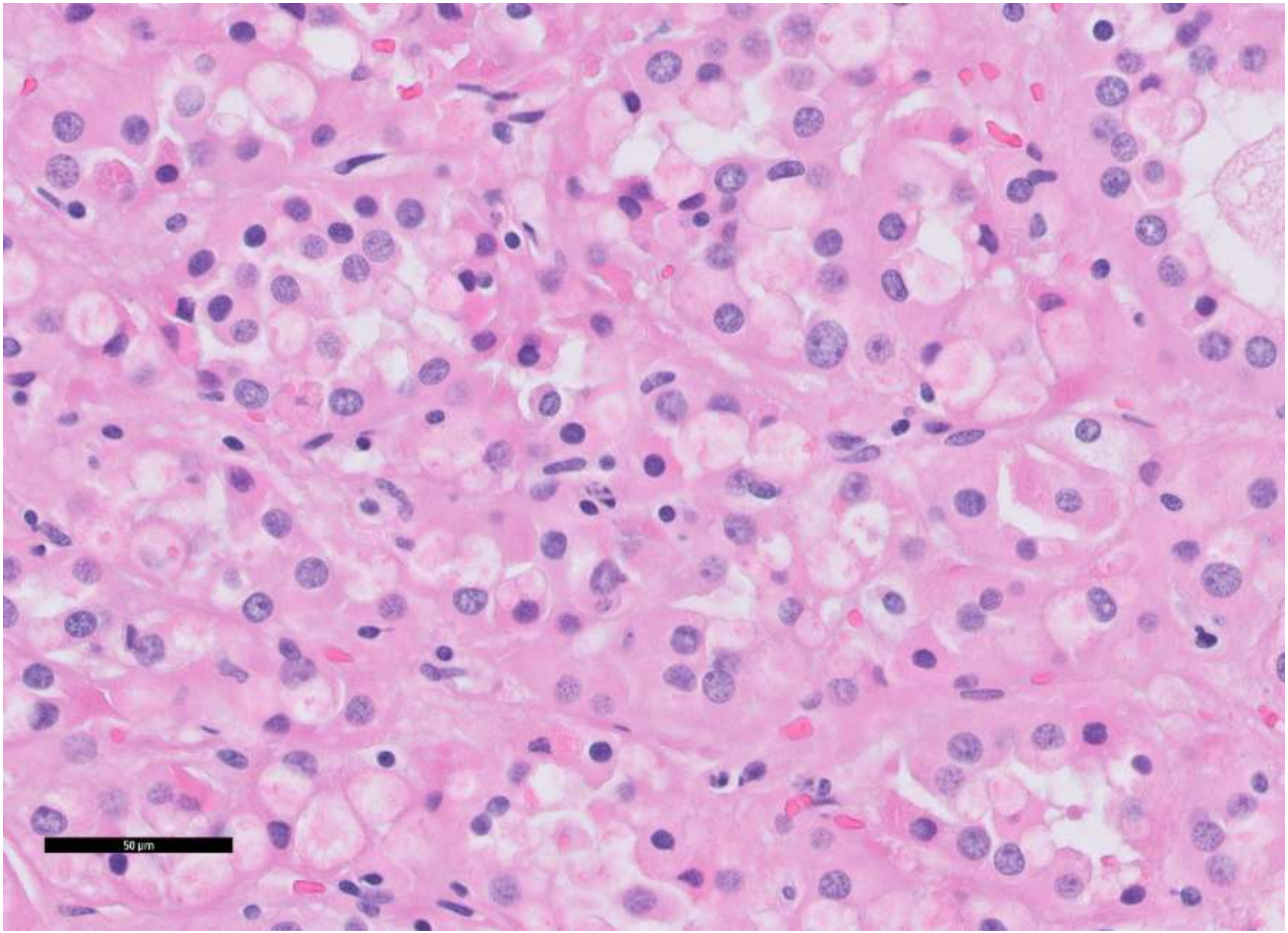
30-year-old F with 12cm left renal mass.

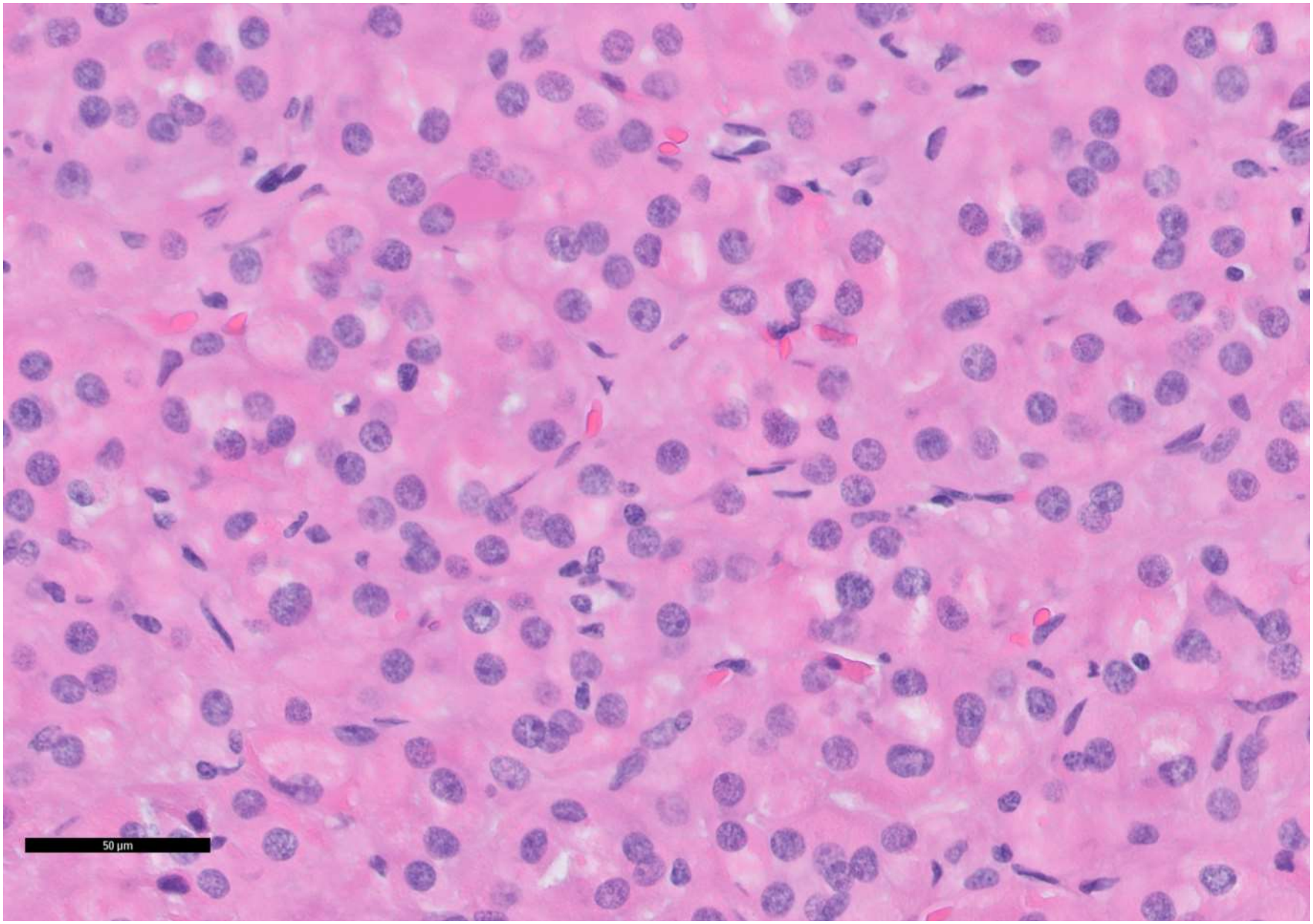



500 µm

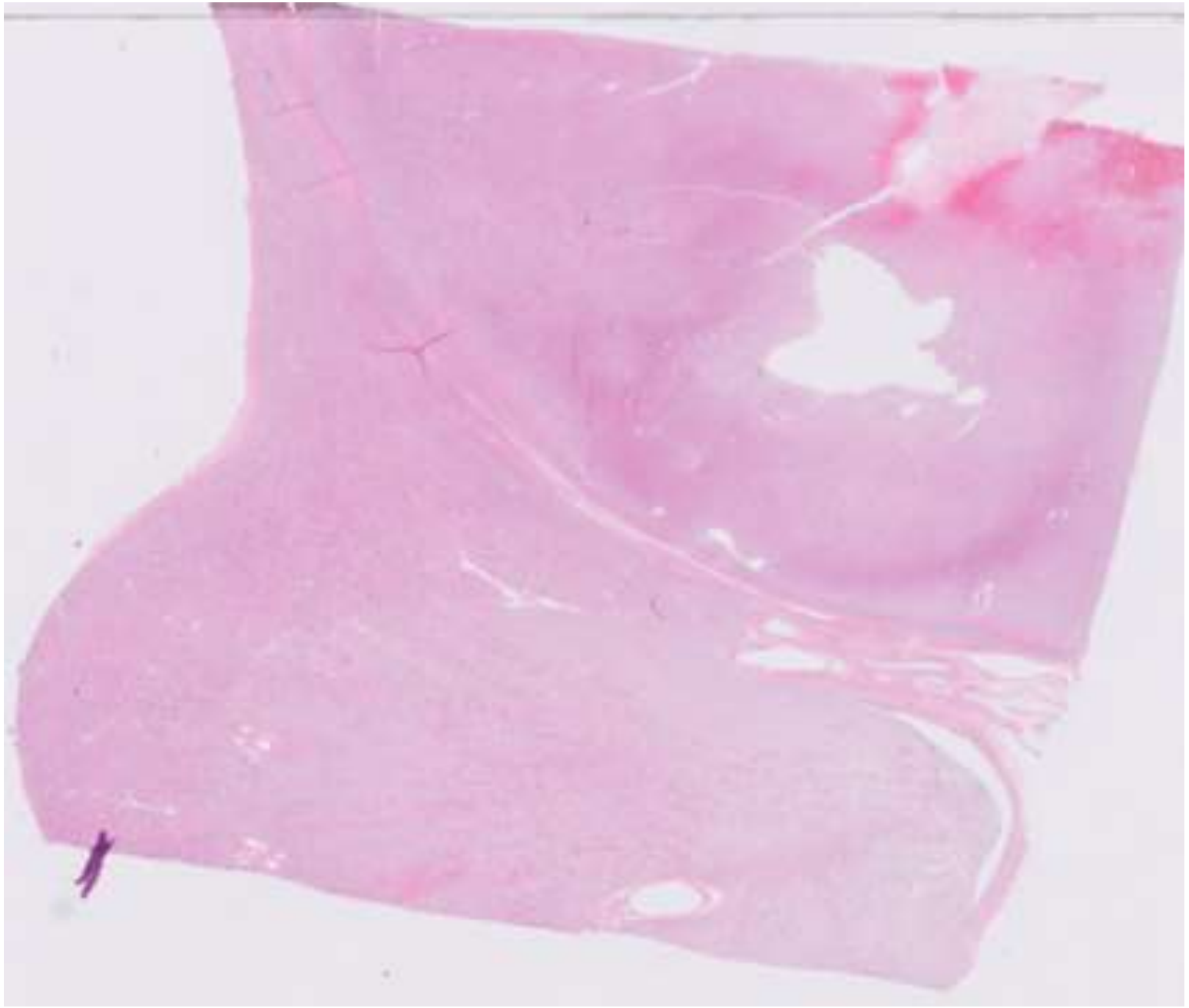

100 µm


100 µm


50 µm


50 µm

tumor



normal

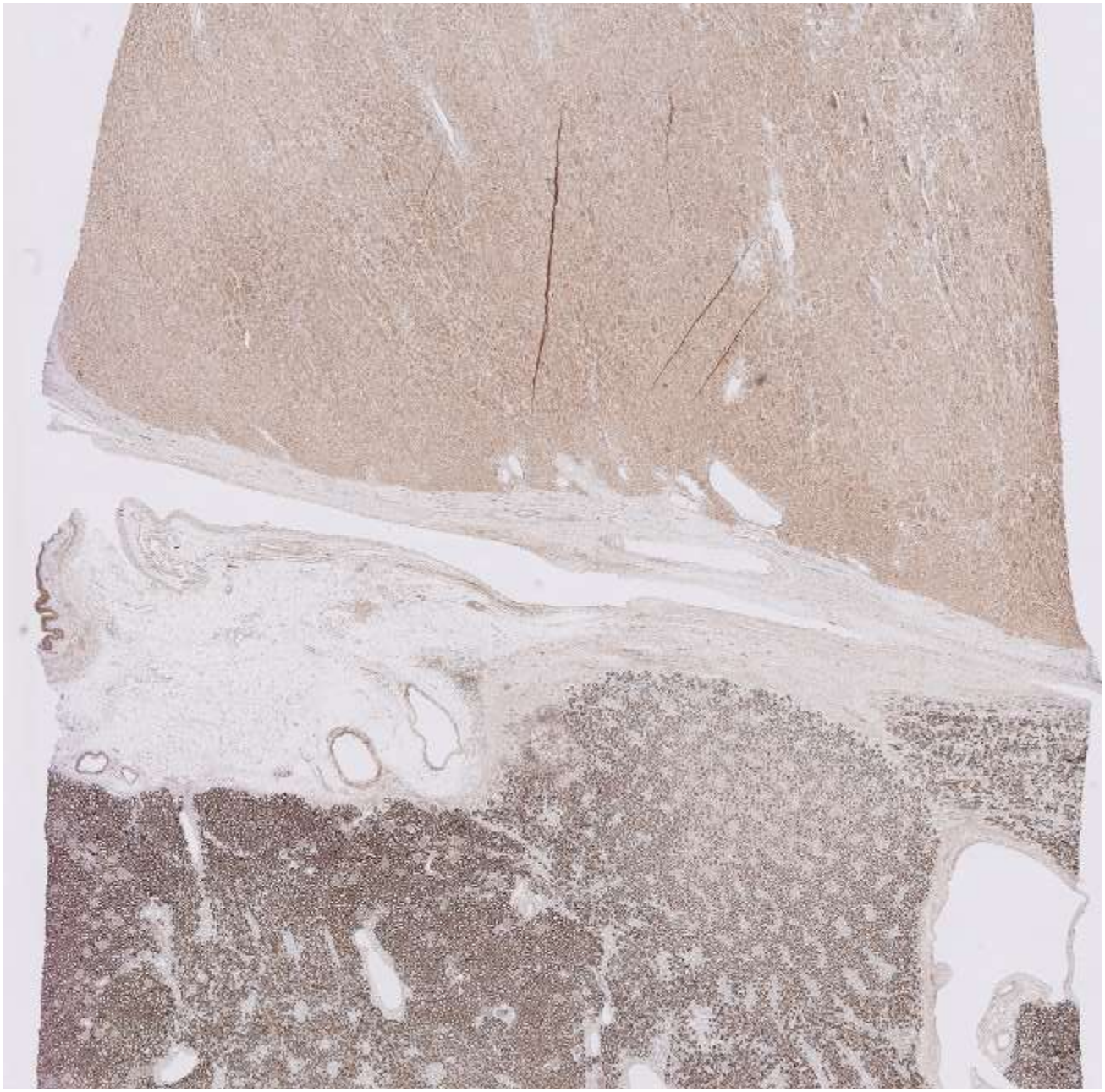
CA IX

CK7

CD117

SDHB

tumor

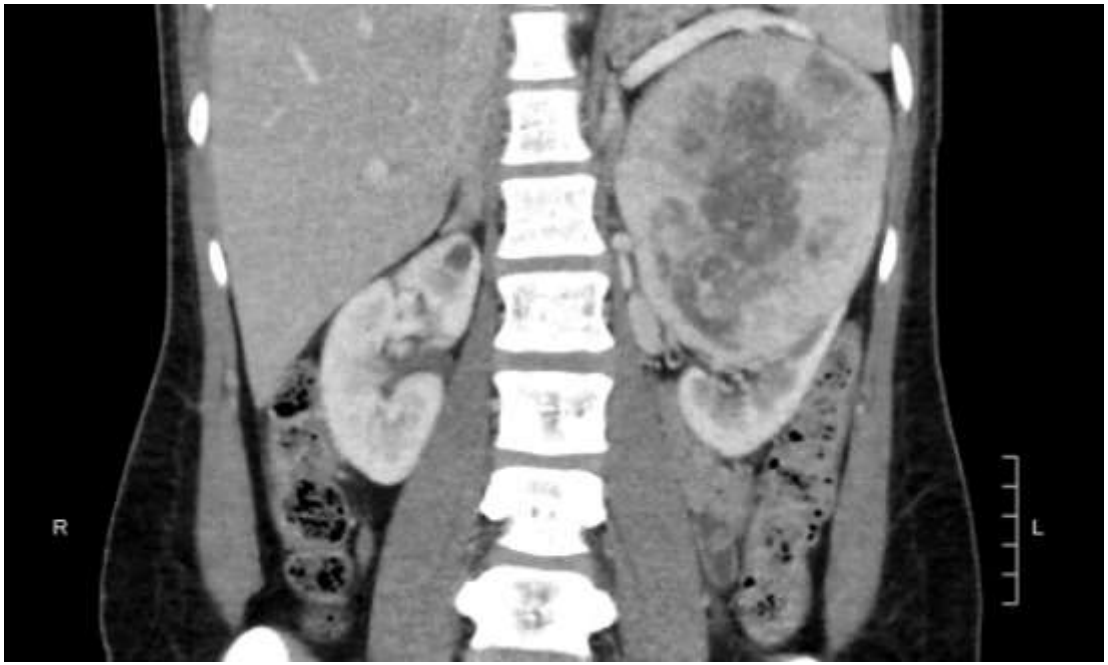


normal

FH

Patient history

- 2012: presented with abdominal pain; a kidney mass was found by ultrasound. Loss of follow up due to difficult access to care.
- 2020:

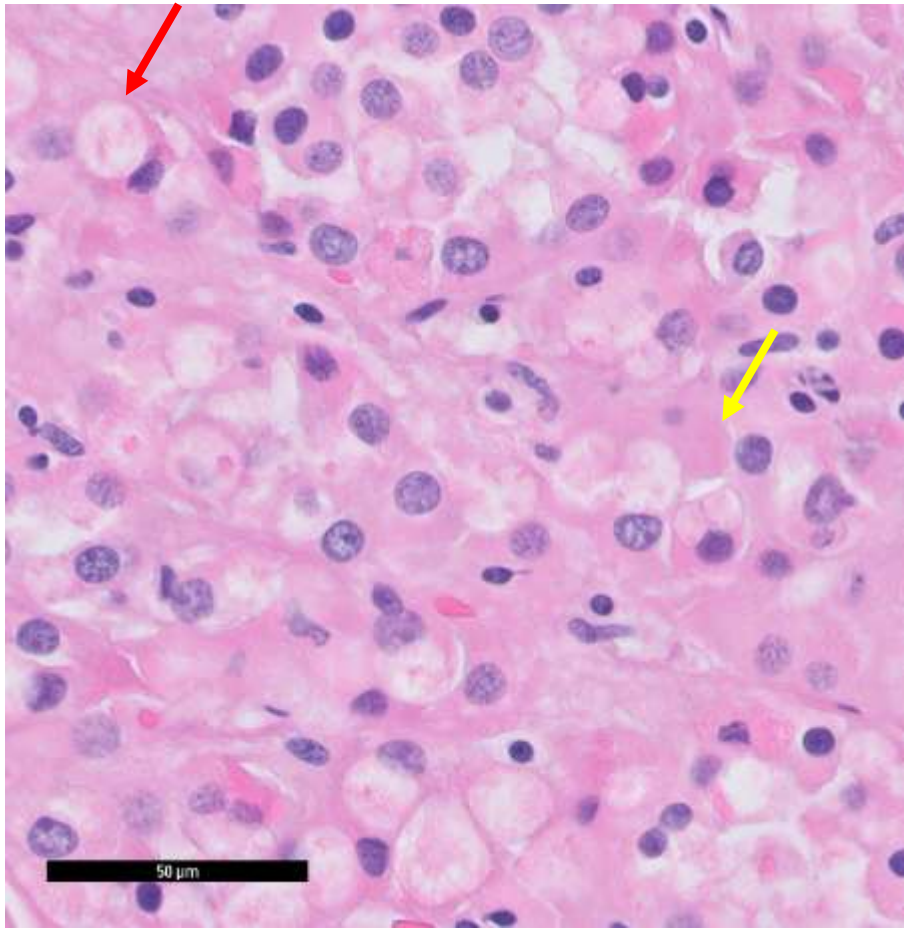


Differential diagnosis

- Hybrid oncocytic tumor of the Birt-Hogg-Dube syndrome
- Succinate dehydrogenase deficient RCC
- Clear cell RCC, granular variant
- Chromophobe RCC, eosinophilic variant
- Tuberous sclerosis associated RCC

Li Y, et al. *Histopathology*. 2018 Mar;72(4):588-600. doi: 10.1111/his.13395.

SDH-deficient RCC



Definition: loss of IHC expression of SDHB (WHO book, 2016)

Histology features:

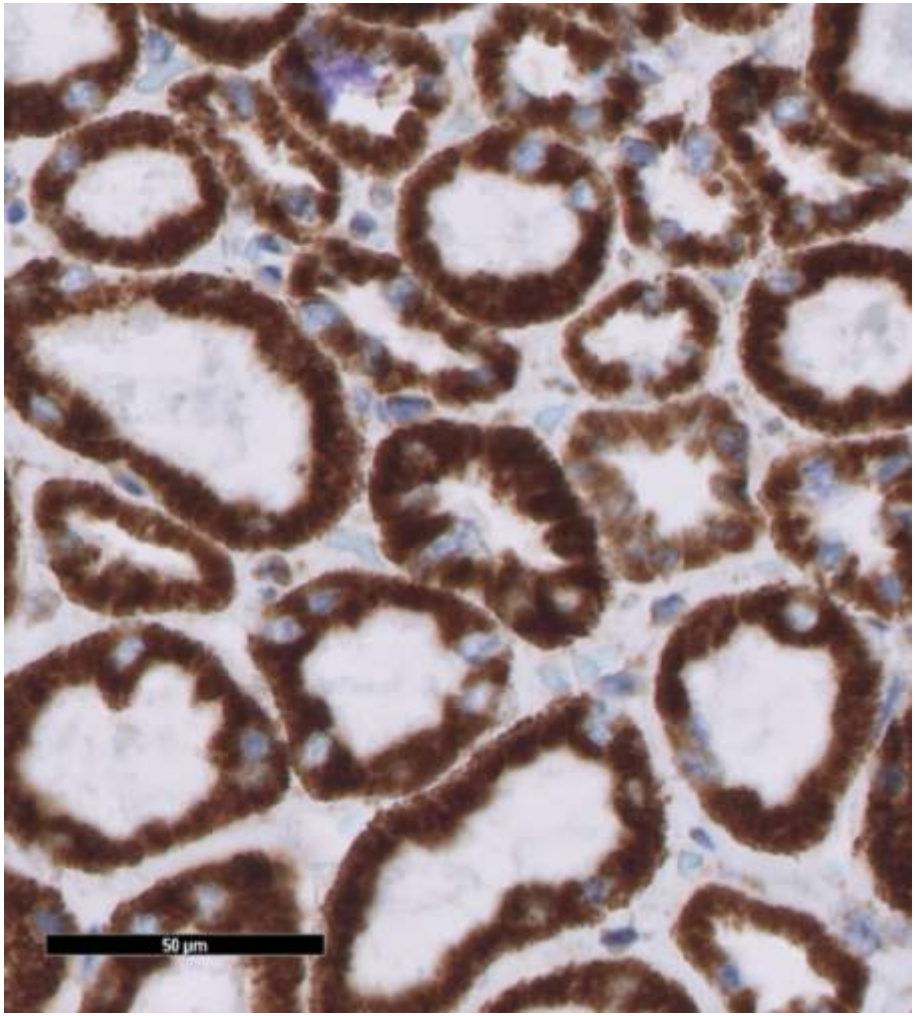
- Eosinophilic and flocculent cytoplasm
- Usually low grade nuclei
- Clear vacuoles
- Entrapped tubules
- Solid architecture

IHC: CD117-, PAX8+, CA IX-, often CK7- and AE1/AE3-

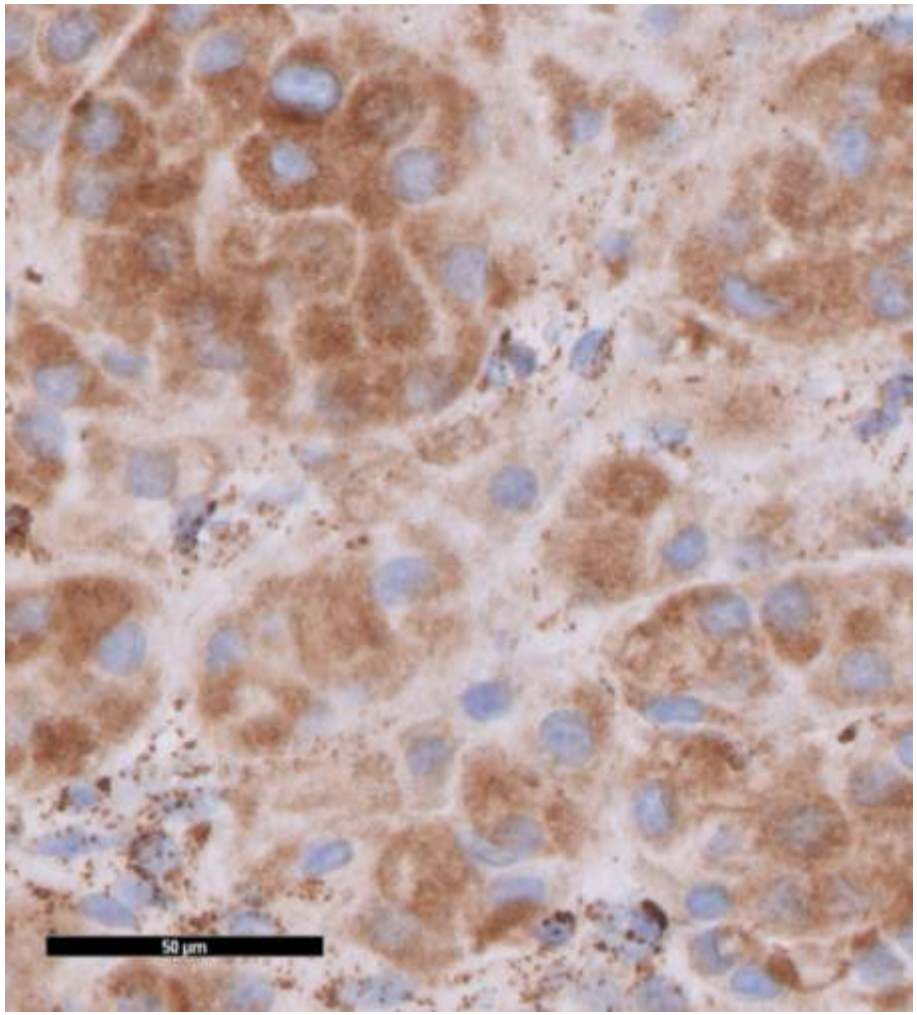
Modern Pathology 2015; 28:80-94
Histopathology 2019; 74(1):31-59

SDHB stain, 40X

normal



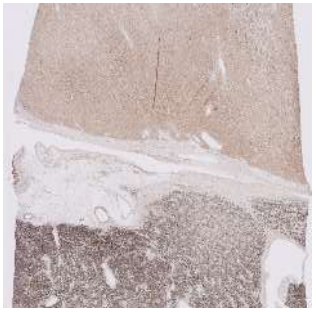
Tumor: **SDHB retained?**



Ab clone: 21A11AE7 (Abcam), incubation: 15 mins; concentration: 1:200; Pretreatment: 20 min in ER2(9.0 pH)

tumor

normal



UCSF Clinical Cancer Genomics Laboratory

UCSF500 Gene Panel Final Report

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
SDHB p.R242H homozygosity, resulting from a germline mutation accompanied by somatic copy-neutral loss of heterozgosity of chromosome 1	NM_003000.2	Pathogenic	507	81%

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

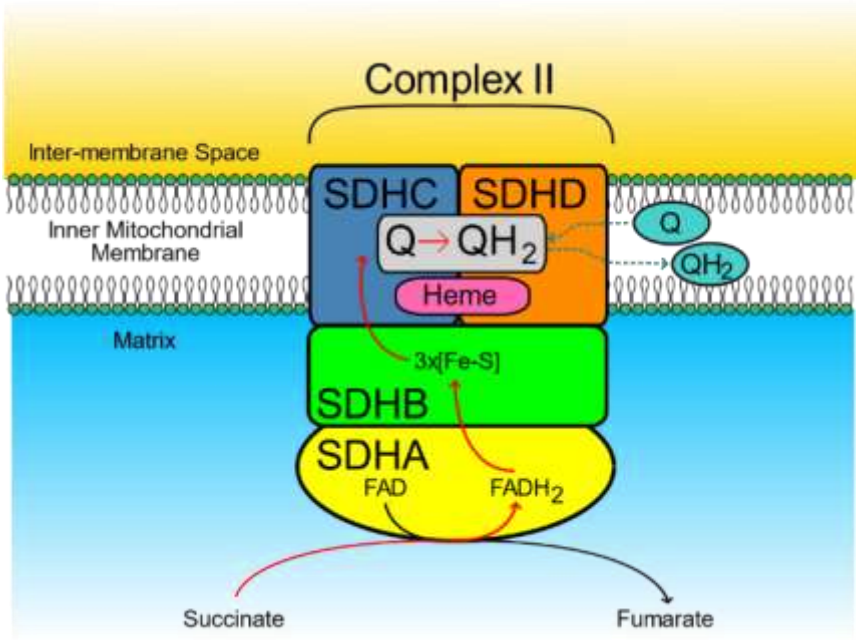
Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
SDHB p.R242H (c.725G>A, p.Arg242His)	NM_003000.2	Pathogenic	486/507	48%/81%

*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist/geneticist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Alterations in the normal samples are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

SDH complex

- Mitochondrial Complex II
- In SDH-deficient RCC, it is most commonly a mutation in *SDHB*. Mutation in any of the subunit could make the entire complex unstable.
- SDHB IPOX stain is used as a screening and diagnostic tool.



By Johnhfst at English Wikipedia - Transferred from en.wikipedia to Commons., Public Domain, https://commons.wikimedia.org/w/index.php?curid=2287606

WHO classification of Tumours of the Urinary System and Male Genital organs, 2016

Gill AJ, Pachter NS, Clarkson A, et al. *N Engl J Med*. 2011 Mar 3;364(9):885-6

SDH-deficient RCC

- Most commonly present in young adulthood (median age: 38 y/o)
- Strongly familial
- Great majority occurs in the setting of germline mutation in one of the SDH genes and a double-hit inactivation.
- Majority of the tumors are confined to the kidney, often without causing any symptom.
- Almost never harbor mutations in *VHL*, *PIK3CA*, *AKT*, *MTOR*, *MET*, or *TP53*.
- 75% of SDH-deficient RCC are low-grade with favorable prognosis (11% metastatic rate)
- Less favorable features: sarcomatoid change, high nuclear grade, coagulative necrosis (70% metastatic rate)
- ~30% of patients develop bilateral or multifocal renal tumor.

WHO classification of Tumours of the Urinary System and Male Genital organs, 2016

Germline SDH deficiency predispose the patient to other neoplasms.

- Mutation in SDH complex is associated with GIST, familial paraganglioma syndromes (PGL1-5) and pheochromocytoma in the family

→ long-term patient surveillance

→ genetic counselling and investigation of family members indicated.

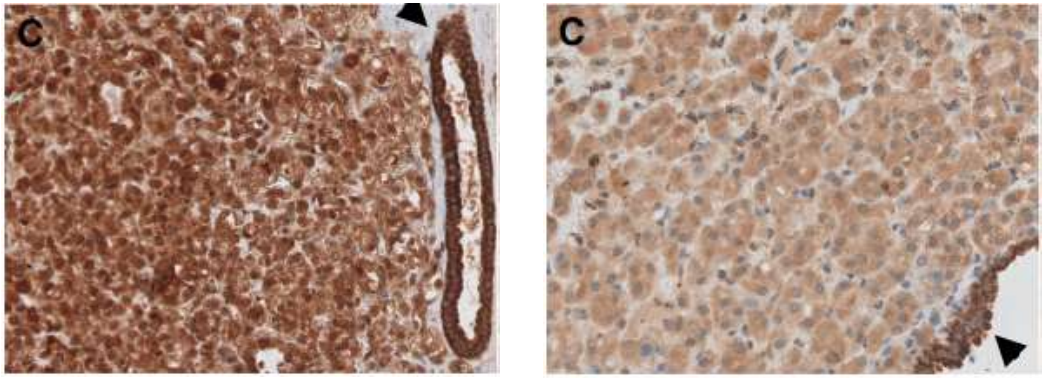
OMIM 185470: SDHB
WHO classification of Tumours of the Urinary System and Male Genital organs, 2016

CASE REPORT Open Access

Positive/retained SDHB immunostaining in renal cell carcinomas associated to germline SDHB-deficiency: case report

Marina Ugarte-Camara[1†], Raul Fernandez-Prado[2*†], Isabel Lorda[3], Gabriela Rossello[2], Carmen Gonzalez-Enguita[4], Pablo Cannata-Ortiz[5†] and Alberto Ortiz[2†]

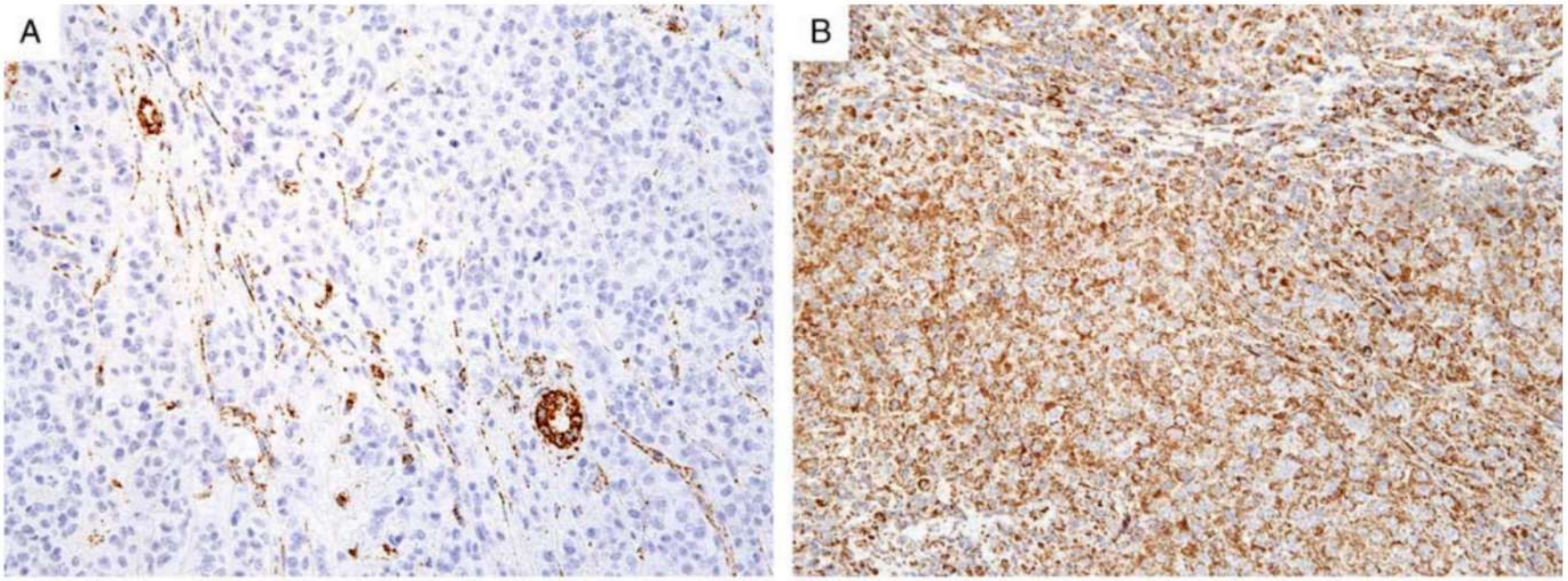
SDHB *c.166_170del* p.Pro56Tyrfs*5



Diagn Pathol. 2019 15;14(1):42

A Clinicopathologic and Molecular Analysis of Fumarate Hydratase-deficient Renal Cell Carcinoma in 32 Patients

Hubert D. Lau, MD, Emily Chan, MD, PhD,† Alice C. Fan, MD,‡ Christian A. Kunder, MD, PhD,§ Sean R. Williamson, MD,‖ Ming Zhou, MD, PhD,¶ Muhammad T. Idrees, MD,# Fiona M. Maclean, MBBS,**†† Anthony J. Gill, MD,‡‡§§‖‖ and Chia-Sui Kao, MD§*



FH stain: 1:2000 dilution, clone J-13; Santa Cruz Biotechnology

Lau HD et al. *Am J Surg Pathol*. 2020 Jan;44(1):98-110. PMID: 31524643.

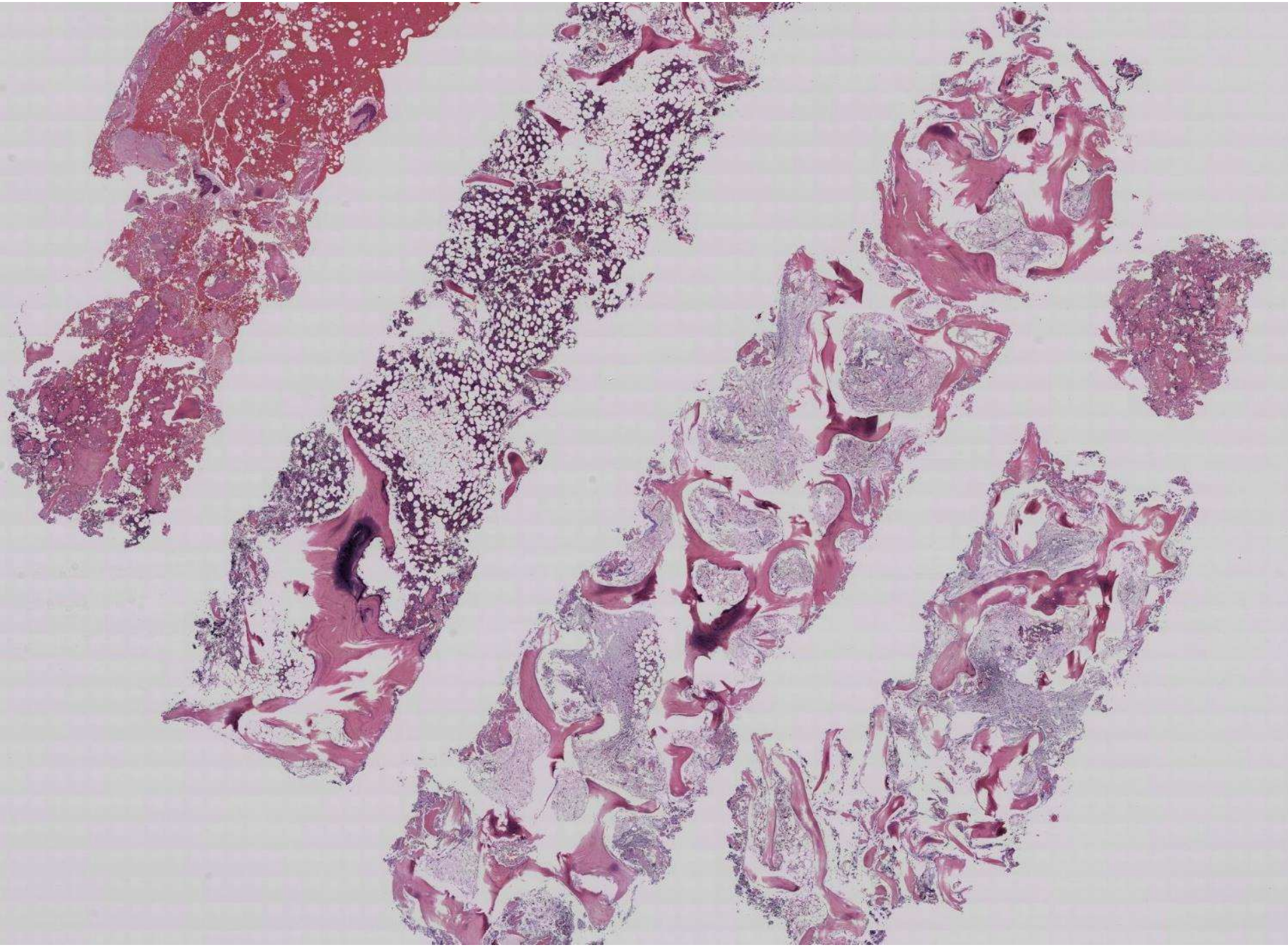
Summary

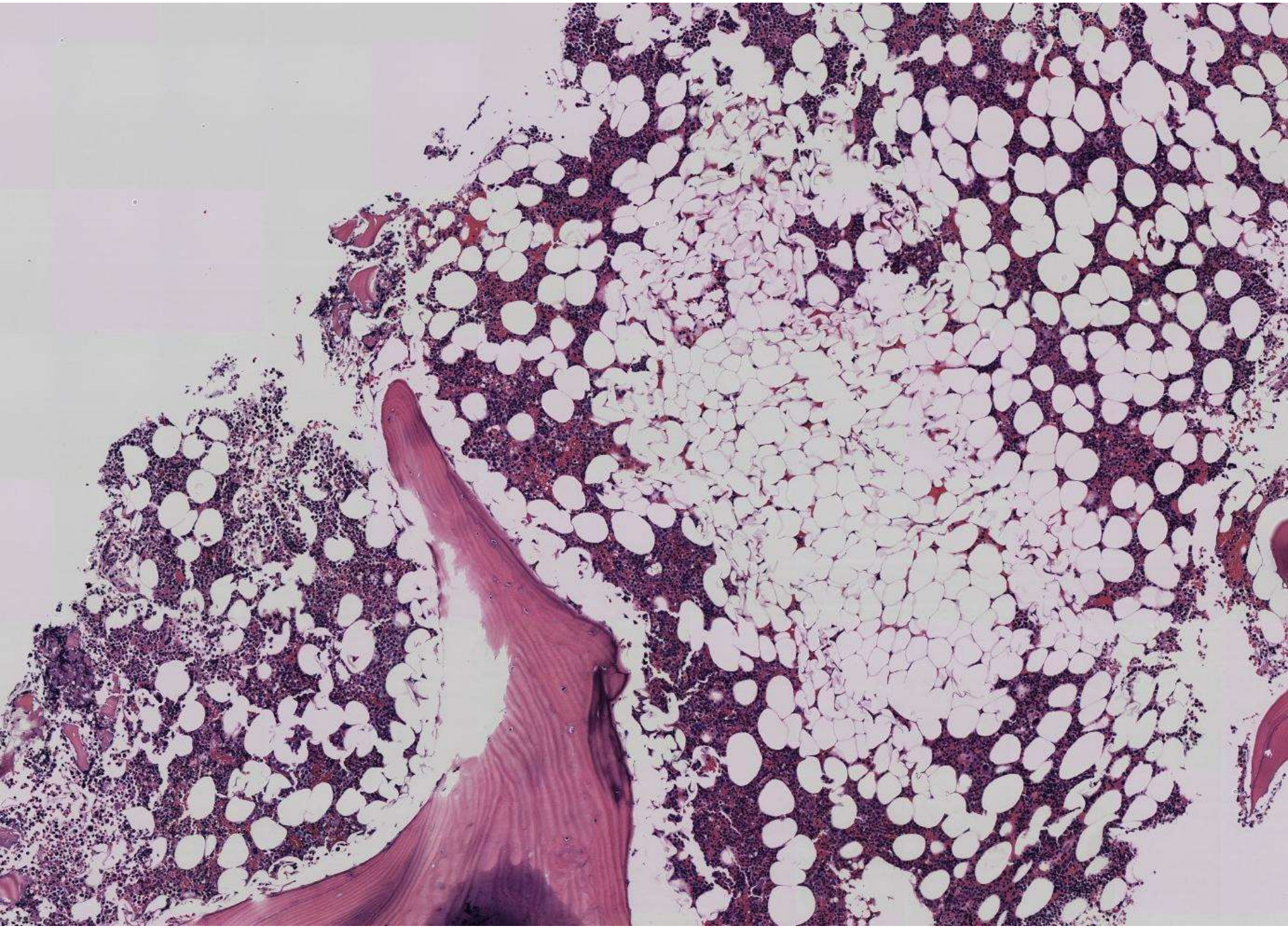
- Renal tumor with eosinophilic and flocculent cytoplasm, intracytoplasmic vacuoles, solid growth pattern, and entrapped tubules in young patient – consider SDH-deficient RCC in the differential diagnosis.
- Perform IHC staining for SDHB on the block with both normal kidney parenchyma and the tumor, interpret with caution.
- If IHC inconclusive and morphology compatible with SDH-deficient RCC, consider molecular testing.

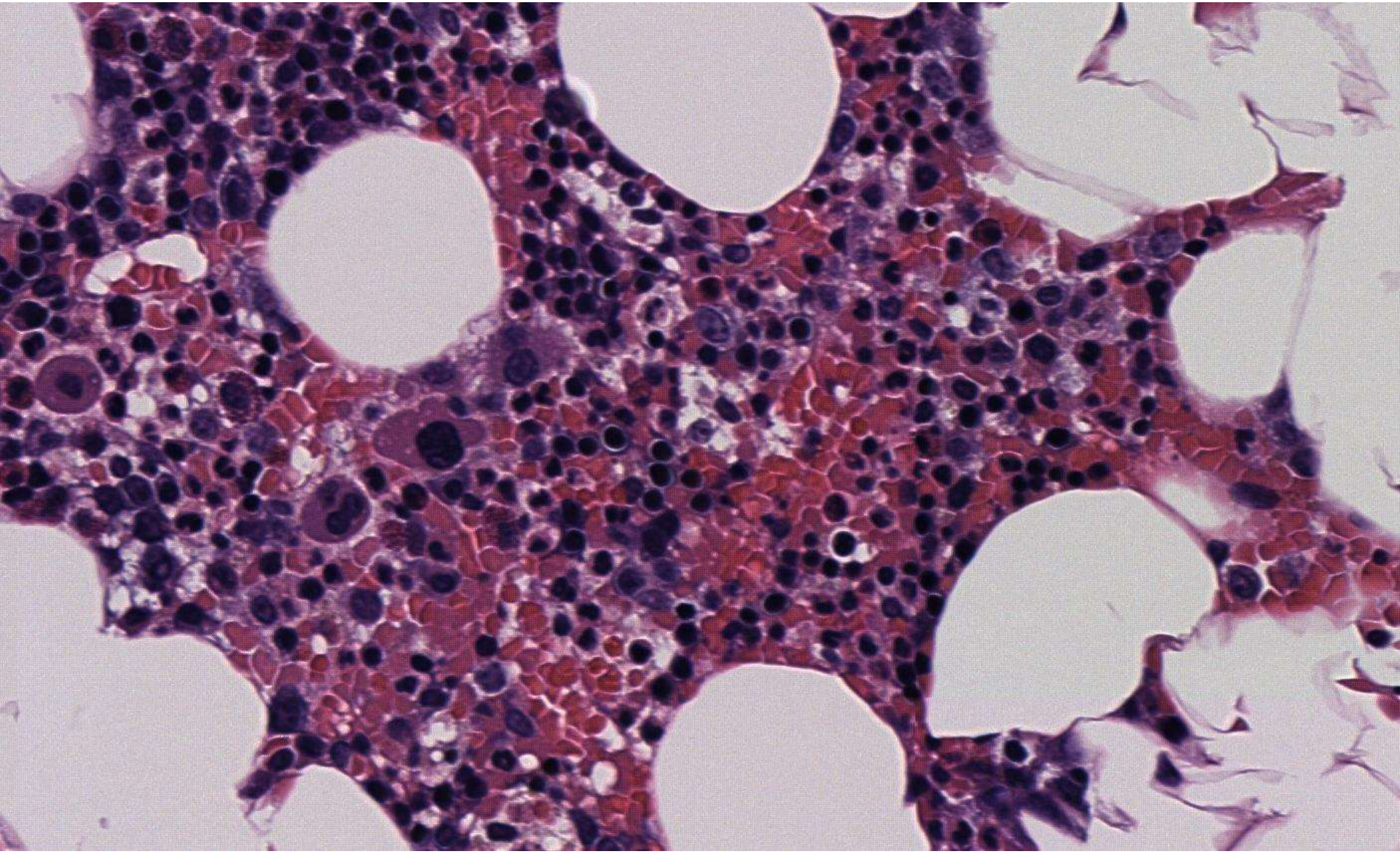
20-0803
scanned slide available!

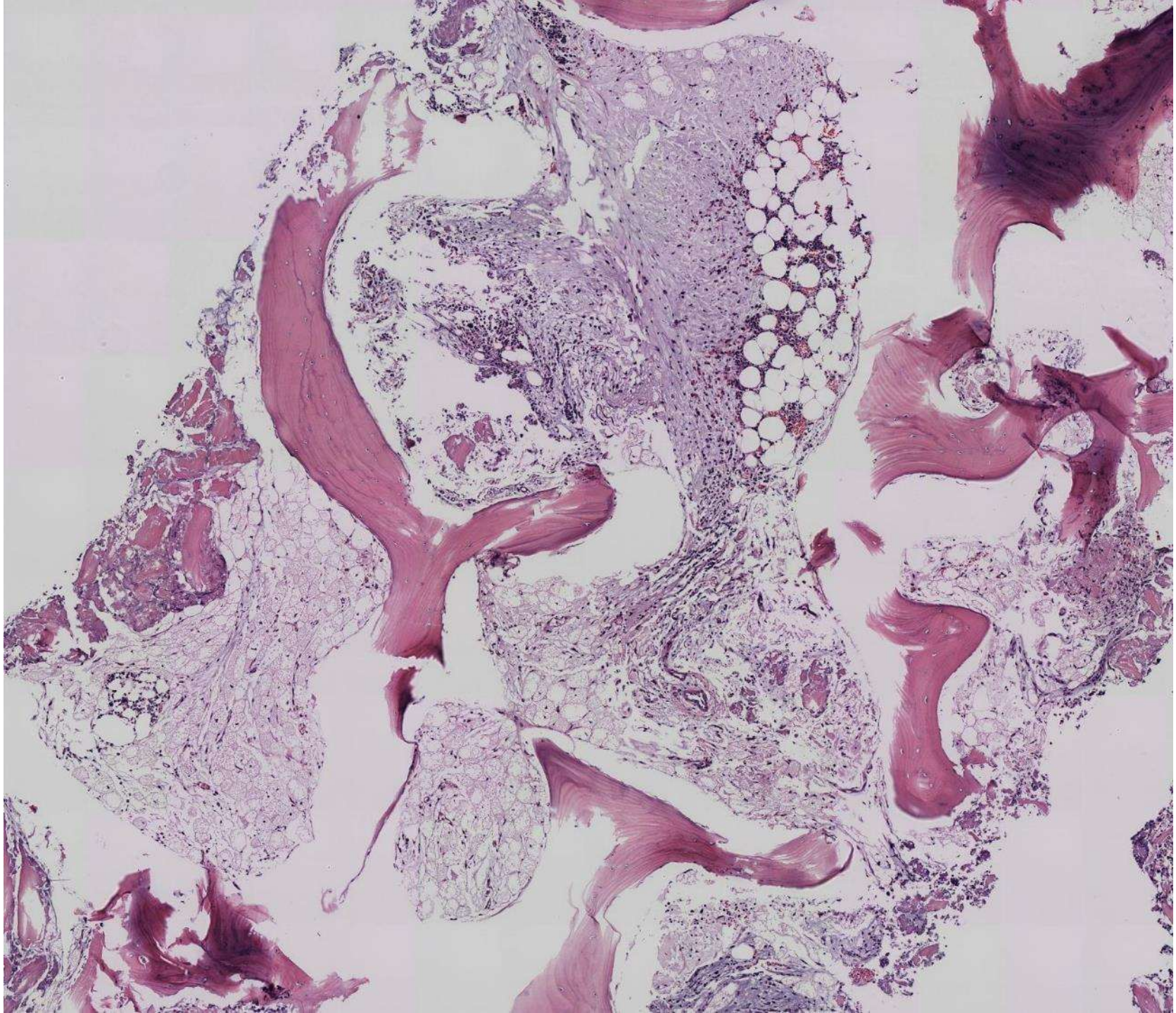
Natalie Patel; El Camino Hospital

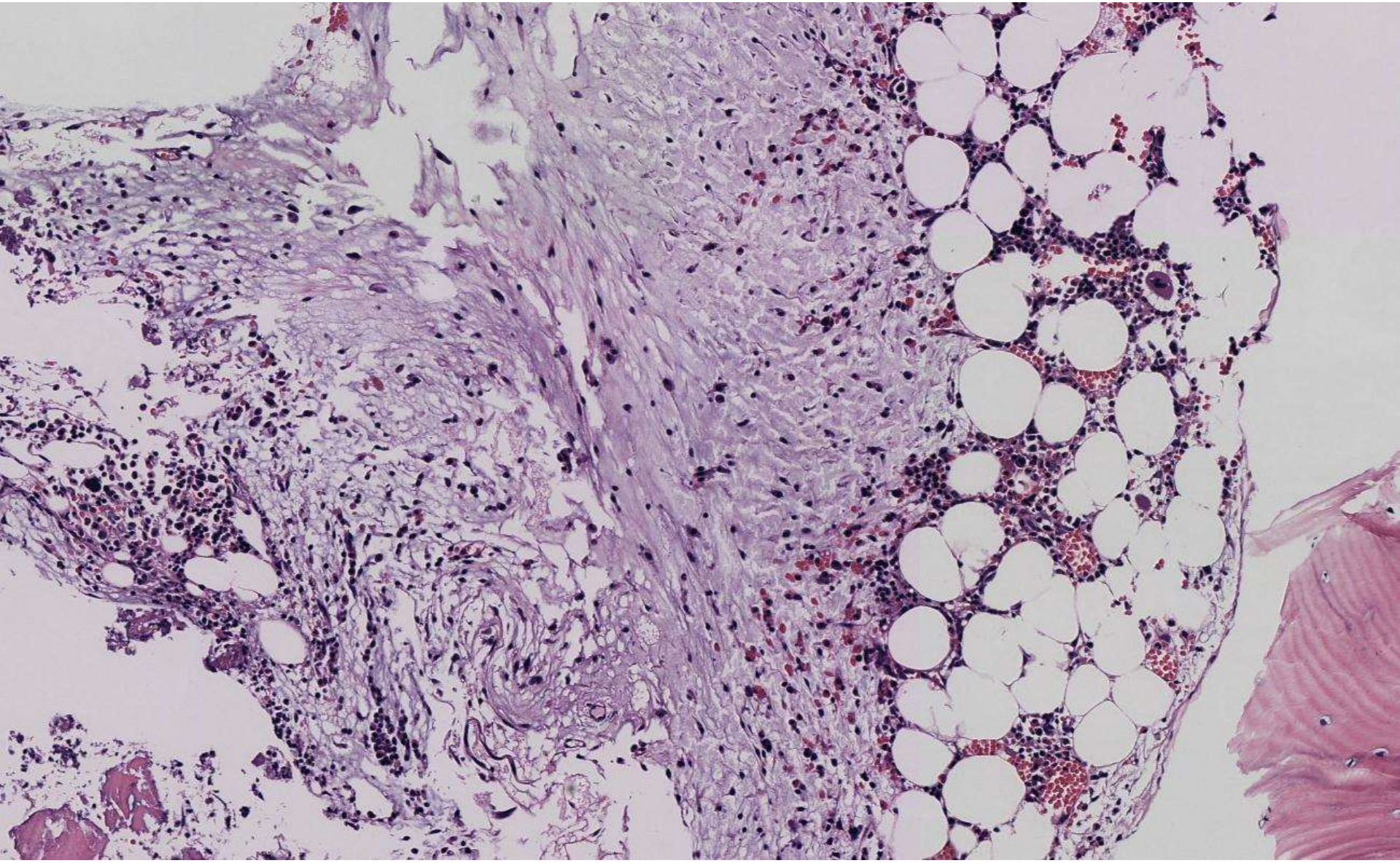
80-year-old M with h/o sciatica, found to have sclerotic lumbar bone lesions in L2 and L3. Bone biopsy performed.

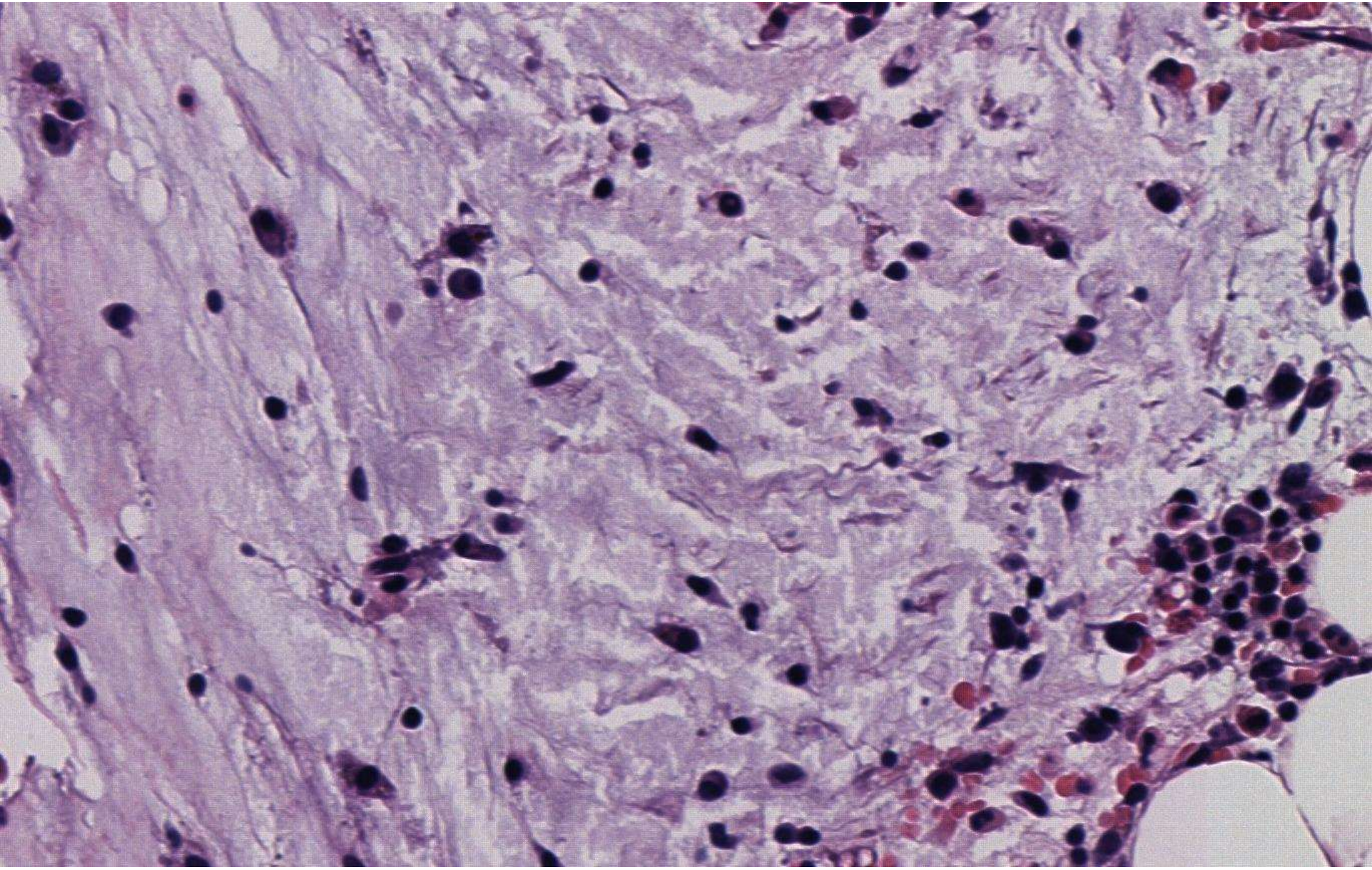


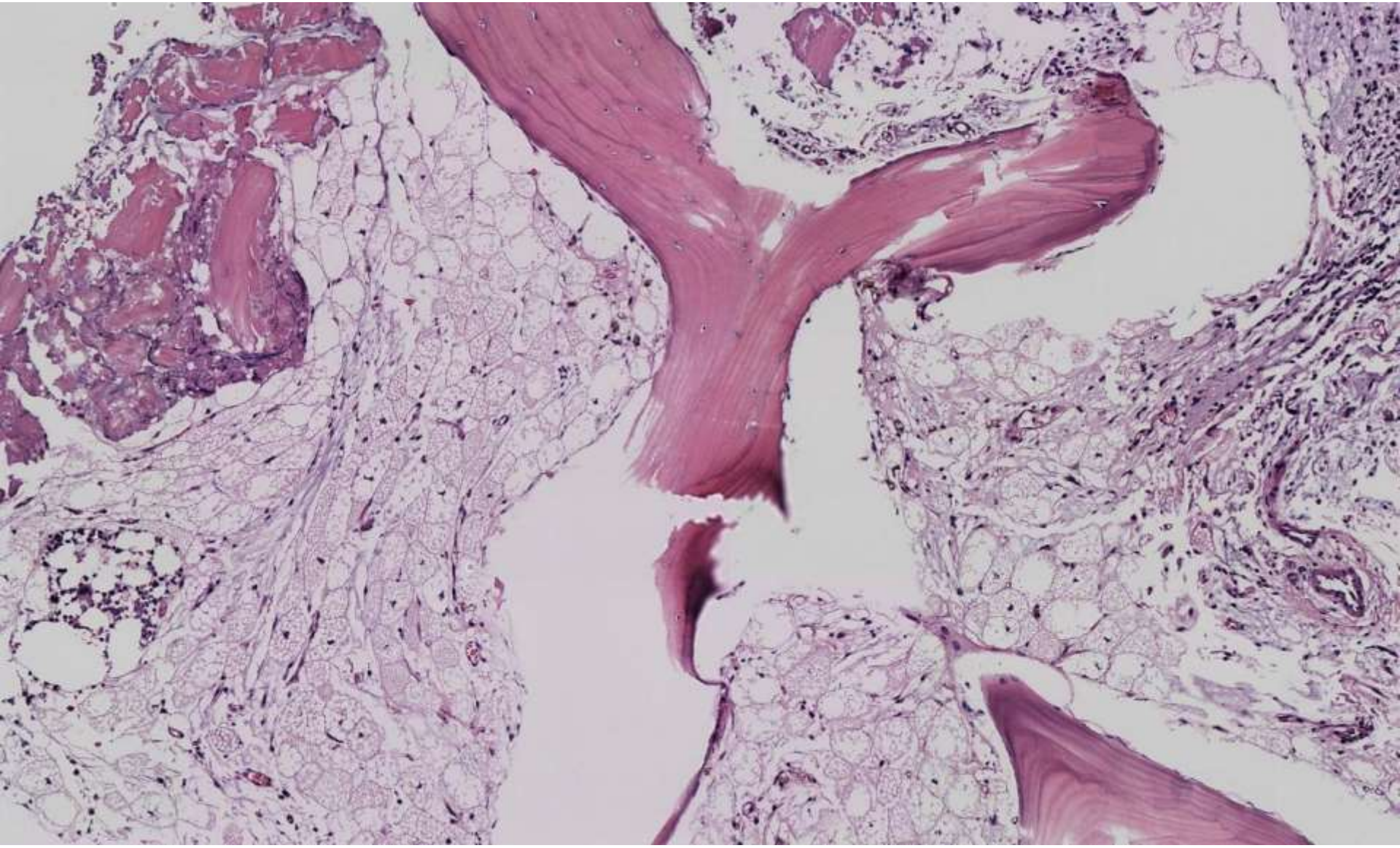


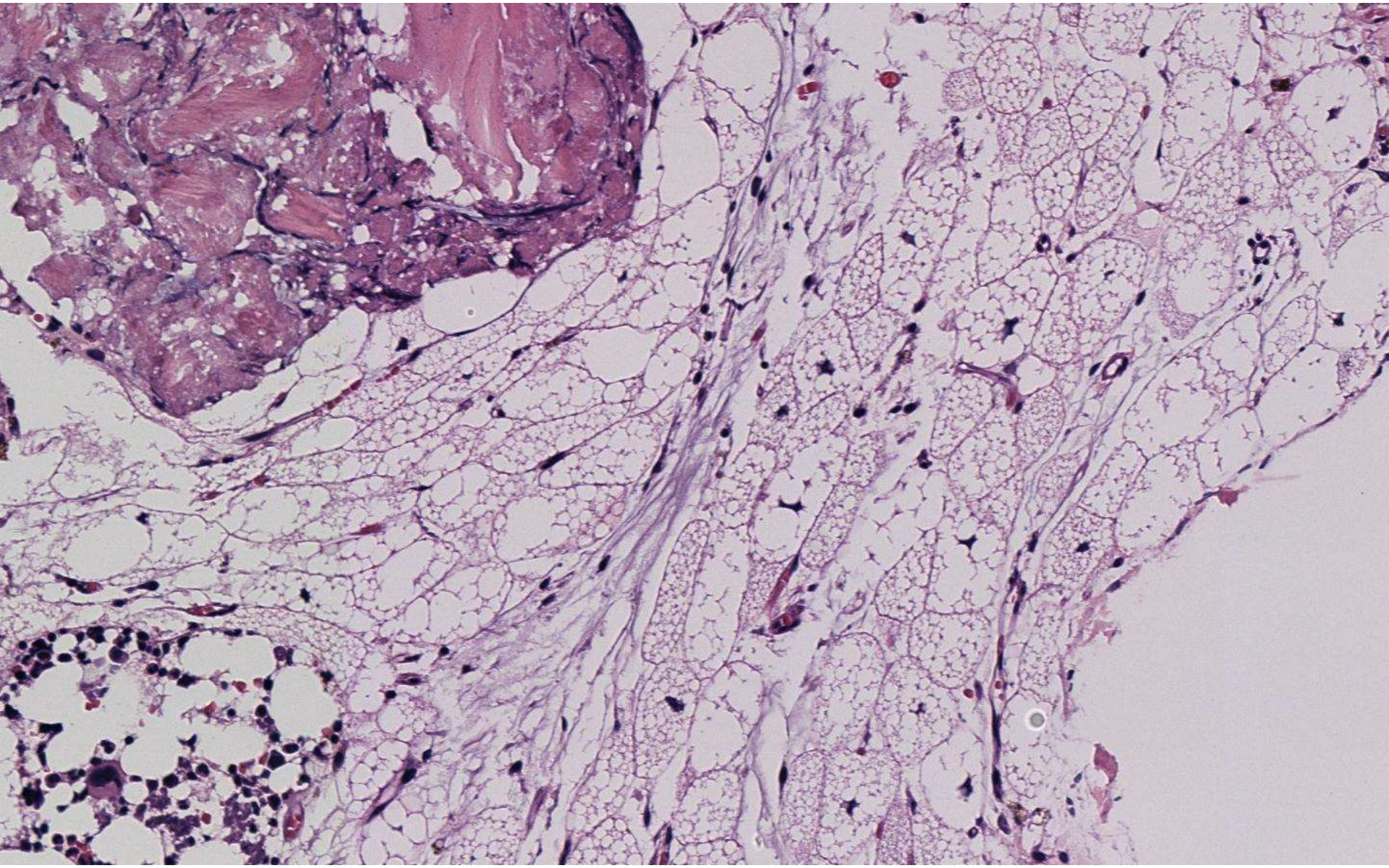


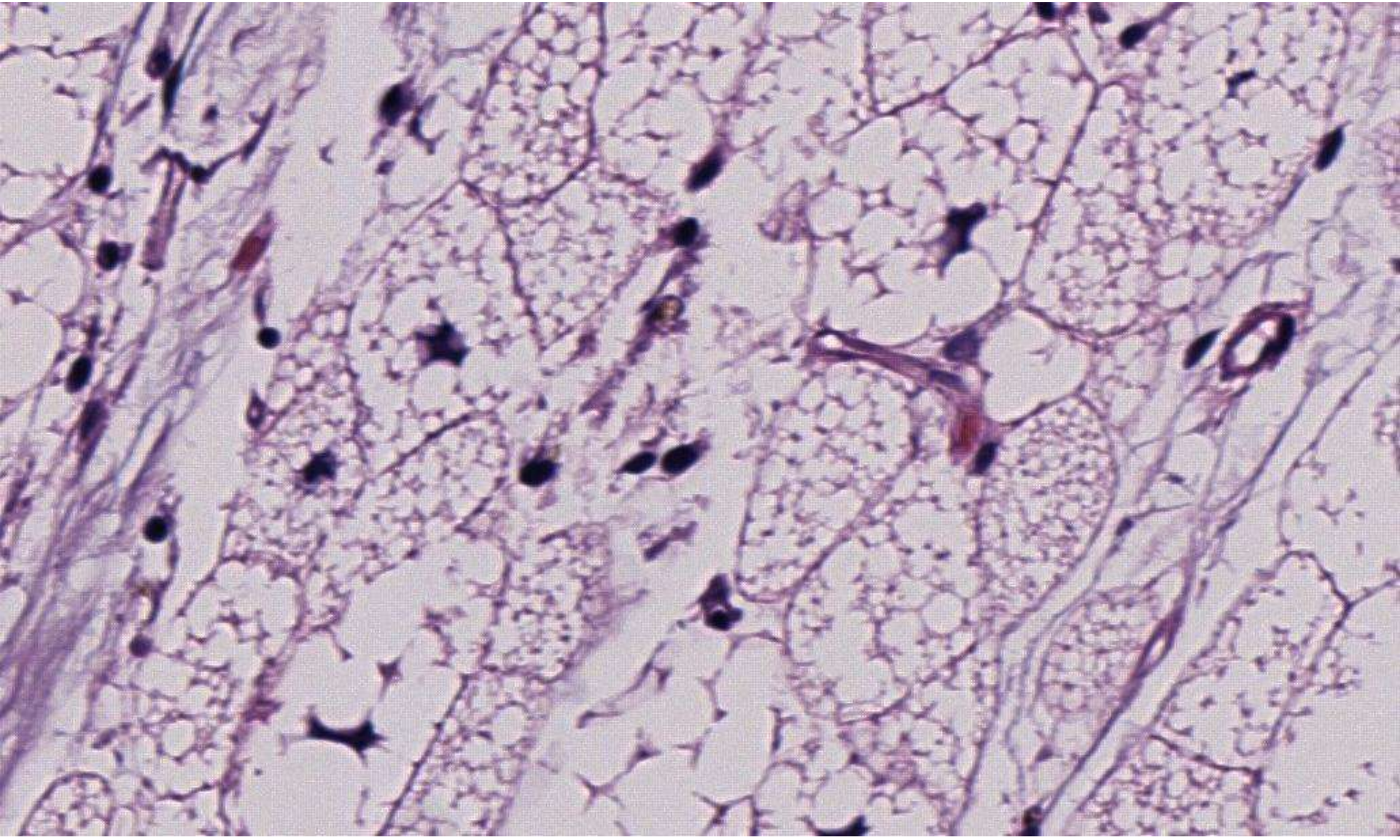


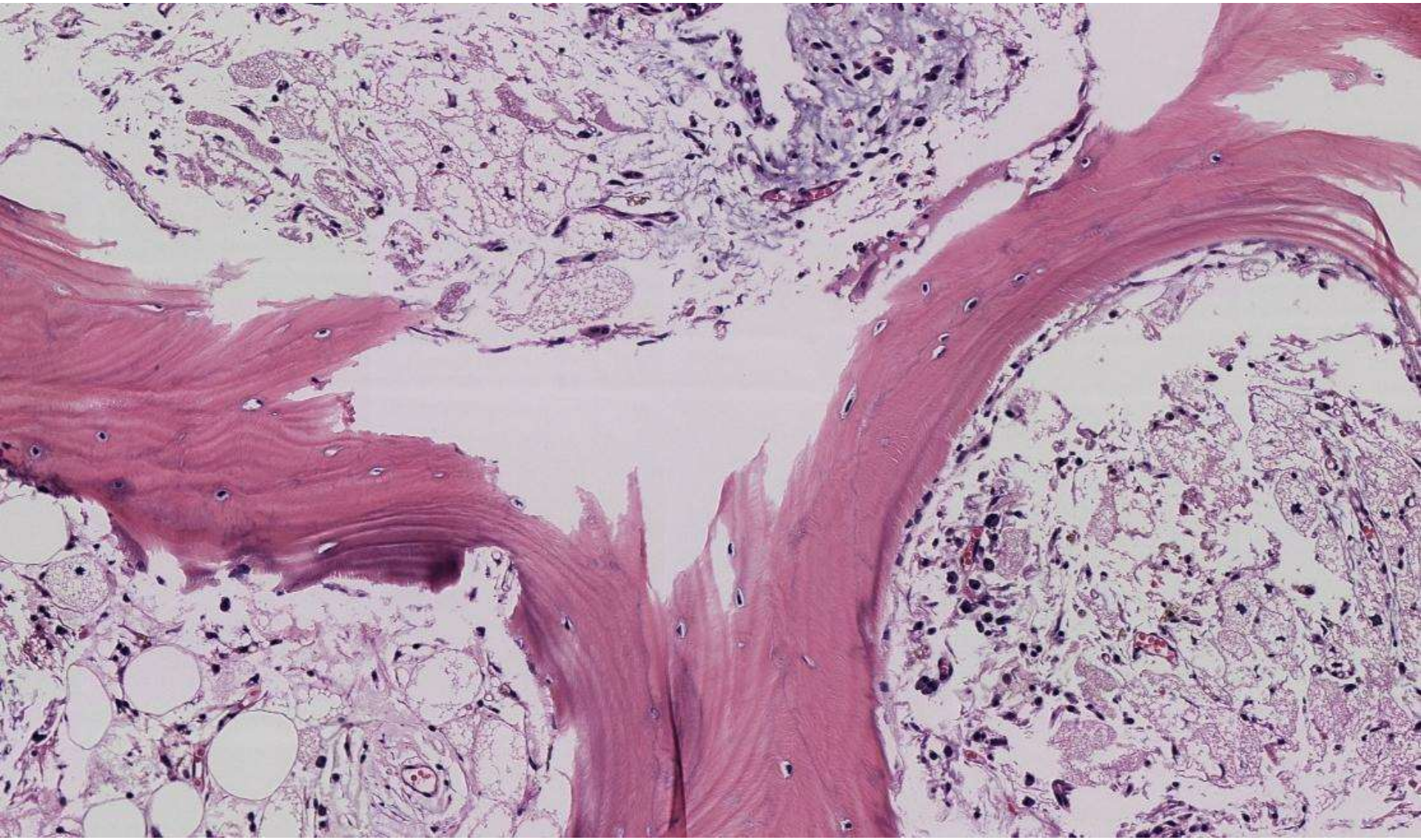






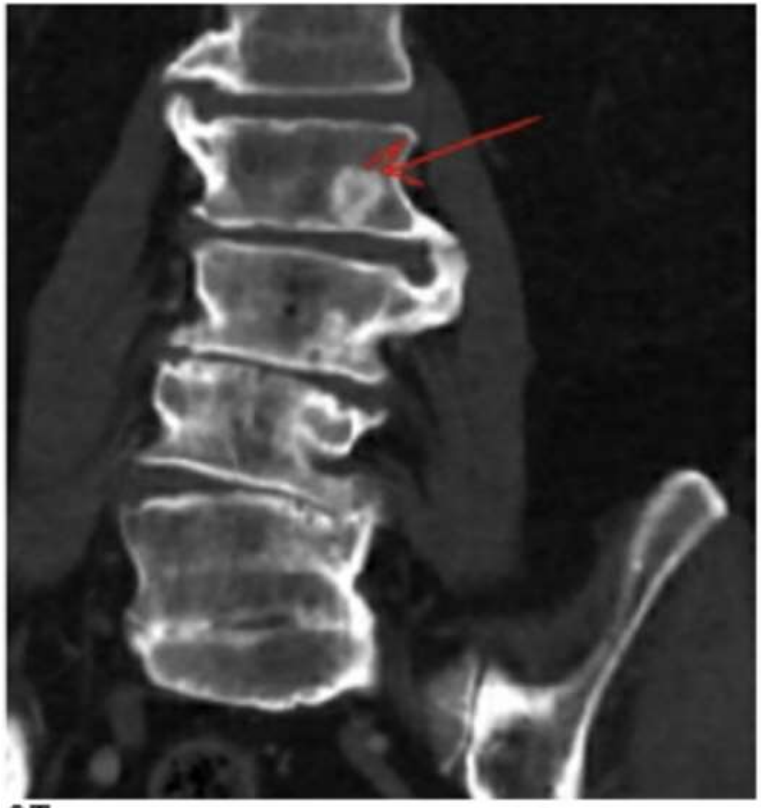


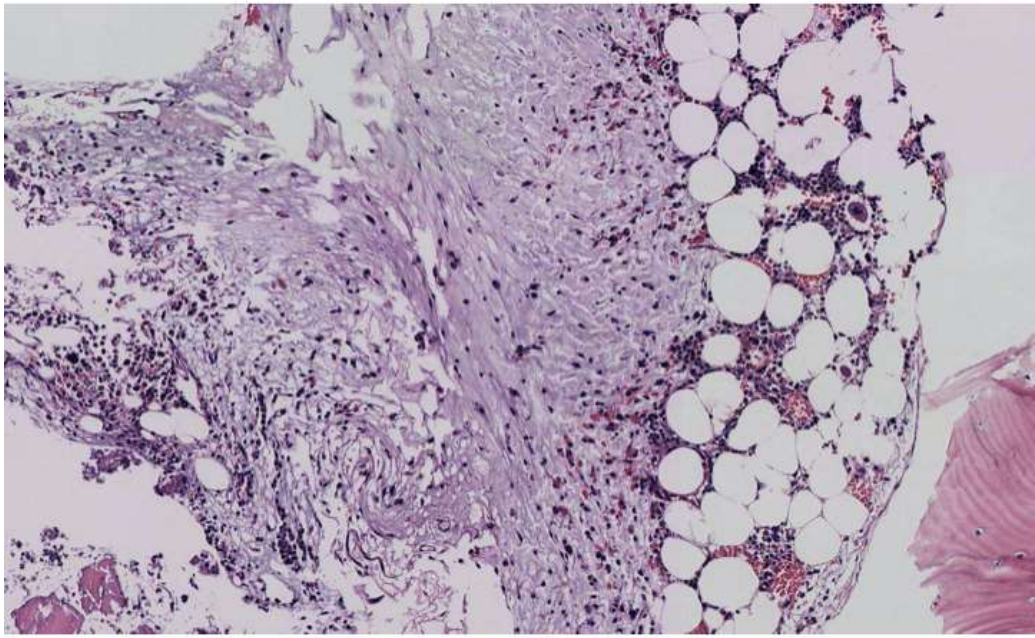


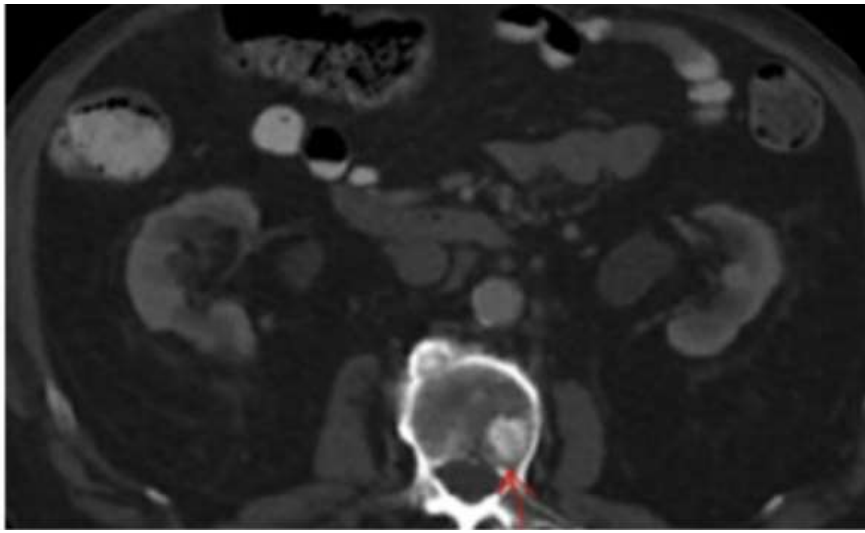


Differential diagnosis

- **Metastatic carcinoma**
- Normal/missed the lesion
- Lymphoma
- Serous atrophy
- Hibernoma
- Lipoblasts/lipomatous lesion





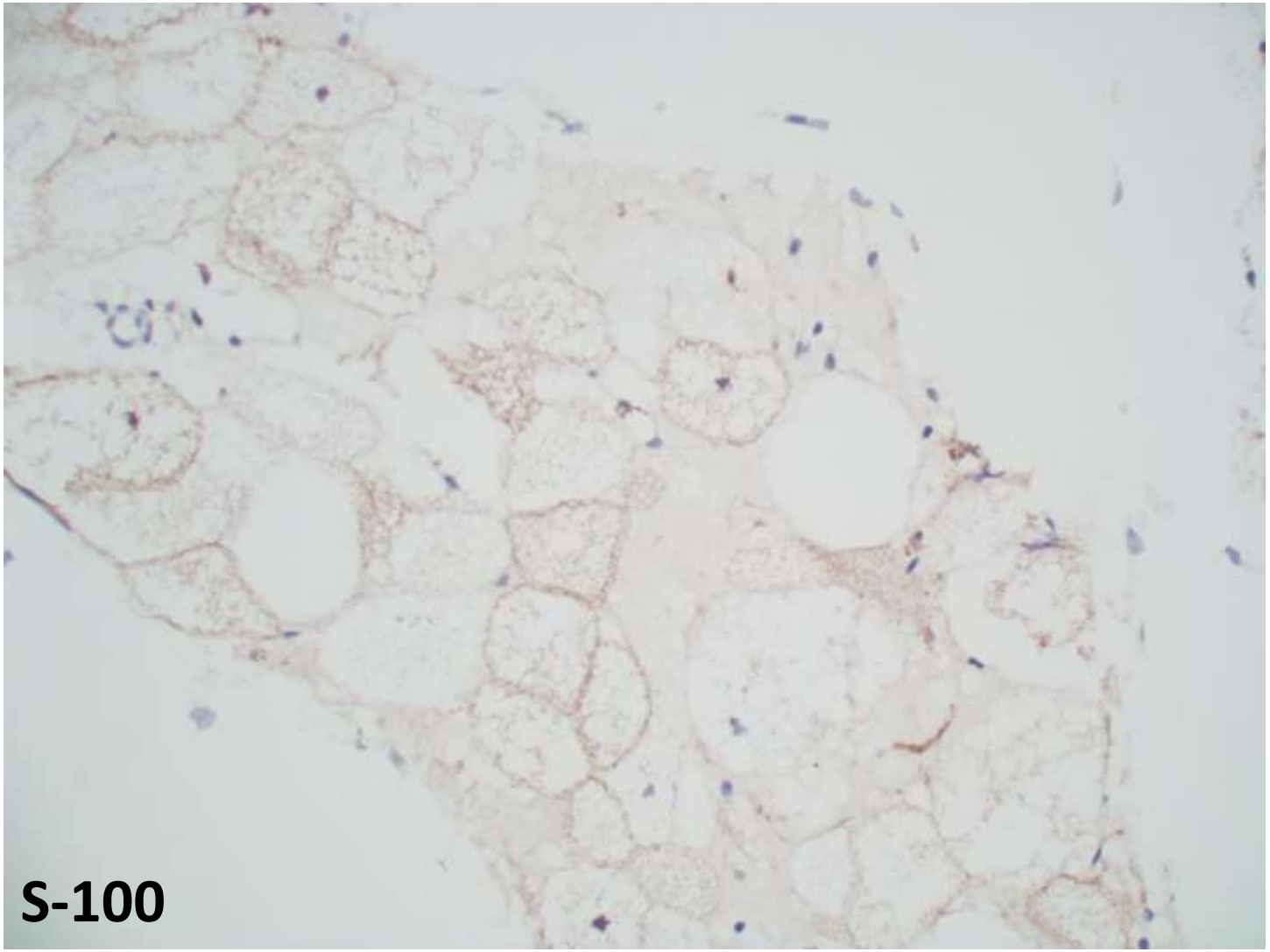


Spinal stenosis and bilateral sciatica

L2- 1.7cm sclerotic bone lesion with intralesional fat --- DDX: atypical hemangioma cannot exclude metastasis

Negative stains

- AE1/AE3
- CD68
- CK5


S-100

Hibernoma

- Hibernoma = benign lipomatous tumor composed of the brown fat
- Brown fat in adults:
  - Found in the upper trunk, paravertebral space and around major arteries
  - Role in thermoregulation, development of obesity and insulin sensitivity
- Soft-tissue hibernoma: found in the subcutaneous and muscle tissue of the hips and the upper trunk

Intraosseous hibernoma

- Rare, approx. 33 cases in the literature
- On imaging mimics: metastatic carcinoma, hemangioma, bone island, or benign notochordal lesion
- Axial skeleton (thoracic – lumbar VB, sacrum)
- Musculoskeletal pain (bulged disc, spinal stenosis) or asymptomatic
- M=F

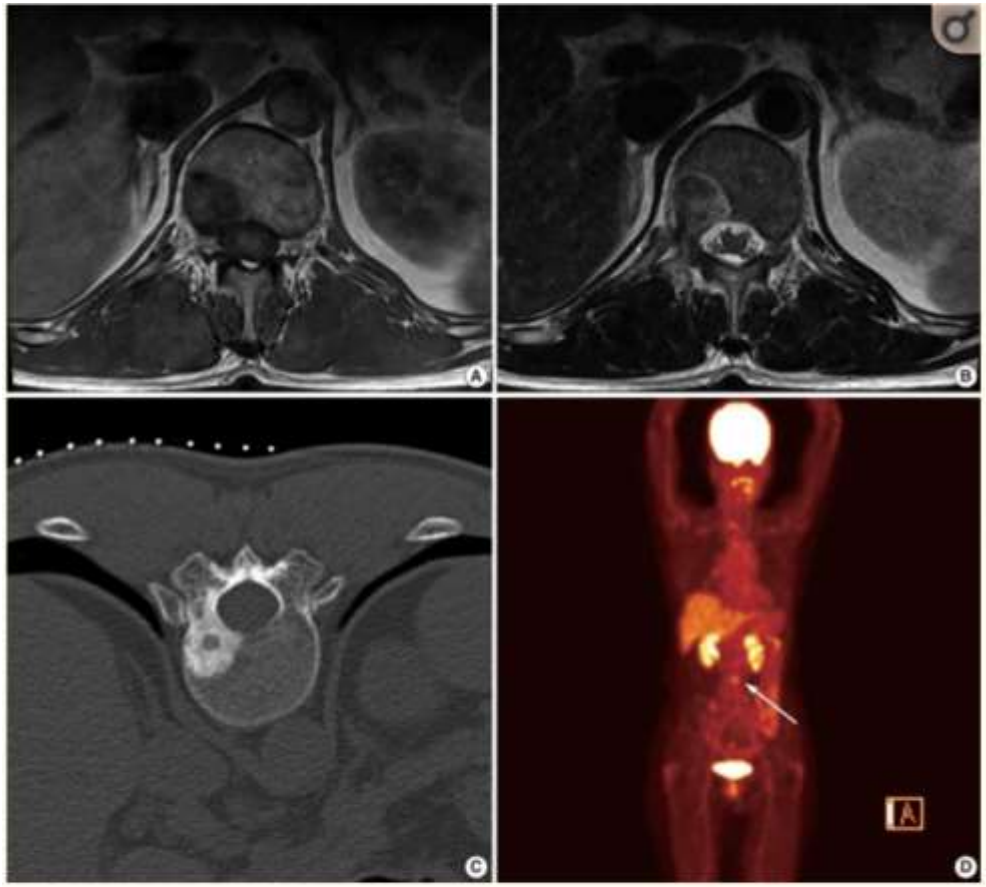
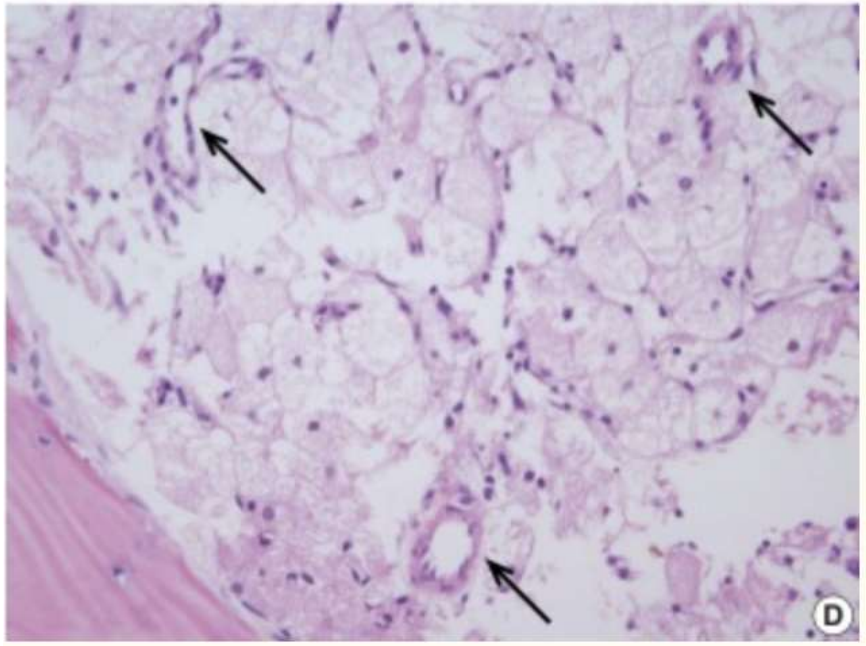


Fig. 1.

Radiologic findings of intraosseous hibernoma. (A) Low signal intensity on T1-weighted magnetic resonance imaging (MRI). (B) Heterogeneous T2 high signal intensity on T2-weighted MRI. (C) Sclerotic change on computed tomography. (D) Mild hypermetabolism on positron emission tomography scan (arrow).

Histology

- Large polygonal cells w/ multivacuolated cytoplasm and centrally located nuclei
- Sheets/clusters/single cells **intermingled** with fatty and hematopoietic marrow elements
- Bland (no atypia or mitotic figures)
- Small medium sized **vessels within** the lesion
- Replaces marrow space between the bony trabeculae **w/o** destroying the bone
- Mild hypertrophy and sclerosis of bony trabeculae
- Mimic: Lipoblasts or foamy histiocytes



Summary

- Benign lesion resulting in pain or found on routine imaging
- Unclear if these are resting cells or a true neoplastic lesion
- Be aware of this entity to avoid misdiagnosis
- Generally only need analgesics, in few cases radiofrequency ablation

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- 5. Bai, S., Mies, C., Stephenson, J. and Zhang, P.J., 2013. Intraosseous hibernoma: a potential mimic of metastatic carcinoma. *Annals of Diagnostic Pathology*, *17*(2), pp.204-206.

20-0804

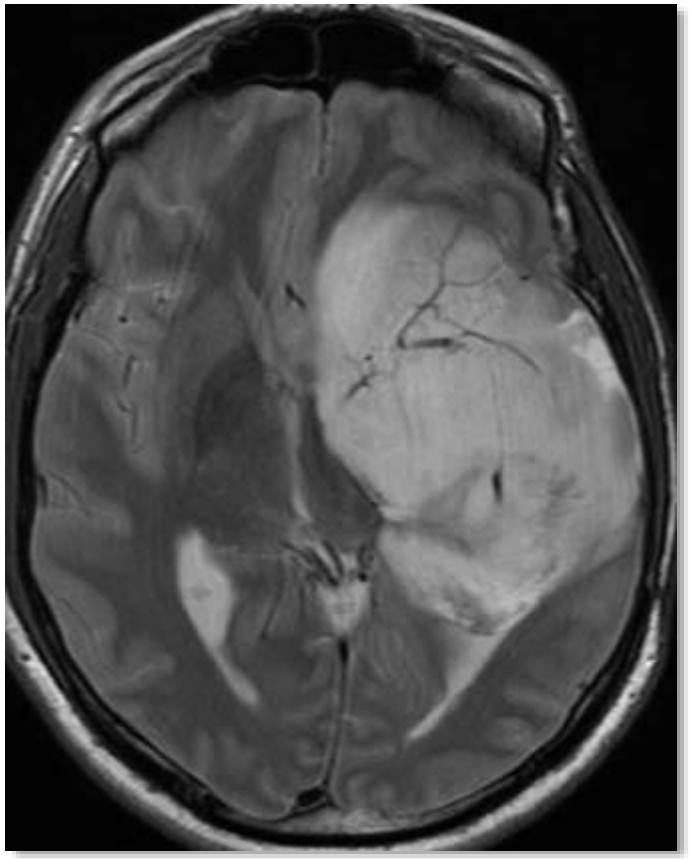
Hannes Vogel; Stanford

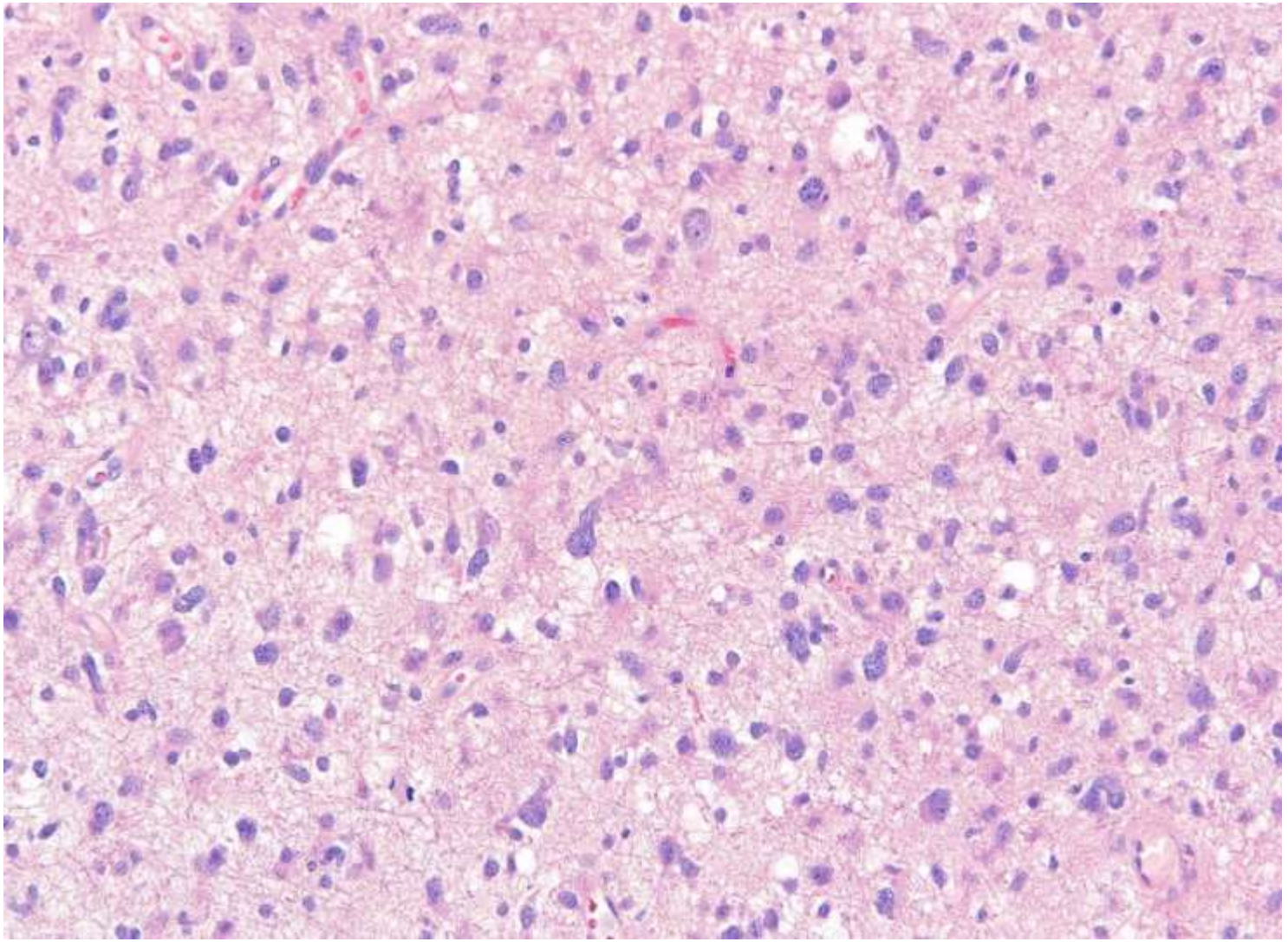
29-year-old M with recurrent temporal lobe tumor 6 years after original resection, now with contrast enhancement. 2014: IDH R132H wild type, p53 mutant, WHO grade II astrocytoma.

August 2020 South Bay Pathology
Case submitted by Hannes Vogel

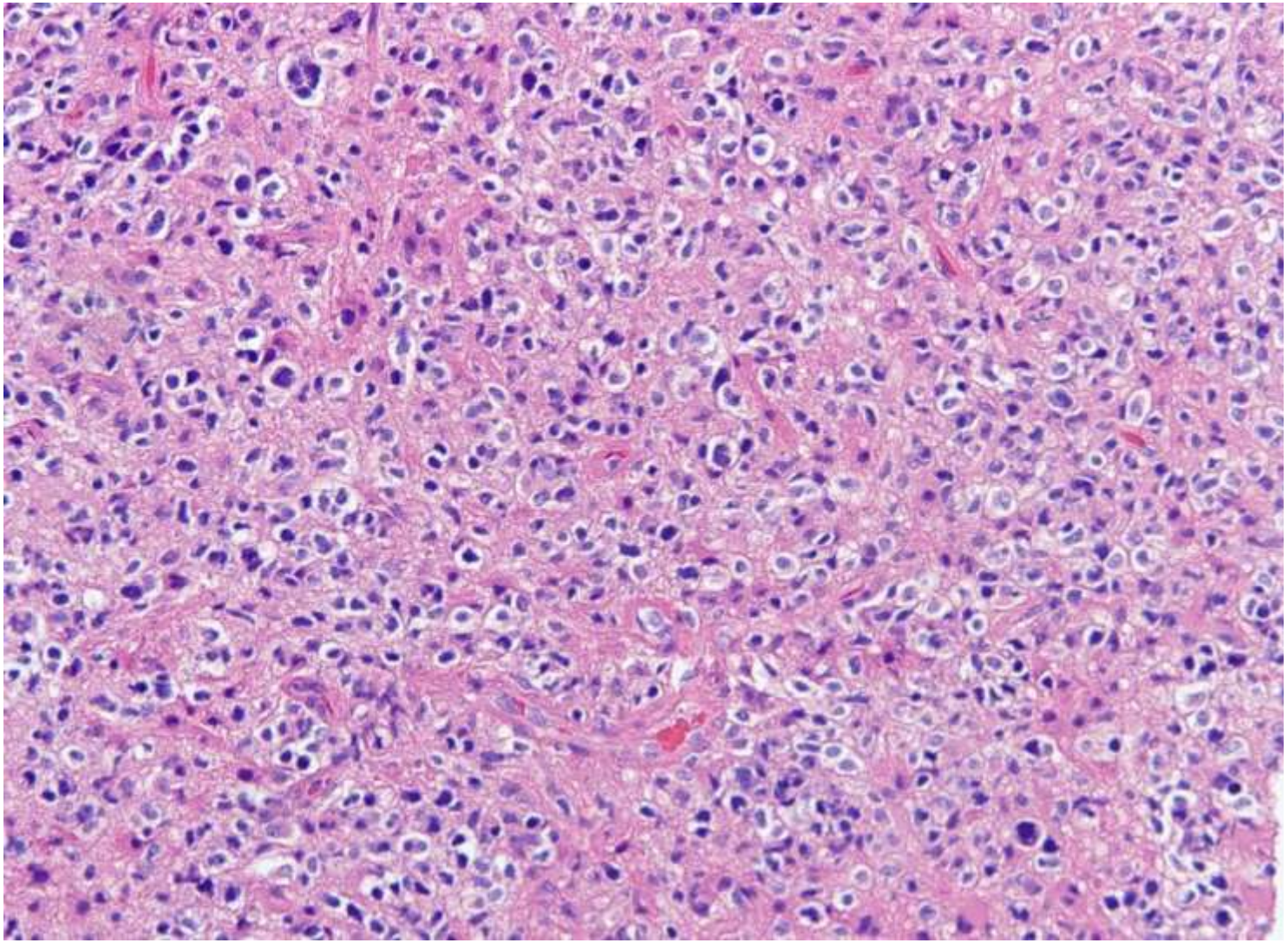
History: 29 year old man with recurrent temporal lobe tumor 6 years after original resection, now with contrast enhancement

2014: IDH R132H wild type, p53 mutant, WHO grade II astrocytoma

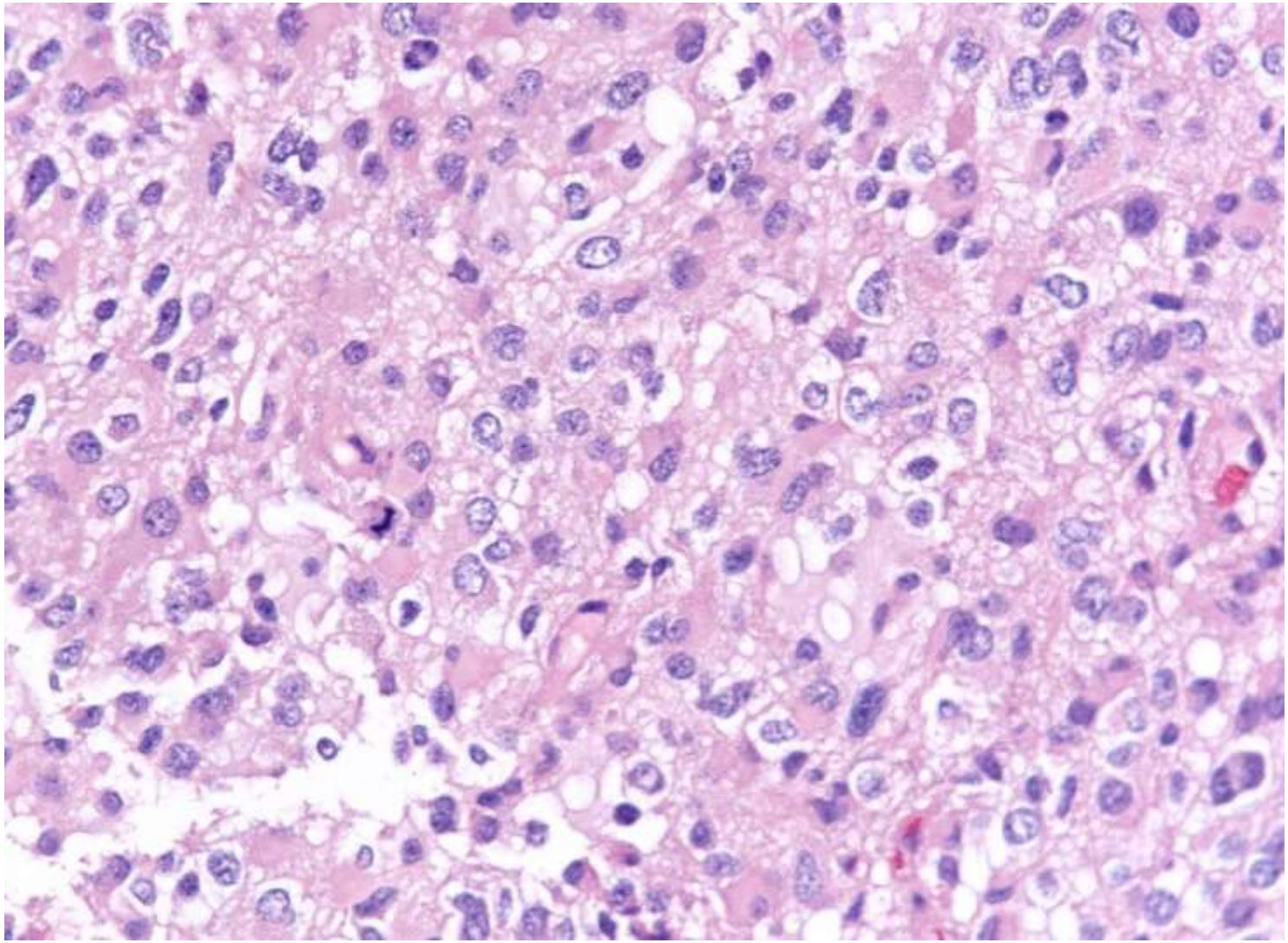




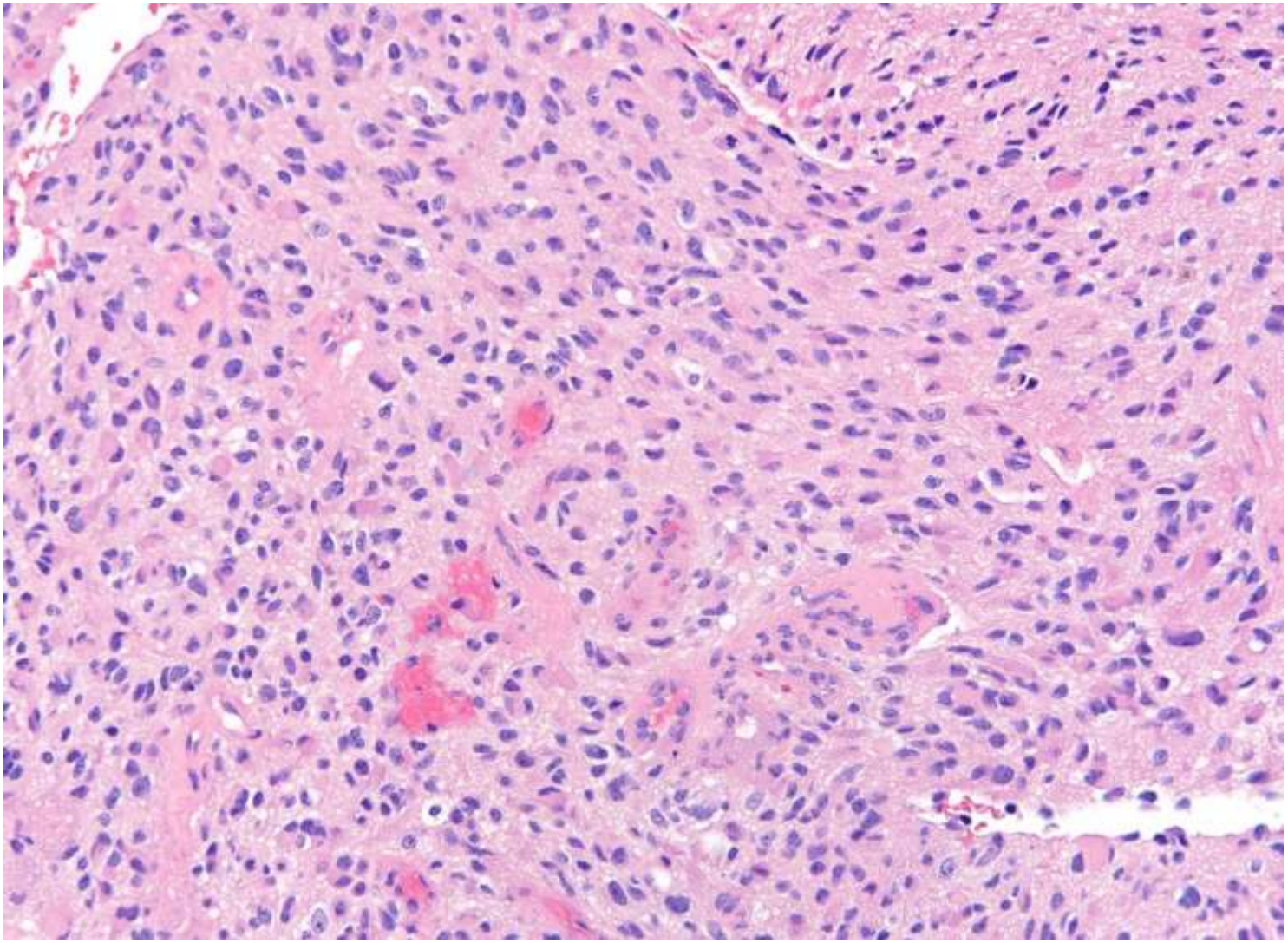
2014



2020



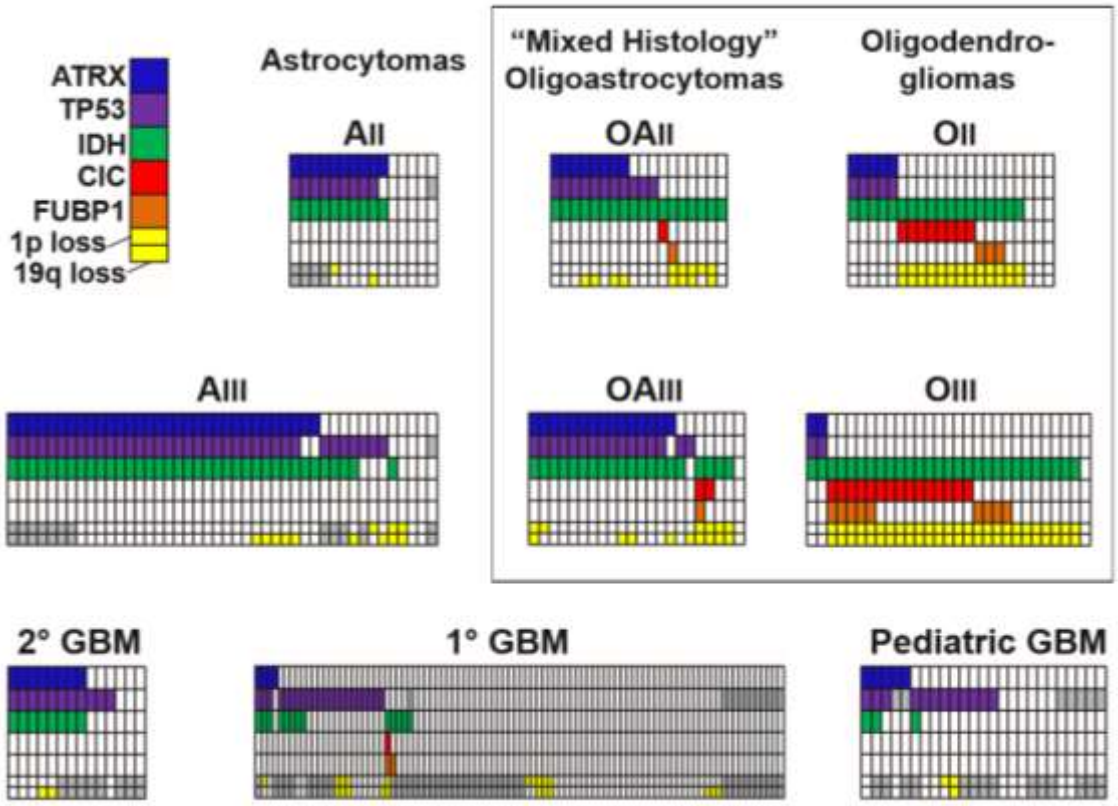
2020



2020

Further workup:

STAMP: Positive for IDH R132L mutation and positive for TP53 P190L mutation



Oncotarget 2012; 3: 710-722

Acta Neuropathologica (2020) 139:603–608
https://doi.org/10.1007/s00401-020-02127-9

CORRESPONDENCE

cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Dominique Figrarella-Branger[4] · Gregory N. Fuller[5] · Caterina Giannini[6] · Eric C. Holland[7] · Robert B. Jenkins[6] · Bette Kleinschmidt-DeMasters[8] · Takashi Komori[9] · Johan M. Kros[10] · David N. Louis[11] · Catriona McLean[12] · Arie Perry[13] · Guido Reifenberger[14,15] · Chitra Sarkar[16] · Roger Stupp[17] · Martin J. van den Bent[18] · Andreas von Deimling[19,20] · Michael Weller[21]

Table 1 IDH-mutant astrocytomas

Astrocytoma, IDH-mutant, grade 2
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or low[a]. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, grade 3
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity[a]. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, grade 4
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion or any combination of these features

Phenopath report

FLUORESCENCE IN SITU HYBRIDIZATION (FISH) REPORT

INTERPRETATION:

Stanford University Medical Center SHS-20-11712,C2

Brain tumor, resection: Glial neoplasm; **positive** for homozygous deletion of p16 by FISH

COMMENTS

Published studies suggest that deletion of the CDKN2A gene, i.e., homozygous loss of p16, as determined by FISH, is associated with shortened overall survival in grade I - III astrocytomas (Reis GF et al., J Neuropath Exp Neurol 74:442-52, 2015).

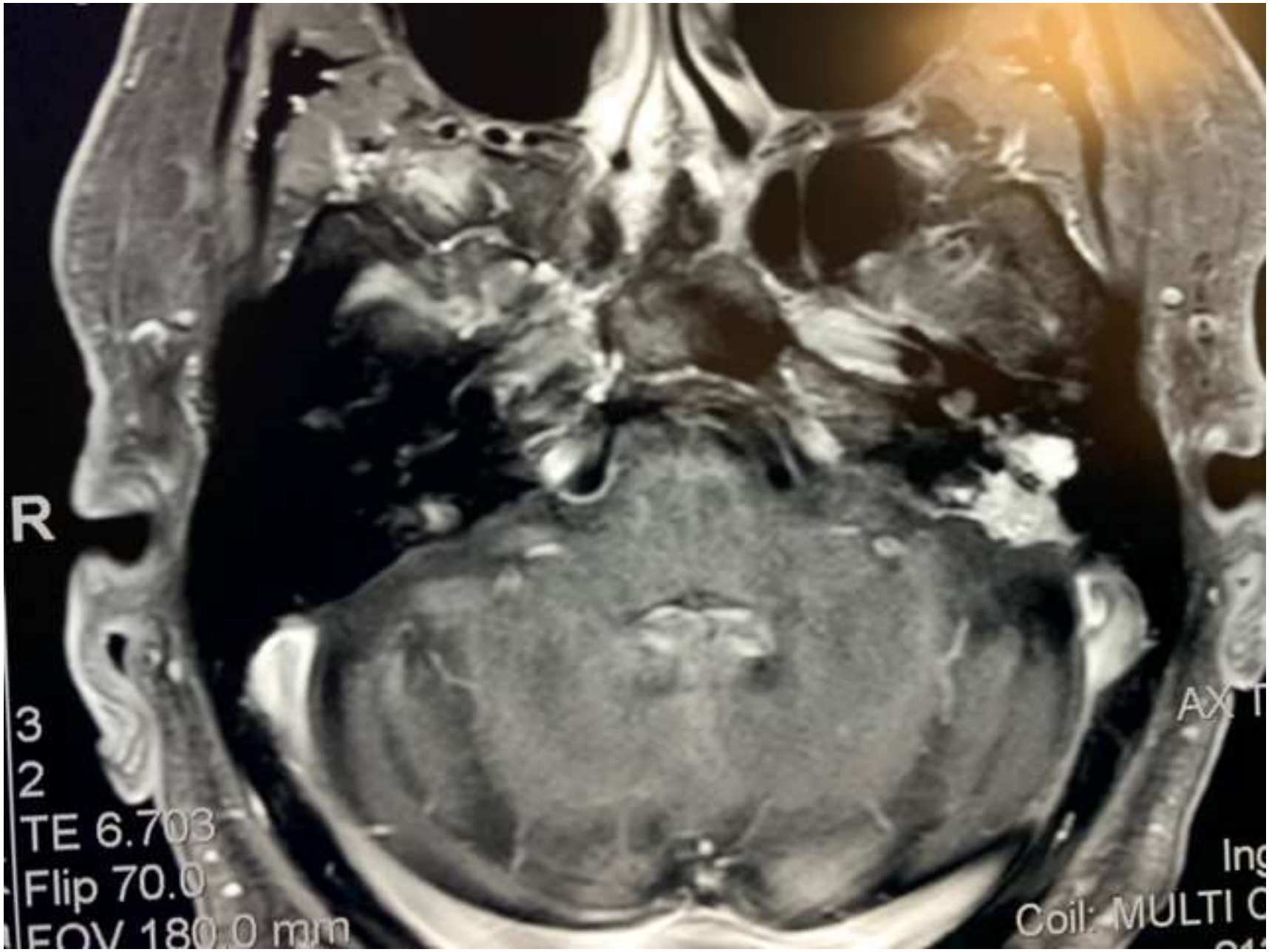
Diagnosis:

Astrocytoma, IDH1 mutant, cIMPACT-NOW Grade 4

20-0805
scanned slide available!

Liz Treynor; Washington Hospital

68-year-old M with hearing loss and pulsatile tinnitus. Left ear/mastoid mass biopsy. Radiology: cholesteatoma. Clinical: r/o Wegener's, IgG4 disease.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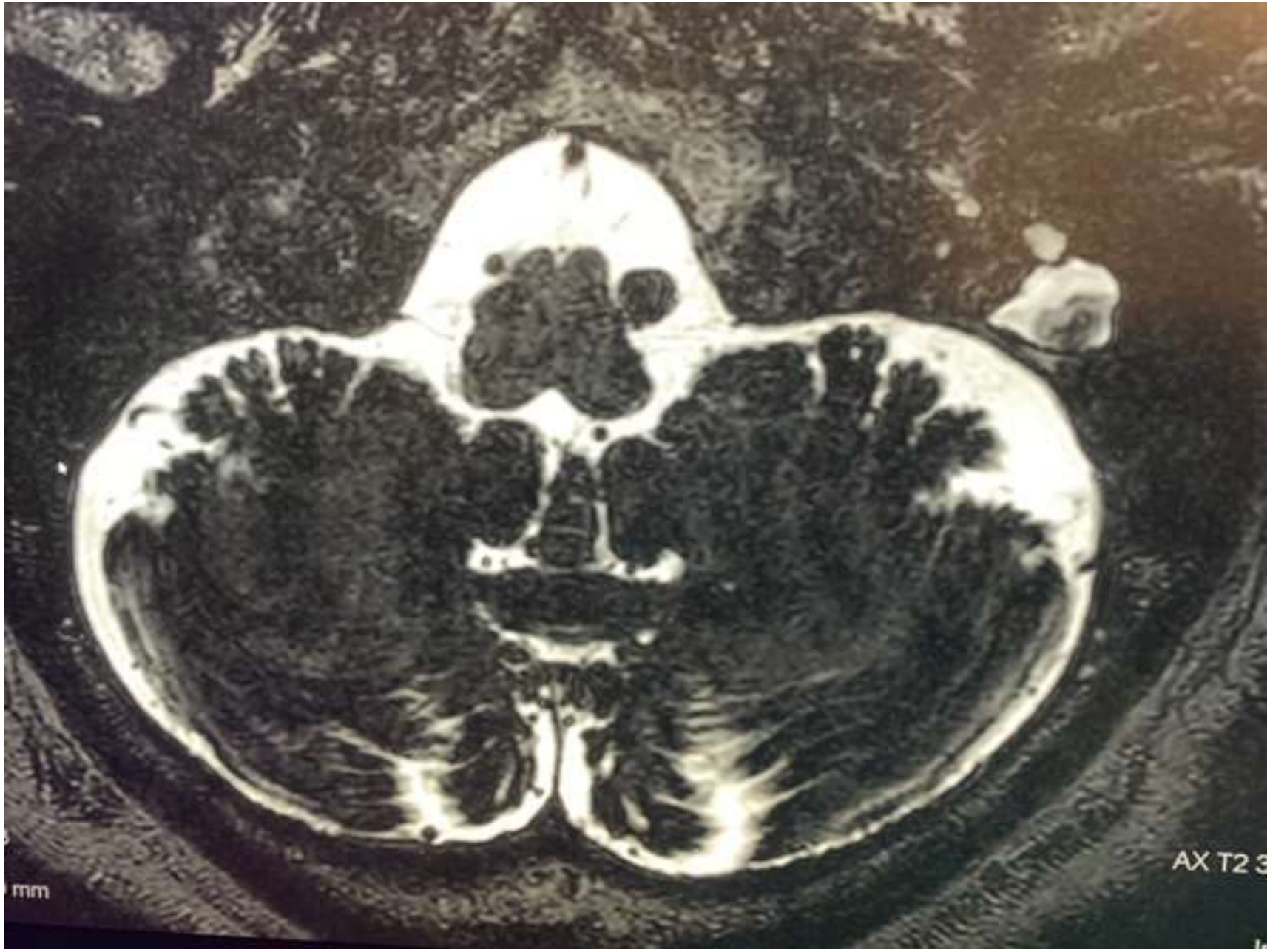
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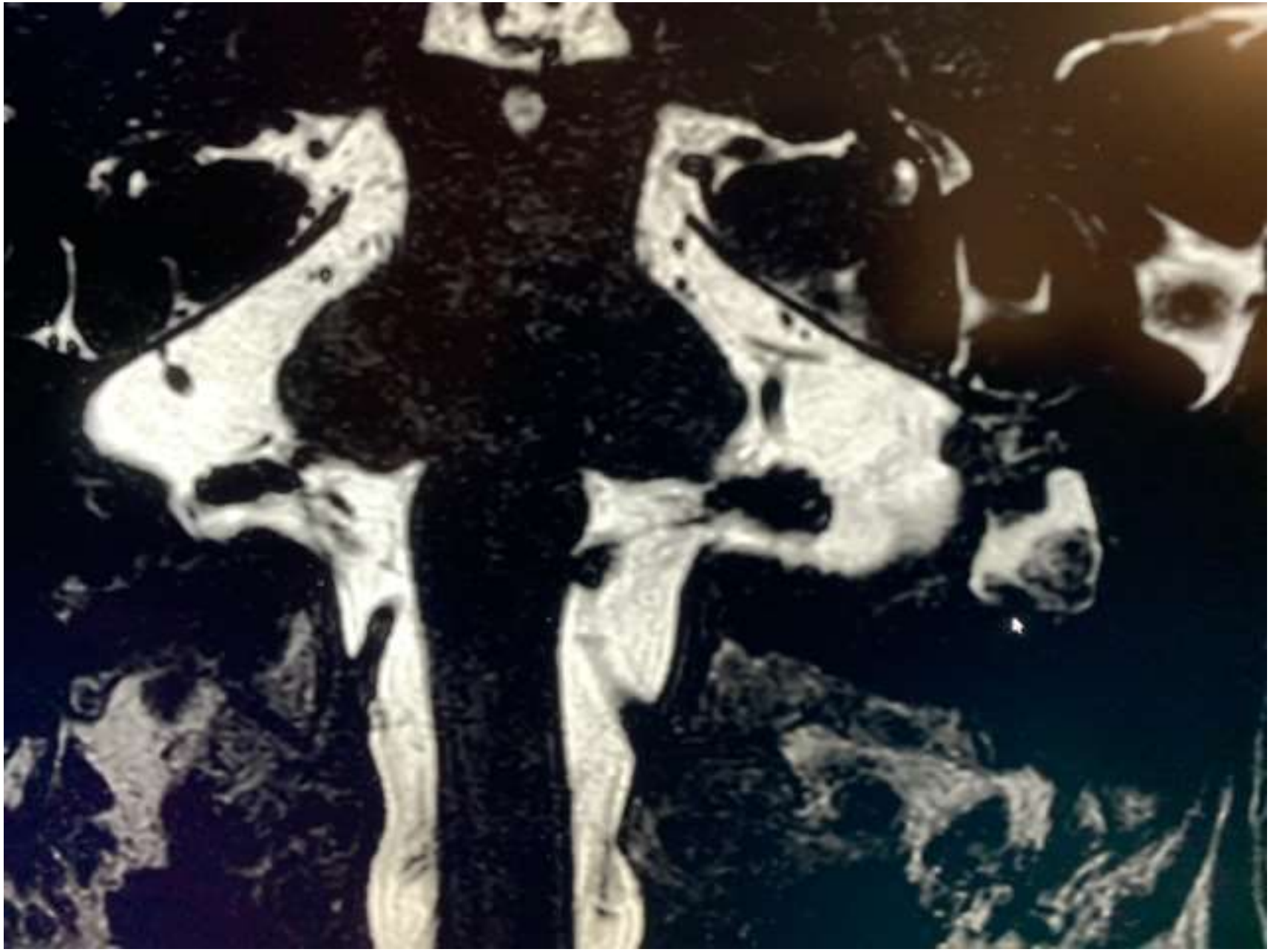
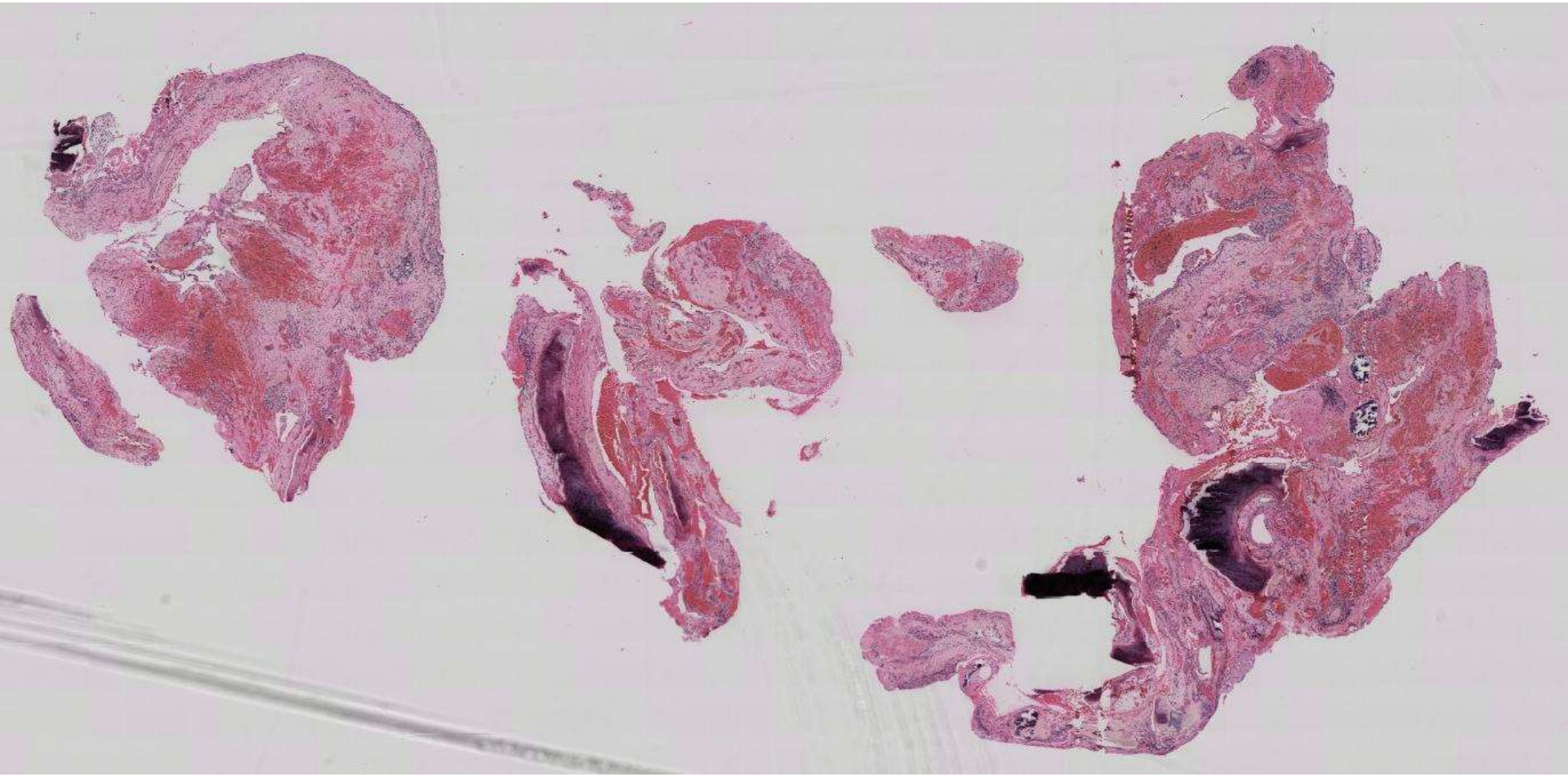
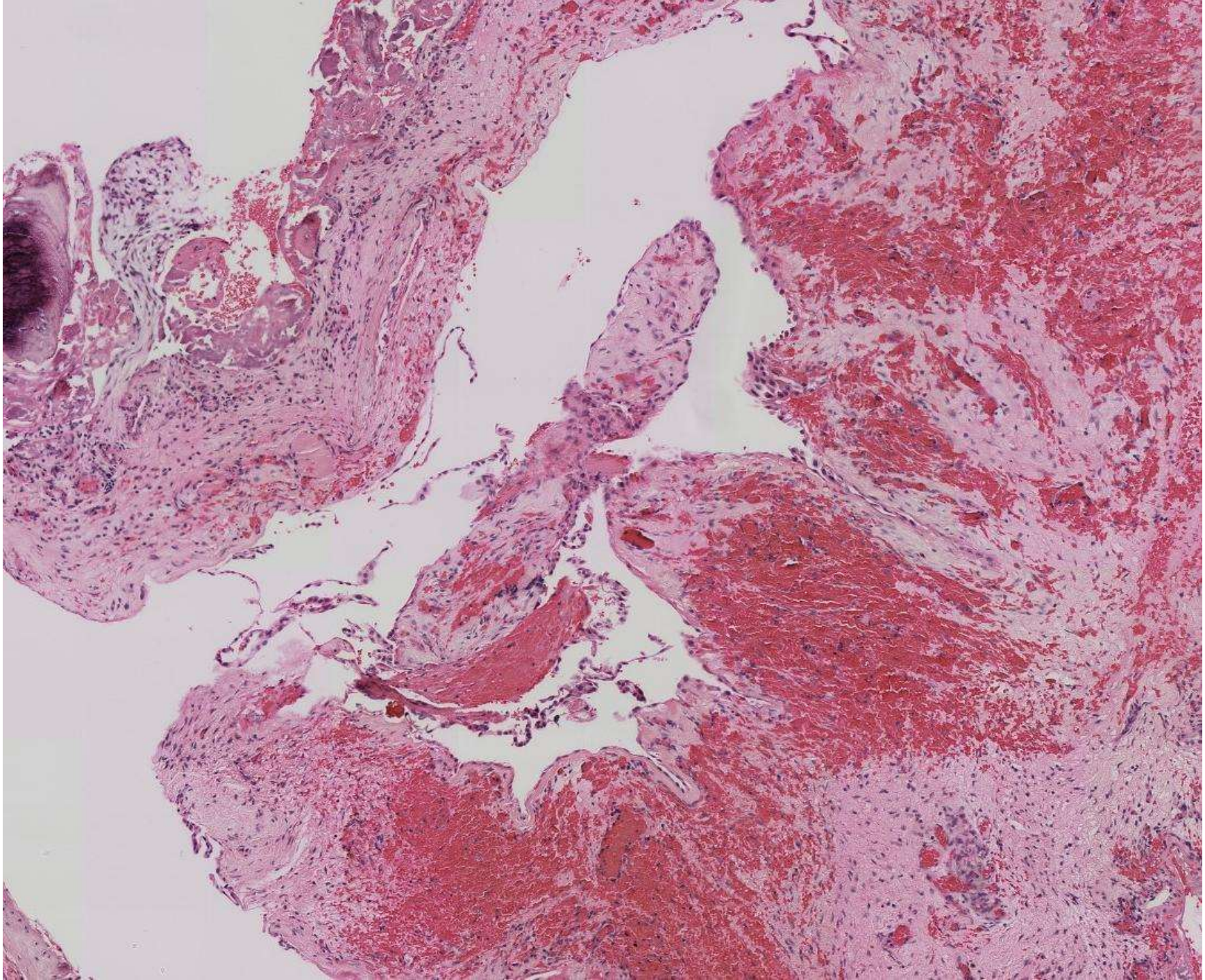
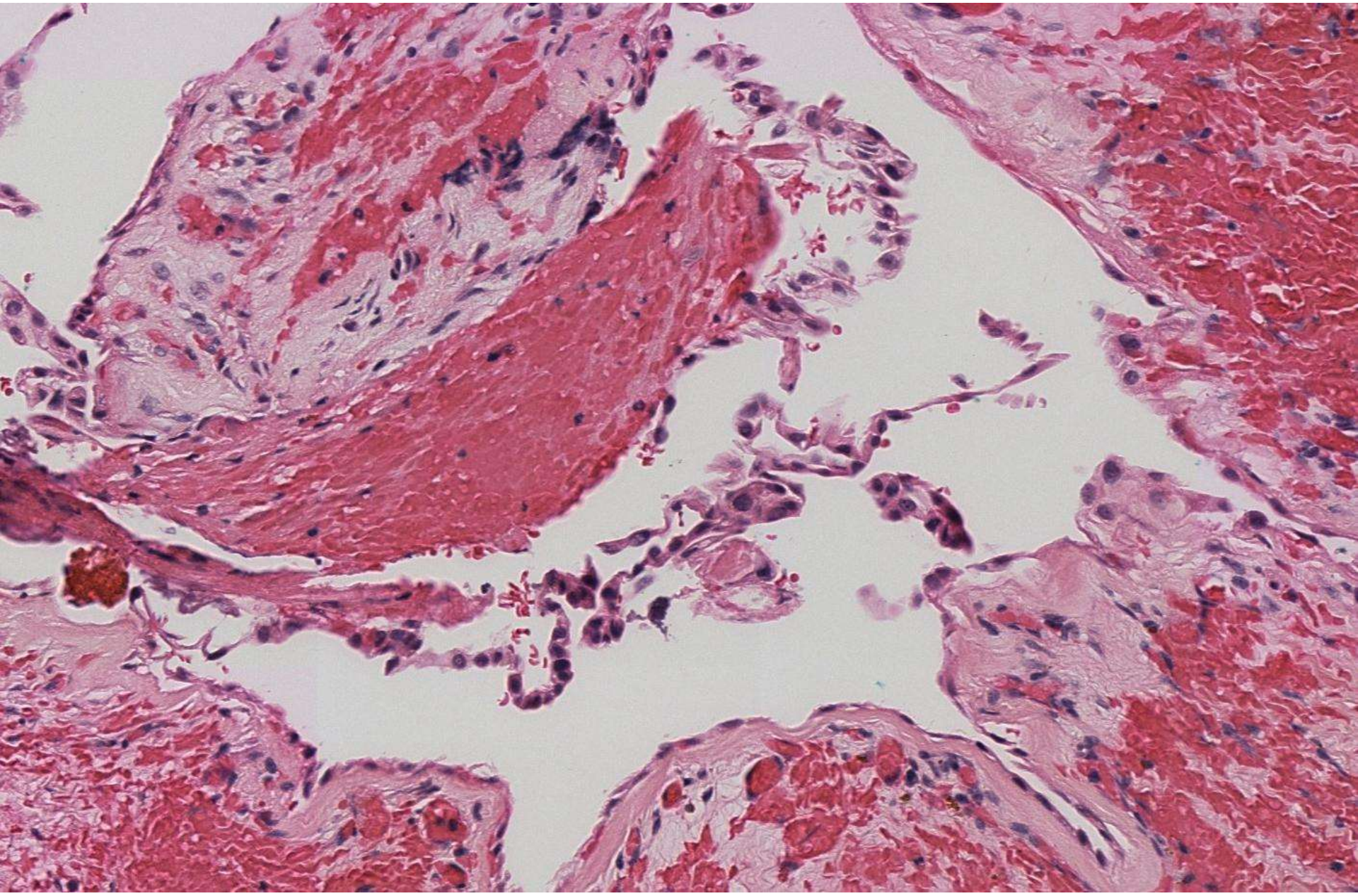
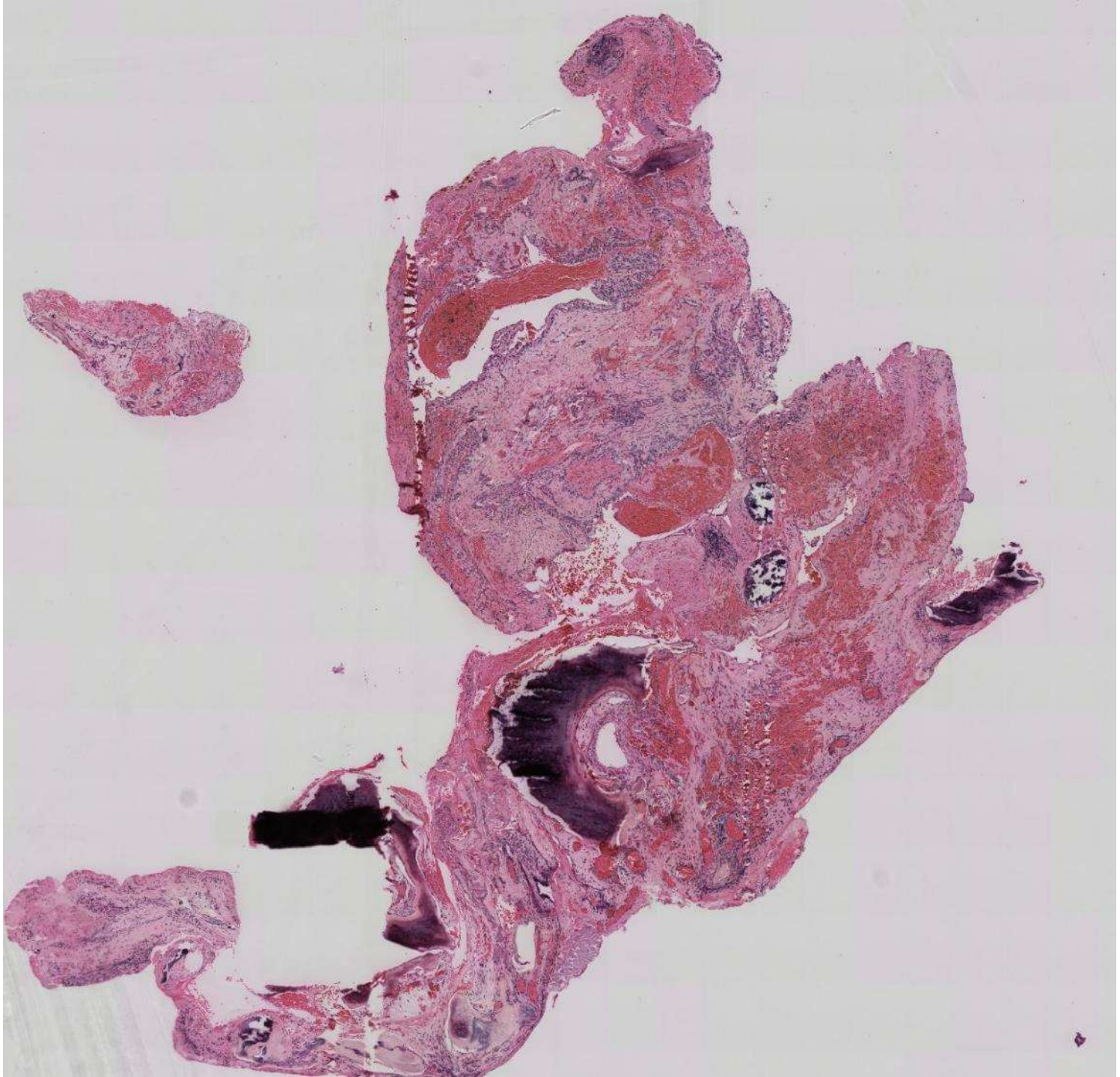
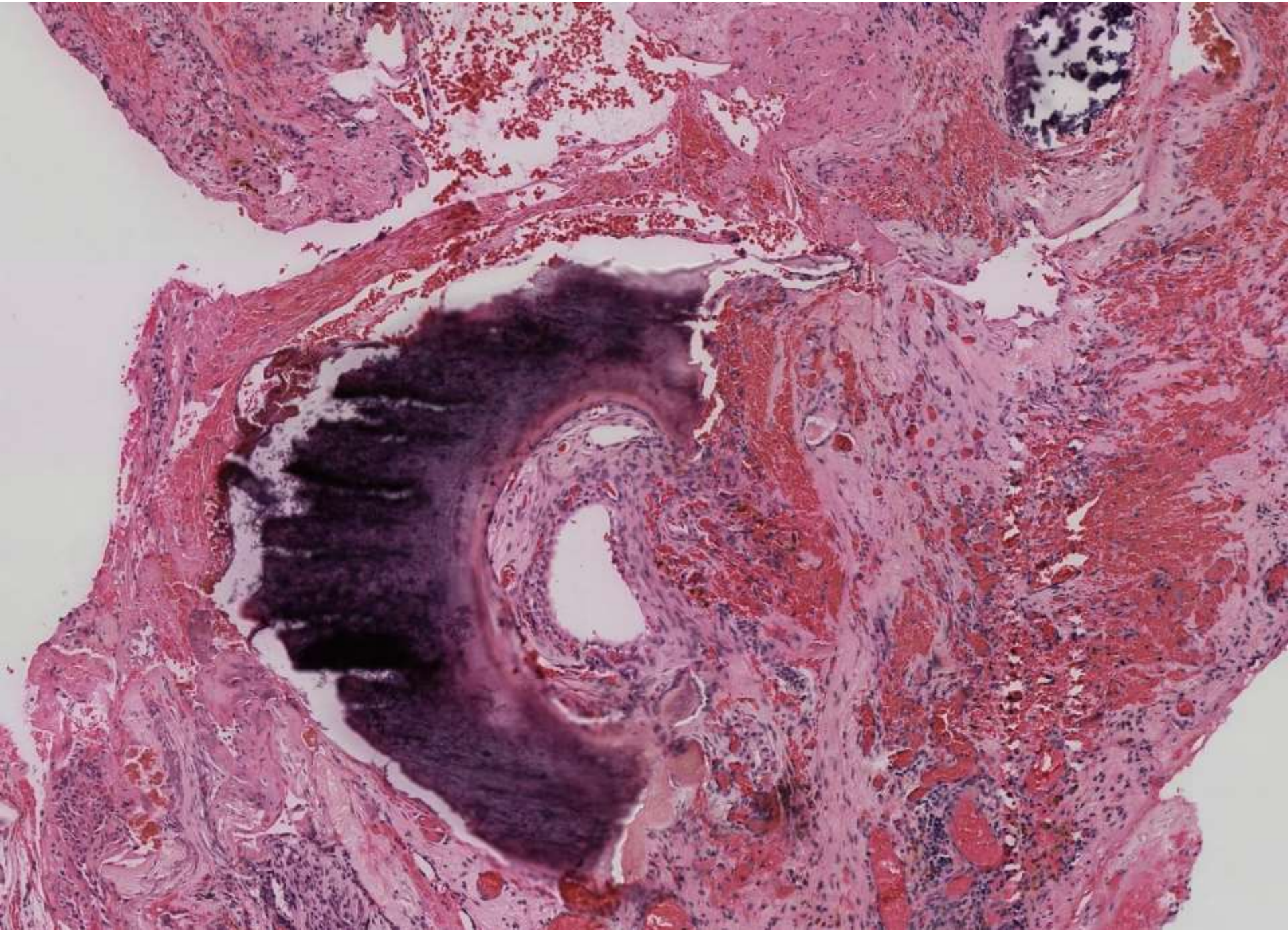


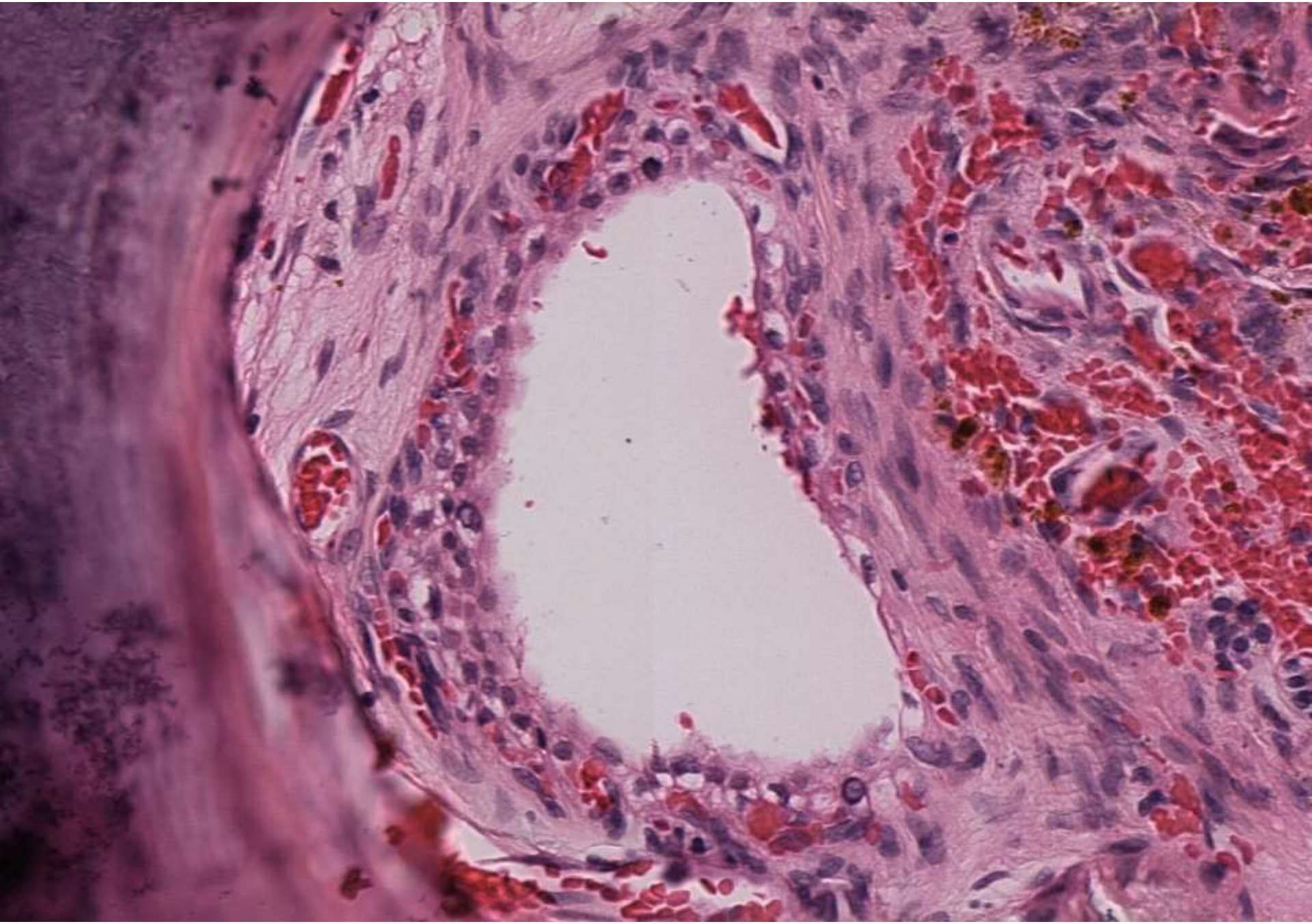


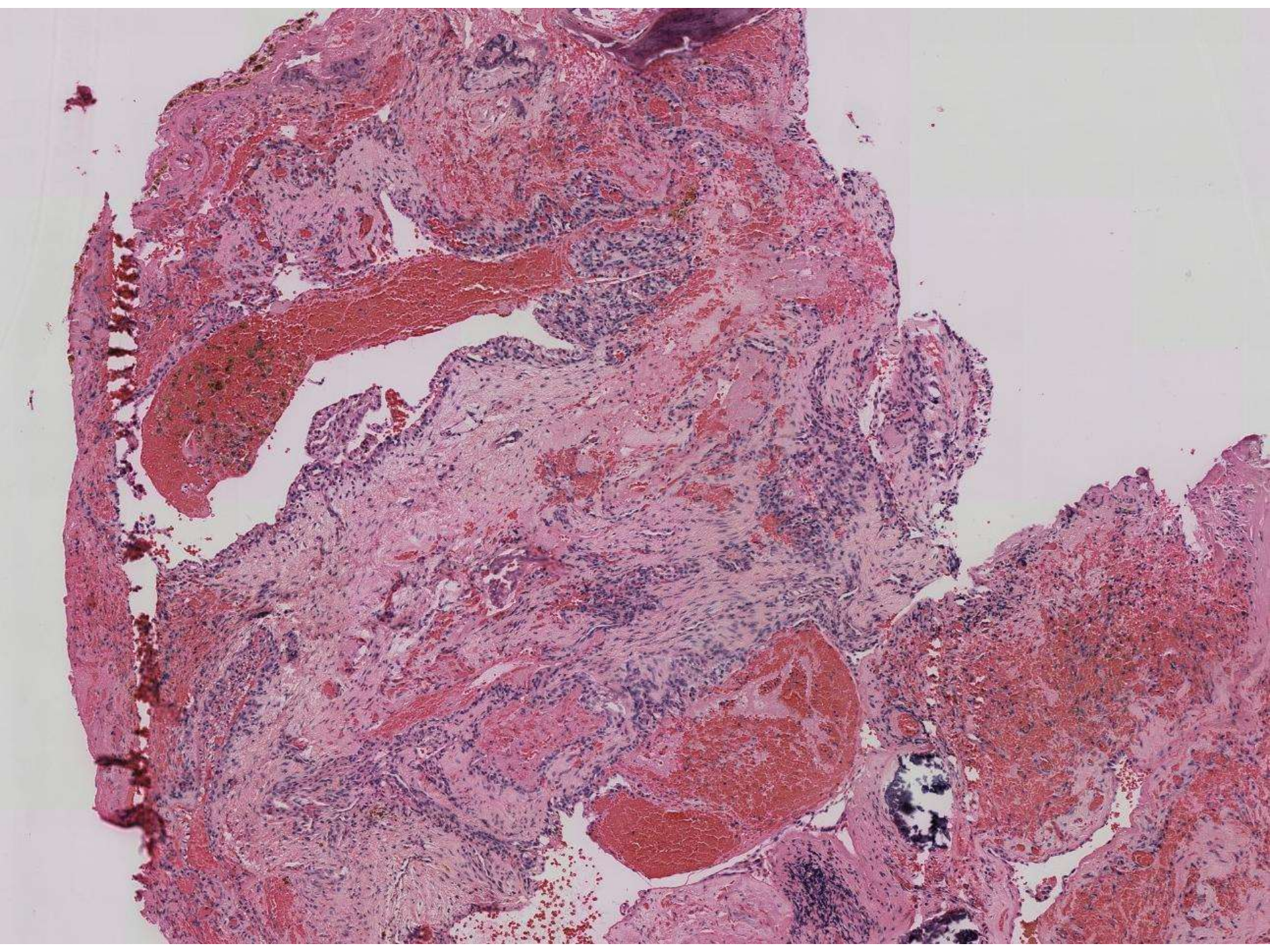


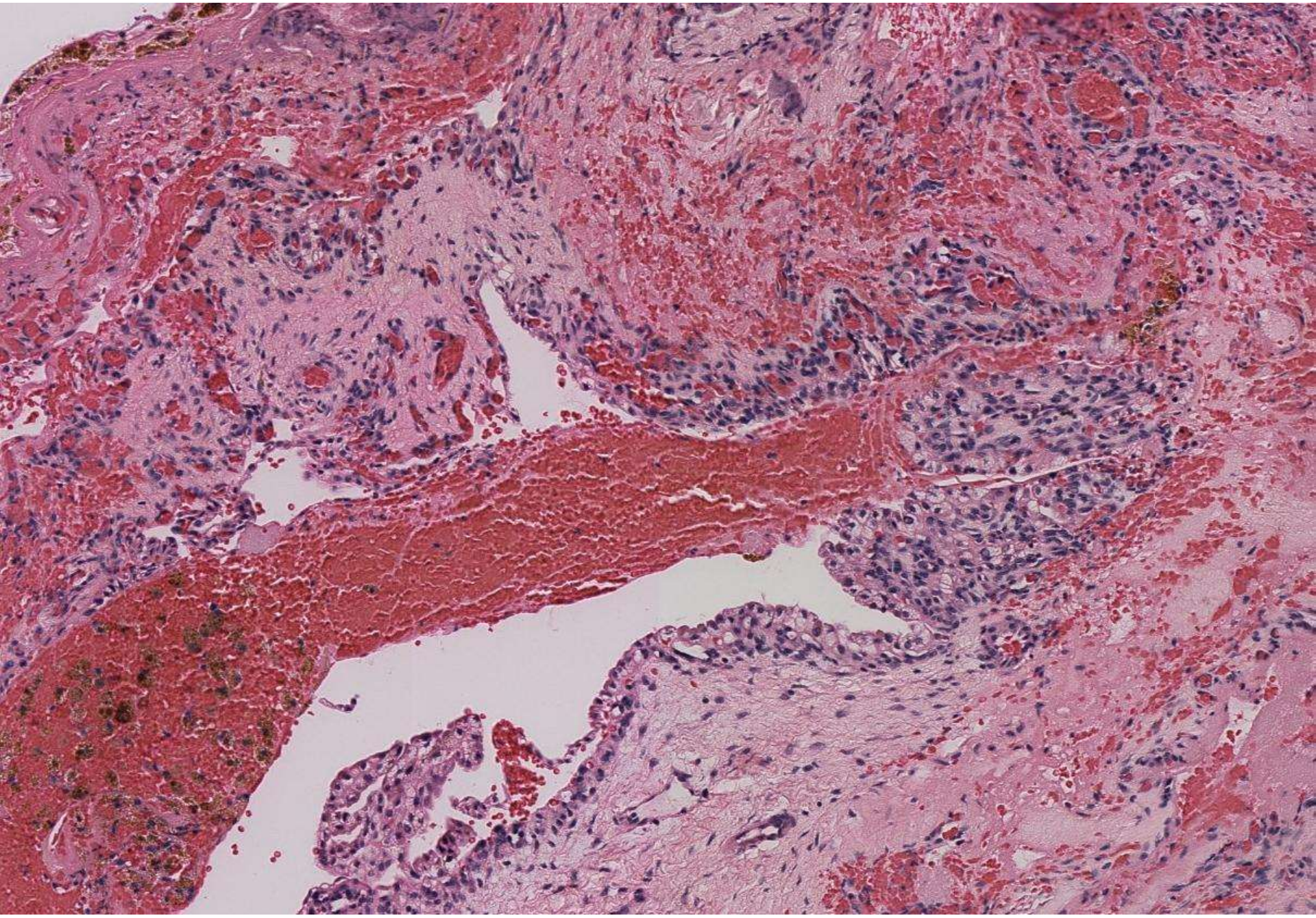


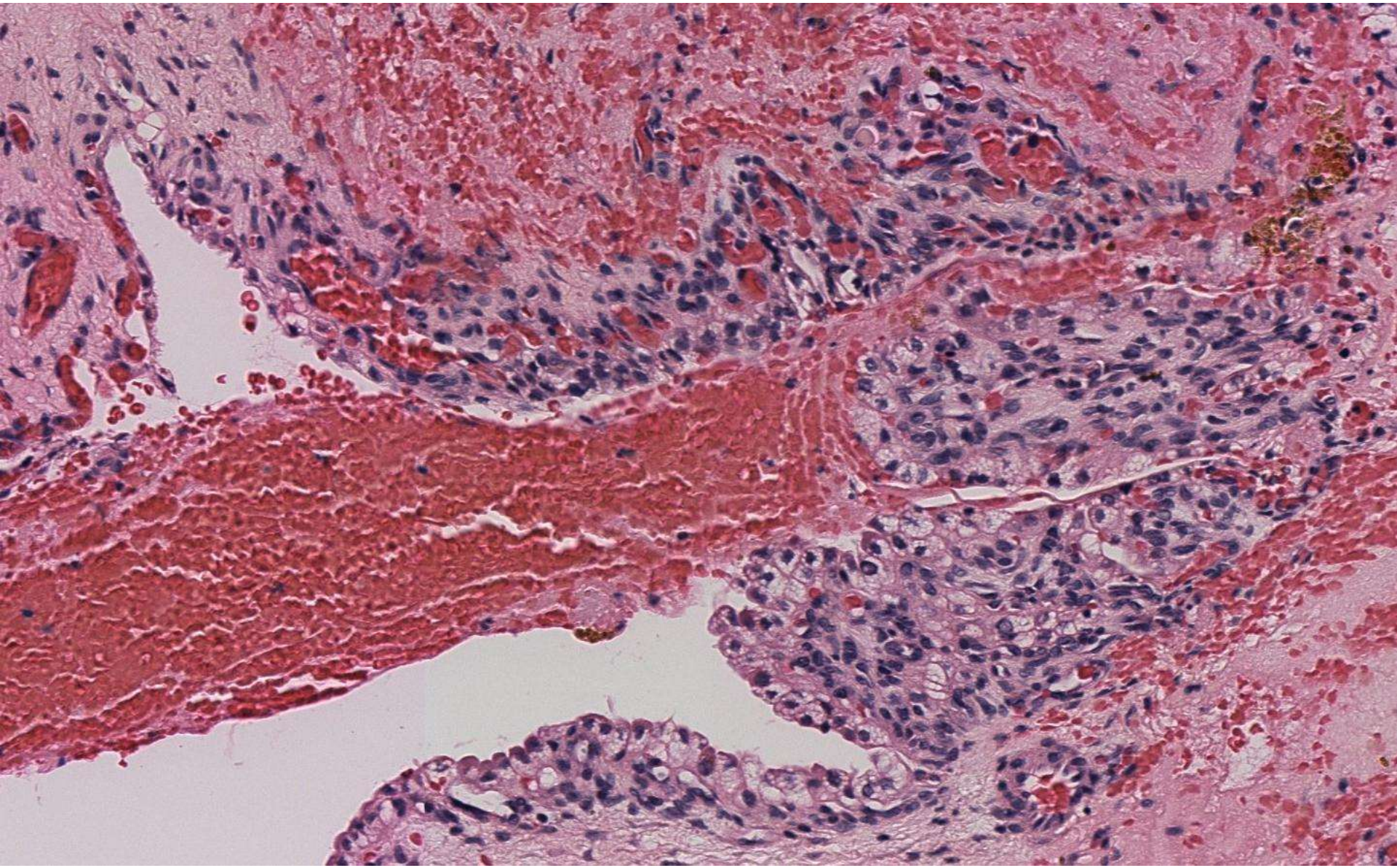


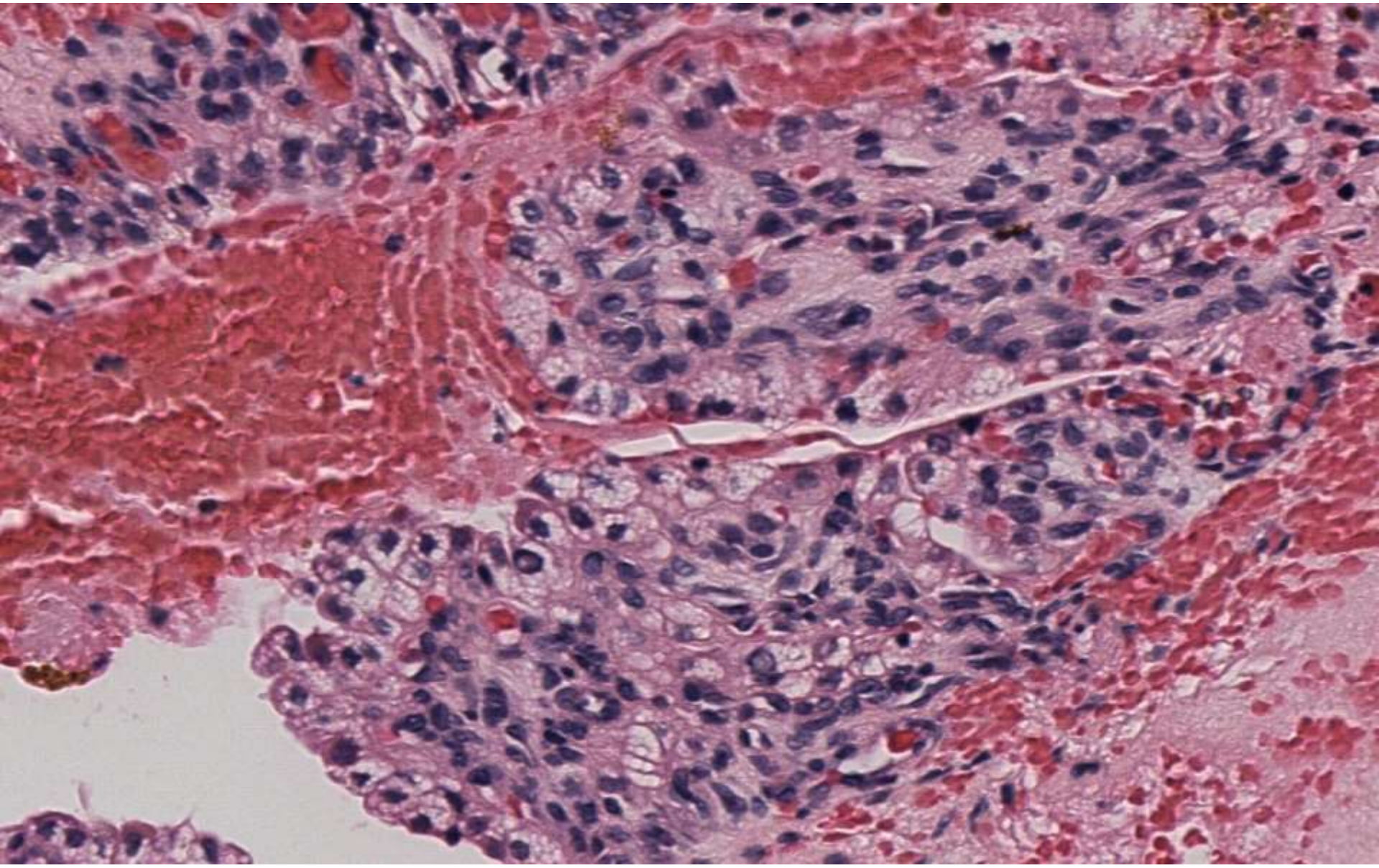


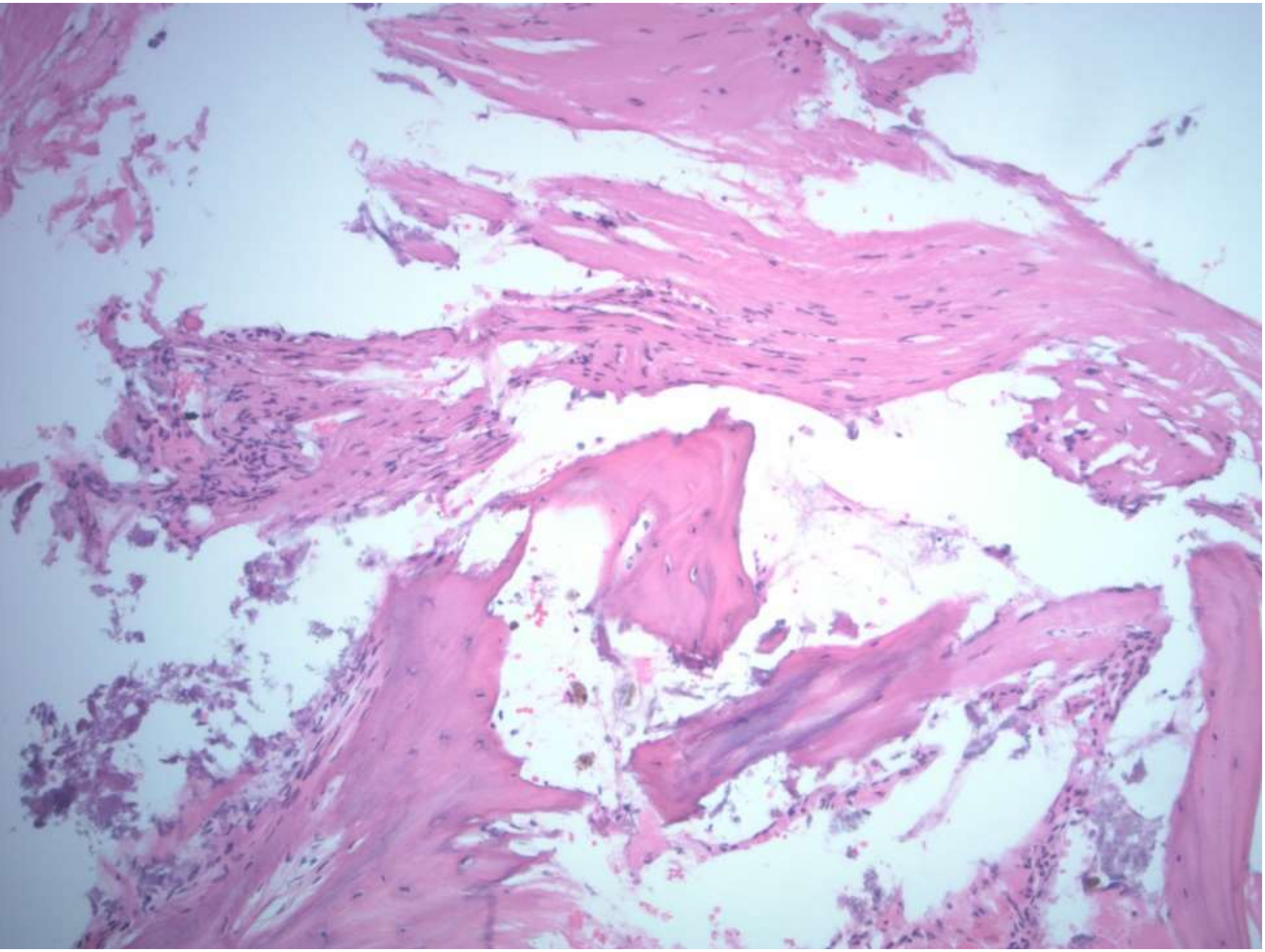


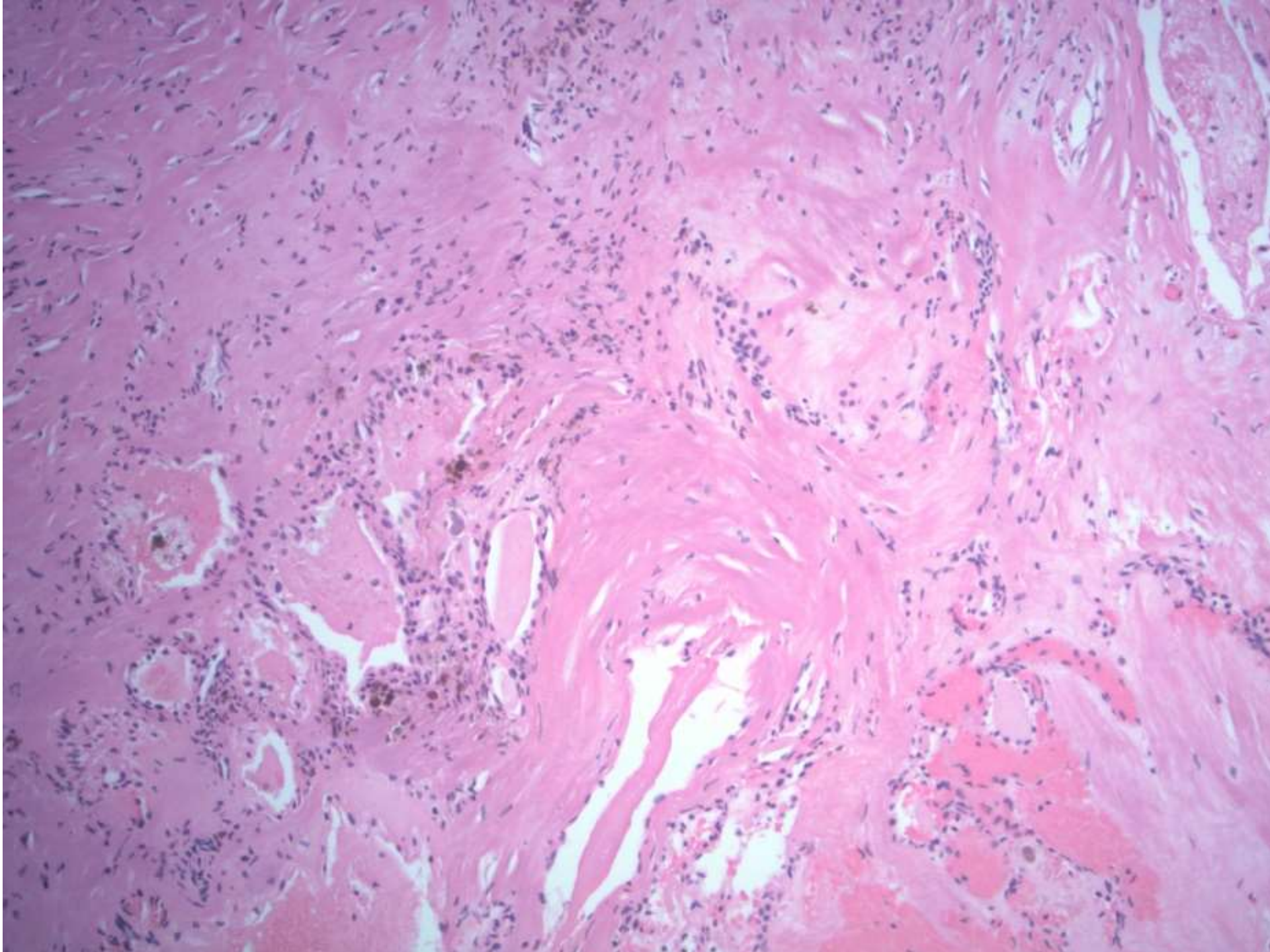


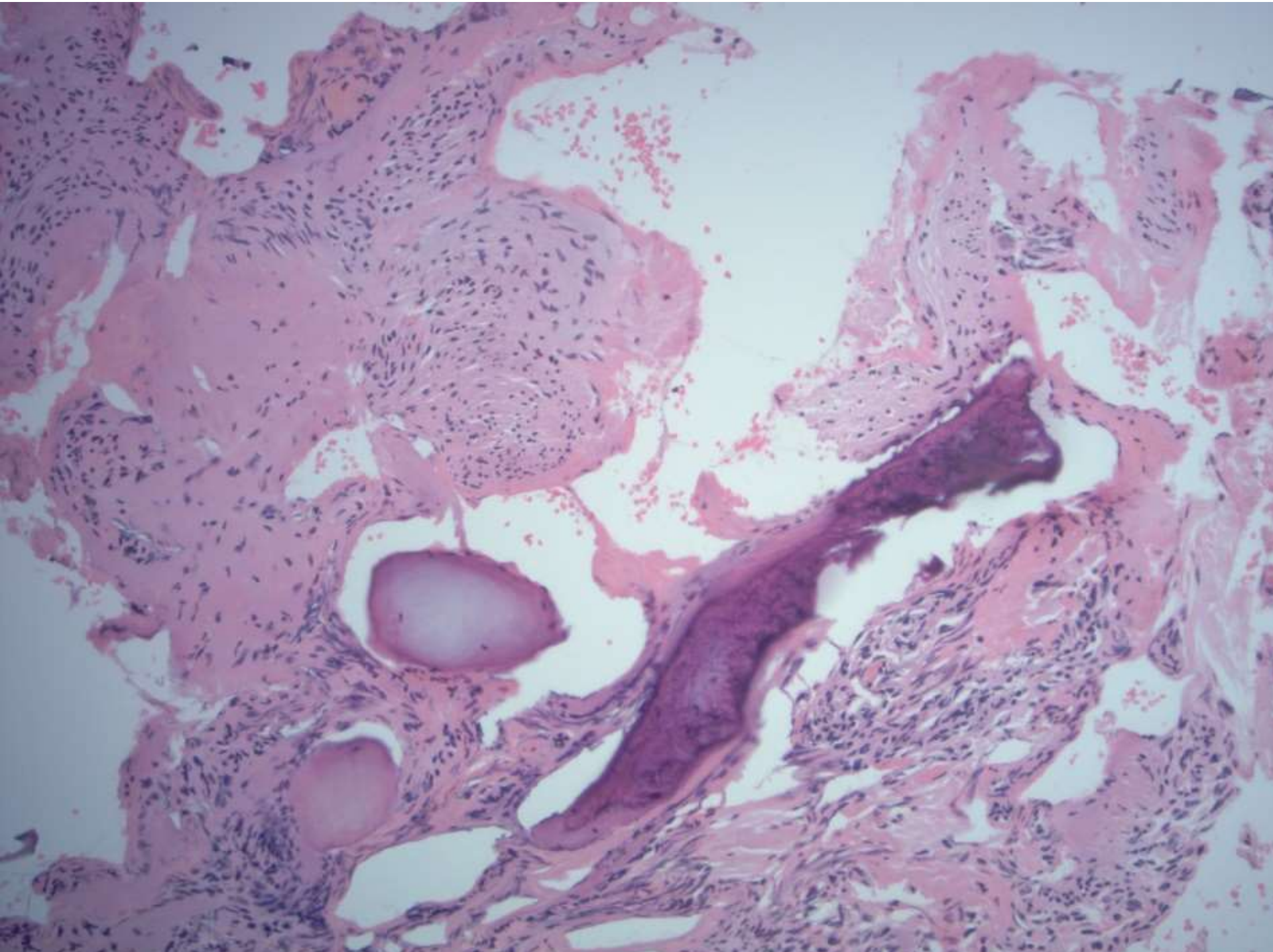










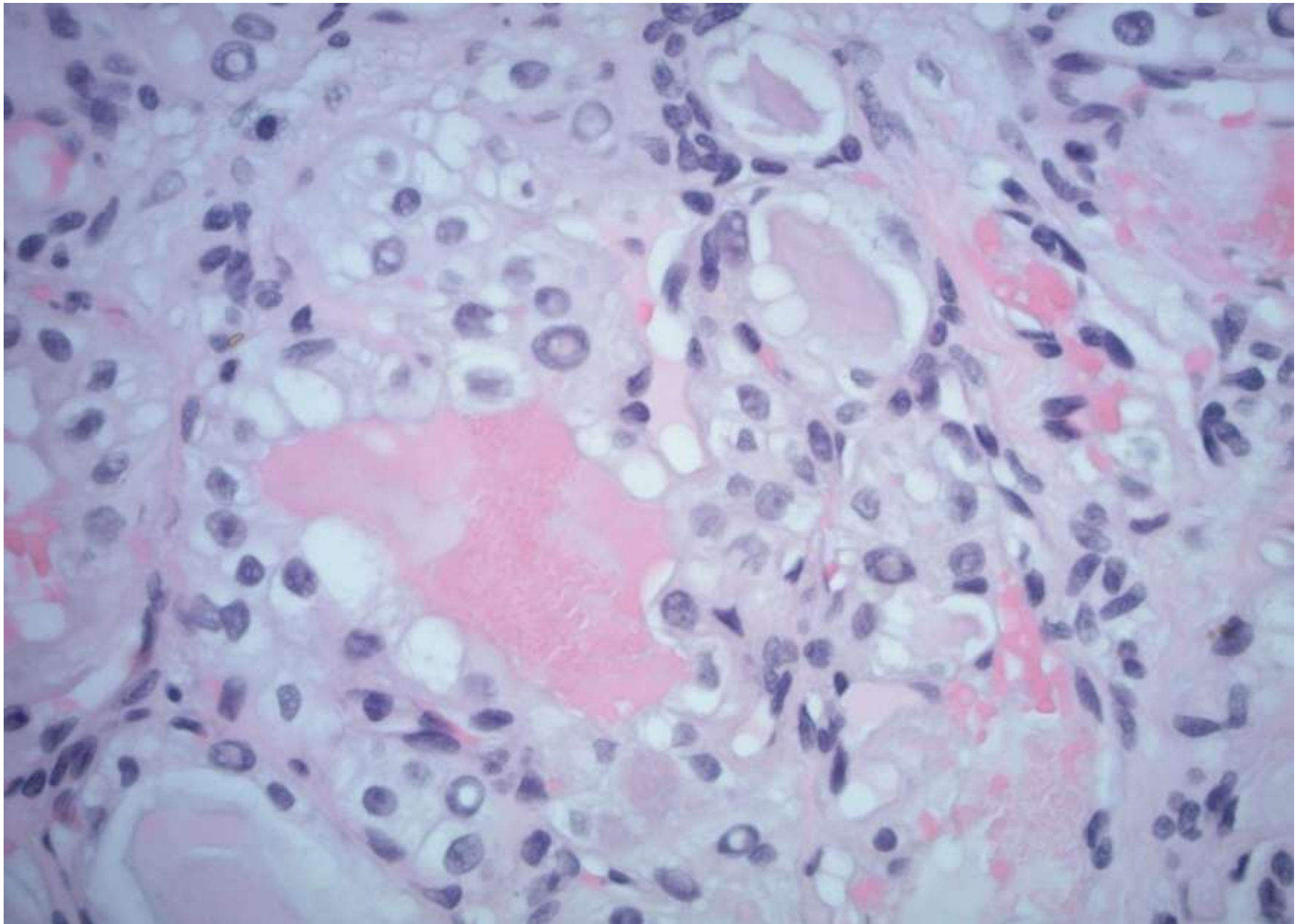


Dr. Google: “Mastoid Ear Mass Differential”

Destructive lesions of the temporal bone (petrous pyramid, middle ear and antrum) have a relatively broad differential including [1]:

- lesions affecting petrous pyramid
  - vestibular schwannoma (acoustic neuroma)
  - meningioma
  - glioma
  - neuroma of trigeminal and facial nerve
  - chordoma
  - glomus jugulare tumor
  - epidermoid of cerebellopontine angle
  - carcinoma of the nasopharynx
  - parotid tumors
  - petrositis (Gradenigo syndrome)
  - intrapetrous ICA aneurysm
  - Langerhans cell histiocytosis
- lesions affecting middle ear, antrum and mastoid
  - cholesteatoma
  - primary or secondary neoplasia
  - glomus jugulare
  - abscess
  - Langerhans cell histiocytosis

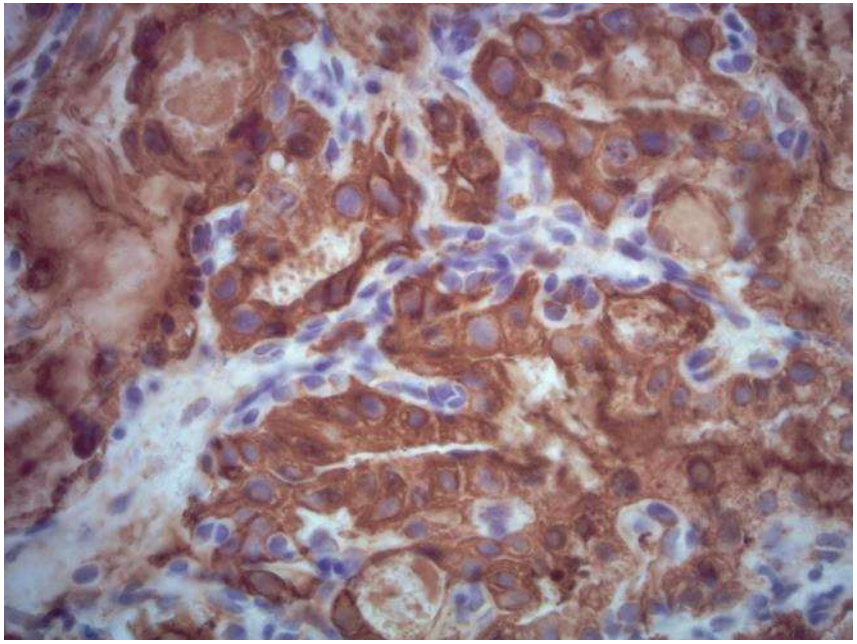
Resection: Involves Petrous Dura



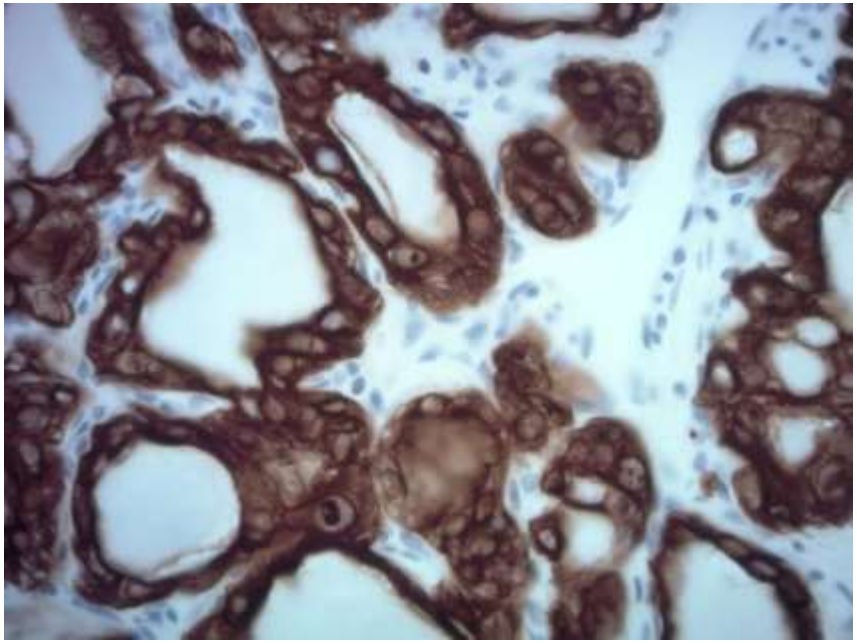
Histologic Differential Diagnosis

- Metastatic Renal or Thyroid Carcinoma
- Endolymphatic Sac Tumor
- Middle Ear Adenoma or ADCA
- Choroid plexus papilloma/ADCA
- Glomus Jugulare
- Paraganglioma

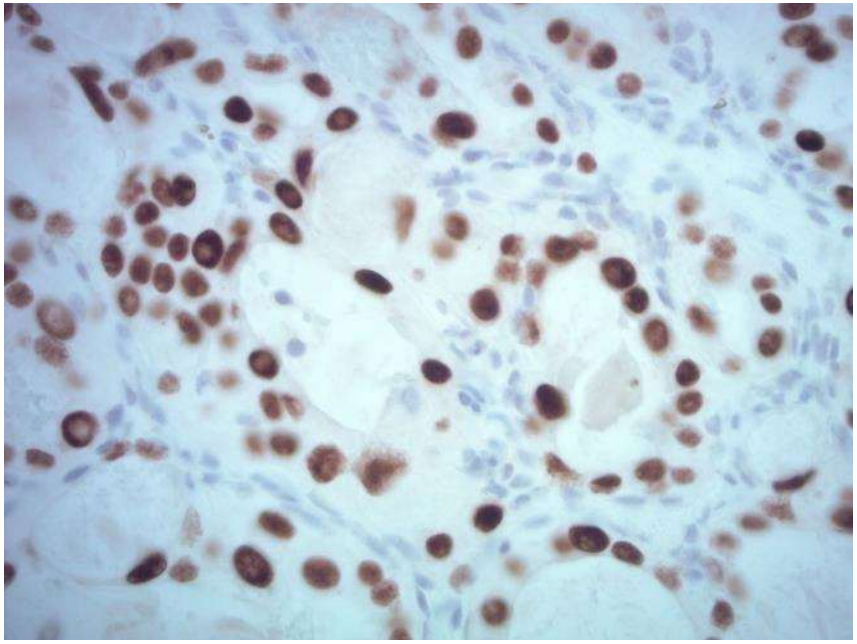
CK7



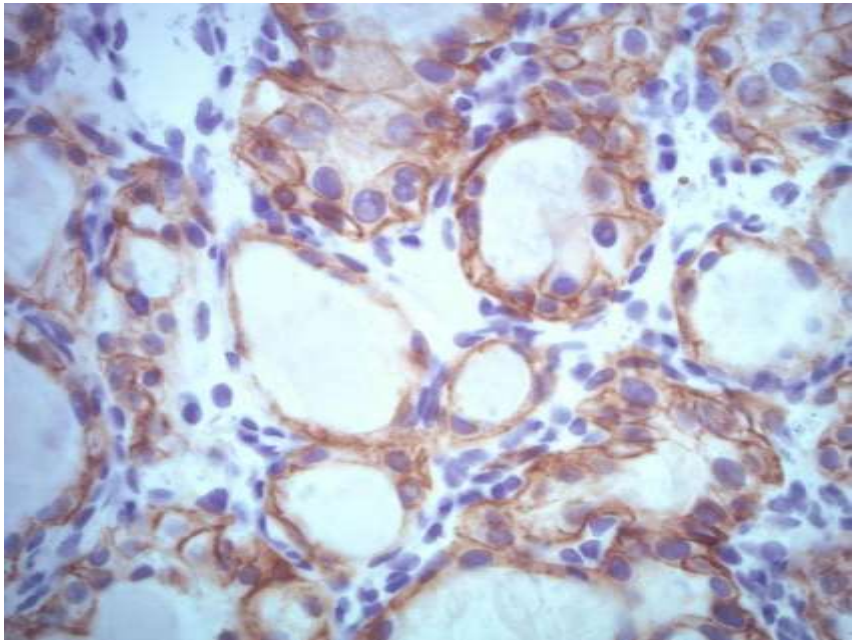
CAM5.2



PAX8



CAIX



NEGATIVE FOR…

- RCC /CD 10 (not metastatic RCC)

- TTF-1 (not metastatic thyroid CA)

- Chromogranin (not middle ear ADCA)
- Synapatophysin (“)
- Mucicarmine (“)

- S100 negative (not choroid plexus adenoma/ADCA)

Dx: Endolymphatic Sac Tumor

- BLAND cuboidal epithelium (no mits or necrosis)
- Highly vascular
- Hemosiderin/hemorrhage/cholesterol clefts
- Colloid-like material in cysts
- Papillary cystic structures

Endolymphatic Sac Tumor (EST): 007

- Looks innocent but may recur and kill:
  - Rare, locally aggressive petrous bone tumor (rare mets per WHO)
- Many confusing aliases, AKA:
  - Papillary ADENOMA of Endolymphatic Sac/Temporal Bone
  - AdenoCARCINOMA of temporal bone/mastoid
  - LG papillary AdenoCARCINOMA of probable ELS origin
- A third of patients w/ EST have von Hippel-Lindau (VHL)
  - i.e., may have 007 other tumors…

Von Hippel -Lindau

- Auto Dominant; 1/39,000
- High Penetrance (90% by 65 yrs)
- VHL gene is a tumor suppressor that regulates VEGF

  →Loss of function leads to angiogenesis / tumorgenesis

VHL Tumors:
The Good, the Bad and the Bloody

Bloody (and sometimes ugly):

- Hemangioblastomas (60-80% of VHL patients)
- Clear Cell Renal Cell Carcinoma
- Endolymphatic Sac Tumors (16% of VHL patients)

Neuroendocrine (Bad, but not superbad):

- Pancreatic NE tumors
- Pheochromocytomas and Paragangliomas

Cystic (Good):

- Cystadenomas of Epididymis/ Broad Ligamament / Pancreas
- Cysts of kidney/pancreas

EST Treatment

- Complete radical resection (may lose cranial nerves)
- +/-pre or post-op XRT
- Cochlear implants for hearing loss

EST Take-Home Points

- Screen all EST patients for VHL (a third have VHL!)
- Know your temporal bone anatomy/high index of suspicion for EST!
  - (looks deceptively bland and reactive)
- PAX8 +/CAIX + but CD10/RCC & TTF-1 neg
  - (r/o metastatic ccRCC / thyroid)

References

Thompson, L. et al. CAIX and PAX-8 Commonly Immunoreactive in EST: A Clinicopathologic Study of 26 Cases with Differential Considerations for Metastatic Renal Cell Carcinoma in von Hippel-Lindau Patients. Head and Neck Pathology (2019) 13: 355-363.

(Note WHO says ELSTs are PAX8 /CAIX negative, but this 2019 reference says otherwise!)

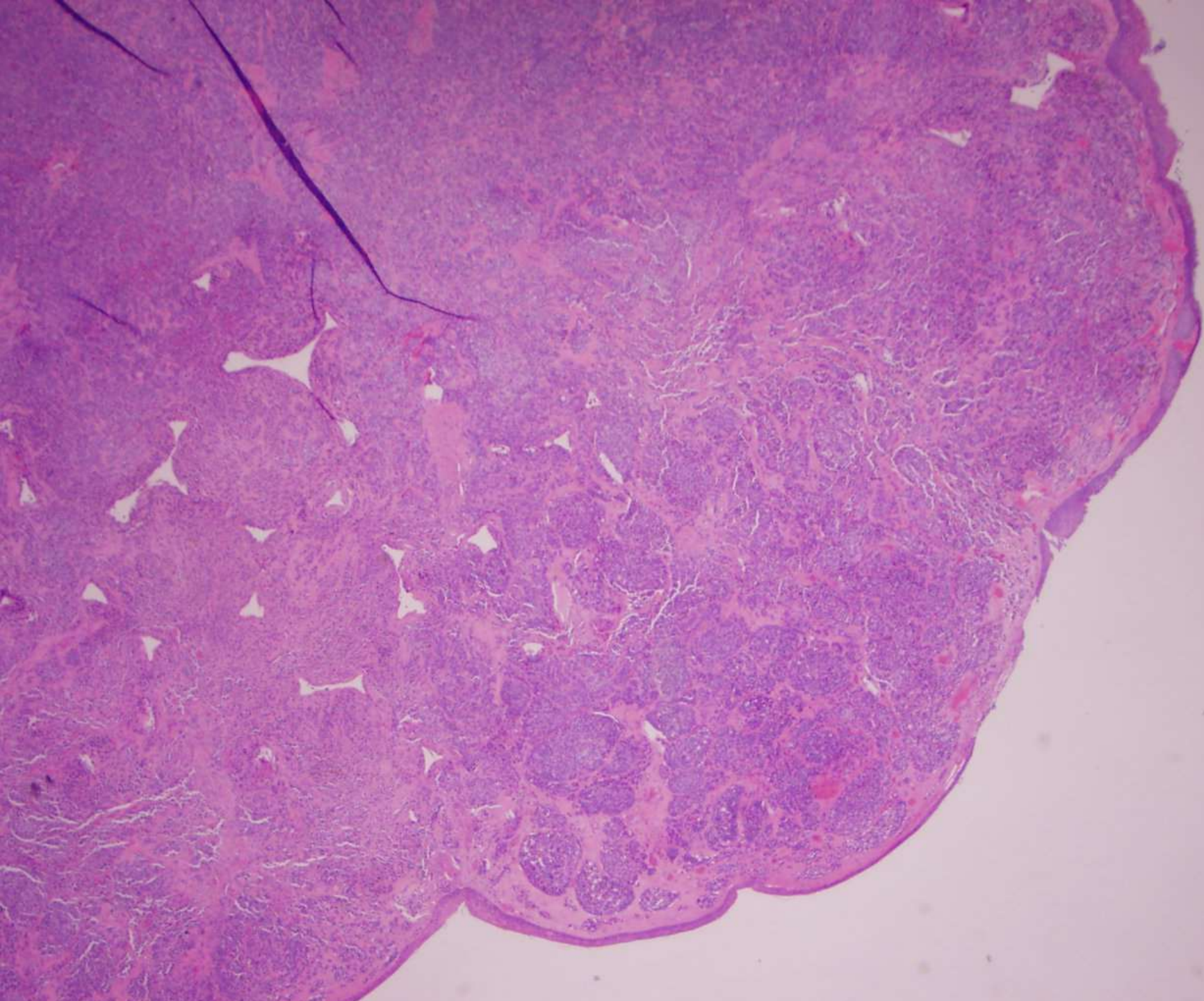
References

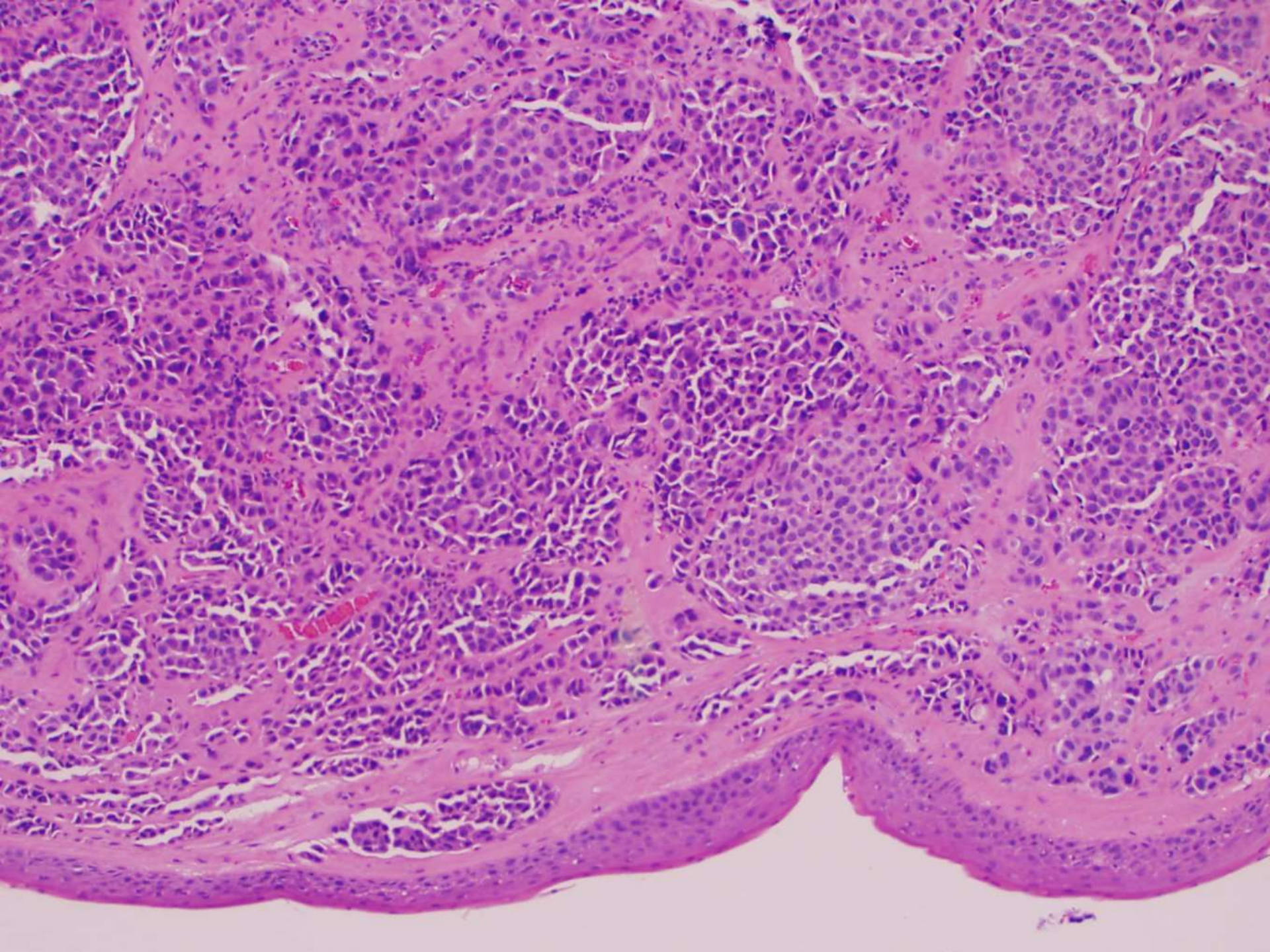
- Ganeshan et al. Tumors in von Hippel-Lindau Syndrome: From Head to Toe—Comprehensive State-of-the-Art Review. Multisystem Radiology, May-June 2018, RSNA 2018, 849-866.
- WHO Classification of Head and Neck Tumors, 2017 ed.

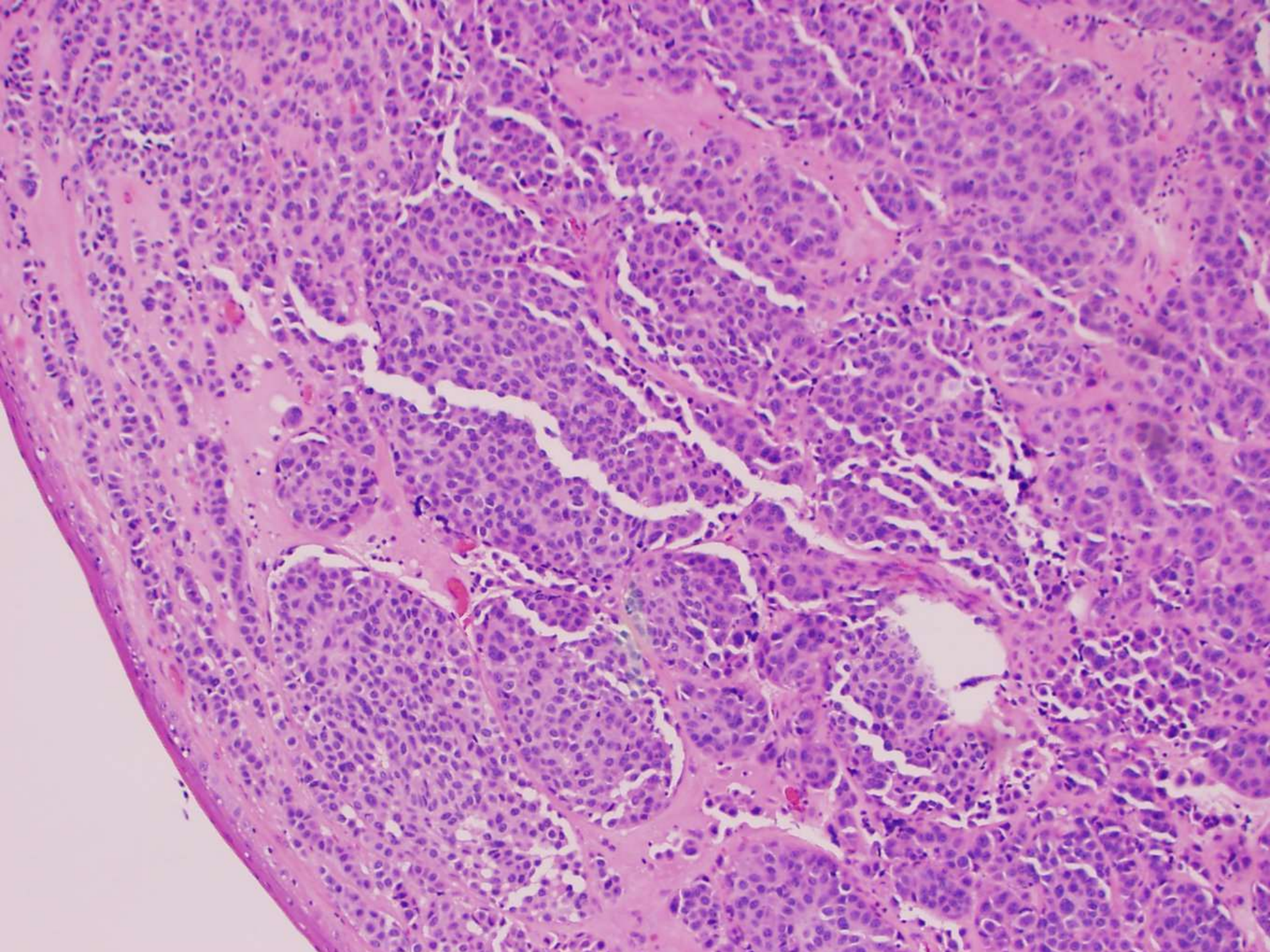
20-0806

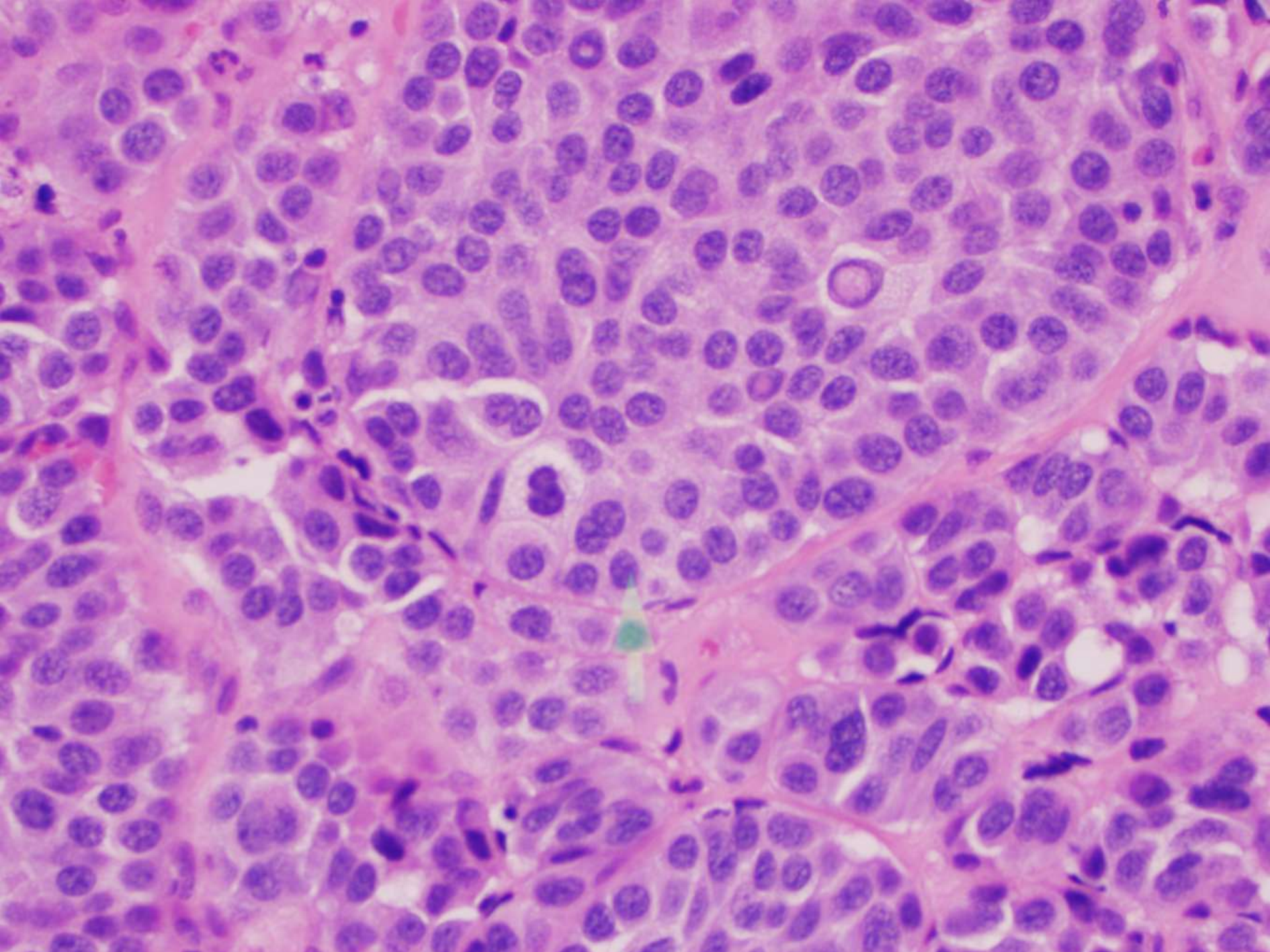
Greg Rumore; Kaiser Diablo

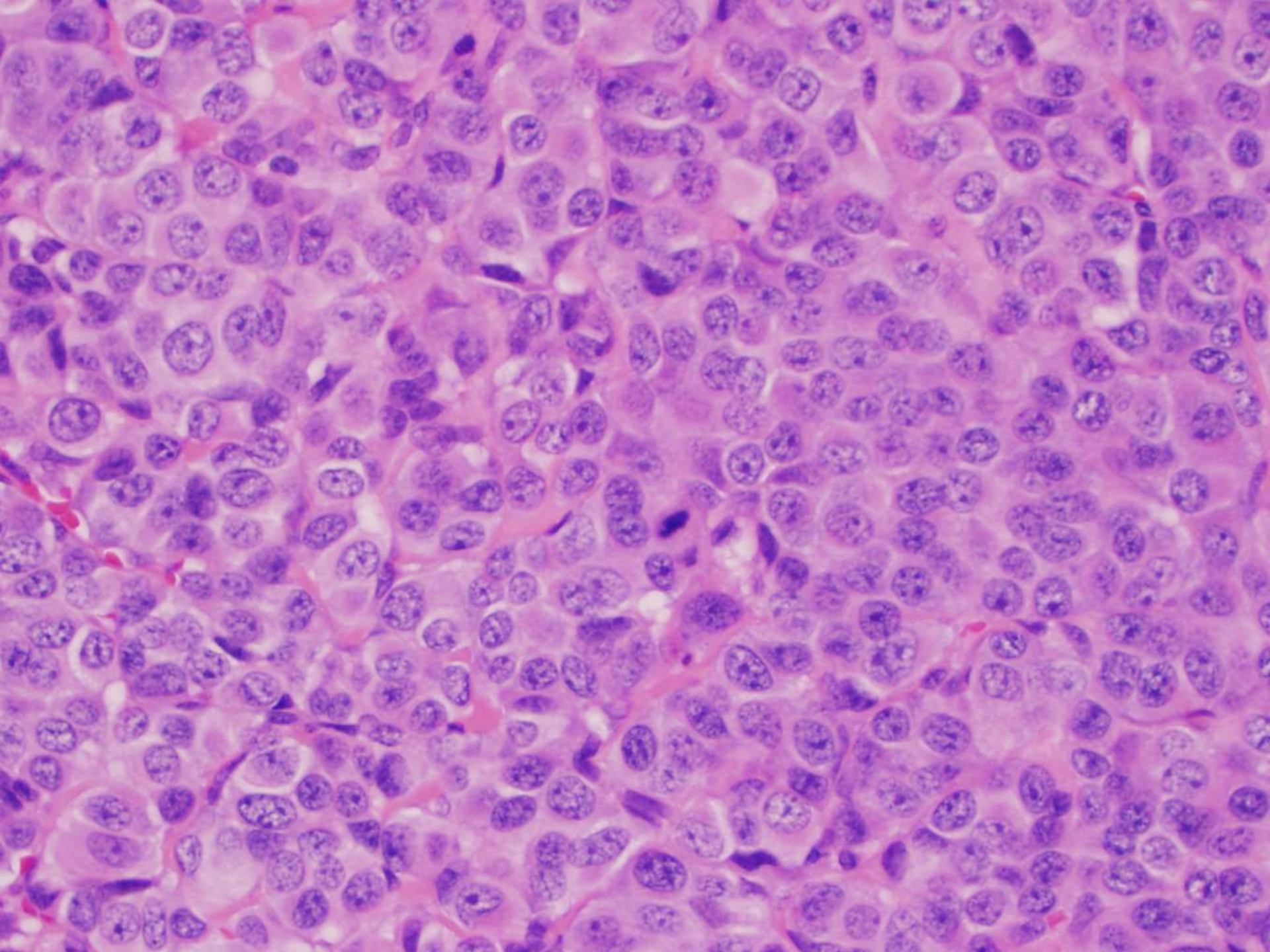
74-year-old M with 1cm left arytenoid mass.

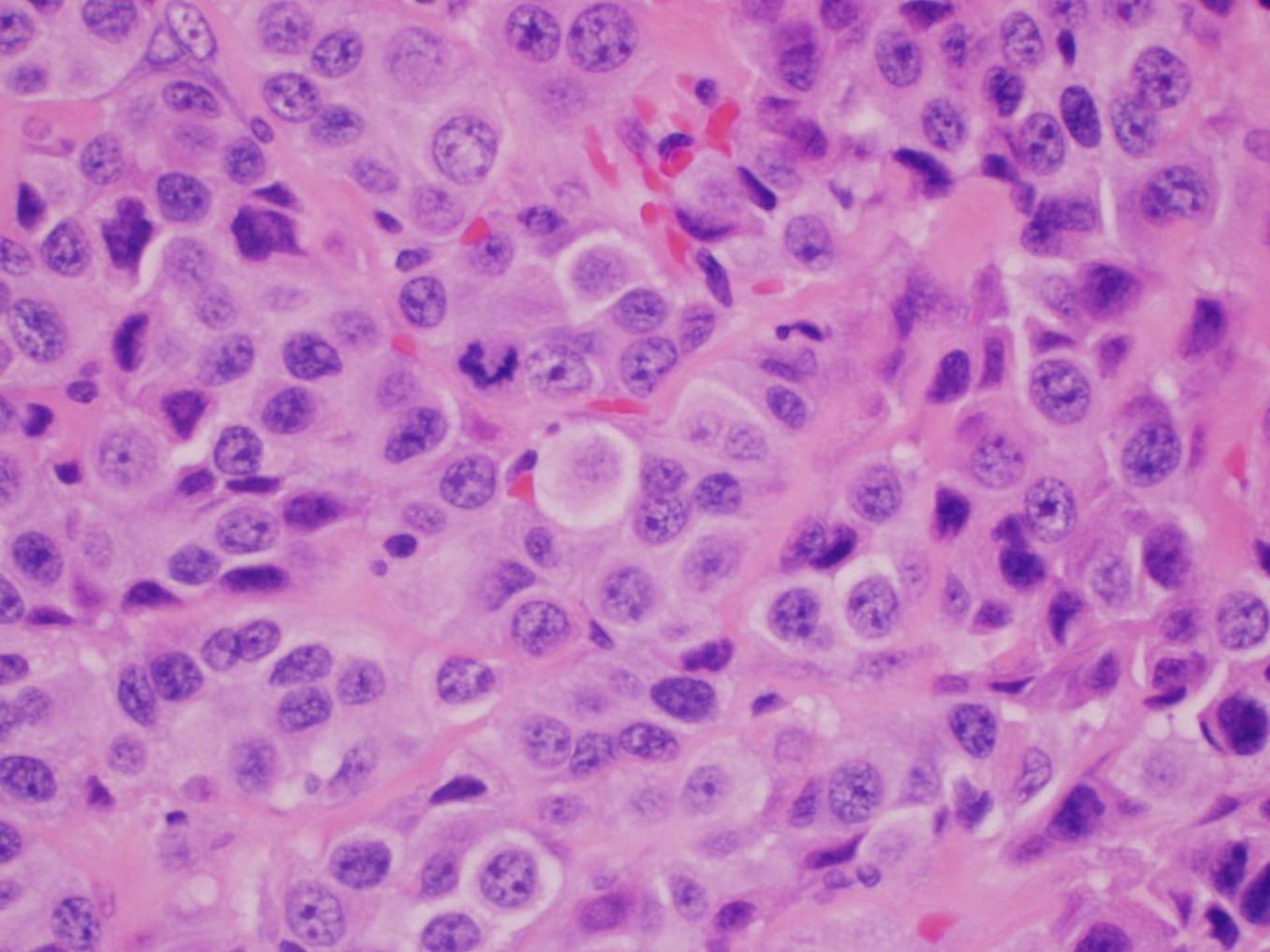


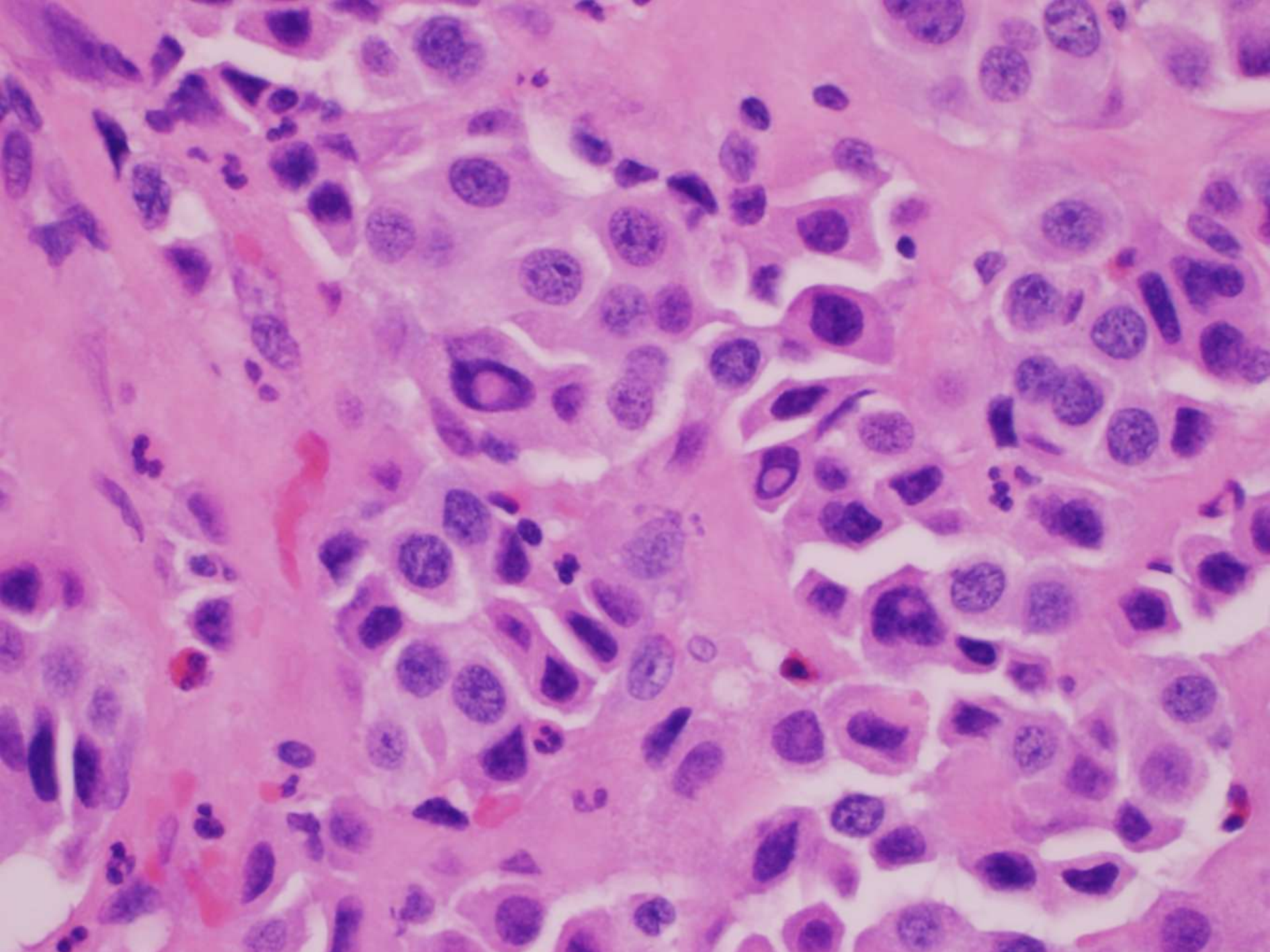


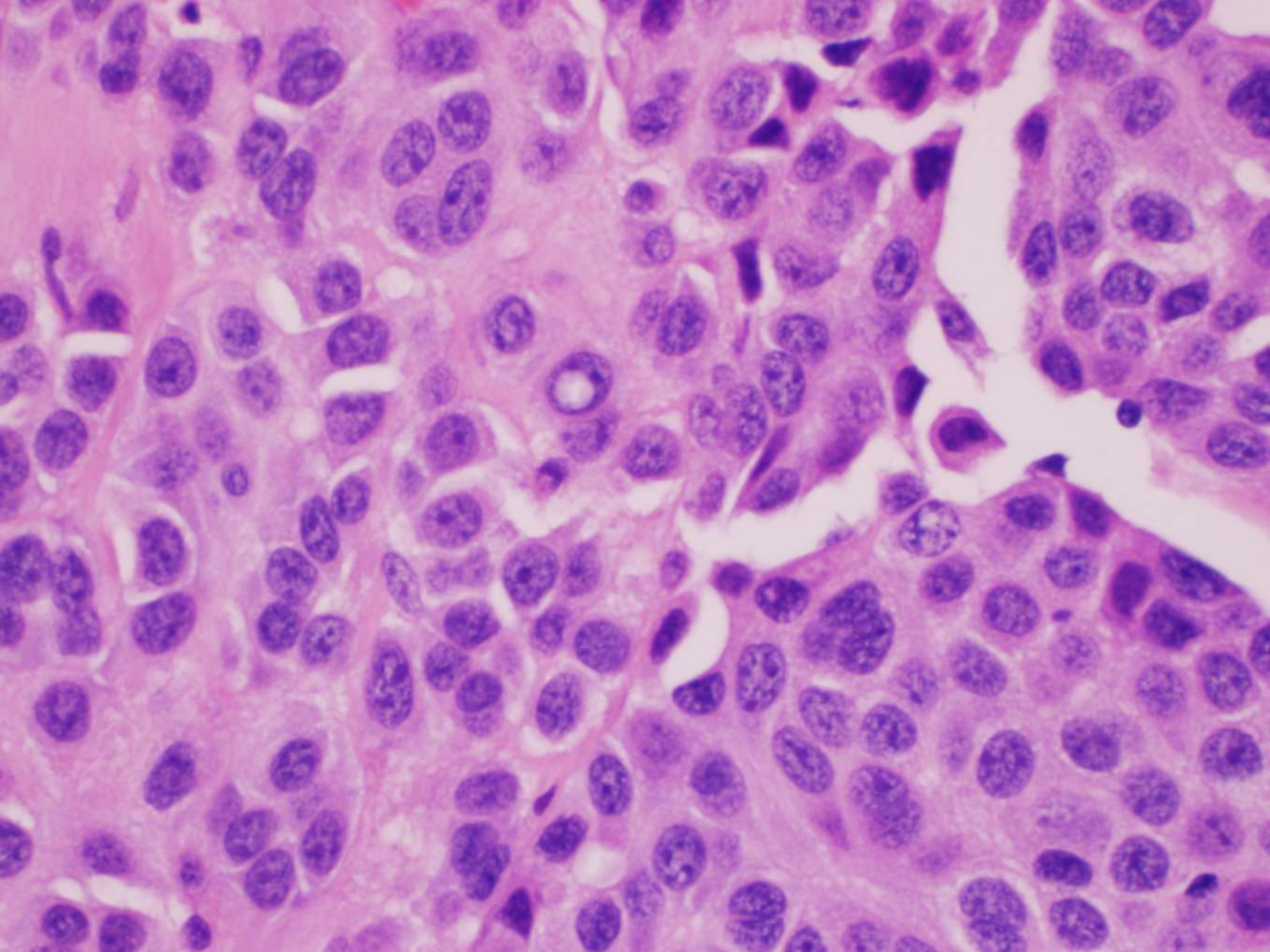


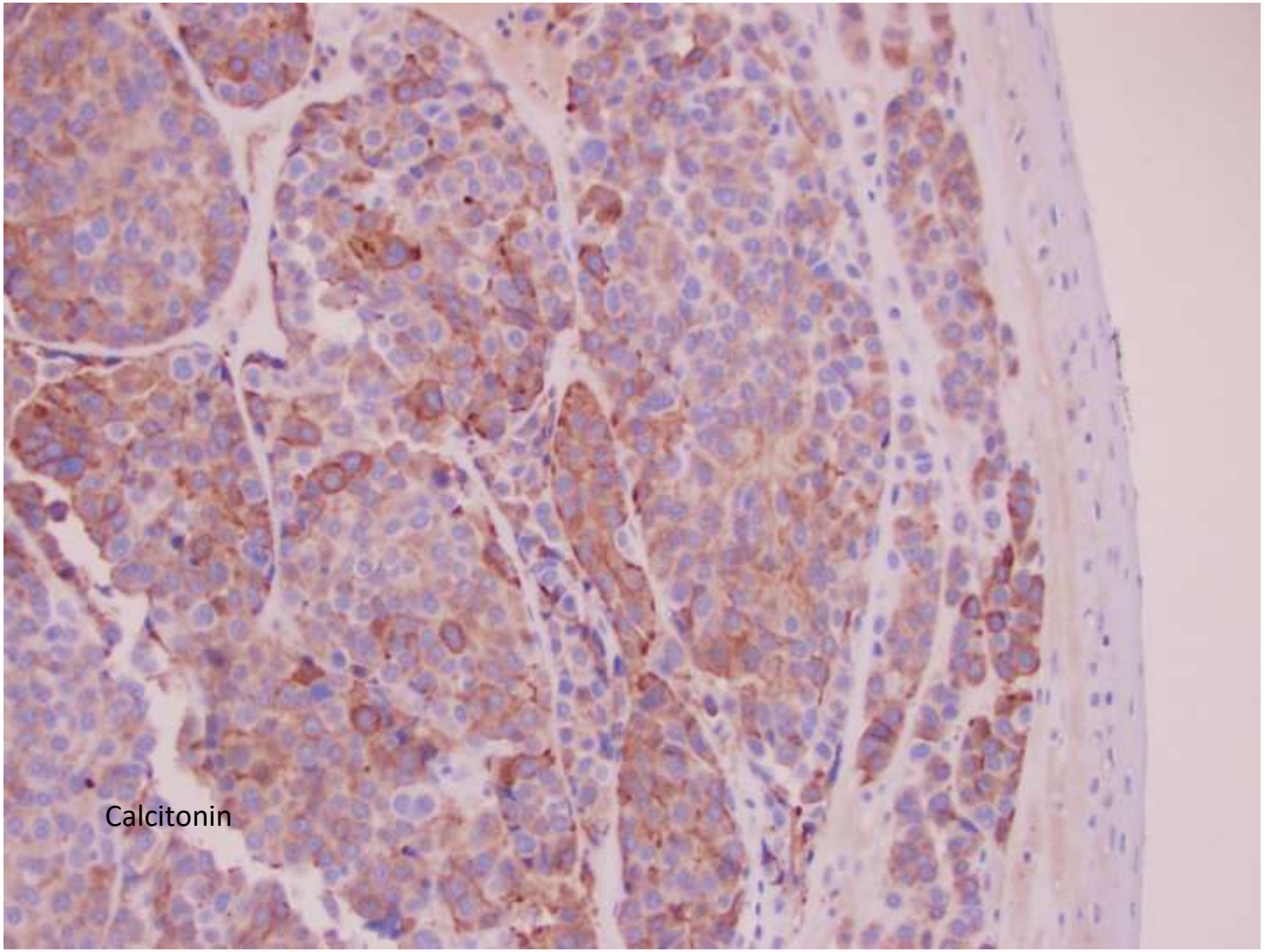


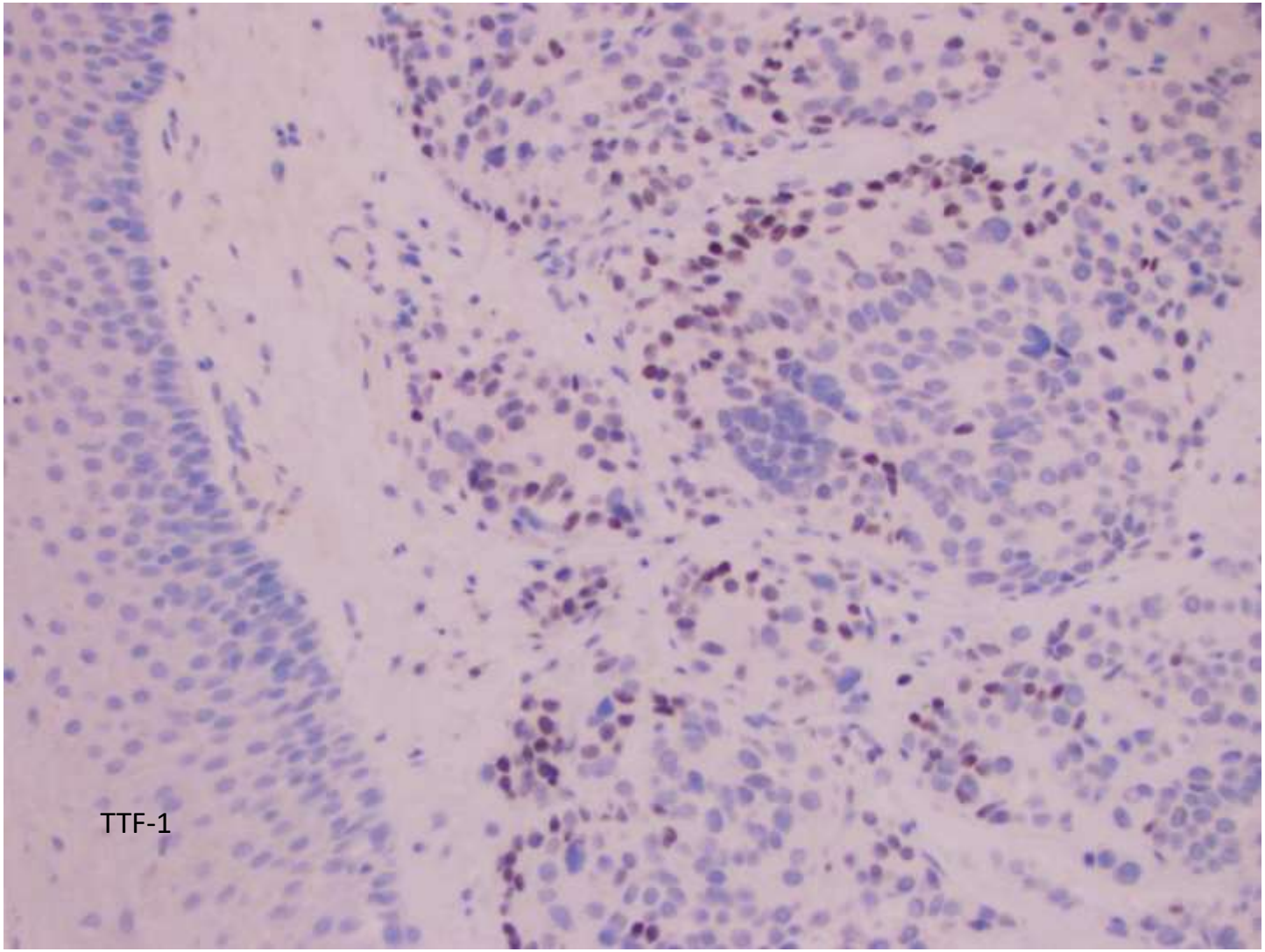









Calcitonin


TTF-1

Differential Diagnosis

- Moderately Differentiated Neuroendocrine Tumor (Carcinoma)
- Medullary Thyroid Carcinoma
- Well Differentiated Neuroendocrine Carcinoma (Carcinoid)
- Poorly Differentiated Neuroendocrine CA-small cell, large cell
- Paraganglioma

IHC/Special Stains

- Synaptophysin-positive
- Chromogranin-positive
- Pancytokeratin-positive
- Calcitonin-positive
- TTF-1-positive
- Thyroglobulin-negative
- Ki-67-<5%
- Amyloid-negative

Diagnosis

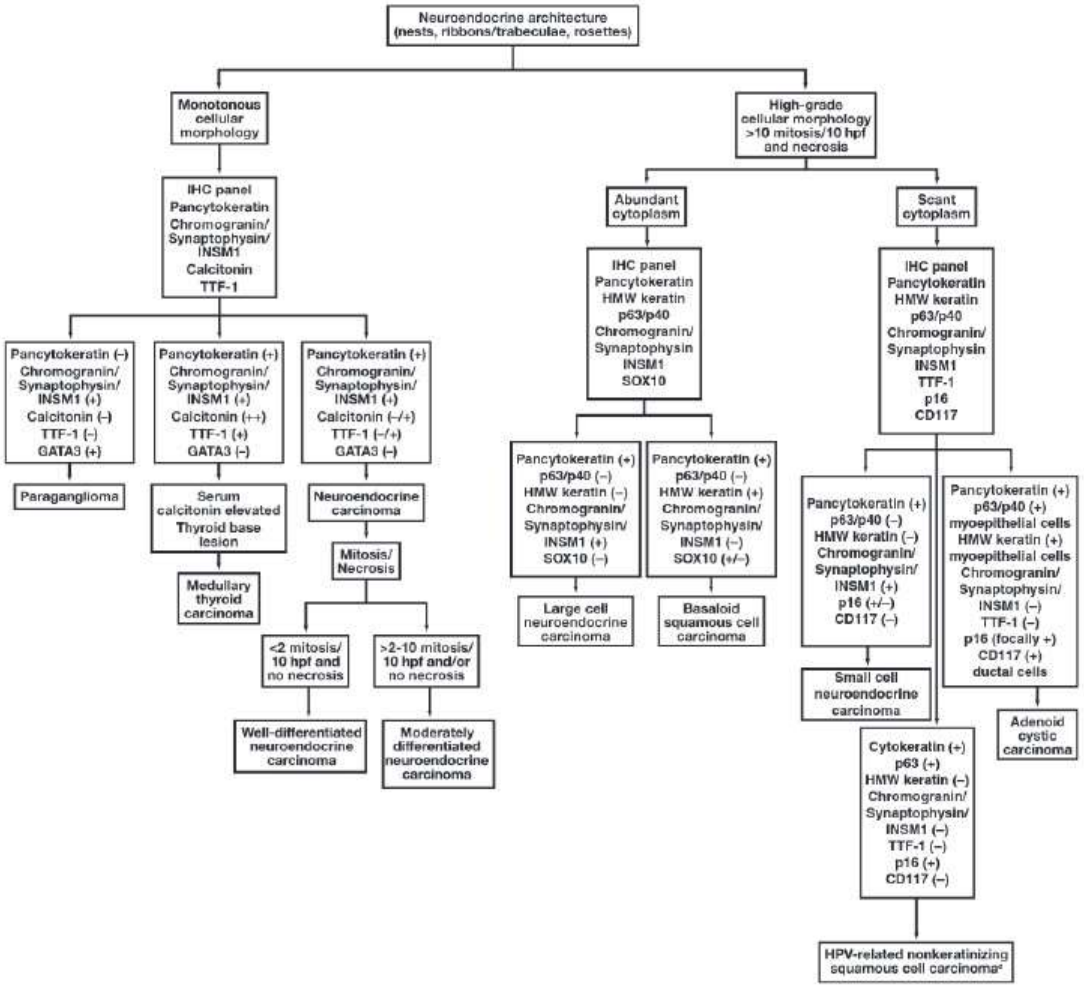
- Moderately Differentiated Neuroendocrine Tumor, Grade 2 (Moderately Differentiated Neuroendocrine Carcinoma)

Factors favoring Neuroendocrine Tumor over Medullary Thyroid CA

- Location in supraglottic larynx (>90%)
- Absence of thyroid mass or history of thyroid CA
- Smoking history
- Normal serum calcitonin
- Male predominance, 6^{th}-7^{th} decades

Mod Diff Neuroendocrine CA vs. Lg. Cell Neuroendocrine Carcinoma

- LG Cell Neuroendocrine CA->10 mitoses/10HPF, Necrosis, Nucleoli
- Mod Diff Neuroendocrine Carcinoma)-2-10 mitoses/10HPF and/or necrosis



From AJCP 2019;152

Prognosis – Mod Diff Neuroendocrine Carcinoma

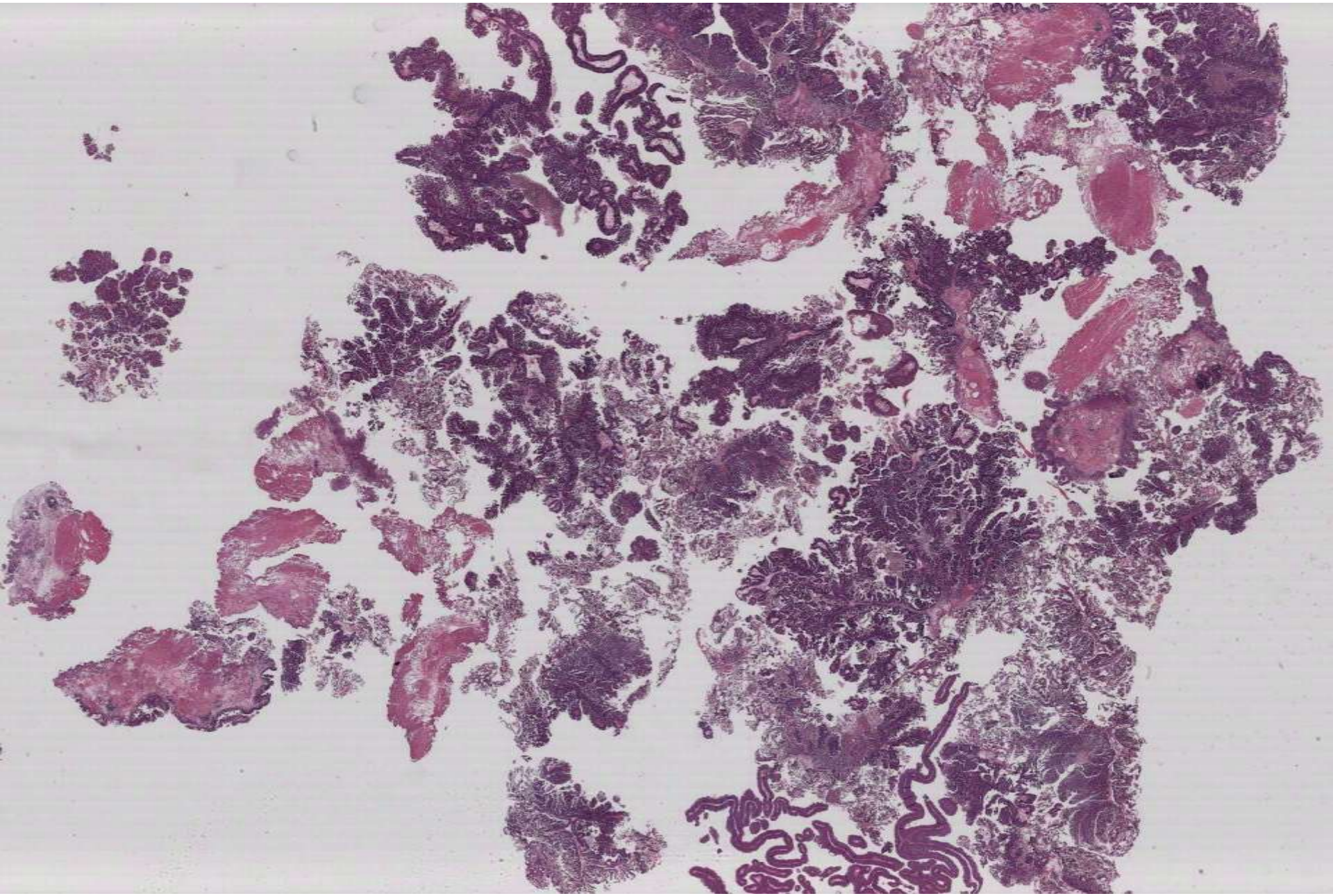
- 30% of patients present with advanced disease
- Recurrence rate 60%
- 5 year survival rate=50%
- >1 CM=twice mortality rate
- RX-radical surgical resection with Neck dissection vs. Surgery/Rad

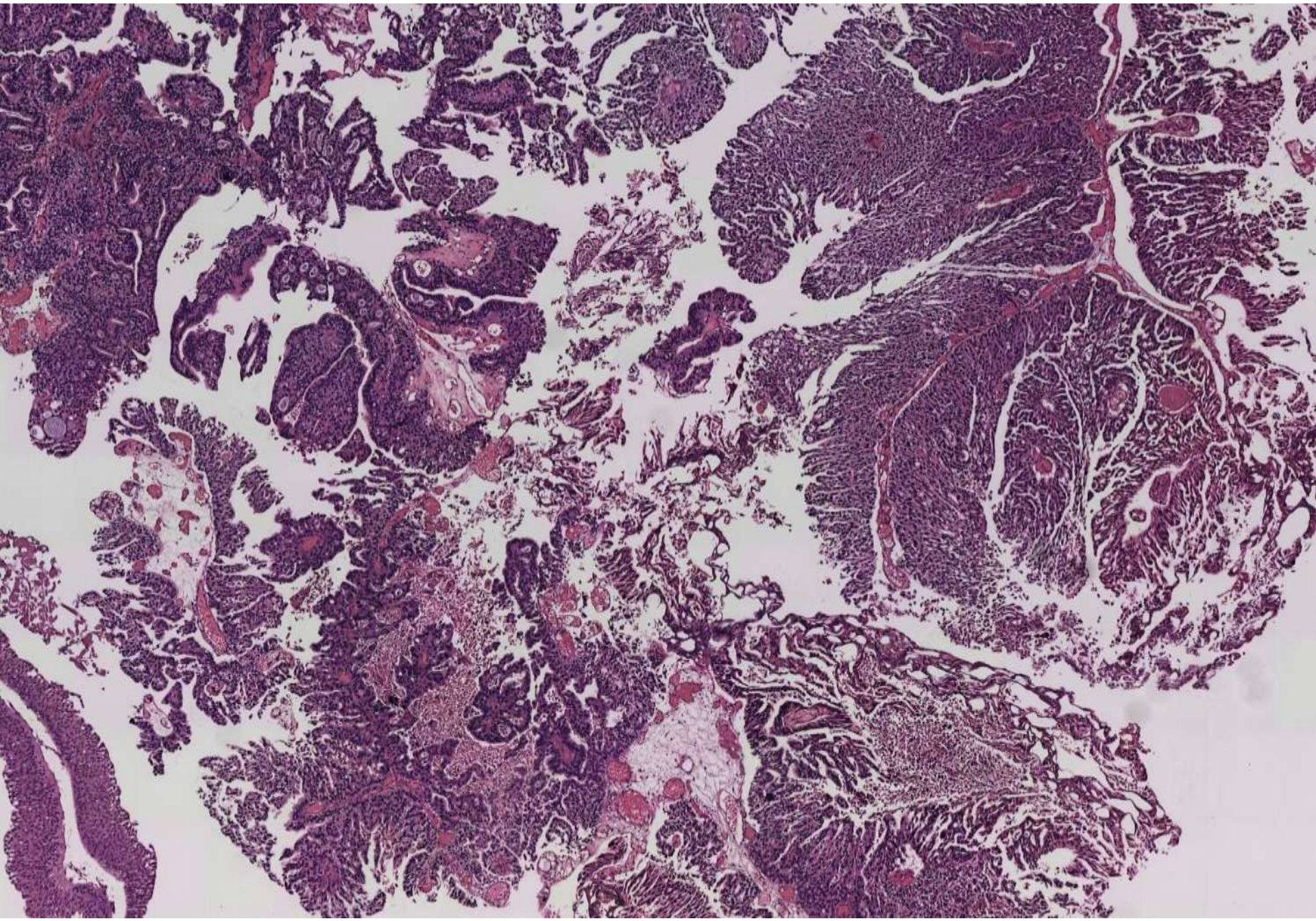
- Reference: Strosberg, C., et al, Update on Neuroendocrine Carcinomas of the Larynx, AJCP 2019; 152: 686-700

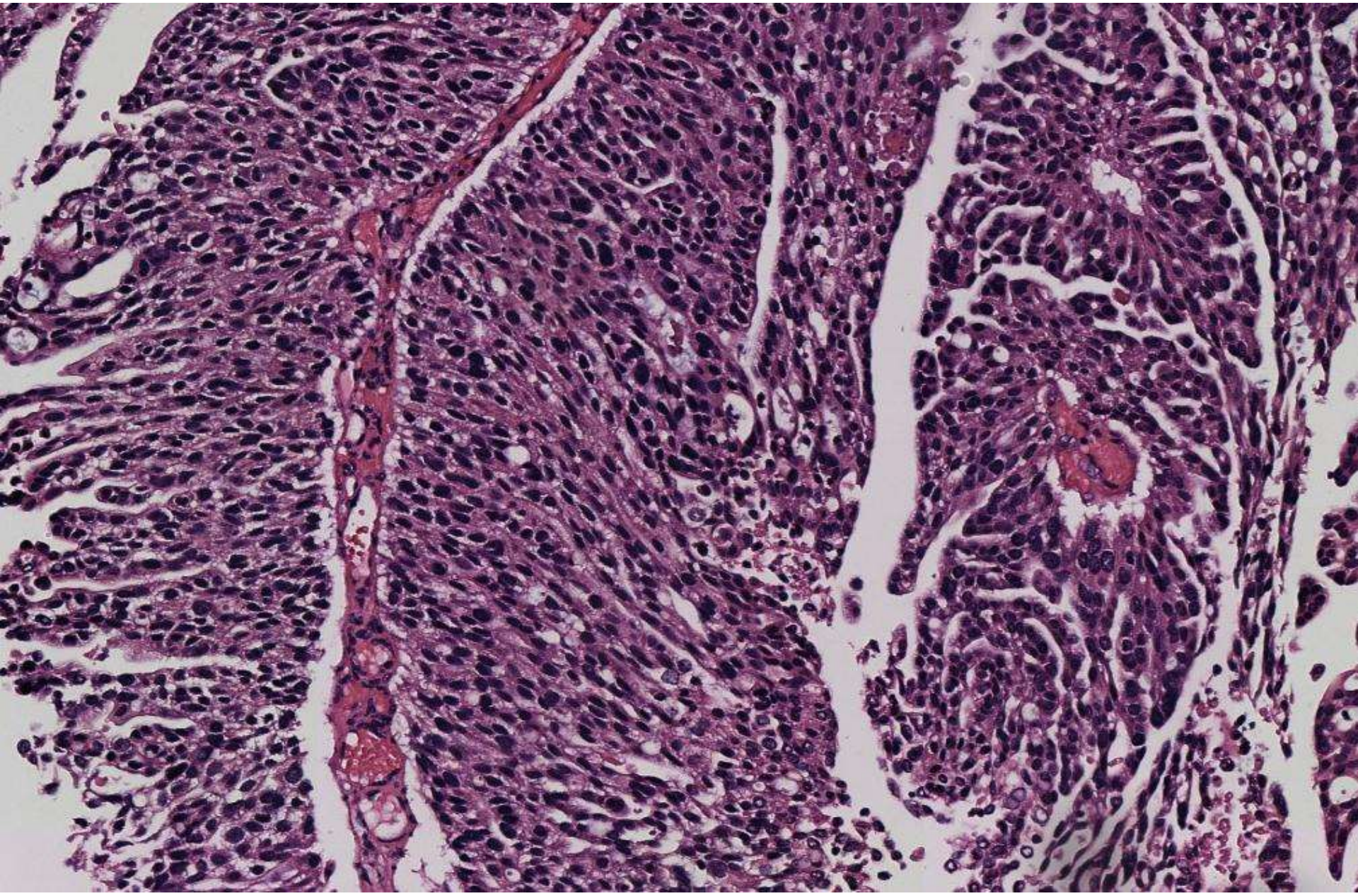
20-0807
scanned slide available!

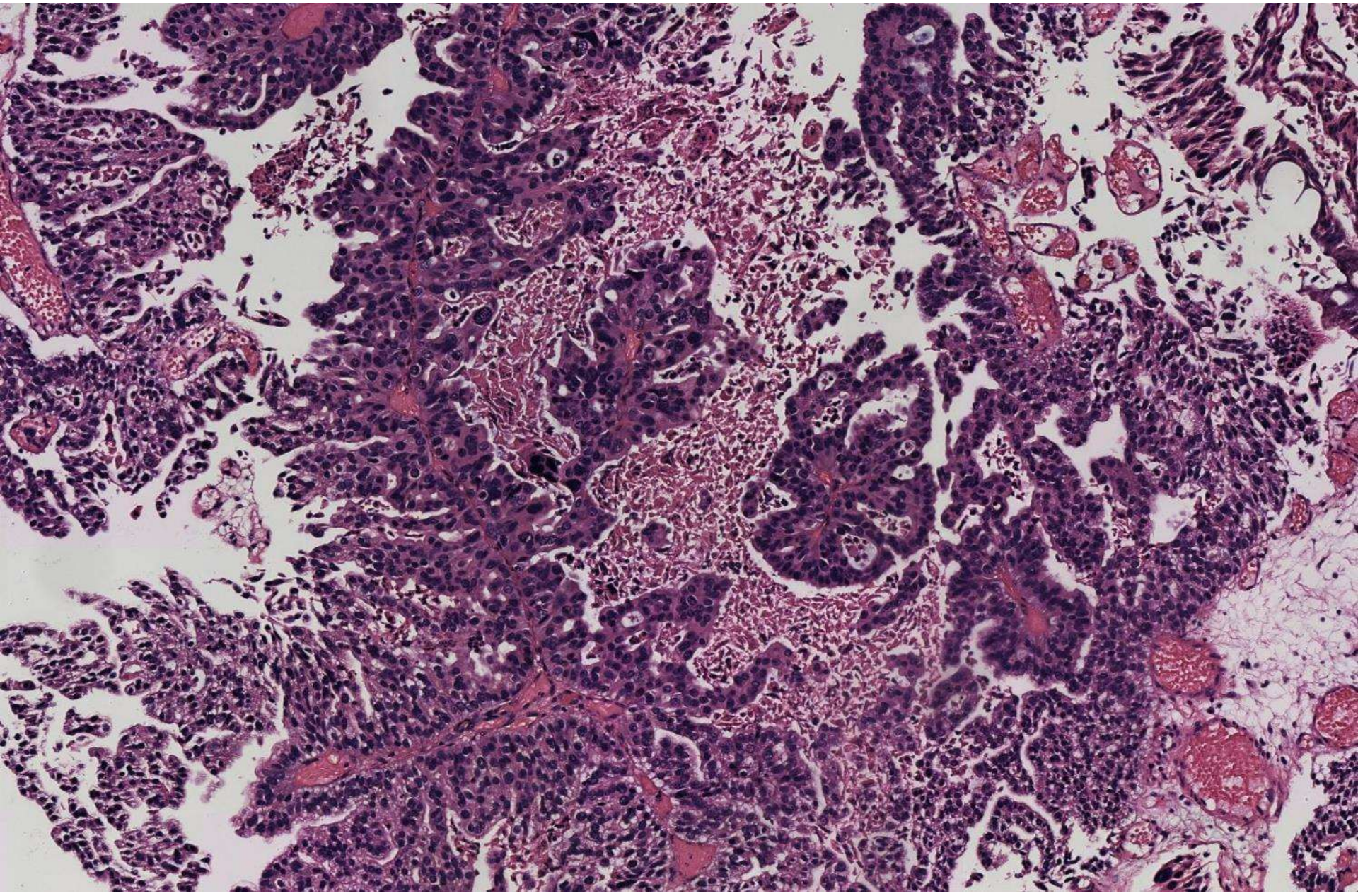
Ankur Sangoi; El Camino Hospital

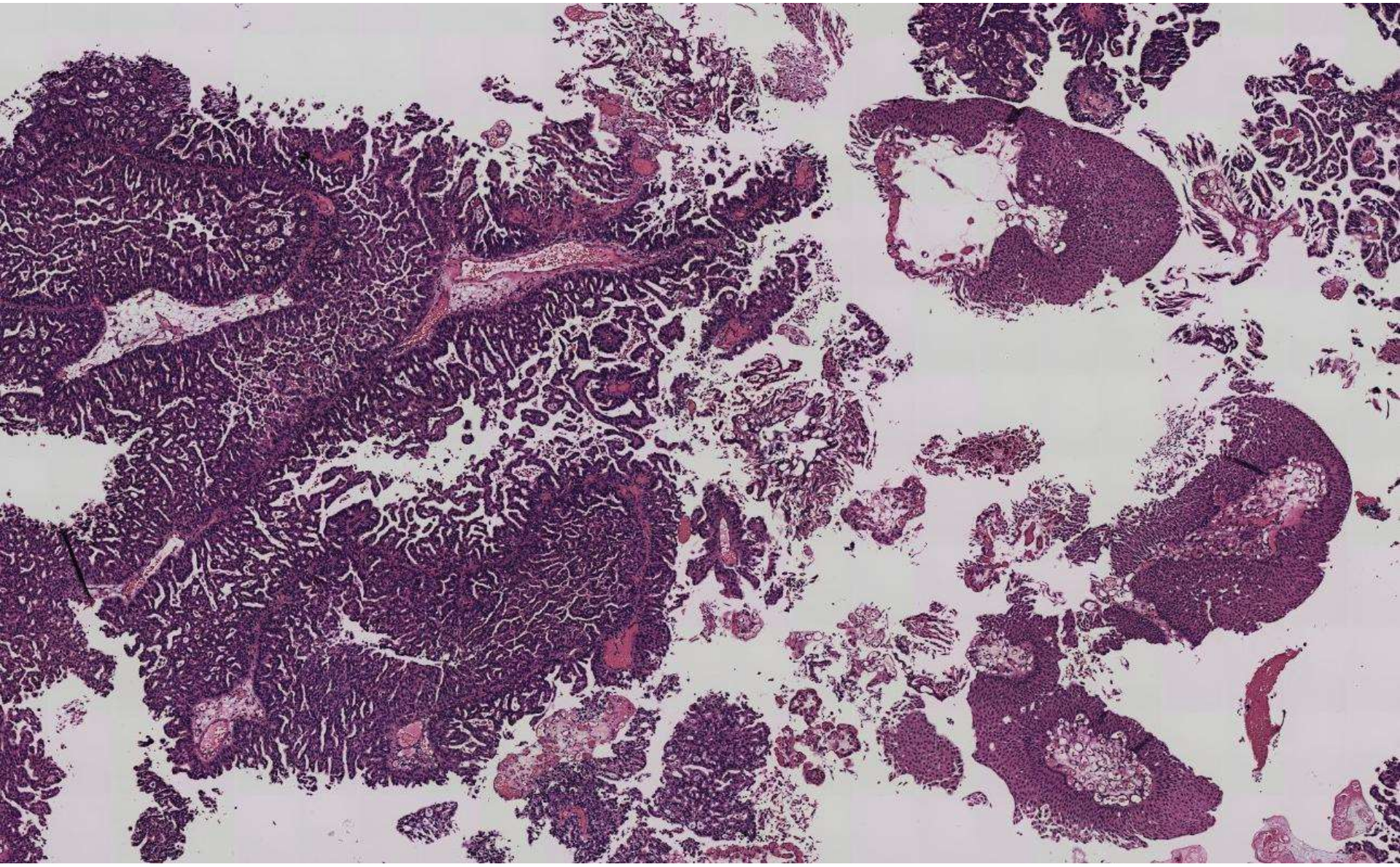
Middle-aged M with bladder tumor, TURBT performed.

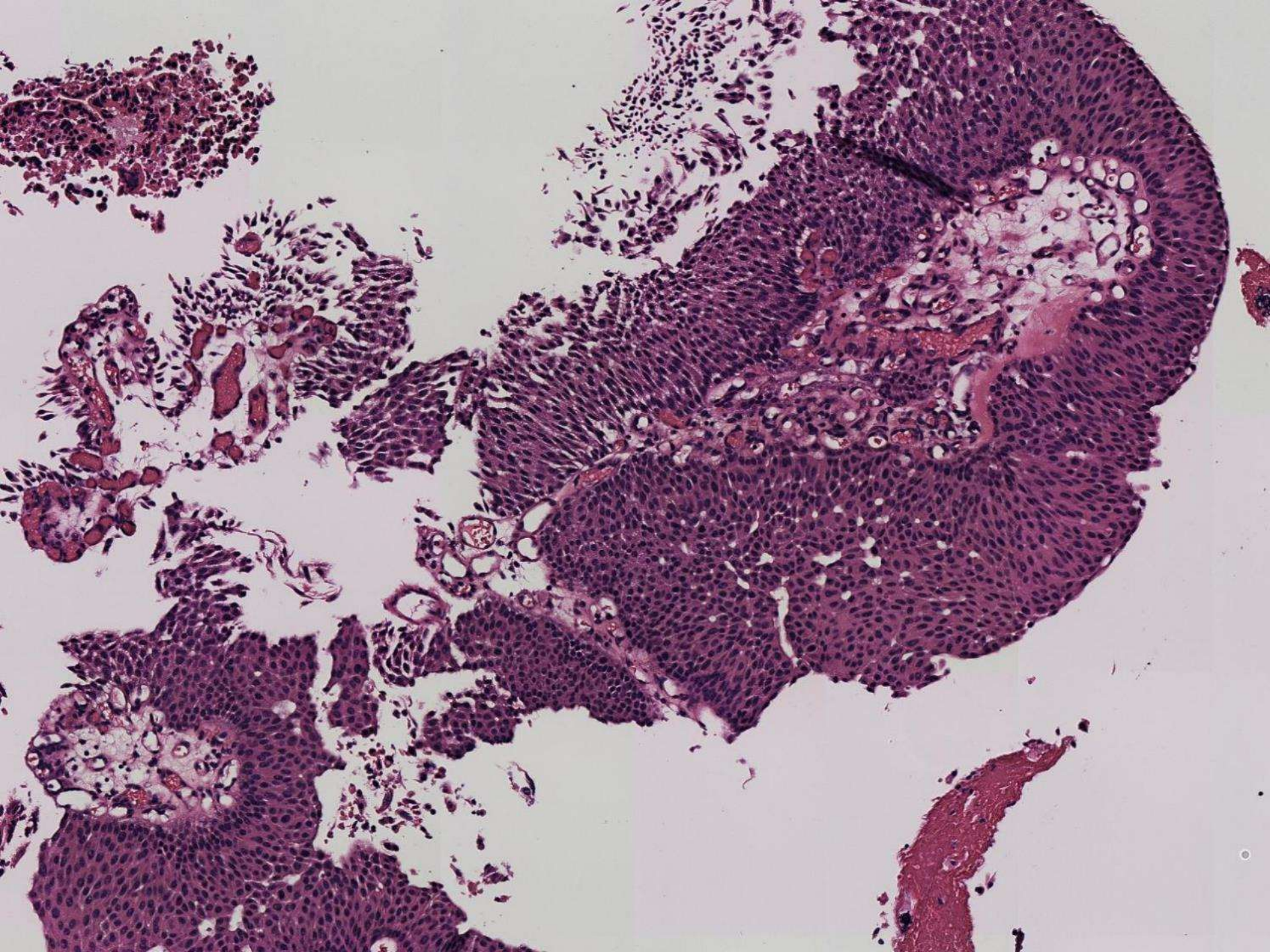


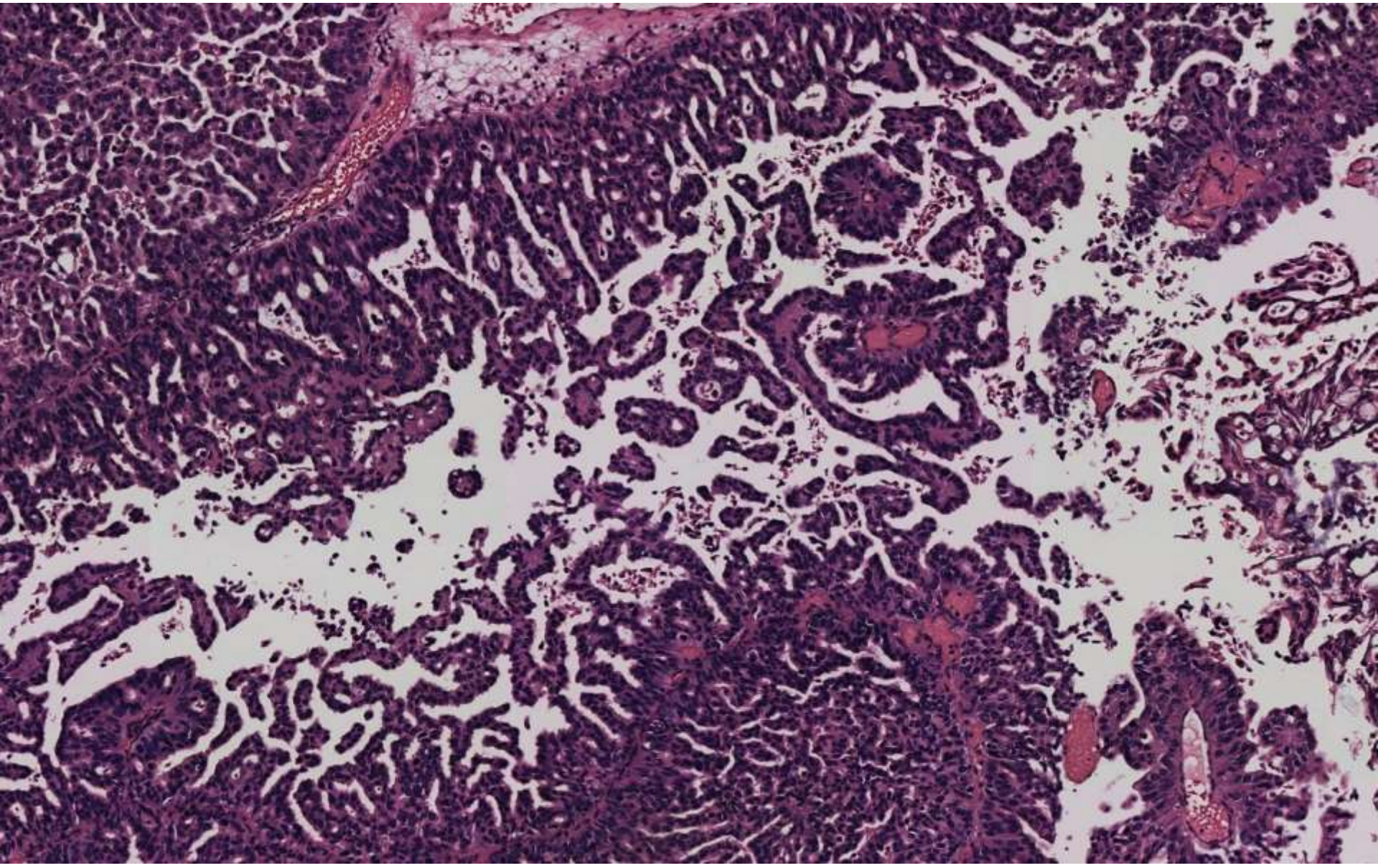


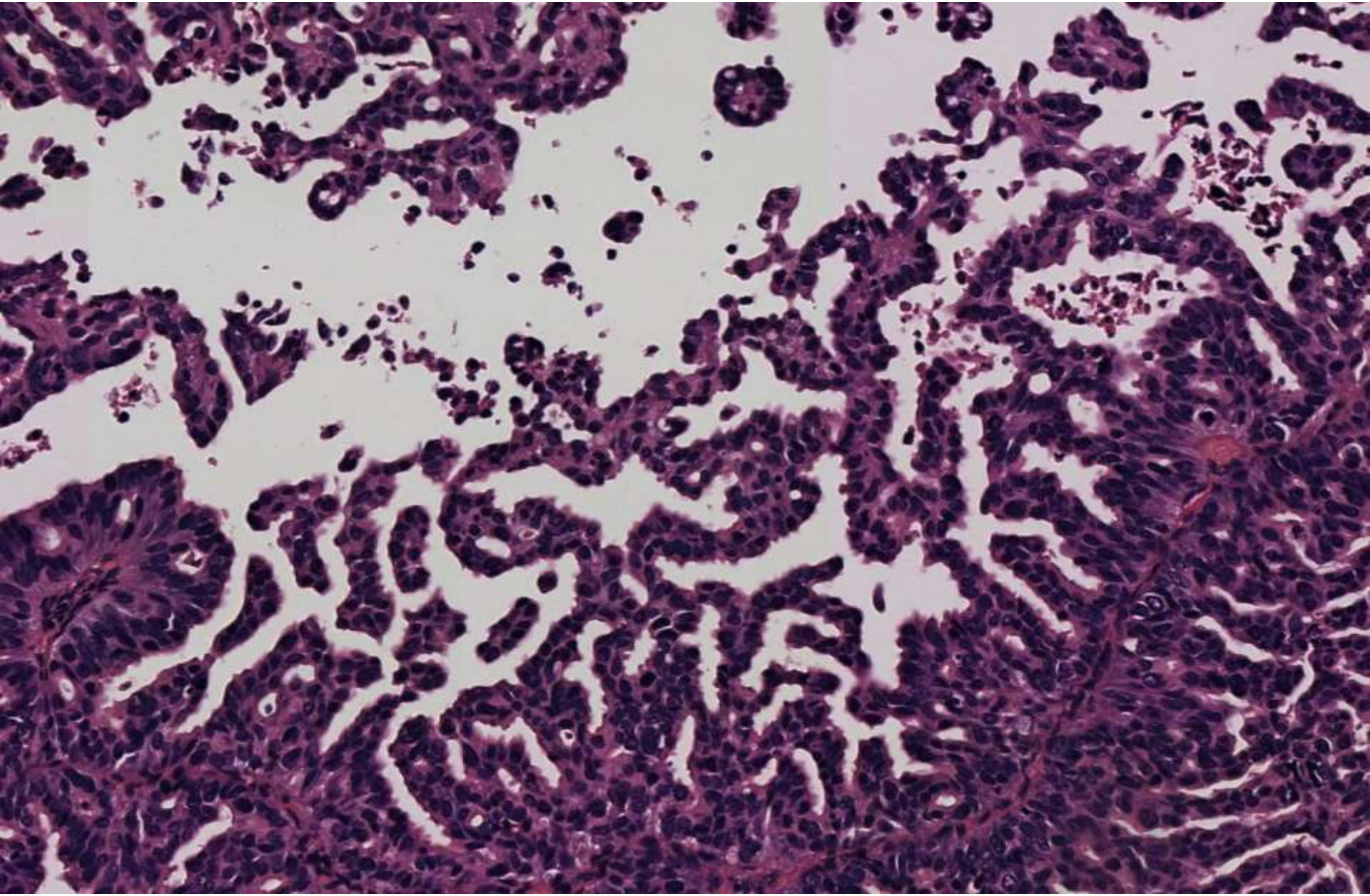


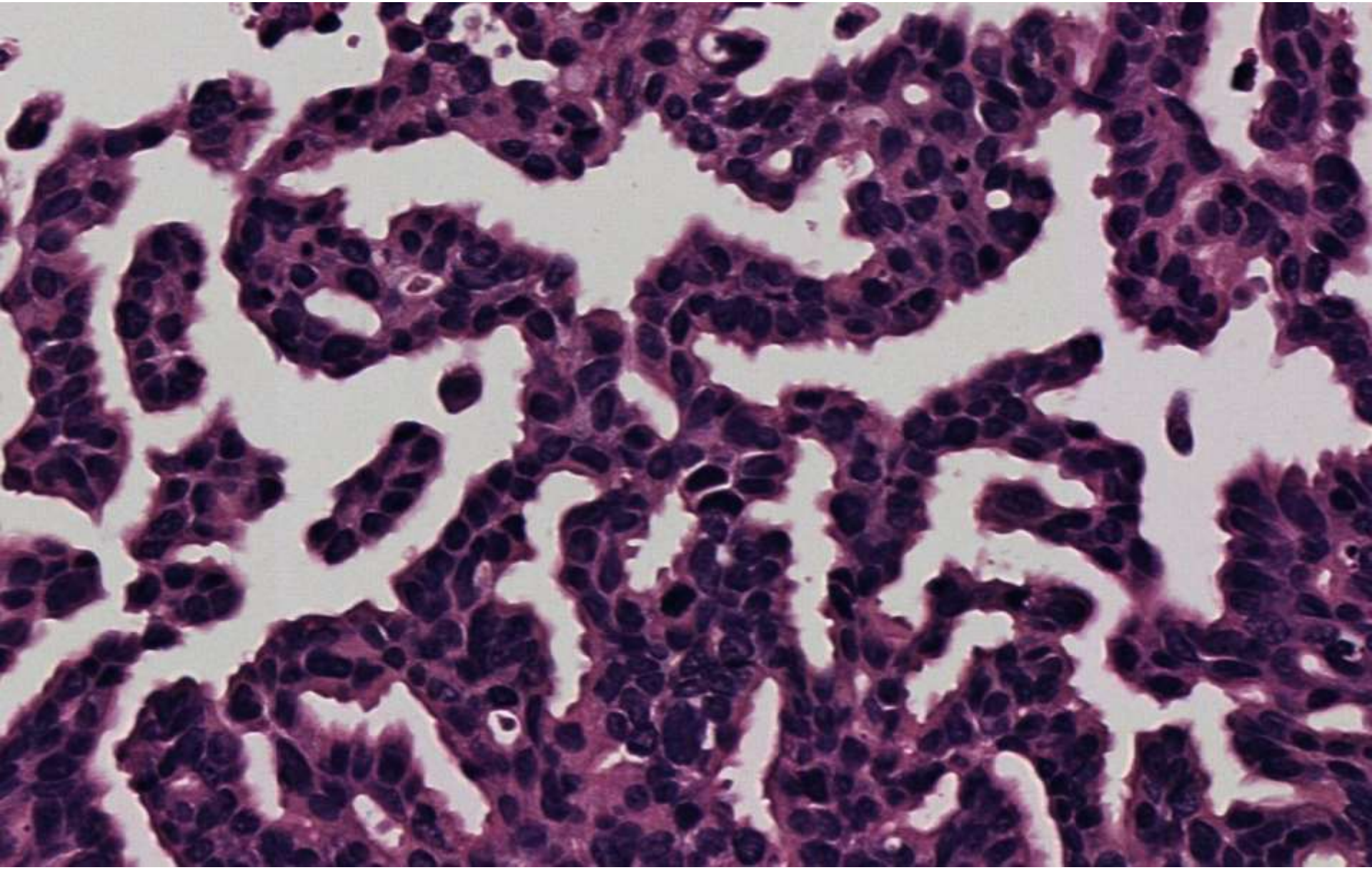


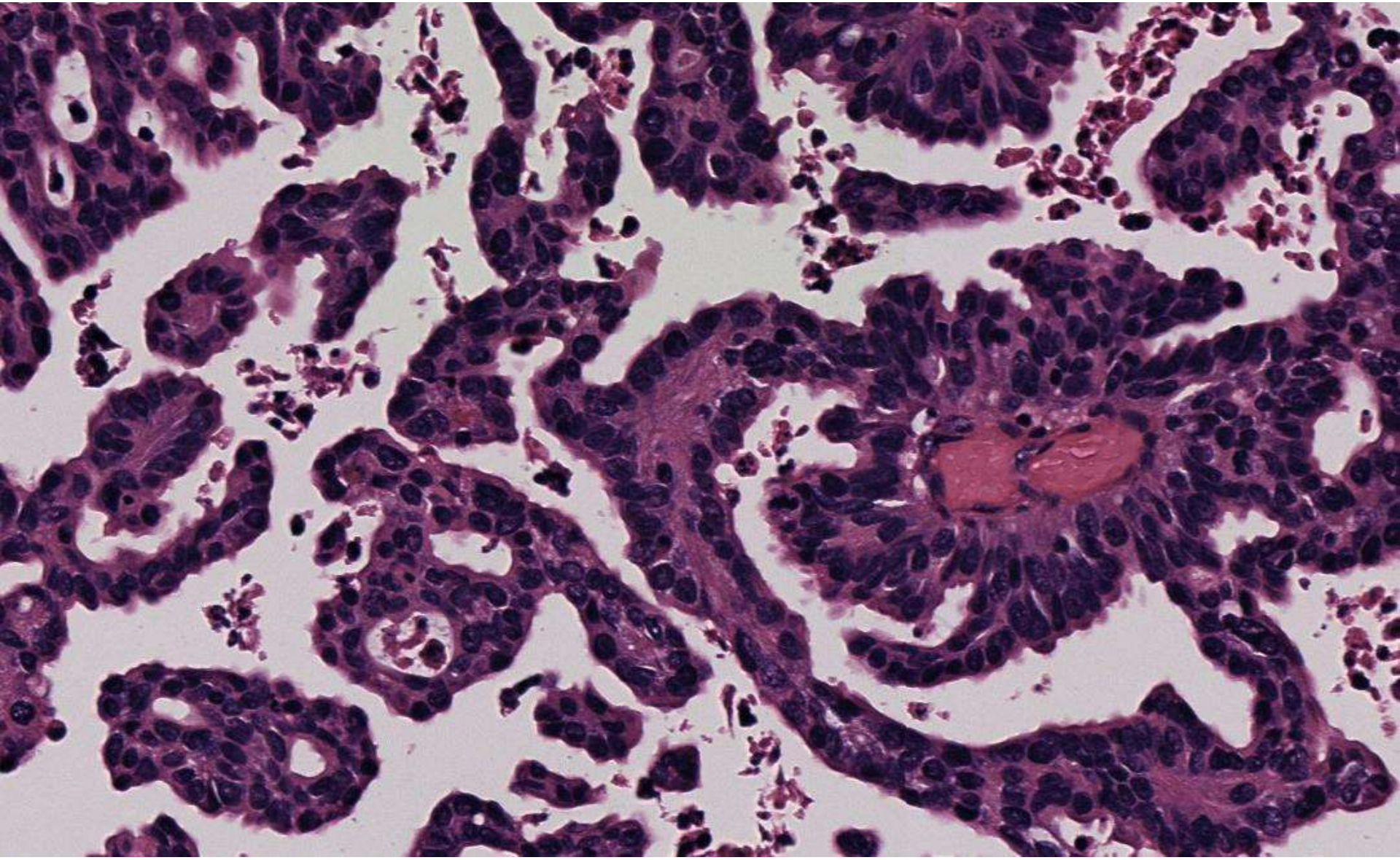




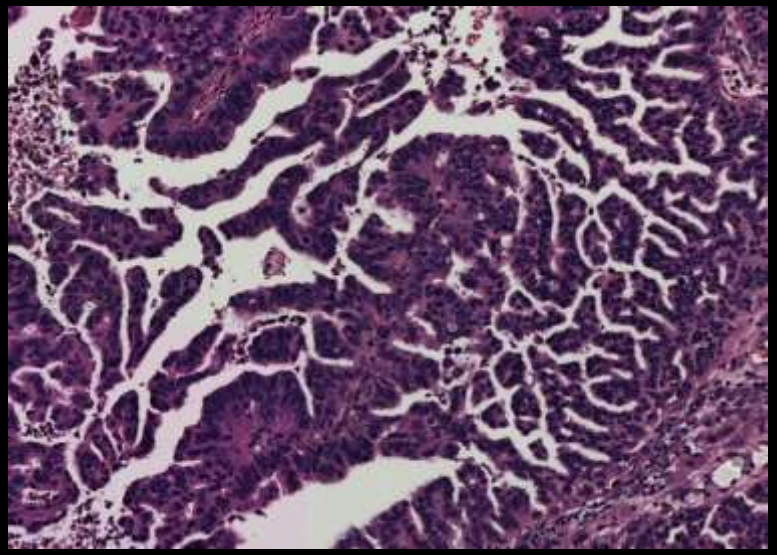


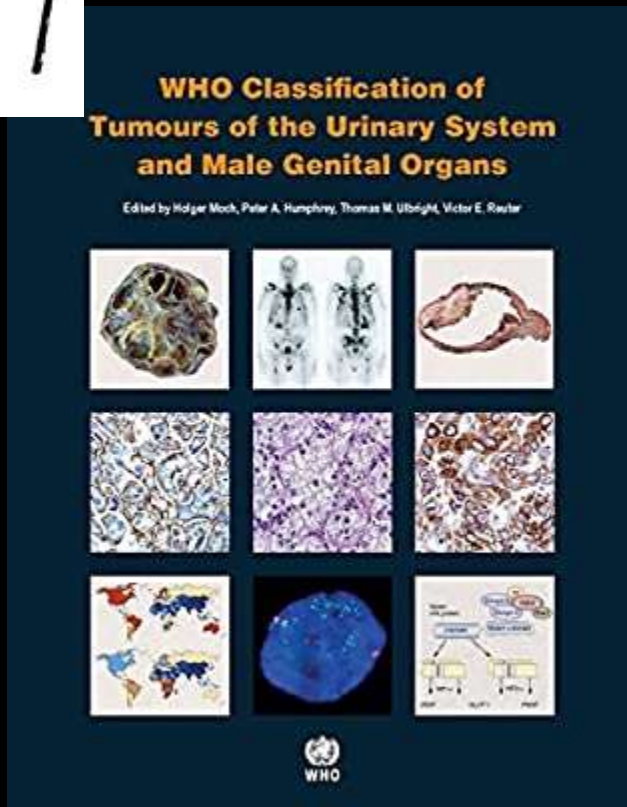




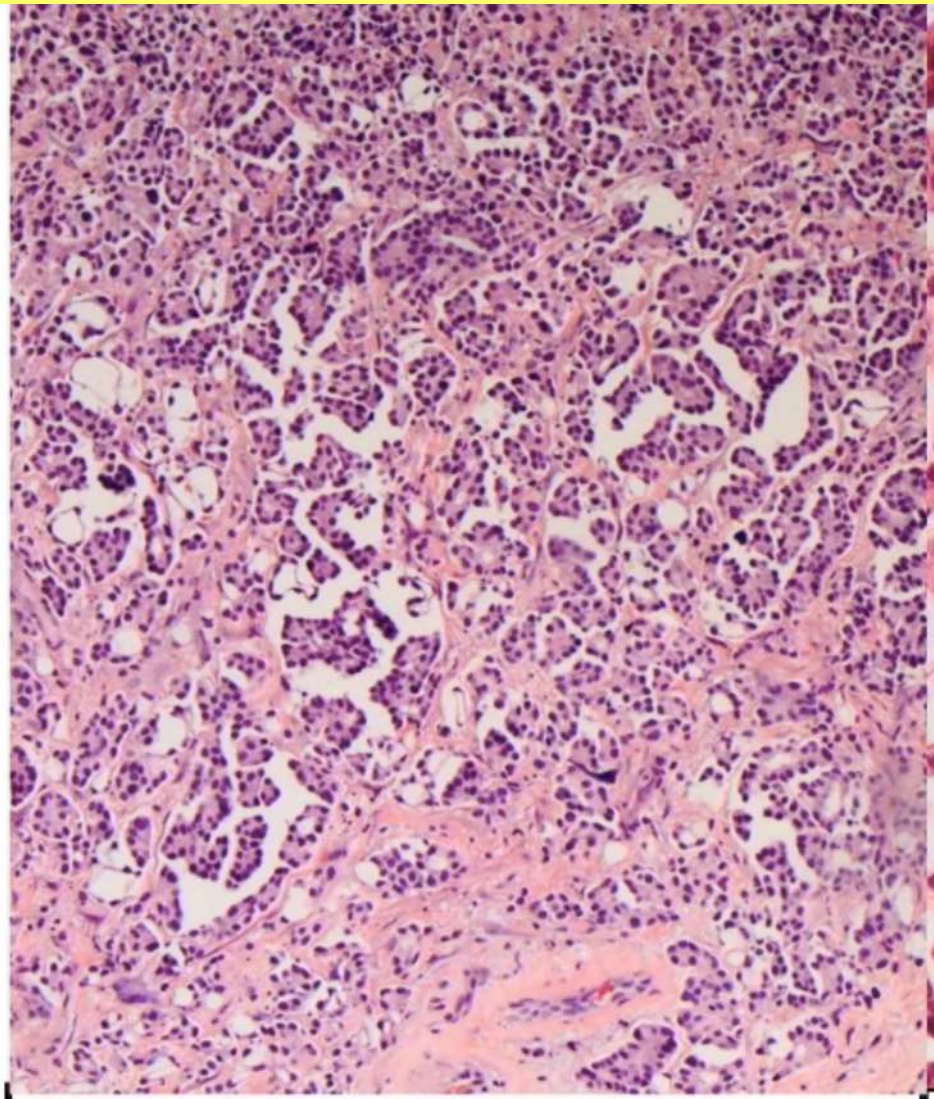


Micropapillary-like architecture may be seen in non-invasive papillary urothelial carcinoma. It is characterized by slender, delicate, filiform processes, rarely with fibrovascular cores. If these processes are only present in the non-invasive component, the tumour should not be classified as micropapillary carcinoma {1653}.

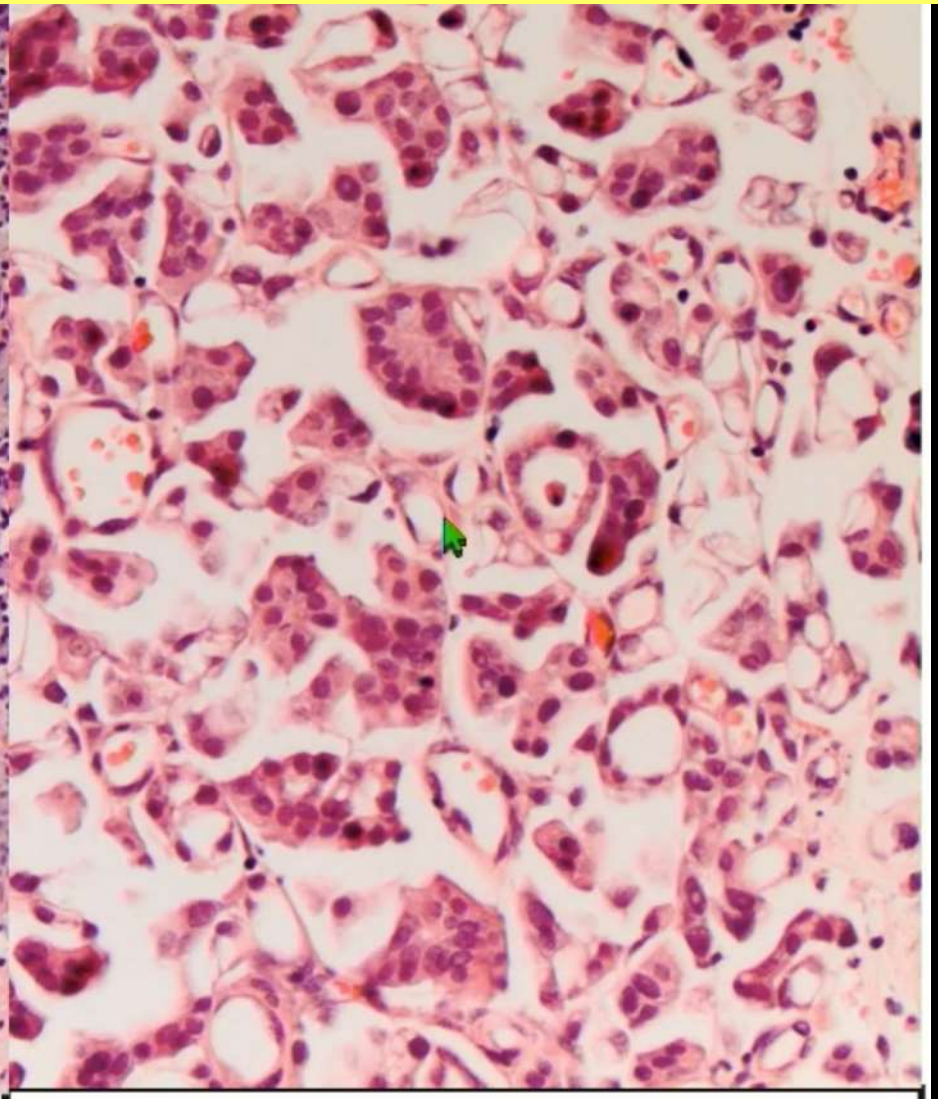




Invasive micropapillary carcinoma



Multiple nests in same lacunar space



Epithelial ring forms and back-to-back lacunae

Human Pathology (2012) 43, 2124–2128

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Original contribution

Noninvasive micropapillary urothelial carcinoma: a clinicopathologic study of 18 cases

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Received 31 March 2012; revised 16 April 2012; accepted 18 April 2012

Keywords:
Bladder;
Micropapillary carcinoma;
Urothelial carcinoma

Summary Noninvasive micropapillary urothelial carcinoma consists of slender tufts of urothelial carcinoma lacking fibrovascular cores analogous to ovarian papillary serous tumors of borderline malignancy. Eighteen noninvasive micropapillary urothelial carcinoma cases were identified from the Pathology Department of The Johns Hopkins Hospital (2000-2011). Patients lacked history of invasive urothelial carcinoma. Two patterns of noninvasive micropapillary urothelial carcinoma were identified: (1) as a variant of noninvasive high-grade papillary urothelial carcinoma (high-grade papillary urothelial carcinoma/micropapillary urothelial carcinoma) (n = 13 cases) and (2) as a variant of urothelial carcinoma in situ (carcinoma in situ/micropapillary urothelial carcinoma) (n = 5 cases with 2 of these patients also having high-grade papillary urothelial carcinoma/micropapillary urothelial carcinoma). Of 18 patients, 16 (88%) were male with a mean age of 71.8 years (range, 54-87 years). Of the 12 patients initially treated with surveillance, Bacillus-Calmette Guérin, or intravesical chemotherapy, 4 did not recur and were without evidence of disease at 6, 21, 24, and 39 months. Four patients experienced recurrences with 3 of them without evidence of disease at 36, 52, and 72 months and with the fourth whose last follow-up was at 84 months when recurrence occurred. One patient is alive at 11 months with disease, and 1 died of other causes at 1 month. Two patients progressed to pT2 and pT3 disease at 5 and 21 months, respectively. It is critical to differentiate and clearly specify in pathology reports whether micropapillary urothelial carcinoma is invasive or noninvasive because invasive micropapillary urothelial carcinoma is an aggressive disease with a high degree of understaging, whereas some cases of noninvasive micropapillary urothelial carcinoma are not necessarily associated with an adverse outcome.

Histopathology. 2020 May 22. doi: 10.1111/his.14161. Online ahead of print.

Non-Invasive Papillary Urothelial Carcinoma with "Micropapillary" Architecture: Clinicopathologic Study of 18 Patients Emphasizing Clinical Outcomes

Ankur R Sangoi [1], Roni M Cox [2], John P Higgins [3], Charles M Quick [4], Jesse K McKenney [2]

Affiliations + expand

PMID: 32443178 DOI: 10.1111/his.14161

Abstract

Aim: Invasive micropapillary carcinoma is a recognized aggressive urothelial carcinoma variant. One prior study focusing on non-invasive (pTa) high grade papillary urothelial carcinoma with micropapillary architecture has been reported.

Methods and results: We collected bladder transurethral resection specimens showing non-invasive high grade papillary urothelial carcinoma with non-hierarchical secondary papillae lacking fibrovascular cores (i.e. micropapillary architecture). Cases with any invasive component or any prior history of invasive urothelial carcinoma were excluded. 20 cases were identified from 16 male and 2 female patients (ages 55-86 years). Micropapillary architecture comprised from 10%-95% (mean 31%), but non-invasive cribriform [15 cases (comprising 5-60%, mean 19%) and villoglandular patterns [9 cases (comprising 5-60%, mean 24%) were commonly admixed. Treatment data were available for 16 patients: surveillance (n=13), cystoprostatectomy (n=1), BCG plus mitomycin (n=1), and BCG (n=1). Follow-up data was available from 16 patients (range 1-128 months, mean 50 months): 13 patients had no new occurrences to date (81%), 2 had stage progression to pT1 papillary urothelial carcinoma (13%) with one dieing of other causes, and 1 died of other causes with no evidence of disease (6%).

Conclusion: Non-invasive urothelial carcinomas with micropapillary architecture are often admixed with non-invasive cribriform and villoglandular patterns. Stage progression to lamina propria invasion in only 2 of 16 patients (13%) is not higher than expected for otherwise typical pTa high grade urothelial carcinomas and no progression to invasive micropapillary carcinoma was identified, adding further support to the current World Health Organization recommendation excluding use of the term "micropapillary" for pTa urothelial carcinoma.

TABLE 1. Clinicopathologic Features of Non-Invasive Papillary Urothelial Carcinoma with "Micropapillary" Architecture

CASE#	AGE	SEX	% MPC*	%CRIB^	%VG"	PRESENTATION	TREATMENT	CLINICAL F/U (MONTHS)
1#	86	M	25	5	0	Hematuria	surveillance	NED (102)
2#	86	M	60	0	0	Residual tumor	surveillance	NED (101)
3	70	M	40	30	30	Recurrent bladder tumor	surveillance	progressed to pT1 (12m); died other disease (47)
4	75	M	15	5	0	Hematuria	BCG+mitomycin	NED (49)
5	83	M	70	20	5	Hematuria	BCG	died other disease (12)
6	68	M	15	0	0	Not available	unknown	none
7	55	M	10	30	60	Not available	surveillance	NED (60)
8	56	M	10	60	20	Recurrent bladder tumor	surveillance	NED (128)
9	58	M	15	0	0	Hematuria	surveillance	NED (121)
10	68	M	95	5	0	Incidental bladder mass on CT	surveillance	NED (35)
11	57	M	40	10	0	Hematuria	Cystoprostatectomy$	NED (75)
12	72	M	50	0	0	Hematuria	surveillance	NED (30)
13	82	M	10	0	15	Hematuria	surveillance	progressed to pT1 (3)
14	80	M	50	0	0	Bladder tumor	unknown	none
15&	68	F	20	5	20	Bladder tumor	surveillance	NED (17)
16&	69	F	30	5	30	Bladder tumor	surveillance	NED (3)
17	61	M	20	5	0	Bladder tumor	surveillance	NED (67)
18	93	M	15	5	0	Bladder tumor	surveillance	NED (41)
19	81	M	10	60	10	Bladder tumor	surveillance	NED (9)
20	60	M	25	25	25	Bladder tumor	surveillance	NED (1)

Sangoi AR, Cox RM, Higgins JP, Quick CM, McKenney JK. Non-Invasive Papillary Urothelial Carcinoma with "Micropapillary" Architecture: Clinicopathologic Study of 18 Patients Emphasizing Clinical Outcomes [published online ahead of print, 2020 May 22]. *Histopathology*.

pTa with "micropapillary" features

- **Behavior similar to traditional pTa PUC**
- **Not precursor to invasive MPC**
- **Avoid using "micropapillary" at all in path report!**

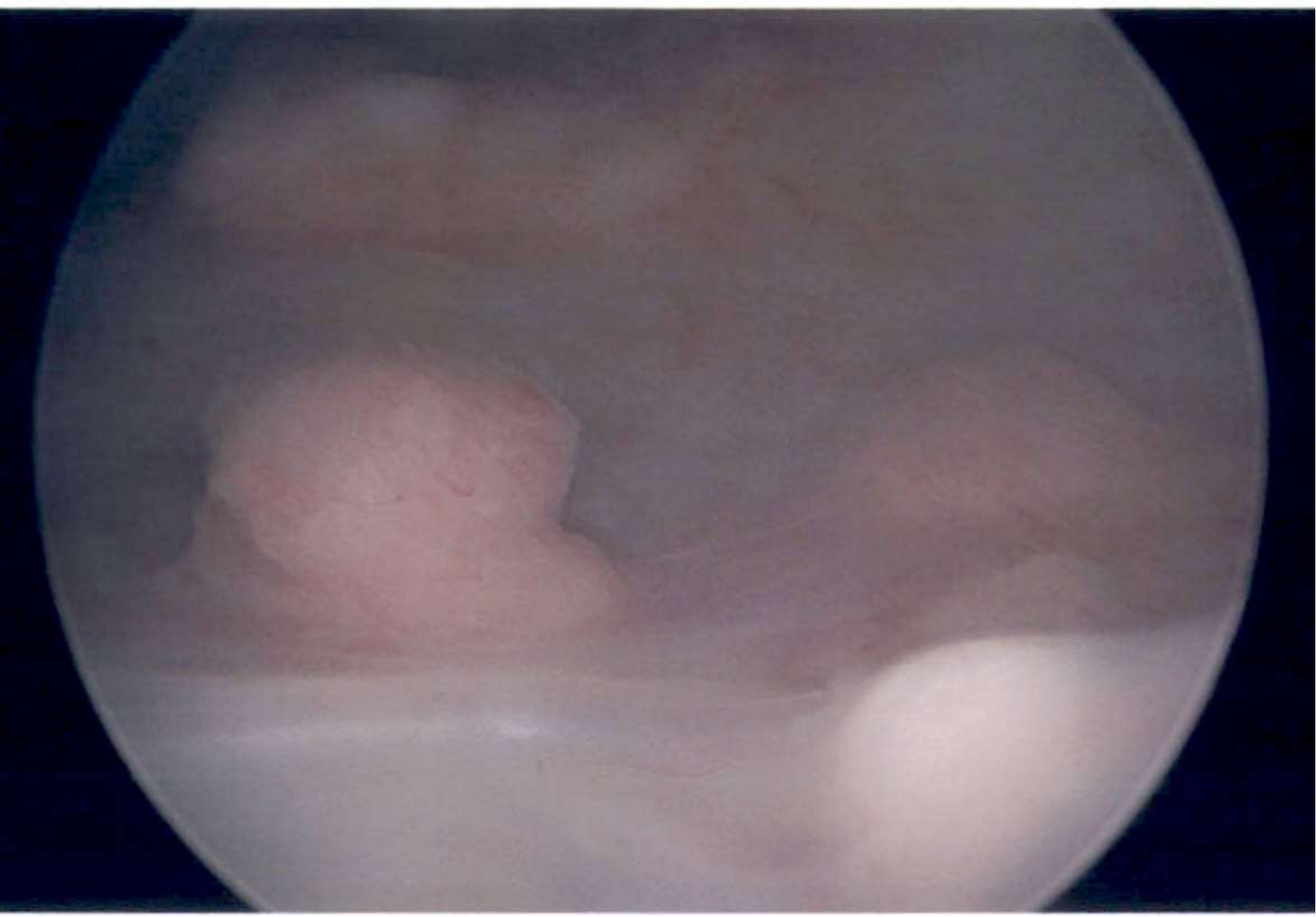
Invasive MPC

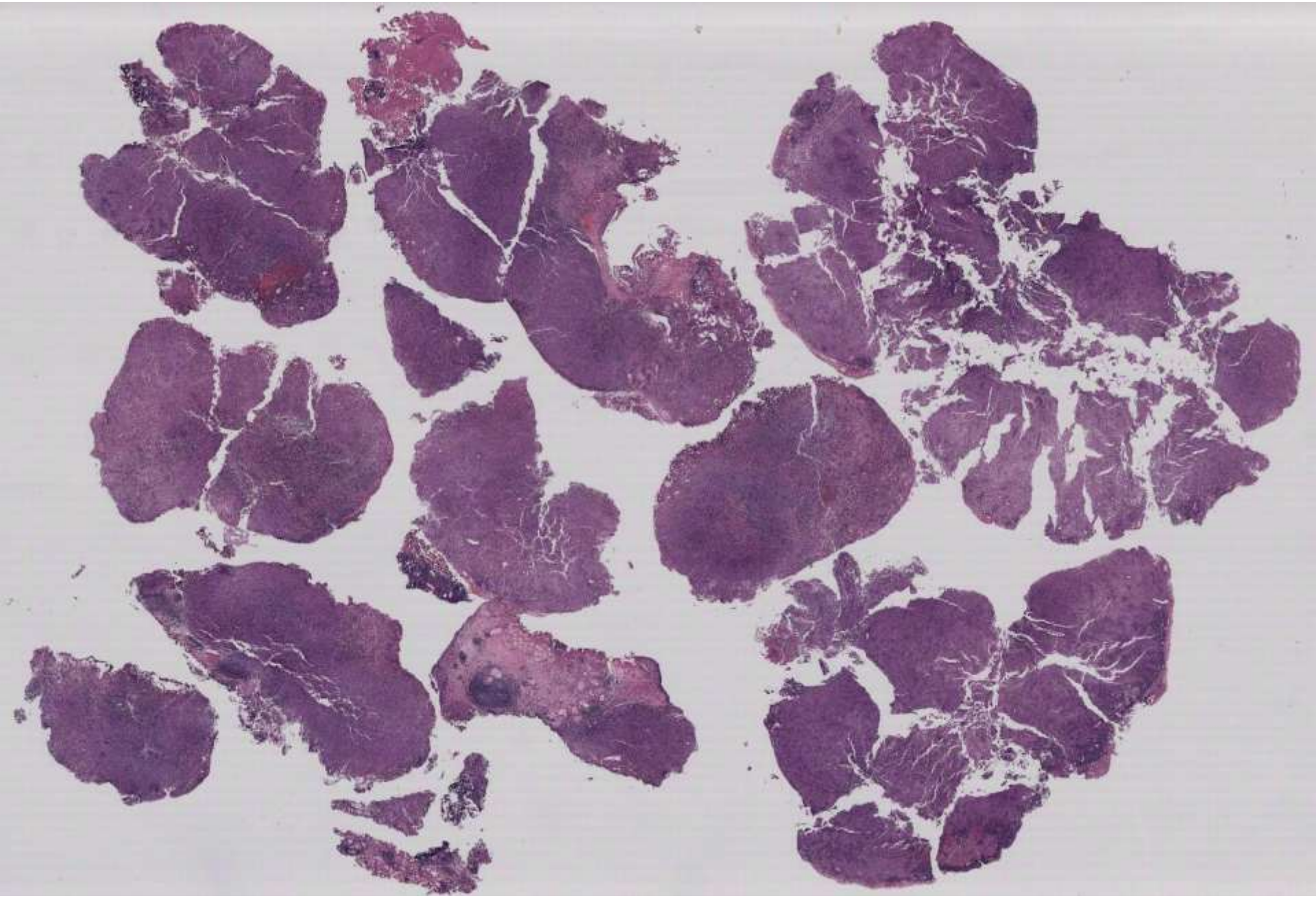
- **Poor prognosis**
- **High stage**
  - Often under-staged at TURBT
  - Consider radical cystectomy for non-muscle inv disease

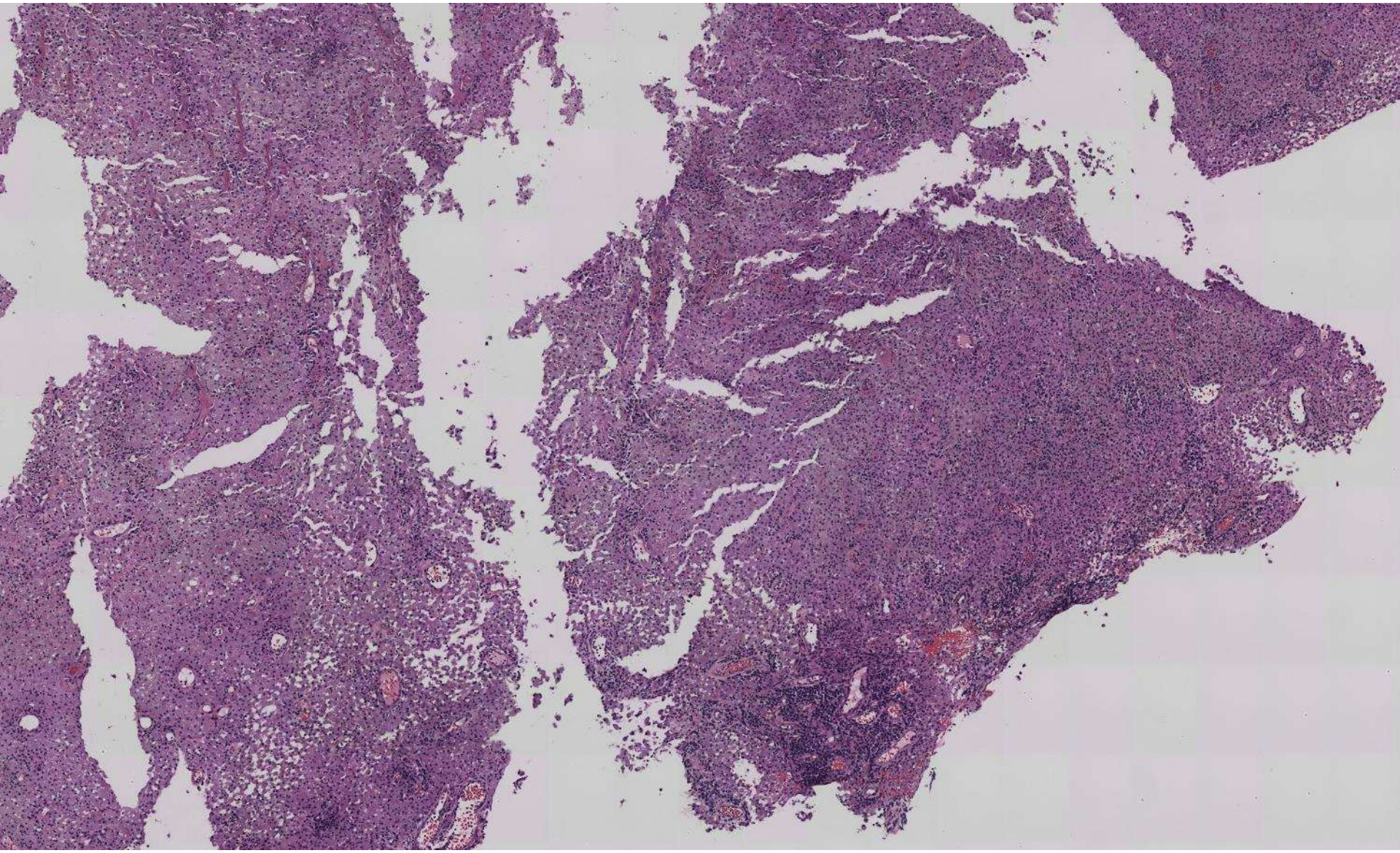
20-0808
scanned slide available!

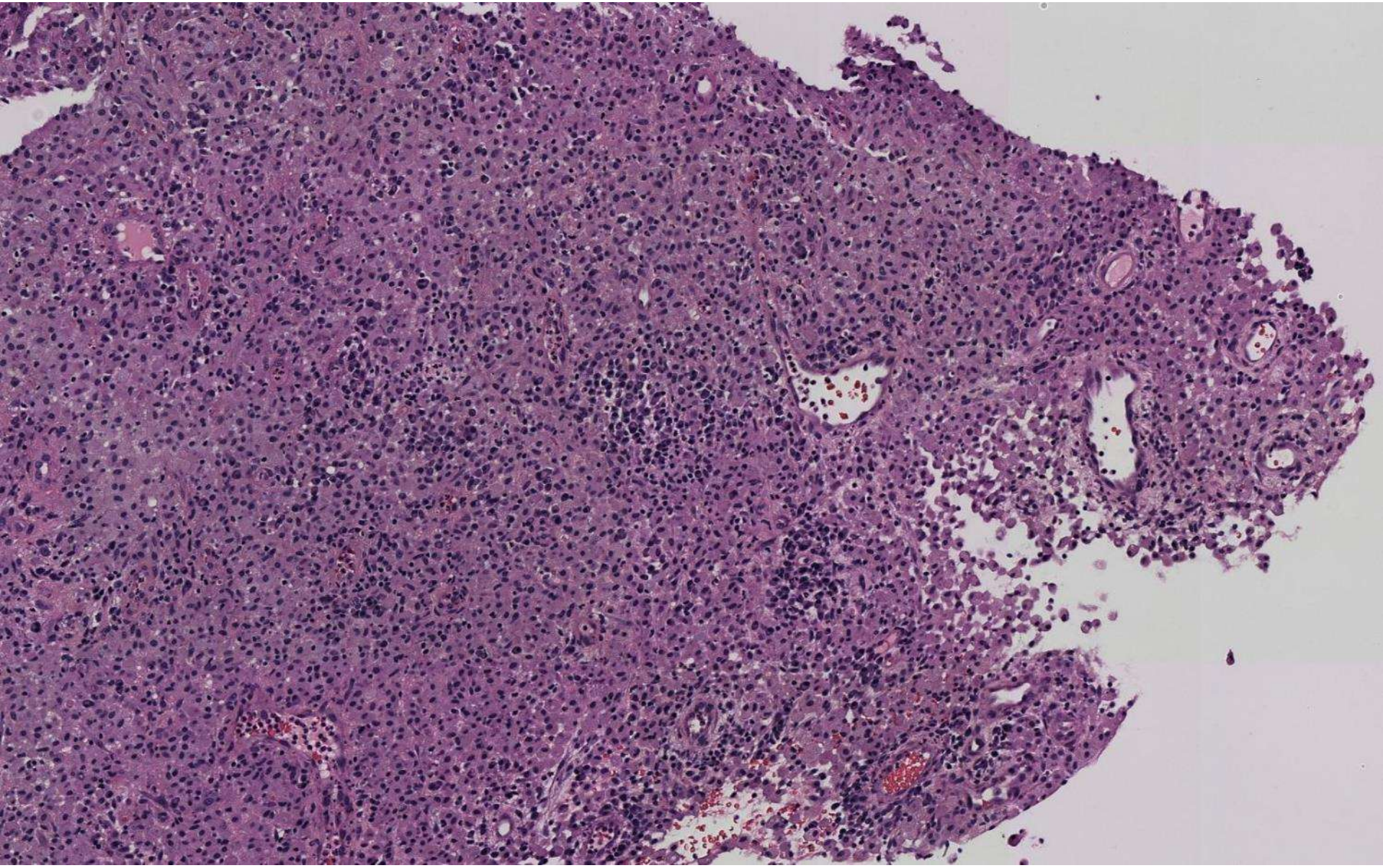
Ankur Sangoi; El Camino Hospital

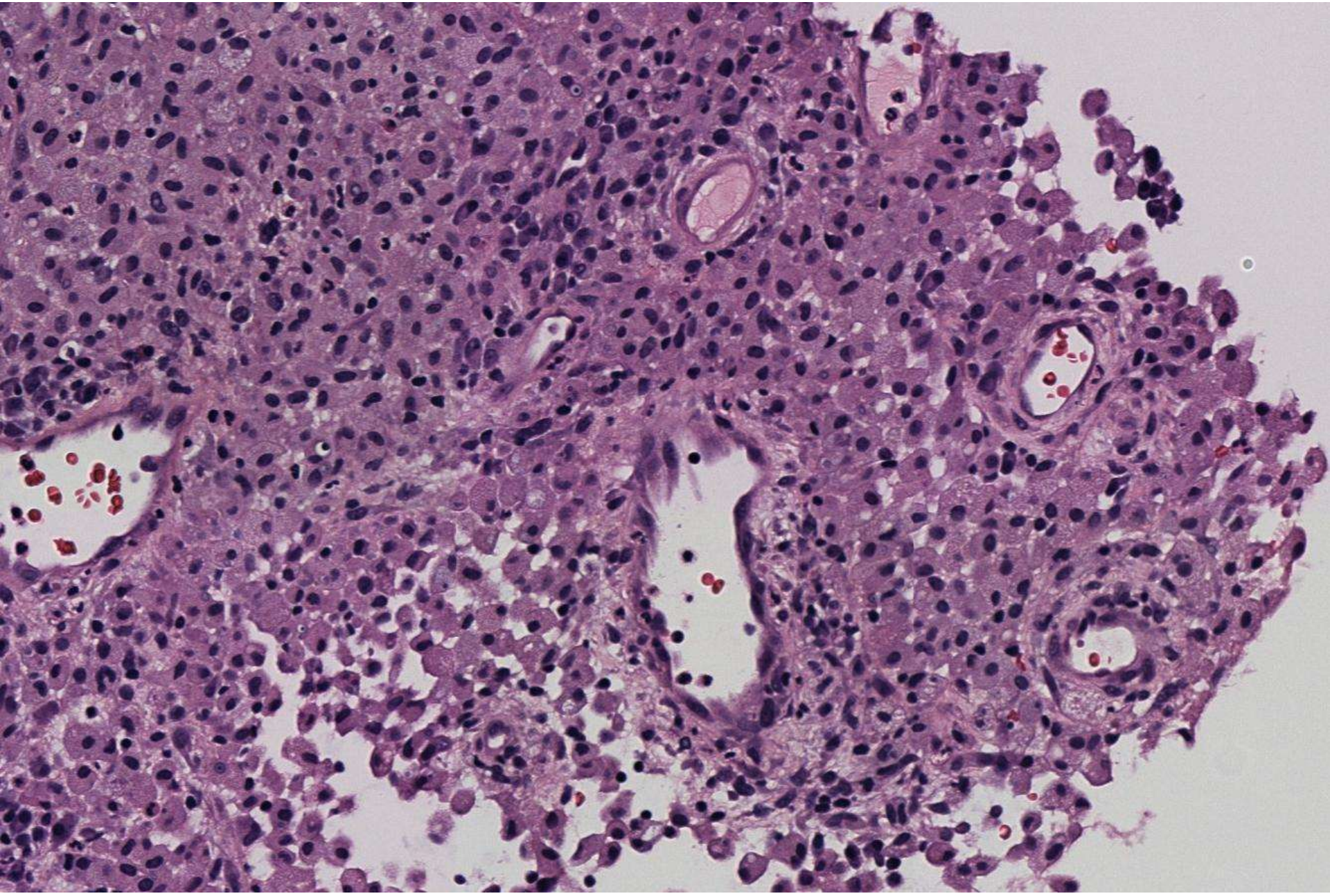
Middle-aged F with bladder tumor, TURBT performed.

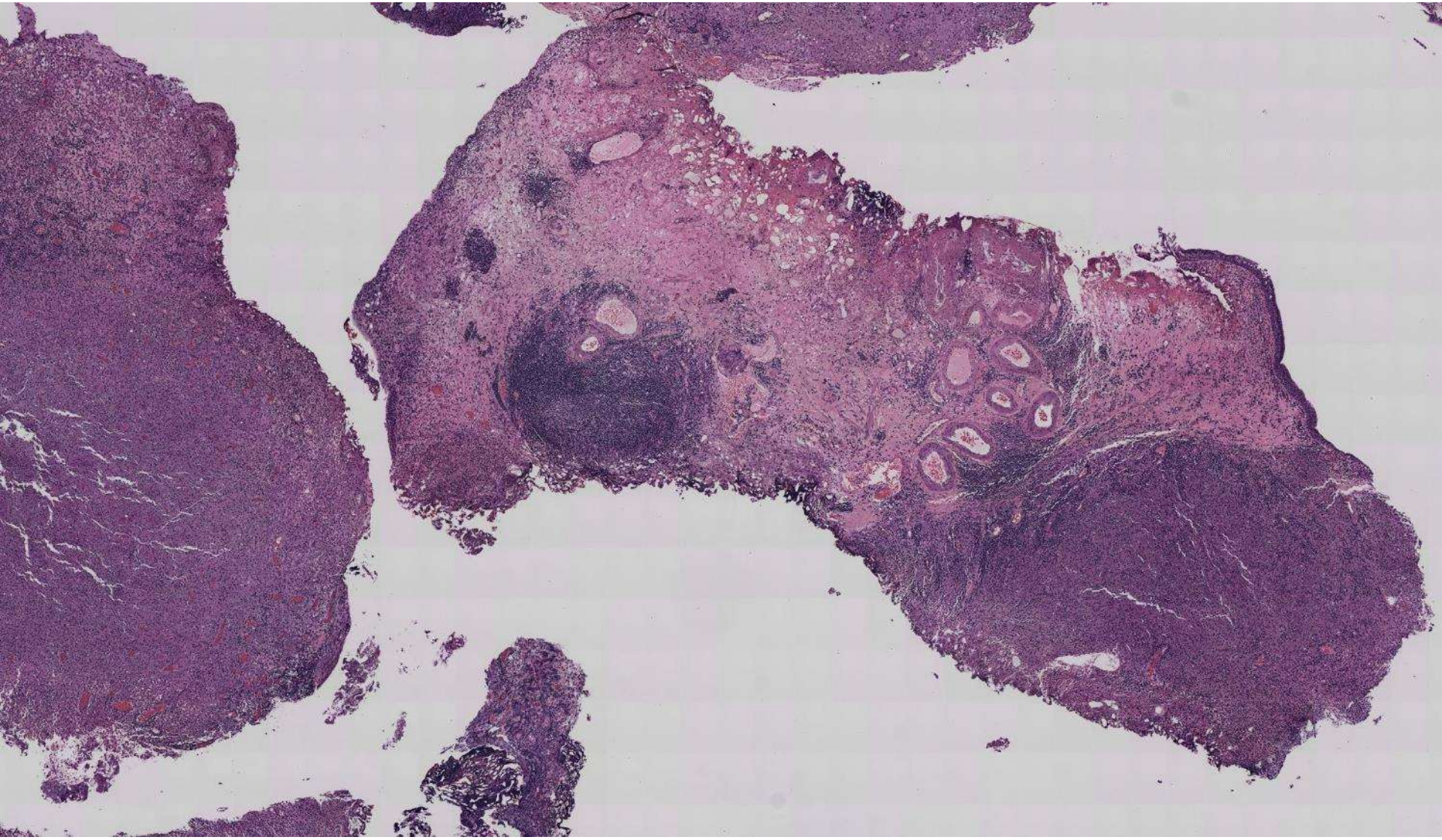


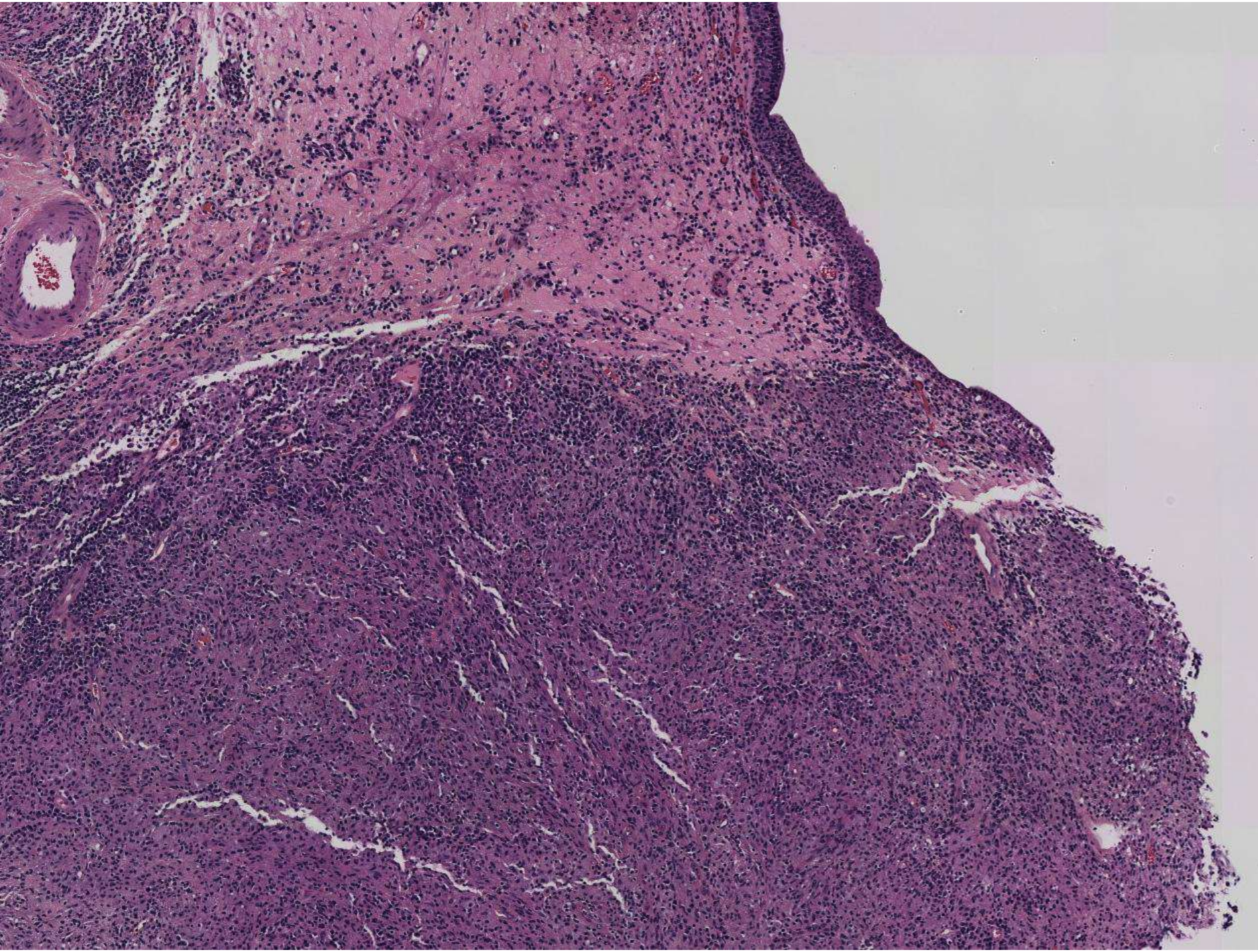


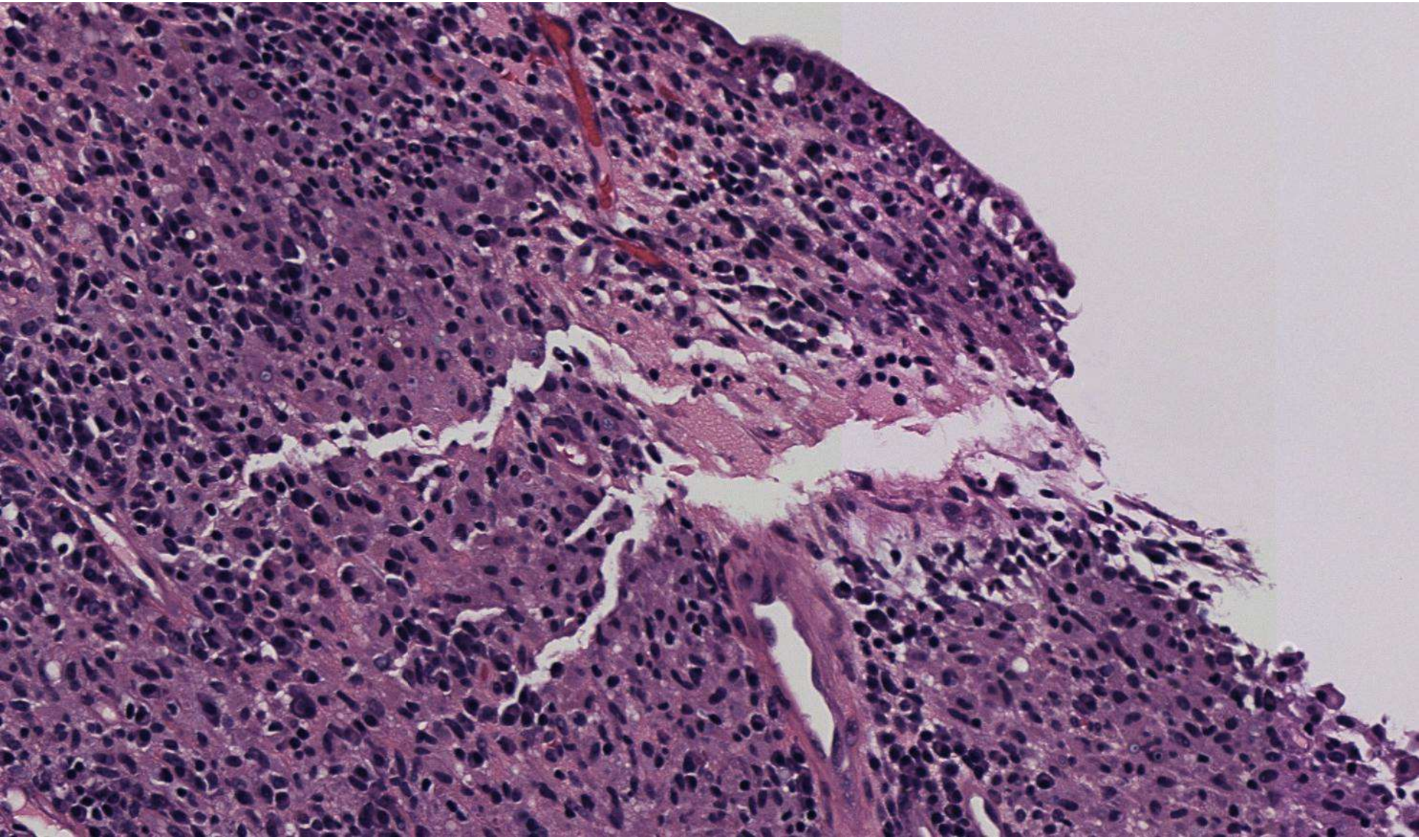


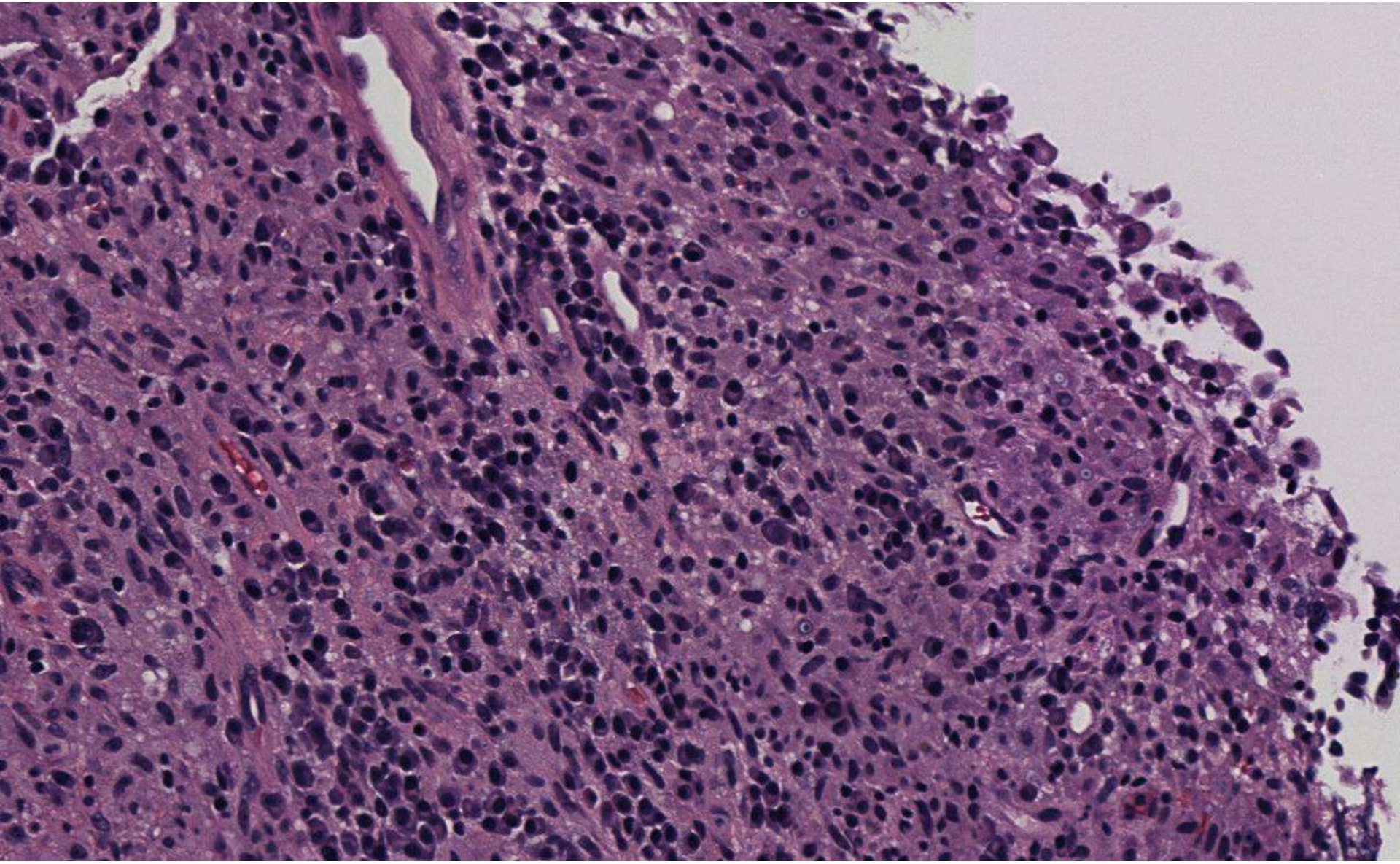


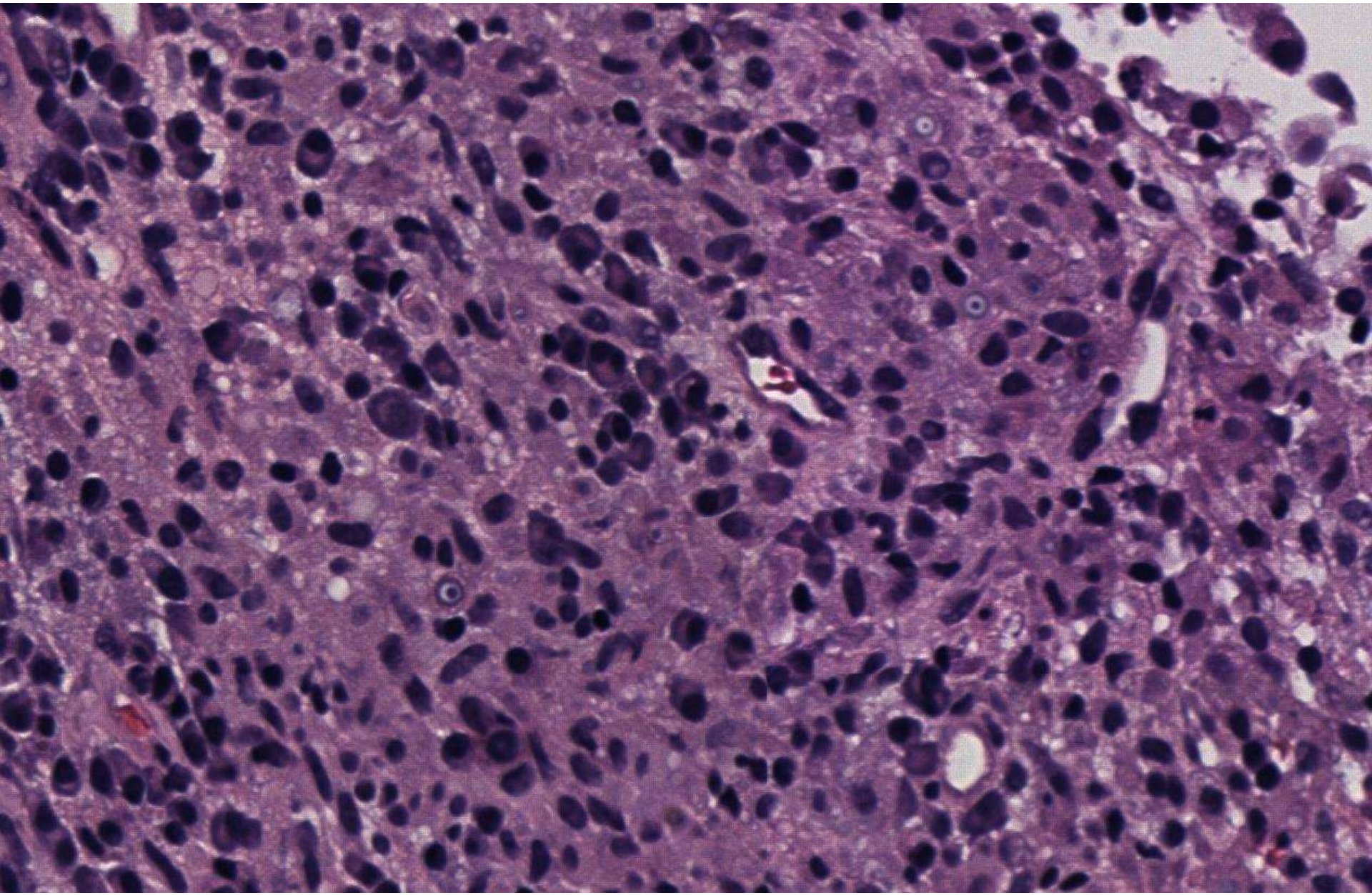


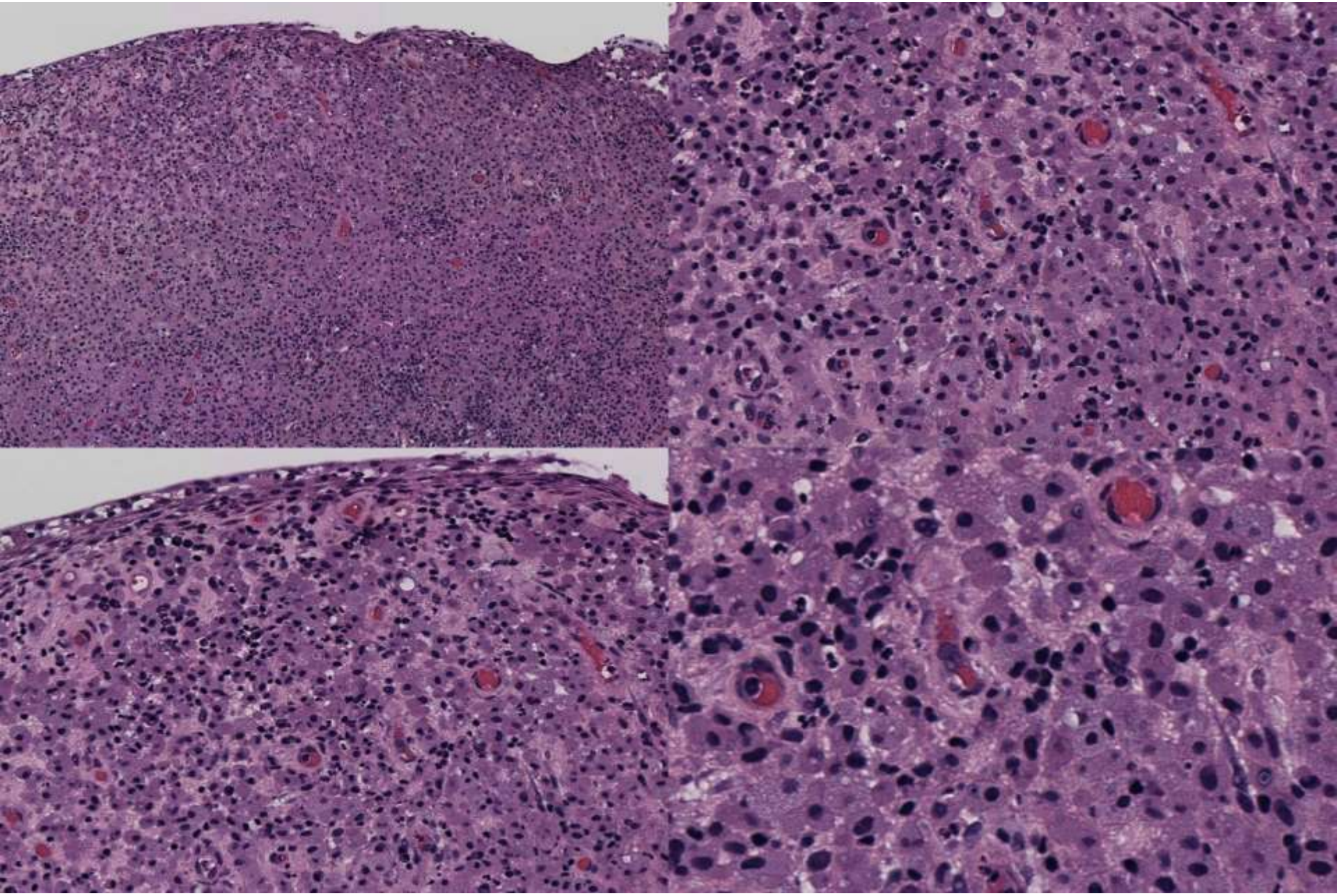


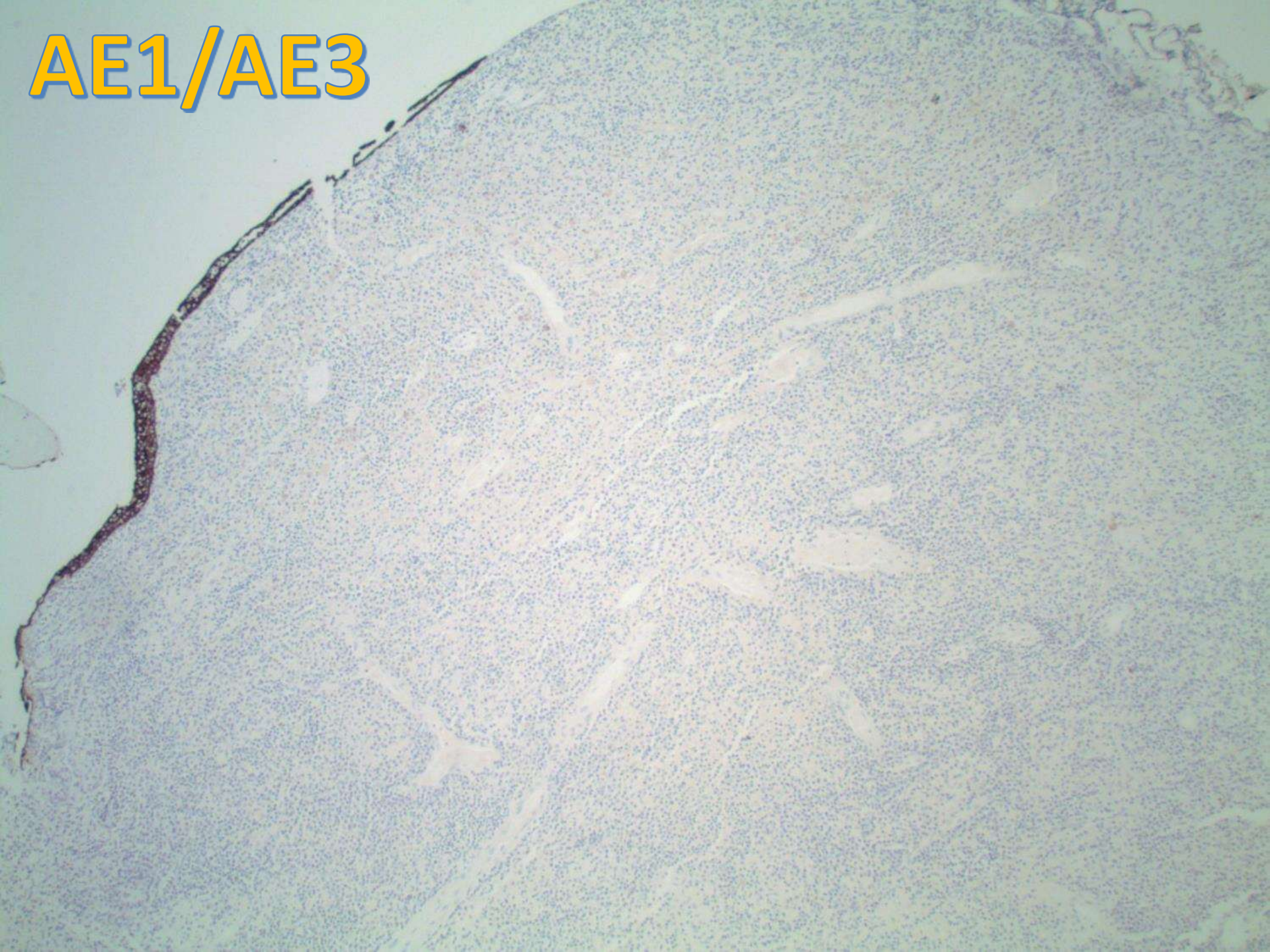


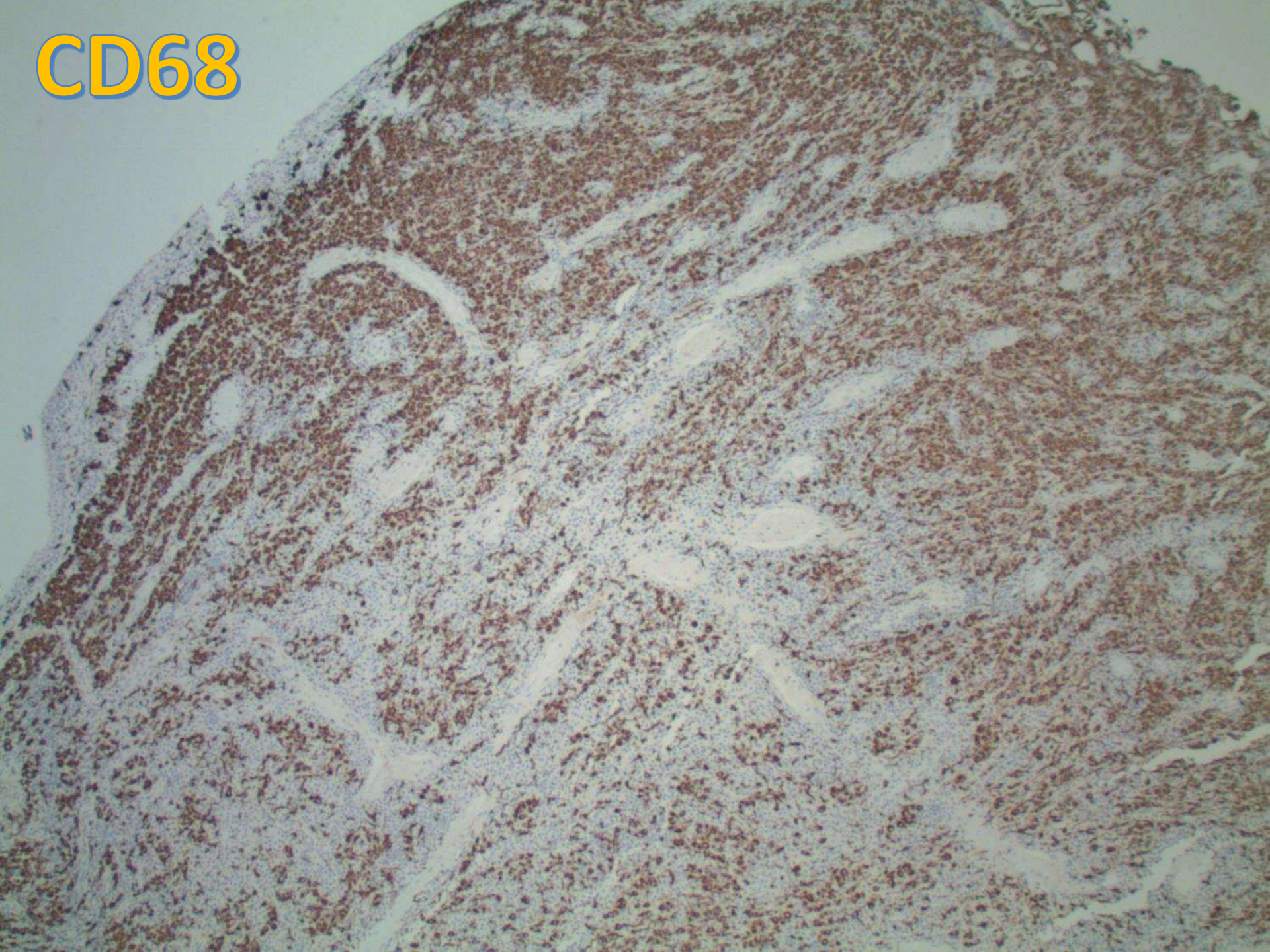









AE1/AE3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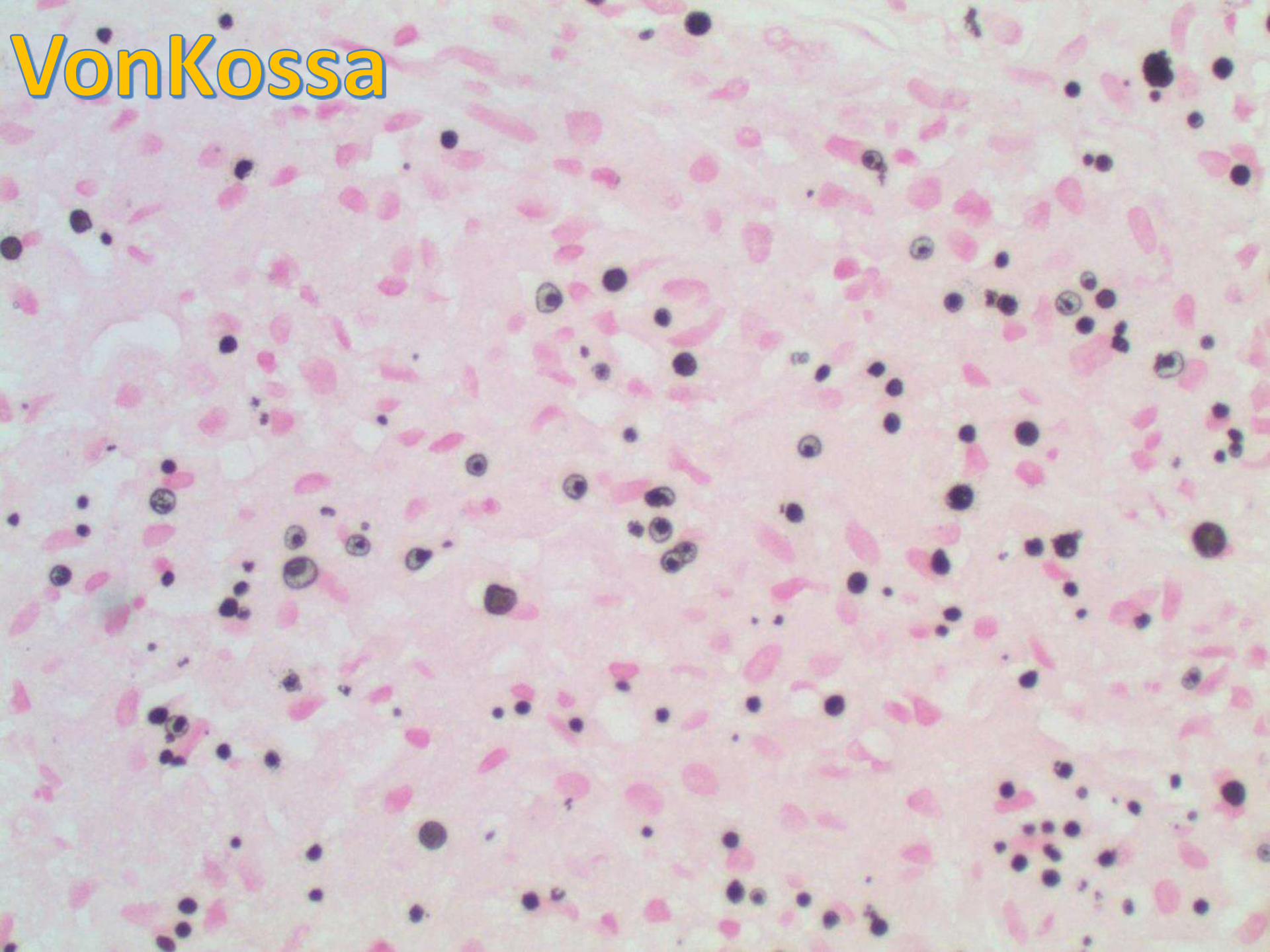
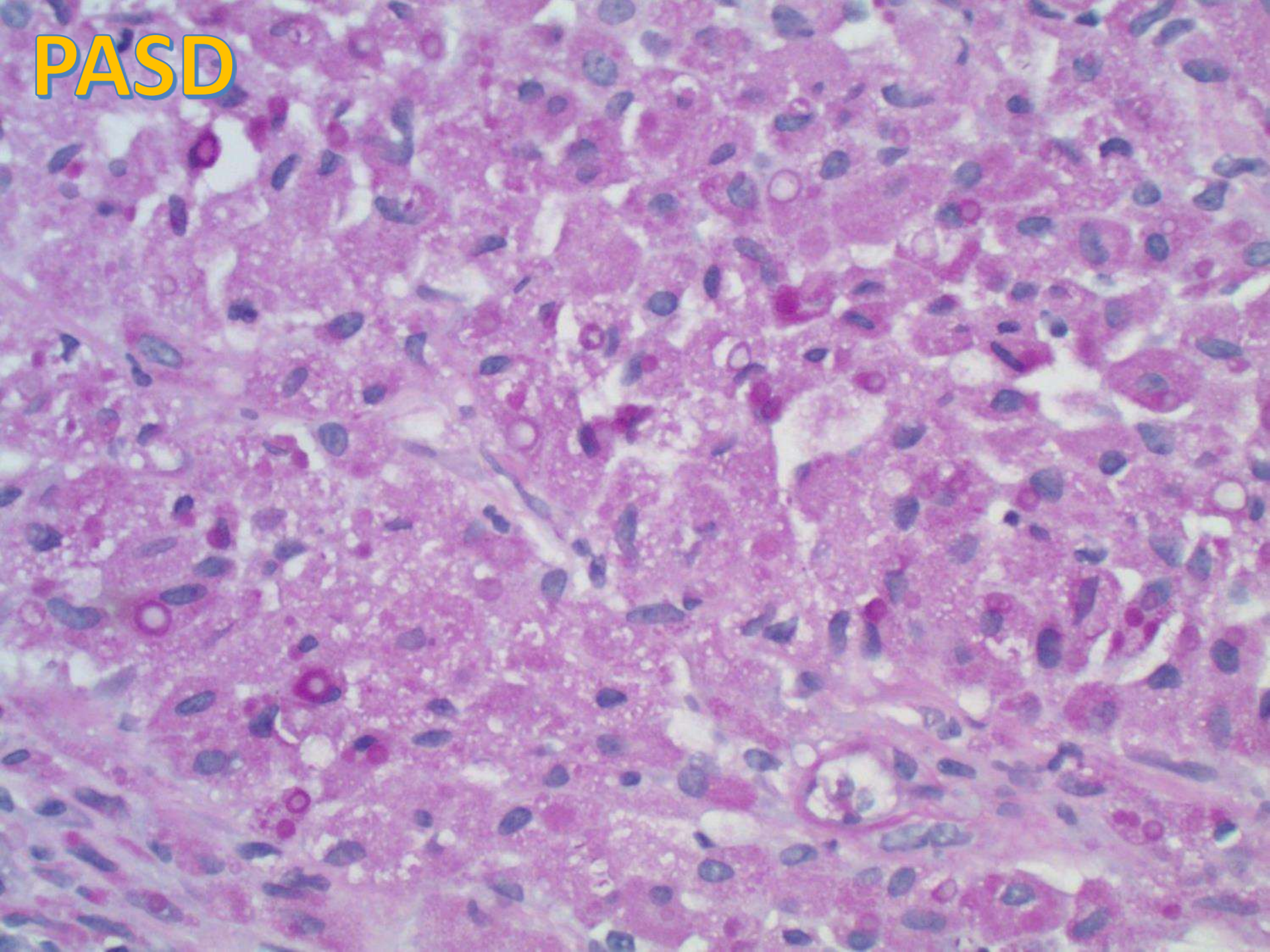

VonKossa


PASD

DDx

- Papillary urothelial carcinoma
- Prostatic adenocarcinoma
- Histiocytic sarcoma
- Myeloid sarcoma
- Extranodal Rosai-Dorman disease
- Malakoplakia

Malakoplakia

"malakos" (soft)
"plakos" (plaque)

- **Uncommon histiocytic disease that occurs in all organs**
  - Frequently: GU tract (esp bladder)
  - Defective phagocytic response to Gram neg organisms (usually E.coli)
  - Intracellular deposition of iron & calcium
    - Michaelis-Gutmann bodies (VK or PAS+)
- **Often misDx clinically as malignant**