DEC 2019 DIAGNOSIS LIST

19-1201: melanoma (hemorrhoid/GI pathology)
19-1202: spindle cell/pleomorphic lipoma (soft tissue/soft tissue pathology)
19-1203: dedifferentiated endometrial carcinoma (uterus/GYN pathology)
19-1204: high grade HPV positive neuroendocrine carcinoma (tonsil/head&neck pathology)
19-1205: portal hypertensive duodenopathy (duodenum/GI pathology)
19-1206: rhabdomyosarcoma (bone marrow/bone&soft tissue pathology)
19-1207: intrapancreatic spleen (pancreas/GI pathology)
19-1208: oncocytic mucoepidermoid carcinoma with lymphoid stroma (salivary gland/head&neck pathology)
19-1209: IgG4 related sclerosing cholangitis (pancreas/GI pathology)
19-1210: giant cell variant glioblastoma, WHO grade IV (brain/neuropathology)

Disclosures
Dec 2, 2019

The following planners and presenters had disclosures:

Ankur Sangoi, MD	Google	Consultant
Keith Duncan, MD	ABBvie	Consultant
Christine Louie, MD	Grail	Consultant

South Bay Pathology Society has determined that these relationships are not relevant to the clinical cases being presented.

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

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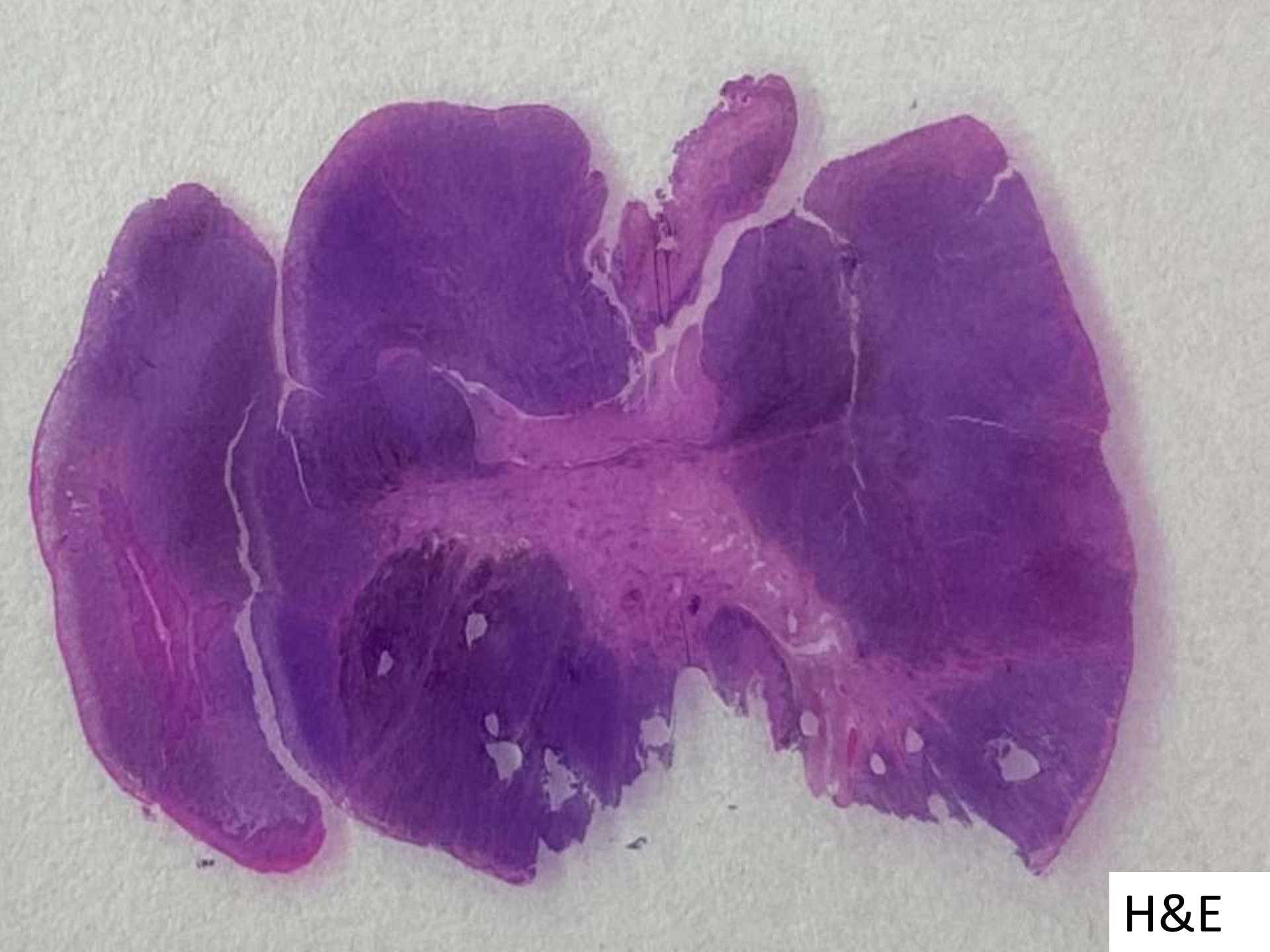
19-1201

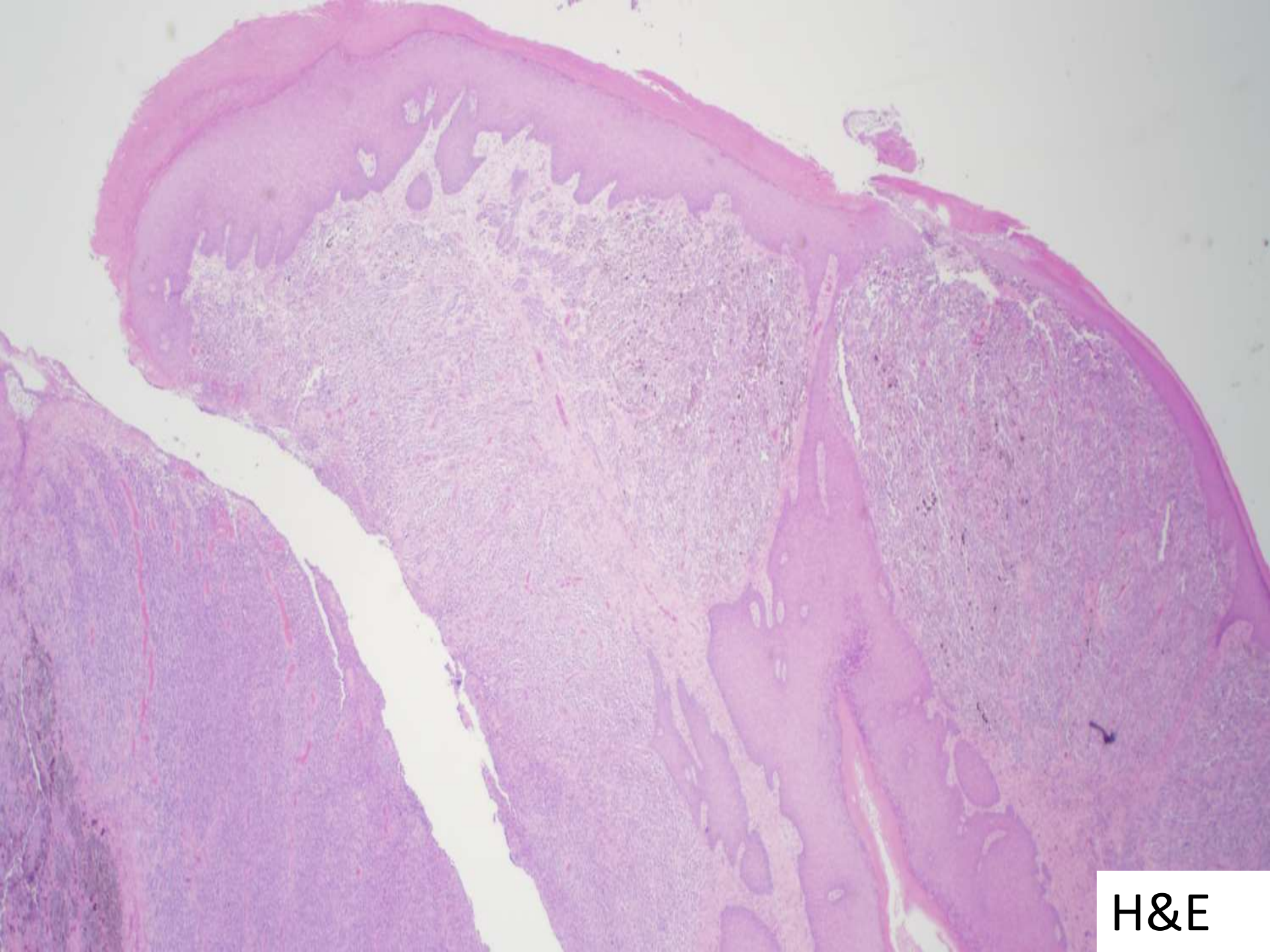
Hannah Lee/Joshua Menke; UCSF

47-year-old female with an internal hemorrhoid, presenting for hemorrhoidectomy.

South Bay Case History

- 47 year old woman with melena and hematochezia for 8 months.
- Colonoscopy showed internal hemorrhoids and otherwise normal.
- She was managed medically for 6 months without improvement and then underwent hemorrhoidectomy for thrombosed necrotic external hemorrhoid


H&E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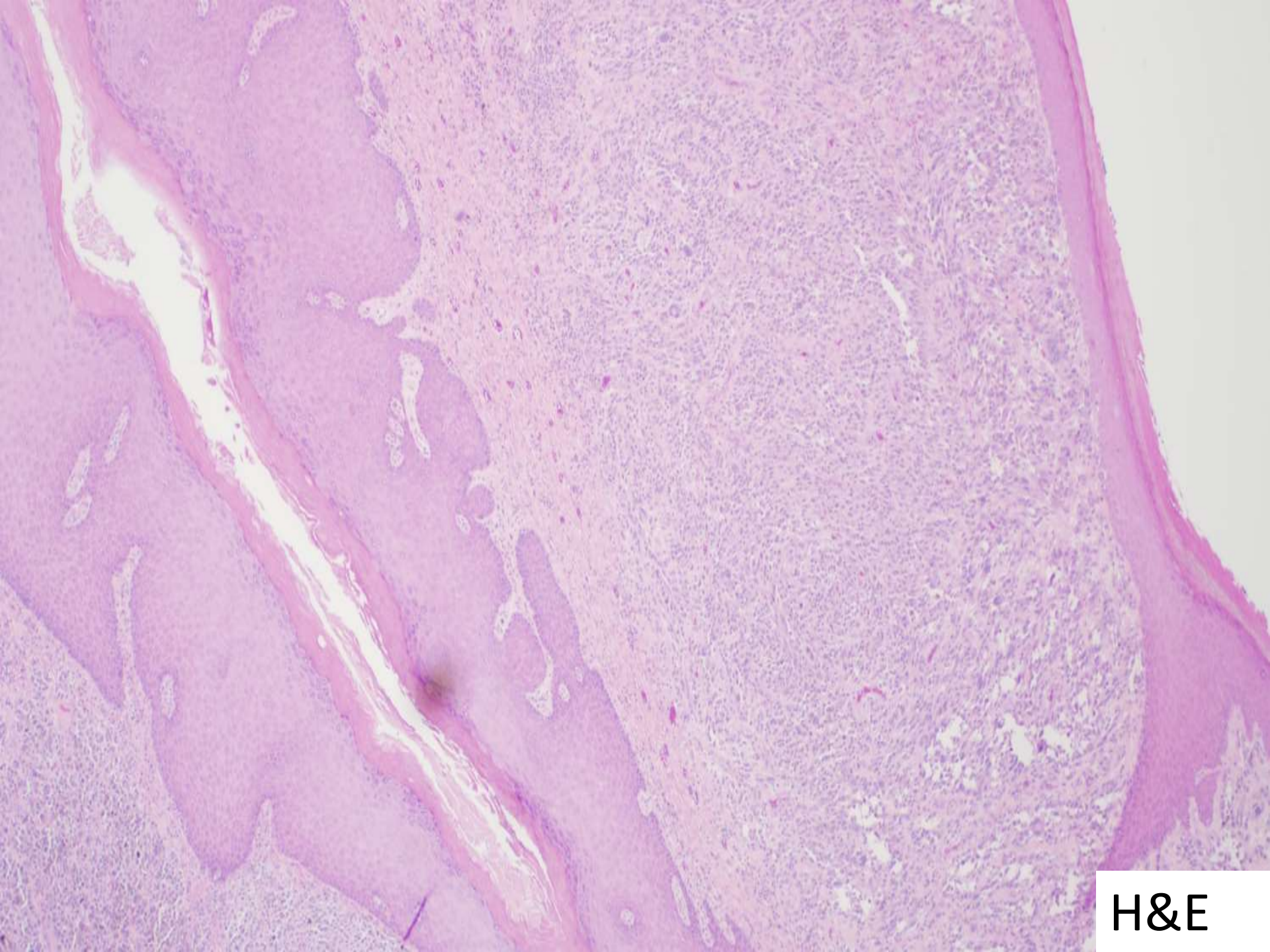
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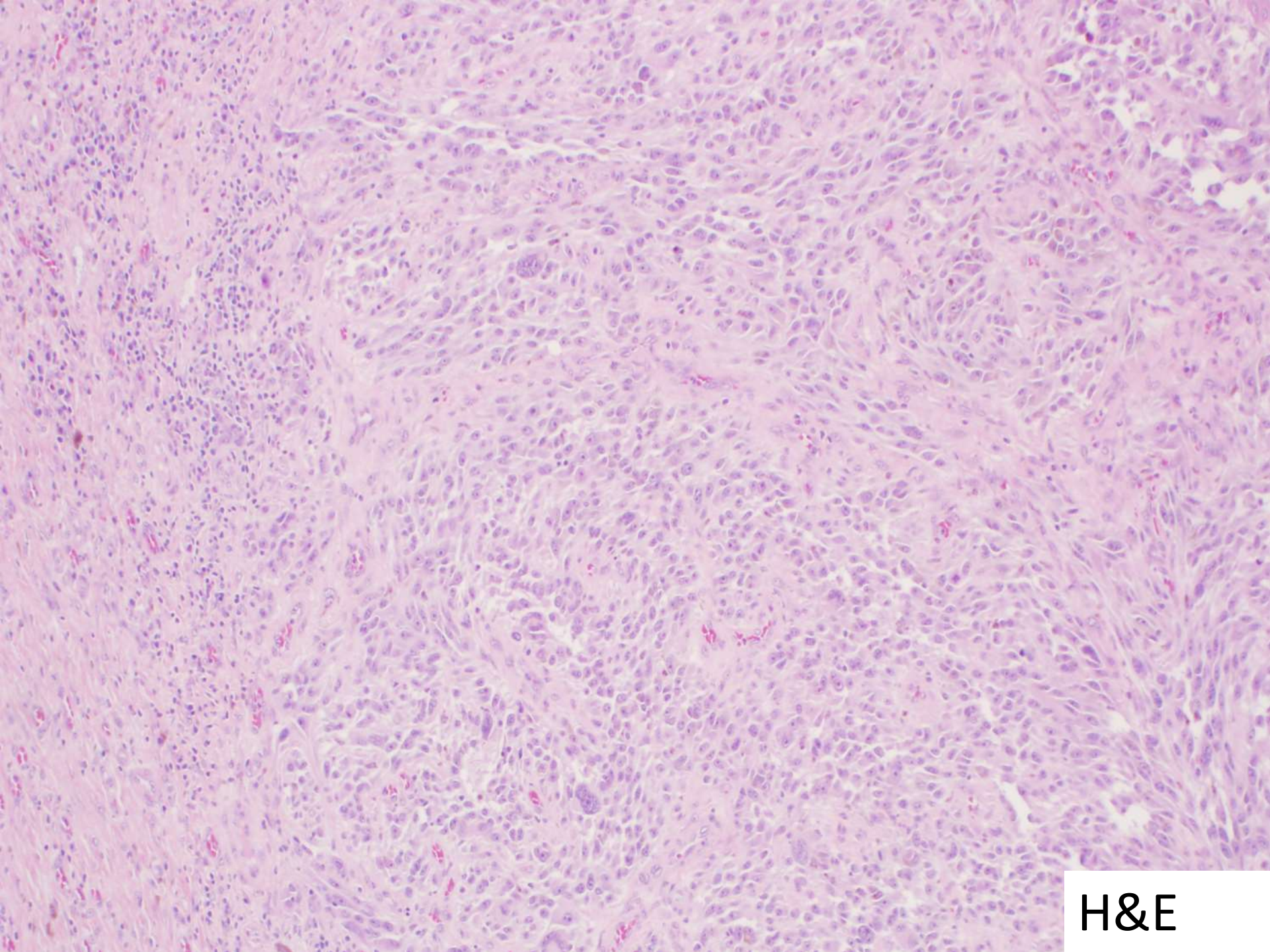
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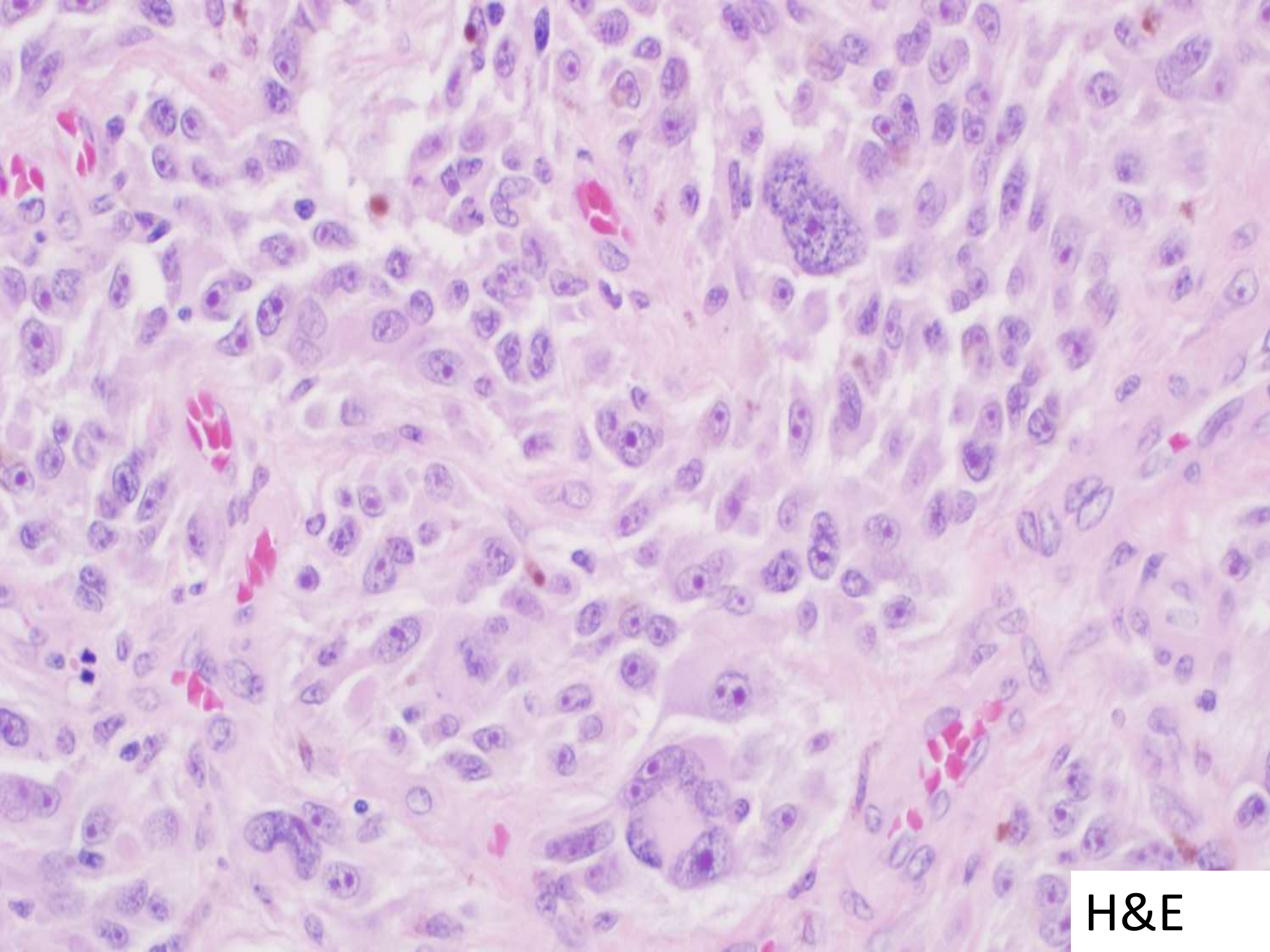
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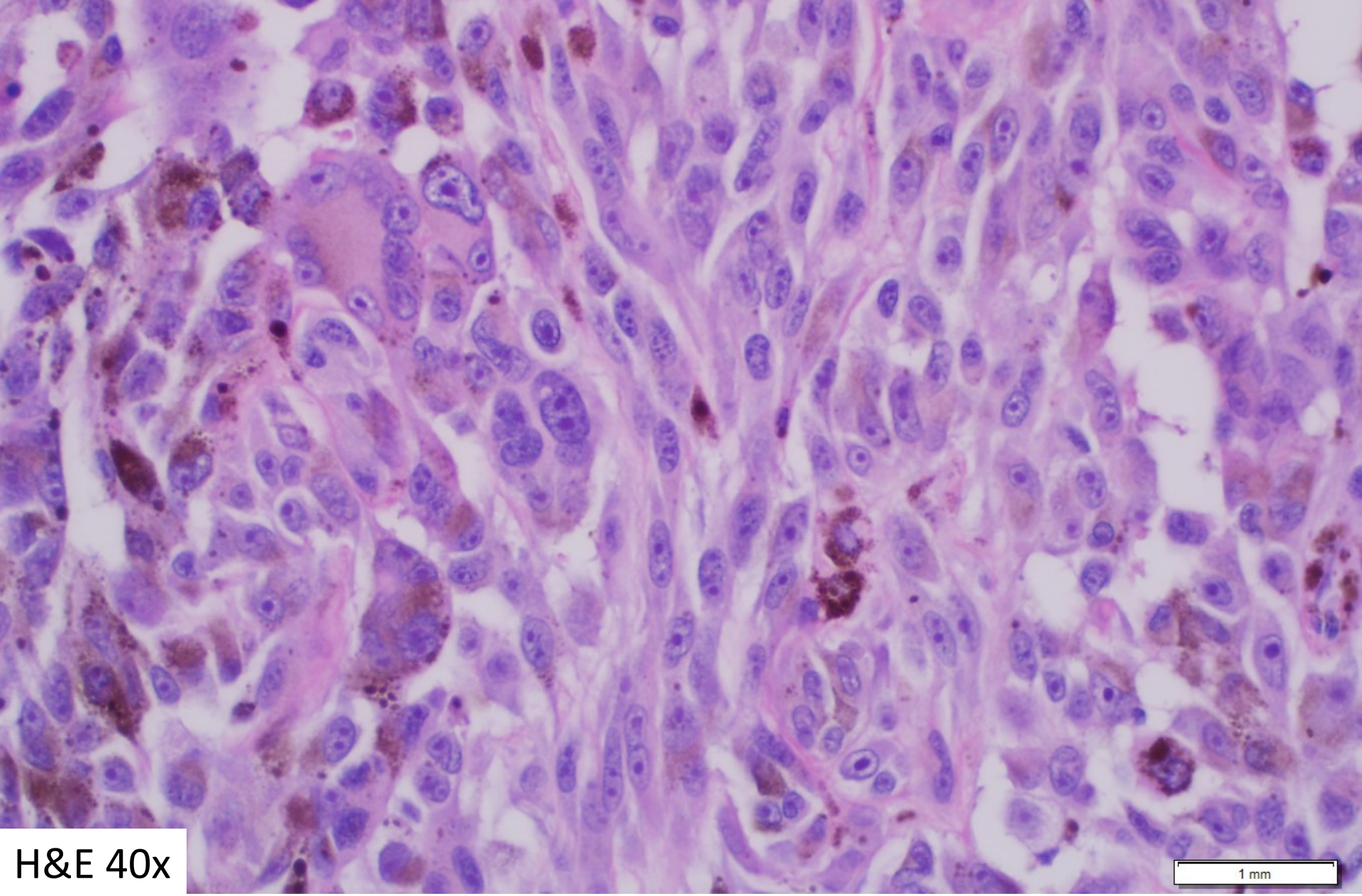
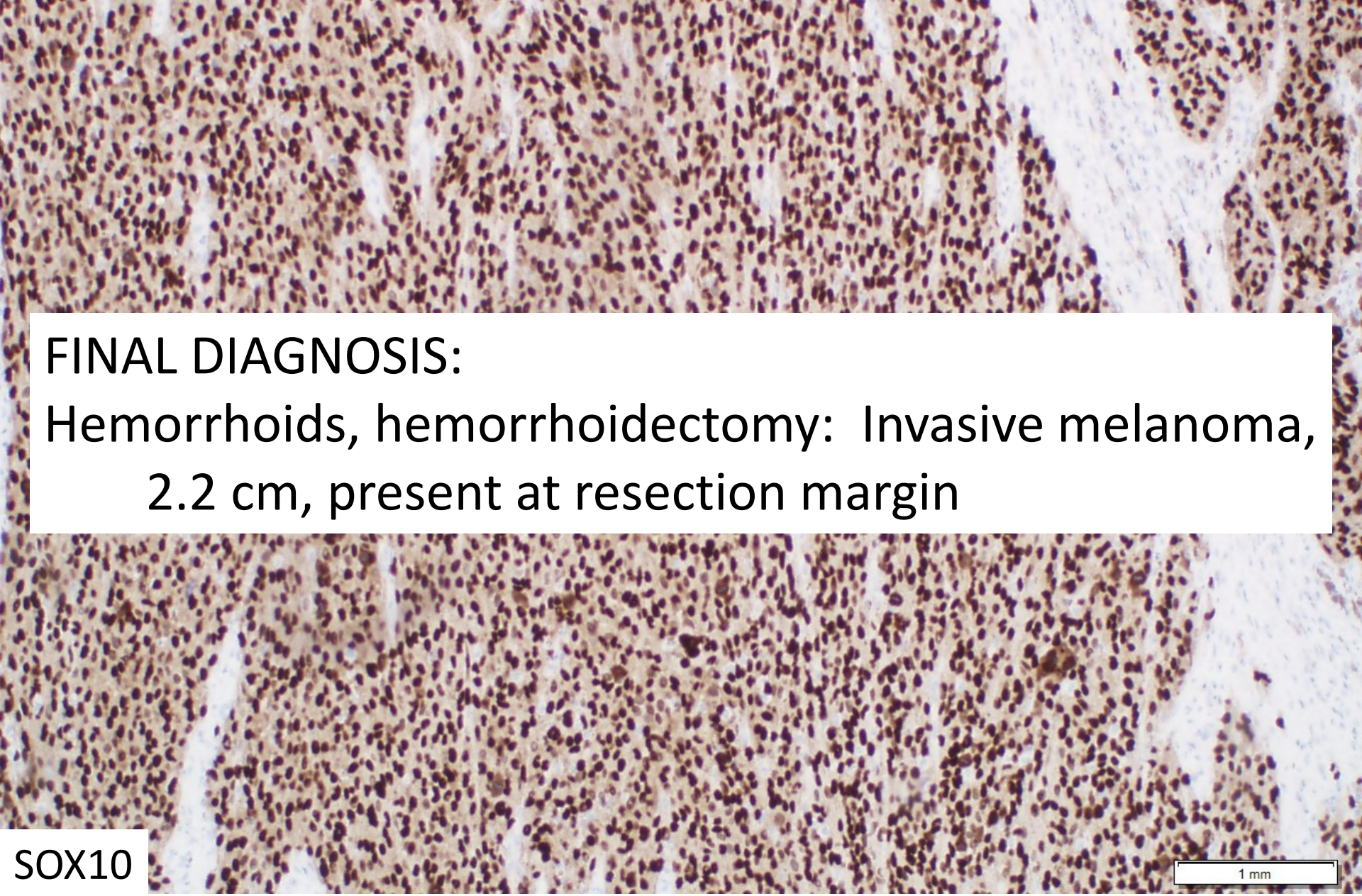

H&E 40x
1 mm


FINAL DIAGNOSIS:
Hemorrhoids, hemorrhoidectomy: Invasive melanoma,
2.2 cm, present at resection margin
SOX10
1 mm

Stanford MEDICINE | Department of PATHOLOGY

What's Hiding In Your Hemorrhoids? A Review of 1,015 Hemorrhoids

David Levy, MD,[1] John Higgins, MD,[1] Christine Y. Louie, MD[2]

Stanford University School of Medicine, Department of Pathology, Stanford, CA[1]; VA Palo Alto Health Care System, Department of Pathology, Palo Alto, CA[2]

Background

Hemorrhoidectomy specimens are routinely submitted for histopathologic evaluation and while a vast majority of specimens submitted as "hemorrhoid" demonstrate the classic features of dilated vascular spaces with or without thrombosis, occasionally, incidental lesions are identified. All specimens submitted as "hemorrhoid" at two hospitals were retrospectively reviewed to examine the prevalence of unexpected findings in hemorrhoidectomy specimens.

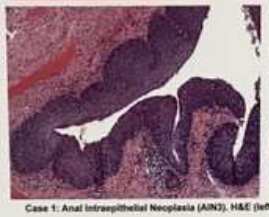
Methods & Materials

Our institutions' databases were searched from 1991-2017 for specimens submitted as "hemorrhoid" or "hemorrhoidectomy." Pathology reports and select slides were reviewed.

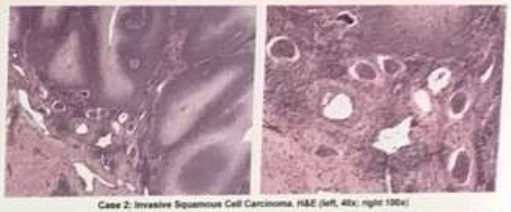
Results

DIAGNOSTIC FINDINGS	
Hemorrhoid	798 (78.6%)
Thrombosed hemorrhoid	127 (12.5%)
Fibroepithelial polyp	35 (3.4%)
Reactive conditions – no hemorrhoidal tissue	21 (2.1%)
Condyloma acuminata	10 (1.0%)
Squamous cell carcinoma in situ/AIN3	9 (0.9%)
Invasive squamous cell carcinoma	2 (0.2%)
Invasive adenocarcinoma	2 (0.2%)
Tubular adenoma	2 (0.2%)
Hyperplastic polyp	2 (0.2%)
Granular cell tumor	1 (0.1%)
Small cell carcinoma	1 (0.1%)
Invasive melanoma	1 (0.1%)
Neurofibroma	1 (0.1%)
Tubulovillous adenoma	1 (0.1%)
Paget's disease	1 (0.1%)
Benign ectopic breast tissue	1 (0.1%)
	1,015 (100%)

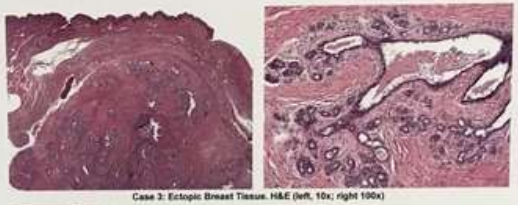
Figures



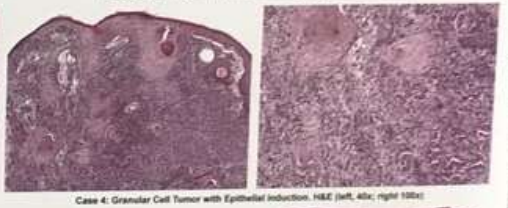
Case 1: Anal Intraepithelial Neoplasia (AIN3). H&E (left, 100x) and p16 Immunohistochemistry (right, 100x)



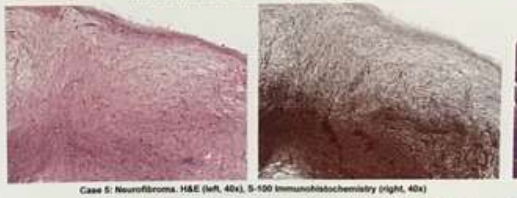
Case 2: Invasive Squamous Cell Carcinoma. H&E (left, 40x; right 100x)



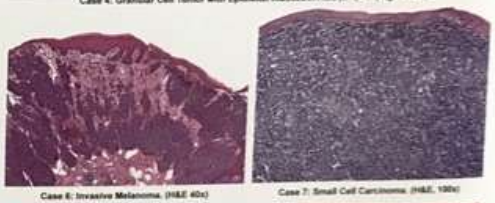
Case 3: Ectopic Breast Tissue. H&E (left, 10x; right 100x)



Case 4: Granular Cell Tumor with Epithelial Induction. H&E (left, 40x; right 100x)

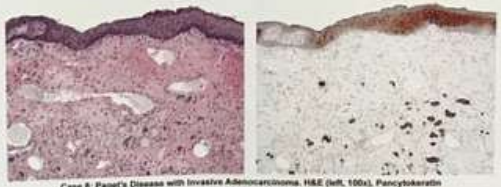


Case 5: Neurofibroma. H&E (left, 40x), S-100 Immunohistochemistry (right, 40x)



Case 6: Invasive Melanoma. (H&E 40x)

Case 7: Small Cell Carcinoma. (H&E, 100x)



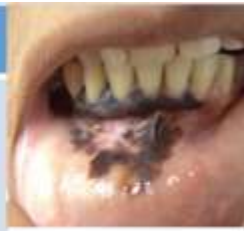
Case 8: Paget's Disease with Invasive Adenocarcinoma. H&E (left, 100x), Pancytokeratin Immunohistochemistry (right, 100x)

Conclusions

- Unexpected findings are occasionally seen in hemorrhoidectomy specimens. Although a majority of cases demonstrated findings consistent with hemorrhoids or thrombosed hemorrhoids, 3.3% showed neoplastic, dysplastic or malignant findings.
- This study emphasizes the importance of submitting hemorrhoidectomy specimens for histopathologic review, as unexpected diagnostic findings may occur that require additional follow up and treatment.

The authors have no conflicts of interest to disclose.
We would like to acknowledge Norm Cyr for his assistance in creating this poster.

	Cutaneous Melanoma	Mucosal Melanoma
Epidemiology	Common, in European background	Rare in US (~1% of melanoma) • 9% of melanomas in blacks in US • 15% of melanomas in Asians in US 25% of all melanoma in China
Primary site	Sun exposed skin	Head and neck (1/3), vulvovaginal (1/3), GI tract (1/3)
Clinical presentation	• Early localized disease • ~10% of patients with locoregional LN involvement • 5 year survival ~90%	• Frequent spread to lymph nodes • Head and neck (21%), anorectal (61%), vulvovaginal (23%) • Distant metastasis (23%) • 5 year survival ~14%
Pathogenesis	• Cutaneous melanocyte origin • Risk factors include sun exposure, family history, nevus count, non-Hispanic white	• Mucosal melanocyte origin (neural crest migration) • No know risk factors
Genetics	• Frequent UV radiation signature • High mutation burden (14.4 mut/Mb) • *BRAF* (50%) and *NRAS*	• Rare to absent UV radiation signature • Low mutation burden (2.7 mut/Mb) • High rate of copy number and structural changes • Genetically heterogeneous (*BRAF* in 8-12%, *KIT,* and other MAPK mutations)



Has a clinician ever gotten a FoundationOne report you didn't know how to interpret????

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

FOUNDATIONONE® CDx

Microsatellite status MS-Stable §
Tumor Mutational Burden 5 Muts/Mb §
CCND1 amplification §
CDK4 amplification §
CRKL amplification §
DIS3 amplification §
EP300 PLCL1(NM_006226)-EP300(NM_001429) fusion (P1; E7) §
FGF19 amplification §
FGF3 amplification §
FGF4 amplification §
KIT amplification §
MLH1 R522W

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Whole genome sequencing of mucosal melanoma

- Low point mutation burden
- High number of structural rearrangements (*TERT, CDK4, MDM2)*
- Mutually exclusive MAPK pathway mutations (*NRAS, NF1, KIT, BRAF*)
- *SF3B1* mutations more common in female genital and anorectal melanomas
- *CTNNB1* mutations implicate a role for WNT signaling defects in the genesis of some mucosal melanomas
- Mutation profiles of majority of mucosal melanomas suggest potential susceptibility to CDK4/6 and/or MEK inhibitors

Newell et al., Nature Comm. 2019.

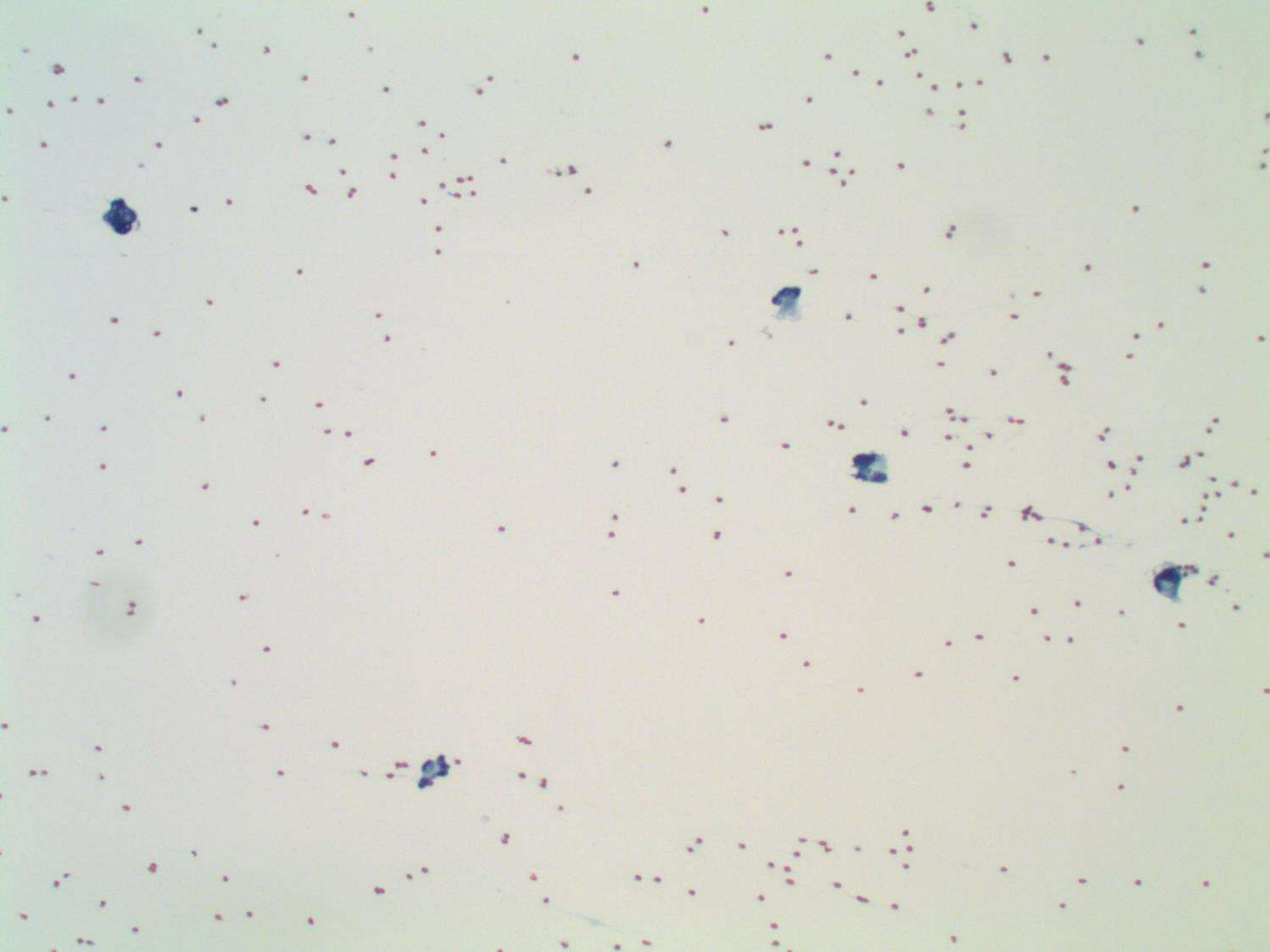
Patient follow up

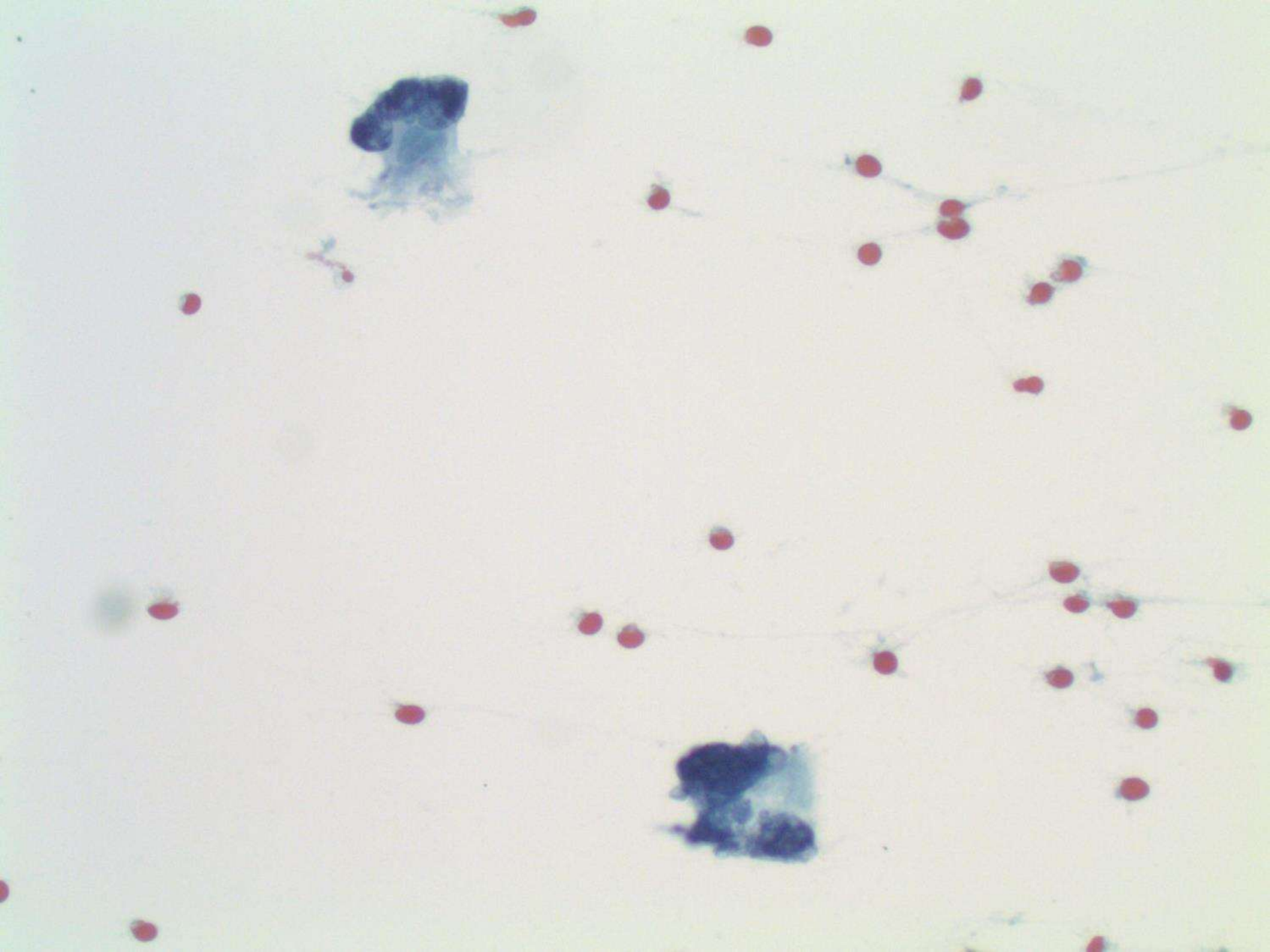
- CT chest, abdomen, pelvis showed no evidence of metastatic disease
- Per cutaneous melanoma staging, patient is pT4bNxcM0
- UCSF melanoma tumor board recommended adjuvant PD-L1 (Nivolumab)
  - Salvage abdominoperitoneal resection post-therapy if local progression
- Status post cycle 2 Nivolumab without side effects and no progression on surveillance PET-CT

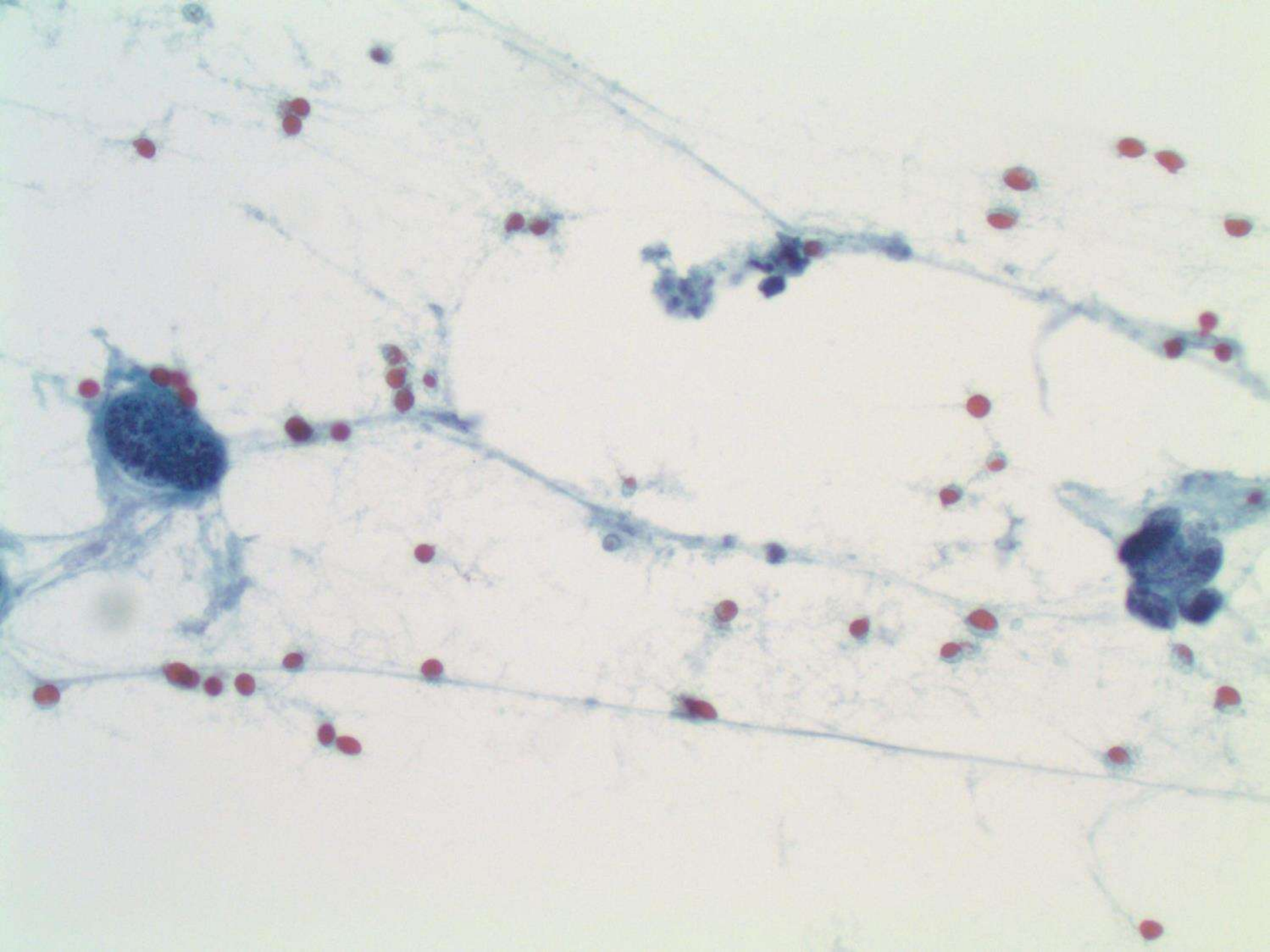
19-1202

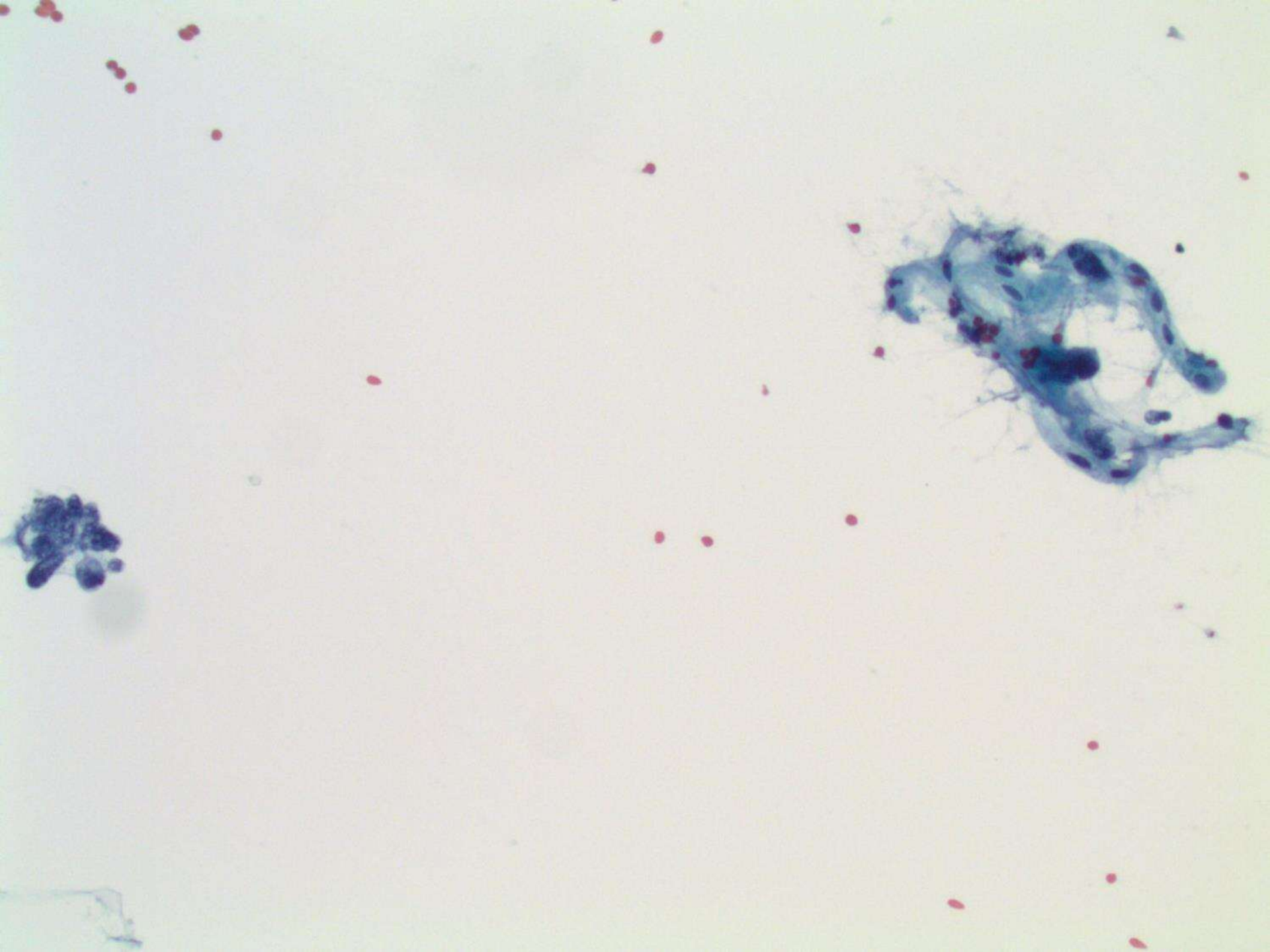
Keith Duncan; Mills-Peninsula

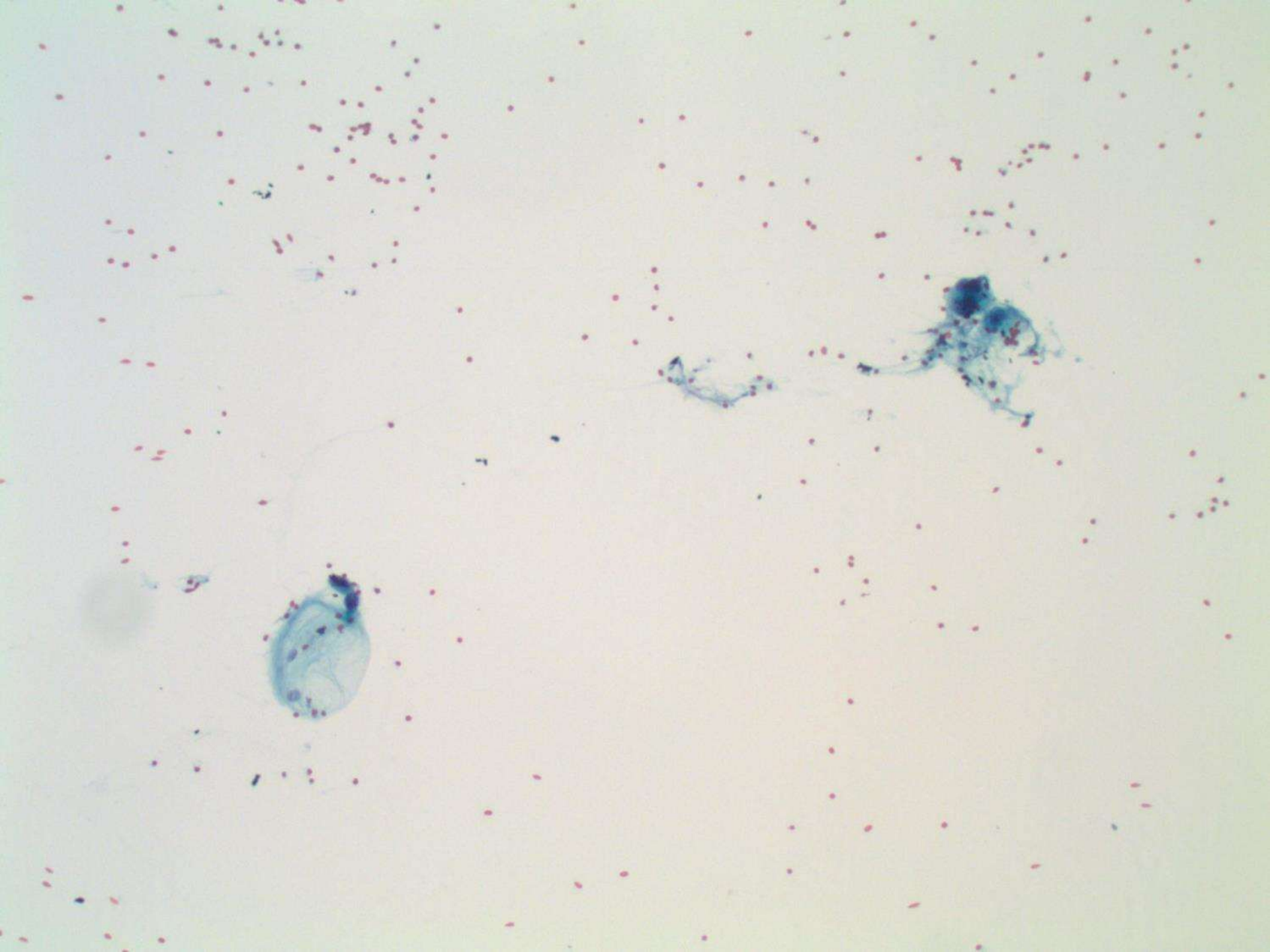
77-year-old male with h/o right parotid pleomorphic adenoma 3 years prior to finding 1cm mass at angle of jaw. Right angle of jaw mass FNA performed.

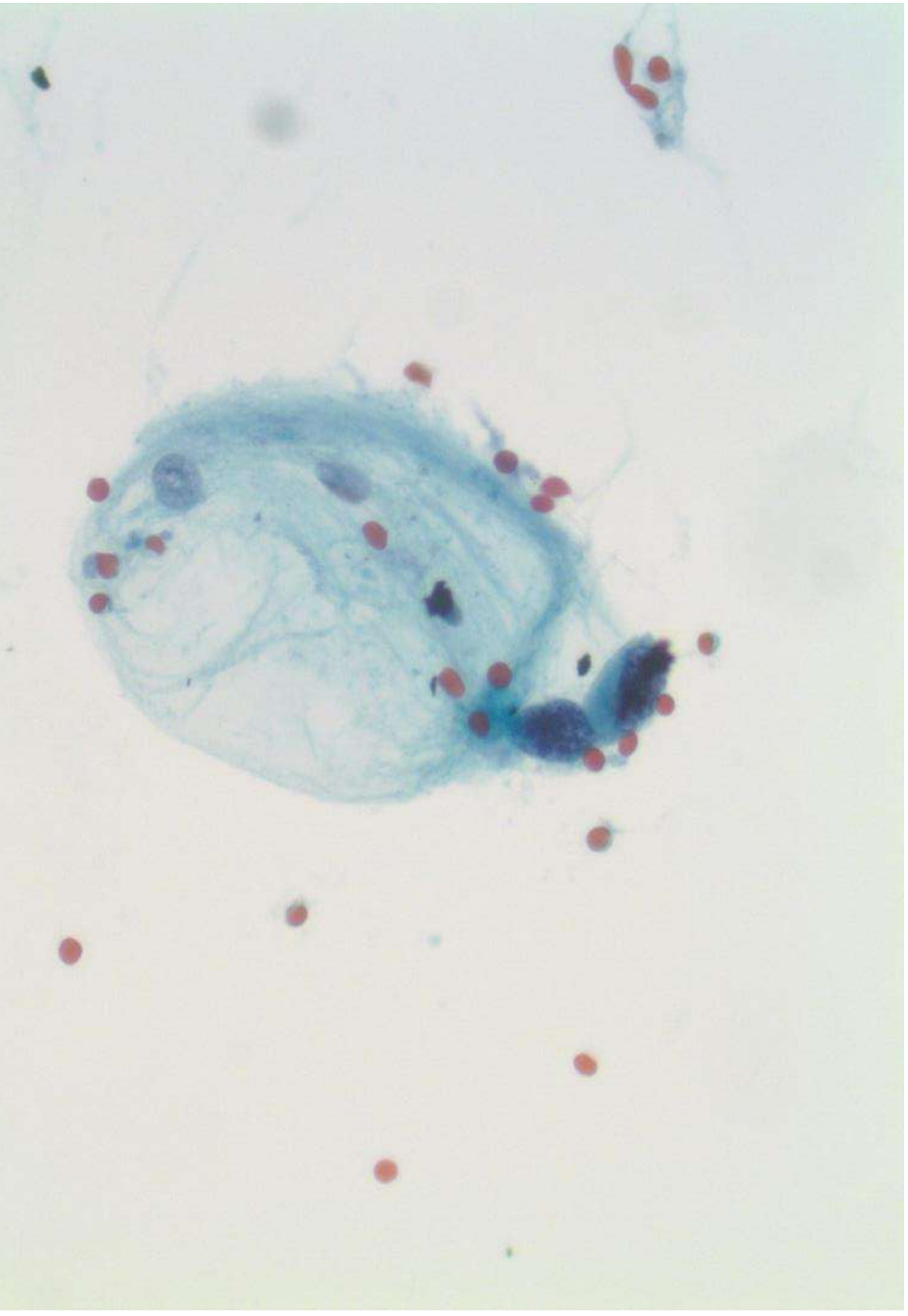


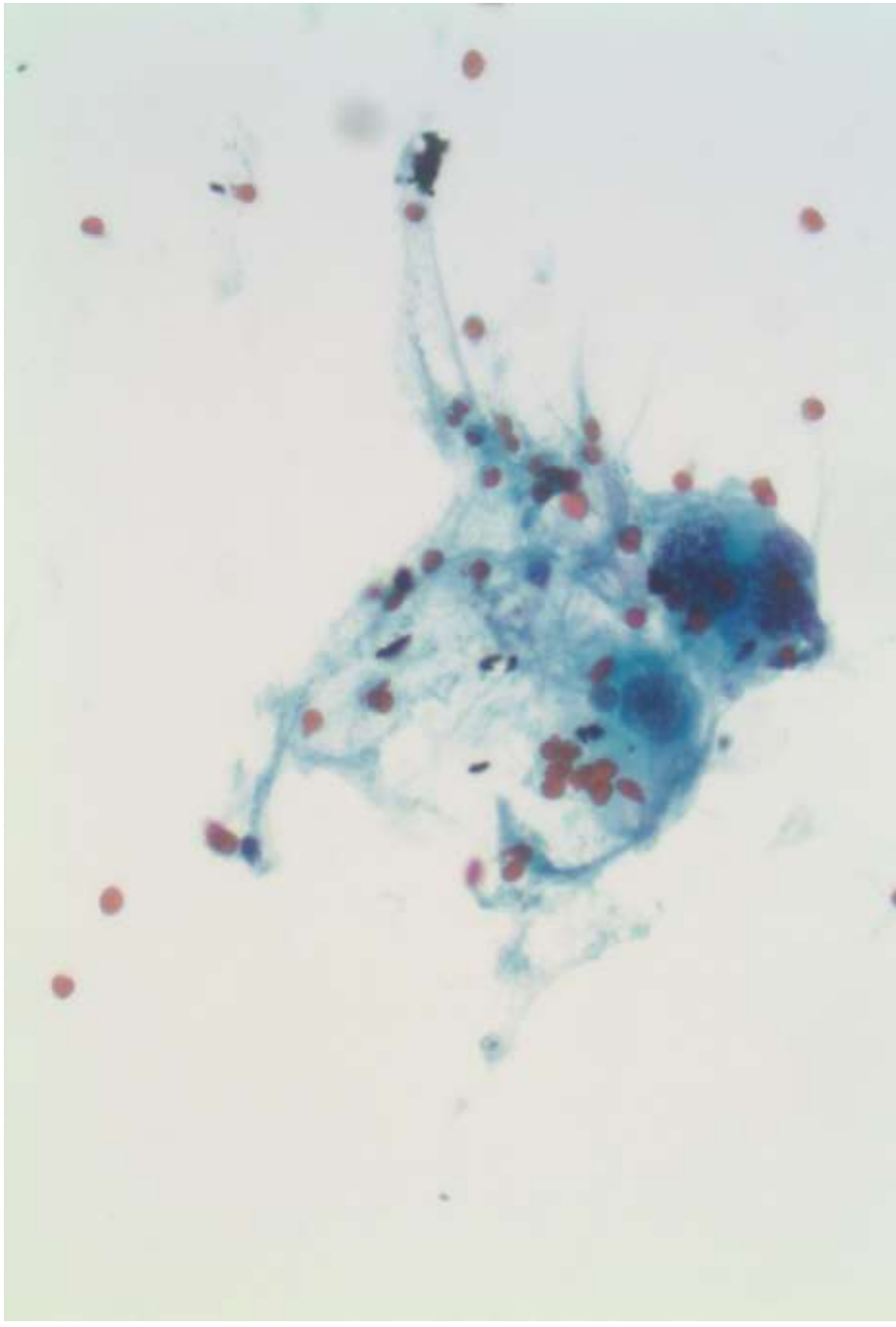


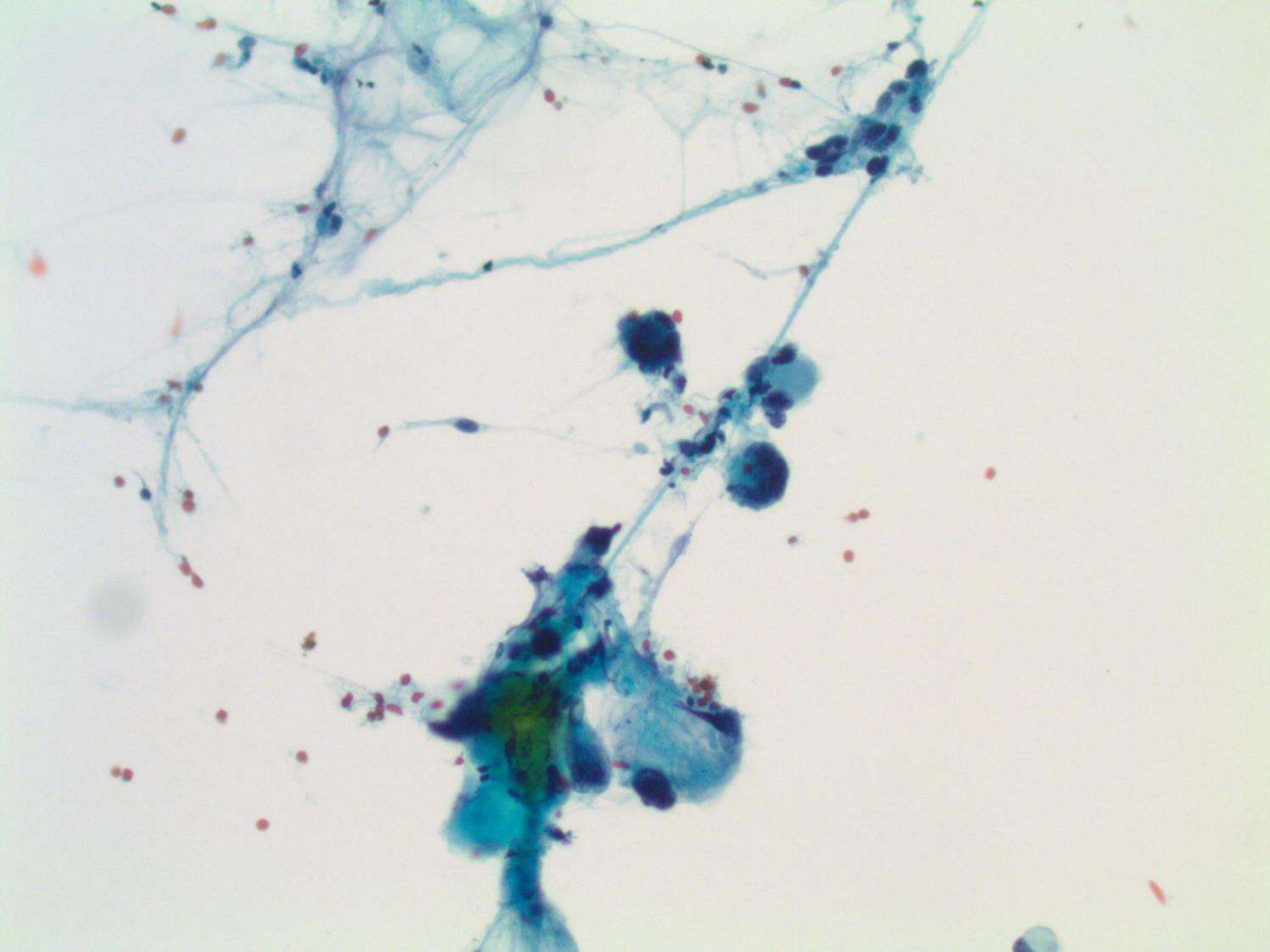


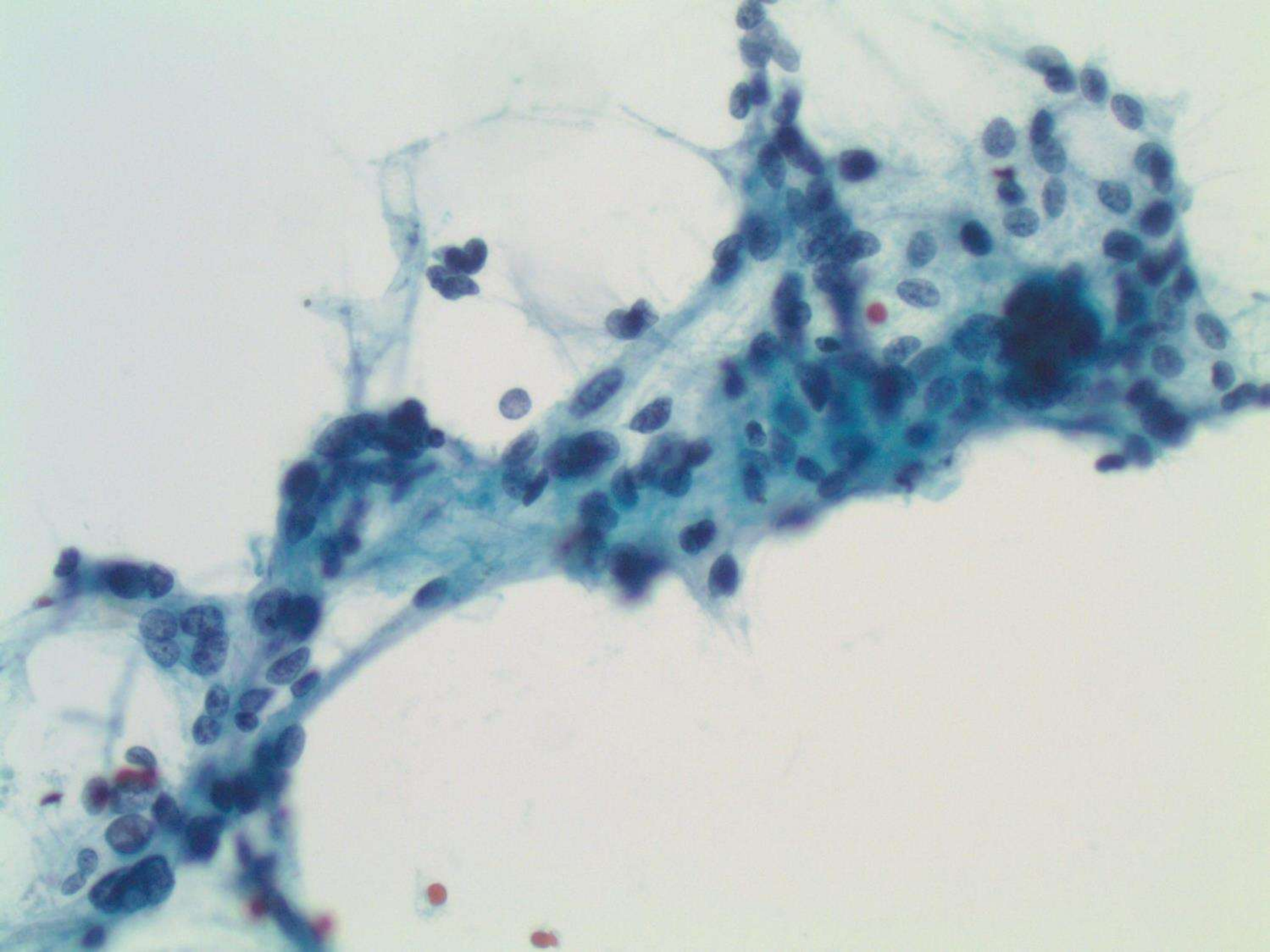


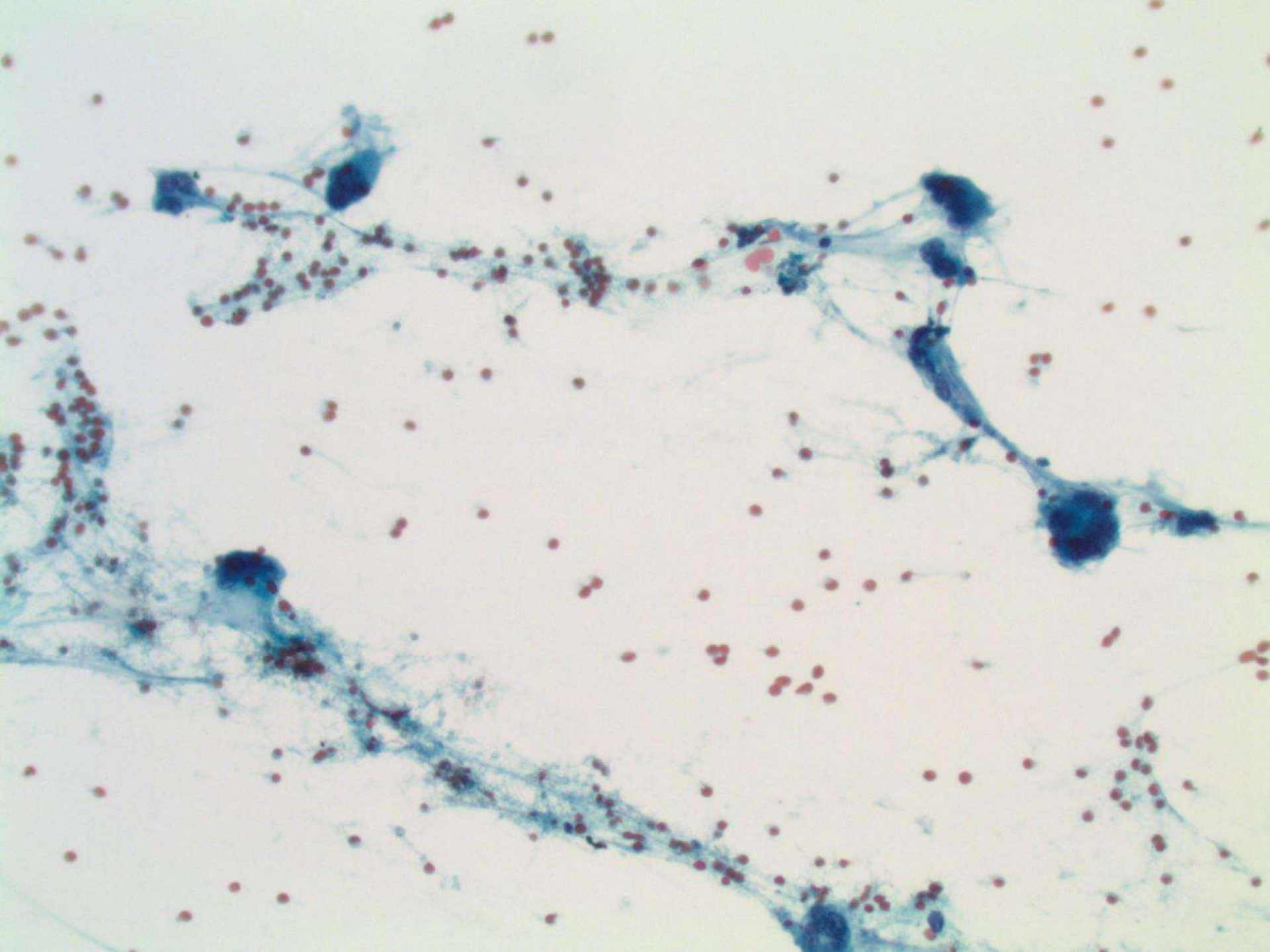


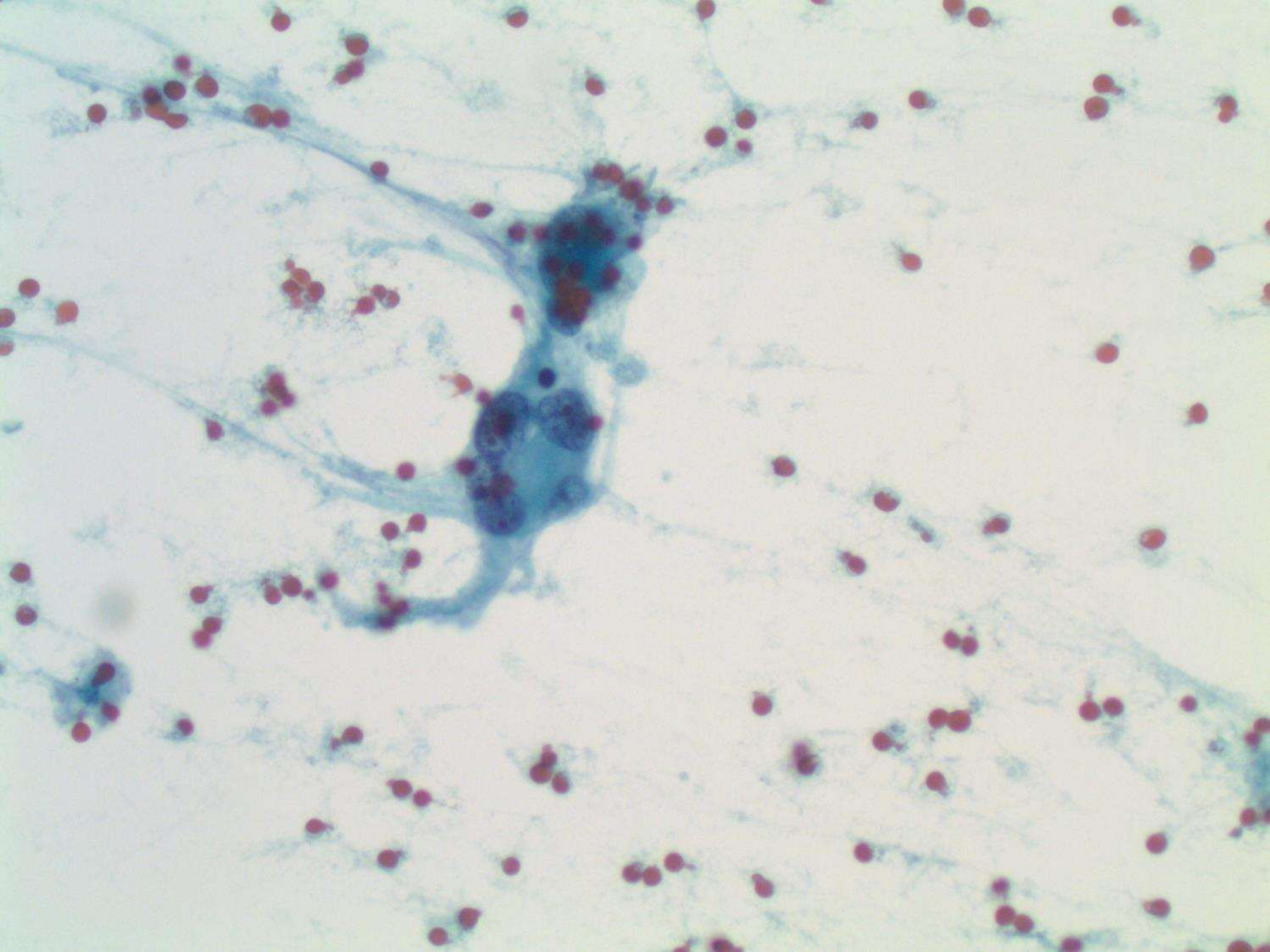


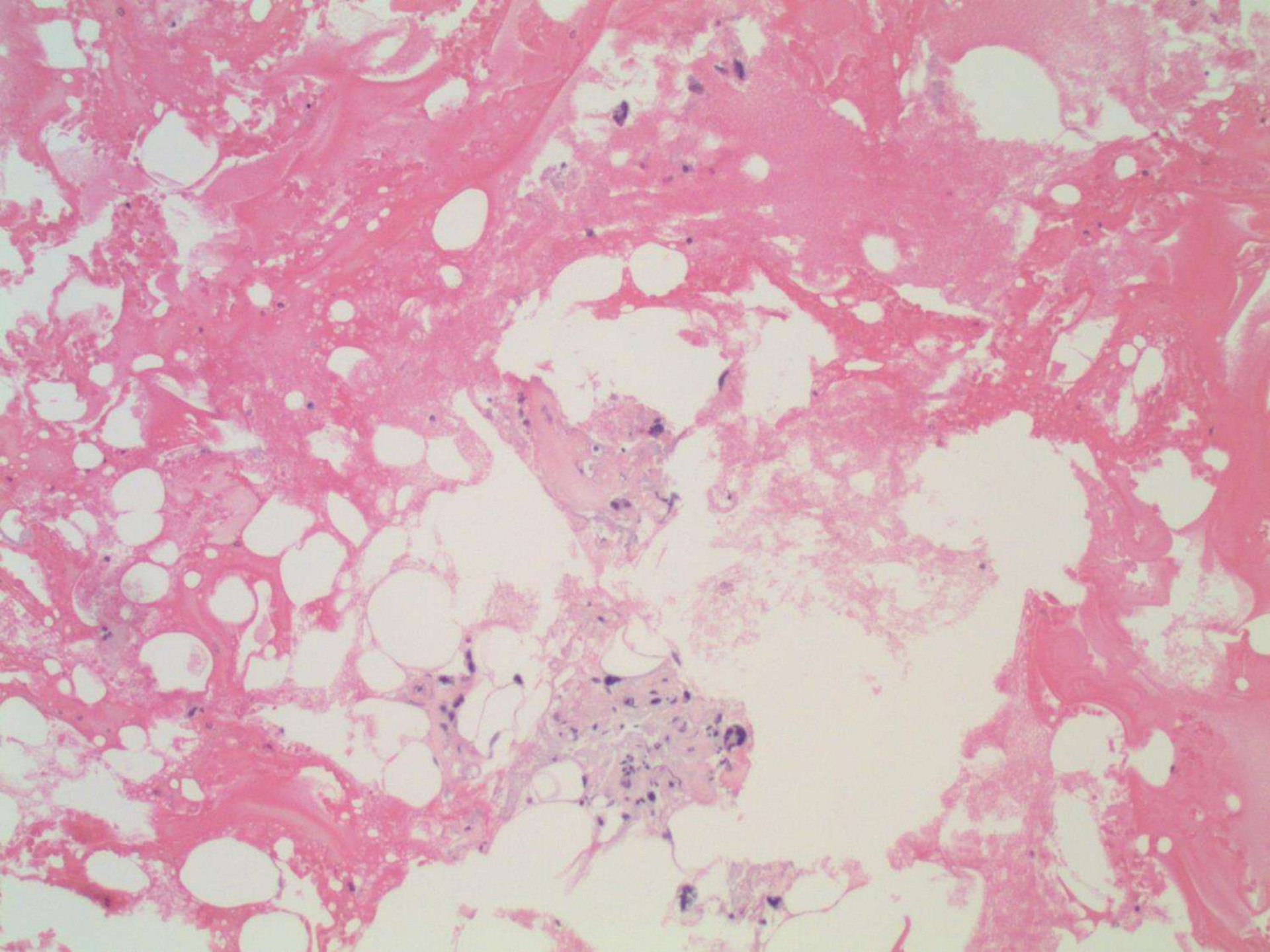


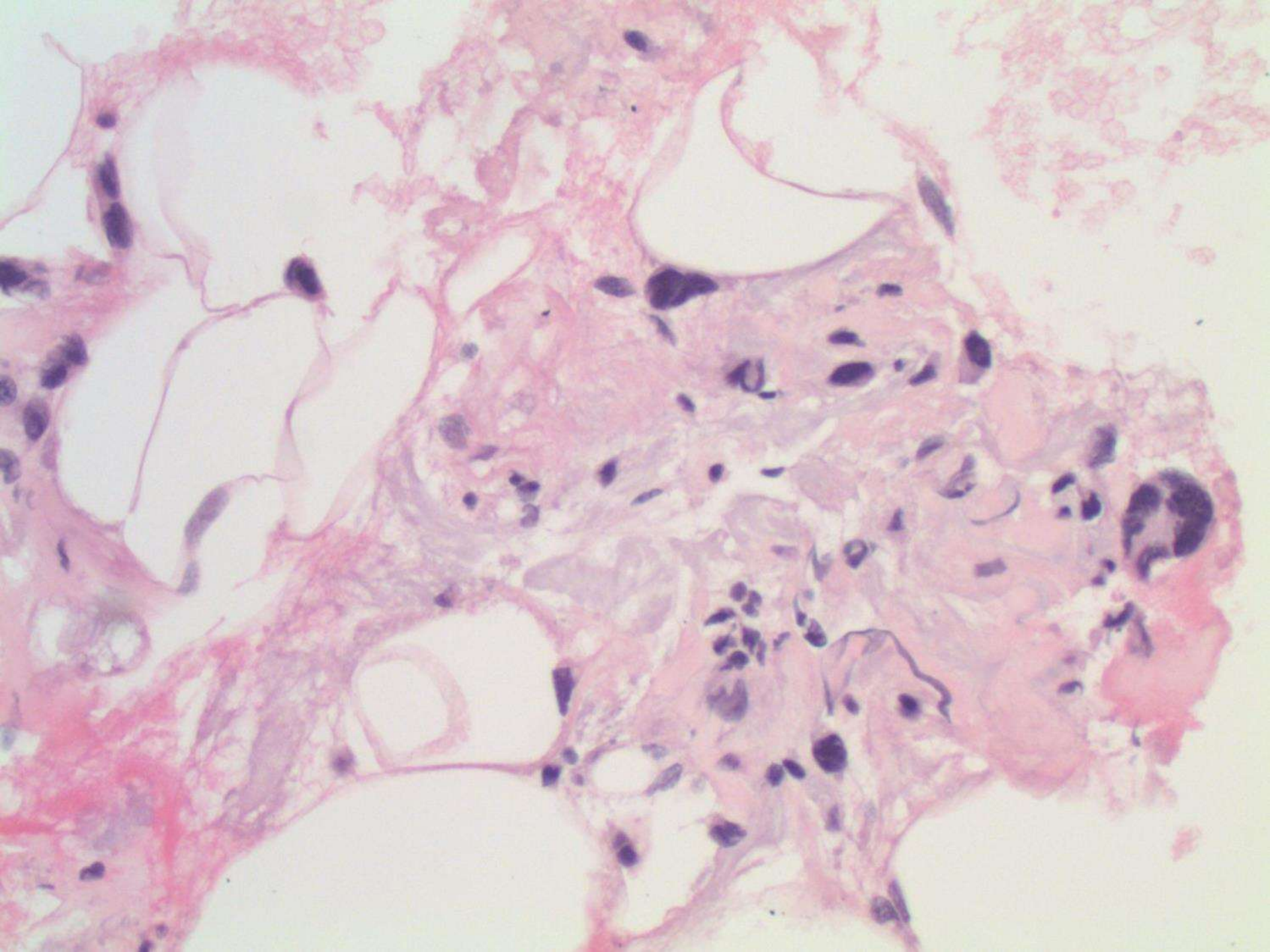


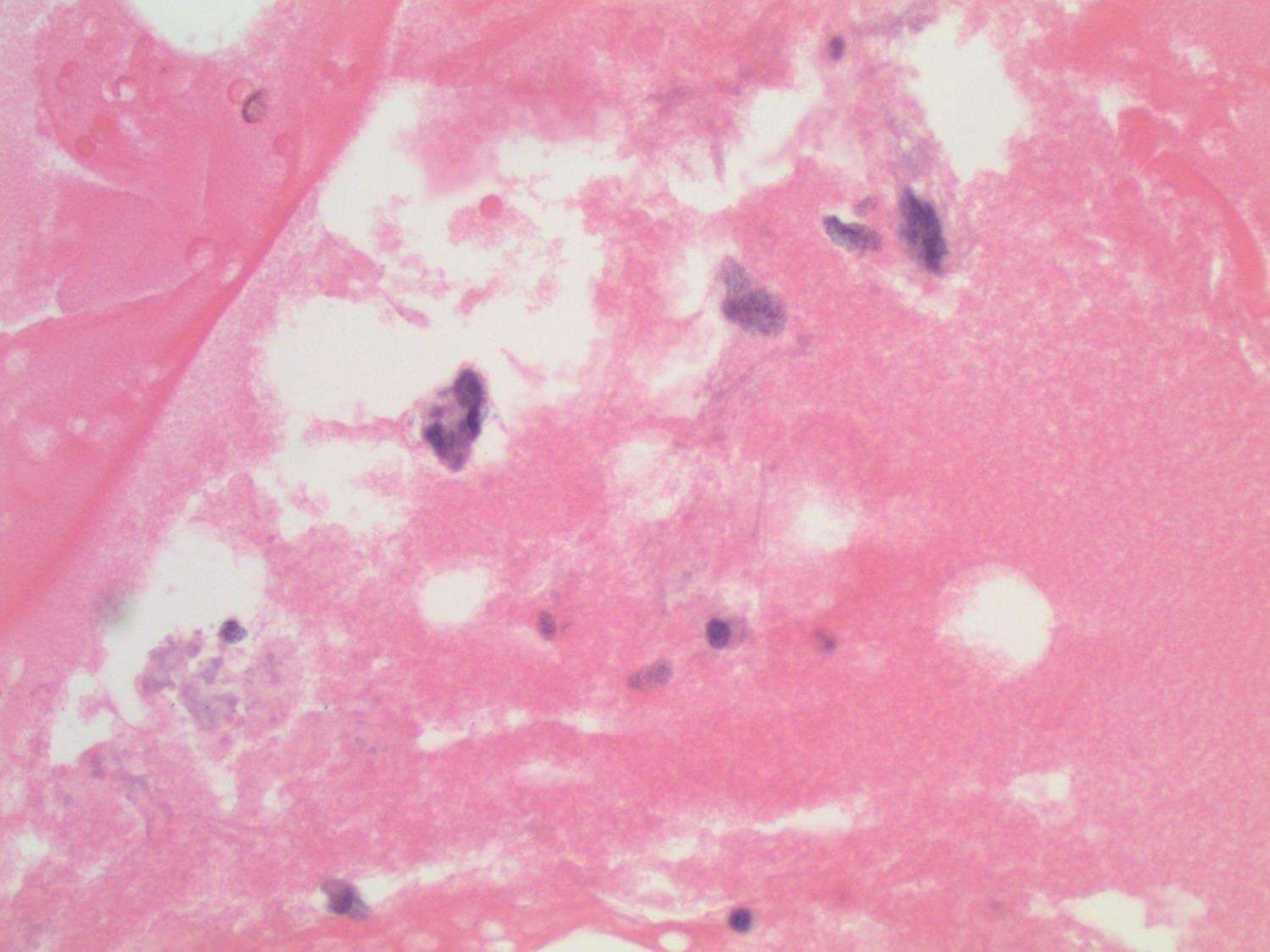


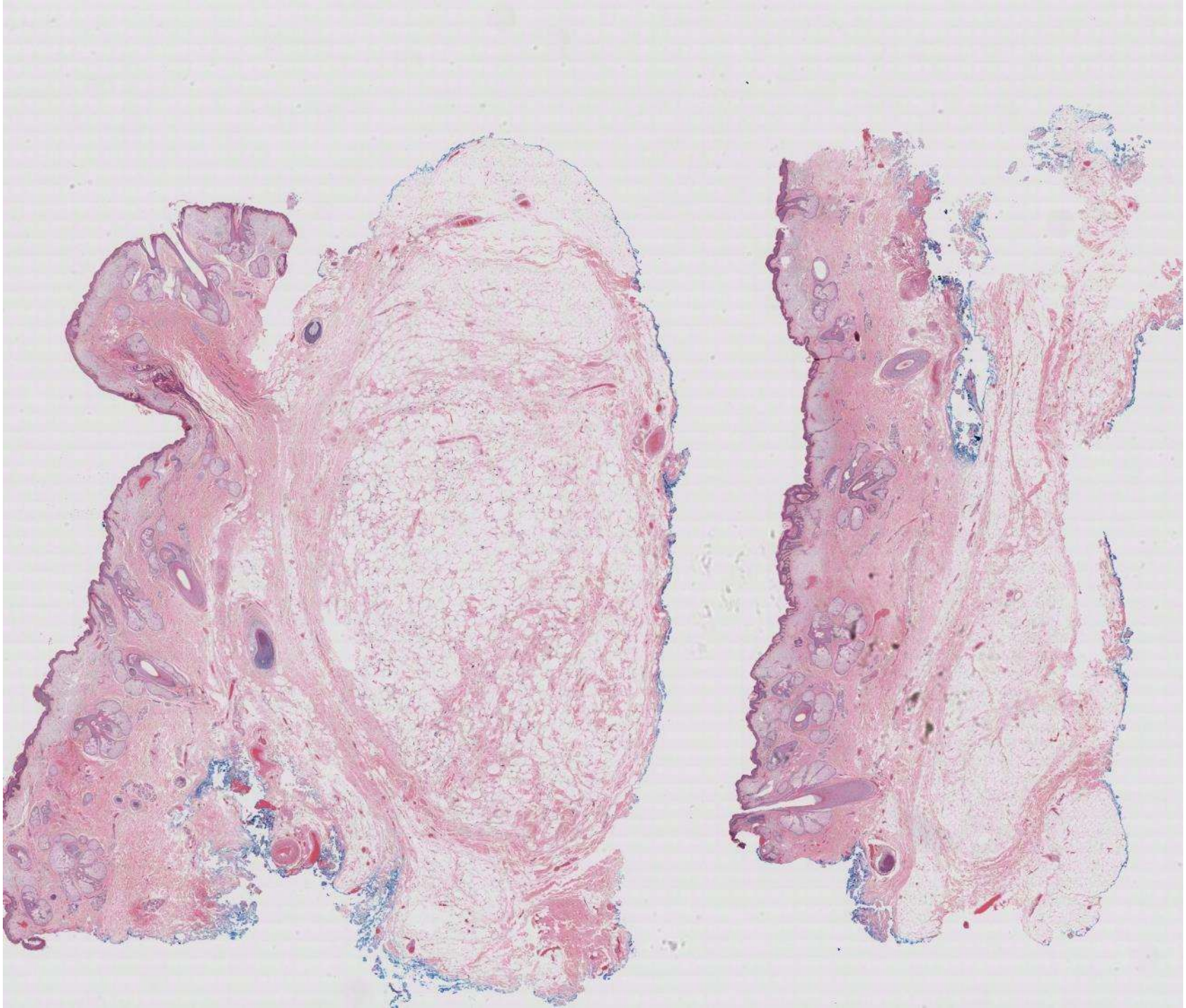


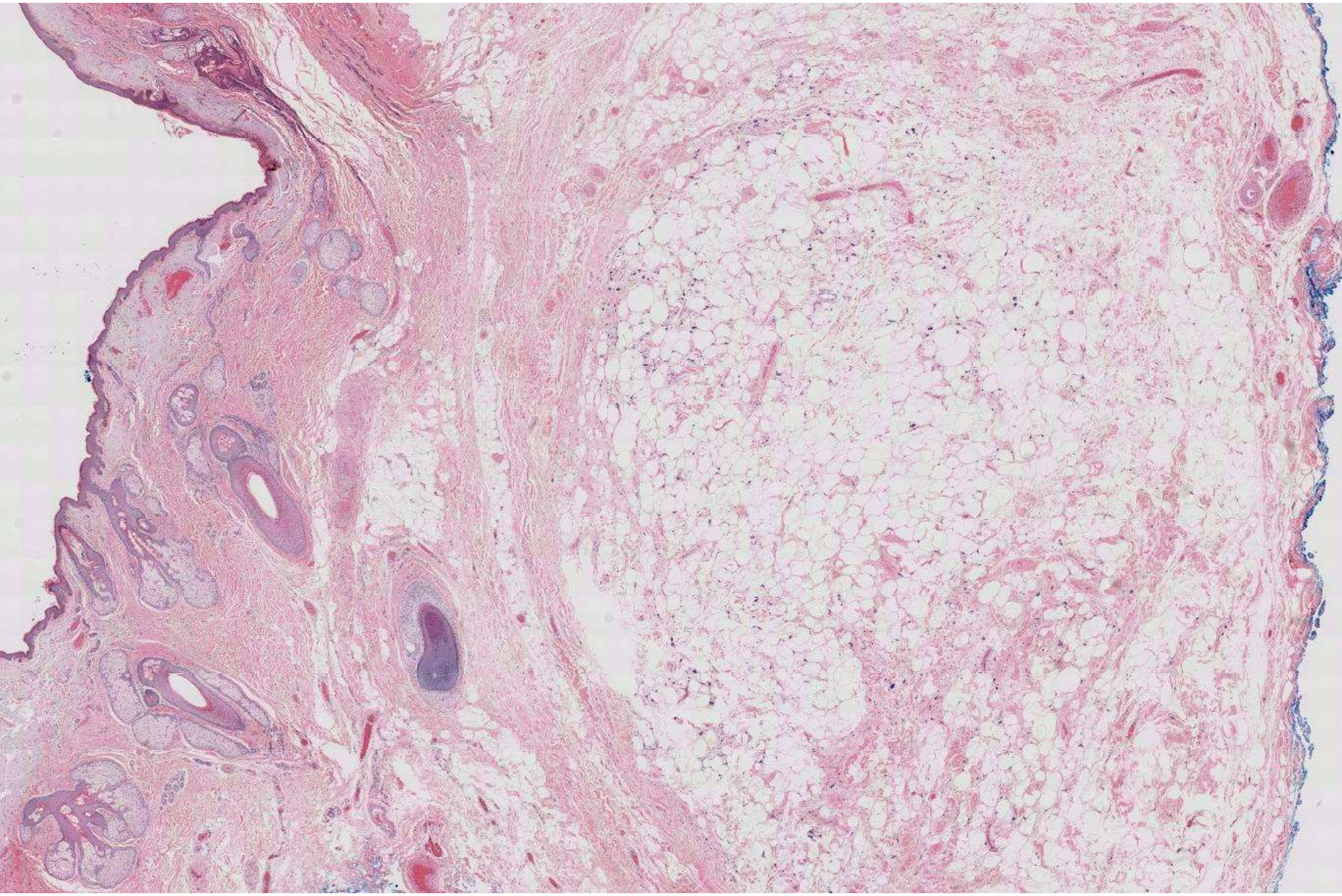


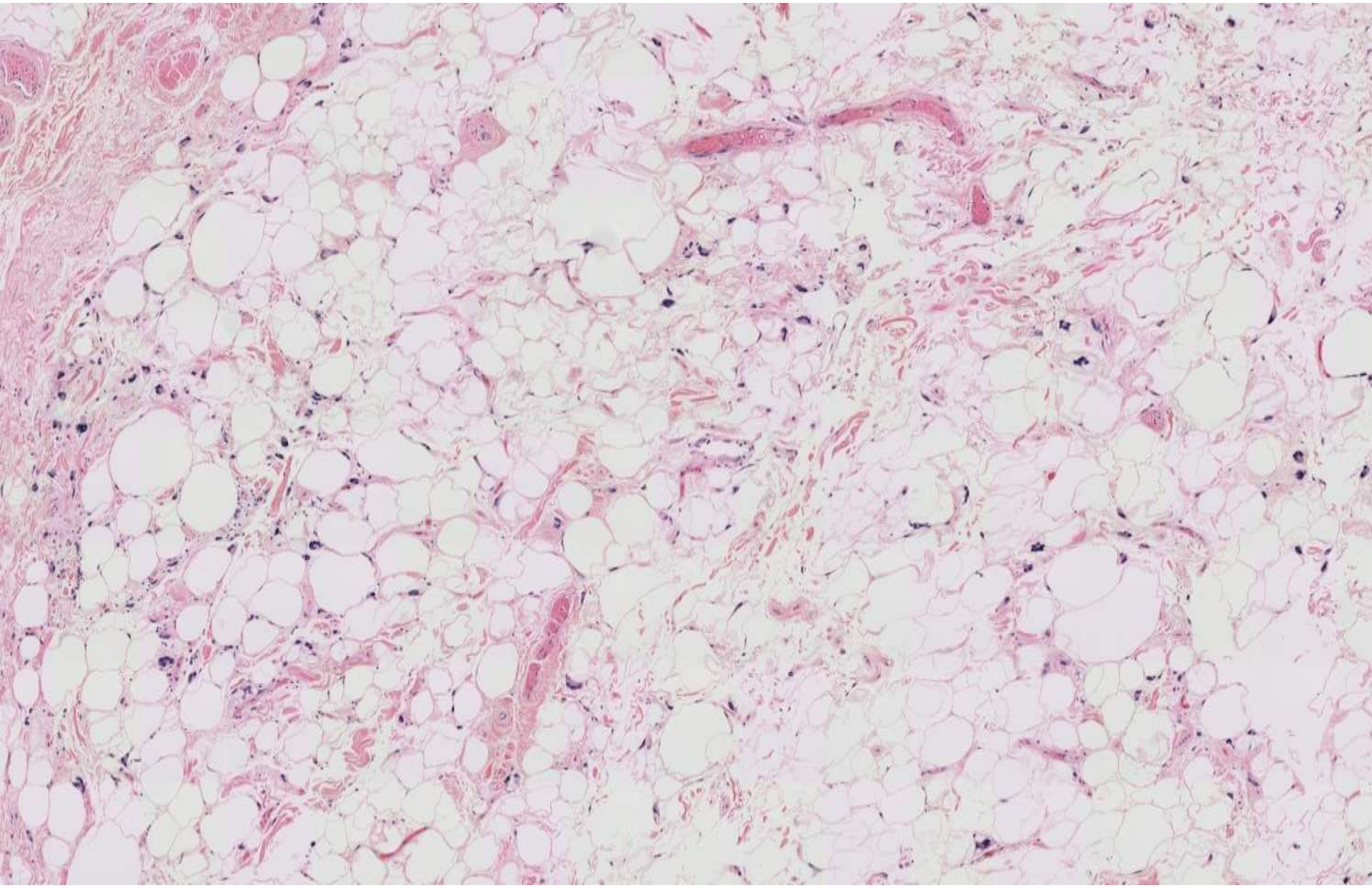


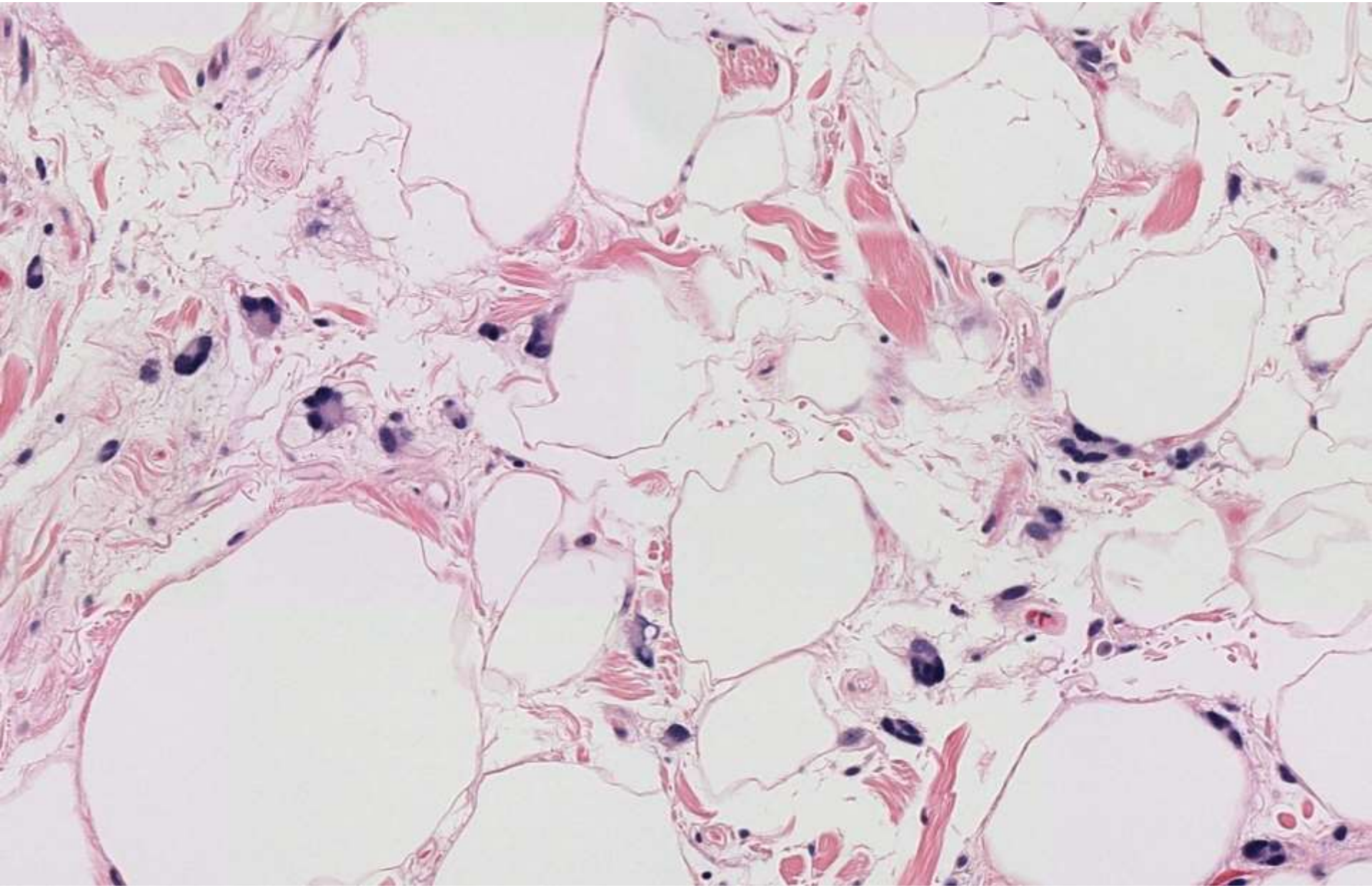


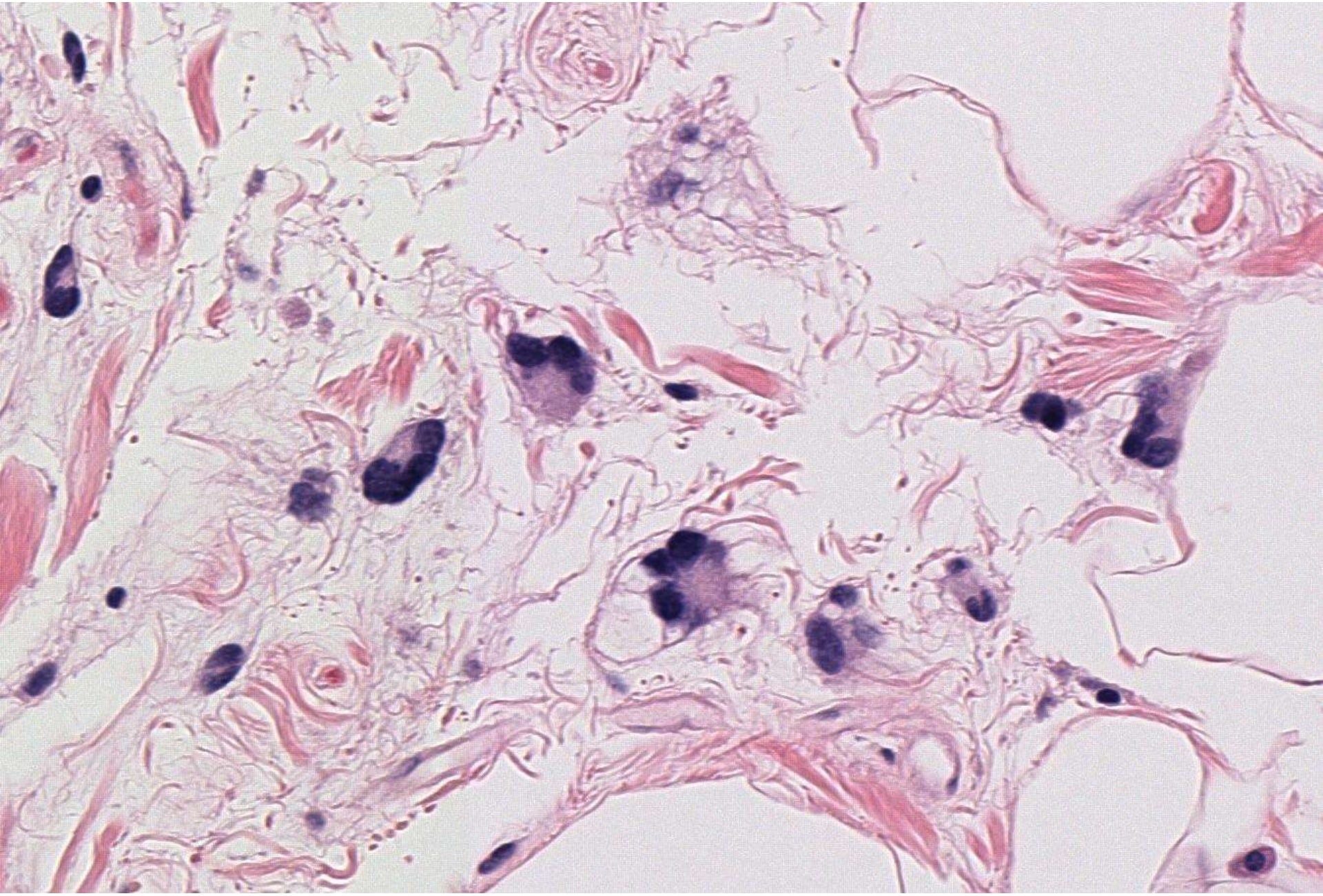












SPINDLE CELL/PLEOMORPHIC LIPOMA

- **EPIDEMIOLOGY**

  PLEOMORPHIC LIPOMA & SPINDLE CELL LIPOMA REPRESENT A CONTINUUM OF BENIGN TUMORS - MOST TUMORS SHOW SOME FEATURES OF BOTH

  70% OCCUR IN SQ TISSUE SHOULDER, BACK & POSTERIOR NECK

  90% MEN

  USUALLY AGES 45 - 65 YEARS

  USUALLY RELATIVELY SUPERFICIAL

SPINDLE CELL/PLEOMORPHIC LIPOMA

- **CYTOLOGY DESCRIPTION**
- ATYPICAL LARGE AND FLORET CELLS WITH BACKGROUND OF MATURE ADIPOCYTES (DIAGN CYTOPATHOL 2005;32:110)
- CELLS MAY APPEAR MALIGNANT (ACTA CYTOL 2000;44:255, DIAGN CYTOPATHOL 2010;38:184)

SPINDLE CELL/PLEOMORPHIC LIPOMA

- **MICROSCOPIC (HISTOLOGIC) DESCRIPTION**
- CIRCUMSCRIBED TUMOR WITH ADIPOCYTES THAT ARE VARIABLE IN SIZE
- PROMINENT FLORET GIANT CELLS (HYPERCHROMATIC, MULTINUCLEATED, WREATH-LIKE NUCLEI) AND SMALL ROUND HYPERCHROMATIC CELLS
- MAY HAVE SPINDLE CELLS
- NO/RARE LIPOBLASTS, NO PROMINENT VASCULARITY

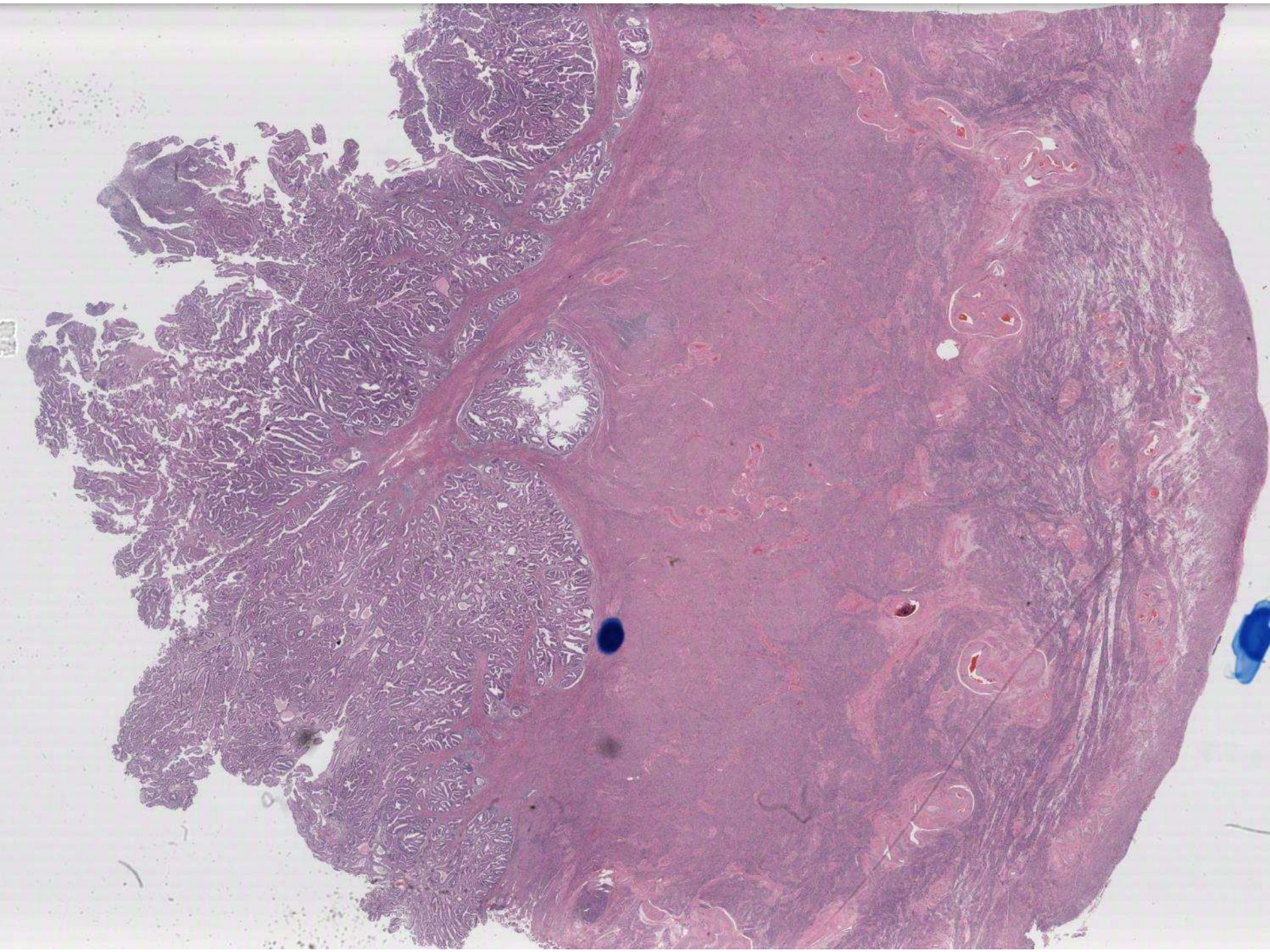
SPINDLE CELL/PLEOMORPHIC LIPOMA **DIFFERENTIAL DIAGNOSIS**

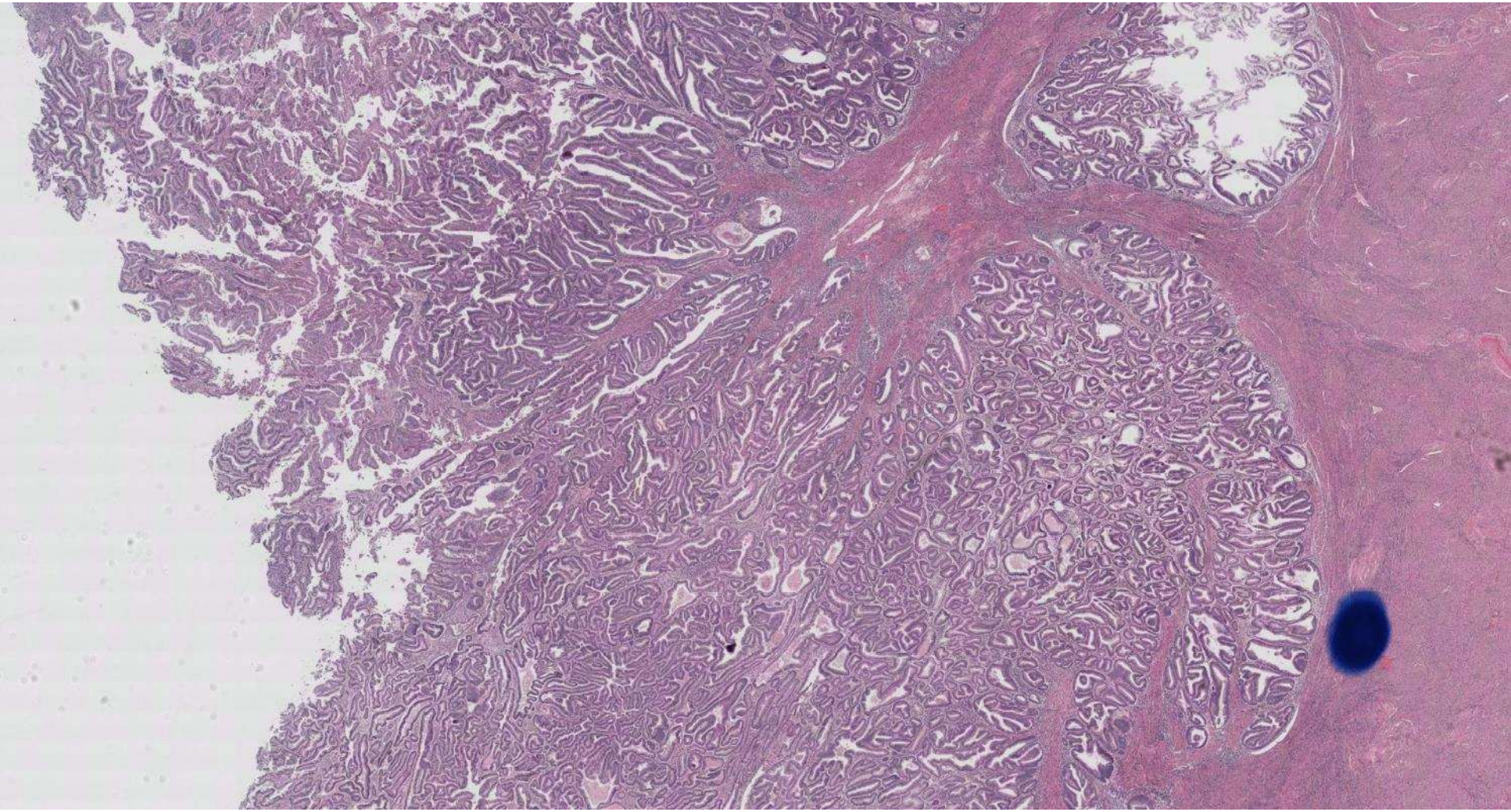
- **NEUROFIBROMA**: DIFFERENT MORPHOLOGY, NO PROMINENT ADIPOSE, STRONGLY S100+, MAY HAVE FLORET CELLS
- **WELL DIFFERENTIATED LIPOSARCOMA**: DEEP LOCATION, MORE LIPOBLASTS, VARIABLE THICK COLLAGEN, VARIABLE FLORET GIANT CELLS, CD34-
- **CELLULAR ANGIOFIBROMA**: VASCULAR TUMOR, BUT SIMILAR CYTOGENETICS
- **LIPOMATOUS HEMANGIOPERICYTOMA**: STAGHORN VASCULAR PATTERN
- **MYXOID LIPOSARCOMA**: LIPOBLASTS AND PLEOMORPHIC SPINDLE CELLS, PROMINENT PLEXIFORM VASCULAR PATTERN, NO THICK COLLAGEN BUNDLES, CD34-
- **SCHWANNOMA**: DIFFERENT MORPHOLOGY, NO PROMINENT ADIPOSE, STRONGLY S100+
- **SOLITARY FIBROUS TUMOR**: PATTERNLESS PATTERN, THIN COLLAGEN FIBERS, NO PROMINENT ADIPOSE, CD99+, BCL2+, CD34+

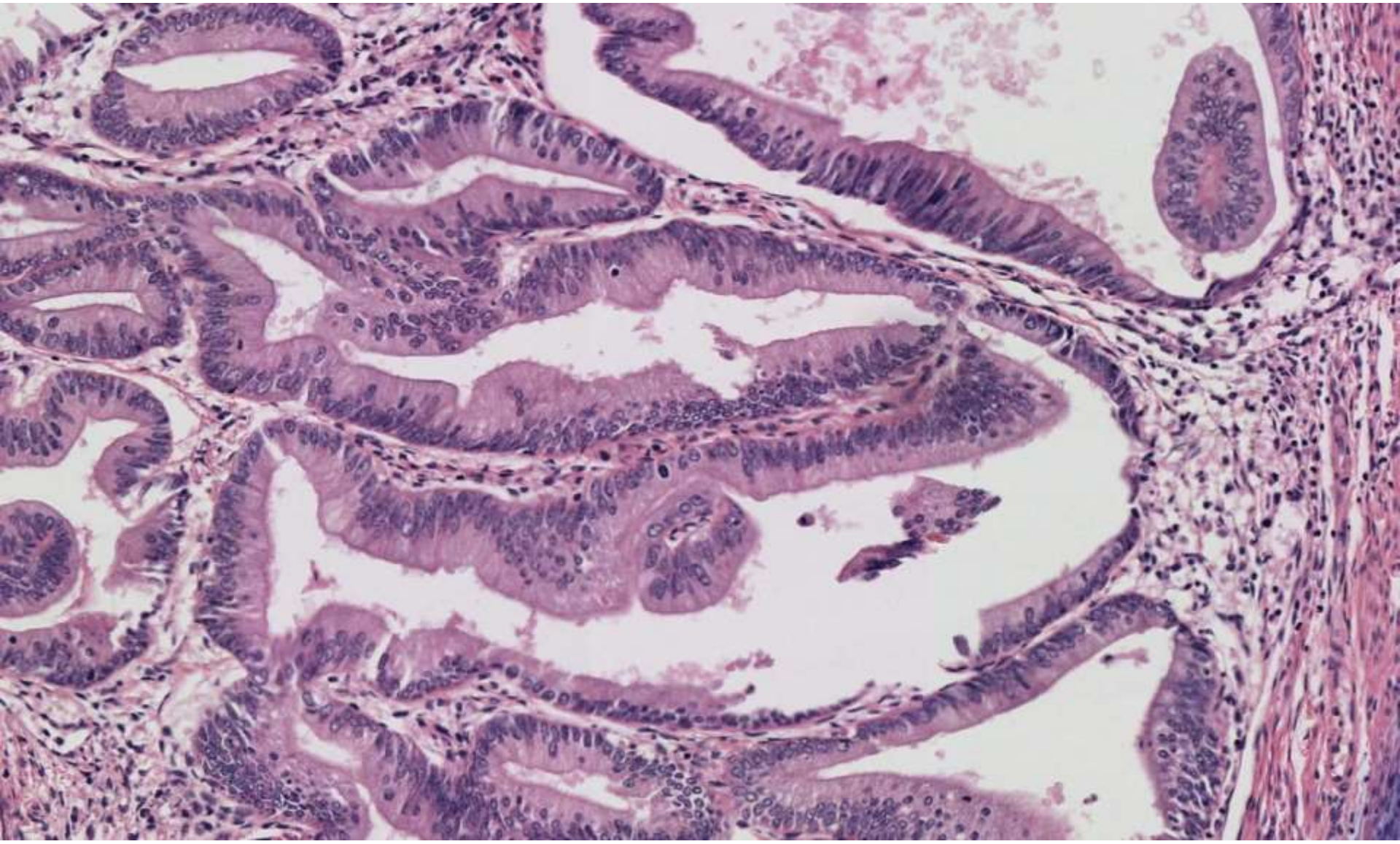
19-1203

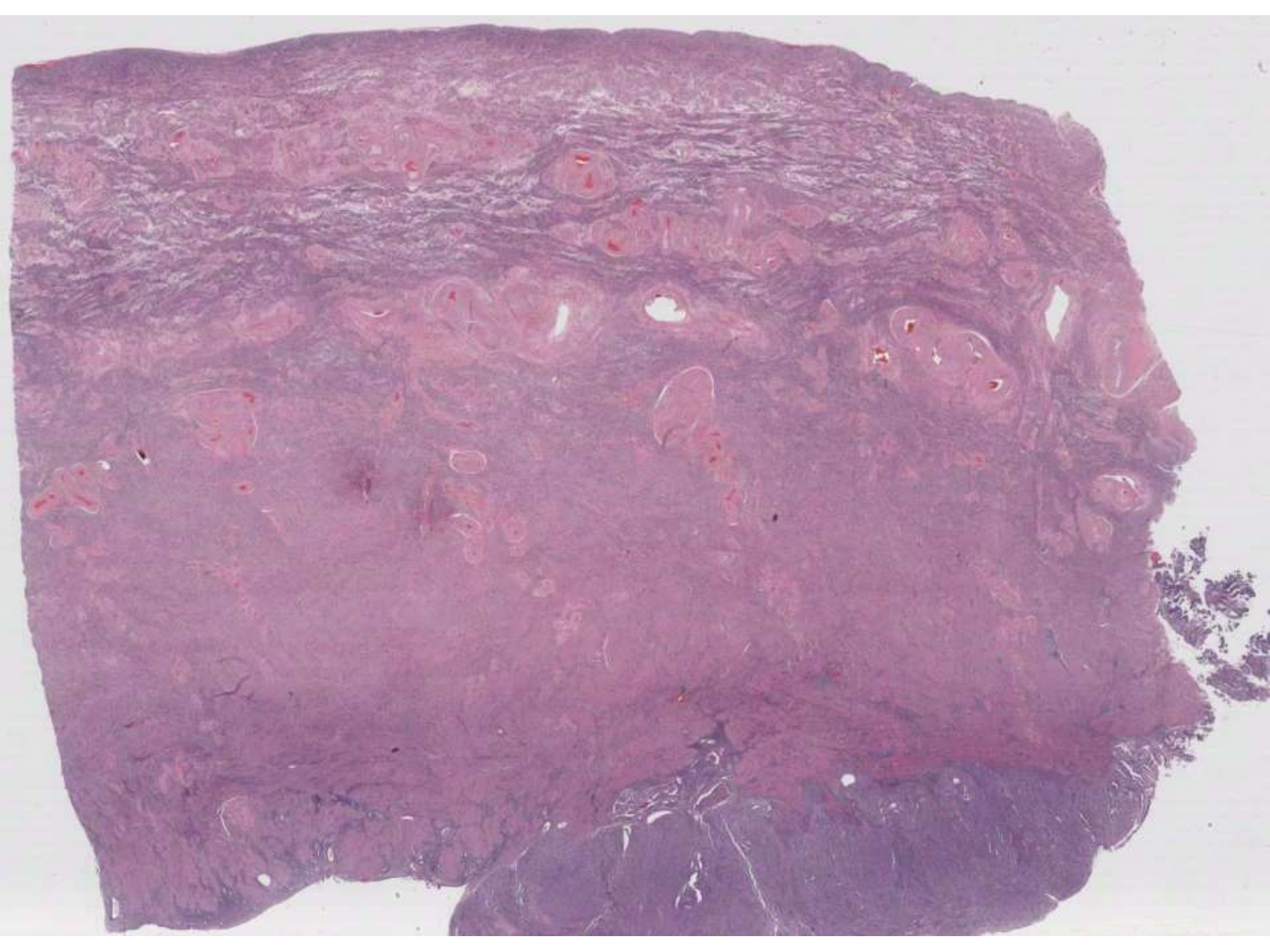
Balaram Puligandla; Kaiser Oakland

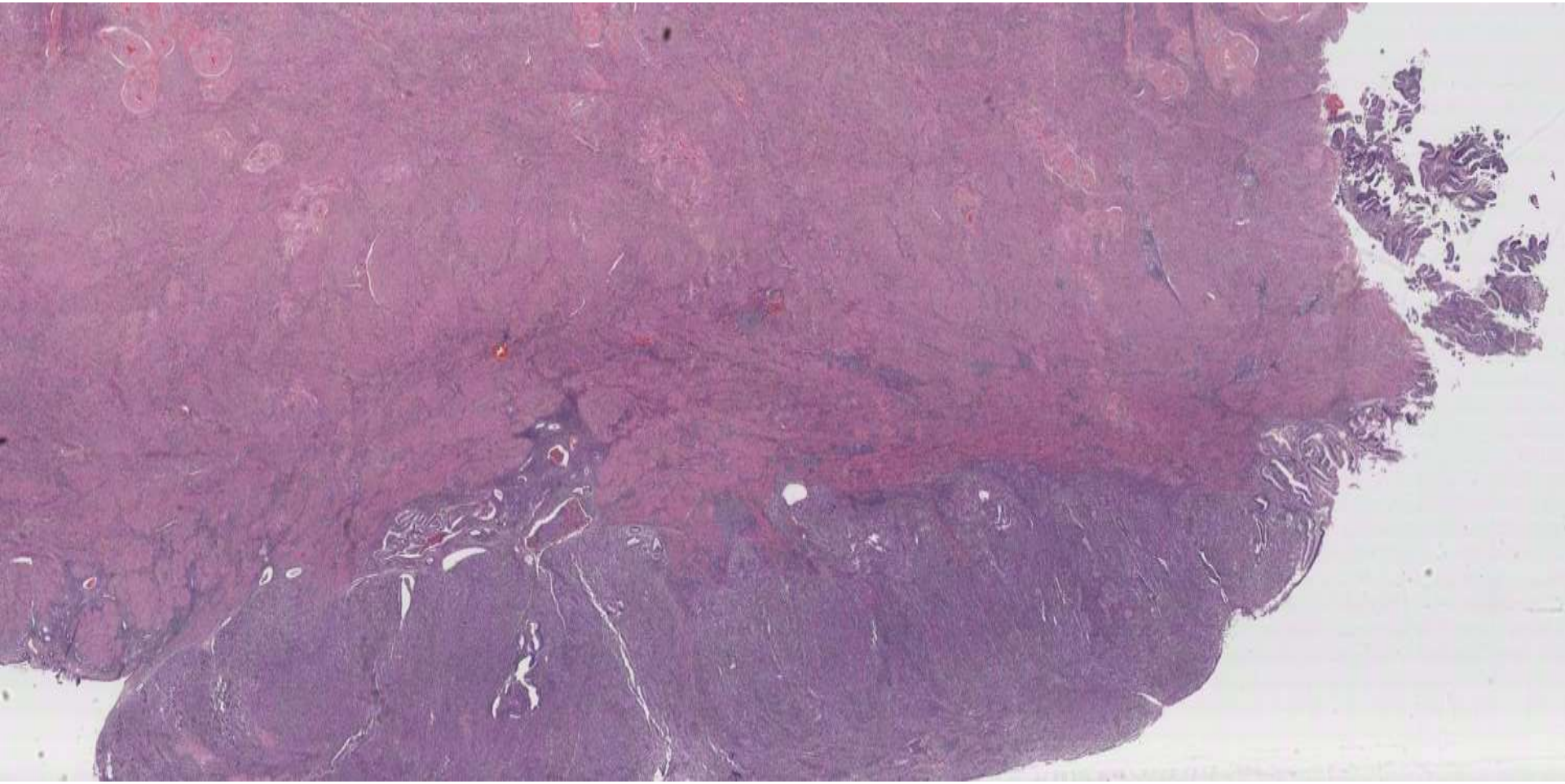
54-year-old female with 3x3cm endometrial mass.

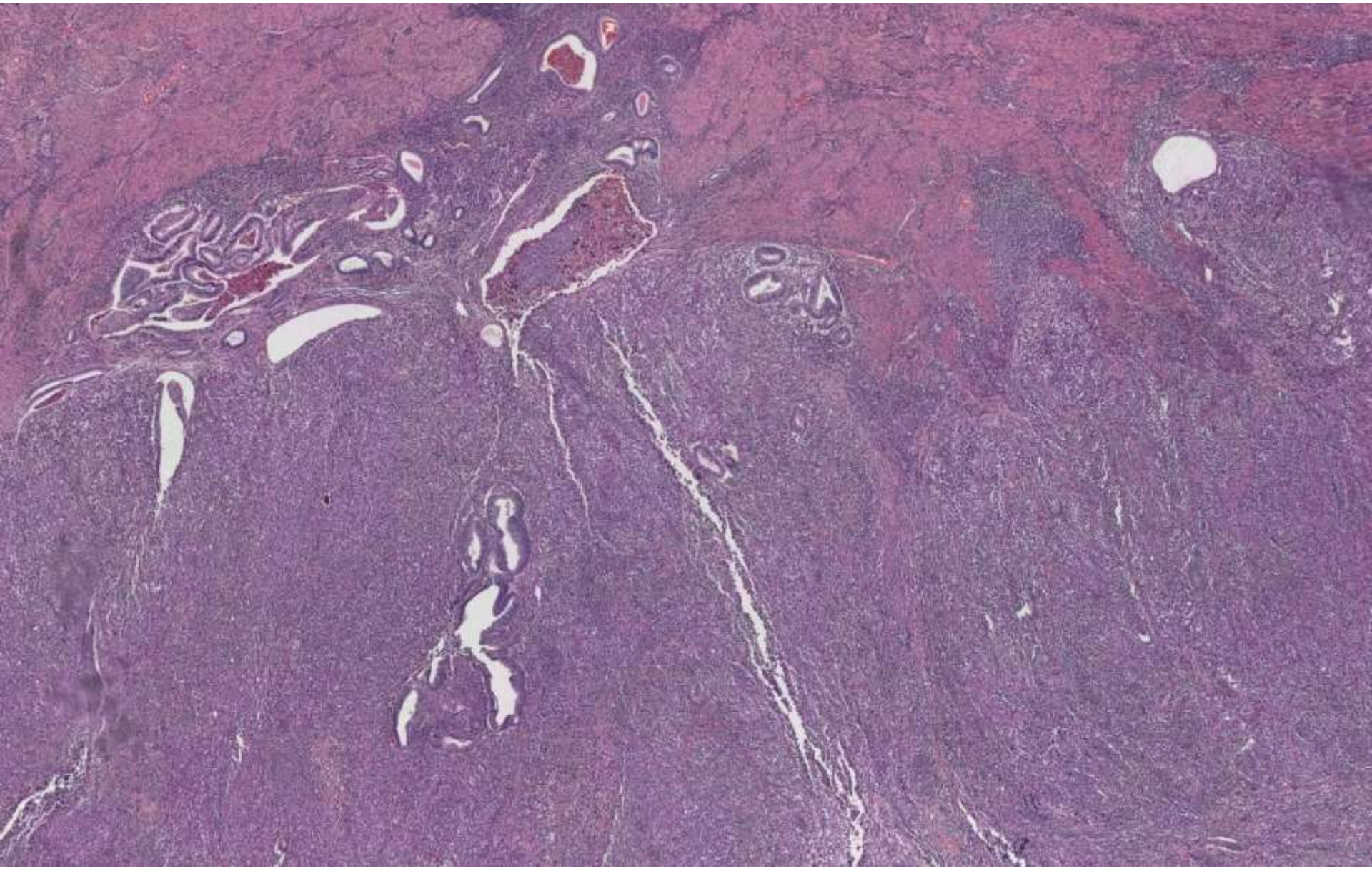


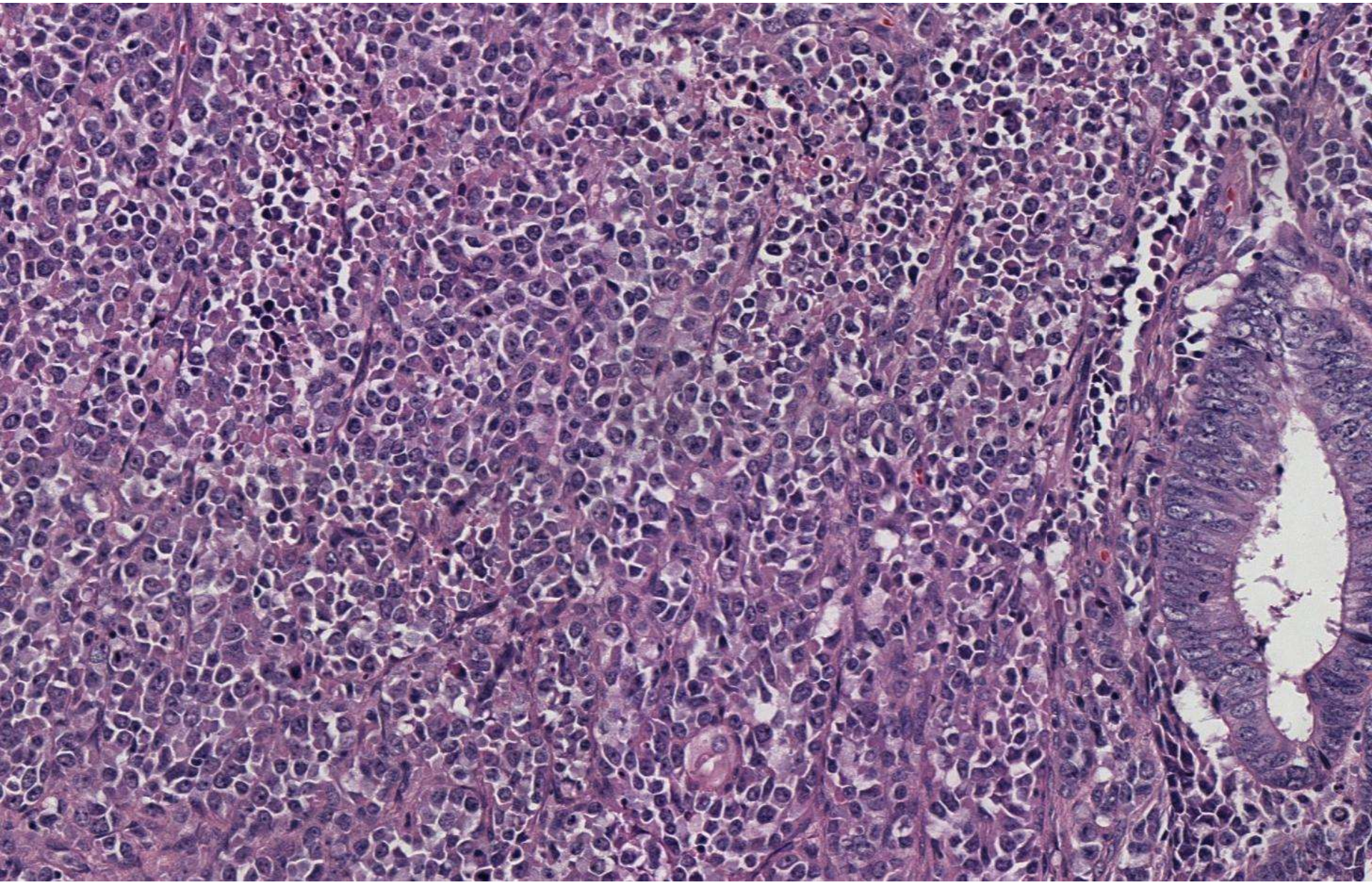


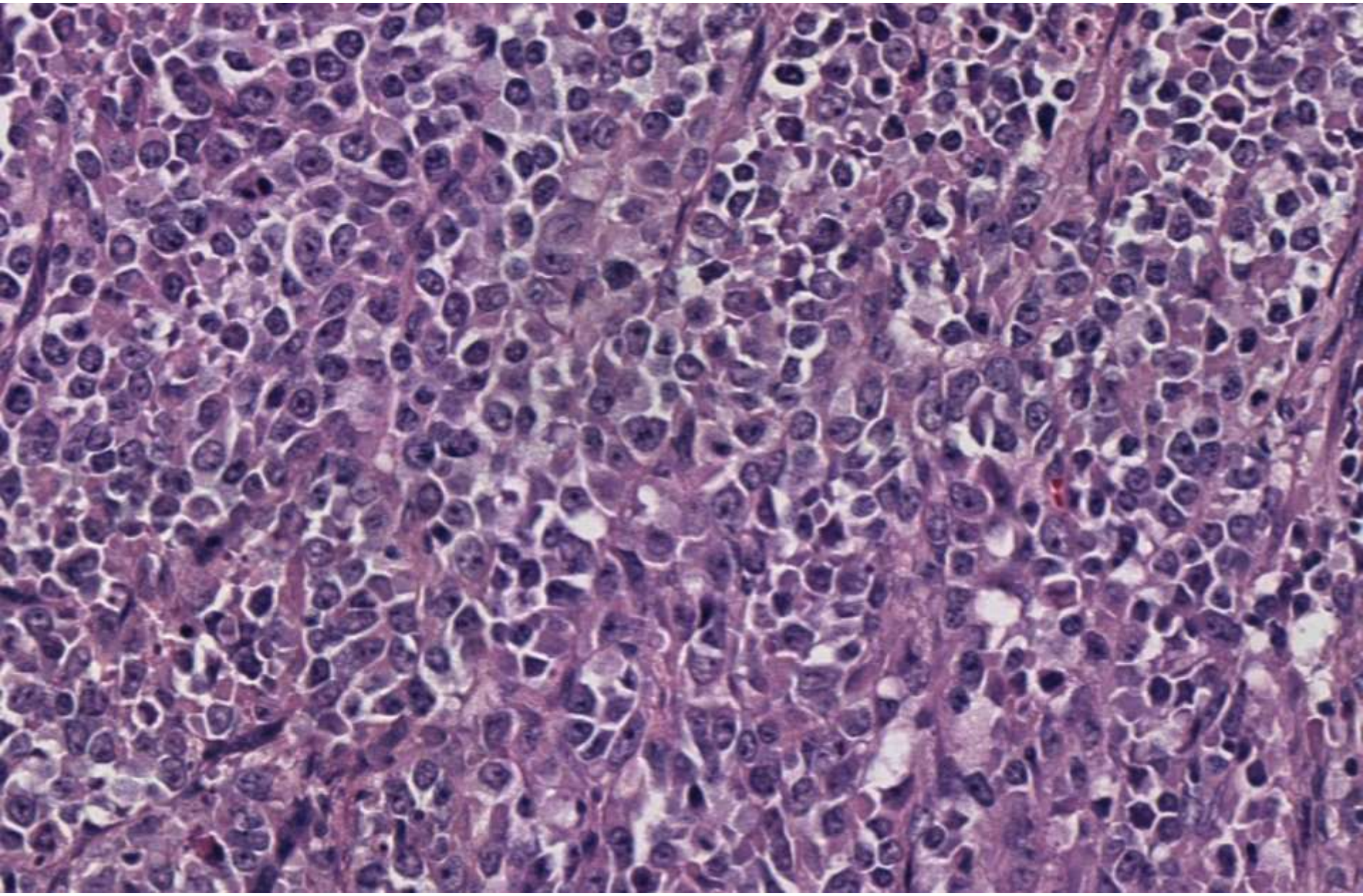


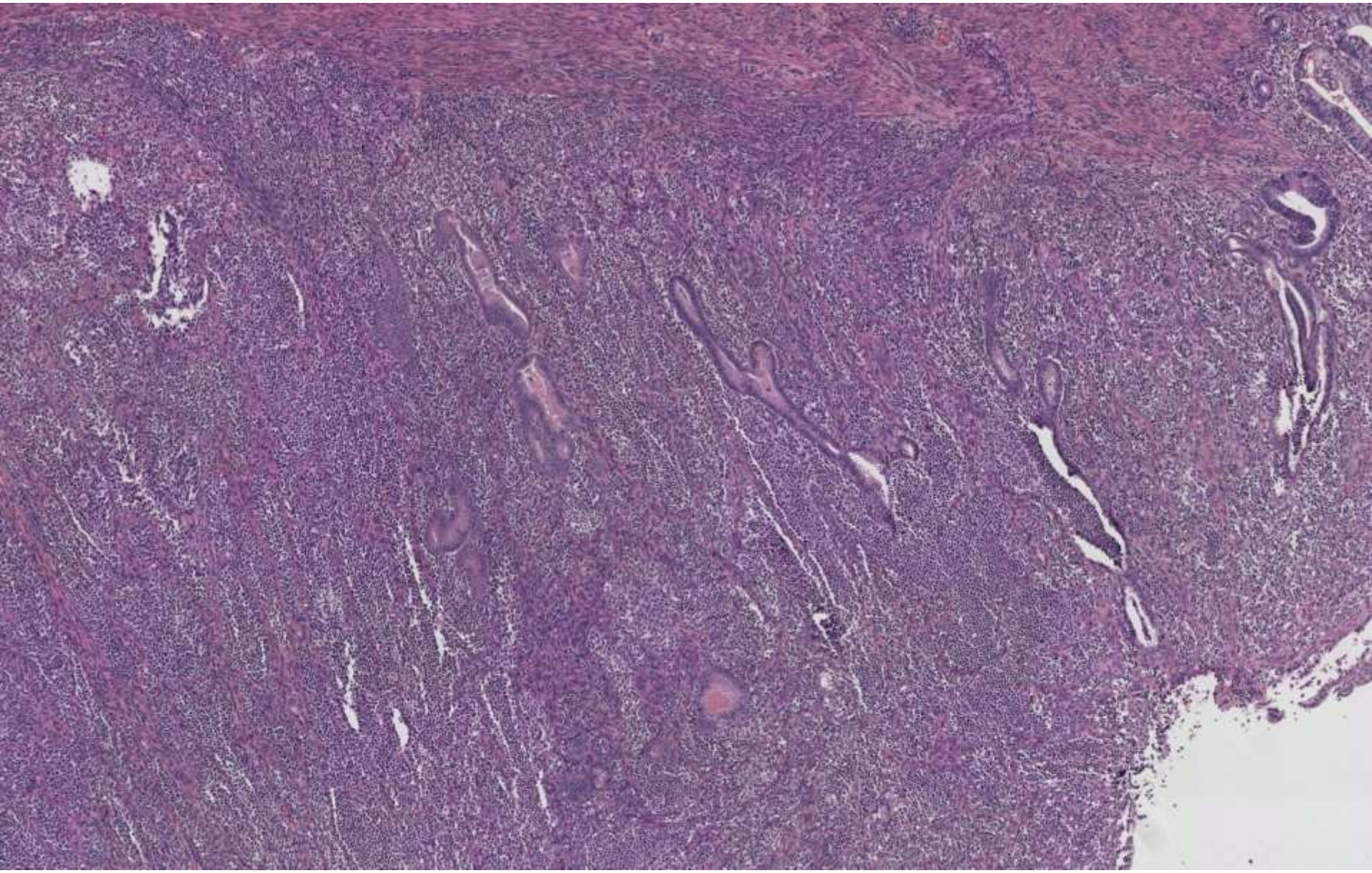


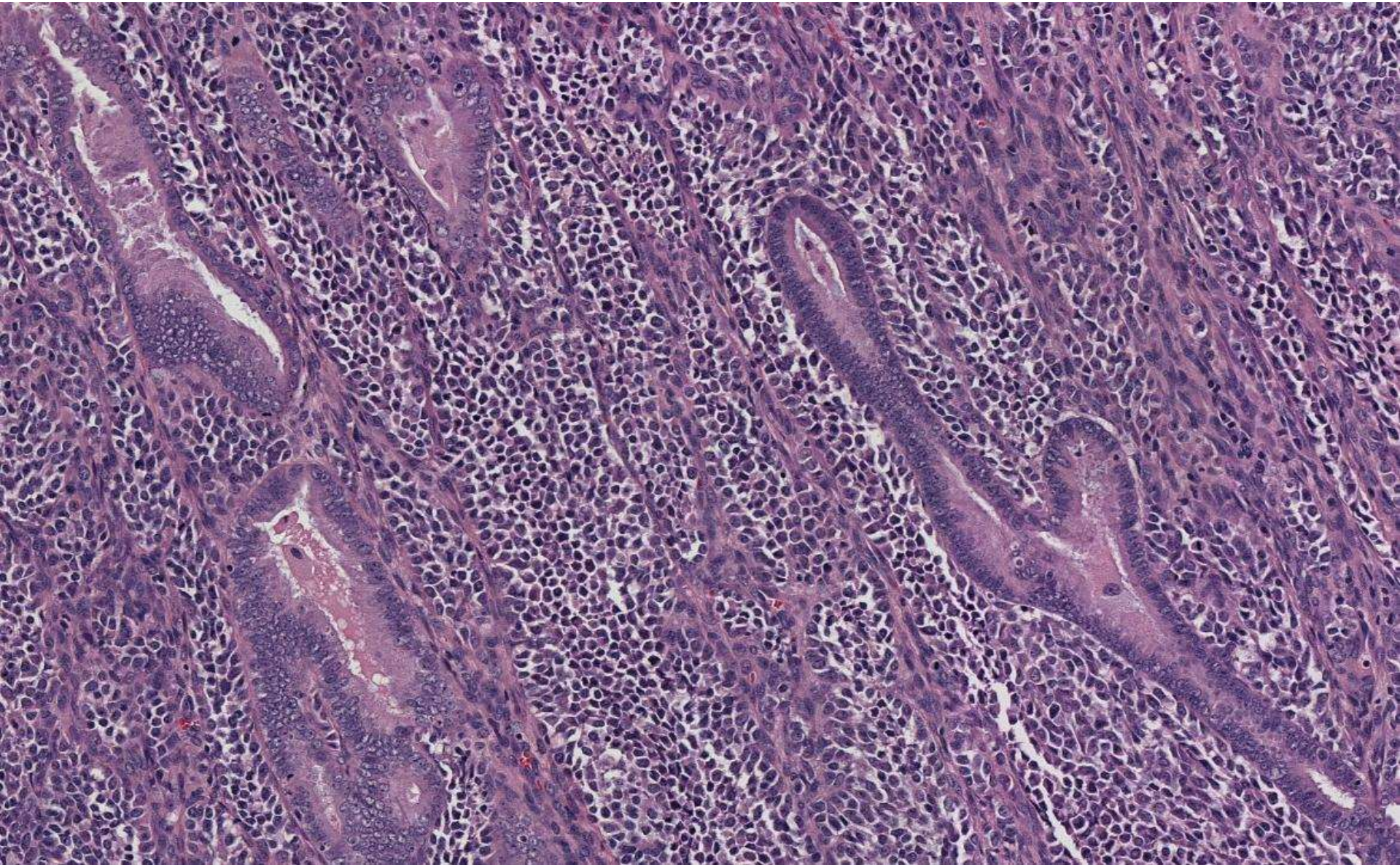


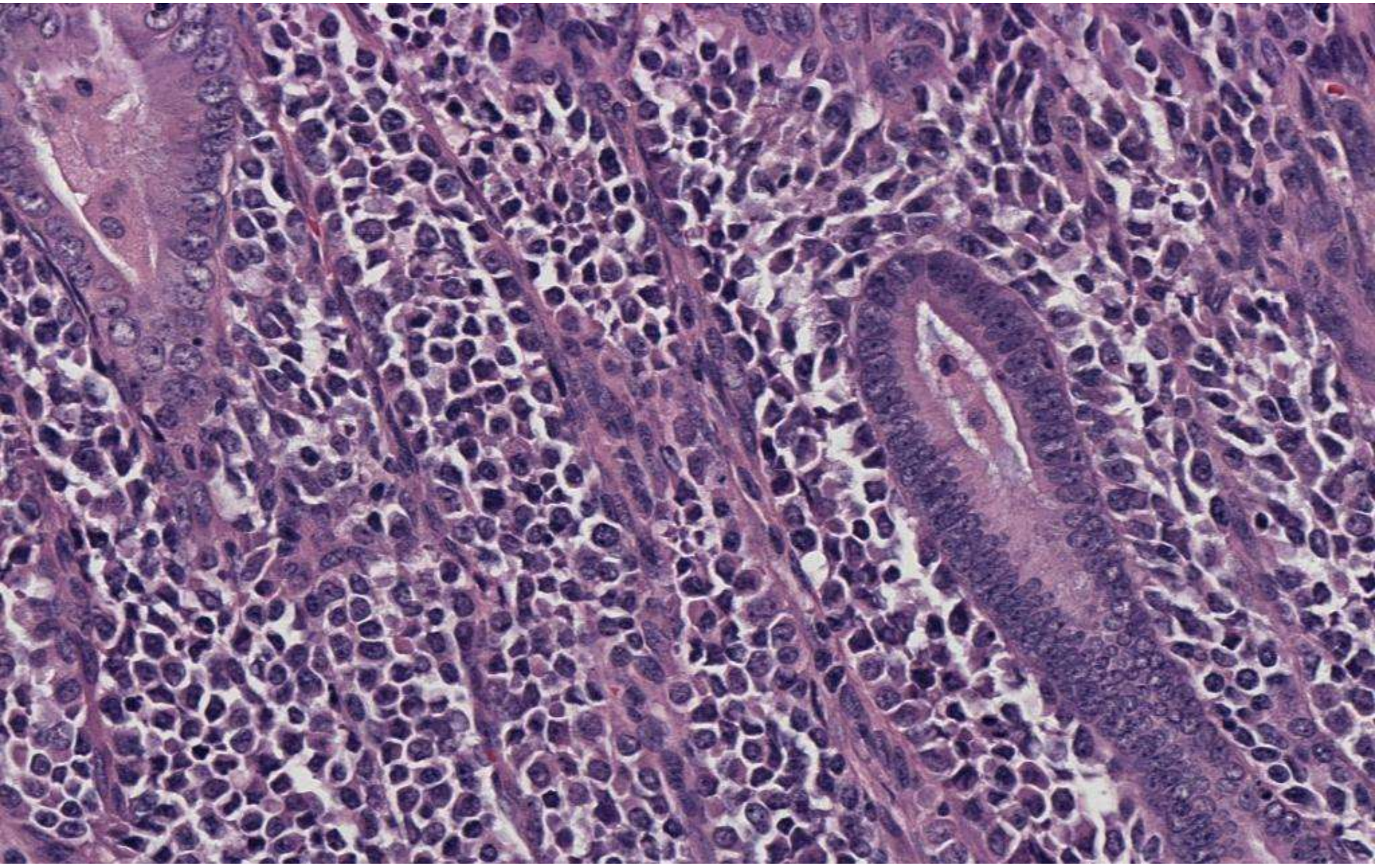










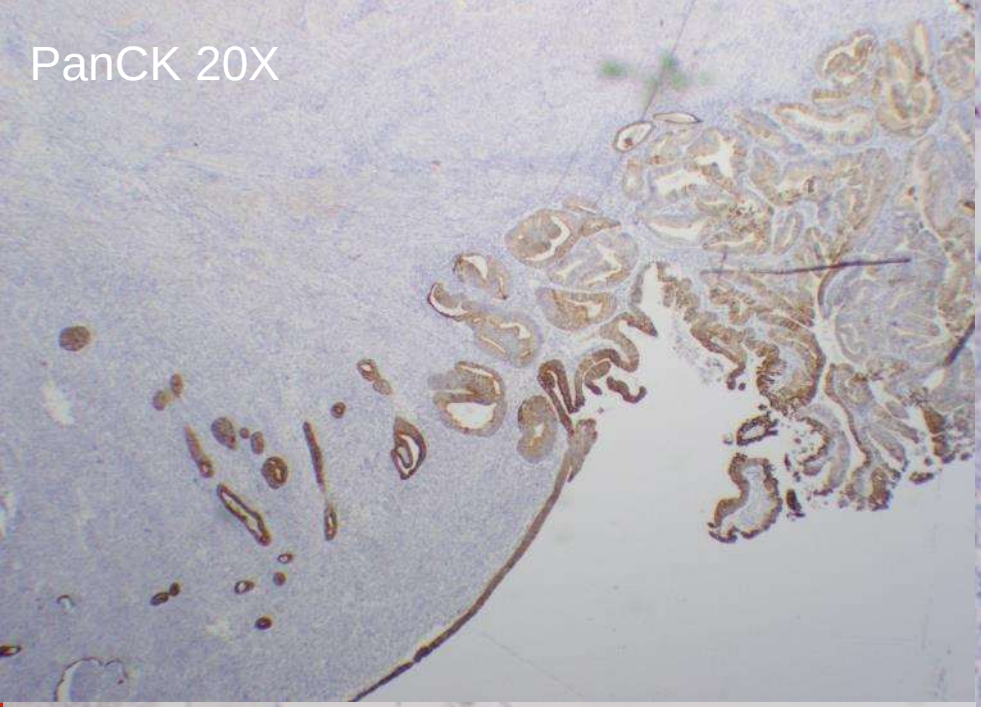


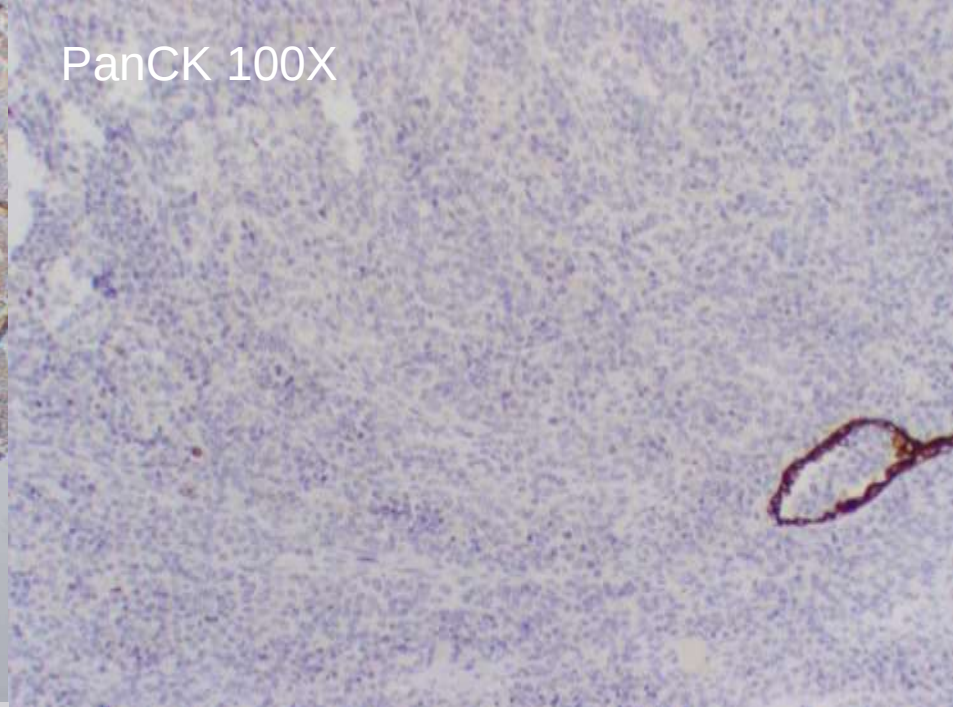
DEDIFFERENTIATED ENDOMETRIAL CARCINOMA

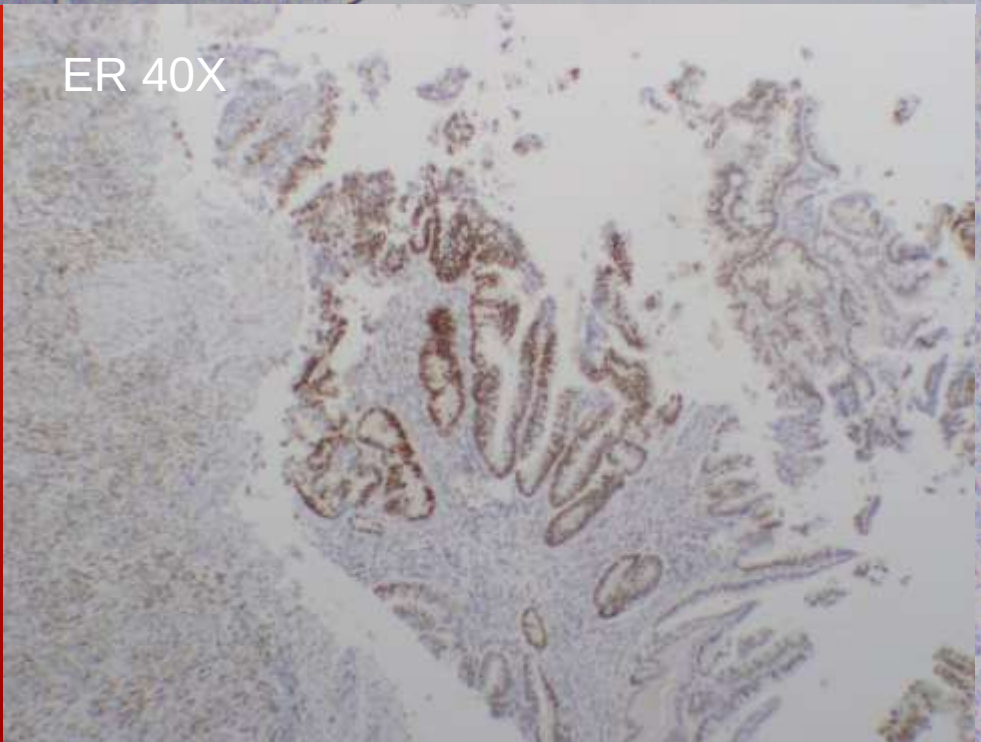
DEDIFFERENTIATED ENDOMETRIAL CARCINOMA

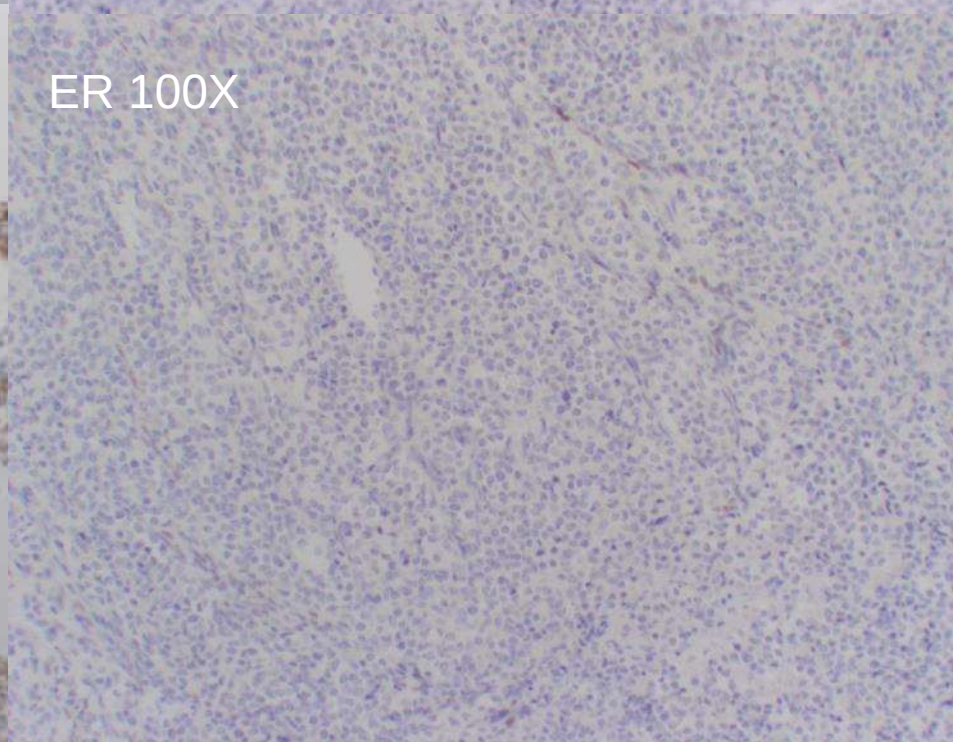
- Admixture of well differentiated endometrioid adeno carcinoma and undifferentiated carcinoma (UC), regardless of amount.
- Undifferentiated carcinoma is characterized by monotonous solid sheets of tumor cells. No cords, nests or trabecula of cells as with the solid component of Grade 3 endometrioid carcinoma.
- Amount of UC does not affect prognosis.
- CK only focally + in the UC component, ER –
- NE markers negative

Altrabulsi et al, Undifferentiated Carcinoma of the Endometrium. AJSP 29: 1316-21, 20


PanCK 20X


PanCK 100X


ER 40X


ER 100X

DEDIFFERENTIATED ENDOMETRIAL CARCINOMA

- Had long been definitionally admixed with Grade 3 endometrioid carcinoma(>50% non morular/squamous solid growth pattern).
- MD Anderson study compared 33 Grade 3 EC with 16 UC.
- UC patients had younger mean age at time of Dx, had more high stage disease and significantly worse prognosis.
- UC constituted 9% of 633 cases of EC reviewed as part of this study, much higher than the 1-2% mentioned in the literature.
- 71% of the US cases were associated with EC, thus the use of the term dedifferentiated endometrial carcinoma.

Altrabulsi et al, Undifferentiated Carcinoma of the Endometrium. AJSP 29: 1316-21, 20

DEDIFFERENTIATED ENDOMETRIAL CARCINOMA

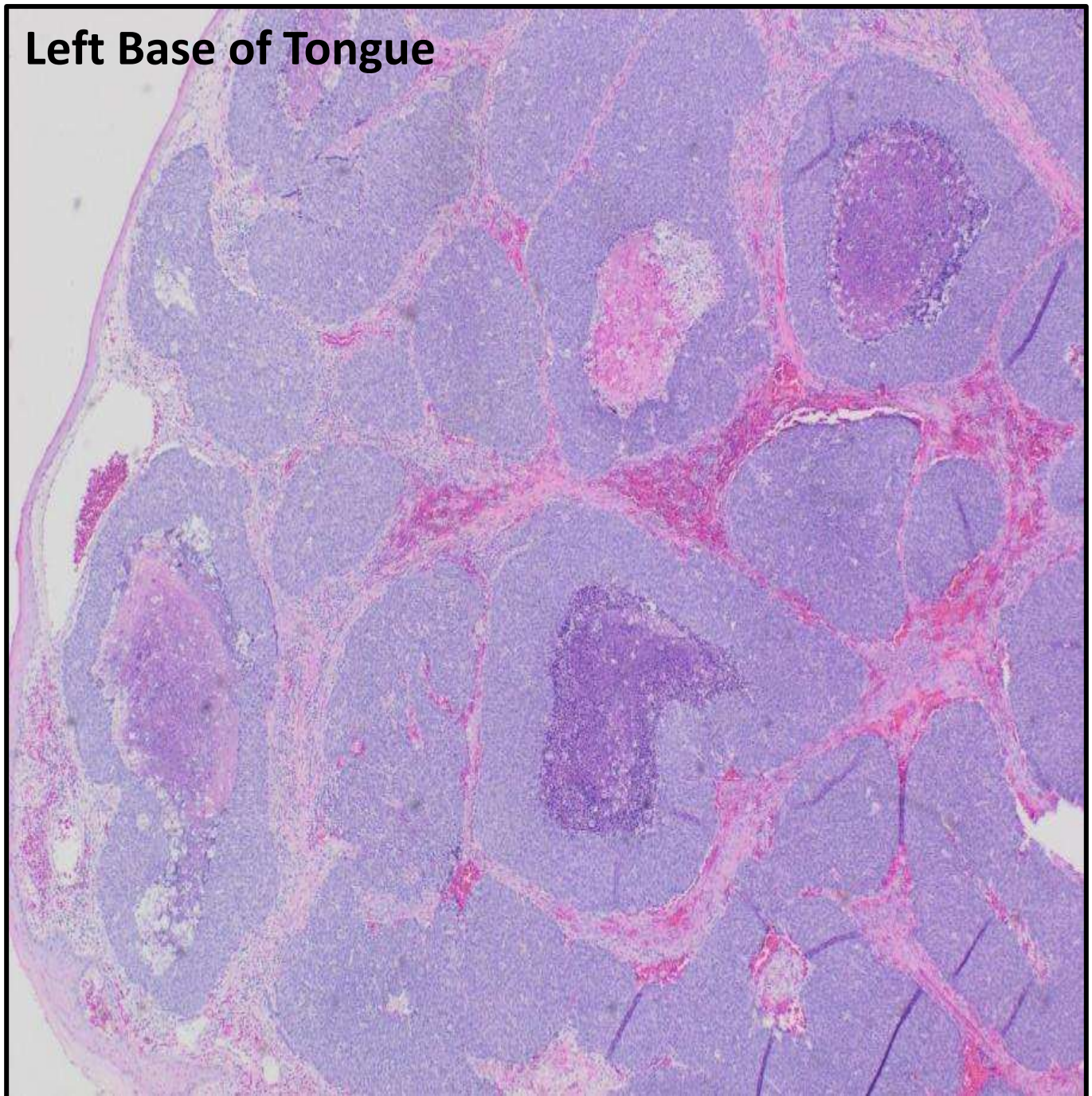
- Stage I Grade 3 EC patients: 14/21 alive with NED (26-164 Mos)
- Stage I UC patients: 2/4 alive with NED (120-192 Mos)
- Our patient is Stage IA and well with no disease at 31 months.

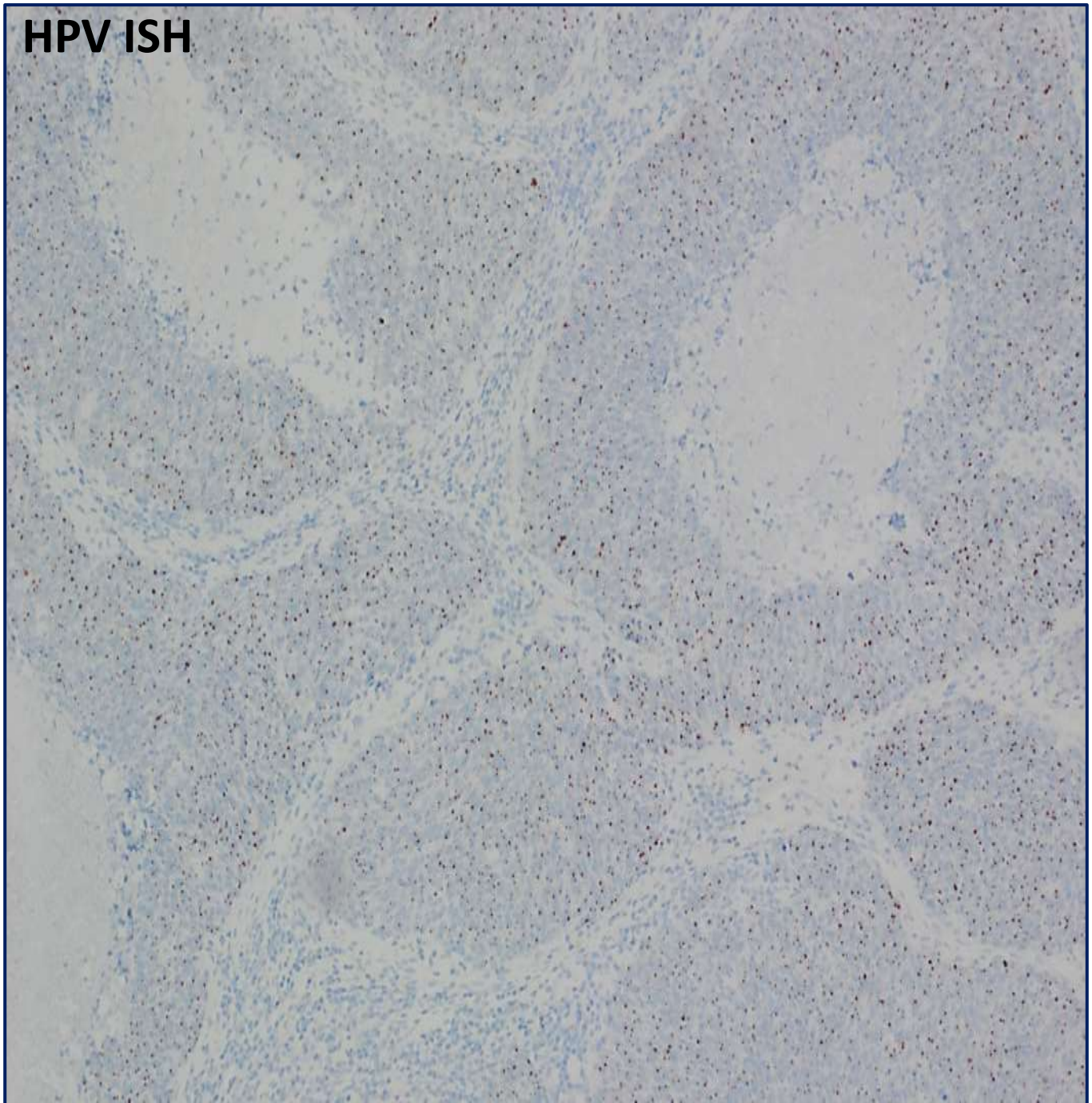
Altrabulsi et al, Undifferentiated Carcinoma of the Endometrium. AJSP 29: 1316-21, 20

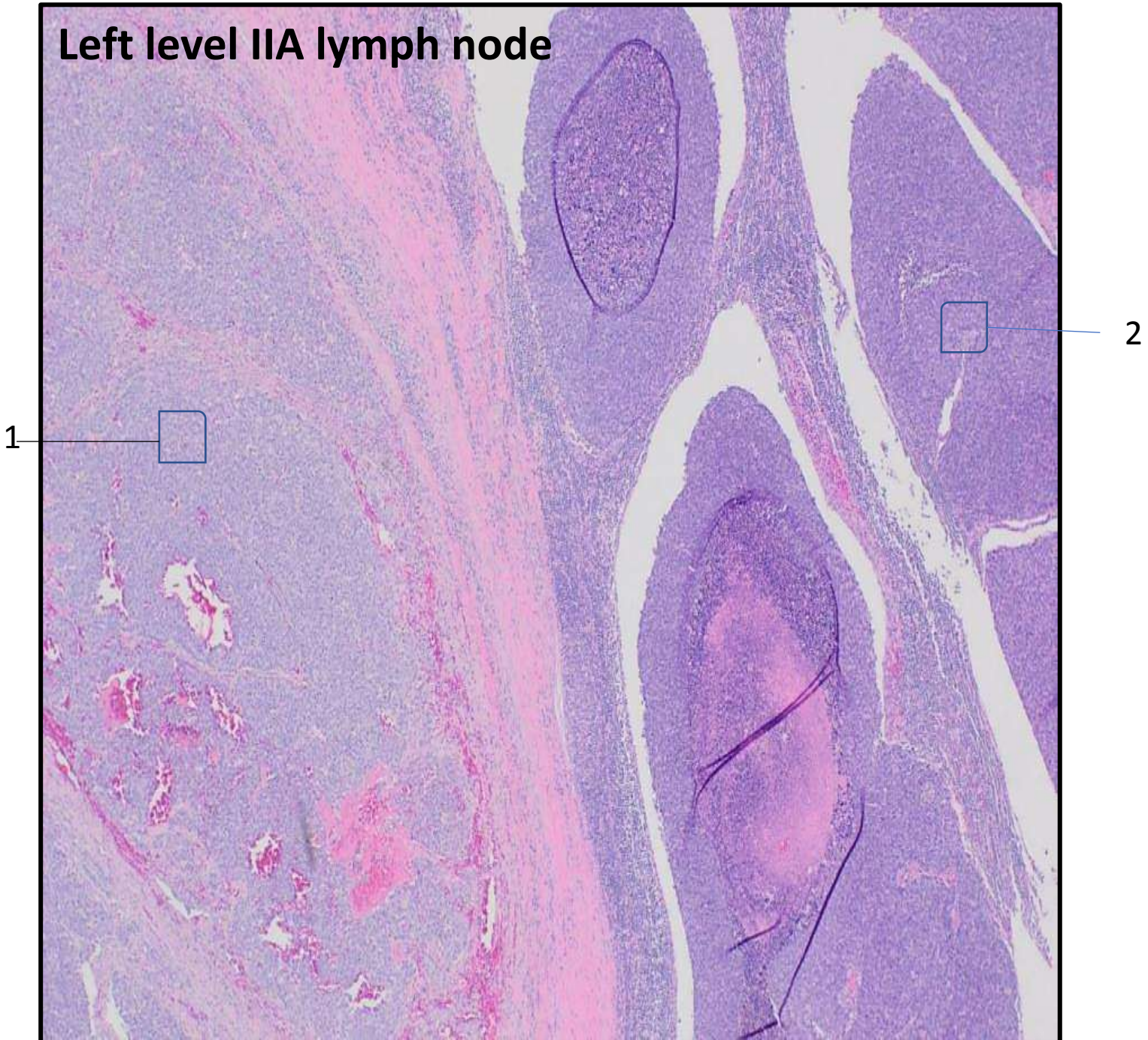
19-1204

Yue Peng/Anniemieke van Zante; UCSF

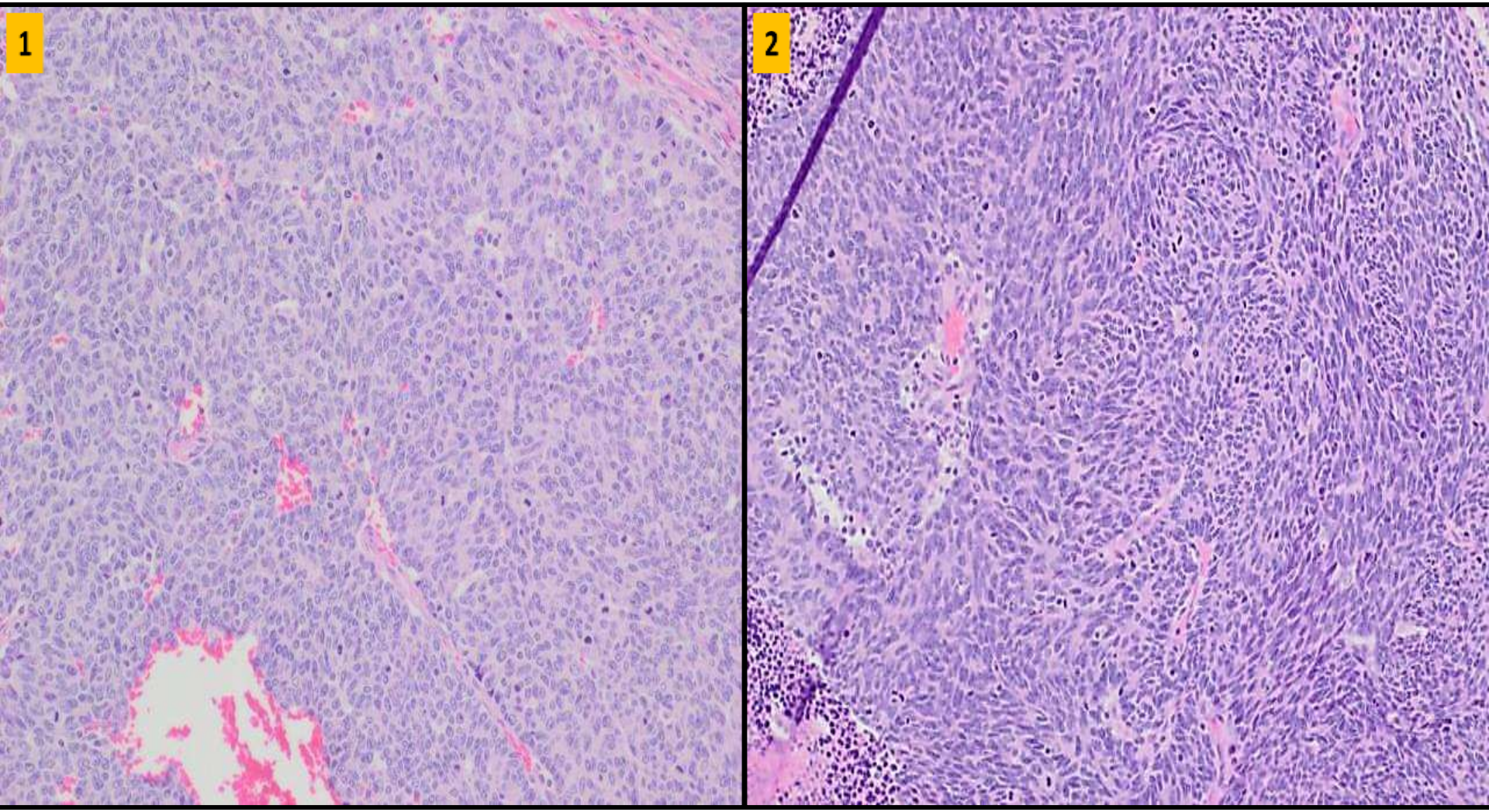
45-year-old male with a left base of tongue mass and a left level IIA lymph node that is suspicious for metastasis. He now undergoes left base of tongue resection, palatine tonsillectomy, and left neck dissection.

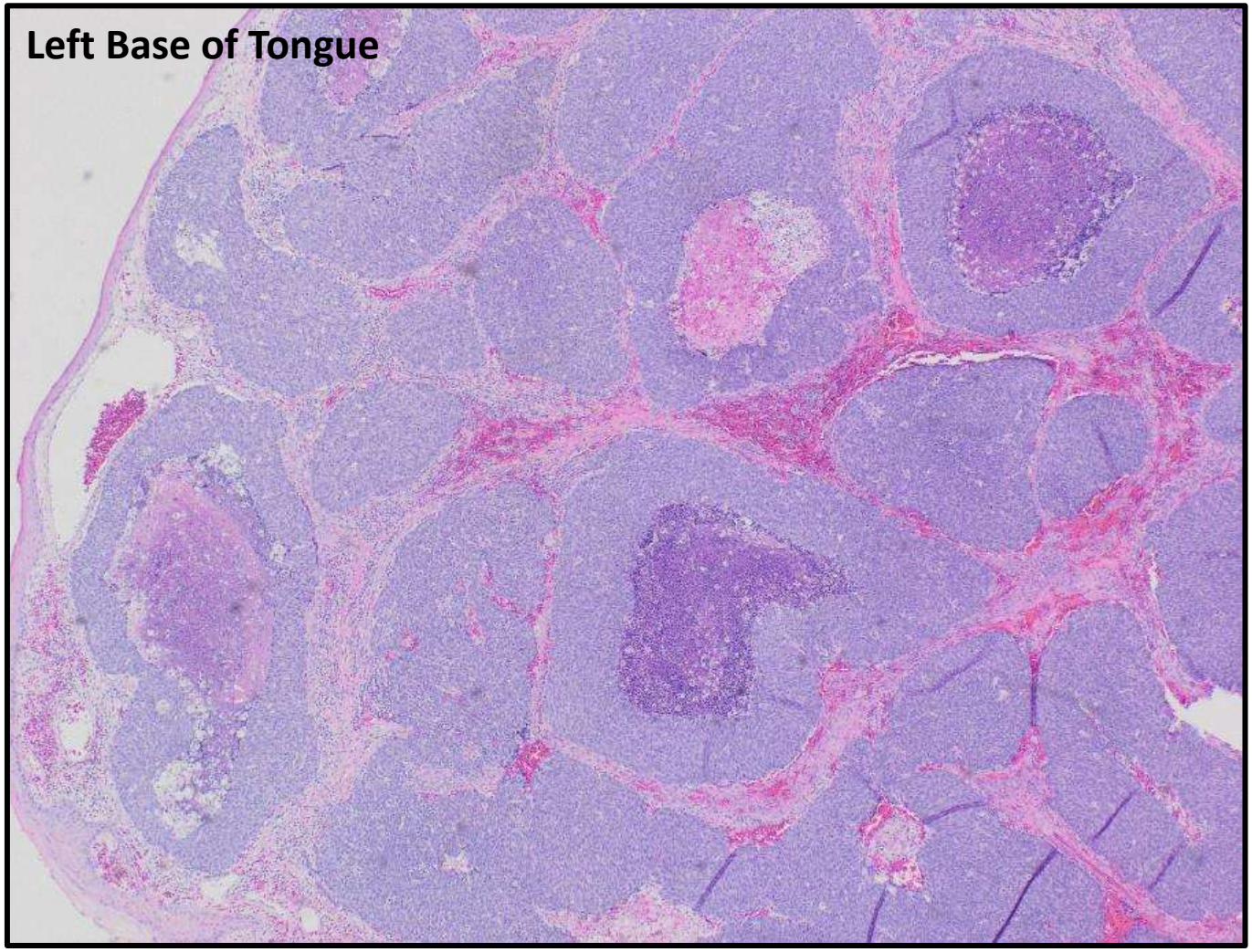

Left Base of Tongue

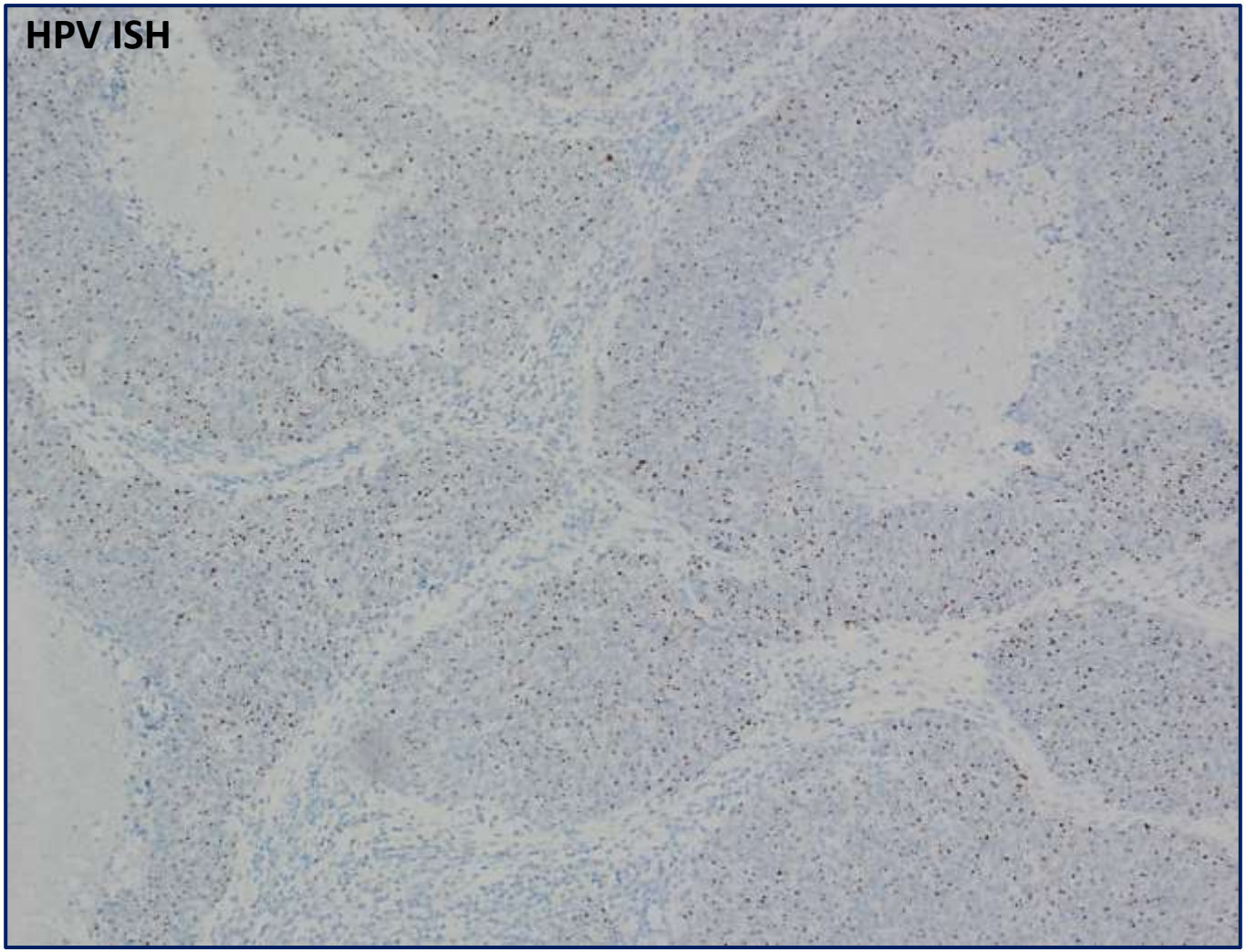

HPV ISH


Left level IIA lymph node
1
2

Left level IIA lymph node




Left Base of Tongue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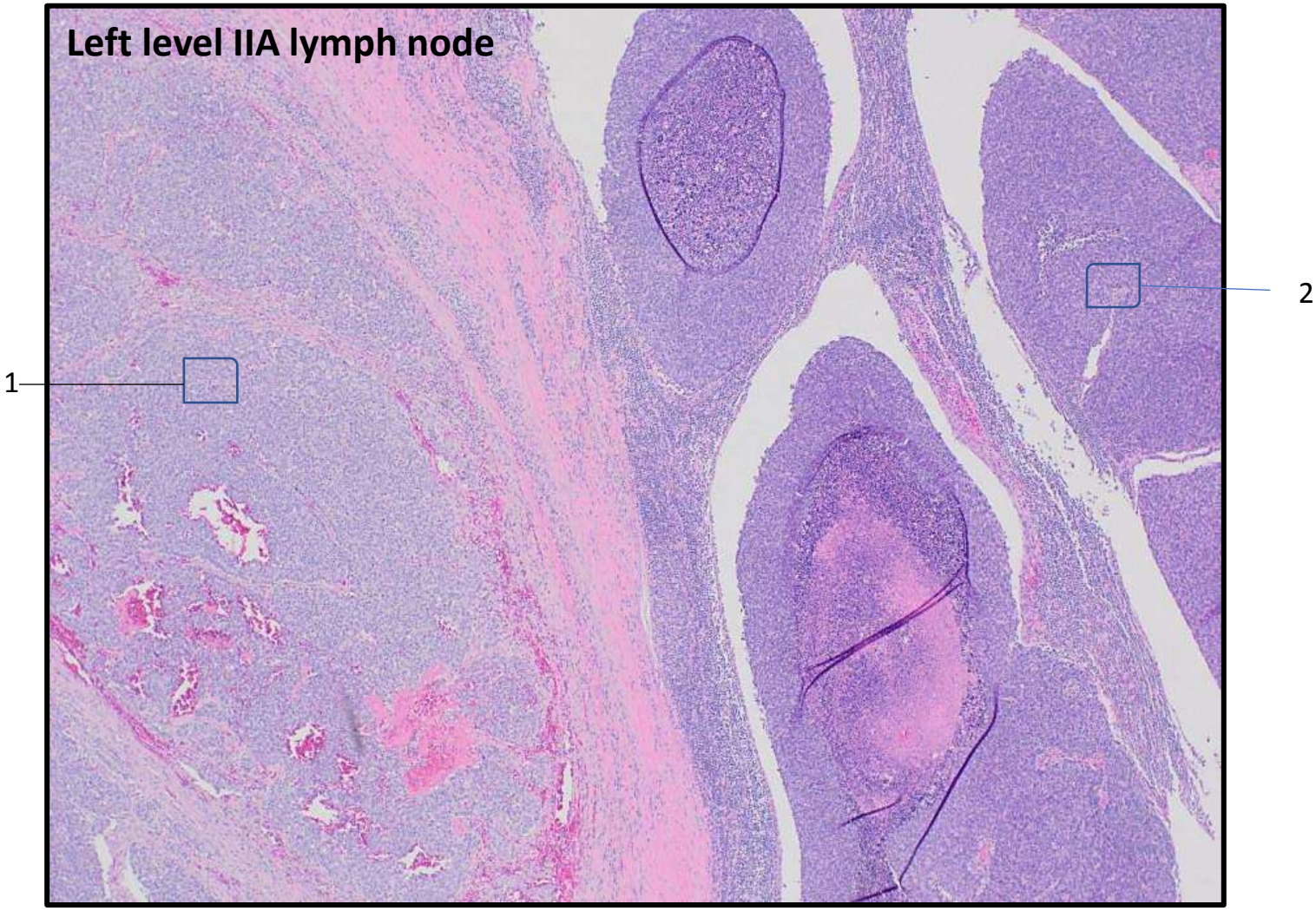
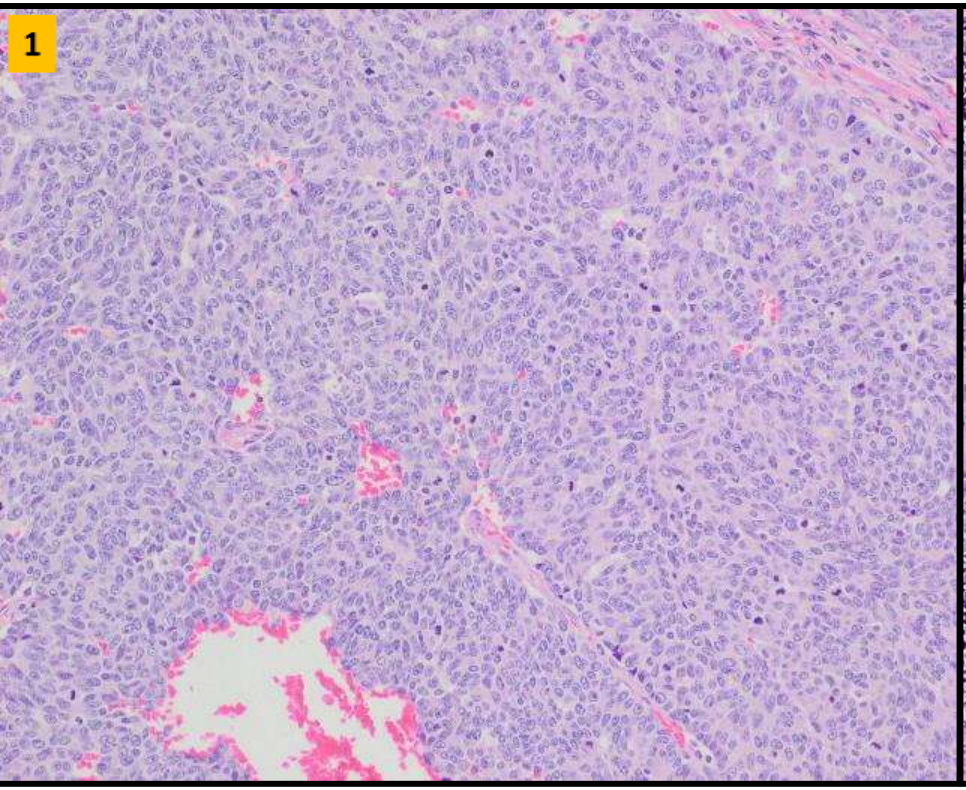
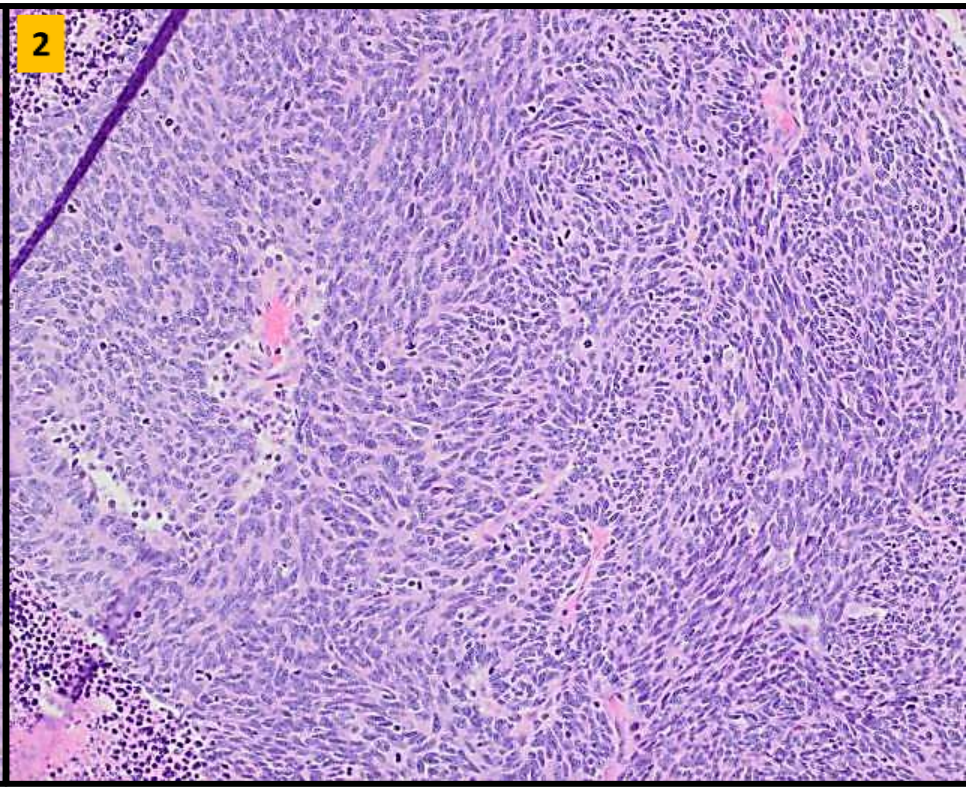
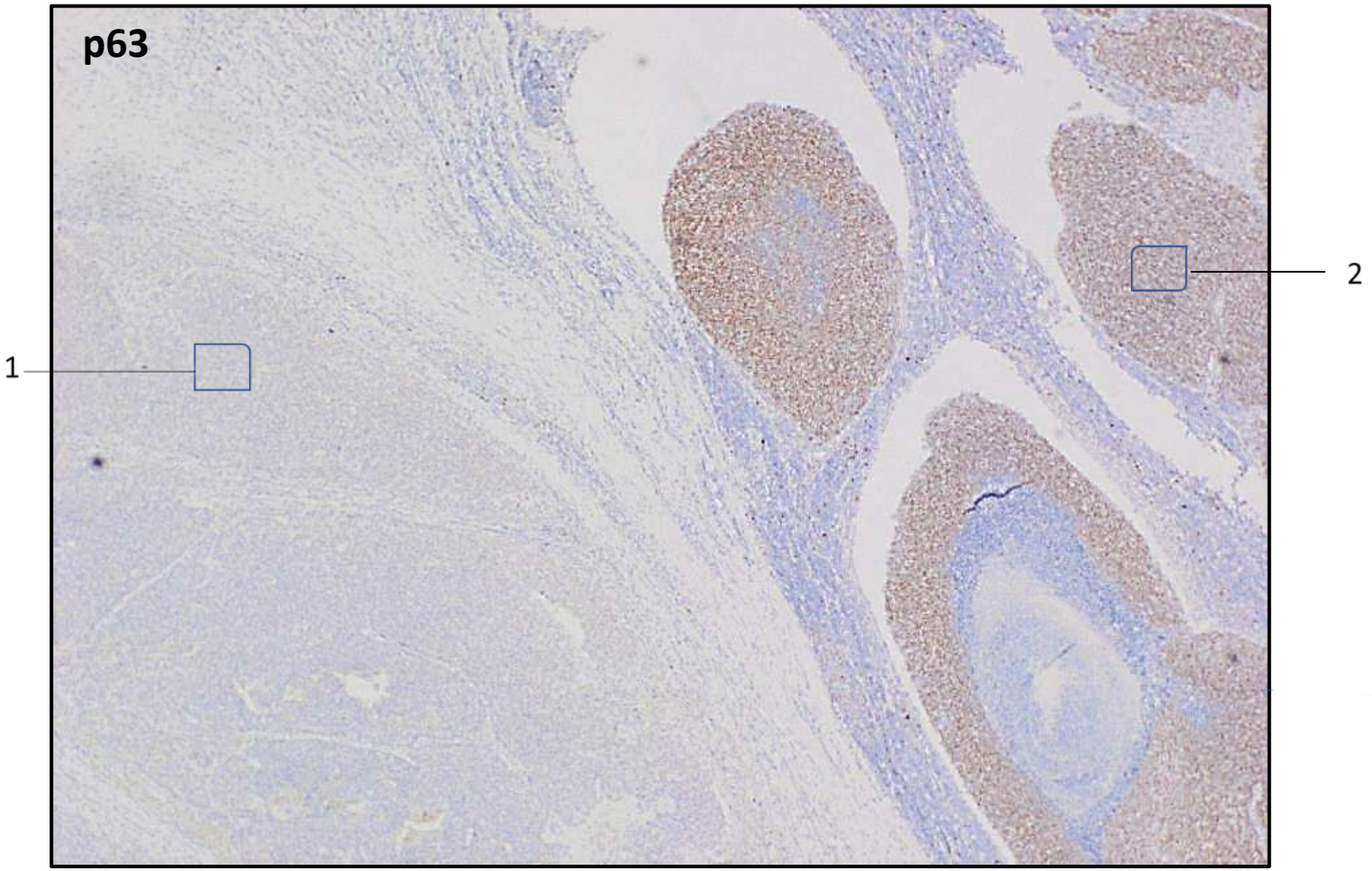

Left level IIA lymph node
1
2

Left level IIA lymph node

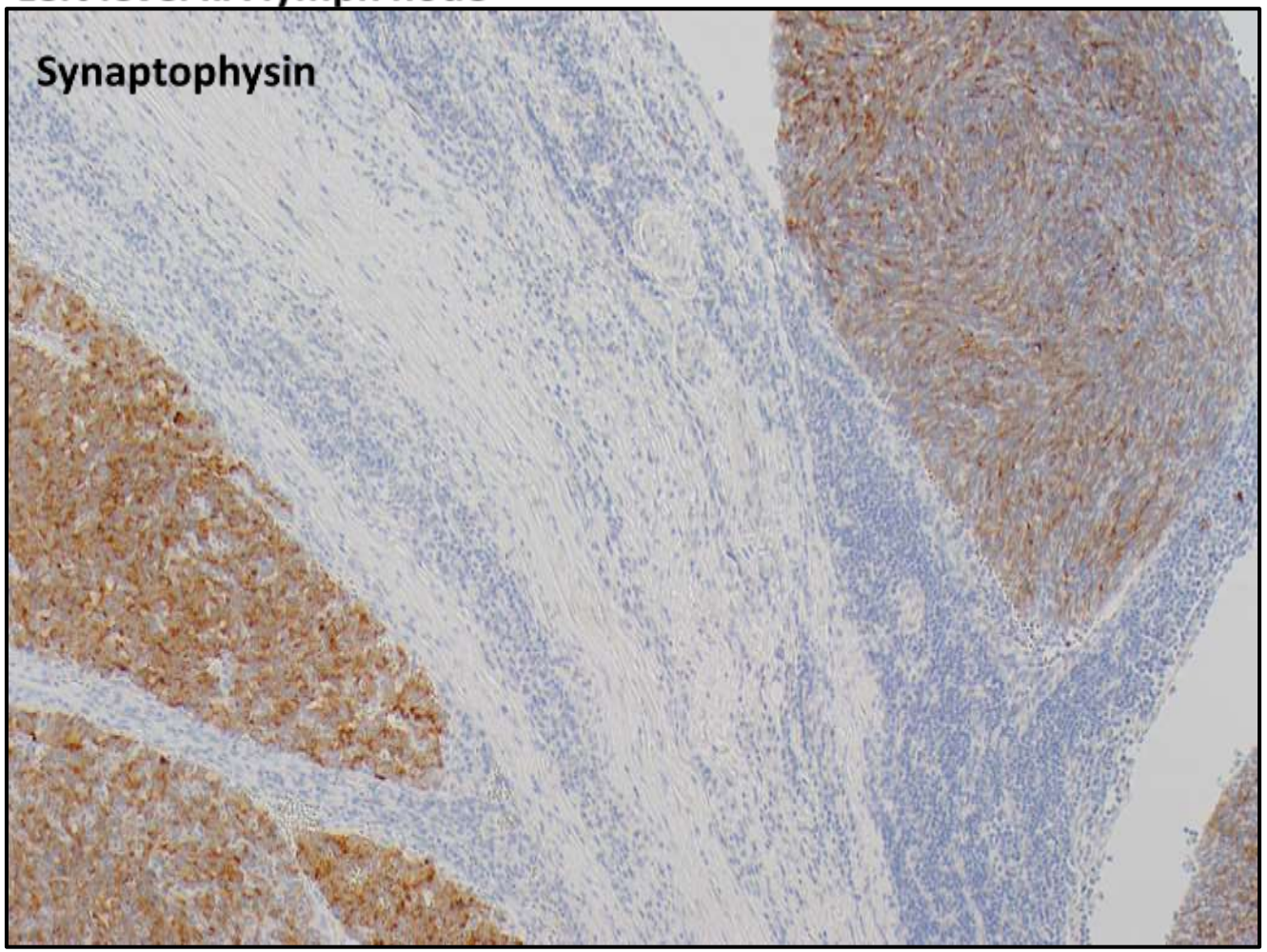




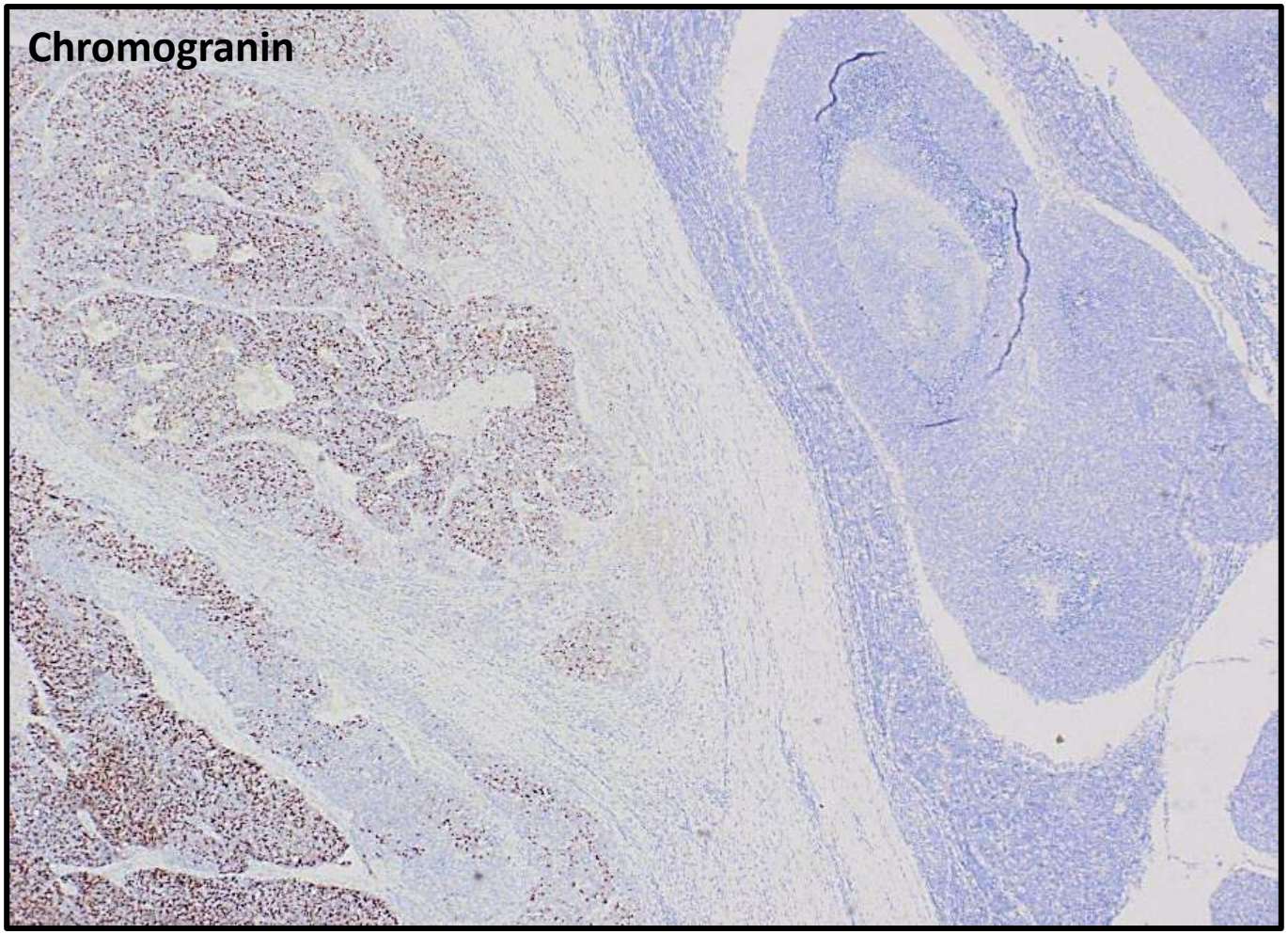
Left level IIA lymph node

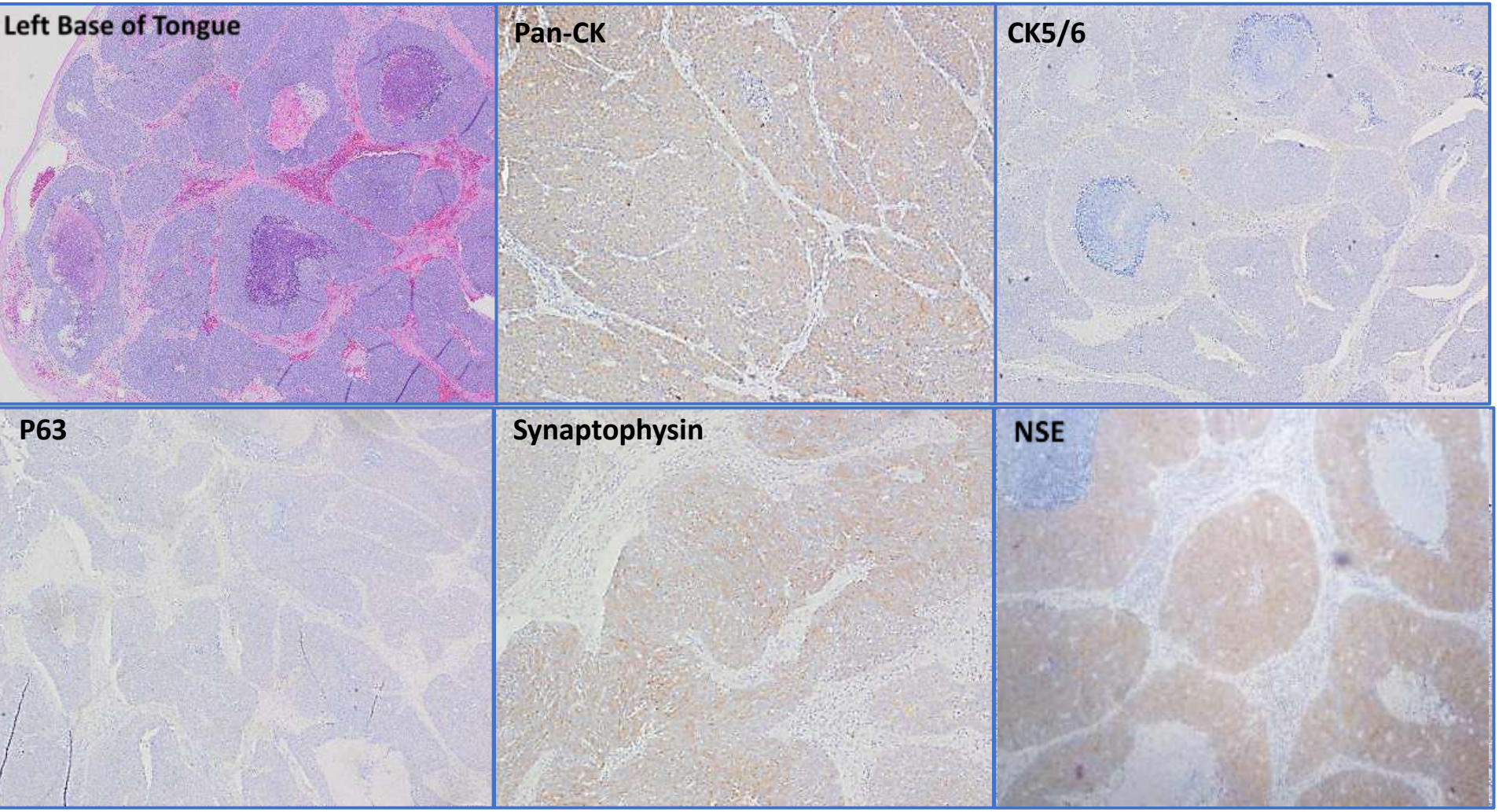


Left level IIA lymph node



Left level IIA lymph node

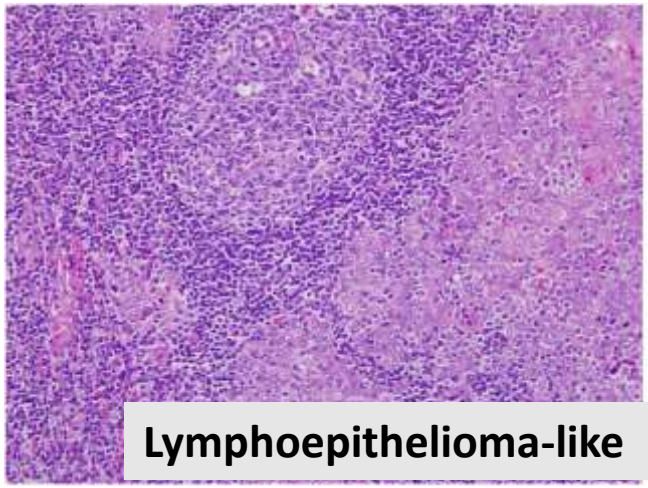


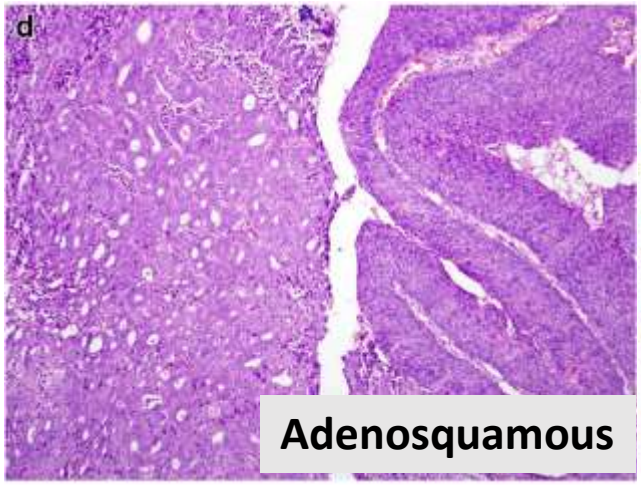

Left Base of Tongue
Pan-CK
CK5/6
P63
Synaptophysin
NSE

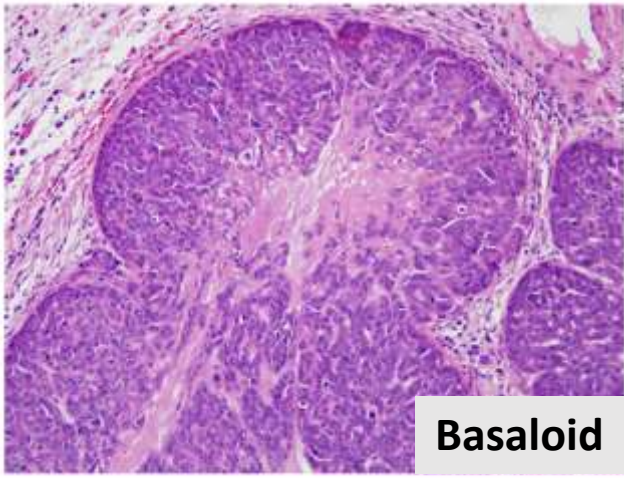
Final Pathologic Diagnosis:

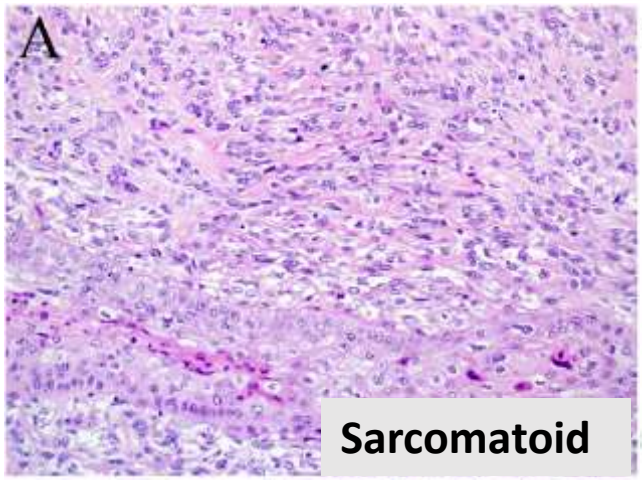
High grade neuroendocrine carcinoma, HPV positive

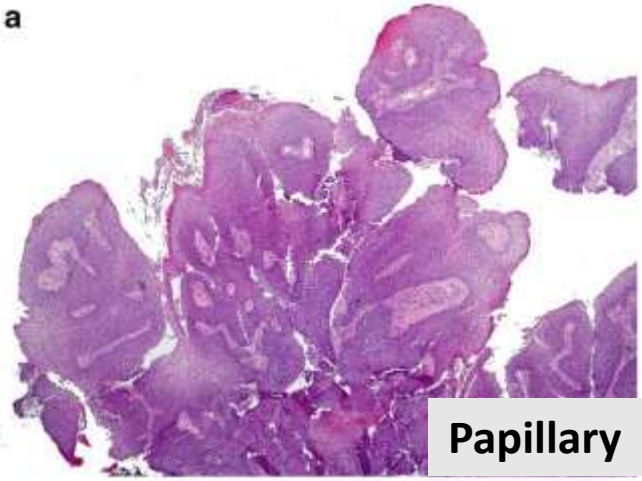
Variants of HPV+ oropharyngeal carcinoma











Westra, Semin Diagn Pathol. 2015 Jan;32(1):42-53

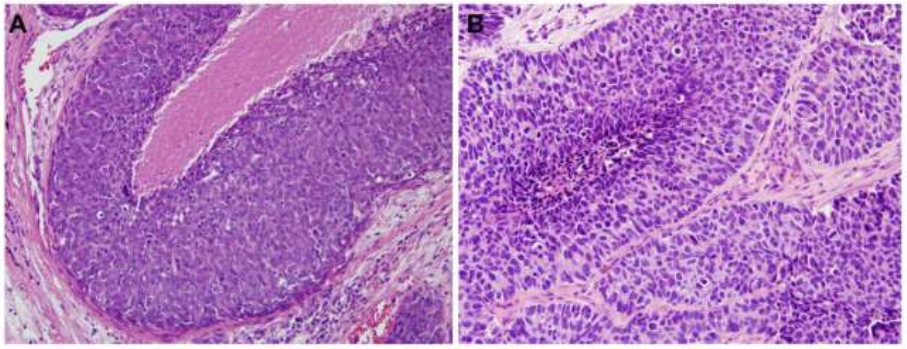
NEC, HPV positive

Table 1

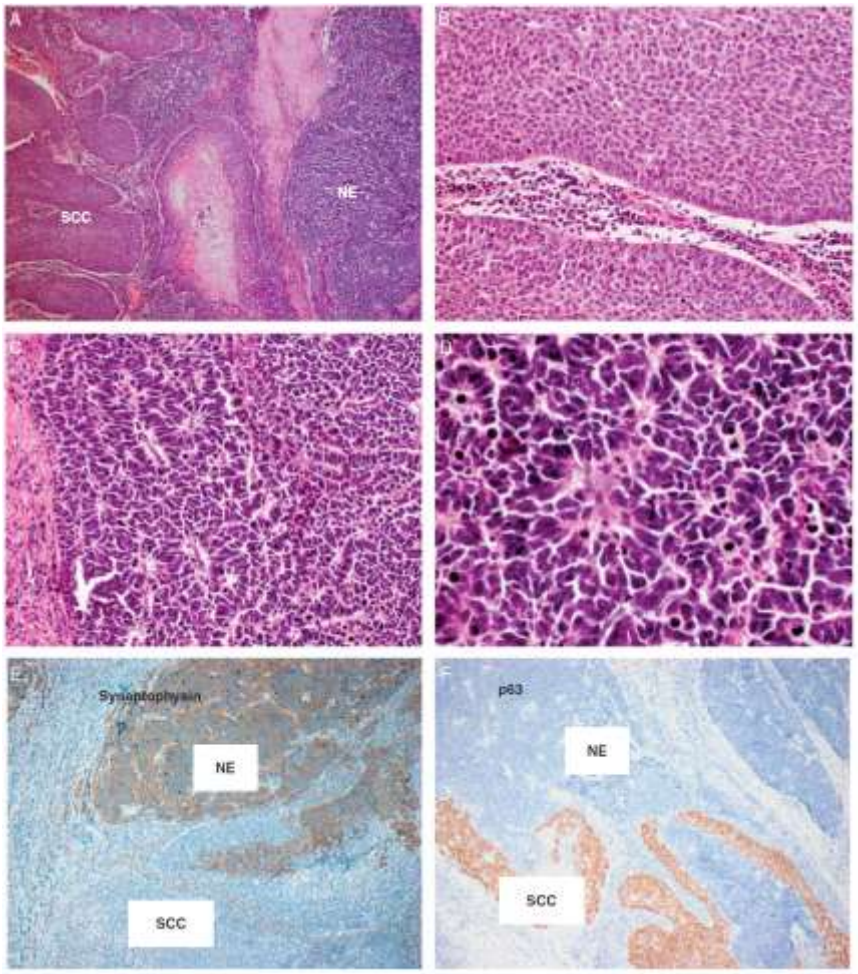
Clinical characteristics of patients with HPV-related small cell carcinoma of the oropharynx

Case #	HPV status	Year	Site	Age	Sex	Pack years	Presentation	Treatment	Clinical course	Outcome	Time to death/last follow-up (months)
1	+	2001	tonsil	65	F	40	lung metastasis	CT	distant metastases	DWD	6
2	+	2006	tonsil	67	M	80	neck metastasis	Surgery/RT/CT	distant metastases	DWD	15
3	+	2009	soft palate	67	M	20	epistaxis	Surgery/RT/CT	complete response	NED	20
4	+	2009	tonsil	55	M	0	neck metastasis	CT/RT	distant metastases	DWD	9
5	+	2010	tonsil	49	M	0	neck metastasis	CT/RT	complete response	NED	5
6	−	1988	base of tongue	72	M	35	odynophagia	surgery	distant metastases	DWD	12
7	−	1993	base of tongue	66	M	50	neck metastasis	surgery/RT/CT	distant metastases	DWD	12
8	−	2007	tonsil	63	M	Unknown	odynophagia	Surgery/RT/CT	distant metastases	DWD	9
9	−	2009	tonsil	83	M	unknown	oropharyngeal mass	CT	distant metastases	DWD	2

CT, chemotherapy; RT, radiation therapy; DWD, dead with disease; NED, no evidence of disease



Bishop and Westra, AJSP 2011



Kraft et al (2012)

Table 1: Published data of NEC cases with tumor sites and results of HPV-sequencing.

Author	Cases	Site	HPV-Type
Bishop et al.(2011) [29]	4	Oropharynx	16
Kraft et al. (2012) [4]	6	Oropharynx	16, 18, 33
Halmos et al (2013) [30]	2	Larynx	16, 18
Bates et al. (2014) [31]	2	Oropharynx	16, 18
Misawa et al. (2016) [25]	2	Oropharynx	16, 18

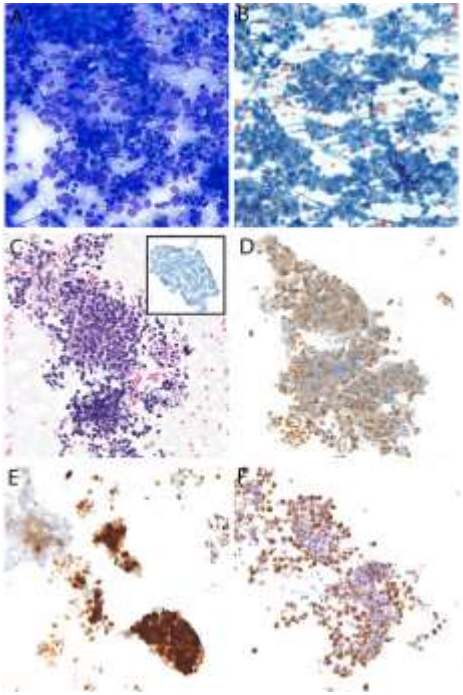


TABLE 2. Clinicopathological Features of HPV-Associated Neuroendocrine Carcinomas of the Head and Neck Diagnosed by FNA

Feature	Cases 1 and 2[a]	Case 3	Case 4	Case 5
Age, y	39	79	63	68
Sex	Female	Female	Male	Male
Biopsy site	Lymph nodes, left neck (levels II and VI)	Lymph node, left neck (level IB)	Lymph node, right neck (levels II and III)	Lymph node, right neck (level II)
Type of procedure	USG FNA by pathologist	USG FNA by pathologist	FNA by pathologist	CTG FNA by radiologist
Morphology (small vs large cell or mixed)	Mixed small and large cell	Predominantly large cell	Mixed small and large cell	Predominantly small cell
Presumed primary site[b]	Larynx	Oropharynx	Nasopharynx	Oropharynx
Histological confirmation	Kidney metastasis	Cervical lymph node dissection	Nasopharynx primary biopsy	Concurrent core biopsy
Distant metastases	Kidney	None to date	Liver and spine	None to date
Status (mo of follow-up)	Died of disease (15)	AWD (12)	Died of disease (8)	AWD (2)
HPV ISH	+	+	N/D	+
HPV PCR (type detected)	N/D	N/D	+ (HPV-18)	N/D
p16 IHC (0-3+)	3+	3+	3+	3+
p53 IHC (0-3+)	1+	1+	1+	1+
Rb IHC (0-3+)	1+	1+	2+	2+

Abbreviations: AWD, alive with disease; CTG, computed tomography–guided; FNA, fine-needle aspiration; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in situ hybridization; N/D, not done; PCR, polymerase chain reaction; Rb, retinoblastoma; USG, ultrasound-guided.

[a]Cases 1 and 2 were from the same patient.

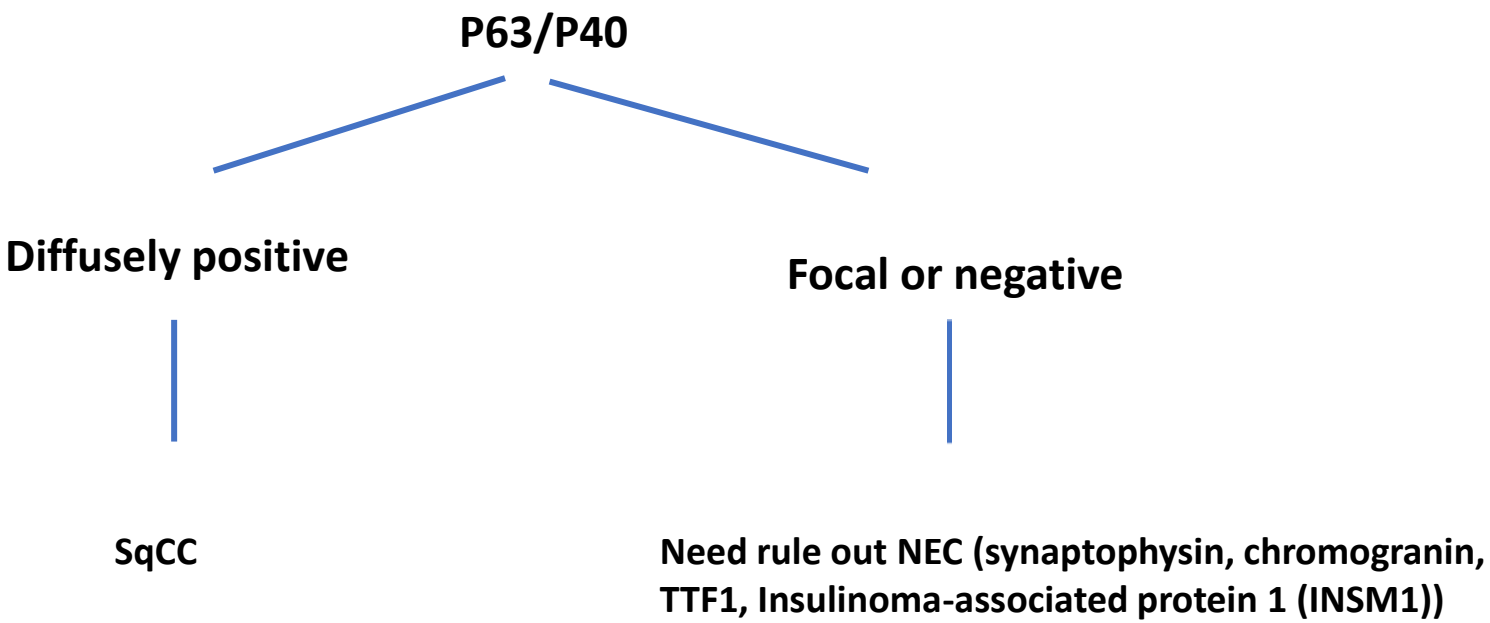
[b]All patients had imaging studies that supported the primary tumor site.

Vickie, Y. Jo et al. 2019. HPV-Associated Neuroendocrine Carcinomas of the Head and Neck in FNA Biopsies: Clinicopathologic Features of a Rare Entity. Cancer Cytopathol. Feb;127(1):26-34.

Oropharyngeal carcinoma	Metastases	Prognosis	Prognosis determined by	Treatment regimen
HPV+ Sqcc	Local	Good	HPV status	**Surgery** + radiation (de-escalation therapy)
HPV+ NEC	Distant	Poor	NEC histology	**Chemo** + radiation (aggressive)

Summary

- HPV-related high grade NEC has been and remains a very rare form of head and neck cancer.
- HPV + SqCC/small cell carcinoma/large cell carcinoma all have a basaloid appearance, high mitotic rates, and frequent necrosis
- High-grade NEC are often mixed with SqCC
- The excellent prognosis of HPV-related oropharyngeal SqCC is trumped by high-grade neuroendocrine carcinoma histology.
- The presence of a NEC component should disqualify any patient with an HPV-OPSqCC from consideration as a candidate for less intensive multimodality therapy (i.e., de-escalation therapy)


P63/P40
Diffusely positive
Focal or negative
SqCC
Need rule out NEC (synaptophysin, chromogranin, TTF1, Insulinoma-associated protein 1 (INSM1))

References:

- Allison DB, Rooper LM, Mustafa S, Maleki Z, Wakely PE Jr, Ali SZ. Cytopathologic characteristics of HPV-related small cell carcinoma of the oropharynx. Cancer Cytopathol. 2019 Feb;127(1):35-43
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- Timothy Bates, Andrew McQueen, Muhammad Shahid Iqbal, Charles Kelly Max Robinson. Small Cell Neuroendocrine Carcinoma of the Oropharynx Harbouring Oncogenic HPV-Infection. Head and Neck Pathol (2014) 8:127–131
- Justin A. Bishop, M.D.1 and William H. Westra, M.D. Human Papillomavirus-Related Small Cell Carcinoma of the Oropharynx. Am J Surg Pathol. 2011 November ; 35(11): 1679–1684.
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- Simon Andreasen. An update on head and neck cancer: new entities and their histopathology, molecular background, treatment, and outcome. APMIS 127: 240–264
- Todd M. Stevens, Justin A. Bishop. HPV-related carcinomas of the head and neck: morphologic features, variants, and practical considerations for the surgical pathologist. Virchows Arch (2017) 471:295–307
- Thompson ED, Stelow EB, Mills SE, Westra WH, Bishop JA. Large Cell Neuroendocrine Carcinoma of the Head and Neck: A Clinicopathologic Series of10 Cases With an Emphasis on HPV Status. Am J Surg Pathol. 2016;40(4):471-8.

19-1205

Philip Bulterys/Christine Louie; VA Palo Alto

65-year-old male with h/o treated HCV cirrhosis, presenting with hematochezia. EGD demonstrated nodular and striking erythematous mucosa in duodenum. Duodenal polyp submitted.

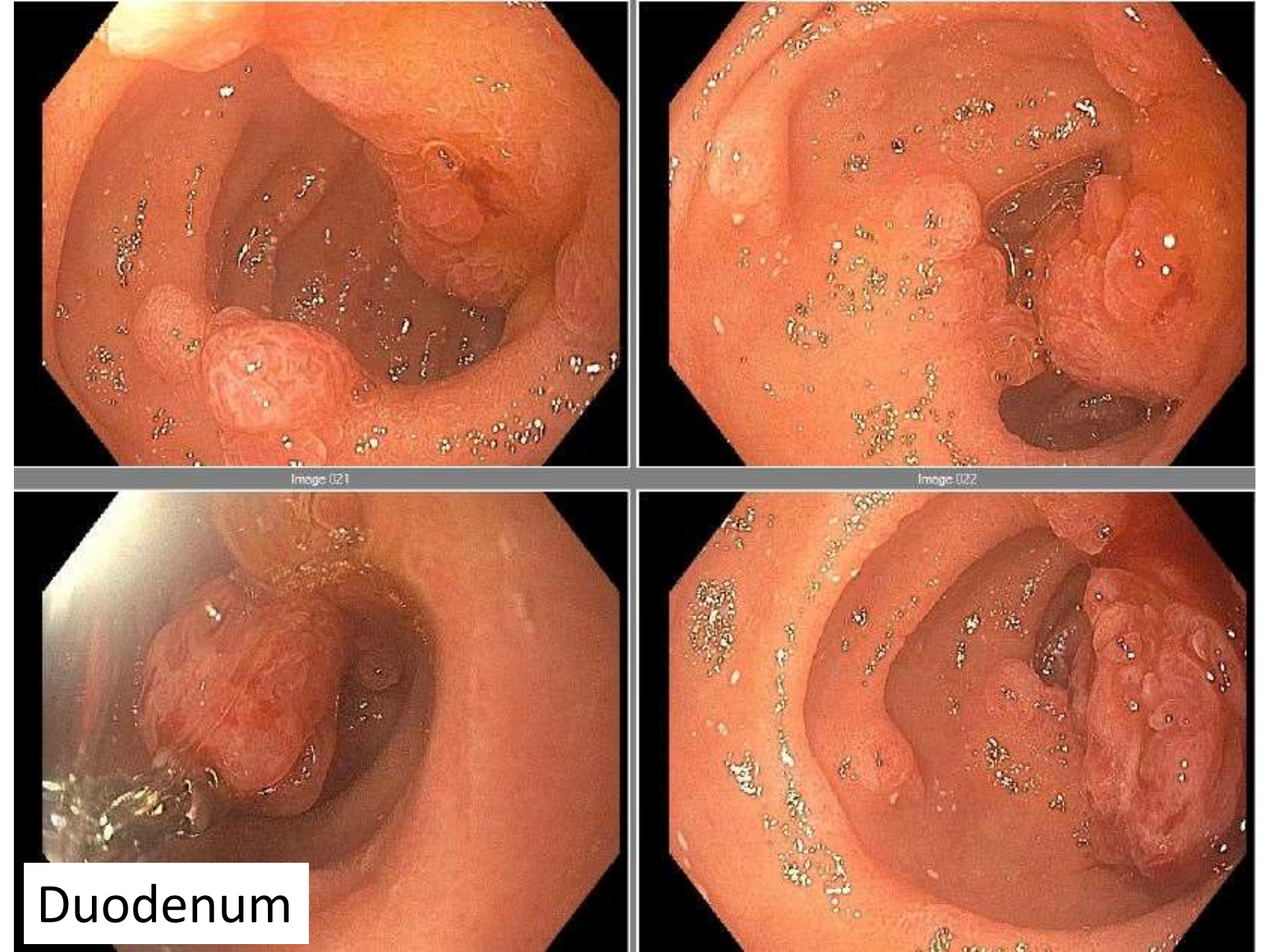
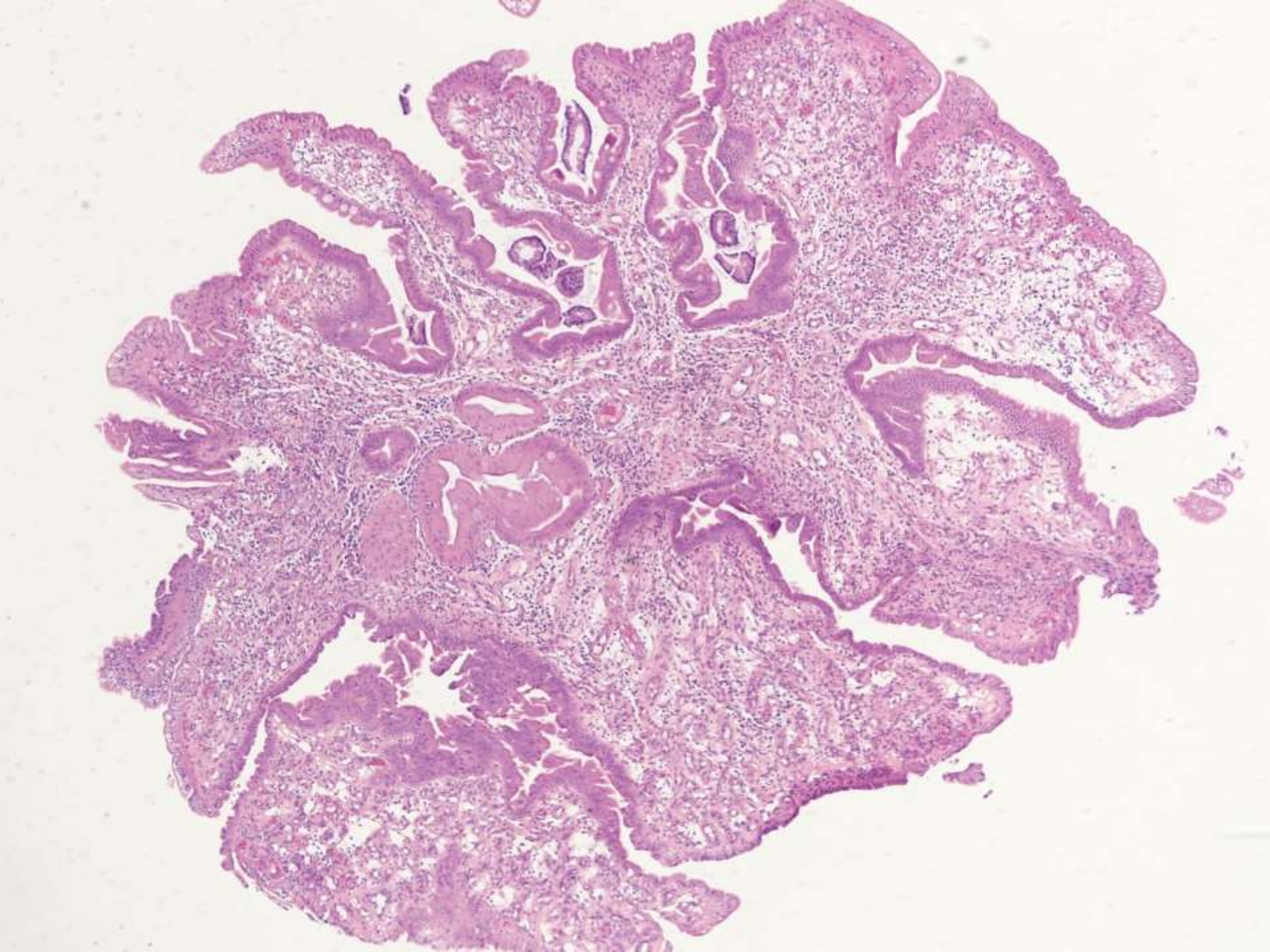
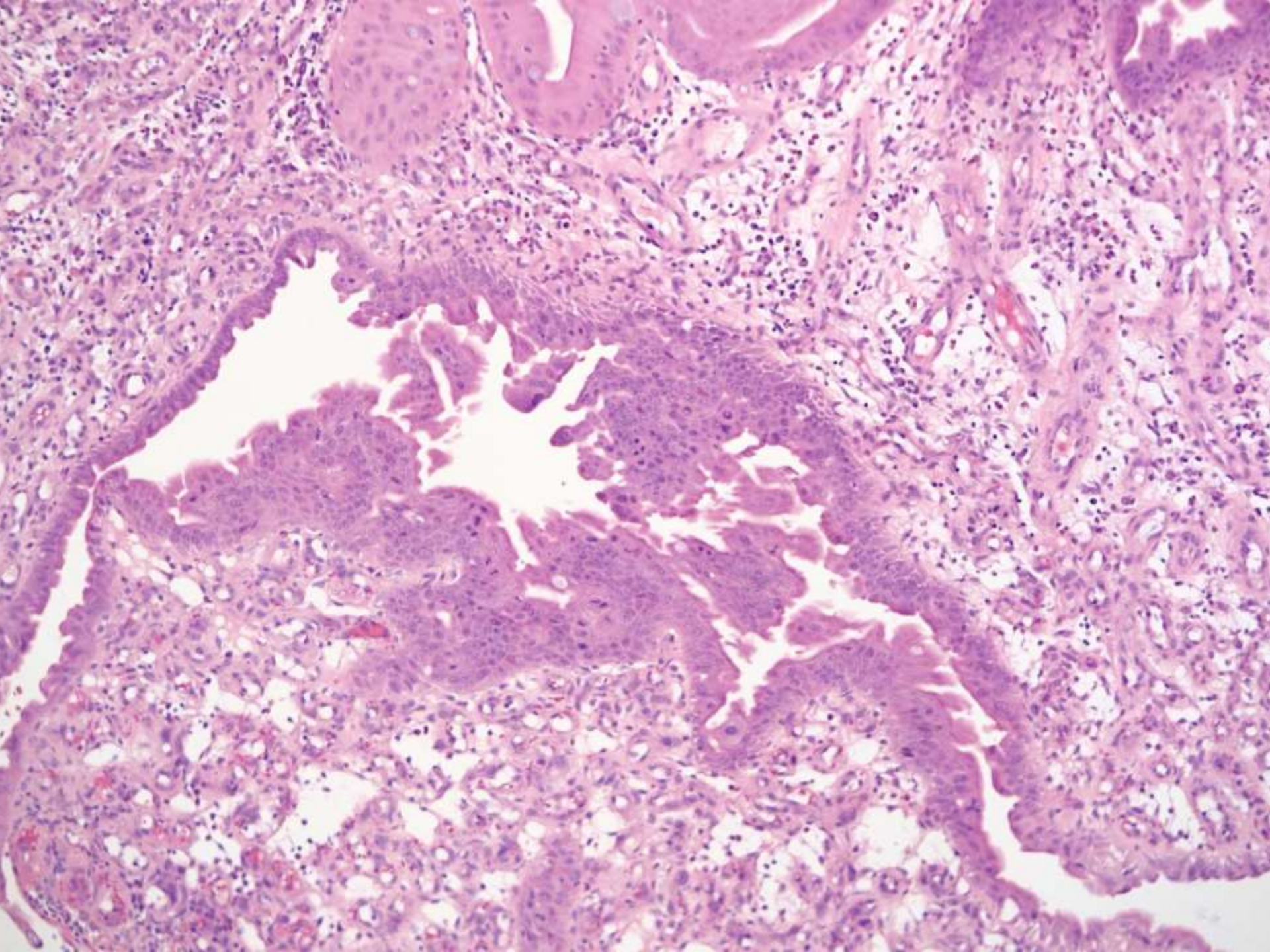
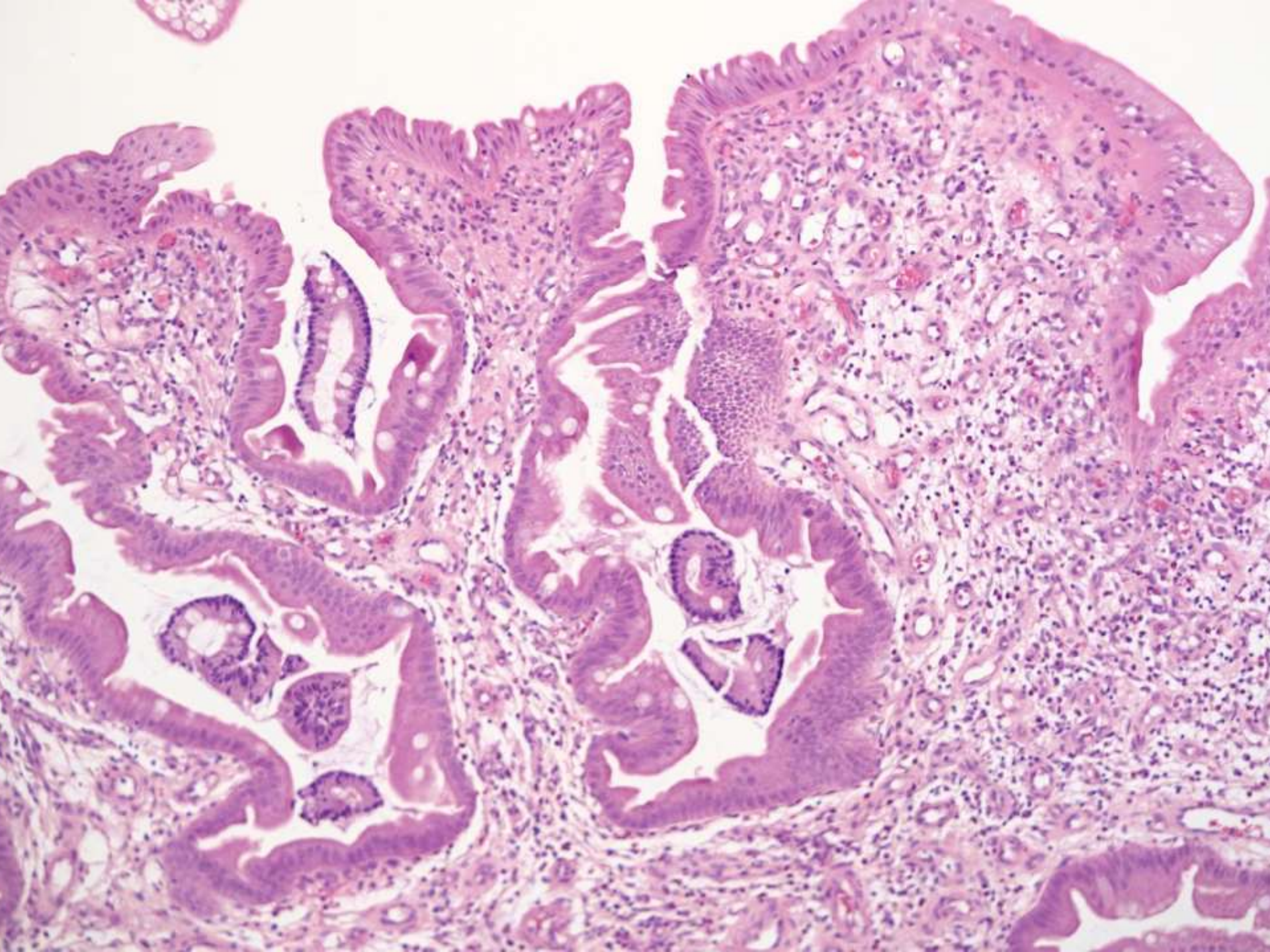
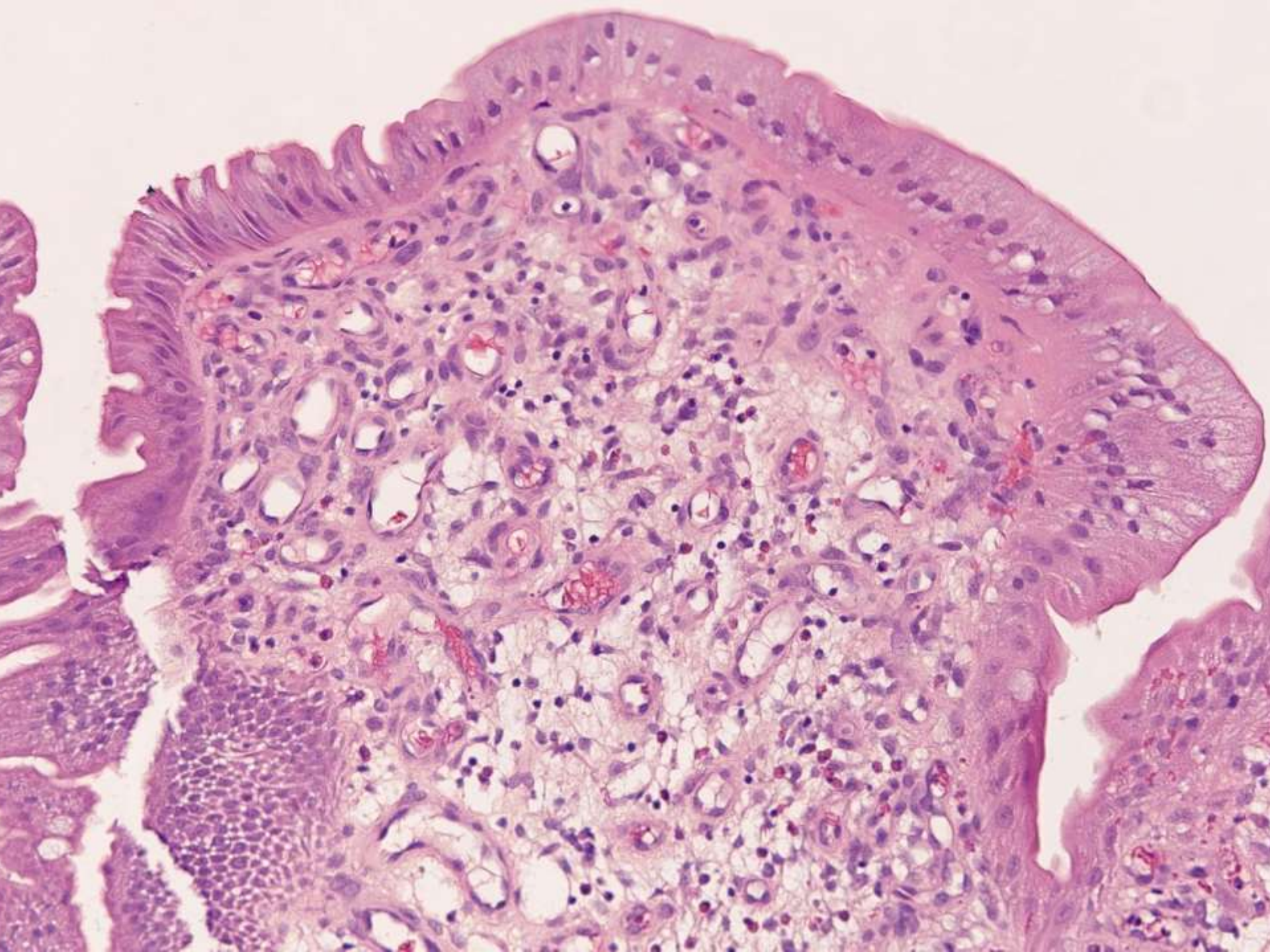


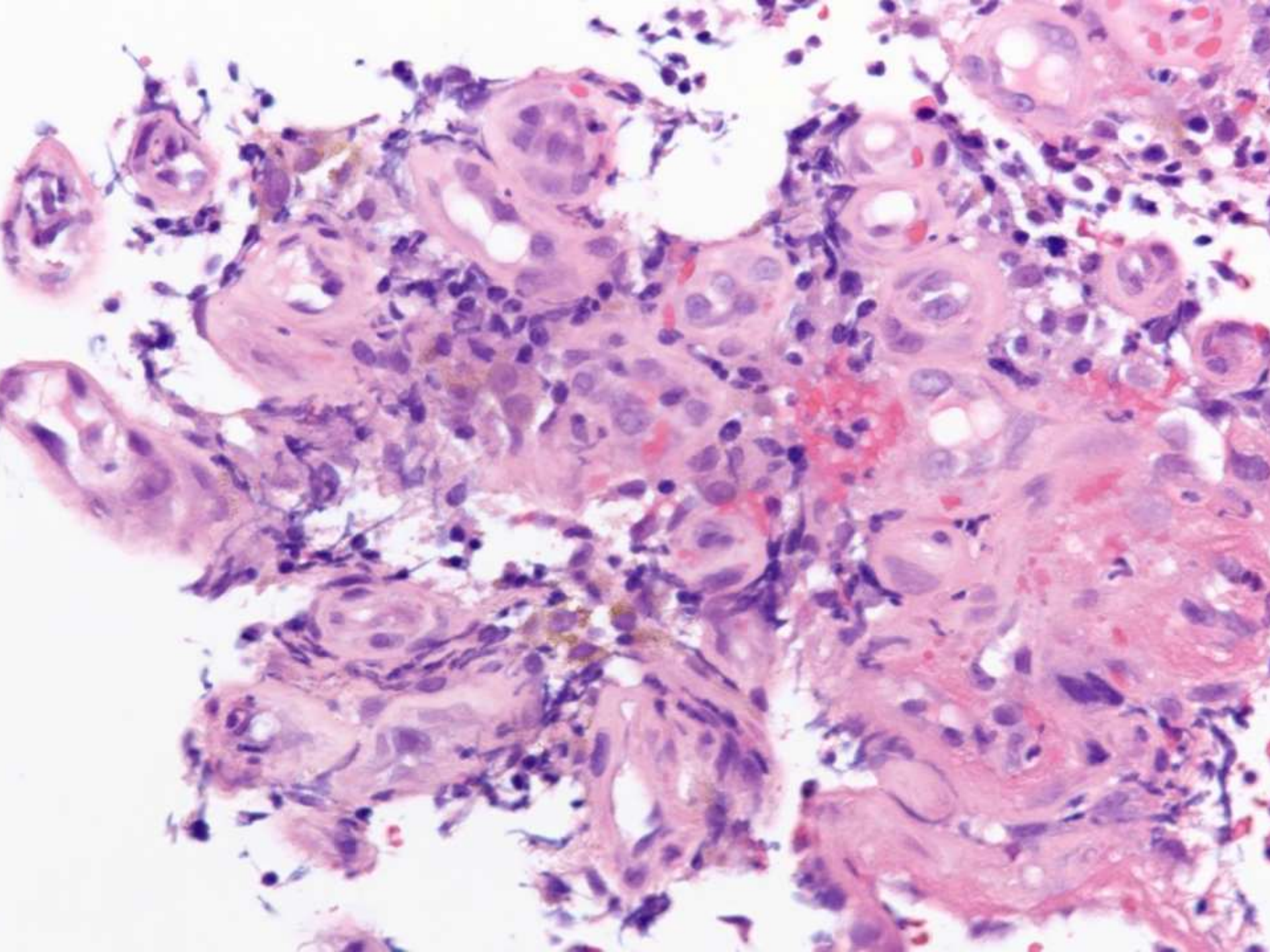
Image 021
Image 022
Duodenum

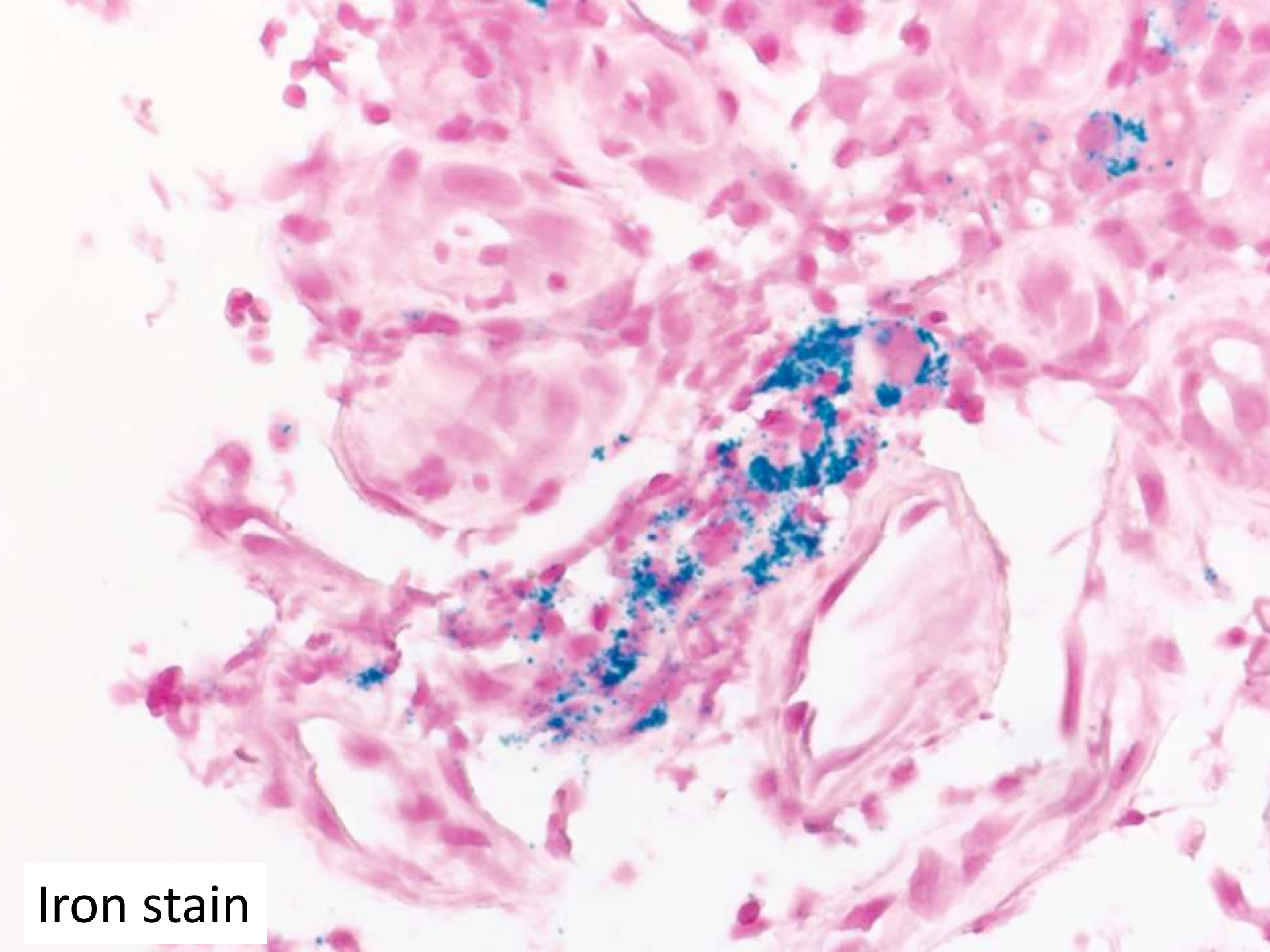











Iron stain

DIAGNOSIS:

-- PORTAL HYPERTENSIVE DUODENOPATHY

-- SIDEROSIS, POSSIBLY RELATED TO CIRRHOSIS

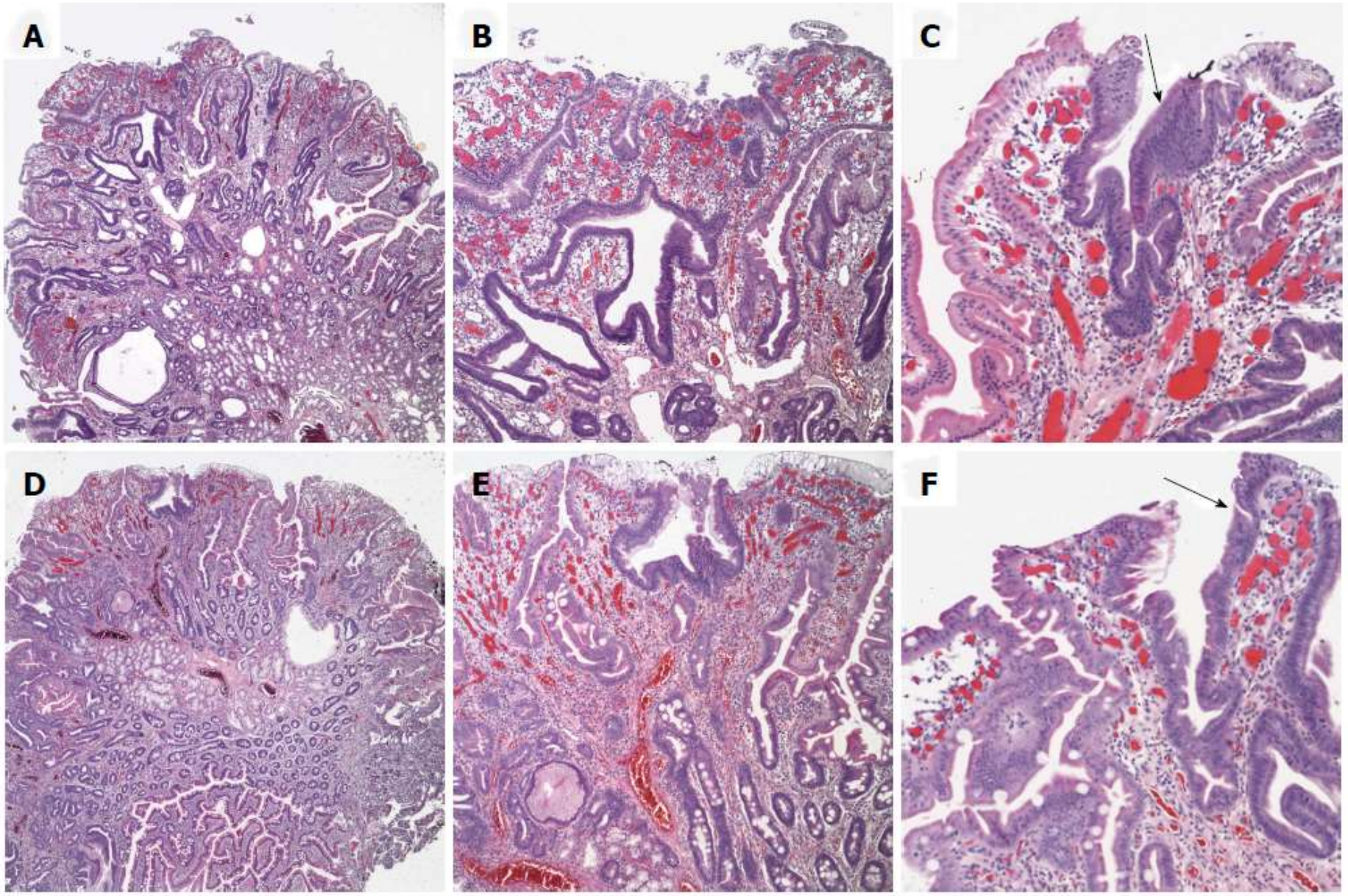
Reports of small intestinal polyps related to portal hypertension

Table 1 Reported small intestinal polyps secondary to portal hypertension (including current case)

Ref.	Age (yr)/ gender	Location(s)	Number/sizes of polyps	Pathologic findings	Etiology of portal hypertension
Current report	52/M	Duodenal bulb to second portion	Greater than 7, majority 1-2 mm, largest 8 mm	Villiform hyperplasia of reactive intestinal and gastric foveolar epithelium, proliferating ectatic and congested lamina propria vessels	Alcoholic cirrhosis
Pillai *et al*[2]	55/M	1st portion of duodenum	"multiple sessile polyps", sizes NS	Polypoid muocsa lined by small intestinal and gastric foveolar type epithelium with ectatic capillaries, fibrosis and smooth muscle proliferation of lamina propria	Alcoholic cirrhosis
Zeitoun *et al*[3]	70/M	2nd portion of duodenum	Single polyp, 3 cm	Numerous thick-walled capillaries with vascular ectasia in lamina propria	Alcoholic cirrhosis
[1]Lemmers *et al*[4]	50/F	Jueuno-ileal	"Several", > 5 mm	Lamina propria vascular dilation and thrombi without epithelial atypia	Hepatitis C cirrhosis
	73/M	Jejunal	Two "bumps", < 5 mm	Not biopsied	Cryptogenic cirrhosis
	67/M	Duodenal	"Several", 5 mm	Lamina propria vascular dilation and inflammation with epithelial atypia and ulceration	Alcoholic cirrhosis
	74/F	Antral/duodenal	"Several", 15 mm	Lamina propria vascular dilation and epithelium with crenellated glands	Hepatitis C cirrhosis
	66/F	Duodenal/jejuno-ileal	"Several", 5/< 5 mm	Not biopsied	Cryptogenic cirrhosis
Devadason *et al*[5]	6 yr/M	1st and 2nd portion of duodenum	"polyps", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	4 yr/F	2nd portion of duodenum	"numerous", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	1 yr/F	2nd portion of duodenum	"polyps", sizes NS	Polyp not biopsied, mucosa adjacent to polyp with ecatsia and congestion of lamina propria with smooth muscle hypertrophy	EHPVO

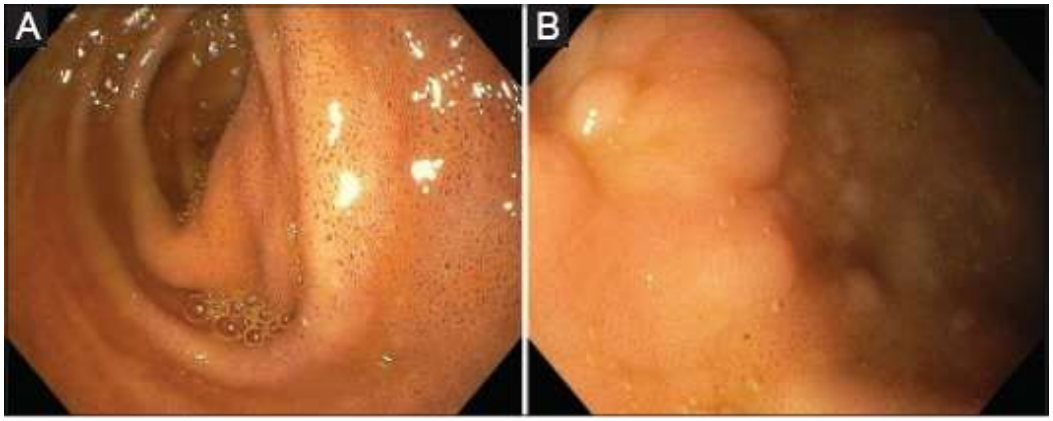
Gurung A, Jaffe PE, Zhang X. WJGE 2015.

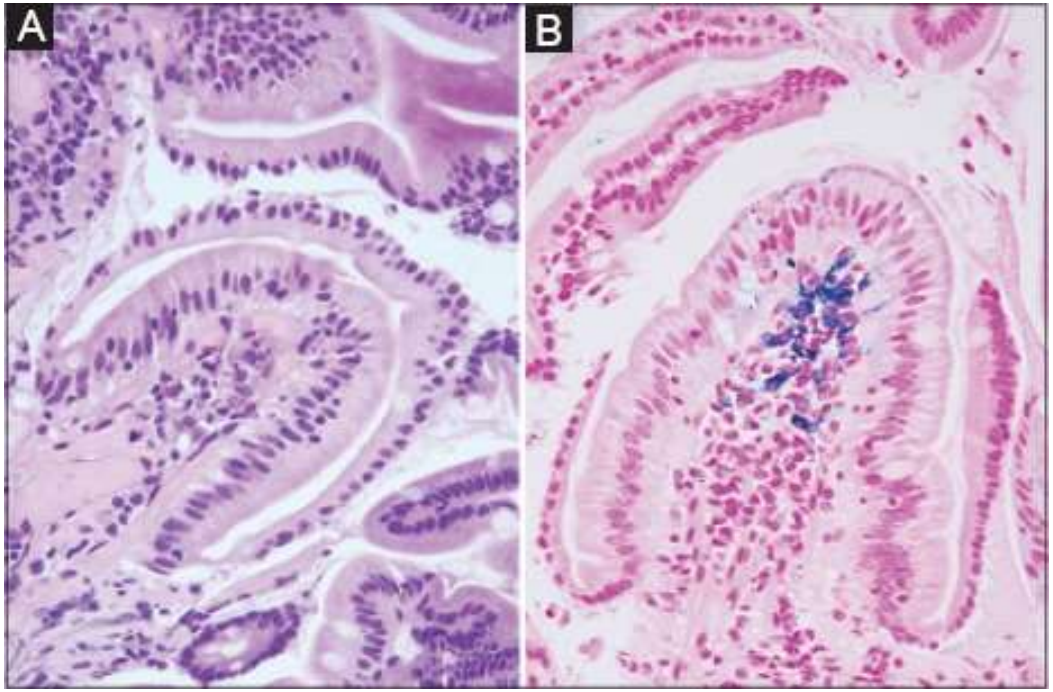
Histologic features



Gurung A, Jaffe PE, Zhang X. WJGE 2015.

Gastric and duodenal siderosis





Main associations:

- Oral iron medications
- Alcohol abuse
- Blood transfusions
- Hemochromatosis
- Decompensated cirrhosis with esophageal varices

Three main patterns of siderosis:

Type A (“non-specific”) variant

- Floating siderosomes
- Located intracellularly in macrophages, stroma, and epithelium

Type B (“iron-pill gastritis”)

- Large clumps of fibrillar iron
- Located extracellularly and in blood vessels, macrophages, and epithelium

Type C (“gastric glandular”) variant

- Free floating siderosomes
- Located in deeper glands of the antrum and fundus

Kothadia JP, Kaminski M, Giashuddin S. Ann Gastroenterol 2016.

Take-home points

1. Portal hypertensive duodenopathy is rare but can sometimes be seen and biopsied

2. Endoscopic findings may include polypoid, ulcerated, or erythematous mucosa

3. Biopsies will show capillary proliferation, congestion, or dilation with foveolar metaplasia, apoptosis, and fibrosis sometimes seen

4. Siderosis within macrophages is nonspecific and may be related to inflammation and hemorrhage but has also been reported in the context of cirrhosis

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2. Kothadia JP, Kaminski M, Giashuddin S. Duodenal siderosis: a rare clinical finding in a patient with duodenal inflammation. *Annals of Gastroenterology* 2016; 29 (3): 379.
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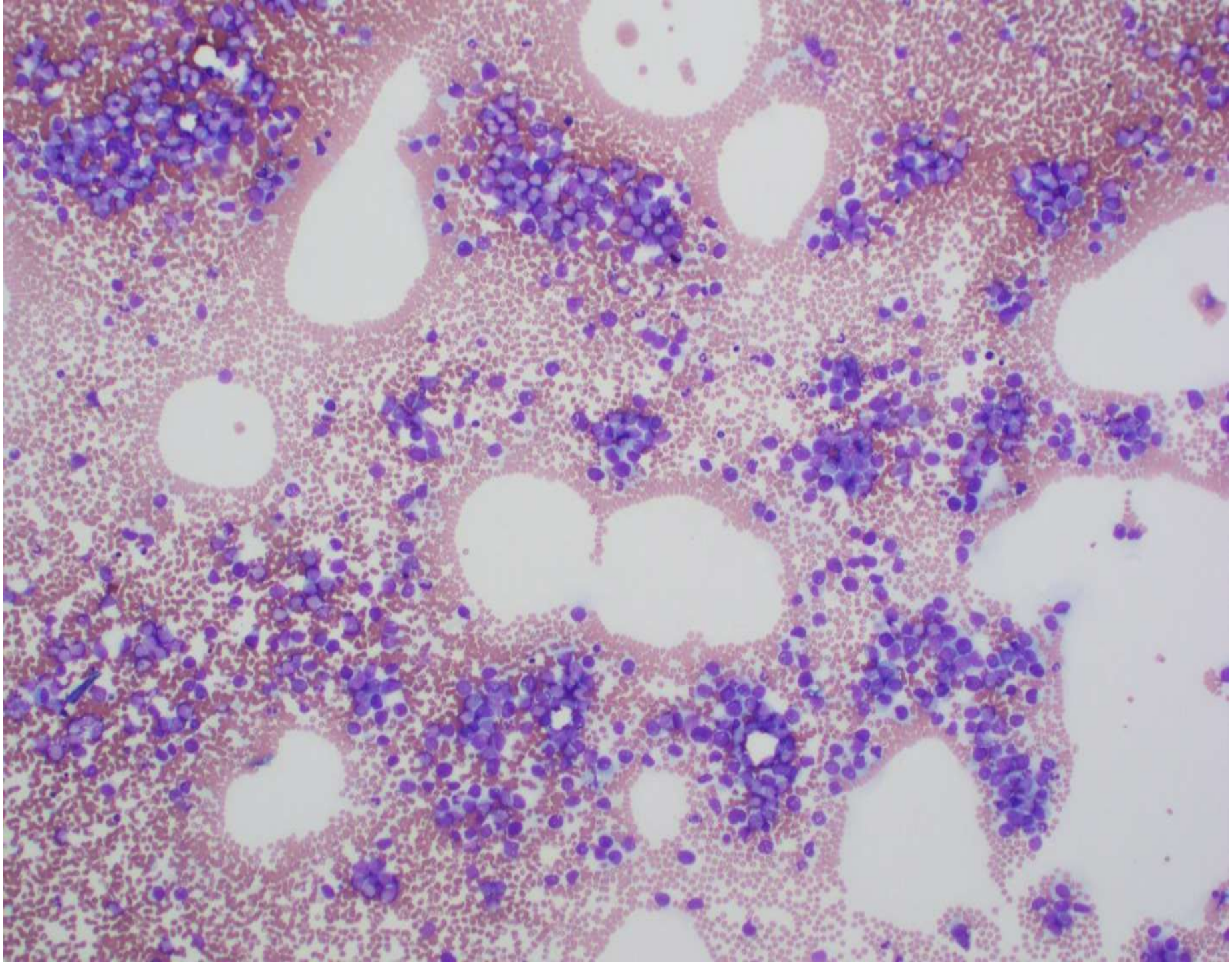
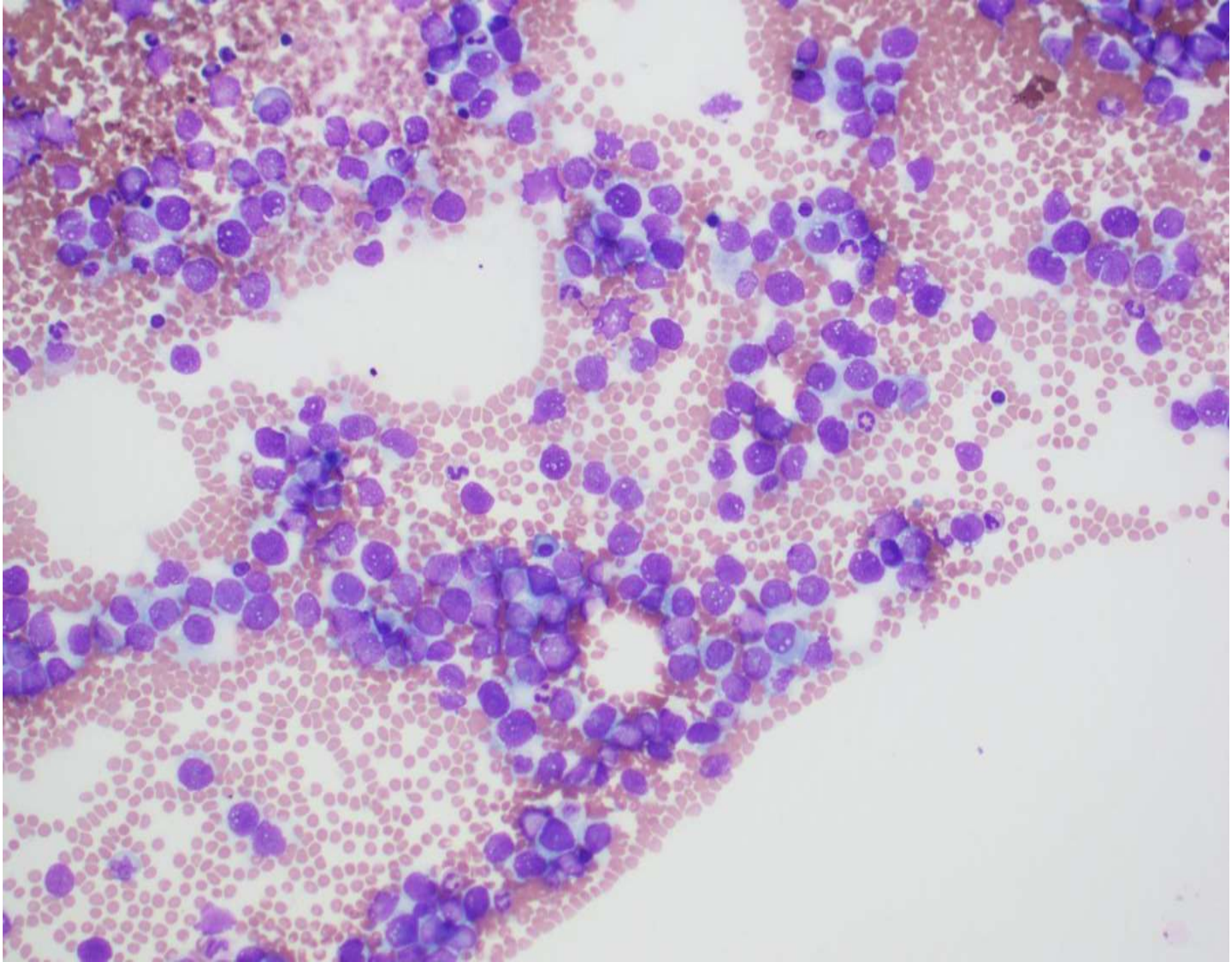
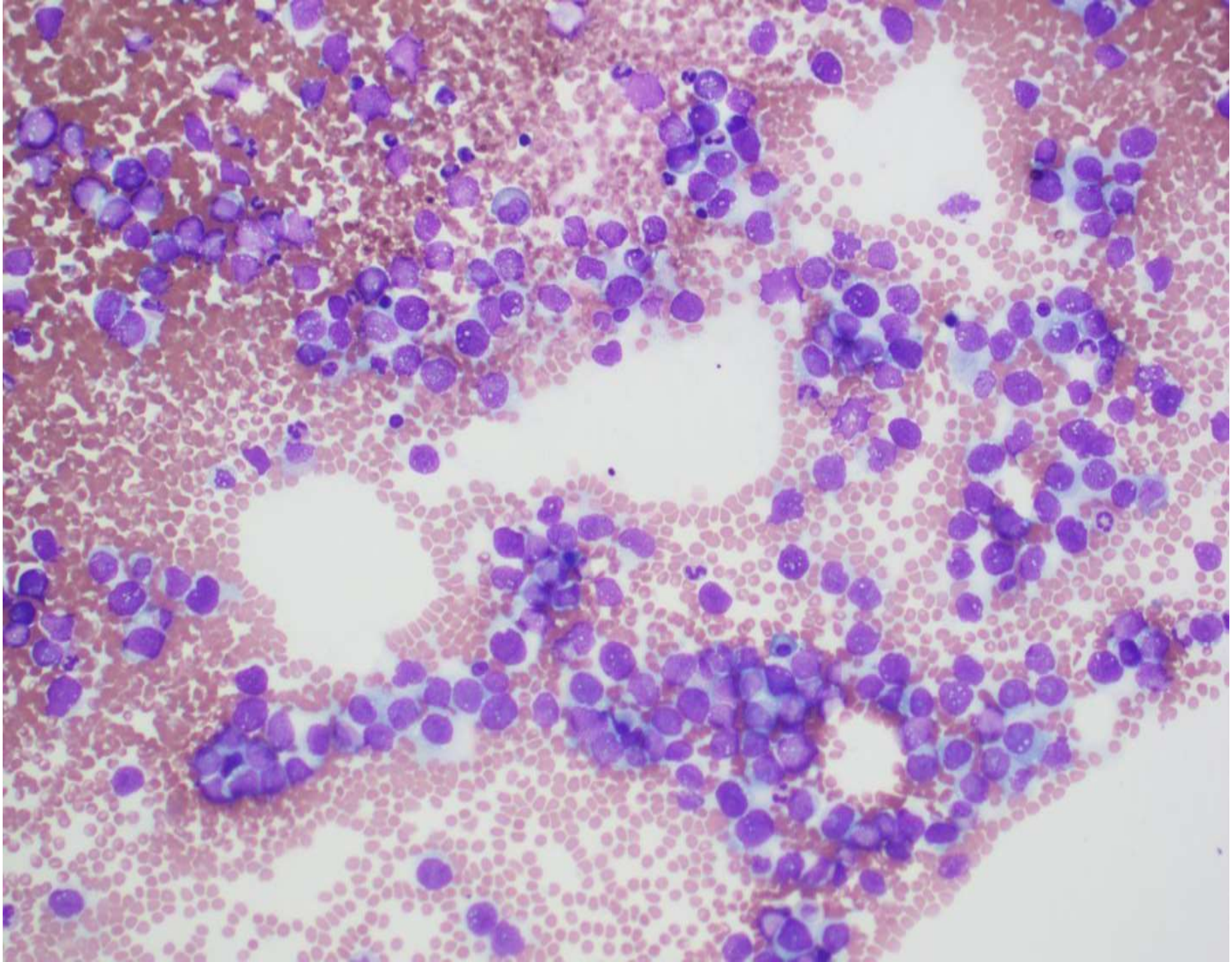
19-1206

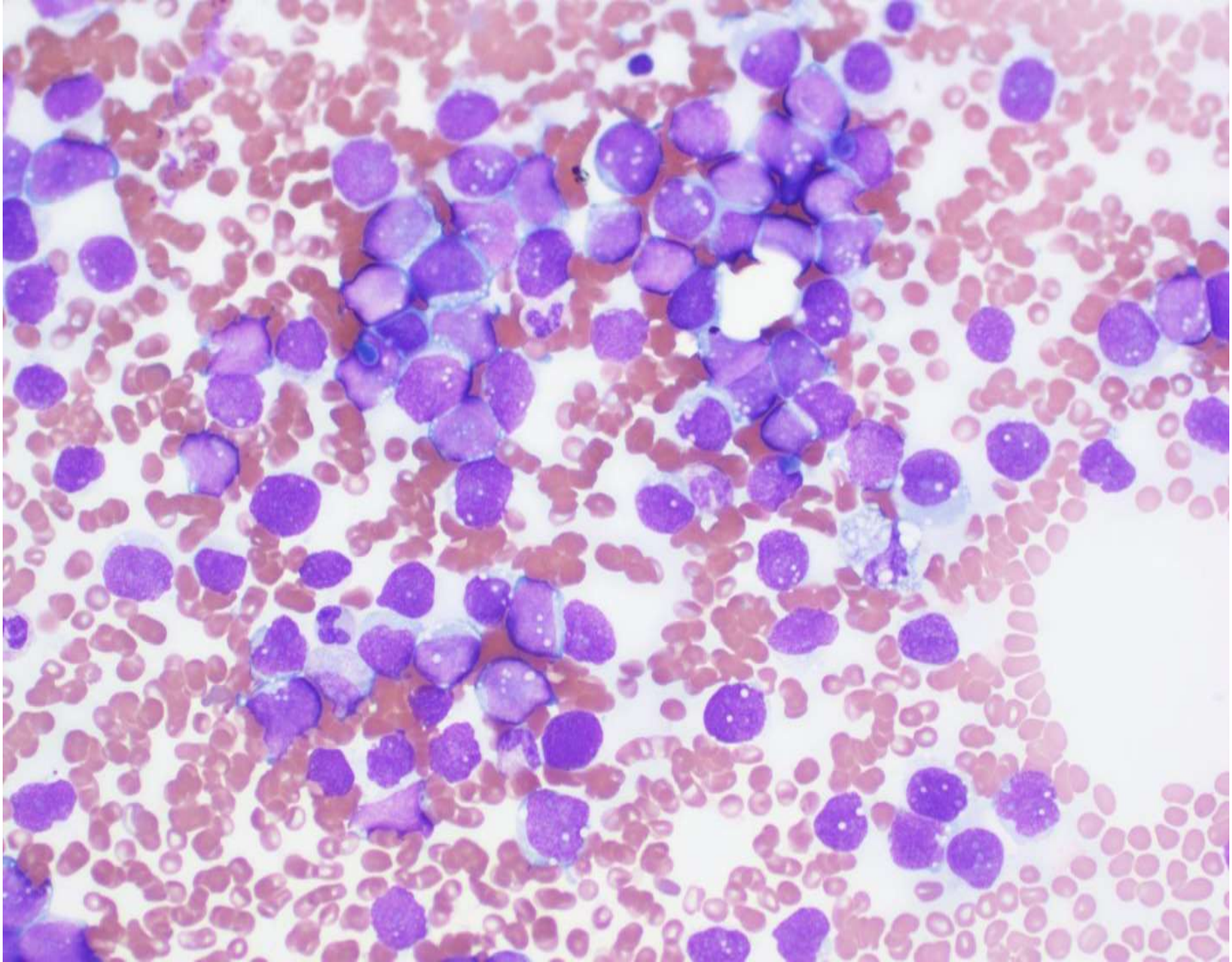
Saba Ali; El Camino Hospital

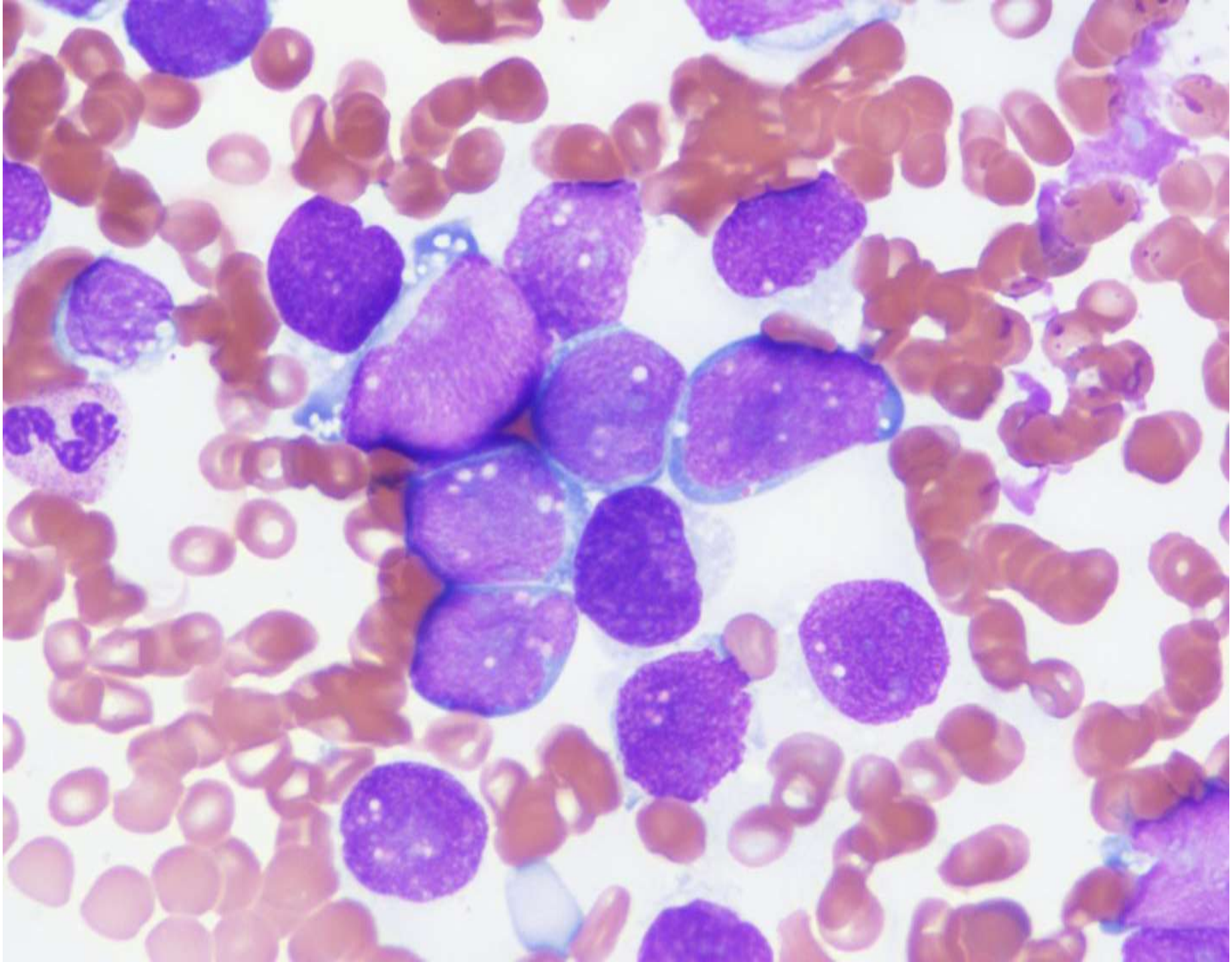
Young adult presents with unexplained pancytopenia. Bone marrow biopsy performed.

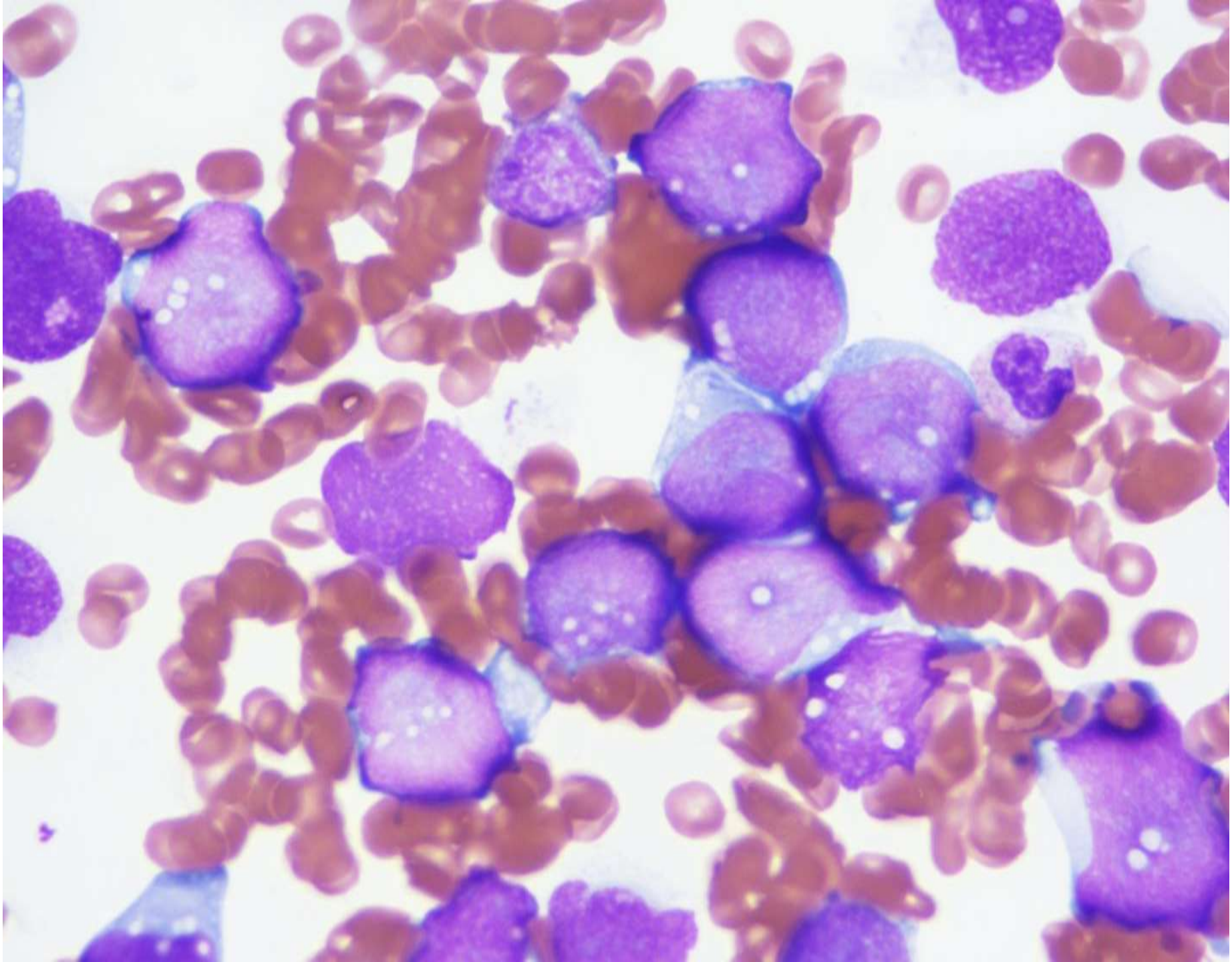


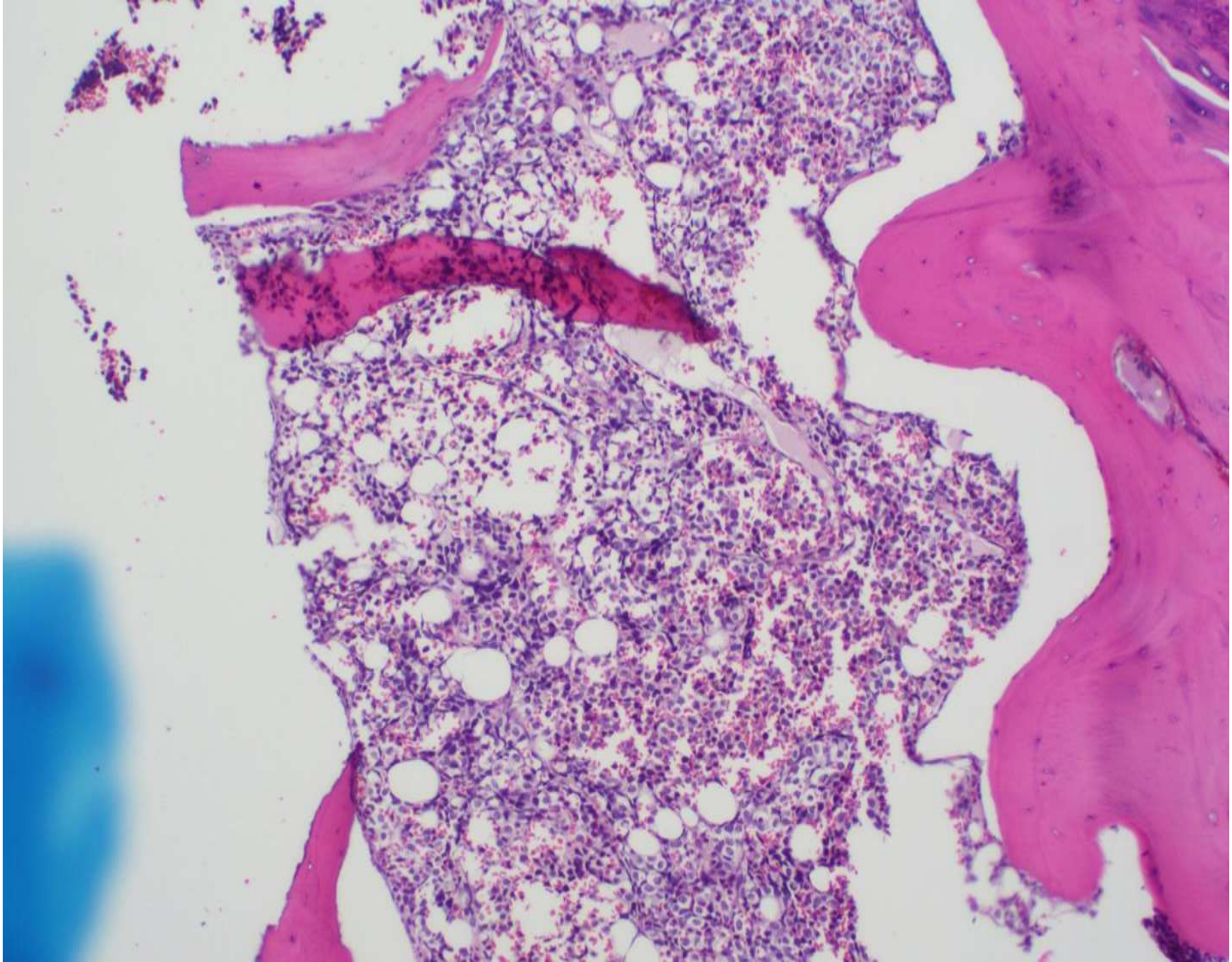


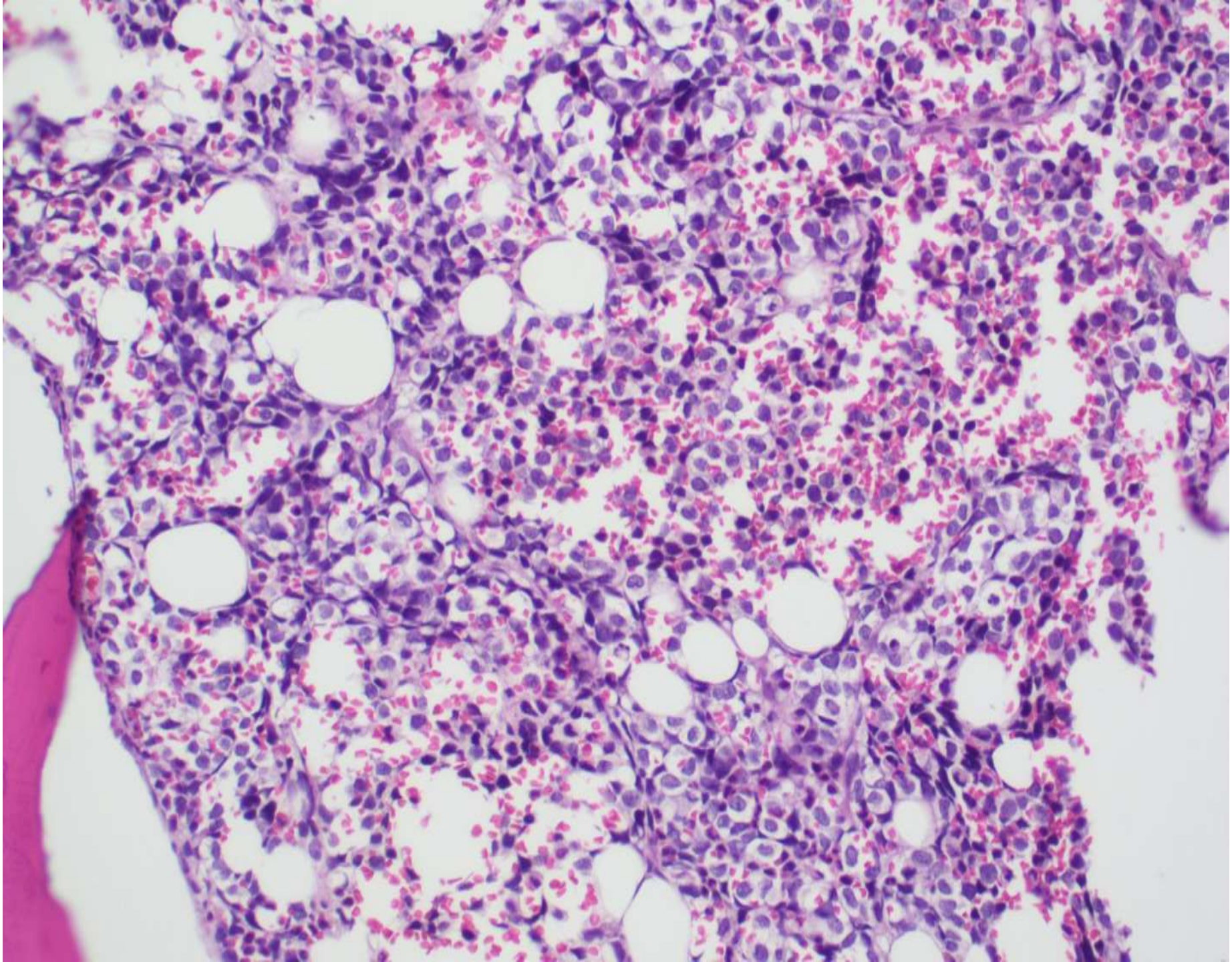












Peripheral blood

- Pancytopenia
- Left-shifted granulocytes
- Absence of blasts

Flow cytometry

- Low side scatter
- High forward scatter
- CD34 and CD45 negative
- CD56 positive
- Myeloid markers (CD13, CD33, CD117, HLA-DR), B-cell, and T-cell markers negative

Diagnosis?

A) AML
B) AMML
C) ALL
D) Metastatic sarcoma
E) Metastatic carcinoma
F) Metastatic small round blue cell tumor
G) Other

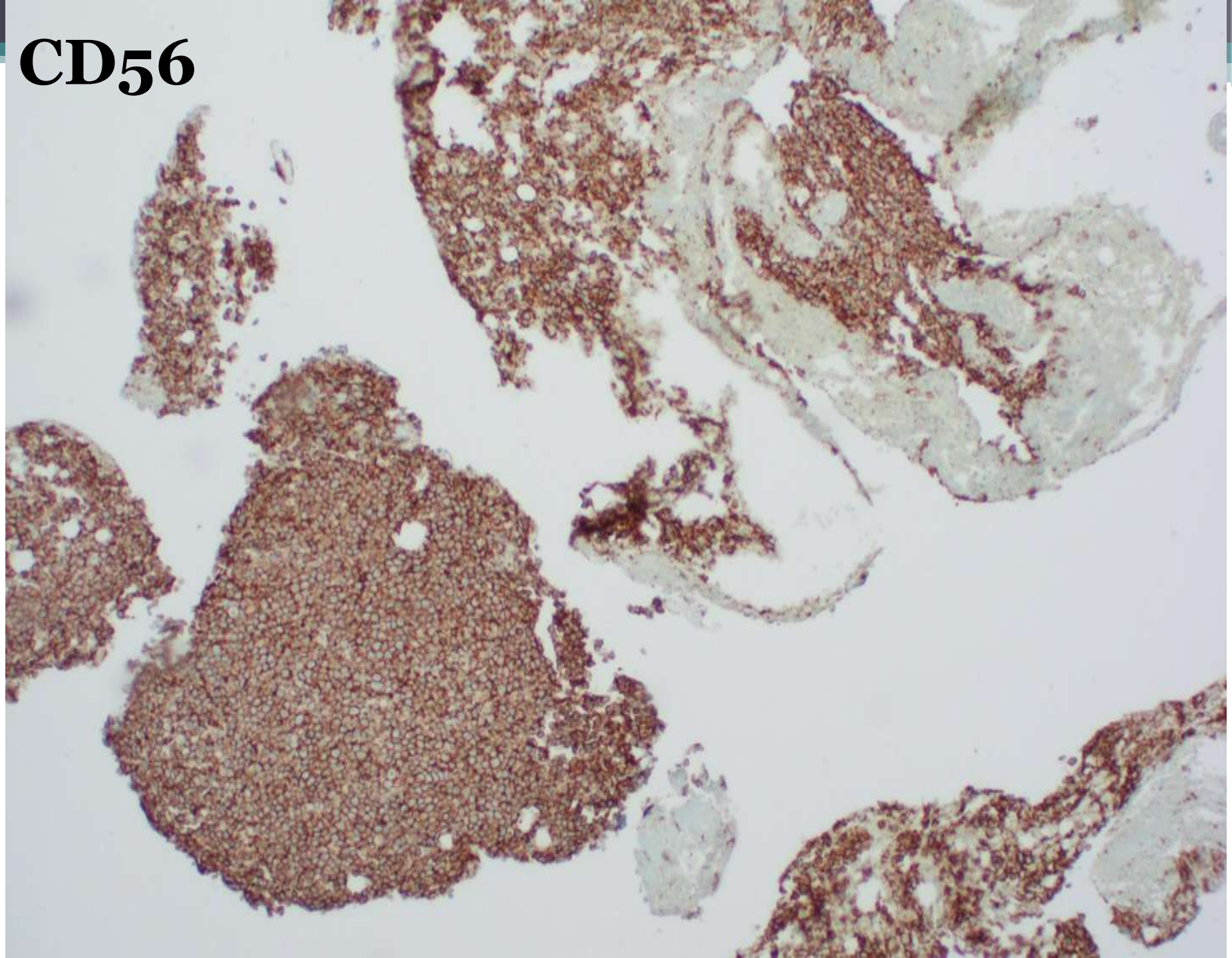
Differential diagnosis

- Acute myeloid leukemia (AML)
- Acute myelomonocytic leukemia (AMML)
- Blastic plasmacytoid dendritic cell neoplasm
- Plasmablastic myeloma
- Peripheral T-cell lymphoma involving marrow
- Acute lymphoblastic leukemia (ALL)
- Metastatic carcinoma/sarcoma
- Metastatic small round blue cell tumor

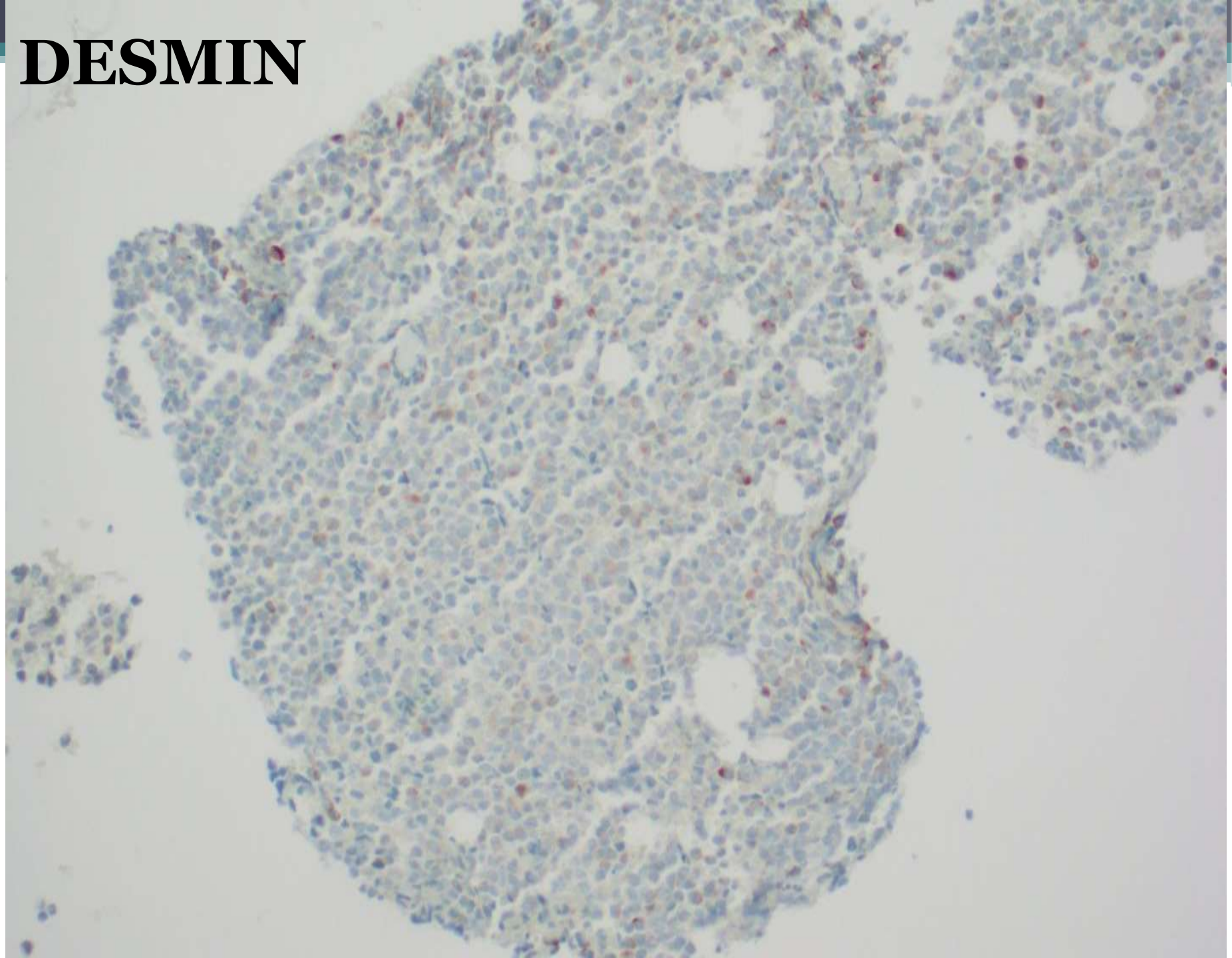
Immunohistochemistry

- CD34: Negative
- MPO: Negative
- CD117: Negative
- CD45: Negative
- CD138: Negative
- AE1/AE3: Negative

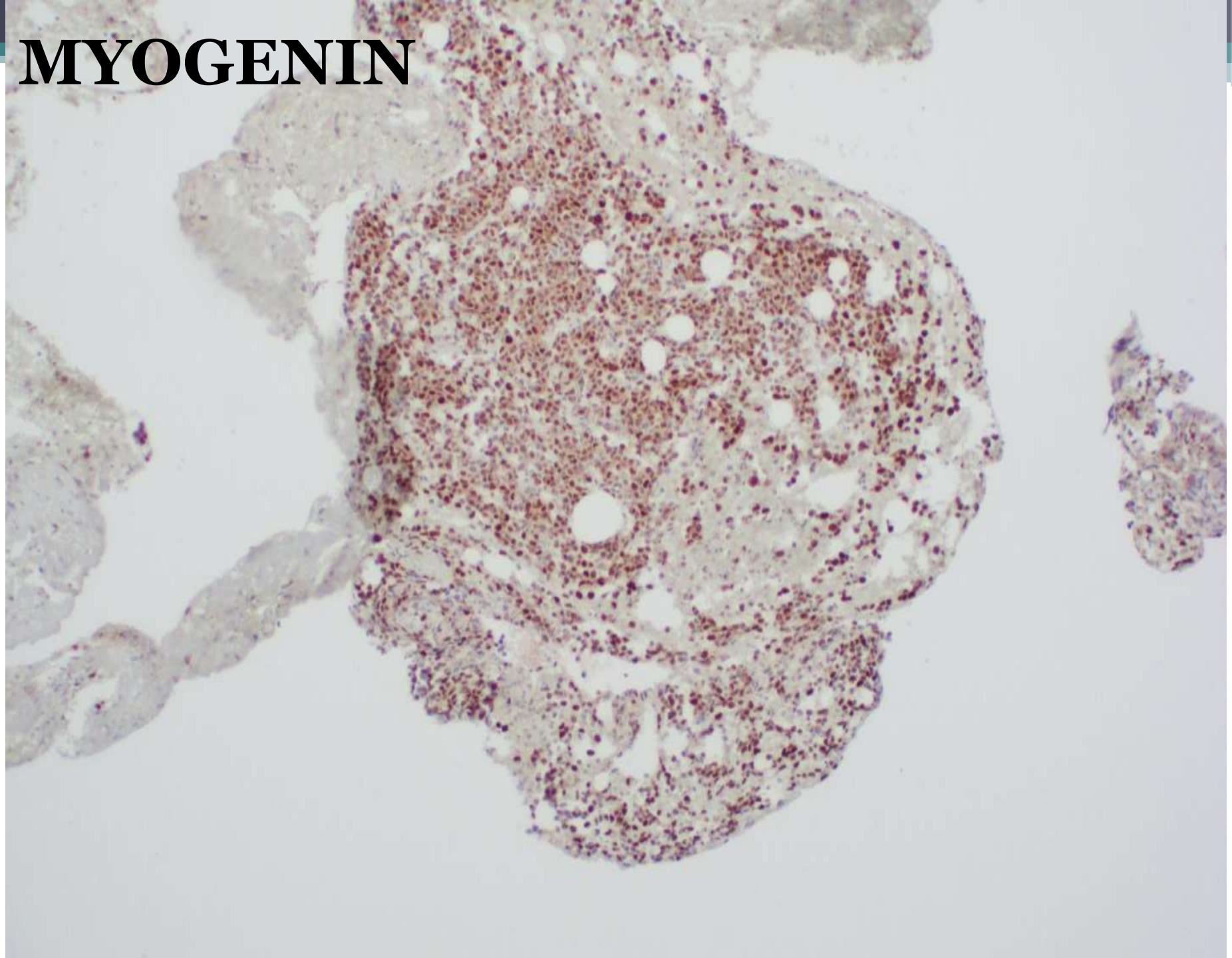
CD56



DESMIN



MYOGENIN



MOLECULAR TESTING

- PAX3-FOXO1 DETECTED (break-apart probe)

IMAGING

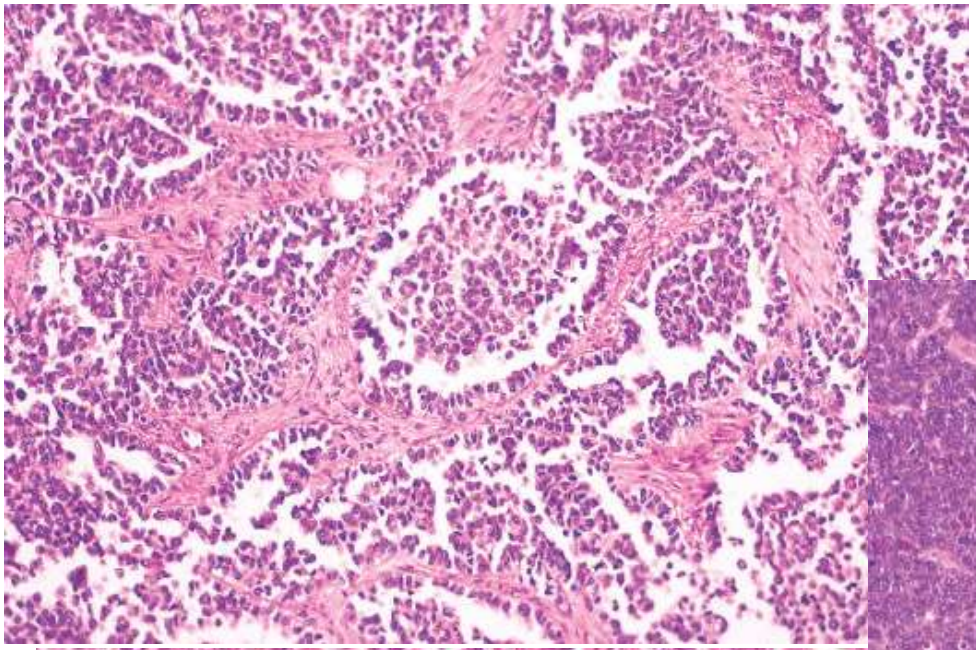
- No solid tissue lesions identified

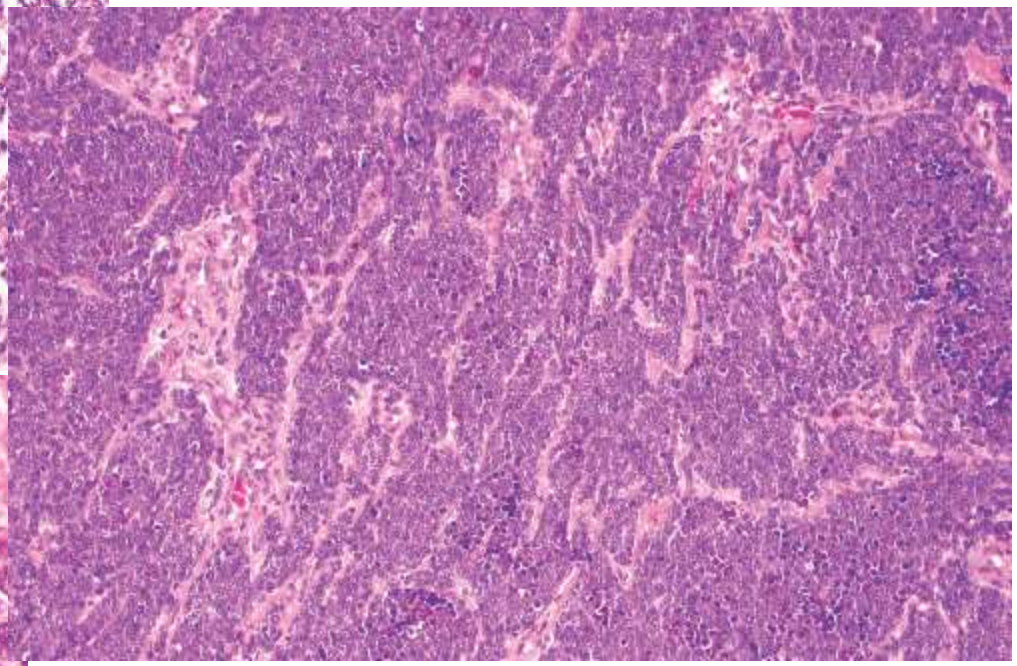
DIAGNOSIS

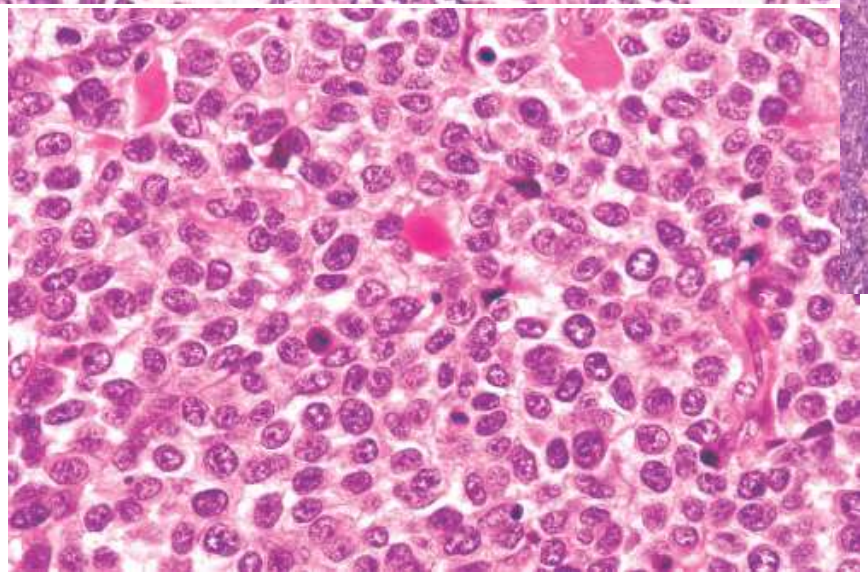
- ALVEOLAR RHABDOMYOSARCOMA
  - Malignant tumor of mesenchymal origin
  - Comprises largest category of soft-tissue sarcomas in children and adolescents
  - Rhabdomyosarcoma classification:
    - Embryonal (65%)
    - Alveolar rhabdomyosarcoma (25%)
    - Pleomorphic
    - Botyroid

- Alveolar RMS occurs in ages 15-20
- Primary sites are:
  - Head
  - Neck
  - Trunk
  - Pelvis
  - Retroperitoneum
- Spread by direct invasion, lymphatic, hematogenous
- Bone marrow lesions found in 30% of metastatic cases
- Rare cases of bone marrow as primary site have been reported

SOFT TISSUE HISTOLOGY







Primary alveolar rhabdomyosarcoma of the bone: two cases and review of the literature

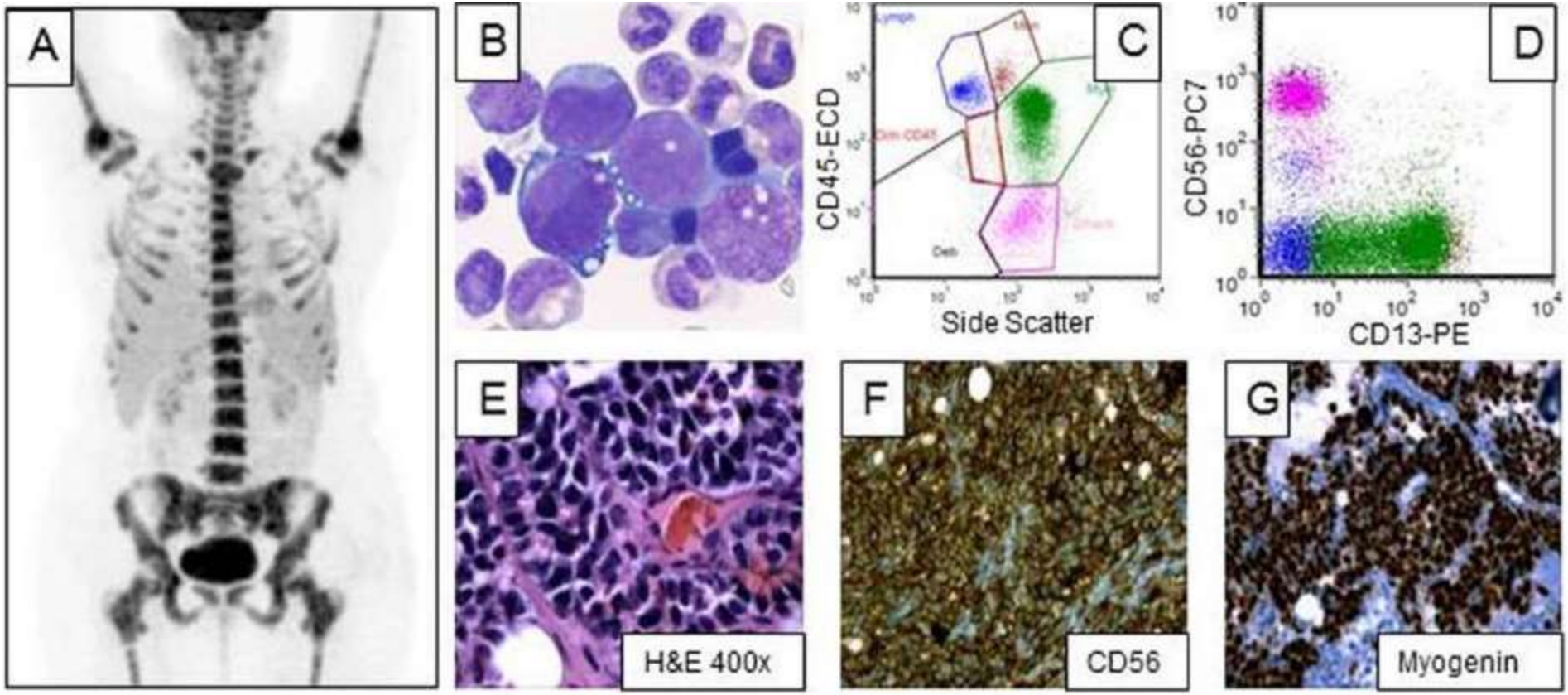
Petra Balogh,[1] Rita Bánusz,[2] Monika Csóka,[2] Zsófia Váradi,[2] Edit Varga,[2,3] and Zoltán Sápi[✉1]

Reported cases of primary alveolar rhabdomyosarcoma of the bone so far without identifiable soft tissue component

Case	Reference	Age	Sex	Follow-up/survival (months)	Treatment	Tumor localization
1	Yamaguchi et al. 2007 [9]	14	m	8 (s)	-Etoposide -Cyclophosphamide -Pirarubicin -Cisplatin -Vincristine	Disseminated BM infiltration, not specified
2	Jani et al. (2009) [7]	16	m	8 (s)	-VP16 -Ifosfamide -Vincristine -Adriamycin -Cyclophosphamide	Disseminated BM infiltration, not specified
3	Kern et al. (2015) [10]	52	f	12 (s)	Not detailed	BM infiltration, not specified
4	Karagiannis et al. (2015) [8]	61	f	7 (f)	-Topotecan -Cyclophosphamide -Vinorelbine (Monotherapy-later)	BM infiltration, not specified
5	Case 1 (current report)	17	m	7 (s)	-Ifosfamid -Carboplatin -Etoposid -Vincristin	Diffuse BM infiltration
6	Case 2 (current report)	9	m	30 (s)	-Ifosfamid -Etoposid -Carboplatin -Topotecan	Tibia, femur, pelvic bones, vertebrae

A Leukemic Presentation of Alveolar Rhabdomyosarcoma in a 52-Year-Old Woman Without an Identifiable Primary Tumor

Jason B. Kern, MD,[1] Anselm Hii, MD,[2] Matthew J. Kruse, MD,[1] Zsolt Szabo, MD, PhD,[1] Pedram Argani, MD,[1] Michele K. Hibbard, PhD,[2] Douglas E. Gladstone, MD,[1] Christian Meyer, MD, PhD,[1] Rui Zheng, MD, PhD,[1] Michael J. Borowitz, MD, PhD,[1] and Amy S. Duffield, MD, PhD[1]



PITFALLS

Expression of ALK1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases.

Cessna MH[1], Zhou H, Sanger WG, Perkins SL, Tripp S, Pickering D, Daines C, Coffin CM.

Am J Surg Pathol. 2009 May;33(5):775-80. doi: 10.1097/PAS.0b013e318191614f.

PAX immunoreactivity identifies alveolar rhabdomyosarcoma.

Sullivan LM[1], Atkins KA, LeGallo RD.

- ALK-1, Pax-5, and CD20 can be positive in rhabdomyosarcoma

Take home points

- Leukemic presentations with sole marrow involvement can occur in RMS
- Patients show pancytopenia without solid tissue component by imaging
- Can be morphologically very similar to blasts, but flow cytometry is a major tip off: CD45 negative, CD56 positive population !
- FISH studies can help confirm
- Occurs in pediatric population, but rare cases occur in adults

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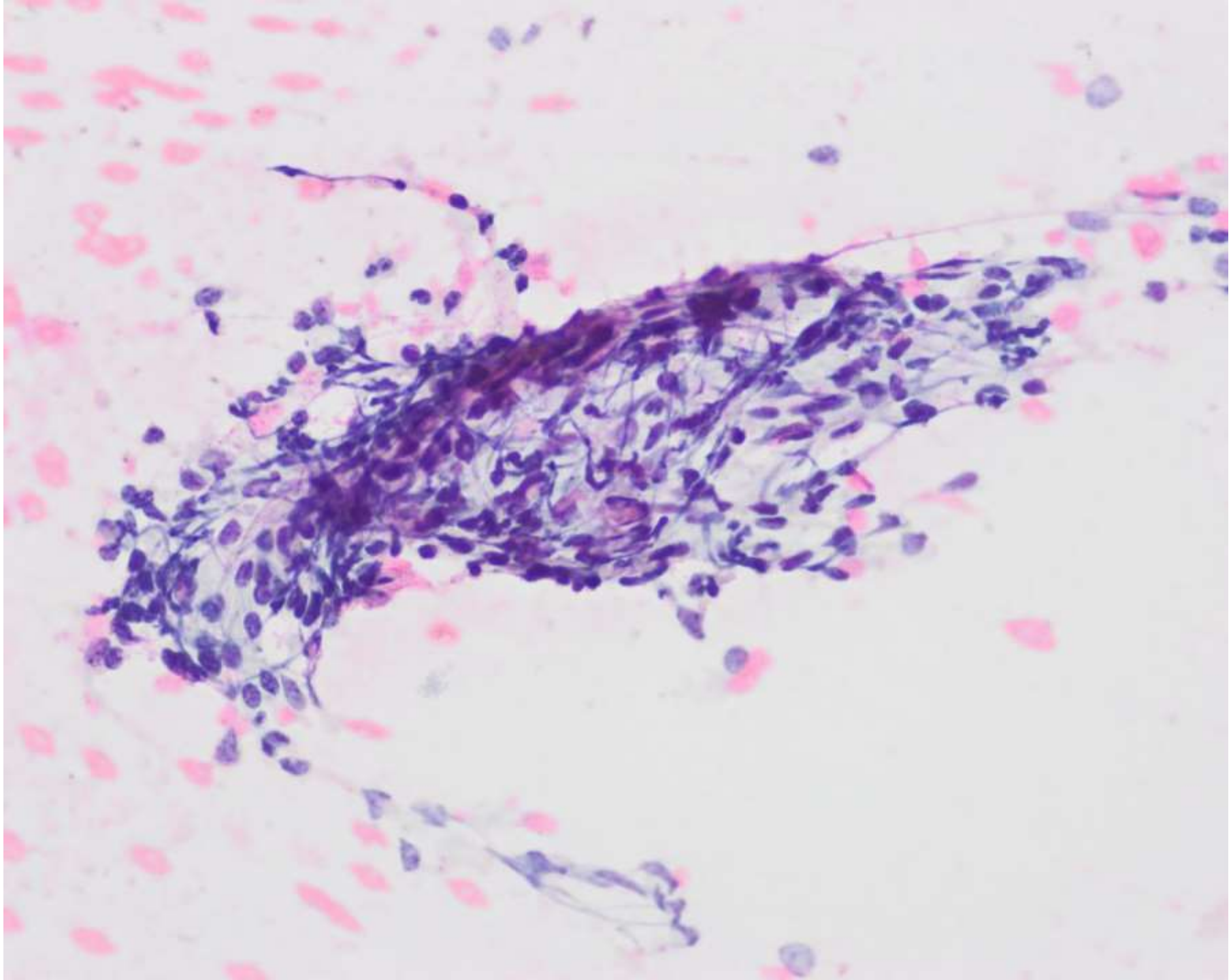
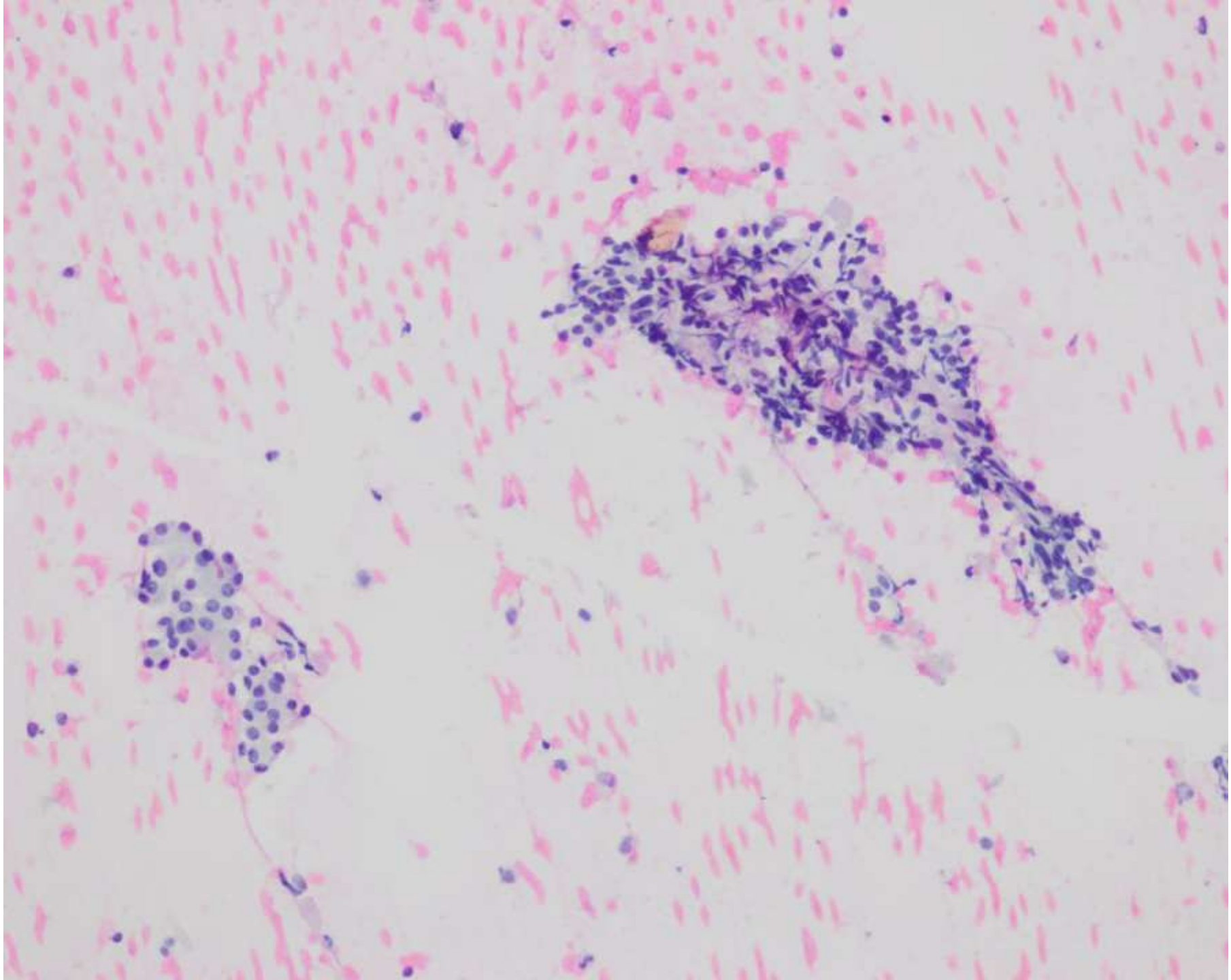
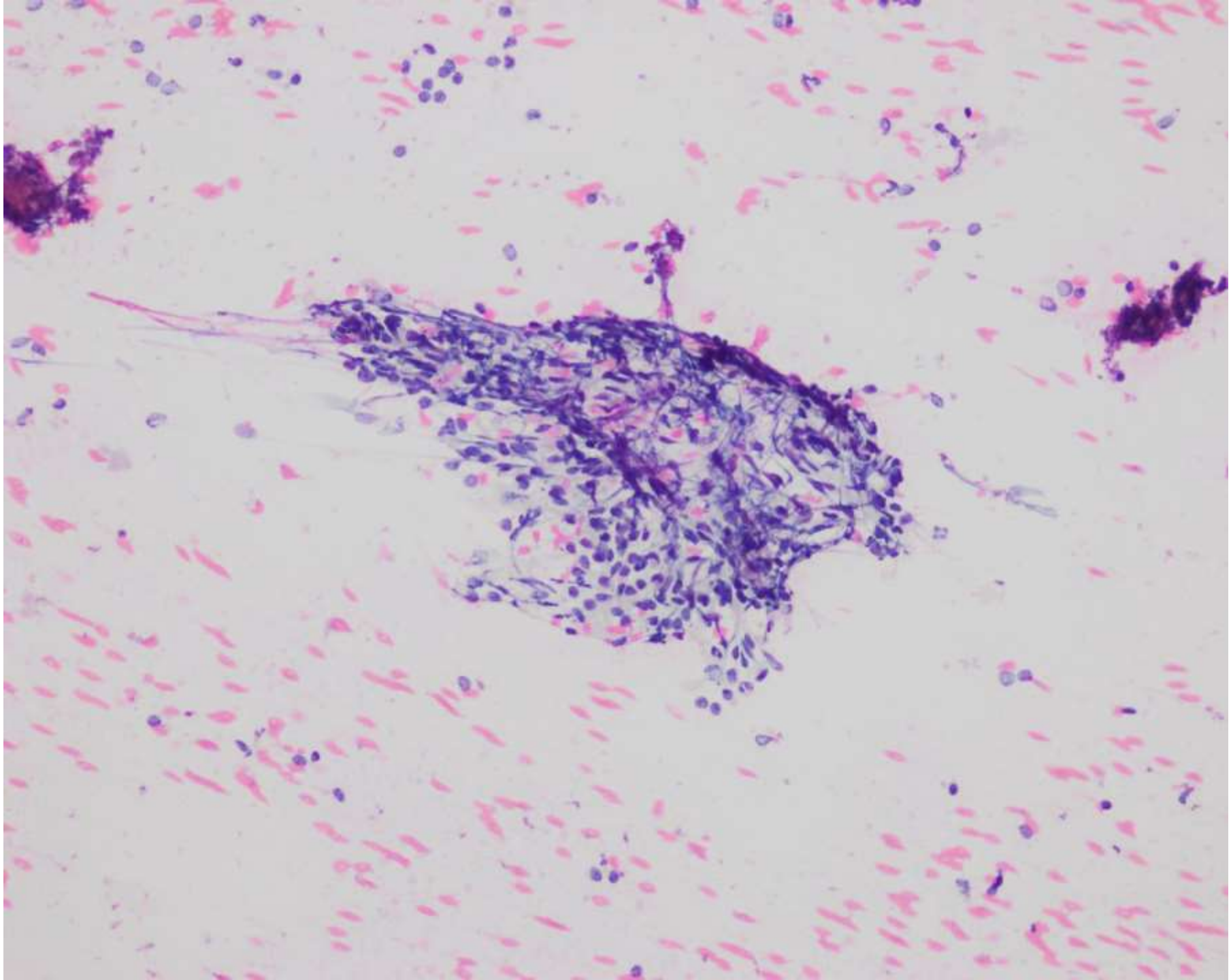
19-1207

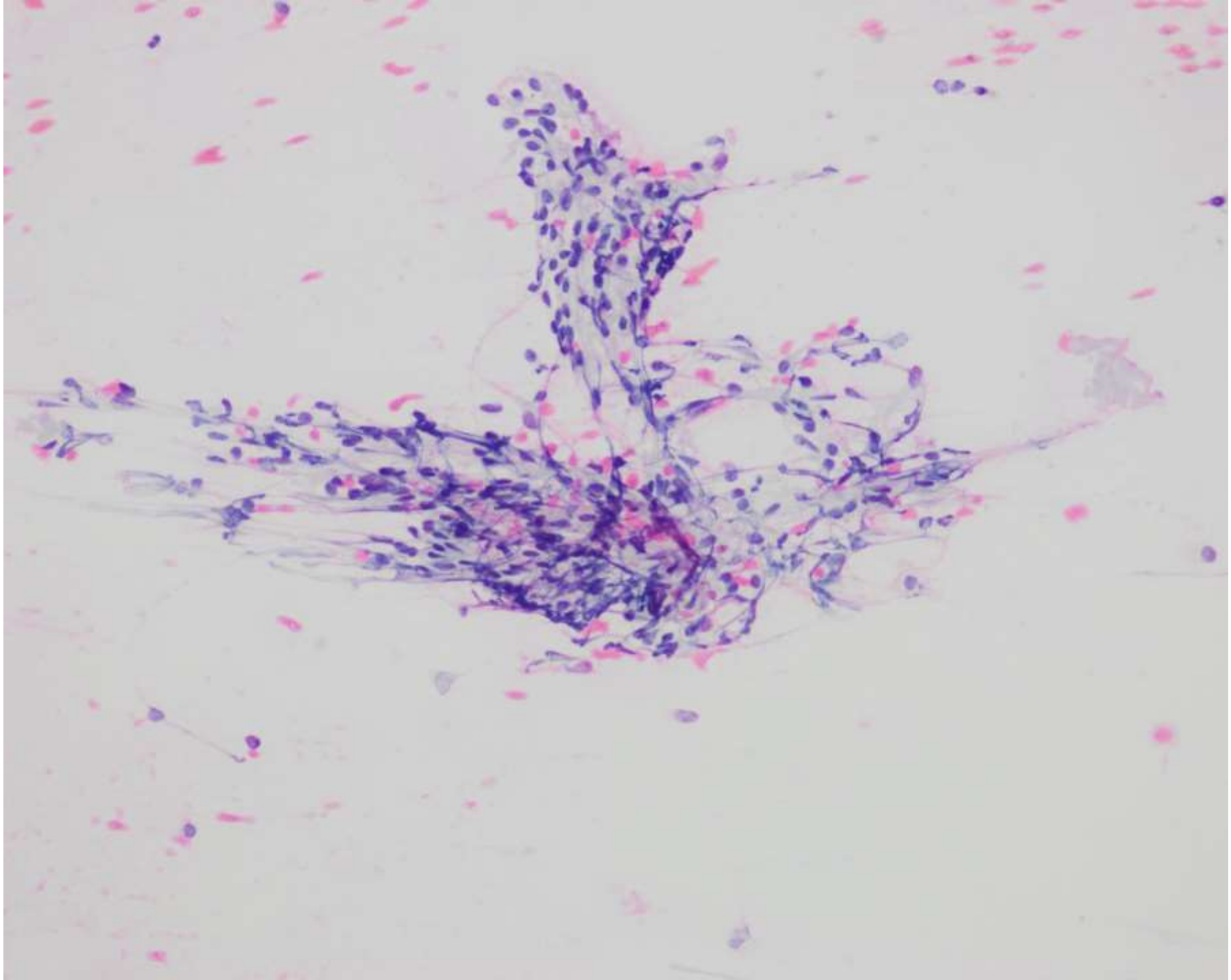
Lucy Han/Vighnesh Walavalkar; UCSF

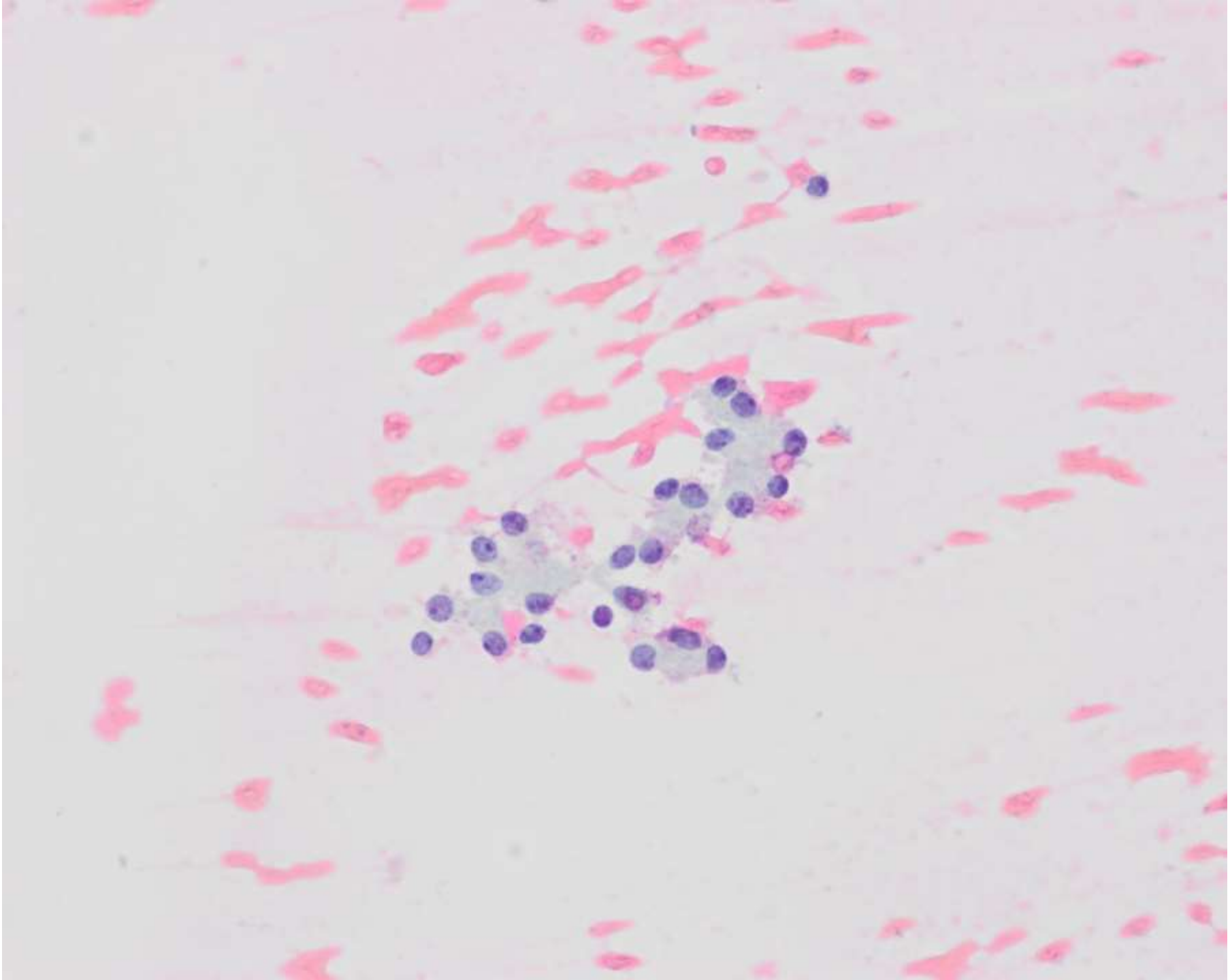
31-year-old male with no prior malignancies was found to have a pancreatic tail mass.

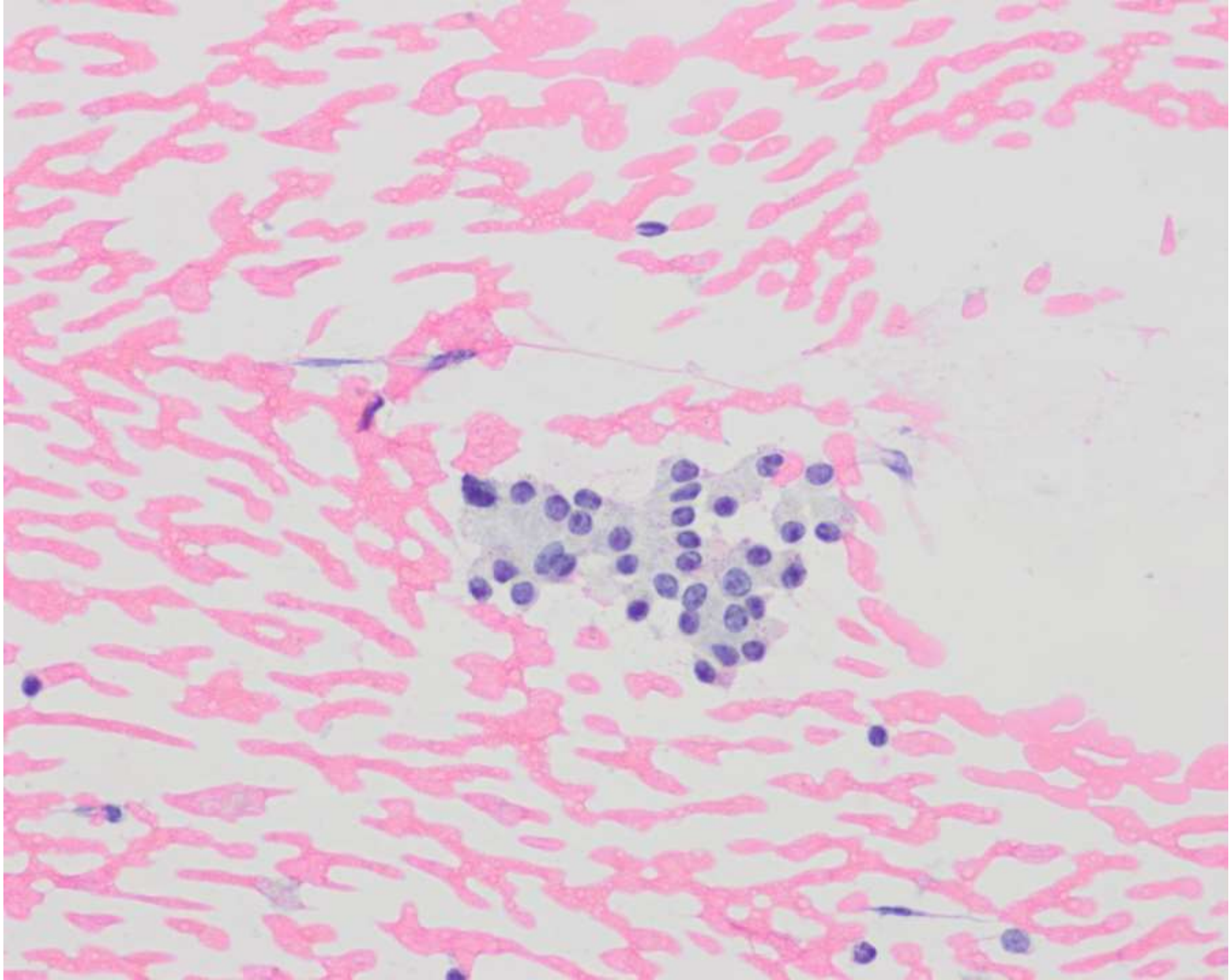


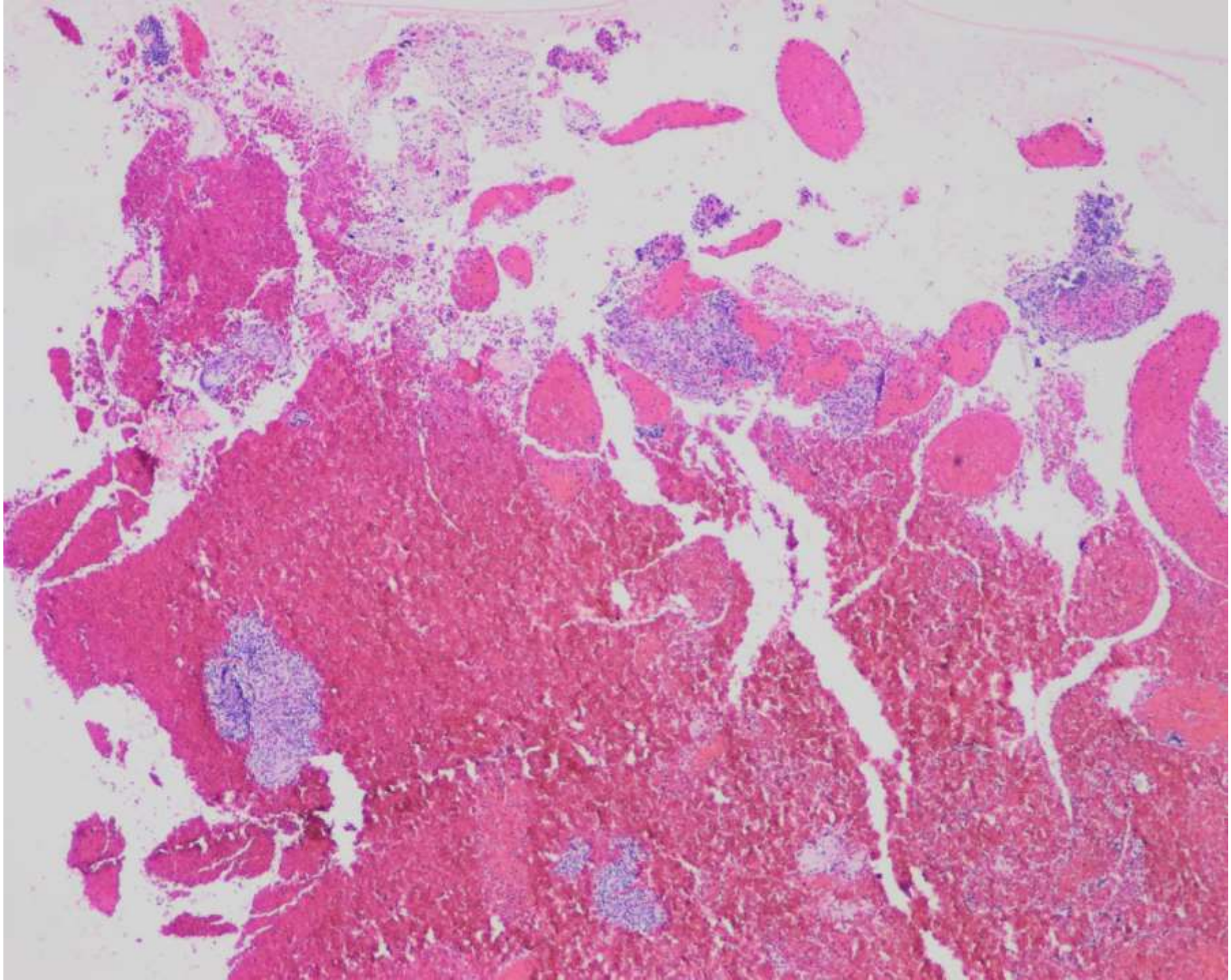


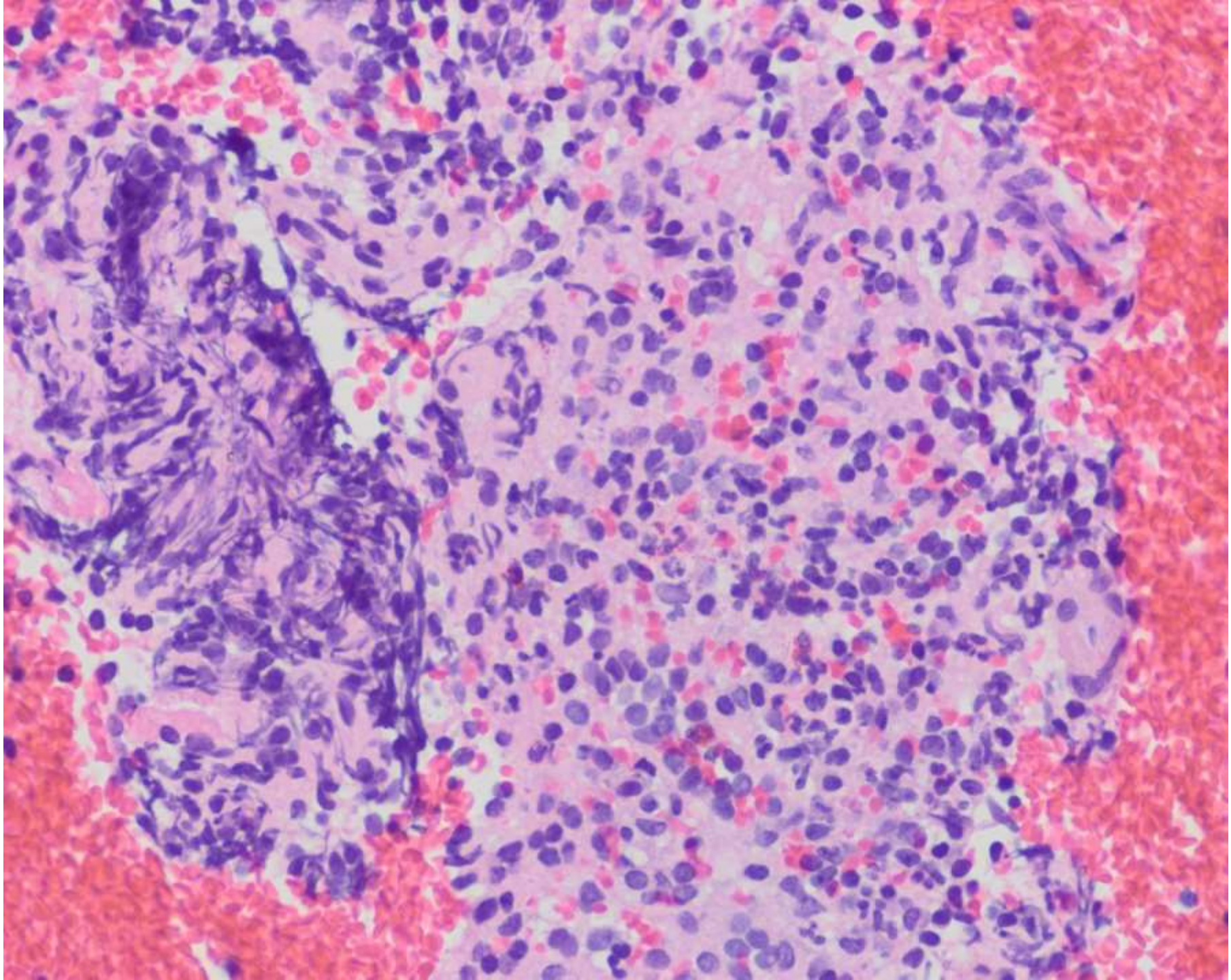


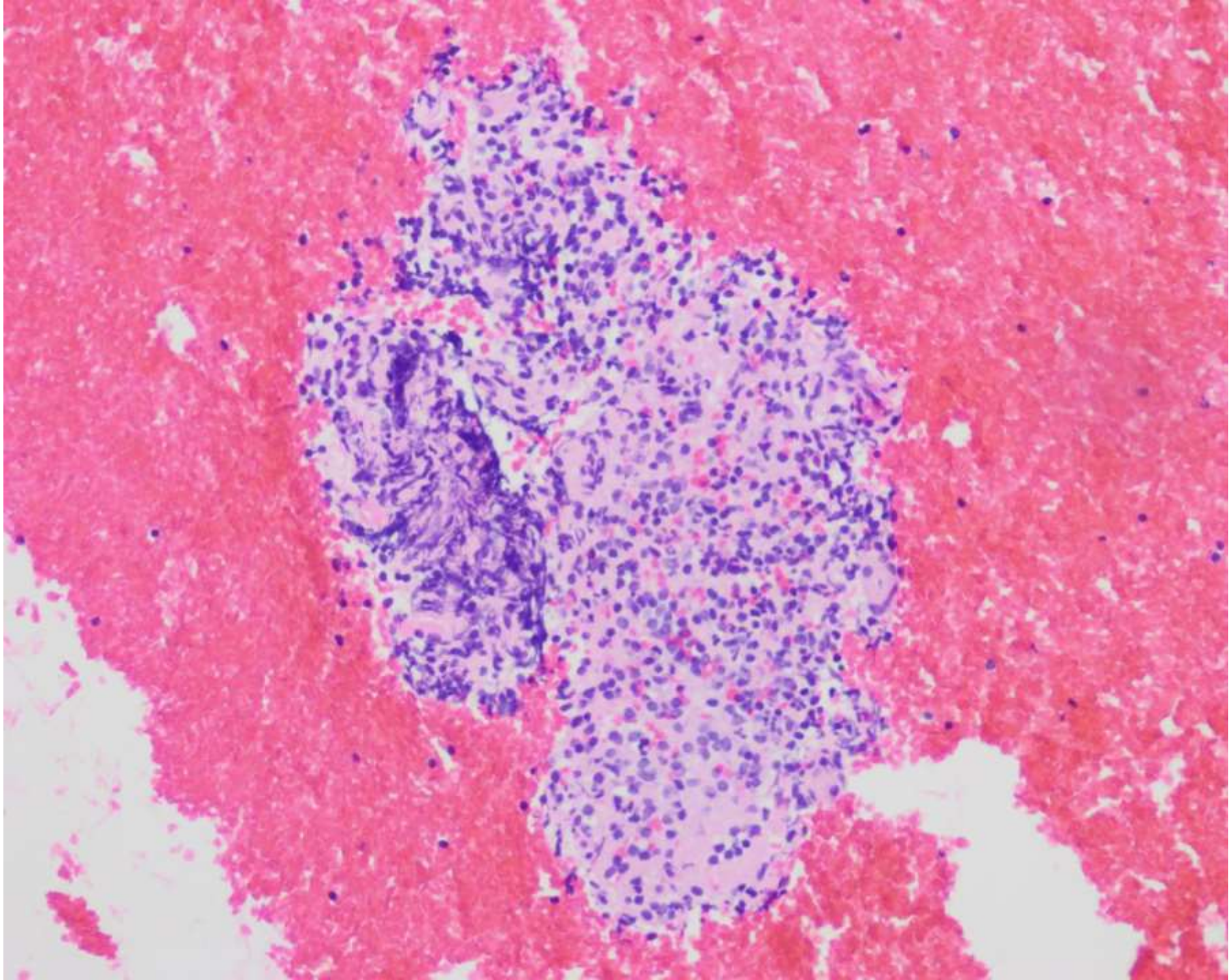


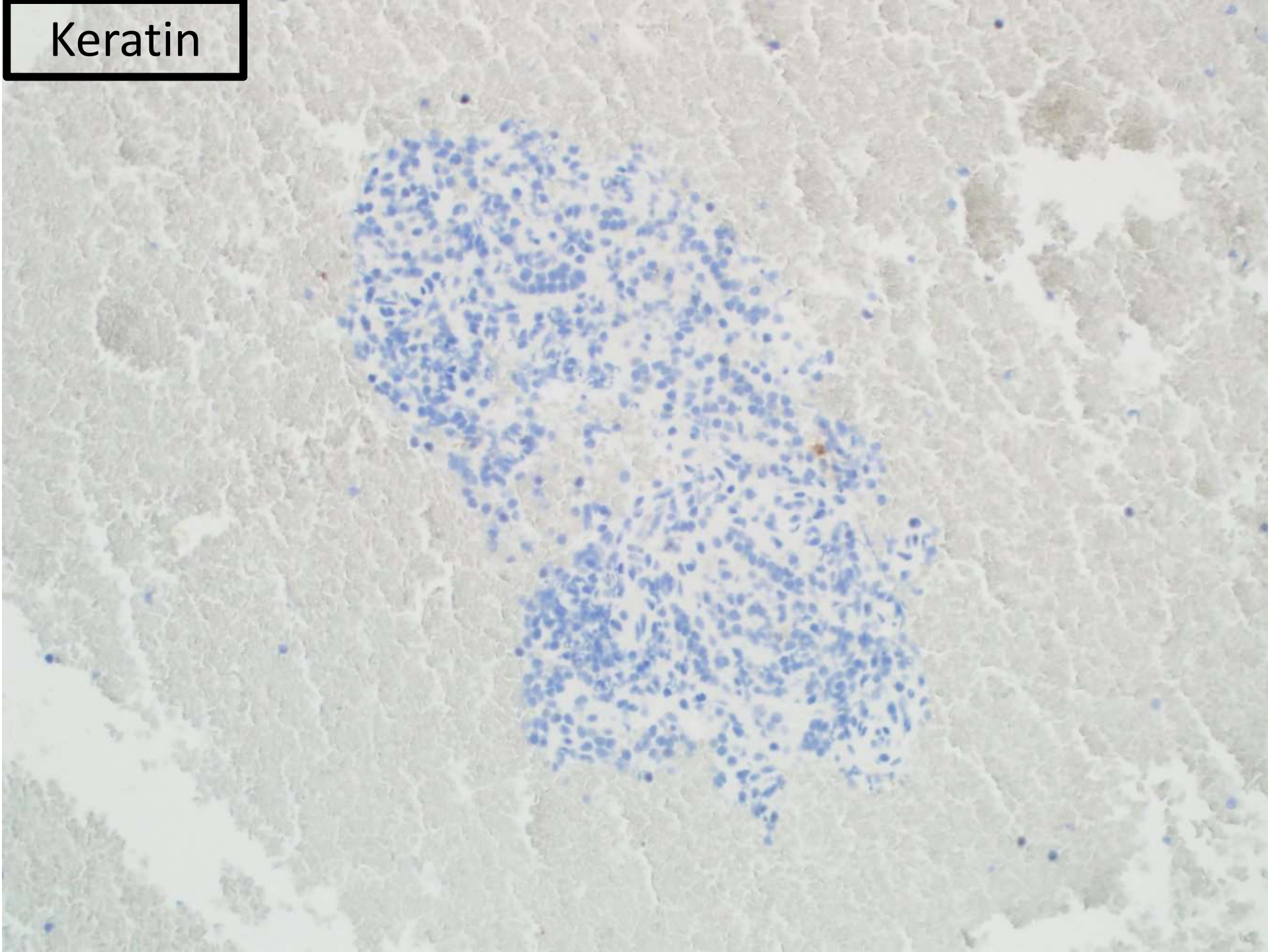


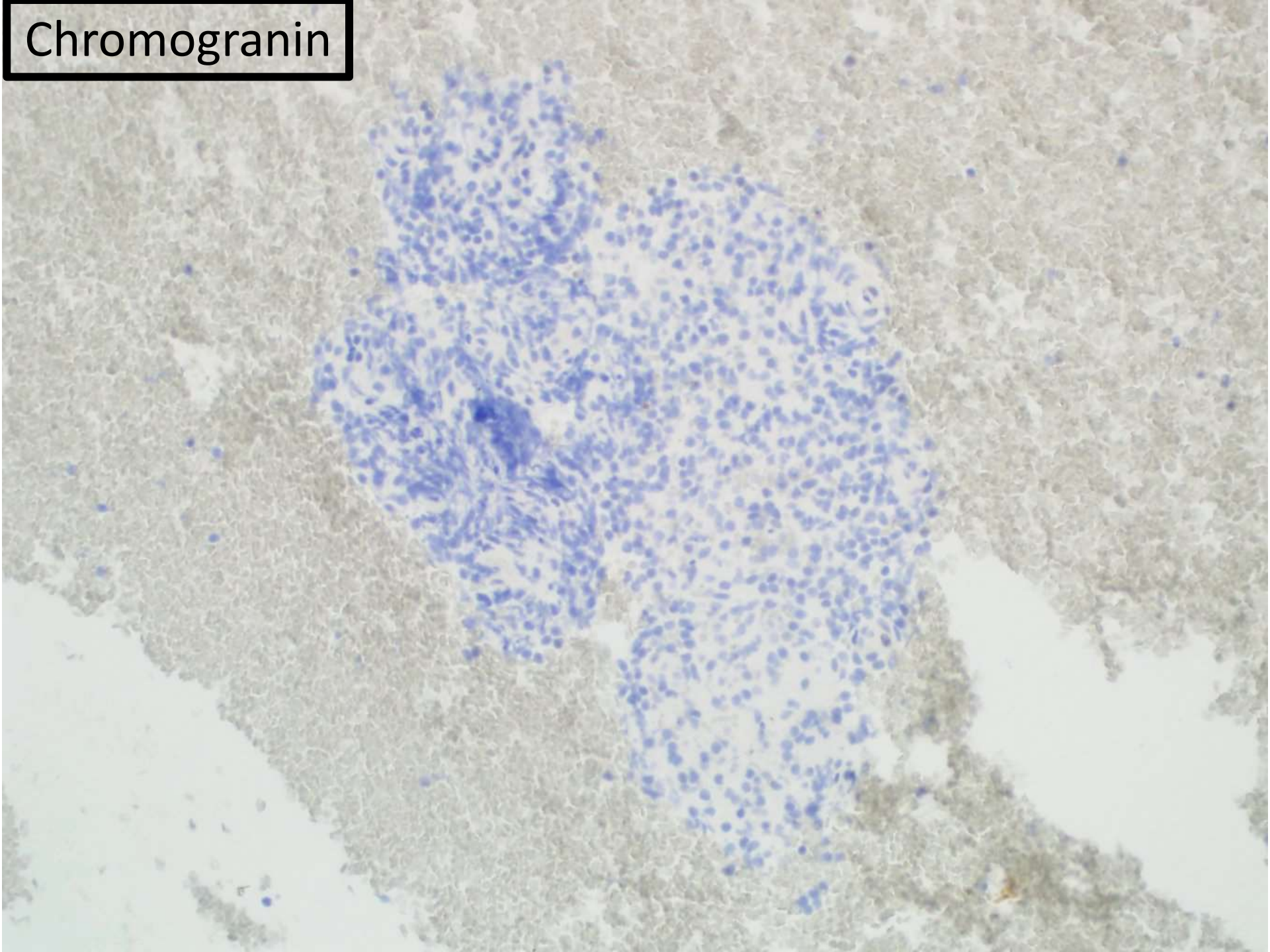









Keratin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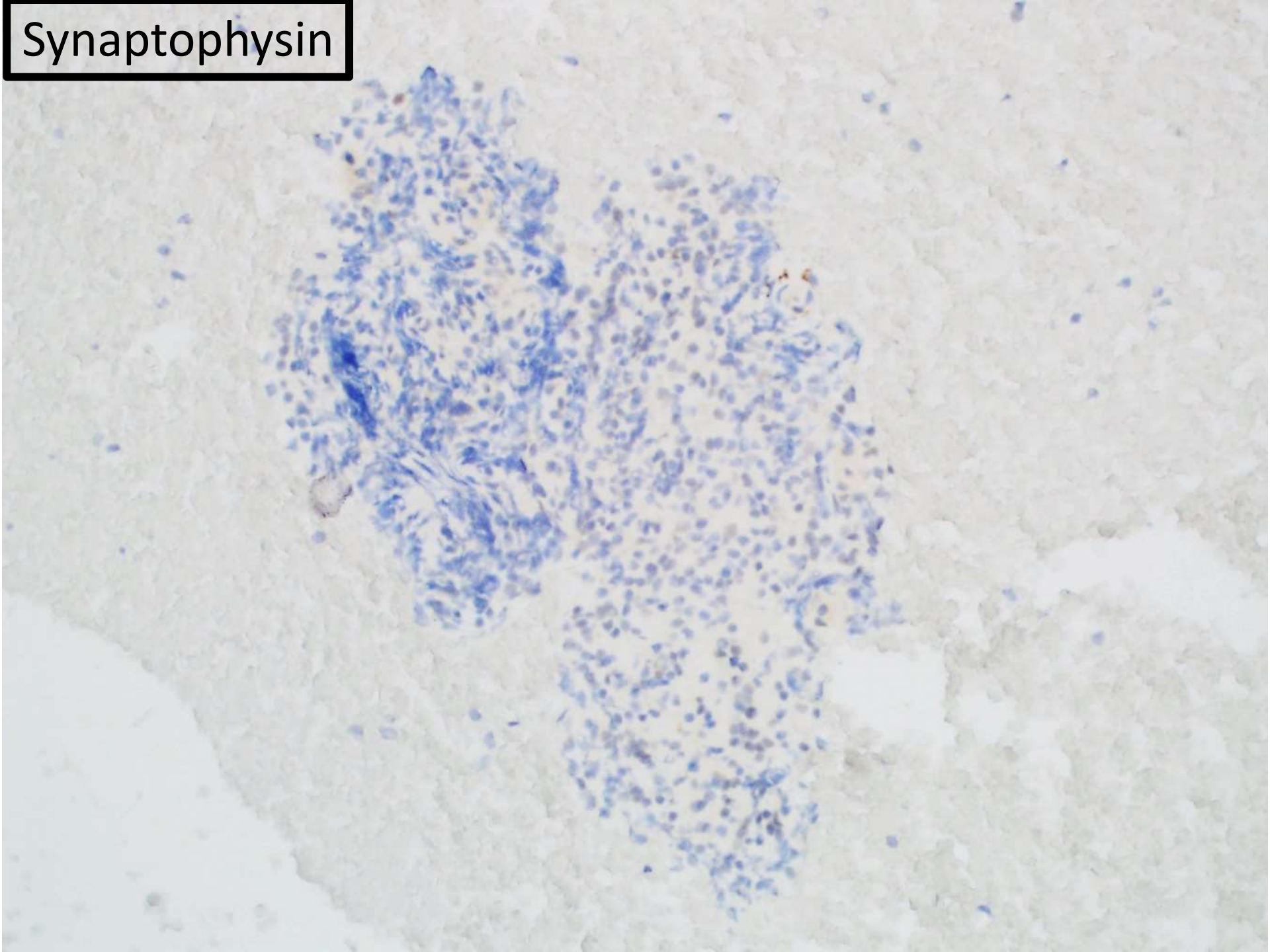
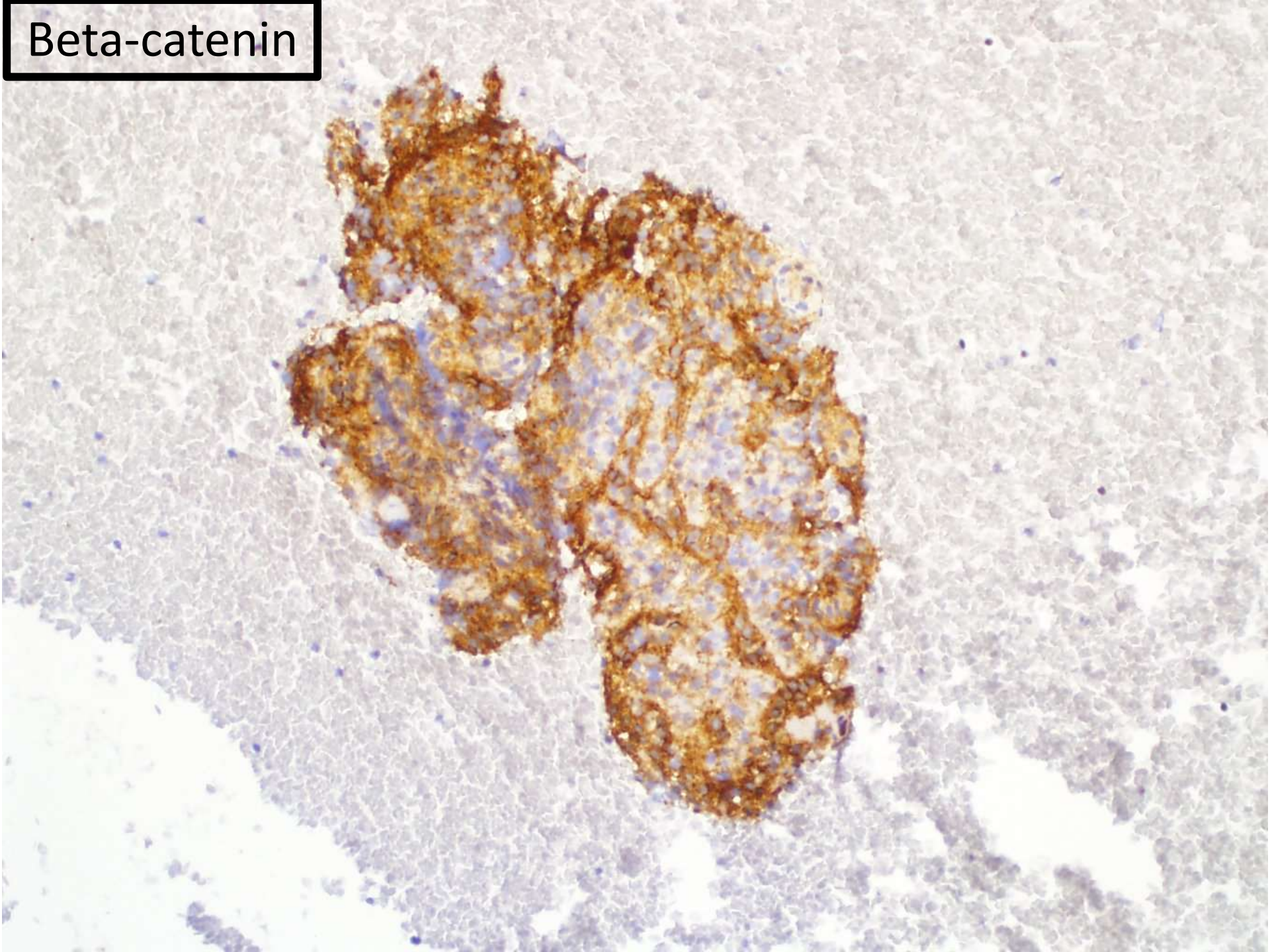
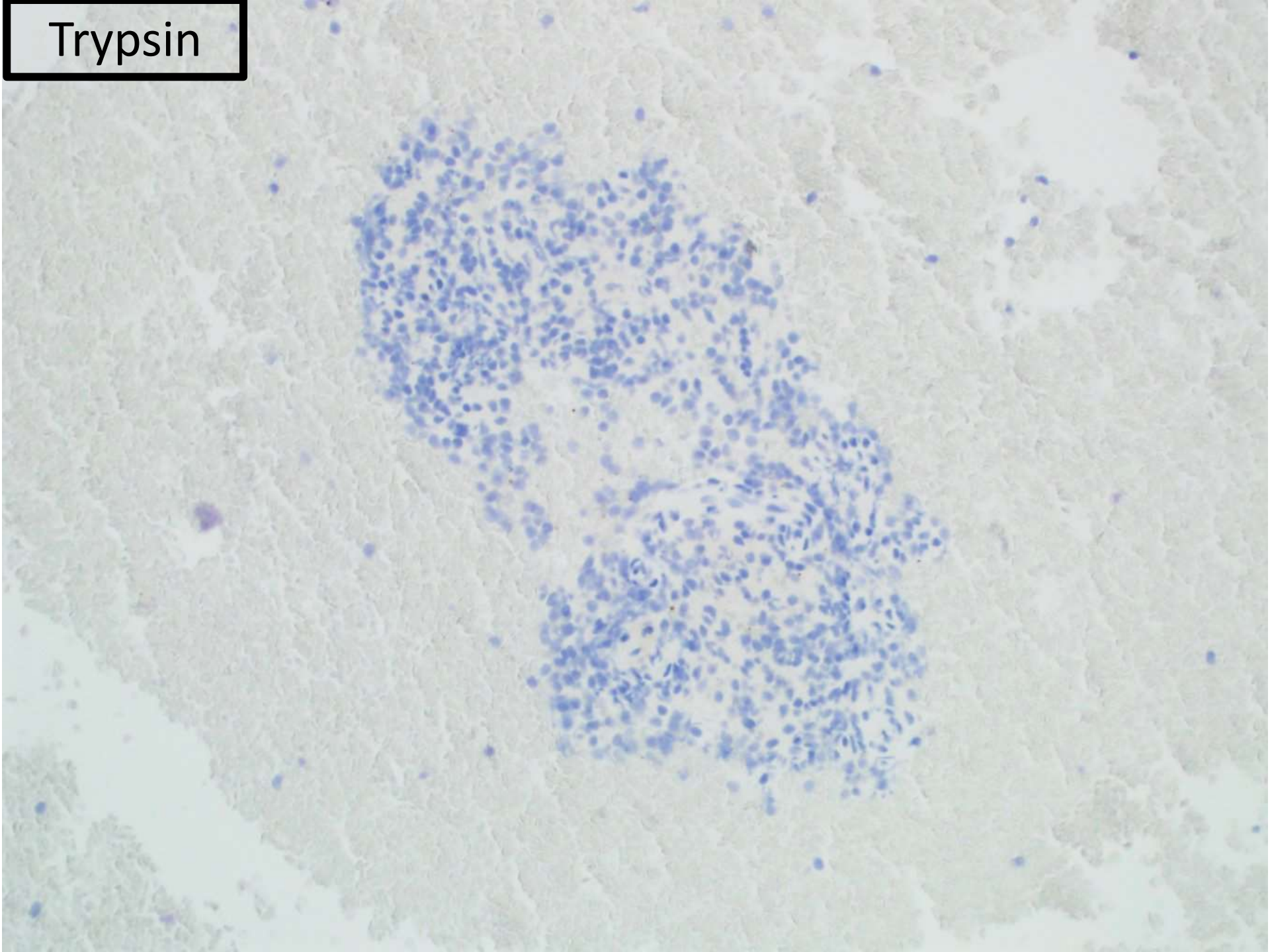

Synaptophysin


Beta-catenin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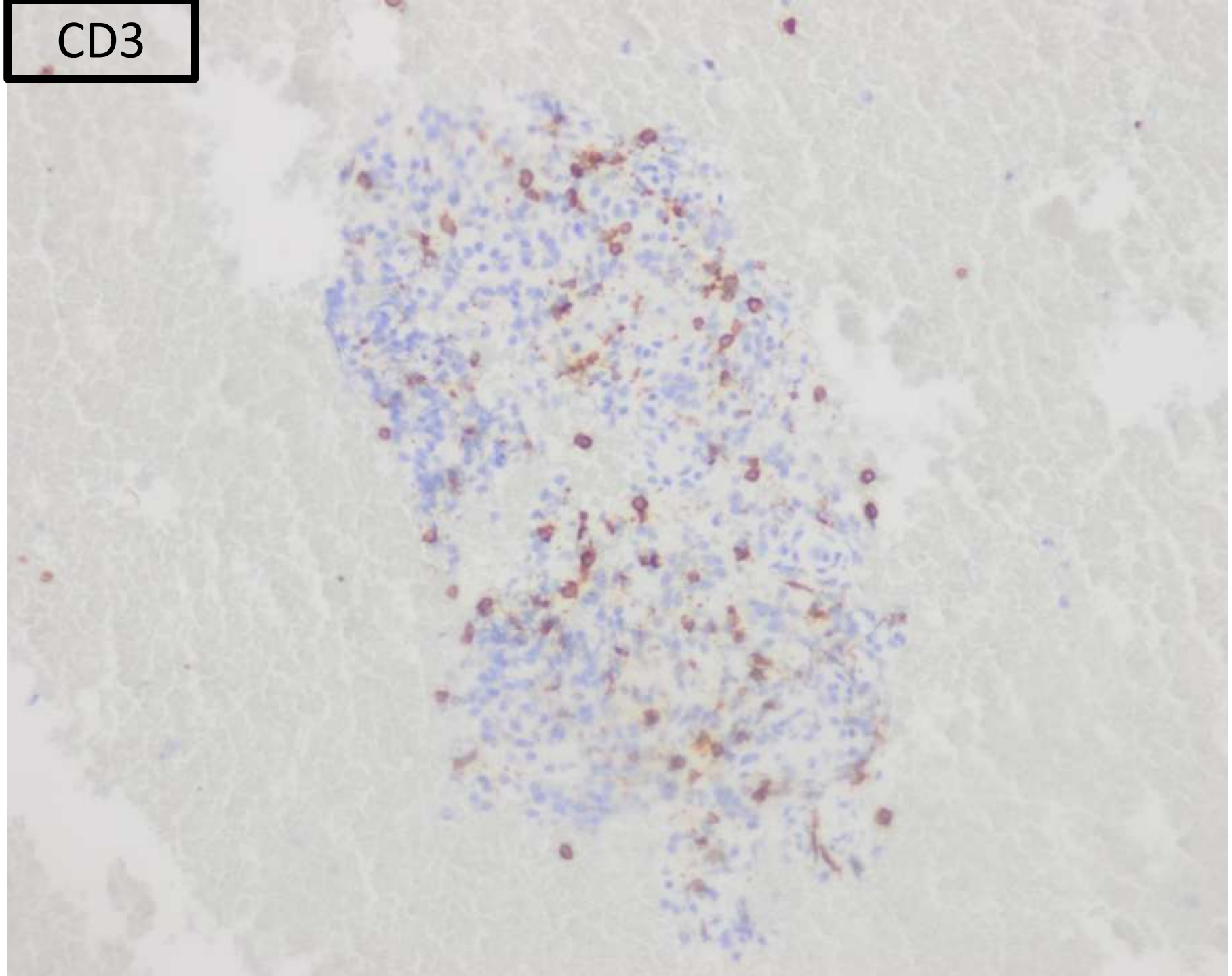
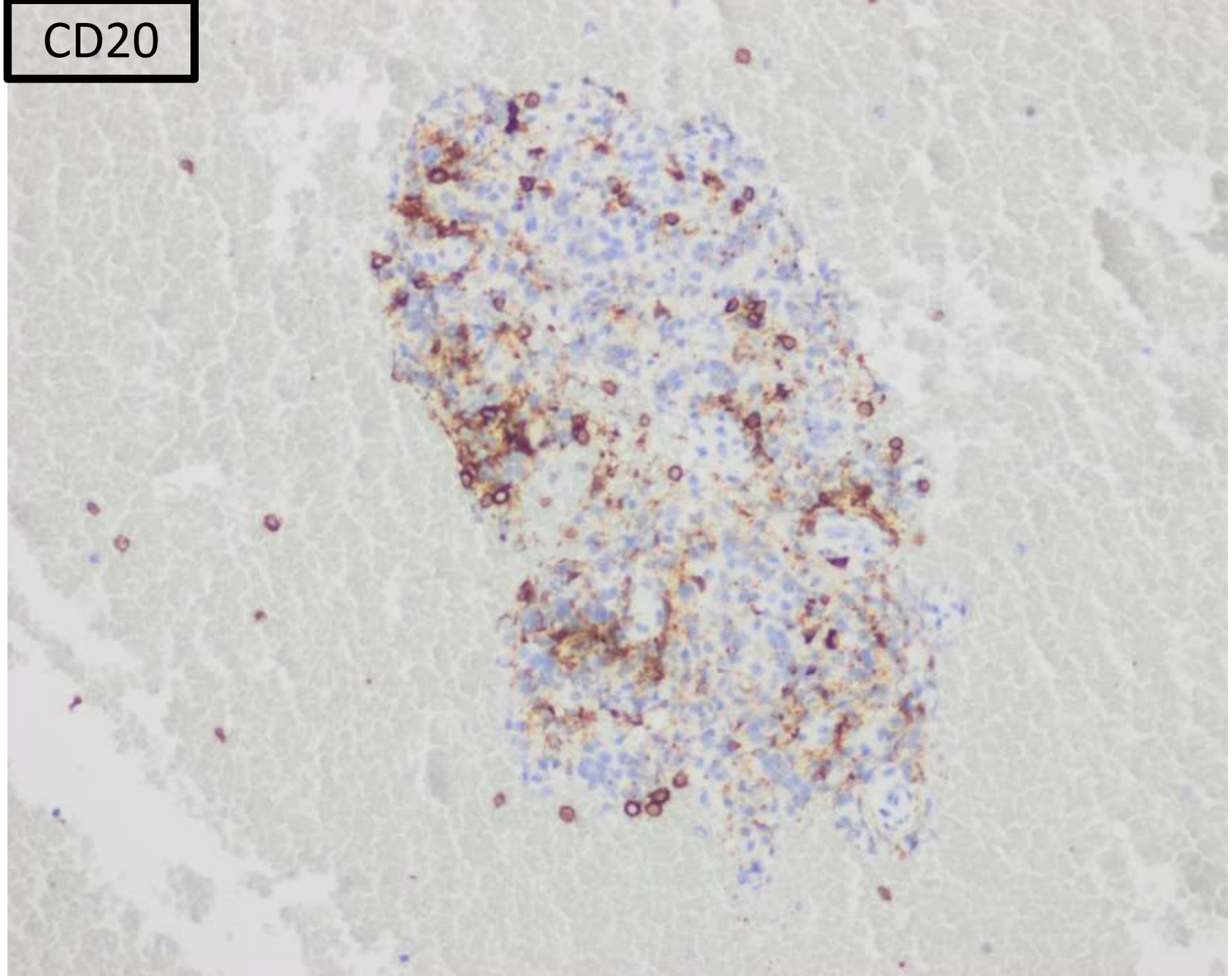
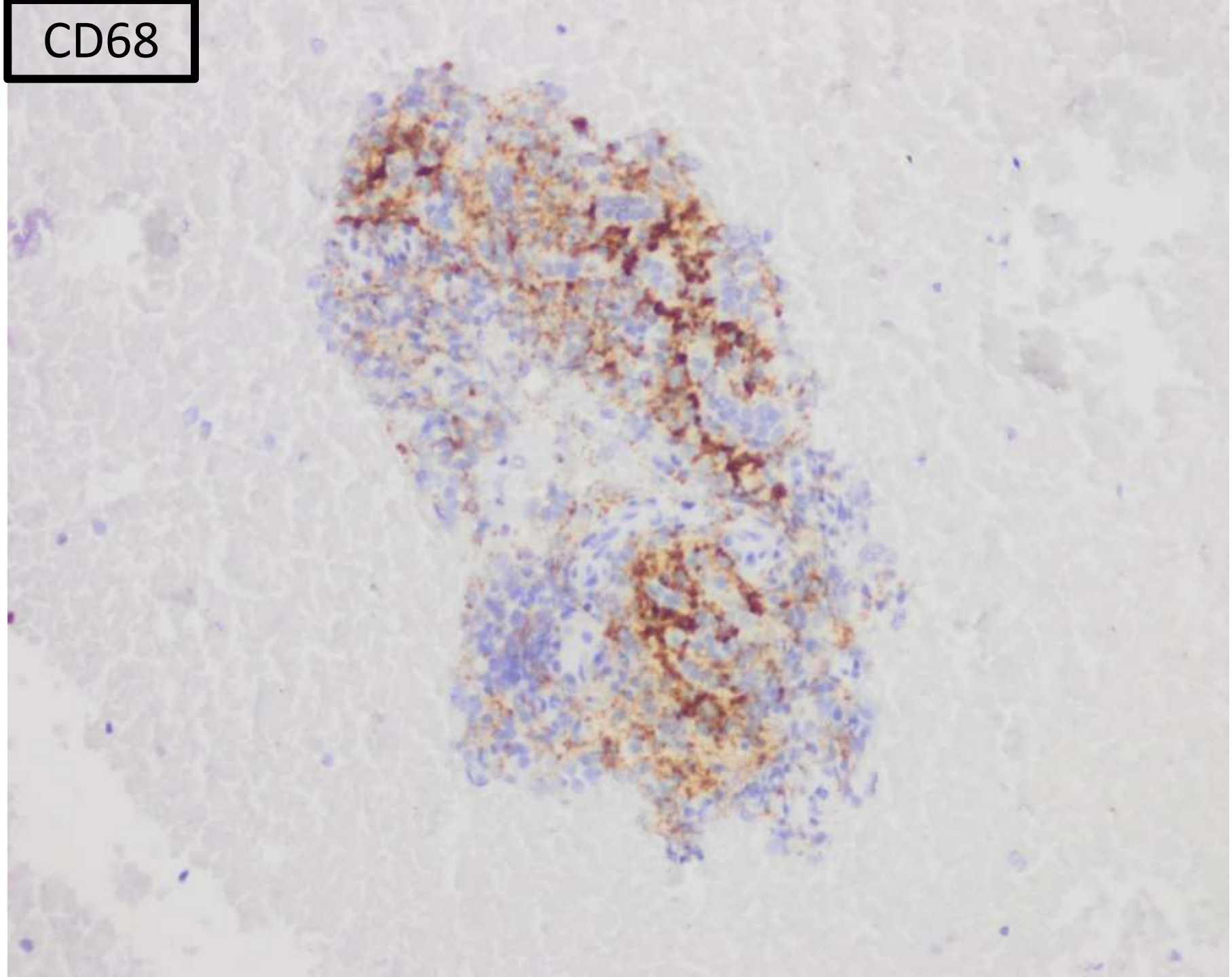
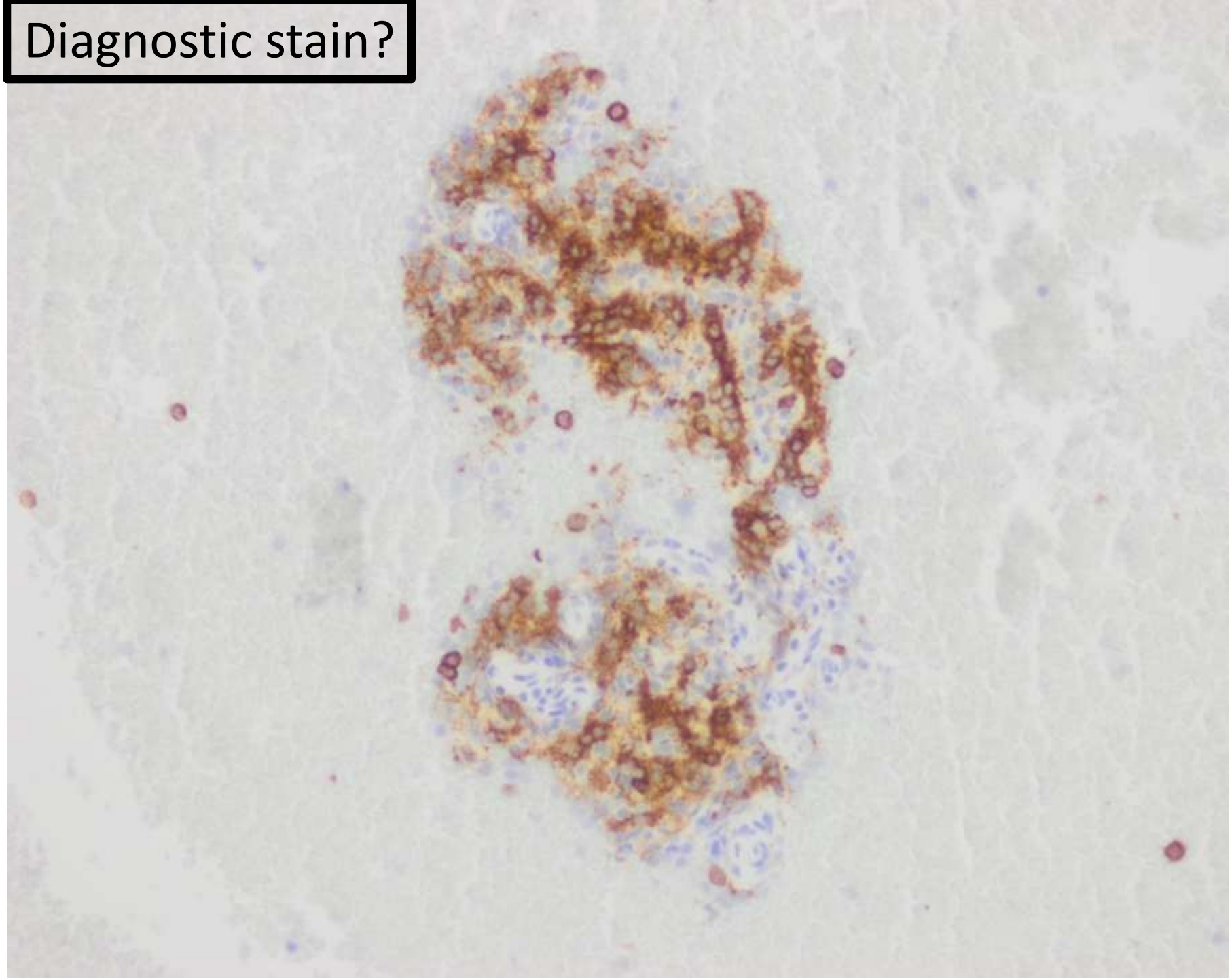

CD3


CD20

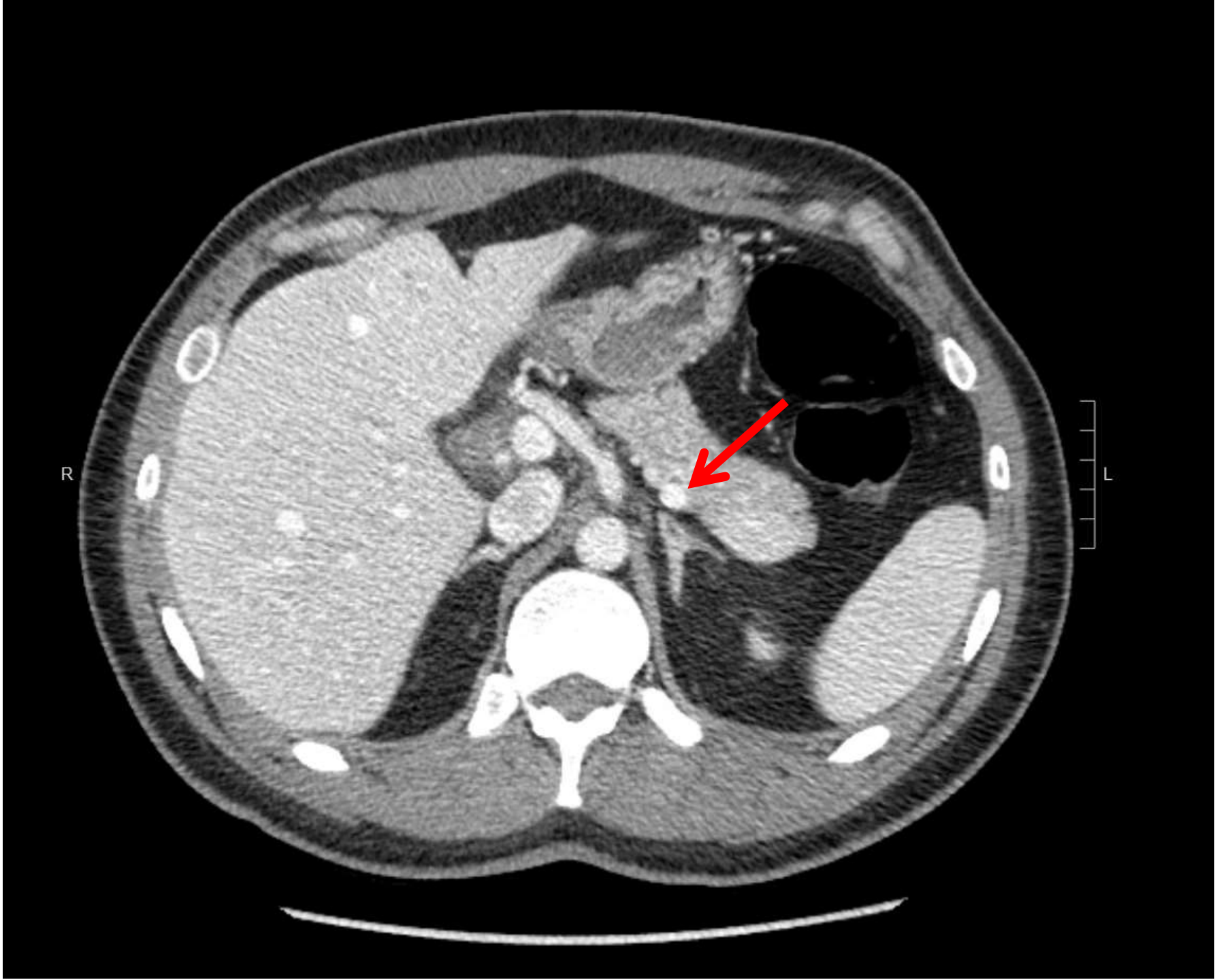

CD68

Diagnostic stain?



History

- The patient is a 31-year-old man with a recent open cholecystectomy for chronic cholecystitis and incidentally found with a distal pancreatic mass.
- Additional history of gun shot wound to abdomen.
- No history of tumor or malignancy.
- He complains of persistent intermittent abdominal pain.
- Imaging:
  - There is a 2.9 x 1.8 cm hyperenhancing mass in the posterior pancreatic tail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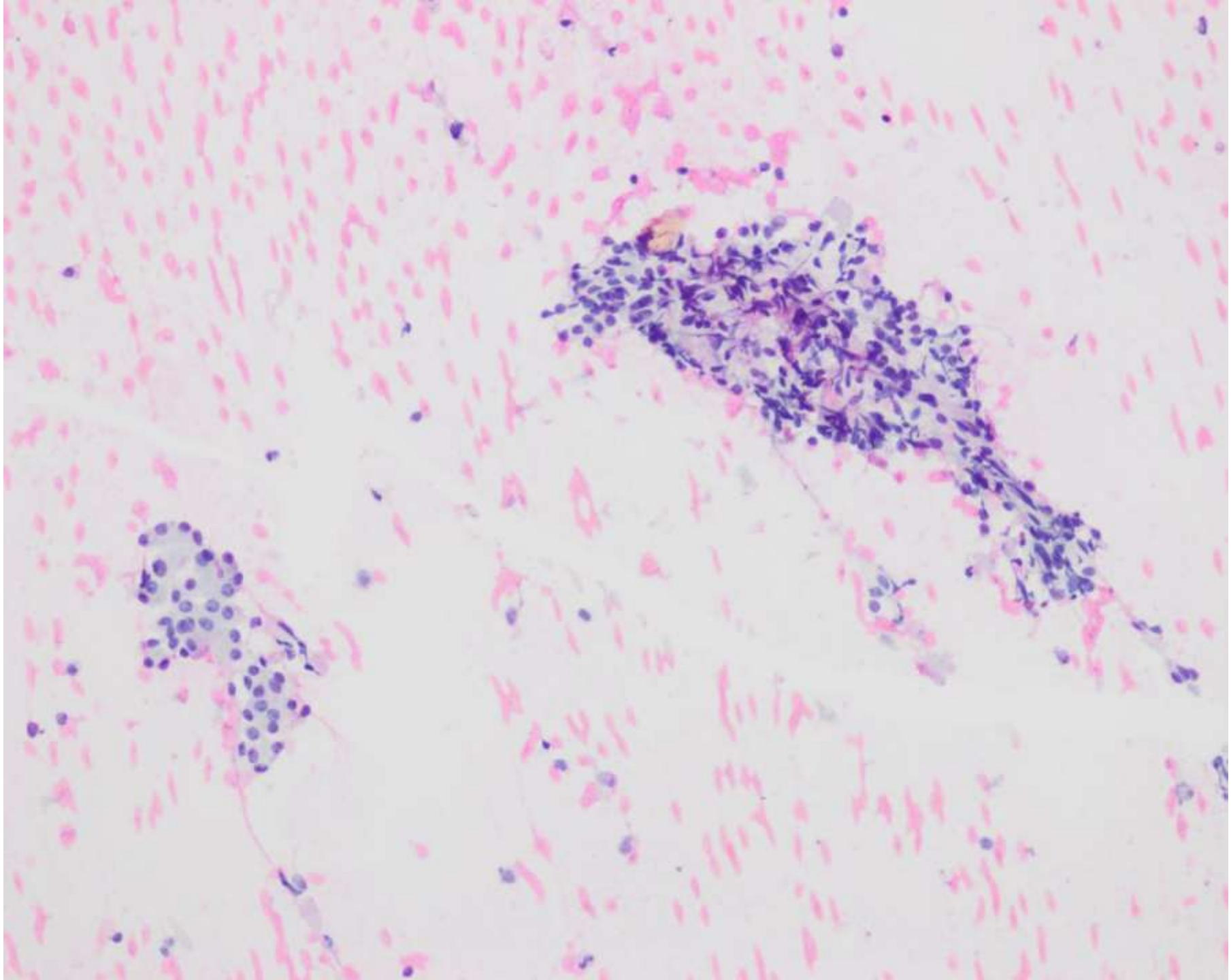
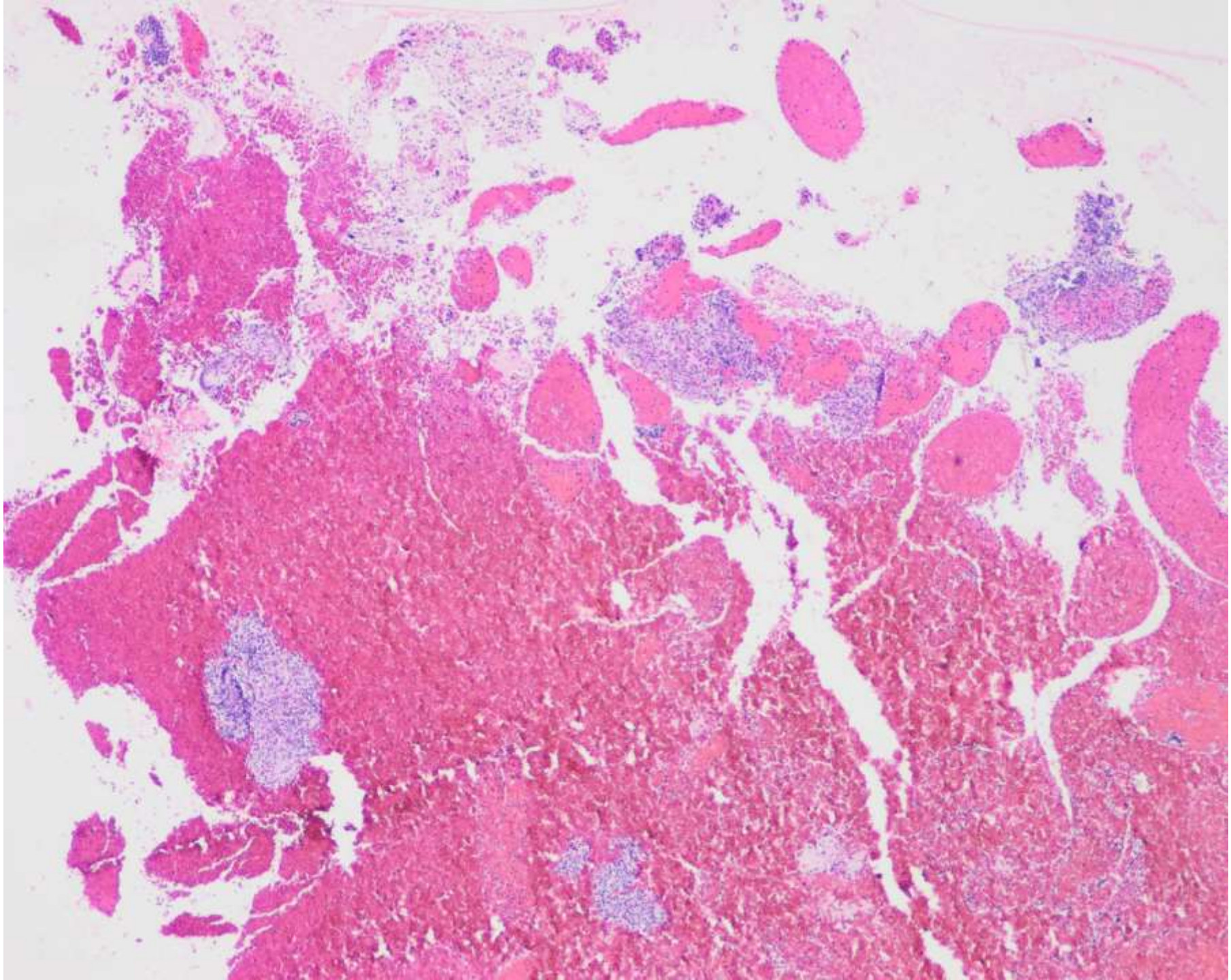
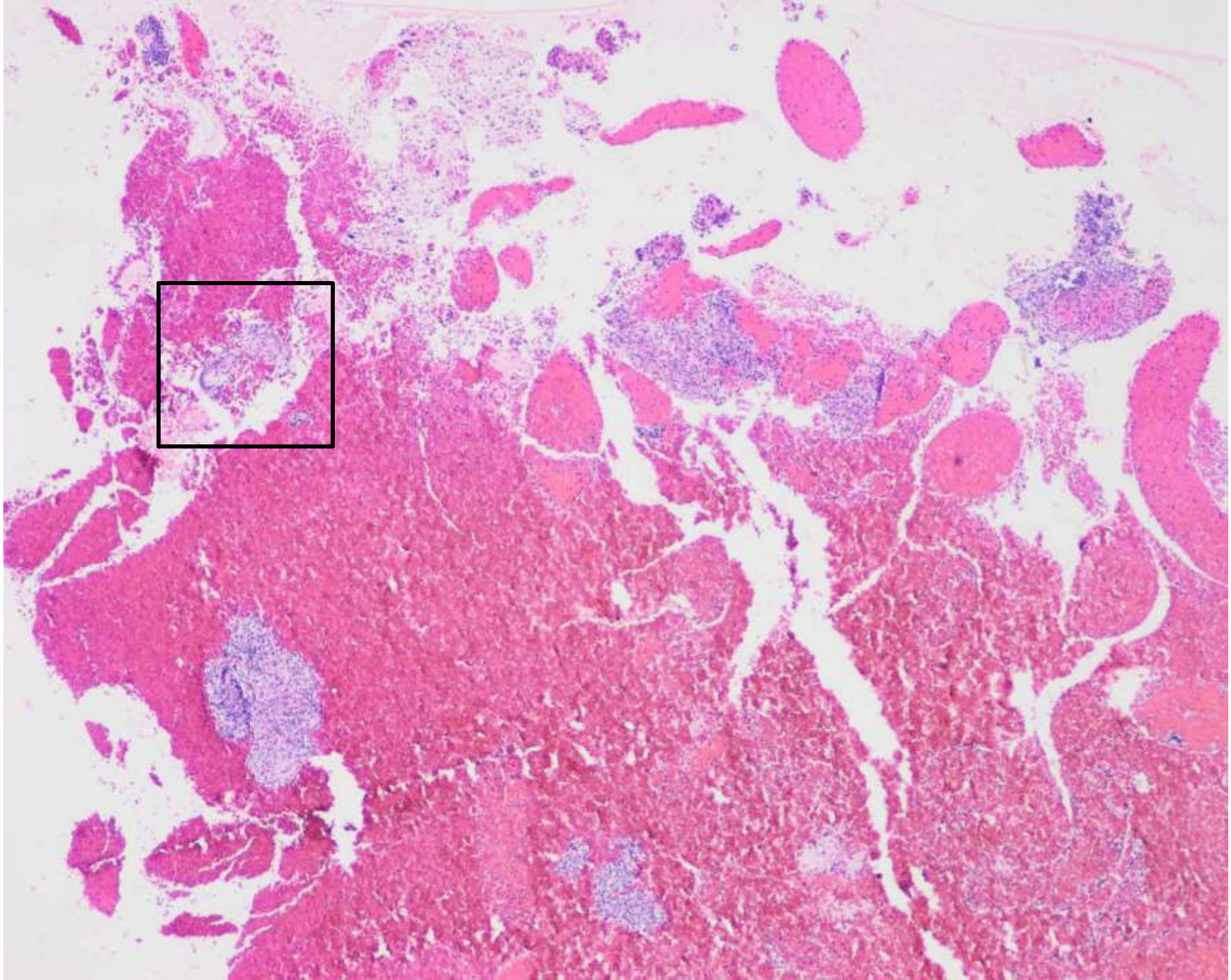
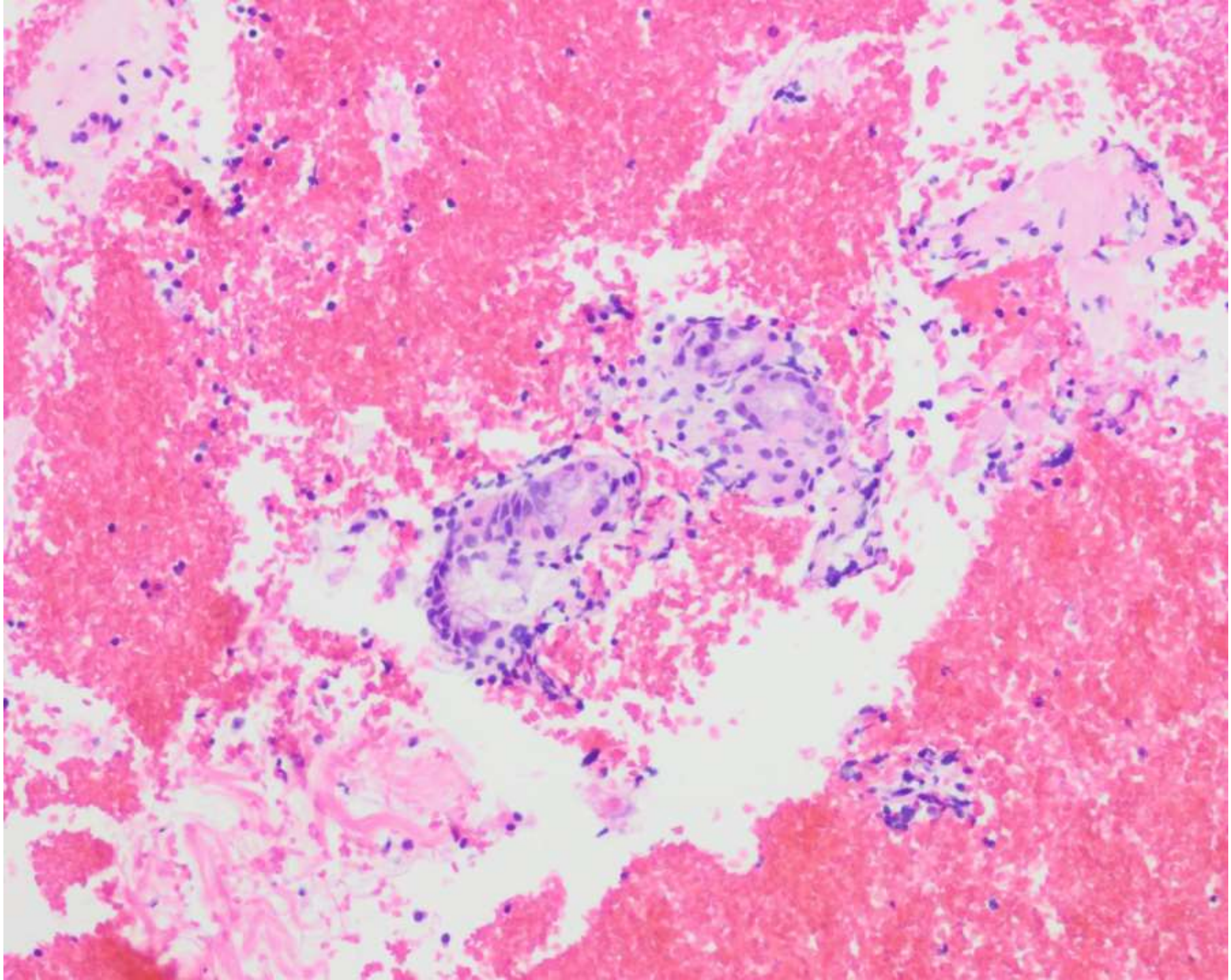
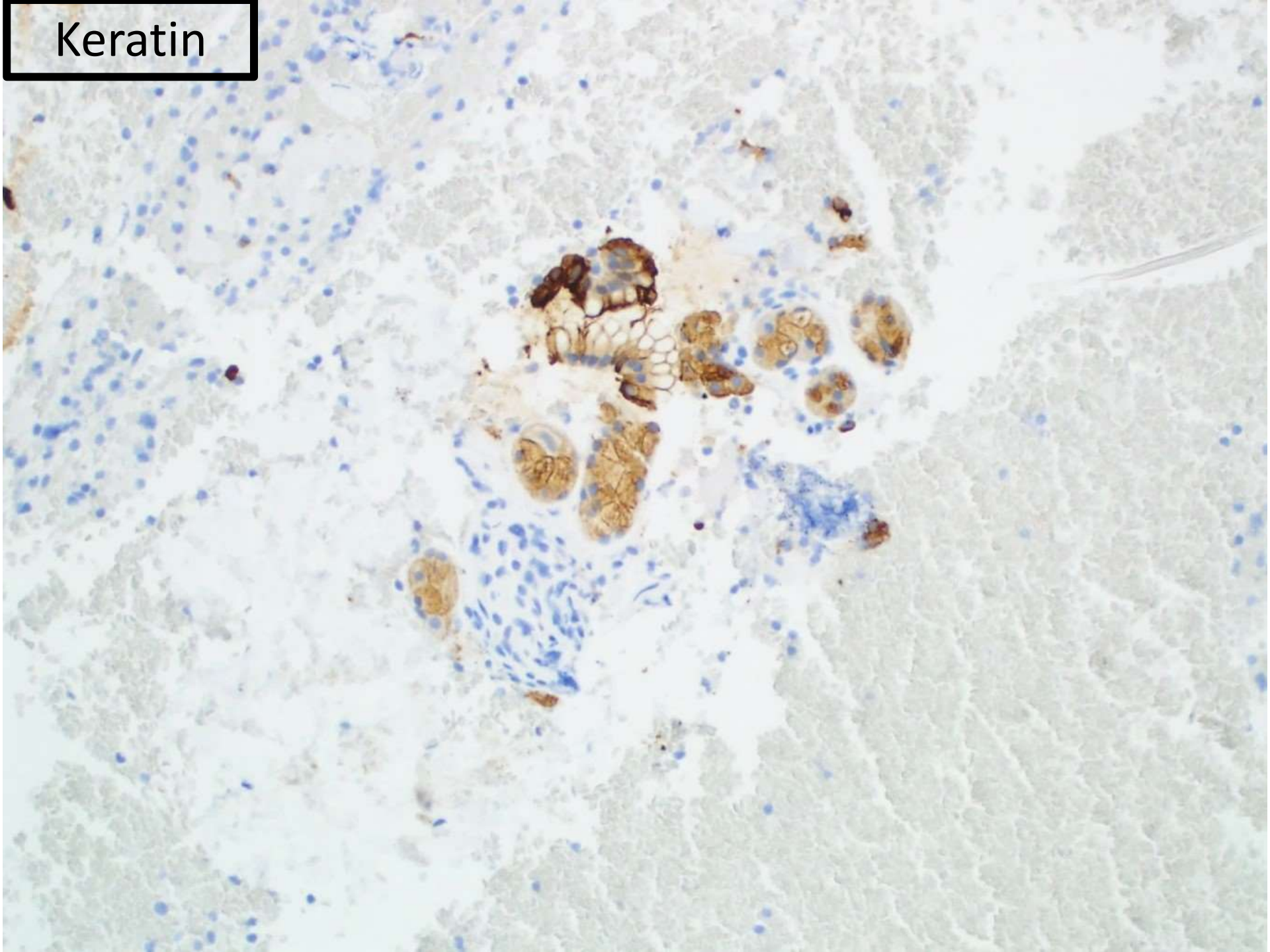
L







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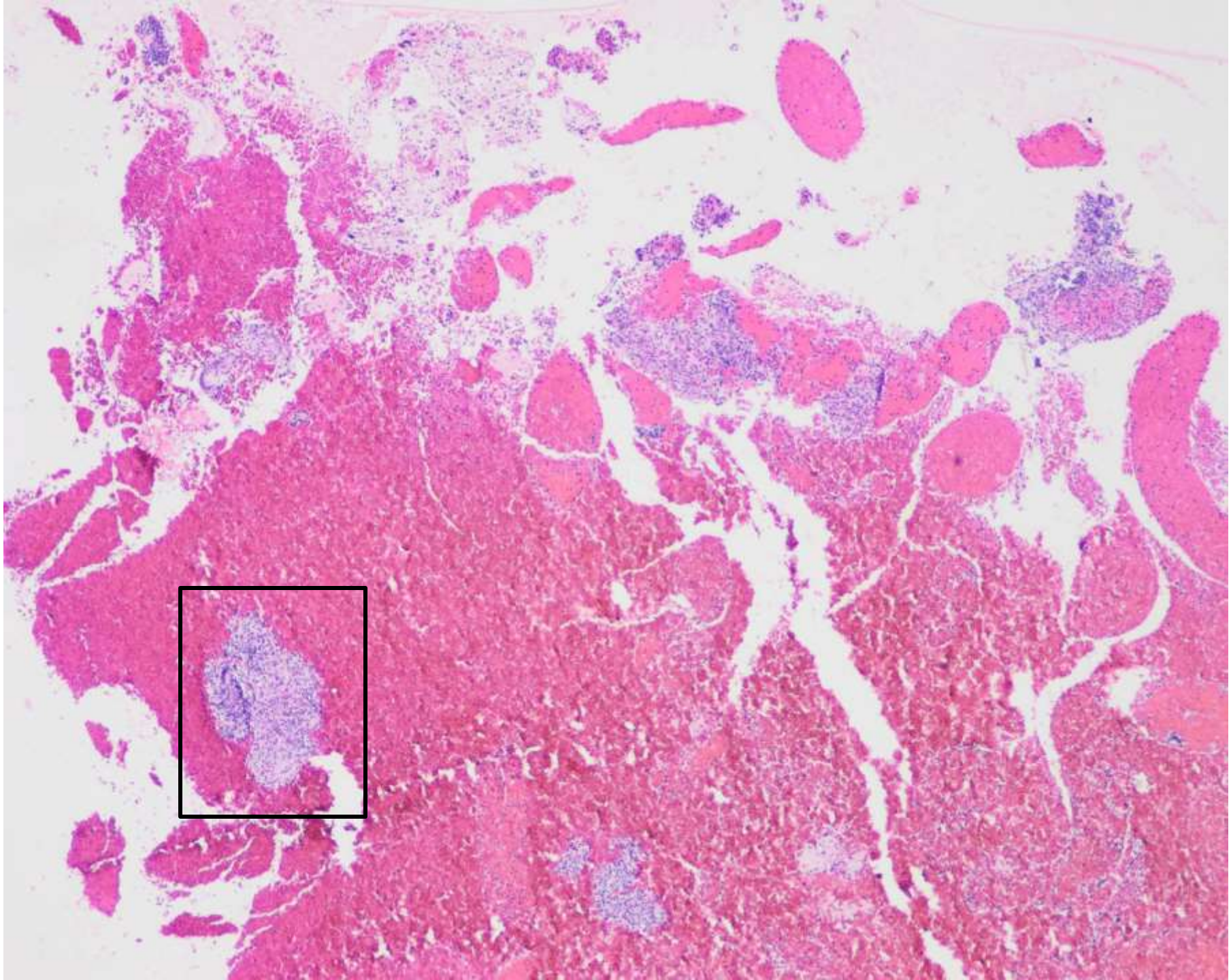

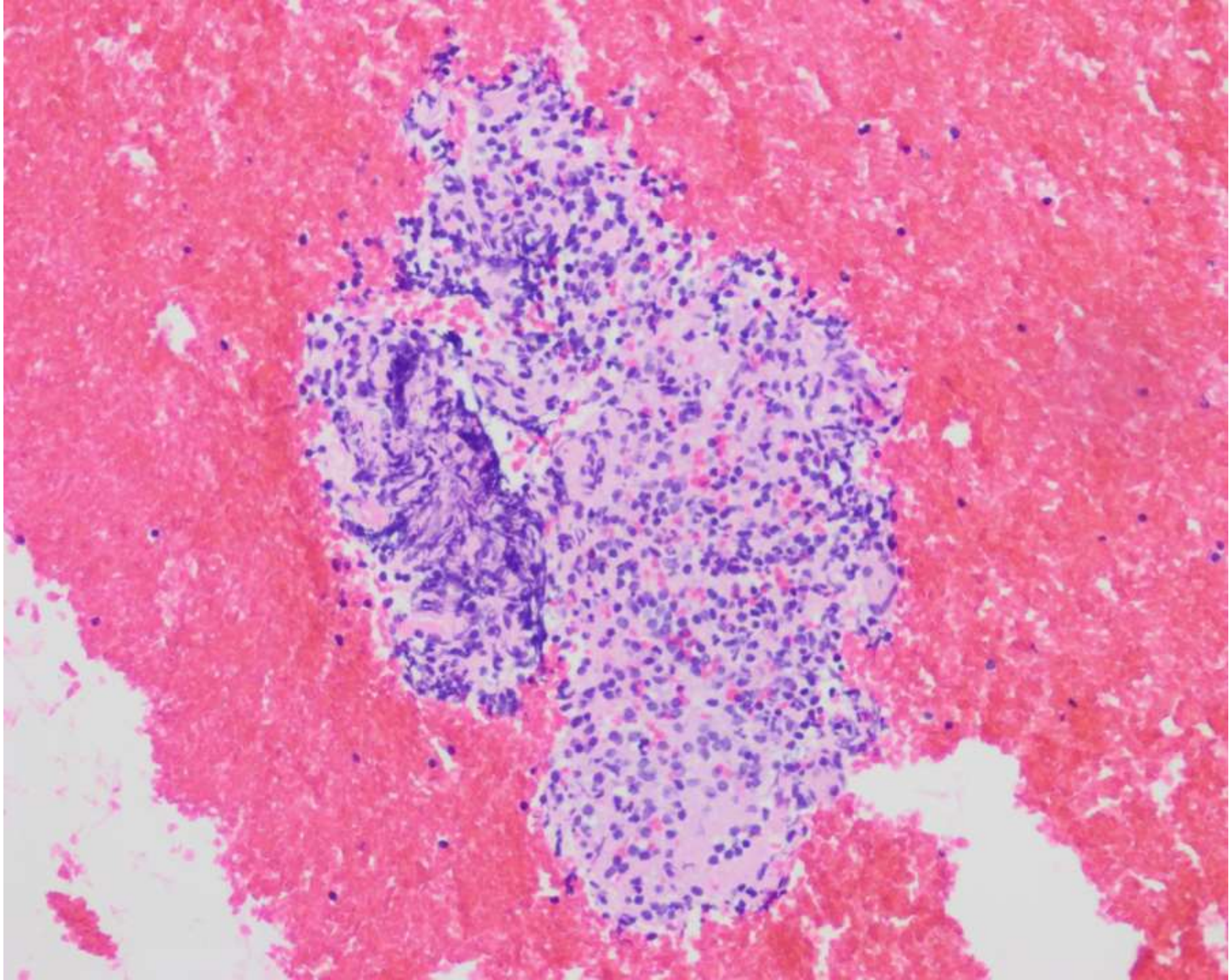

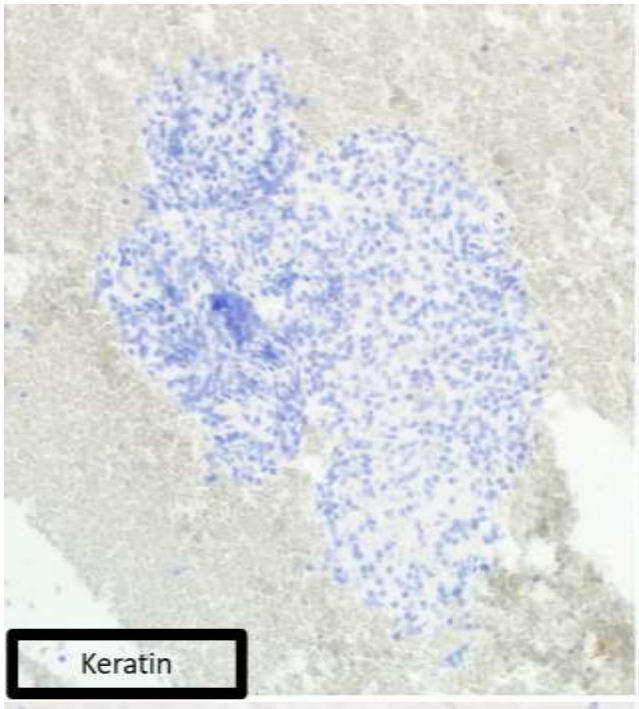
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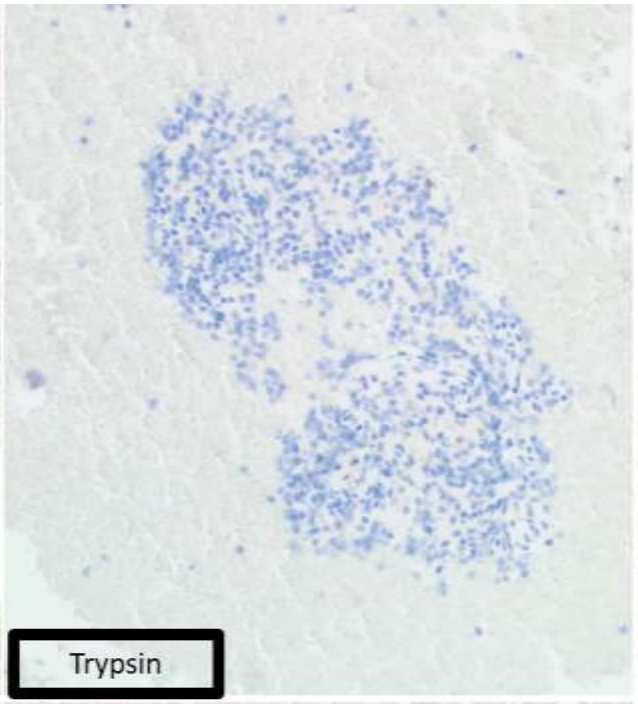
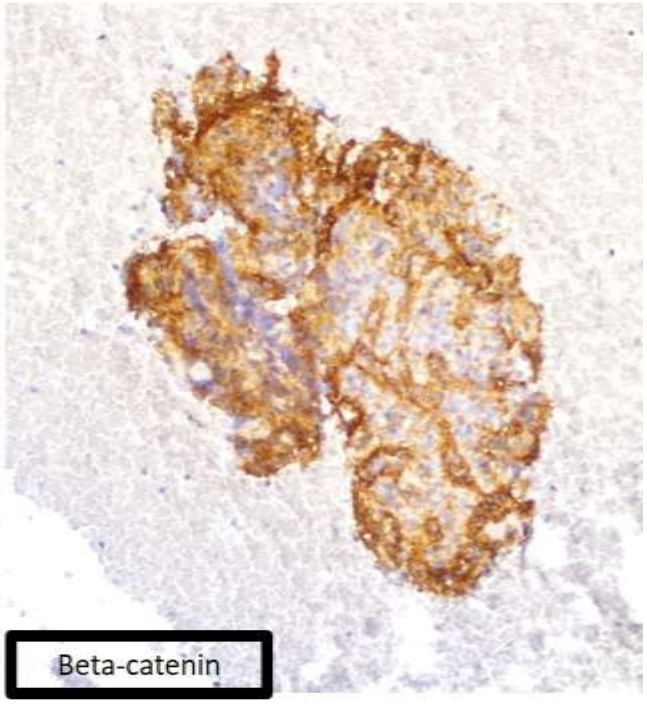
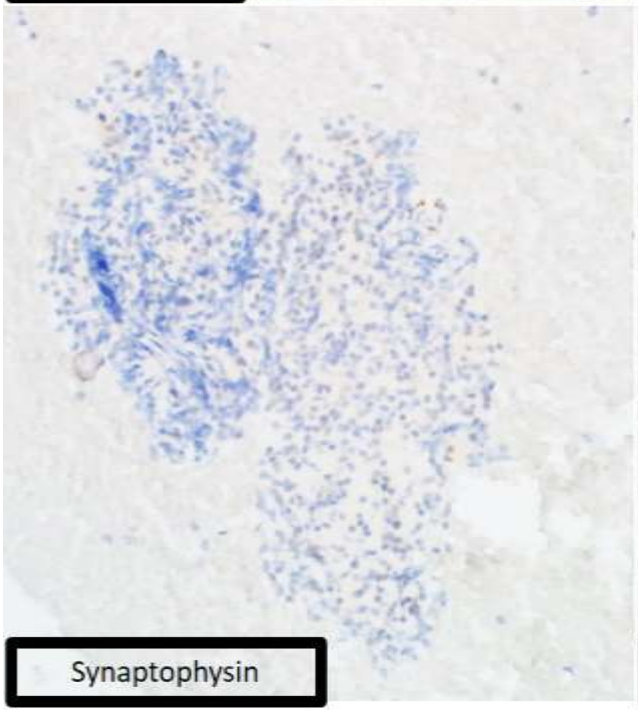
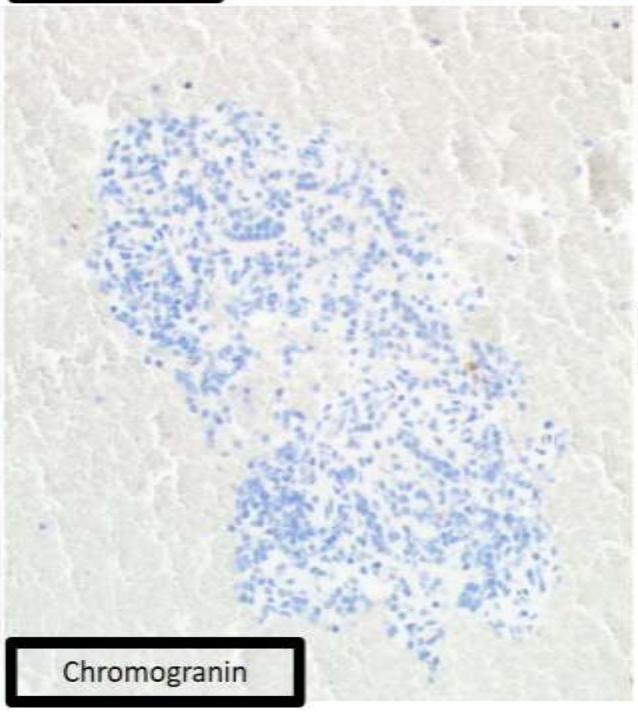
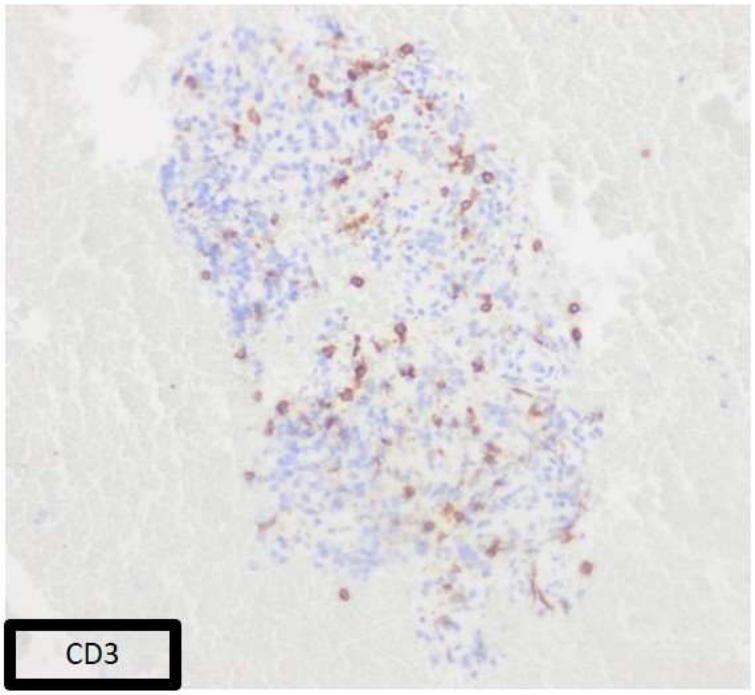
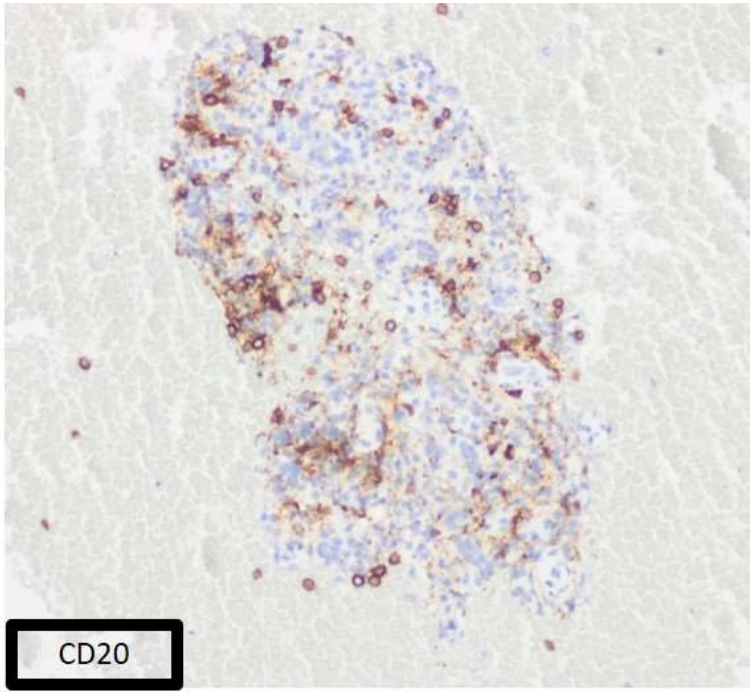

Trypsin


Beta-catenin


Synaptophysin


Chromogranin


CD3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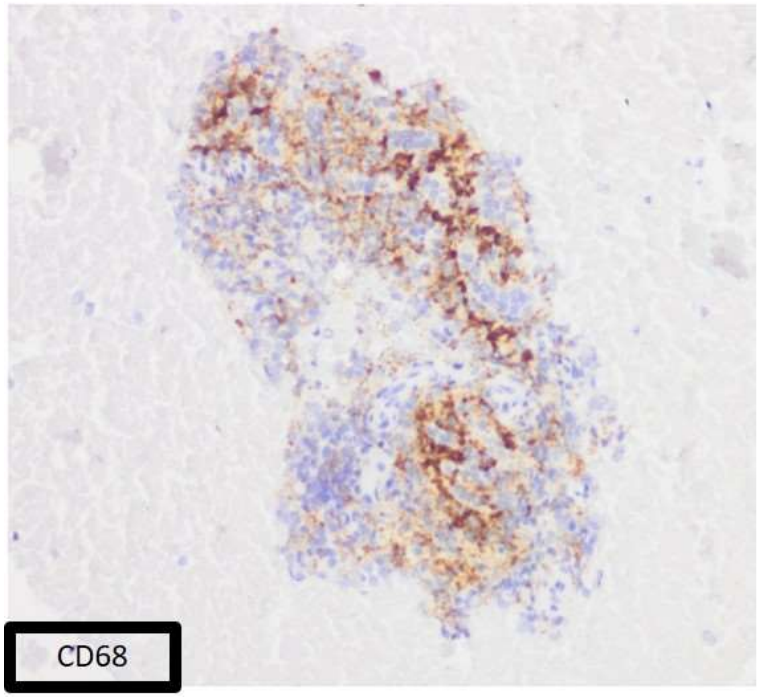
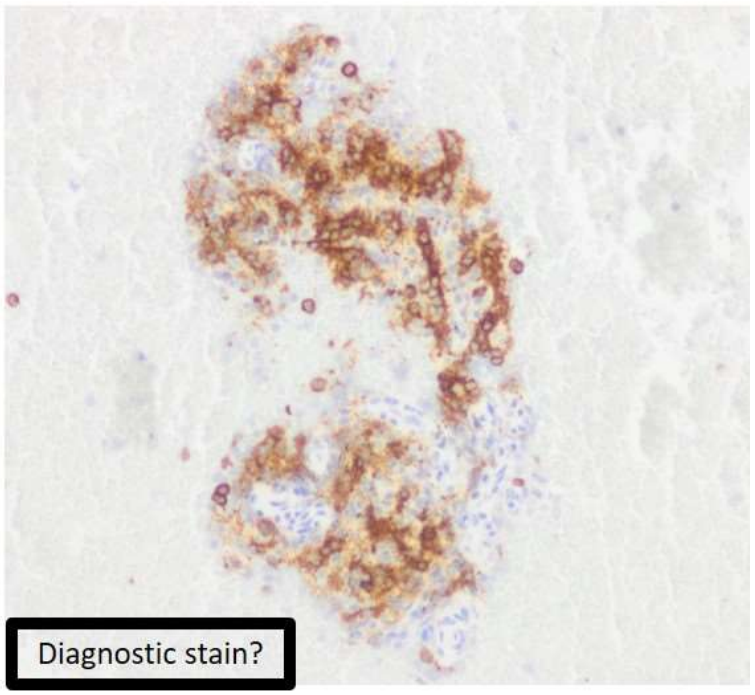
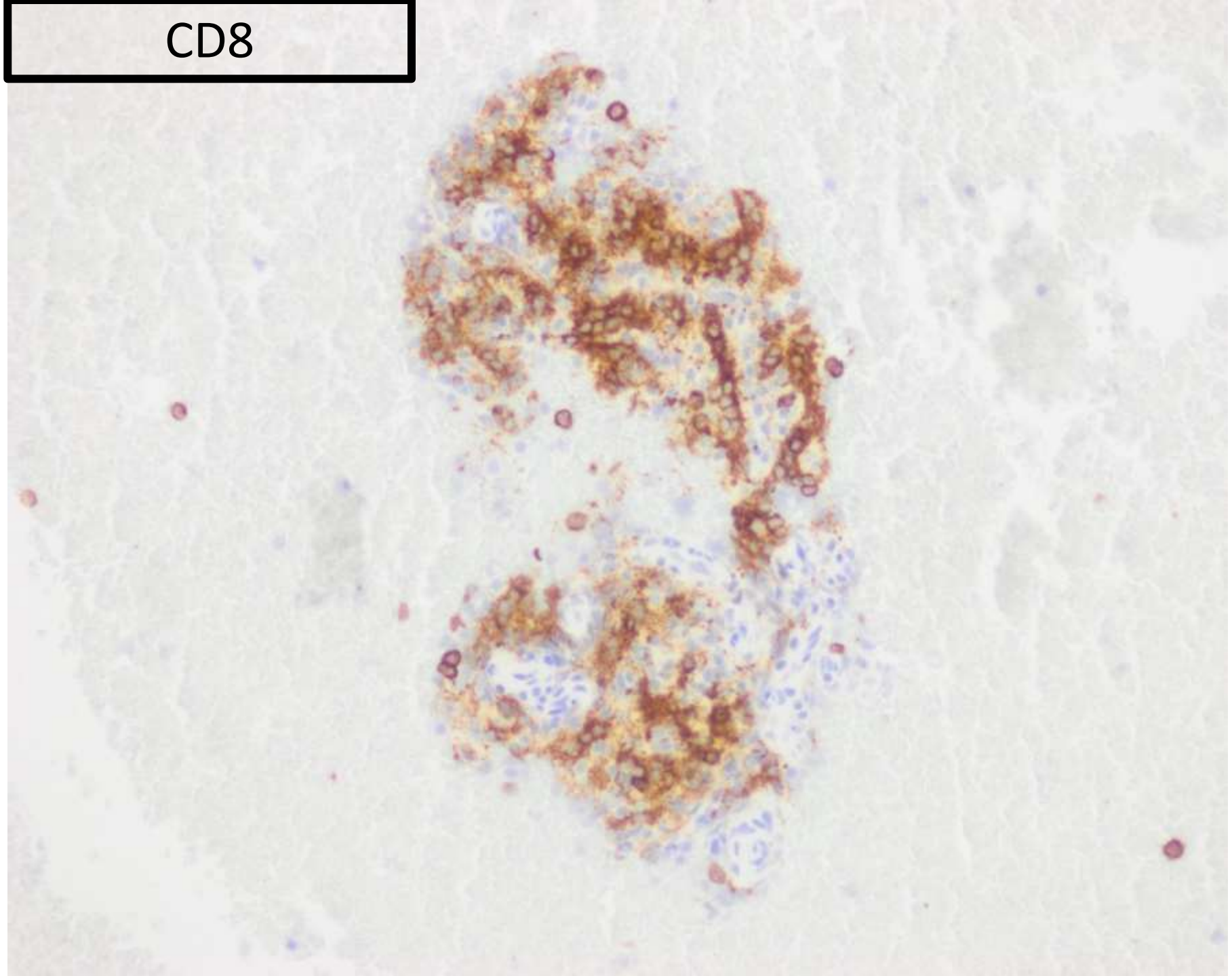
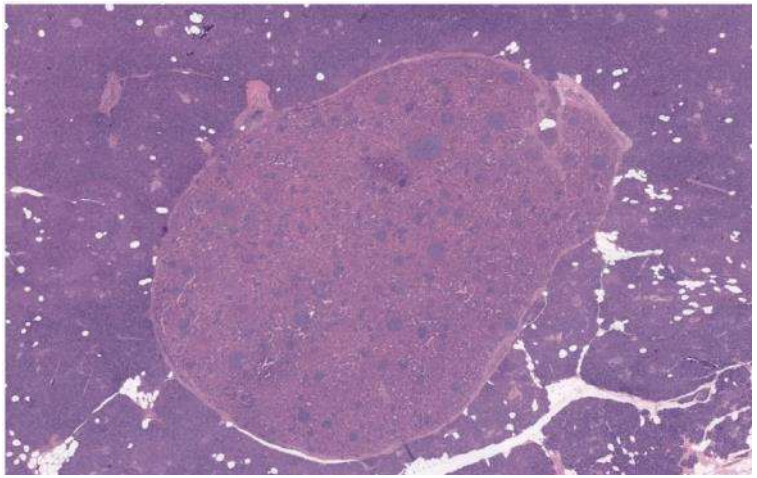

CD68


Diagnostic stain?


CD8

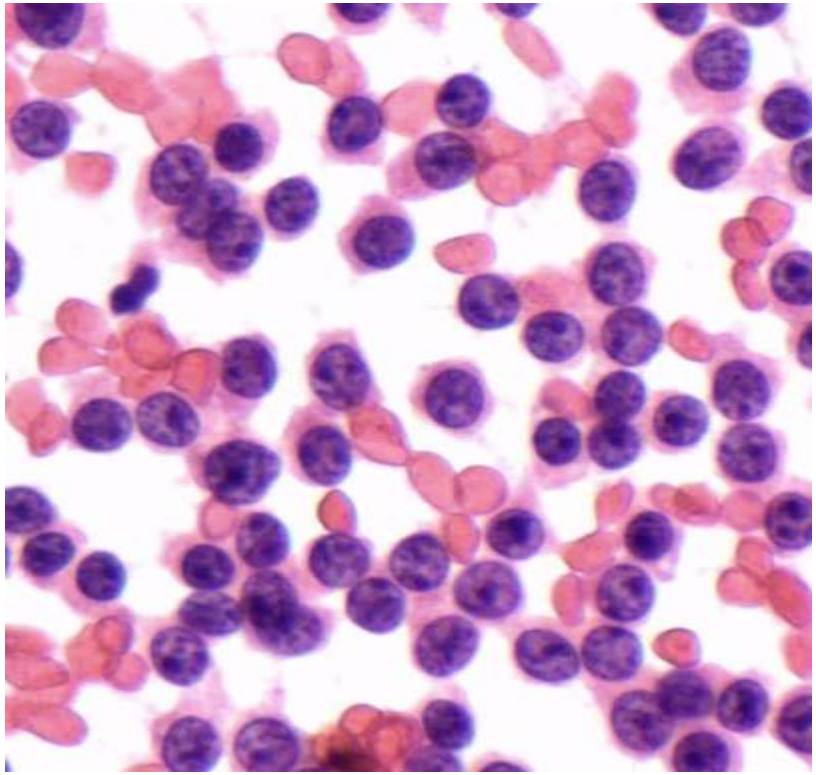
Intrapancreatic Accessory Spleen (IPAS)

- Congenital anomaly of failure of fusion.
- Accessory spleen incidence: 10%-20%.
- Most ectopic spleens are near the splenic hilum, pancreatic tail, greater omentum, splenic ligament.
  - Present in pancreatic tail in 11-17% of cases.
- Rarely detected
  - Small
  - No clinical symptoms

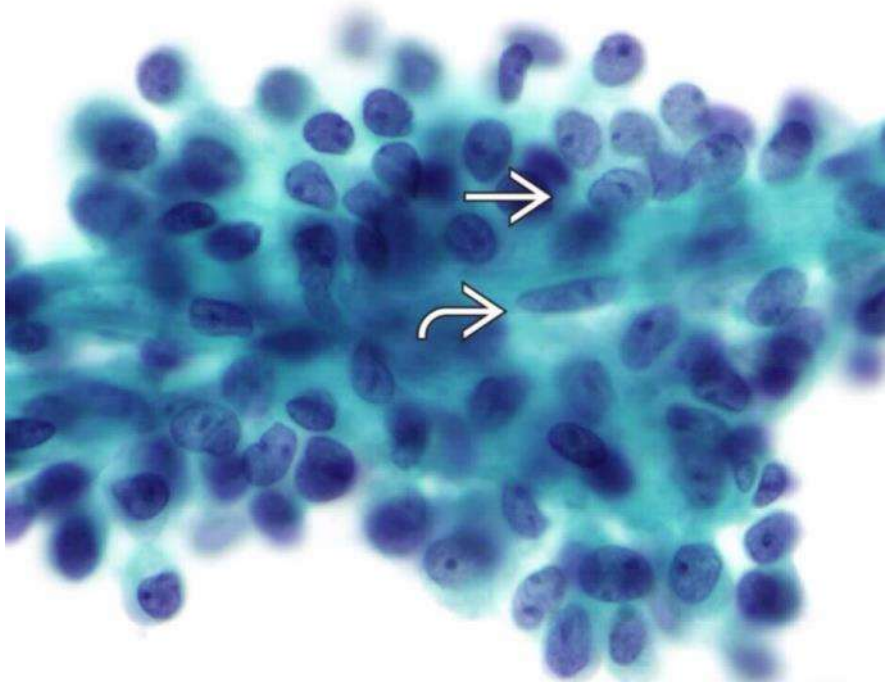


Differential Diagnosis

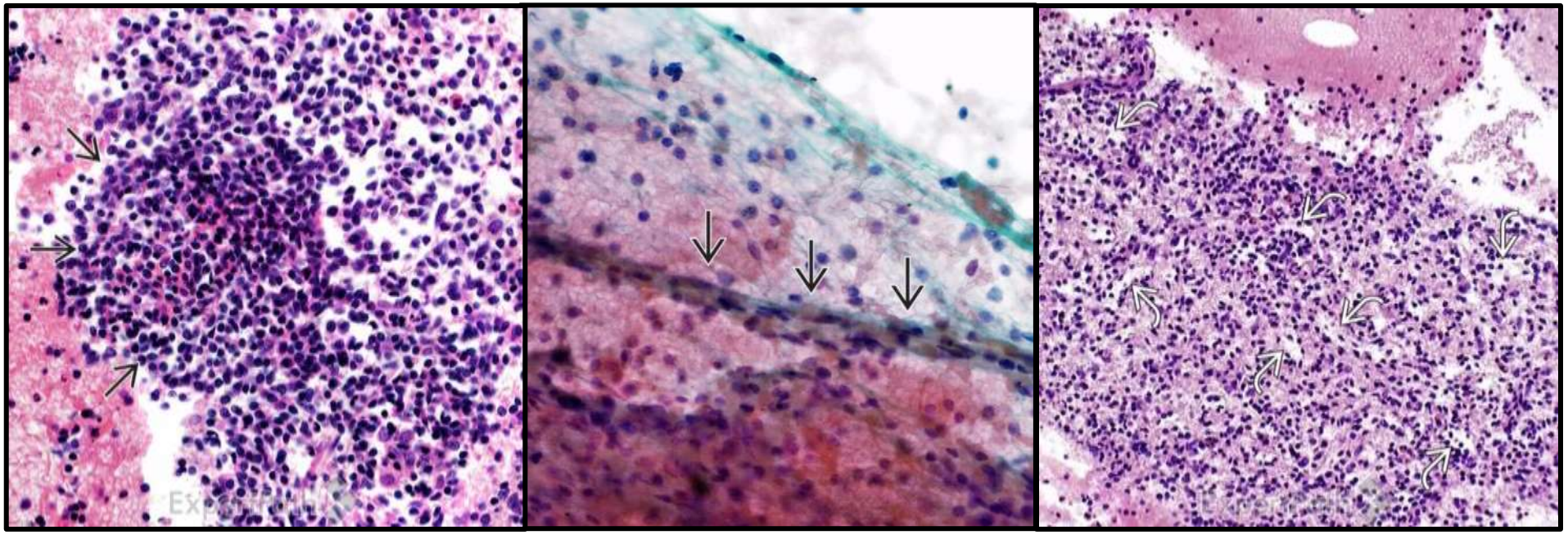
Neuroendocrine Tumor (P-NET)



Solid Pseudopapillary Neoplasm



IPAS Histology



Lymphoid aggregate

Vessels

Splenic Sinuses

ExpertPath

Treatment

- None required.
- Therapy required only with:
  - Idiopathic thrombocytopenic purpura (ITP)
  - Symptoms due to compression
  - Torsion
  - Spontaneous rupture of hemorrhage

Clinical Features of IPAS

Table 1 Patients' epidemiologic data and symptoms

Items	Median (range), n/d (%)
Age (year)	52 (0–81)
<40	23/105 (22)
40 ≤≤ 65	61/105 (58)
>65	21/105 (20)
Gender	
Male/female	1.23 (58/47)
Location	
Tail	101/105 (96)
Body	2/105 (2)
Head	2/105 (2)
Size (cm)	1.5 (0.3–5.1)
≤1 cm	13/92 (14)
≤2 cm	74/92 (80)
>2 cm	18/92 (20)
Symptoms	
Incidental	73/100 (73)
Abdominal pain	16/100 (16)
Nonspecific gastrointestinal symptoms	14/100 (14)
Symptoms of pancreatic hormone excess	4/100 (4)
Weight loss	2/100 (2)

Li BQ et al. HPB. 2018;20(11):1004-1011

Preoperative Diagnoses

Items	n/d (%)
Preoperative diagnosis	
p-net	45/52 (87)
SPT	7/52 (14)
IPAS	2/52 (4)
Metastasis	2/52 (4)
Pancreatic cancer	2/52 (4)
Pancreatic neoplasm	4/52 (8)
Retroperitoneal sarcoma	1/52 (2)
Not mentioned	3/52 (6)
Diagnostic modality	
Postoperative pathology	52/92 (57)
FNA pathology	18/92 (20)

Li BQ et al. HPB. 2018;20(11):1004-1011

FNA Pathology of IPAS

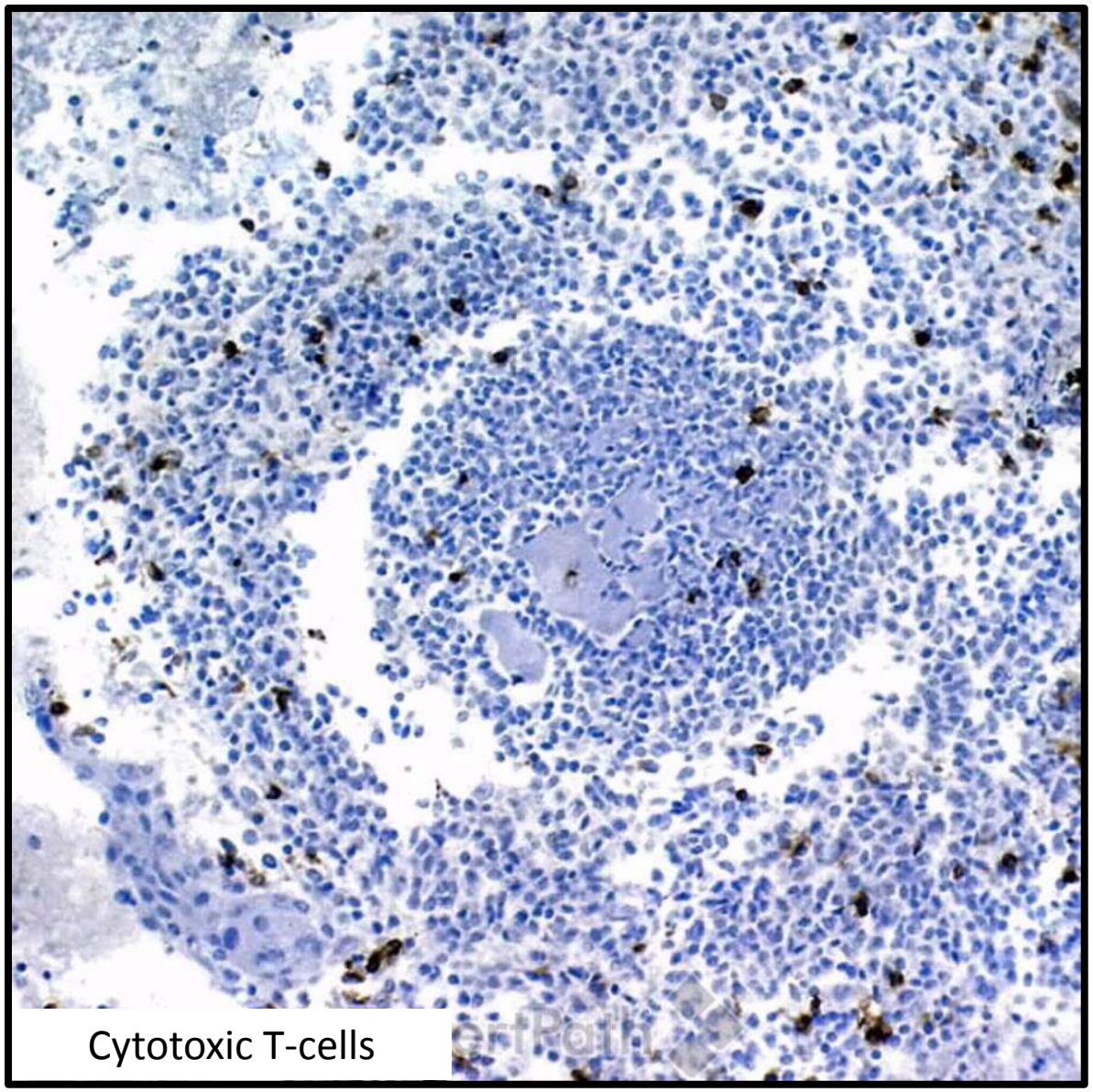
FNA pathology	IPAS	19/33
	p-net	6/33
	Non-diagnosis	5/33
	No evidence for malignancy/ neoplasm	3/33

Treatment

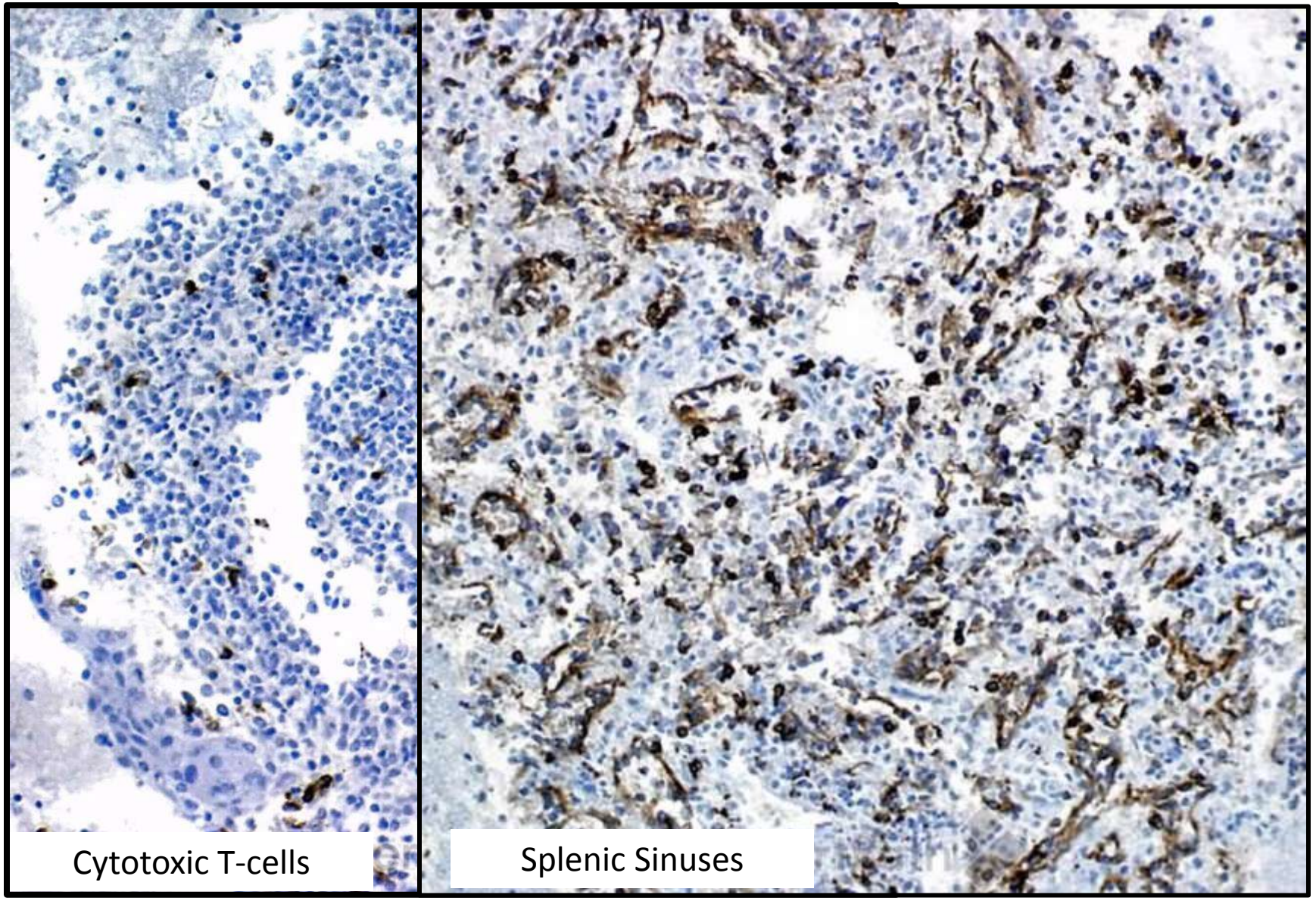
Items	n/d (%)
Treatment	
Non-surgical treatment	42/94 (45)
Surgical treatment	52/94 (55)
Open surgery	34/52 (65)
Minimal invasive surgery	18/52 (35)
Distal pancreatectomy	26/52 (50)
Distal splenopancreatectomy	19/52 (37)
pancreatic tail resection	5/52 (10)
Pancreatic tail and spleen resection	1/52 (2)

Li BQ et al. HPB. 2018;20(11):1004-1011

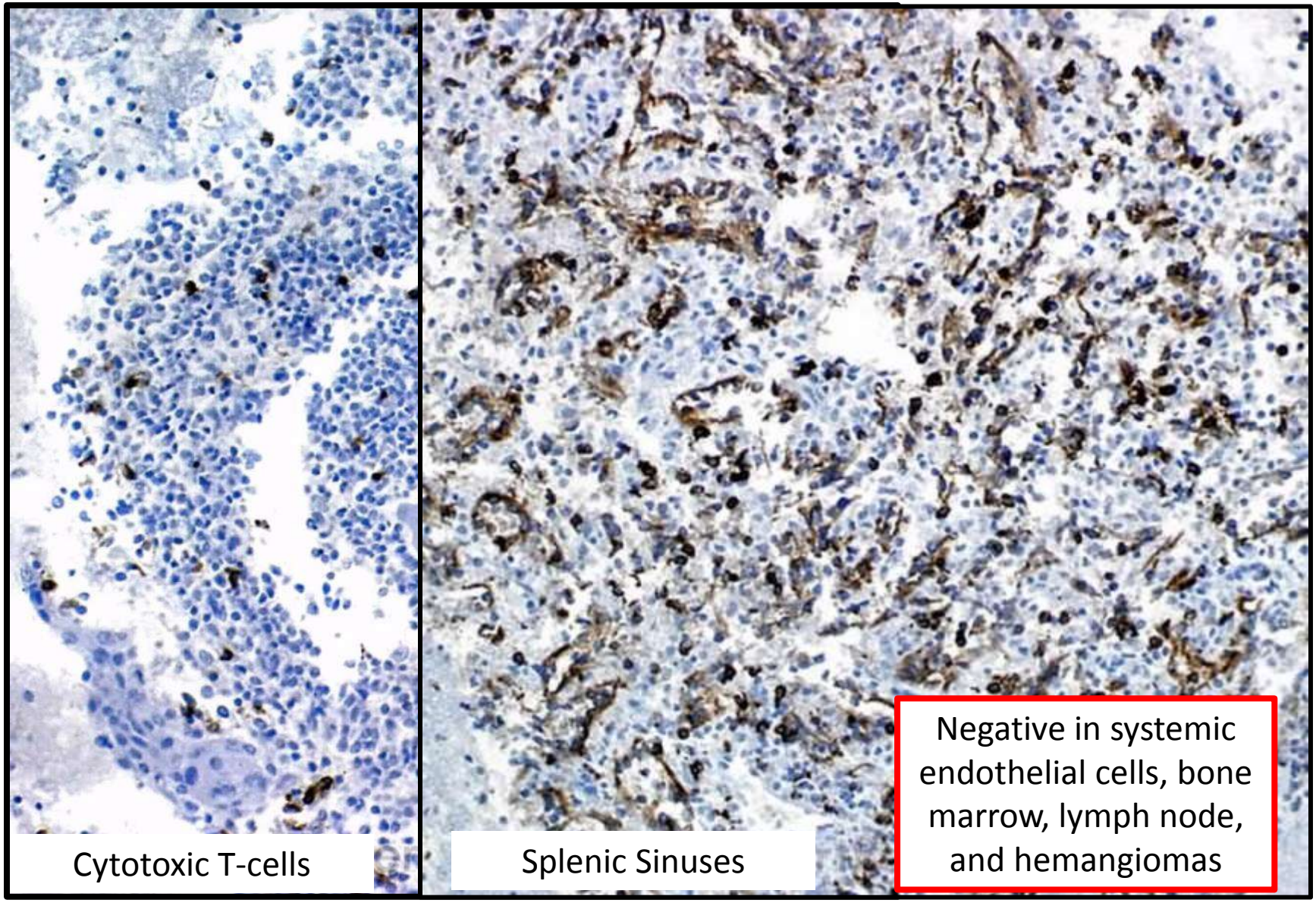
CD8 Immunohistochemical Stain



CD8 Immunohistochemical Stain



CD8 Immunohistochemical Stain



Summary

- Accessory spleen is not rare.
- May be confused with P-NET and SPN.
- CD8 is a helpful marker in FNA specimen.

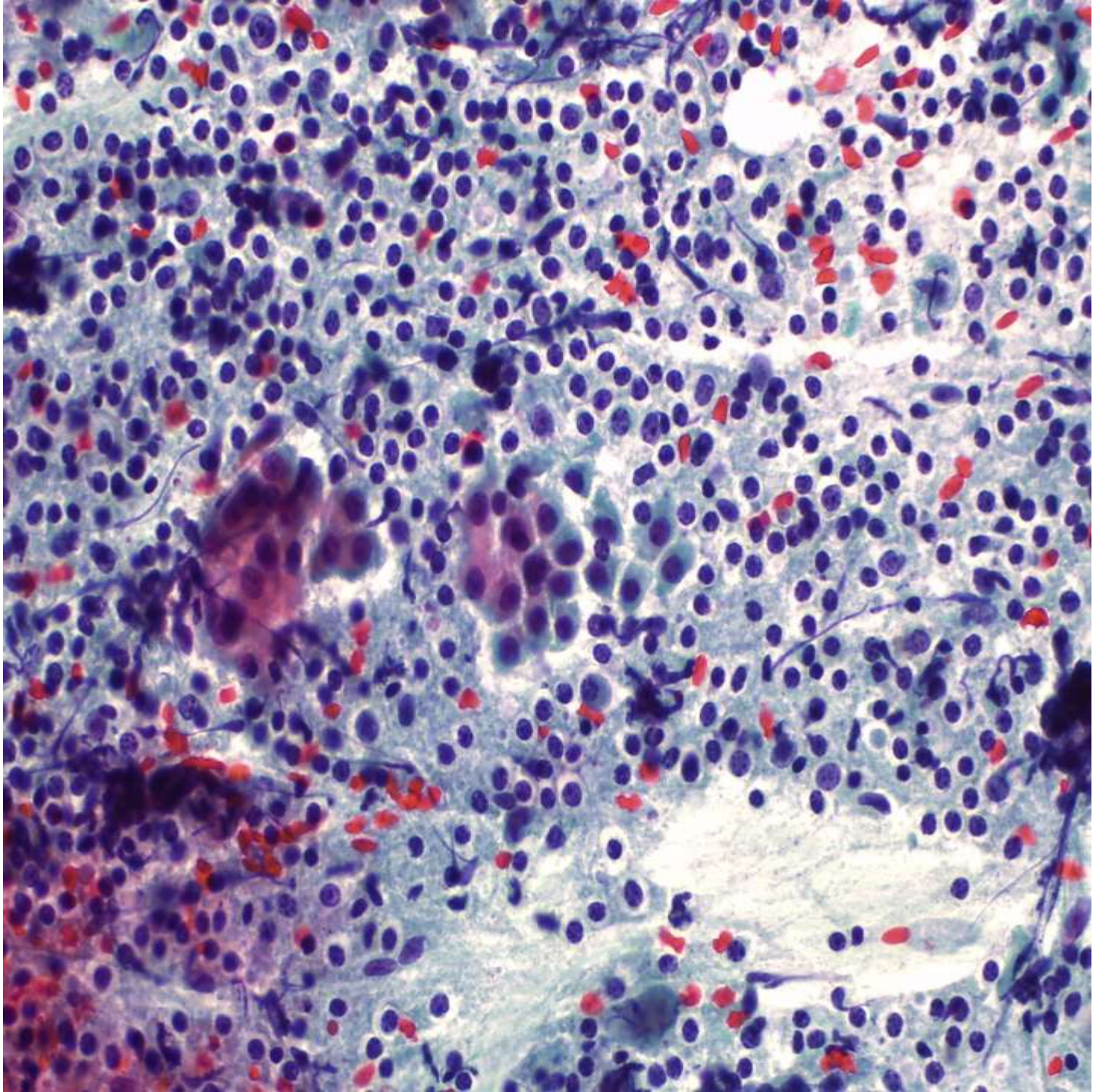
References

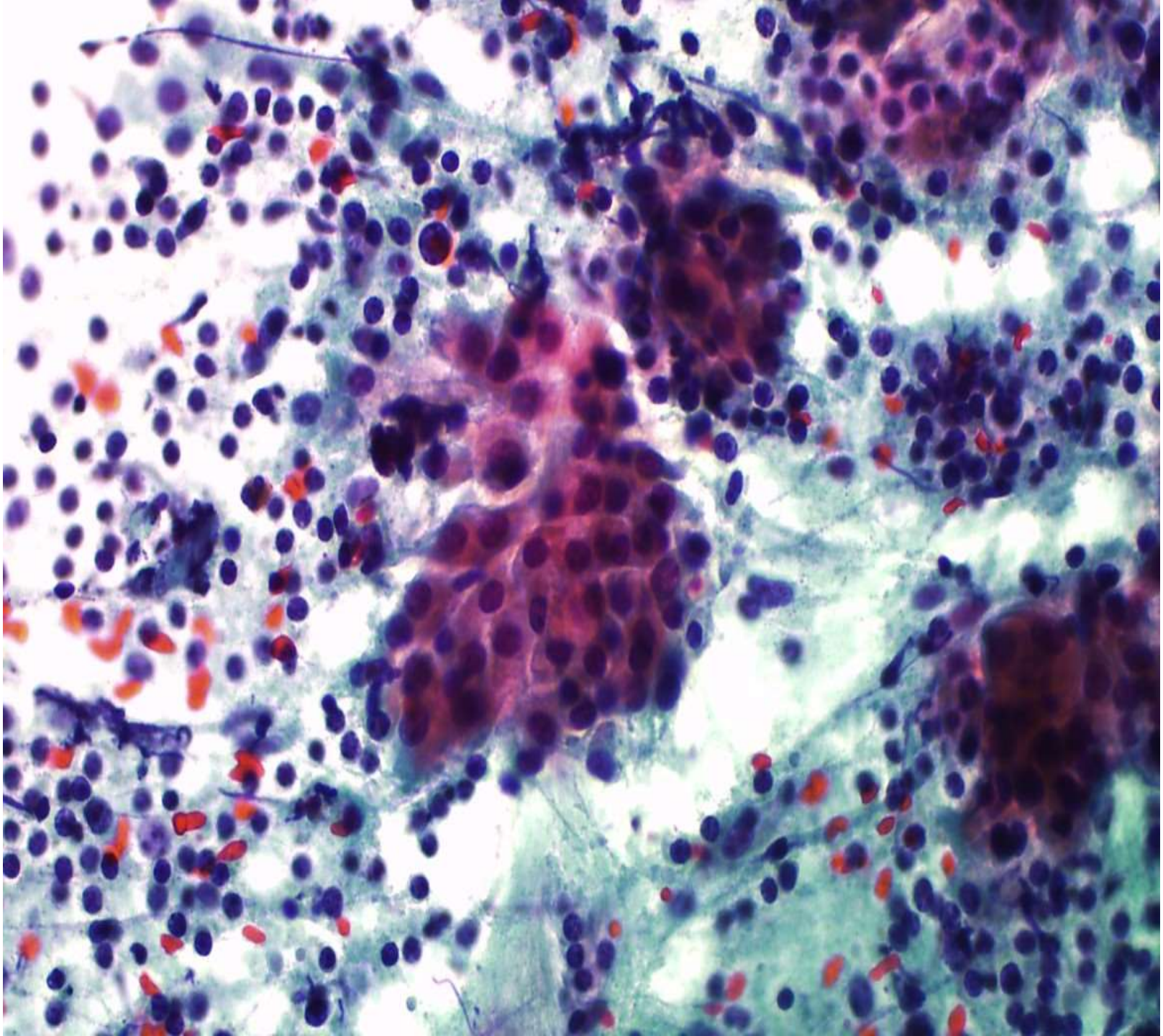
- Saunders, T. A., Miller, T. R., & Khanafshar, E. (2016). Intrapancreatic accessory spleen: utilization of fine needle aspiration for diagnosis of a potential mimic of a pancreatic neoplasm. *Journal of gastrointestinal oncology*, *7*(Suppl 1), S62–S65. doi:10.3978/j.issn.2078-6891.2015.030
- Santos MPD, Rezende AP, Santos PVD Filho, Gonçalves JE, Beraldo FB, Sampaio AP. Intrapancreatic accessory spleen. *Einstein (Sao Paulo)*. 2017;15(3):366–368. doi:10.1590/S1679-45082017RC3942
- Li BQ, Xu XQ, Guo JC. Intrapancreatic accessory spleen: a diagnostic dilemma. HPB (Oxford). 2018 Nov;20(11):1004-1011. doi: 10.1016/j.hpb.2018.04.004. Epub 2018 May 26. Review. PubMed PMID: 29843985.
- Zurek Munk-Madsen, M., Zakarian, K., Sandor Oturai, P., Hansen, C. P., Federspiel, B., Fallentin, E., & Linno Willemoe, G. Intrapancreatic accessory spleen mimicking malignant tumor: three case reports. *Acta Radiologica Open*. 2019; 8(6) 1–5.

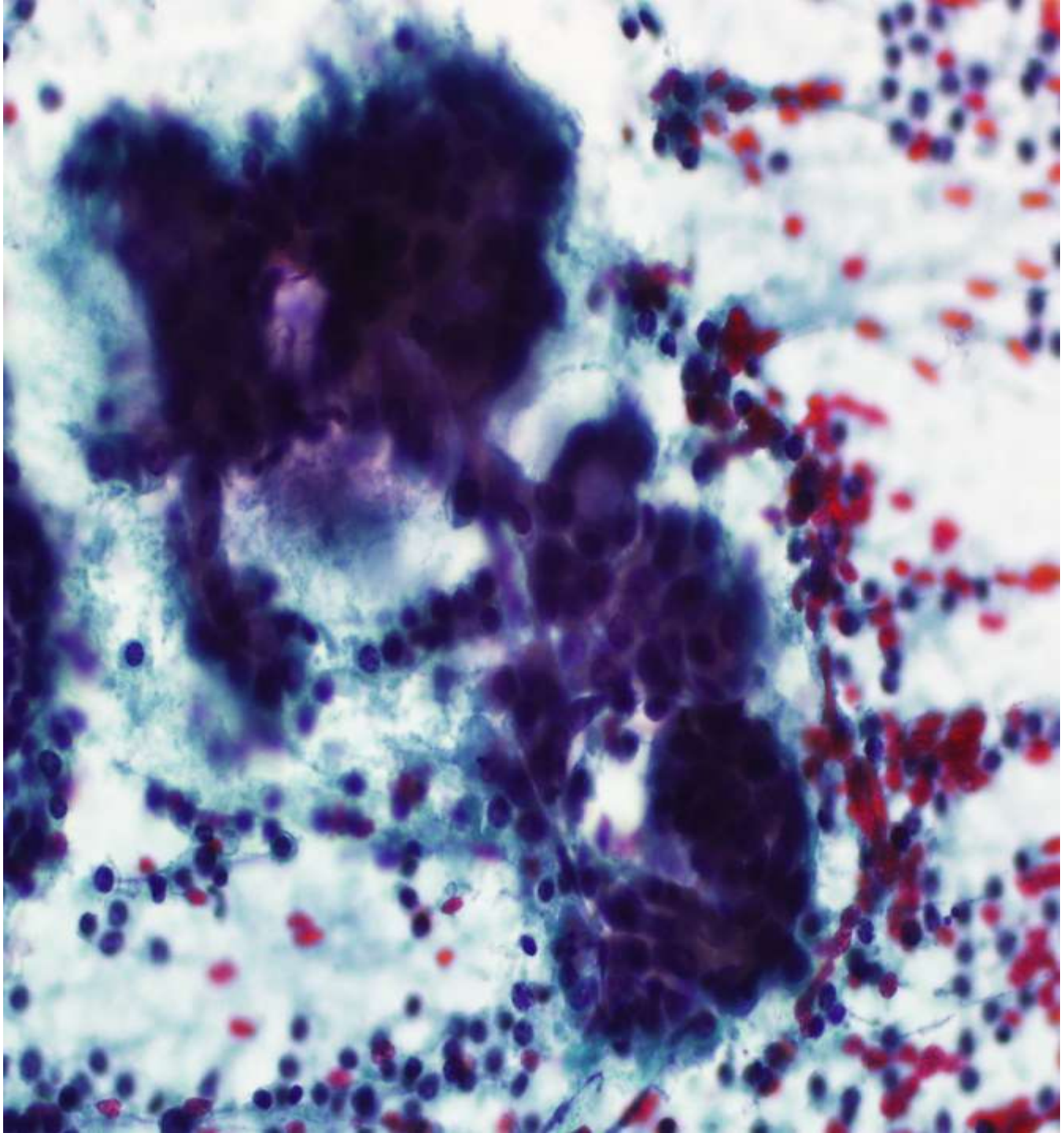
19-1208

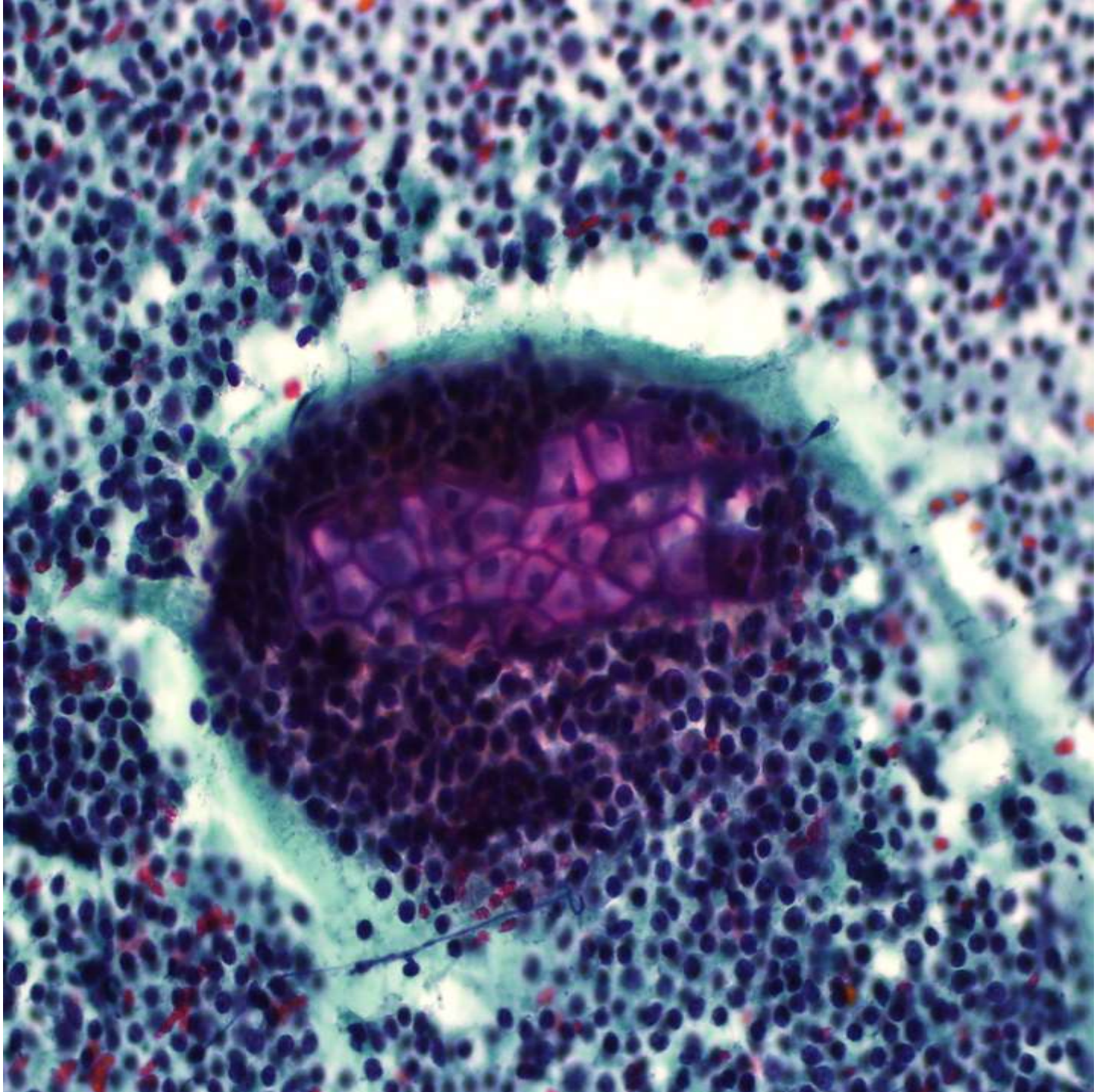
Lucy Han/Joshua Menke; UCSF

29-year-old female with a left parotid gland mass, present for 9 years.









29-year-old woman with a left parotid gland mass for 9 years

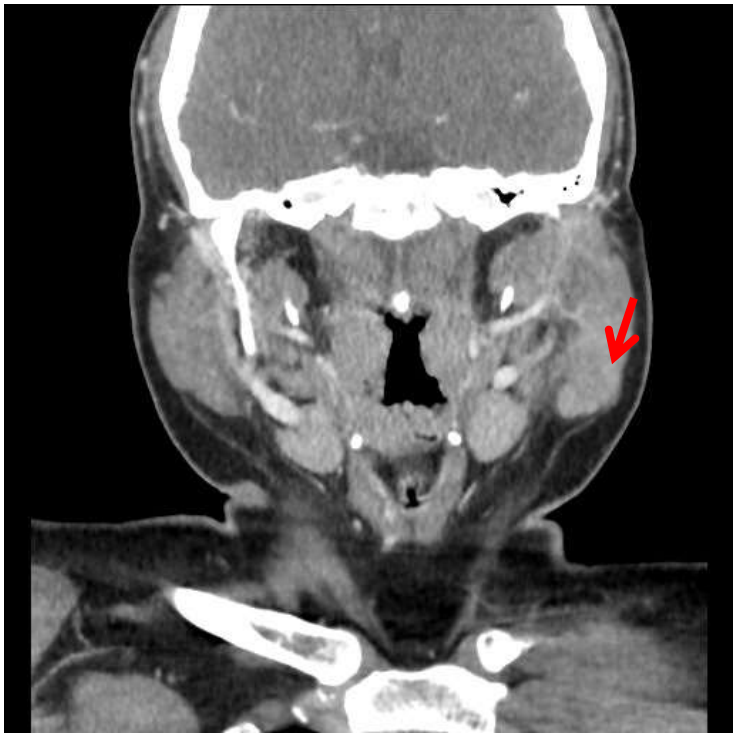
Lucy Han, Josh Menke

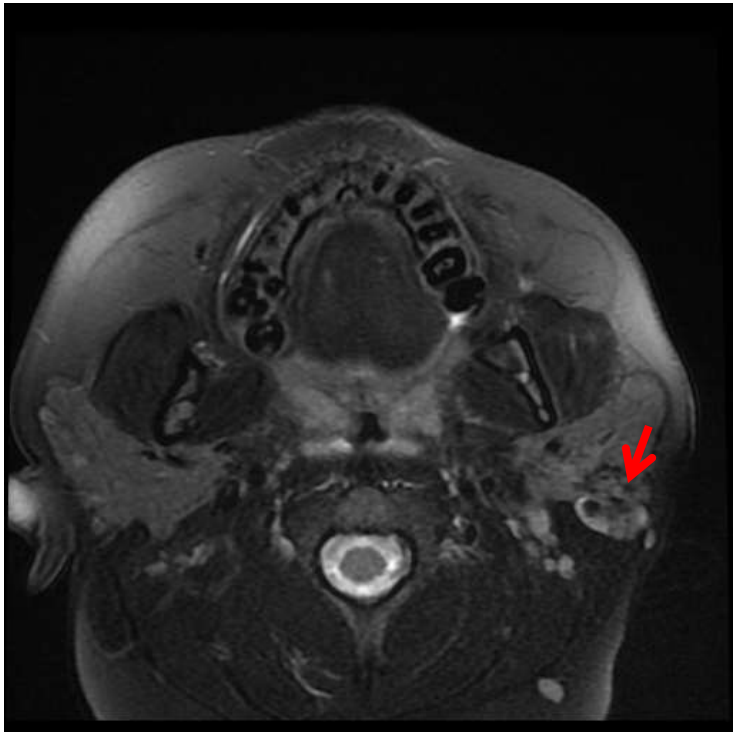
San Francisco General Hospital

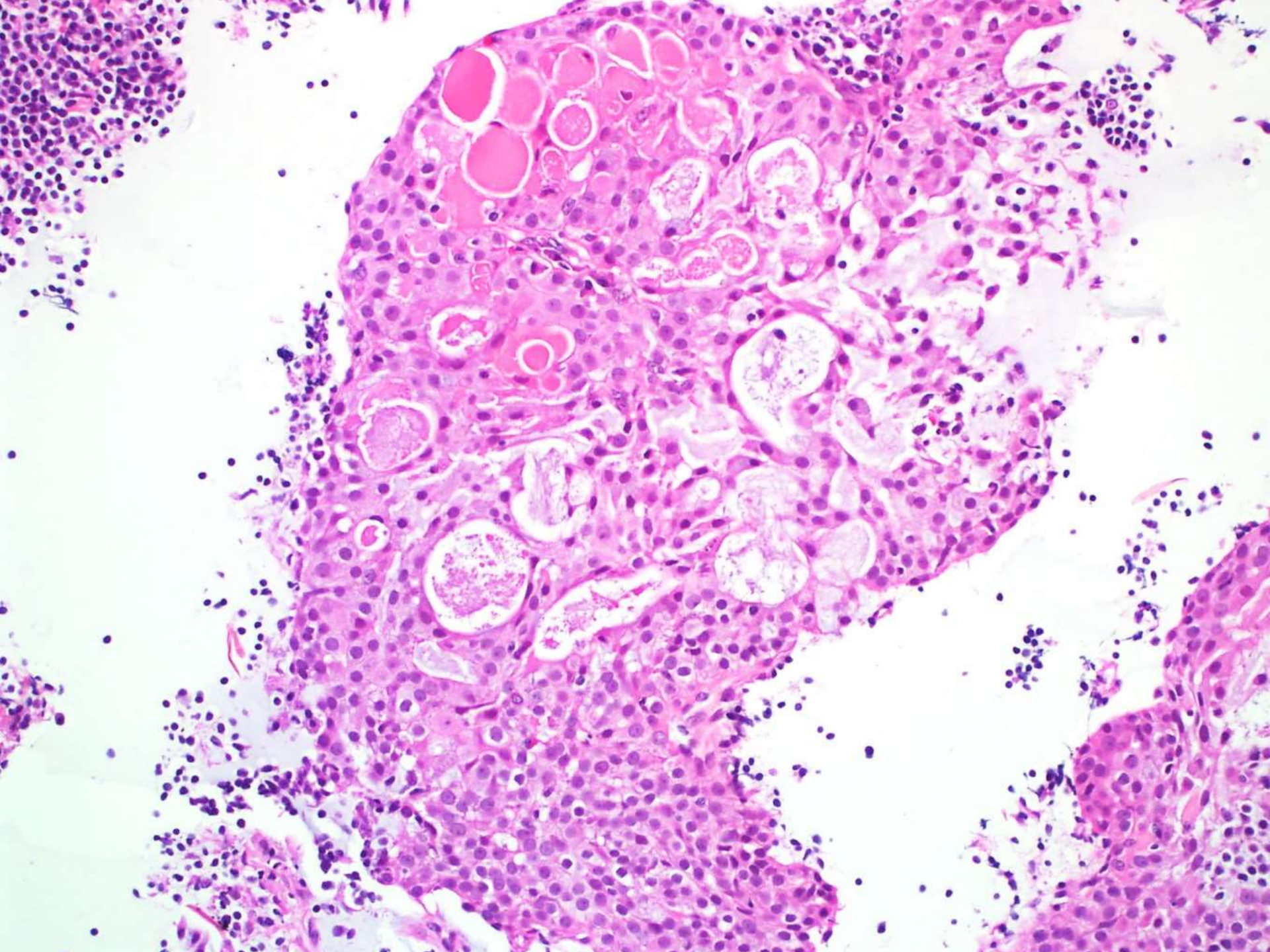
University of California San Francisco

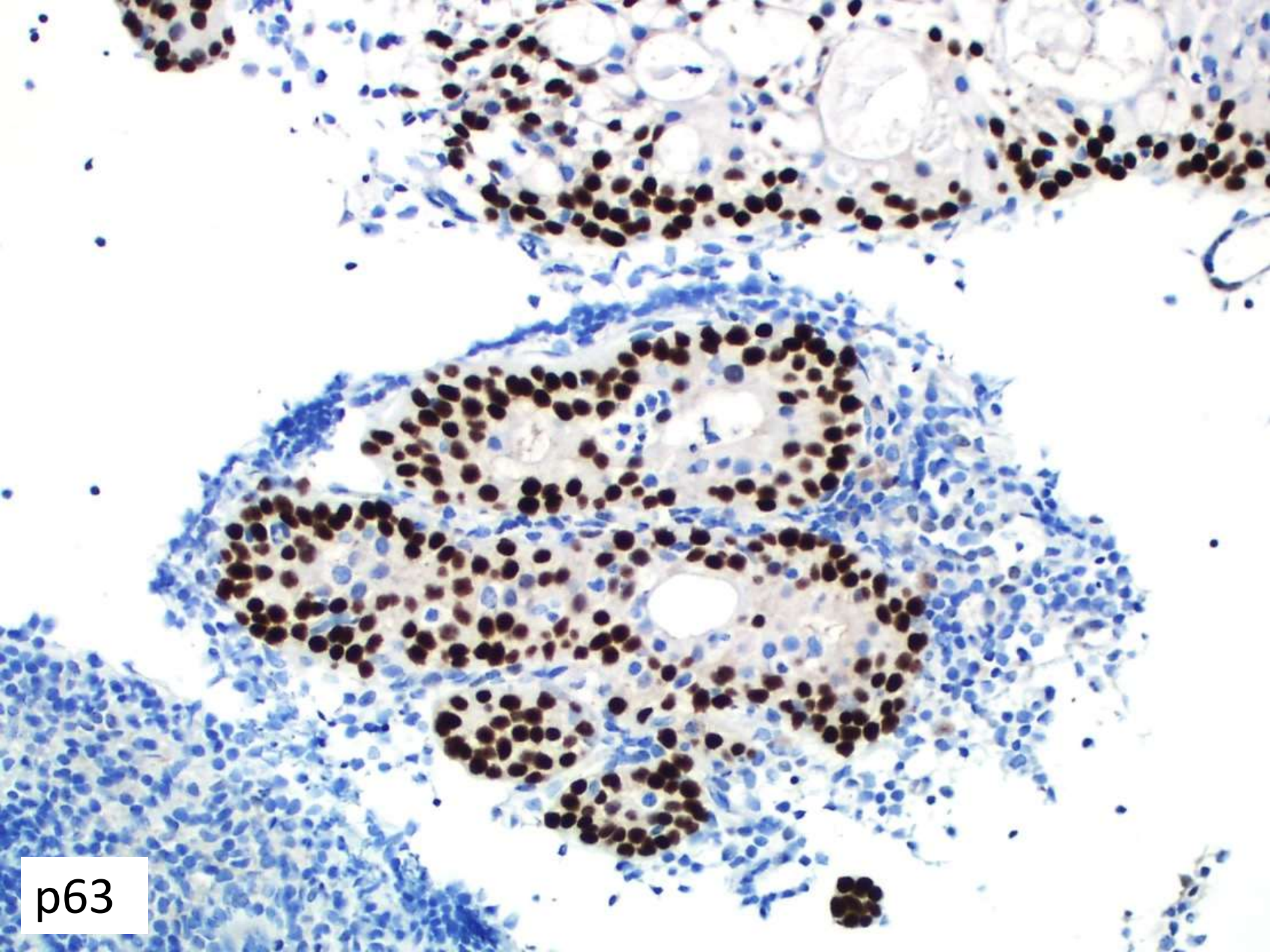
Imaging

- Heterogenous enhancing 2.8 cm mass within the left parotid gland and bilaterally enlarged level II lymph nodes.



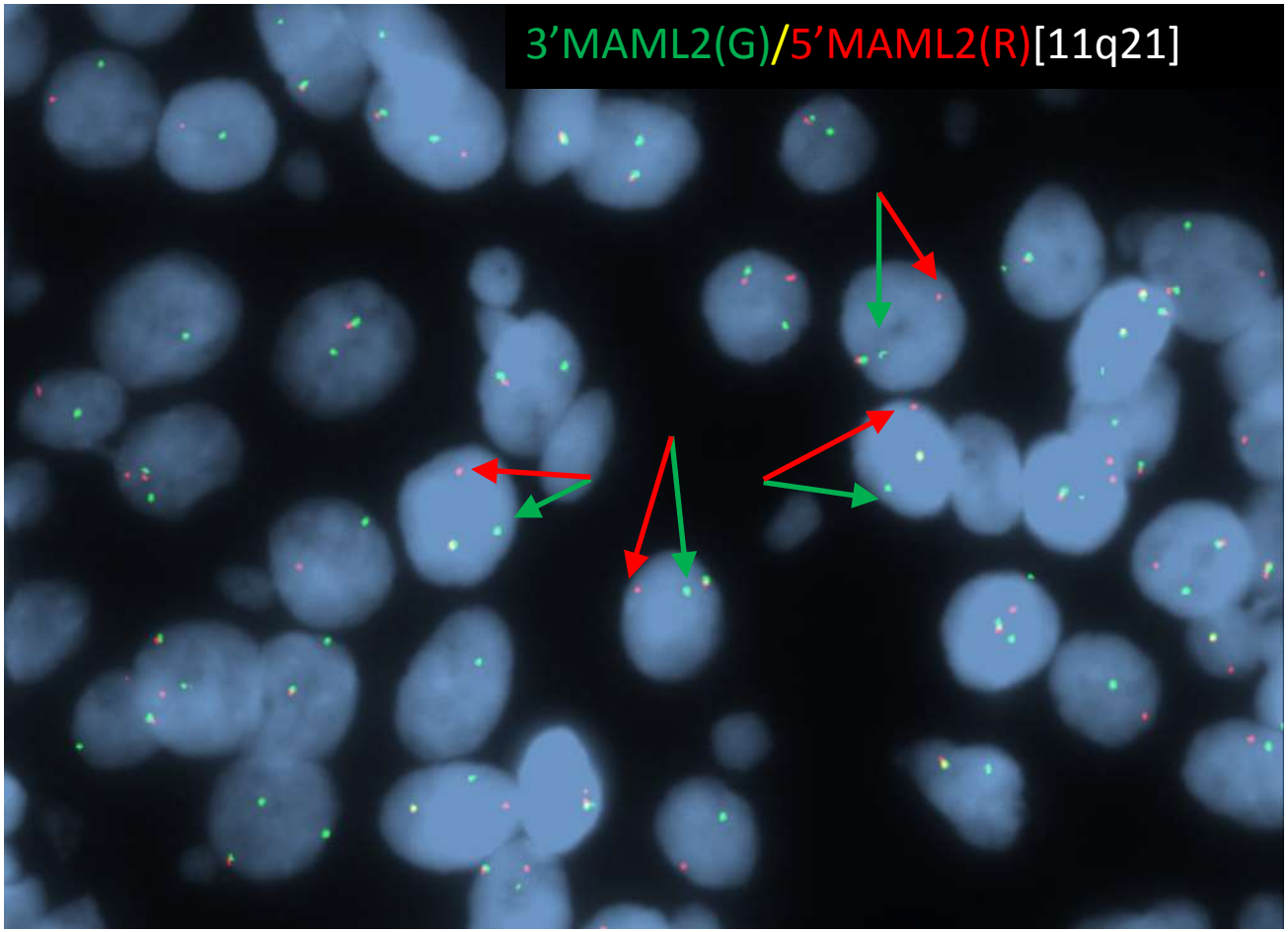


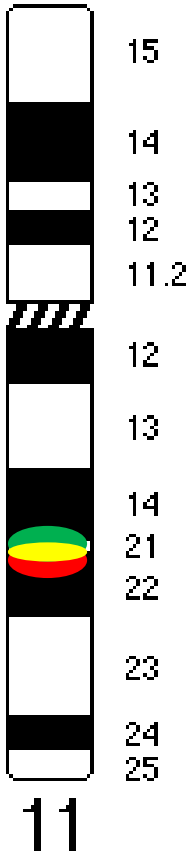



p63

MAML2 FISH Rearrangement

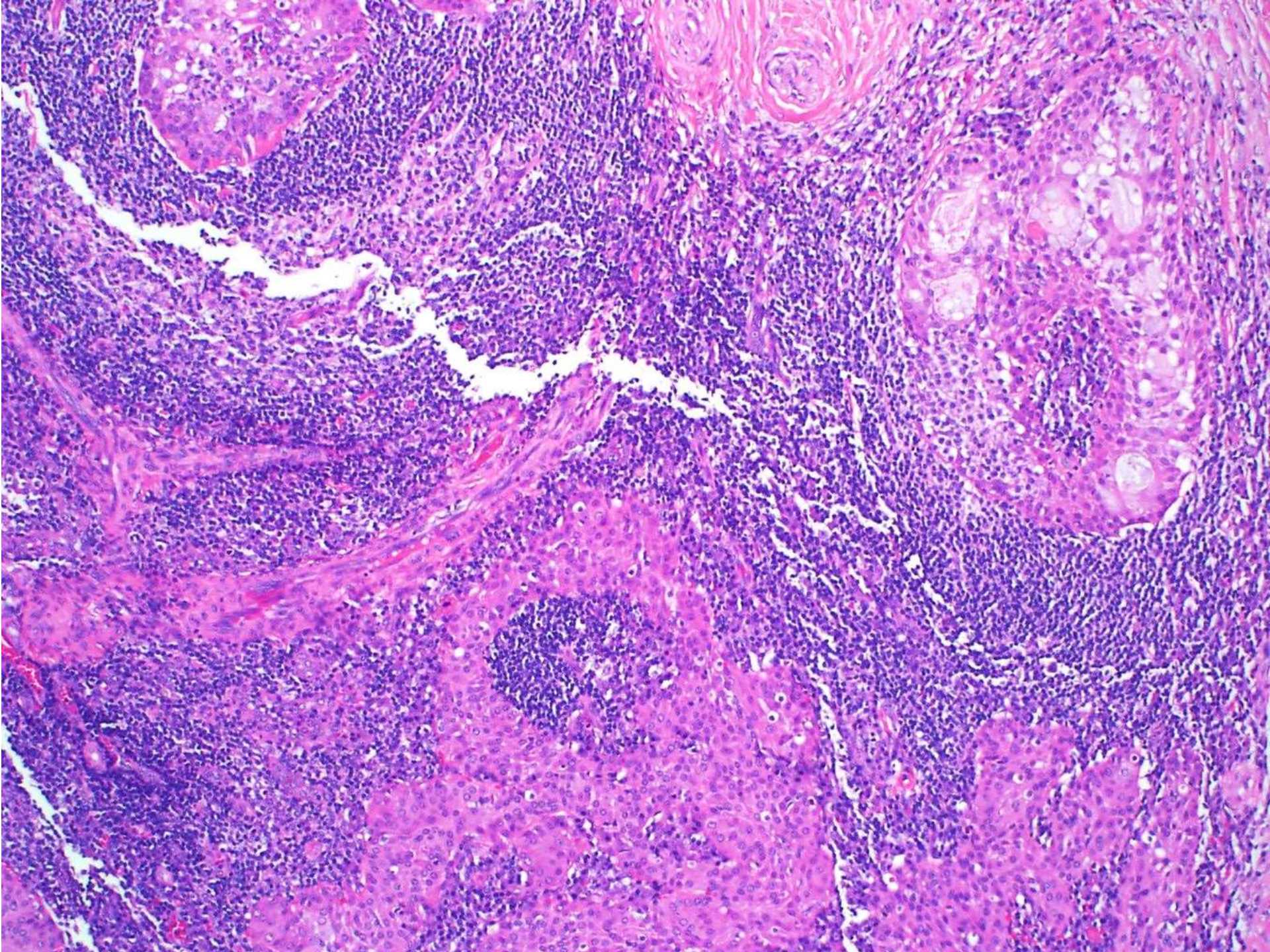
Image demonstrates separation of 3'MAML2 and 5'MAML2 probe signals



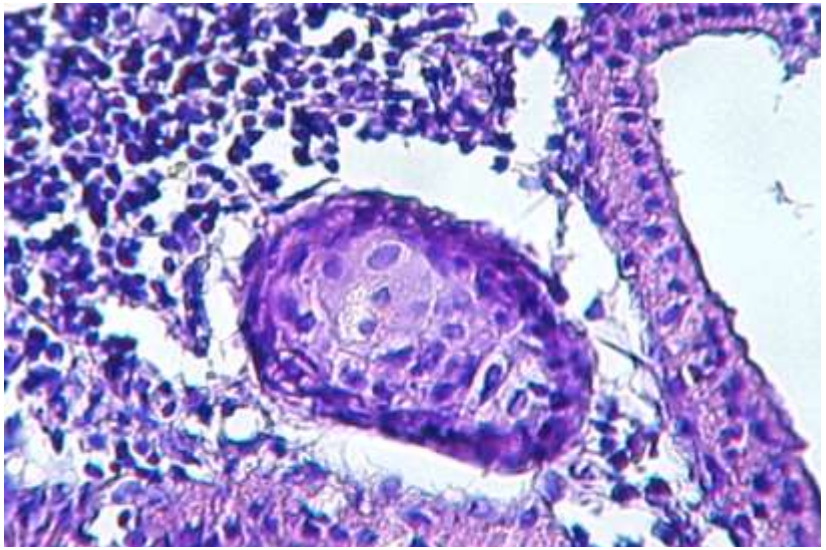


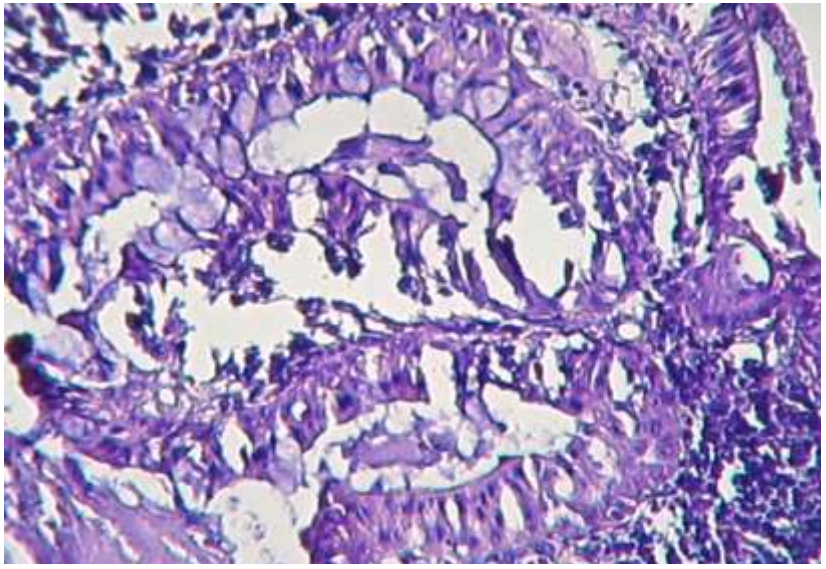
Mayo Clinic Genomics Laboratory c/o Dr. Katherine B. Geiersbach

Final diagnosis:
Oncocytic mucoepidermoid carcinoma with lymphoid stroma (aka Warthin-like mucoepidermoid carcinoma)



Warthin Tumor

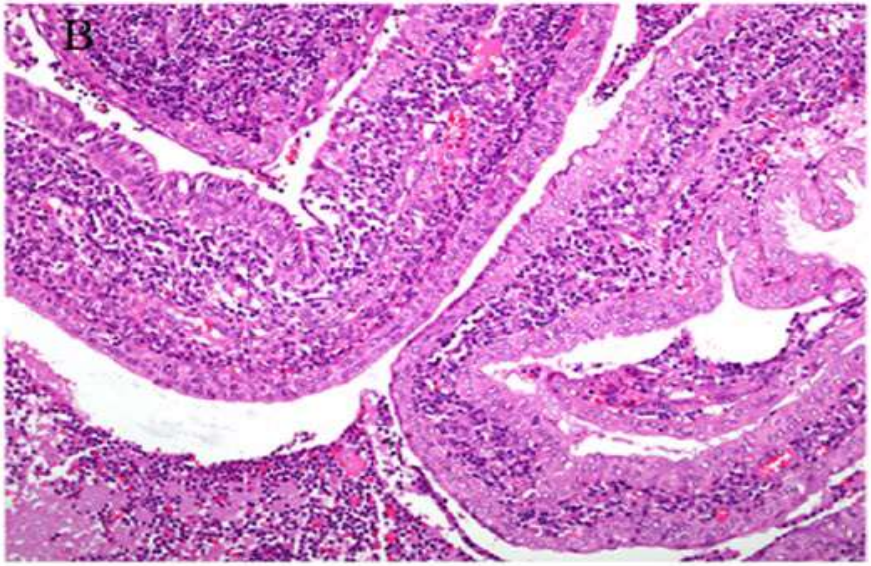


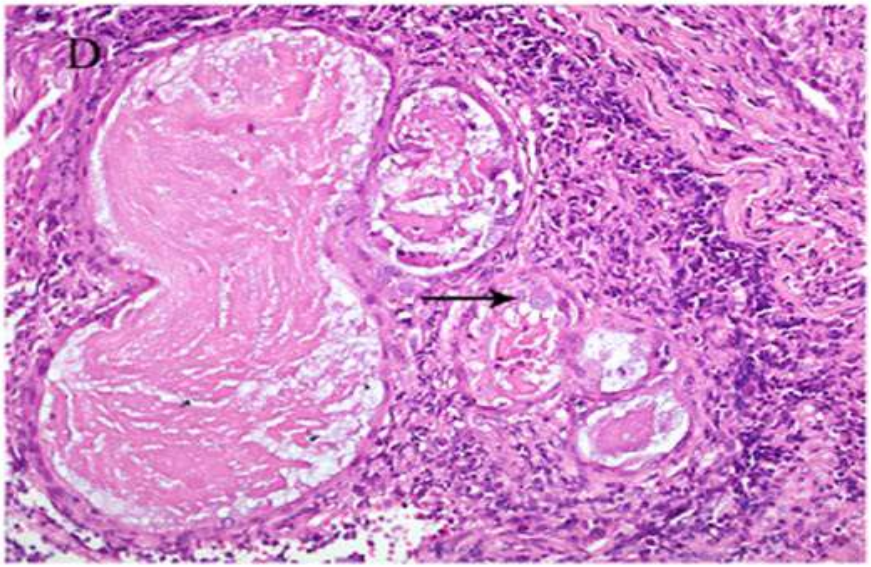


Benign Tumor
Elderly population
Associated with smoking, often bilateral
Unclear associated genetic alteration
Can have squamous and mucinous metaplasia. • Inflammation • Infarction • Following FNA
Conservative treatment or simple resection

Faur A et al. Rom J Morphol Embryol. 2009;50(2):269-73.

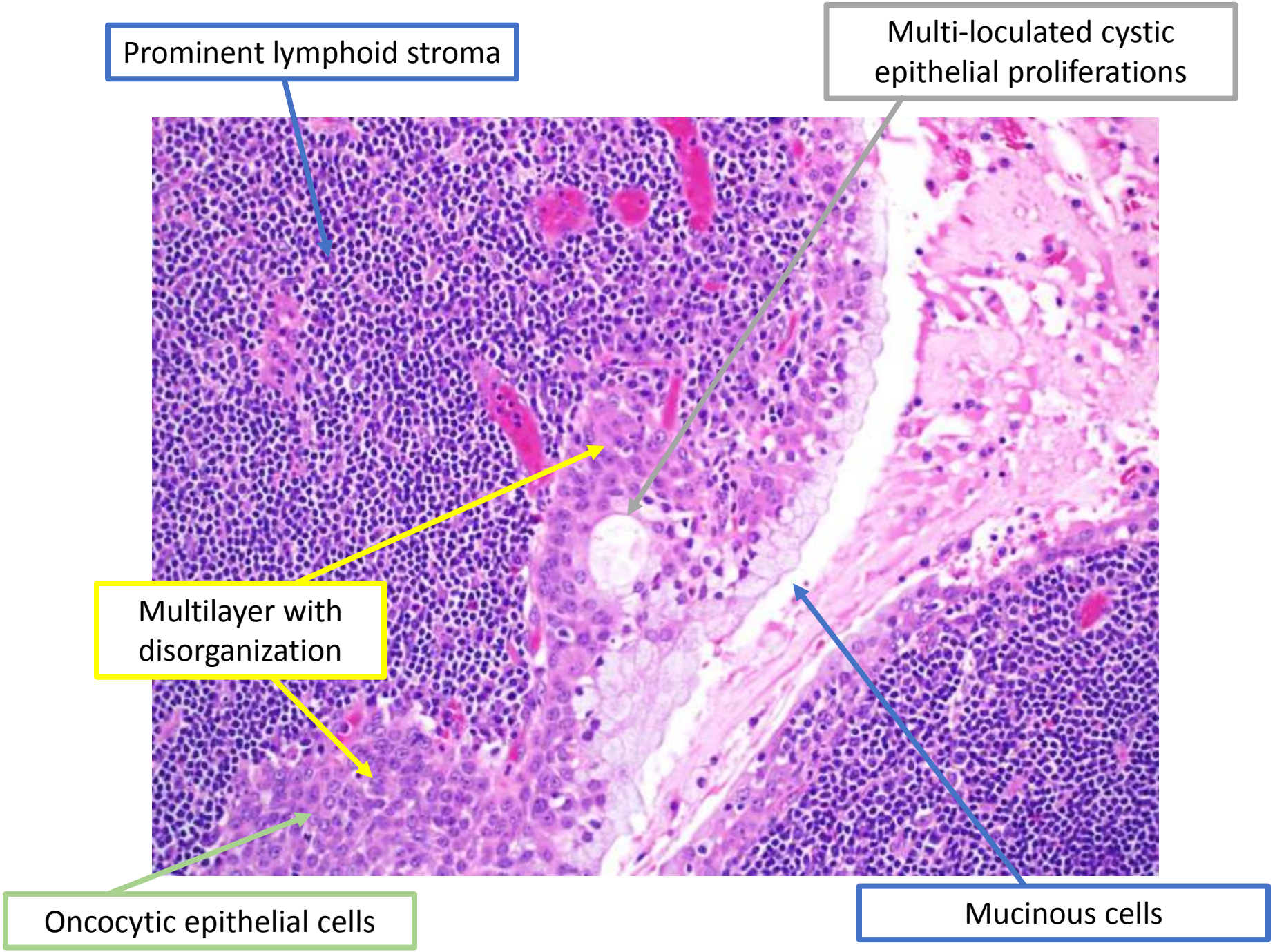
Warthin-like Mucoepidermoid Carcinoma





Malignant Tumor
Wide age range
Wide morphologic spectrum
CRTC1-MAML2 CRTC3-MAML2
Composed of epidermoid, intermediate, and mucous cells. • Oncocytic epithelium • Can be bland • Few mitotic figures
Parotidectomy, possible neck dissection, radiation

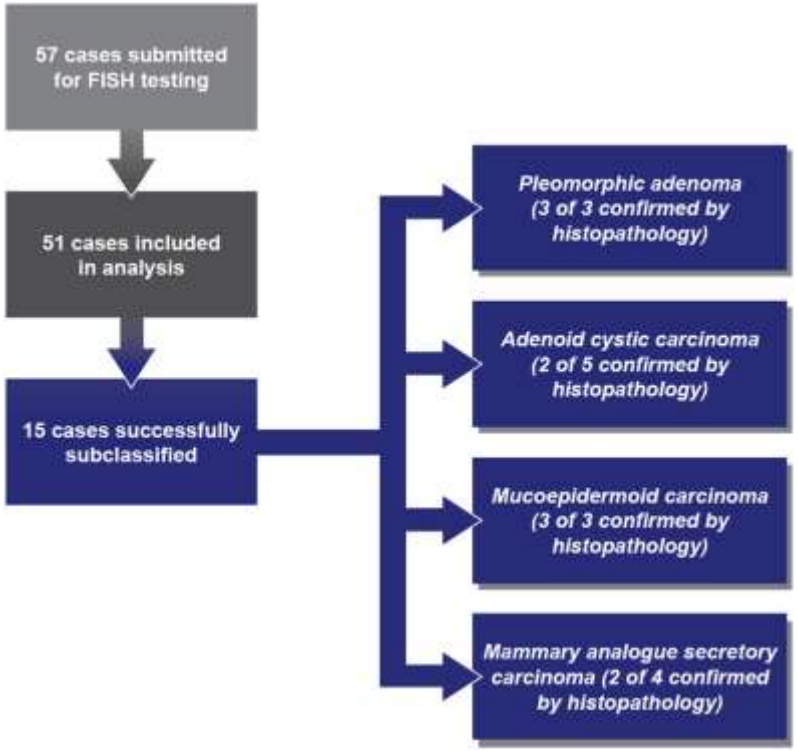
Garcia JJ. Human Pathology. 2011;42:2001-2009.

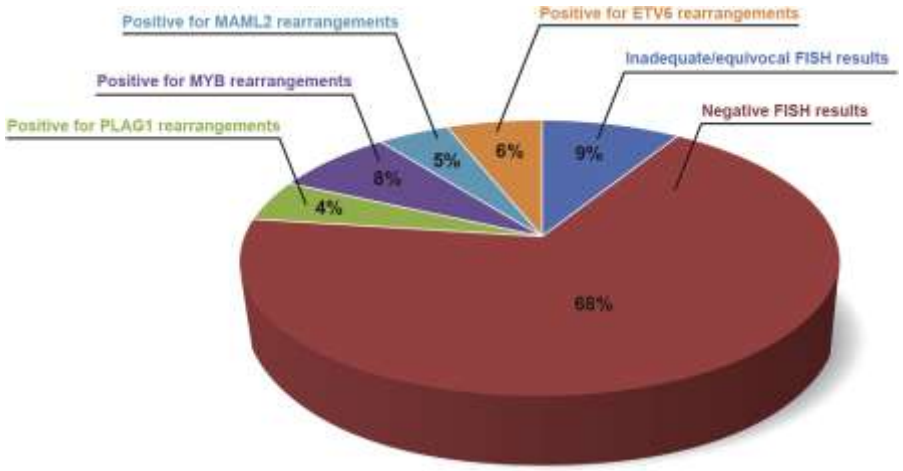

Prominent lymphoid stroma
Multi-loculated cystic epithelial proliferations
Multilayer with disorganization
Oncocytic epithelial cells
Mucinous cells

Indications for *MAML2* FISH

- Warthin's-like tumor in a young patient.
- Mucinous differentiation
- Areas deviating from the bilayered appearance of a classic Warthin's tumor or oncocytic cystadenoma
- Absence of prior fine-needle aspiration biopsy or trauma (which can induce squamous or mucinous metaplasia)

Diagnostic utility of FISH on salivary gland FNA cell block





Darras et al. Journal of the American Society of Cytopathology. 2019;8:157e164

Take Home Points

- Mucoepidermoid carcinoma can show marked morphologic and immunophenotypic overlap with Warthin's tumor
- *MAML2* rearrangement is diagnostic of mucoepidermoid carcinoma and can be performed on cytology cell blocks
- Cytology specimens are rich sources of neoplastic tissue for various molecular tests

References

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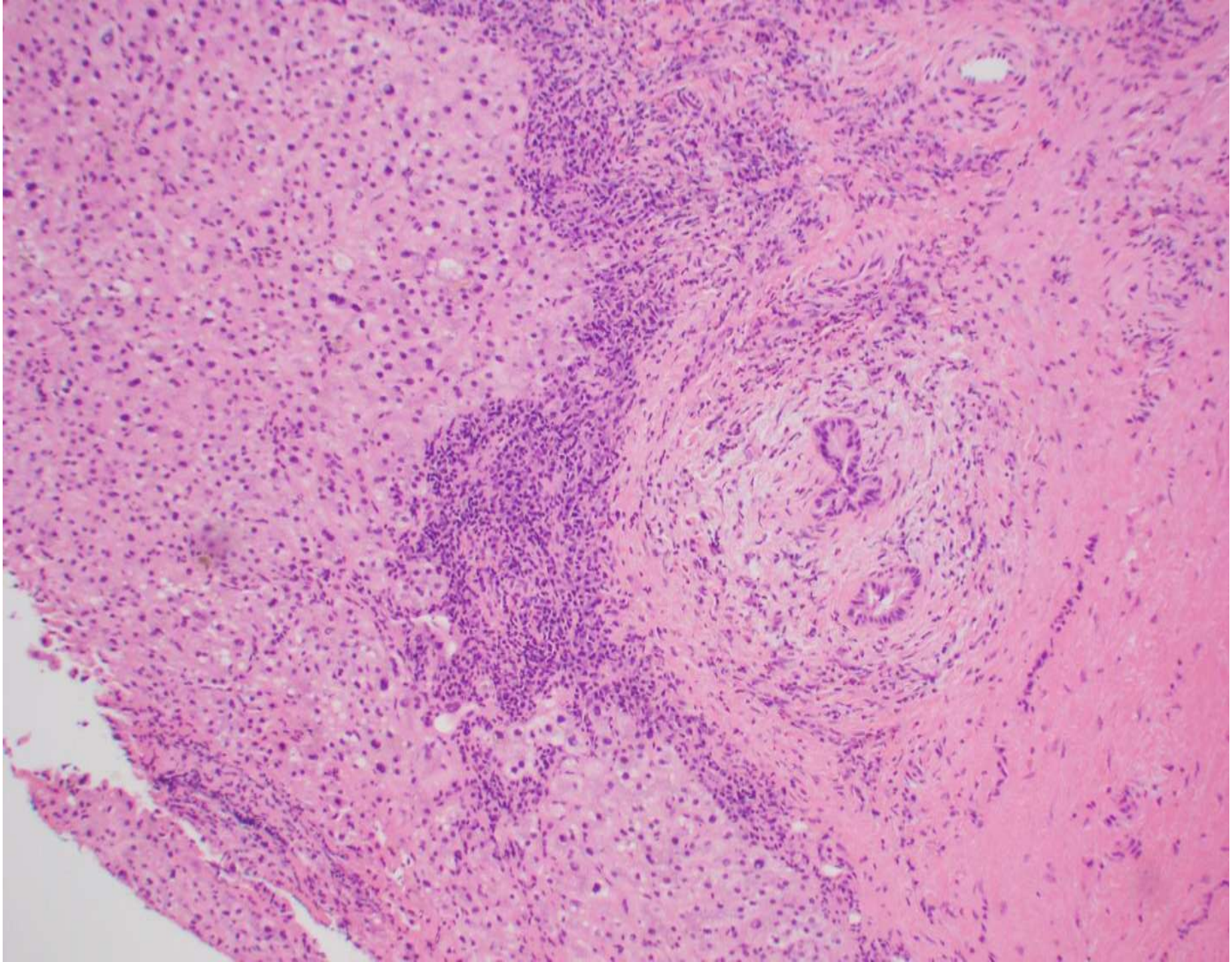
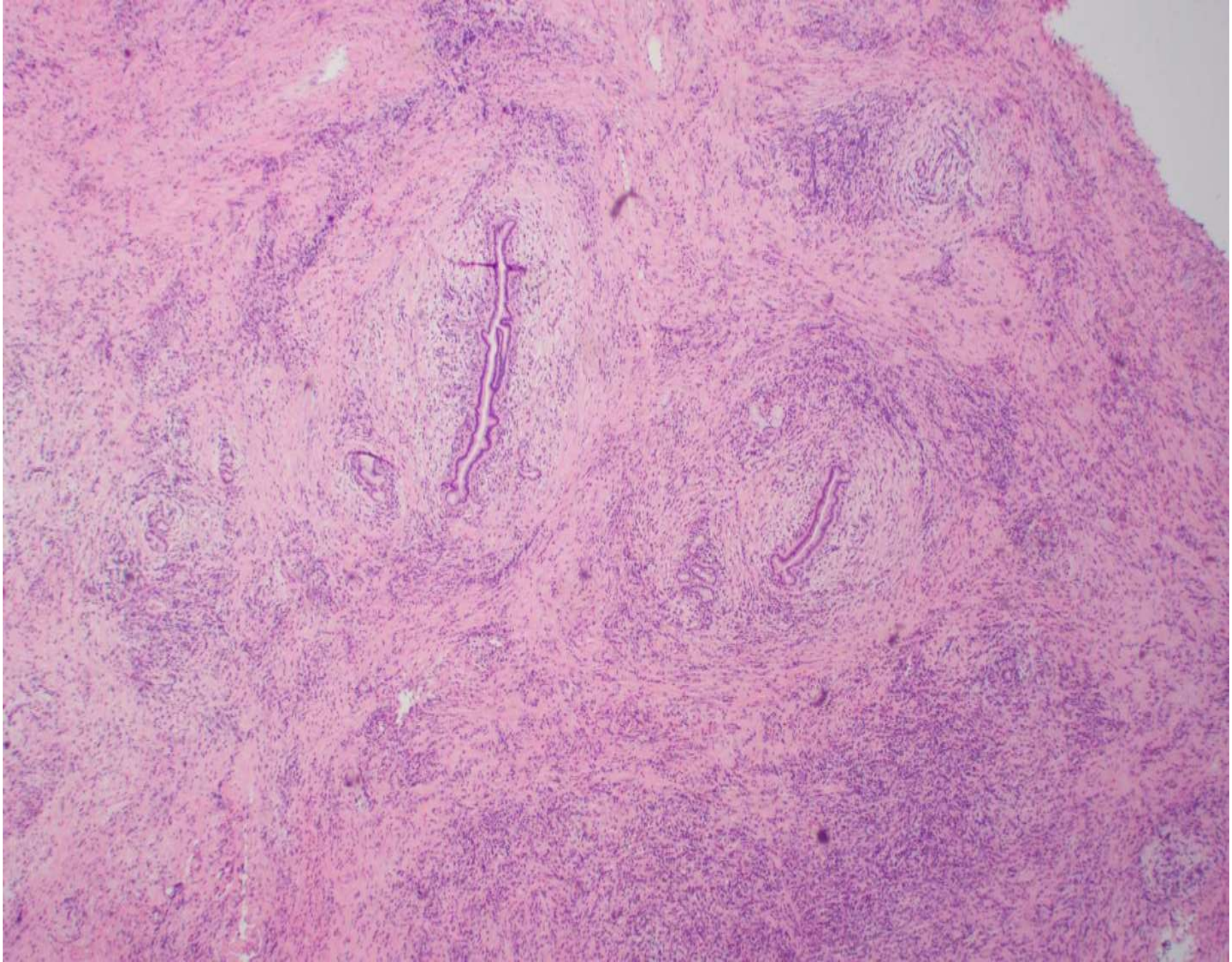
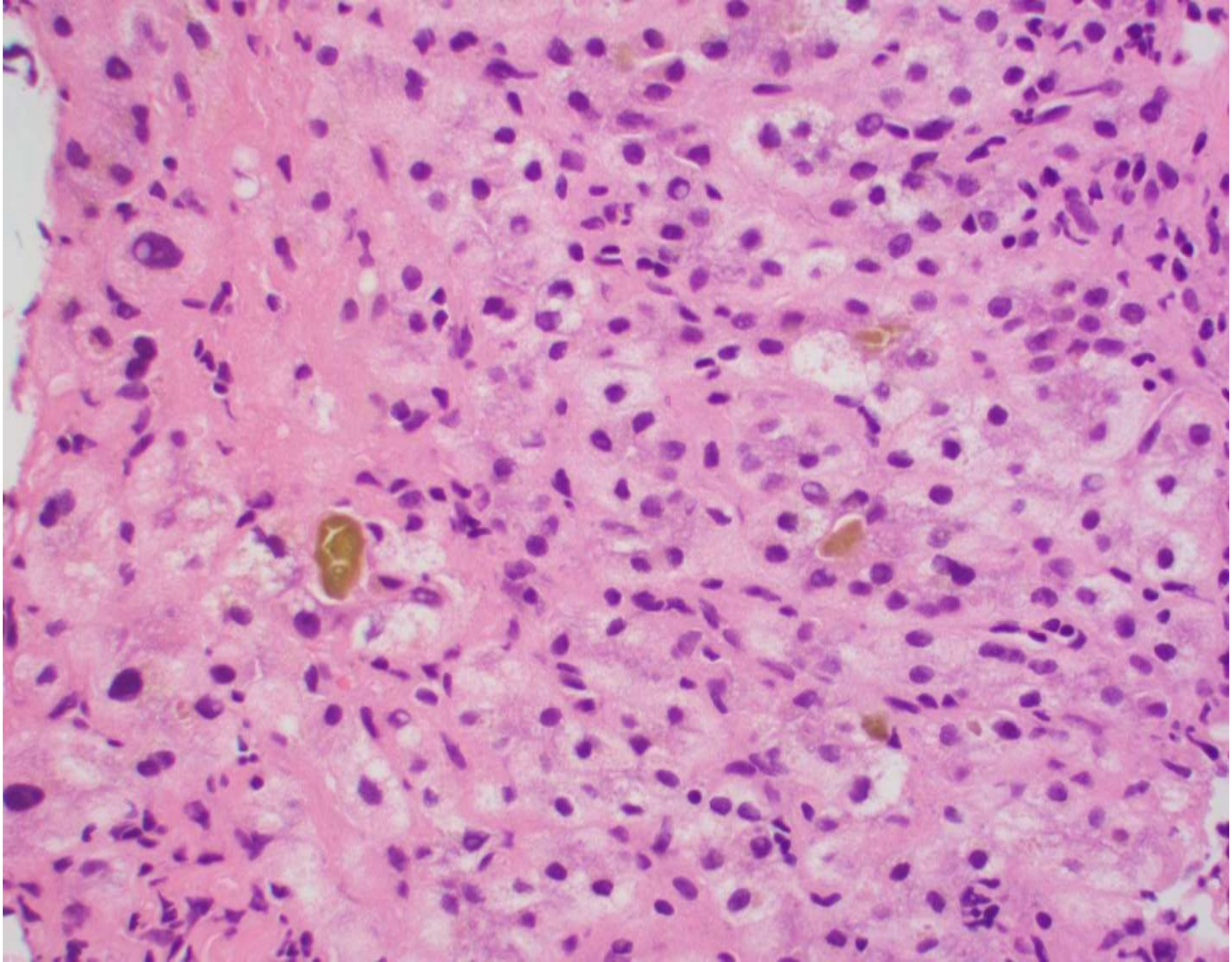
19-1209

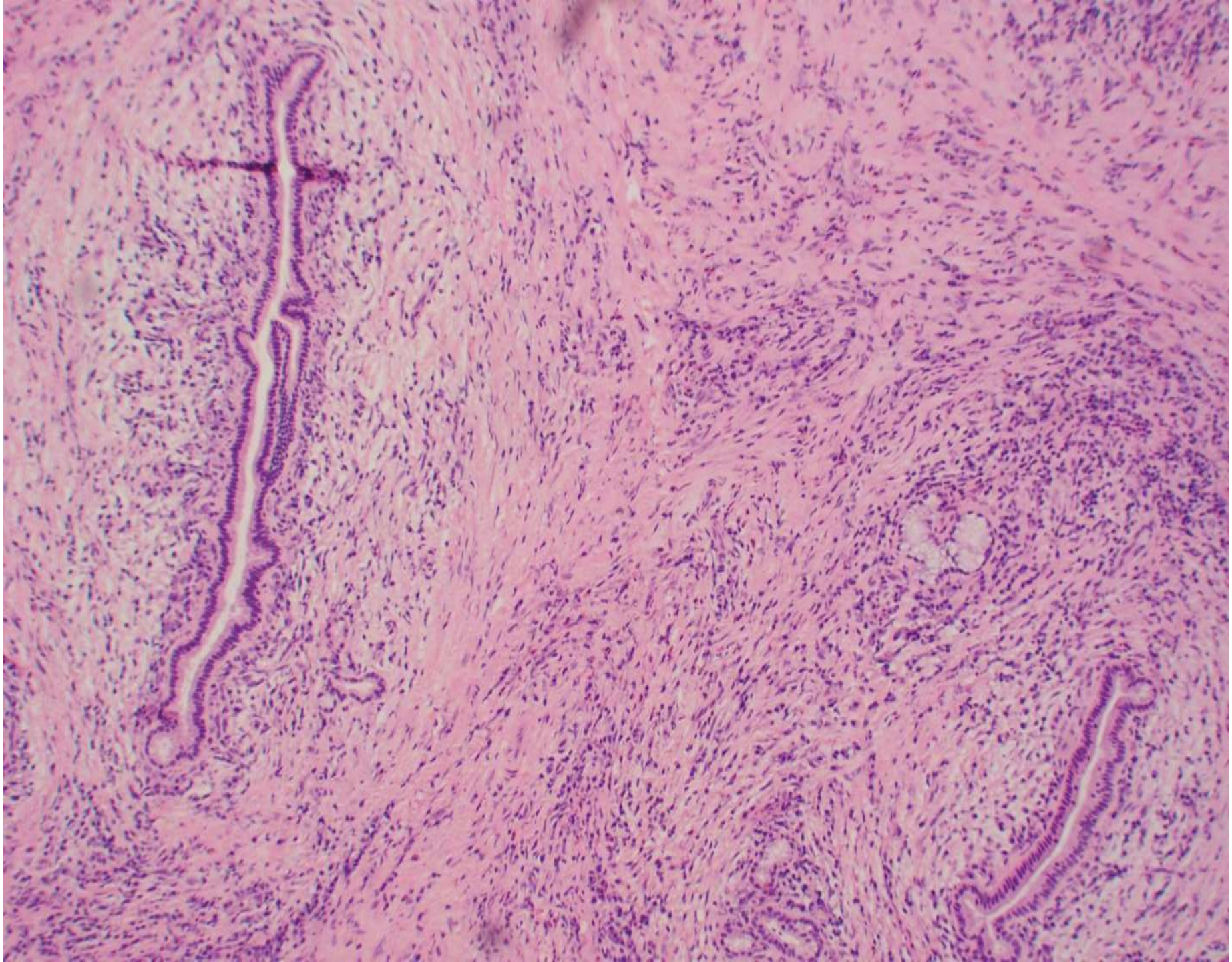
Sava Grujic; Kaiser San Jose

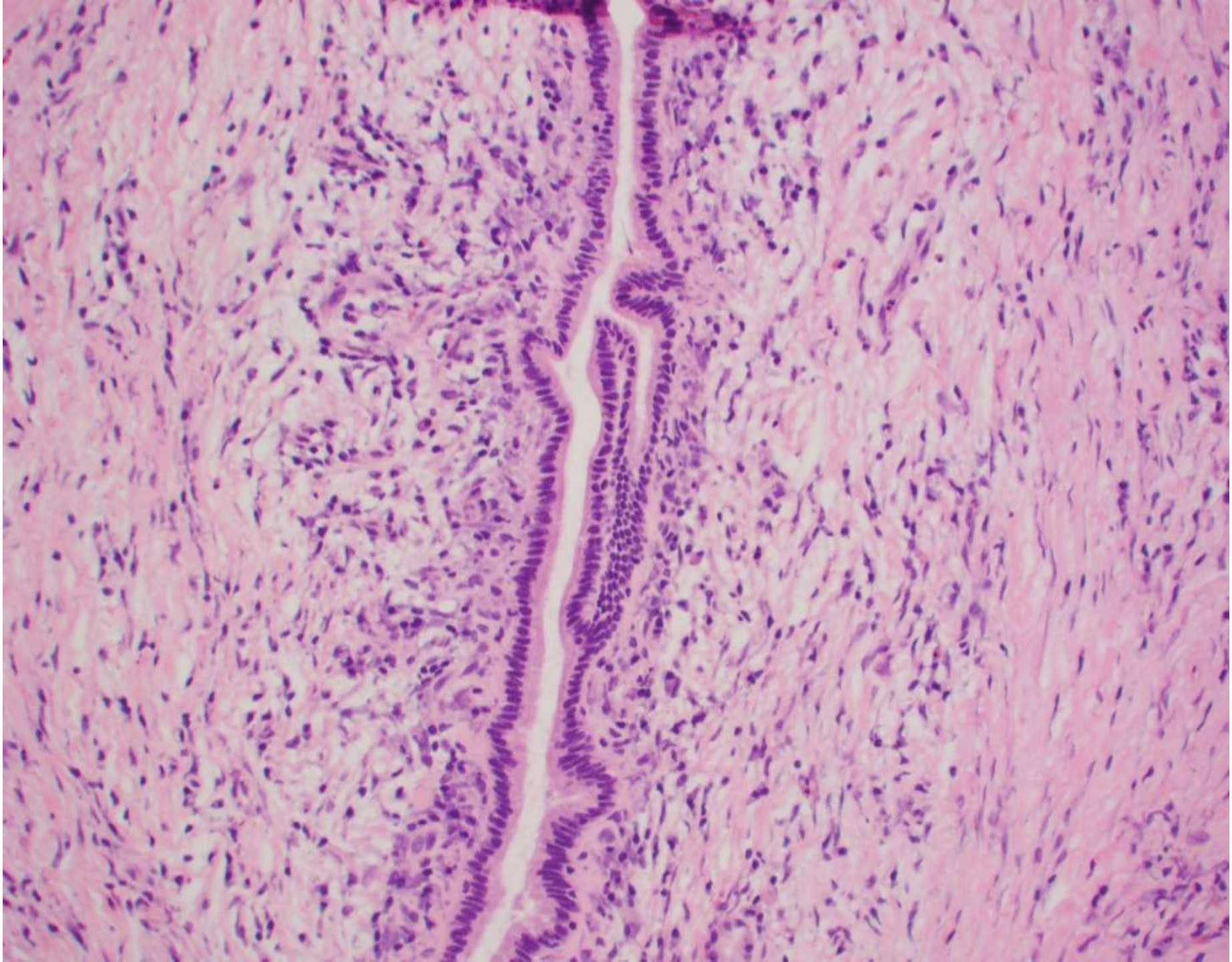
60-year-old male presented with obstructive jaundice. CT demonstrated pancreatic head mass. FNA of pancreatic mass was interpreted as atypical/suspicious for malignancy. During Whipple procedure, suspicious liver lesion was sent for frozen to exclude malignancy.

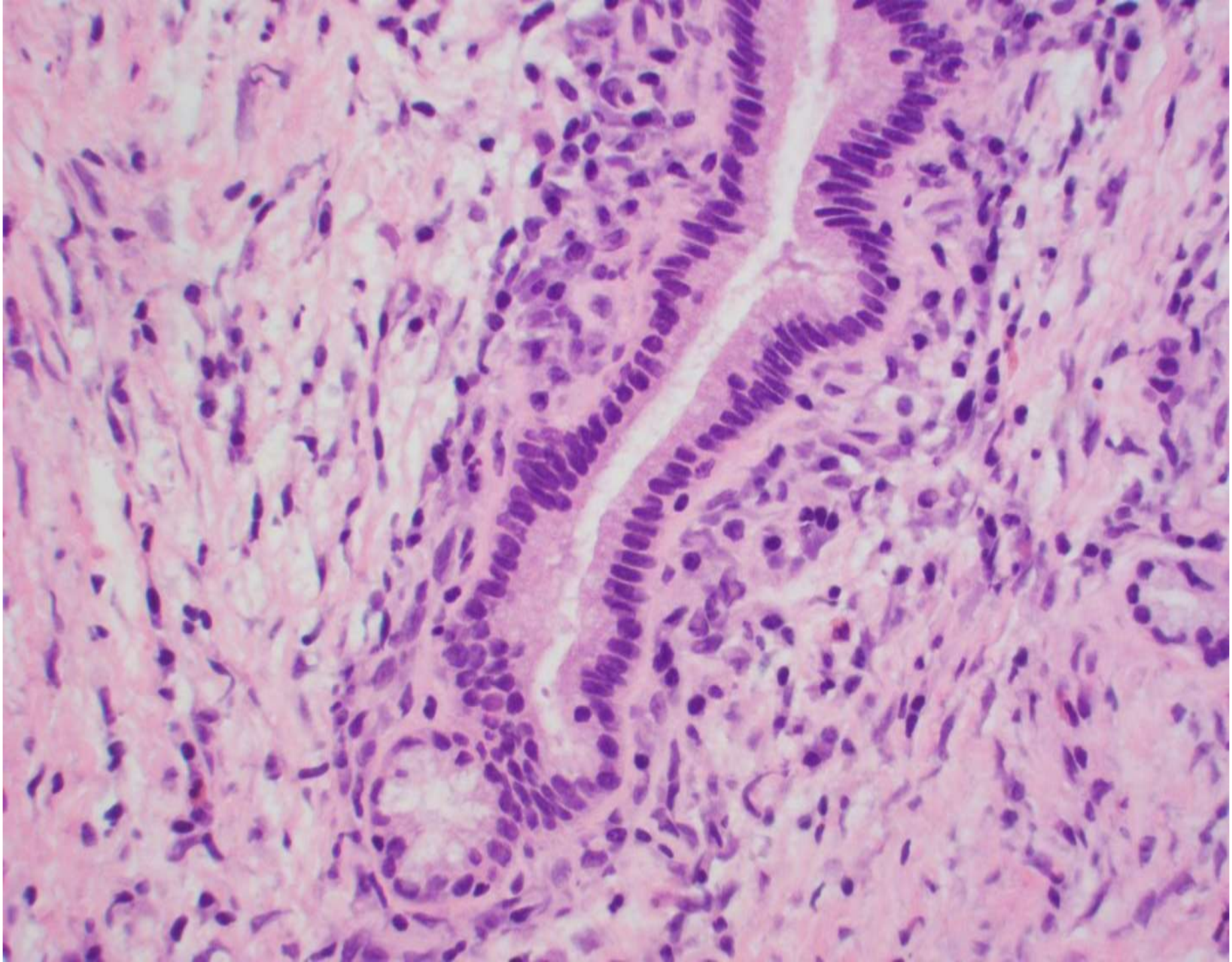












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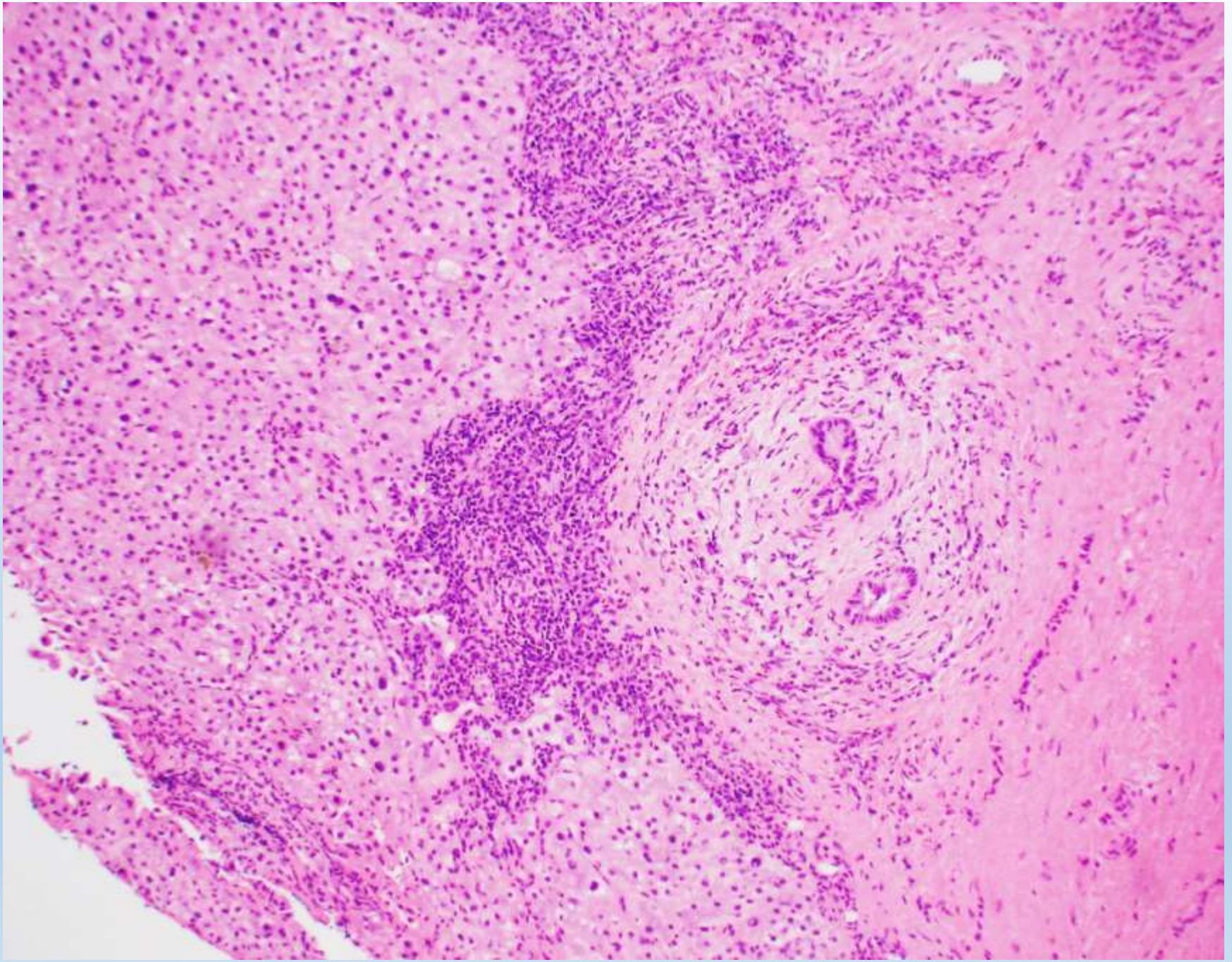
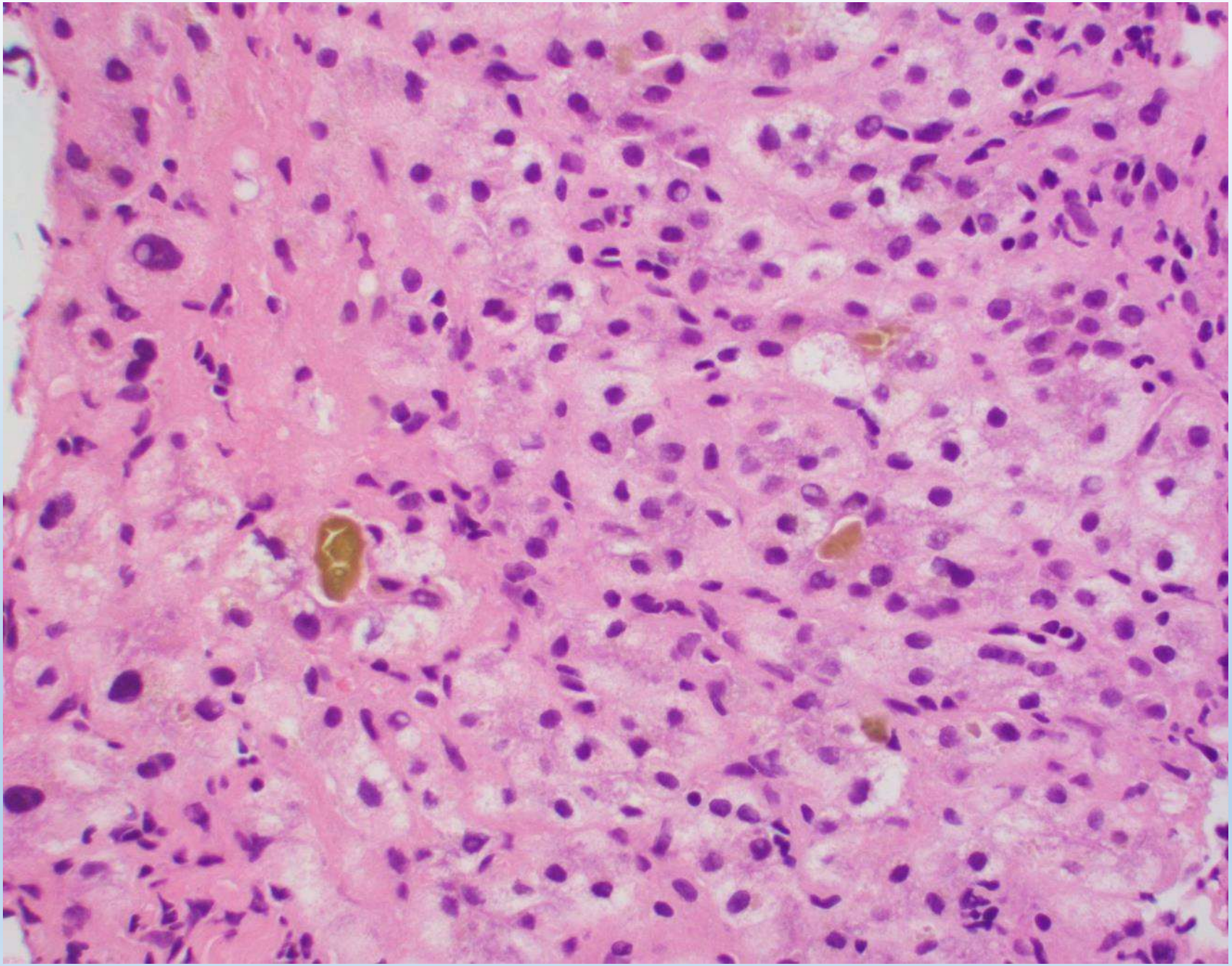
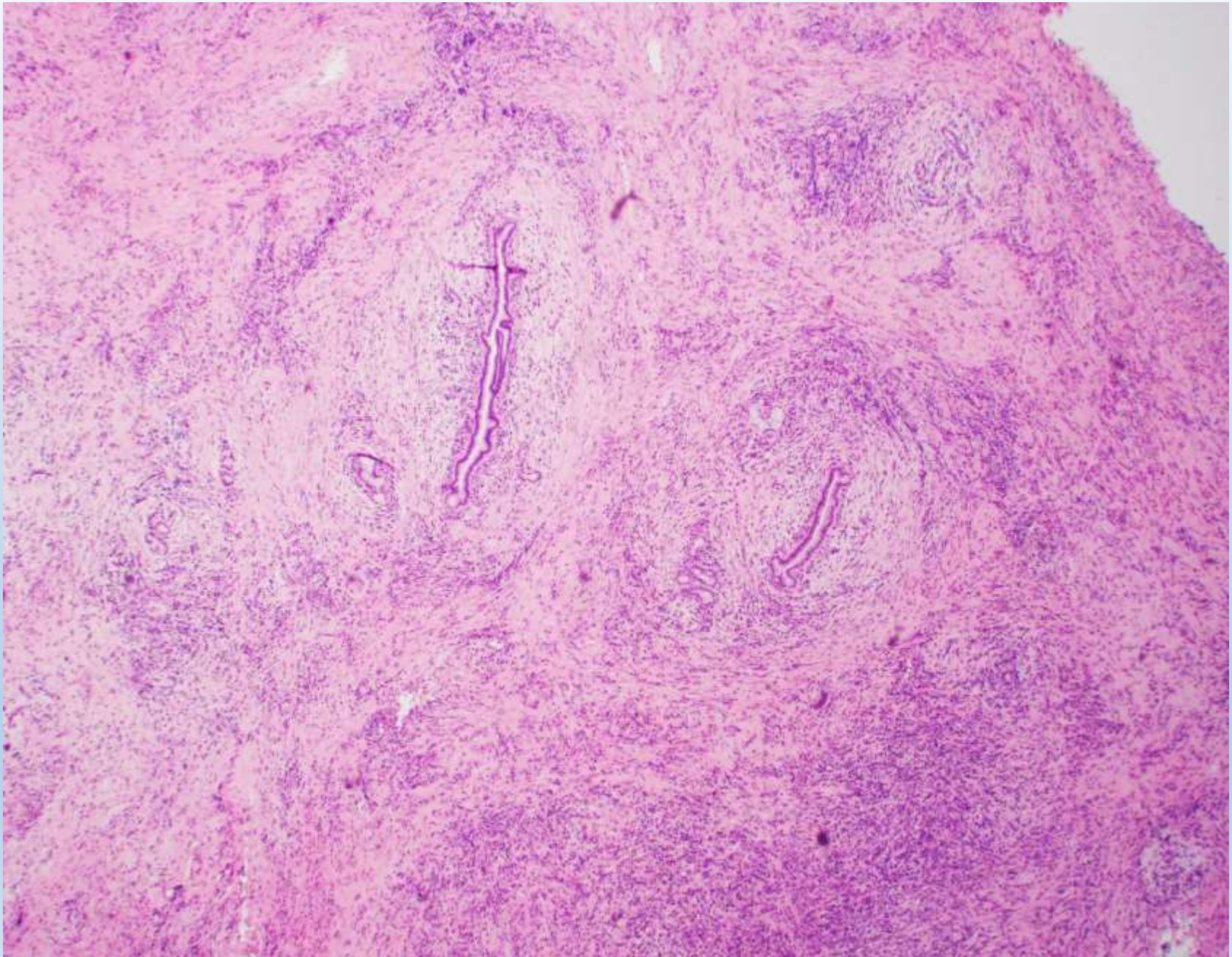
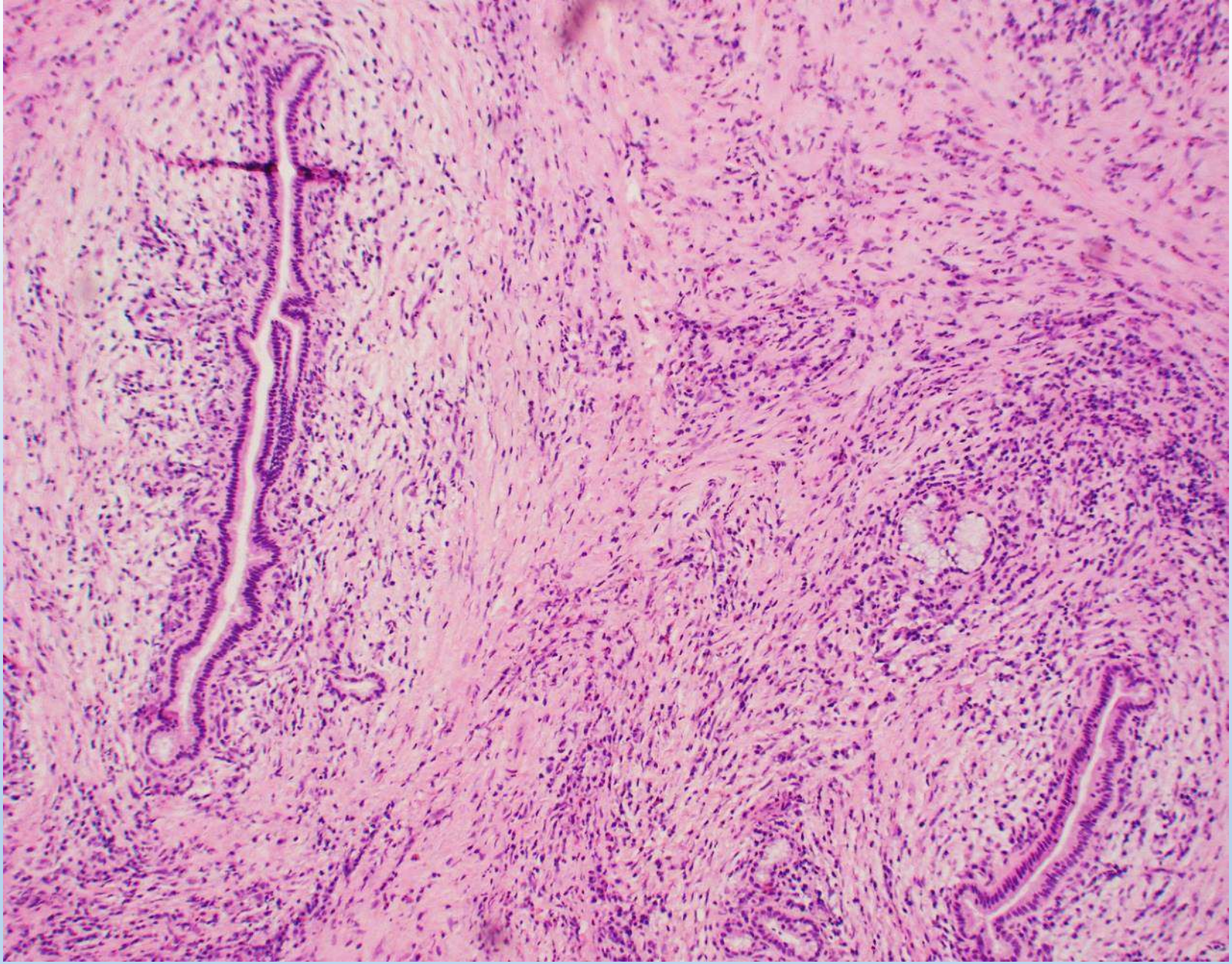
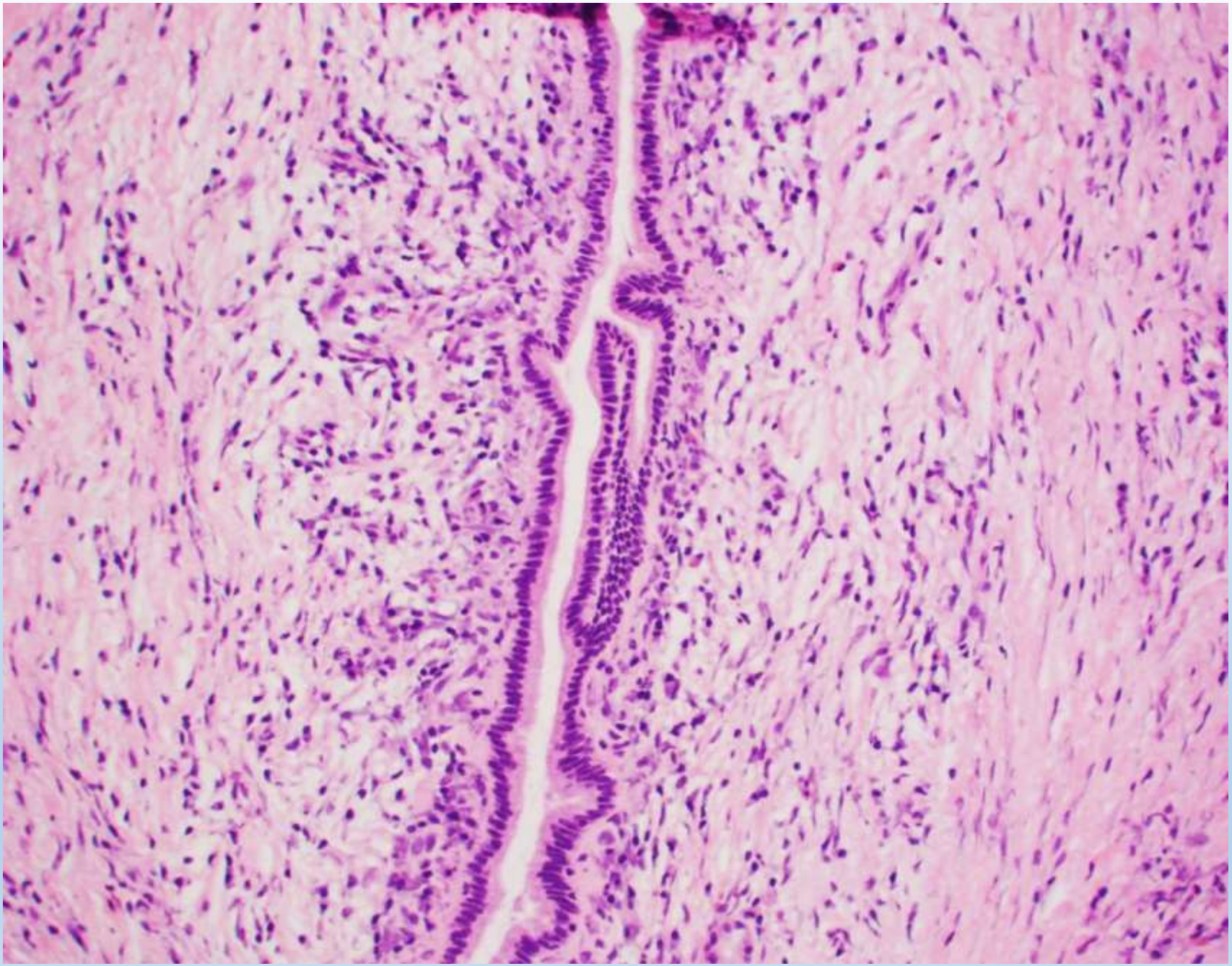
Sava Grujic, MD Kaiser San Jose

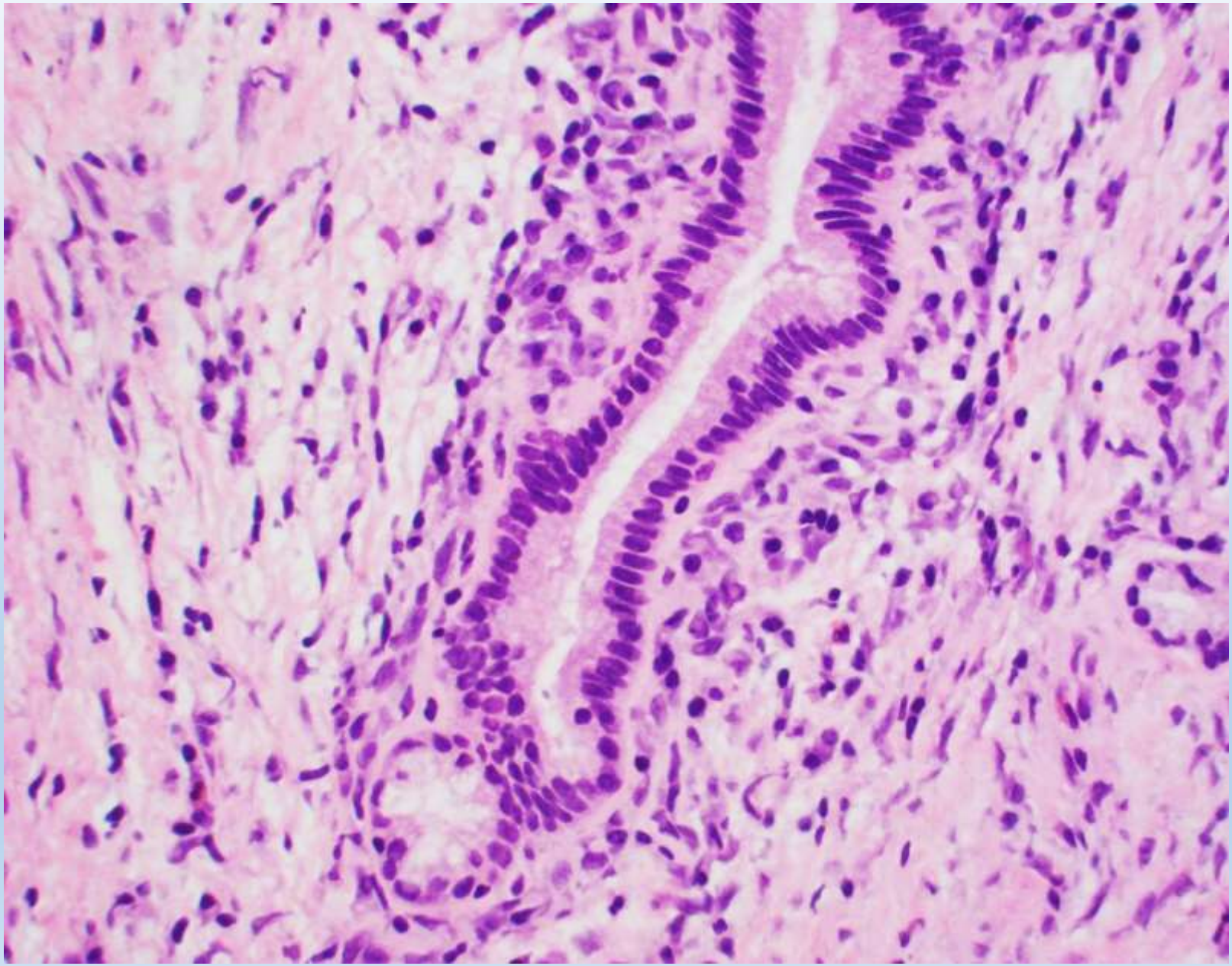




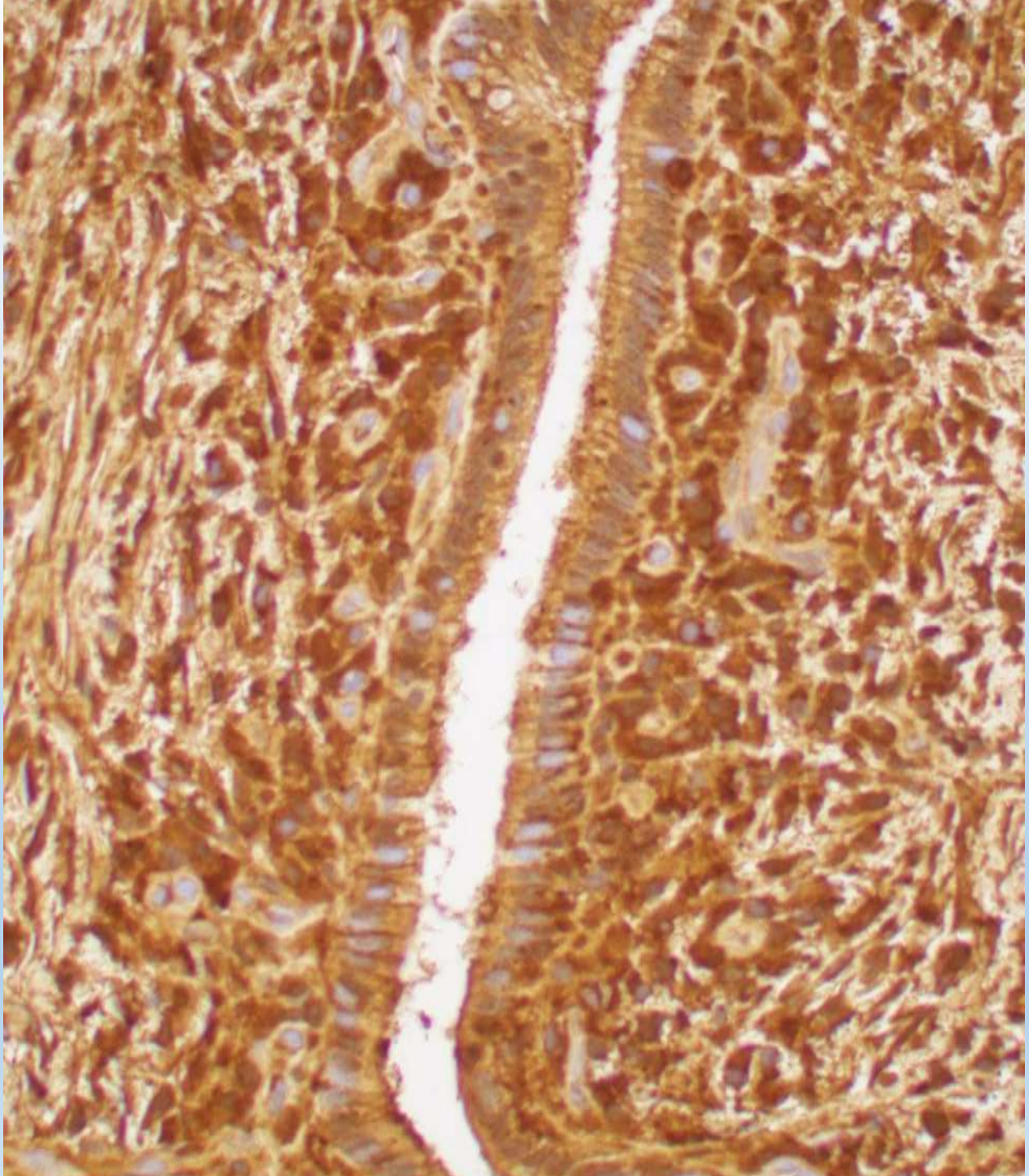




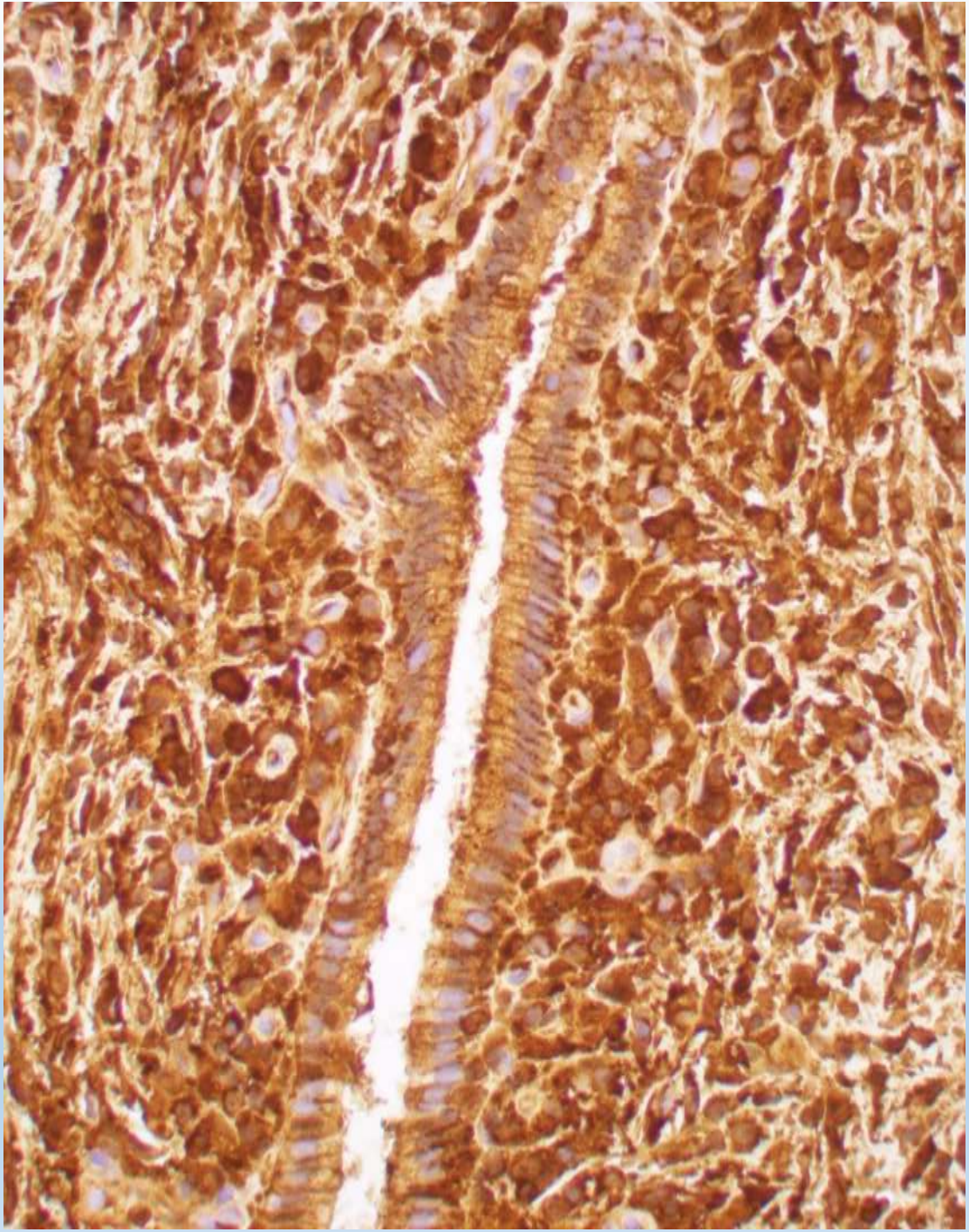




IgG



IgG4



Dx: IgG4 Related Sclerosing Cholangitis
Cholestasis with ductular reaction c/w large bile duct obstruction

Results

Result Information

Flag: **Abnormal** Status: Final result (Collected: 2/25/2019 08:58)

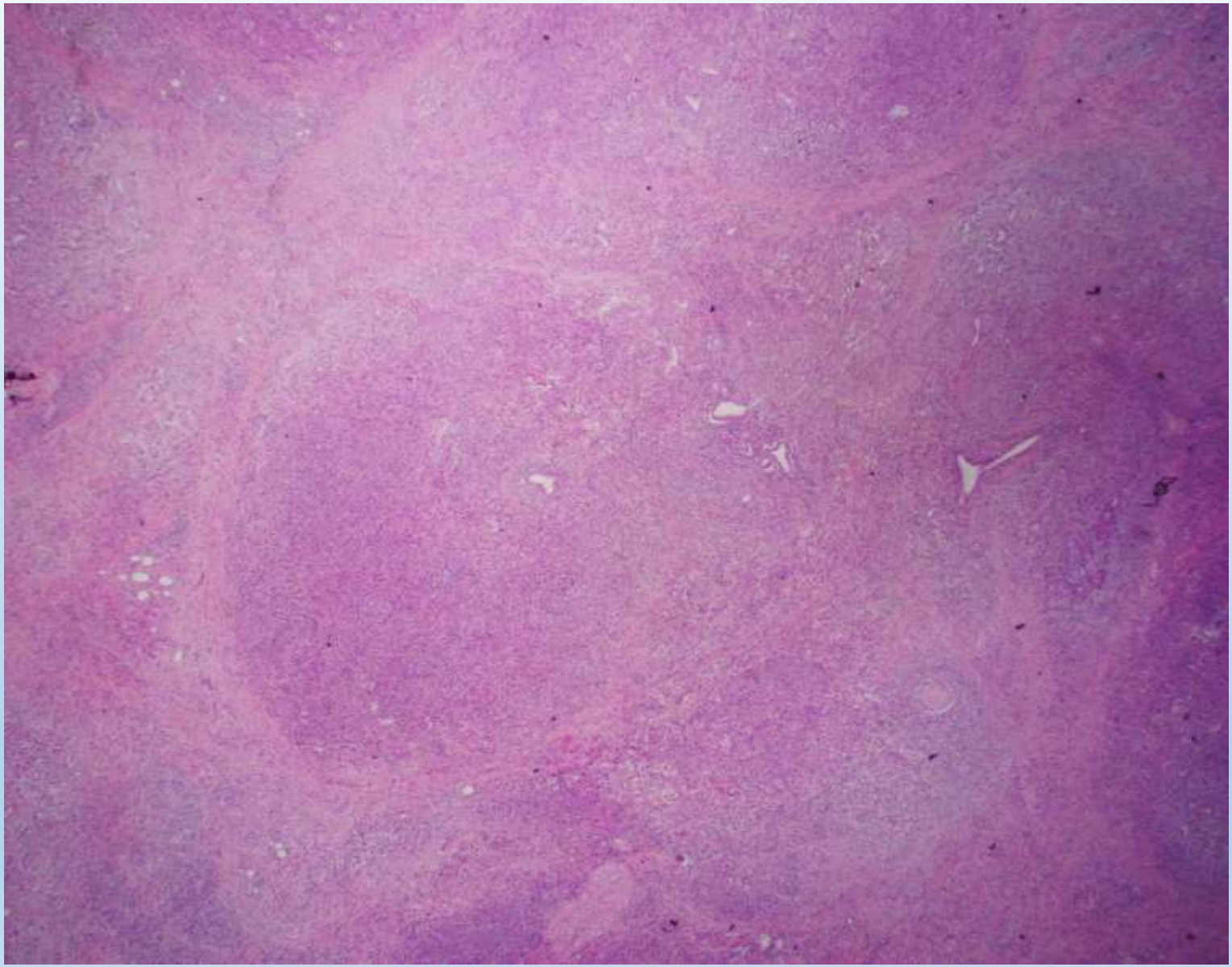
IGG SUBCLASS PANEL (SUBCLASSES 1,2,3,4)

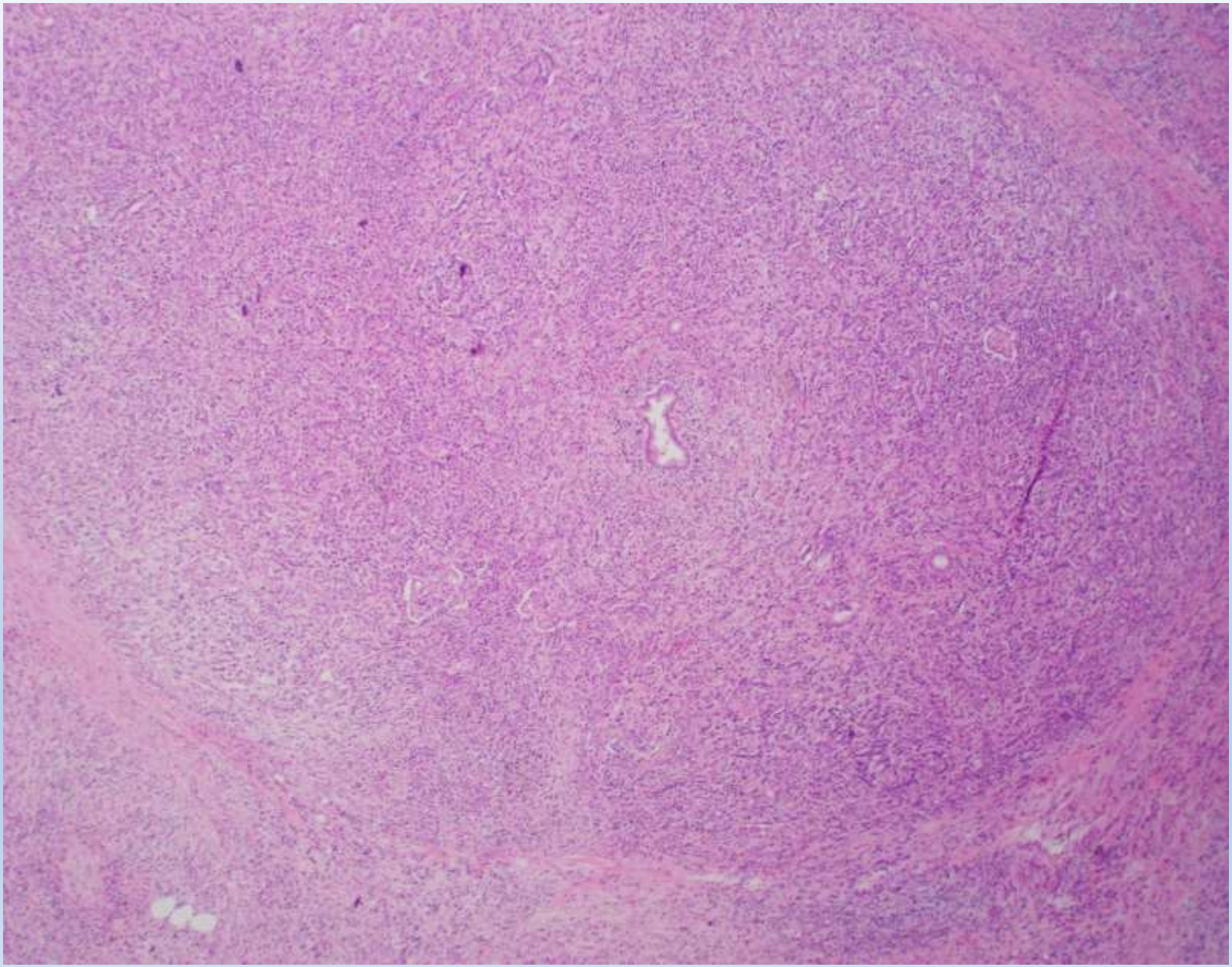
Status: **Final result** Visible to patient: **Yes (kp.org)** Next appt: **11/14/2019 at 09:15 AM in Ophthalmology (T**

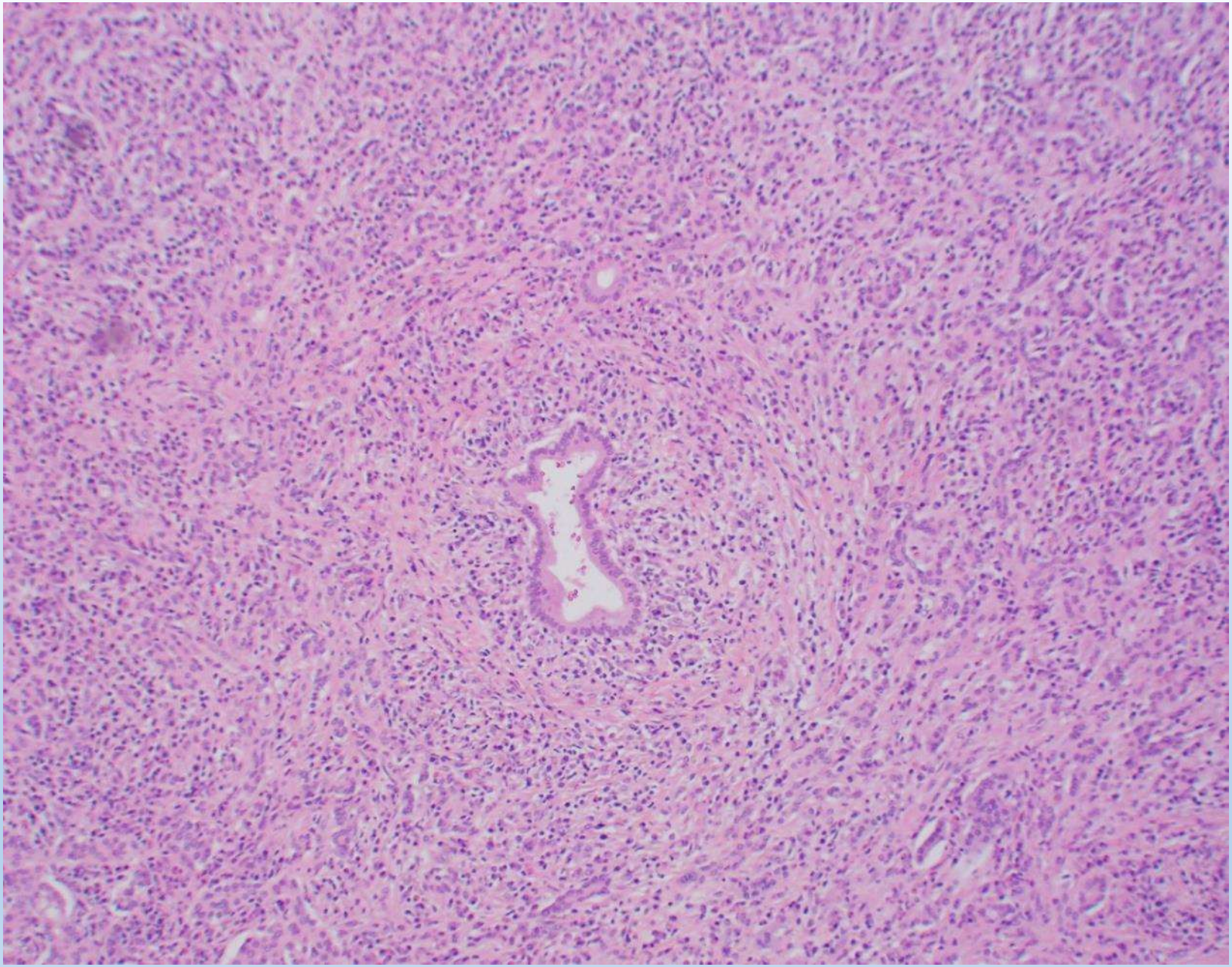
	Ref Range & Units	8mo ago
IGG-1	382 - 929 mg/dL	423
IGG-2	241 - 700 mg/dL	532
IGG-3	22 - 178 mg/dL	37
IGG-4	4 - 86 mg/dL	414.6 ^
IGG	694 - 1618 mg/dL	1296

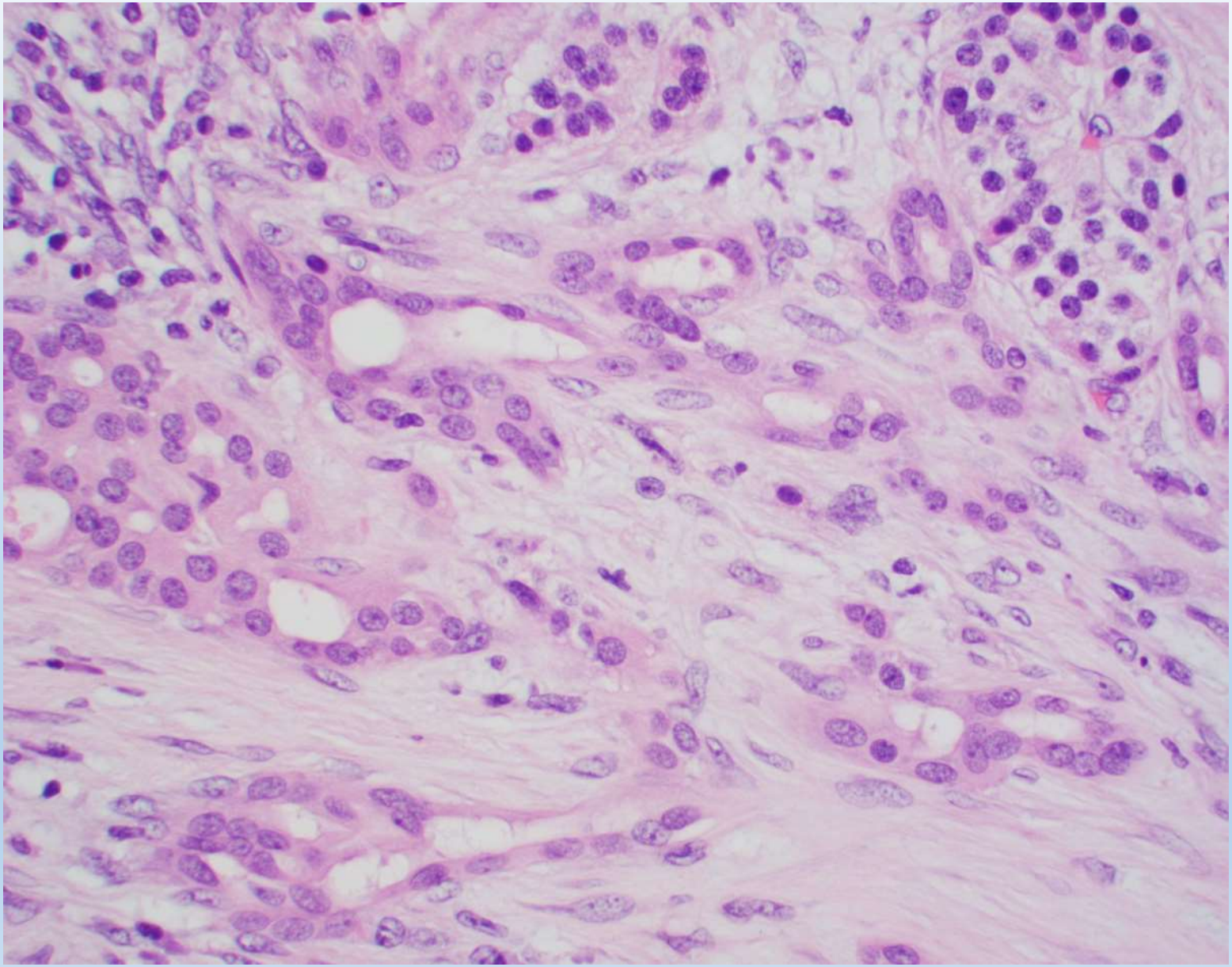
Specimen Collected: 02/25/19 08:58

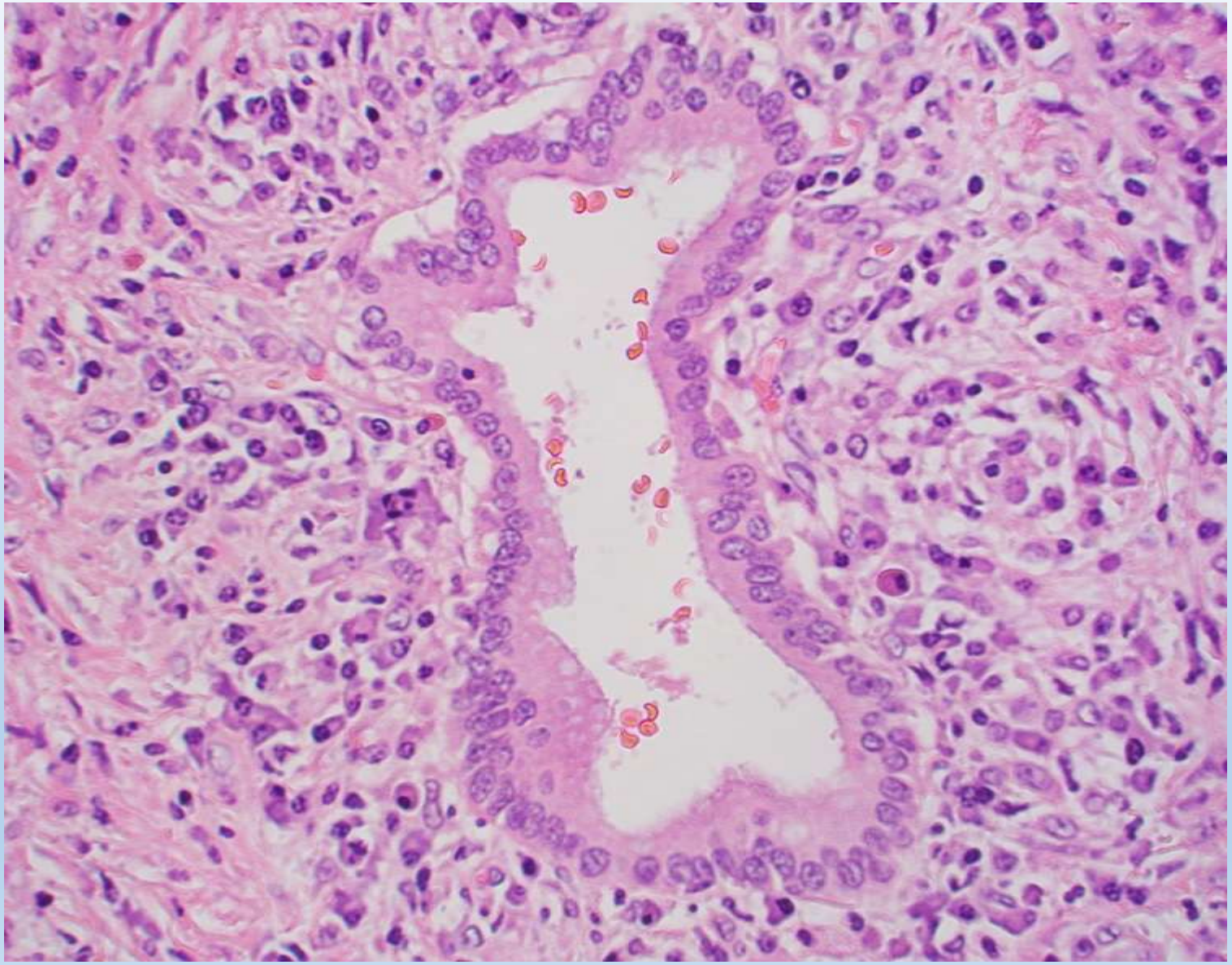
Lab Flo



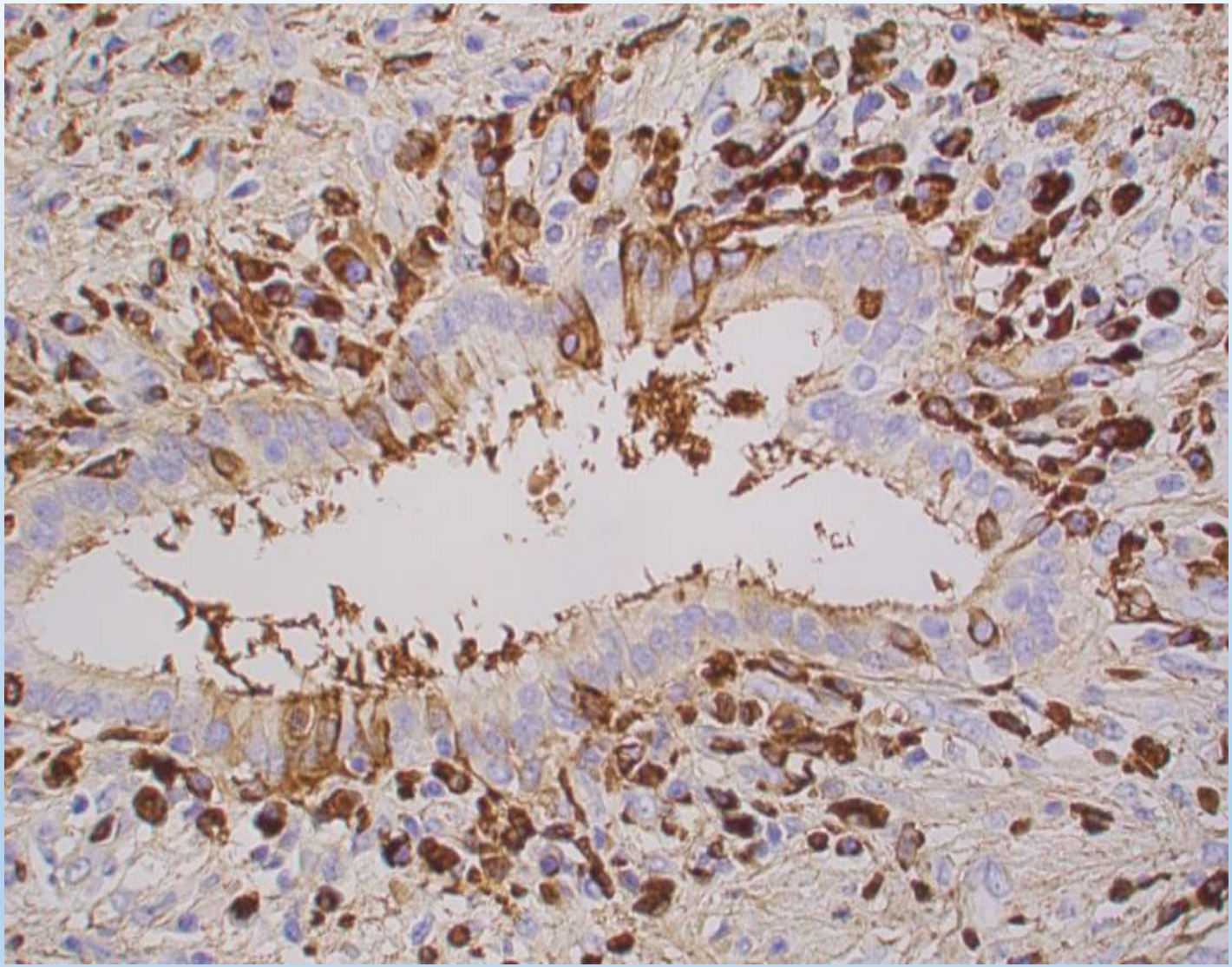


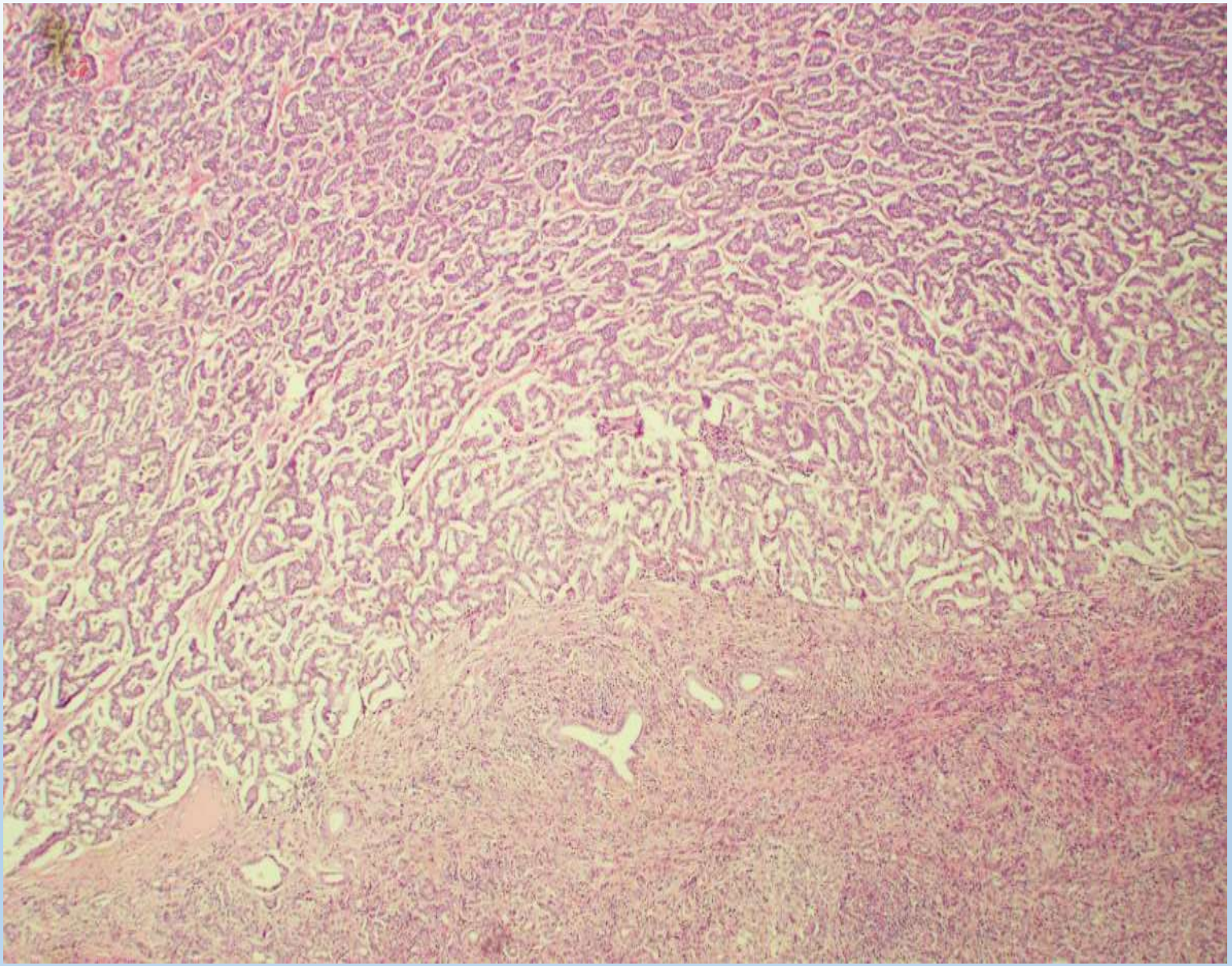


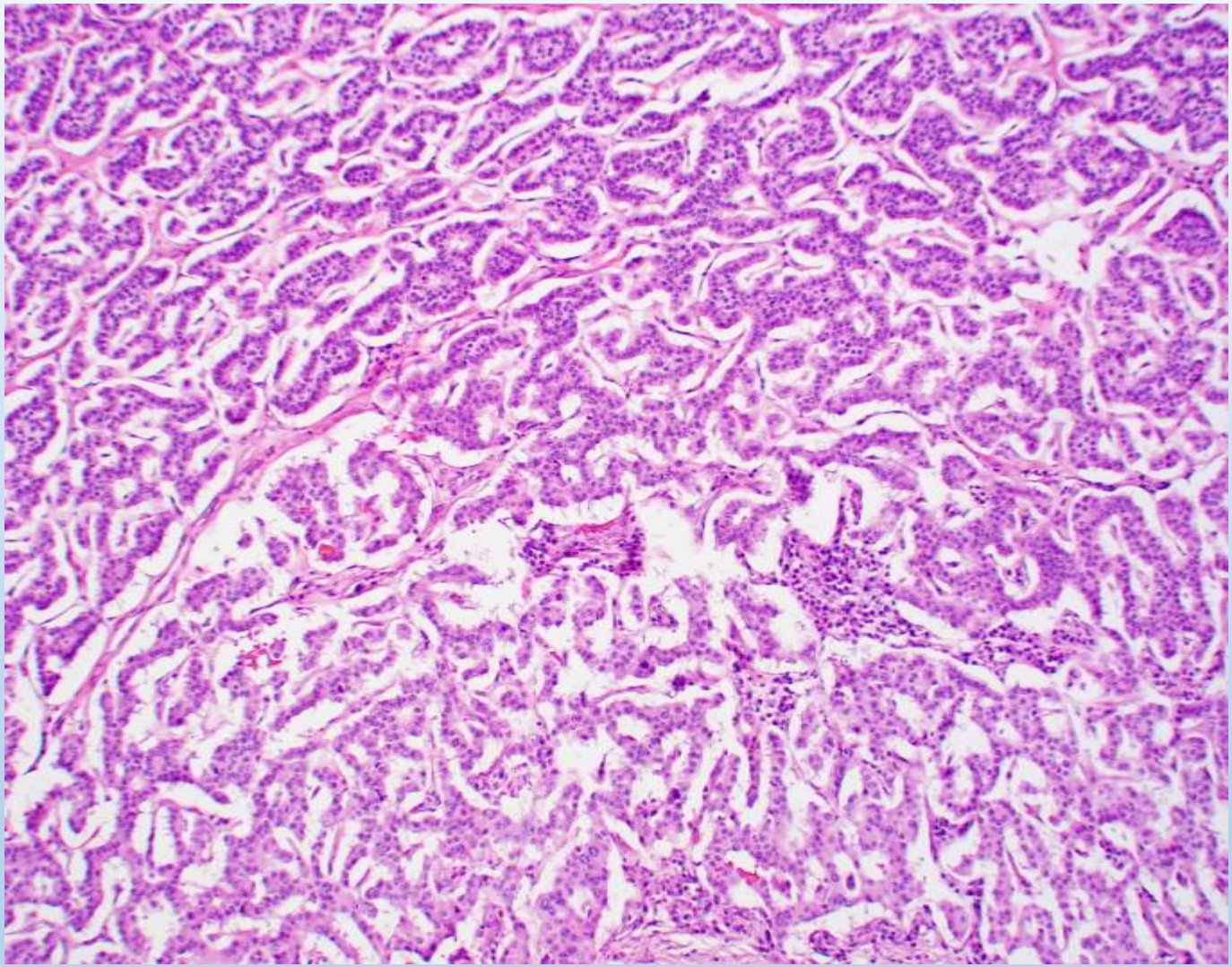


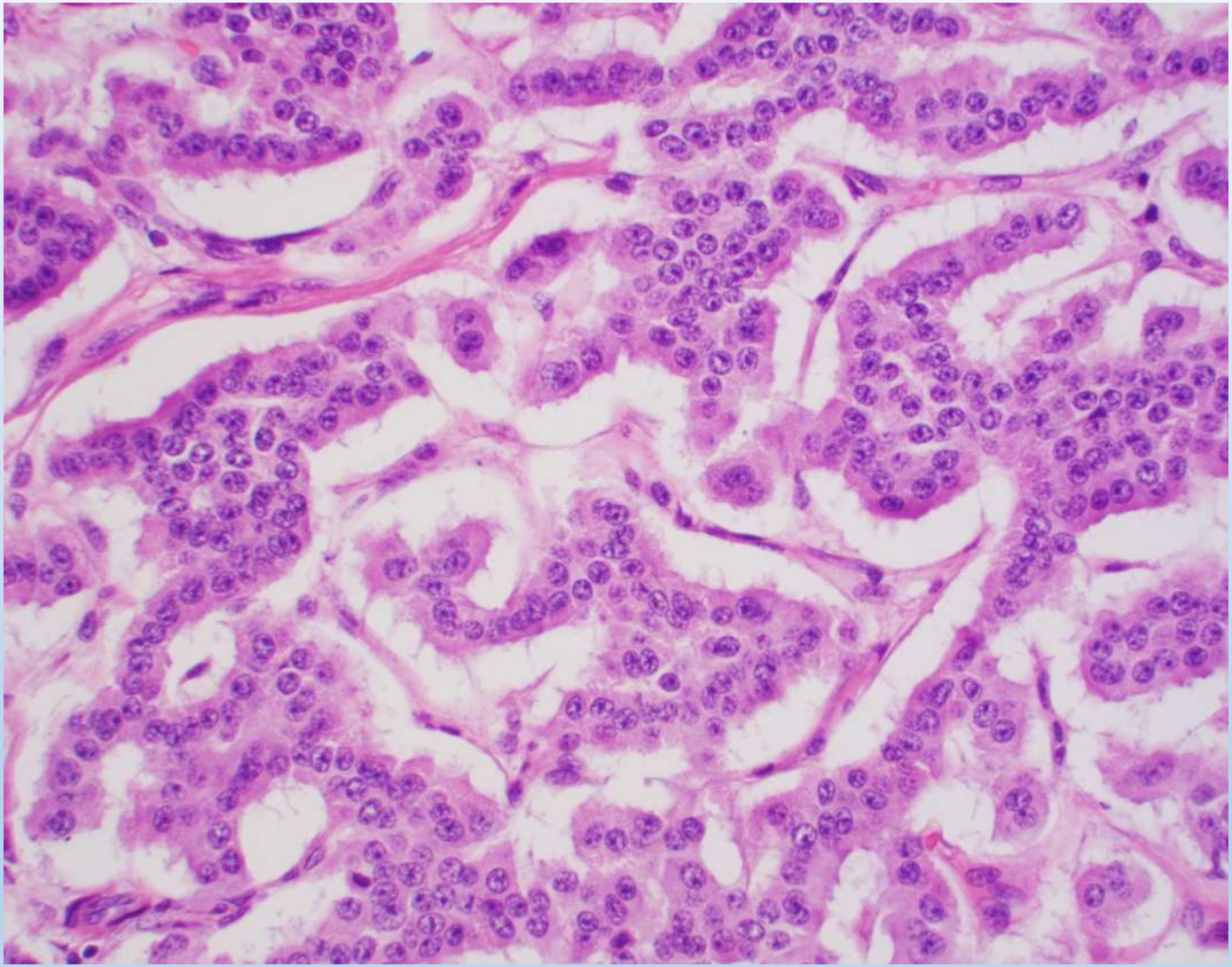


IgG4

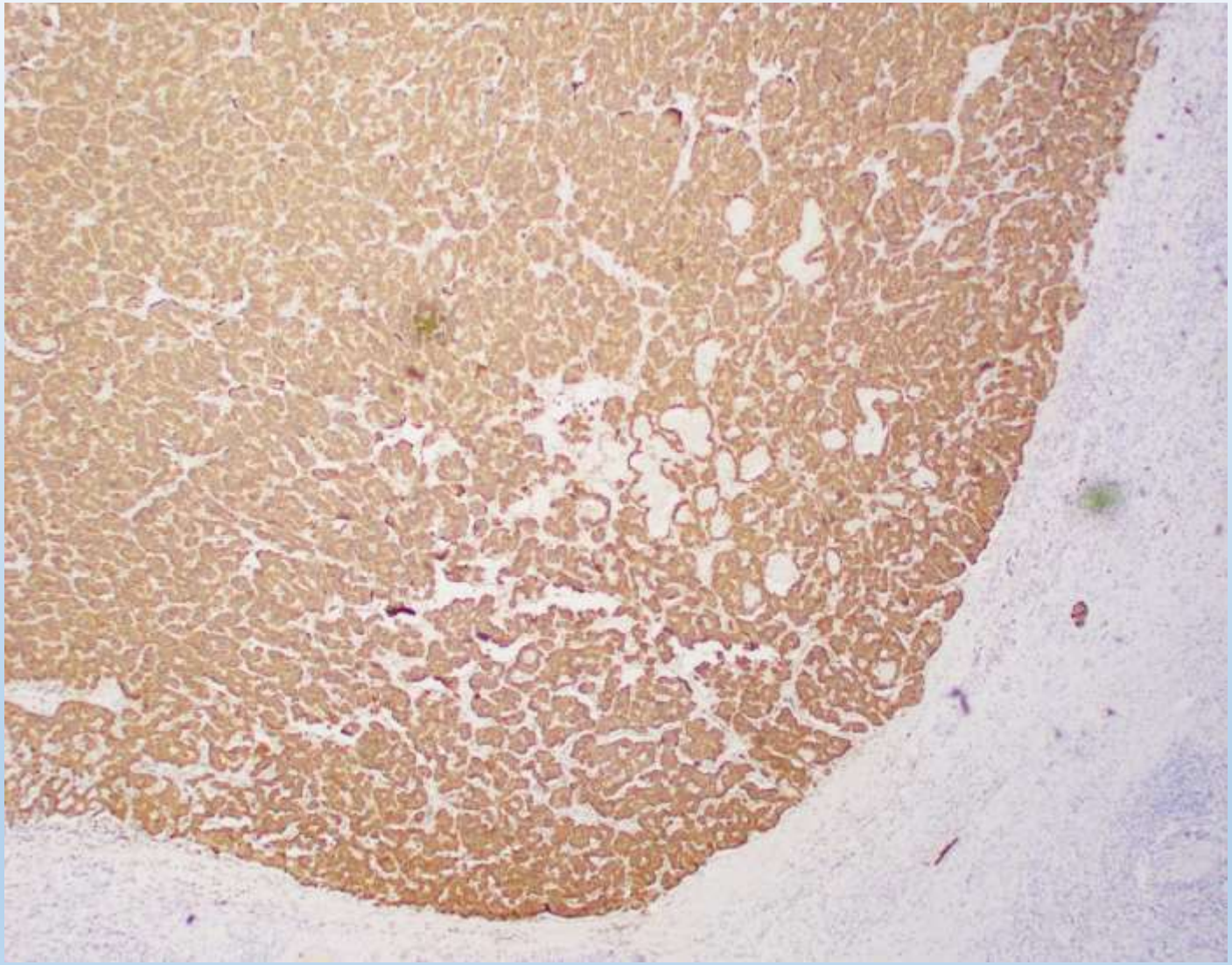








Chr.



Dx: Autoimmune Pancreatitis, Type 1 IgG4 related
NET Grade 1

- Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that is capable of affecting multiple organs.

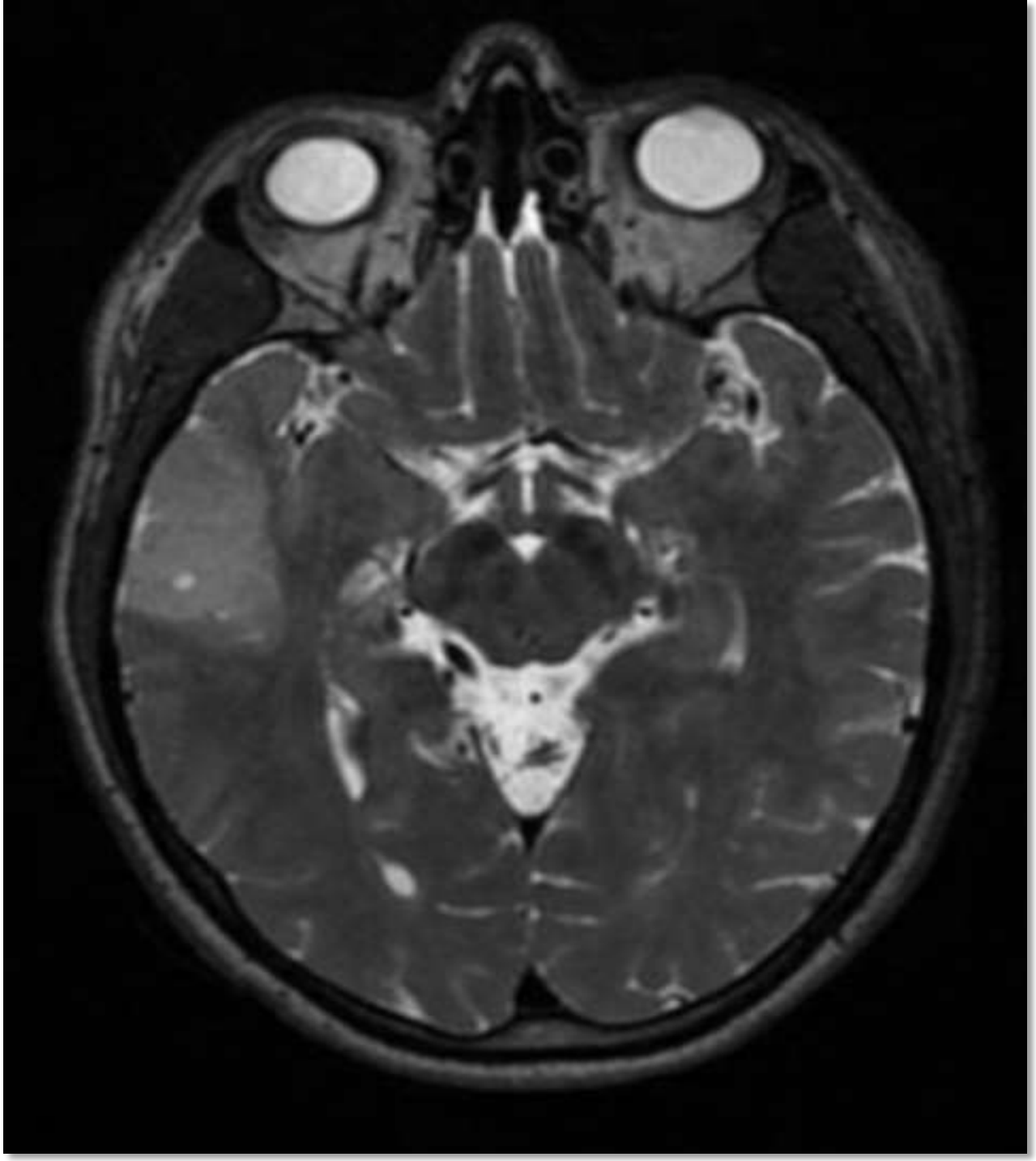
  Common forms of presentation include:
- Type 1 (IgG4-related) autoimmune pancreatitis (AIP)
- IgG4-related sclerosing cholangitis, typically occurring together with type 1 AIP
- Major salivary gland enlargement or sclerosing sialadenitis; termed IgG4-related Mikulicz disease, when presenting with the combination of lacrimal, parotid, and submandibular gland enlargement
- Orbital disease, often with proptosis
- Retroperitoneal fibrosis, frequently with chronic periaortitis and often affecting the ureters, leading to hydronephrosis and renal injury
- The involved organs share a number of core pathologic features and striking clinical and serologic similarities, including tumor-like swelling of involved organs, a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, and a variable degree of fibrosis that has a characteristic "storiform" pattern. Elevated serum concentrations of IgG4 are common.

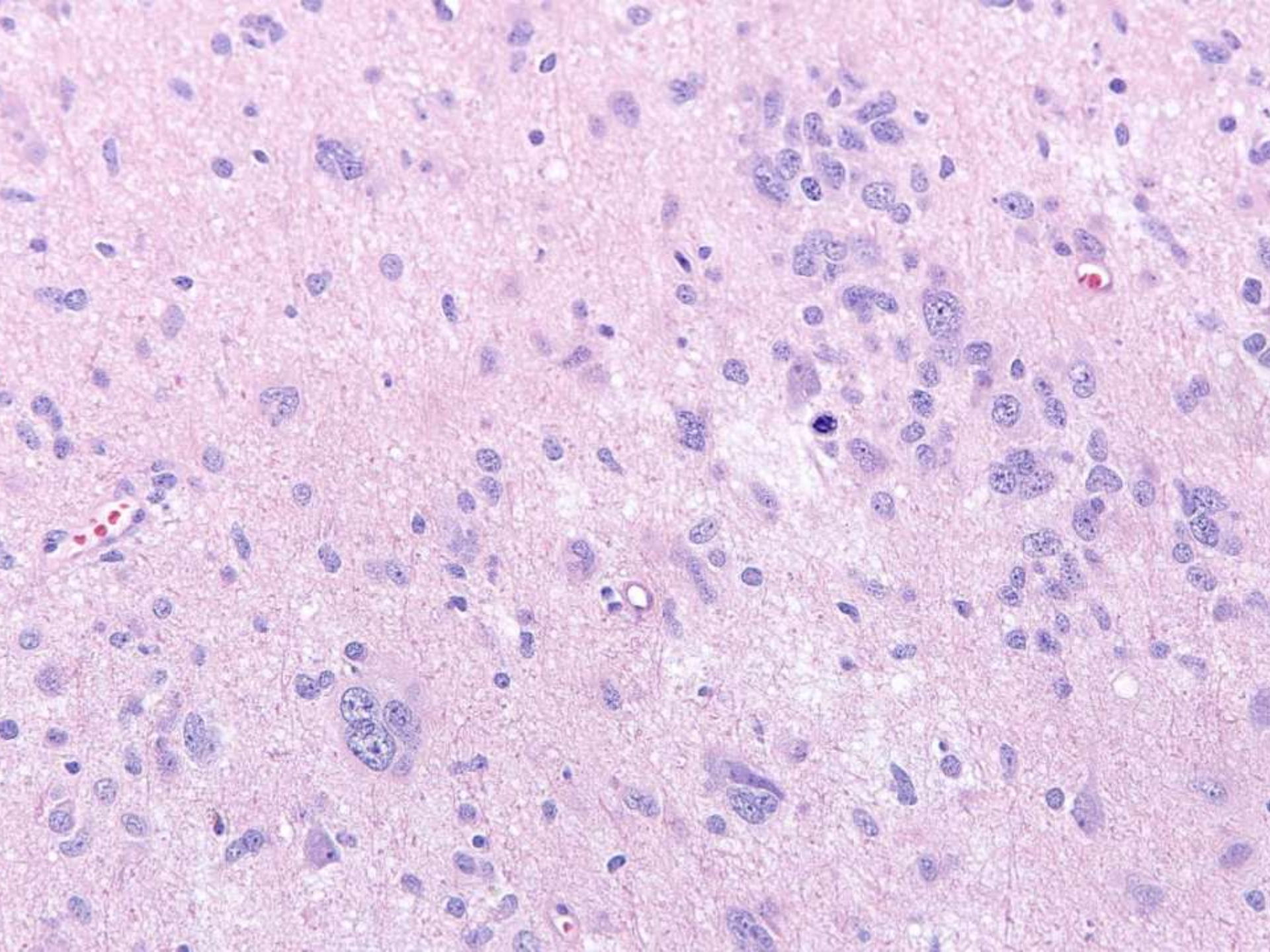
- The hallmarks of IgG4-related disease (IgG4-RD) are dense lymphoplasmacytic infiltrations with a predominance of IgG4-positive plasma cells in the affected tissue, usually accompanied by some degree of fibrosis and often by obliterative phlebitis and an increased number of eosinophils. Serum IgG4 levels are elevated in approximately two-thirds of the patients, while a sizeable minority of patients have normal serum IgG4 concentrations even before treatment, despite the presence of the typical histopathologic changes in tissue. A good initial therapeutic response to glucocorticoids is characteristic, particularly if excessive tissue fibrosis has not supervened.
- The pathogenesis of IgG4-related disease remains incompletely understood, but there is growing evidence that the disease is autoimmune in character, with an important role for T cells, especially CD4+ and T-follicular helper cells and that the IgG4 antibodies are not themselves pathogenic.
- IgG4-related sclerosing cholangitis is the most common extrapancreatic manifestation of type 1 AIP (IgG4-related), present in over 70 percent of such patients. It rarely occurs in the absence of pancreatitis.

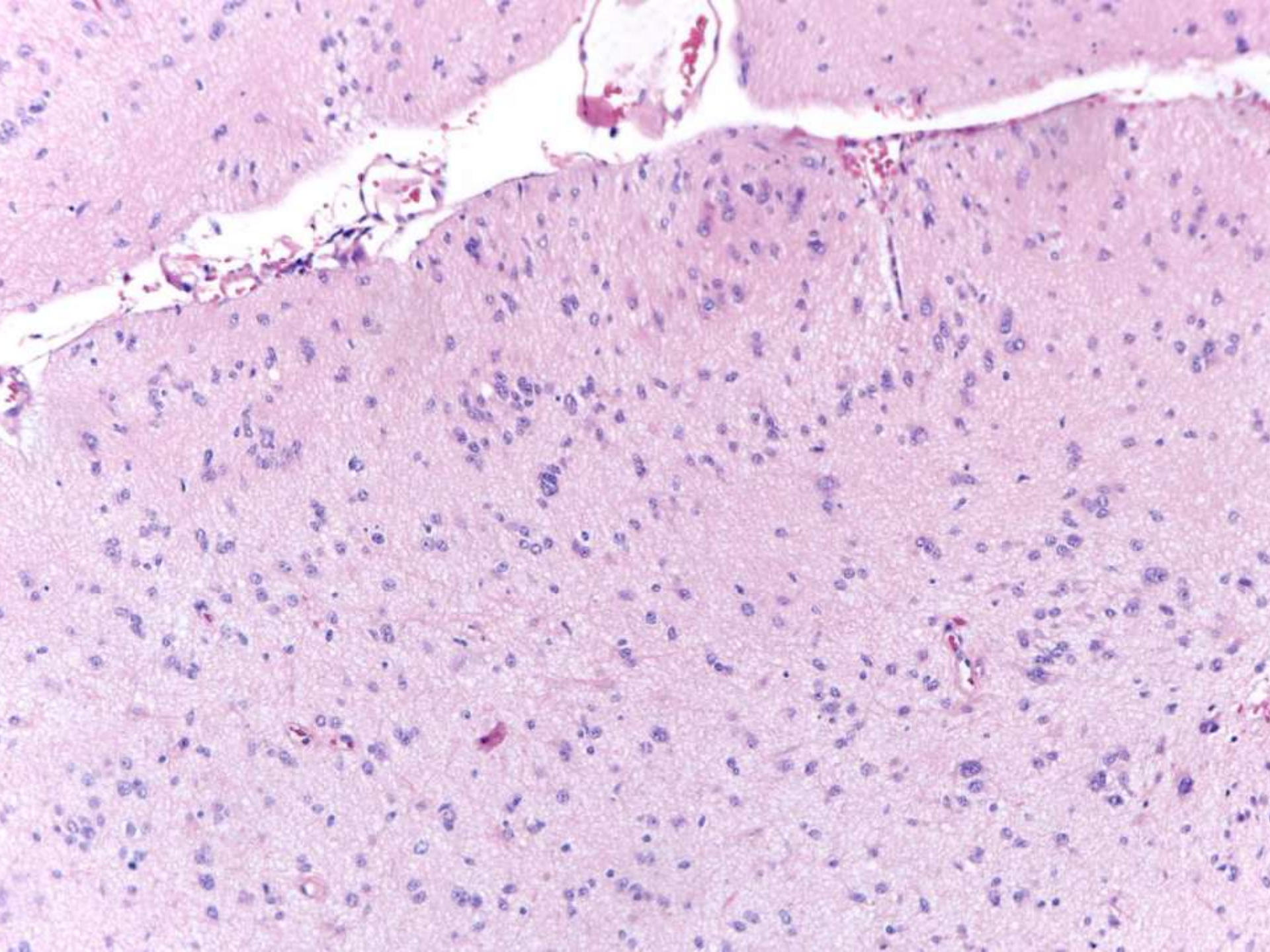
19-1210

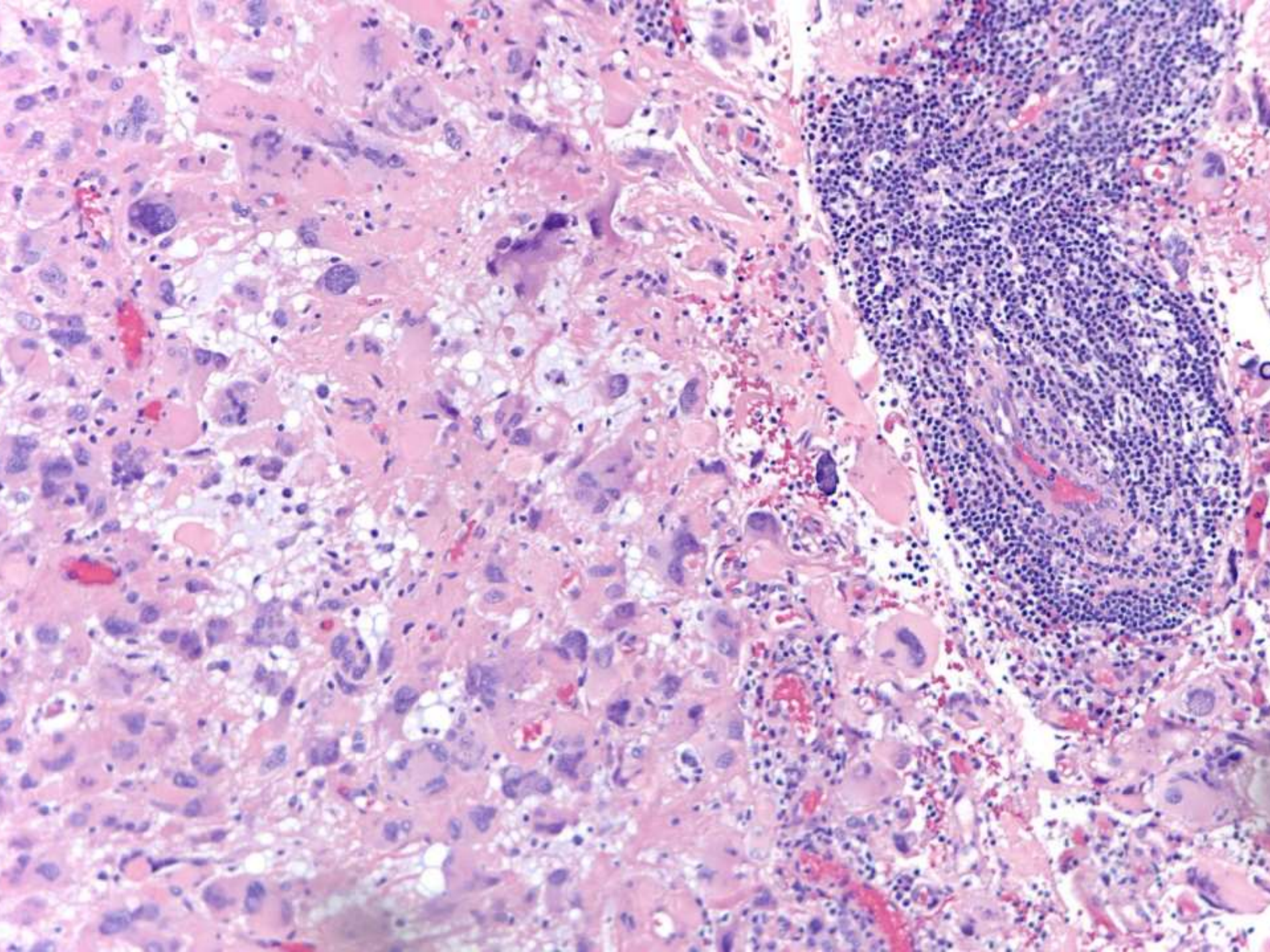
Romain Cayrol/Hannes Vogel; Stanford

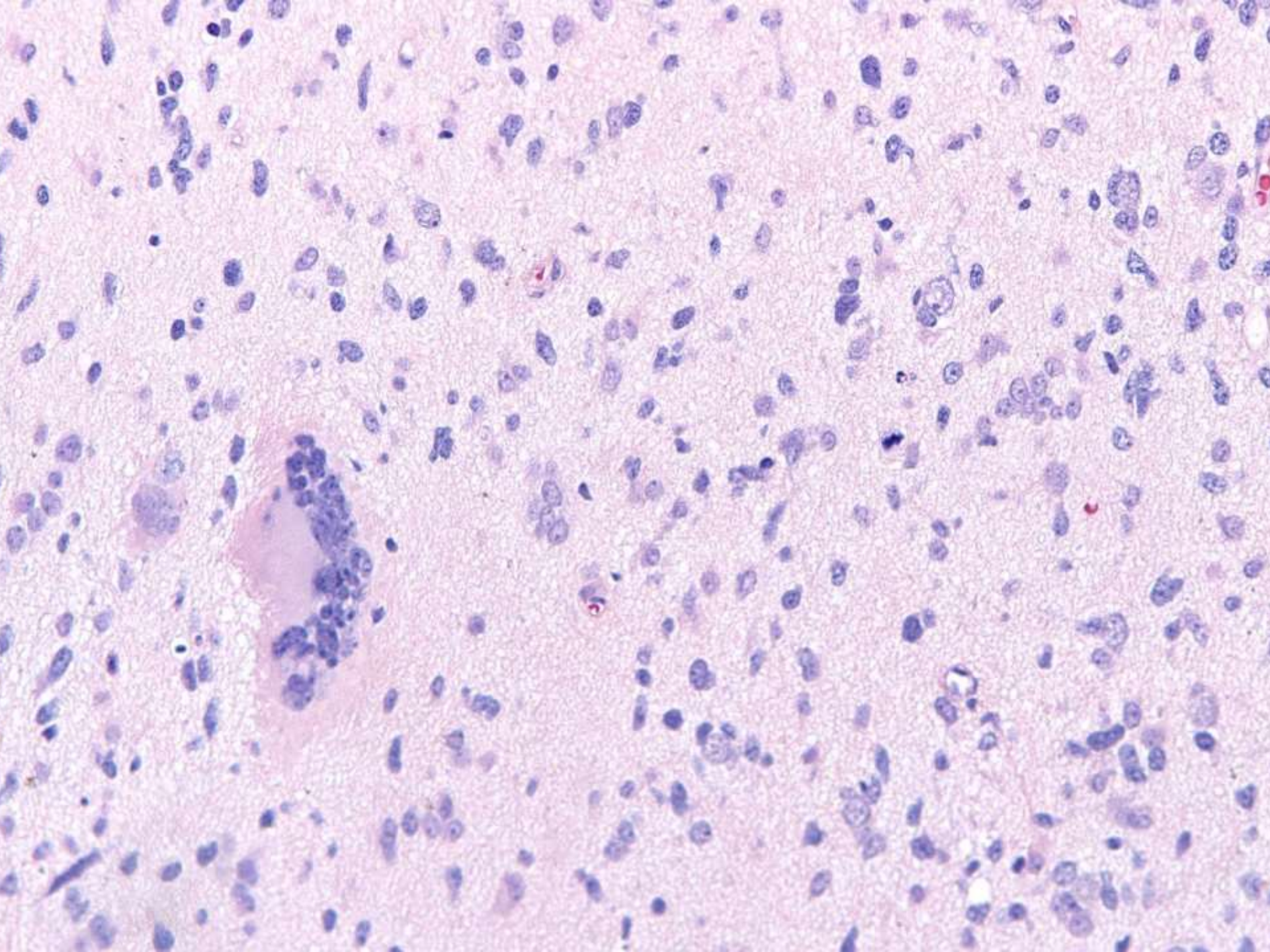
56-year-old female with a seizure and newly-discovered brain lesion. MRI: hyperintense mass involving the cortex and subcortical white matter of the right inferior and middle temporal gyri, most consistent with an infiltrative glioma with cystic change, as well as several foci of enhancement which may present a higher grade component.

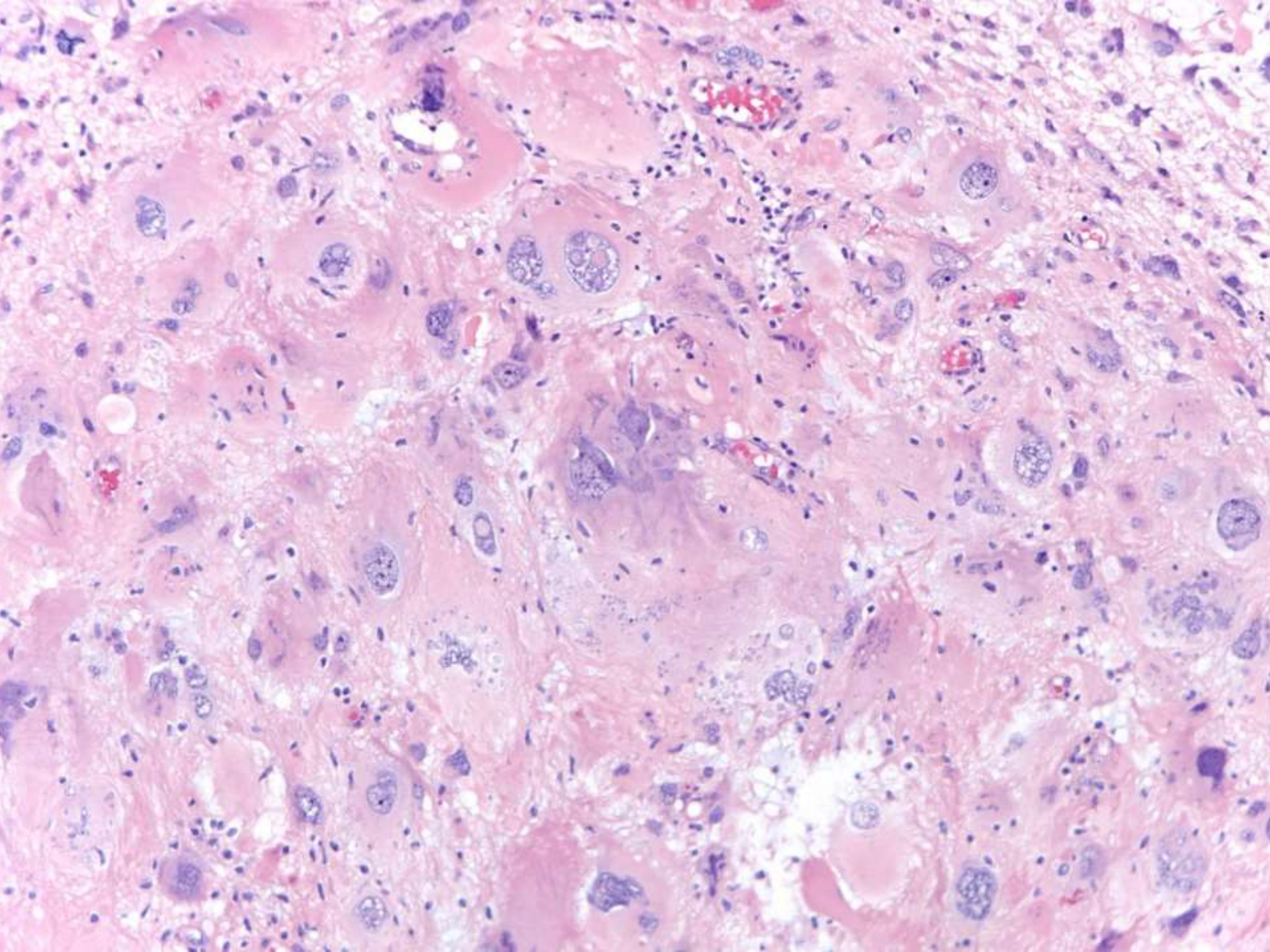


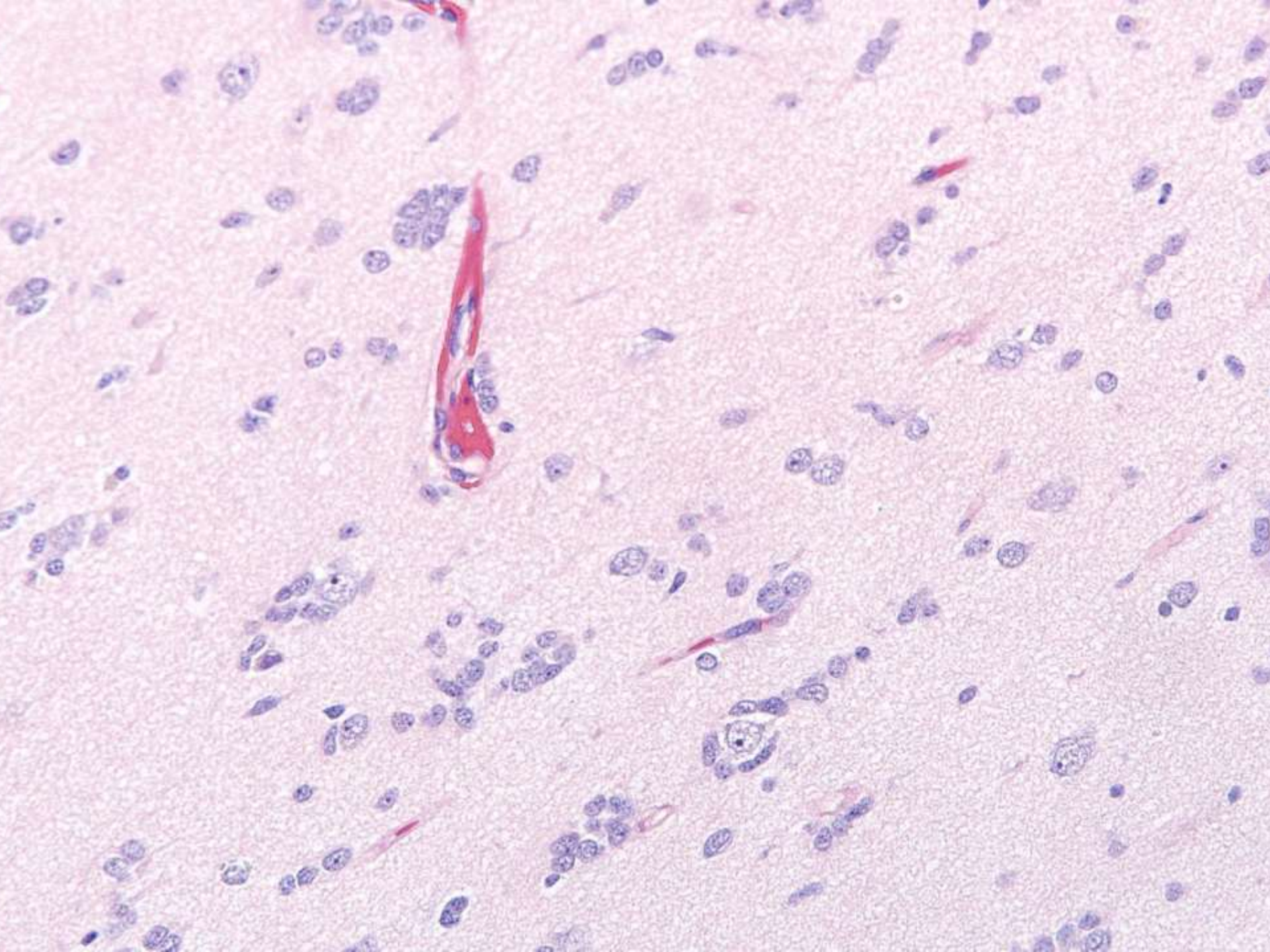


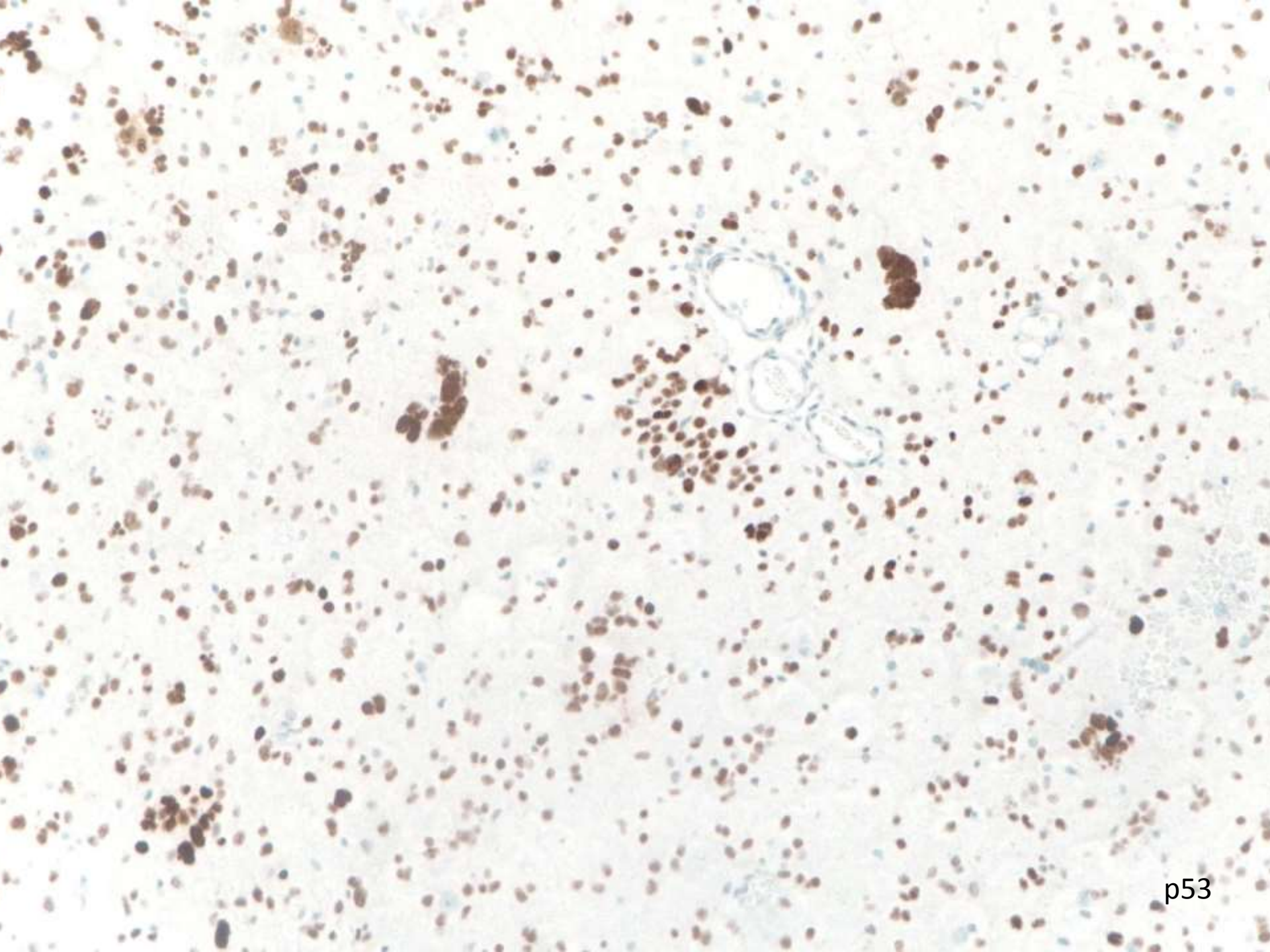


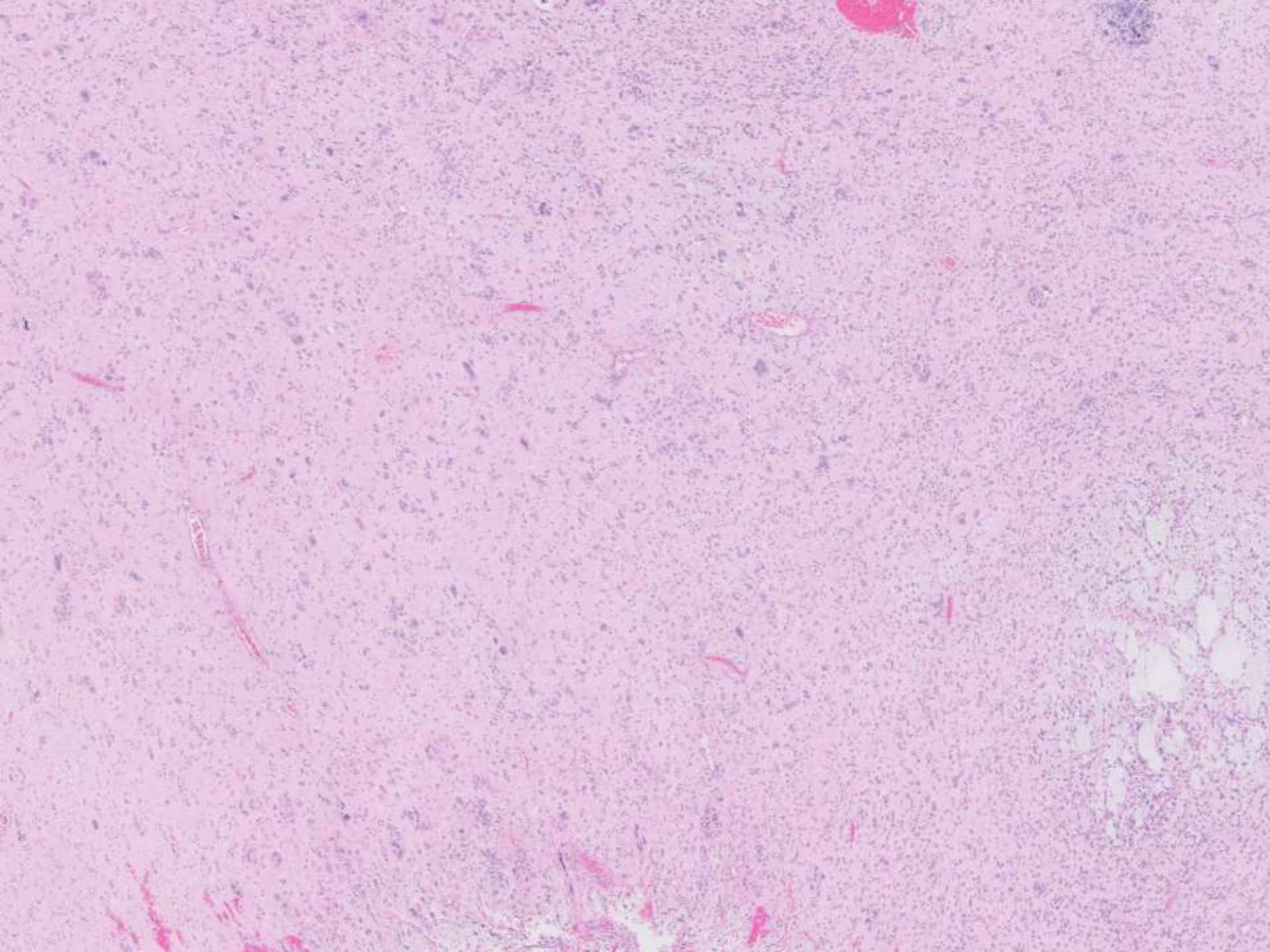


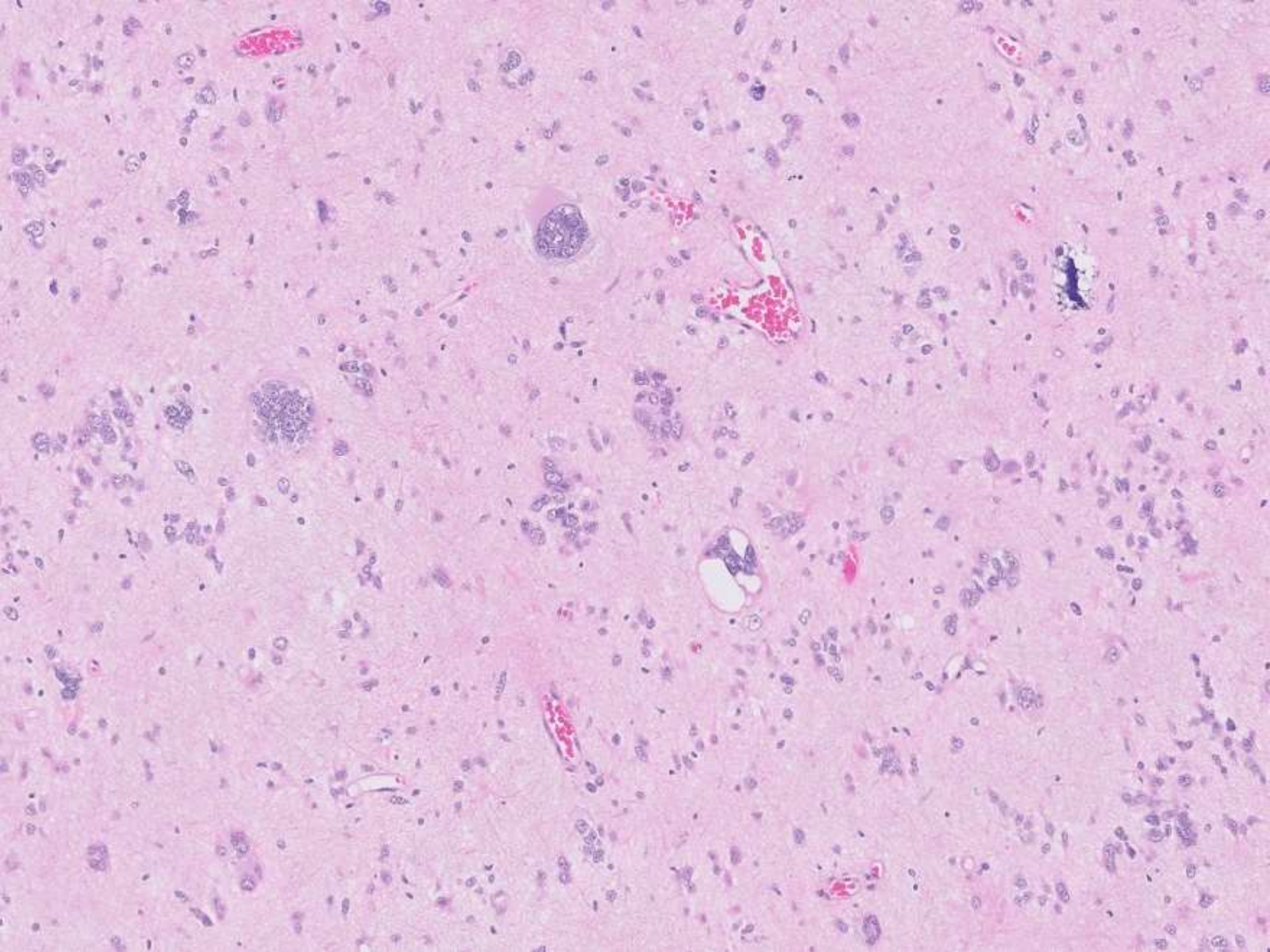


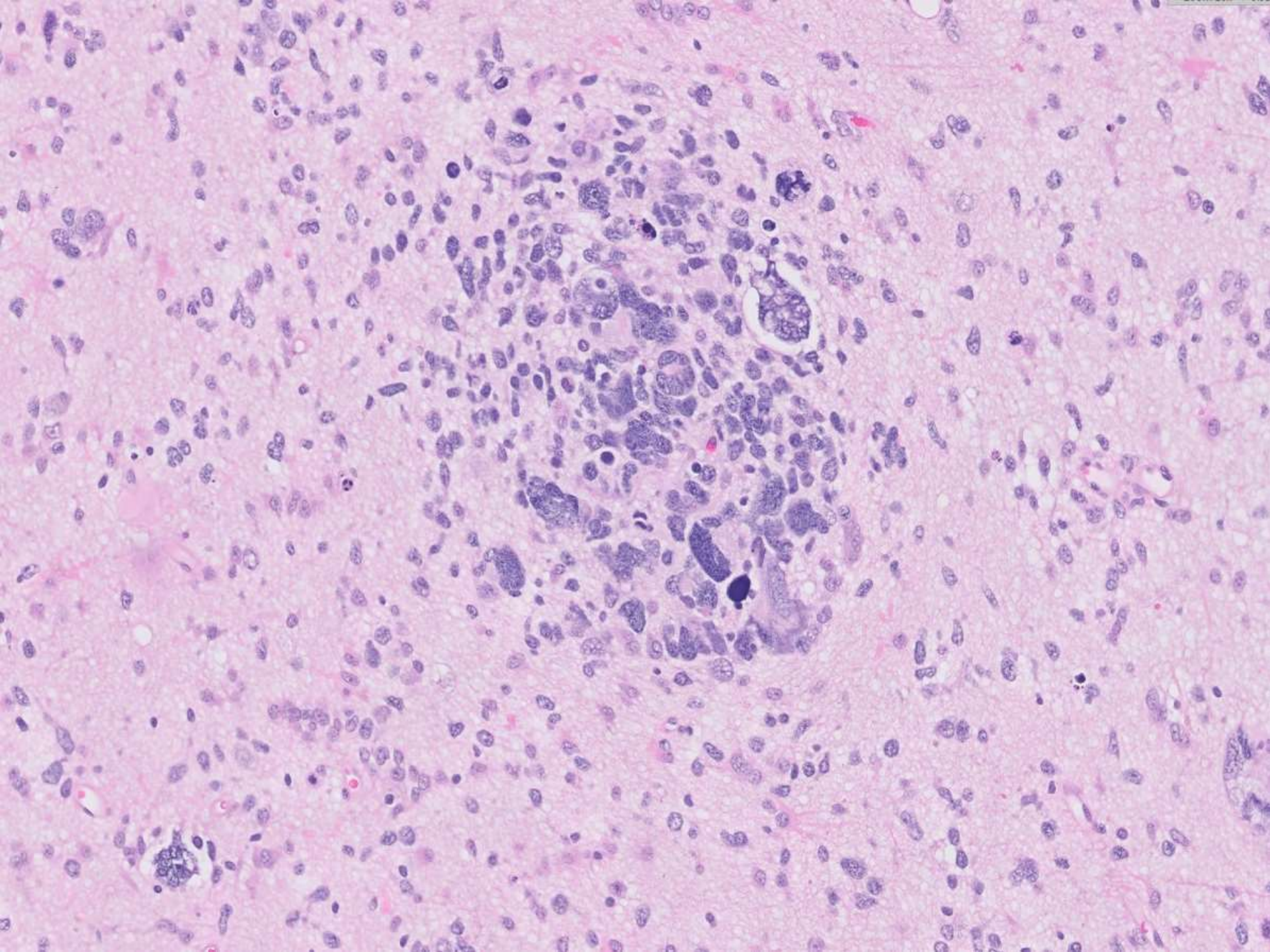


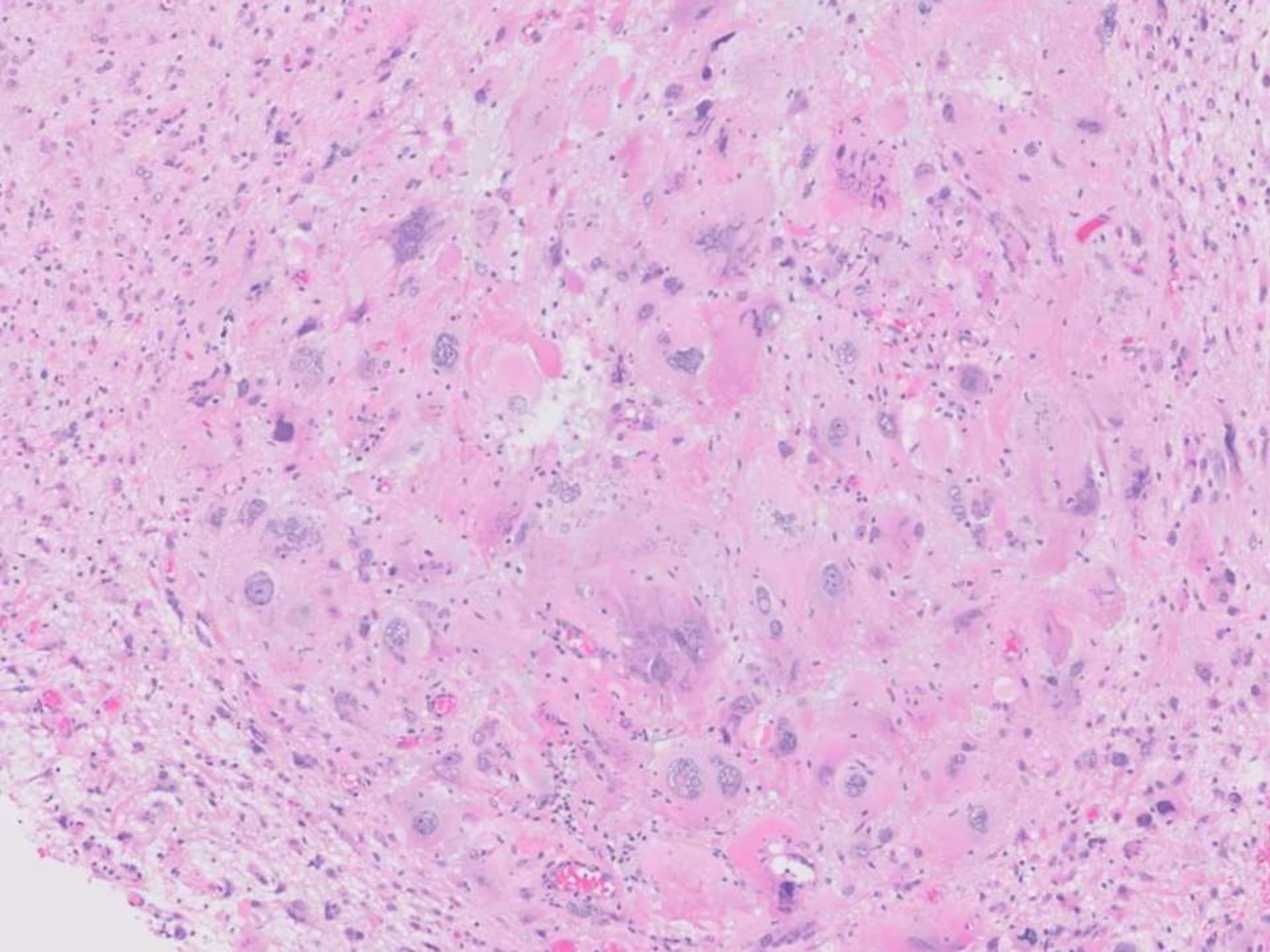



p53









Immunohistochemistry

- IDH1 R132H negative
- ATRX retained
- P53 positive

- A. BRAIN, GLIOMA, RESECTION
- -- MALIGNANT GLIOMA WITH GIANT CELLS, IDH R132H WILDTYPE, PENDING MOLECULAR STUDIES

    - No necrosis, no microvascular proliferation

- A. BRAIN, GLIOMA, RESECTION, MUTATIONAL PROFILING BY STAMP
  - -- POSITIVE FOR *RB1* Q736X MUTATION
  - -- POSITIVE FOR *TP53* E285K MUTATION
  - -- POSITIVE FOR *EGFR* AMPLIFICATION

- A. BRAIN, GLIOMA, RESECTION
- -- *GLIOBLASTOMA, IDH WILD-TYPE, GIANT CELL VARIANT WHO GRADE IV*
  - *"Following the recent cIMPACT (consortium to Inform Molecular and Practical Approaches to CNS Taxonomy) recommendations these findings warrant the diagnosis of diffuse astrocytic glioma, IDH-wildtype, with molecular features of a glioblastoma, WHO grade IV."*

consortium to Inform Molecular and Practical Approaches to CNS Taxonomy Not Official WHO (cIMPACT NOW)

cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

Acta Neuropathologica (2018) 136:805–810

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]

Multiple studies have concluded that a substantial subset of IDH-wildtype diffuse or anaplastic astrocytomas that occur in adults and would be considered as WHO grade II or III based on histologic criteria (no microvascular proliferation or necrosis) have an aggressive clinical course, with overall patient survival times equal to or only slightly longer than patients with IDH-wildtype glioblastoma, WHO grade IV [4, 8, 9, 32, 34]. Nevertheless, biologically more

We reached consensus that the following were the minimal molecular criteria for identifying an IDH-wildtype diffuse astrocytic glioma that, despite appearing histologically as a WHO grade II or III neoplasm, would follow an aggressive clinical course more closely resembling that of an IDH-wildtype glioblastoma:

1. *EGFR* amplification

   OR

2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+ 7/− 10)

   OR

3. *TERT* promoter mutation

These conclusions are based on the findings that those histologic IDH-wildtype diffuse astrocytic gliomas of WHO grade II or III which carry *EGFR* amplification, + 7/− 10 or *TERT* promoter mutation are associated with significantly shorter patient survival compared to patients with other WHO grade II or III gliomas, and patients have outcomes similar to patients with IDH-wildtype glioblastoma [1, 2,

C-IMPACT NOW

- Diffuse astrocytic glioma, IDH wildtype, with molecular features of a glioblastoma, WHO grade IV
  - No necrosis or microvascular proliferation

1. *EGFR* amplification

   OR

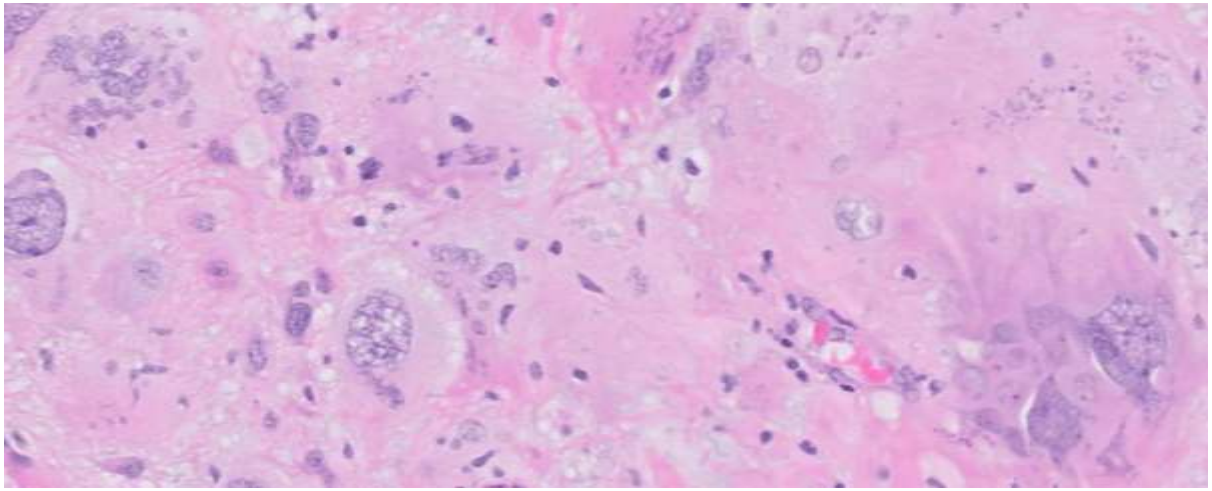
2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+ 7/− 10)

   OR

3. *TERT* promoter mutation

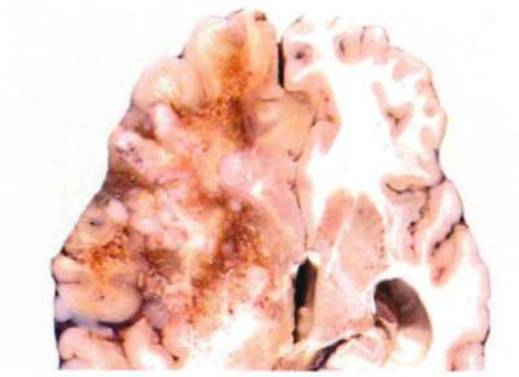
Glioblastoma, giant cell variant

- Rare variant of IDH wildtype glioblastoma, WHO grade IV
  - Giant multinucleated cells and occasional abundant reticulin network
- <1% of glioblastoma
- Younger patients (44 to 51 year old), including children
- Often well circumscribed neoplasms centered on the subcortical white matter and deeper grey matter of the cerebrum
  - Ring enhancing lesion

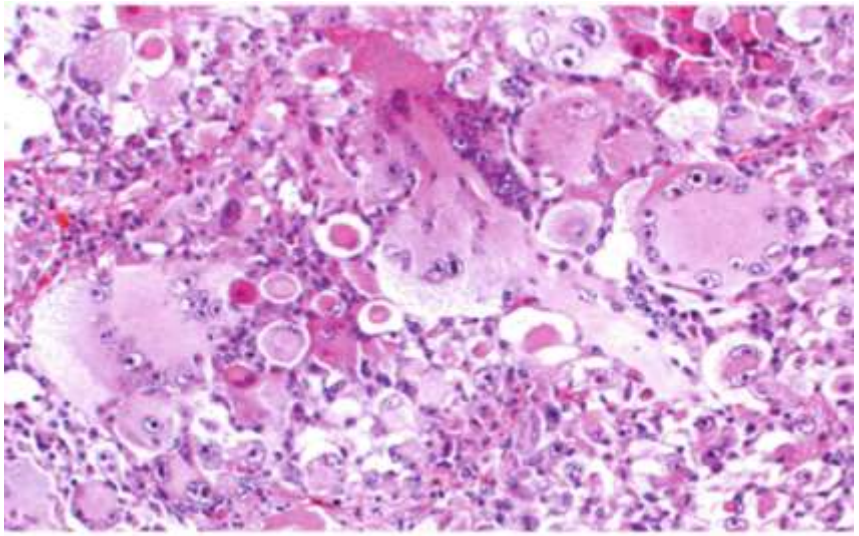


Glioblastoma, giant cell variant

- Well circumscribed, firm tumor with necrosis and hemorrhage



- Atypical glial cells with numerous multinucleated giant cells and an occasional reticulin network
  - Cytoplasmic inclusions can be seen
  - Palisading and/or geographic necrosis
  - Microvascular proliferation is less common



- Prognosis slightly better compared to IDH wildtype glioblastomas
  - 10 versus 13 months
  - 5 year survival rate 3.4% versus >10%

Glioblastoma, giant cell variant

	Primary GBM (IDH-wildtype)	Gliosarcoma	Giant cell GBM	Secondary GBM (IDH-mutant)
Age at GBM diagnosis	59 years	56 years	44 years	43 years
Male-to-female ratio	1.4	1.4	1.6	1.0
Length of clinical history	3.9 months	3.0 months	1.6 months	15.2 months
IDH1/2 mutation	0%	0%	5%	100%
PTEN mutation	24%	41%	33%	5%
ATRX expression loss	0%	0%	19%	100%
TERT mutation	72%	83%	25%	26%
TP53 mutation	23%	25%	84%	74%
Loss of 19q	4%	18%	42%	32%
EGFR amplification	42%	5%	6%	4%

Light blue, typical for IDH-wildtype GBMs; yellow, typical for IDH-mutant GBMs. Giant cell GBM shares characteristics with both GBM types.

Conclusion

- Following cIMPACT guidelines diffuse astrocytic tumors, IDH wildtype, without necrosis and microvascular proliferation can be diagnosed as WHO grade IV based on molecular features
  - **EGFR** amplification
  - **TERT promoter** mutation
  - Combined chromosome 7 gain and chromosome 10 loss (**-10/+7**)

- Giant cell glioblastoma are **rare variants** of IDH wildtype glioblastoma with a **slightly better prognosis**
  - Differential diagnosis with poorly differentiated carcinoma, epithelioid gliovlastoma and pleomorphicxanthoastrocytoma

References

cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

Acta Neuropathologica (2018) 136:805–810

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]