Disclosures
March 5, 2018

Dr. Francisco Beca has disclosed that he has financial relationships with the following commercial interests: Path AI (salary), Gilead Sciences (Equity). South Bay Pathology Society has determined that these relationships are not relevant to the clinical case being presented.

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

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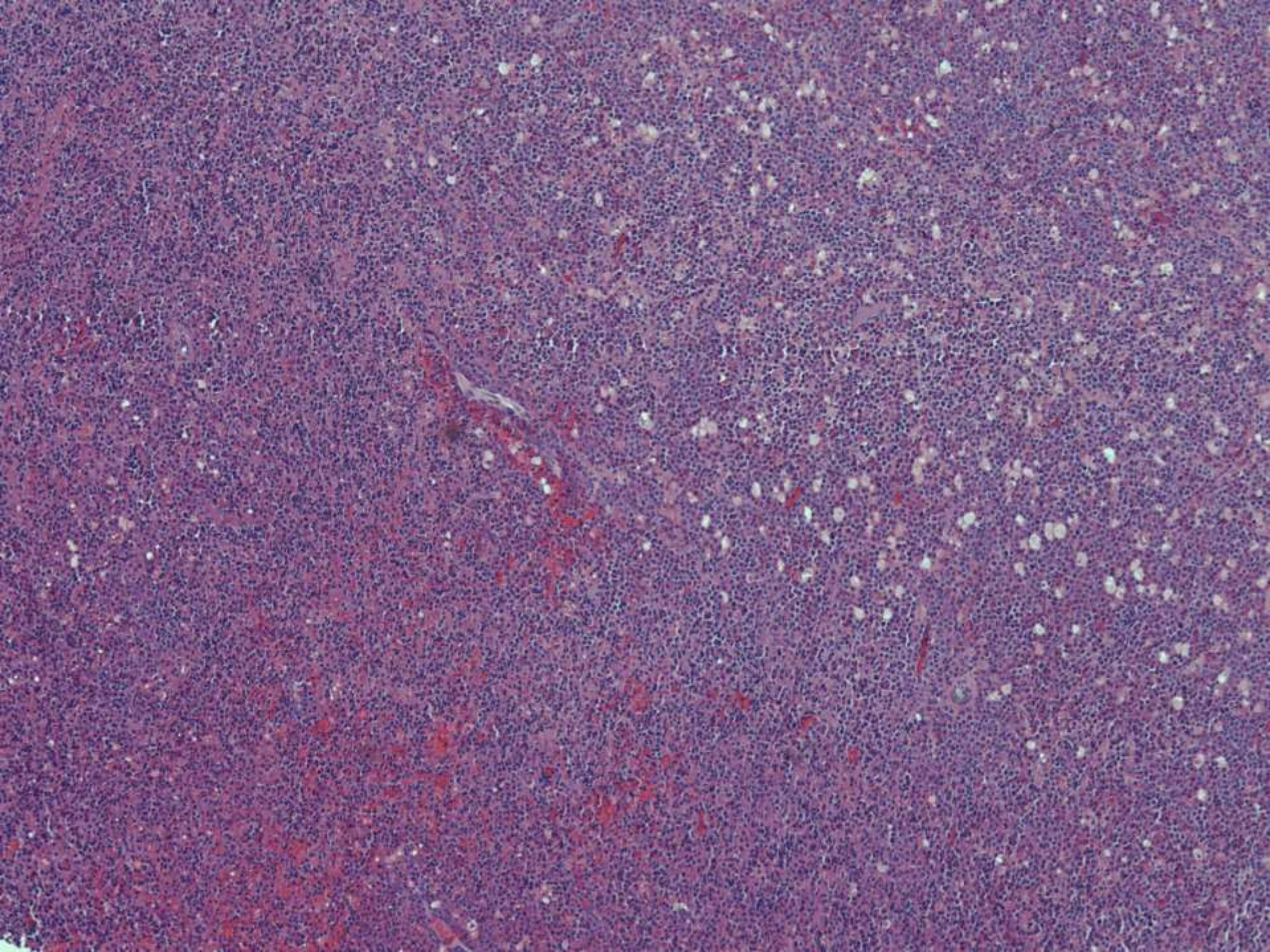
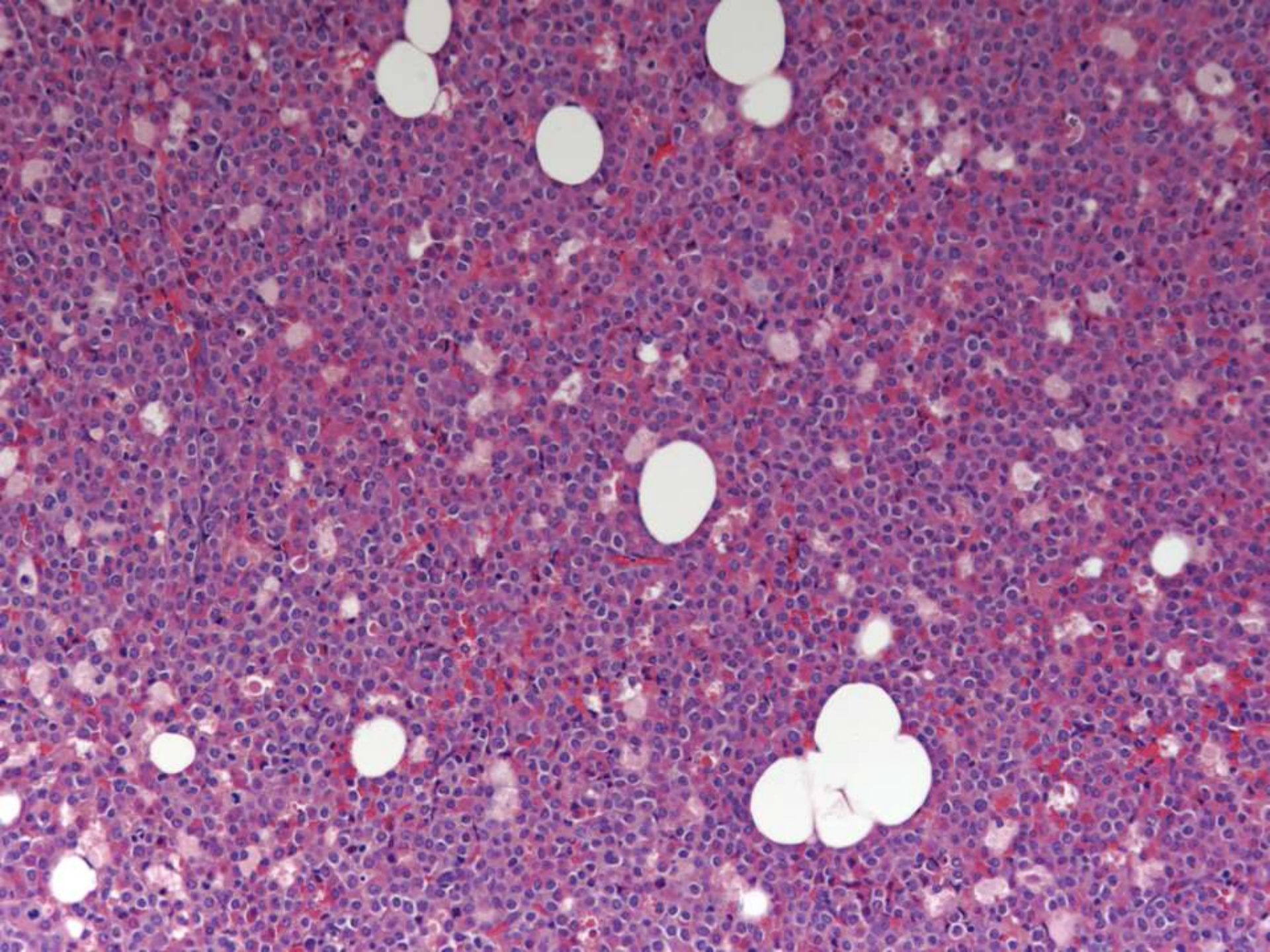
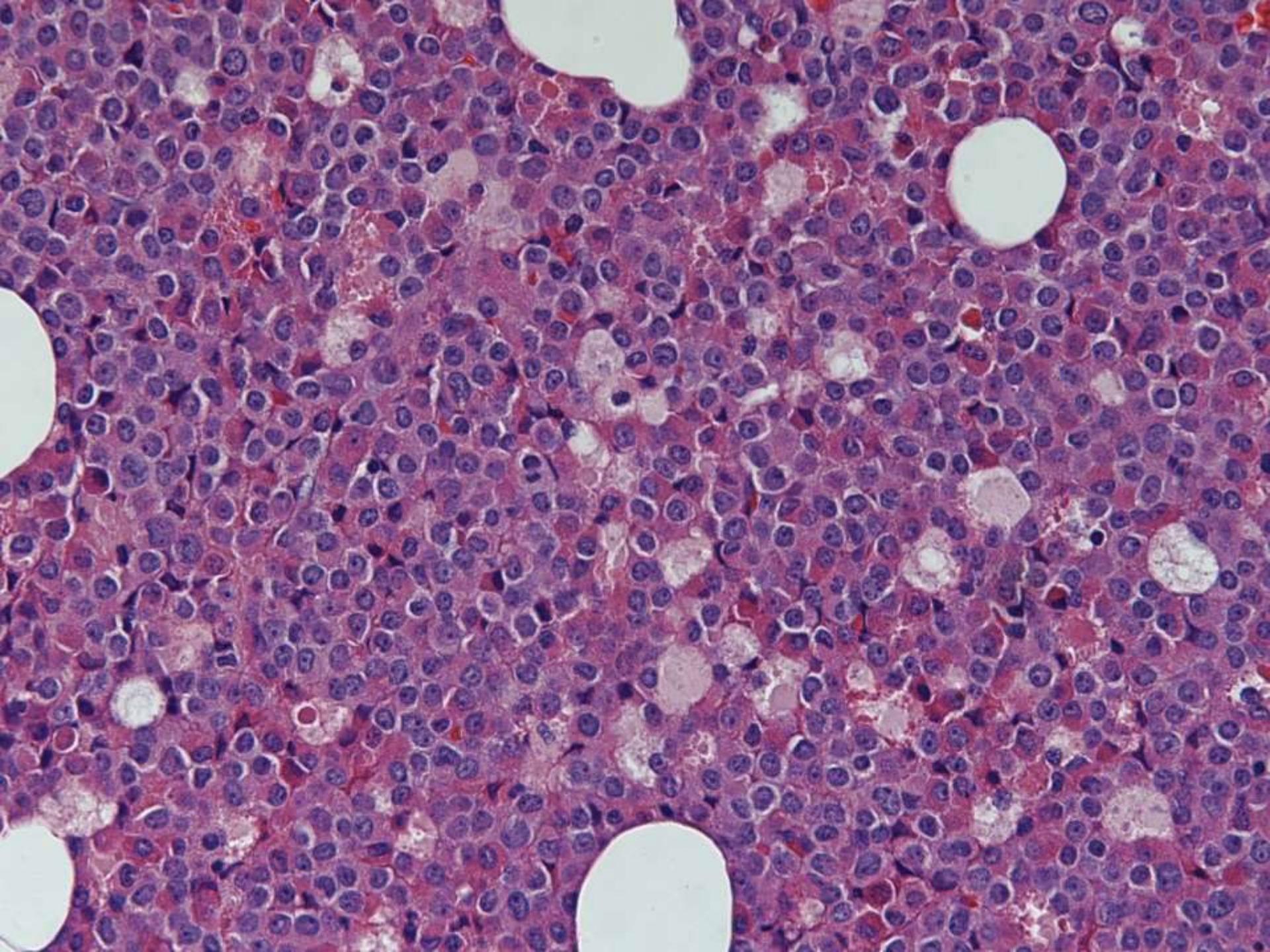
SB 6251

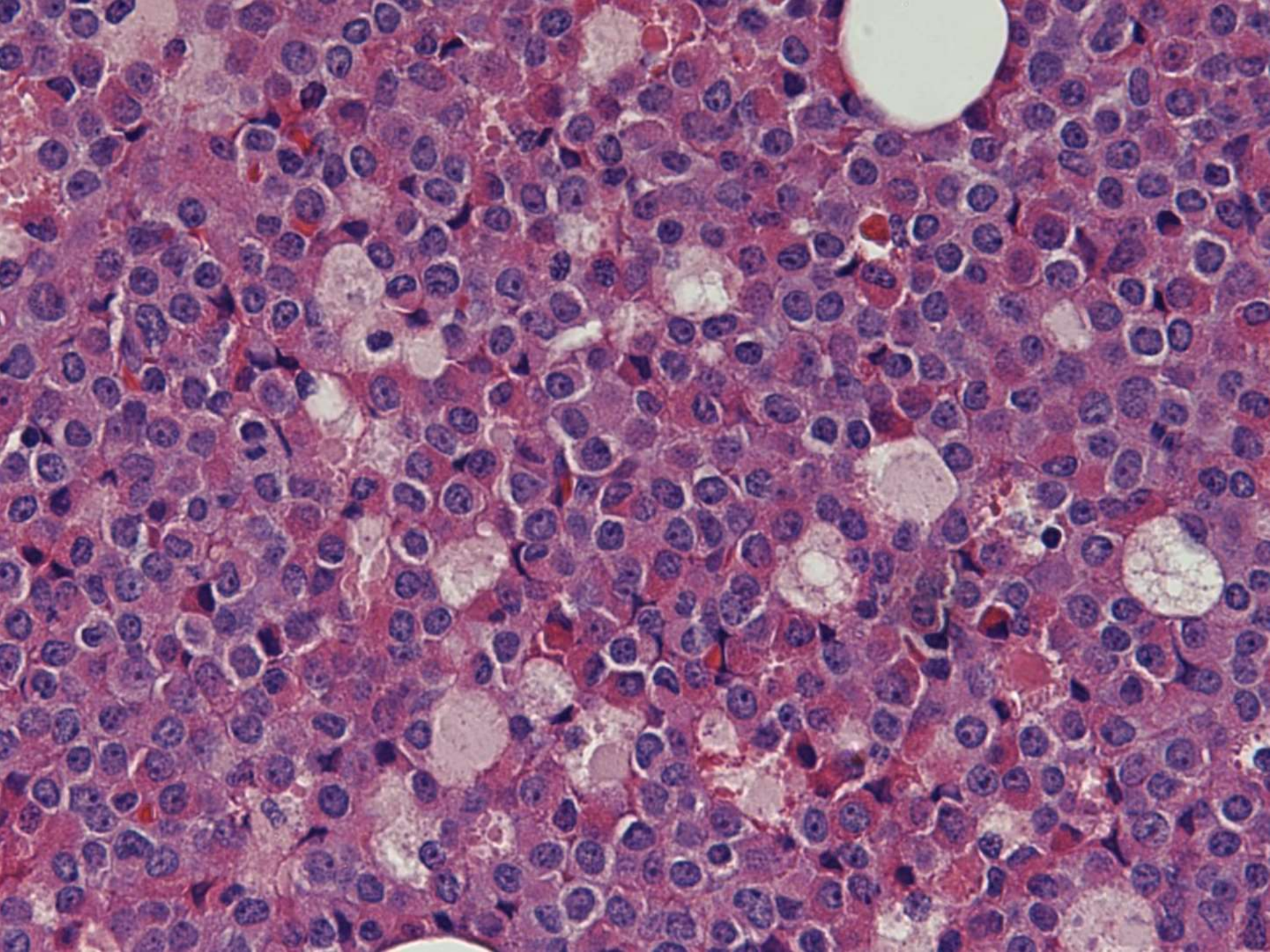
Jonathan Lavezo/Hannes Vogel/Don Born; Stanford

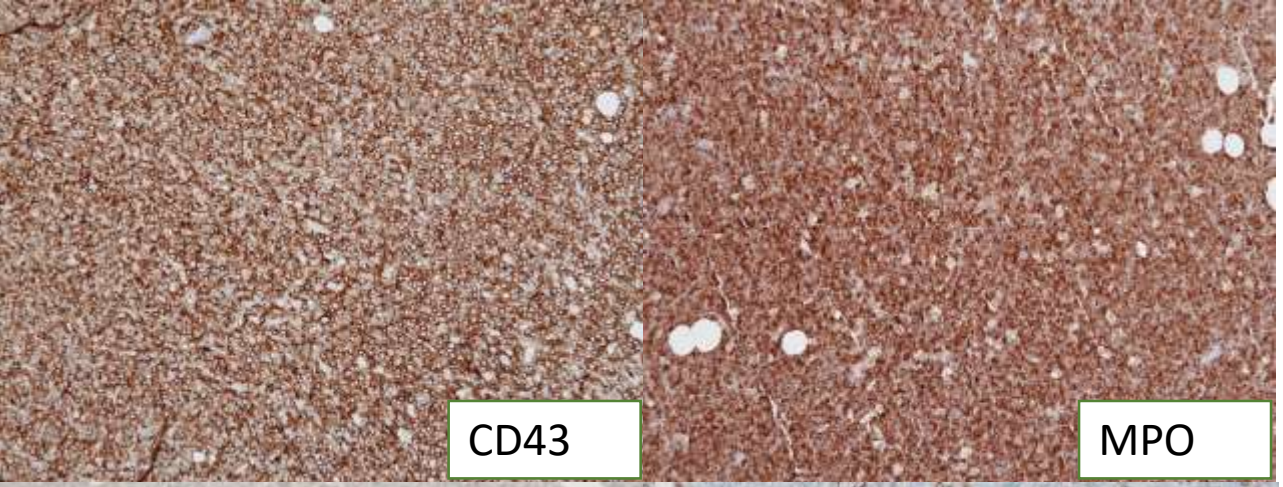
31-year-old female with 3week h/o progressive bilateral leg weakness, numbness, and tingling with an associated 1.5yr h/o episodic thoracic rib pain. MRI shows 4.8cm intradural extramedullary enhancing mass extending from T5-T7.

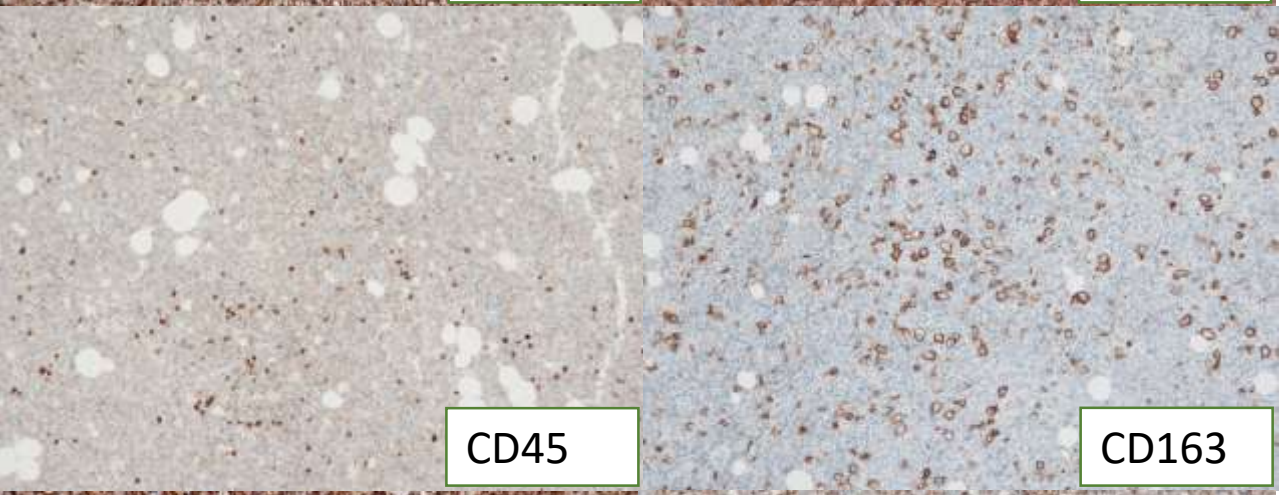












Negative

CKMIX
SOX10
PAX7
MYOGENIN
MYOD1
CD34
CD117
C123
CD56
CD138
CHROMO
SYNAPTO

MYELOID SARCOMA - FEATURES

- Defined as a tumor mass consisting of myeloid blasts at an anatomical site other than bone marrow
- M:F - 1.2:1, median age 56 (1mo to 89yr)
- Same etiology as AML and other myeloid neoplasms (MDS, MPN)
- Absence of underlying AML or other myeloid neoplasm in approximately one quarter
  - Detection of AML/other should be considered equivalent of a diagnosis of AML

MYELOID SARCOMA – IHC CHARACTERIZATION

- Promyelocytic cases lack CD34 and TdT, but express MPO and CD15
- Myelomonocytic are homogeneously positive for CD68 with MPO and CD68 (or CD163 confined to distinc CD34 negative subpopulations
- Monoblastic variant expresses CD68 and CD163 but lacks MPO and CD34
- Rare erythroid, megakaryoblastic variants and foci of plasmacytoid dendritic cell differentiation

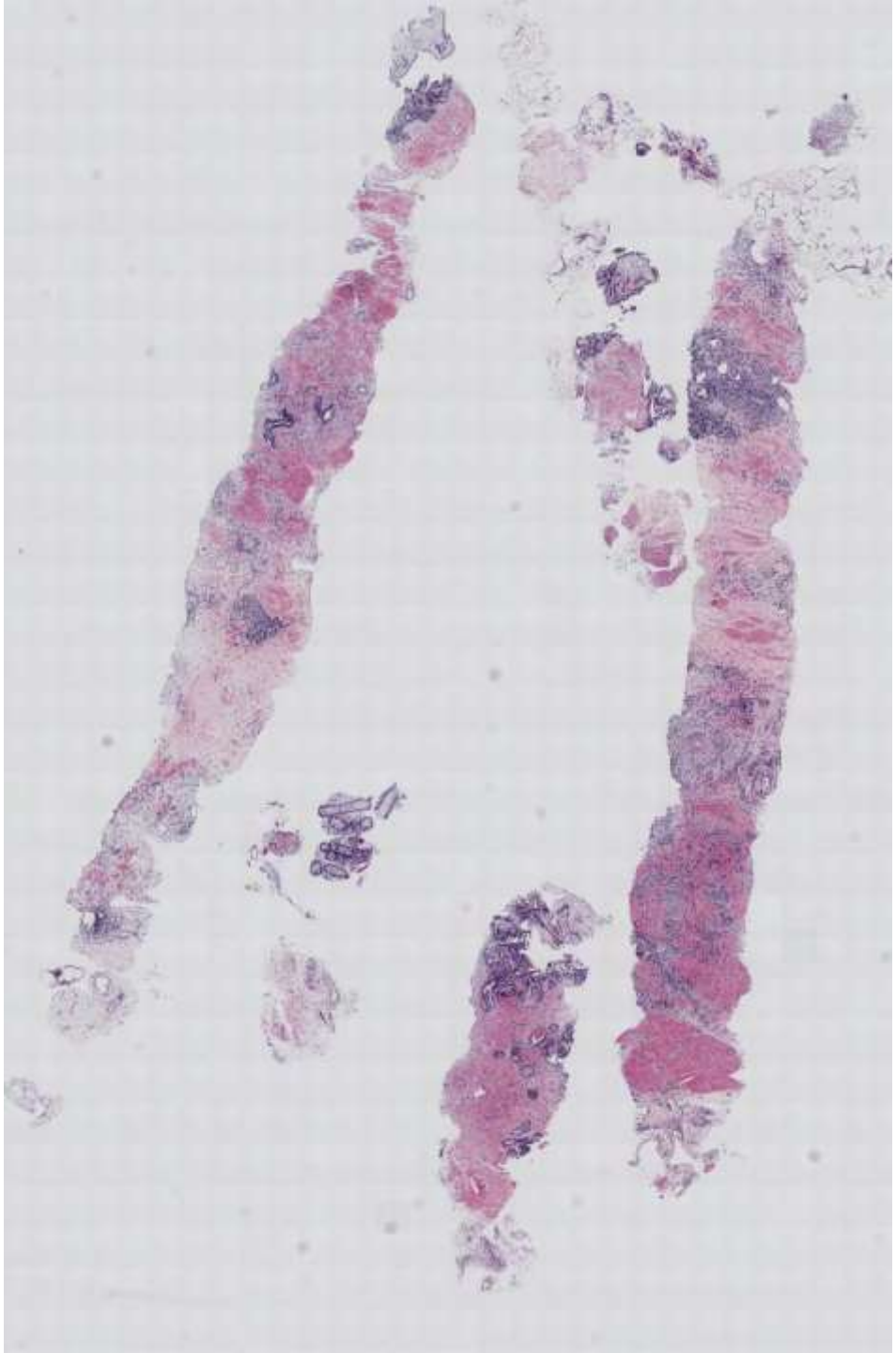
MYELOID SARCOMA – TREATMENT

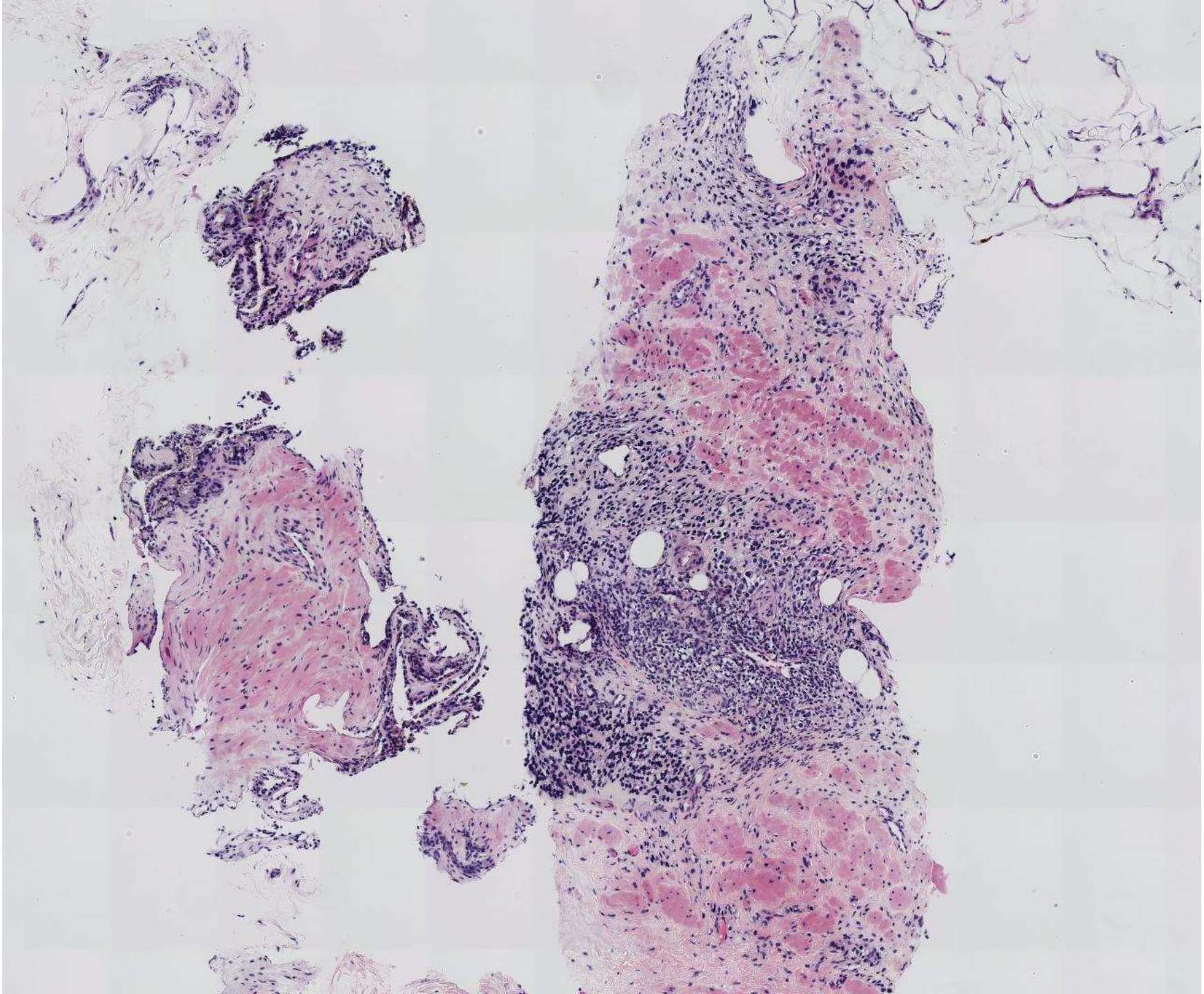
- 5 year survival for patients treated with allogenic bone marrow transplantation 47%
- Radiotherapy and surgery sometimes used upfront in patients who need tumor debulking or rapid symptom relief
- Our Patient:
  - Subtotal resection
  - Discharged to Rehab
  - No further follow-up to date

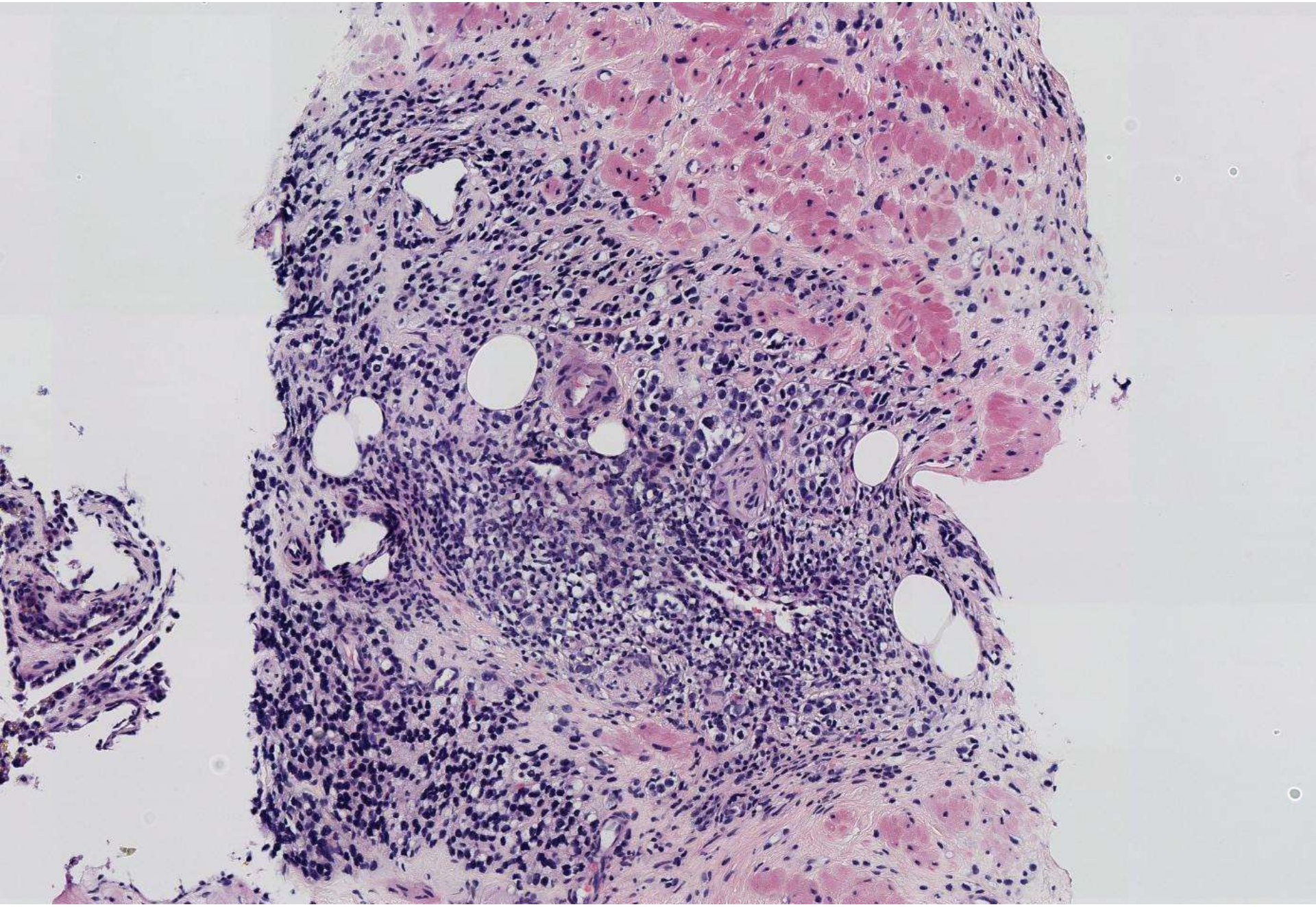
SB 6252

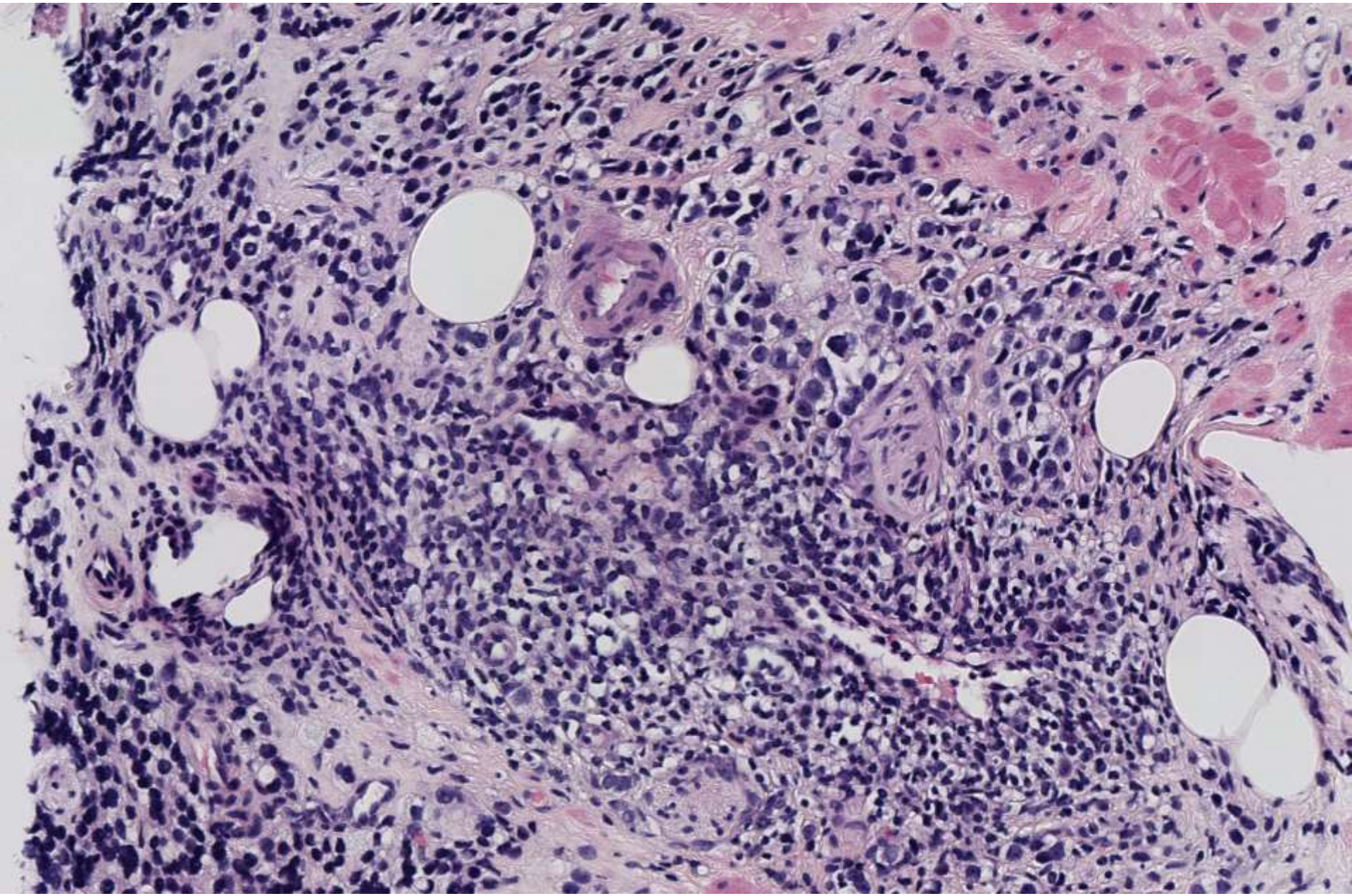
Ankur Sangoi; El Camino Hospital

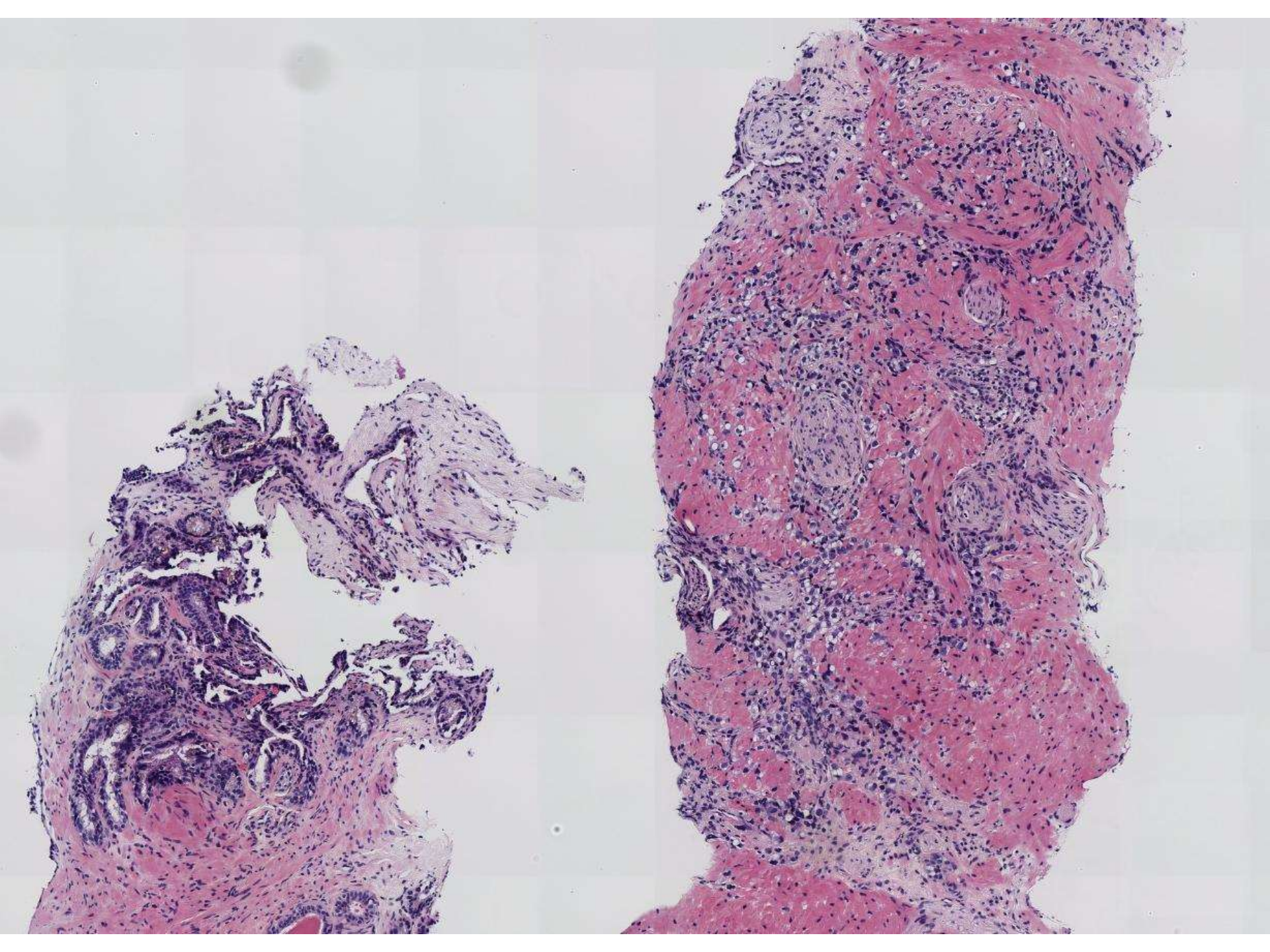
72-year-old male with seminal vesicle biopsy. No other history provided.

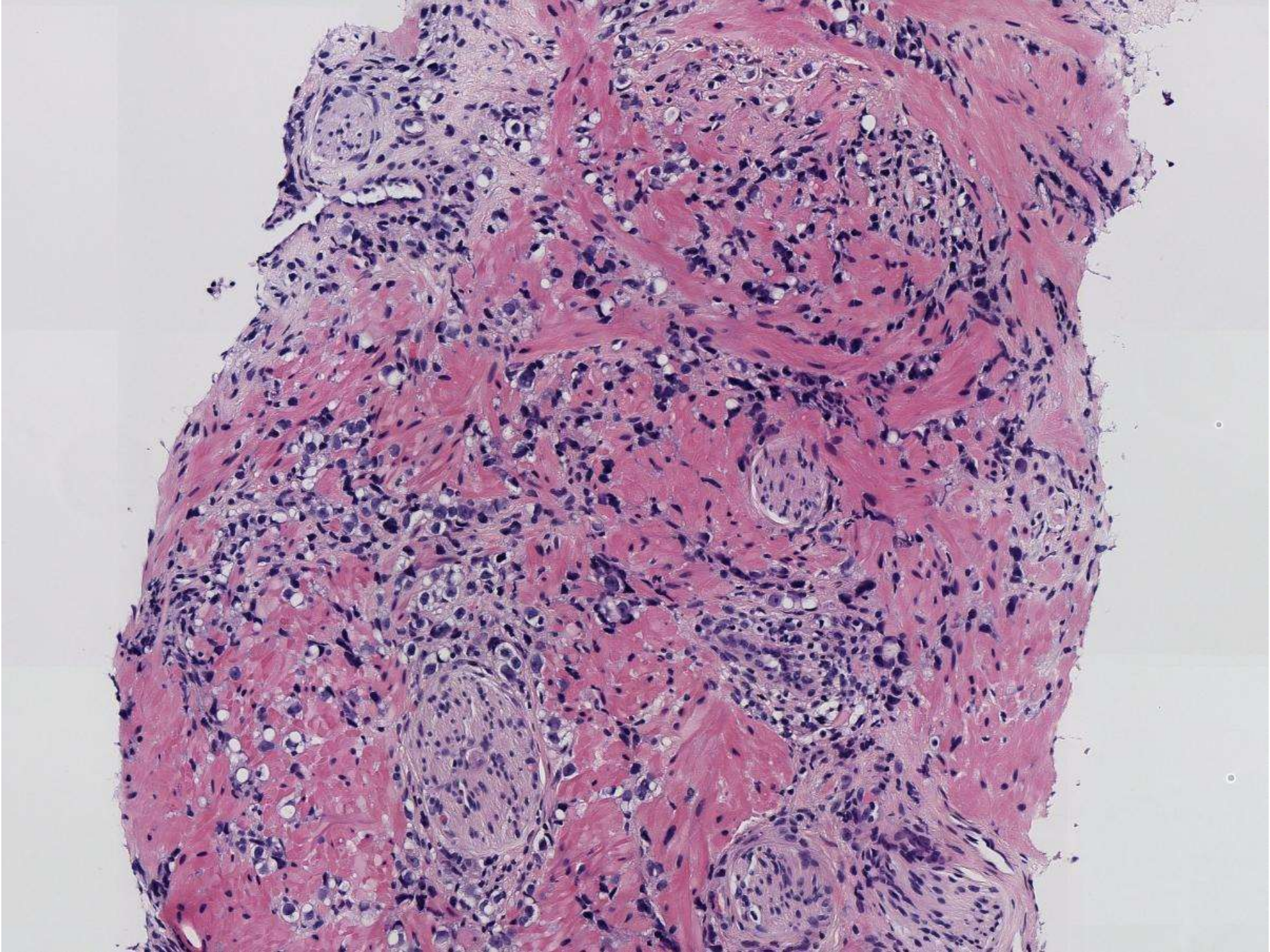


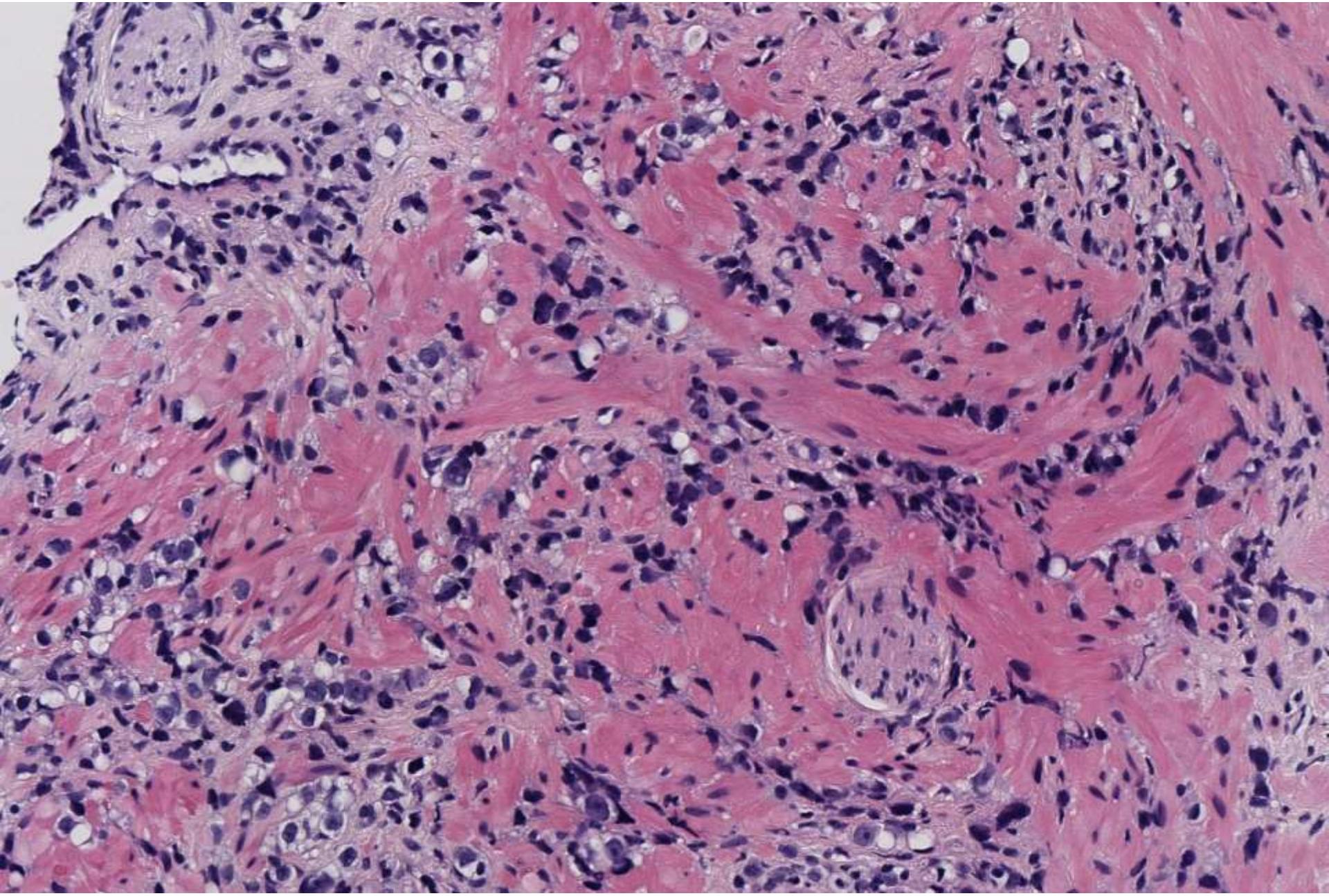


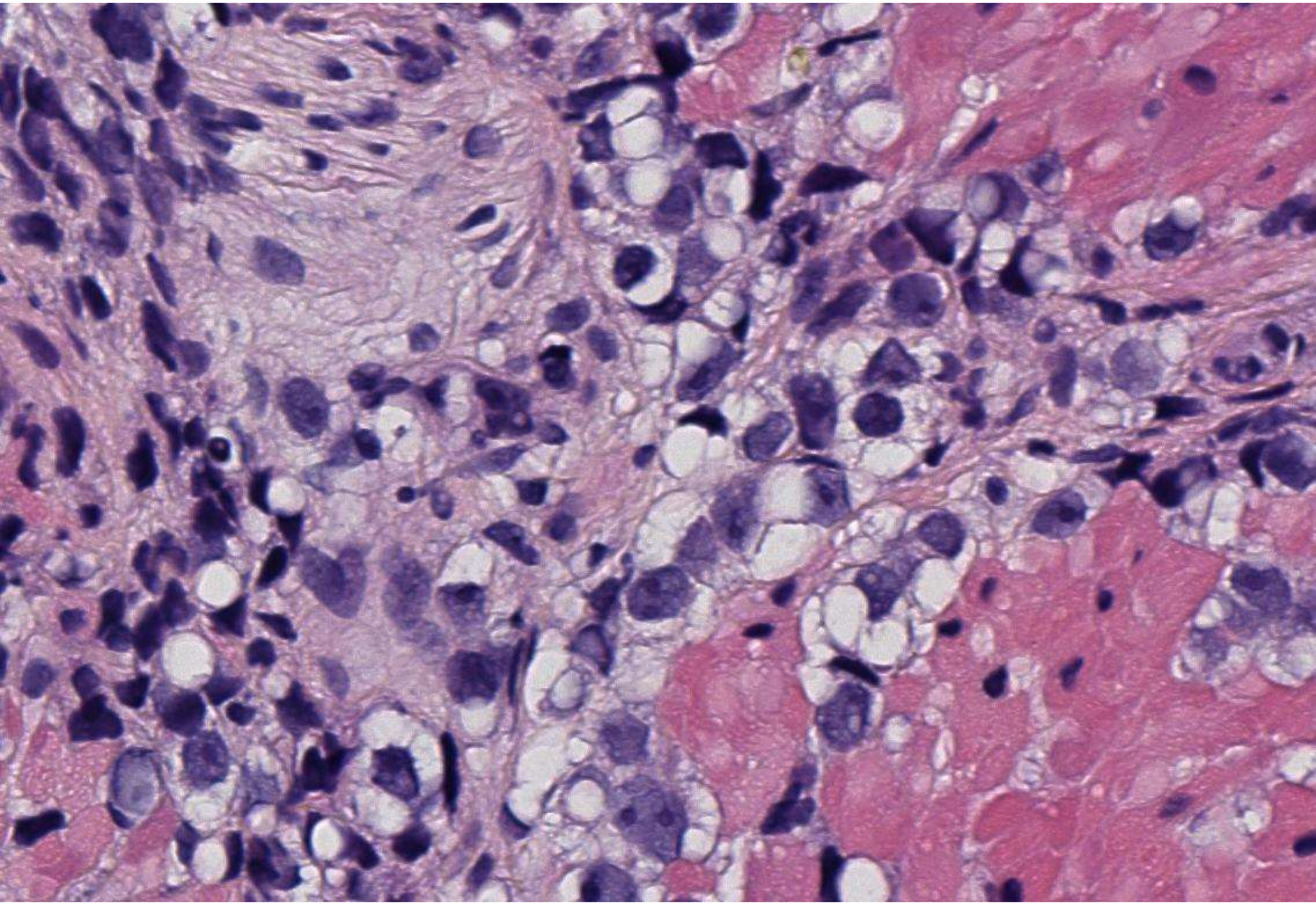












DDx

- **Grade group 5 prostatic adenocarcinoma**
  - Grade 4+5 vs 5+4
- **“treated” prostatic adenocarcinoma**
- **Plasmacytoid urothelial carcinoma**
- **Signet ring adenocarcinoma**
  - Direct invasion (bladder/colon) vs metastasis
- **Lymphoma**

Call to Urologist…

- **Patient had history of Grade 4+4 prostate cancer one year ago**
  - High clinical/radiographic stage
  - Has been on androgen-deprivation therapy (ADT)

Non-surgical treatments for prostate cancer

- **Androgen-deprivation therapy (ADT)**
  - Typically reserved for high-risk locally or systemically advanced disease not amenable to curative surgery
  - LHRH agonists/antagonists, cytochrome p450 inhib
    - Maximum androgen blockage
  - 5a-reductase inhibitors
    - “milder” form of ADT
- **Radiation therapy (RT); ablative therapy**
  - Can be used as primary therapy with curative intent for low-intermediate risk disease
- **Chemotherapy & immune-based therapy**
  - Used for androgen-independent disease

PATHOLOGICAL CHANGES IN BENIGN AND MALIGNANT PROSTATIC TISSUE FOLLOWING ANDROGEN DEPRIVATION THERAPY

VICTOR E. REUTER

ABSTRACT

Several retrospective studies, as well as prospective trials, have demonstrated that neoadjuvant total androgen ablation therapy leads to involutional changes in prostatic carcinoma and may have the potential to downstage operable prostate cancer. Following androgen deprivation therapy, virtually all prostates contain residual adenocarcinoma, although it may be extremely focal in up to 25% of cases. Morphological changes observed in treated prostatic adenocarcinoma include loss of glandular architecture, cytoplasmic vacuolization, and nuclear pyknosis. Involutional changes may be so dramatic that pathologists unaware of these changes will have difficulty in identifying residual disease. Similar changes may be seen in metastatic sites. Electron microscopy of treated tumors suggest that involution is due to programmed cell death (apoptosis). High grade prostatic intraepithelial neoplasia is present less frequently and usually only focally. Treated carcinoma exhibits a paradoxical high Gleason score but its proliferation rate and degree of aneuploidy is less than grade-matched, untreated tumors. Thus, grading of pretreated adenocarcinoma by conventional methods may be misleading and should be avoided. Treatment-related changes are also present in benign prostatic tissue and these include glandular atrophy, basal cell prominence and hyperplasia, and stromal hypercellularity. Several studies suggest pathologic downstaging of the tumor, but it remains unclear whether this finding will result in increased local control. UROLOGY **49**(Suppl 3A): 16–22, 1997.

Clinical understaging of operable prostate cancer is a common problem that undermines our attempts to gain local control by radical prostatectomy. In fact, clinical stage T2 prostatic carcinomas may have a positive surgical margin rate as high as 46% at the time of prostatectomy.[1] Luteinizing-hormone–releasing hormone (LHRH) analogs and nonsteroidal antiandrogens have provided effective alternatives to traditional androgen deprivation for the treatment of disseminated prostatic carcinoma.[2–5] Several reports have suggested an improved clinical response rate and survival with total androgen blockade as compared to traditional hormonal therapy.[4–11] Analogs of LHRH induce a chemical castration by markedly reducing serum levels of biologically active luteinizing hormone (LH), which in turn shuts off androgen release by testicular Leydig cells.[12] Following castration (chemical or surgical), low concentrations of androgens produced by the conversion of adrenal steroids at target tissue sites remain in the serum and are capable of stimulating the growth of prostatic carcinoma cells.[3,13,14] By blocking nuclear androgen receptors present in target tissues, antiandrogens such as flutamide inhibit the trophic effects of adrenal-derived androgens and thereby complete the hormonal blockade.[15–17]

Several retrospective and prospective histological studies of radical prostatectomies following neoadjuvant total androgen ablation therapy have demonstrated significant involutional changes in normal prostatic tissue as well as residual prostatic adenocarcinoma.[18–20] These studies have attempted to assess the effectiveness of neoadjuvant total androgen ablation for the treatment of clinically localized prostatic carcinoma. In this review I examine the morphological changes in prostatic adenocarcinoma and benign prostatic tissue associated with neoadjuvant therapy.

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PII 0090-4295(97)00164-7

TABLE I. ***Pathologic findings in normal prostate and prostatic carcinoma following androgen blockade***

Stroma
Focal hypercellularity
Focal lymphocytic/histiocytic infiltrate
Basal cell epithelium
Basal cell prominence
Basal cell hyperplasia
"Immature squamous metaplasia"
Squamous metaplasia
Secretory acinar epithelium
Loss of hyperplastic glandular architecture
Cytoplasmic clearing
Nuclear pyknosis
Prostatic intraepithelial neoplasia (PIN)
Cytoplasmic clearing
Nuclear pyknosis
Loss of nucleolar prominence
Infiltrating prostatic adenocarcinoma
Cytoplasmic clearing
Nuclear pyknosis
Loss of nucleolar prominence
Loss of glandular architecture
Cytoplasmic vacuolization and mucinous degeneration

Take home points

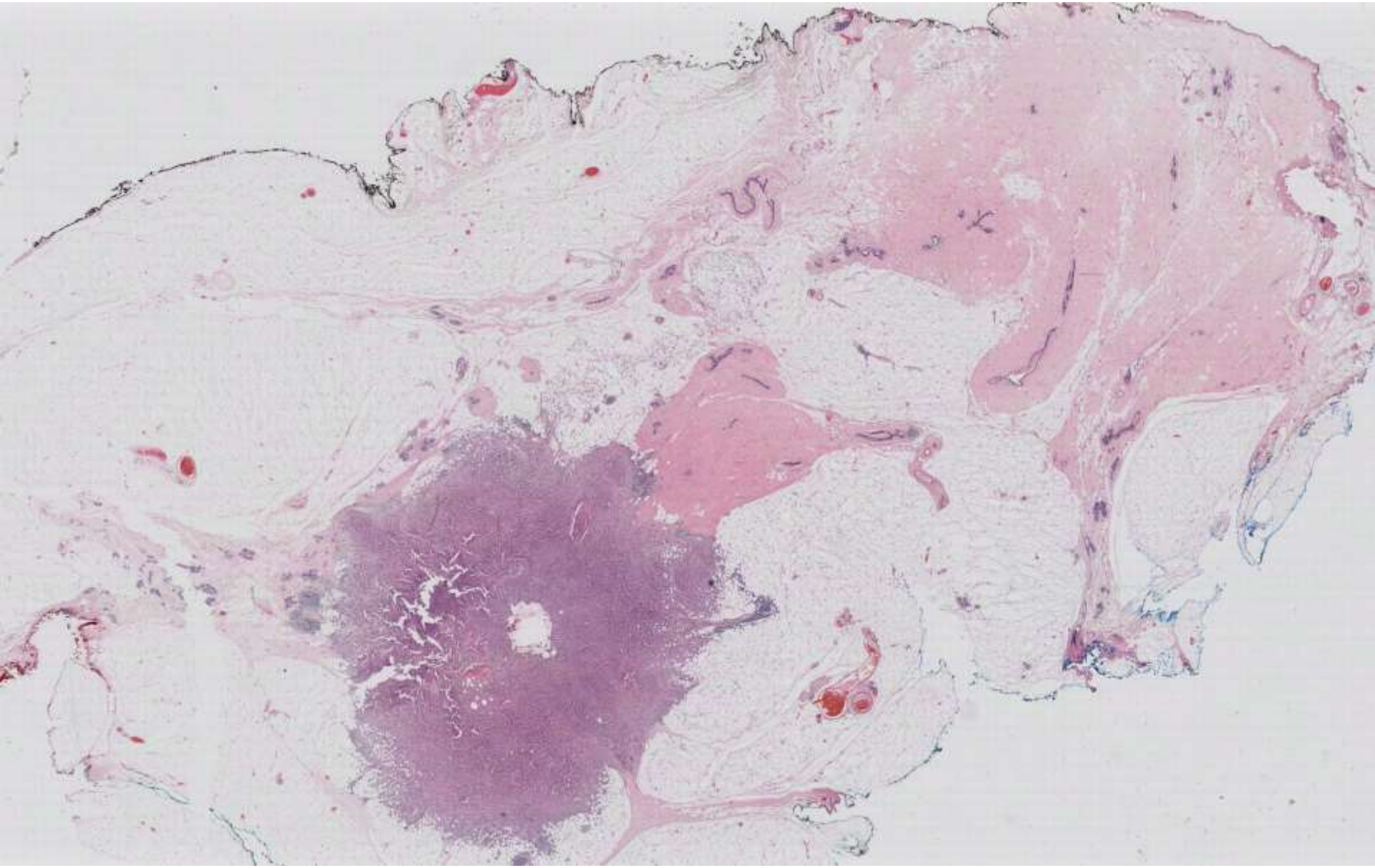
- **When encountering funny-looking prostate cancer (and/or when only seminal vesicles are biopsied)**
  - Inquire about prior therapy
    - If treated → DON'T GRADE TUMOR!

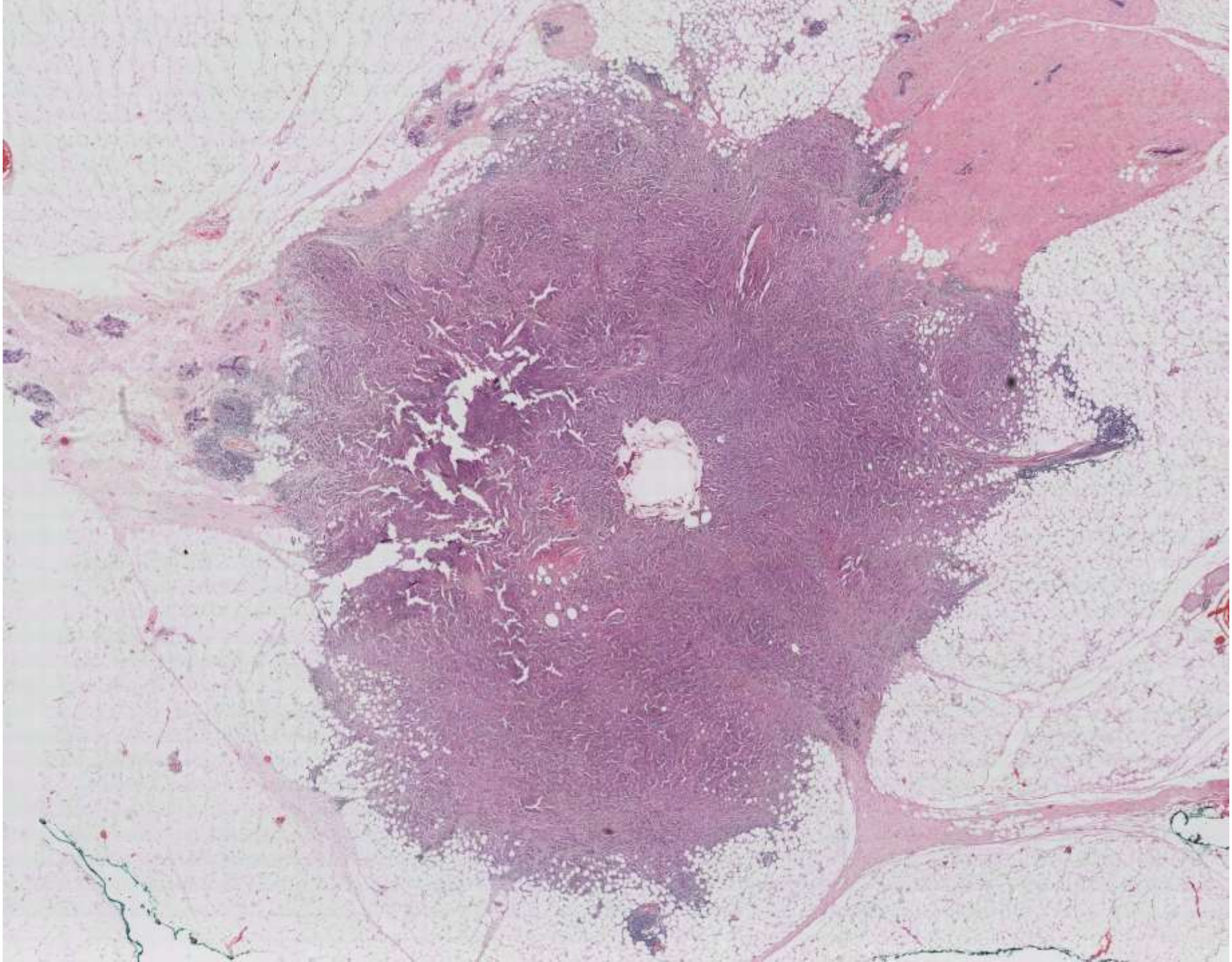
    (OKAY to grade if tumor shows no obvious treatment effect)

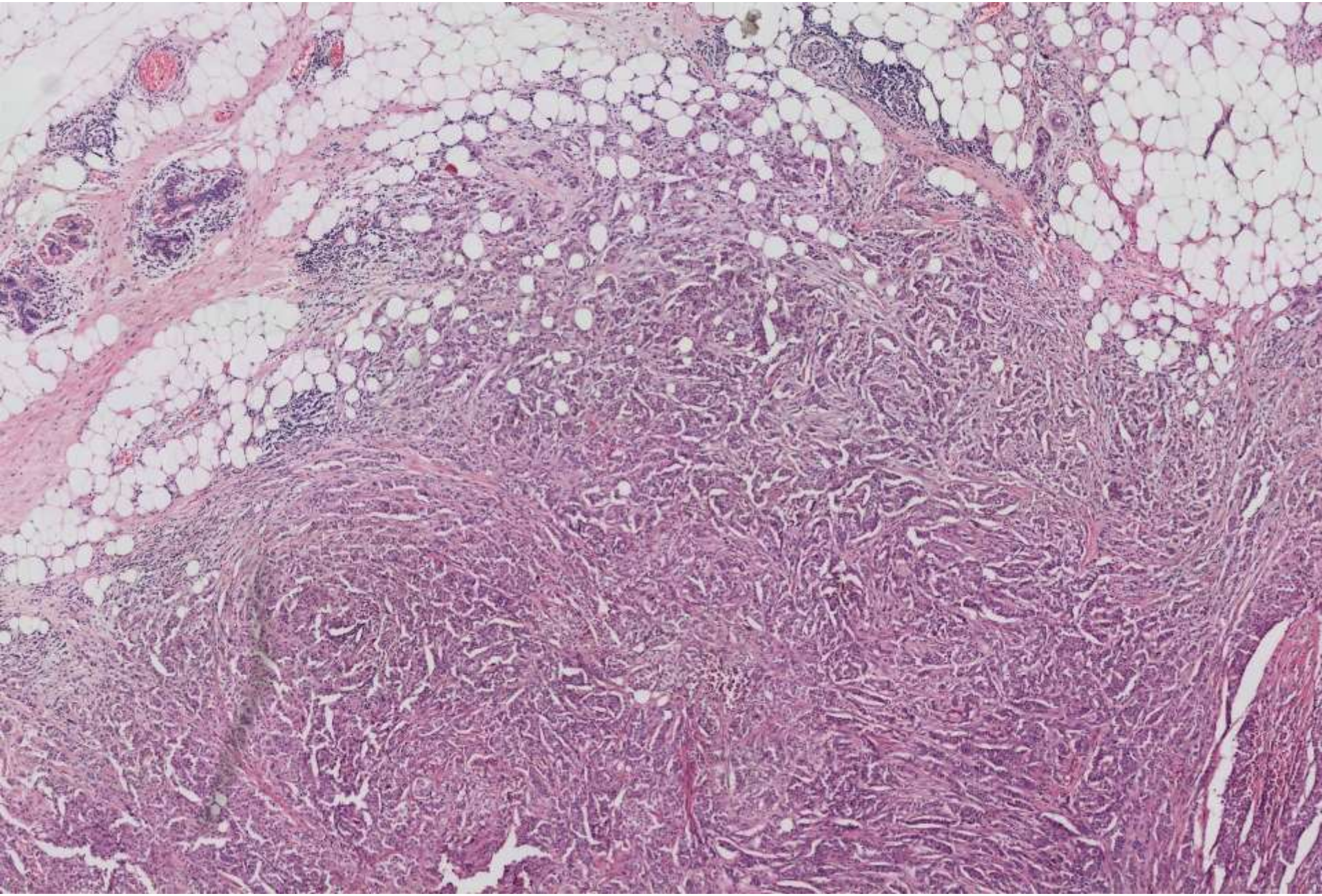
SB 6253
[scanned slide available]

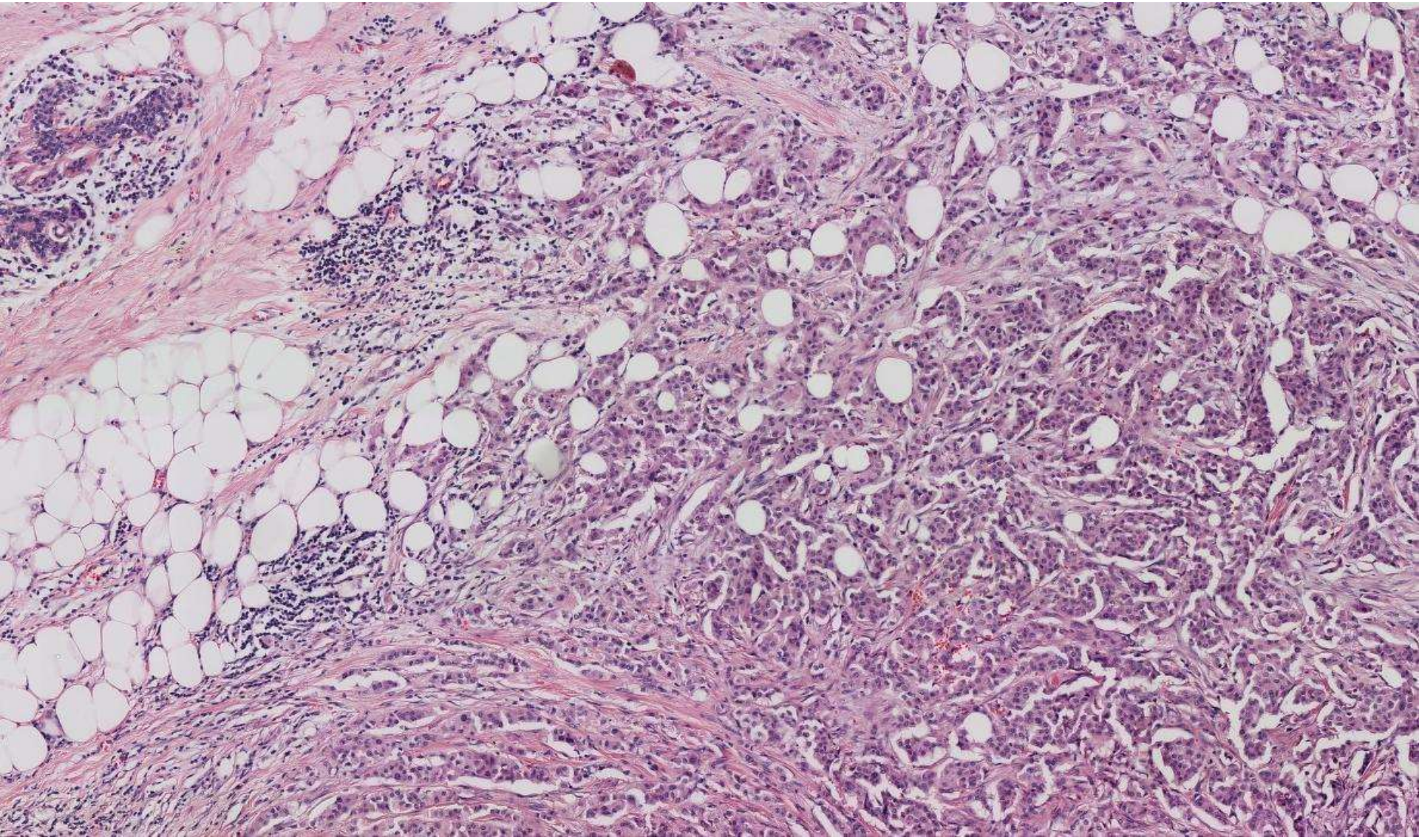
Li Lei/Yiting Li/Megan Troxell; Stanford

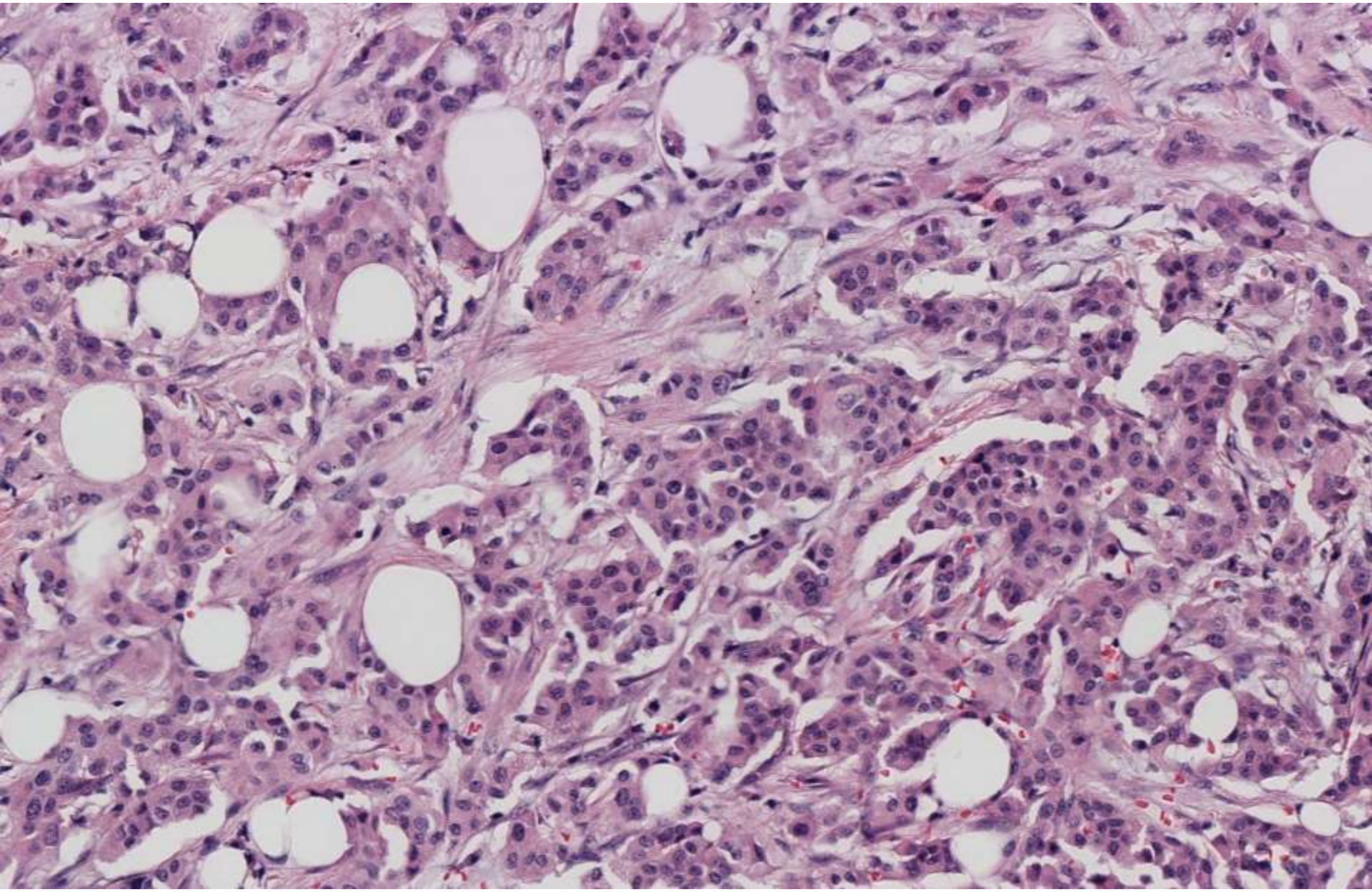
65-year-old female with bilateral breast masses, right breast palpable mass measuring 9mm on ultrasound, and left breast mass-like area measuring 2mm on ultrasound.

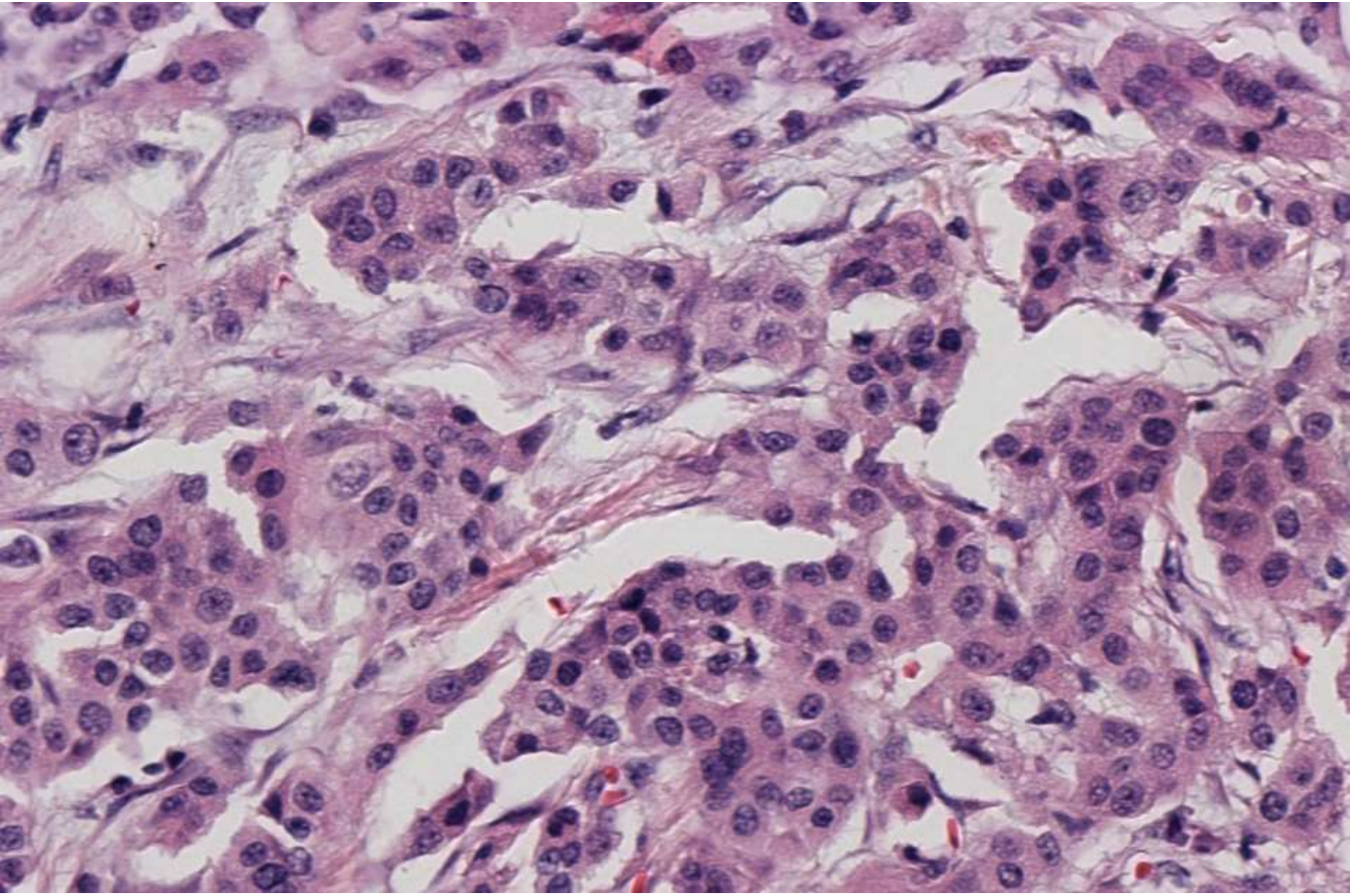












Ancillary Studies

- Estrogen Receptor Expression: **NEGATIVE (0%)**
- Progesterone Receptor Expression: **NEGATIVE (0%)**
- Ki67 proliferative rate: 15-20%
- HER2 by Immunohistochemistry: **NEGATIVE (1+)**
- HER2 Gene Status by FISH: **NOT AMPLIFIED**

Differential Diagnosis

- Infiltrating breast carcinoma
  - Morphologically low grade but triple negative
  - Multiplicity
  - Lack of in situ lesions

Differential Diagnosis

- Infiltrating breast carcinoma

- Metastatic neoplasm
  - Initial presentation
  - History not given
  - Histologic or immunophenotypic overlap

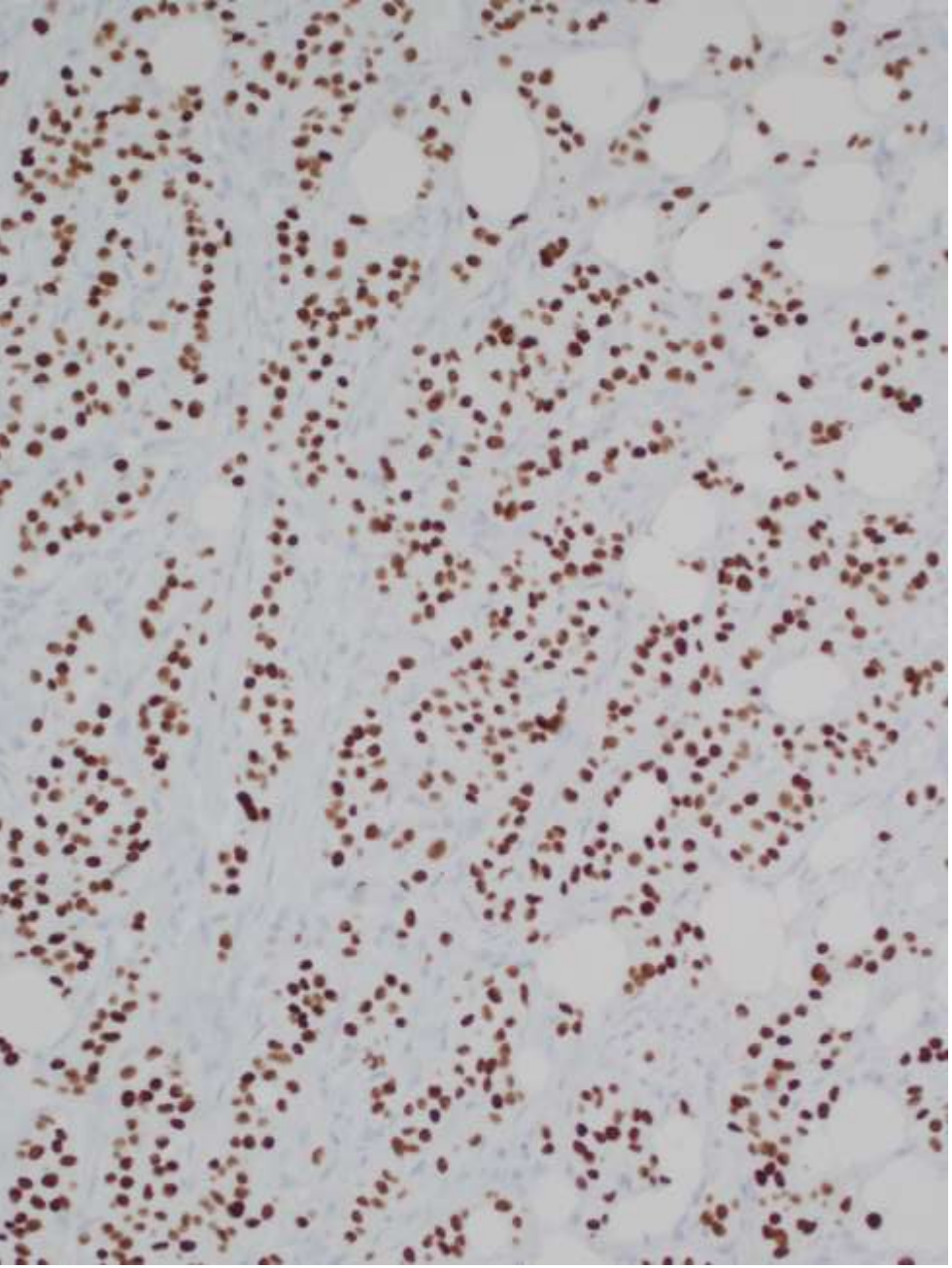
Additional Immunohistochemistry Work-up

Positive

- CK7
- TTF1
- NapsinA
- E-cadherin

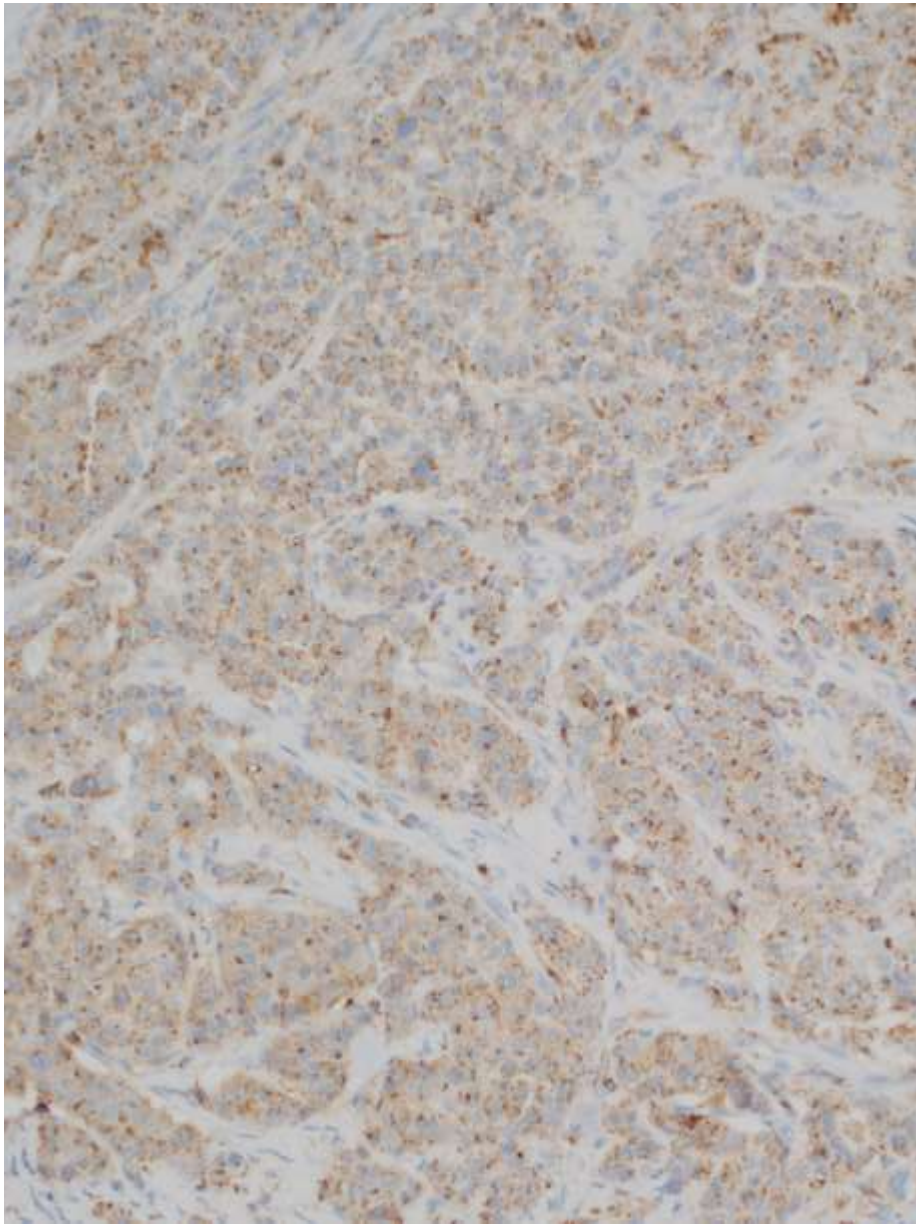
Negative

- GATA3
- BRST2 (GCDFP15)
- Androgen receptor
- Thyroglobulin
- Synaptophysin

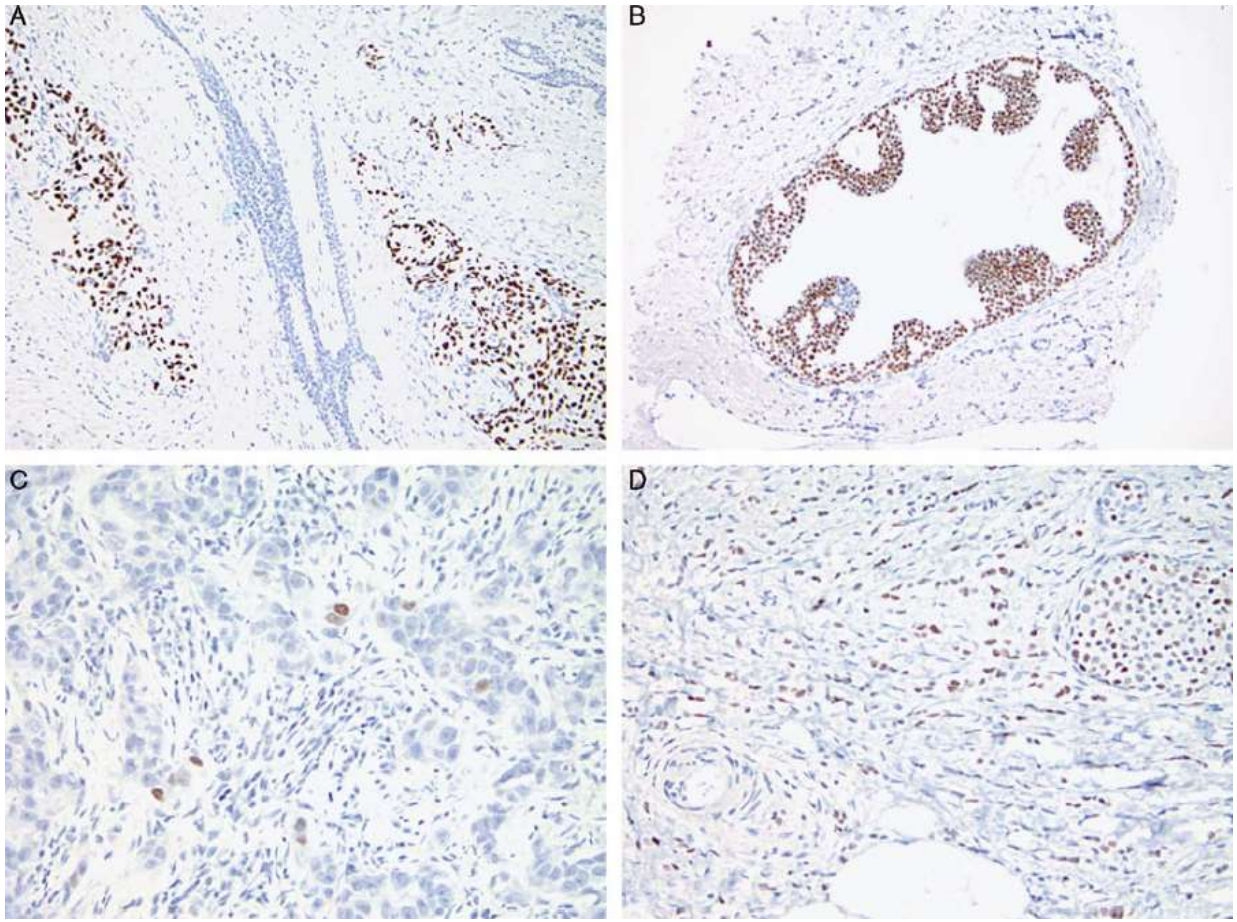


TTF1 (L)

Napsin A



TTF-1 expression (SPT24) was detected in 2.4% of breast carcinomas (13/546 cases)



Schnitt SJ, et al. Am J Surg Pathol 2010;34:1881

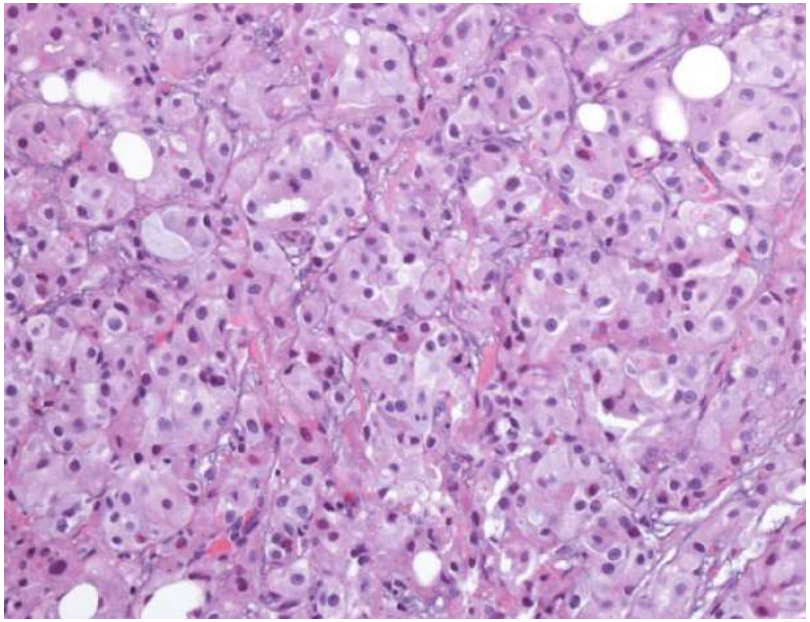
TTF-1: The Chosen Clone Matters ?

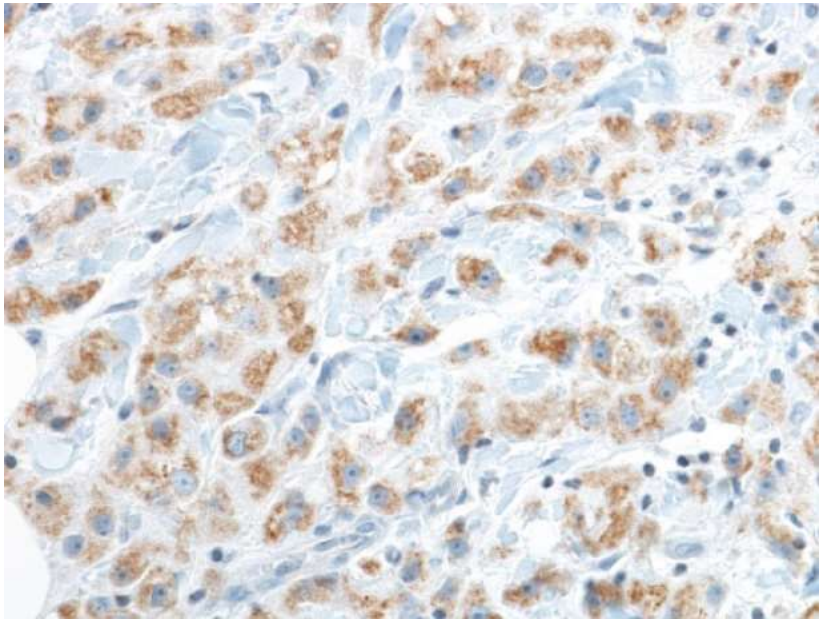
Table 2. Performance of 8G7G3/1 and SPT24 clonal antibodies in differentiating breast carcinoma and pulmonary carcinoma

	8G7G3/1	SPT24
Sensitivity	71.6%	70.7%
Specificity	99.9%	100%
Positive predictive value	99.3%	100%
Negative predictive value	95.0%	95.1%
Accuracy rate	95.5%	95.4%

Ni YB, Histopathology 2014;64: 504

Aberrant Expression of Napsin A in Breast Carcinoma With Apocrine Features (32/48 cases)





Vitkovski T, et al. Int J Surg Pathol. 2016;24:377

GATA3: A Multispecific But Potentially Useful Marker

TABLE 1. Expression of GATA3 in 2040 Epithelial Neoplasms

Tumor Type	Positive/Total, n (%)
Adrenocortical carcinoma	3/27 (11)
Basal cell carcinoma, skin	61/62 (98)
Benign skin adnexal tumors (see text)	24/24 (100)
Breast, ductal carcinoma, primary	164/179 (92)
Breast, ductal carcinoma, metastatic	49/51 (96)
Breast, lobular carcinoma	38/38 (100)
Colon, adenocarcinoma	2/142 (1)
Endometrium, adenocarcinoma	6/89 (7)
Germ cell tumor, seminoma	0/76
Germ cell tumor, choriocarcinoma	11/11 (100)
Germ cell tumor, endodermal sinus tumor	6/6 (100)
Germ cell tumor, pure embryonal carcinoma	0/5* (40)
Liver, hepatocellular carcinoma	1/47 (2)
Liver, cholangiocarcinoma	5/57 (9)
Lung, adenocarcinoma	6/71 (8)
Lung, small cell carcinoma	0/30
Lung, carcinoid	0/11
Small, intestine, carcinoid	0/18
Malignant mesothelioma	37/64 (58)
Merkel cell carcinoma	0/4
Ovary, serous carcinoma	4/73 (6)
Ovary, other carcinomas	0/25
Pancreas, adenocarcinoma	23/62 (37)
Pancreas, neuroendocrine tumor	0/15
Prostate, adenocarcinoma	2/95 (2)
Rectum, adenocarcinoma	0/27
Renal cell carcinoma, chromophobe	18/35 (51)
Renal oncocytoma	6/35 (17)
Renal cell carcinoma, other than chromophobe	3/154 (2)
Salivary gland, adenoid cystic carcinoma	5/17 (29)
Salivary gland, ductal carcinoma	6/14 (43)
Squamous cell carcinoma, skin	25/31 (81)
Squamous cell carcinoma, cervix	7/21 (33)
Squamous cell carcinoma, larynx	8/36 (16)
Squamous cell carcinoma, lung	9/74 (12)
Stomach, adenocarcinoma	6/133 (5)
Thymoma	0/41
Thyroid, papillary carcinoma	3/55 (5)
Thyroid, follicular carcinoma	1/20 (5)
Thyroid, anaplastic carcinoma	1/11 (9)
Urothelial carcinoma, low grade	22/22 (100)
Urothelial carcinoma, high grade	27/32 (84)

Miettinen M, et al. Am J Surg Pathol 2014;38:13

Final diagnosis

- **ADENOCARCINOMA, CONSISTENT WITH METASTATIC PULMONARY ORIGIN**

Follow-up

- PET CT scan:
  - 3.7 cm right lower lobe spiculated mass
  - mediastinal lymphadenopathy
  - disseminated liver and bone metastasis

- Treated with chemoradiation for stage 4 lung cancer; Alive 4 months after the diagnosis

Summary

- Tumors metastatic to the breast are far less common than primary breast cancer
- 10-30% of breast metastases may represent the initial presentation of disease
- Primary: contralateral breast, hematolymphoid malignancies, melanoma, lung cancer, ovarian serous carcinoma, etc.

Histologic Features of Breast Metastasis

- Unusual histology
- Lack of accompanying DCIS
- Lack of central elastosis or desmoplasia
- Presence of periductal or perilobular growth pattern
- Multiplicity
- Subcutaneous location
- Lack of calcification (or presence of psammomatous calcification)
- Abundant lymphangietic tumor

Troxell ML. Semin Diagn Pathol. 2017;34:479

Overlapping histologic patterns between primary and metastatic breast tumors

- Micropapillary: ovary, urothelial, lung
- Mucinous: colorectal, ovary, lung
- Signet ring: gastric, colorectal, plasmacytoid variant of urothelial carcinoma, lymphoma
- Single file infiltration: lymphoma

Troxell ML. Semin Diagn Pathol. 2017;34:479

SB 6254

Sharon Wu; El Camino Hospital

64-year-old male presents with eosinophilia and thrombocytopenia. Recent clinical encounters for diarrhea and atrial fibrillation. Total IgE and tryptase are normal. Vitamin B12 level 7179pg/mL (high), testing for strongyloides and tuberculosis negative. CBC: Hgb 14.7/plt 118/wbc 15.14 (neutrophils 7.2%, lymphs 10.4%, monos 3.2%, eo's 78.2%), abs eo's 11.8.

Bone marrow aspirate/biopsy performed.

Clinical History

- 64-year-old man with eosinophilia and thrombocytopenia.
- Recent clinical encounters for diarrhea and atrial fibrillation
- Total IgE normal
- Tryptase normal
- Vitamin B12 level 7,179 pg/mL (**H**)
- Testing for strongyloides and tuberculosis negative

CBC

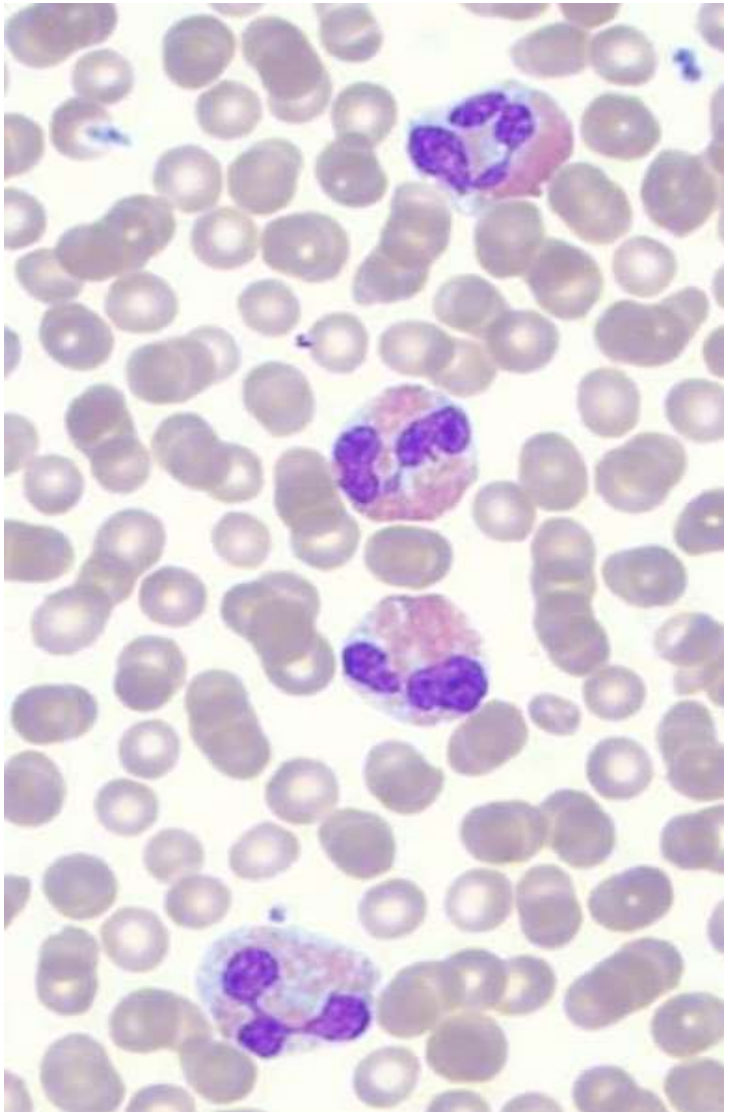
Hgb 14.7 g/dL

Plt 118 K/uL

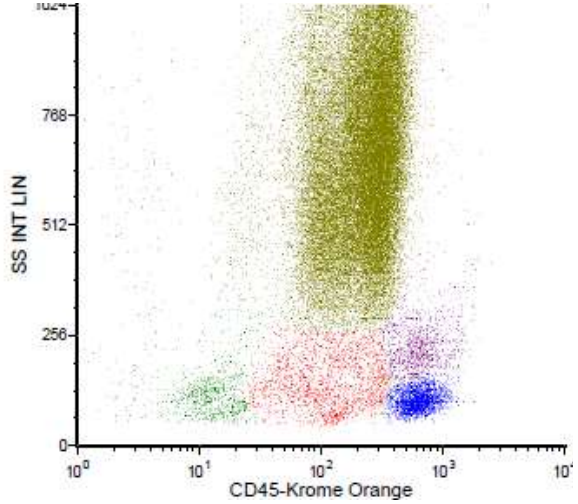
WBC 15.14 k/uL

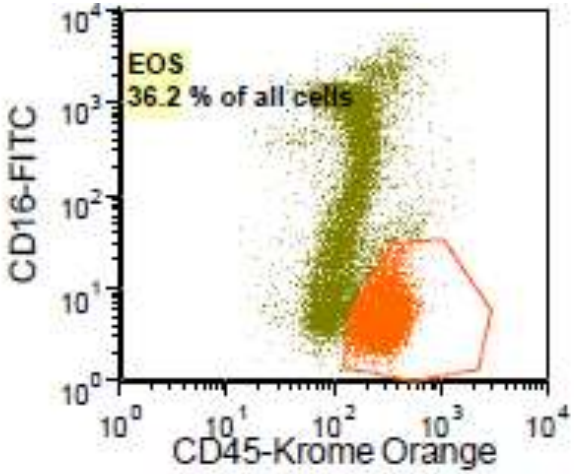
- Neutrophils 7.2%
- Lymphs 10.4%
- Monos 3.2%
- Eos 78.2%

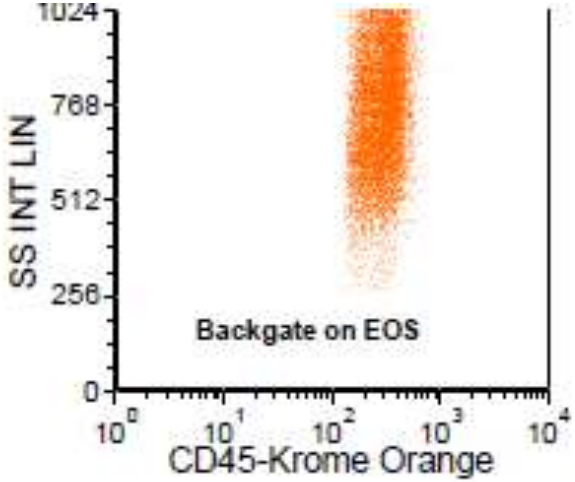
Absolute eos: 11.8 K/uL

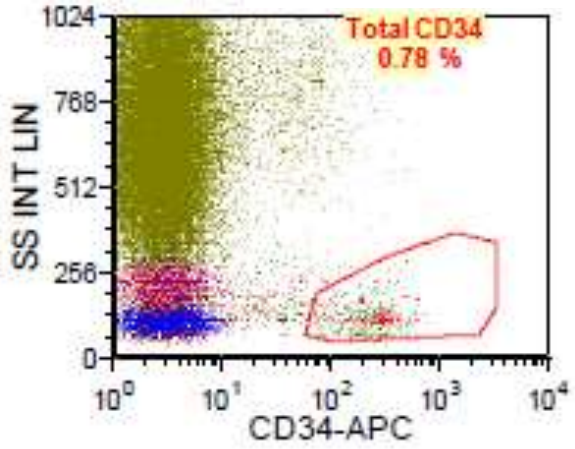


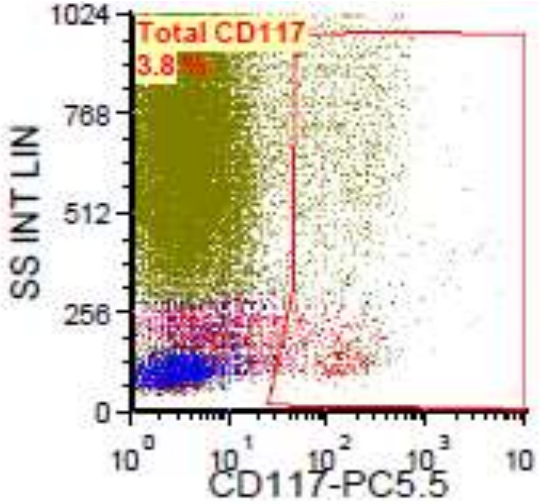
Bone Marrow Aspirate Flow Cytometry

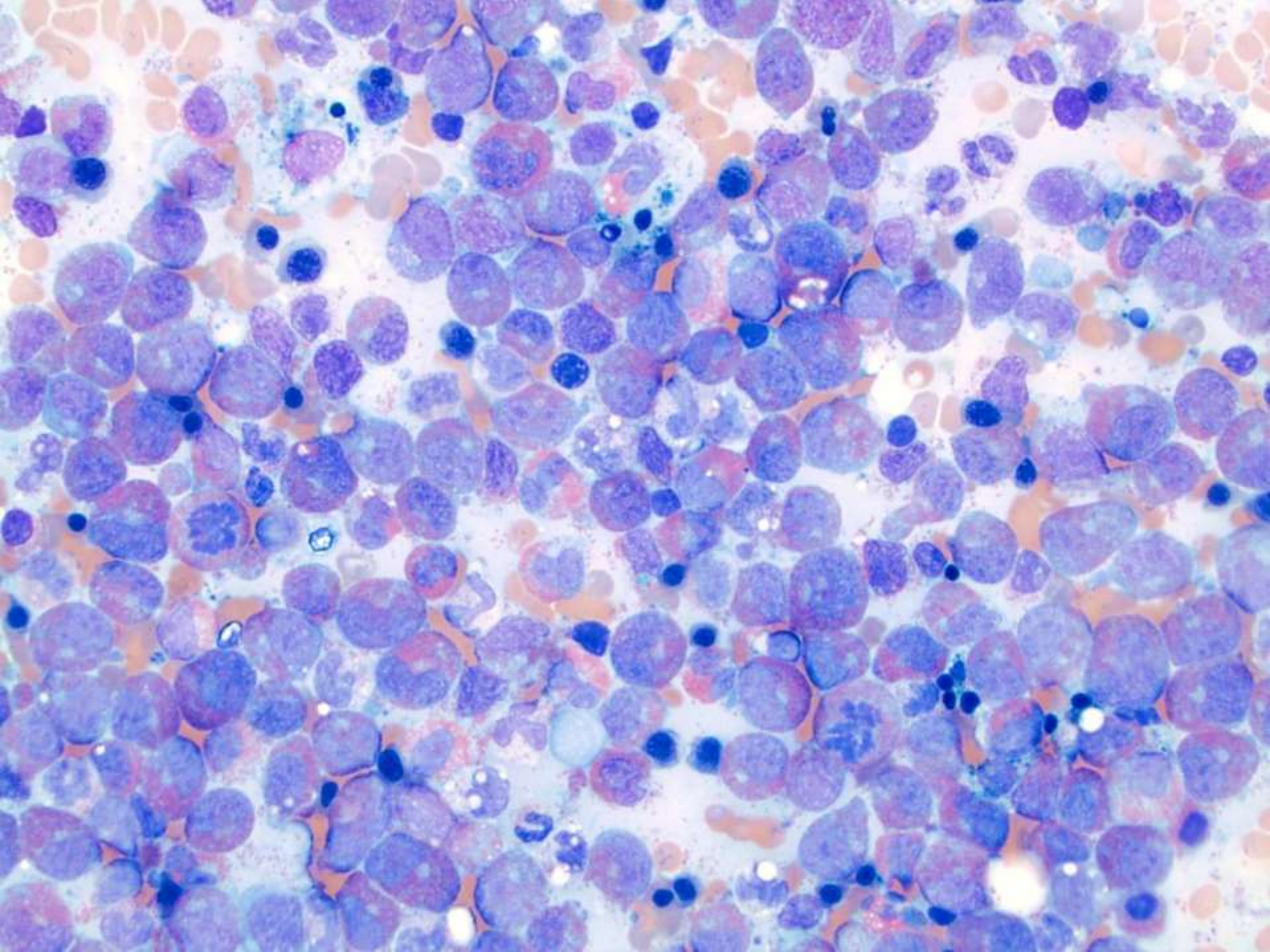


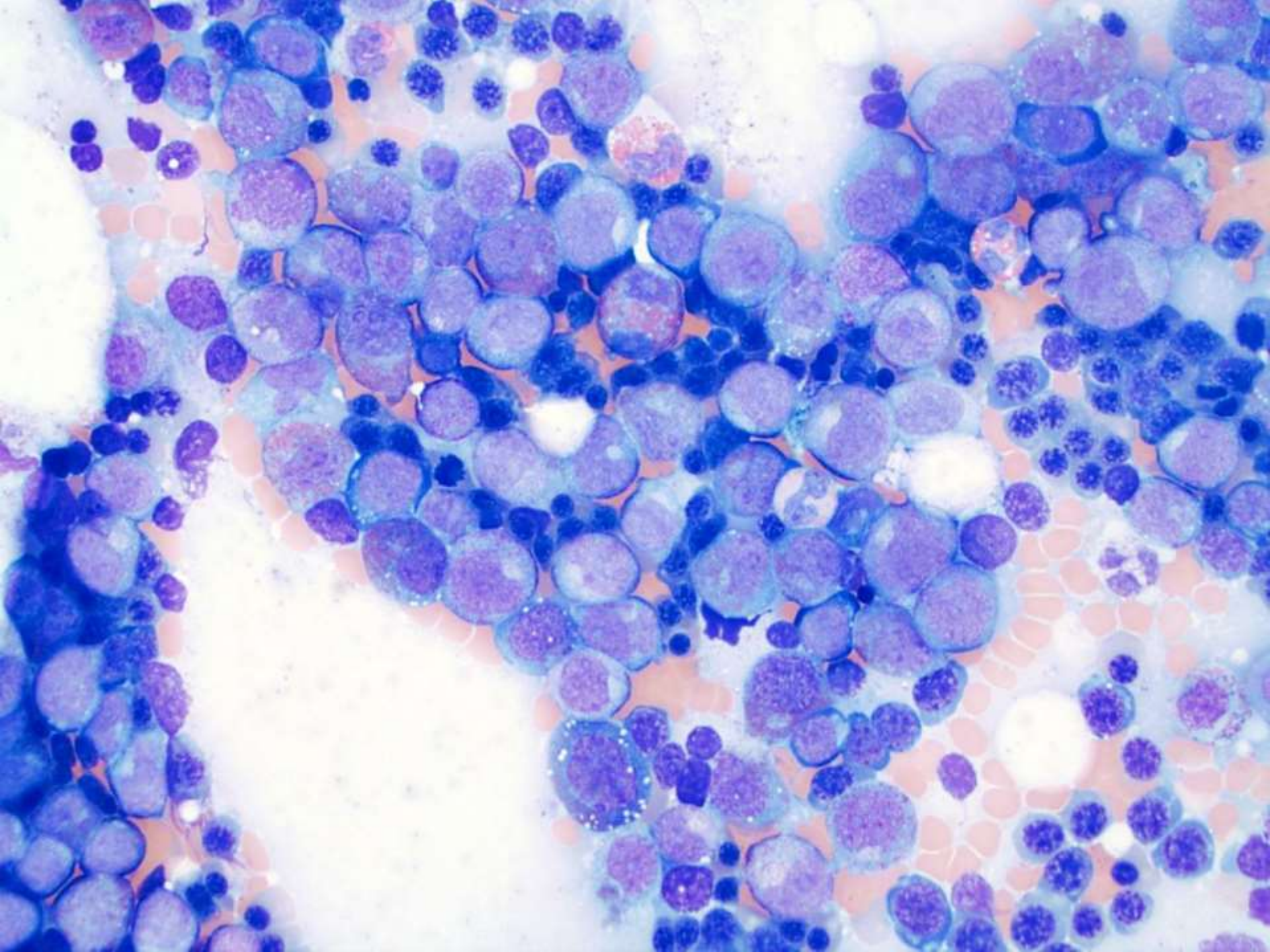


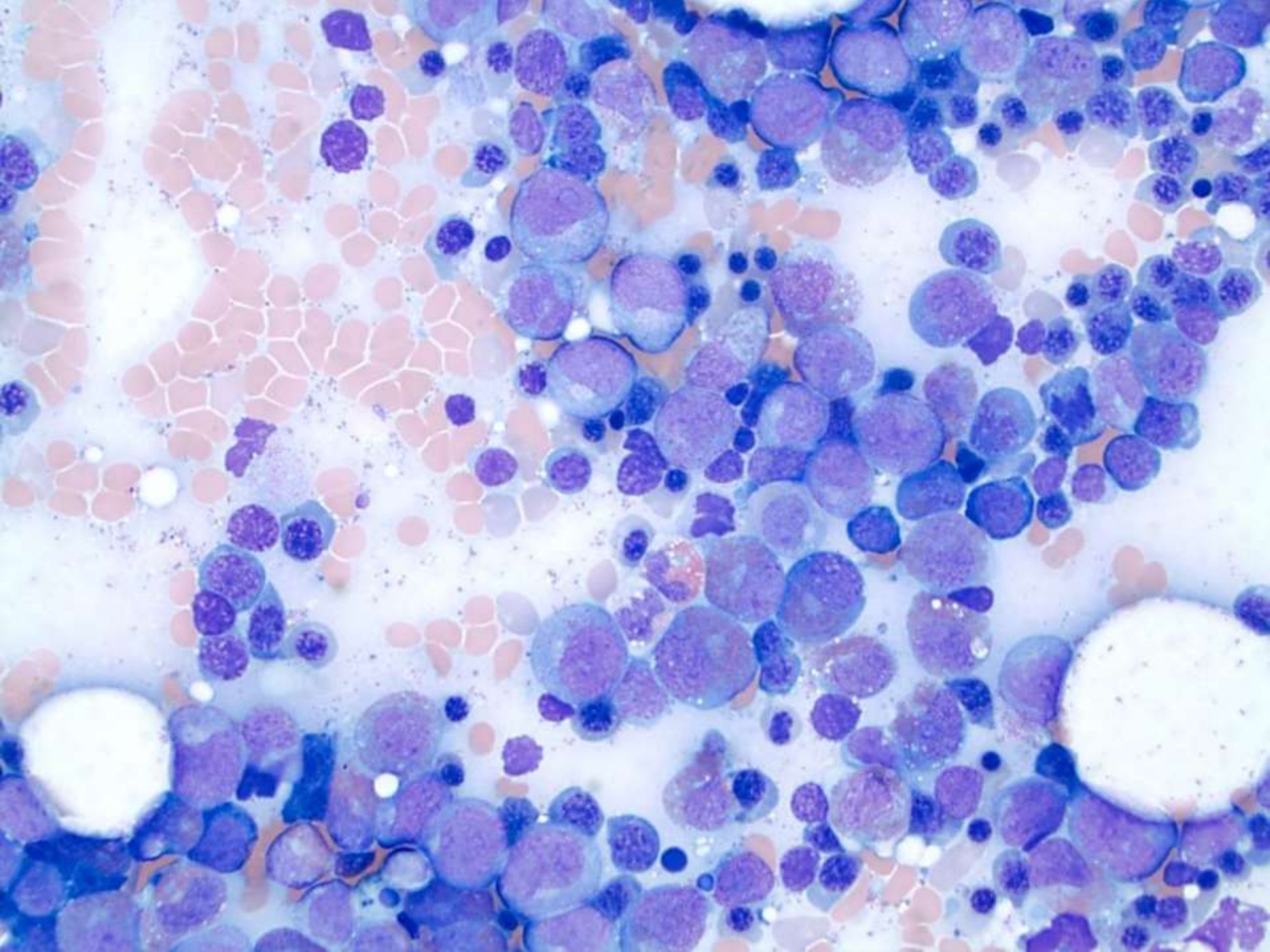


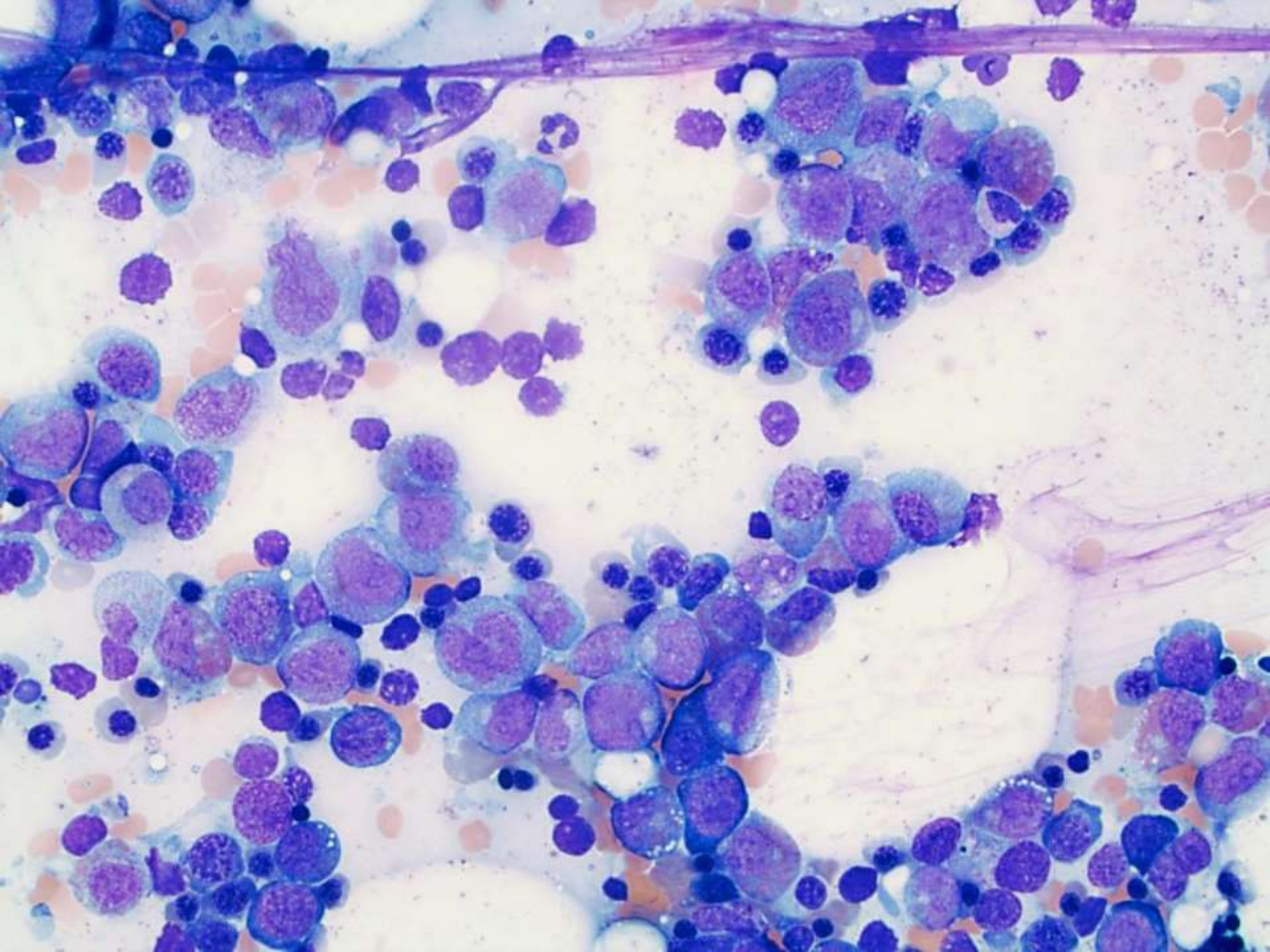


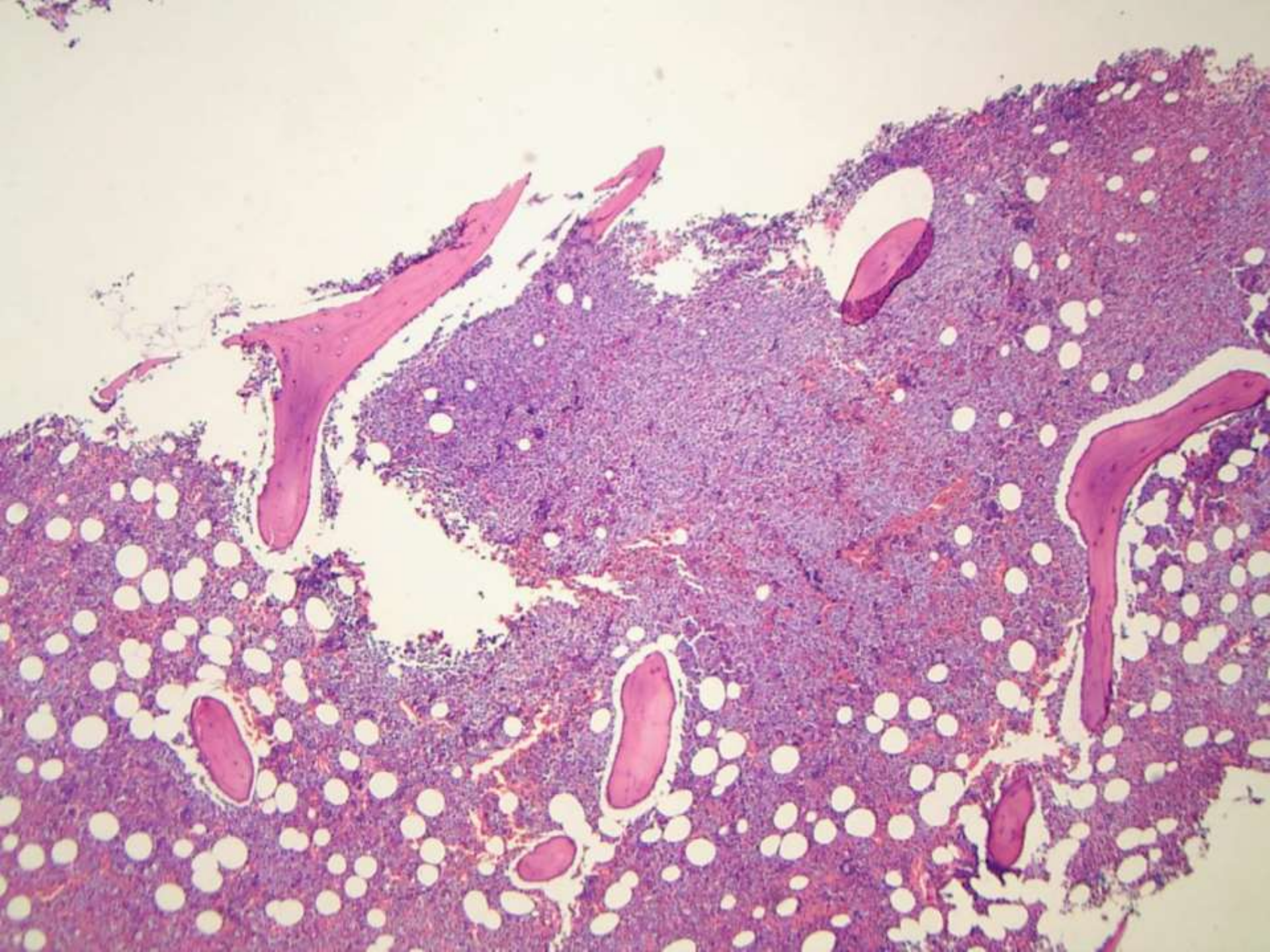


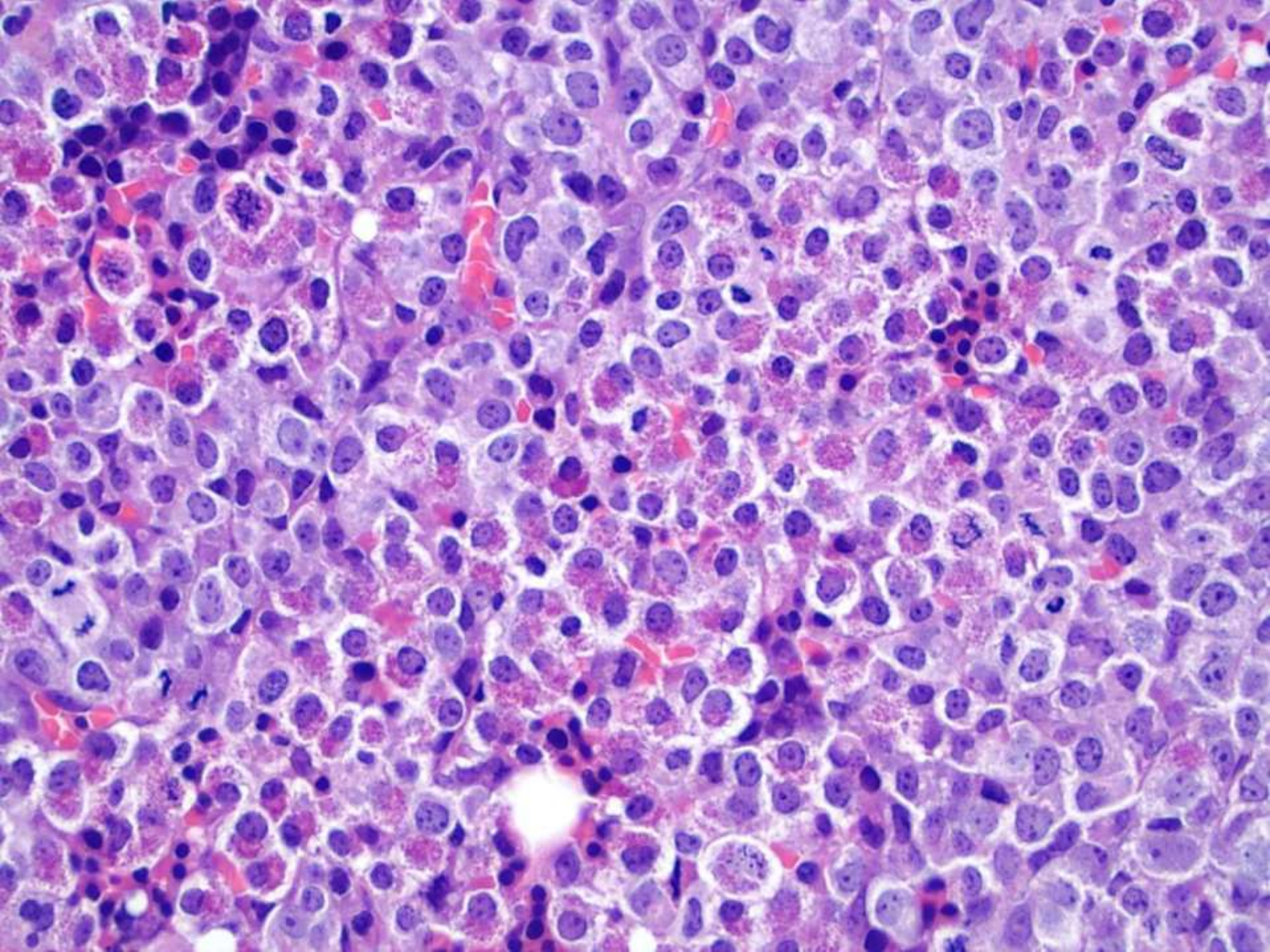


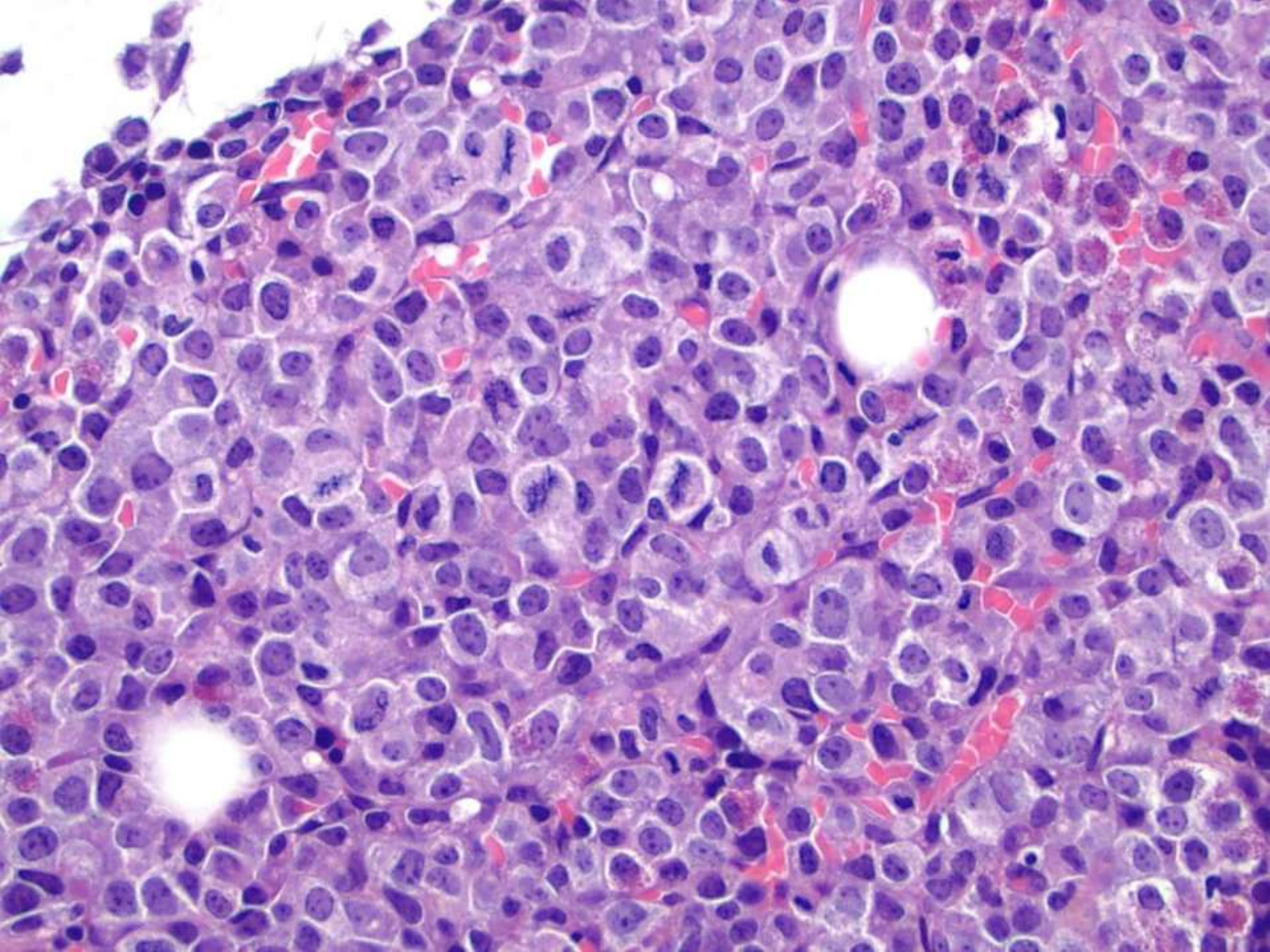


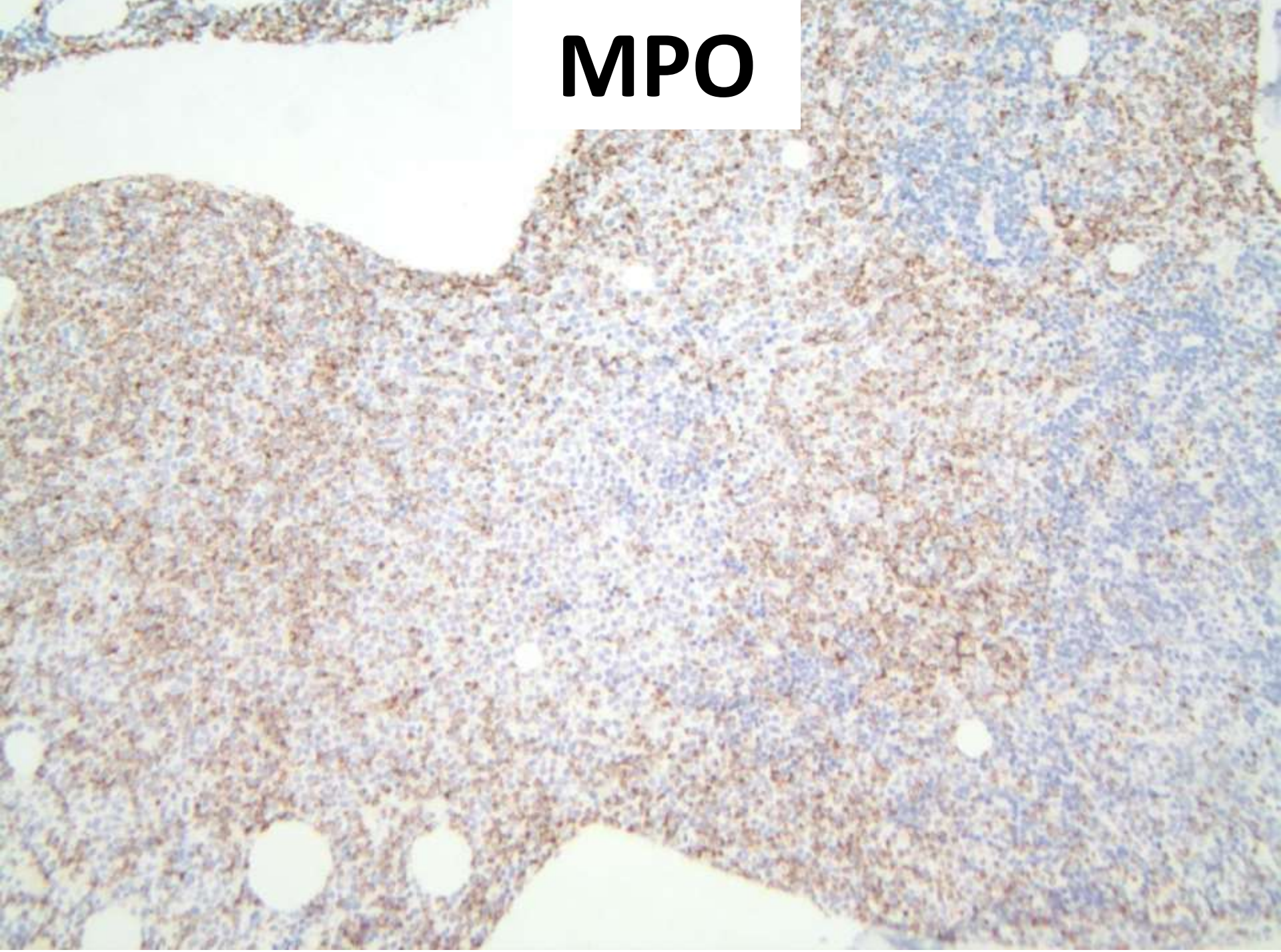








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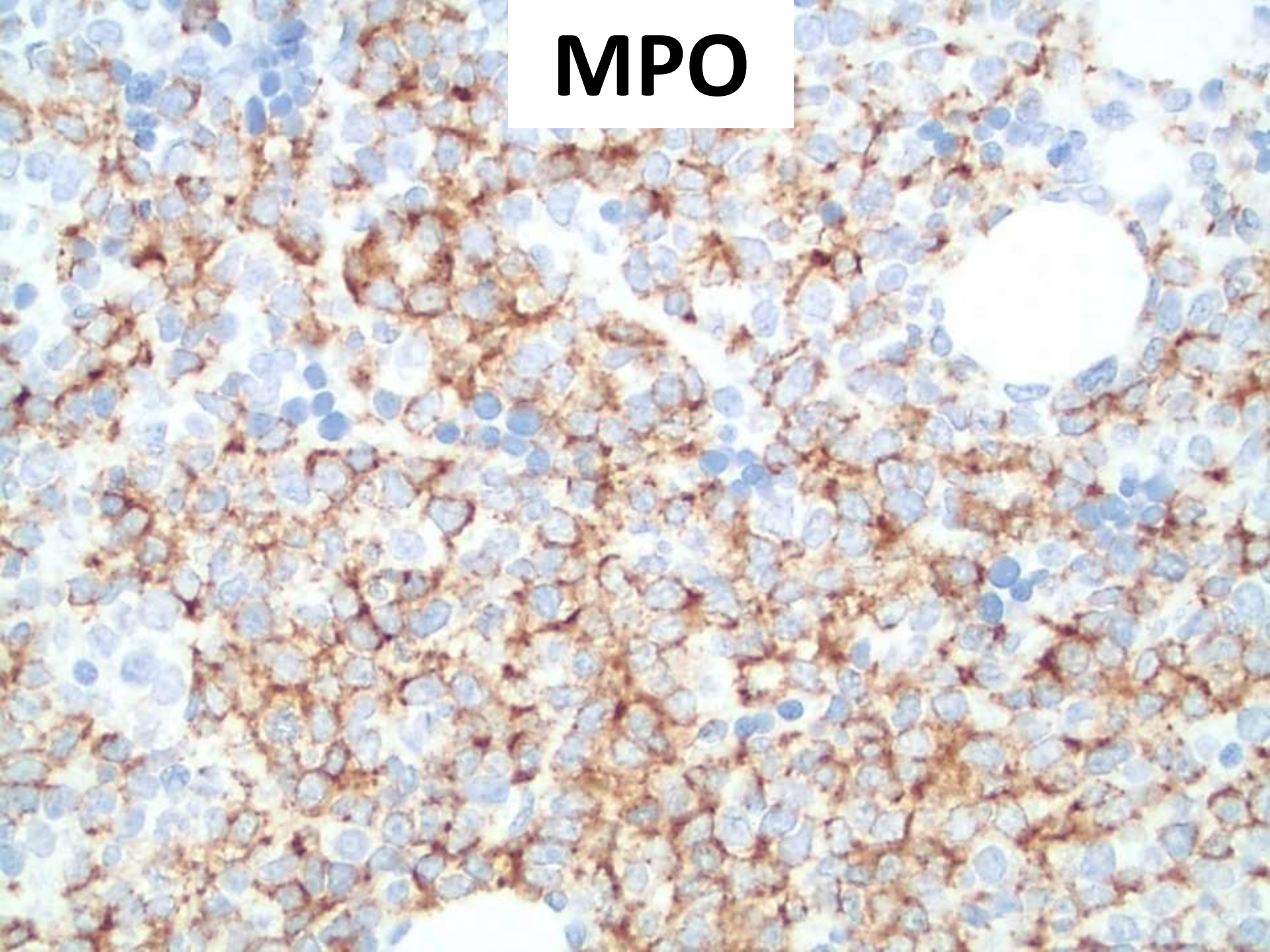
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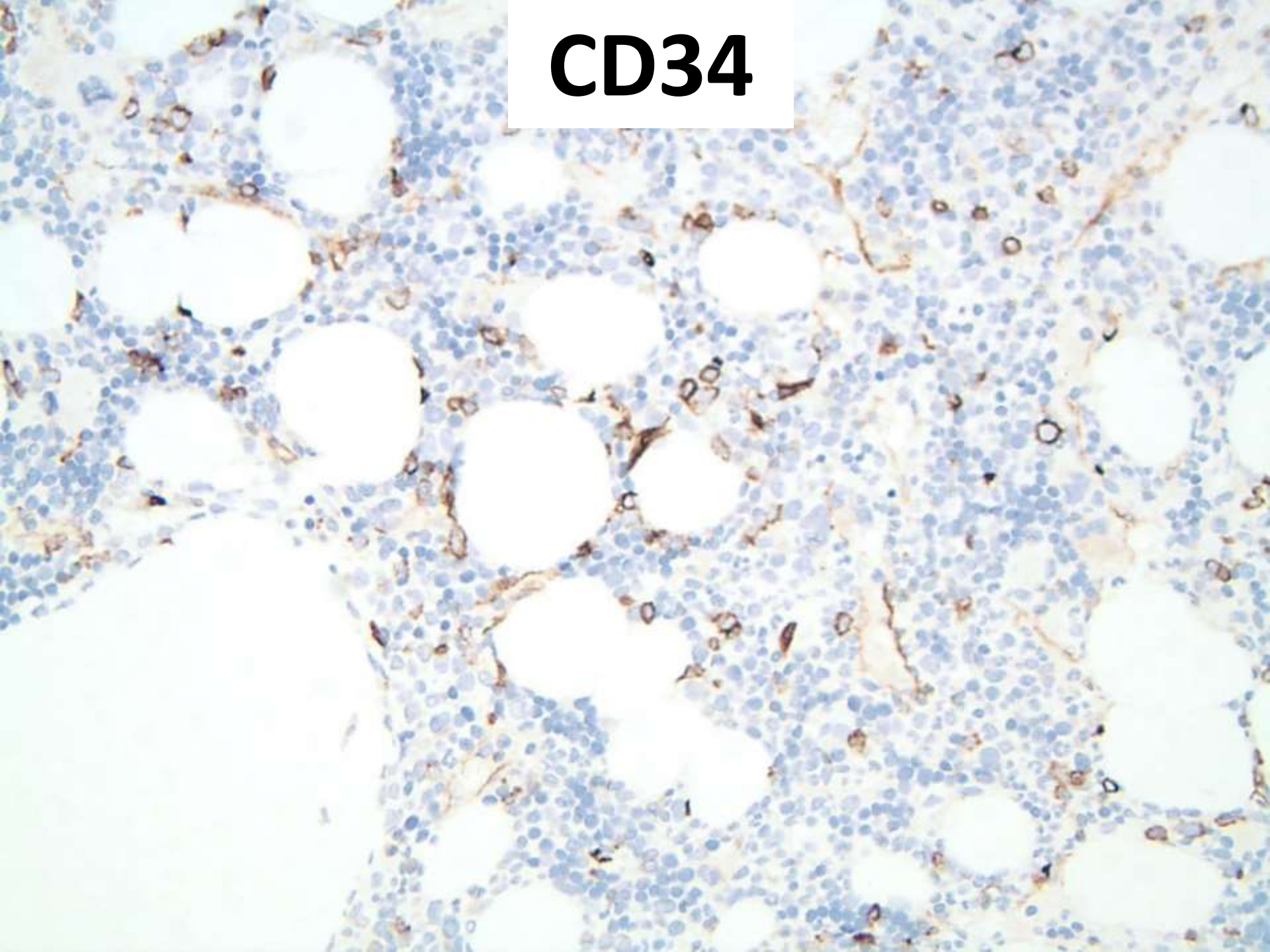
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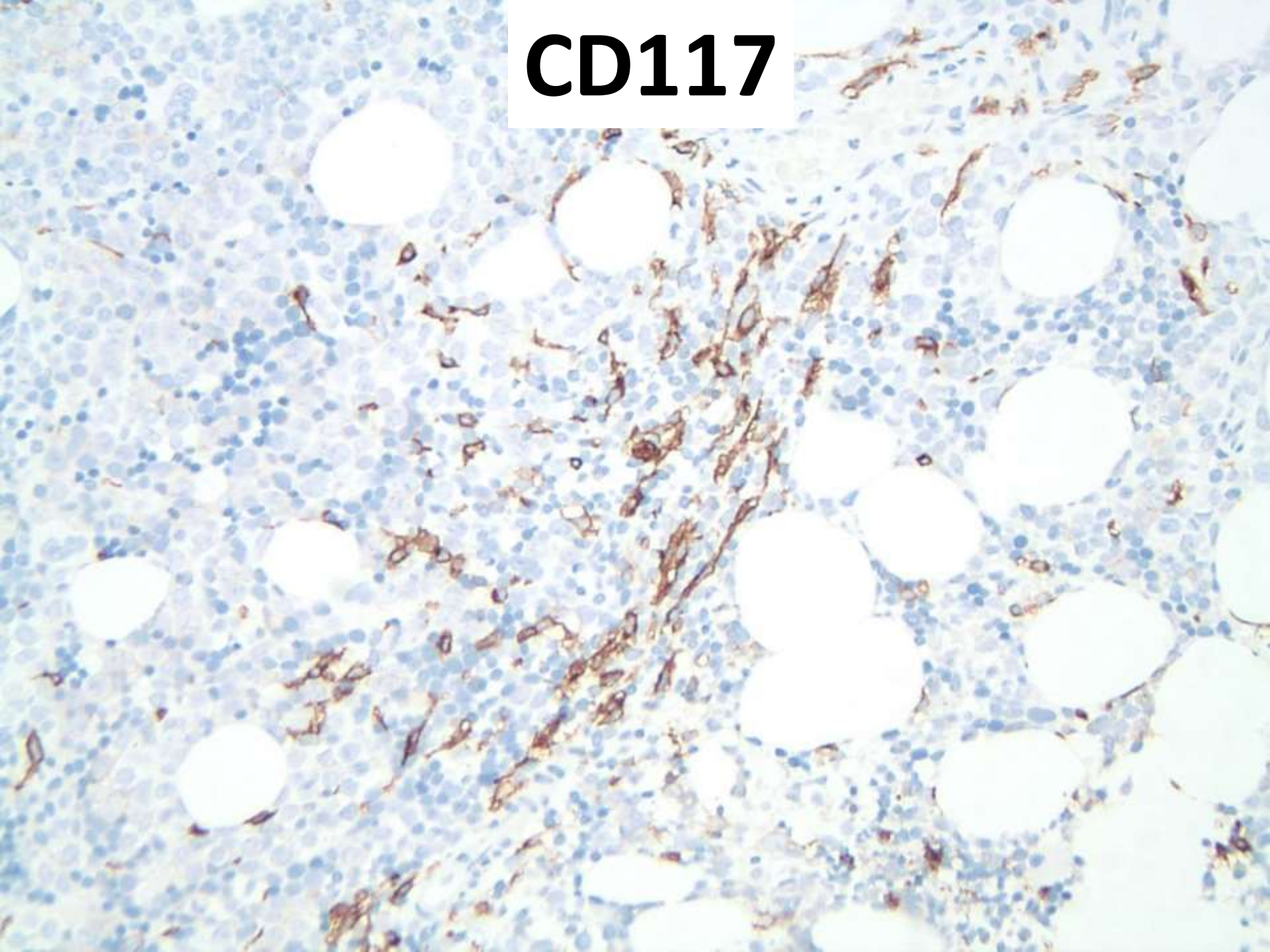
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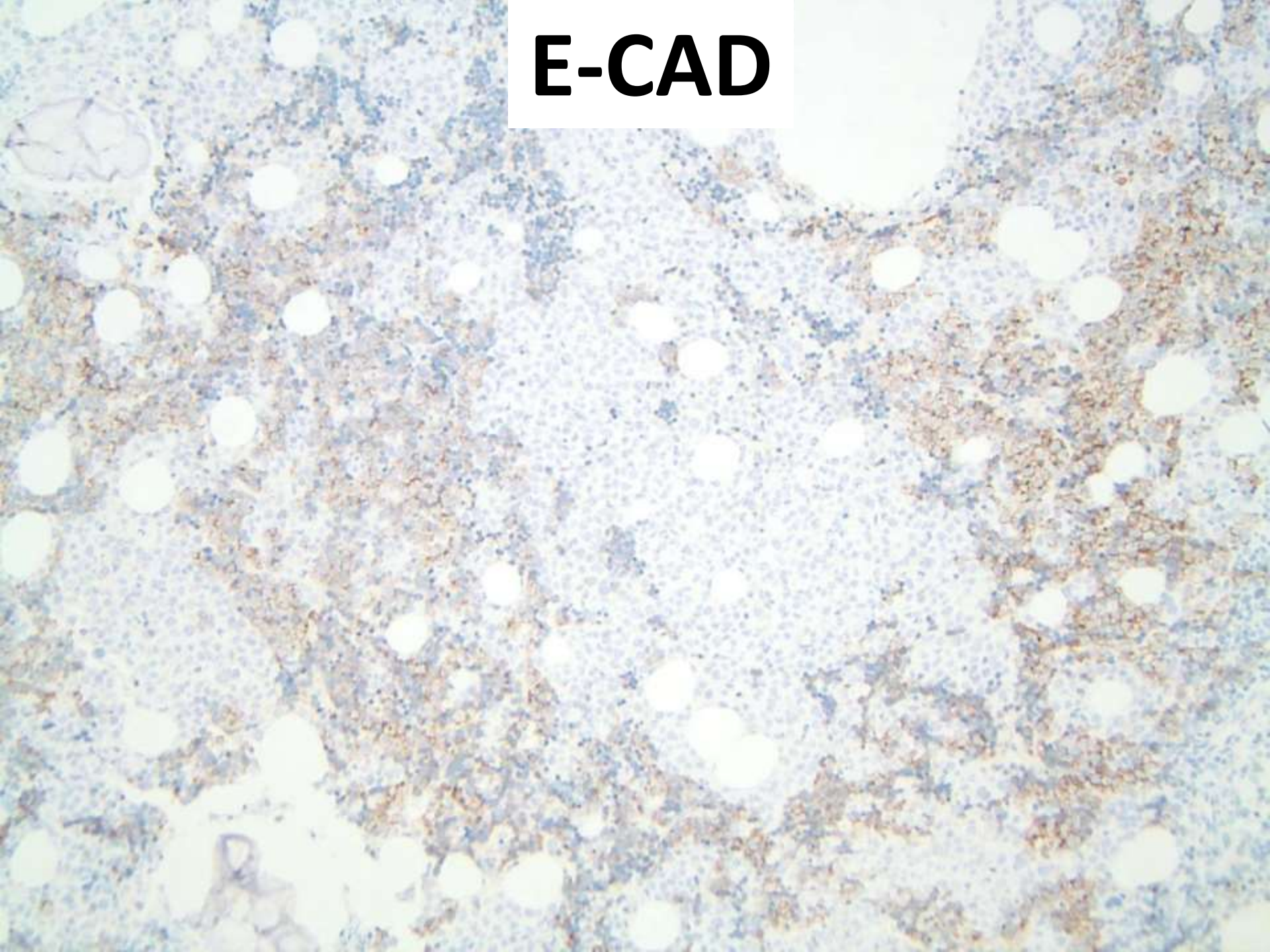
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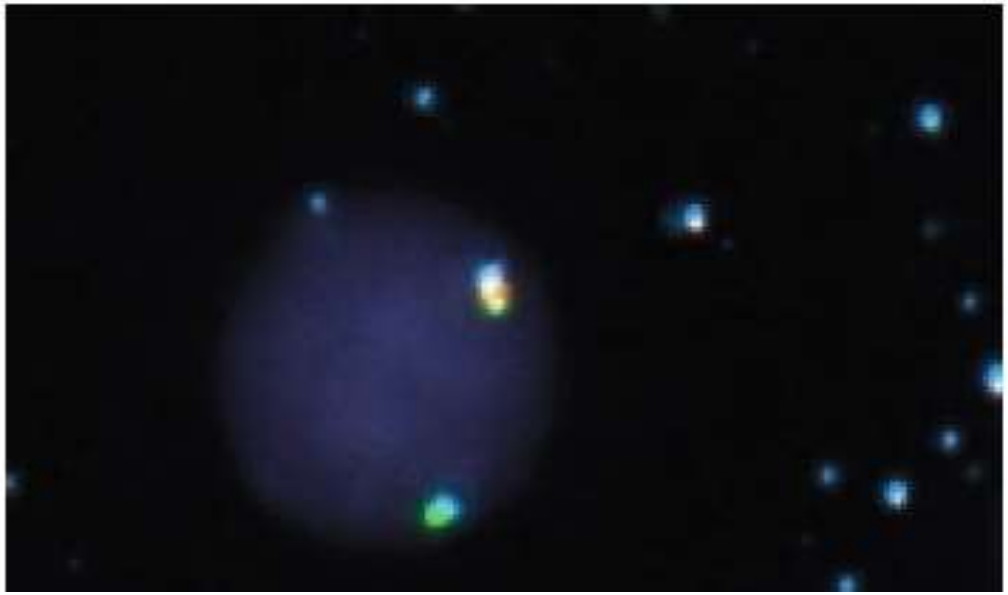
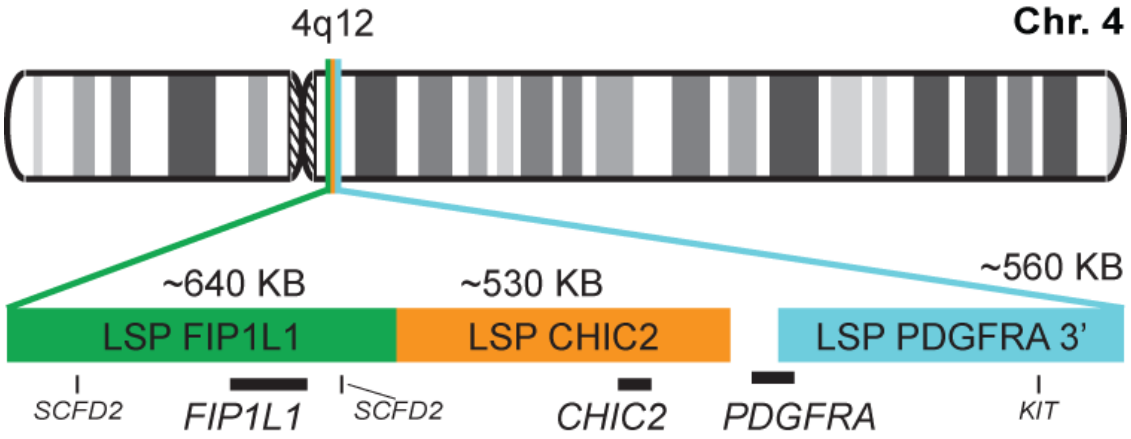
FISH



PDGFRa (4q12): 1GRA 1 GA



Diagnosis

- Myeloid neoplasm associated with eosinophilia and rearrangement of ***PDGFRα***

- **Chronic eosinophilic leukemia**
- Acute myeloid leukemia
- Lymphoblastic leukemia/lymphoma
- Overlap with systemic mastocytosis

Chronic eosinophilic leukemia

- Absolute eosinophil count of >1.5 K/uL

And at least 1 of the following:

- >5% blasts in the bone marrow (met)
- >2% blasts in the periphery (not met)
- A clonal genetic abnormality (met)

Myeloid neoplasm associated with eosinophilia and rearrangement of ***PDGFRa***

- *FIP1L1-PDGFRa* fusion oncoprotein
- 800 kb interstitial deletion on Chr 4 (*CHIC2*)
- Disrupts autoinhibitory juxtamembrane domain of PDGFRA
- Constitutionally activated tyrosine kinase
- Complete hematologic and molecular remission with **imatinib** therapy

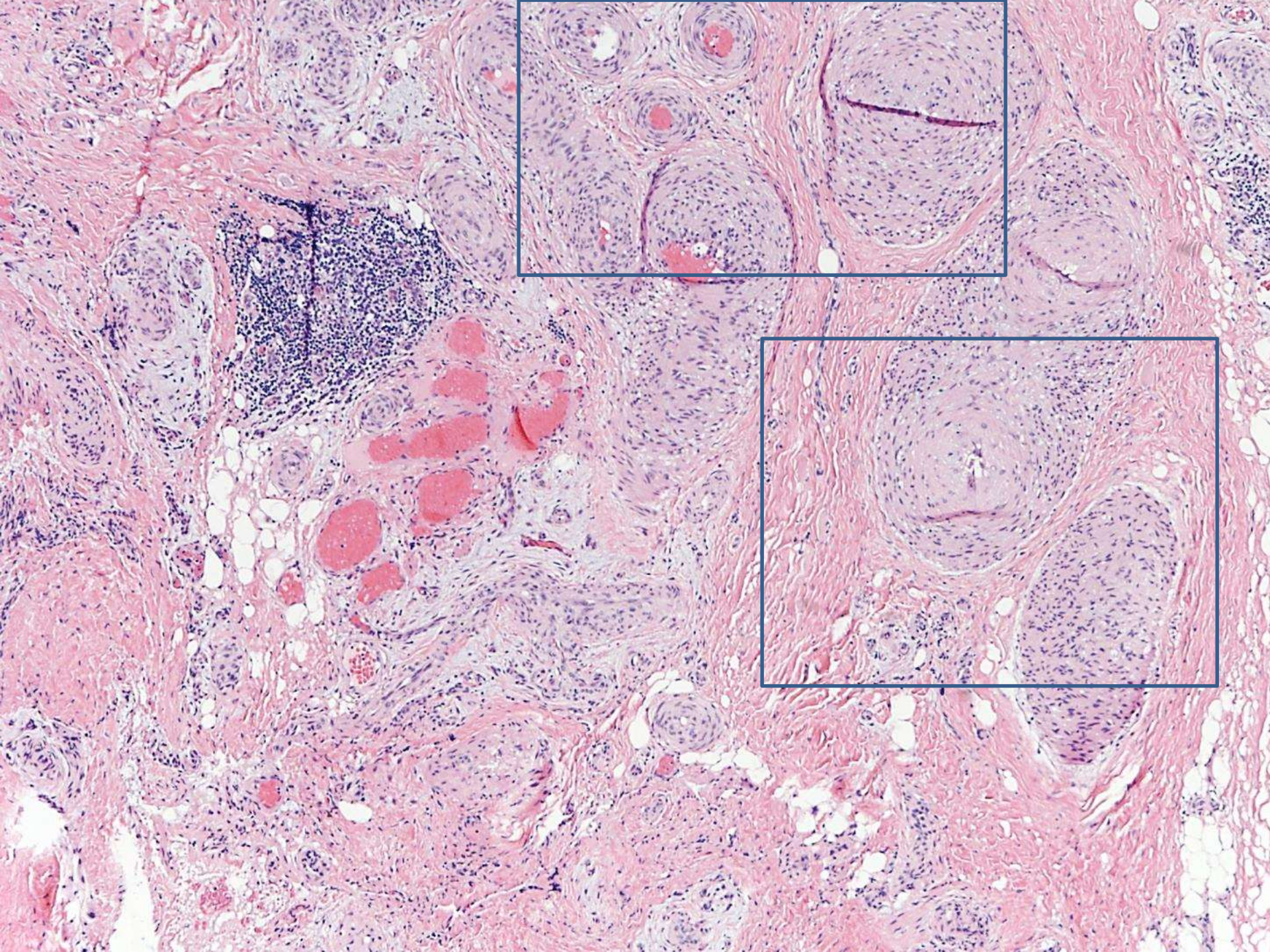
Patient Course

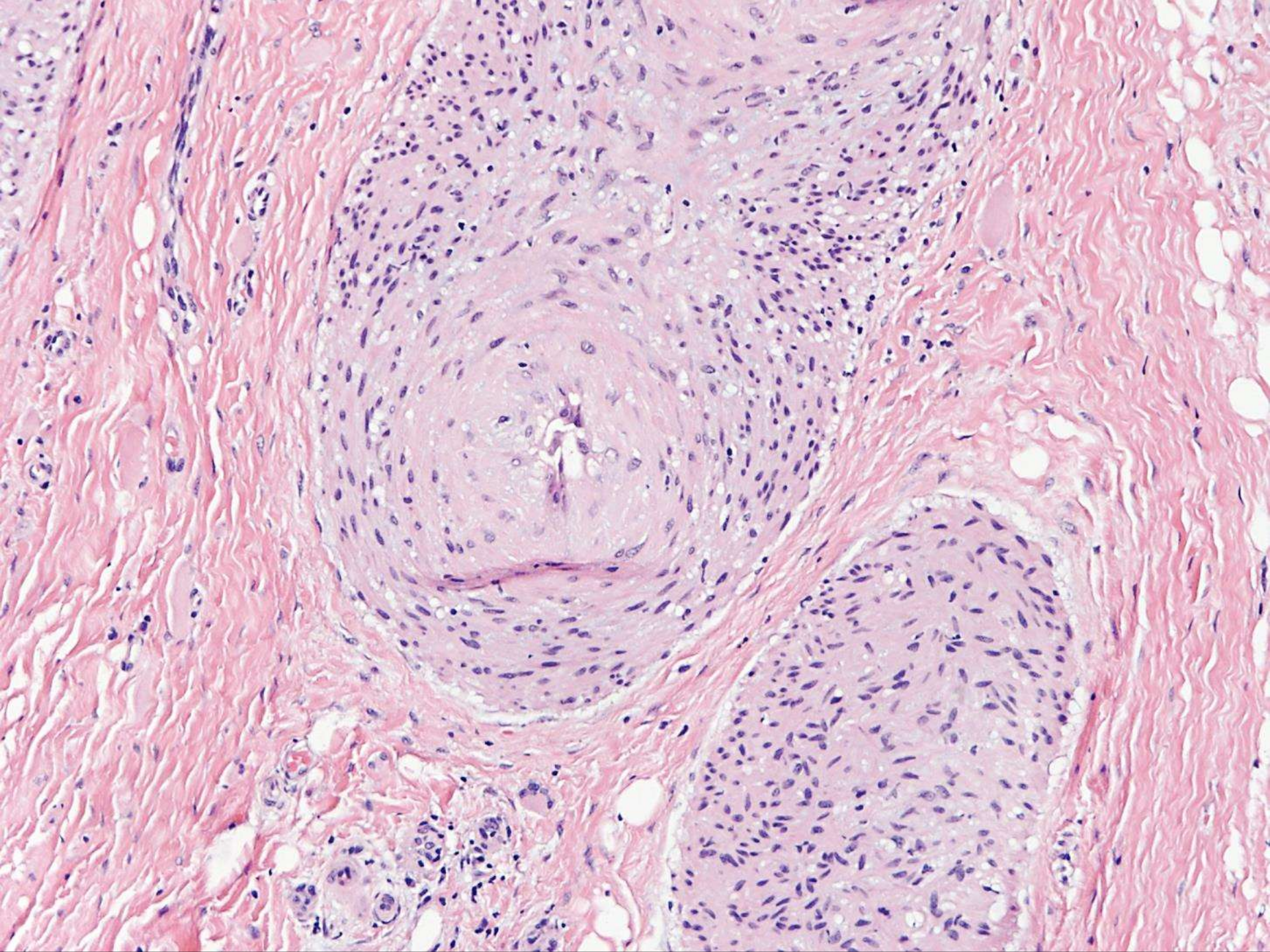
- 100 mg imatinib PO daily since diagnosis
- Eosinophilia and thrombocytopenia resolved
- Clinically well

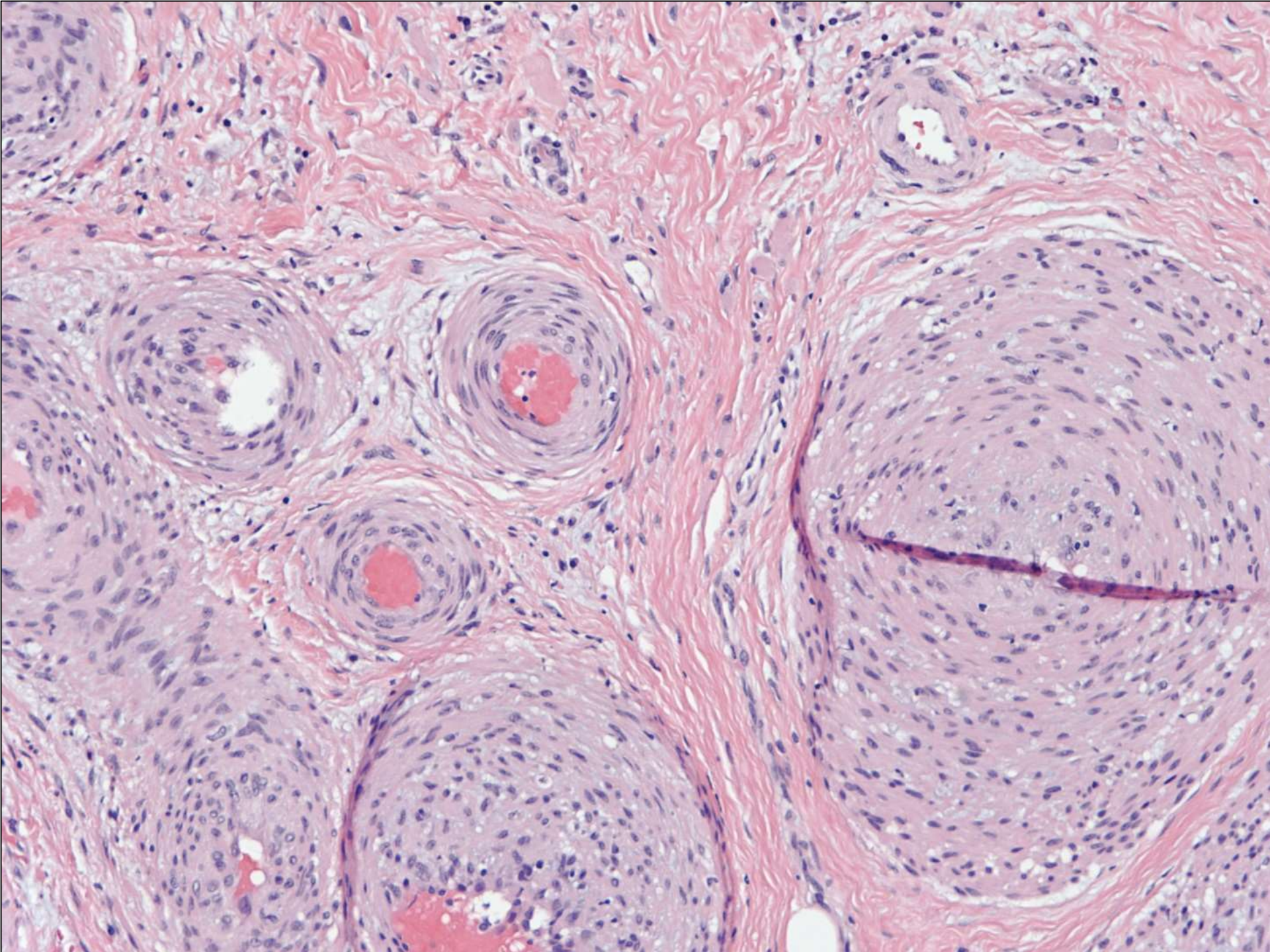
SB 6255

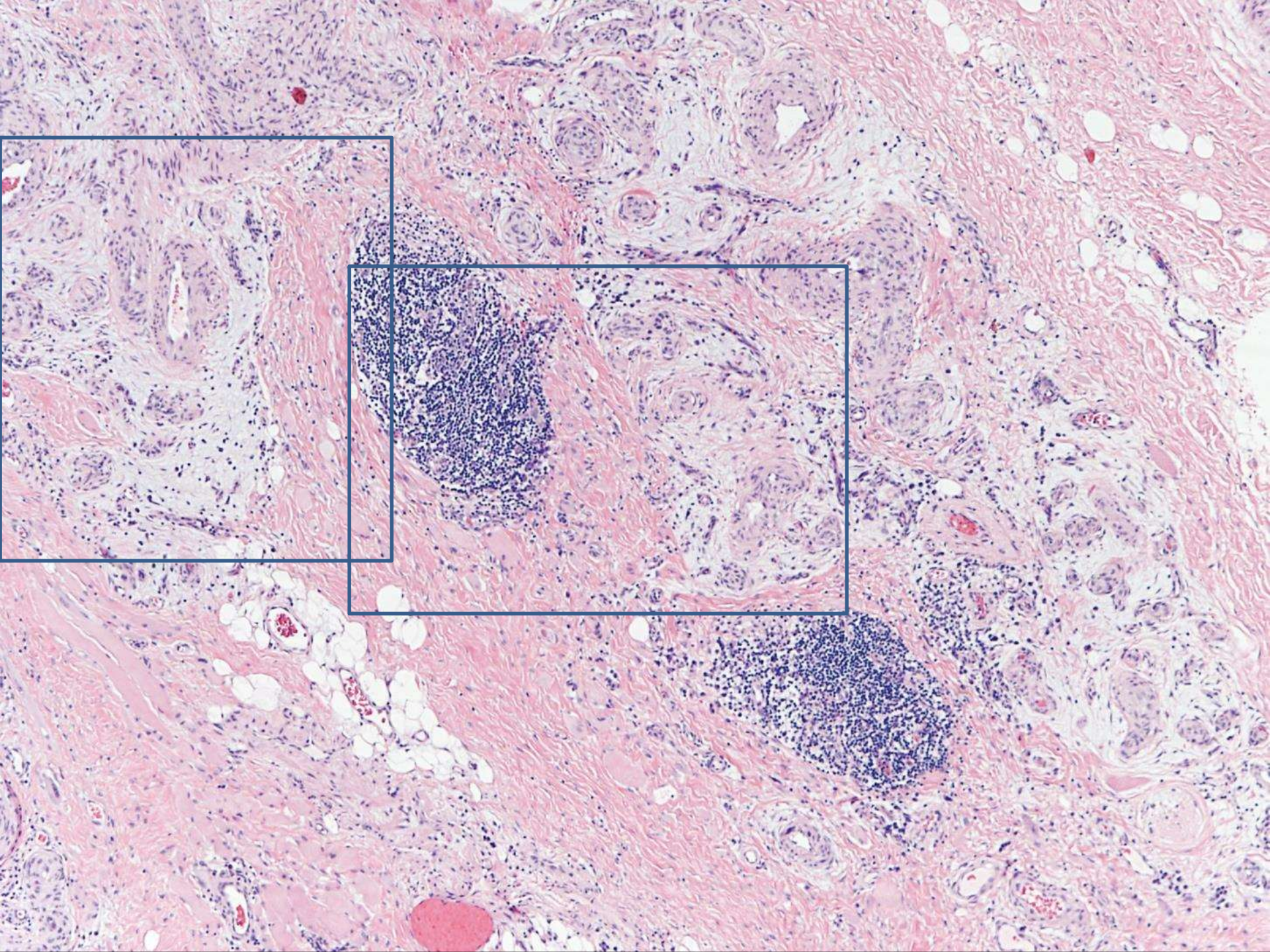
Francisco Beca/Eduardo Zambrano; Stanford

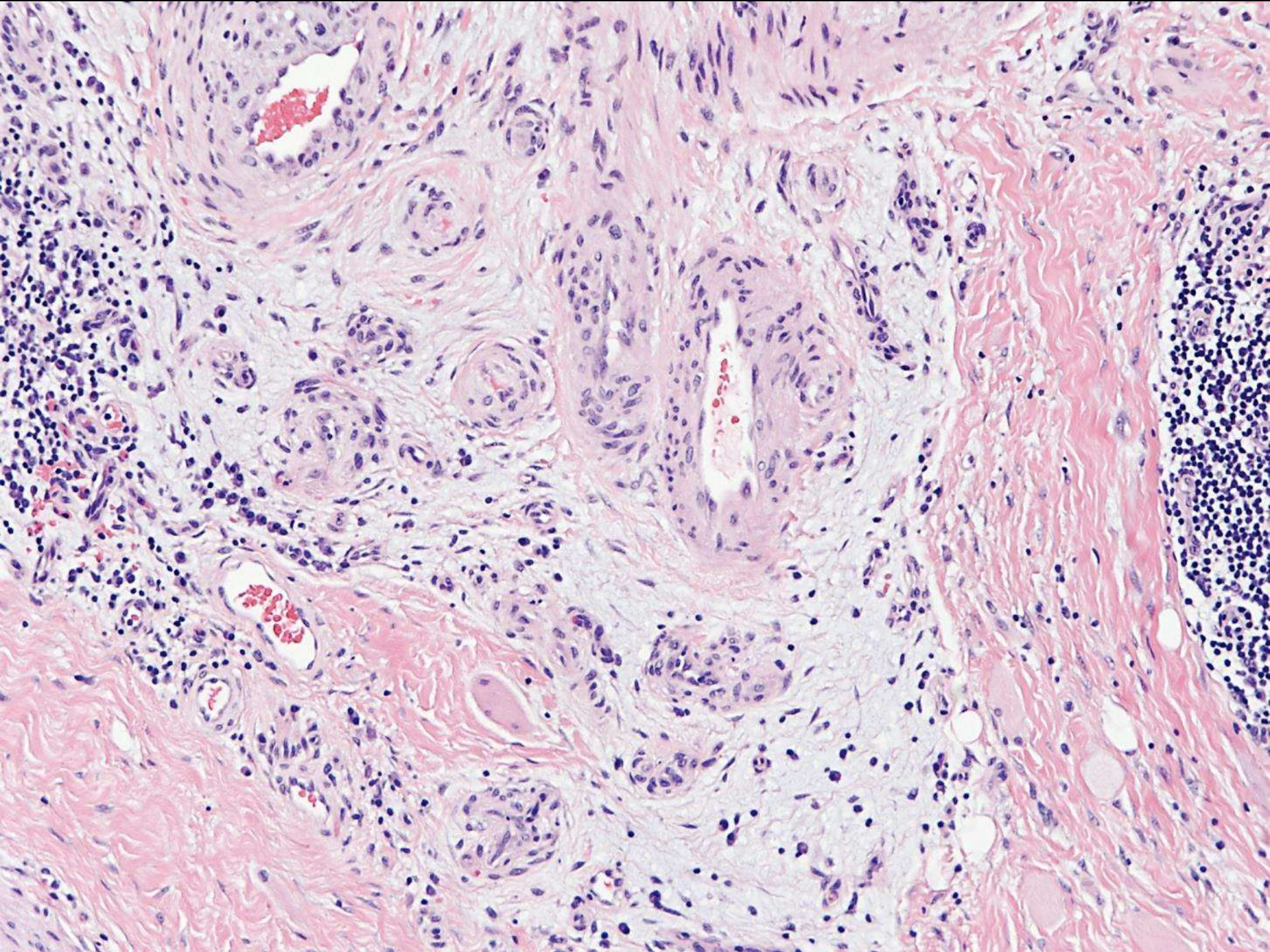
11-year-old female with lesion of left gastrocnemius muscle.

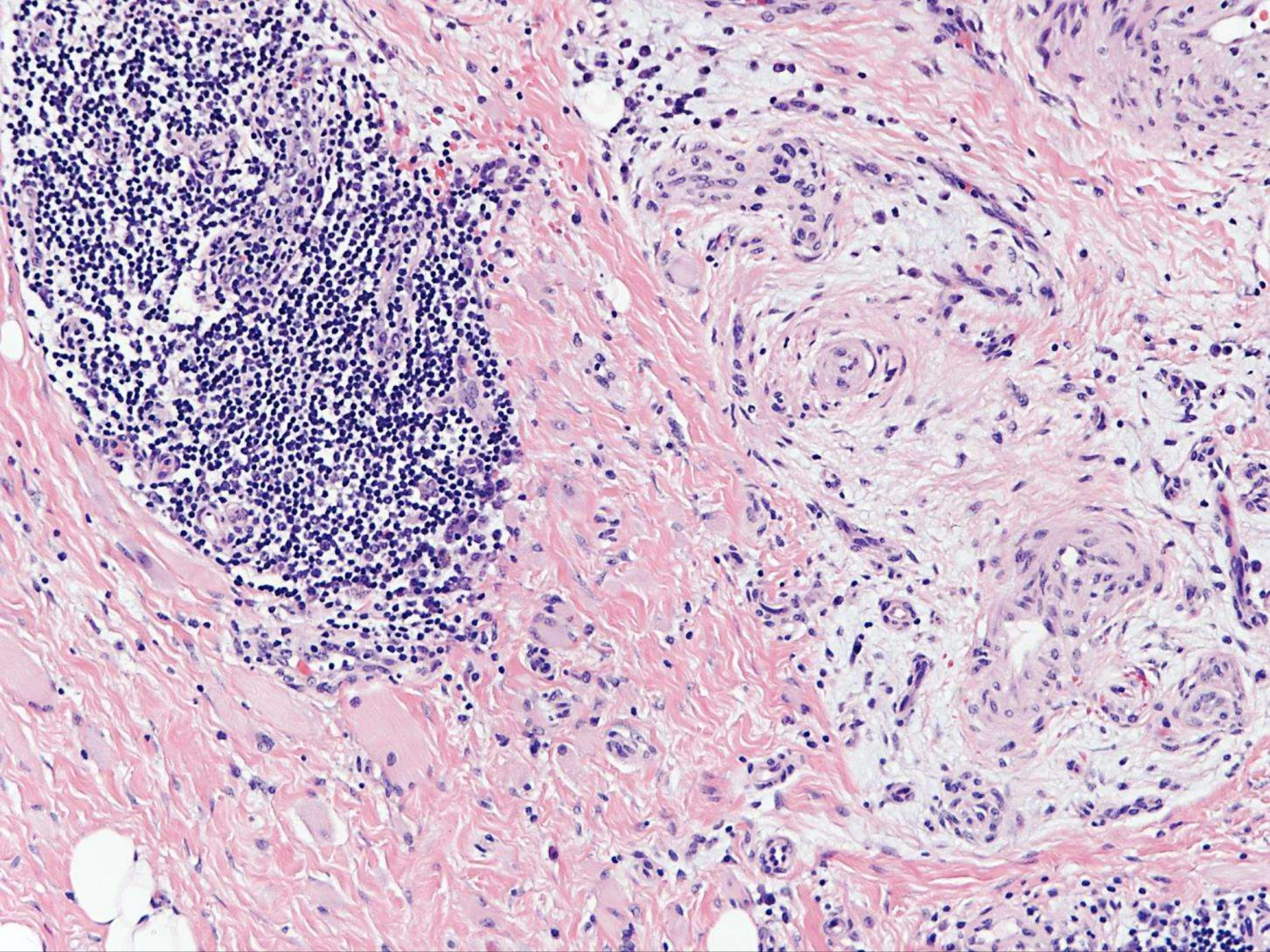


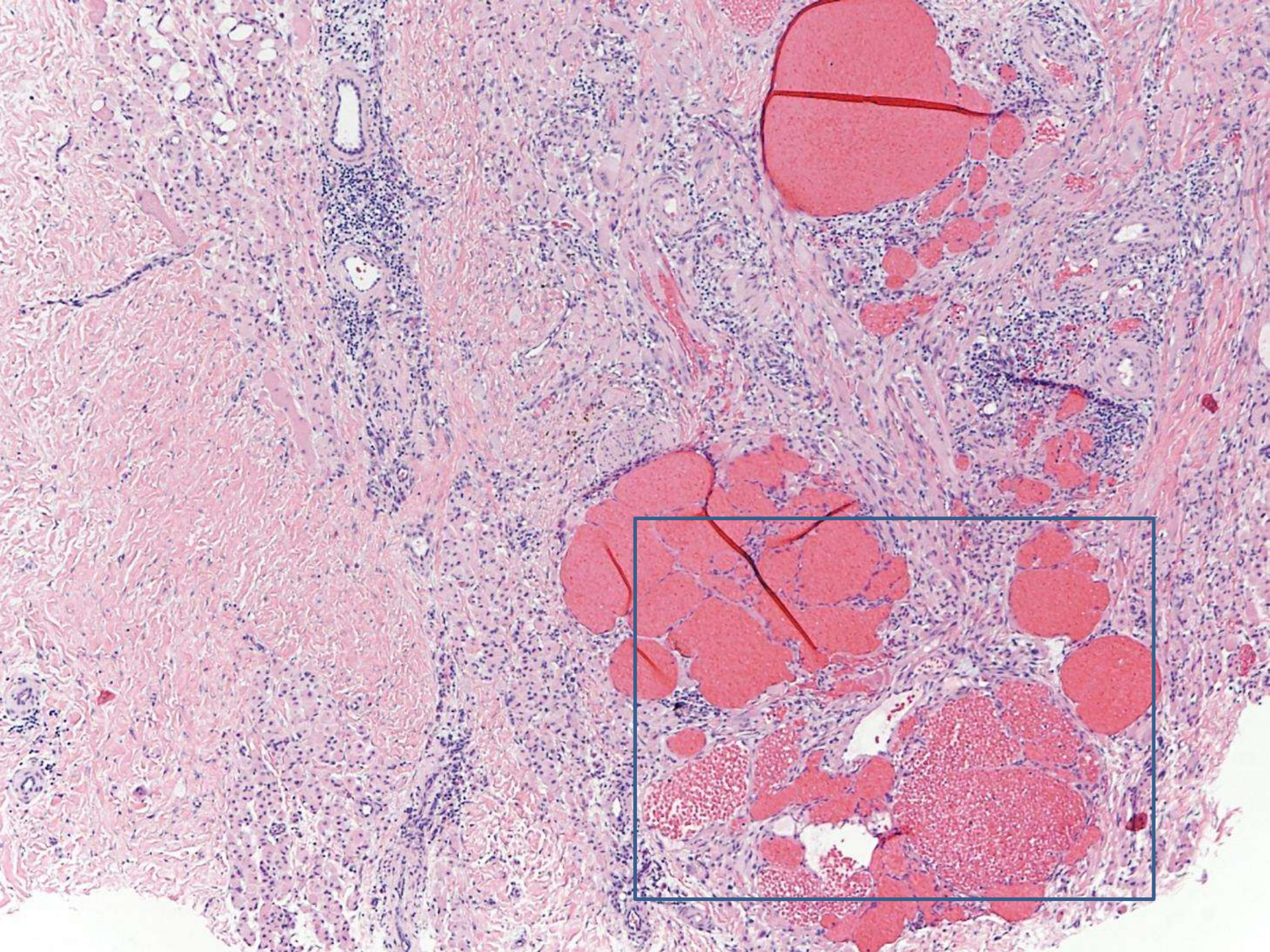


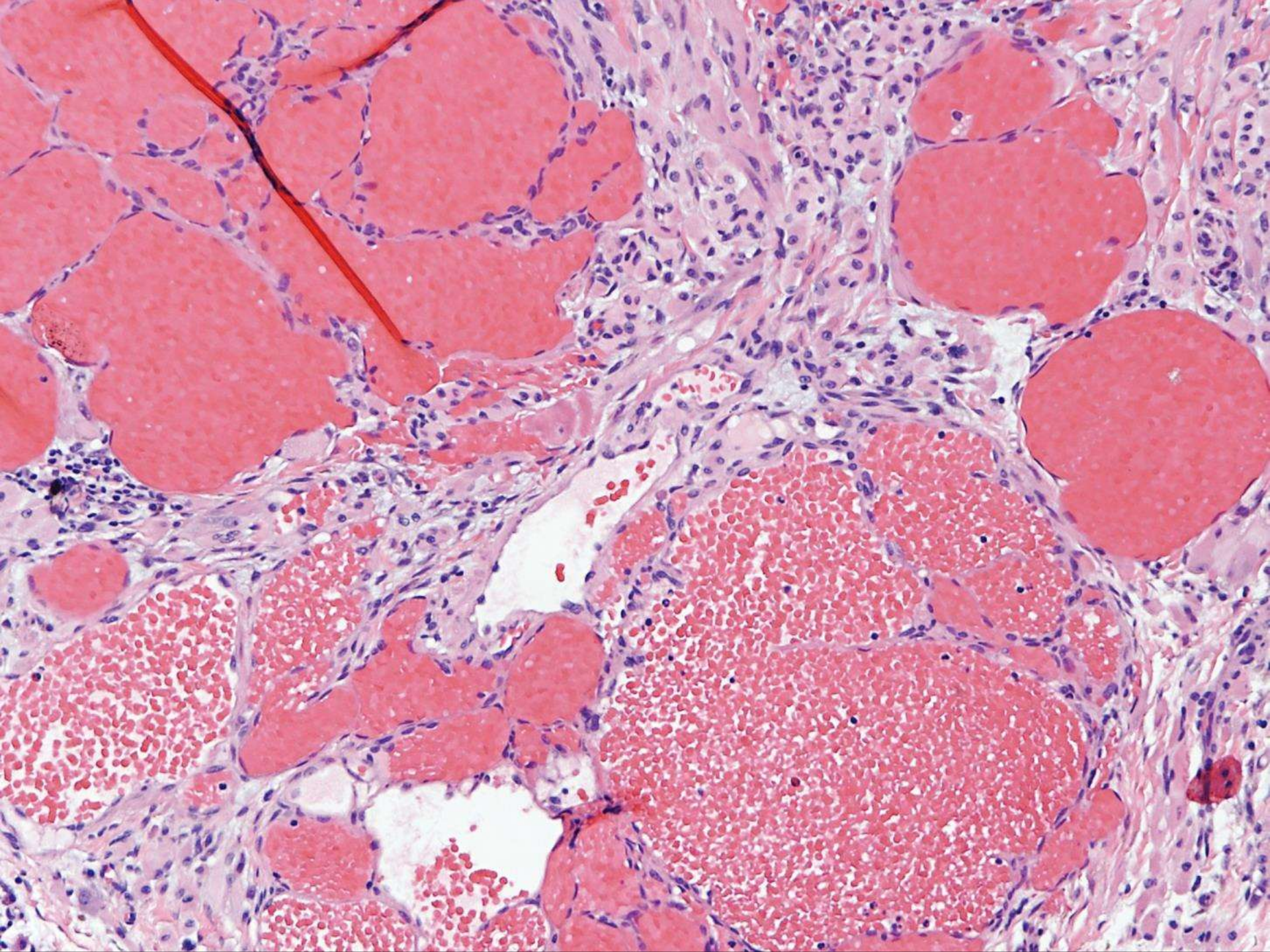












LPS-17-01255

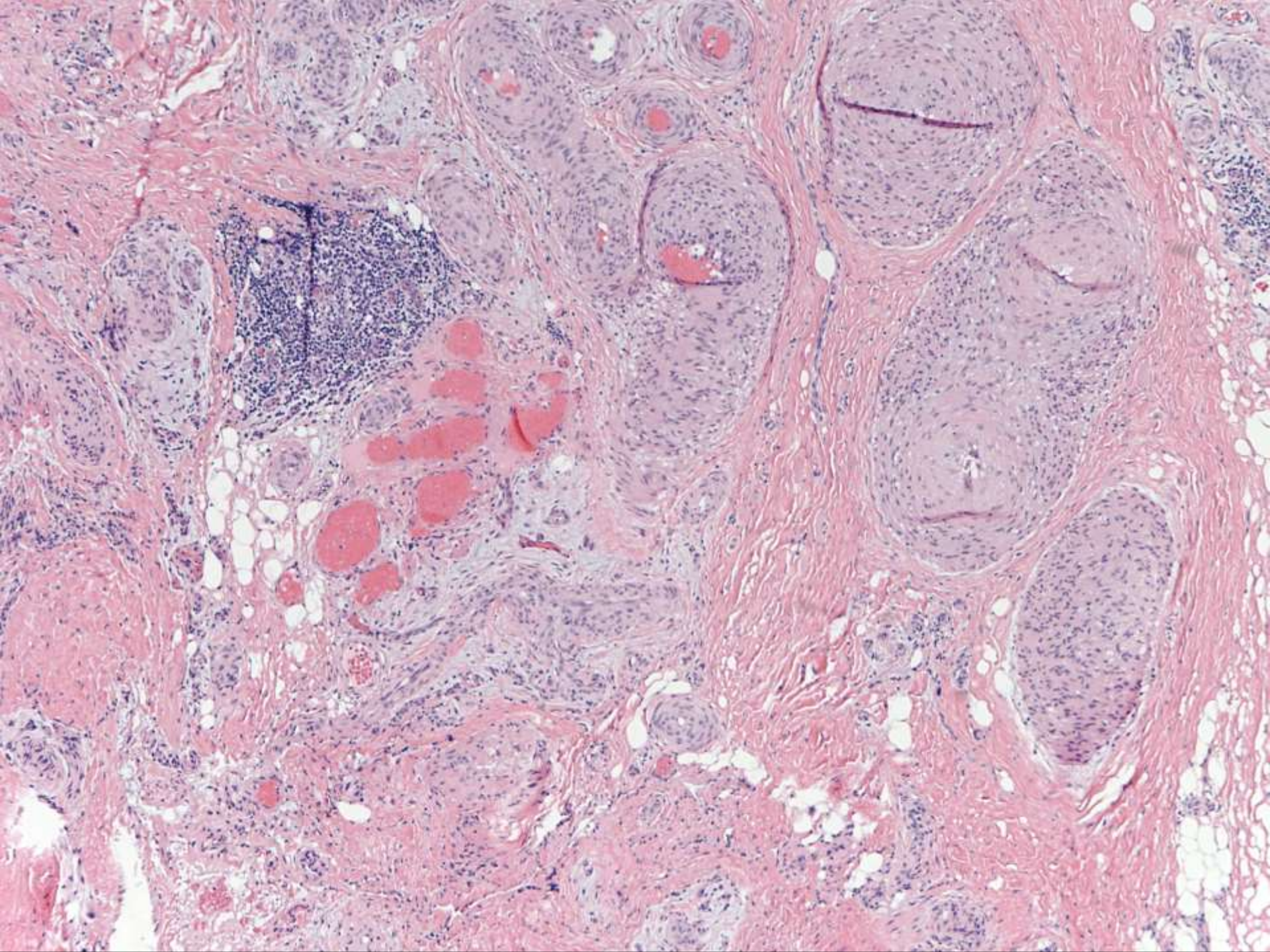
Francisco Beca MD, PhD / Eduardo Zambrano MD, MS
Department of Pathology, Stanford University School of Medicine
March 2018

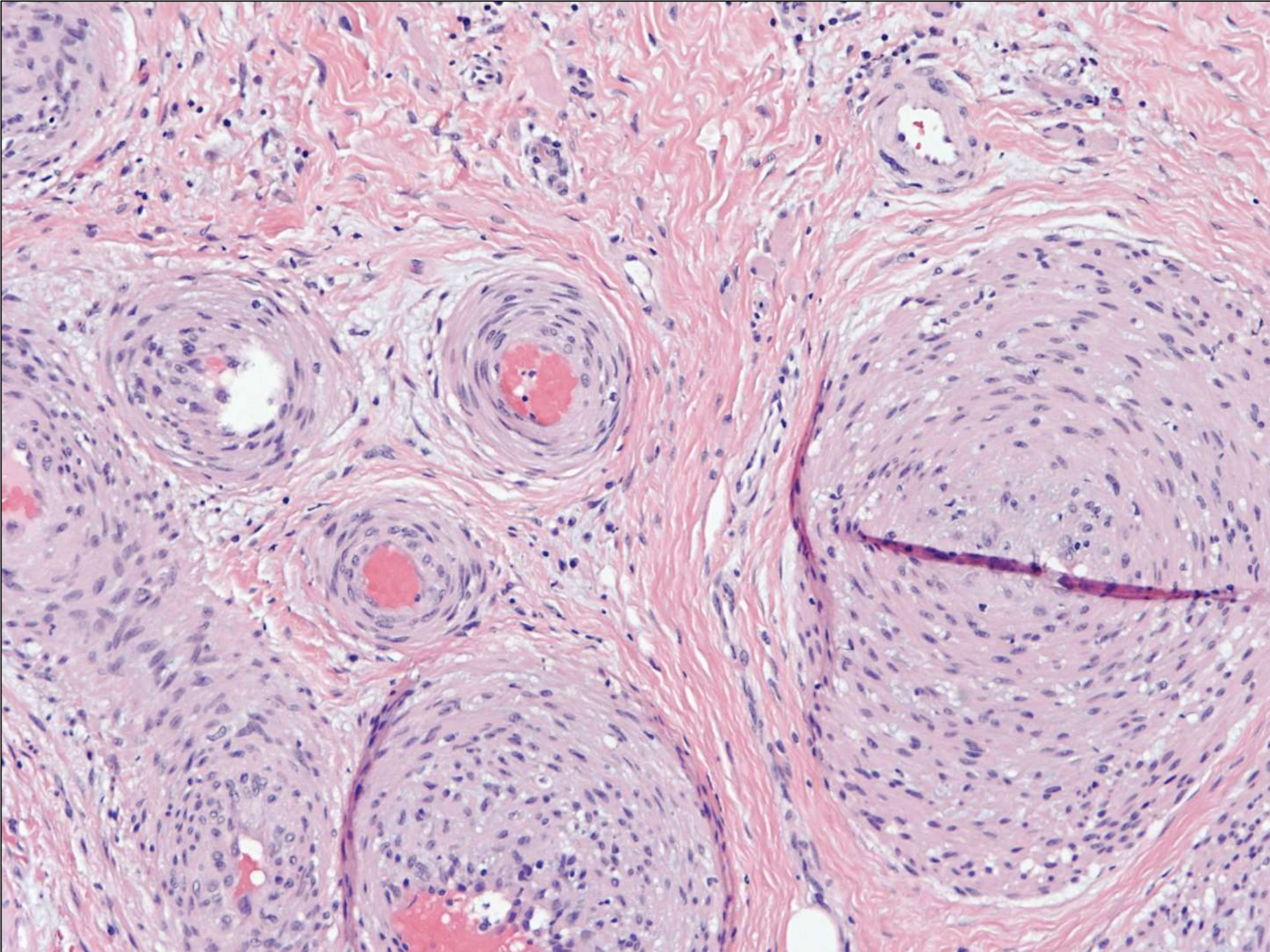
Clinical History:

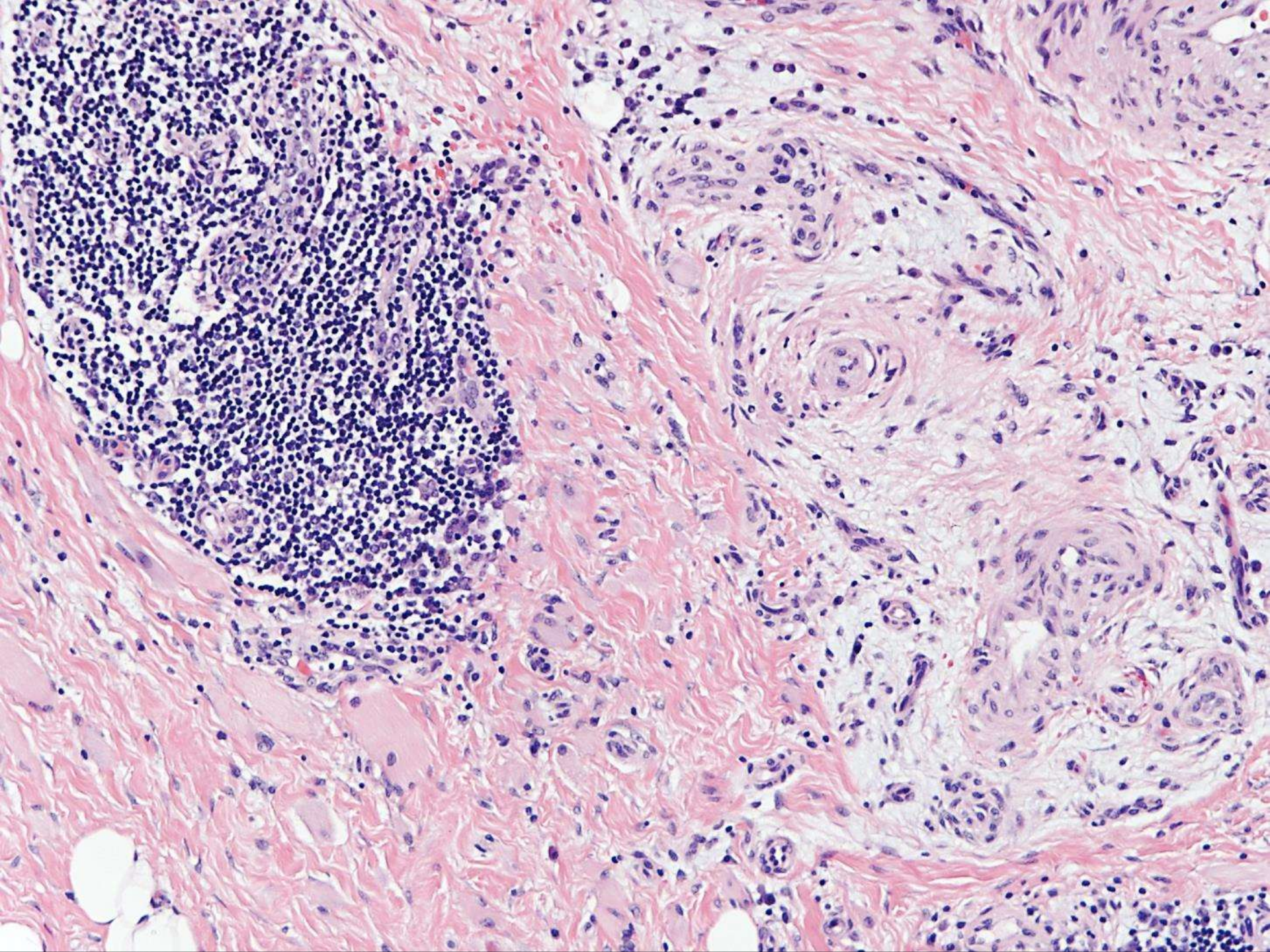
11 year-old female with lesion (1.6 x 2.5 x 3.6cm) of the left gastrocnemius muscle

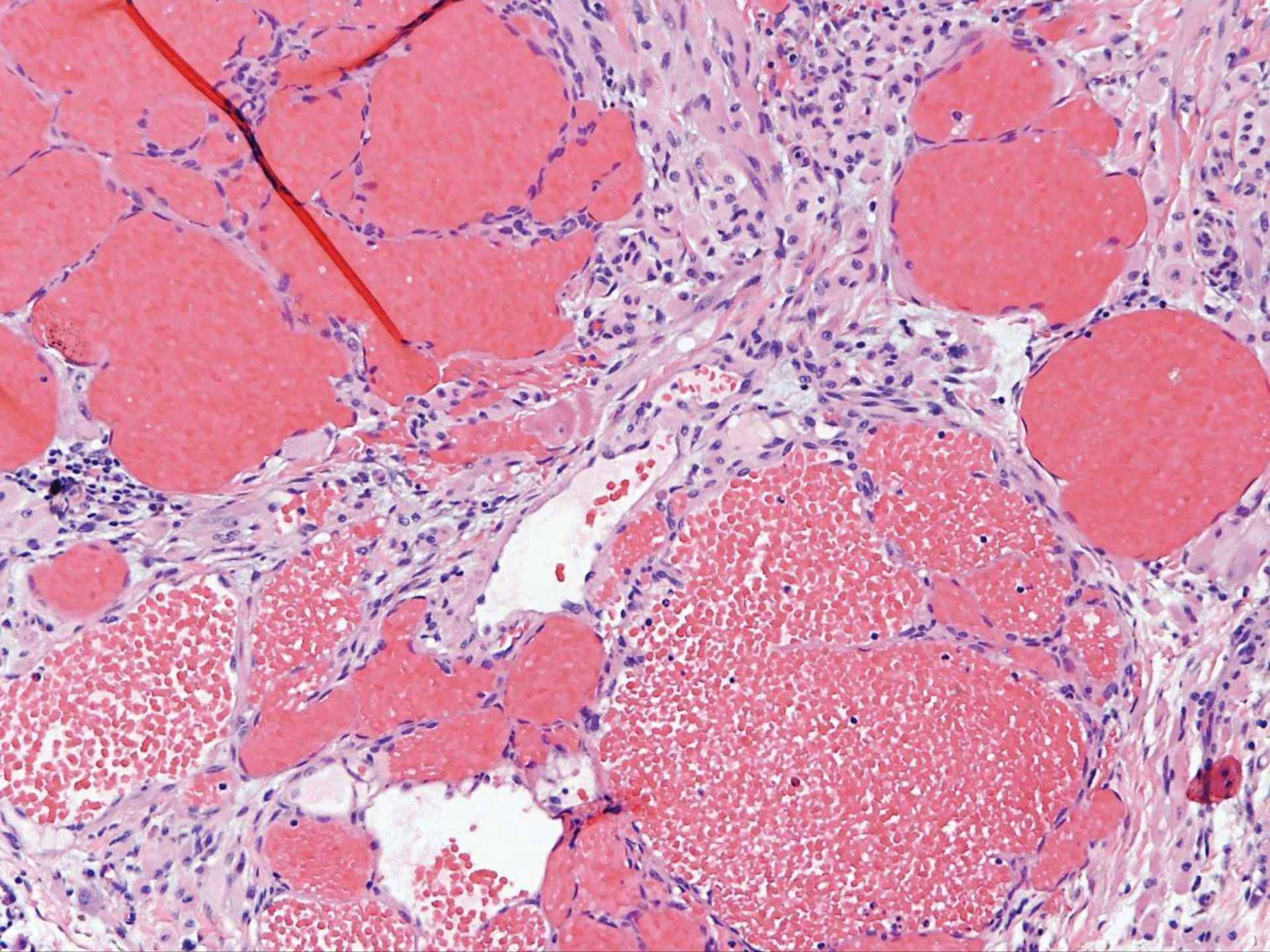
Per Medical Record:

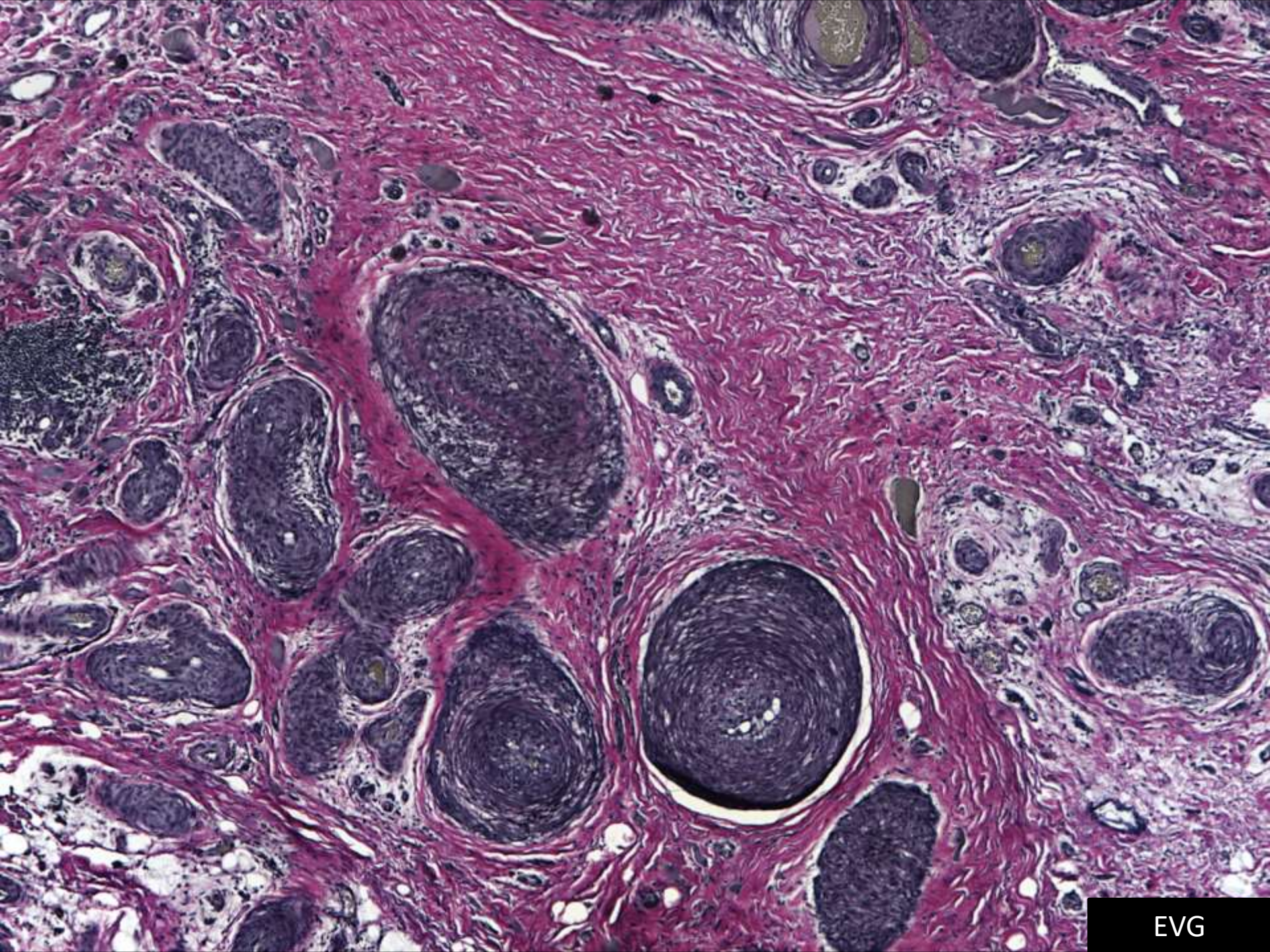
- "…began to report pain in the left calf and was toe walking around August 2016. They also noticed for the first time that her left calf was smaller than her right calf."
- Unremarkable PMH, 2 healthy siblings







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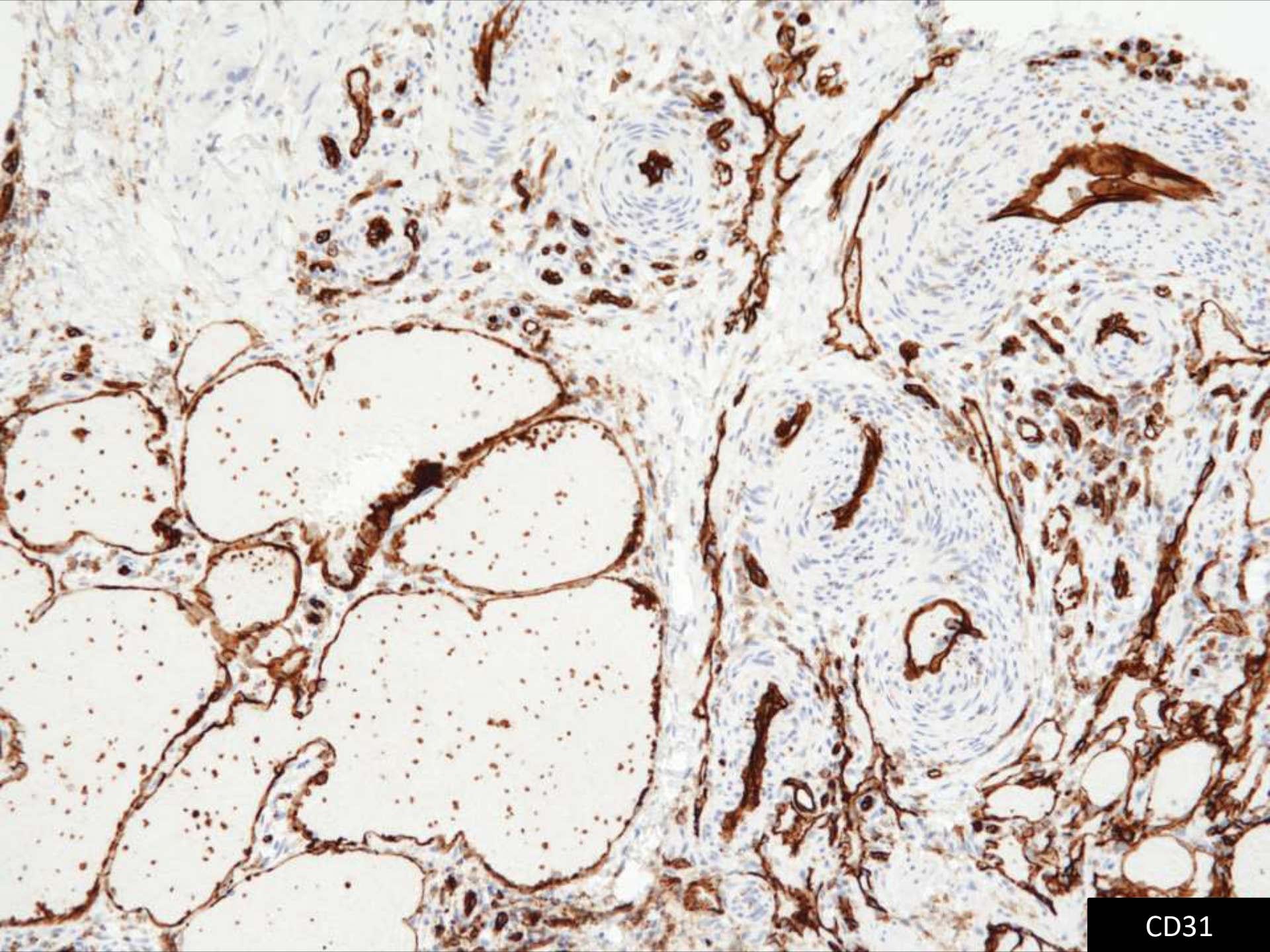
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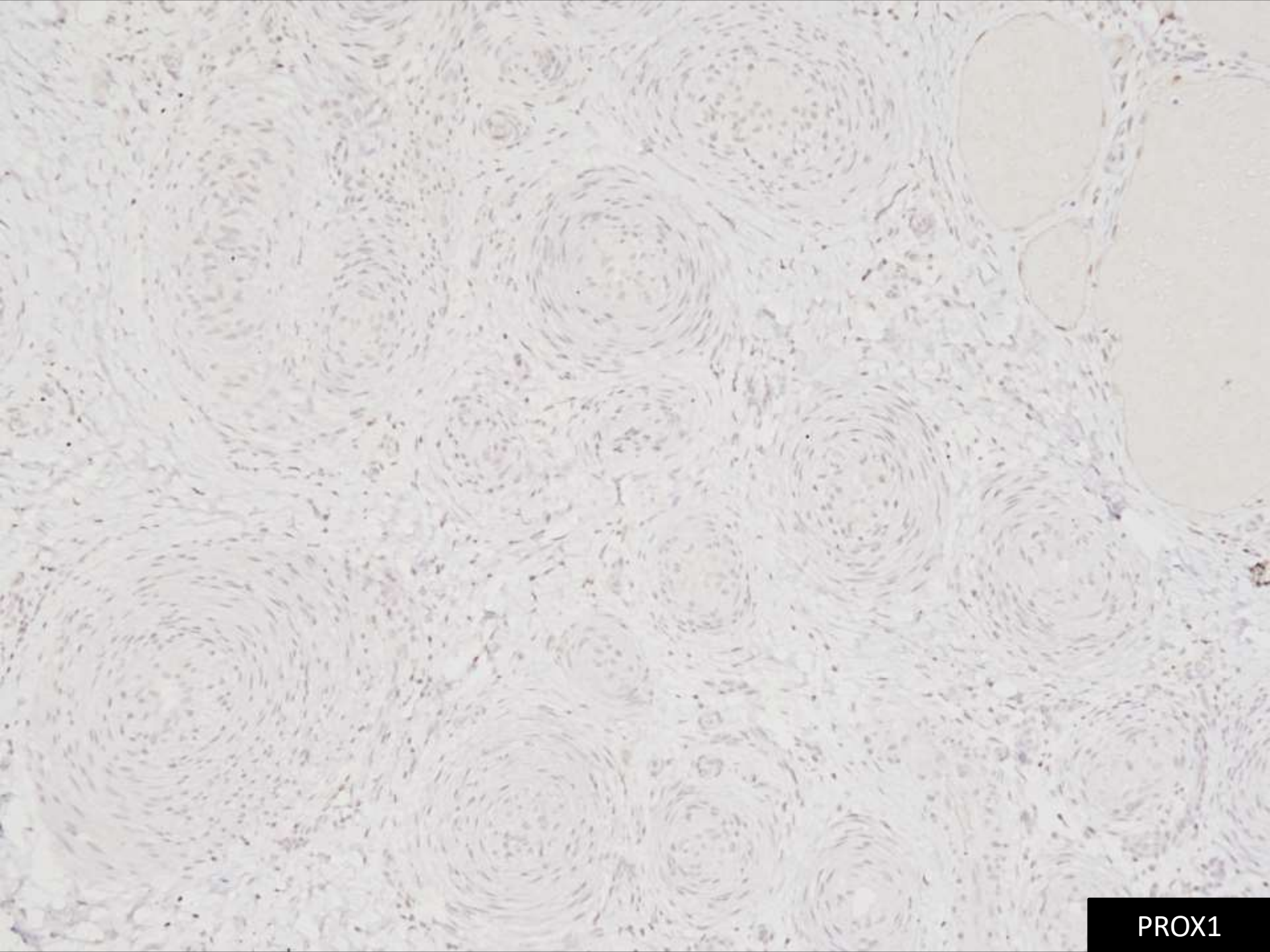
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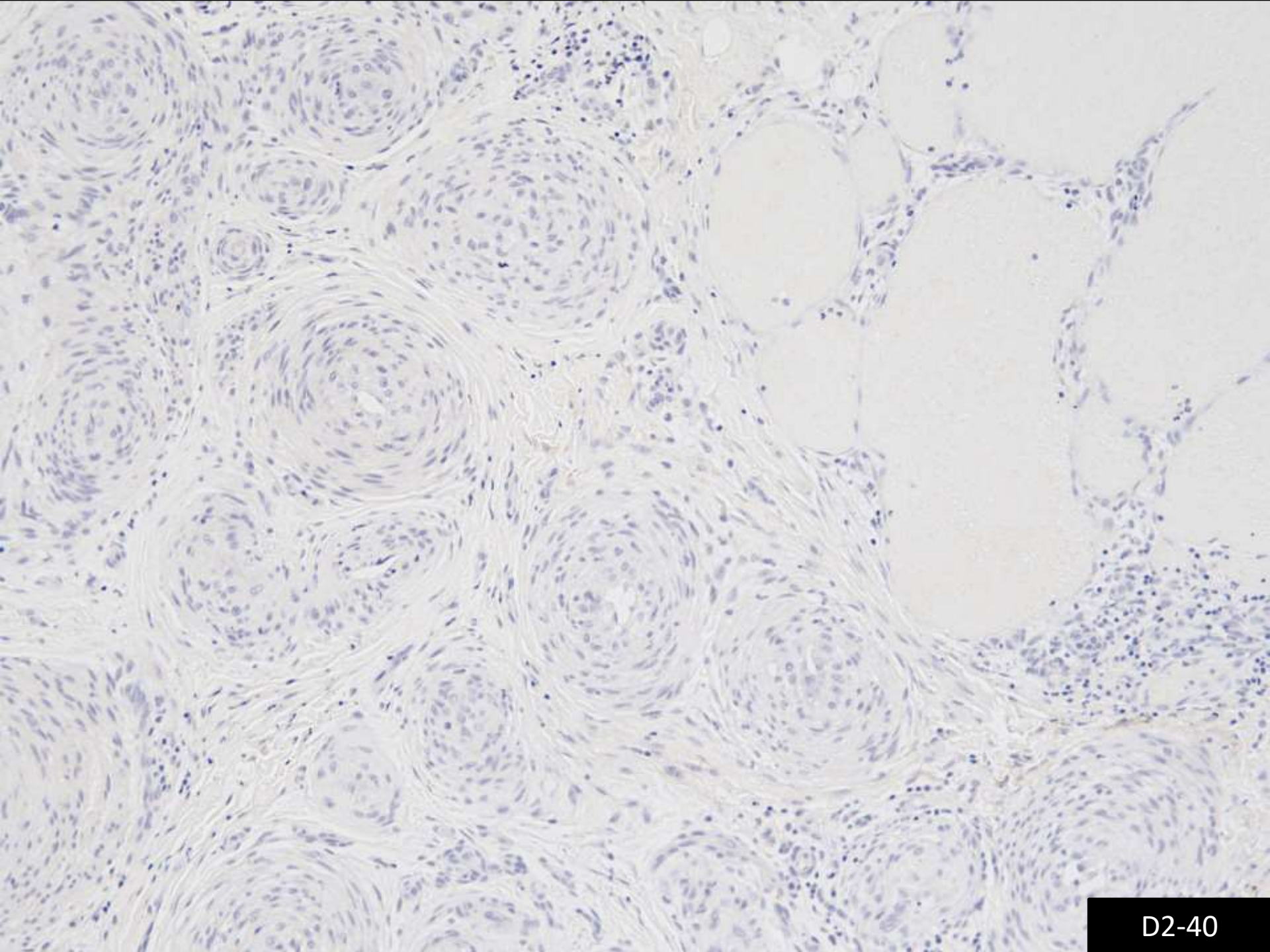
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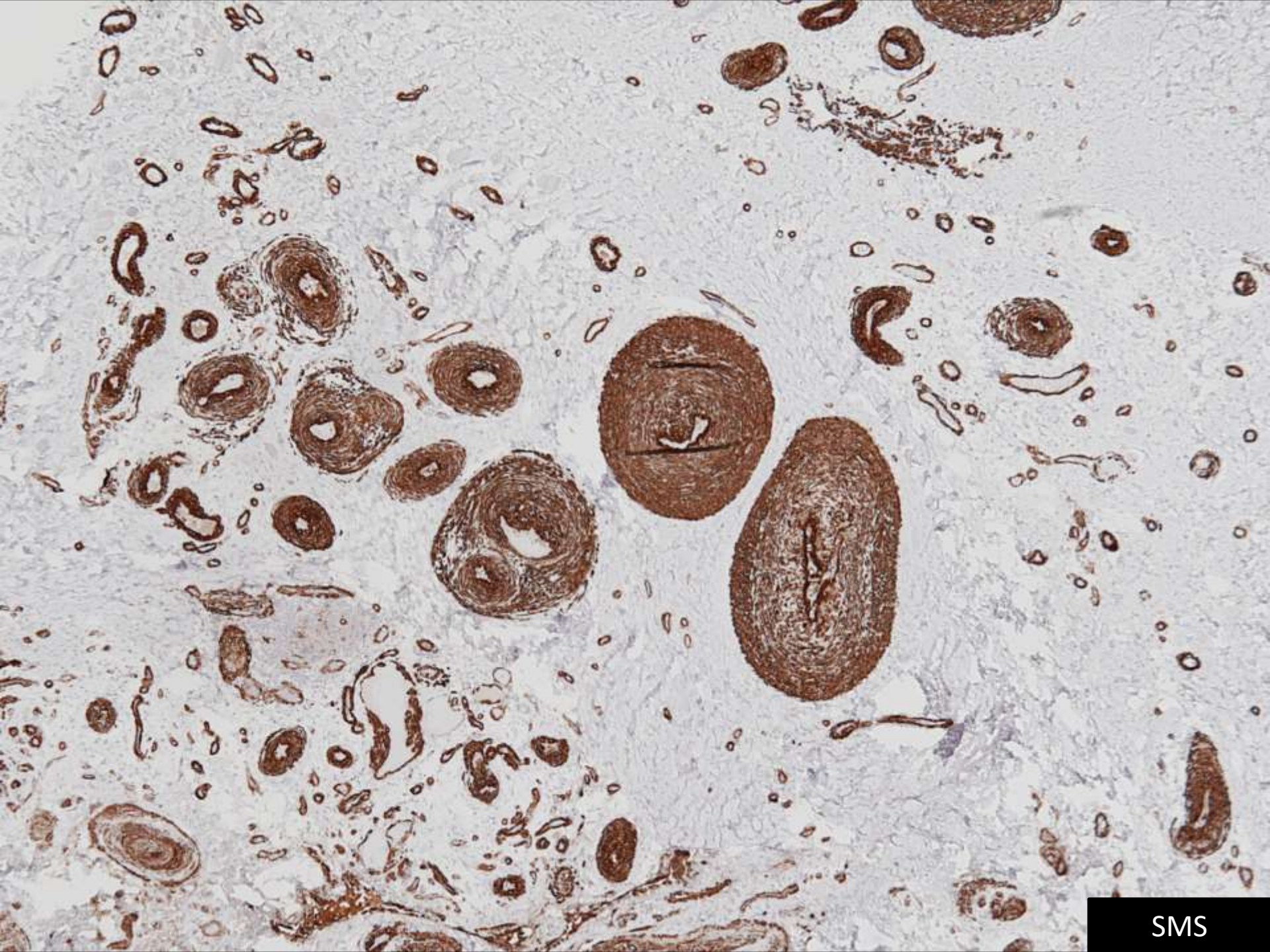

SMS

Differential diagnoses

Mesenchymal neoplasm/hamartomatous lesion:

- Common venous malformation (VM)
  - Hemangioma
  - Arteriovenous malformation
- Fibro-adipose vascular anomaly (FAVA)
- PTEN-associated malformations
  - PHOST - PTEN Hamartoma of Soft Tissue

FAVA - Fibro-Adipose Vascular Anomaly

- First described in 2(
- Cohort of 18 patien Hemangiomas/PHOST

TABLE 1. Clinical Features of FAVA C

Patient	Age (y)/Sex	Age at Presentation	Signs and Symptoms
1	29/F	12	f mass with severe calf pain
			ed ankle dorsiflexion
			rficial phlebectasia
2	13/M	Infancy	ist/forearm mass and severe pain
			ed wrist dorsiflexion
3	17/F	11	f mass and severe pain
			ed ankle dorsiflexion
			phy
4	21/F	13	f mass and pain
5	17/F	Birth	f mass and severe pain
			ed ankle dorsiflexion
			phy
6	14/F	Infancy	f mass and severe pain
			ed ankle dorsiflexion
			neous lymphatic vesicles
7	11/F	2	rficial phlebectasia
8	17/F	Early childhood	ist/forearm mass, no significant pain
9	18/F	13	ist/forearm mass with severe pain
			f mass with tenderness
10	17/M	Neonate	ed ankle dorsiflexion
			f mass and moderate to severe pain
11	32/F	28	ed ankle dorsiflexion
12	24/F	23	f mass and pain
13	33/F	Childhood	ptomatic R thigh mass; incidental finding
14	8/F	6	gh mass and severe pain
			f mass and severe pain
			ed ankle dorsiflexion
15	15/M	10	gh mass and moderate to severe pain
16	21/F	20	f mass and severe pain
17	1.25/M	1	f mass, difficulty in walking
18	9	5	f mass and severe pain
			ed ankle dorsiflexion

AVM indicates arteriovenous malformation; licable; R, right; VM, venous malformation.

TABLE 2. Major Features of FAVA Versus VM of the Extremity

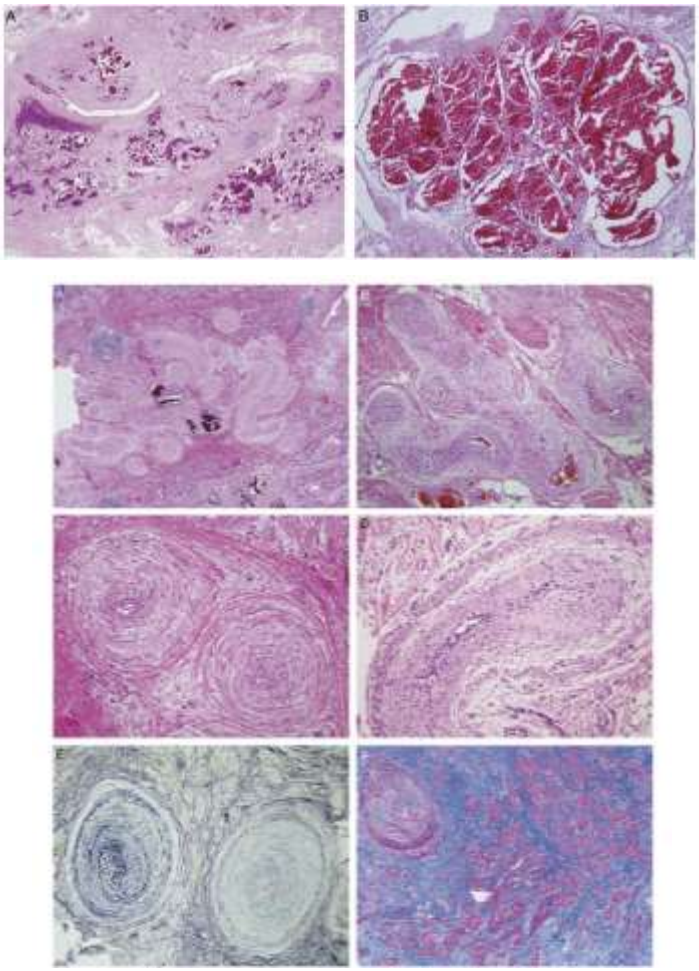
Features	FAVA	~~Common VM~~
Age at presentation	Any age, worsens in early adolescence	Any age, worsens in early adolescence
Pain	Very common, disproportionately severe, can be persistence, focal, or neurogenic	Episodic pain, many VMs asymptomatic
Contracture	Common	Typically absent, functorial impairment less severe
Magnetic resonance imaging features	Solid, heterogeneous, diffuse moderate to strong enhancement, occasional phleboliths	Typical fluid signal, phlebolith are common patchy heterogeneous enhancement
US features	Solid, hyperechoic muscle with dilated veins	Blood-filled, compressible spaces
Risk of thromboembolism	Present (with large phlebectasia)	Typically minor
Cutaneous findings	Largely absent	+/−
Location	Predilection to calf (gastrocnemius) and wrist	Quadriceps > gastrocnemius
Type of venous channels	Phlebectasia	Spongiform >> phlebectasia
Sex	Female > male	No sex predilection
Topography	Follows predictable muscular and neuronal distribution	Variable
Inheritance	None	Specific mutations in some patients
Pathology	Fibrosis, vessels, fat, inflammation	Vessel walls
Lymphatic component	Occasionally present	Typically absent
Treatment	Sclerotherapy > surgical	Surgical > sclerotherapy

FAVA indicates fibro-adipose vascular anomaly; VM, venous malformation.

Alomari, AI et al., J Pediatr Orthop. 2014

PHOST – PTEN Hamartoma of Soft Tissue

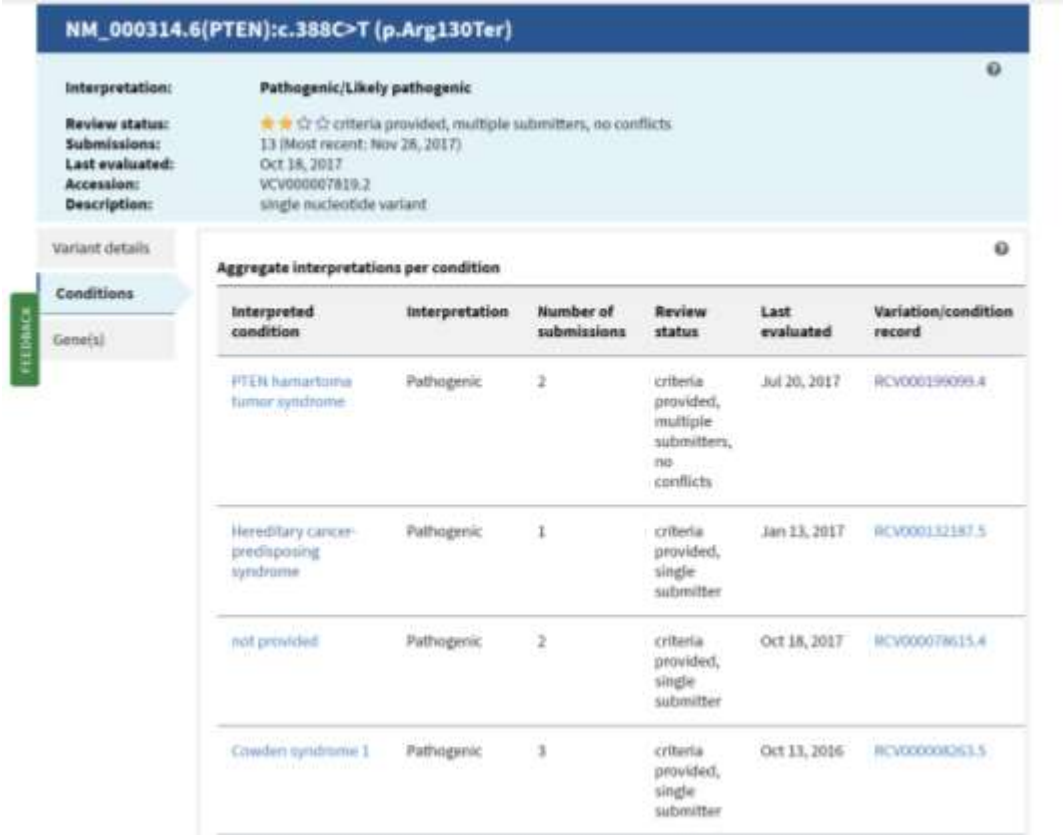
- First described in 2012
- Consisting of:
  - Variable admixture of mature adipose tissue and dense/myxoid fibrous tissue
  - Vascular component with:
    - clusters of venous channels some with excessively muscularized walls
    - tortuous thick walled arteries with concentric muscular hyperplasia
  - Lymphoid follicles
  - Foci of bone or hypertrophic nerves with "onion bulb" proliferation of spindle cells
- Associated with Cowden Syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS) in 50% of cases
- 85% patients with PTEN germline mutations



Kurek KC et al.,Am J Surg Pathol. 2012

Molecular pathology

- STAMP – Solid Tumor Mutation Panel
  - PTEN c.388C>T (p.Arg130Ter)



NM_000314.6(PTEN):c.388C>T (p.Arg130Ter)

Interpretation: Pathogenic/Likely pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts
Submissions: 13 (Most recent: Nov 28, 2017)
Last evaluated: Oct 18, 2017
Accession: VCV000007819.2
Description: single nucleotide variant

Variant details | Conditions | Gene(s)

FEEDBACK

Aggregate interpretations per condition

Interpreted condition	Interpretation	Number of submissions	Review status	Last evaluated	Variation/condition record
PTEN hamartoma tumor syndrome	Pathogenic	2	criteria provided, multiple submitters, no conflicts	Jul 20, 2017	RCV000199099.4
Hereditary cancer-predisposing syndrome	Pathogenic	1	criteria provided, single submitter	Jan 13, 2017	RCV000132187.5
not provided	Pathogenic	2	criteria provided, single submitter	Oct 18, 2017	RCV000078615.4
Cowden syndrome 1	Pathogenic	3	criteria provided, single submitter	Oct 13, 2016	RCV000082653.5

Diagnosis

- Fibro-adipose vascular anomaly (FAVA)
- PTEN-associated malformations
  - PHOST - PTEN Hamartoma of Soft Tissue

Take Home Messages

PHOST - PTEN Hamartoma of Soft Tissue:

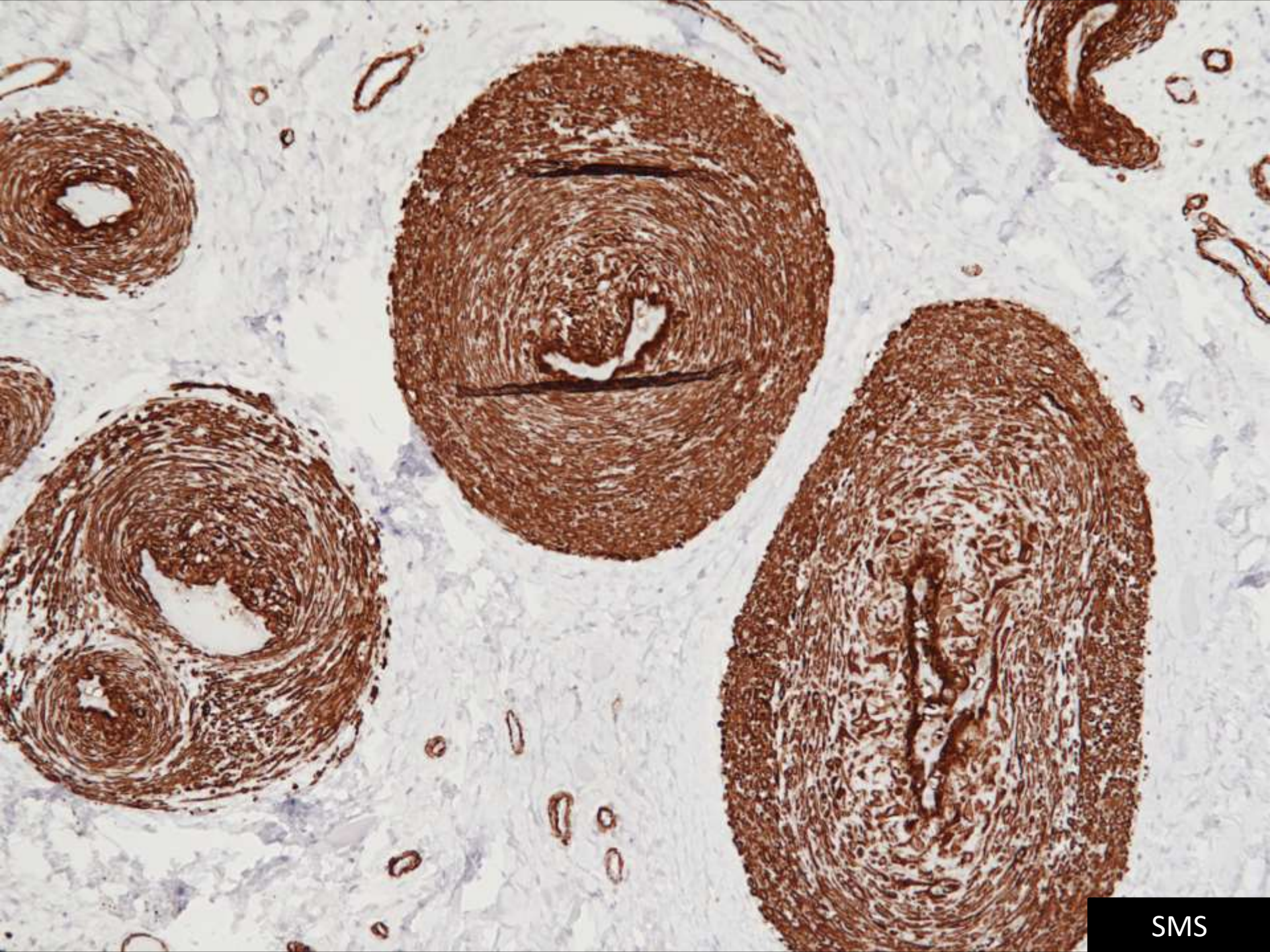
- ✓ Recently described
- ✓ Benign vascular neoplasia/hamartomatous lesion
- ✓ Associated with Cowen and Bannayan-Riley-Ruvalcaba syndromes
- ✓ The differential diagnosis with FAVA is difficult

  - somatic mutation analysis can be helpful

- ✓ Unknown clinical significance of germline mutation testing

PHOST – PTEN Hamartoma of Soft Tissue

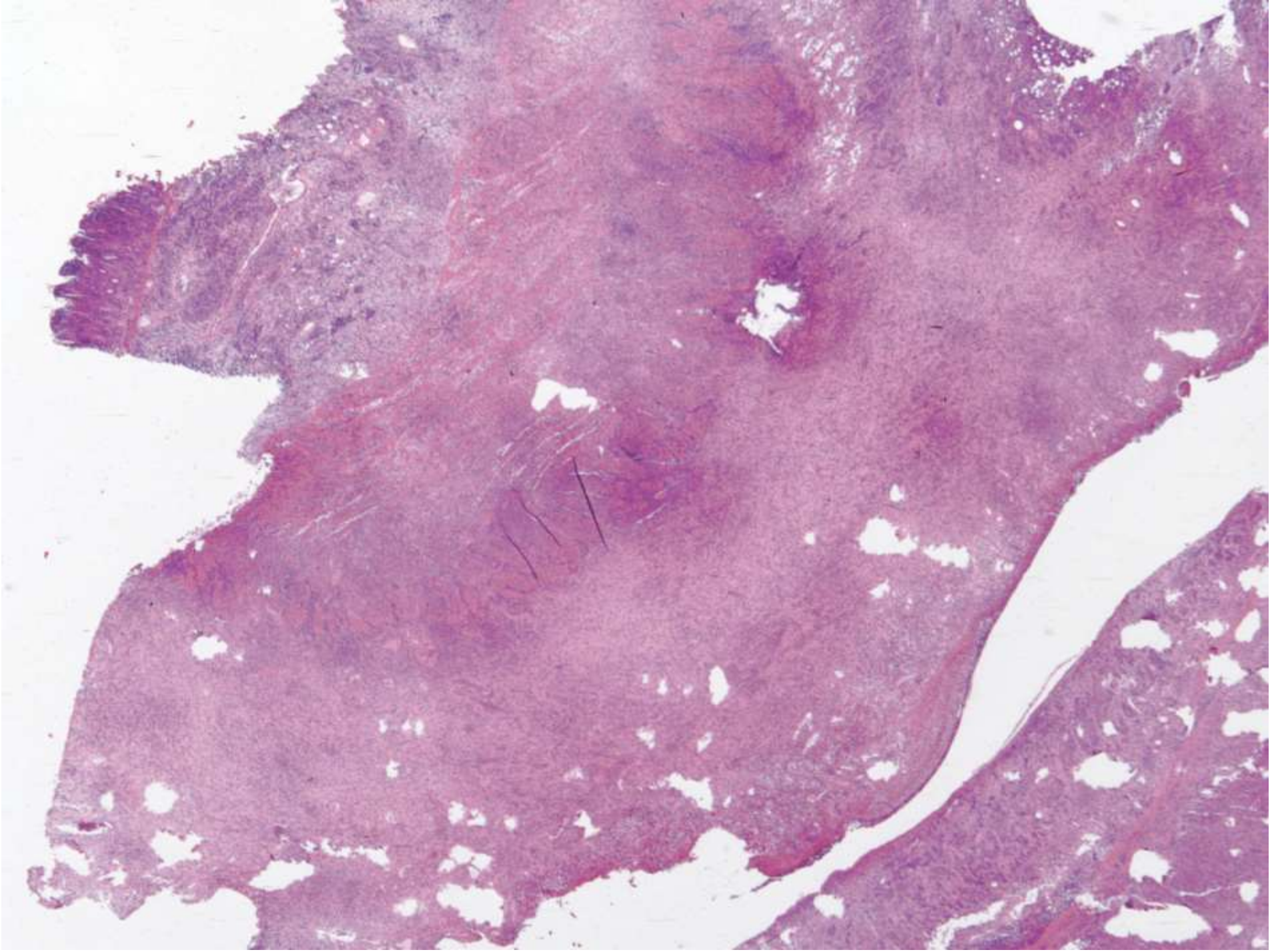
Francisco Beca MD, PhD / Eduardo Zambrano MD, MS
Department of Pathology, Stanford University School of Medicine
March 2018

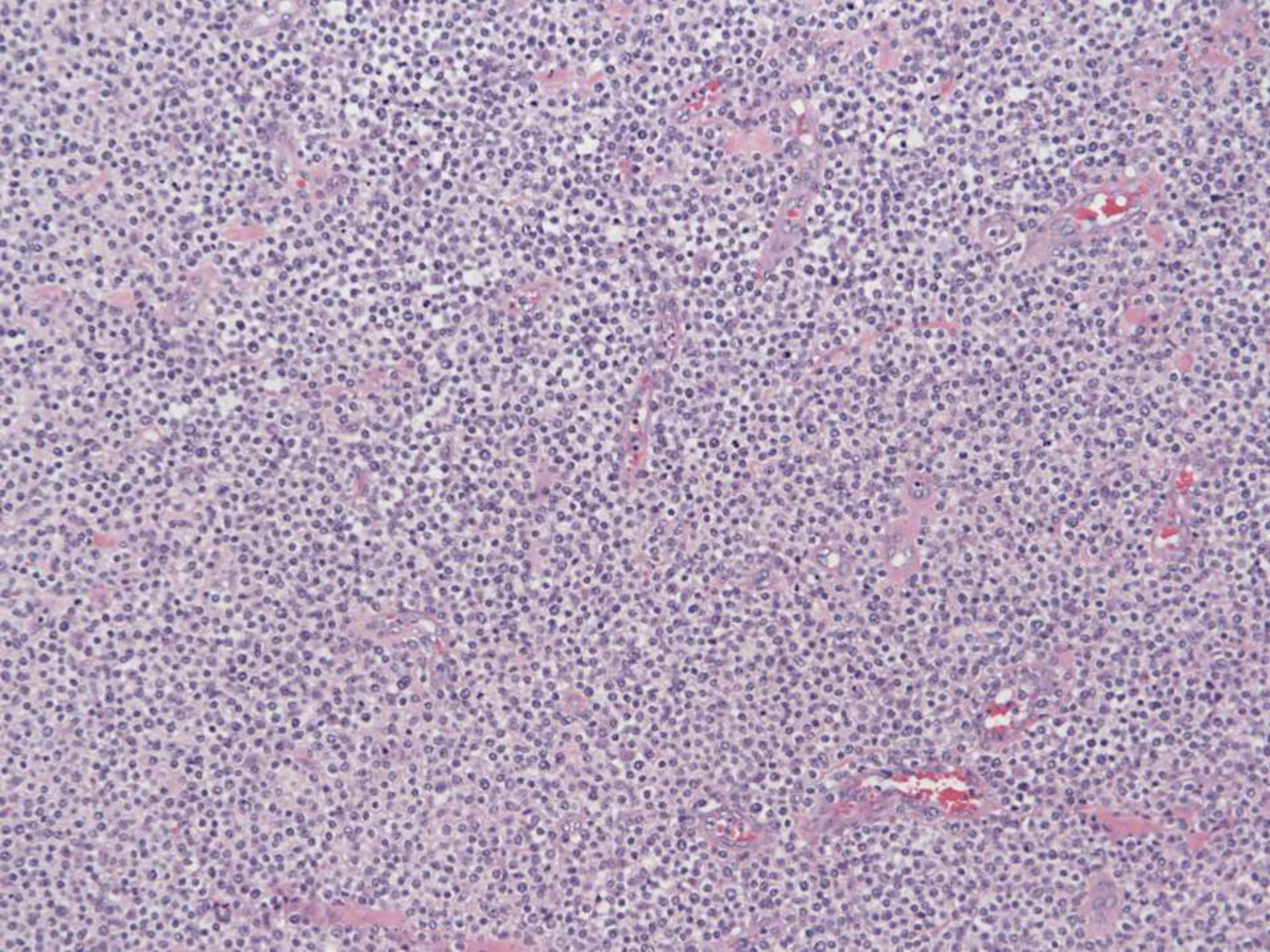

SMS

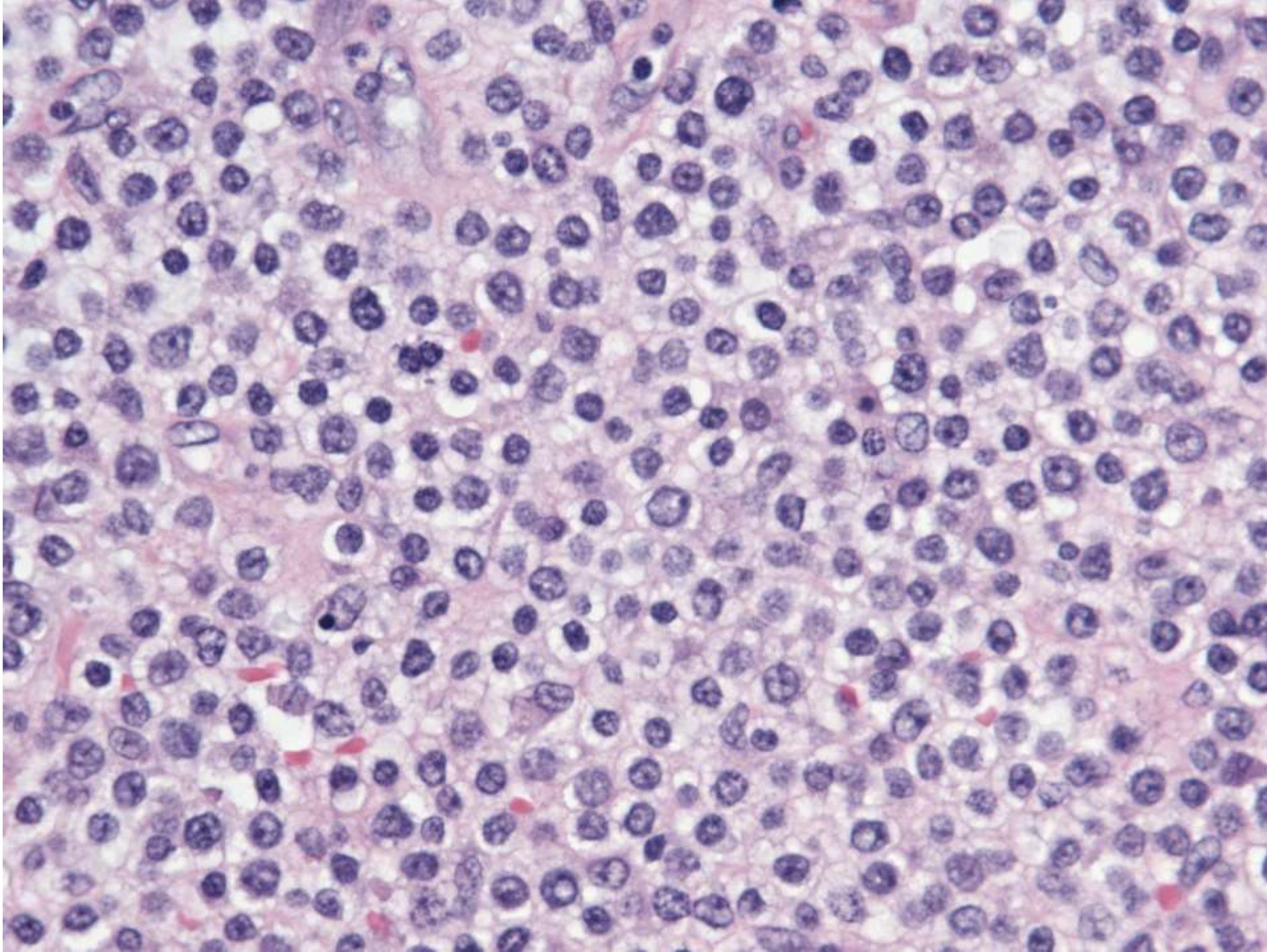
SB 6256

Oscar Silva/Roger Warnke; Stanford

75-year-old male with small bowel obstruction.







DIAGNOSIS?

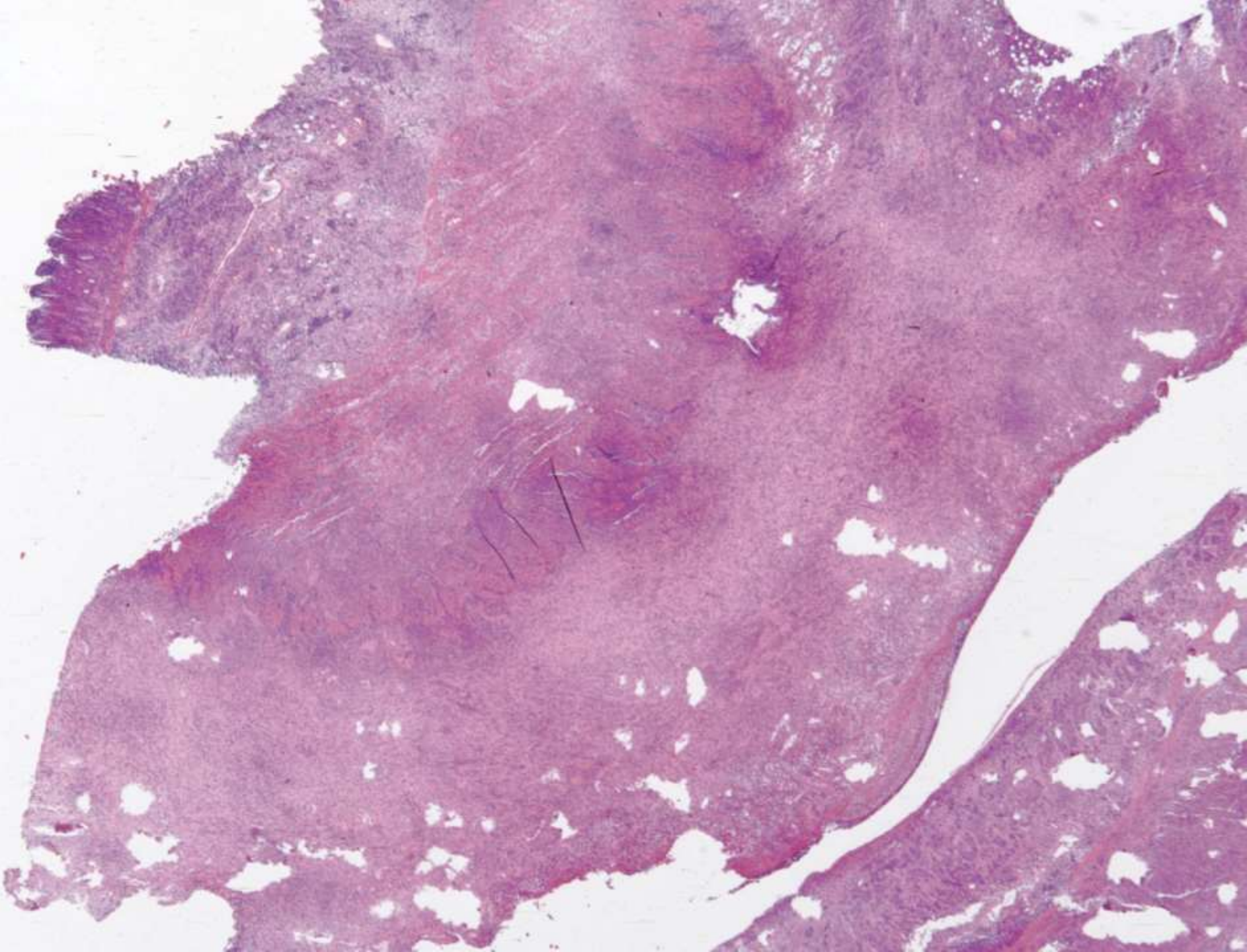
South Bay Pathology Society

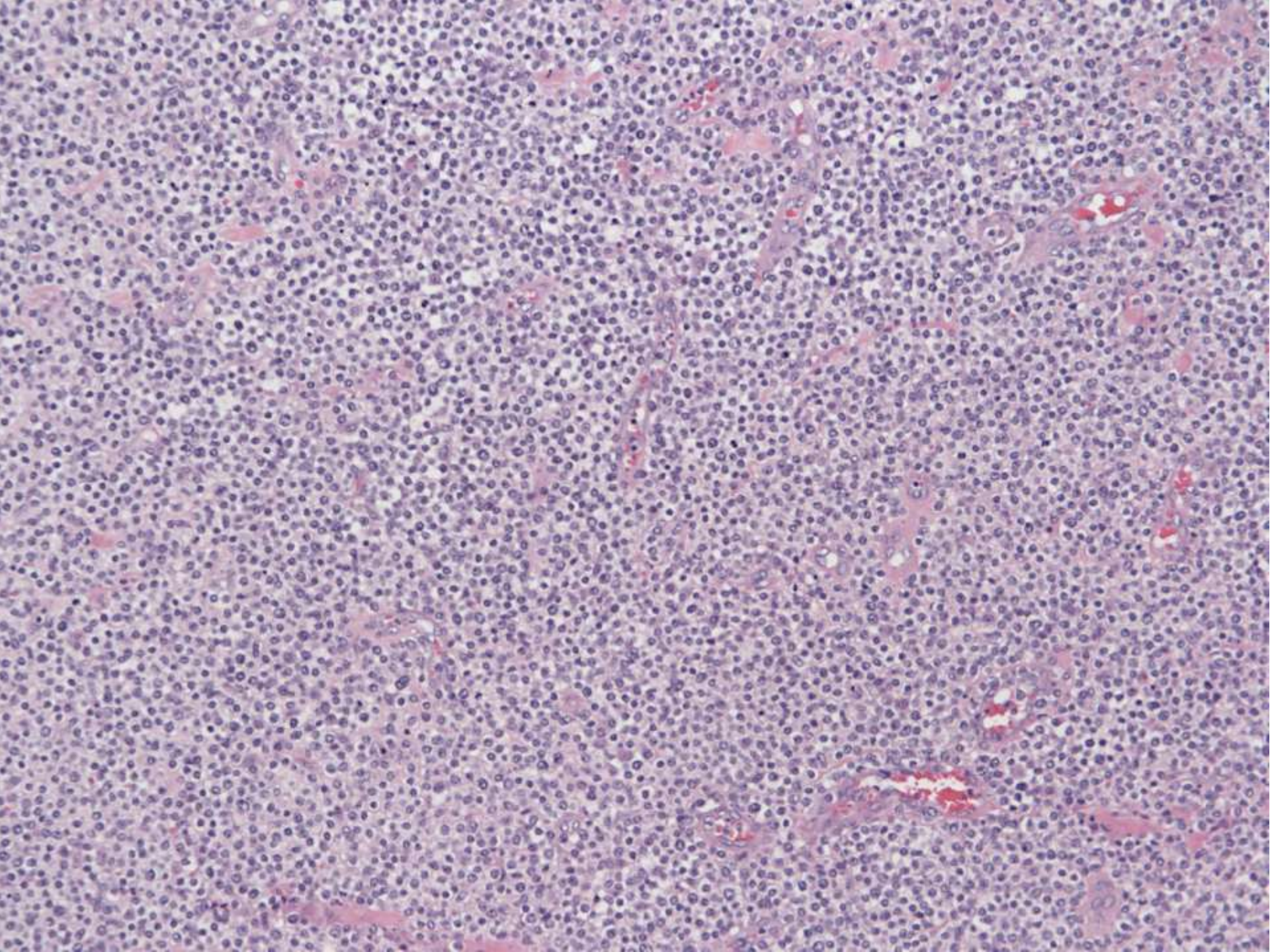
March 5, 2018

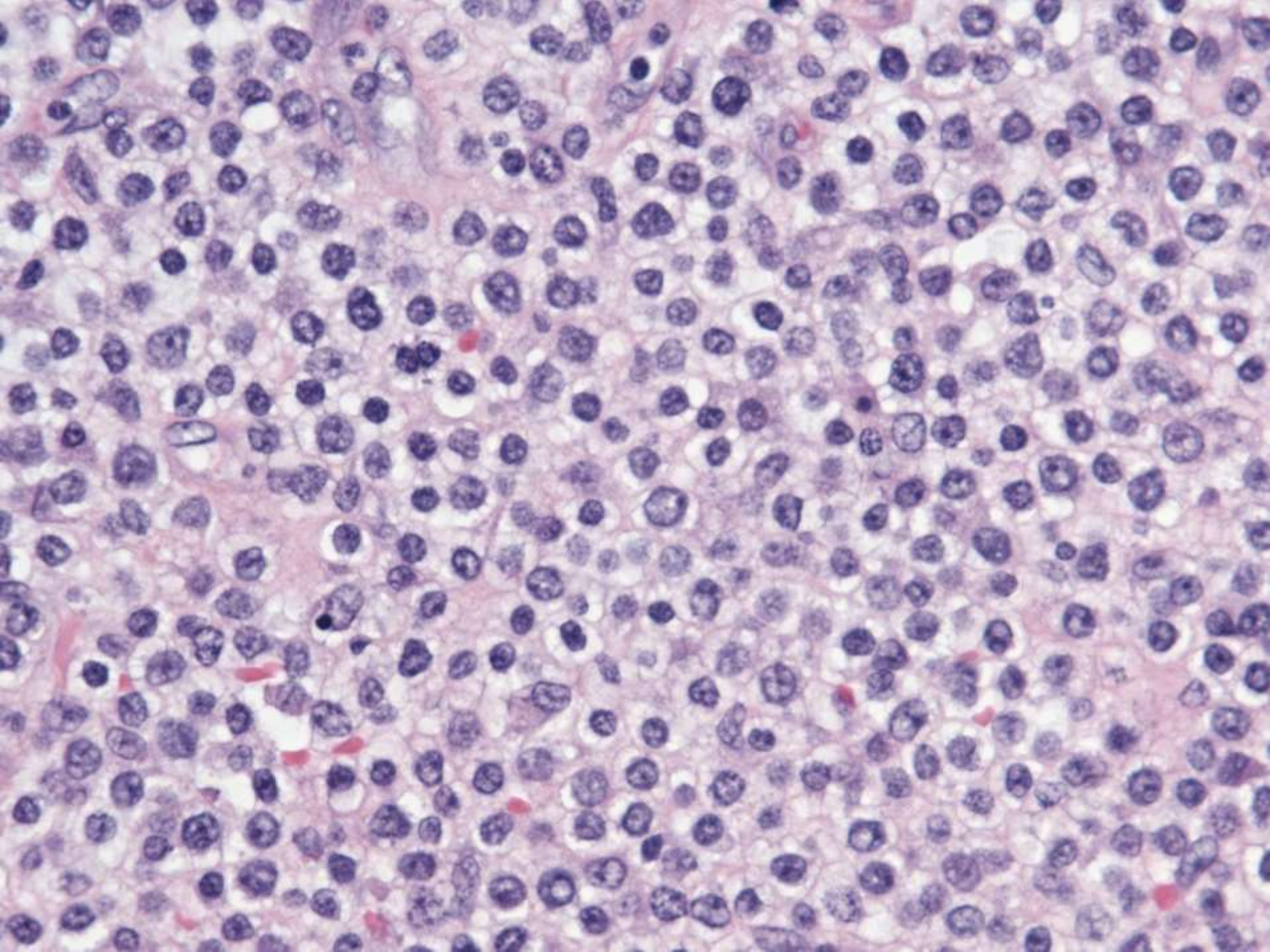
Oscar Silva, MD PhD & Roger Warnke, MD

Stanford University

65 year old male with small bowel obstruction

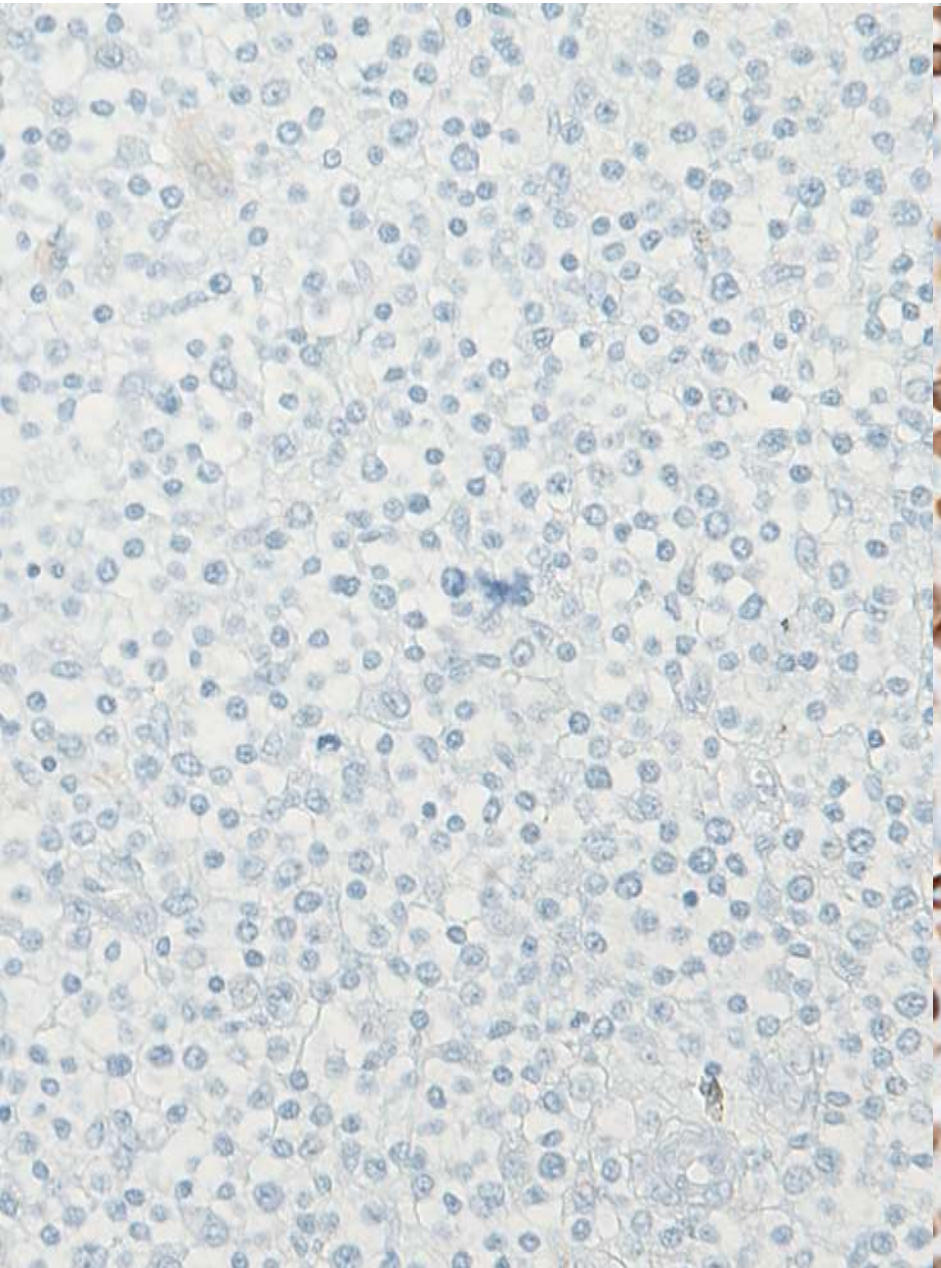


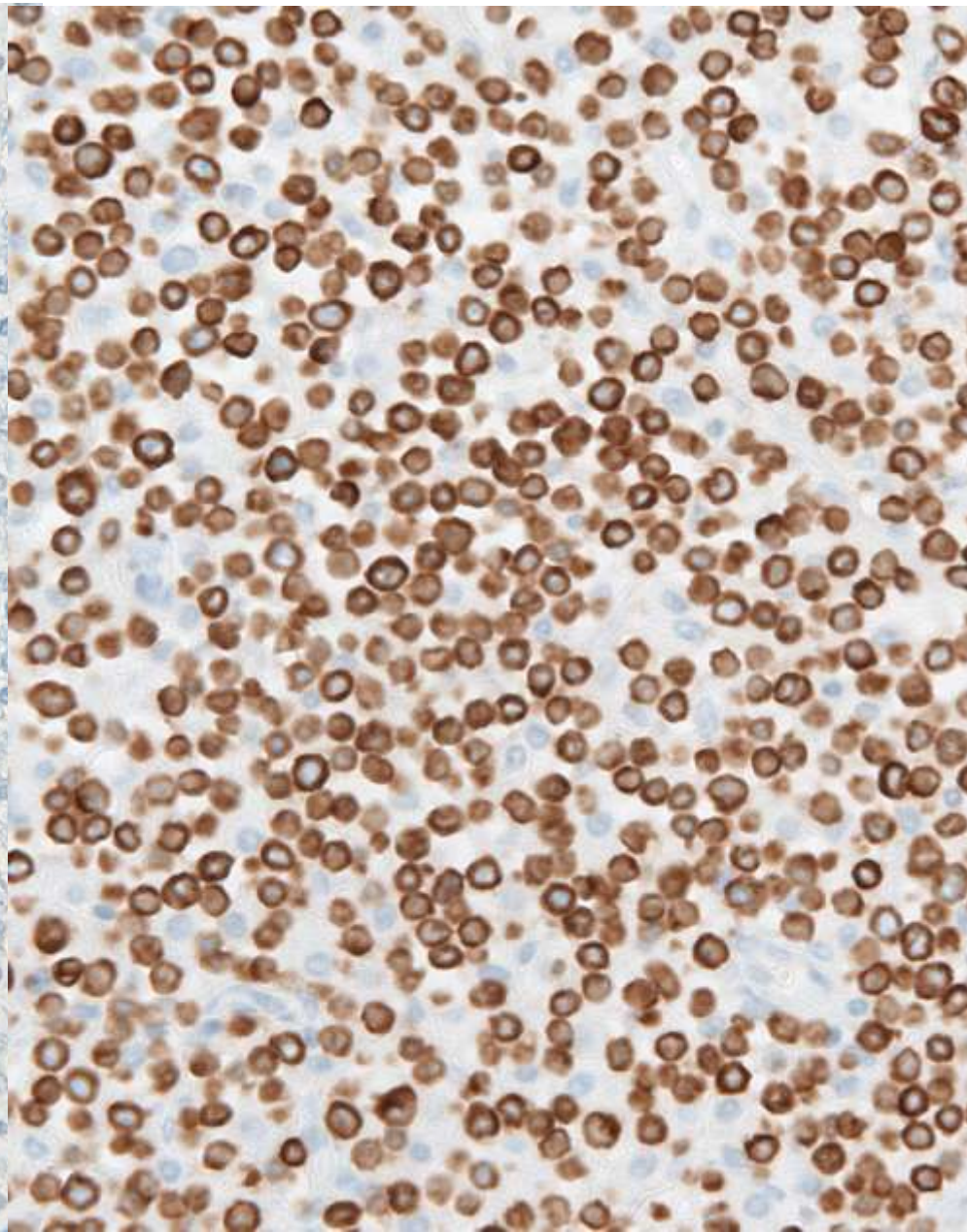


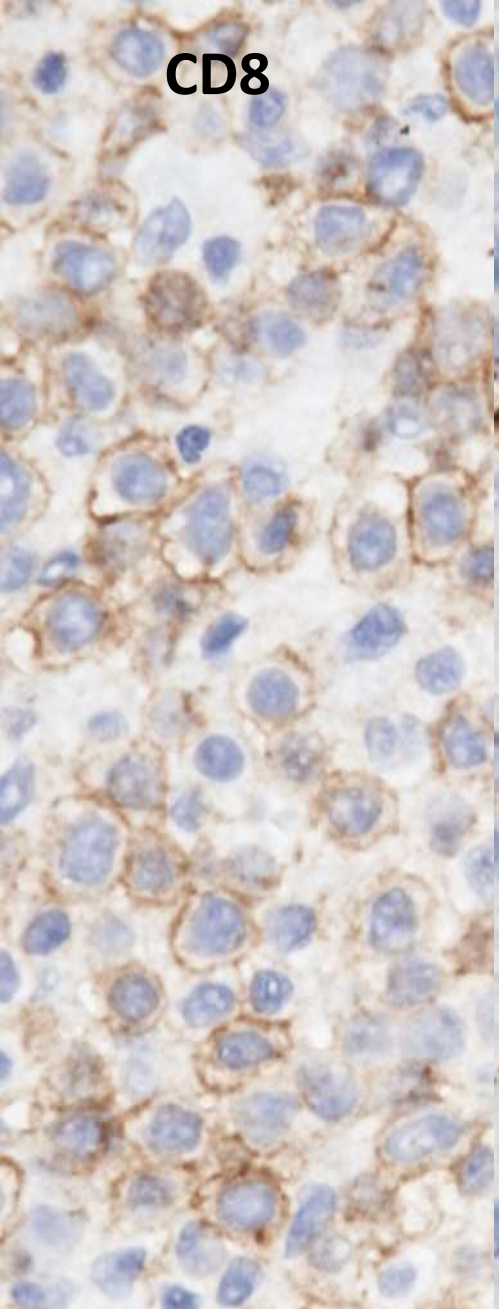


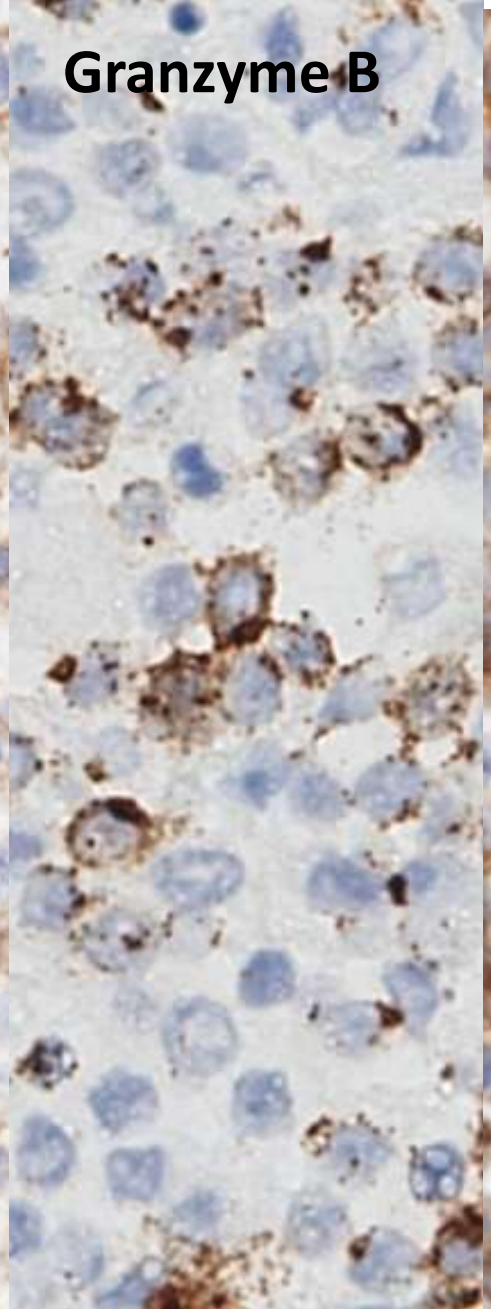
CD20

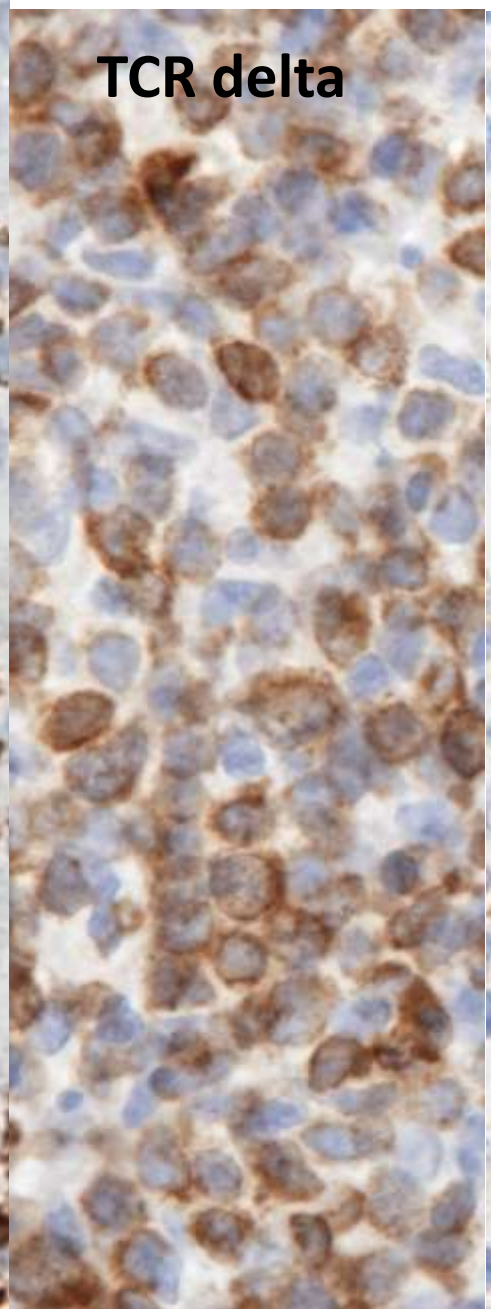
CD3

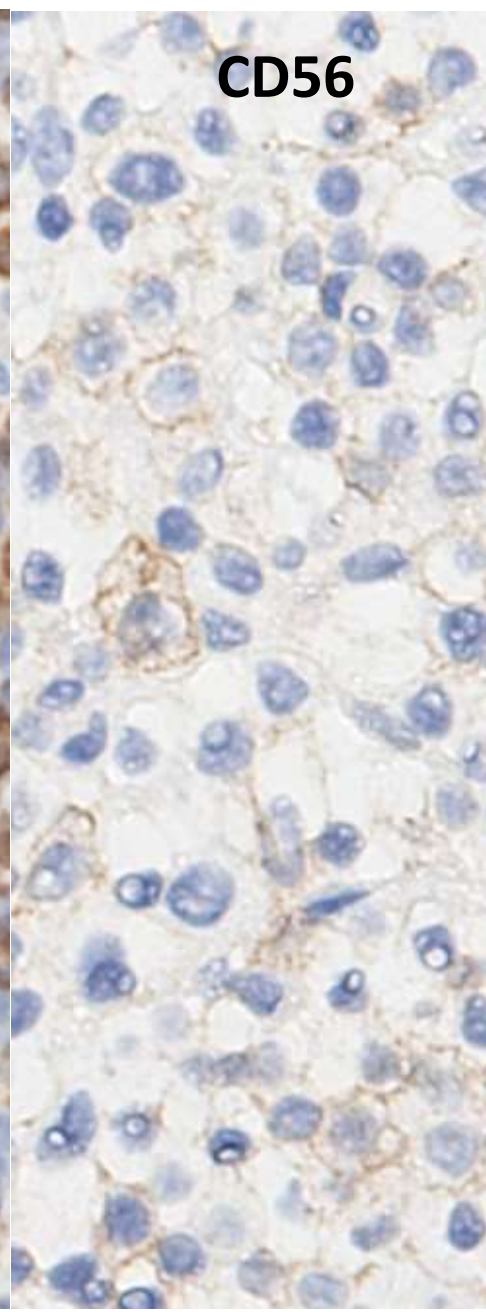












CD4 negative

TIA positive

TCR beta (-)

EBV negative

MEITL (Monomorphic epitheliotropic intestinal T cell lymphoma)

Feature	EATL (formerly known as Type I EATL)	MEITL (formerly known as Type II EATL)
Ethnicity (excess incidence)	Northern European	Asian, Hispanic
Risk Factors	Celiac disease	None recognized
Morphology	Polymorphic	Monomorphic
Usual immunophenotype	CD3+, CD5-, CD4-, CD8-, CD56-, CD103+, CD30+/-, cytotoxic+	CD3+, CD5-, CD4-, CD8+, CD56+, CD103+/-, CD30-, cytotoxic+, MATK+
T-cell receptor expression	Alpha beta > gamma delta	Gamma delta > alpha beta
Genetics	1q32.2-q41 and 5q34-q35.2 gains	8q24 gain (*MYC*); mutations in *STAT5B (60%) & SETD2 (90%)*
Localization	Small intestine (jejunum & ileum)	Small intestine (jejunum)

2017 WHO (Table 14.04)

MEITL: clinical presentation and prognosis

Often present as a tumor mass and can have diffuse spread to mesenteric lymph nodes, stomach (5% of cases) or large bowel (16% of cases)

Symptoms may include: perforation, obstruction, bleeding

Clinical aggressive, median survival is 7 months

5 year overall and complete response rates are poor: 46% and 48%, respectively

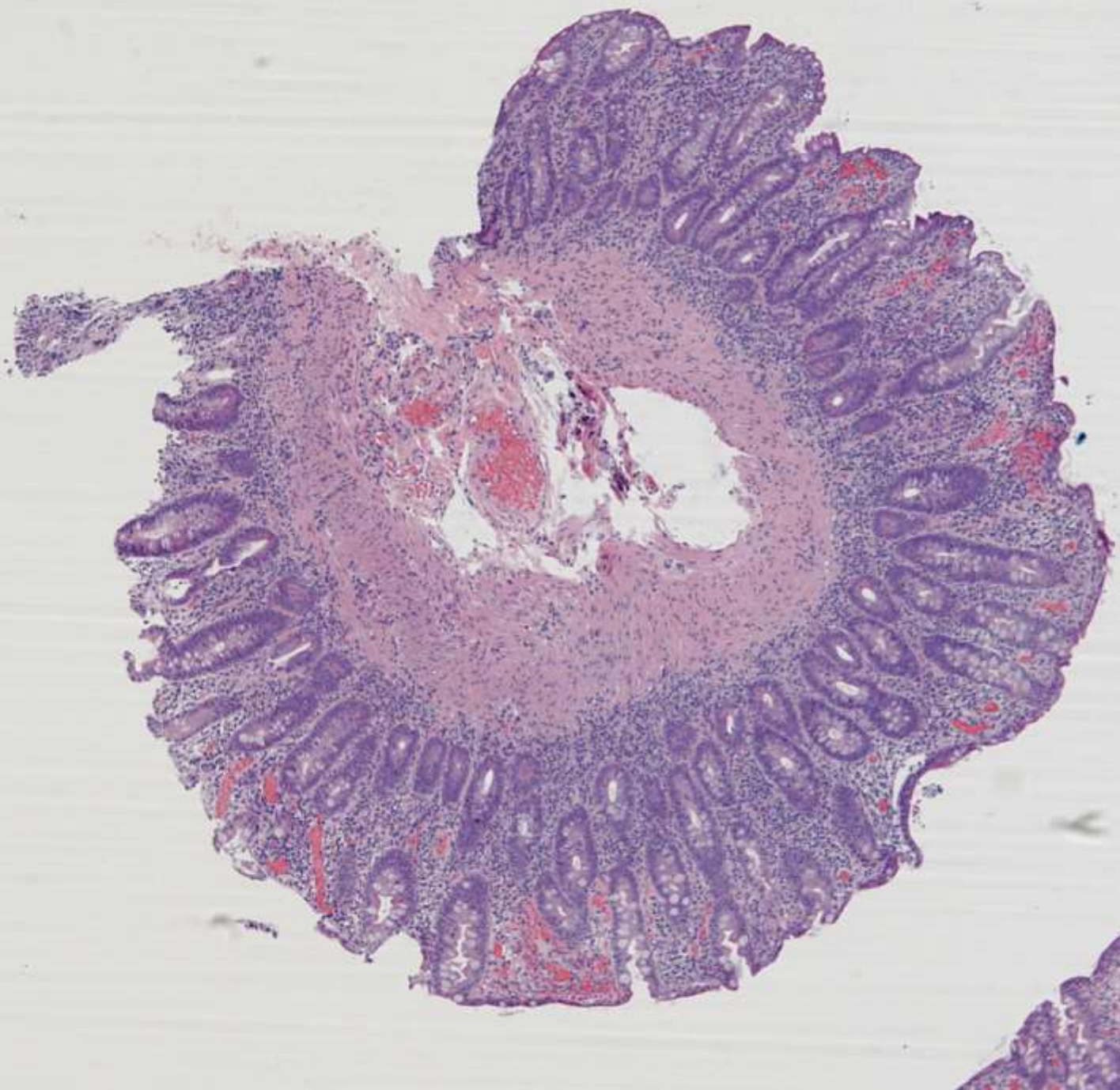
Treatment is usually surgery and chemotherapy (and possibley transplant)

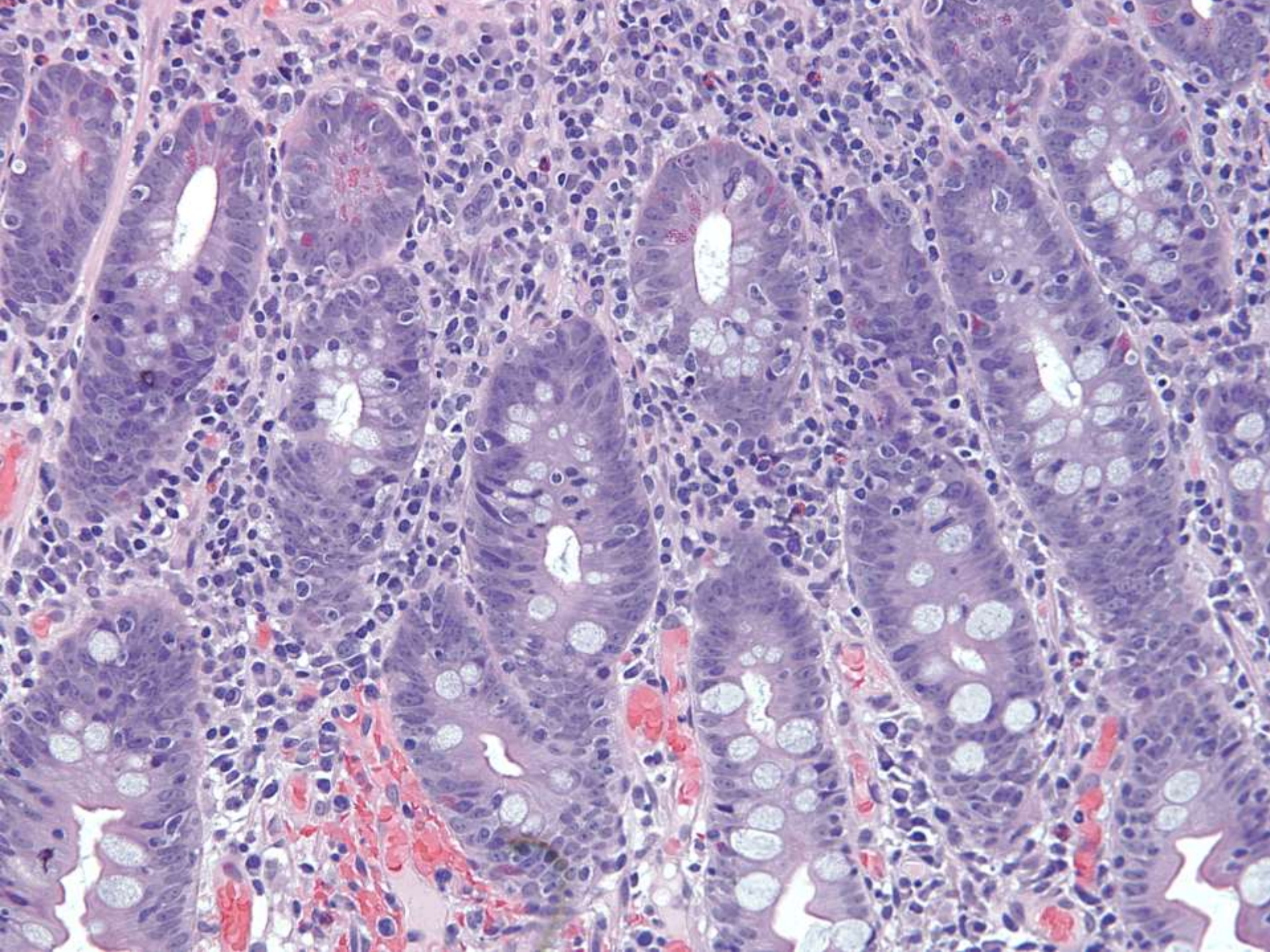
Unfortunately no clinical follow-up is available for this case as it was received in consultation.

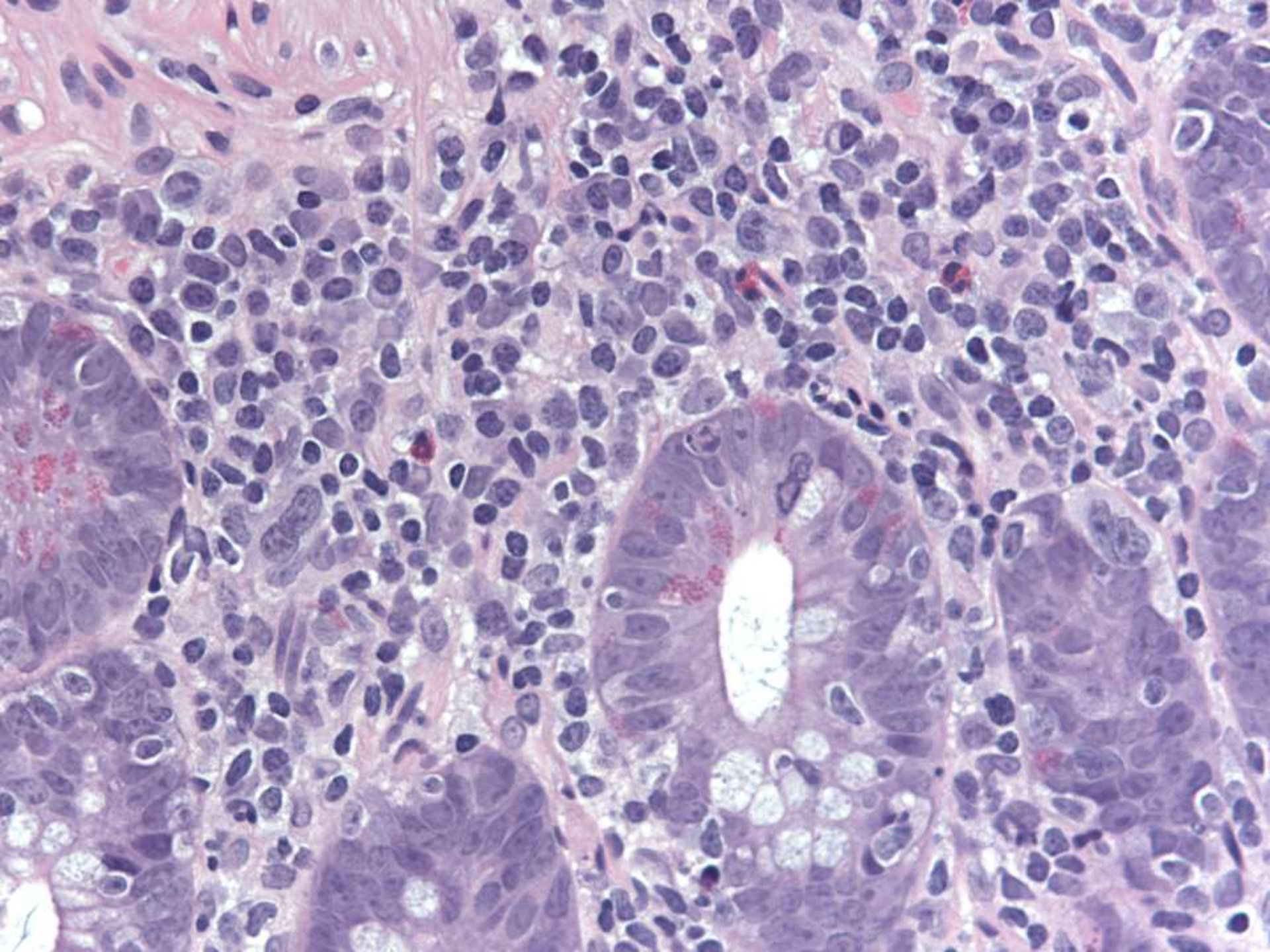
SB 6257

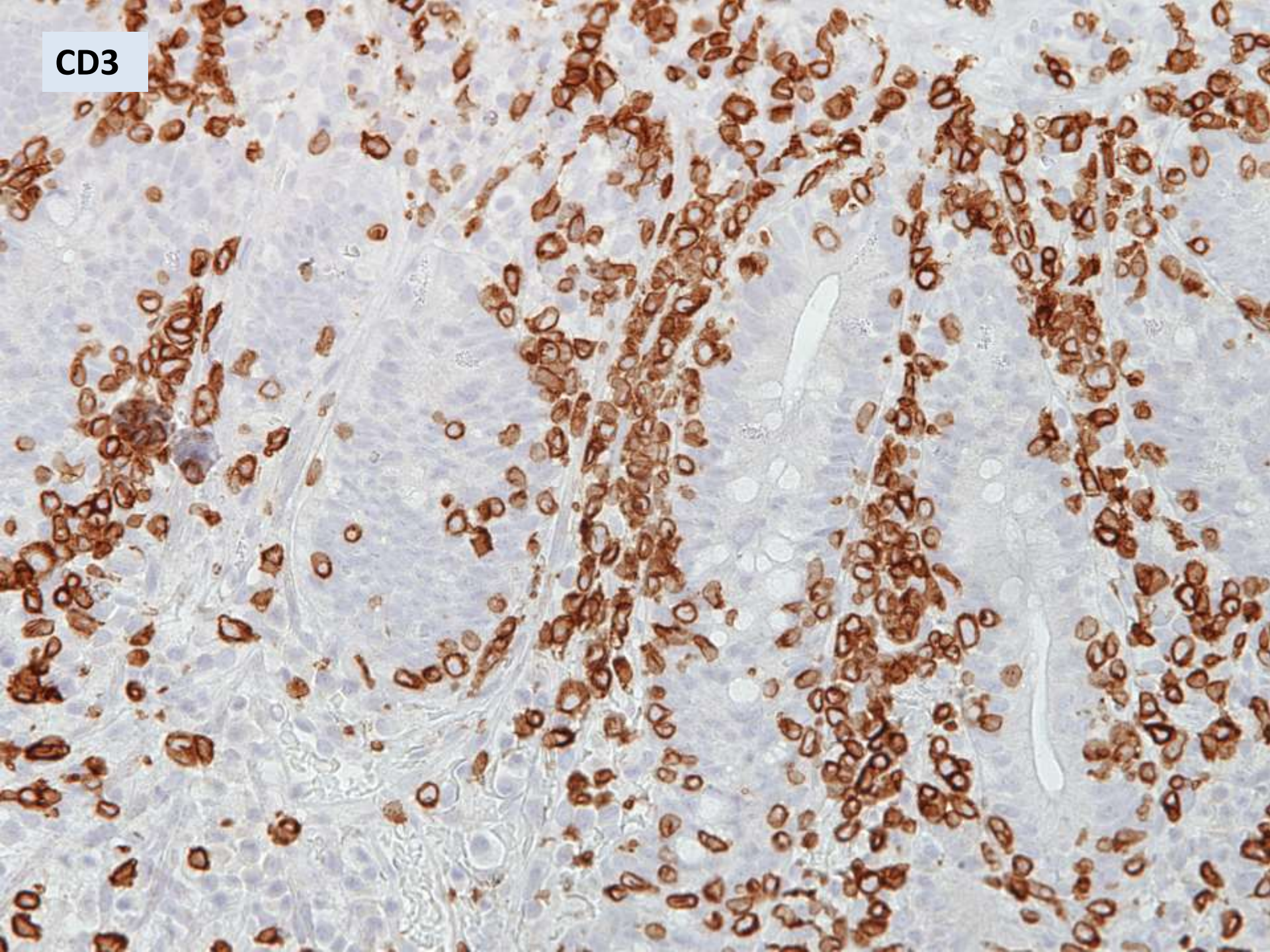
Erna Forgo/Teri Longacre; Stanford

61-year-old with long-standing history of celiac disease, now with refractory symptoms and malabsorption that are no longer controlled by diet and steroids.



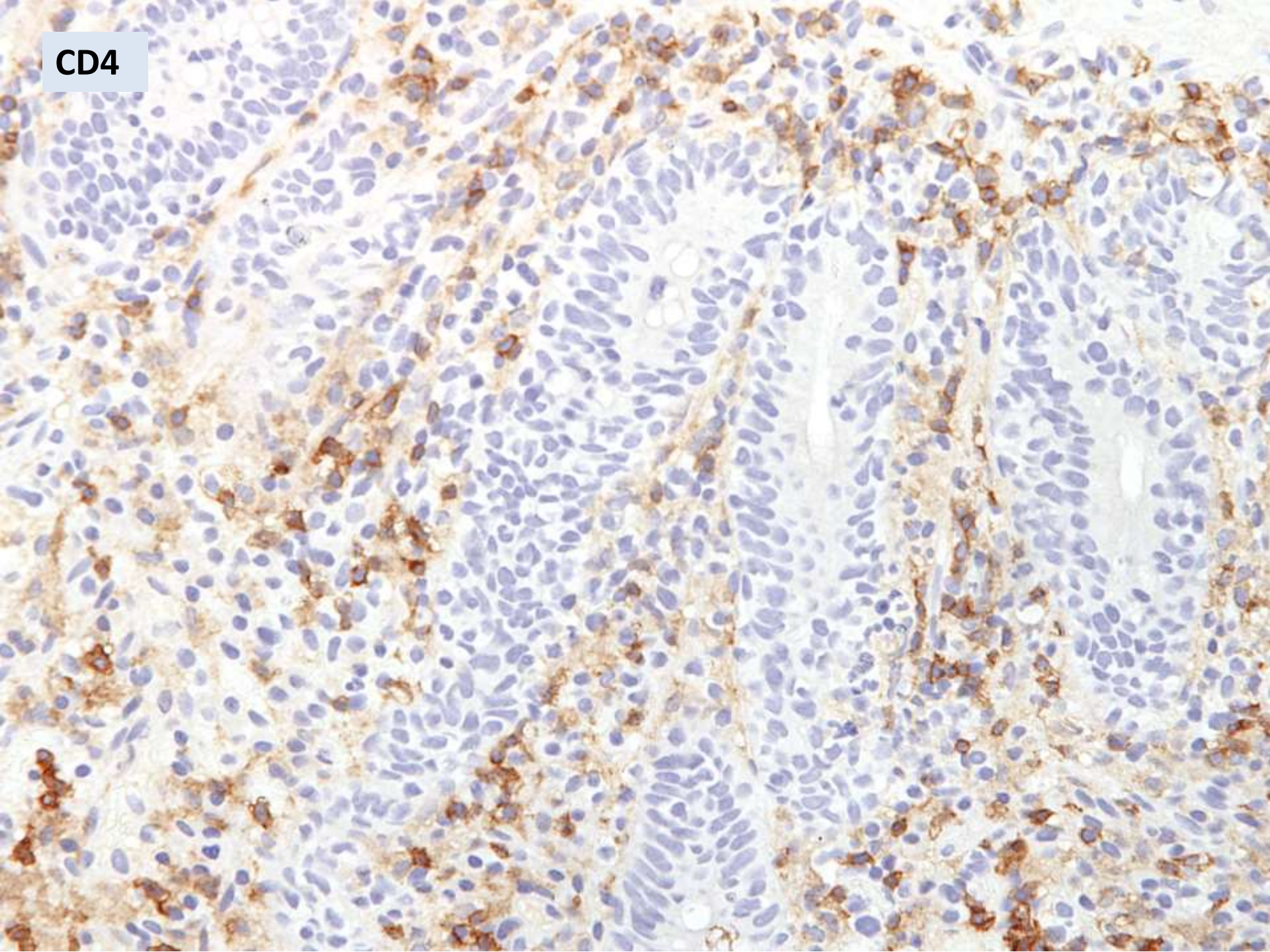


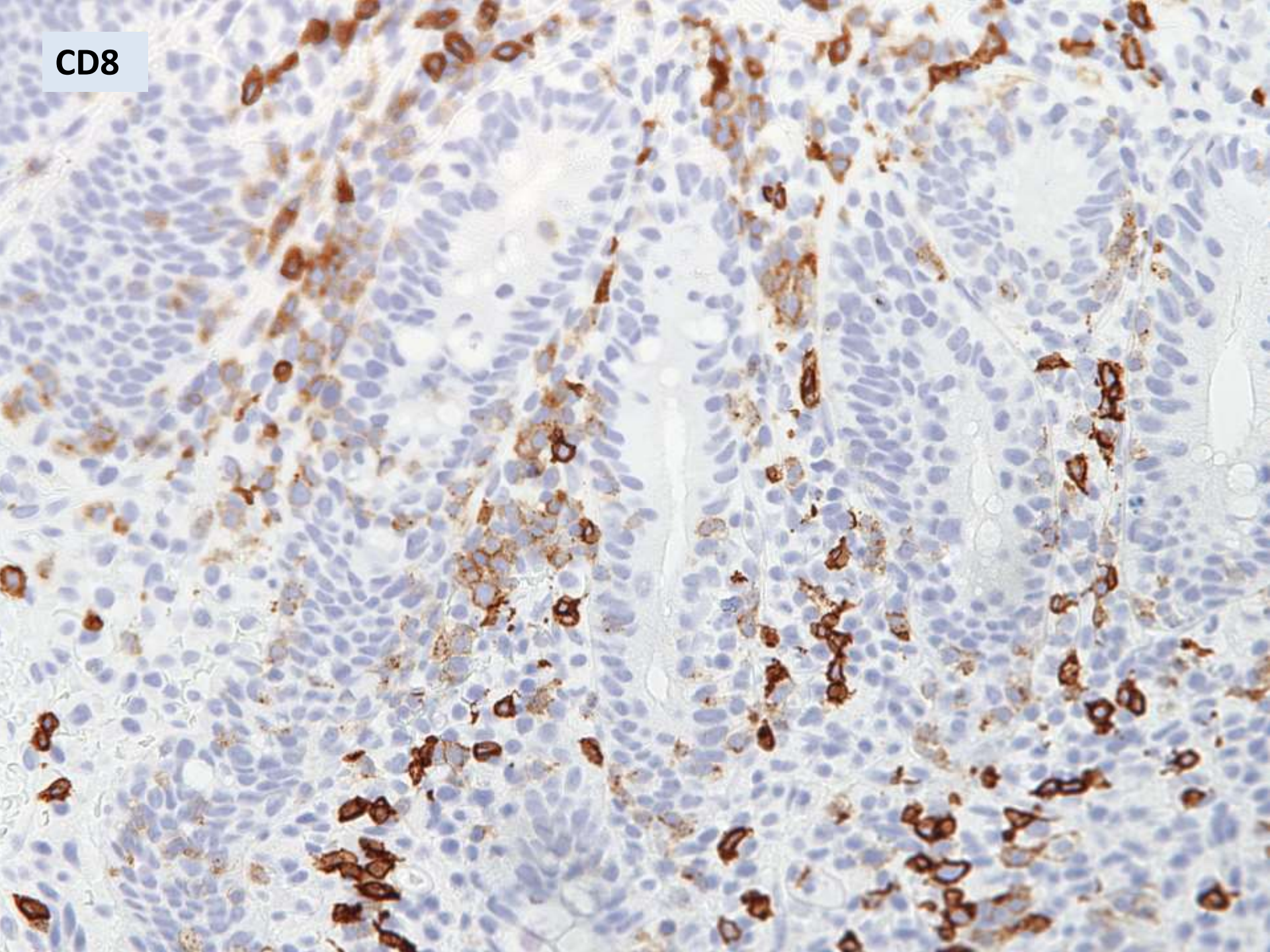



CD3

Differential Diagnosis

- Infection
- Celiac disease
- Refractory celiac disease type I
- Refractory celiac disease type II
- Lymphoma


CD4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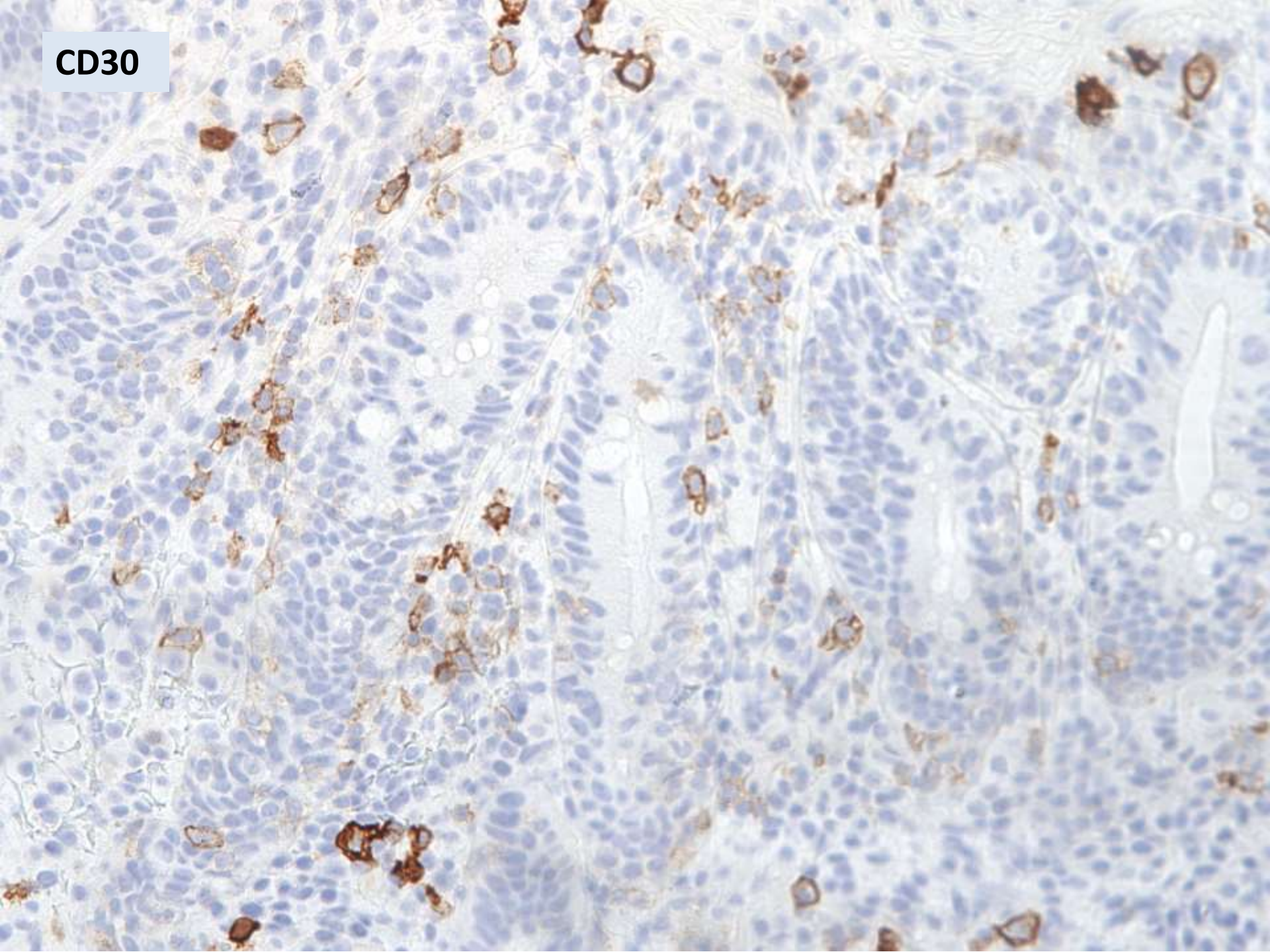

CD30

Additional Work up

- CD56, EBV ISH negative
- CMV, PAS, GMS, and AFB were also negative

Diagnosis

Enteropathy Associated T-Cell Lymphoma, Type I

Additional Patient History

- History of celiac disease since 2005, well controlled with diet until 2015
- 2015: Weight loss, night sweats, symptoms no longer controlled by diet alone
- 2016: GI bx series – villous blunting with increased intraepithelial lymphocytes, consistent with severe celiac disease
  - No evidence of aberrant T-cell antigen expression

Additional Patient History

- Continued to have symptoms with diet and steroids → evidence of malabsorption
- Jan 2017: GI bleeding with ulcerated lesion in the small intestine
  - GI bx series: **villous blunting with increased intraepithelial lymphocytes**
    - Flow cytometry: very small population of T- or NK- cells expressing CD2, CD9 and **CD30**; not expressing CD3 and CD5
    - Molecular study for T-cell clonality was **positive**

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

- Should be considered in patient with refractory sprue unresponsive to glucocorticoids
- Both have aberrant T-cell monoclonality
- Multiple chronic, benign-appearing, non-mass forming ulcers, most frequently in jejunum
- Similar presentation to severe celiac disease

Refractory Celiac Disease

- 2-5% of celiac disease patients:
  - No initial response to a gluten-free diet
  - Experienced initial clinical improvement on diet, but develop disease refractory to gluten abstinence
- **Type I**: normal population of IELs
- **Type II**: aberrant/pre-malignant population of IELs based on clonality analysis of T-cell receptors and immunophenotyping
  - Can progress to EATL (1020x increase in relative risk)

How do we tell them apart?

Disease	Histology	Immunophenotype	T-Cell Clonality	Prognosis
Celiac disease (untreated)	Increased IELs, villous atrophy, crypt hyperplasia, lymphoplasmacytic infiltrate in lamina propria	IELs: predominance of CD3+, CD8+ T cells (rare CD4+ cells; rare CD56+ cells; few CD4-/CD8- γδ cells)	Polyclonal	Good, with proper diet
Refractory celiac disease	Same as for celiac disease, sometimes with histologic changes of ulcerative jejunitis	Type I IELs: Predominance of CD3+, CD8+ T cells Type II IELs: Predominance of CD3+, CD4-/CD8- T cells Lamina propria: mixture of CD4+ and CD8+ T cells	Type I: Polyclonal Type II: Almost always monoclonal	Moderately poor; patients may die of malnutrition, or develop lymphoma
Ulcerative jejunitis	One or more mucosal ulcers with many inflammatory cells	IELs: Predominance of CD3+, CD4-/CD8- T cells Ulcer base: mixture of CD4+ and CD8+ T cells and other inflammatory cells	Monoclonal	Moderately poor; patients may die of malnutrition or perforation, or develop lymphoma

T-Cell Lymphomas of Small Intestine

Disease	Histology	Immunophenotype	T-Cell Clonality	Prognosis
Type I (Enteropathy -associated)	Lymphoma: medium and large atypical cells or anaplastic large cells	Lymphoma: CD3+, CD4-, CD8−/+, CD56-, CD30+/−	Monoclonal	Very poor
(80-90%)	Adjacent mucosa: as for celiac disease	IELs: as for refractory sprue and ulcerative jejunitis	Monoclonal; same clone as the EATL	
Type II (Intestinal)	Lymphoma: monomorphic medium-sized cells	Lymphoma: CD3+, CD4−, CD8+, CD56+, CD30−	Monoclonal	Very poor
(10-20%)	Adjacent mucosa: as for celiac disease in some; may not show enteropathy	IELs: CD3+, CD4-, CD8+, CD56+ cells	Monoclonal; same clone as the EATL	

EATL Prognosis

- In one study of 31 patients, 84% died of lymphoma or from complications of therapy[1]

- In another study, the median survival was 3 months, and 70% of patients died within 6 months[2]

[1]Gale J et al. *J Clin Oncol.* 18:795-803 2000
[2]A Chott A et al. *Am J Pathol.* 153:1483-1490 1998

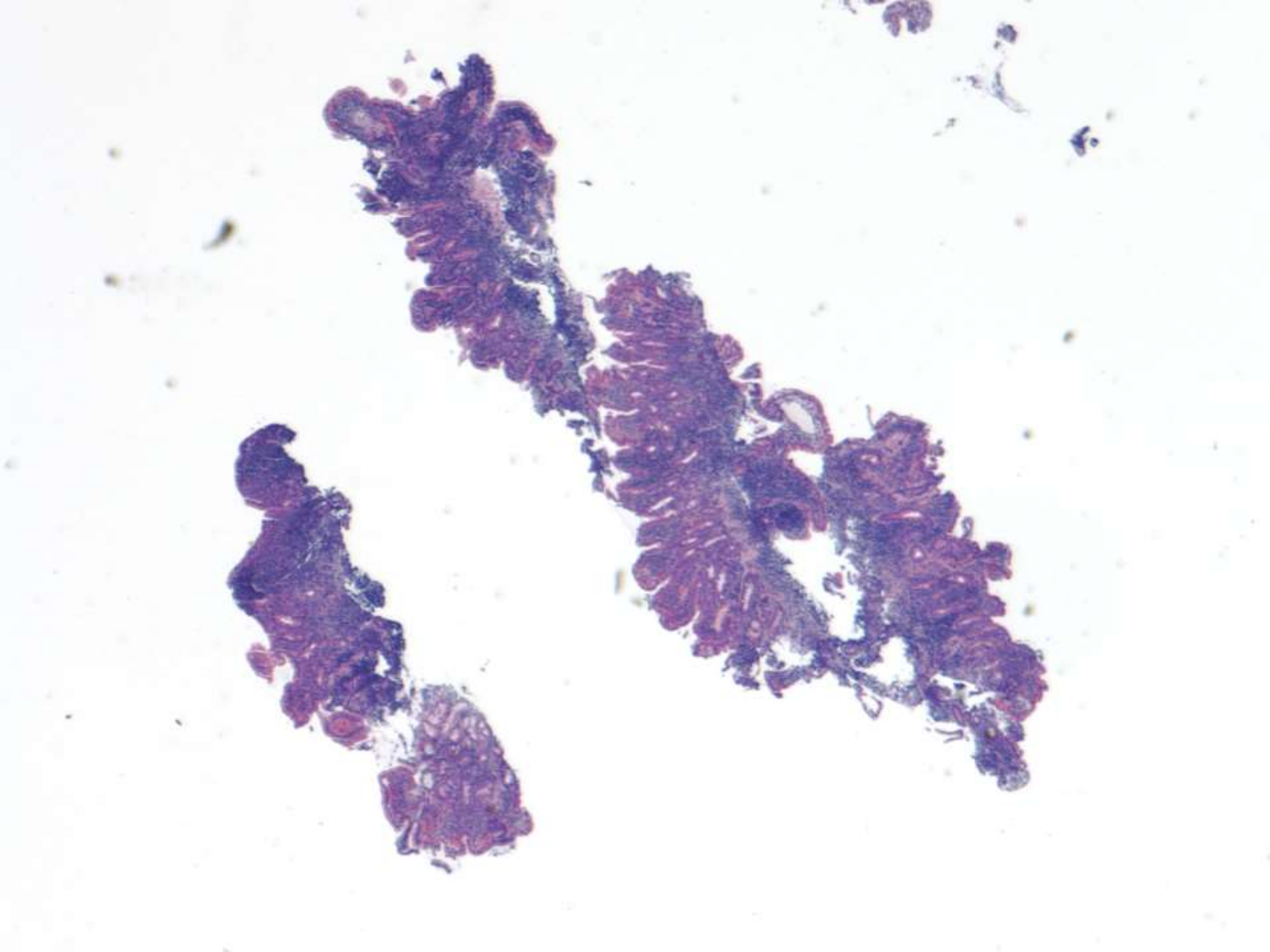
Follow-up

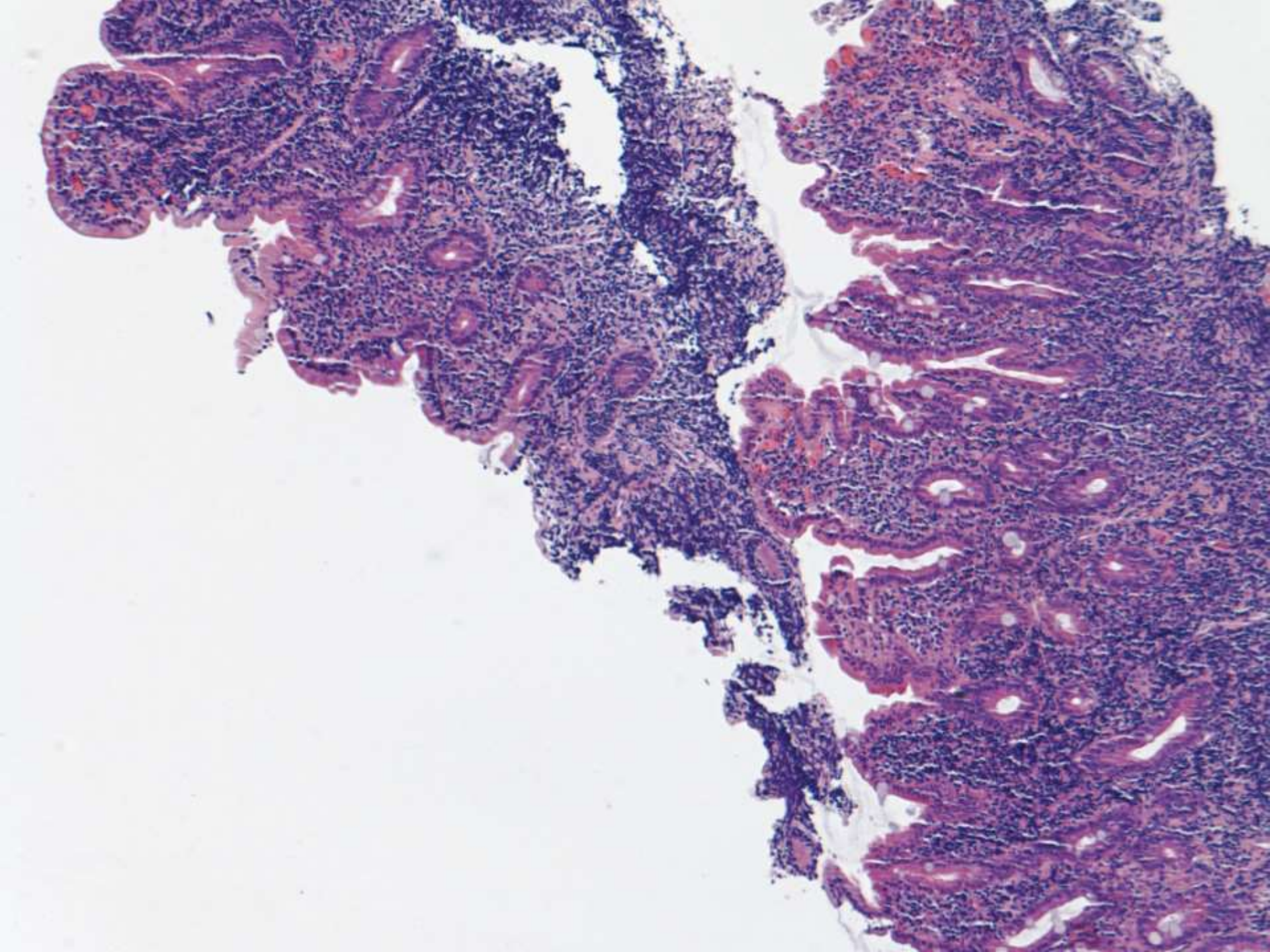
- GI bleed under control s/p IR coil embolization
- He elected to pursue therapy
  - Started CHOEP chemotherapy x 1 cycle
  - Complicated by aspergillus pneumonia, multiple pulmonary emboli likely secondary to a lower extremity deep vein thrombi
  - After cycle 2 he developed acute gangrenous hemorrhagic cholecystitis and a large intraluminal GI arterial bleed resulting in hemorrhagic shock and coagulopathy
- Transitioned to comfort care and passed away

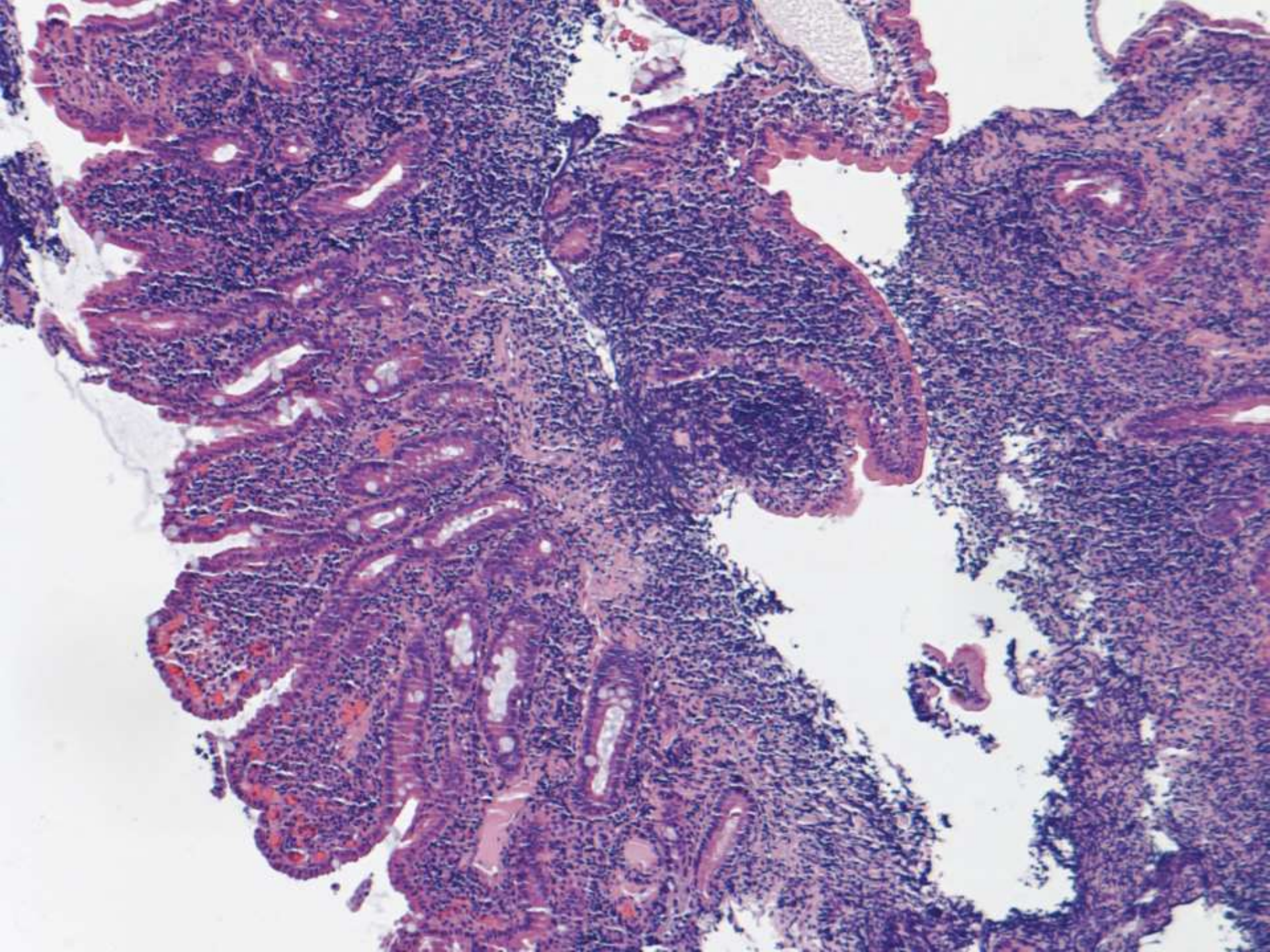
SB 6258

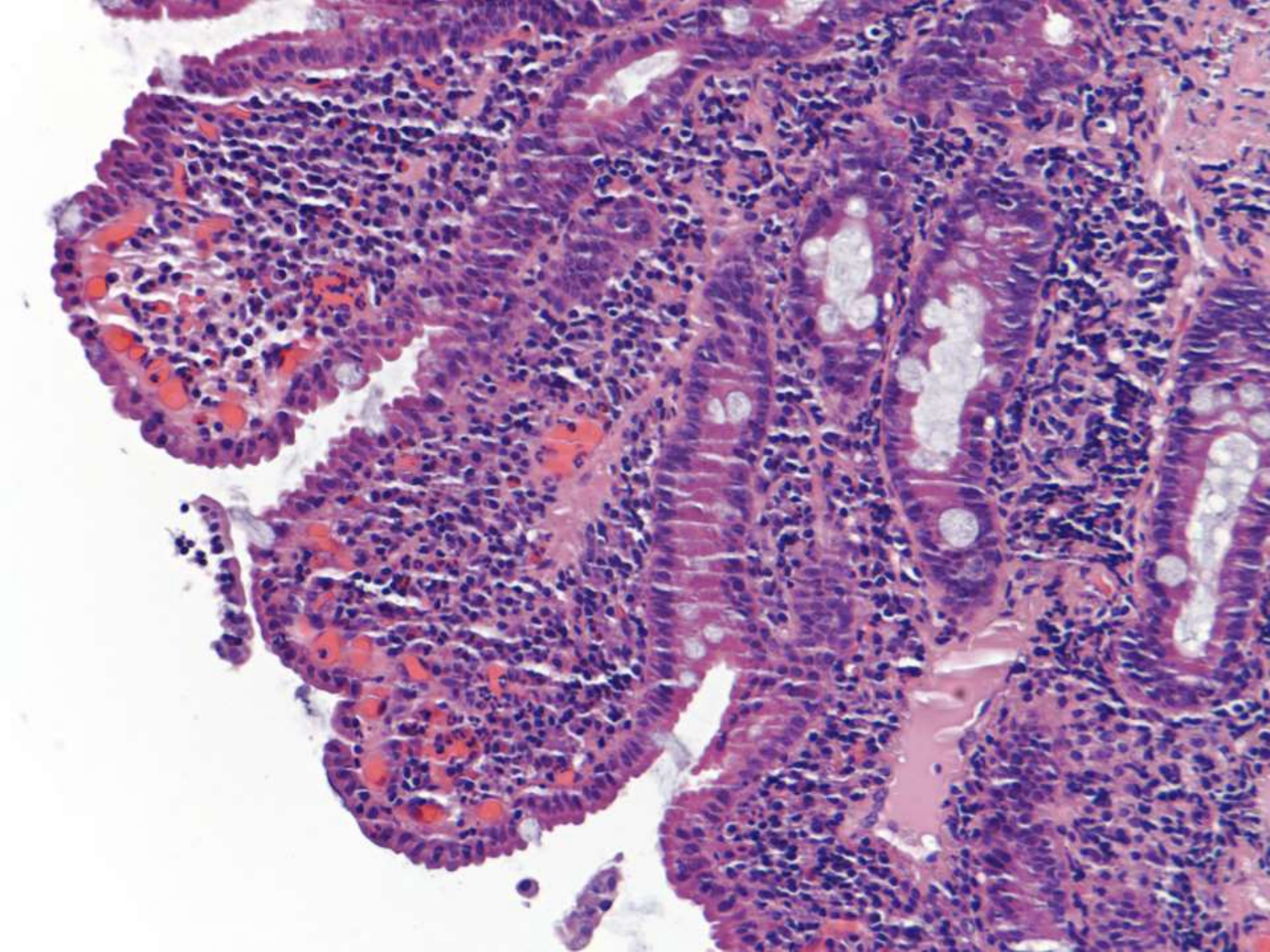
Sebastian Fernandez-Pol/Yaso Natkunam; Stanford

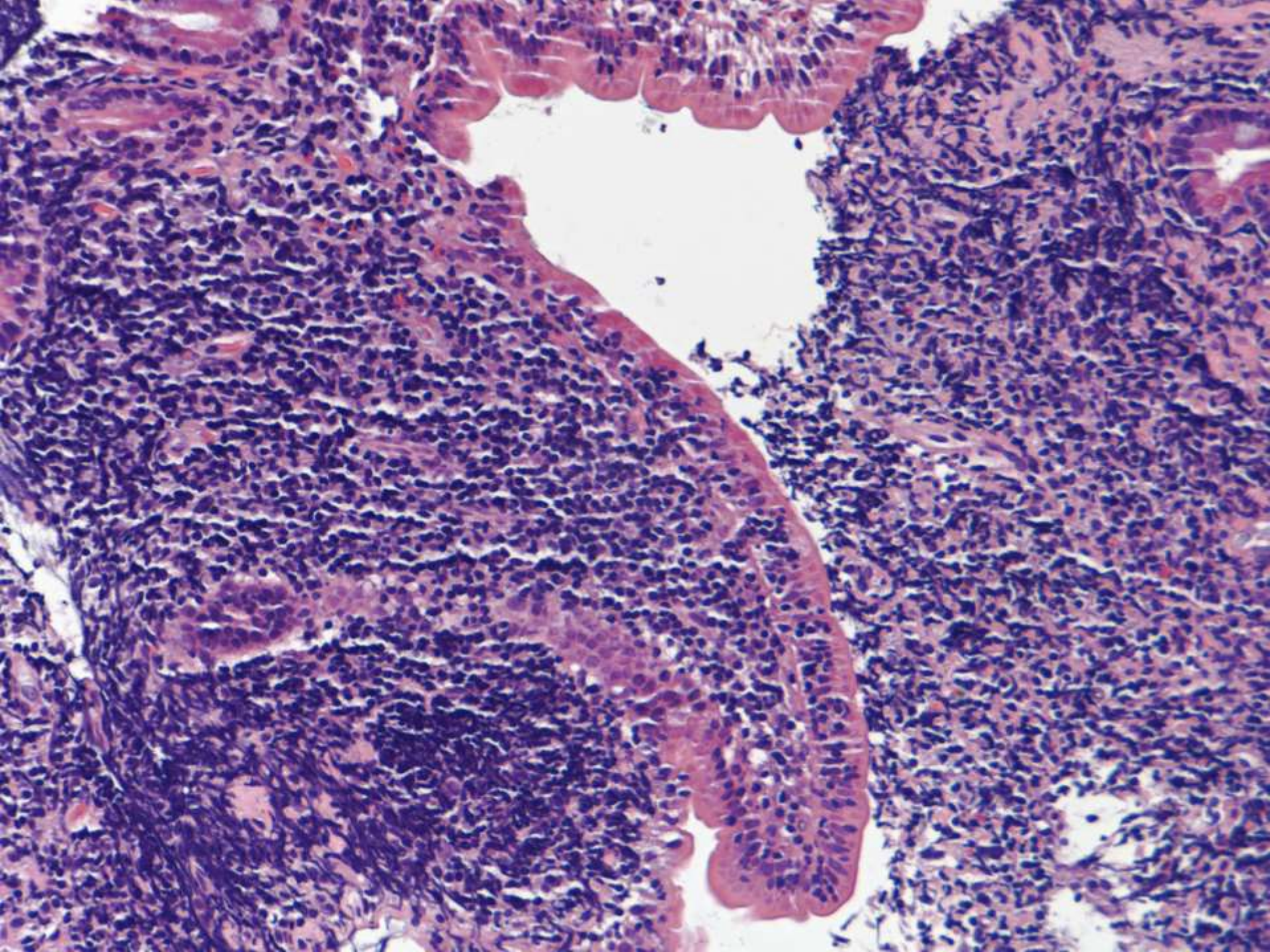
50-year-old female presenting with weight loss. Upper endoscopy is significant for loss of normal villous appearance of the mucosa. She is being followed closely because a previous duodenal bulb biopsy showed an atypical lymphoid infiltrate and clonal TCR-beta and gamma rearrangements. She has a history of abdominal symptoms since 2002 including gas, diarrhea, decreased appetite, and vomiting.

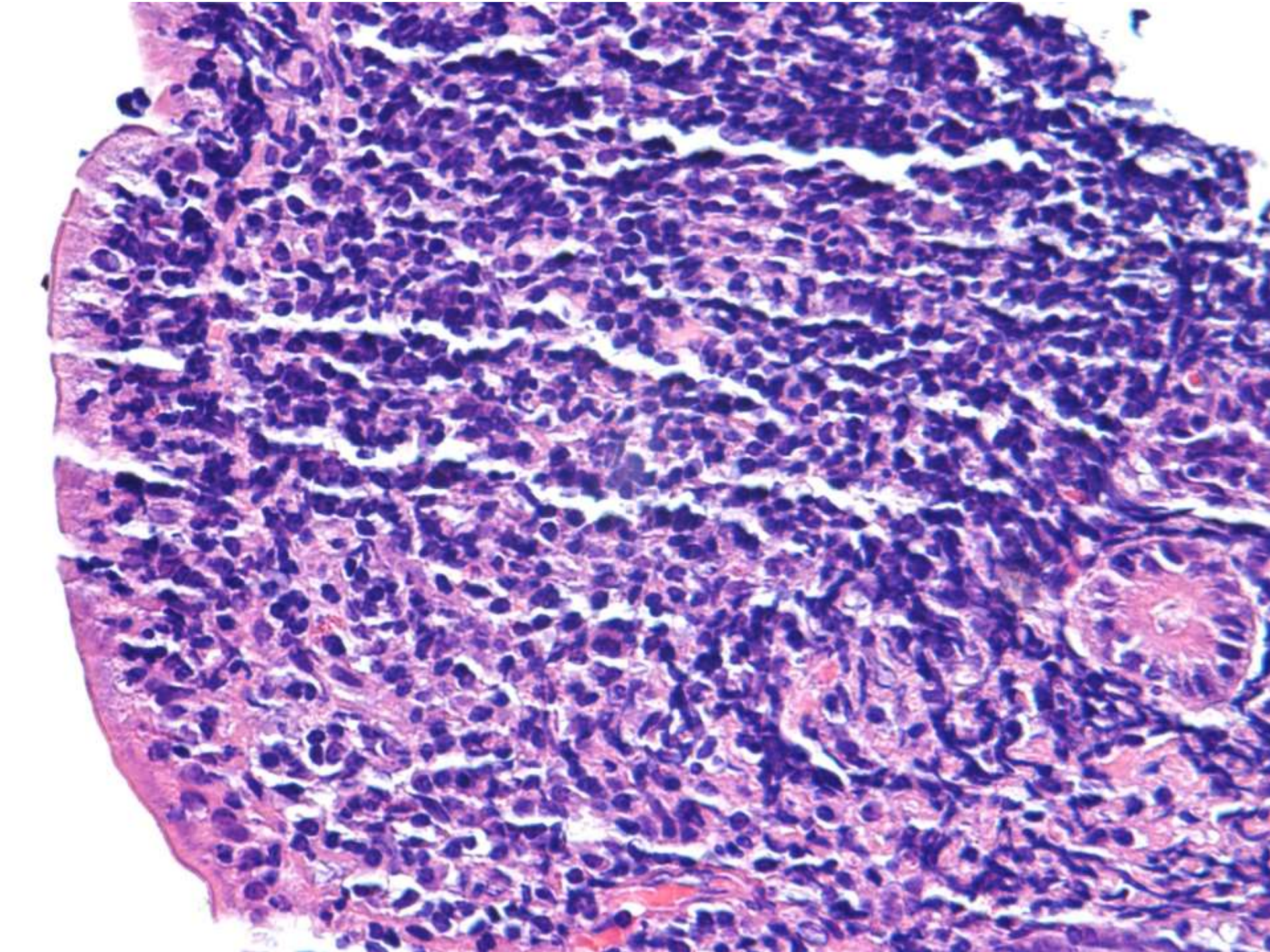


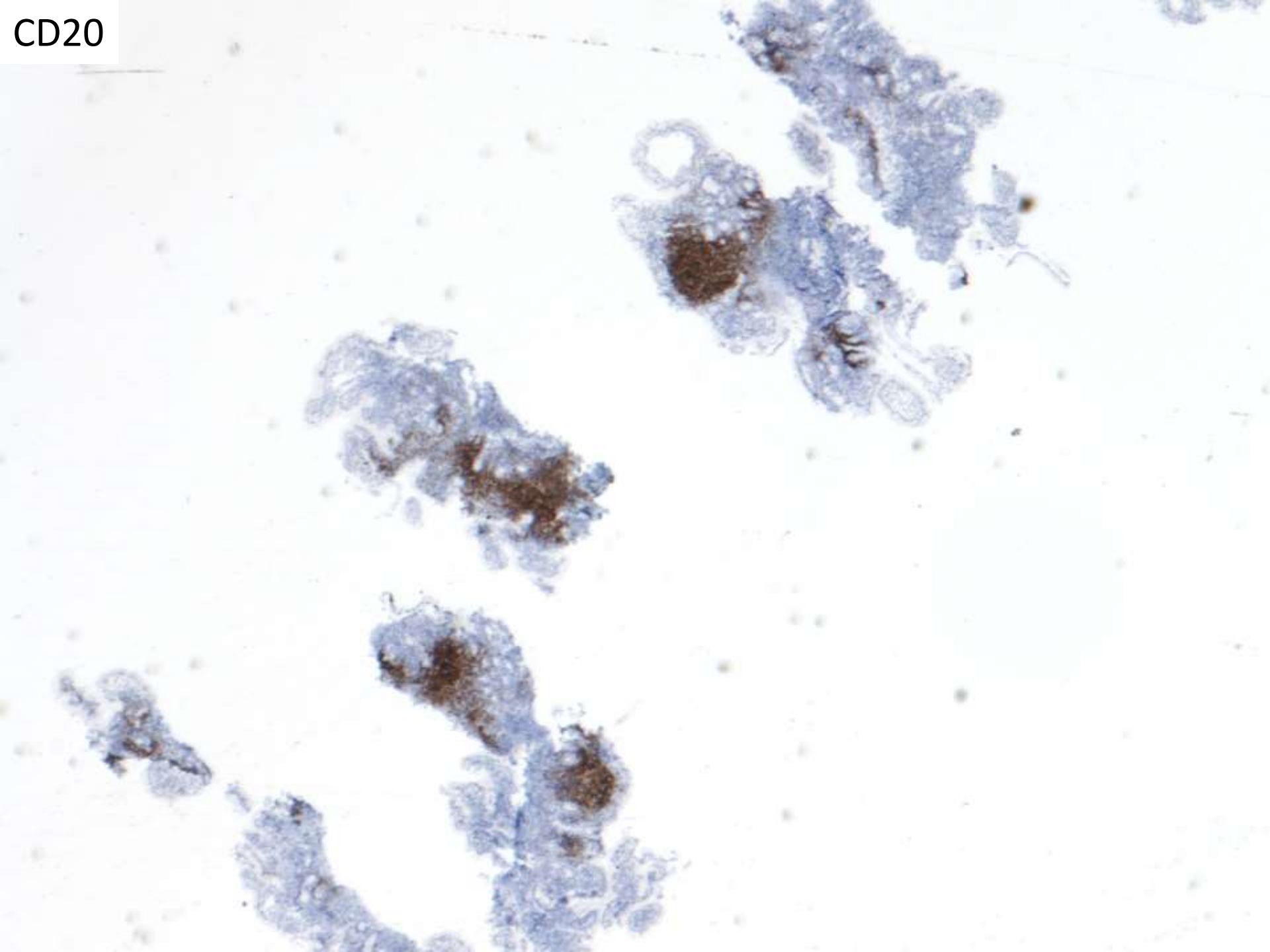




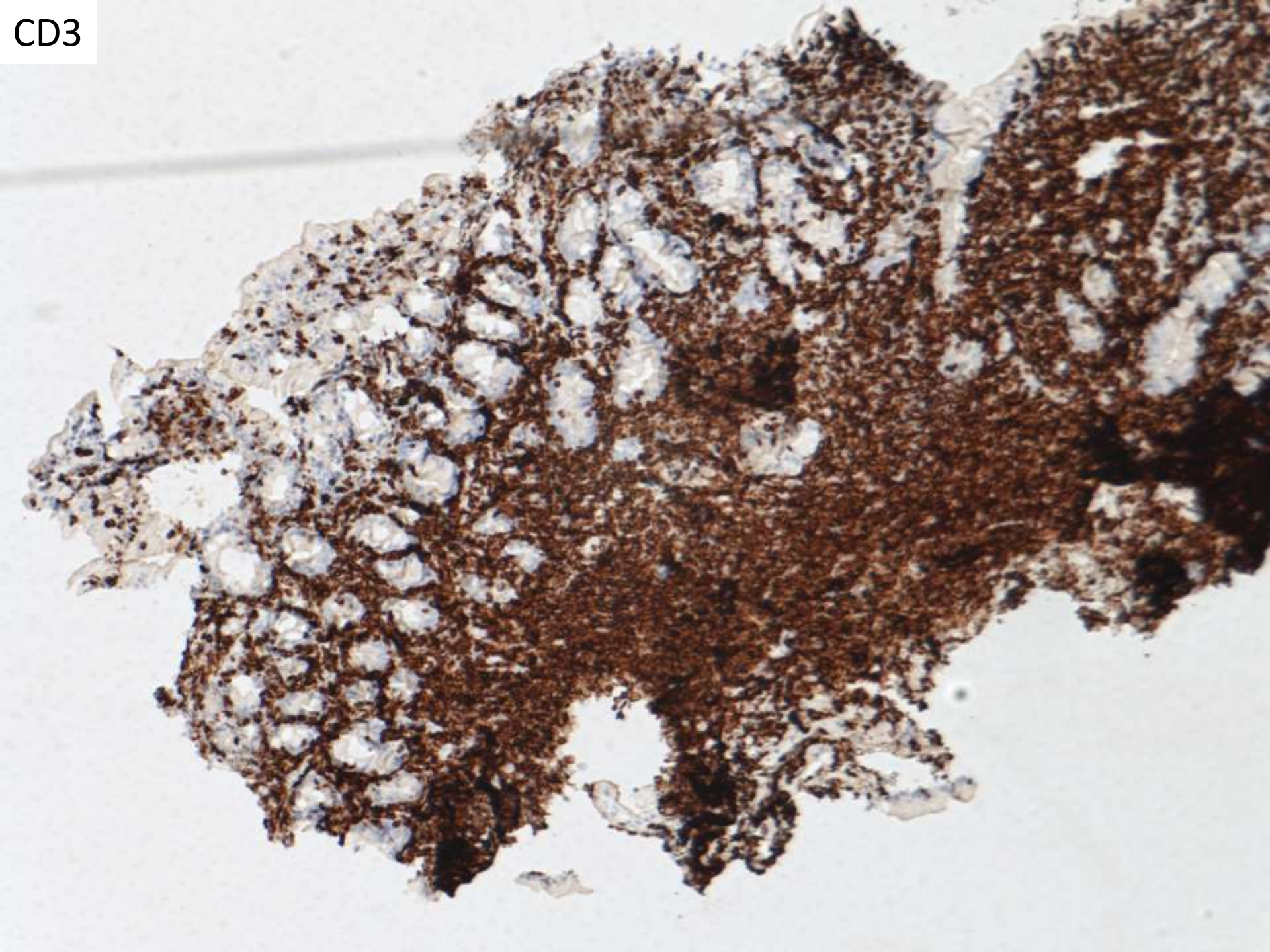




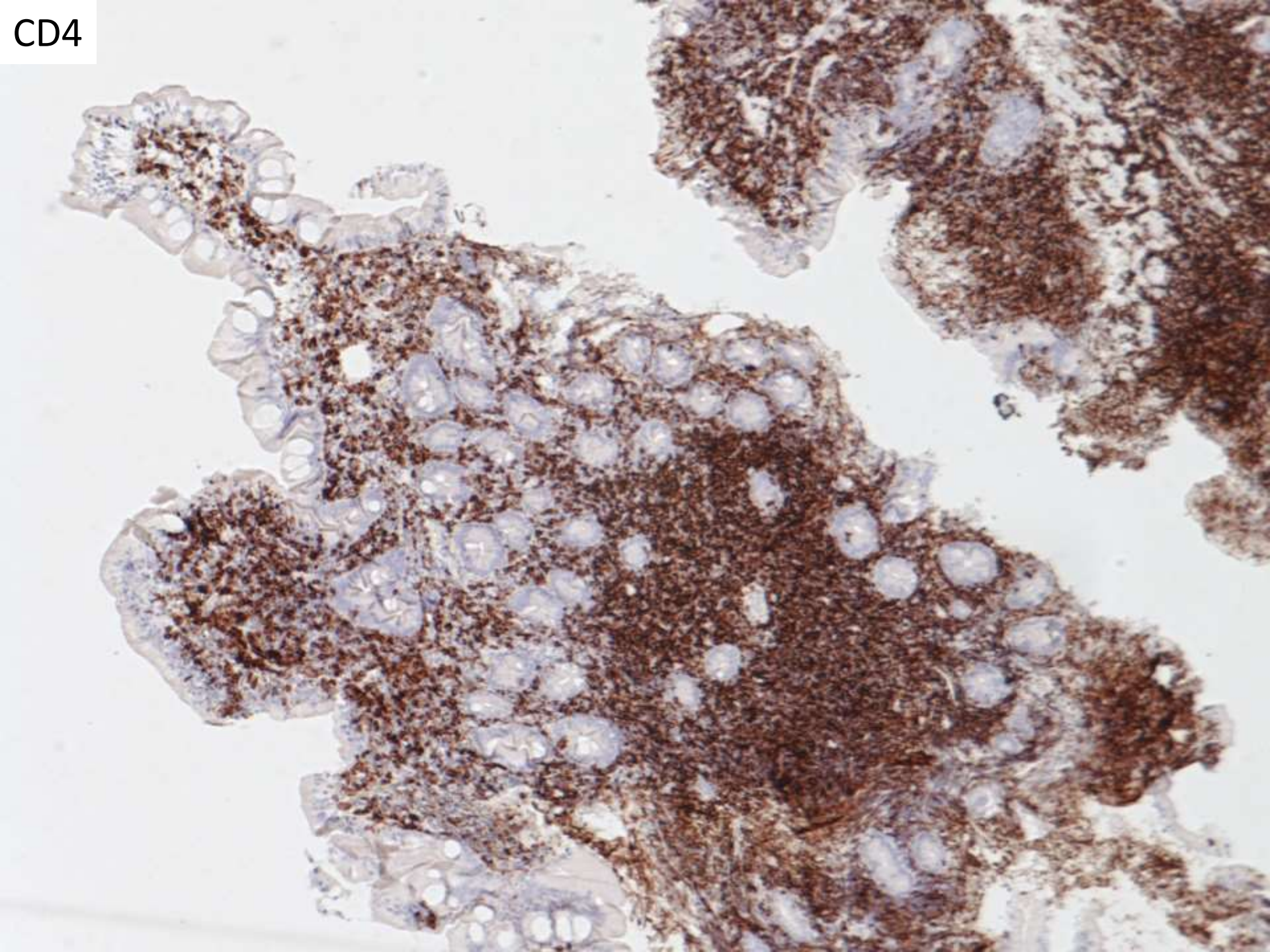


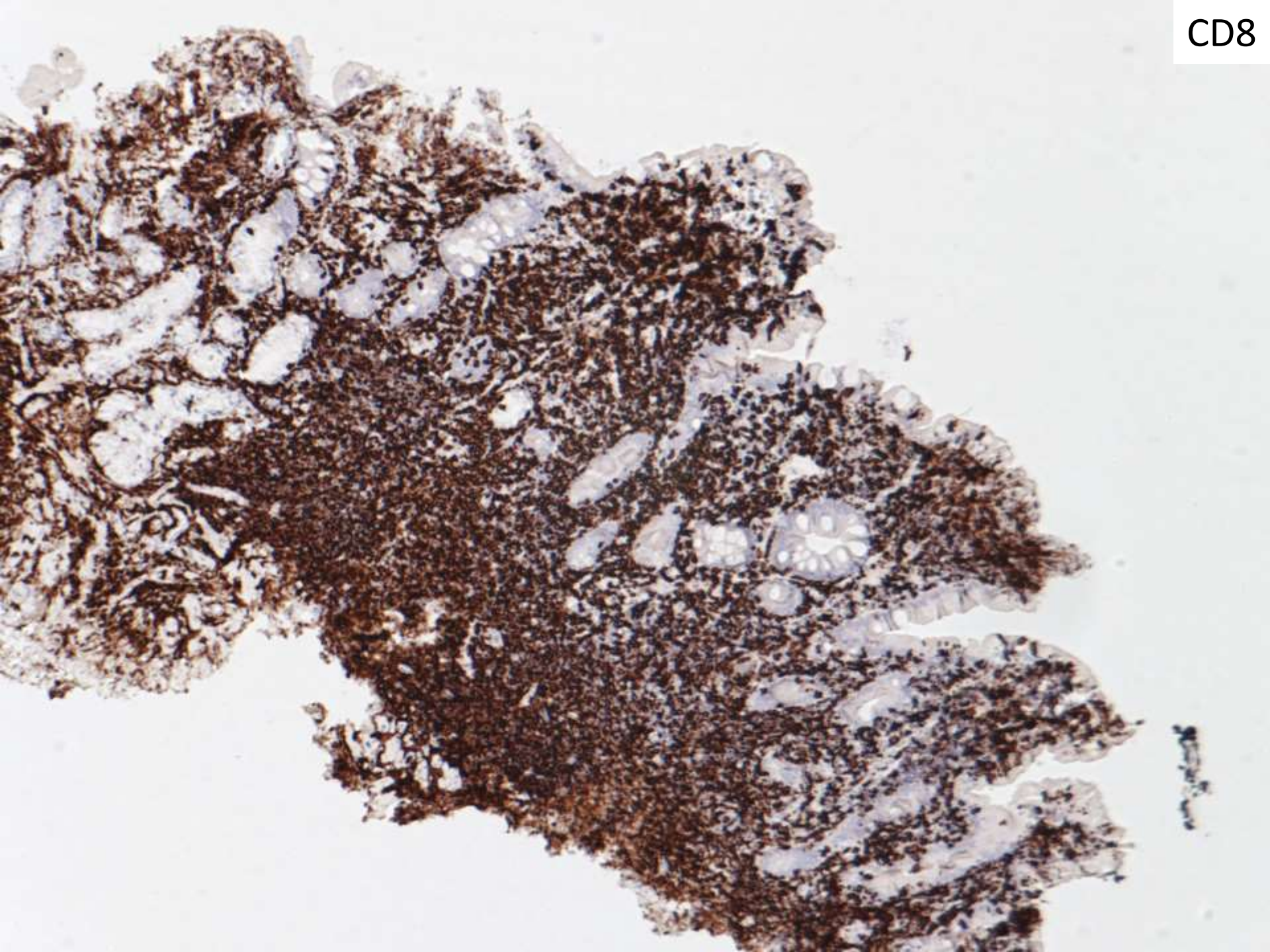

CD20

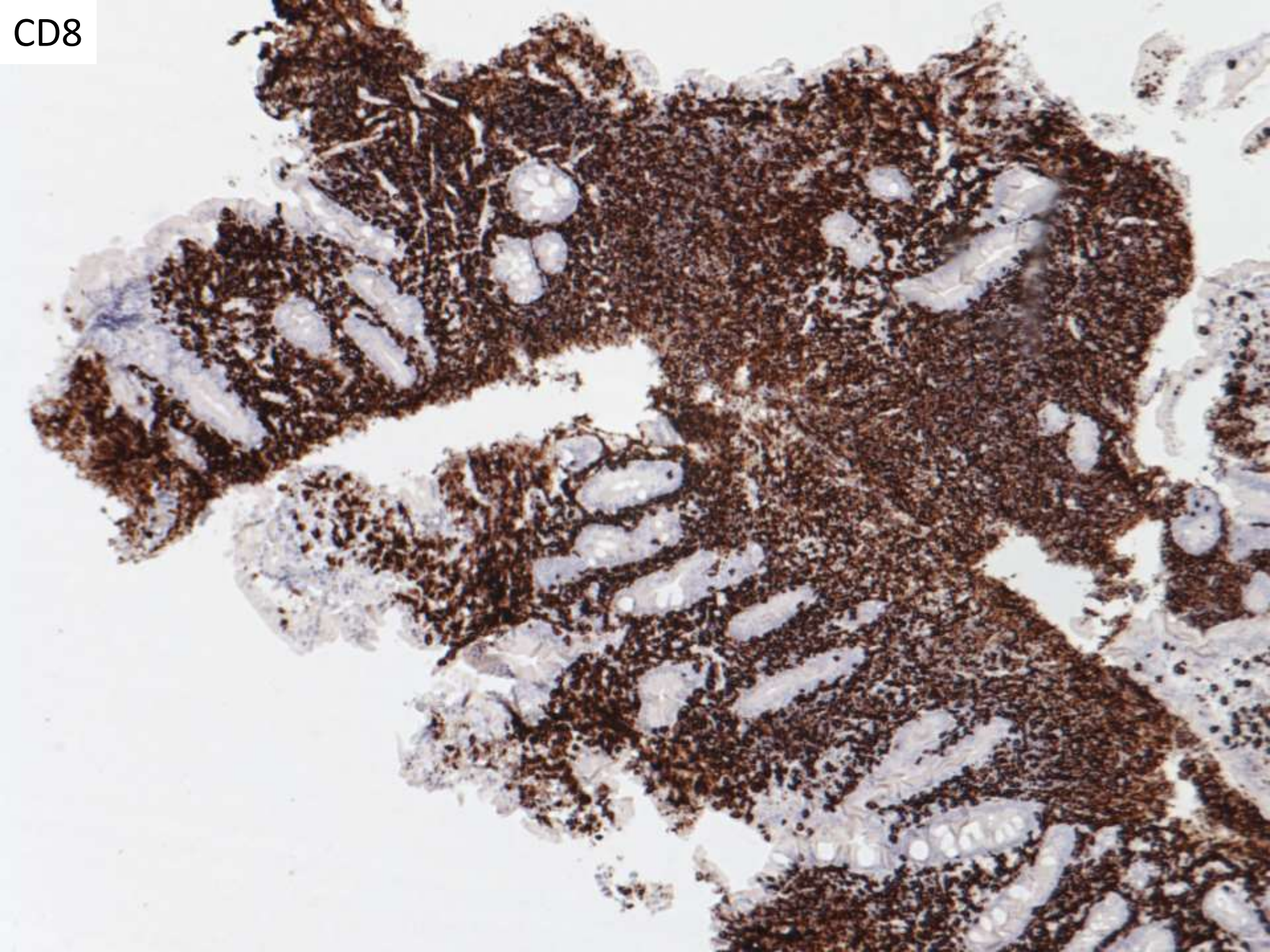

CD3

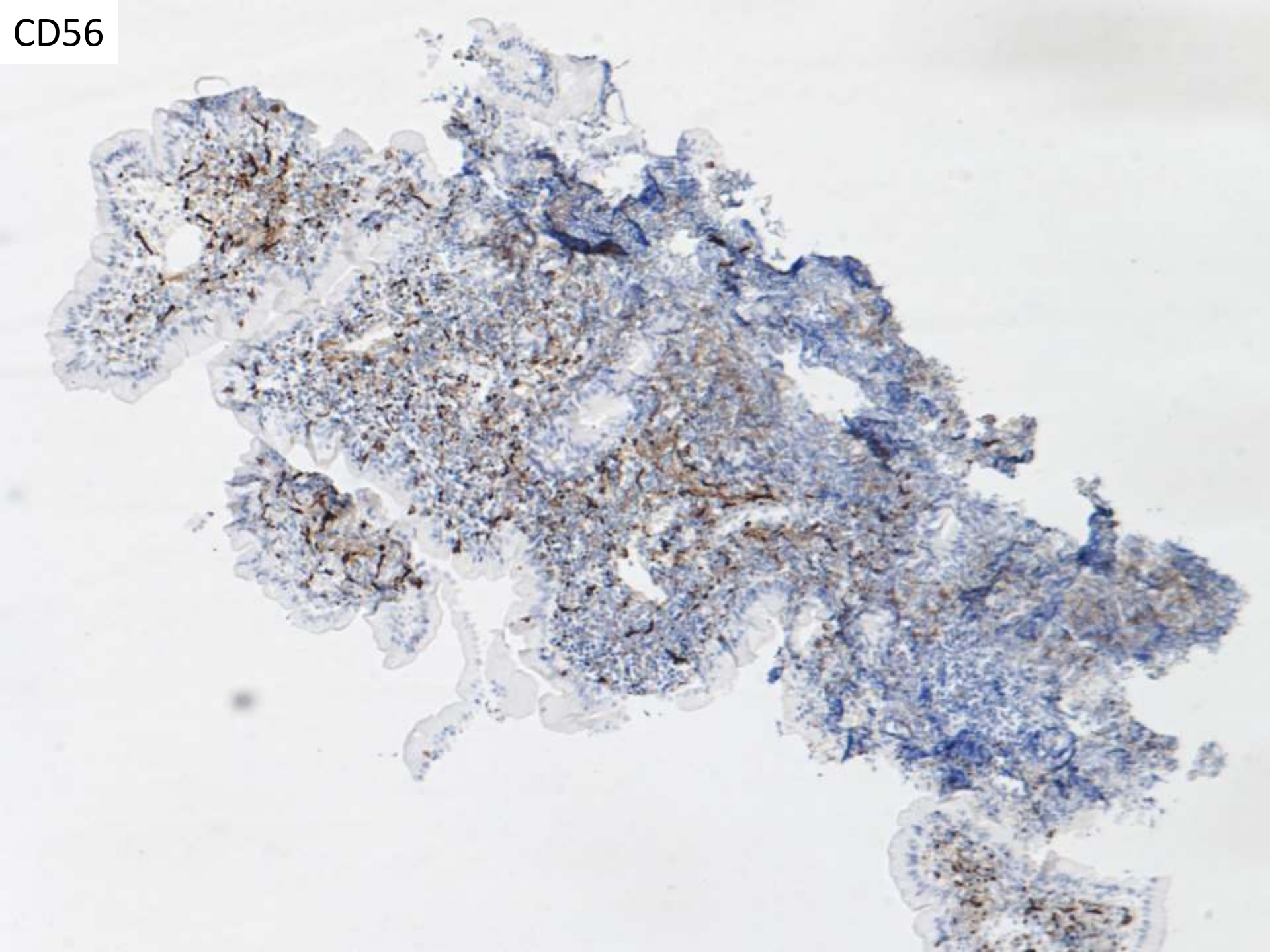

CD3

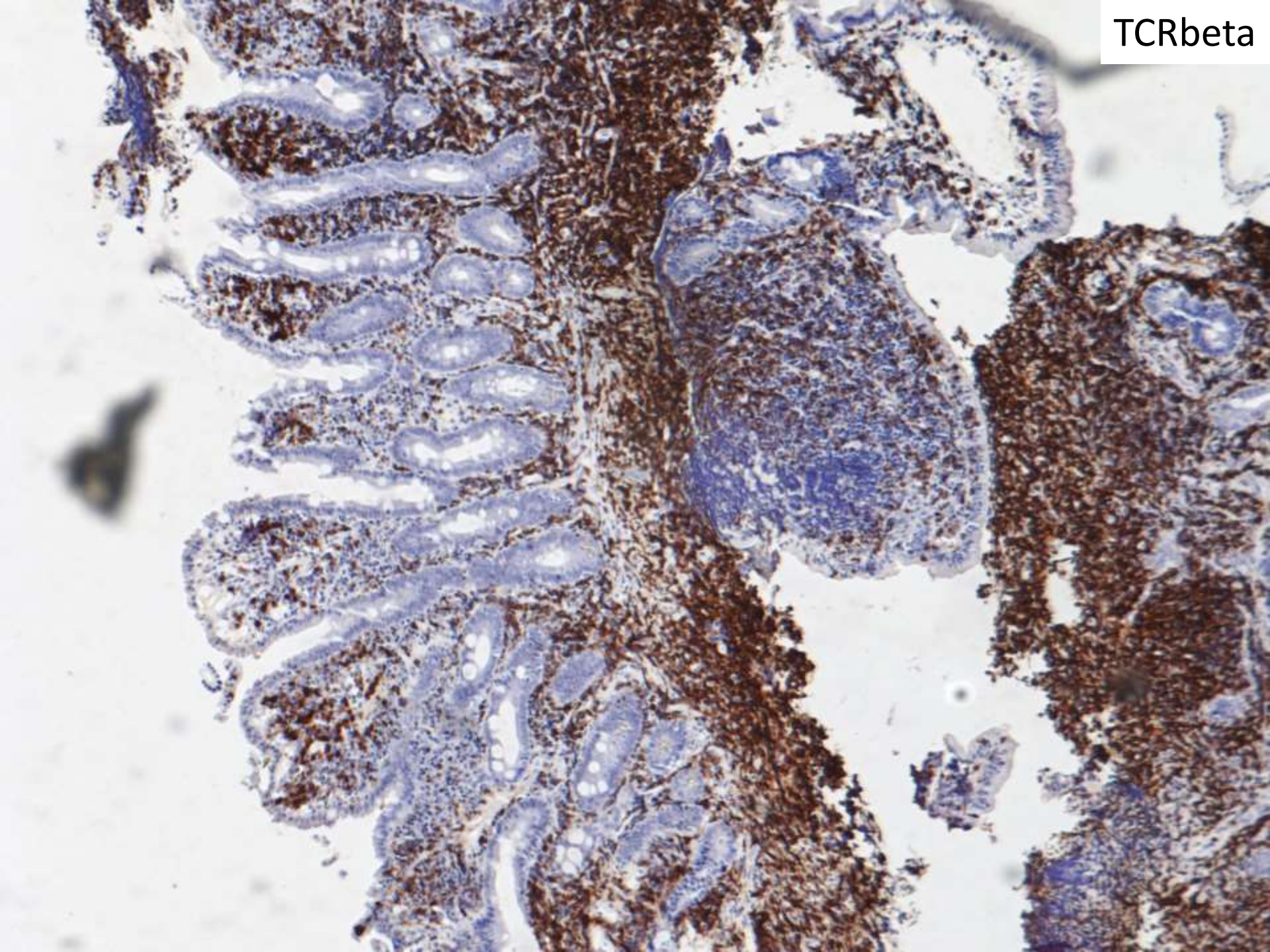

CD3

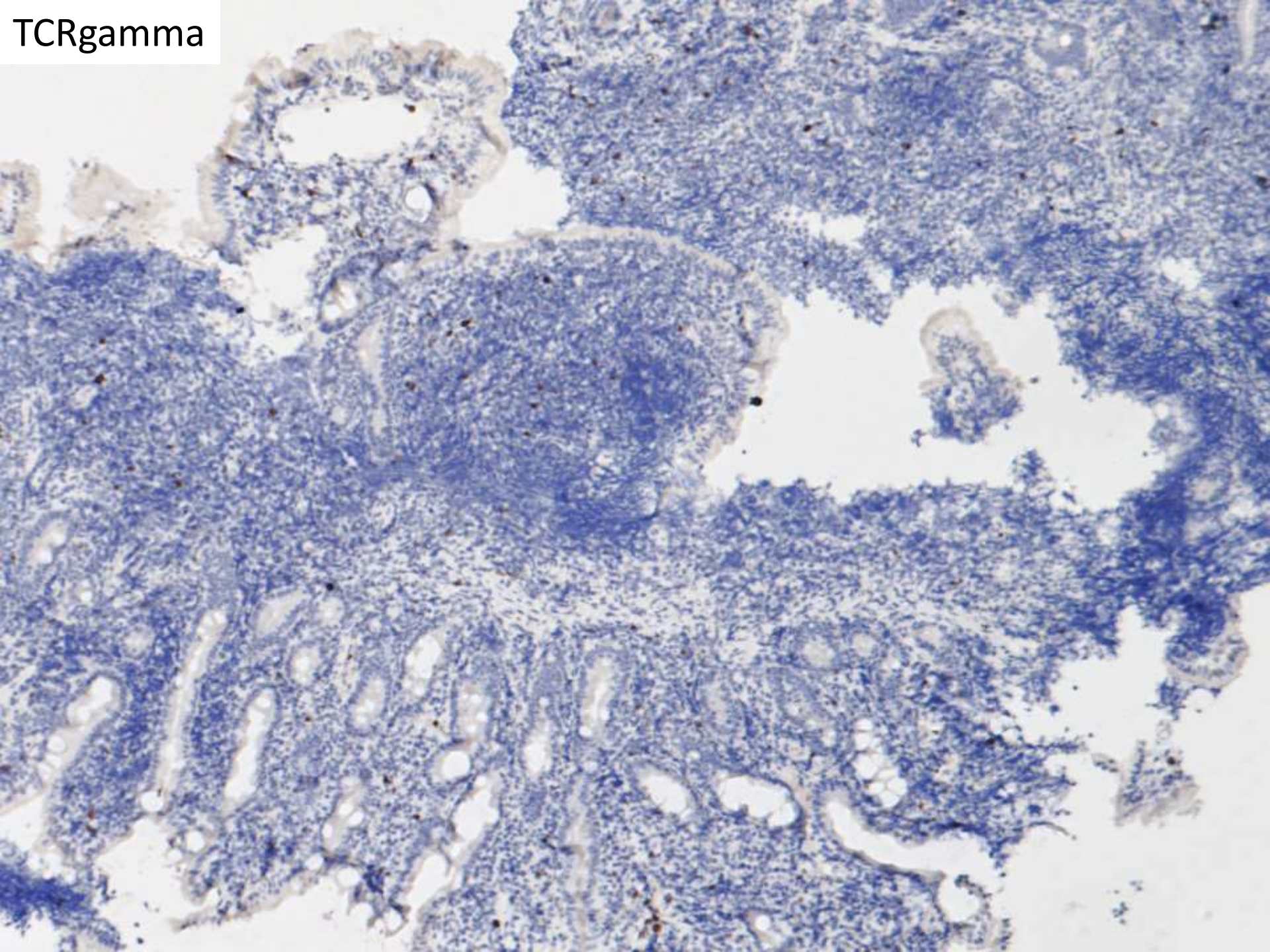

CD4


CD8


CD8


CD56


TCRbeta


TCRgamma

Additional stains performed

- CD21 highlights few scattered follicular dendritic cell networks in the B-cells regions.
- CD7 highlights intraepithelial and lamina propria T-cells.
- CD5 may be lost or dim in a subset of the T-cells.
- TIA-1 and granzyme are positive in a subset of the intraepithelial and lamina propria T-cells.
- Perforin highlights few cells, both in the epithelium and lamina propria.
- Ki-67 highlights a minor subset of the T-cells.

Case summary

- Prominent CD3+, CD56- infiltrate with a lot of CD8 and CD4
- Non-destructive

- Differential diagnosis:
  - **Indolent T-cell lymphoproliferative disorder of the GI tract**
  - T-cell lymphoma (EATL, MEITL, ALCL, NOS)
  - Refractory celiac disease

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

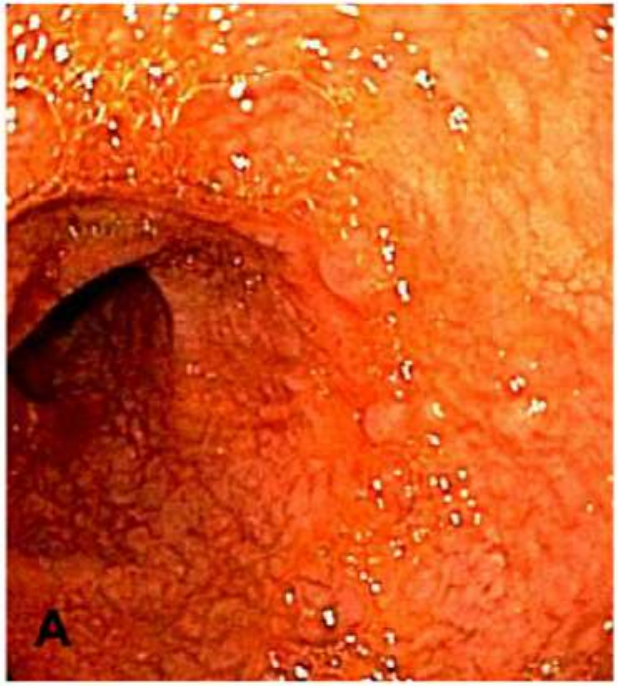
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
* *Indolent T-cell lymphoproliferative disorder of the GI tract** *
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Provisional entities are listed in italics.
*Changes from the 2008 classification.

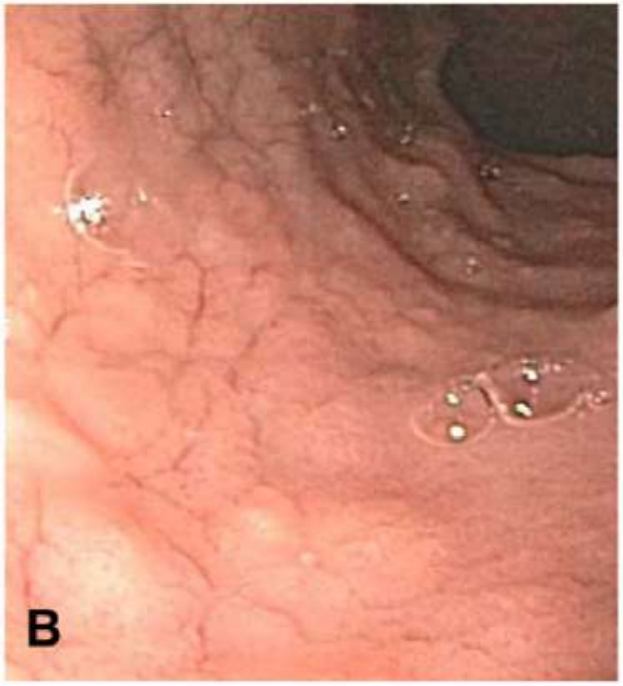
Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract

Endoscopic appearance

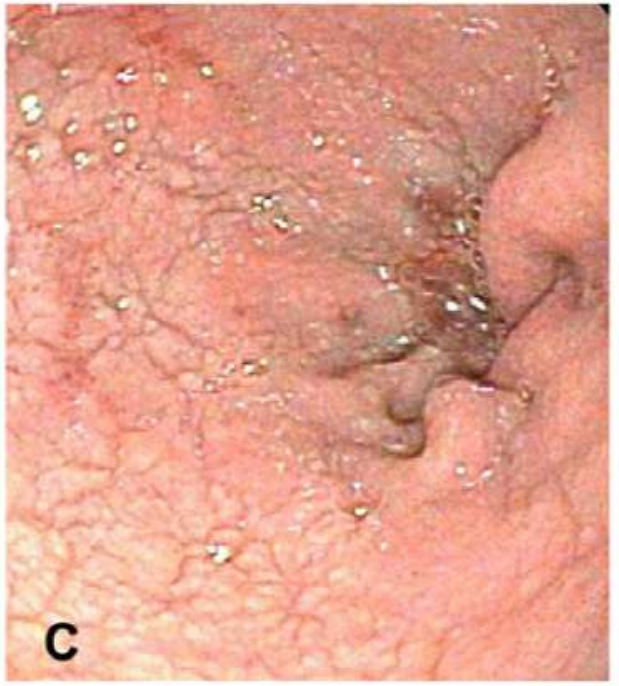
Diffuse mucosal nodularity



Flattening of mucosal folds, vague nodularity and fissures



Cobblestone appearance with extensive scalloping and fissures; erythema and erosions are also present



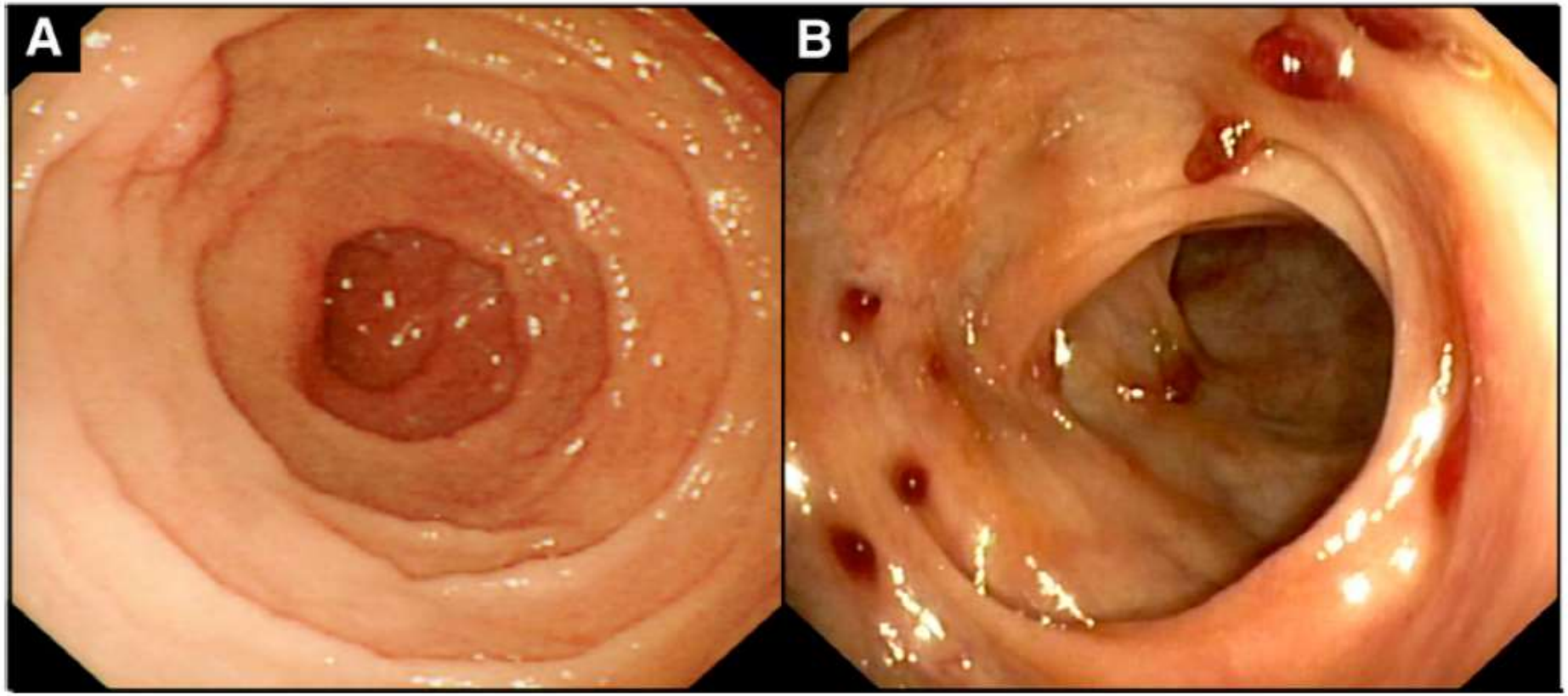
Matnani, et al, 2017

Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract

Endoscopic appearance

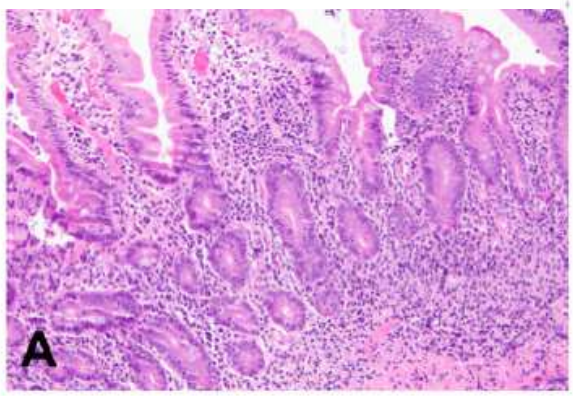
Irregular appearance of duodenal mucosa

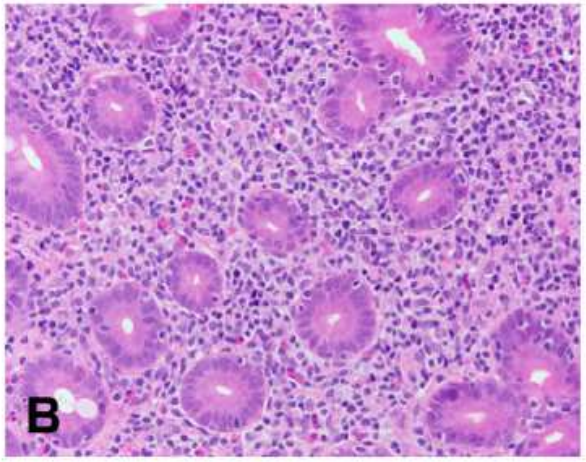
Multiple small polyps with mucosal erythema in the colon

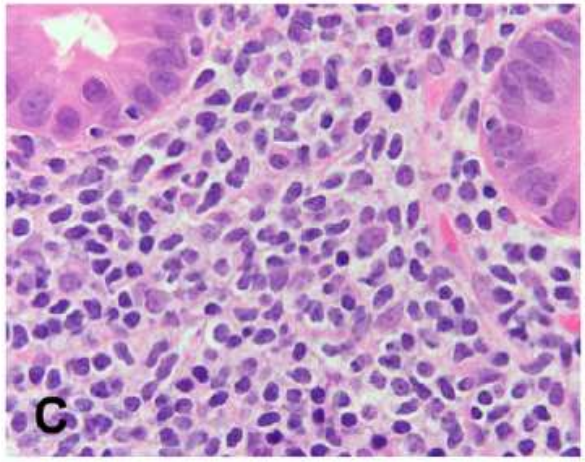


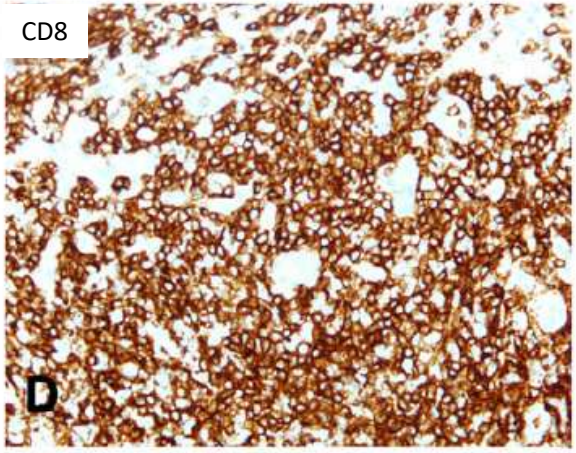
Perry *et al,* 2013

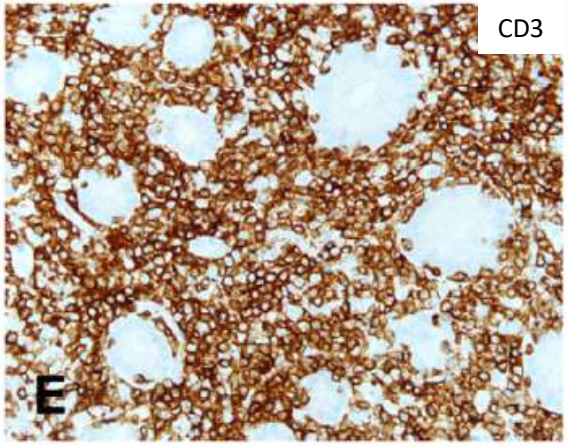
CD8+ T-cell LPD of the GI tract

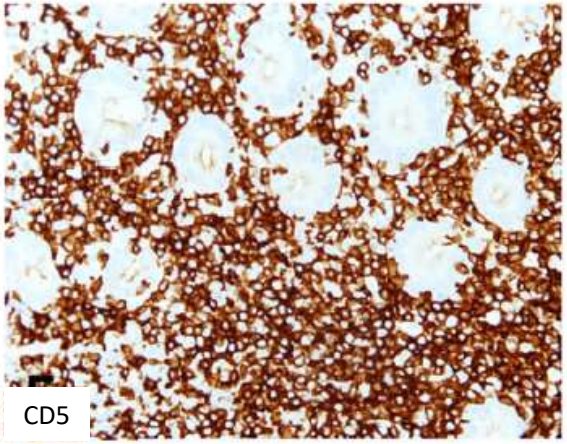


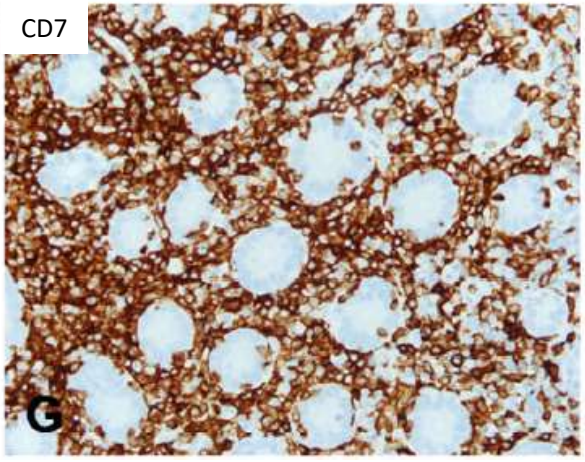


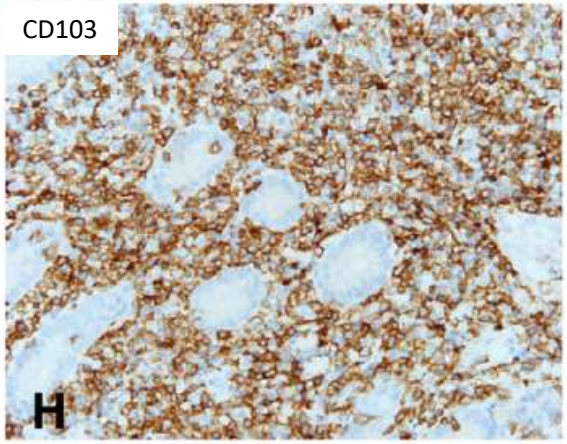


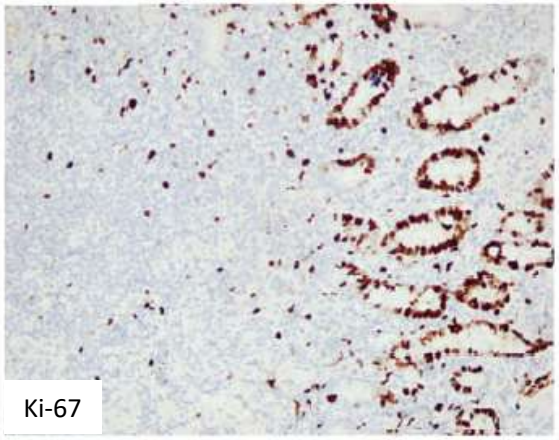






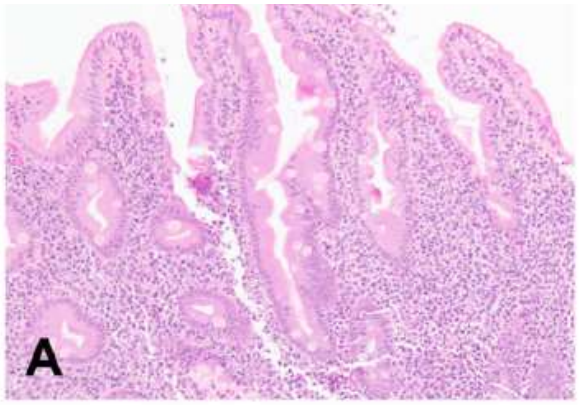


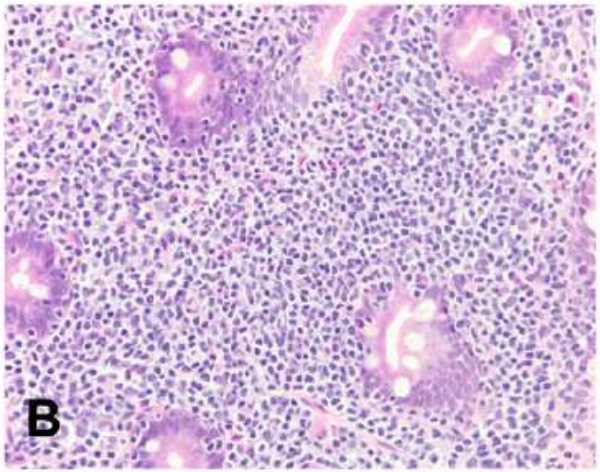


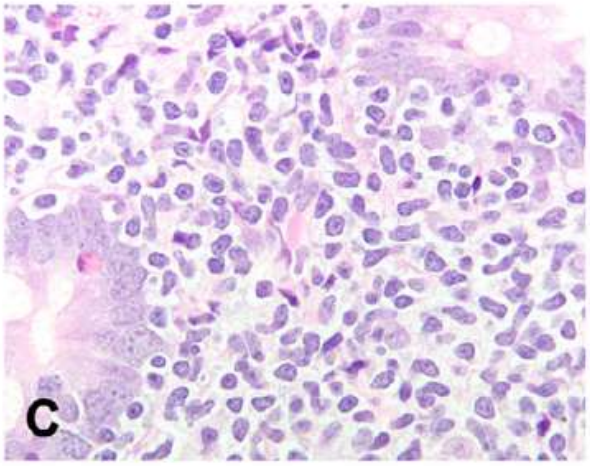


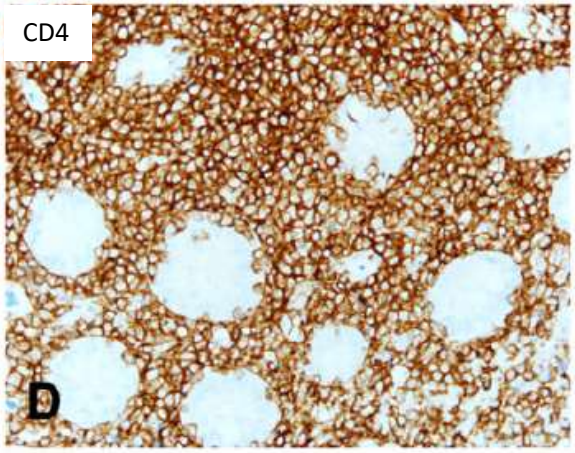
Matnani et al, 2017

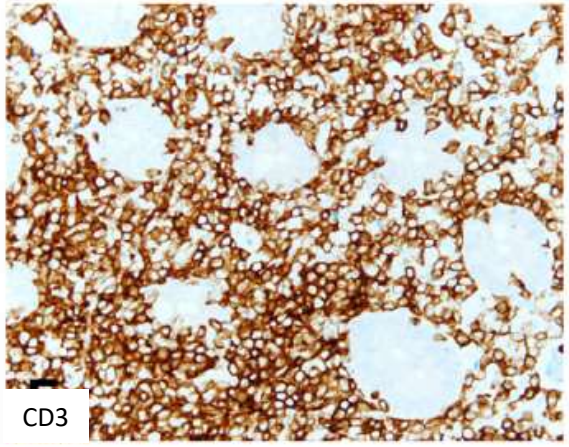
CD4+ T-cell LPD of the GI tract

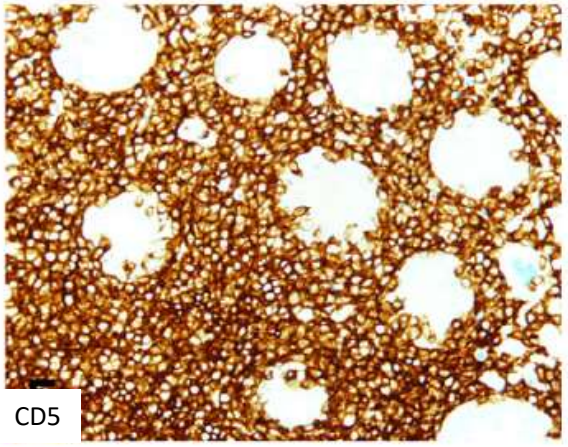


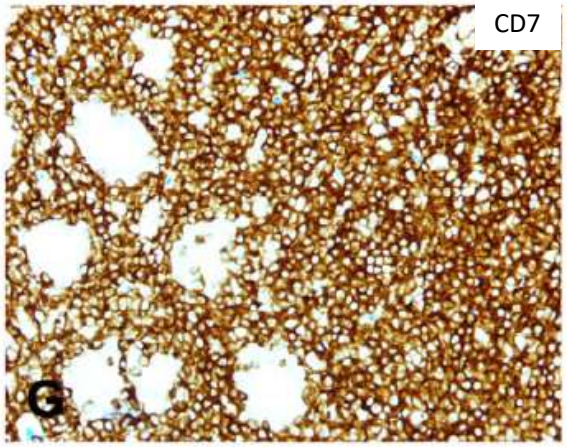


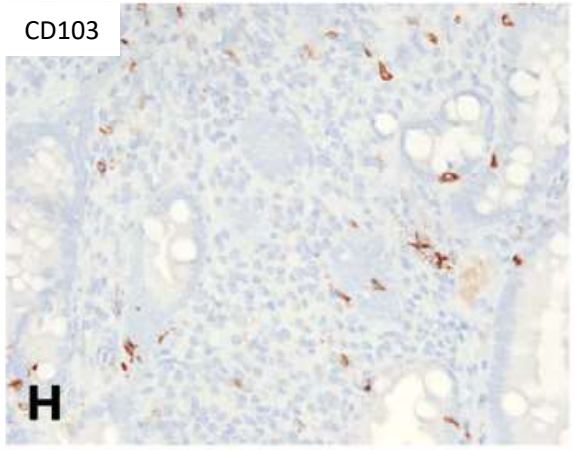


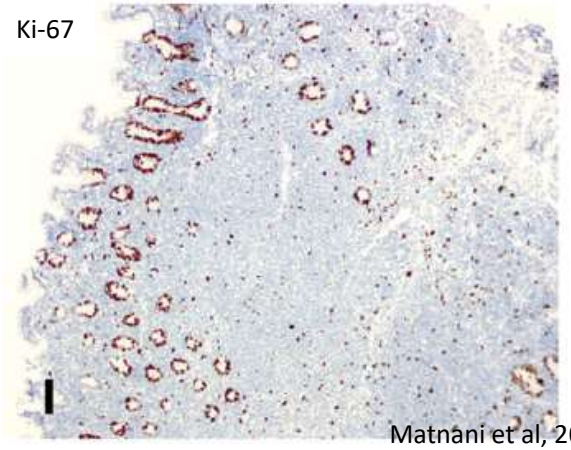




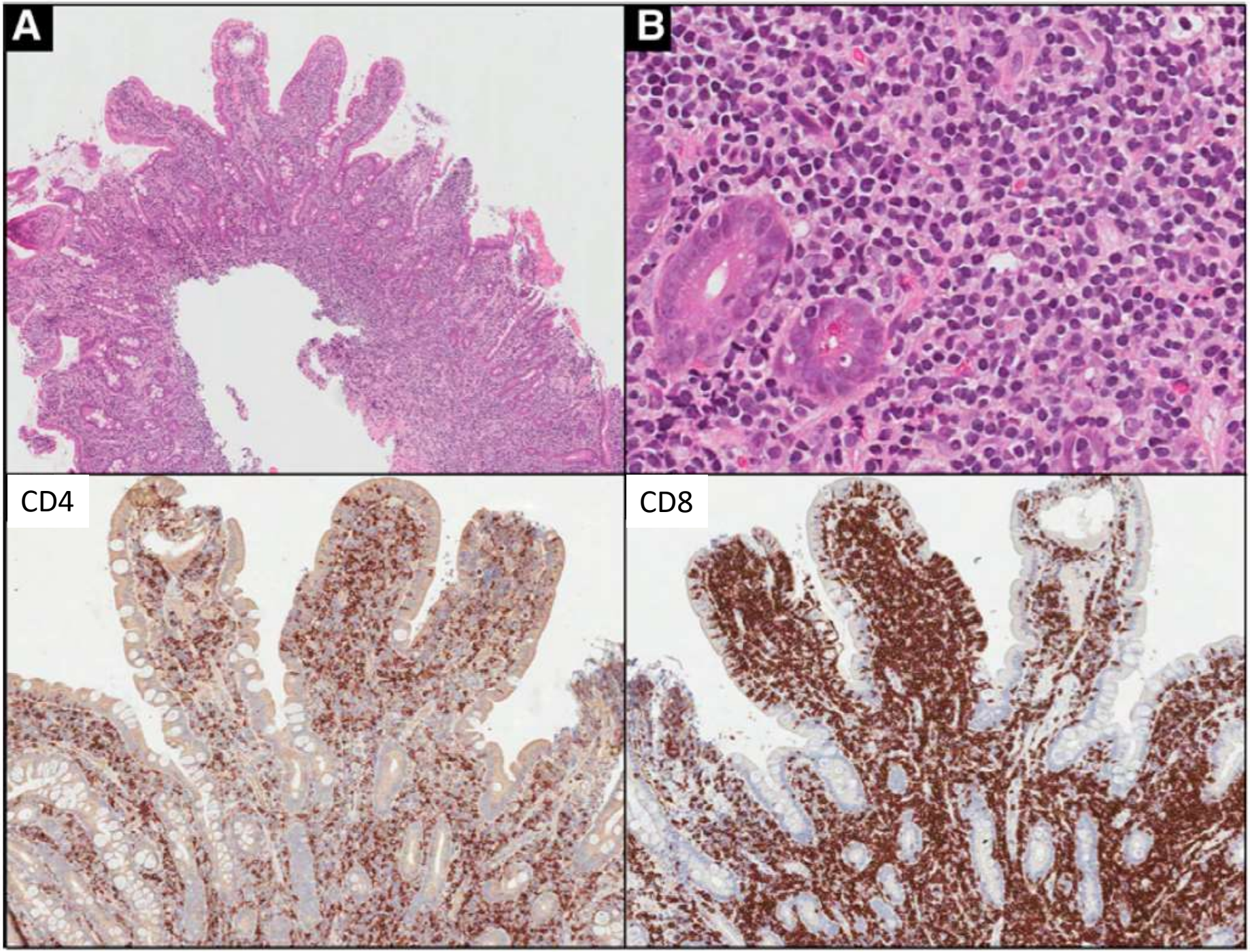








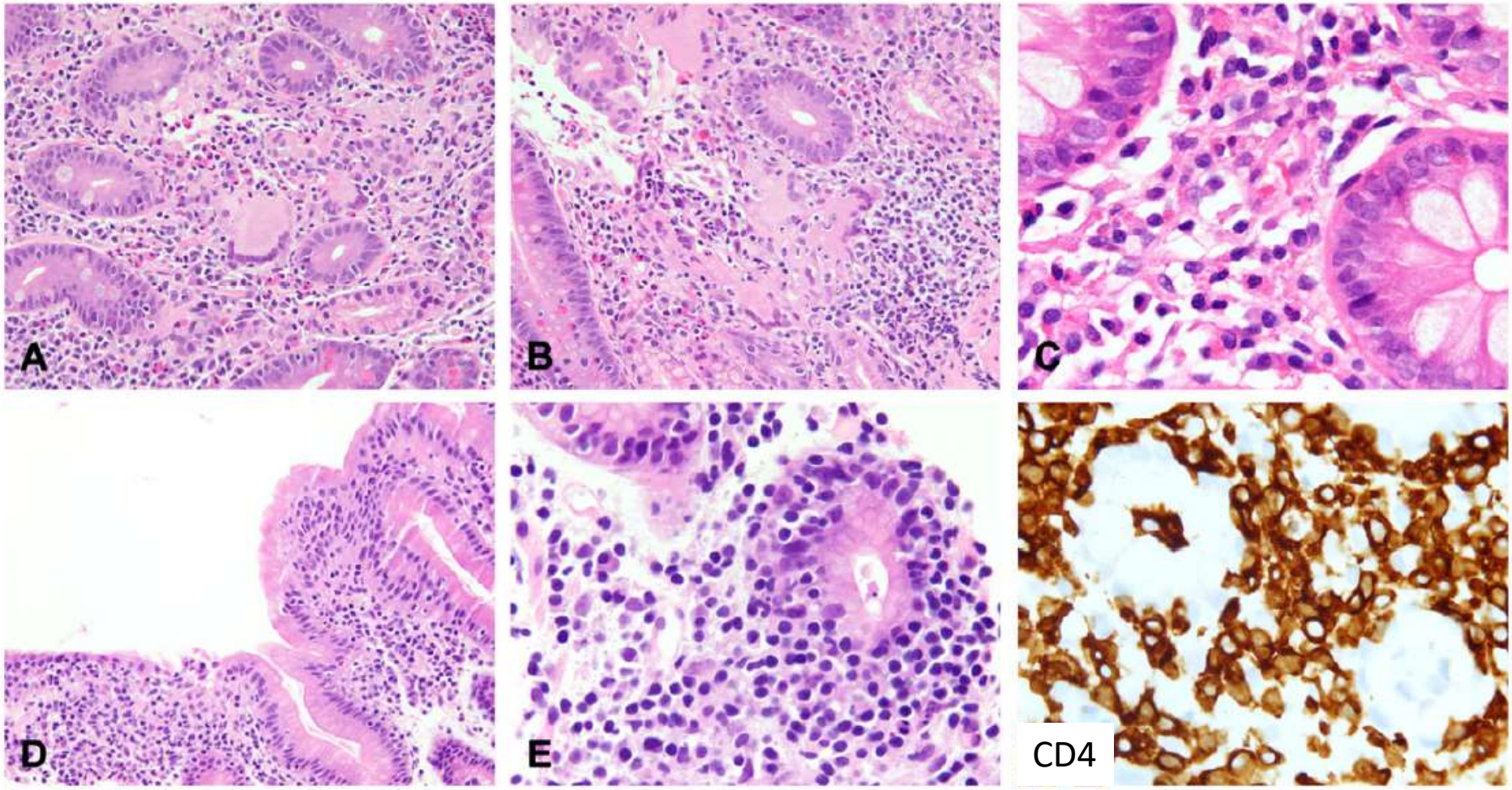
Matnani et al, 2017


A
B
CD4
CD8

Unusual histopathologic features and patterns of colon and stomach infiltration

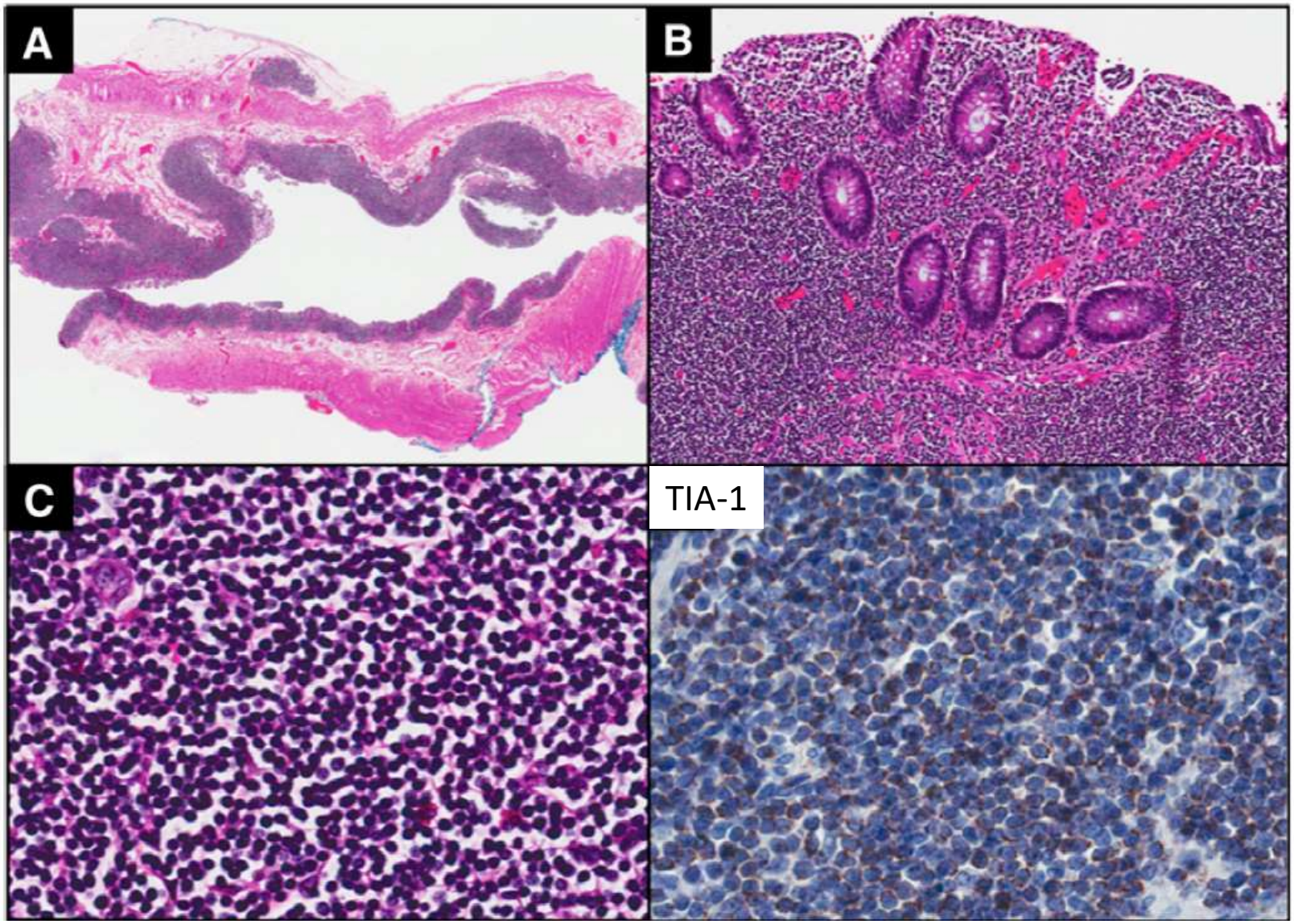
Scattered multinucleated giant cells

Distinct granulomas surrounding damaged crypts



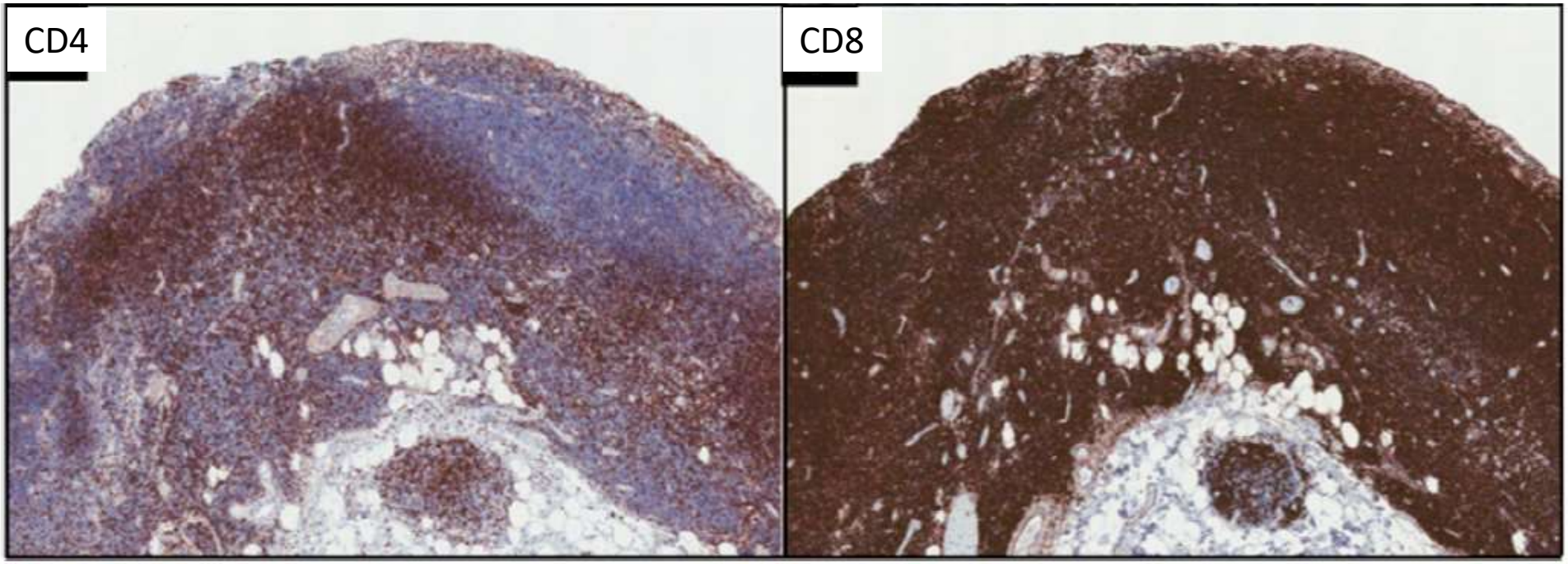
Focal infiltration of the epithelium

Indolent T-LPD of the ileum
Patient alive at 168 months



Perry *et al,* 2013

Indolent T-LPD of the ileum
Patient alive at 168 months



Perry *et al,* 2013

Immunohistochemistry and clonality

Table 2. Immunohistochemical and molecular findings in 10 cases of indolent T-LPD of the GI tract

Case	CD3	CD4/CD8	CD2	CD5	CD7	CD30	CD56	TIA1	GRZB	TCR-BF1	TCR-G	Ki67, %	EBER	TCR-PCR
1	+	−/+	+	+	+	−	−	+	−	+	NA	5-10	−	Clonal
2	+	−/+	+	+	+	−	−	+	−	NA	NA	5-10	−	Clonal
3	+	−/+	NA	+	NA	NA	−	+	−	+	−	NA	−	Clonal
4	+	−/+	+	+	+	−	−	+	NA	+	−	5	−	Clonal
5	+	−/−	+	−	+	−	−	−	NA	+	−	NA	−	Clonal
6	+	+/−	+	−	−	−	−	−	−	+	−	NA	NA	Clonal
7	+	−/+	NA	+	−	NA	−	+	−	NA	NA	5	−	Clonal
8	+	−/+	NA	+	−	−	−	+	−	+	−	5	−	Clonal
9	+	−/+	+	+	+	−	−	NA	−	NA	NA	5	NA	Clonal
10	+	−/+	+	+	+	−	−	+	+	+	NA	5	−	Clonal

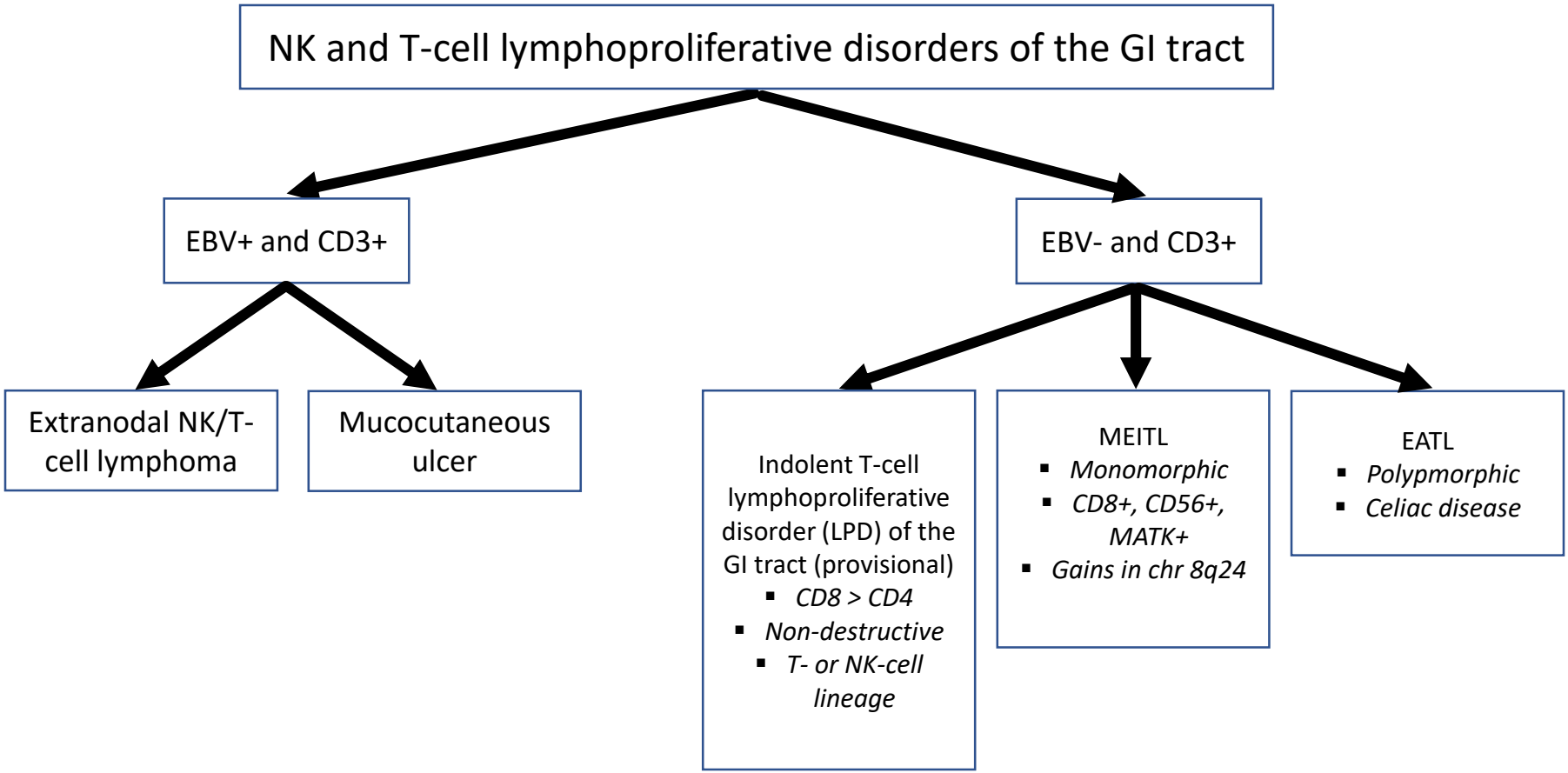
EBER, Epstein-Barr virus-encoded RNA; GRZB, granzyme B; NA, not available; TCR-BF1, T-cell receptor β F1; TCR-G, T-cell receptor γ; TCR-PCR, T-cell receptor-γ chain gene rearrangement by polymerase chain reaction; $^{+}$, positive; $^{-}$, negative.

No evidence of STAT3 SH2 domain mutation or activation

Indolent T-cell lymphoproliferative disease of the gastrointestinal tract

Anamarija M. Perry,[1] Roger A. Warnke,[2] Qinglong Hu,[3] Philippe Gaulard,[4] Christiane Copie-Bergman,[4] Serhan Alkan,[5] Huan-You Wang,[6] Jason X. Cheng,[7] Chris M. Bacon,[8] Jan Delabie,[9] Erik Ranheim,[10] Can Kucuk,[11] XiaoZhou Hu,[11] Dennis D. Weisenburger,[12] Elaine S. Jaffe,[13] and Wing C. Chan[11]

- 10 cases of GI involvement by indolent T-cell LPD
- 9-175 months follow up (median 38 months)
  - 6 patients received chemotherapy because of an initial diagnosis of peripheral T-cell lymphoma, with little or no response
  - 4 were followed without therapy
  - 9 patients were alive with persistent disease and 1 was free of disease


NK and T-cell lymphoproliferative disorders of the GI tract
EBV+ and CD3+
EBV- and CD3+
Extranodal NK/T-cell lymphoma
Mucocutaneous ulcer
Indolent T-cell lymphoproliferative disorder (LPD) of the GI tract (provisional)
CD8 > CD4
Non-destructive
T- or NK-cell lineage
MEITL
Monomorphic
CD8+, CD56+, MATK+
Gains in chr 8q24
EATL
Polypmorphic
Celiac disease

Indolent T-cell lymphoproliferative disorder of the GI tract

- Negative serologies
- Villus architecture normal
- Less frequent intraepithelial lymphocytes
- Clonal TCR rearrangements

Refractory celiac disease

- Anti-TG, anti-endomysial
- Abnormal villi
- Intraepithelial lymphocytes

Type 1

- Normal phenotype, CD3+, CD8+
- Polyclonal TCR

Type 2

- Intraepithelial lymphocytes
- Abnormal CD8-, CD5-
- Can have CD30 (indicates EATL)

Summary

- Indolent T-cell lymphoproliferative disorder of the GI tract
  - Non-destructive expansion of lamina propria
  - Most are CD8+ but can be CD4+ or CD4-/CD8-
  - Positive for clonal TCR gene rearrangements
  - Significant morbidity
  - Not aggressive
  - Does not respond to chemotherapy
  - Rule out more aggressive lymphomas, refractory celiac

References

- Perry AM, Warnke RA, Hu Q, Gaulard P, Copie-Bergman C, Alkan S, *et al.* Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. *Blood* 2013; **122**: 3599–3606.

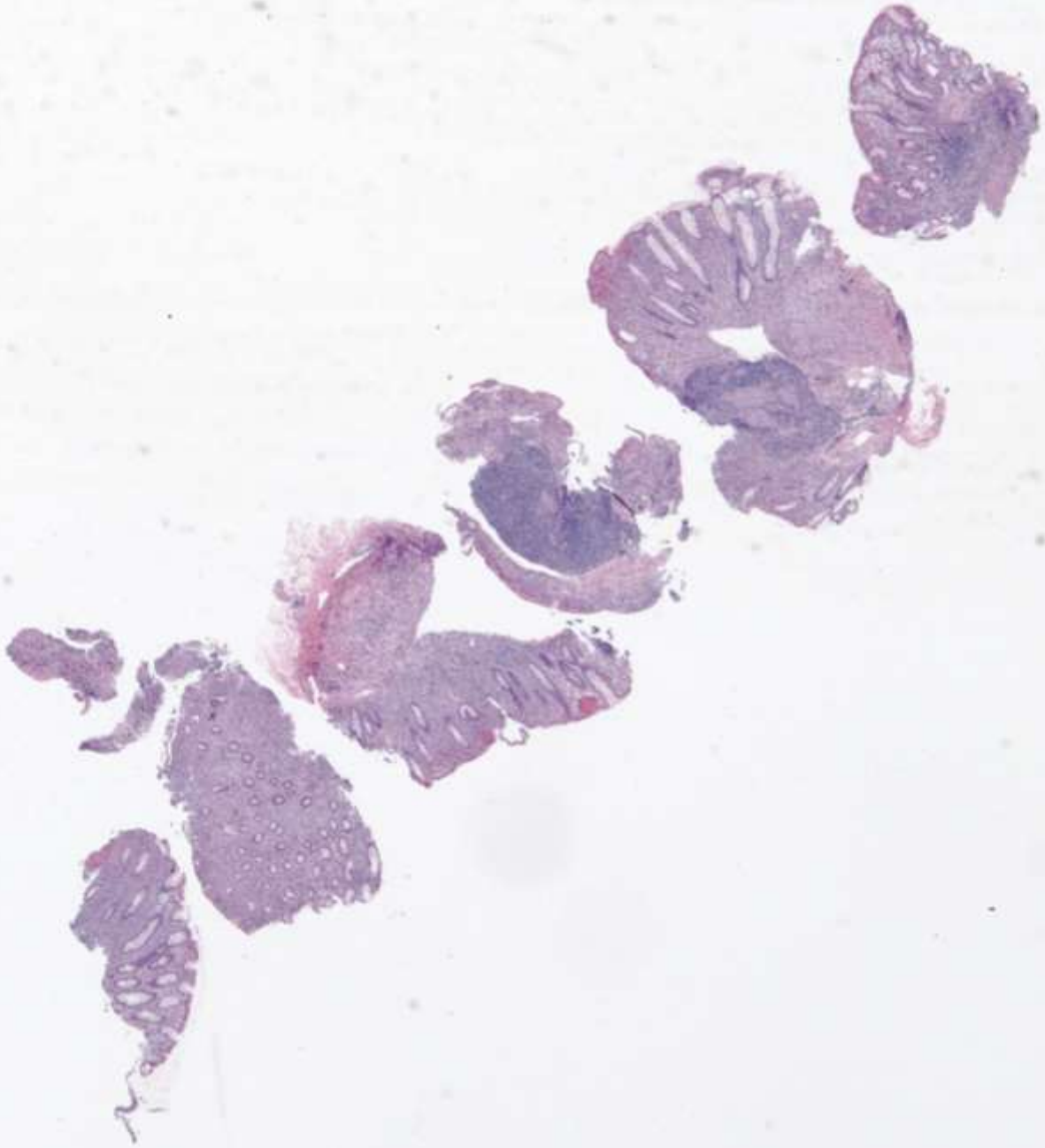
- Matnani R, Ganapathi KA, Lewis SK, Green PH, Alobeid B, Bhagat G. Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: a review and update: Indolent T- and NK-cell LPDs of the GI tract. Hematological Oncology [Internet]. 2017;35(1):3–16.

SB 6259

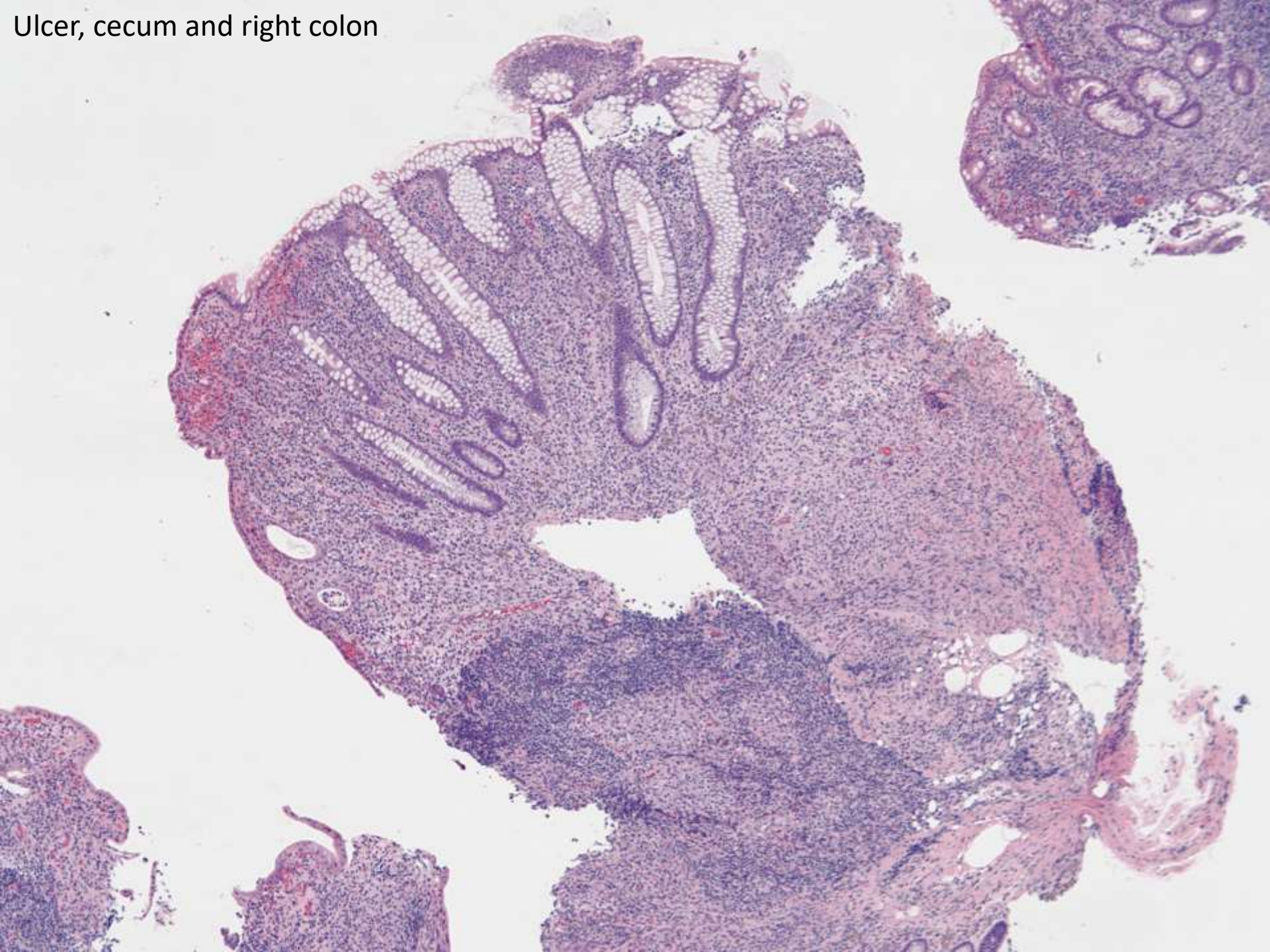
Sebastian Fernandez-Pol/Oscar Silva/Yaso Natkunam; Stanford

78-year-old male who underwent screening colonoscopy. He was found to have multiple polyps that are tubular adenomas and also multiple small ulcerations in the transverse and ascending colon and cecum which were biopsied. The patient also has a history of prostate adenocarcinoma Gleason 3+3 with minimal volume on biopsy.

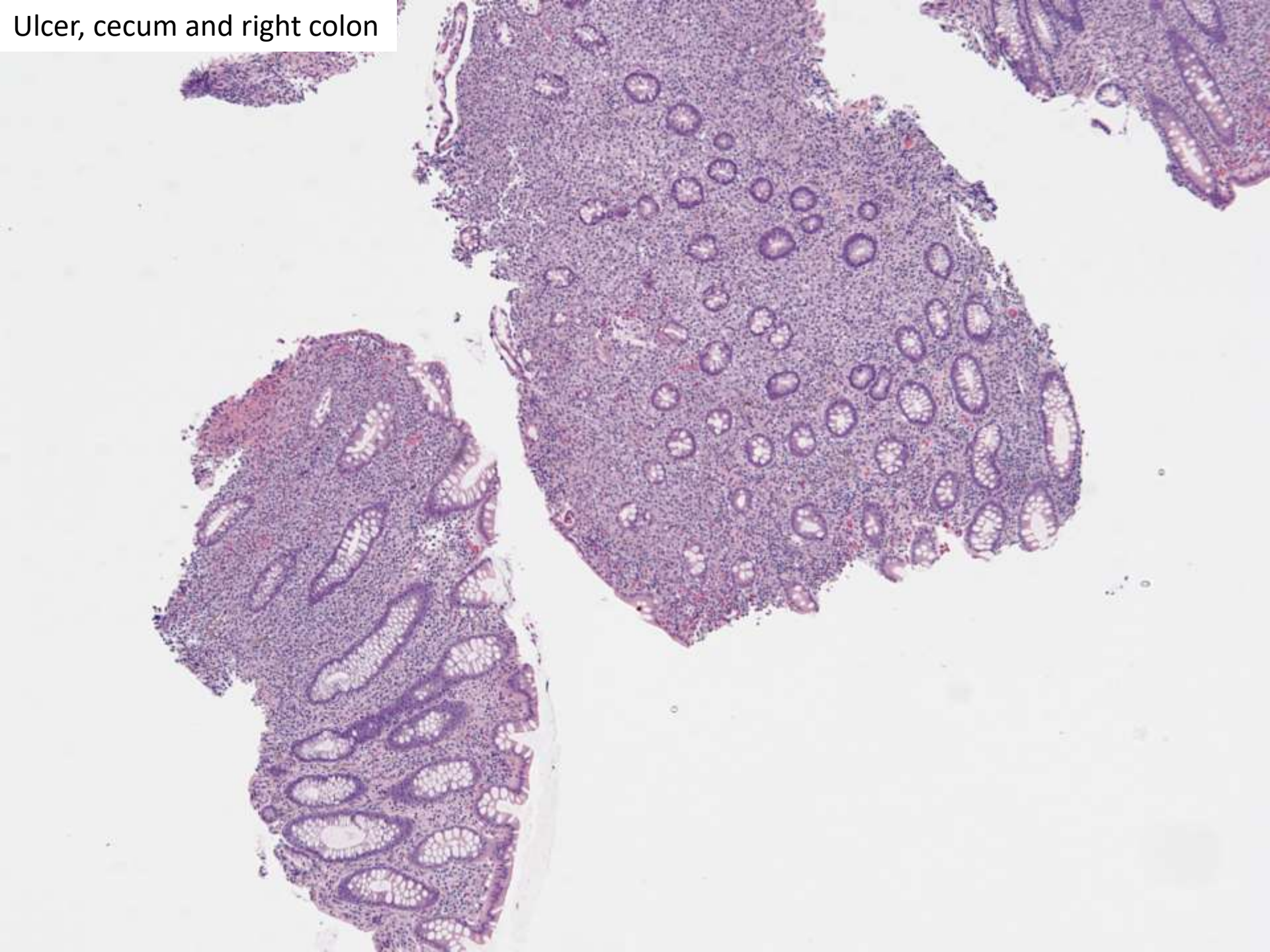
Ulcer, cecum and right colon

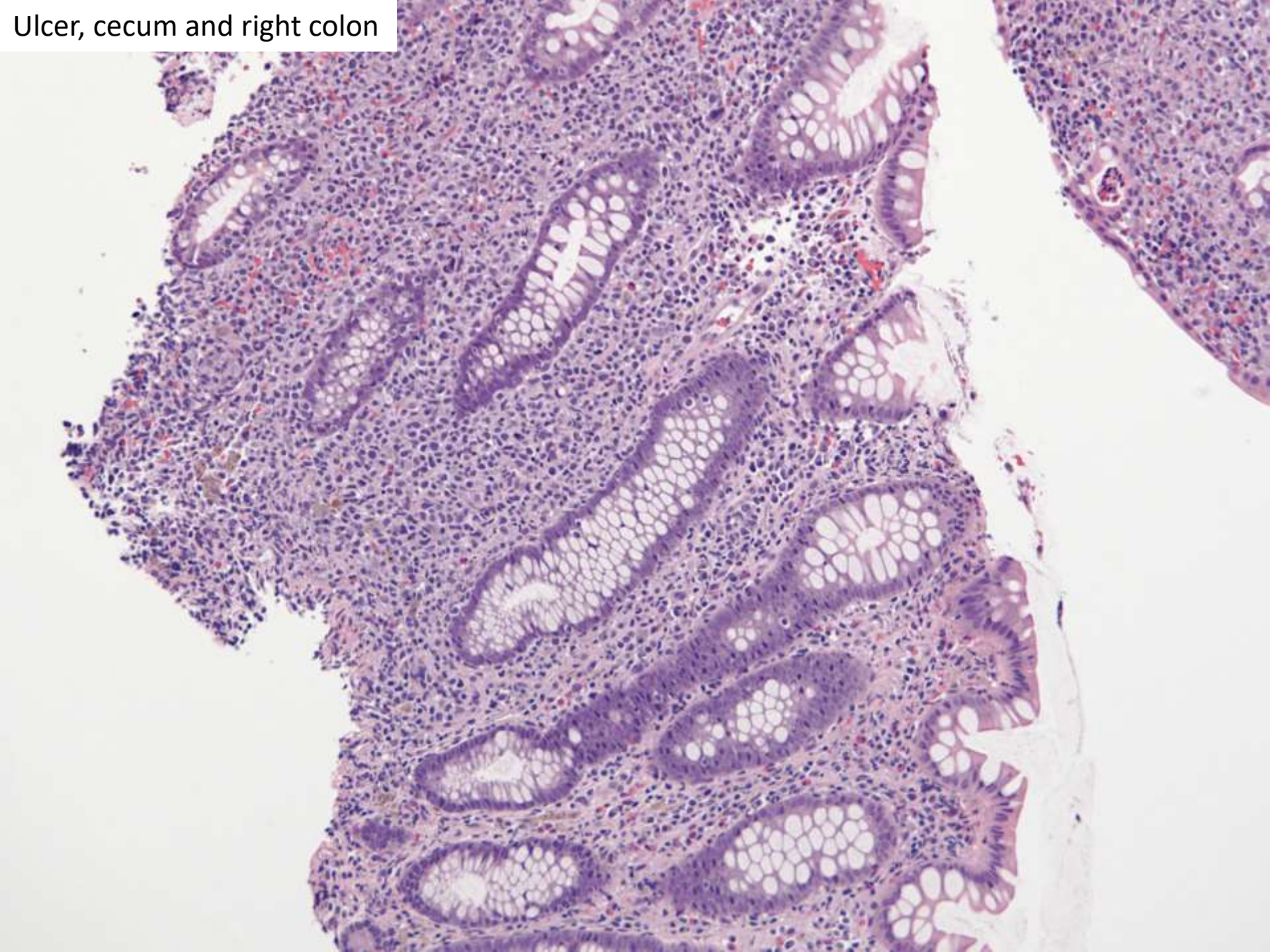


Ulcer, cecum and right colon

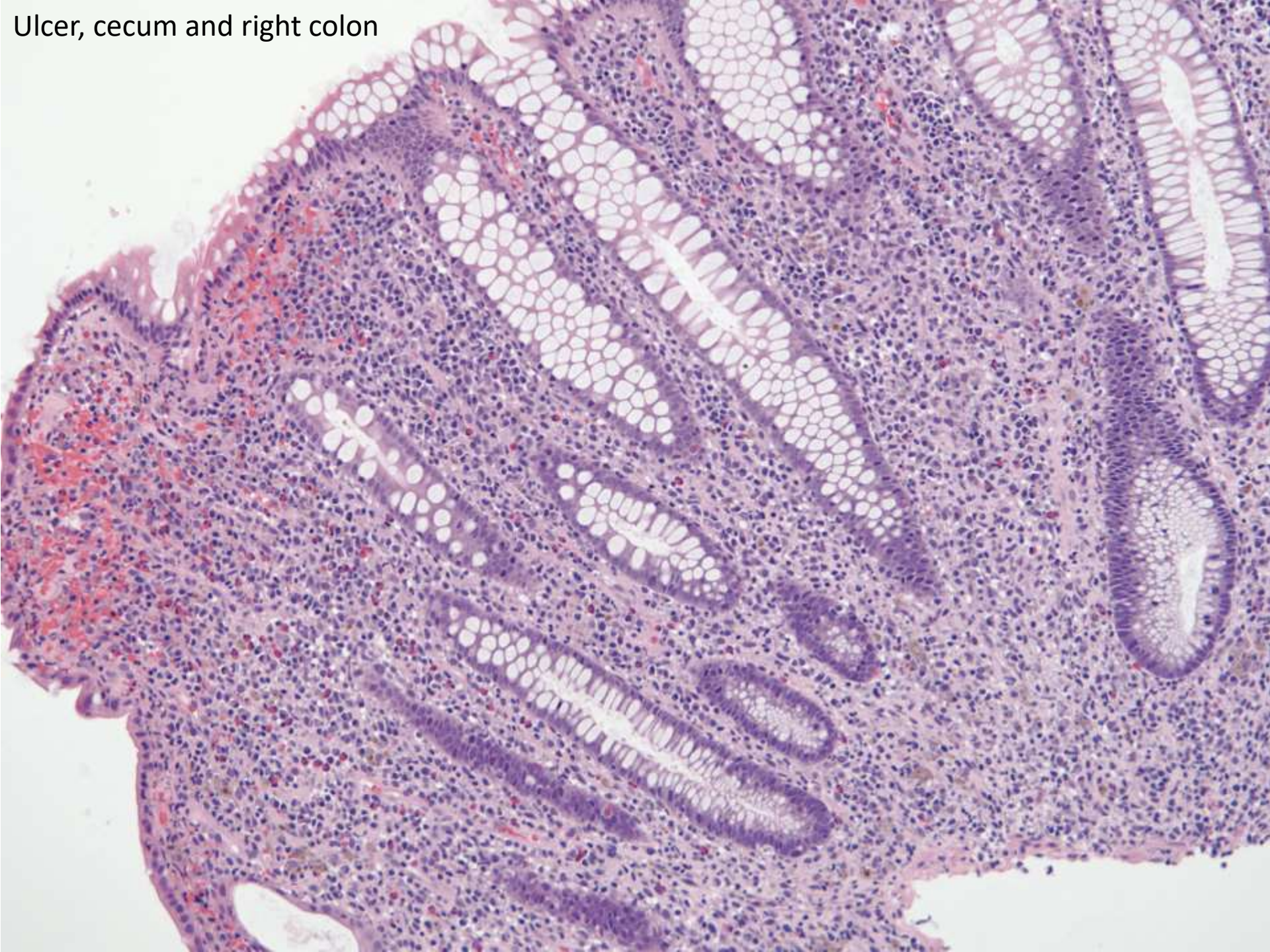


Ulcer, cecum and right colon

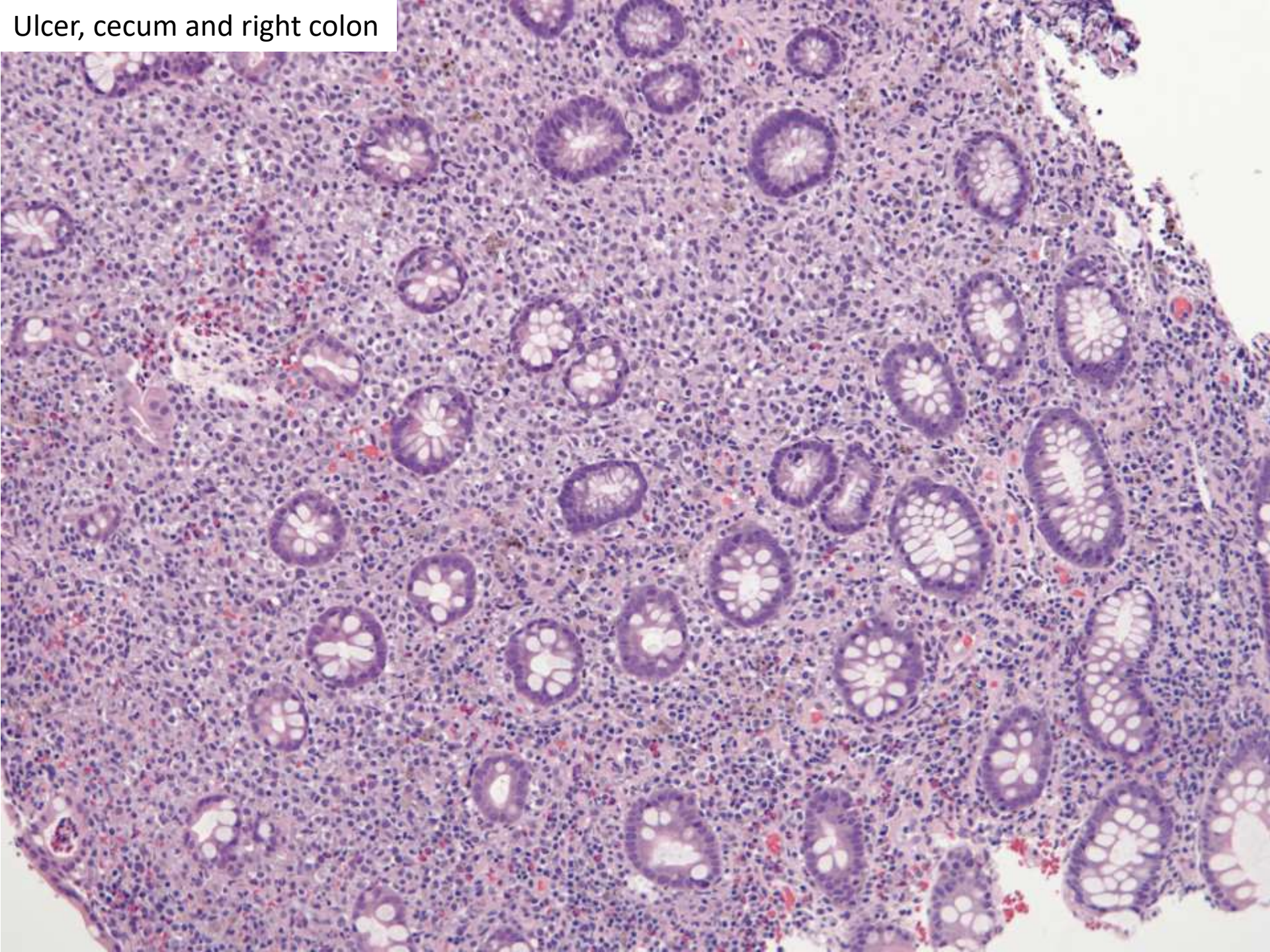



Ulcer, cecum and right colon

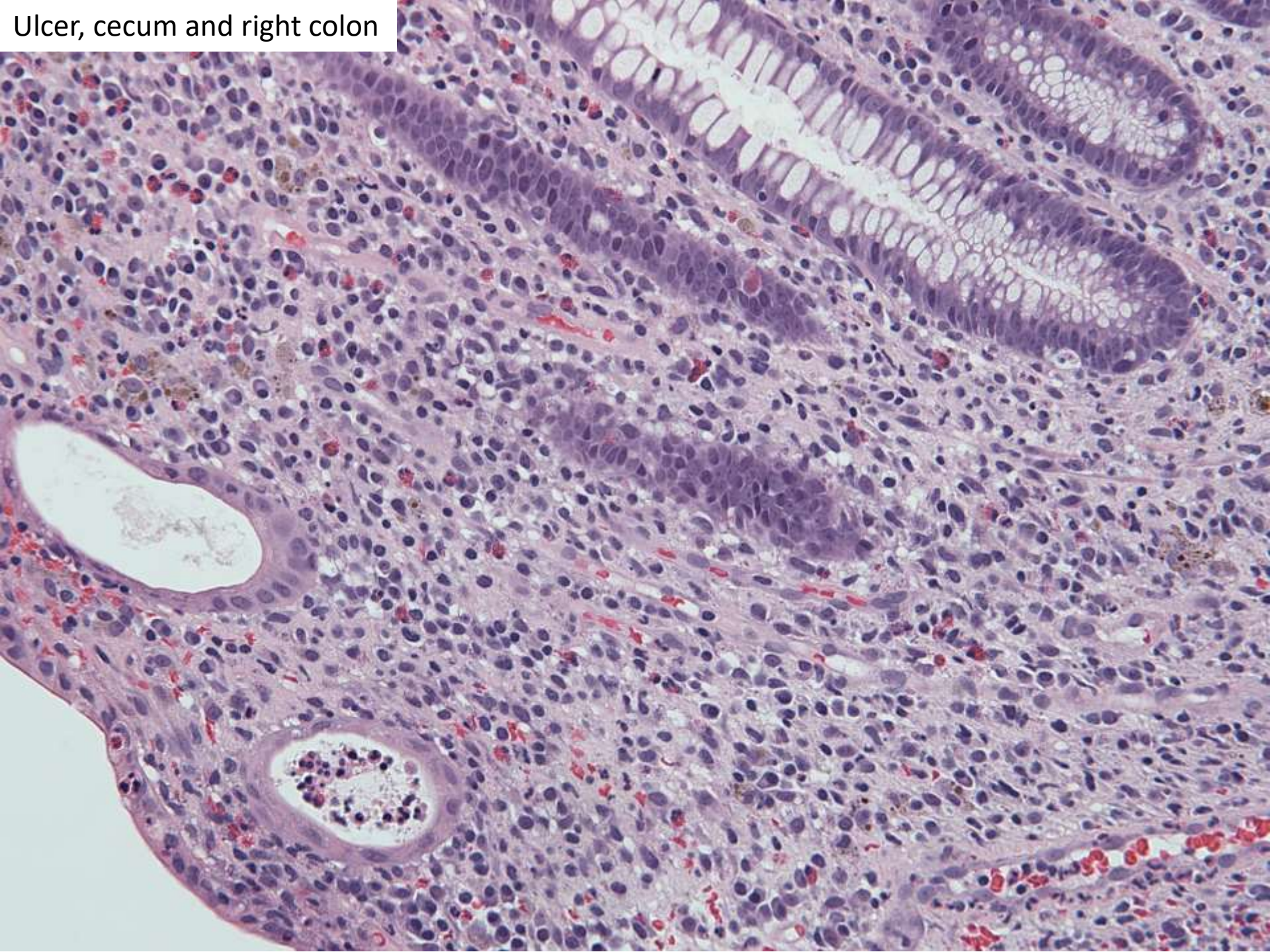
Ulcer, cecum and right colon



Ulcer, cecum and right colon

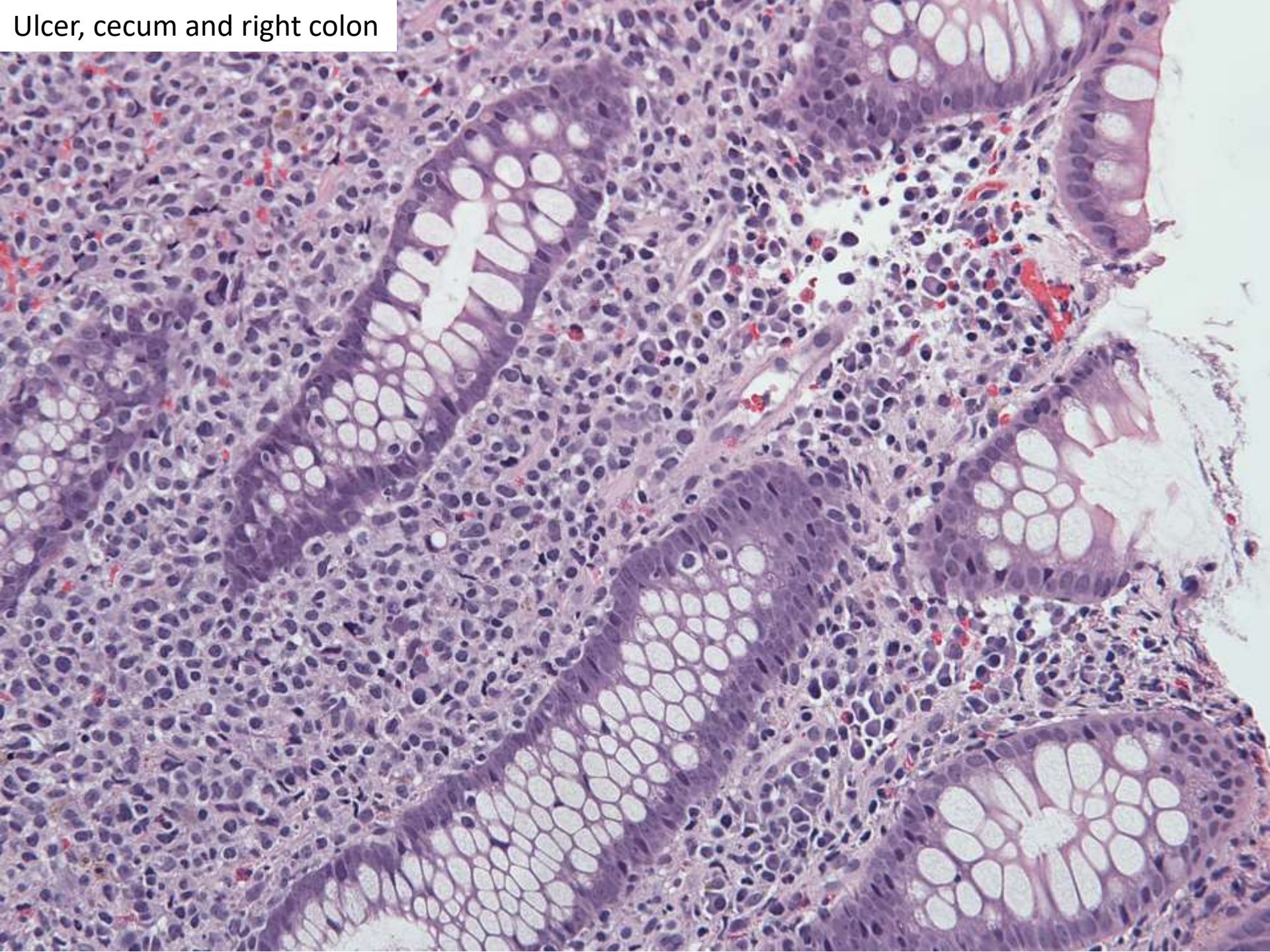


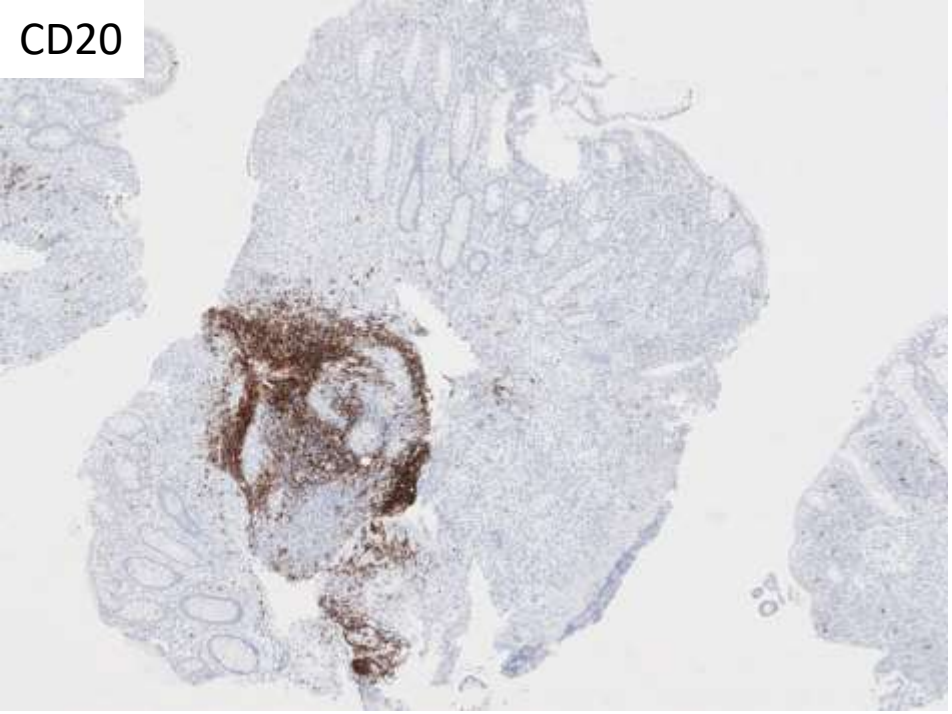
Ulcer, cecum and right colon

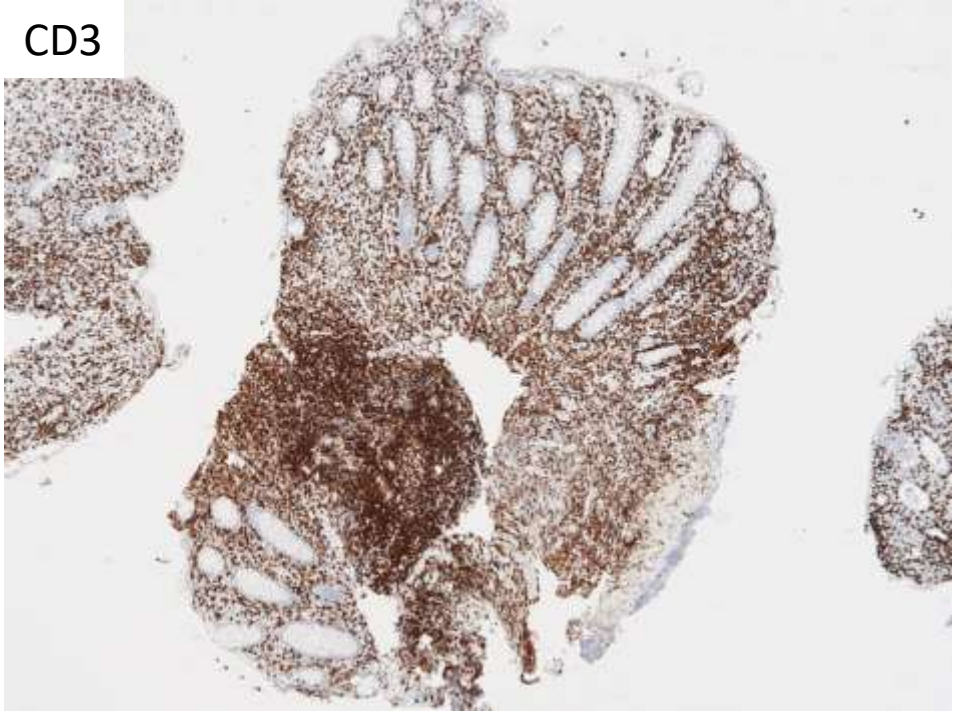


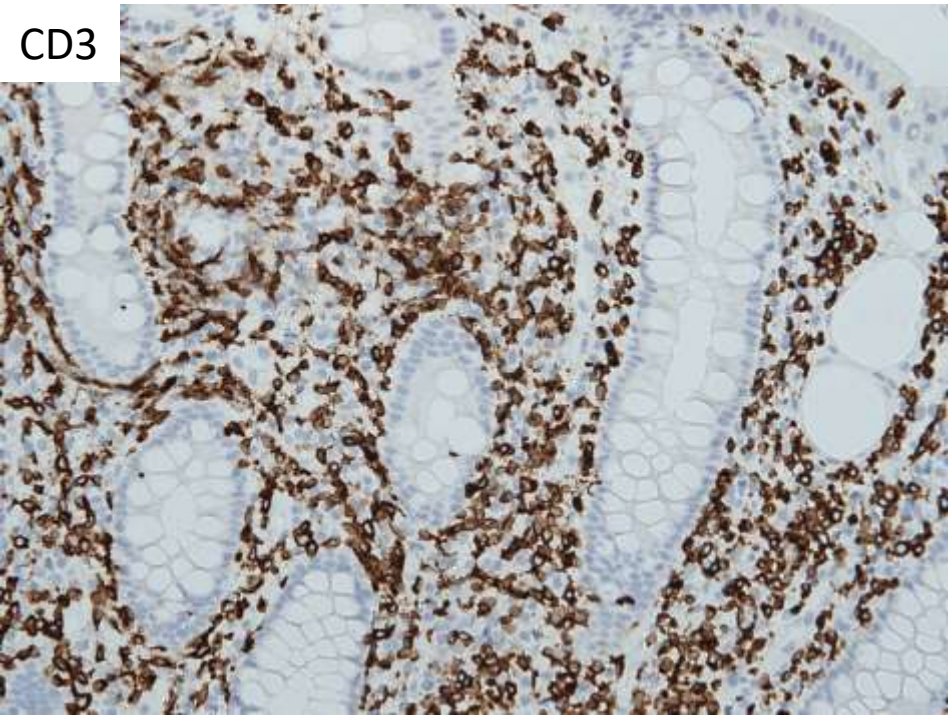

Ulcer, cecum and right colon

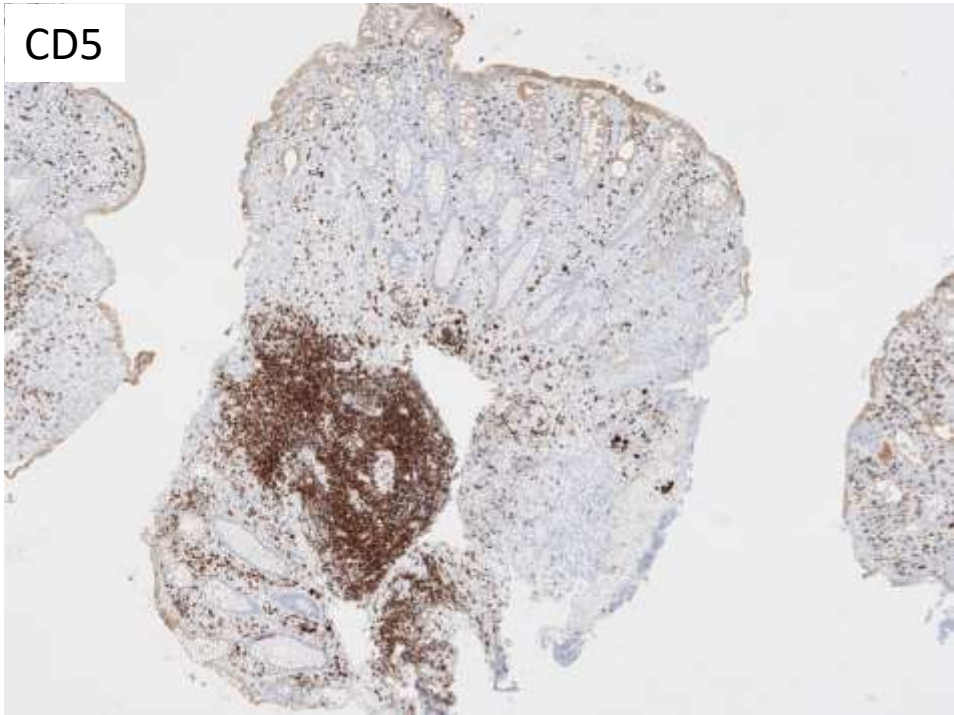
Ulcer, cecum and right colon

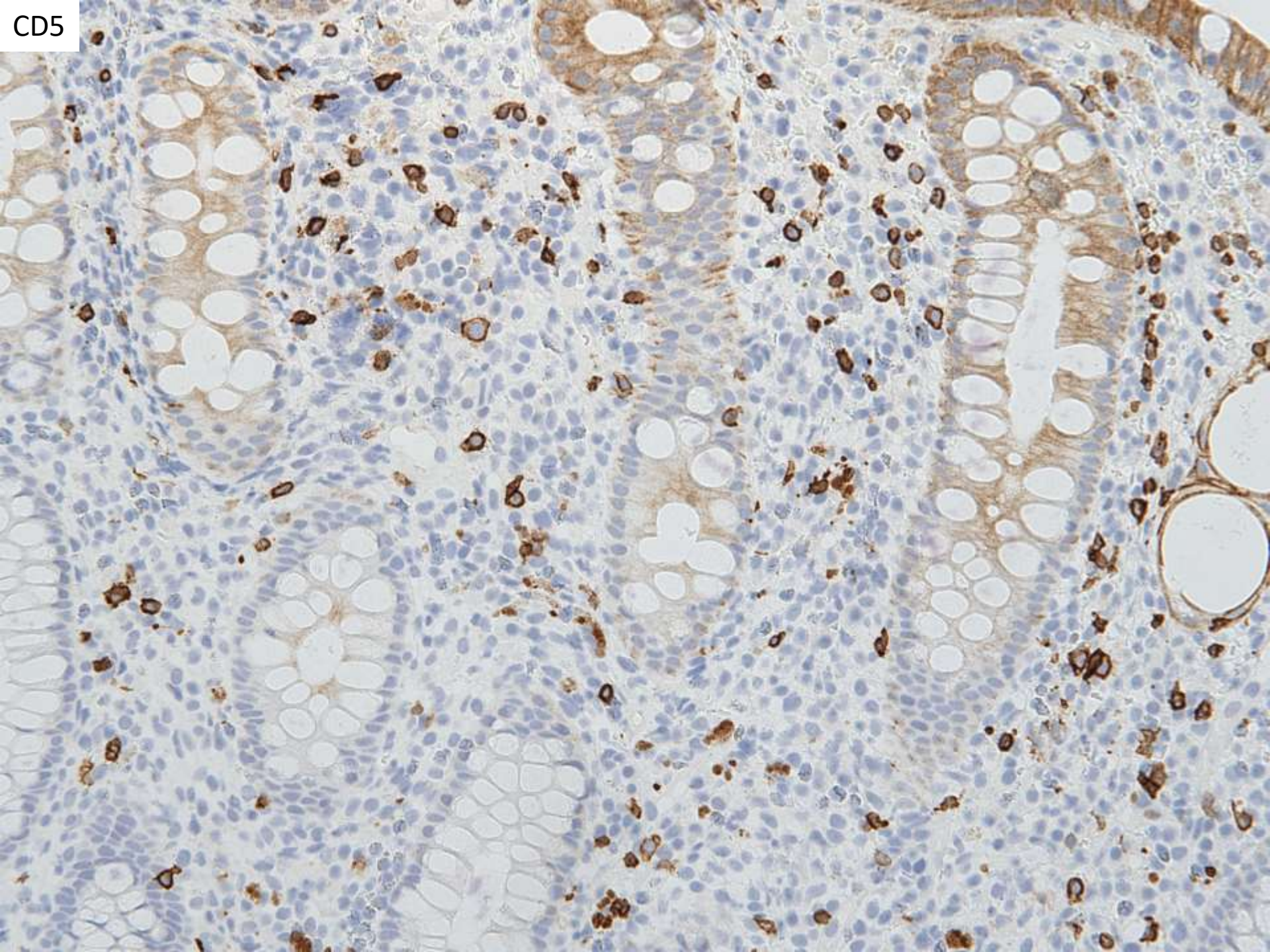



CD20

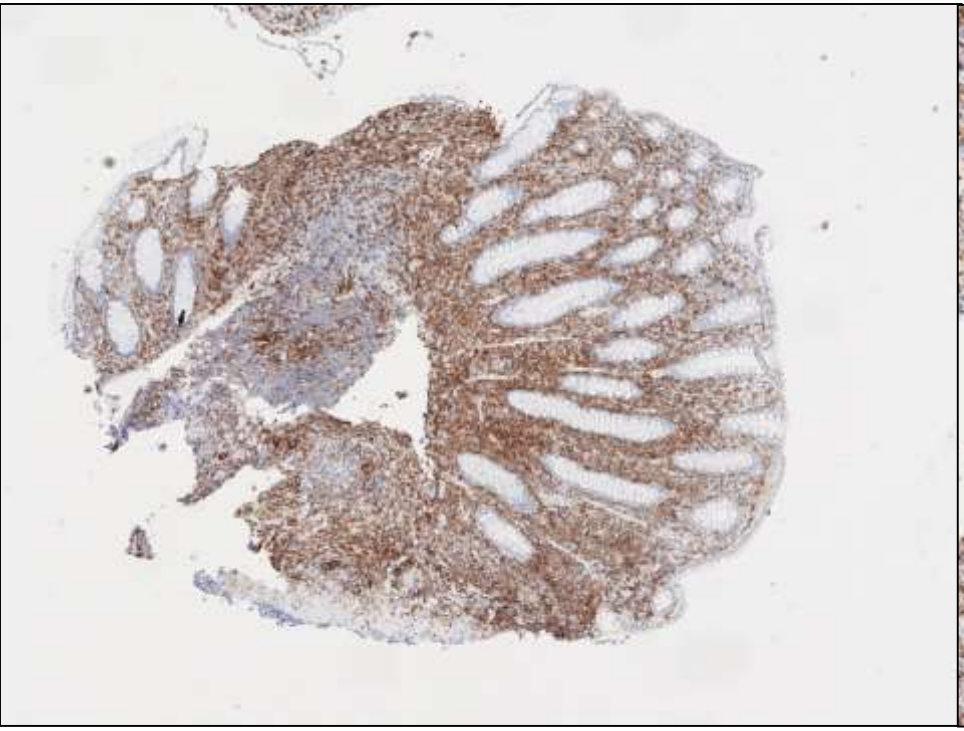

CD3


CD3

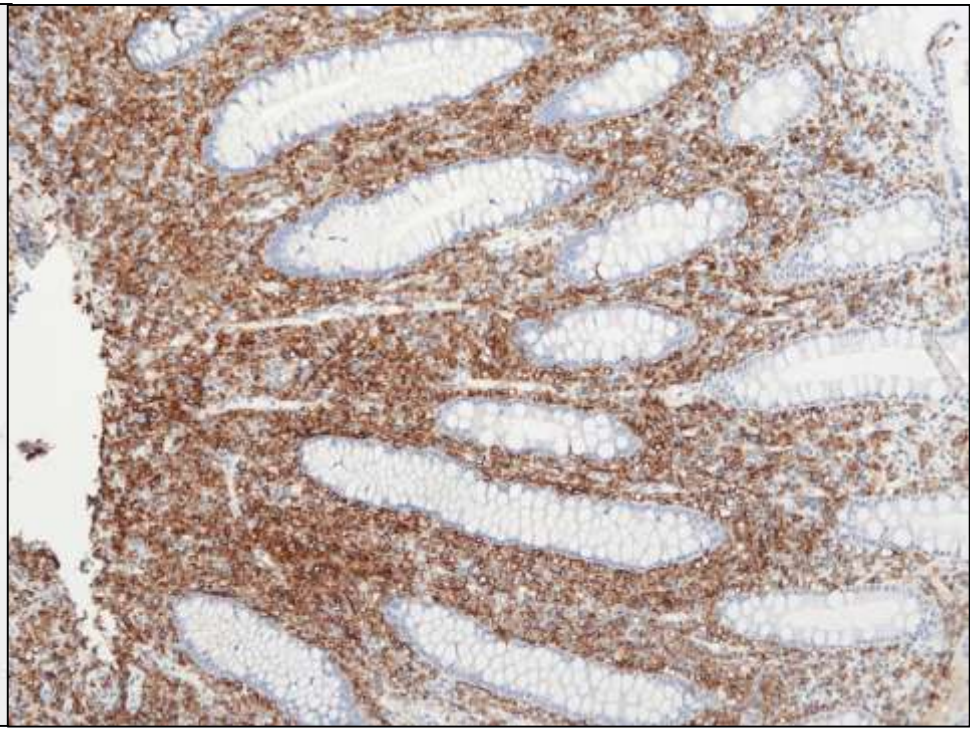

CD5

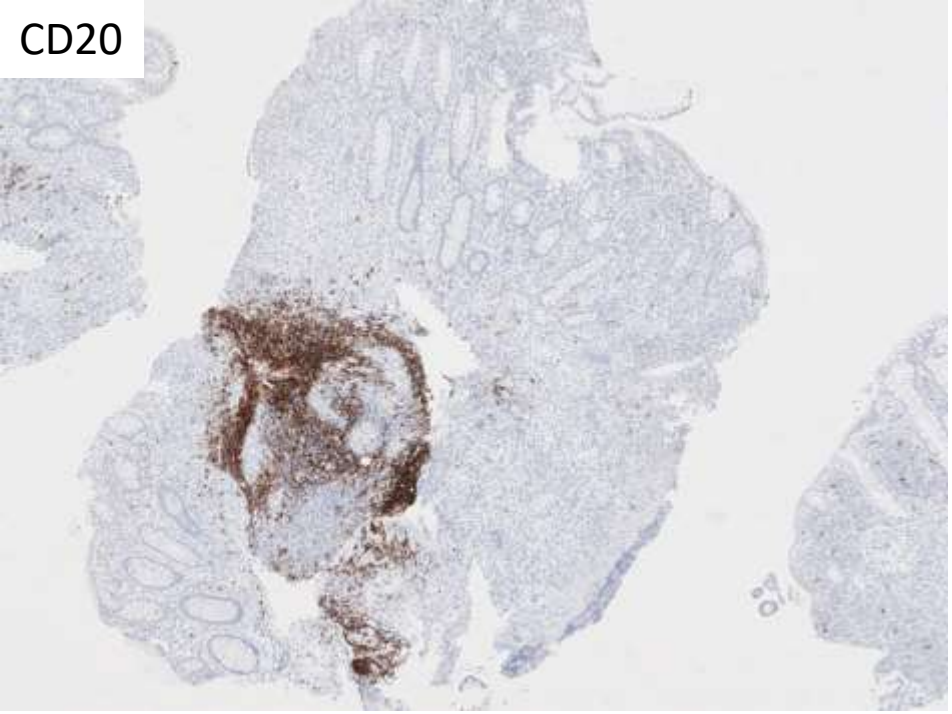

CD5

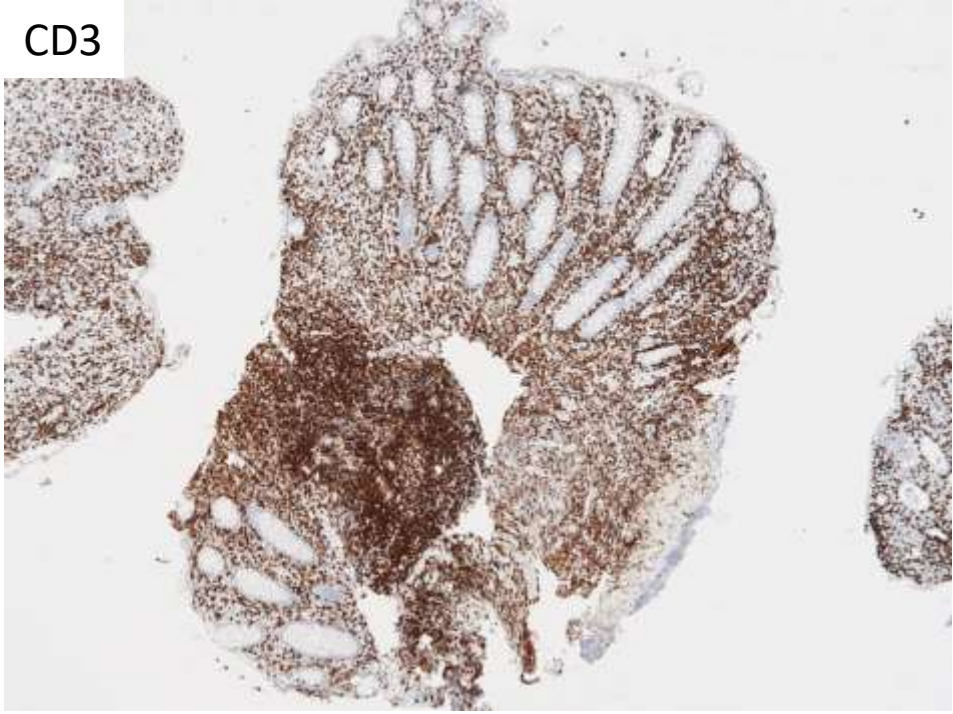
CD56

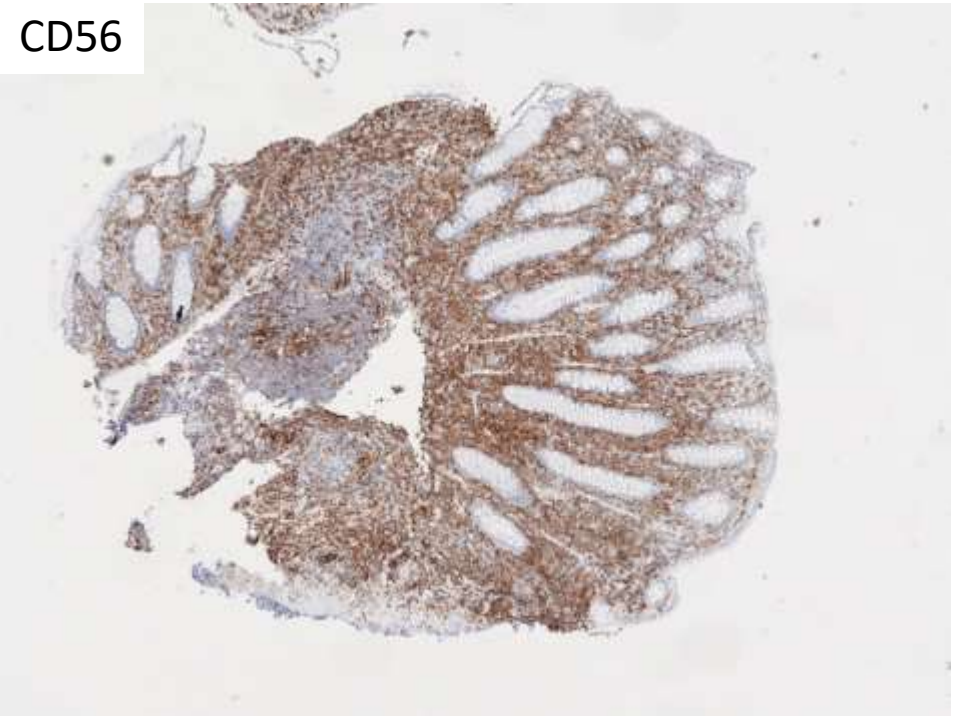


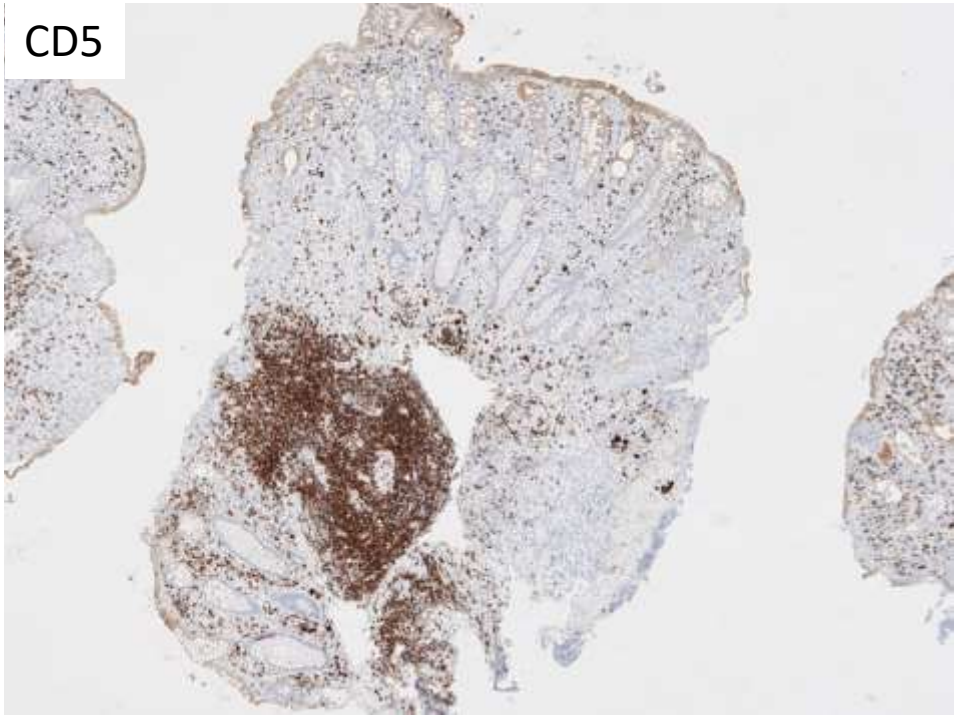
CD56




CD20


CD3

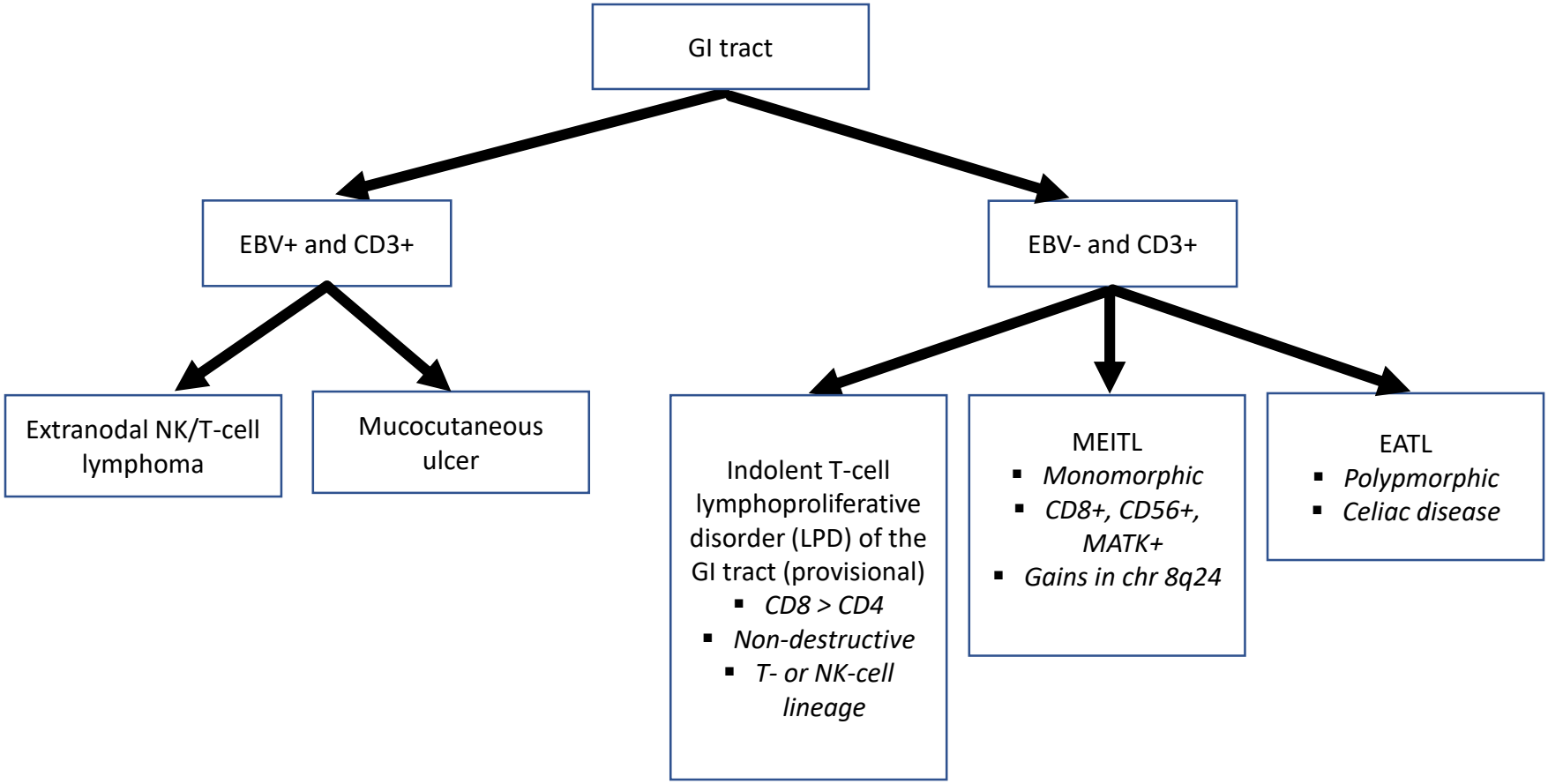

CD56


CD5

CD3+, CD56+, CD5- population

Differential diagnosis

- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
- Extranodal NK/T-cell lymphoma, nasal type
  - EBER was negative
- **Indolent NK-cell lymphoproliferative disorder (LPD) of the GI tract**


GI tract
EBV+ and CD3+
EBV- and CD3+
Extranodal NK/T-cell lymphoma
Mucocutaneous ulcer
Indolent T-cell lymphoproliferative disorder (LPD) of the GI tract (provisional)
CD8 > CD4
Non-destructive
T- or NK-cell lineage
MEITL
Monomorphic
CD8+, CD56+, MATK+
Gains in chr 8q24
EATL
Polypmorphic
Celiac disease

NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series

Adnan Mansoor,[1] Stefania Pittaluga,[2] Paul L. Beck,[3] Wyndham H. Wilson,[4] Judith A. Ferry,[5] and Elaine S. Jaffe[2]

[1]Department of Pathology & Laboratory Medicine/Calgary Laboratory Services, Calgary, AB; [2]Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD; [3]Division of Gastroenterology, University of Calgary, Calgary, AB; [4]Metabolism Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD; and [5]Department of Pathology Massachusetts General Hospital, Boston, MA

Table 1. Demographics, clinical presentation, endoscopic findings, and follow-up

Patient no.	Age, y/sex	Clinical presentation	Gastrointestinal site(s)	Endoscopic findings	Follow-up (months)
1*	31/M	Asymptomatic, elective colonoscopy	Stomach, small intestine, colon	Superficial erythematous lesions	A/P (84)
2	27/F	Abdominal pain, hematochezia	Stomach	Multiple, superficial ulcers	A/P (23)
3	29/F	Constipation, rectal bleeding	Colon	Ulcerative lesions	A† (31)
4	53/M	Asymptomatic	Stomach, duodenum	Gastric lesions	A/P (30)
5	46/F	Chronic vague abdominal symptoms	Duodenum, colon	Superficial ulcers	A/P (36)‡
6	64/F	Abdominal pain, diverticulosis	Colon	Multiple erosions/ulcers	A/P (22)
7	61/F	Vague abdominal symptoms, history of polyps	Duodenum, colon	Multiple ulcerations	A/P (120)‡
8	68/F	Abdominal pain, diarrhea, diverticulosis	Colon	Ulcerations	A (22)‡

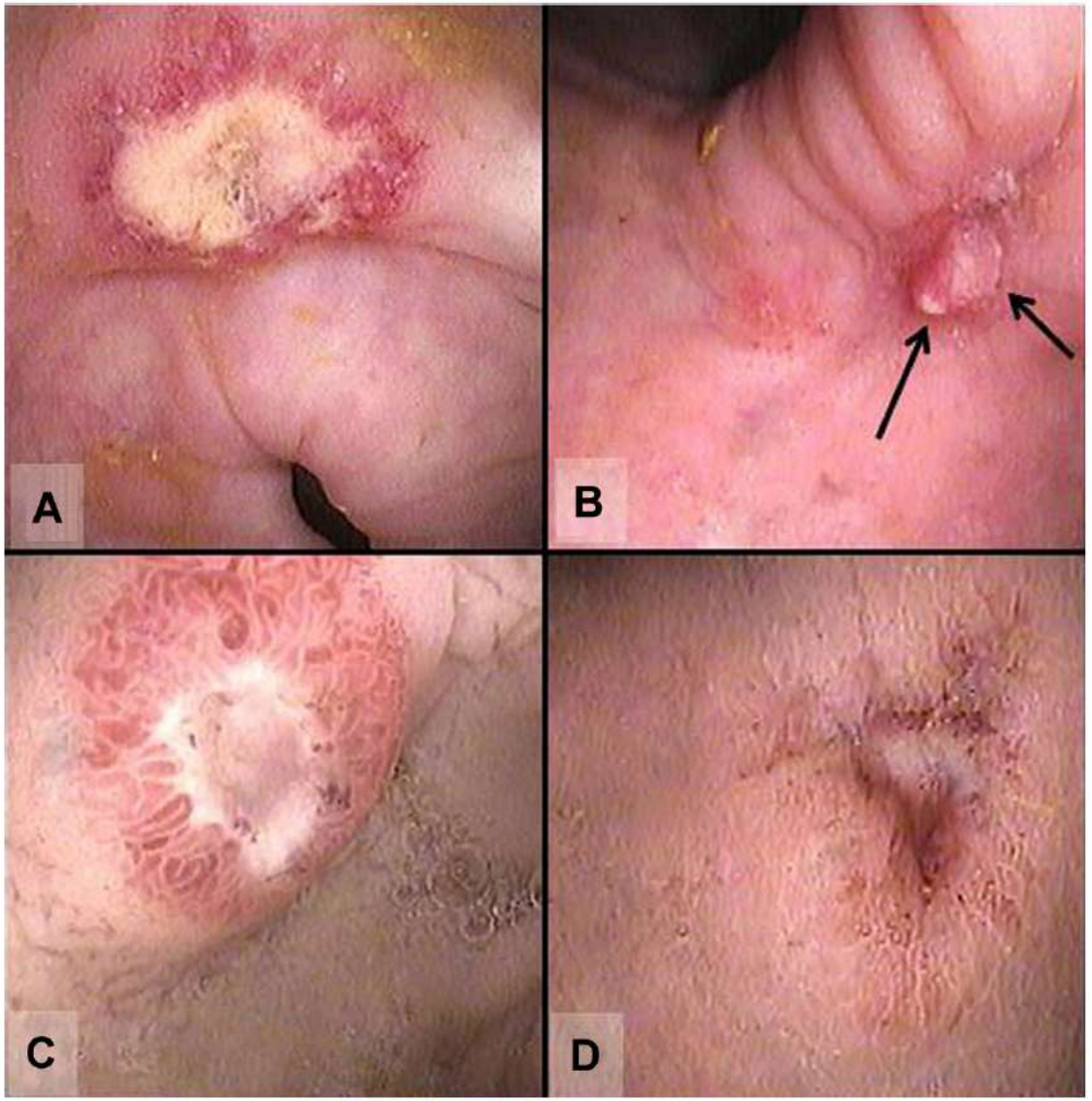
- All patients alive (22-120 months; median, 30 months)
  - 3 treated with CHOP (2 auto-BMT)
    - 2 of 3 asymptomatic but with biopsy proven persistent disease

Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood 2011;117: 1447–1452.

Endoscopic images of NK-cell enteropathy

Ulcers

Nodular or polypoid appearance



Duodenal

Raised ulcer-like lesions surrounded by erythema and edema

Gastric

Small punctuate deep ulcers in the stomach

Mansoor, 2011

Histology

- Mucosal glands were displaced because of dense atypical cellular infiltrate
- In advanced stages, sheets of atypical cells with destruction of mucosal glands were noted
- There was in general an absence of epitheliotropism identified in glandular epithelium
- No angiocentricity or angiodestructive pattern of growth was seen in any patient
- Focal infiltration of the submucosa was seen rarely, but in most instances the muscularis mucosa, if observed, was intact

Immunohistochemistry

Table 2. Immunophenotypic and molecular studies

Patient no.	cCD3	CD56	TIA/GRZB	CD7	CD5	CD4/CD8	CD20	CD43	EBER	TCR
1	+	+	+	+	−	−	−	+	−	Polyclonal
2	+	+	NA	+	−	−	−	+	−	Polyclonal
3	+	+	+	+	−	−	−	+	−	Polyclonal
4	+	+	+	+	−	−	−	+	−	Polyclonal
5	+	+	+	+	−	−	−	NA	−	Polyclonal
6	+	+	+	+	−	−	−	+	−	Polyclonal
7	+	+	+	+	−	−	−	+	−	Oligoclonal
8	+	+	+	NA	−	−	−	+	−	Polyclonal

cCD3 indicates cytoplasmic CD3; GRZB, Granzyme B; EBER, Epstein-Barr virus-encoded RNA; TCR, T-cell receptor-γ gene rearrangement by polymerase chain reaction; +, positive; −, negative; and NA, not applicable.

- CD3+, CD56+, EBER-
  - Negative EBER helps rule out extranodal NK/T cell lymphoma nasal type and mucocutaneous ulcer

Summary

Indolent NK-cell lymphoproliferative disorder (NK-cell enteropathy)

- Expands lamina propria, usually non-destructive
- Rule out extranodal NK/T cell lymphoma and mucocutaneous ulcer with EBER stain
- Does not progress
- Should not be treated with chemotherapy

References

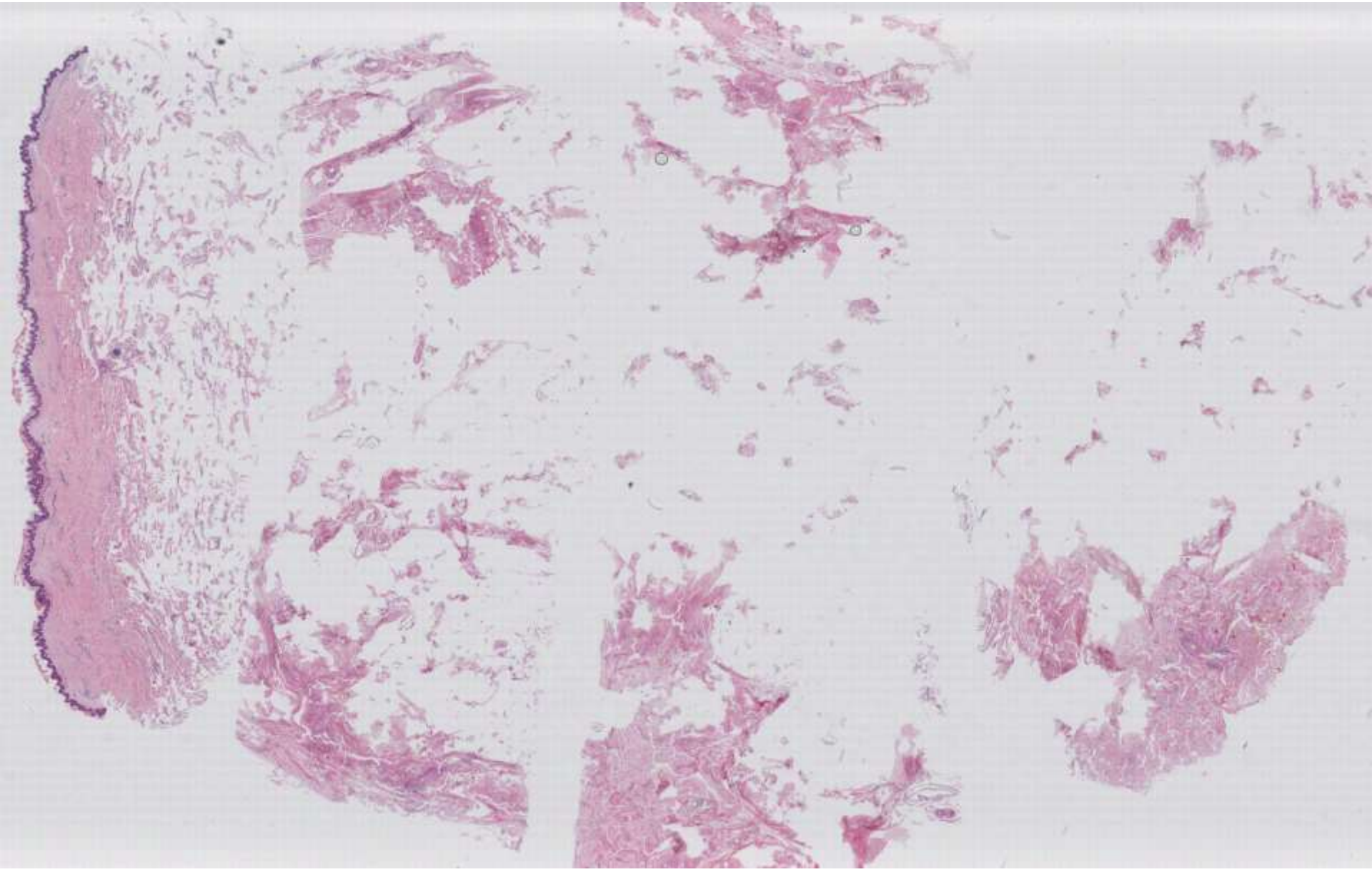
- Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood [Internet]. 2011 [cited 2017 Aug 8];117(5):1447–52. Available from: http://www.bloodjournal.org/content/117/5/1447.short

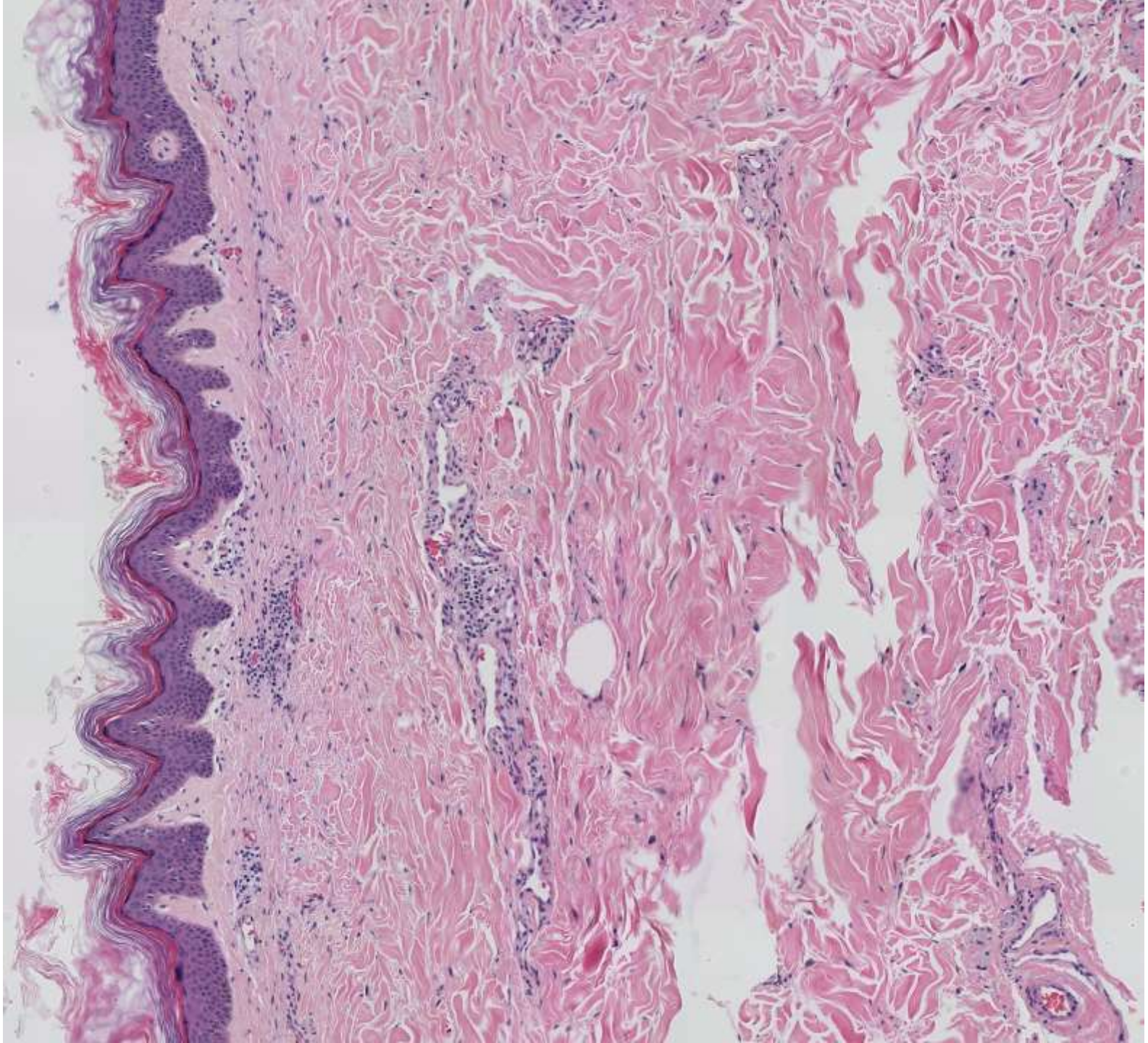
- Matnani R, Ganapathi KA, Lewis SK, Green PH, Alobeid B, Bhagat G. Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: a review and update: Indolent T- and NK-cell LPDs of the GI tract. Hematological Oncology [Internet]. 2017 Mar [cited 2017 Sep 21];35(1):3–16. Available from: http://doi.wiley.com/10.1002/hon.2317

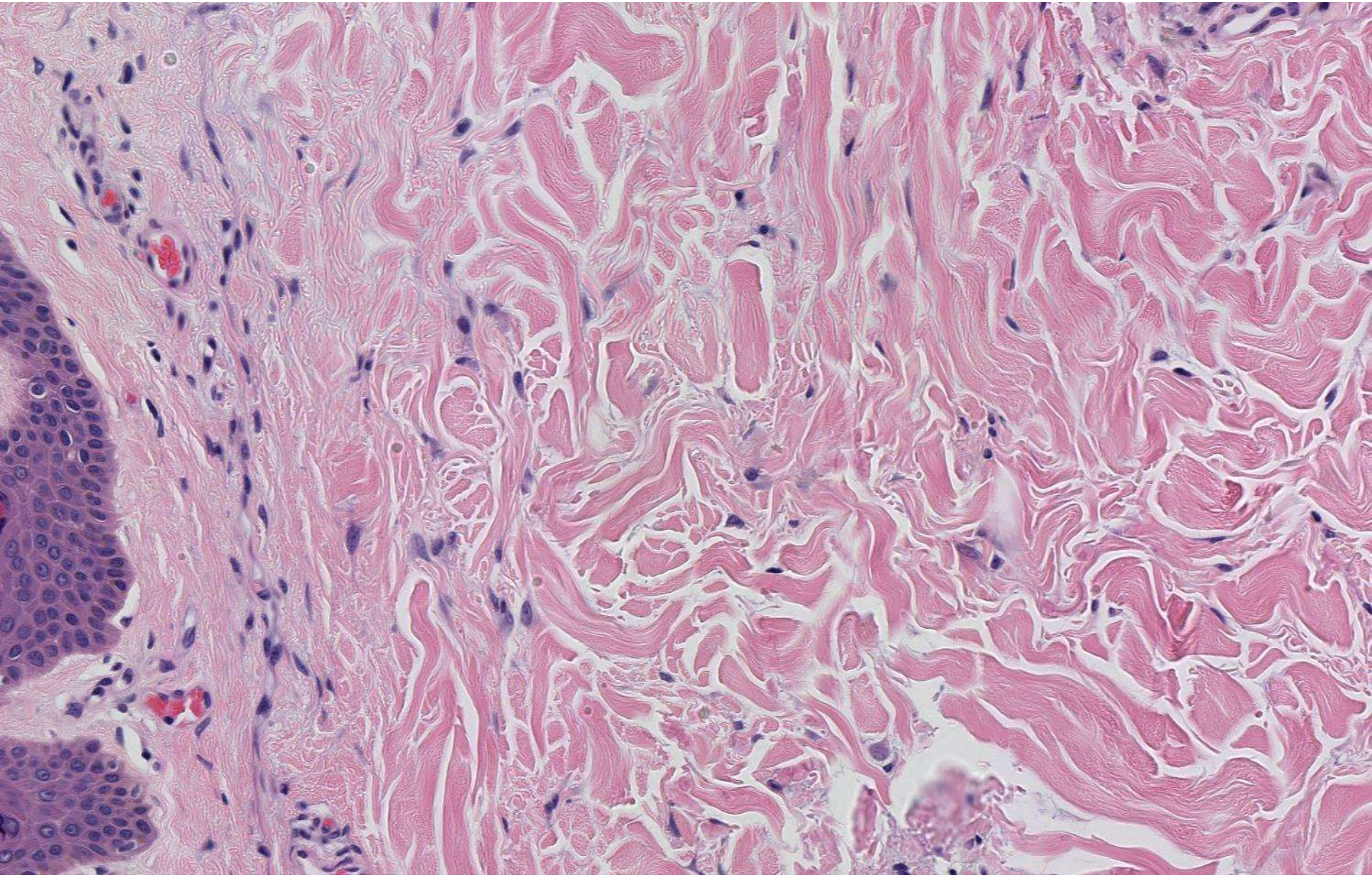
SB 6260
(scanned slide available)

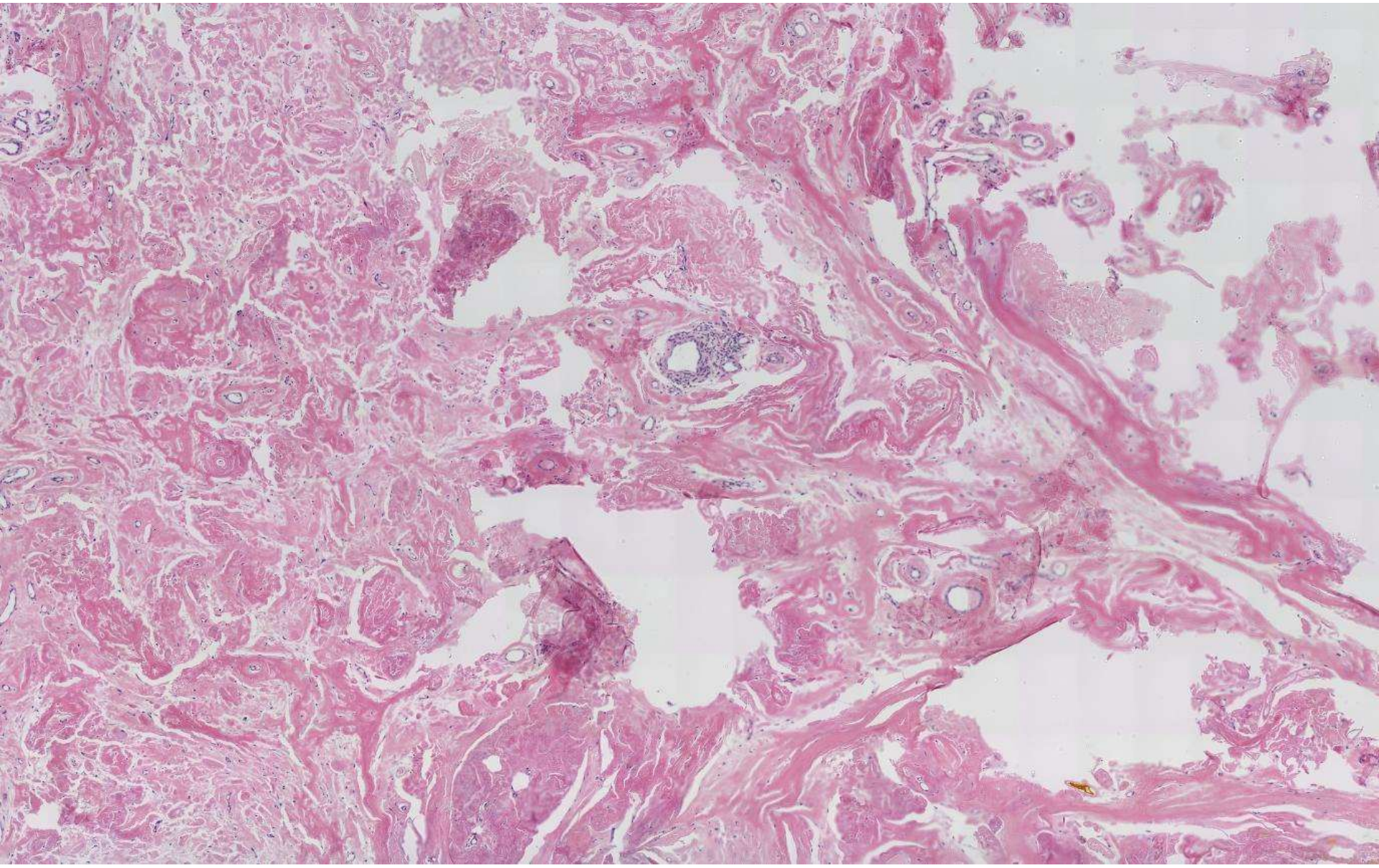
Ankur Sangoi; El Camino Hospital

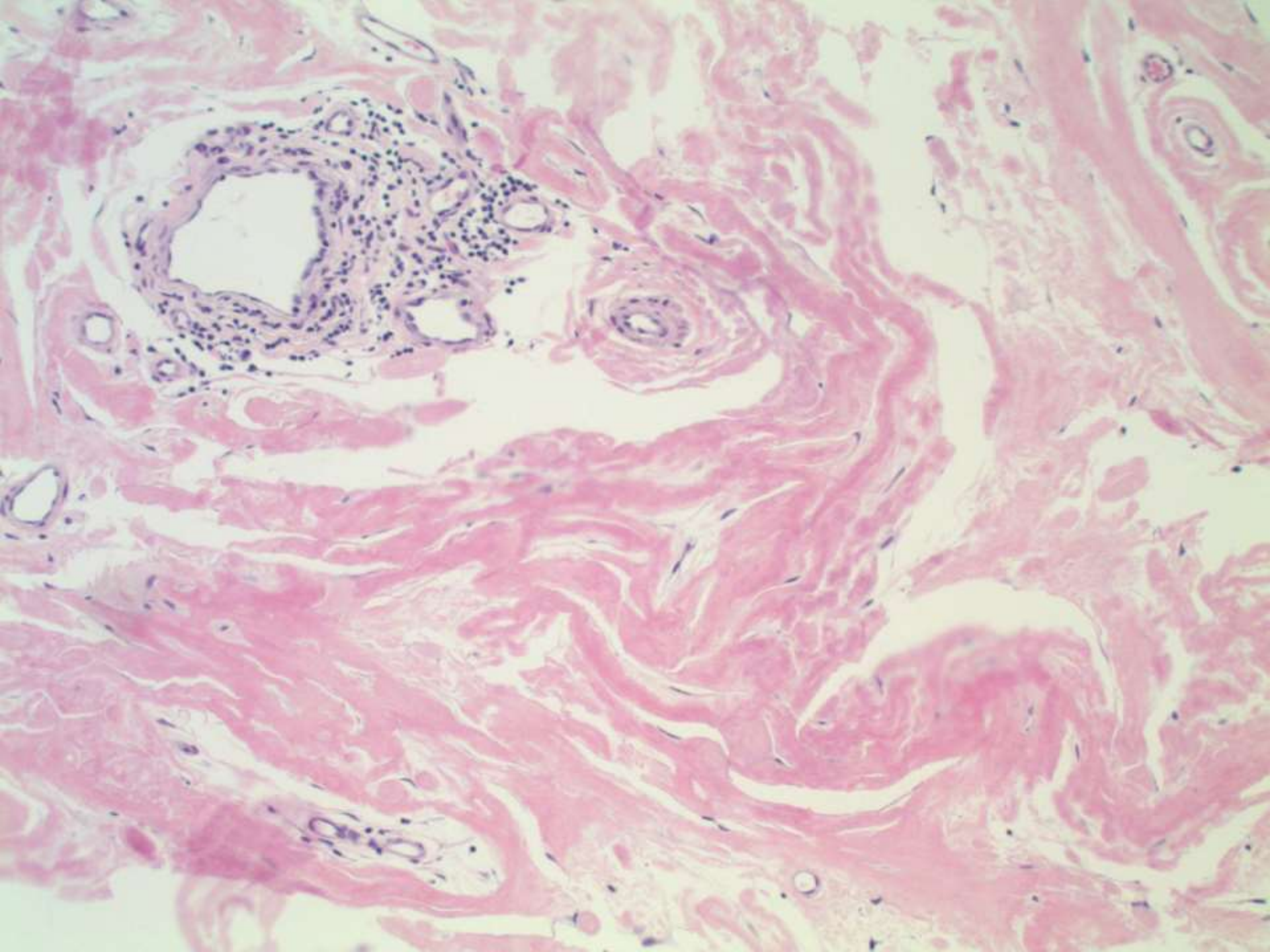
72-year-old male with 55cm abdominal mass excision revealing a 24cm pale tan fibrous homogenous well-defined mass.

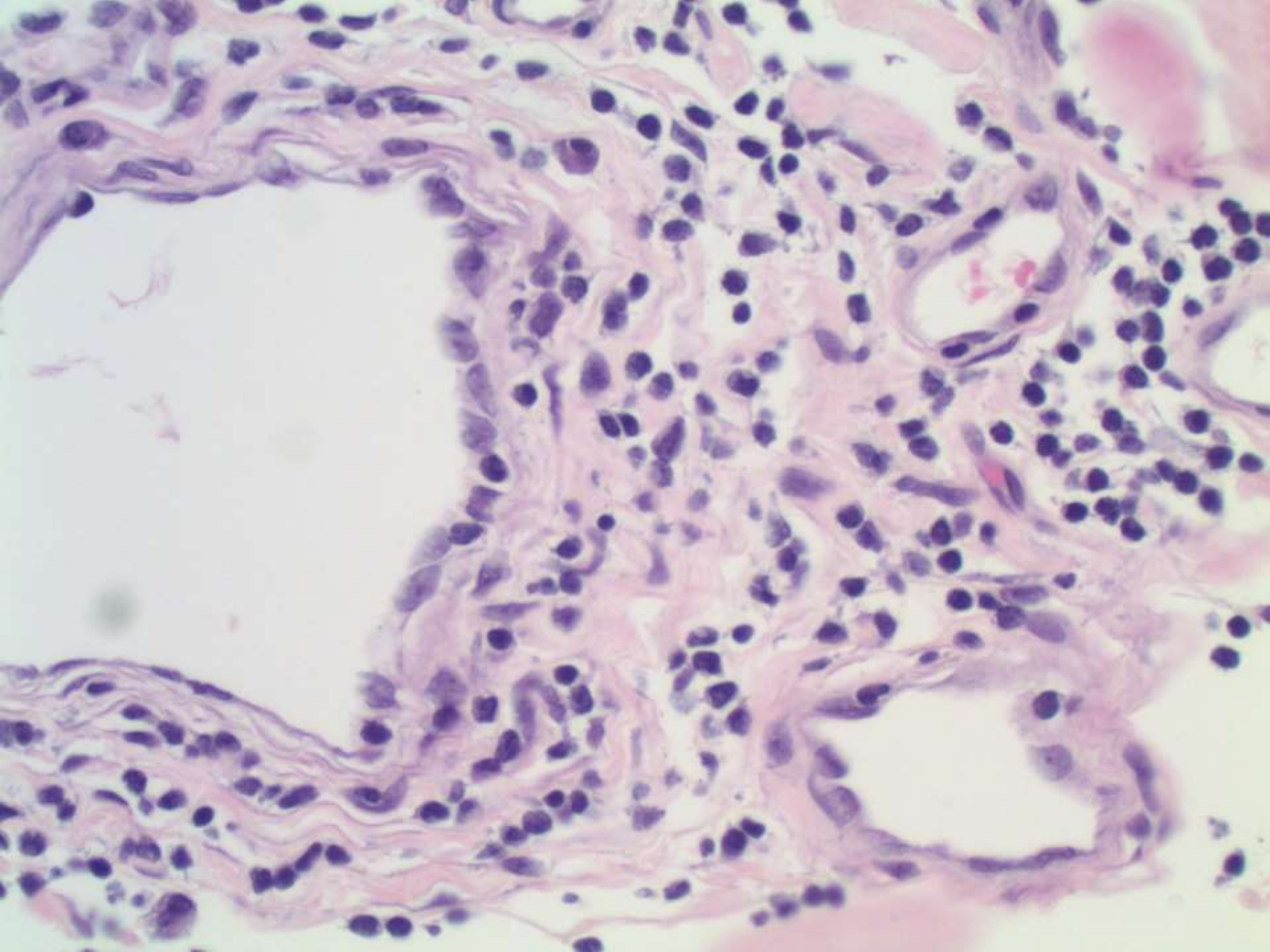


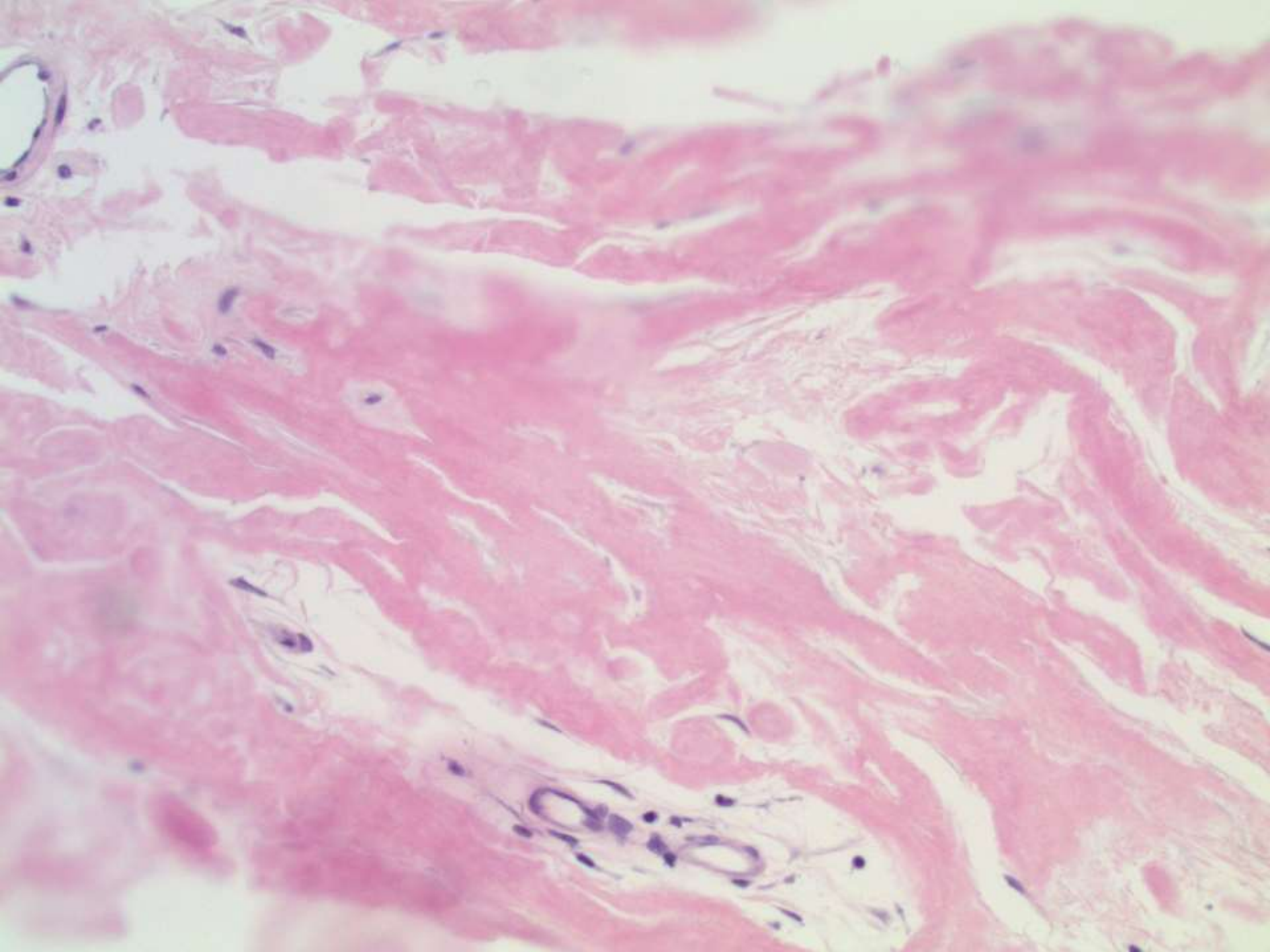


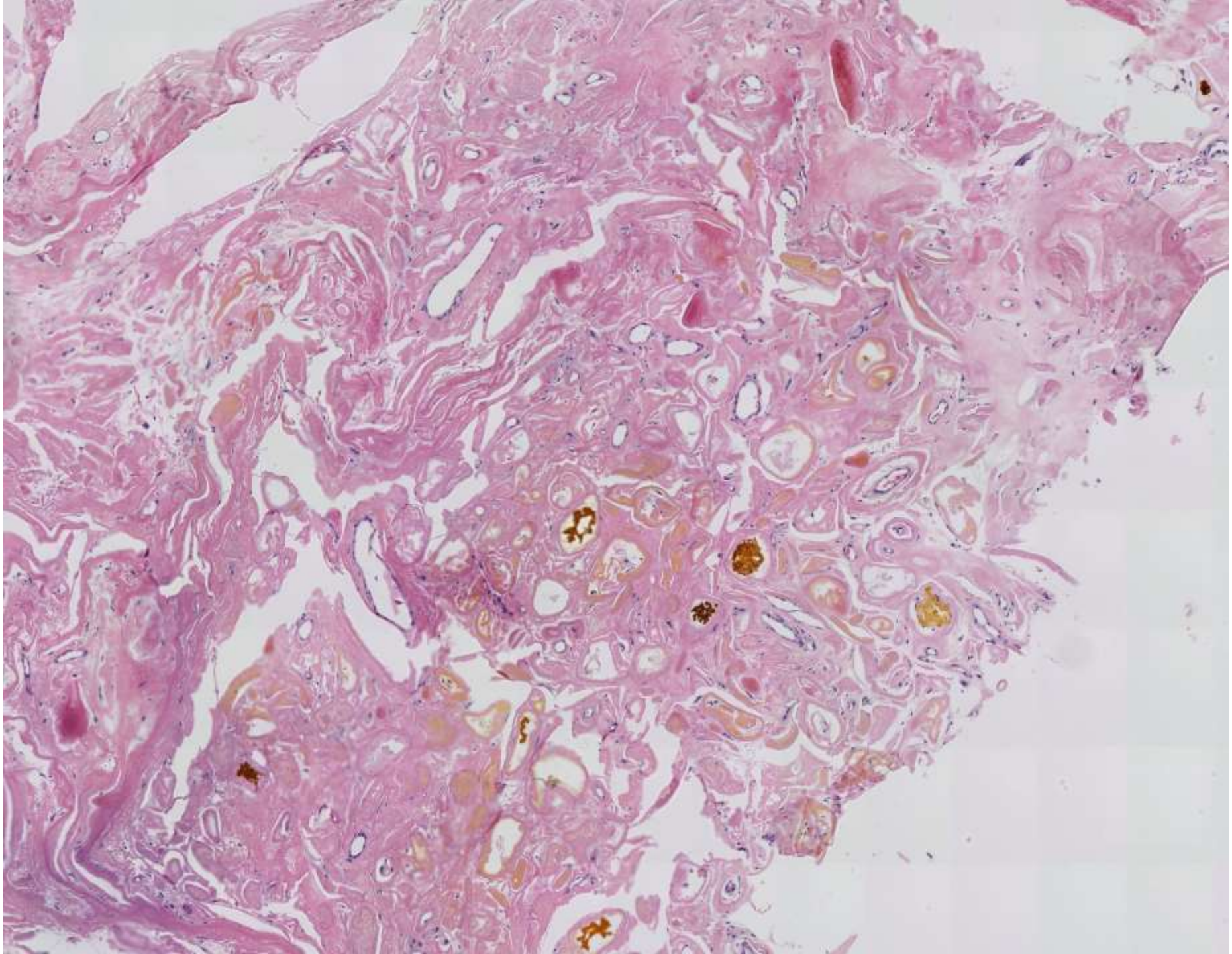


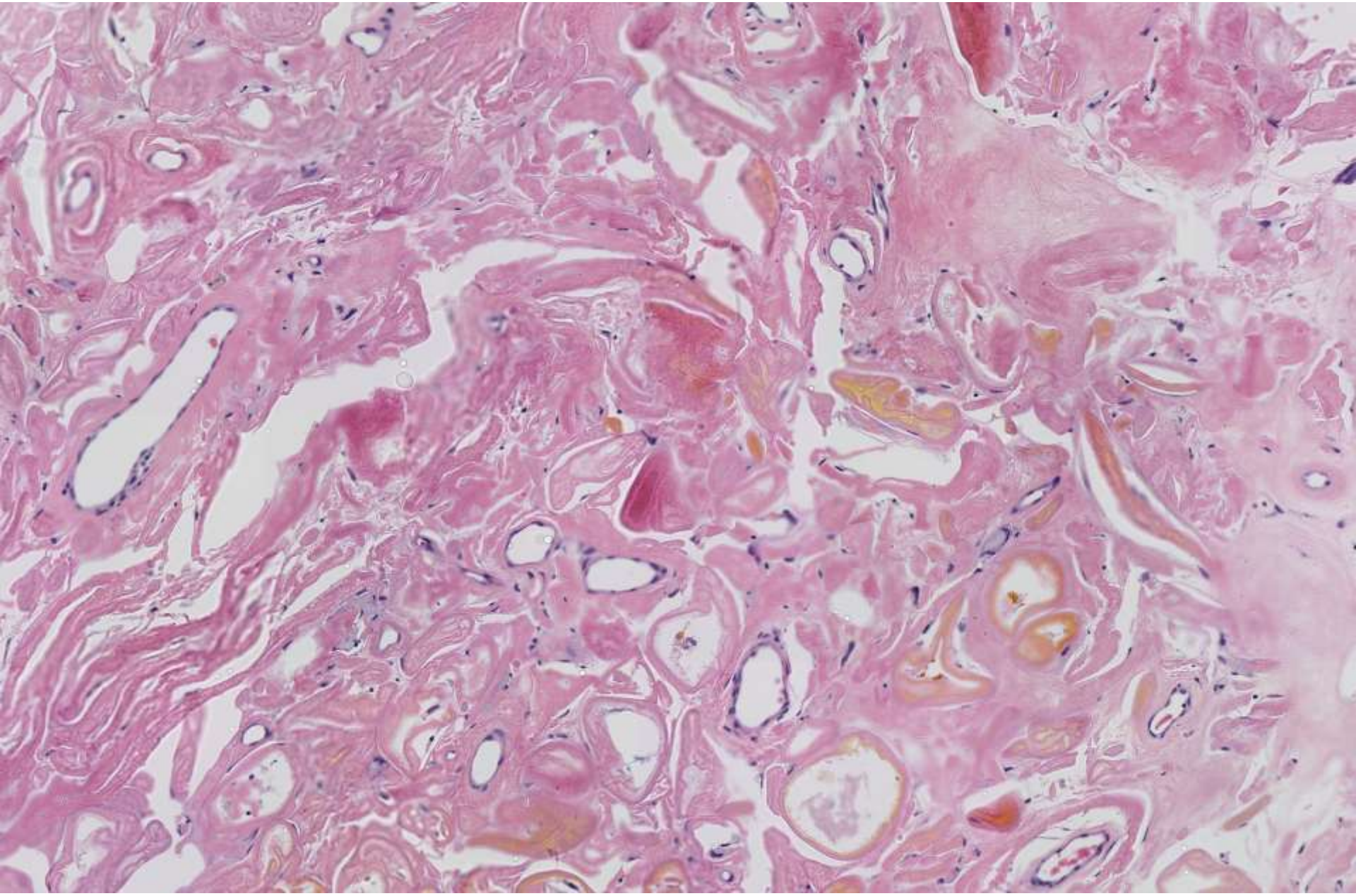


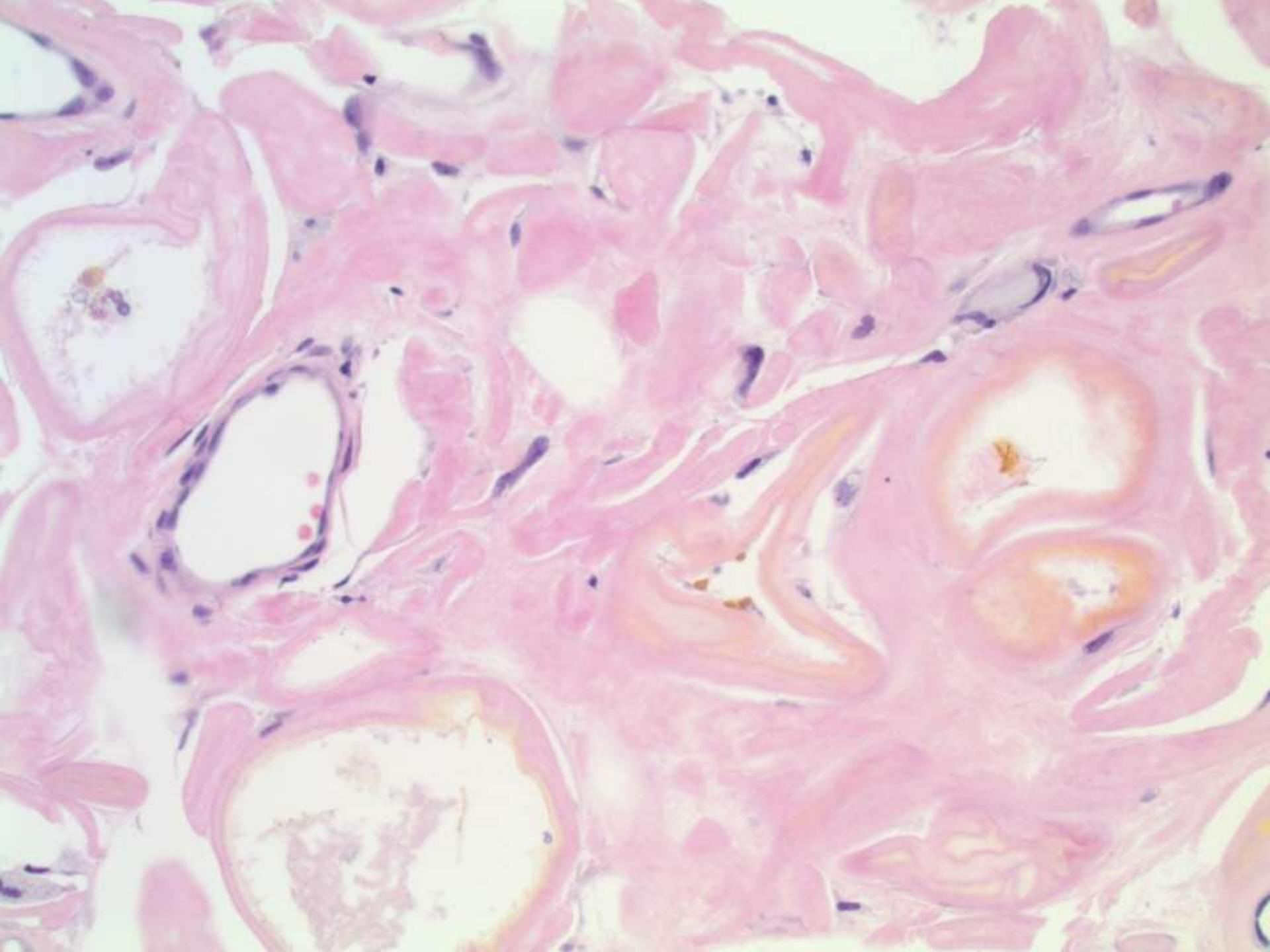






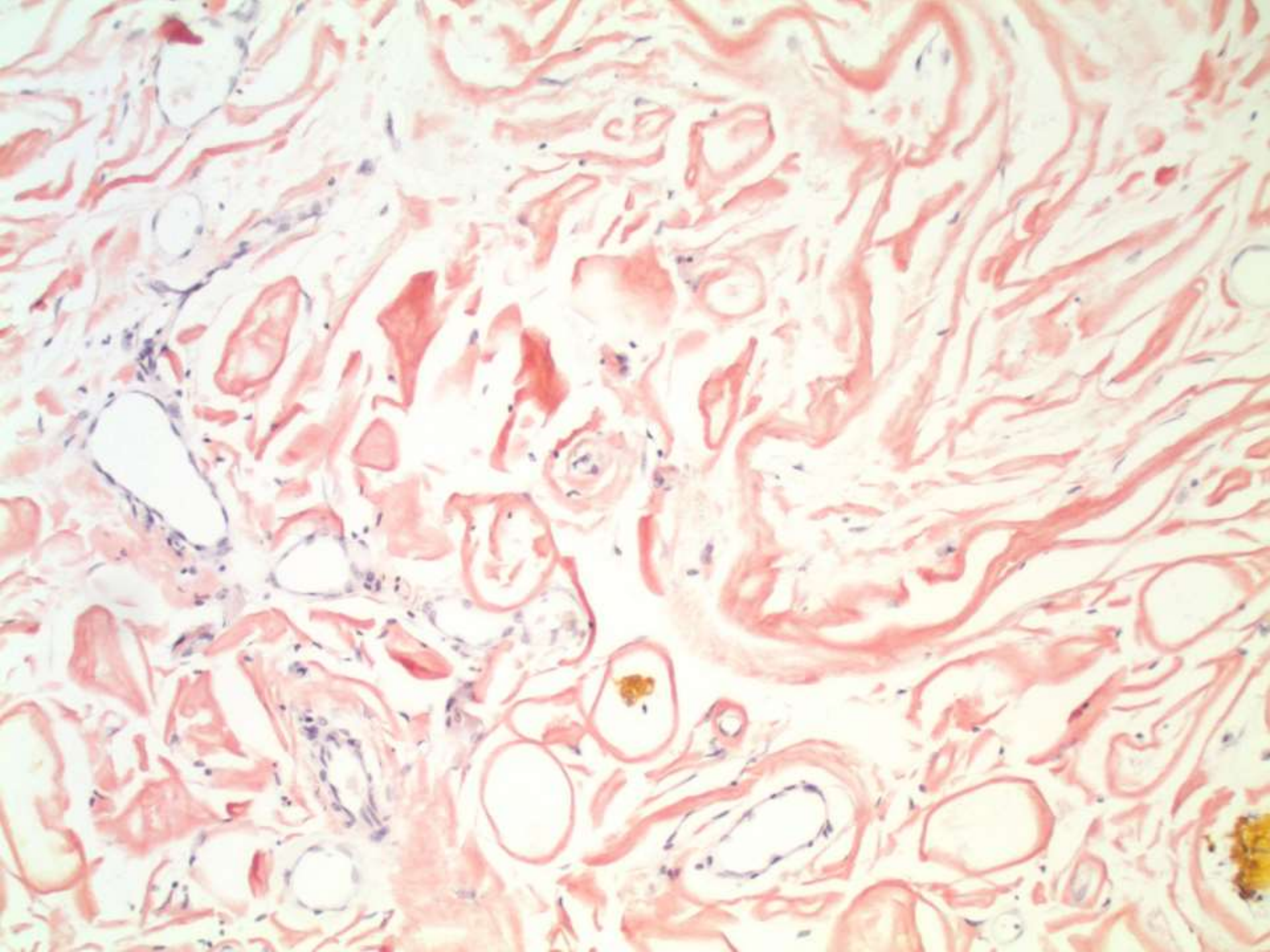


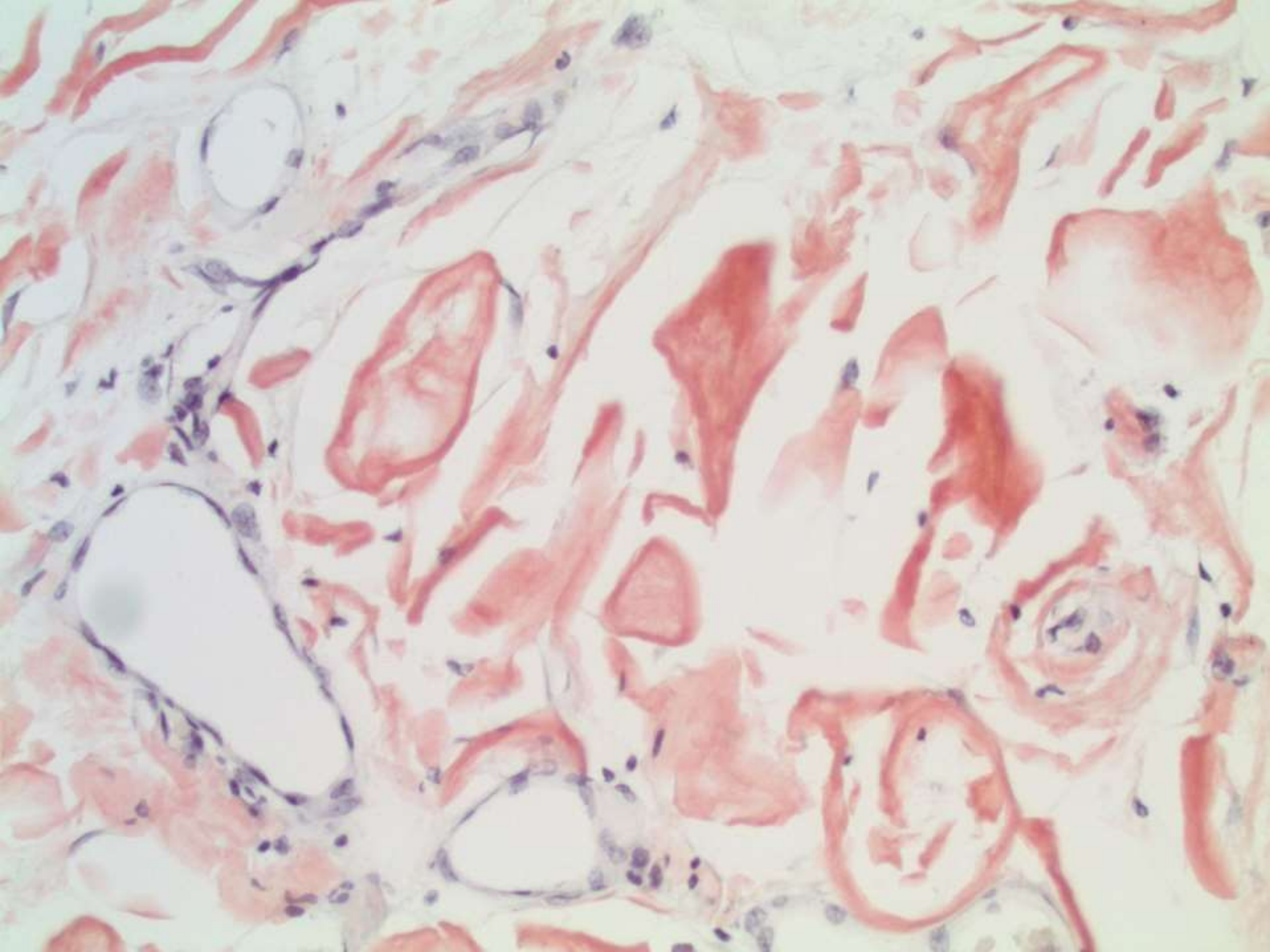


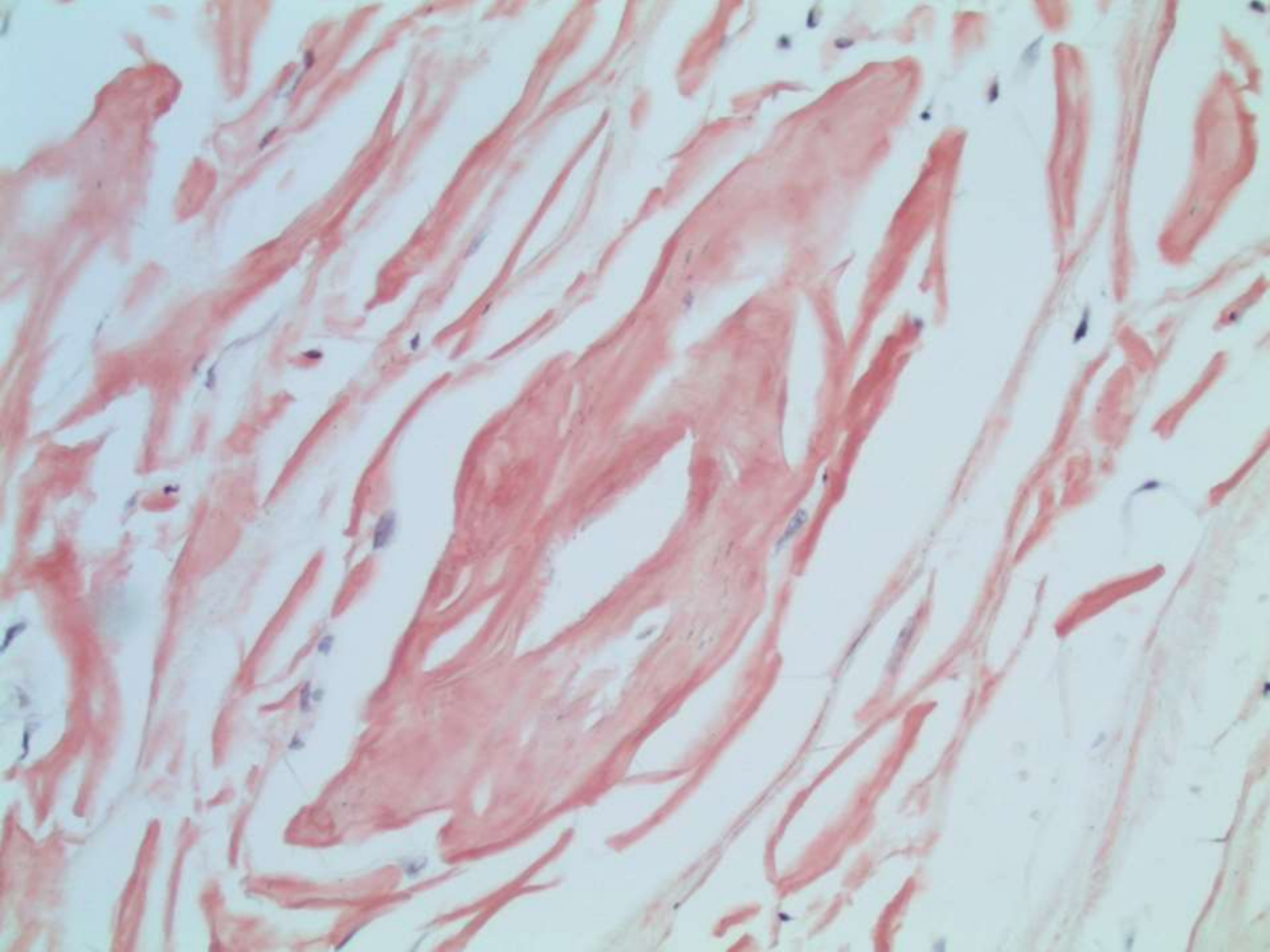


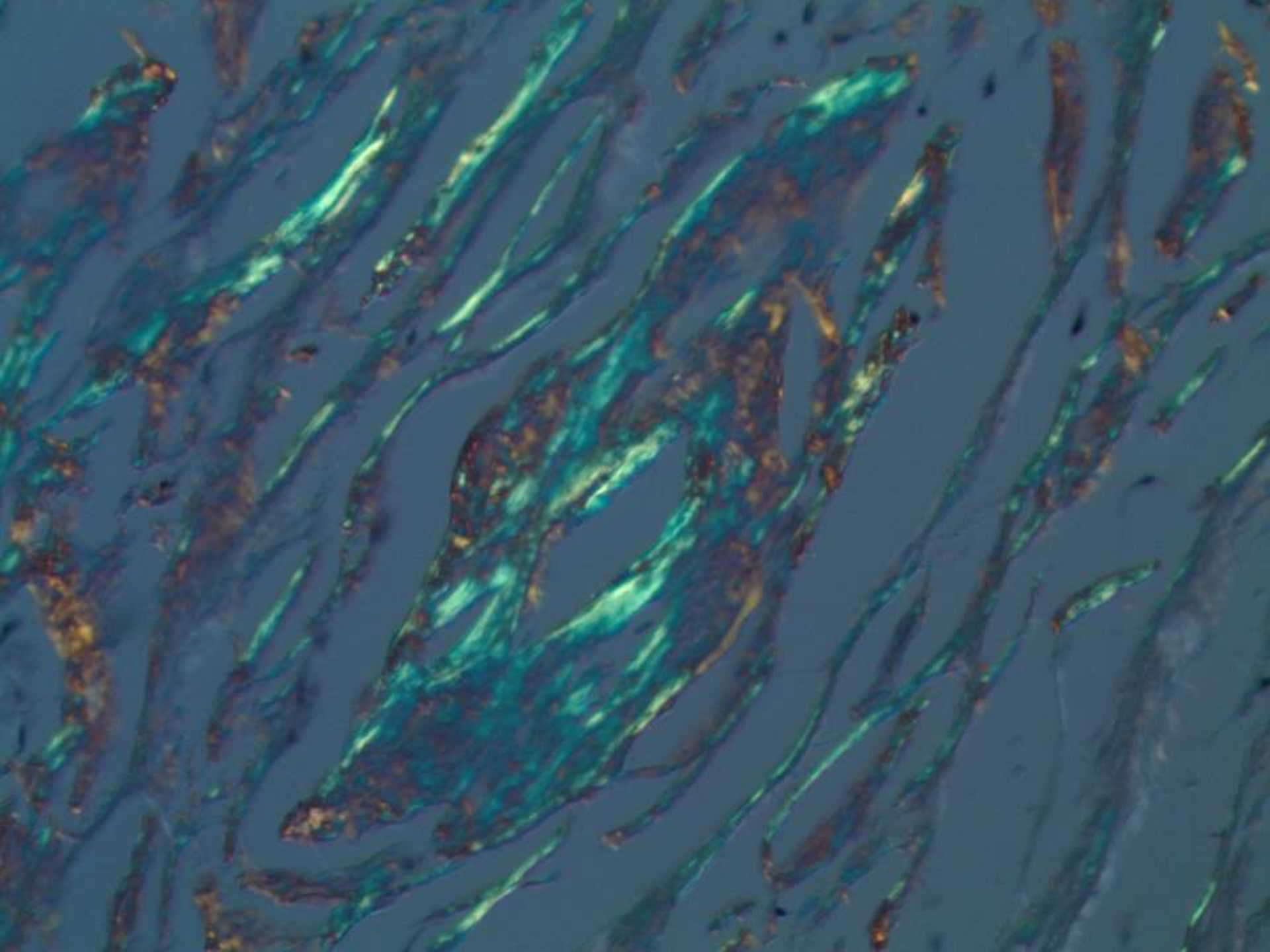
DDx

- Fat necrosis
- Amyloidosis (amyloidoma)
- Crystal or light chain deposition
- Calcified fibrous tumor
- Non-specific stromal hyalinization









DDx

- Fat necrosis
- Amyloidosis (amyloidoma)
- Crystal or light chain deposition
- Calcified fibrous tumor
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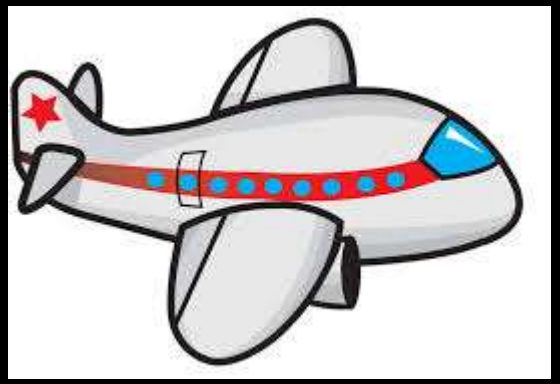
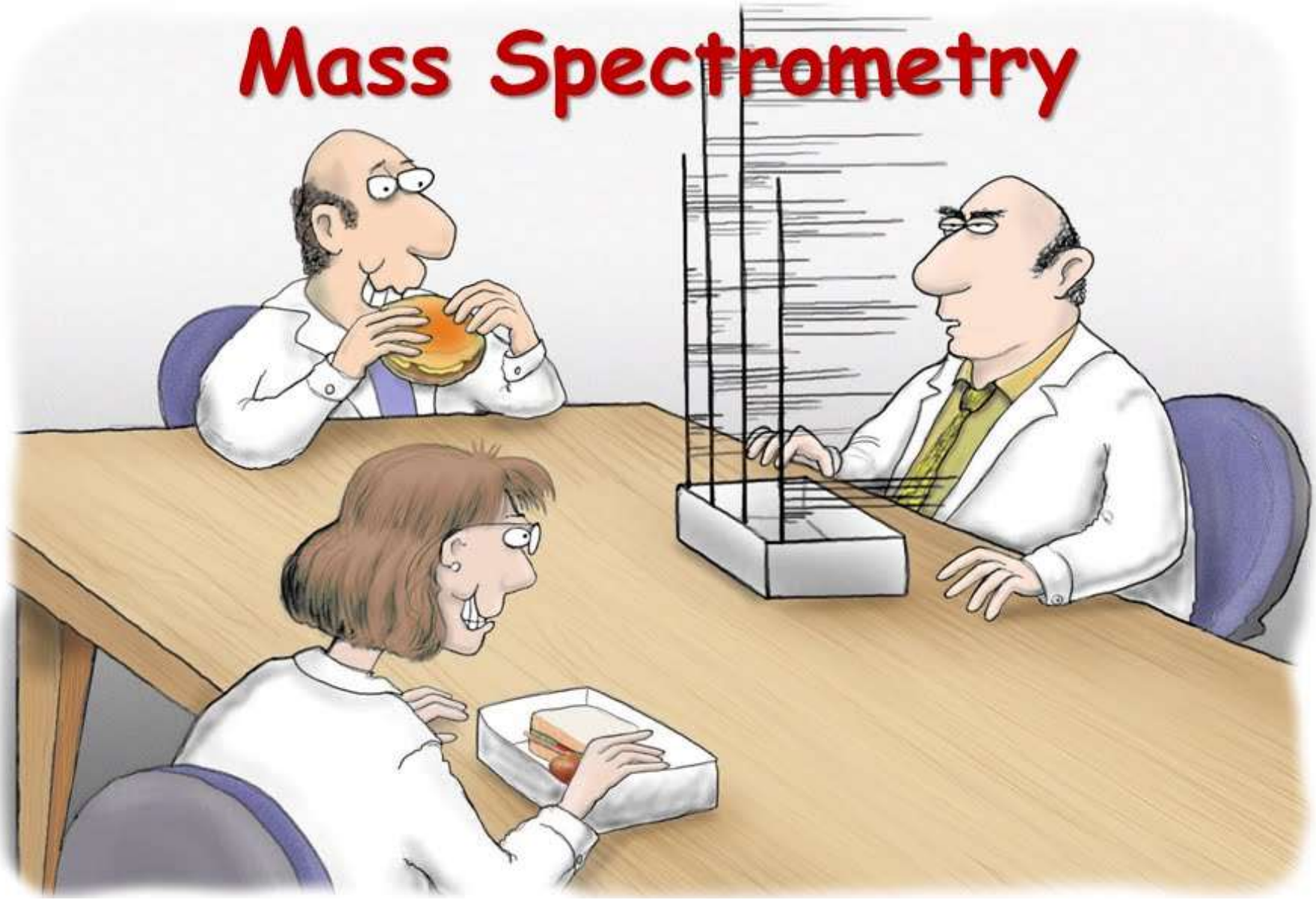
Dx:

- **Amyloidosis (amyloidoma)**

NOW WHAT?



Mass Spectrometry



"Okay—who put my lunch through the mass spectrometer..?"

Liquid chromatography tandem mass spectrometry

- **AIns peptide protein**
  - Insulin type amyloid deposition

Final diagnosis

- **Amyloidosis (amyloidoma)**
  - AIns (insulin) type
  - Consistent with iatrogenic form of localized amyloidosis to areas of insulin injection in diabetic patients

Protein precursor of amyloid deposits

Protein class	Precursor protein (abbreviation)	Amyloid type	Clinical type
High-density apolipoproteins	(Apo) serum AA	AA	Associated with amyloid-complicating chronic infections or inflammatory diseases, and some heredofamilial periodic fever syndromes such as familial Mediterranean fever.
	Apolipoprotein A-I (ApoAI)	AApoAI	Age-related amyloid occurring in the aortic intima, and some hereditary neuropathic or cardiopathic amyloidoses[1,2]. May deposit in heart, liver, or kidney; C-terminal variants deposit in larynx and skin.
	Apolipoprotein A-II (ApoAII)	AApoAII	Some hereditary nephropathic amyloidoses[3].
	Apolipoprotein A-IV (ApoAIV)	AApoAIV	Renal (medullary) amyloidosis.
	Apolipoprotein C-II (ApoCII)	AApoCII	Some hereditary nephropathic amyloidoses[4].
	Apolipoprotein C-III (ApoCIII)	AApoCIII	Some hereditary nephropathic amyloidoses[5].
Immunoglobulin (Ig) gene superfamily	Ig L chain/Ig H chains (IgL/IgH)	AL/AH	Primary and myeloma-associated amyloidosis.
	Beta-2 microglobulin	Abeta2m	Dialysis amyloidosis. Variant molecule has been described in a family affected by gastrointestinal disease, autonomic neuropathy, and sicca syndrome due to amyloid[6].
Neuroendocrine	(Pro)Calcitonin	ACal	Amyloid complicating C-cell thyroid tumors.
	Islet amyloid	AIAPP	Islet cell amyloid in insulinomas, type II diabetes mellitus, and aging[7].
	Atrial natriuretic peptide	AANF	Isolated atrial amyloidosis of aging.
	Prolactin/Apro	APro	Prolactinomas/aging.
	Insulin	AIns	Local amyloid complicating use of the insulin pump.
Cytoskeleton-related	Gelsolin	AGel	Hereditary neuropathic amyloid associated with corneal lattice dystrophy and cutis laxa (Meretoja syndrome)[8].
	Keratin	Does not yet have nomenclature designated	Cutaneous amyloid.
	Keratoepithelin	AKer	Hereditary granular, lattice, and Avellino corneal dystrophies[9].
Transport protein	Transthyretin (TTR; prealbumin)	ATTR	Hereditary neuropathic and/or cardiopathic amyloids; vitreous amyloidosis; leptomeningeal or renal amyloid in some kindreds; senile systemic amyloidosis[10].

Cerebrovascular/neurodegeneration	Amyloid precursor protein (APP)	ABeta	Hereditary and sporadic Alzheimer disease; congophilic cerebral angiopathy[11,12].
	Prion protein (PRP)	APrPsc	Hereditary and sporadic spongiform encephalopathies[13].
	BRI gene product	ABri/ADan	Hereditary dementias (British and Danish types)[14].
	Cystatin C (Cys - C)	ACys	Hereditary cerebrovascular hemorrhage with amyloidosis (Icelandic type)[15].
Coagulation protein	Fibrinogen alpha chain	AFib	Hereditary nephropathic amyloidosis[16].
Enzyme	Lysozyme	ALys	Hereditary nephropathic amyloidosis; may have marked hepatic, splenic and gastrointestinal amyloid deposits[16].
Very low-density lipoprotein (LDL)/Chylomicron-associated apolipoprotein	Apolipoprotein IV (Apo AIV)	AApoAIV	Renal medulla and systemic disease[17].
Lung surfactant protein	Lung surfactant protein	ASPC	Interstitial lung disease[18].
Galectin	Galectin 7	AGAl7	Localized skin[19].
Other	Keratoepithelin	AKer	Various familial corneal dystrophies[9].
	Lactoferrin	ALac	Corneal amyloidosis associated with trichiasis.
	Odontogenic ameloblast-associated protein	AOaap	Calcifying epithelial odontogenic tumors (CEOTs).
	Semenogelin 1	ASem1	Senile seminal vesicle amyloid.
	Lactadherin	AMed	Senile aortic amyloid; media deposition.
	Leukocyte chemotactic factor 2	ALect2	Amyloid nephropathy; hepatic amyloid.
	Corneodesmosin	ACor	Localized amyloid involving cornified epithelia, hair follicles.
	Enfuvirtide	AEnf	Localized amyloid occurring at the injection site of an HIV therapeutic [20].
	p53 (tumor suppressor)	Ap53	Amyloid aggregates in tumor cell lines and breast tumors[21].