Disclosures
June 3, 2020

Dr. Ankur Sangoi has disclosed a financial relationship with Google (consultant). Dr. Joe Rabban has disclosed a financial relationship with Merck (spouse is employee). Dr. Karen Matsukuma has disclosed a financial relationship with Diaceutics (consultant). South Bay Pathology Society has determined that these relationships are not relevant to the planning of the activity (Dr. Sangoi) or the clinical cases being presented.

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

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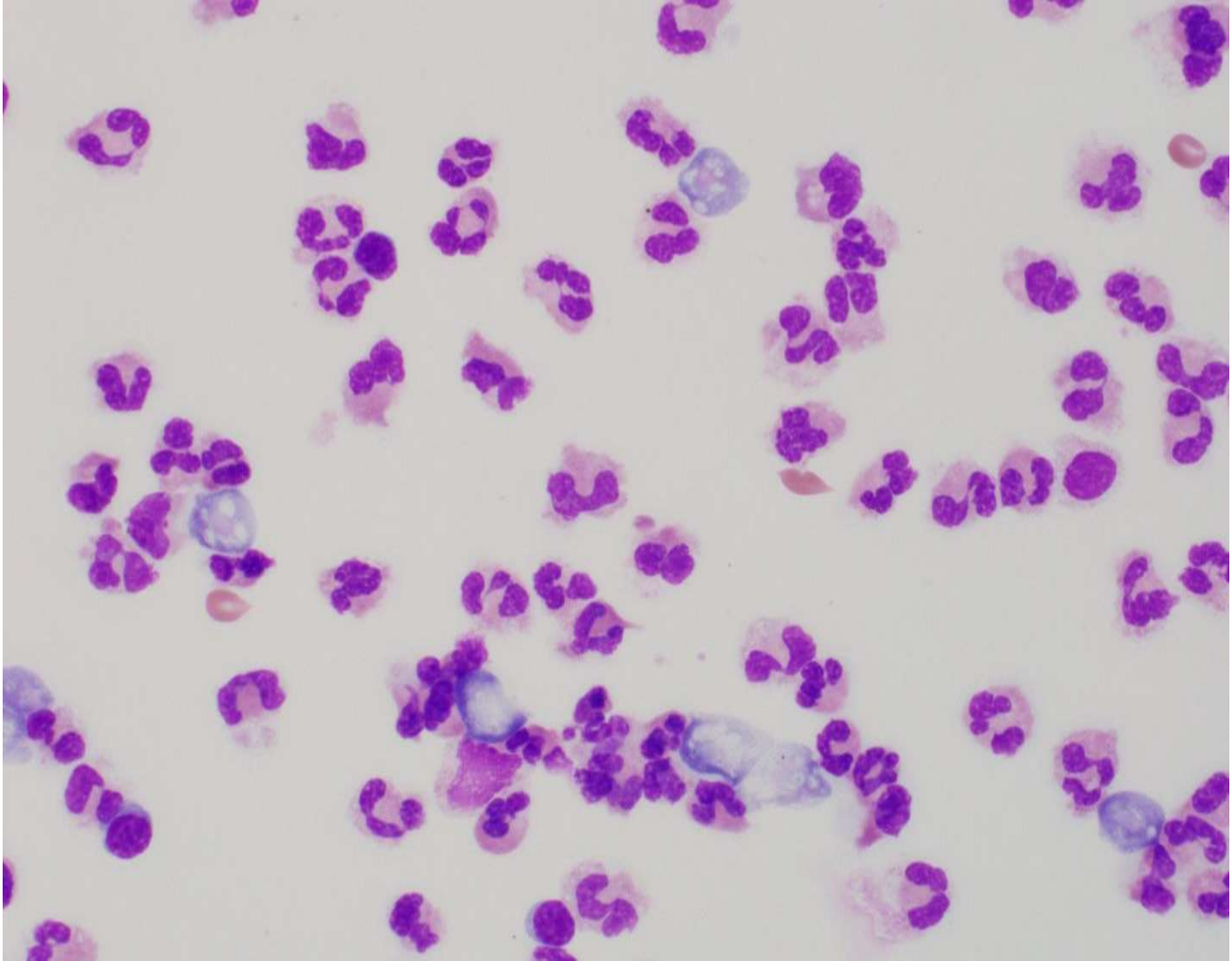
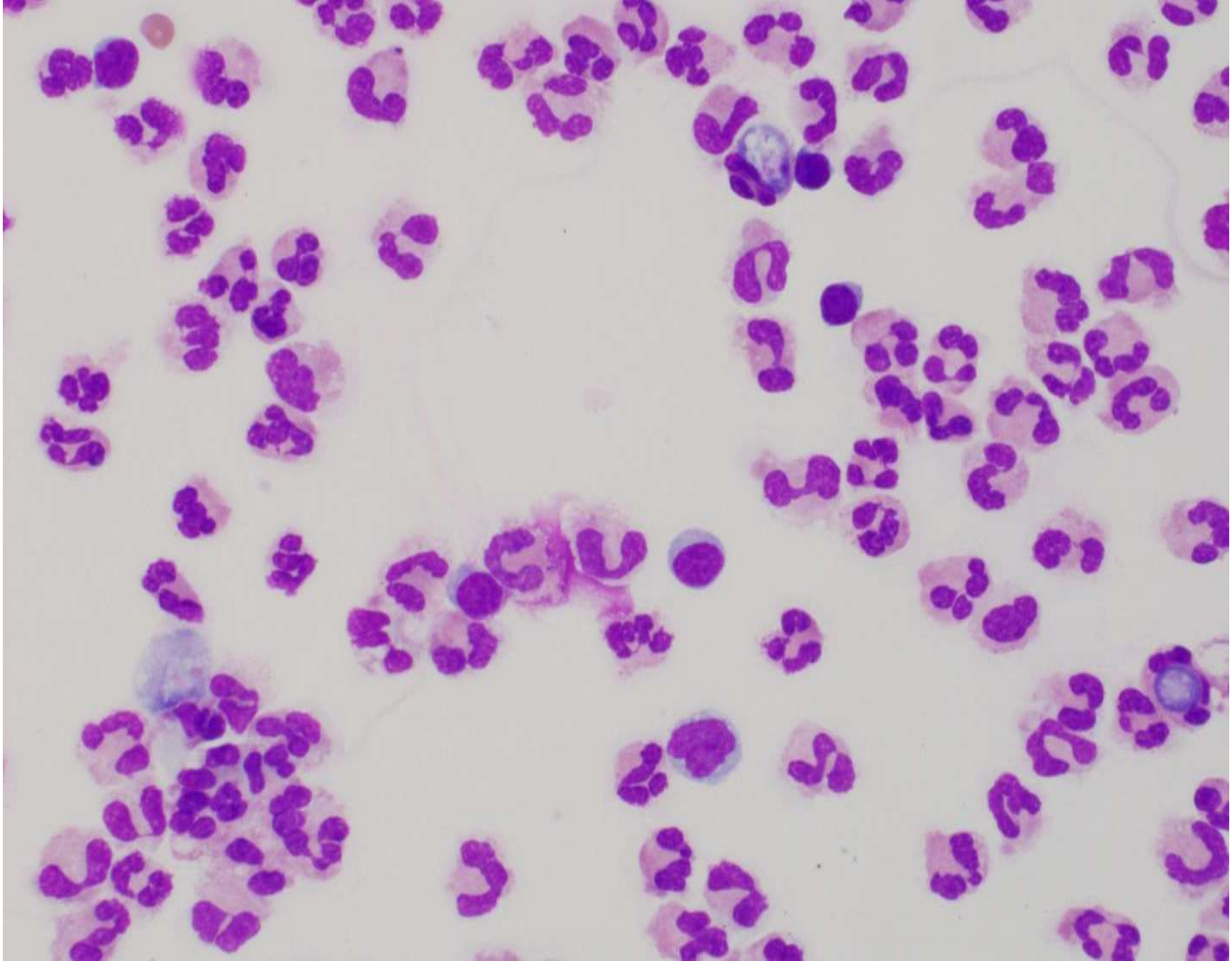
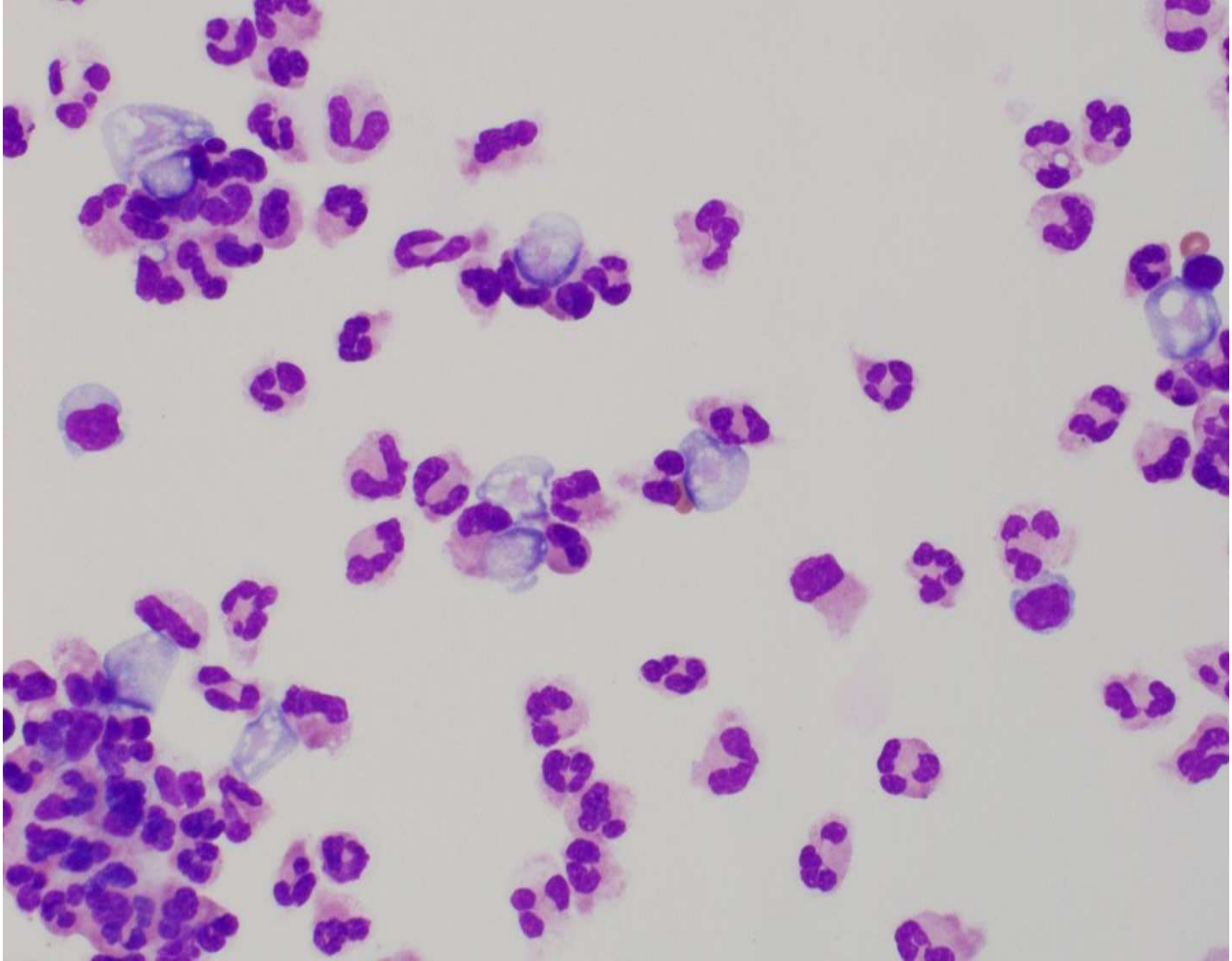
20-0601

Caroline Temmins; Santa Clara Valley Medical Center

44-year-old M with h/o left testicular MTB, status post orchiectomy and right testicular MTB, with recent trip to India and 2-hour lay-over in Hong Kong. Presents from home with 1 day of cold-like symptoms and progressive altered mental status.

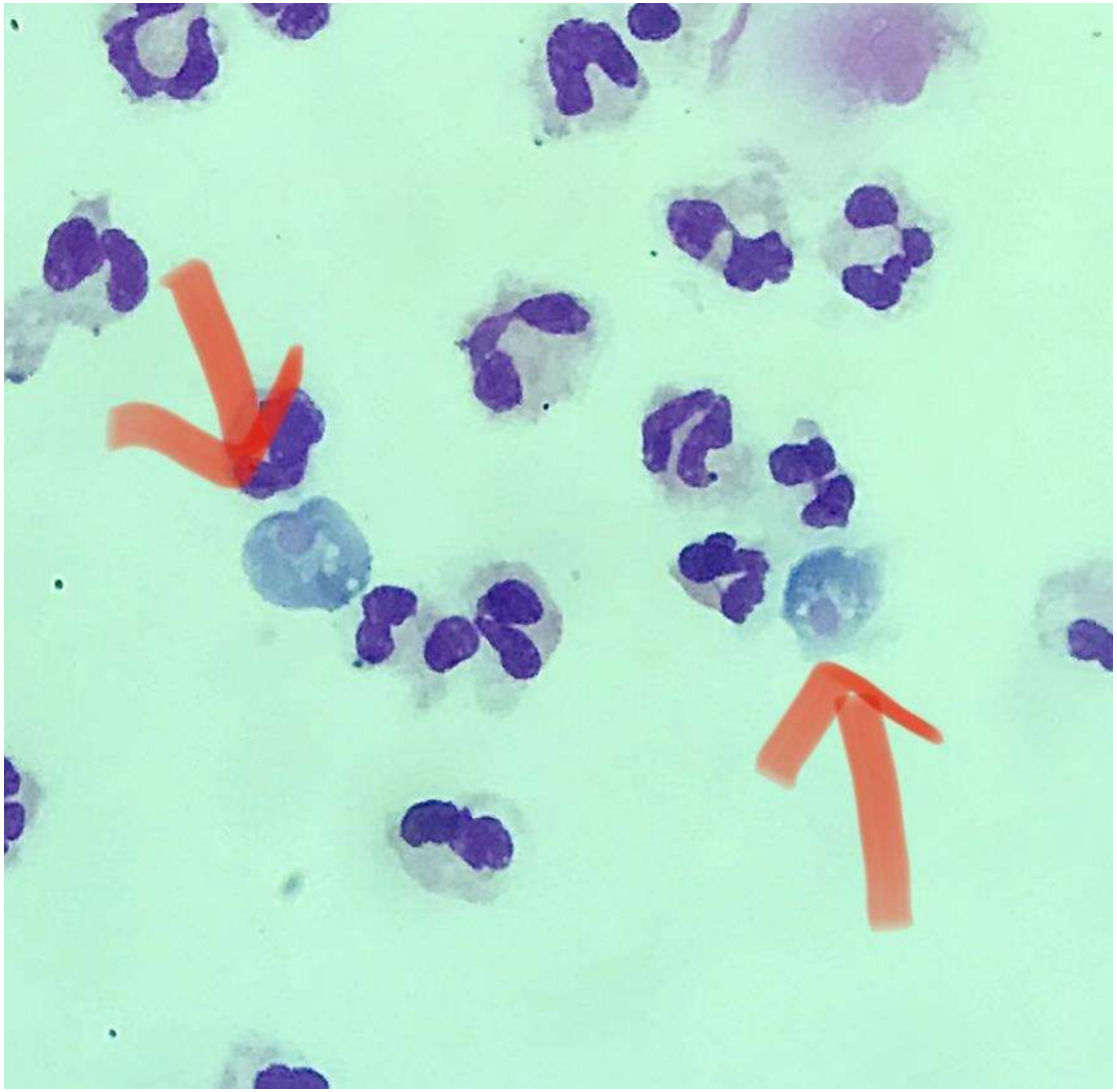






Clinical history

- 44 year old man with recent travel to India, and exposure to a swimming pool in Chennai, presented with exhaustion, progressing to encephalopathy with fevers, sore throat, and cough.
- Admitted for presumptive bacterial meningitis.
- CSF: WBC 2083 (91% neutrophils), glucose 87, protein 477, elevated OP
- Started on vancomycin, ctx, and one dose of acyclovir



Naegleria fowleri

- trophozoite is the infective stage of the amoeba. They are ~10-30um in diameter and contain a nucleus with a large, centrally placed karyosome surrounded by a halo
- Histologically, the trophozoite can be mistaken for a degenerating cell, monocyte, or macrophage

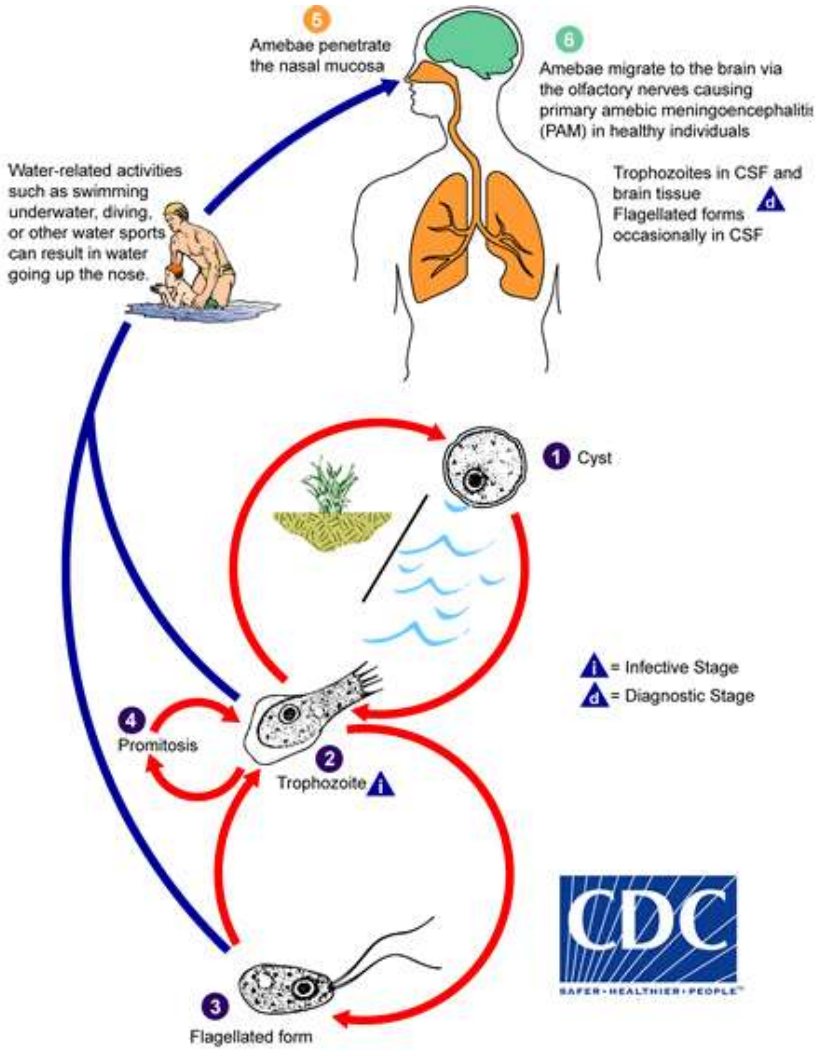
Where is it found?

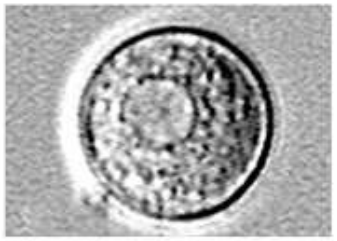
- *Naegleria fowleri* is found around the world. In the United States, the majority of infections have been caused by *Naegleria fowleri* from freshwater located in southern-tier states. The ameba can be found in:
- Bodies of warm freshwater, such as lakes and rivers
- Geothermal water, such as hot springs
- Warm water discharge from industrial plants
- Geothermal drinking water sources
- Swimming pools that are poorly maintained, minimally-chlorinated, and/or un-chlorinated
- Water heaters. *Naegleria fowleri* grows best at higher temperatures up to 115°F (46°C) and can survive for short periods at higher temperatures.
- Soil
- *Not* found in salt water, like the ocean.

How common is Naegleria fowleri infection?

- *Naegleria fowleri* infections are rare.
- In the 10 years from 2009 to 2018, 34 infections were reported in the U.S.
- Of those cases, 30 people were infected by recreational water, 3 people were infected after performing nasal irrigation using contaminated tap water, and 1 person was infected by contaminated tap water used on a backyard slip-n-slide.

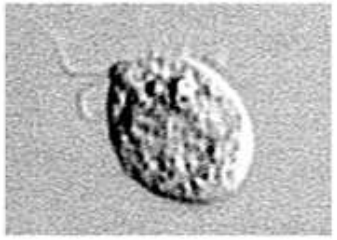
- While infections with *Naegleria fowleri* are rare, they occur mainly during the summer months of July, August, and September. Infections are more likely to occur in southern-tier states, but can also occur in other more northern states. Infections usually occur when it is hot for prolonged periods of time, which results in higher water temperatures and lower water levels.
- The fatality rate is over 97%. Only 4 people out of 145 known infected individuals in the United States from 1962 to 2018 have survived.





Cyst stage

Trophozoite stage



Flagellated stage

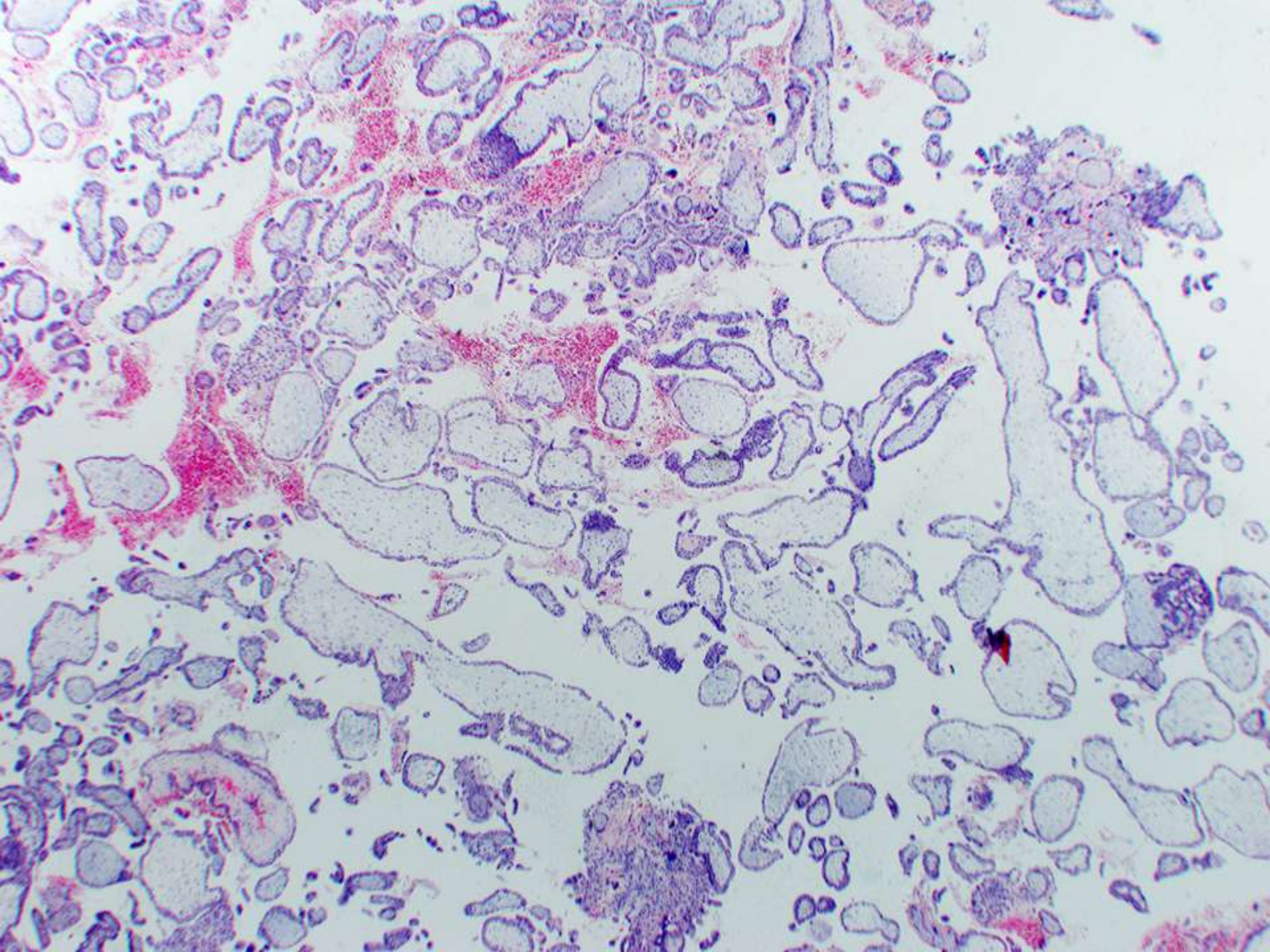
Hospital course

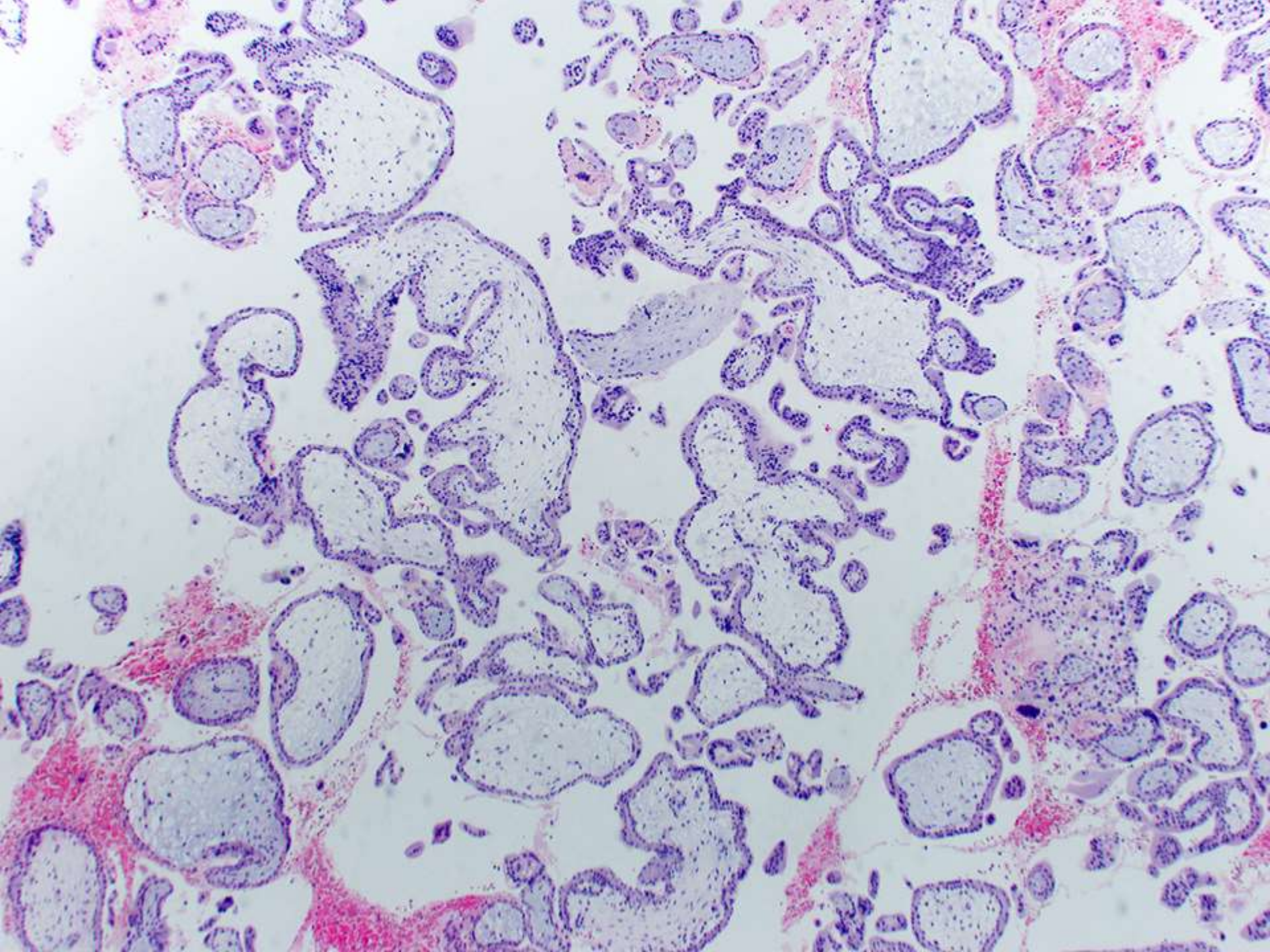
- Presented with 1 day of cold-like symptoms and progressive acute encephalopathy, found to have significant CSF pleocytosis, initially thought to be bacterial meningitis, treated for such, failed to respond to broad spectrum antibiotics.
- N. fowleri diagnosed on CSF slide. CDC and county public health made aware.
- Miltefosine obtained as treatment of last resort.
- Mayo Clinic N. fowleri PCR positive
- Rapid decompensation with hydrocephalus and uncal herniation.
- Met criteria for clinical diagnosis of brain death. Kept on vasopressor support until family could arrive and say goodbyes.

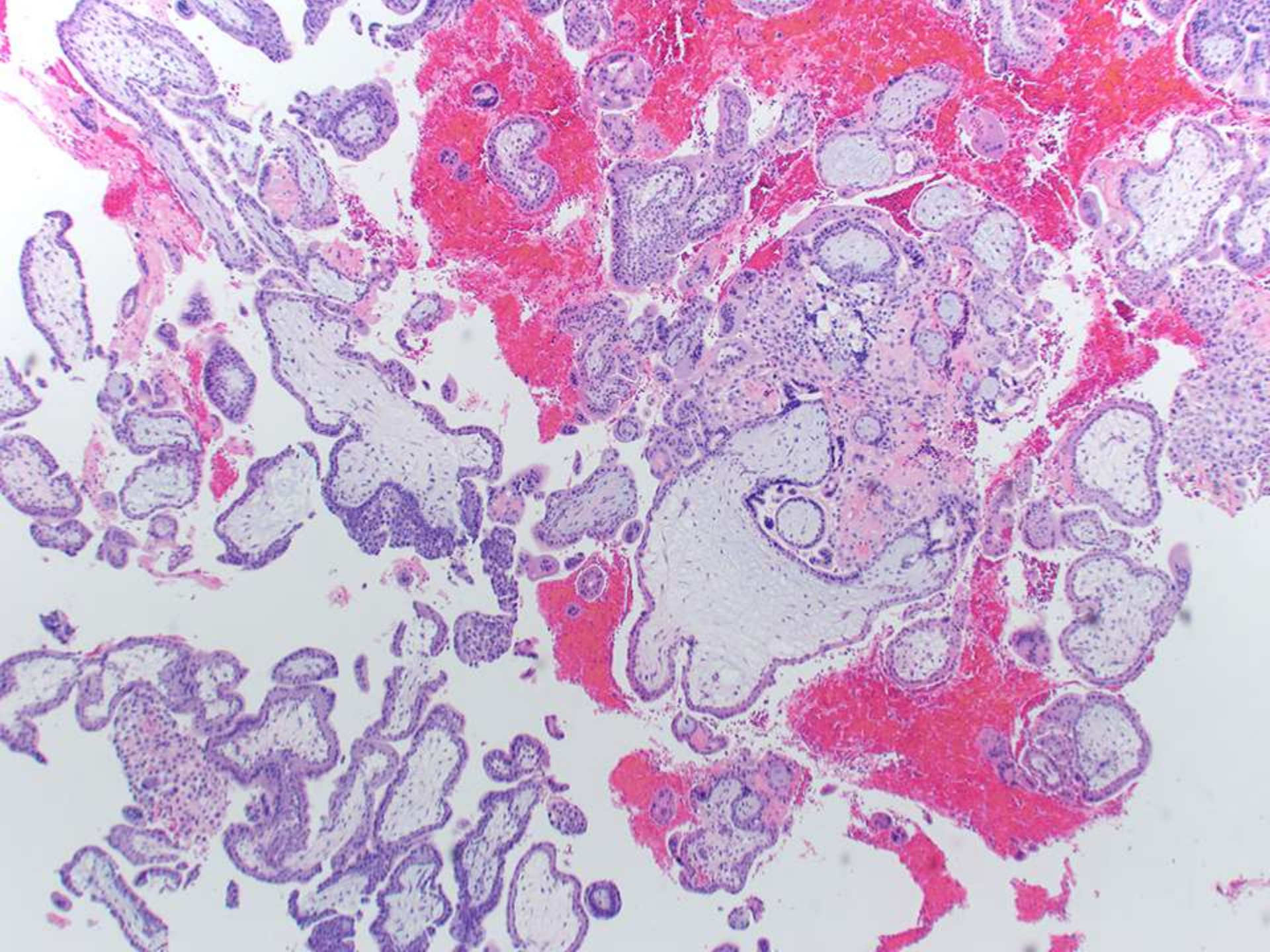
20-0602

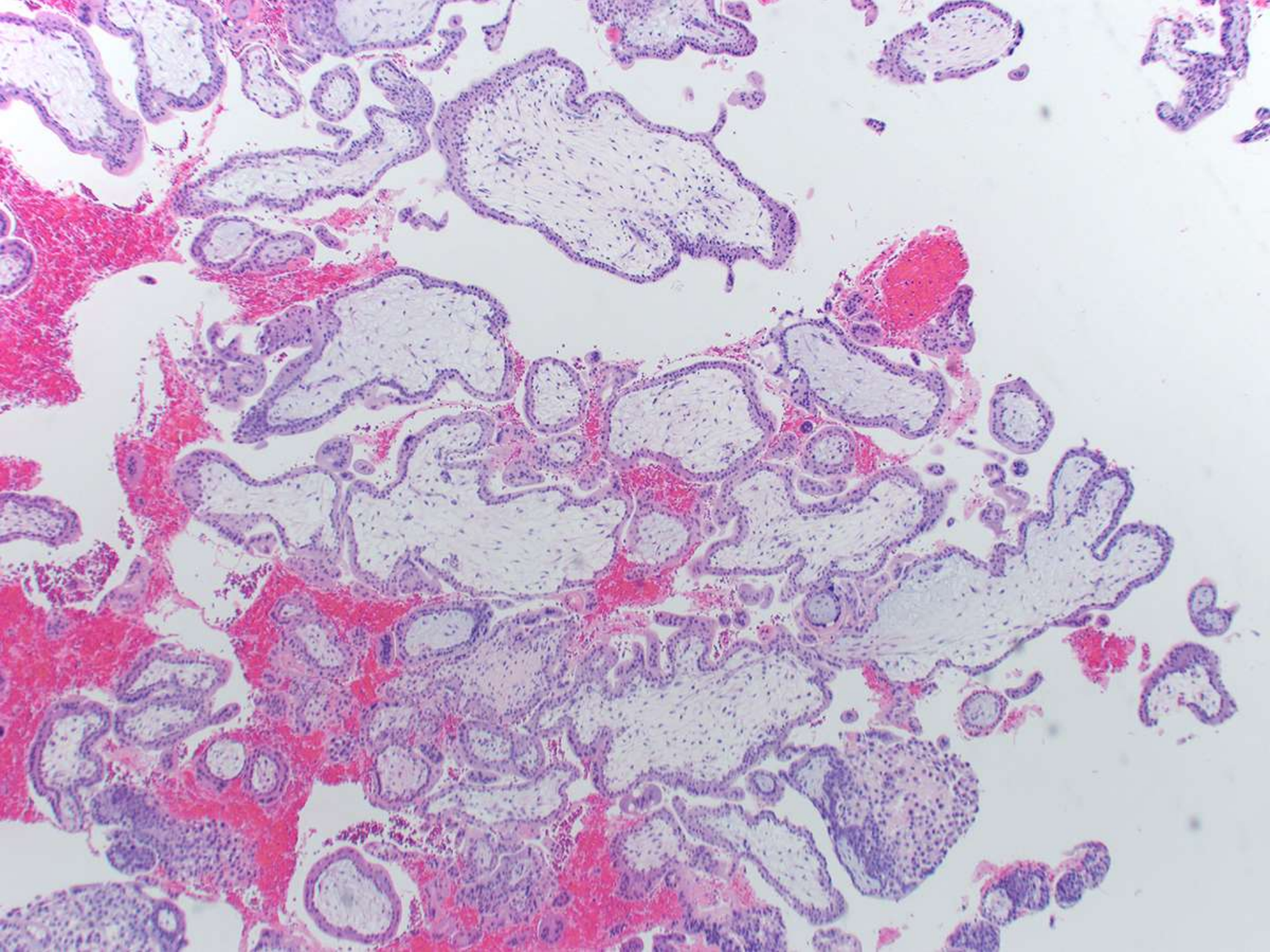
Joe Rabban; UCSF

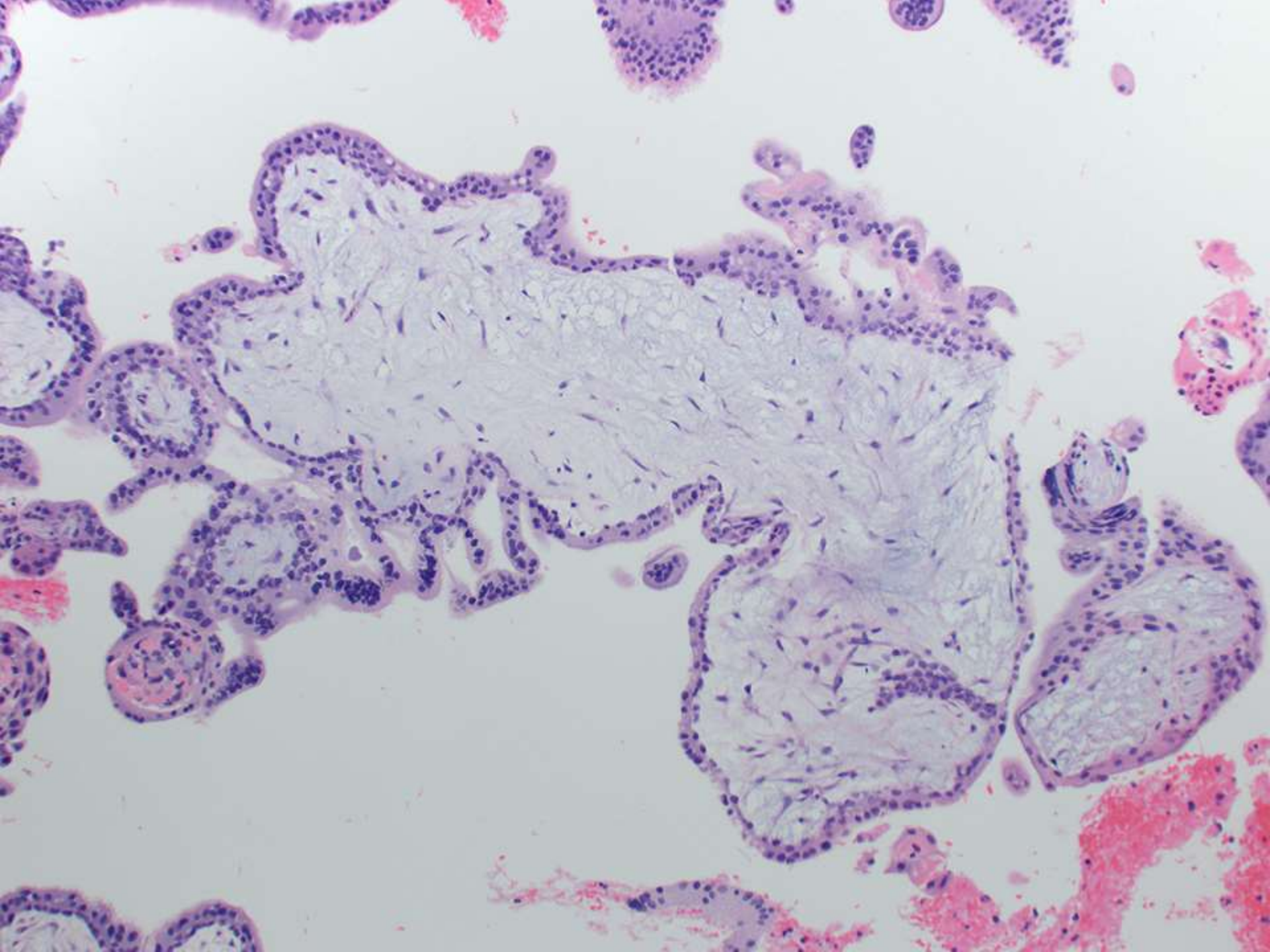
43-year-old F with an early 1st trimester spontaneous miscarriage. She underwent uterine aspiration. Gross examination showed normal chorionic villi without fetal tissue. The morphologic findings were deemed abnormal and DNA genotype testing was performed to exclude an early molar pregnancy. The test showed diploid genotype but the chorionic villi did not contain any of the alleles present in the maternal decidual tissue.

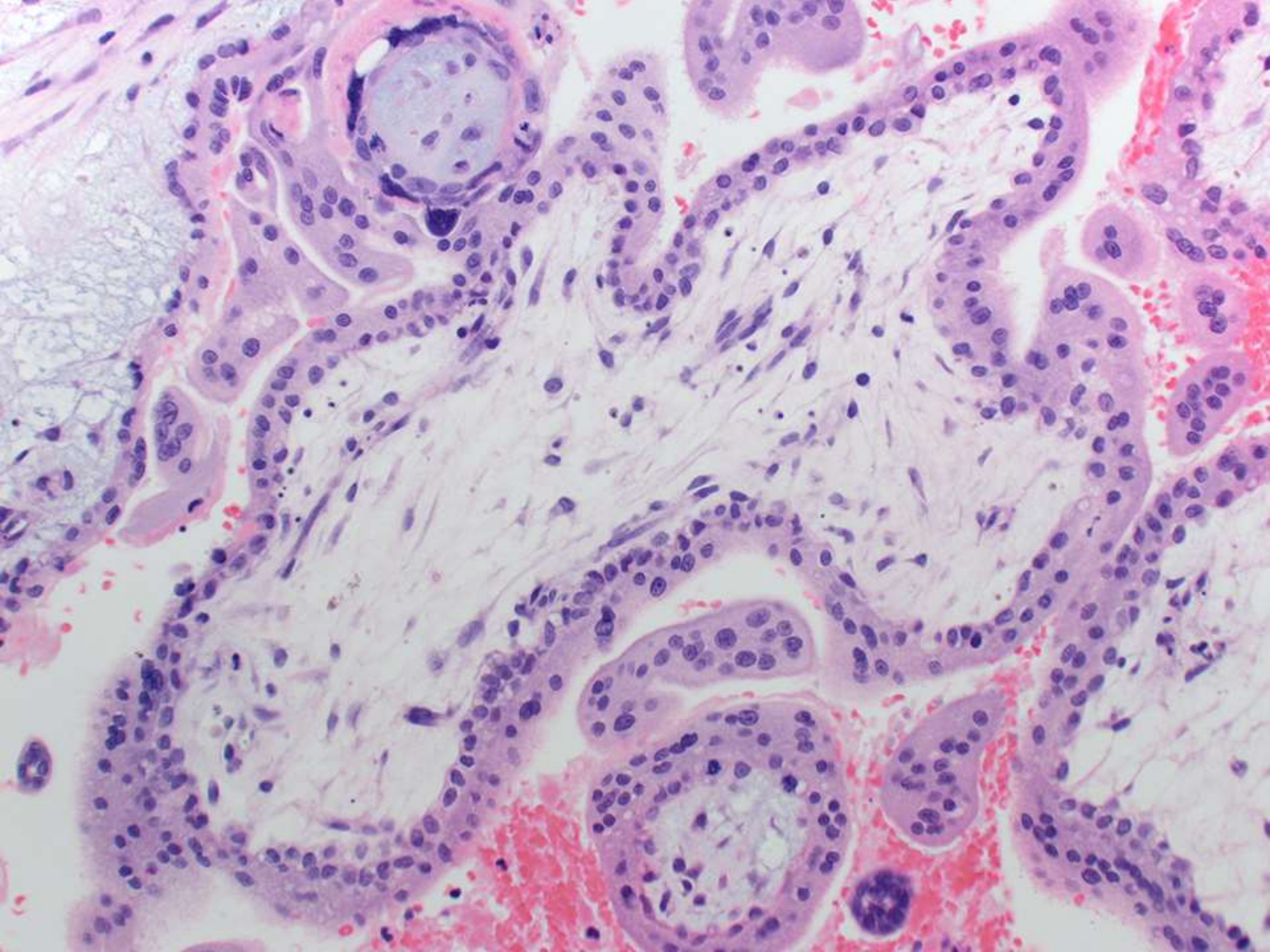












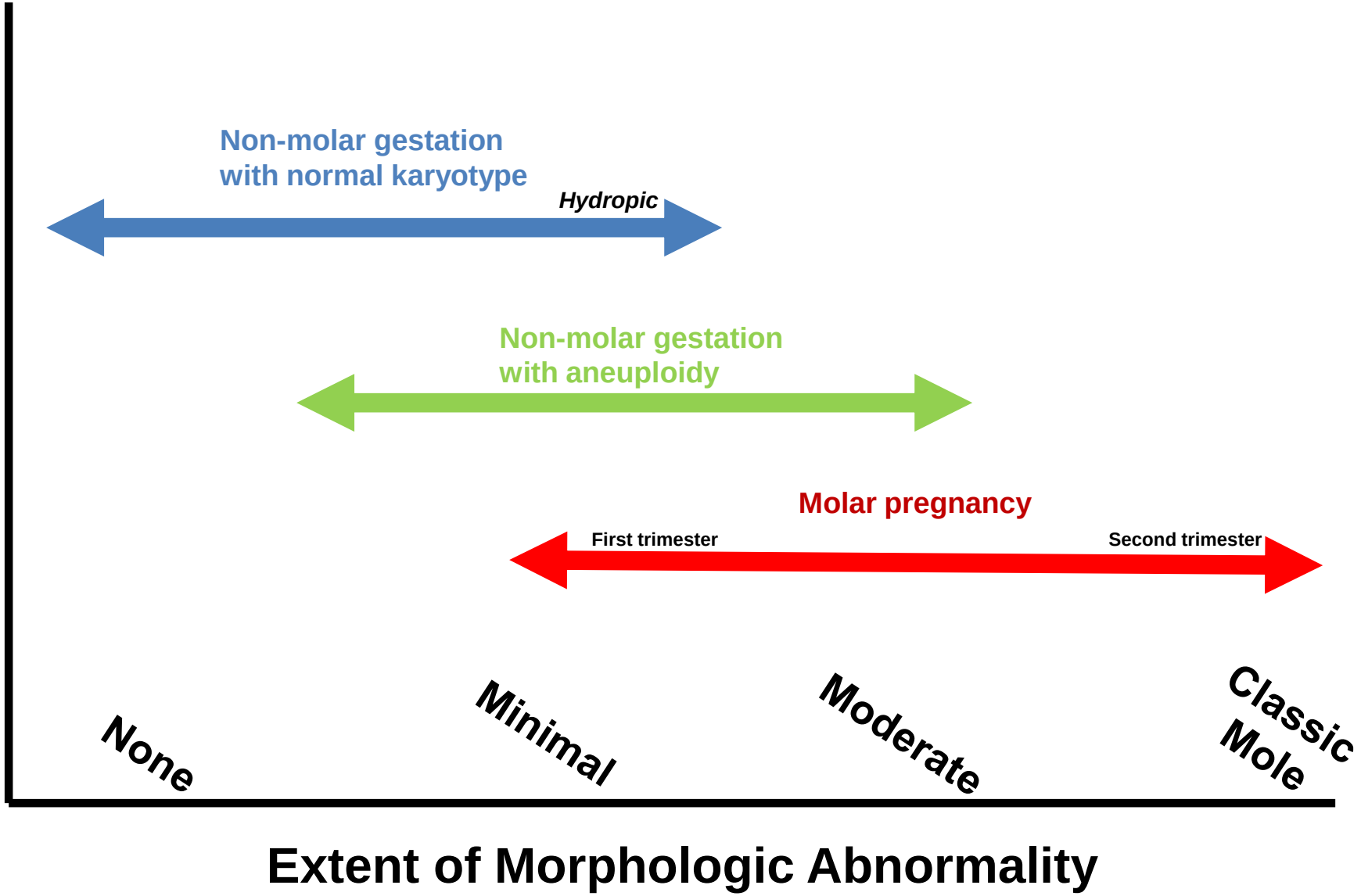
Work up of abnormal villi in POC specimens

Practical Questions

1. **How much villous abnormality is enough to trigger ancillary testing to rule out a molar pregnancy ?**

2. **Which ancillary test (p57, ploidy, genotype test) is best to order ?**

How much “abnormality” is enough to trigger testing ?



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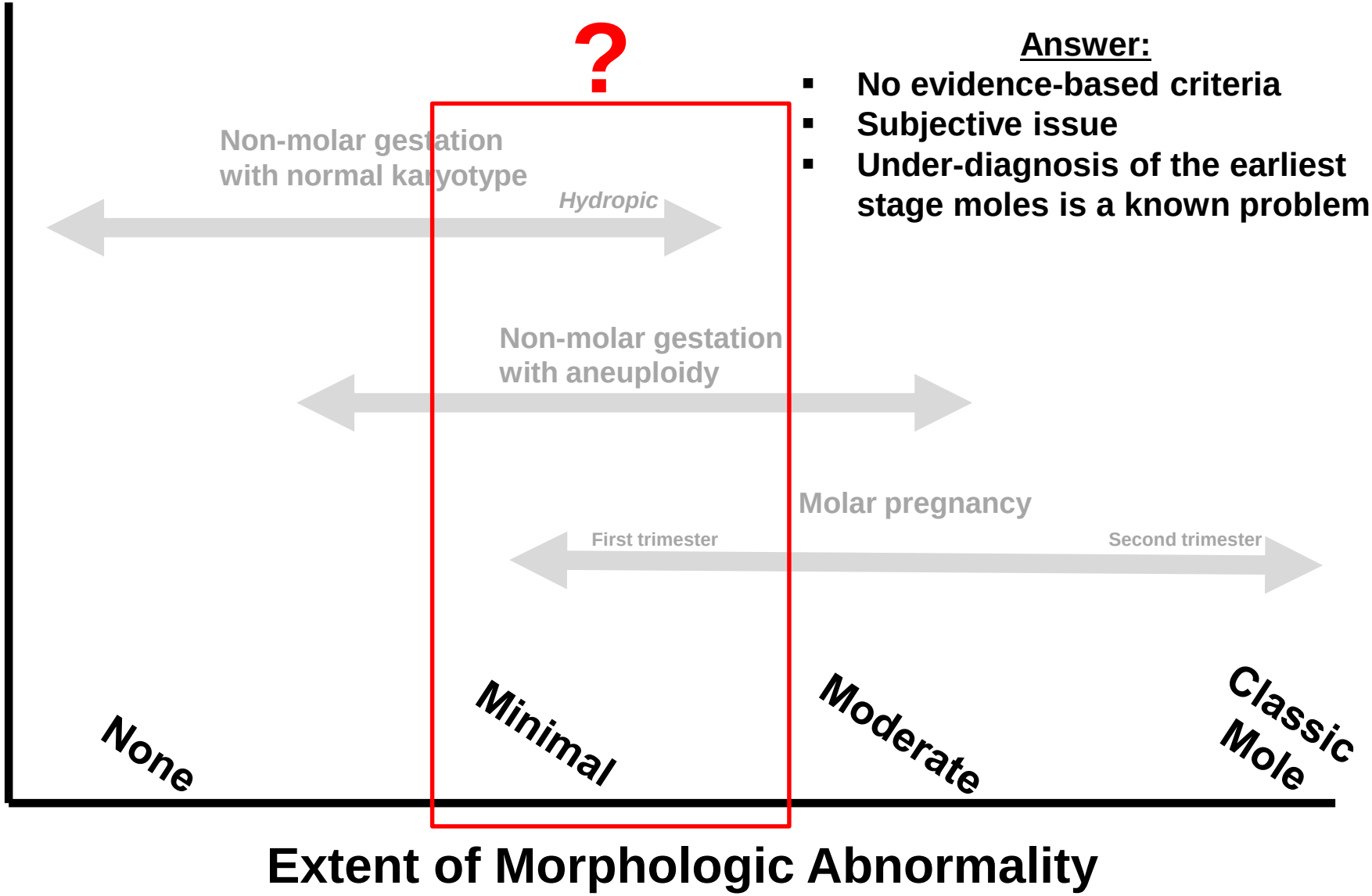


Answer:

- **No evidence-based criteria**
- **Subjective issue**
- **Under-diagnosis of the earliest stage moles is a known problem**

My Personal Threshold for Ordering Testing

Based on years of using a "very low" threshold

***Any 2 or more of these features*:**

Villous Architecture
Large
Cisterns
Invaginations, inclusions, protrusions
Apoptosis in mesenchyme

Trophoblast Proliferation
Patchy (or more)
Lace-like (cribriform)

Trophoblast Atypia
Present

Options for Tests to Rule Out Molar Pregnancy

Cause of Abnormal Morphology	DNA Genotype	p57 IHC
Non-molar gestation with hydropic change or aneuploidy	Biparental diploid	Intact
Complete mole	Diandric diploid	Absent
Partial mole	Diandric triploid	Intact

International Journal of Gynecological Pathology
30:101–116, Lippincott Williams & Wilkins, Baltimore

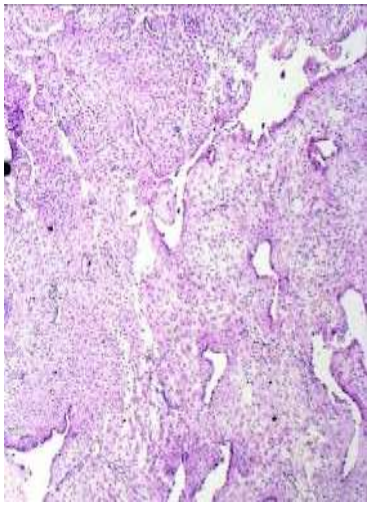
Review

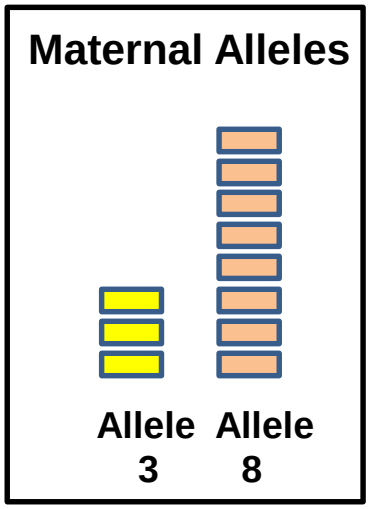
Hydatidiform Moles: Ancillary Techniques to Refine Diagnosis

Brigitte M. Ronnett, M.D., Cheryl DeScipio, Ph.D., and Kathleen M. Murphy, Ph.D.

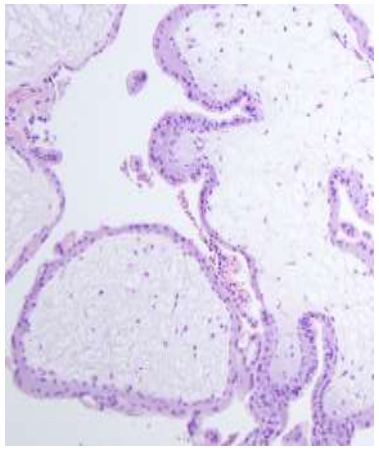
SBPS Case: Genotype Testing

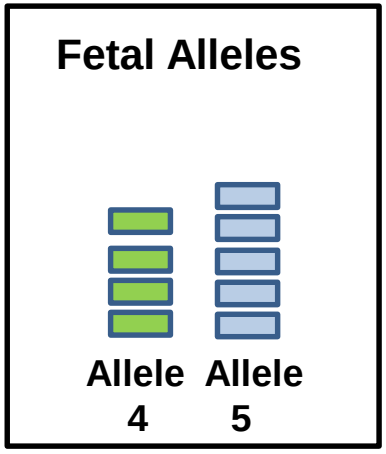
Decidua





Chorionic villi





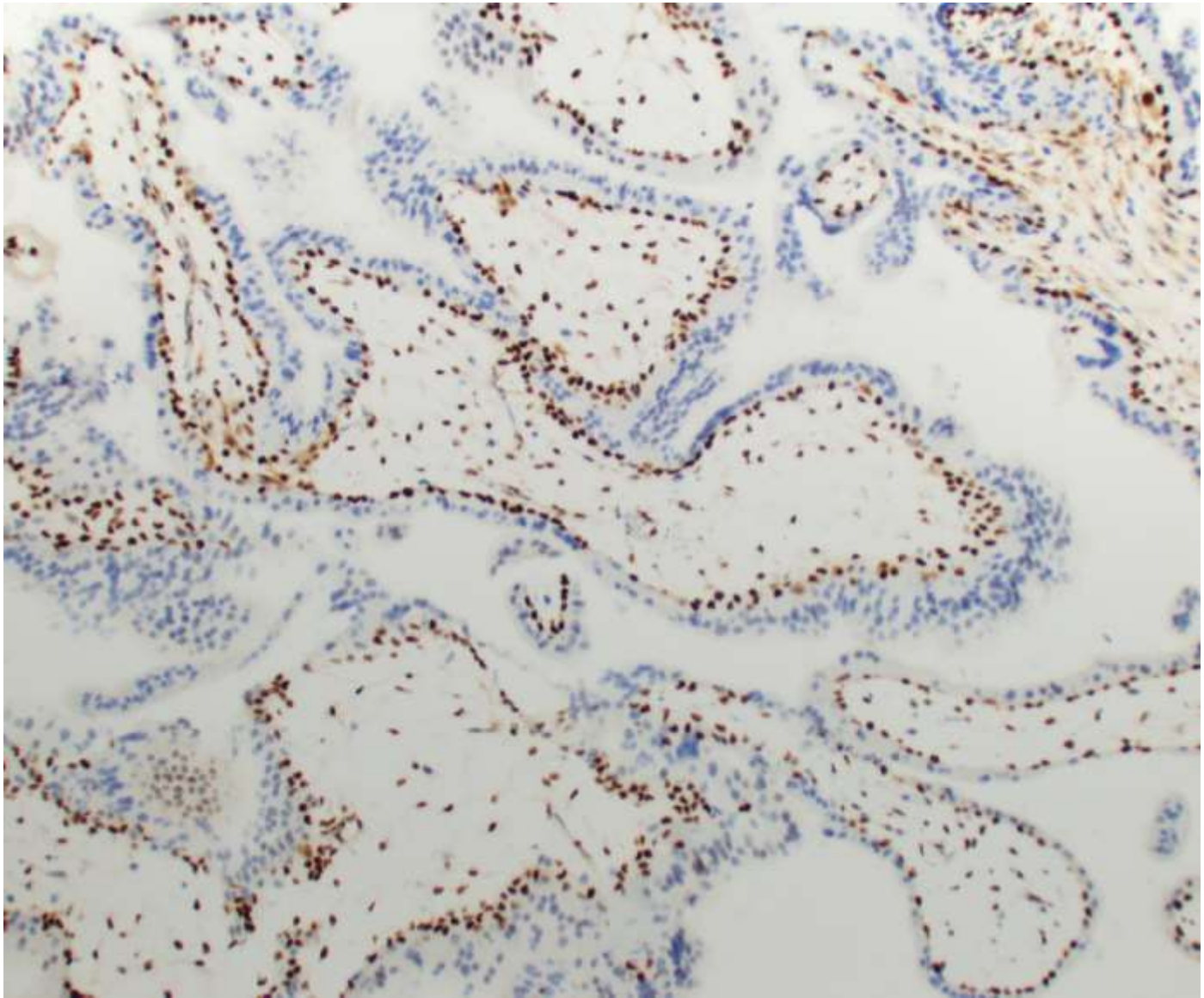
<u>Genotype result of fetal tissue:</u>

- **Diploid**
- **No maternal alleles**

- *Interpretation:*
  "Dispermic complete mole"

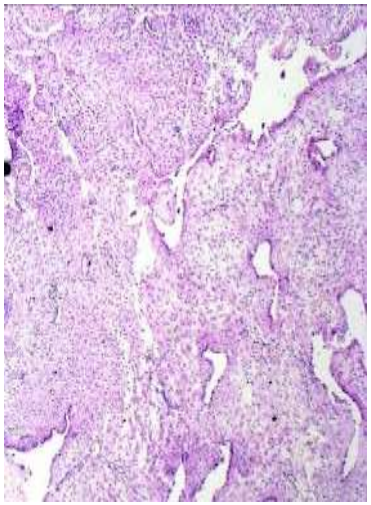
SBPS Case

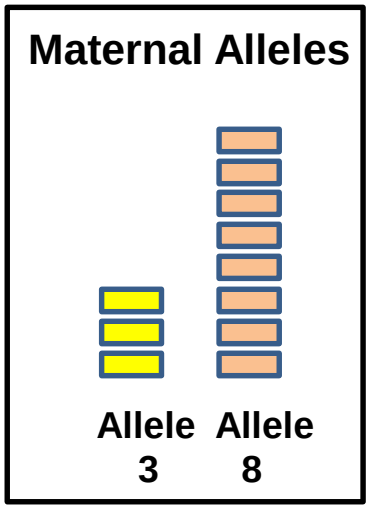
P57 IHC



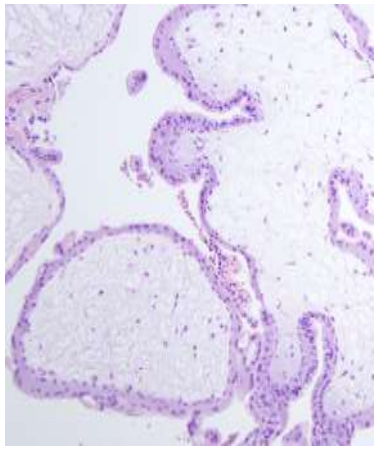
SBPS Case: Genotype Testing

Decidua





Chorionic villi



Explanation for genotype for POC using egg donor:

1 allele from father
1 allele from egg donor
0 alleles from "carrier"

SBPS Case

Final Diagnosis

1. Non-molar gestation using a donor egg

2. Abnormal villous morphology like due to non-molar aneuploidy

Teaching Point: Potential Pitfalls of Genotype Testing

Genotype of donor egg pregnancy can be misinterpreted as dispermic complete mole

How to avoid this pitfall
➢ **Communication of use of a donor egg** -clinician to surgical pathologist -surgical pathologist to molecular pathologist
➢ **Use p57 IHC to triage use of genotype testing**
➢ **Molecular pathologist:** -examine allelic heterozygosity/homozygosity ratios

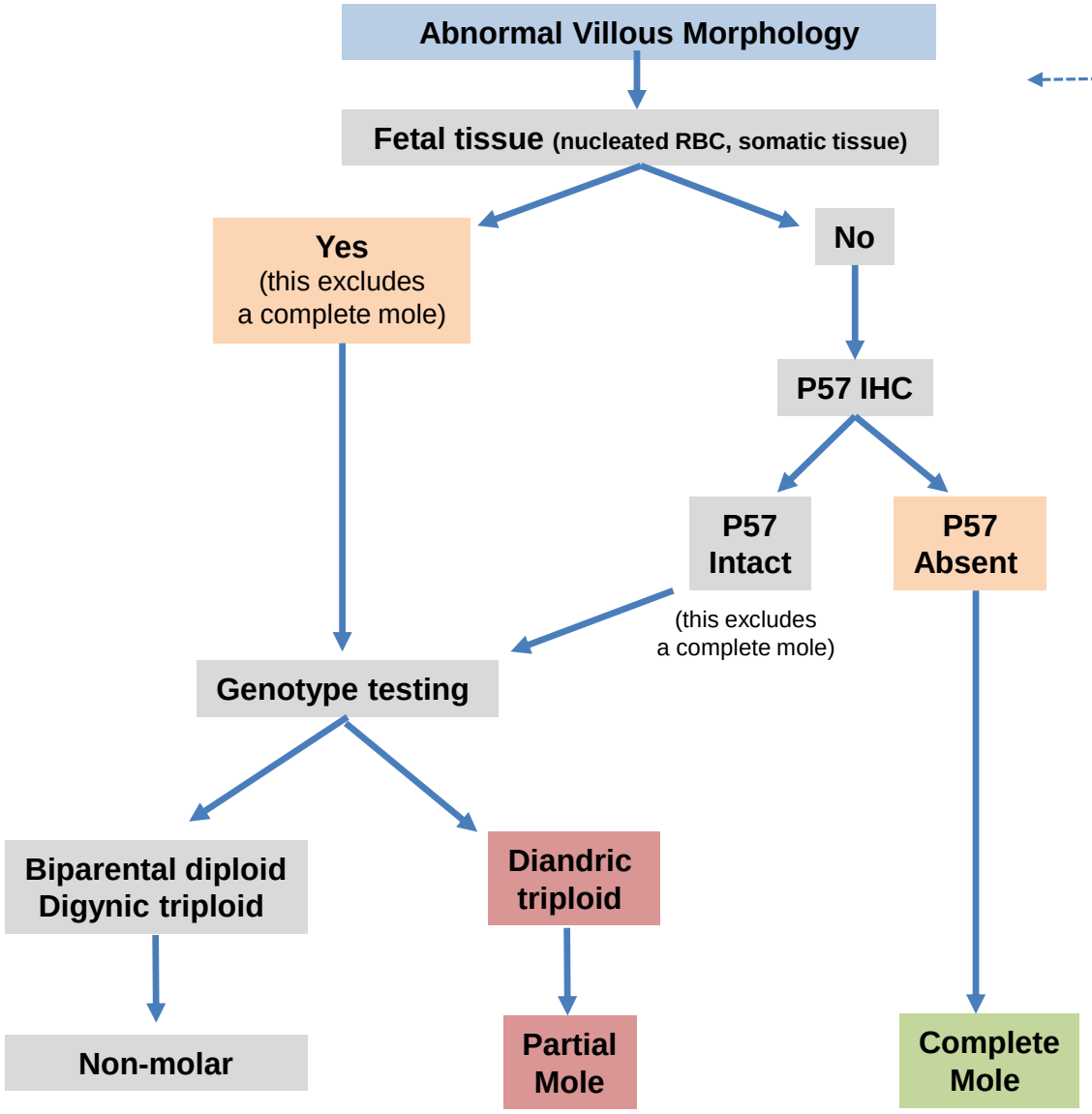
International Journal of Gynecological Pathology
37:191–197, Lippincott Williams & Wilkins, Baltimore

Original Article

DNA Genotyping of Nonmolar Donor Egg Pregnancies With Abnormal Villous Morphology: Allele Zygosity Patterns Prevent Misinterpretation as Complete Hydatidiform Mole

Nancy M. Joseph, M.D., Ph.D., Caryll Pineda, MLS(ASCP)CM, and Joseph T. Rabban, M.D., M.P.H.

1 (of many) Option* for Triaging Tests to Rule Out Molar Pregnancy



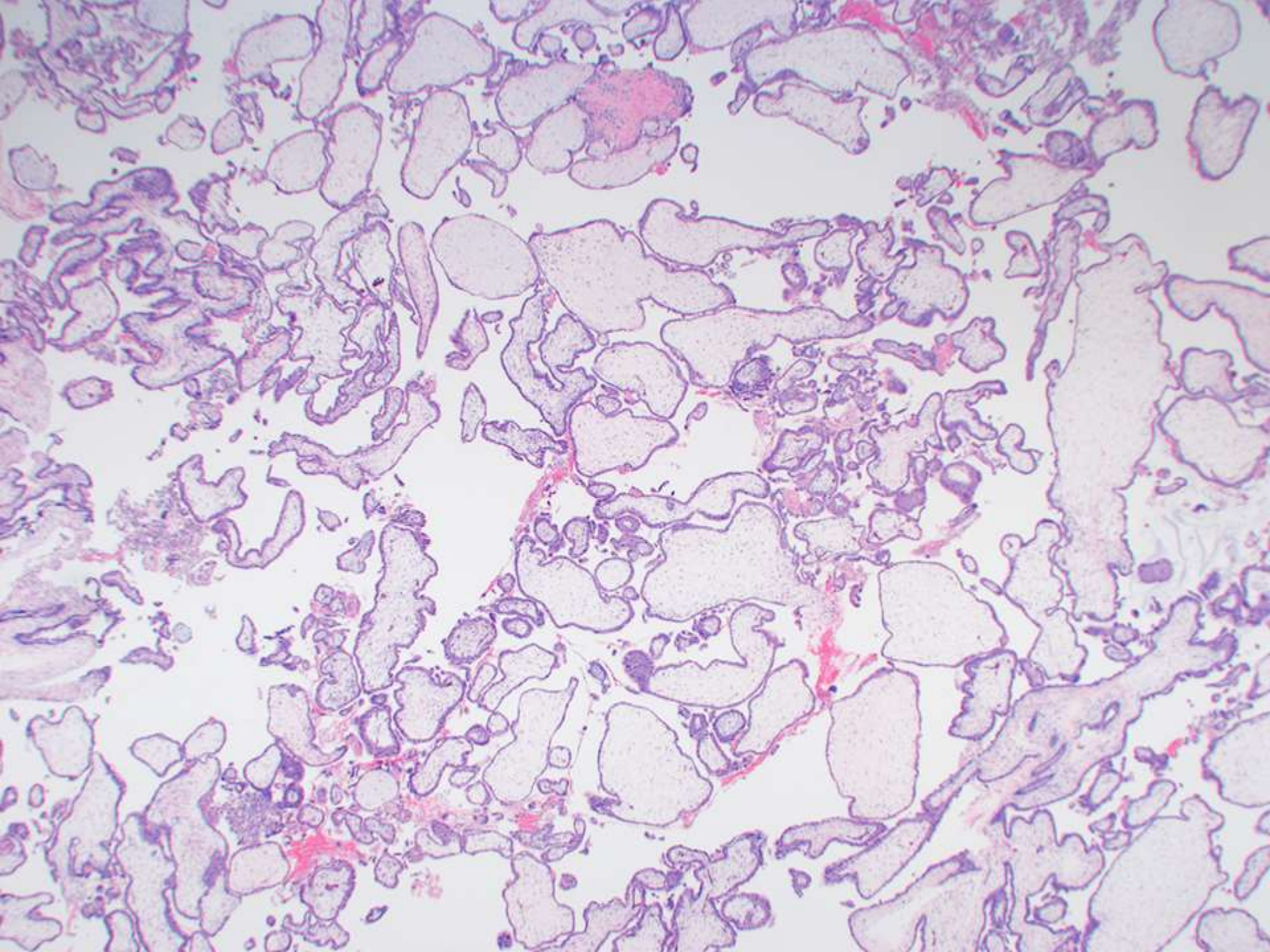
Clinical data for triage not shown
-Prenatal fetal test results
-Donor egg pregnancy

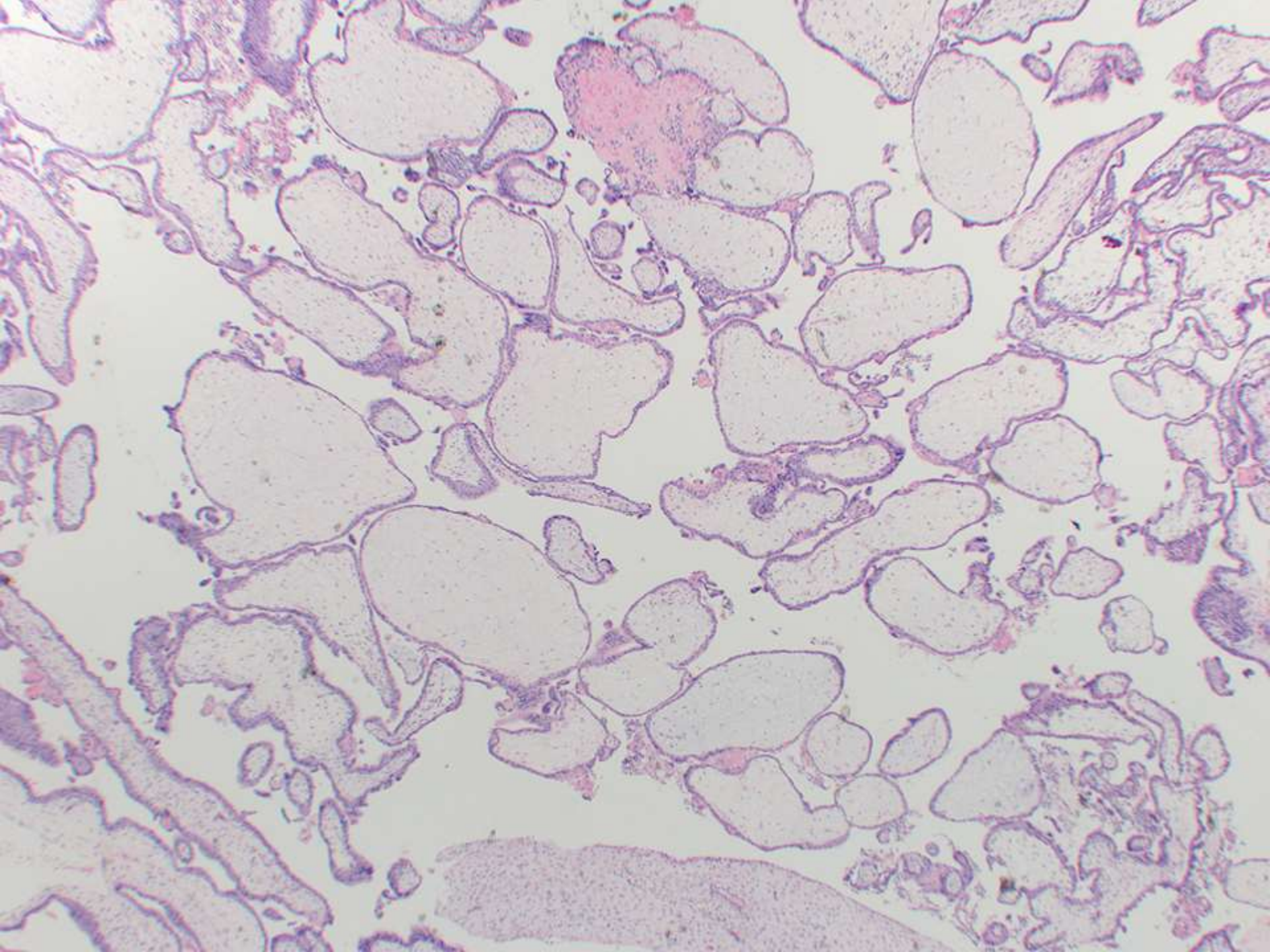
Exceptions exist:
-Twin POC with a mole
-Biparental complete mole
-Mosaicism

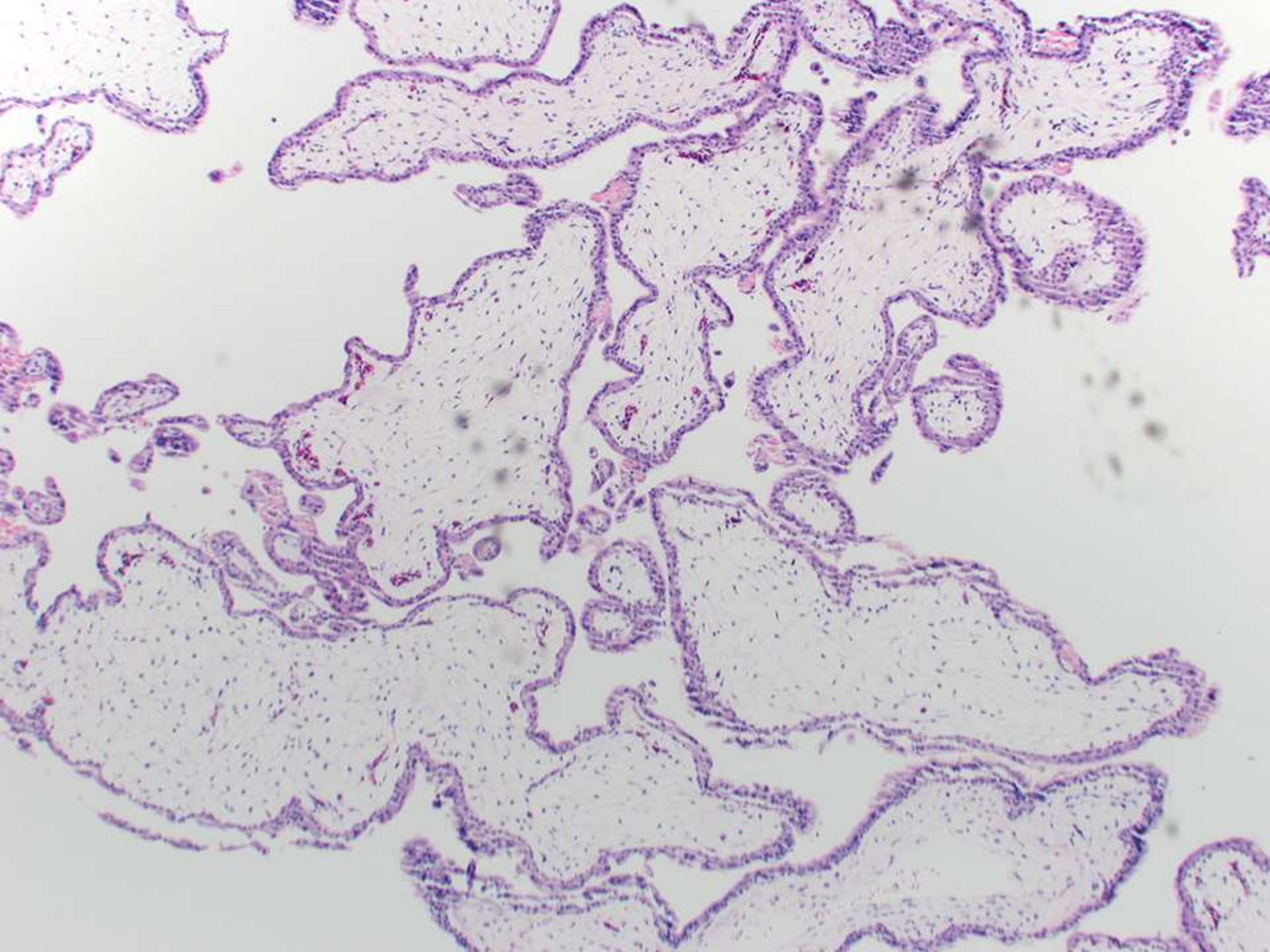
20-0603

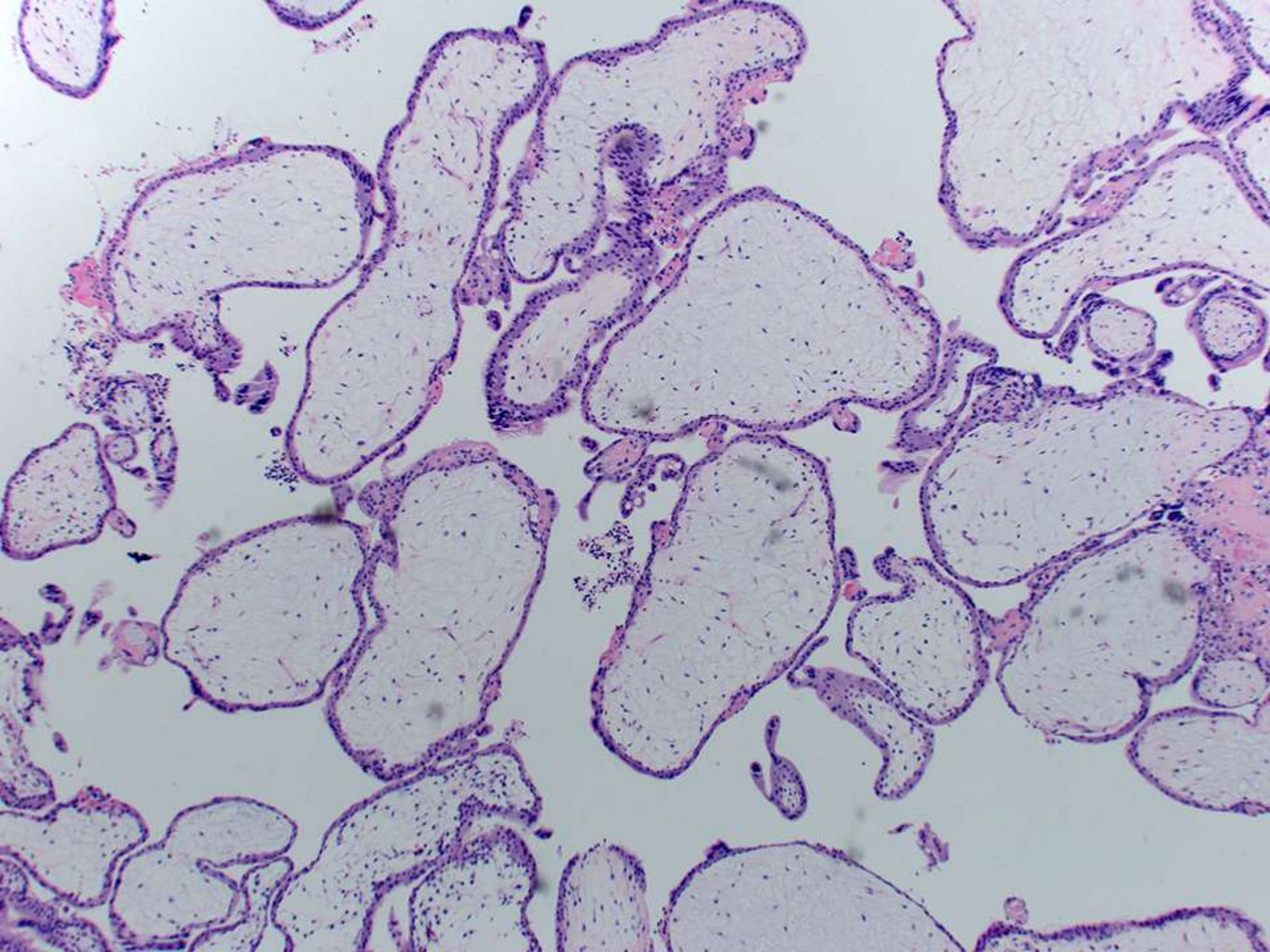
Joe Rabban; UCSF

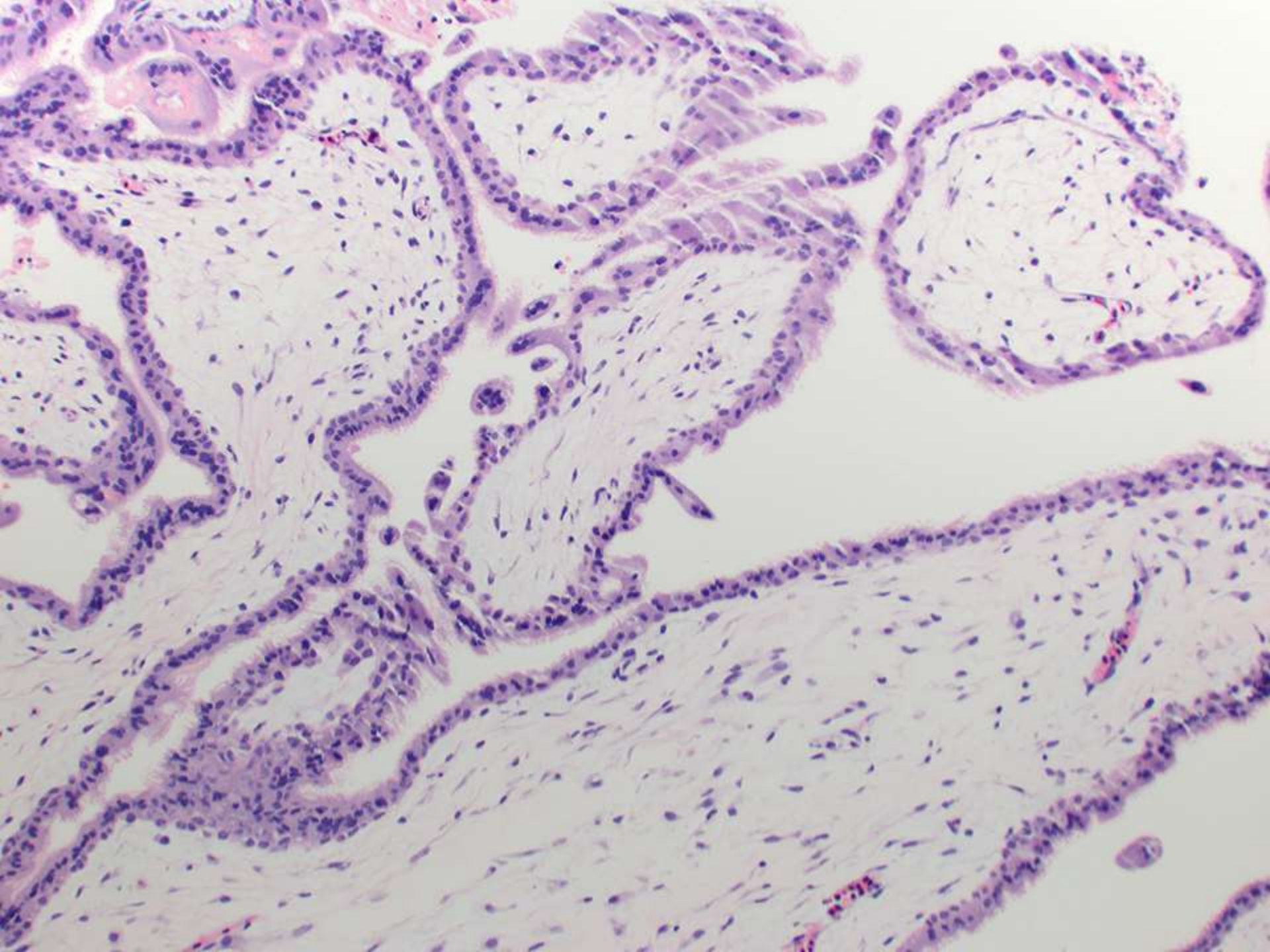
30-year-F with an early 1st trimester miscarriage. She underwent uterine aspiration. The clinician sent part of the specimen for fetal aneuploidy testing and the remainder for surgical pathology evaluation. Gross examination showed normal chorionic villi; no fetal tissue. The fetal test result was triploidy (69, XXY).

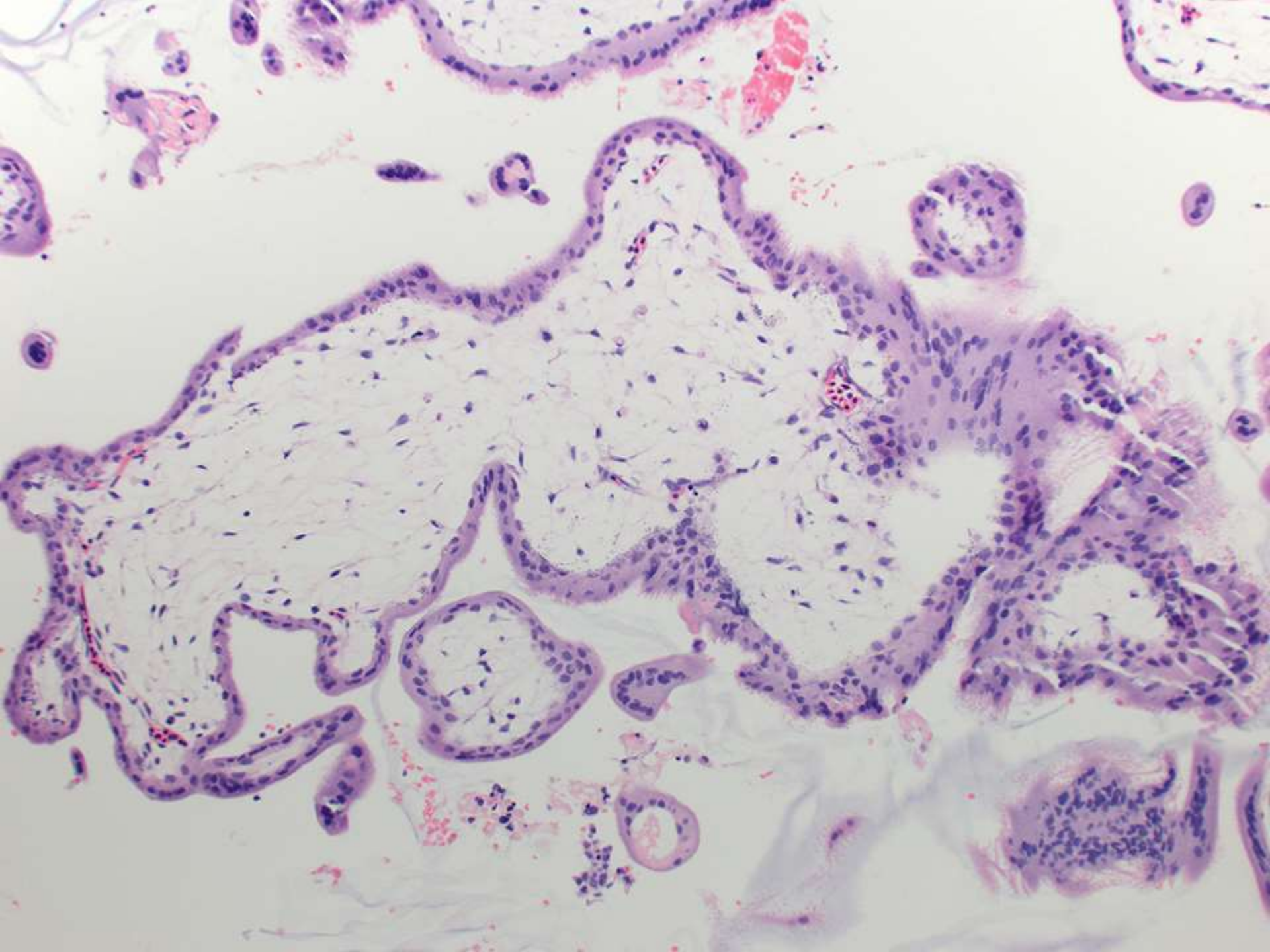












Utility of fetal aneuploidy test results to the surgical pathologist when evaluating abnormal villi in POC specimens

Context of fetal testing:

Prenatal screening (advanced maternal age)
Prenatal work-up of ultrasound abnormalities
Work up of miscarriage

Examples of results:

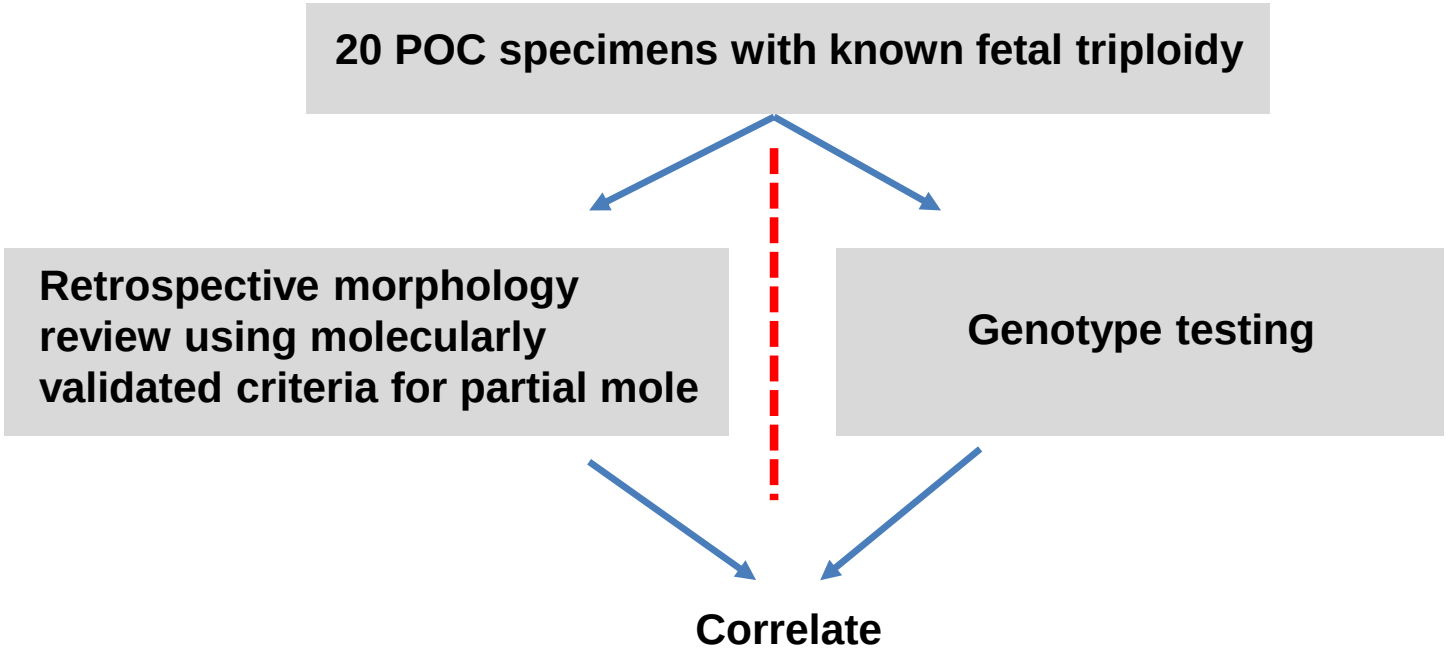
Single chromosomal aneuploidy: trisomy, monosomy
Triploidy

Source of results:

Often:	**not communicated to surgical pathologist**
Sometimes:	**in the POC specimen requisition form**
Sometimes:	**in the electronic medical records**

Fetal Triploidy on Prenatal Test

	Diandric Triploidy	Digynic Triploidy
Risk for subsequent gestational trophoblastic disease	Yes (very low risk)	No
Manage by: -6 months surveillance serum hCG -6 months contraception during surveillance	Yes	No
Distinction by ploidy test alone	No	
Distinction by genotype test	Yes	
Relative frequency	?	
Morphologic distinction	?	



ORIGINAL ARTICLE

Prevalence of Partial Hydatidiform Mole in Products of Conception From Gestations With Fetal Triploidy Merits Reflex Genotype Testing Independent of the Morphologic Appearance of the Chorionic Villi

Lucy M. Han, MD, James P. Grenert, MD, PhD,† Arun P. Wiita, MD, PhD,‡ Molly Quinn, MD,§ Victor Y. Fujimoto, MD,§ and Joseph T. Rabban, MD, MPH**

(*Am J Surg Pathol* 2020;44:849–858)

Best molecularly-validated morphology criteria for partial mole

Highest Predictive Value (90%)**:**

Cisterns and villous size ≥ 2 mm

Triggers for genotype testing (any 1)

- **Cisterns**
- **Villous size ≥ 2 mm**
- **Villous inclusions**
- **Dual population of villi**

Original Article

Partial Hydatidiform Mole: Histologic Parameters in Correlation With DNA Genotyping

Natalia Buza, M.D. and Pei Hui, M.D., Ph.D.

Int J Gynecol Pathol Vol. 32, No. 3, May 2013

POC Specimens with Fetal Triploidy

65% are partial moles

-only 23% exhibit classic morphology

-most show only focal, limited abnormalities

-30% originally signed out as non-molar using H&E only (no ancillary testing)

Recommendation

Obtain genotype testing regardless of the morphologic appearance of the villi

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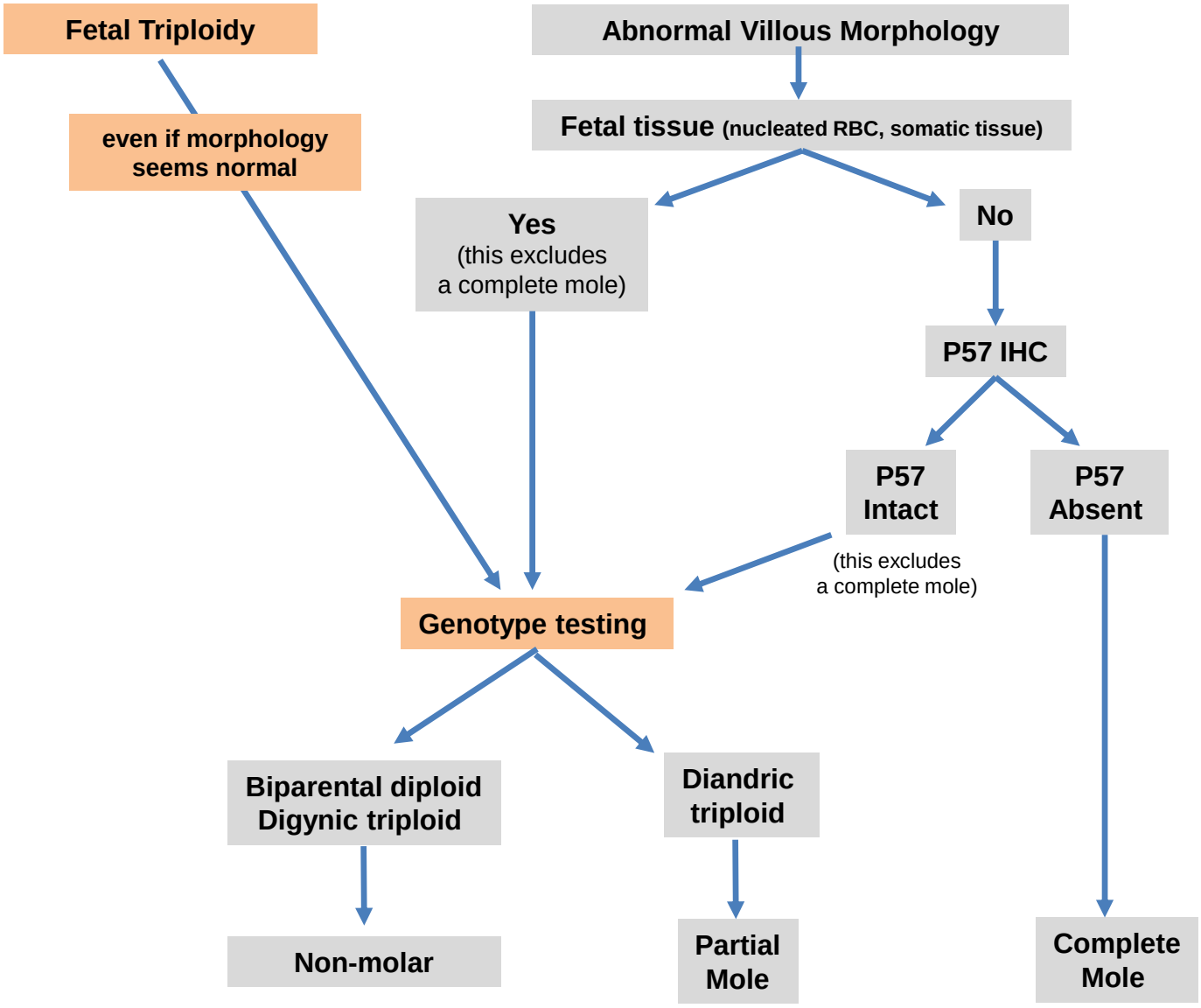
(*Am J Surg Pathol* 2020;44:849–858)

SBPS Case: Final Diagnosis

Partial mole (diandric triploid)

1 (of many) Option* for Triaging Tests to Rule Out Molar Pregnancy

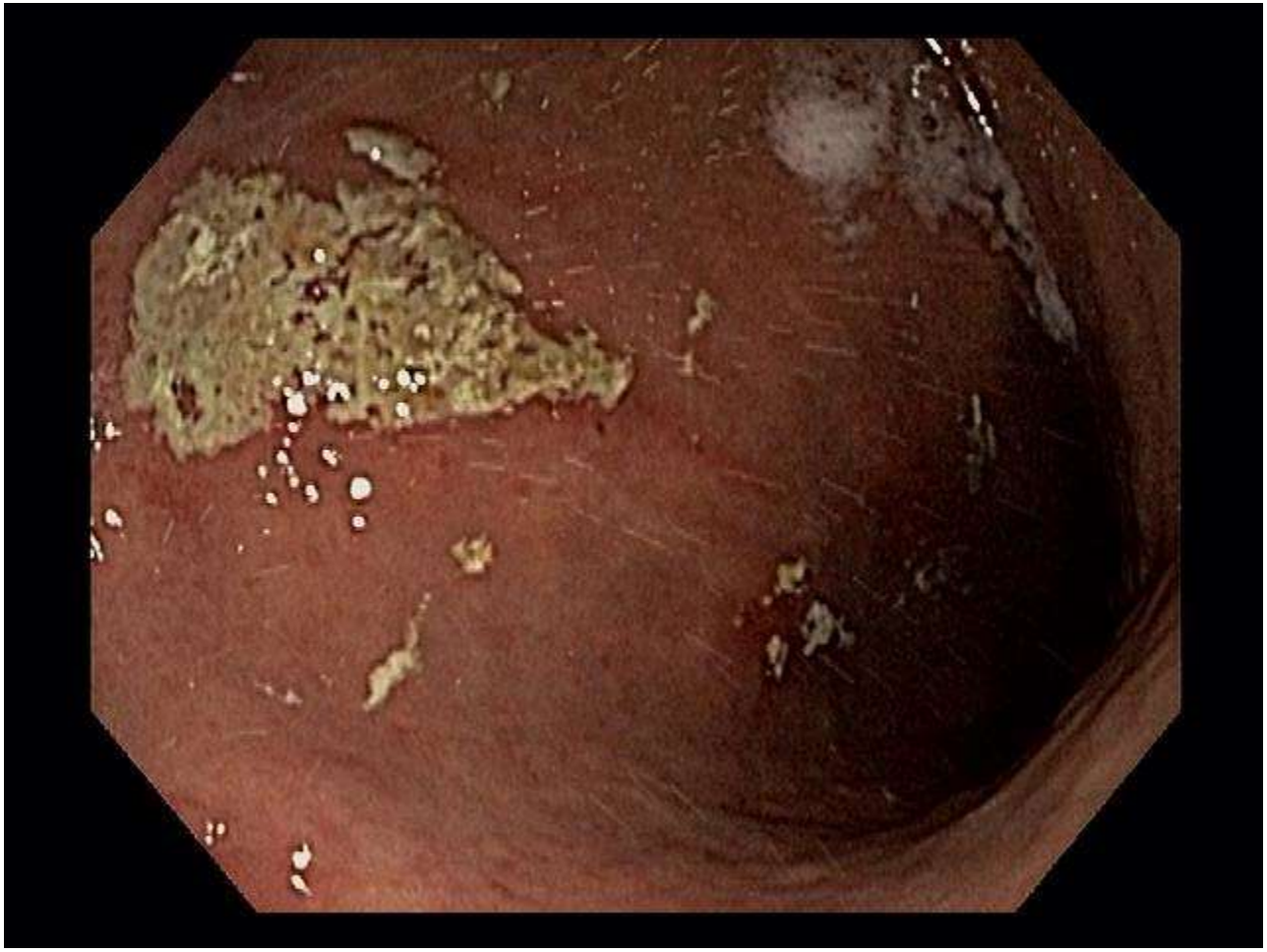


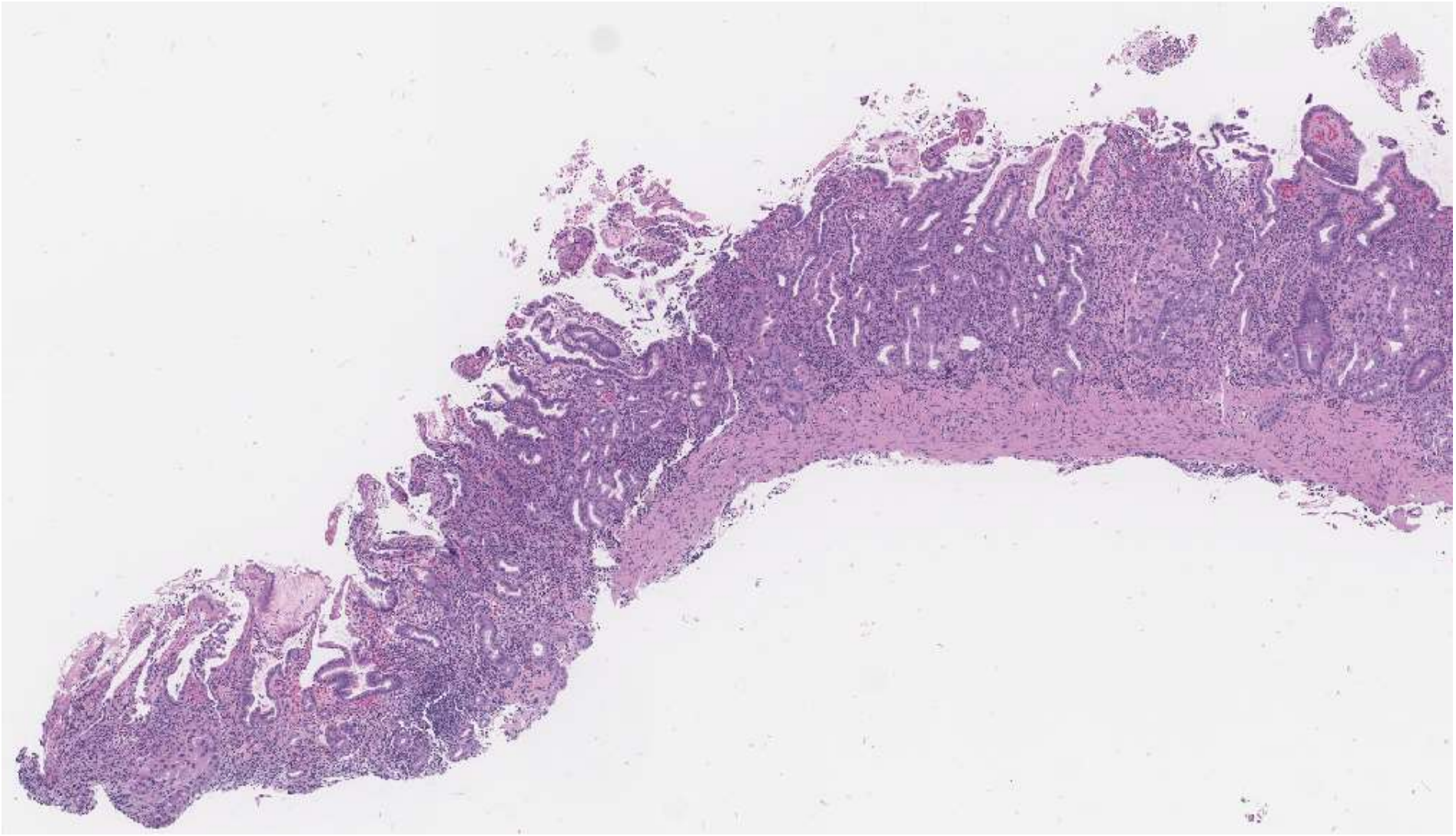
Exceptions exist:
-Twin POC with a mole
-Biparental complete mole
-Mosaicism

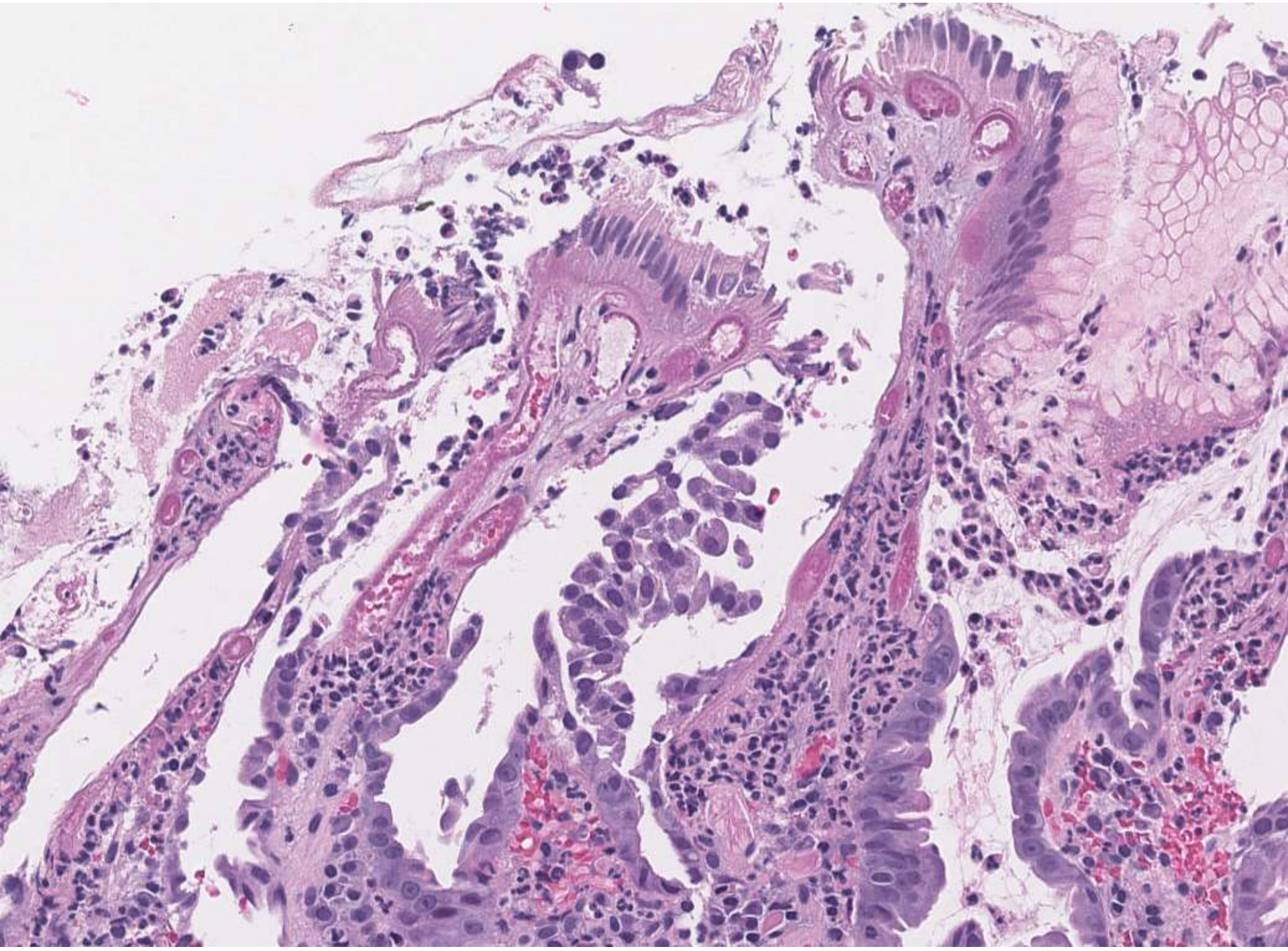
20-0604

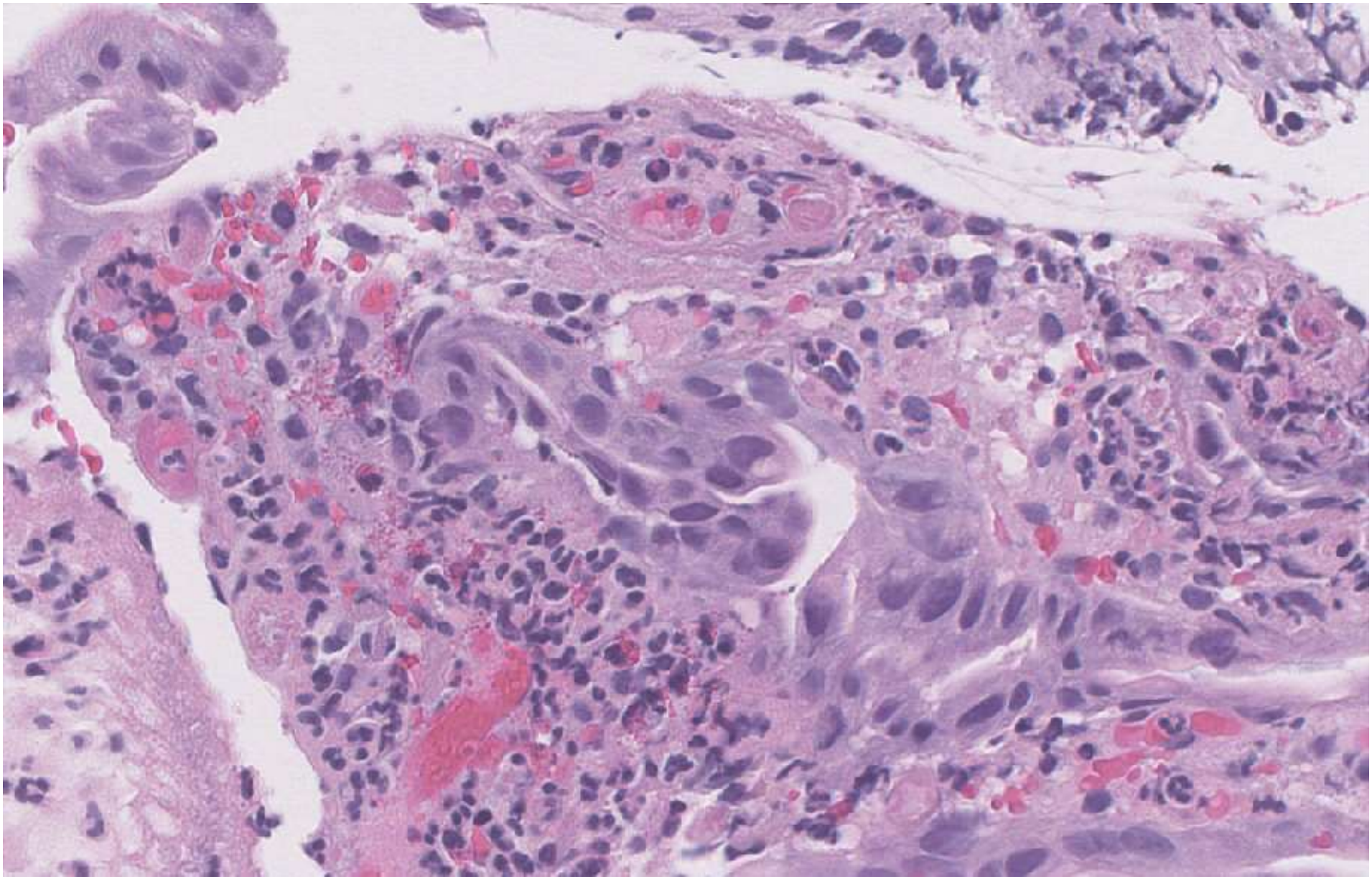
Karen Matsukuma; UC Davis

68-year-old M, past medical h/o CVA and Afib, on apixaban and aspirin. Presents to ED for melana. EGD: 2cm area with adherent material (thought to be food residue) noted in proximal body of stomach. The underlying erythematous mucosa was biopsied. Esophagus/duodenum were normal.









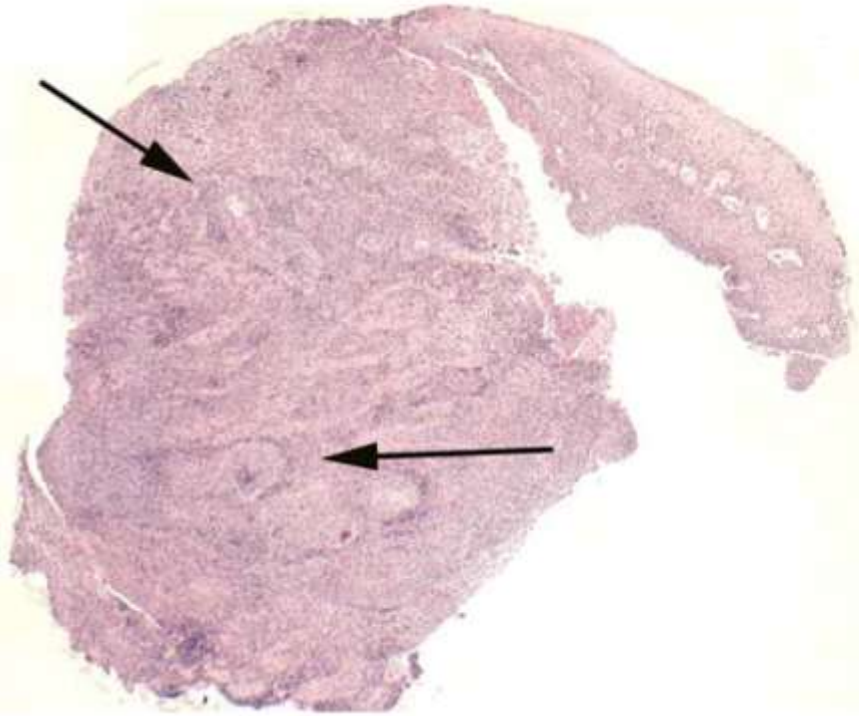
Diagnosis

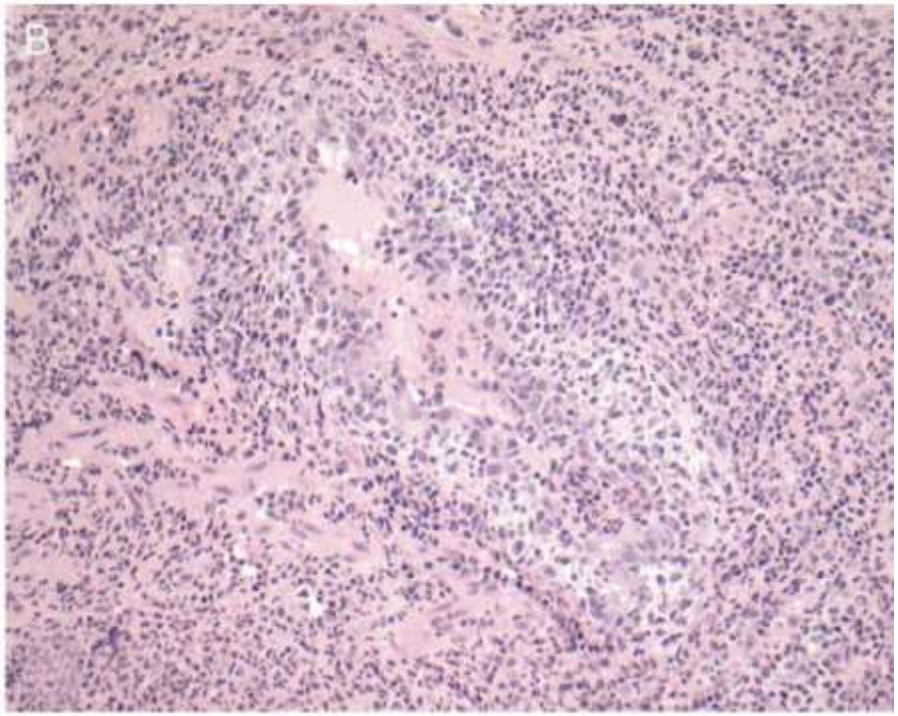
- Doxycycline-induced gastric injury
  - Erosion, superficial necrosis/fibrin
  - Characteristic eosinophilic vascular degeneration/fibrinoid change of superficial capillaries
  - Fibrin microthrombi
  - Endoscopic “white exudate” common

Doxycycline-induced UGI injury

- Reported in esophagus, stomach, duodenum
- In esophagus, findings are:
  - Ulceration
  - Inflammation of mucosal and submucosal vessels
  - Characteristic perivascular edema and fibroblastic response (“halo”); can mimic granuloma
  - Endothelialitis, endothelial sloughing into lumen

“Halo” sign around vessels





Medlicott et al, AJSP 2013

Background

- First described in the gastric mucosa by Xiao et al, AJSP 2013 (2 cases)
- Esophageal changes subsequently reported by Medlicott et al, AJSP 2013 (2 cases)
- Largest case series Shih et al, AJSP 2017 (14 patients)
- Prompt resolution of mucosal injury after cessation of medication in all cases
- The vascular changes appear to be quite specific for doxycycline
- Possible mechanism: Doxycycline may promote vasoconstriction, inhibit angiogenesis

Doxycycline Toxicity

- Clinically, well-known to give rise to UGI symptoms
- Complicating factors: when medication is taken, how much fluid taken, dysmotility?
- Prescribed for acne, UTIs, Lyme disease, PID, malaria prophylaxis

Patient Follow-up

- Our patient had been prescribed doxycycline as part of triple therapy for *Helicobacter* (by his PCP)
- No *H. pylori* was present by IHC on the biopsy
- Repeat EGD after cessation of the drug demonstrated normal gastric mucosa

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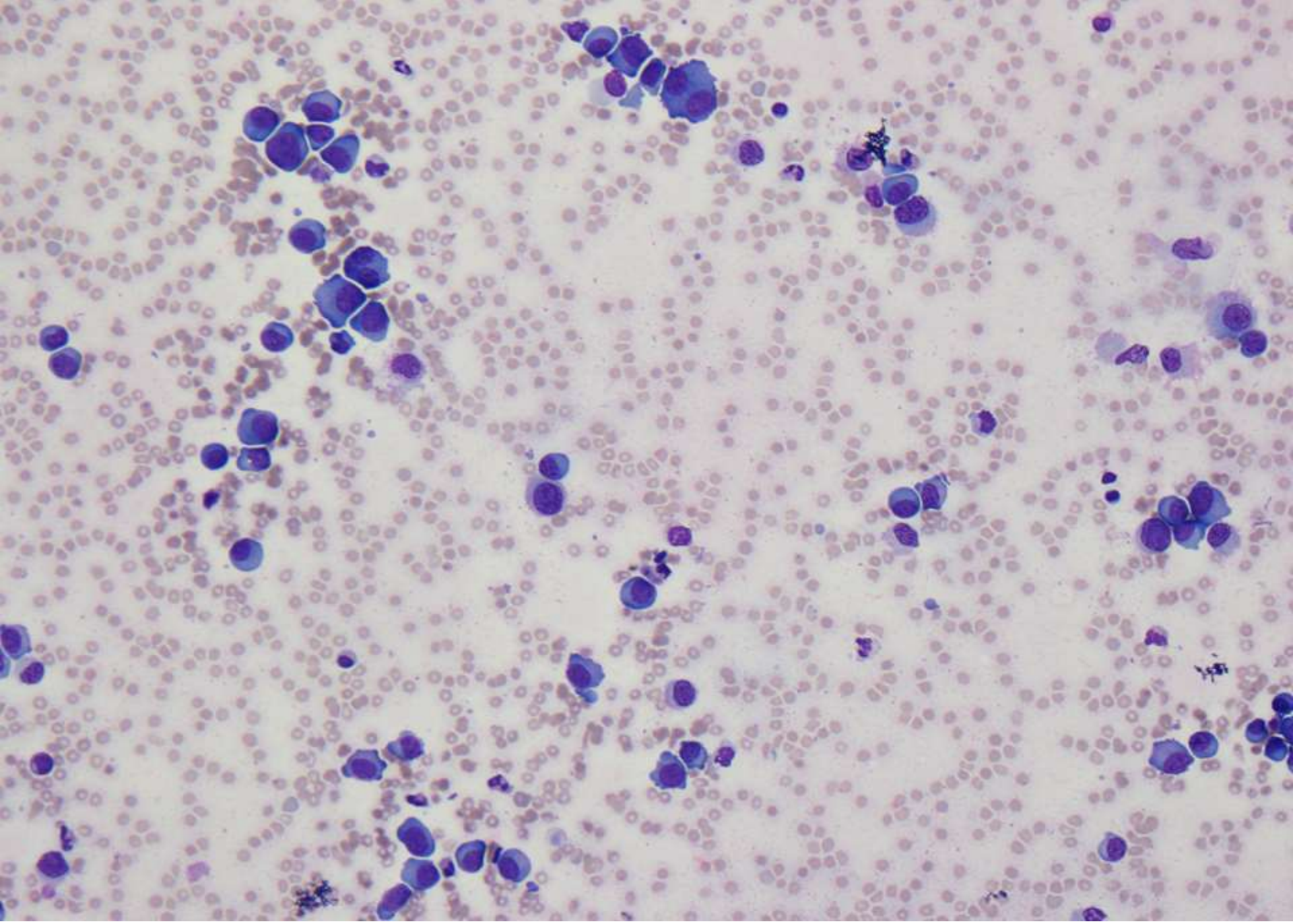
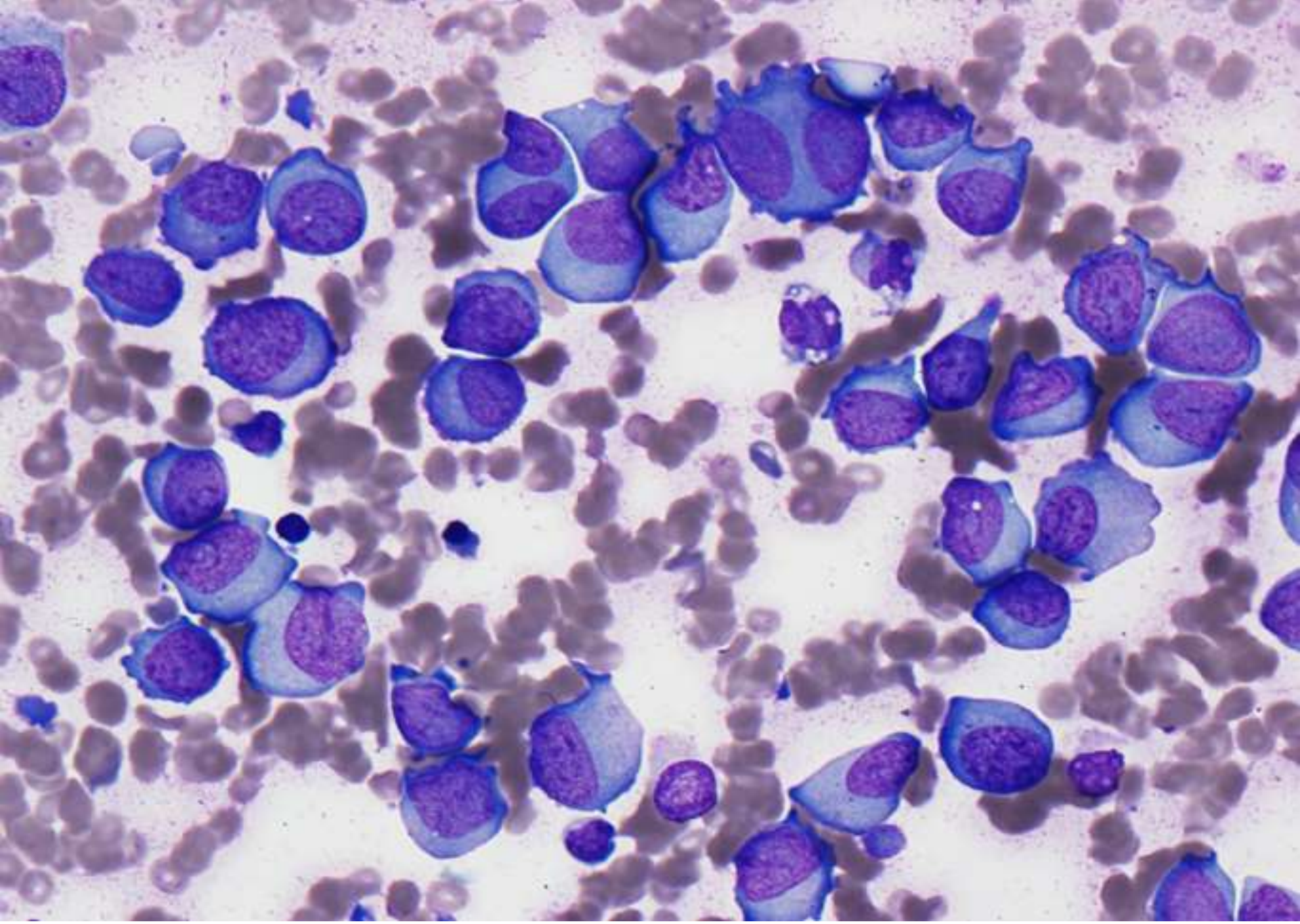
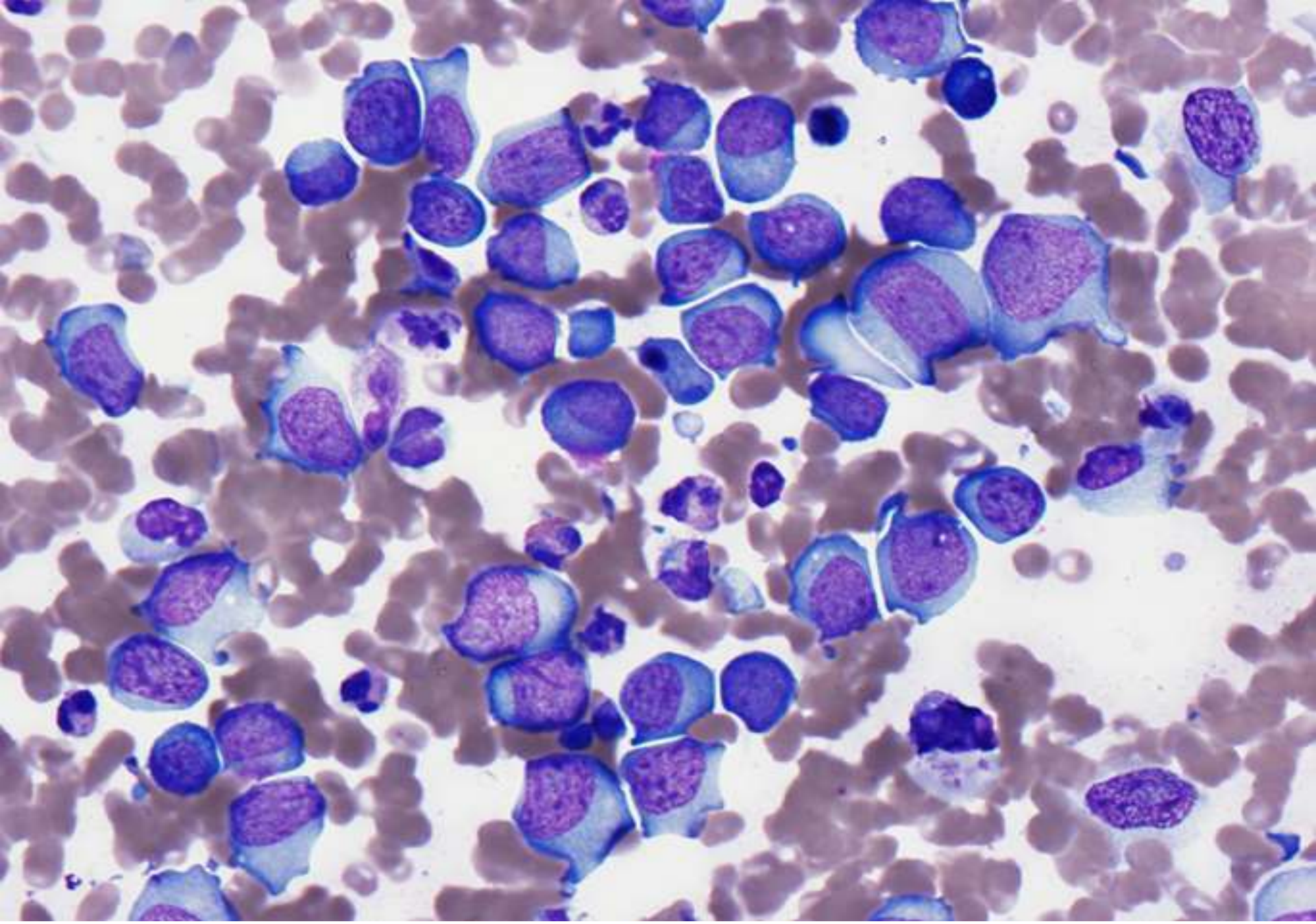
20-0605

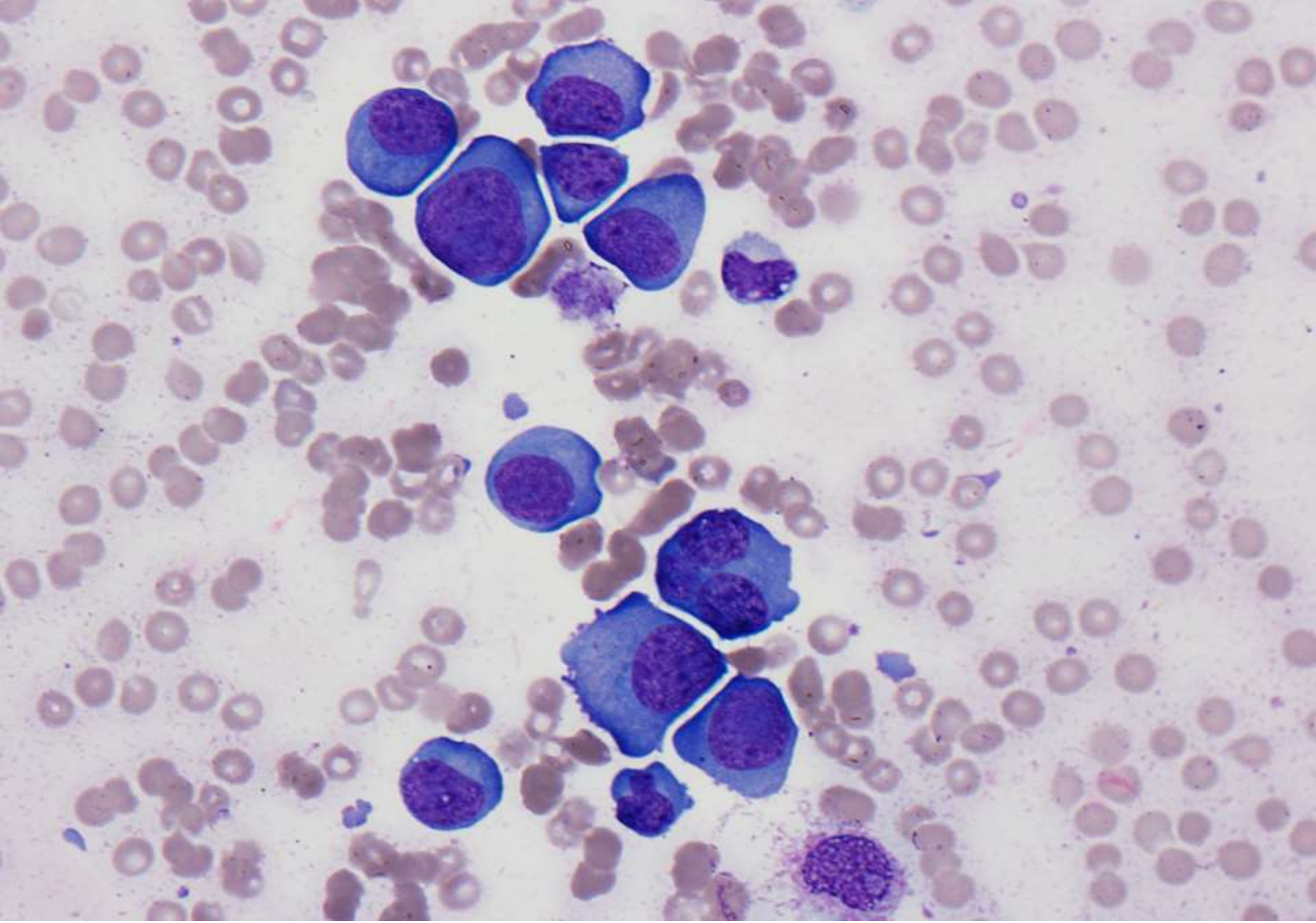
Laura Brown/Yie Xie; UCSF

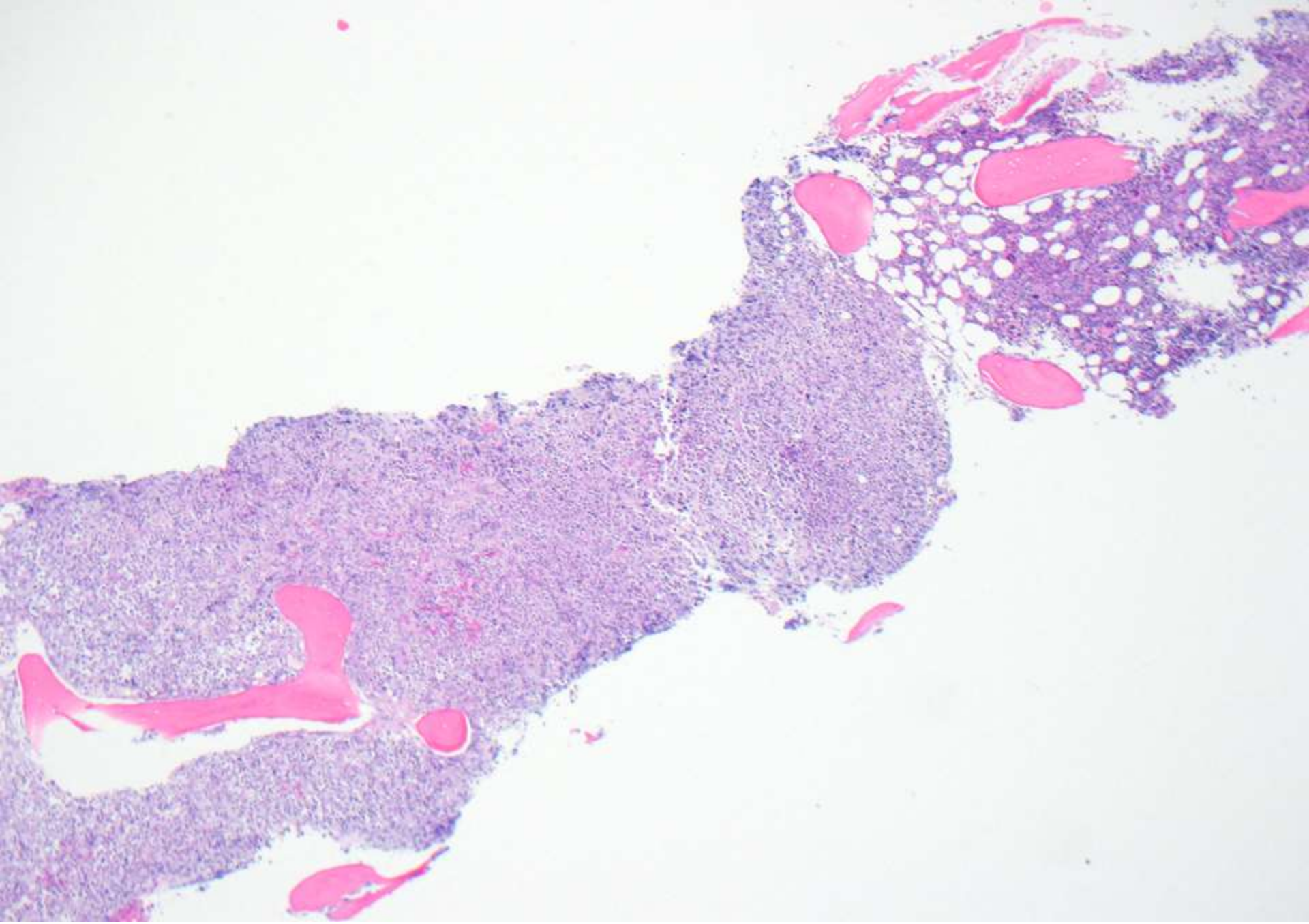
66-year-old M with h/o Hep B presents with diffuse lymphadenopathy and B-symptoms. Undergoes bone marrow aspirate/biopsy.

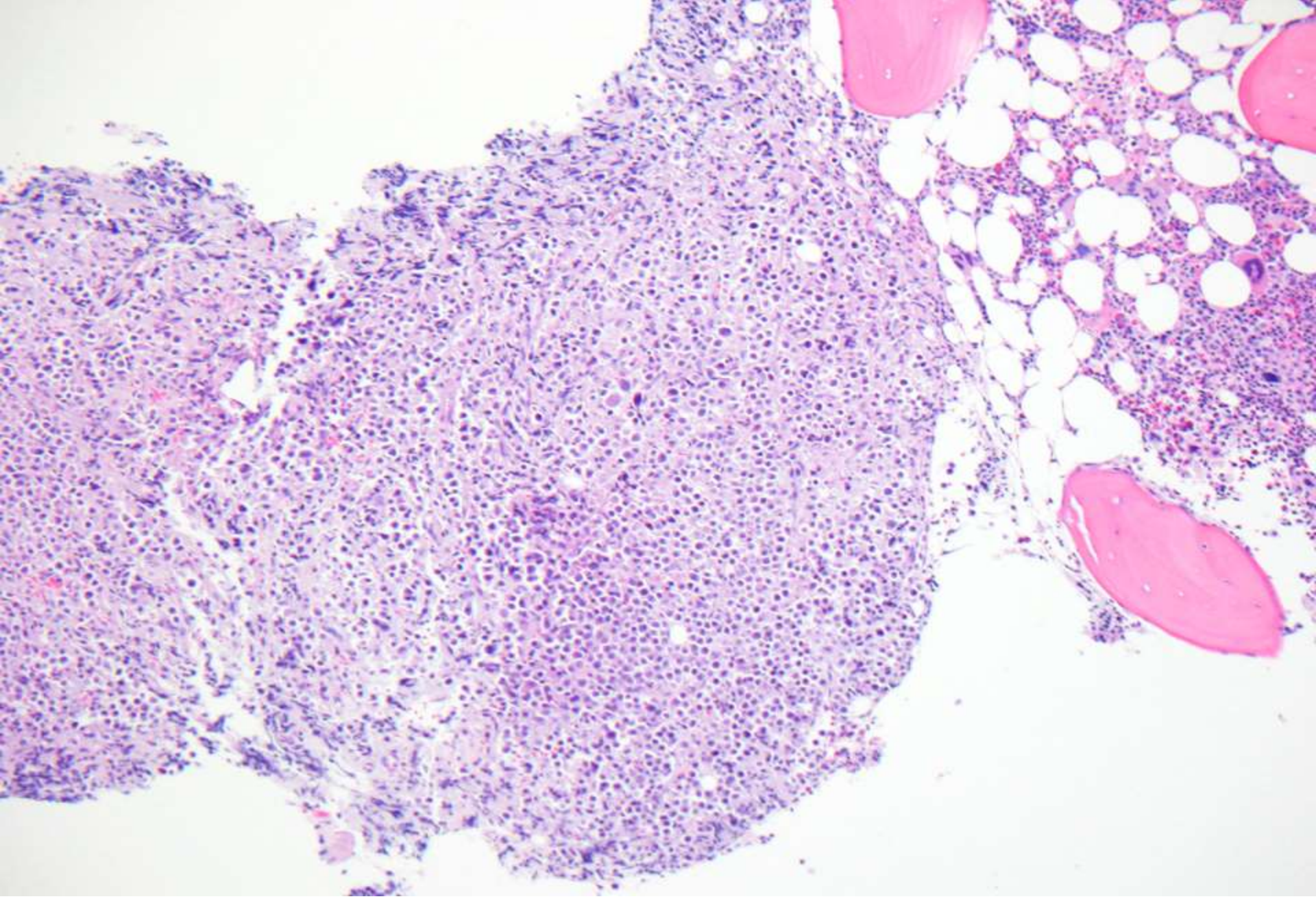


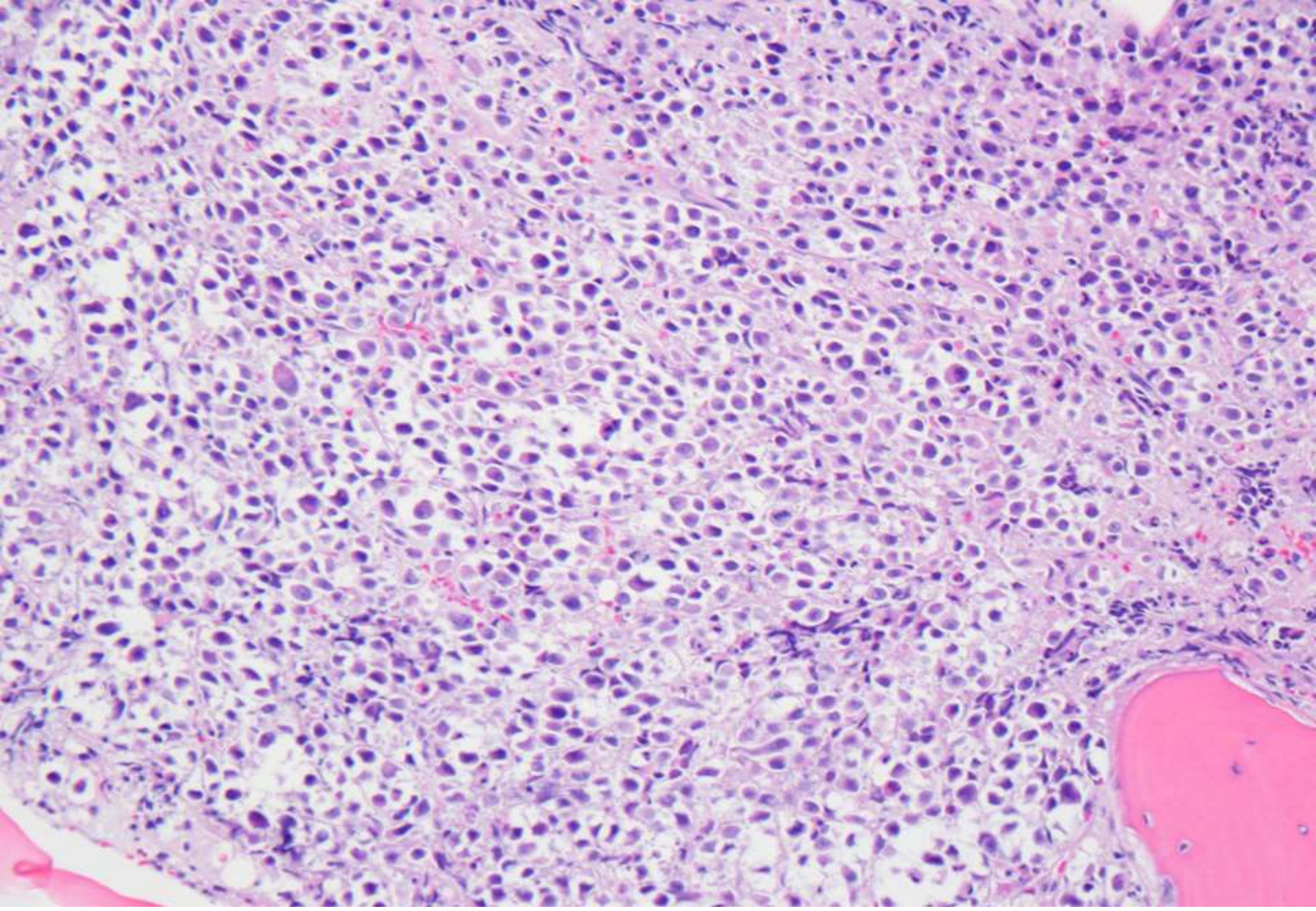


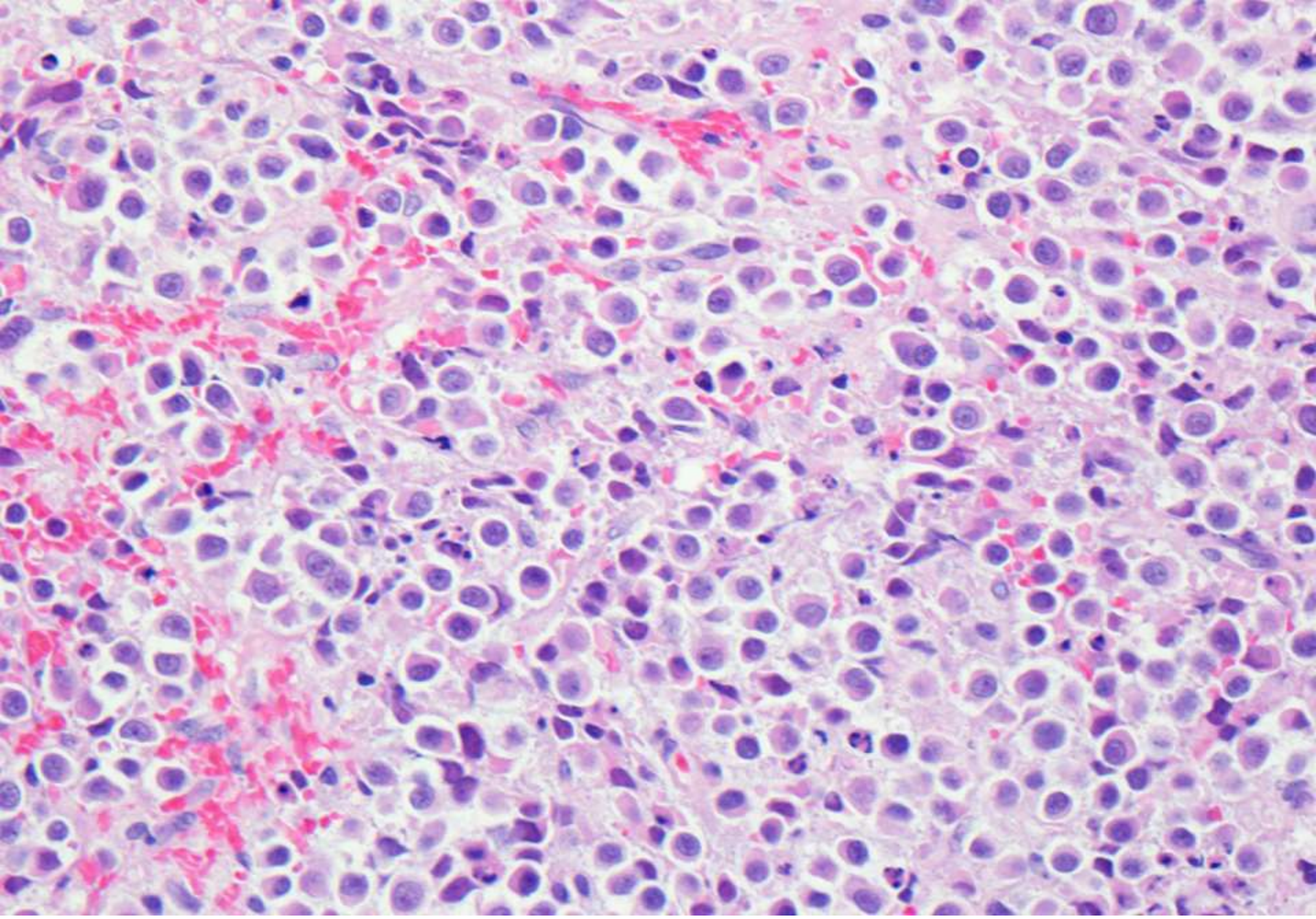


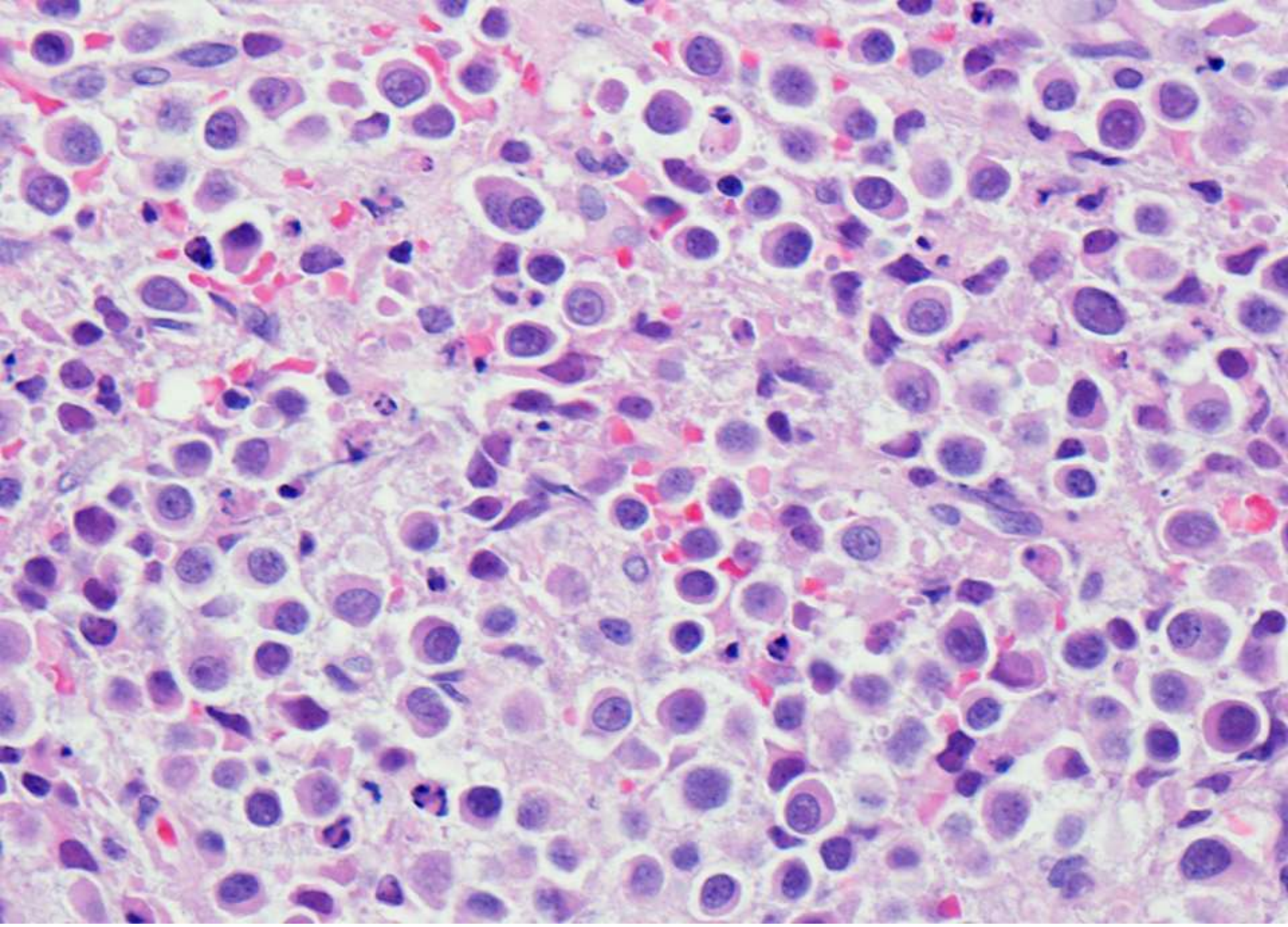


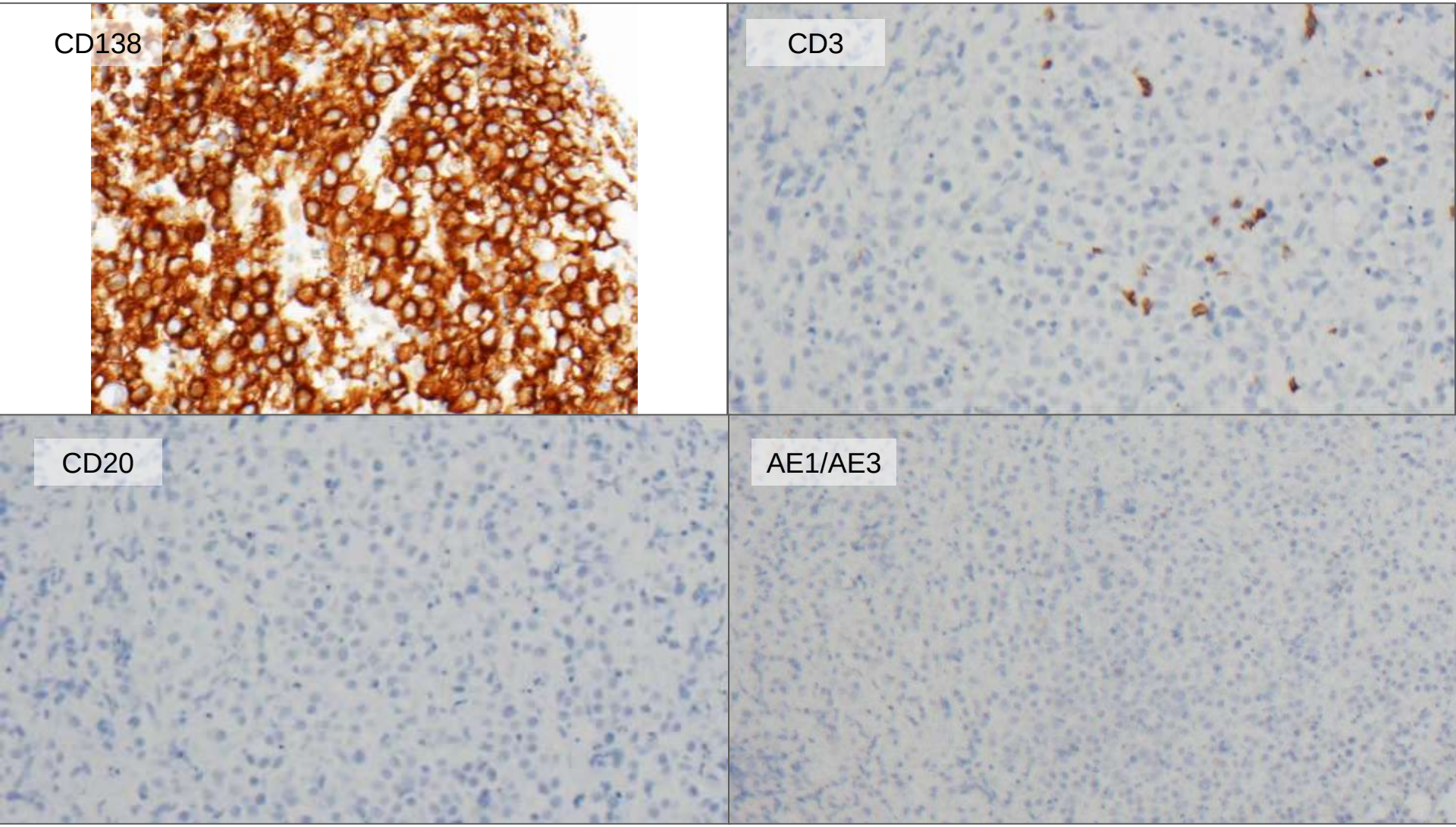










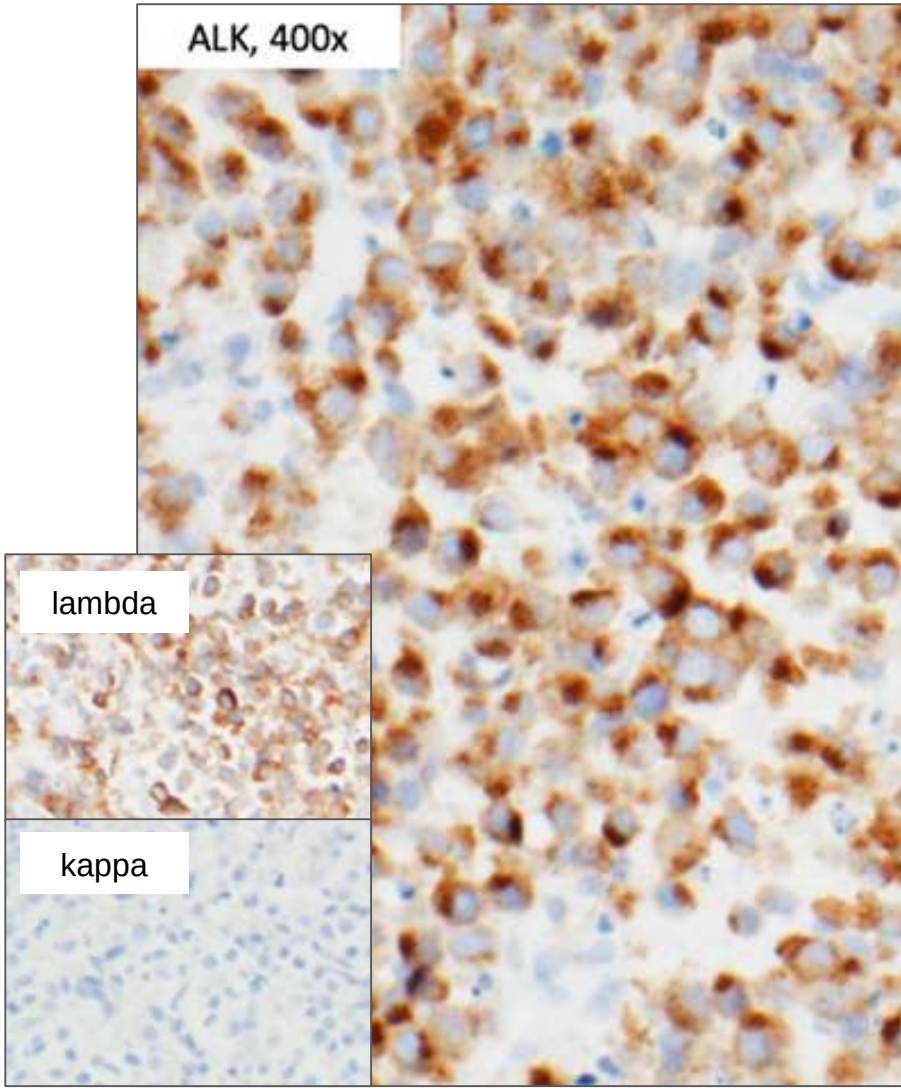

CD138
CD3
CD20
AE1/AE3

Differential diagnosis

- **Plasmablastic myeloma**
- Plasmablastic lymphoma
- ALK+ LBCL
  - ALK+ ALCL
- Extracavitary PEL
- HHV8+ DLBCL, NOS

Immunophenotype

- **Positive IHC:** CD138, lambda, OCT2, MUM1, EMA, and ALK.
- **Negative IHC:** CD20, CD79a, CD3, kappa, PAX5, CD30, EBER, HHV8, AE1/AE3.
- **Flow cytometry:** variable CD45, weak CD64, and intracellular lambda immunoglobulin. All other antigens tested were negative.

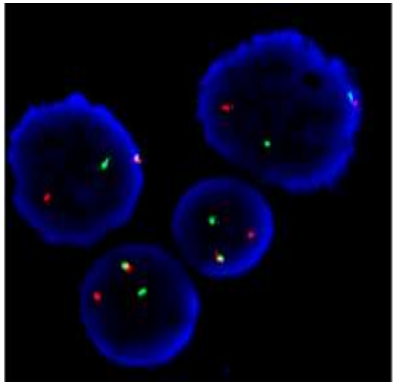


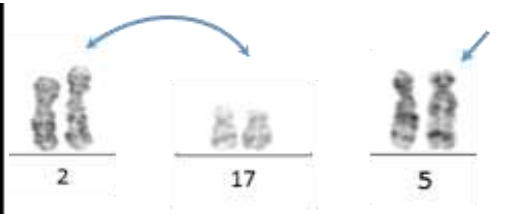
Differential diagnosis

- ~~Plasmablastic myeloma~~
  - History of MM
  - Paraprotein, bone lesions, etc
  - ALK-
- ~~Plasmablastic lymphoma~~
  - HIV
  - EBV+, ALK-
- ALK+ LBCL
- ~~ALK+ ALCL~~
  - CD30+, T-cell antigens +/-
- ~~Extracavitary PEL~~
  - Extranodal, HIV
  - EBV+, HHV8+, ALK-
- ~~HHV8+ DLBCL, NOS~~
  - HIV+/-
  - HHV8+, ALK-

Genetics

- **Karyotype:** 43-46,XY,add(1)(p22),?t(2;17)(p23;q23),add(5)(q35),-13,-14,der(16)t(?3;16)(q11.2;p13.3),+2-3mar[9]/44-46,idem,-3[10]/46,XY[1]
- **FISH:** POSITIVE for ALK rearrangement.





Images courtesy of Joe Qi

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
CLTC-ALK gene fusion	NM_004859-NM_004304	Pathogenic	255	N/A

ALK+ Large B-cell Lymphoma

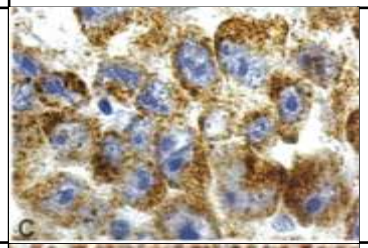
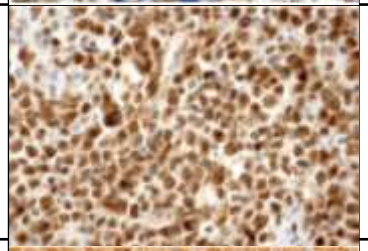
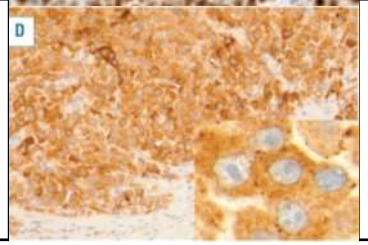
- Clinical:
  - Very rare lymphoma occurring over a wide age range, M>>F.
  - Not associated with immunosuppression.
  - Mostly involves LN; often presents at advanced stage.
  - Bone marrow is involved in 25%.
  - 11 mo survival with stage III/IV disease; longer if early stage and in childhood.
- Morphology:
  - Diffuse or sinusoidal cohesive infiltrate of immunoblastic or plasmablastic cells with prominent nucleoli and amphophilic cytoplasm.
  - Occasionally atypical multinucleated tumor cells.
- Immunophenotype:
  - Positive: ALK, EMA (strong), CD138, MUM1, cIg (usually IgA), MYC (variable, weak), rarely cytokeratin or nonspecific T-cell markers like CD4, CD43.
  - Negative or weak/partial: CD20, CD79a, PAX5, CD45, CD30, HHV8, EBV
- Genetics
  - Most commonly t(2;17)(p23;q23) (CLTC-ALK).
  - Occasionally t(2;5)(p23;q35), (NPM1-ALK)
  - Rarely cryptic insertion of ALK into 4q22-24 or ALK fusion to SQSTM1, SEC31A, or others.
  - Complex karyotype is common.

ALK+ Large B-cell Lymphoma

	Plasmablastic myeloma	**Plasmablastic lymphoma**	**Primary effusion lymphoma**	**ALK+ LBCL**	**HHV8+ DLBCL**
Location	Bone/bone marrow	Extranodal, H&N	Pleural fluid, extracavitary	Nodal	Nodal
Paraprotein	Often	Rarely	No	No	No
HIV association	No	Strong	Strong	No	Strong
EBV	-	+/-	+	-	-
HHV8	-	-	+	-	+
Genetics	Myeloma-associated changes	Complex karyotype, MYC translocation	Complex karyotype	ALK rearranged	N/A

ALK+ Large B-cell Lymphoma

- ALK IHC staining pattern may correlate with the underlying genetic abnormality.
- SQSTM1 (5q35.3) is located very near NPM1 (5q35.1), thus, the cytogenetic findings may be similar.
- t(2;17) may be cryptic/difficult to detect.

Translocation	ALK staining pattern	
t(2;17)(p23;q23) CLTC-ALK		Coarse granular cytoplasmic
t(2;5)(p23;q35) NPM1-ALK		Cytoplasmic, nuclear, or nucleolar staining
t(2;5)(p23;q35) SQSTM1-ALK		Cytoplasmic staining with fine, dispersed granules and dot-like accentuation

2016 WHO; Haematologica 2011 Mar;96(3):464-7

Summary

- ALK+ LBCL is a rare and aggressive lymphoma with plasmablastic morphology, that expresses plasma cell markers and is often negative for B and T cell antigens.
- A high degree of suspicion is required for accurate diagnosis.
- The pattern of ALK IHC staining may suggest the underlying genetic abnormality.

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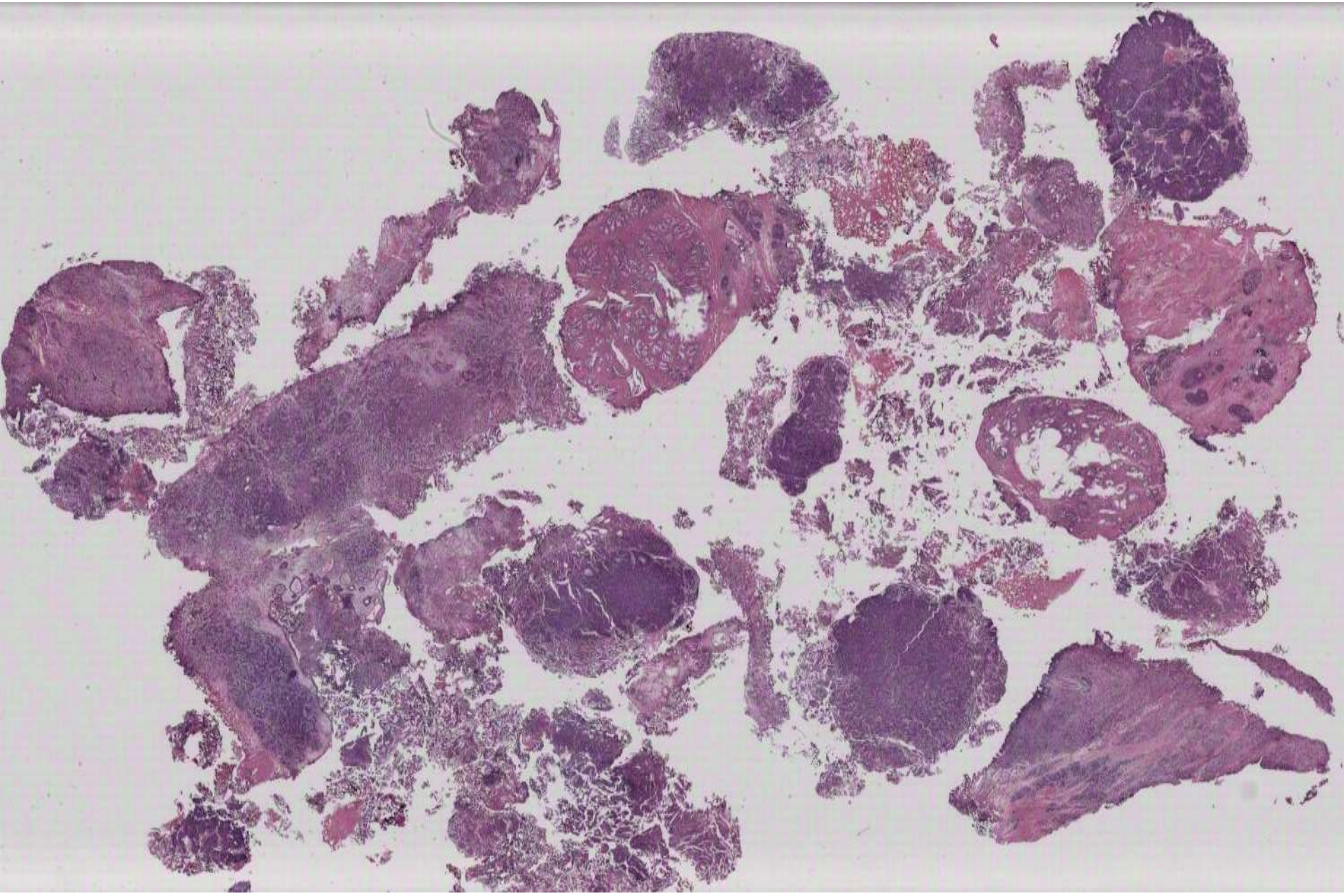
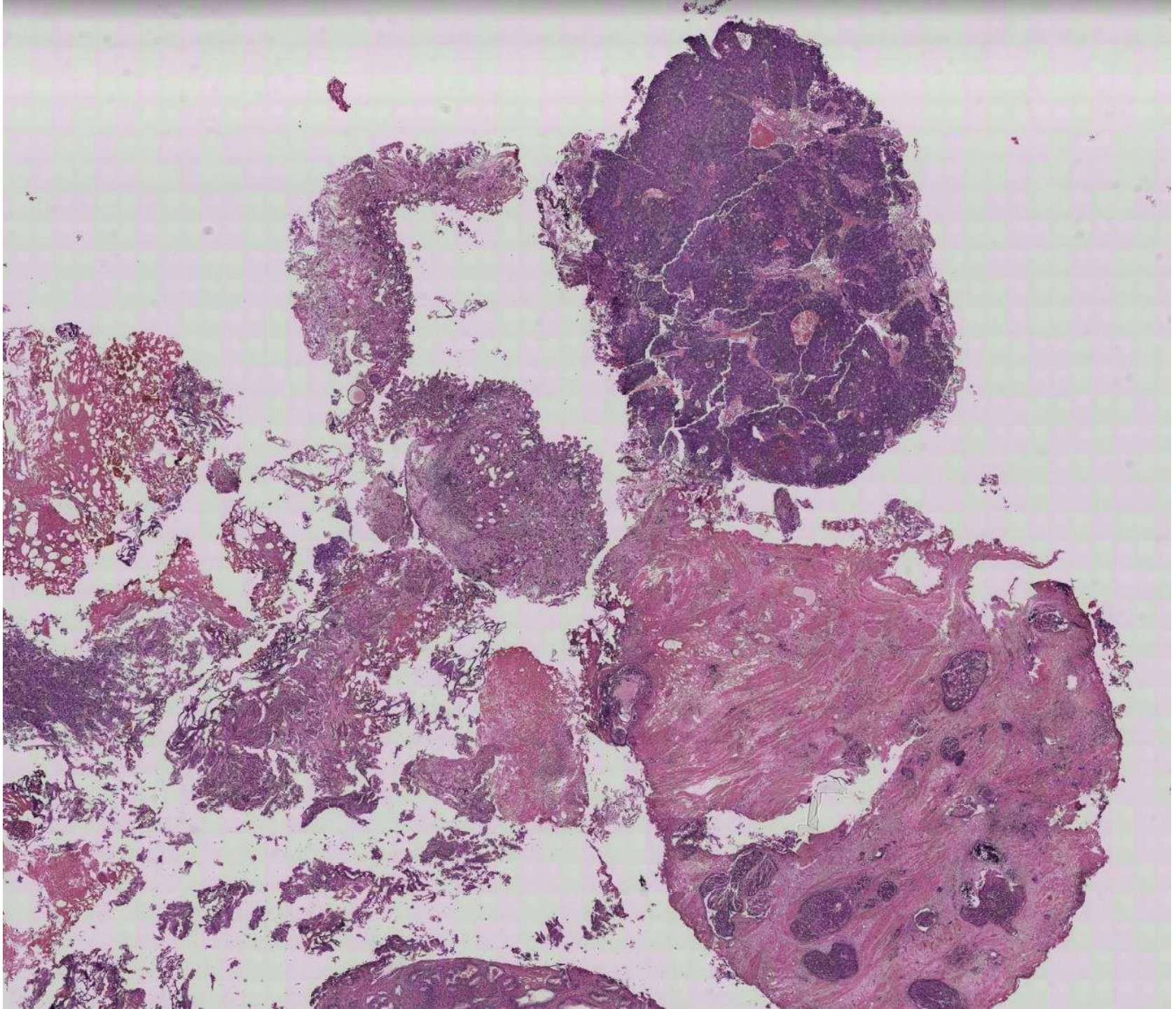
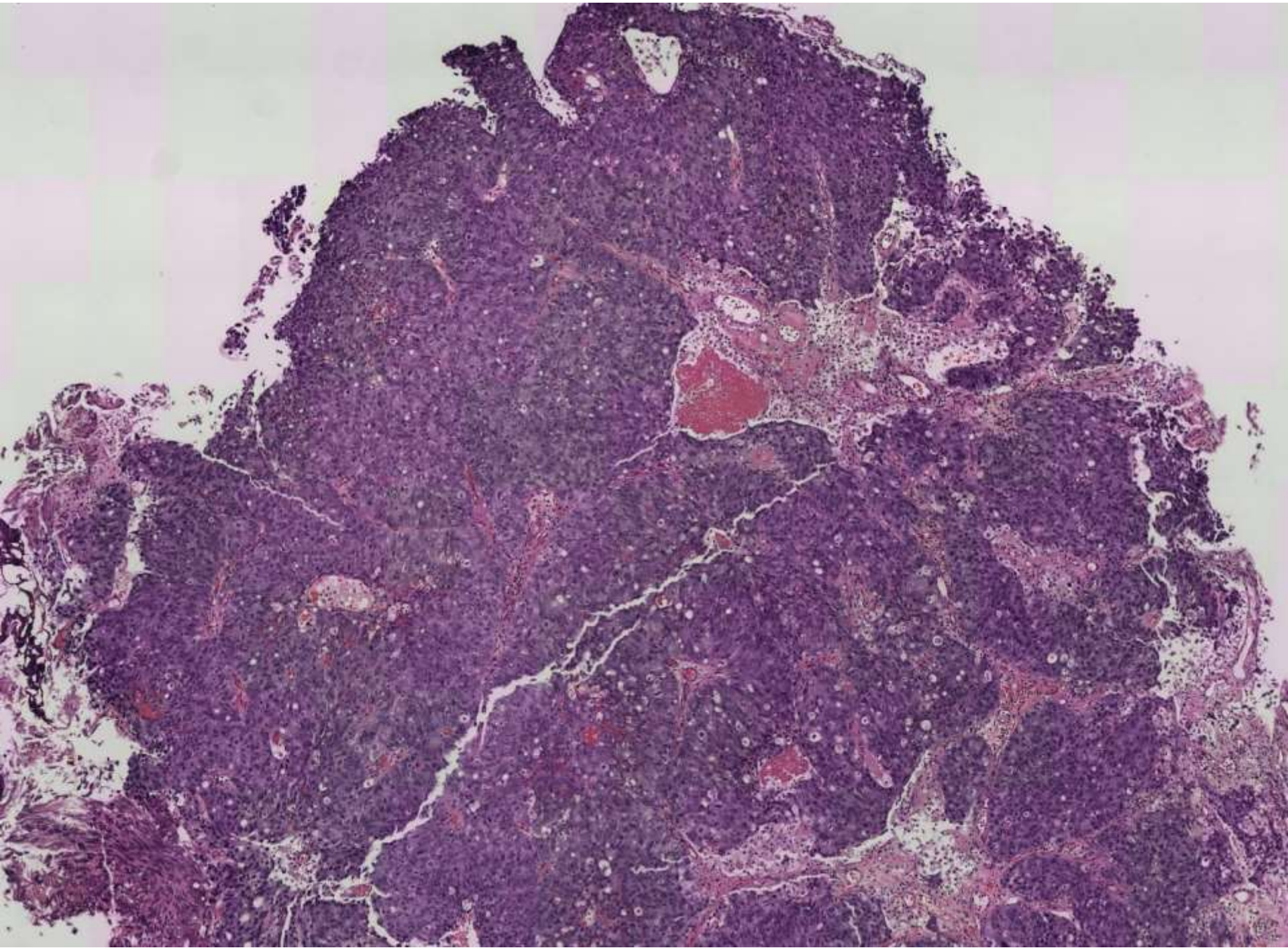
20-0606
(scanned slide avail!)

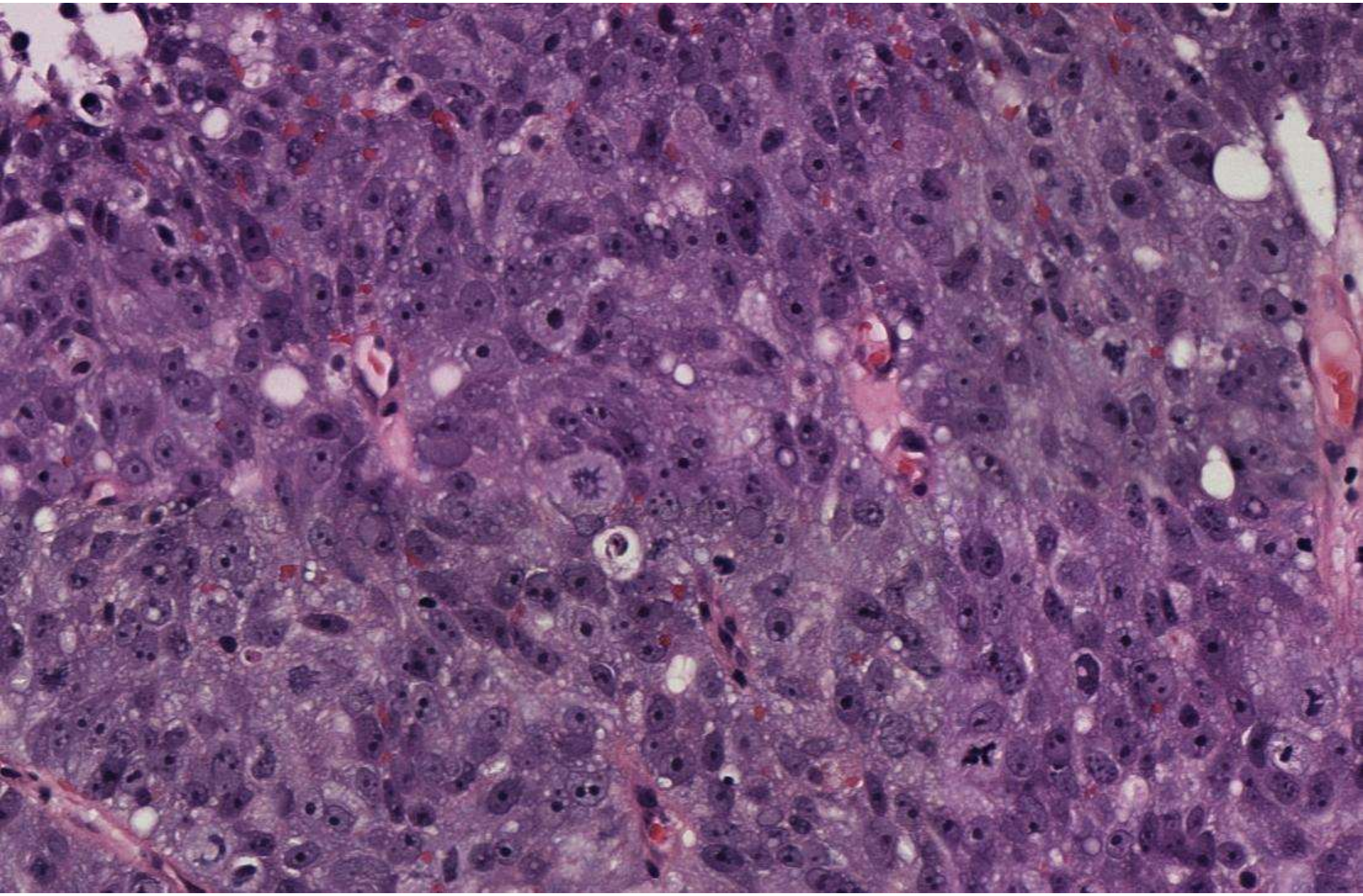
Ankur Sangoi; El Camino Hospital

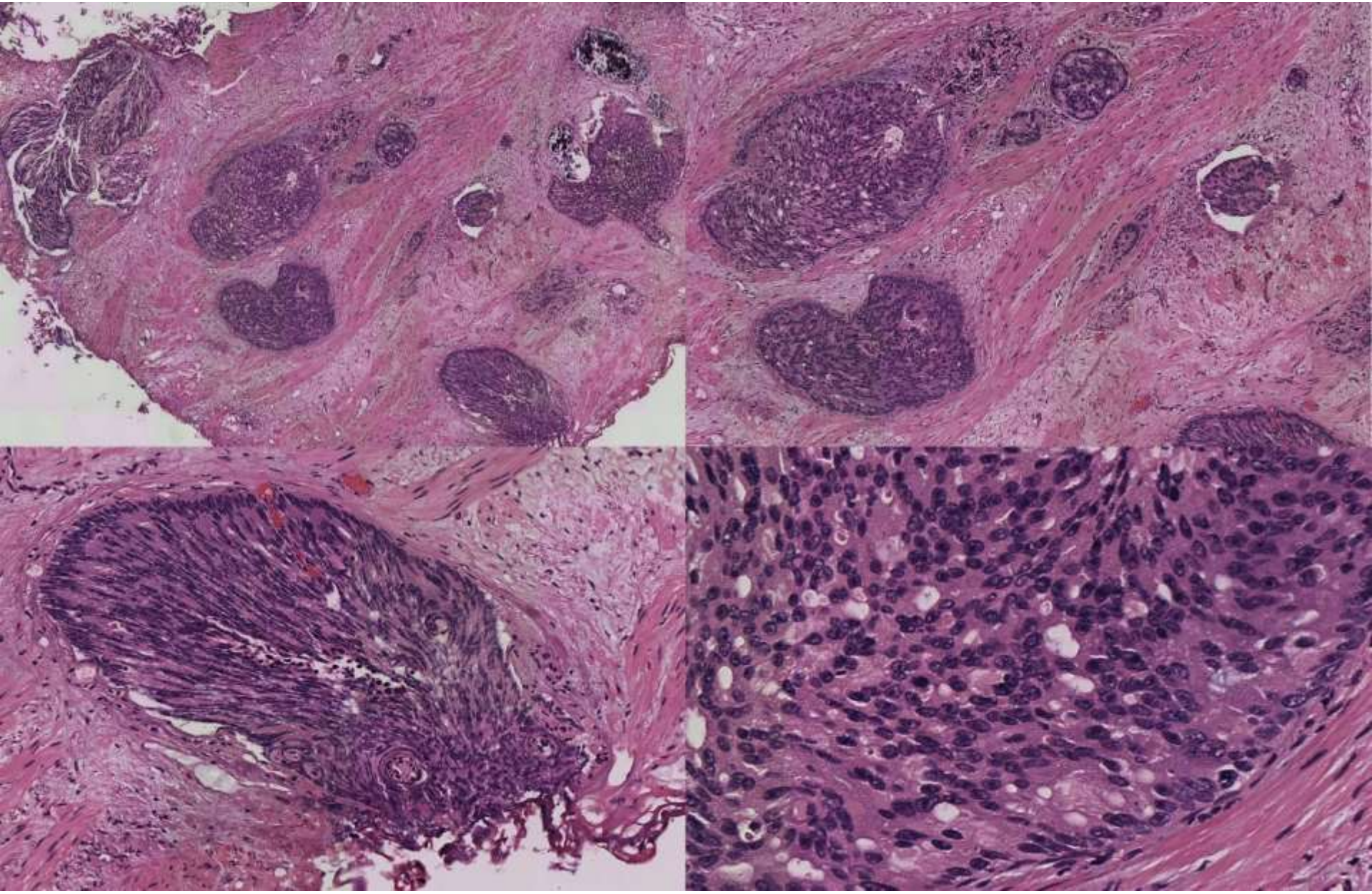
75-year-old-M with BPH and bladder neck lesion, transurethral resection of bladder/prostate performed.

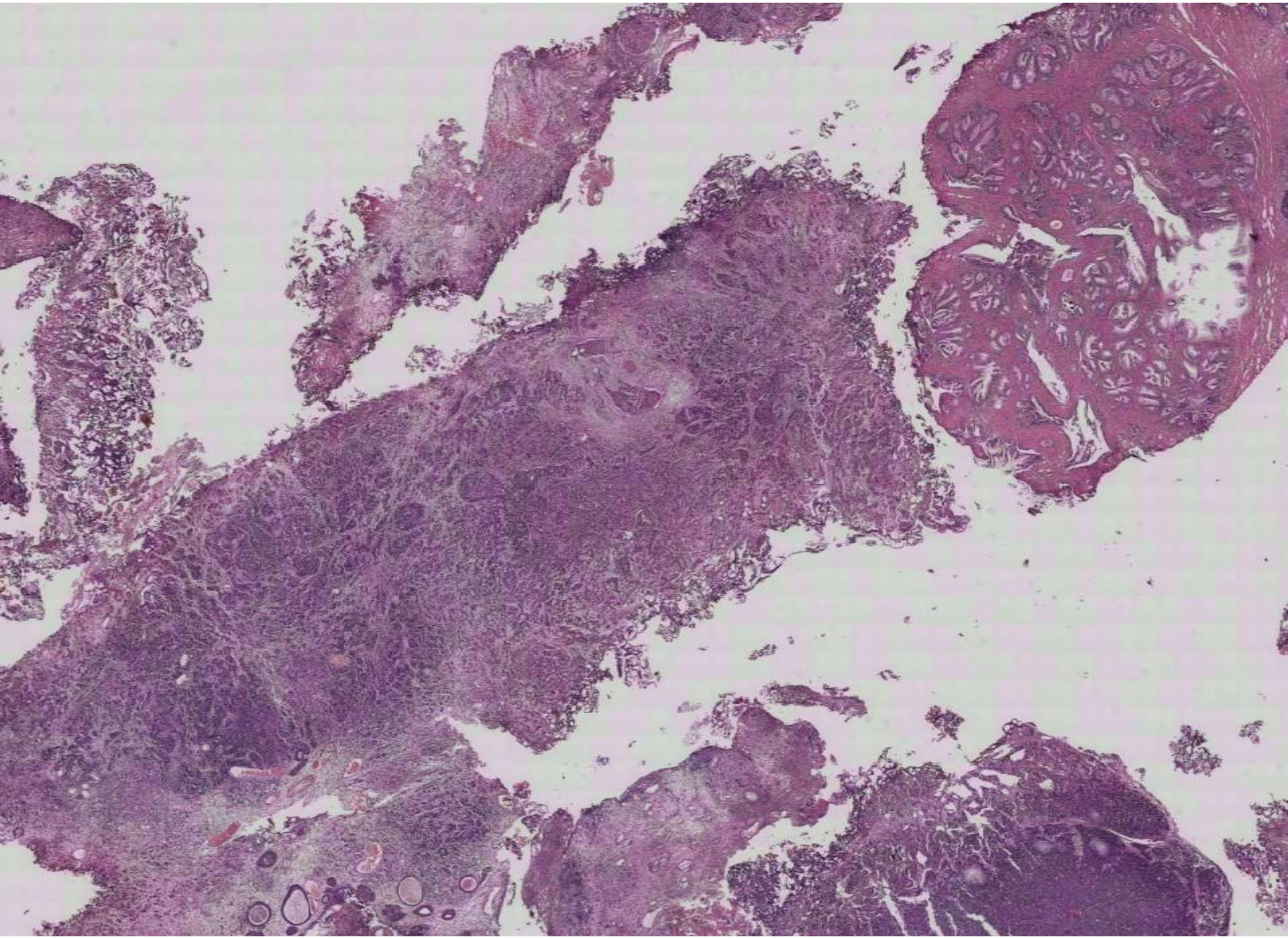


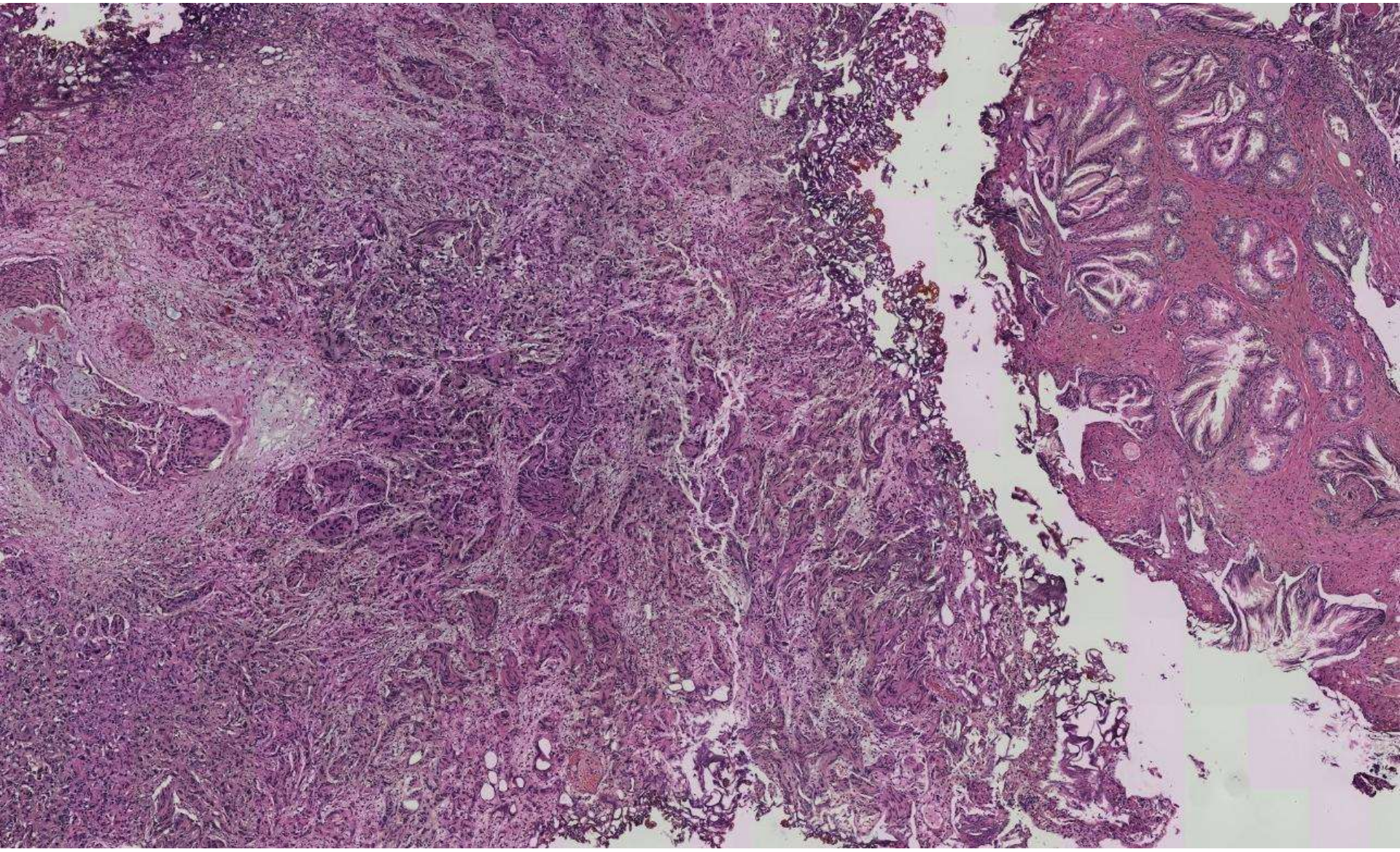


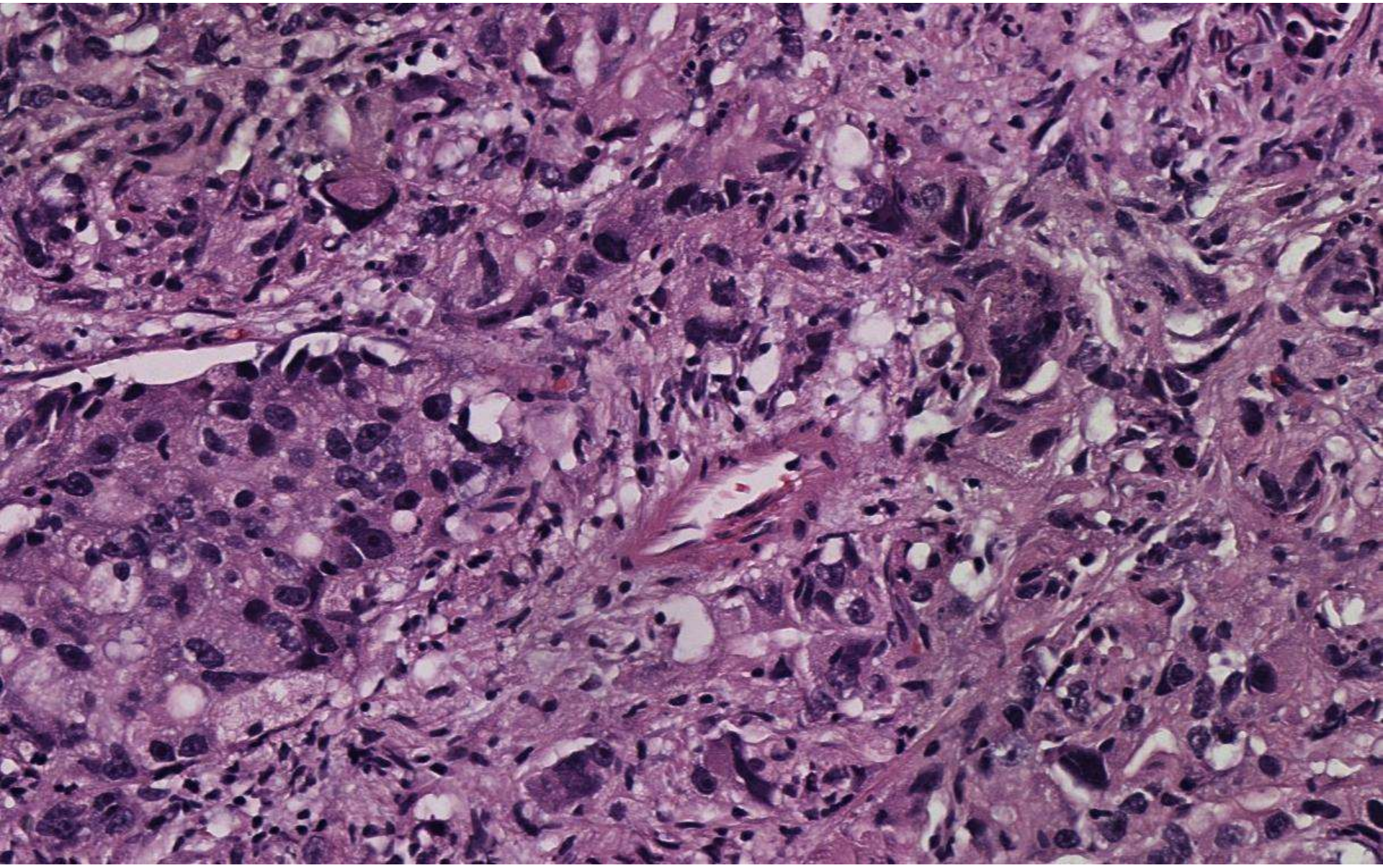


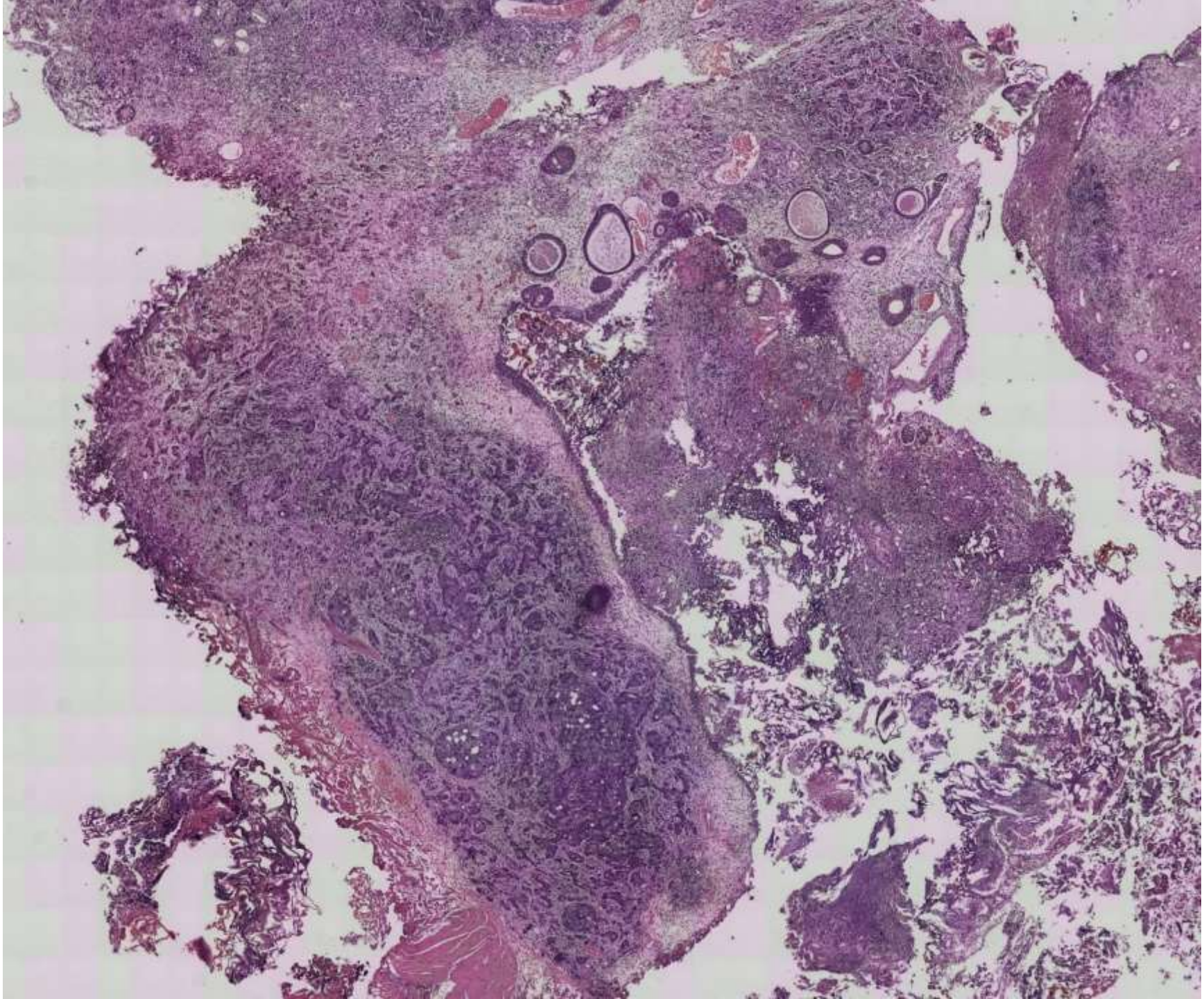


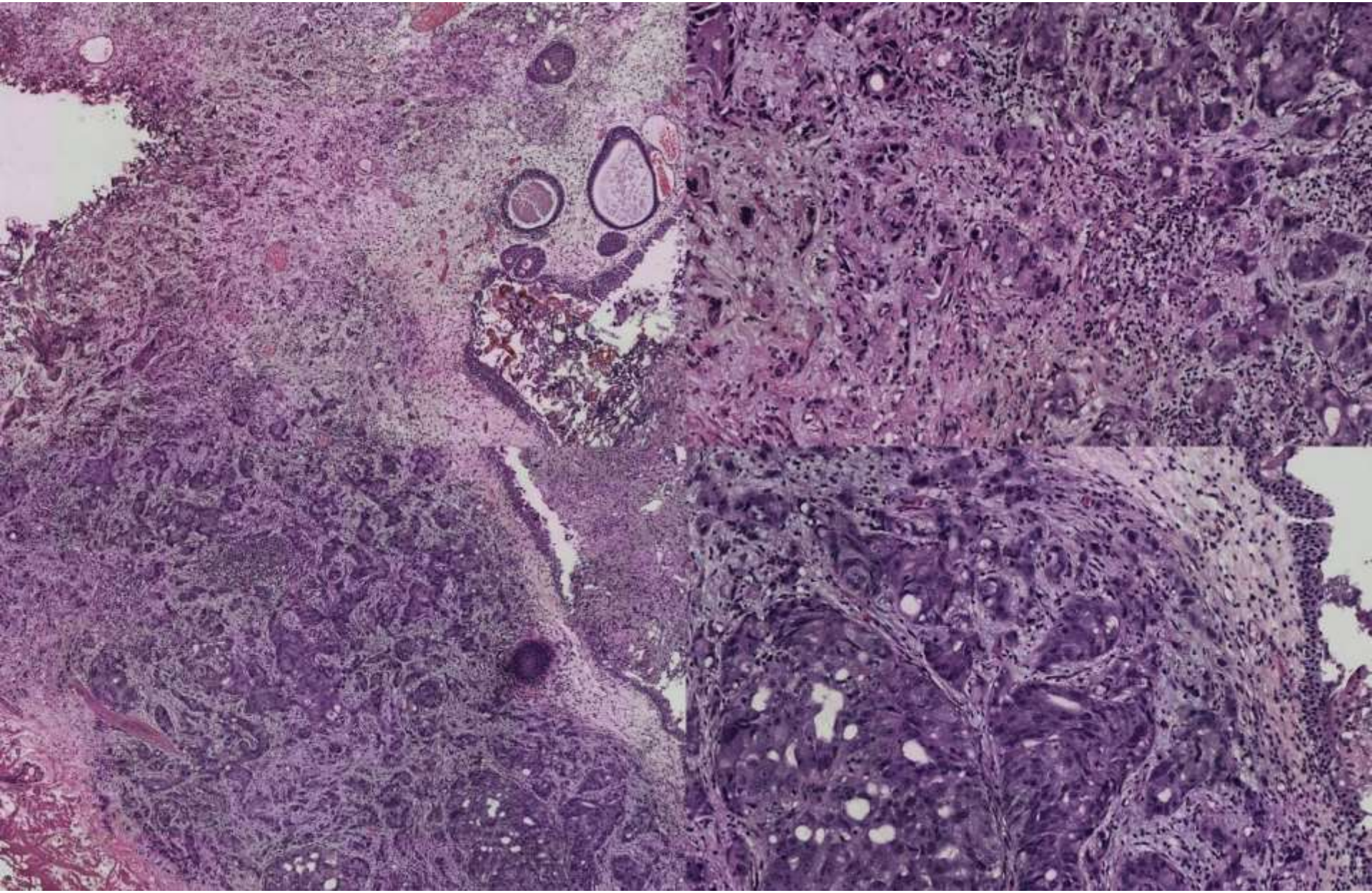


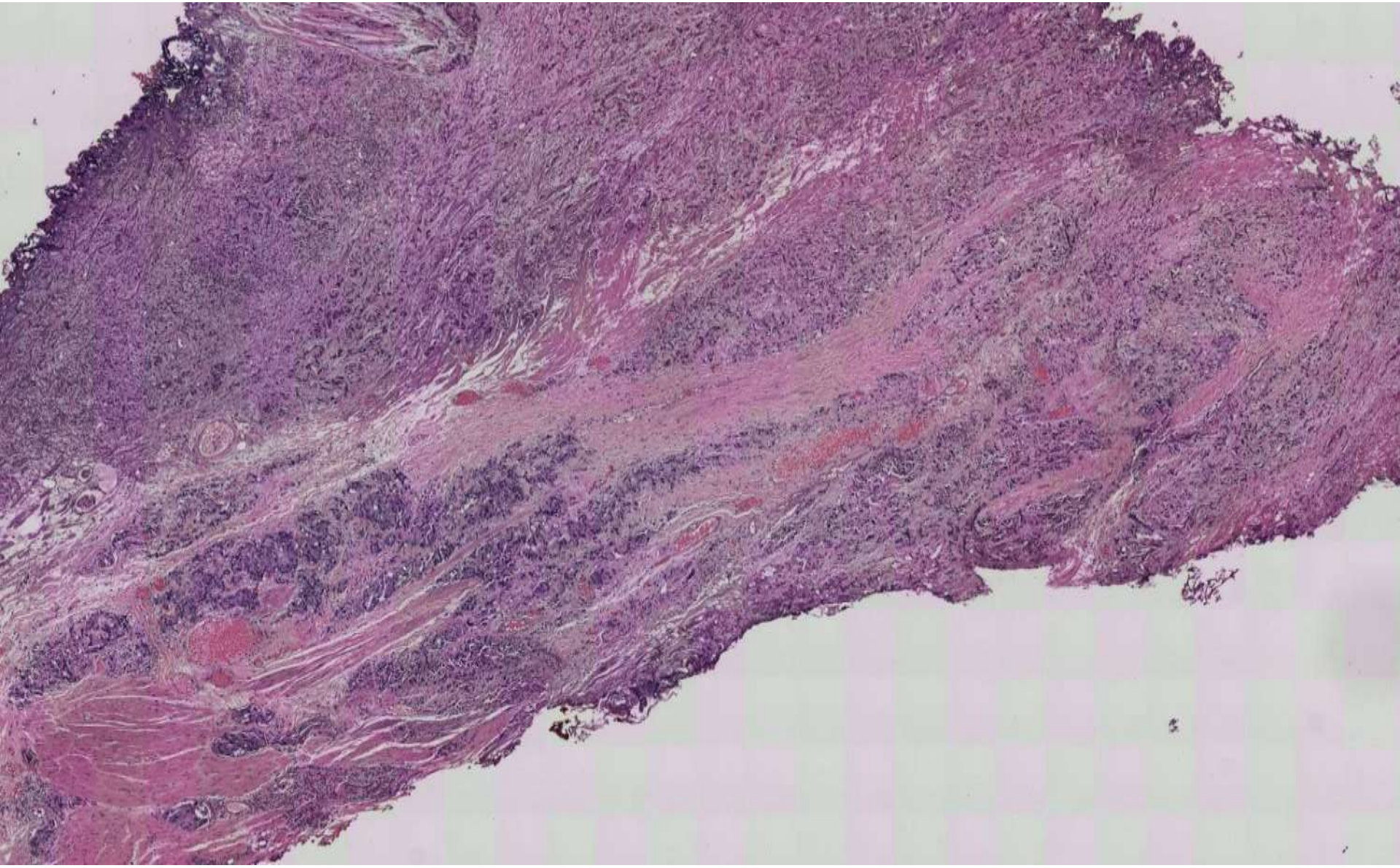


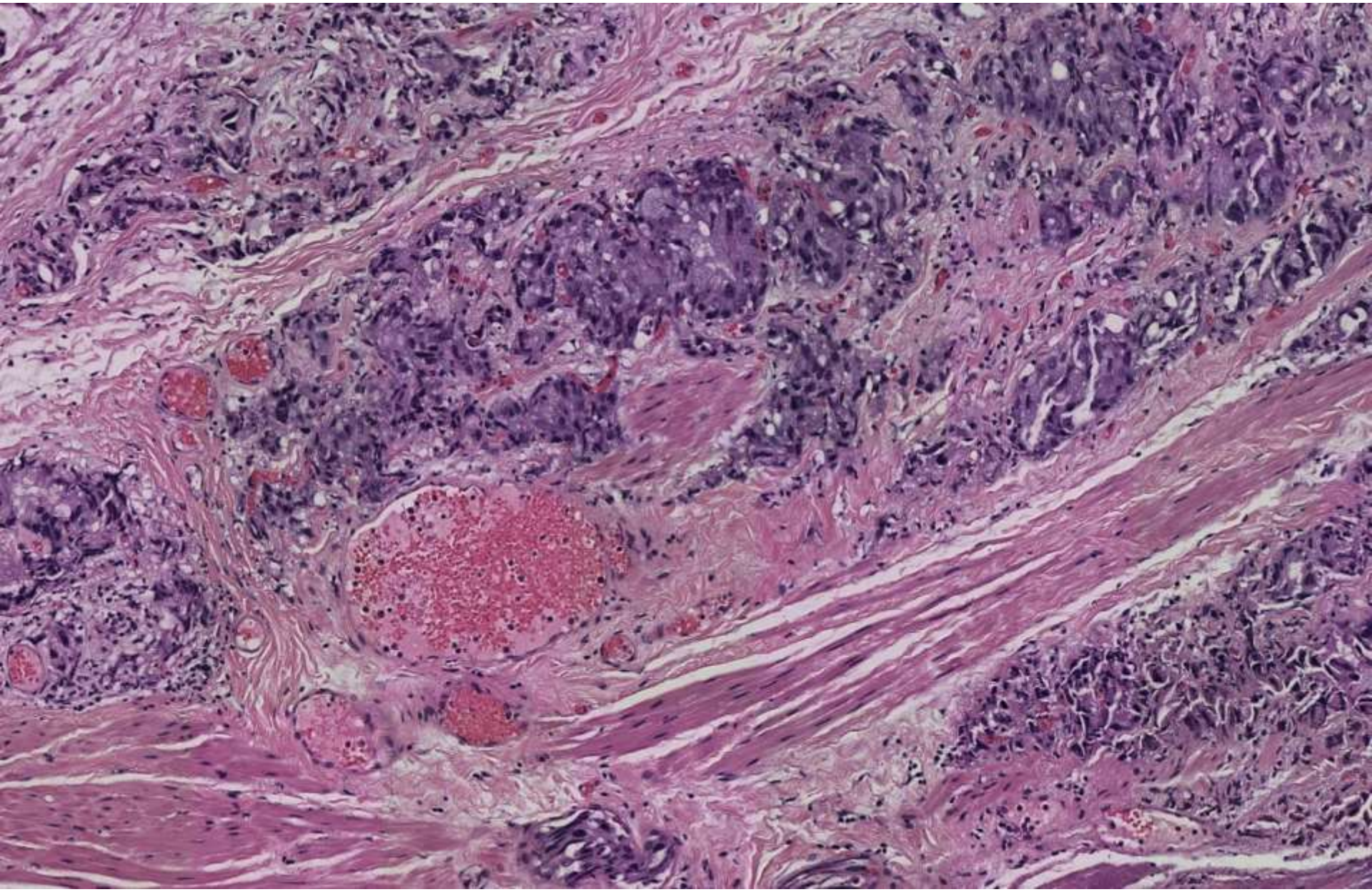








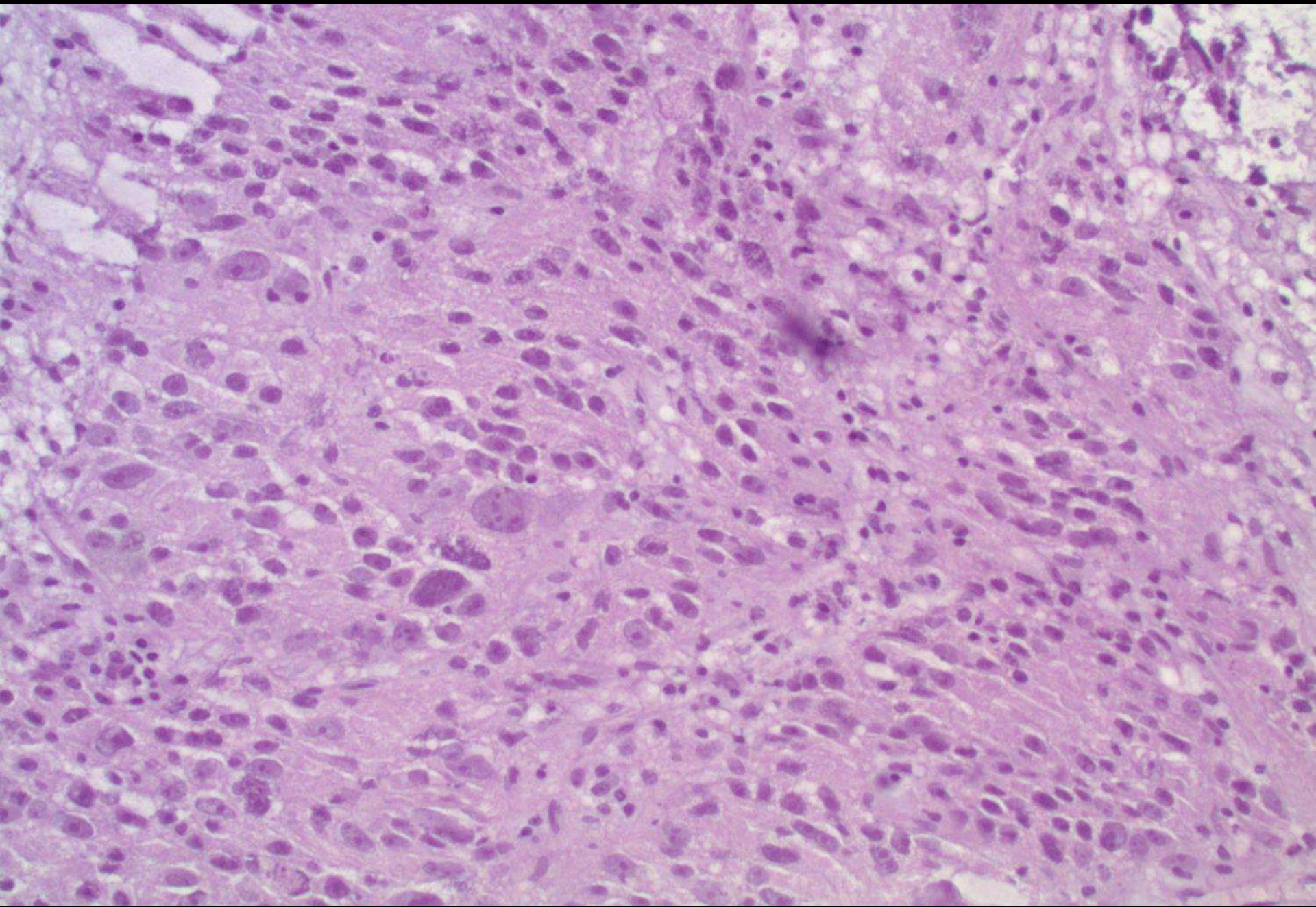




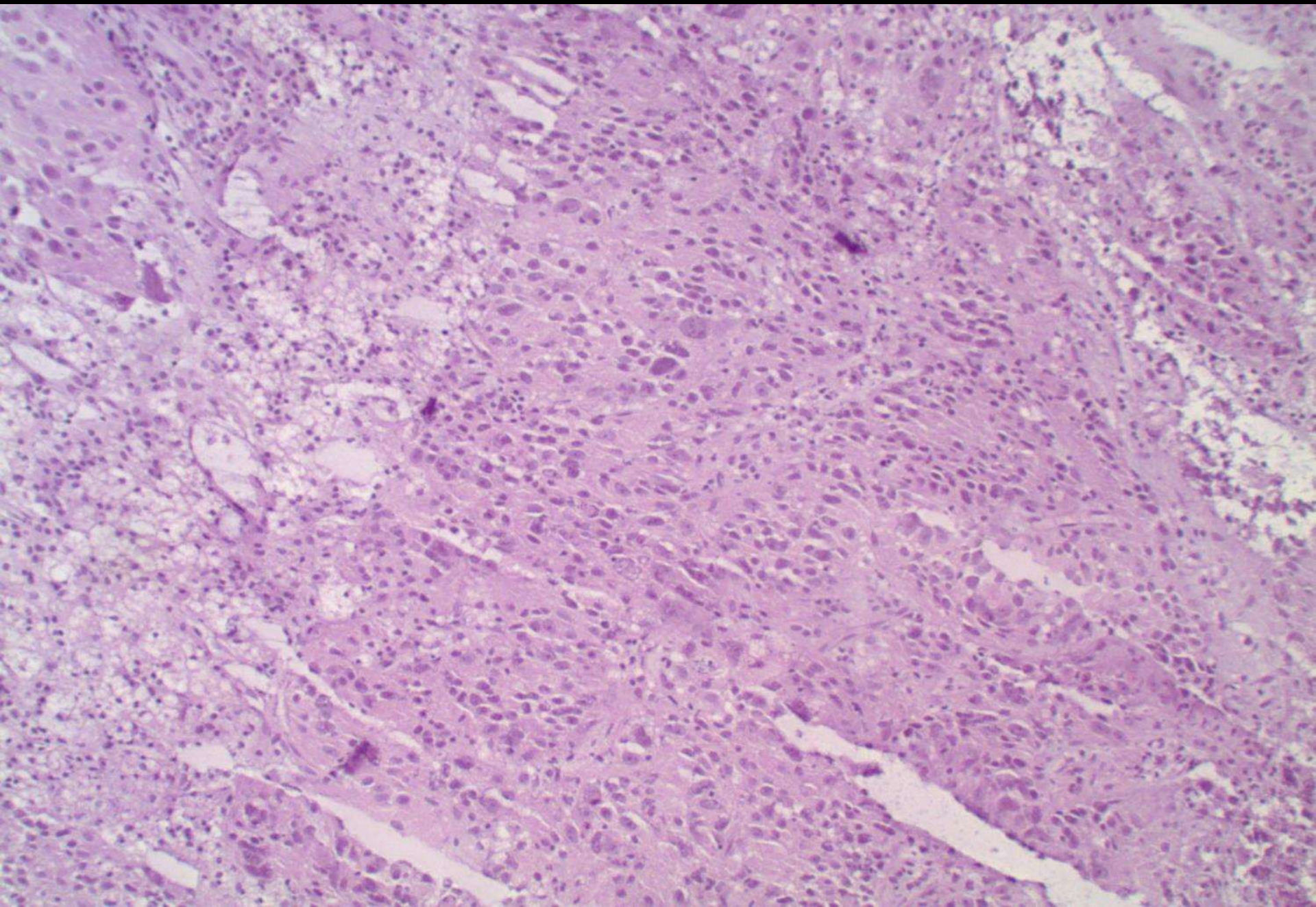
DDx

- High grade urothelial carcinoma
- High grade prostatic adenocarcinoma
- Urothelial + prostatic carcinoma
- High grade neuroendocrine carcinoma
- Melanoma
- Metastatic carcinoma

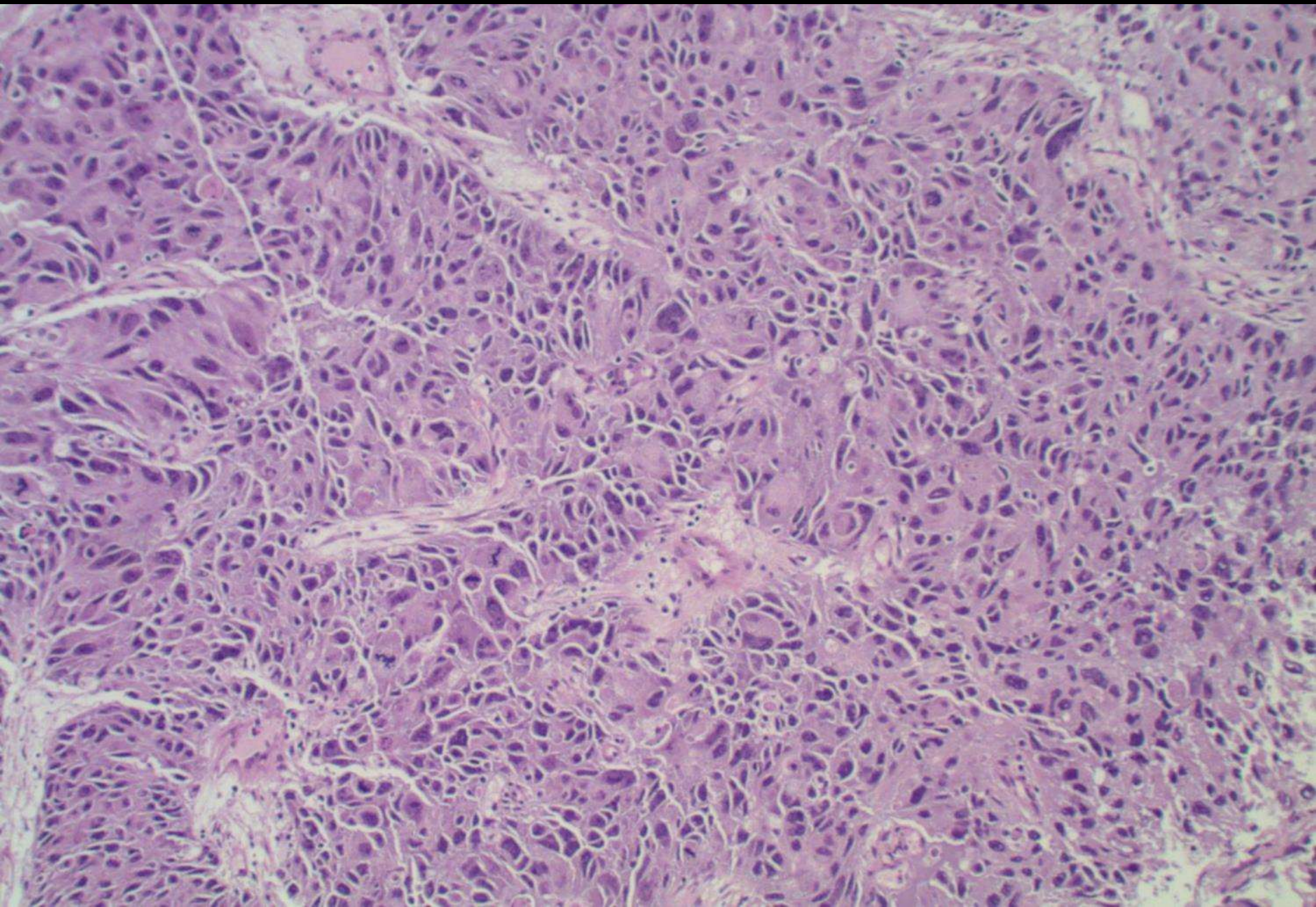
frozen section



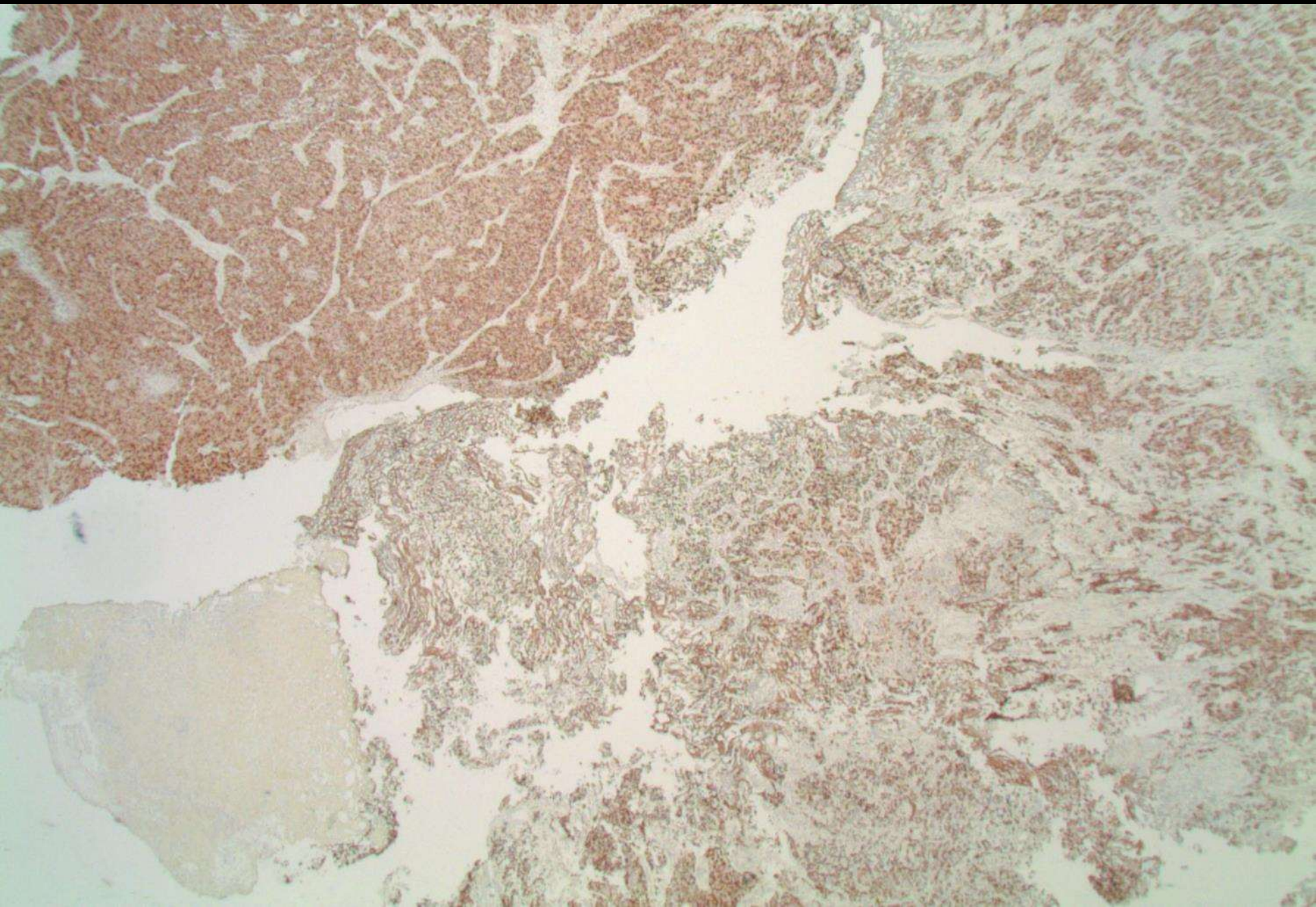
frozen section



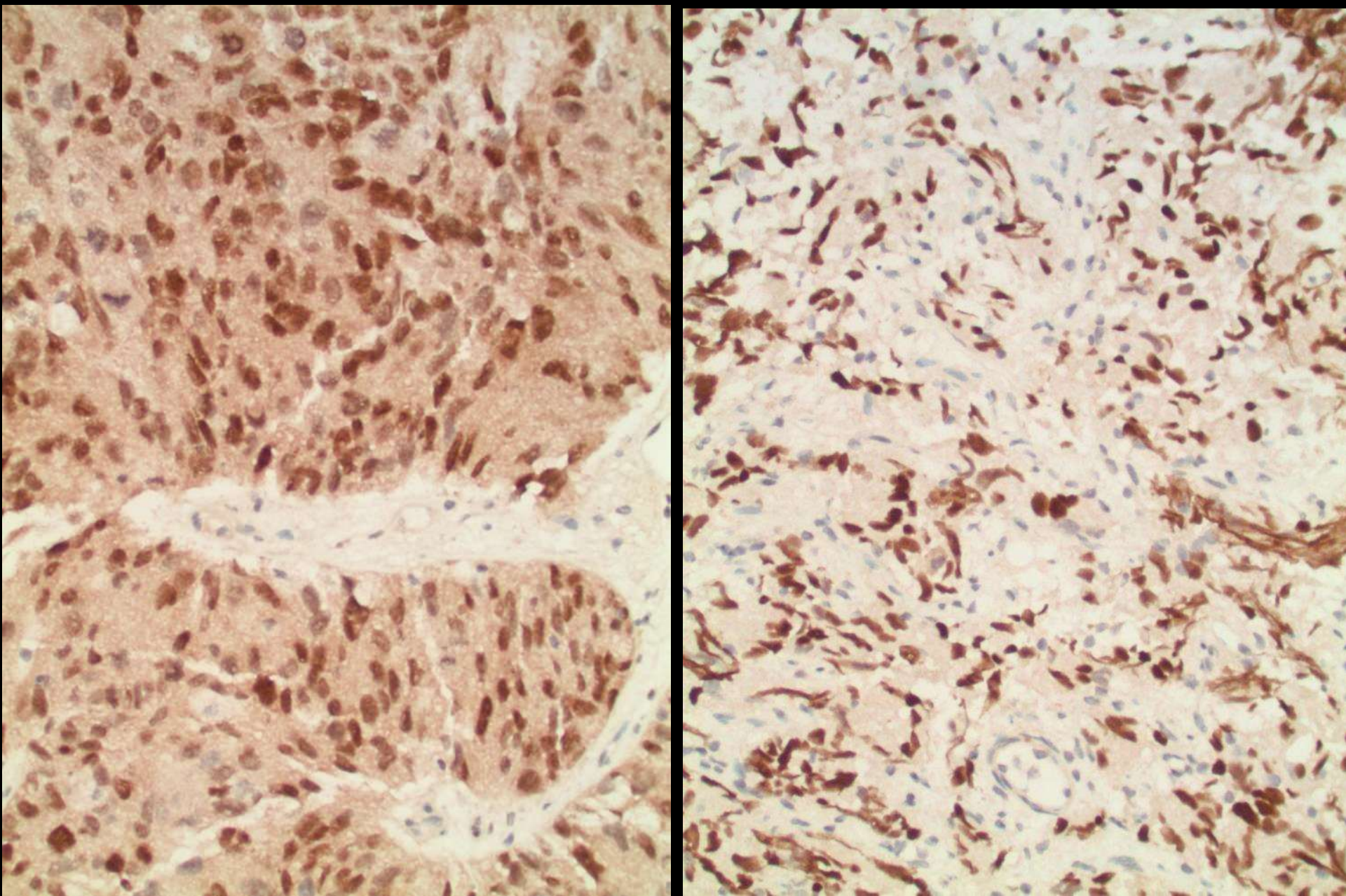
permanent of frozen section



NKX3.1 (brown) + PSAP (red)



NKX3.1 (brown) + PSAP (red)



Prostatic Adenocarcinoma With Focal Pleomorphic Giant Cell Features

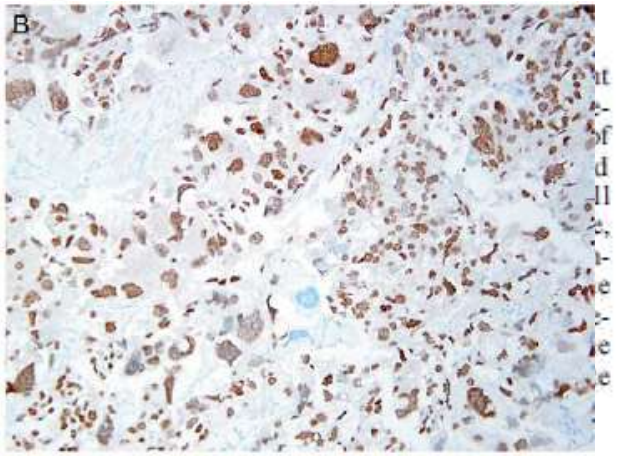
A Series of 30 Cases

Abdullah M. Alharbi, MD, Angelo M. De Marzo, MD, PhD, Jessica L. Hicks, MSc, Tamara L. Lotan, MD, and Jonathan I. Epstein, MD

Abstract: Prostatic adenocarcinoma with focal pleomorphic giant cell features is rare with the only prior series consisting of 6 cases. From 2005 to 2018, we identified 29 cases from our consult service and 1 case from our own institution. Men ranged in age from 39 to 90 years (median = 75.5). Diagnostic specimens consisted of needle biopsies (n = 13); transurethral resections (n = 7), urethral/bladder biopsies (n = 8), radical prostatectomy (n = 1), and orchiectomy (n = 1). In all cases, there was usual acinar prostatic adenocarcinoma, where the highest grade in all cases was Gleason score 9 to 10 (Grade Group 5). On average, 68% of the involved cores had cancer with a maximum percent of cancer averaging 55%; on average, transurethral resections had 85% of the area involved by cancer. Areas of cancer showing pleomorphic giant cell features were focal (< 5%). Two of the needle biopsies showed extraprostatic extension. The radical prostatectomy had seminal vesicle invasion and positive margins with lymphovascular invasion. Prostatic adenocarcinoma with focal pleomorphic giant cell features is always accompanied by extensive usual acinar prostate adenocarcinoma where the highest grade in all cases was Gleason score 9 to 10 (Grade Group 5). Although the pleomorphic component is focal, it can mimic urothelial carcinoma. IHC can be misleading as PSA staining is often negative or focal in both the pleomorphic and usual prostatic adenocarcinoma components. NKX3.1 is the most sensitive prostate marker, but was still focal in 1 usual prostatic adenocarcinoma and negative in 2 pleomorphic components. Prostatic adenocarcinoma with focal pleomorphic giant cell features has a dismal prognosis. In men with no prior diagnosis of prostate adenocarcinoma and >1-year follow-up, 7/19 (37%) were dead at a median of 8 months after diagnosis. Of the 7 men with a prior history of prostate adenocarcinoma, 4/7 (57%) were dead at a median of 7 months after diagnosis of recurrent prostate adenocarcinoma with pleomorphic giant cell features.

Key Words: NKX3.1, PSA, P501S, HOXB13, GATA3, androgen receptor, prostate adenocarcinoma

(*Am J Surg Pathol* 2018;42:1286–1296)



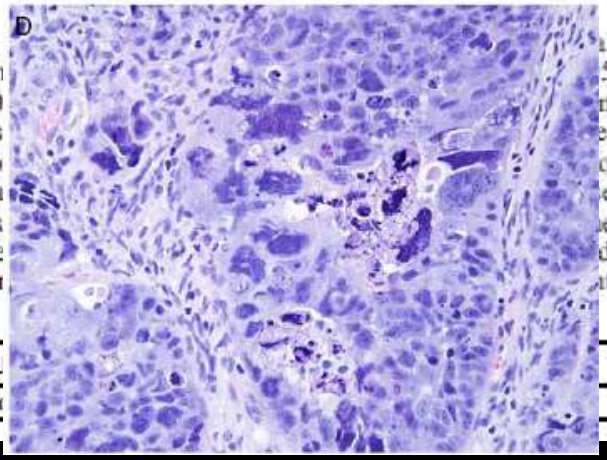


TABLE 4. Imunohistochemical Profile of 10 Cases of Pleomorphic Giant Cell Carcinoma

% Positive Tumor	NKX3.1 (%)		PSA (%)		P501S (%)		GATA3		Ki-67 (%)		p53		Cyclin-D1		PTEN		ERG		AR		HOXB13	
Cells/Case	U	P	U	P	U	P	U	P	U	P	U	P	U	P	U	P	U	P	U	P	U	P
1.	30	−	<5	−	<5	−	+	F	20	30	−	−	R	R	R	L	−	−	+	−	30	−
2.	80	50	70	50	60	10	−	−	10	<5	+	+	L	L	L	L	−	−	+	+	80	80
3.	100	50	<5	<5	−	−	−	−	20	20	+	+	R	R	L	L	−	−	+	+	30	30
4.	100	90	R+	R+	<5	<5	−	−	<5	<5	−	−	R	R	L	L	−	−	+	+	50	5
5.	100	100	<10	−	50	5	−	−	30	30	+	+	R	R	L	L	−	−	+	+	80	50
6.	<5	−	<5	−	<5	−	−	−	90	90	−	−	L	L	L	L	−	−	F	−	NA	NA
7.	90	90	80	5	90	90	−	−	20	20	−	−	R	R	L	L	−	−	+	+	80	1
8.	60	90	−	5	−	90	−	−	20	80	−	−	L	L	L	L	−	−	+	+	NA	NA
9.	80	5	−	−	7	1	W	W	70	30	+	+	R	R	L	L	−	−	+	+	70	1
10.	80	80	−	−	−	−	−	-	20	50	−	−	R	R	L	L	−	−	+	+	10	1

TABLE 6. Description of Reported Cases

	References	Age (y)	Gleason Score	Pleomorphic Component (%)	Follow-up
1.	4	77	4+5=9	NA	NA
2.	4	45	4+5=9	5	Dead in 9 mo
3.	3	59	4+5=9 Squamous cell carcinoma	5	Dead in 1 y with disease
4.	3	71	5+4=9 Small cell carcinoma	5	Progressive mets. in 2 y
5.	3	61	4+5=9	5	Alive 1 y, with disease
6.	3	62	5+4=9	70	Large perineal recurrence after brachytherapy at 3 y
7.	3	66	4+5=9	5	Radical prostatectomy with EPE and SVI
8.	3	76	4+5=9 Ductal	5	Alive at 3 mo with disease
9.	1	81	5+4=9	5	1 y Mets. bones, dead of disease

Prostatic vs Urothelial

- Areas of less pleomorphic/more uniform tumor → prostatic
- Infiltrating cords (not nests) → prostatic
- Cribriform tumor glands → prostatic

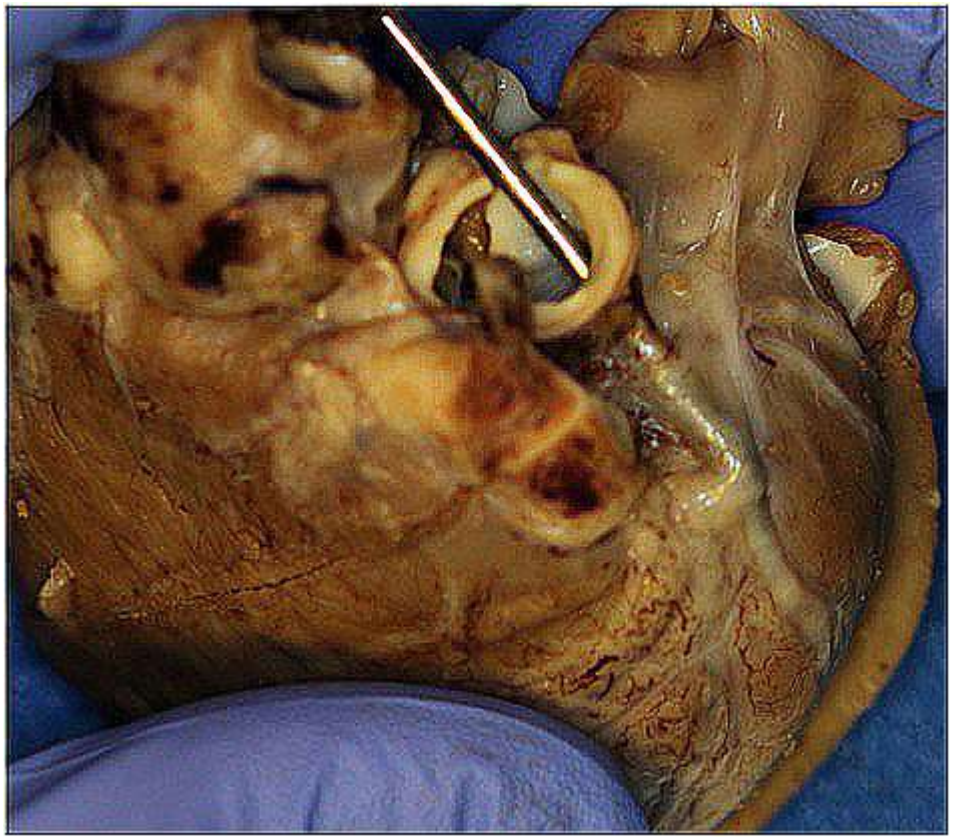
- CAUTION on discohesive prostatic tumor around blood vessel → mimic papillary urothelial carcinoma!
- CAUTION on pagetoid extension prostatic tumor → mimic urothelial CIS!

- **Panel approach!**
- **NKX3.1>>>P501S>PSA**
- **CAUTION on GATA3+**

20-0607

Justin Kurtz/Serena Tan; Stanford

3-month-old ex-full term F with several episodes of pulseless ventricular tachycardia and acute global left ventricular failure. Heart catheterization showed diffuse narrowing of the coronary arteries, and abdominal CT showed opacifications of the splenic and mesenteric vessels. She underwent an orthotopic heart transplant.

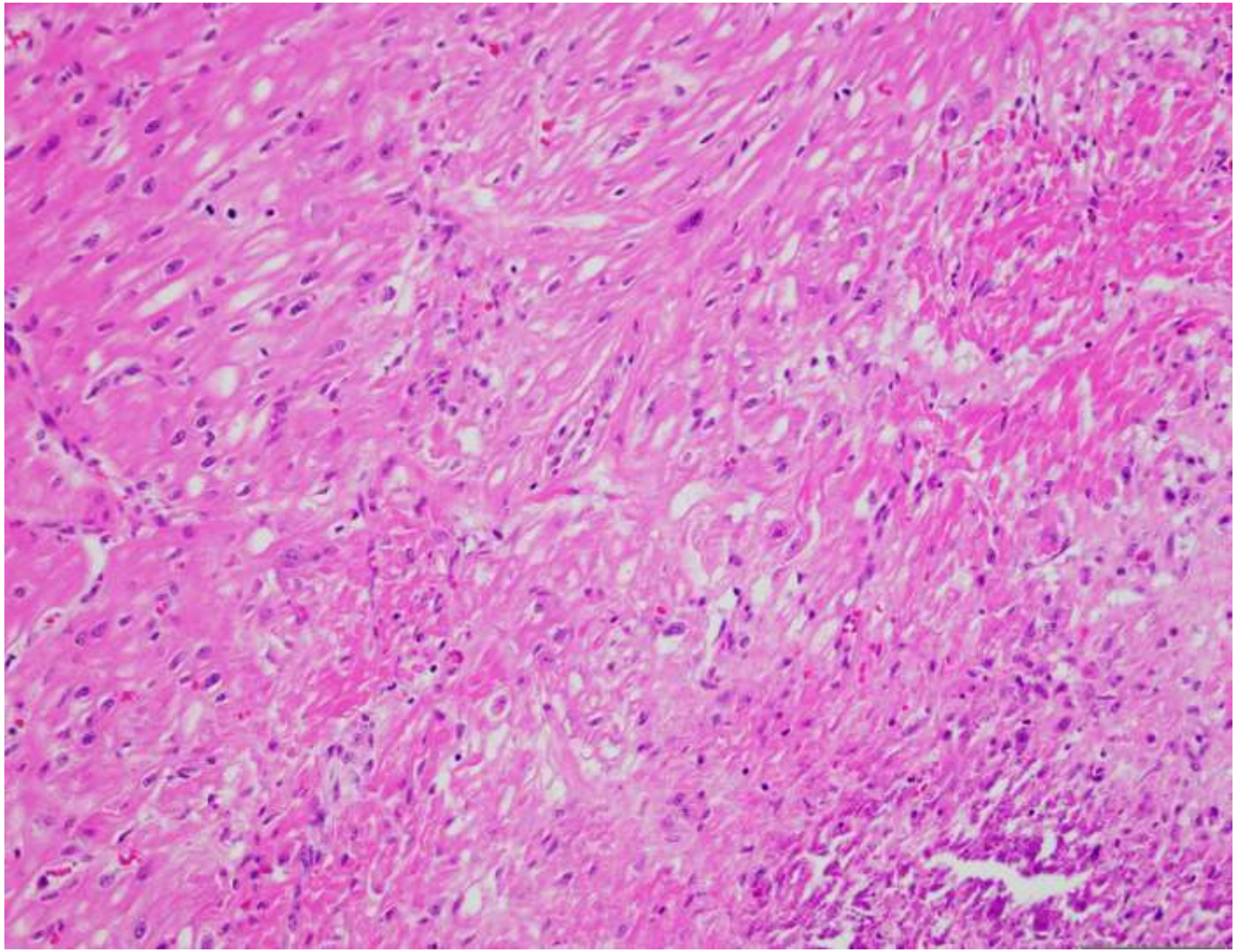


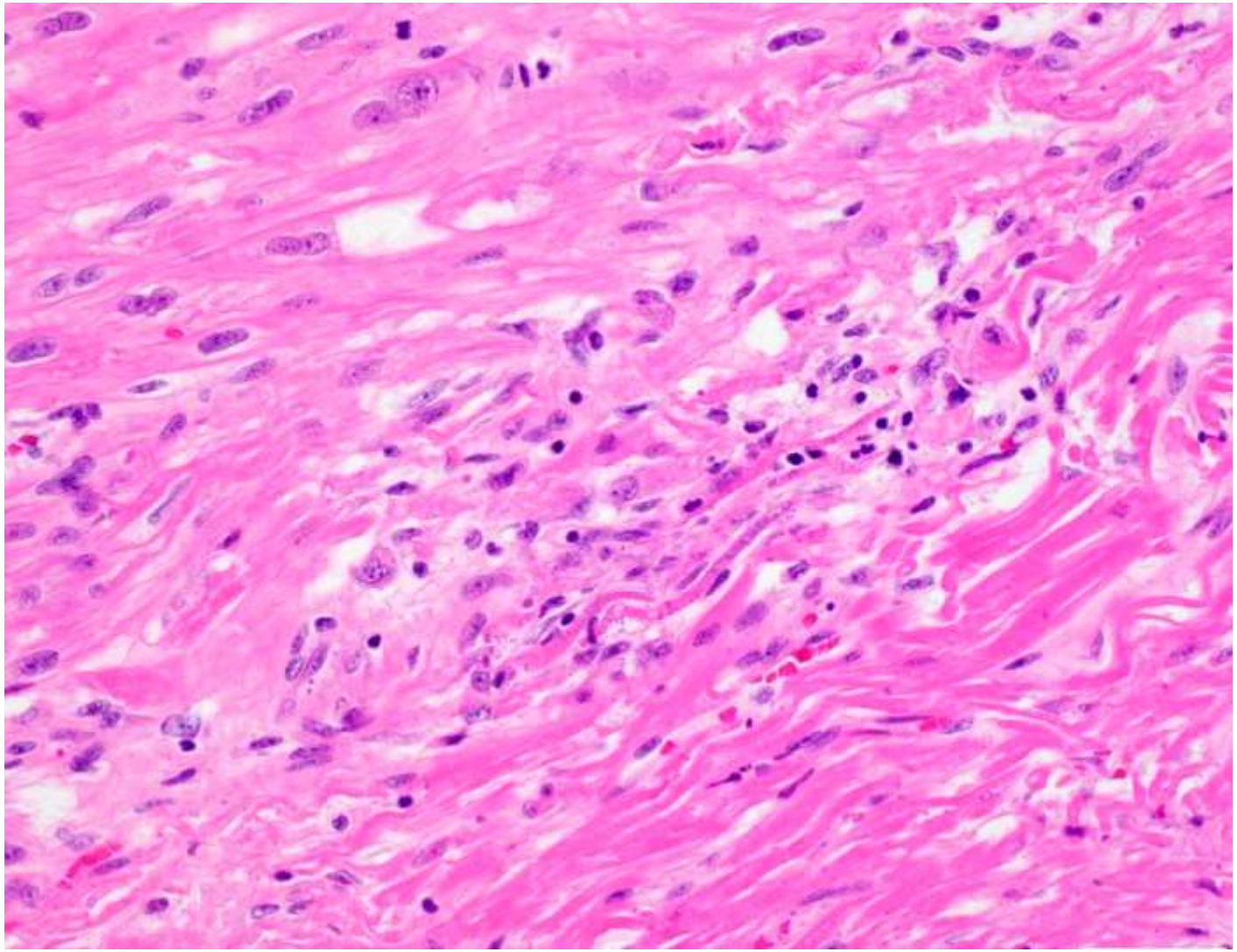
Gross Examination

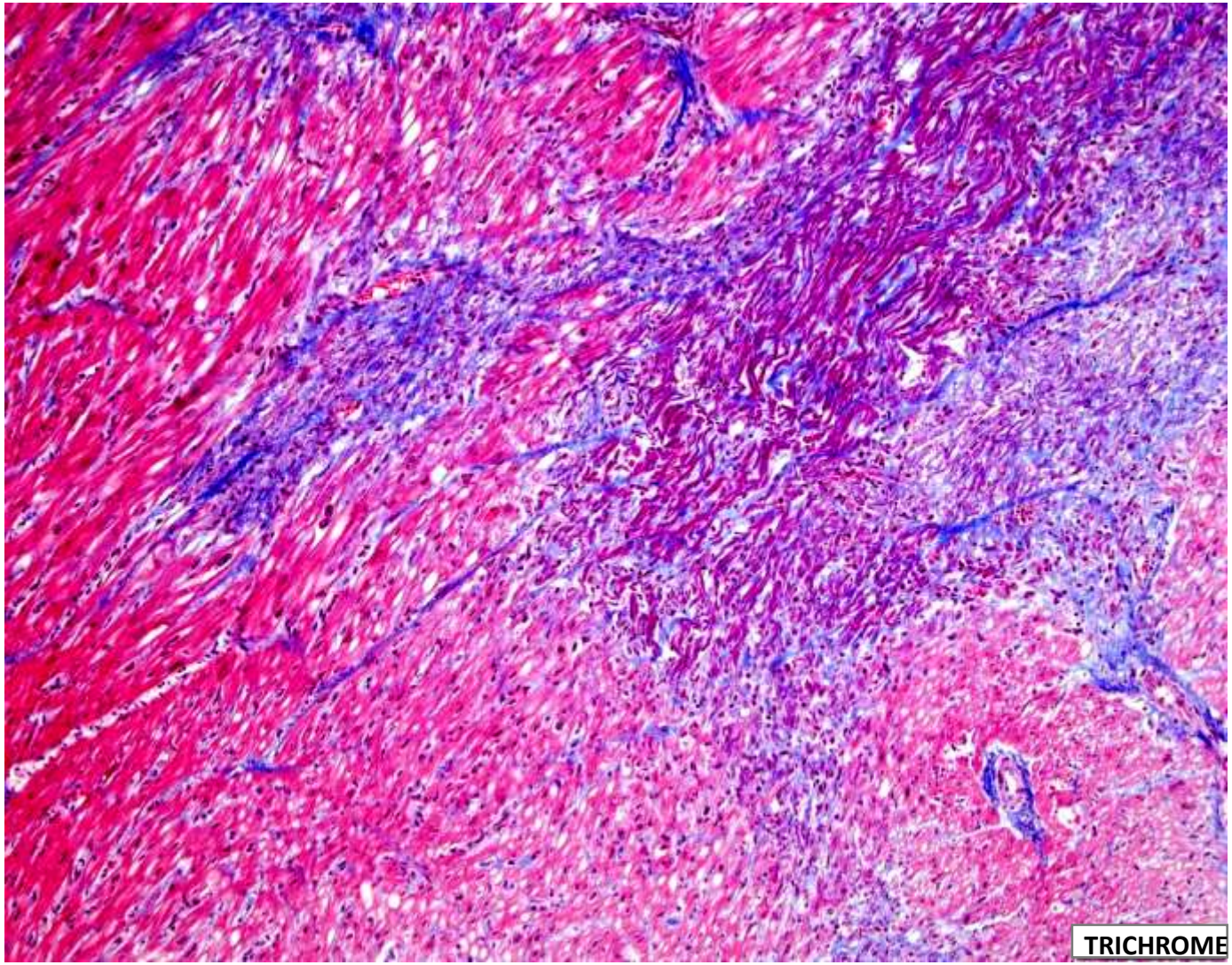
Occlusion of left and right coronary arteries

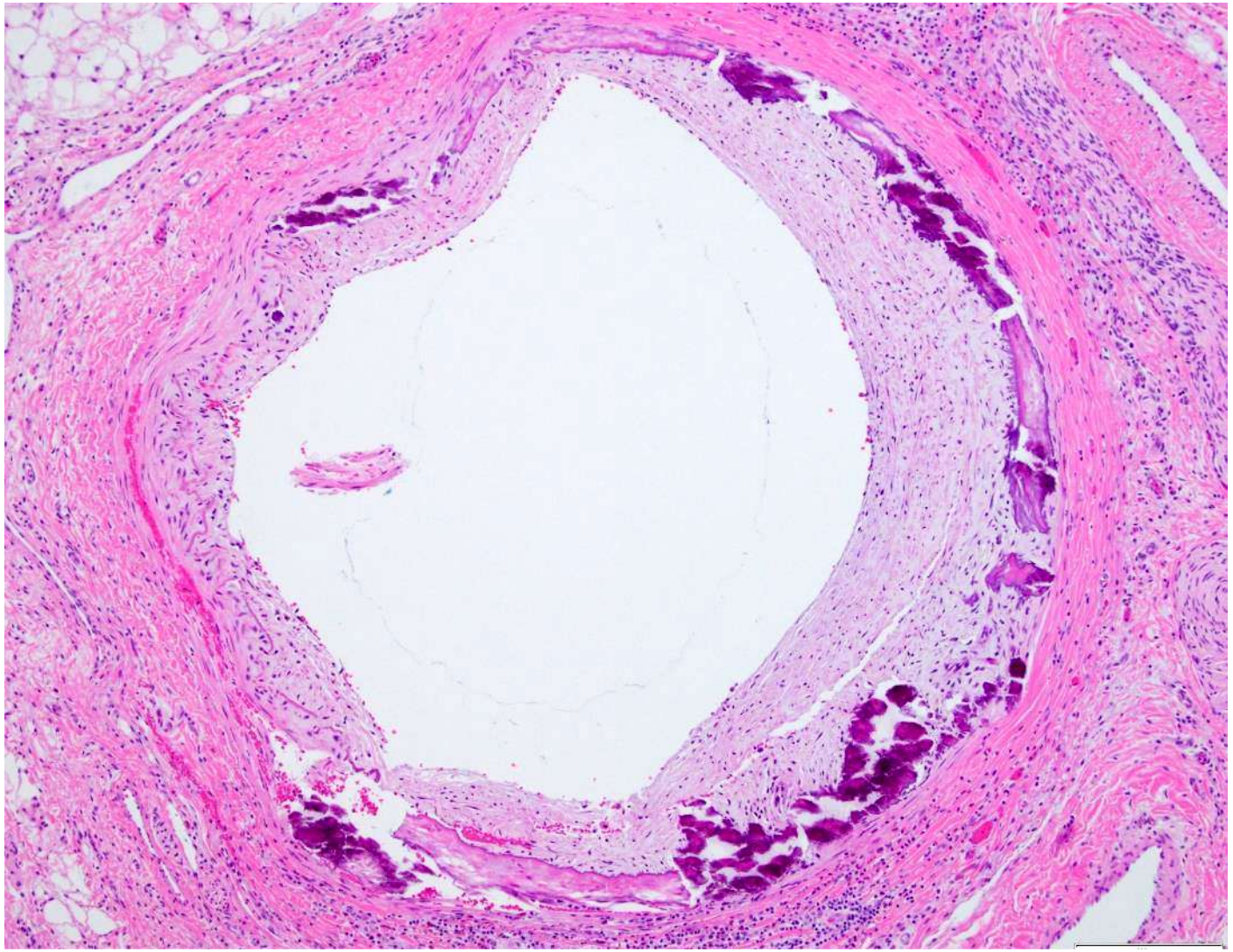
Left descending artery – tortuous with multiple collaterals

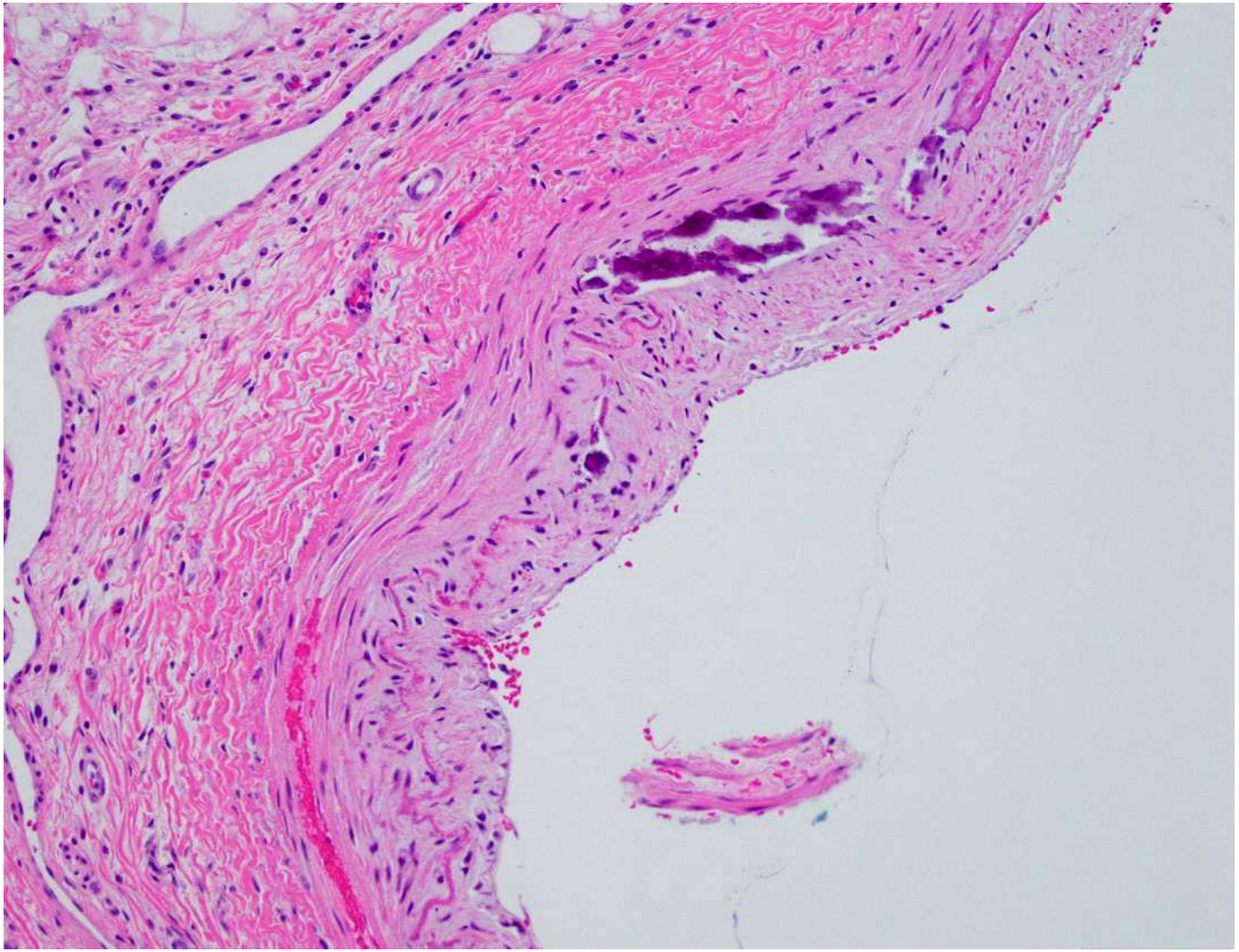
Patchy myocardial discoloration of ventricular walls

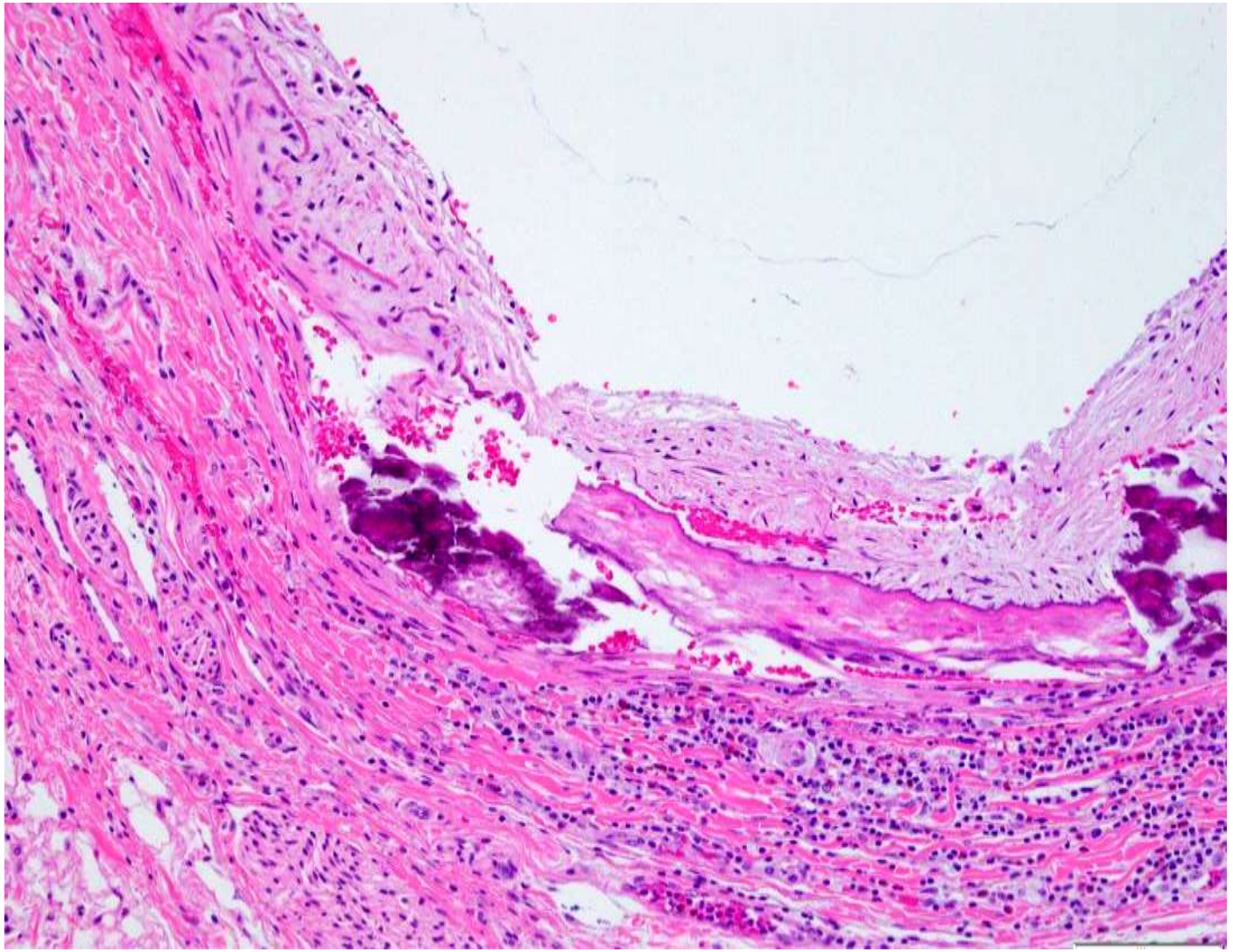


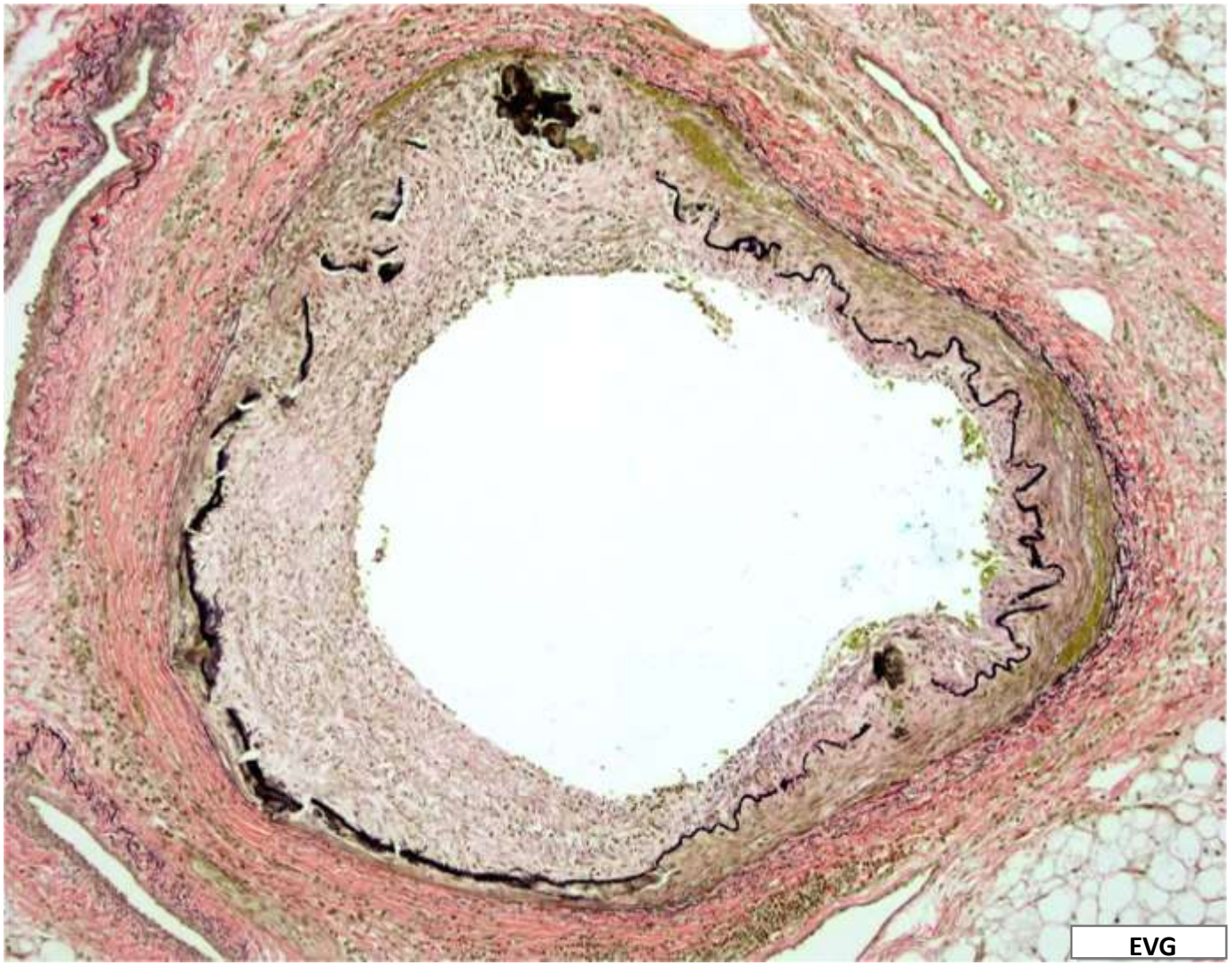



TRICHROME





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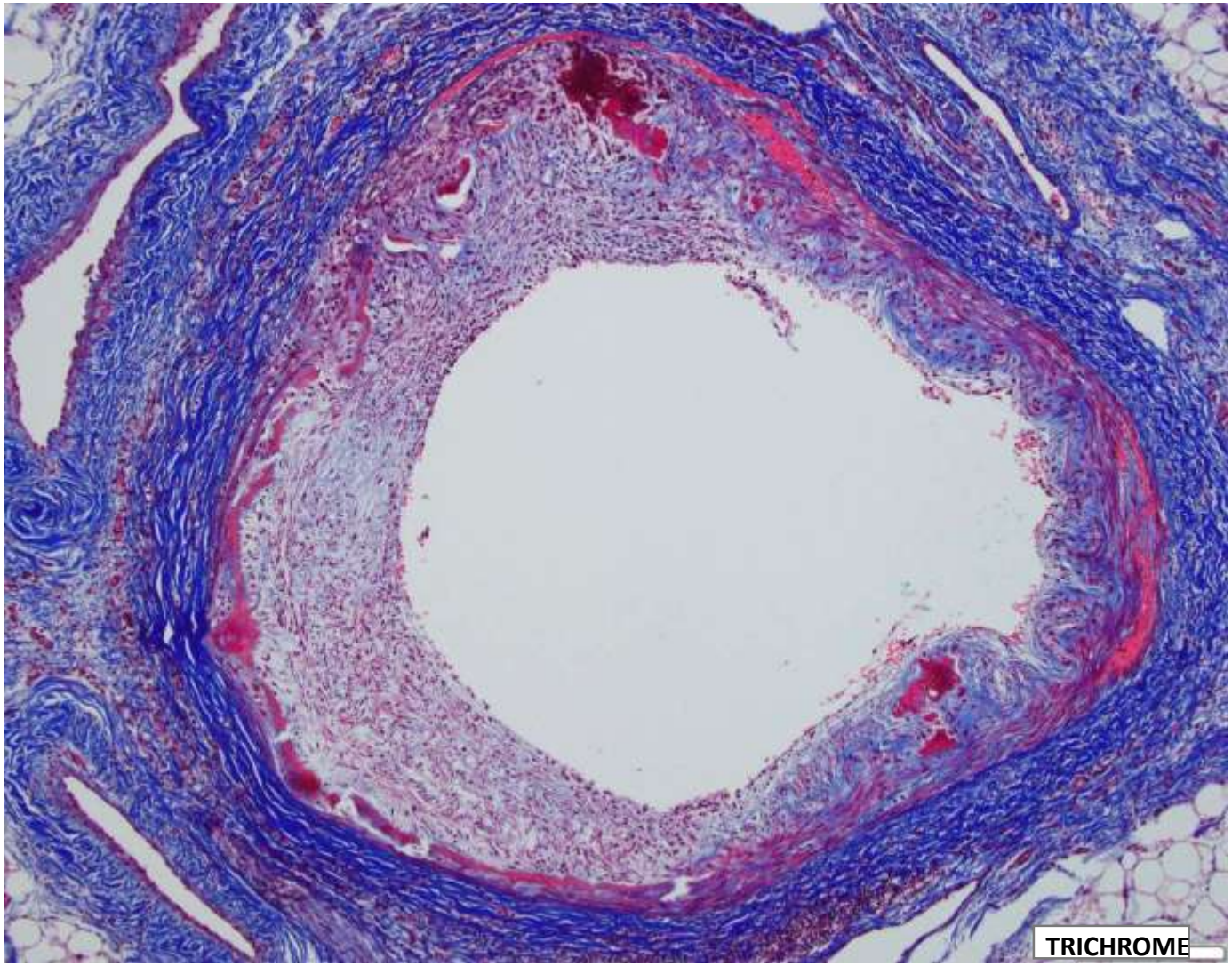
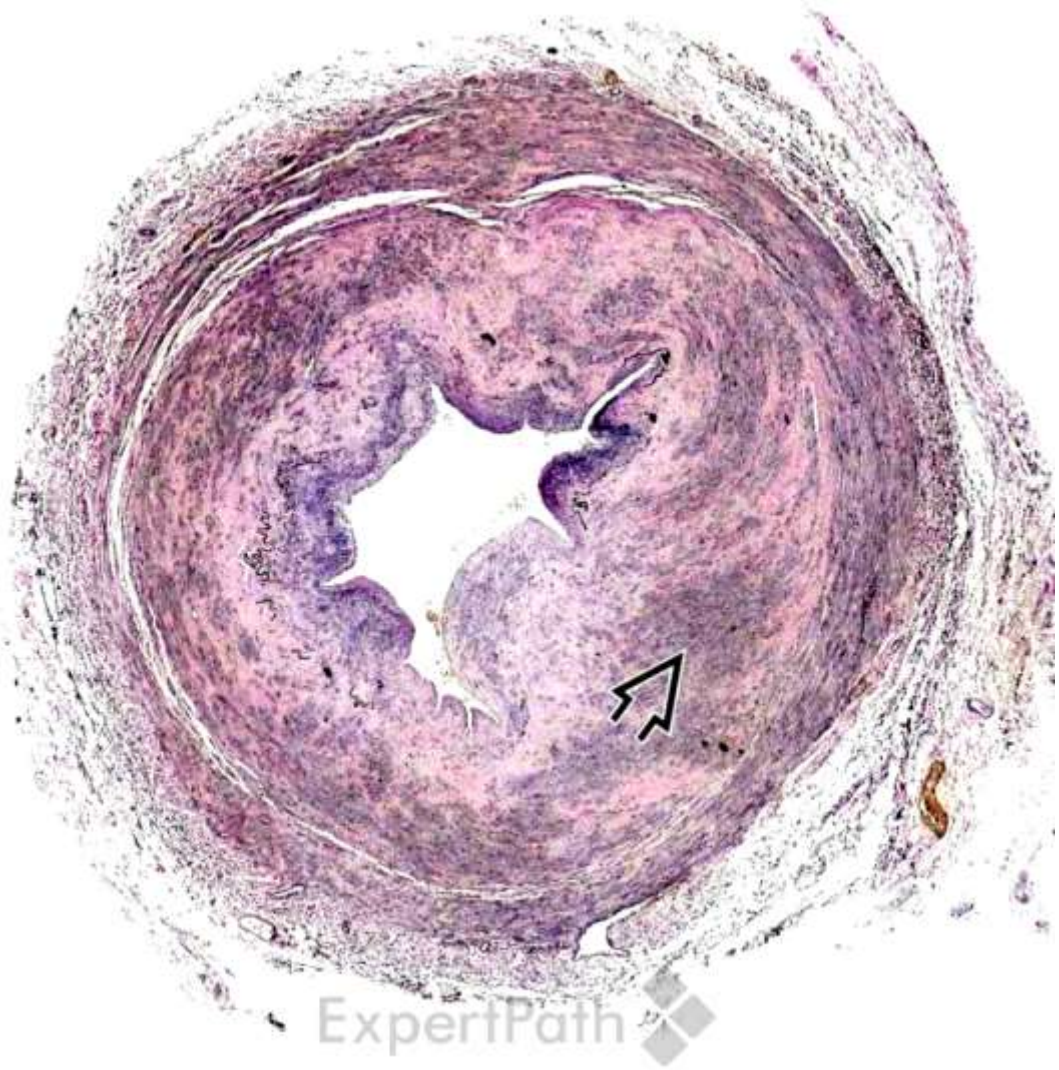

TRICHROME

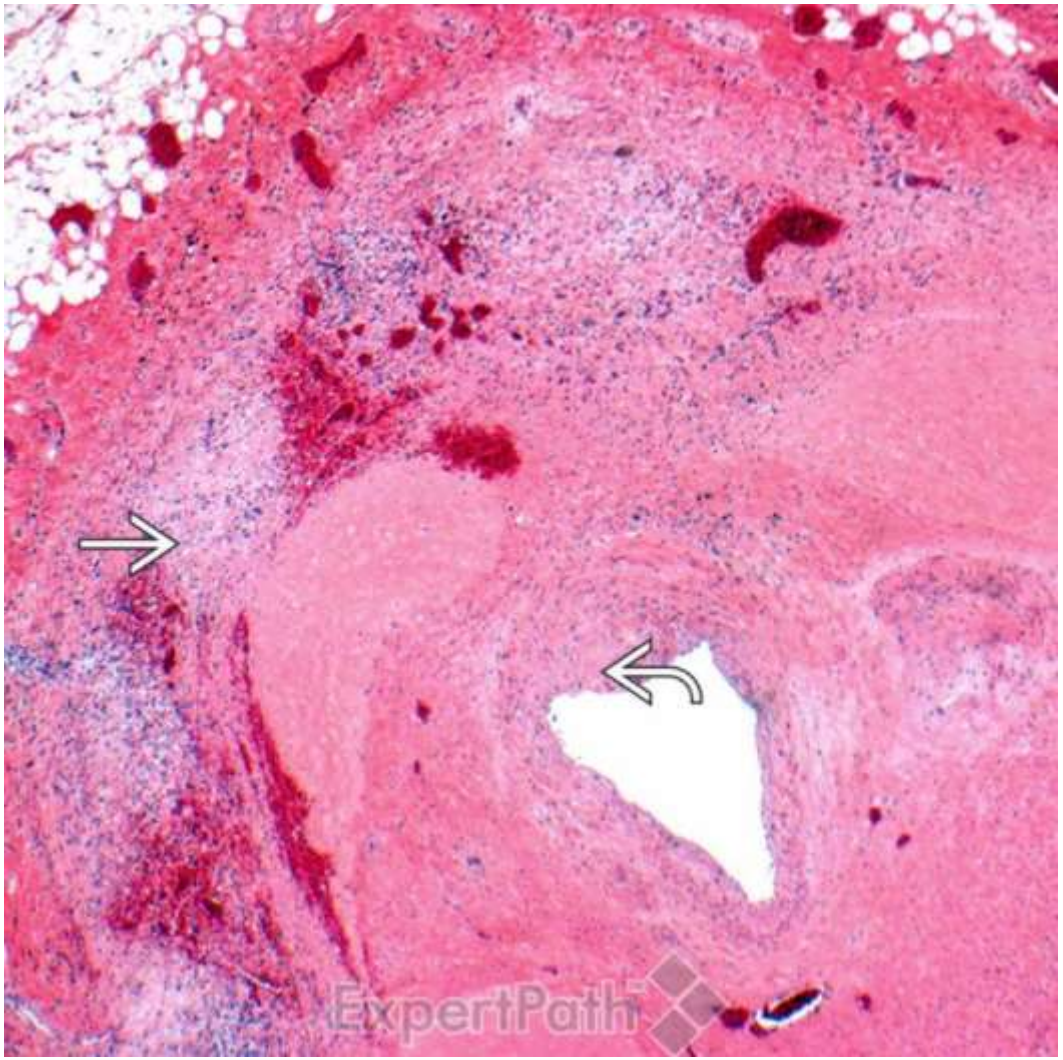
Differential Diagnosis

Fibromuscular Dysplasia
Kawasaki Disease
Early-Onset Atherosclerotic Disease
Generalized Arterial Calcification of Infancy



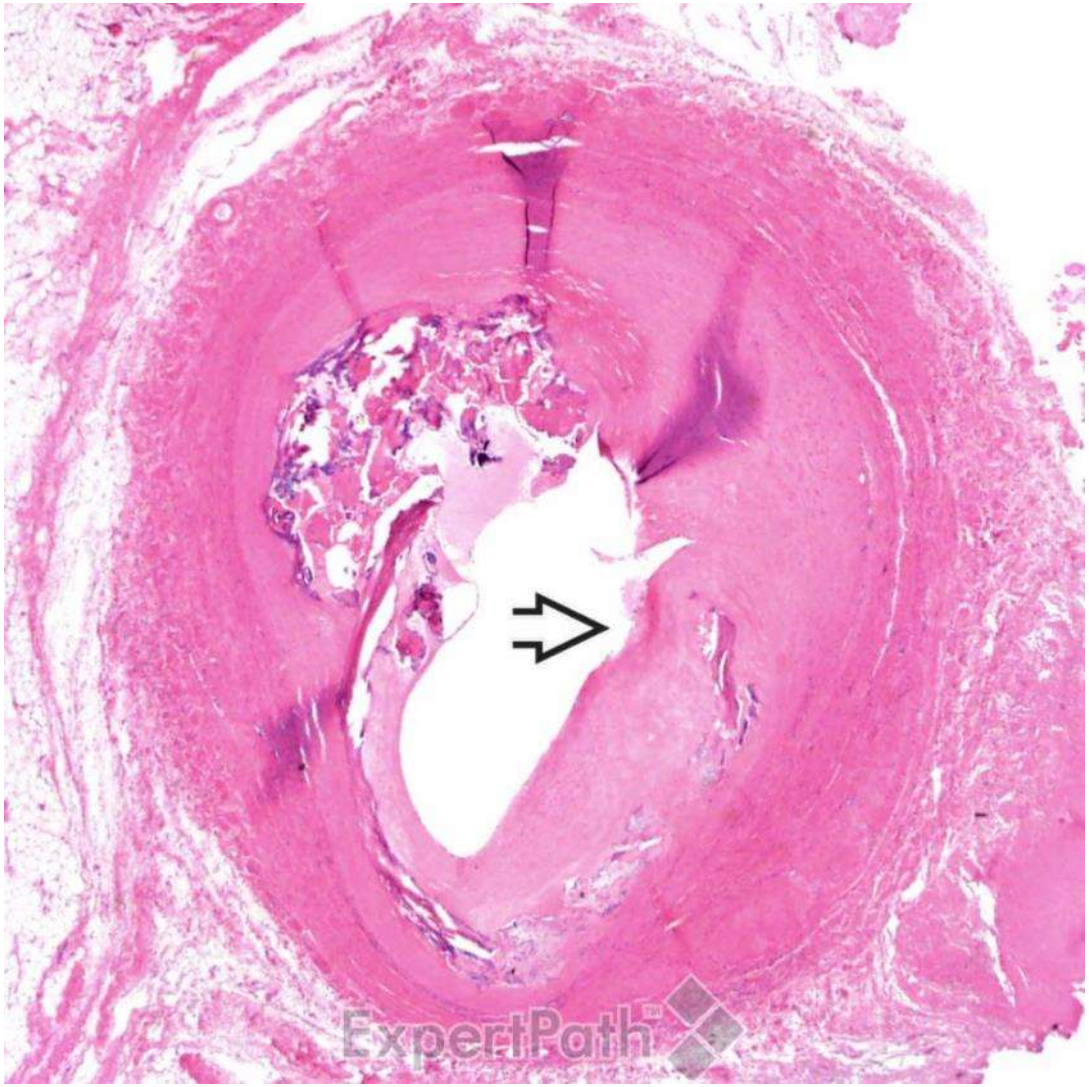
Fibromuscular Dysplasia

- Fibromuscular proliferation of artery
- Most often involves media, though intimal fibroplasia can also be seen
- Calcifications are not a feature
- Vast majority involve kidney, presenting with renovascular disease (e.g. hypertension)



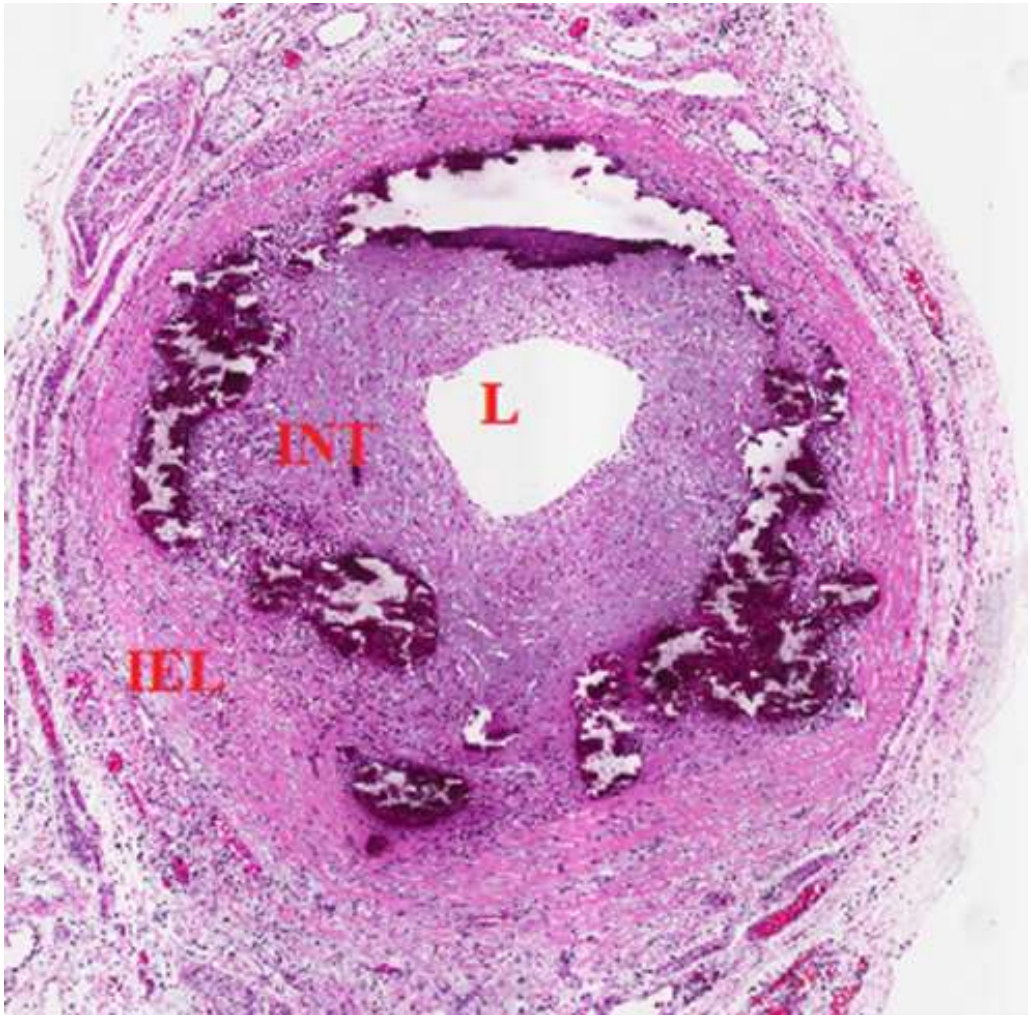
Kawasaki Disease

- Acute multi-systemic febrile illness
- Coronary vasculitis + Mucocutaneous findings
- Phases:
  - Acute: Vasculitis
  - Subacute: Medial organization, intimal fibrosis +/-aneurysmal thinning, calcification, thrombosis
  - Chronic: Coronary aneurysms and/or stenosis



Early-Onset Athero-Sclerotic Disease

- Progressive degenerative inflammatory process
- Can present in prenatal/infancy periods, possibly related to maternal smoking (*Can J Cardiol* 2008;24(2):137-141)
- Different stages of intimal injury/proliferation → atheromatous plaque formation
- Calcifications are usually associated with the plaque



Generalized Arterial Calcification of Infancy

- Rare autosomal recessive disorder
- Abnormal calcification of internal elastic lamina of large and medium sized arteries
- Marked myointimal proliferation → arterial stenosis
- Congestive heart failure, hypertension, myocardial ischemia

Forensic Science International **254** (2015) e7-e12

Fibromuscular Dysplasia

Kawasaki Disease

Early-Onset Atherosclerotic Disease

Generalized Arterial Calcification of Infancy (GACI)

Genetic Testing:

Two heterozygous truncating mutations in the ***ABCC6*** gene

1) c.2787+1G>T transversion in iVS21 of *ABCC6*, occurring at an invariant position of the donor splice site → aberrant mRNA processing
2) c.3421C>T transition in exon 24 → arginine codon (CGA) converted to termination codon (IGA)

Genetics of spontaneous pathologic arterial calcifications in childhood

Generalized Arterial Calcification of Infancy (GACI)

Abnormal calcification of internal elastic lamina of medium/large vessels

⟺

ENPP1 mutations
(helps prevent abnormal calcium deposition)

Pseudoxanthoma Elasticum (PXE)

Ectopic mineralization and fragmentation of elastic fibers of connective tissues (skin, vessels, eyes)
+Pseudoxanthomatous skin lesions
+Angioid streaks in retina

⟺

ABCC6 mutations
(exact role unknown)

An Unusual Severe Vascular Case of Pseudoxanthoma Elasticum Presenting as Generalized Arterial Calcification of Infancy

G. Le Boulanger,[1] C. Labrèze,[2] A. Croué,[3] L.J. Schurgers,[4] N. Chassaing,[5] T. Wittkampf,[6] F. Rutsch,[6] and L. Martin[1]*

Am J Med Genet A. 2010 Jan;152A(1):118-23

Two brothers

- Older: Uncomplicated PXE developed in adolescence, mutations in *ABCC6*
- Younger: Died of condition reminiscent of GACI, but no *ENPP1* mutations

Immunohistochemical findings of PXE (matrix Gla protein/fetuin-A) in this GACI case

Proposed:

1) *ABCC6* may be a relevant candidate gene in some cases of GACI with no mutations in the *ENPP1* gene
2) GACI may be an atypical and severe end of the vascular phenotype spectrum of PXE

Generalized Arterial Calcification of Infancy and Pseudoxanthoma Elasticum Can Be Caused by Mutations in Either ENPP1 or ABCC6

Am J Hum Genet. 2012 Jan 13;90(1):25-39

92 probands with a clinical history of GACI

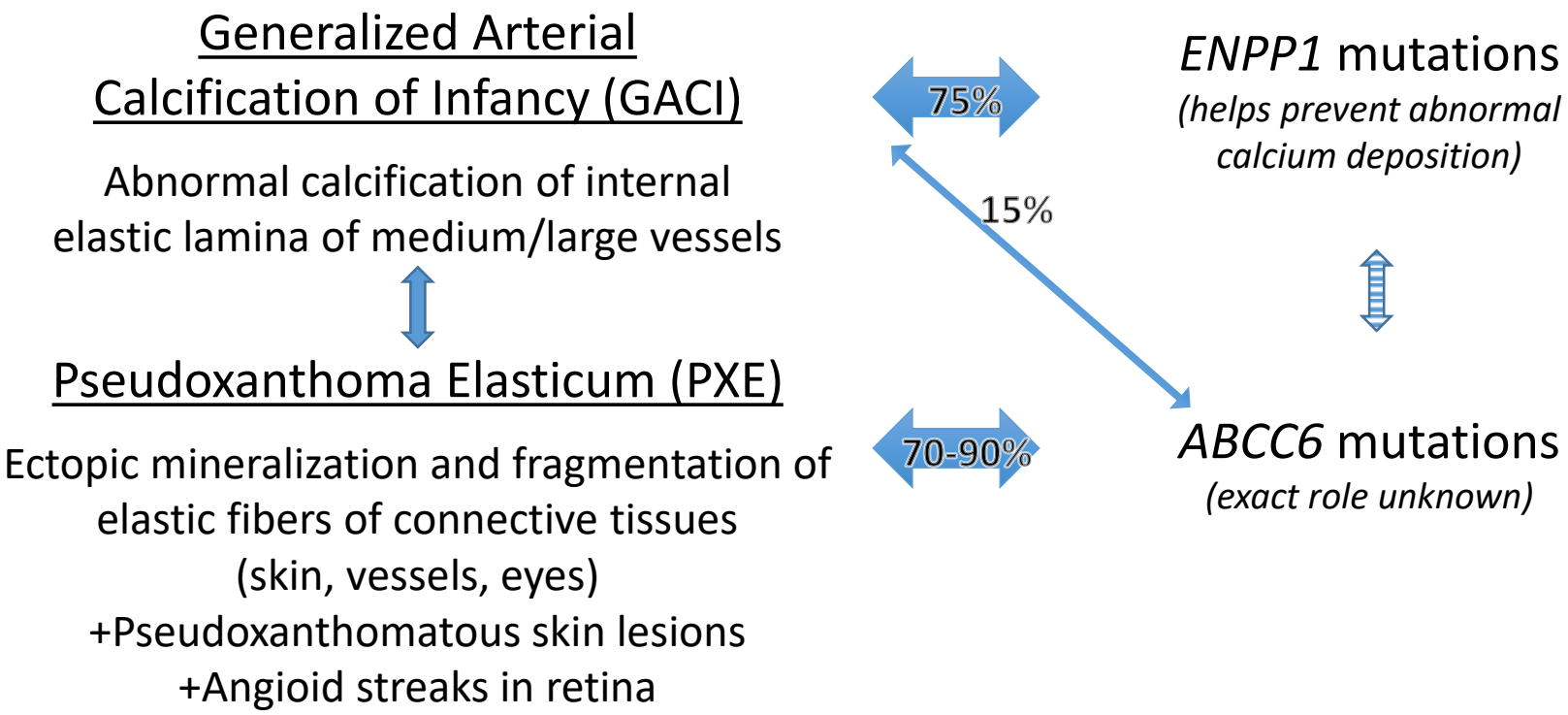
- 3 patients with biallelic *ENPP1* mutations developed typical signs of PXE later in life (5-8 years)

- Of 28 patients without *ENPP1* mutations, 14 had pathogenic *ABCC6* mutations

GACI and PXE: two ends of clinical spectrum of ectopic calcification

ABCC6 and *ENPP1* mutations might lead to alterations of the same physiological pathways

Genetics of spontaneous pathologic arterial calcifications in childhood



Clinical Follow-up

Many cases of GACI historically presented at autopsy

Outcomes improving with bisphosphonate therapy

Transplantation is rare; only one previous case report

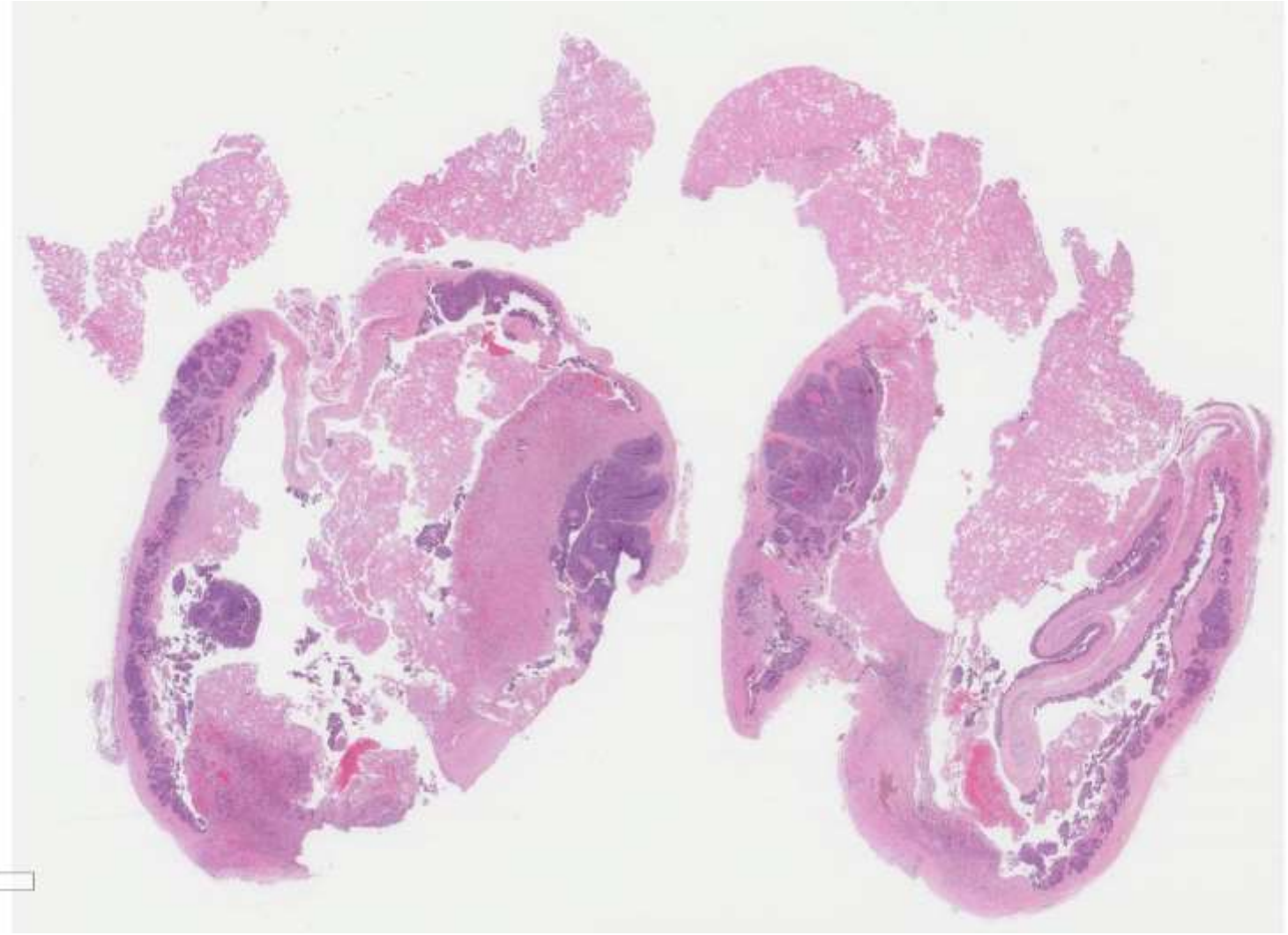
Patient is doing well nearly a year post transplant, recently started on Pamidronate

As of now, she has not developed features of PXE

20-0608

Connie Chen/Josh Menke; UCSF

68-year-old M with a finger mass.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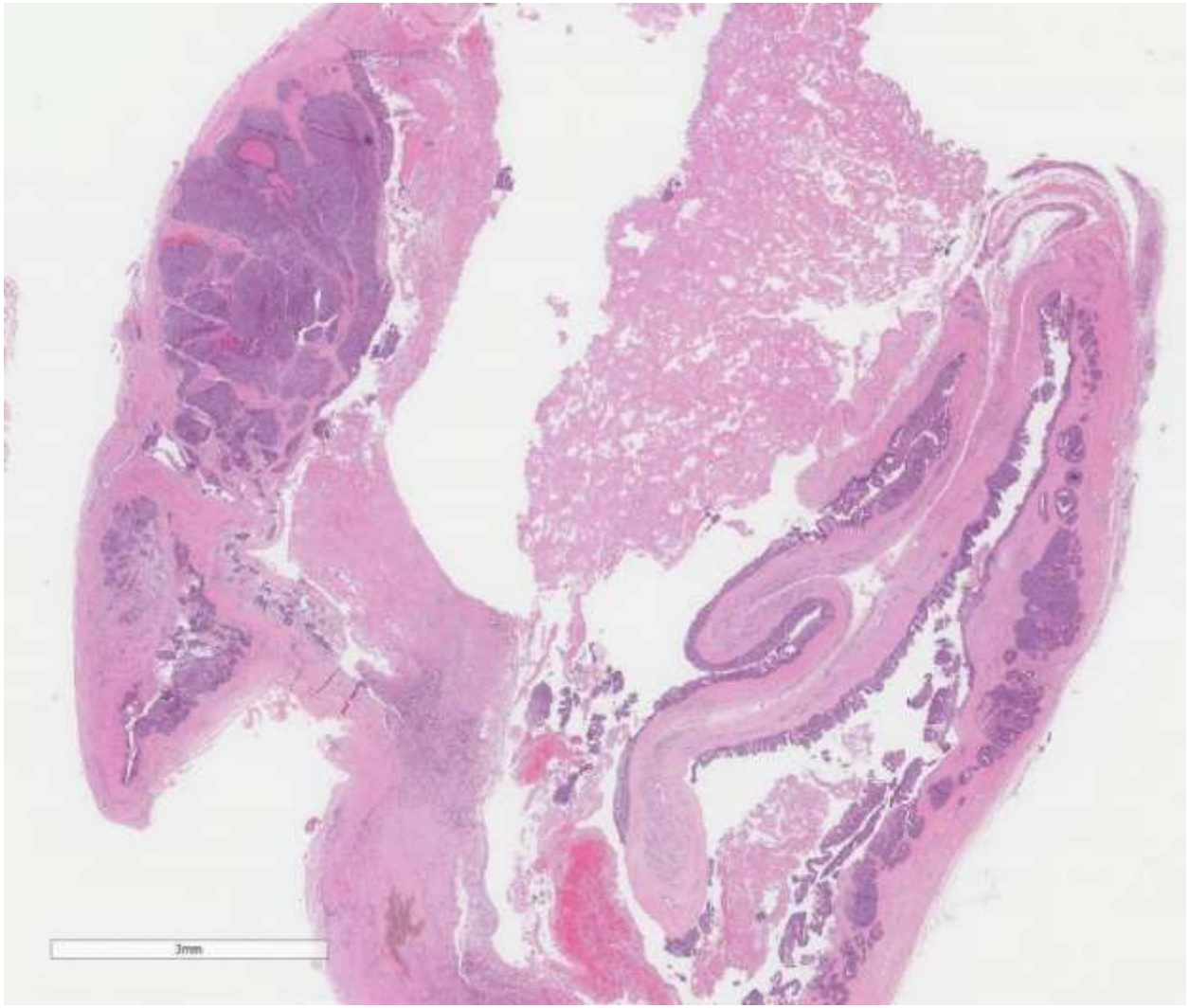
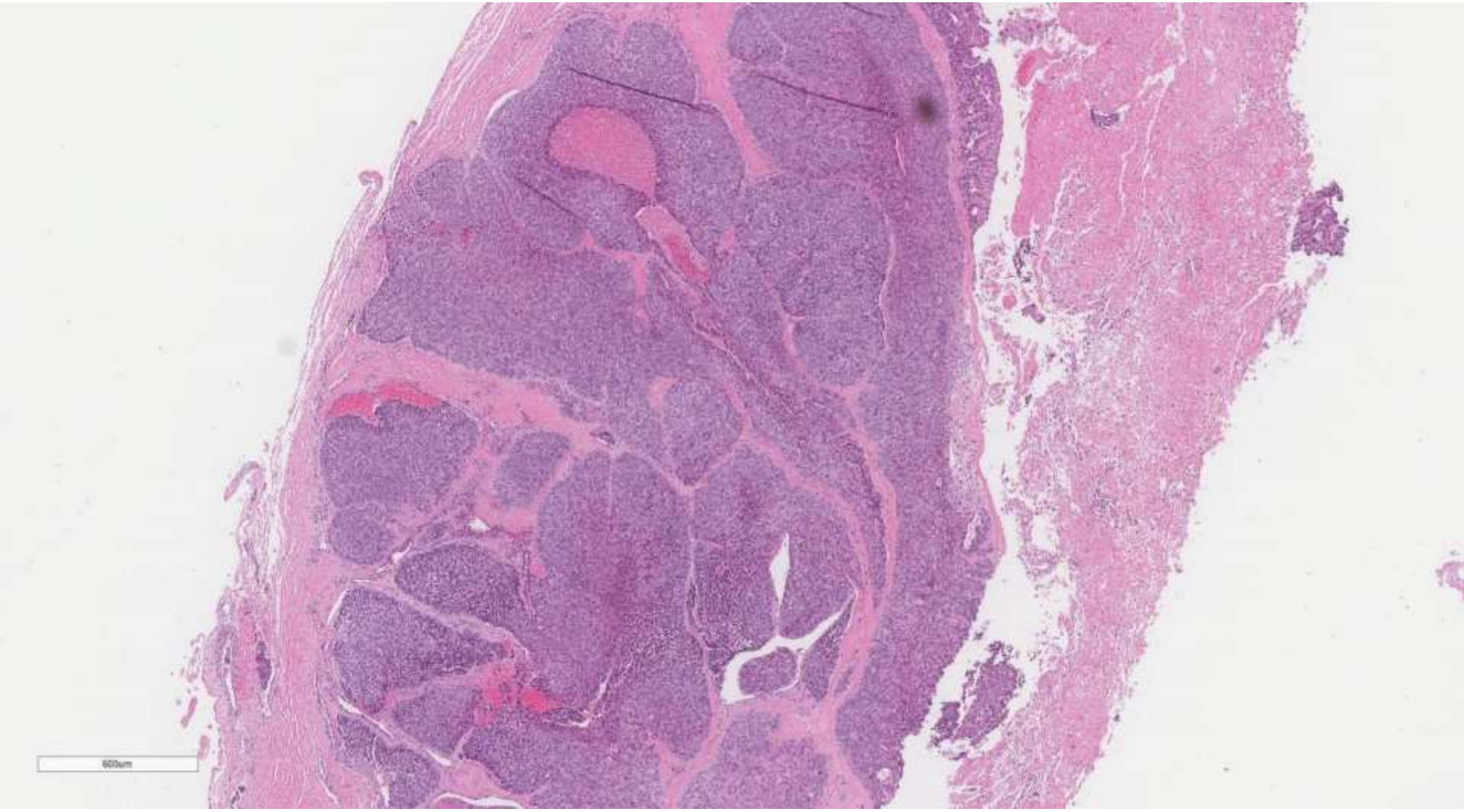

3mm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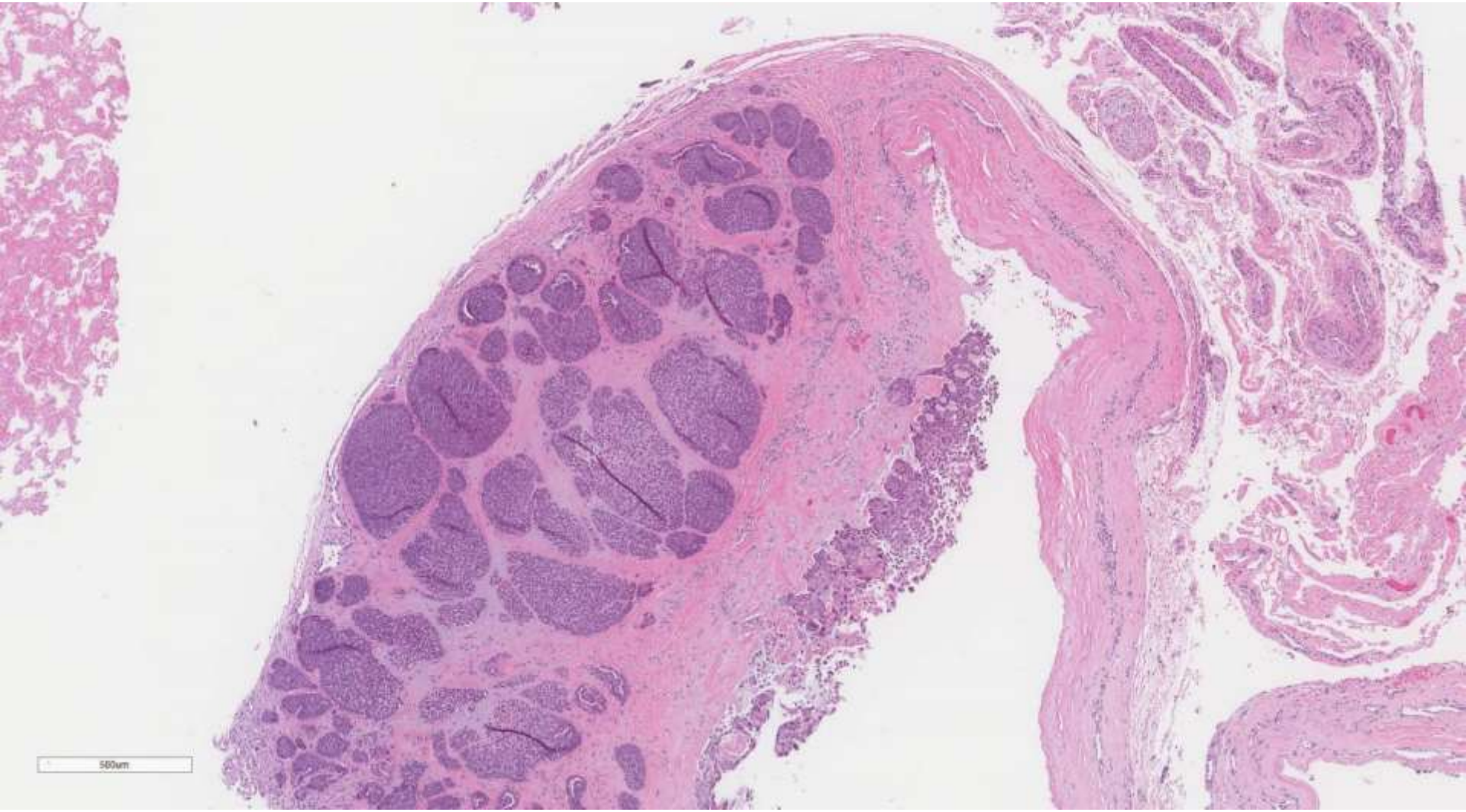
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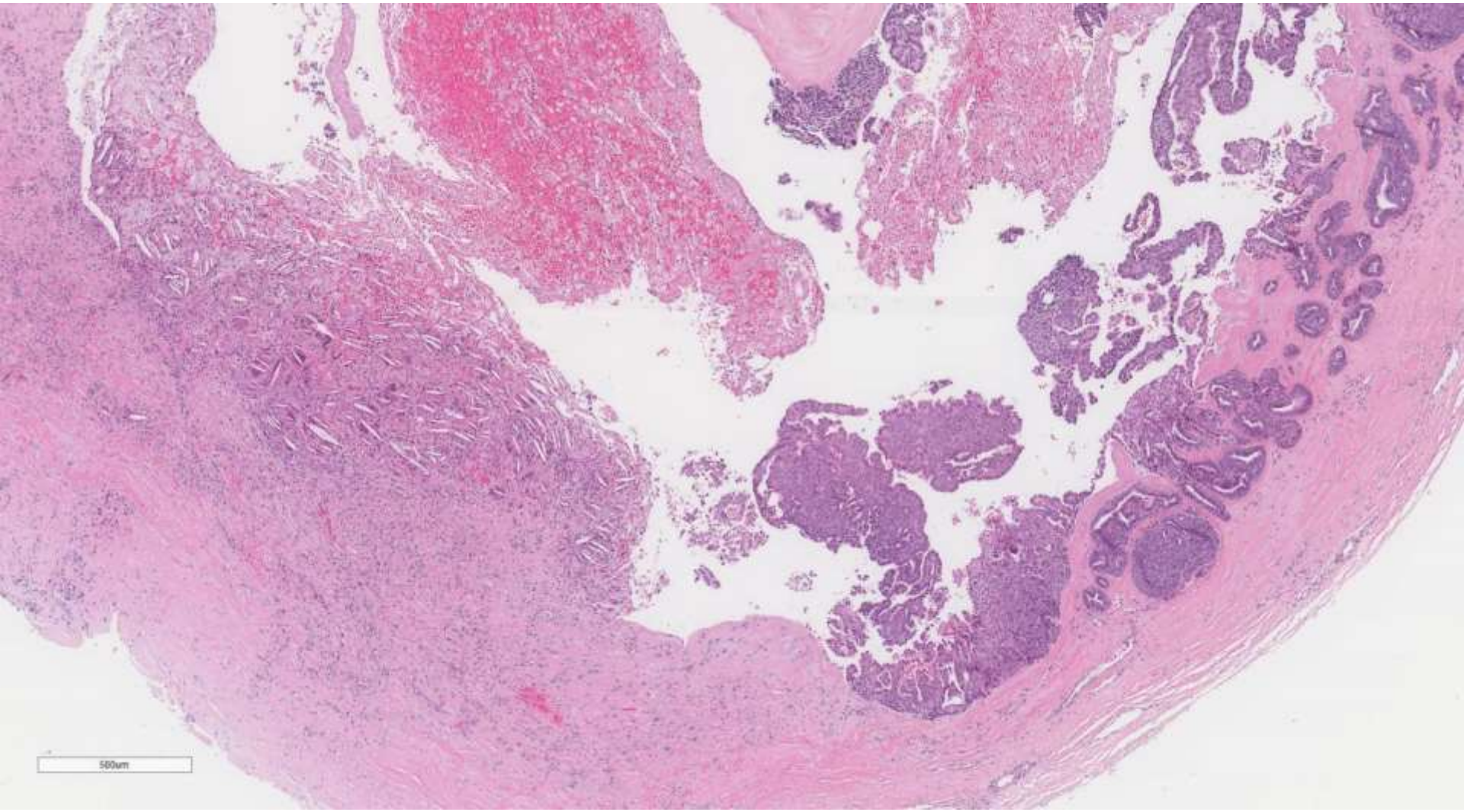
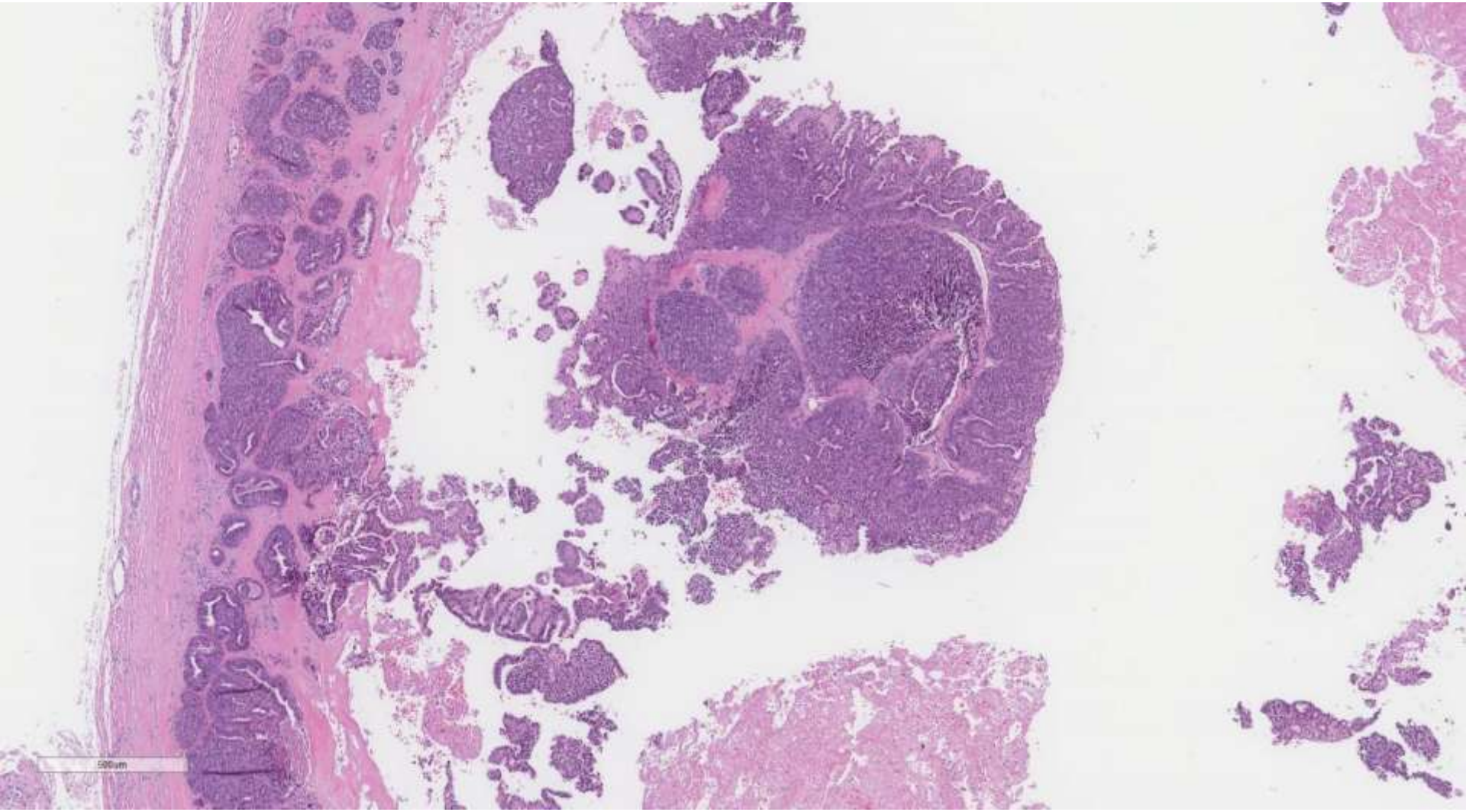

500um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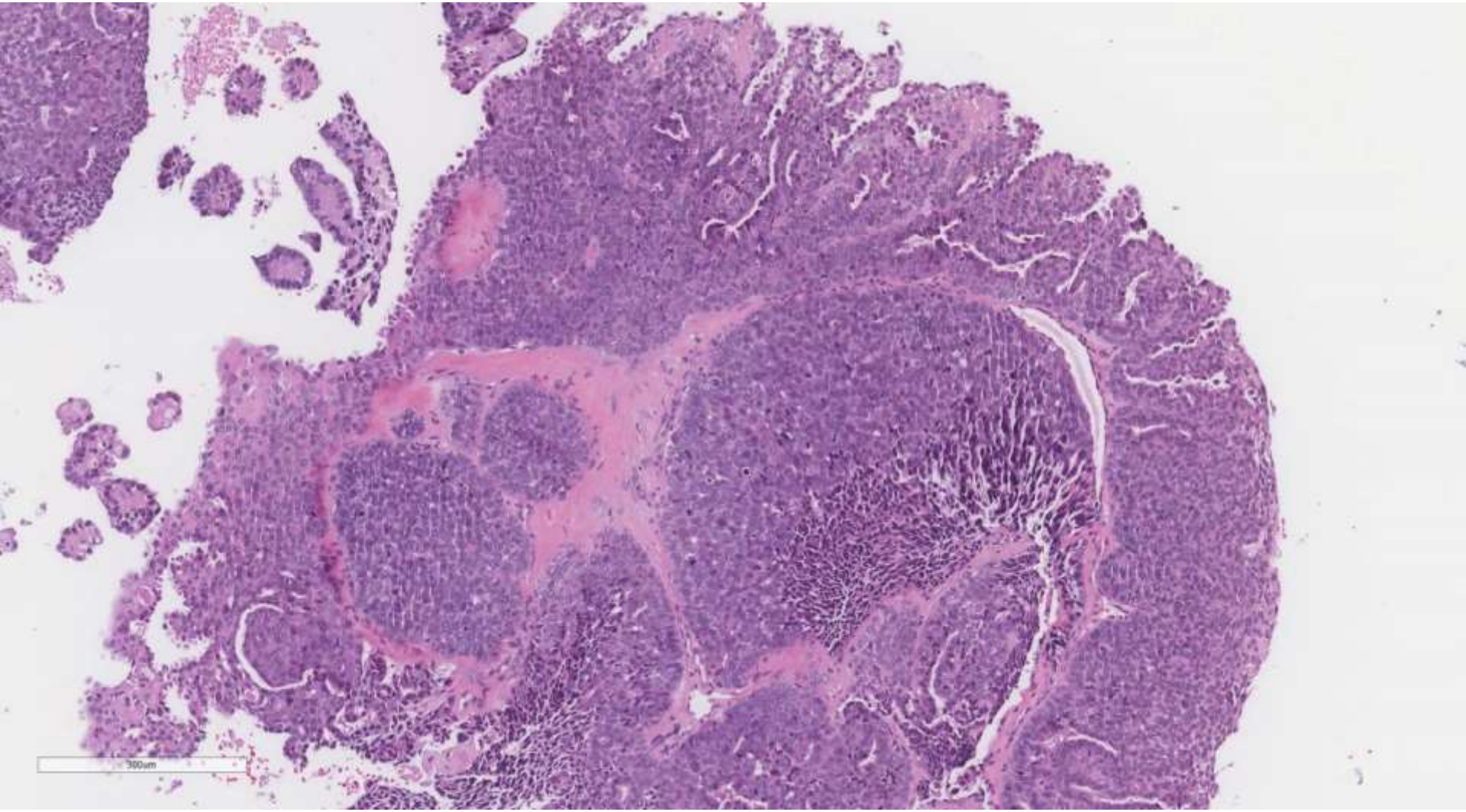
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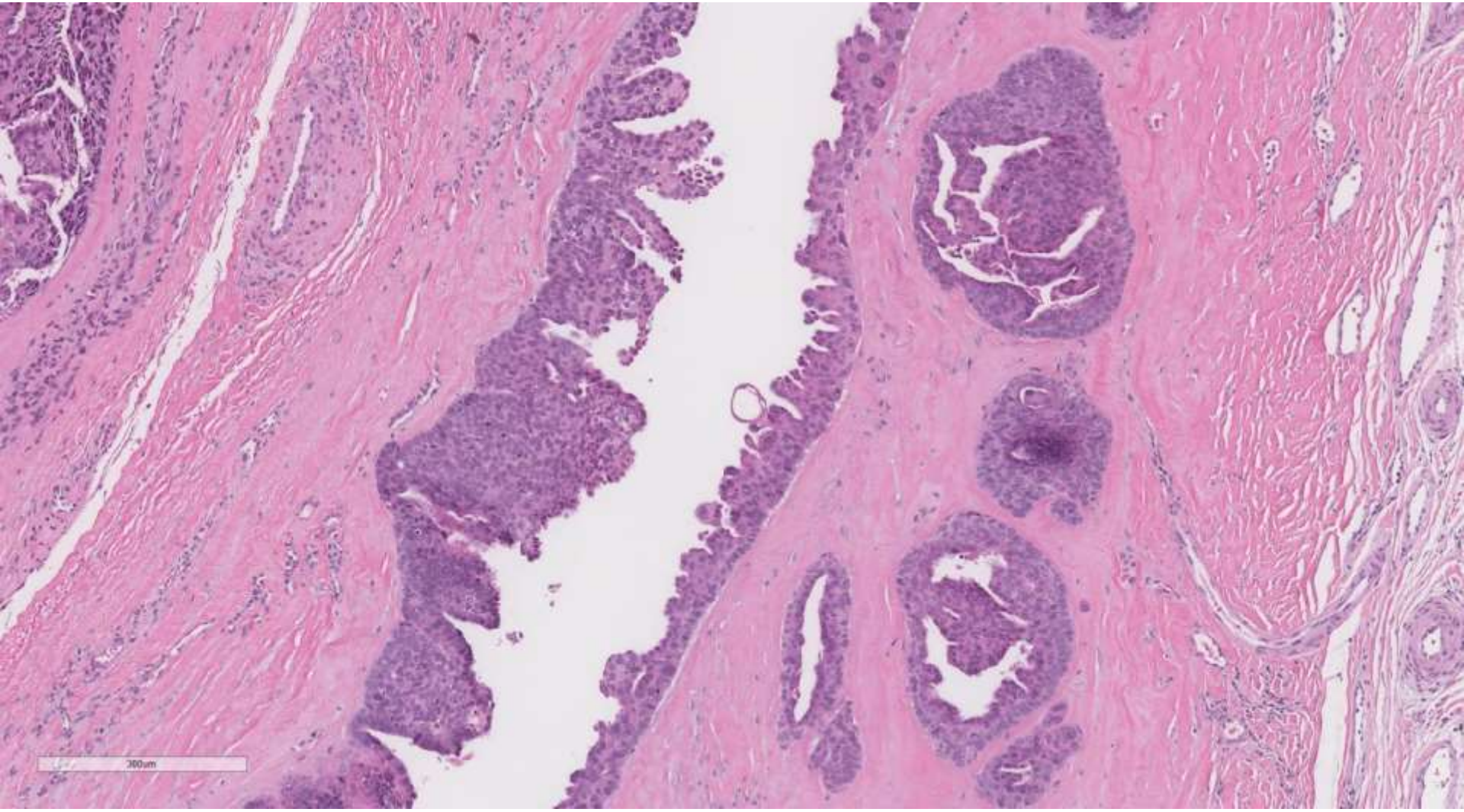
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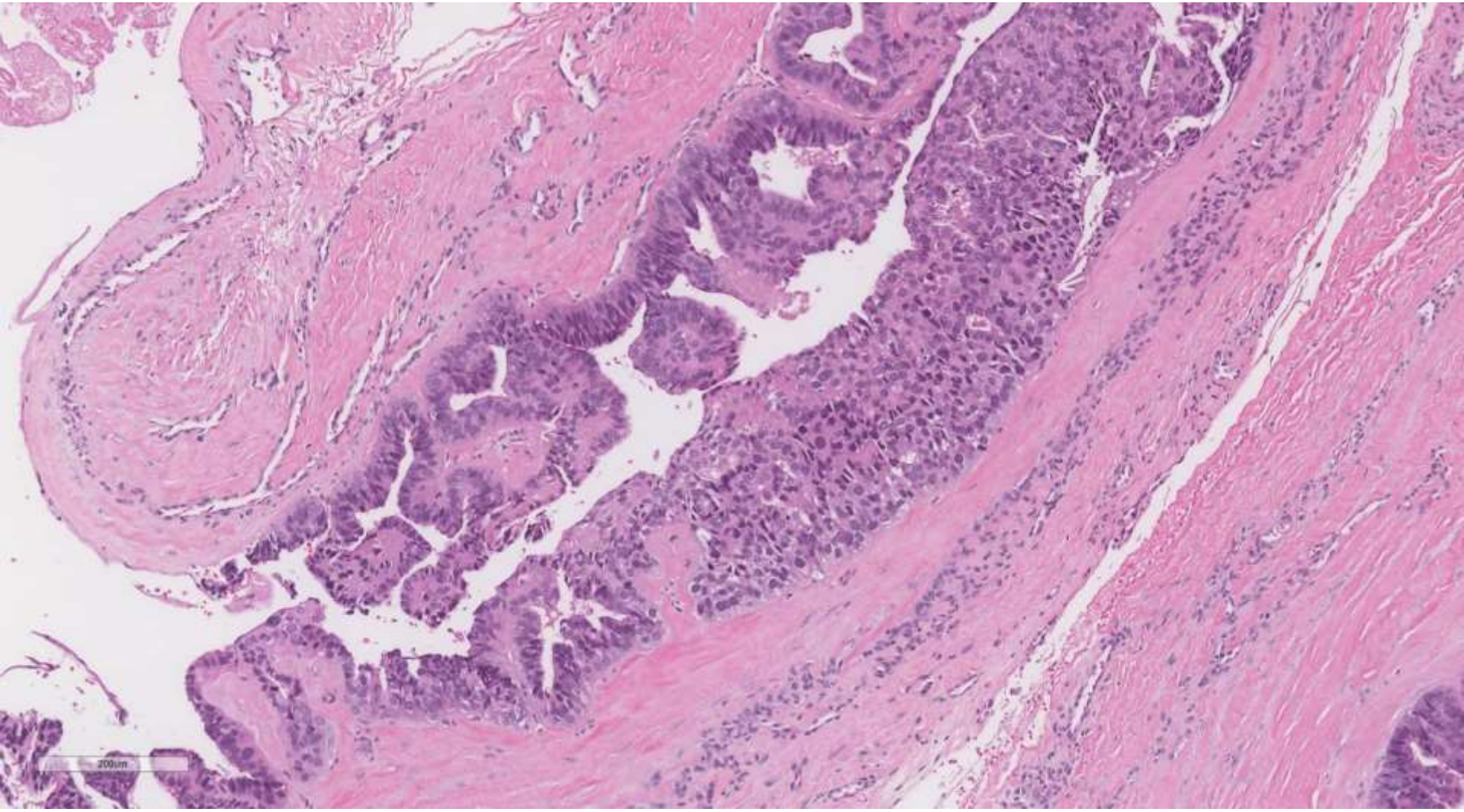
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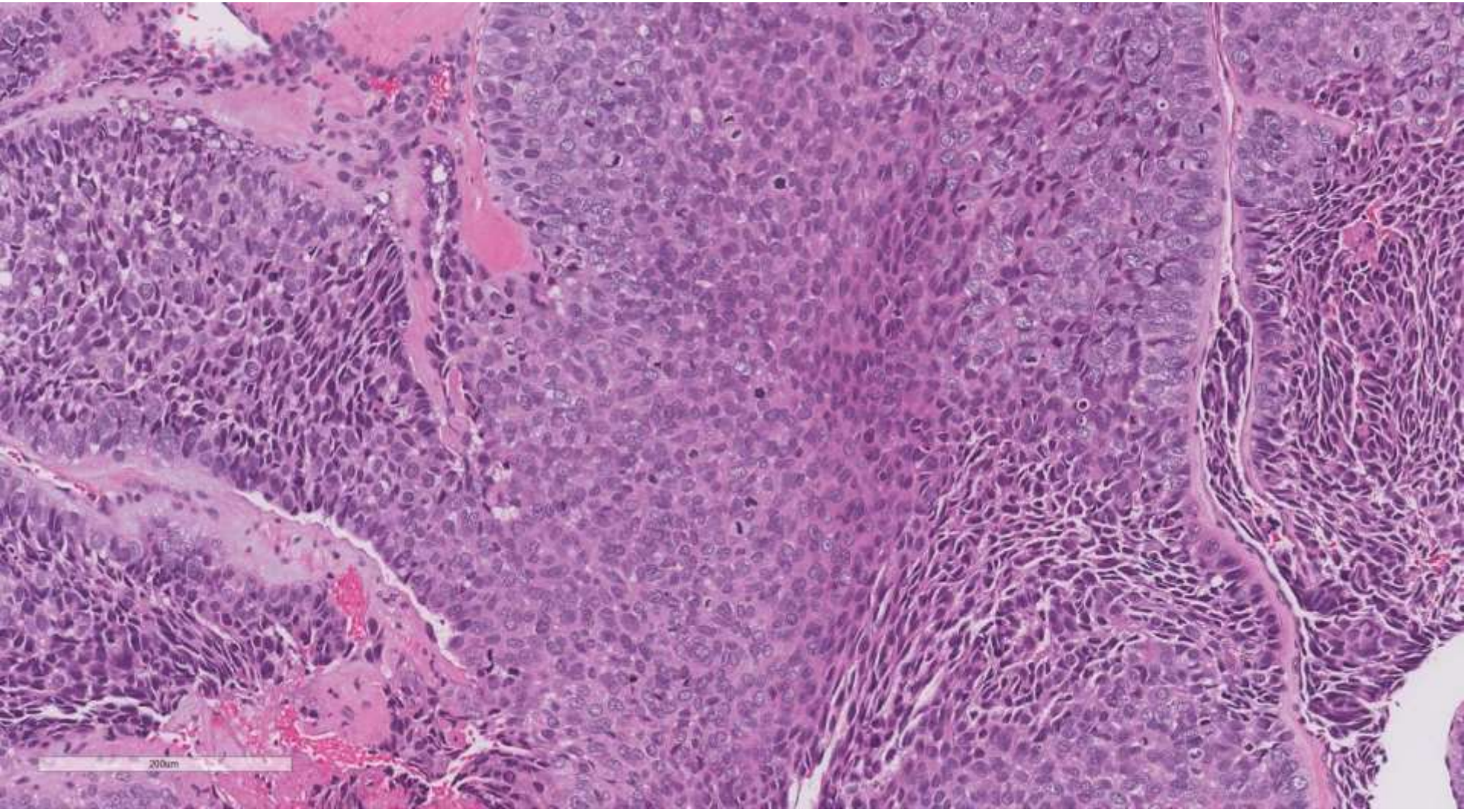
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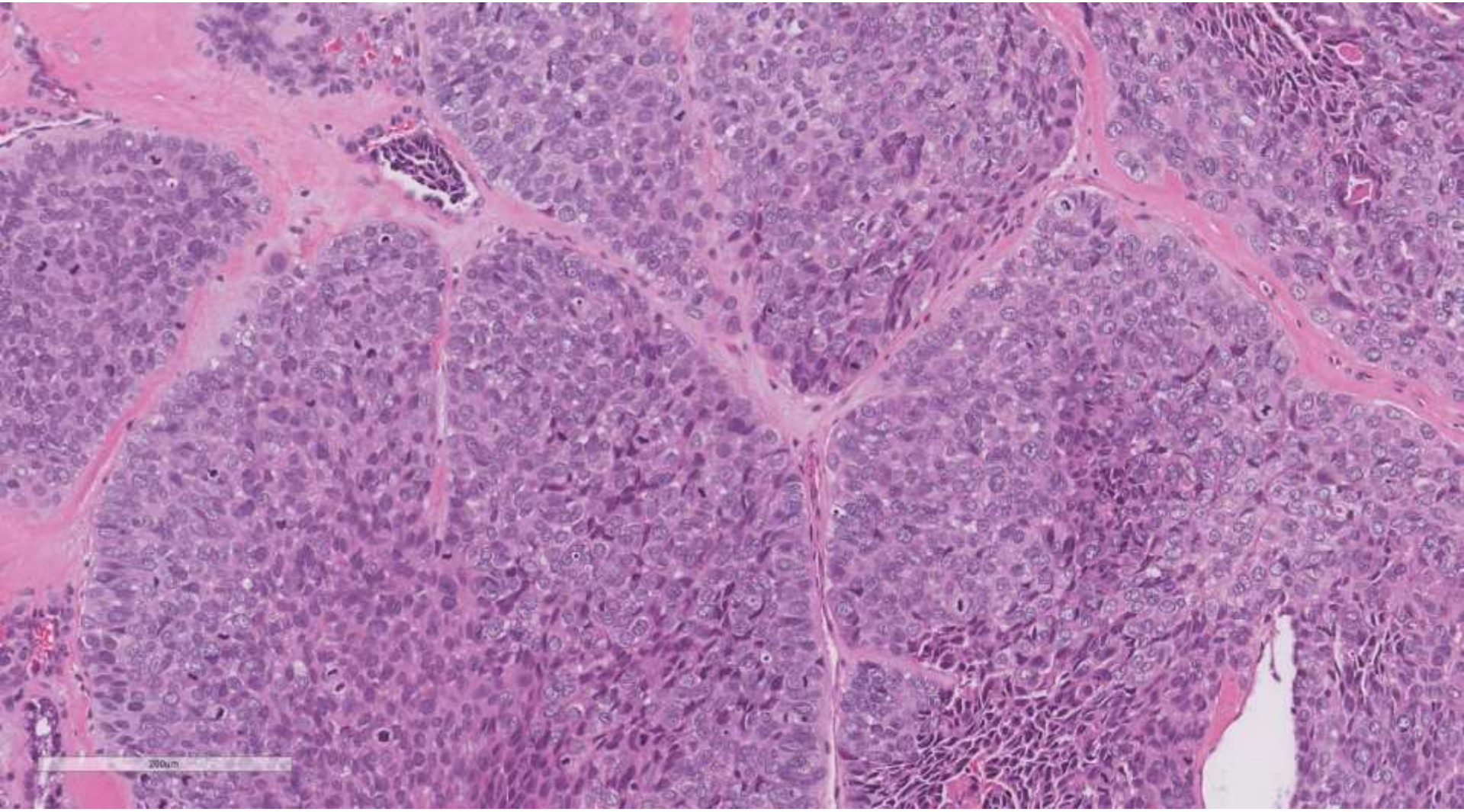
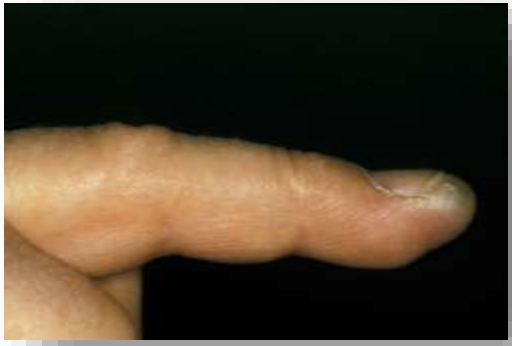

200µm

CLINICAL HISTORY

- 68-year-old man with a left long finger mass
- Orthopedic clinical impression at excision: giant cell tumor of tendon sheath

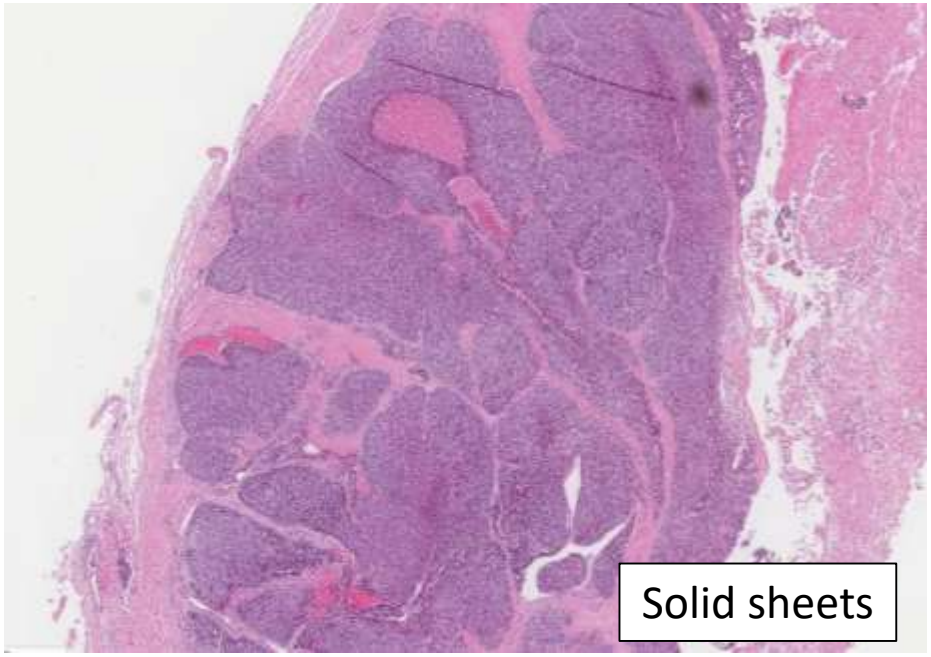


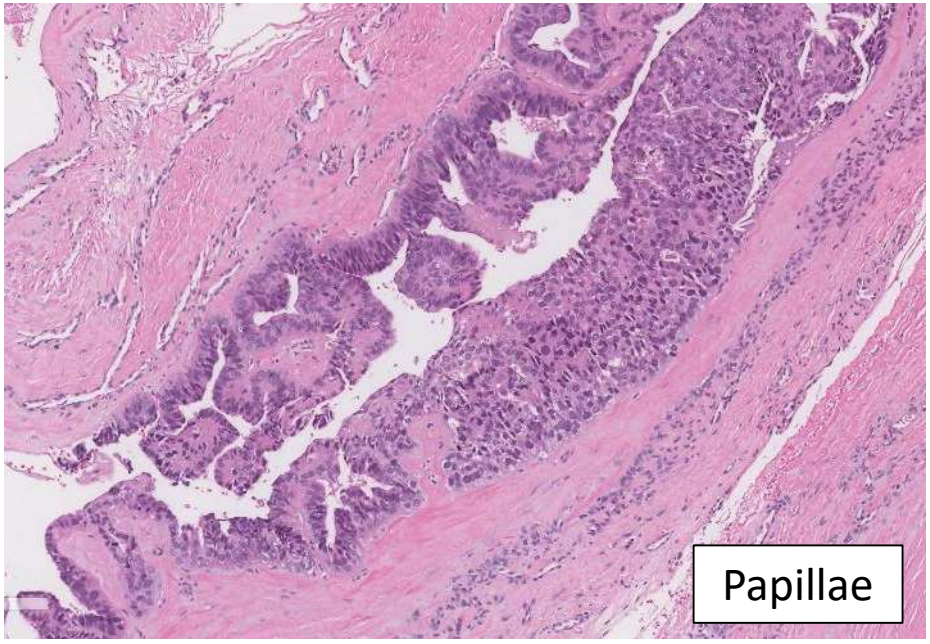
From Altmann, et al. *Clin Cosmet Investig Dermatol* 2015

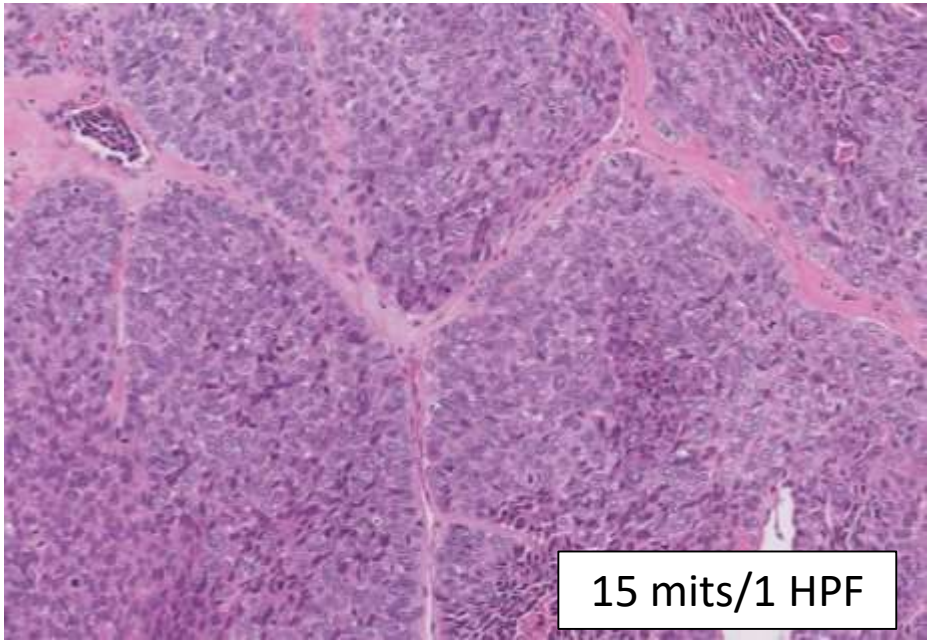
GROSS DESCRIPTION

- 1.8 cm disrupted cyst with yellow-orange friable material
- Entirely submitted


Solid and cystic


Solid sheets


Papillae


15 mits/1 HPF

FINAL DIAGNOSIS:

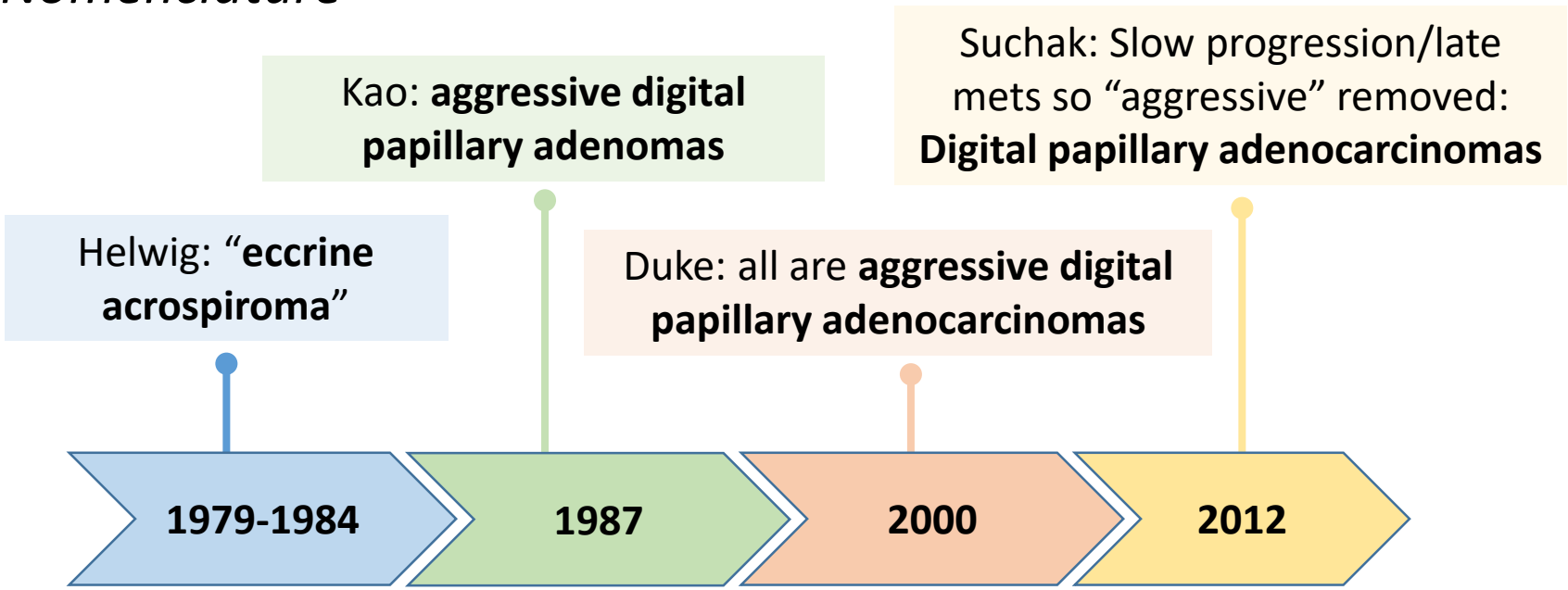
Soft tissue, left long finger, excision:

Digital papillary adenocarcinoma

History

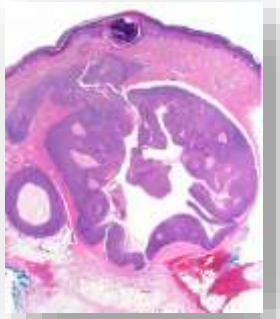
- Rare cutaneous tumor of eccrine differentiation
- ~100 cases in literature
- Common presentation: solitary slowly enlarging nodule on volar surfaces of fingers and toes in men aged 50-70s, +/-pain

Nomenclature

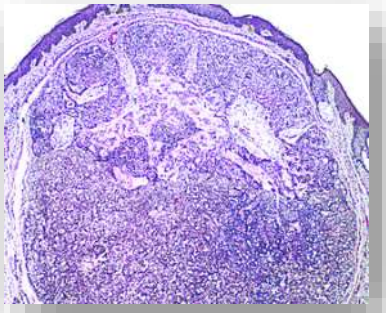


Differential Diagnoses

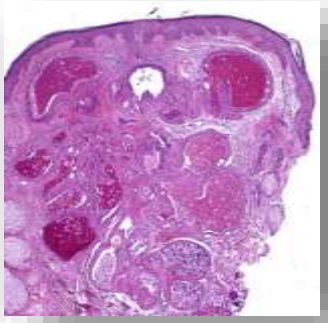
- Acral hidradenoma
- Hidradenocarcinoma
- Tubular apocrine adenoma
- Papillary eccrine adenoma
- Metastatic papillary adenocarcinoma of thyroid, breast, or GI origin



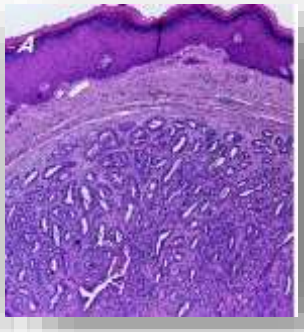
Wiedemeyer et al. *Am J Surg Path* 2020



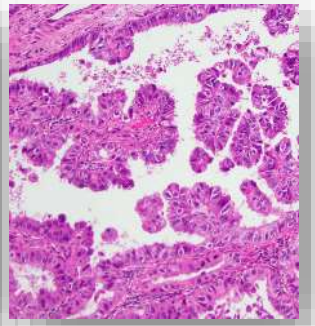
Mark R. Wick, M.D.



Ito, *T. J Am Acad Derm* 2014

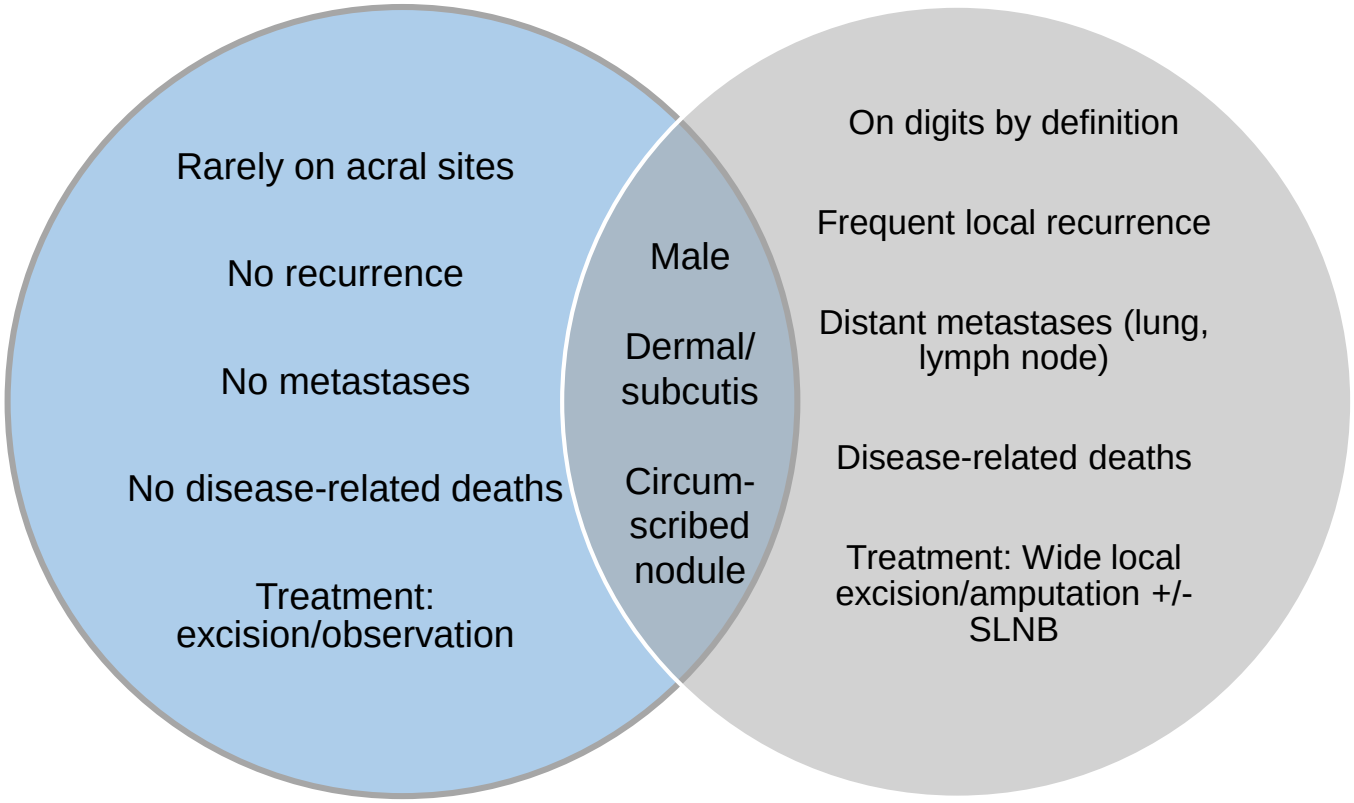


Anthony J. Perri, MD



Negar Rassaei, M.D

Clinical Features of Hidradenoma vs. DPA

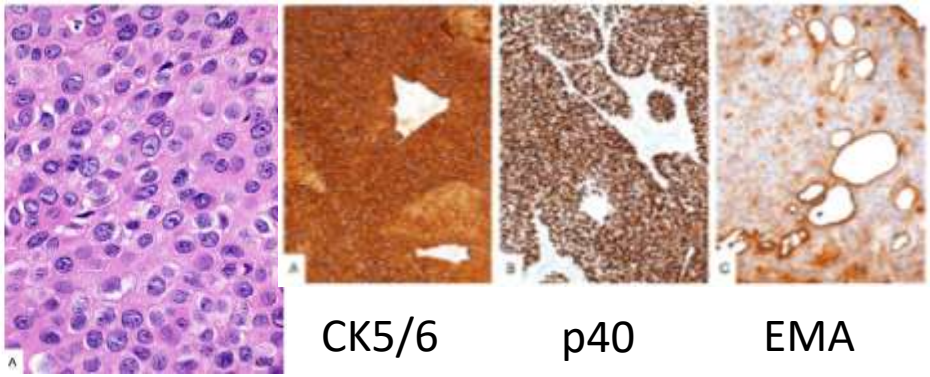


Clinicopathologic Characterization of Hidradenoma on Acral Sites

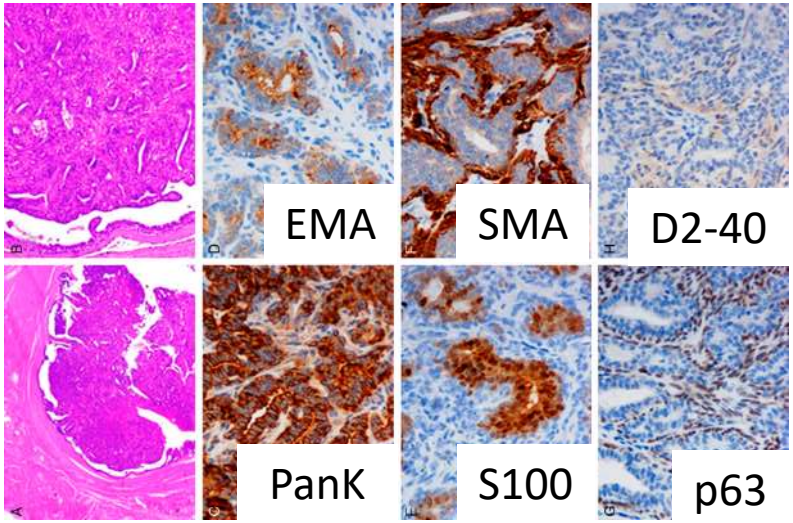
A Diagnostic Pitfall With Digital Papillary Adenocarcinoma

Katharina Wiedemeyer, MD,† Pavandeep Gill, MD,* Michelle Schneider, MD,* Peter Kind, MD,‡ and Thomas Brenn, MD, PhD, FRCPath*§‖*

Wiedemeyer et al. *Am J Surg Pathol* 2020



Suchak et al. *Am J Surg Pathol* 2012



Hidradenomas:

Negative for S100, SMA, and Desmin
(not pictured)

Digital Papillary Adenocarcinomas:

Positive for S100 and SMA

TAKE-HOME POINTS

- Digital papillary adenocarcinomas (DPAs) are rare tumors of eccrine differentiation that occur on fingers and toes
- DPAs can histologically and clinically overlap with other sweat gland tumors, notably acral hidradenomas
- Metastasis reported in 14-26%; if not re-excised or amputated, 50% local recurrence
- High index of suspicion, histological features are key, +/- IHC can help guide diagnosis

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