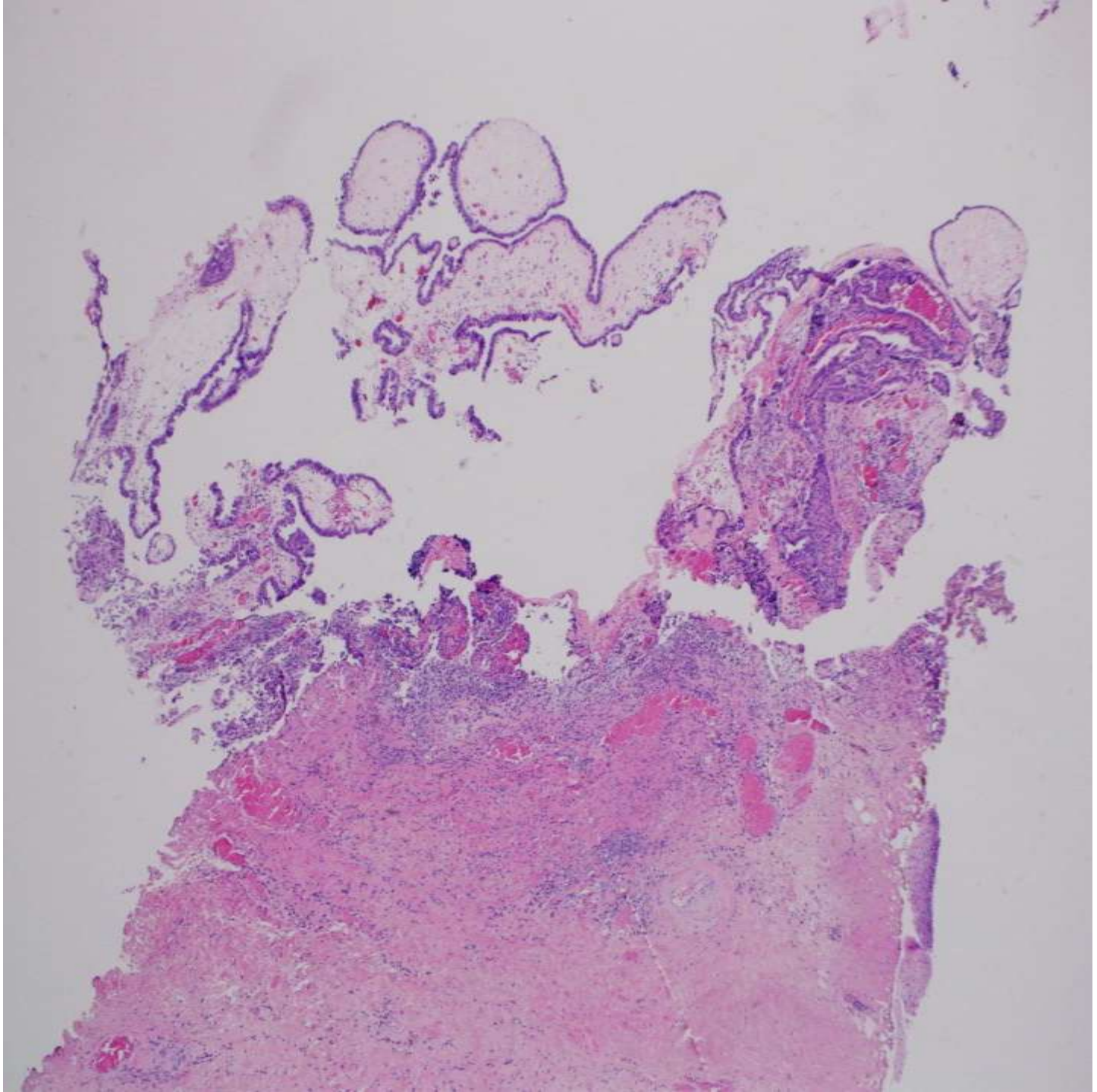
# FEB 2020 DIAGNOSIS LIST

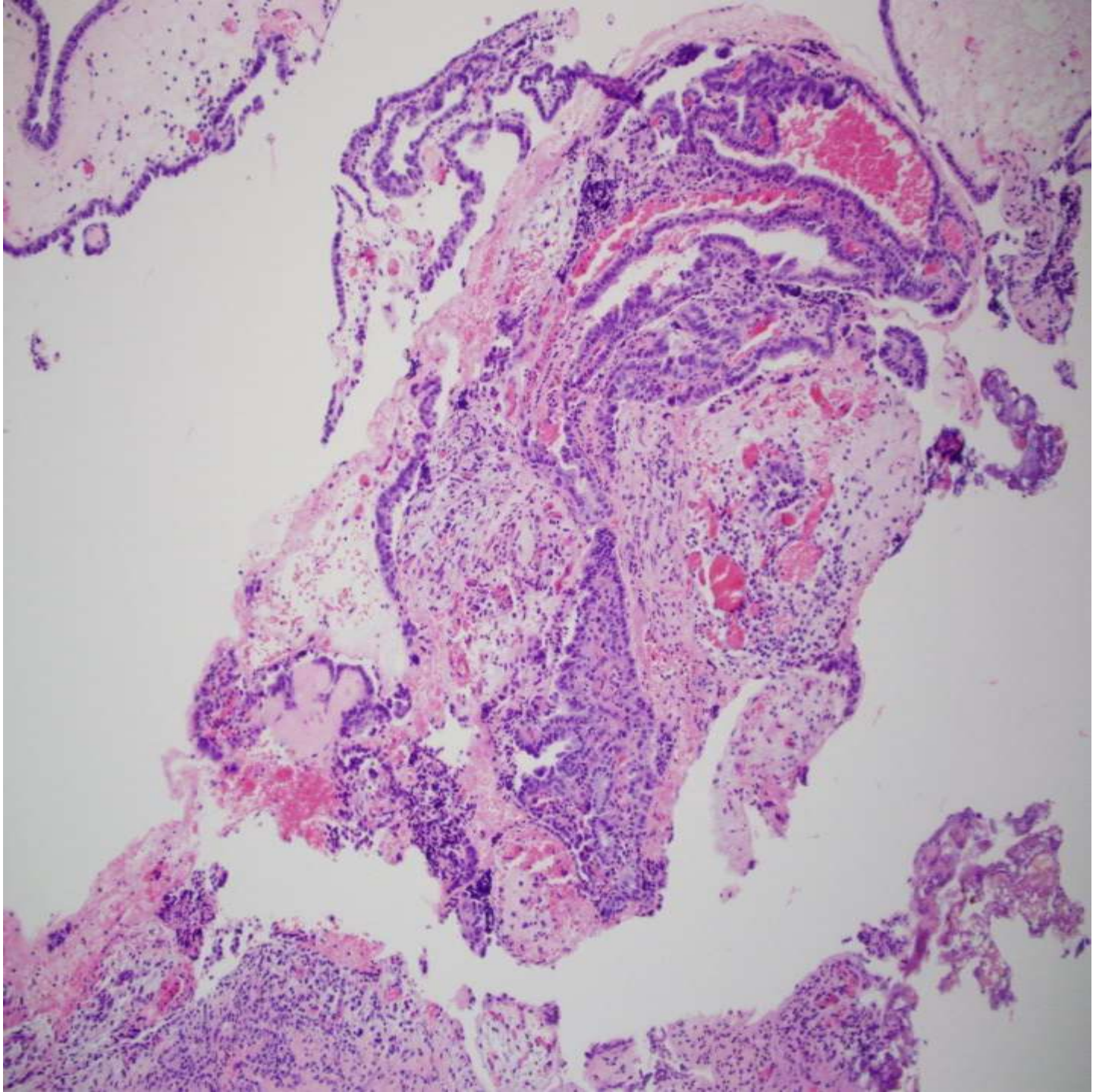
20-0201: clear cell carcinoma (urethra/GU pathology)
20-0202: renal cell carcinoma with leiomyomatous stroma, TSC1 mutated (kidney/GU pathology)
20-0203: necrotizing myopathy, favored secondary to PD1 inhibitor (muscle/neuropathology)
20-0204: NTRK fusion sarcoma (cervix/GYN pathology)
20-0205: leiomyoma with fumarate hydratase deficiency morphology (uterus/GYN pathology)
20-0206: follicular lymphoma with features suspicious for histiocytic sarcoma (lymph node/hematopathology)
20-0207: lymphoepithelioma-like carcinoma (bladder/GU pathology)
20-0208: primary melanoma (bladder/GU pathology)
20-0209: low grade fibromyxoid sarcoma, DOG1+ (soft tissue/soft tissue pathology)
20-0210: CD8 positive cutaneous T-cell lymphoma (skin/dermatopathology & hematopathology)

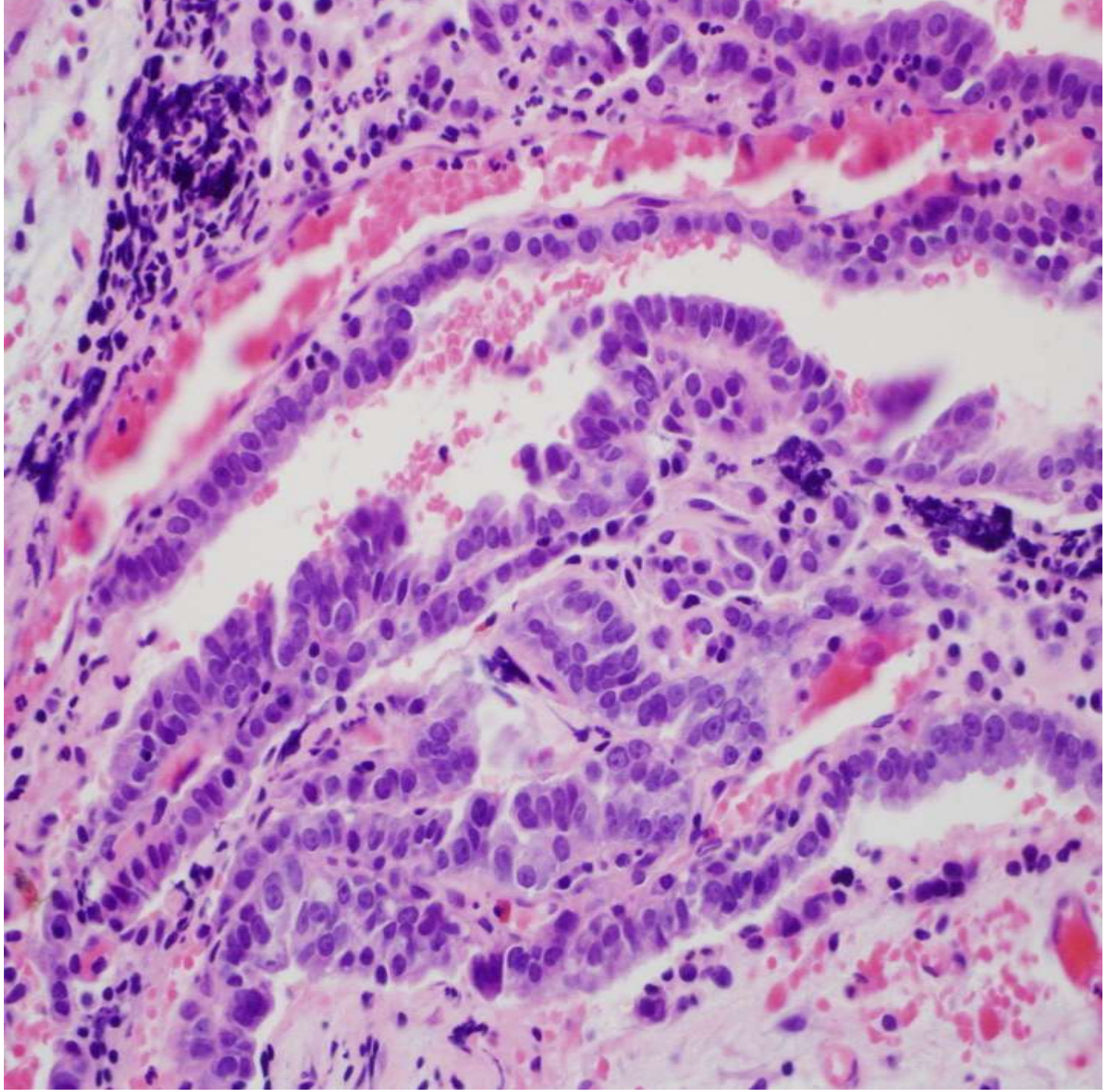
# 20-0201

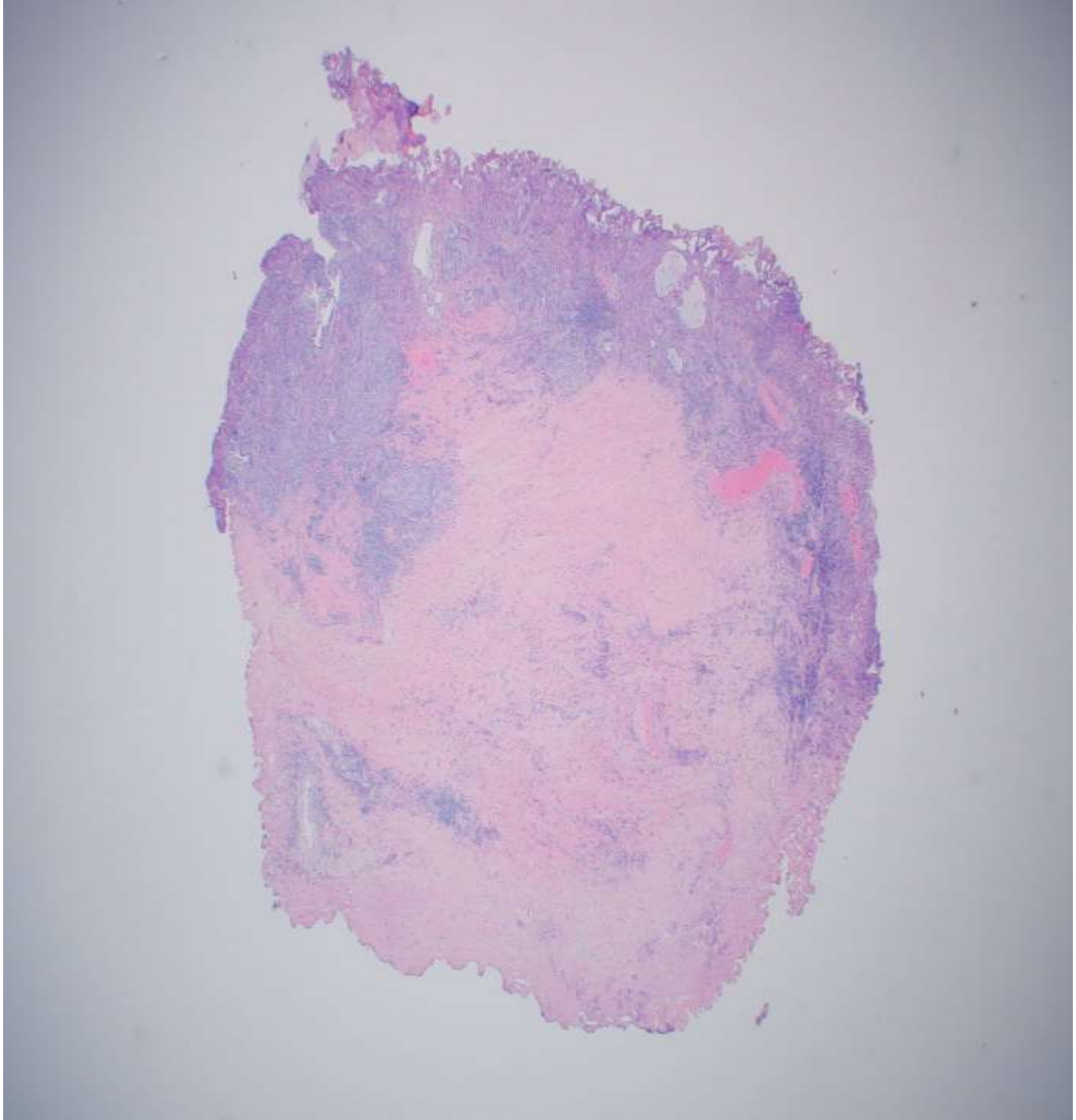
**Christian Sebastian/Emily Chan/Jeff Simko; UCSF**

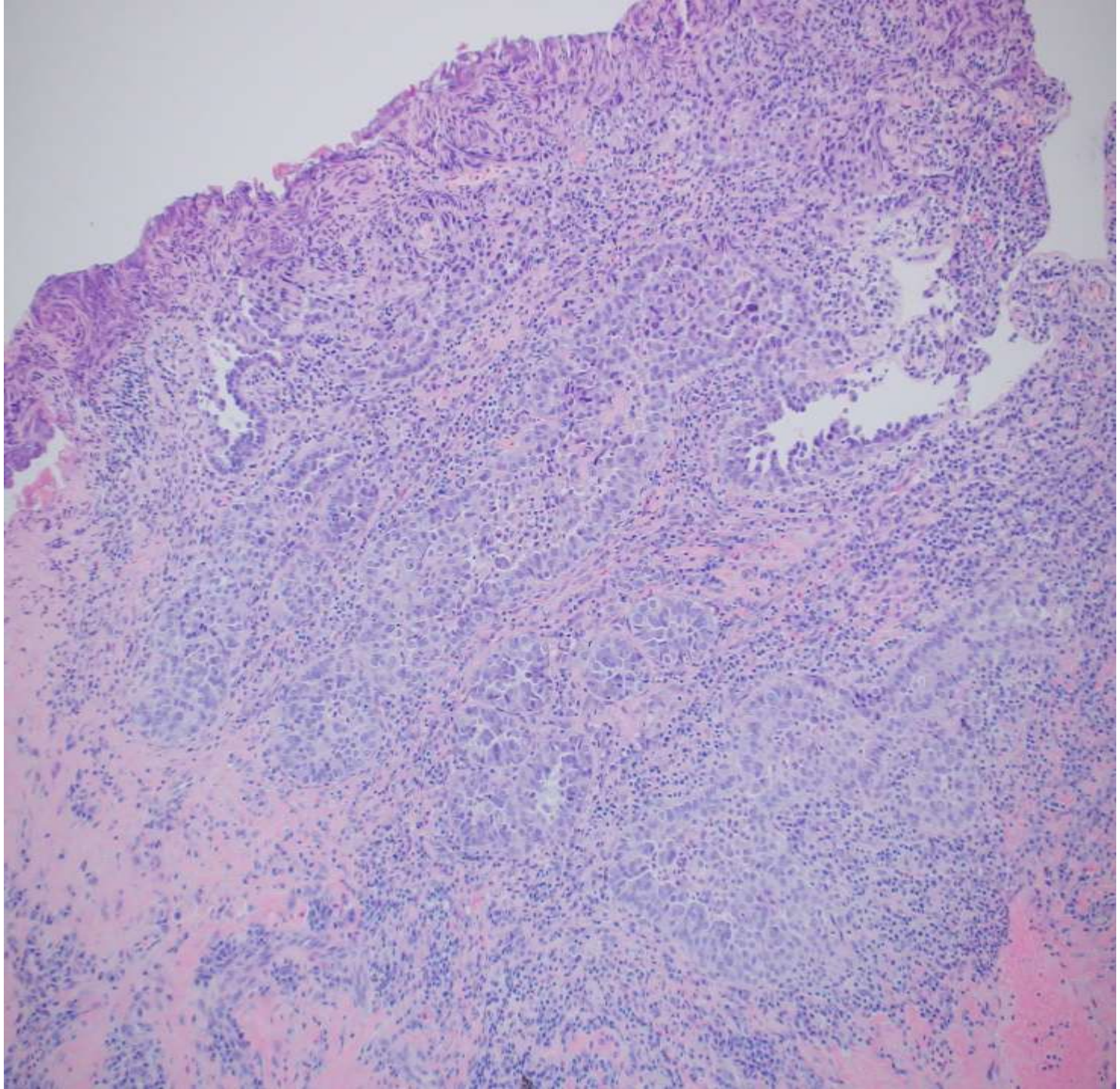
66-year-old M with h/o colorectal cancer treated with radiation >15 years prior, now with a urethral stricture. He undergoes transurethral resection of a papillary mass in the left lateral proximal bulbar and prostatic urethra.

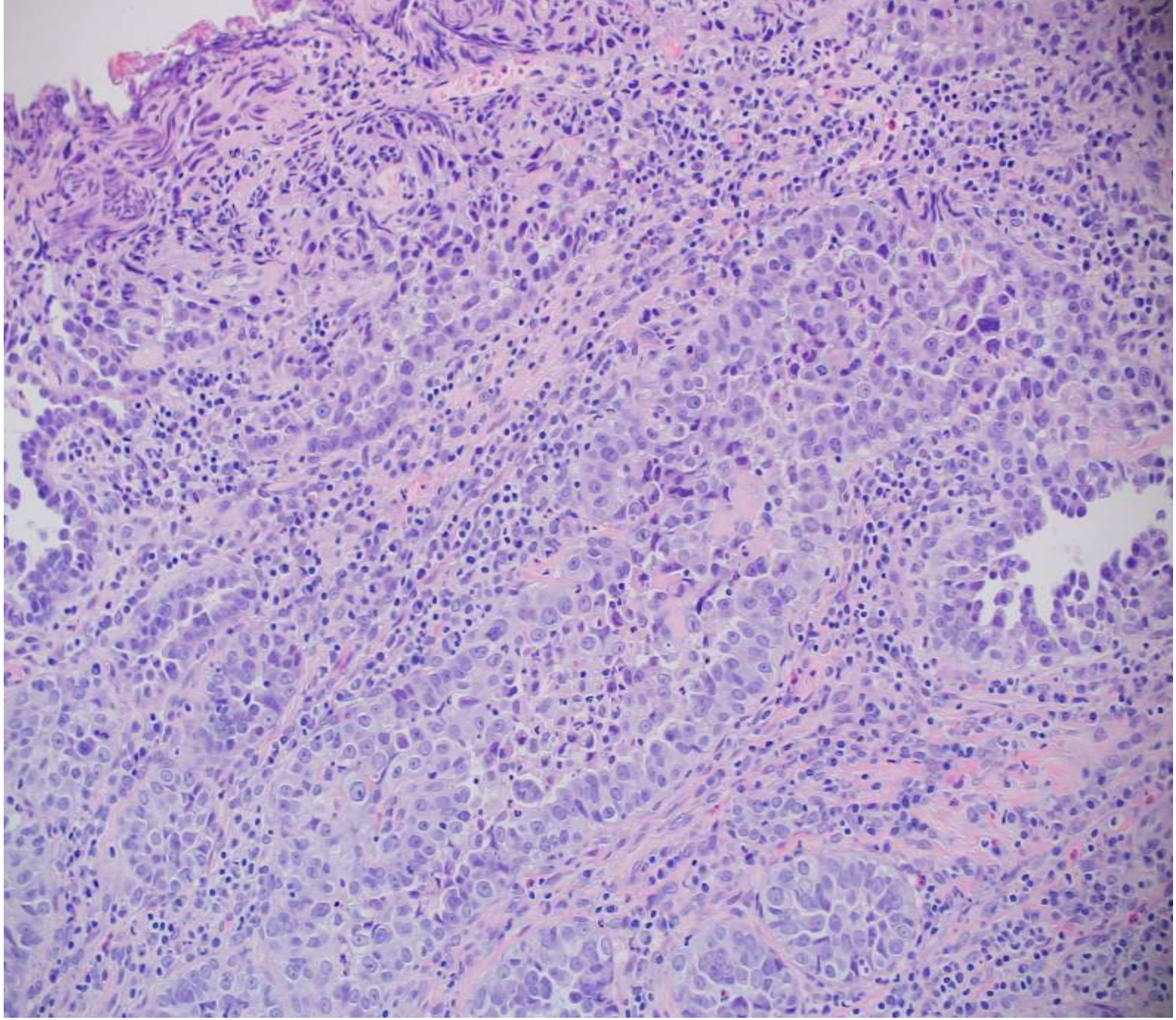


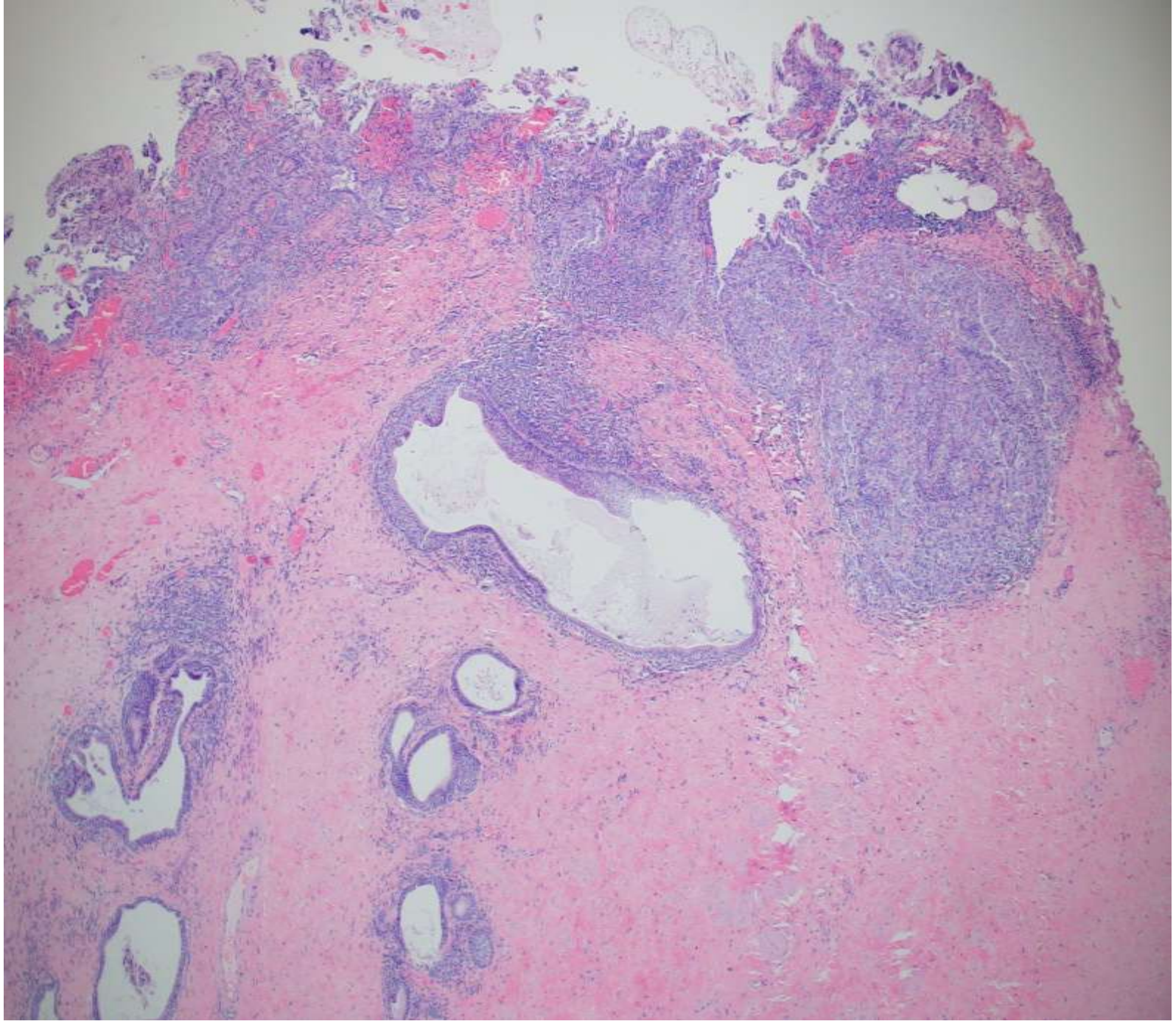


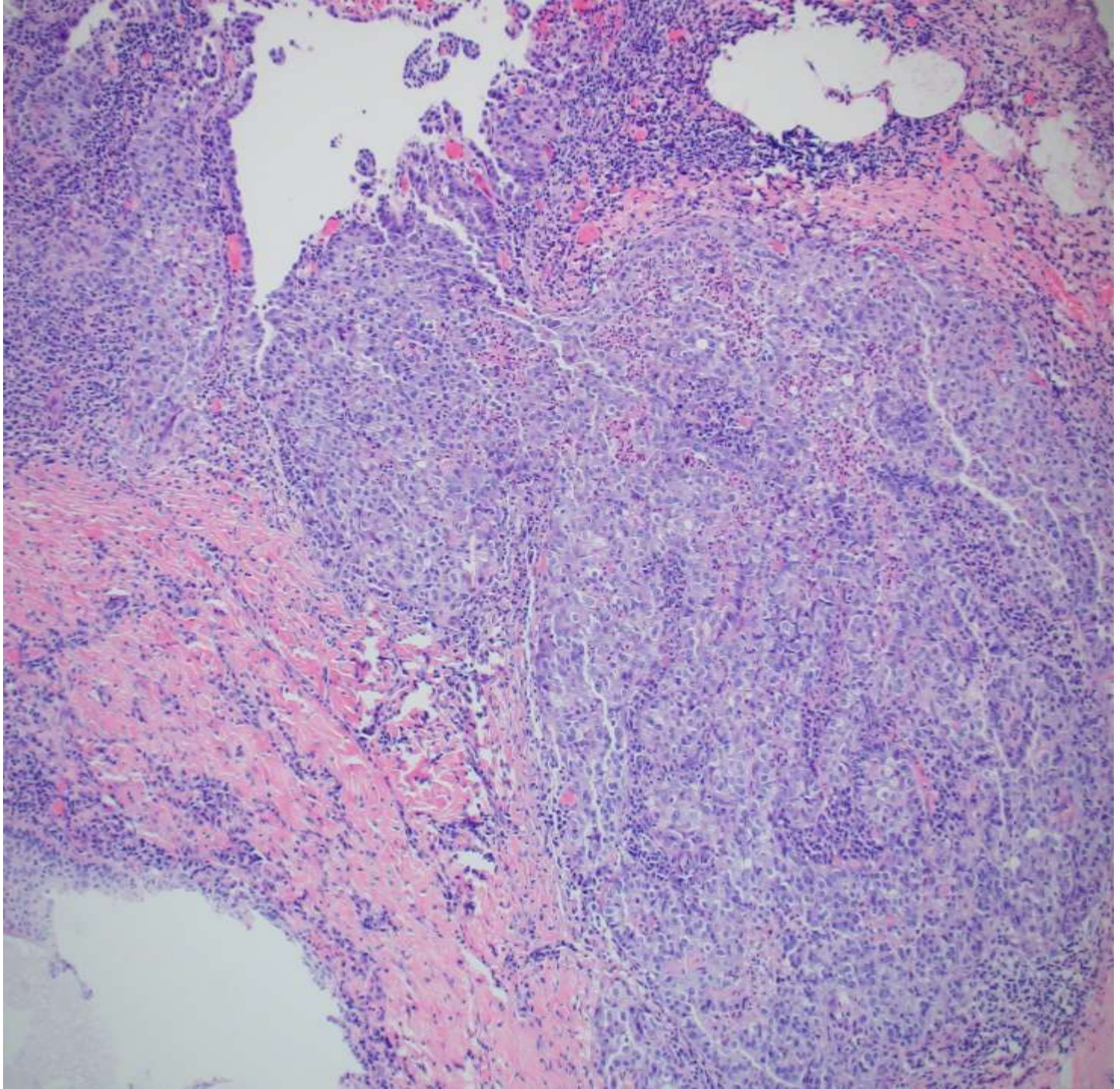


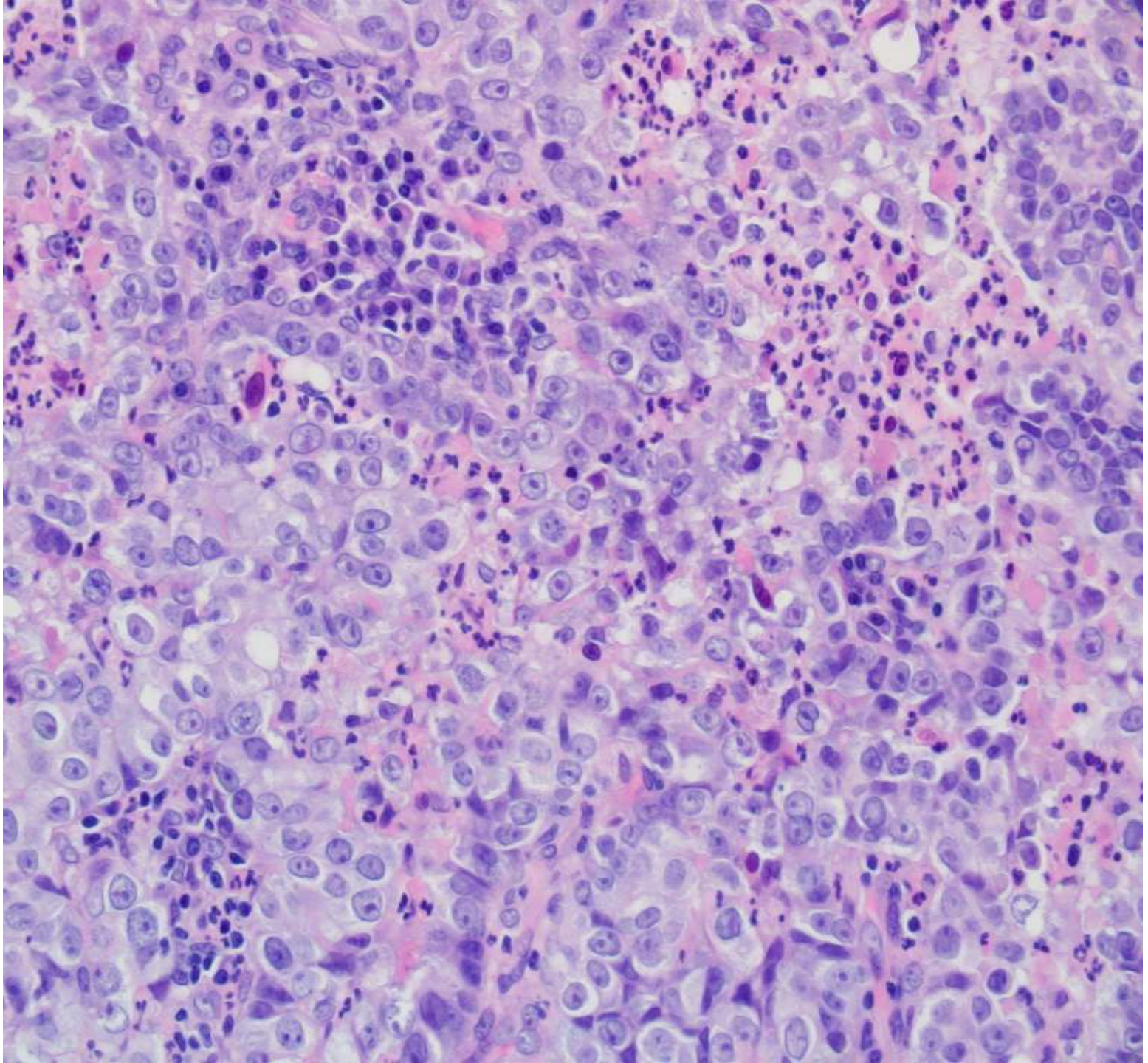






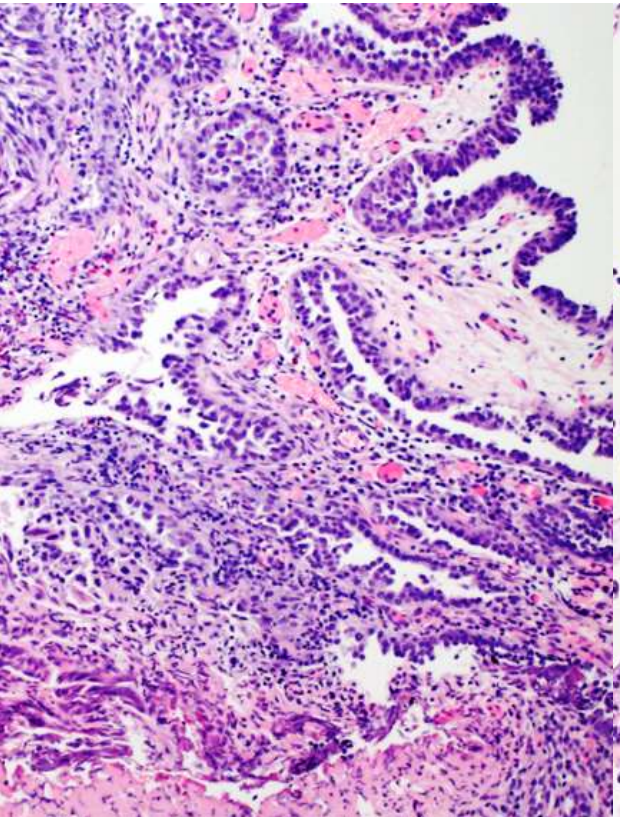


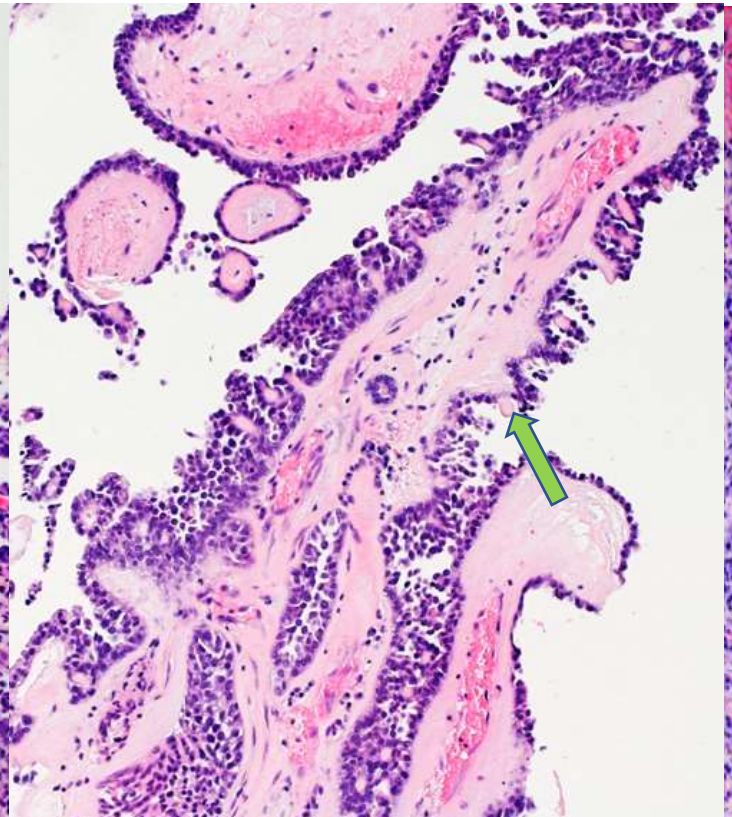


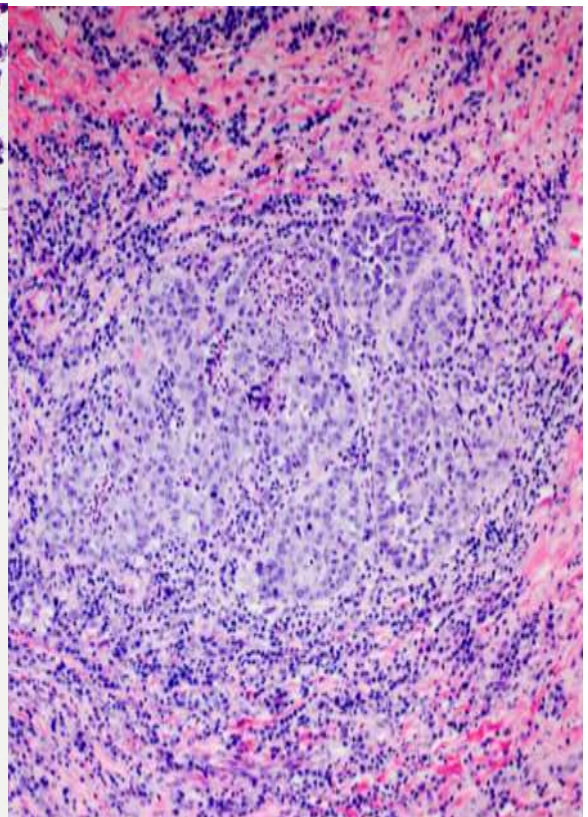


# Architecture:  Variable.

- Tubulocystic, papillary, and solid architecture.
- Hyalinized fibrovascular cores.

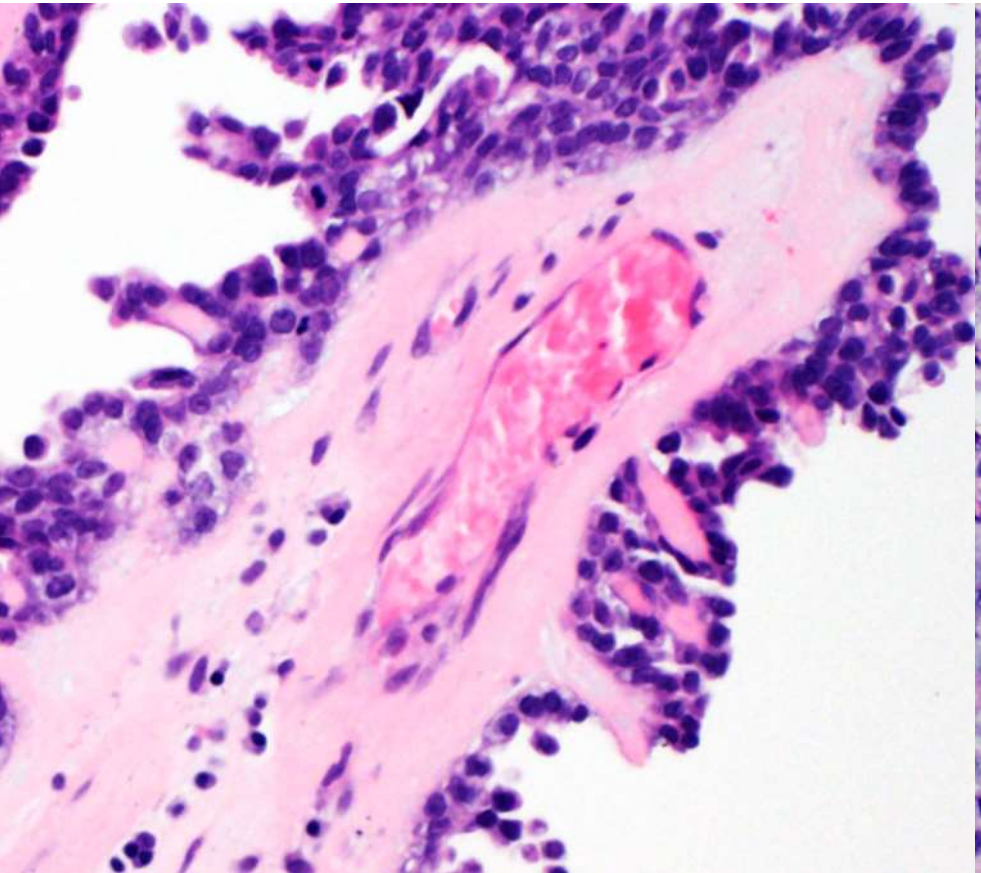


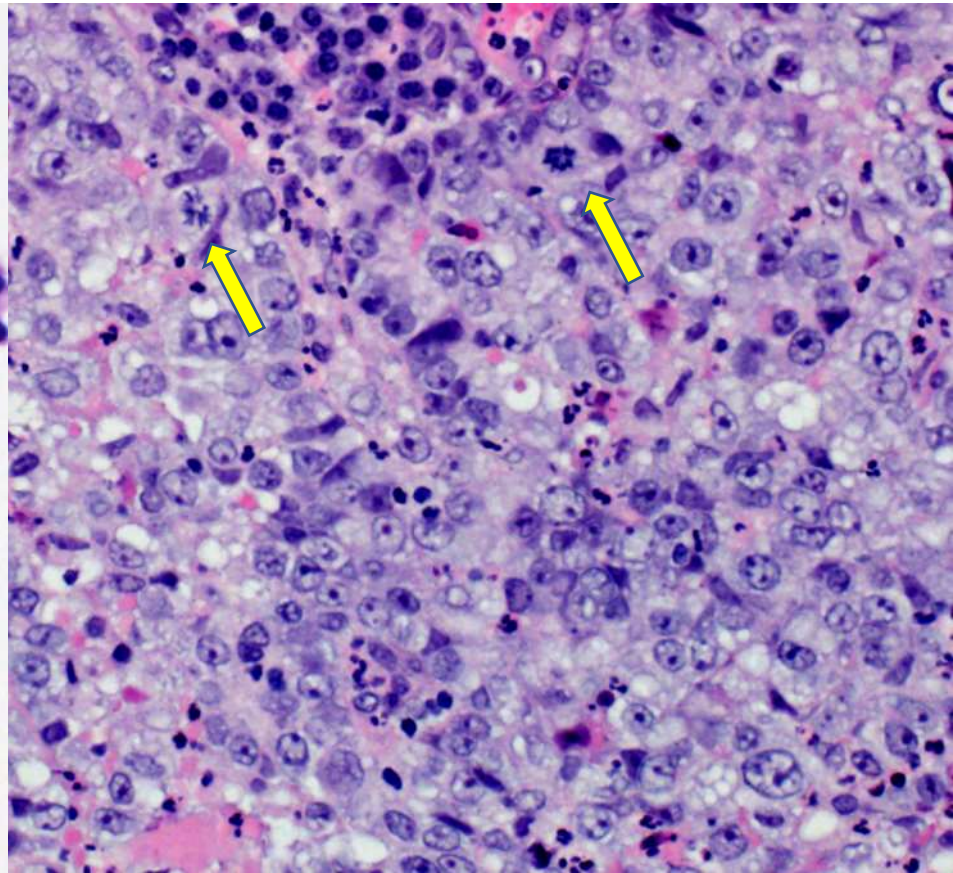




# Cytology

- Single/pseudostratified layer of atypical hobnail cells in papillary and glandular foci.
- Variable amounts of clear to eosinophilic cytoplasm.
- Focally high mitotic rate.  Some areas with uniformity to nuclei.





# Differential diagnosis.

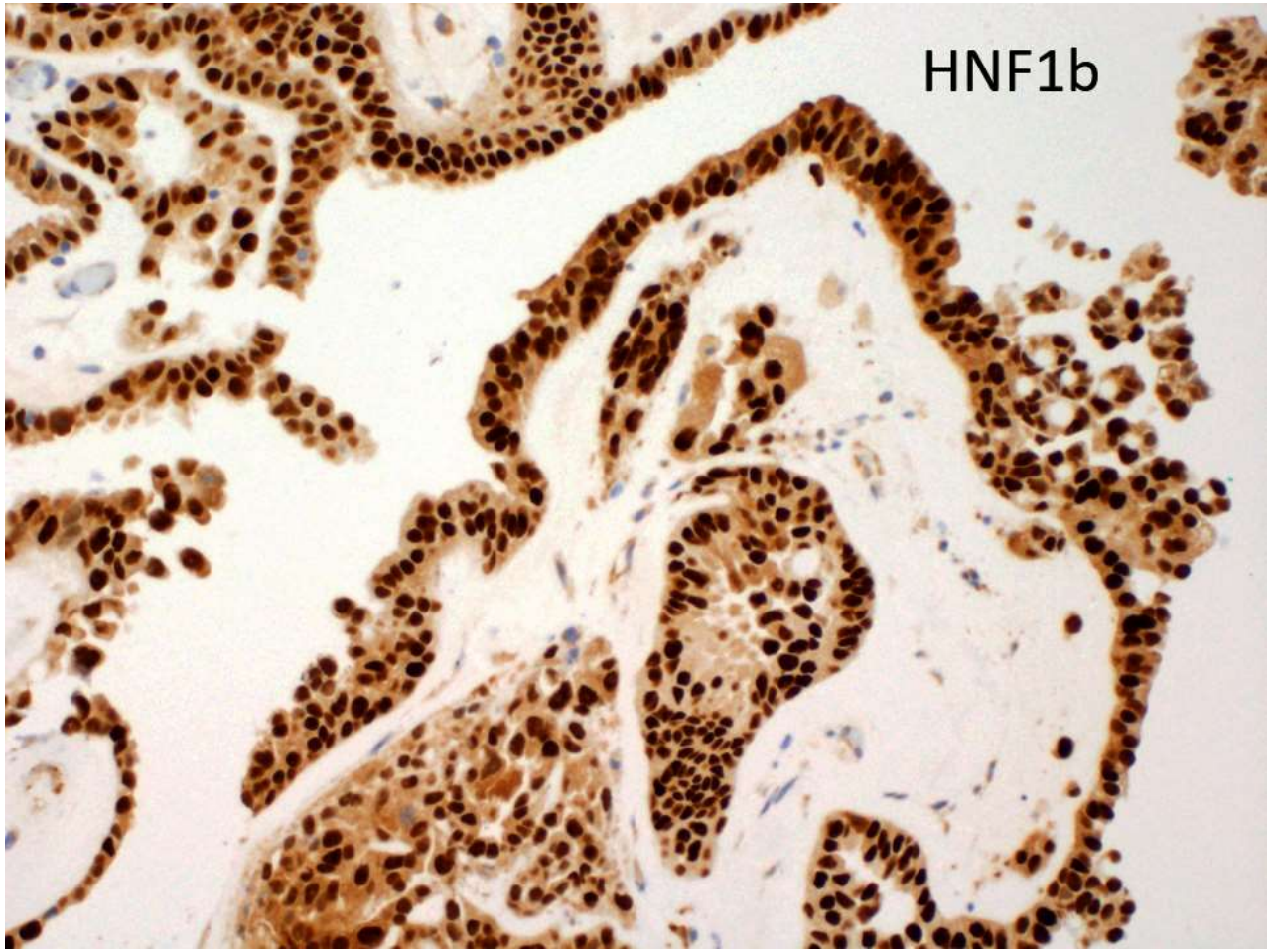
Primary

- Urothelial carcinoma.
  - Gata-3+, P63+, Uroplakin+, CK20+.
- Clear cell adenocarcinoma.
  - Pax-8+, Napsin+, HNF1b+, Ki67 >10%
- Nephrogenic adenoma.
  - Pax-8+, HNF1b -
- Adenocarcinoma of urethra.
  - CK20+, CDX-2+, Beta-catenin cytoplasmic.

Metastatic/direct extension

- Prostatic adenocarcinoma.
  - NKX3.1+, PSA+.
- Colonic adenocarcinoma.
  - CDX2+, SATB2+, CK20+, nuclear beta-catenin.
- Metastatic GYN clear cell adenocarcinoma (if female).
  - Pax-8+, Napsin+, HNF1b+ (Exclude with imaging).
- Metastatic cervical adenocarcinoma.

# Immunohistochemistry




Pax-8: Positive

Napsin: Variable/positive

HNF1b: Positive

AMACR: Positive

P63: Negative

Gata-3: Negative

NKX3.1: Negative

PSA: Negative

P53: Non-contributory

Ki67: >10%

# Differential diagno

Nomenclature: Can be confused with more common *clear cell variant of urothelial carcinoma*.

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- Nephrogenic adenoma.
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- Metastatic GYN clear cell adenocarcinoma (if female).
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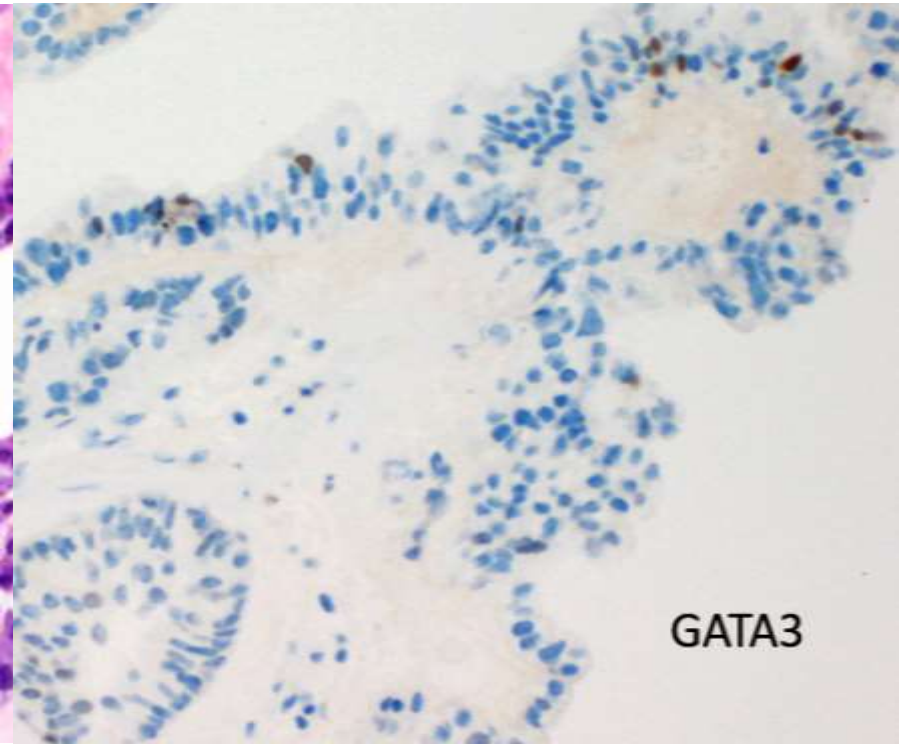
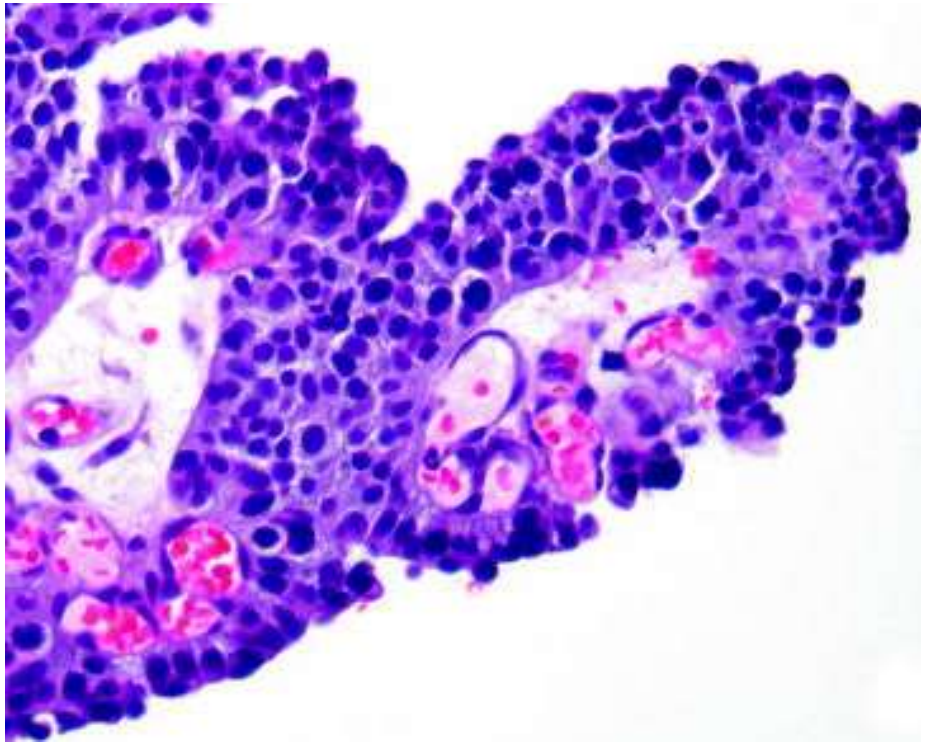
# Clear cell adenocarcinoma of the GU tract.

- Rare subtype of urothelial adenocarcinoma of uncertain histogenesis.
- Occurs more often in women (2-3:1), often in association with urethral diverticulum.
- Histologically and immunophenotypically analogous to clear cell carcinoma of gynecologic origin.
  - MAY NOT ALWAYS HAVE CLEAR CELLS.
- Rarity makes prognostication difficult, but may behave more aggressively than other urotheilal carcinomas when matched for stage.
  - Often treated with cystectomy +/- adjuvant chemoradiotherapy.
  - Do not respond to intravesicular therapy.
  - TURBT of low stage lesions has been successful

# Differential diagnosis: High-Grade Papillary Urothelial Carcinoma



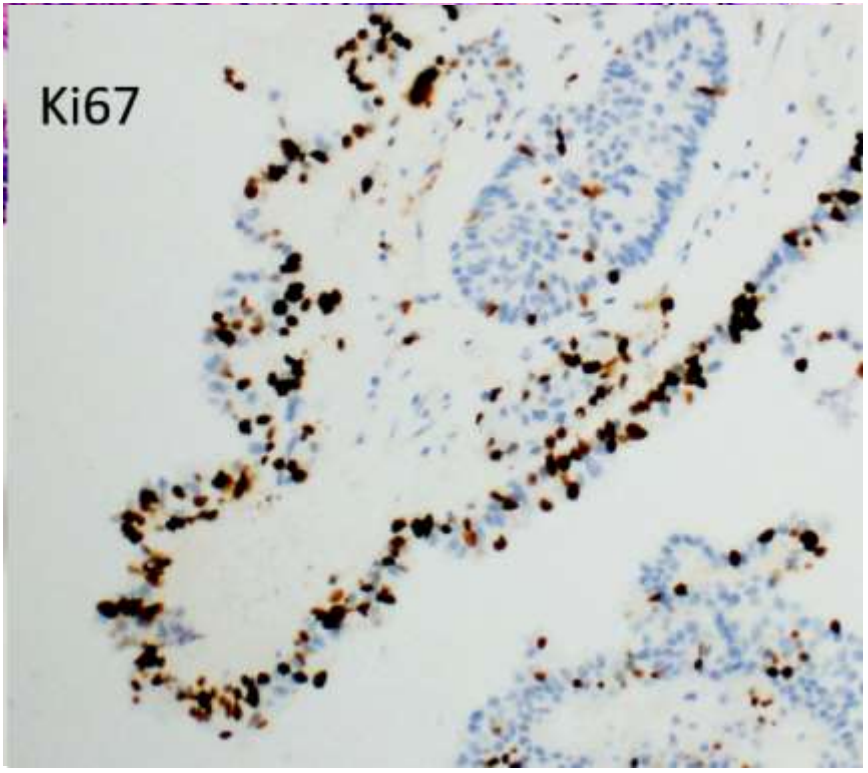

VS



- Single/pseudostratified with hobnail cells
- PAX8+
- Napsin/HNF1b +
- GATA3-, p63-

- Multilayered epithelium, no hobnail cells, greater nuclear pleomorphism.
- Gata3 +
- P63+
- Pax8-/Napsin-/HNF1b-

# Differential diagnosis: Nephrogenic Adenoma

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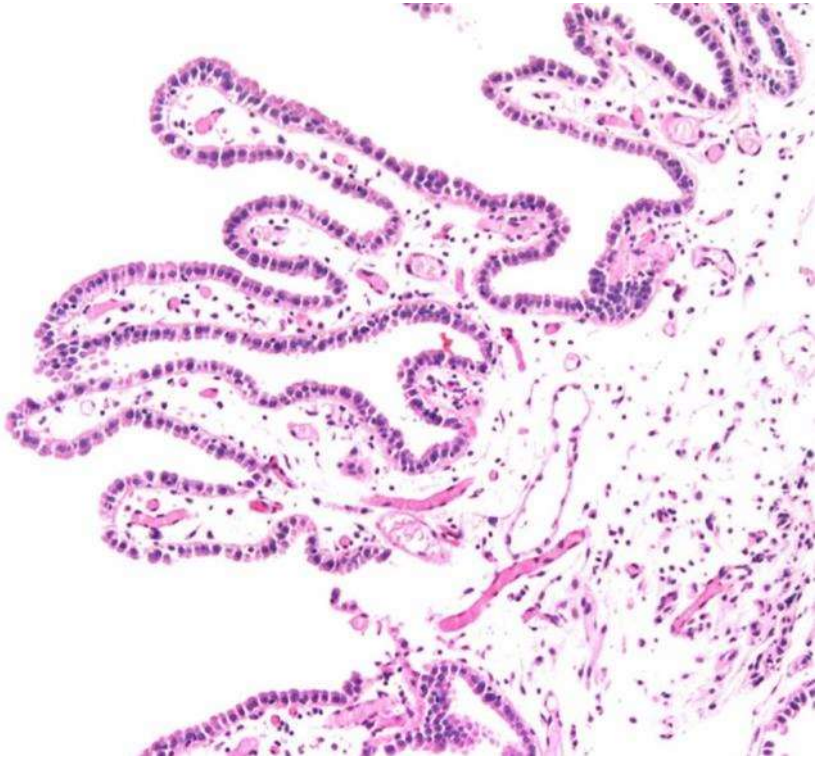


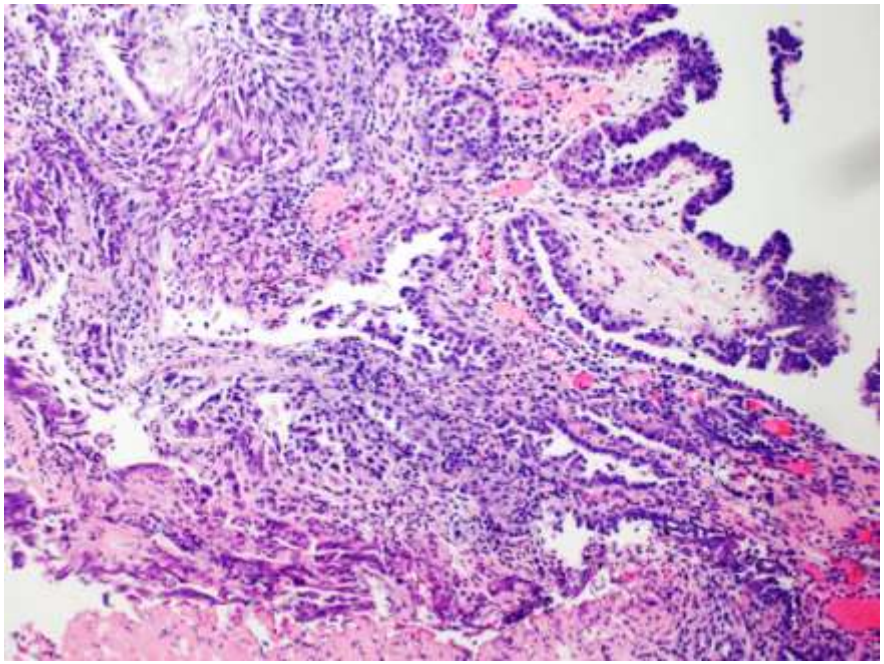
Clear cell adenocarcinoma.

- Increased nuclear atypia, frequent mitosis
- P53 aberrant.
- Ki67 10-80%

Nephrogenic adenoma

- No significant nuclear atypia or mitoses.
- Rarely solid architecture.
- P53 wt
- Ki67 < 5%

# Differential diagnosis: Prostatic adenocarcinoma



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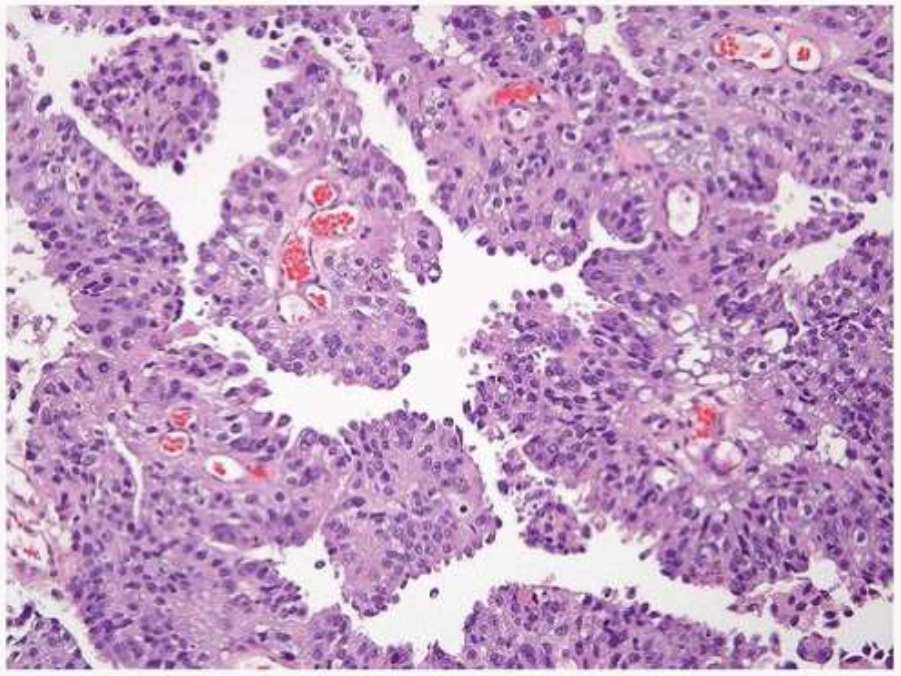


Clear cell adenocarcinoma.
- AMACR + HMWCK - P63 -
- PAX8+
- NKX3.1 -

Prostatic adenocarcinoma with pseudopapillary architecture.
- AMACR + HMWCK - P63 -
- NKX3.1 +
- PSA+

Image from Gordetski J. Epstein, J; Am J Surg Pathol 2014;38:941–945

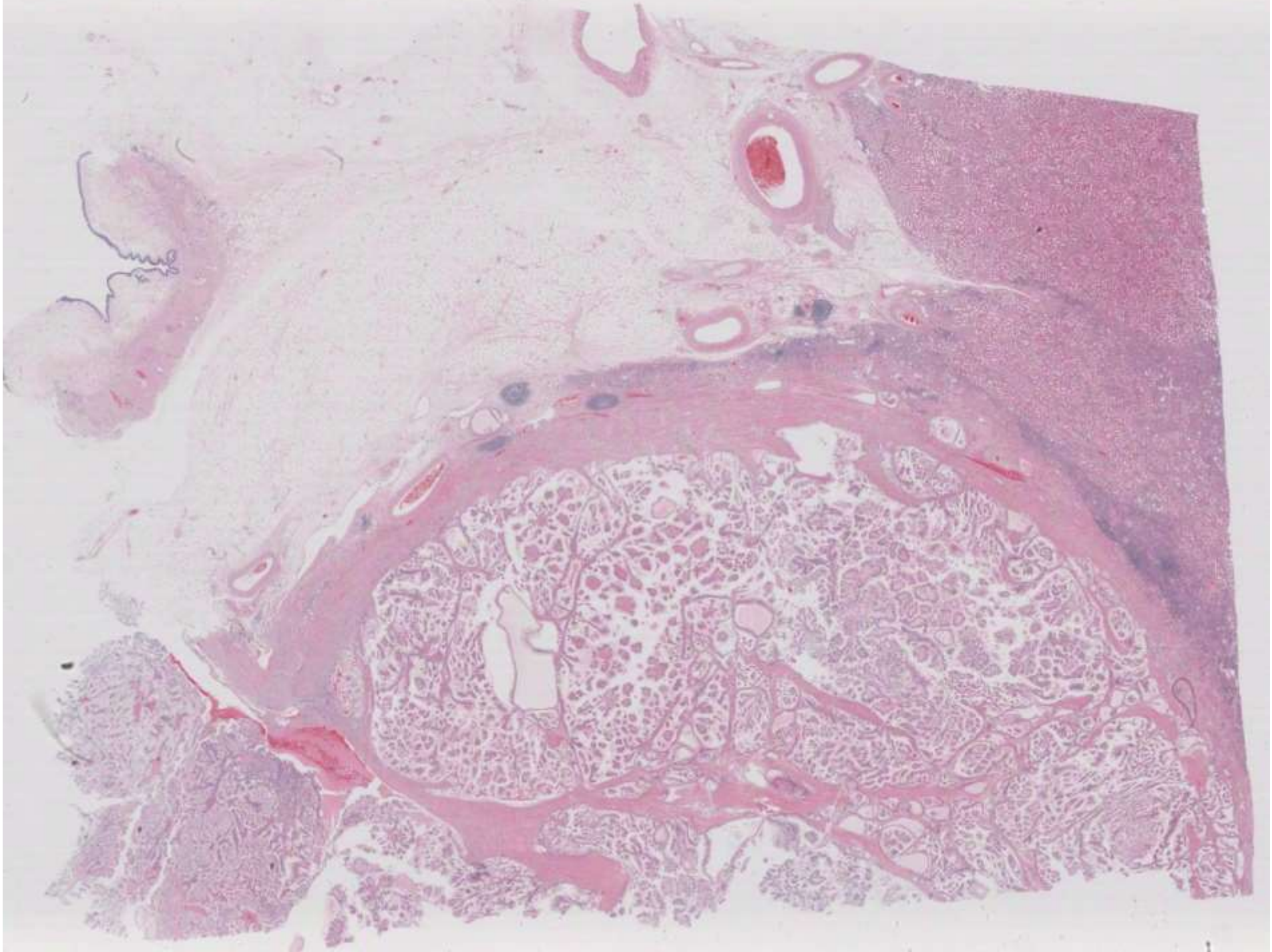
# Follow up.

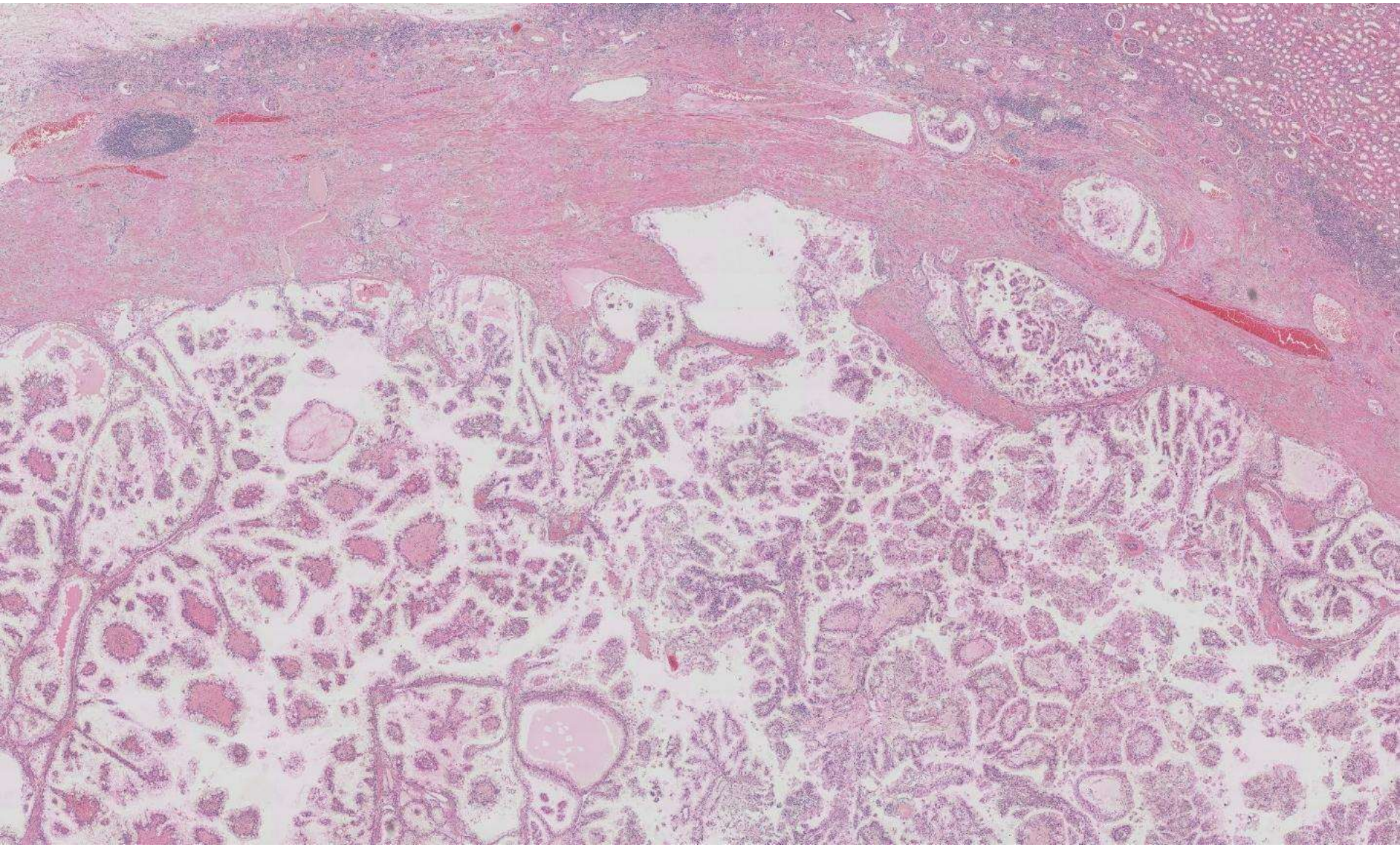
Our patient underwent radical cystoprostatectomy and pelvic LND 1/2018 w/ residual pT1 disease on final pathology. He remains disease free as of 12-2019

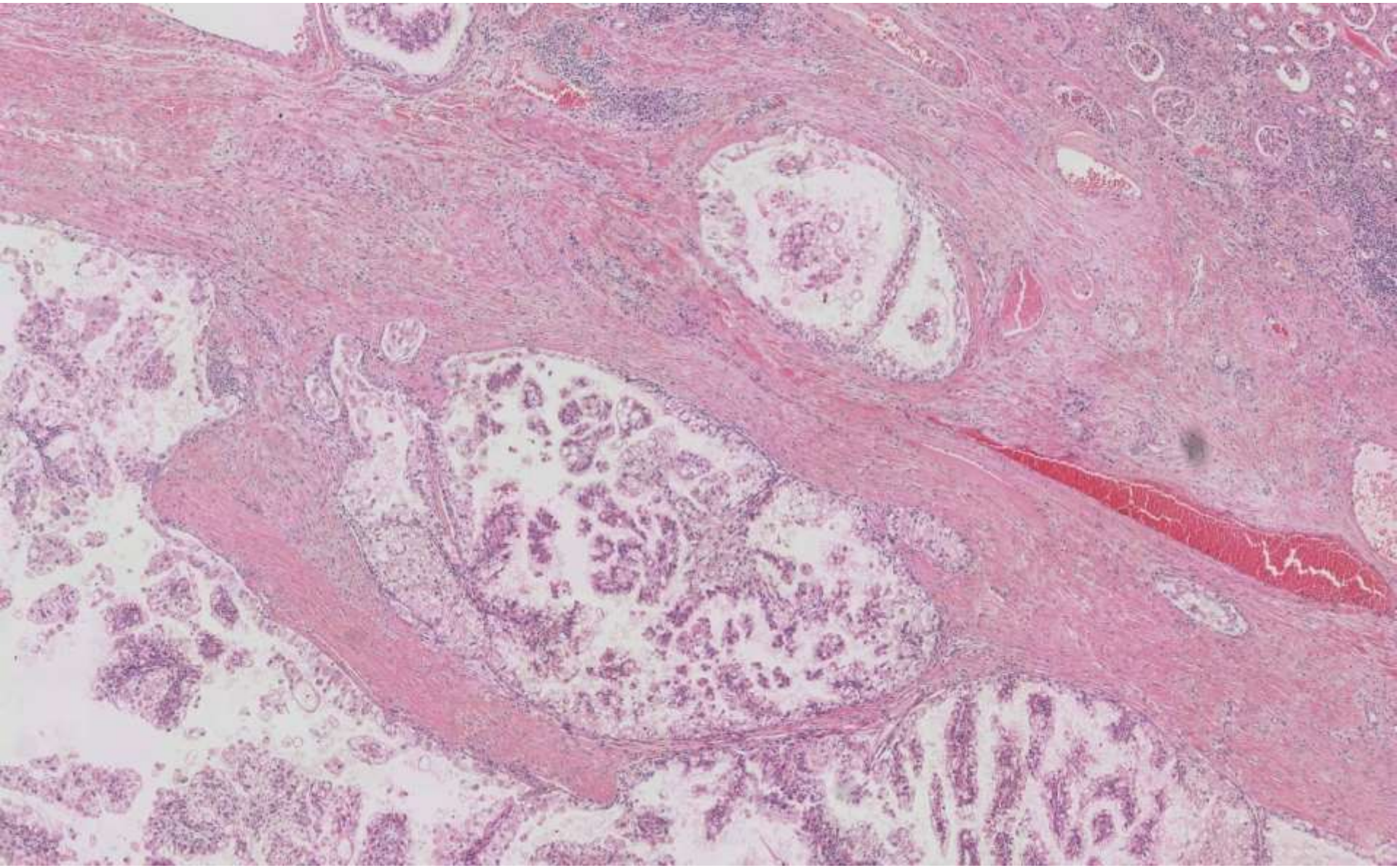
# 20-0202
# scanned slide available!

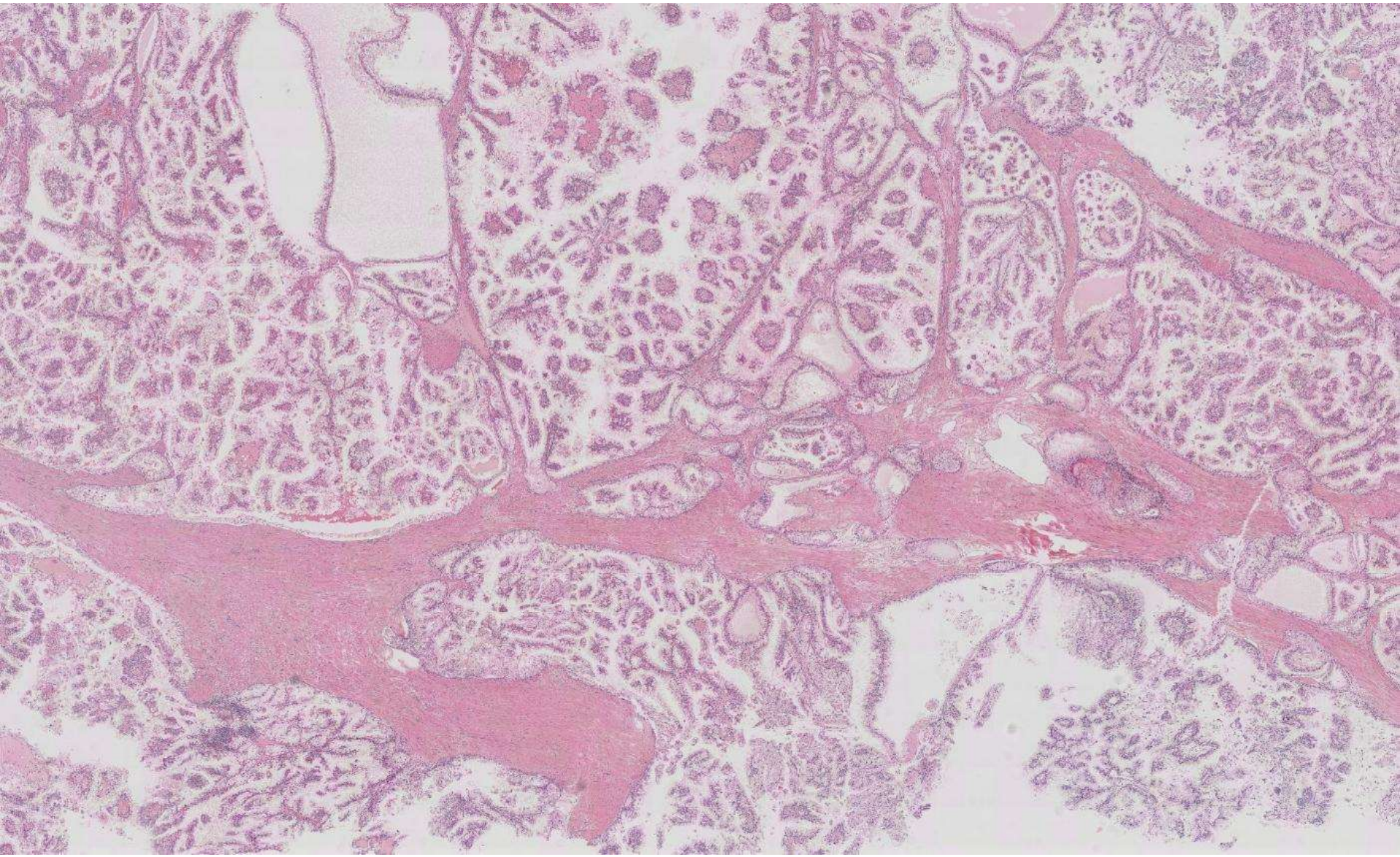
**Emily Chan; UCSF**

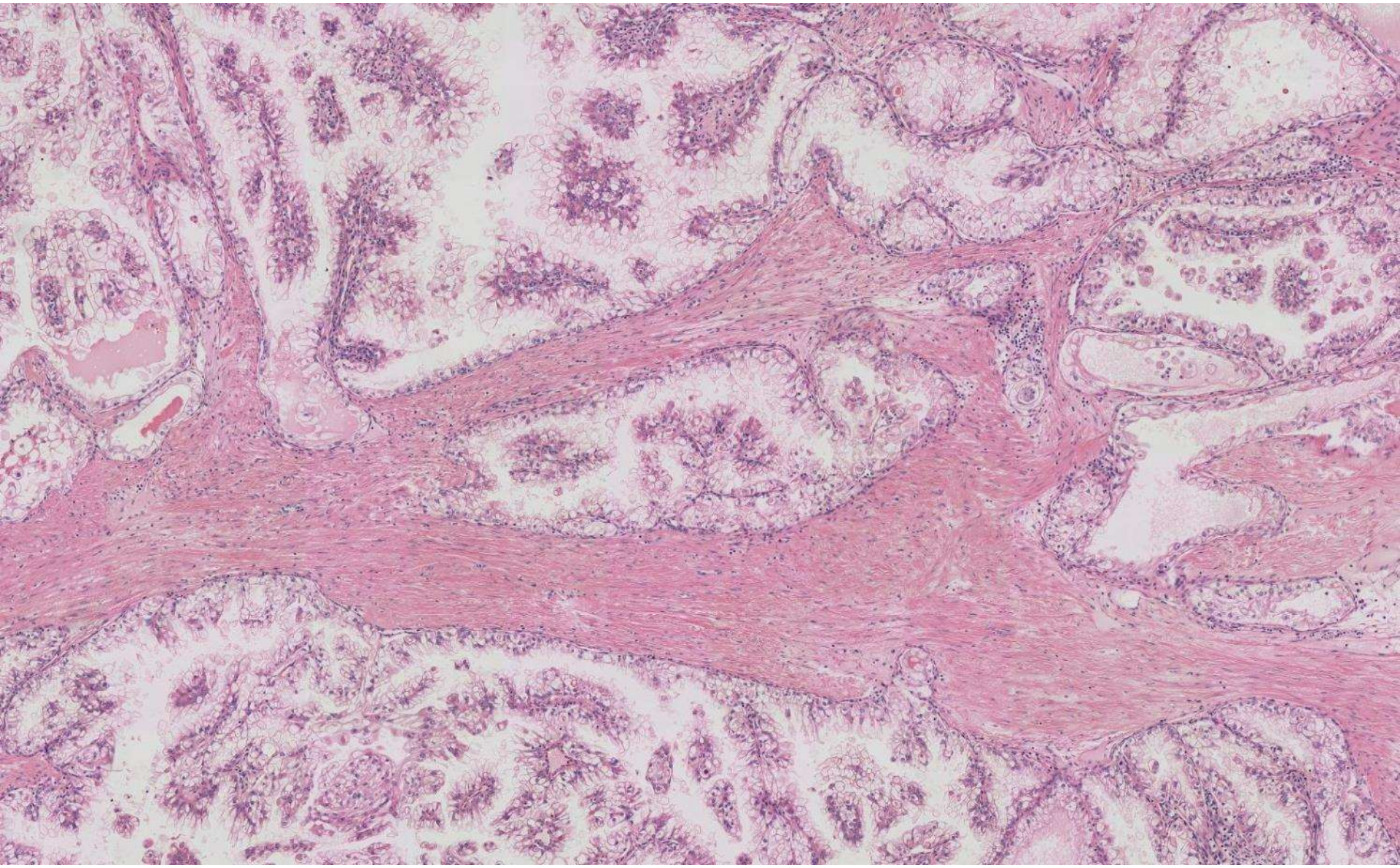
48-year-old F with incidental 5.8cm enhancing left lower pole renal mass, and a few small but prominent left periaortic lymph nodes.

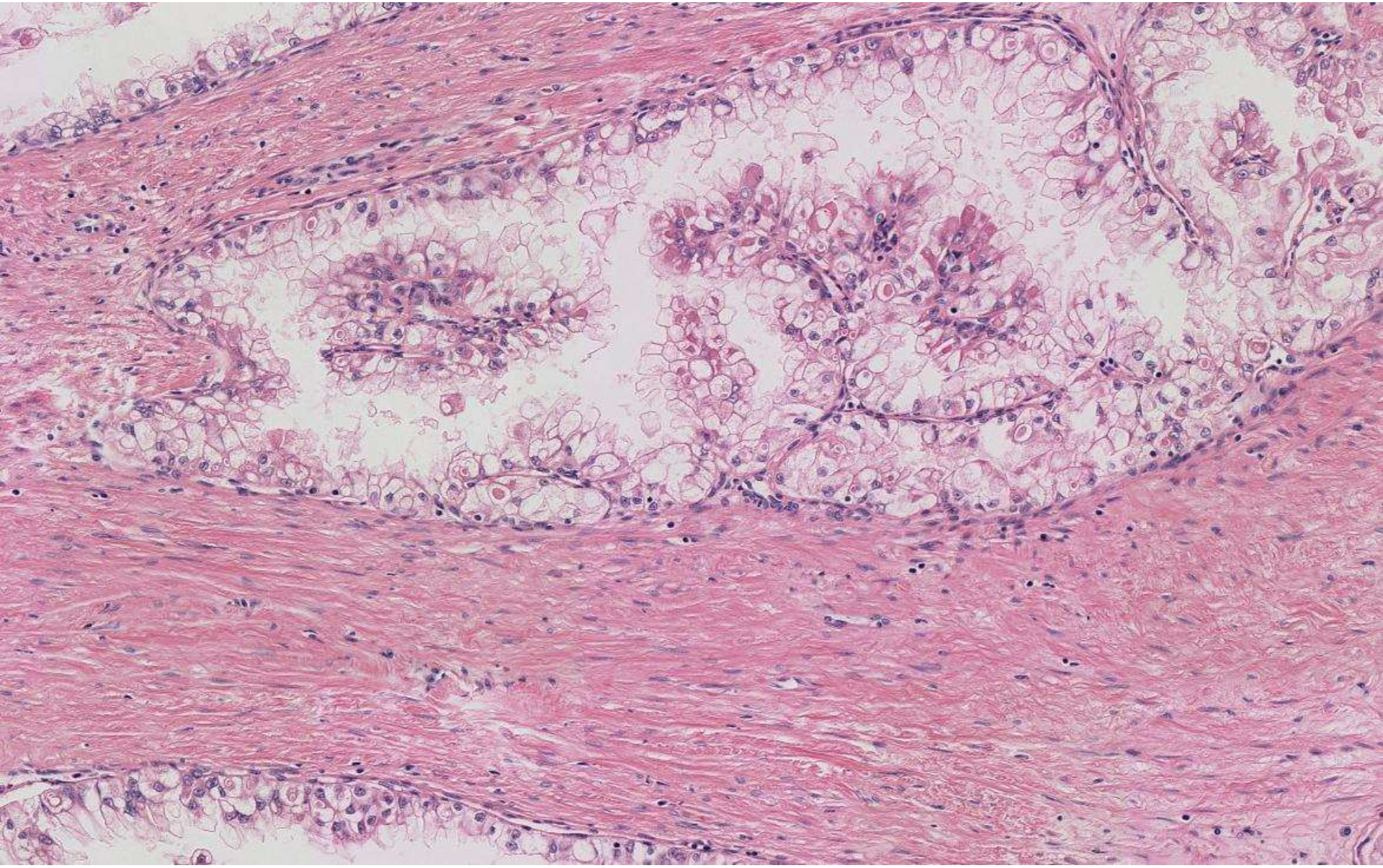


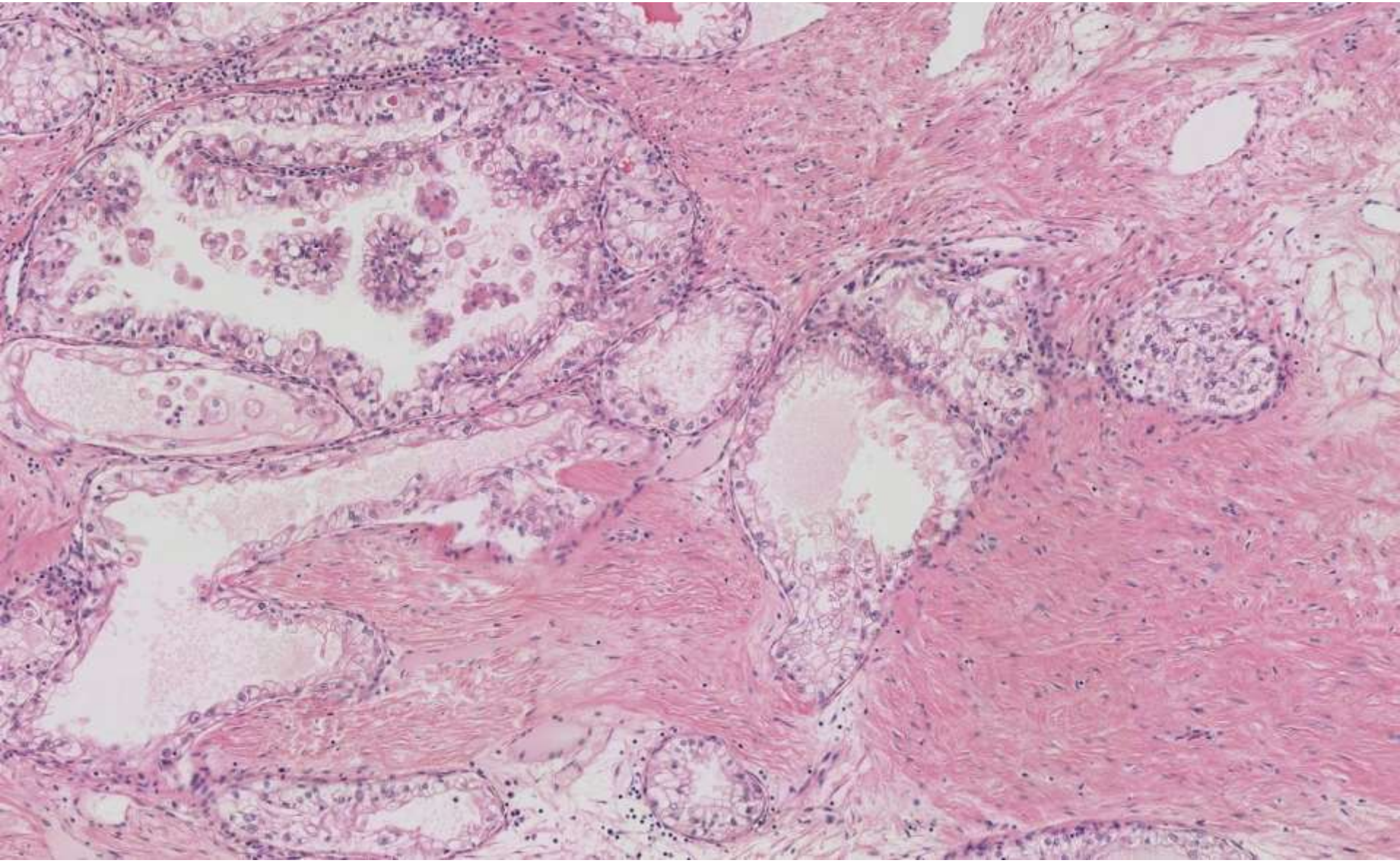


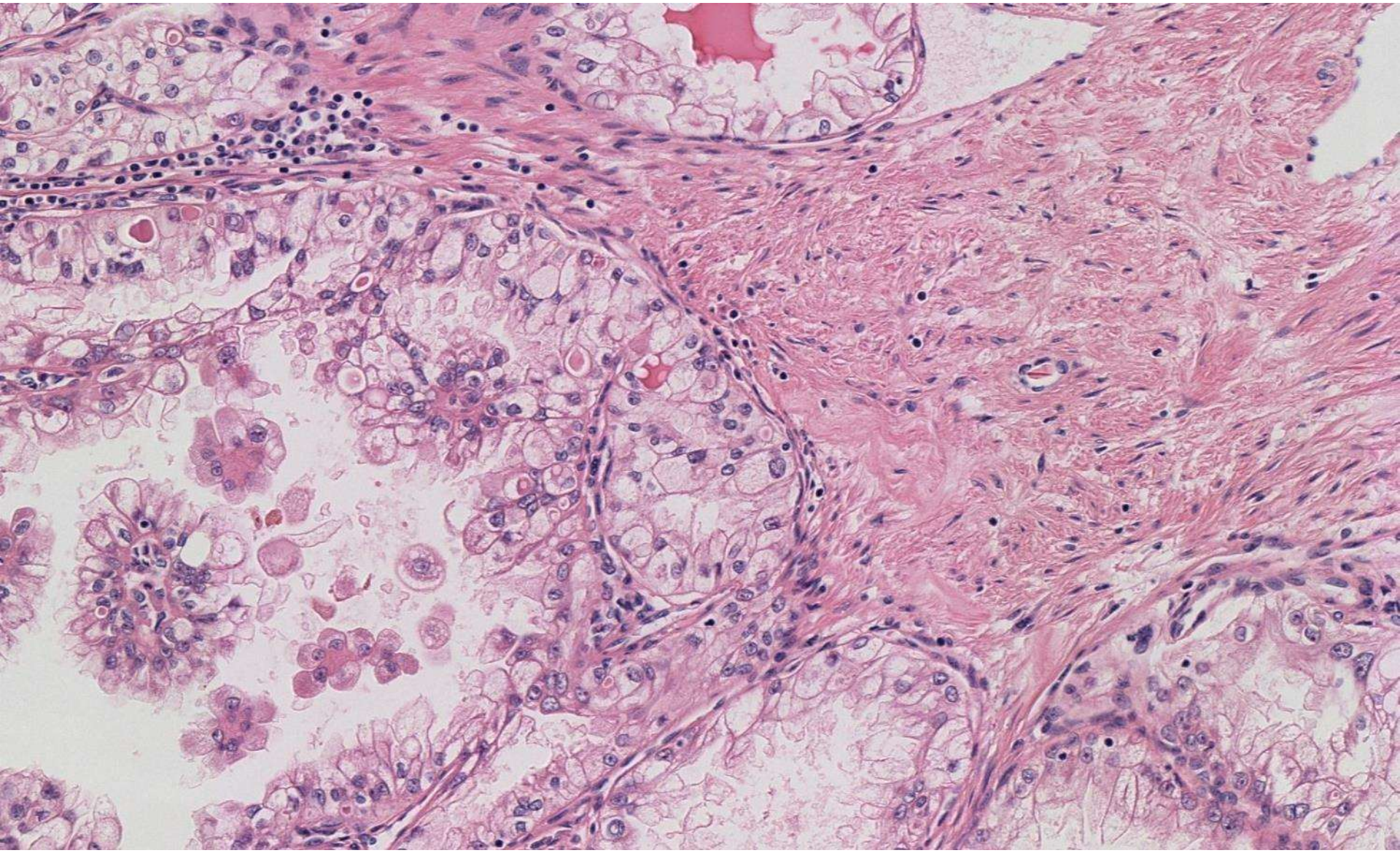


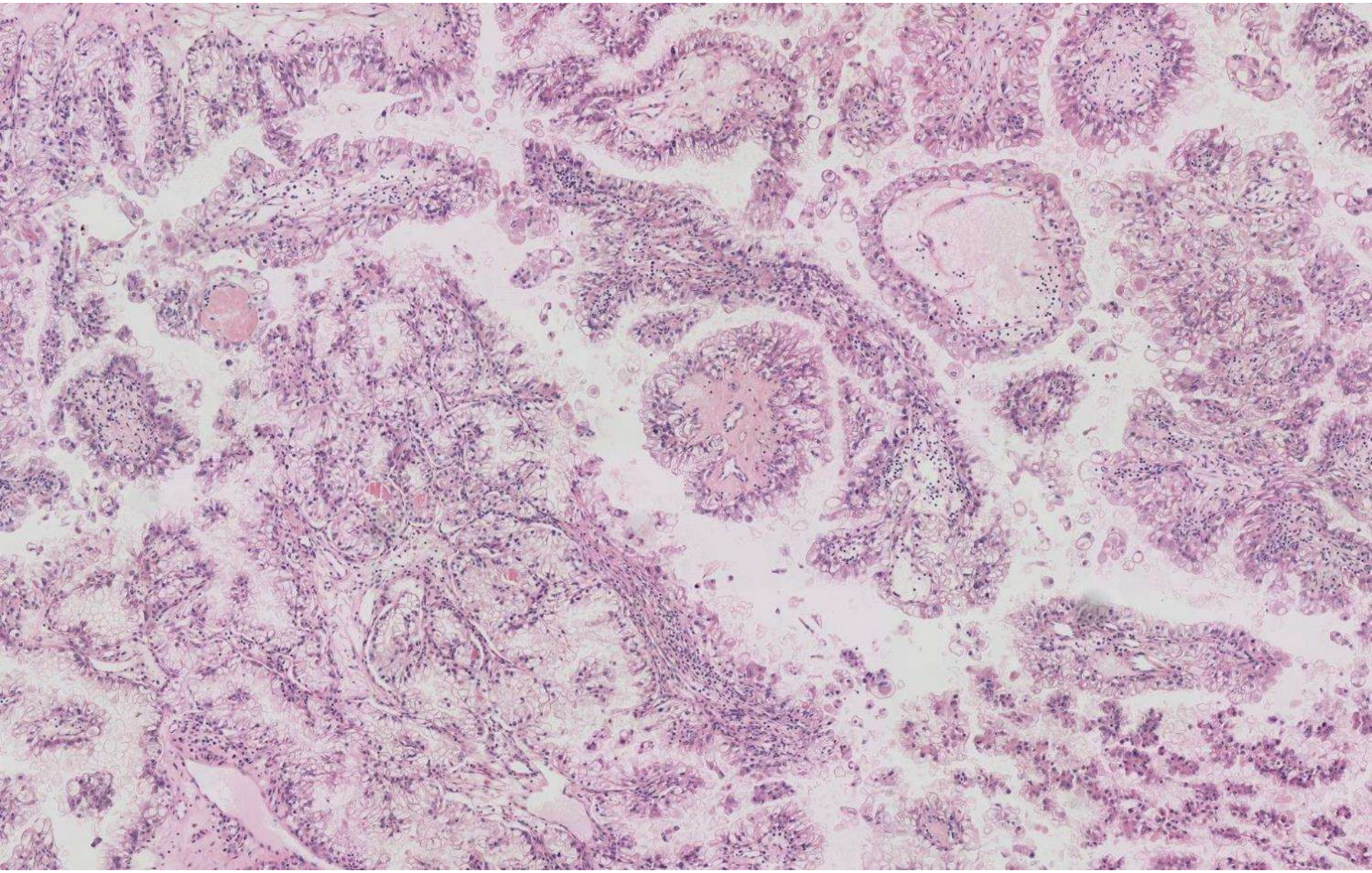


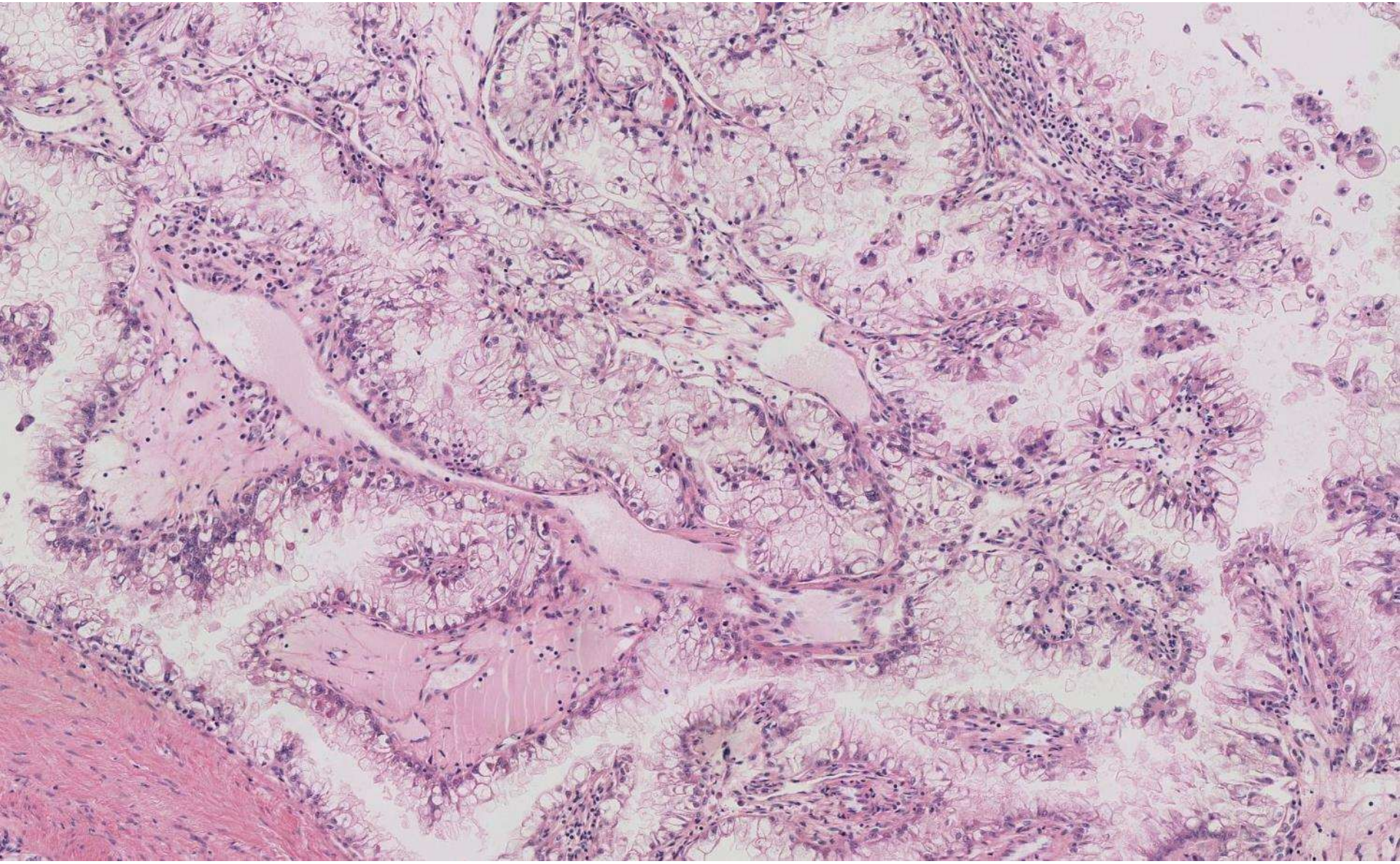


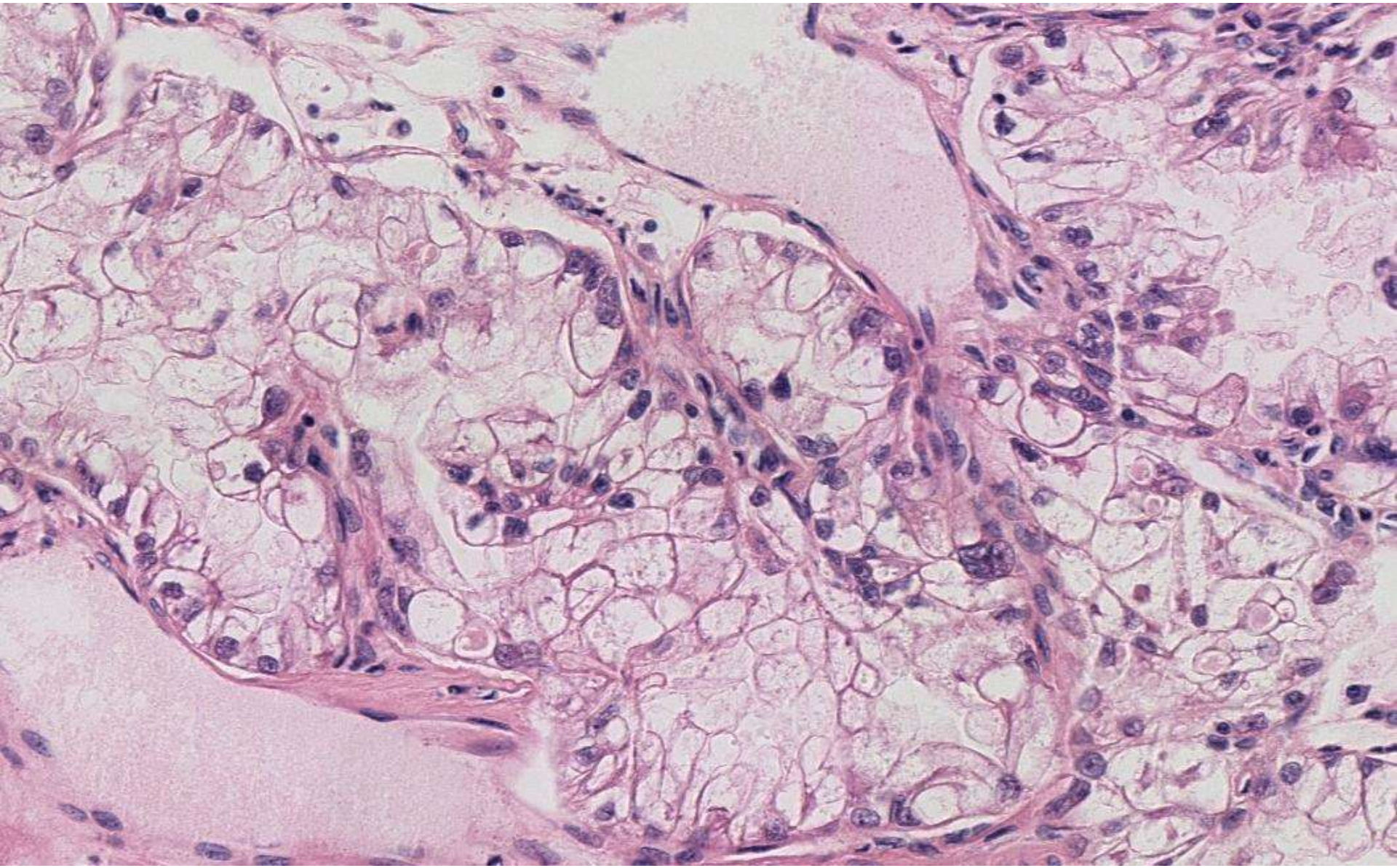


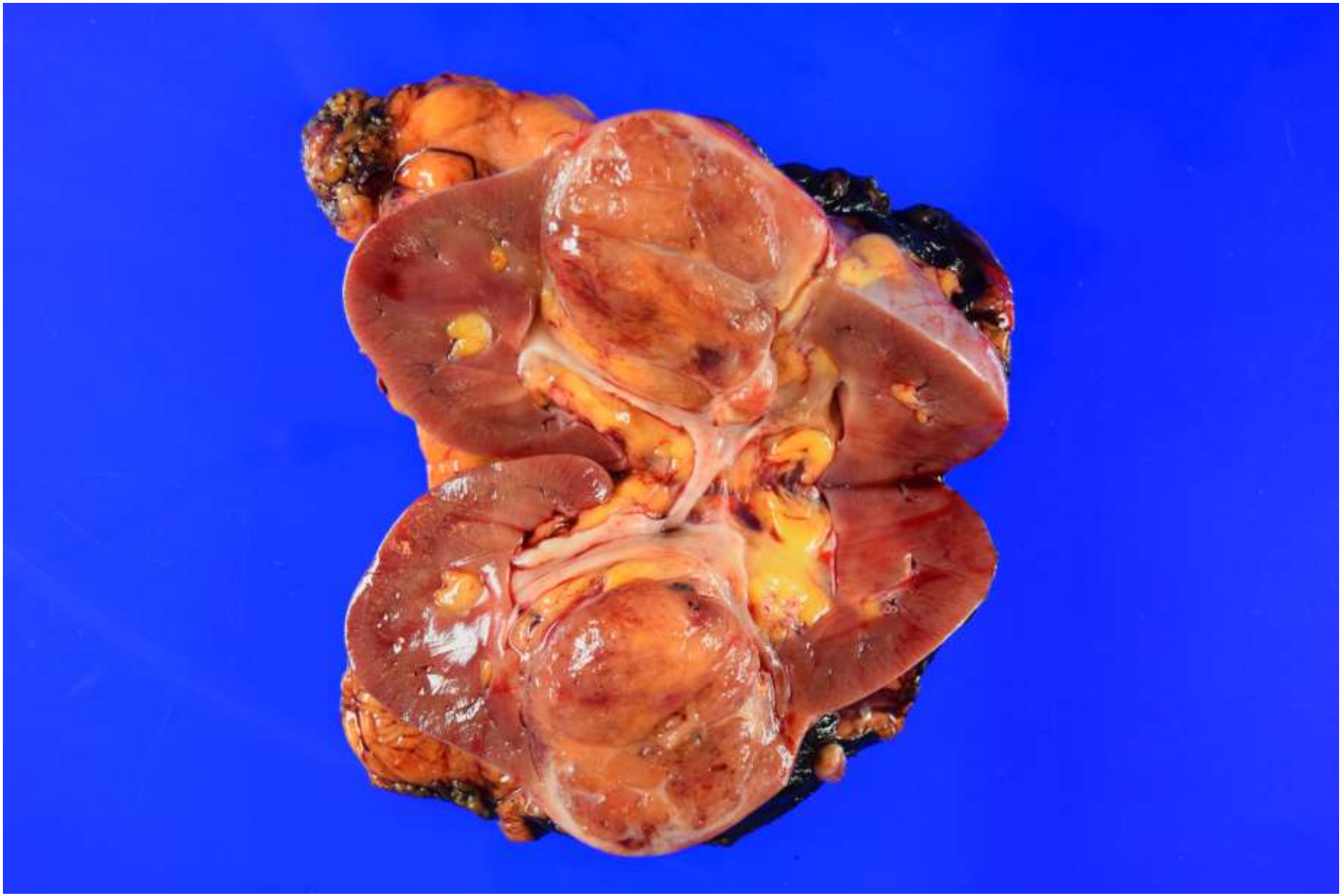


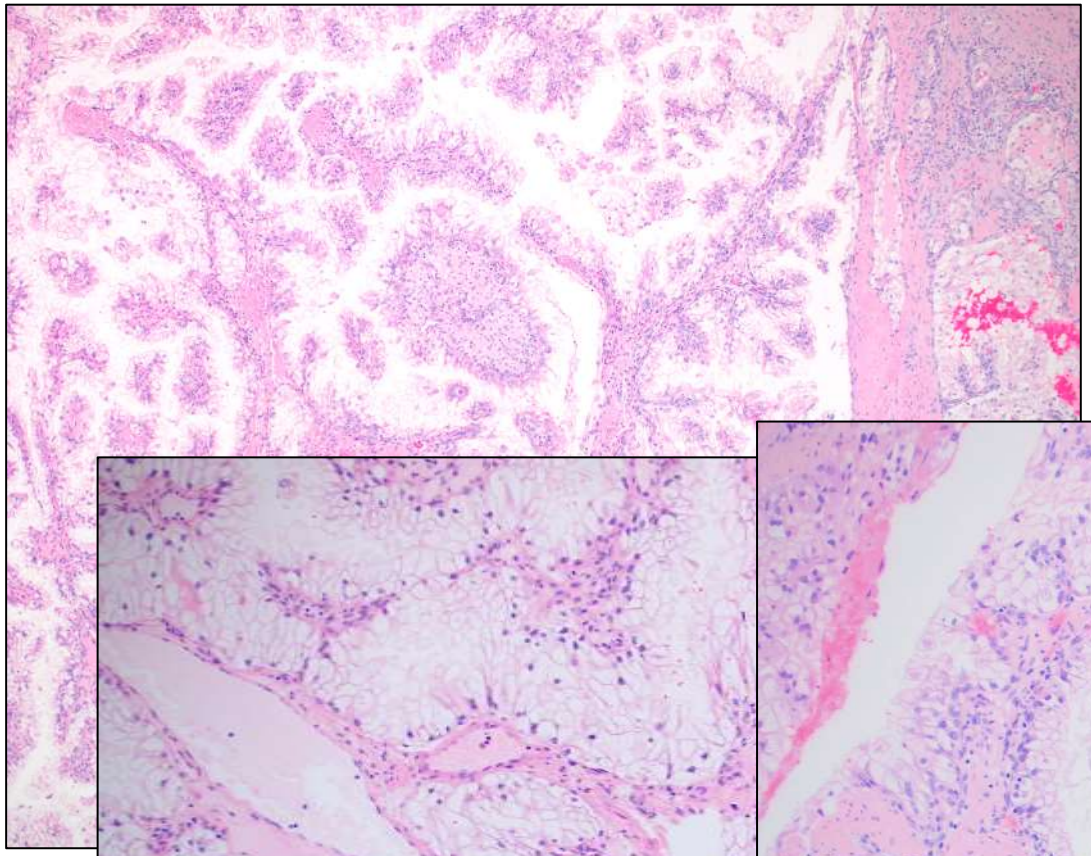


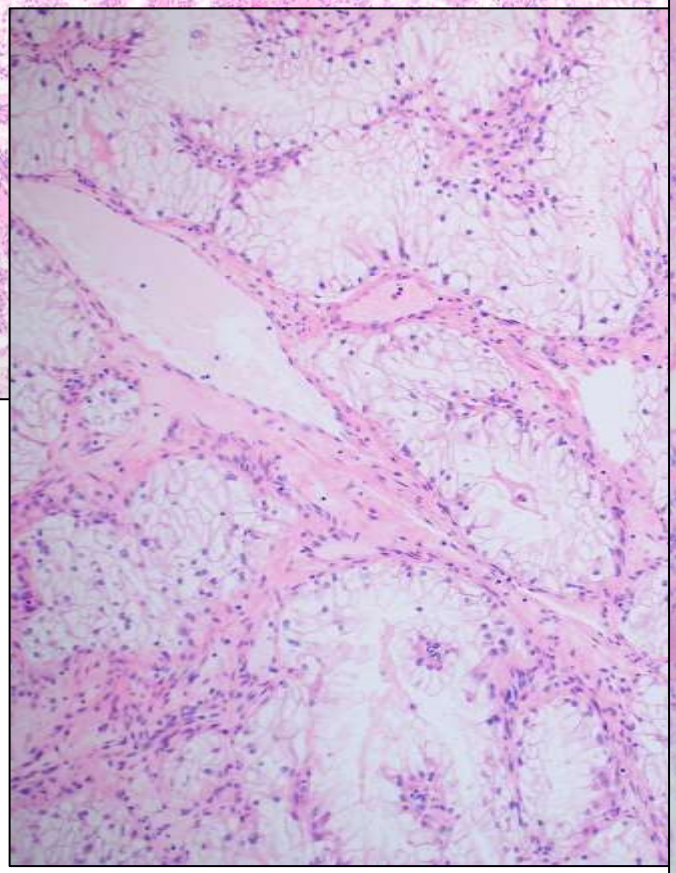


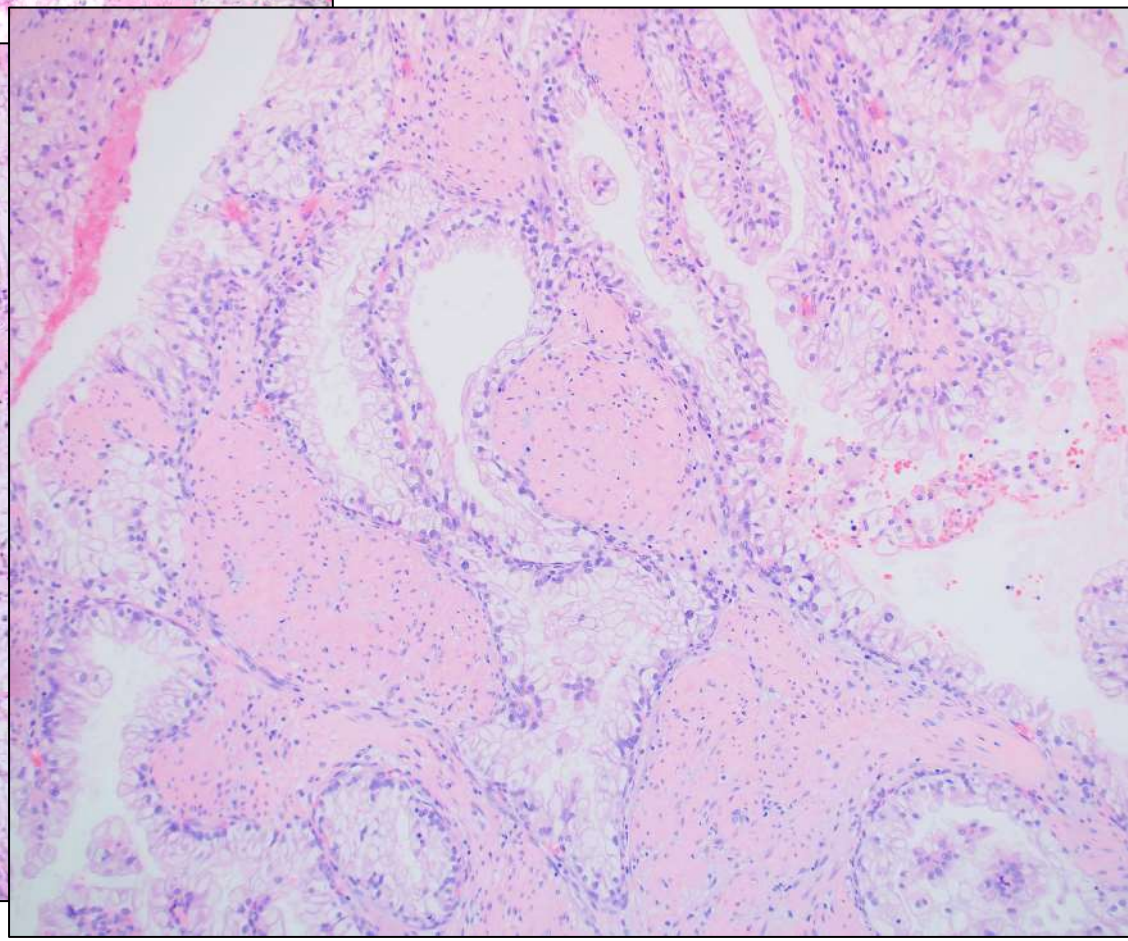








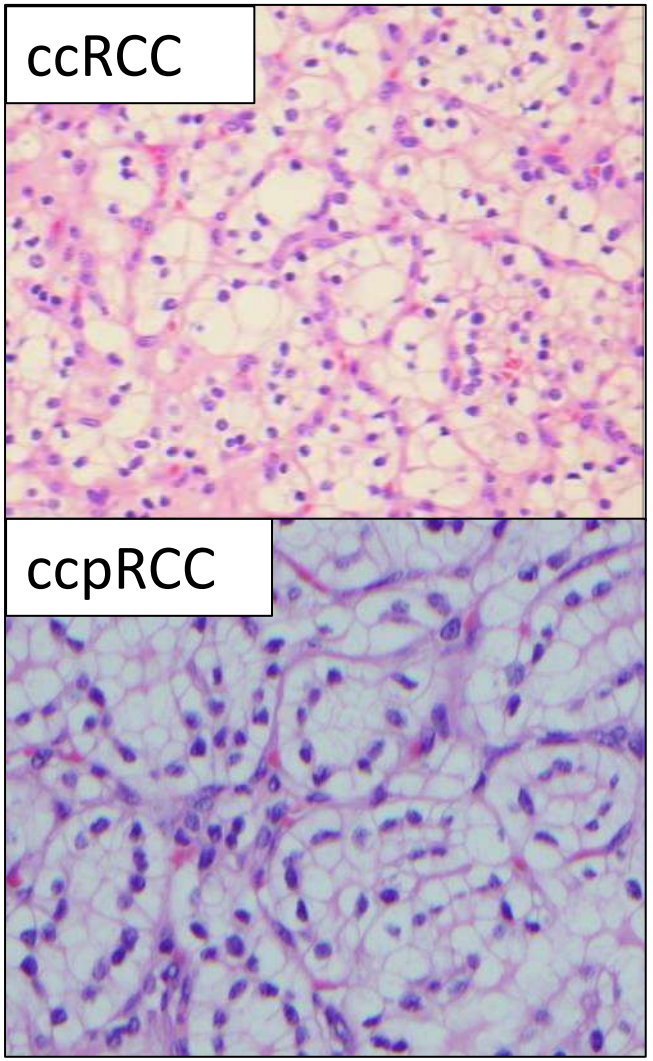




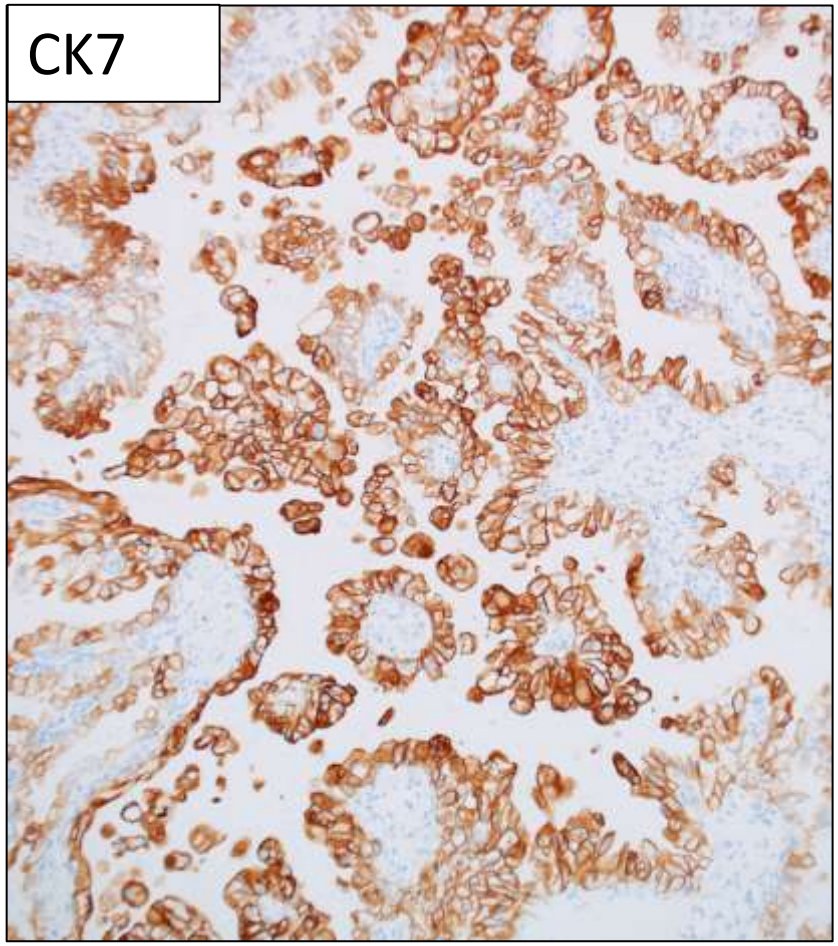
Current case

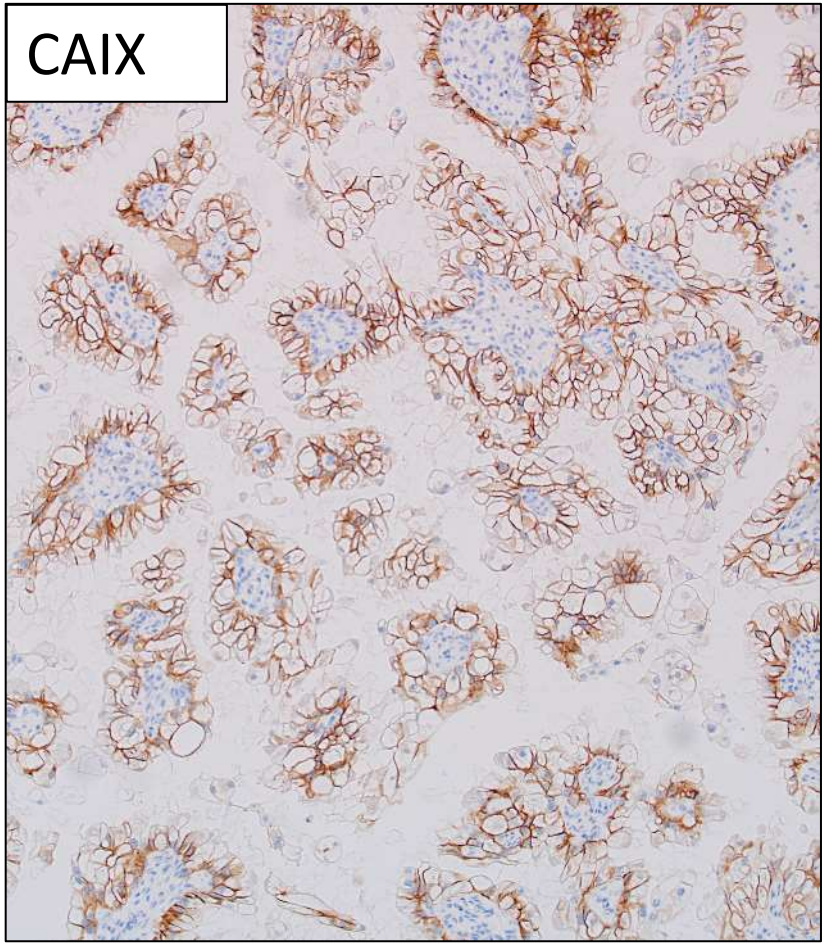
# Differential diagnosis

- **RCC with leiomyomatous stroma**
- Clear cell RCC
- Clear cell papillary RCC
- Translocation associated RCC
- RCC, unclassified



# Current case: IHC workup



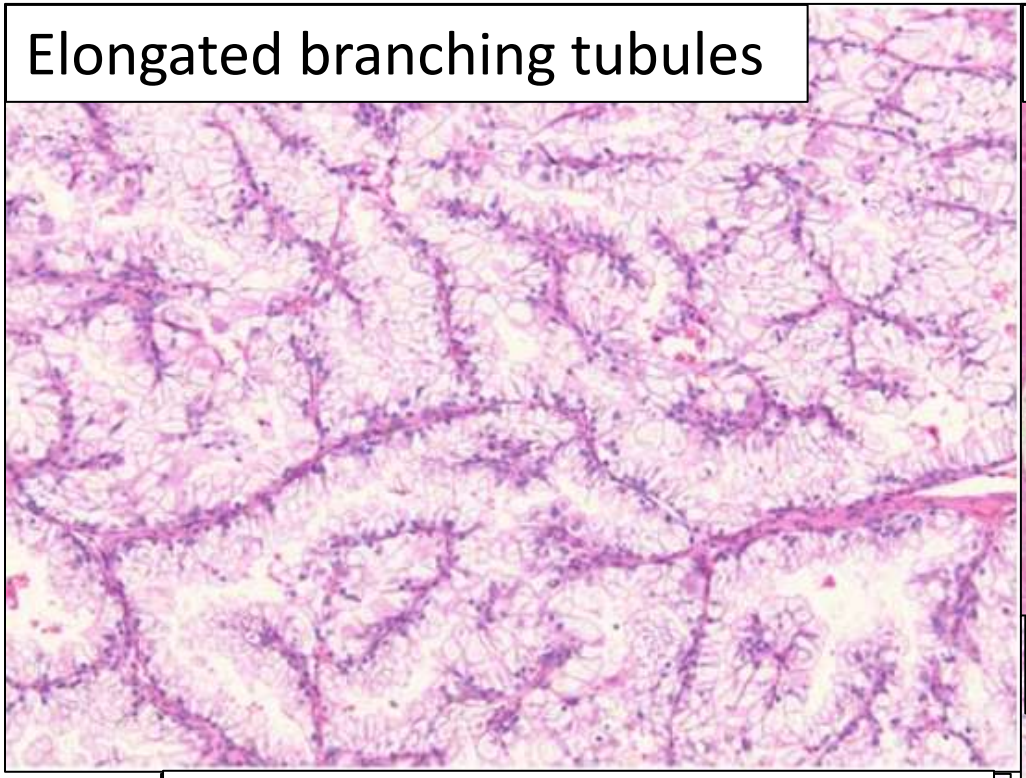




MelanA, TFE3 Negative

# Renal cell carcinoma with leiomyomatous stroma

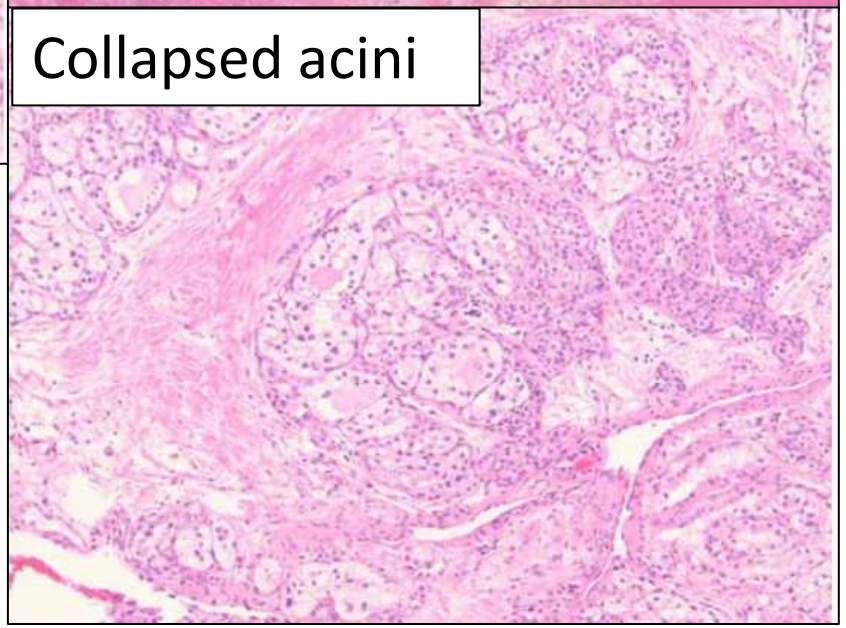
- 2016 WHO emerging/provisional entity
- Previously called RAT (renal angiomyoadenomatous tumor)
- Histology: Branching tubules lined by cells with abundant clear to granular cytoplasm, admixed with smooth muscle stroma
- IHC: CK7 diffuse positive, CAIX circumferential (but can have areas of cup-like)

Elongated branching tubules

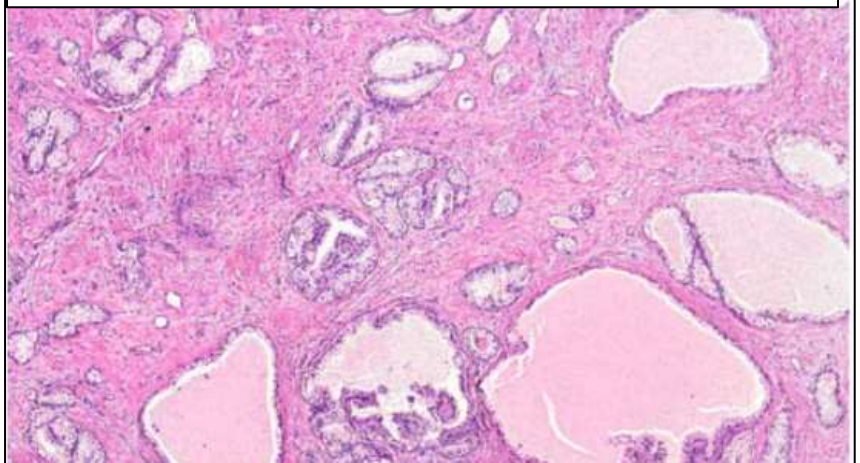


Papillary

Collapsed acini



Variable amounts of smooth muscle stroma



Shah et al AJSP 2019

# Genetic Underpinnings of Renal Cell Carcinoma With Leiomyomatous Stroma

*Megan Parilla, MD, Mir Alikhan, MD, Mustafa Al-Kawaaz, MD, Sushant Patil, PhD, Sabah Kadri, PhD, Lauren L. Ritterhouse, MD, PhD, Jeremy Segal, MD, PhD, Carrie Fitzpatrick, PhD, and Tatjana Antic, MD*

AJSP 2019

# "Renal Cell Carcinoma With Leiomyomatous Stroma" Harbor Somatic Mutations of *TSC1*, *TSC2*, *MTOR*, and/or *ELOC* (*TCEB1*): Clinicopathologic and Molecular Characterization of 18 Sporadic Tumors Supports a Distinct Entity

*Rajal B. Shah, MD,* Bradley A. Stohr, MD, PhD,† Zheng Jin Tu, PhD,* Yuan Gao, MD,‡ Christopher G. Przybycin, MD,* Jane Nguyen, MD, PhD,* Roni M. Cox, MD,* Fariborz Rashid-Kolvear, MD,‡ Michael D. Weindel, MD,* Daniel H. Farkas, PhD, HCLD,* Kiril Trpkov, MD,‡ and Jesse K. McKenney, MD**

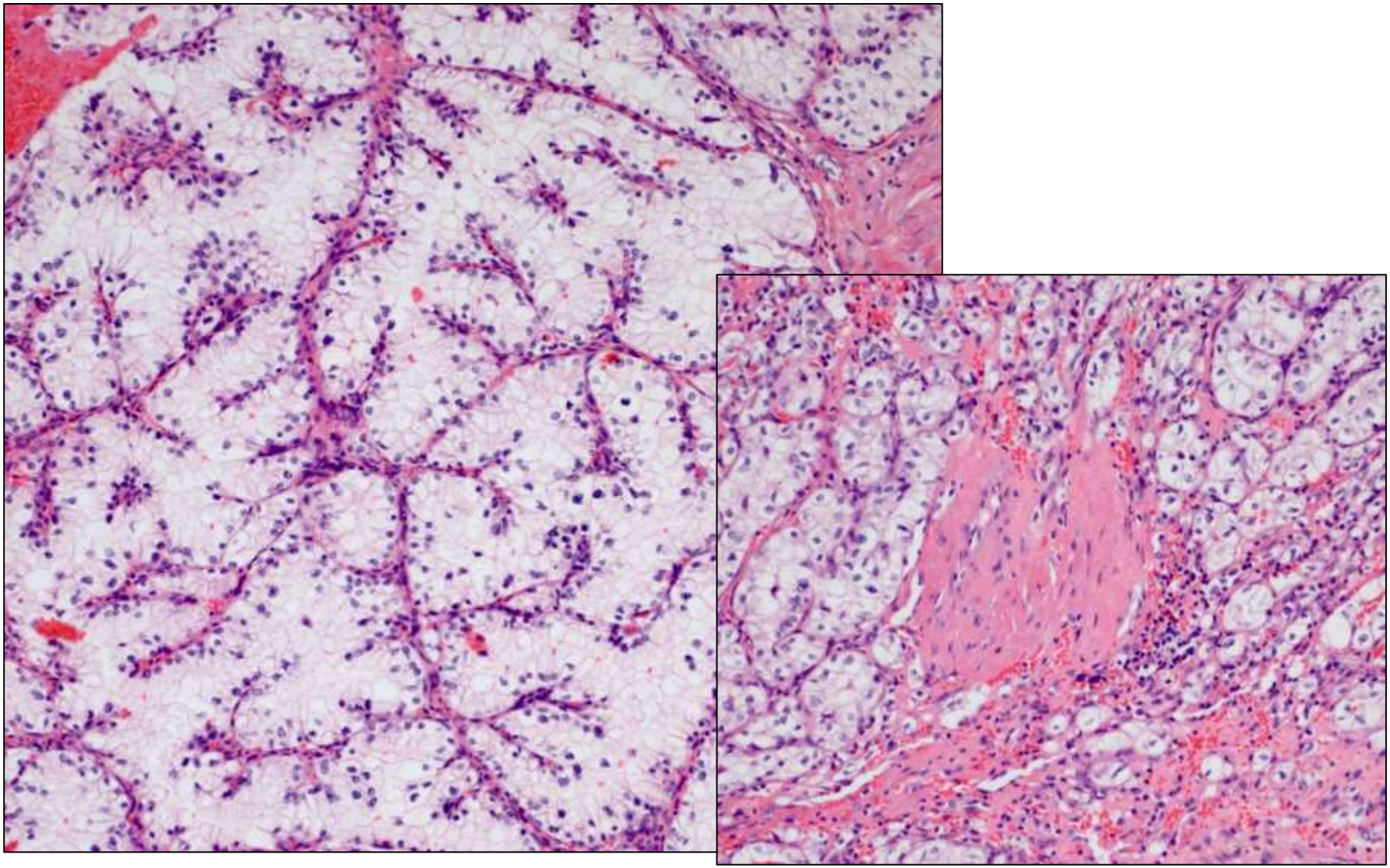
AJSP 2019

# Genetics of RCC with leiomyomatous stroma

- Parilla et al: 15 cases
  - TCEB1: 3 cases
  - TSC1/2: 5 cases (one with known TSC)
  - VHL: 2 cases
  - None of the above: 5 cases (likely ccpRCC?)
- Shah et al: 14 cases
  - TCEB1: 2 cases
  - TSC1/2: 7 cases
  - MTOR: 6 cases

*one case had both TCEB1 and TSC1 mutation

# October 2018 Southbay
# RCC with leiomyomatous stroma -TCEB1 mutated

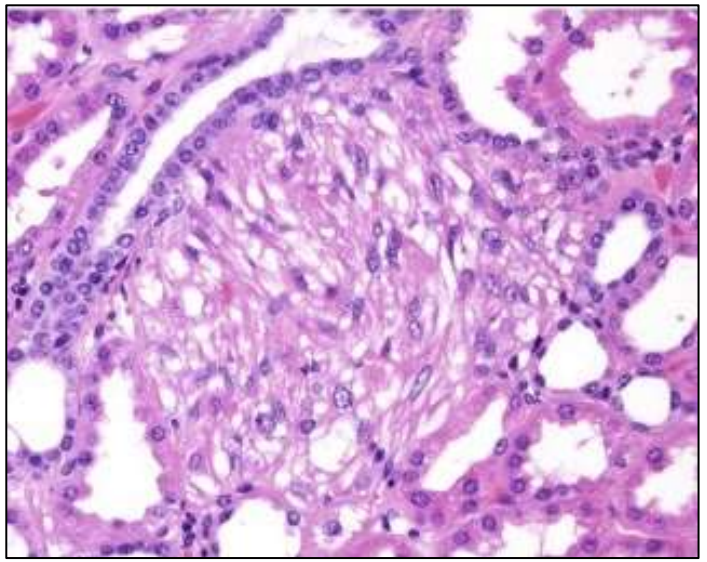


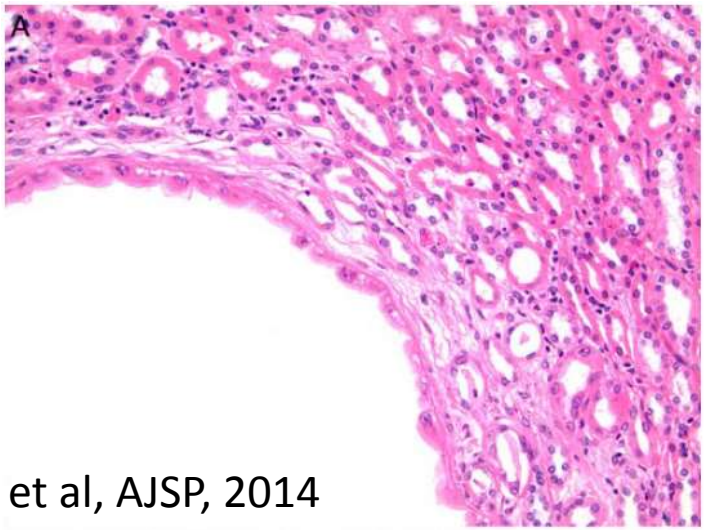
Current case UCSF500:

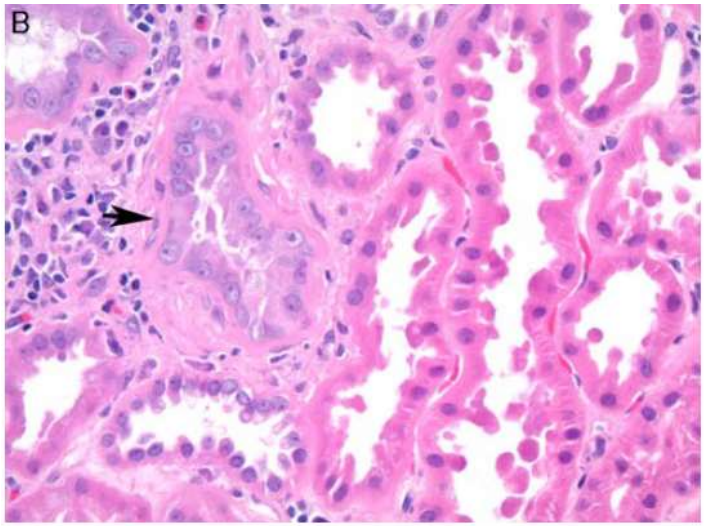
TSC1 p.Q654* mutation with copy neutral loss of heterozygosity of chromosome 9q

# TSC1/2-mutated RCC can be germline or sporadic: Need to assess for tuberous sclerosis!

- Background kidney changes in TSC
  - AML, including tumorlets
  - Cysts lined by prominent eosinophilic cytoplasm
  - Renal tubules with cytoplasmic atypia and/or peritubular hyalinization
- Recommend genetic counseling






Guo et al, AJSP, 2014

# Diagnosis without Molecular Available

- RCC with leiomyomatous stroma
- CK7 and CAIX positive
- Many have underlying mutations in either TCEB1, TSC1/2, or MTOR. Molecular testing can be performed to distinguish these possibilities if clinically indicated.
- Recommend genetic counseling (particularly if young or see any features of TSC in background kidney-need to look!)
- Thought to be more clinically indolent than ccRCC

# Putative Drivers of Aggressiveness in *TCEB1*-mutant Renal Cell Carcinoma: An Emerging Entity with Variable Clinical Course

*Renzo G. DiNatale[a,b,c], Alexander N. Gorelick[c,d], Vladimir Makarov[b], Kyle A. Blum[a], Andrew W. Silagy[a], Benjamin Freeman[a], Diego Chowell[b], Julian Marcon[a], Roy Mano[a], Alex Sanchez[a], Kyrollis Attalla[a], Stanley Weng[a], Martin Voss[e], Robert J. Motzer[e], Paul Russo[a], Jonathan A. Coleman[a], Victor E. Reuter[f], Ying-Bei Chen[f], Timothy A. Chan[b], Ed Reznik[c], Satish K. Tickoo[f,*], A. Ari Hakimi[a,*]*

- Identified 4 cases with high stage disease
  - Two cases with metastatic disease
  - Three cases pT3 or higher
  - Two cases WHO grade 3/4

European Urology Focus, 2019

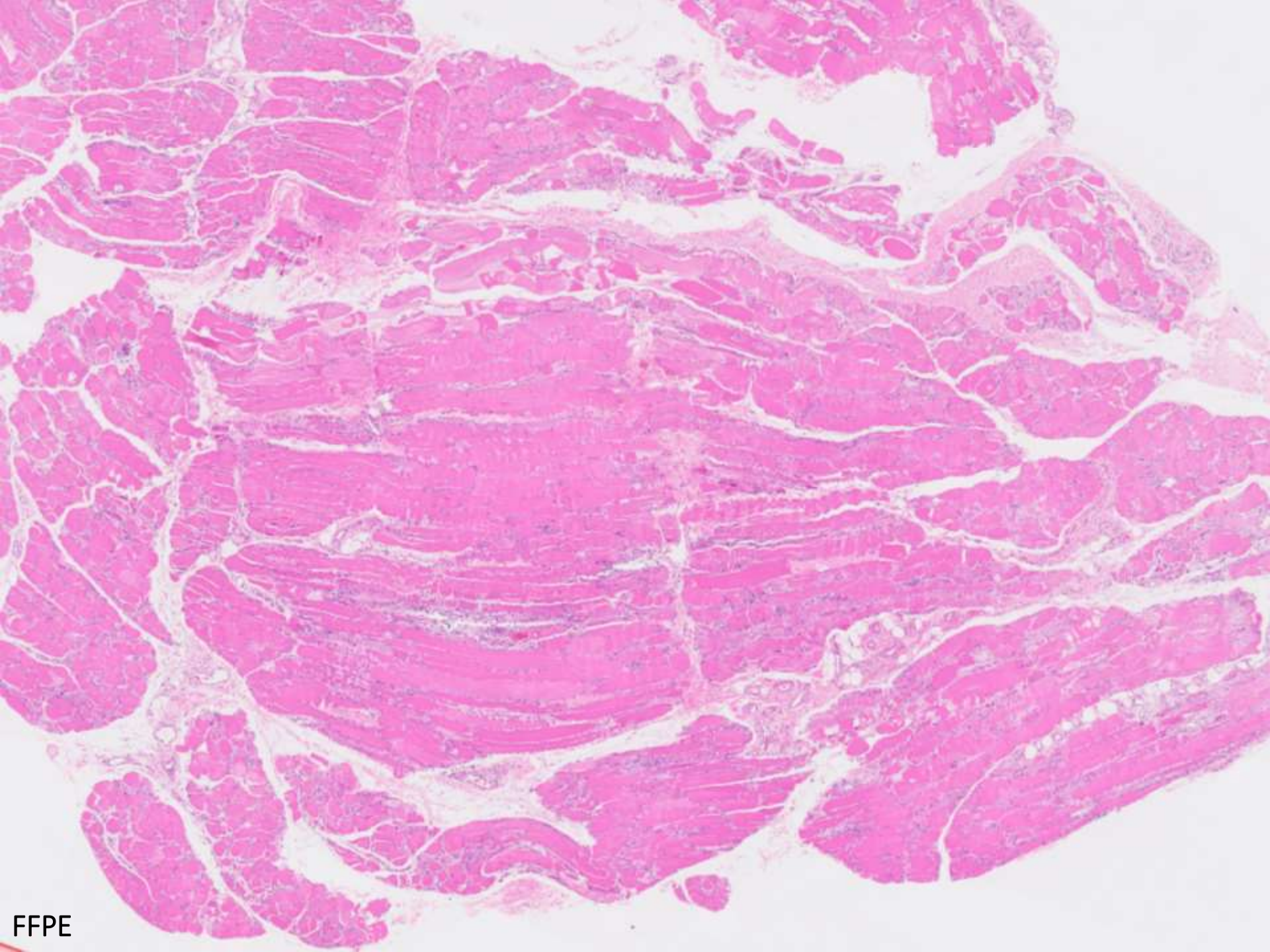
# Diagnosis without Molecular Available

- RCC with leiomyomatous stroma
- CK7 and CAIX positive
- Many have underlying mutations in either TCEB1, TSC1/2, MTOR. Molecular testing can be performed to distinguish these possibilities if clinically indicated.
- Recommend genetic counseling (particularly if young or see any features of TSC in background kidney-need to look!)
- ~~Thought to be more clinically indolent than ccRCC~~

# 20-0203

**Romain Cayrol/Hannes Vogel; Stanford**

48-year-old F who presents with progressive proximal muscle weakness for 3 months. H/O stage III serous ovarian cancer Dx in 2016, Tx w/chemo+XRT. Recurrence in 2018 Tx with XRT+pembrolizumab (anti-PD1). Progression of disease Tx w/olaparib (PARP inhibitor). CK up to 1758U/L. Electrodiagnostic studies show mixed myopathic & neurogenic abnormalities, most c/w a diffuse myopathy w/secondary denervation.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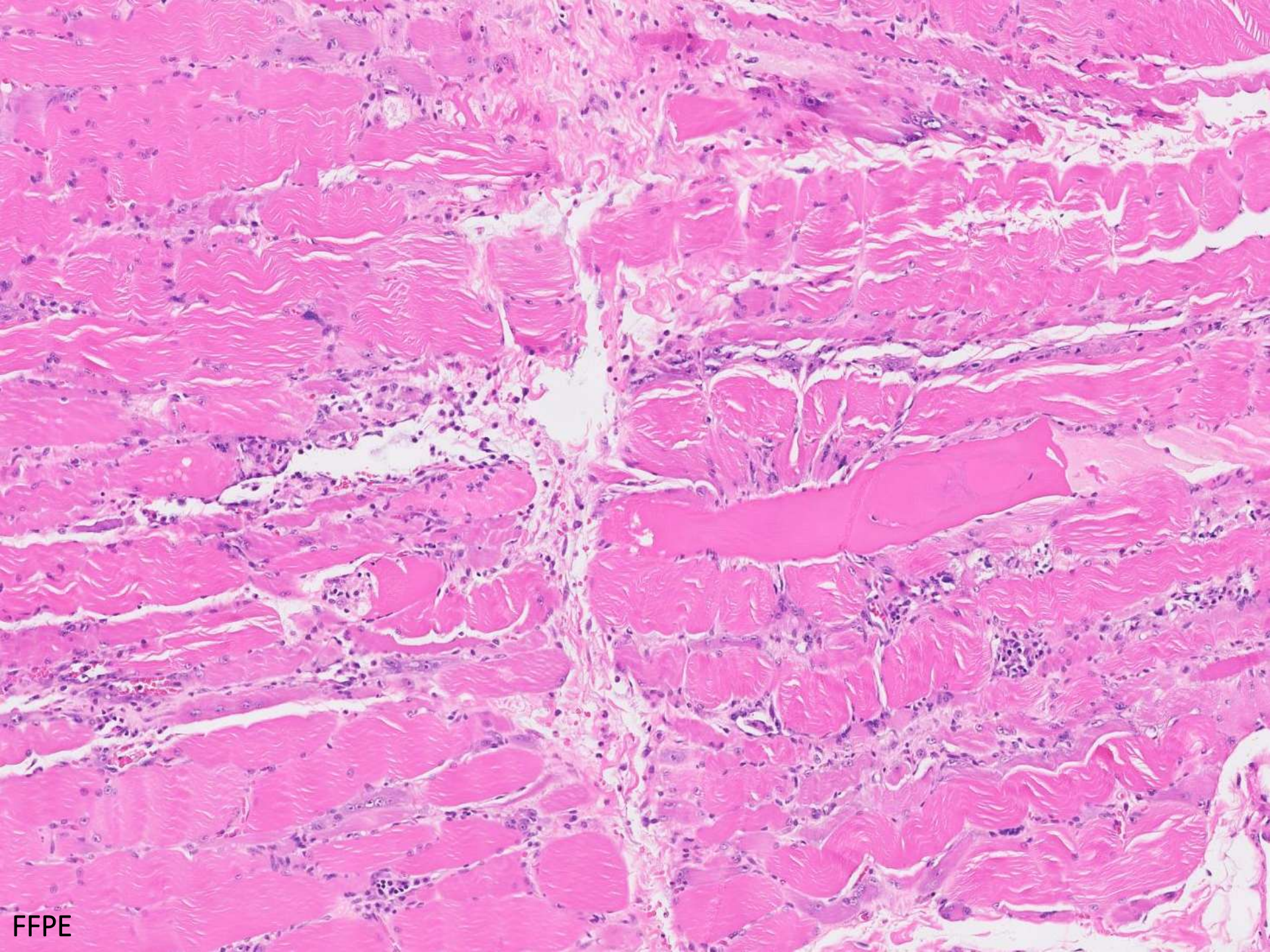
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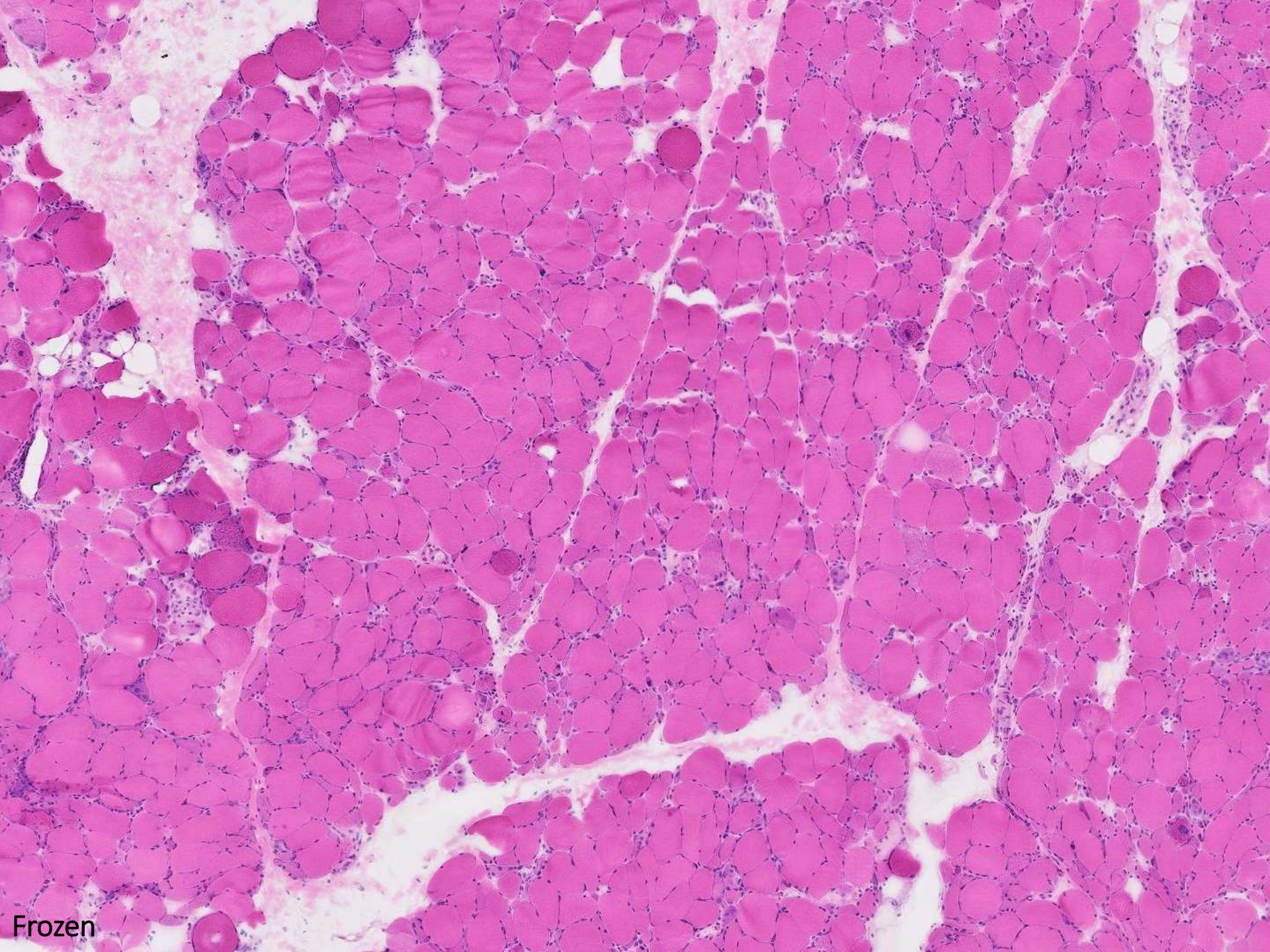
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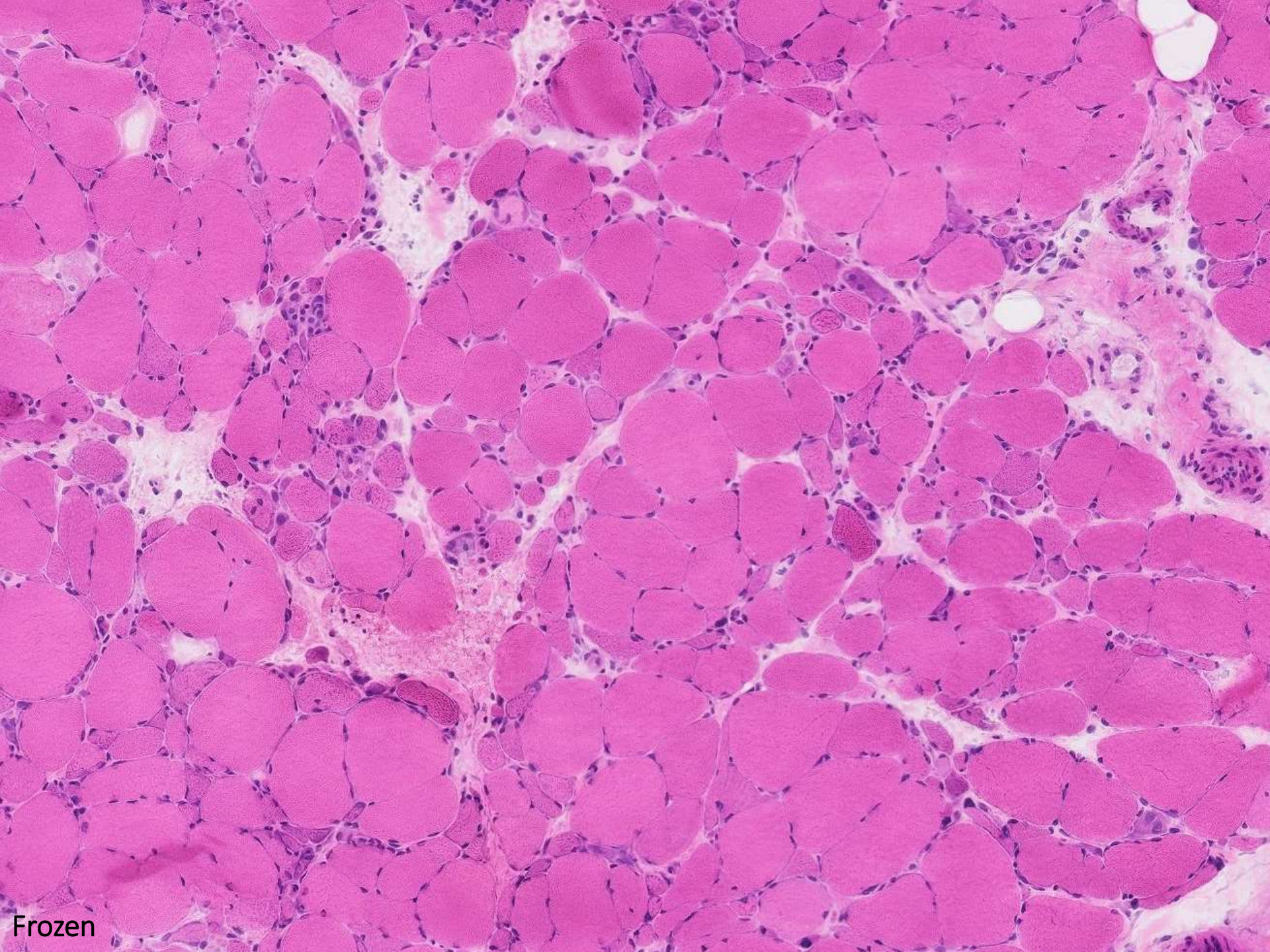
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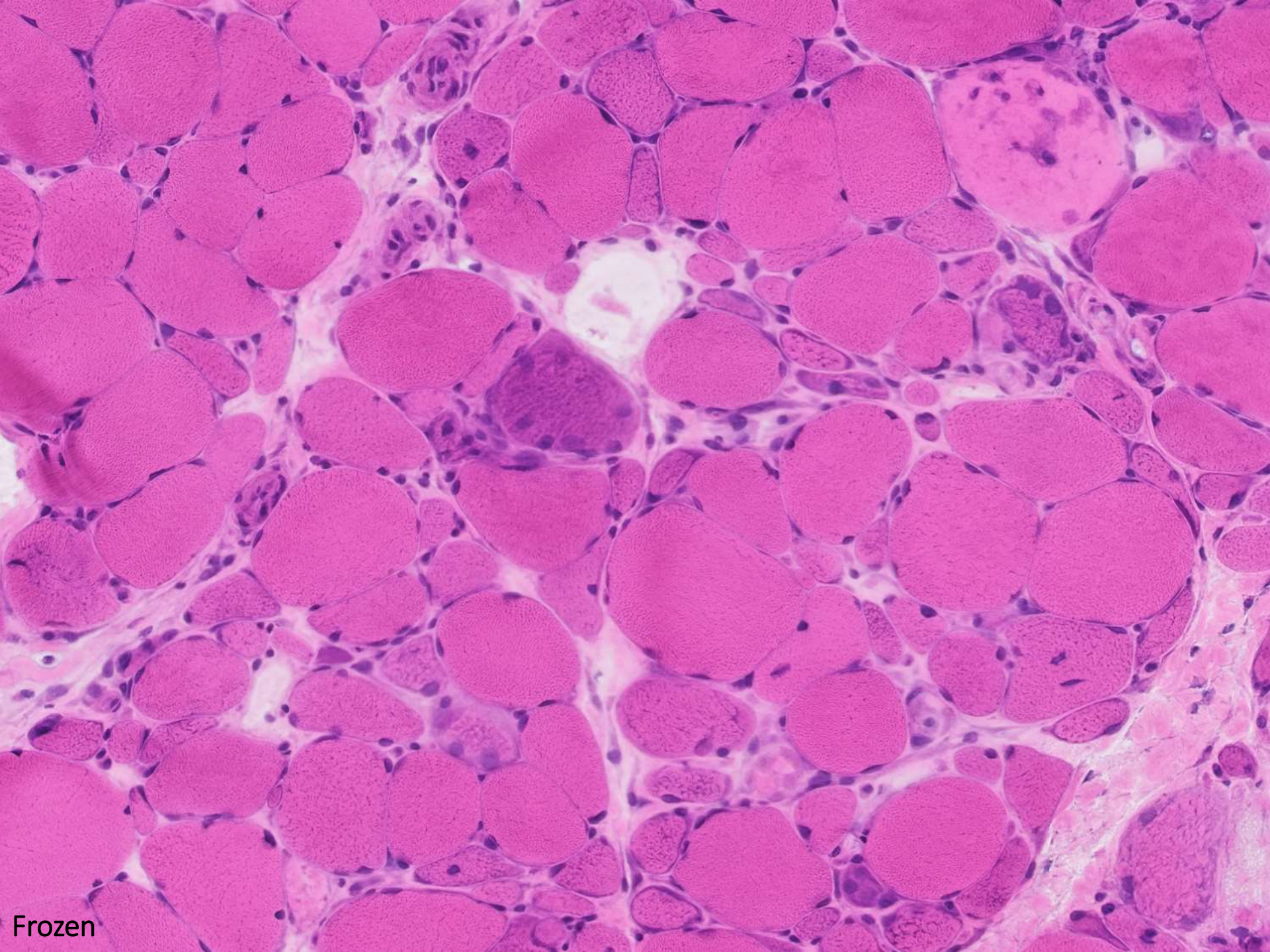
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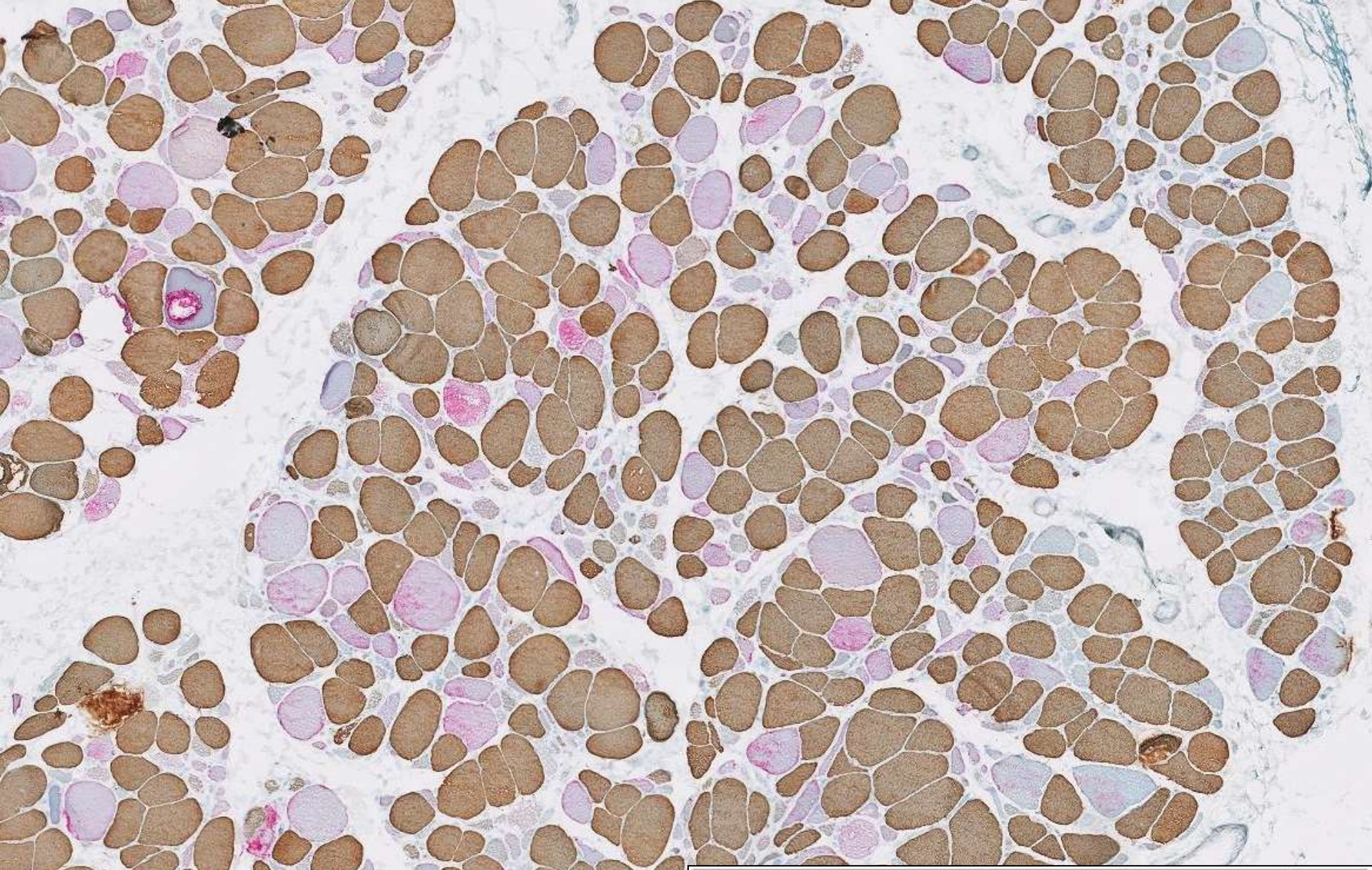
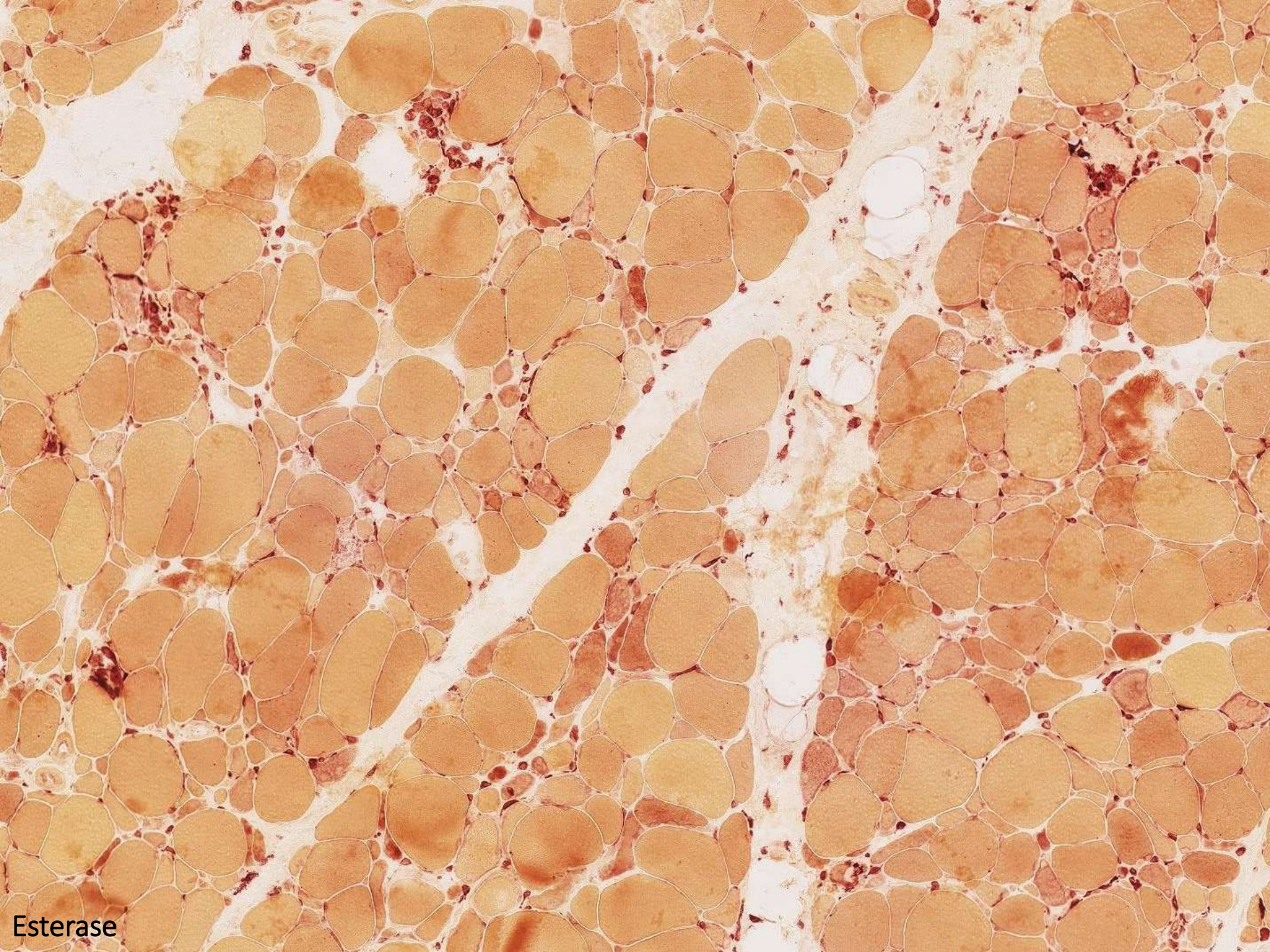


| ATPase fiber type | I | 2A | 2B | 2C |
|---|---|---|---|---|
| Fiber type | Slow | Fast aerobic | Ultrafast glycolytic | Mixed |
| MyHC isoform | I | IIA | IIX | Hybrid I and IIA |
| MyHC gene | *MYH7* | *MYH2* | *MYH1* | Mixed |
| ATPase staining pH 10.4 | Light brown | Brown | Dark brown | Dark brown |
| ATPase staining pH 4.6 | Dark brown | No reaction (pale) | Light brown | Dark brown |
| ATPase staining pH 4.3 | Dark brown | No reaction (pale) | No reaction (pale) | Light brown |
| MyHC double staining | Brown | Red | No reaction (light blue) | Red-brown |

Double myosin immunohistochemistry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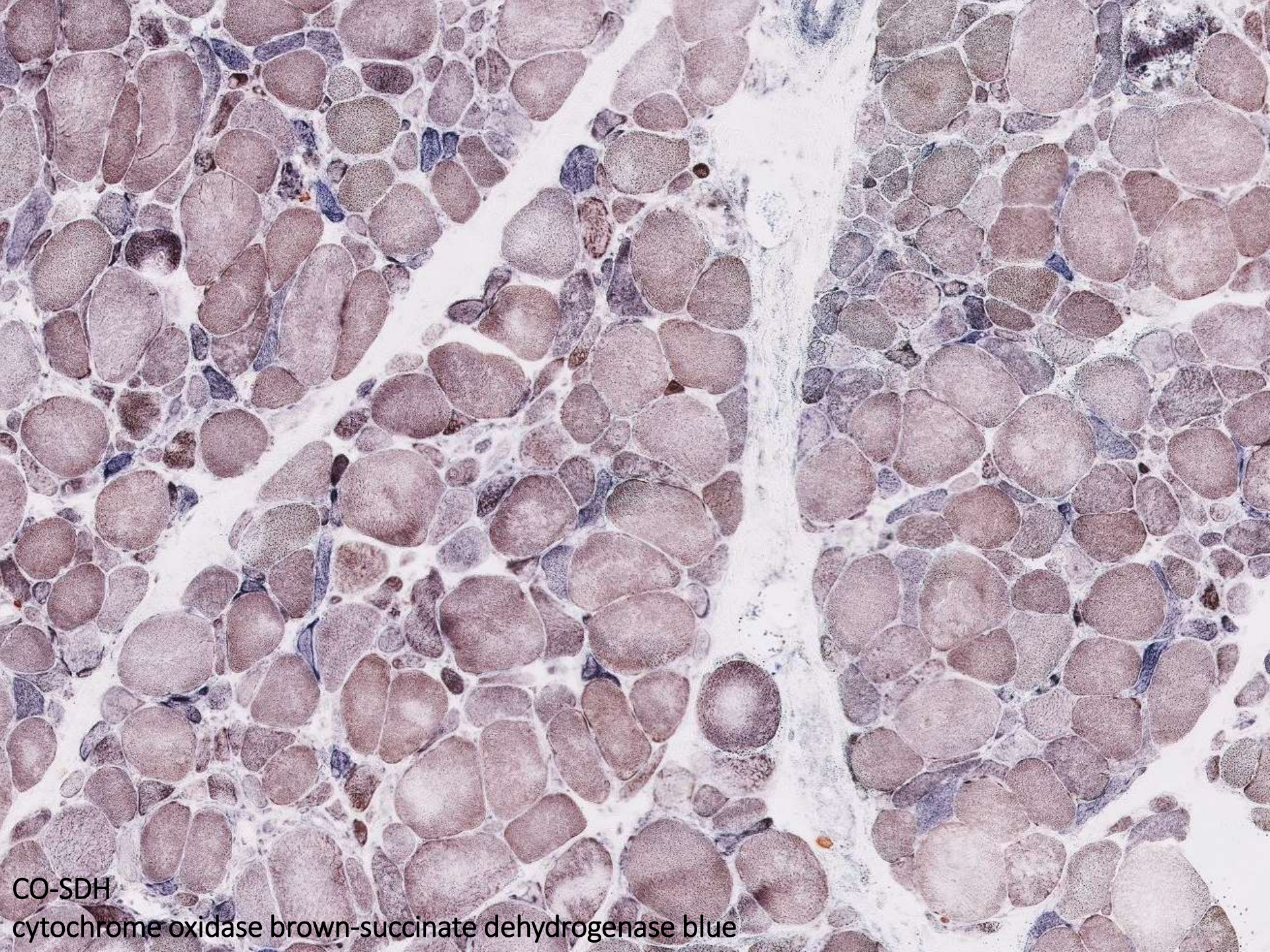
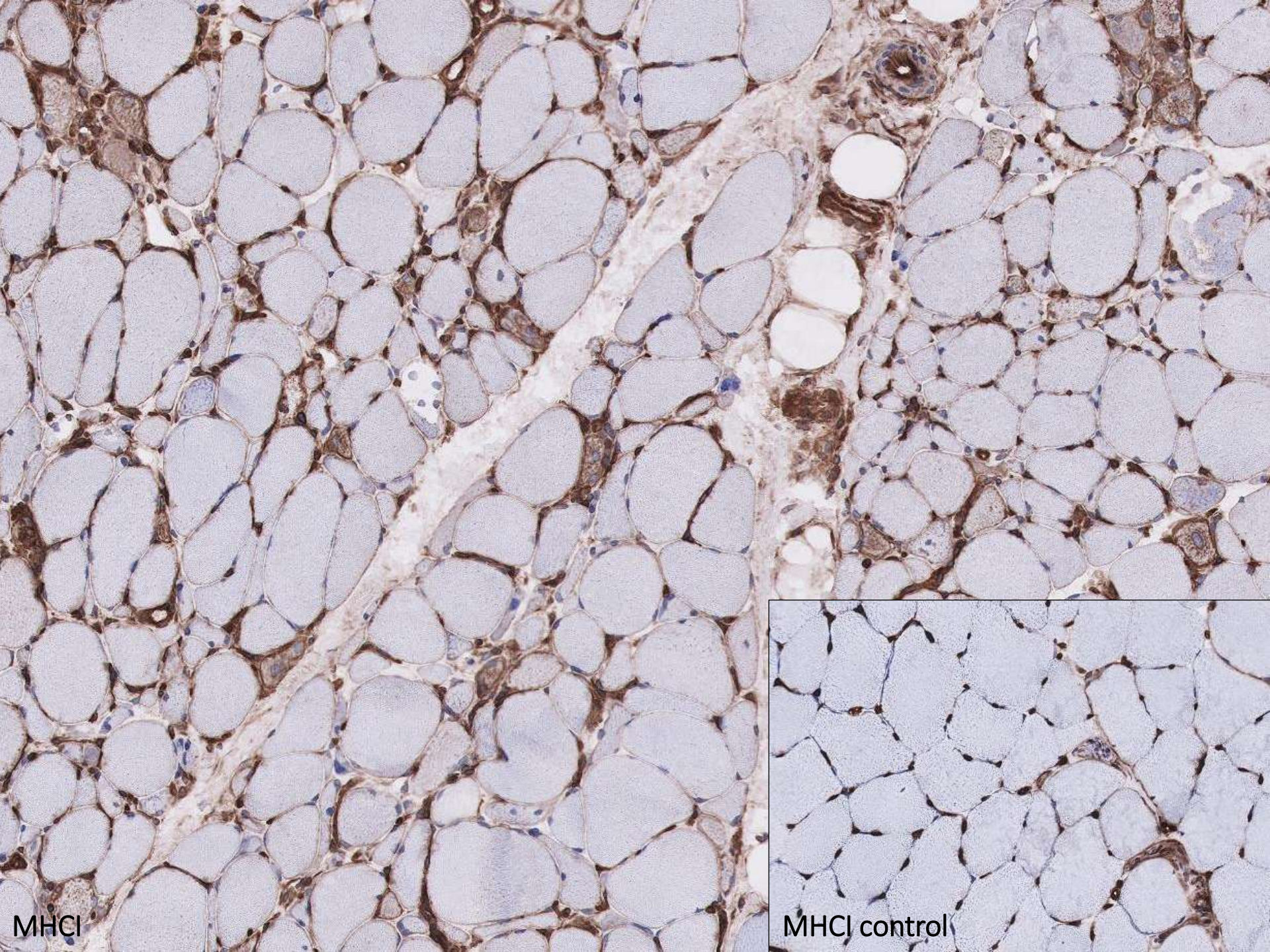
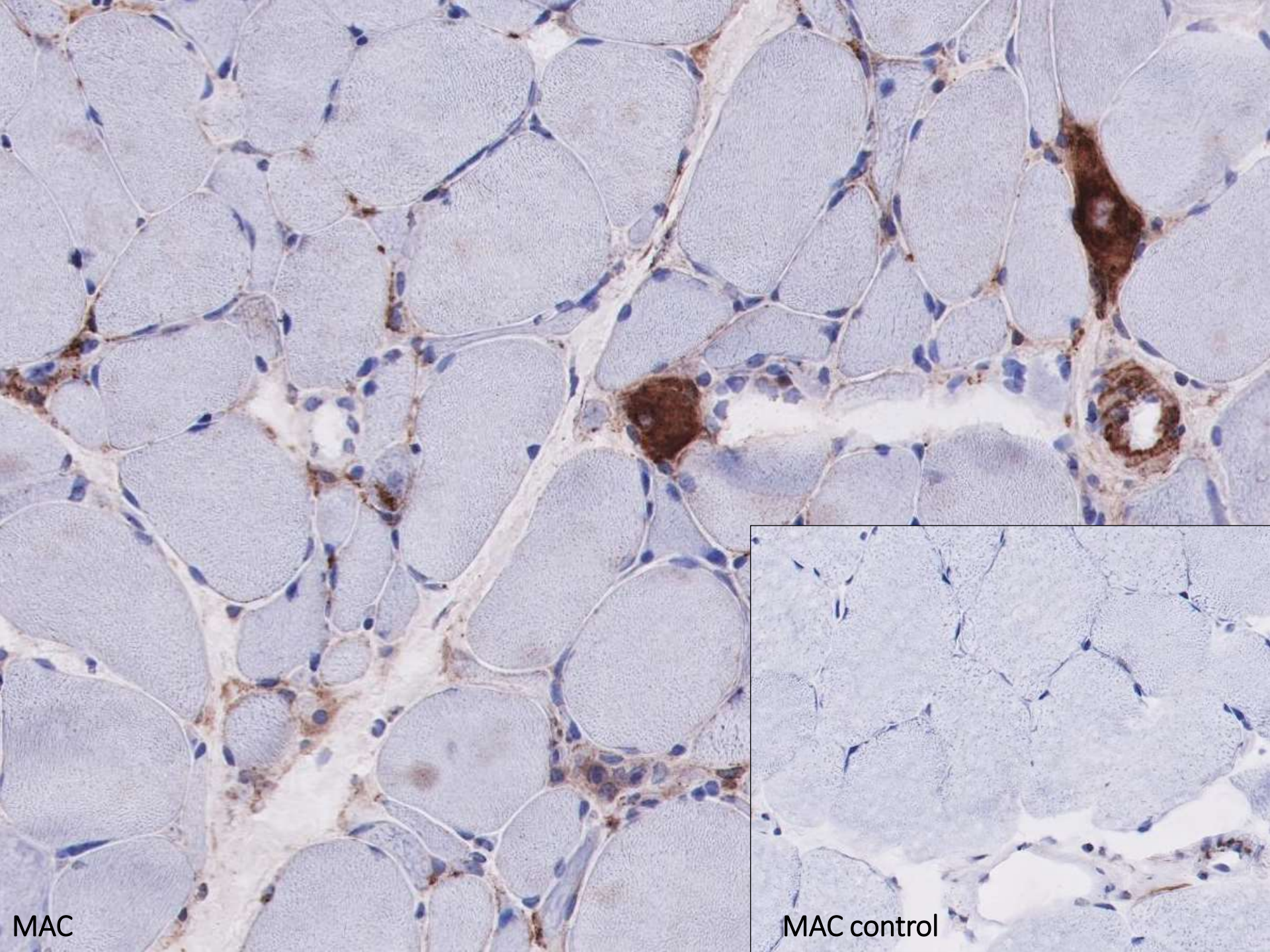


CO-SDH
cytochrome oxidase brown-succinate dehydrogenase blue


MHCI
MHCI control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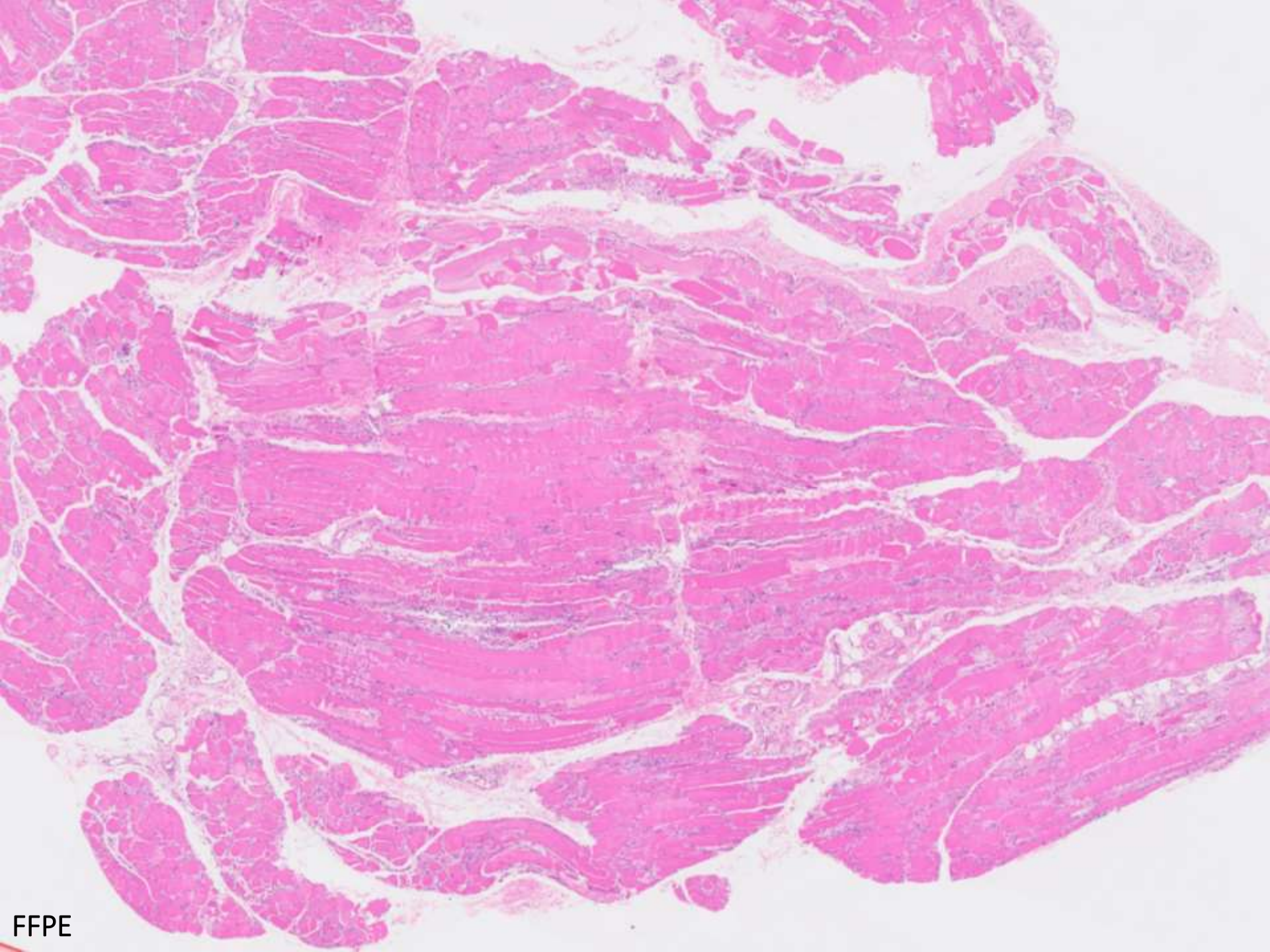
- 48 year old female with who presents progressive proximal muscle weakness for 3 month
- History of stage III serous ovarian cancer dx 2016 treated with chemotherapy and radiation
- Recurrence in 2018 treated with radiation and pembrolizumab (anti-PD1). Progression of disease treated with olaparib (PARP inhibitor)
- CK up to 1758 U/L
- Electrodiagnostic studies show mixed myopathic and neurogenic abnormalities, most consistent with a diffuse myopathy with secondary denervation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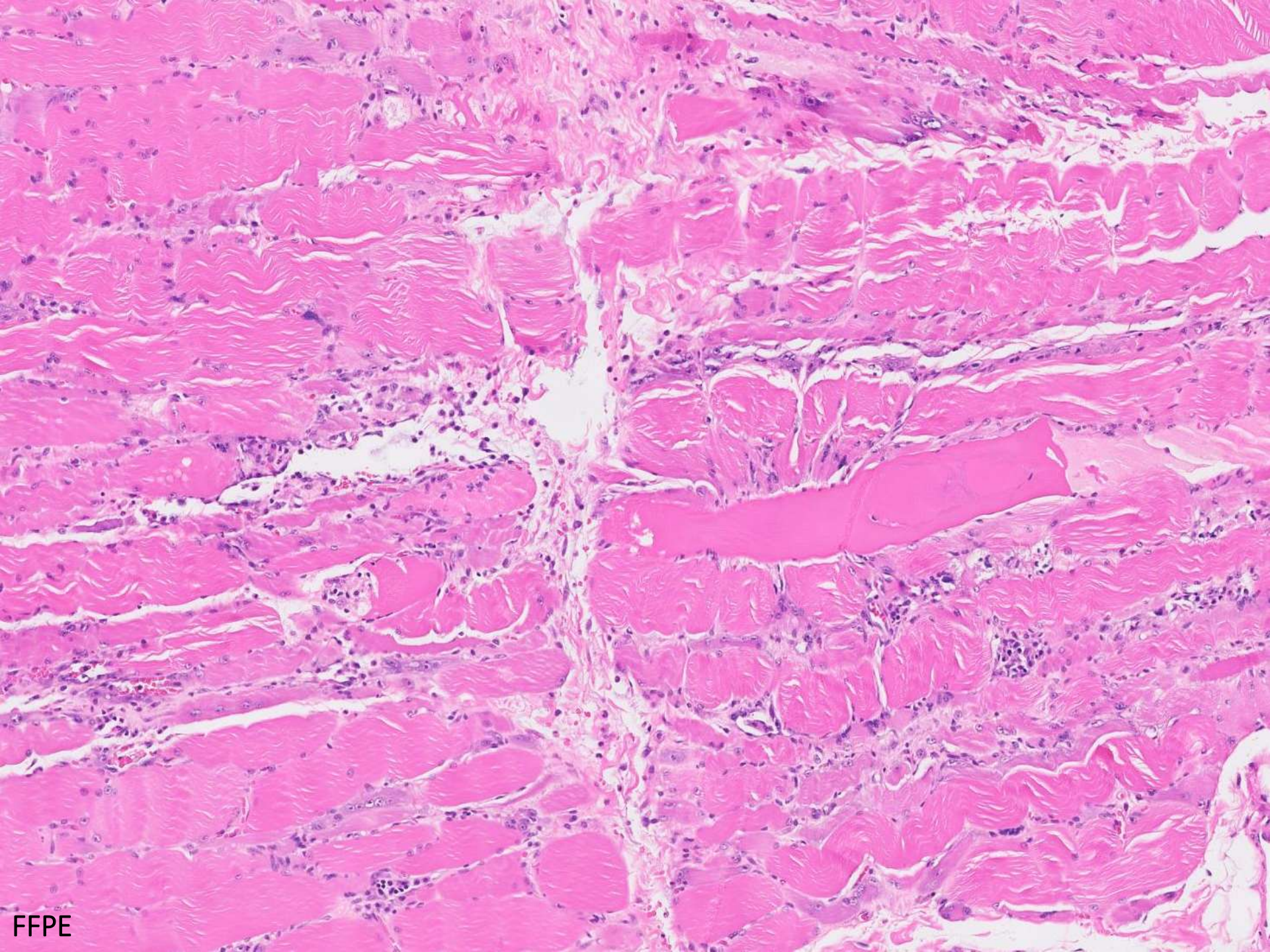
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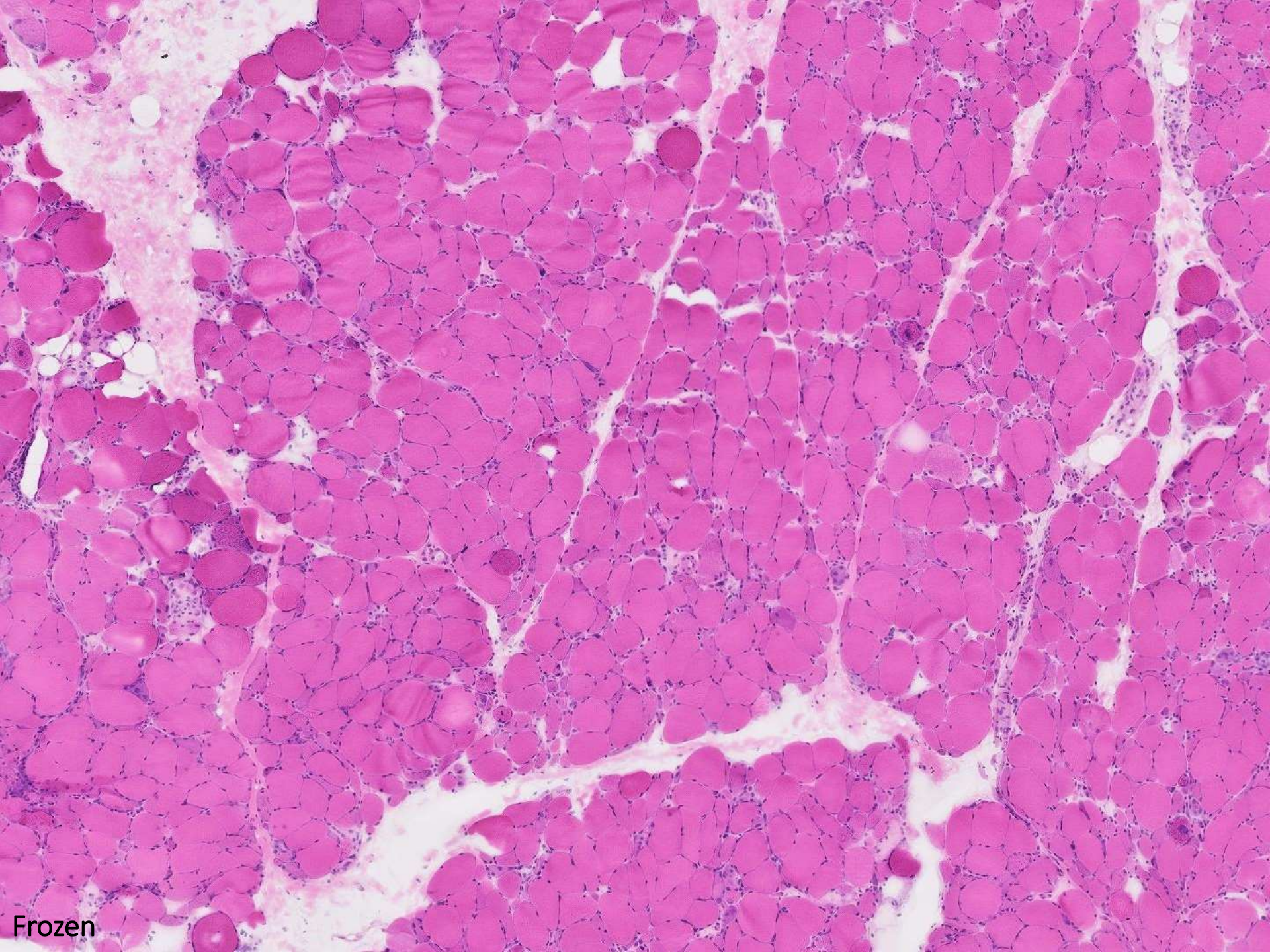
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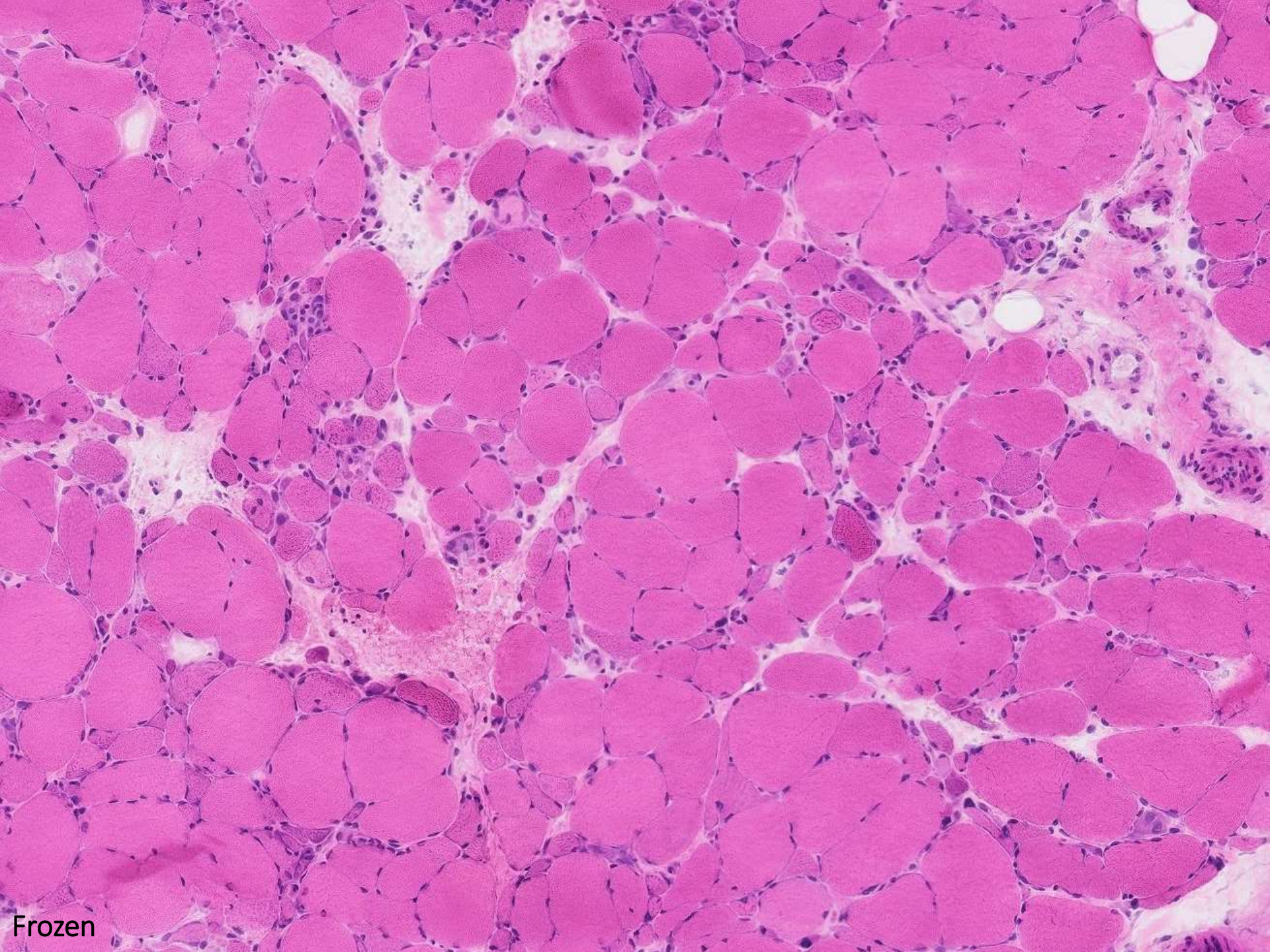
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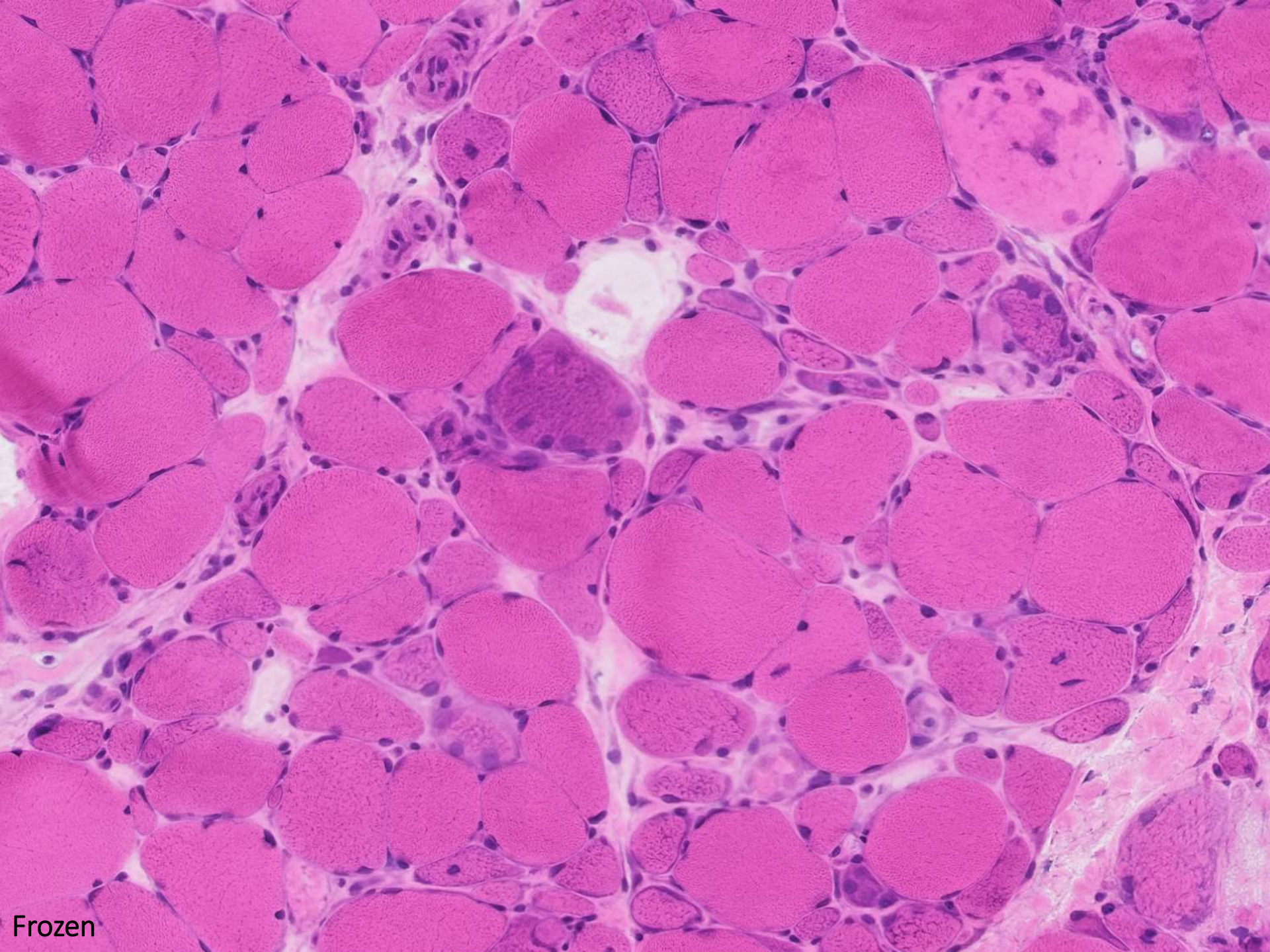
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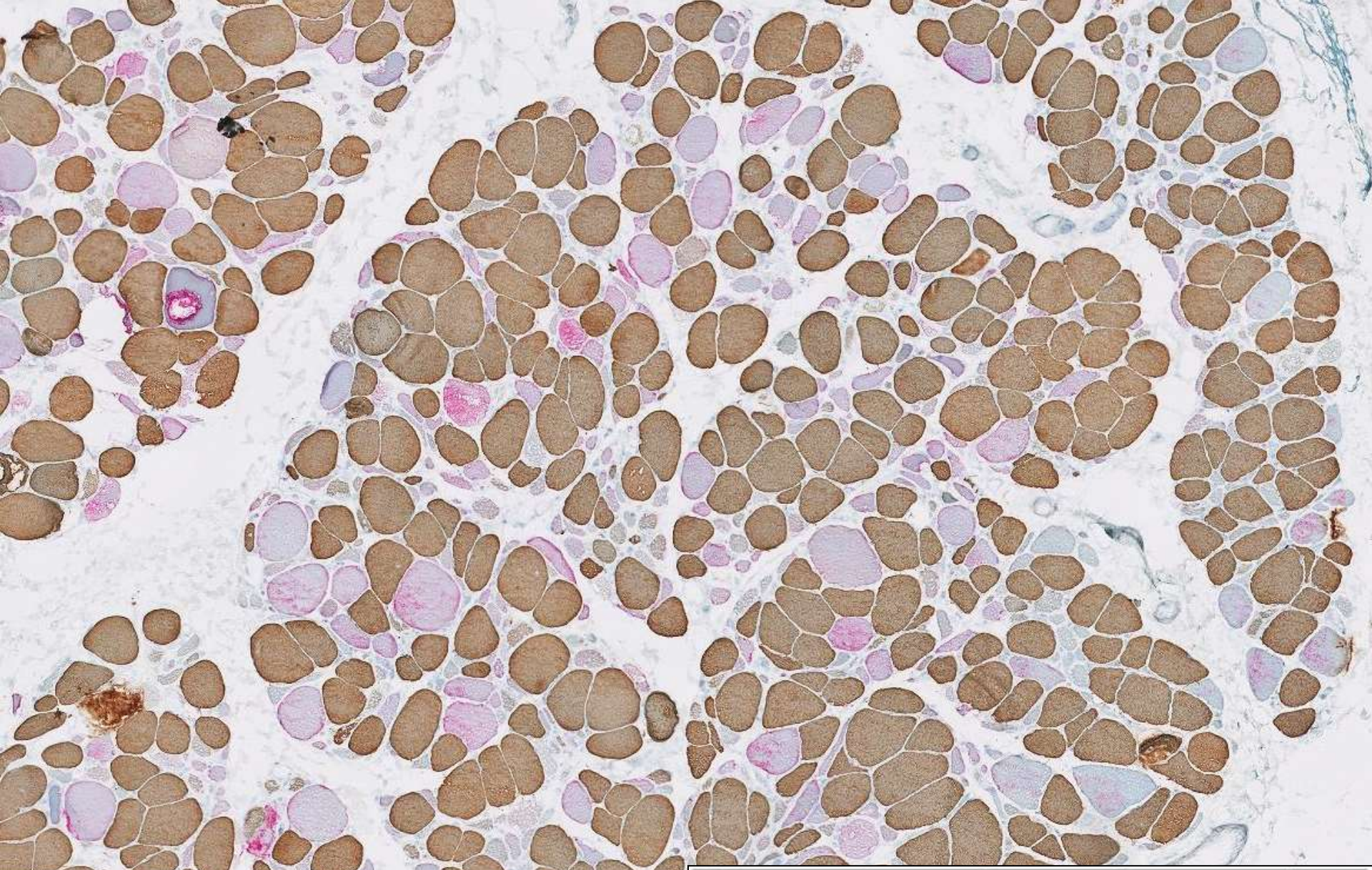

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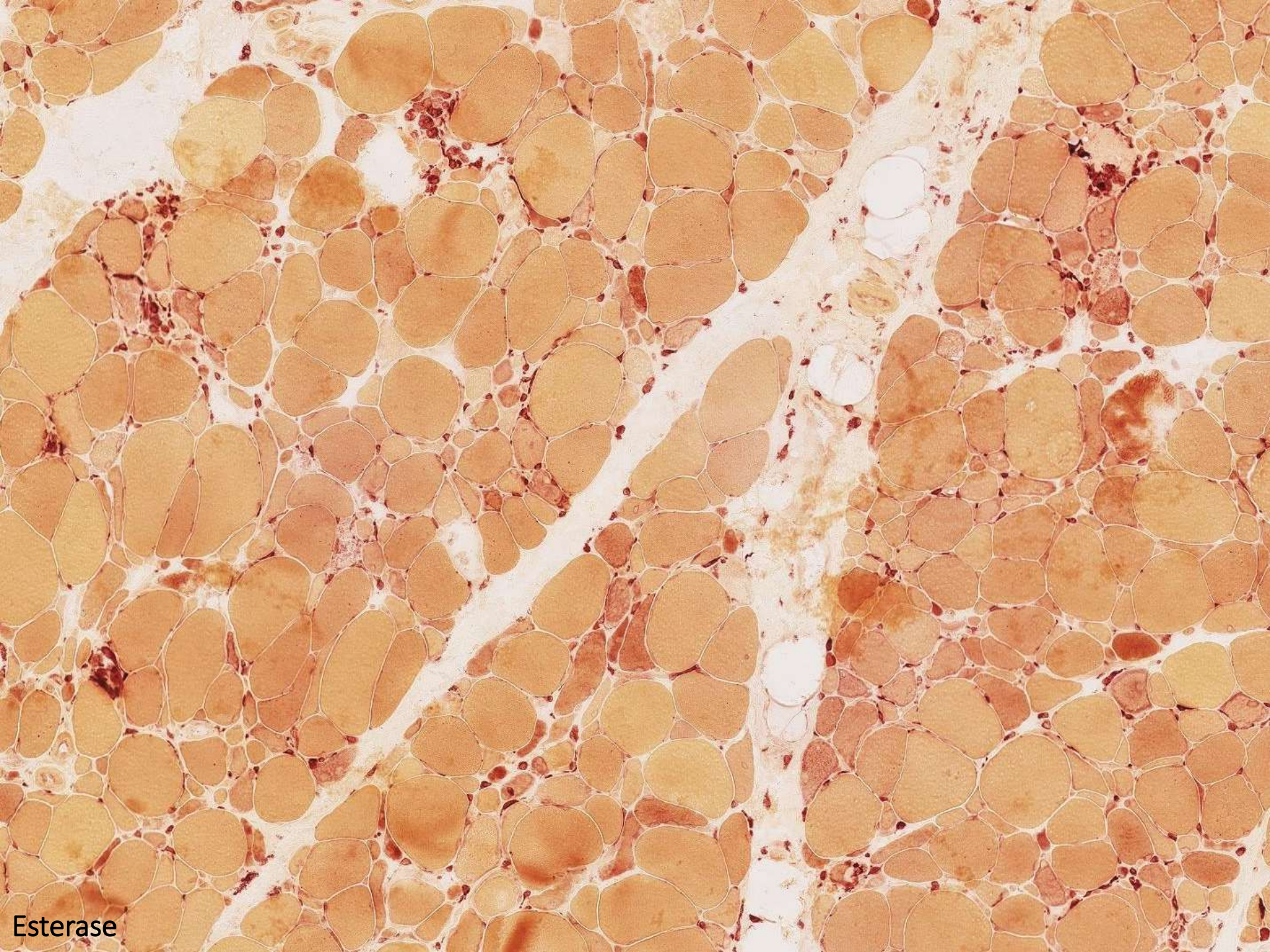
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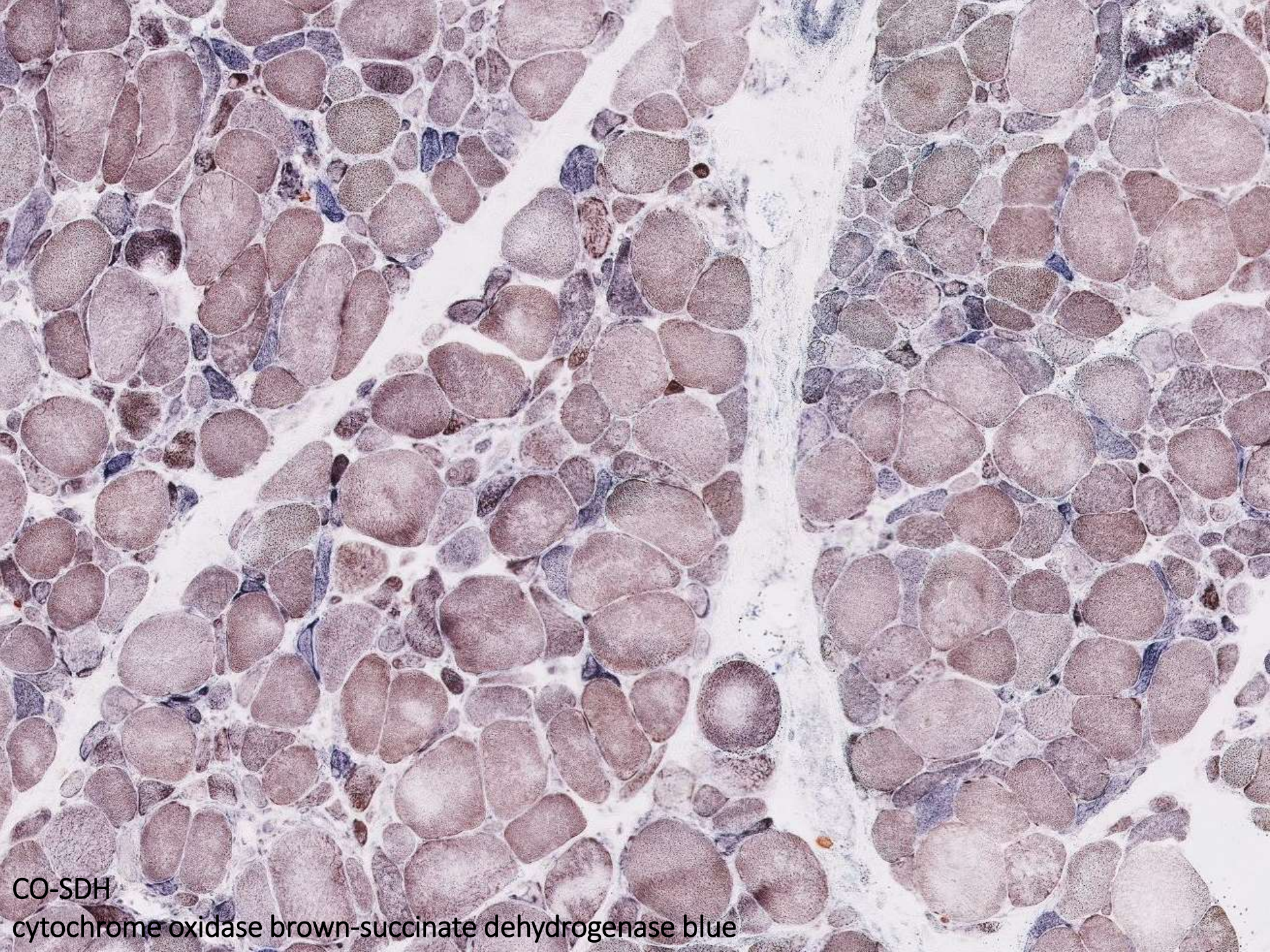

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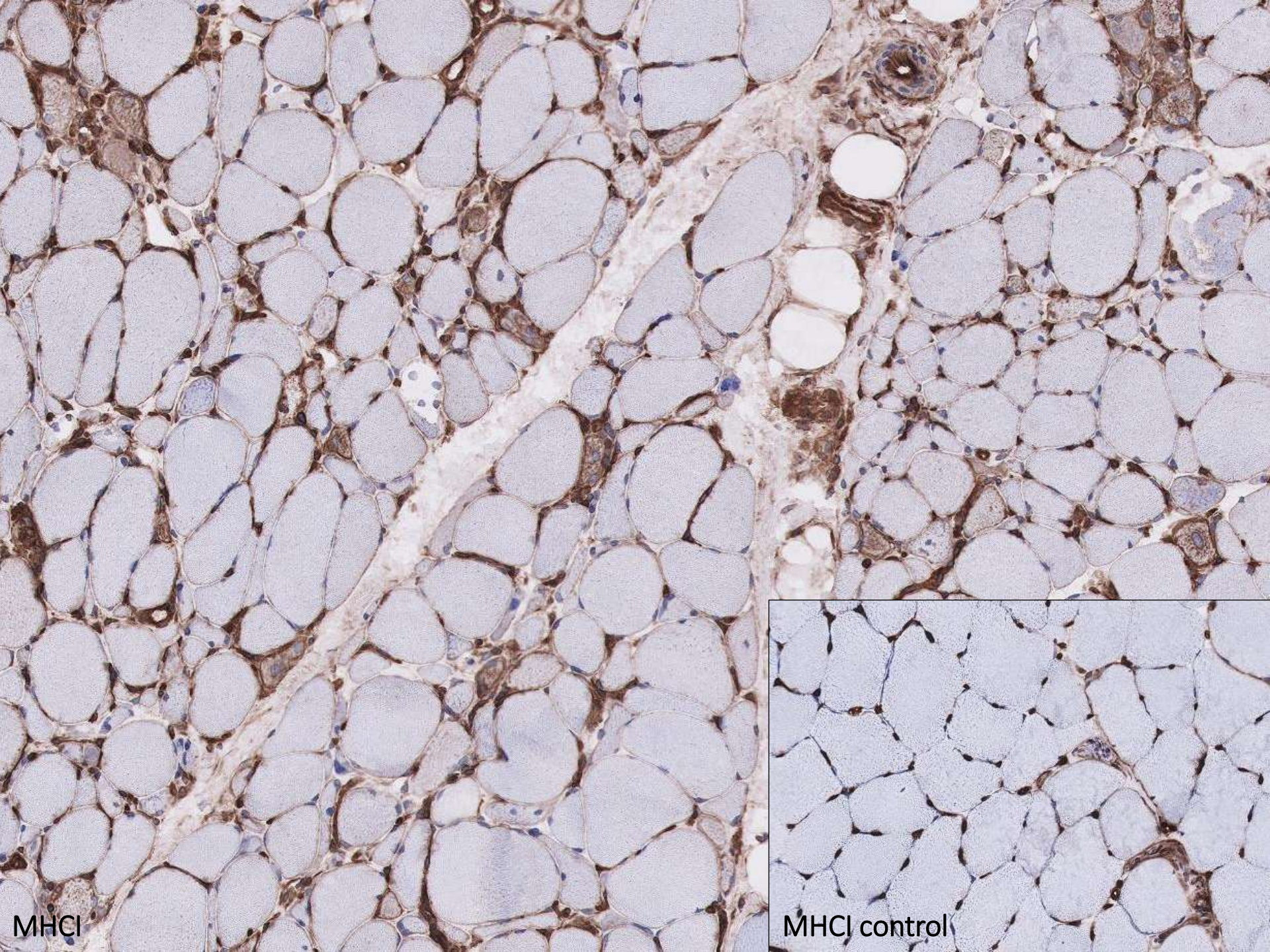
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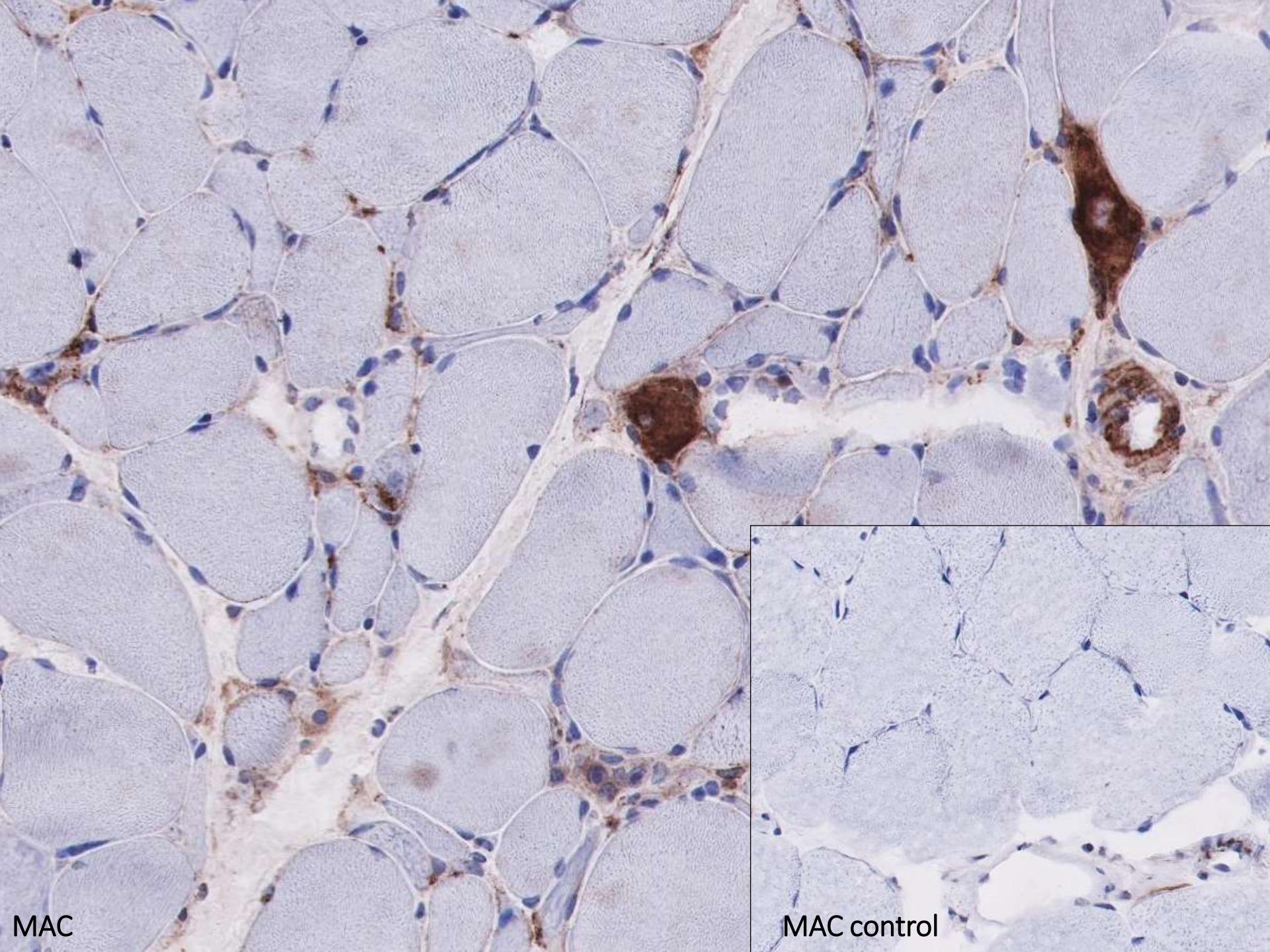
MAC
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# Diagnosis

- SKELETAL MUSCLE, RIGHT BICEP, BIOPSY

# Diagnosis

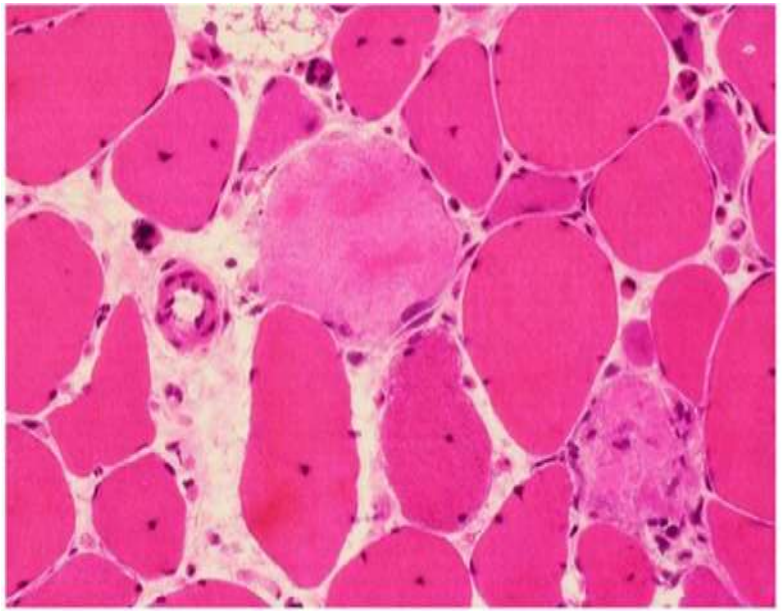
- SKELETAL MUSCLE, RIGHT BICEP, BIOPSY
  -- NECROTIZING MYOPATHY

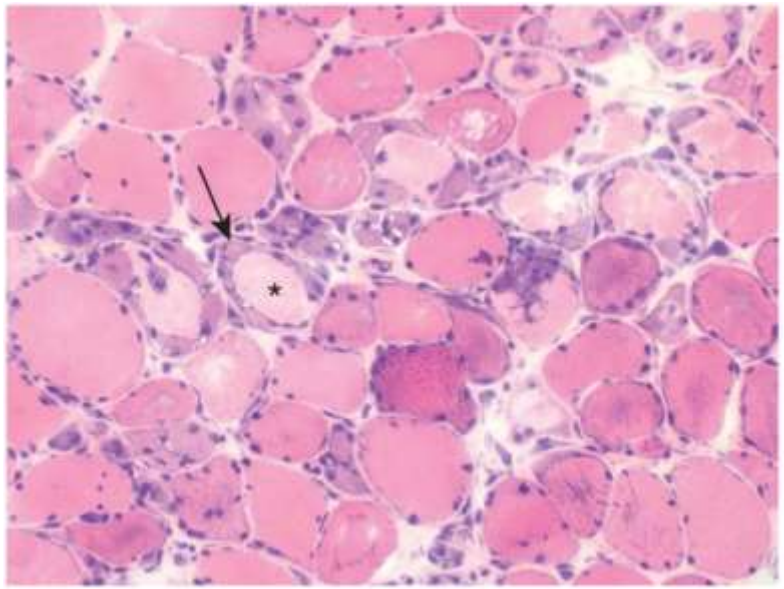
COMMENT: The differential diagnosis for a necrotizing myopathy is broad, but given the histologic features and the clinical history of PD-1 inhibitor, a toxic/metabolic (drug effect) is favored. However paraneoplasia and a primary autoimmune myopathy (polymyositis, including anti-HMGCR, anti-SRP or anti-synthetase) may display the pathology seen in this case.

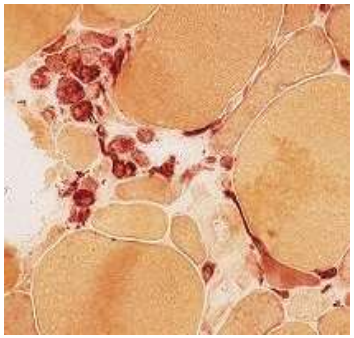
Further clinical and serological correlation is recommended.

# NECROTIZING MYOPATHY

- Immune mediated necrotizing myopathy
- Recently recognized entity
  - Prominent myofiber necrosis, regeneration and myophagocytosis
  - Minimal inflammation
- Immune mediated mechanism
- Heterogeneous group of disease with many etiologies







# NECROTIZING MYOPATHY

- Clinical features
  - Subacute (weeks to months), moderate to severe, symmetrical proximal progressive muscle weakness
  - Myalgia, respiratory fatigue, facial weakness, fatigue, weight loss
  - Elevated creatine phosphokinase (CK, often > 3000 U/L)
  - MRI can identify active inflammation and chronic muscle damage
  - Myopathic changes on electromyogram

# NECROTIZING MYOPATHY

- Myositis specific autoantibodies
  - Anti-HMGCoAR (25-50%), cholesterol biosynthesis pathway, +/- statin exposure (alimentary statins), +/- malignancy, moderate weakness, IVIG
  - Anti-SRP (20-40%), ribonucleotide protein, severe weakness, elevated CKs, prolonged immunotherapy, myocardial involvement
  - Seronegative (25-40%), likely heterogeneous group of diseases, association with malignancy, consider other causes of muscle necrosis
- Potential risk factors
  - Viral infection, genetic (mostly HLA genes), malignancy, connective tissue disease, drugs/toxins, metabolic defects, etc.

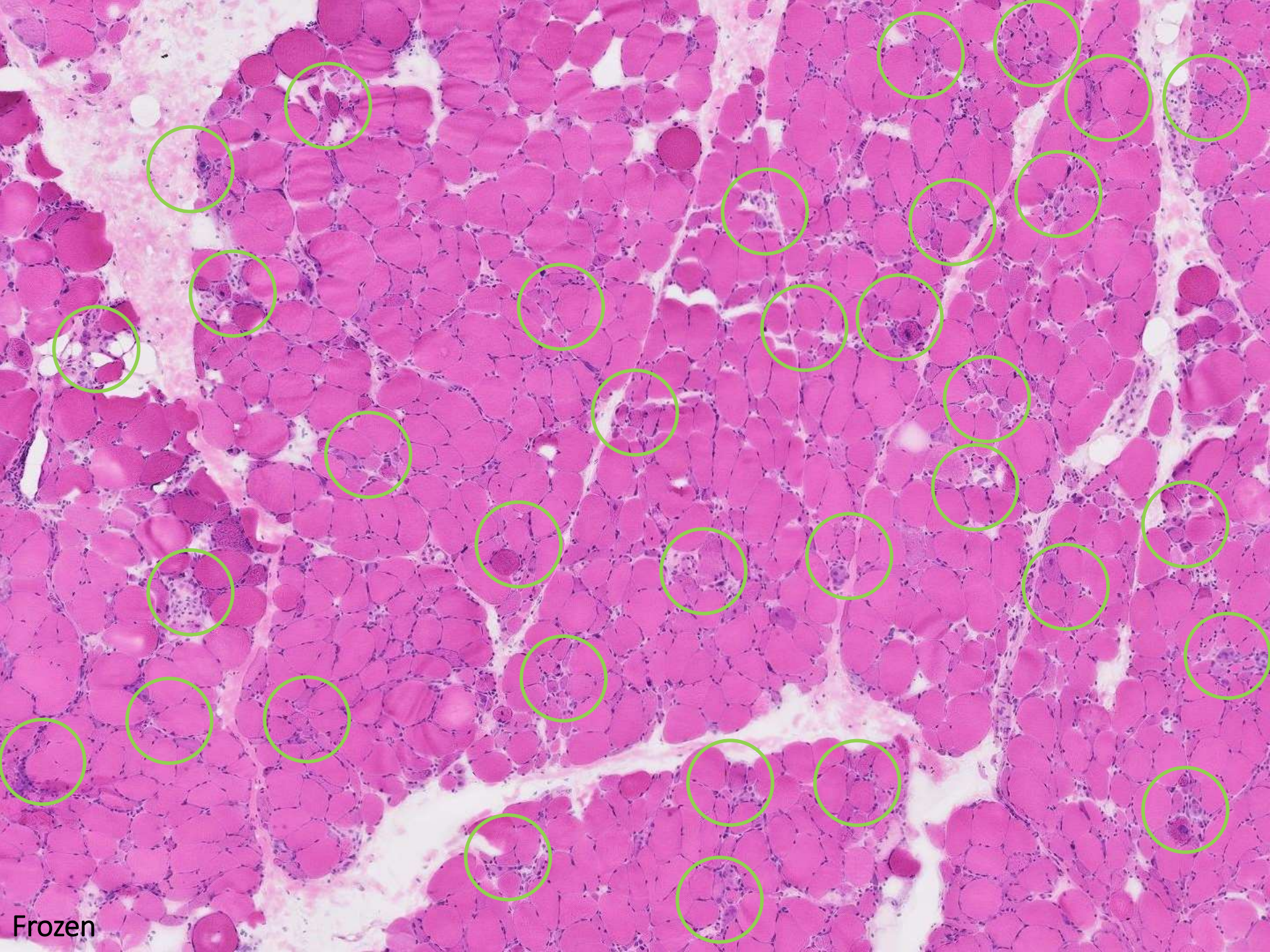
Non-immunological causes of muscle necrosis [1,5,141,142,149].

| | |
|---|---|
| Drugs | Statins (pharmacological and alimentary) (*) |
| | Multiple others reported, including: fibrates, cyclosporine, tacrolimus, propofol, labetolol, telbivudine, antipsychotics, voriconazole, malarone Epsilon-aminocaproic acid, ipecac, organophosphates, entecavir, zidovudine, colchicine, selective serotonin reuptake inhibitors, lithium, large doses of intravenous steroids |
| Drugs of abuse | Alcohol |
| | Cocaine |
| | Opiates |
| | Phencyclidine (Angel dust) |
| Toxins | Some wild mushrooms |
| | Snake venom |
| Needle myopathy | Focal necrosis caused by intramuscular injection of drugs and toxins |
| Infections | Hepatitis B, C (*), E |
| | HIV (*) |
| | Other viral (*): Influenza A or B, adenovirus, Epstein Barr Virus, Coxsackie |
| | Bacterial and parasitic infections |
| Metabolic | Genetic disorders of glycogenoylisis and glycosis |
| | Disorders of lipid metabolism |
| | Mitochondrial myopathies |
| | Hypokalaemia |
| | Hypocalcaemia |
| | Hypophosphataemia |
| | Nonketotic hyperosmotic disorders |
| | Diabetic ketoacidosis |
| | Thyroid dysfunction |
| | Adrenal insufficiency |
| Other | Muscular dystrophy |

# NECROTIZING MYOPATHY

- PD1 inhibitors are associated with immune related adverse events in many systems including the skin, the GI tract, endocrine, hepatic and pulmonary.

- Recent literature describes a necrotizing myopathy associated with PD1 inhibitors (Seki M et al, 2019; 19 cases)
  - 85% myalgias, 70% muscle weakness, 70% ocular involvement reminiscent of Myasthenia Gravis, 53% had bulbar symptoms, 30% respiratory involvement, 20% heart involvement, Elevated CK (average 5000)
  - No classic myositis specific antibody (anti-tintin and/or anti-Kv1.4 in 68% of cases)
  - Multifocal confluent foci of myofiber necrosis/regeneration with aberrant MHC class I
  - Rare CD4 and CD8 T cells (CD4 < CD8)
  - Treatment generally effective with gradual improvement in most patients
    - STOP PD1 inhibitor, +/- immunosuppression, +/- IVIG, +/- plasma exchange, +/- tacrolimus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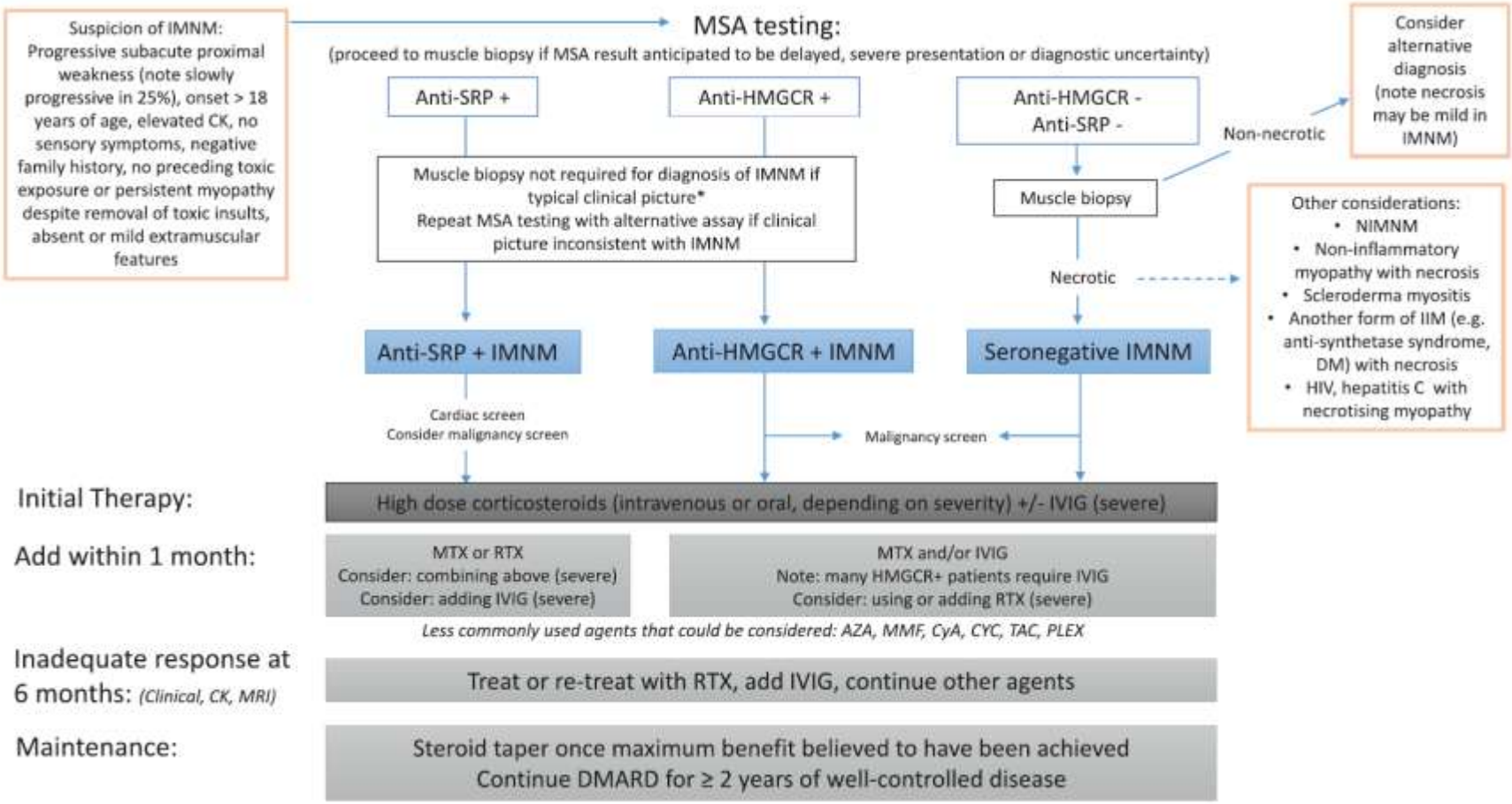
# NECROTIZING MYOPATHY



# SUMMARY

- Immune mediated necrotizing myopathy is a recently described type of autoimmune myopathy
  - Myofiber necrosis and regeneration with minimal inflammation
- Subdivided by autoantibody
  - Anti-SRP, anti-HMGCoAR and seronegative
- PD-1 inhibitors have been associated with an inflammatory myopathy characterized by multifocal small groups of necrotic/regenerating myofibers
- Clinical and serological correlation is essential

# REFERENCES


- Inflammatory myopathy associated with PD-1 inhibitors. Seki M, Uruha A, Ohnuki Y, Kamada S, Noda T, Onda A, Ohira M, Isami A, Hiramatsu S, Hibino M, Nakane S, Noda S, Yutani S, Hanazono A, Yaguchi H, Takao M, Shiina T, Katsuno M, Nakahara J, Matsubara S, Nishino I, Suzuki S. J Autoimmun. 2019 Jun;100:105-113

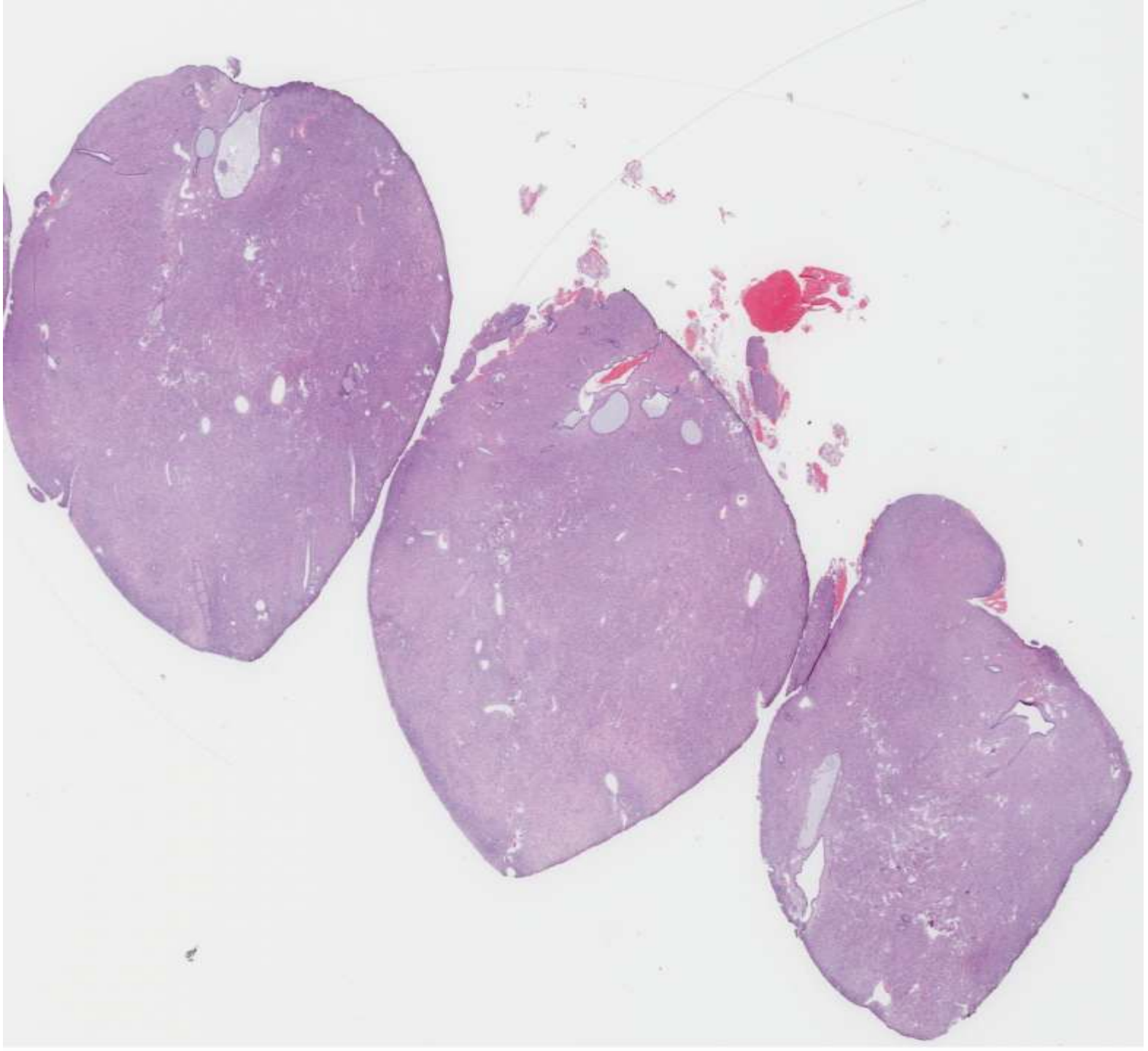
- Immune-mediated necrotising myopathy: A critical review of current concepts. Day JA, Limaye V. Semin Arthritis Rheum. 2019 Dec;49(3):420-429

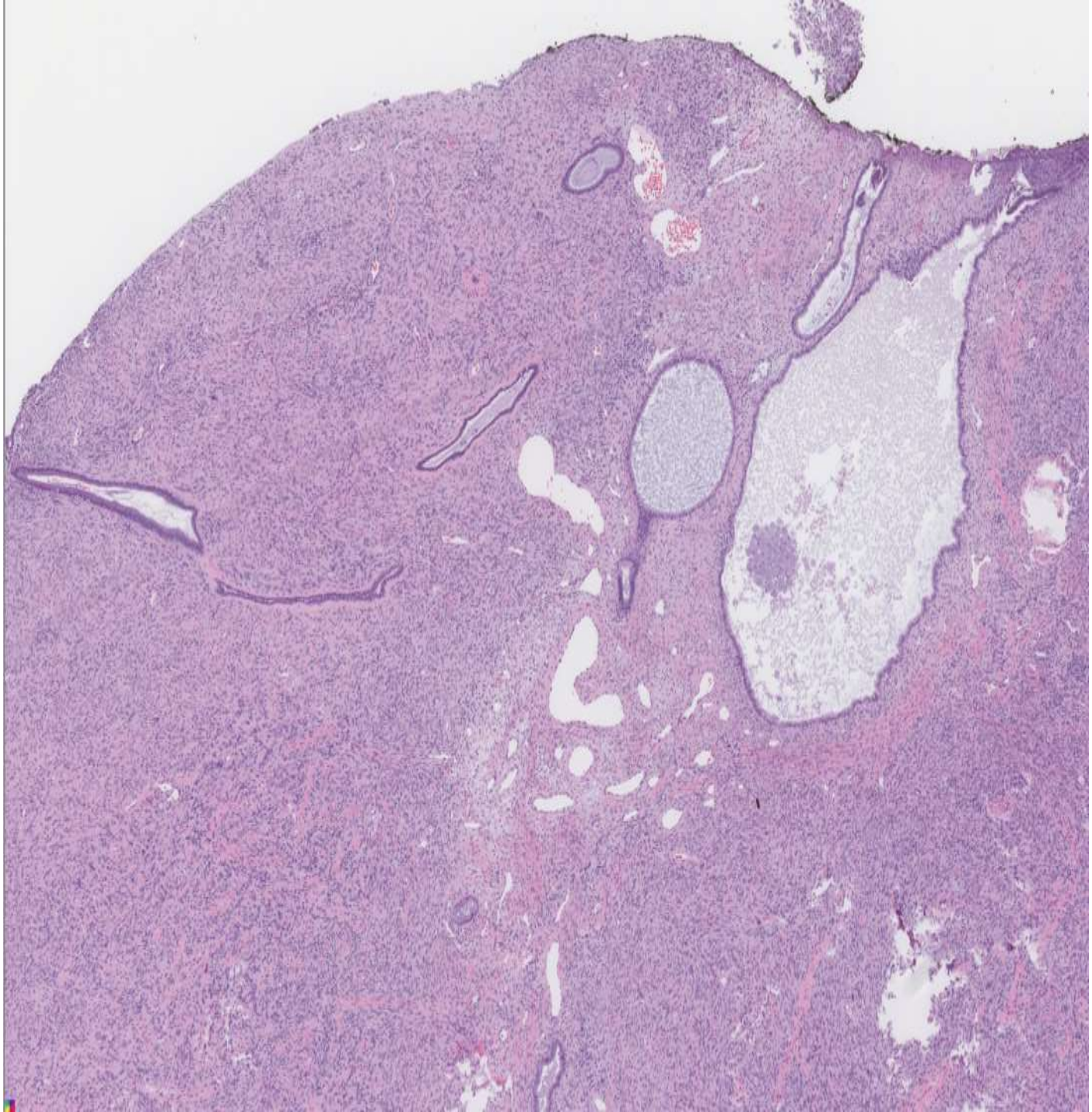
- Immune-Mediated Necrotizing Myopathy. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Curr Rheumatol Rep. 2018 Mar 26;20(4):21.

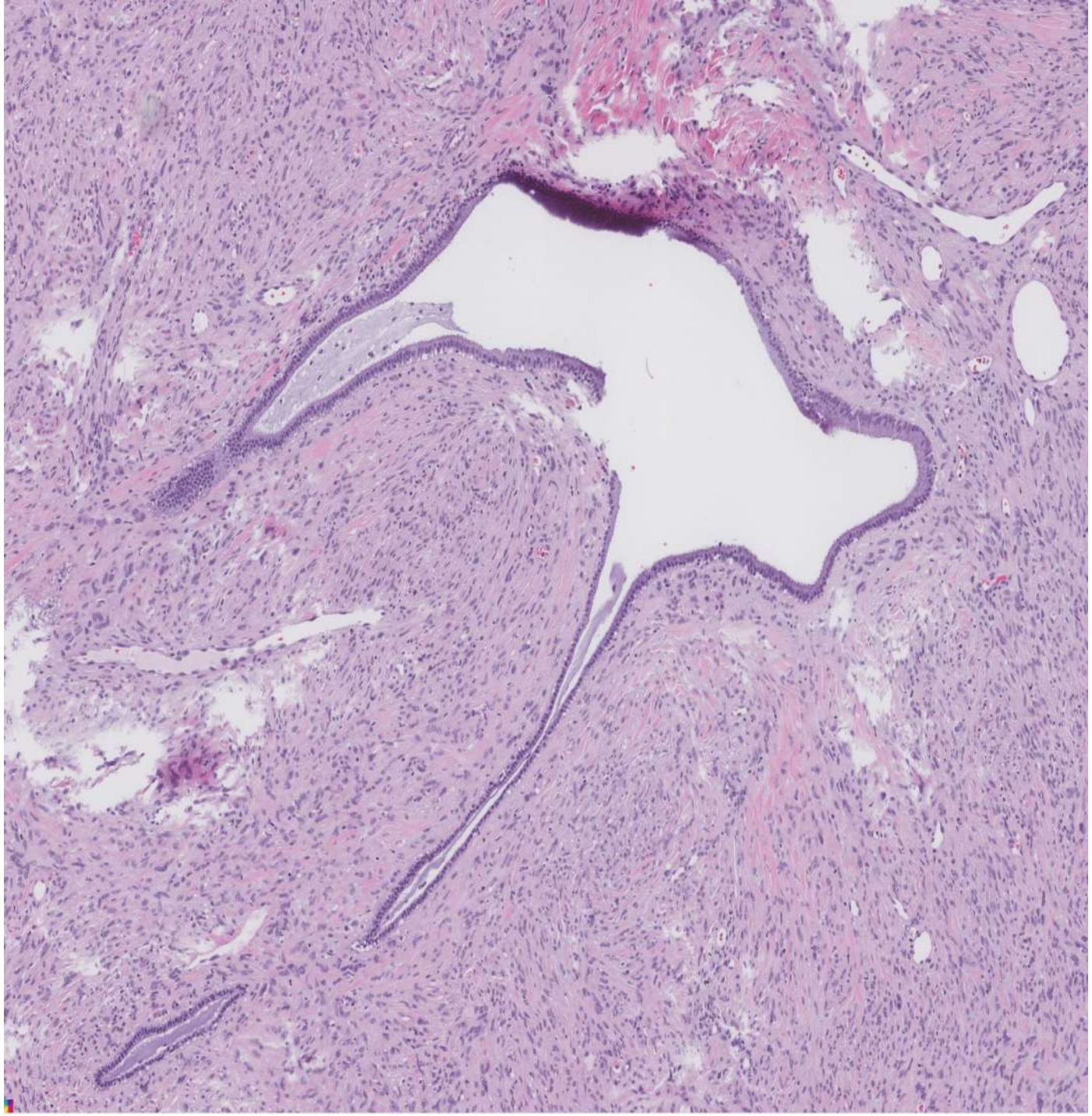

# 20-0204

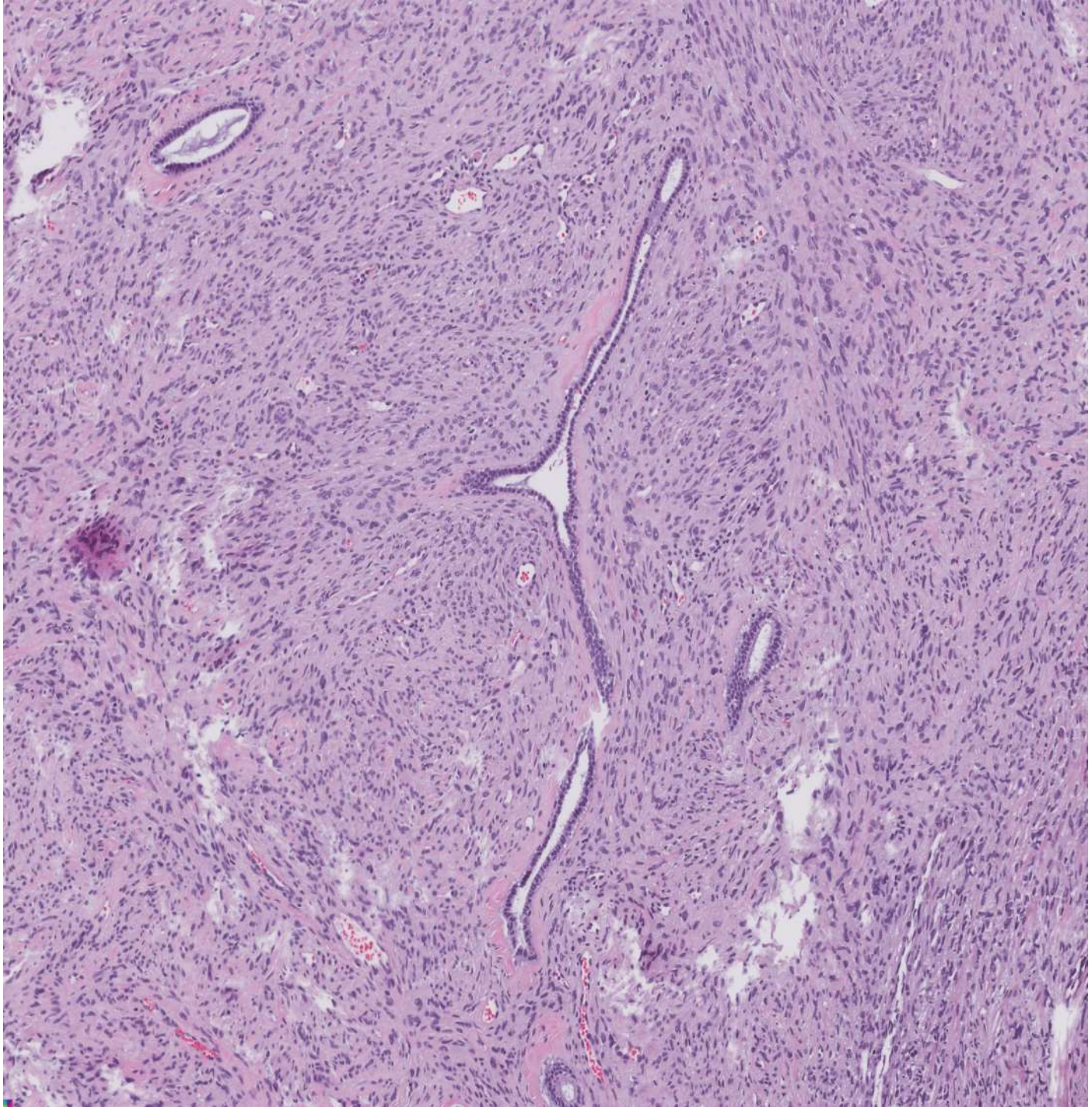
**Joseph Rabban; UCSF**

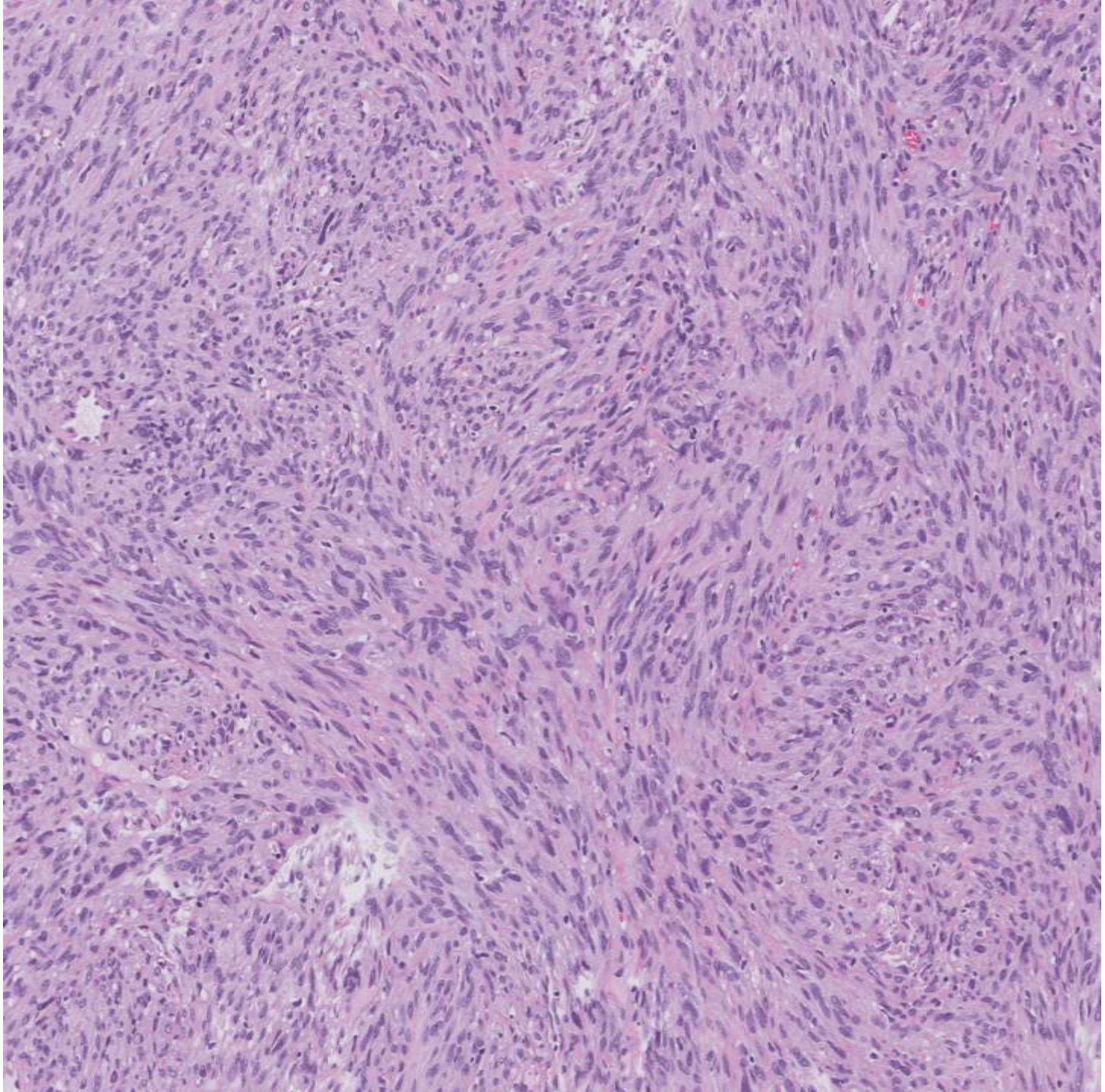
49-year-old F with 1.8cm prolapsed uterine fibroid at the cervical os that was locally excised.

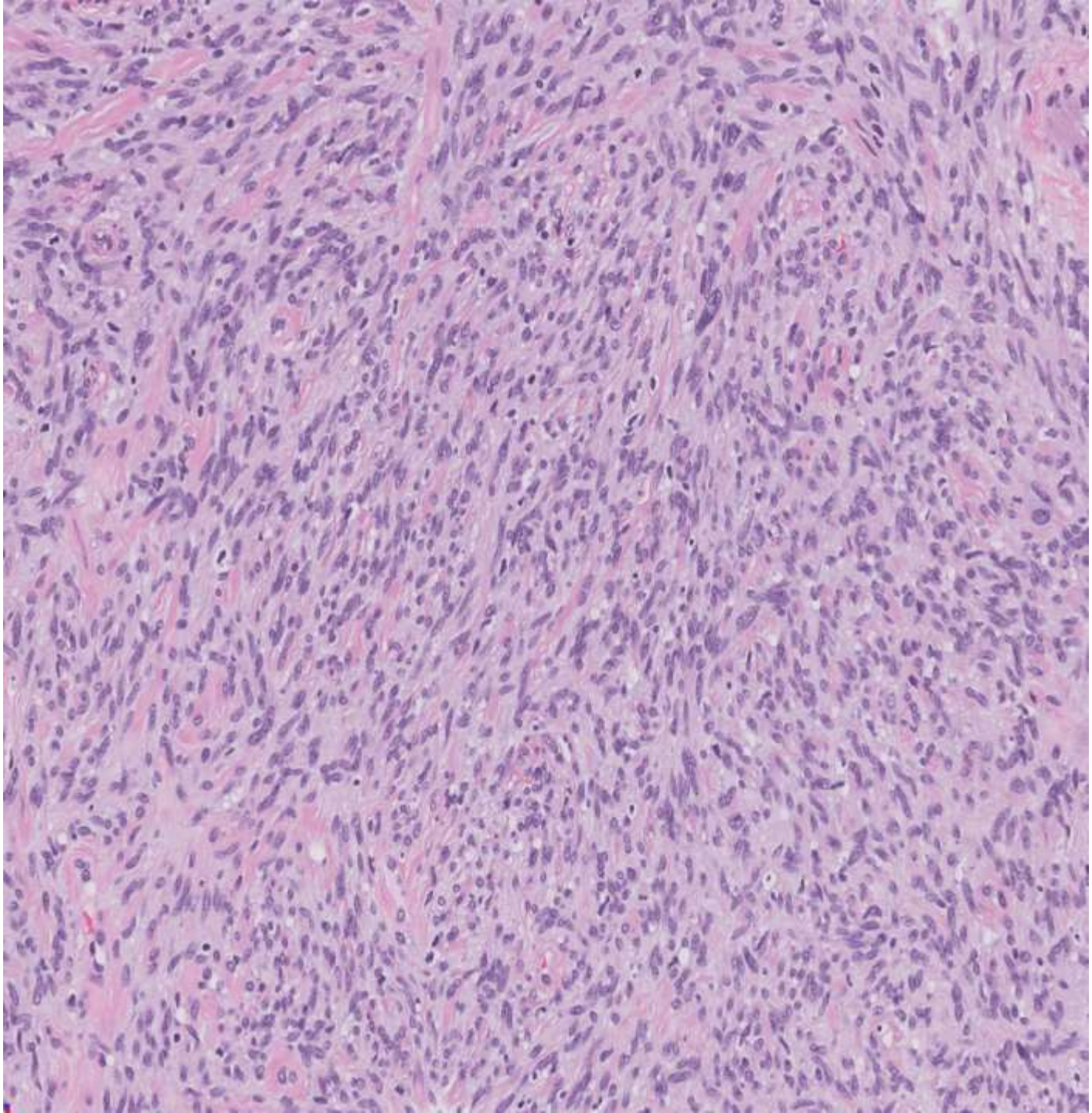


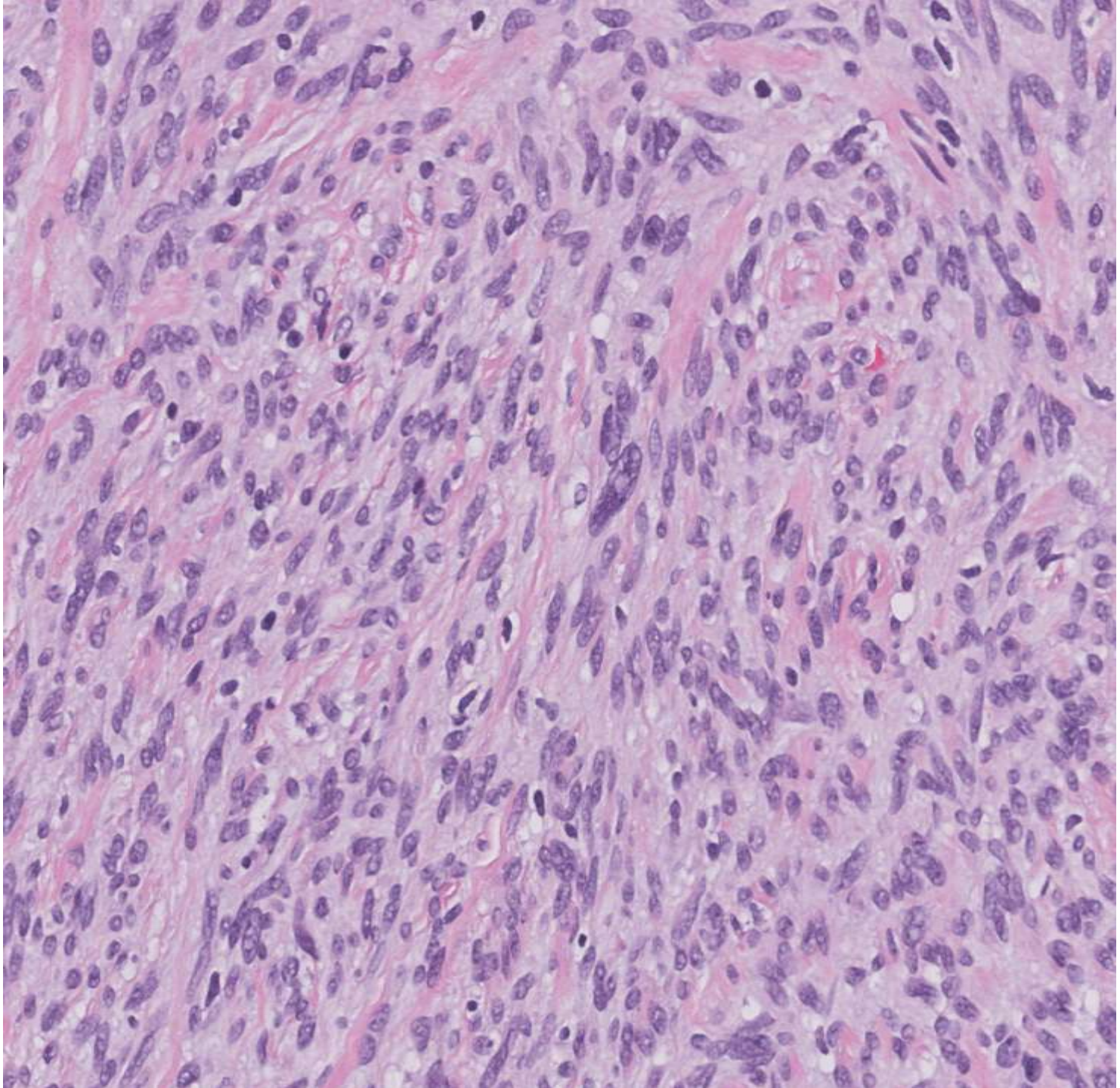












**Low grade fascicular spindle cell tumor of uterus**
**Mild / focal moderate atypia; rare mitoses**

| Initial Differential Diagnosis | Markers: All Negative Results |
|---|---|
| Leiomyoma variant | Desmin, caldesmon, SMM, SMA |
| Adenosarcoma variant | ER |
| PEComa | HMB45 |
| Inflammatory myofibroblastic tumor | ALK |
| | |
| Endometrial stromal tumor variant | CD10, ER, cyclinD1, CD117, BCOR |
| Sarcomatoid carcinoma | Keratin, CK7, p63, p16 |

ORIGINAL ARTICLE

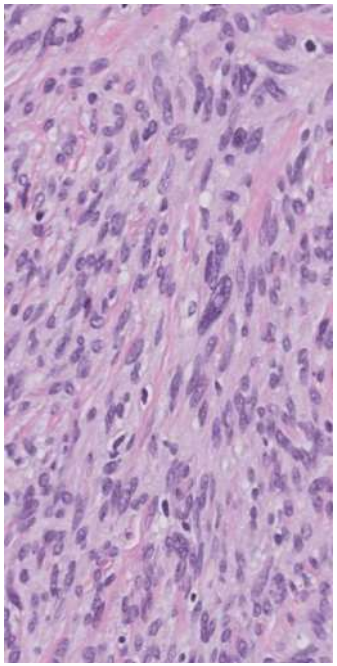
# *NTRK* Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

*Sarah Chiang, MD,* Paolo Cotzia, MD,* David M. Hyman, MD,† Alexander Drilon, MD,‡ William D. Tap, MD,§ Lei Zhang, MD,* Jaclyn F. Hechtman, MD,* Denise Frosina, BS,* Achim A. Jungbluth, MD, PhD,* Rajmohan Murali, MBBS, MD, FRCPA,* Kay J. Park, MD,* Robert A. Soslow, MD,* Esther Oliva, MD,‖¶ A. John Iafrate, MD, PhD,‖¶ Ryma Benayed, PhD,* Marc Ladanyi, MD,* and Cristina R. Antonescu, MD**

**Abstract:** Tropomyosin receptor kinase (Trk) inhibitors have shown high response rates in patients with tumors harboring *NTRK* fusions.

**Key Words:** *NTRK*, uterine sarcoma, fibrosarcoma

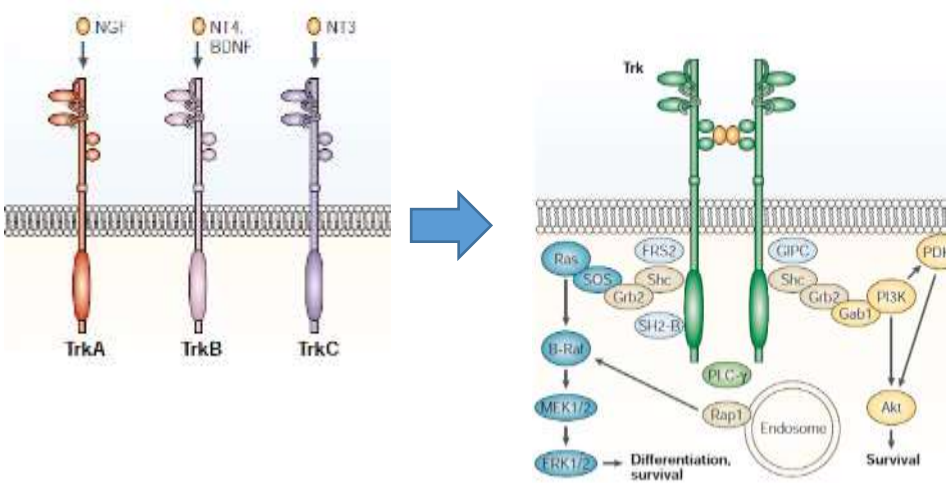
(*Am J Surg Pathol* 2018;42:791–798)



- **Young women (20-40)**
- **Cervical mass / polyp**
- **“Fibrosarcoma-like”**
  - Fascicular growth
  - Spindle cells with mild/mod atypia
  - Variable mitoses
- **Negative for myoid, endometrial stromal markers**
- **Positive for S100**

# *NTRK* = neurotrophic tyrosine receptor kinase

| Gene | Protein | Main Receptor Ligand |
|---|---|---|
| *NTRK1* | Tropomyosin receptor kinase A (TrkA) | Nerve growth factor |
| *NTRK2* | Tropomyosin receptor kinase B (TrkB) | Brain-derived neurotrophic factor |
| *NTRK3* | Tropomyosin receptor kinase C (TrkC) | Neurotrophin 3 |

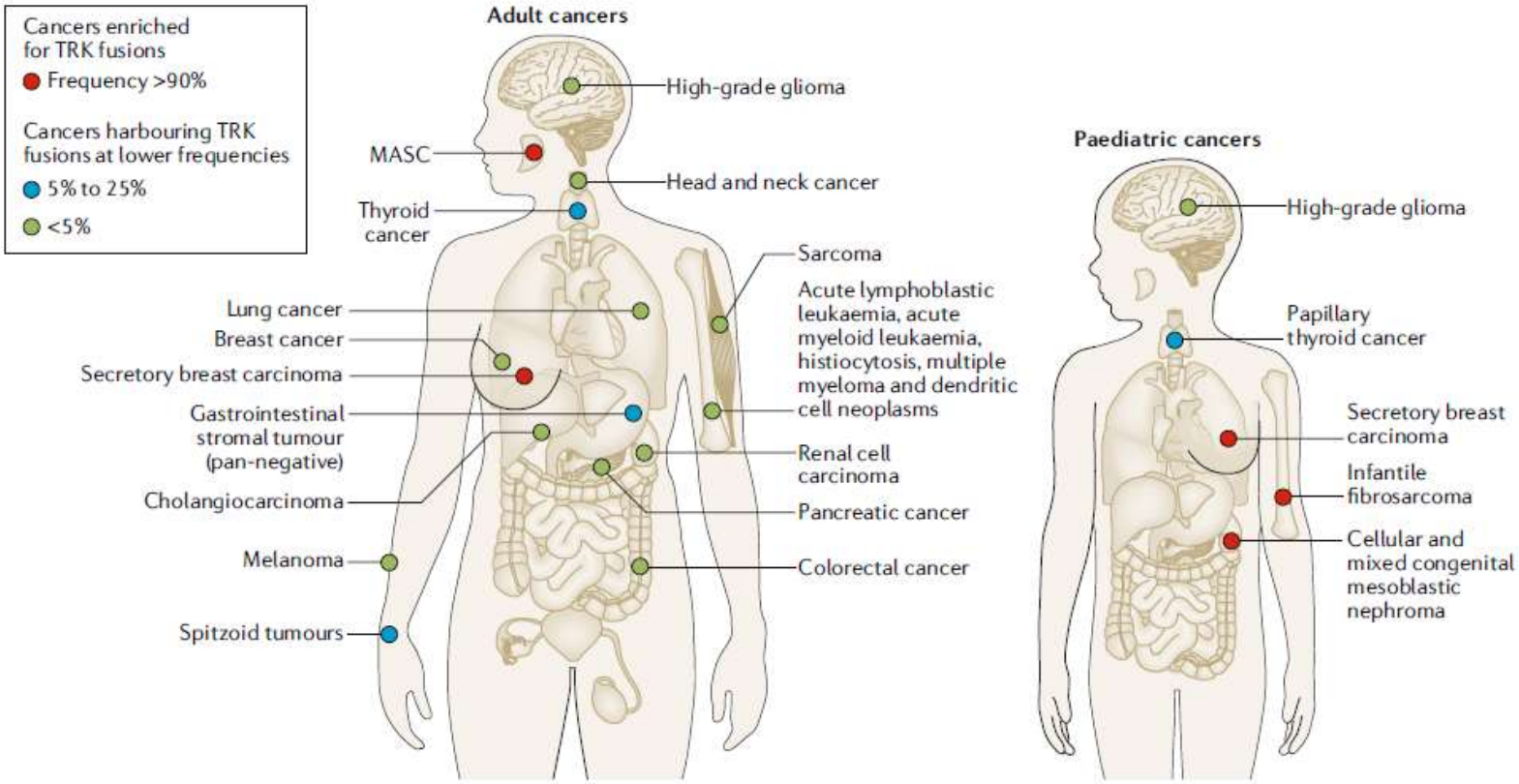



| Normal roles |
|---|
| Mediate neurotrophin activation of signaling cascade |
| Developmental role: nervous system |
| Regulatory role: pain, appetite, proprioception, memory |

Figures reprinted by permission of Springer Nature from Chao. Nat. Rev. Neurosc. 2003; 4: 299-309

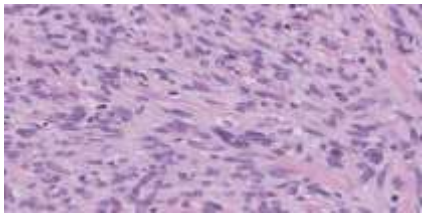
# *NTRK* fusion is recognized in an expanding spectrum of malignancies

Two groups:
1. Tumors highly enriched for *NTRK* fusion
2. Tumors with low prevalence of *NTRK* fusion




Figures reprinted by permission of Springer Nature from Cocco et al. Nat. Rev. Clin. Onc. 2018; 15: 731-747

# Clinical relevance of recognizing *NTRK* fusion cervical sarcoma



1. **Metastatic / recurrent potential in a subset**

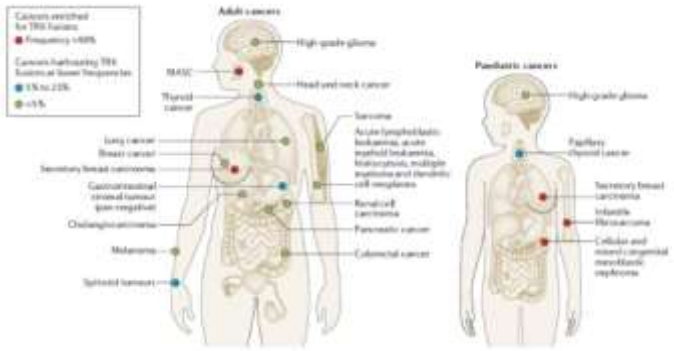
   *-not enough cases to identify prognostic variables*

| | Stage I | Metastasis / Local recurrence | Death |
|---|---|---|---|
| **Chiang et al. AJSP 2018** | **4/4** | **1/4** | **1/4** |
| **Croce et al. Mod Pathol 2019** | **5/7** | **2/6** | **0** |
| **Rabban et al. Histopath. 2020** | **3/3** | **1/3** | **0** |
| **Michael et al. AJSP 2019** | **1/1** | **0** | **0** |

2. **Targeted therapy approved by FDA for *NTRK* fusion positive tumors**

   -agnostic to tumor type / origin

| "Basket" Clinical Trials | TRK inhibitor |
|---|---|
| NCT02122913 trial<br>SCOUT trial<br>NAVIGATE trial<br><br>Drilon et al. NEJM 2018 | **Larotrectinib** |
| ALKA-372 trial<br>STARTRK-1 trial<br>STARTRK-2 trial<br><br>Doebele et al. Lanc Oncol 2020 | **Entrectinib** |



- **Detection Methods for *NTRK* fusion**

| |
|---|
| **DNA or RNA sequencing** |
| **RT-PCR** |
| **FISH** |
| **IHC: pan-TRK** (Trk A, Trk B and Trk C) |

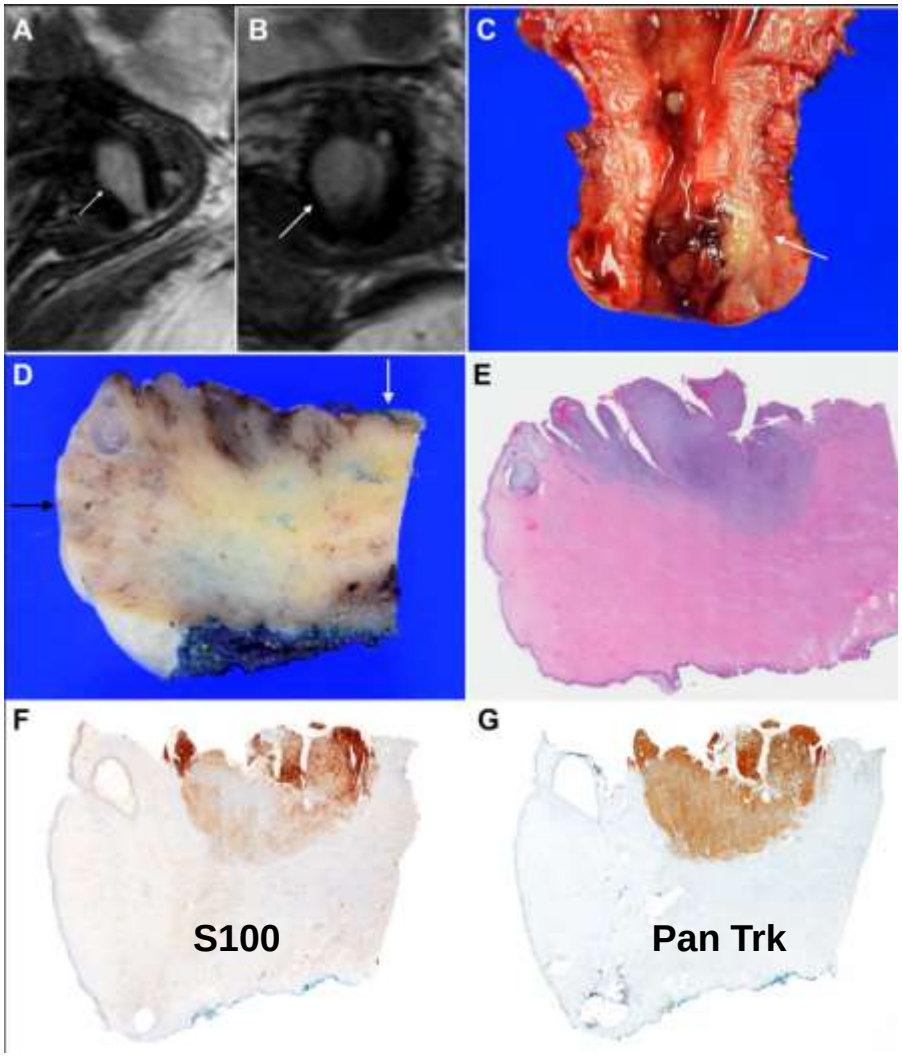
- **Pan-TRK IHC**

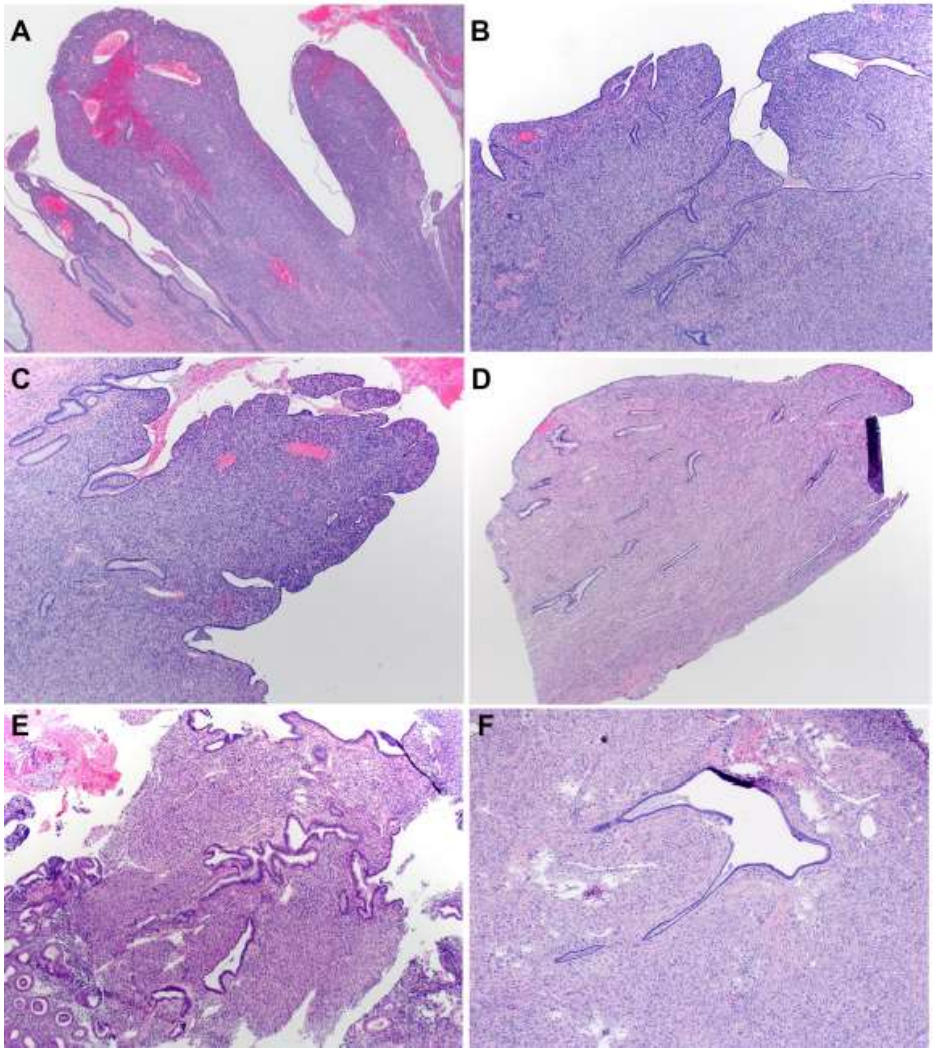
| Fusion | Staining Pattern |
|---|---|
| **None** | **None** |
| ***NTRK1*** | **Cytoplasmic** (diffuse / moderate to strong) |
| ***NTRK2*** | **Cytoplasmic** (diffuse / moderate to strong) |
| ***NTRK3*** | **Nuclear +/- cytoplasmic** (diffuse / moderate to strong) |

| | |
|---|---|
| **Sensitivity** | **~81%-97 %** *(lower for NTRK3)* |
| **Specificity** | **~92%-98%** |

Rudzinski, AJSP 2018
Gatalica, Mod Pathol 2019
Hechtman, AJSP 2017
Hung, Histopath 2018
Suurmeijer, Gene Chr Canc 2019
Solomon, Mod Pathol 2019

**S100 often positive in mesenchymal tumors with *NTRK* fusion**




Histopathology. 2020 Jan 23. doi: 10.1111/his.14069. [Epub ahead of print]

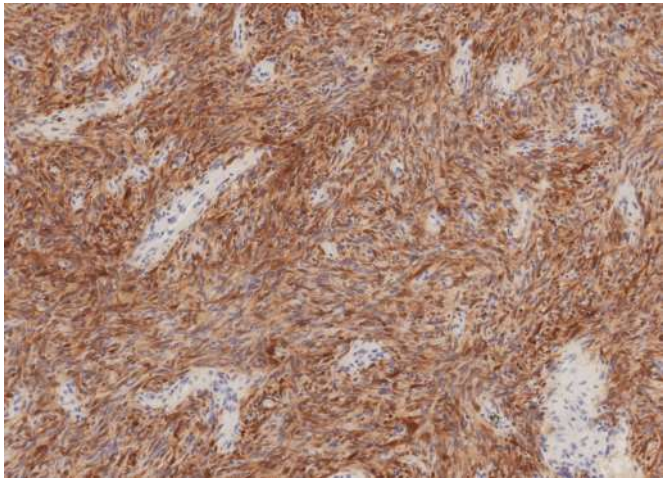
# NTRK Fusion Cervical Sarcoma: A Report of 3 Cases, Emphasizing Morphological and Immunohistochemical Distinction from Other Uterine Sarcomas, including Adenosarcoma.

Rabban JT[1], Devine P[1], Sangoi AR[2], Poder L[3], Alvarez E[4], Davis JL[5], Rudzinski E[6], Garg K[1], Bean GR[1].

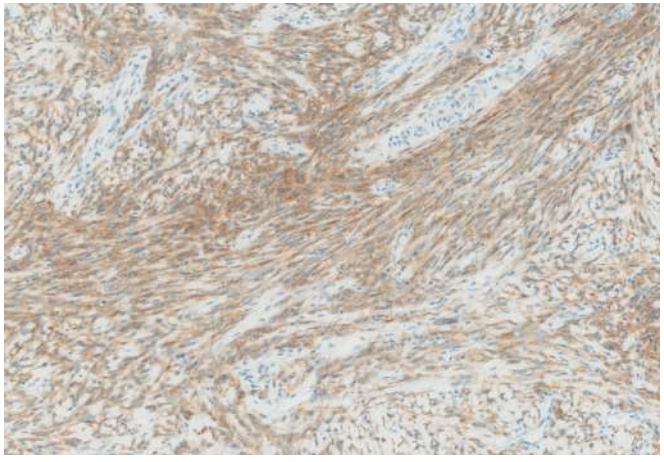
## South Bay case 20-204

**Diagnosis: *NTRK* fusion cervical sarcoma**

**S100**

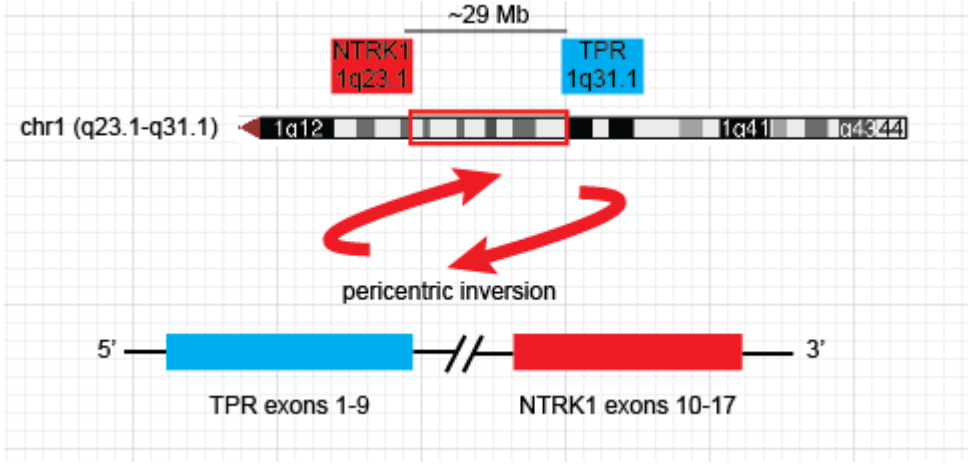


**Pan Trk**



**UCSF500 NGS test:**

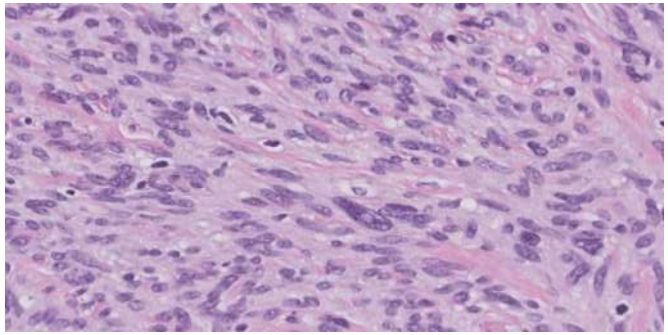
***TPR – NTRK1 fusion***



## South Bay case 20-204

## Take-home Message

**Uterine fibrosarcoma-like or adenosarcoma-like tumor**
**Morphology and IHC don't fit classical differential diagnosis**



**S100 or pan Trk stain**

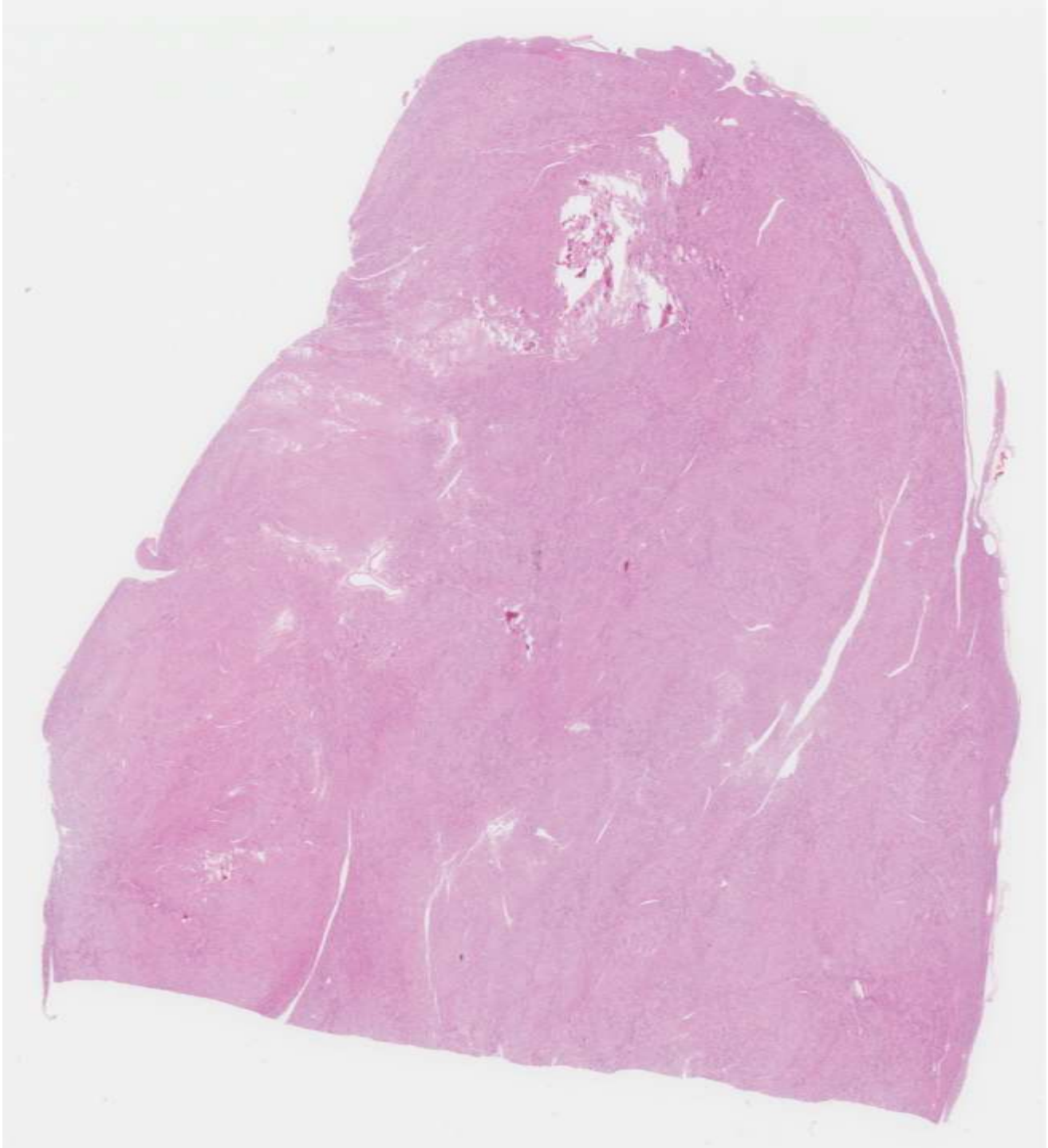
**Positive** — **Work up *NTRK* fusion**

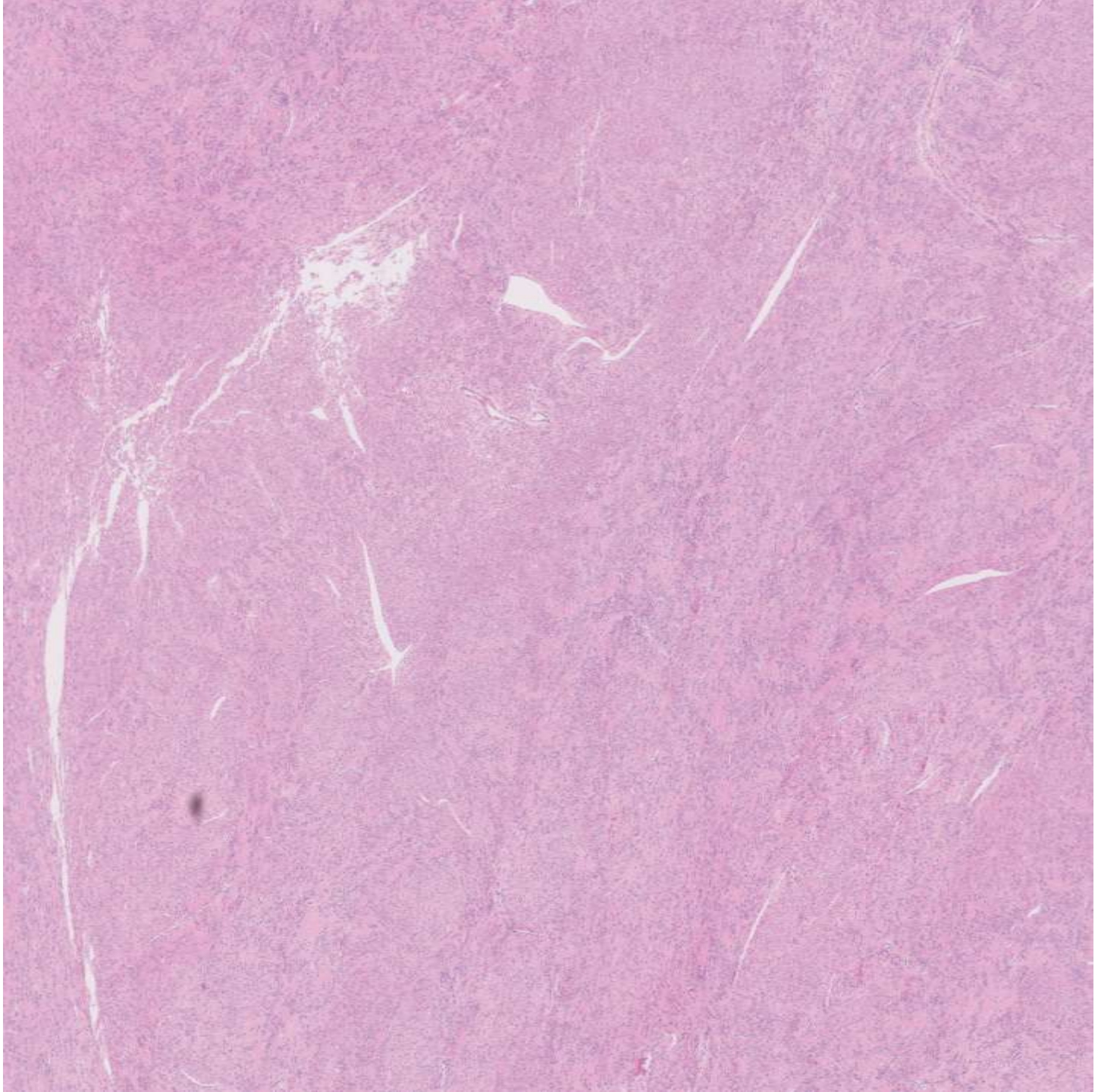
**Negative** — **Descriptive Diagnosis**

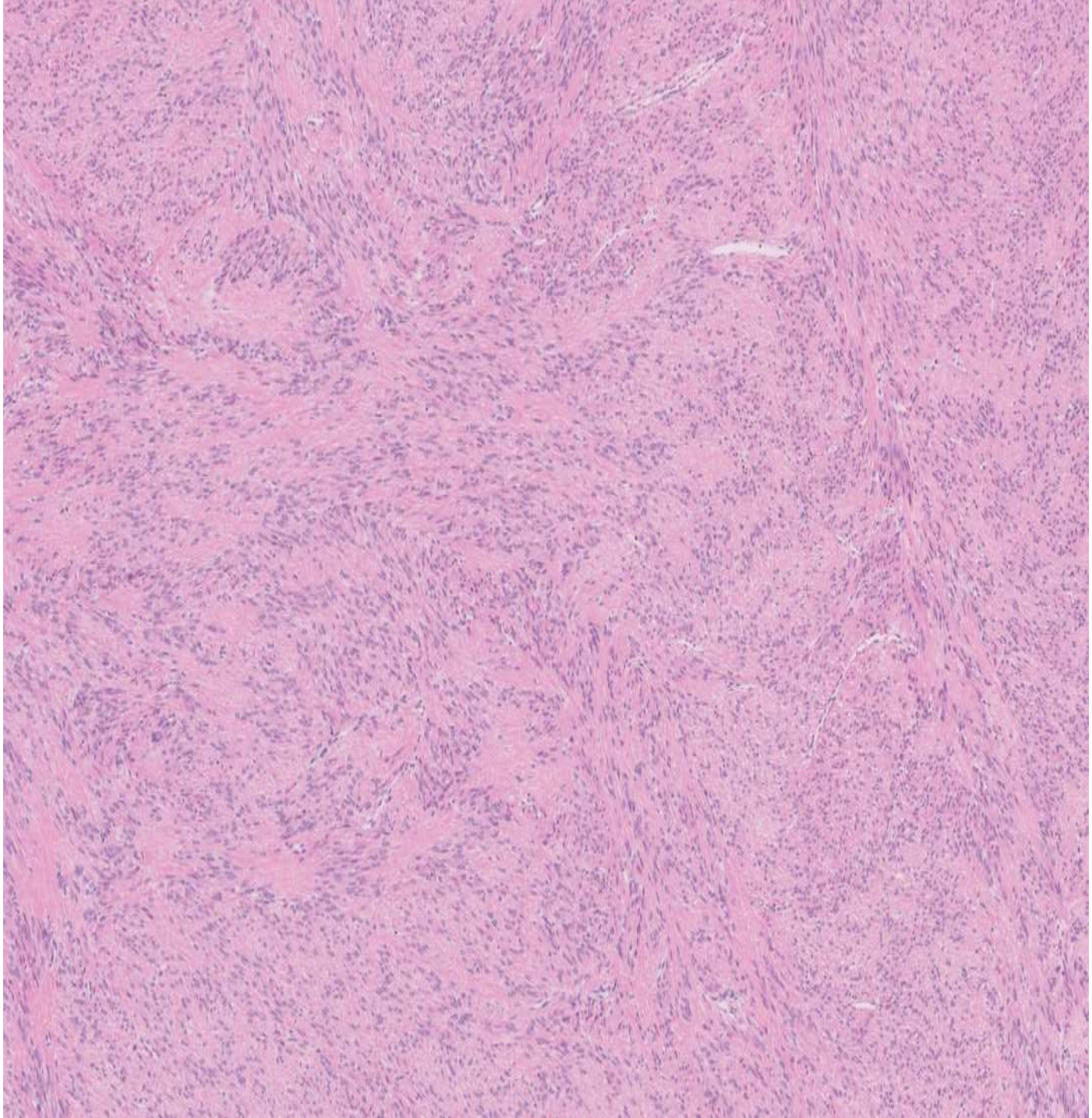
# 20-0205

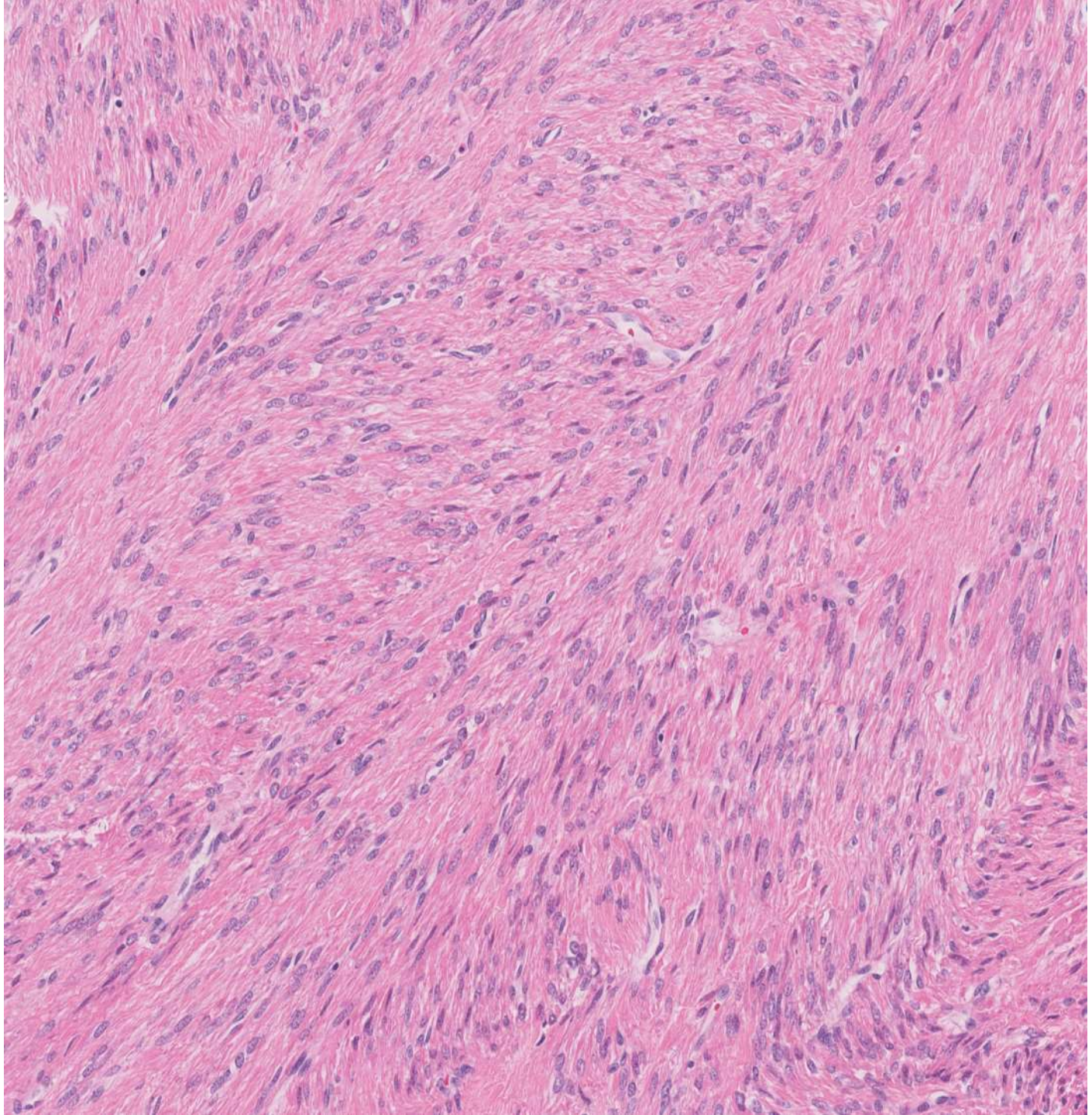
**Joseph Rabban; UCSF**

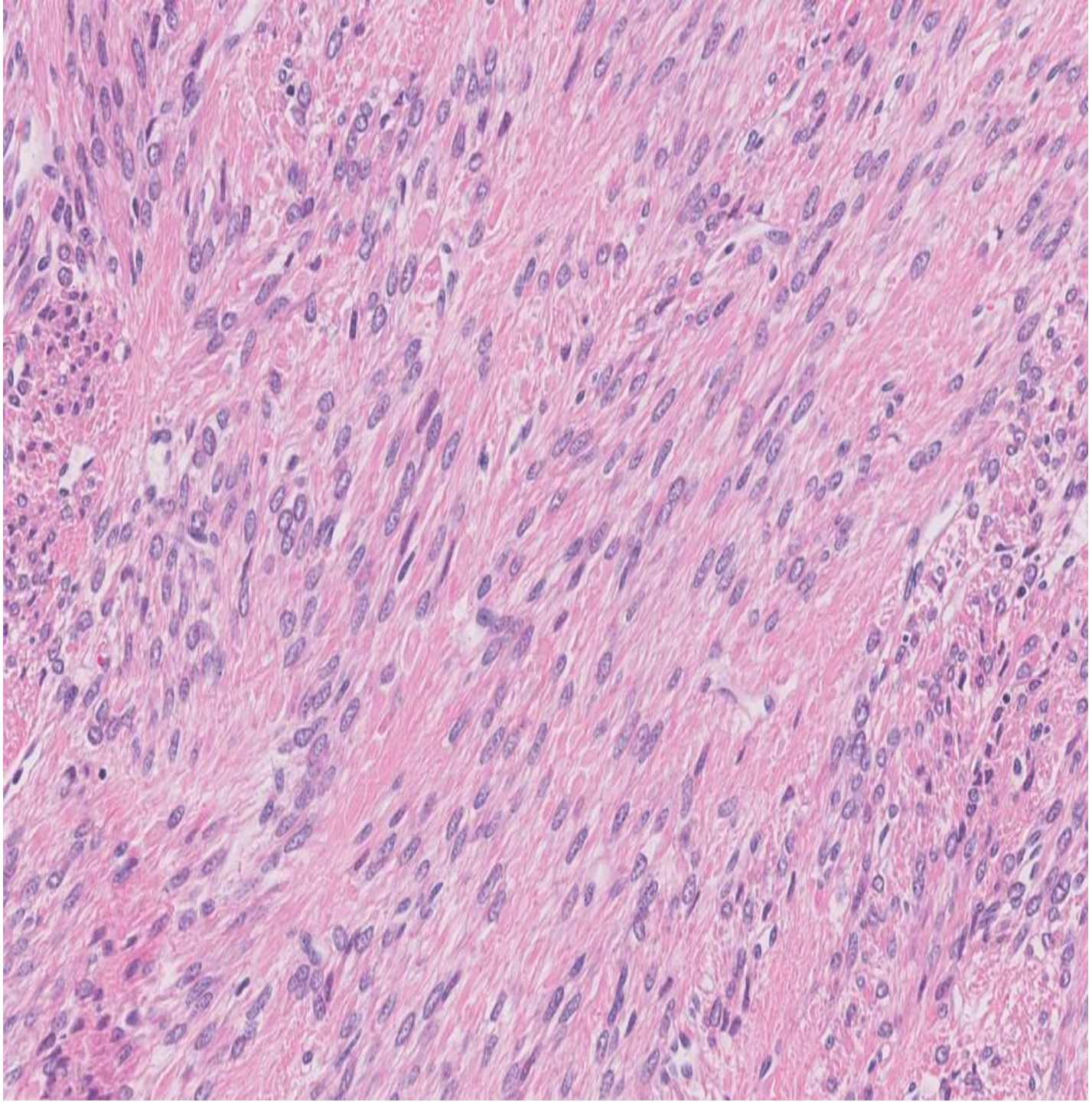
36-year-old F with multiple large fibroids who underwent myomectomy. Gross exam was consistent with conventional leiomyomas, with no features suspicious for sarcoma.

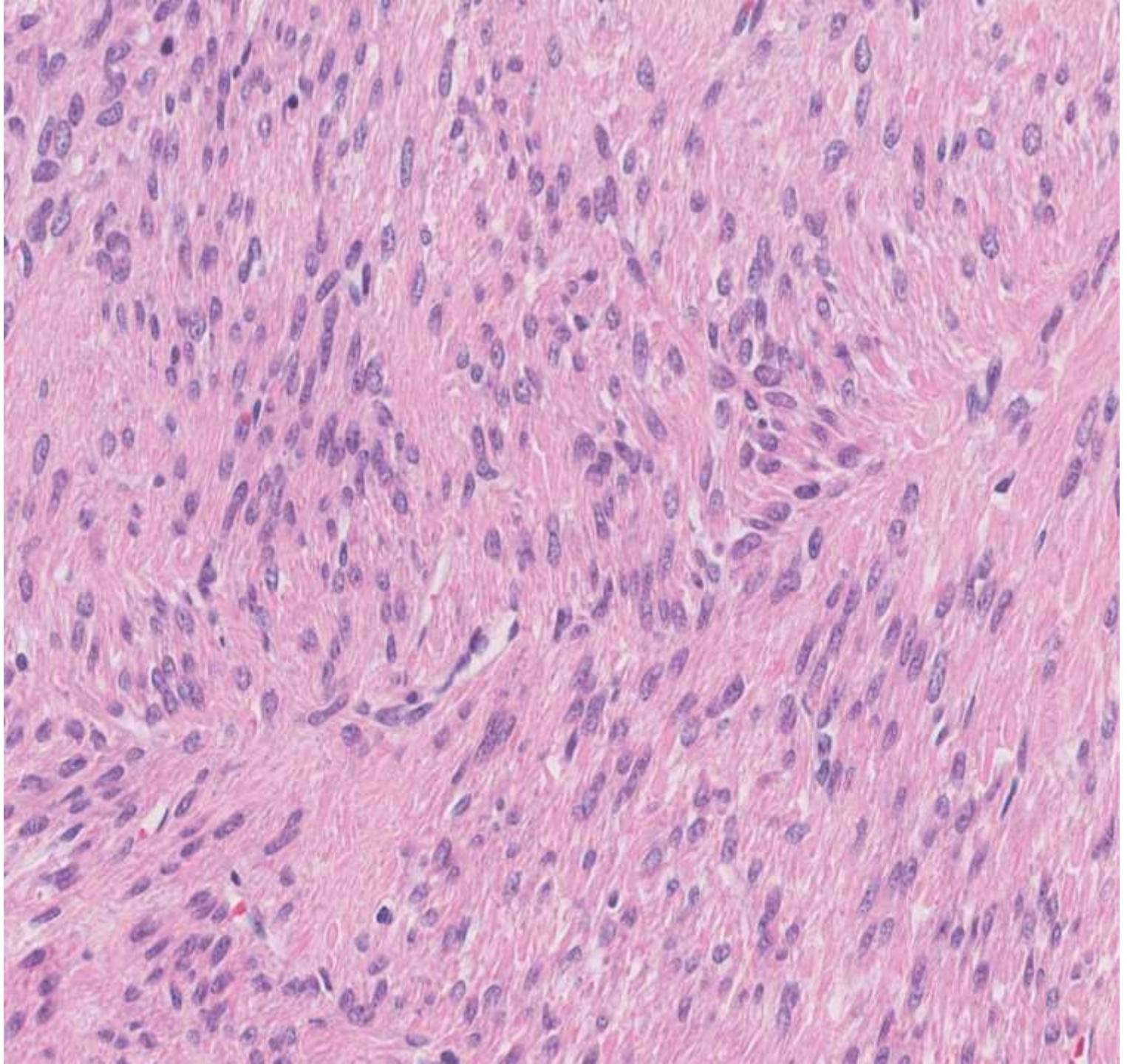


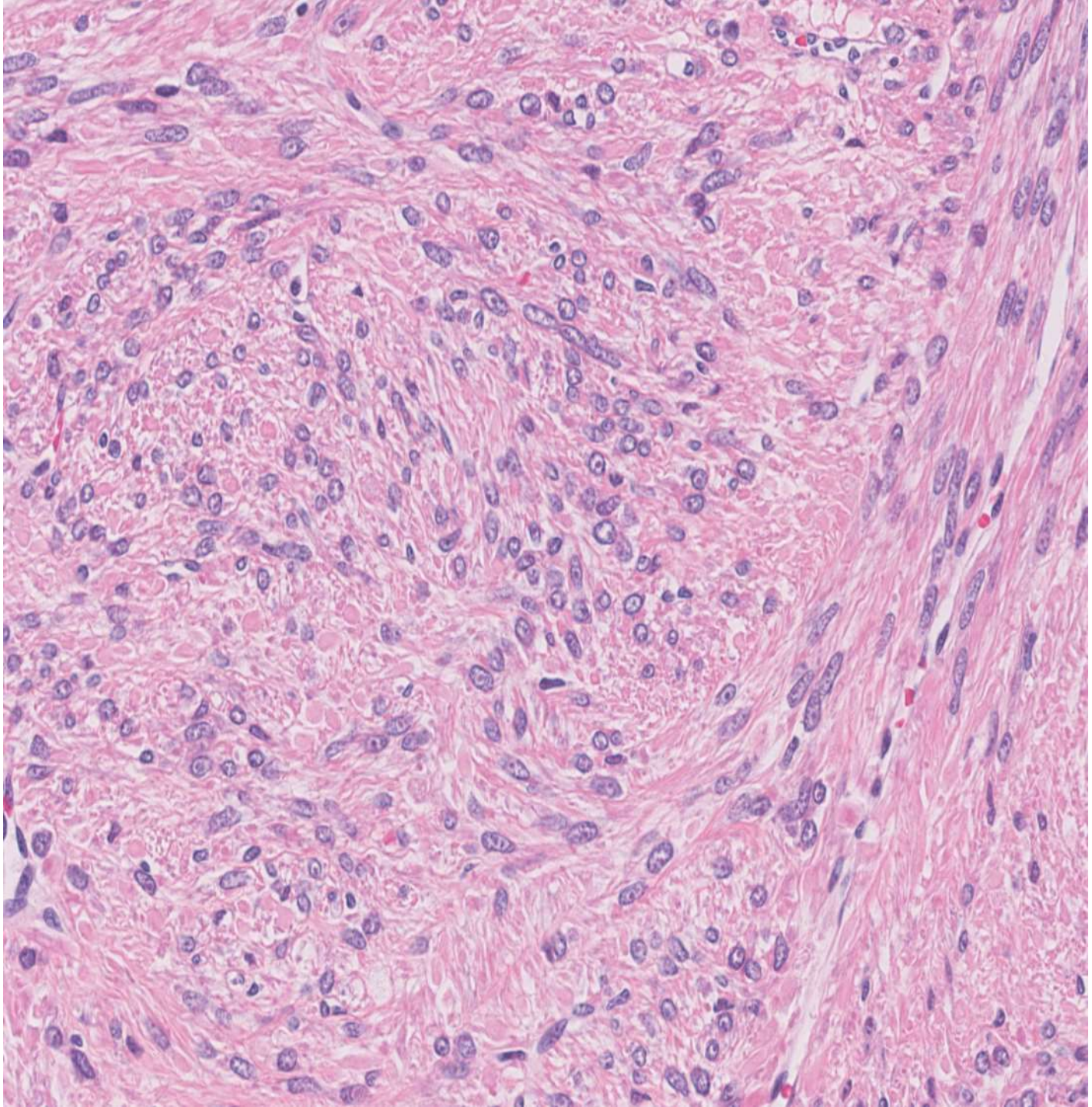


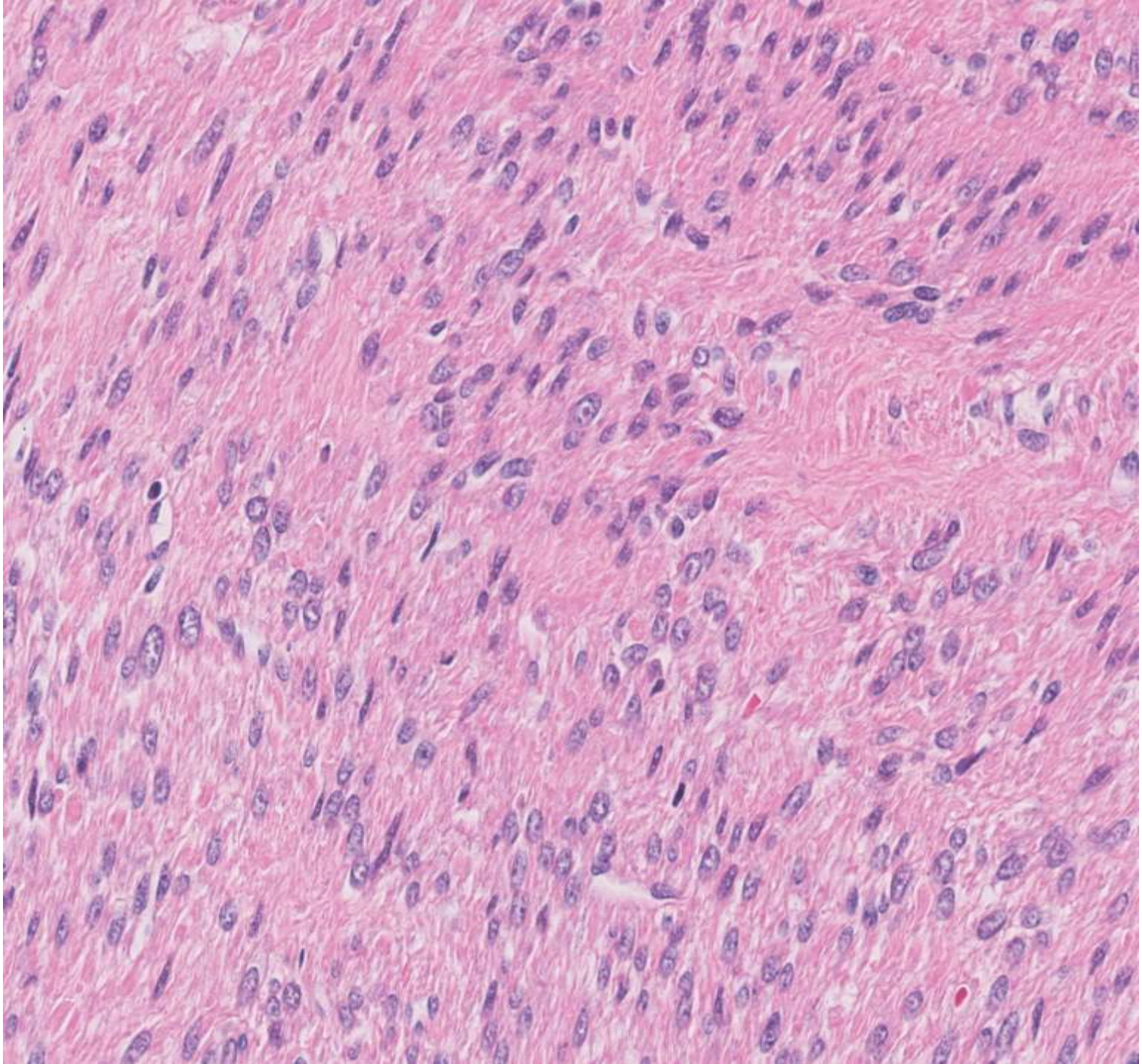












# Hereditary Leiomyoma Renal Cell Carcinoma Syndrome (HLRCC)

- **Germline Mutation in Fumarate Hydratase gene** (Krebs cycle)
- **Autosomal dominant**

- **Most affected women:**

| **Average age 28** |
| --- |
| **Uterine and/or cutaneous leiomyomas** |
| Multiple, large, painful |

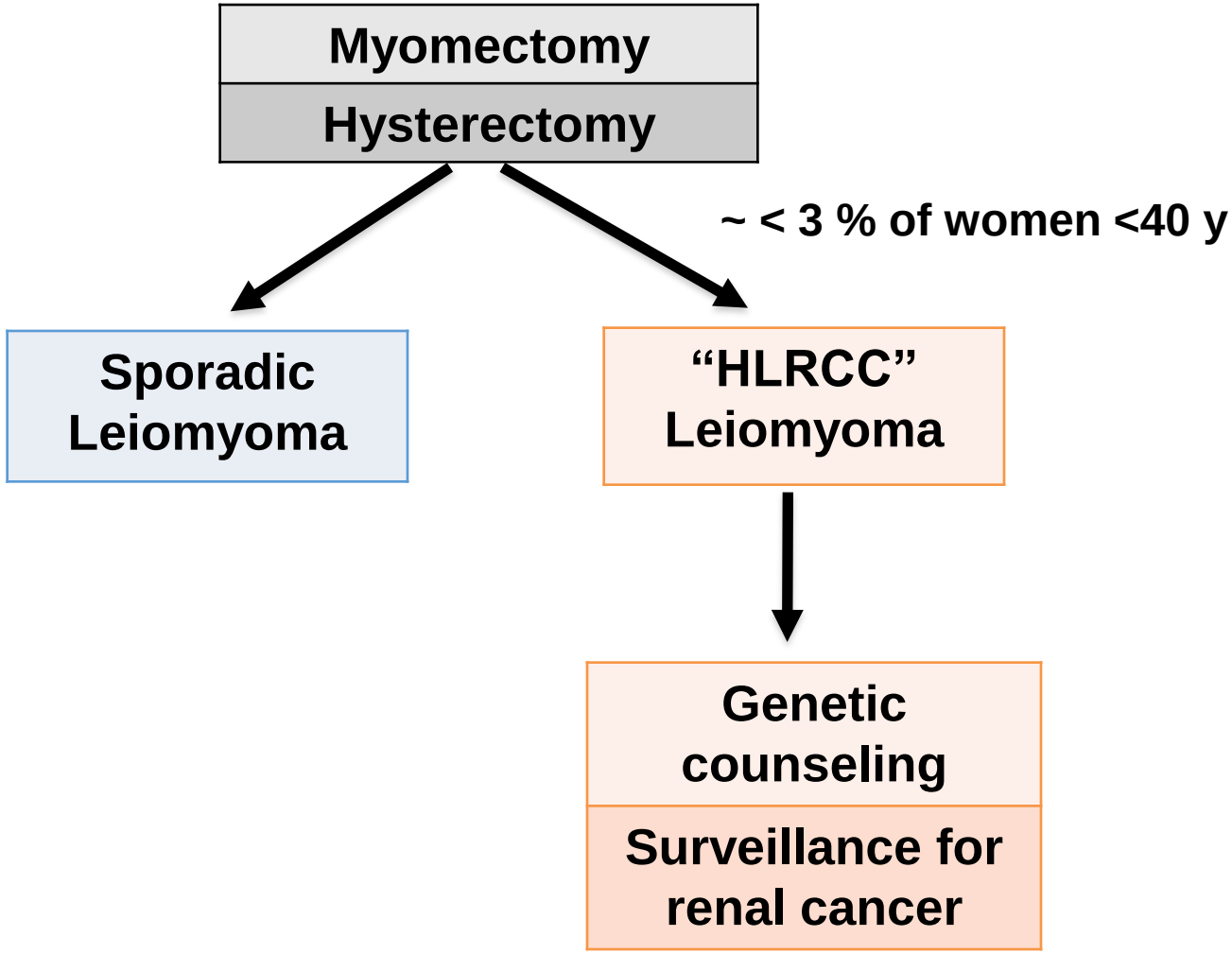
- **10-15% affected women:**

| **Average age 36** |
| --- |
| **Renal cell carcinoma** |
| Advanced stage / aggressive |

Launonen et al. Proc. Natl. Acad. Sci. 2001; 98: 3387.
Tomlinson et al. Nat Genet. 2002;30:406-410
Alam et al. . Br J Dermatol. 2005;153:11-17
Toro et al. Am J Hum Genet. 2003;73:95-106.

# Hereditary Leiomyoma Renal Cell Carcinoma Syndrome (HLRCC)

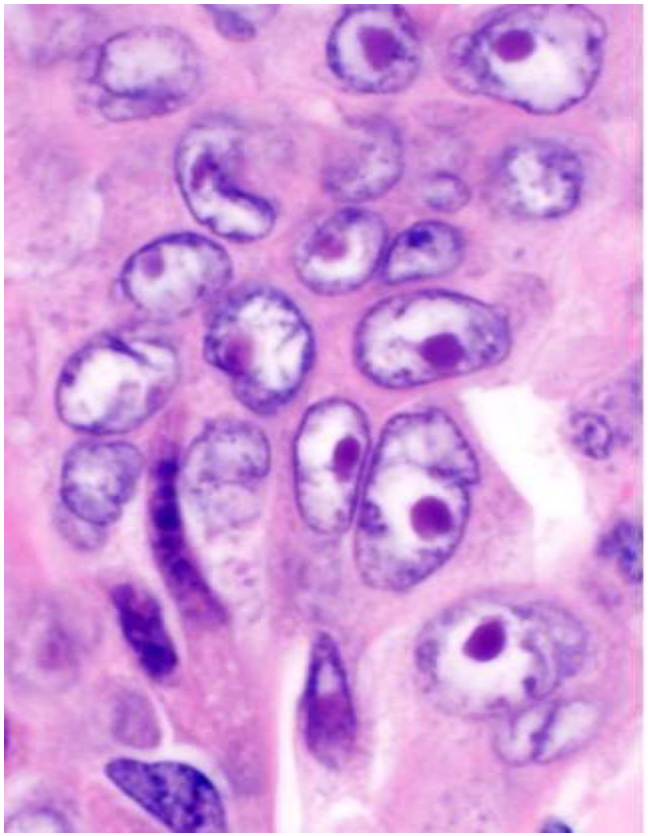
*Is Screening Possible Using Pathology of Leiomyoma ?*



# Similar Morphology in Tumors of HLRCC Syndrome

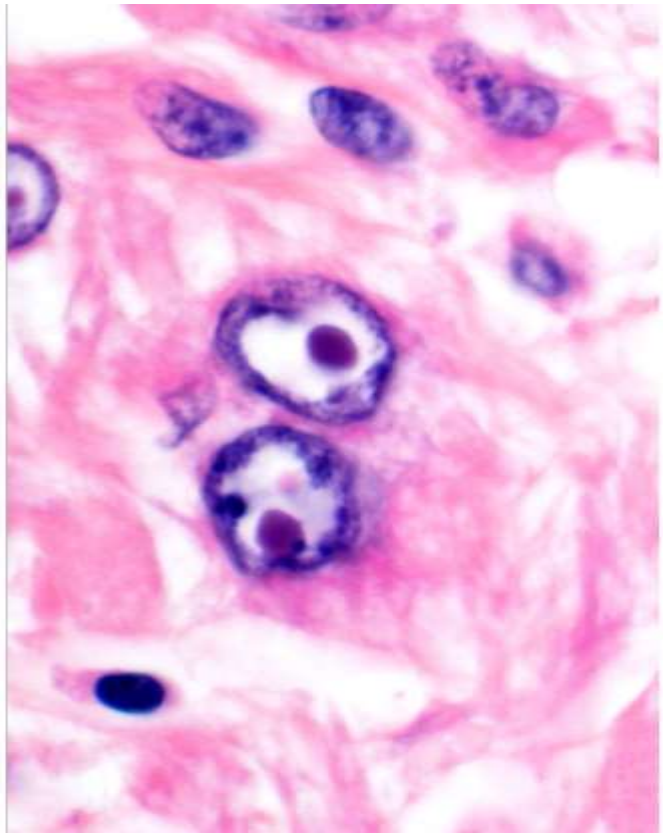
***Macronucleoli surrounded by halo***

## Renal Cell Carcinoma



Chen et al. Am J Surg Pathol 2014;38:627–637

## Uterine Leiomyoma

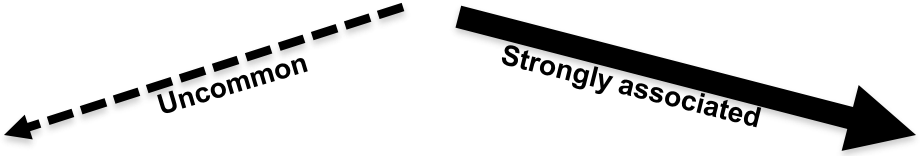


Reyes et al. Mod. Pathol. 2014; 27: 1020.
Sanz-Ortega et al. Am. J. Surg. Pathol. 2013; 37: 74.
Joseph et al. Am. J. Surg. Pathol. 2015; 39: 1529.

# Morphology of Fumarate Hydratase Deficient Uterine Leiomyoma

| Low Magnification Clues |
| --- |
| Alveolar-pattern edema |
| Staghorn-shape blood vessels |
| Chain-like distribution of tumor cells |

| High Magnification Criteria |
| --- |
| Macro-nucleoli surrounded by halo |
| Cytoplasmic eosinophilic globules |




**Normal Fumarate Hydratase**

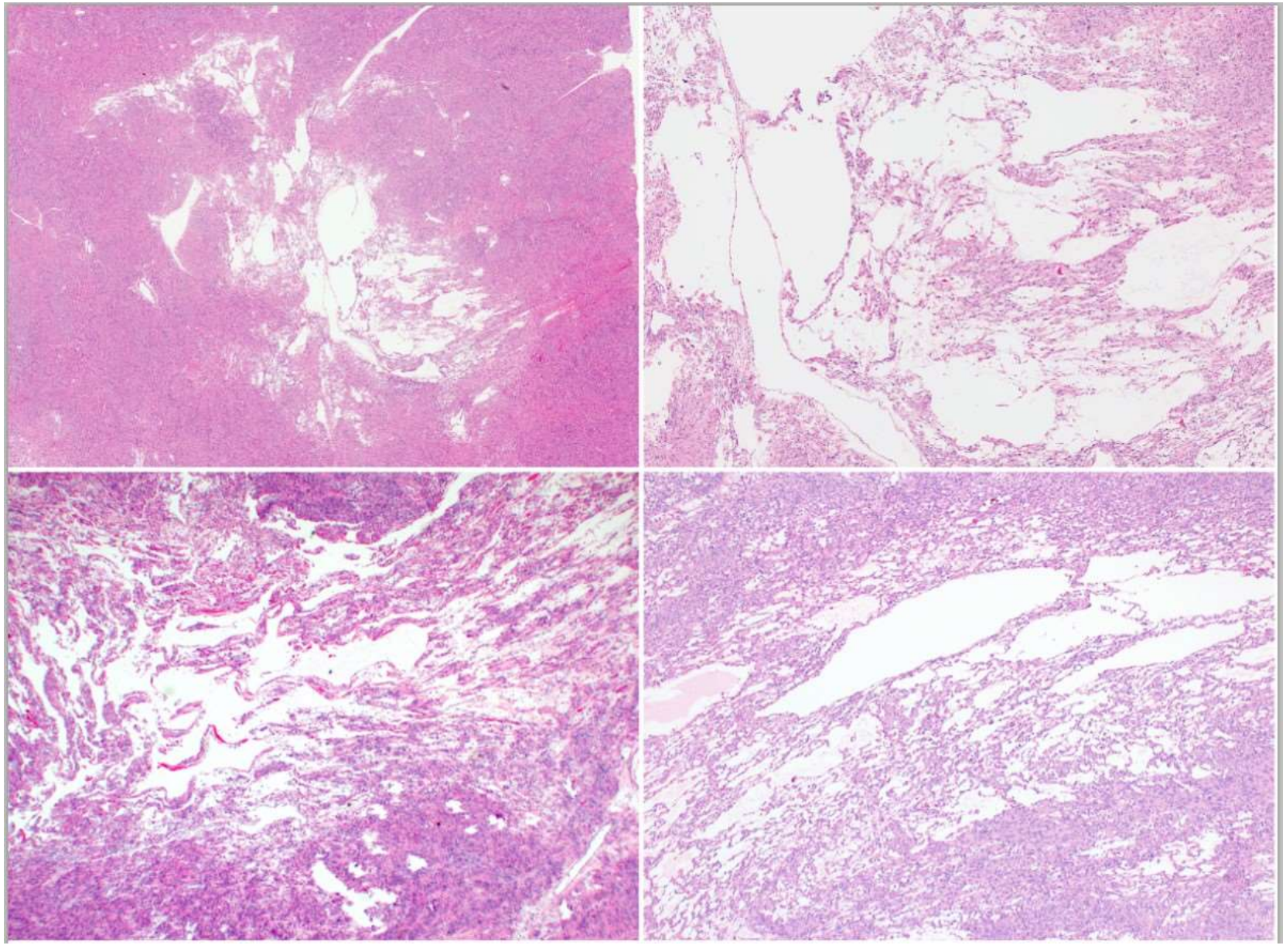
**Fumarate Hydratase-Deficiency**

- **Somatic mutation** (not HLRCC)
- **Germline mutation** (HLRCC)

Reyes et al. Mod. Pathol. 2014; 27: 1020.
Sanz-Ortega et al. Am. J. Surg. Pathol. 2013; 37: 74.
Joseph et al. Am. J. Surg. Pathol. 2015; 39: 1529.

# FH-d Morphology

## Alveolar pattern edema



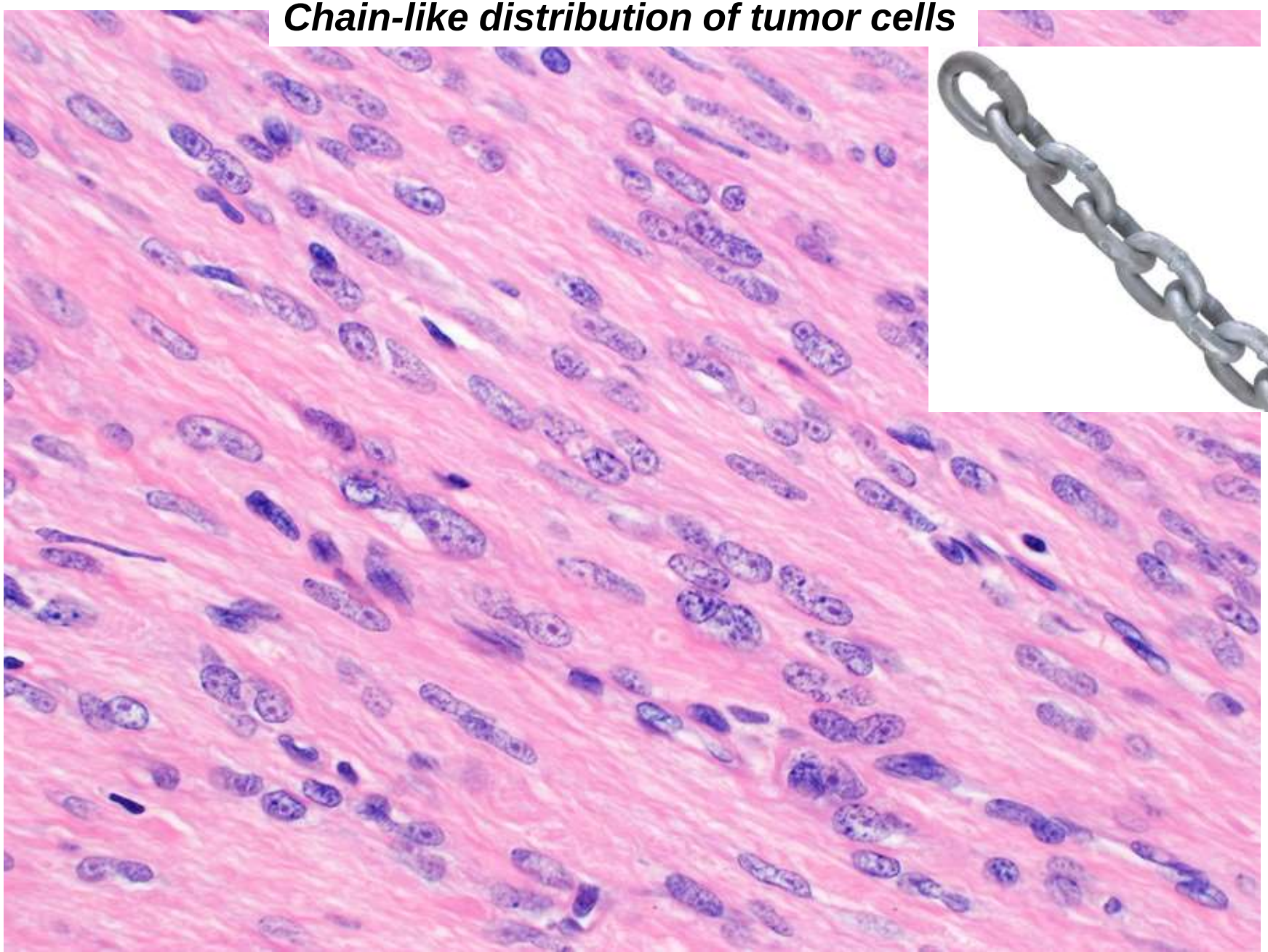
# FH-d Morphology

## Staghorn shape vessels

https://en.wikipedia.org/wiki/Antler

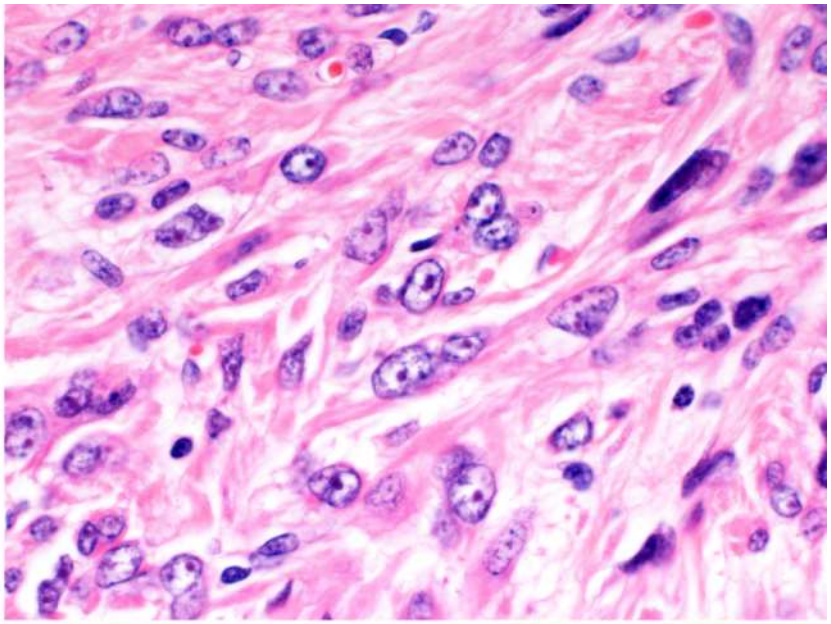
# FH-d Morphology

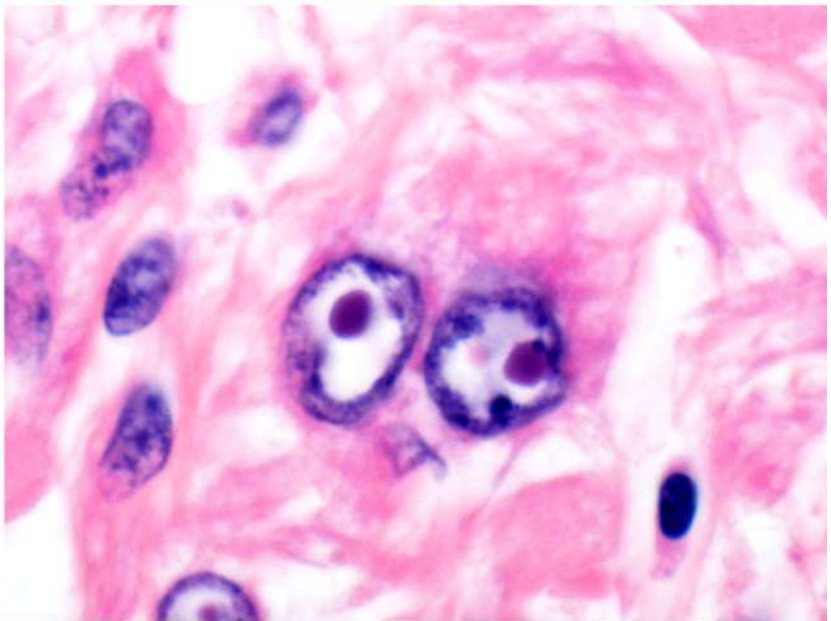
***Chain-like distribution of tumor cells***



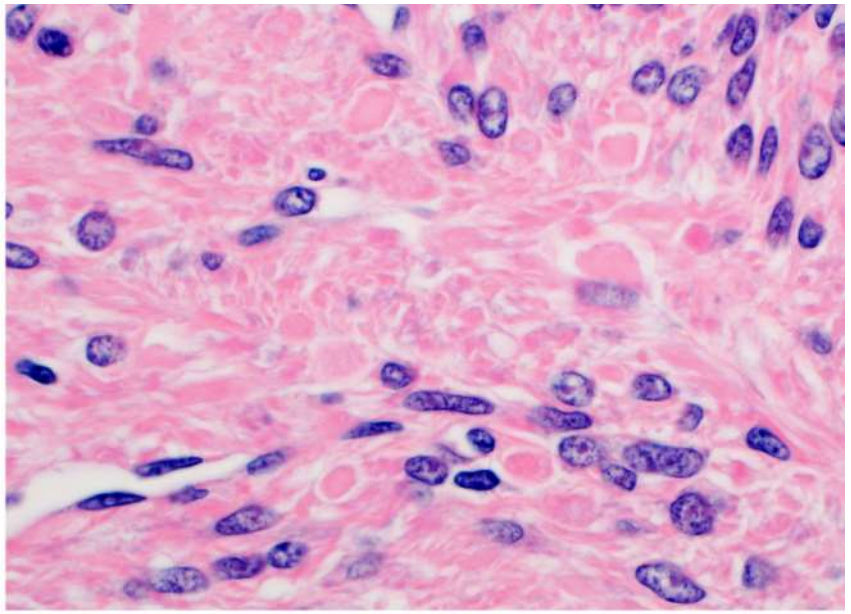
# FH-d Morphology

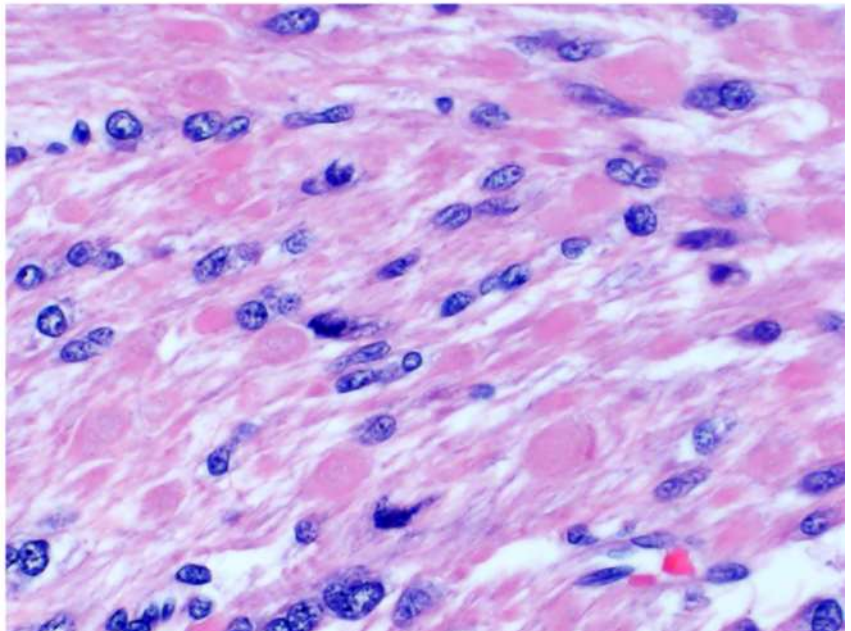
## Macronucleoli surrounded by halo





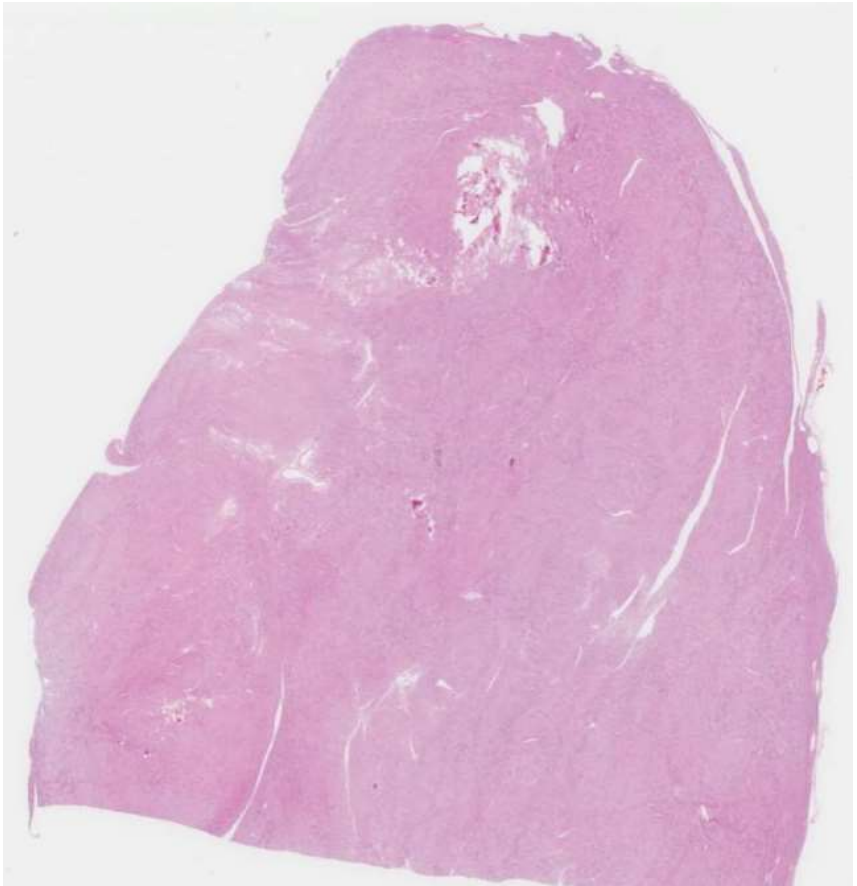
## Eosinophilic Globules

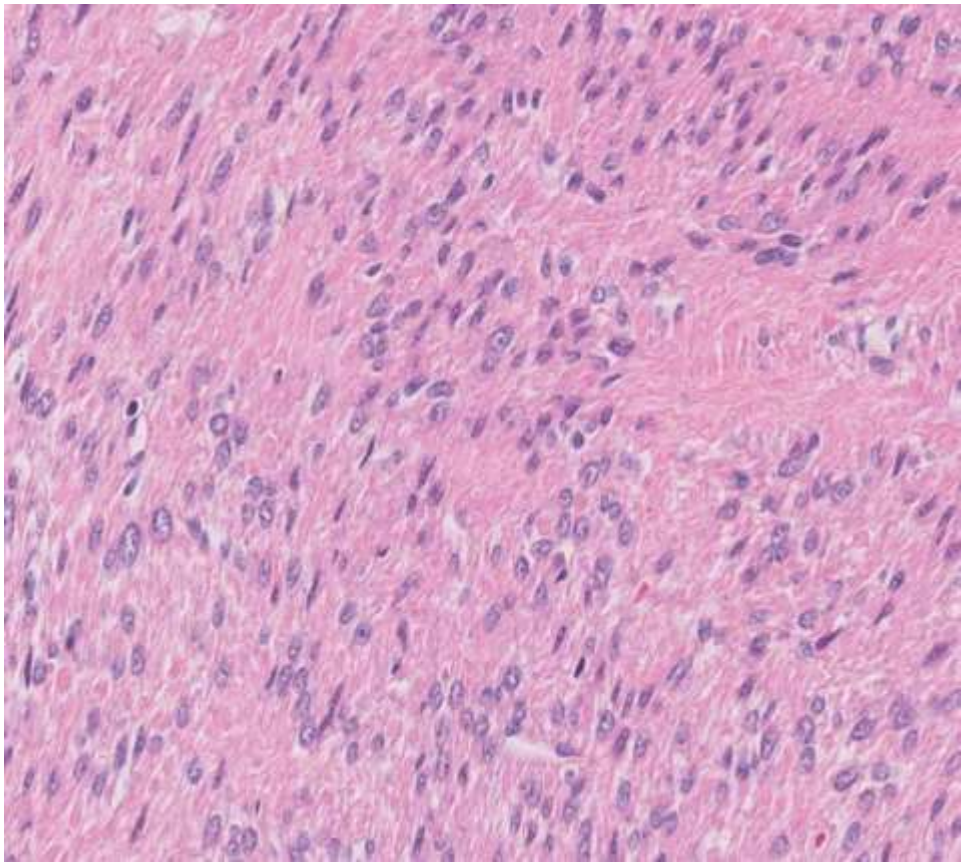




# South Bay case 20-205

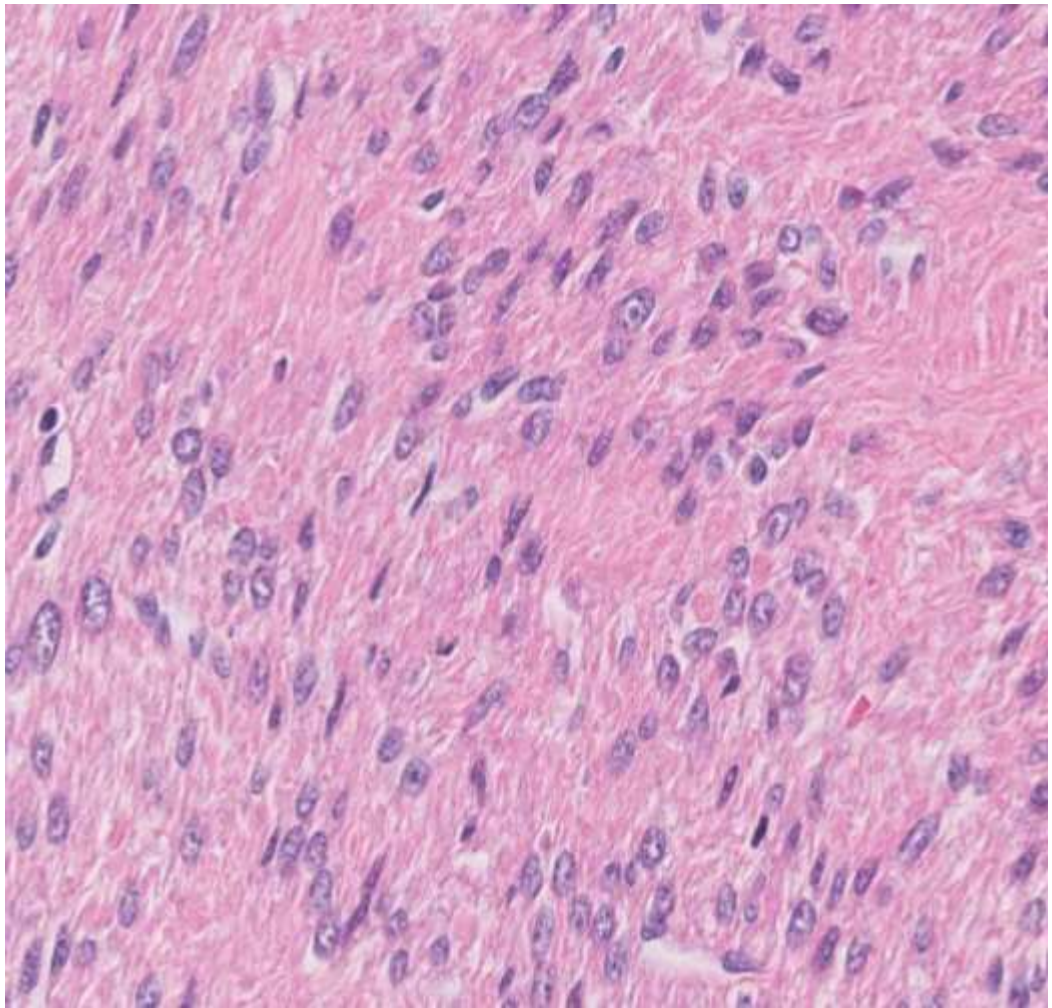
| Low mag clues | |
|---|---|
| Alveolar edema | ? maybe |
| Staghorn vessels | ? maybe |
| Chain-like pattern | focal |





# South Bay case 20-205

| High Magnification Criteria | |
|---|---|
| Macronucleoli | Yes-but focal, and on the smaller end of spectrum |
| Eosinophilic globules | Yes-but focal |



# South Bay case 20-205

## Practical Questions:

**How much FH-d morphology needs to be present to raise concern ?**

*Is there a minimum % of the leiomyoma that must show FH-d findings ?*

*Is there a minimum size required to be a macro-nucleolus ?*

**Is there a role for FH immunostain ?**

ORIGINAL ARTICLE

# Prospective Detection of Germline Mutation of *Fumarate Hydratase* in Women With Uterine Smooth Muscle Tumors Using Pathology-based Screening to Trigger Genetic Counseling for Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome

## *A 5-Year Single Institutional Experience*

*Joseph T. Rabban, MD, MPH,* Emily Chan, MD, PhD,* Julie Mak, MS, LCGC,† Charles Zaloudek, MD,* and Karuna Garg, MD**

*Am J Surg Pathol* 2019;43:639–655

- No minimum requirement for FH-d morphology. Any amount counted.
- 30 cases with FH-d morphology out of 2,060 patients (subset pursued genetic testing)
  - 50% went on to test positive for FH germline mutation
    - 40% with FH germline mutation had NORMAL FH staining

## South Bay case 20-205

**Final Diagnosis:** **Leiomyoma with FH-d morphology**

**Genetic Diagnosis:** **Pathogenic FH germline mutation**

### Take Home Messages

1. **Apply a low threshold for reporting FH-d morphology.**

   *Particularly in young women (<40 yrs)*

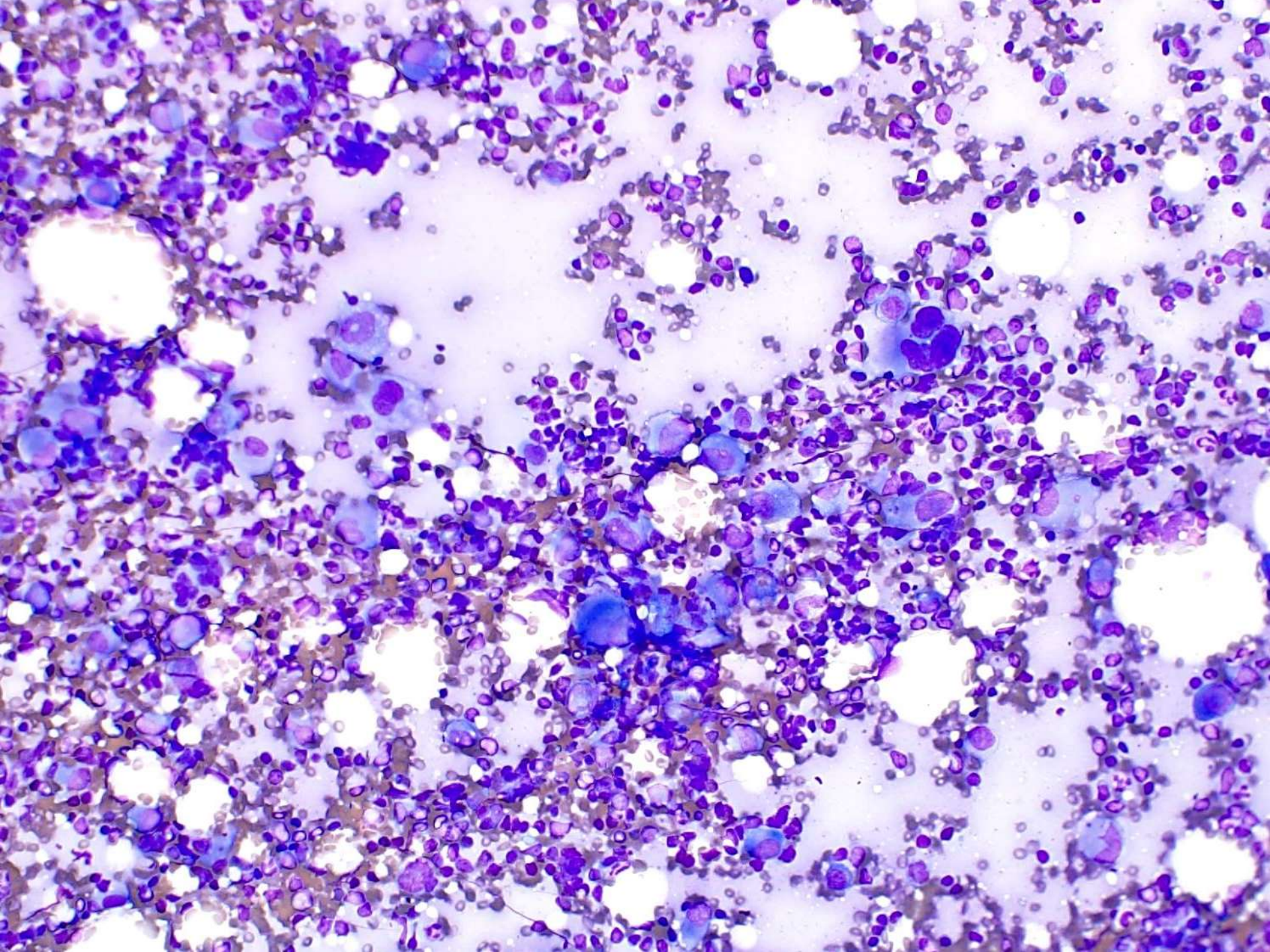
2. **H&E stain is sufficient. Avoid FH immunostain.**

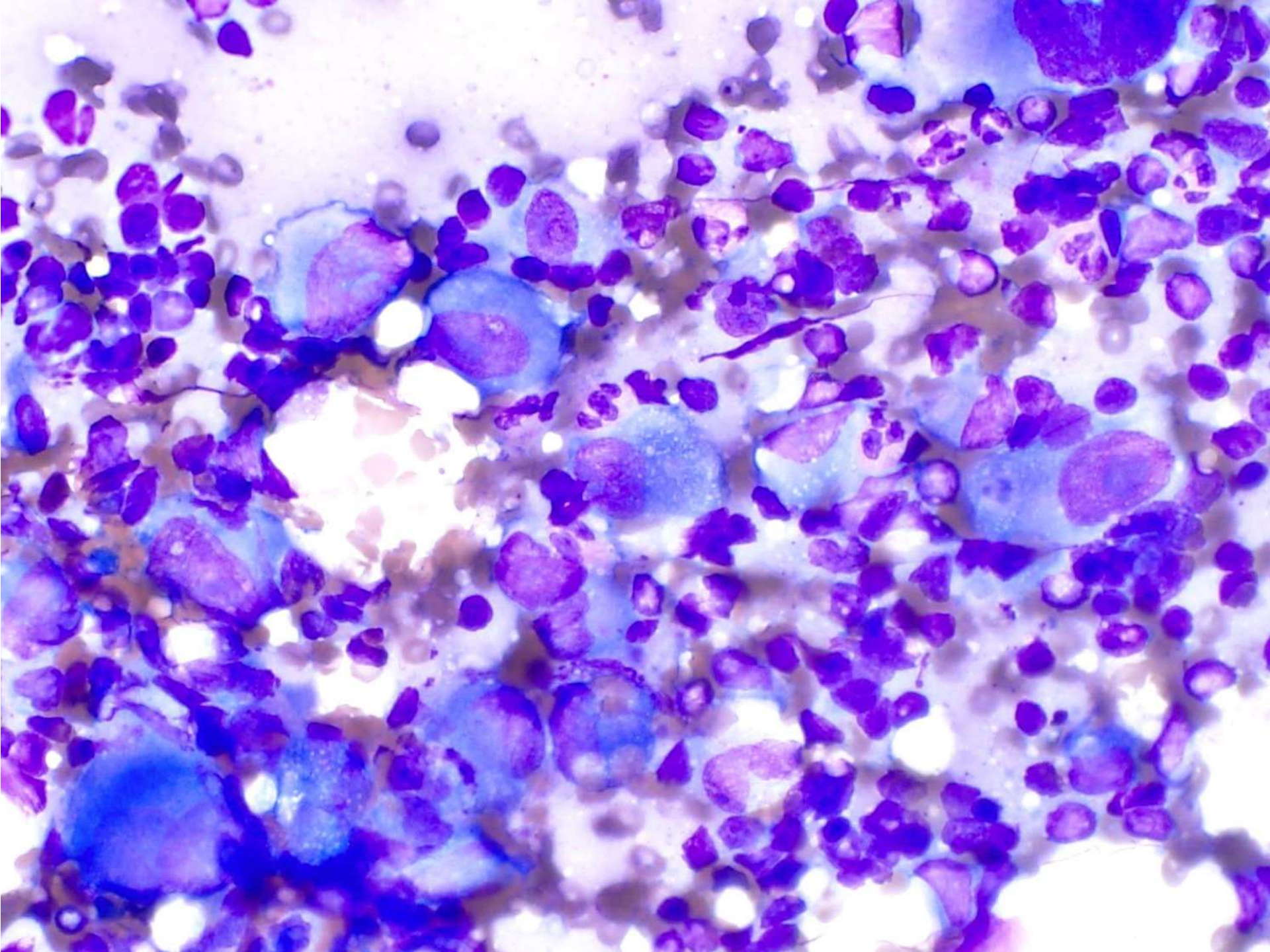
   *An intact result does not exclude FH germline mutation.*
   *An abnormal result does not prove FH germline mutation.*

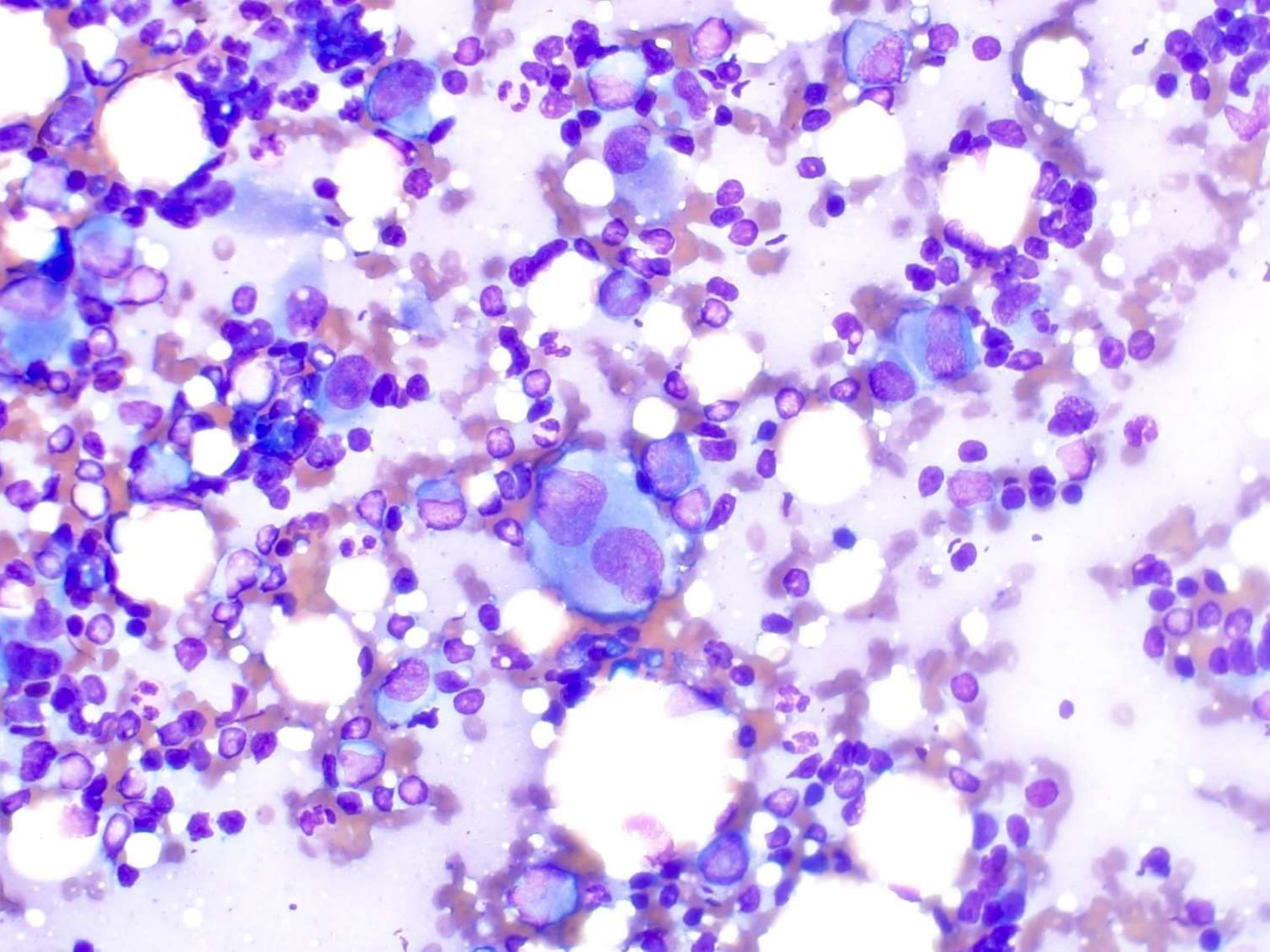
# 20-0206

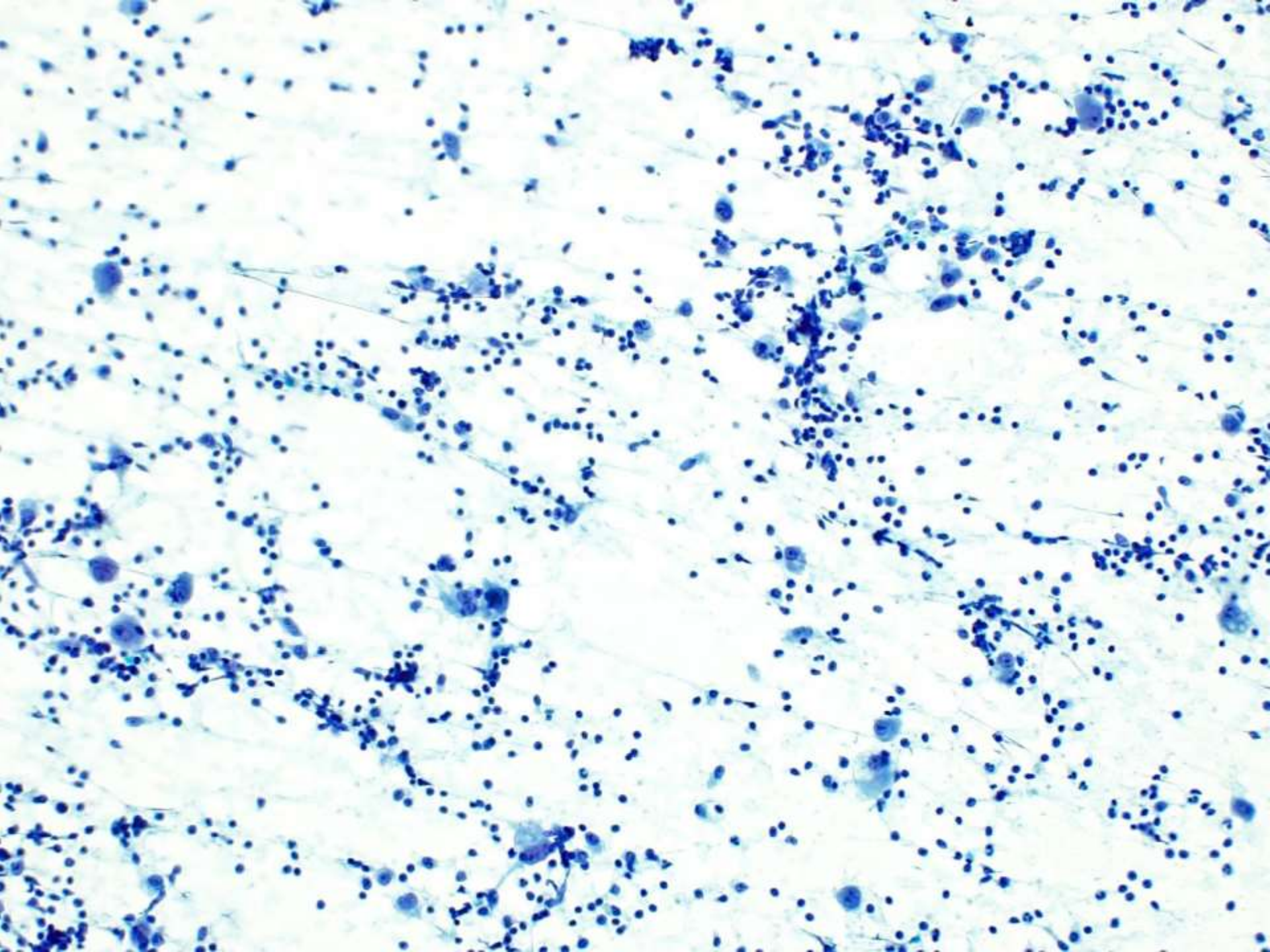
**Sara Zadeh/Brock Martin; Stanford**

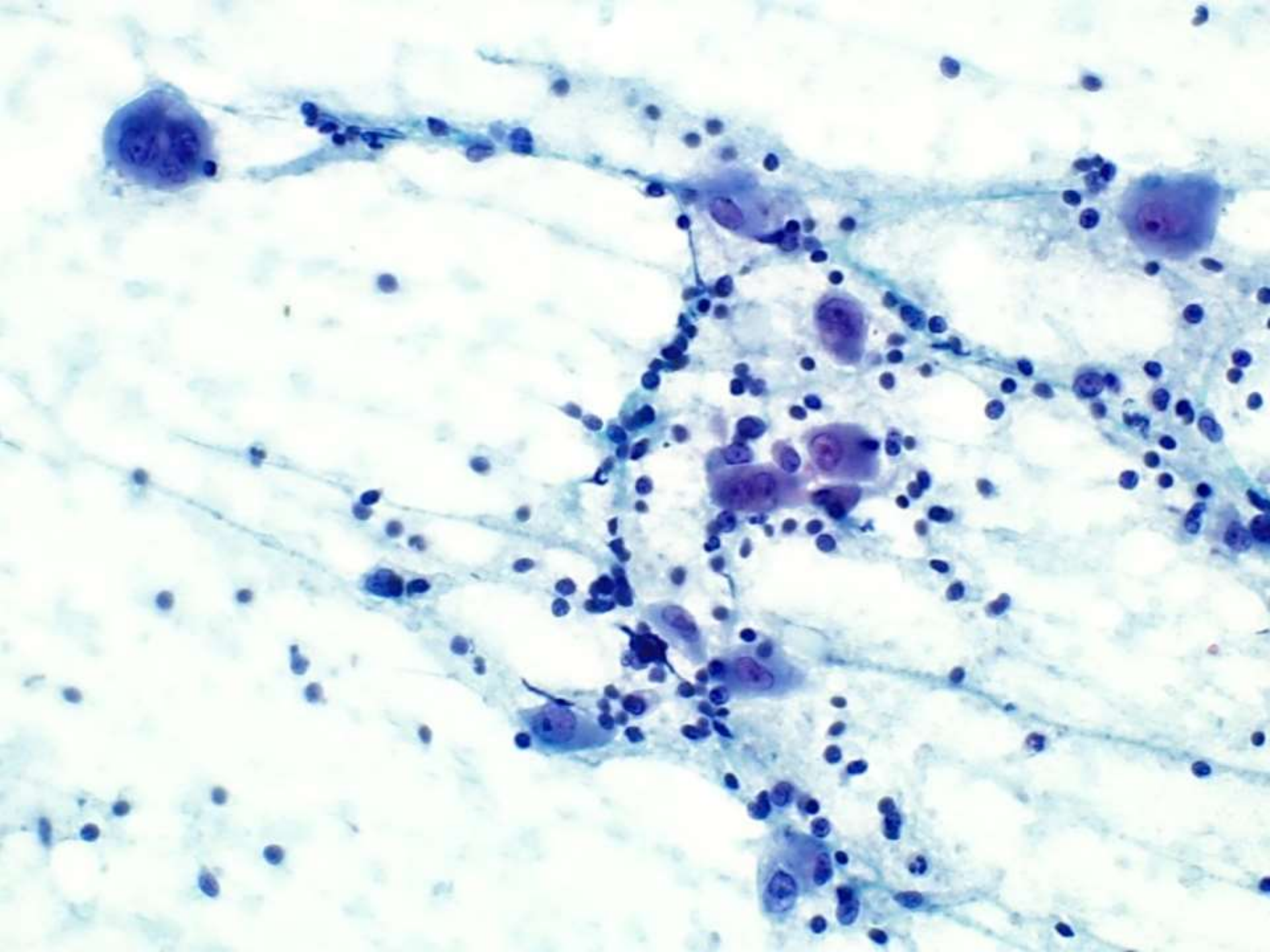
78-year-old F follicular lymphoma and mixed response to radiation therapy. FNA of non-responding cervical lymph nodes performed.

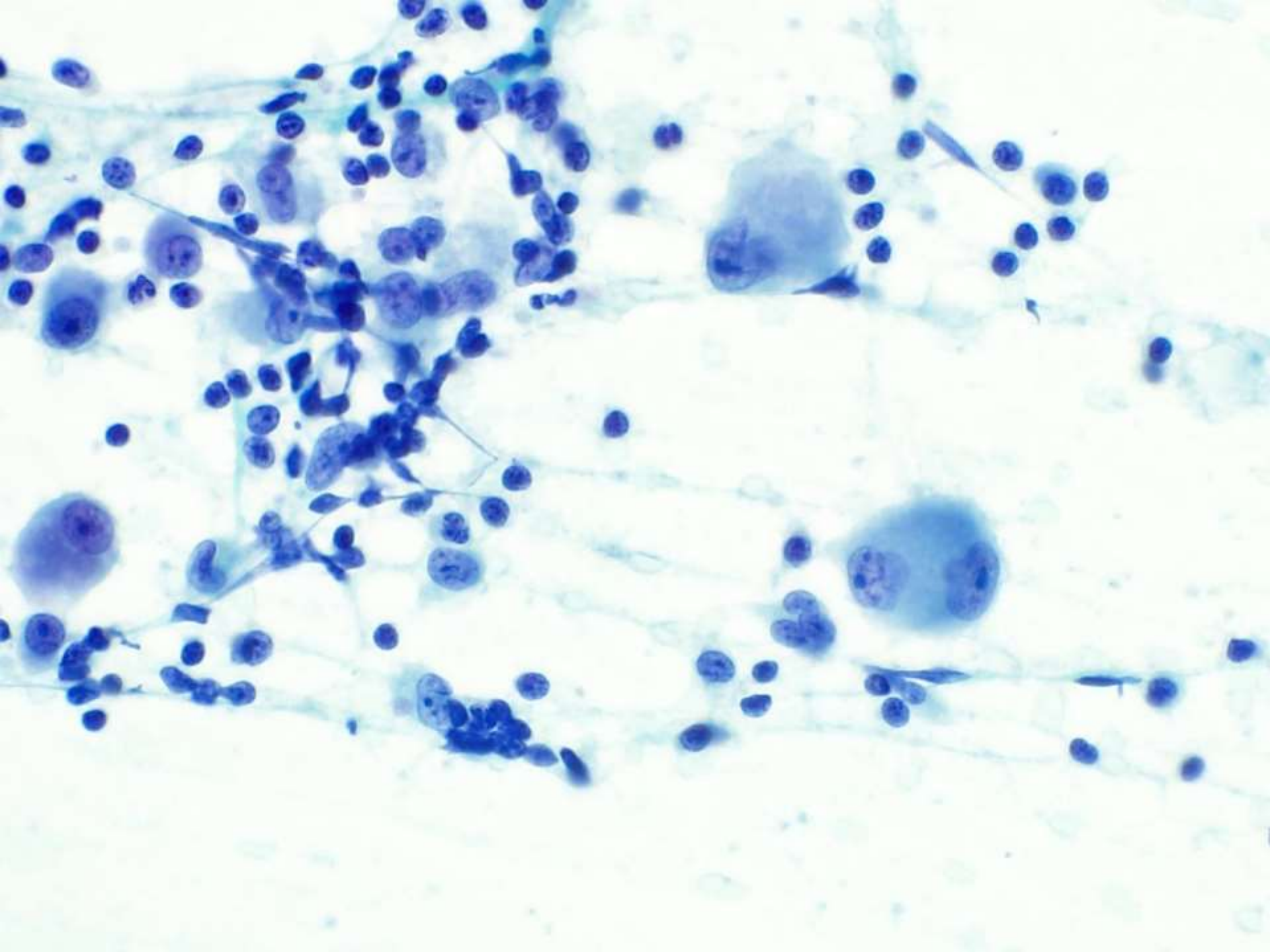


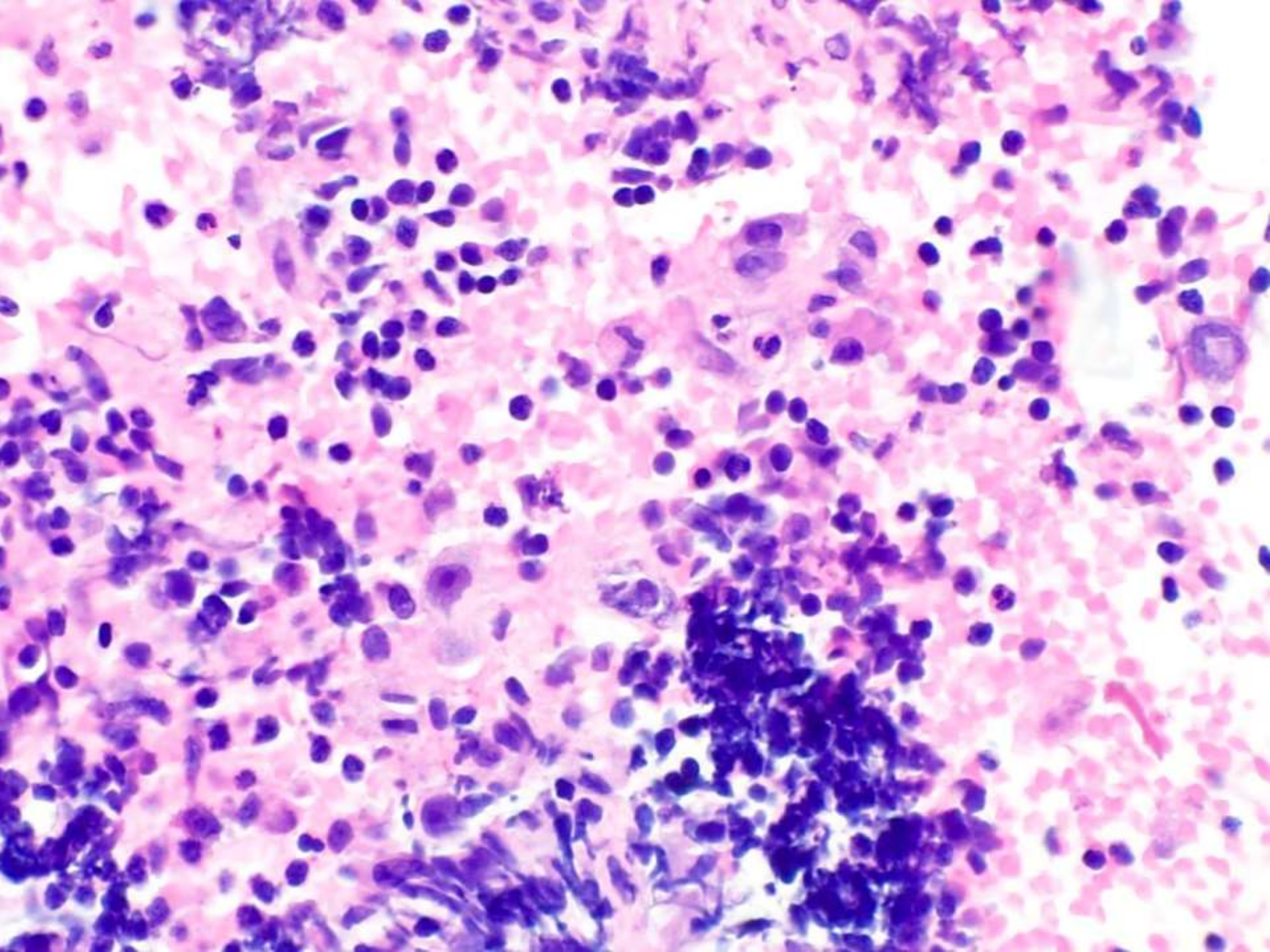


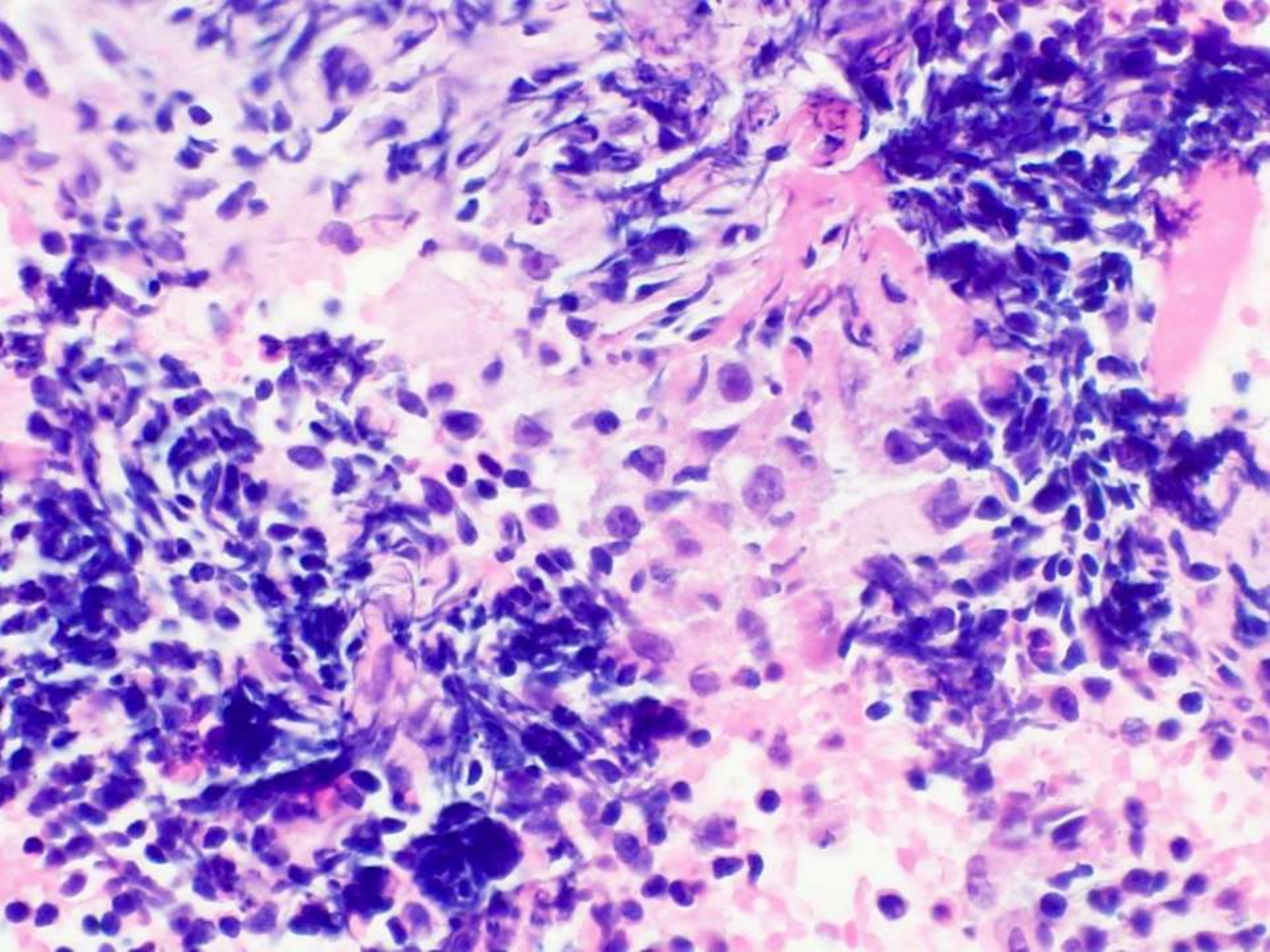


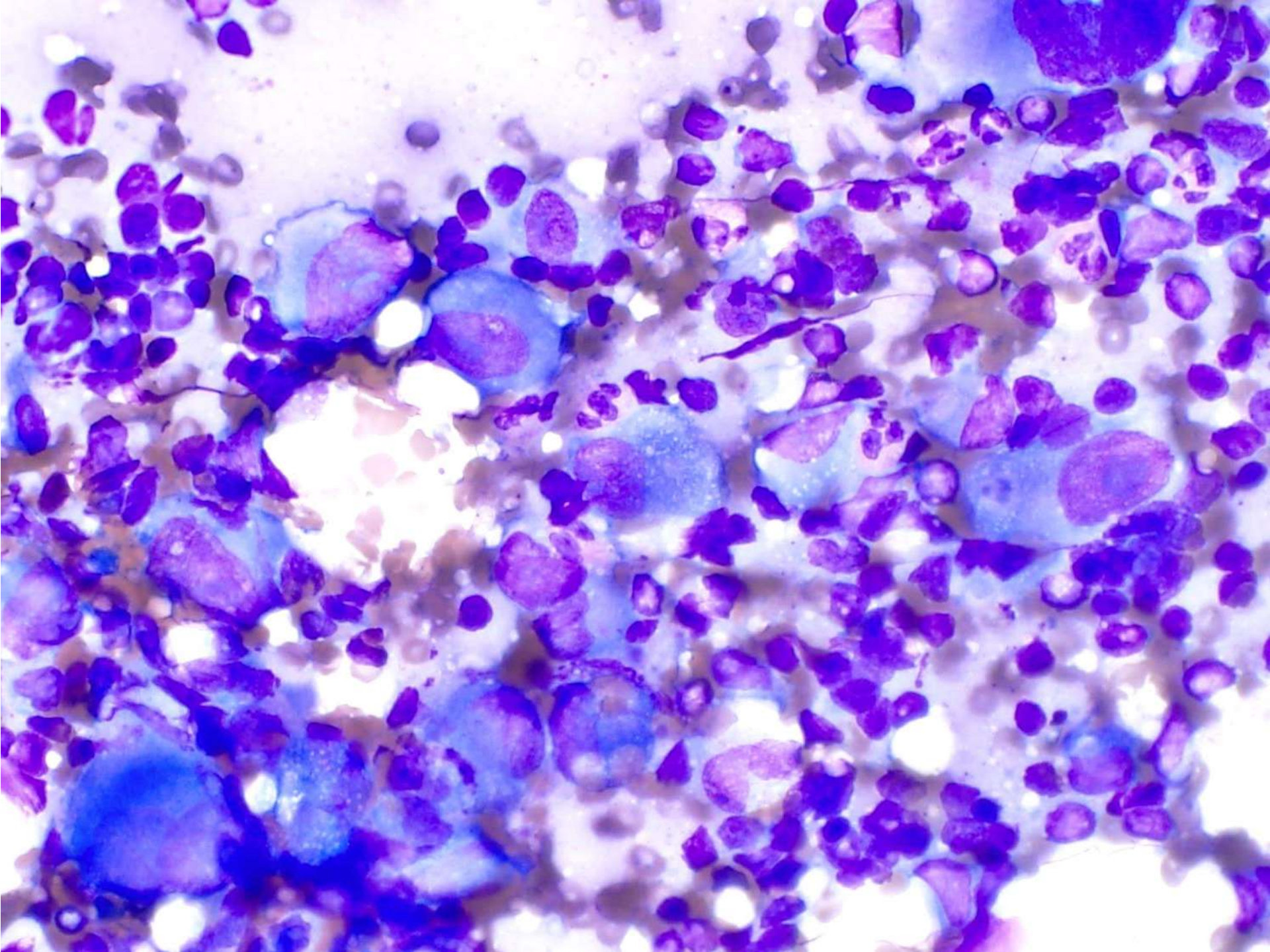


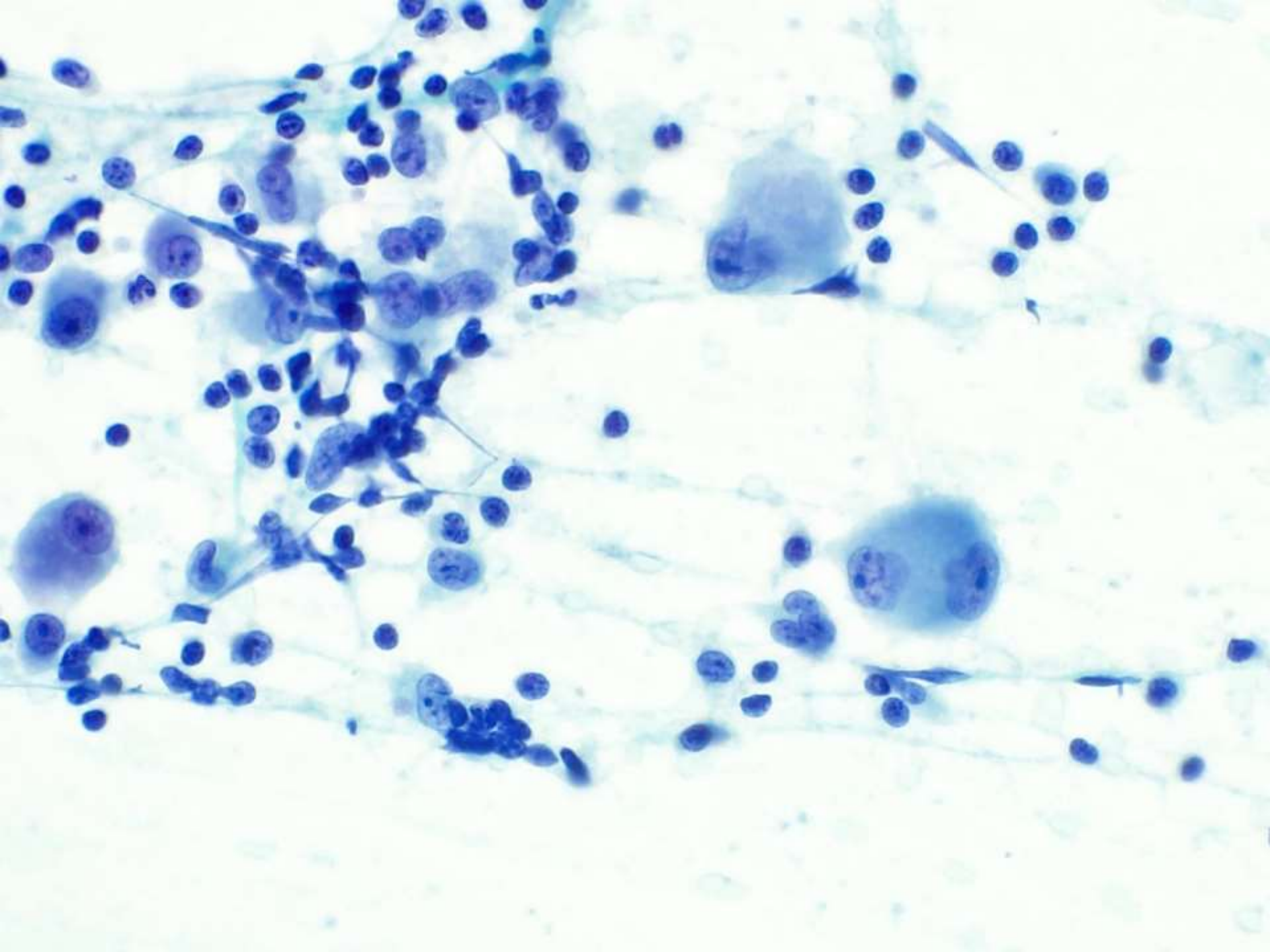


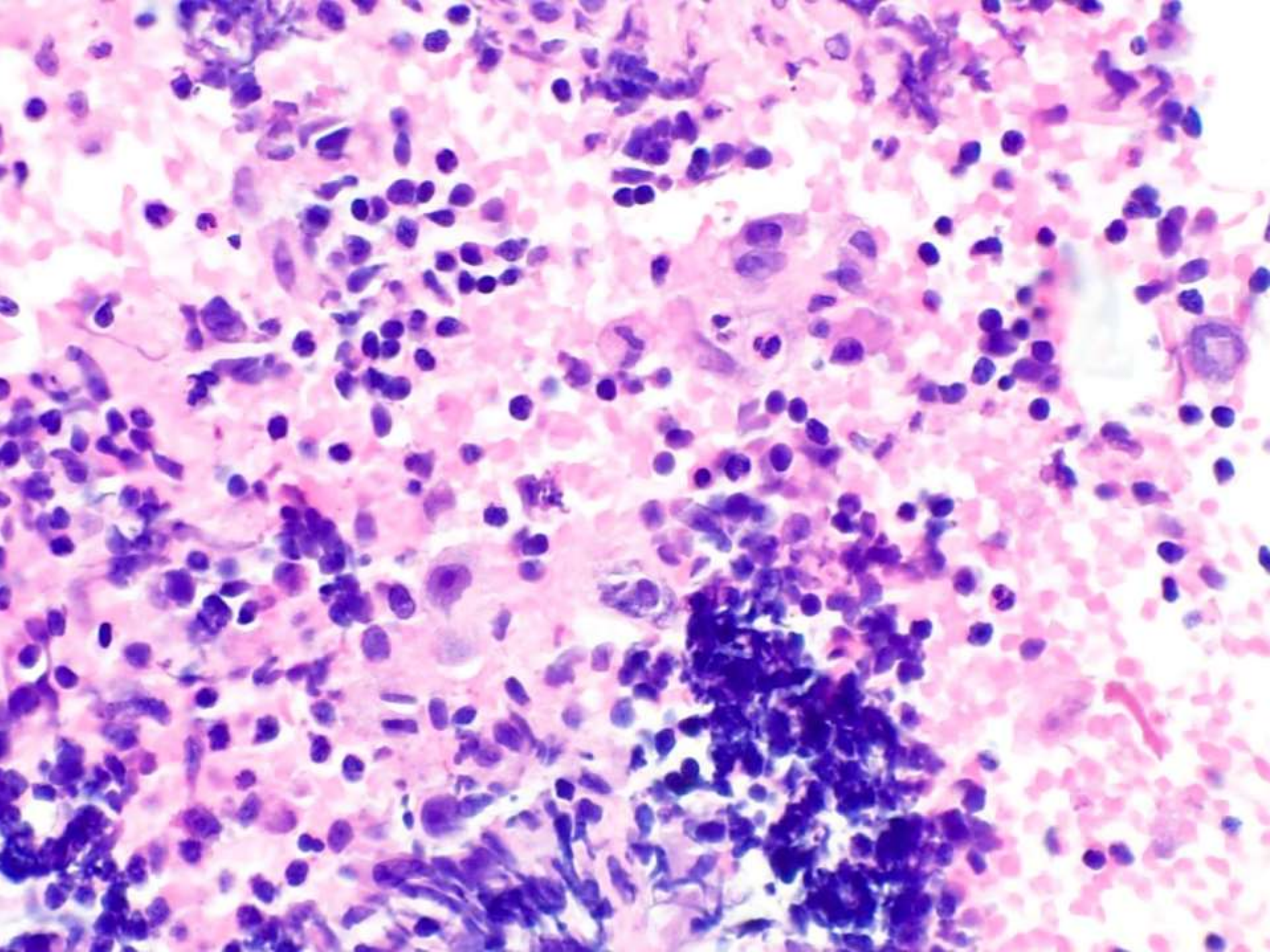


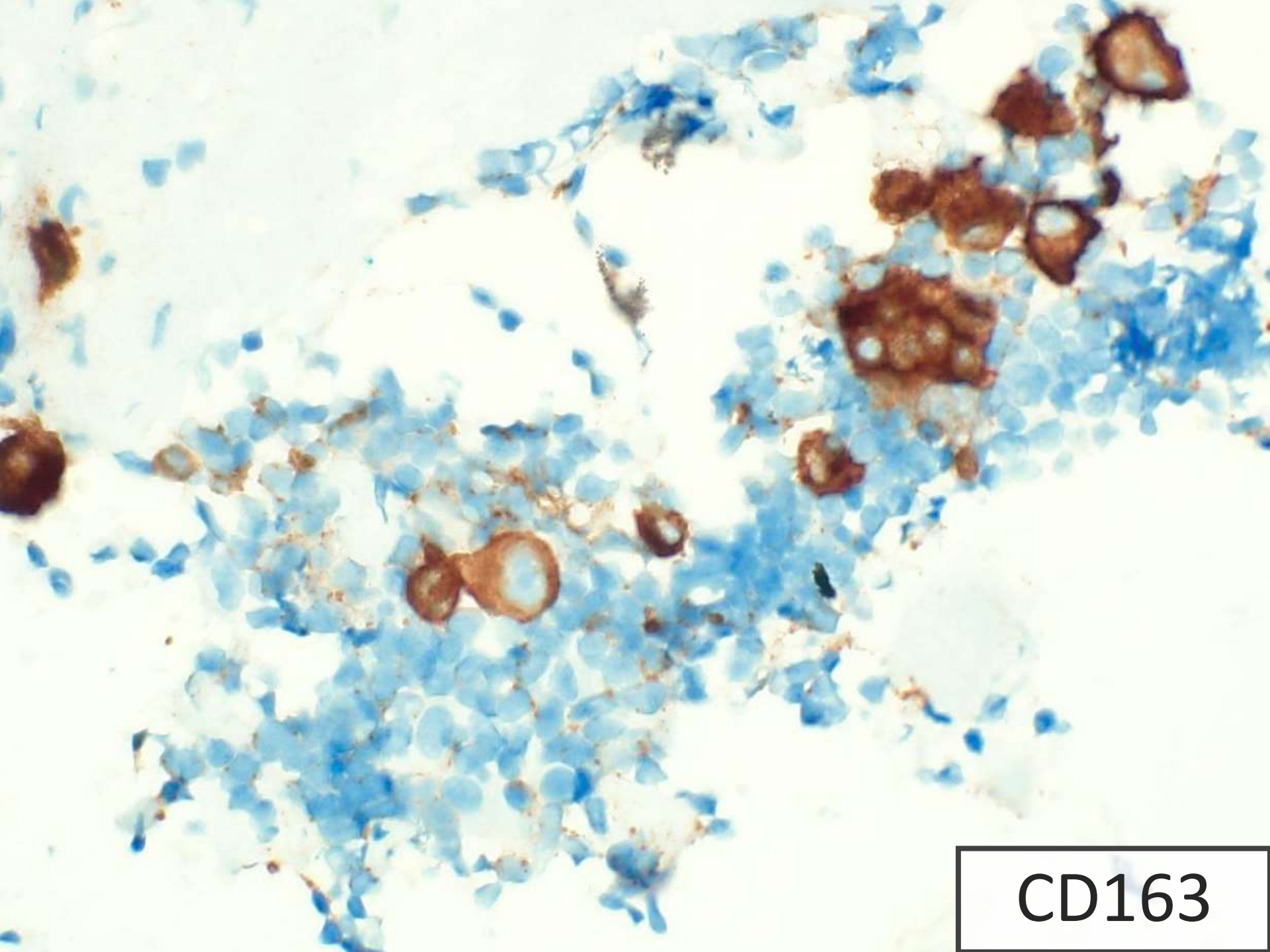


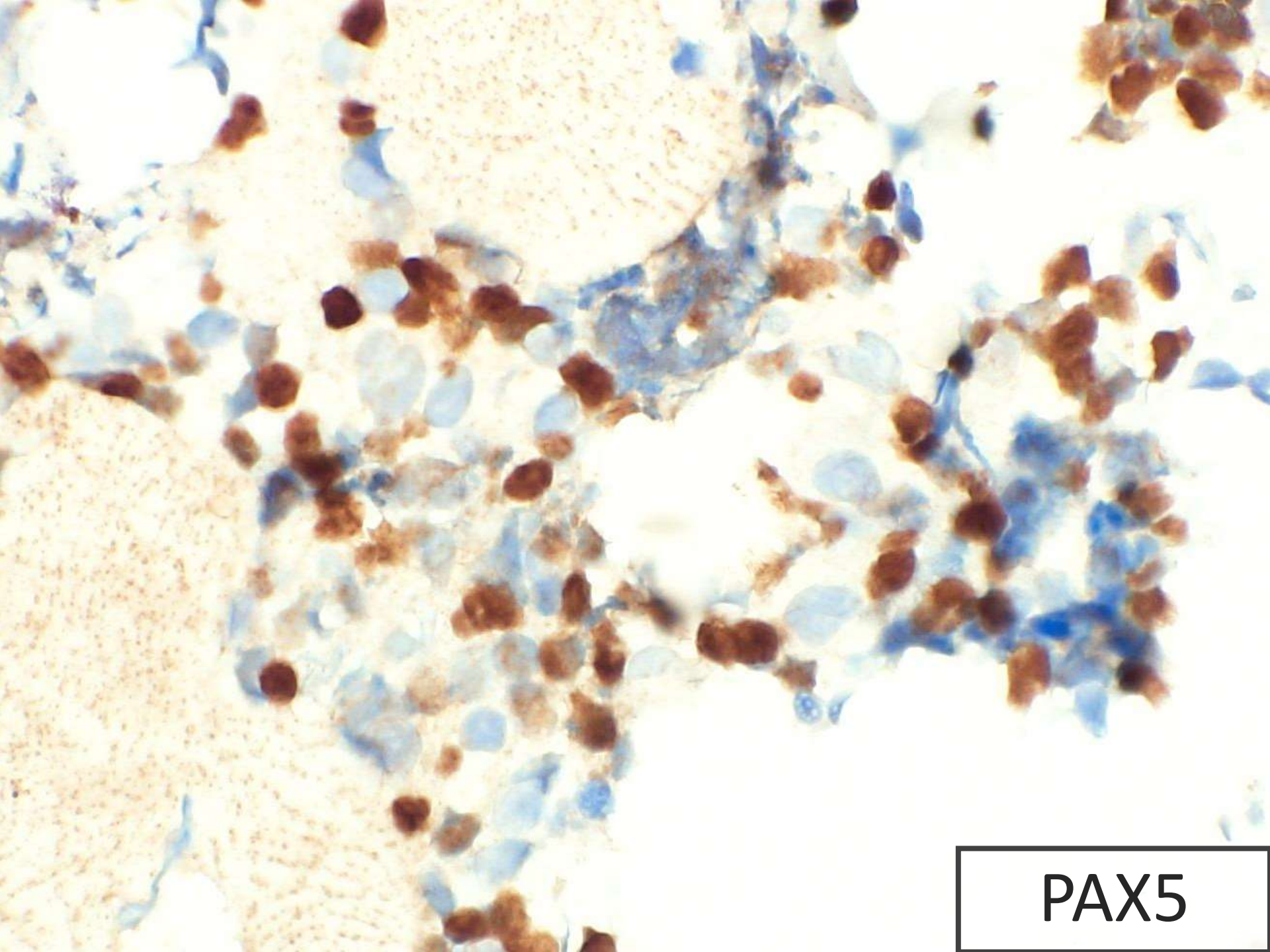








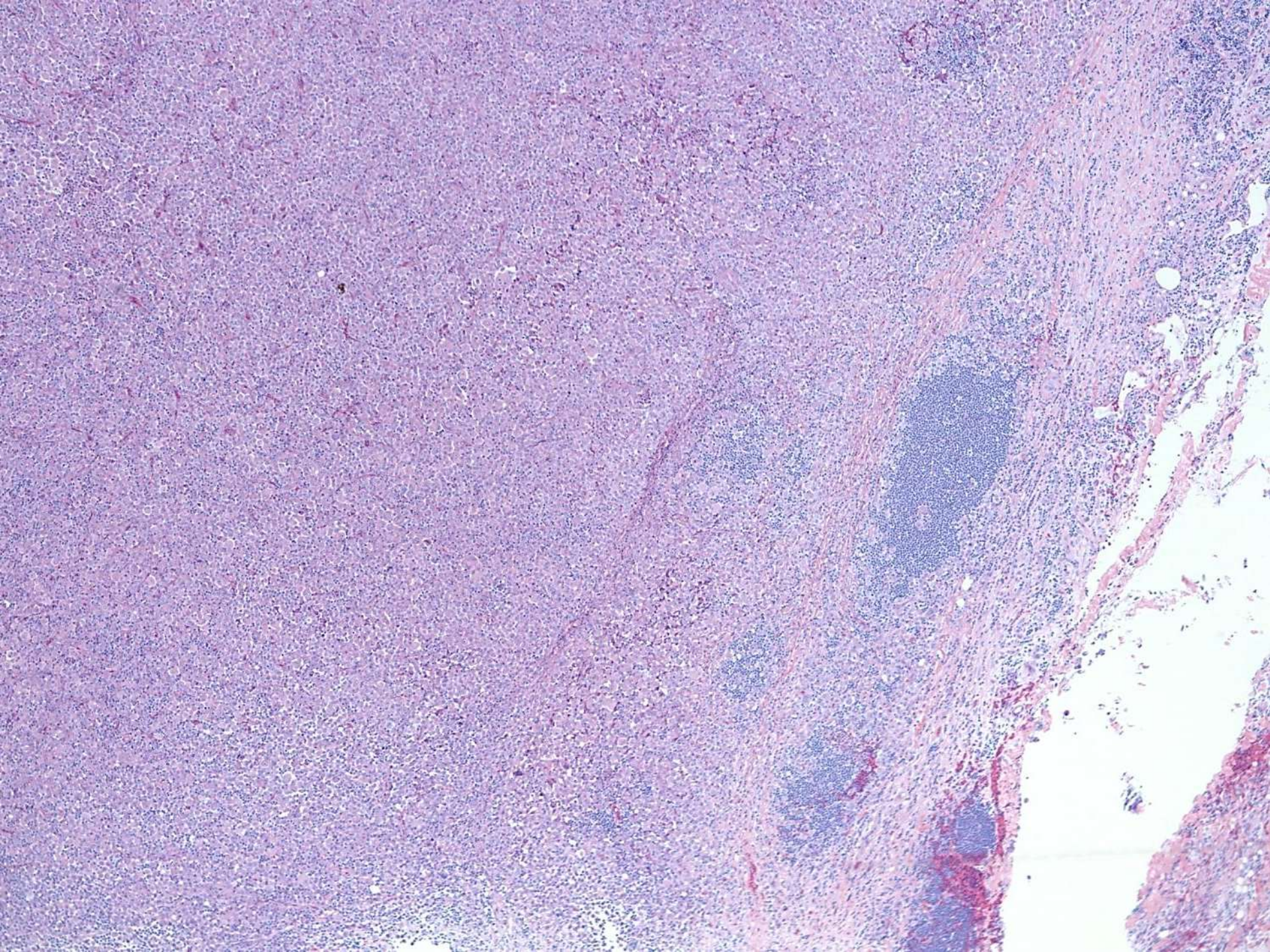

CD163

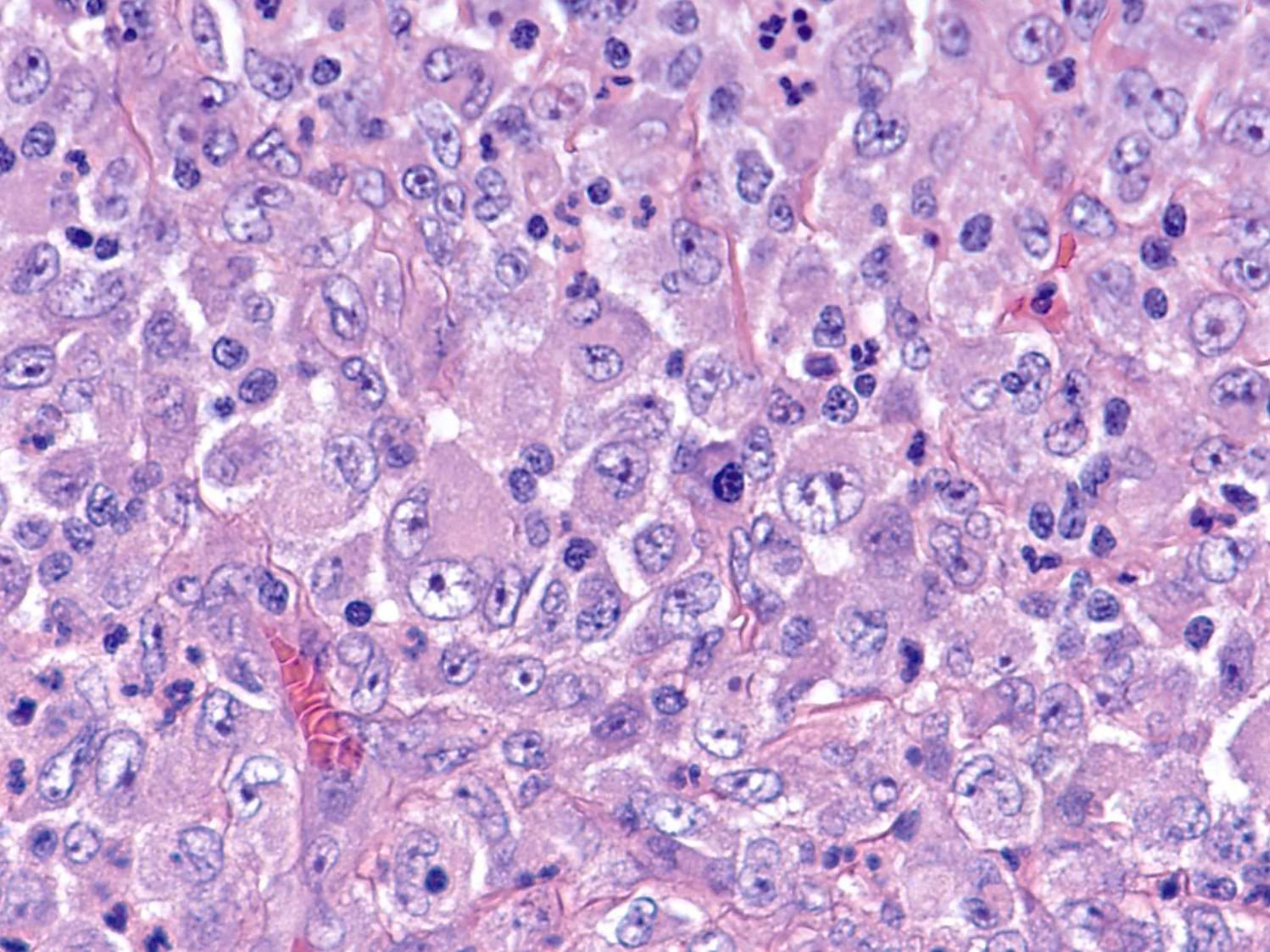

PAX5

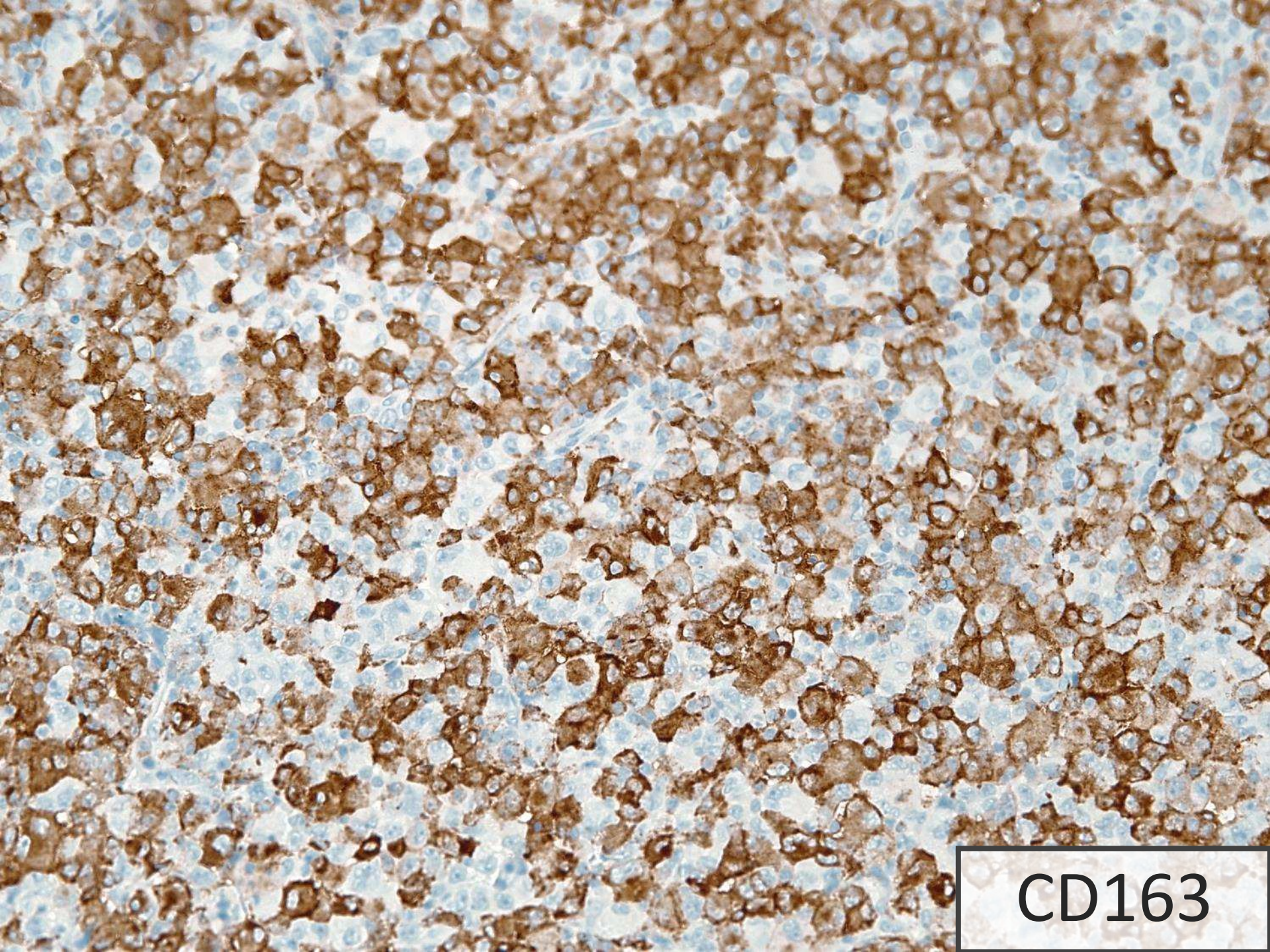
# FNA Diagnosis: Follicular lymphoma with features suspicious for histiocytic sarcoma

Excisional Biopsy: Histiocytic sarcoma with focal areas of residual grade 1-2 follicular lymphoma


Excisional Biopsy



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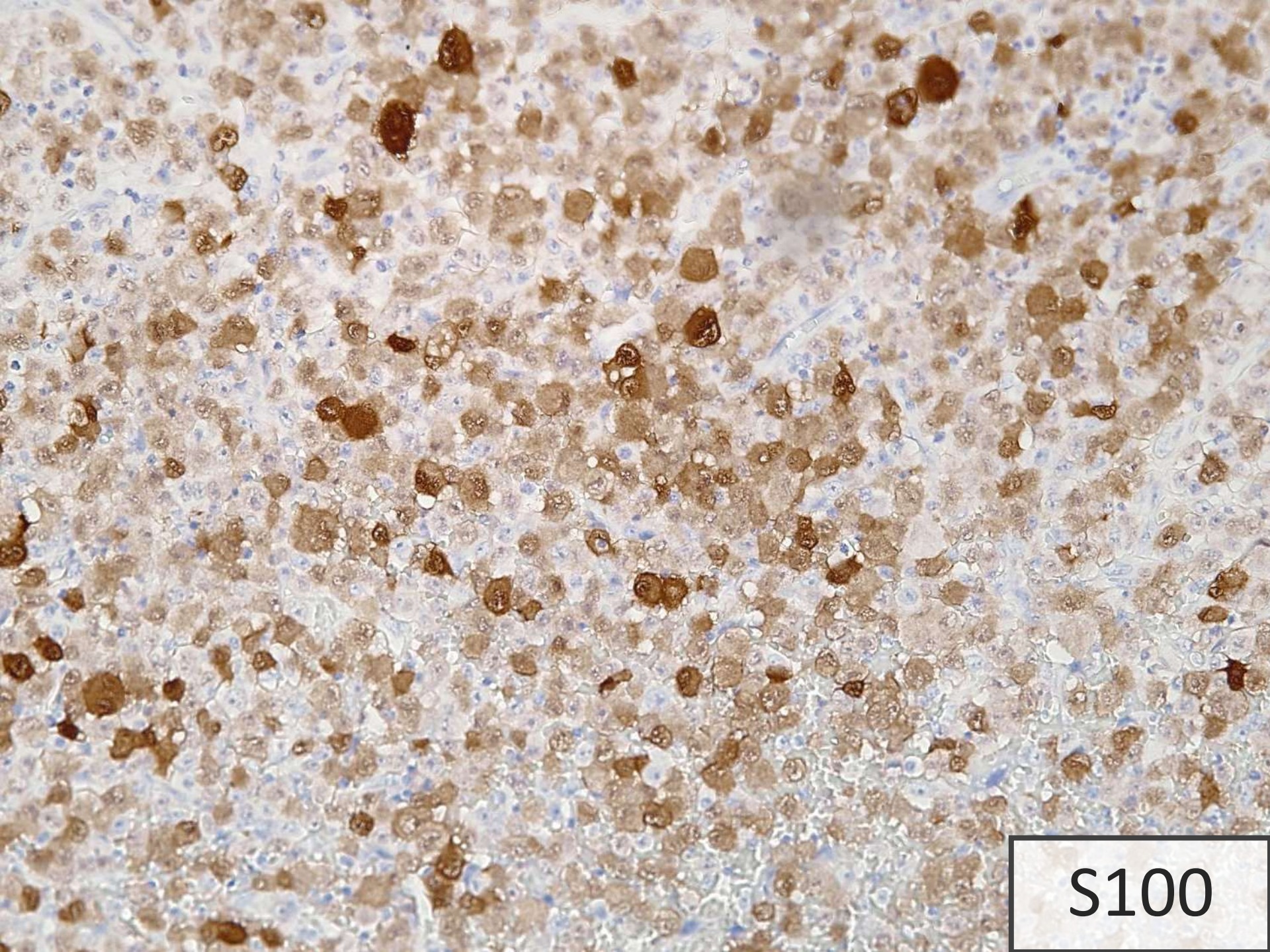
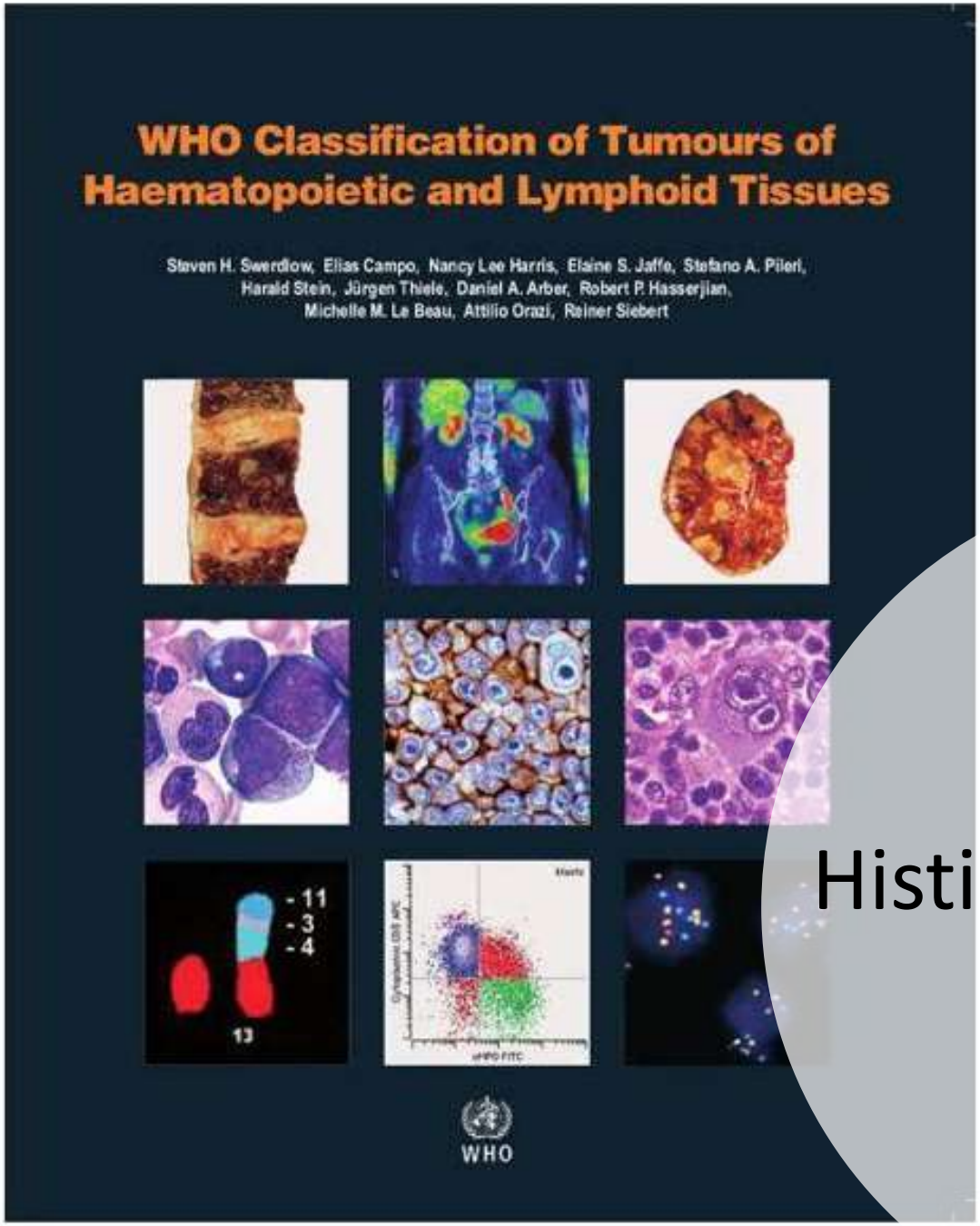

S100


BCL2




# Histiocytic Sarcoma

# Differential Diagnosis

- Anaplastic large cell lymphoma
- High-grade B-cell lymphoma
- Hodgkin lymphoma
- Myeloid sarcoma
- Follicular dendritic cell sarcoma
- Langerhans cell sarcoma

- Melanoma
- Epithelioid sarcoma
- Epithelioid angiosarcoma
- Unclassified pleomorphic sarcoma

# Immunohistochemistry

**Positive**

- **Histiocyte marker: CD68, CD163 (CD11c, lysozyme, PU.1)**
- CD45
- HLA-DR
- S100 (subset +)
- CD31 (subset +)
- Ki-67: 5-50%

**Negative**

- Epithelial: keratins, EMA
- B-cell markers: PAX5, CD20
- T-cell markers: CD4*, CD8
- Myeloid: CD13, CD33, MPO
- Dendritic: CD21, CD23, CD35
- Langerhans cell: CD1a* and langerin
- Melanocytic: SOX10, Melan A, HMB-45
- Vascular: CD34, ERG
- CD15 and CD30

* May be focally positive

# Immunohistochemistry

## Positive

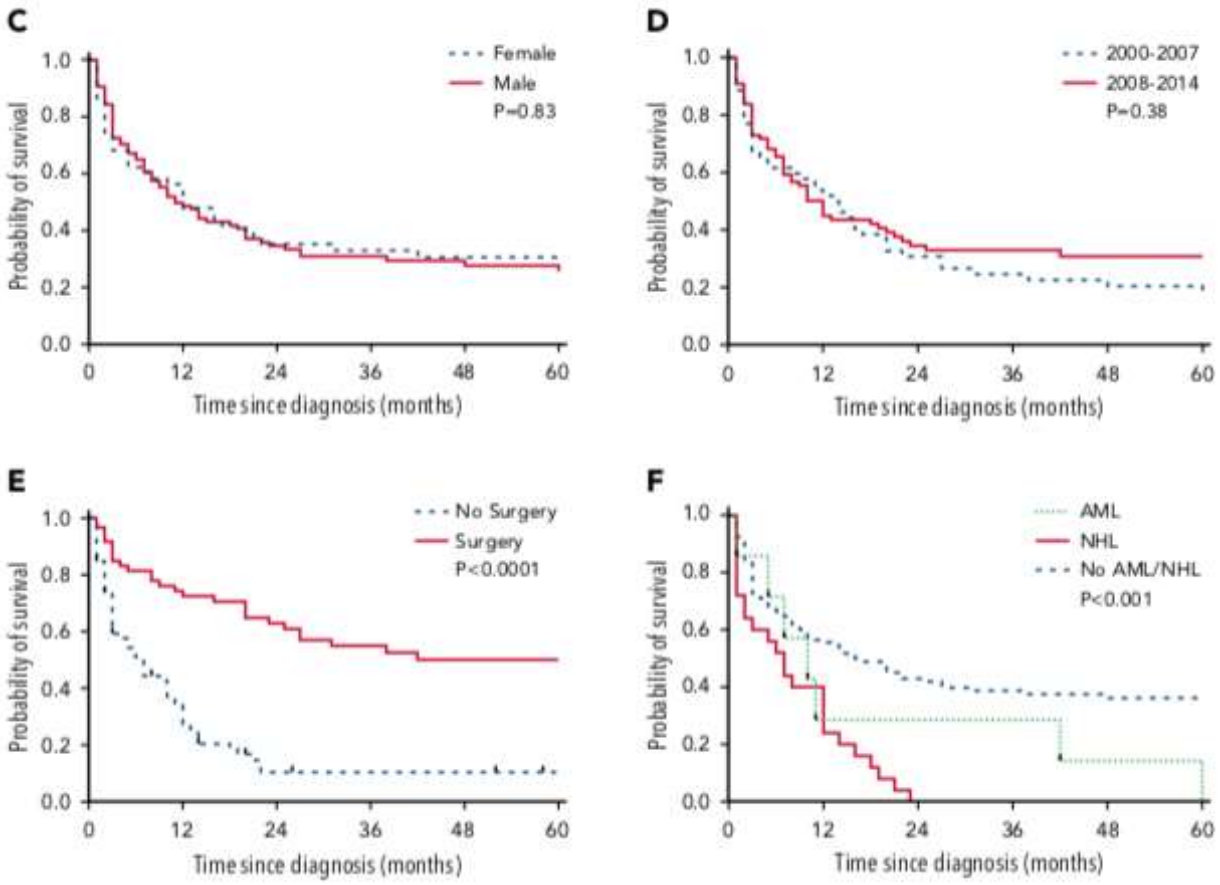
- **Histiocyte marker: CD68, CD163 (CD11c, lysozyme, PU.1)**
- CD45
- HLA-DR
- S100 (subset +)
- CD31 (subset +)
- Ki-67: 30-40%
- BCL2
- PDL1 (variable)

## Negative

- Epithelial: keratins, EMA
- B-cell markers: PAX5, CD20
- T-cell markers: CD4*, CD8
- Myeloid: CD13, CD33, MPO
- Dendritic: CD21, CD23, CD35
- Langerhans cell: CD1a* and langerin
- Melanocytic: SOX10, Melan A, HMB-45
- Vascular: CD34, ERG
- CD15 and CD30
- BRAF (V600E)
- Others: CD123. CD117, CD38, desmin, EBV ish

* May be focally positive

# Overall Survival




Kommalapati, A. et al. (2018). Histiocytic sarcoma: a population-based analysis of incidence, demographic disparities, and long-term outcomes. *Blood*, *131*(2), 265

Modern Pathology (2019) 32:830–843
https://doi.org/10.1038/s41379-018-0200-x

ARTICLE

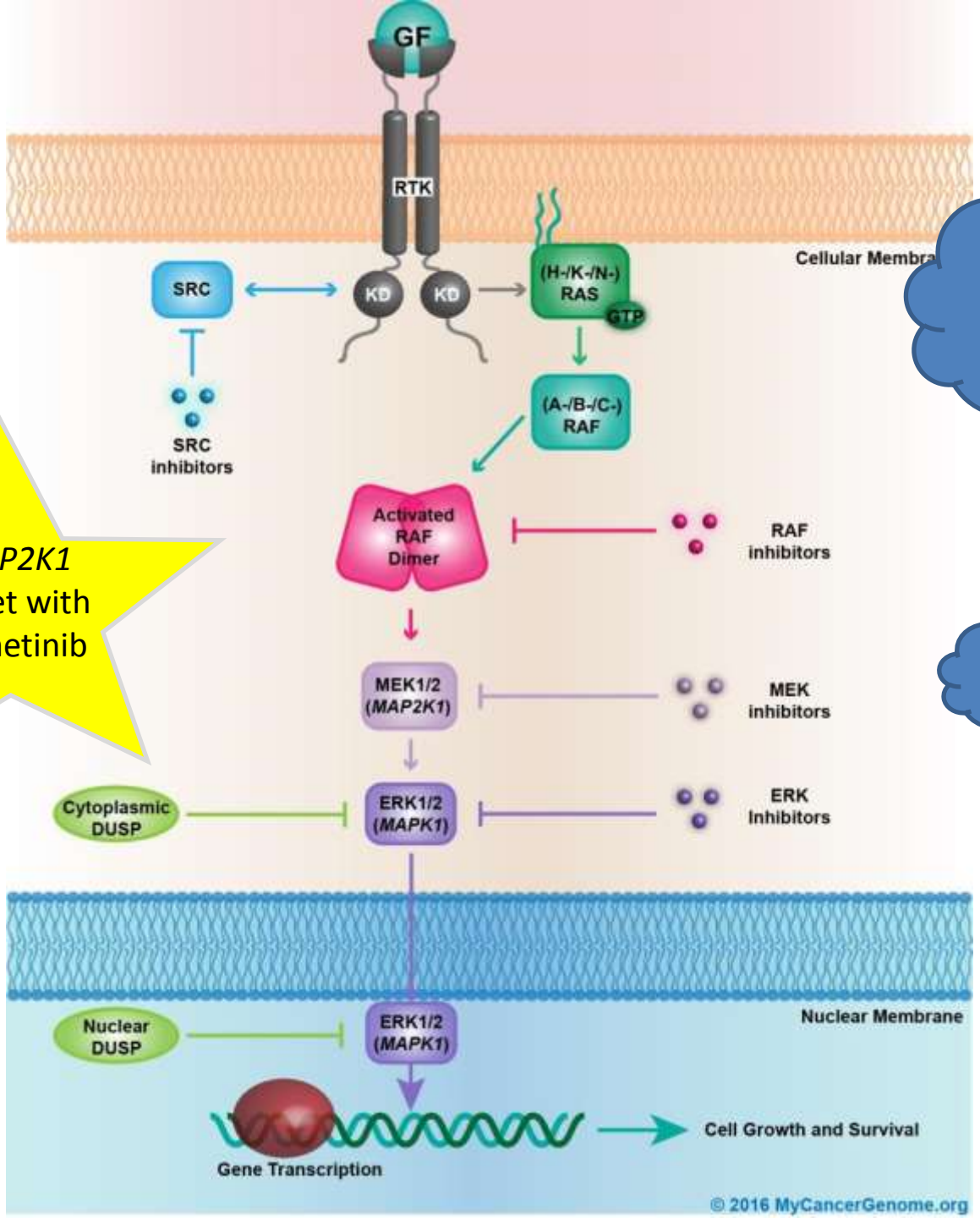
# Identification of diverse activating mutations of the RAS-MAPK pathway in histiocytic sarcoma

Vignesh Shanmugam[1,2] · Gabriel K. Griffin[1,2] · Eric D. Jacobsen[2,3] · Christopher D. M. Fletcher[1,2] · Lynette M. Sholl[1,2] · Jason L. Hornick[1,2]

Received: 22 October 2018 / Revised: 24 November 2018 / Accepted: 24 November 2018 / Published online: 9 January 2019


## Abstract

Recent studies have demonstrated recurrent activating mutations involving the classical MAPK and PI3K signaling pathways in a large proportion of histiocytic neoplasms, such as Langerhans cell histiocytosis. However, very little is known about the molecular genetics of histiocytic sarcoma, a rare aggressive malignant neoplasm that shows pathologic characteristics of mature macrophages. Here we report the genomic characteristics of a large cohort of histiocytic sarcomas ($n = 28$) using a targeted next-generation sequencing approach to identify driver alterations. We identified recurrent mutations involving the RAS-MAPK signaling pathway (*MAP2K1*, *KRAS*, *NRAS*, *BRAF*, *PTPN11*, *NF1*, *CBL*) in a majority (57%) of histiocytic sarcoma cases and report a clinical response to a MEK inhibitor (Cobimetinib) in a patient with a *NF1*-mutated histiocytic sarcoma. A smaller subset of cases (21%) also showed mutations resulting in activation of the PI3K signaling pathway (*PTEN*, *MTOR*, *PIK3R1*, *PIK3CA*). In addition, the tumor-suppressor gene *CDKN2A* was the most frequently altered gene (46%). Further, a subset of histiocytic sarcoma cases shows striking molecular genetic similarities to B cell lymphomas, supporting a clonal relationship between B cell neoplasms and a subset of histiocytic sarcomas. These findings support a cooperative role for MAPK, PI3K, and cyclin-CDK4/6-INK4 signaling in the pathogenesis of histiocytic sarcoma and provide a rational basis for targeting these pathways.




*MAP2K1*
Target with
Trametinib

*IGHJ5-BCL2*

*PPM1D*

*BIRC3*

*CREBBP*

*PIM1*

# Take Away Points: Histiocytic Sarcoma

- If you see large atypical cells in a patient with follicular lymphoma, think of histiocytic sarcoma!
- Must exclude mimics with IHC
- Median overall survival is 6 months
- Can occur in isolation (~75%) or in association with other heme neoplasms (~25%) via transdifferentiation
- RAS-MAPK pathway, PI3K pathway, and *CDKN2A* gene alterations

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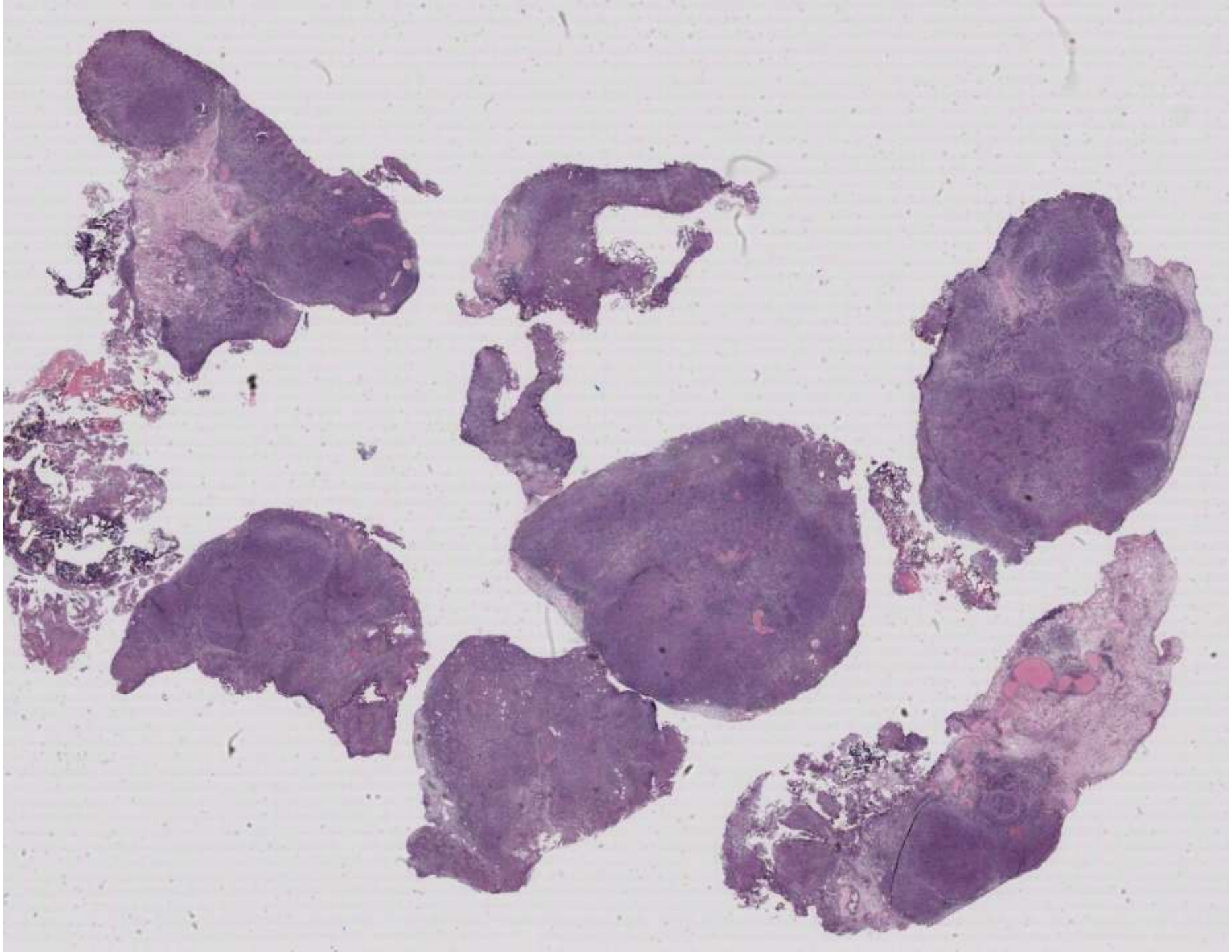
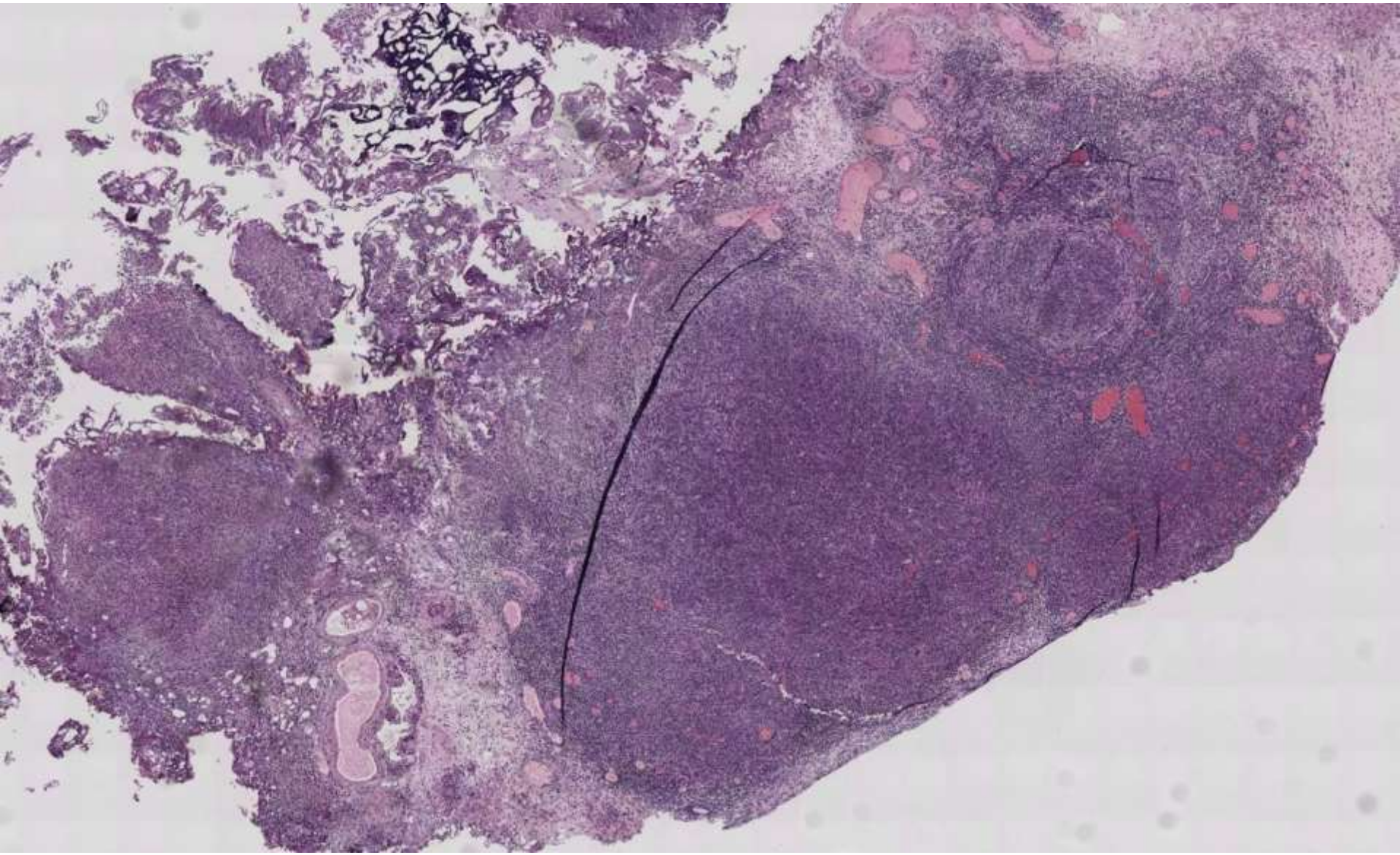
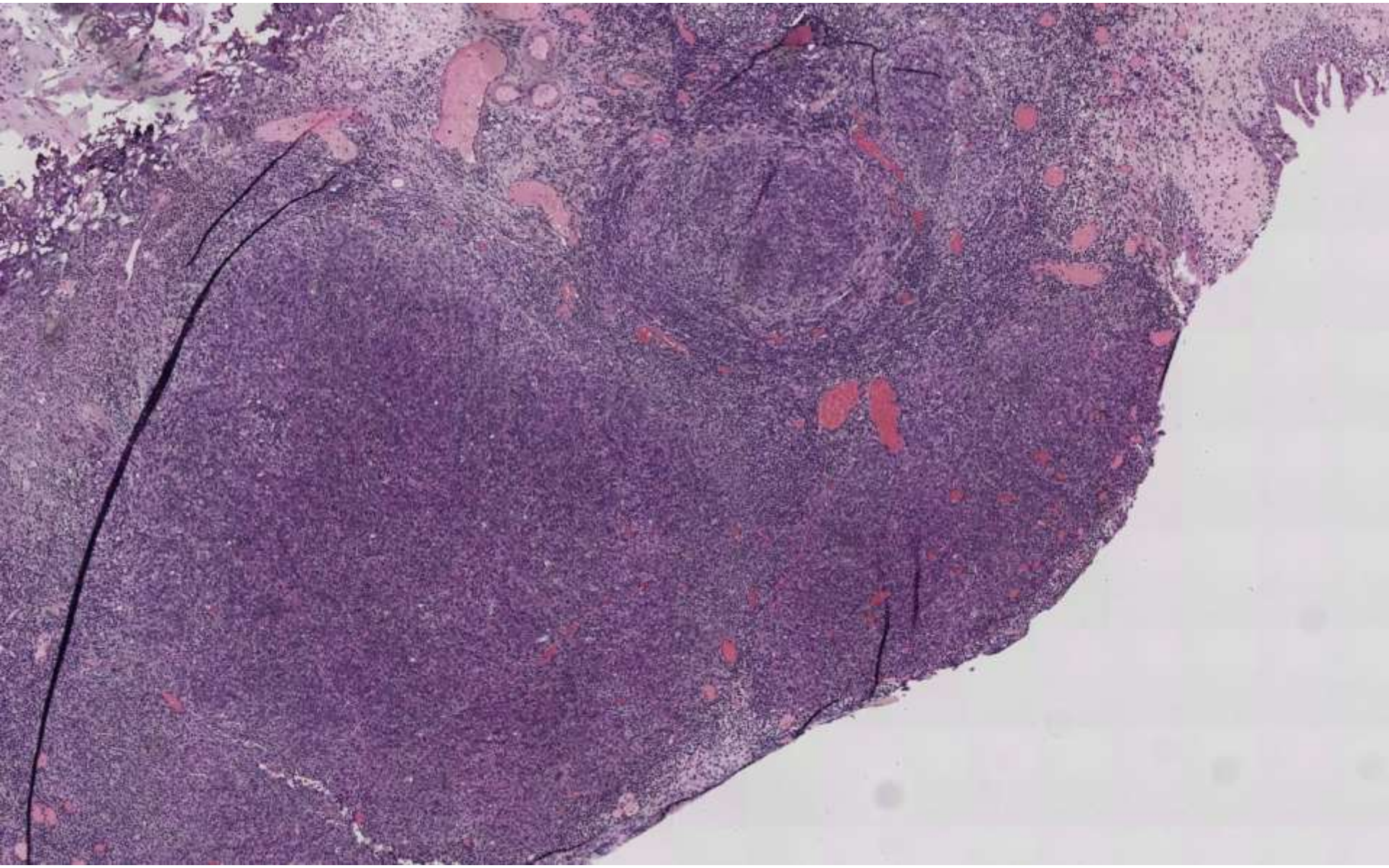
# 20-0207
# scanned slide available!

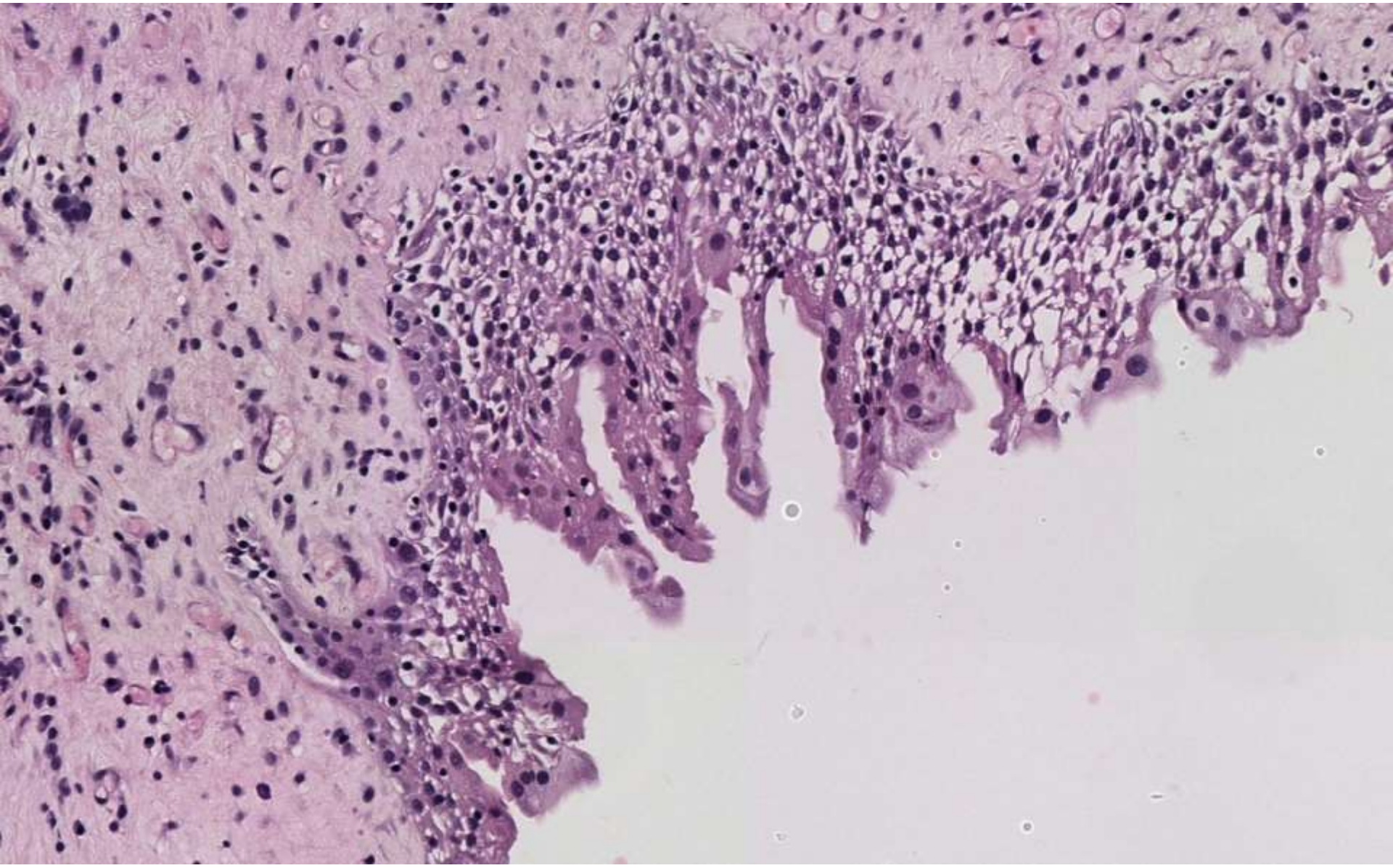
**Ankur Sangoi; El Camino Hospital**

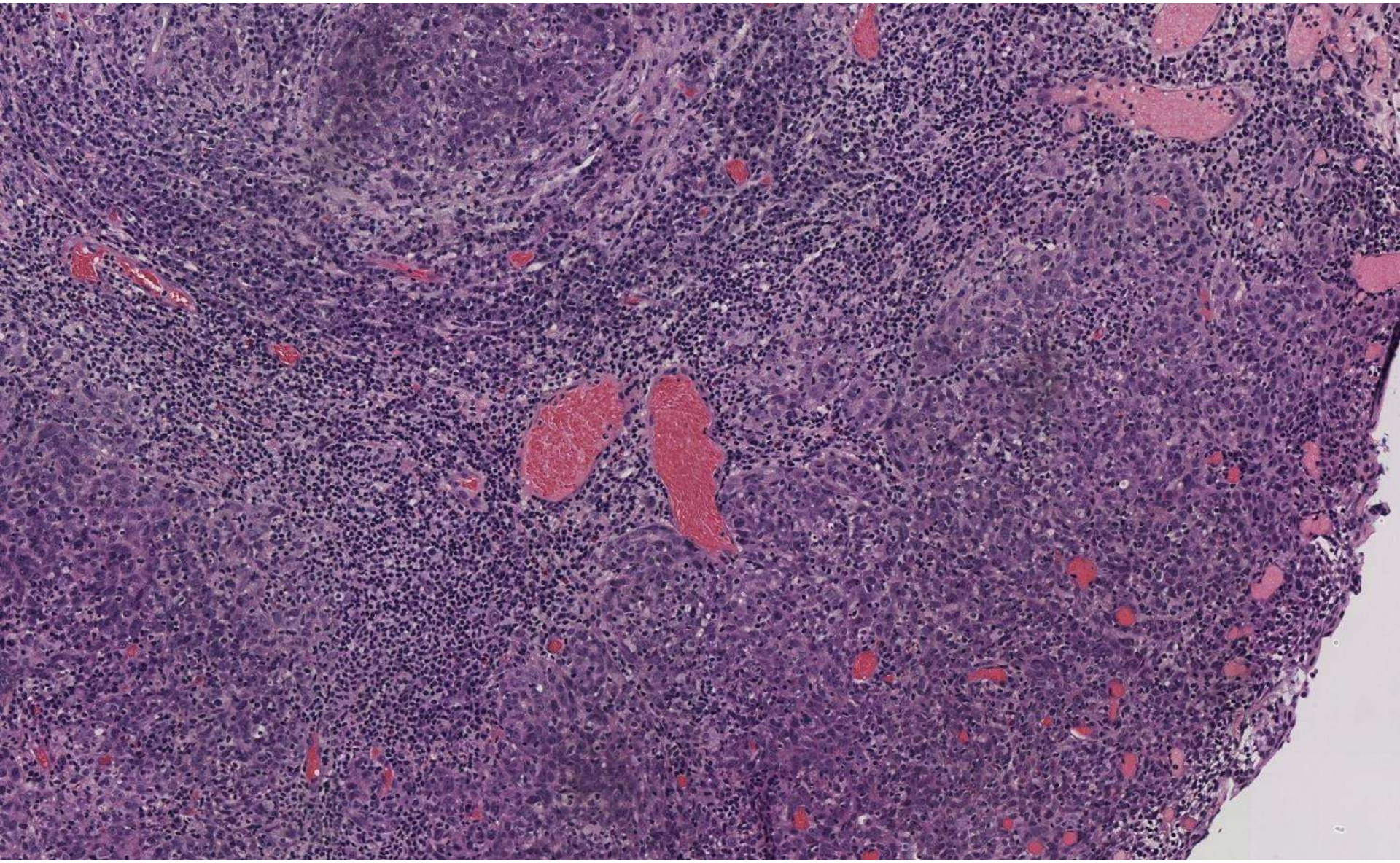
84-year-old M with bladder mass, TURBT.

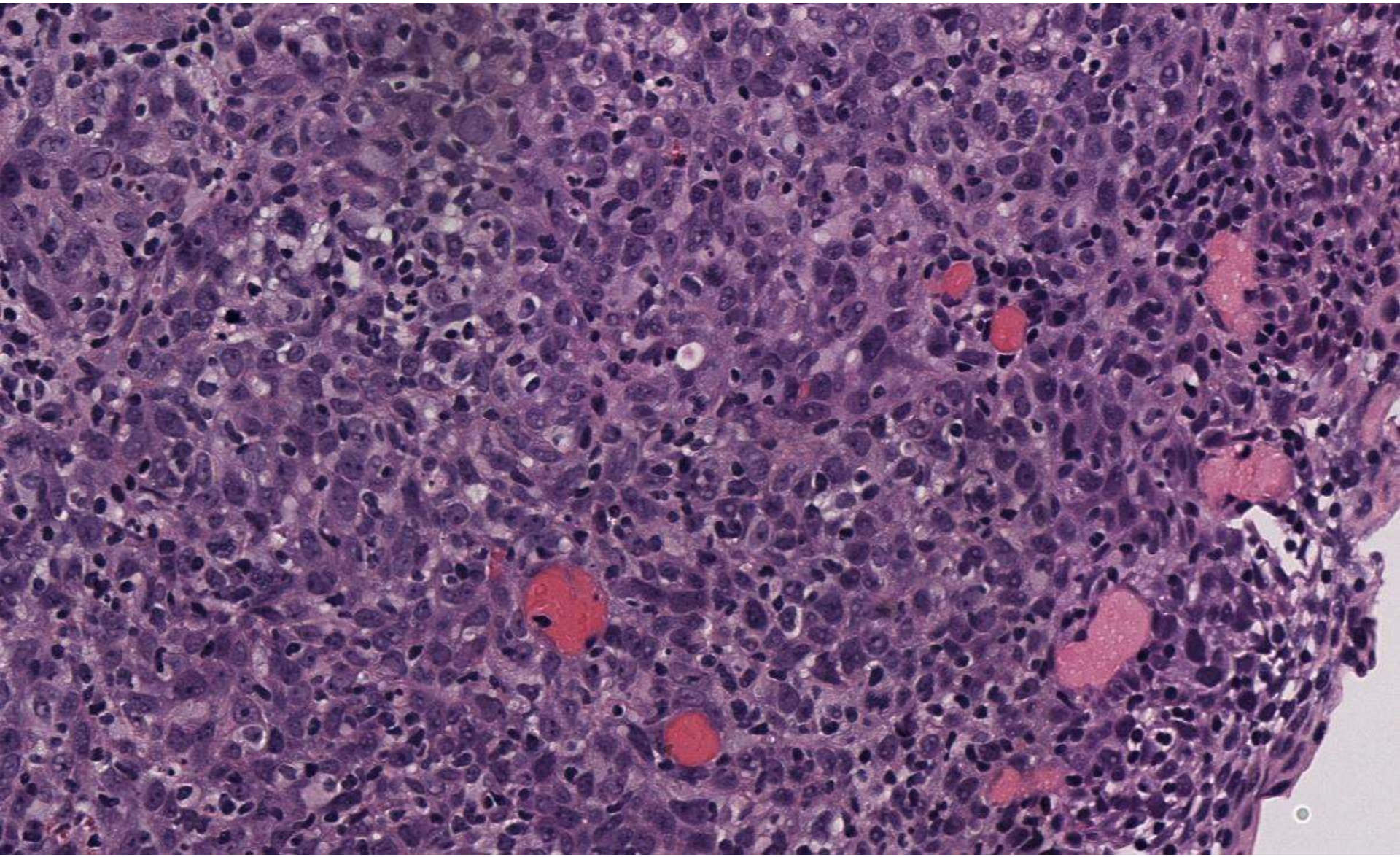


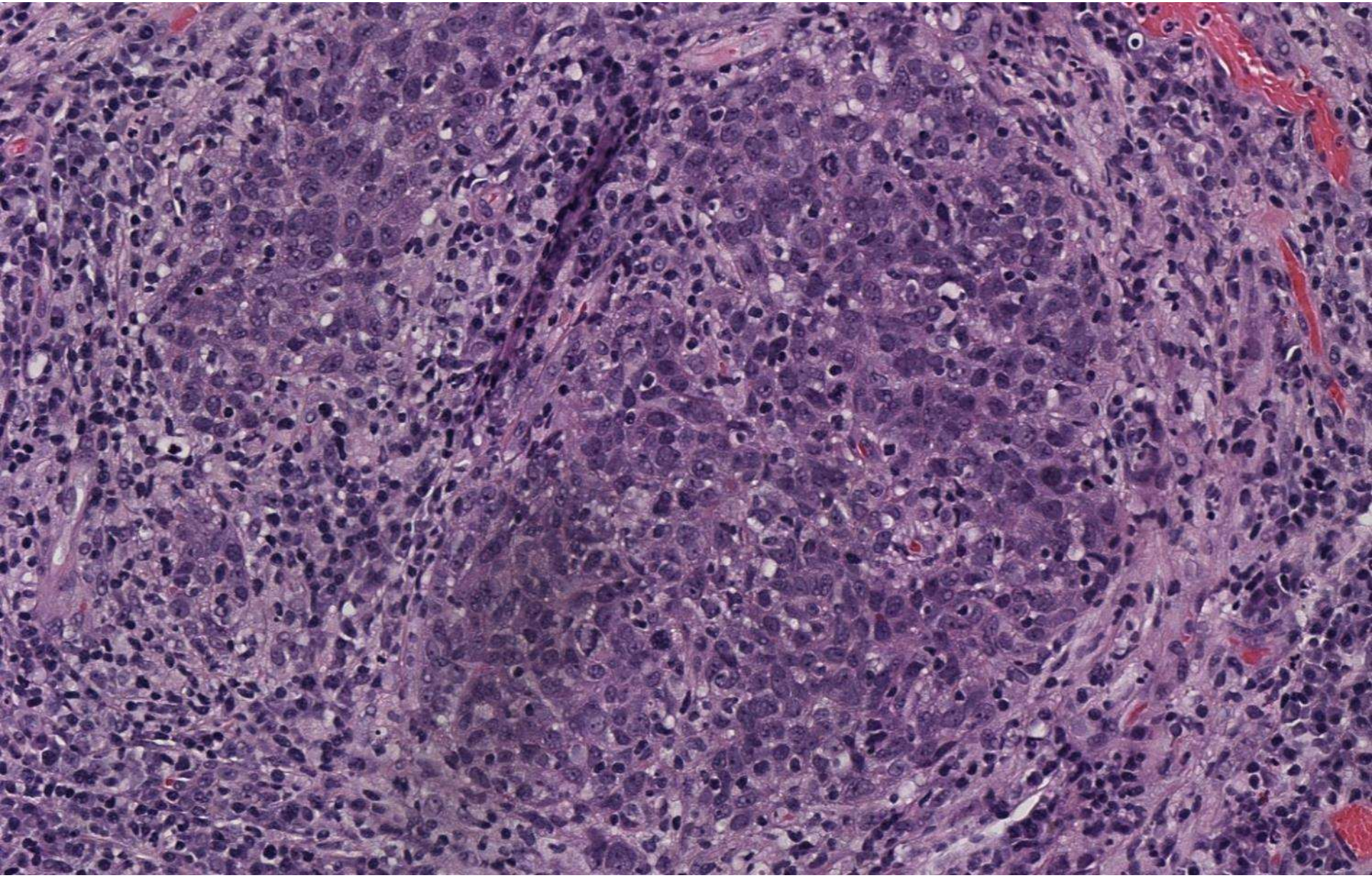


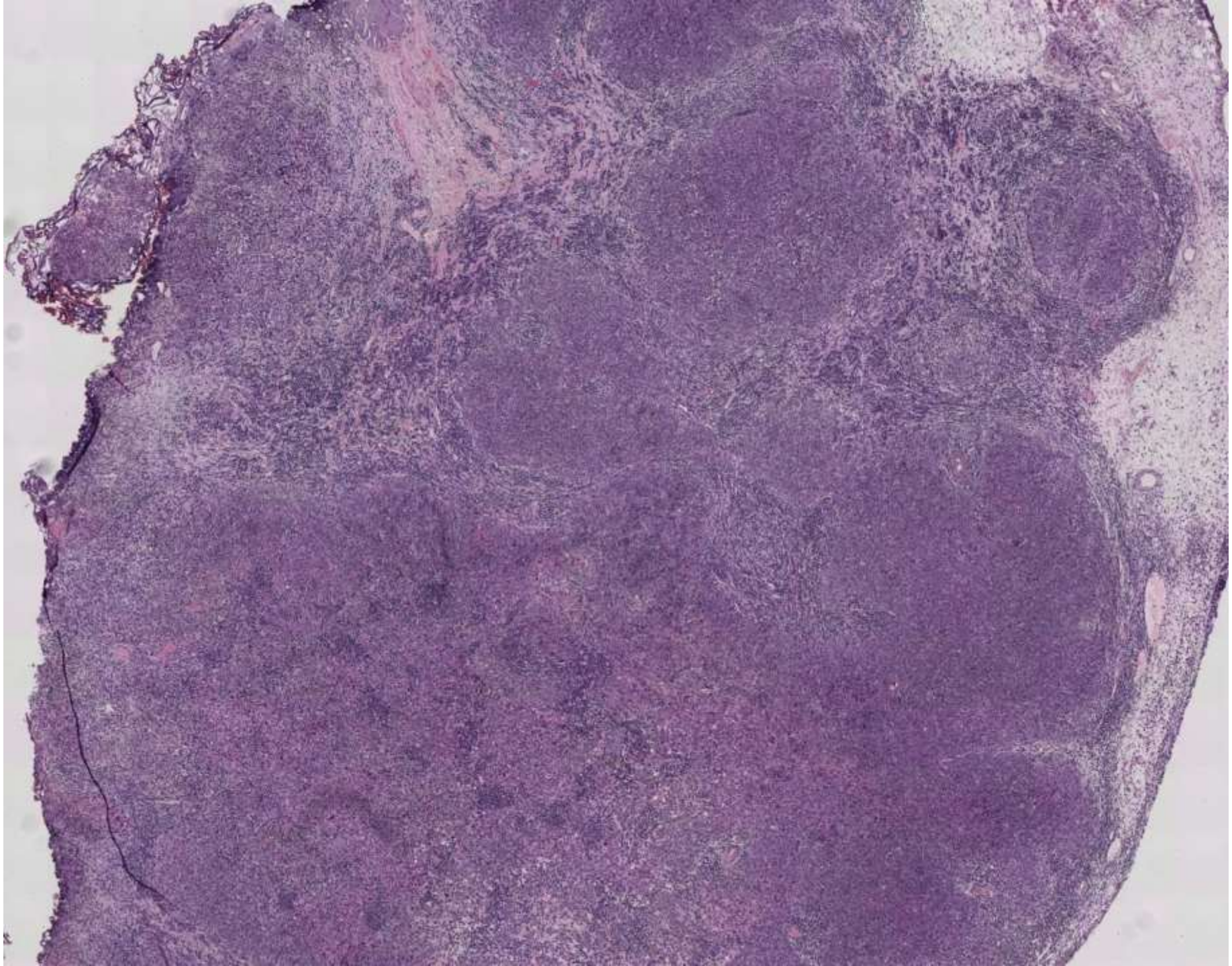


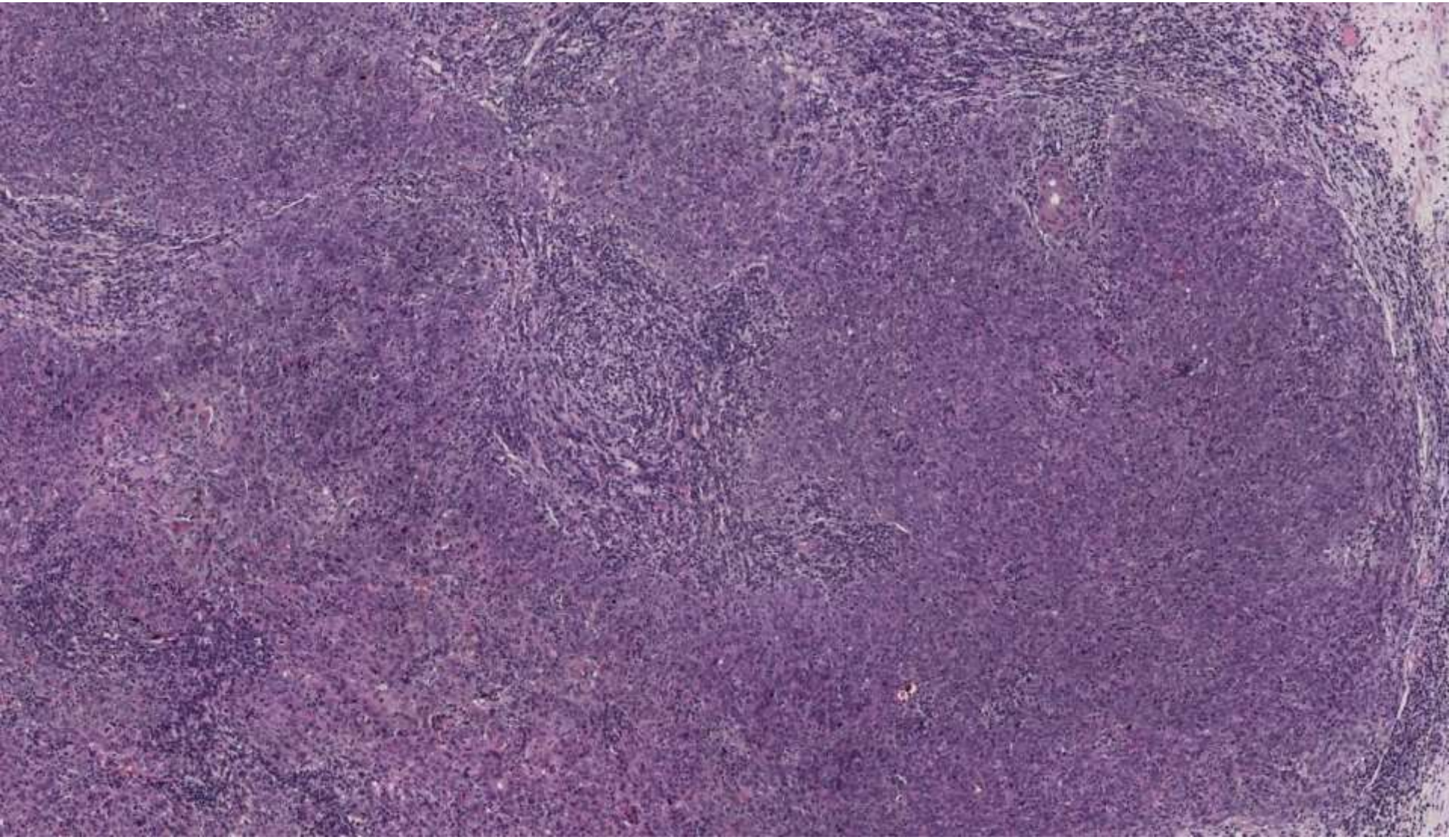


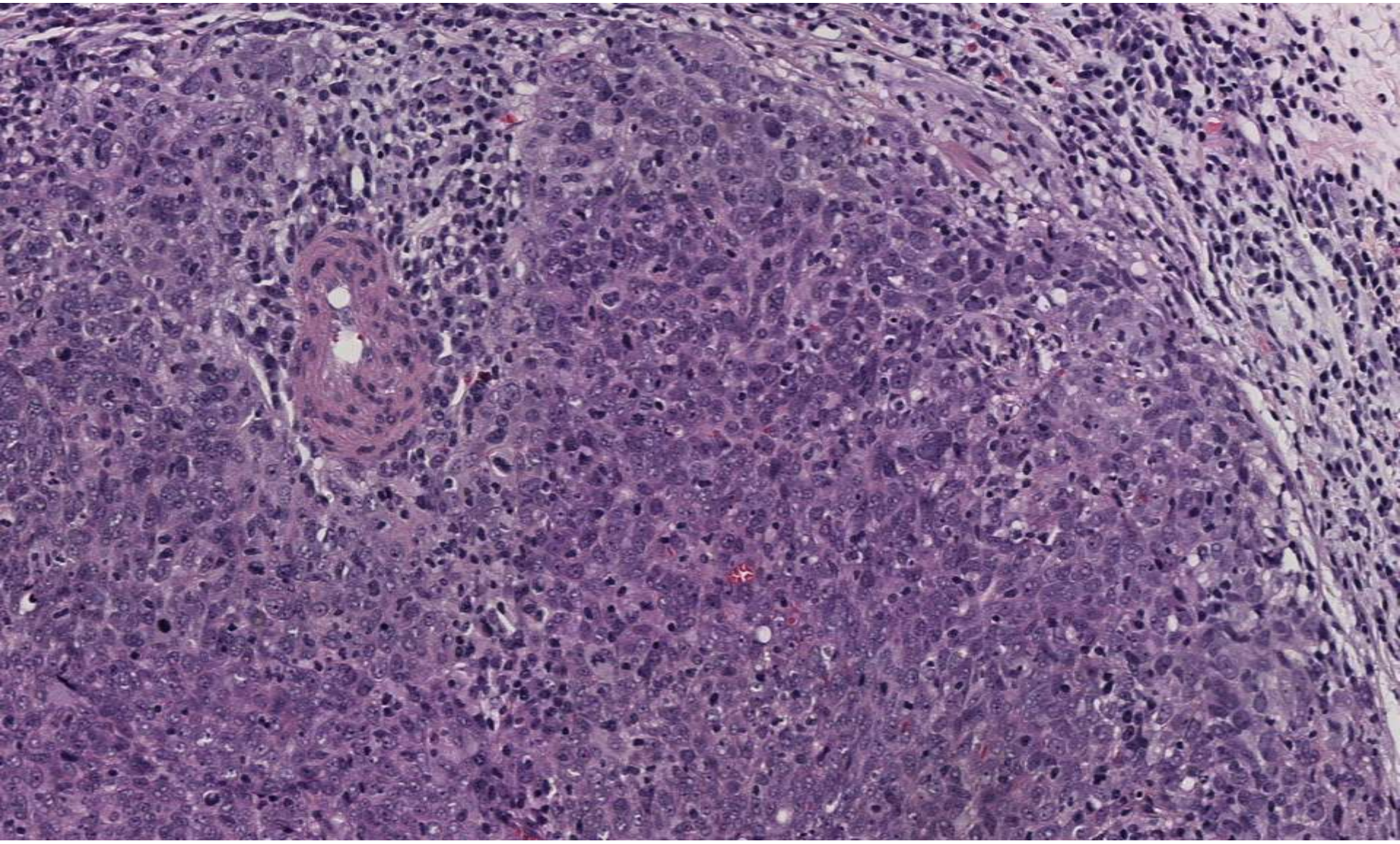


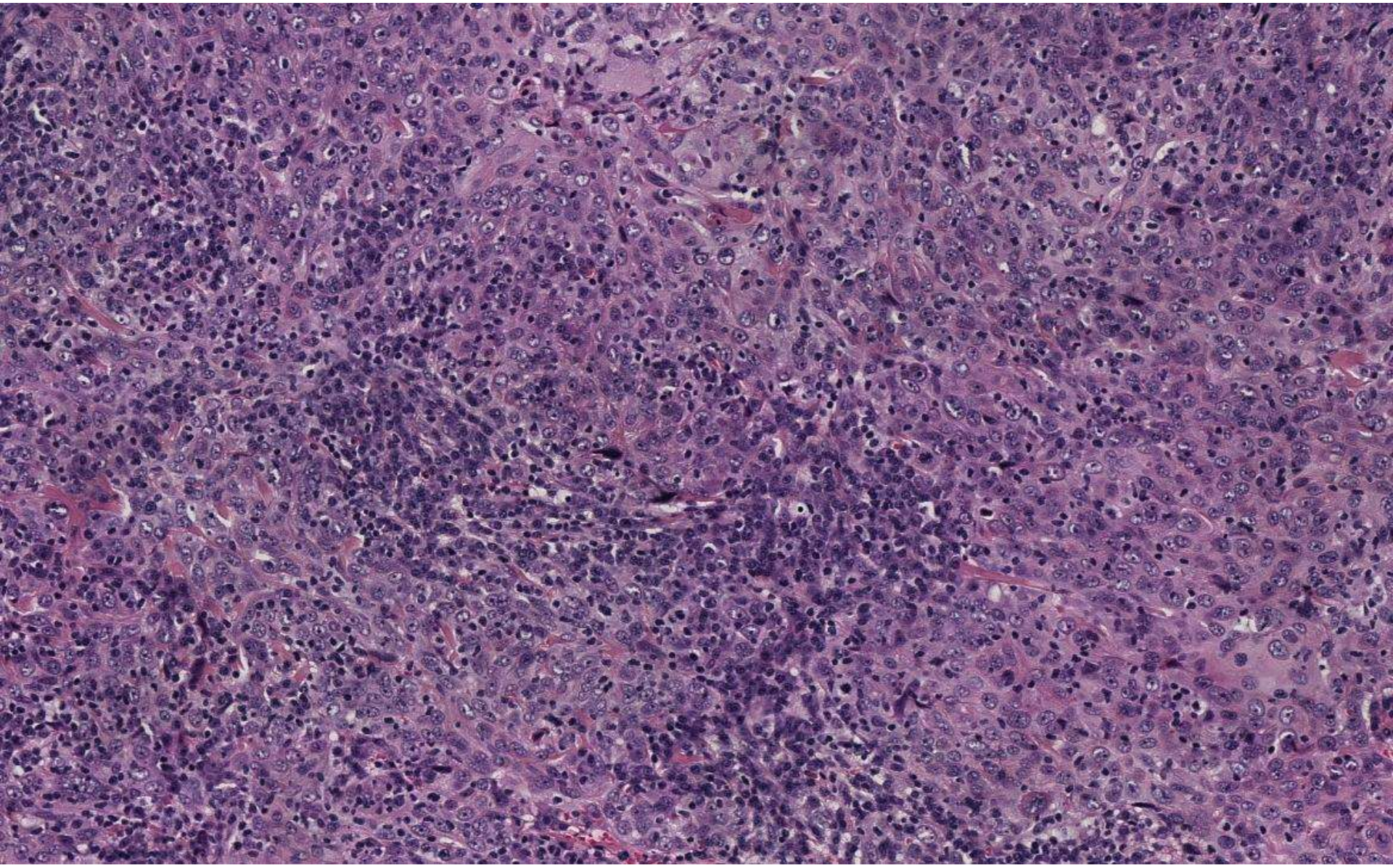


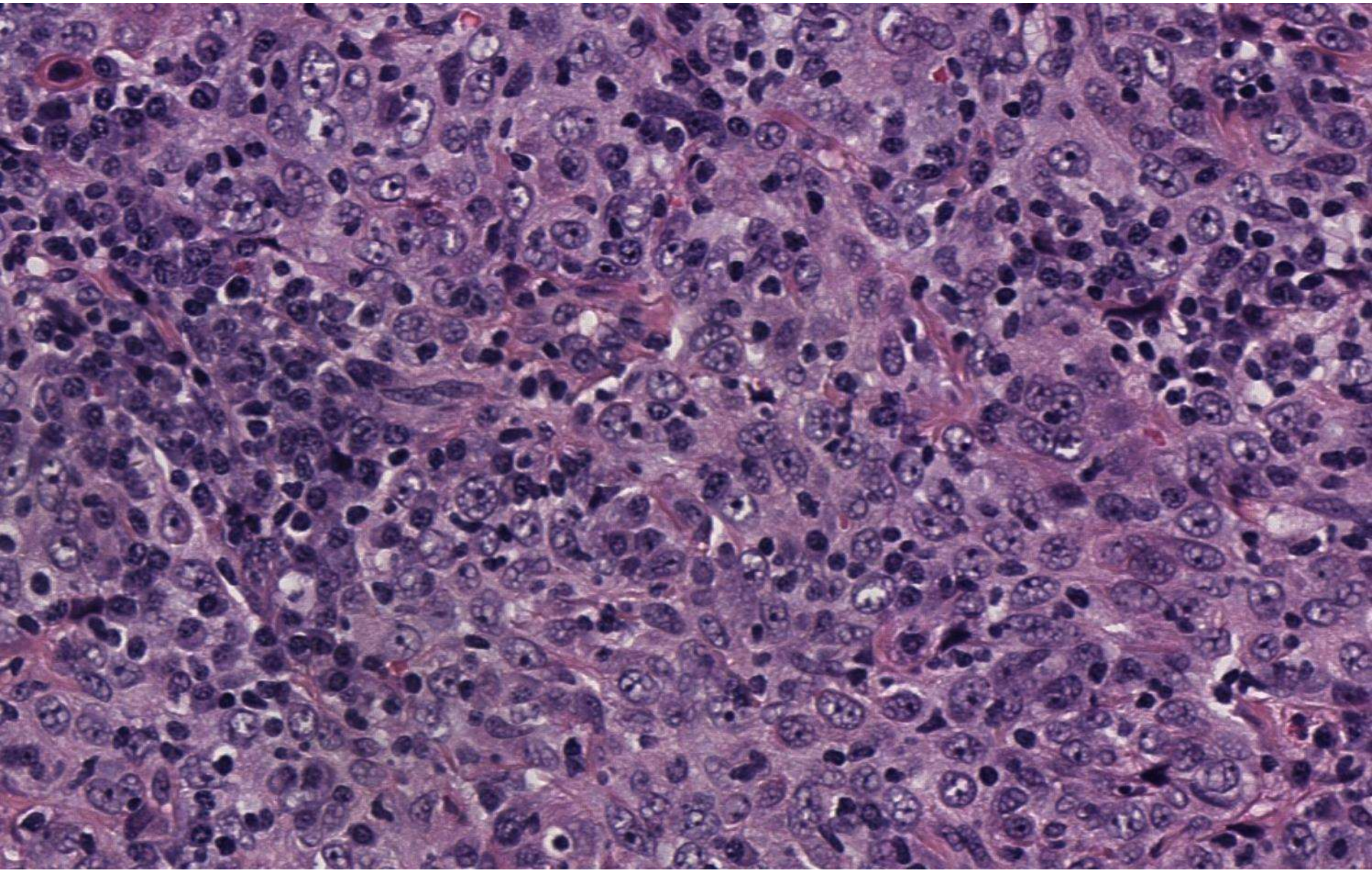






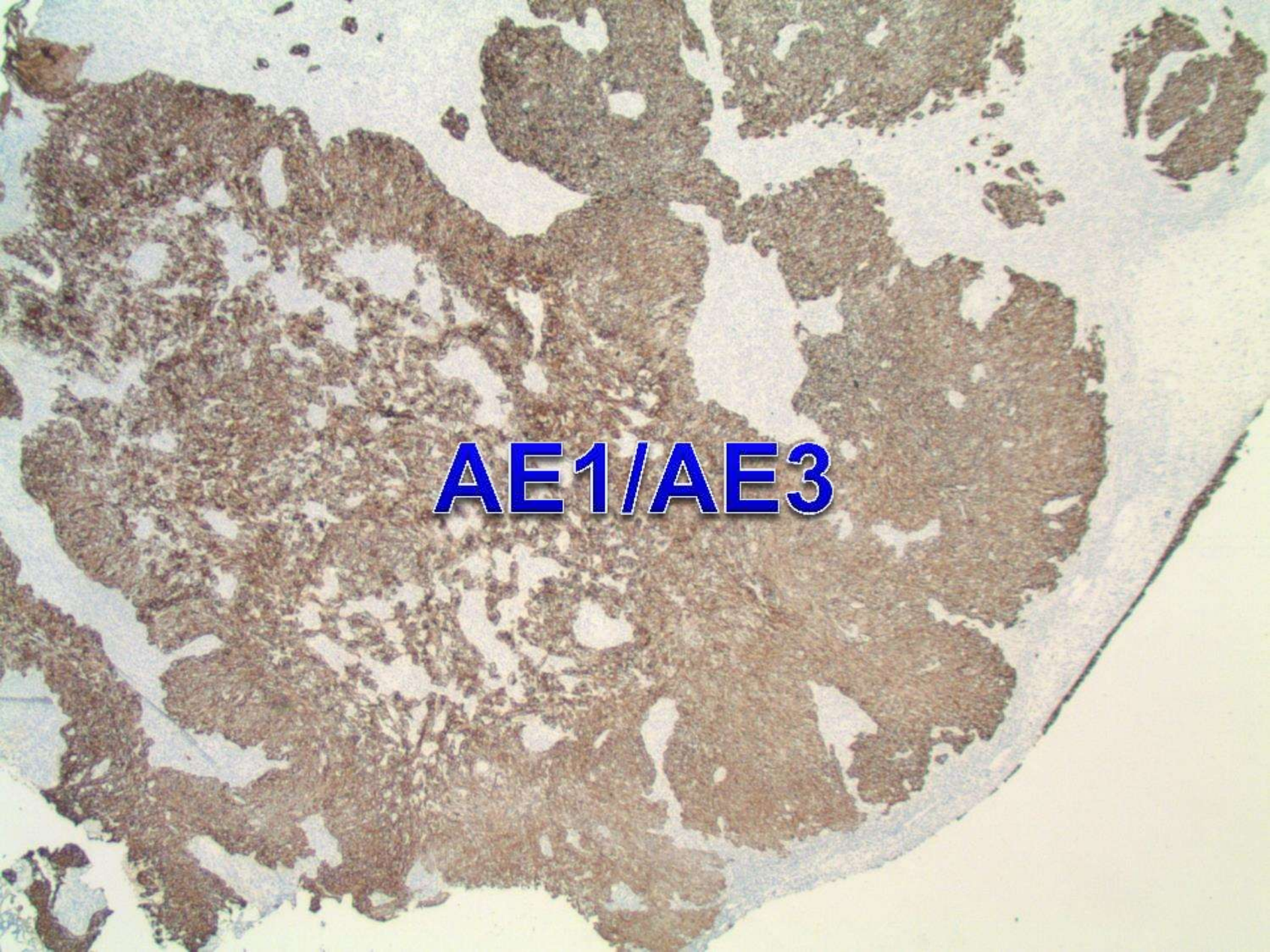


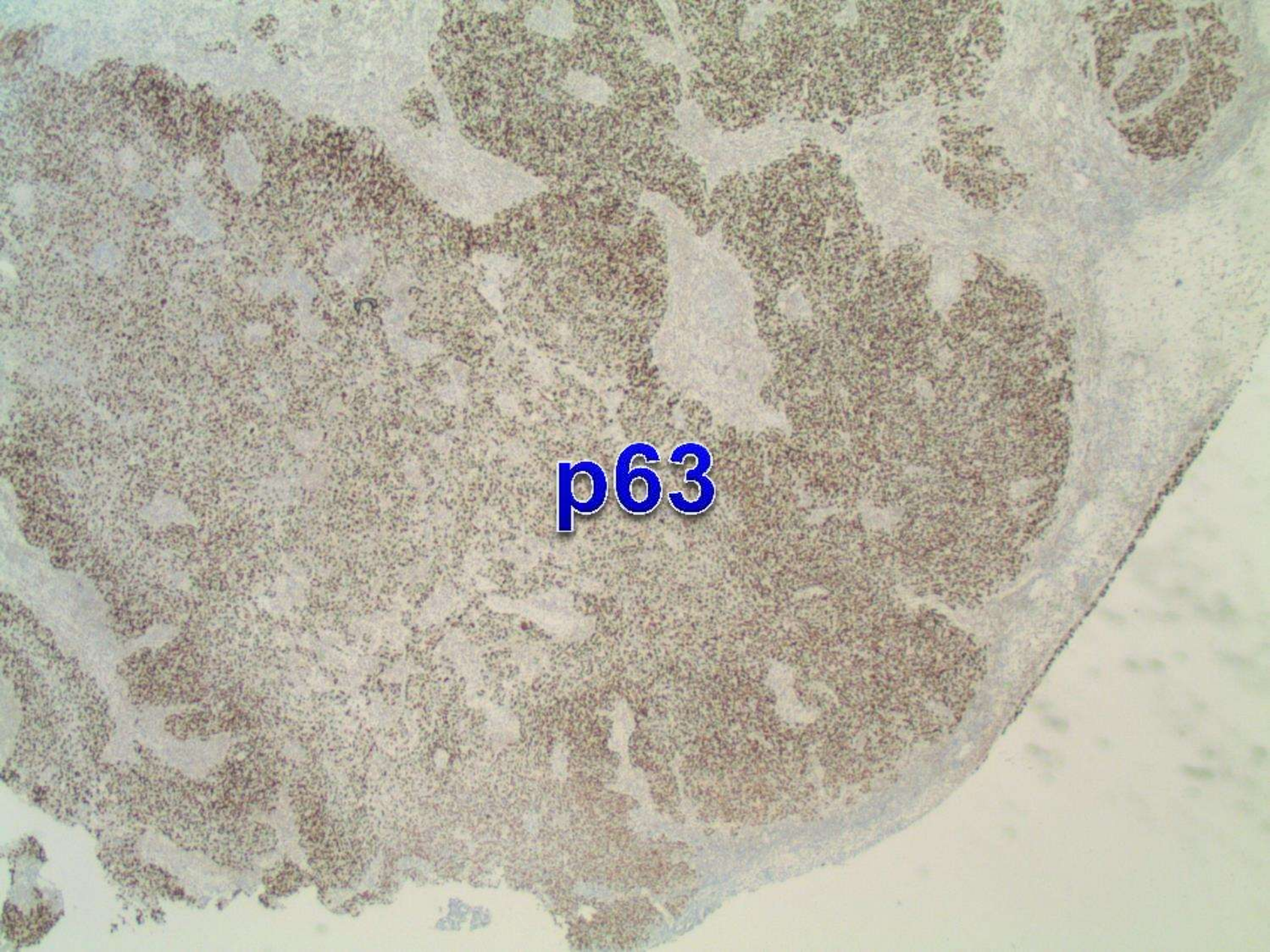


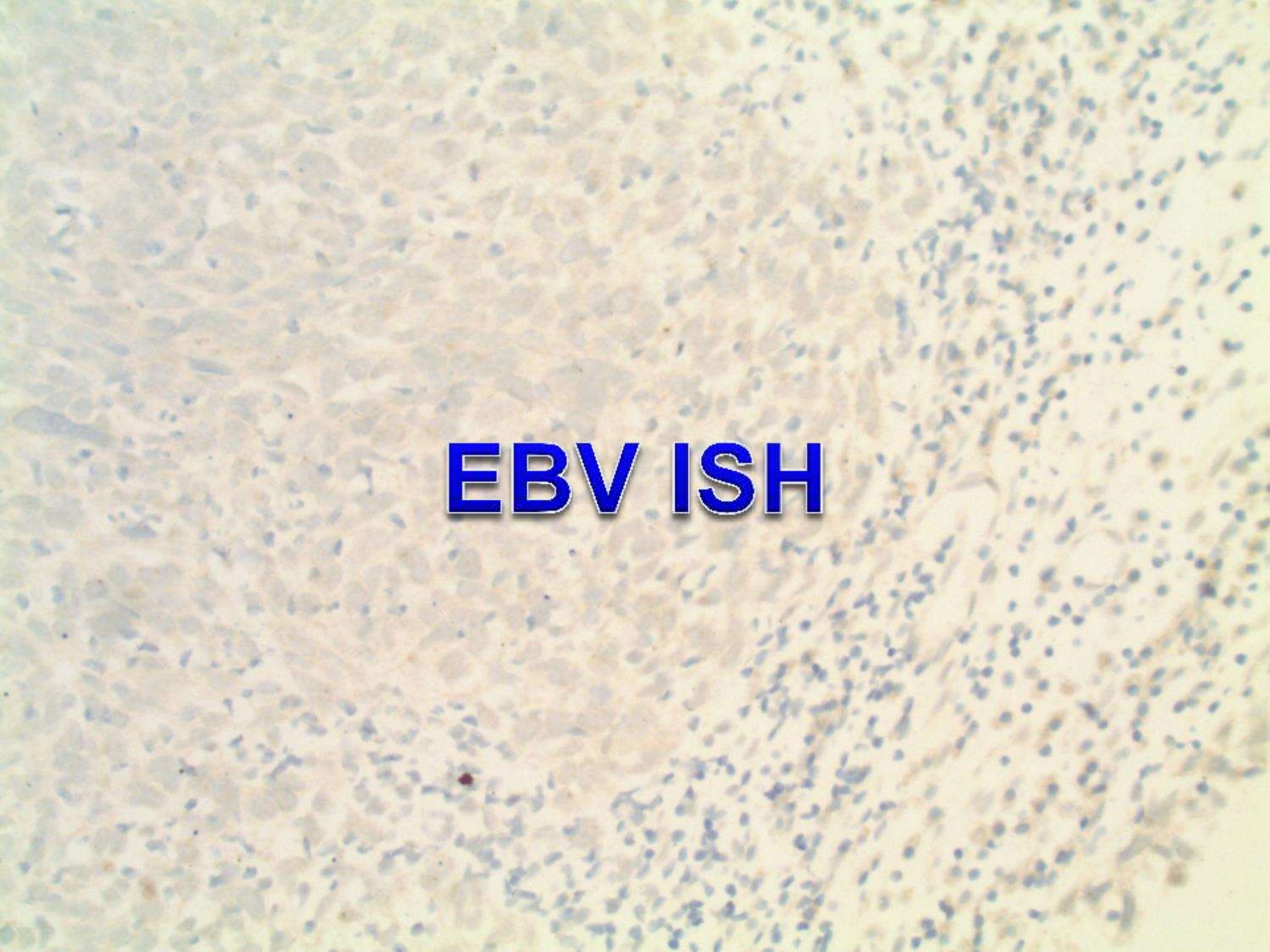


# DDx

- Lymphoepitheloma-like carcinoma
- Urothelial carcinoma with prominent lymphoid stroma
- Lymphoma
- Small cell carcinoma


AE1/AE3


p63


EBV ISH

# FINAL DIAGNOSIS

- **Lymphoepithelioma-like carcinoma**
  - Primary urothelial origin

# DDx of LEL-like carcinoma

- **Urothelial carcinoma with prominent lymphoid stroma**
  - Lacks syncytia of cells
  - Poorly differentiated urothelial histology
- **Lymphoma**
  - CD45+ and keratin –
- **Small cell carcinoma**
  - Neuroendocrine features
  - keratin+ and NE IHC+

# Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases

Ecaterina F Tamas[1], Matthew E Nielsen[2], Mark P Schoenberg[2] and Jonathan I Epstein[1,2,3]

[1]*Department of Pathology, Johns Hopkins Hospital, Baltimore, MD, USA;* [2]*Department of Urology, Johns Hopkins Hospital, Baltimore, MD, USA and* [3]*Department of Oncology, Johns Hopkins Hospital, Baltimore, MD, USA*

**We studied 28 cases of lymphoepithelioma-like carcinoma of the bladder, one case in the renal pelvis, and one in the urethra. The mean age of the patients was 67.6 years with 21 (70%) males. Seventeen cases (56.7%) were pure with the remaining mixed with other patterns of carcinoma, including invasive urothelial carcinoma (*n* = 10), invasive adenocarcinoma (*n* = 3), and squamous cell carcinoma (*n* = 2). The surface demonstrated carcinoma *in situ* (CIS) in six cases, noninvasive high-grade papillary urothelial carcinoma in three cases, and *in situ* adenocarcinoma in one case. In 19/30 (66%) cases, there was a heavy lymphocytic infiltrate and in the remaining 11/30 (34%) cases a mixed inflammatory infiltrate. None of the 26 cases labeled for EBV-encoded RNA by *in situ* hybridization. Tumor stages at presentation were: seven cases T1 (23%); 14 cases T2 (47%); seven cases T3 (23%); and two cases T4 (7%). Treatment consisted of radical cystectomy in 13/30 cases (43%); partial cystectomy in 4/30 cases (13%); nephrectomy in one case (3%), and transurethral resection often followed by radiation or chemotherapy in 12/30 (40%) cases. The mean follow up for patients without progression was 31 months. Eight of 27 cases with follow-up (30%) cases had tumor recurrence, with seven patients having metastases. In cases treated with cystectomy, the 5-year actuarial recurrence-free risk was 59% (62 and 57%, for pure and mixed cases, respectively). Lymphoepithelioma-like carcinoma, whether in pure or mixed form, has a similar prognosis to ordinary urothelial carcinoma when treated by cystectomy. Of the three pure cases treated by chemotherapy, two were free of disease at 4 and 65 months and the third had recurrent disease at 17 months. Given the association of lymphoepithelioma-like carcinoma with urothelial carcinoma in 47% of our cases and its propensity for multifocality, partial cystectomy would typically be ill advised for lymphoepithelioma-like carcinoma.**

*Modern Pathology* (2007) **20**, 828–834; doi:10.1038/modpathol.3800823; published online 1 June 2007

# Lymphoepithelioma-like Carcinoma of the Urinary Bladder: Clinicopathologic, Immunohistochemical, and Molecular Features

*Sean R. Williamson, MD,* Shaobo Zhang, MD,* Antonio Lopez-Beltran, MD,† Rajal B. Shah, MD,‡ Rodolfo Montironi, MD, FRCPath, IFCAP,§ Puay-Hoon Tan, MD,‖ Mingsheng Wang, MD,* Lee Ann Baldridge, BA, HT(ASCP),* Gregory T. MacLennan, MD,¶ and Liang Cheng, MD*#*

**Introduction:** Lymphoepithelioma-like carcinoma (LELC) in the urinary tract is a rare malignancy, named for its resemblance to nasopharyngeal undifferentiated carcinoma or lymphoepithelioma. Investigation of immunohistochemical and molecular characteristics of bladder LELC is limited. The pathogenesis and biological behavior of these tumors are controversial.

**Materials and Methods:** We examined clinicopathologic features of the urinary tract LELC, including light microscopy; immunohistochemistry for cytokeratin 7 (CK7), CK20, 34βE12, p53, p63, α-methylacyl-CoA racemase, thyroid transcription factor-1, Epstein-Barr virus latent membrane protein-1, and CD30; in situ hybridization for human papillomavirus; and UroVysion fluorescence in situ hybridization (FISH).

**Results:** We identified tumors from 34 patients, the largest series to date, (male:female, 2.8:1), ranging from 54 to 84 years of age (mean, 70 years). Urothelial carcinoma in situ was identified in 50% of patients. 34βE12 (75%), CK7 (57%), and p63 (53%) were frequently positive in tumor cells, whereas thyroid transcription factor-1 and CD30 were consistently negative. Expression of p53 was noted in a subset of tumors (61%), whereas CK20 staining was negative with weak positivity in a single case. UroVysion FISH showed frequent chromosomal abnormalities similar to those of urothelial carcinoma. In tumors with concurrent urothelial, squamous, sarcomatoid, and glandular components, identical FISH abnormalities were noted in both areas. In situ hybridization for human papillomavirus and immunostaining for Epstein-Barr virus were negative in all studied lesions. Five patients with pure or predominant LELC tumors treated with transurethral resection and followed by chemotherapy were alive without evidence of disease at 2 to 5 years. In contrast, 2 patients treated in this manner with < 50% LELC morphology had death from disease or distant metastasis.

**Discussion:** Urinary tract LELC is a rare histologic variant of urothelial carcinoma. The frequent presence of UroVysion FISH abnormalities, urothelial carcinoma in situ, and p53 positivity by immunohistochemistry in cases of urinary tract LELC suggests a similar pathogenesis to high-grade invasive urothelial carcinoma. In contrast to typical urothelial carcinoma, CK20 is frequently negative in LELC. Our findings support the hypothesis that pure or predominant LELC may be treated with transurethral resection and chemotherapy. However, a large-scale study with long-term follow-up is needed to better understand the biological behavior of urinary bladder LELC.

**Key Words:** urinary bladder, urinary tract, lymphoepithelioma-like carcinoma, TCC variants, genitourinary tract, histogenesis, differential diagnosis

(*Am J Surg Pathol* 2011;35:474–483)

In the nasopharynx, undifferentiated carcinoma associated with a dense lymphoid infiltrate has been designated as "lymphoepithelioma" or "lymphoepithelial carcinoma" for its histologic intermingling of syncytially arranged, malignant epithelial cells and a variable lymphoplasmacytic infiltrate.[3,5] Other similar appearing lesions have been described in various other body sites including the urinary bladder, where they are commonly termed "lymphoepithelioma-like carcinoma" (LELC).[1,19]

# RNA Expression Profiling of Lymphoepithelioma-Like Carcinoma of the Bladder Reveals a Basal-Like Molecular Subtype



Ujjawal Manocha,* Jordan Kardos,* Sara Selitsky,* Mi Zhou,* Steven M. Johnson,† Cori Breslauer,† Jonathan I. Epstein,‡ William Y. Kim,*§¶ and Sara E. Wobker*†

*From the UNC Lineberger Comprehensive Cancer Center,* and the Departments of Pathology and Laboratory Medicine,† Medicine,§ and Genetics,¶ University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and the Departments of Pathology, Urology and Oncology,‡ Johns Hopkins Hospitals, Baltimore, Maryland*

Accepted for publication September 5, 2019.

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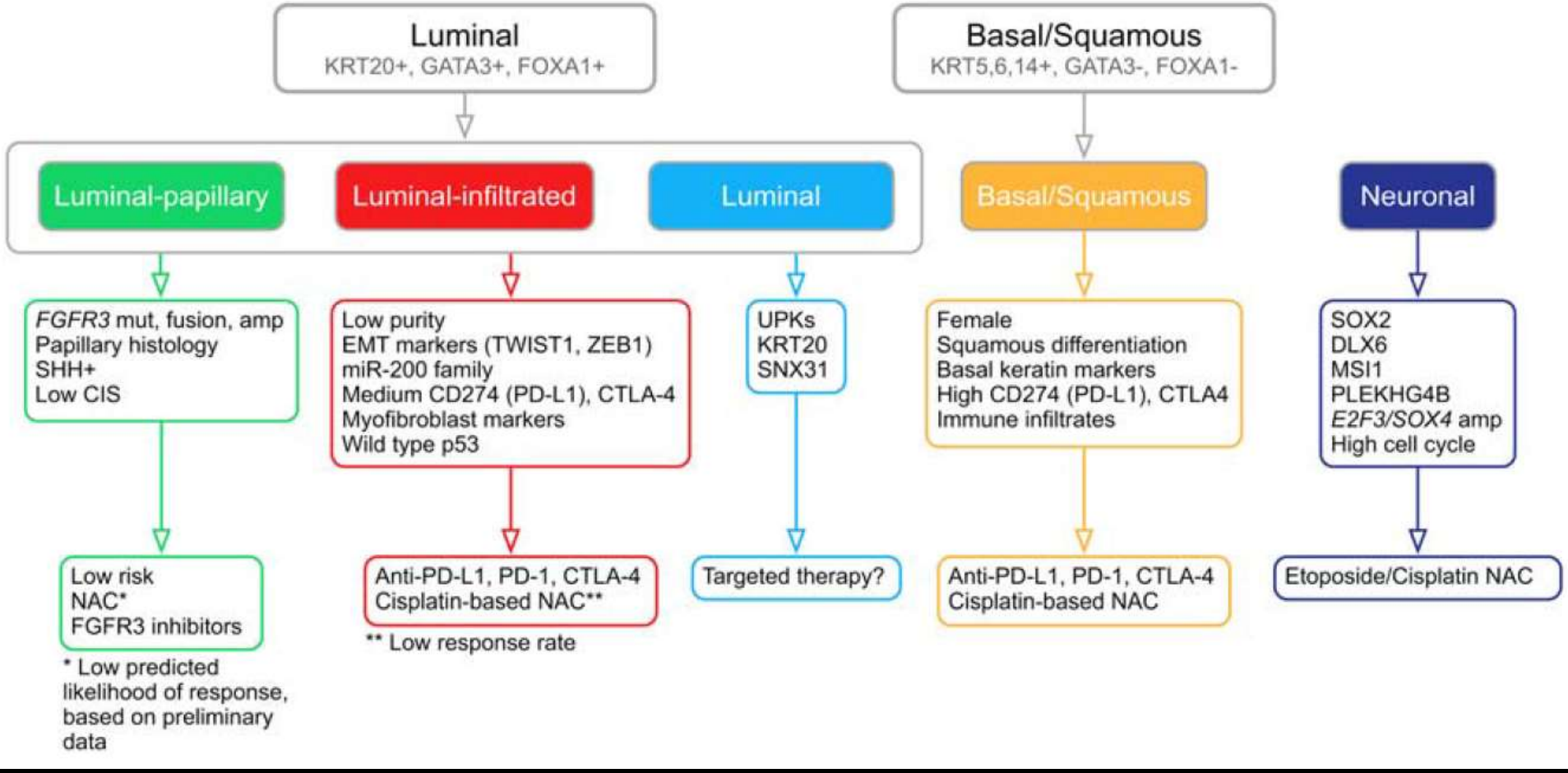
Lymphoepithelioma-like carcinoma of the bladder (LELC-B) is a rare subtype of urothelial carcinoma consisting of undifferentiated epithelial cells within a dense inflammatory cell infiltrate. We set out to molecularly characterize LELC-B through RNA expression profiling as well as immunohistochemistry (IHC) to understand its underlying biology. Sixteen cases of LELC-B were identified at Johns Hopkins University. RNA sequencing was performed on 14 cases. IHC staining for programmed cell death ligand 1 (PD-L1) and mismatch repair proteins MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MSH6, and PMS1 homolog, mismatch repair system component 2 (PMS2) was performed. Transcriptomic profiling of LELC-B showed that they are enriched in a basal-like phenotype, with 12 of 14 LELC-B cases correlating to the basal centroid of the bladder cancer analysis of subtypes by gene expression 47 (BASE47) predictive analysis of microarrays (PAM) classifier. Gene signature analysis confirmed the lymphocyte infiltration profile consistent with the histomorphology. LELC-B lacked features to explain the robust lymphocytic infiltrate, such as loss of mismatch repair protein expression or expression of Epstein-Barr virus transcripts. Nonetheless, PD-L1 IHC was positive in 93% of LELC cases. Our study demonstrates that LELC-B tumors are enriched in a basal-like molecular subtype and share a high level of immune infiltration and PD-L1 expression, similar to basal tumors. The basal-like phenotype is consistent with the known sensitivity of LELC-B to chemotherapy and suggests that immune checkpoint therapy should be explored in this rare disease. *(Am J Pathol 2020, 190: 134–144; https://doi.org/10.1016/j.ajpath.2019.09.007)*




*Adv Anat Pathol* 2020;27:36–43

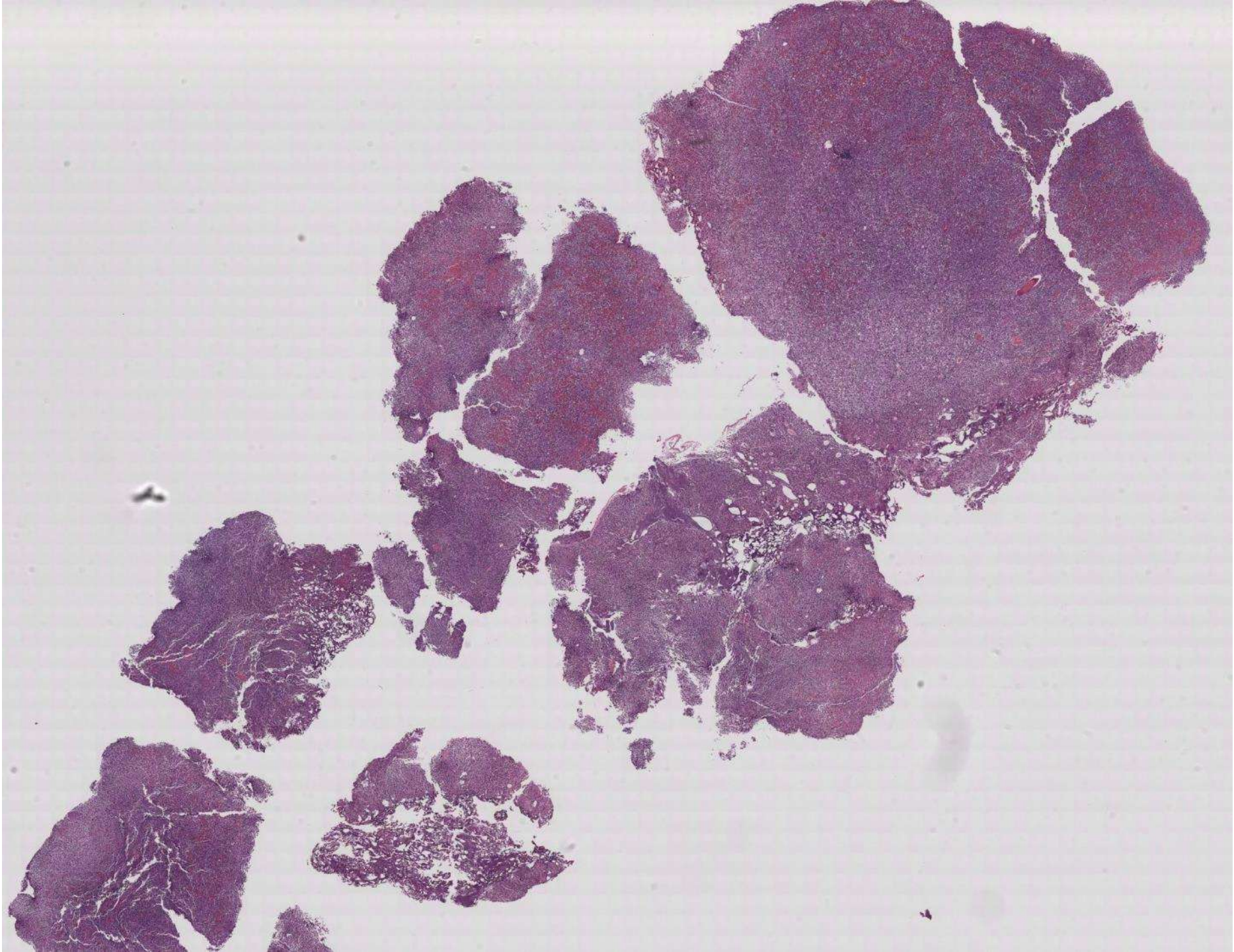
# LEL-like carcinoma

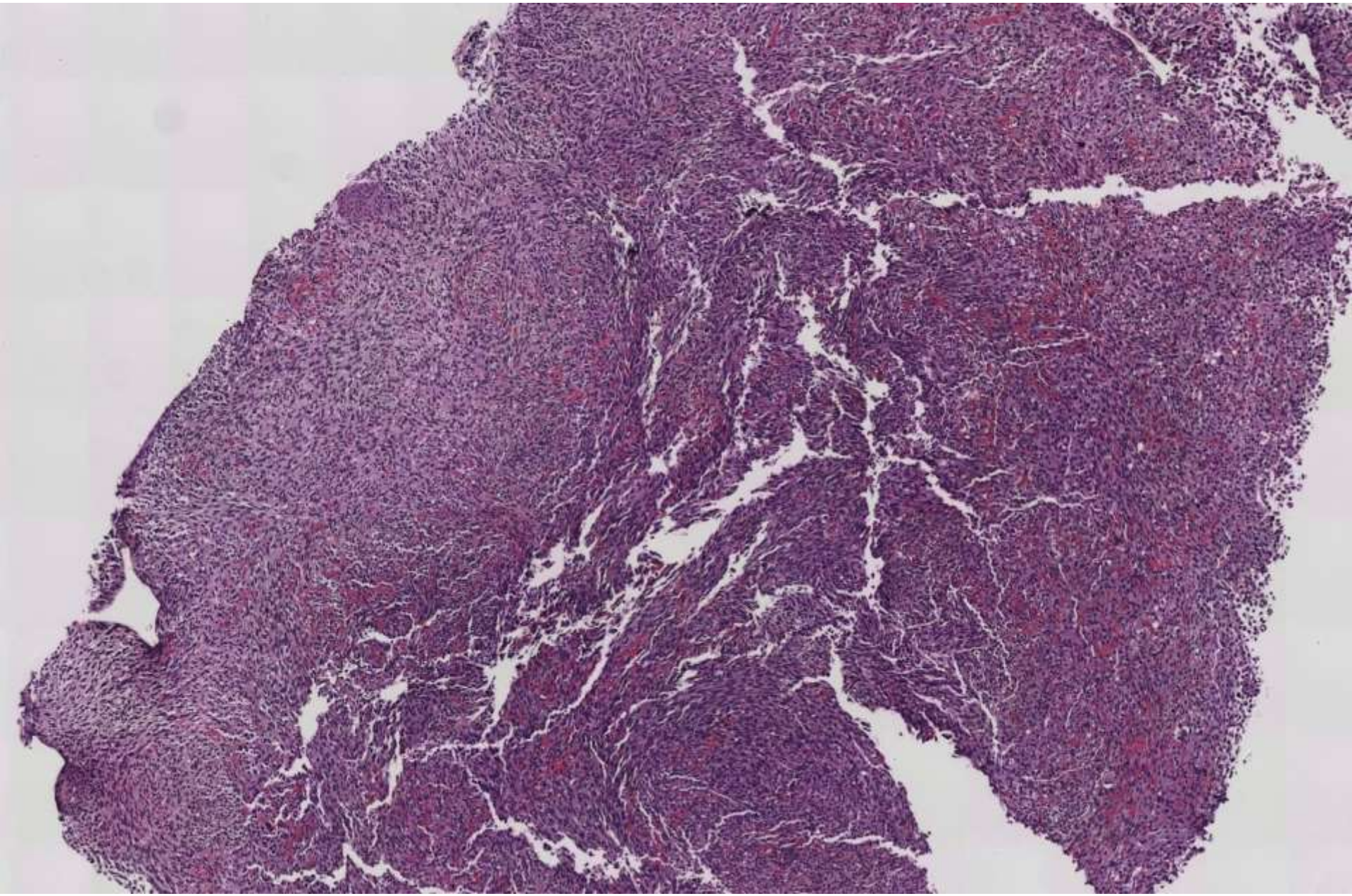
- **Can be pure or mixed in form**
- **Lack EBV ISH**
- **Frequently CK20**
- **basal-like phenotype**
  - High PDL1 expression
- **Can be treated like typical urothelial carcinoma, with similar prognosis**

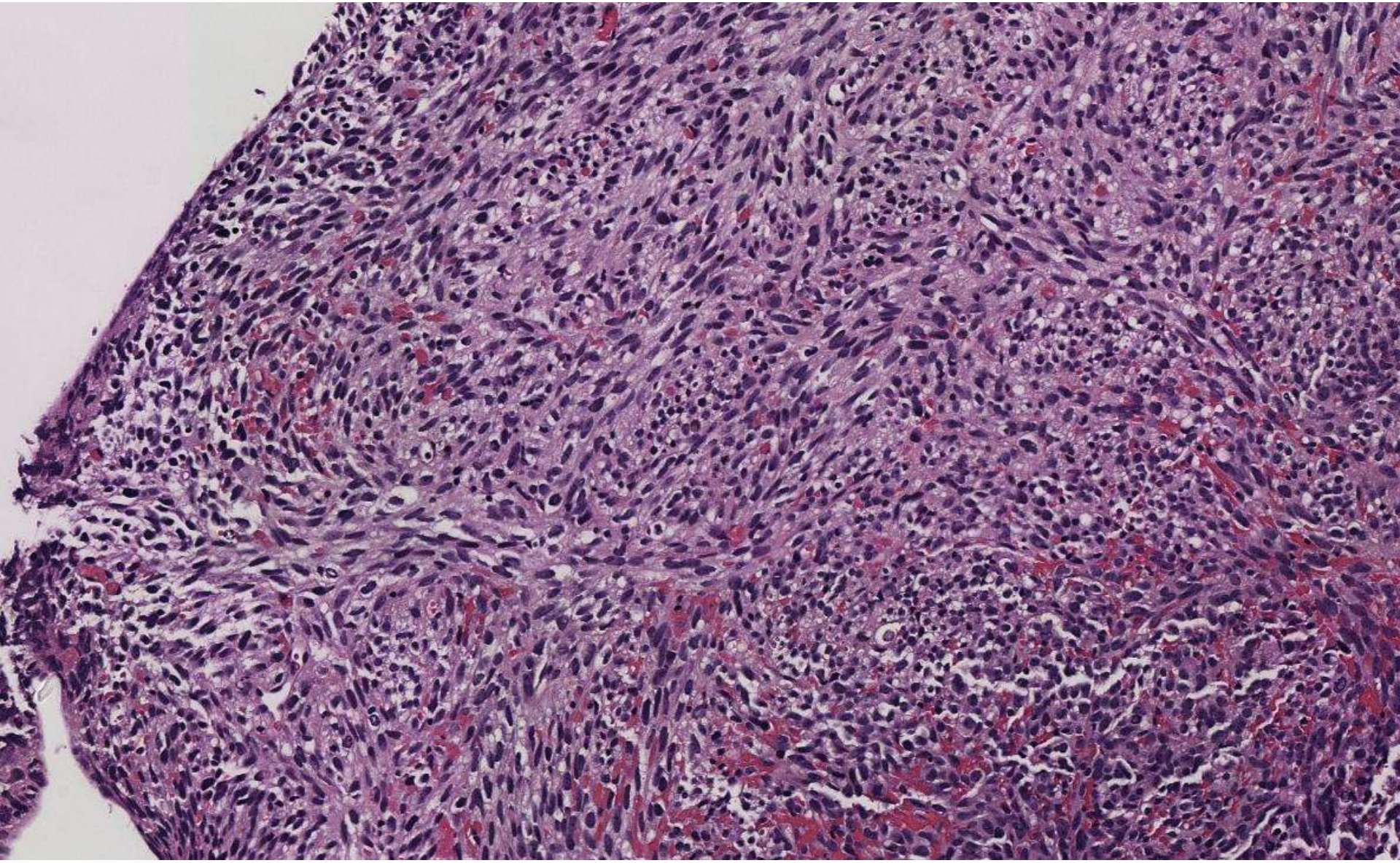
# 20-0208
# scanned slide available!

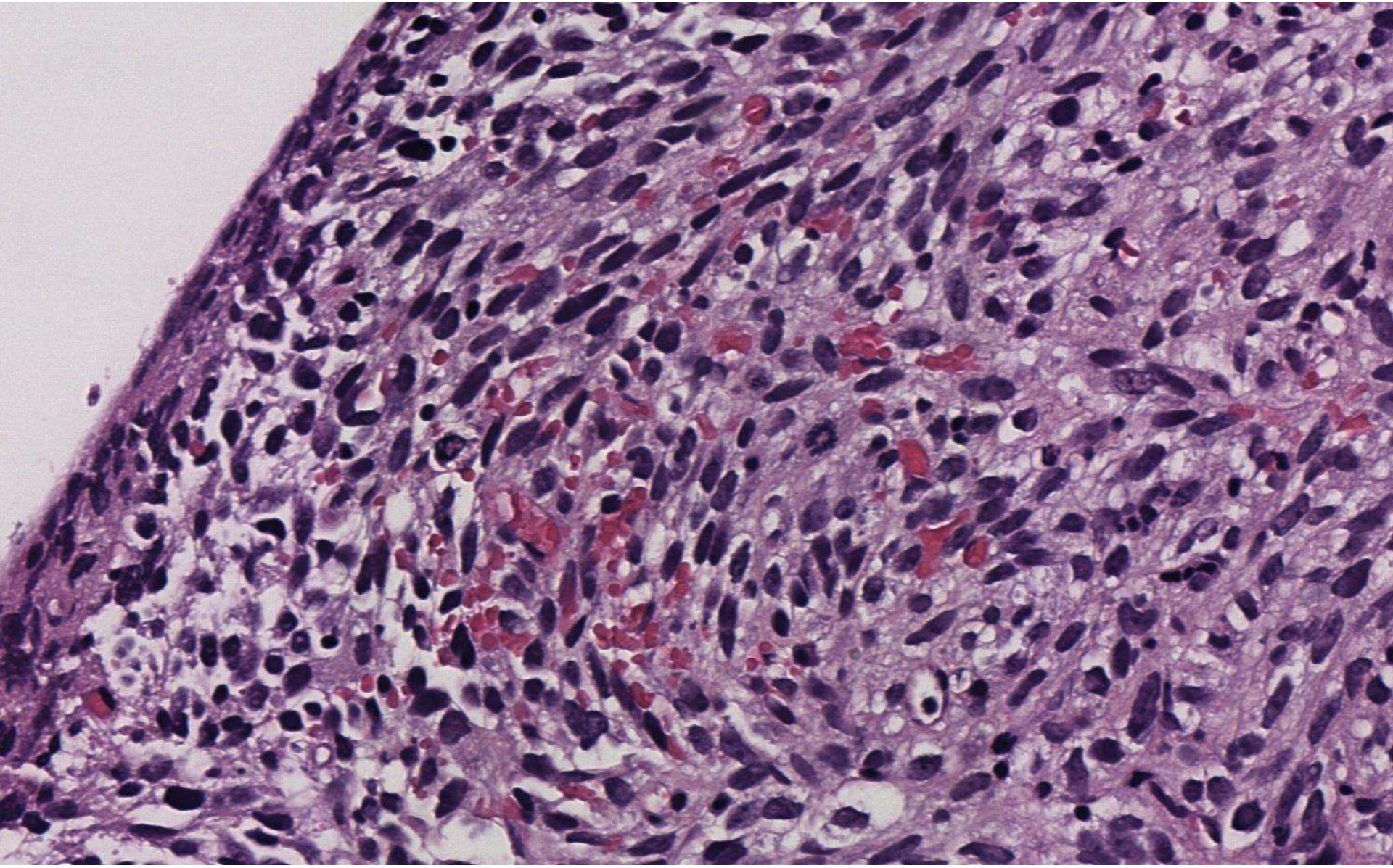
**Ankur Sangoi; El Camino Hospital**

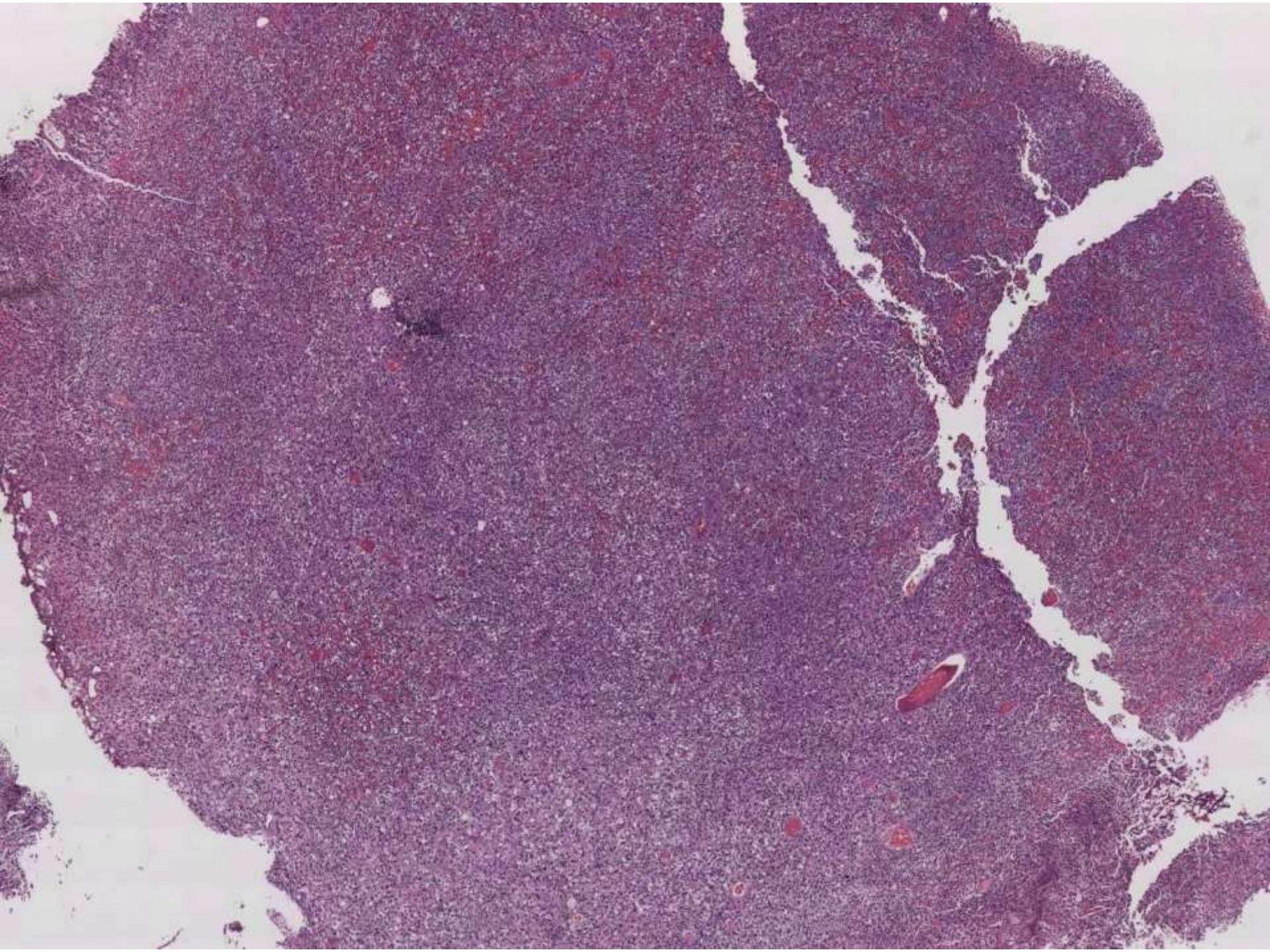
88-year-old F with bladder mass, TURBT.

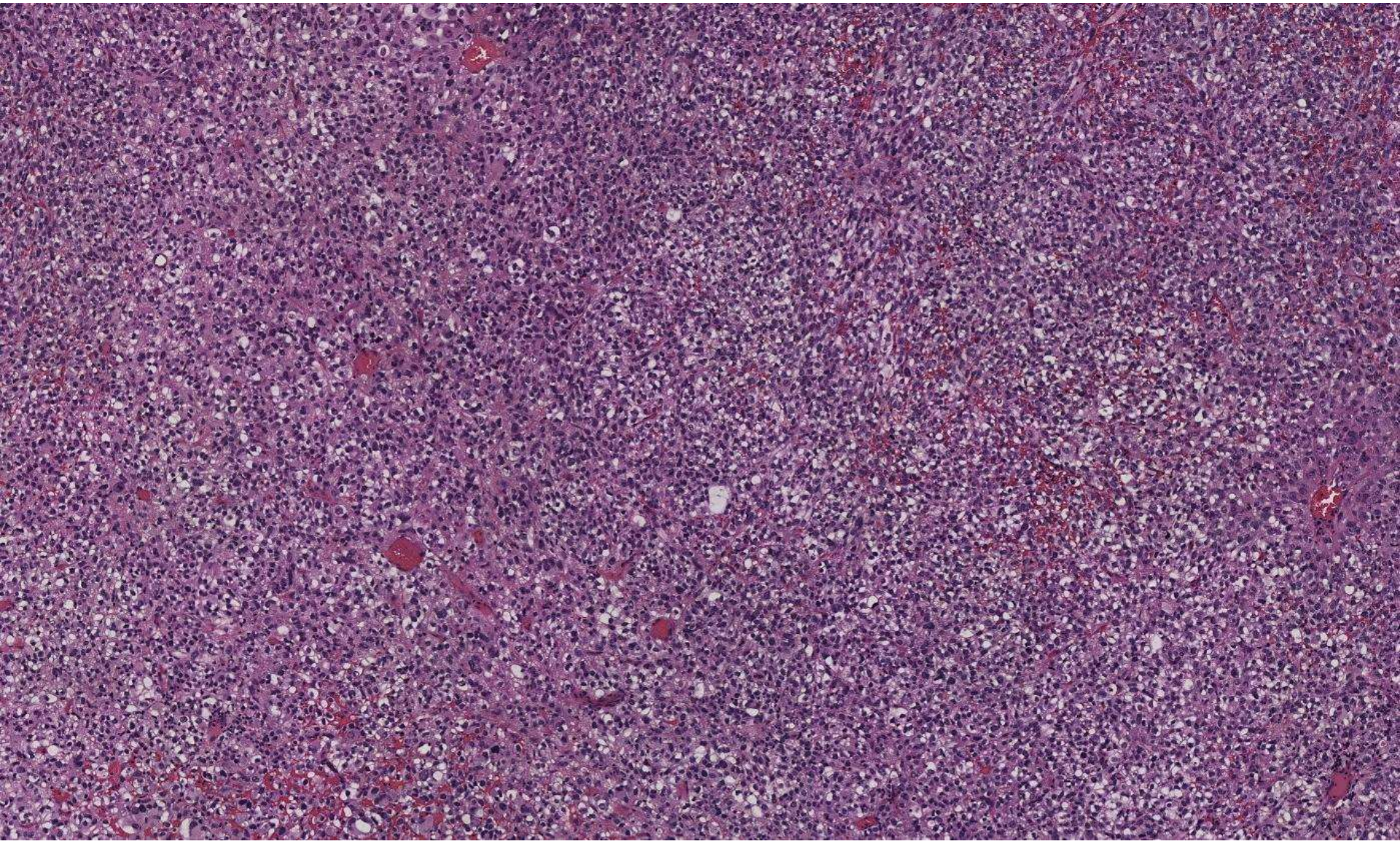


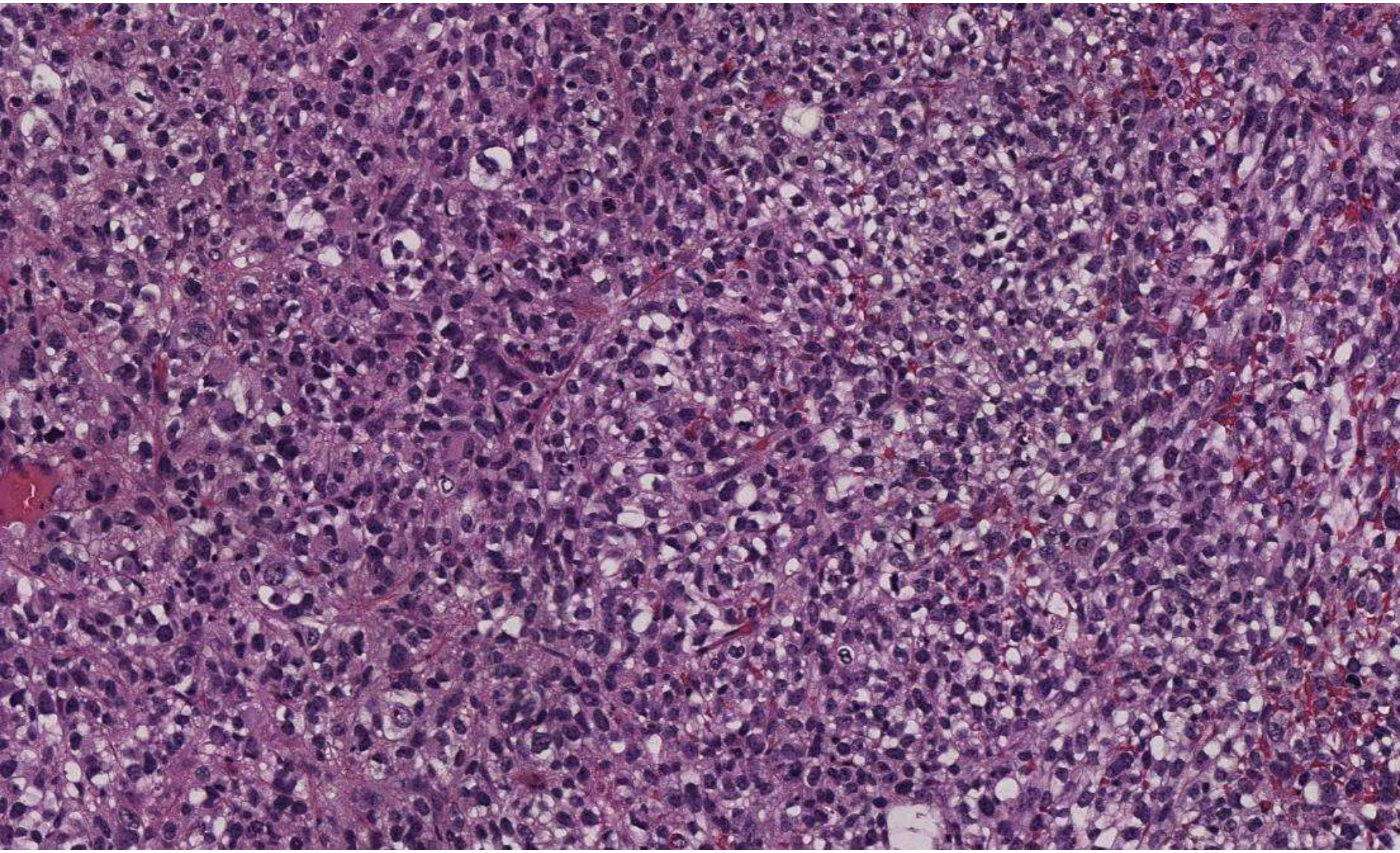


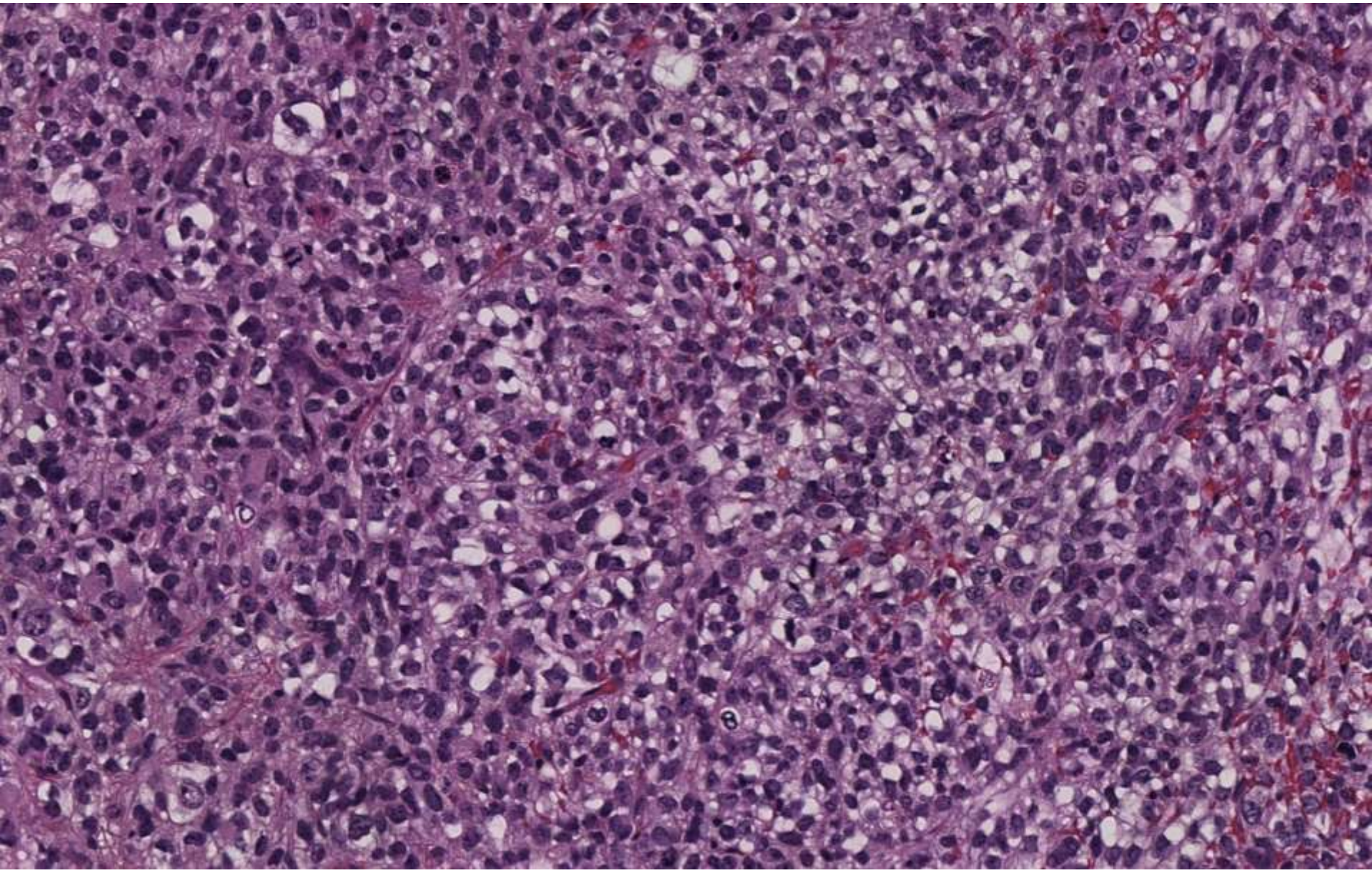


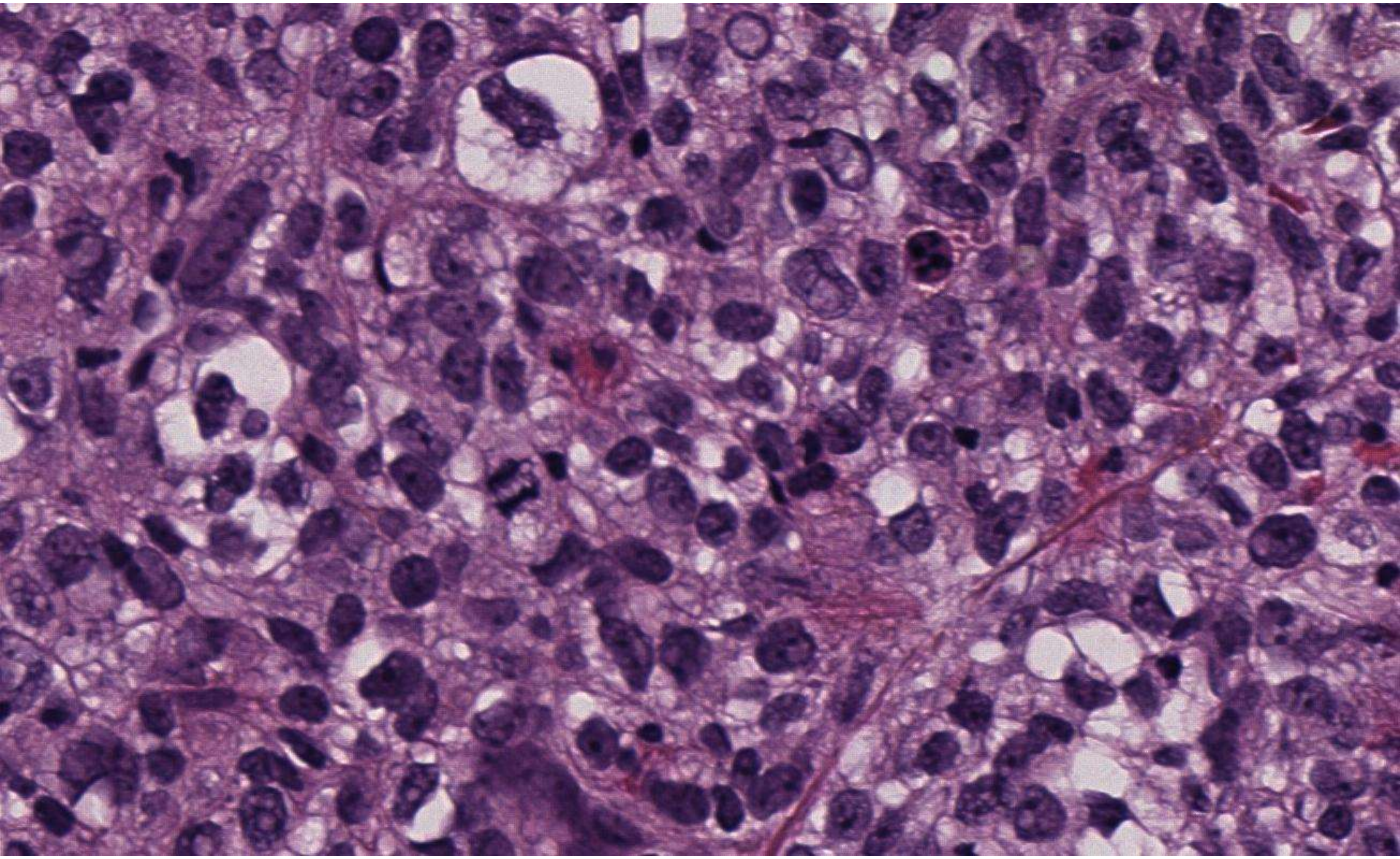






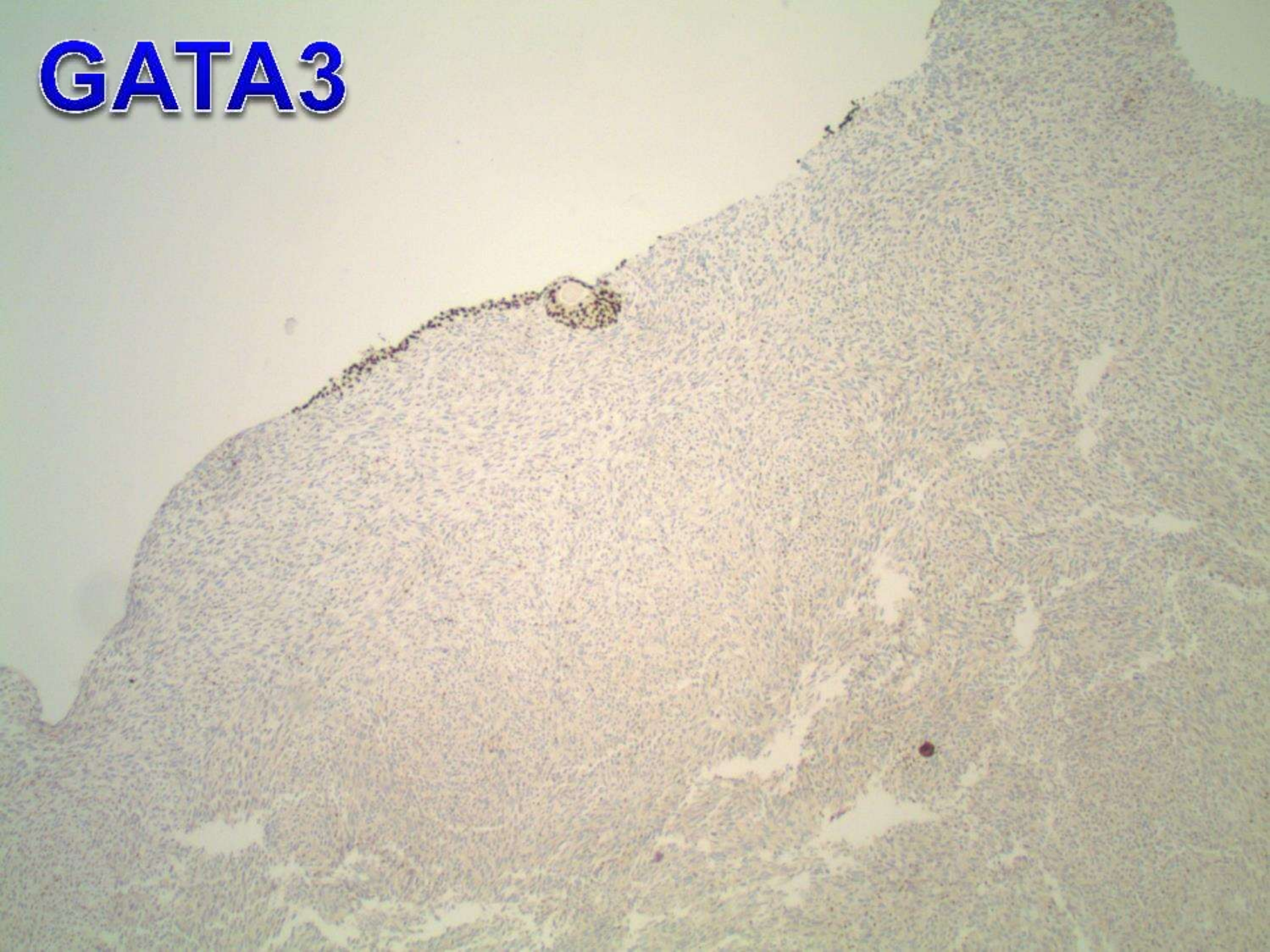


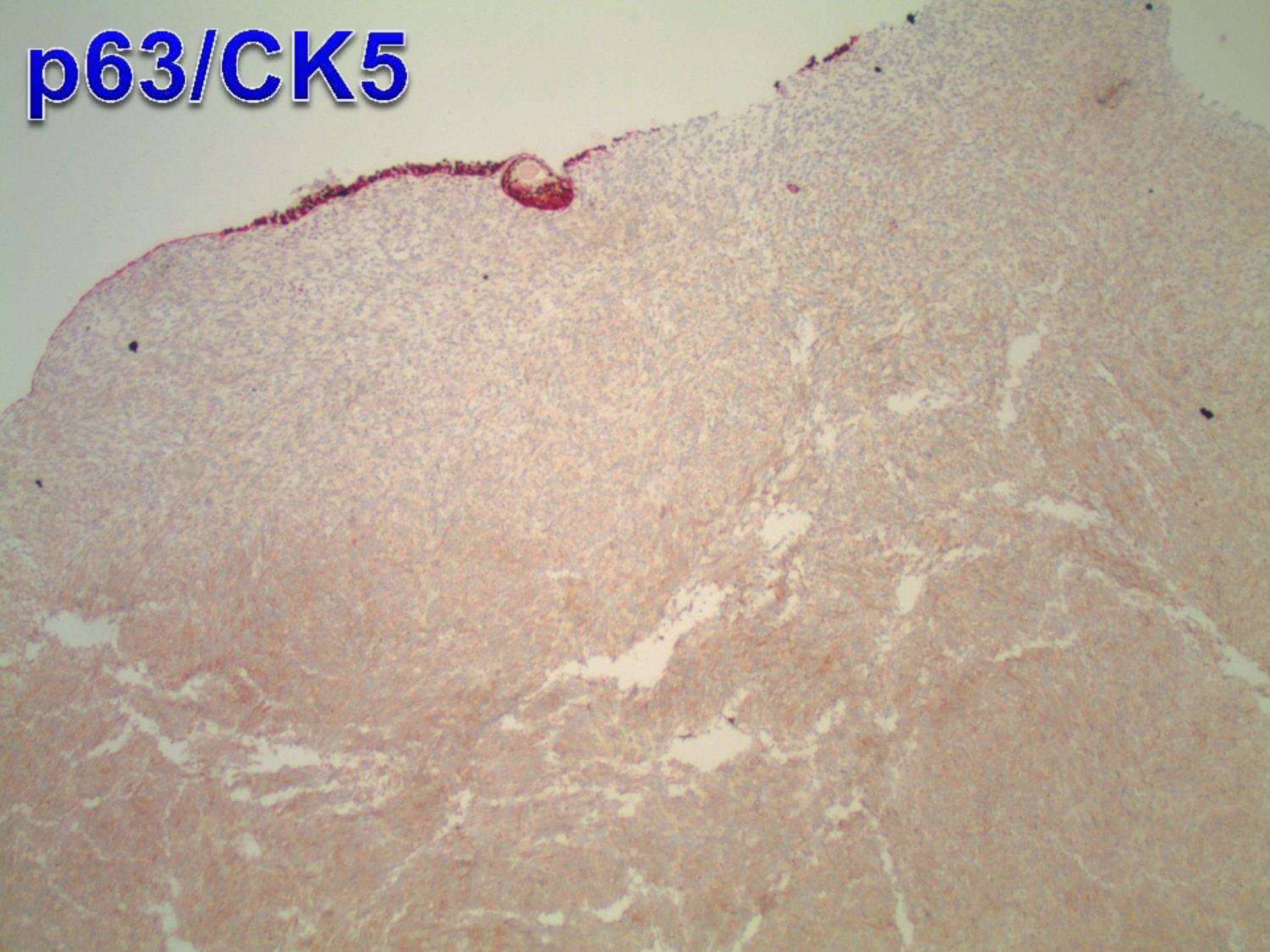


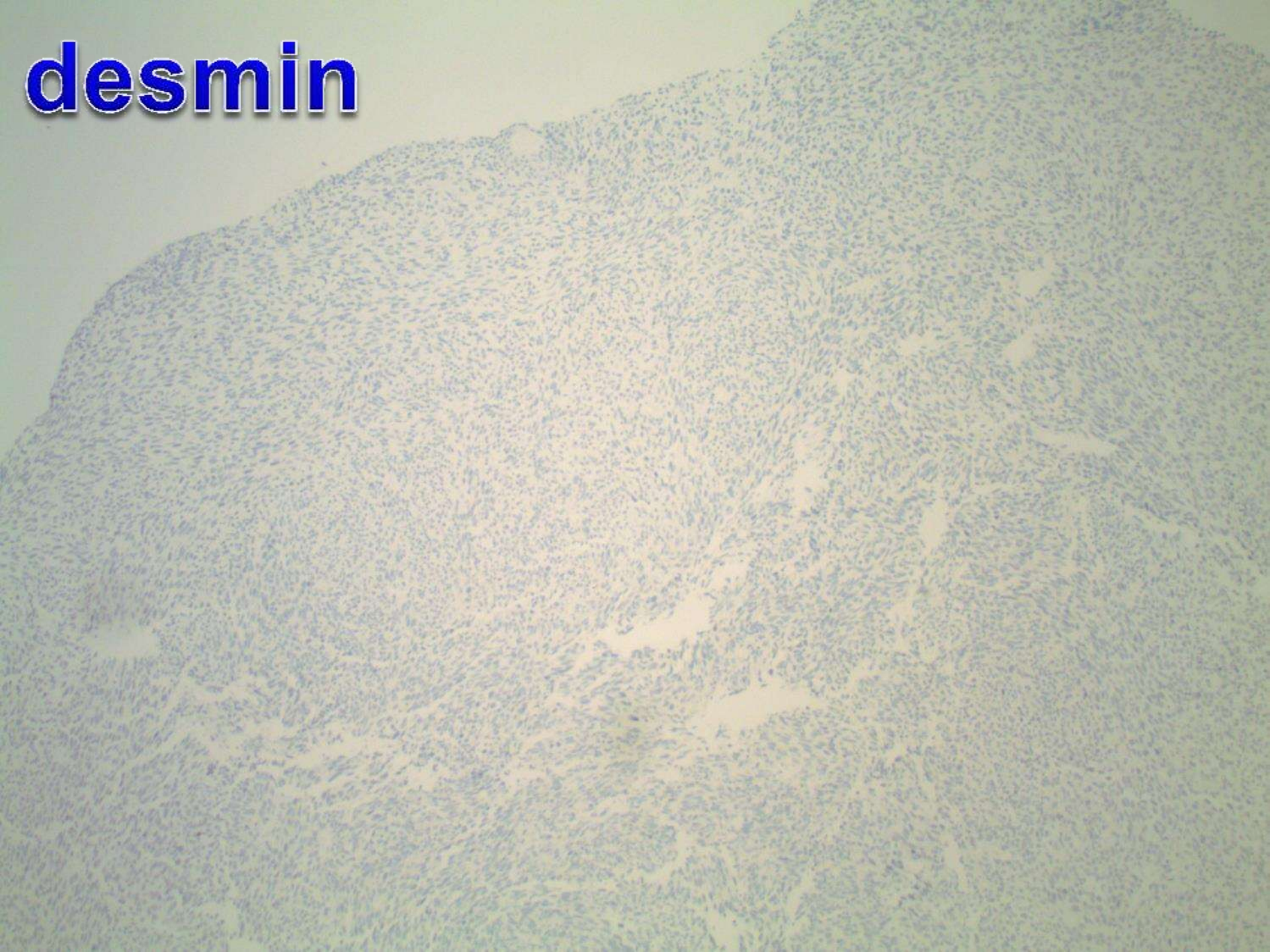


# DDx

- Sarcomatoid urothelial carcinoma
- Paraganglioma
- PEComa
- Endometrial stromal sarcoma
- Epithelioid angiosarcoma
- Epithelioid leiomyosarcoma
- Peripheral nerve sheath tumor
- Solitary fibrous tumor
- GIST
- melanoma
- Pleomorphic undifferentiated sarcoma


GATA3


p63/CK5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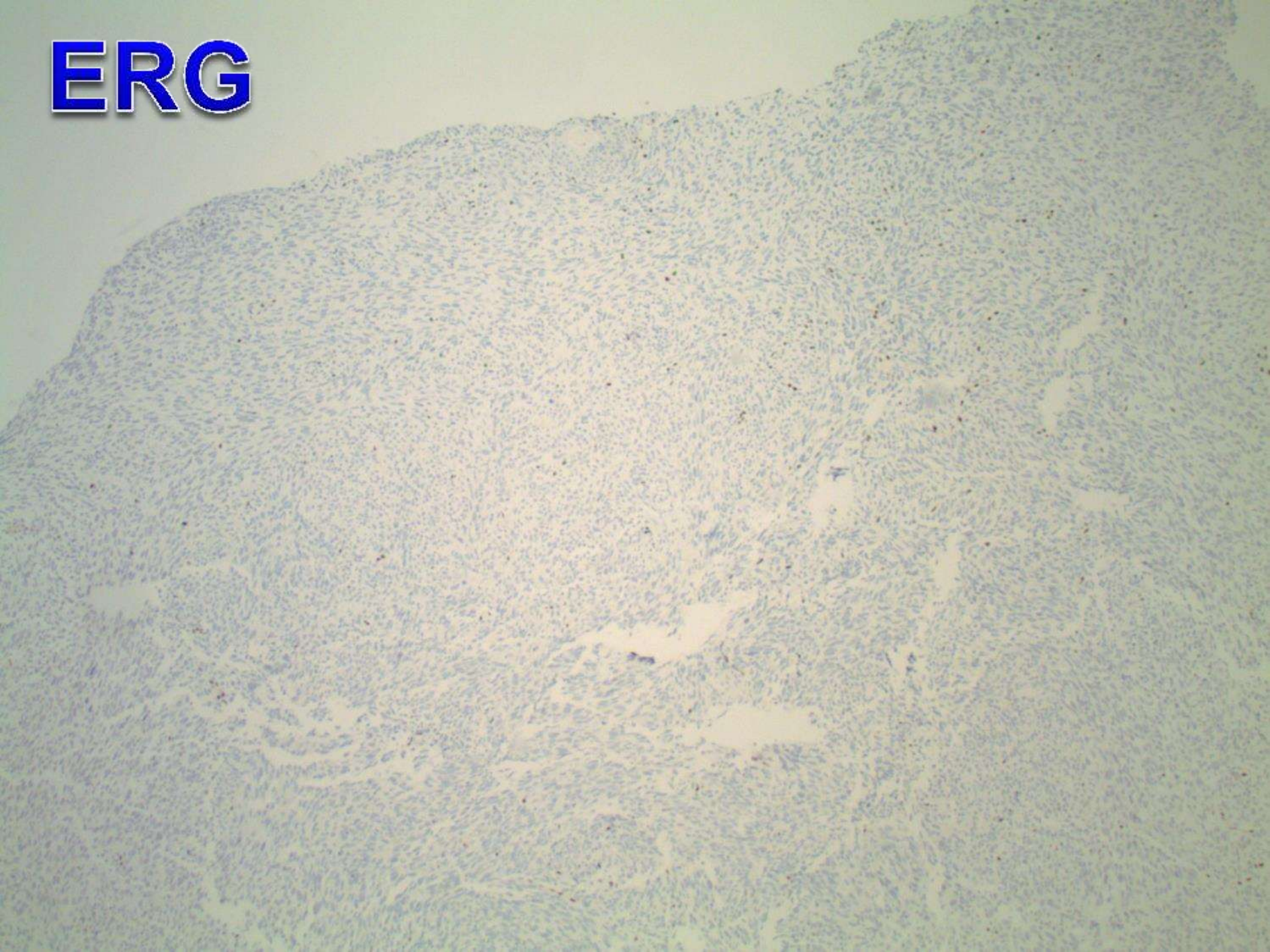
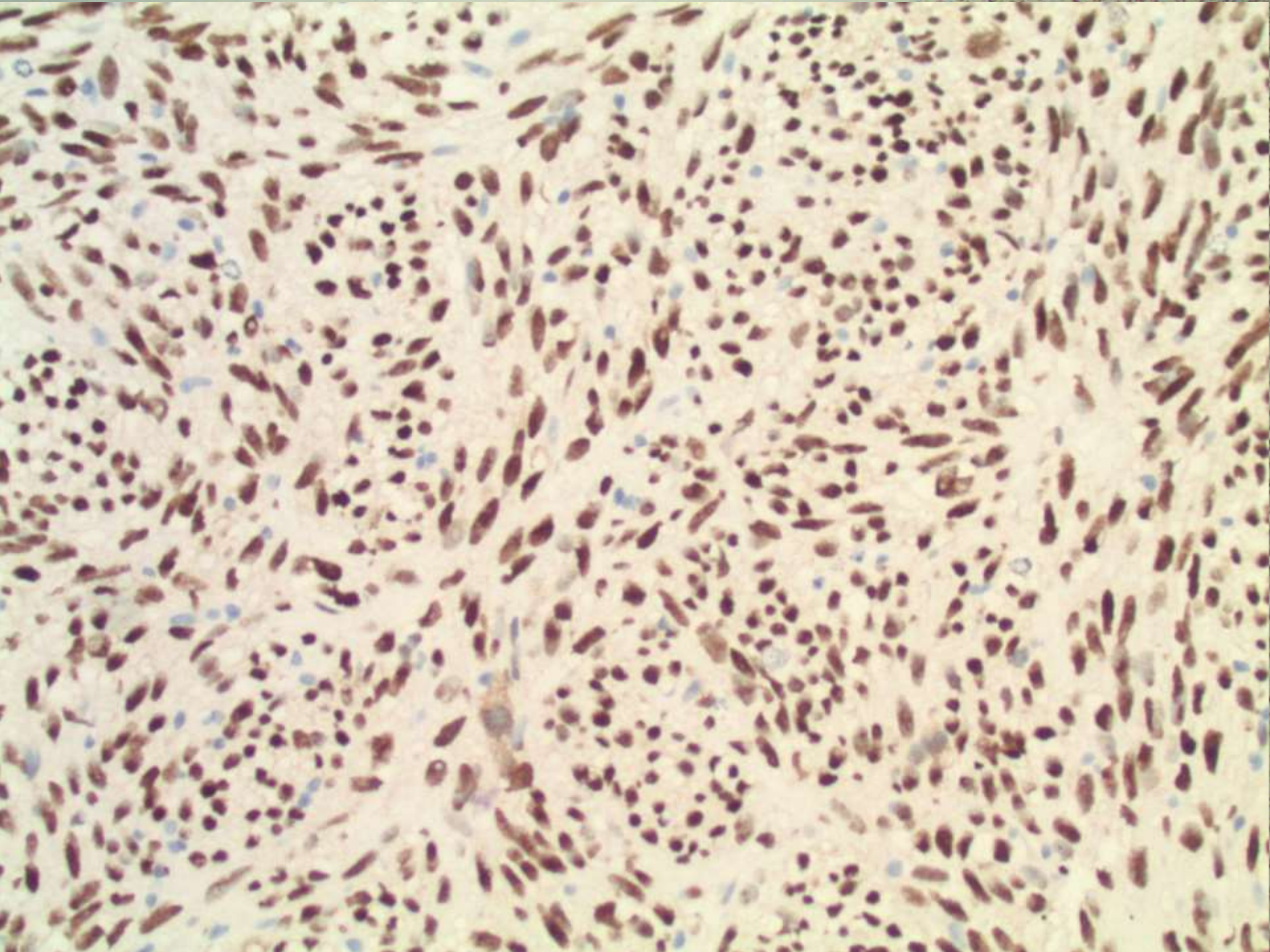
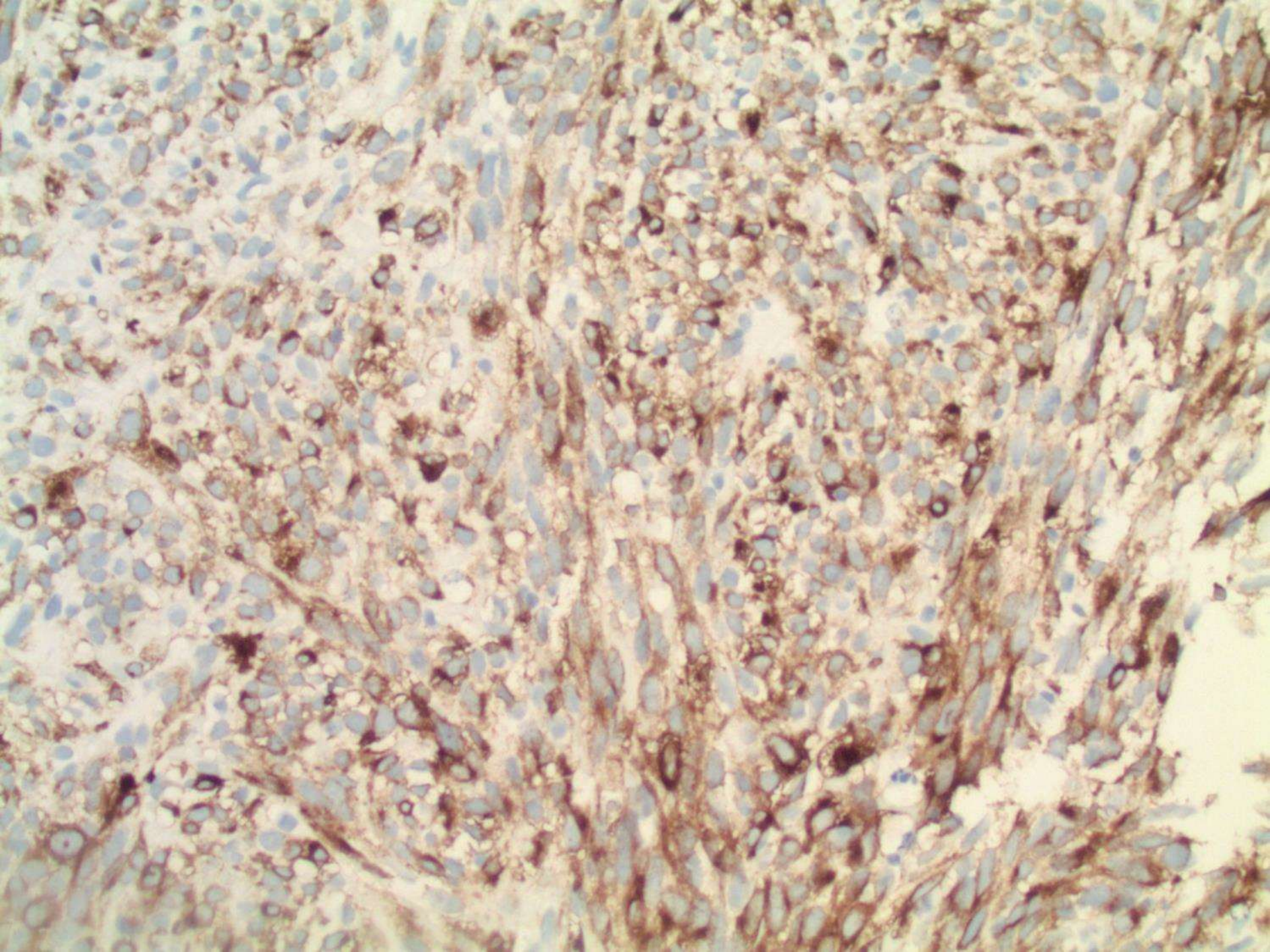

ERG





# FINAL DX: MELANOMA


- **Presumably prior bladder**
  - RARE!
- **Follow up**
  - BRAF mutation negative
  - Being worked up for possible visceral metastasis

# 20-0209

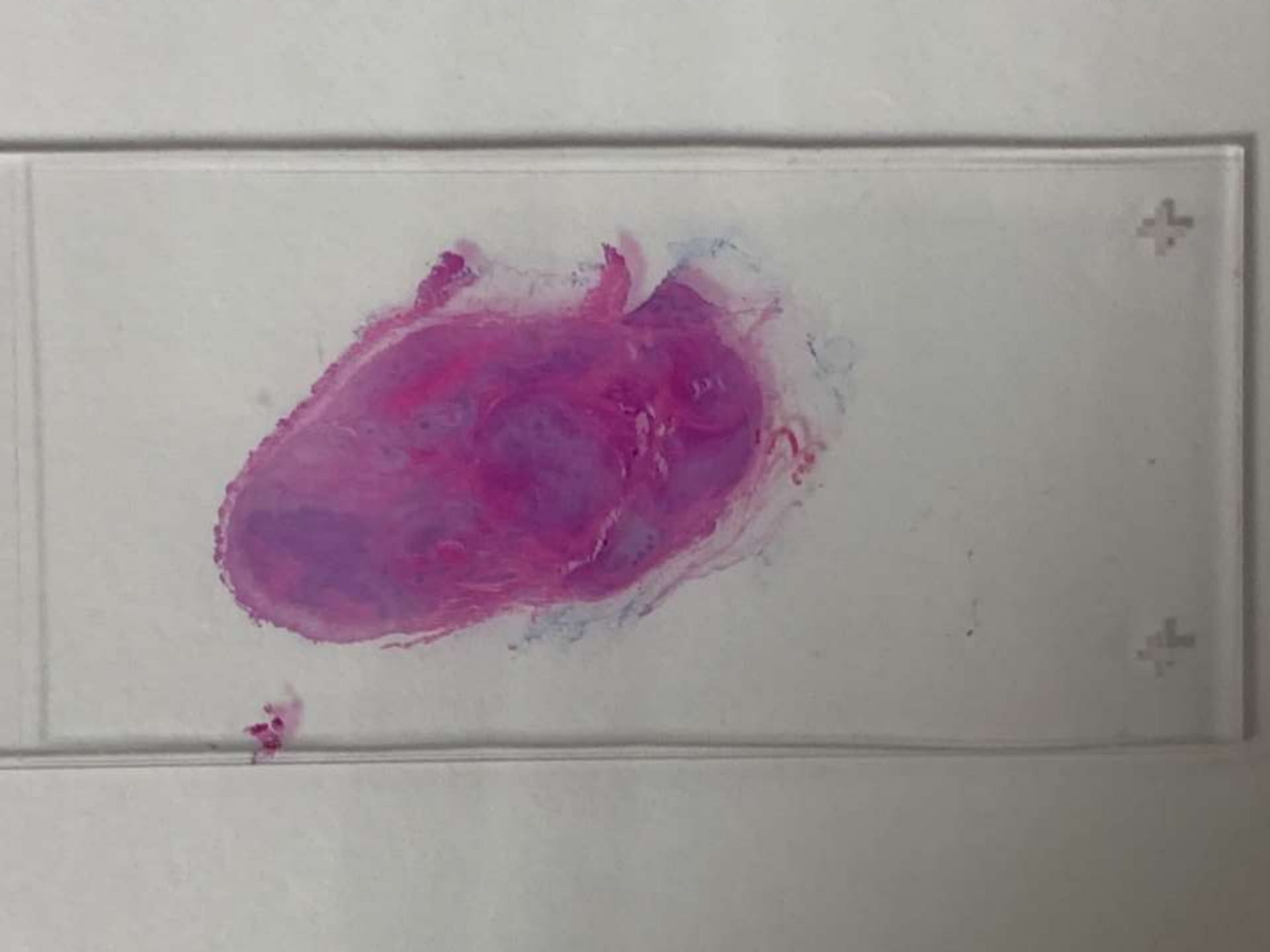
**Matthew Koo/Greg Charville; Stanford**

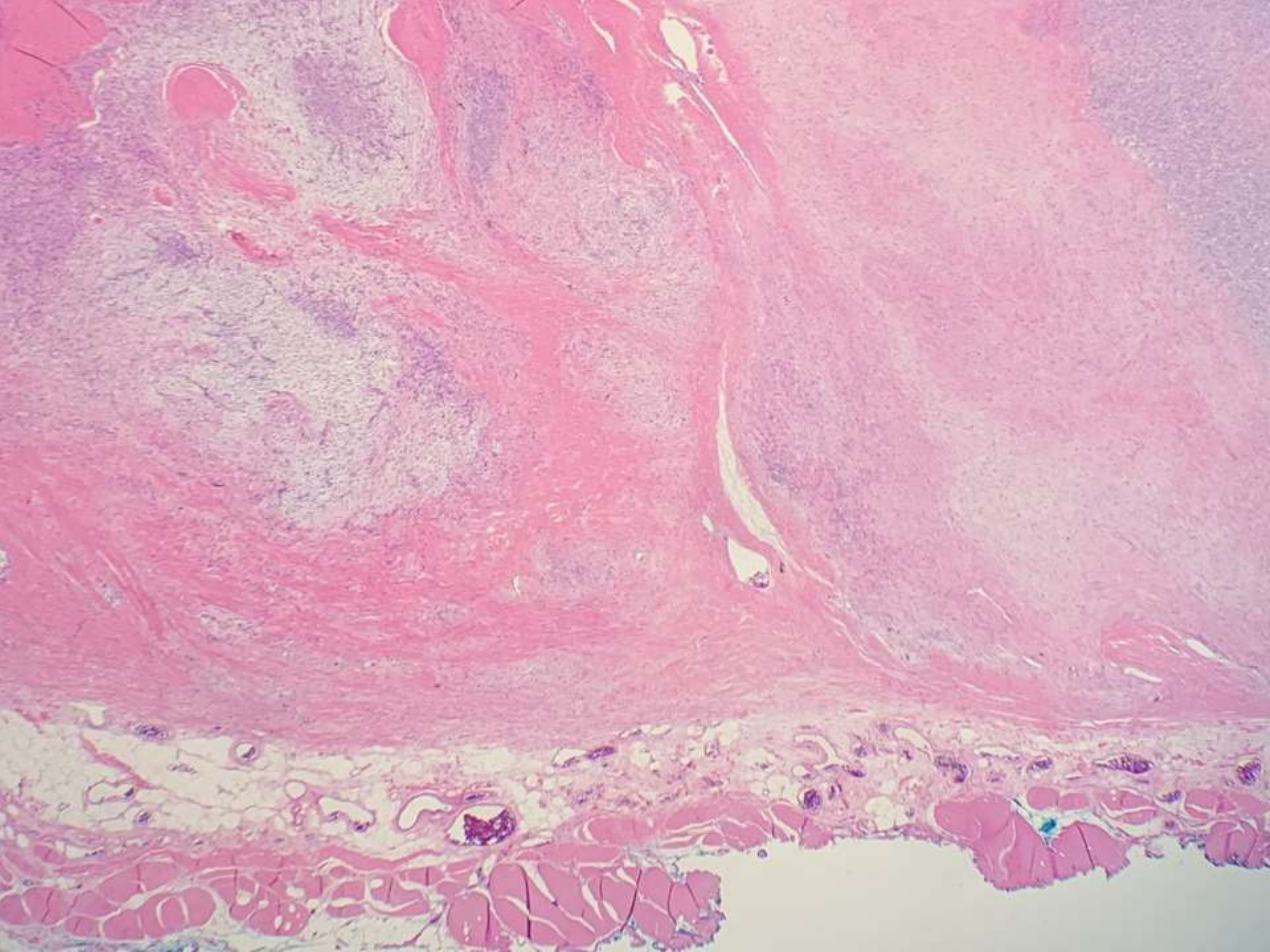
62-year-old M with abdominal mass.

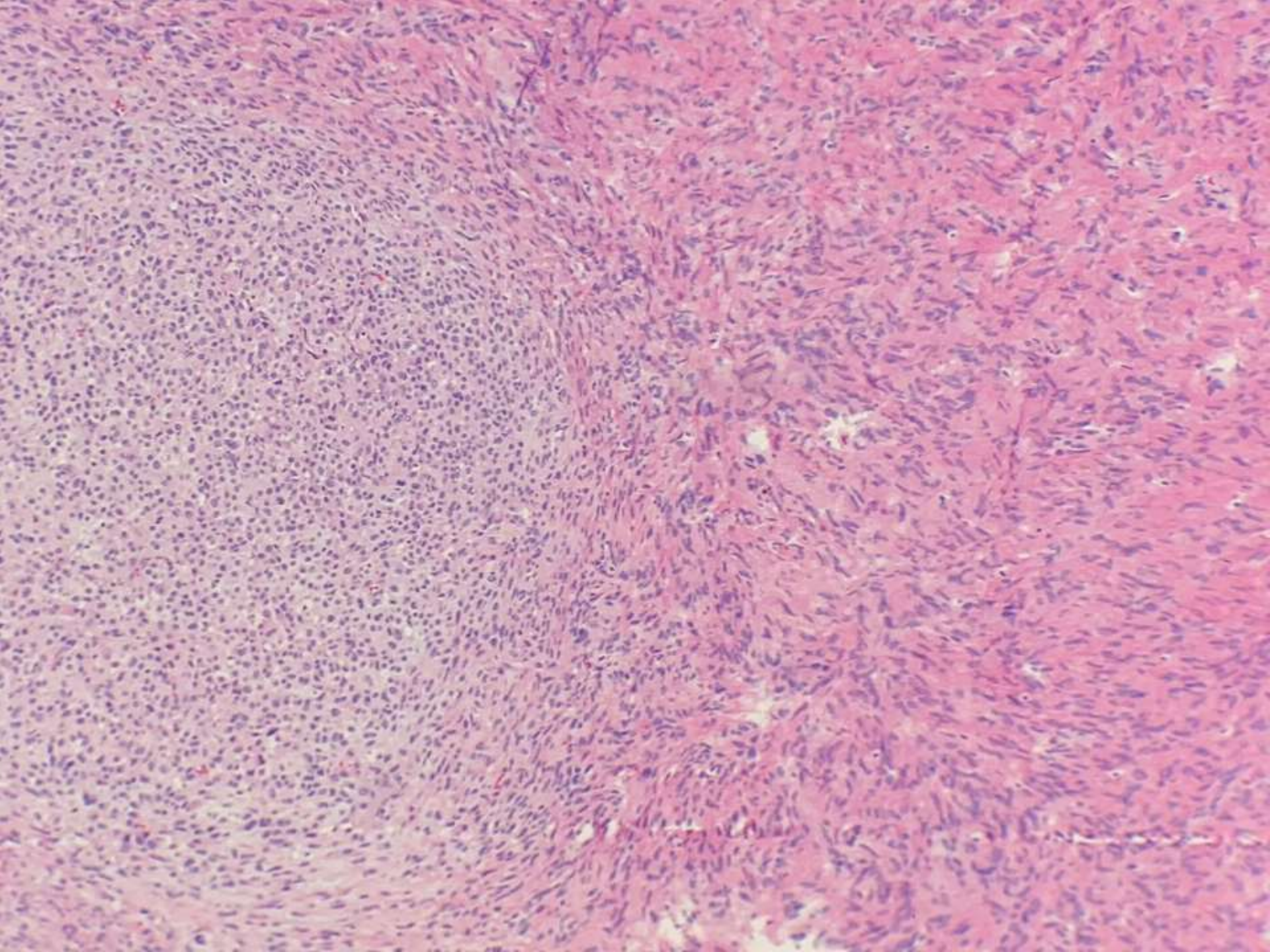
# 62-year-old man with abdominal mass

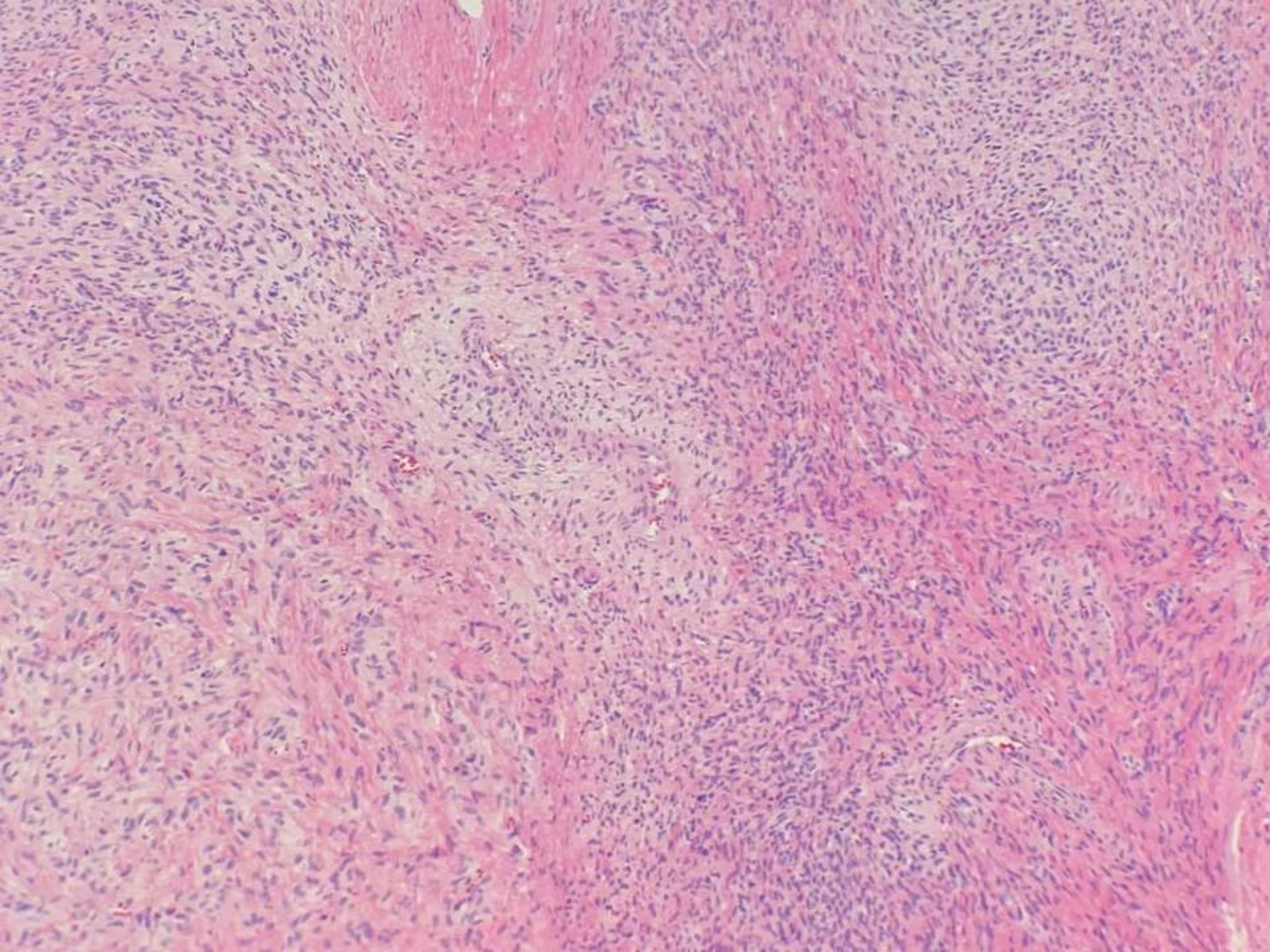
- Clinical history
  - 2.5 x 2.5 cm (8/2018) → 3.3 x 2.6 x 2.6 (4/2019)

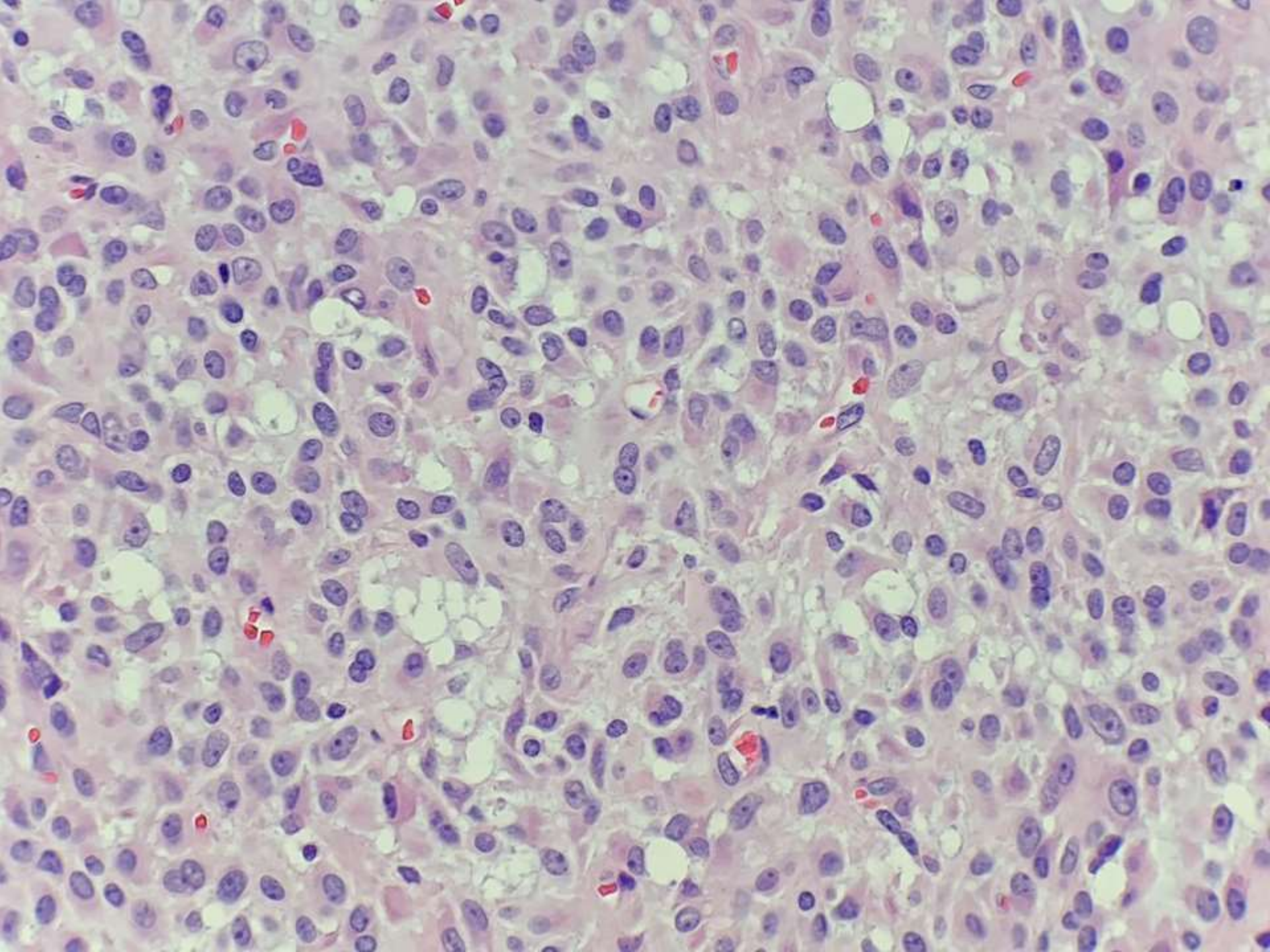
- Gross examination
  - 5.5 x 3.6 x 3.3 cm whorled white-tan lobulated nodule

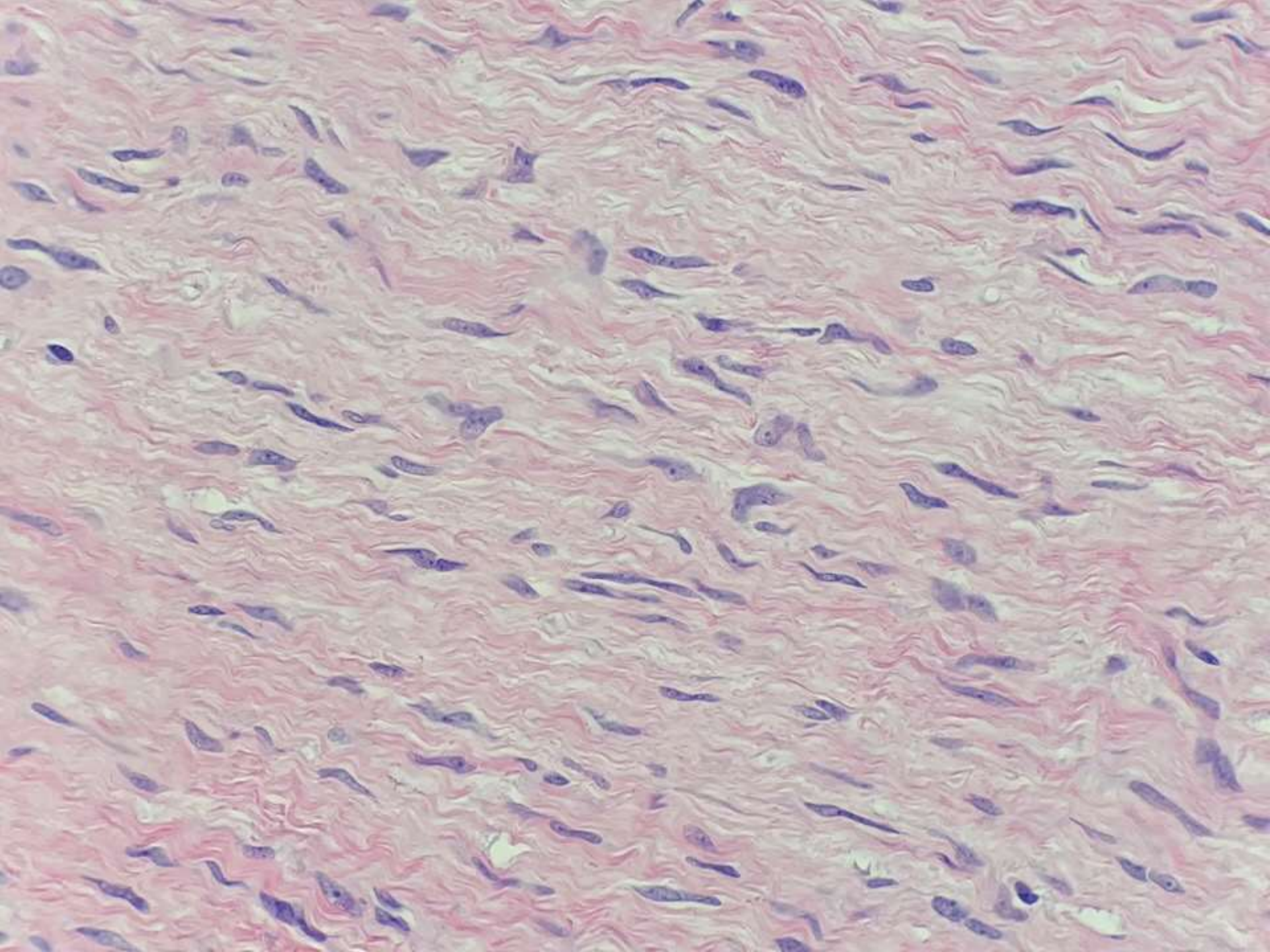


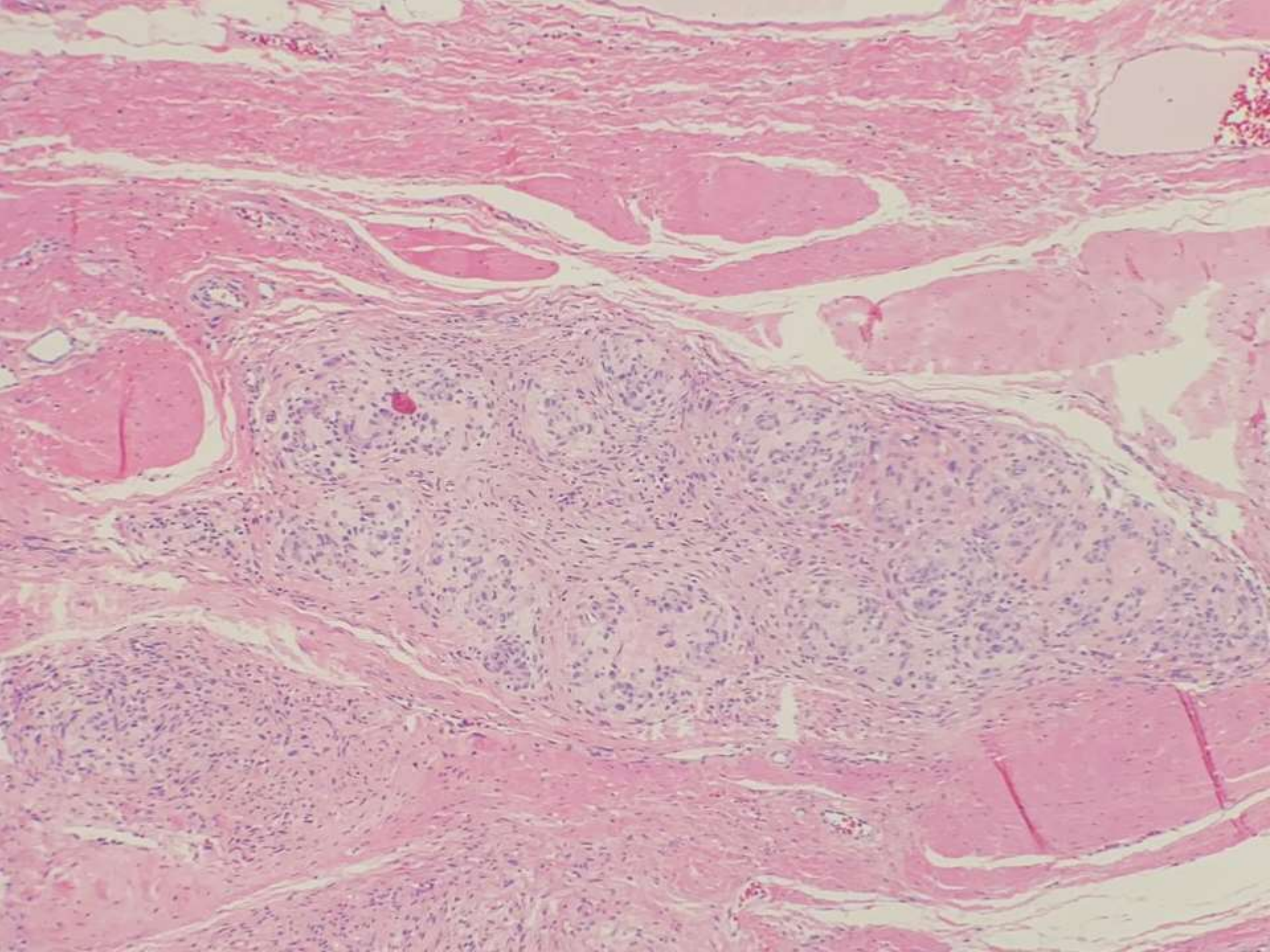


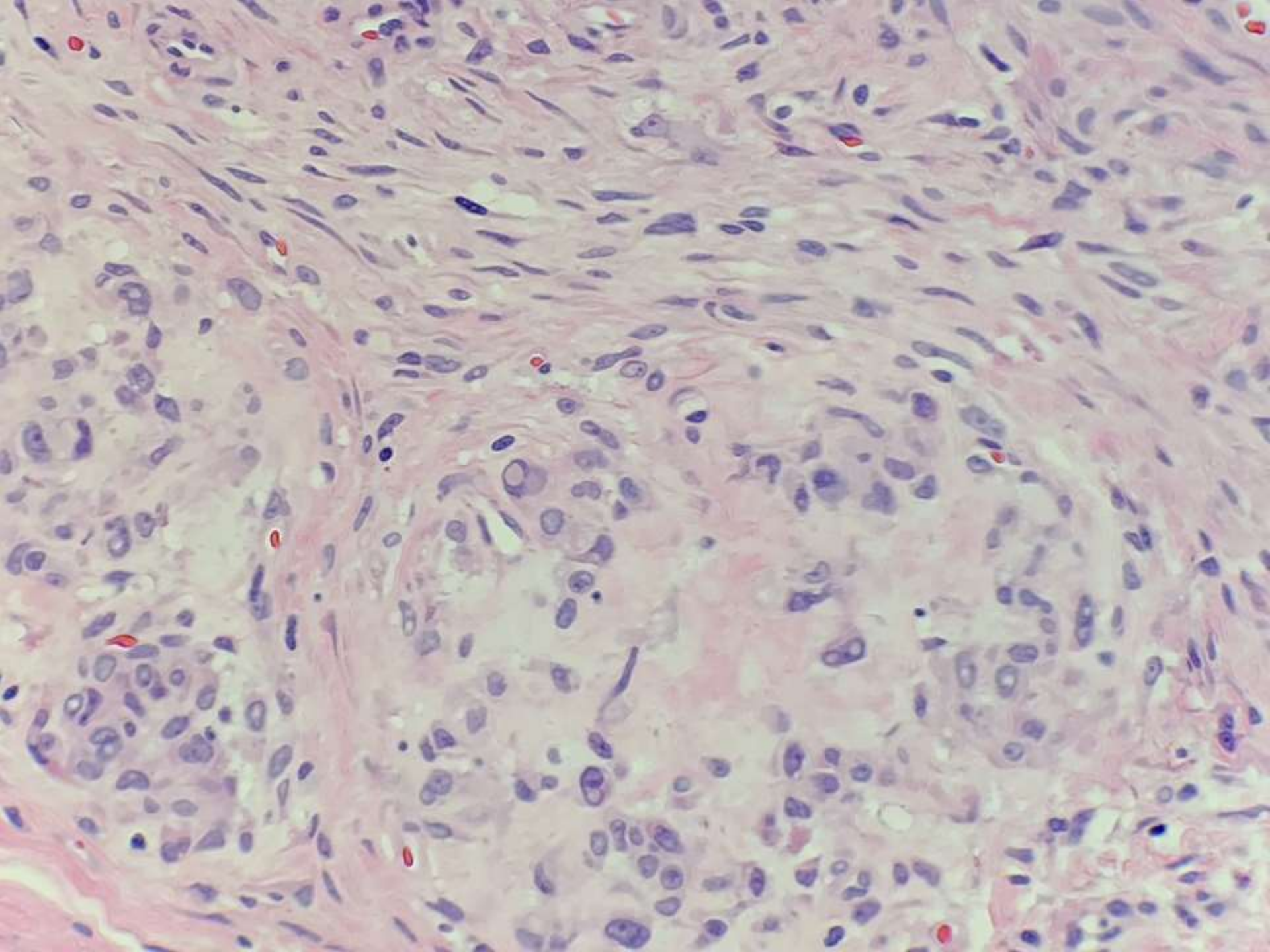




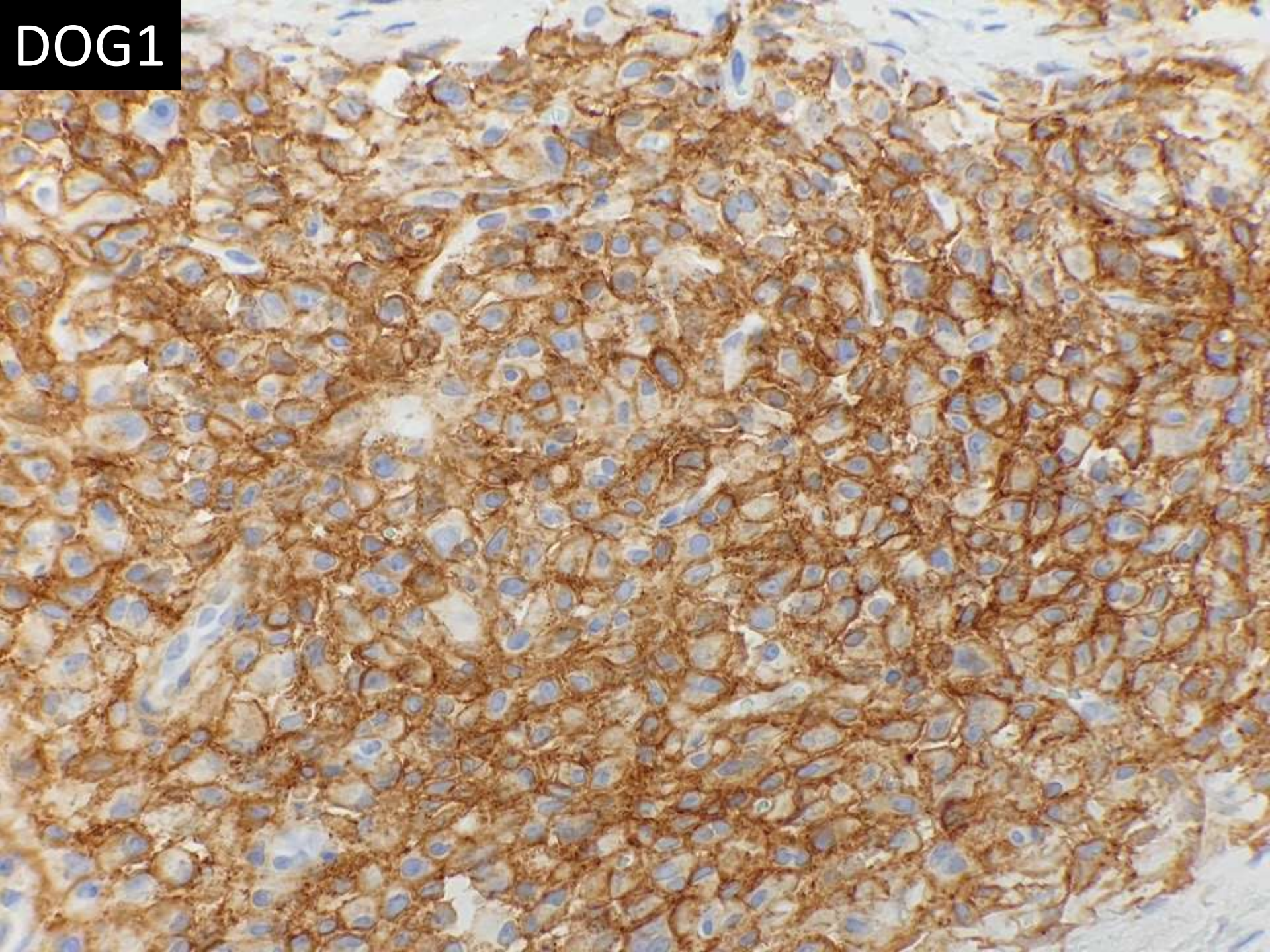


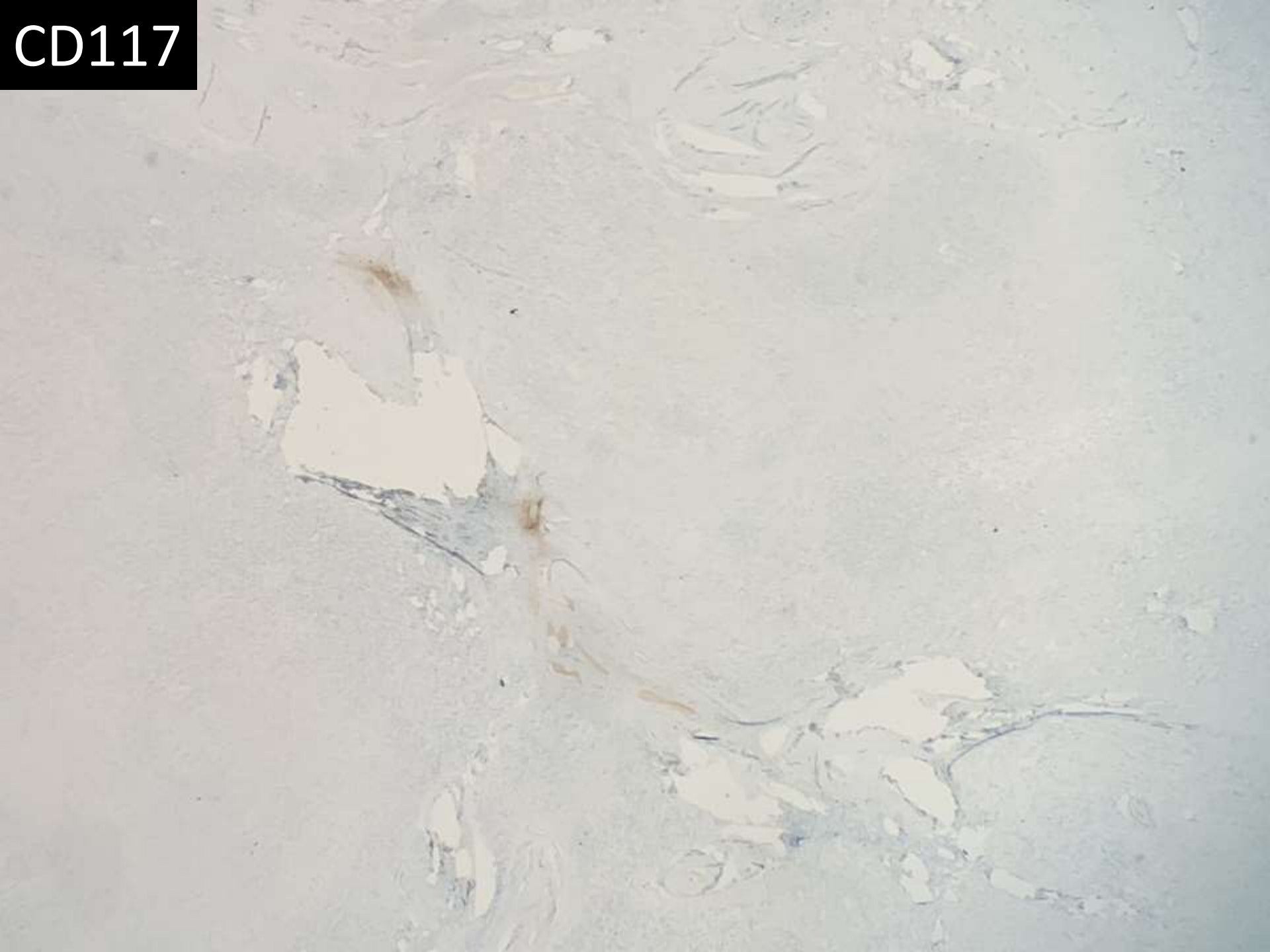


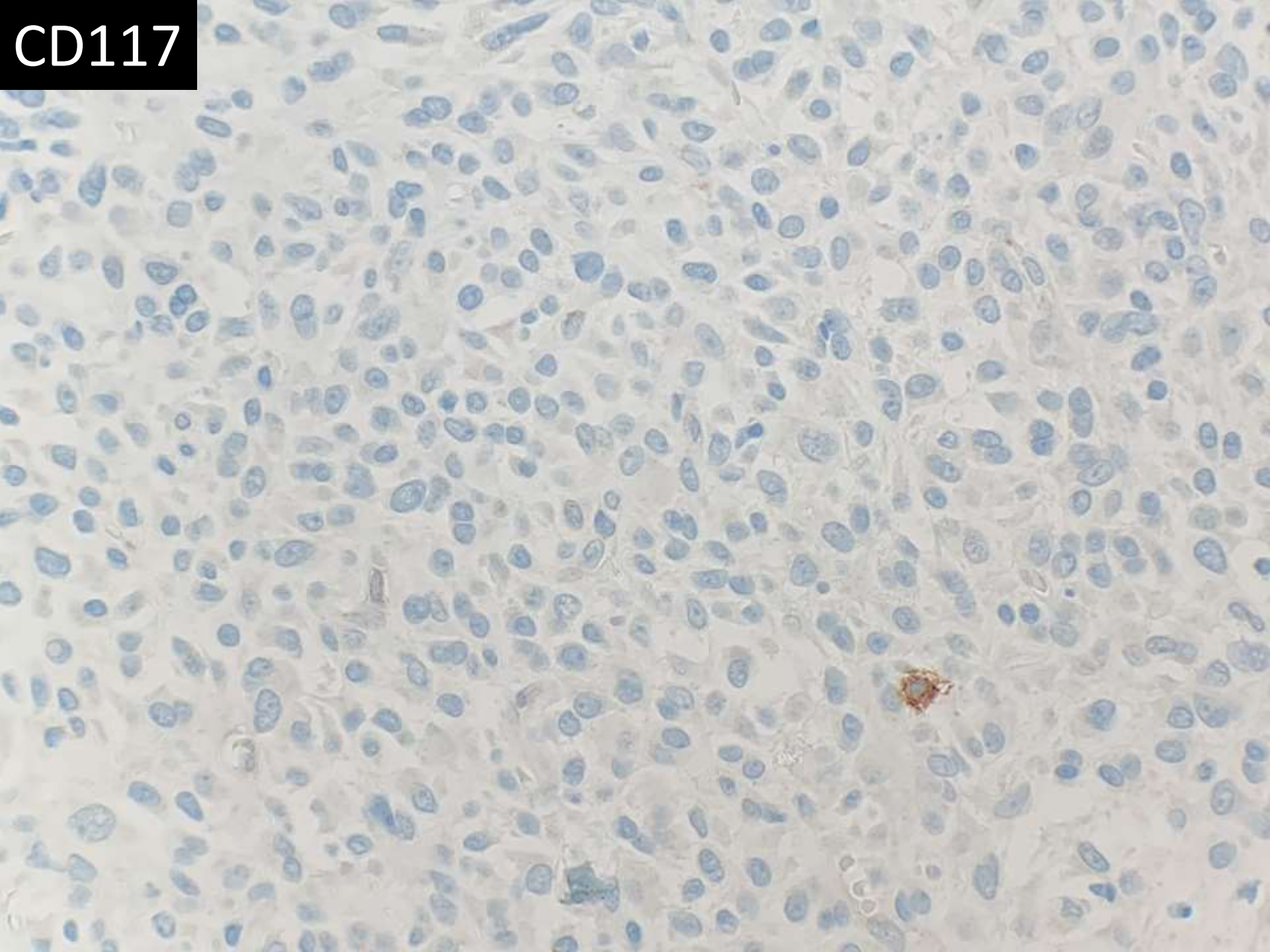





DOG1

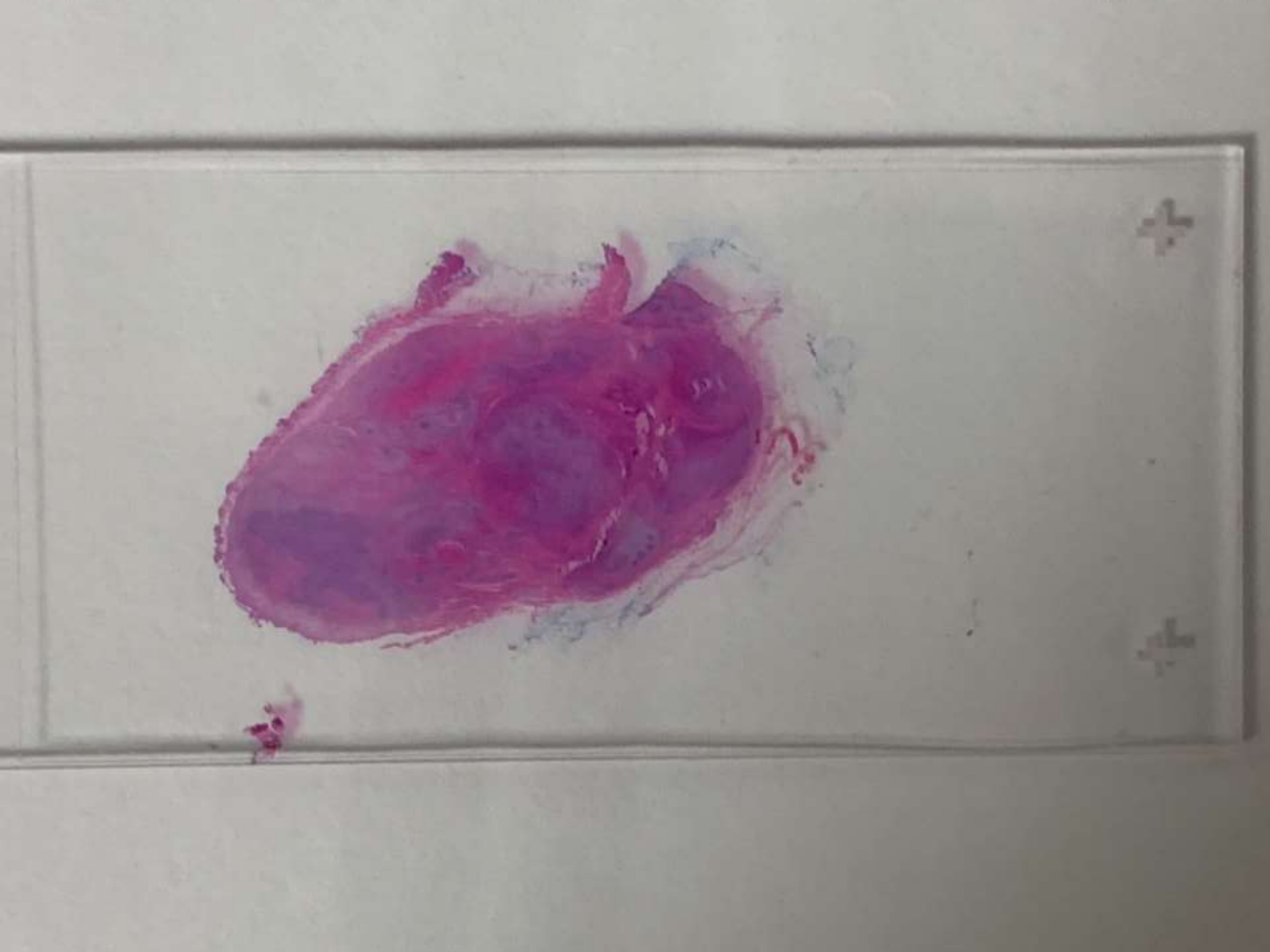

DOG1

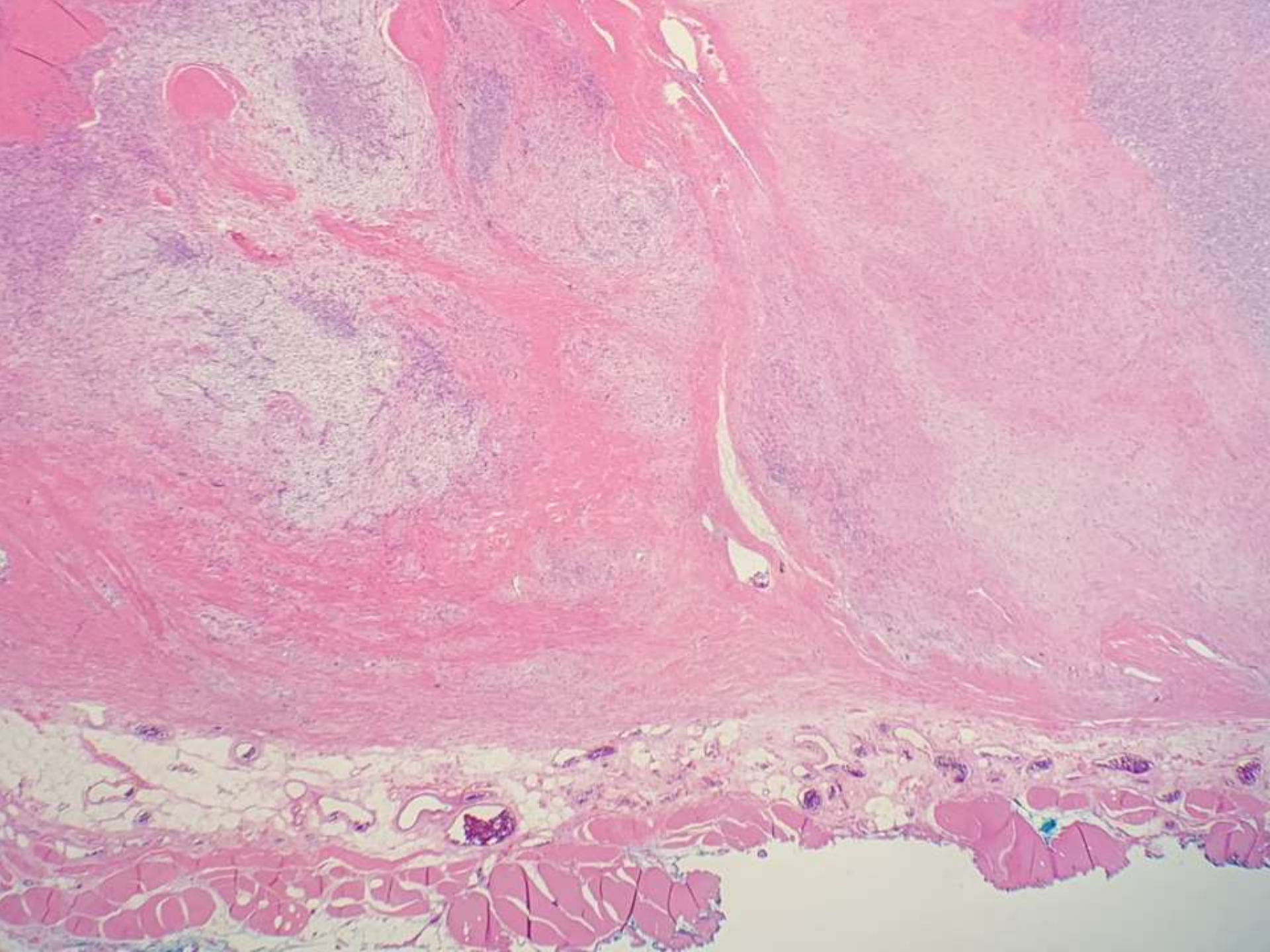

CD117

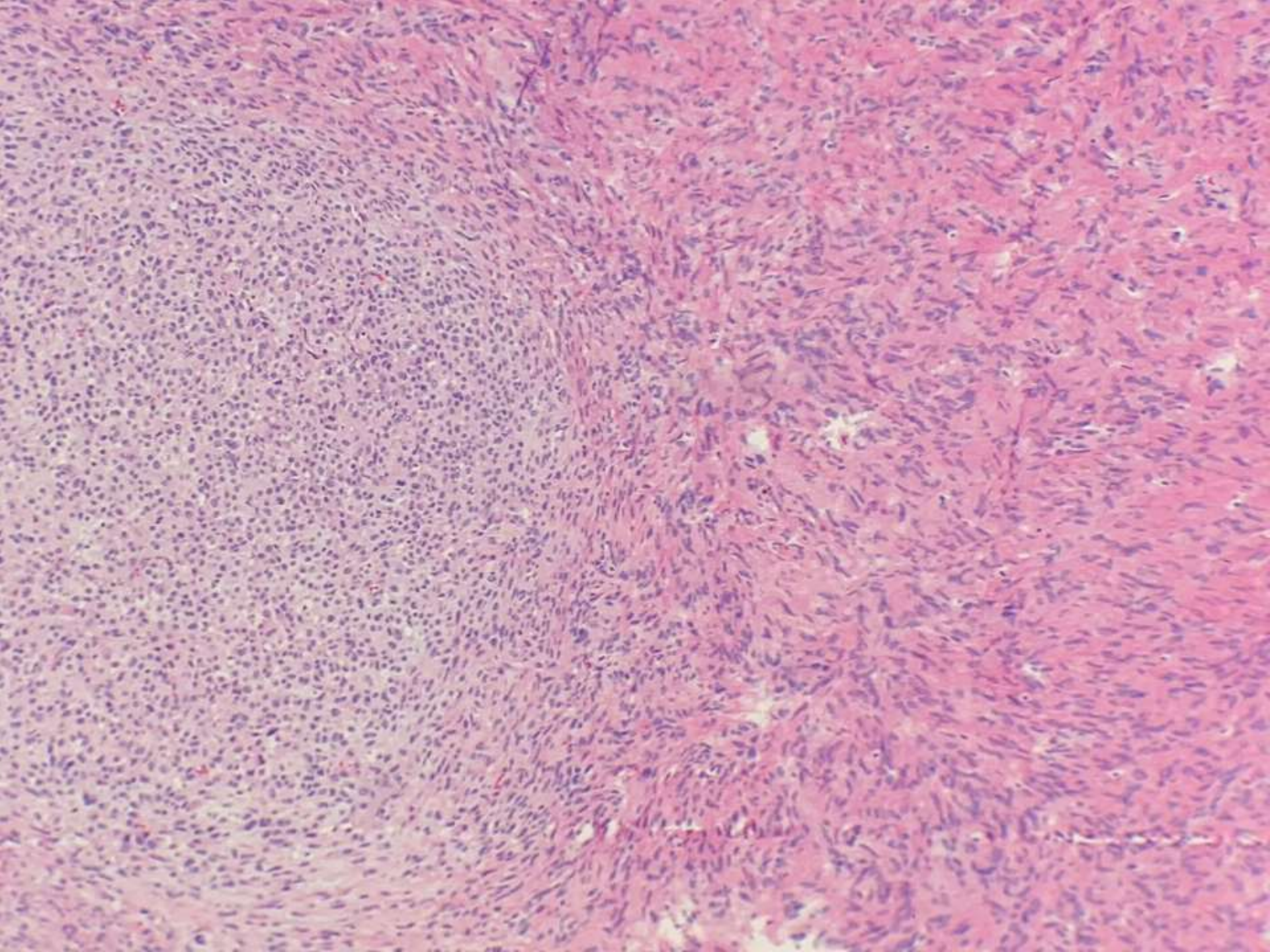

CD117

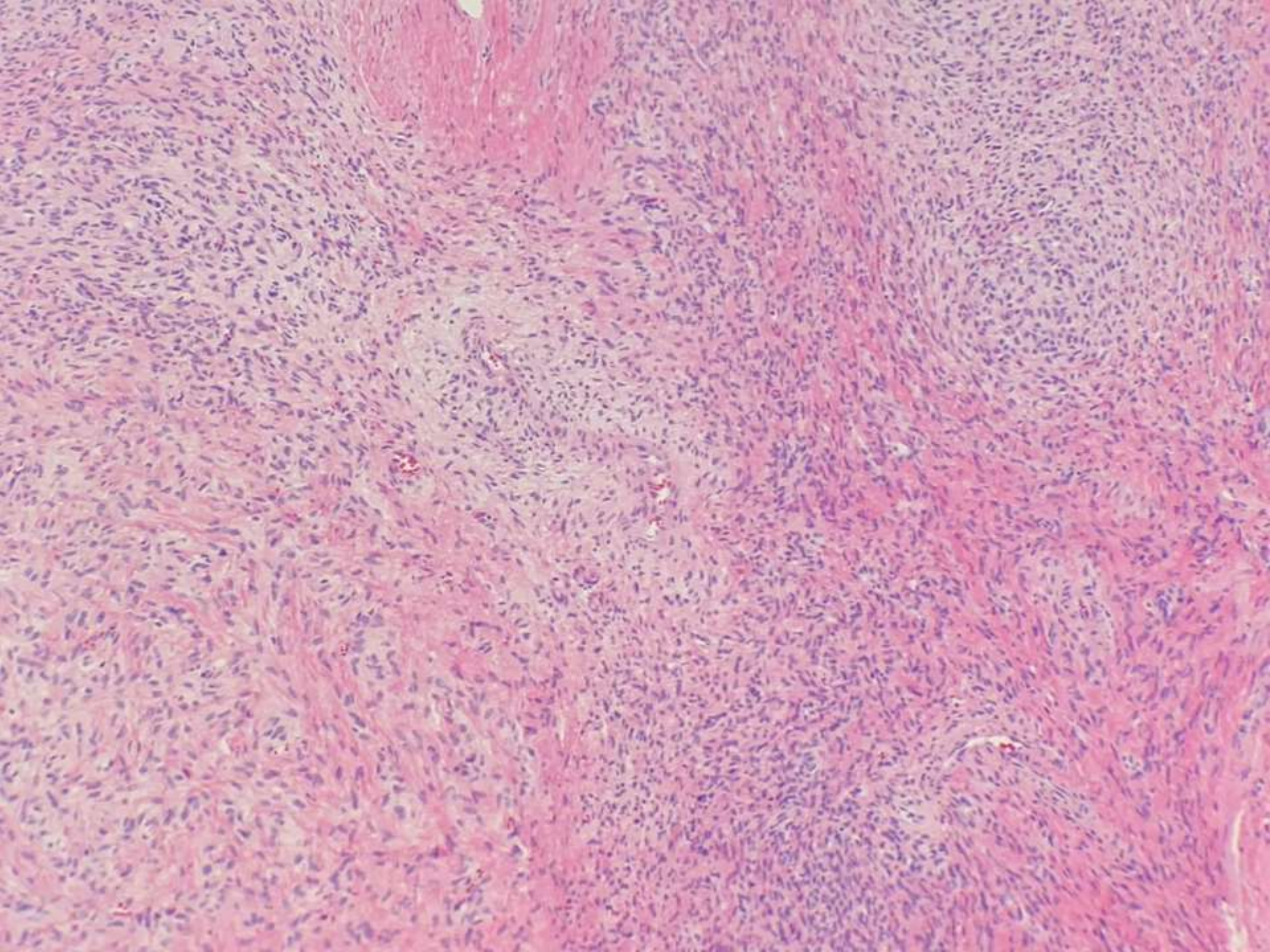
# Additional Immunohistochemistry

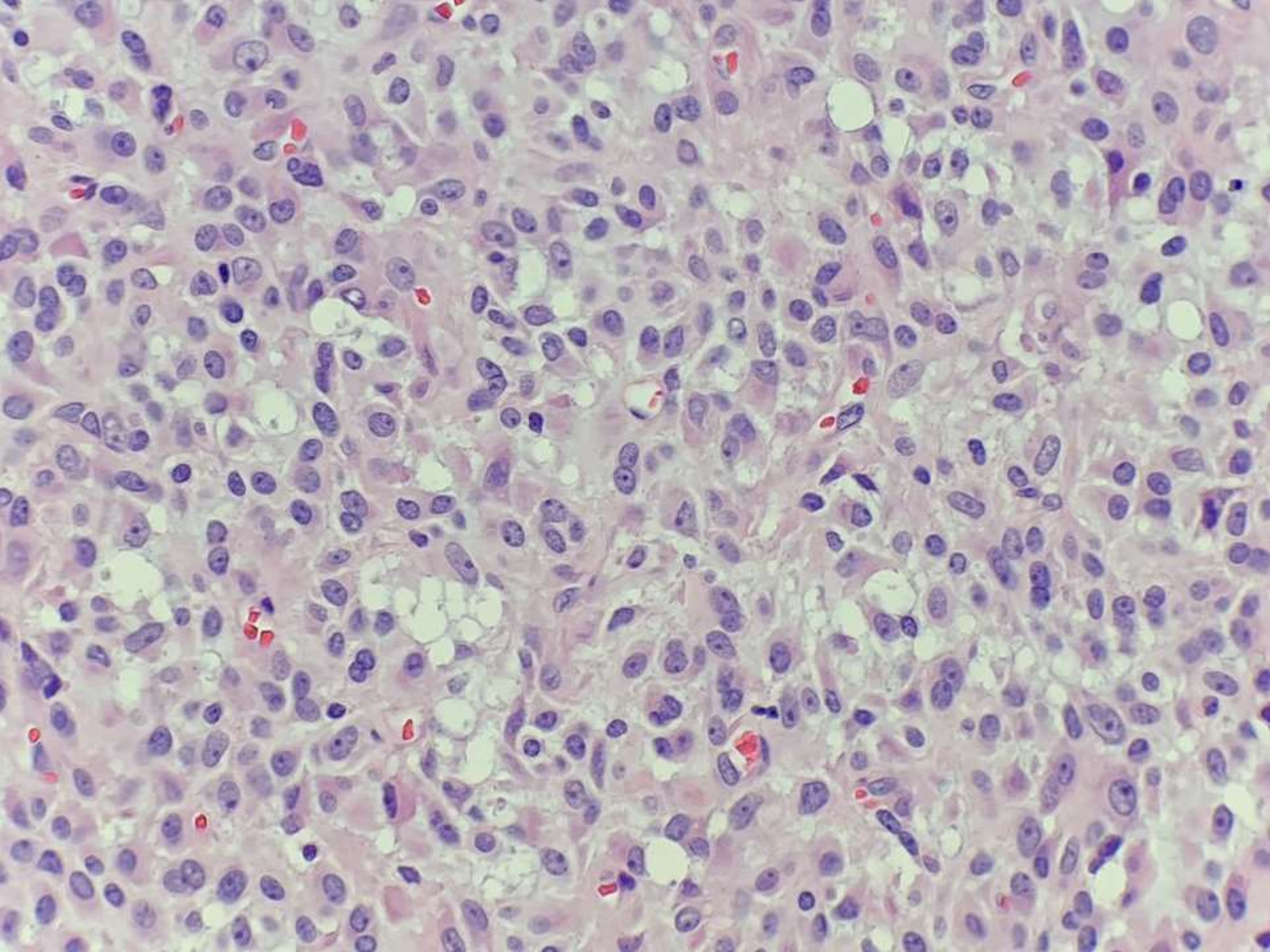
- Negative
  - CKAE1+Cam5.2, EMA, S100, HMB45, CD34, MDM2

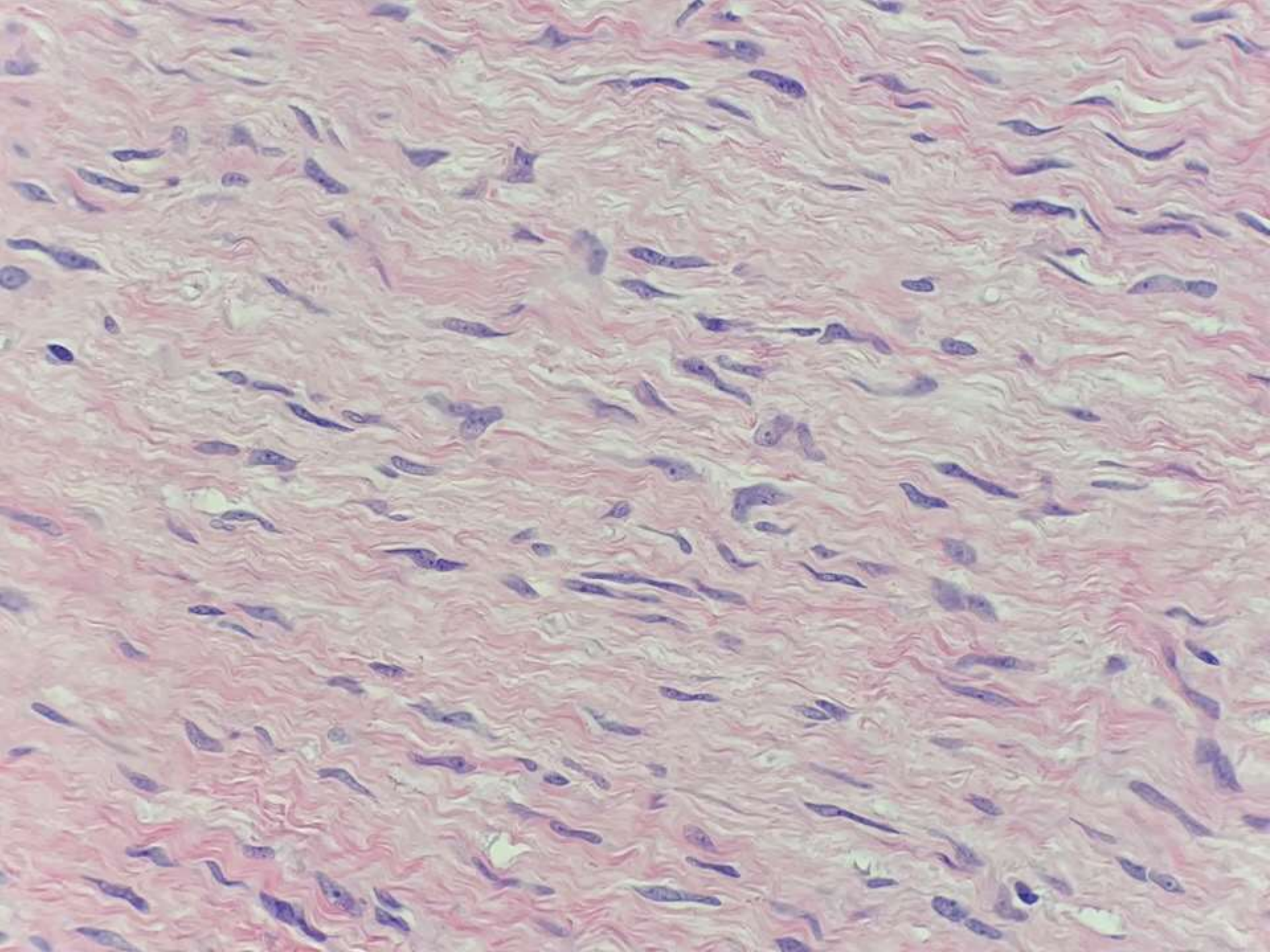


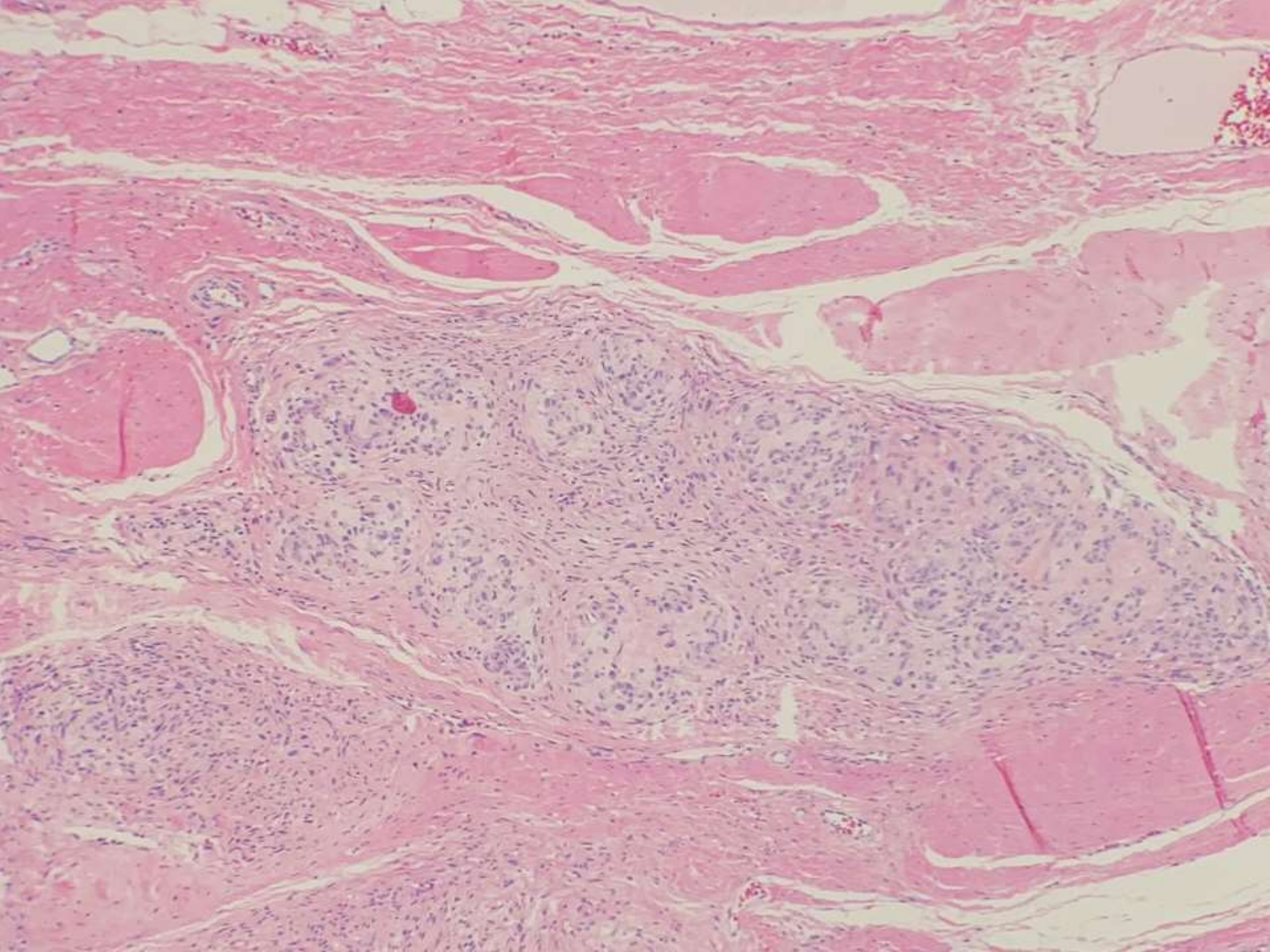


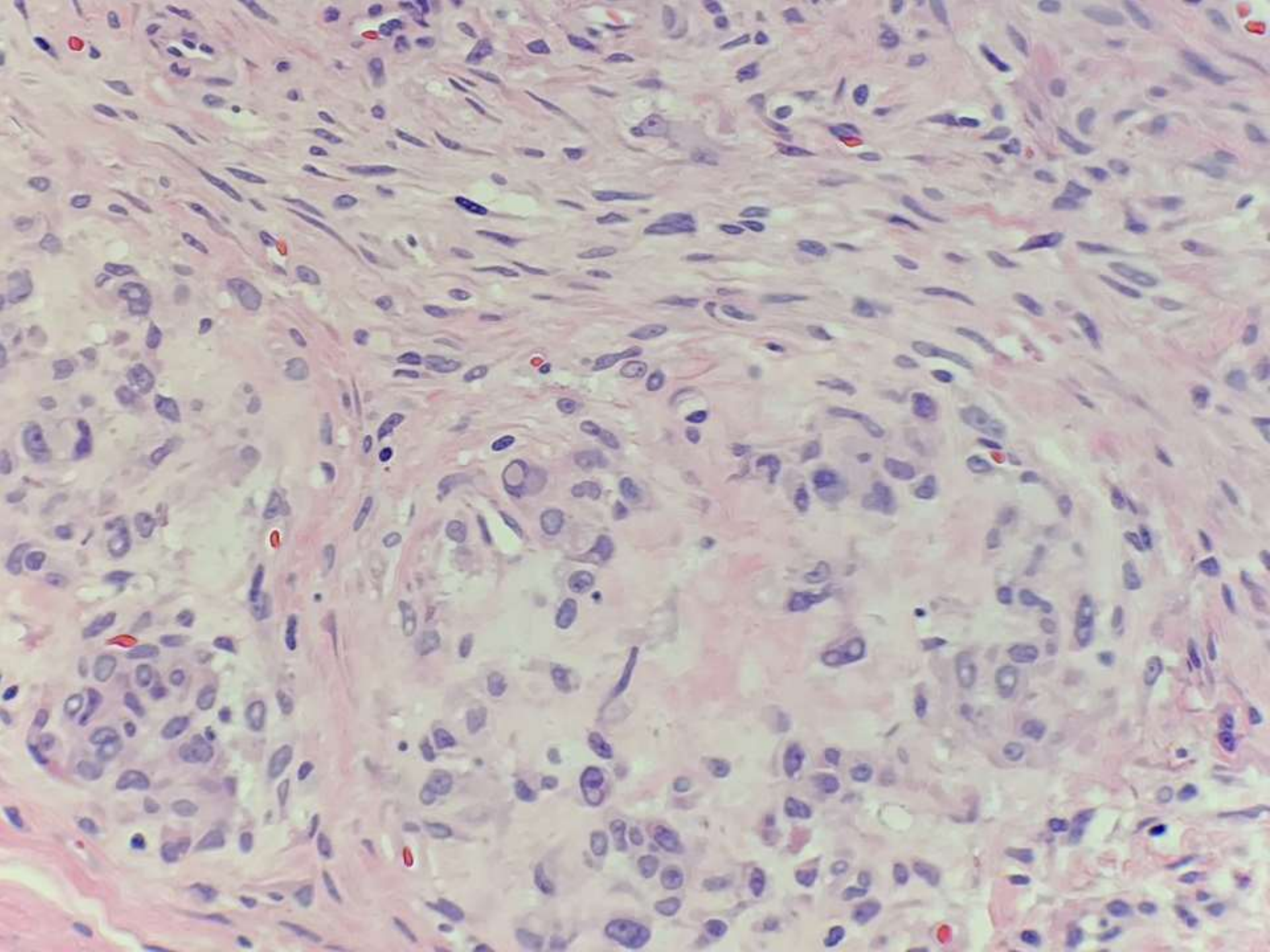




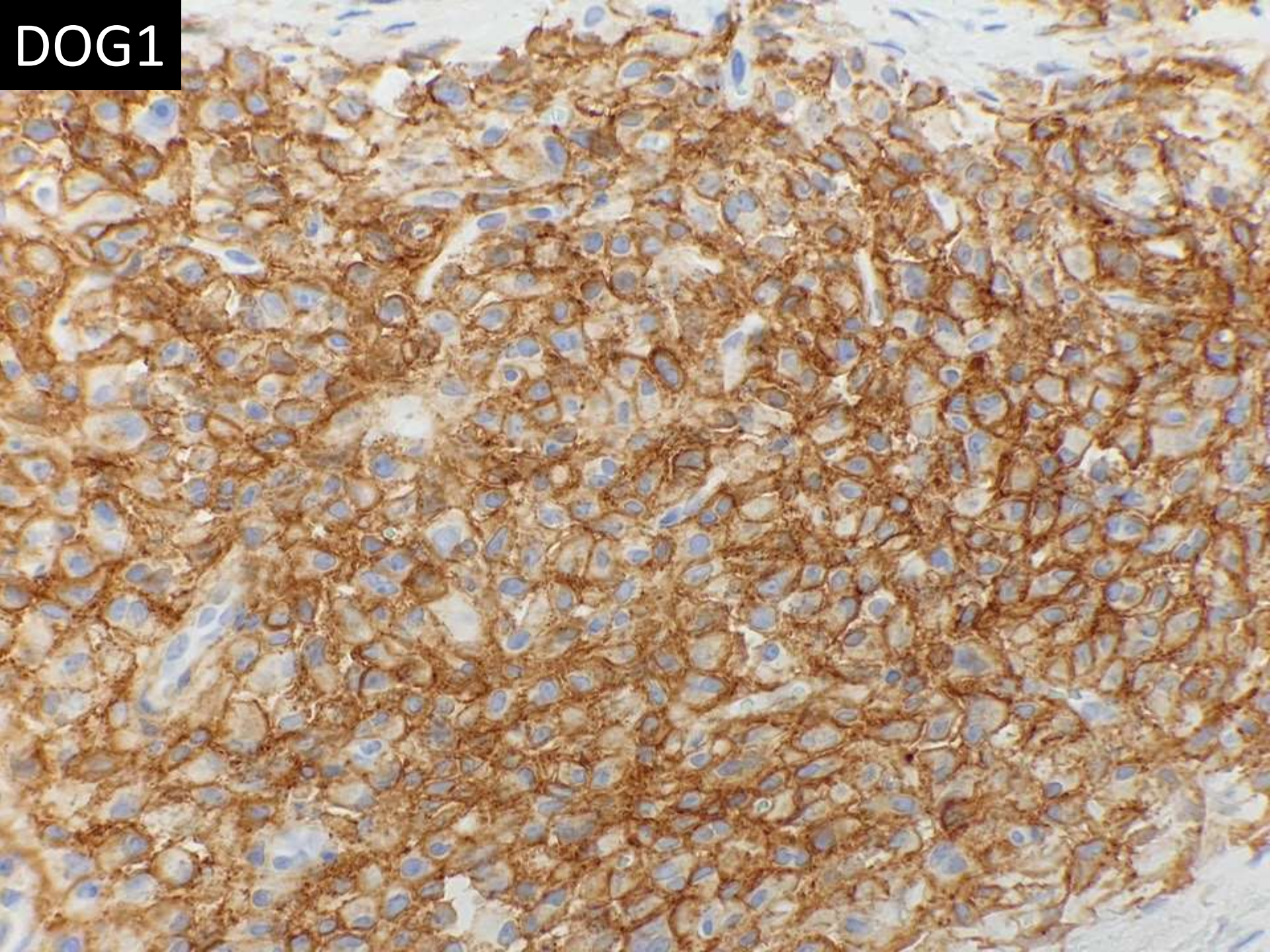


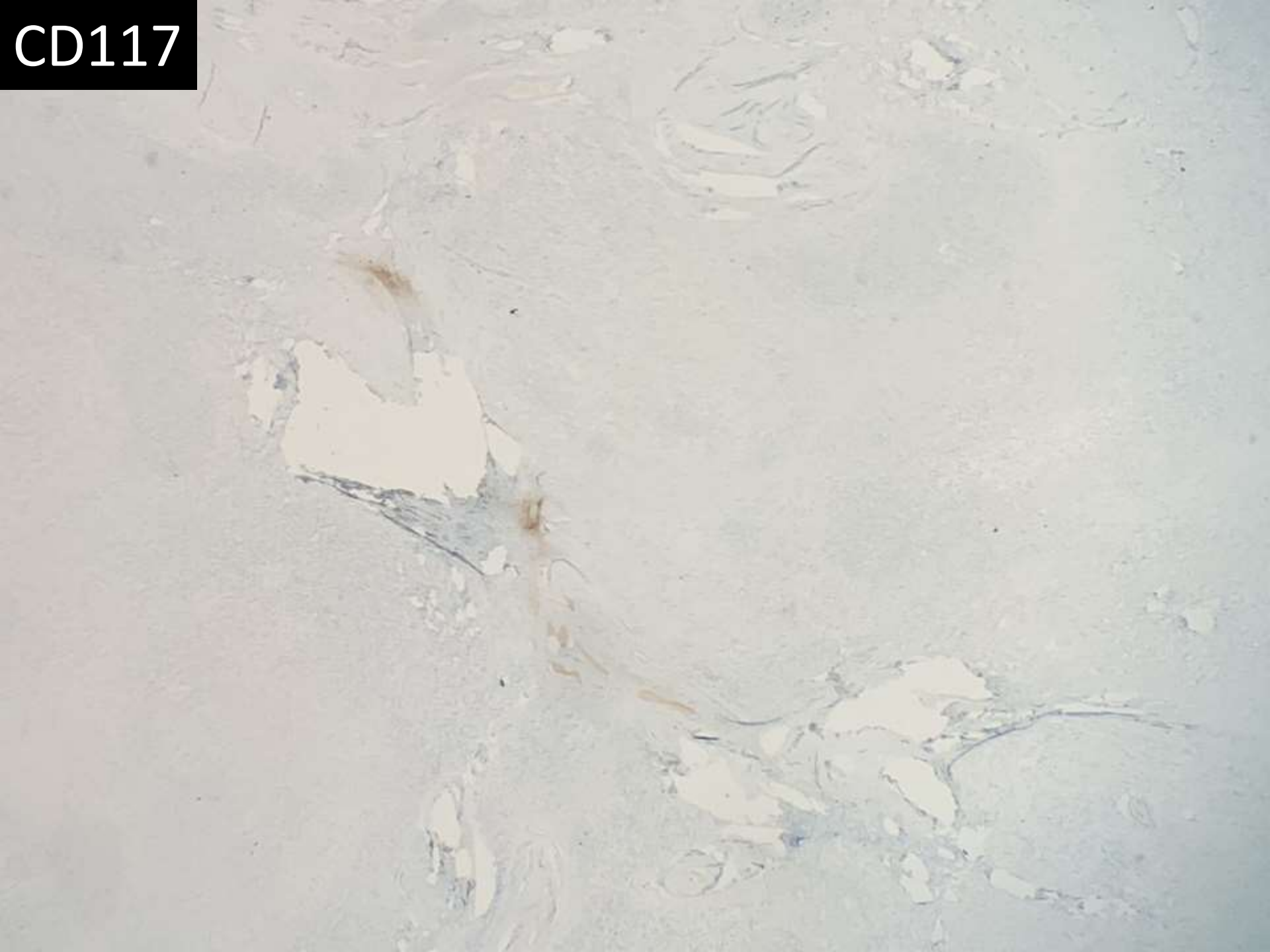


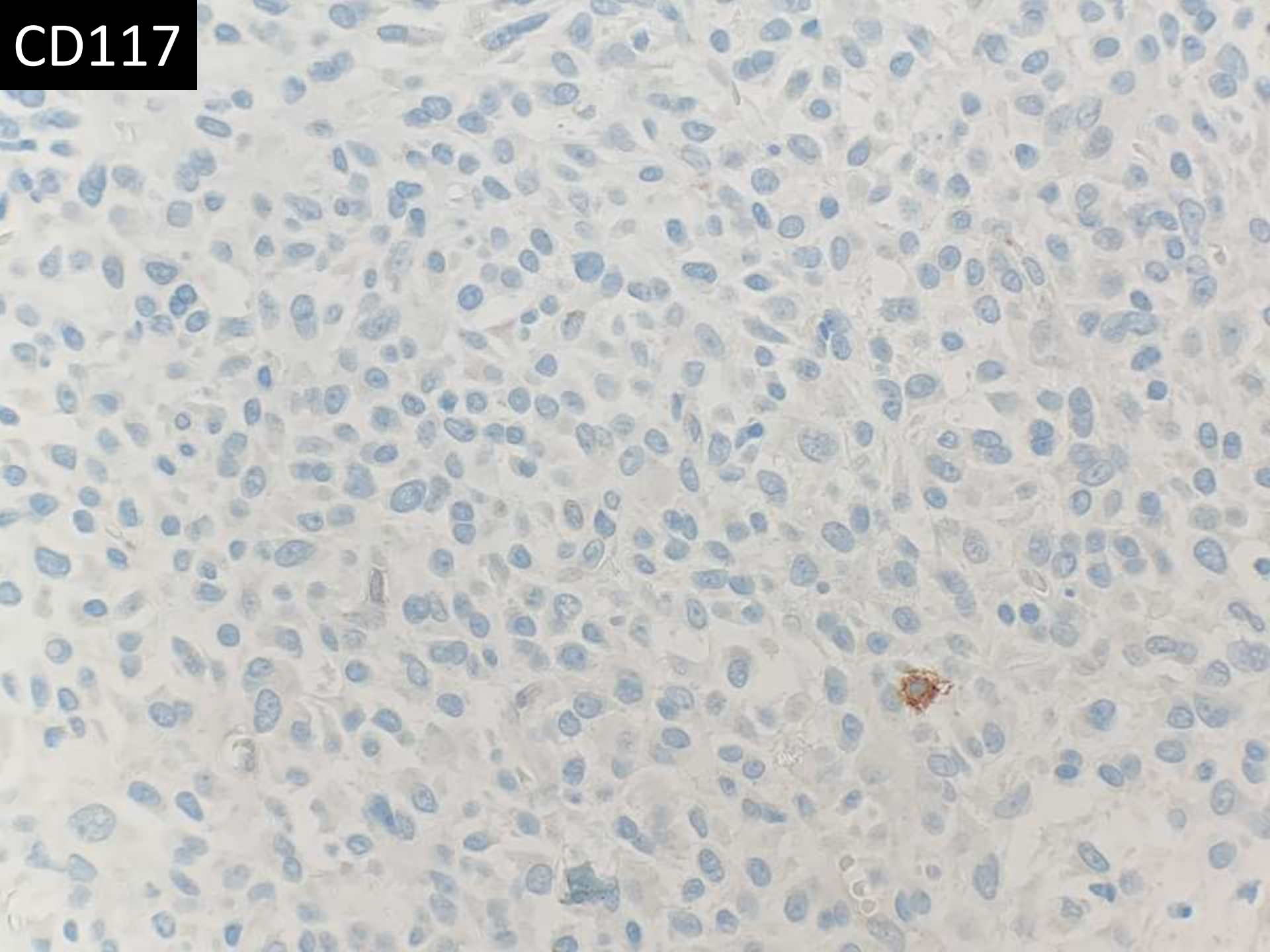




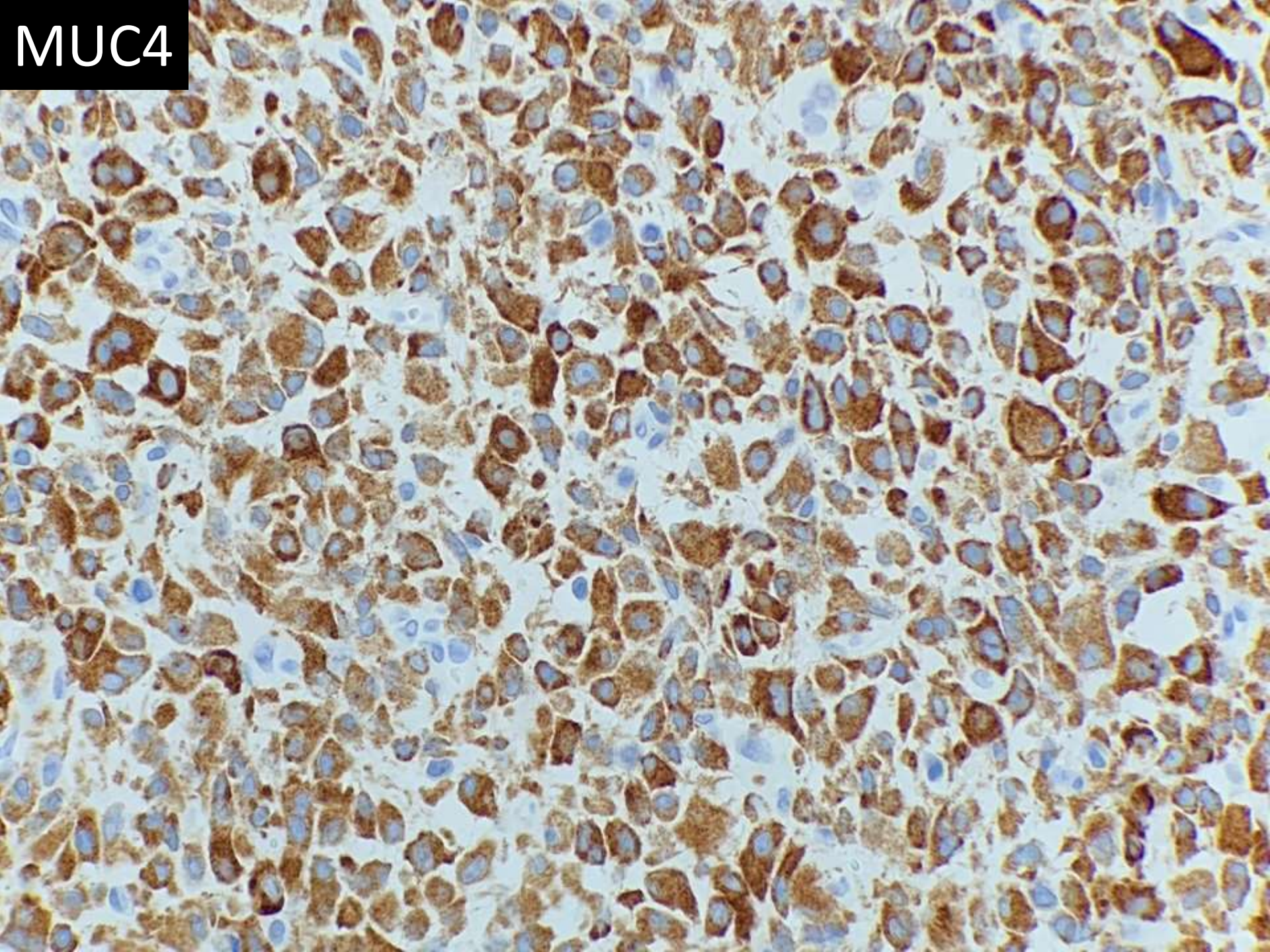

DOG1


DOG1


CD117


CD117


MUC4


MUC4

# Additional Immunohistochemistry

- Negative
  - CKAE1+Cam5.2, EMA, S100, HMB45, CD34, MDM2

# DIAGNOSIS

- Low-grade fibromyxoid sarcoma (LGFMS)

# DOG1+ LGFMS

International Journal of Surgical Pathology
2015, Vol. 23(6) 454–460

DOI: 10.1177/1066896915593801
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## DOG1 Expression in Low-Grade Fibromyxoid Sarcoma: A Study of 11 Cases, With Molecular Characterization

Khin Thway, FRCPath[1], Wen Ng, FRCPath[1], Charlotte Benson, MRCP[1], John Chapman, FRCPath[2], and Cyril Fisher, MD, DSc, FRCPath[1]

[1] Thway et al. DOG1 Expression in Low-Grade Fibromyxoid Sarcoma: A Study of 11 Cases, With Molecular Characterization. Int J Surg Pathol. 2015 Sep;23(6):454-60.

# DOG1+ LGFMS

**Table 1.** Low-Grade Fibromyxoid Sarcoma: Molecular Features and Immunohistochemical MUC4 and DOG1 Expression[a].

| Case No. | Morphology | Molecular Characteristics (*FUS-CREB3L2* Fusion Transcripts With RT-PCR or *FUS* or *EWSR1* Rearrangement With FISH) | MUC4 Expression | DOG1 Expression (Positive or Negative) | DOG1 Expression Intensity | % of Cells Expressing DOG1 |
|---|---|---|---|---|---|---|
| 1 (index case) | Hyalinized stroma only; no myxoid areas | *FUS-CREB3L2* | + | Positive | Strong | 100% |
| 2 | Classical | N/A | + | Negative | | |
| 3 | Classical | *FUS-CREB3L2* | + | Positive | Weak | 10% |
| 4 | Classical | *FUS-CREB3L2* | + | Negative | | |
| 5 | Classical | *FUS-CREB3L2* | + | Negative | | |
| 6 | Classical | *FUS-CREB3L2* | + | Positive | Moderate | 50% |
| 7 | Classical | *FUS-CREB3L2* | + | Positive | Strong | 75% |
| 8 | Hyalinized stroma only; no myxoid areas | *FUS-CREB3L2* | + | Positive | Weak | 30% |
| 9 | Classical | *FUS-CREB3L2* | + | Negative | | |
| 10 | Classical | *EWSR1* rearrangement | + | Negative | | |
| 11 | Classical | *FUS-CREB3L2* | + | Positive | Weak | 5% |

Abbreviations: FISH, fluorescence in situ hybridization; N/A, not applicable; RT-PCR, reverse transcription-polymerase chain reaction.
[a]Classical indicates that both typical fibrous and myxoid areas were present in the tumor. + for MUC4 indicates diffusely positive.

[1] Thway et al. DOG1 Expression in Low-Grade Fibromyxoid Sarcoma: A Study of 11 Cases, With Molecular Characterization. Int J Surg Pathol. 2015 Sep;23(6):454-60.

# DOG1+ LGFMS

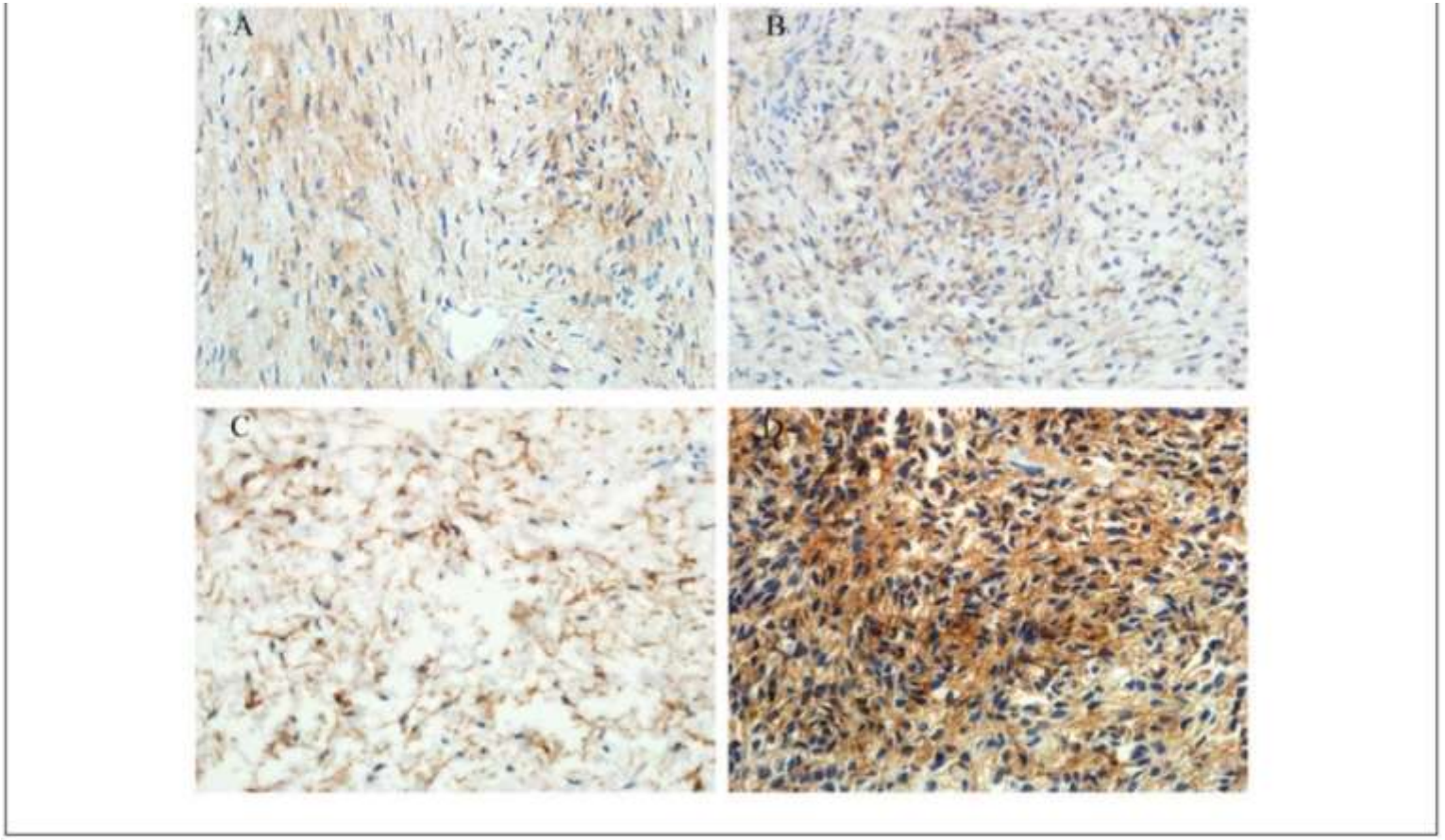


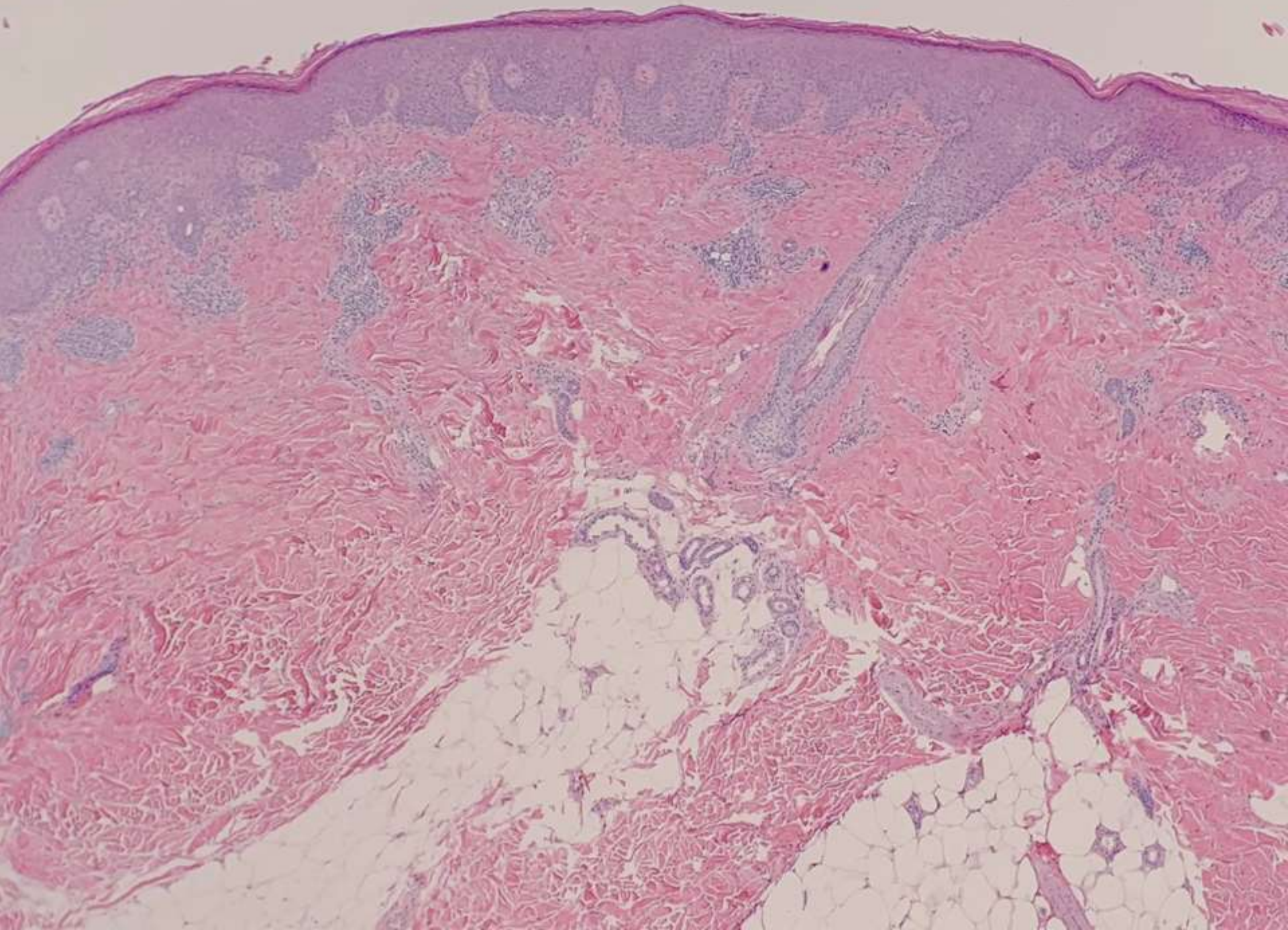

**Figure 2.** (A-D) These examples of molecularly proven LGFMS show a spectrum of DOG1 expression. Focal moderate cytoplasmic expression is seen in A and B, and seen accentuating a cellular whorl (B). (C) This example shows DOG1 expression in most cells, but the tumor is relatively sparsely cellular. (D) This case shows a cellular focus, in which there is diffuse and strong expression of DOG1.

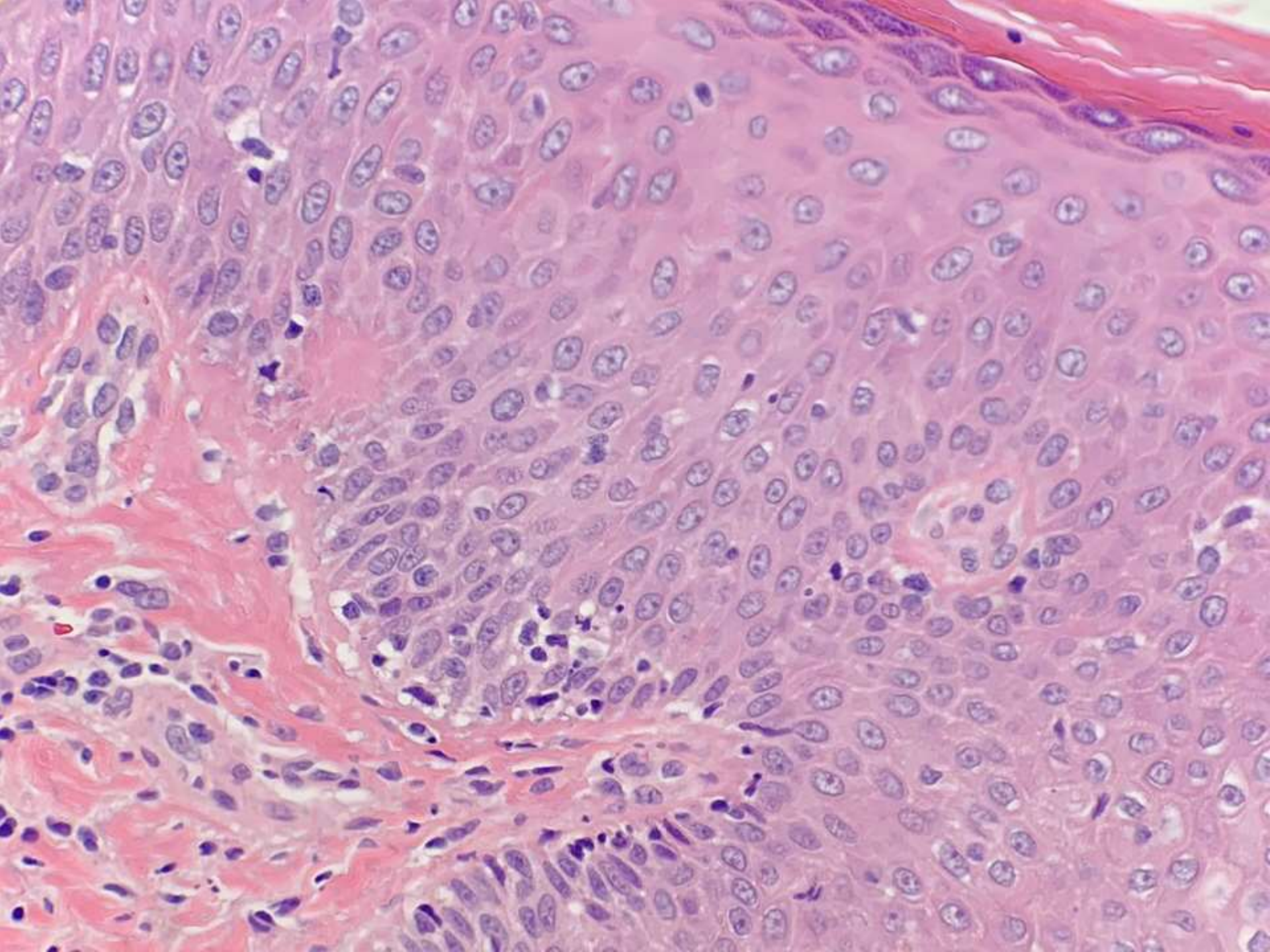
[1] Thway et al. DOG1 Expression in Low-Grade Fibromyxoid Sarcoma: A Study of 11 Cases, With Molecular Characterization. Int J Surg Pathol. 2015 Sep;23(6):454-60.

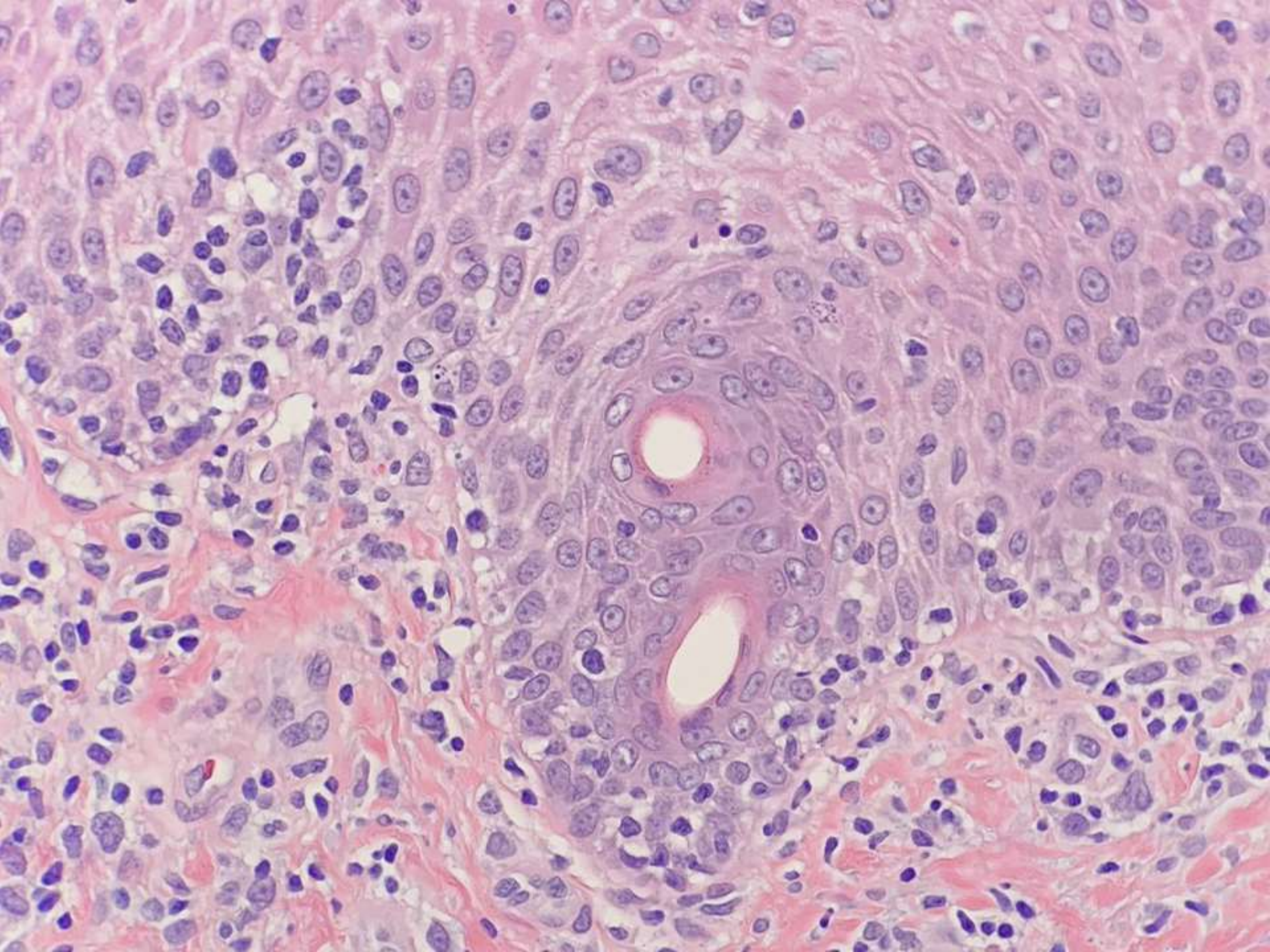
# 20-0210

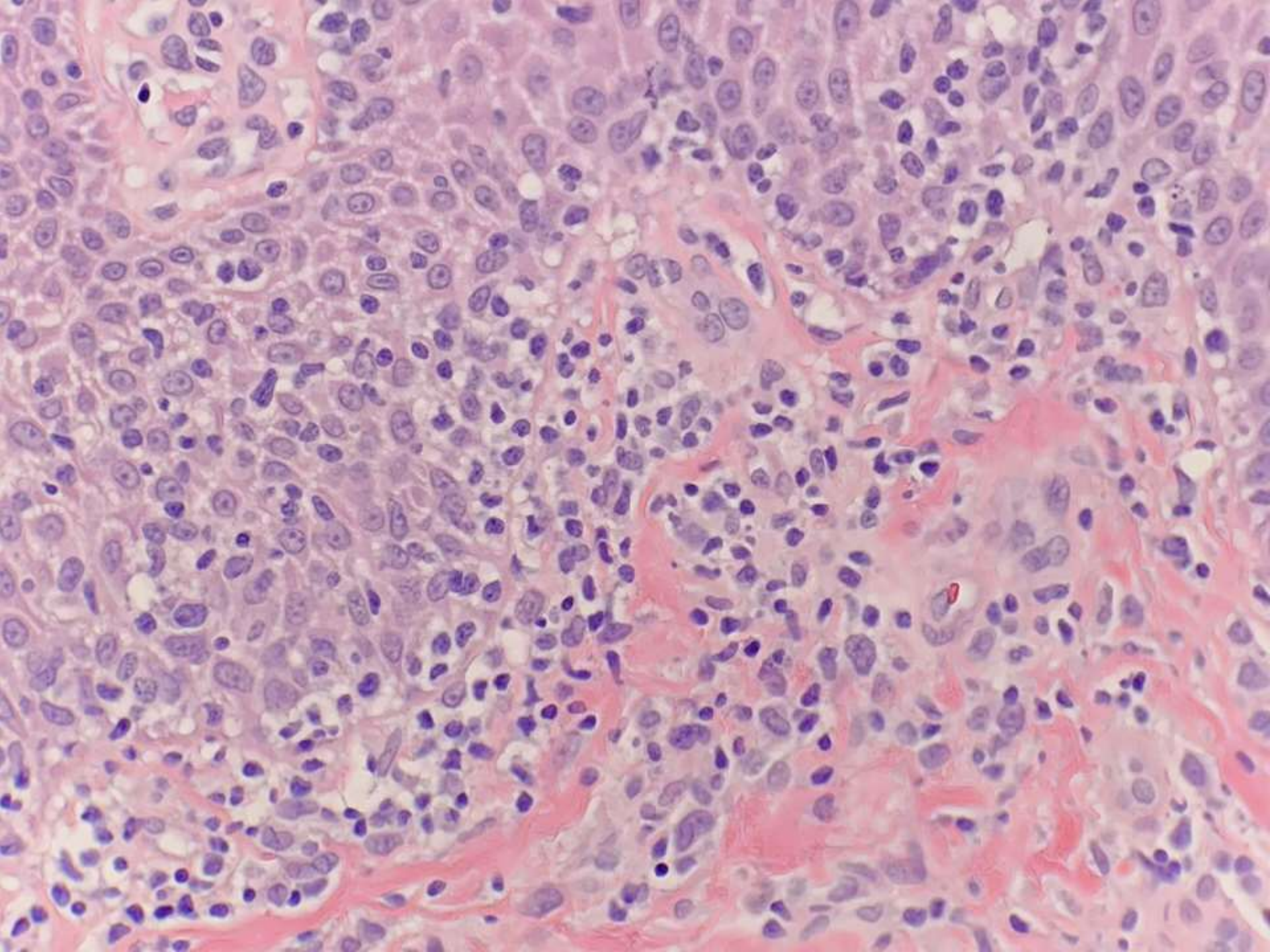
**Matthew Koo/Roberto Novoa; Stanford**

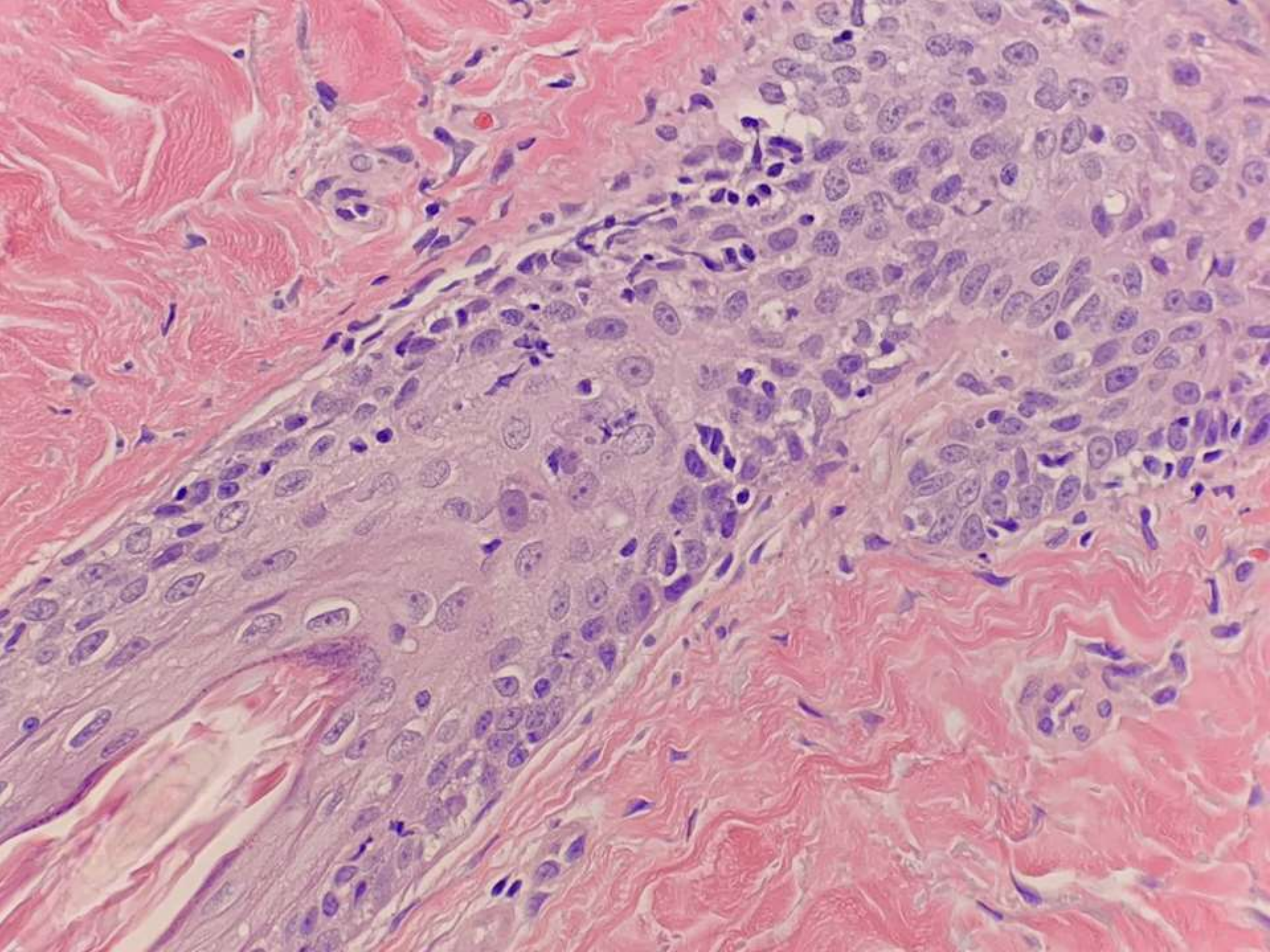
65-year-old M with rapidly progressive diffuse pink patches.

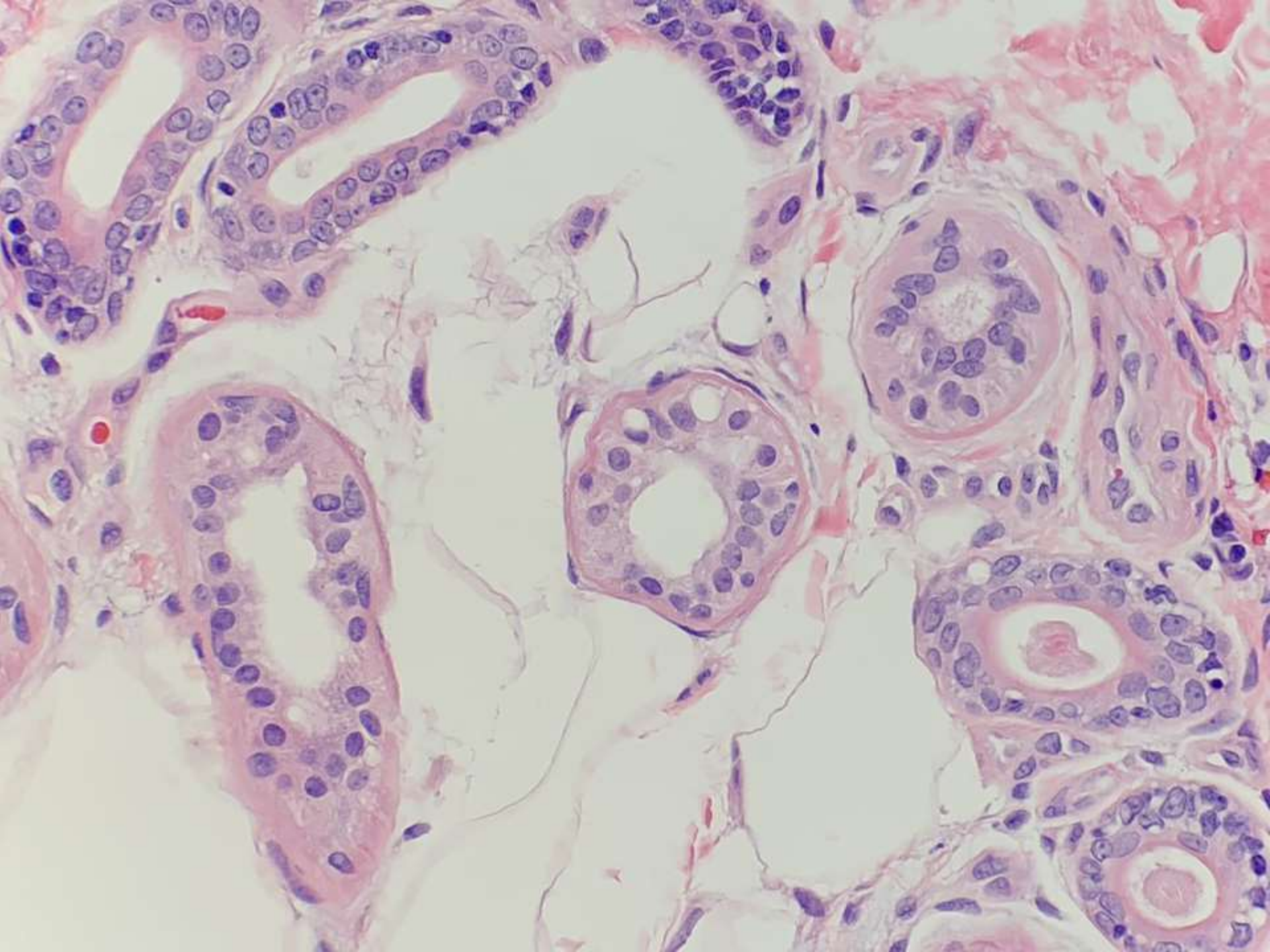


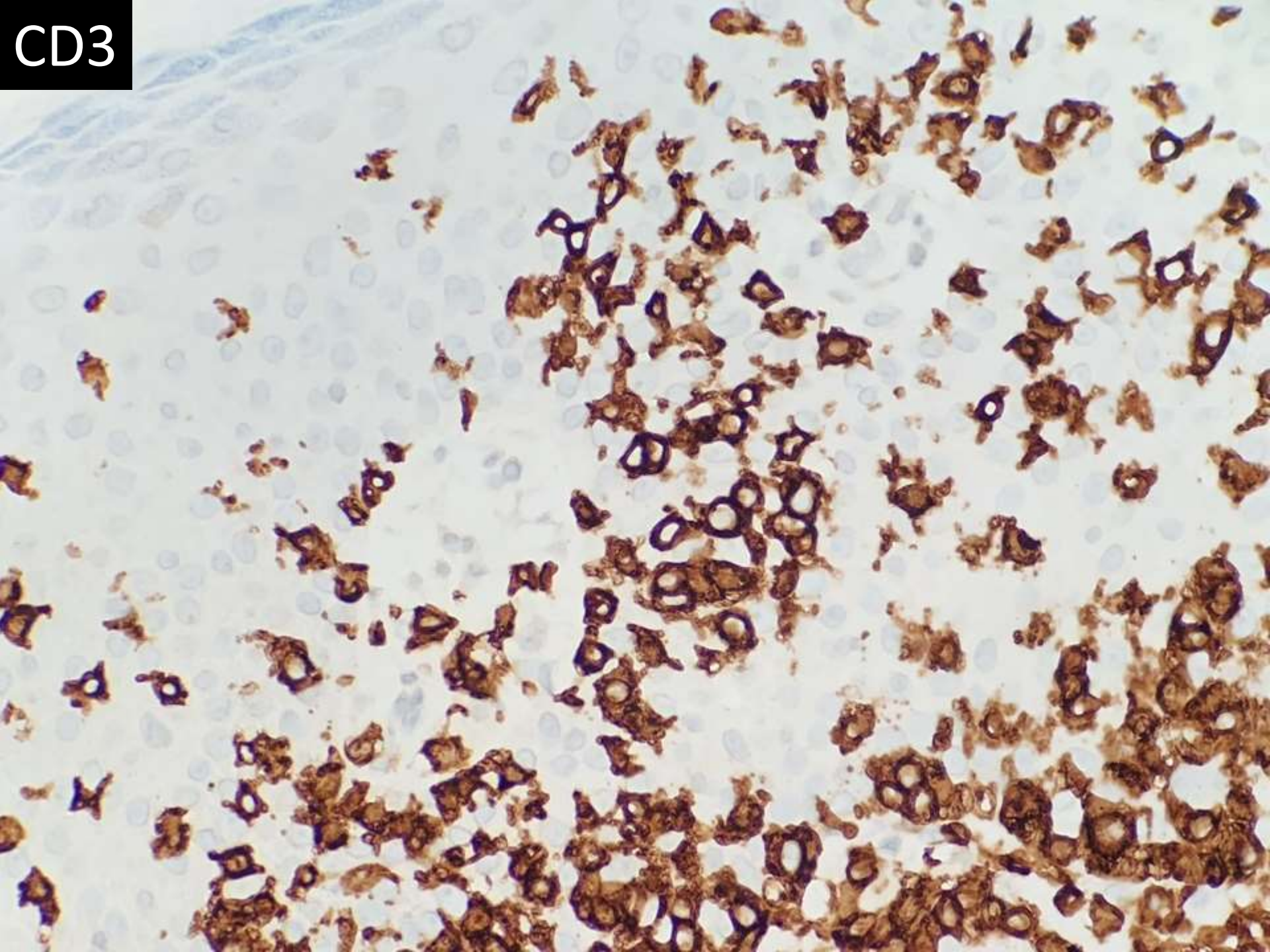


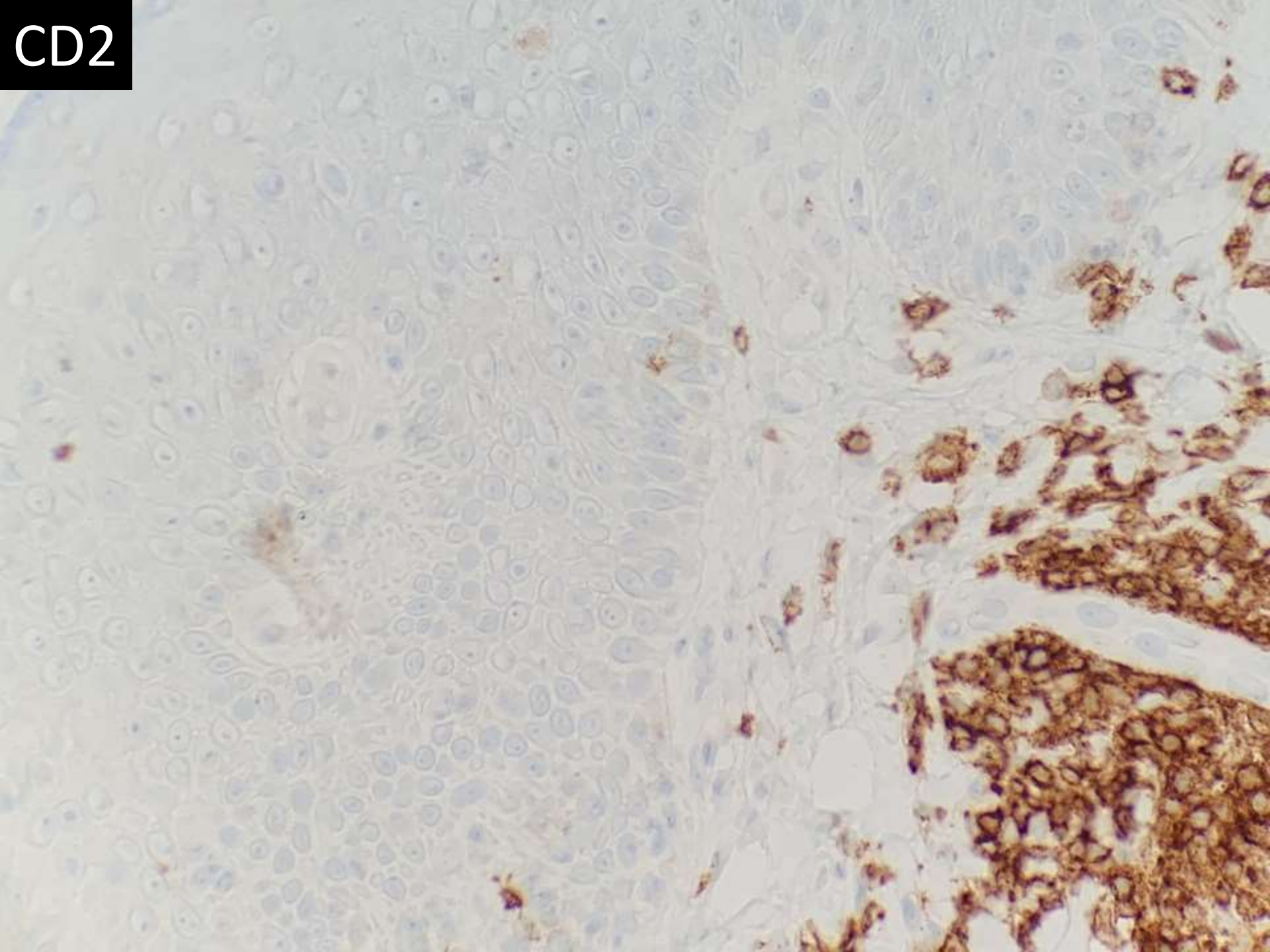


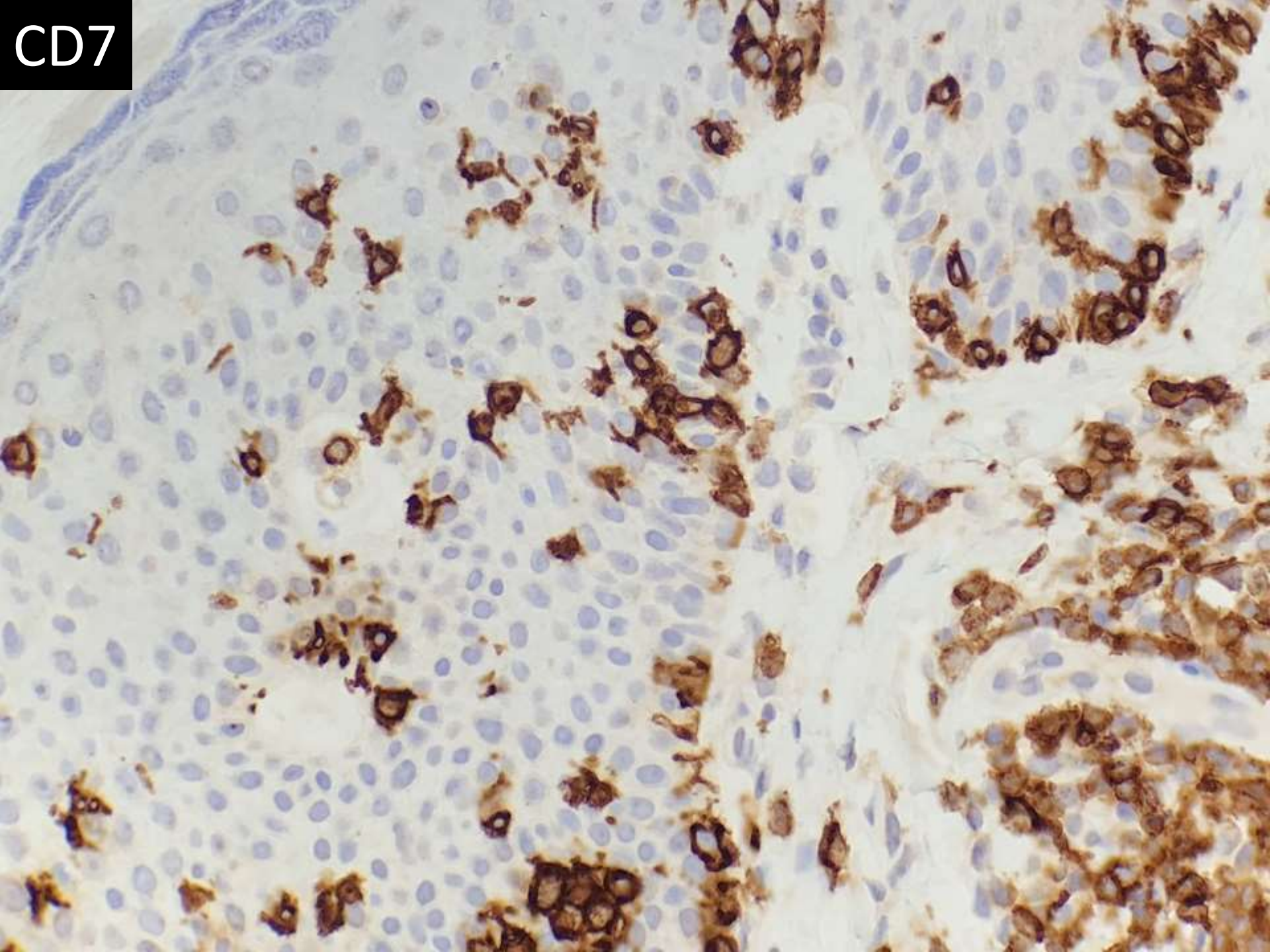


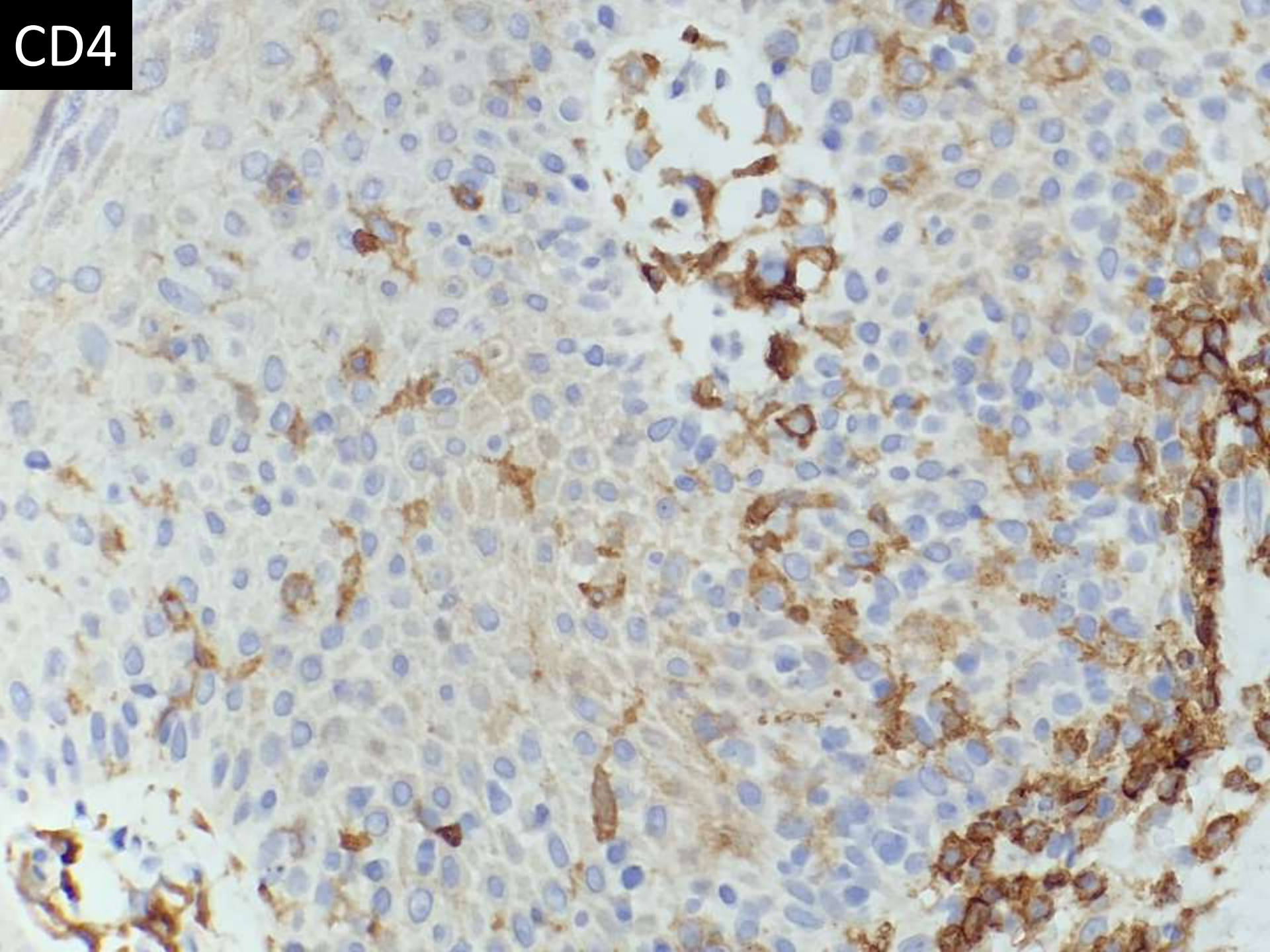


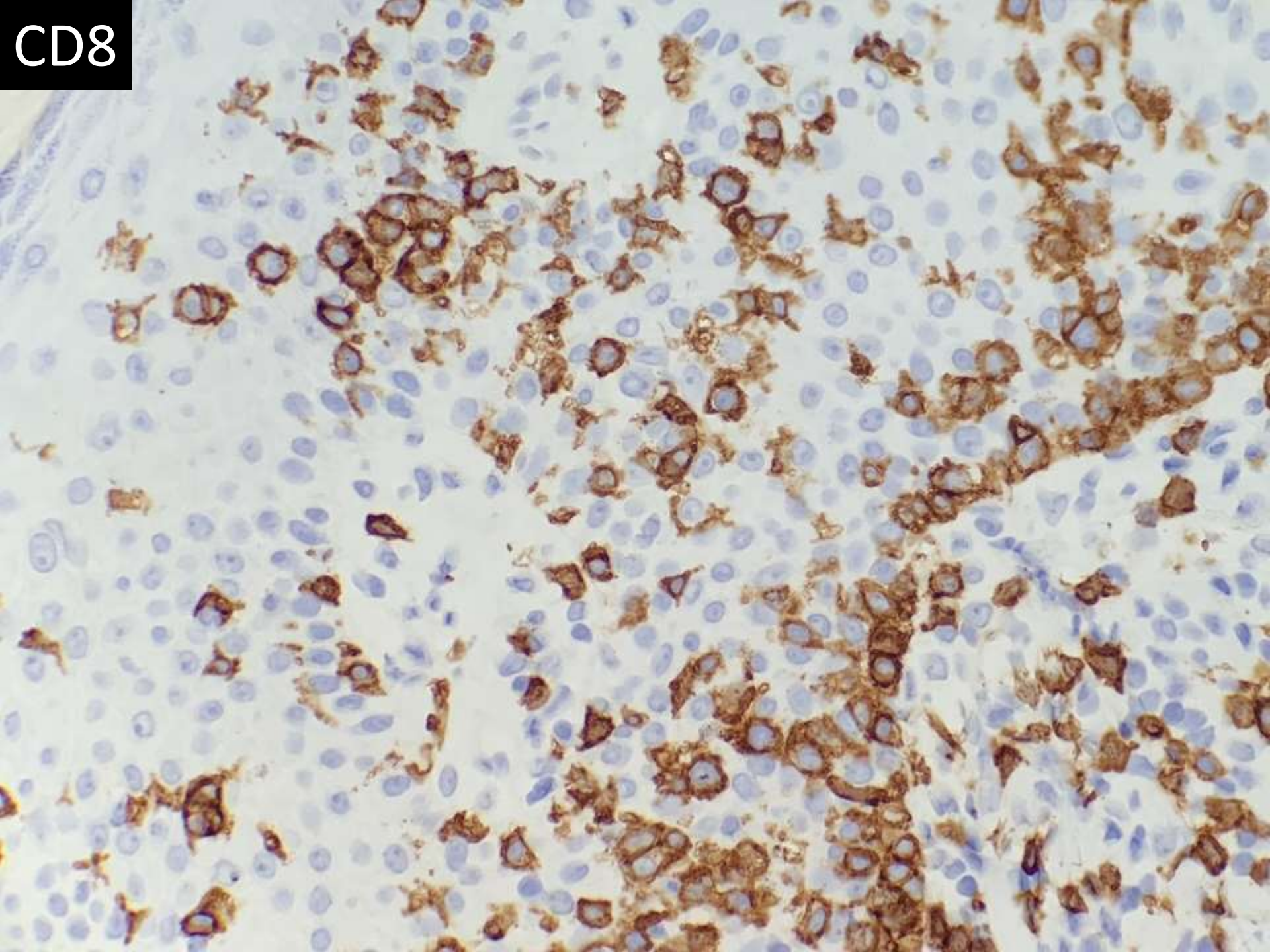



CD3


CD2


CD7


CD4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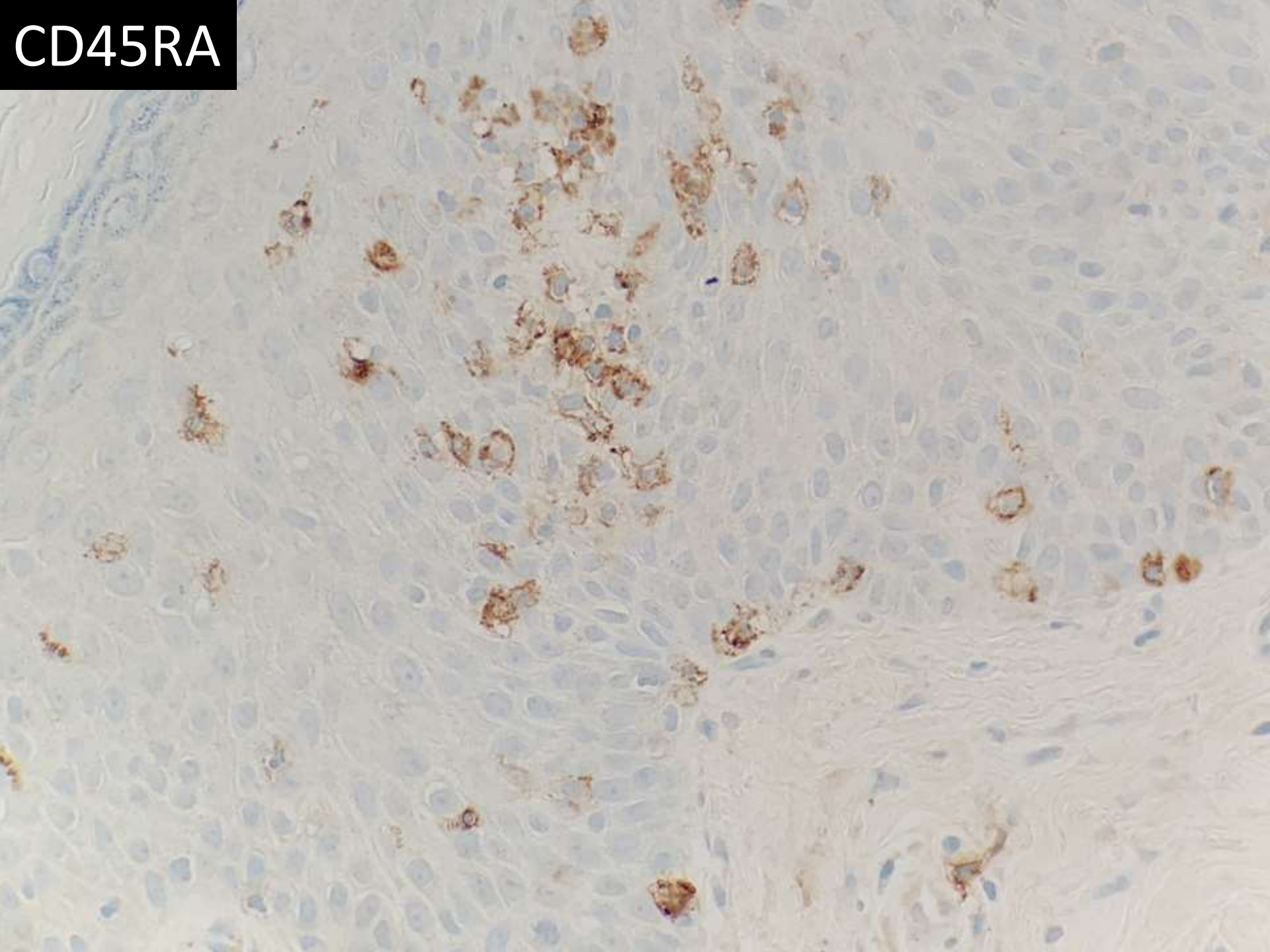
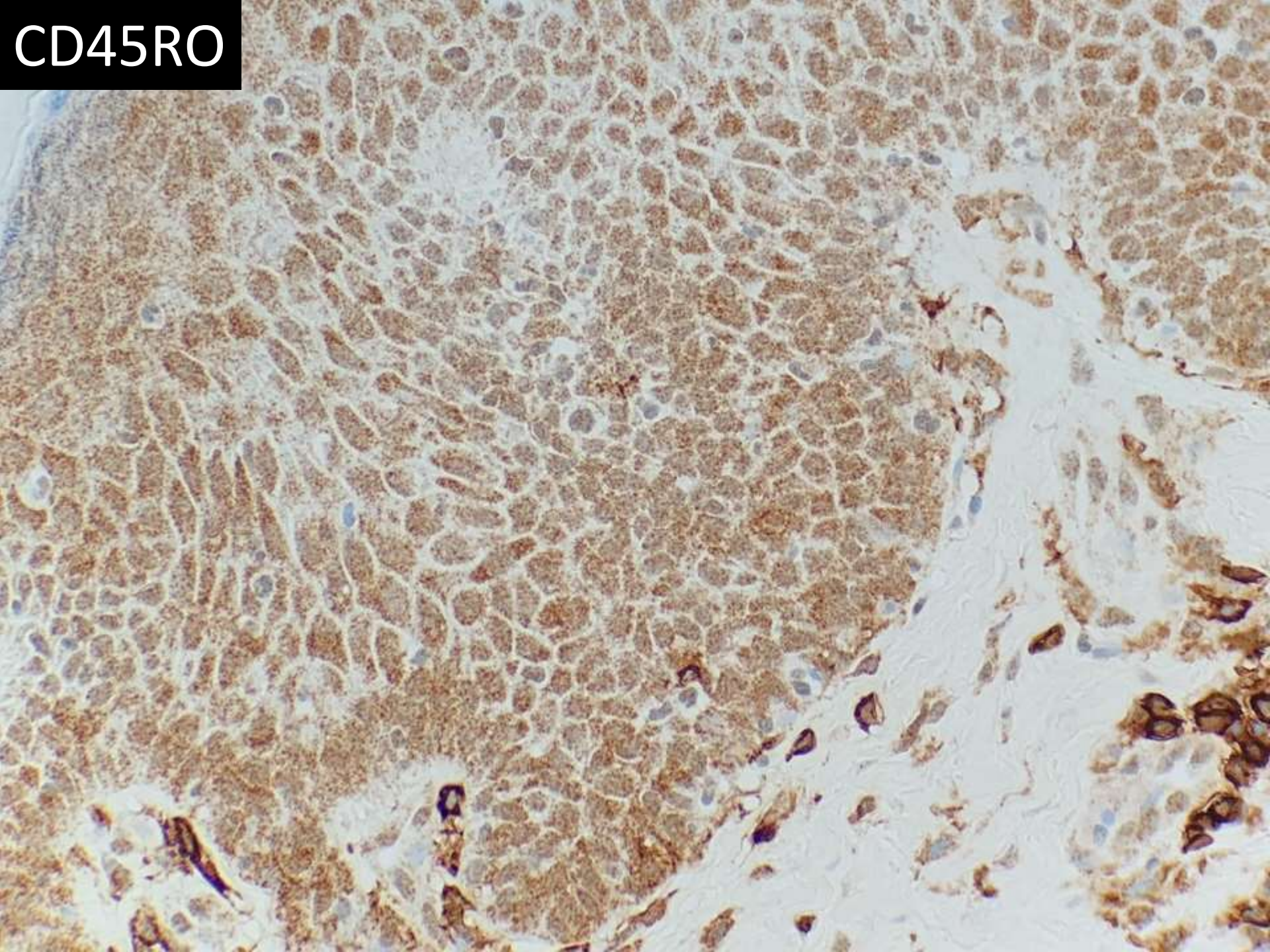

CD45RA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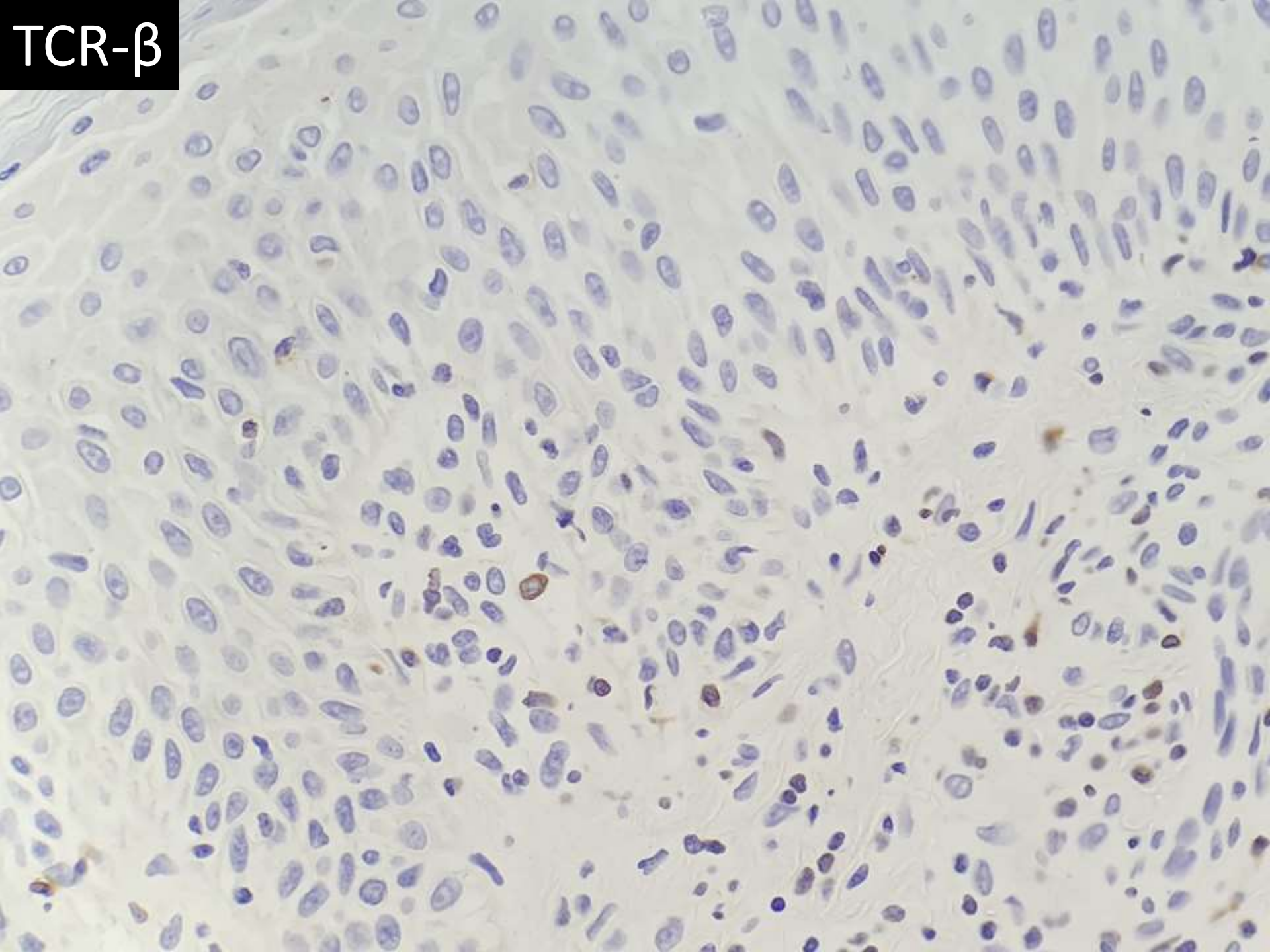
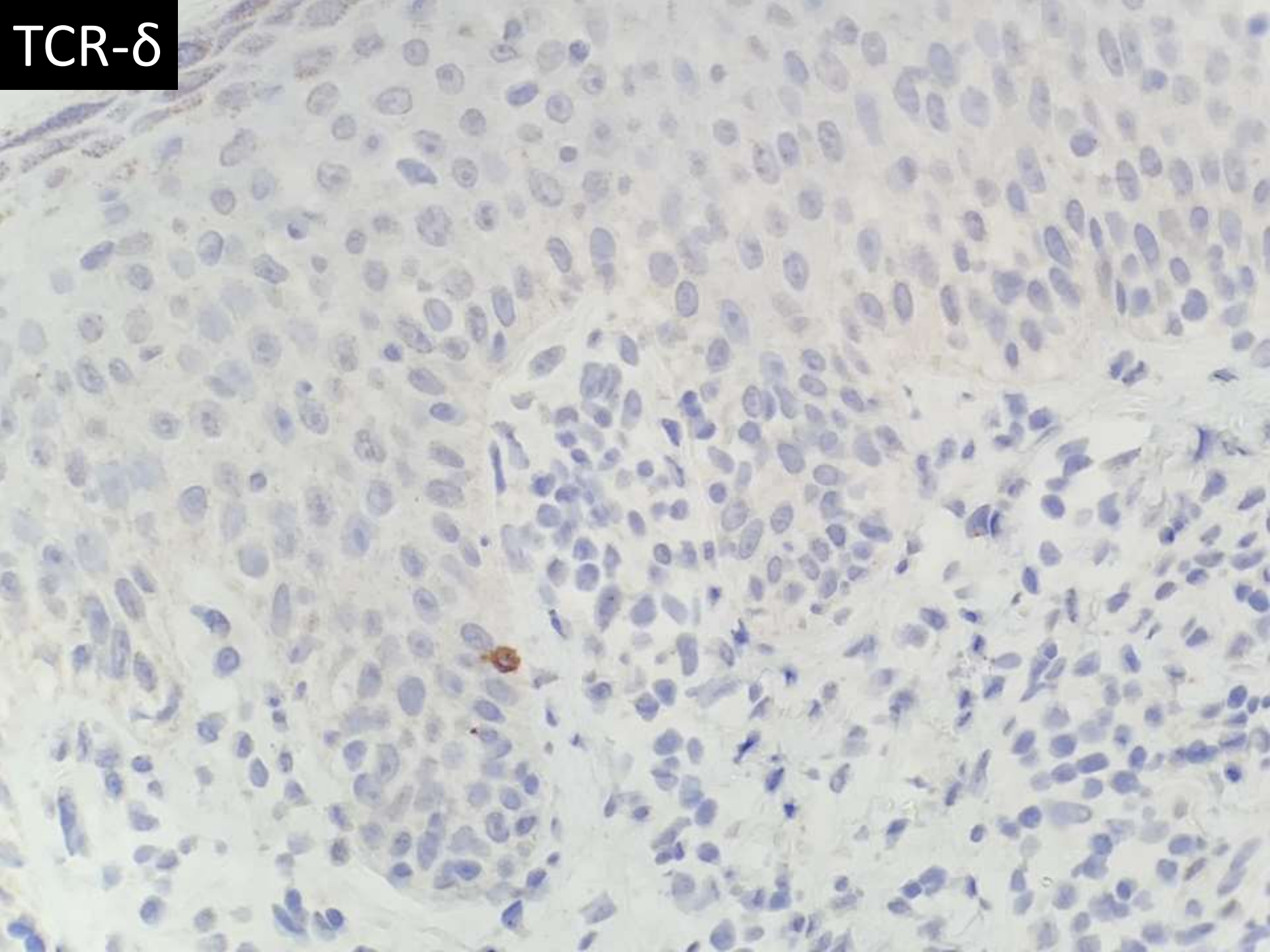
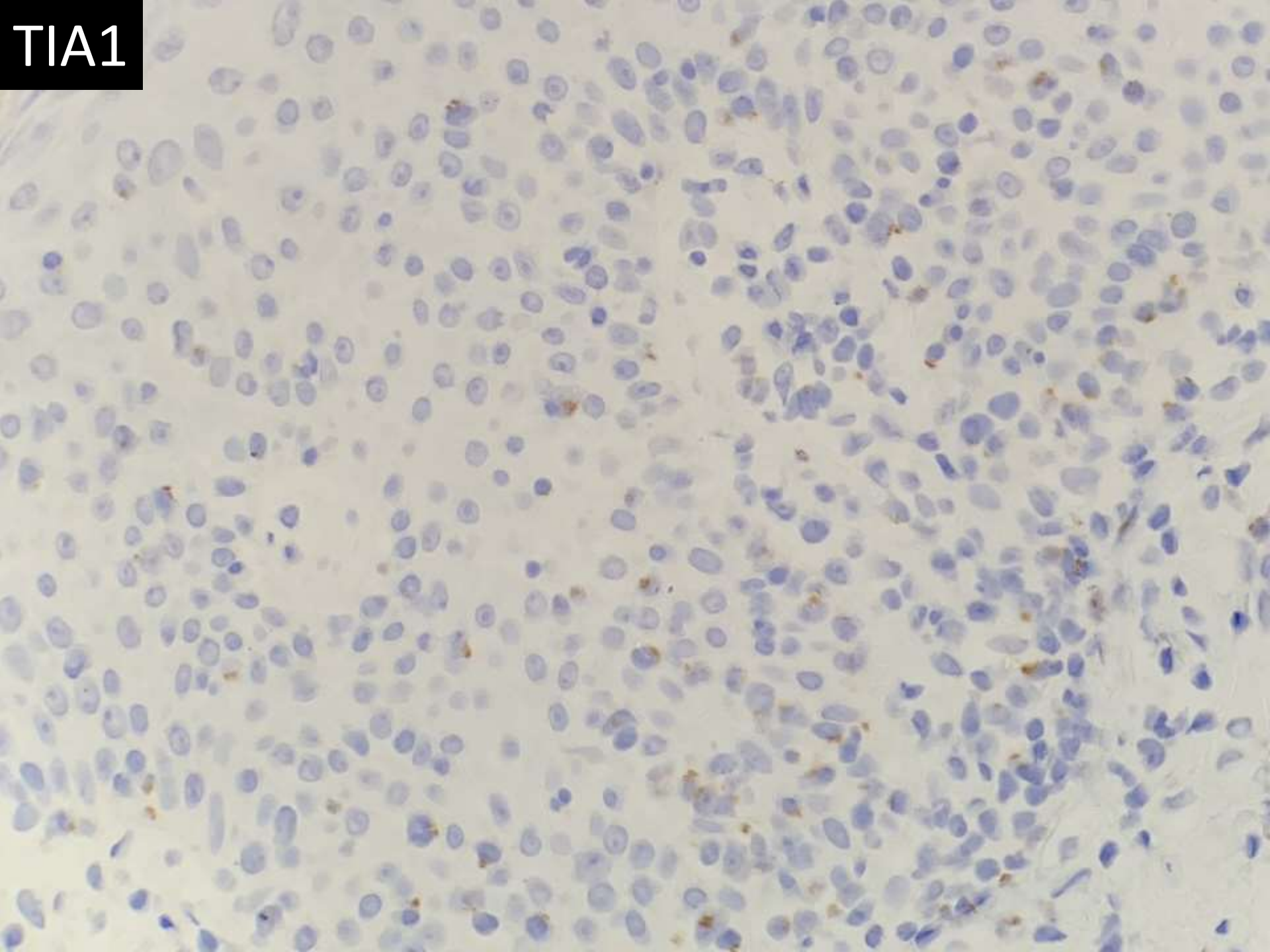

TCR-β


TCR-δ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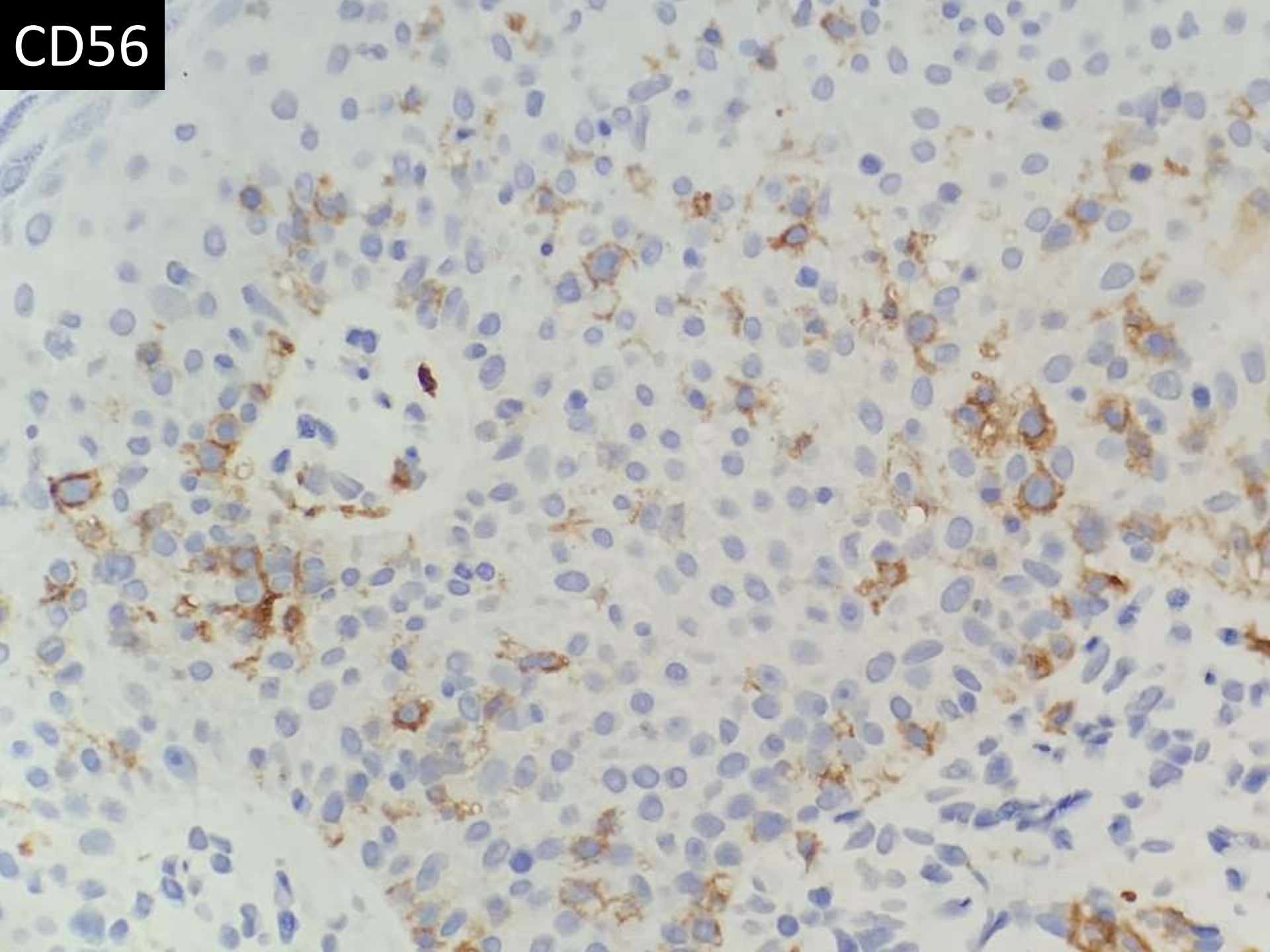
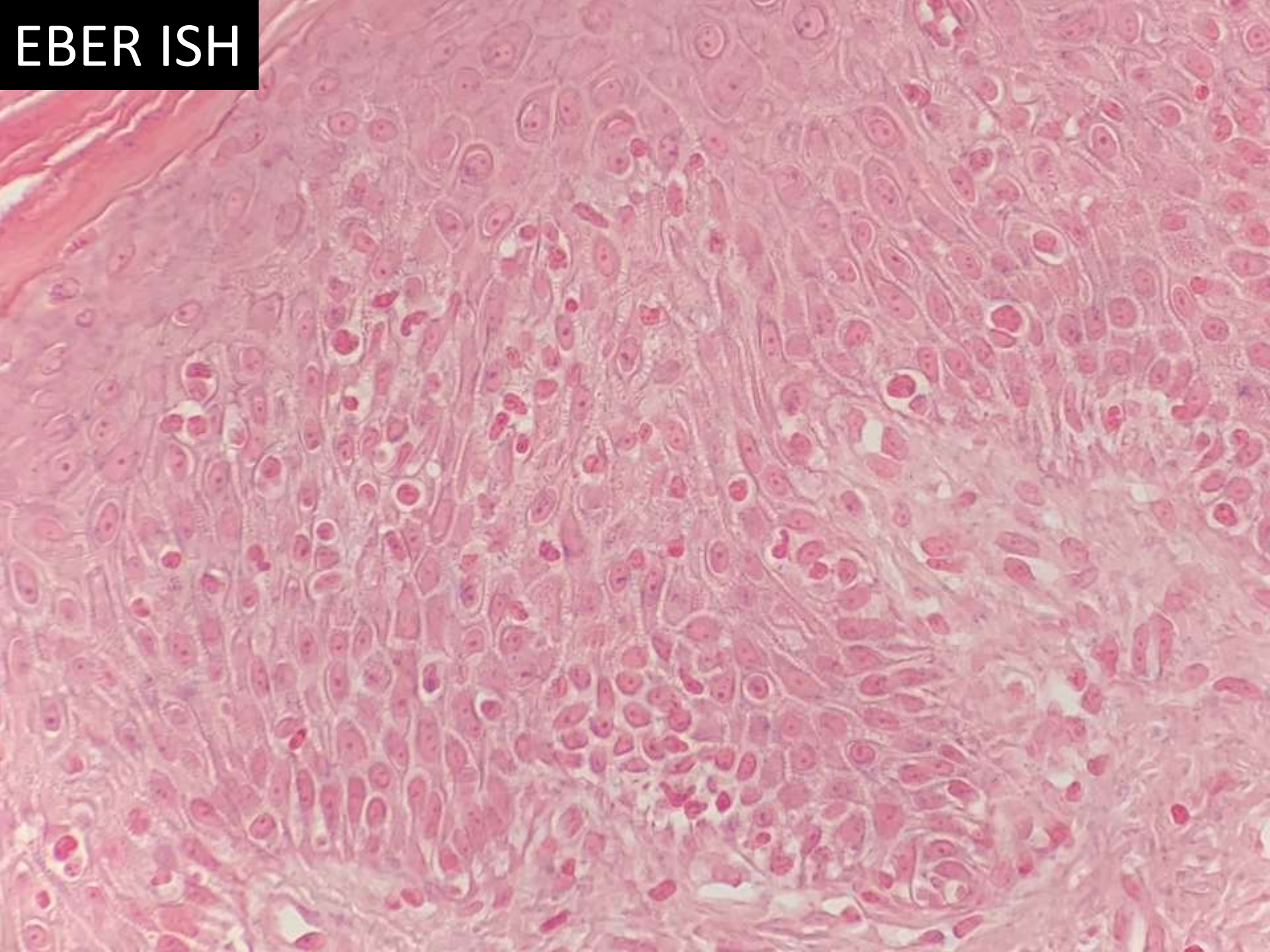
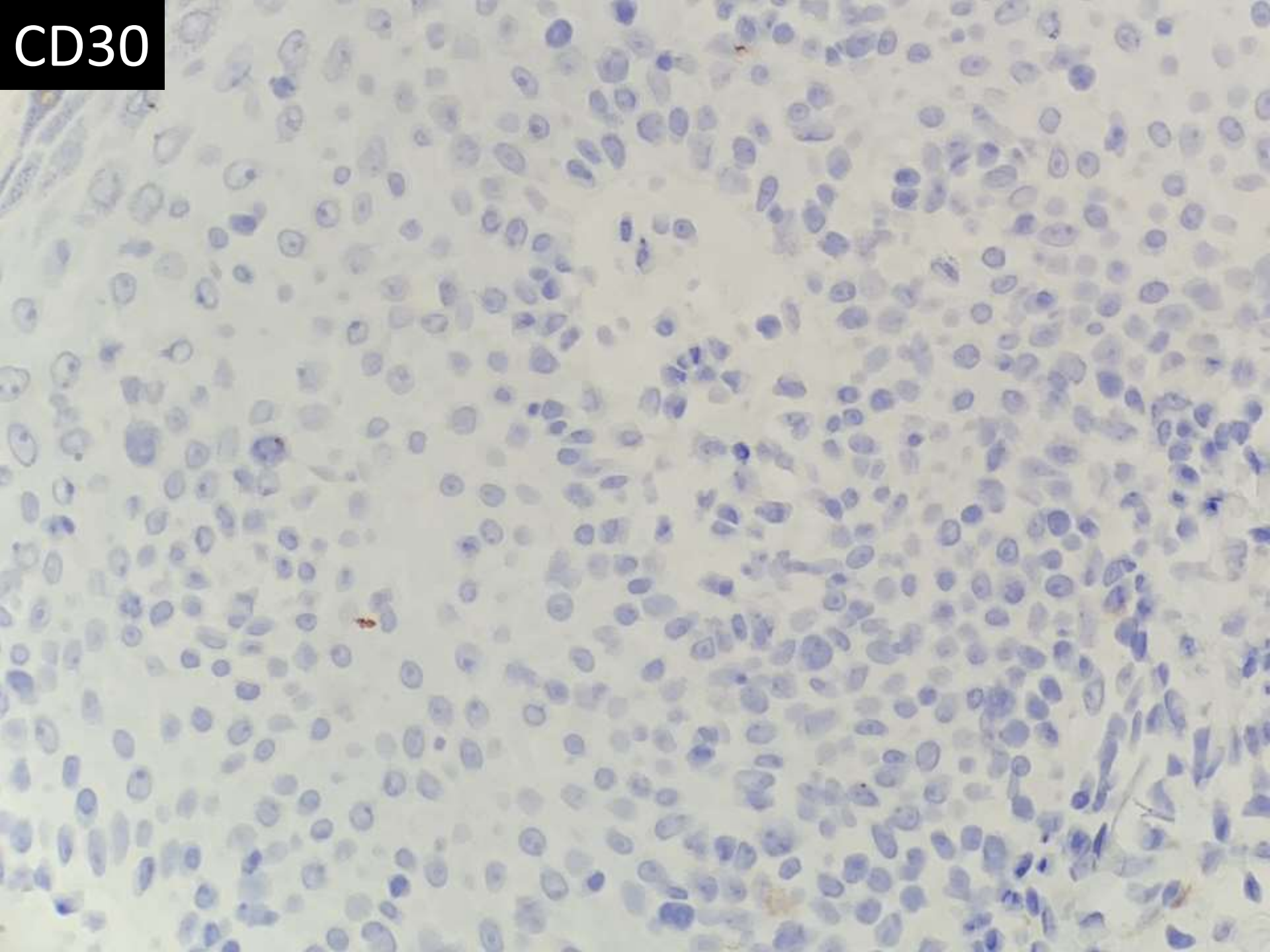
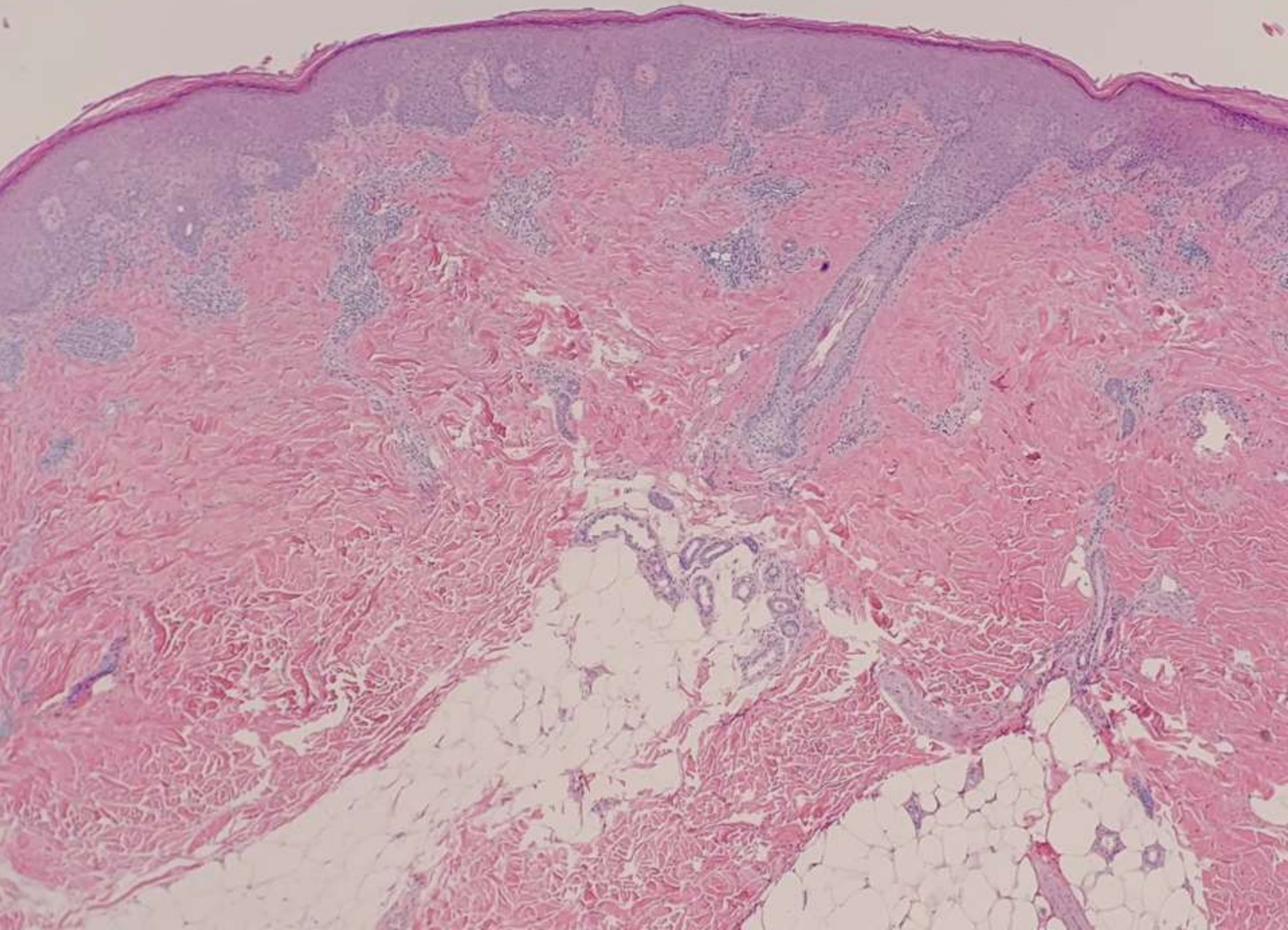
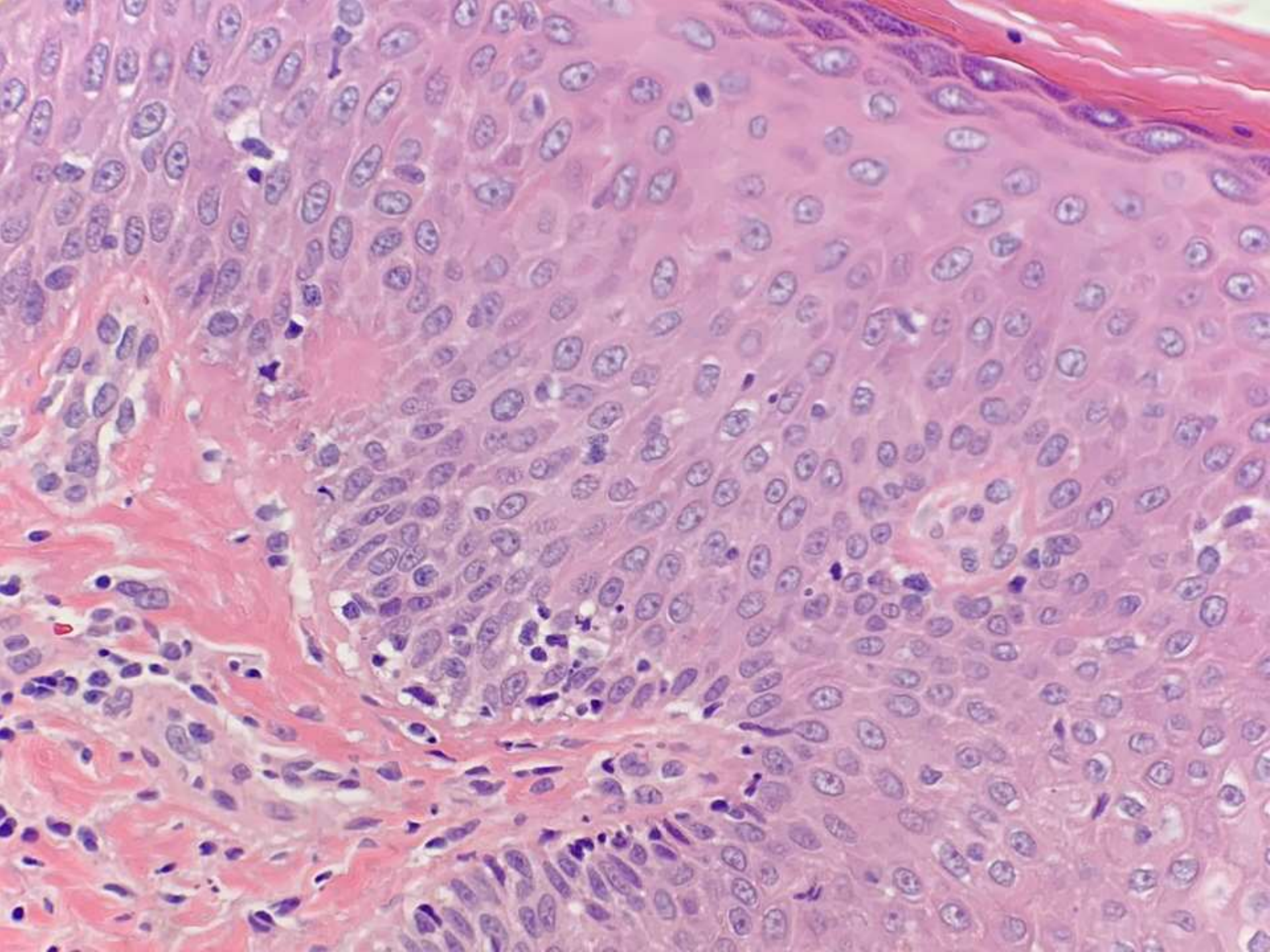
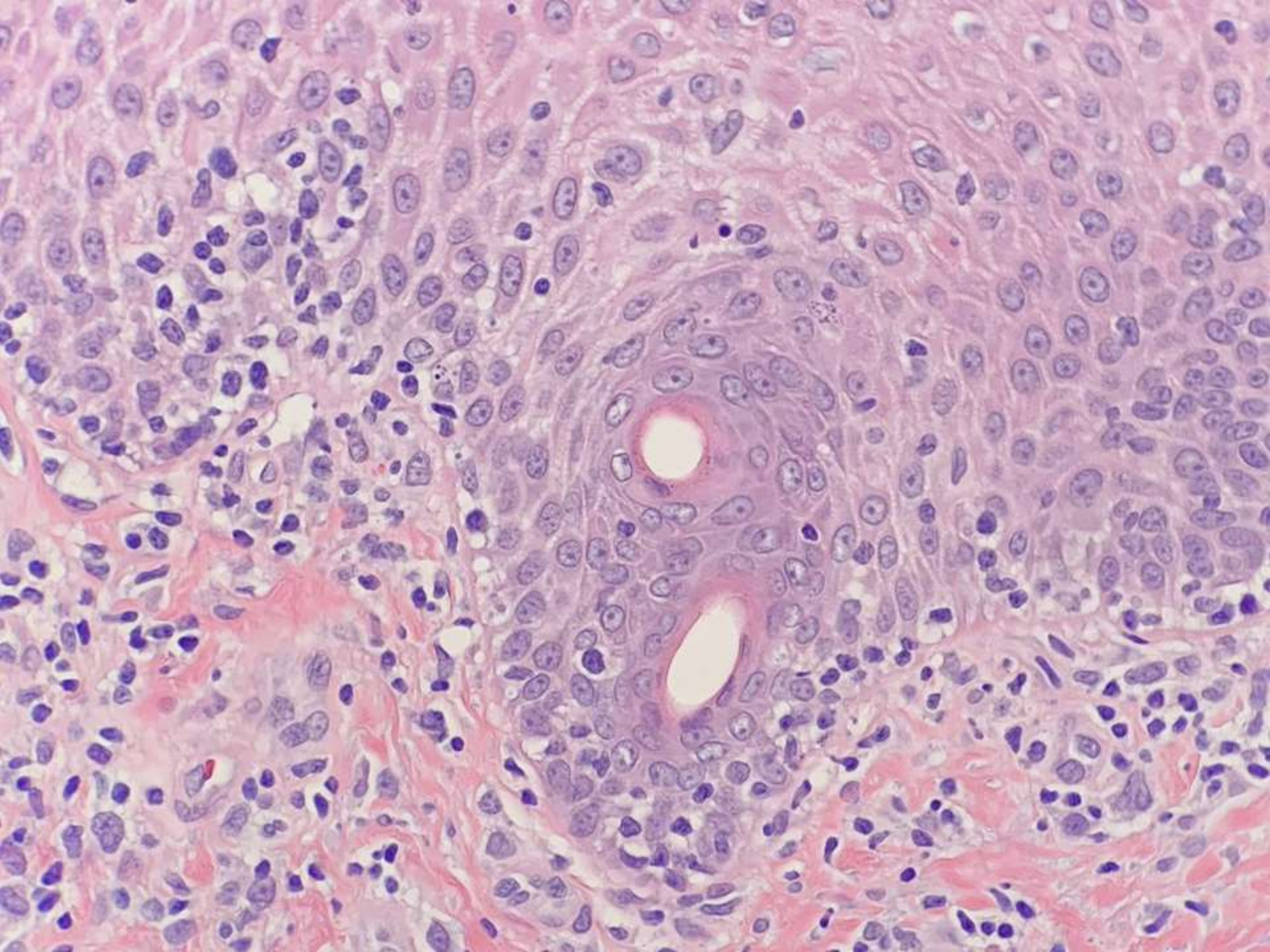

CD56

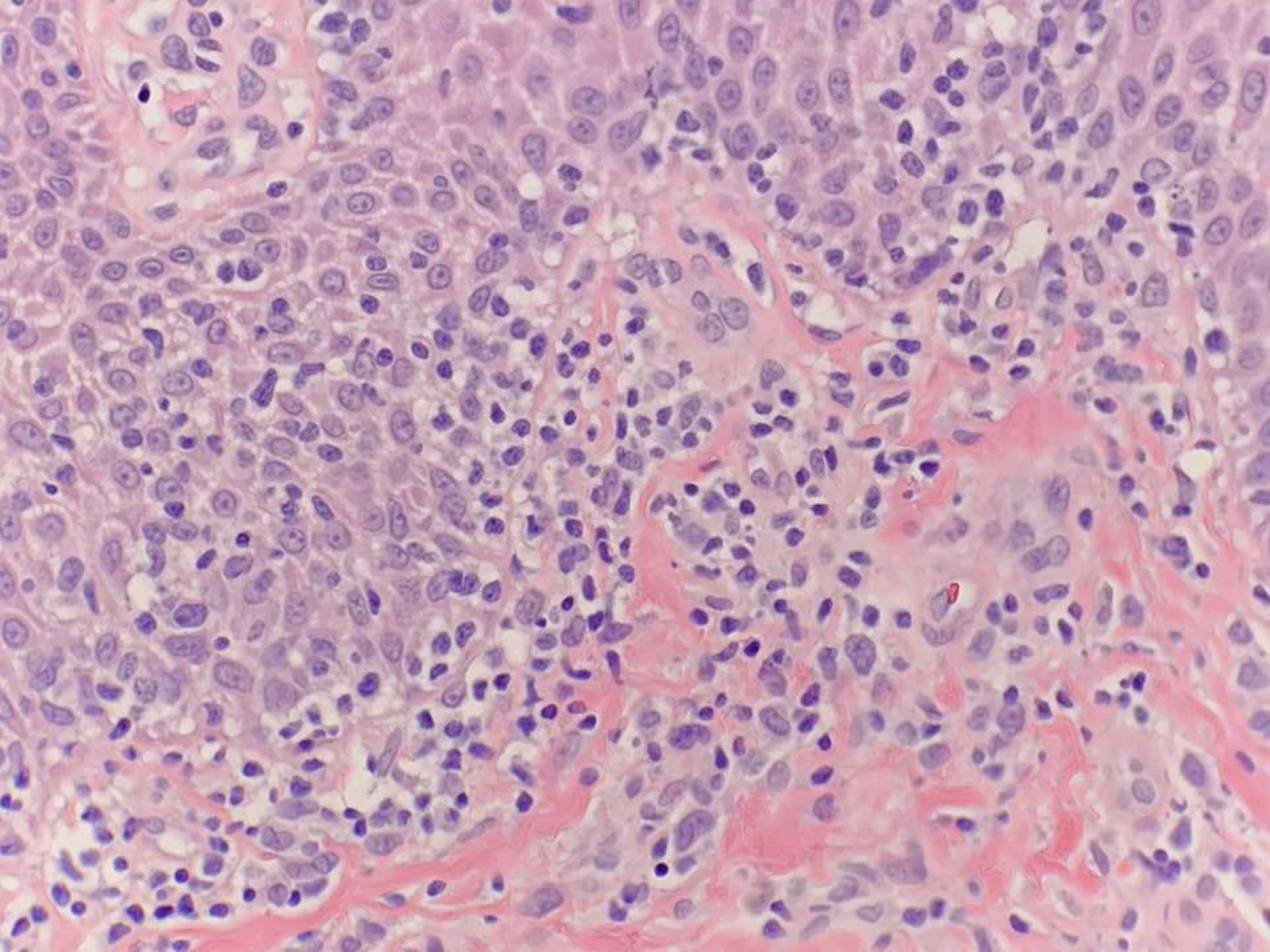

EBER ISH

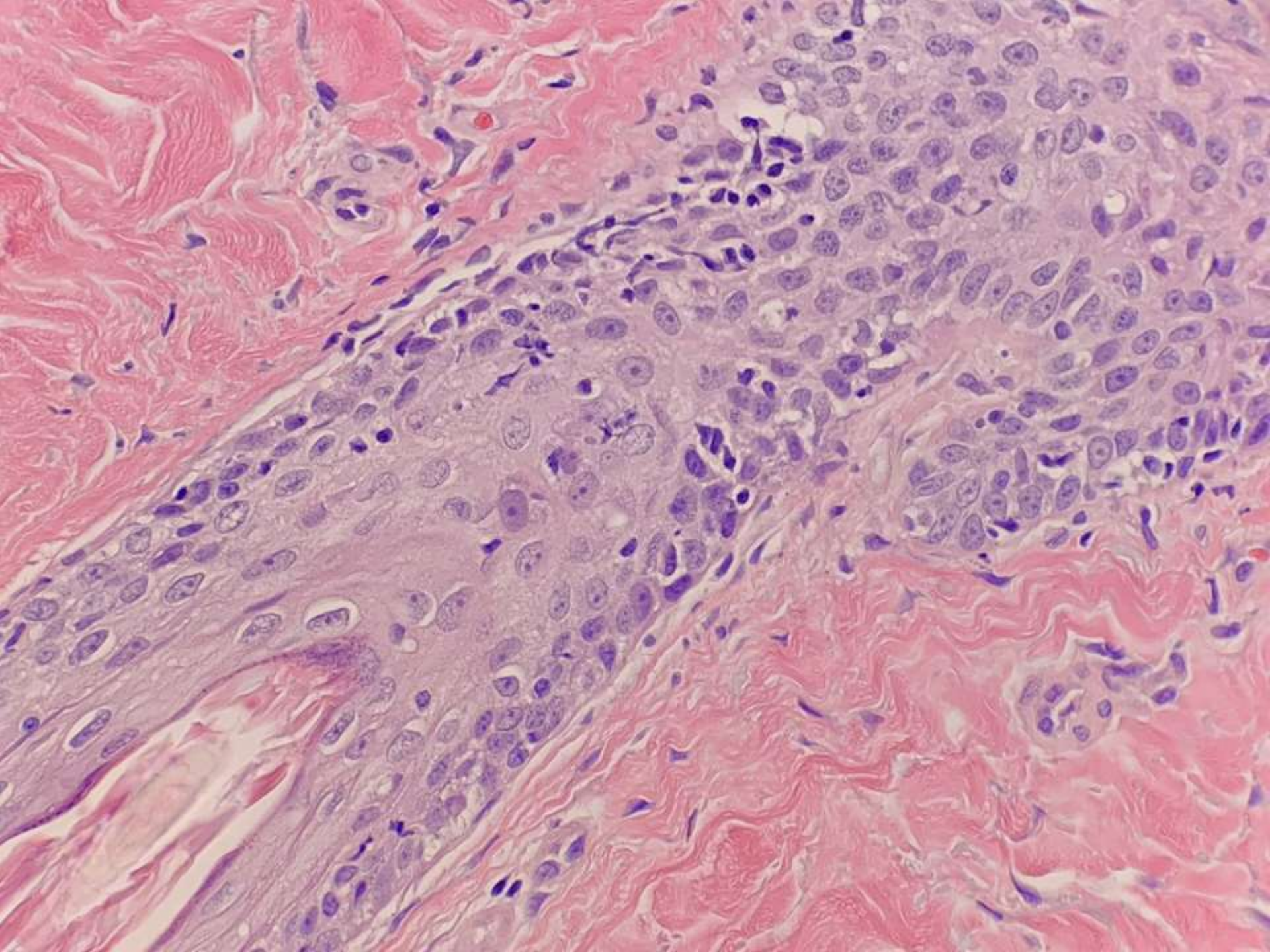

CD30

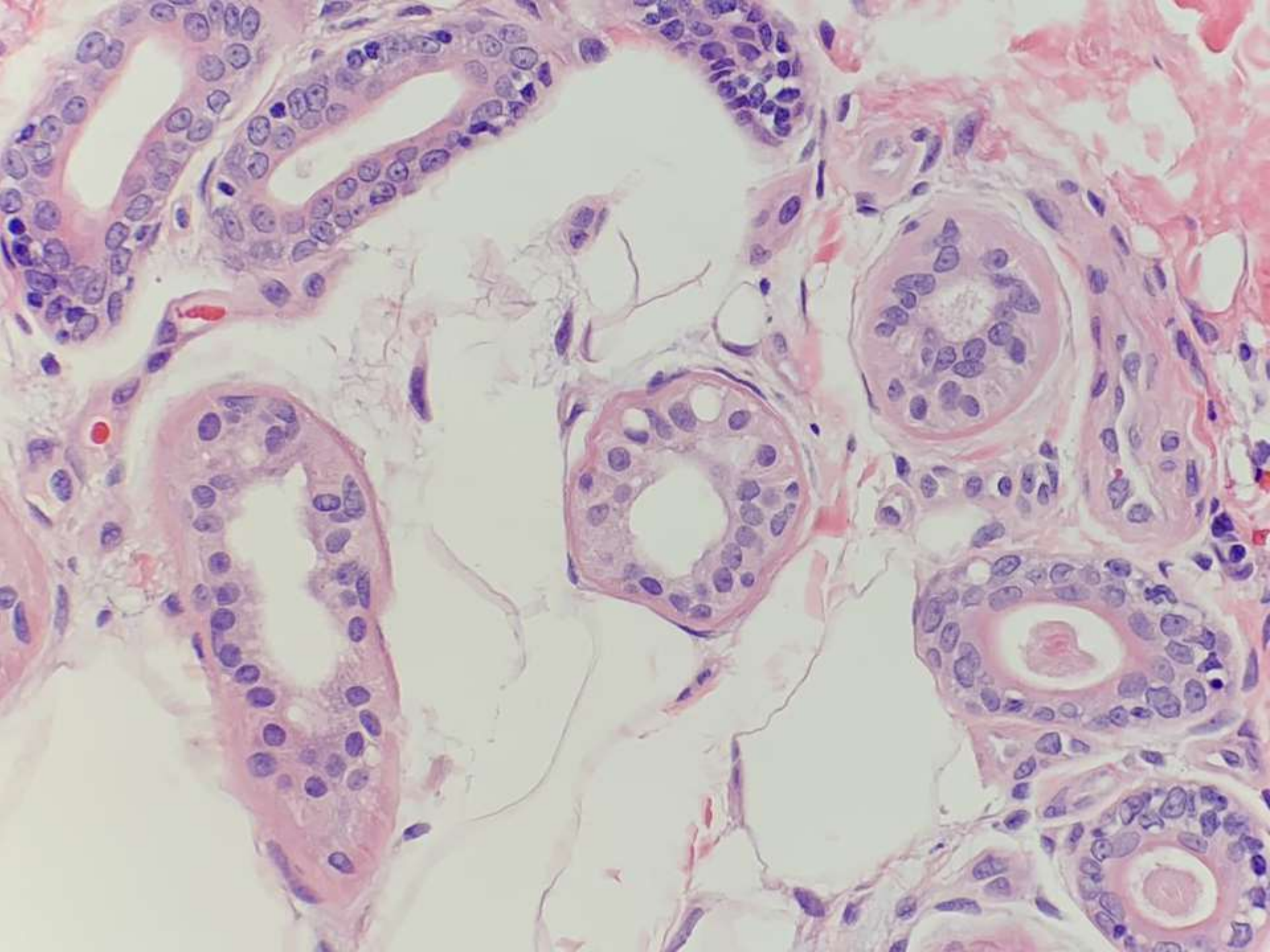


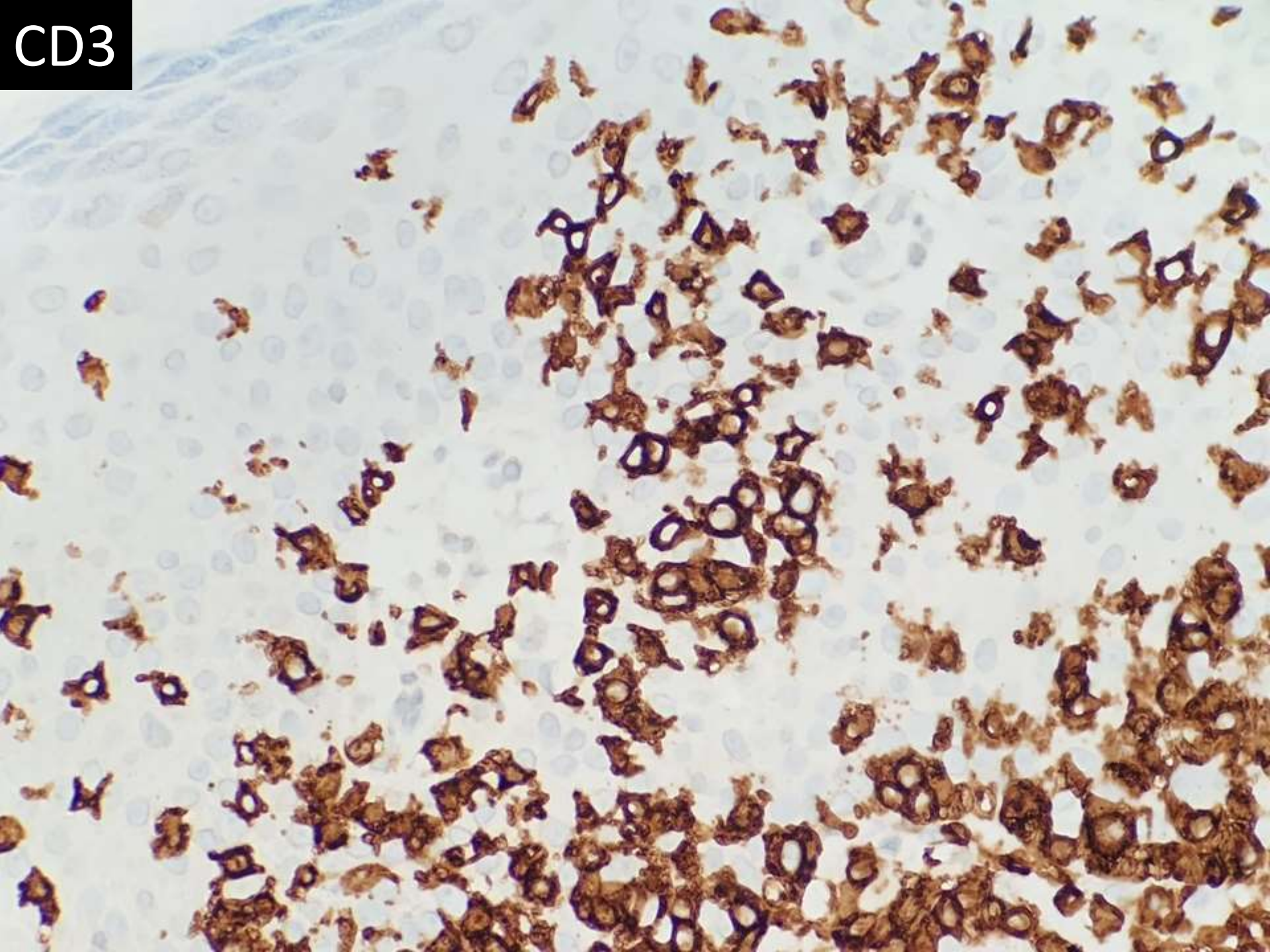








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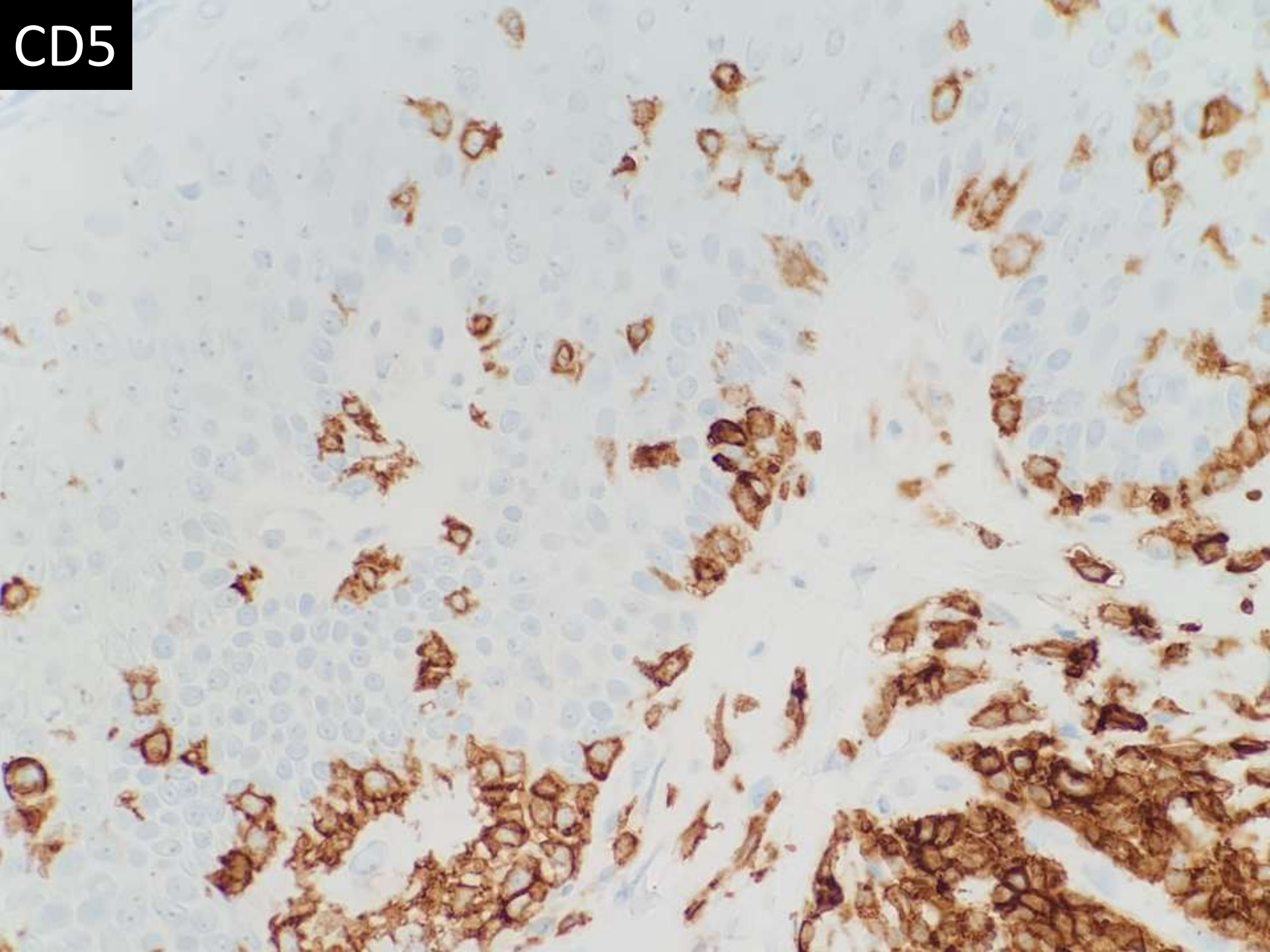
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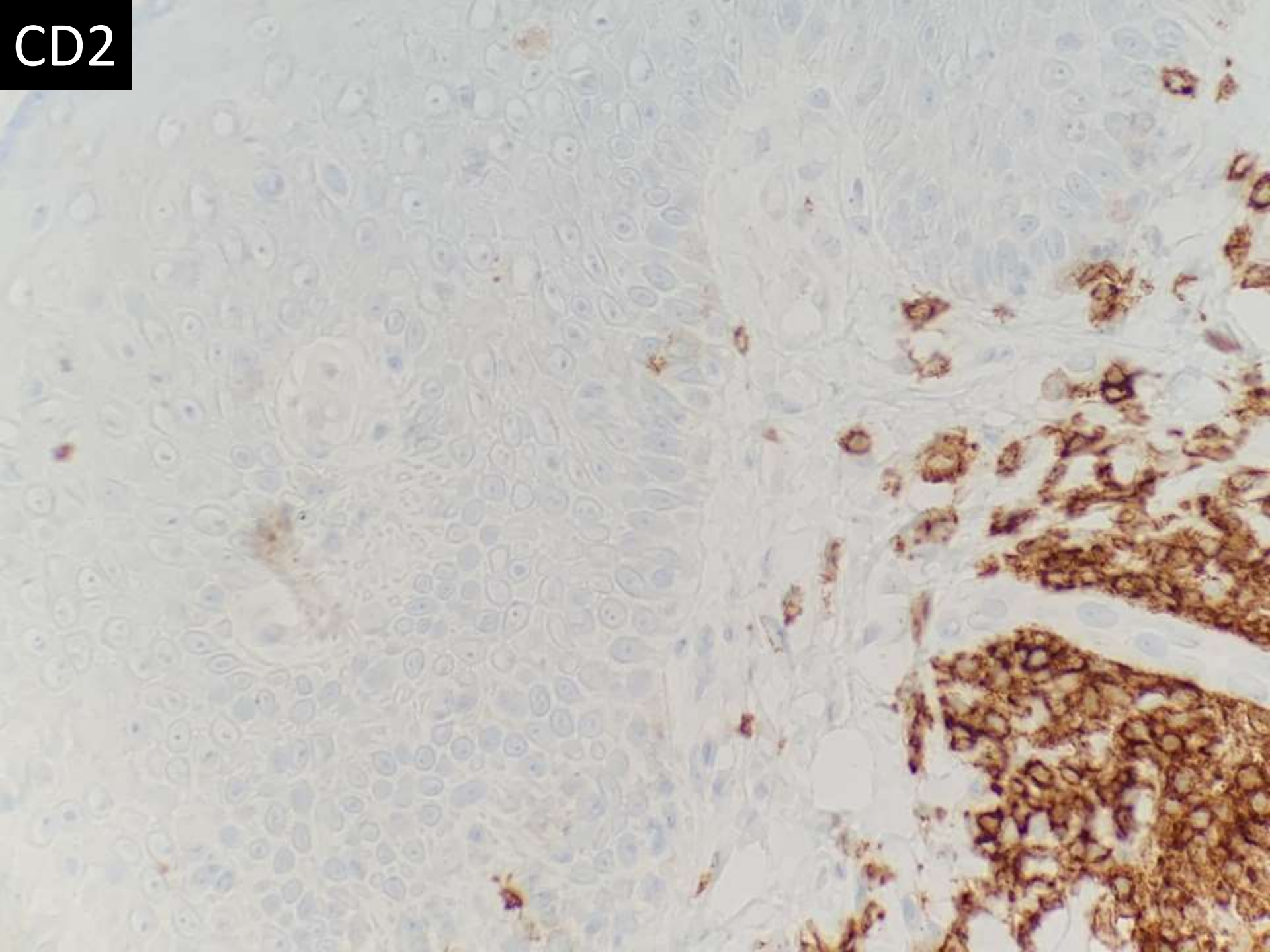
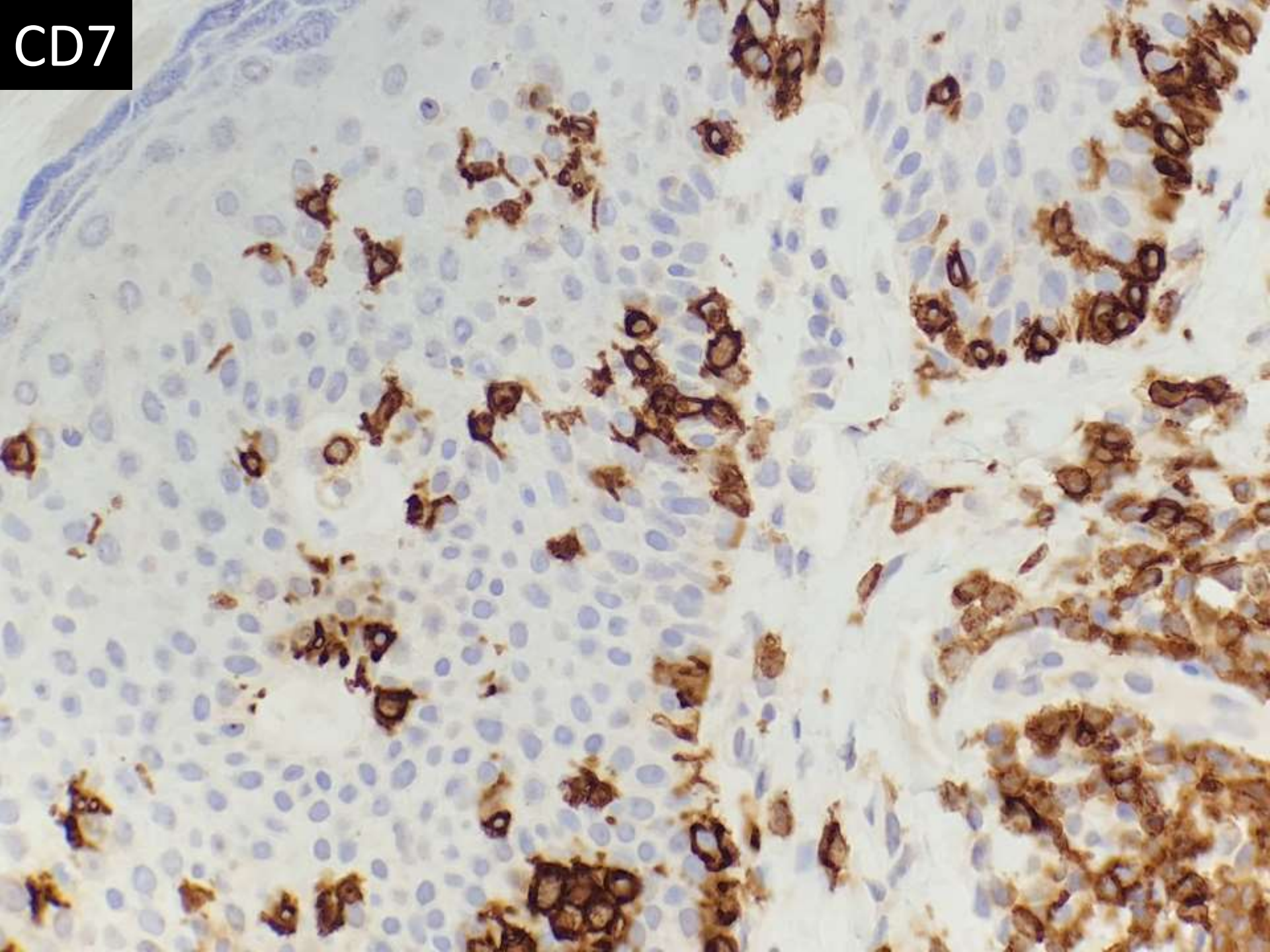
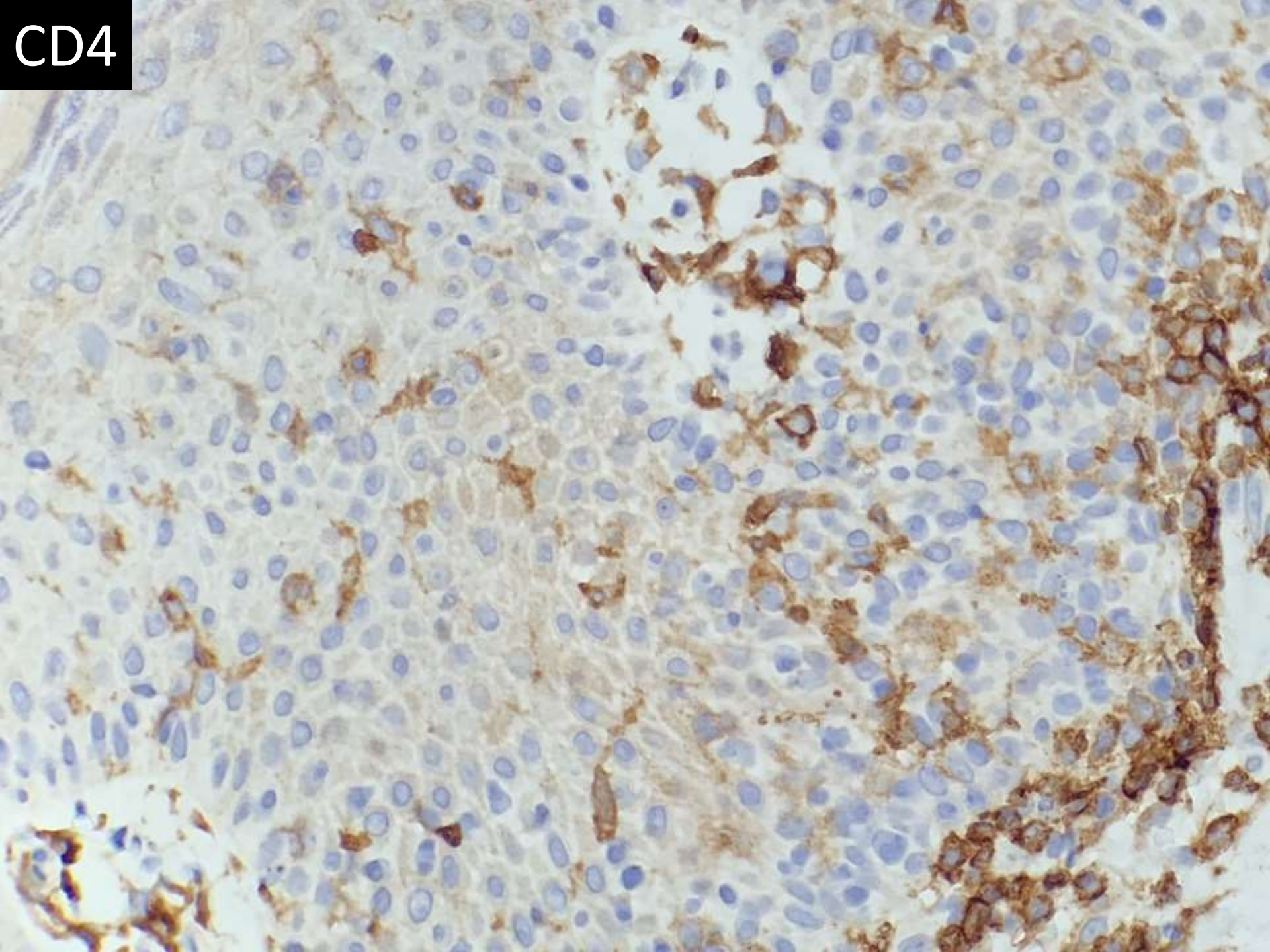

CD2


CD7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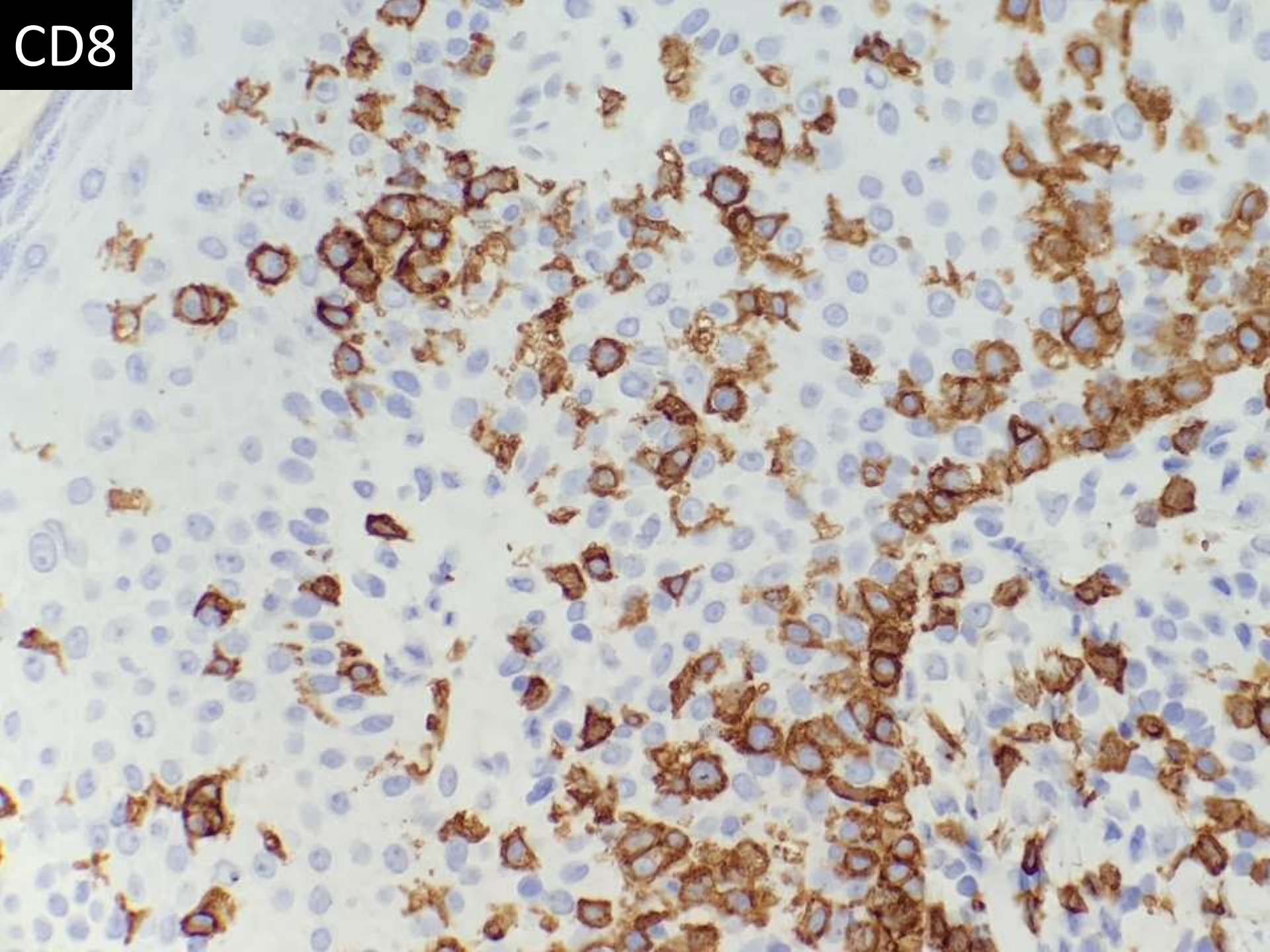
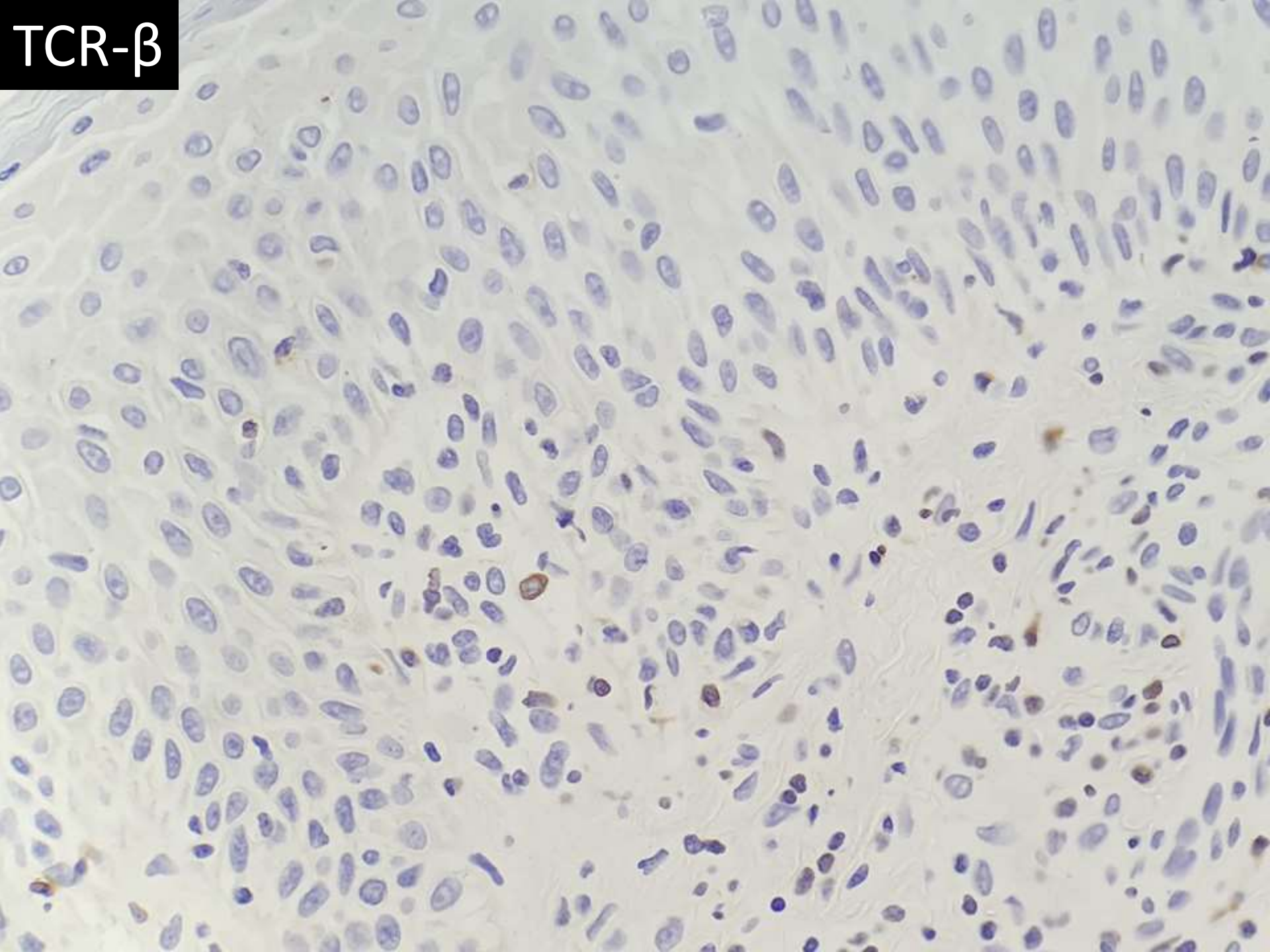
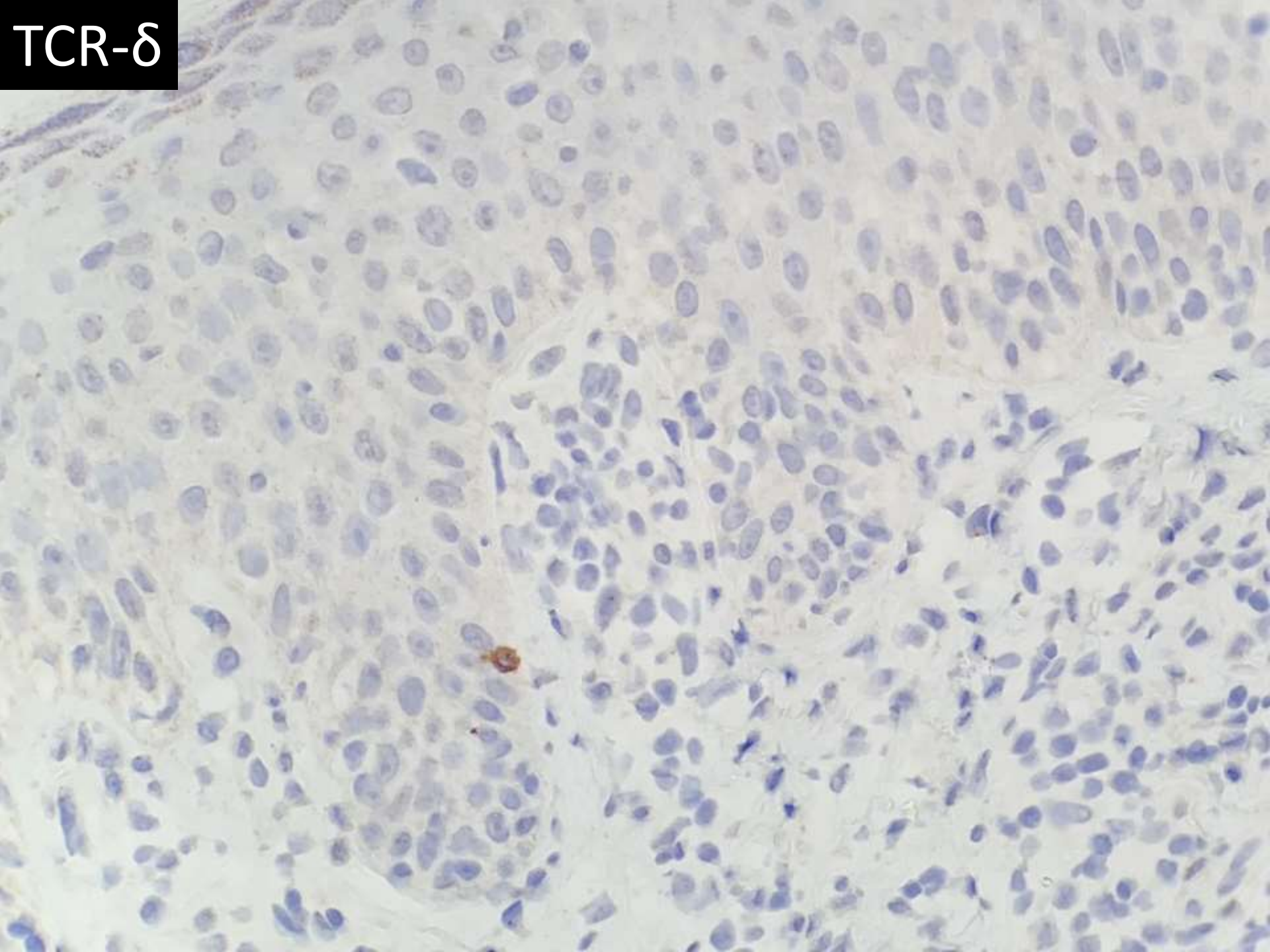
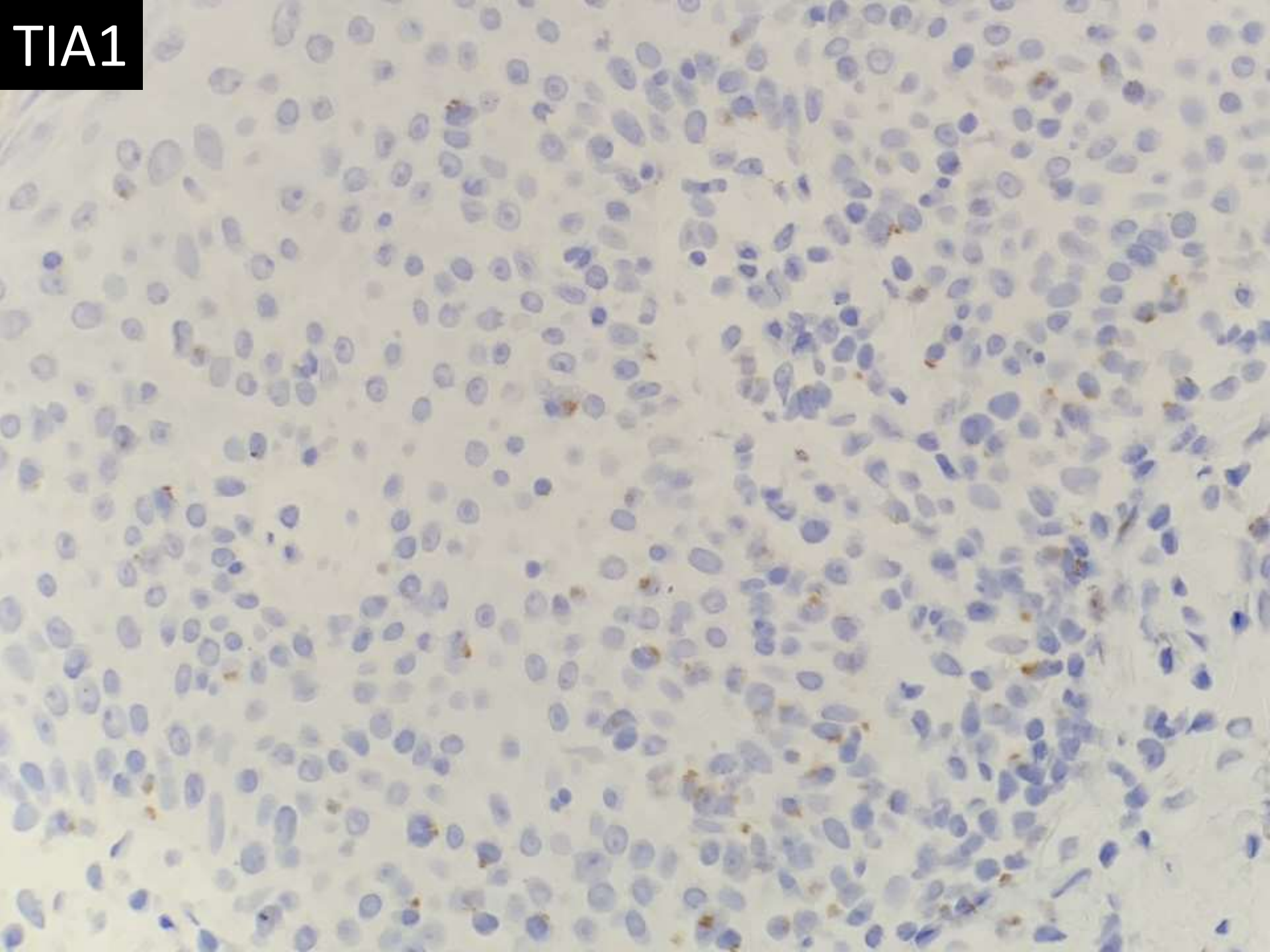

CD8


TCR-β


TCR-δ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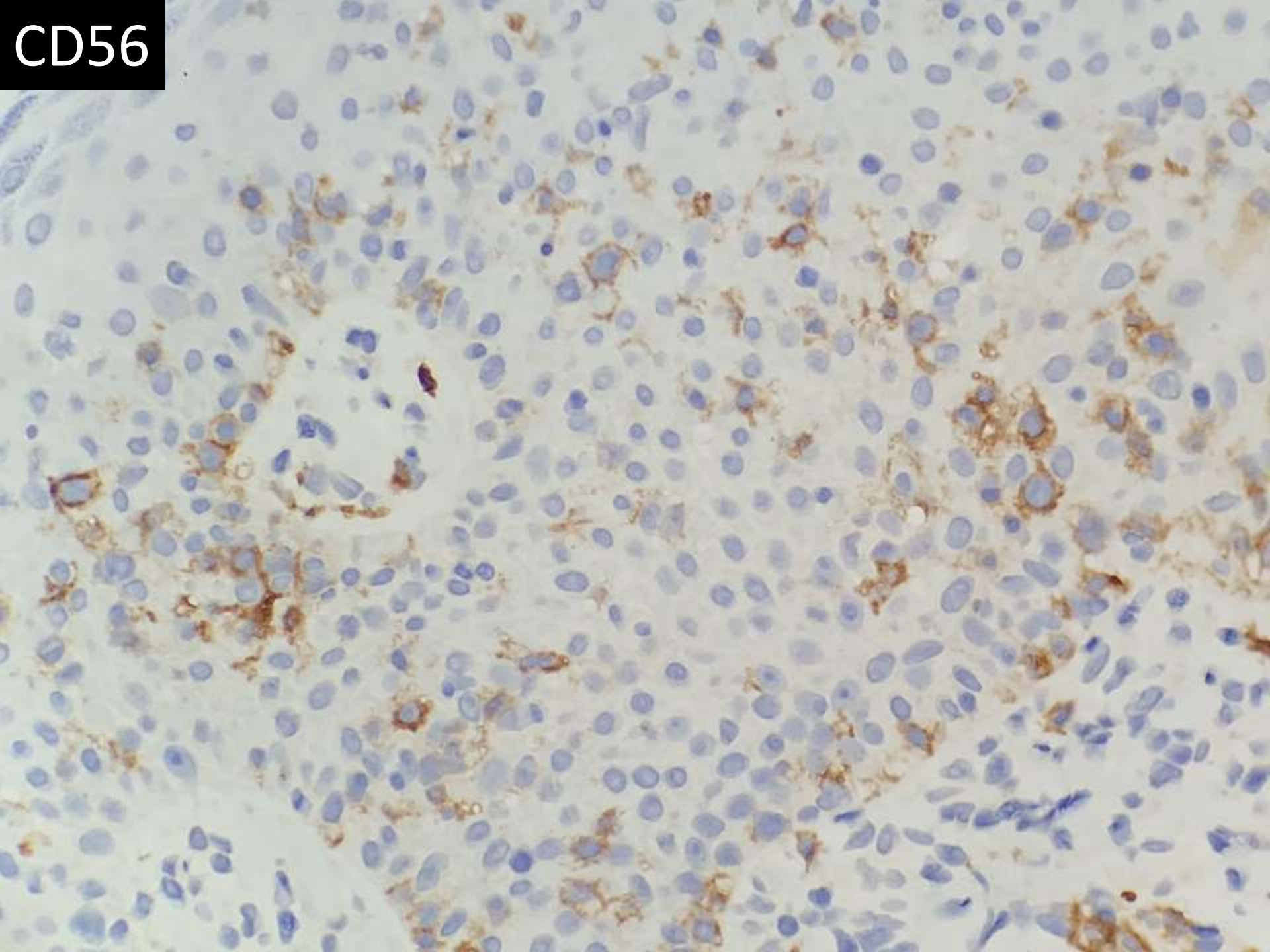
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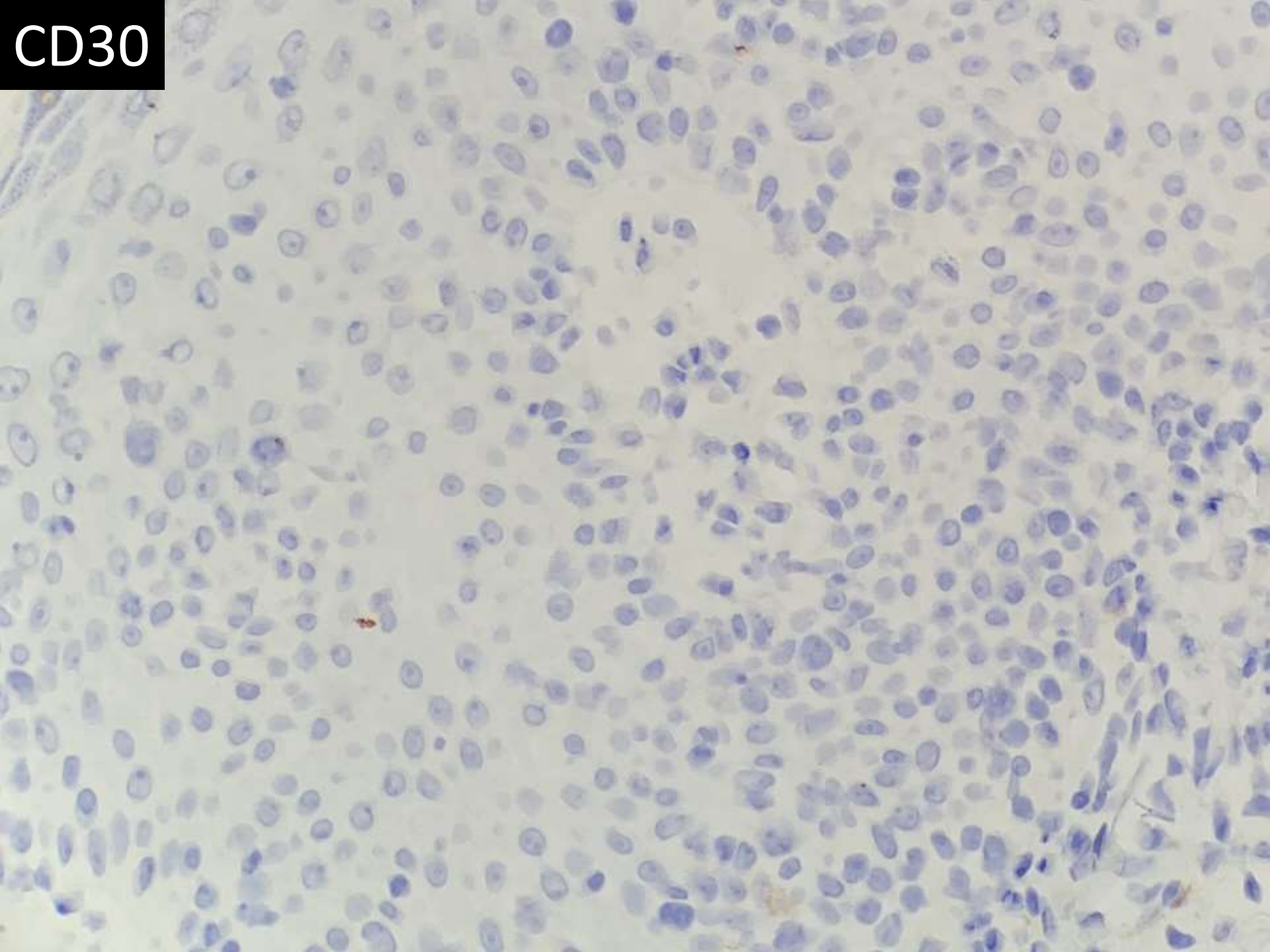
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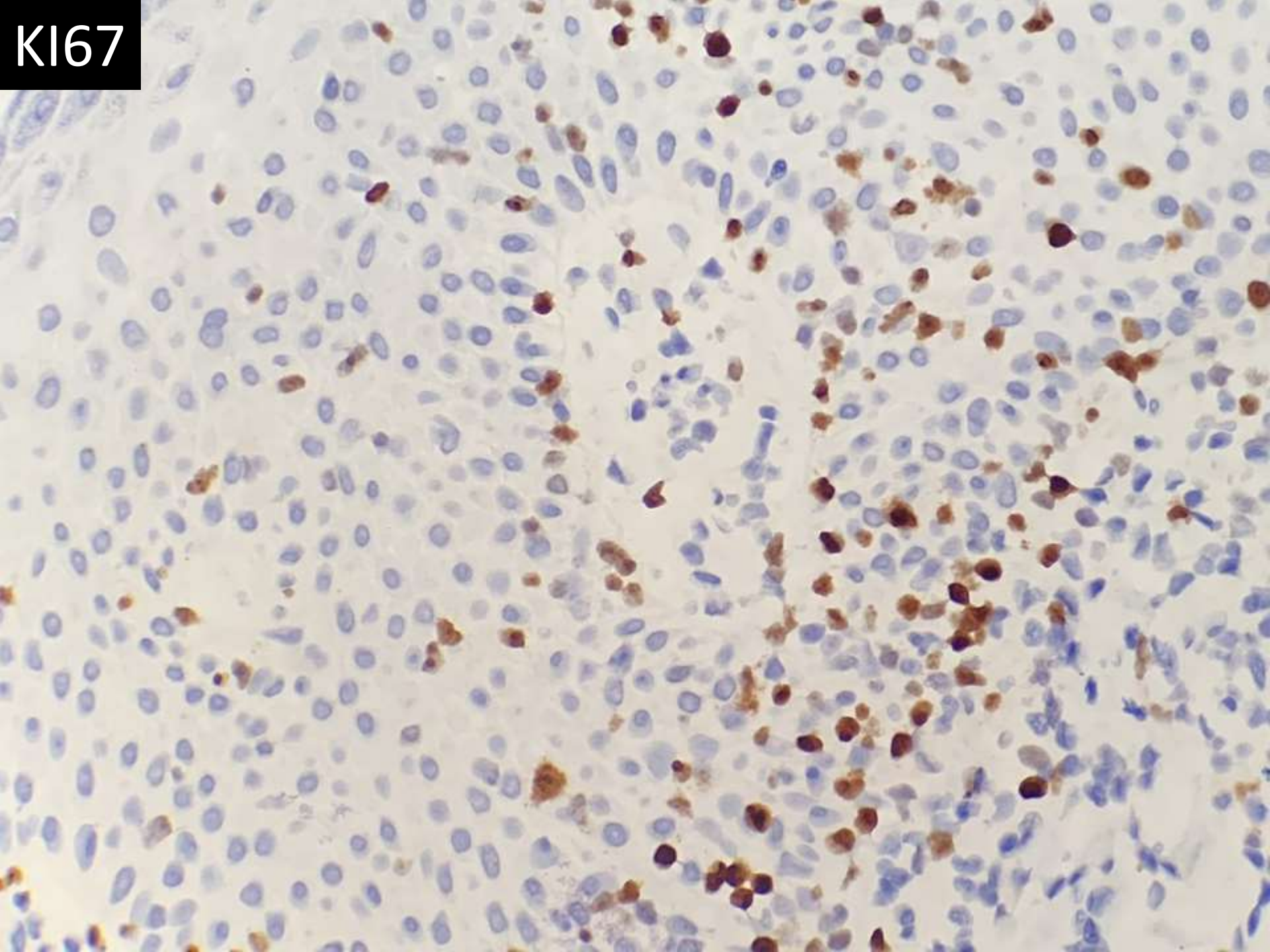
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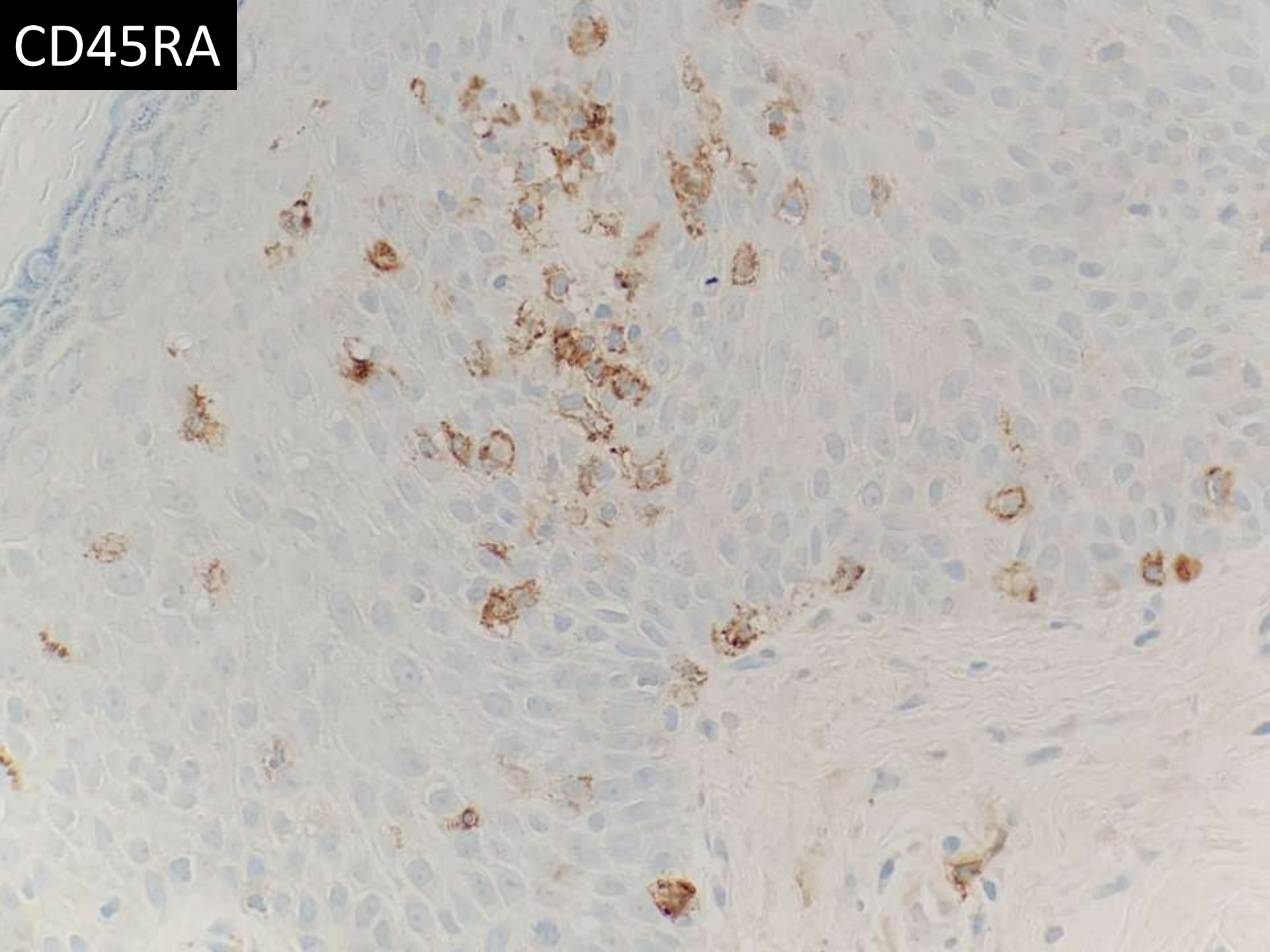
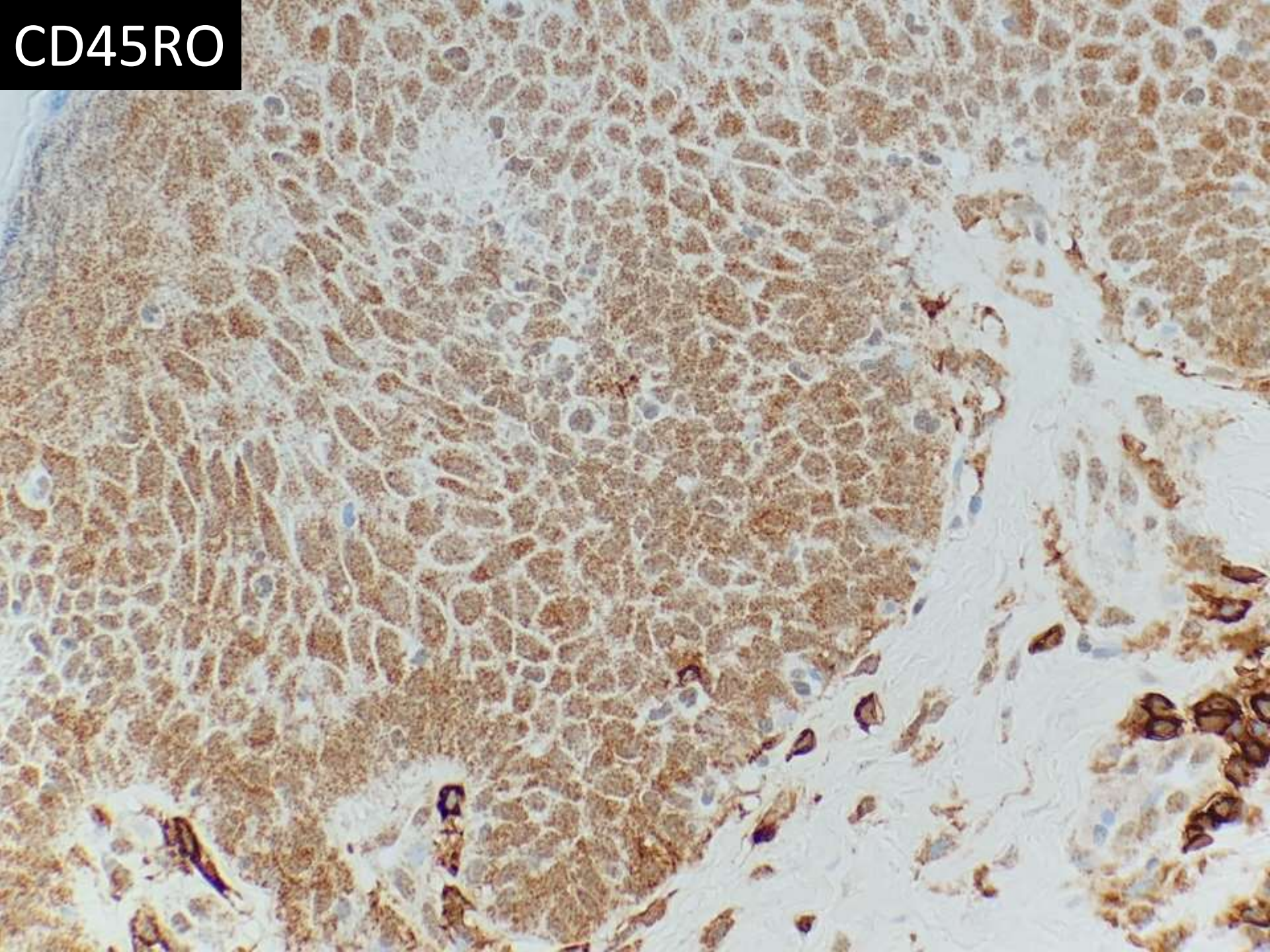
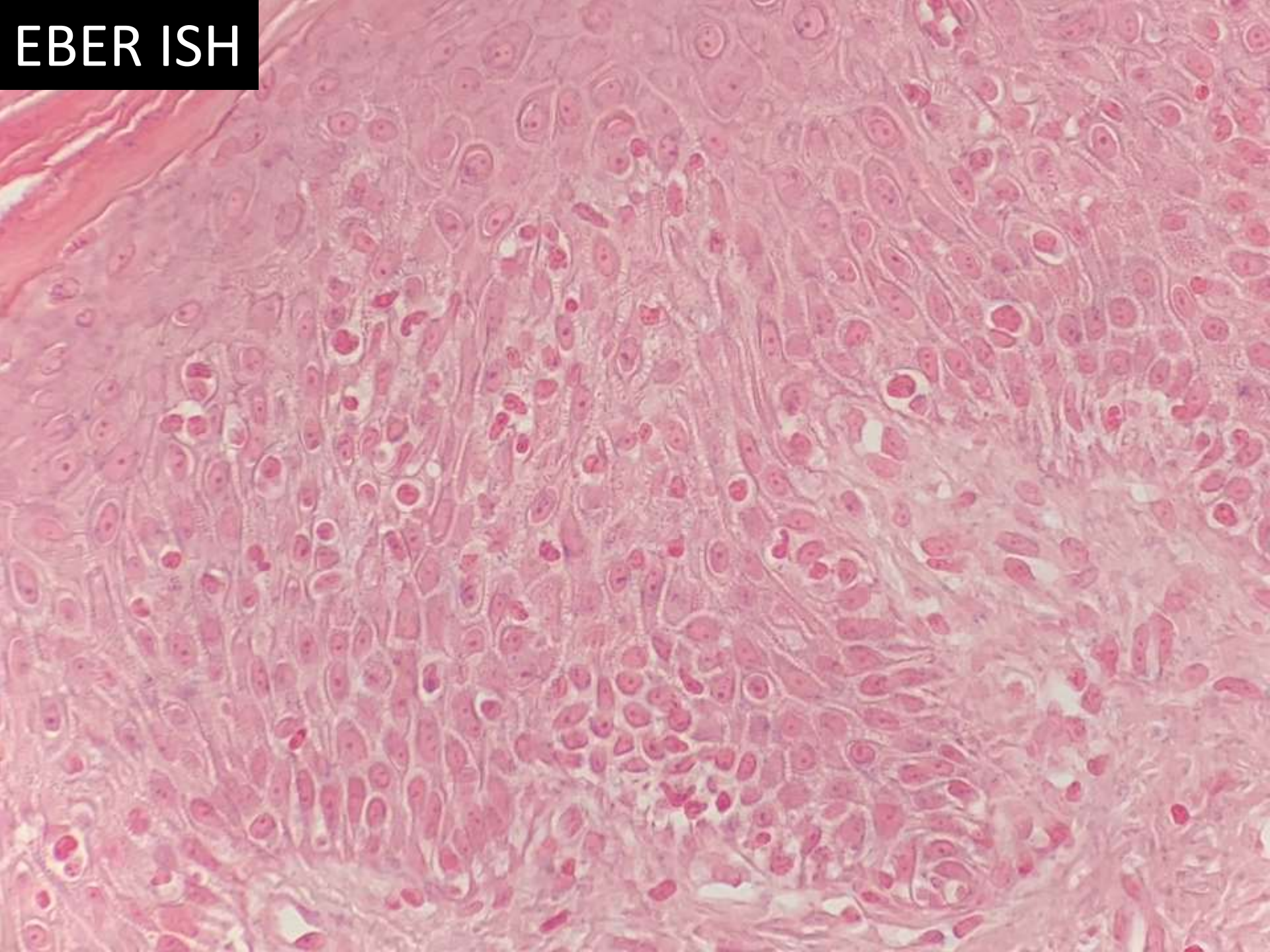

CD45RA


CD45RO


EBER ISH

# DIAGNOSIS

- CD8-positive cutaneous t-cell lymphoma with epidermotropism and cytotoxic marker expression (see comment)

- COMMENT: Although CD8+ mycosis fungoides is a consideration based on the histomorphologic appearance, the overall clinical picture (rapidly progressive diffuse patches and plaques) and immunophenotypic profile (CD3+/CD8+/CD2-/CD7+/CD45RA+/CD45RO-/TCR-beta) is worrisome for primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma. Mycosis fungoides, in contrast, is typically CD2+/CD7-/CD45RA-/CD45RO+.

# Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma

- Epidemiology
  - <1% of all cutaneous T-cell lymphomas
  - Mainly in adults
- Clinical Presentation
  - Commonly: generalized skin lesions (eruptive papules, nodules, and tumors with central ulceration and necrosis)
  - Less frequently: localized ulcerated nodules, tumors, or plaques
  - May disseminate to viscera ; lymph nodes typically spared

# Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma

- Histopathology
  - Small -to-medium or medium-to-large with pleomorphic or blastic nuclei
  - Variably prominent epidermotropism
  - +/- epidermal necrosis, ulceration, and blistering
- Immunophenotype
  - +: CD3, CD8, TCR-beta, CD45RA, TIA1, granzyme B, perforin
  - +/-: CD7
  - -/+: CD5, CD4, CD30 (not diffuse)
  - -: CD2, TCR-delta, CD45RO, EBER ISH

# Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma

- Differential diagnosis
  - Mycosis fungoides (may be CD8+ and express cytotoxic markers)
    - Slow progression (years to decades): patches→plaques→tumors
    - Typically CD2+/CD7-/CD45RA-/CD45RO+
  - Lymphomatoid papulosis, type D (CD30+, CD8+)
    - Many relapsing-remitting papular, papulonecrotic, or nodular skin lesions in various stages
    - CD30-positive (diffuse, strong)
  - Primary cutaneous γδ T-cell lymphoma
    - TCR-delta positive, TCR-beta negative

# Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma

- Prognosis
  - Aggressive: median survival 12 months
  - No known difference in survival between small-to-medium and medium-to-large cytomorphology or between localized and diffuse disease involvement