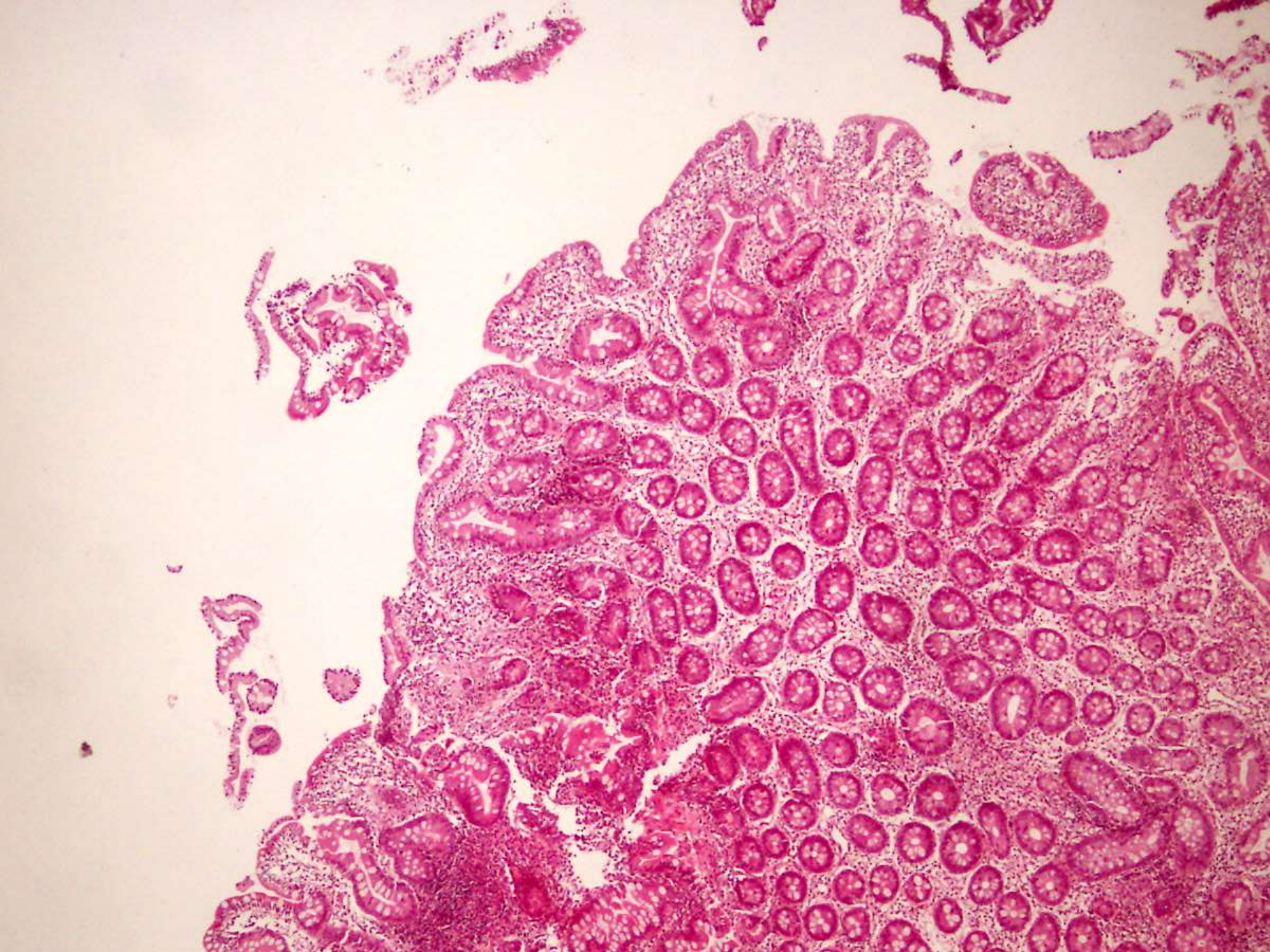
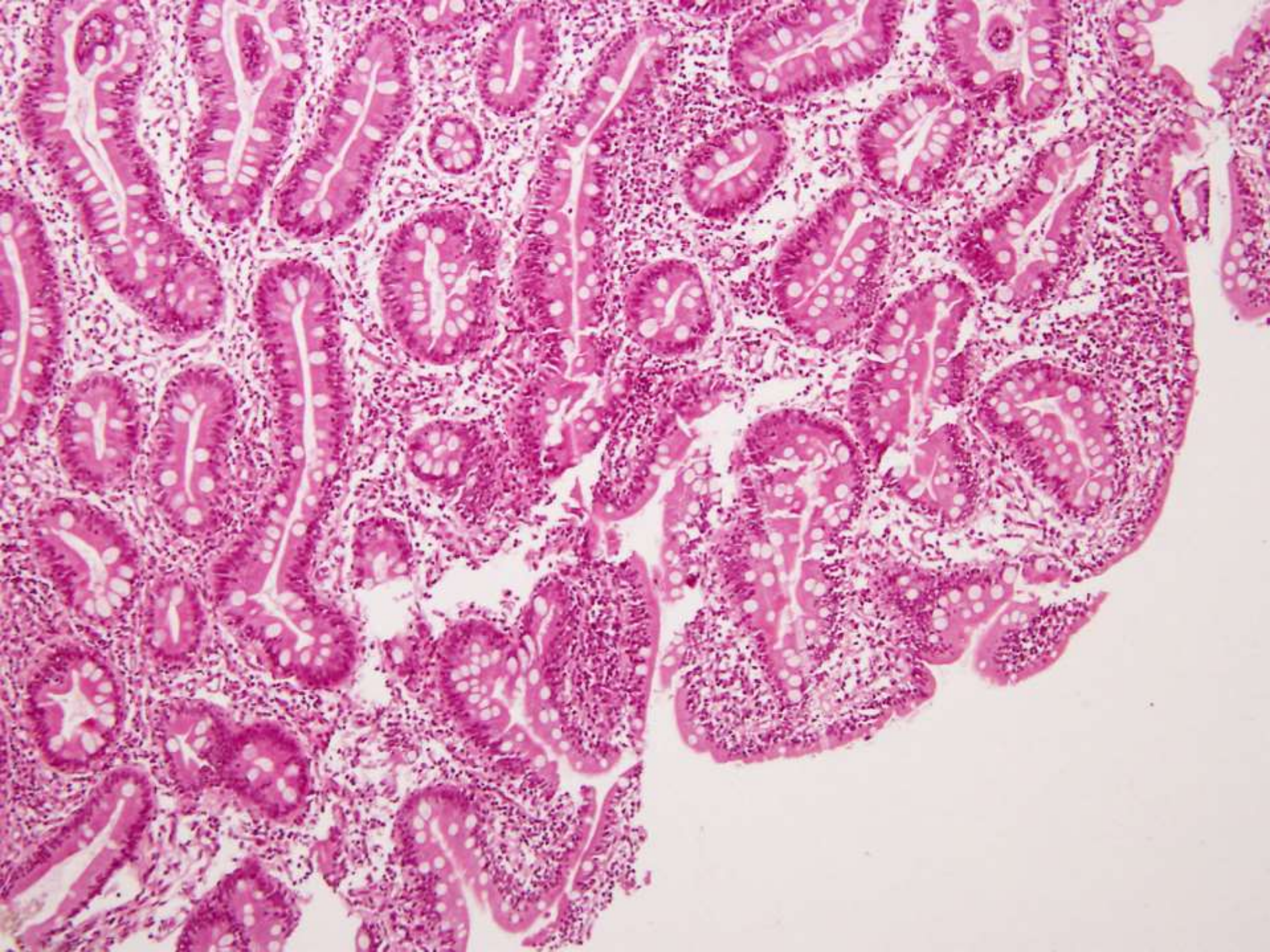
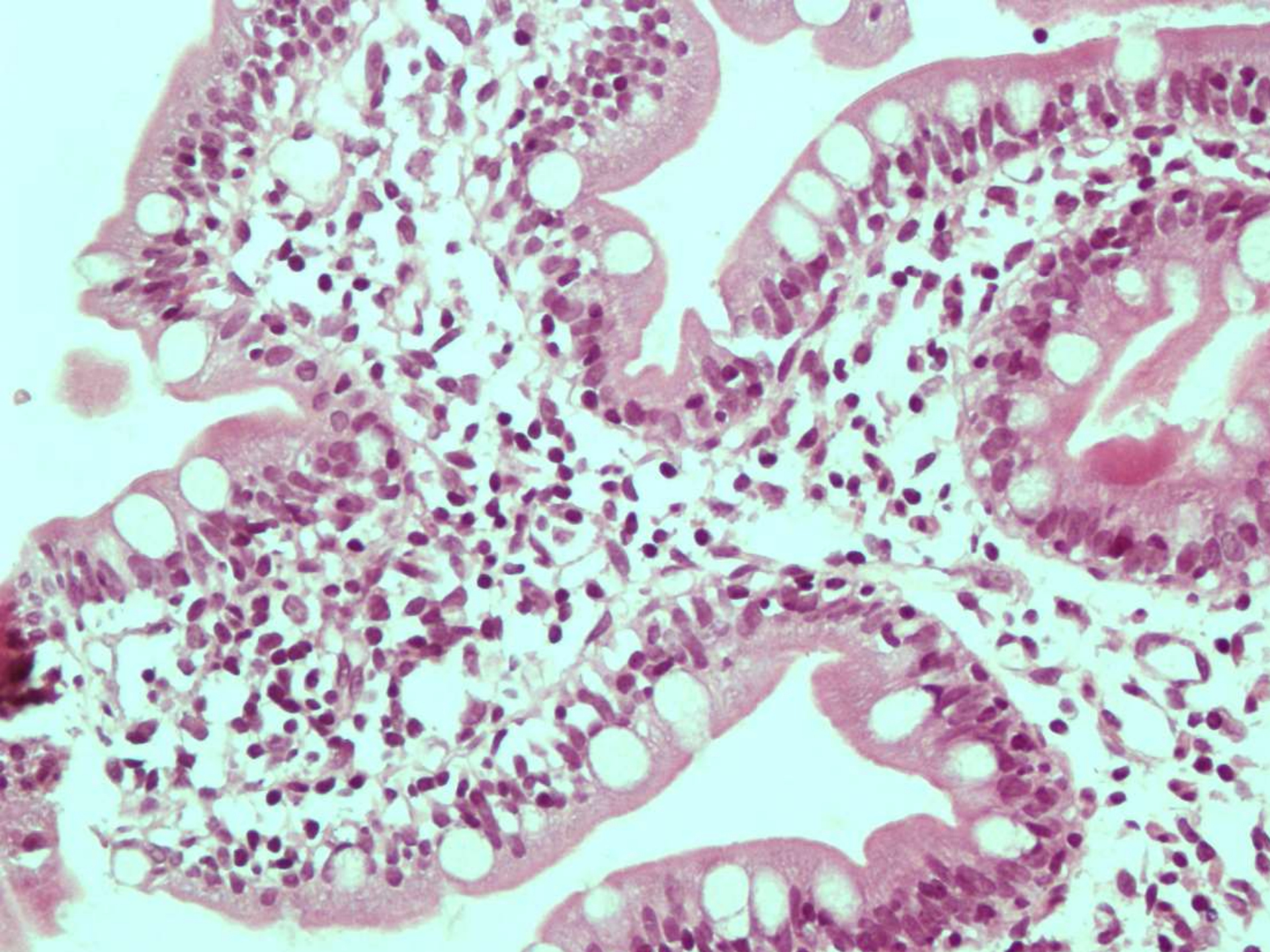
19-1101

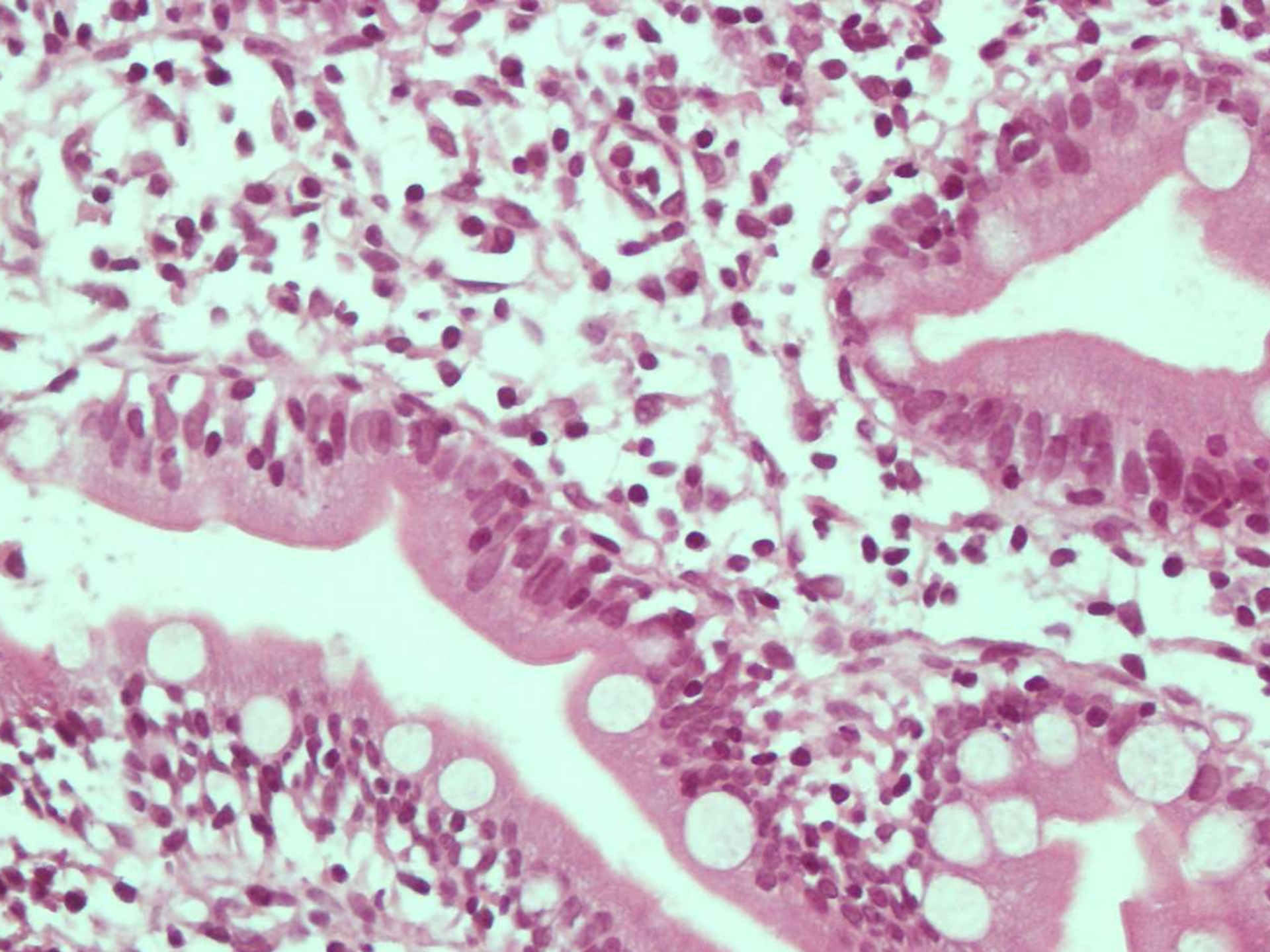
Nabeen Nayak; Sir Ganga Ram Hospital, New Dehli

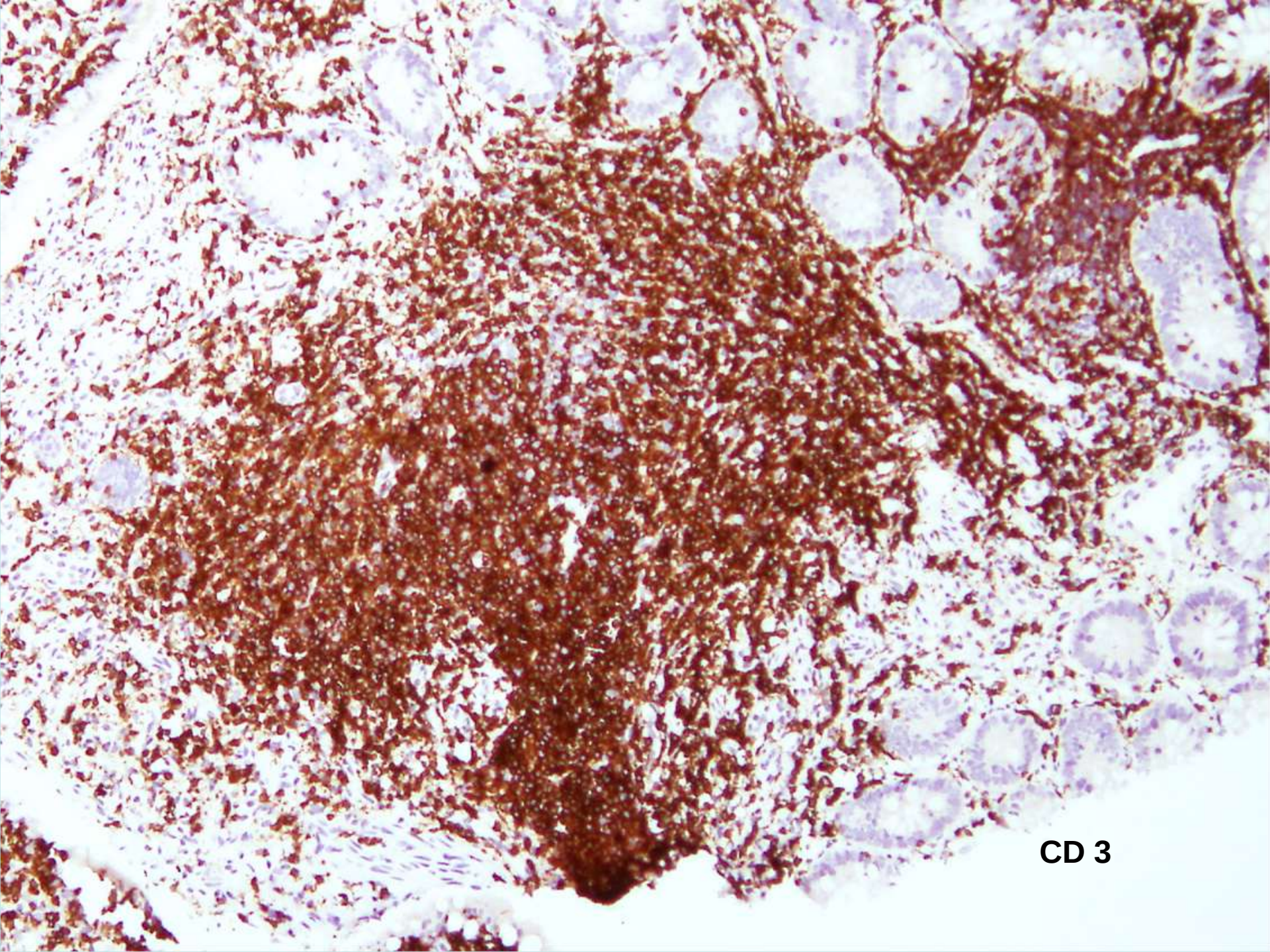
38-year-old male presented with intermittent colicky abdominal pain, loose motions, and weight loss over a 3-month period. He had similar complaints years earlier for which empirical anti-tubercular therapy was instituted to which he responded after 9 months. Present colonoscopy showed ileal nodularity, CT enterography revealed thickening and dilatation of lower CBD as well as mild dilated IHBR with prominent ileal folds. HIV Elisa was negative. Jejunal biopsy done.

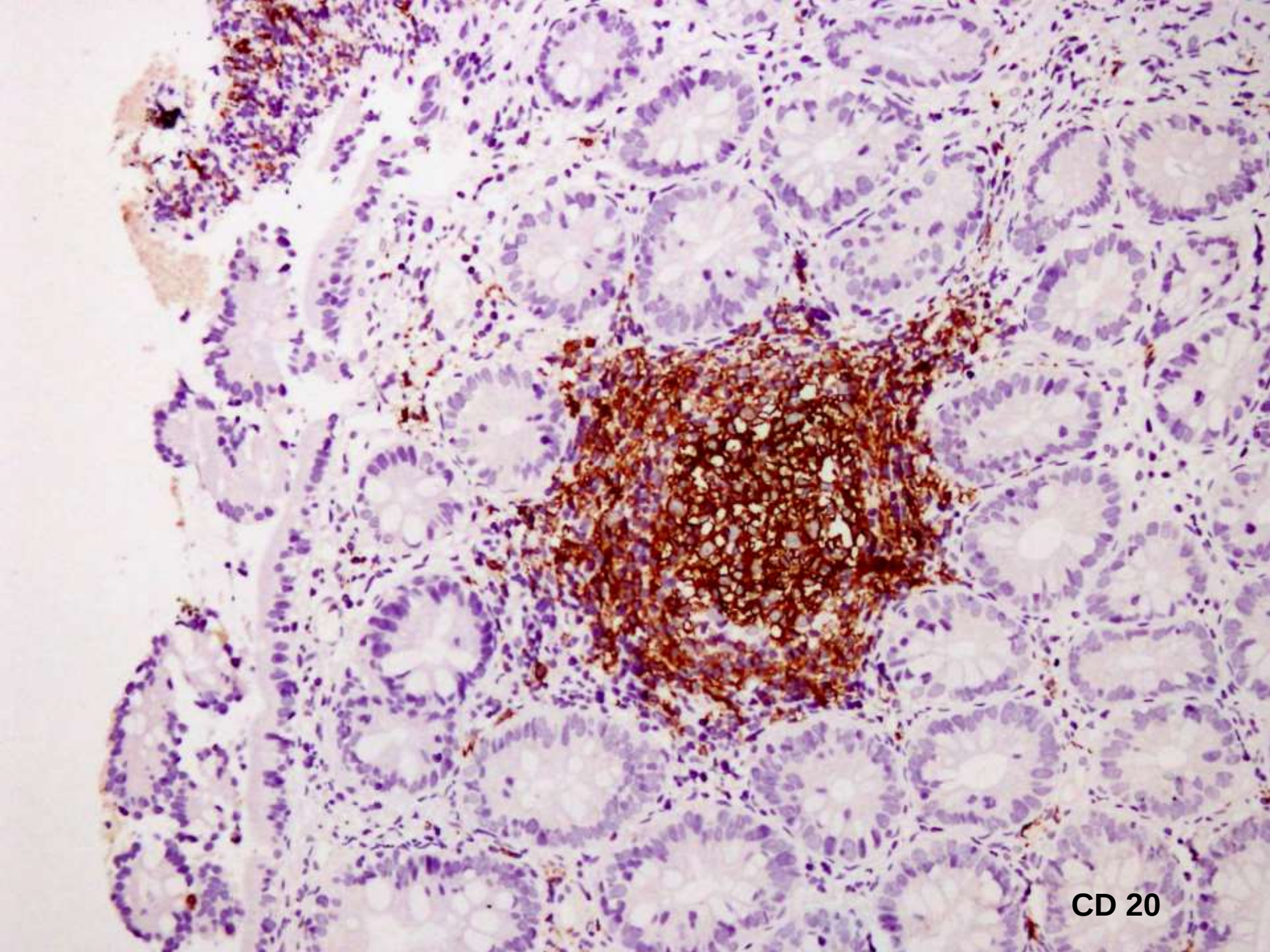









CD 3


CD 20

- Moderate villus atrophy with mild to moderate crypt hyperplasia.
- Increased inflammatory cells, mostly lymphocytes in lamina propria.
- IEL counts average 60 lymphocytes/100 Epithelial cells.
- **Markedly reduced plasma cells** in lamina propria.
- No microorganisms detected

These features point to an inflammatory enteropathy associated with defective terminal maturation of B lymphocytes such as in **Common Variable Immunodeficiency (CVID).**

Only the results of a LFT done in another hospital available at this time showed Albumin – **4.4** g/dl, Globulin – **1.9** g/dl & A/G ratio – **1.8**

With a probable diagnosis of CVID relevant test results were requested

SERUM IMMUNOGLOBULINS:

	Value	Ref. Range
IgA	< 2.0 mg/dl	35 – 350 mg/dl
IgG	528.8 mg/dl	650 – 1600 mg/dl
IgM	< 20.0 mg/dl	50 – 300 mg/dl

FLOW CYTOMETRY:

CD19 B cells	119/ul	112 -618/ul
CD20 B cells	119/ul	98 – 150/ul
CD3 + cells	1151/ul	619 – 2525/ul
CD4 + cells	682/ul	286 – 1316/ul
CD8 + cells	395/ul	130 - 1118/ul

ANTI-TRANSGLUTAMINASE ANTIBODY - Negative

Stool biofire multiplex PCR for Organisms - Giardia lamblia & Isospora

No Gluten sensitivity

DIAGNOSIS - Chronic Jejunitis associated with Common Variable Immunodeficiency (CVID)

CVID is a heterogeneous disorder, predominantly of the adaptive immune system with variably defective peripheral blood B cell maturation & terminal differentiation, having a prevalence of 1 in 25,000 to 1 in 50,000. Diminished & defective antibody production due to reduced CD27+ isotype-switched memory B cells lead to repeated infections.

Chronic enteropathy is present in 75-80% and GI symptoms in 40-65% cases of CVID (Mathieu, U et al. Curr Gastroenterol Rep 2016,18(4):17)

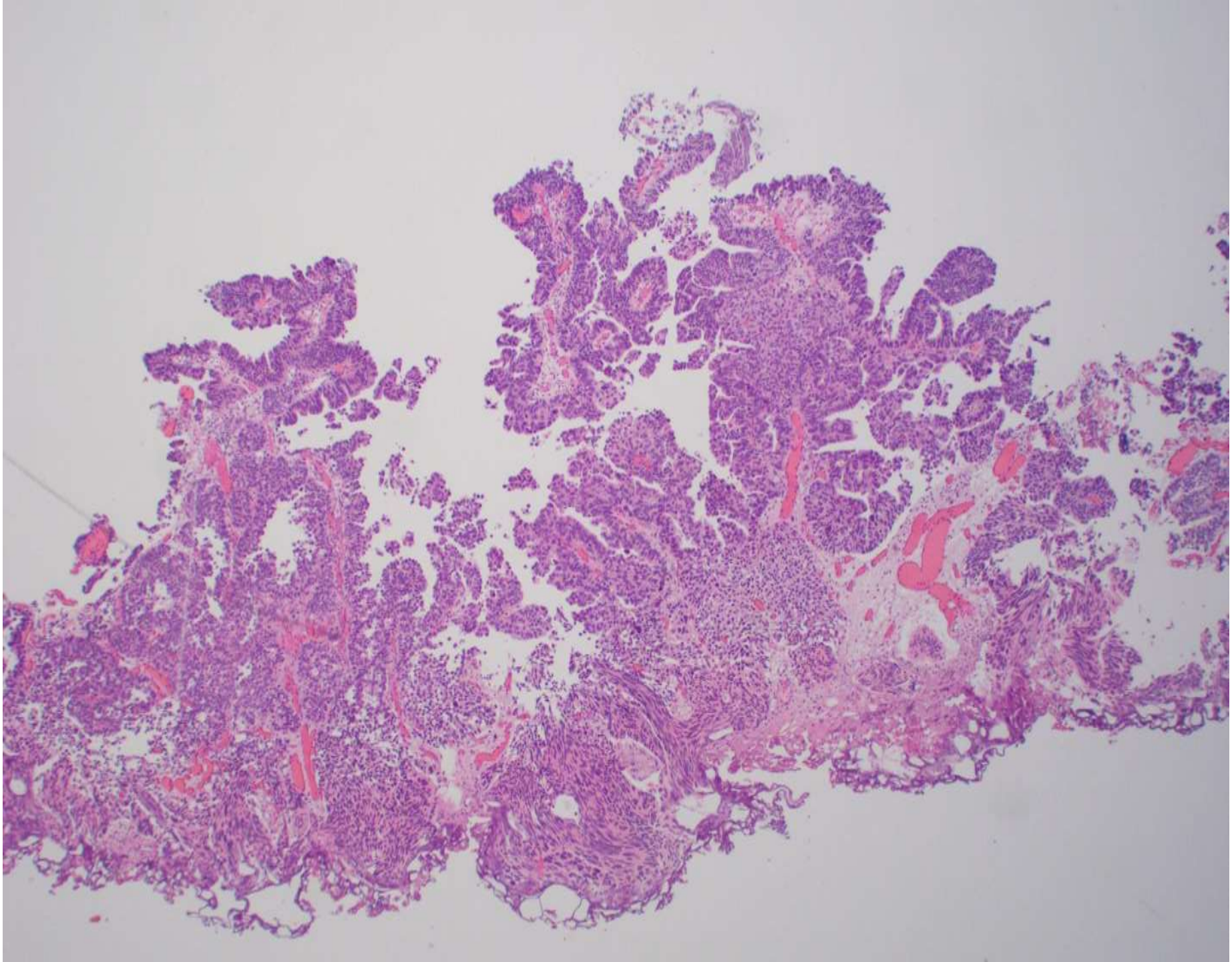
On the basis of criteria laid down by ESID & PAGID the gastroenterologist labeled our case as **"Probable CVID"** and treated him with IVIG, Septran and Metranidazole.

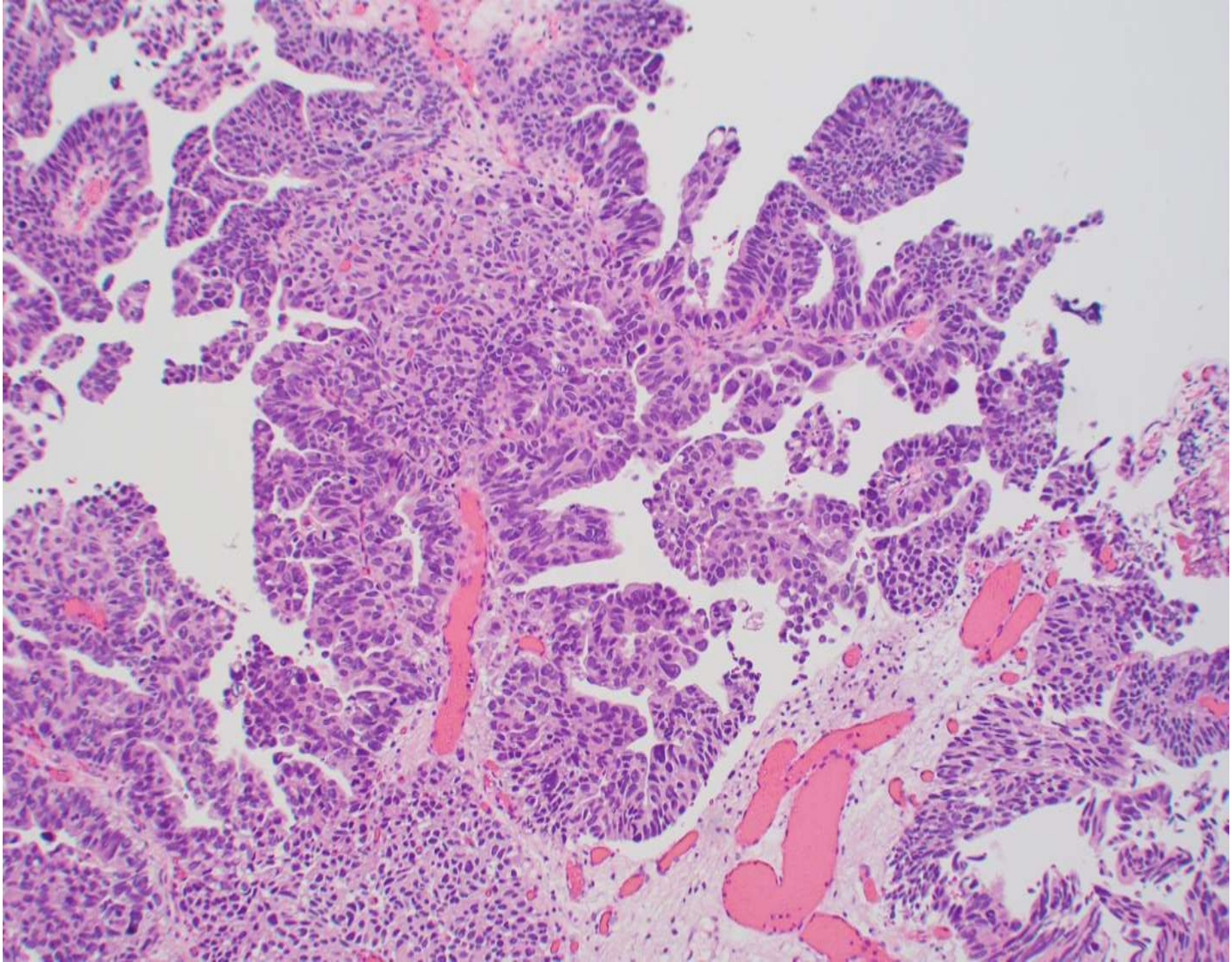
At follow up after 2 weeks his symptoms had significantly improved and he had gained weight.

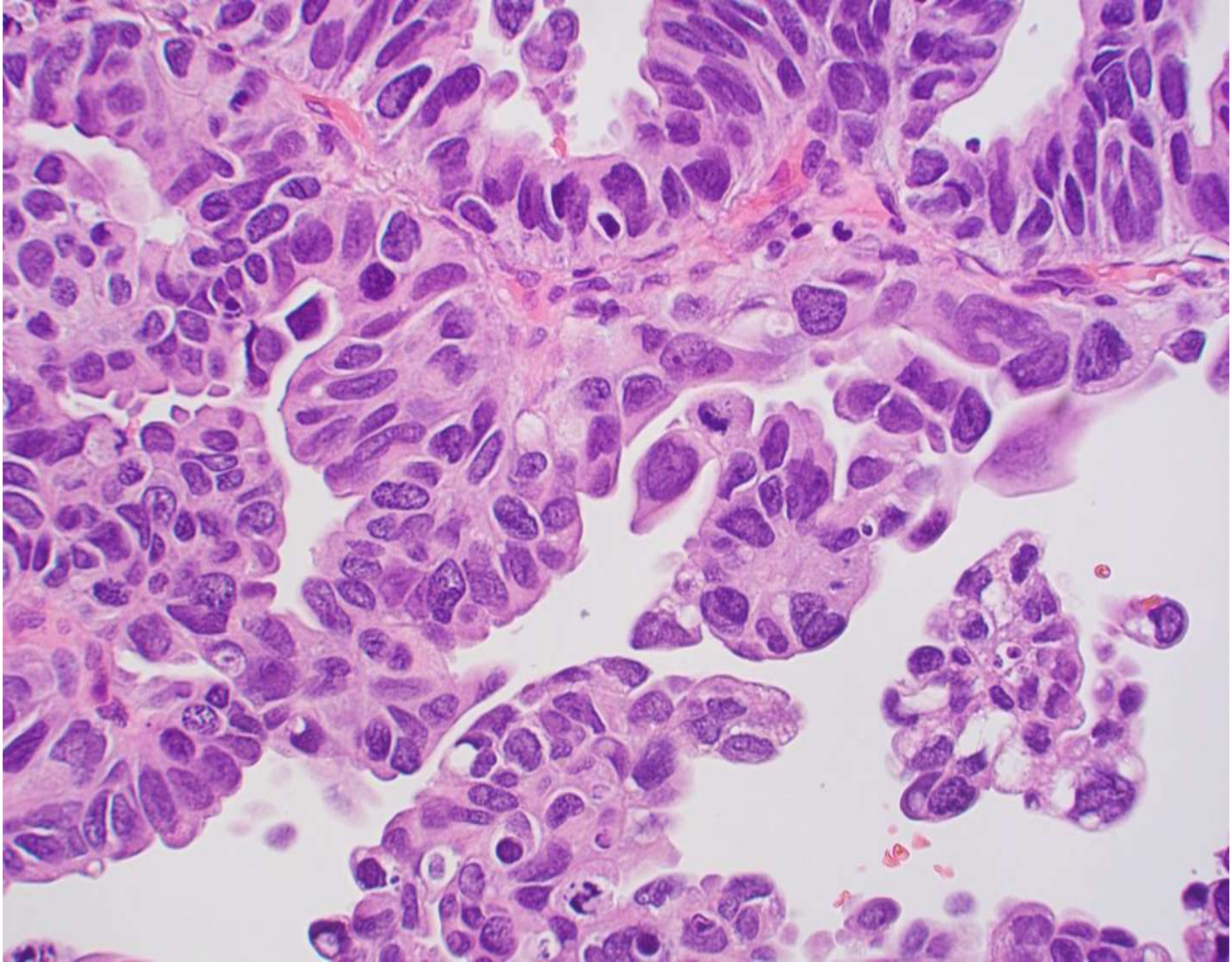
19-1102
scanned slide available!

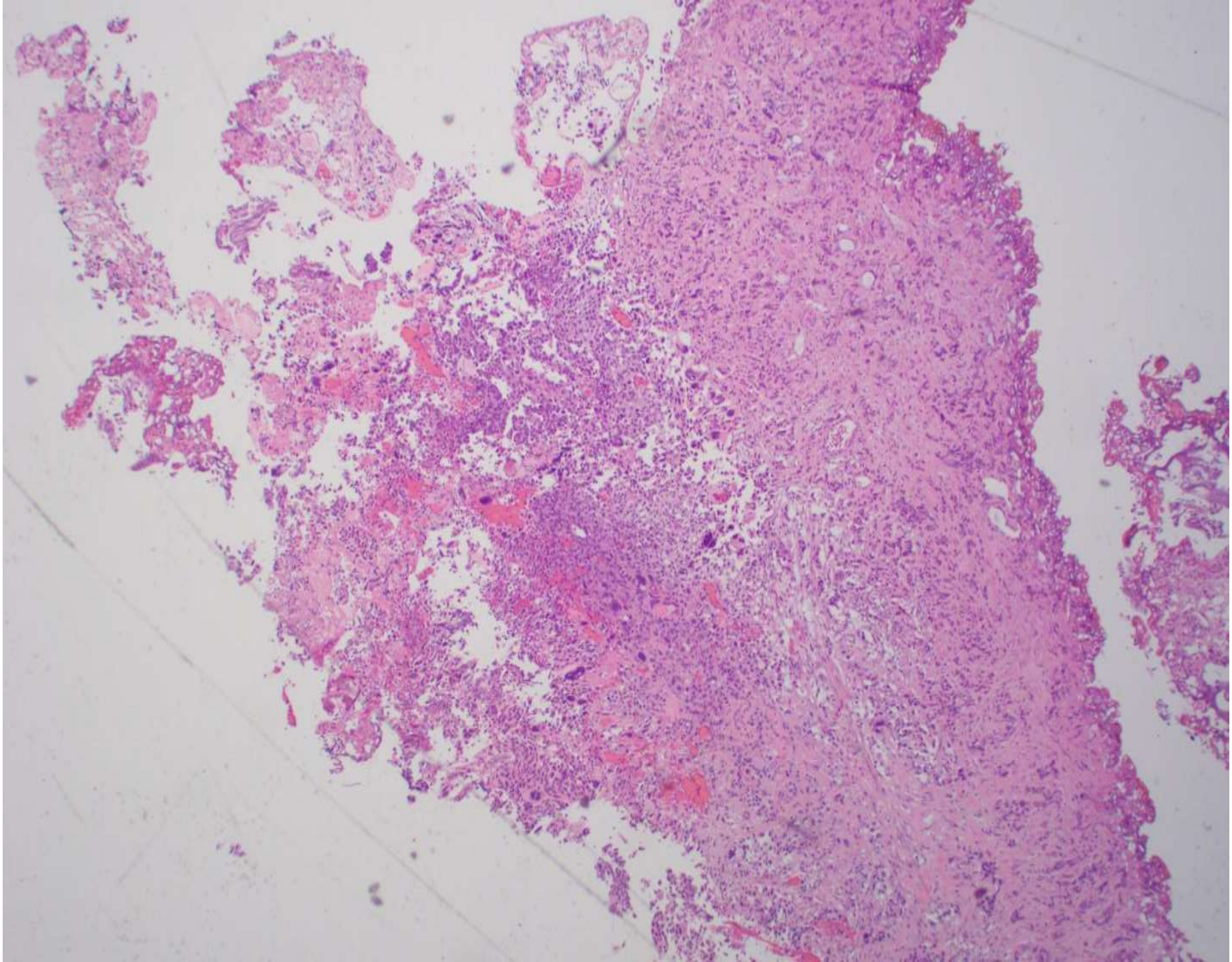
Sava Grujic; Kaiser San Jose

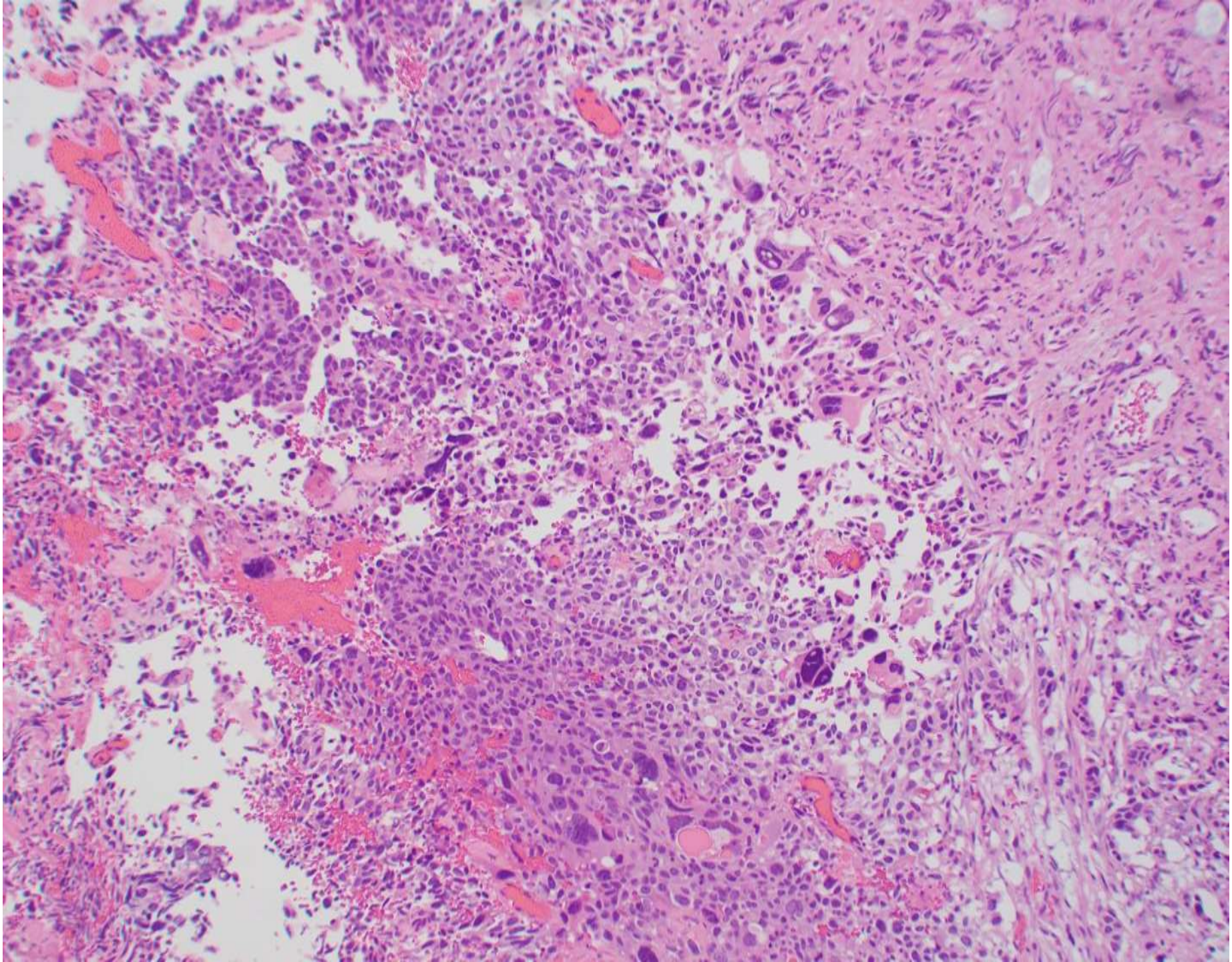
58-year-old male with bladder tumor.

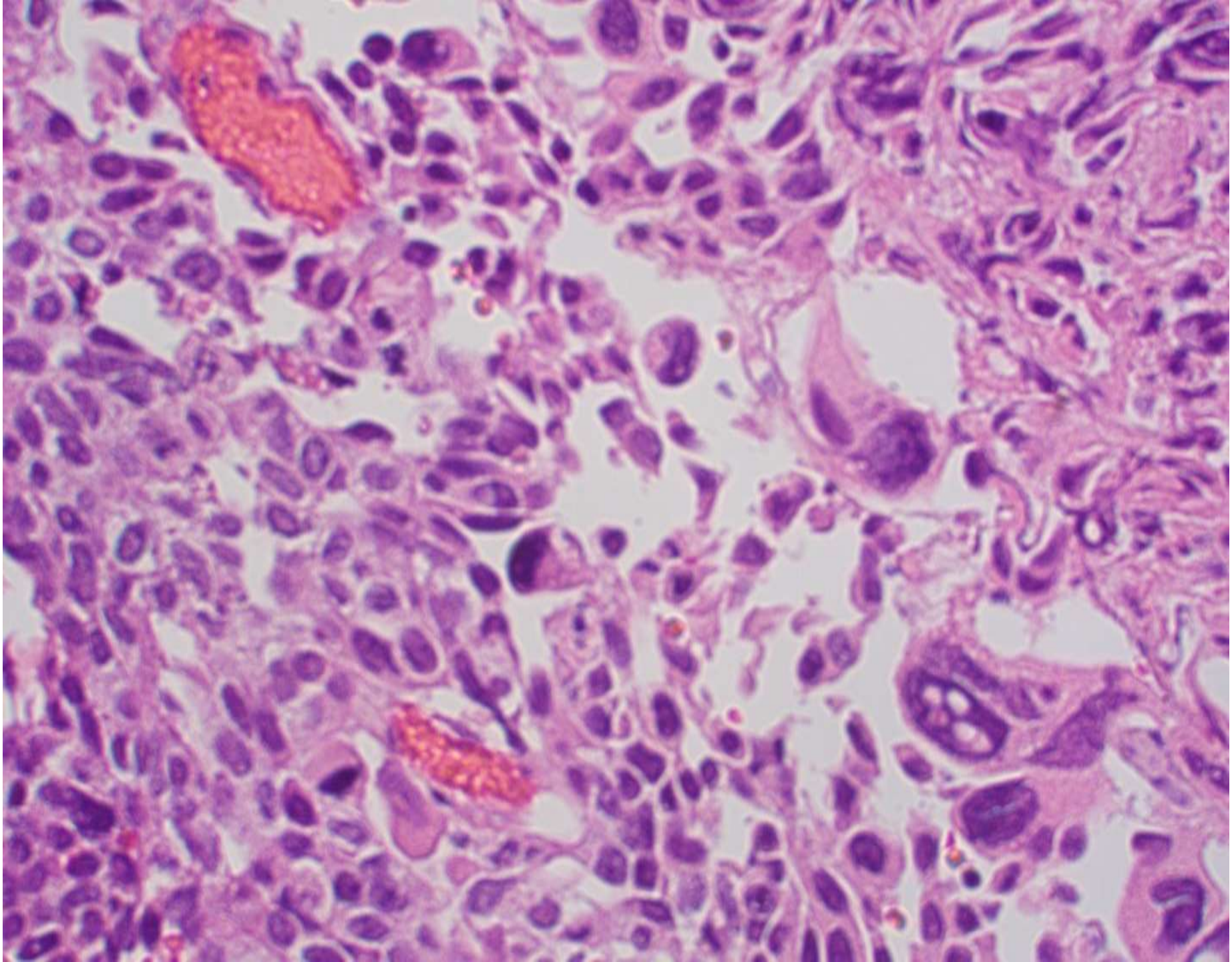


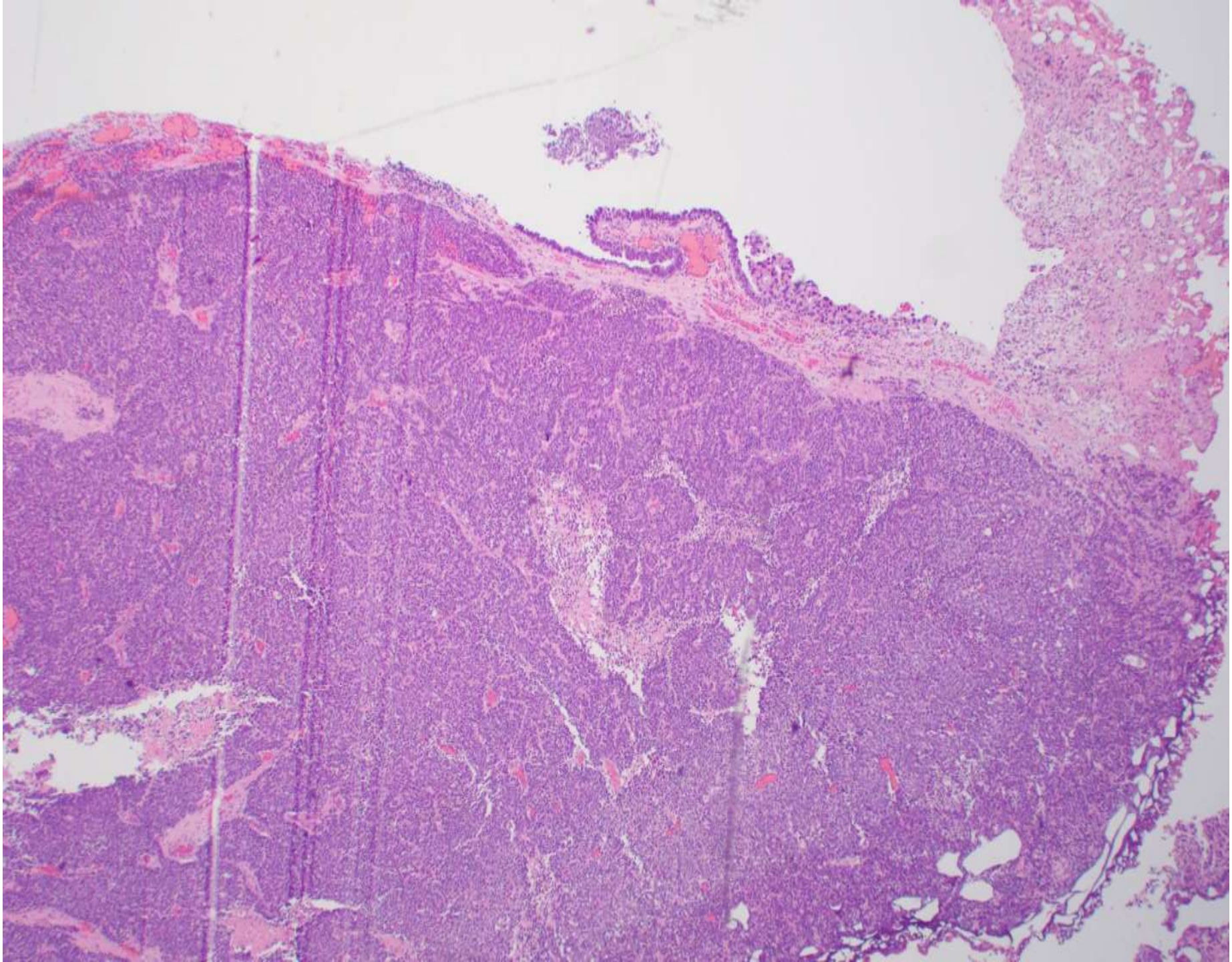


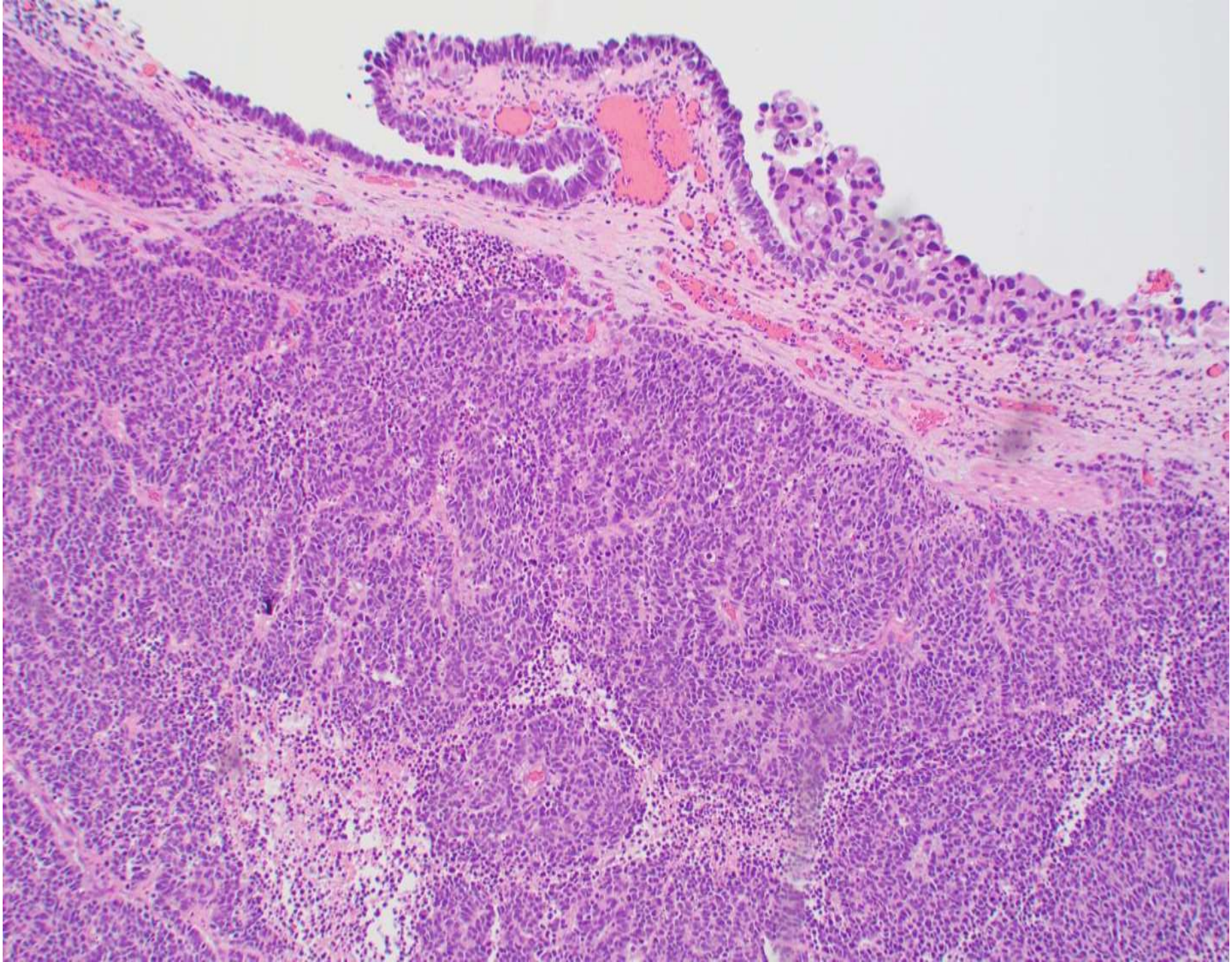


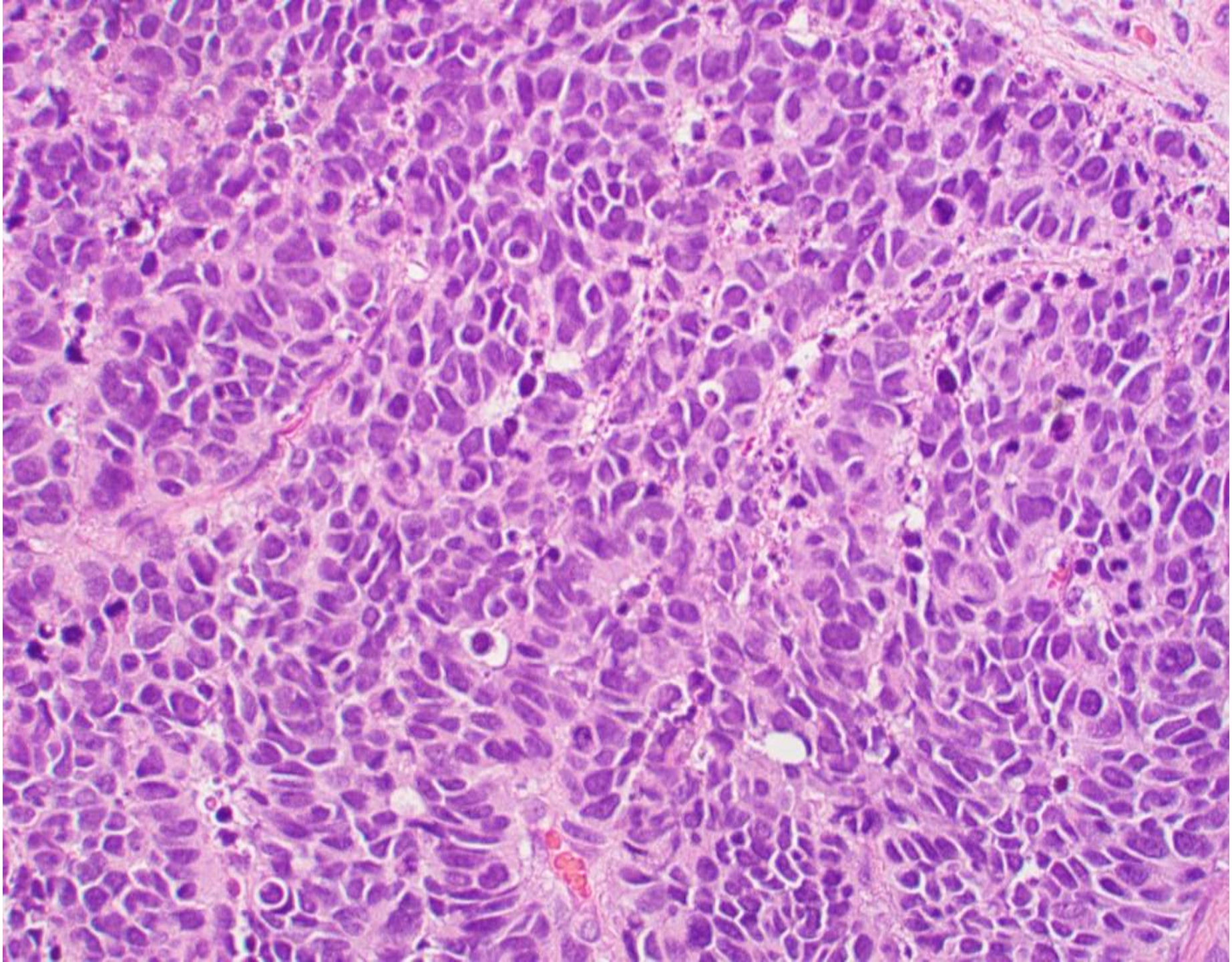


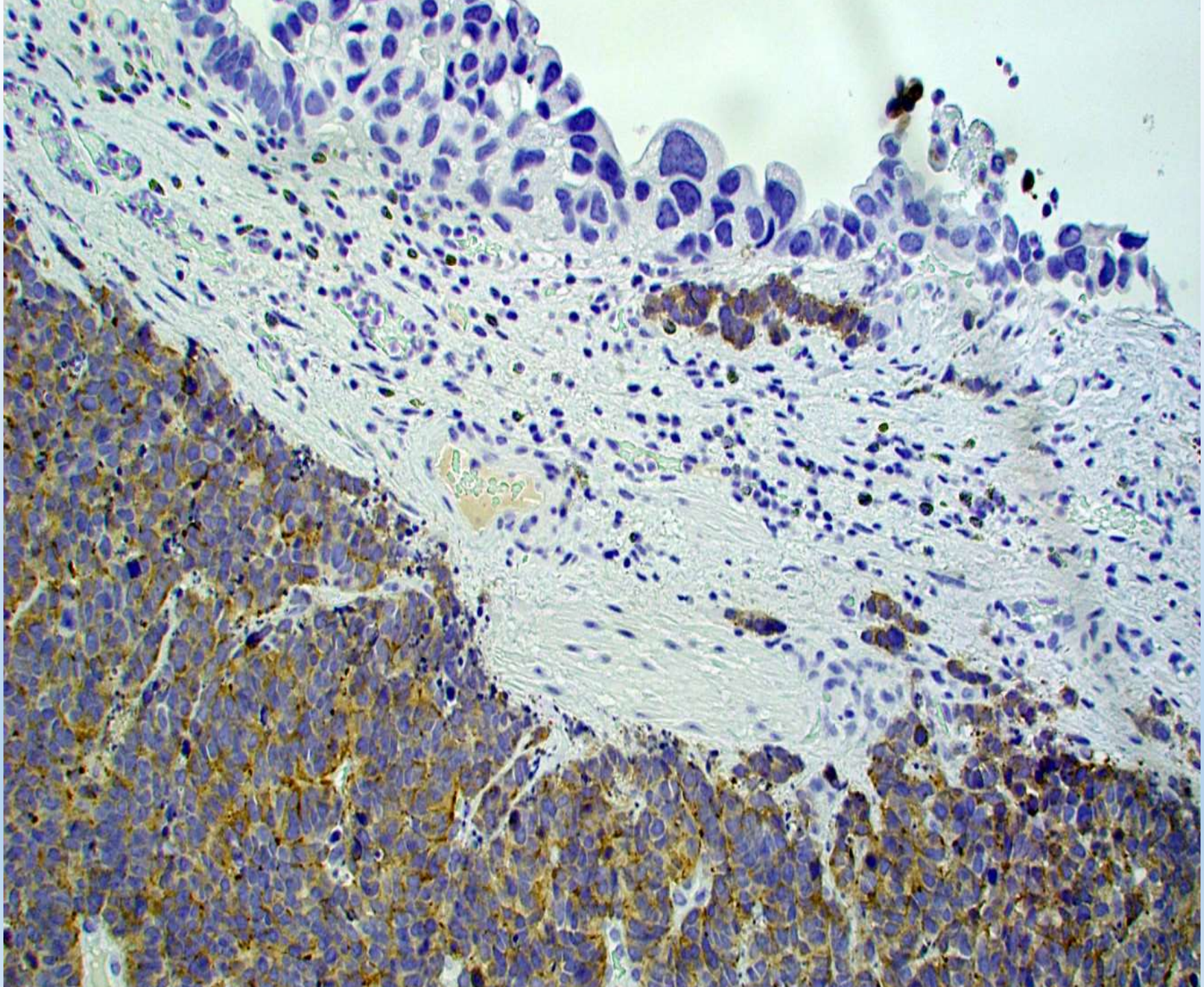


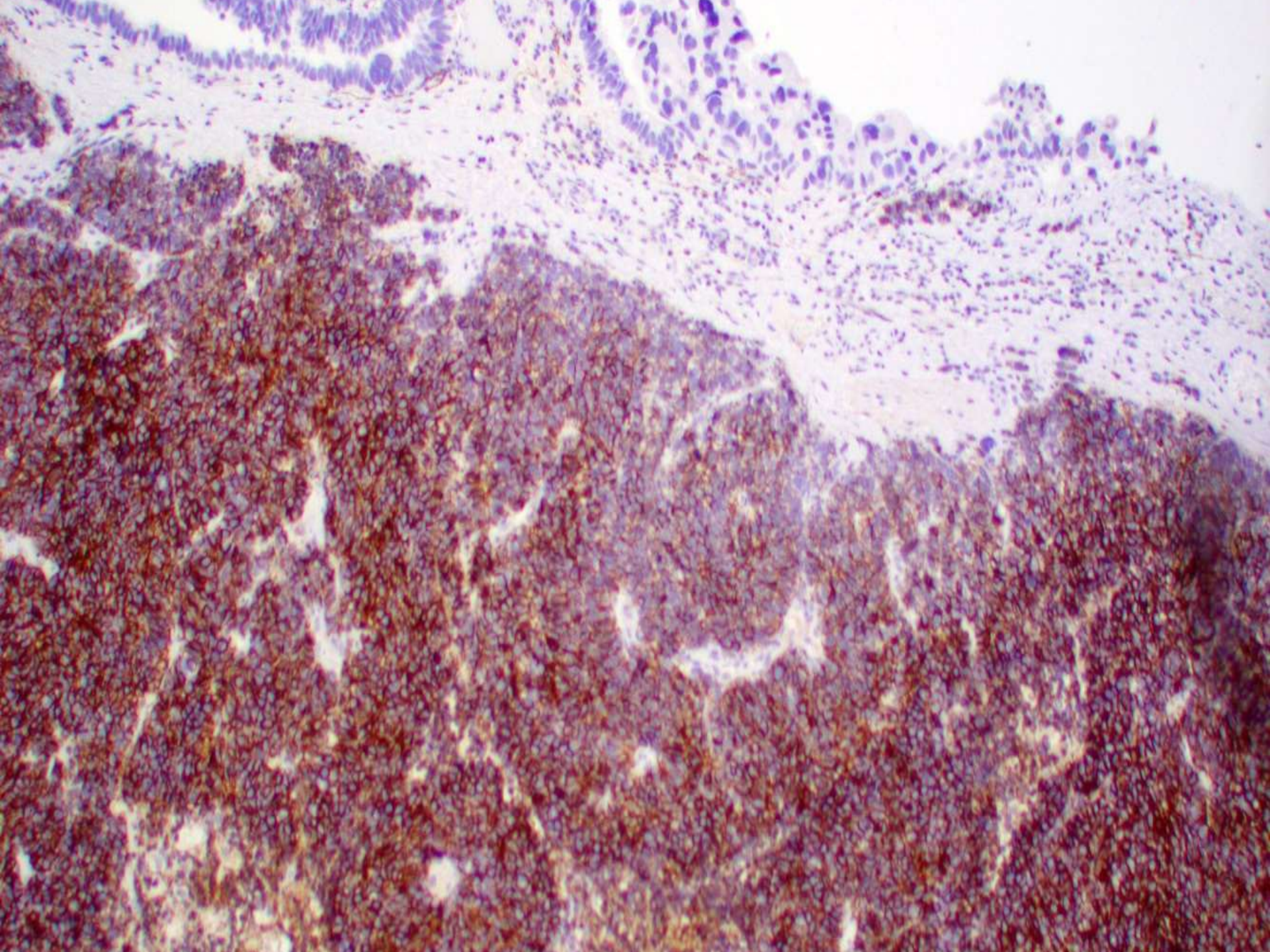


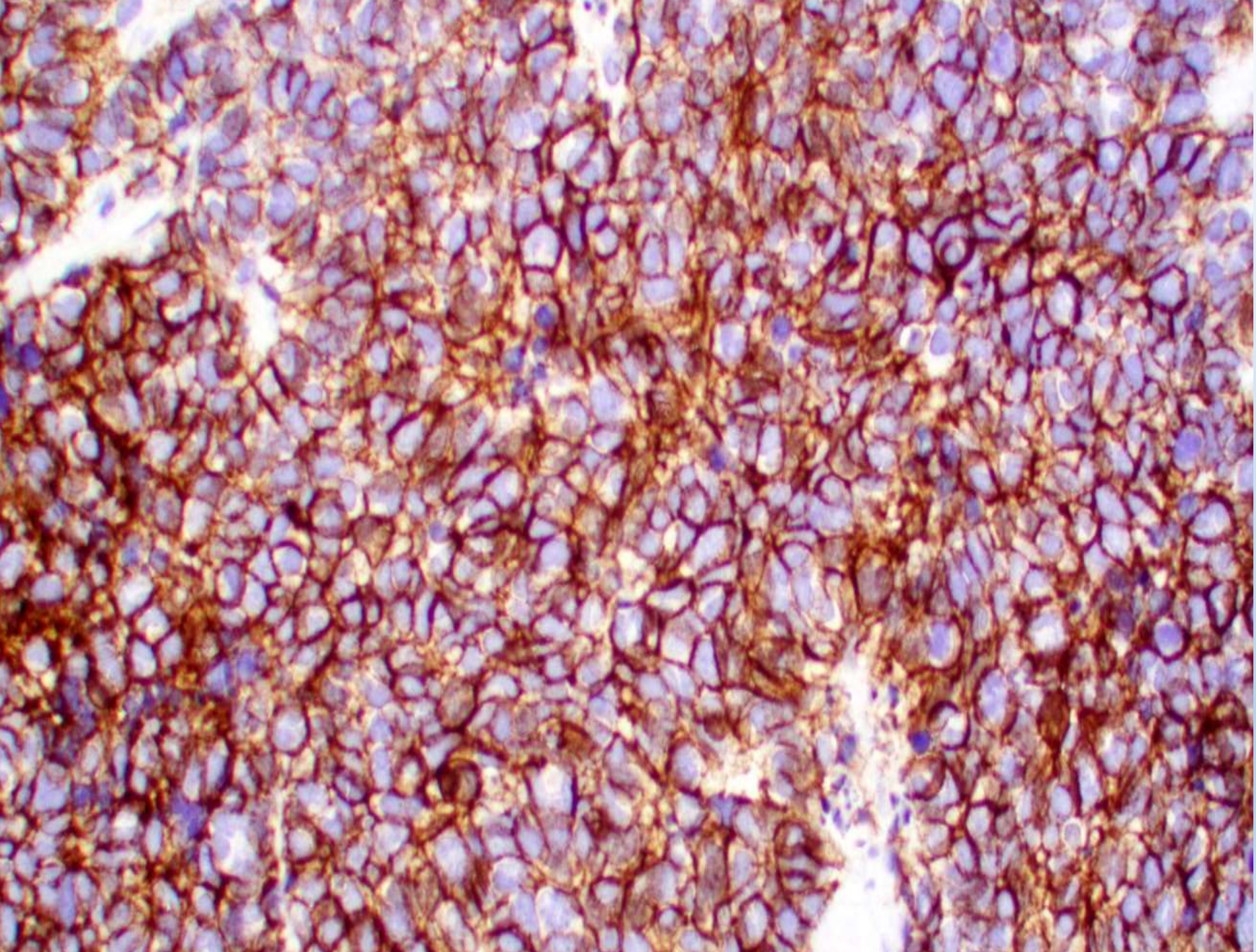












Service: STR AMBULATORY SURGER\ **Primary Pathologist:** SAVA GRUJIC M.D.

Final Diagnosis **Date Signed Out:** 9/13/2019 10:08

BLADDER TUMOR:

- MIXED SMALL CELL NEUROENDOCRINE CARCINOMA (APPROXIMATELY 35%) AND HIGH-GRADE PAPILLARY UROTHELIAL CARCINOMA (APPROXIMATELY 65%)
- TUMOR INVADES MUSCULARIS PROPRIA (DETRUSOR MUSCLE)
- LYMPHOVASCULAR INVASION IS PRESENT
- PATHOLOGIC STAGING: T2, NX, SEE SYNOPTIC REPORT BELOW FOR ADDITIONAL

Terminology

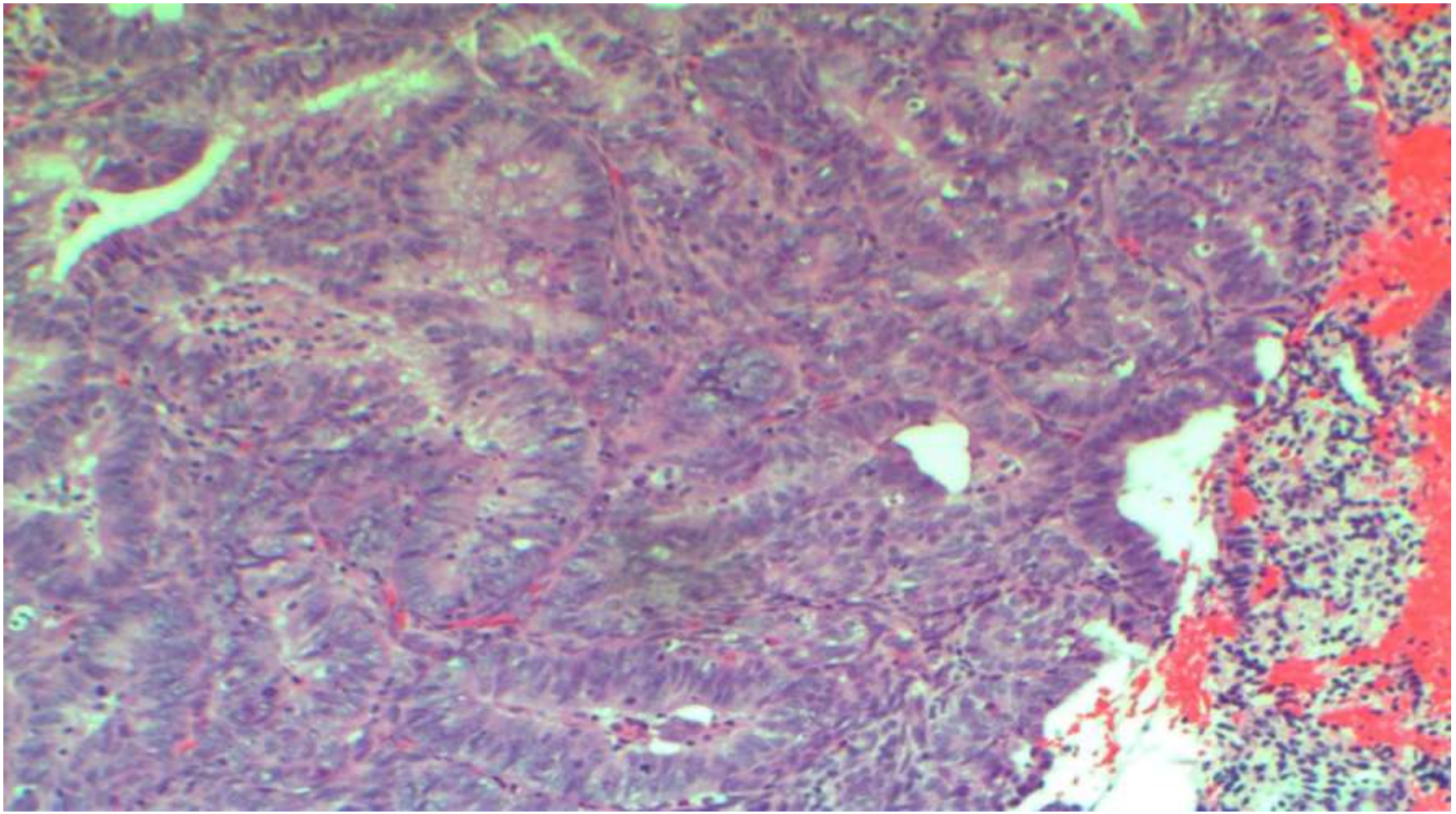
- WHO classification does not have a separate category for mixed tumors
- “For a tumor to be classified as SmCC, the small cell histology must constitute the majority of the tumor. Some SmCCs contain a lesser component of urothelial carcinoma (invasive or non-invasive) or other variant histology such as squamous, glandular or sarcomatous differentiation.”
- “SmCC is typically positive for synaptophysin, chromogranin and neuron-specific enolase, but the lack of expression of these markers should not exclude the diagnosis of SmCC.”
- SmCC is characterized by an aggressive clinical course with advanced stage at presentation and propensity for metastasis

19-1103

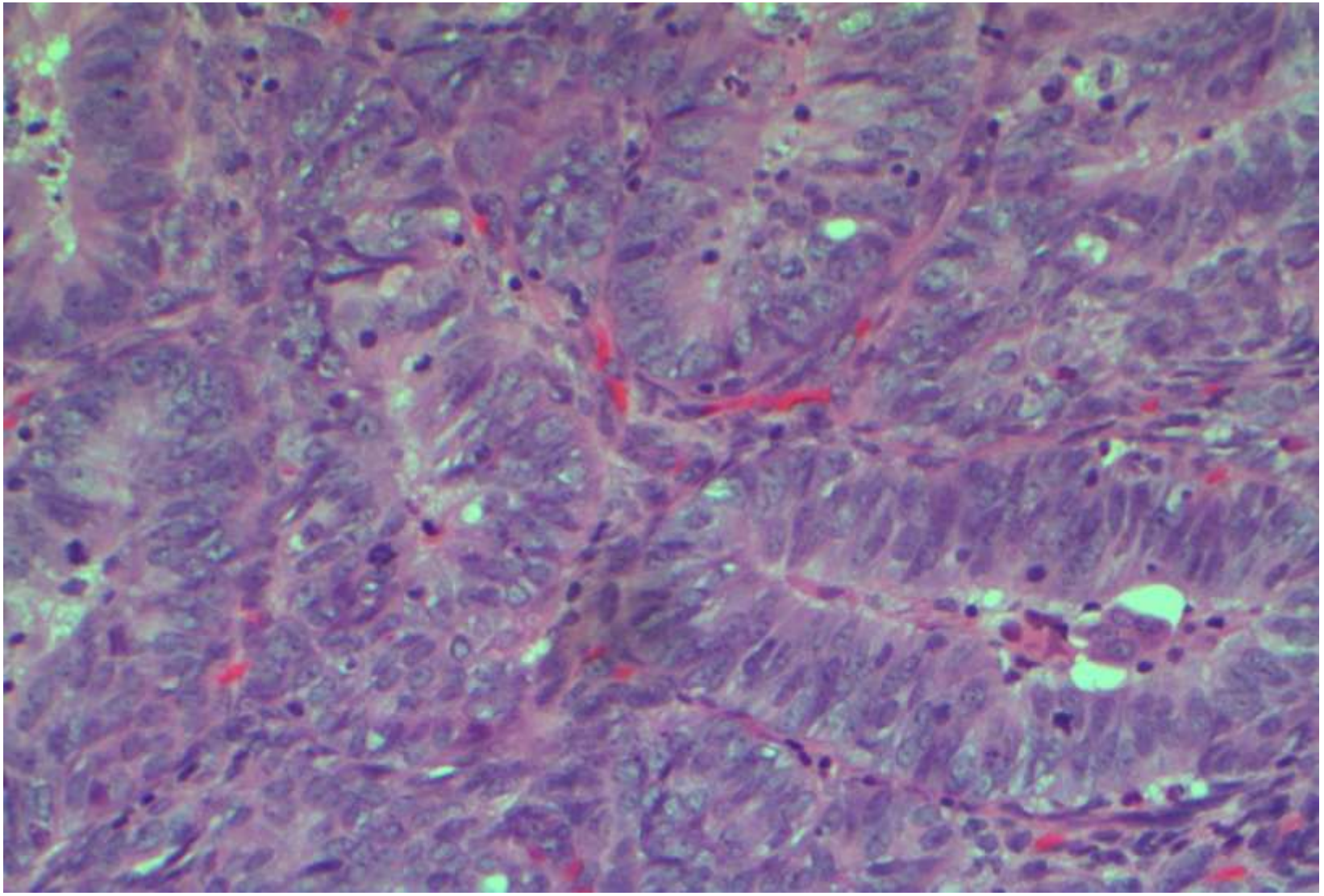
Chris Hansen; CHOMP

71-year-old female presents with post-menopausal bleeding. TAH/BSO performed.

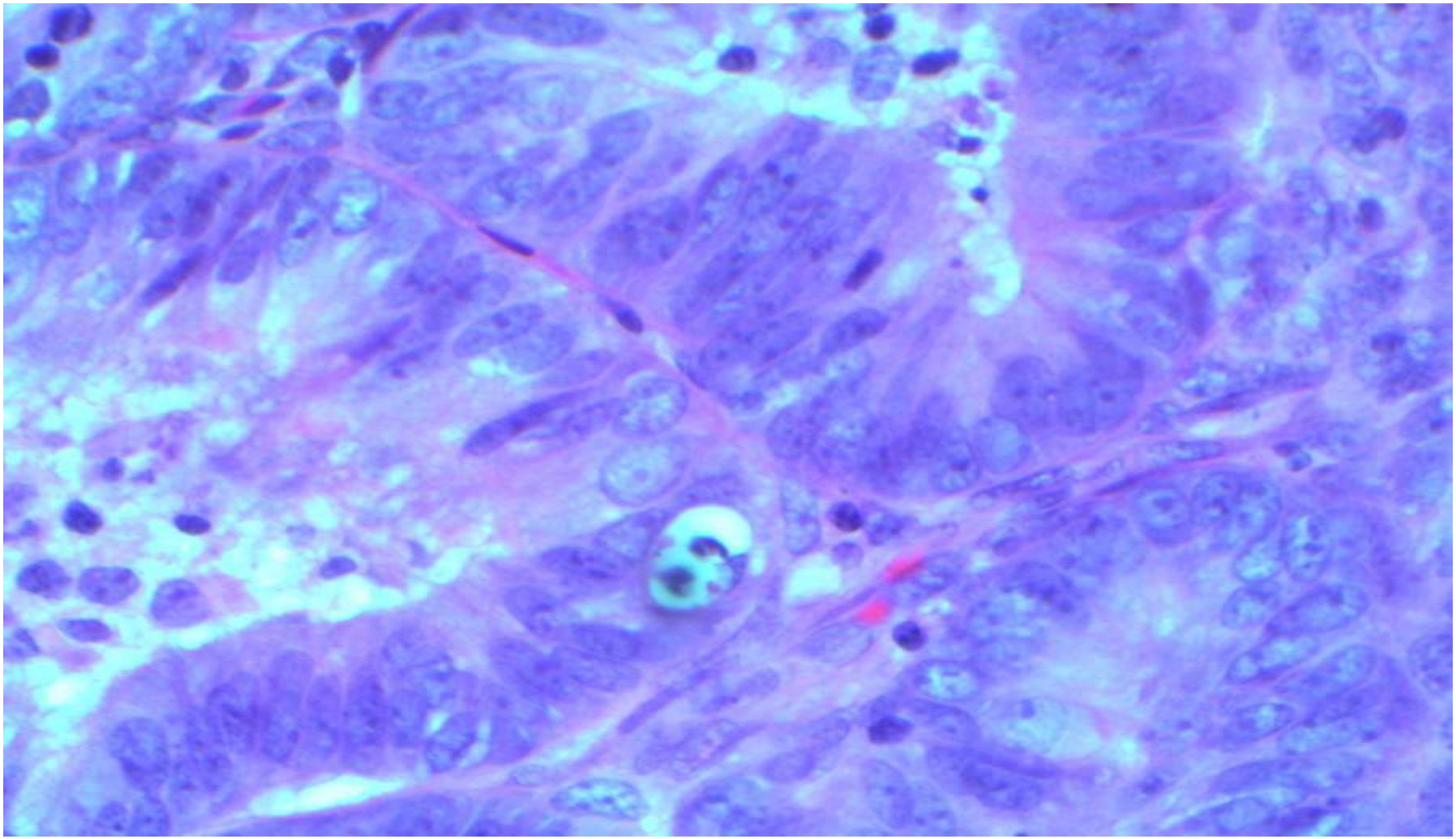
Endometrium



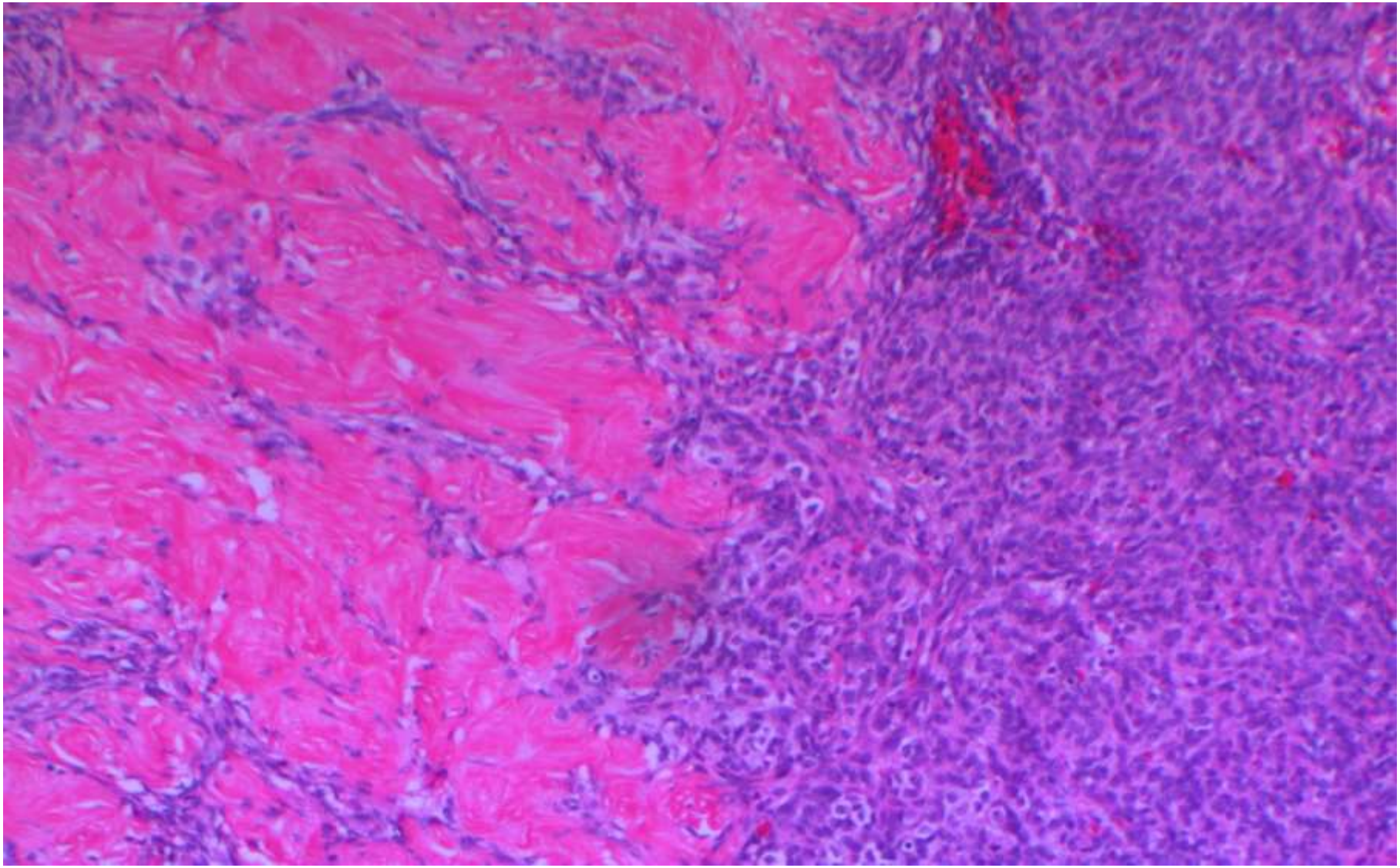
Endometrium



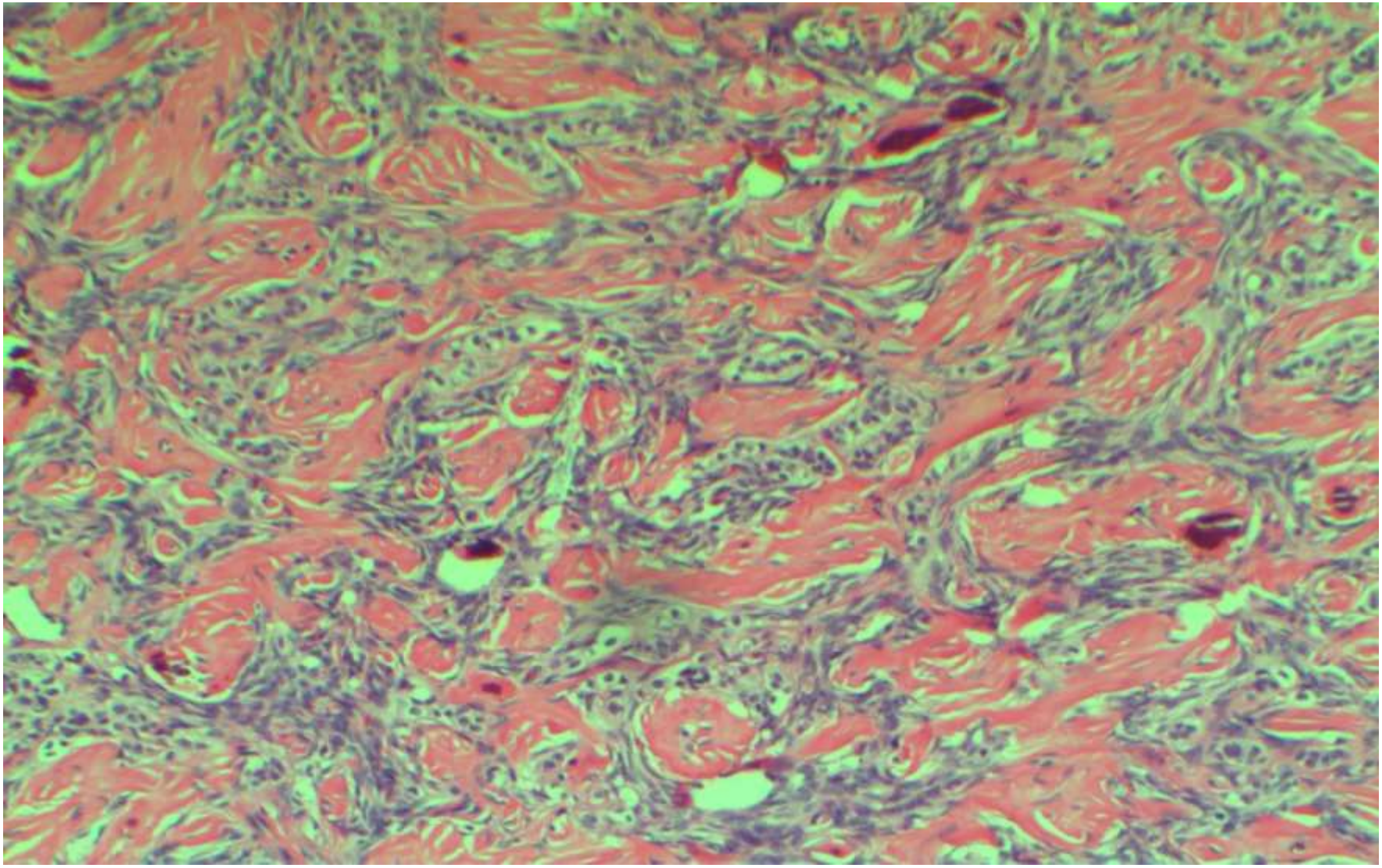
Endometrium



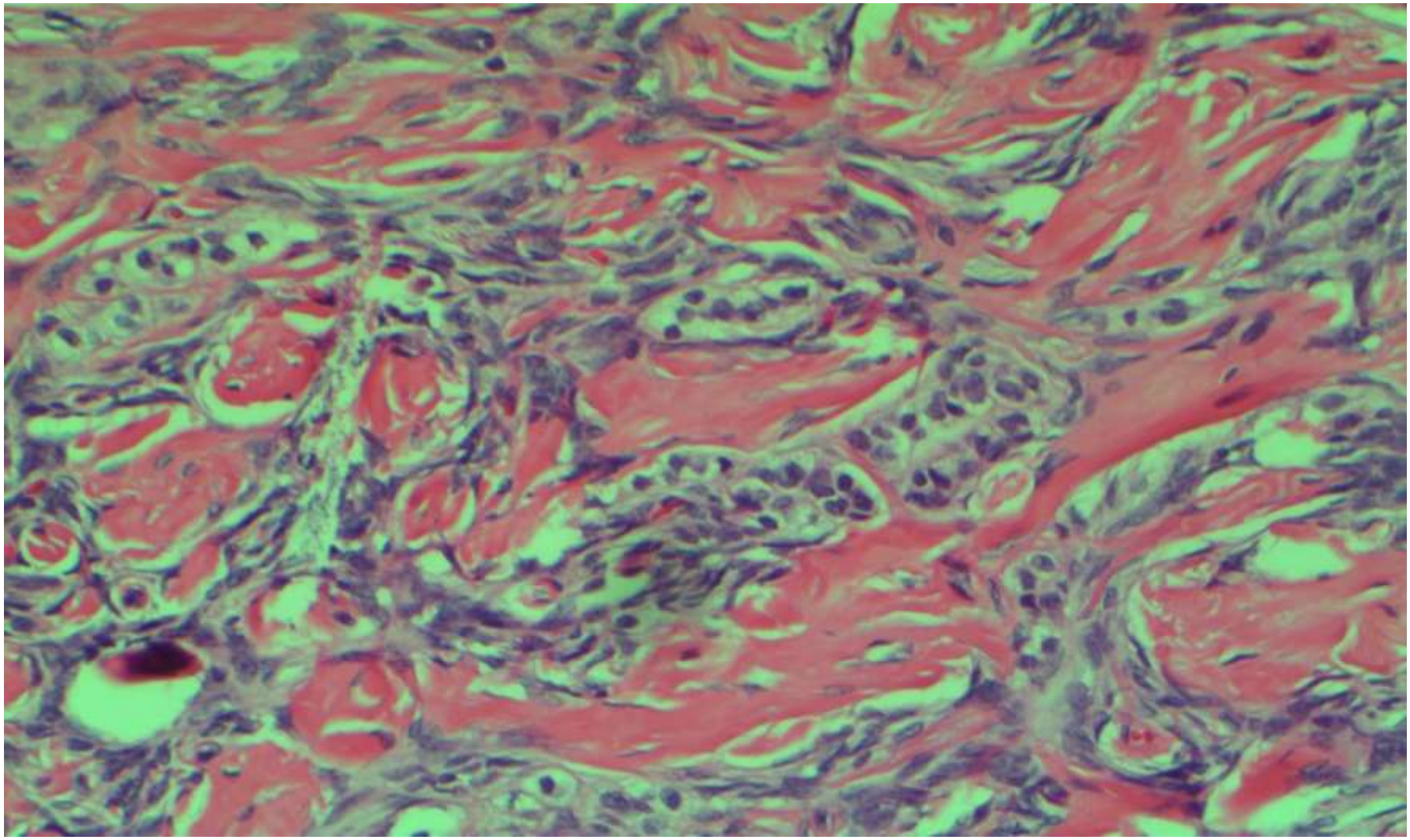
Ovarian nodule



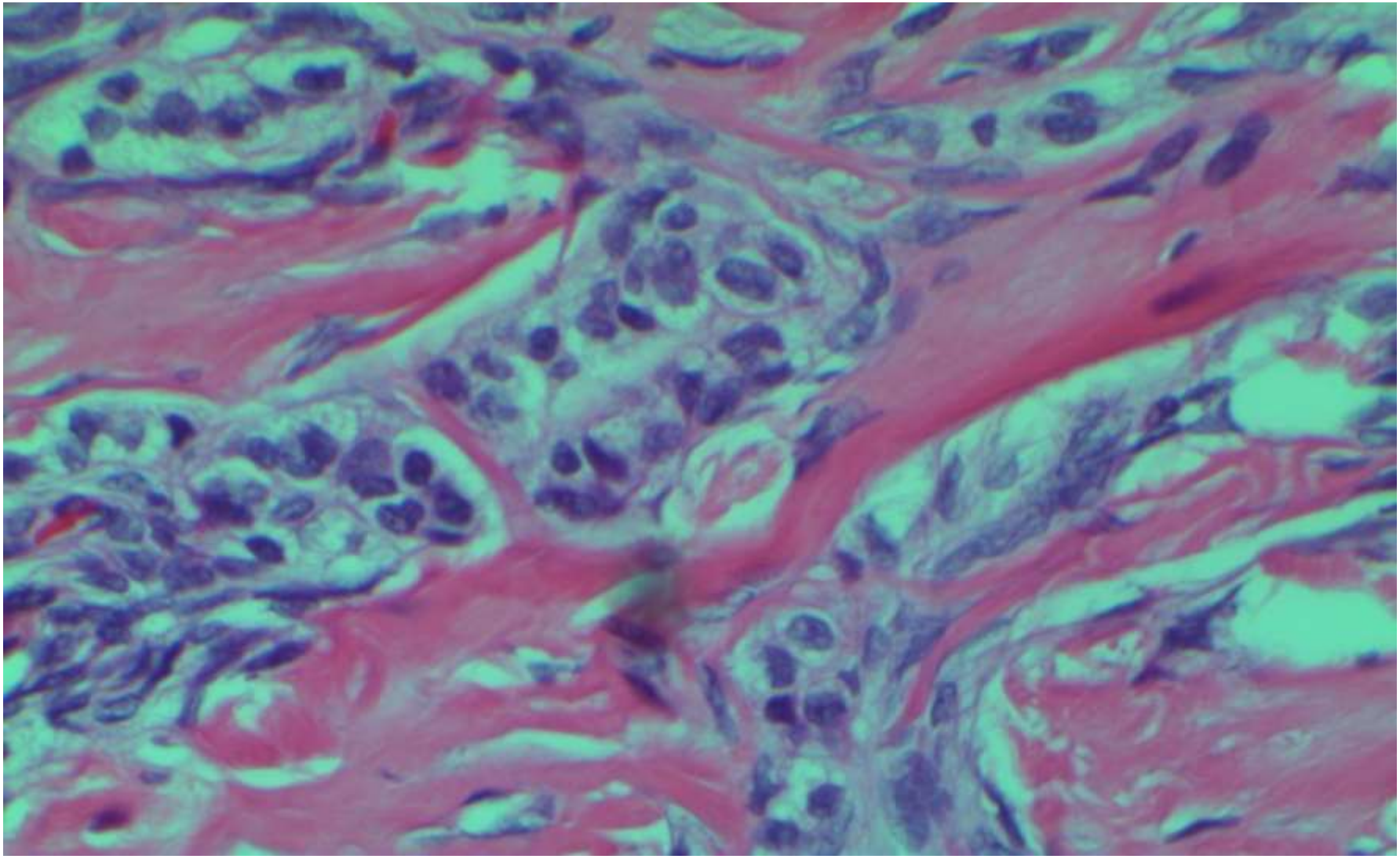
Ovarian nodule



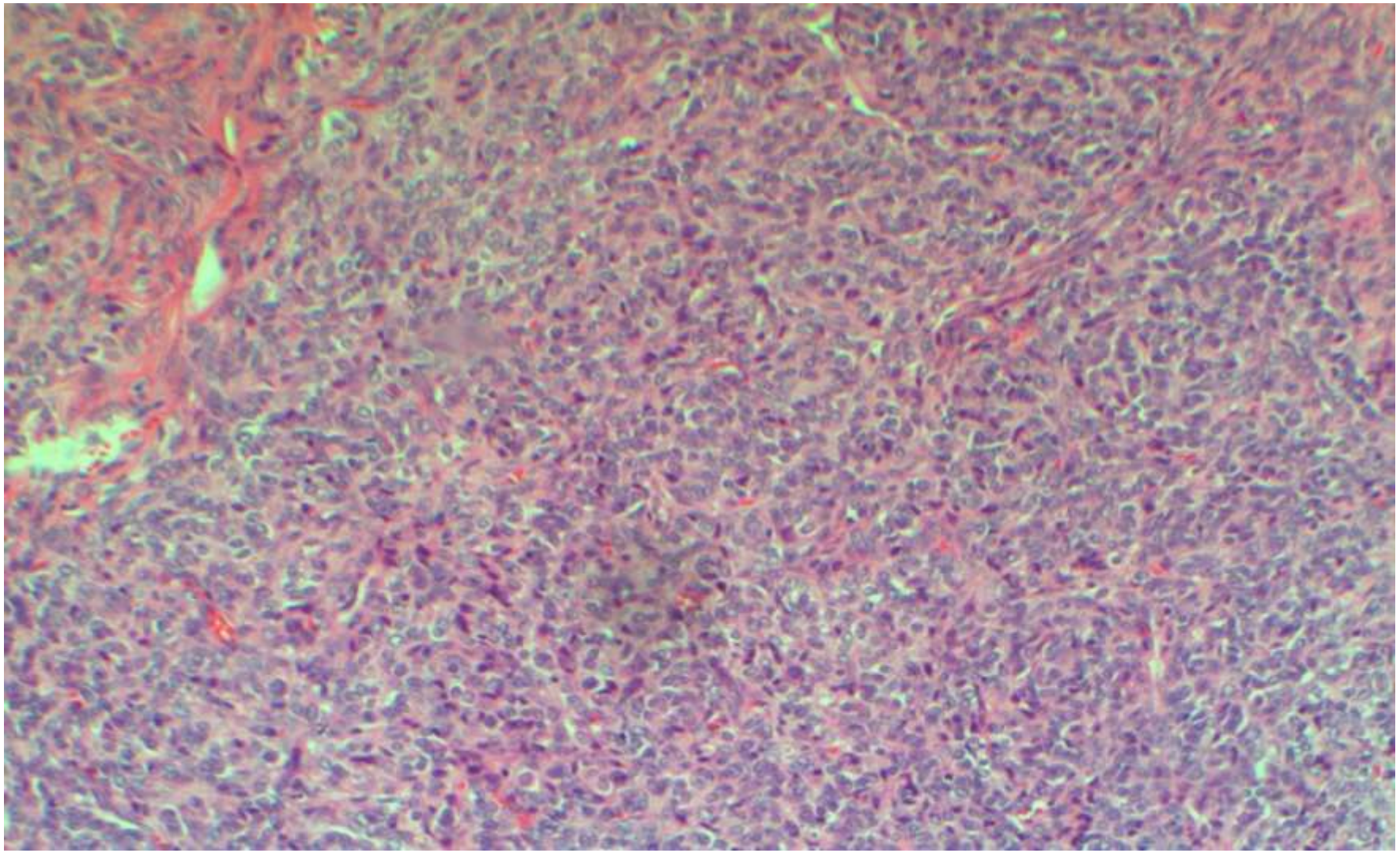
Ovarian nodule



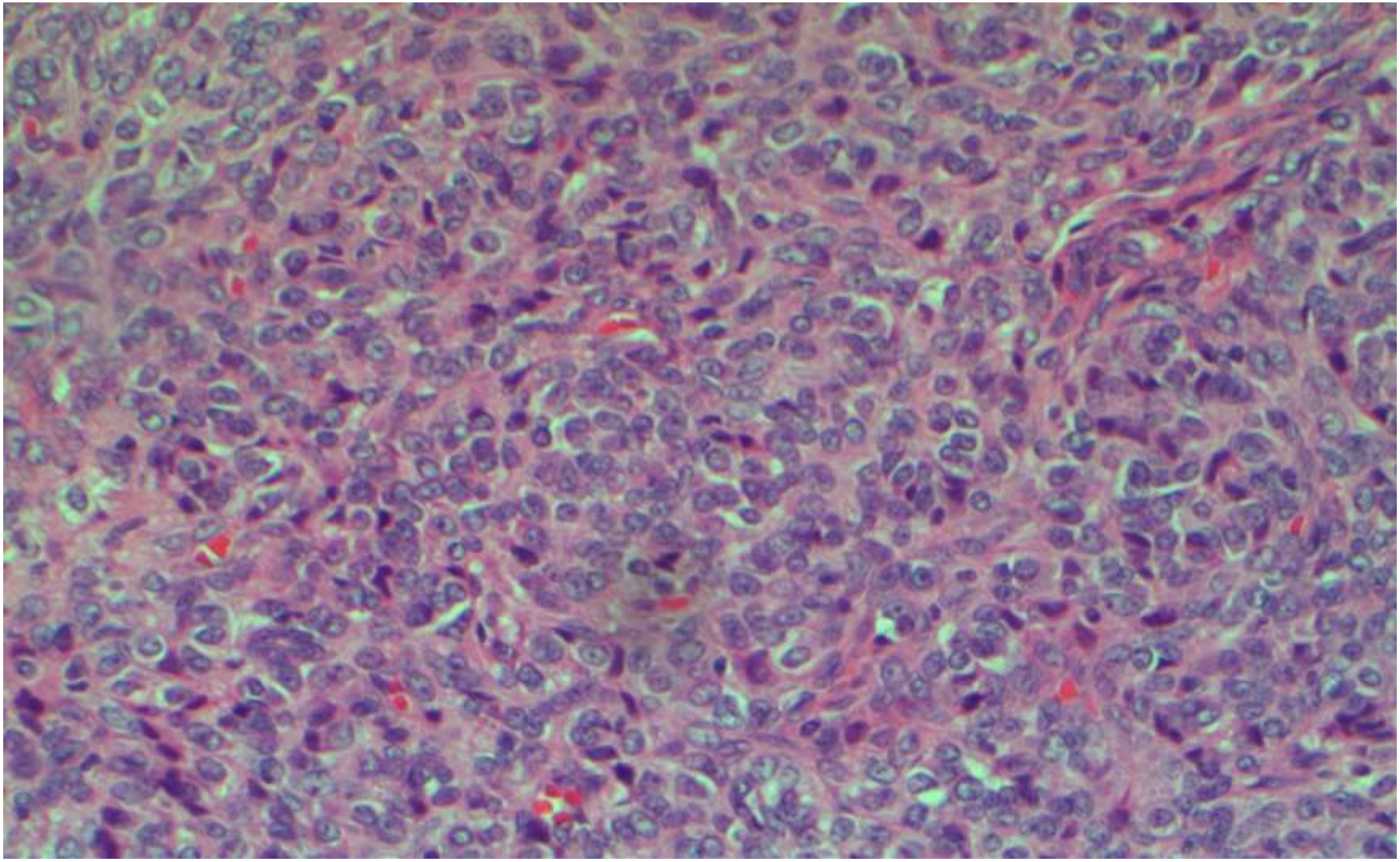
Ovarian nodule



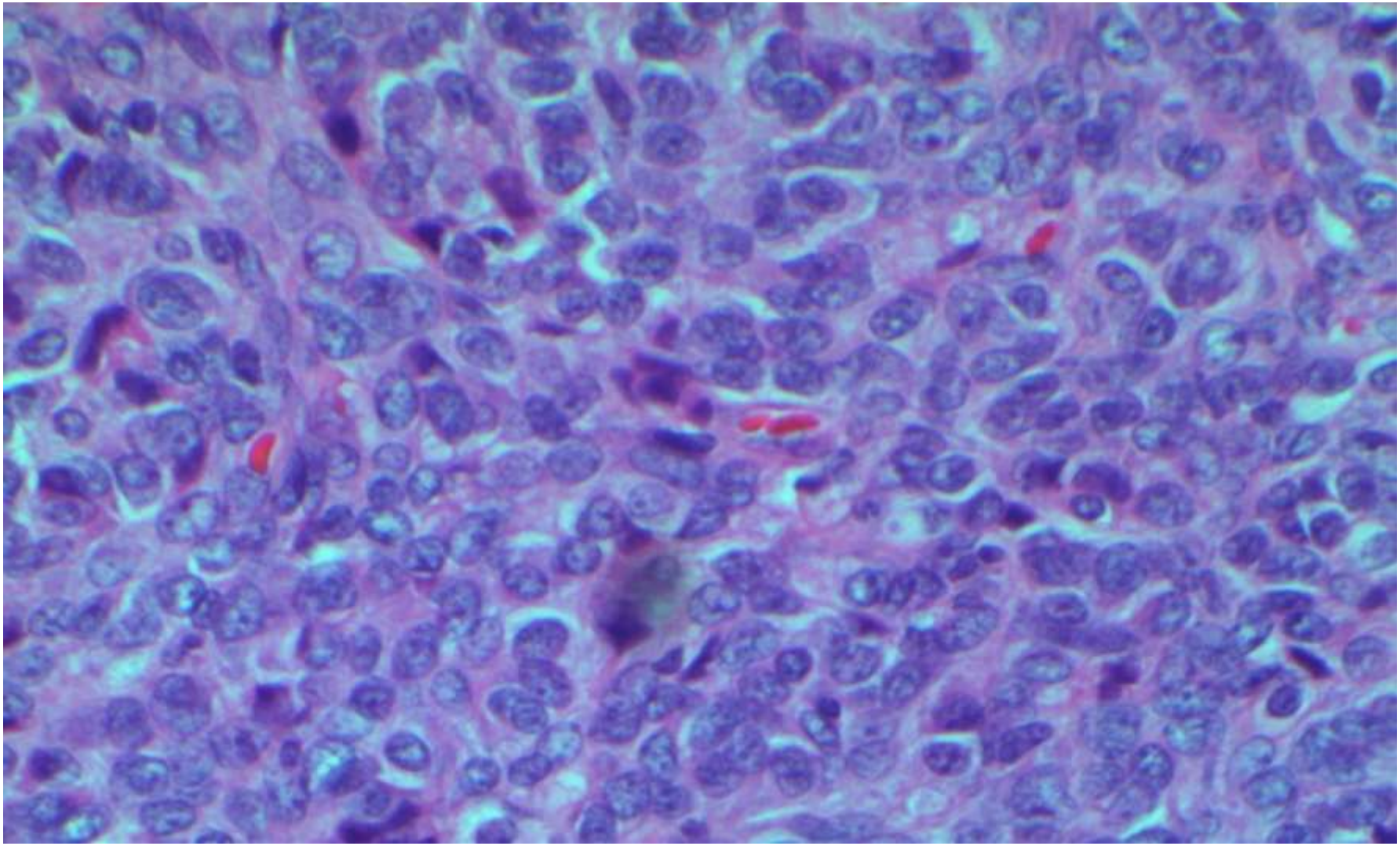
Ovarian nodule



Ovarian nodule



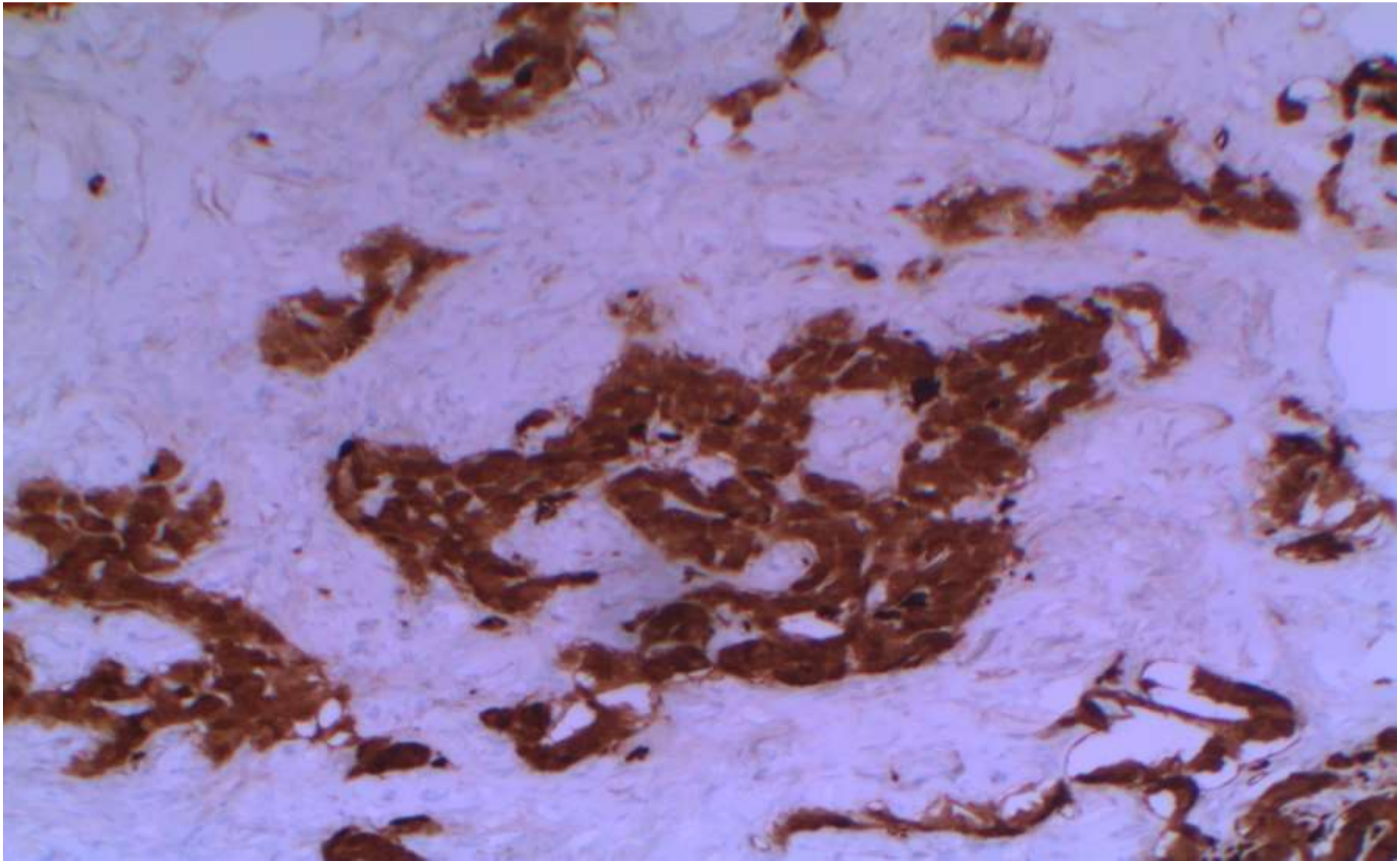
Ovarian nodule



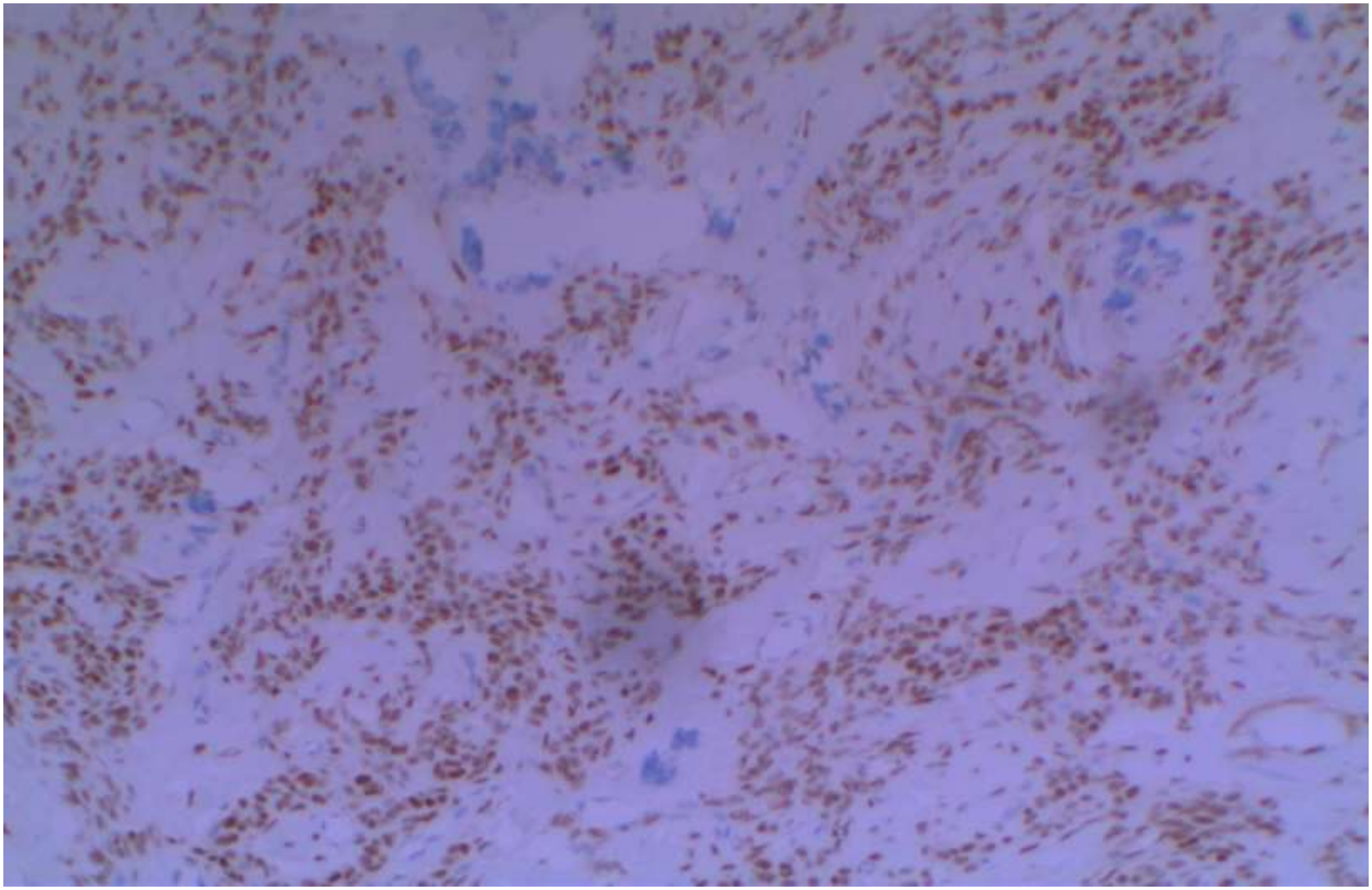
First case, Ovarian nodule immunostains

- PAX8, CK7, endocrine markers, WT1 Negative
- Calretinin, PR and Inhibin Positive
- FOXL2 402 C>G Positive

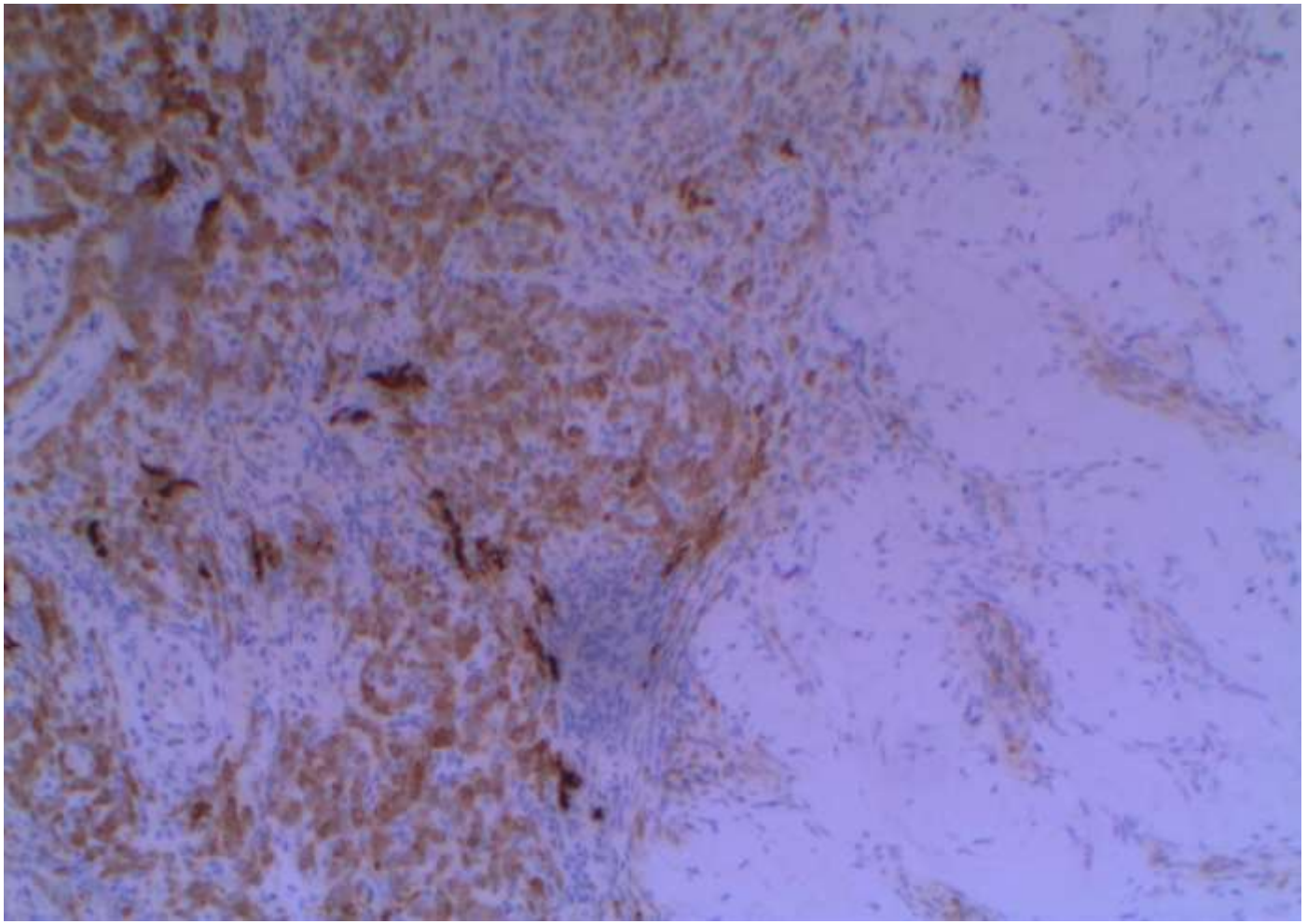
First case Ovarian nodule Calretinin



Frist case Ovarian nodule PR



Frist case Ovarian nodule Inhibin



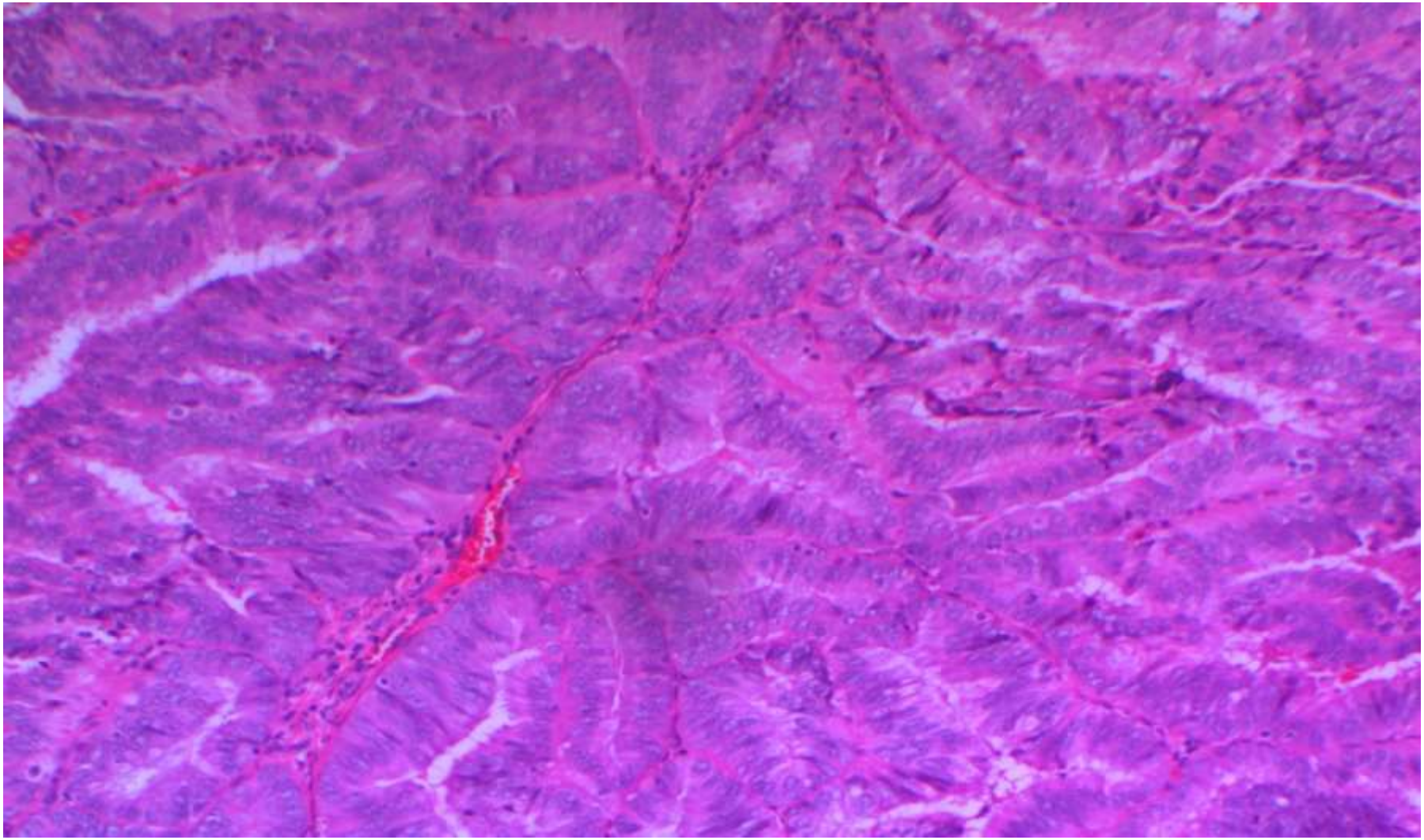
First case Ovarian Nodule

- Adult Granulosa Cell Tumor
- Associated Complex Atypical Hyperplasia

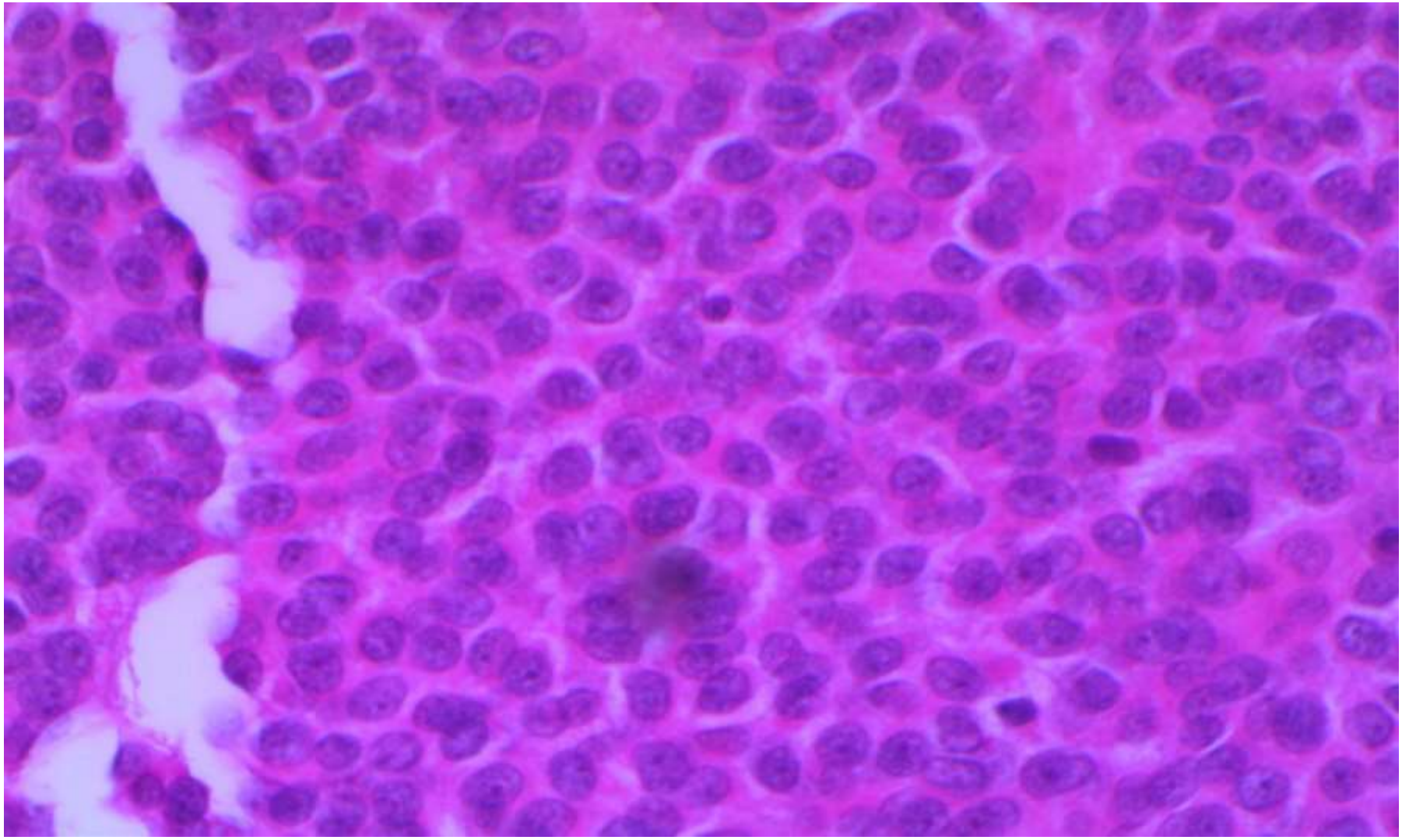
3 months later-second case

- 71 year old with abnormal cervical pap and benign ECC
- Hysterectomy
  - Grade I endometrioid adenocarcinoma
  - 1.5 cm ovarian nodule

Endometrium



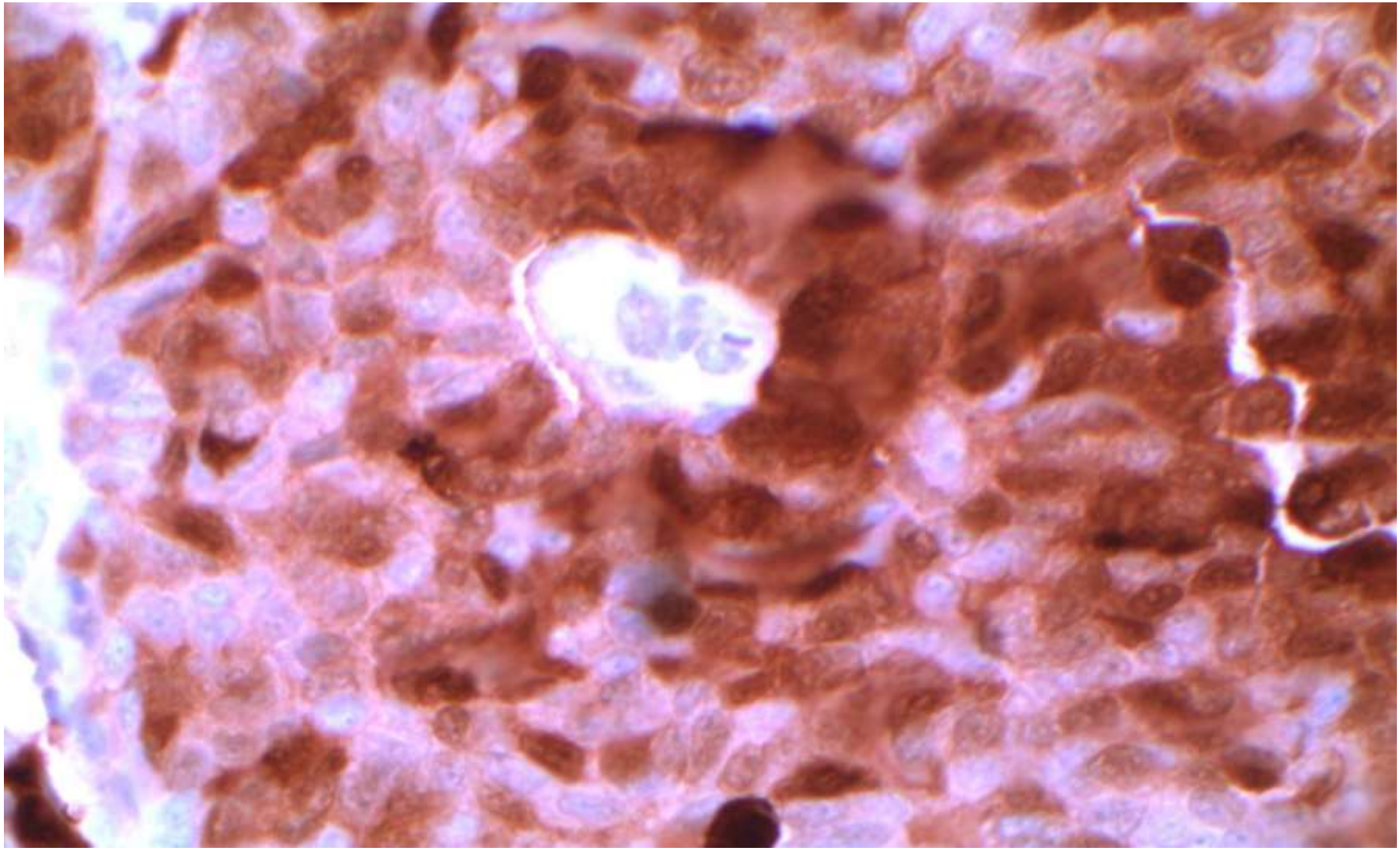
Ovarian nodule



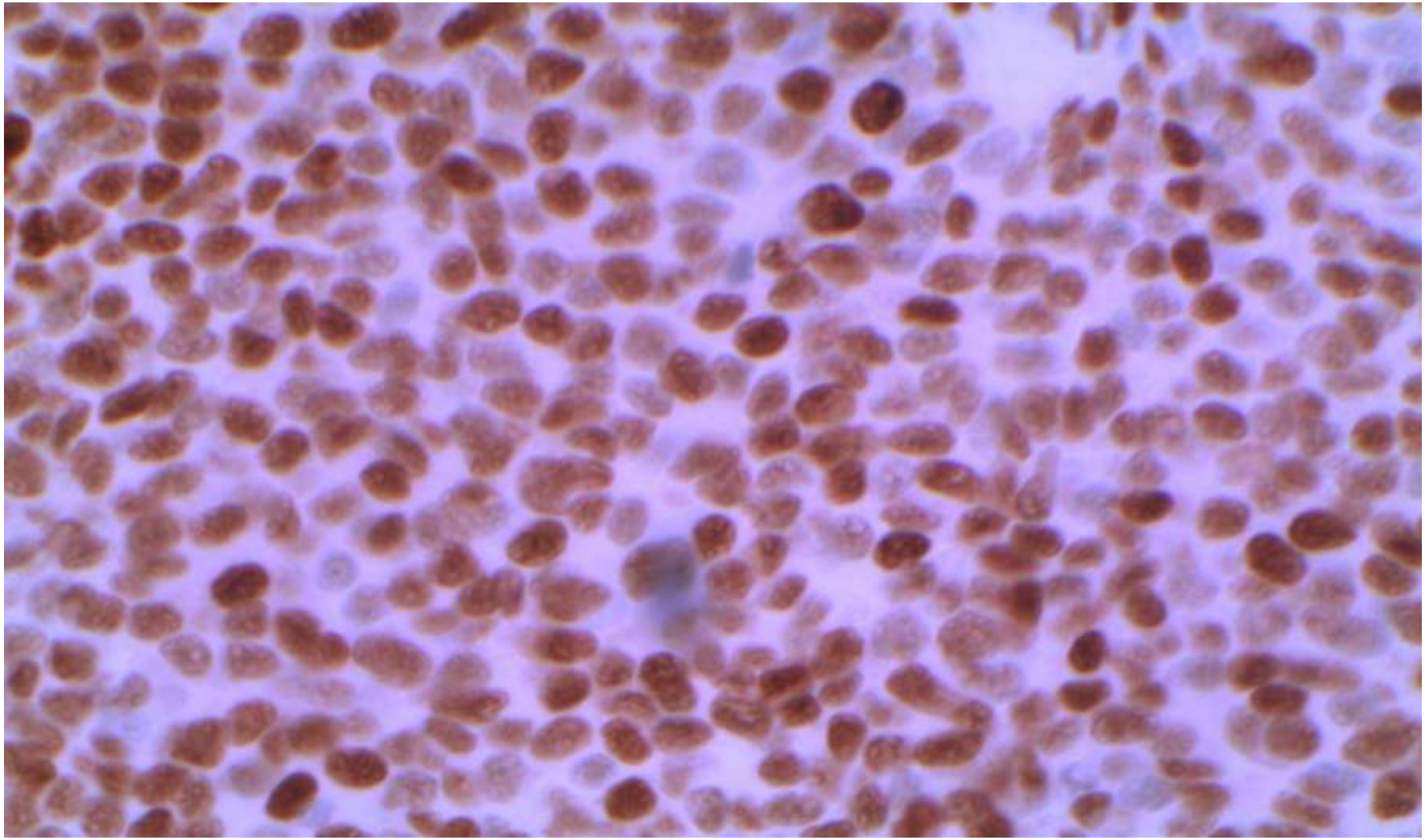
Ovarian nodule

• WT1, endocrine markers	Negative
• PR, Inhibin and Calretinin	Positive
• FOXL2 402 C>G	Positive

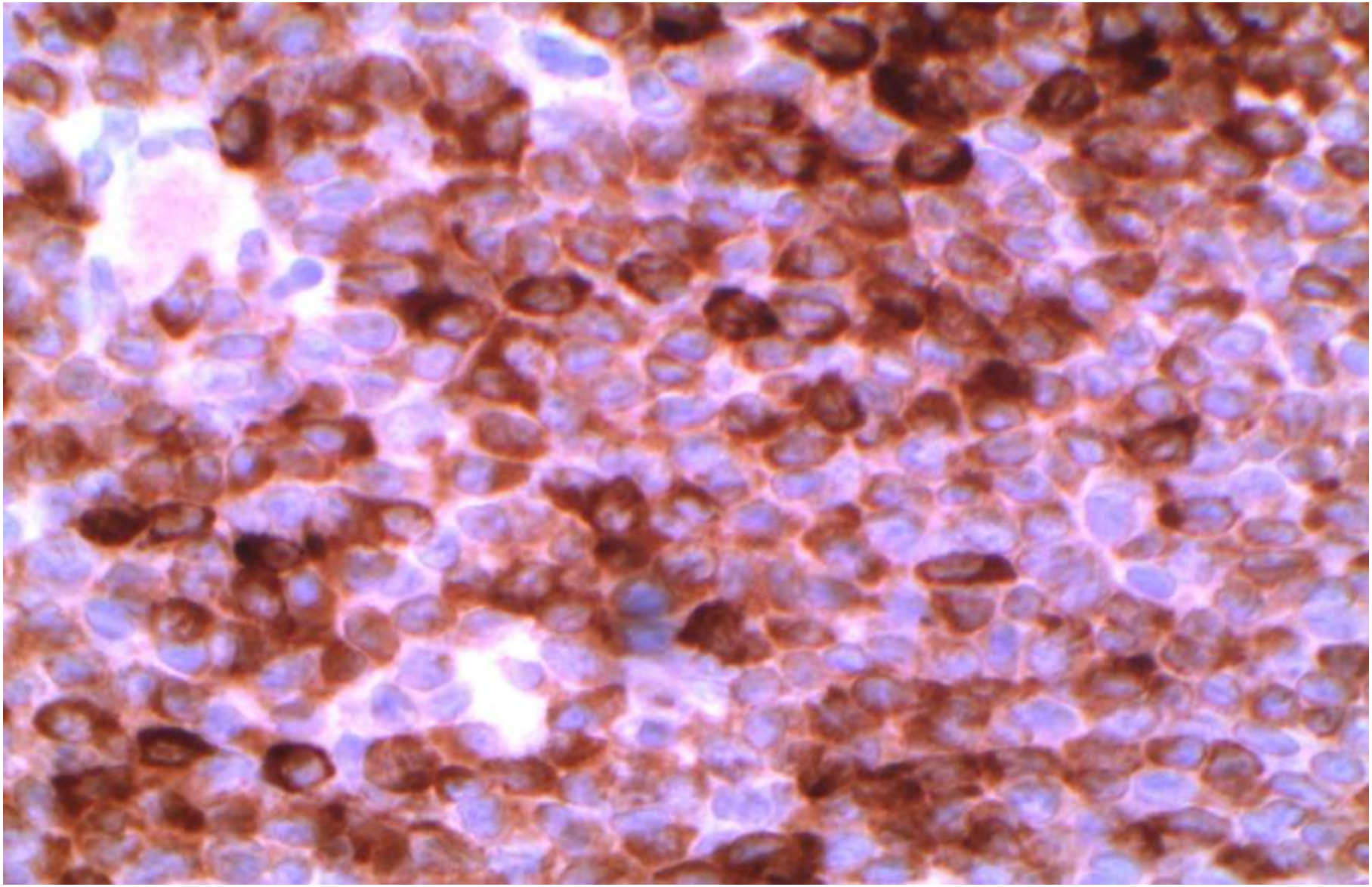
Second case Calretinin



Second case PR



Second case Inhibin



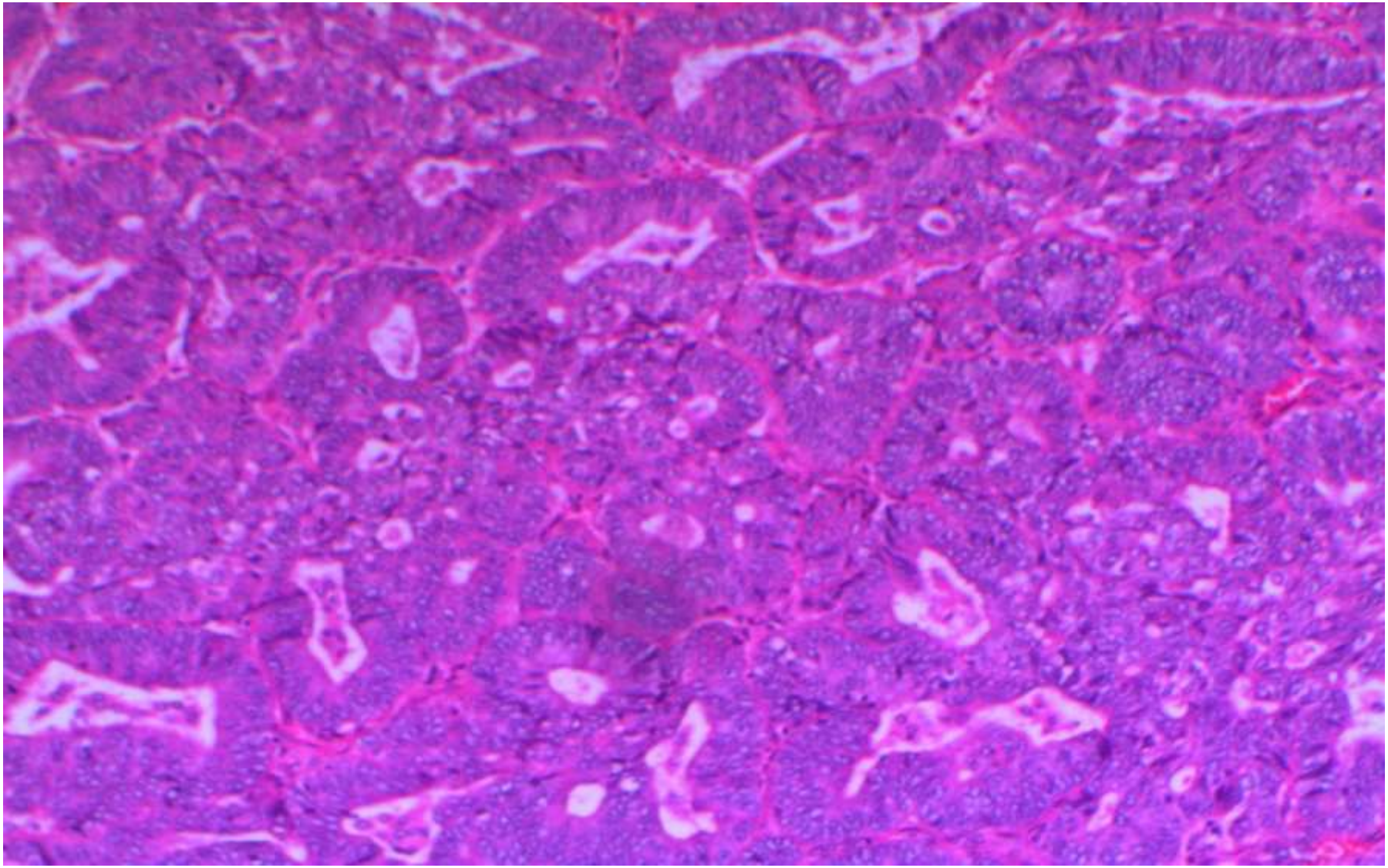
Second case

- Adult Granulosa Cell Tumor
- Associated Endometrial Endometrioid adenocarcinoma

One week later-third case

- 81 y.o. with post menopausal bleeding
- Endometrial biopsy
- Endometrioid adenocarcinoma, Grade I

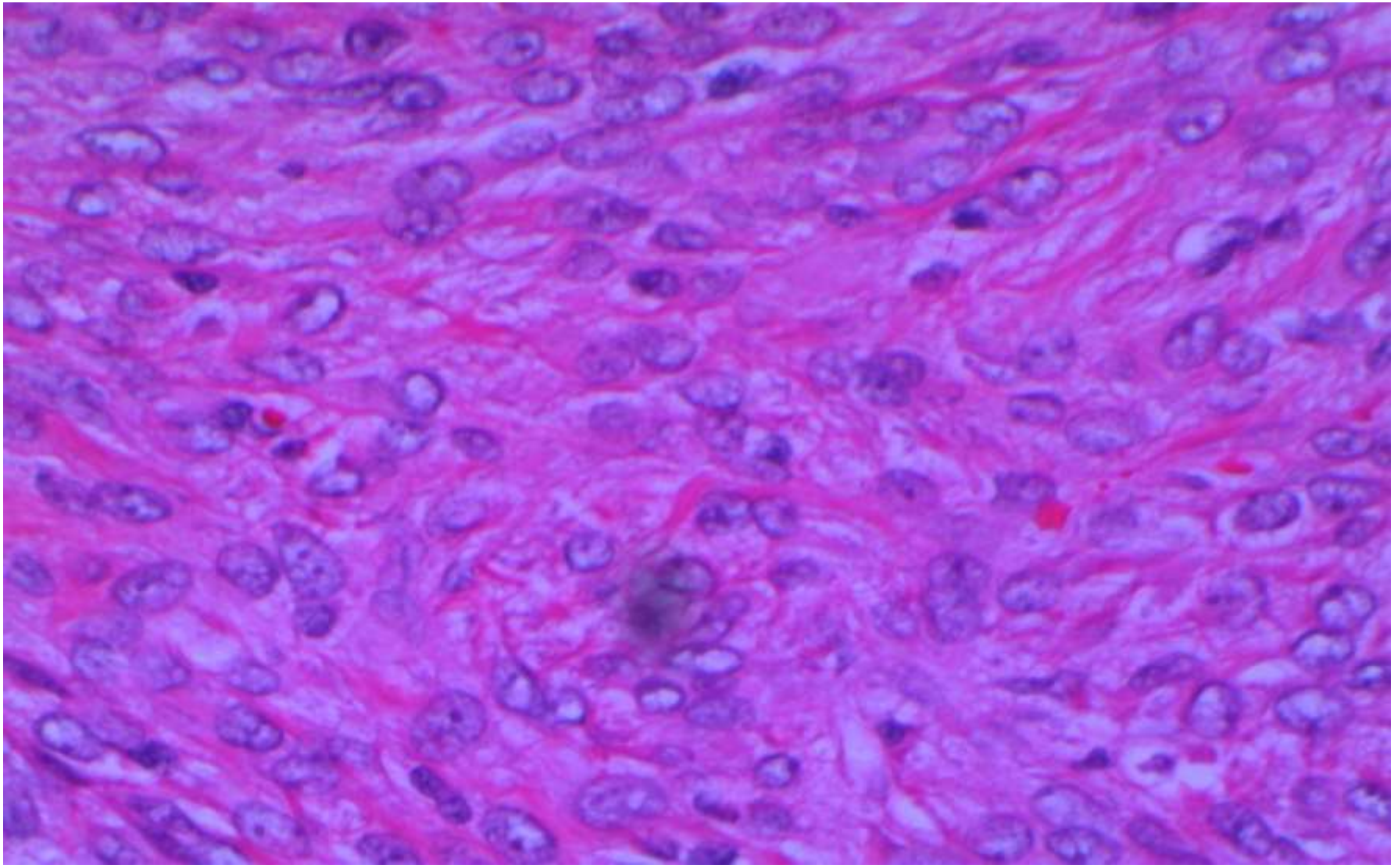
Endometrial biopsy



Hysterectomy

- Endometrial Endometrioid adenocarcinoma, Grade I
- Ovarian nodule 2.3 cm

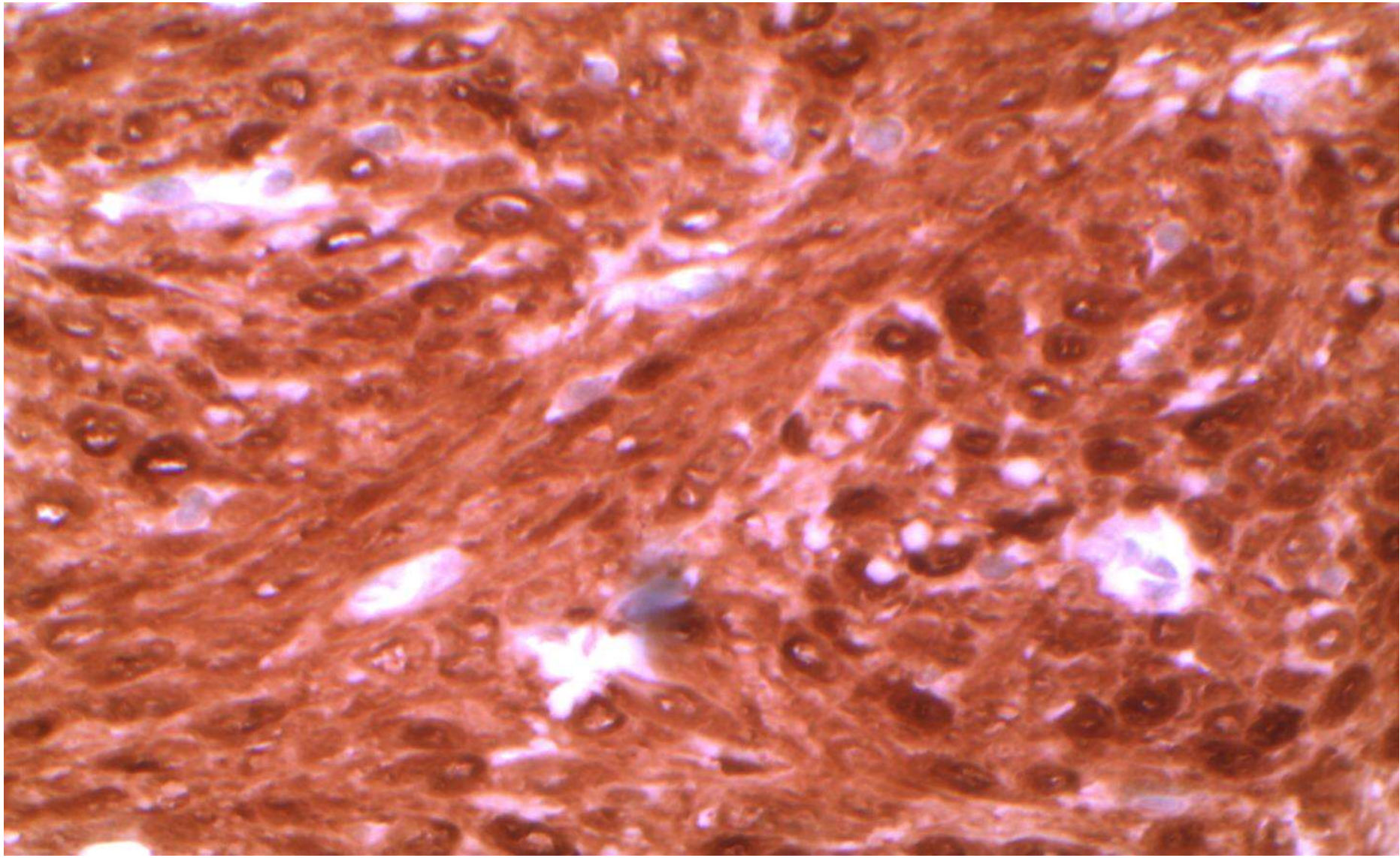
Ovarian nodule



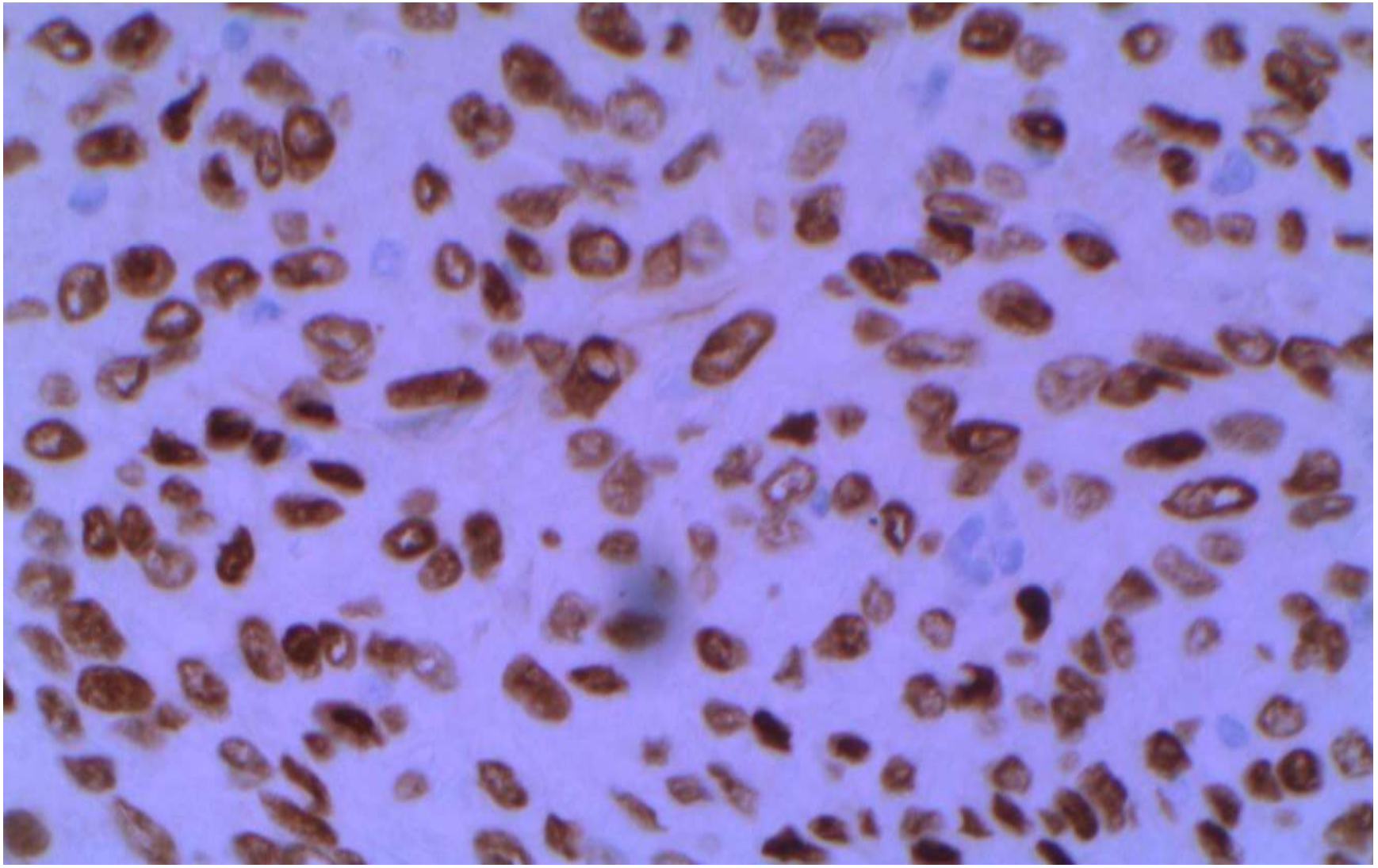
Ovarian nodule

- CK7 Negative
- PR, SF1, Inhibin and Calretinin Positive
- FOXL2 402 C>G Positive

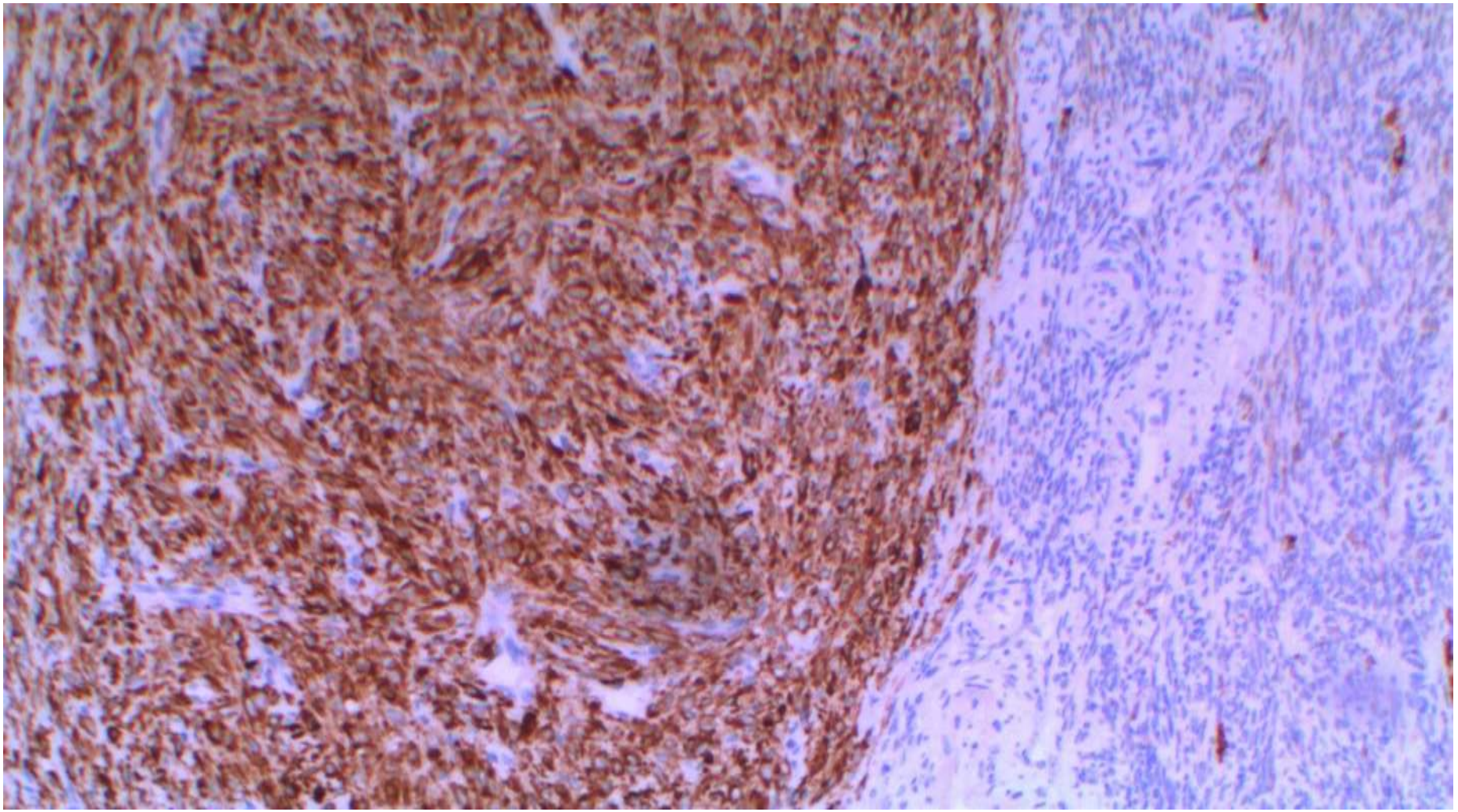
Third case Calretinin



Third case PR



Third case Inhibin



Third case

- Adult Granulosa Cell Tumor
- Associated Endometrioid adenocarcinoma

SEX CORD-STROMAL TUMORS

- SCTSs are 7% of all malignant ovarian neoplasm
- The vast majority of these tumors are of low malignant potential or benign.
- Long term prognosis is good.
- Excessive estrogen production influences end organ responses.
- Endometrial and breast cancer must be remembered.

ADULT GRANULOSA CELL TUMORS SURVIVAL

- Overall 5-year survival rates are nearly 90%.
- In patients with extraovarian spread at the time of diagnosis, 5-year survival is 33-53%.

GRANULOSA CELL TUMORS
ADULT TYPE

- PROGNOSTIC FACTORS
  - Tumor stage
  - Tumor size
  - Rupture
  - Nuclear atypia

Granulosa Cell tumor, adult

Lobulated surface, 95% unilateral
Trabecular, insular and solid patterns
Nuclear folds/grooves
Call-Exner bodies
Inhibin and Calretinin positive, CK7 negative
FOXL2 402 C>G mutation
Trisomy 12 (adult and juvenile)
Inhibin serum marker

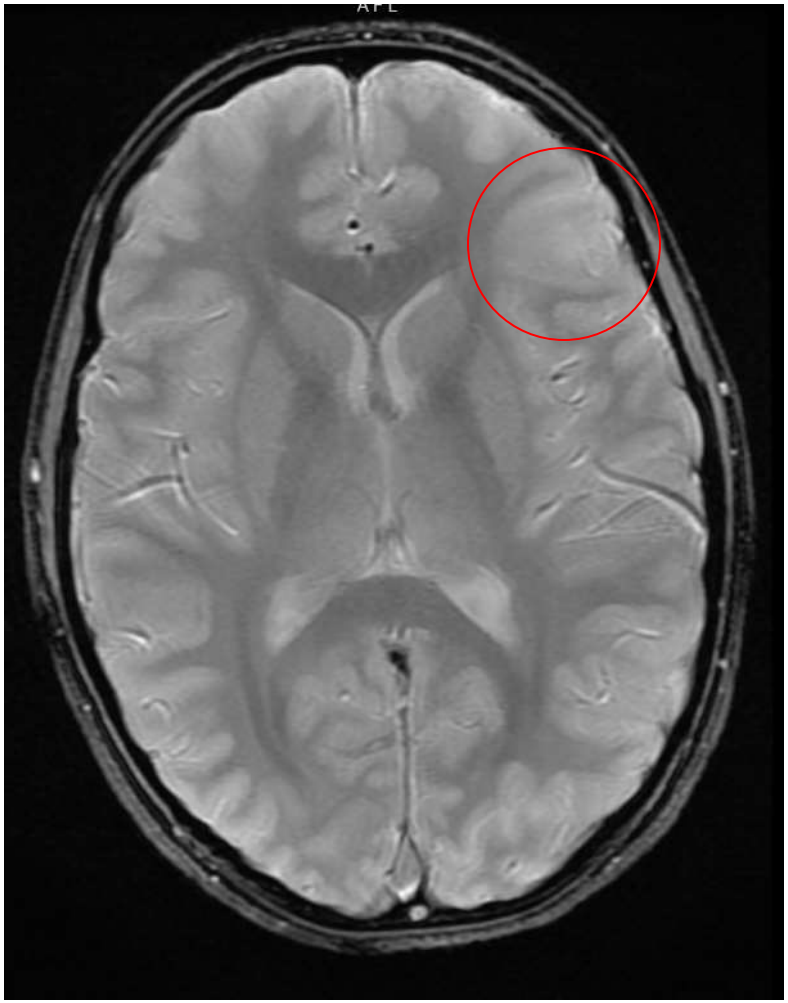
Adult Granulosa Cell Tumor

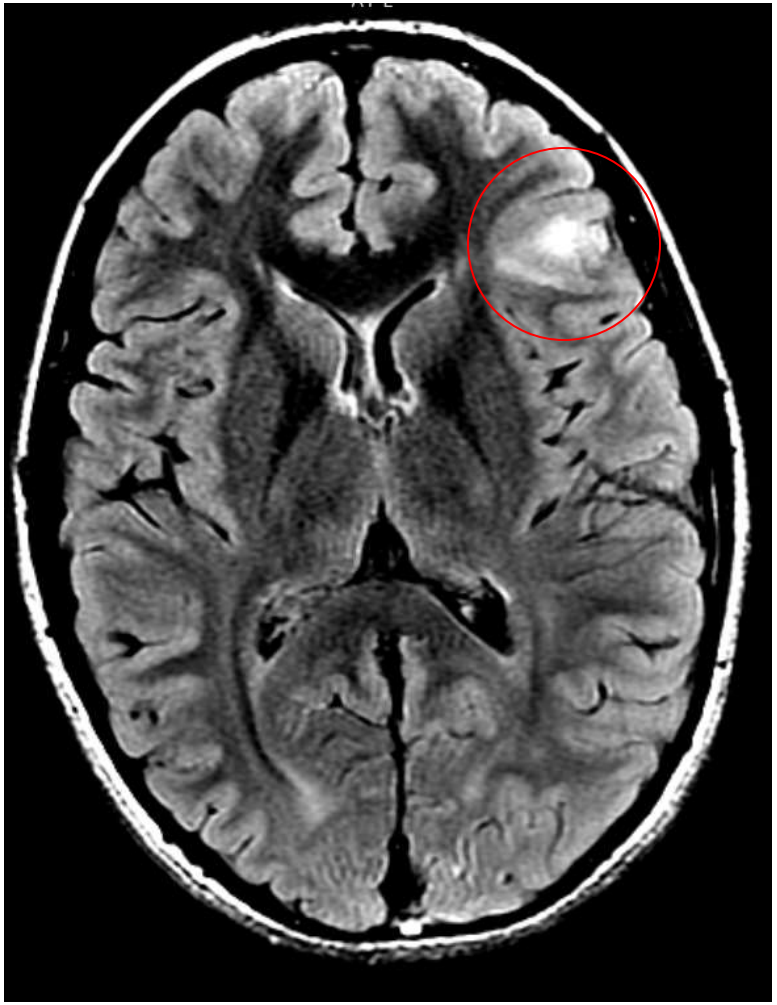
- DDX
  - Brenner
  - Carcinoid
  - Endometrial stromal sarcoma
  - Metastasis

19-1104

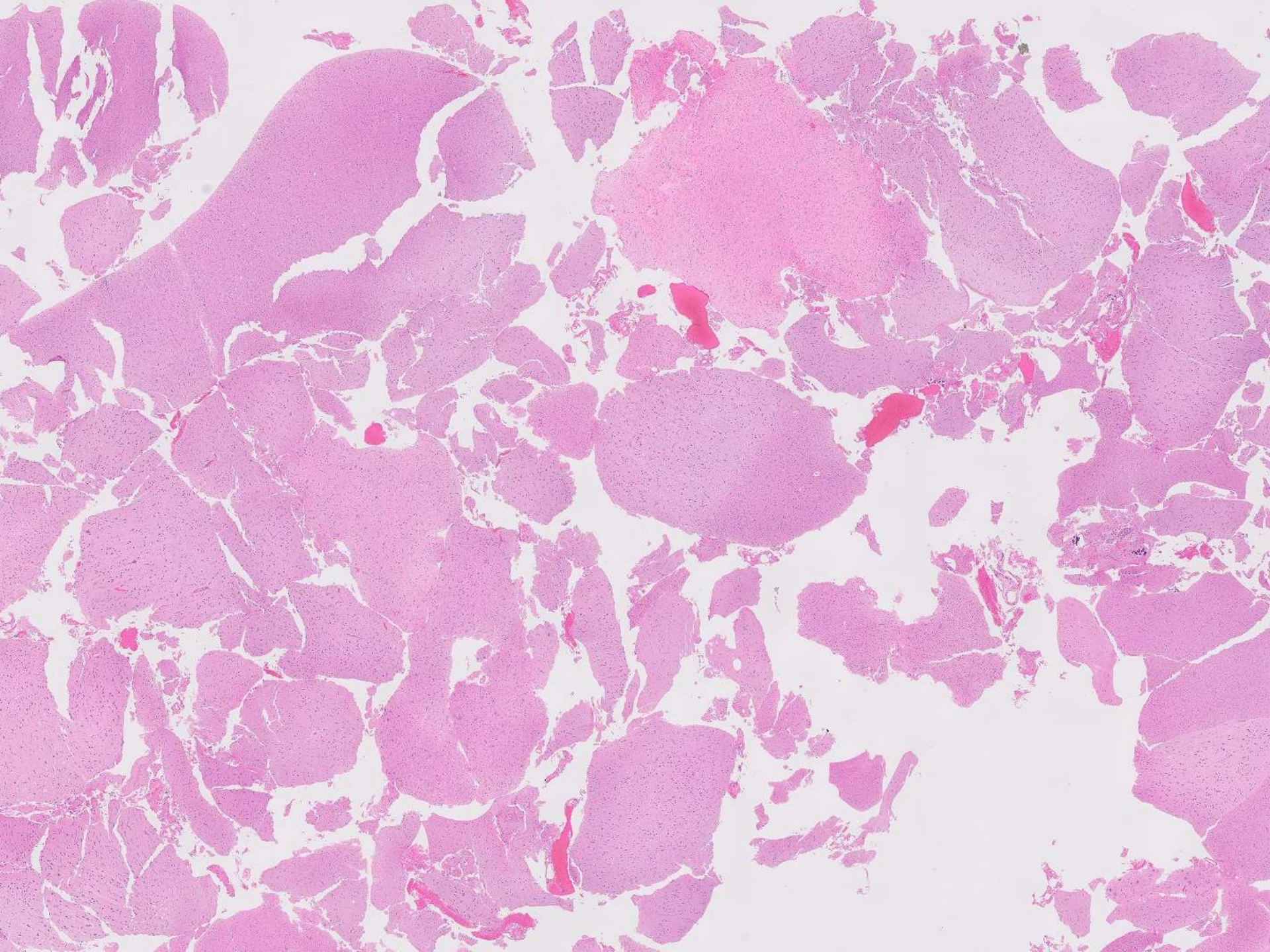
Romain Cayrol/Saman Ahamadian/Hannes Vogel; Stanford

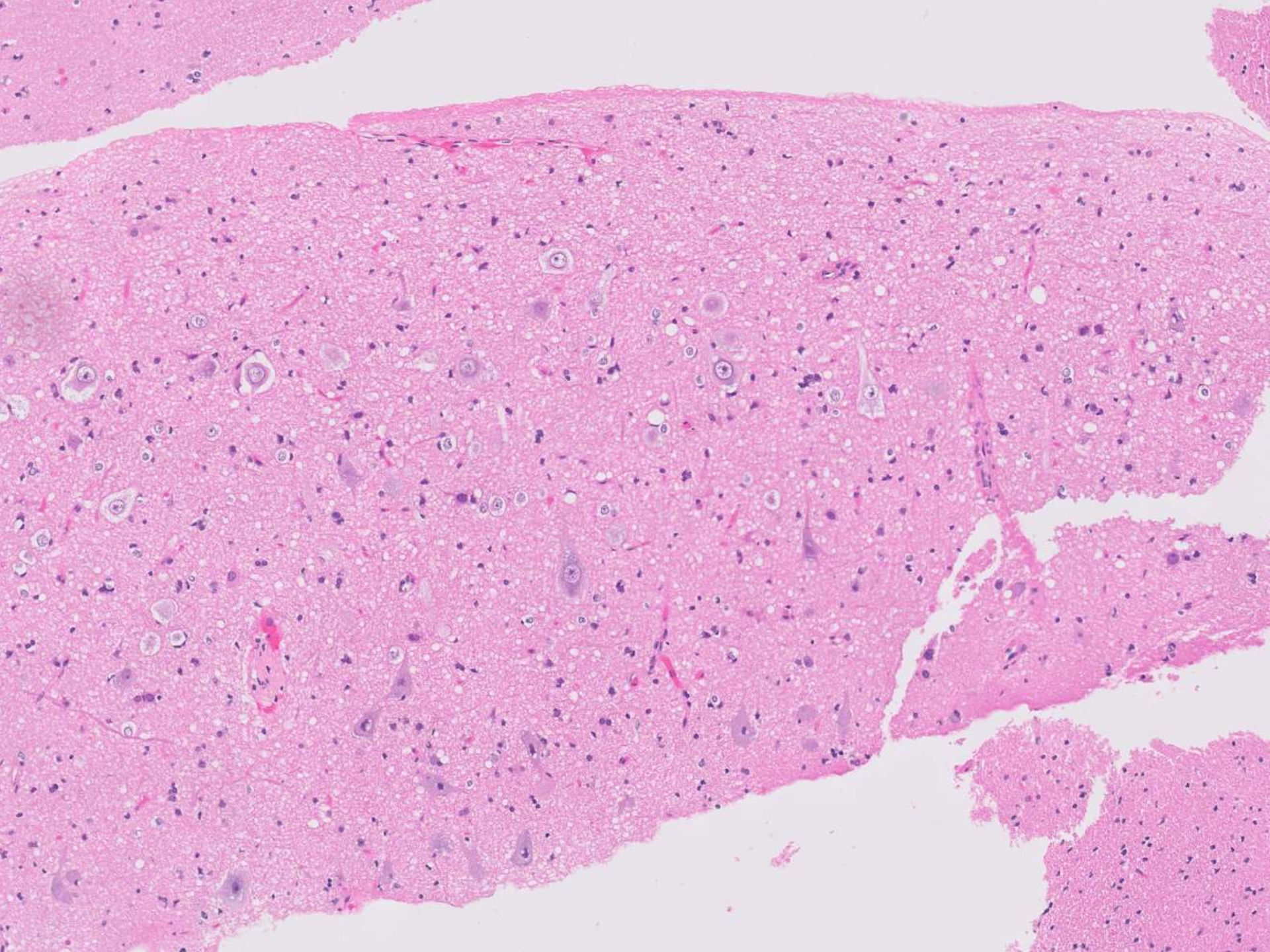
14-year-old left-handed male with 11-year h/o medical refractory epilepsy. He currently has 0-20 seizures per day. EEG demonstrates a left frontal epileptogenic focus.

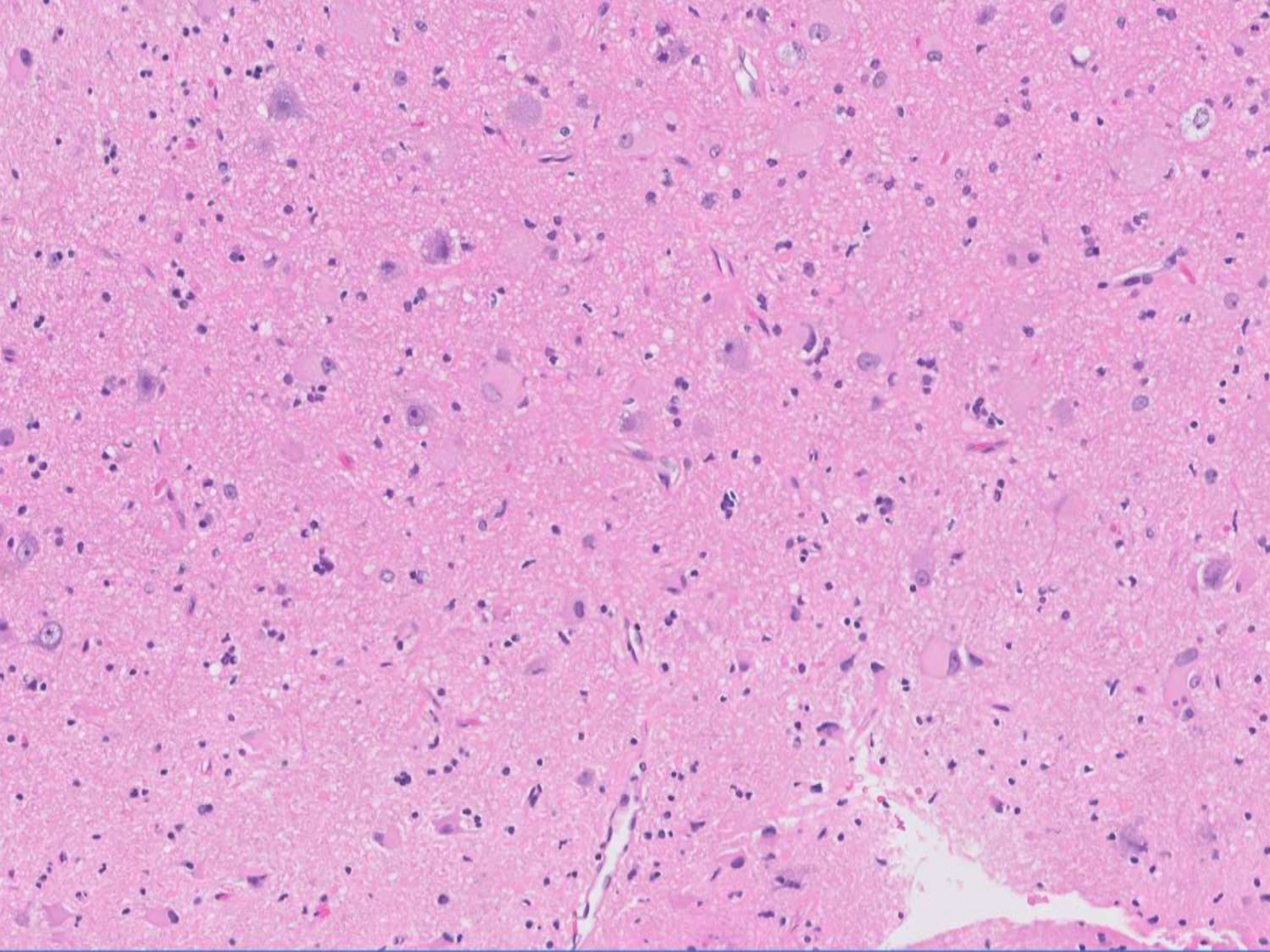


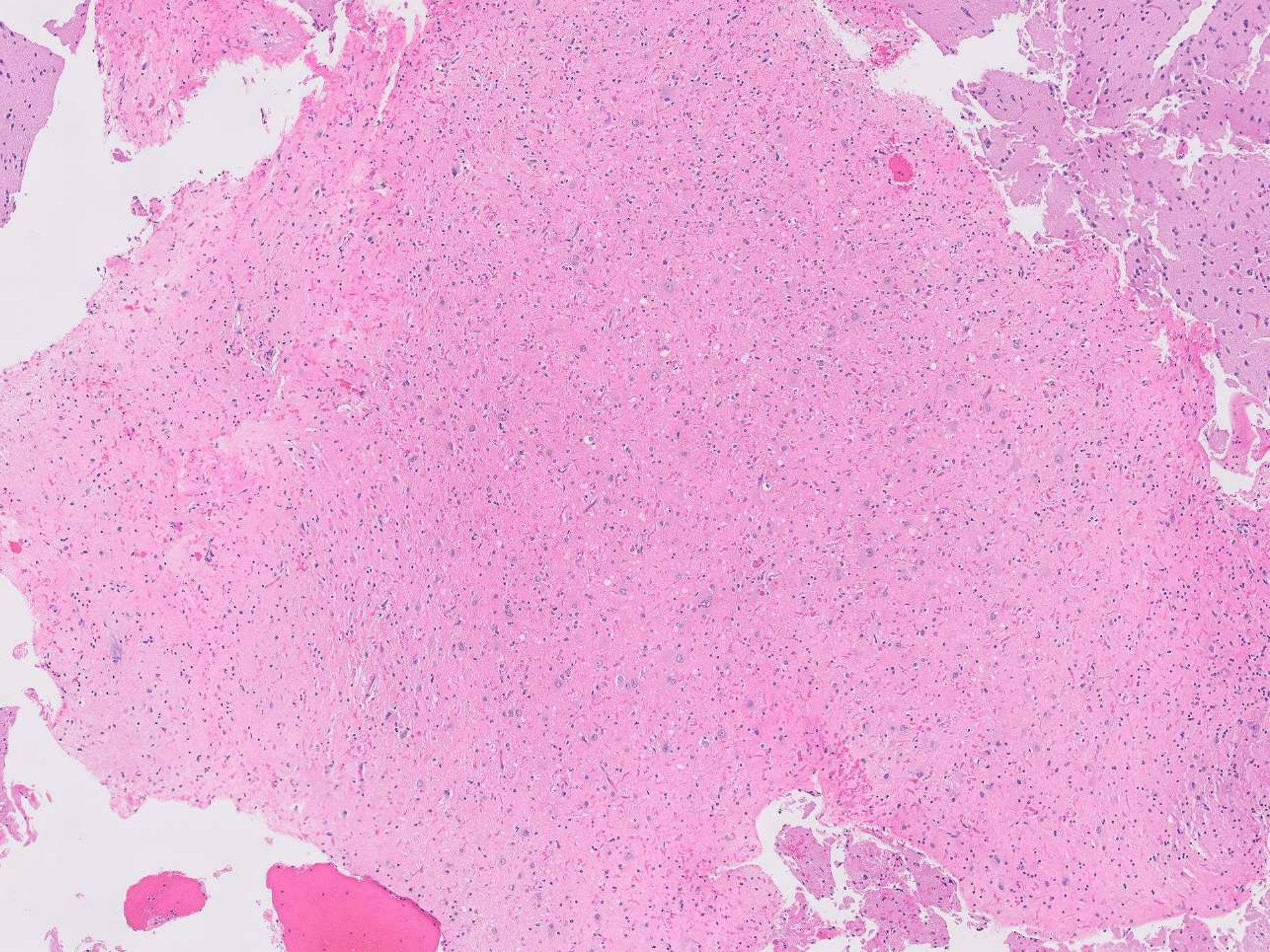


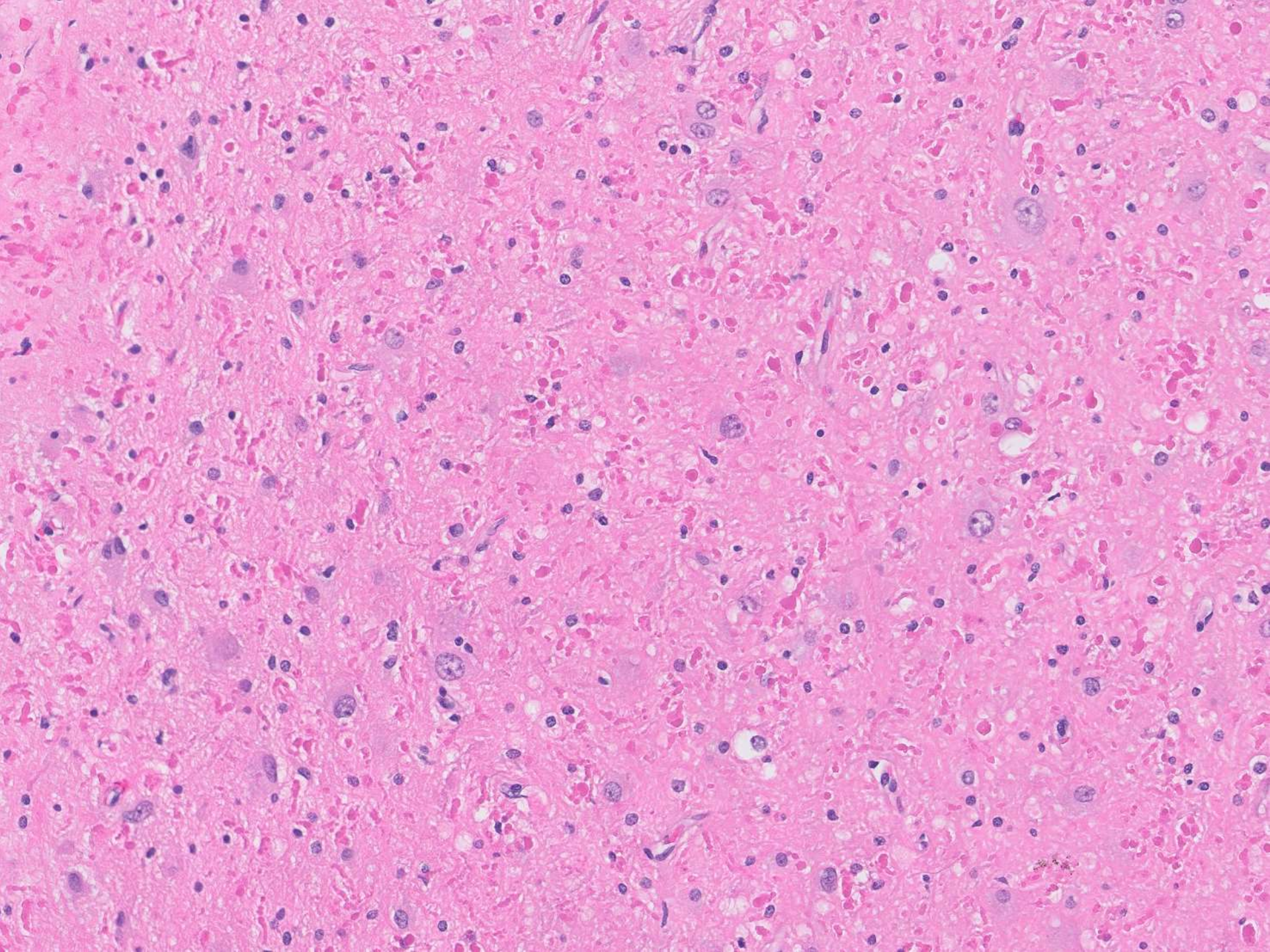
- MRI demonstrates a left frontal cortical gray matter thickening and blurring of the gray/white matter junction associated with increased FLAIR signal abnormality and mild cortical thickening

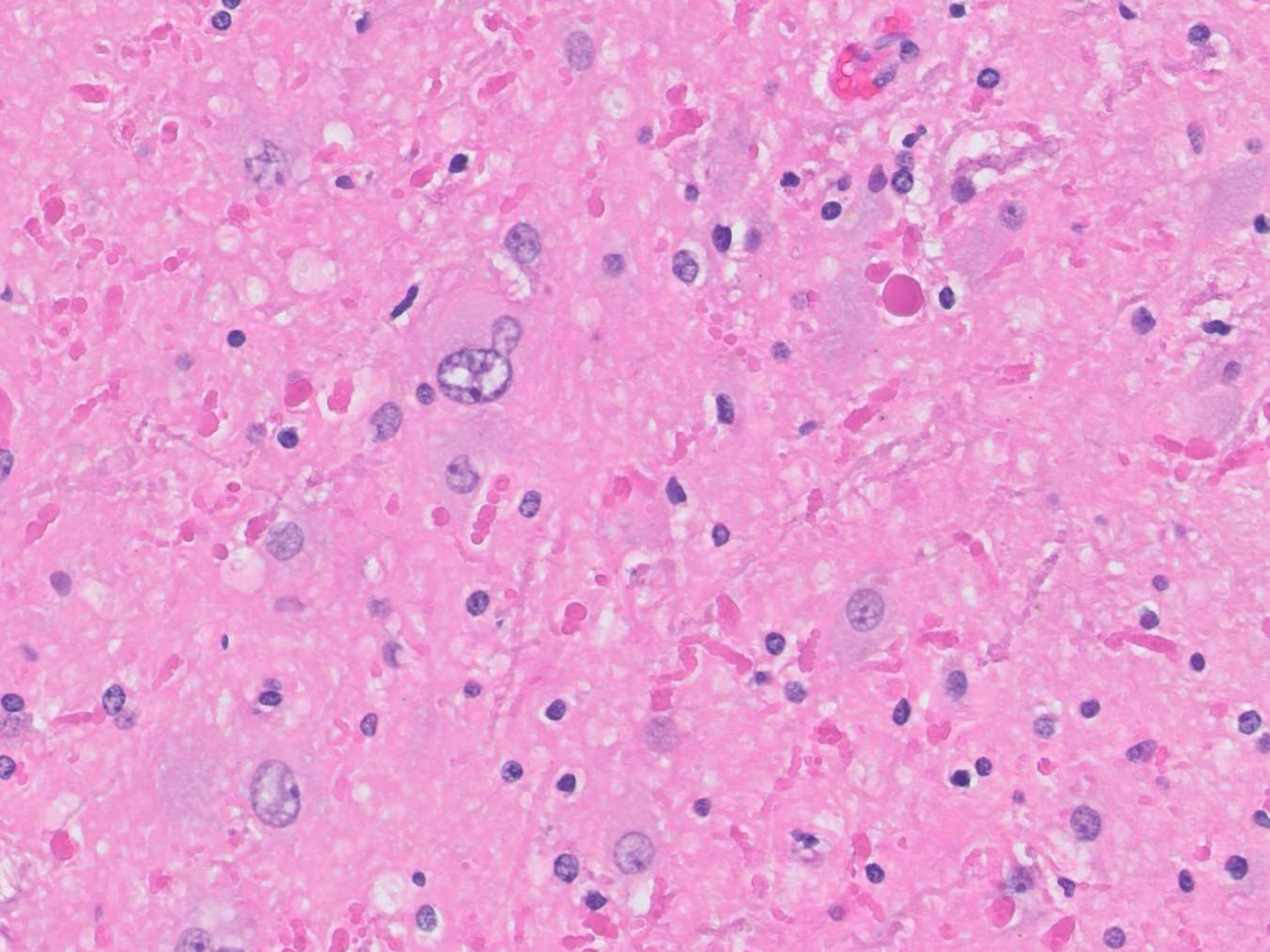












Diagnosis

- A and B. BRAIN, LEFT FRONTAL LOBE, CUSA ASPIRATE

  -- FOCAL CORTICAL DYSPLASIA TYPE IIB WITH PROMINENT ROSENTHAL FIBERS

Epilepsy

- Seizures are a common occurrence, affecting an estimated 8 to 10% of the population over a lifetime
  - Treatment depends on etiology
  - Multiple etiologies: metabolic, genetic, structural, immune, infectious and unknown

- Surgical resection is an effective treatment used in drug resistant epilepsy with focal epileptogenic area
  - 20 to 30% have a structural causes
    - Malformations and tumors

Table 1. Principal histopathologic categories of brain lesions associated with drug-resistant focal epilepsies submitted to epilepsy surgery

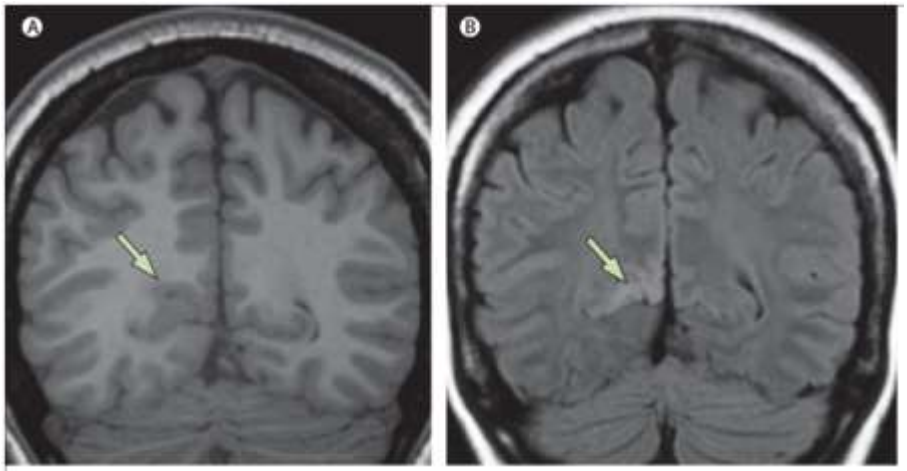
		Mean age at	
	n (%)	Onset	Surgery
Hippocampal sclerosis	2,071 (36.8)	11.4	33.6
Tumors	1,160 (20.7)	16.9	27.2
Cortical malformations	1,067 (19.0)	6.0	17.7
No lesion	363 (6.5)	13.1	28.0
Scars	321 (5.7)	10.9	25.4
Vascular malformations	305 (5.4)	23.4	34.5
Dual pathology	209 (3.7)	9.5	26.7
Encephalitis	95 (1.7)	11.3	18.4
Double pathology	12 (0.2)	6.8	11.9
Total	5,603	12.2	27.9

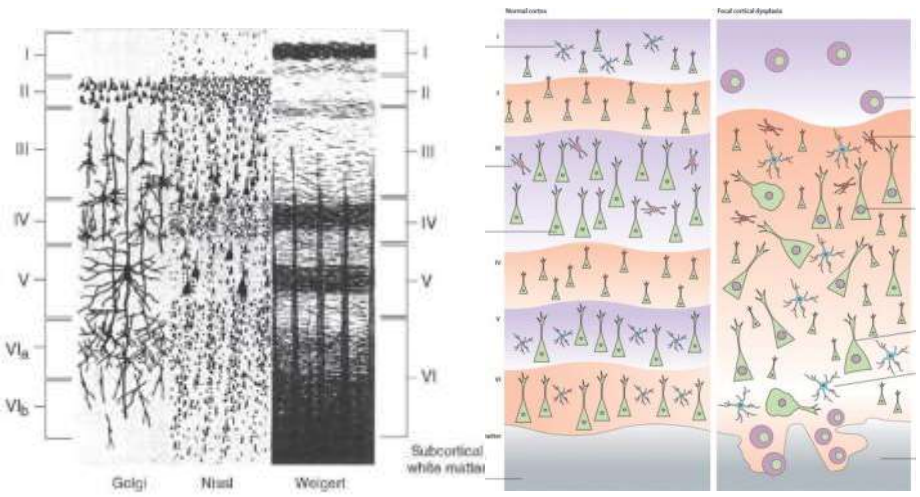
Data retrieved from the German Neuropathology Reference Center for Epilepsy Surgery. Age at onset/surgery = mean age of patients at onset of spontaneous seizure activity (in years) and surgery (in years), respectively. Dual pathology includes hippocampal sclerosis with another principal pathology.[5] Double pathology refers to two etiologically independent pathologies (hippocampal sclerosis not included).[6]

Blümcke I et al. Epilepsia. 2016 Mar;57(3):348-58.

Focal Cortical Dysplasia (FCD)

- Localized area of cortical maldevelopment with varying degrees of dyslamination, immature or giant neurons, dysmorphic neurons, balloon cells
- Developmental migration defect
- Imaging :
  - FCD type I: Often multilobar, nonenhancing
  - FCD type II: Extratemporal locations, cortical thickening, loss of grey-white junction, hyperintense juxtacortical T2 signal/FLAIR
  - Abnormal signal in subgyral white

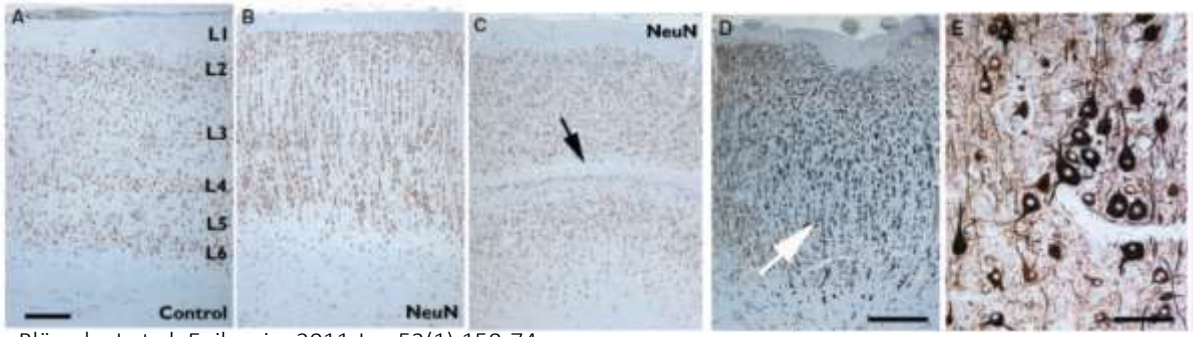




Najm IM, Sarnat HB, Blümcke I. Neuropathol Appl Neurobiol. 2018 Feb;44(1):18-31

Focal Cortical Dysplasia (FCD)

- Histologic classification International League Against Epilepsy (ILAE)
- Imaging :
  - FCD type I
  - FCD type II
  - FCD tye III
- Surgical resection principal treatment for drug-resistant FCD
  - FCD II and FCD III have better outcomes



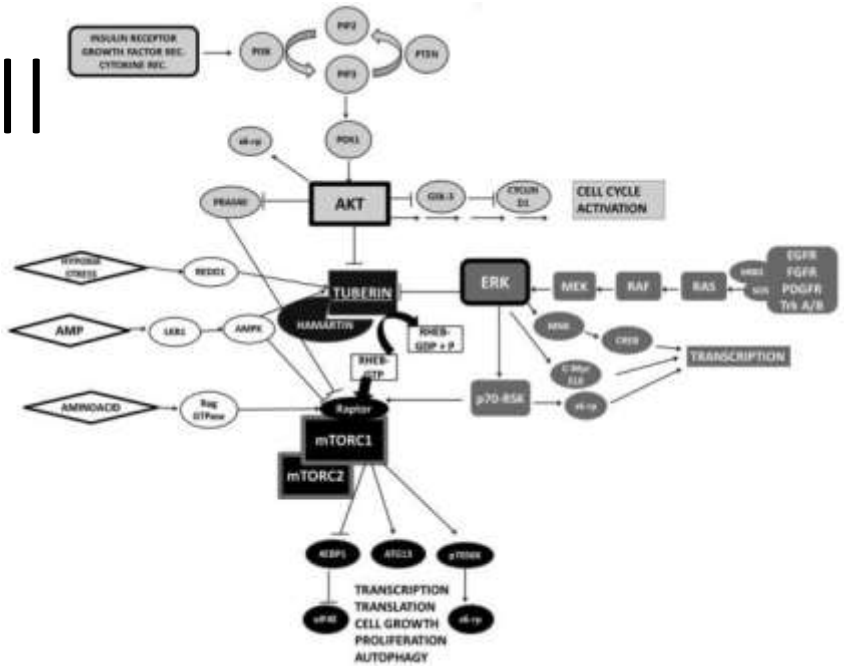
Blümcke I et al. Epilepsia. 2011 Jan;52(1):158-74.

Table 1. Suggestions for an update to the three-tiered international league against epilepsy classification system of focal cortical dysplasia (FCD; Modified from Blömcke *et al.*, 2011)

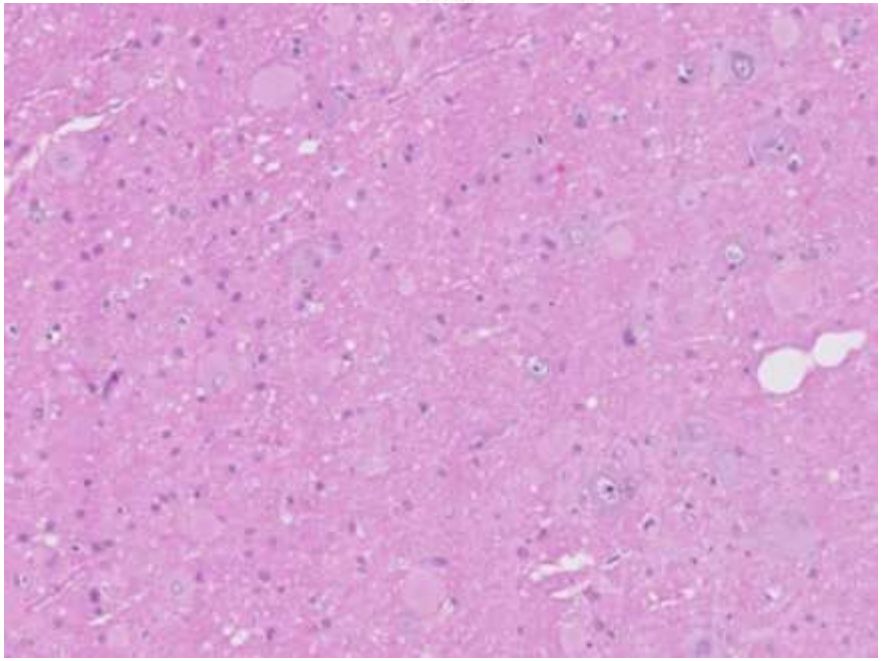
	Histology	*Update needed*	*Comments*
FCD type I (isolated)			
FCD type I a	Abnormal radial cortical lamination	Yes	Molecular biomarkers needed to confirm specific pathomechanism
FCD type I b	Abnormal tangential cortical lamination	Yes	Molecular biomarkers needed to confirm specific pathomechanism
FCD type I c	Abnormal radial and tangential cortical lamination	No	Molecular biomarkers needed to confirm specific pathomechanism
FCD type II (Isolated)			
FCD type II a	Dysmorphic neurons	Yes	Introduce genetic findings of mTOR activation
FCD type II b	Dysmorphic neurons and balloon cells	Yes	Introduce genetic findings of mTOR activation and new variant at bottom-of-sulcus
FCD type III (associated)			
FCD type III a	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis	No	Molecular and clinical biomarkers needed to differentiate between secondary (acquired) or primary aetiology
FCD type III b	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor	No	Molecular and clinical biomarkers needed to differentiate between secondary (acquired) or primary aetiology
FCD type III c	Cortical lamination abnormalities adjacent to vascular malformation	No	Molecular and clinical biomarkers needed to differentiate between secondary (acquired) or primary aetiology
FCD type III d	Cortical lamination abnormalities adjacent to any other lesion acquired during early life	Yes	Molecular and clinical biomarkers needed to differentiate between secondary (acquired) or primary aetiology; introduce FCD type IIId with loss of layer 4 neurons in occipital lobe

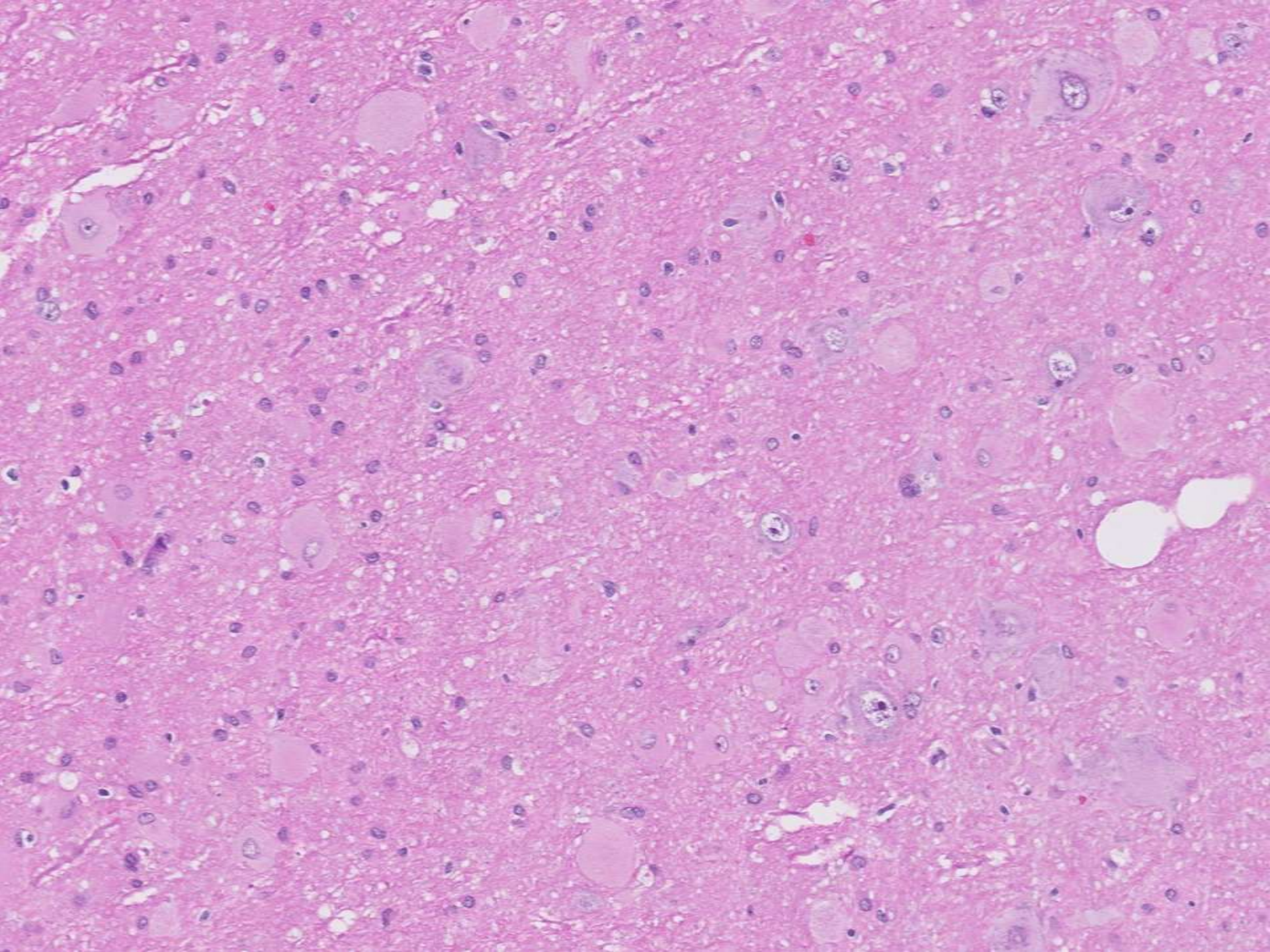
Najm IM, Sarnat HB, Blümcke I. Neuropathol Appl Neurobiol. 2018 Feb;44(1):18-31

FCD II



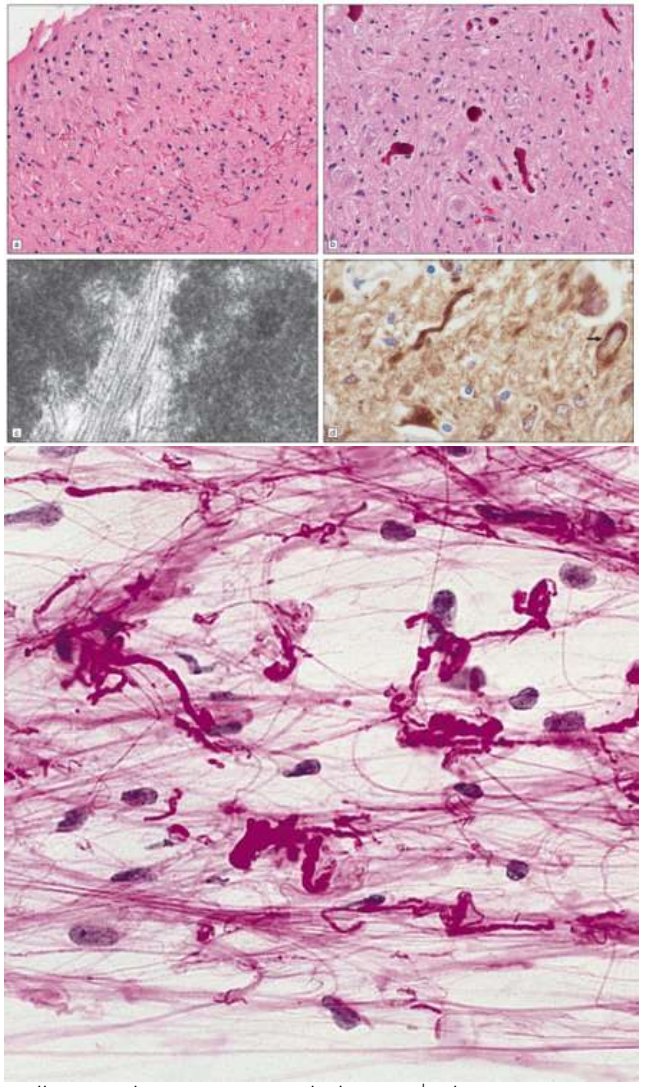
- Most frequent FCD
  - Dysplastic and megaloblastic neurons (cytoplasmis neurofilament +)
  - FCD IIb presence of balloon cells (often CD34 or nestin +)
- Associated with mTOR somatic mutations activation
  - Tuberous sclerosis, hemimegalencephaly and FCDII
  - Post-zygotic mosaicism
- Differential diagnosis:
  - Ganglioglioma
  - Glioma
  - Macrophage infiltration





Rosenthal Fibers (RF)

- 1898- German pathologist Werner Rosenthal noted elongated inclusions associated with an ependymoma
  - "glossy formation of little bulbs or wavy sausages"
  - Eosinophilic, waxy structures on H&E
  - Amorphous granular material and 10nm filaments on EM
- Chronic reactive glial tissue, Alexander disease (GFAP mutation) and some neoplasms (pilocytic astrocytomas, ganglioglioma, pleomorphic xanthoastrocytoma)
- Cytoplasmic inclusion of intermediate filament (GFAP), ubiquitin, heat shock proteins (HSP27), and α-B-crystallin



Ellison and Love, Neuropathology, 3rd Edition, 2013

Summary

- FCD IIb with abundant RFs
  - RF reminiscent of the changes seen in Alexander disease, a leukodystrophy secondary to point mutations in the GFAP gene
- 2 other cases with similar histology were seen at Stanford
  - 1 case report in the literature in 2009, no GFAP mutation identified

- Differential diagnosis with pilocytic astrocytoma and ganglioglioma

- Patient follow-up: 3 months without seizures but still on medication (valproic acid)
  - Cognitive and behavioral status remained impaired with social skills and language most severely affected
  - Receives special services in school

References

- Review: The international consensus classification of Focal Cortical Dysplasia - a critical update 2018. Najm IM, Sarnat HB, Blümcke I. Neuropathol Appl Neurobiol. 2018 Feb;44(1):18-31.

- International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods. Blümcke I, Aronica E, Miyata H, Sarnat HB, Thom M, Roessler K, Rydenhag B, Jehi L, Krsek P, Wiebe S, Spreafico R. Epilepsia. 2016 Mar;57(3):348-58.

- The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R. Epilepsia. 2011 Jan;52(1):158-74.

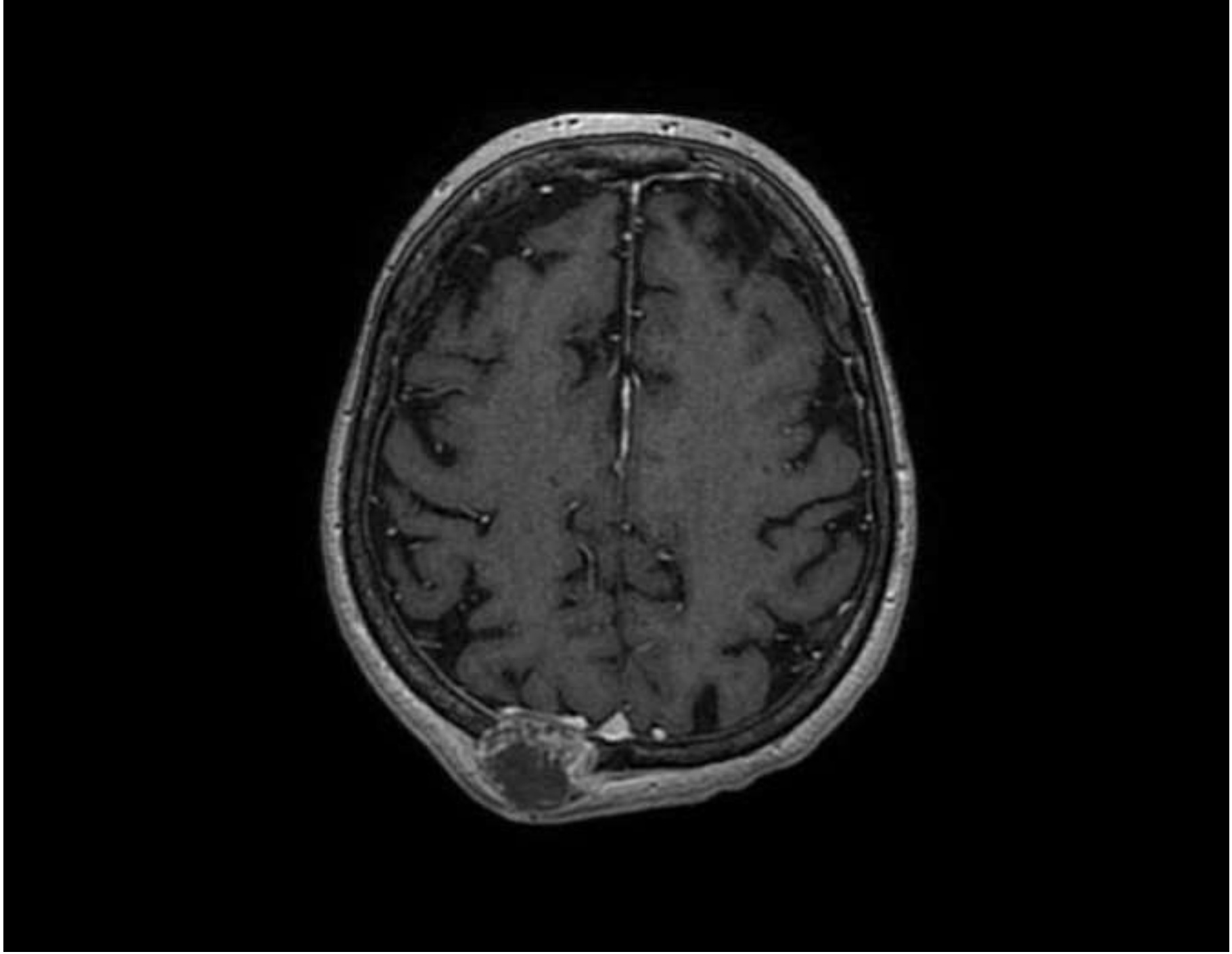
- Cortical dysplasia with prominent Rosenthal fiber formation in a case of intractable pediatric epilepsy. Khanlou N, Mathern GW, Mitchell WG, Salamon N, Pope WB, Yong WH, Vinters HV. Hum Pathol. 2009 40(8):1200-4

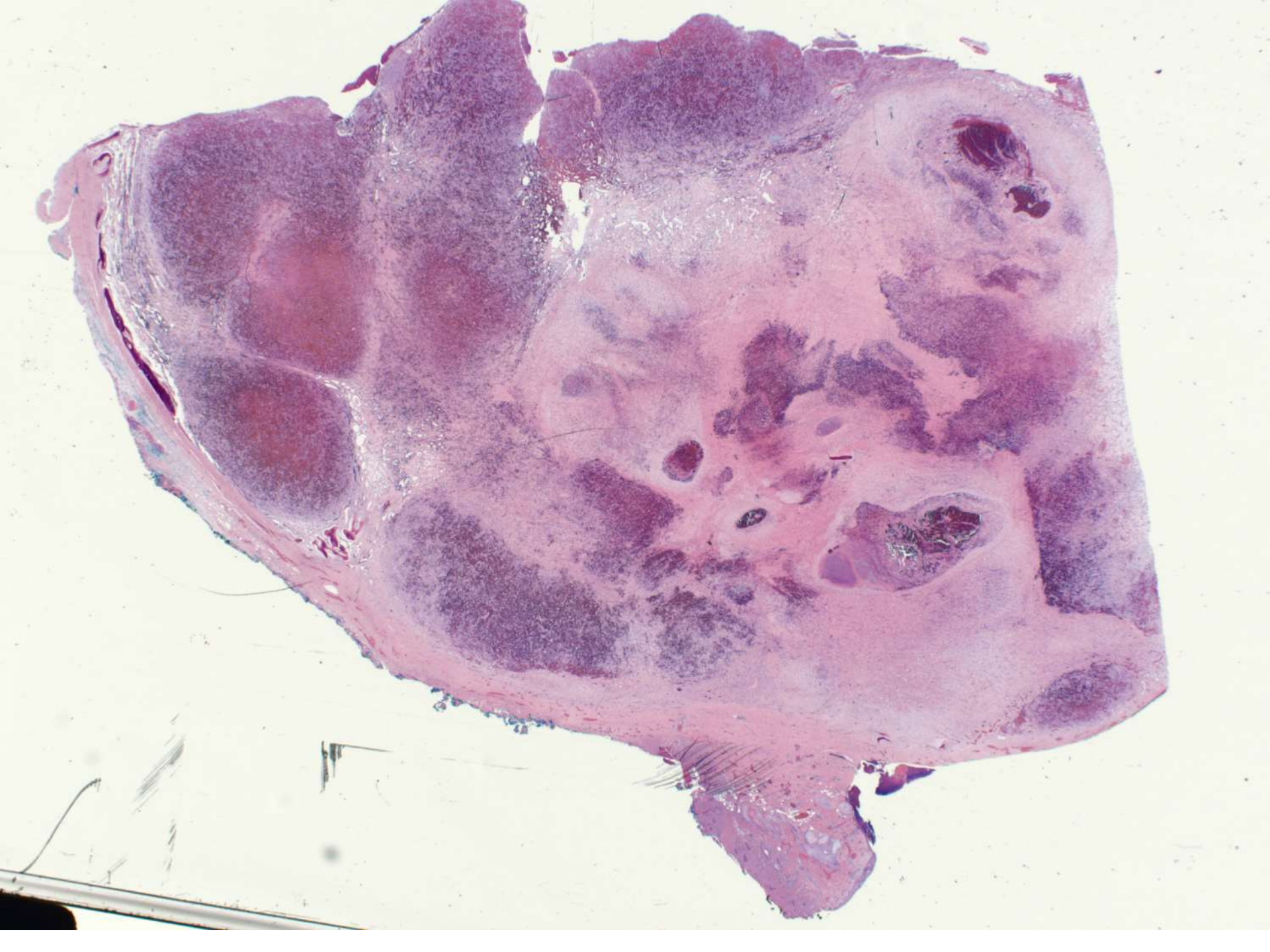
- Ellison and Love, Neuropathology, 3rd Edition, 2013

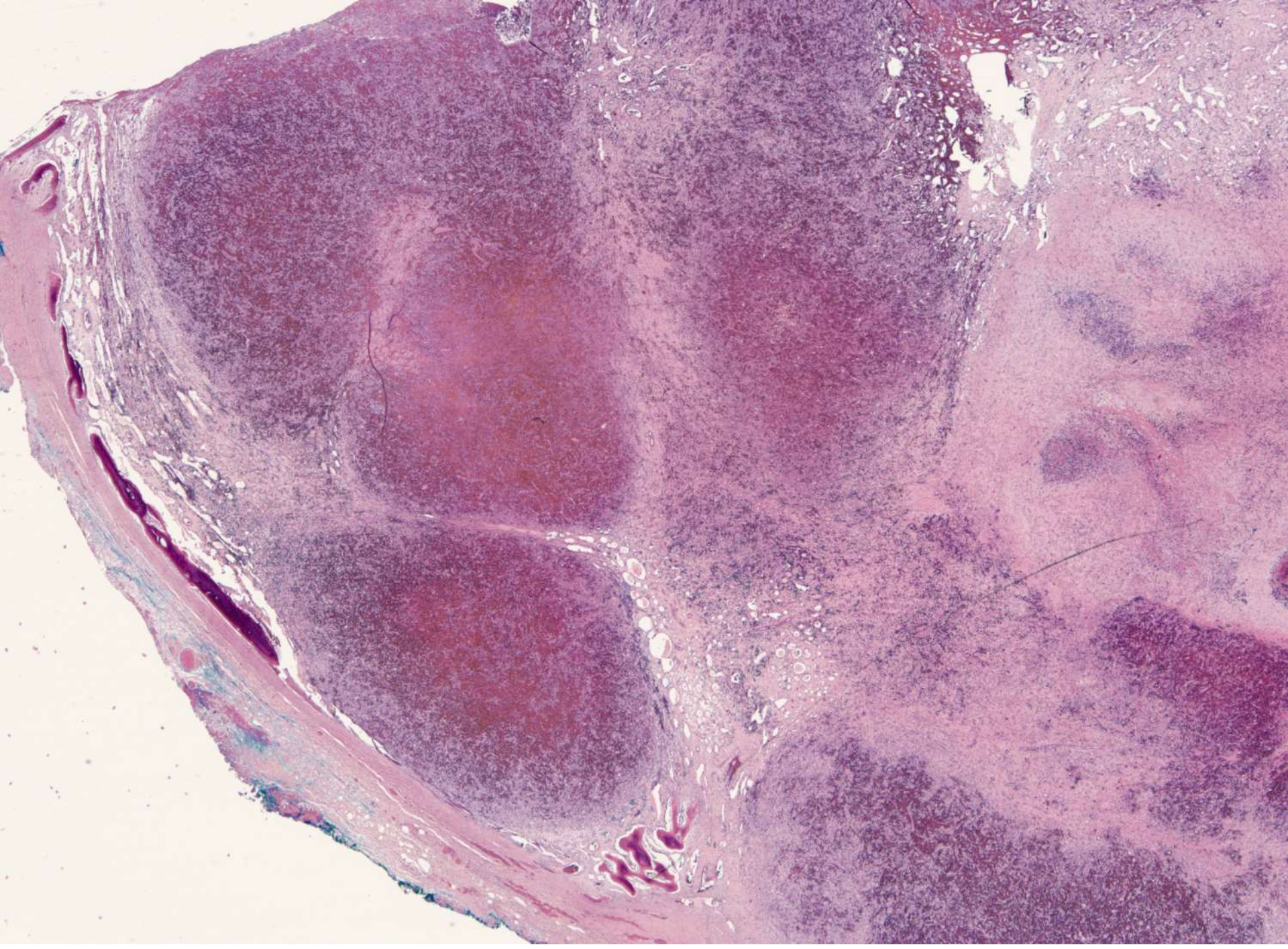
19-1105

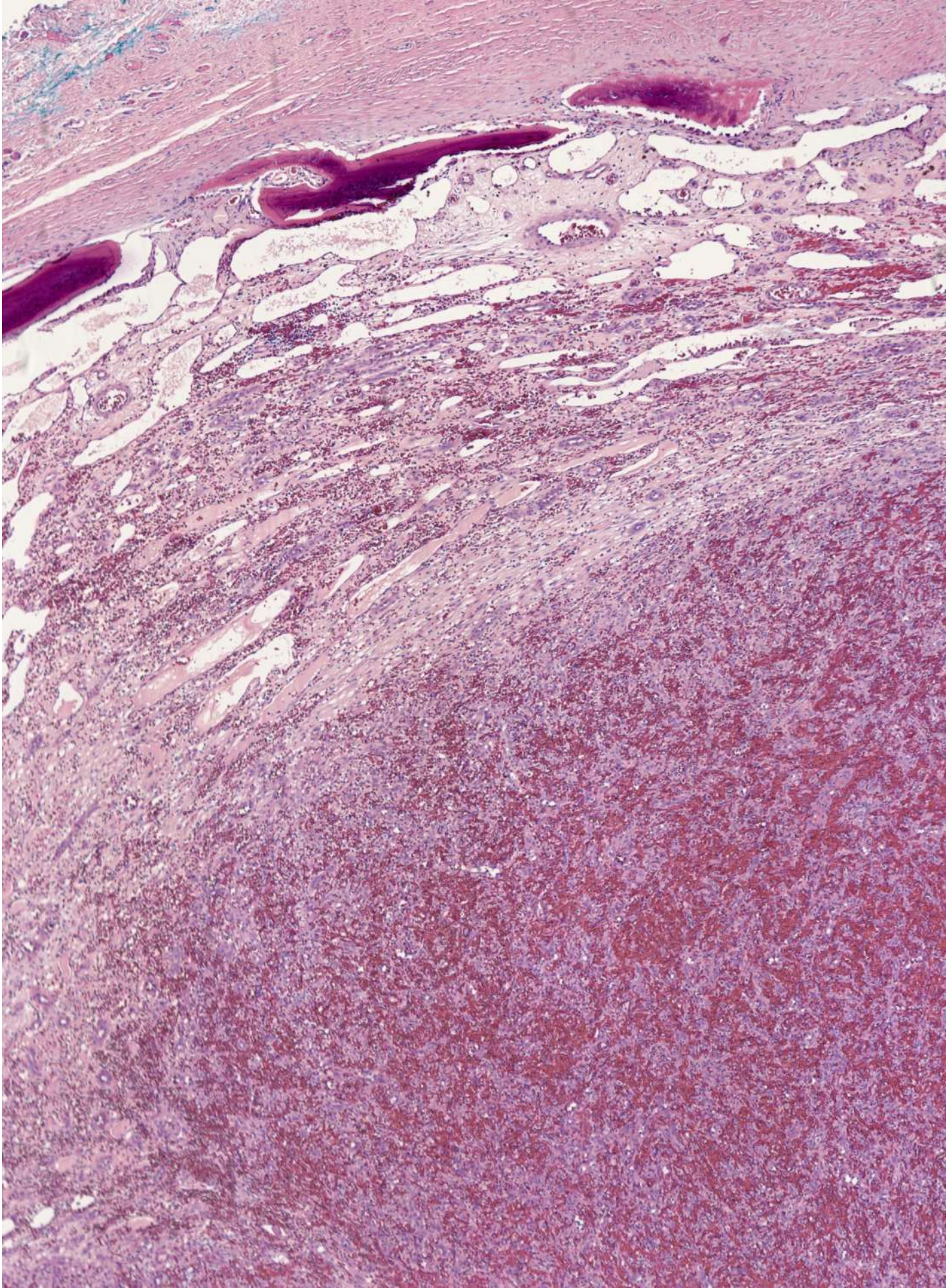
Dennis Adams/Greg Charville; Stanford

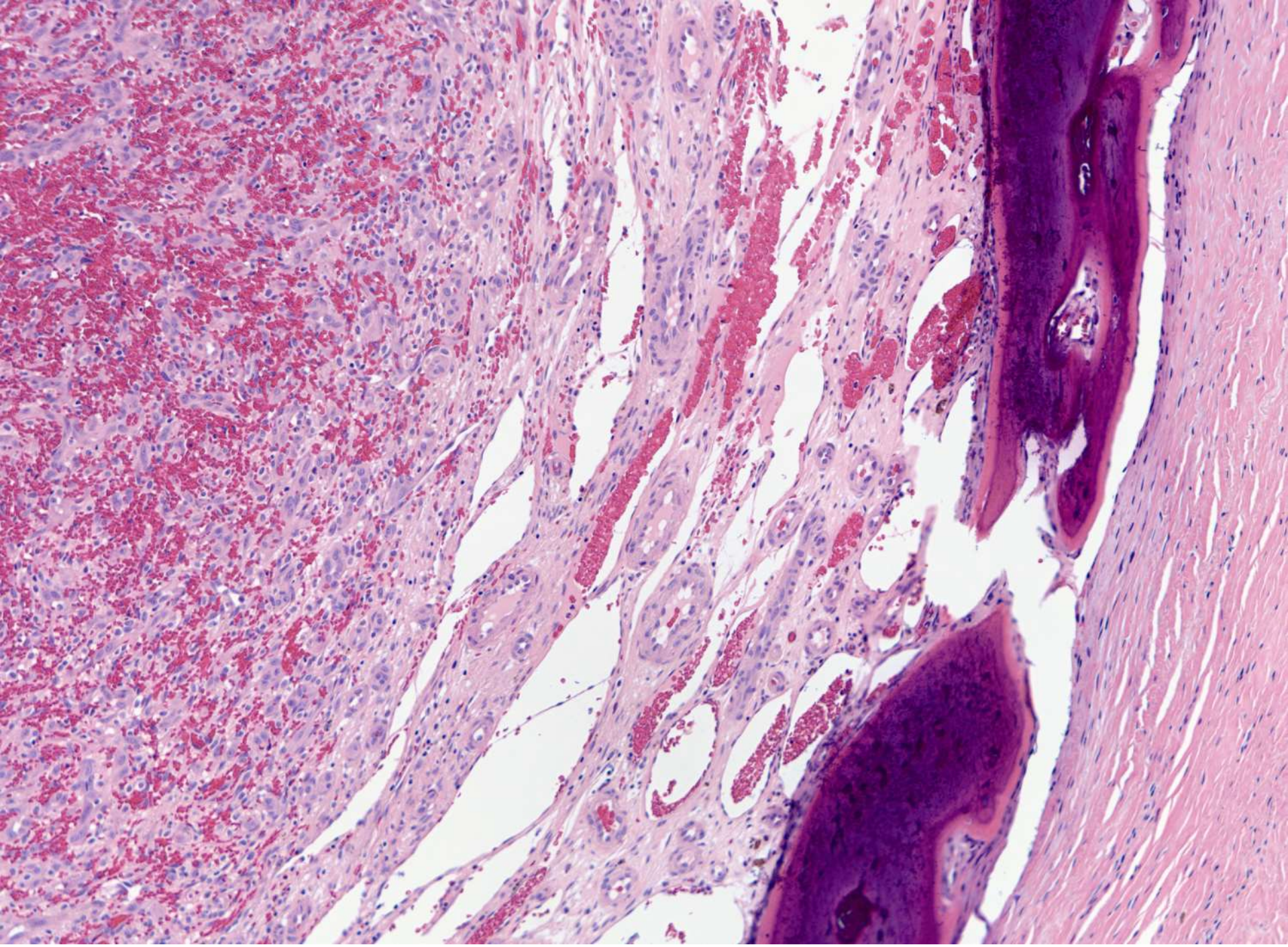
75-year-old female who presented with an enlarging vertex scalp mass. MRI revealed 2.4 x 3.2 x 3.4cm mass centered in the right parietal calvaria/scalp eroding the inner/outer table.

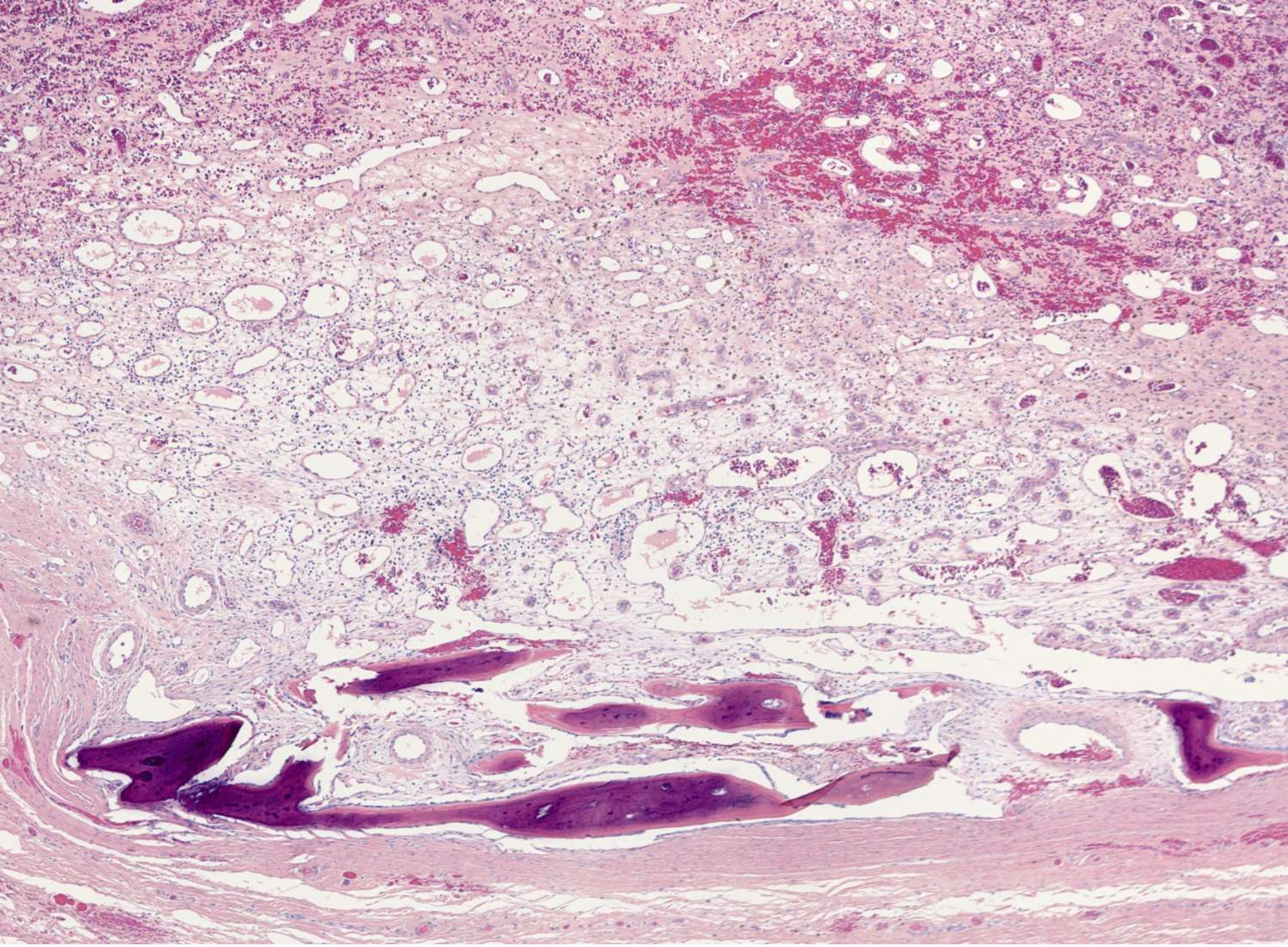


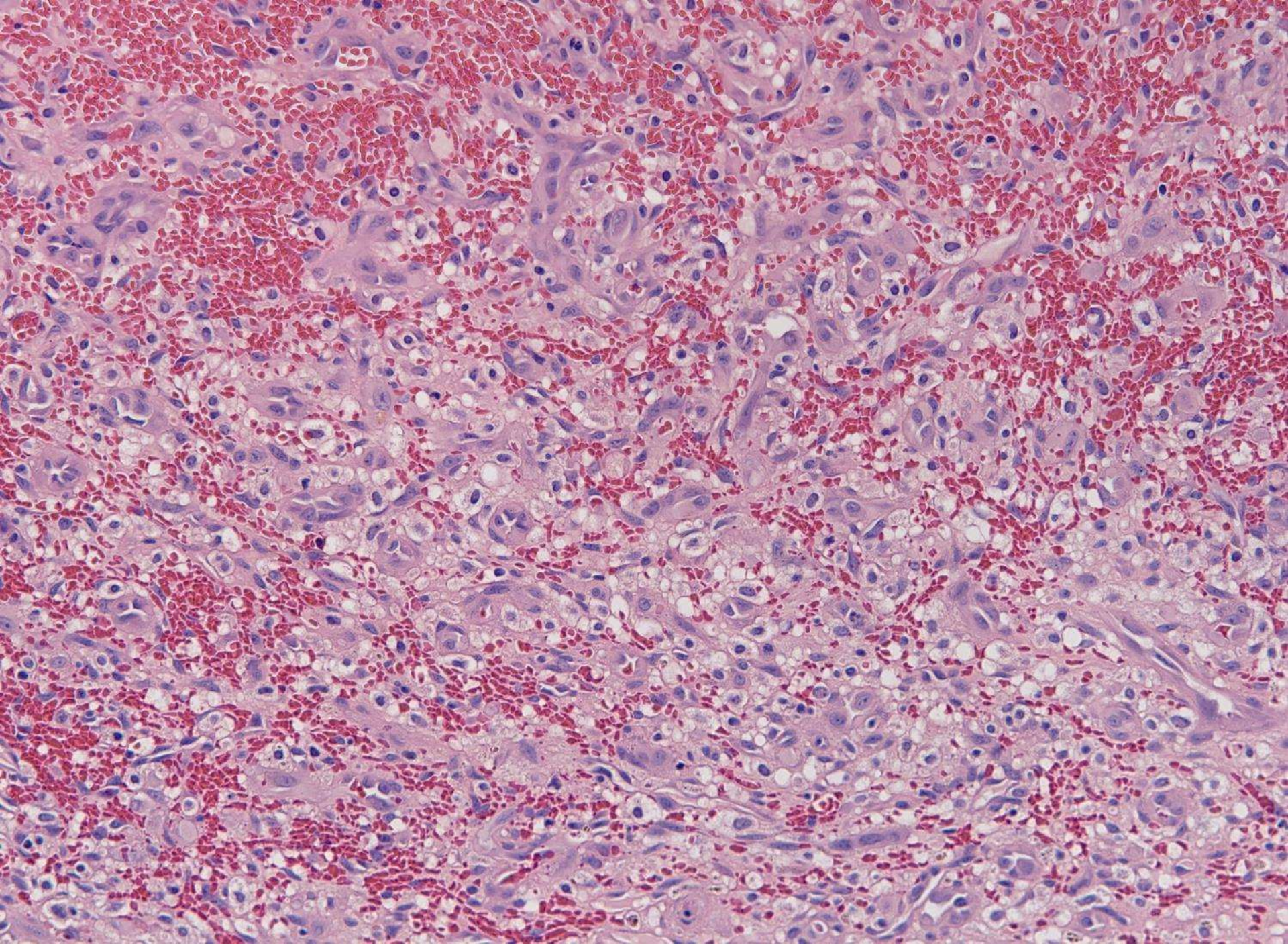


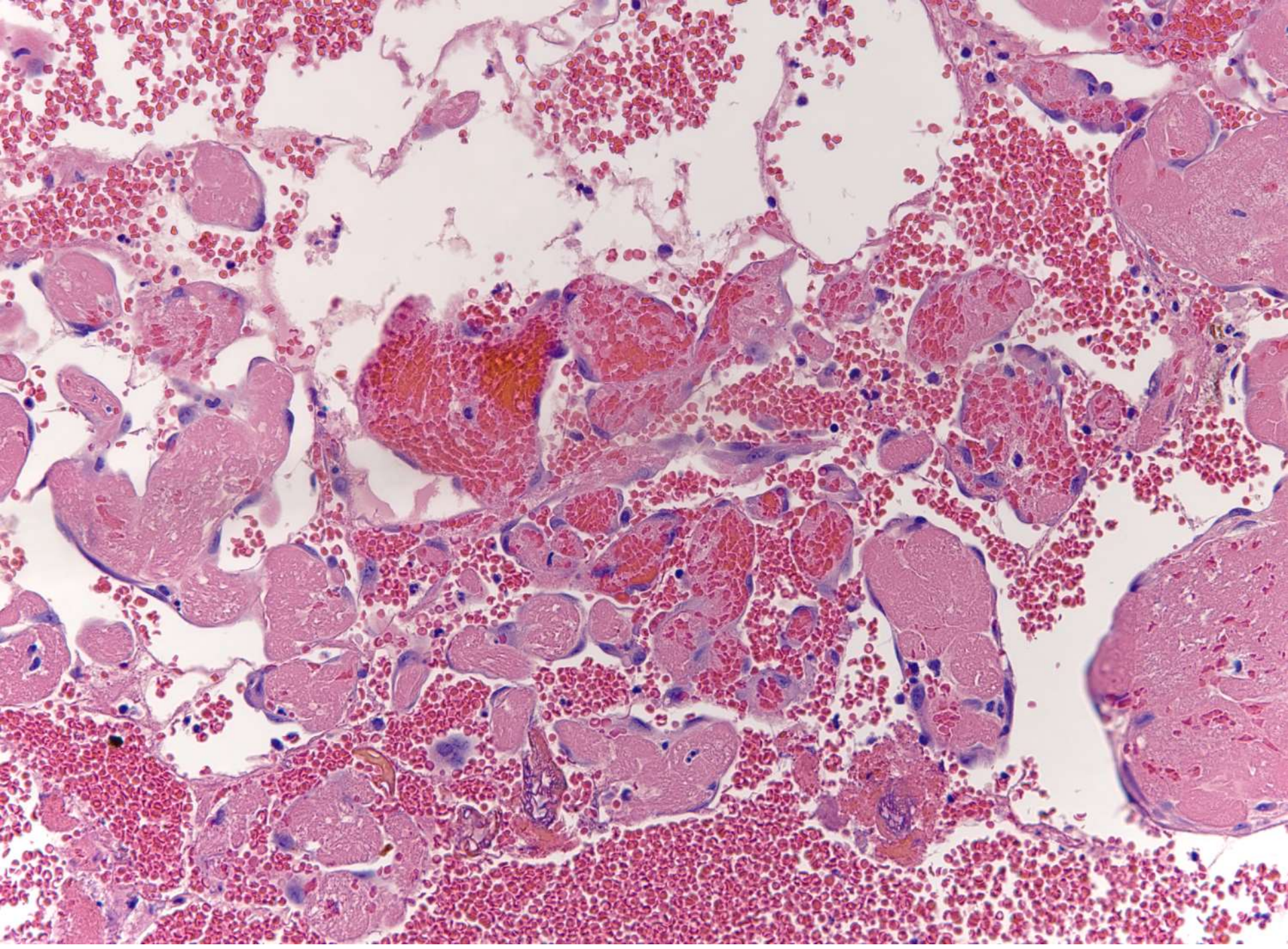


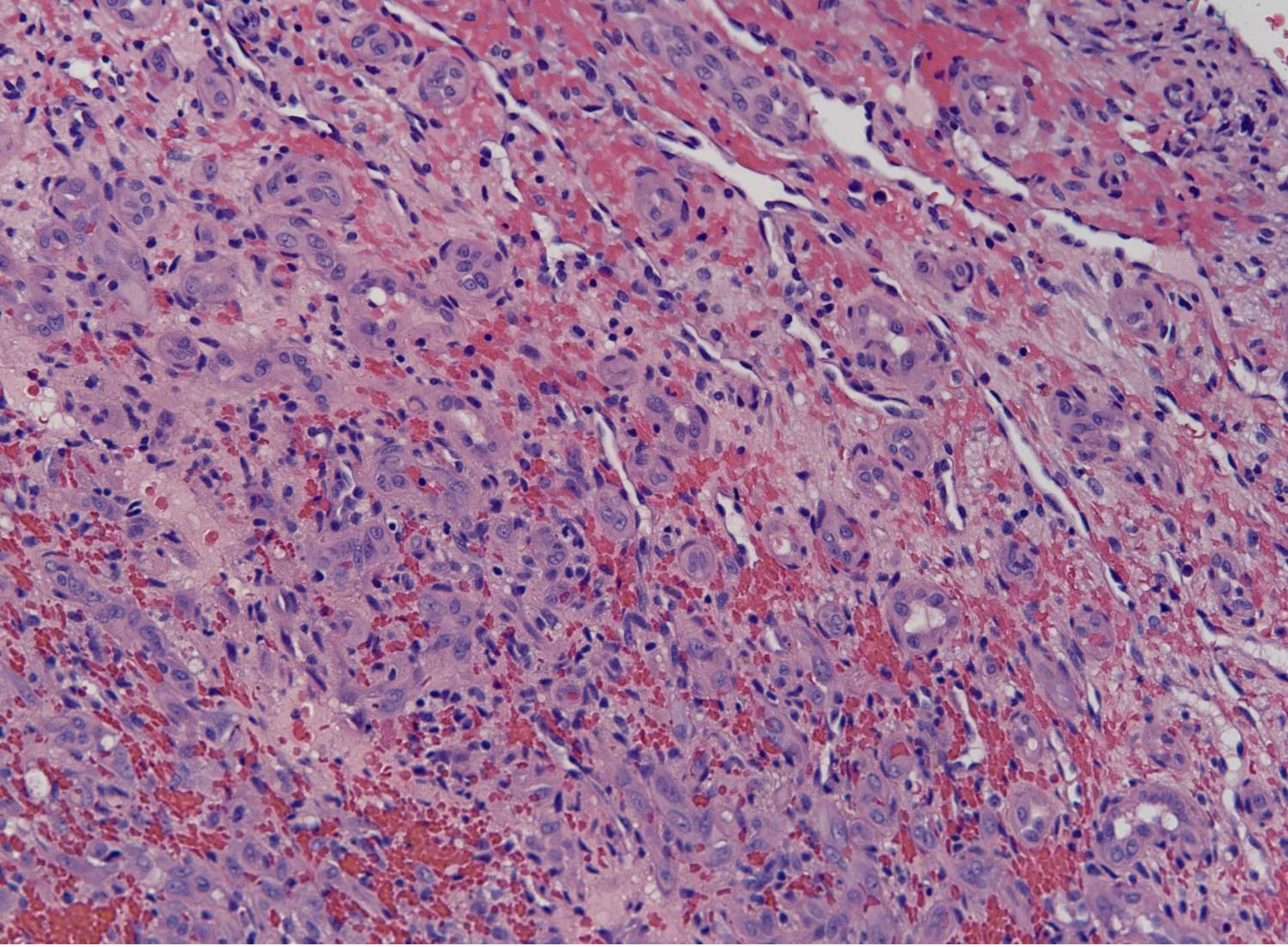


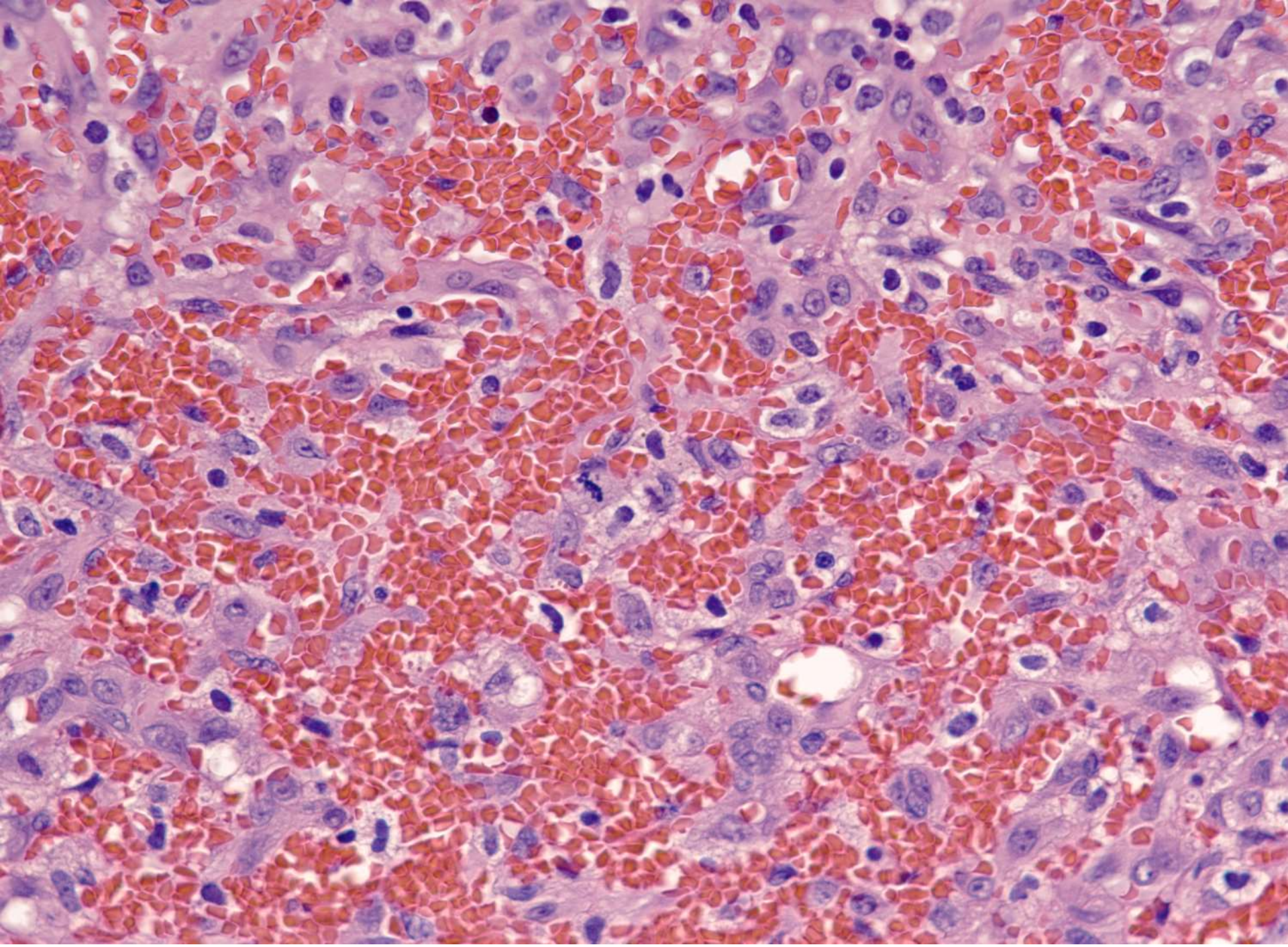












Clinical history

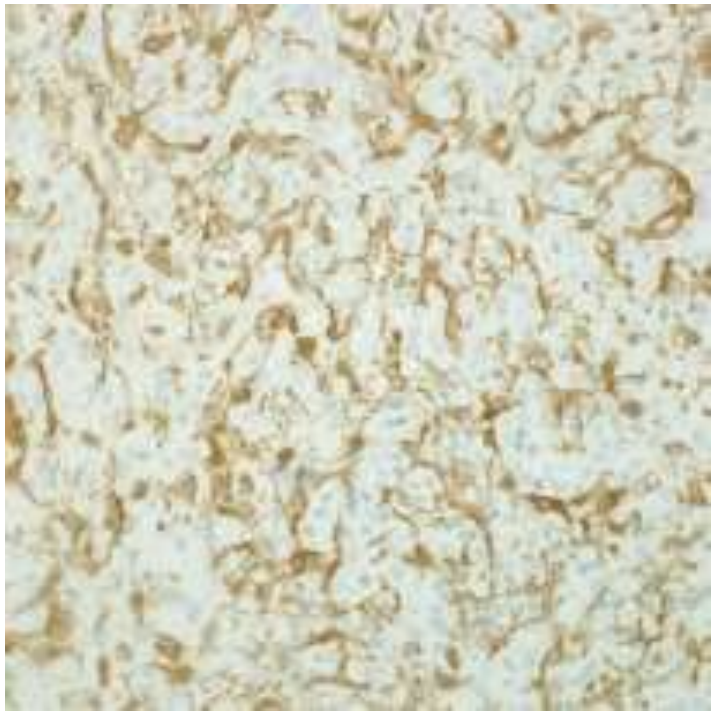
- H/o melanoma and endometrial adenoCA
- Presented to dermatologist c/o lump on her head
- Bx → “lipoma”
- Referred to surgeon for excision
- Op report: “did not resemble a lipoma and had a calcified cystic like wall. […] Surprisingly I did not feel any skull under the lesion.”

Clinical history

- Excision dx → hemangioma of bone
- CT followed by MRI
- Neuro-oncology TB: recurrent lesion, therefore worrisome for angiosarcoma

IHC results

- Positive: CD31, CD34
- Negative: CK-mix, EMA, SMA (pericytes), HHV-8



Diagnosis

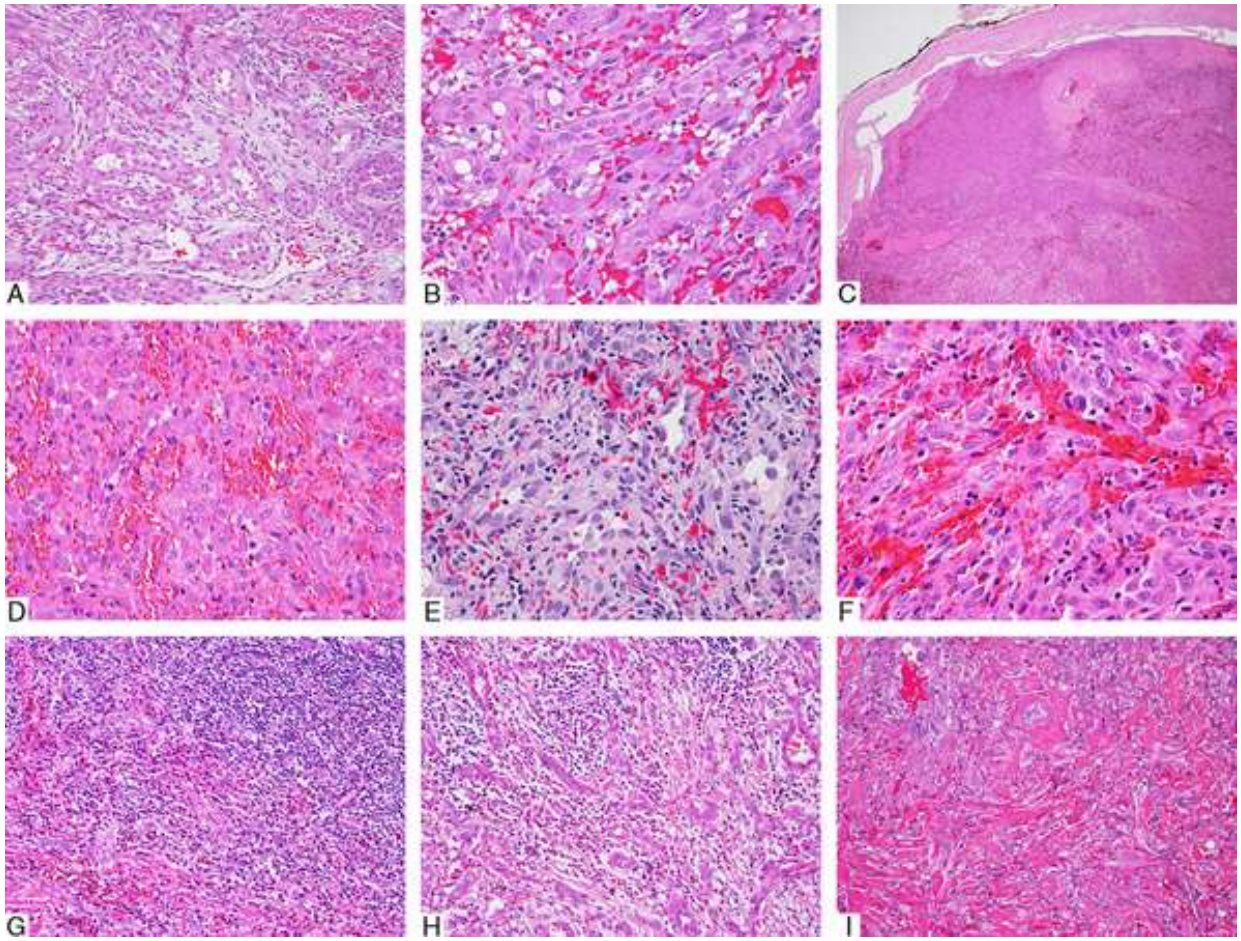
- 19-1105
  - BONE AND SOFT TISSUE, POSTERIOR SKULL TUMOR, EXCISION
    - EPITHELIOID HEMANGIOMA (SEE COMMENT)

- Follow-up: no recurrence at 6-month MRI

Epithelioid hemangioma (of bone?)

- Classified as a benign vascular tumor
- Histologic features
  - Generally well-circumscribed
  - Lobular growth pattern
  - Larger (well-developed, arteriolar-like) peripheral vessels in fibromyxoid stroma surrounding centrally located cellular foci
  - Variable morphology, from well-formed vessels with epithelioid (hobnail, “tombstone”) features and eosinophilic cytoplasm, to spindled cells in sheets or subtly vasoformative
  - Extravasated red blood cells, inflammatory infiltrate, cytoplasmic vacuoles, occasional mitotic figures, osteoclast-like giant cells

Huang et al., AJSP 2015



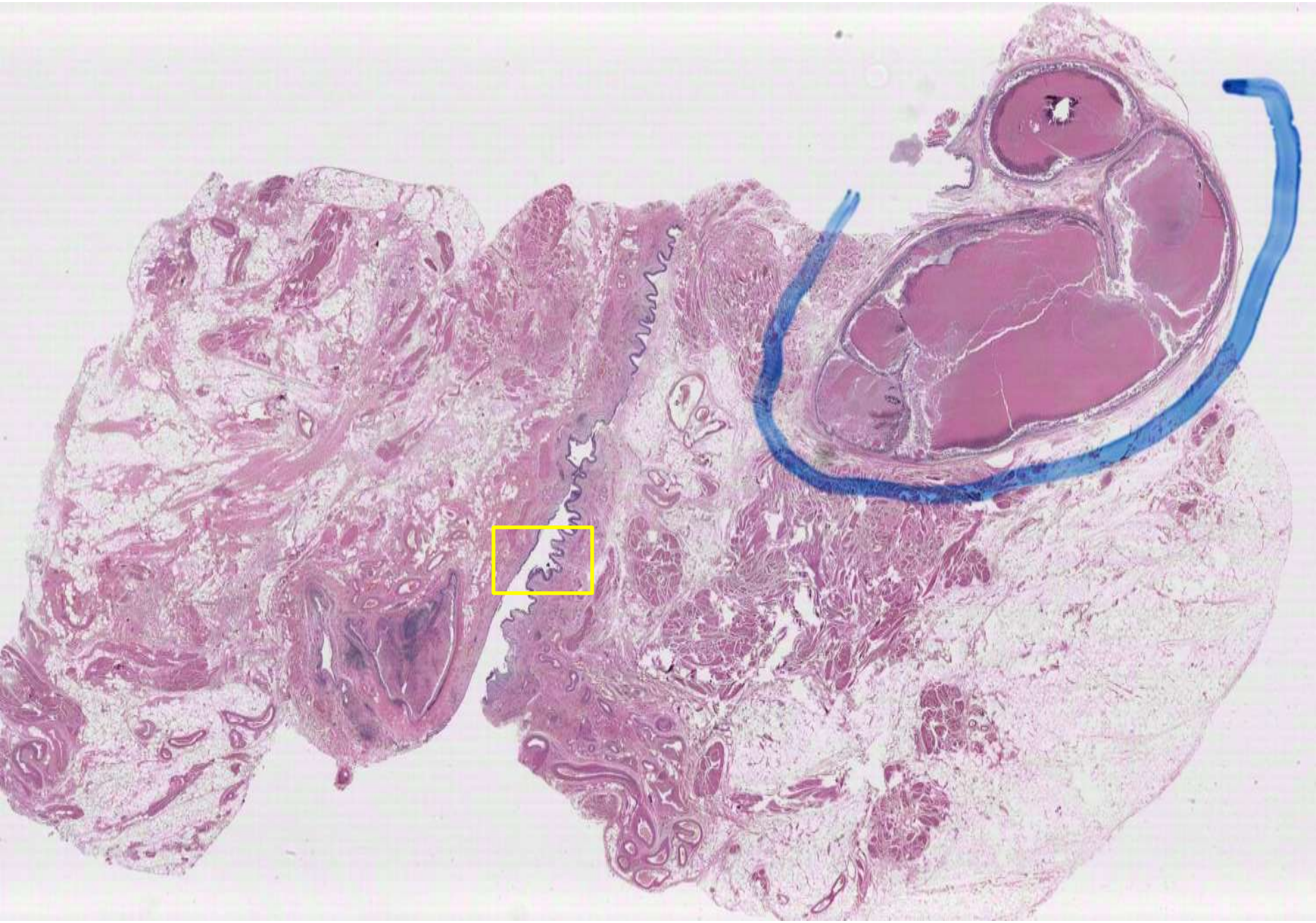
Papke and Hornick, Virchows Archiv 2019

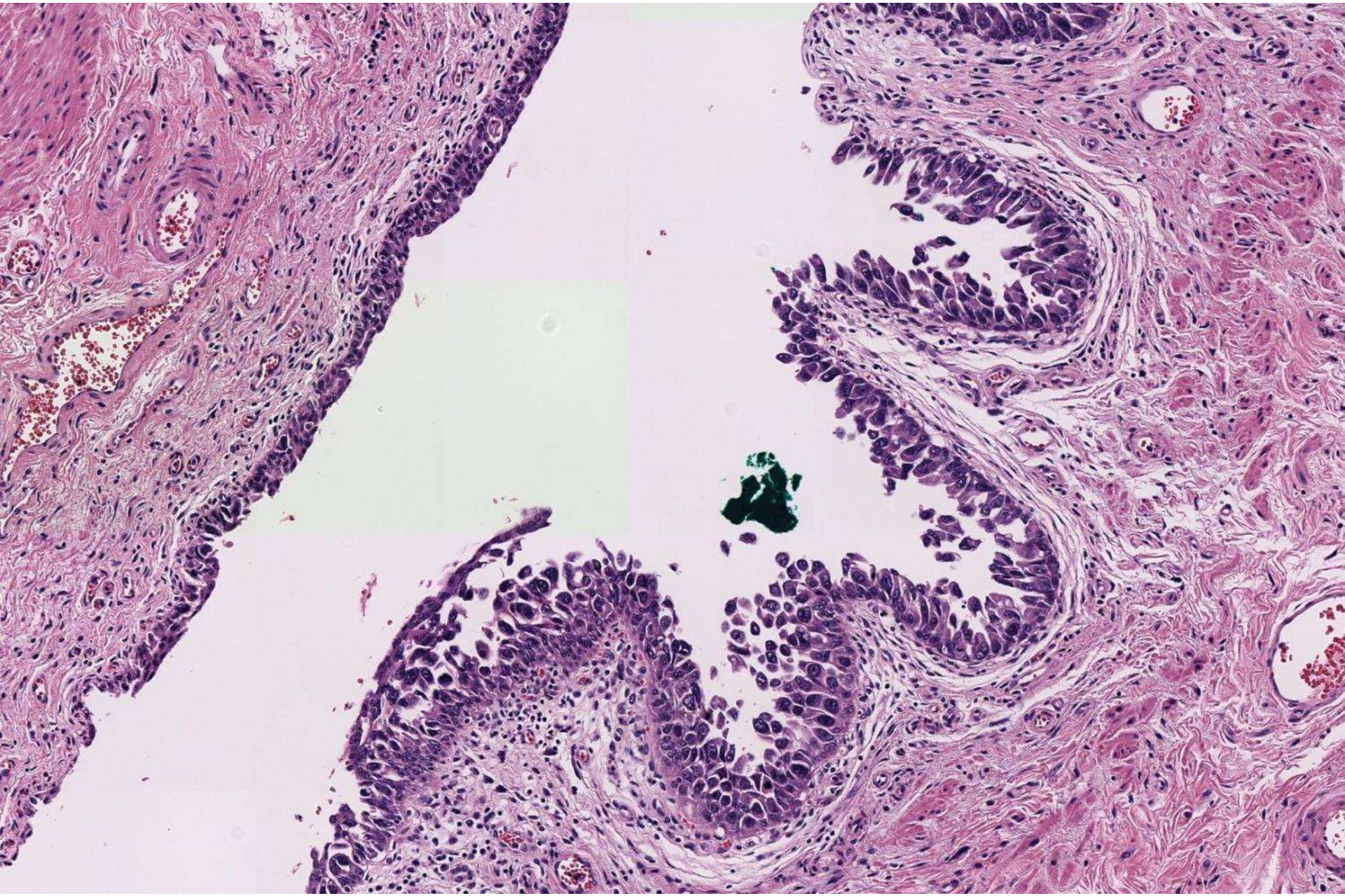
Neoplasm	Genetic alteration (prevalence)	Immunohistochemical markers (sensitivity)
Epithelioid hemangioma	*WWTR1-FOSB*, *ZFP36-FOSB* (20% cellular subtype); *FOS-VIM*, *FOS-MBLNI*, *FOS-lincRNA*, *FOS*-(unknown) (50% cellular subtype)	FOSB (75% conventional subtype; 100% ALHE subtype; 10% cellular subtype)
Tufted angioma/kaposiform hemangioendothelioma	*GNA14* mutation (unknown)	No specific markers
Anastomosing hemangioma Hepatic small vessel neoplasm Lobular capillary hemangioma	*GNA11* mutation, *GNA14* mutation, *GNAQ* mutation (? nearly 100%)	No specific markers
Composite hemangioendothelioma	*PTBP1-MAML2* (rare) *EPC1-PHC2* (rare)	Synaptophysin (subset of aggressive cases; unknown sensitivity overall)
Pseudomyogenic hemangioendothelioma	*SERPINE1-FOSB* (? 55%) *ACTB-FOSB* (? 45%)	FOSB (nearly 100%)
Epithelioid hemangioendothelioma	*WWTR1-CAMTA1* (85%) *YAP1-TFE3* (5%)	CAMTA1 (85%) TFE3 (5%)
Post-radiation angiosarcoma	*MYC* amplification (100%) *FLT4* amplification (25%) *PTPBR* mutation (45%) *PLCG1* mutation (15%)	MYC (nearly 100%)
Primary angiosarcoma	Complex karyotype (? 25%) *KDR* mutation (25%) *CIC* rearrangement or point mutation (10%)	No specific markers

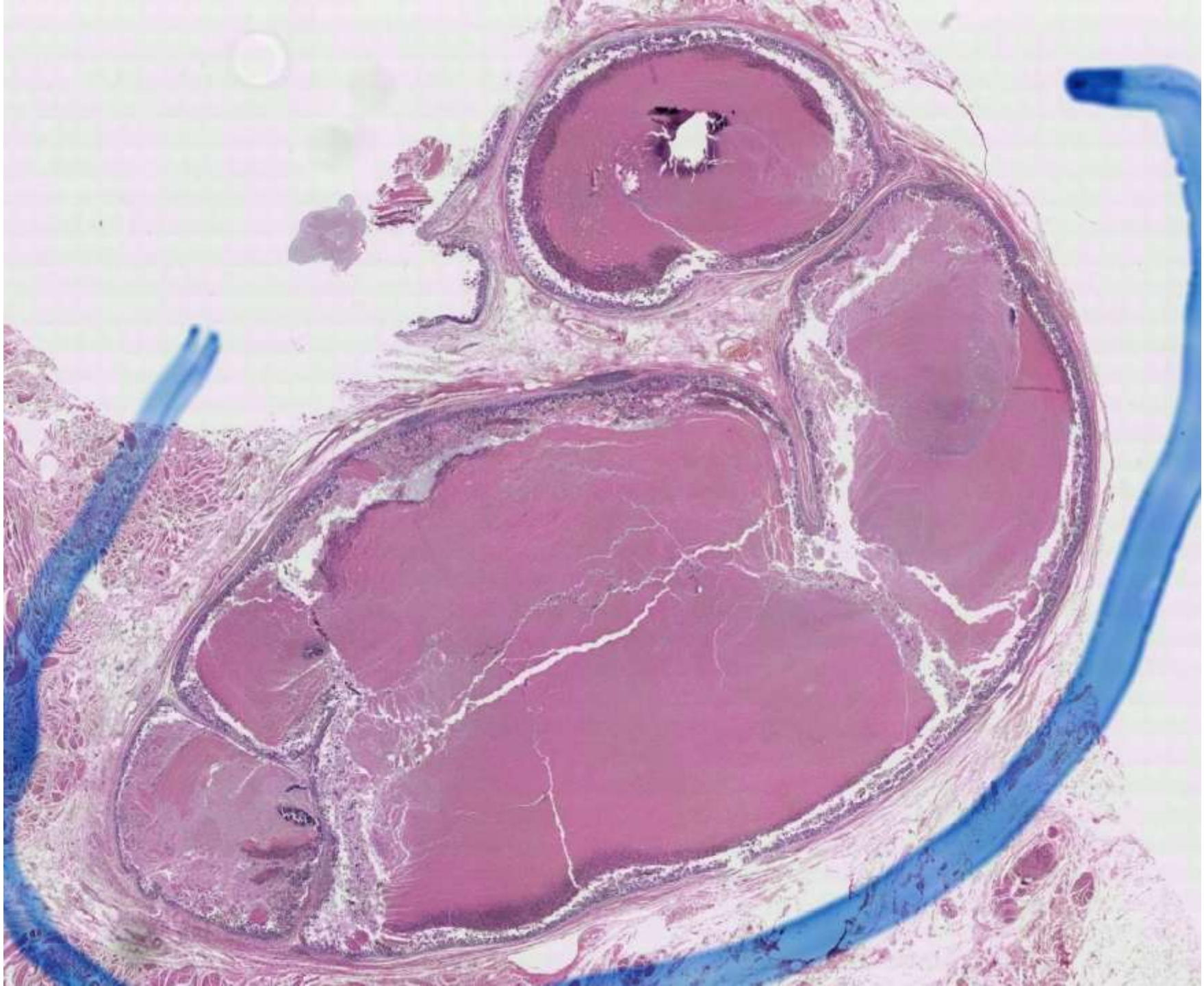
19-1106

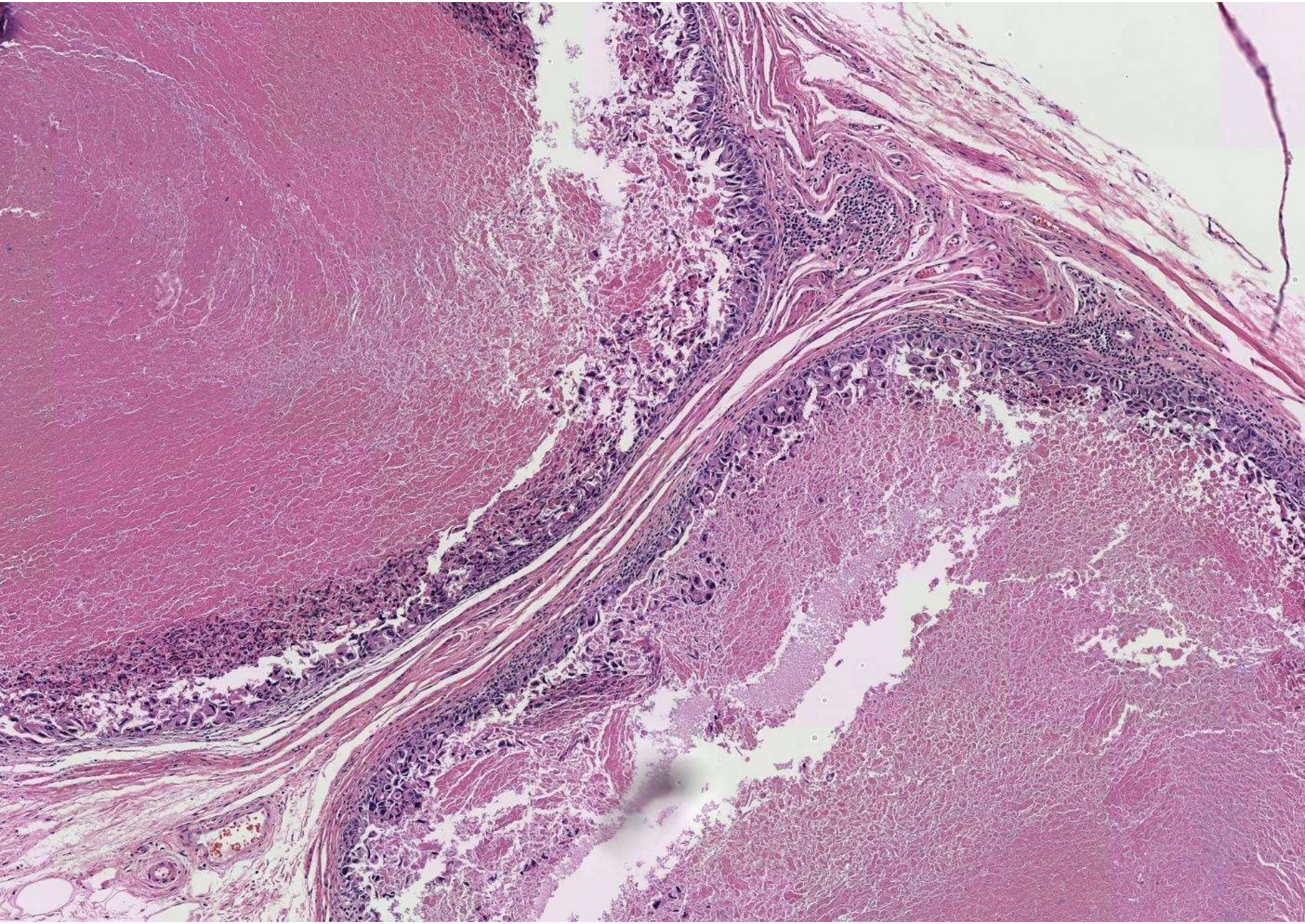
Ankur Sangoi; El Camino Hospital

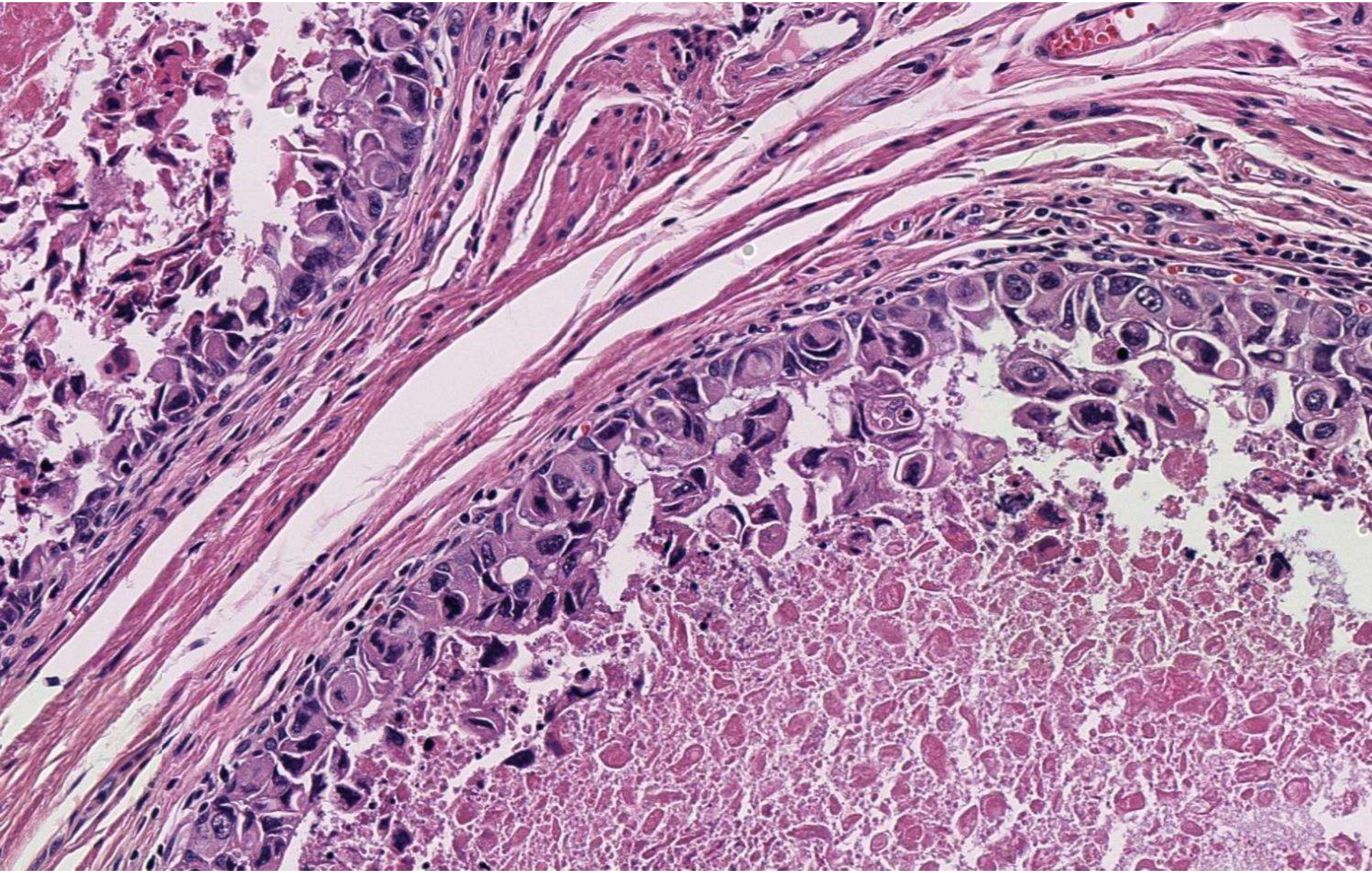
72-year-old male with biopsy-proven pT1 urothelial carcinoma, undergoes radical cystectomy. Away from the biopsy bed, a firm nodule was found in the bladder wall.



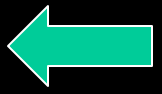








Final diagnosis: urothelial CIS colonizing urachus

- **pTis** 
- **pT1**
- **pT2**

Patterns of Urachal Remnant Involvement by Urothelial Carcinoma

Intraluminal Noninvasive Spread Can Mimic a Deep-seated Bladder Invasion

Lisa Han, MD, Alexander Gallan, MD,* and Gladell P. Paner, MD*†*

Am J Surg Pathol • Volume 43, Number 4, April 2019

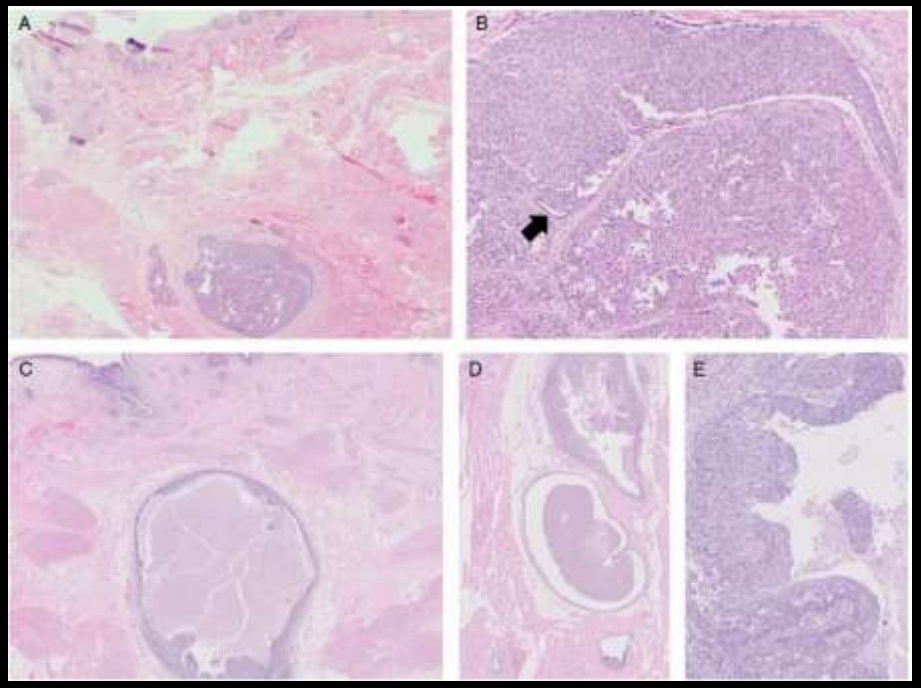


TABLE 1. Clinicopathologic Characteristics of Bladder Cancer Cystectomies With Incidental Urachal Remnants Involved by Urothelial Carcinoma

			Main Bladder Urothelial Carcinoma			Urachal Remnants			Urachal Remnant Tumor	
Case	Age (y)/ Sex	Specimen	Stage	Dome Involved	Overlying Urachal Remnant	Location	Transected Segment(s), Largest Size	Benign Epithelium	Type	Deepest Extent (+Deeper than Bladder Tumor)
1	68/M	CP	pTis	Yes	CIS	Dome	Multiple, <1 mm	Urothelial	CIS	MP, upper half+
2*	86/M	CP	pT2b	No	CIS (separate focus)	Dome	Single, 3 mm	Cuboidal	Noninvasive HG PUC (inverted)	MP, lower half
3	65/M	CP	pT1	Yes	CIS and noninvasive HG PUC	Dome	Multiple, 7 mm (tubulocystic)	Urothelial	Noninvasive HG PUC and CIS	MP, lower half+
4	53/M	CP	pT1	Yes	Noninvasive HG PUC	Dome	Multiple, 2 mm	Urothelial and glandular	CIS	MP, upper half+
5	87/M	CP	pT3b	Yes	CIS	Dome	Single, 3 mm	Absent	CIS	MP, upper half
6	64/M	CP	pT4a	Yes	Invasive†	Dome	Multiple tight aggregate, 8.5 mm	Absent	CIS†	MP, upper half
7	87/M	PC	pTis	Yes	CIS	Dome	Single, 2 mm	Cuboidal	CIS	MP, lower half+
8‡	59/M	CP	pTis	No	Benign urothelium	Dome	Multiple, 2 mm	Urothelial and glandular	CIS	MP, upper half+

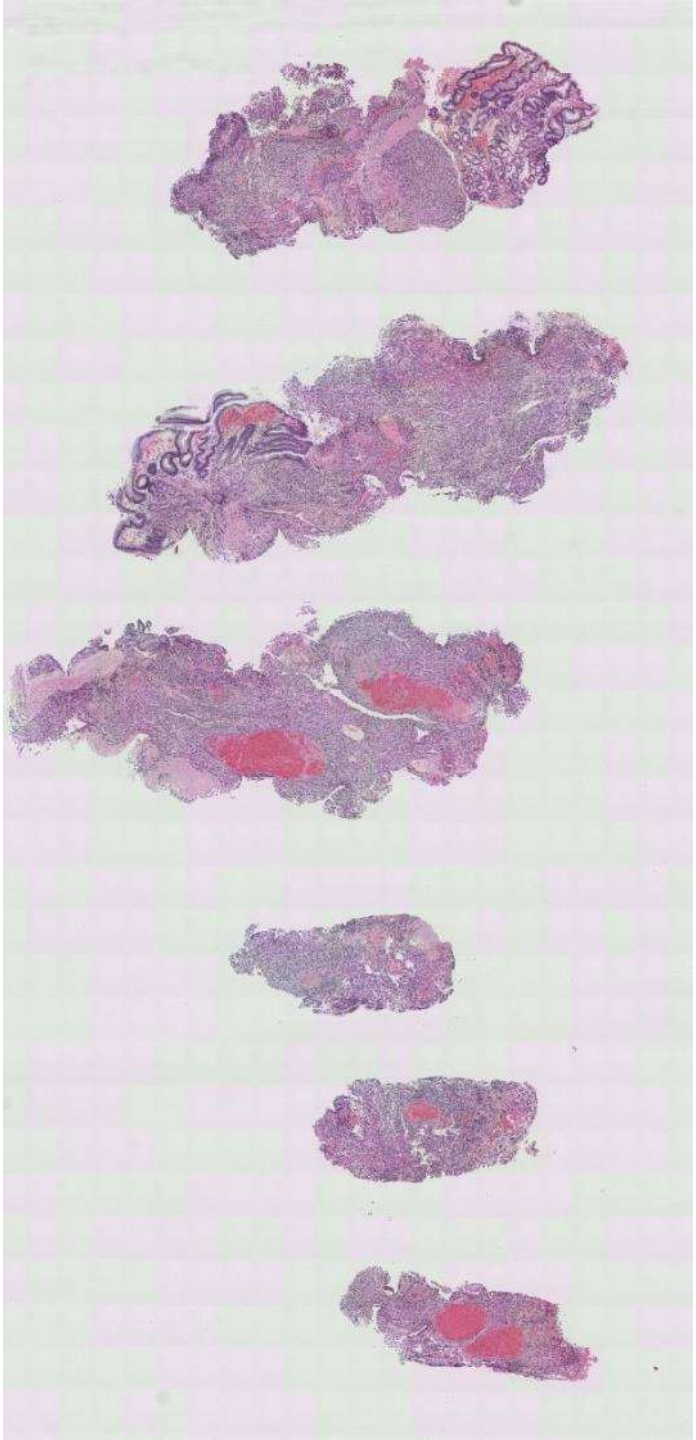
Take home points

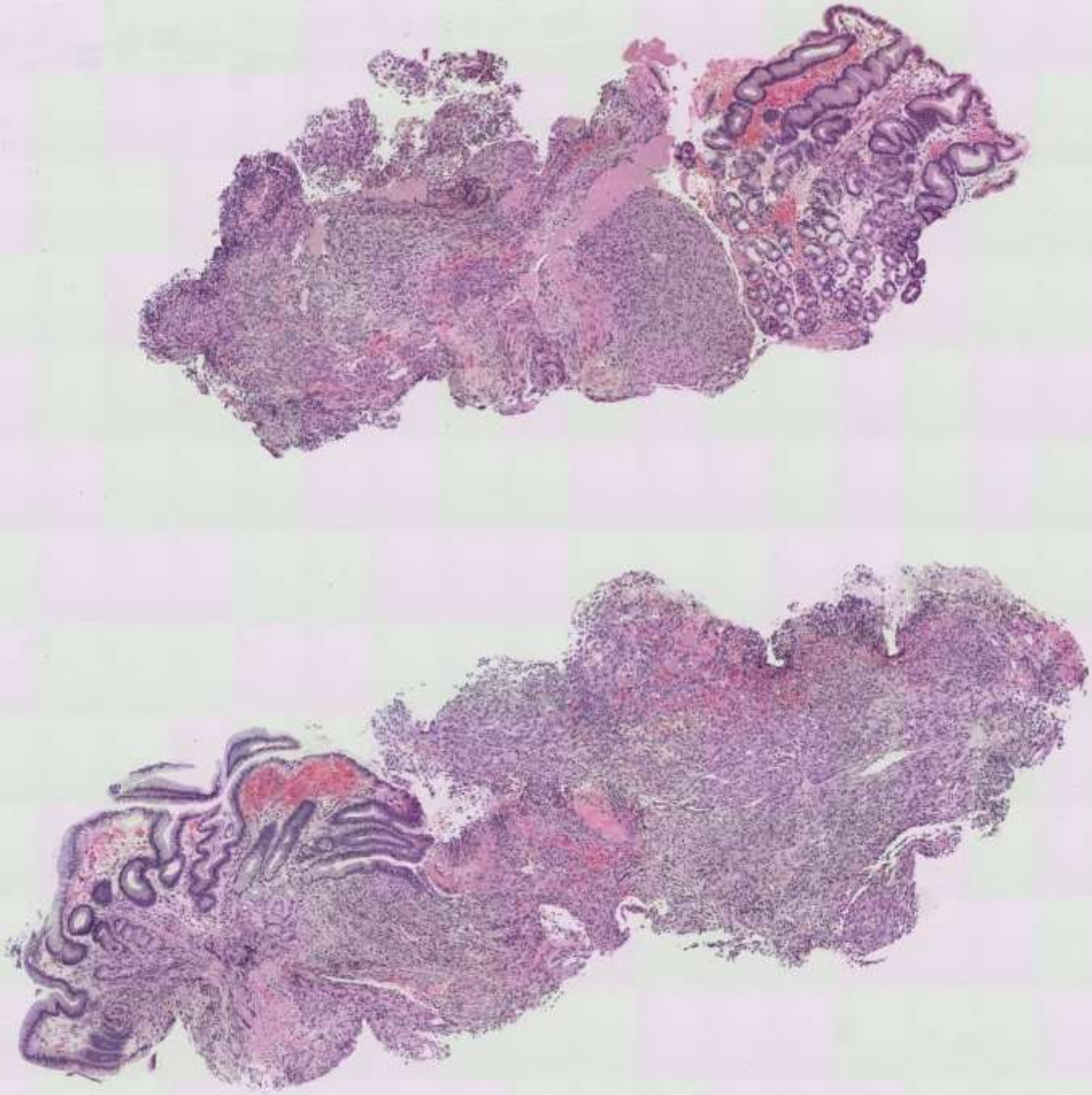
- **Urothelial carcinoma involving urachus can be:**
  - Contiguous spread bladder urothelial carcinoma
  - Separate focus concomitant to bladder urothelial carcinoma
  - Primary urachal carcinoma
- **Caution not to over-interpret urachal remnant involvement by non-invasive urothelial carcinoma as INVASION**
  - Could OVERstage!

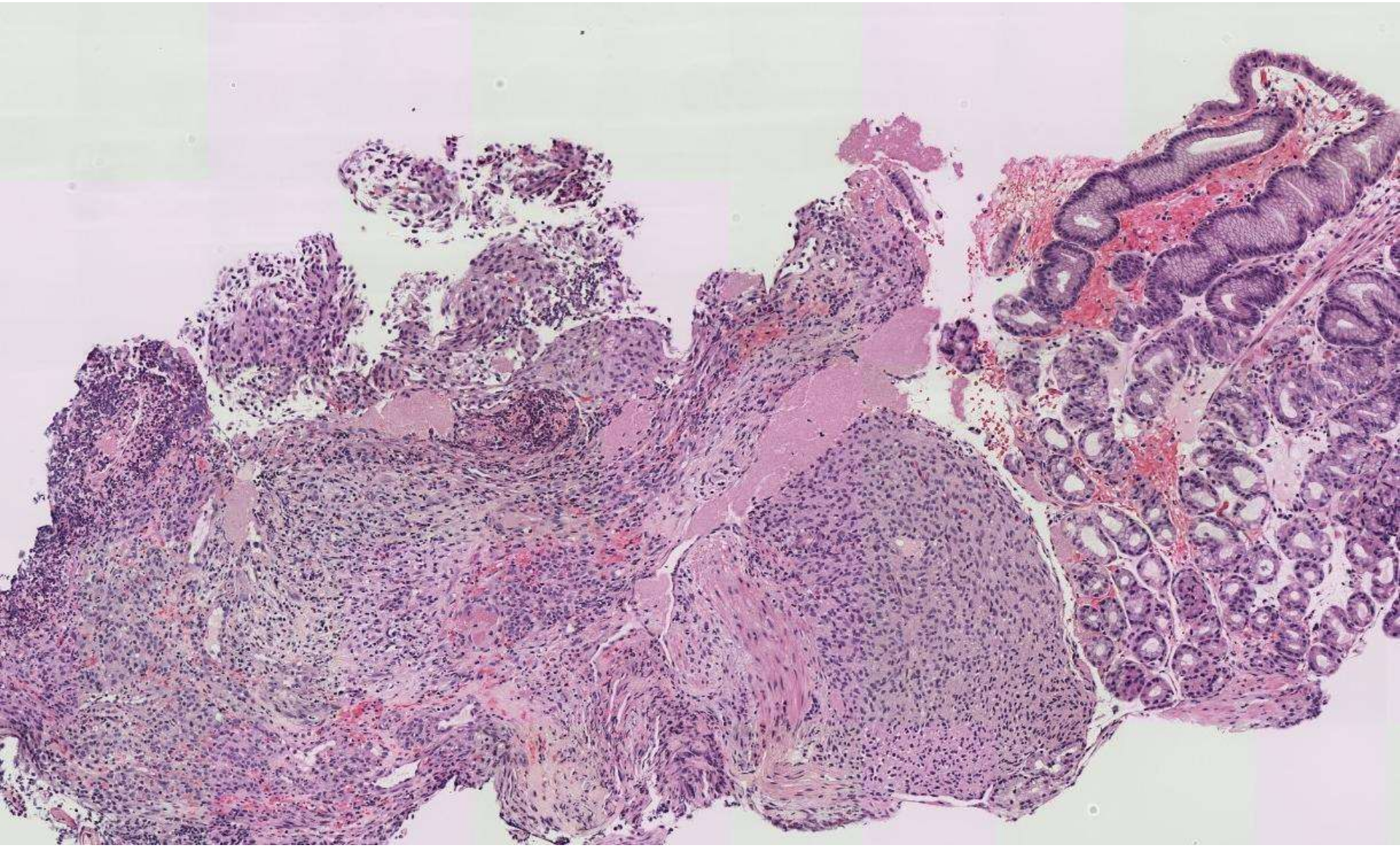
19-1107
scanned slide available!

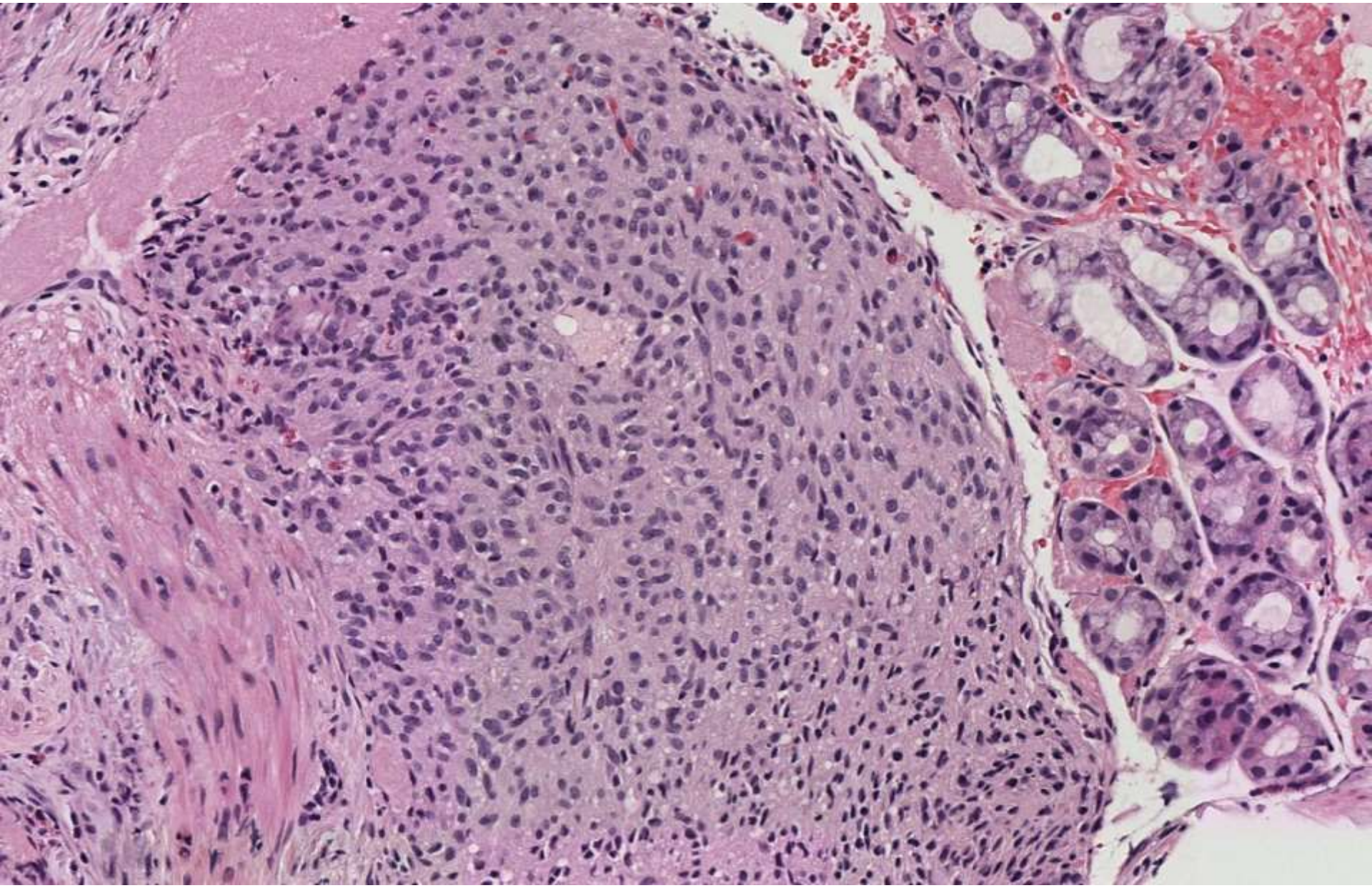
Natalie Patel; El Camino Hospital

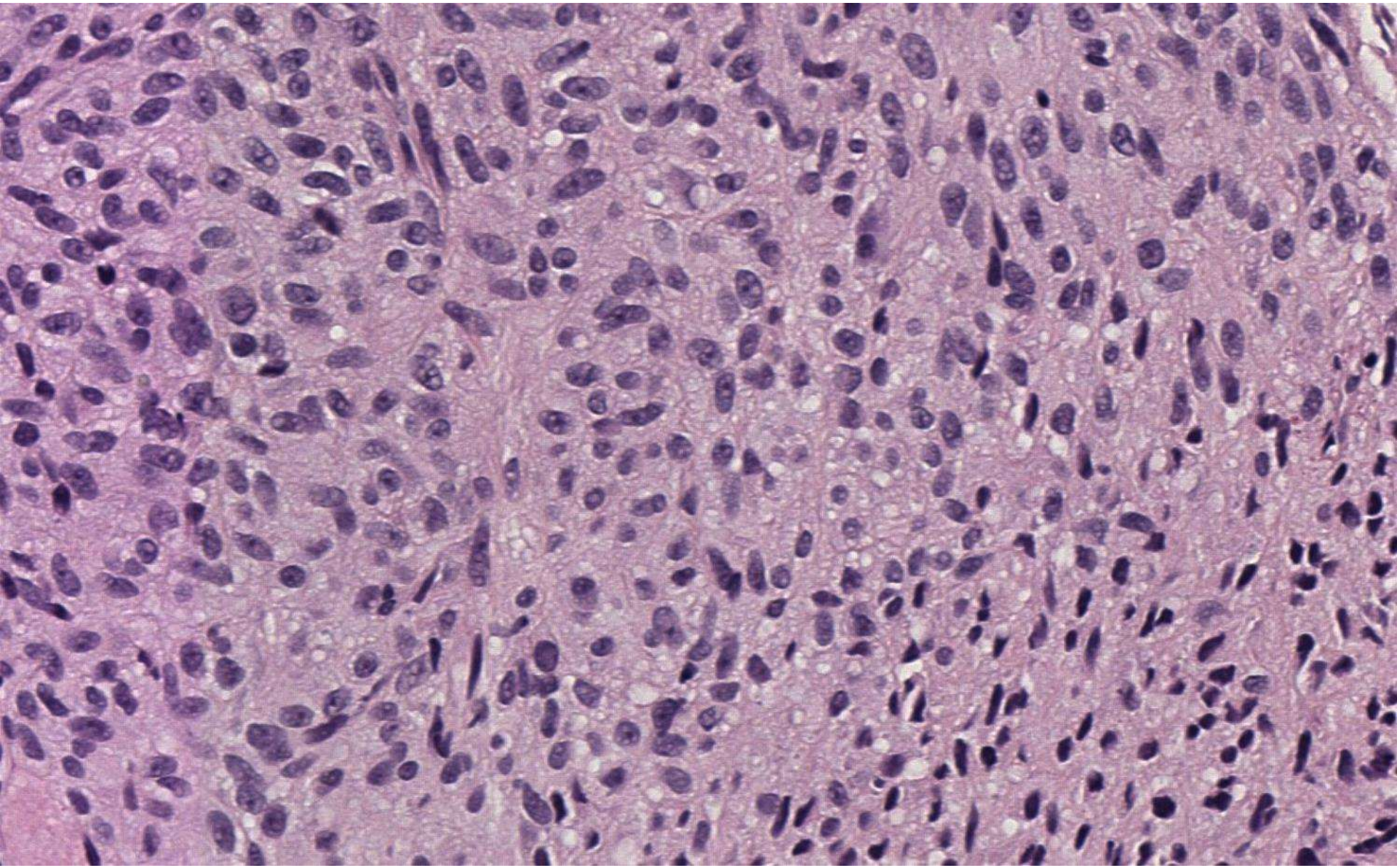
29-year-old male presents with anemia. Found to have ulcerated gastric lesion, biopsied.

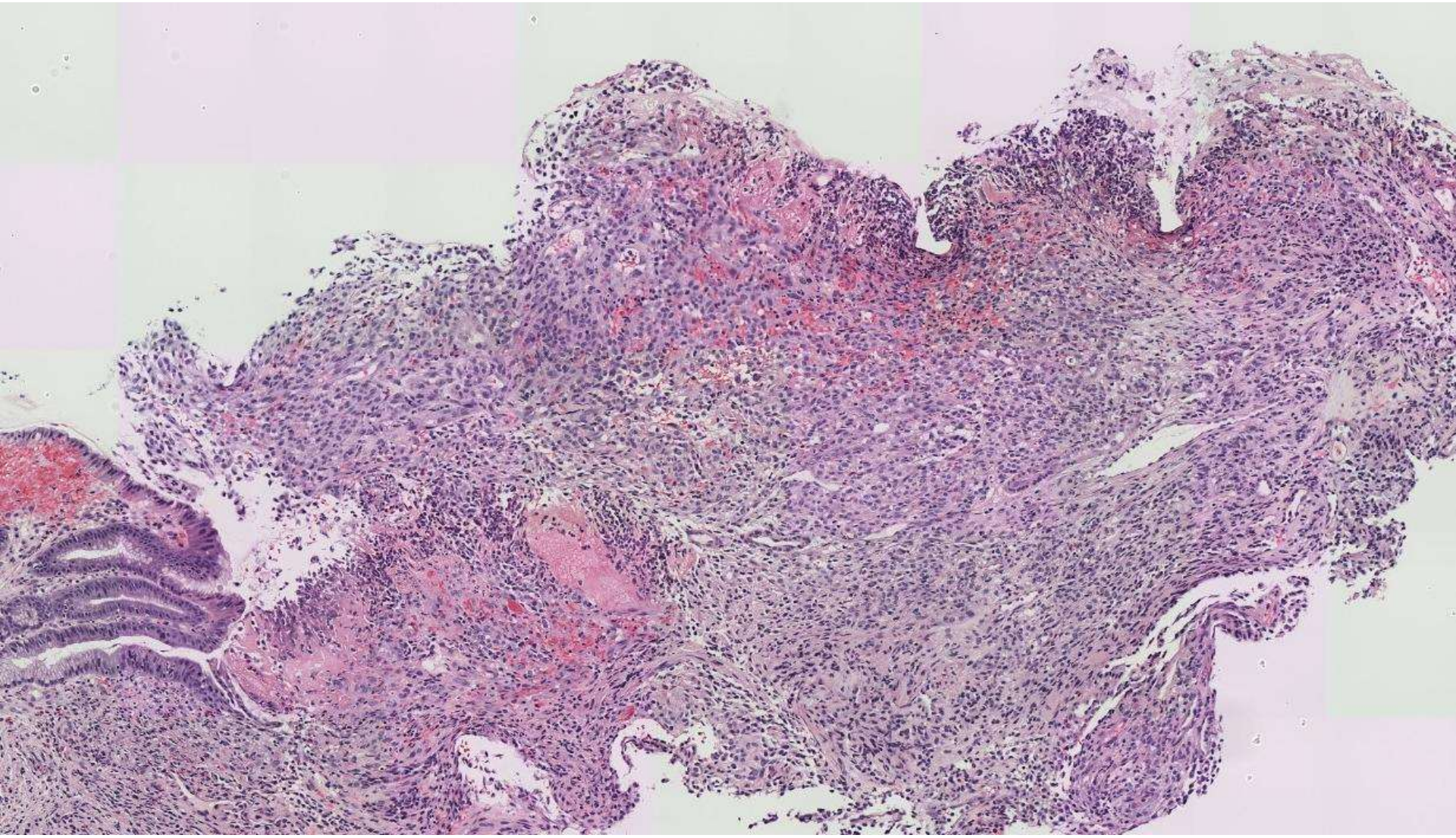


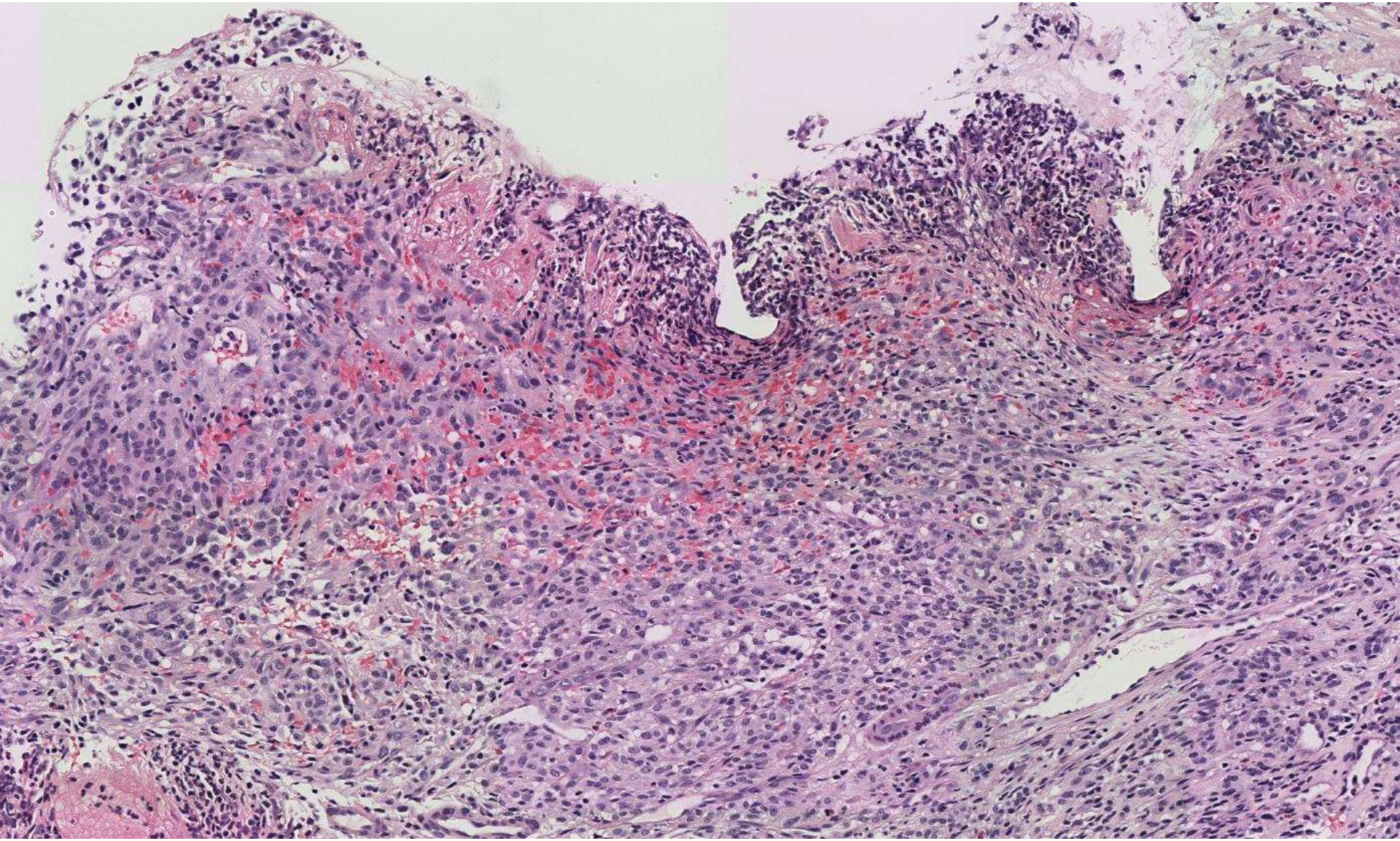


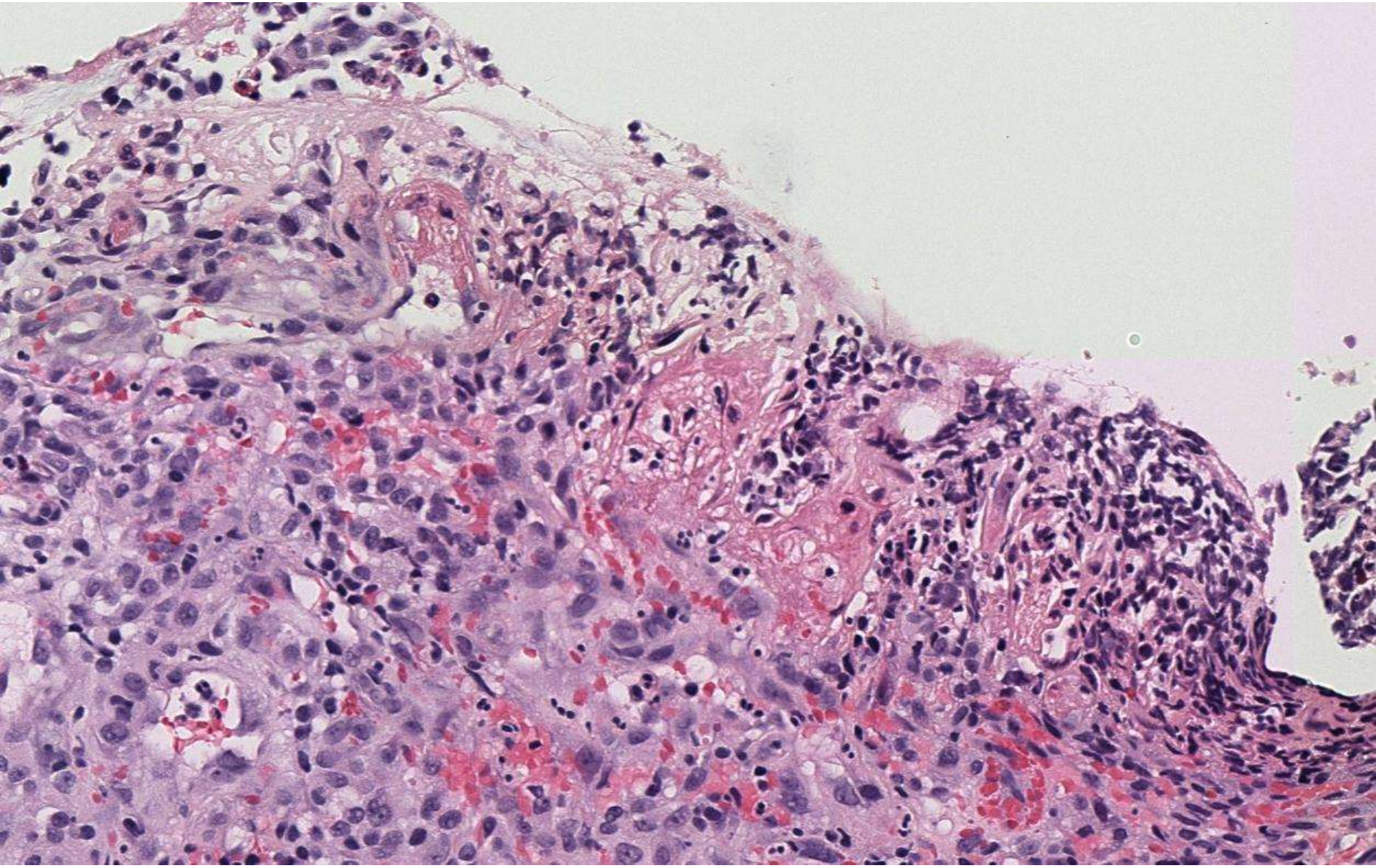


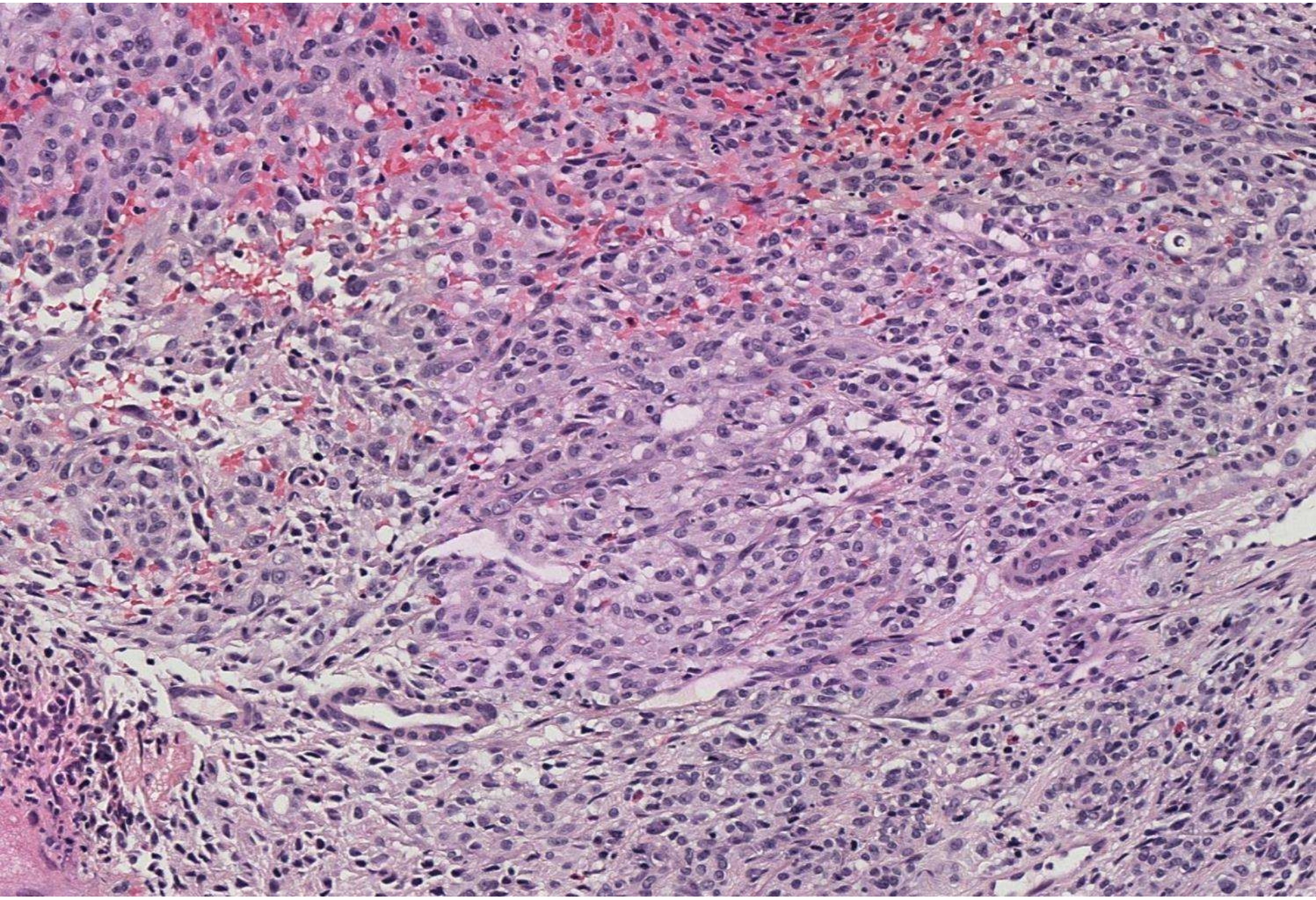


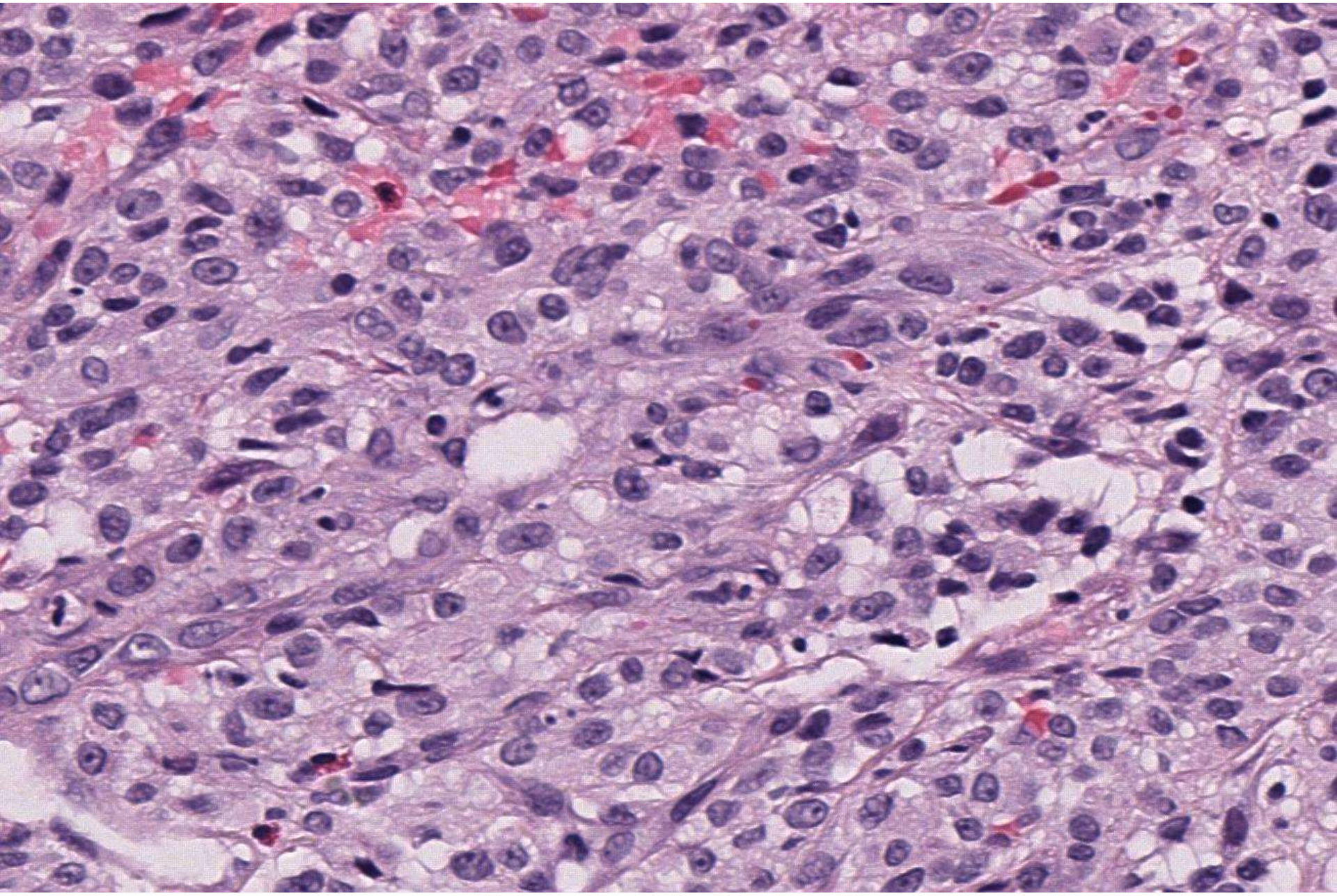


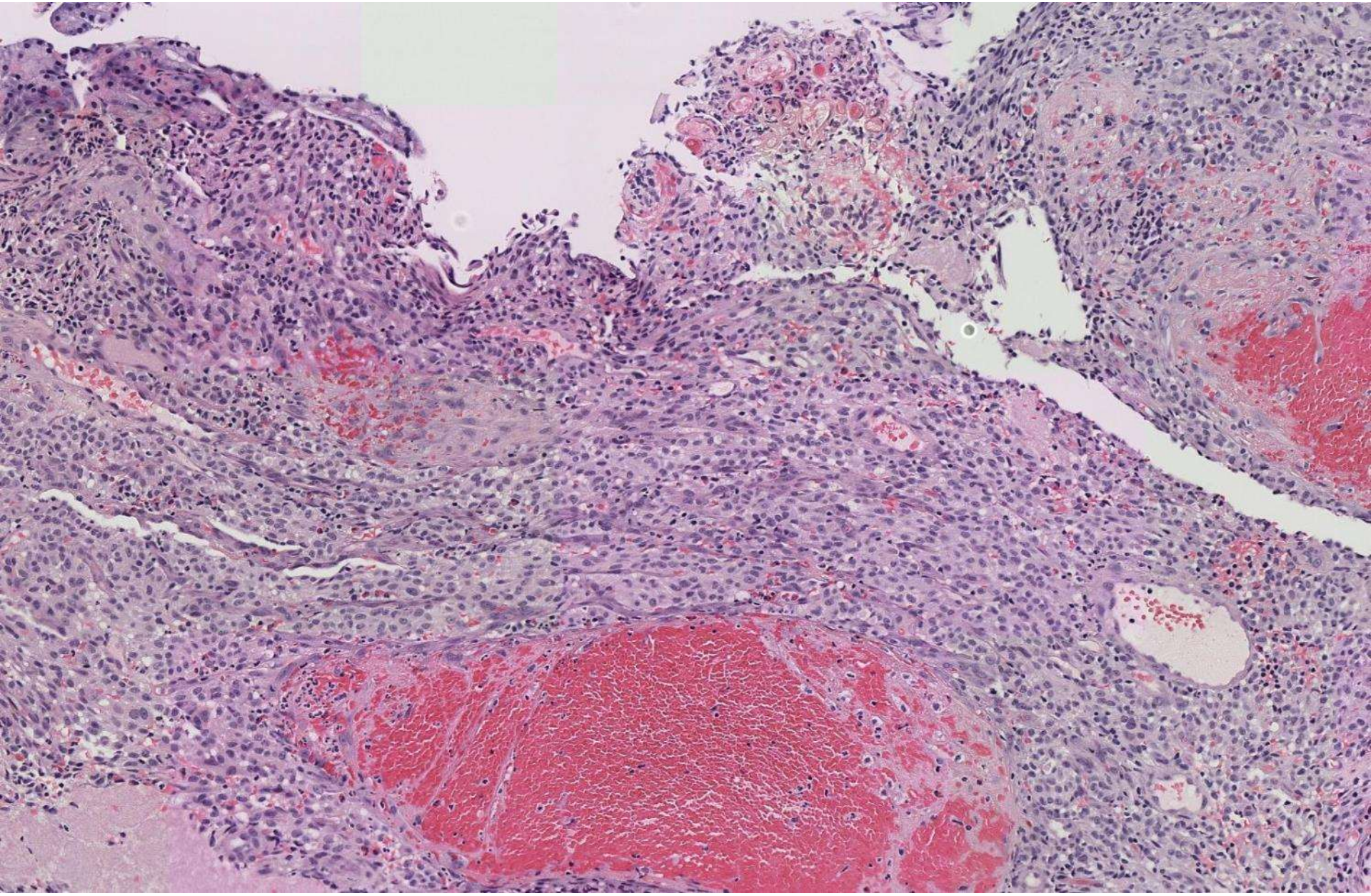


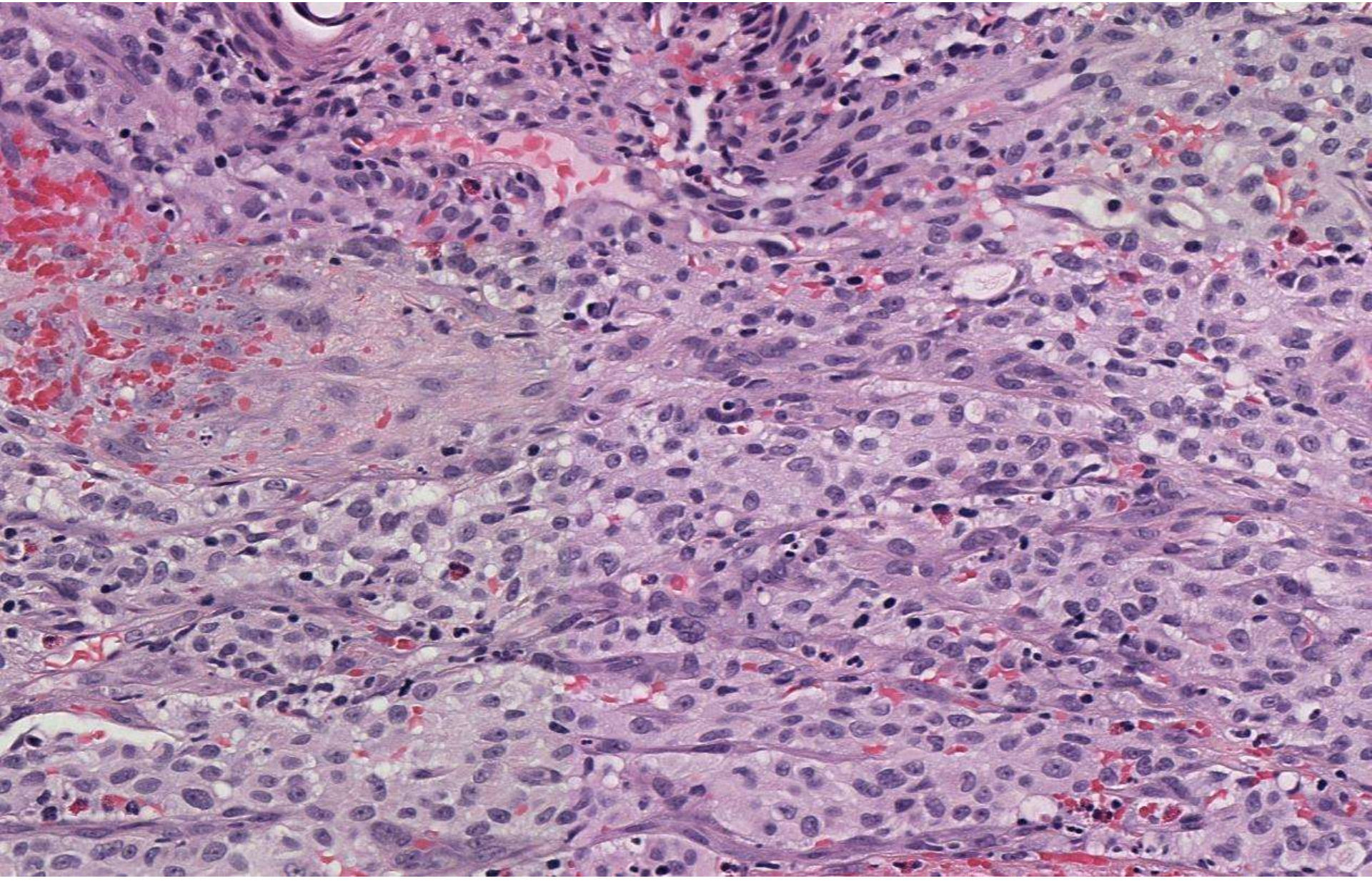












Differential Diagnosis

- GIST
- Well differentiated NET
- Glomus tumor
- Benign epithelial peripheral nerve sheath tumor
- Paraganglioma

Less likely:

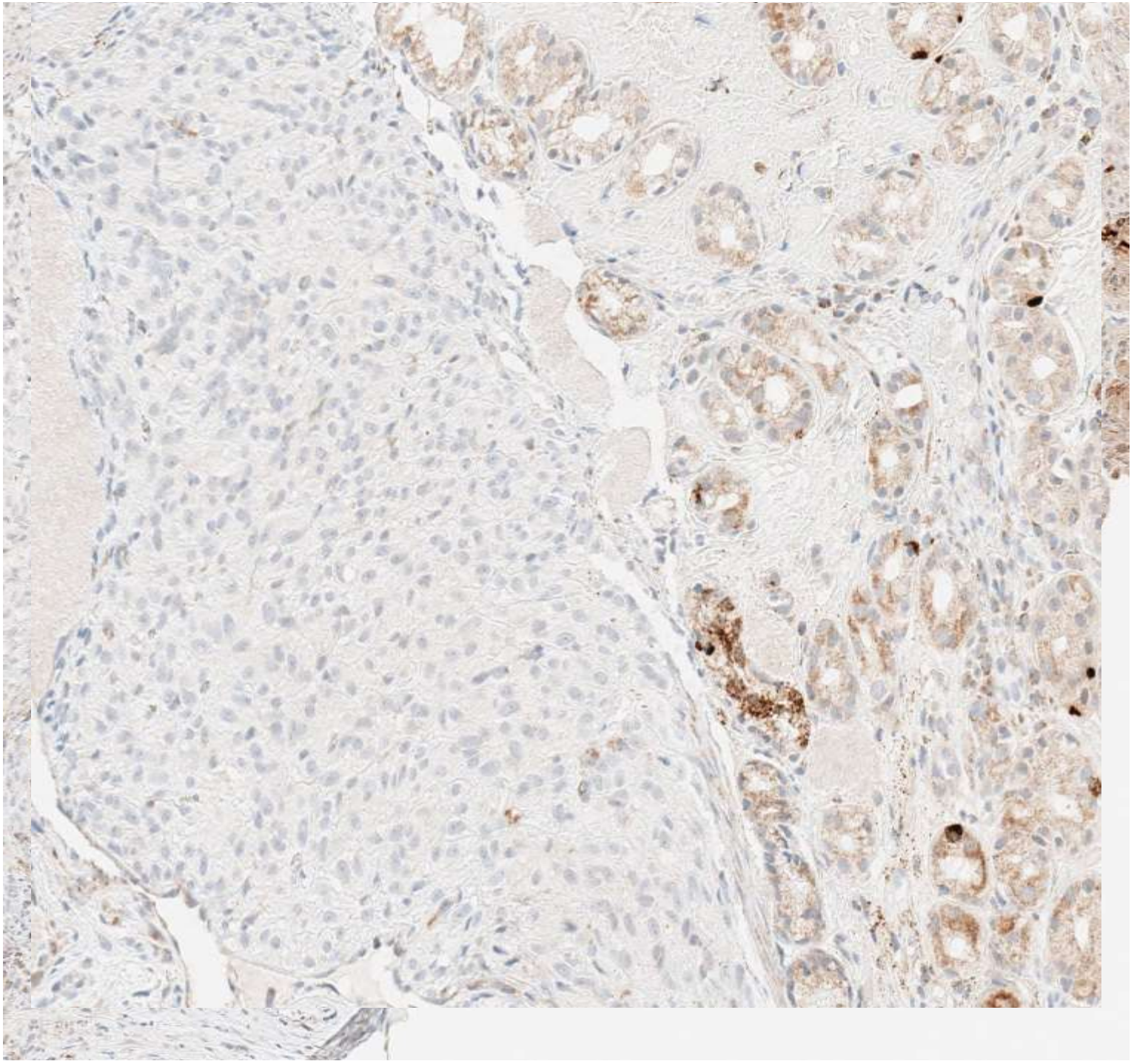
- Melanoma
- Carcinoma

Immunohistochemistry

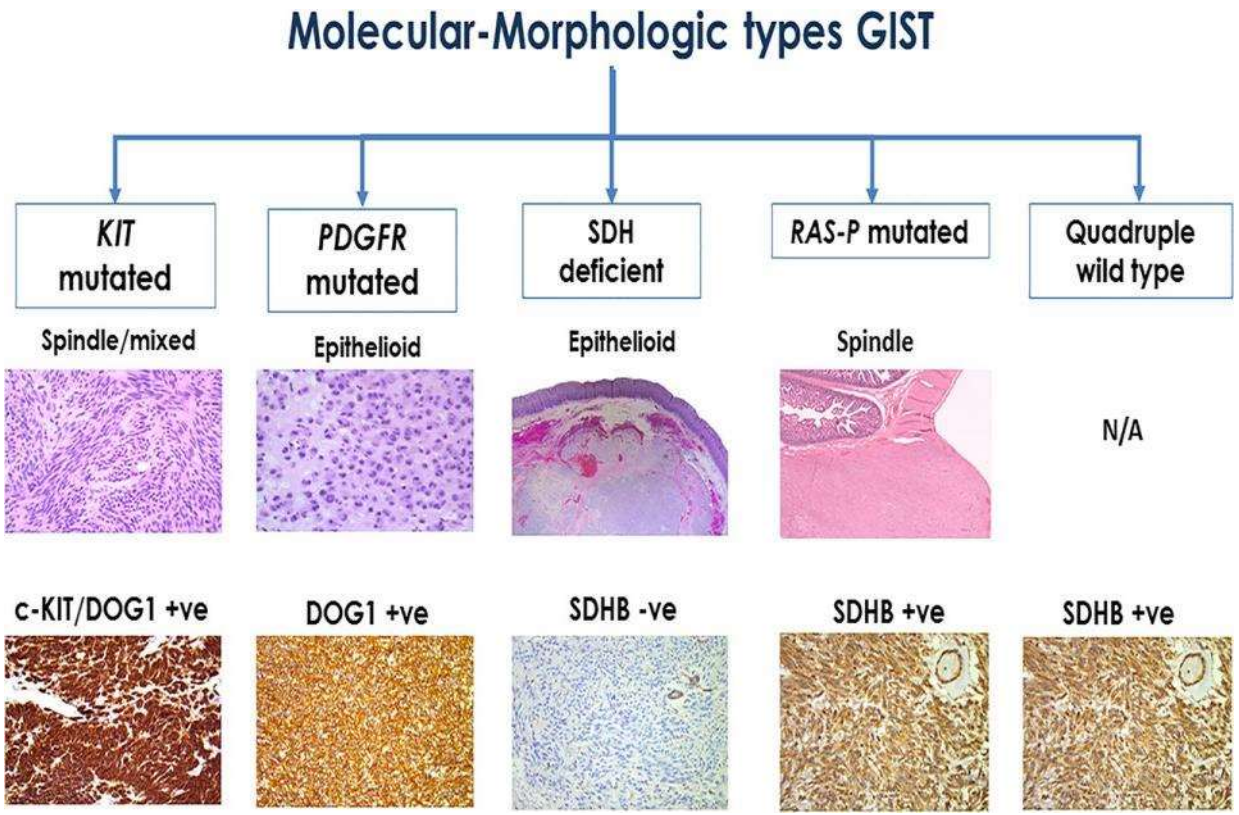
- CD117 (C-kit): Positive
- DOG-1: Positive
- CD34: Positive
- Desmin: Negative
- S-100: Negative

Molecular testing

- C-kit mutation: not detected
- PDGFRa mutation: not detected
- IHC : loss of SDHB in tumor cells, patchy retention of SDHA
  - High probability of germline SDH mutation



An algorithm demonstrating the morphological and molecular correlations in GISTs. GIST, gastrointestinal stromal tumour; PDGFR, platelet-derived growth factor receptor; SDH, succinate dehydrogenase.



Runjan Chetty, and Stefano Serra J Clin Pathol 2016;69:754-760

Molecular classification of GISTs

Kit or PDGFRa mutated (85-90%)

- SPORADIC
  - Kit mutation
    - Exon 11: 60-70%
    - Exon 9: 10-15%
  - PDGFRa mutation
    - Exon 18: 4%-5%
    - Exon 12 and 14
- SYNDROMIC
  - Familial GIST syndrome
  - PDGRa mutation

Wild type Kit/PDGRa (10-15%)

- SPORADIC
  - SDHB deficient-Pediatric and young adults (20-40%)
  - BRAF mutation (V600E): 15% of wild type GIST
- SYNDROMIC
  - NF1: multicentric, jejunum predilection
  - Carney's triad: Multicentric, gastric epithelioid GIST
    - Paraganglioma, pulmonary chondroma---Sporadic
  - Carney-Stratakis Syndrome: GIST and paraganglioma
    - Germline mut

SDHB-deficient GISTS

- Almost exclusively in children or young adults
- Female > Male
- Gastric location (distal/antral)
- Despite mets, survival is long compared to typical GISTs
- Size and mitotic rate have **no role** in clinical behavior
- Resistant to imatinib, but greater sensitivity to second line agents

Morphologic features of SDH-Deficient GISTs

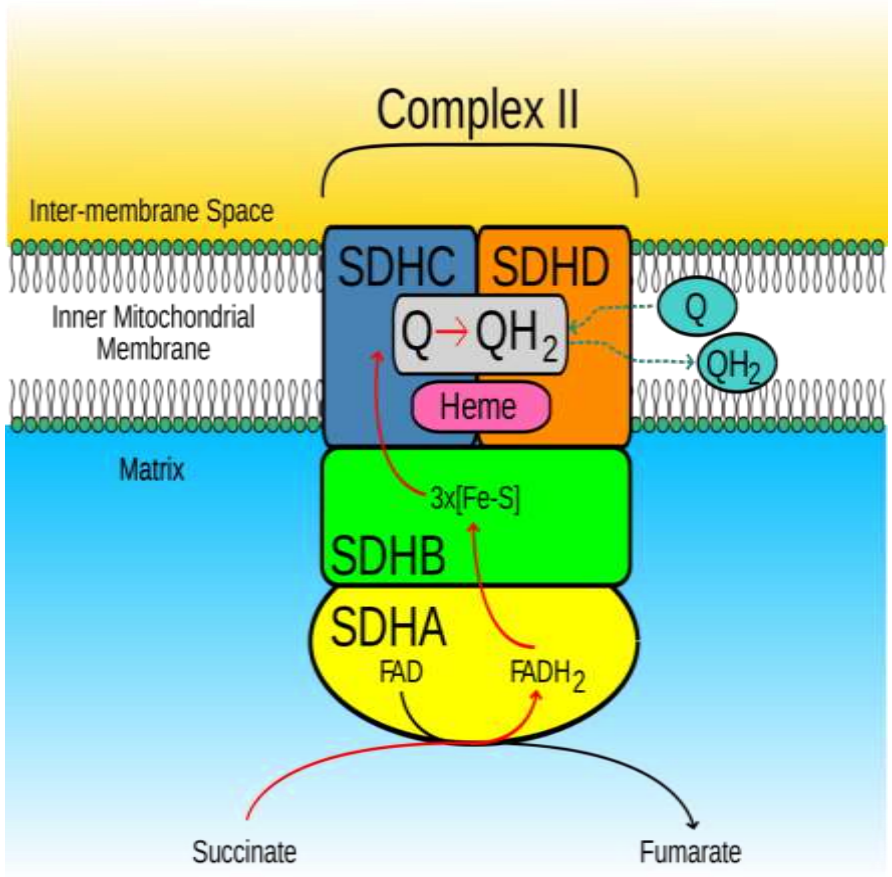
- Multicentric and/or multinodular with plexiform growth pattern/ dumb-bell shaped
- Epithelioid or mixed spindle/epitheloid
- Frequently have LVI and lymph node mets
- Mucosal ulceration
- Indolent
- Ckit and DOG-1 positive

SDH deficient GISTS

- Germline and/or somatic loss-of-function mutations in **any of the four** constituents of the SDH complex
  - Resulting in inactivation of both alleles
- In some cases mechanism of inactivation maybe epigenetic

- Most frequently mutated is SDHA (30%)
- Mutations of SDHB, SDHC and SDHD (20%)
- Mutation in any subunit results in :
- SDHC epimutations resulting in promoter hypermethylation (50%)
- ↑ succinate → overexpressed IGFR1 → HIF-1-VEGF → growth

The succinate dehydrogenase (SDH) family consists of a tetrad of subunits.



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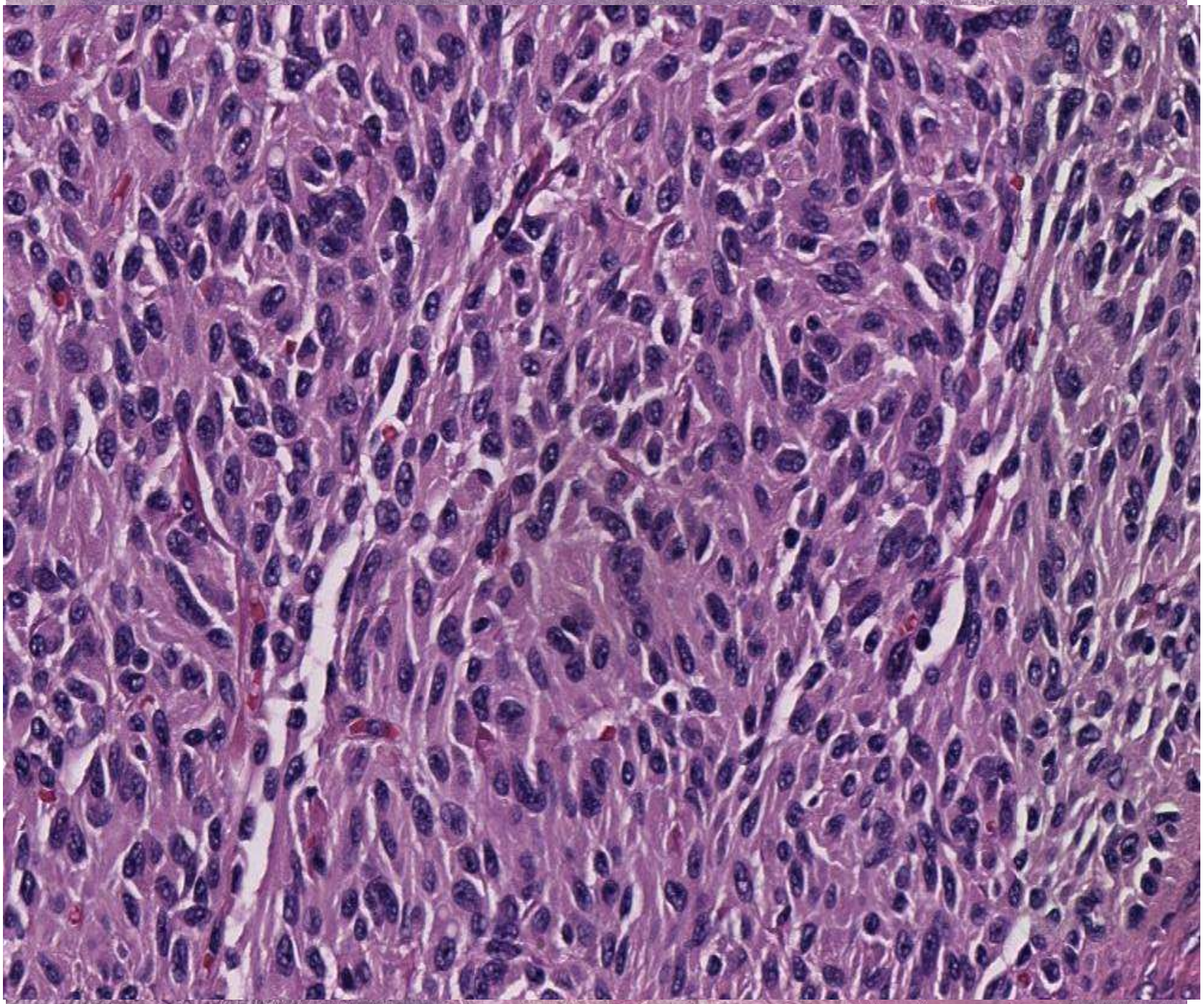
- Associated with 4 subgroups:
  - 1. Carney's triad
  - 2. Carney-Stratakis syndrome
    - Germline mutations in SDHB and SDHC or inactivating mutations in SDHD
  - 3. Pediatric GIST
  - 4. Sporadic GIST in young adults



Use of IHC as screening

- SDHB and SDHA – **normal staining:** granular and cytoplasmic
- If any subunits of SDH complex is lost →SDHB degradation
- Loss of SDHB staining = inactivation of SDHA, SDHB, SDHC, SDHD
- Loss of SDHA = mutated SDHA
- Intact SDHA = may still have SDHA mutation (nonfunctional protein expression); therefore best to have both as screening

Take home points

- C-kit and PDGFRa Negative → Syndromic or other mutations
  - (SDHB deficient GISTS, NF-1, BRAF mutated)
- Morphology and clinical info can be a clue
- Negative IHCs for SDHA and SDHB diagnostic of SDH deficient GISTs
- Unknown mutated GISTs (C-kit/PDGFRa, SDH/RAS-P) wild type GISTS, 5%

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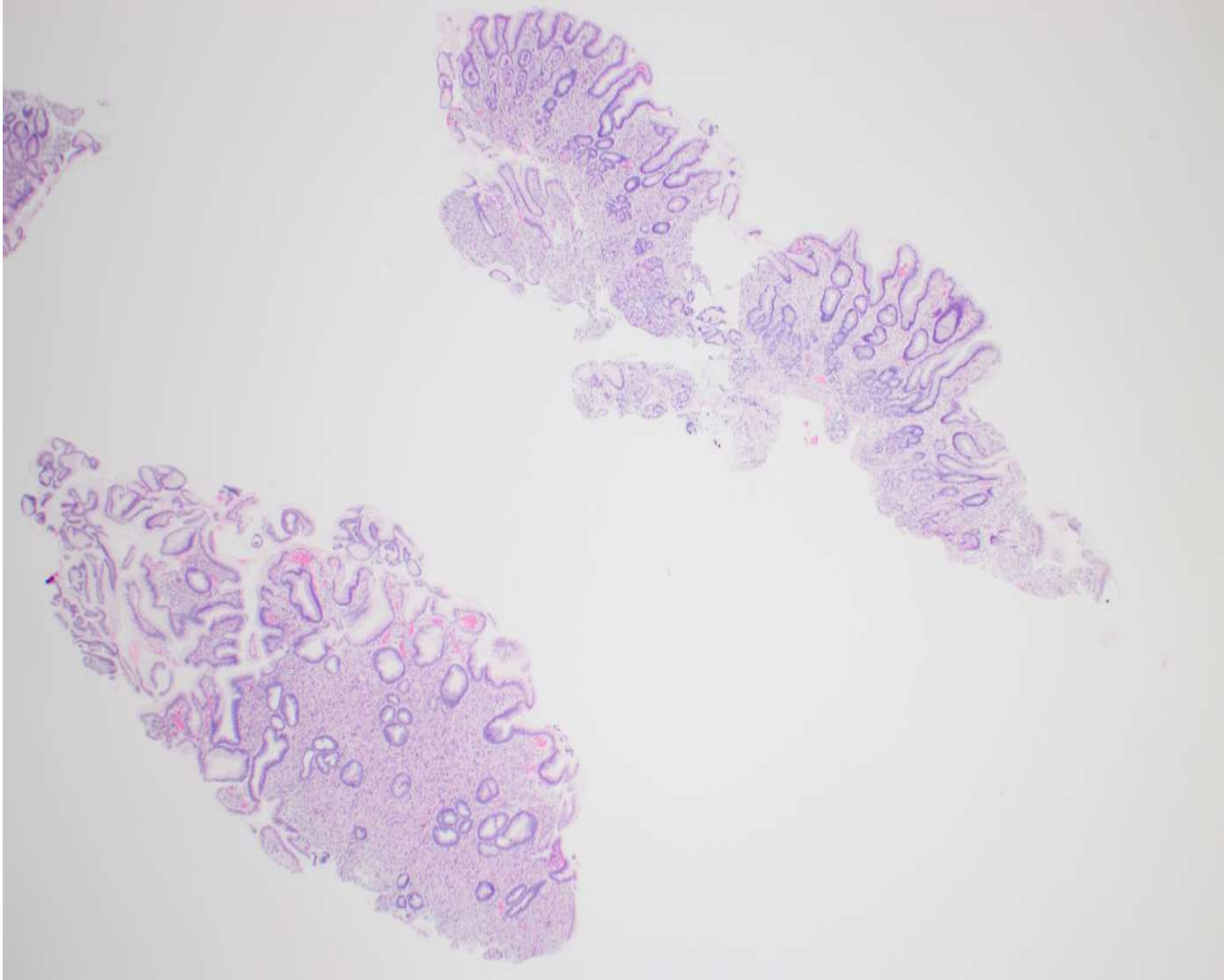
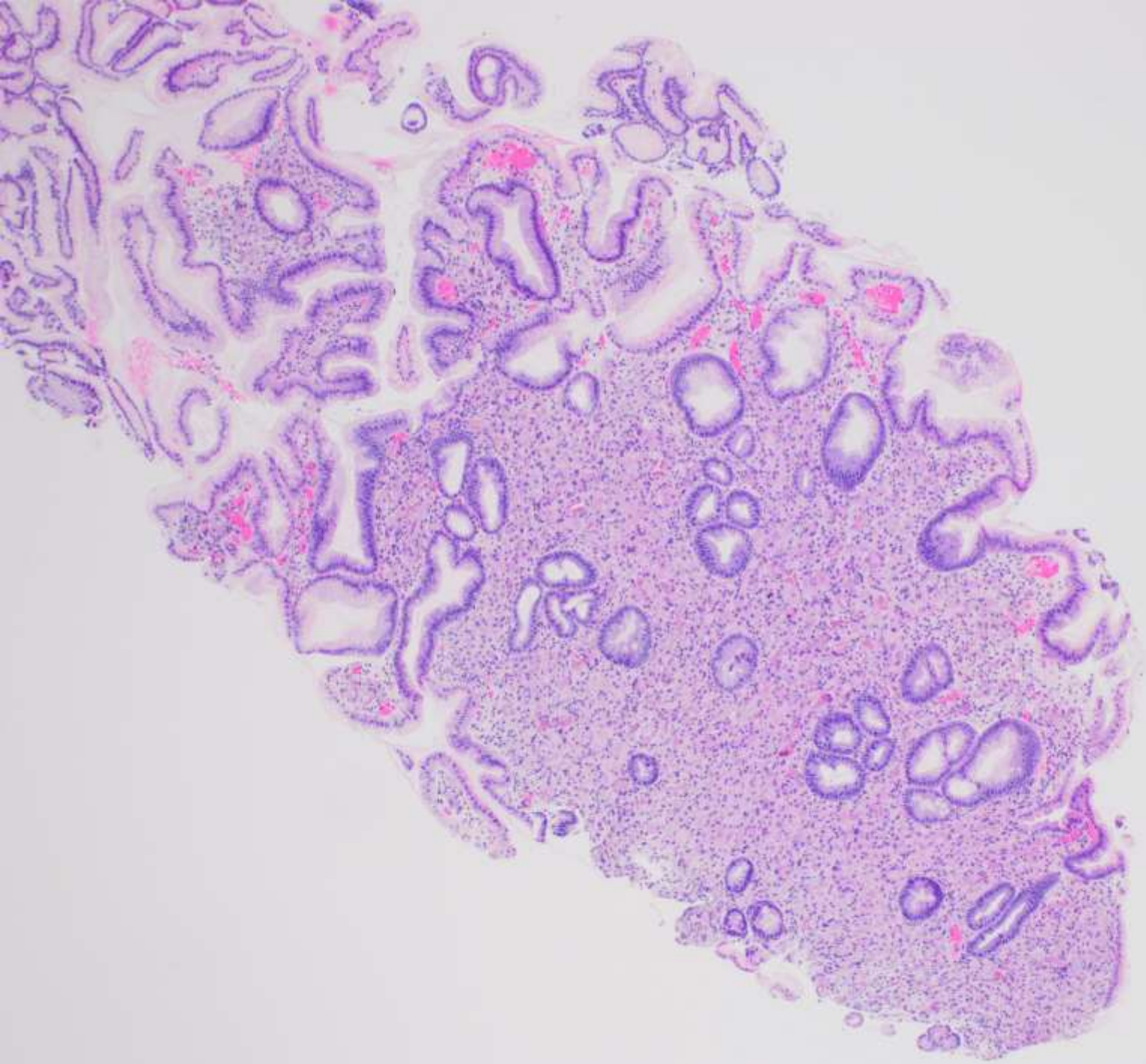
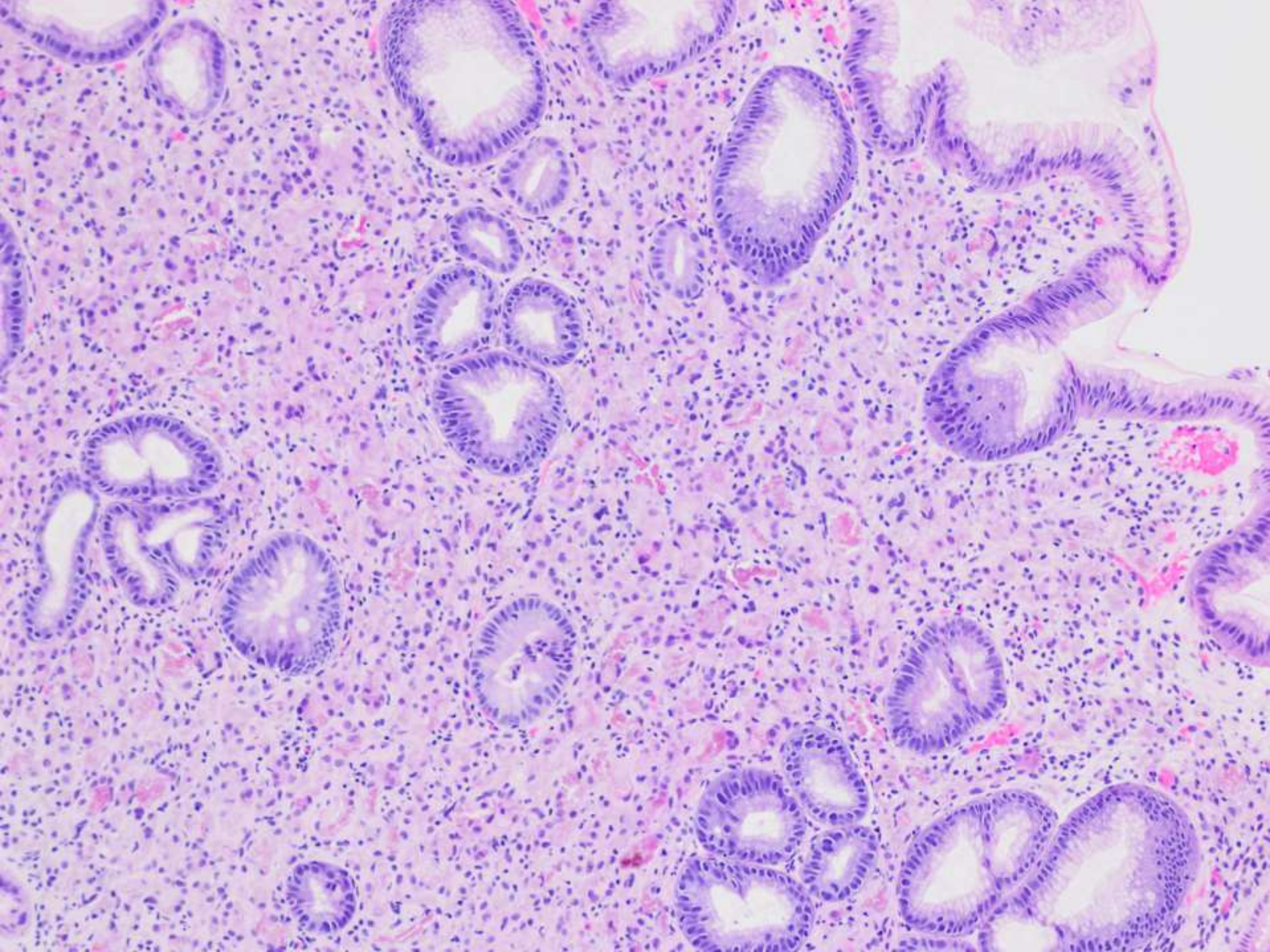
19-1108

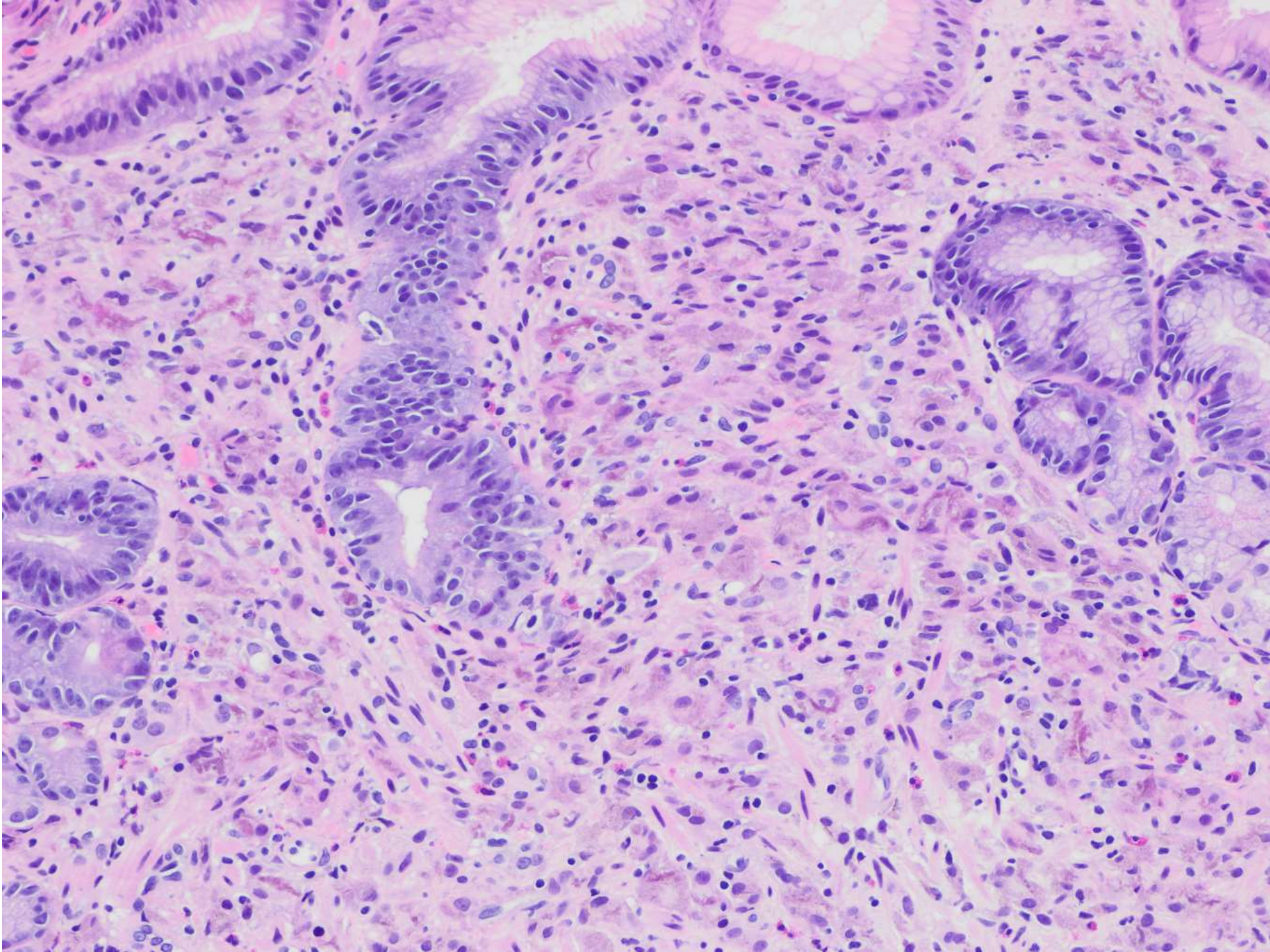
Tyler Janowski/Sarah Umetsu; UCSF

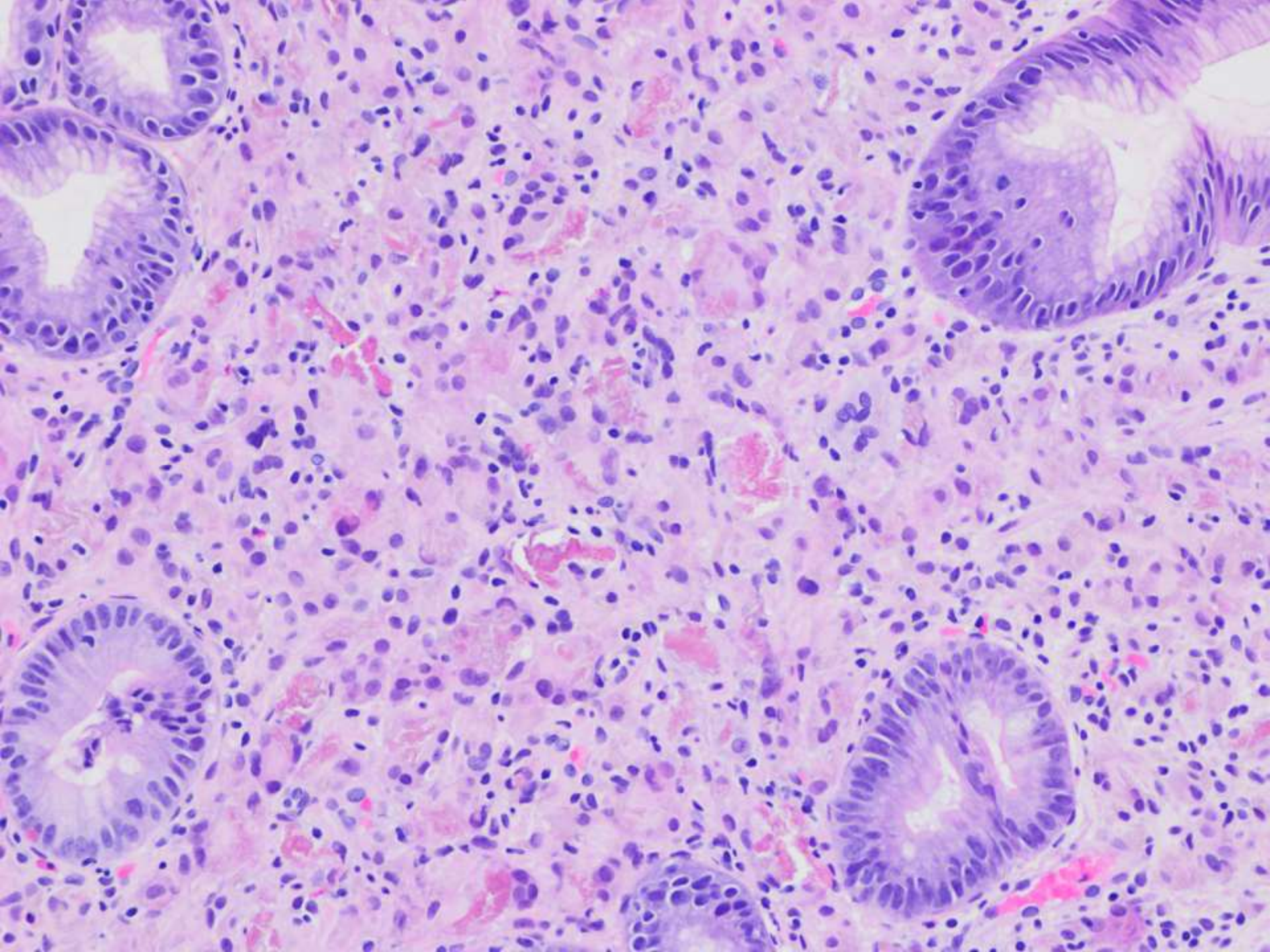
58-year-old male with h/o chronic kidney disease, on dialysis, presents with dysphagia and noted to have a thickening of the distal esophagus on CT. Biopsy performed.

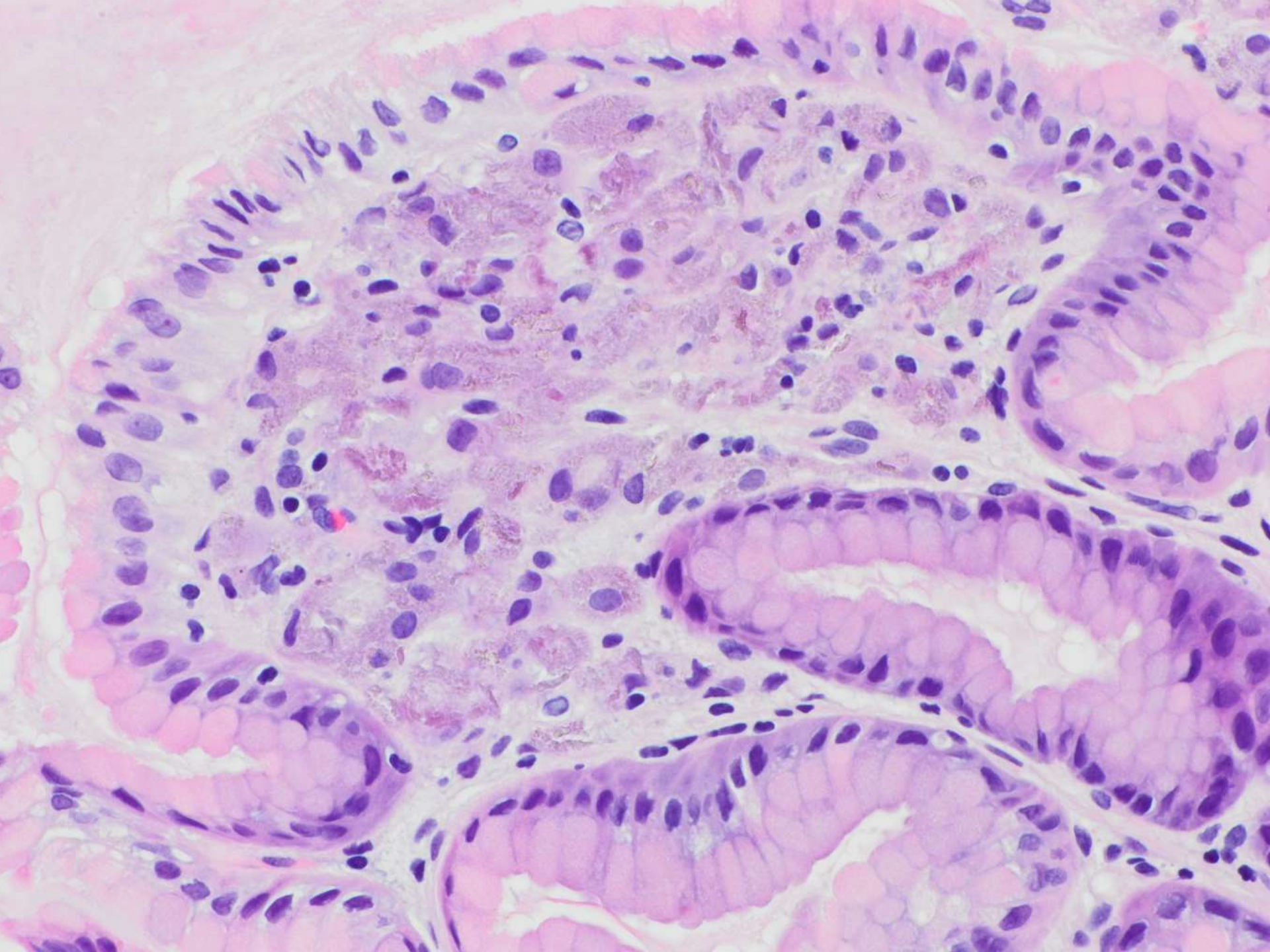












Final Diagnosis

- **Gastric ulcer, biopsy:** Gastric mucosa with foreign material and prominent histiocyte accumulation in the lamina propria; see comment.
- **Comment:** …given the morphologic features of the mineral-like material and the prominent histiocytic accumulation, the features are most consistent with *Lanthanum deposition.*

Histopathology

Histopathology 2017, **70**, 1072–1078. DOI: 10.1111/his.13178

Lanthanum deposition from oral lanthanum carbonate in the upper gastrointestinal tract

Raza S Hoda,[1] Soma Sanyal,[2] Jerrold L Abraham,[2] Jamie M Everett,[1,*] Gregory L Hundemer,[3] Eric Yee,[4,†] Gregory Y Lauwers,[1,‡] Nina Tolkoff-Rubin[3] & Joseph Misdraji[1]

[1]*Department of Pathology, Massachusetts General Hospital, Boston, MA,* [2]*Department of Pathology, SUNY Upstate Medical University, Syracuse, NY,* [3]*Department of Medicine, Nephrology Service, Massachusetts General Hospital, and* [4]*Department of Pathology, Beth Israel Beth Israel Deaconess Medical Center, Boston, MA, USA*

Peculiar Histiocytic Lesions With Massive Lanthanum Deposition in Dialysis Patients Treated With Lanthanum Carbonate

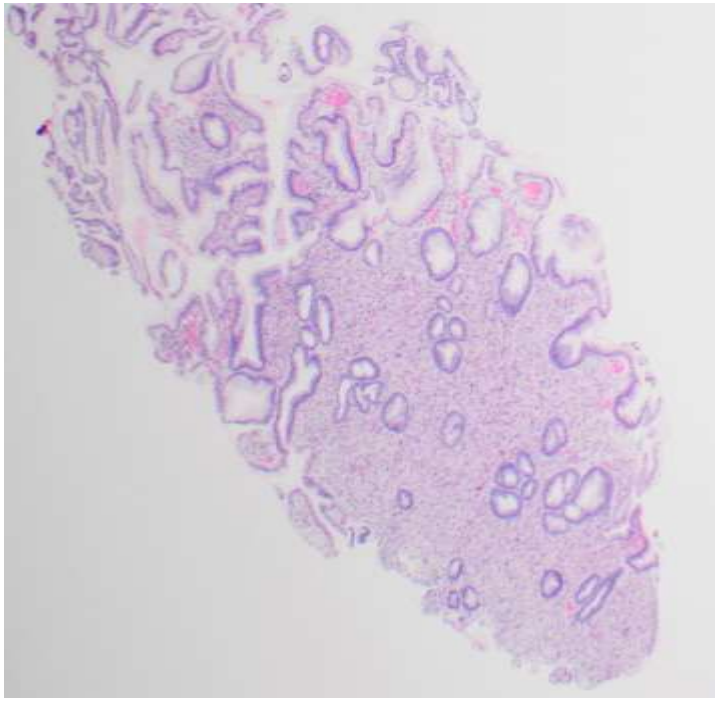
Joji Haratake, MD, PhD, Chikao Yasunaga, MD, PhD,† Akifumi Ootani, MD, PhD,‡ Shohei Shimajiri, MD, PhD,§ Atsuji Matsuyama, MD, PhD,§ and Masanori Hisaoka, MD, PhD‖*

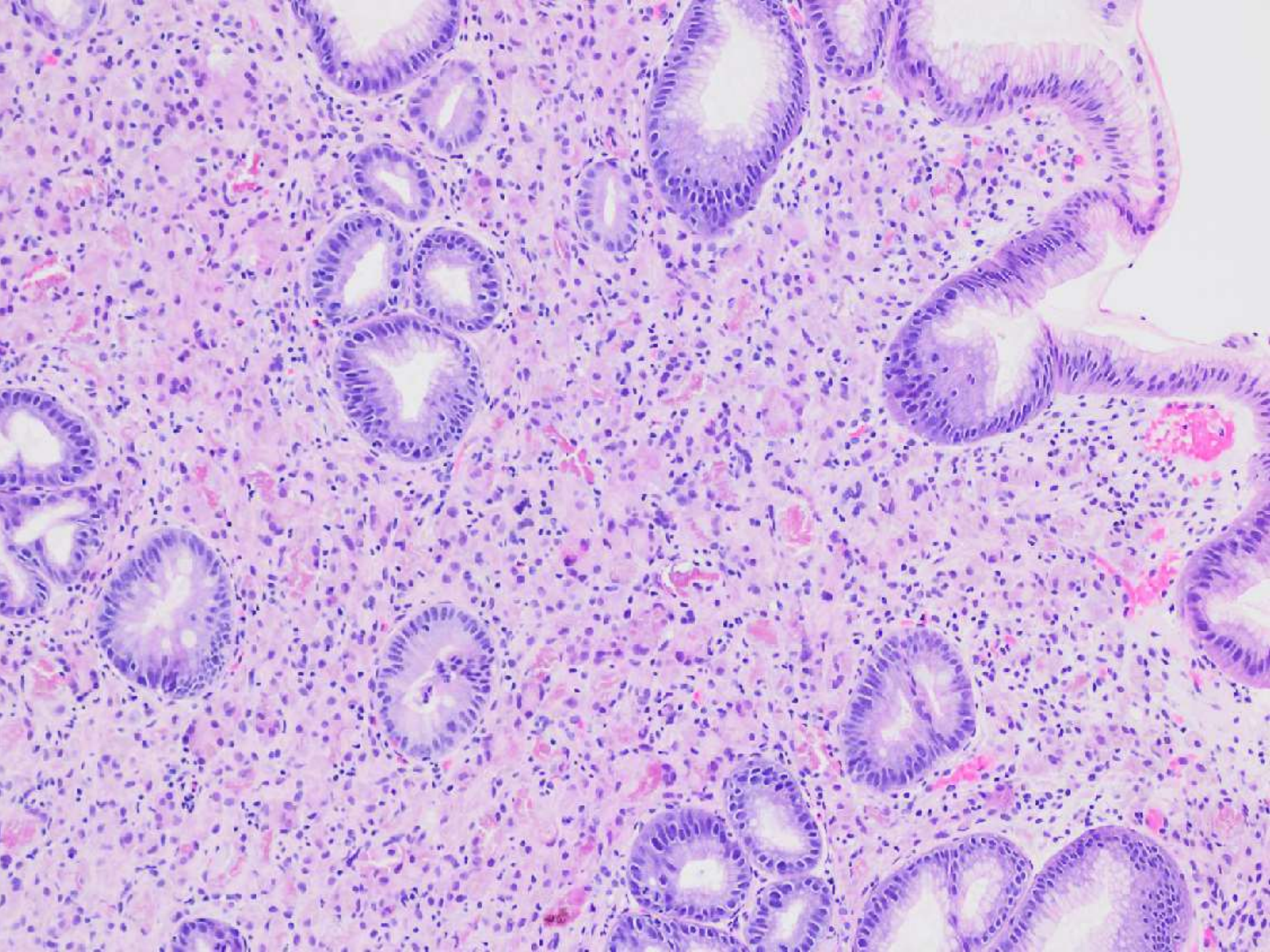
Lanthanum carbon

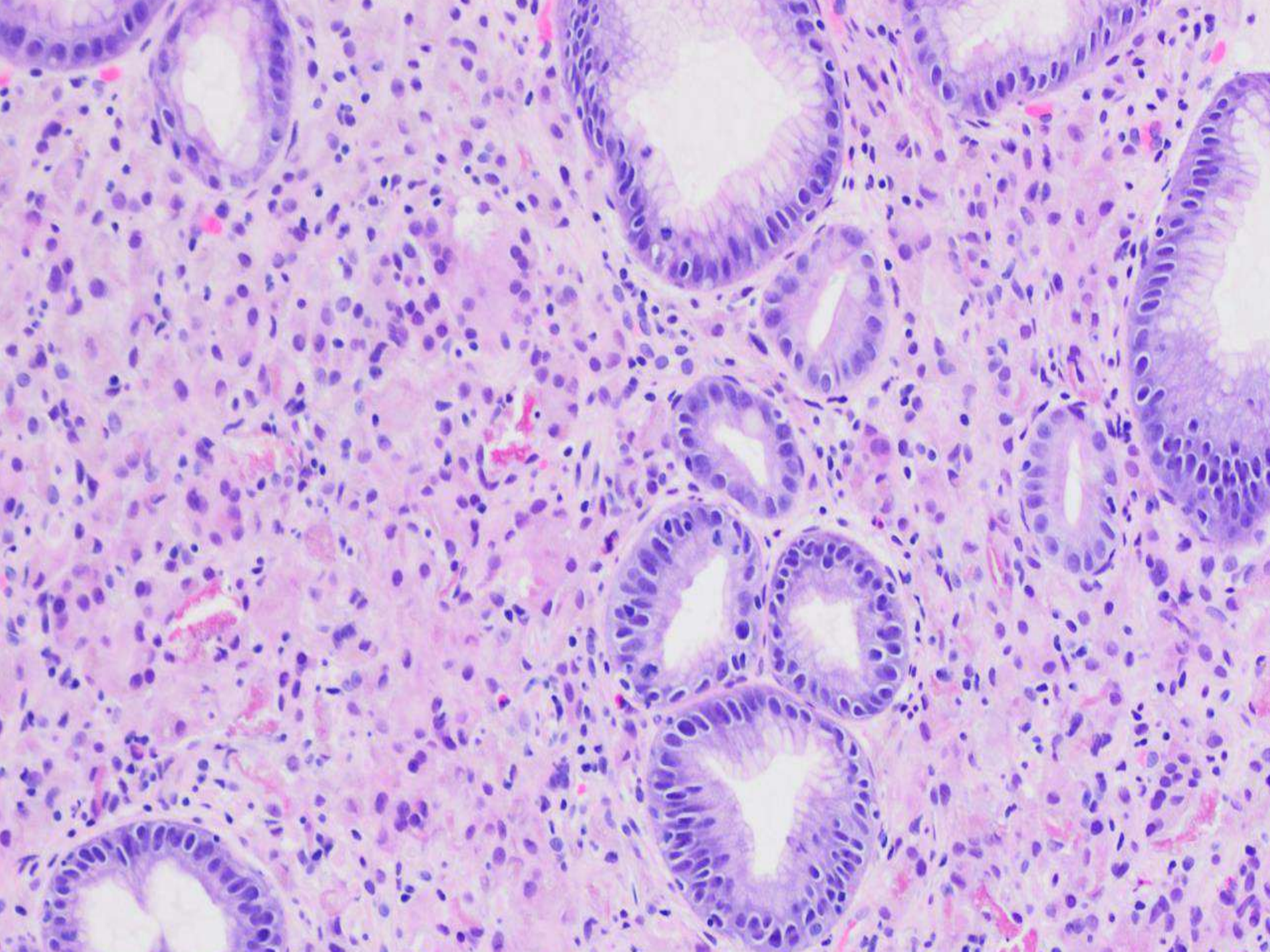
- Orally administered, non-calcium based phosphate binder
  - Used to treat hyperphosphatemia in patients with CKD/Dialysis
  - Absorbed and excreted through the GI tract
    - Relatively poor uptake and can deposit elsewhere….bones, liver, nodes, etc.
- Clinical symptoms are vague
  - Nausea, vomiting, dysphagia, reflux
- Endoscopic findings non-specific
  - Gastritis, erosions/ulceration, gastric polyps, duodenal involvement

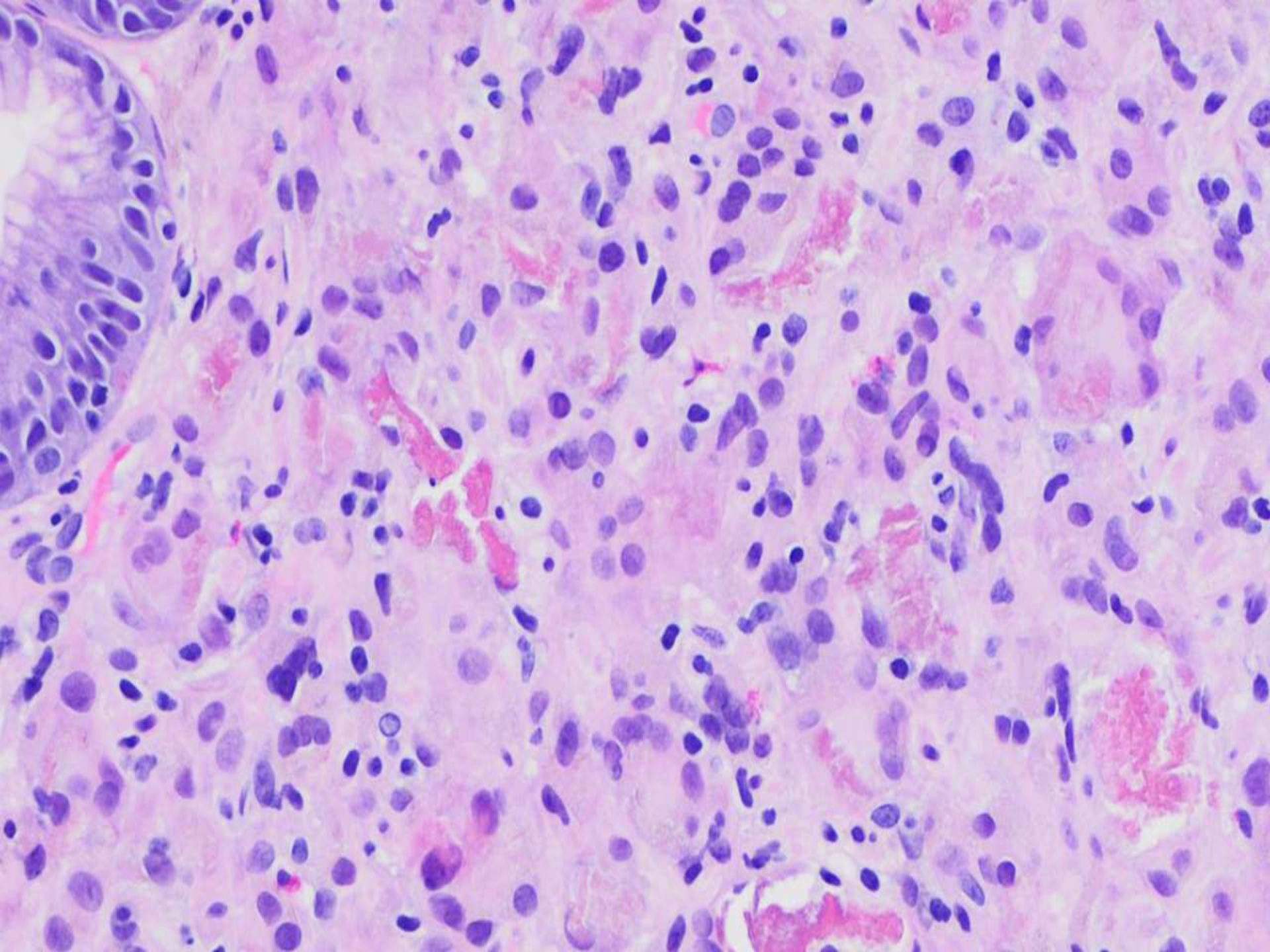
Histology

- Histiocytic accumulation of amphophilic granular material within the lamina propria, just below the surface epithelium.
- Positive for:
  - PAS
  - PAS-D
  - Iron (in some cases)
- Negative for:
  - VonKossa
  - GMS
  - Fite







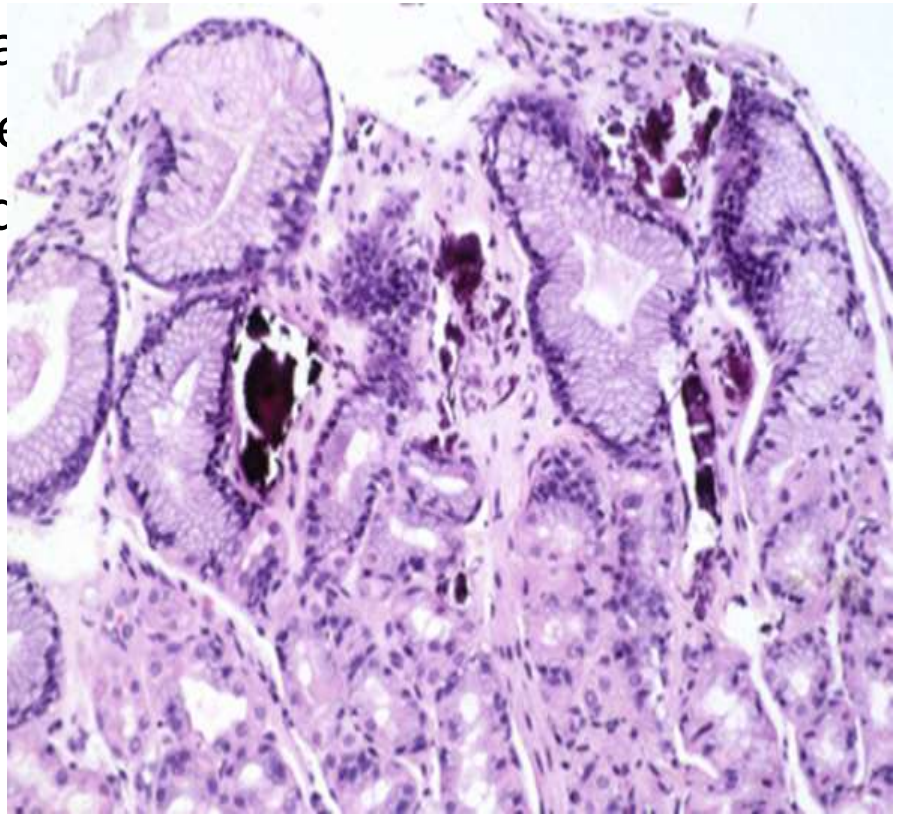


Differential Diagnosis

- Gastric mucosal calcinosis
- Iron-pill gastritis
- Polystyrene
- Bile acid sequestrants
- Infection

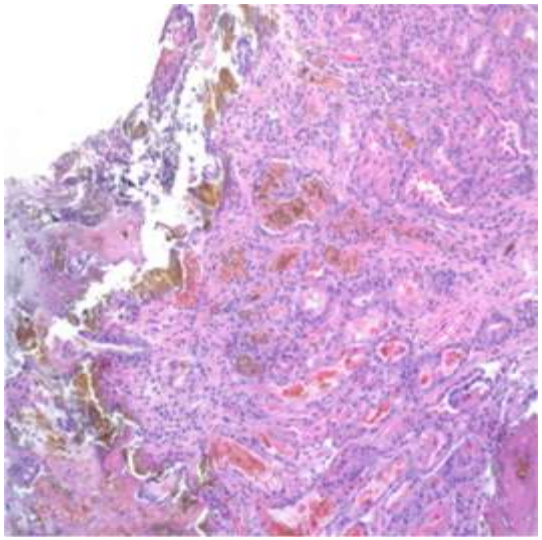
Why it is not…

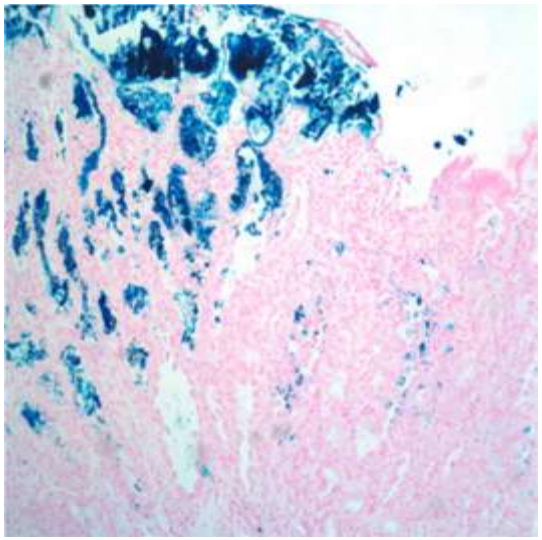
- **Gastric mucosal calcinosis**
  - Associated with transplant patients
  - Larger in size, more ba
  - Also located subepithe
  - Can be seen in antacic
    - Aluminum containing



Why it is not…

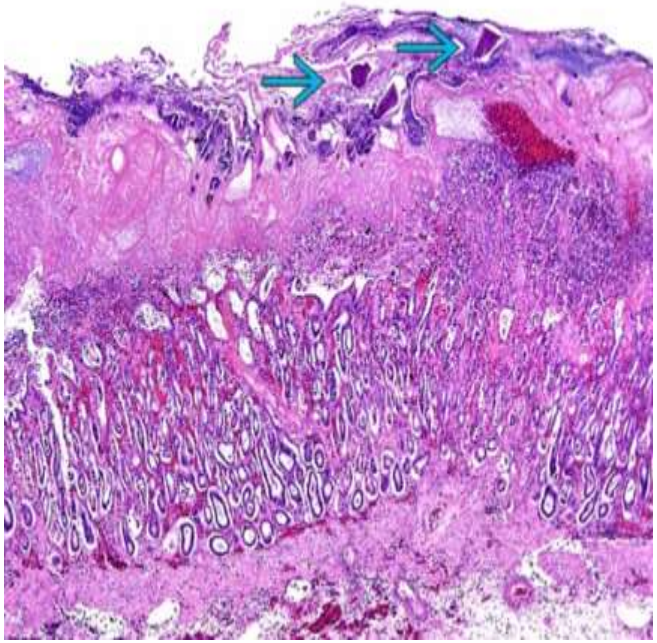
- **Iron-pill gastritis**
  - Clinical presentation- Anemia
  - Associated with erosion of surface epithelium
  - Diffuse staining on iron stain

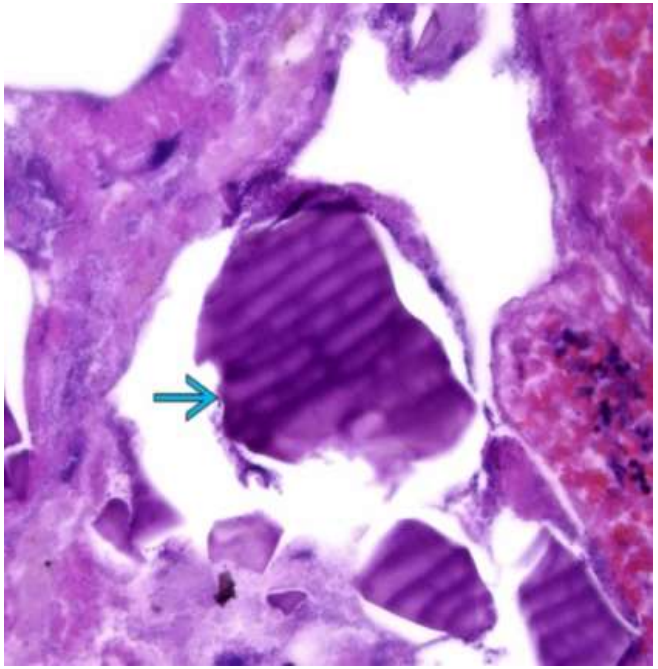




Why it is not…

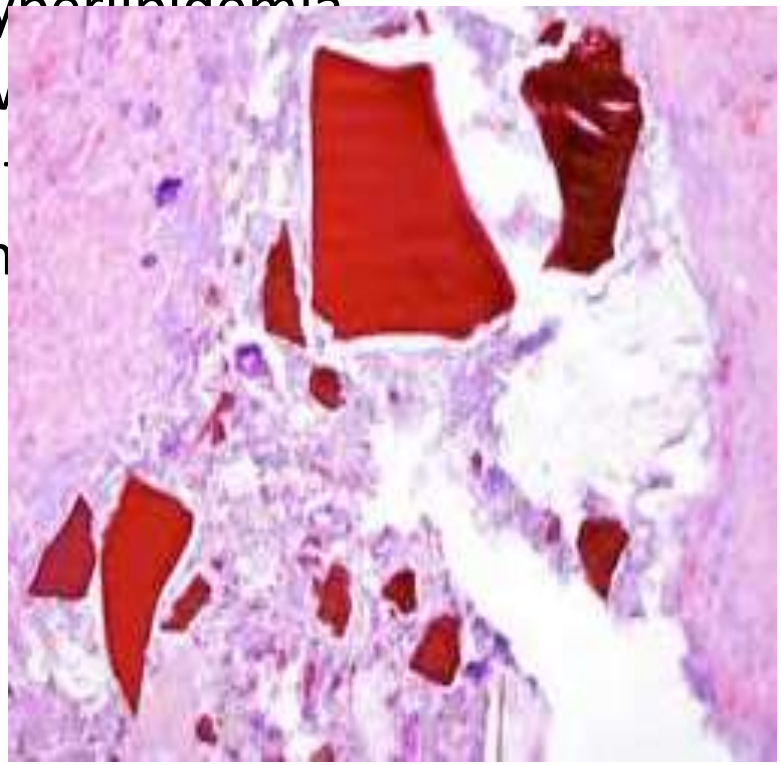
- **Polystyrene**
  - Clinical presentation- Hyperkalemia
    - Can also be using for chronic kidney disease…
  - Fish-scale appearance
  - Purple





Why it is not…

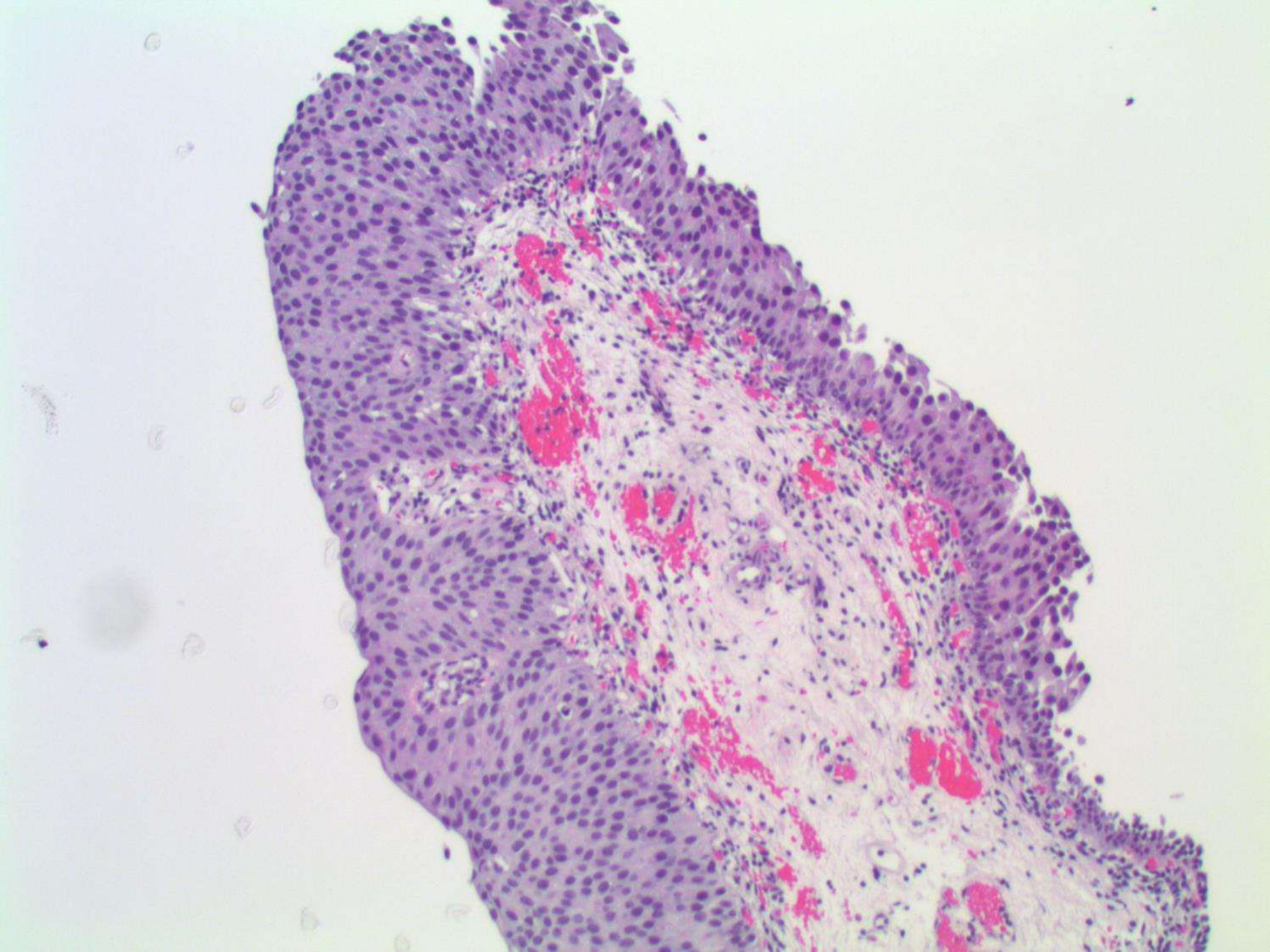
- **Bile acid sequestrants (Cholestyramine and Colesevelam)**
  - Clinical presentation- Hyperlipidemia
  - Homogeneous red-brow
  - No mucosal involvemen
  - Endoscopy usually norm

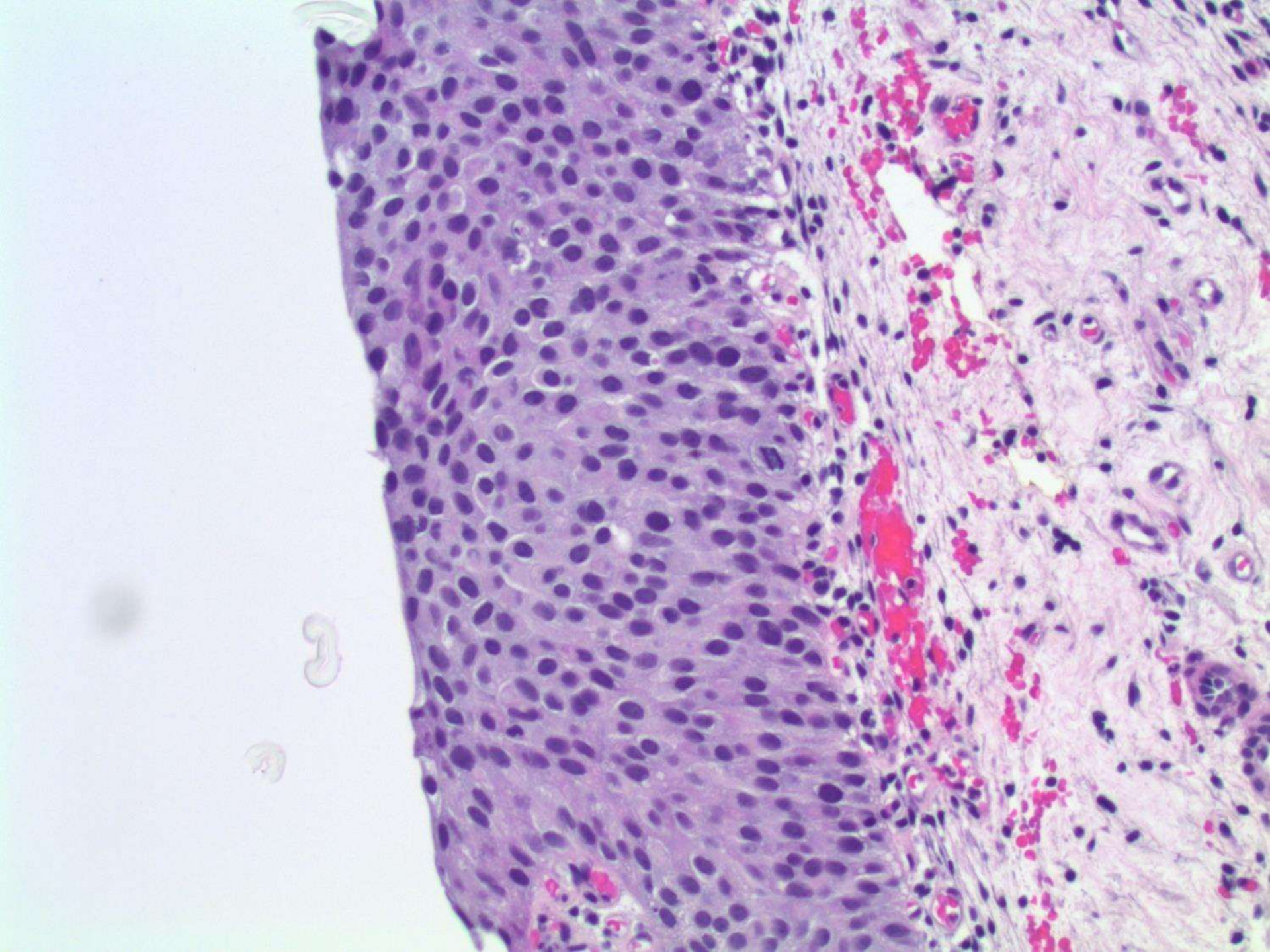


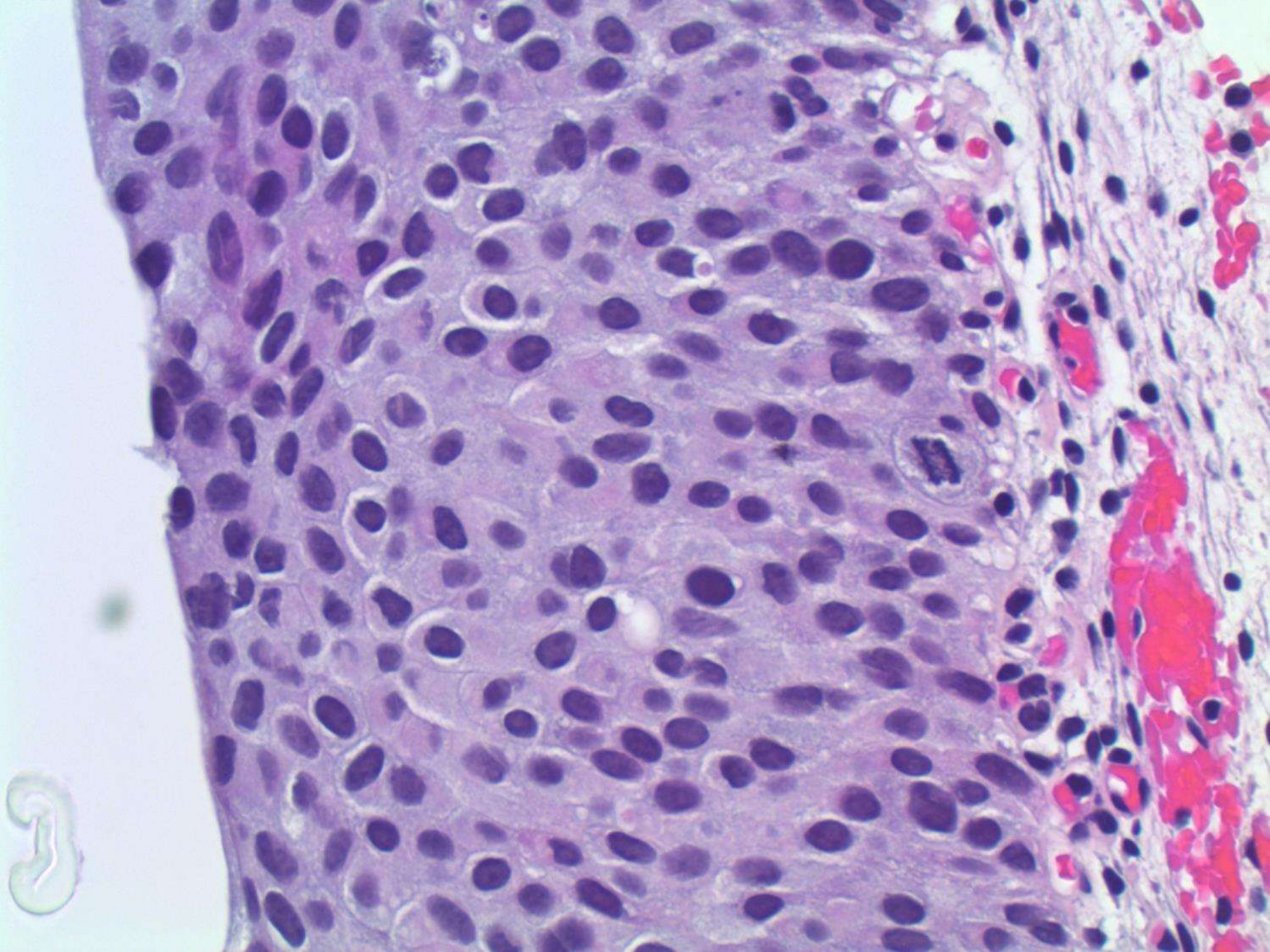
19-1109

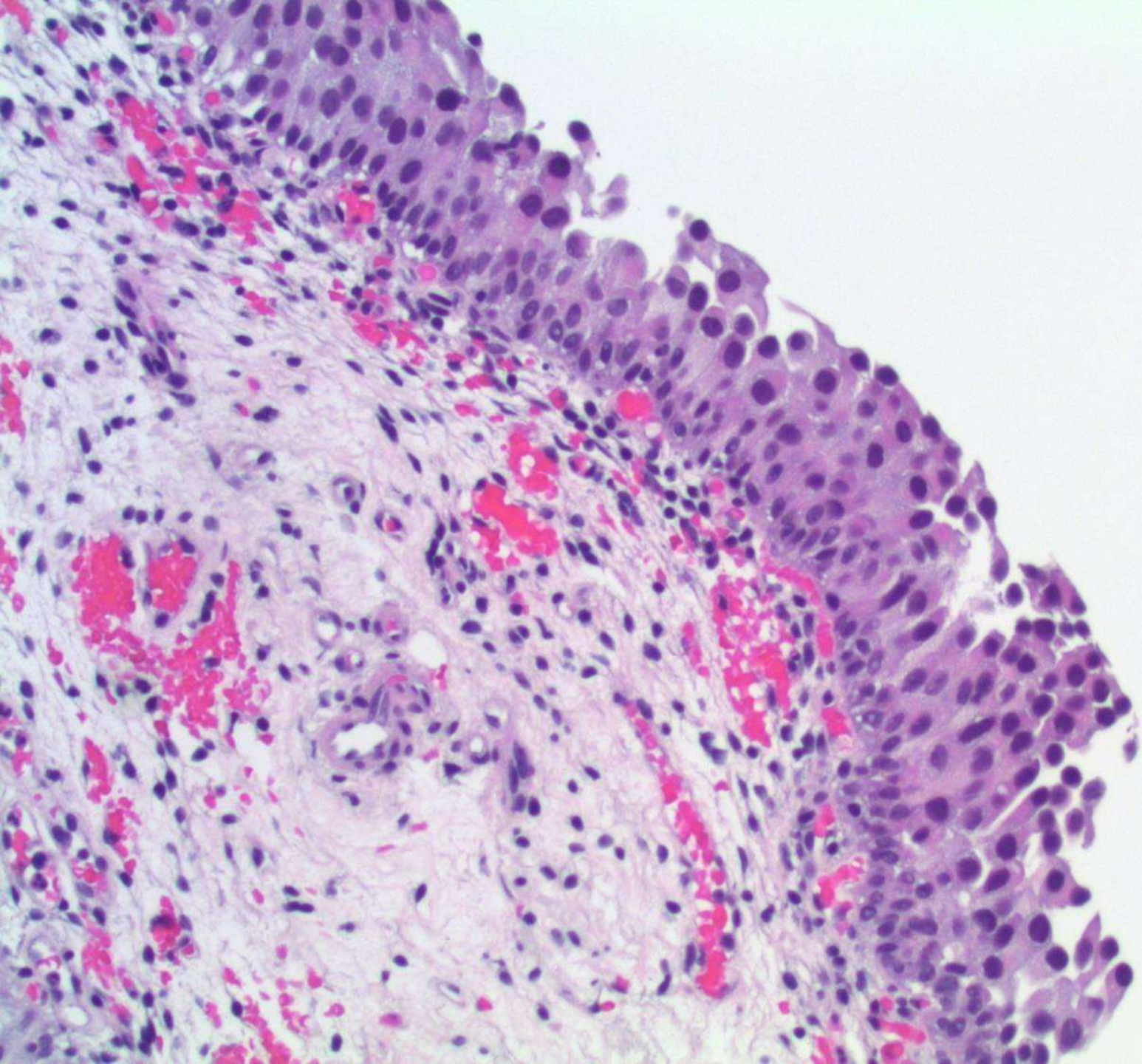
Ankur Sangoi; El Camino Hospital

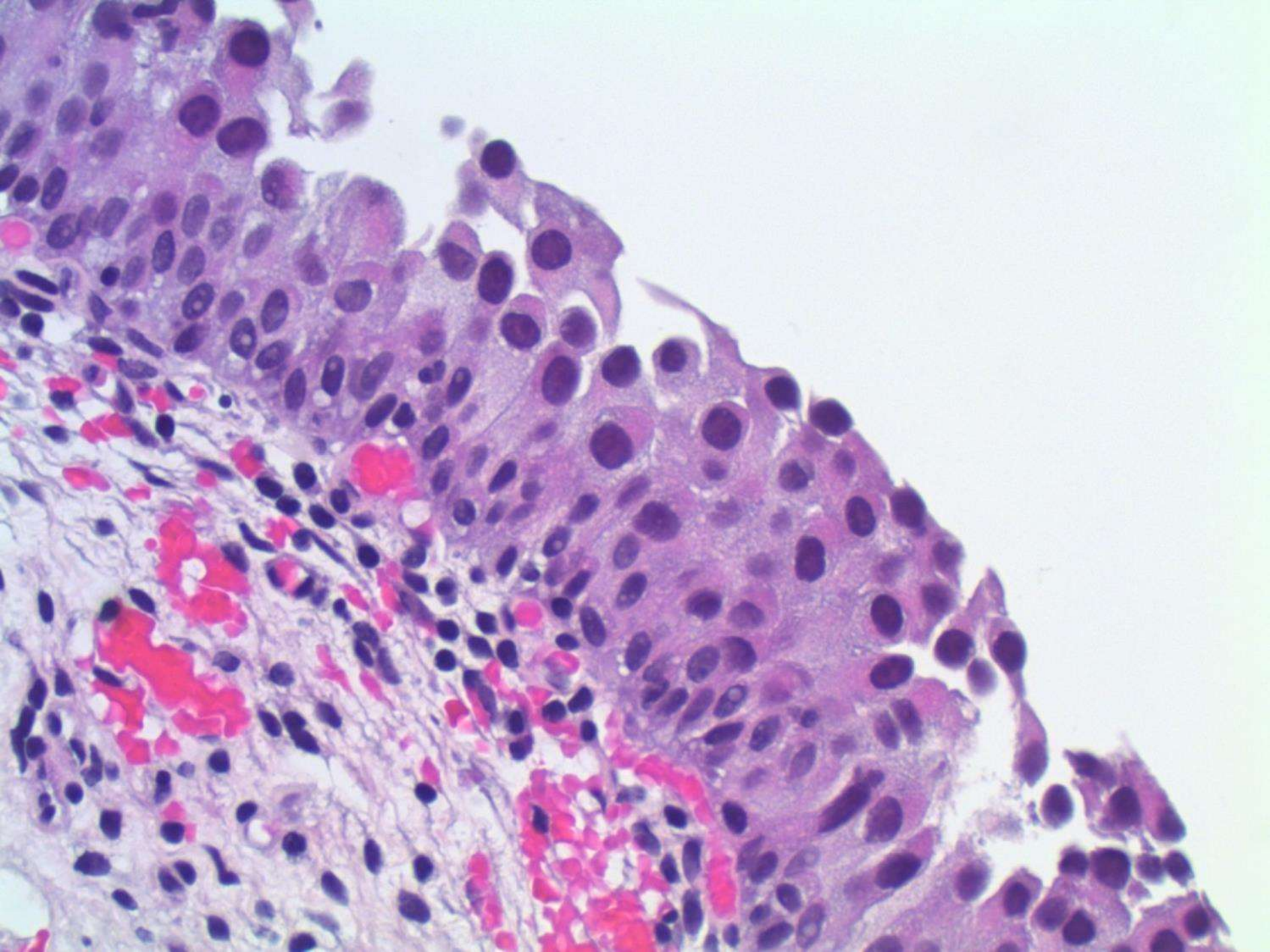
Middle-aged male presents with hematuria. Cystoscopy with biopsy of lesions performed.







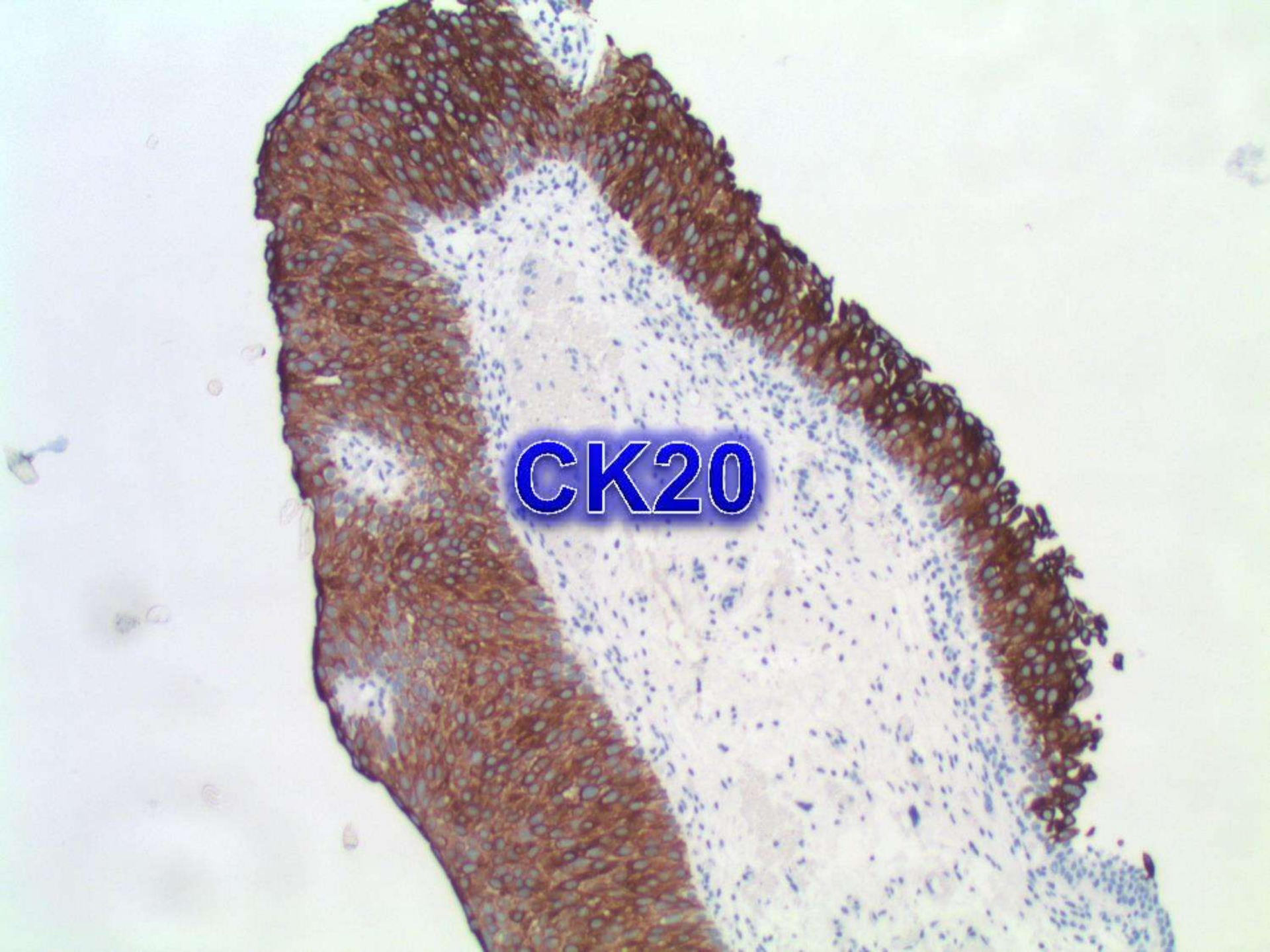




DDx

- **Urothelial carcinoma in situ**

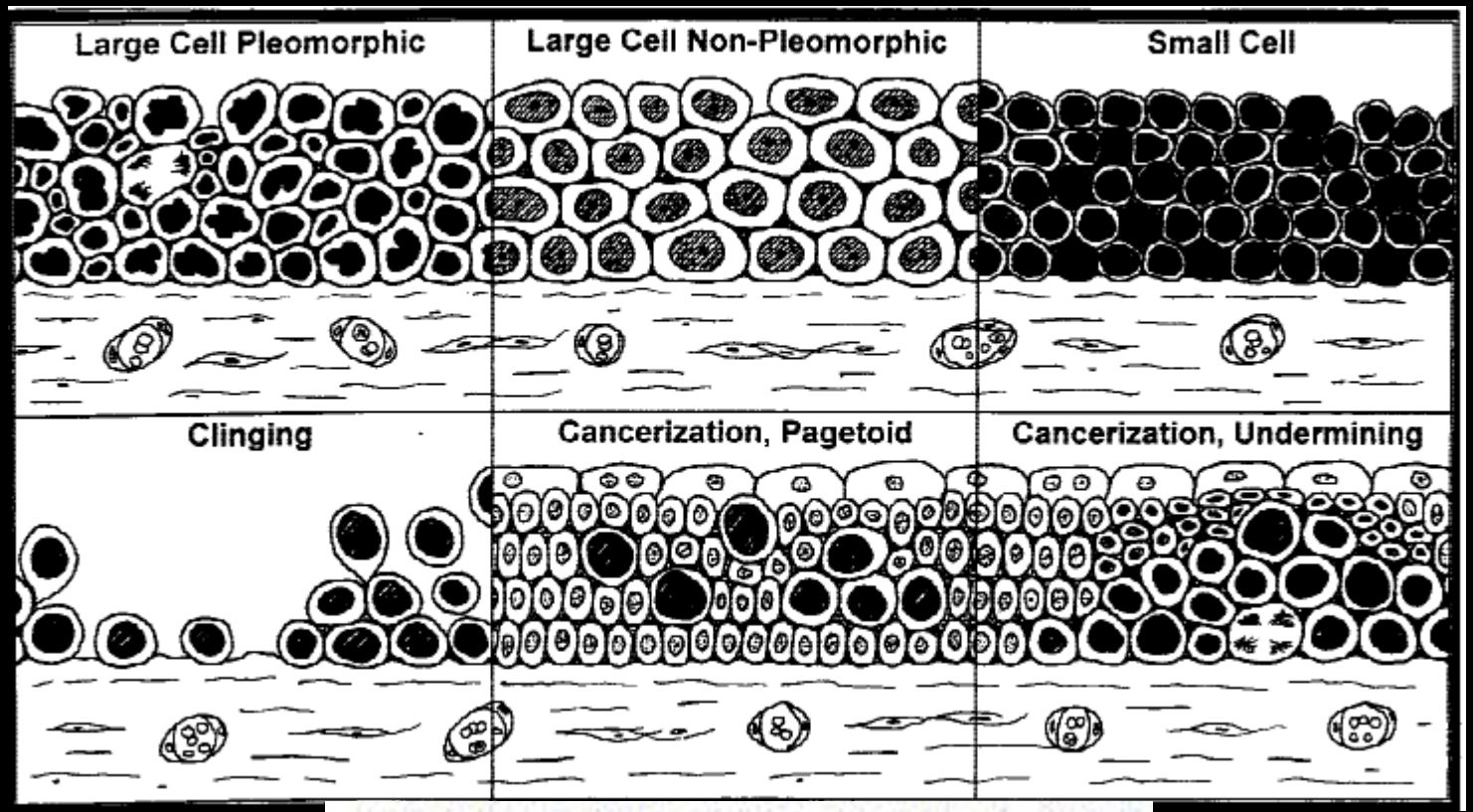
- **Reactive**
  - BCG/mitomycin
  - Radiation
  - Viropathic
  - Flat pattern nephrogenic adenoma


CK20

Final Dx:

- **Urothelial carcinoma in situ with plasmacytoid features**
  - CIS pattern previously undescribed
  - Triad of morphologic features
    - Abnormal architecture w/cellular rounding
    - Moderately enlarged eccentrically located nuclei
    - Dense globular eosinophilic cytoplasm
  - Similar IHC profile of typical CIS
    - CK20 most useful stain

Previous 5 patterns of urothelial CIS



Am J Surg Pathol, Vol. 25, No. 3, 2001

Carcinoma In Situ With Plasmacytoid Features

A Clinicopathologic Study of 23 Cases

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Am J Surg Pathol epub ahead of print

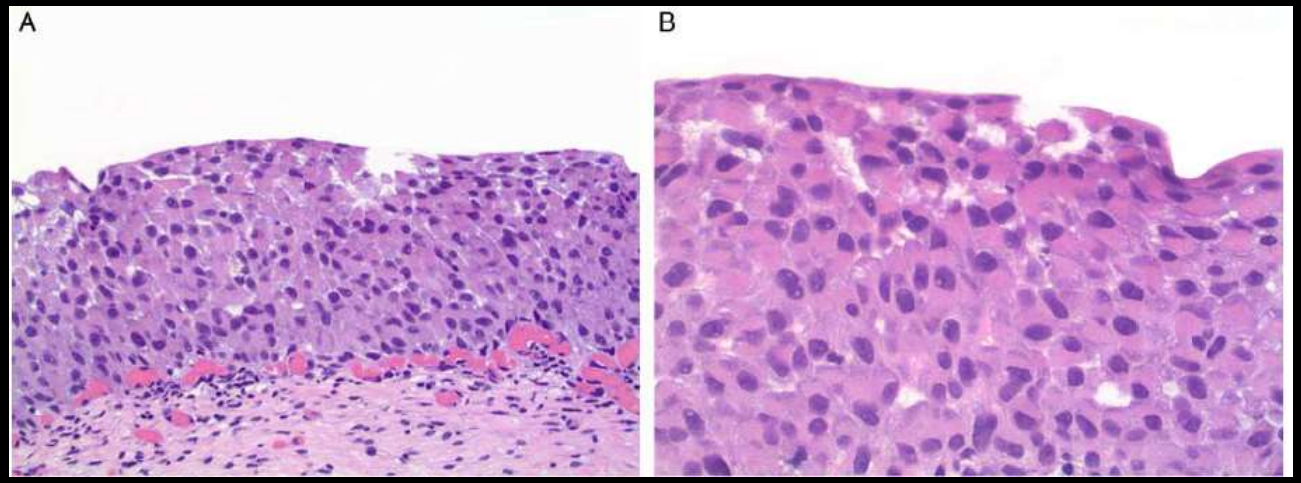


TABLE 1. Clinicopathologic Features of 23 Cases of P-CIS

Case No.	Sex	Age (y)	Prior Neoplasm	Concomitant Neoplasm	Therapy	Subsequent Neoplasm	Status (mo)
1	Male	63	None	None	BCG	P-CIS; pT1 nested on cystectomy	AWD (49)
2	Female	67	None	None	BCG	HG pTa	AWD (29)
3	Female	68	None	None	BCG	Typical CIS	AWD (28)
4	Male	73	None	None	BCG	Typical CIS and LG pTa	AWD (56)
5	Male	58	LG pTa; AUS	None	Mitomycin	Multiple LG pTa	ANED (66)
6	Male	64	None	HG pTa	BCG	None	ANED (40)
7	Male	64	HG pTa	None	BCG	None	ANED (49)
8	Male	66	pT2N1 renal pelvis; typical CIS	None	BCG	None	ANED (52)
9	Male	67	None	pT4a on TURP	BCG	pT4aN0 on cystectomy	AWD (41)
10	Male	69	Remote history pTa NOS	HG pTa; dysplasia	Mitomycin	positive urine cytology	AWD (26)
11	Male	69	Typical CIS	Typical CIS	BCG and mitomycin	P-CIS	ANED (26)
12	Male	73	None	pT2	BCG	pT2N0 at cystectomy; liver metastasis	AWD (115)
13	Male	73	Typical CIS	None	BCG	HG pTa; typical CIS; pT2N1 at cystectomy	AWD (16)
14	Male	74	LG pTa	None	BCG	None	ANED (15)
15	Male	75	HG urine cytology	Typical CIS	BCG	Positive urine cytology	ANED (7)
16	Male	76	LG pTa; HG urine cytology	None	BCG	Typical CIS	ANED (61)
17	Male	82	LG pTa	None	BCG	None	ANED (52)
18	Male	83	HG urine cytology; HG pTa	None	BCG	Atypical urine cytology	ANED (11)
19	Female	86	HG pT3 renal pelvis	None	BCG	Liver metastasis	DOD (29)
20	Male	86	HG and LG pTa	None	BCG	Typical CIS	ANED (28)
21	Male	87	Typical CIS; HG pT1	None	BCG	AUS	ANED (7)
22	Male	90	HG pTa	HG pTa	Surveillance	None	DUC; NED (24)
23	Male	91	HG pT1 and pTa; typical CIS	None	Surveillance	None	DUC; NED (39)

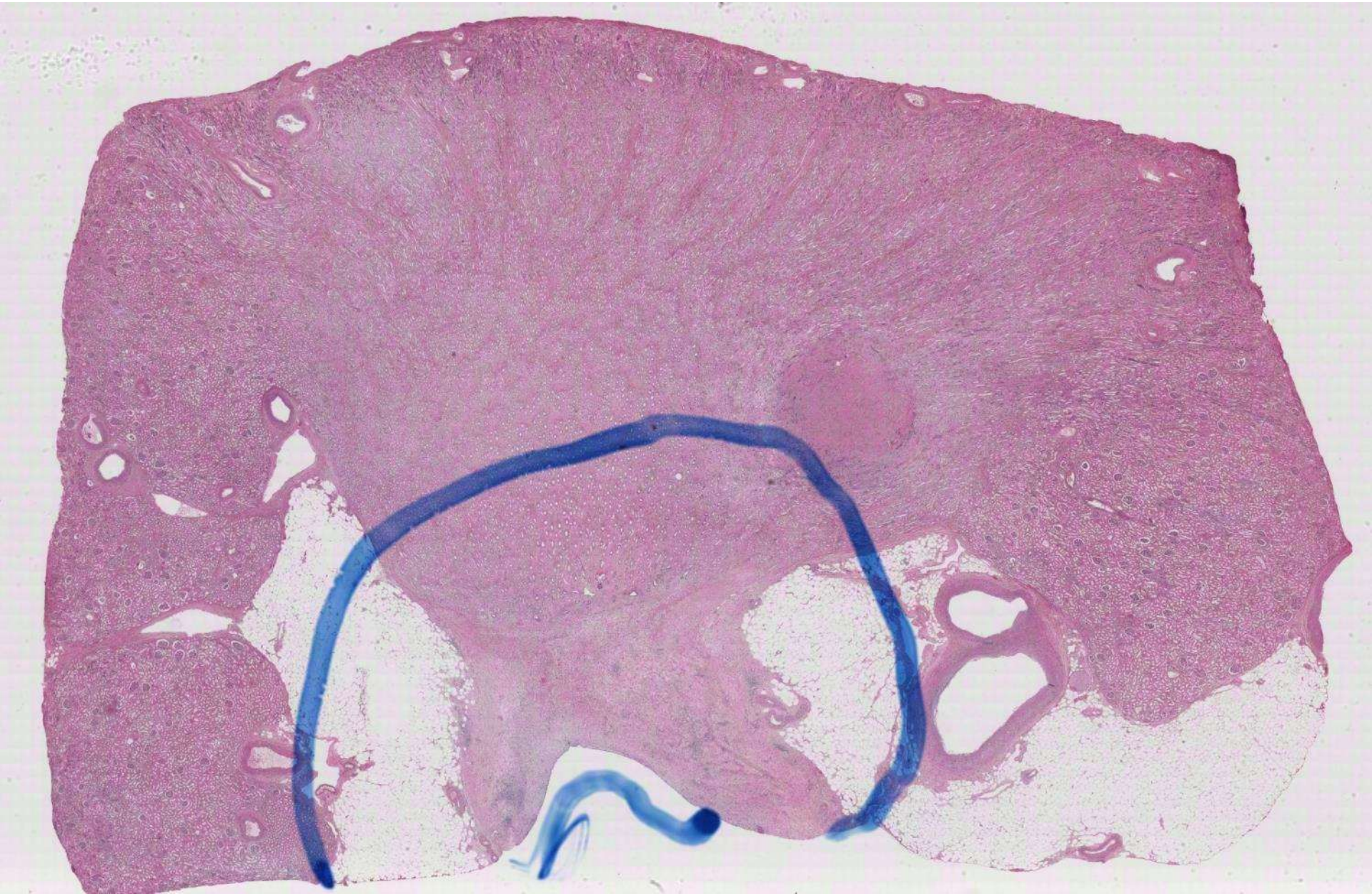
DDx of plasmacytoid CIS

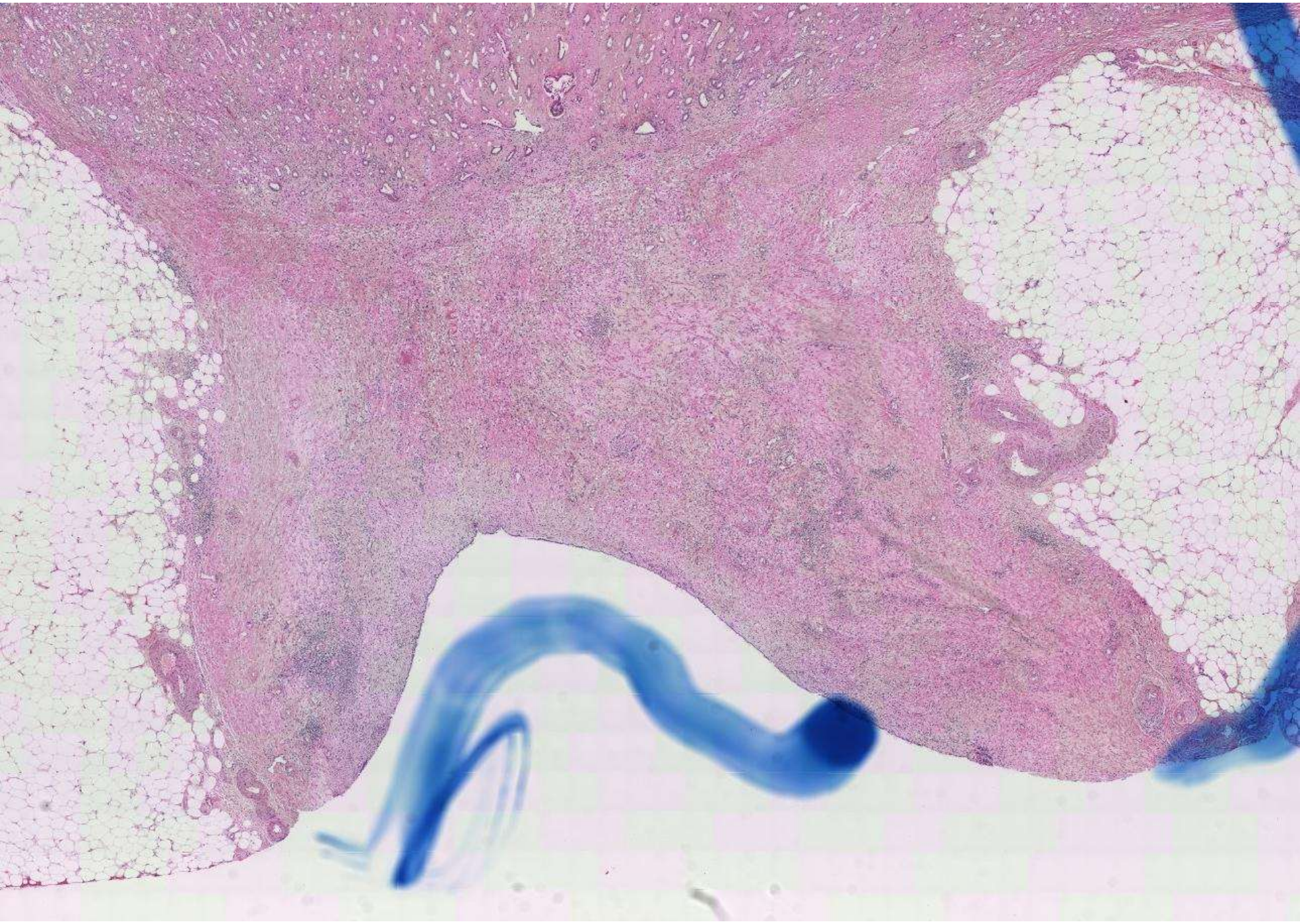
- **BCG/mitomycin**
  - Nonglobular cytoplasmic eosinophilia
  - Lack eccentric nuclear localization
- **Radiation**
  - Nuclear/cytoplasmic vacuolization, multinucleation, associated stromal changes
- **Viropathic**
  - Smudgy chromatin, lack architectural changes
- **Flat pattern nephrogenic adenoma**
  - Smaller cells, less cytoplasm; PAX8+

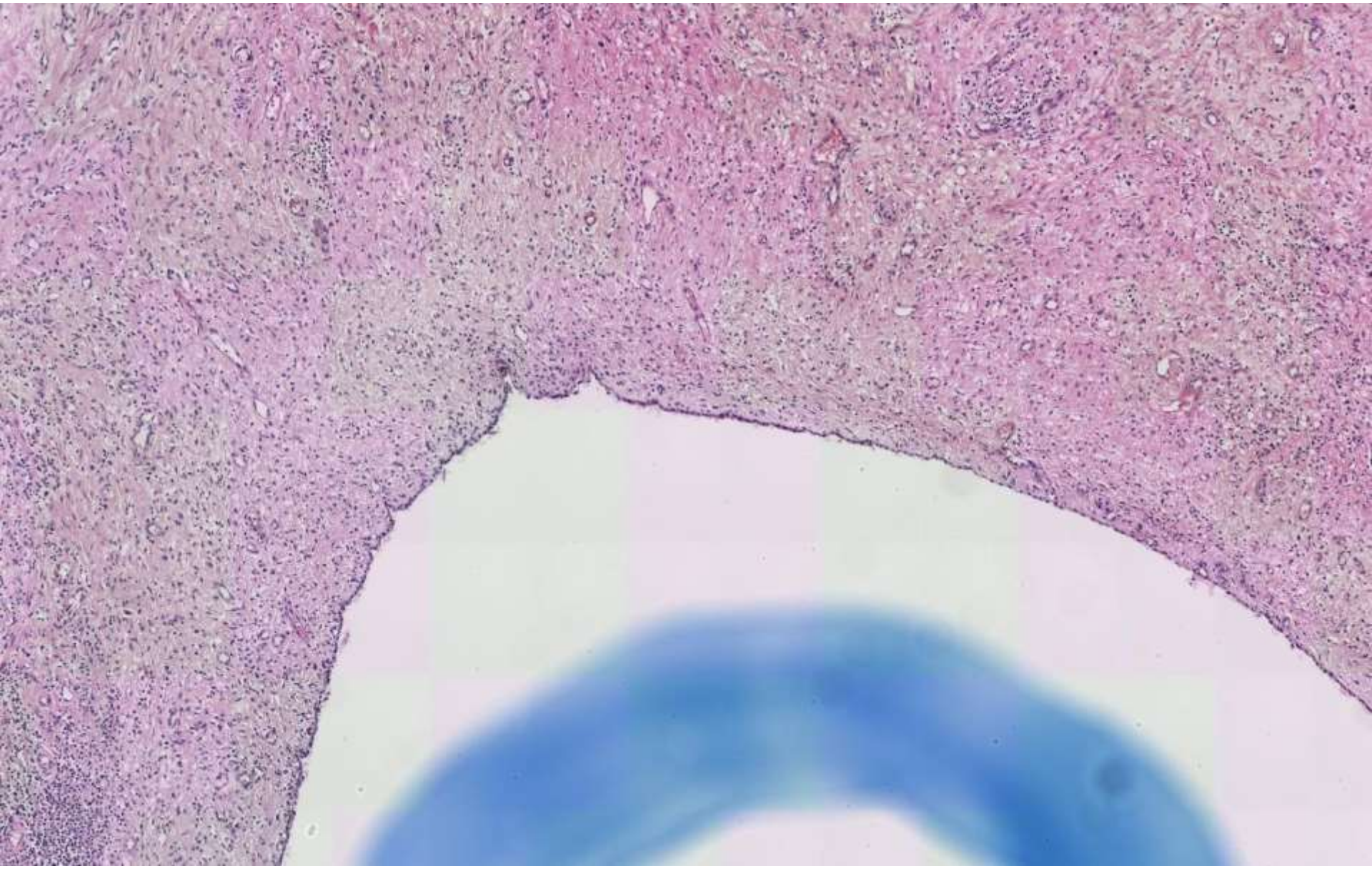
19-1110
scanned slide available!

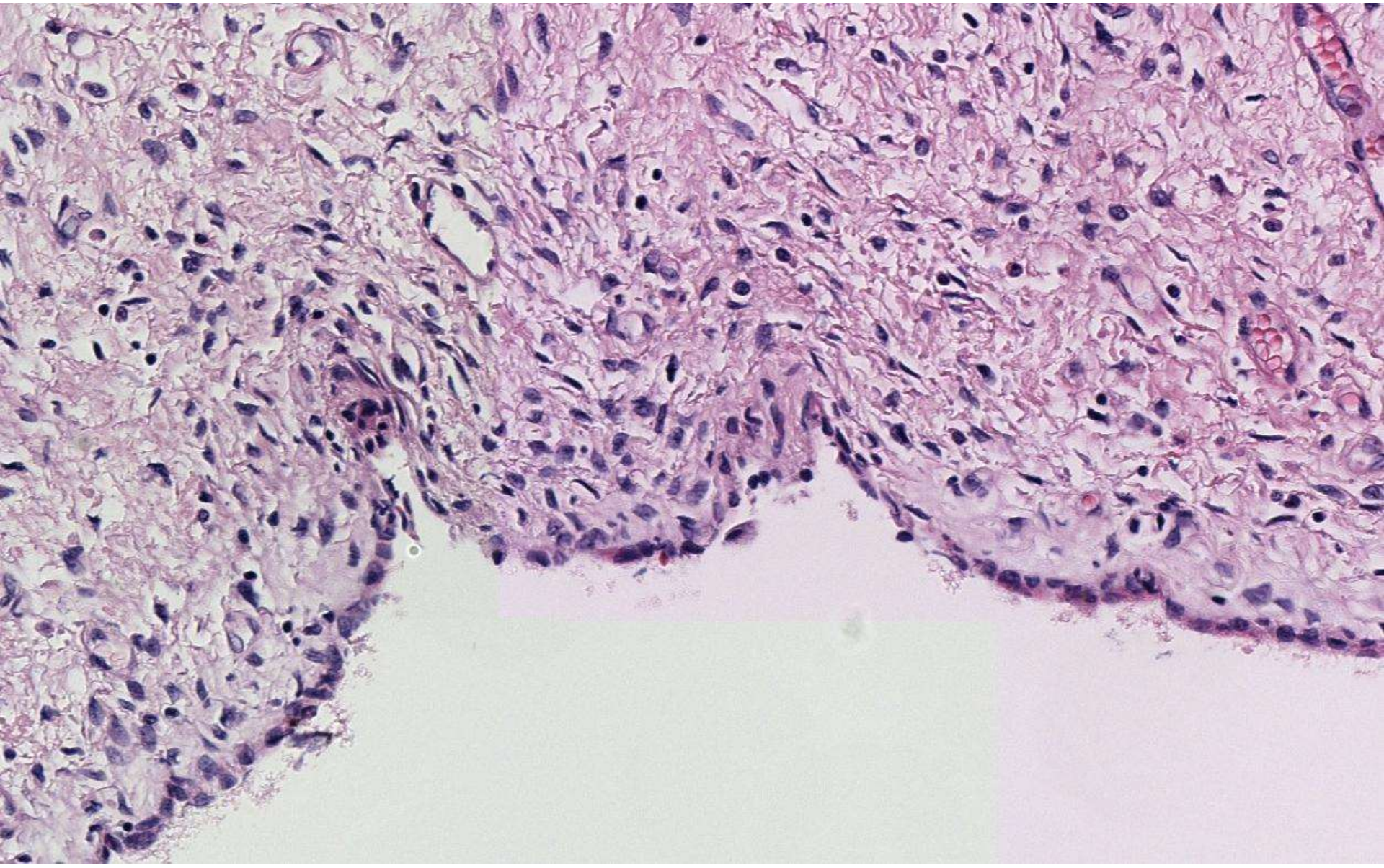
Ankur Sangoi; El Camino Hospital

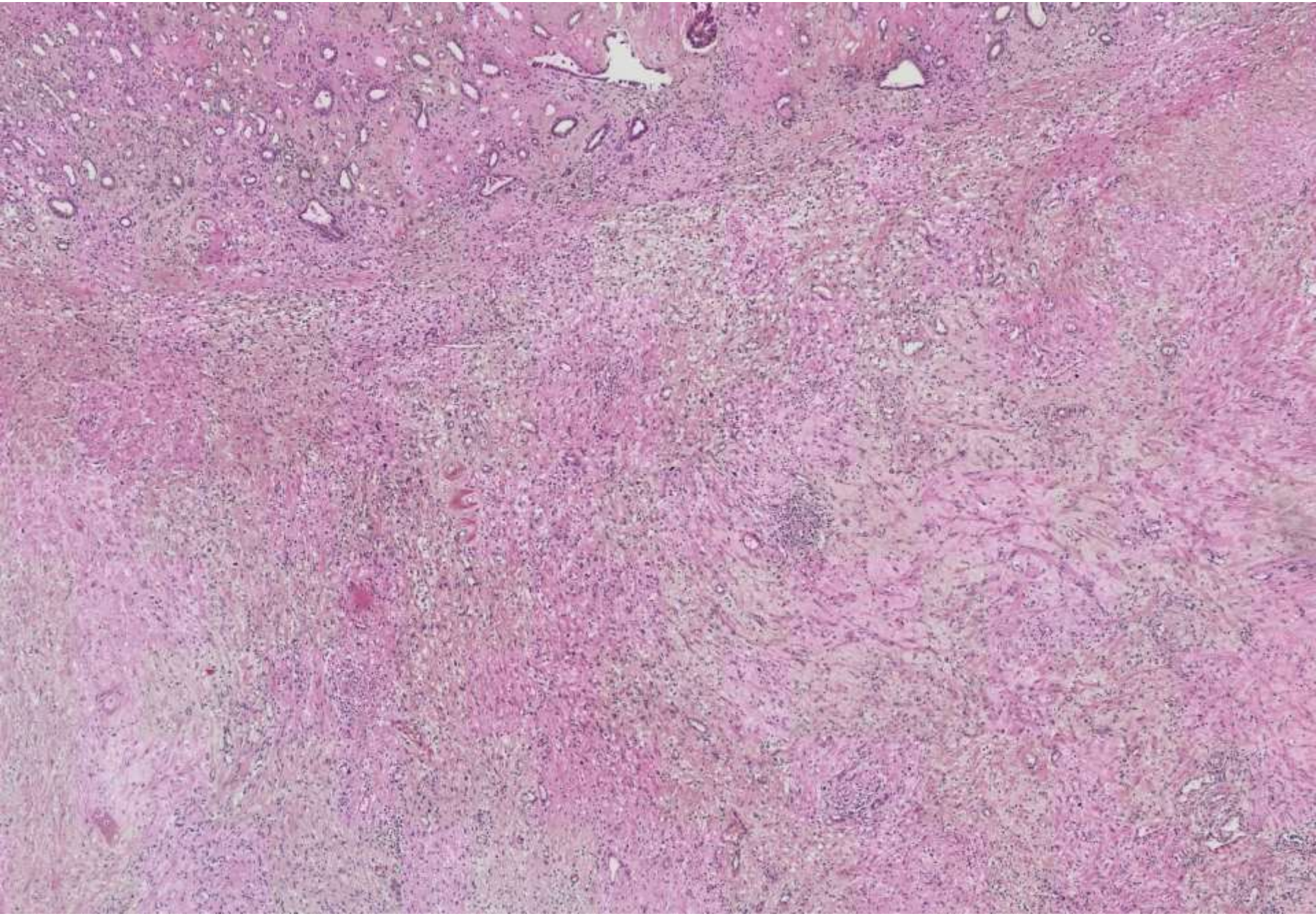
Middle-aged male undergoes nephro-ureterectomy. Gross examination reveals unusual 2cm granular area in the upper pole of the renal pelvis.

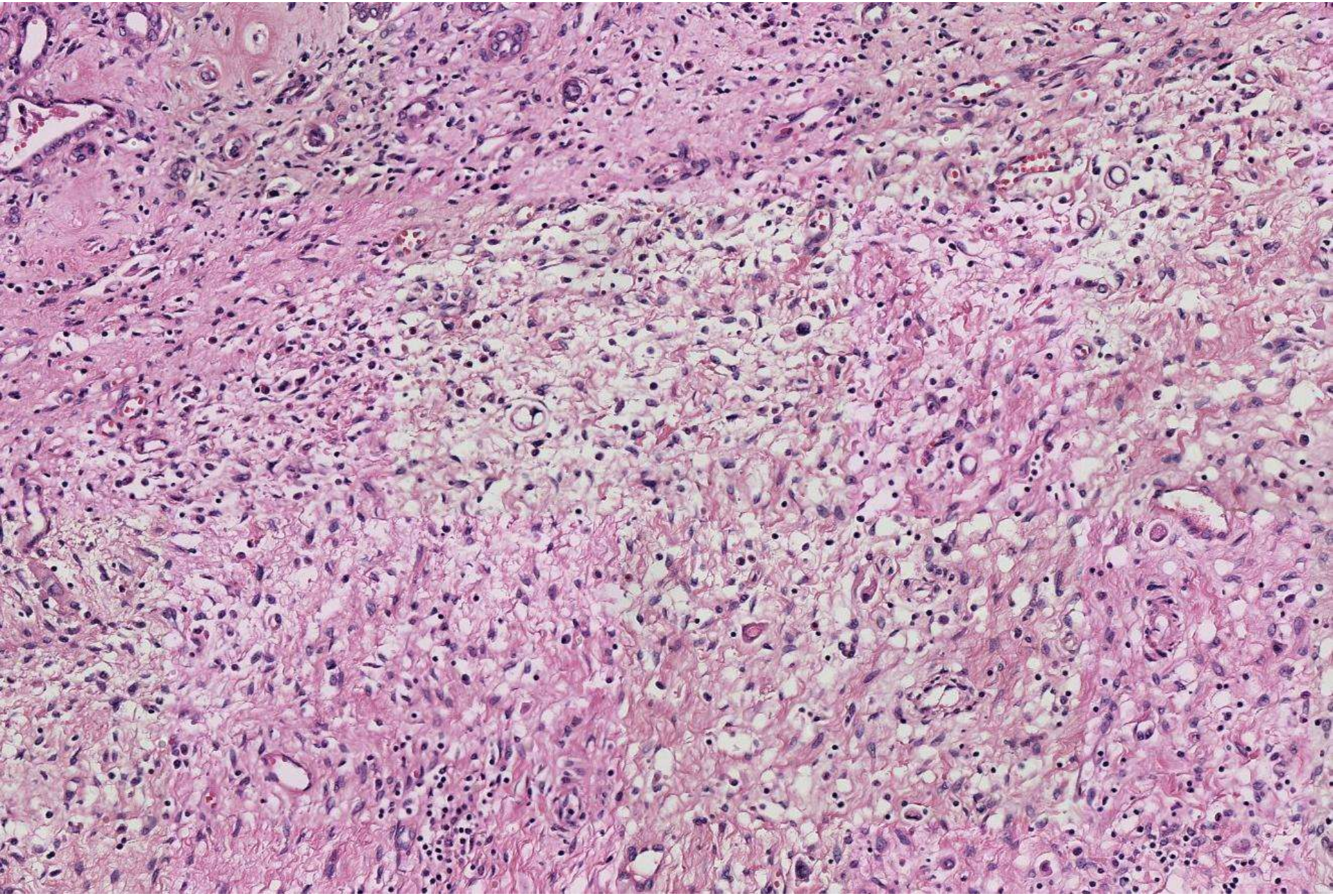


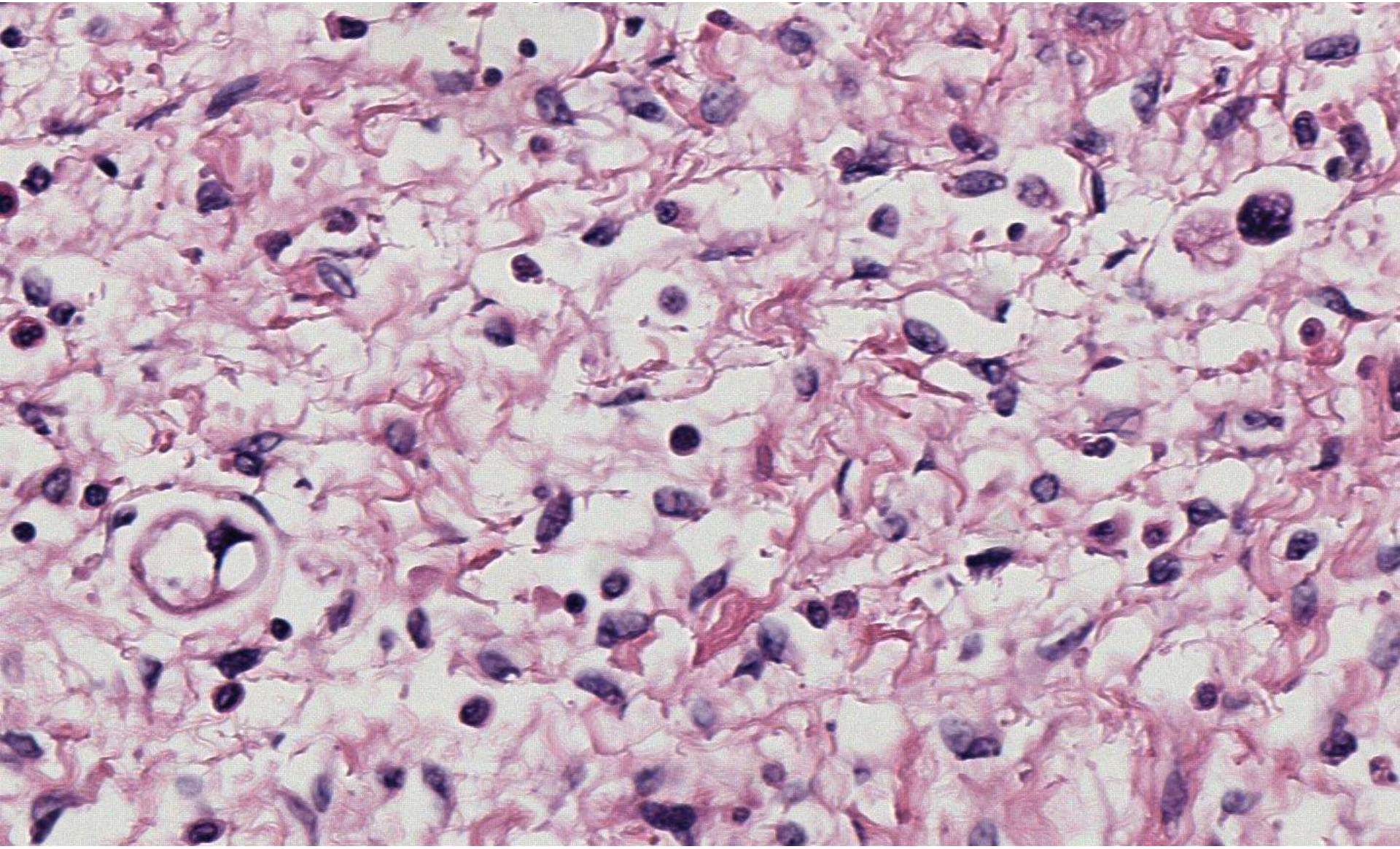


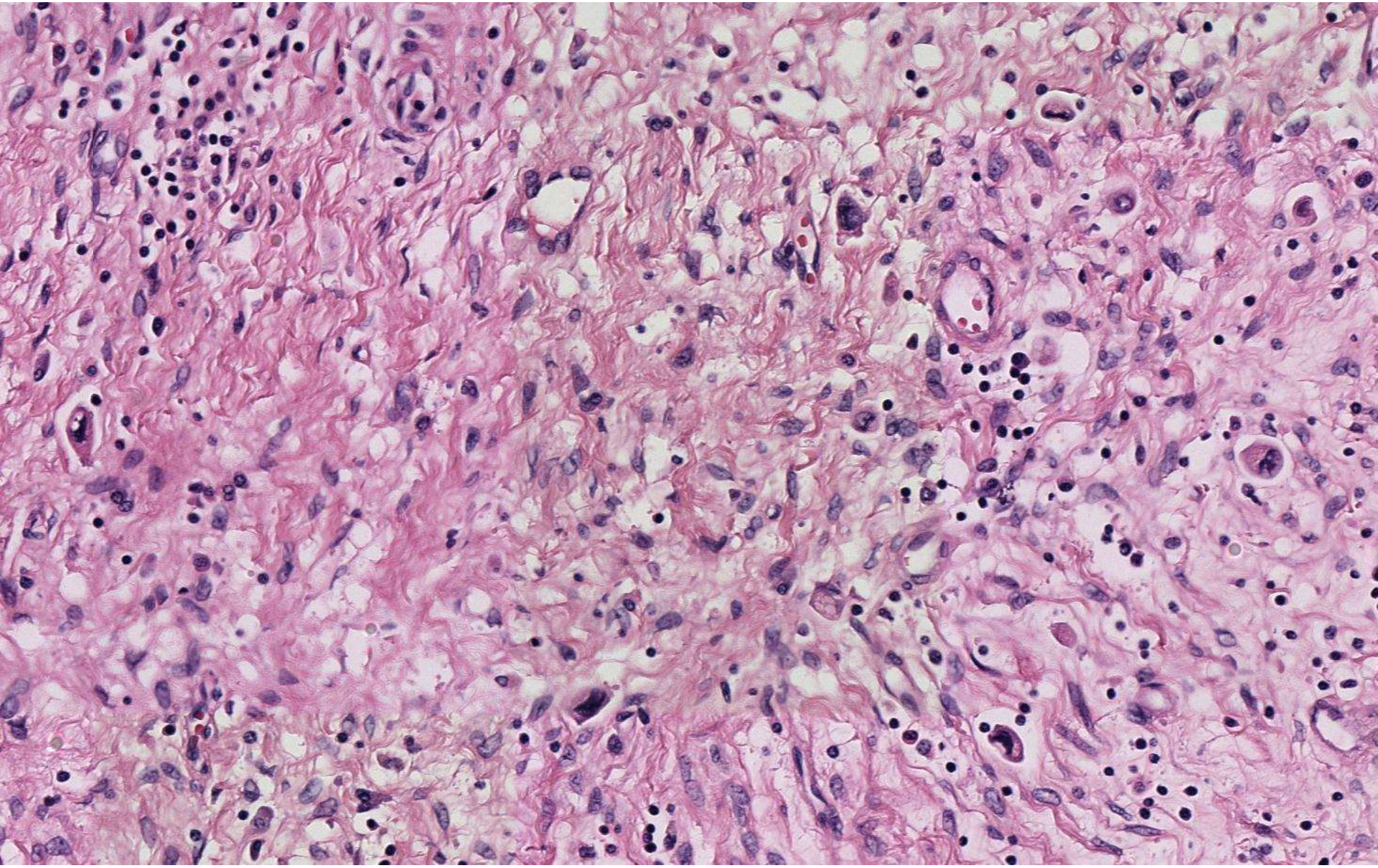


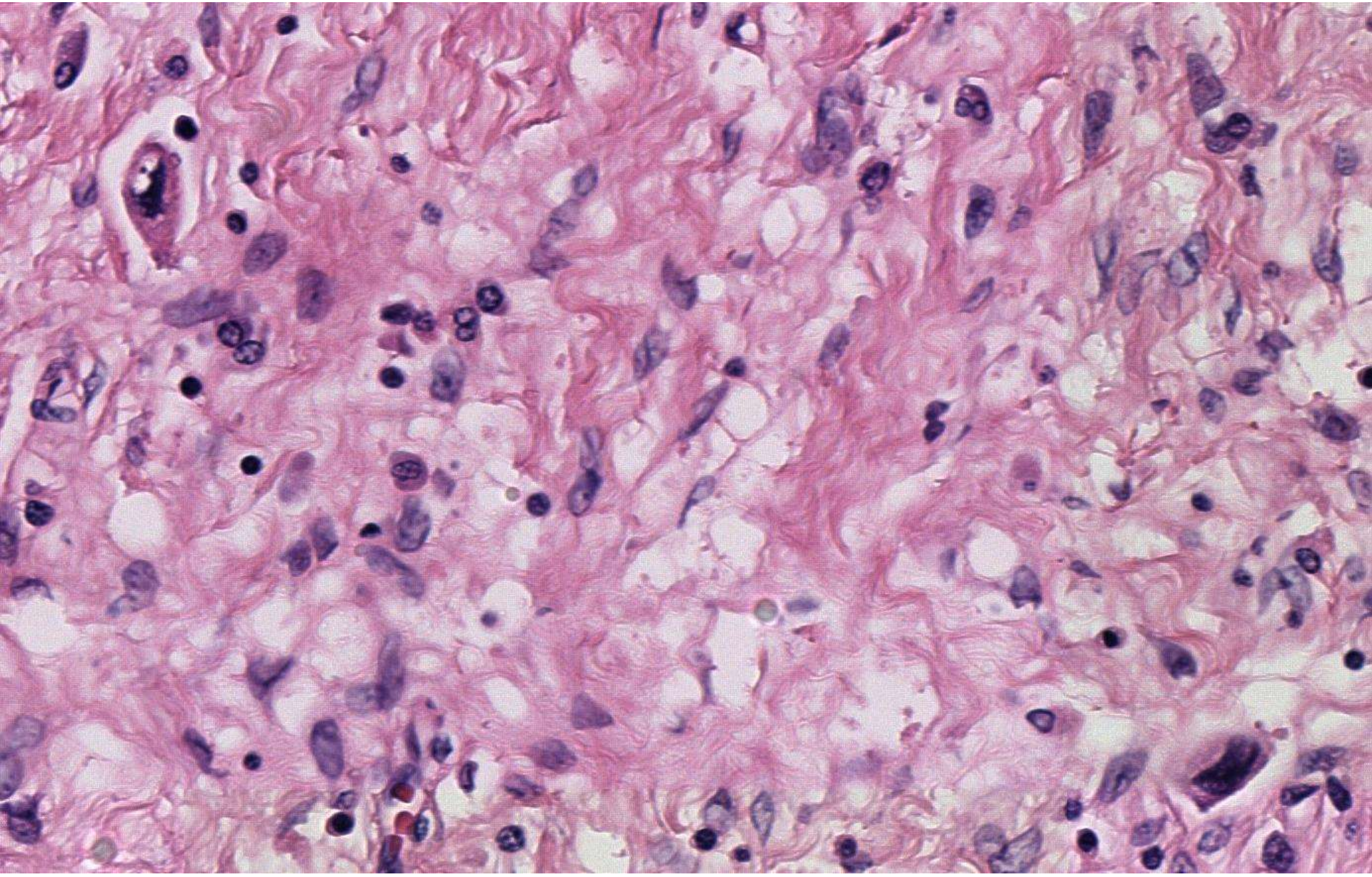


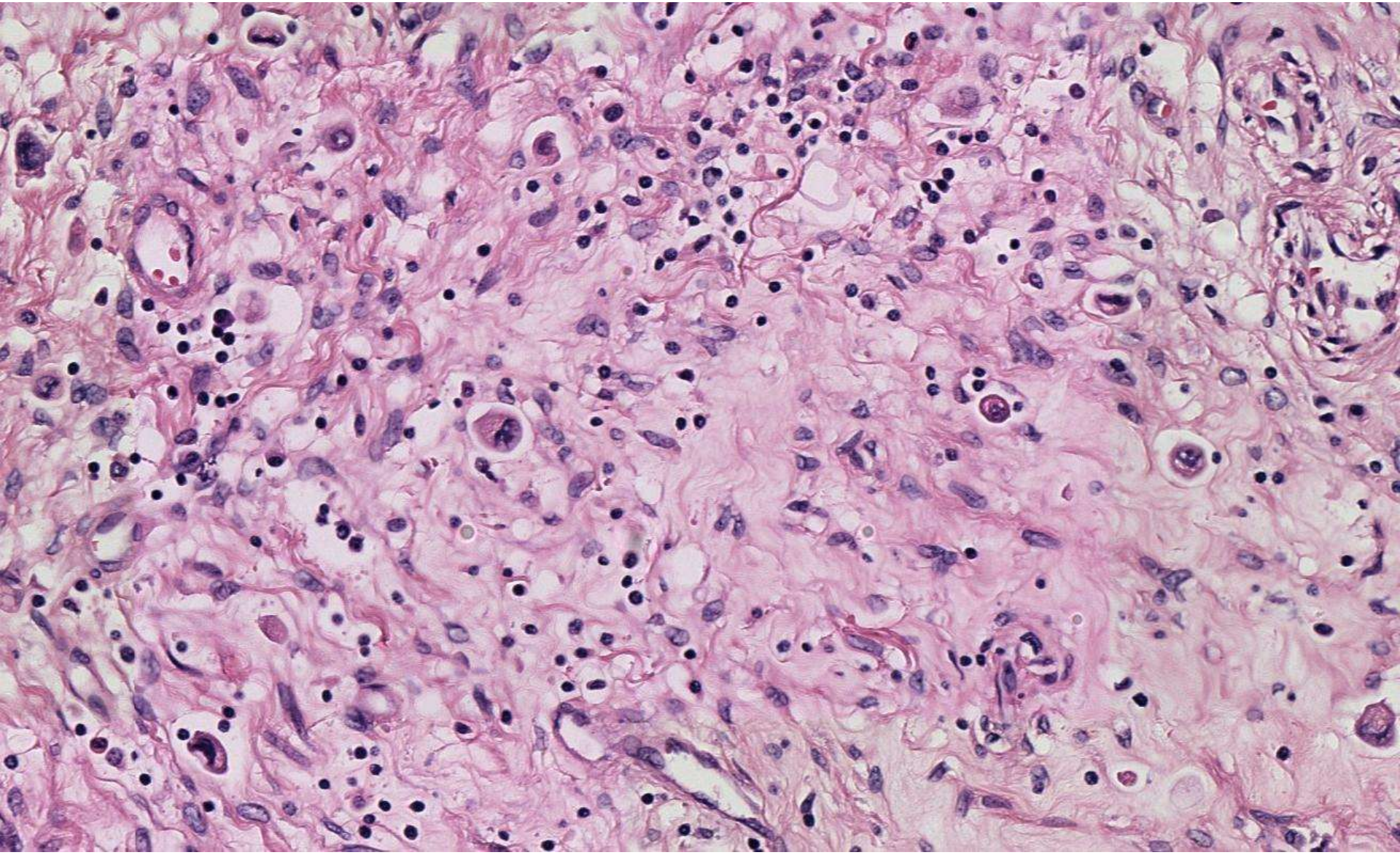


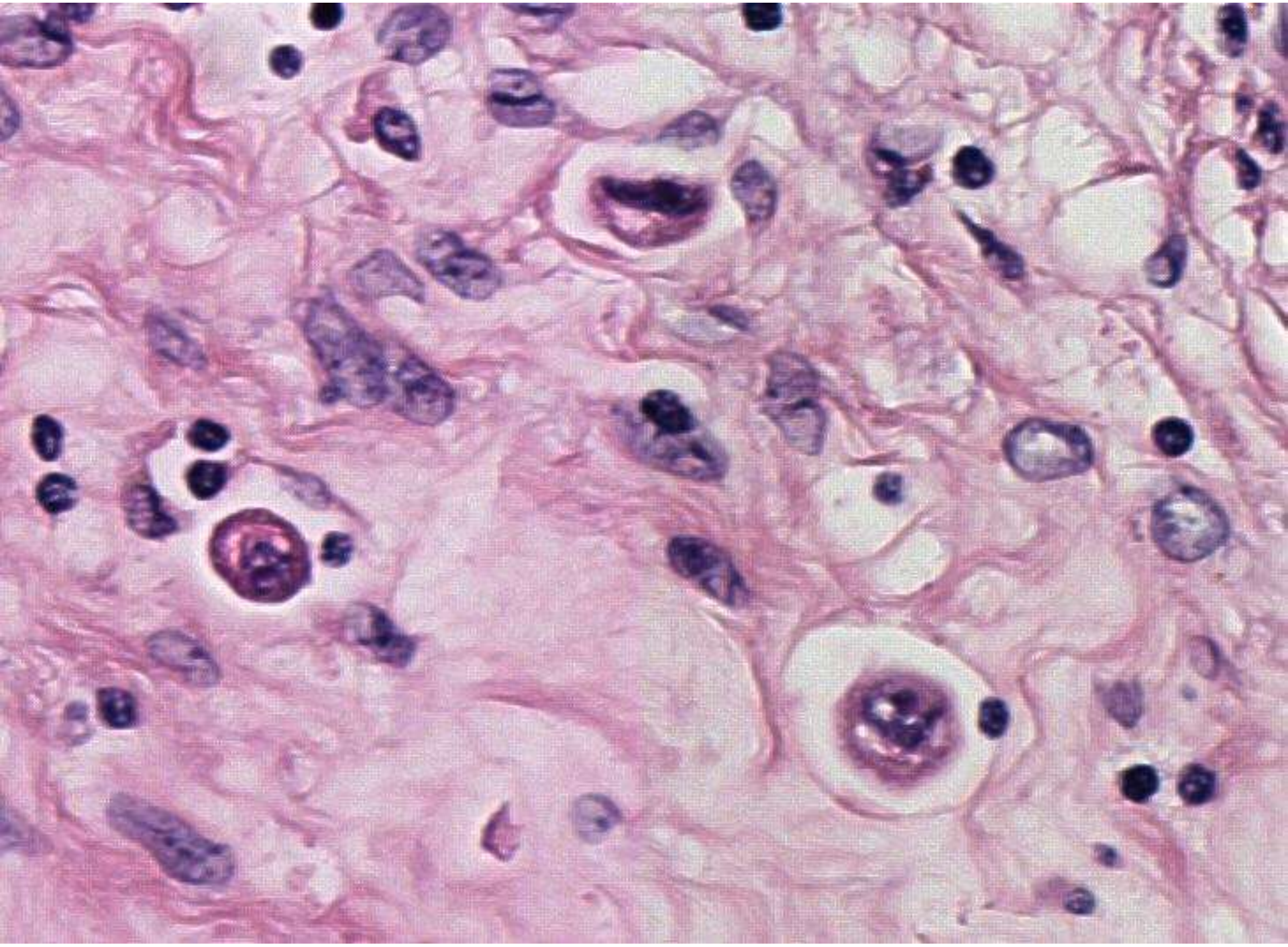






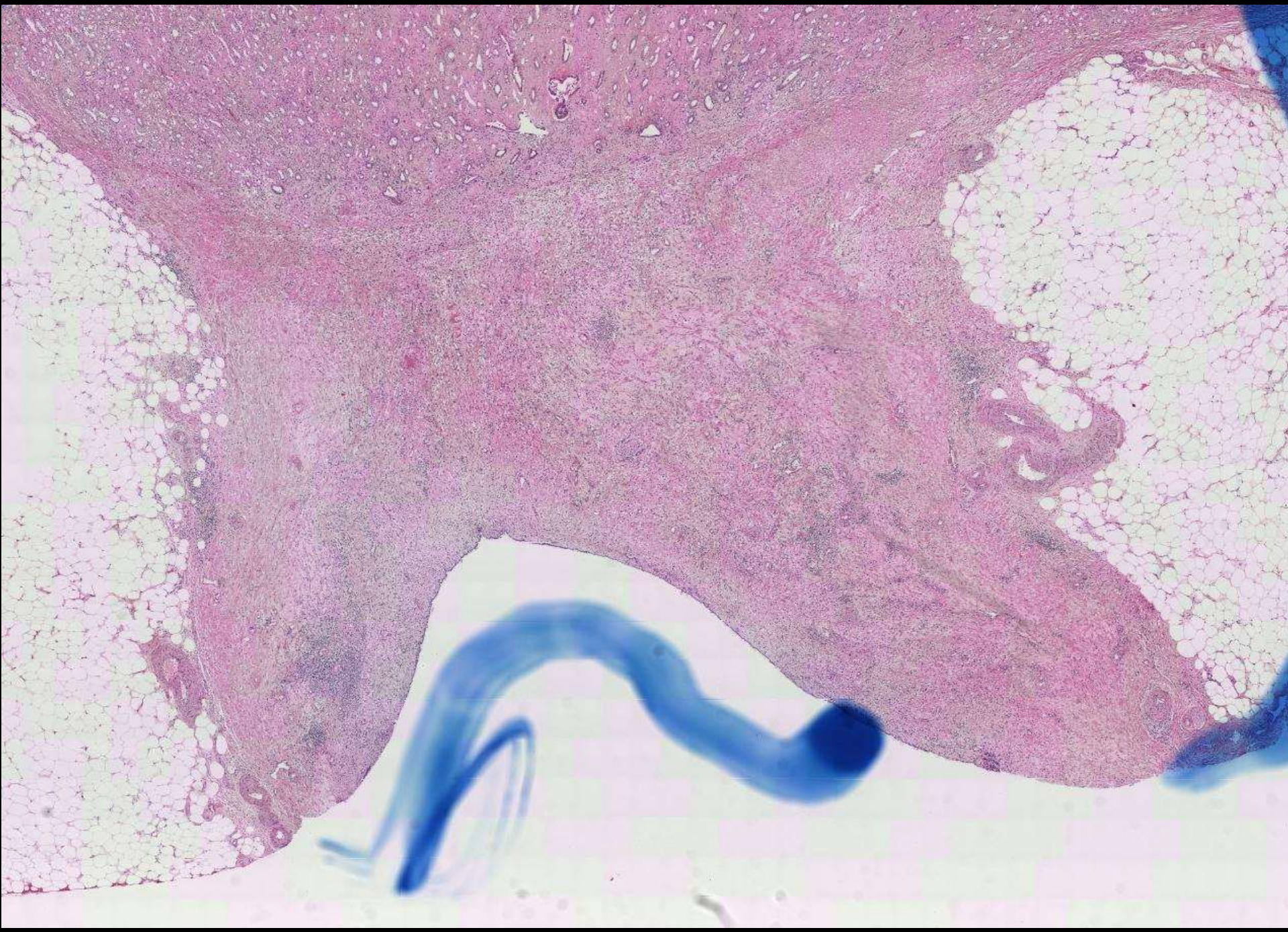


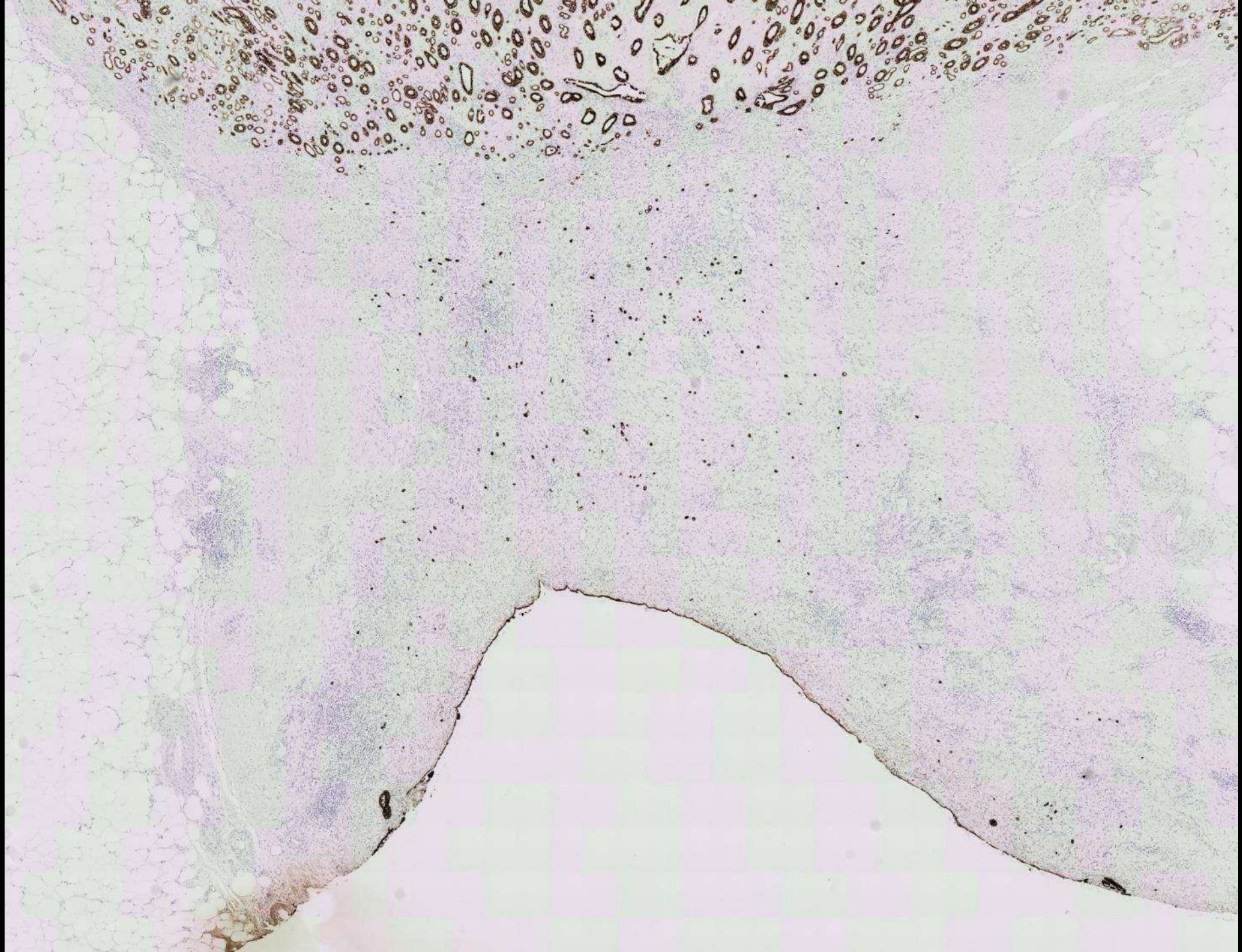


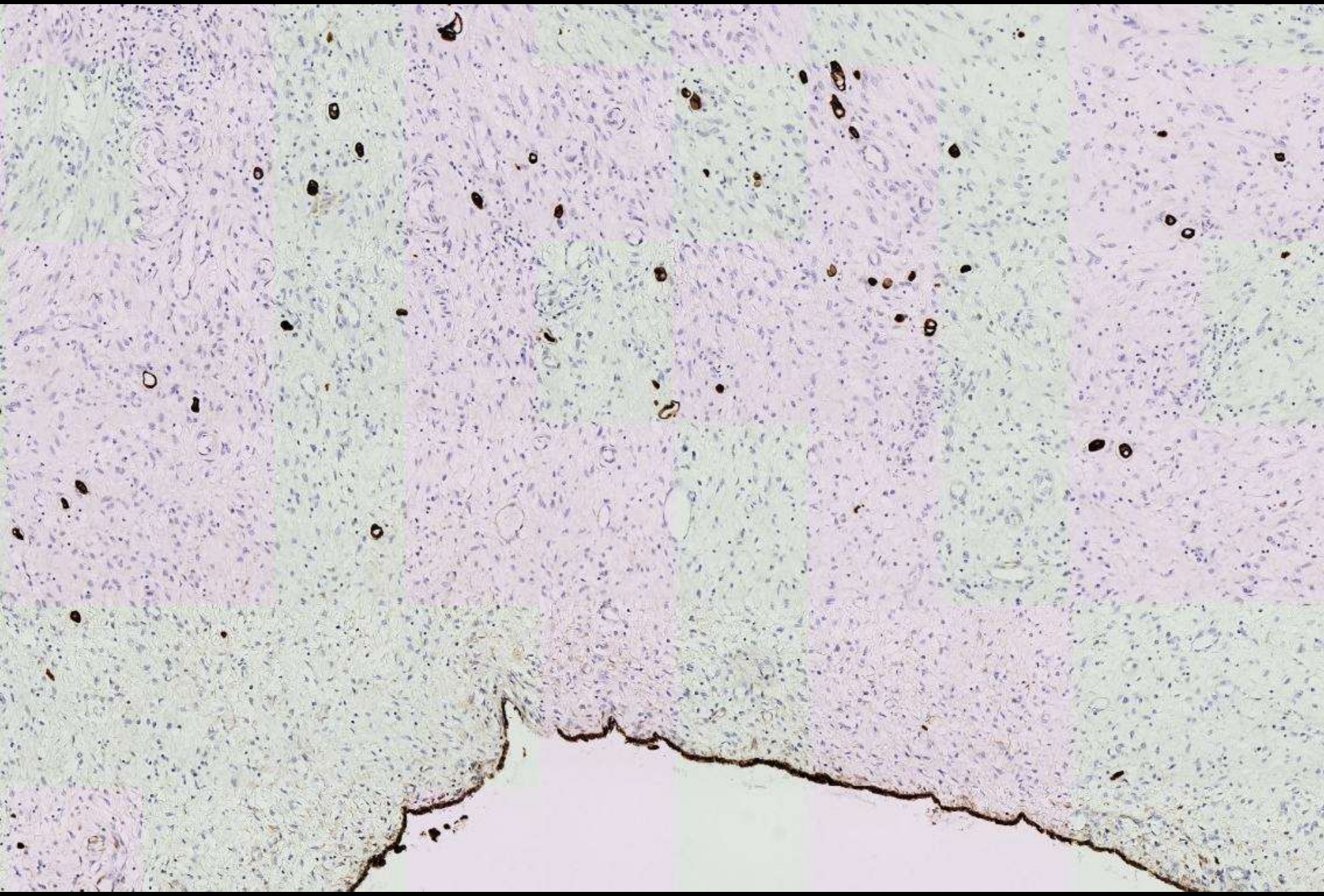


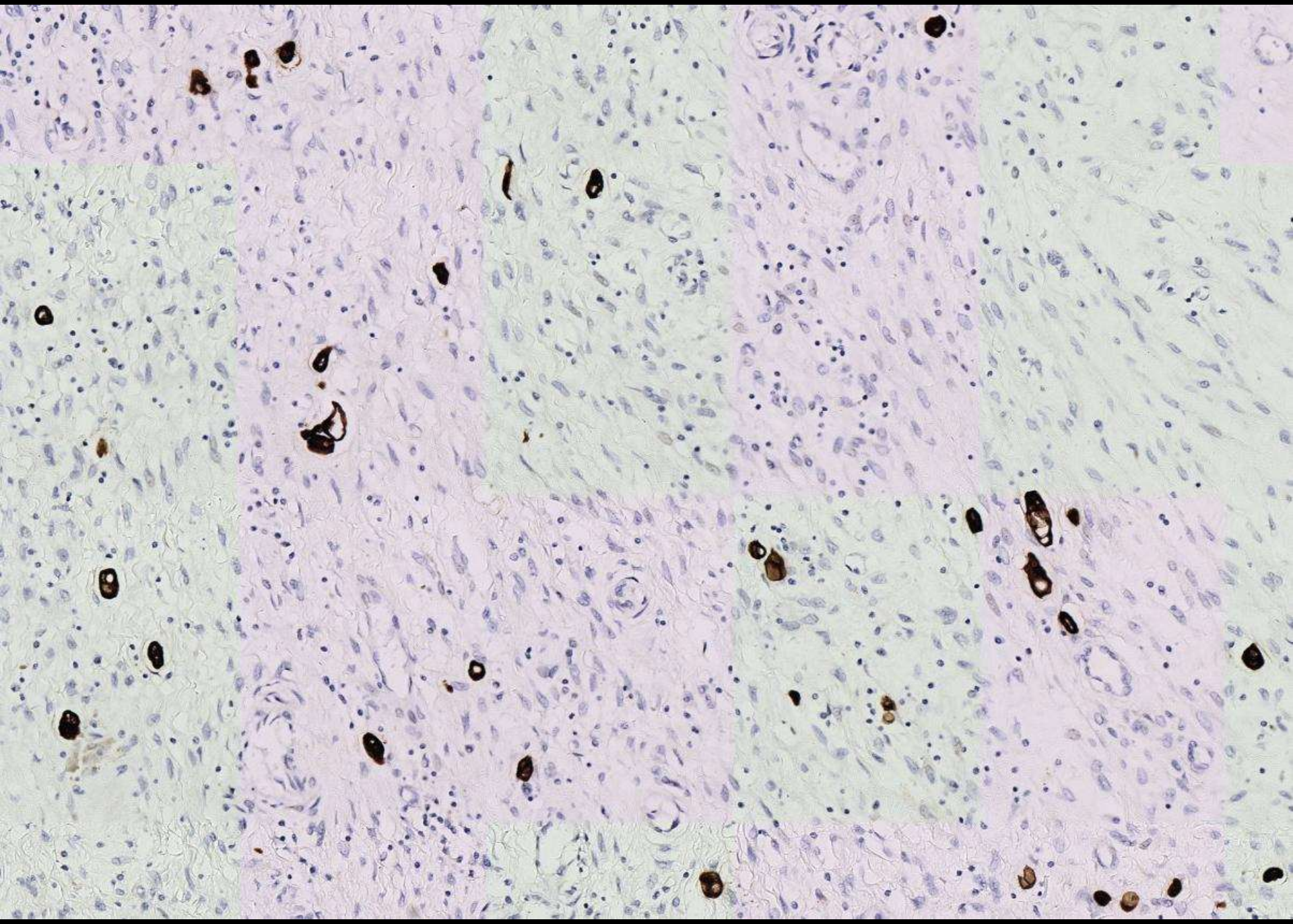
DDx

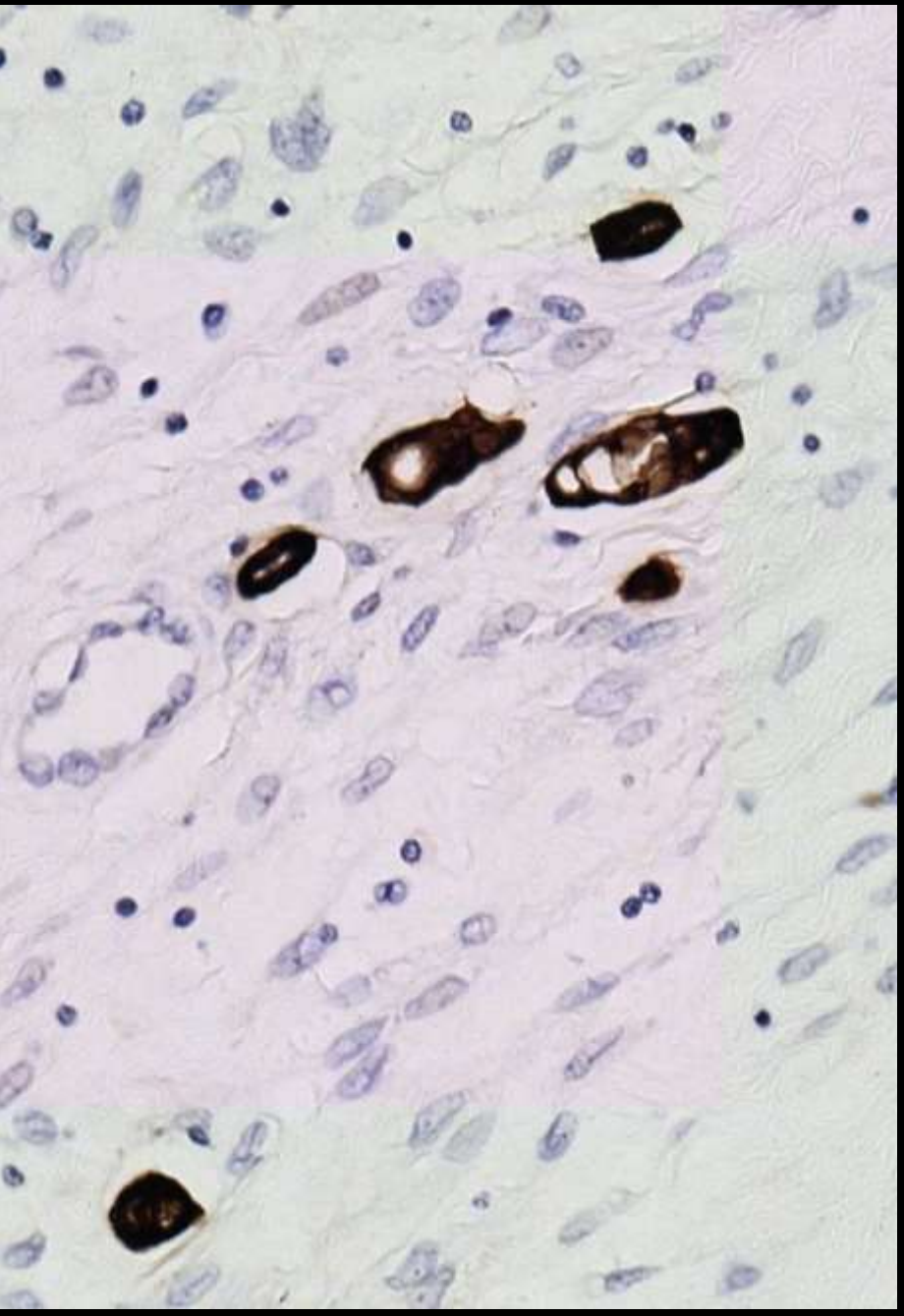
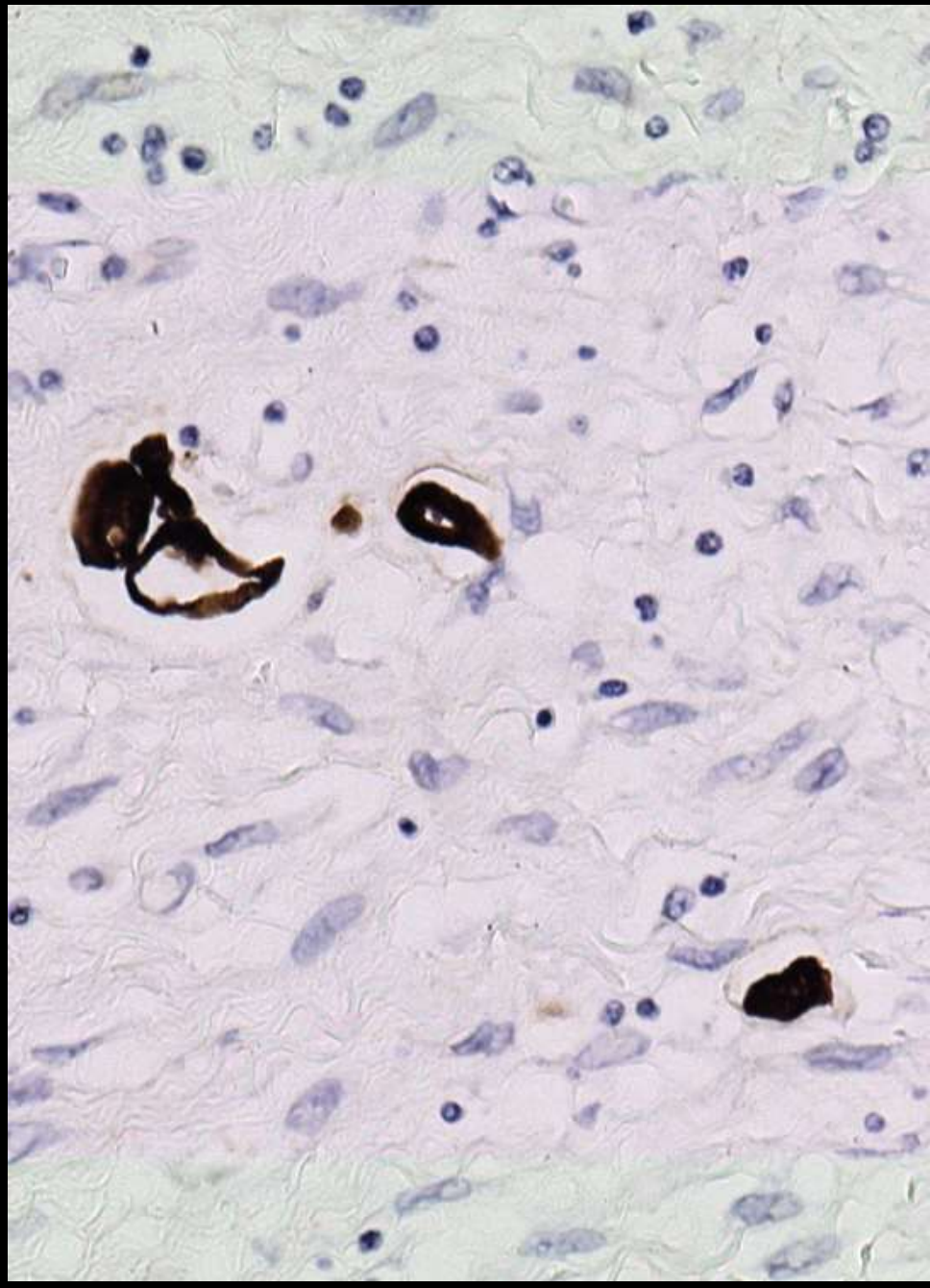
- Urothelial carcinoma
- Renal cell carcinoma
- Leukemia/lymphoma/myeloma
- De-diff liposarcoma
- Inflammatory myofibroblastic tumor
- metastasis









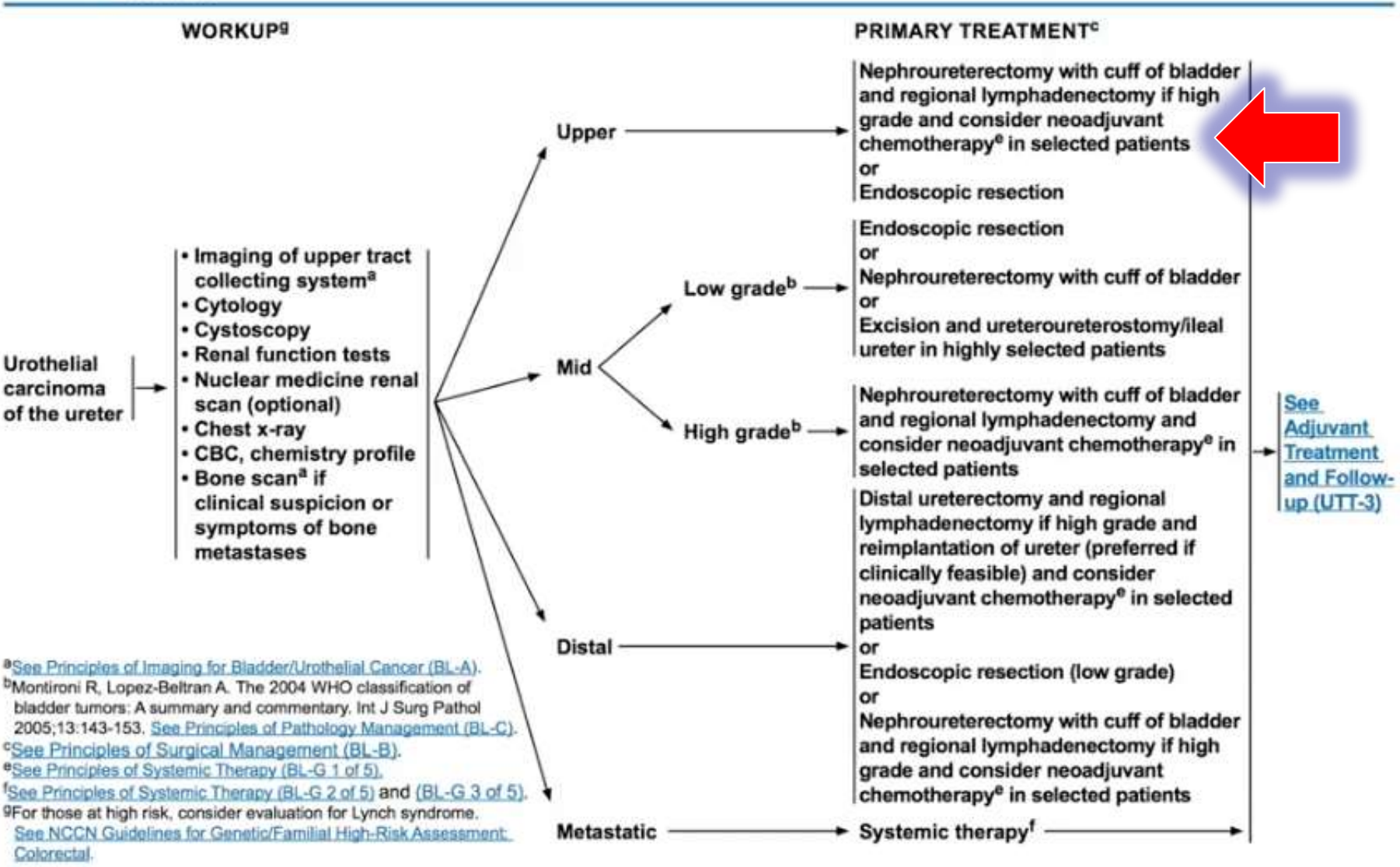



- **Several months prior to neph-U**
  - Diagnosed with metastatic urothelial carcinoma in retroperitoneal LN
  - Imaging at that time showed 2cm renal pelvic mass
    - Presumed primary
- **received neoadjuvant therapy prior to neph-U**

DIAGNOSIS

- **Residual urothelial carcinoma**
  - s/p neoadjuvant therapy

NCCN Guidelines Version 5.2018
Upper GU Tract Tumors



[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[c] See Principles of Surgical Management (BL-B).
[e] See Principles of Systemic Therapy (BL-G 1 of 5).
[f] See Principles of Systemic Therapy (BL-G 2 of 5) and (BL-G 3 of 5).
[g] For those at high risk, consider evaluation for Lynch syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

REMINDERS

Universal Lynch Syndrome Screening Should be Performed in All Upper Tract Urothelial Carcinomas

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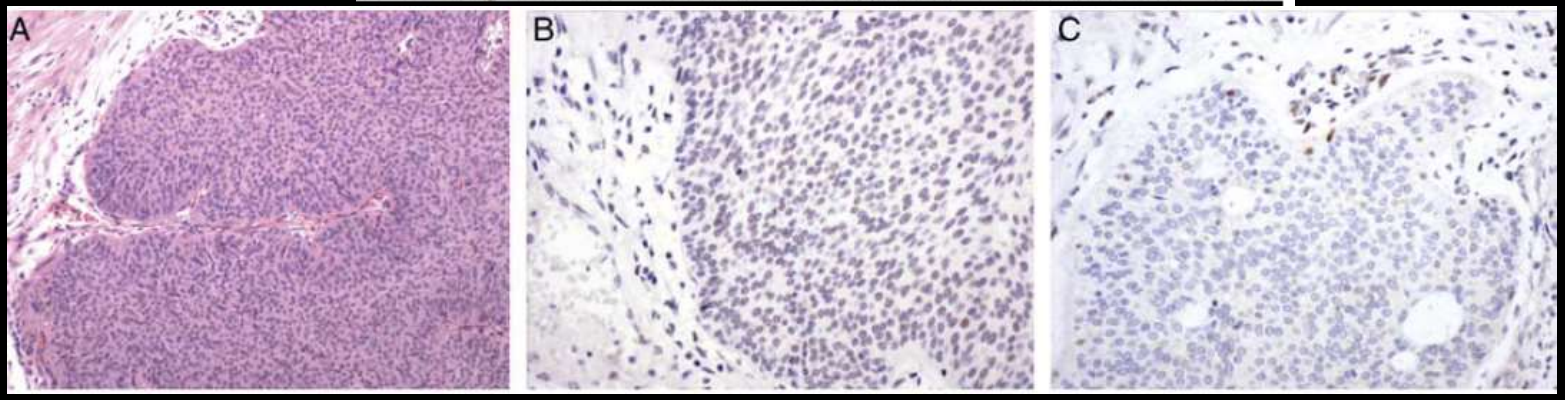

PDL1 IHC

FGFR mutation (bladder)