South Bay Pathology Society
October 2024

Disclosures
October 7, 2024

The activity planners and faculty listed below have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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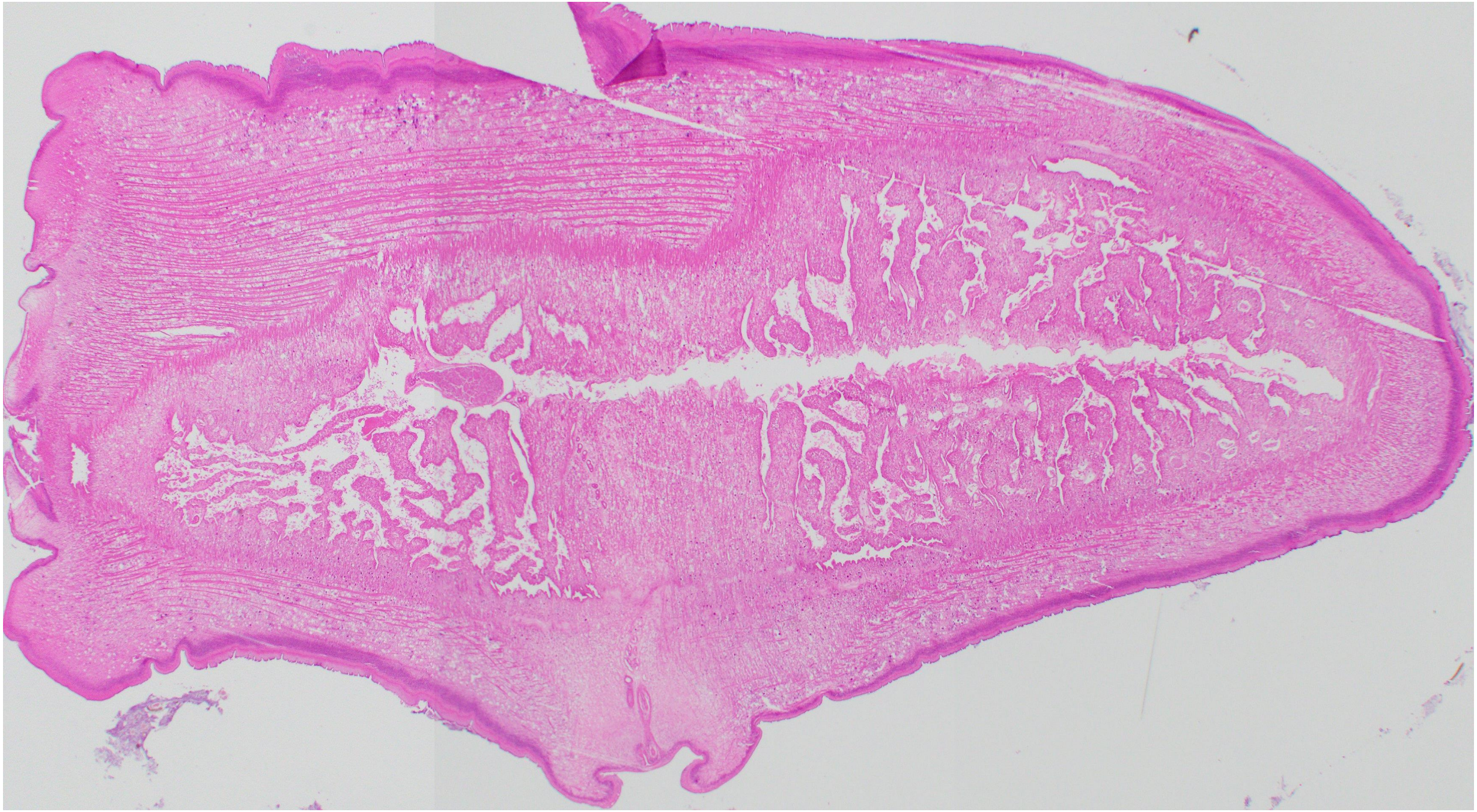
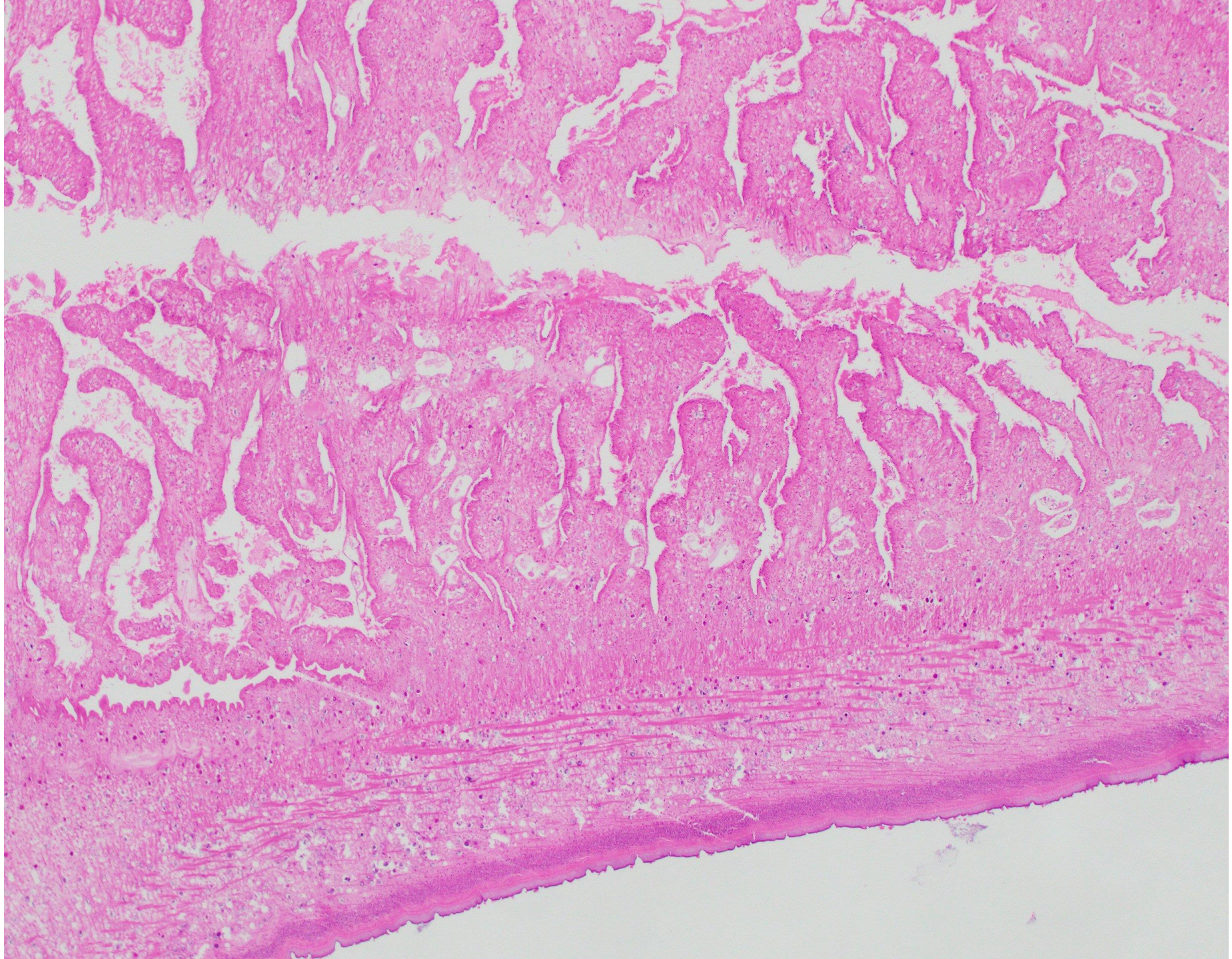
24-1001

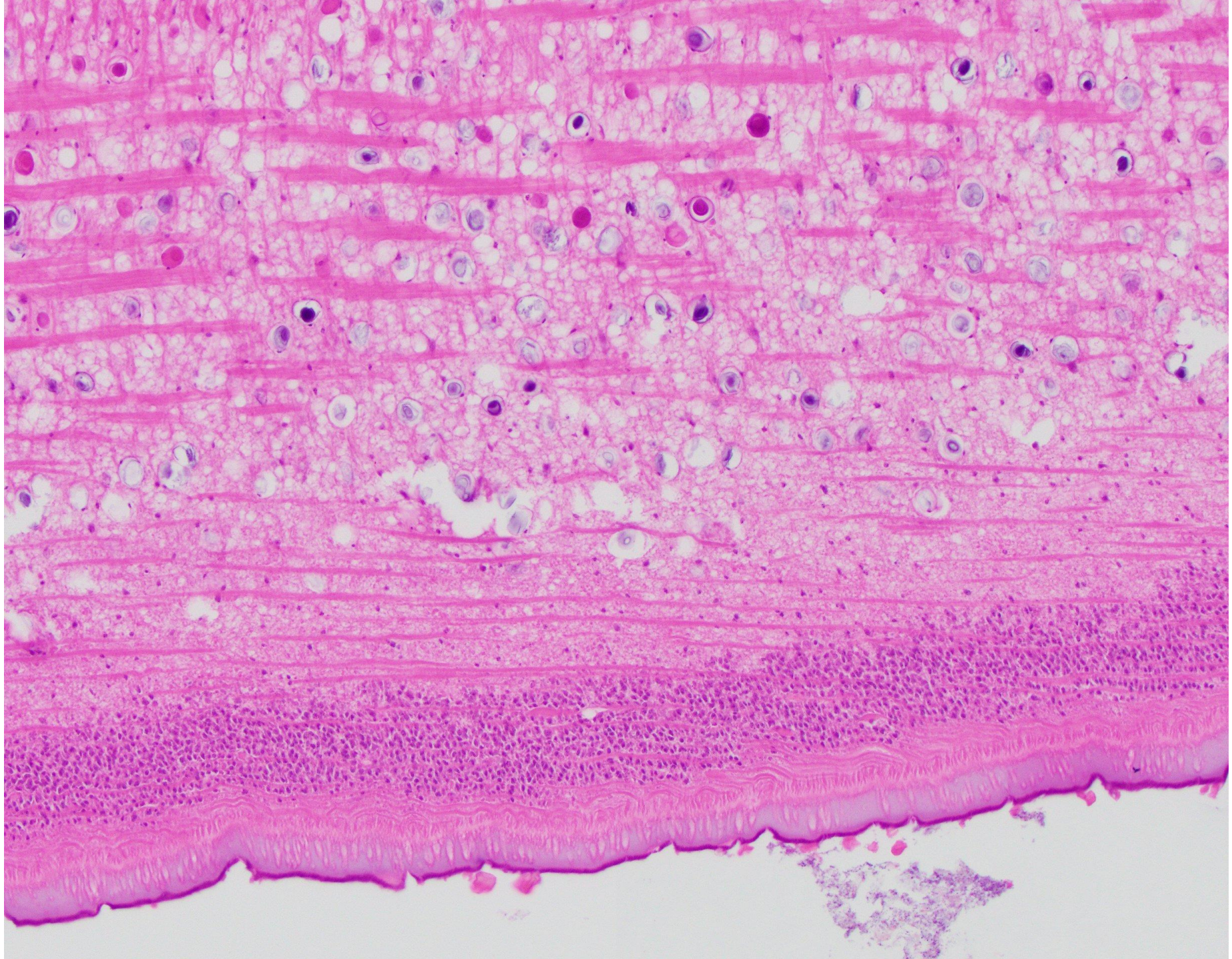
24-1001 - Anne Cheng and Hubert Lau: Stanford and Palo Alto VA

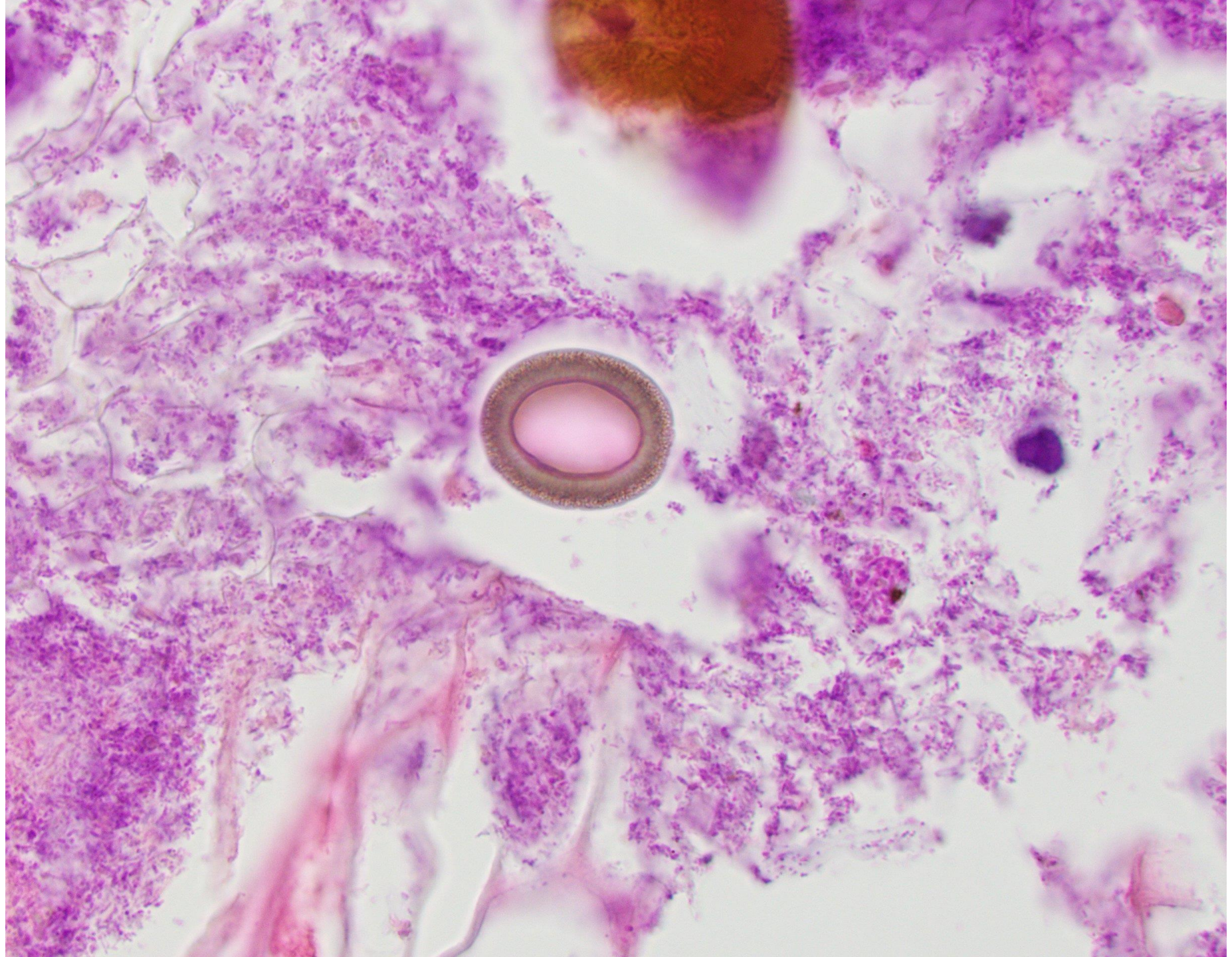
~50-year-old man who contacted his primary care provider about gas and something “coming from my anus and moving down my leg.” Recent travel to Ethiopia. Endorses upset stomach, nausea, and diarrhea while he was there. CBC shows microcytic RBCs (MCV 71 fL) and mild relative monocytosis (11%) and eosinophilia (9%). Stool sample sent for surgical pathology.


1 cm

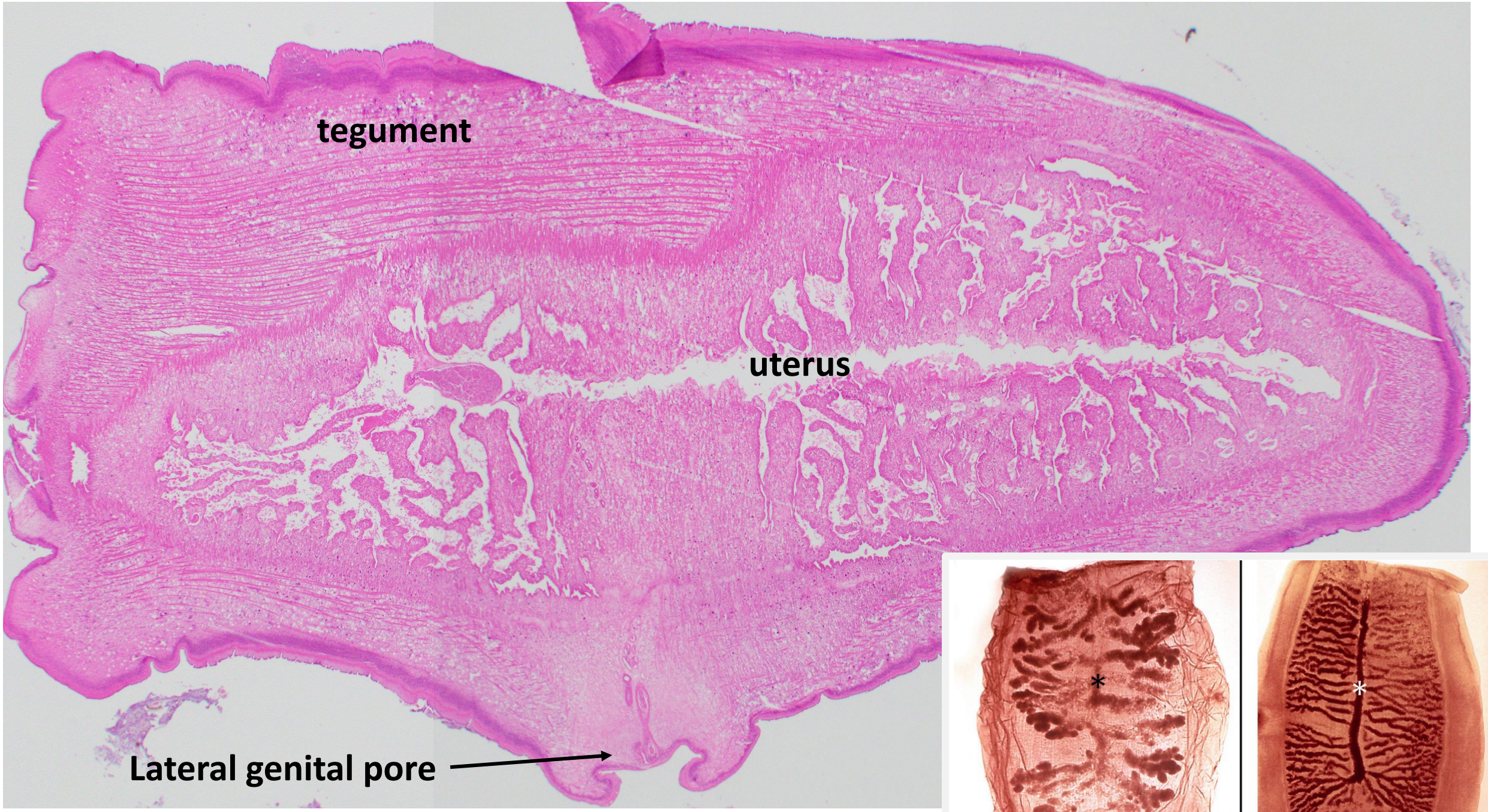




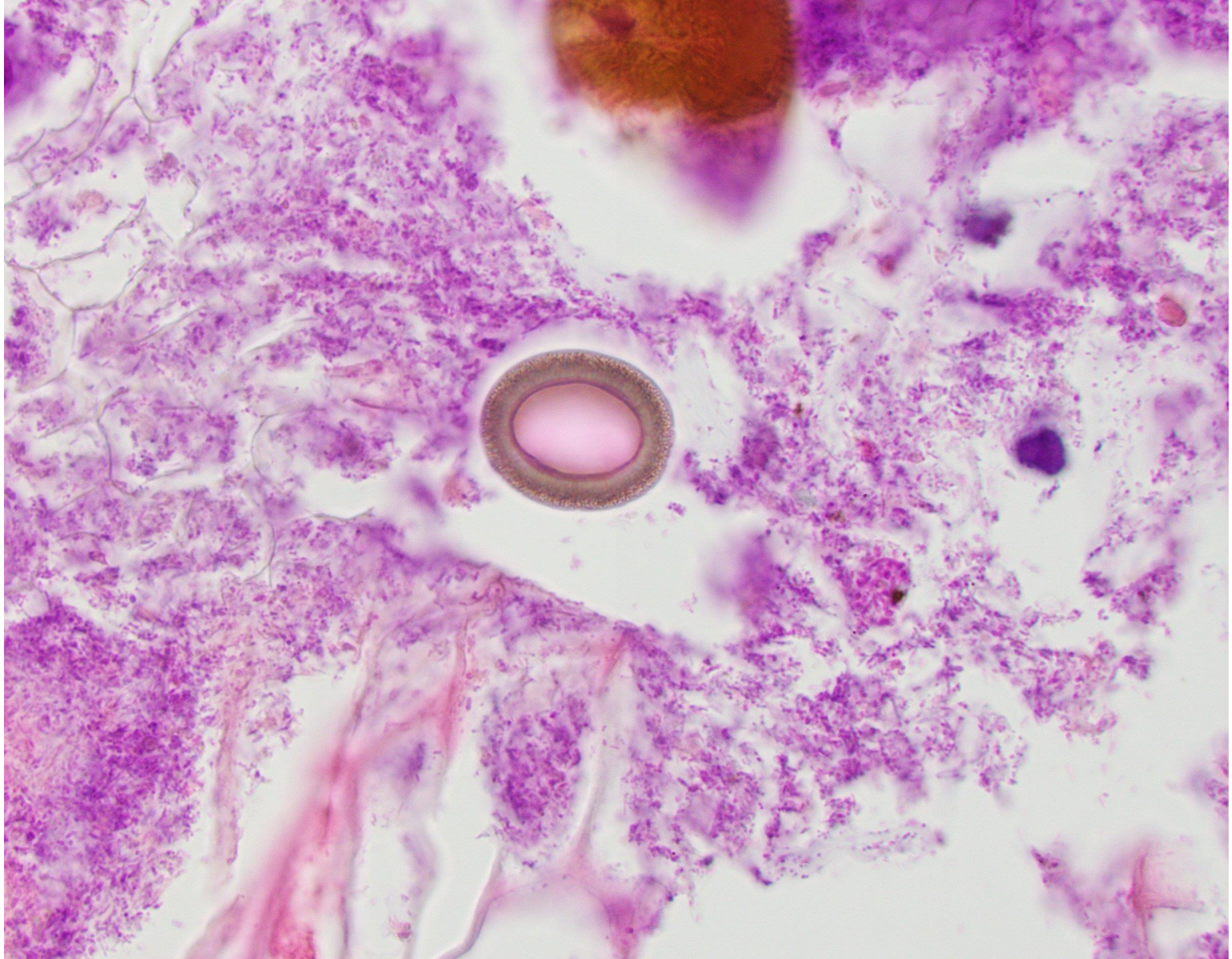




DIAGNOSIS?


tegument
uterus
Lateral genital pore

Calcareous corpuscles
Mineral concretions found in all cestodes
Believed to possibly protect worm from metabolic acid

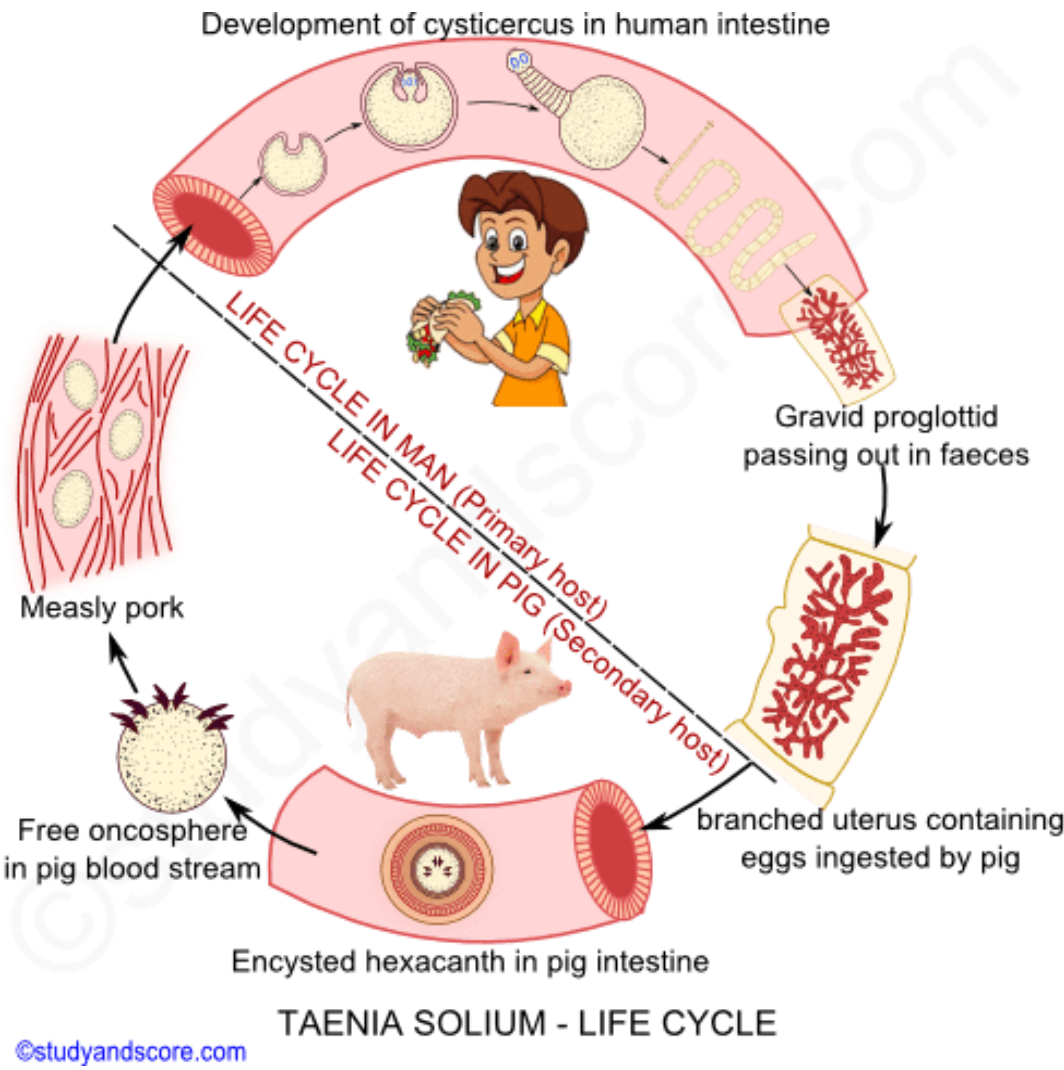


31-43 um
Thick radiate shell

Usually contains oncosphere
with 6 refractile hooklets

Life cycle

1. Proglottids / eggs shed into environment
2. Eaten by cattle (T. saginata) or pigs (T. solium)
3. Travels from intestine to muscle of the intermediate host
    a. Eggs hatch in small intestine
    b. Oncospheres (1st larval stage) travel to muscle
    c. Cysticercus (2nd larval stage) develops
4. Undercooked meat eaten by human
    a. Cysticercus --> protoscolex --> scolex --> proglottids
1. After 2 months gravid proglottids shed



Take home summary

- Clinical: Often asymptomatic, abdominal pain, weight loss, rarely obstruct biliary tree
- Diagnosis: O&P, gross exam, coproantigen testing, molecular
- Treatment: praziquantel or albendazole
- Speciating important because T. solium can cause cysticercosis

References

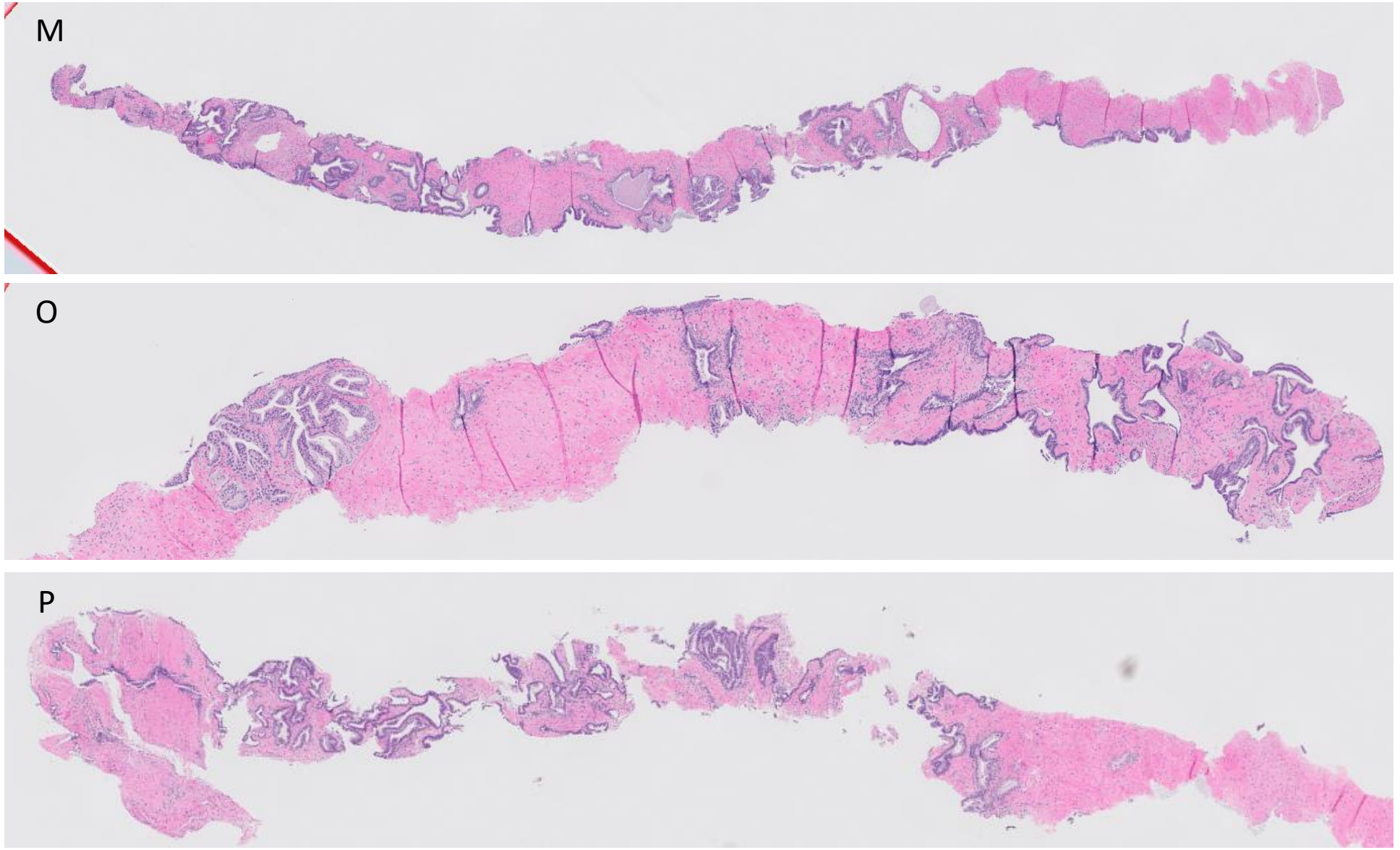
- Mathison, B. A., & Pritt, B. S. (2022). Parasites of the Gastrointestinal Tract. In Encyclopedia of Infection and Immunity (pp. 170–173). essay, Elsevier Science. Retrieved July 30, 2024.
- (2008). Calcareous Corpuscles. In: Mehlhorn, H. (eds) Encyclopedia of Parasitology. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-48996-2_487

24-1002

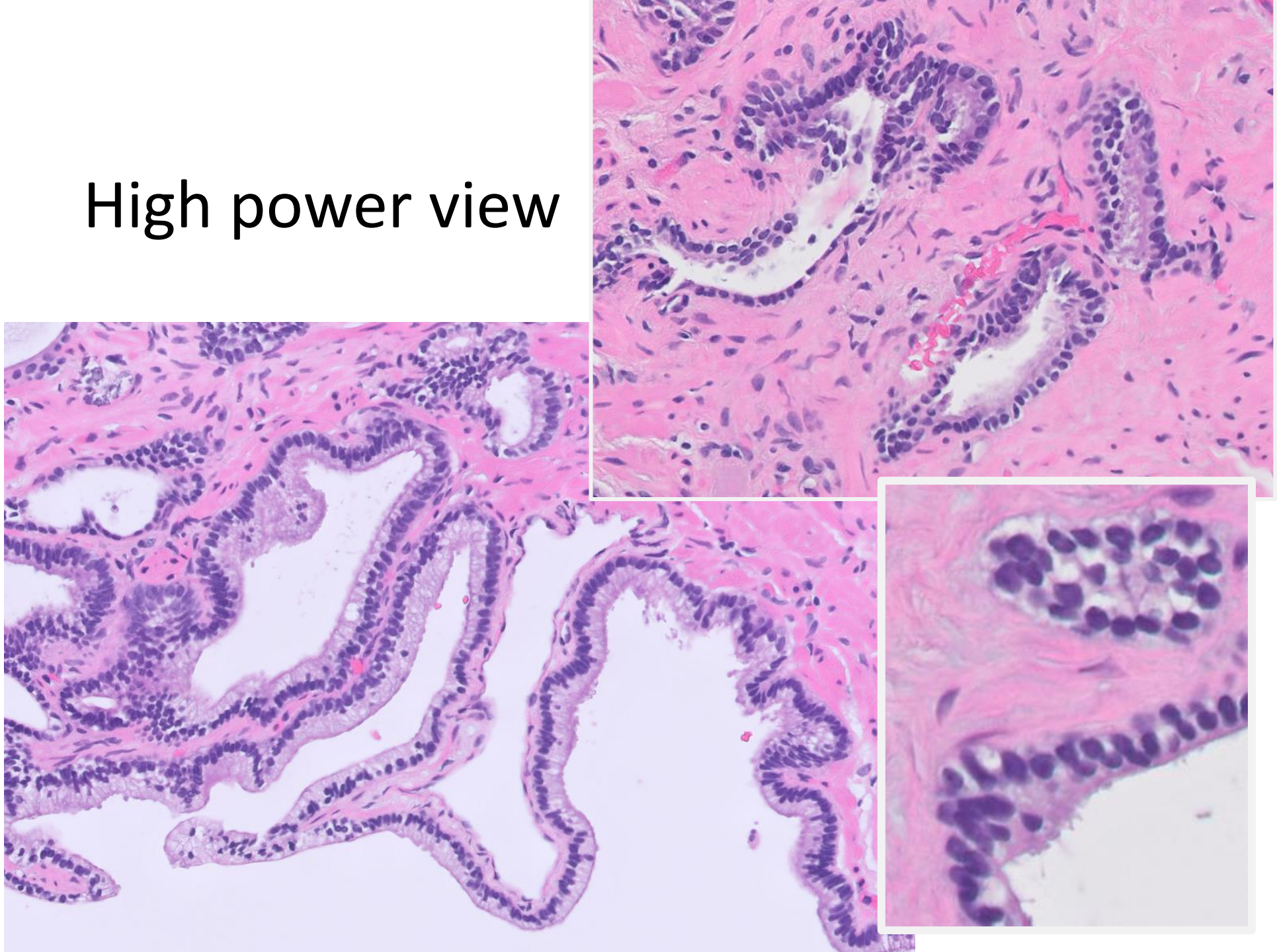
Anne Cheng and Emily Chan: Stanford

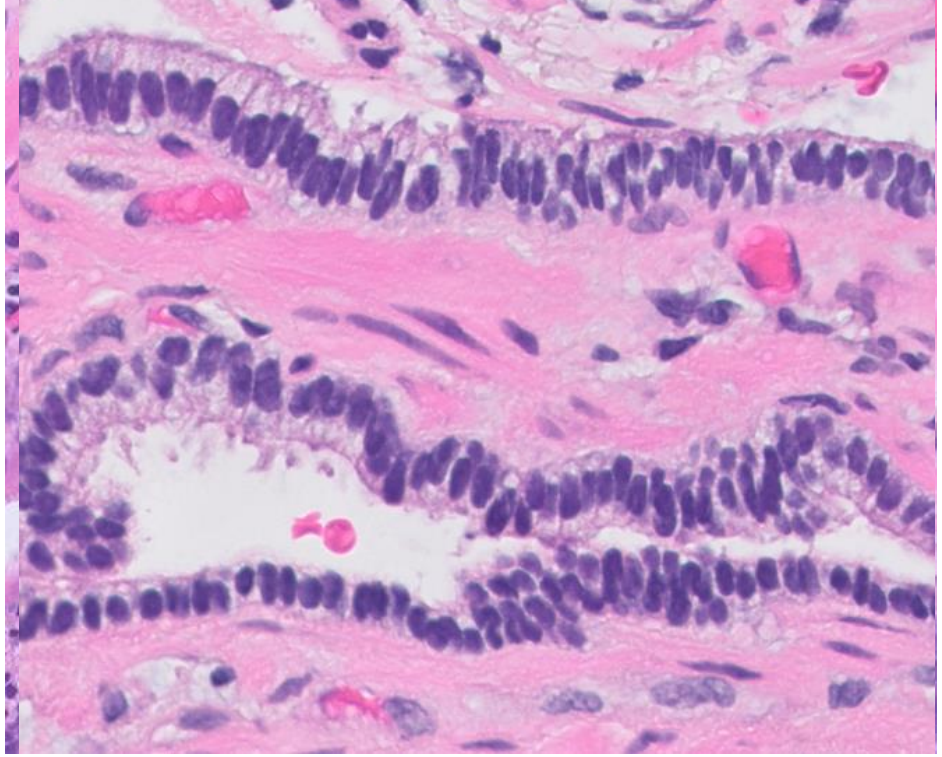
72-year-old man with PSA of 5.3. No prior prostate biopsies.

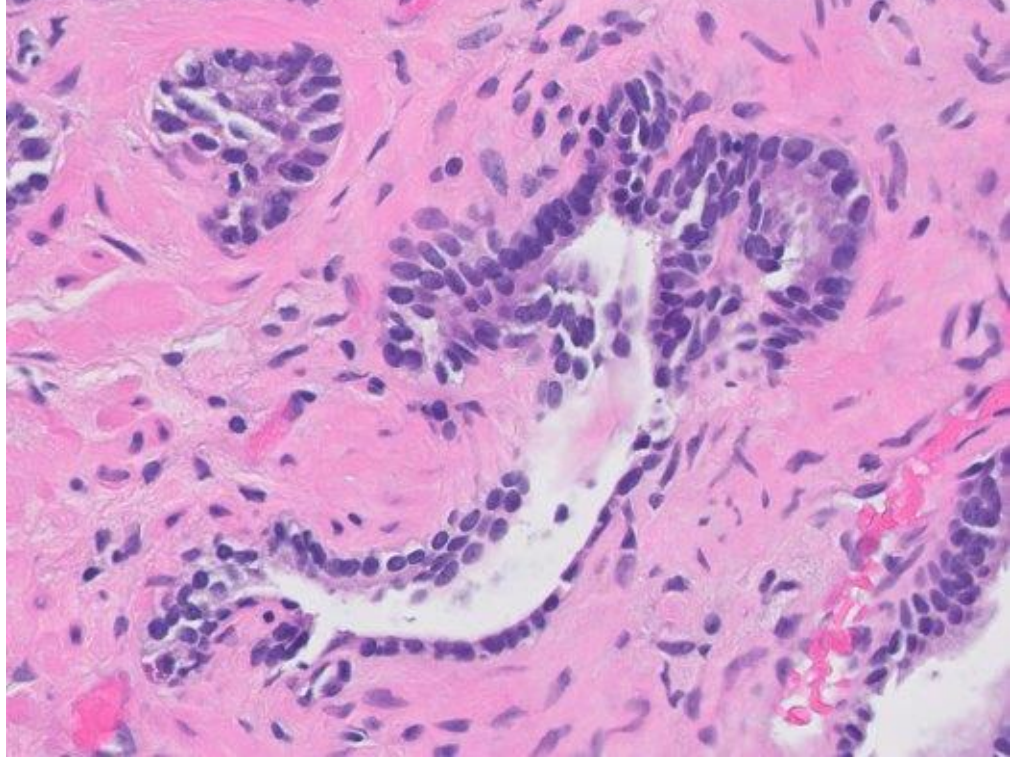
Low Power View

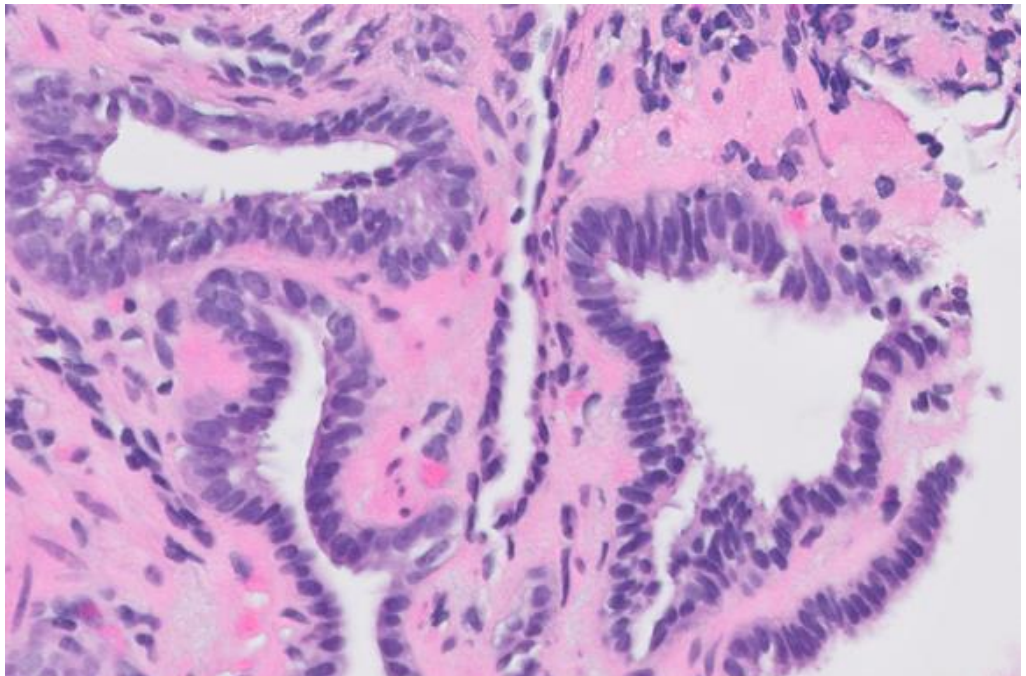


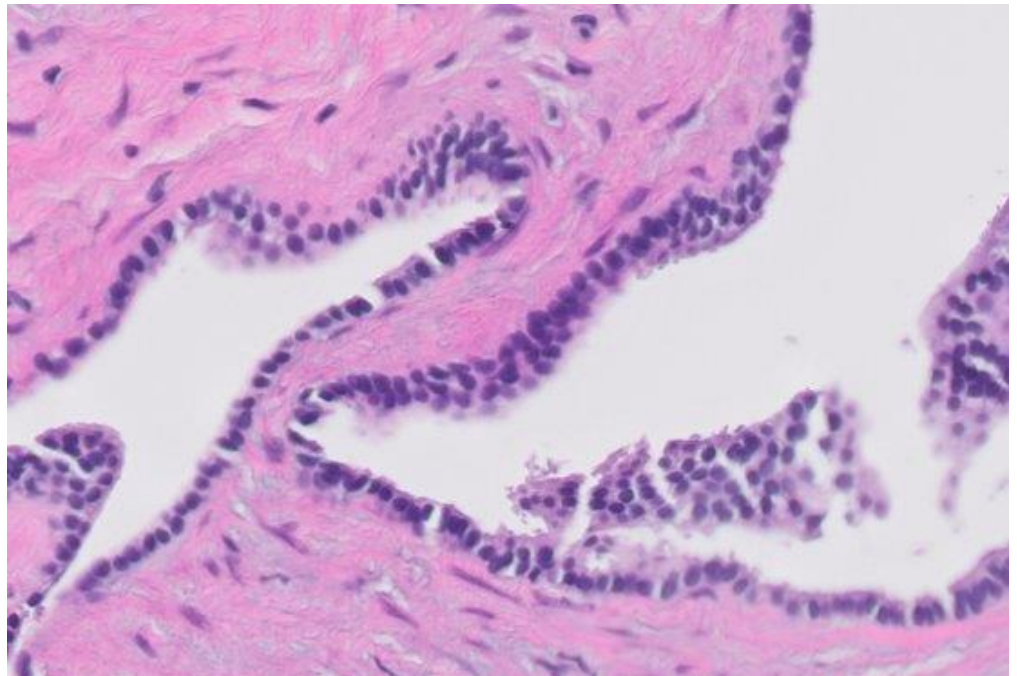
High power view

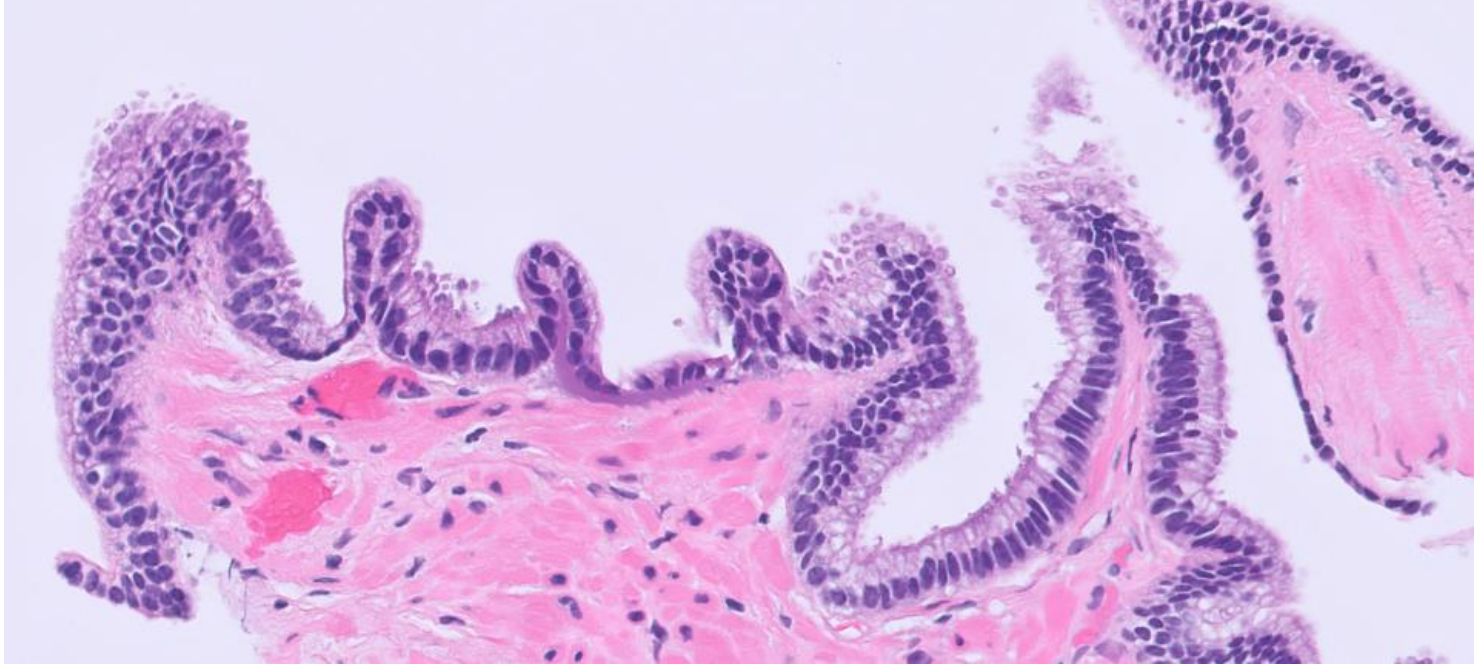


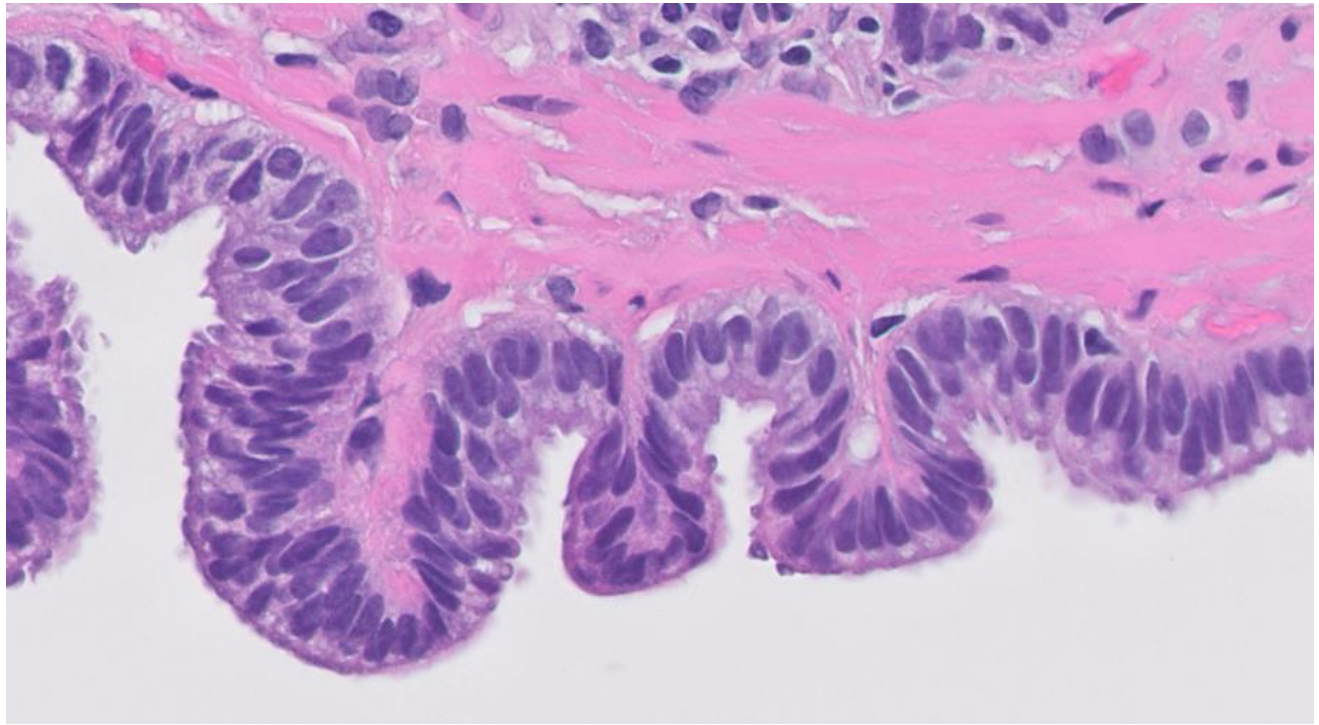




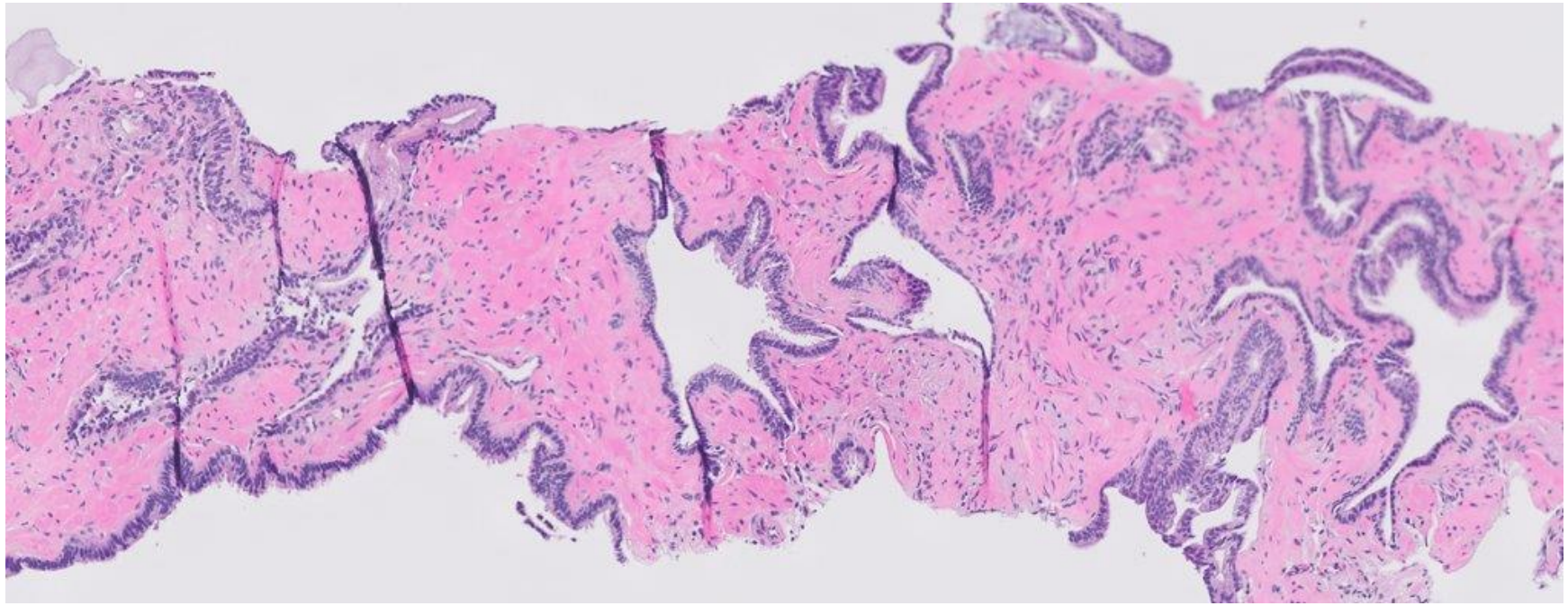


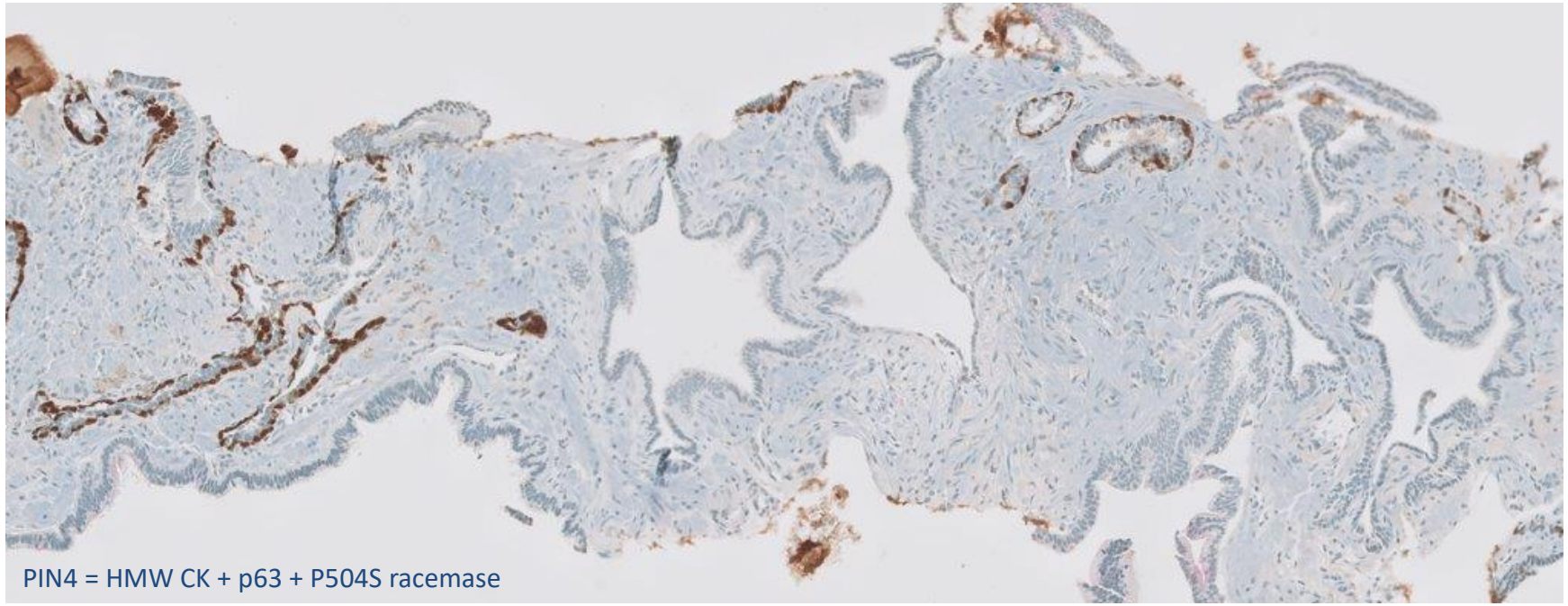




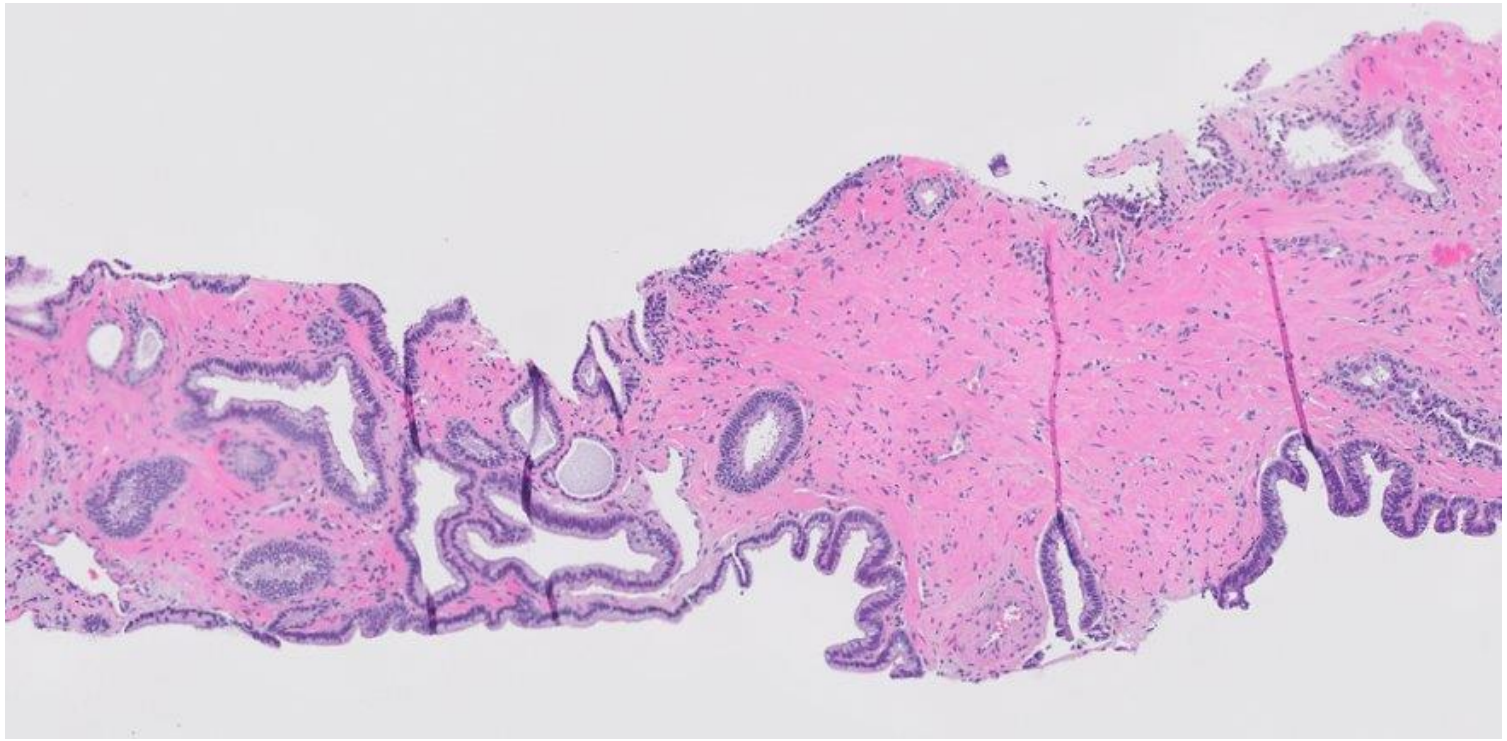


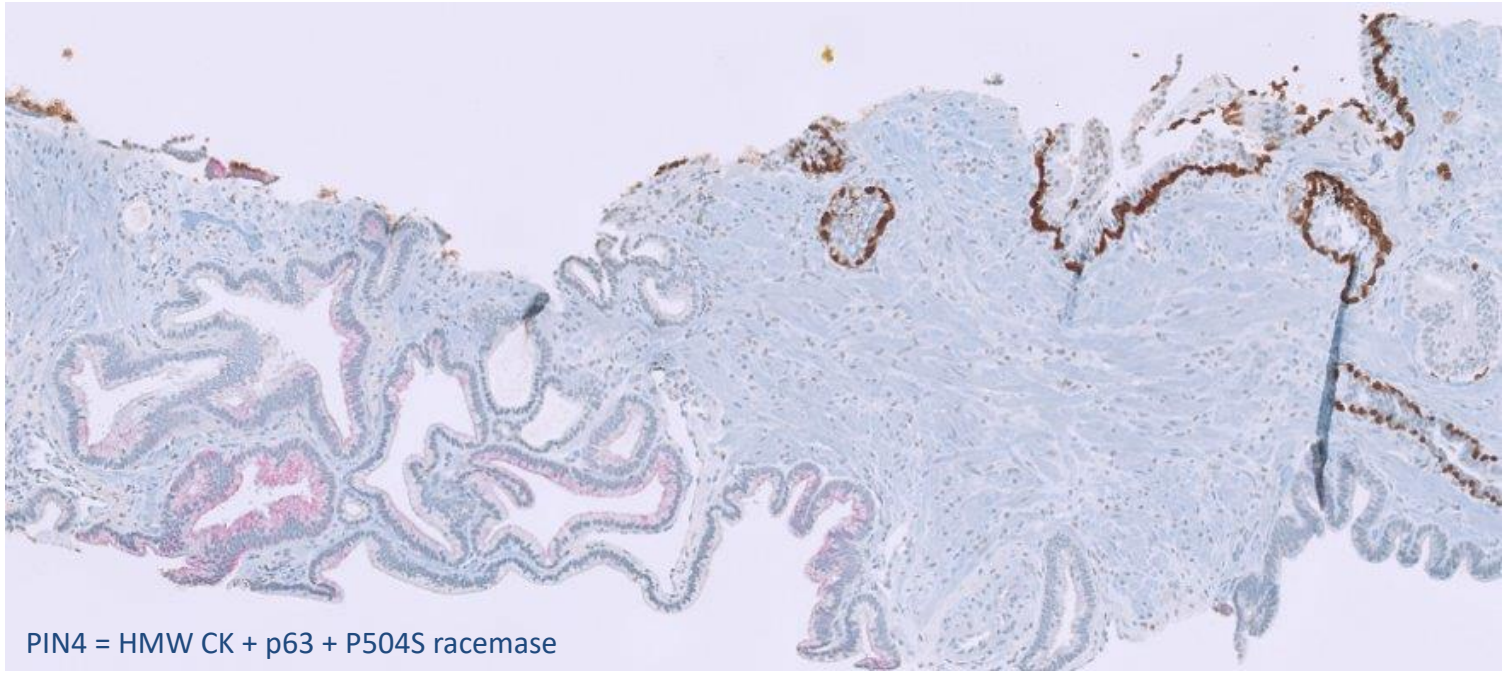
DIAGNOSIS?





PIN4 = HMW CK + p63 + P504S racemase





PIN4 = HMW CK + p63 + P504S racemase

PIN-like adenocarcinoma

- A variant of acinar adenocarcinoma (WHO 2022)
- Often misdiagnosed as ductal carcinoma or HGPIN
- 1.3% incidence in biopsies
- Other names:
  - PIN-like carcinoma
  - PIN-like ductal adenocarcinoma
  - PIN-like (ductal) adenocarcinoma

1. Paulk A, Giannico G, Epstein JI. PIN-like (Ductal) Adenocarcinoma of the Prostate. Am J Surg Pathol. 2018 Dec;42(12):1693-1700.
2. Kench, J. (n.d.). *Prostatic acinar adenocarcinoma*. World Health Organization. https://tumourclassification.iarc.who.int/chaptercontent/36/100
3. Kaur HB, Salles DC, Paulk A, Epstein JI, Eshleman JR, Lotan TL. PIN-like ductal carcinoma of the prostate has frequent activating RAS/RAF mutations. Histopathology. 2021 Jan;78(2):327-333. doi: 10.1111/his.14224. Epub 2020 Sep 24. PMID: 32740981; PMCID: PMC7775281.

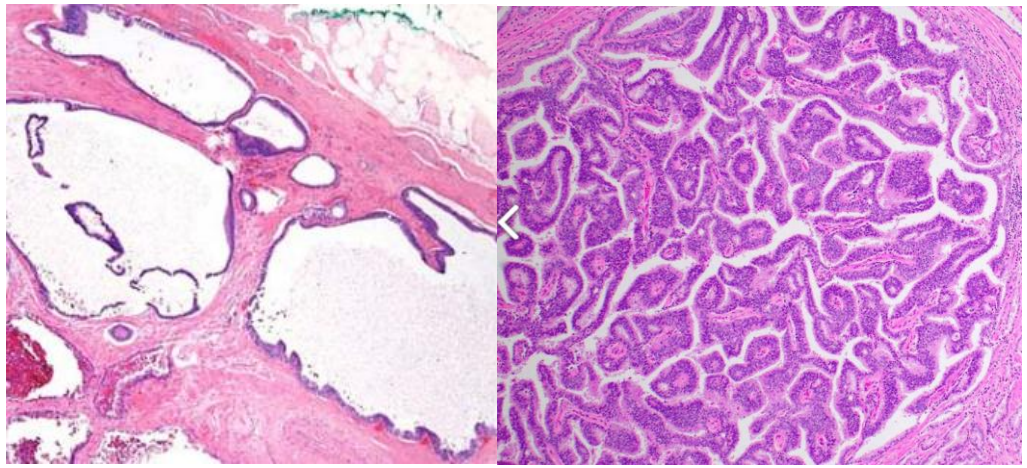
Morphology

PIN-like

- Lower grade nuclei
- Pseudostratified columnar epithelium
- Dilated cystic glands
  - flat, tufts, thin papillary
  - Hint: long strips of epithelium at edge of core
- Can be associated with a distinct acinar/ductal component

Ductal

- Higher grade nuclei
- Pseudostratified columnar epithelium
- More complex architecture
  - Papillary, cribriform
- More volume



1. Findeis S, Huang H. Ductal adenocarcinoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/prostateprostaticduct.html. Accessed October 5th, 2024.
2. Paulk A, Giannico G, Epstein JI. PIN-like (Ductal) Adenocarcinoma of the Prostate. Am J Surg Pathol. 2018 Dec;42(12):1693-1700.
3. Kaur HB, Salles DC, Paulk A, Epstein JI, Eshleman JR, Lotan TL. PIN-like ductal carcinoma of the prostate has frequent activating RAS/RAF mutations. Histopathology. 2021 Jan;78(2):327-333. doi: 10.1111/his.14224. Epub 2020 Sep 24. PMID: 32740981; PMCID: PMC7775281.

Molecular & Behavior

PIN-like

- 60% RAS/RAF pathway activation
- Clinically Indolent
  - 5 of 6 cases had EPE
  - No metastasis or recurrence
  - Better outcomes

Ductal

- 50% MMR and HR mutations
- Clinically Aggressive
  - Behaves like Gleason score 8-10 of acinar carcinoma
  - Higher risk of treatment failure
  - Worse outcomes

1. Paulk A, Giannico G, Epstein JI. PIN-like (Ductal) Adenocarcinoma of the Prostate. Am J Surg Pathol. 2018 Dec;42(12):1693-1700.
2. Kaur HB, Salles DC, Paulk A, Epstein JI, Eshleman JR, Lotan TL. PIN-like ductal carcinoma of the prostate has frequent activating RAS/RAF mutations. Histopathology. 2021 Jan;78(2):327-333. doi: 10.1111/his.14224. Epub 2020 Sep 24. PMID: 32740981; PMCID: PMC7775281.

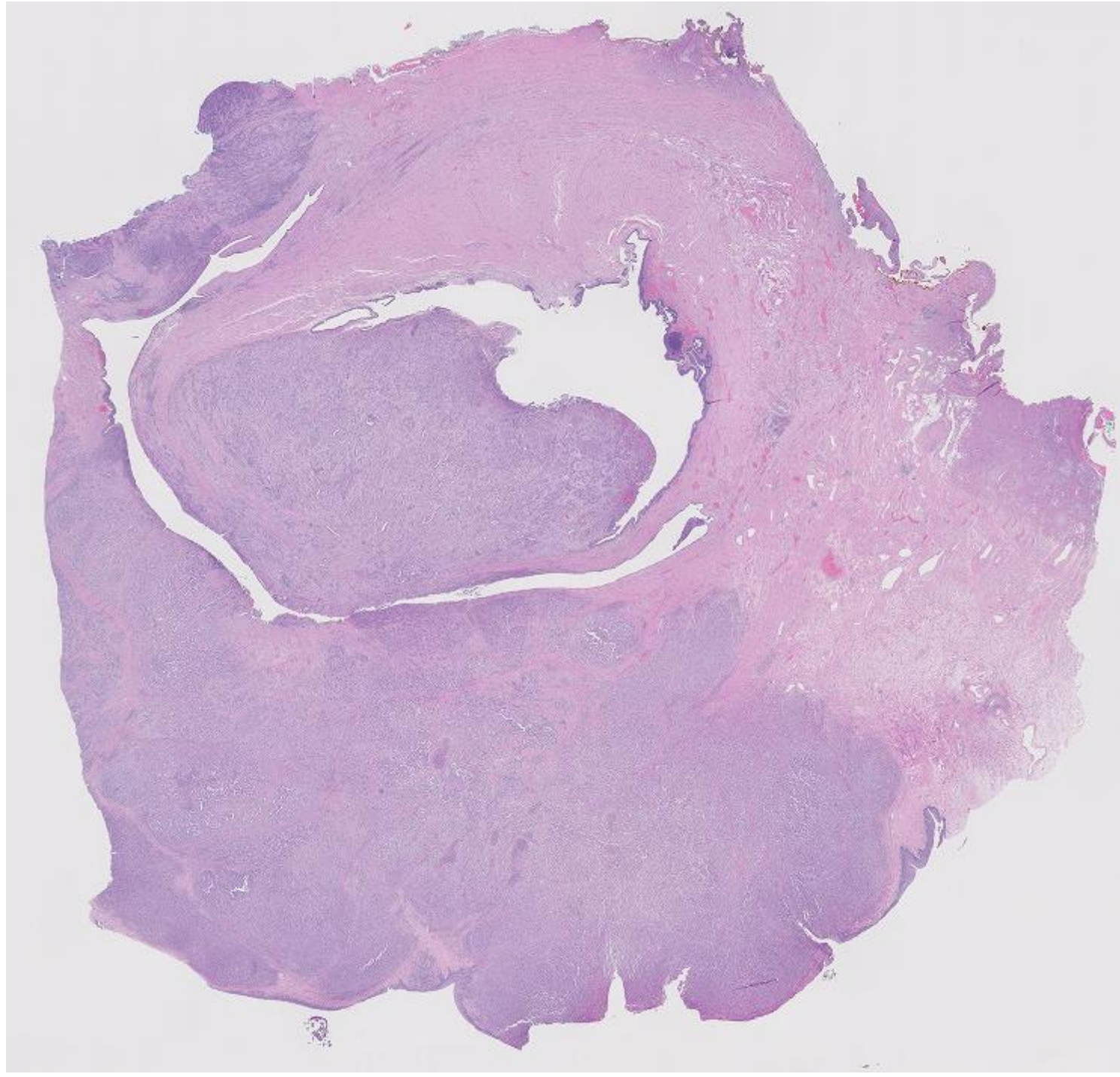
Take home message

- Challenging diagnosis. Great mimicker!
  - Benign prostate
  - High grade PIN
  - Ductal carcinoma
- Distinct low grade variant of acinar adenocarcinoma
- In pure form: Gleason pattern 3
- If architecturally complex: Gleason pattern 4

24-1003

Brooke Liang and Emily Chan; Stanford

65-year-old female with a history of hypercholesterolemia, GERD, chronic UTIs and endometriosis found to have a posterior urethral mass



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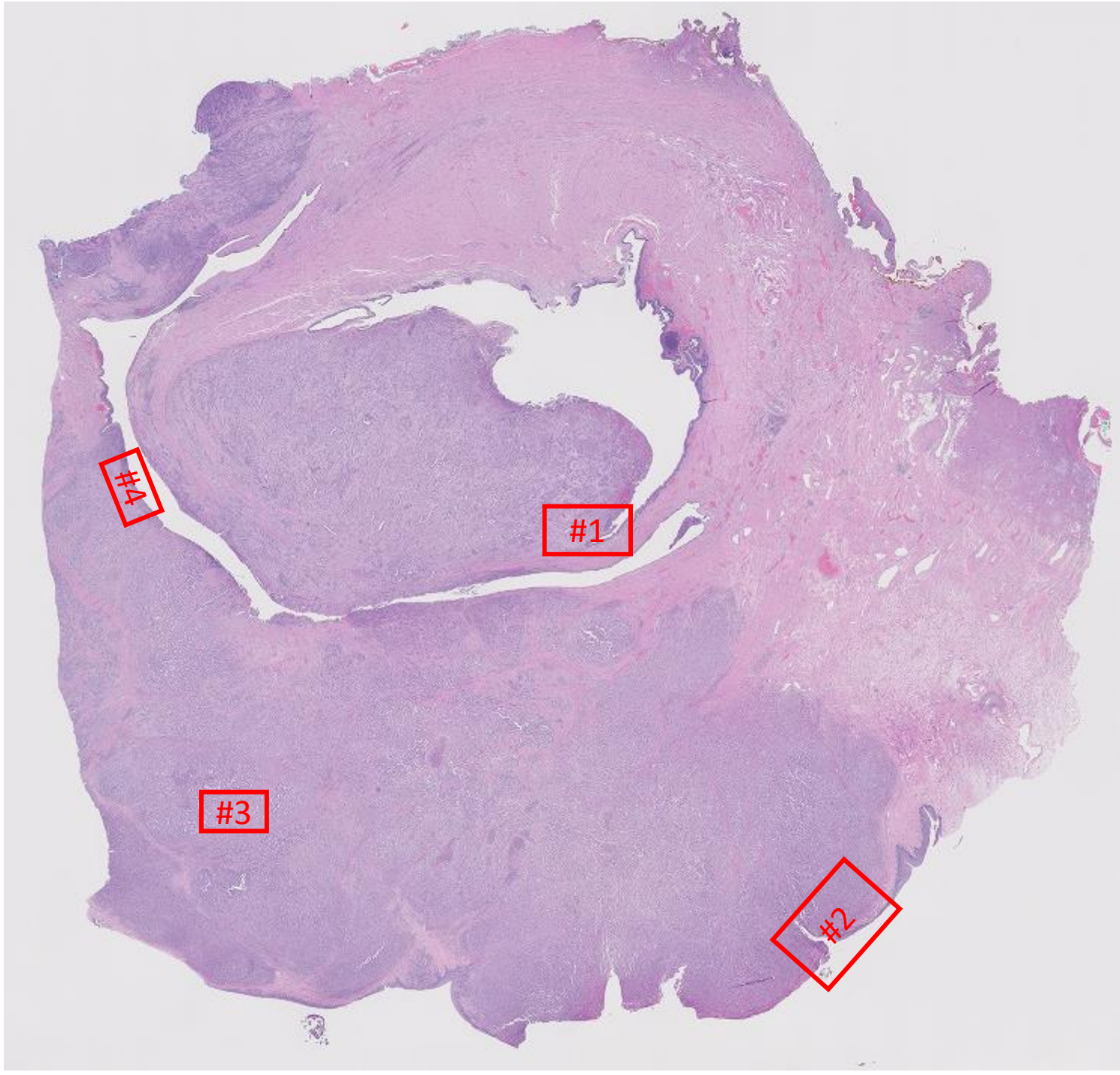
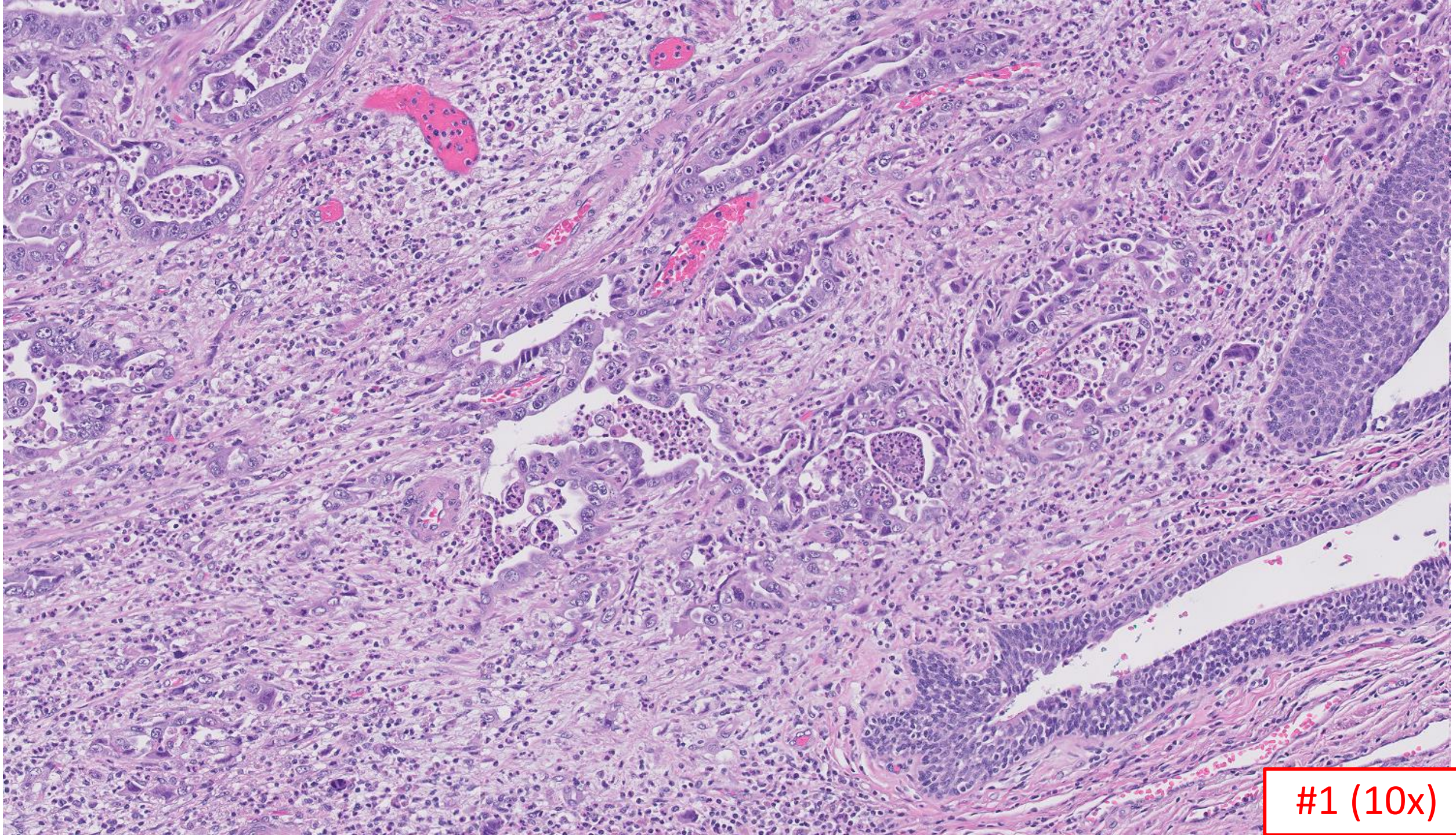
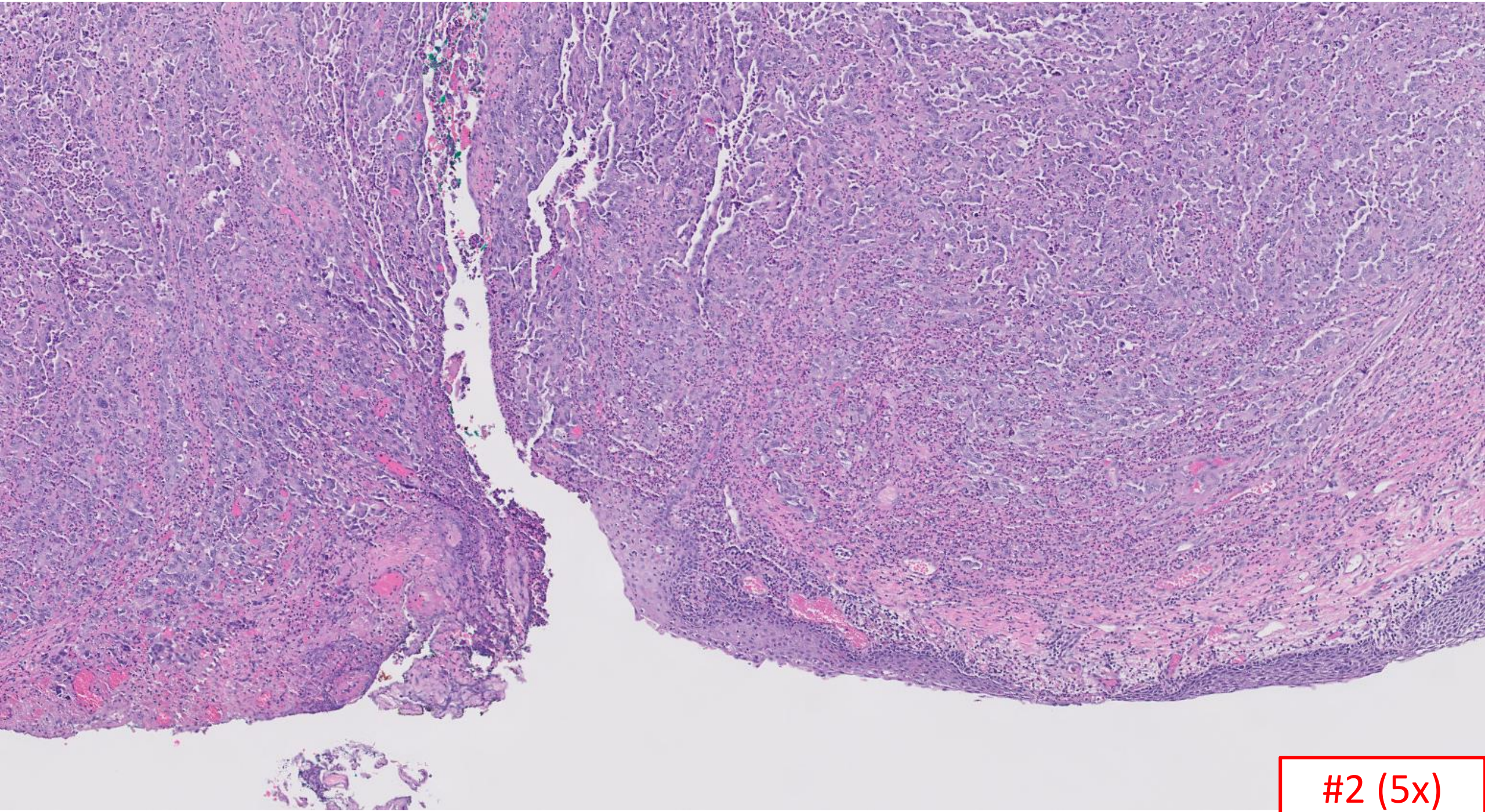
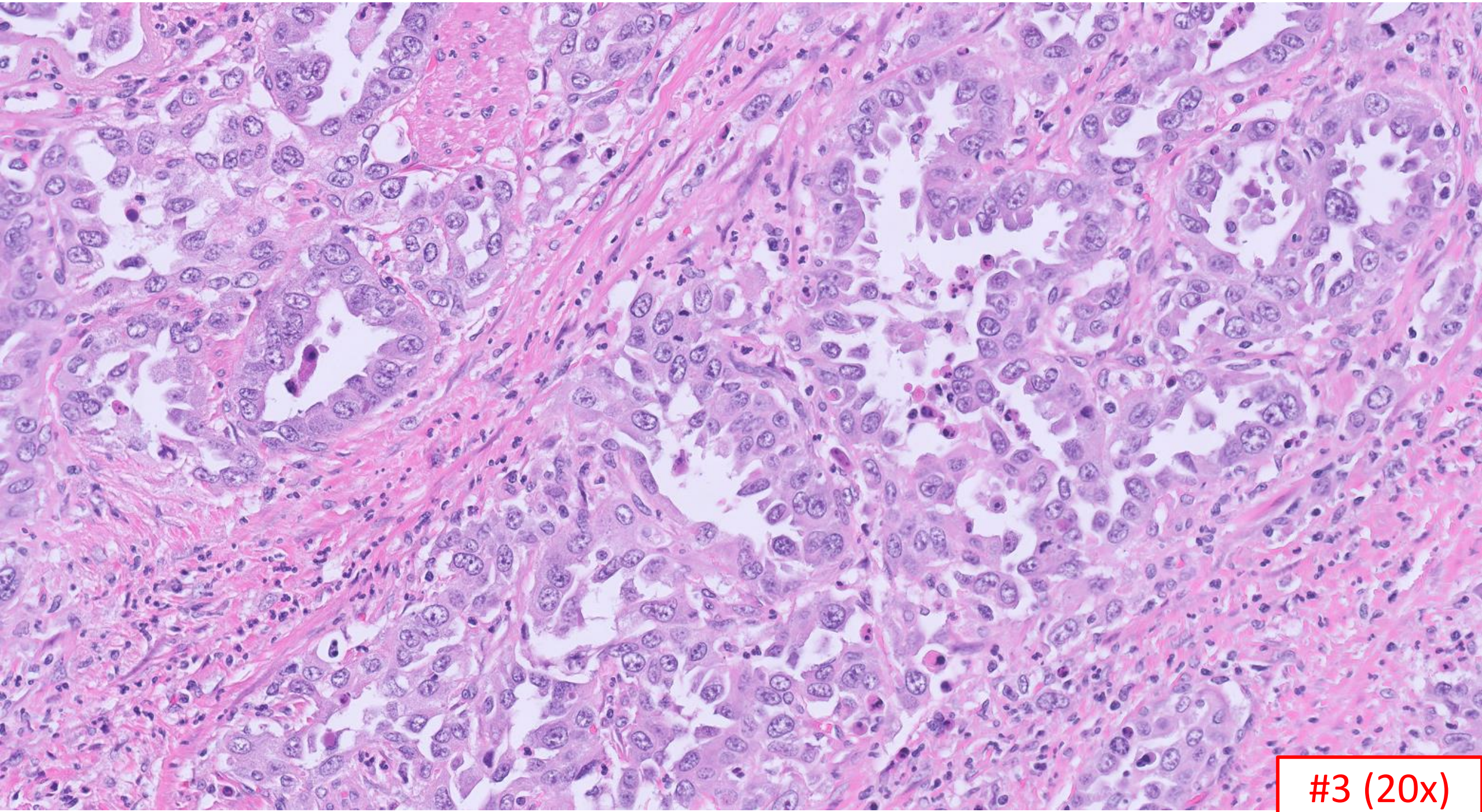


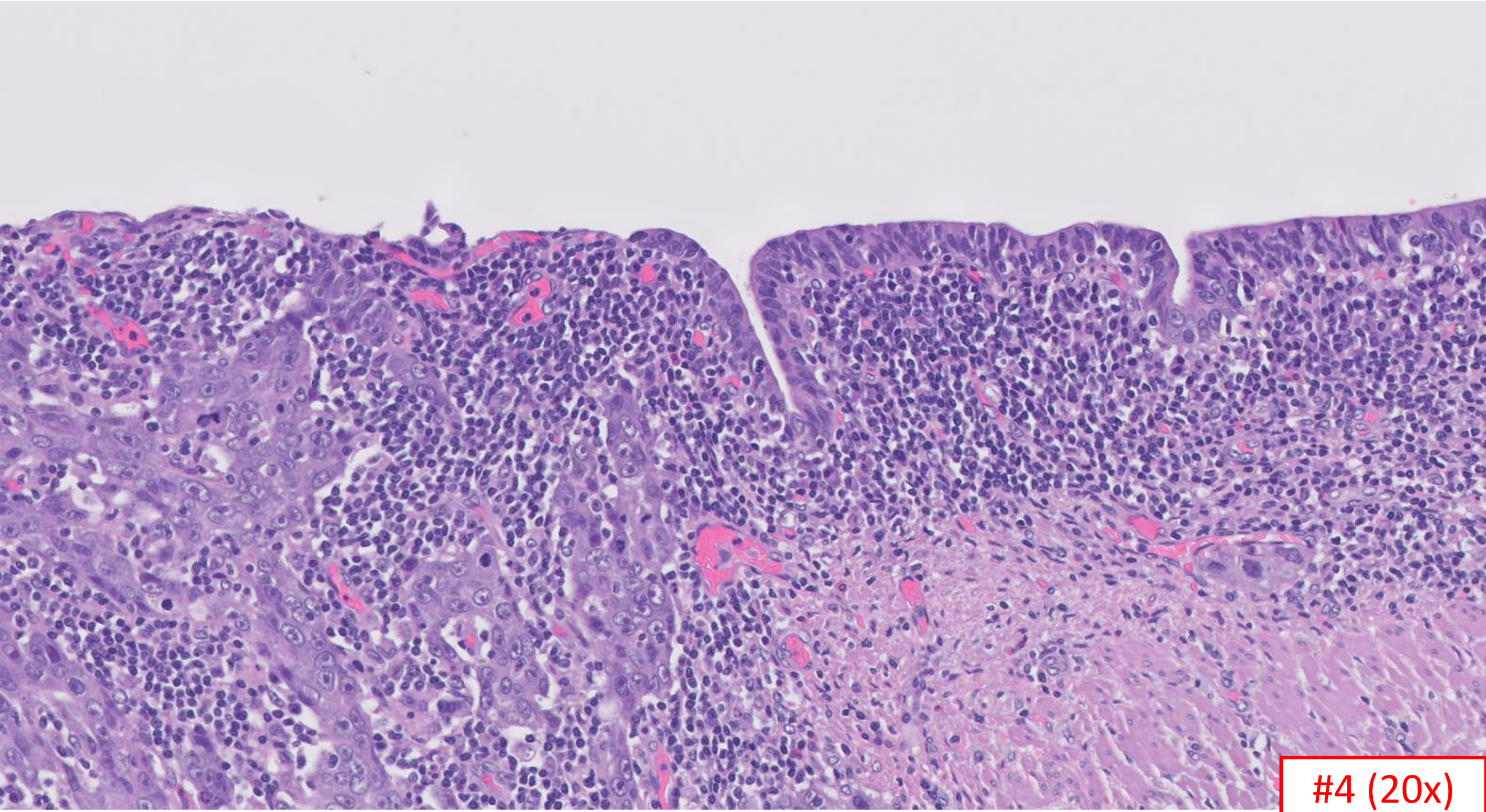
0.25x


#1 (10x)



#2 (5x)


#3 (20x)


#4 (20x)

DIAGNOSIS?

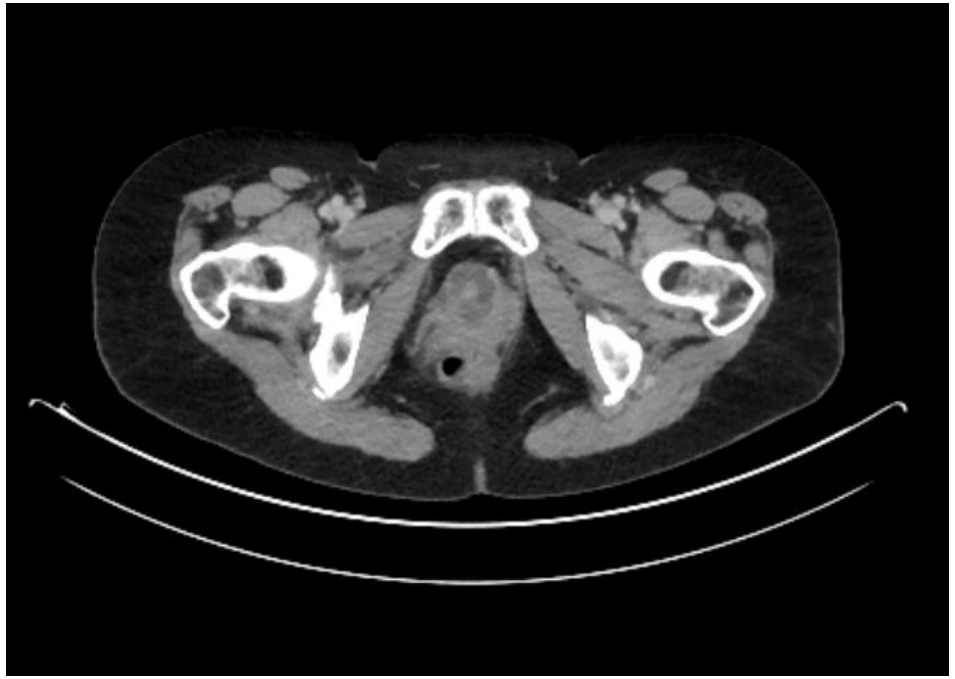
History:

- 65-year-old female with a history of hypercholesterolemia, GERD, endometriosis and chronic UTIs, found to have a posterior urethral mass

- Patient underwent urothelial biopsy (which was inconclusive) followed by neoadjuvant chemotherapy for presumed urothelial carcinoma

- She then underwent en bloc resection of the bladder, urethra, anterior vaginal wall, uterus, and bilateral fallopian tubes and ovaries, with pelvic lymph node dissection

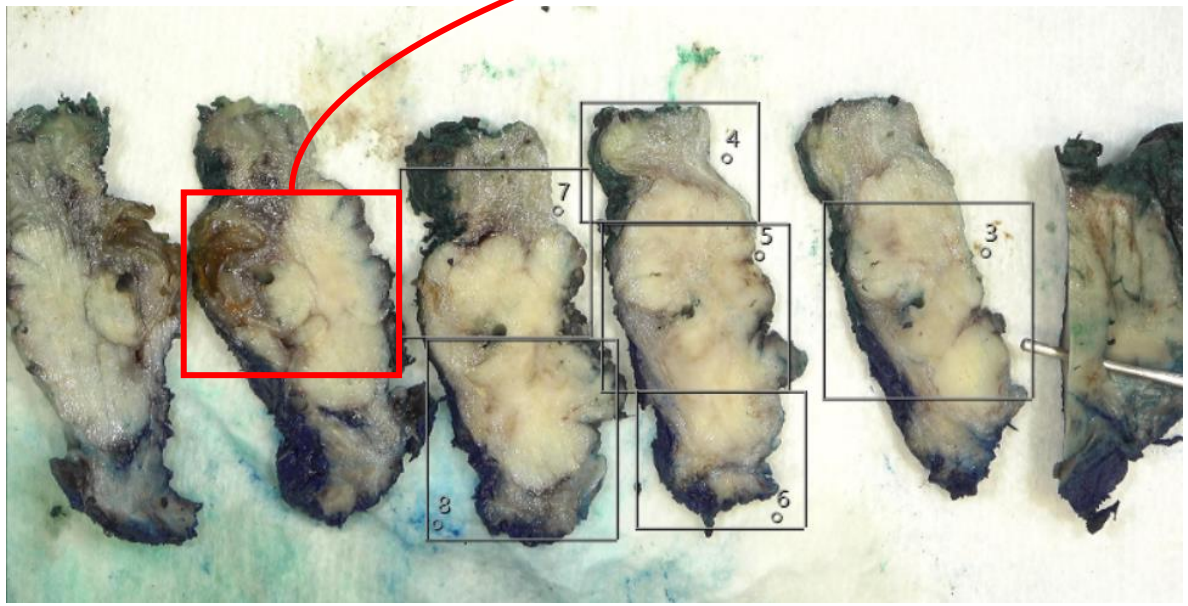
Imaging and Gross

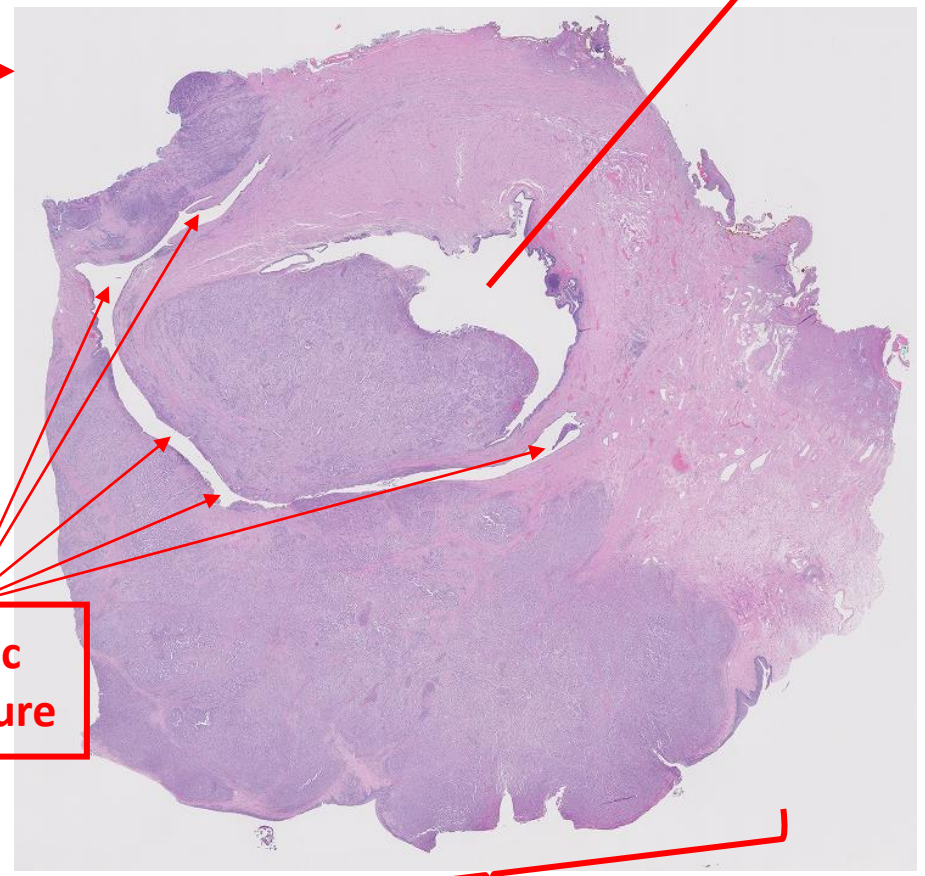


2.9 x 1.9 x 2.1 cm PET-avid mass circumferentially encasing the urethra

Mass noted to ulcerate through anterior vaginal mucosa clinically and on gross examination

Gross and H&E



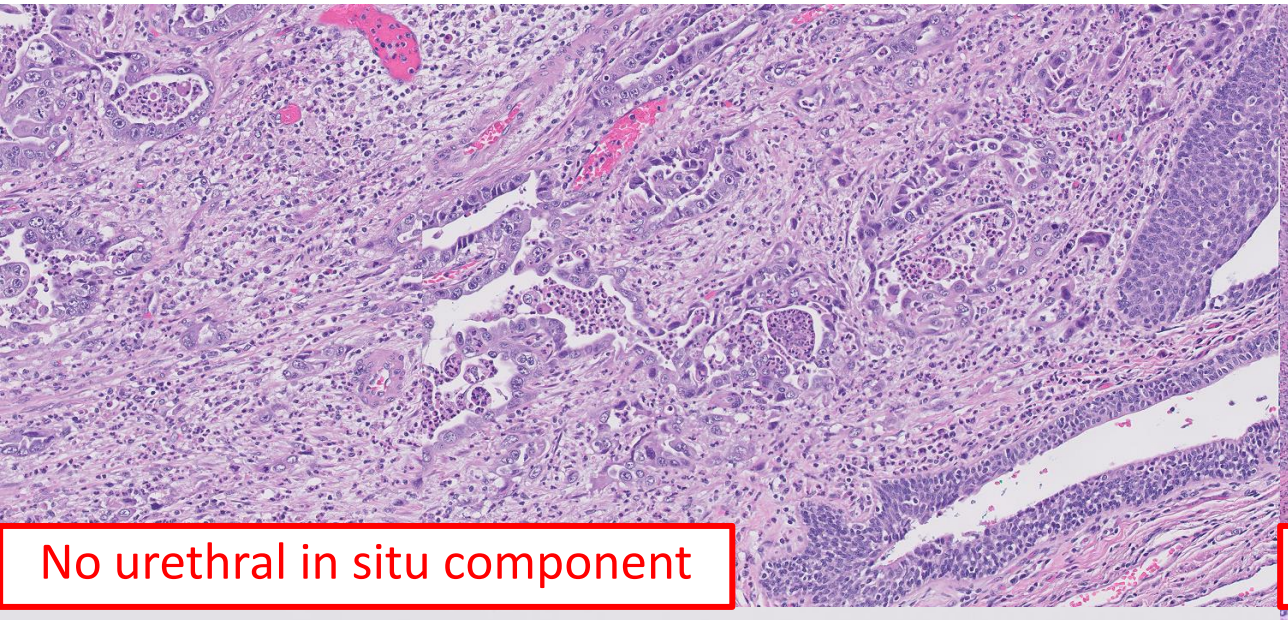


Urethra

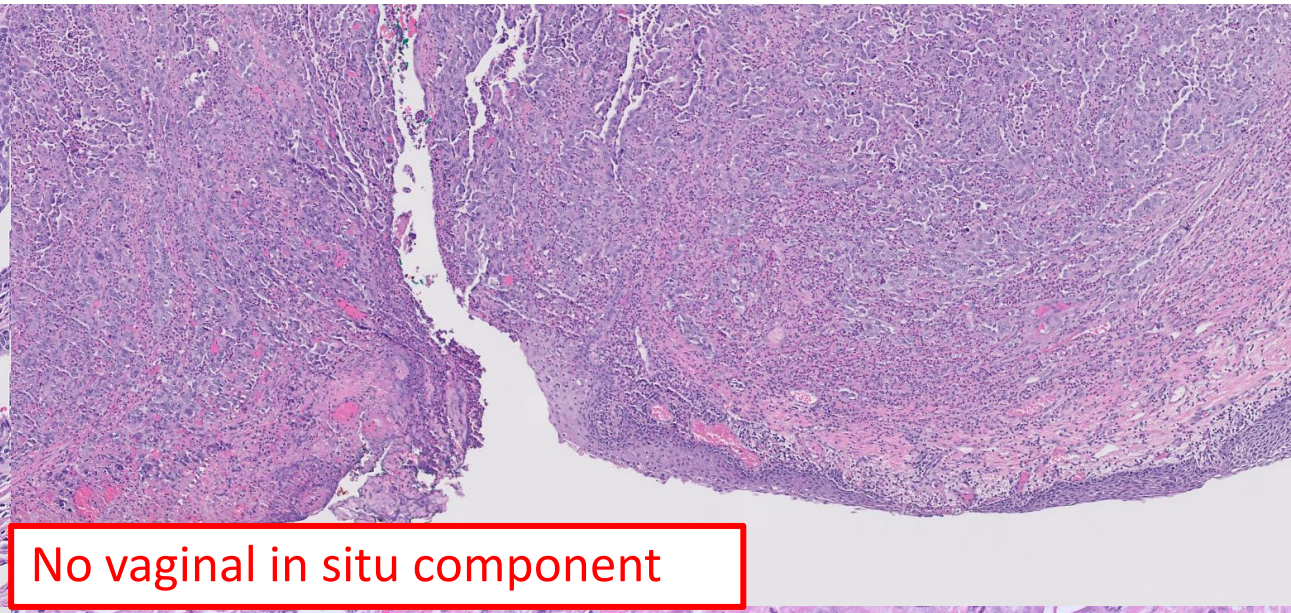
Cystic Structure

Anterior Vagina

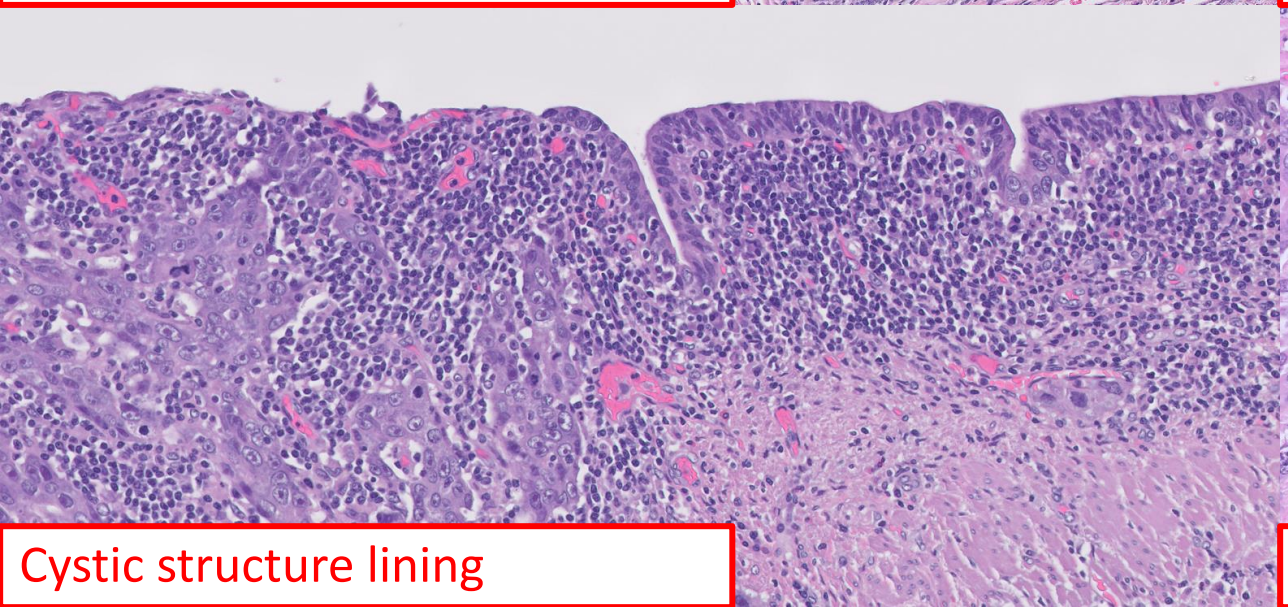
H&E Summary



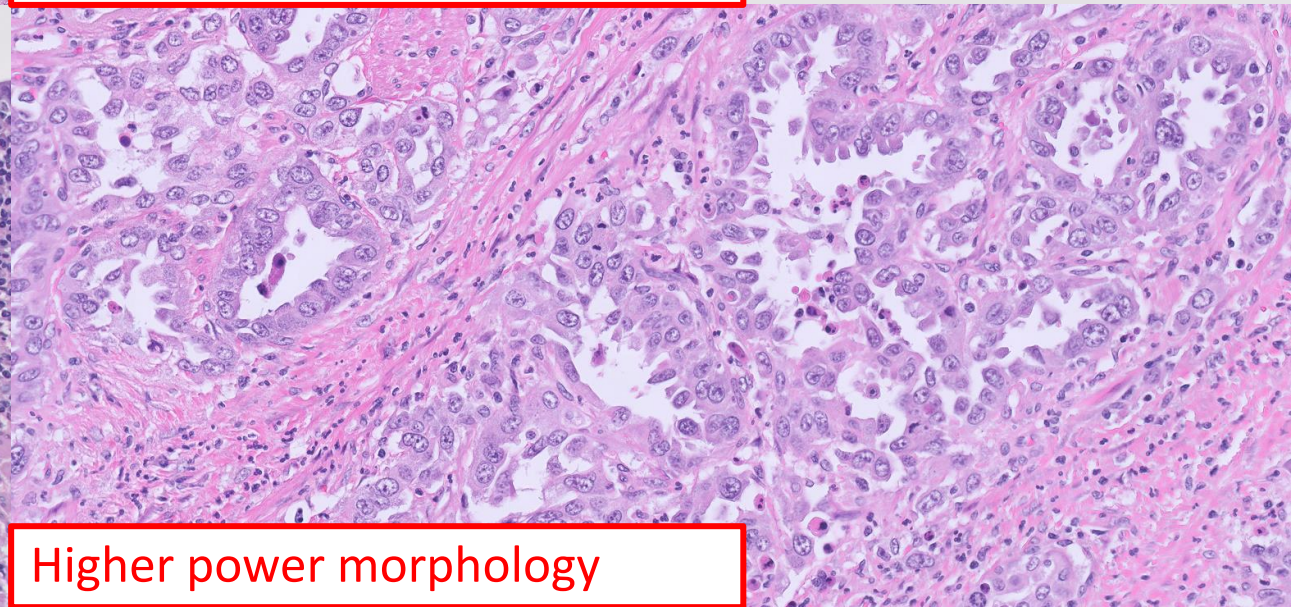
No urethral in situ component



No vaginal in situ component



Cystic structure lining



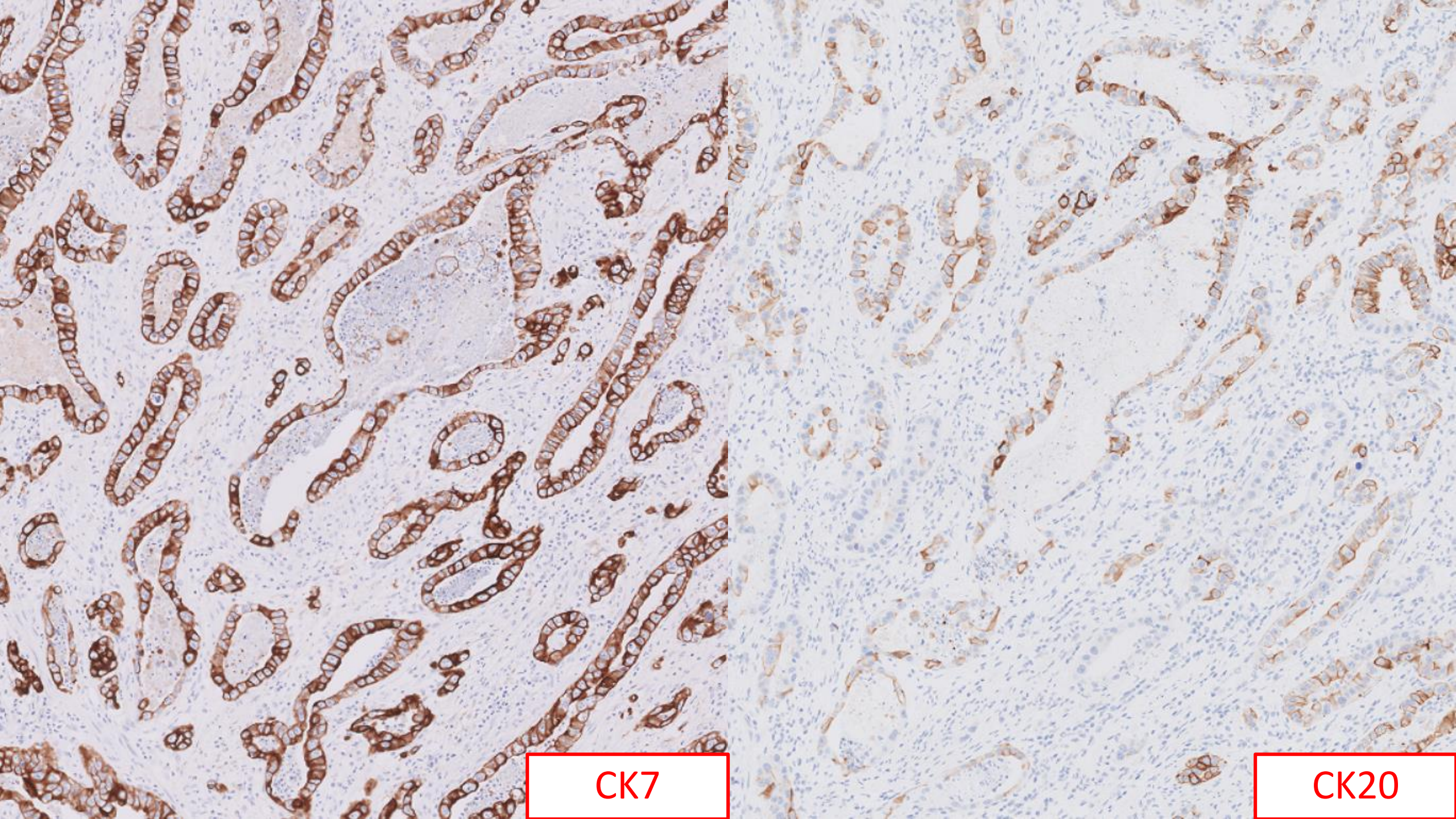
Higher power morphology

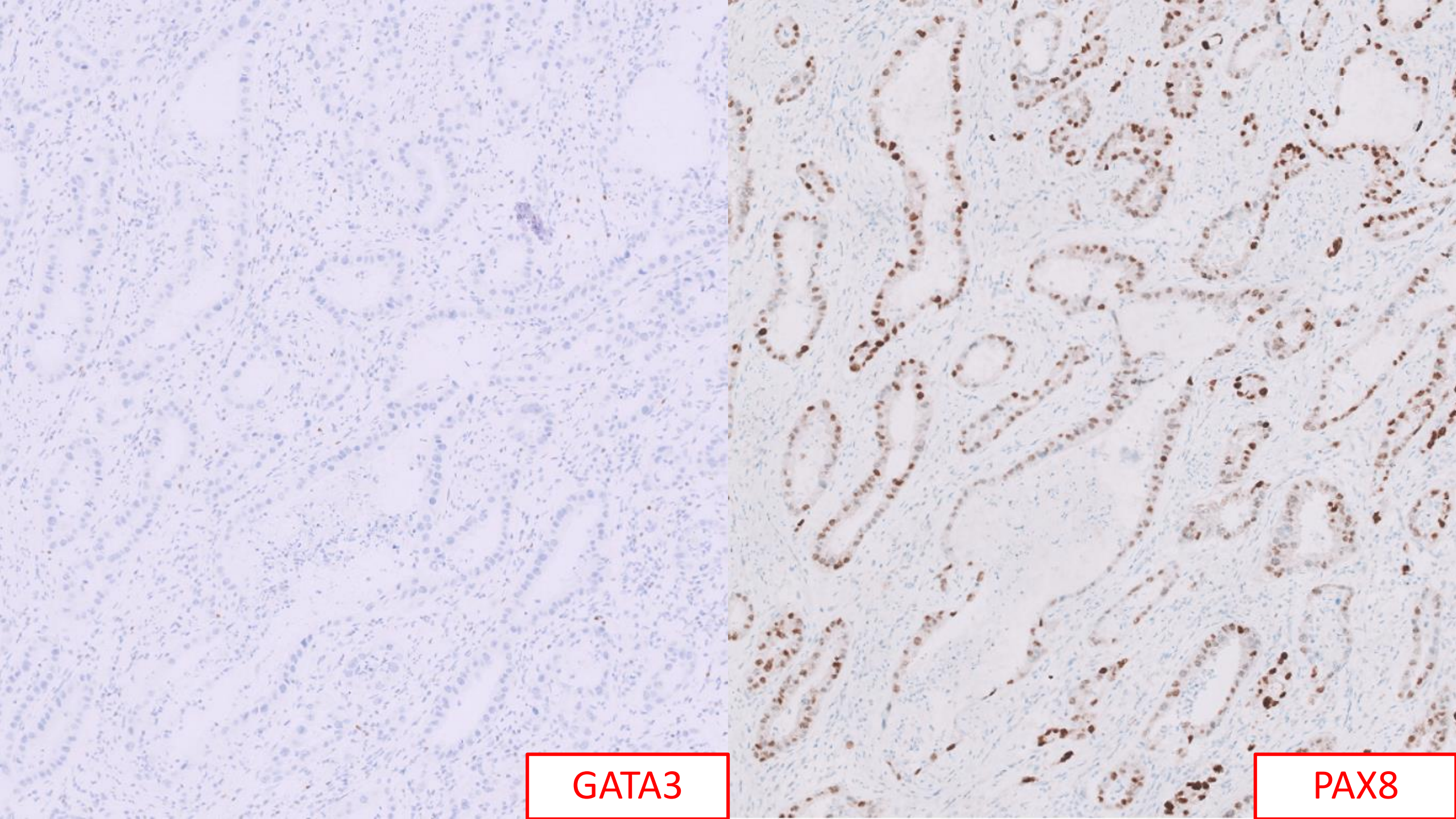
Differential Diagnosis?

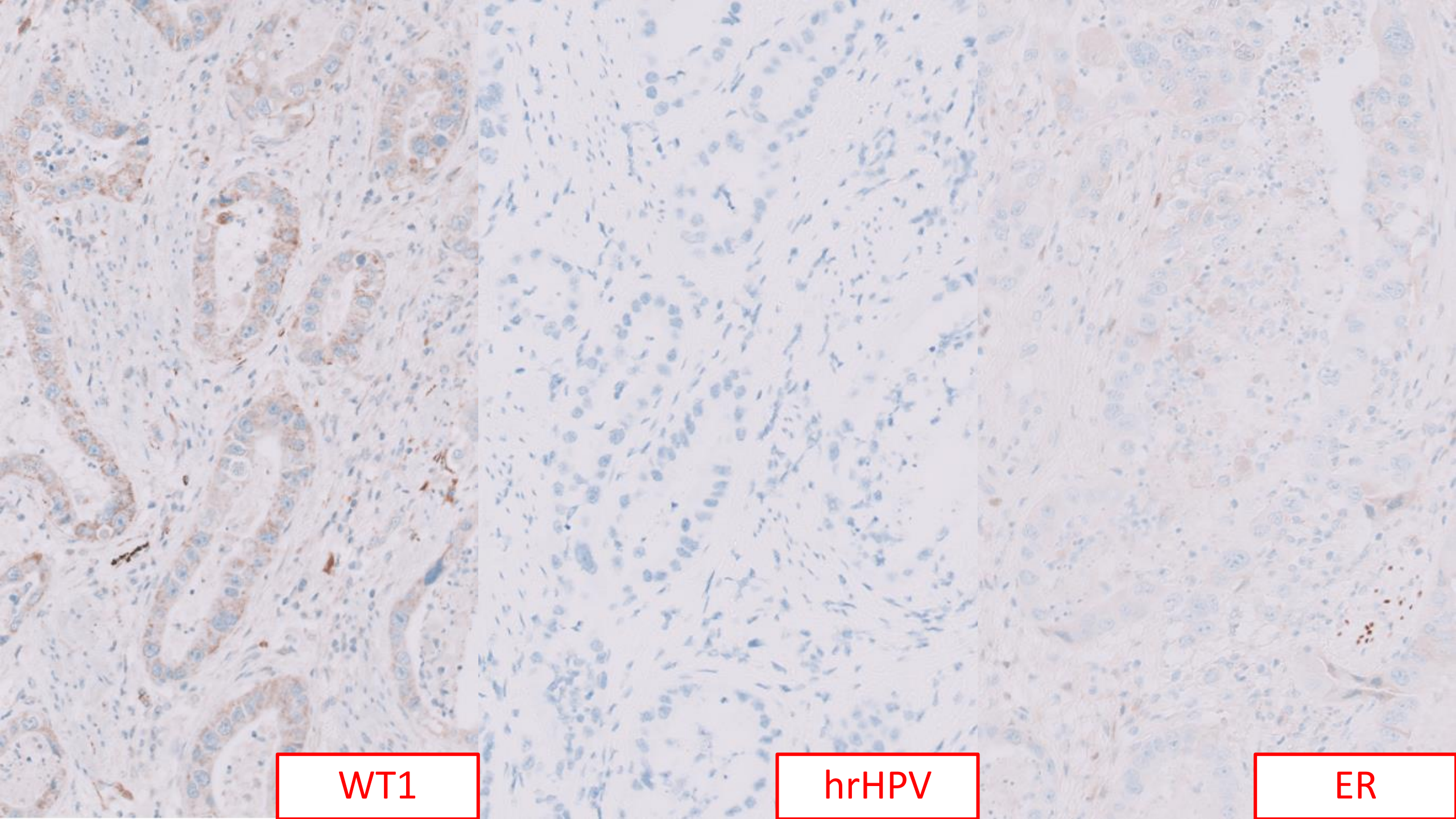
Differential Diagnosis

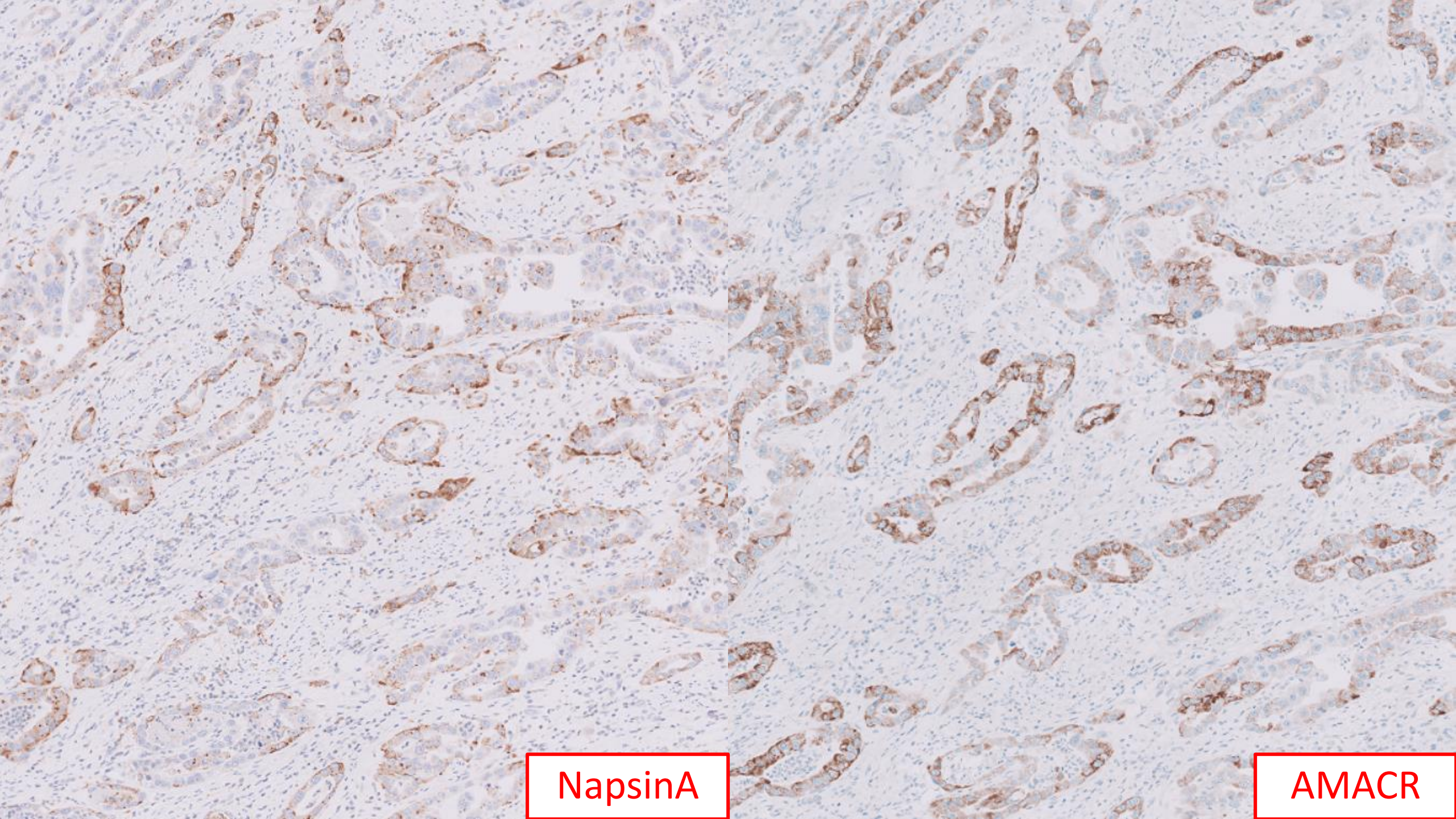
- Urothelial carcinoma (with glandular differentiation / poorly differentiated)
- Adenocarcinoma NOS of the urinary tract
- Clear cell adenocarcinoma of the urinary tract / vagina
- Endometrioid carcinoma of the urinary tract / vagina
- Mesonephric adenocarcinoma of the vagina
- HPV-associated adenocarcinoma of the vagina
- Metastasis

Immunohistochemistry


CK7
CK20


GATA3
PAX8


WT1
hrHPV
ER


NapsinA
AMACR

IHC Summary

Positive	Negative
CK7	GATA3
CK20 (patchy)	p63
PAX8	CDX2
NapsinA	WT1
AMACR	High risk HPV ISH
	Estrogen receptor
	Progesterone receptor

Diagnosis

Diagnosis

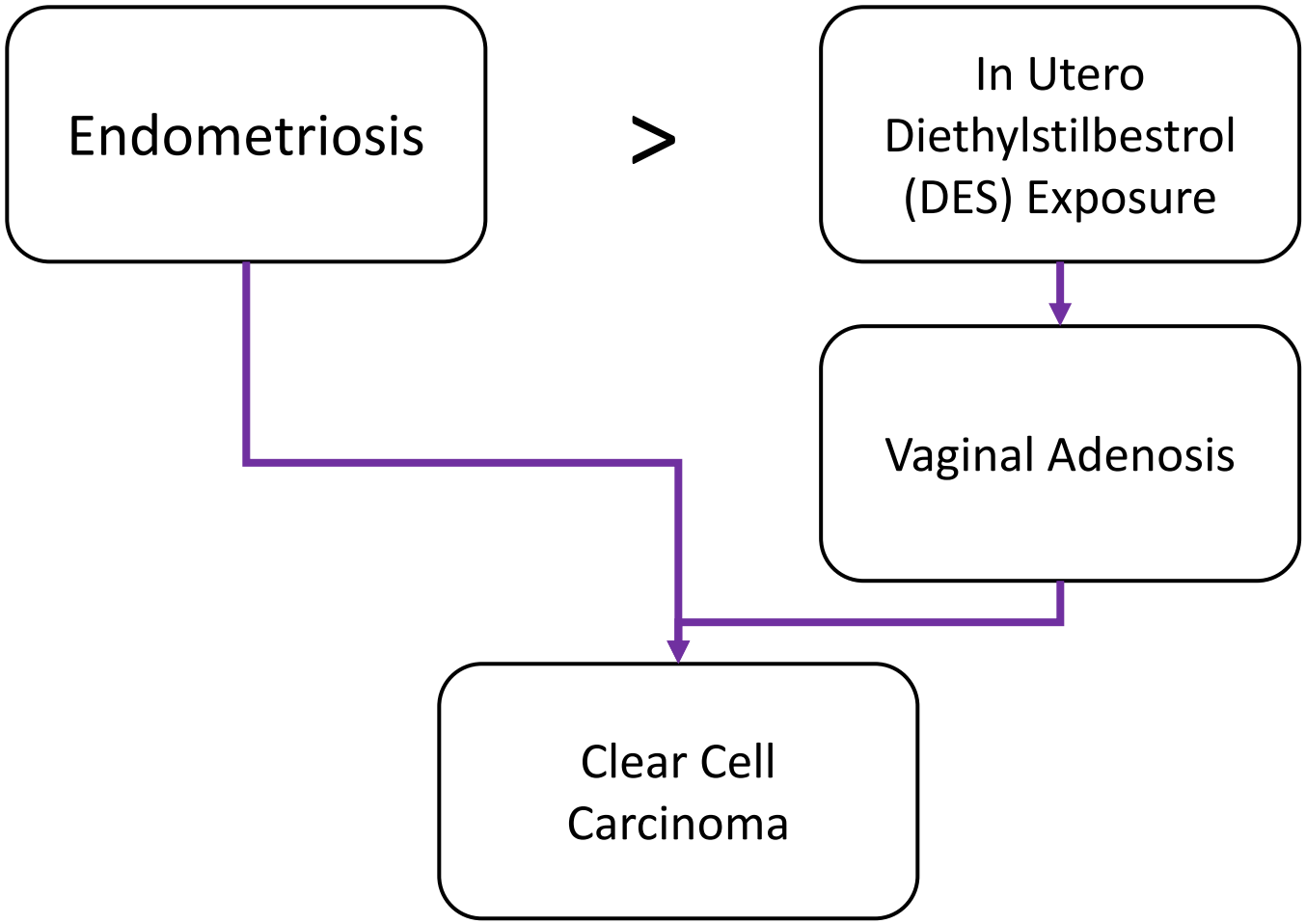
- **Clear cell adenocarcinoma**, invading both periurethral and vaginal stroma with ulceration of both urethral and vaginal mucosa

Comment: Staging this tumor is challenging because its site of origin lies between the urethra and vagina. If considered a urethral tumor, the AJCC stage would be ypT3N2. If considered a vaginal tumor, the tumor stage would be ypT2bN1.

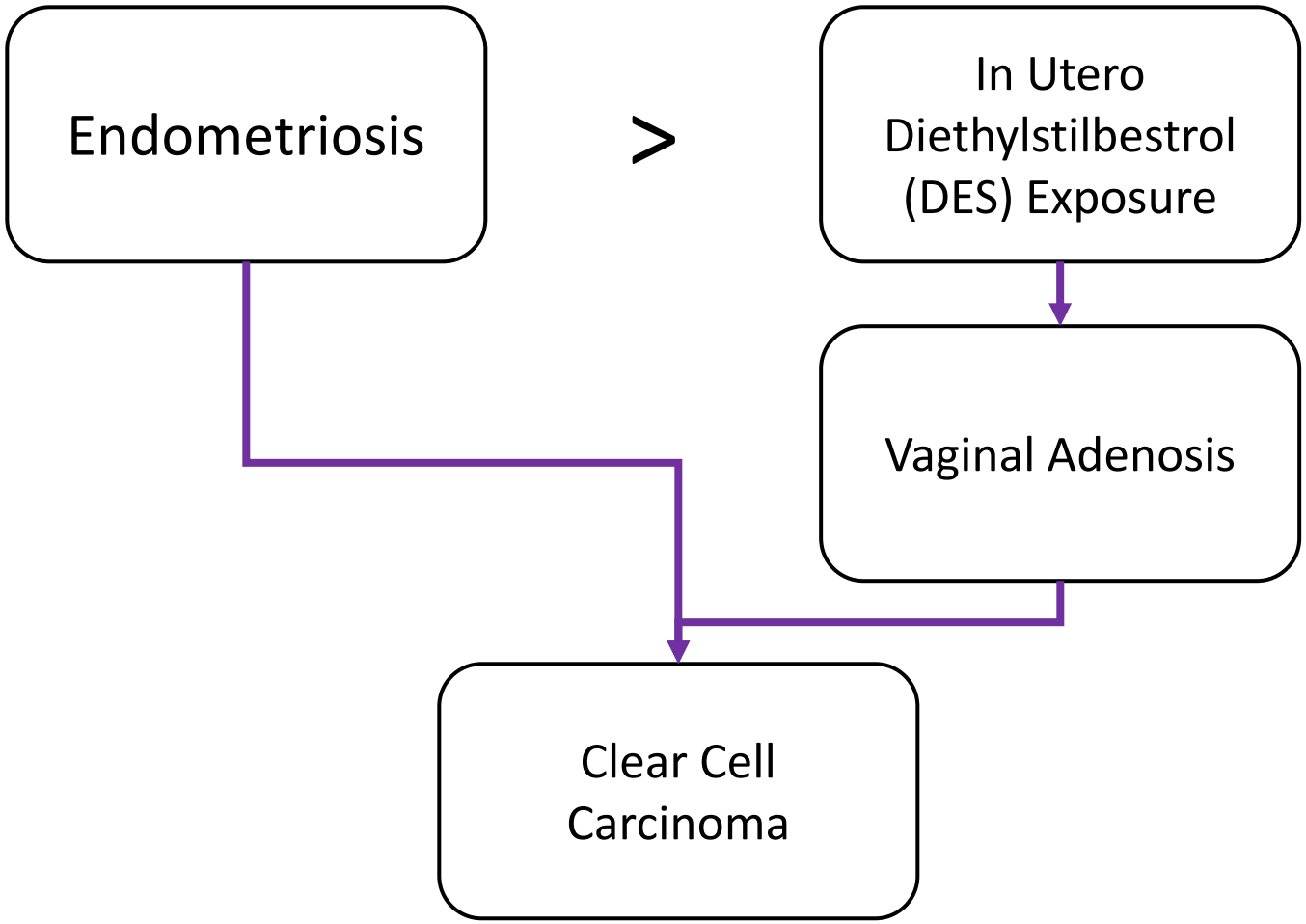
Etiology

Endometriosis > In Utero Diethylstilbestrol (DES) Exposure

Etiology


Endometriosis
>
In Utero Diethylstilbestrol (DES) Exposure
Vaginal Adenosis
Clear Cell Carcinoma

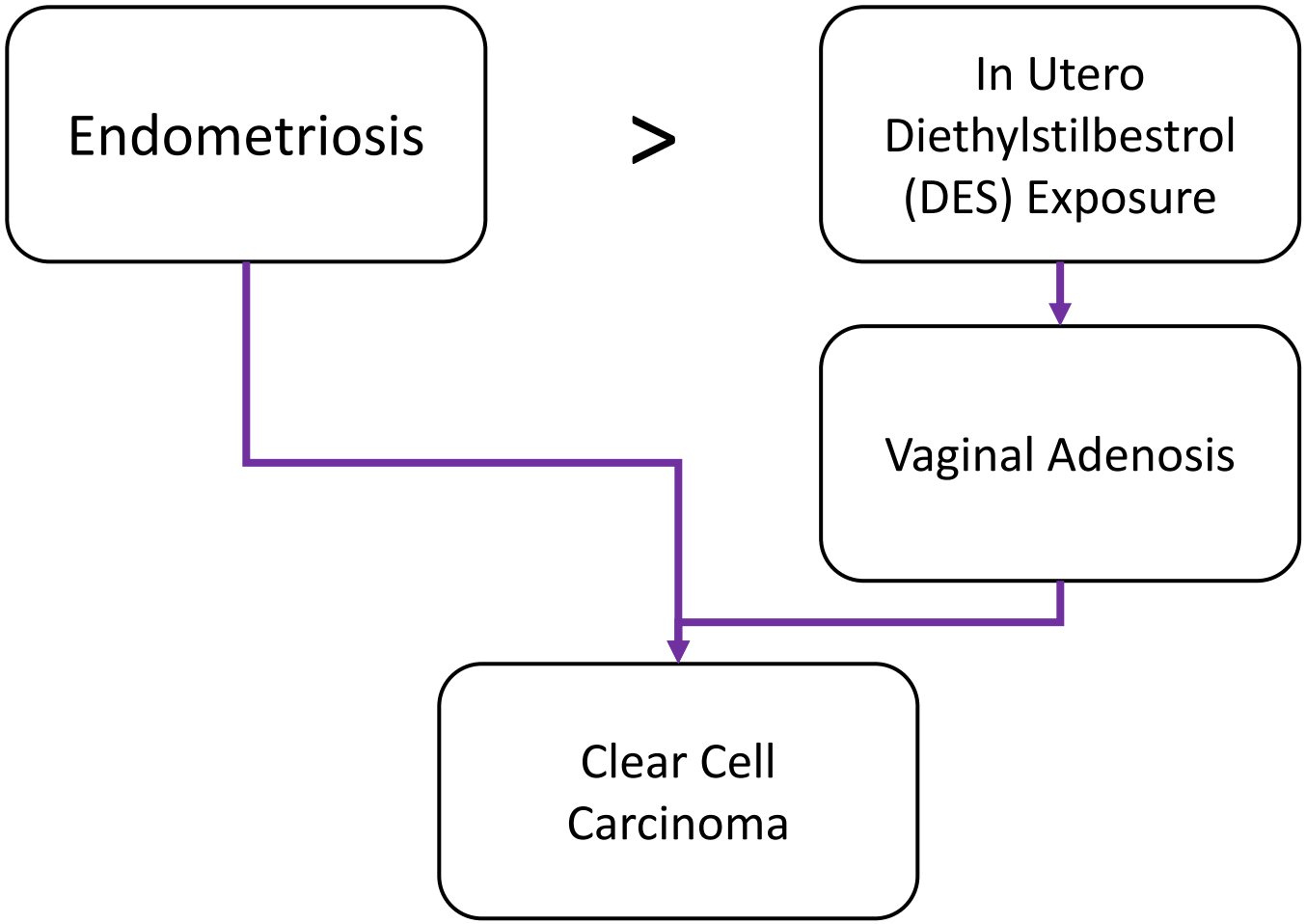
Etiology



The DES Era

1947 DES approved by FDA to prevent early pregnancy loss

Etiology



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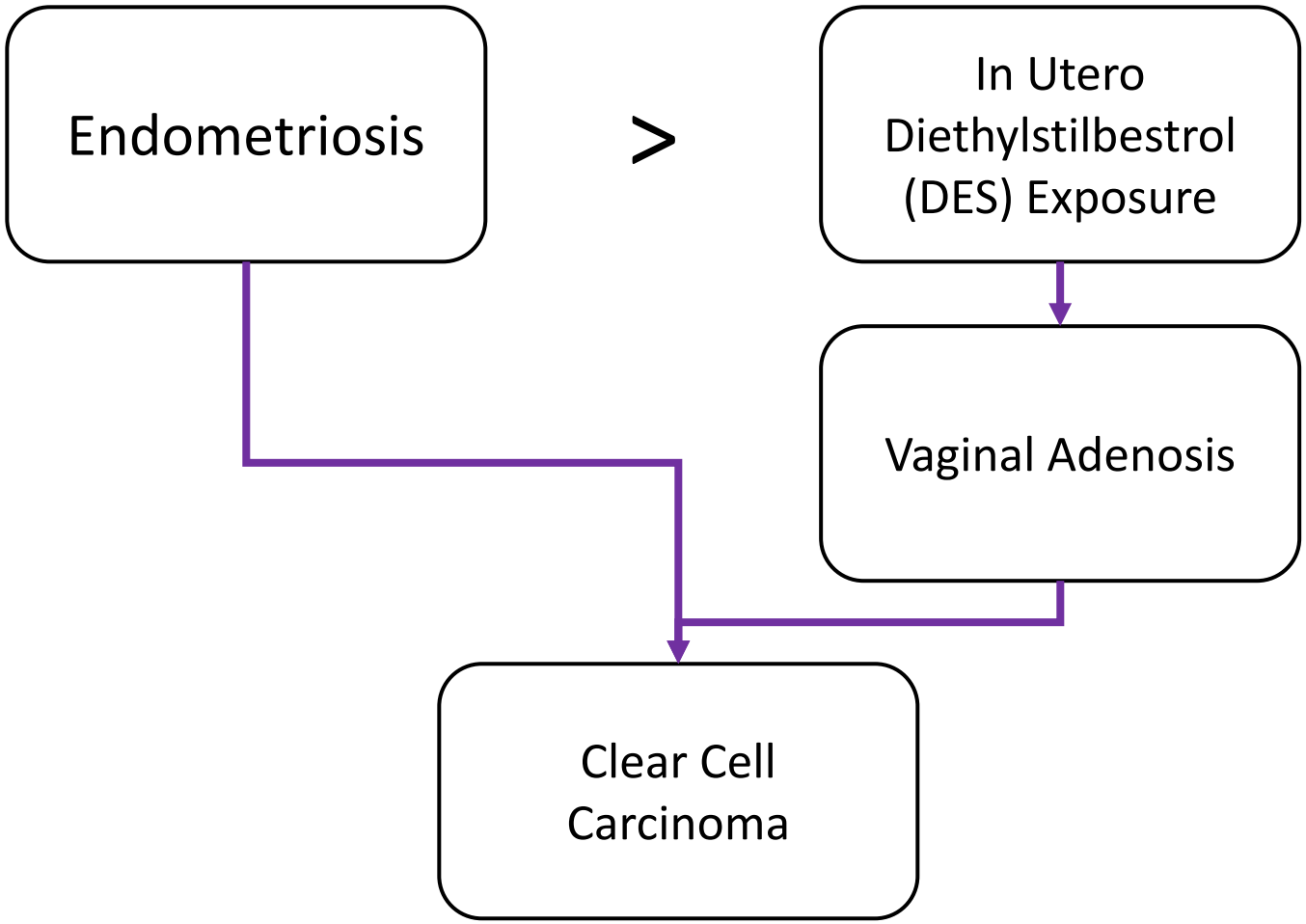
1953 A placebo control trial showed DES did not prevent miscarriages or premature births

Etiology



The DES Era

1947 DES approved by FDA to ~~prevent early pregnancy loss~~

1953 A placebo control trial showed DES did not prevent miscarriages or premature births

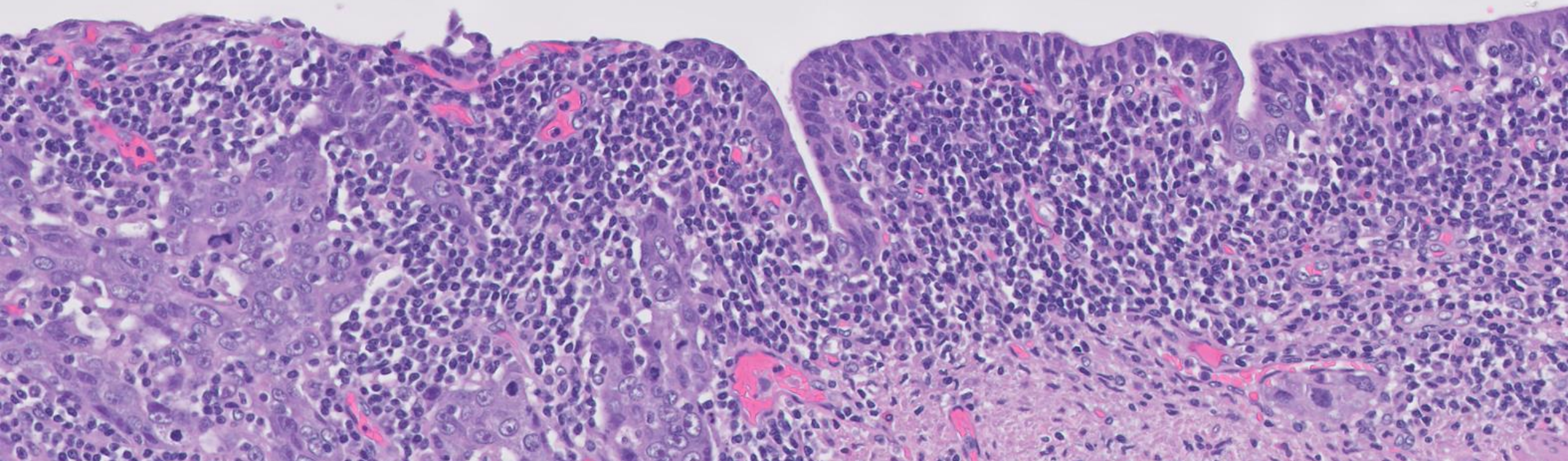
1971 Vaginal adenocarcinoma in girls / young women with in utero DES exposure reported. DES taken off market.

Etiology of our Patient's Carcinoma

- Patient has a history of endometriosis, status post laparoscopy in 1987
- Patient born in 1959 and, following our diagnosis of clear cell carcinoma, reported a history of in utero DES exposure to her clinician

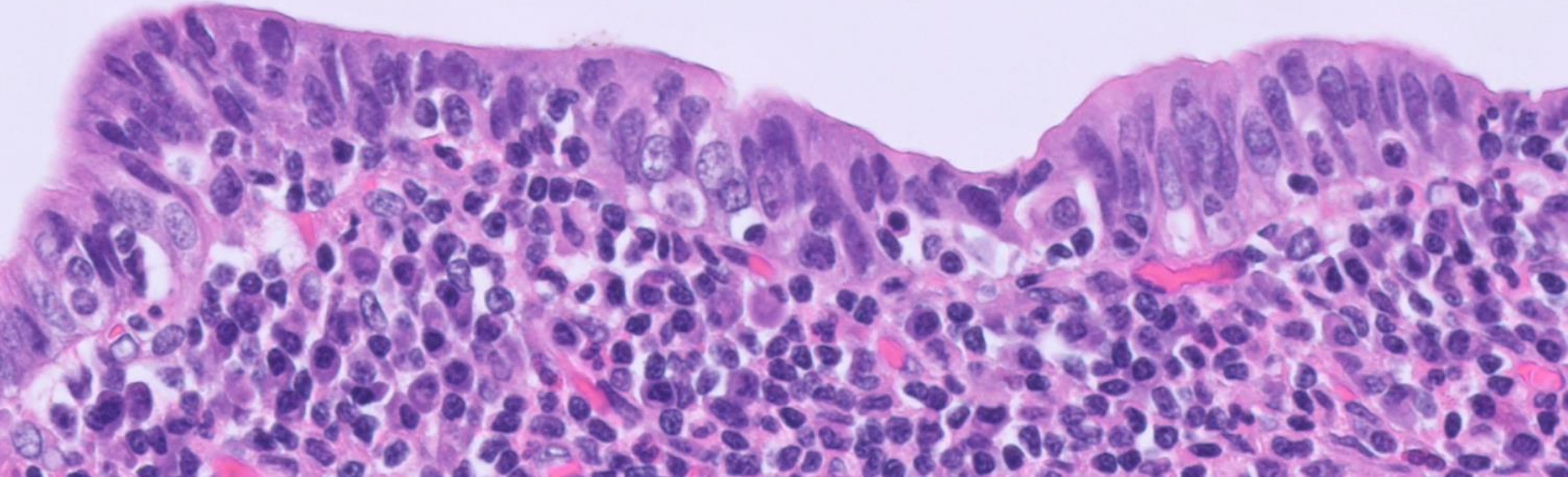
Etiology of our Patient's Carcinoma

- Patient has a history of endometriosis, status post laparoscopy in 1987
- Patient born in 1959 and, following our diagnosis of clear cell carcinoma, reported a history of in utero DES exposure to her clinician
- Tumor appears to arise from benign cystic structure that may represent endometriosis or adenosis



Etiology of our Patient's Carcinoma

- Patient has a history of endometriosis, status post laparoscopy in 1987
- Patient born in 1959 and, following our diagnosis of clear cell carcinoma, reported a history of in utero DES exposure to her clinician
- Tumor appears to arise from benign cystic structure that may represent endometriosis or adenosis



Take-Home Points

- Consider **clear cell carcinoma** on the differential when:
  - Morphology:
    - Tubulocystic / solid arrangements of malignant cells with clear or eosinophilic cytoplasm. Often with hobnailing.
  - Immunophenotype:
    - Positive: CK7, PAX8, Napsin-A, AMACR, HNF-1-β
    - Negative: ER, PR, WT1
    - May show aberrant p53
  - History:
    - Endometriosis
    - Diethylstilbestrol (DES exposure)

    } Look for an in situ component
- Traditional staging may not apply
    - Thorough description helpful

Questions?

References

Brimo F, Raspollini MR, Cheng L, et al. Clear cell adenocarcinoma of the urinary tract. In: WHO Classification of Tumours Editorial Board. Urinary and male genital tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2022 [cited YYYY Mmm D]. (WHO classification of tumours series, 5th ed.; vol. 8). Available from: https://tumourclassification.iarc.who.int/chapters/36.

Gilcrease MZ, Delgado R, Vuitch F, Albores-Saavedra J. Clear cell adenocarcinoma and nephrogenic adenoma of the urethra and urinary bladder: a histopathologic and immunohistochemical comparison. *Hum Pathol*. 1998;29(12):1451-1456. doi:10.1016/s0046-8177(98)90015-6

Herbst AL, Kurman RJ, Scully RE, Poskanzer DC. Clear-cell adenocarcinoma of the genital tract in young females. Registry report. *N Engl J Med*. 1972;287(25):1259-1264. doi:10.1056/NEJM197212212872501

Waggoner SE, Mittendorf R, Biney N, Anderson D, Herbst AL. Influence of in utero diethylstilbestrol exposure on the prognosis and biologic behavior of vaginal clear-cell adenocarcinoma. *Gynecol Oncol*. 1994;55(2):238-244. doi:10.1006/gyno.1994.1284

Staats PN, Young RH, Kong CS. Clear cell carcinoma of the vagina. In: WHO Classification of Tumours Editorial Board. Female genital tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2020 [cited 2024 Oct 3]. (WHO classification of tumours series, 5th ed.; vol. 4). Available from: https://tumourclassification.iarc.who.int/chapters/34.

Waggoner SE, Mittendorf R, Biney N, Anderson D, Herbst AL. Influence of in utero diethylstilbestrol exposure on the prognosis and biologic behavior of vaginal clear-cell adenocarcinoma. *Gynecol Oncol*. 1994;55(2):238-244. doi:10.1006/gyno.1994.1284

White MC, Weir HK, Soman AV, Peipins LA, Thompson TD. Risk of clear-cell adenocarcinoma of the vagina and cervix among US women with potential exposure to diethylstilbestrol in utero. *Cancer Causes Control*. 2022 Aug;33(8):1121-1124. doi: 10.1007/s10552-022-01598-3. Epub 2022 Jun 29. PMID: 35767133; PMCID: PMC9377316.

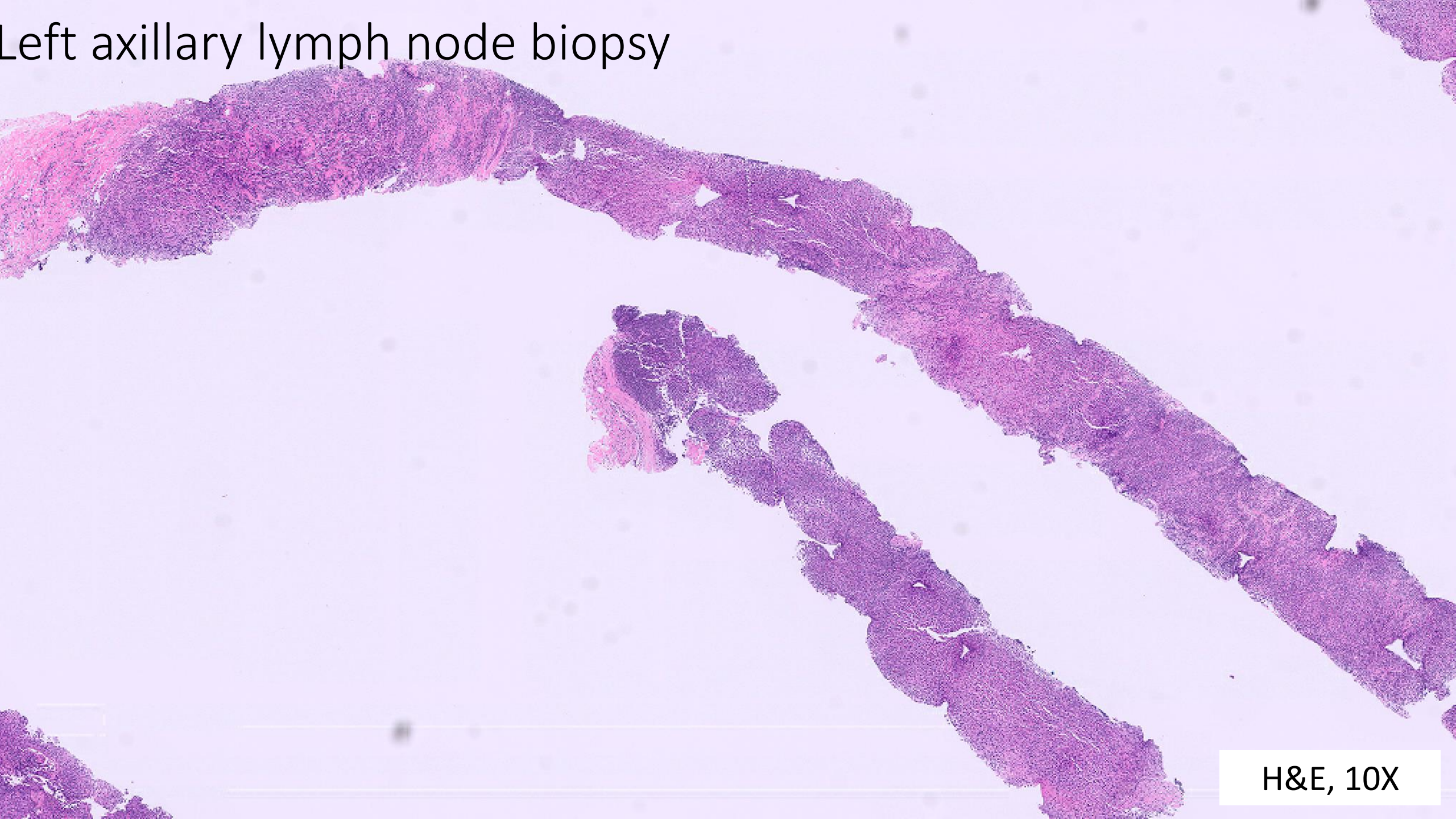
24-1004

Nivaz Brar, and Jason Kurzer; Stanford

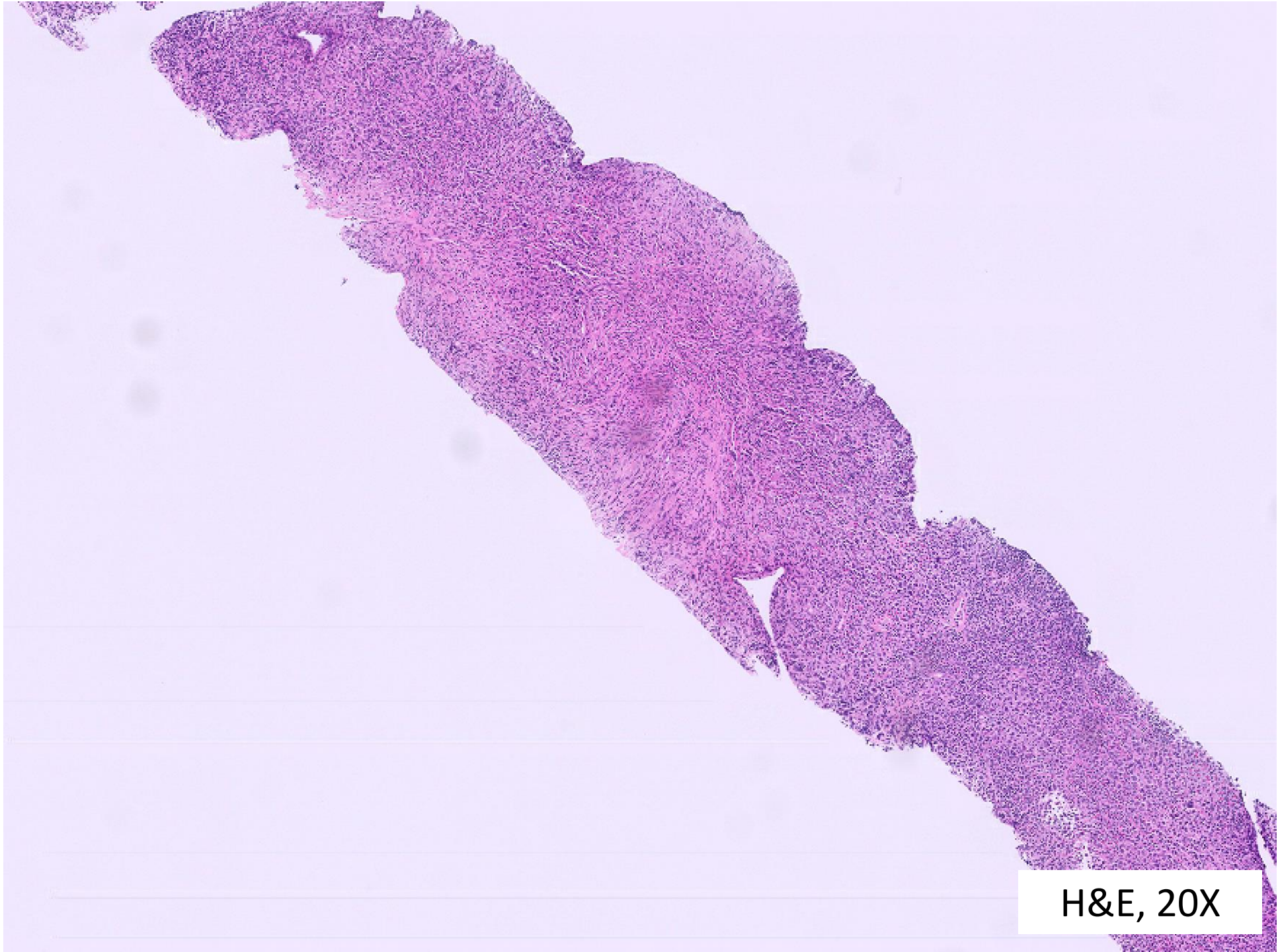
36-year-old female with a history of breast cancer presenting with bilateral axillary lymphadenopathy.

PET-CT imaging shows mediastinal lymphadenopathy and profound lymphadenopathy above and below the diaphragm.

Left axillary lymph node biopsy



H&E, 10X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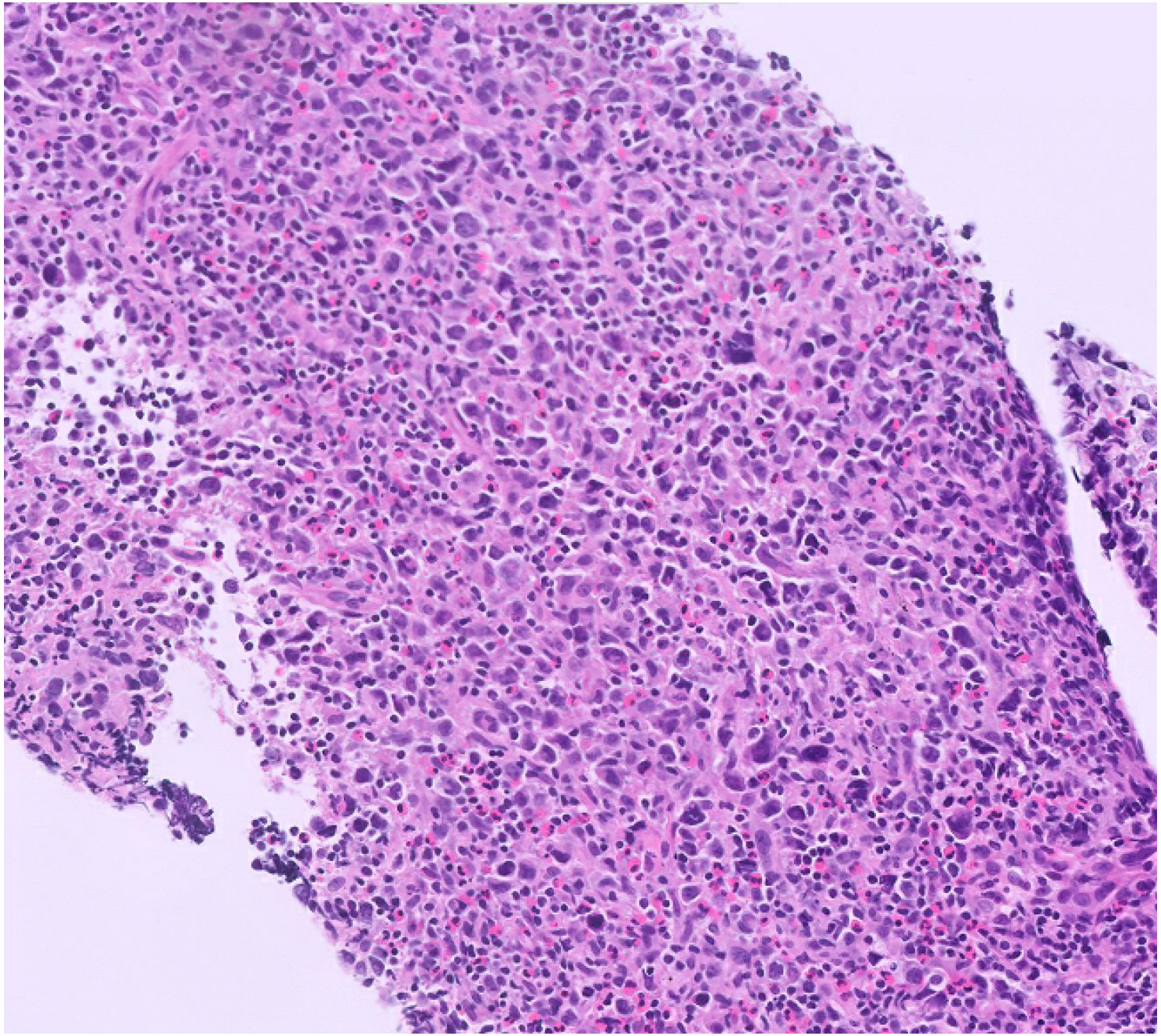

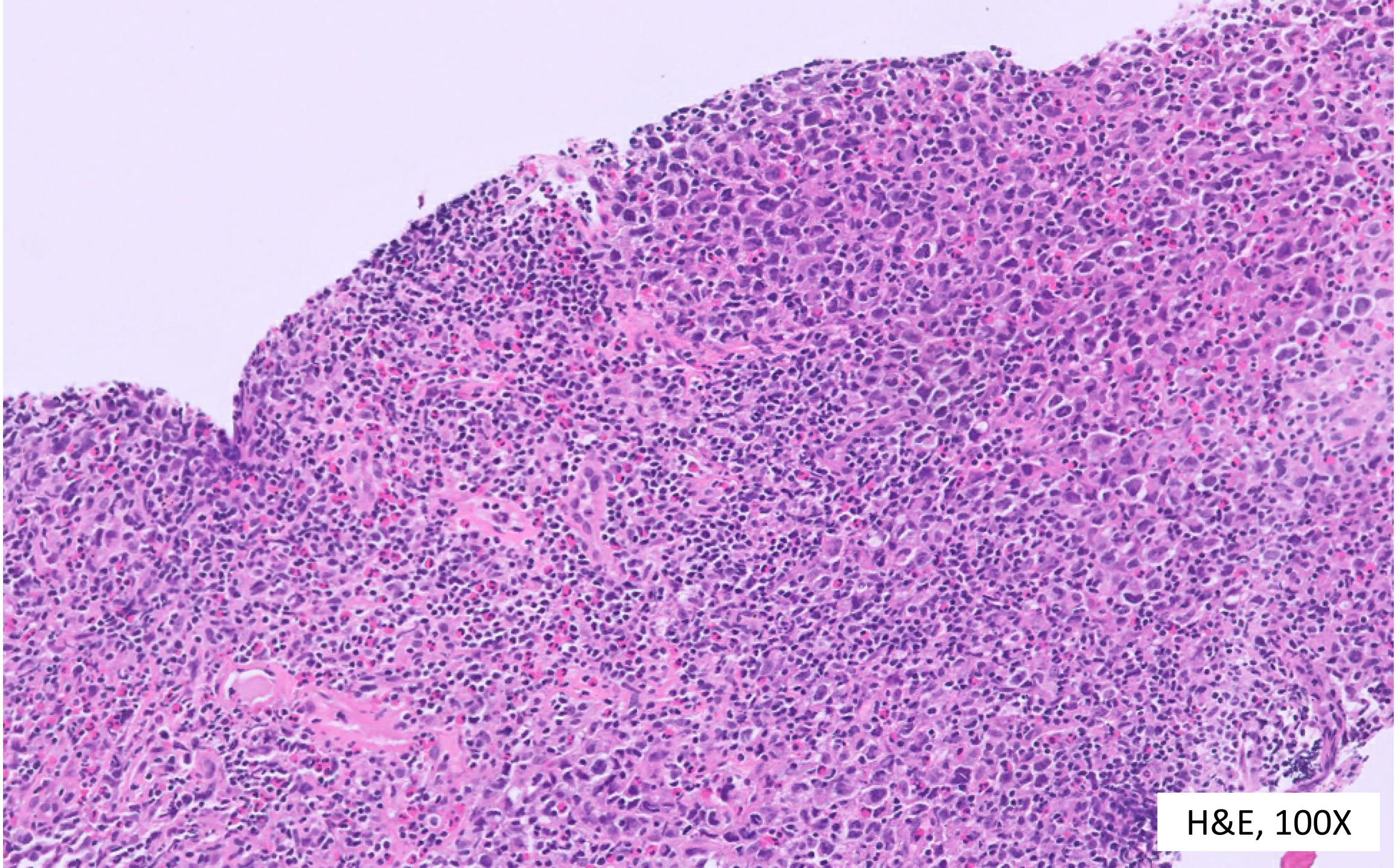
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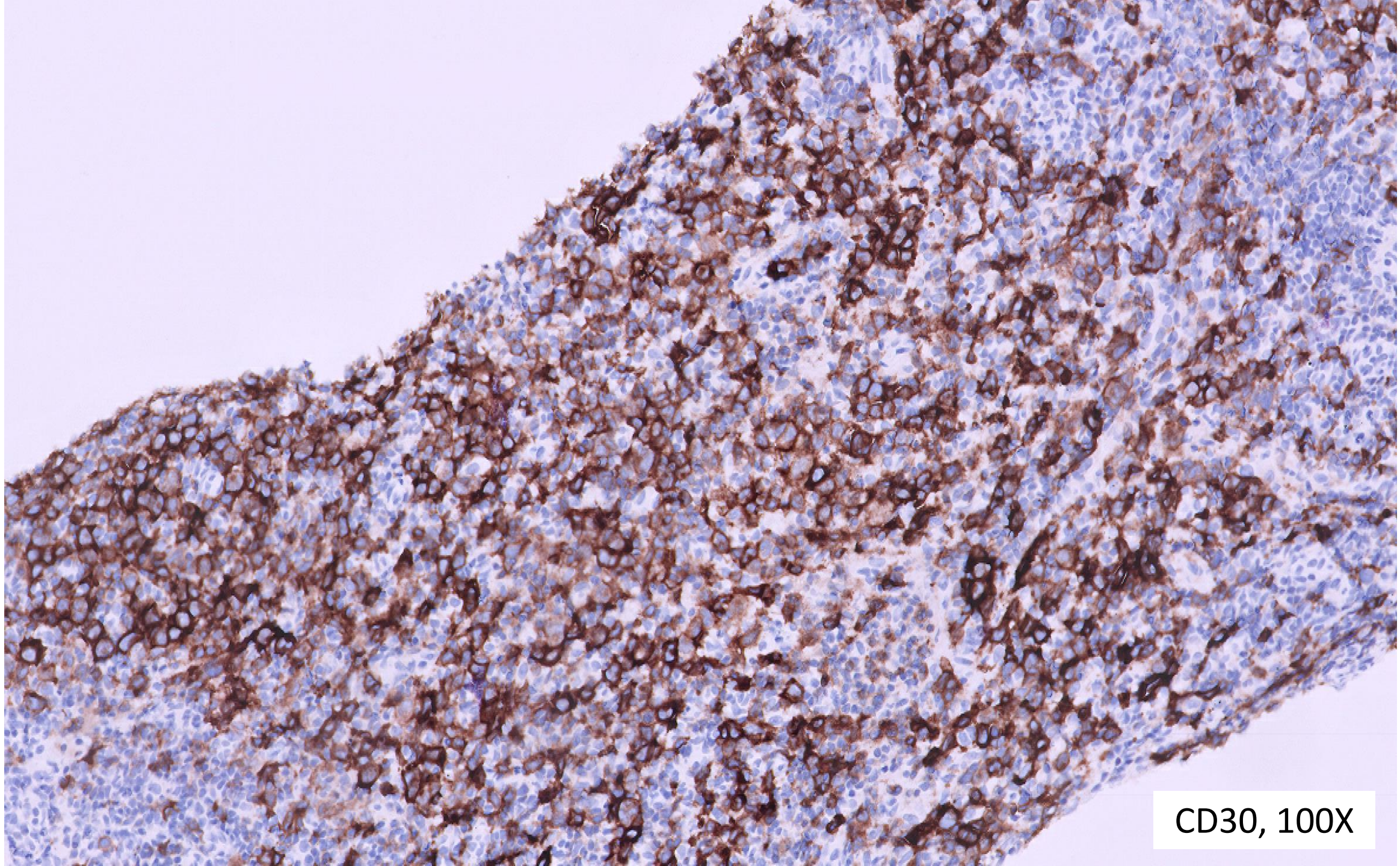
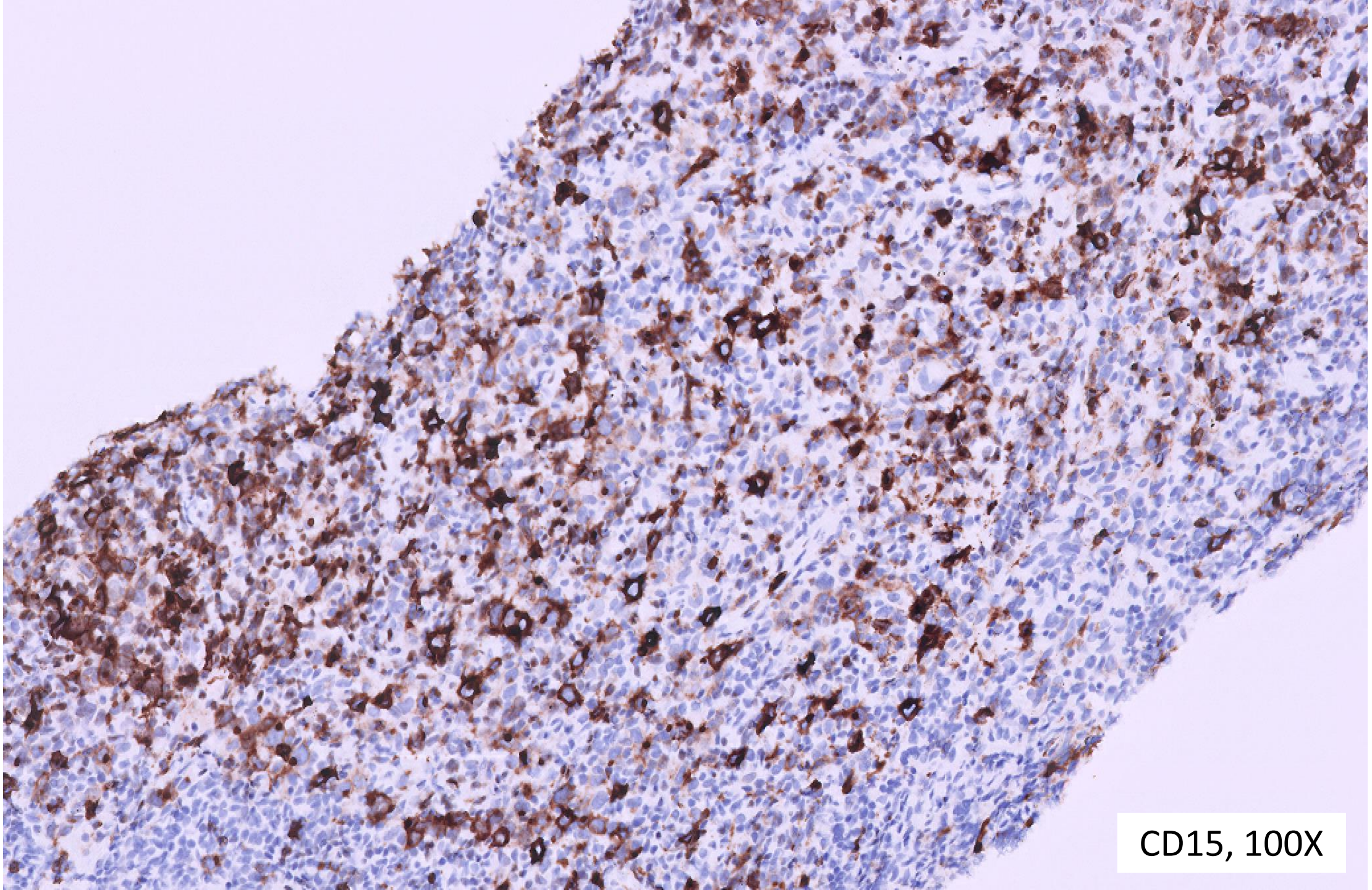

CD30, 100X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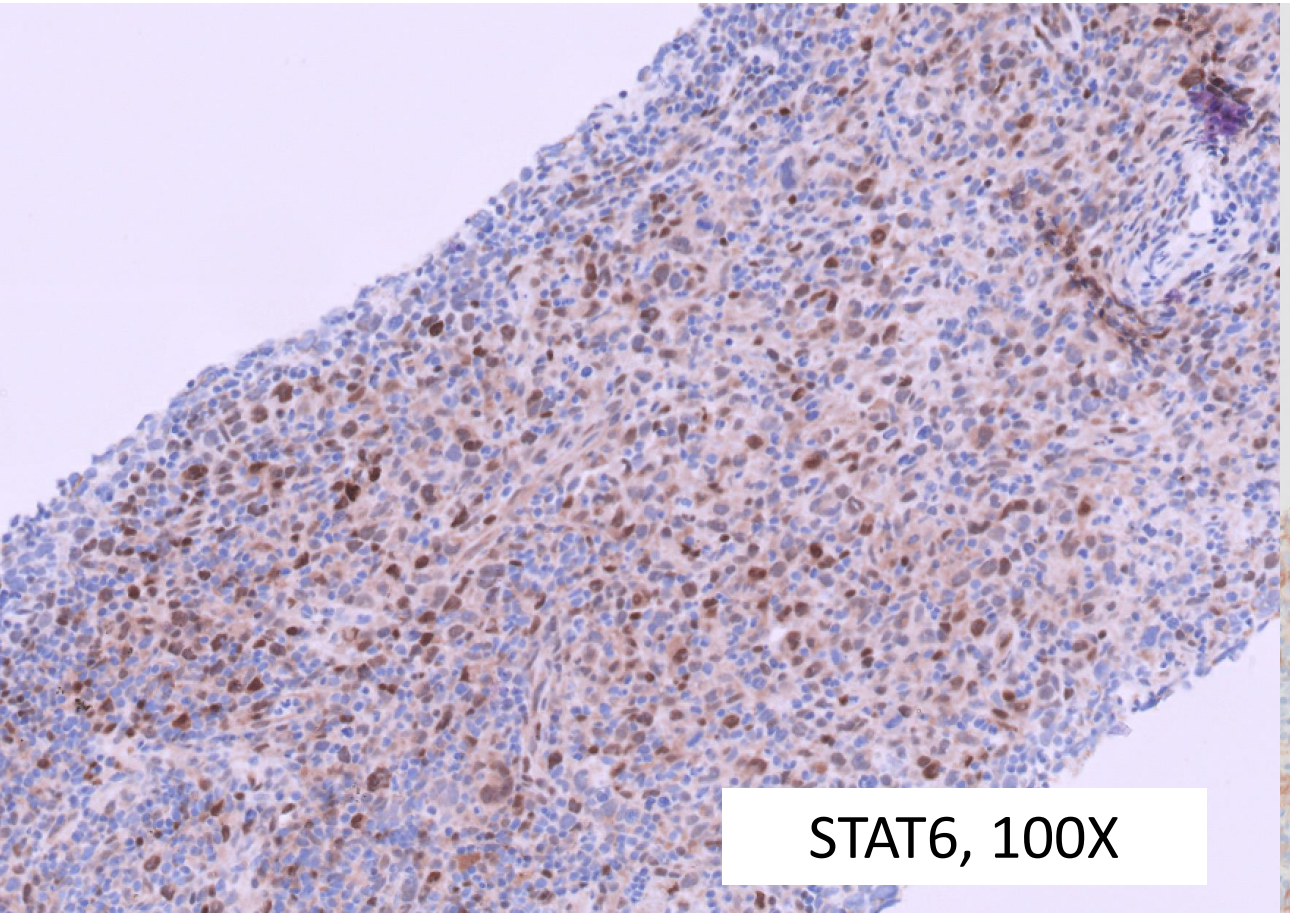
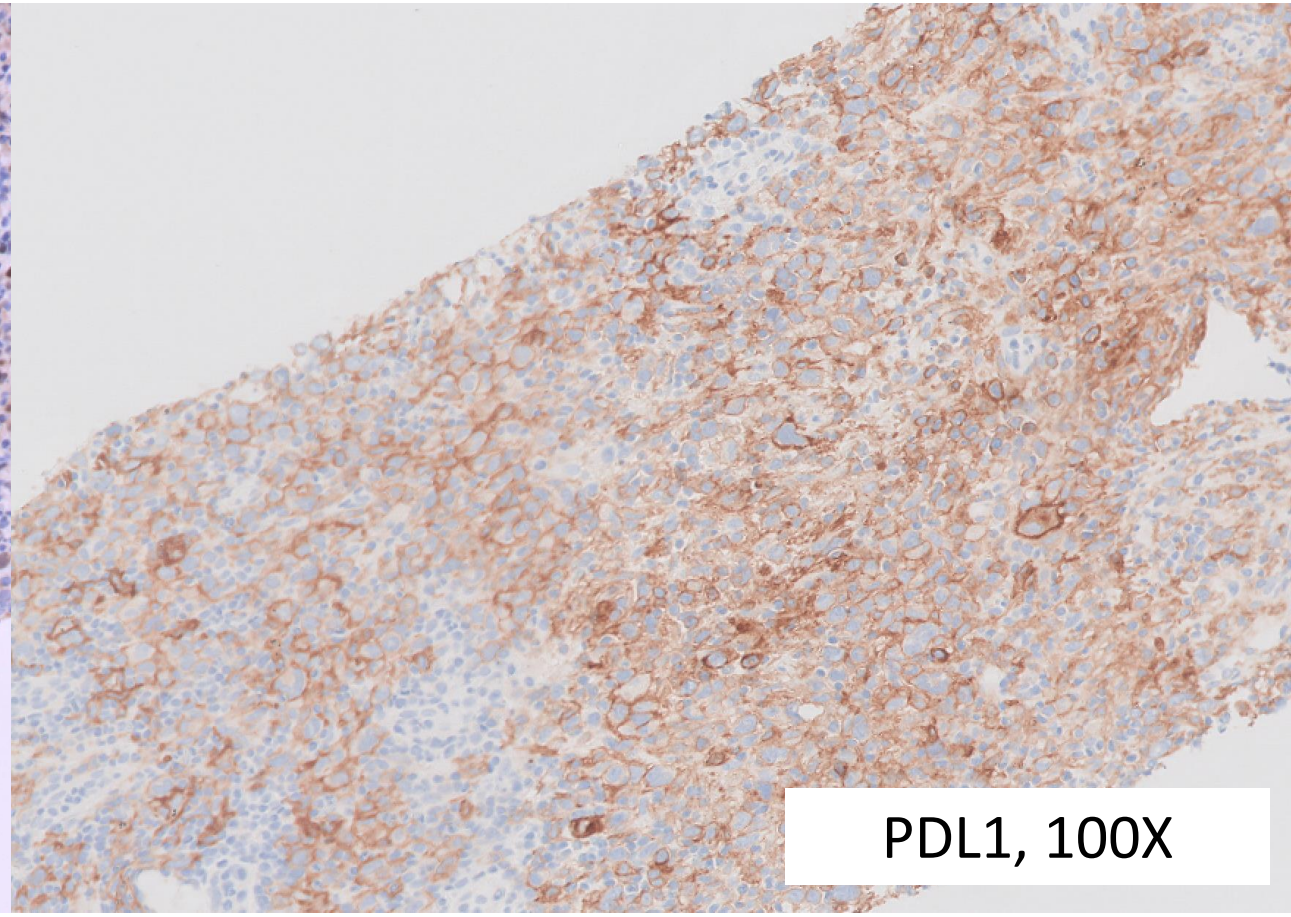
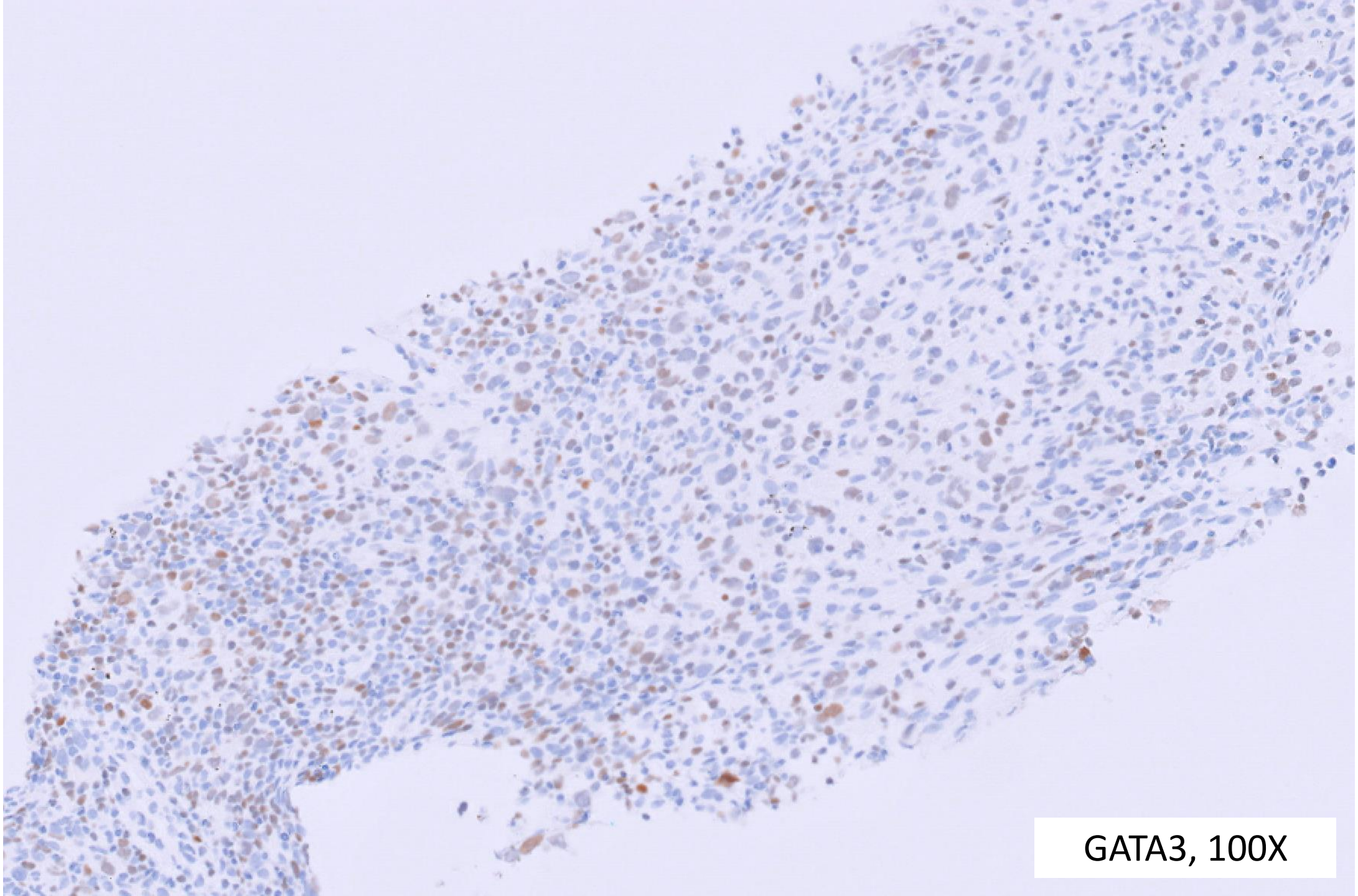


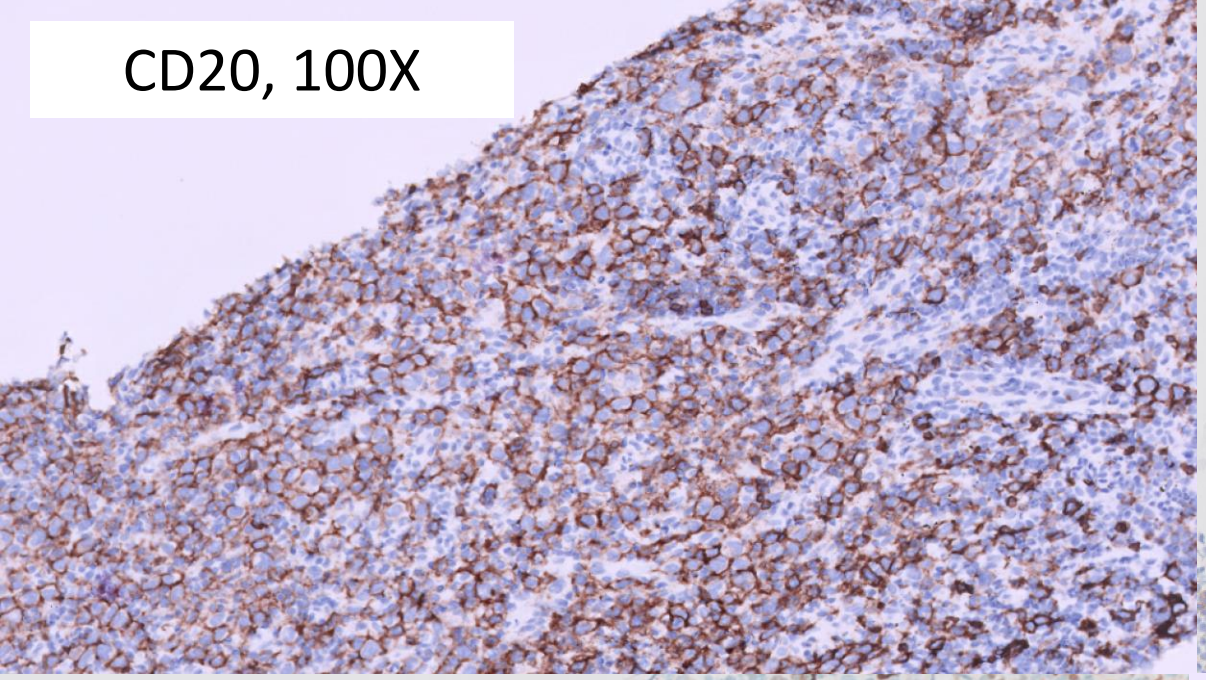
STAT6, 100X

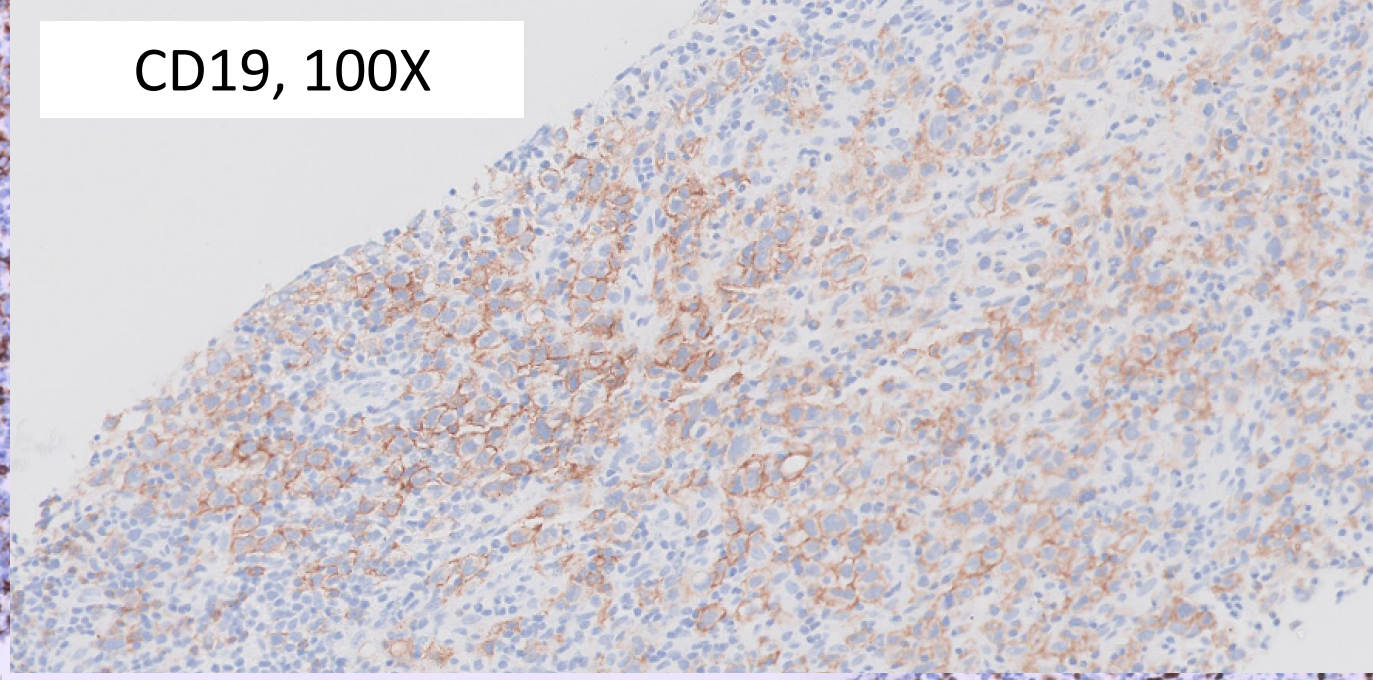


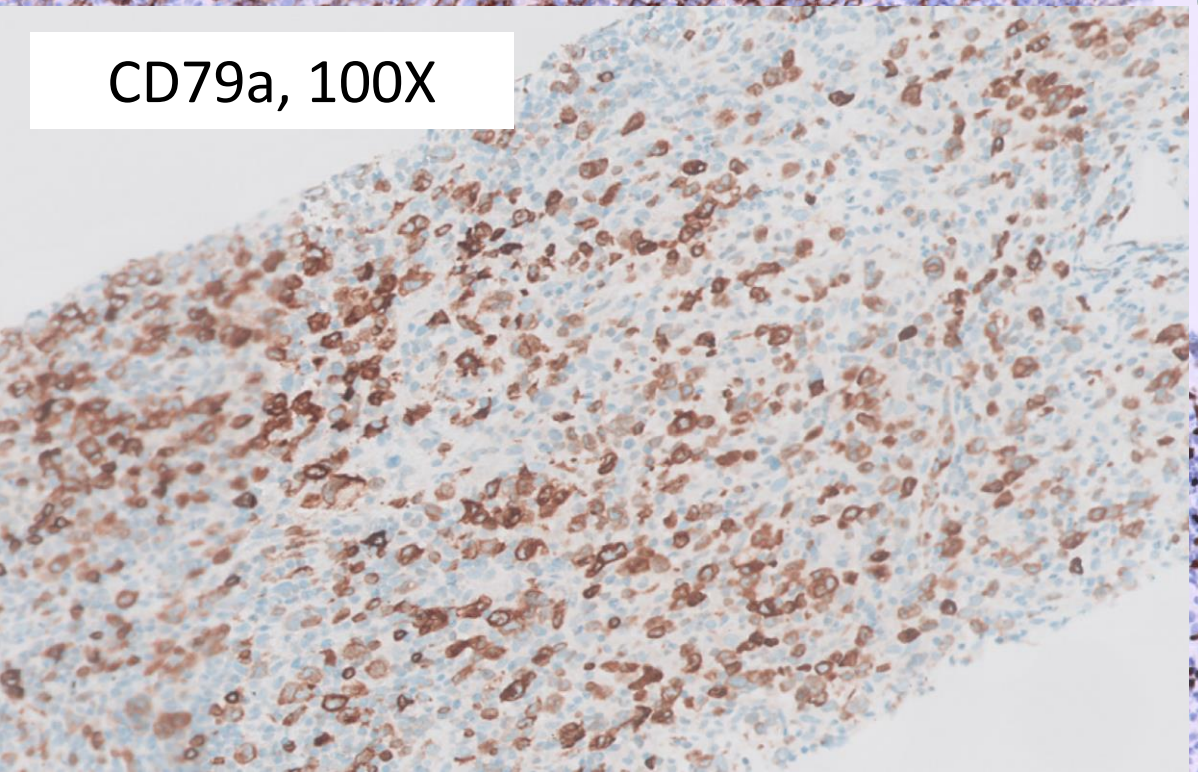
PDL1, 100X

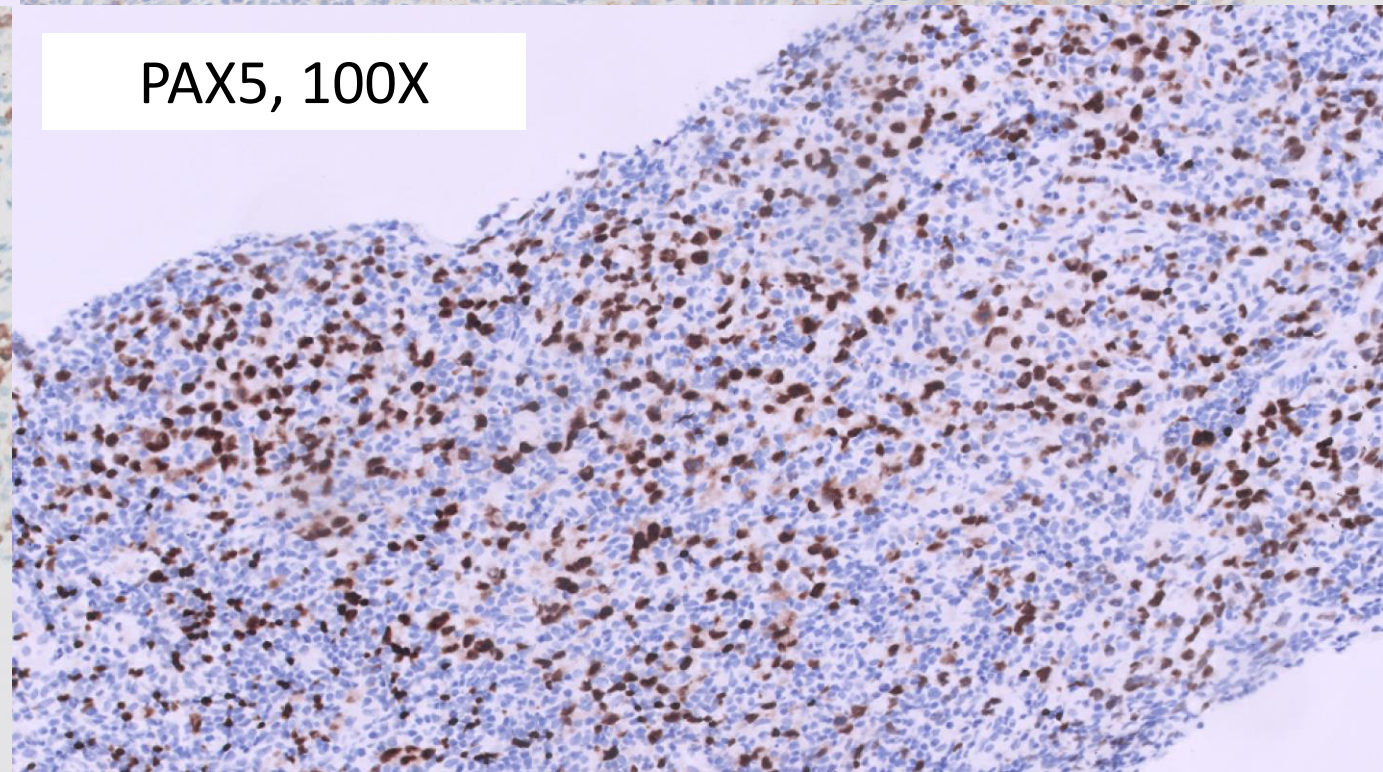


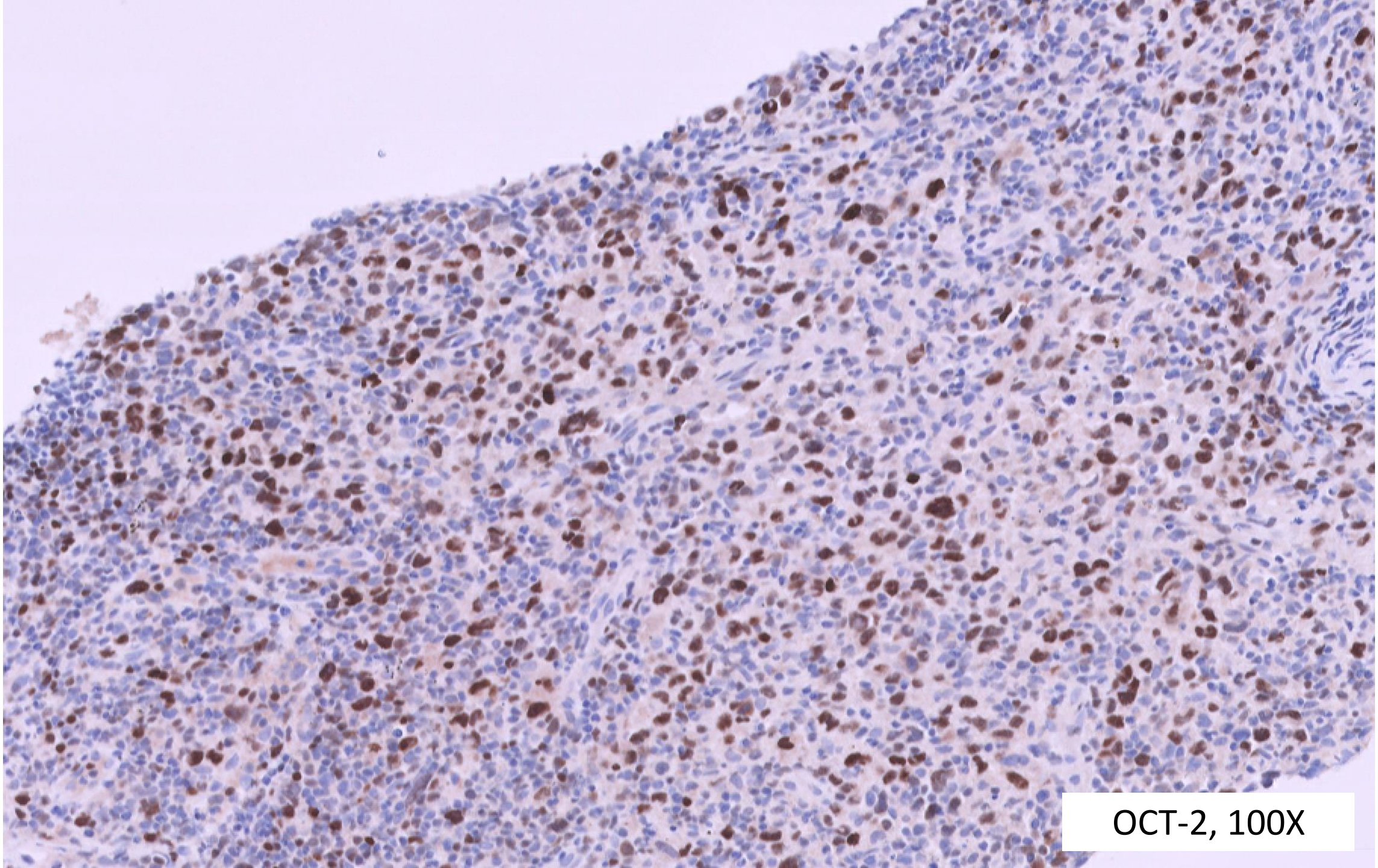
GATA3, 100X

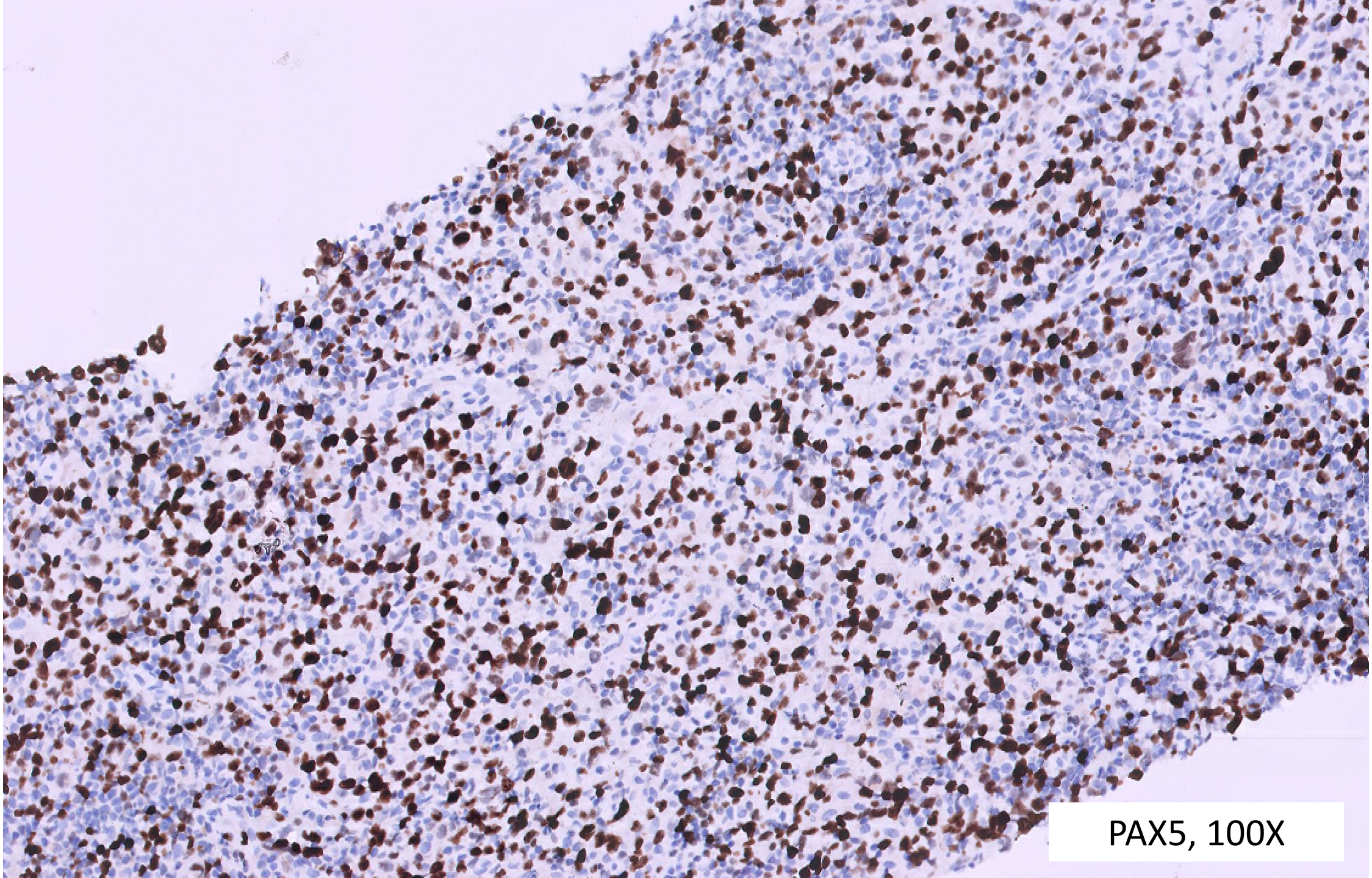

CD20, 100X


CD19, 100X


CD79a, 100X


PAX5, 100X


OCT-2, 100X


PAX5, 100X

IHC

- Positive for:
  - CD30, CD15, STAT6, PDL1, GATA3, CD20, CD19, CD79a, PAX5, OCT-2, BOB1, MUM1
  - Ki67 >90%
- Negative for:
  - EBV, MEF2B, CD22, CD10 and BCL6

DIAGNOSIS?

Diagnosis

- Favor mediastinal grey zone lymphoma

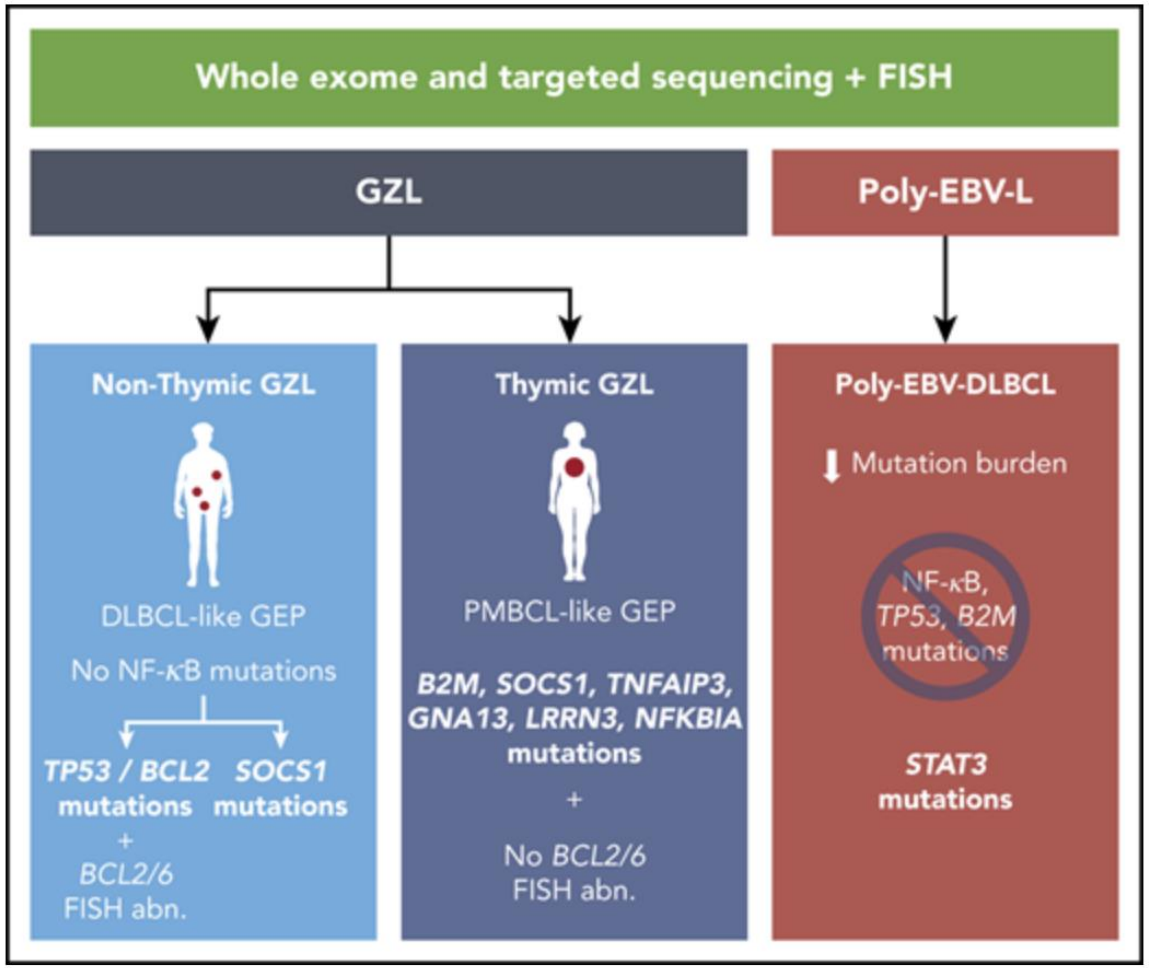
Mediastinal Grey Zone Lymphoma

- Rare entity that presents in the mediastinum of primarily young men (30 years) with morphologic, immunophenotypic, and molecular similarities with both primary mediastinal B-cell lymphoma (PMBCL) and classic Hodgkin lymphoma (CHL, commonly nodular sclerosis type)
- Clinical features: anterior mediastinal mass, cough, dyspnea, supraclavicular lymphadenopathy, B-symptoms, superior vena cava syndrome
- Histology:
  - MGZL CHL-like show sheet like proliferation of large atypical Reed-Sternberg-like cells in a background of inflammation of fibrosis. The inflammatory infiltrate composed of eosinophils, lymphocytes, plasma cells, and histiocytes (similar to NSCHL).
  - MGZL PMBCL-like monomorphic with a proliferation of medium-sized to large neoplastic cells without an inflammatory infiltrate. Atypical pleomorphic cells may be present.
- IHC: Retained B-cell program strong CD20, CD19, and CD79a and/or PAX5, OCT2, BOB1. Must be PAX5 and CD20 positive with an additional B-cell marker. CD30+, CD15+/-, MUM1+, BCL6+, CD10-, EBV-.
- Prognosis: Worse prognosis than CHL (87% 5 year survival rate)[1] and PMBCL (80-90% 5 year survival)[2]
- Differential: CHL, PMBCL, diffuse large B-cell lymphoma NOS, EBV+ diffuse large B-cell lymphoma, T-cell histiocyte rich large B-cell lymphoma

1. Siegel et al. (2022). Cancer statistics, 2022. *CA: a cancer journal for clinicians*.
2. Dabrowska-Iwanicka et al. (2014) Primary mediastinal large B-cell lymphoma. *Curr Hematol Malig Rep.*

Overlapping molecular features

- GZL with thymic niche involvement are found to have molecular overlap with PMBCL and CHL including:
  SOCS1 (45%), *B2M* (45%), *TNFAIP3* (35 %), *GNA13* (35%), *LRRN3* (32%), and *NFKBIA* (29%)
- GZL without thymic niche involvement found mutations in the following apoptosis associated genes:
  TP53 (39%), *BCL2* (28%), and *BIRC6* (22%)
- These findings suggest different cells of origin



Sarkozy et al. Mutational landscape of gray zone lymphoma. *Blood* 2021

Conclusions

- Diagnostic difficulty as this entity represents a spectrum of disease rather than a distinct process
- No current molecular characterization

References

- WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; Forthcoming 2024. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.who.int/.
- Qasrawi Ayman, et al. Trends and outcomes of gray zone lymphoma in the United States: a population-based registry study. *Biol. Blood Marrow Transplant.* 2020;26(3):S230.
- Uczkowski D, Ashraf H, Cherry M, Dimov N. Gray zone lymphoma: A case report and comprehensive review of literature. *Leuk Res Rep*. 2023;19:100372. Published 2023 May 27. doi:10.1016/j.lrr.2023.100372
- Dabrowska-Iwanicka A, Walewski JA. Primary mediastinal large B-cell lymphoma. *Curr Hematol Malig Rep*. 2014;9(3):273-283. doi:10.1007/s11899-014-0219-0 PMBL survival
- Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: a cancer journal for clinicians*, *72*(1), 7–33.
- Pileri S, Tabanelli V, Chiarle R, Calleri A, Melle F, Motta G, Sapienza MR, Sabattini E, Zinzani PL, Derenzini E. Mediastinal Gray-Zone Lymphoma: Still an Open Issue. *Hemato*. 2023; 4(3):196-206. https://doi.org/10.3390/hemato4030016

24-1005

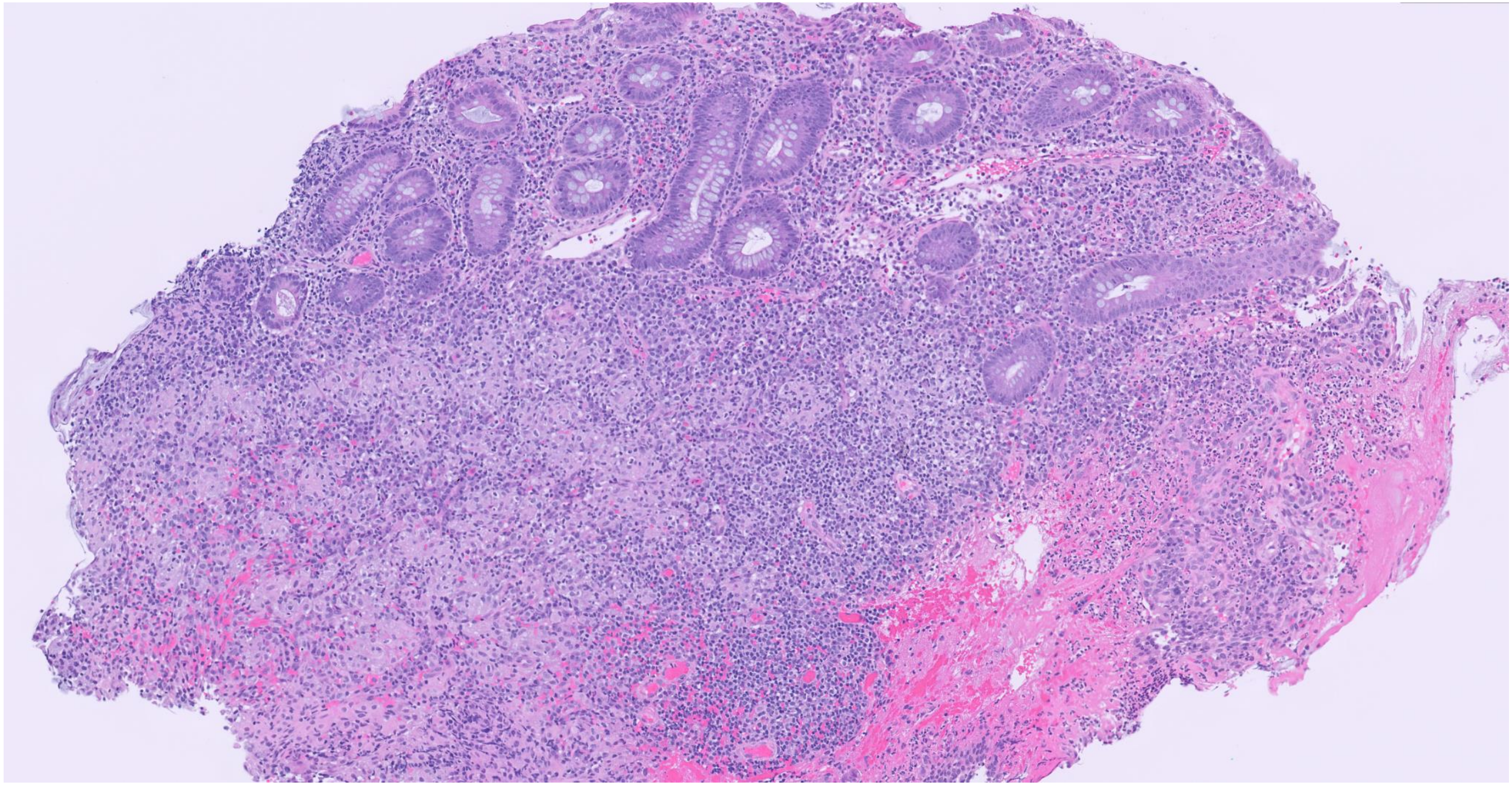
Polina Burov/ Steven Morrow Chirieleison/ David Bingham; Stanford

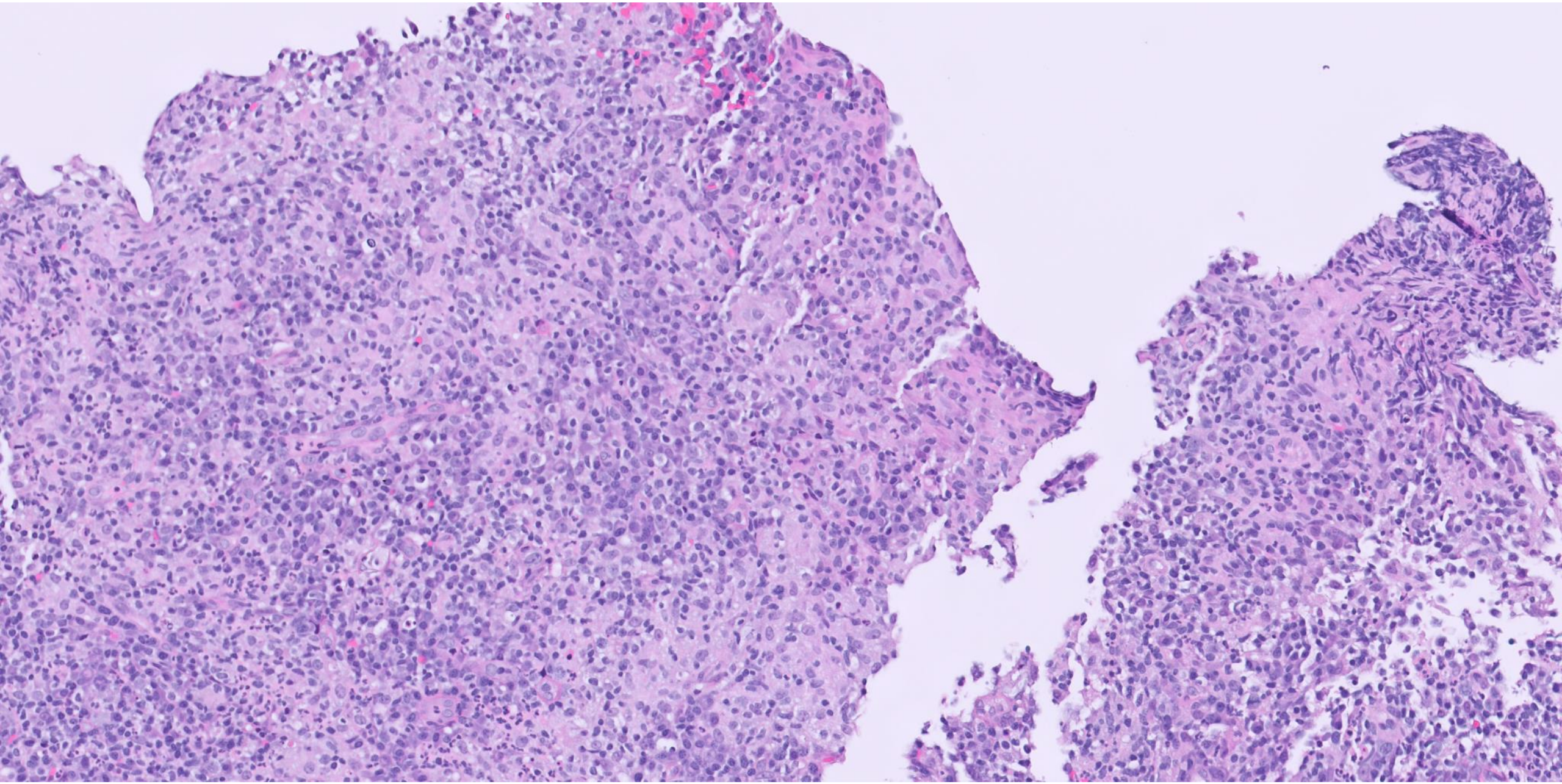
18 y.o. female with ongoing Crohn’s disease underwent routine follow-up

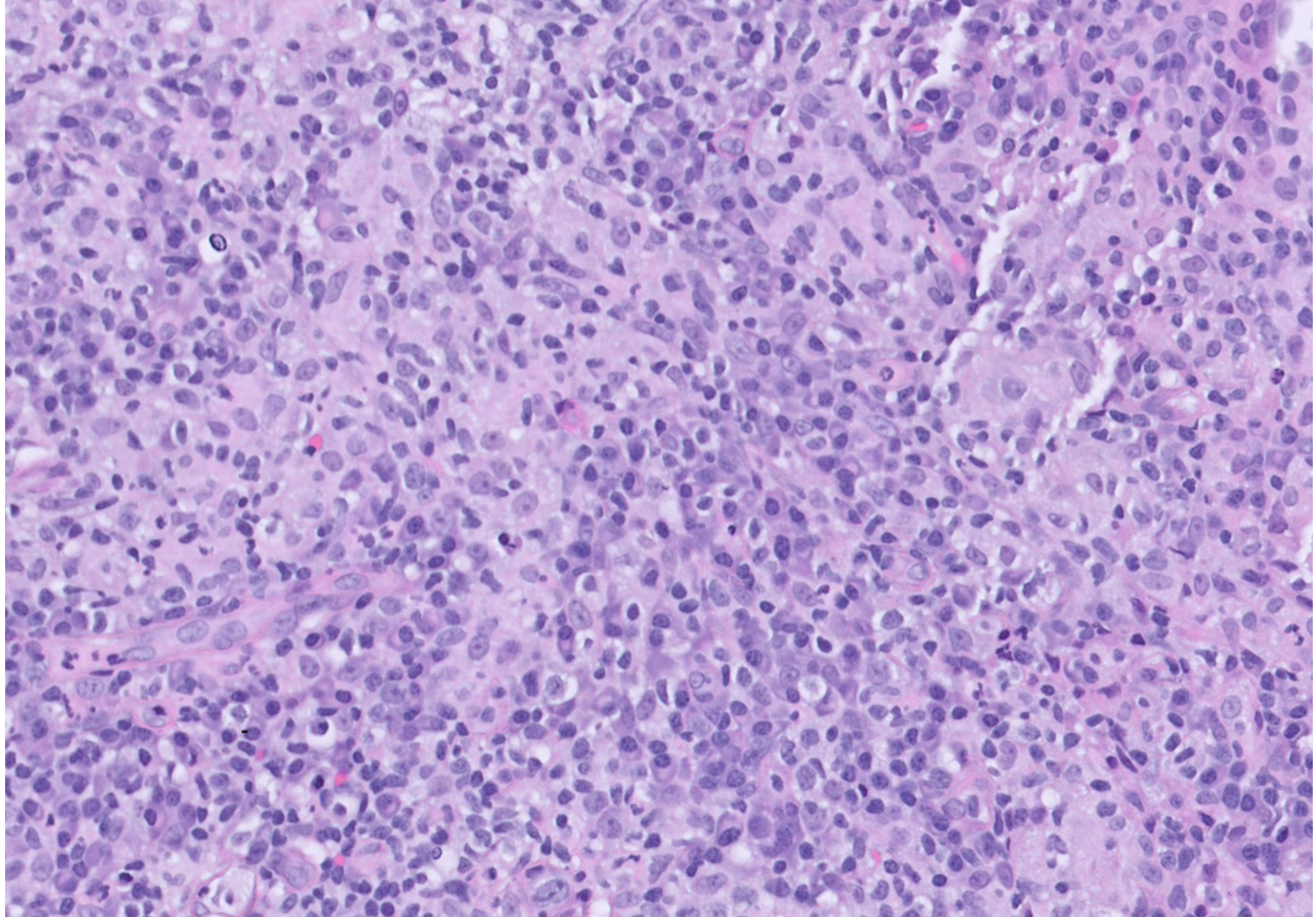
Colonoscopy: Small polypoid lesions (~1cm) were detected in 3 distinct areas. Two nodules with ulcerated top at 45 cm and 65 cm to the anus were biopsied. No symptoms, the patient was in clinical remission.

Previous diagnosis: Crohn's disease involving terminal ileum 06/22/2023

Medications (for the past 3 years): infliximab, methotrexate

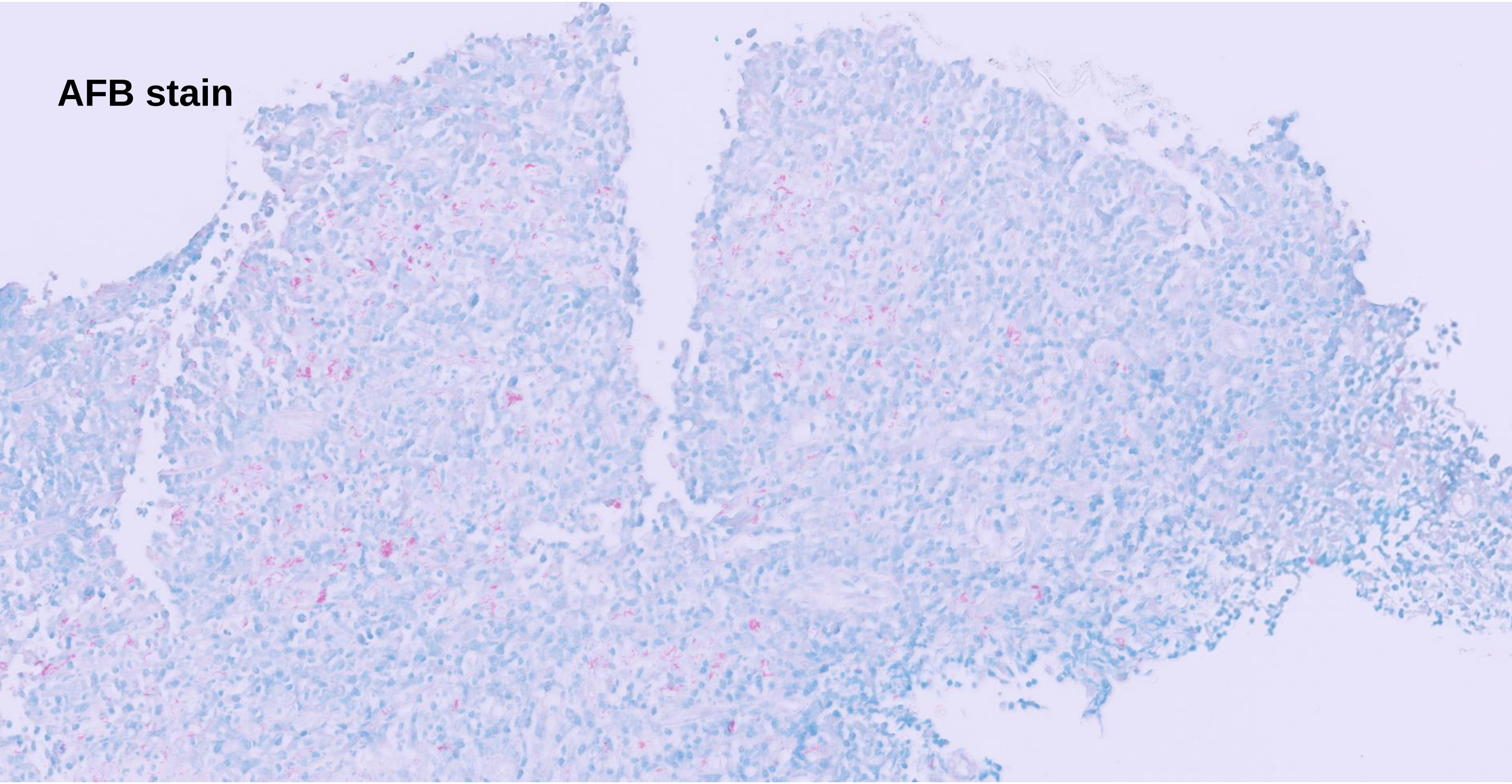




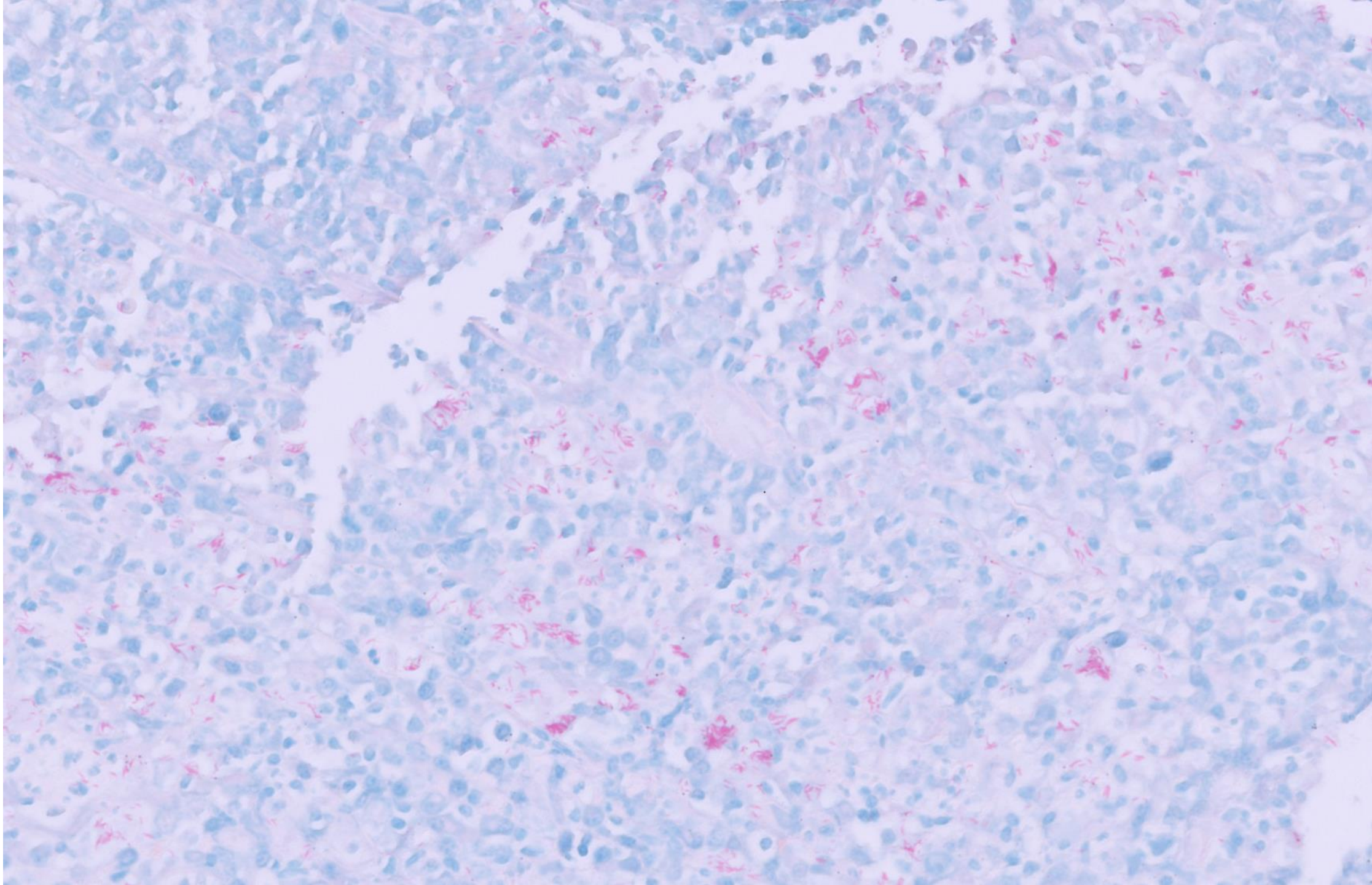


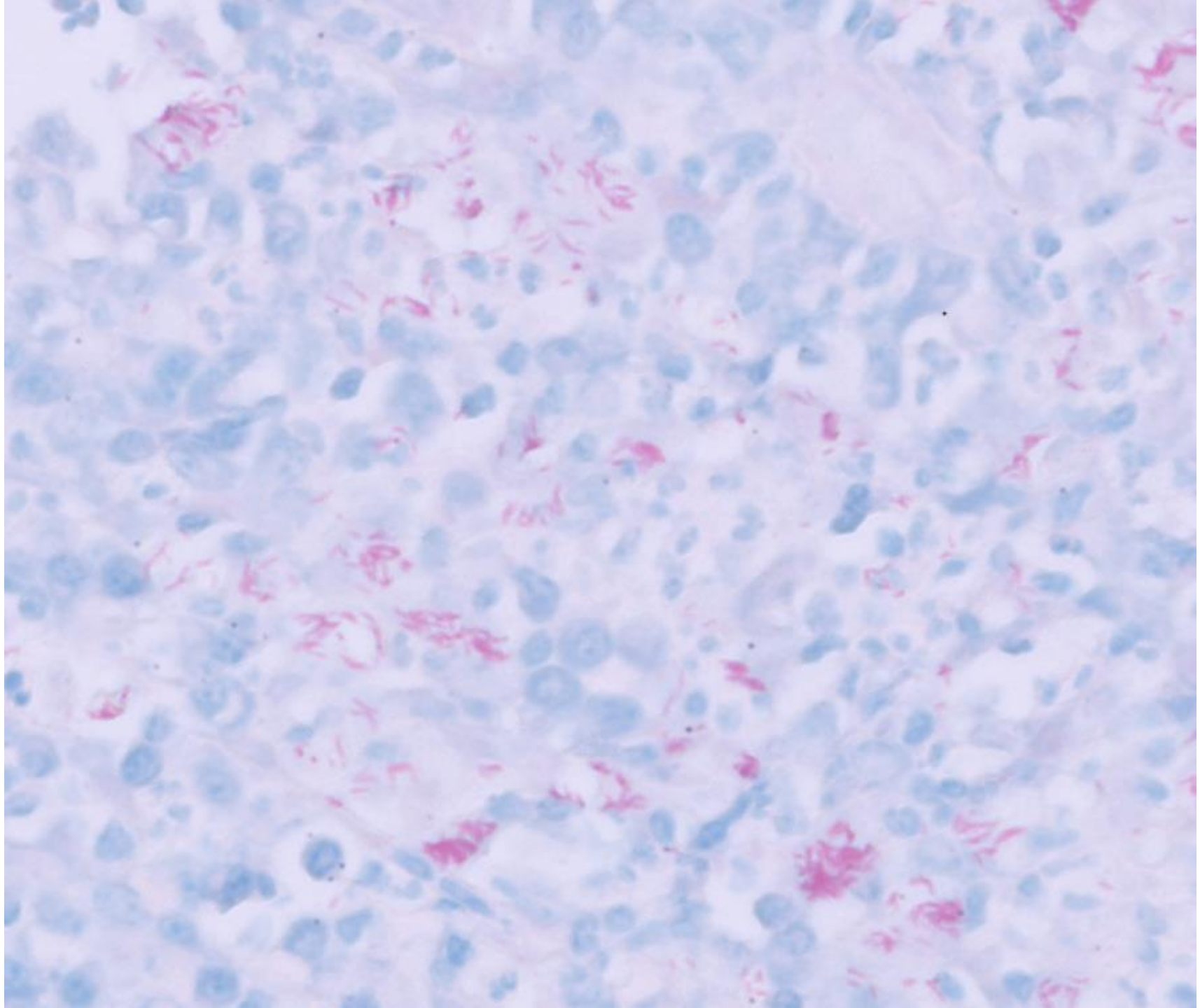
DIAGNOSIS?

AFB stain



AFB stain





Histology/Final diagnosis

Colon, Ulcerated Raised Mucosa at 45 cm, Biopsy:

- **Chronic active colitis with ulceration**
- **Acid fast organisms identified on AFB stain**

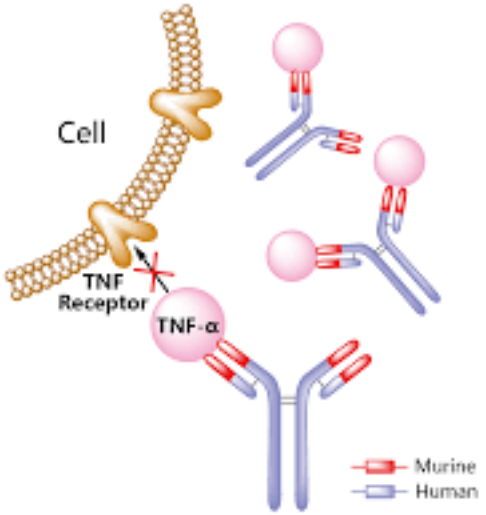
Colon, Nodule at 65 cm, Biopsy:

- **Chronic active colitis with ulceration**
- **Acid fast organisms identified on AFB stain**

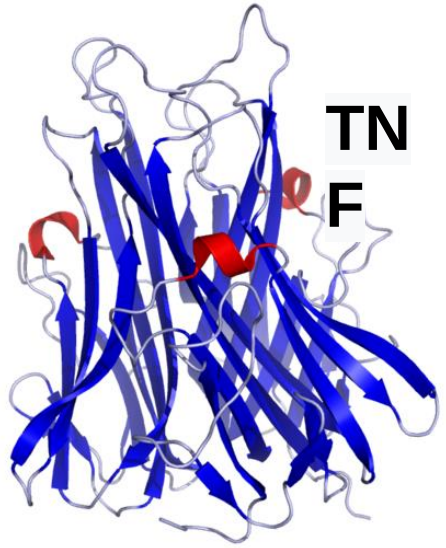
Molecular:

PCR: **POSITIVE** for Mycobacterium avium complex.
Complex members include M. avium subspecies and M. intracellulare

Discussion



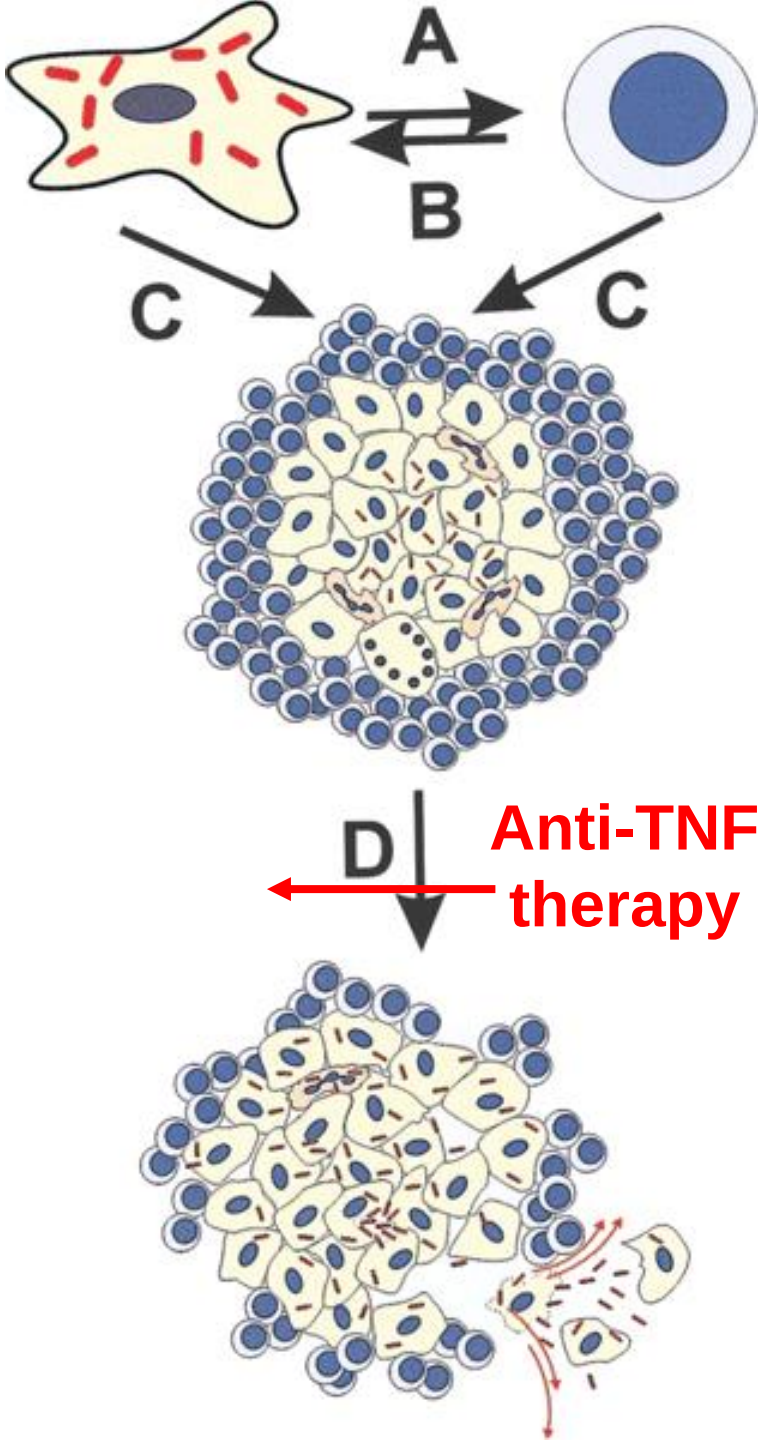
What is the TNF-α?



cytokine involved in the cytotoxic effect of macrophages against intracellular pathogens, **granuloma formation,** apoptosis and prevention of dissemination of infection to other sites.

- Infliximab neutralizes the biologic activity of TNF-α by inhibiting binding to its receptors. In contrast to some other TN inhibitors (eg, etanercept), infliximab **can also induce apoptosis of activated lymphocytes in the gut mucosa;**
- Patients receiving TNF-α antagonists are at an increased risk for granulomatous infectious diseases. The most frequent manifestation - **tuberculosis** (TB) reactivation, but cases of **nontuberculous mycobacterial** (NTM) infection were reported as well.

Anti-TNF therapy can cause **sequestering granulomas to break down** => can lead to disseminated disease.



Multiple steps of action of TNF in antibacterial and inflammatory responses to Mycobacterium tuberculosis infection:

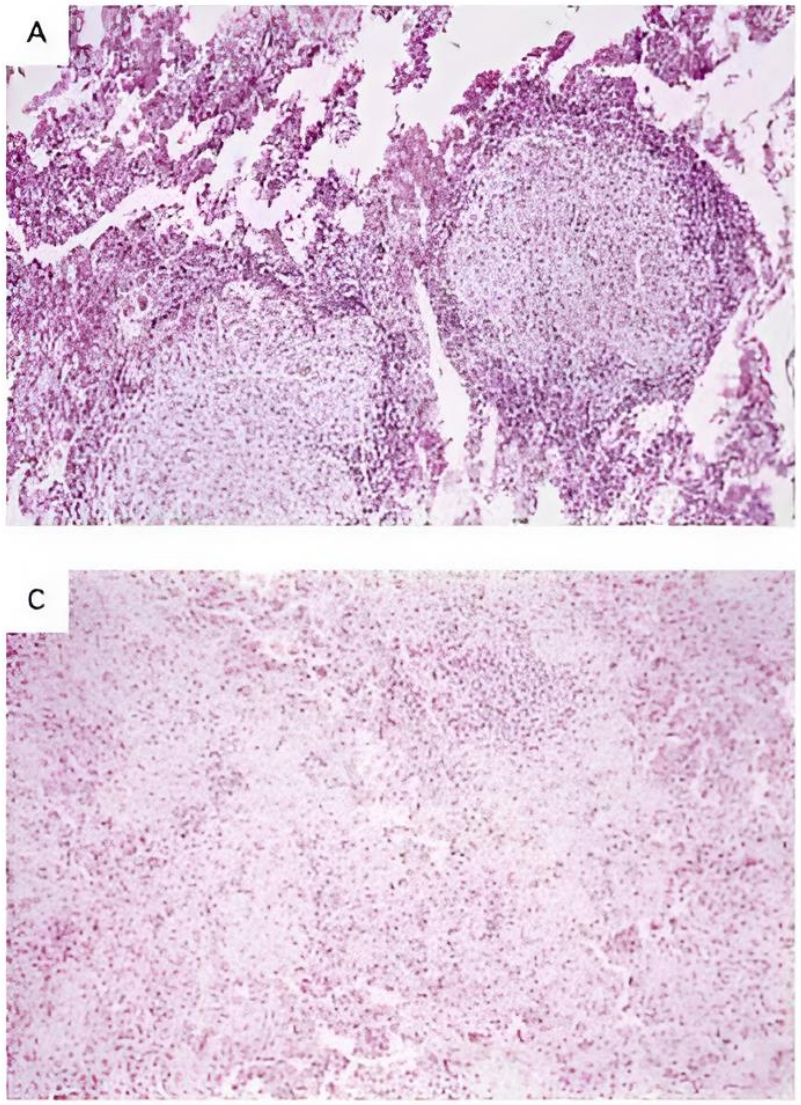
A. Macrophage-derived TNF acts as a costimulus for T cells.
B. T cell—derived TNF primes macrophages for mycobactericidal activity.
C. Macrophage- and T cell—derived TNF, together with IFN-γ and chemokines, induces recruitment and organized accumulation of mononuclear cells into highly structured granulomas. TNF and IFN-γ also regulate excessive inflammation by inducing apoptosis of T cells.

D. Anti-TNF therapy results in granuloma breakdown and dissemination of mycobacteria.

Source: Ehlers, S. (2005). Tumor Necrosis Factor and Its Blockade in Granulomatous Infections: Differential Modes of Action of Infliximab and Etanercept? Clinical Infectious Diseases, 41(Supplement_3), S199-S203. https://doi.org/10.1086/429998

Source: Keane J, Gershon S, Wise RP, et al.: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001, 345:1098-104. 10.1056/NEJMoa011110.

Photomicrographs of Lung Specimens from a Patient with Tuberculosis Who Did Not Receive Infliximab (Panel A) and the Patient with Tuberculosis Who Did Receive Infliximab (Panel C).



The specimen from the patient **who did not receive infliximab** shows **well-formed granulomas** with negligible overt necrosis *(Panel A; hematoxylin and eosin, ×100).*

The specimen of lung parenchyma from the patient **who received infliximab** shows prominent interstitial fibrosis and lymphoid inflammation, **without granulomas** *(Panel C, hematoxylin and eosin, ×100).*

Relevance for pathologists

An estimated hundreds of thousands of patients in the US currently receive infliximab treatment, with studies citing figures around 3 million patients treated with infliximab over its history.

Studies have shown that neutralizing TNF-α can result in increased immune cell infiltration and potentially aberrant immune responses.

These findings suggest that interrupting TNF-α activity can lead to an **abnormal immune response to tuberculosis (and other granulomatous processes), with significant pathological consequences, such as impaired granuloma integrity and disease reactivation.**

Drug-specific RR of TB

Infection	No. of patients (no. of patients per 100,000 patients treated), by drug		
	Infliximab[a]	Etanercept[b]	P[c]
Aspergillosis	17 (8.63)	7 (6.19)	.243
Candidiasis	20 (10.15)	6 (5.31)	.061
Bartonellosis	1 (0.51)	0 (0)	.563
Coccidioidomycosis	11 (5.58)	1 (0.88)	.013
Cryptococcosis	10 (5.08)	8 (7.08)	.179
Histoplasmosis	37 (18.78)	3 (2.65)	<.0001
Legionellosis	1 (0.51)	0 (0)	.563
Leprosy	1 (0.51)	0 (0)	.563
Listeriosis	17 (8.63)	1 (0.88)	.0006
Nontuberculous mycobacterioses	22 (11.17)	7 (6.19)	.066
Nocardiosis	7 (3.55)	1 (0.88)	.090
Pneumocystosis	1 (0.51)	0 (0)	.563
Salmonellosis	0 (0)	2 (1.77)	.031
Toxoplasmosis	4 (2.03)	0 (0)	.101
Tuberculosis	106 (53.81)	32 (28.32)	<.0001
Total	255 (129.44)	68 (60.18)	<.0001

[a] Rates were calculated on the basis of 197,000 patients treated with infliximab.
[b] Rates were calculated on the basis of 113,000 patients treated with etanercept.
[c] Significance was determined by Poisson analysis.

It has been shown that the risk of TB reactivation depends on the specific biologic agent used, with the highest risk associated with the anti-TNF-α monoclonal antibodies **adalimumab** and **infliximab**.

The newer TNF-α inhibitors certolizumab pegol and golimumab, as well as non-TNF-α inhibitor biologics, have not been associated with an increased risk of TB to date, ***but further observation is required before making any definite conclusions.***

Combining TNF-α inhibitor treatment with methotrexate or azathioprine increases the risk of TB reactivation.

Source: Robert S. Wallis, Michael Broder, John Wong, David Beenhouwer, Granulomatous Infections Due to Tumor Necrosis Factor Blockade: Correction, *Clinical Infectious Diseases*, Volume 39, Issue 8, 15 October 2004, Pages 1254–1255, https://doi.org/10.1086/424455

NTM infection

NTM are a group of environmental bacteria and opportunistic pathogens which can cause various pathological conditions, most commonly **pulmonary** infection.

They usually occur in **immunosuppressed** individuals, especially in impaired T helper 1 or macrophage function, **such as AIDS, and conditions under treatment with anti-TNFα therapy.**

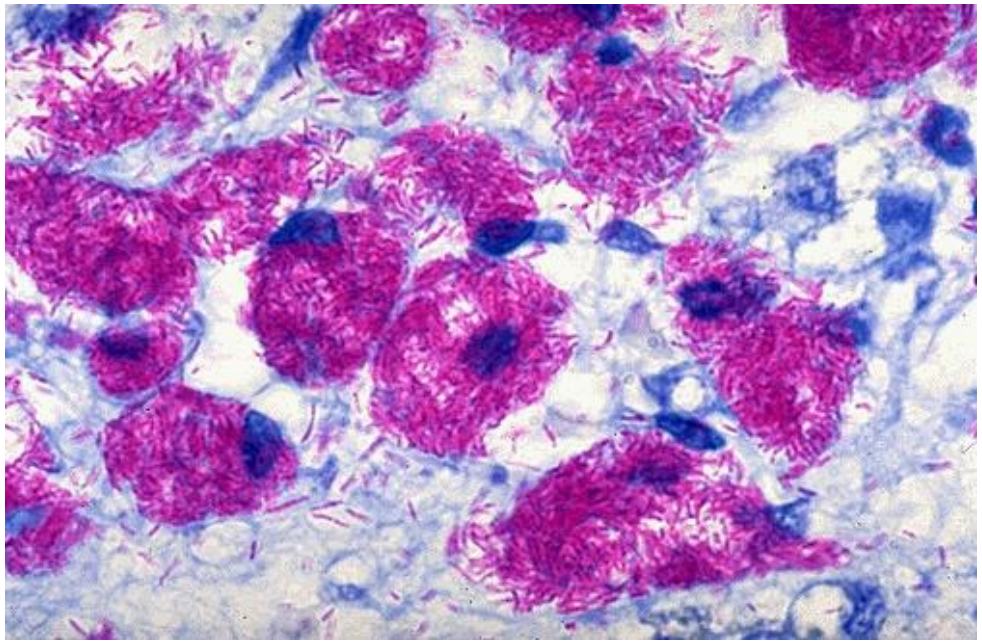
NTM infection is mainly caused by MAC (about 80%).

M. tuberculosis complex	
M. tuberculosis	
M. bovis	
M. africanum	
M. leprae	
Nontuberculous mycobacteria	
Slowly growing mycobacteria	
M. kansasii	(Photochromogens, Runyon group I)
M. marinum	
M. gordonae	(Scotochromogens, Runyon group II)
M. scrofulaceum	
M. avium complex	(Nonchromogens, Runyon group III)
M. avium	
M. intracellulare	
M. terrae complex	
M. ulcerans	
M. xenopi	
Rapidly growing mycobacteria	(Runyon group IV)
M. fortuitum	
M. chelonae	
M. abscessus	

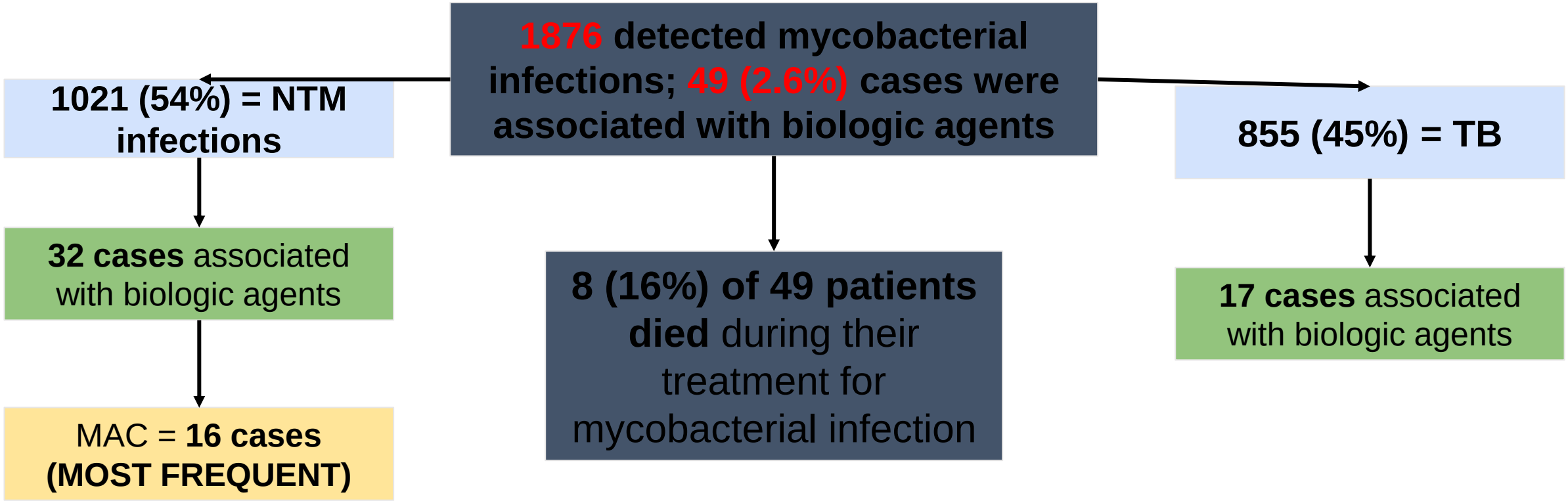
Source: Hirano T, Matsuura M, Nakase H. Pulmonary Mycobacterium avium Infection in a Patient with Crohn's Disease under Azathioprine Treatment. Case Rep Gastroenterol. 2014 May 15;8(2):182-5. doi: 10.1159/000363376.

MAC epidemiology

- **Prevalence** = 1.4 to 6.6 per 100,000 population.
- **Women had a higher prevalence,** up to 1.6 fold relative to men.
- The 5-year and 10-year all-cause mortality rates in patients with MAC pulmonary disease (MAC PD) have been reported as **23.9% and 46.5%**, respectively, and the corresponding **MAC-specific mortality rates were 5.4% and 15.7%**
- **Untreated MAC PD = MAC-PD can gradually progress and cause significant morbidity and mortality, with a 5-year mortality rate of more than 25%.**
- The mortality rate for extrapulmonary NTM was 2% and for disseminated NTM disease was 50%.



Mycobacterial and Other Serious Infections in Patients Receiving Anti-Tumor Necrosis Factor and Other Newly Approved Biologic Therapies: Case Finding through the Emerging Infections Network



18 patients were receiving **infliximab**, 12 were receiving etanercept, 8 were receiving rituximab, 3 were receiving adalimumab, and 8 were receiving unspecified biologic therapy.

Source: Kevin L. Winthrop, S. Yamashita, S. E. Beekmann, P. M. Polgreen, on behalf of the Infectious Diseases Society of America Emerging Infections Network, Mycobacterial and Other Serious Infections in Patients Receiving Anti-Tumor Necrosis Factor and Other Newly Approved Biologic Therapies: Case Finding through the Emerging Infections Network, *Clinical Infectious Diseases*, Volume 46, Issue 11, 1 June 2008, Pages 1738–1740, https://doi.org/10.1086/587989

Teaching points

- Be mindful of immunocompromised patients (whether congenital or acquired) and maintain a low threshold for ordering special stains (AFB and GMS stains), to detect potential microorganisms. It's especially relevant if patients get **infliximab, adalimumab.**

  While the newer TNF-α inhibitors golimumab and certolizumab pegol and non-TNF-α inhibitor biologics do not seem to be associated with the same risk of TB reactivation as earlier TNF-α inhibitors, **caution is warranted until longer-term data are available.**

- Be mindful that the patient may also be asymptomatic.

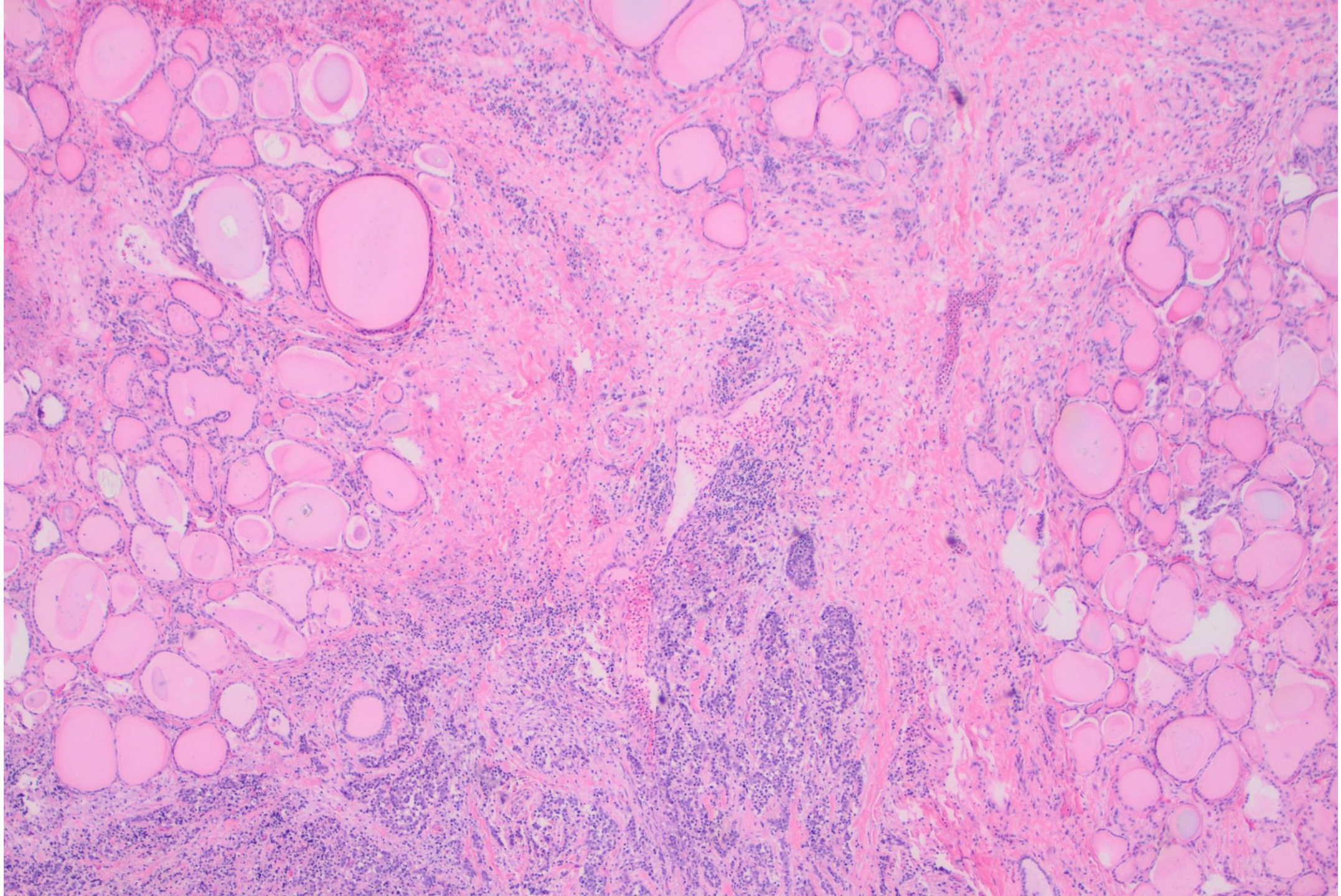
References

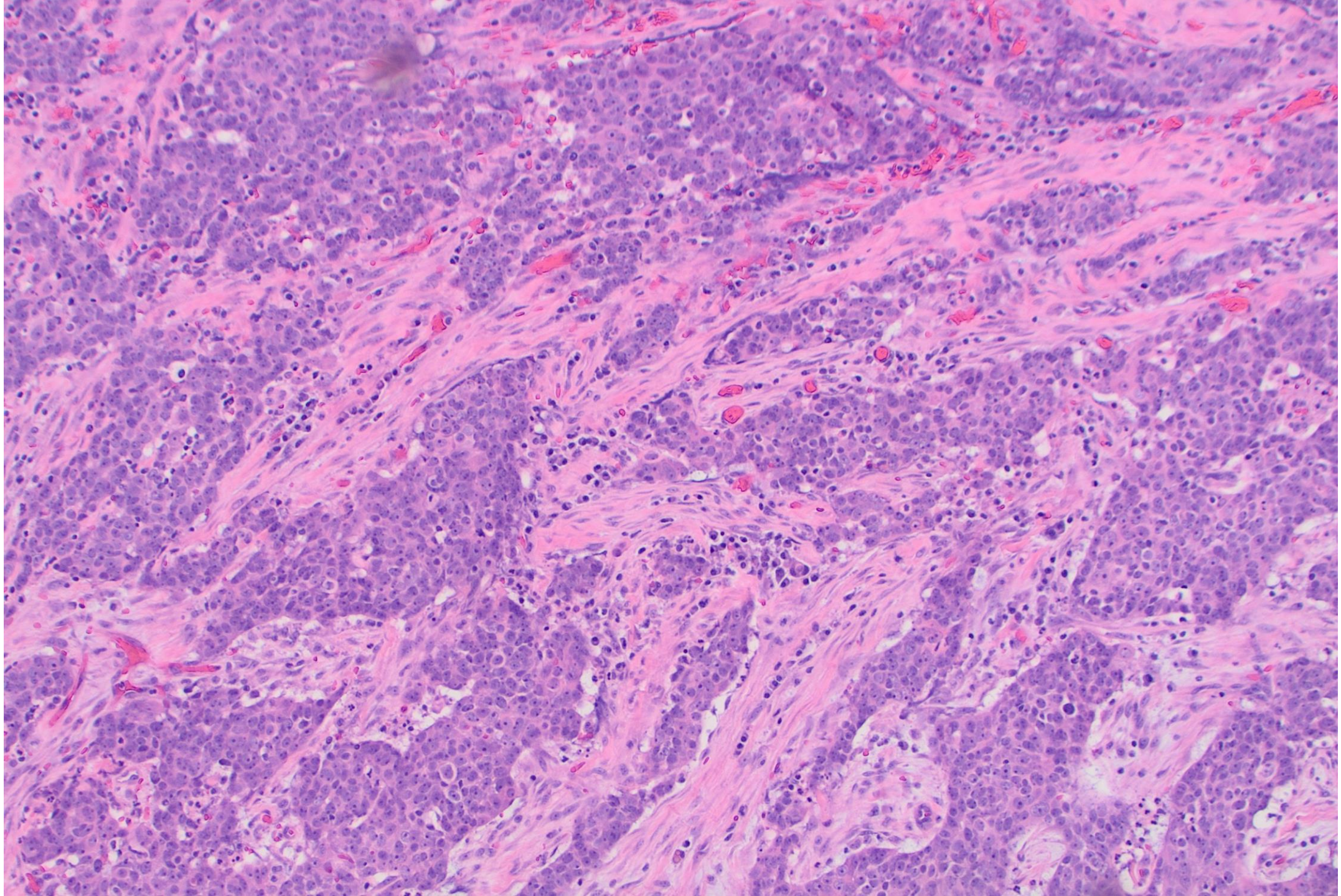
1. Silva DAAD, Silva MVD, Barros CCO, Alexandre PBD, Timóteo RP, Catarino JS, Sales-Campos H, Machado JR, Rodrigues DBR, Oliveira CJ, Rodrigues V. TNF-α blockade impairs in vitro tuberculous granuloma formation and down modulate Th1, Th17 and Treg cytokines. PLoS One. 2018 Mar 15;13(3):e0194430. doi: 10.1371/journal.pone.0194430.
2. Mycobacterial diseases developed during anti-tumour necrosis factor-α therapy. Jung-Wan Yoo, Kyung-Wook Jo, Bo-Hyung Kang, Mi Young Kim, Bin Yoo, Chang-Keun Lee, Yong-Gil Kim, Suk-Kyun Yang, Jeong-Sik Byeon, Kyung-Jo Kim, Byong Duk Ye, Tae Sun Shim. European Respiratory Journal Nov 2014, 44 (5) 1289-1295.
3. Kevin L. Winthrop, S. Yamashita, S. E. Beekmann, P. M. Polgreen, on behalf of the Infectious Diseases Society of America Emerging Infections Network, Mycobacterial and Other Serious Infections in Patients Receiving Anti-Tumor Necrosis Factor and Other Newly Approved Biologic Therapies: Case Finding through the Emerging Infections Network, Clinical Infectious Diseases, Volume 46, Issue 11, 1 June 2008, Pages 1738–1740.
4. Stefan Ehlers, Tumor Necrosis Factor and Its Blockade in Granulomatous Infections: Differential Modes of Action of Infliximab and Etanercept?, *Clinical Infectious Diseases*, Volume 41, Issue Supplement_3, August 2005, Pages S199–S203, https://doi.org/10.1086/429998
5. Ricotta EE, Adjemian J, Blakney RA, Lai YL, Kadri SS, Prevots DR. Extrapulmonary Nontuberculous Mycobacteria Infections in Hospitalized Patients, United States, 2009-2014. Emerg Infect Dis. 2021 Mar;27(3):845-852. doi: 10.3201/eid2703.201087.
6. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement
I. Solovic, M. Sester, J.J. Gomez-Reino, H.L. Rieder, S. Ehlers, H.J. Milburn, B. Kampmann, B. Hellmich, R. Groves, S. Schreiber, R.S. Wallis, G. Sotgiu, E.H. Schölvinck, D. Goletti, J.P. Zellweger, R. Diel, L. Carmona, F. Bartalesi, P. Ravn, A. Bossink, R. Duarte, C. Erkens, J. Clark, G.B. Migliori, C. Lange. European Respiratory Journal Nov 2010, 36 (5) 1185-1206; doi: 10.1183/09031936.00028510.
1. Katrak SS, Li R, Reynolds S, Marks SM, Probst JR, Chorba T, Winthrop K, Castro KG, Goswami ND. Association of Tumor Necrosis Factor α Inhibitor Use with Diagnostic Features and Mortality of Tuberculosis in the United States, 2010-2017. Open Forum Infect Dis. 2021 Dec 22;9(2):ofab641. doi: 10.1093/ofid/ofab641.
2. Keane J, Gershon S, Wise RP, et al.: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001, 345:1098-104. 10.1056/NEJMoa011110

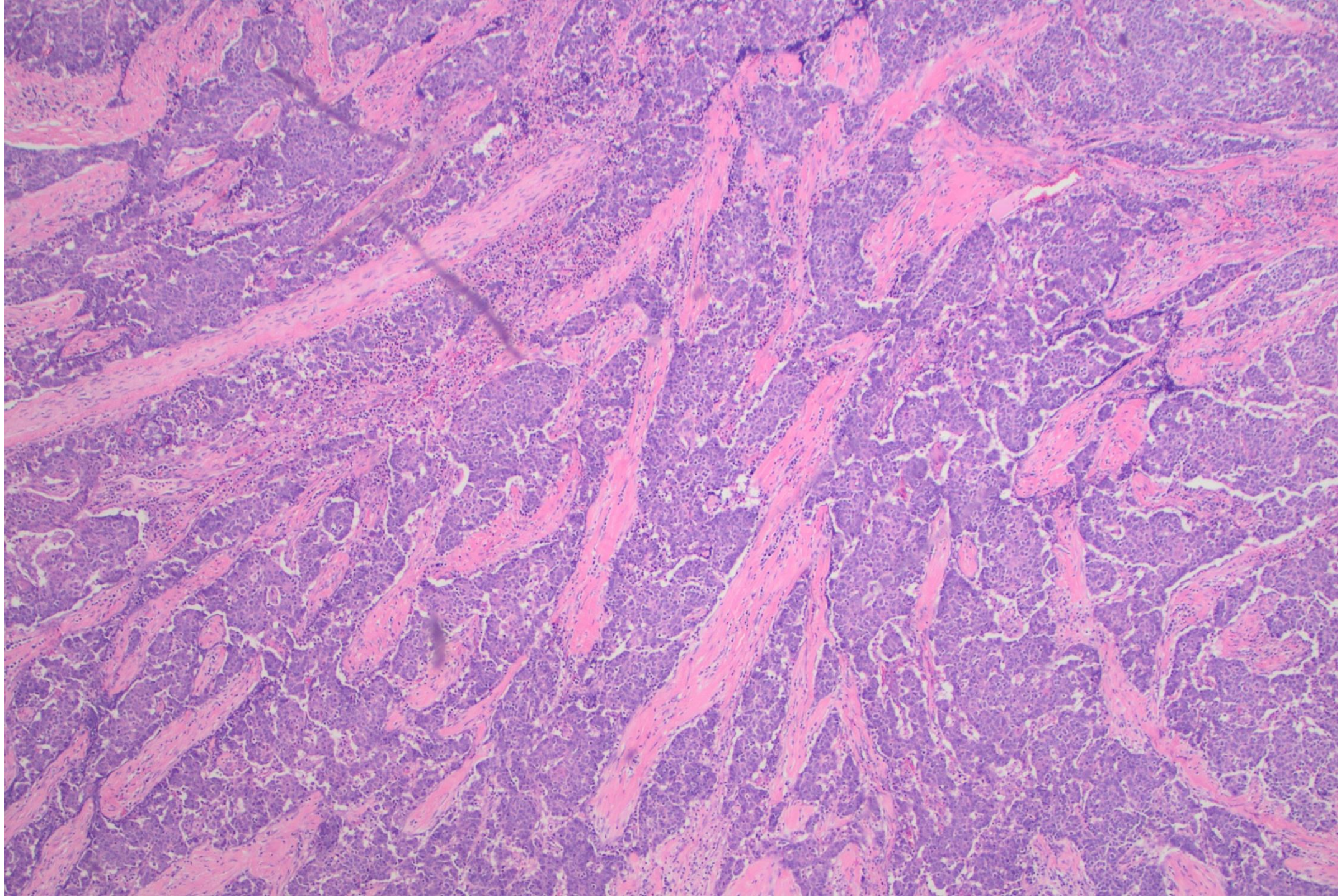
24-1006

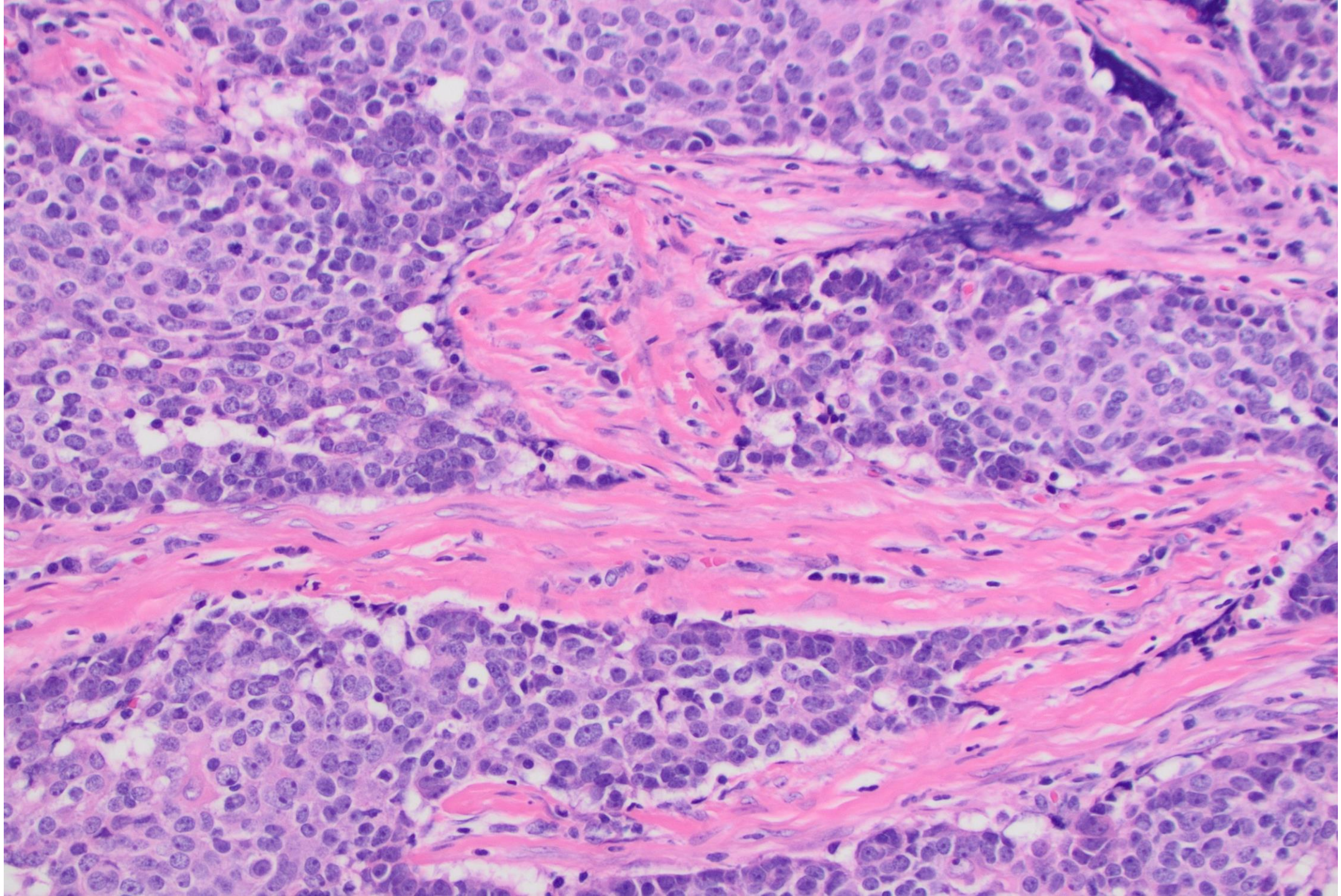
Gregory J. Rumore M.D; The Permanente Medical Group

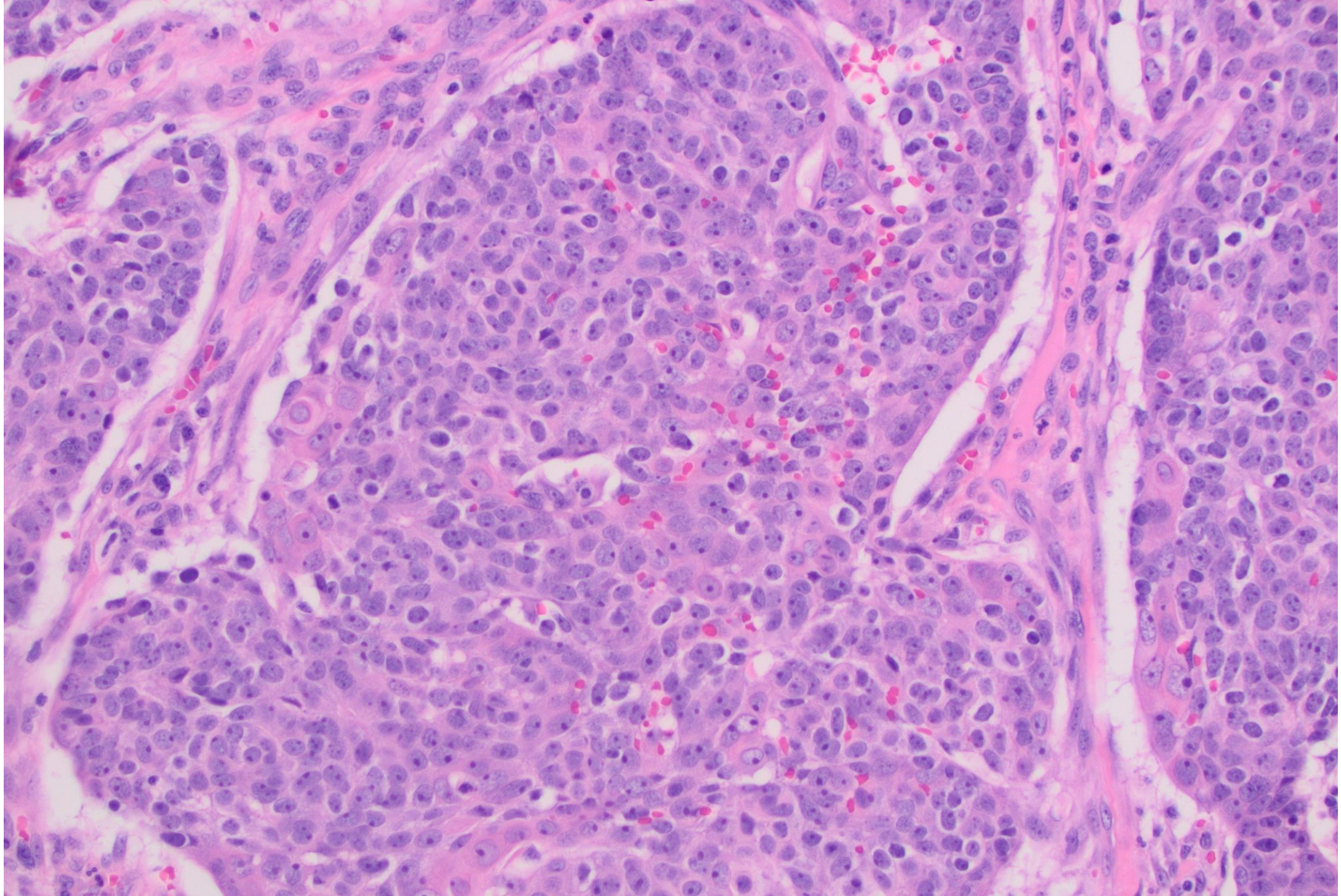
67 y.o. female with 5cm mass R lower pole of thyroid

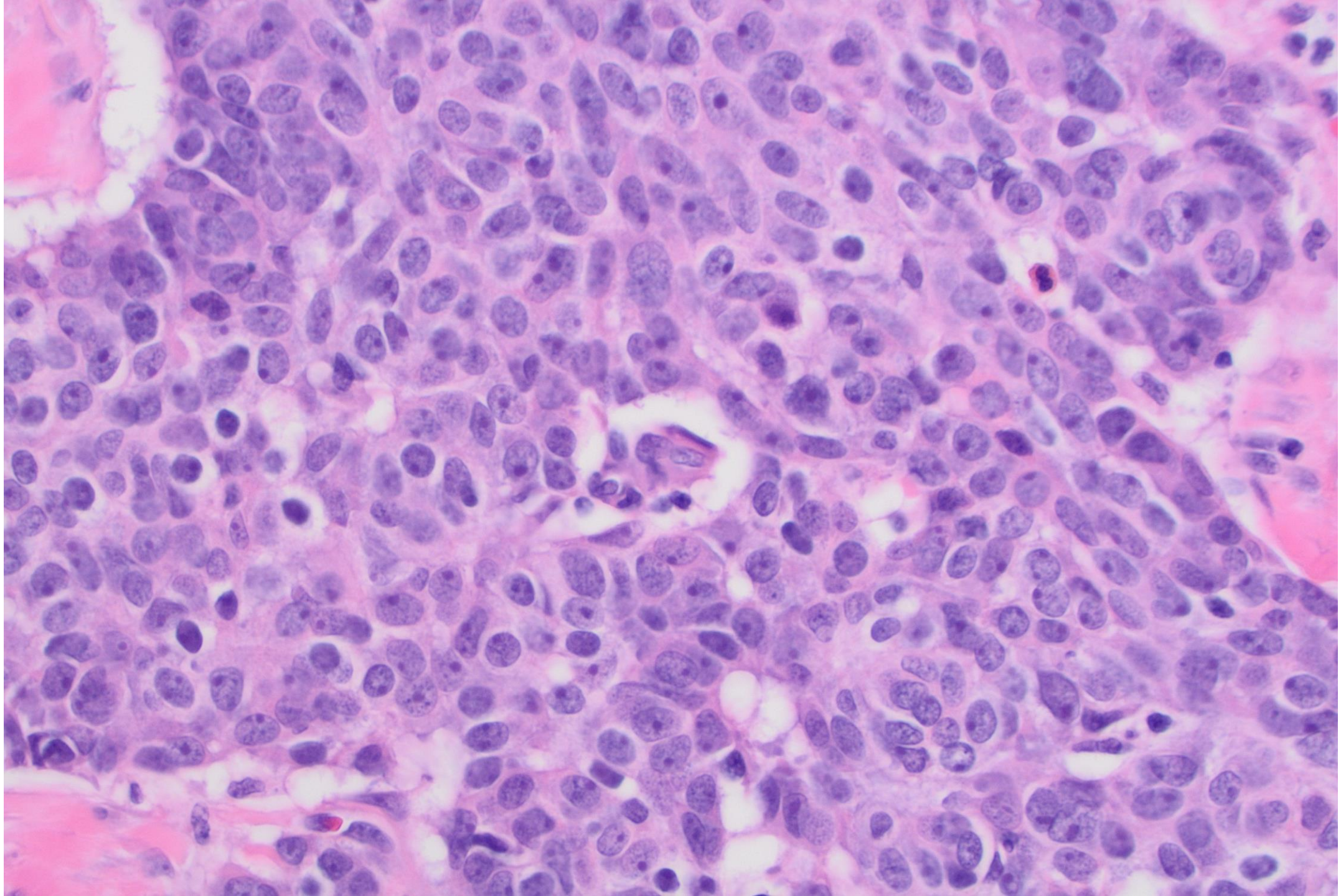


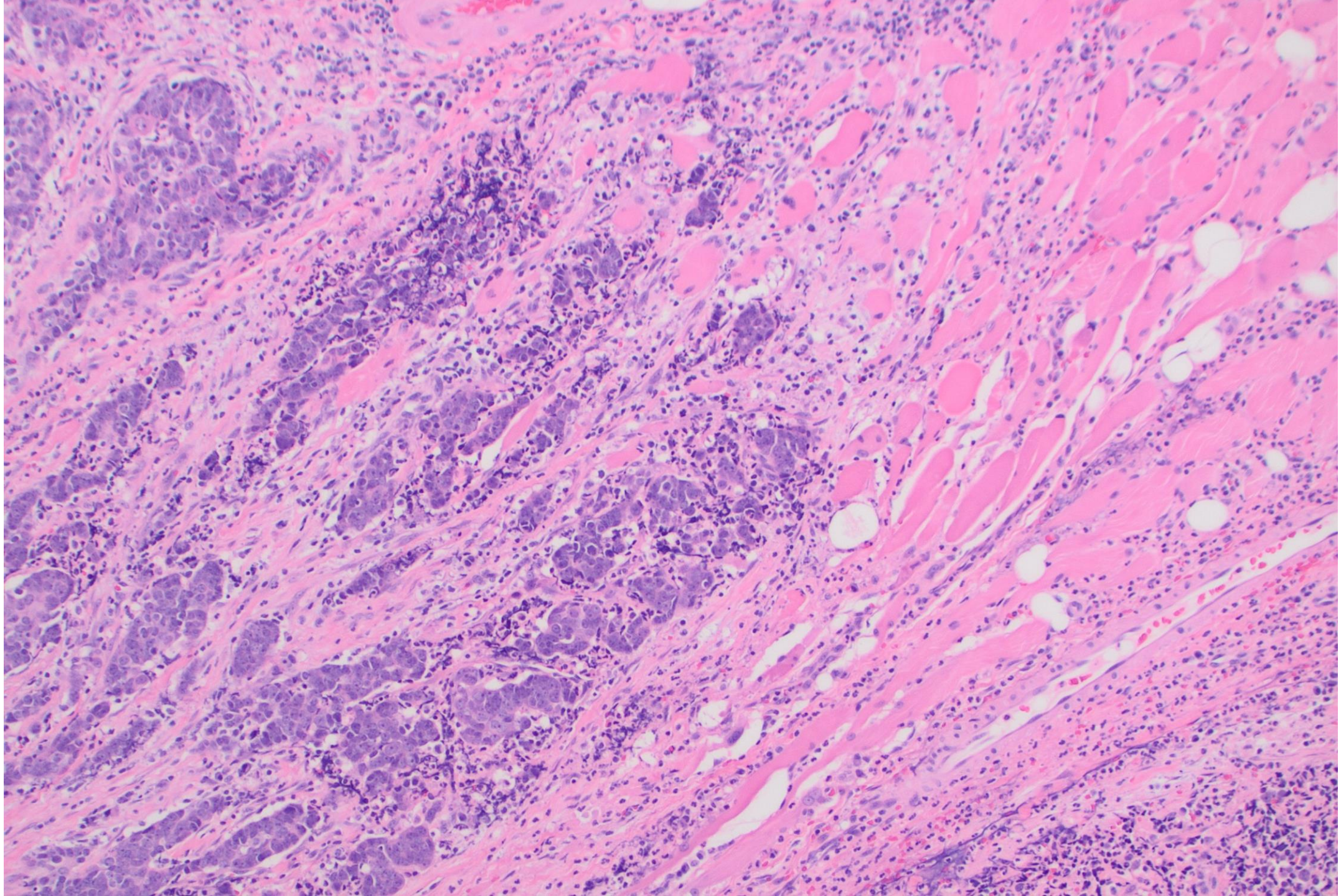




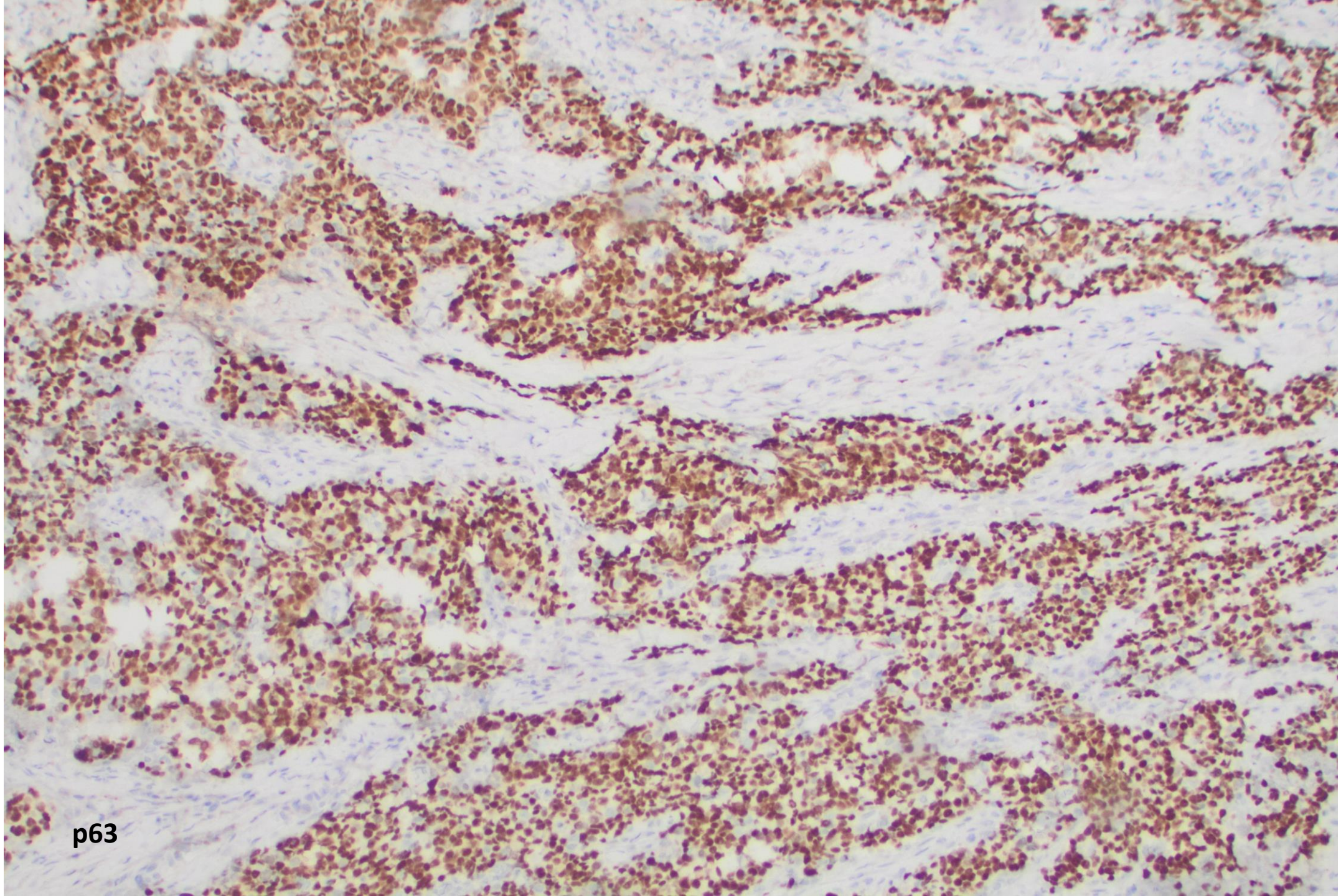


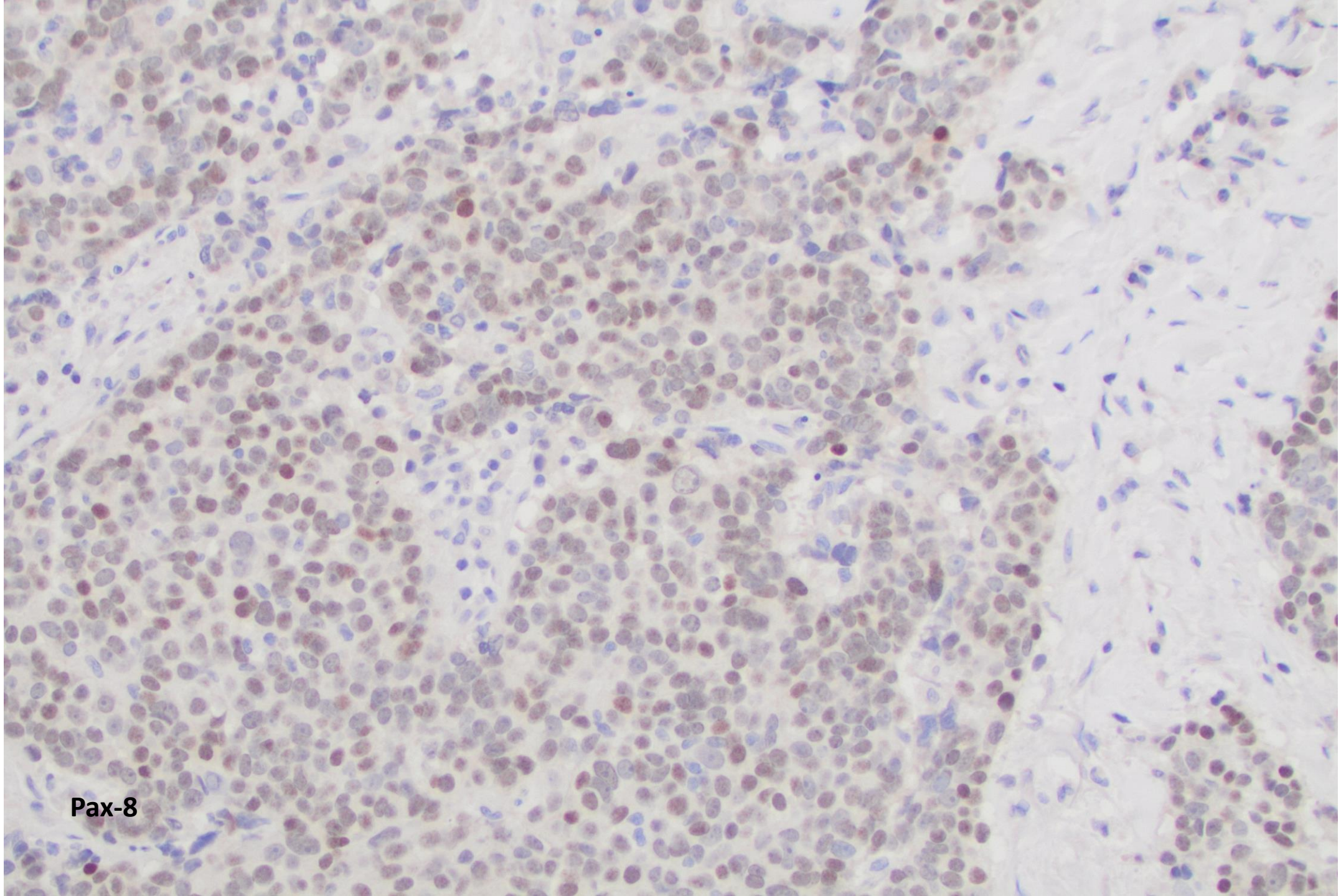


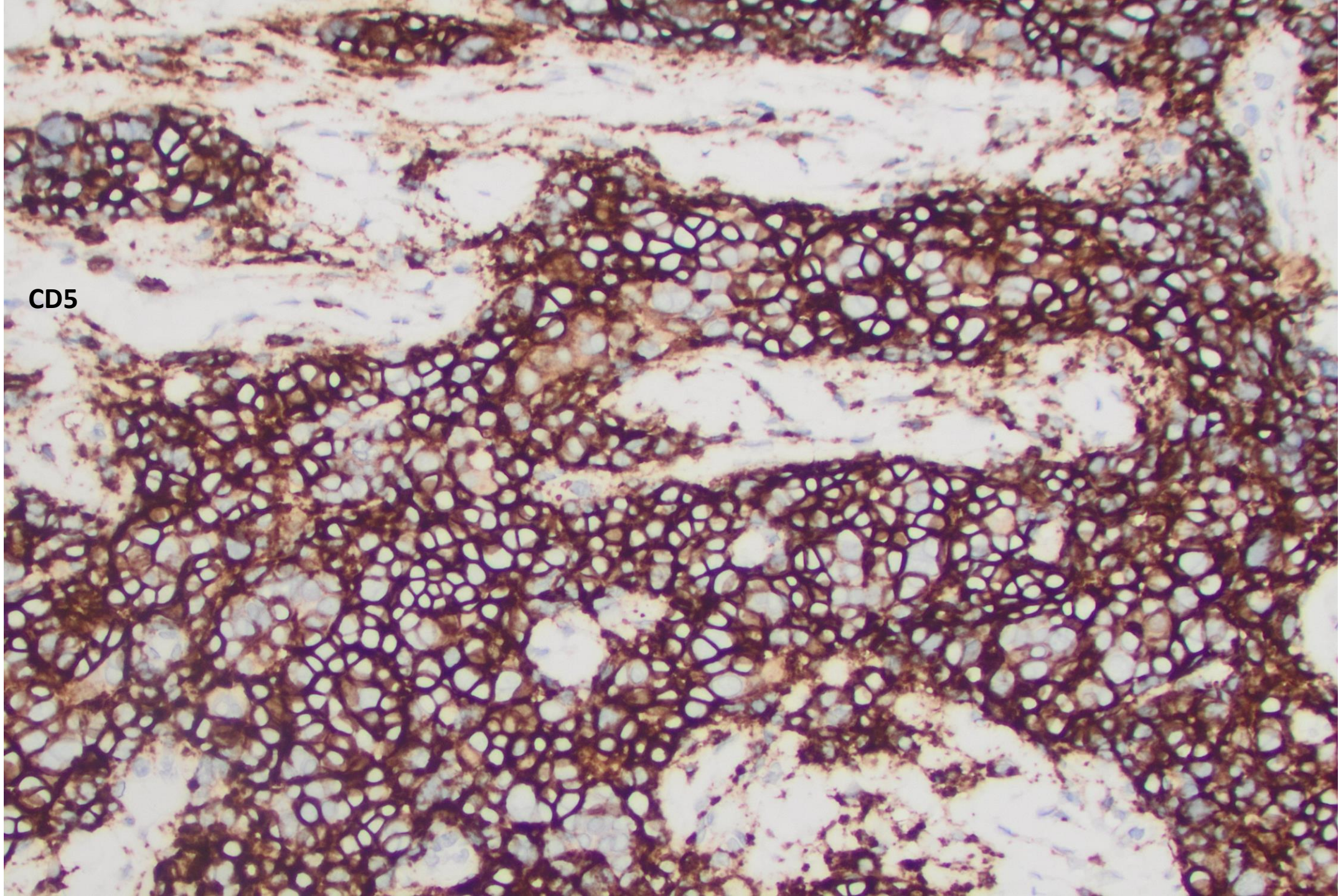


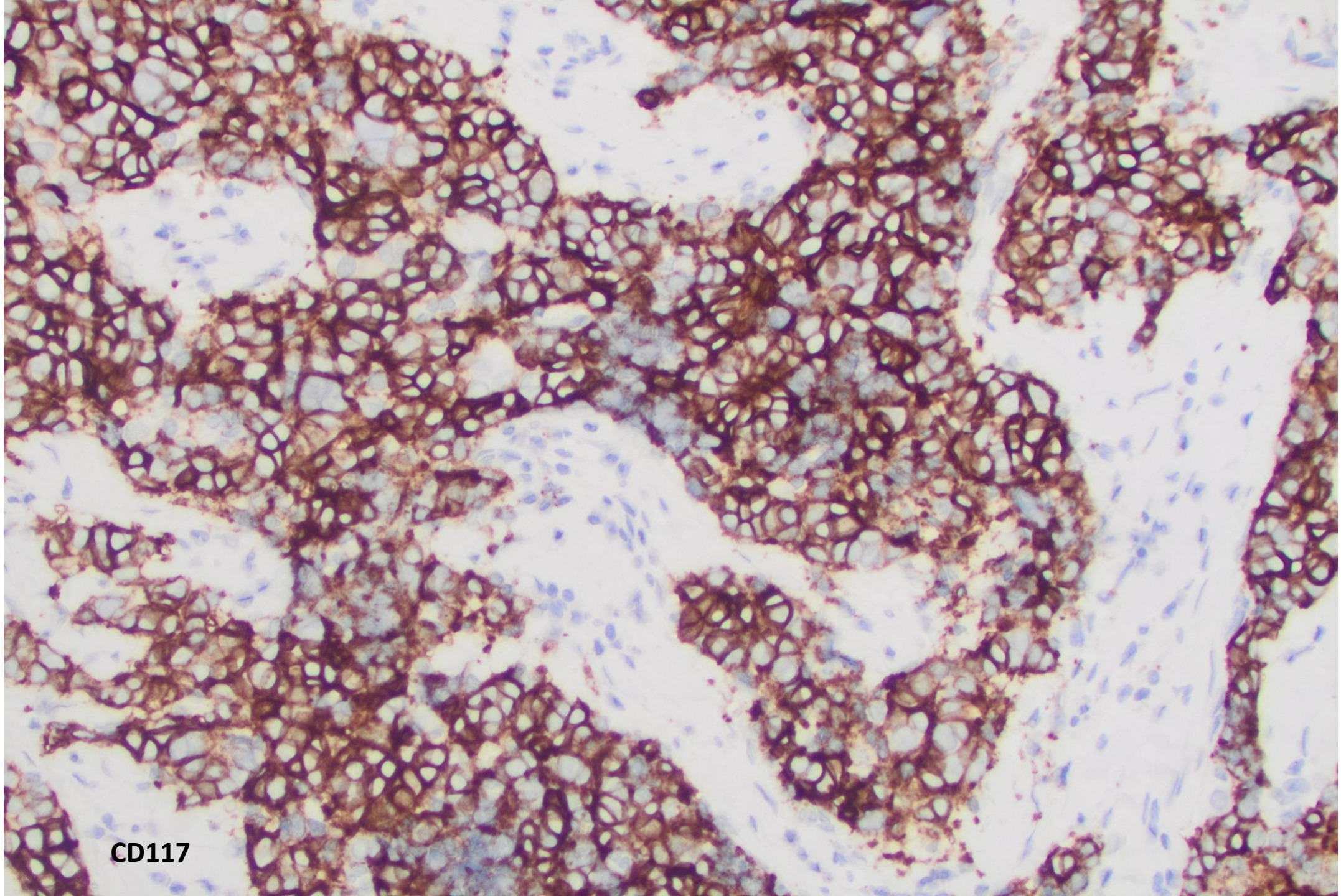


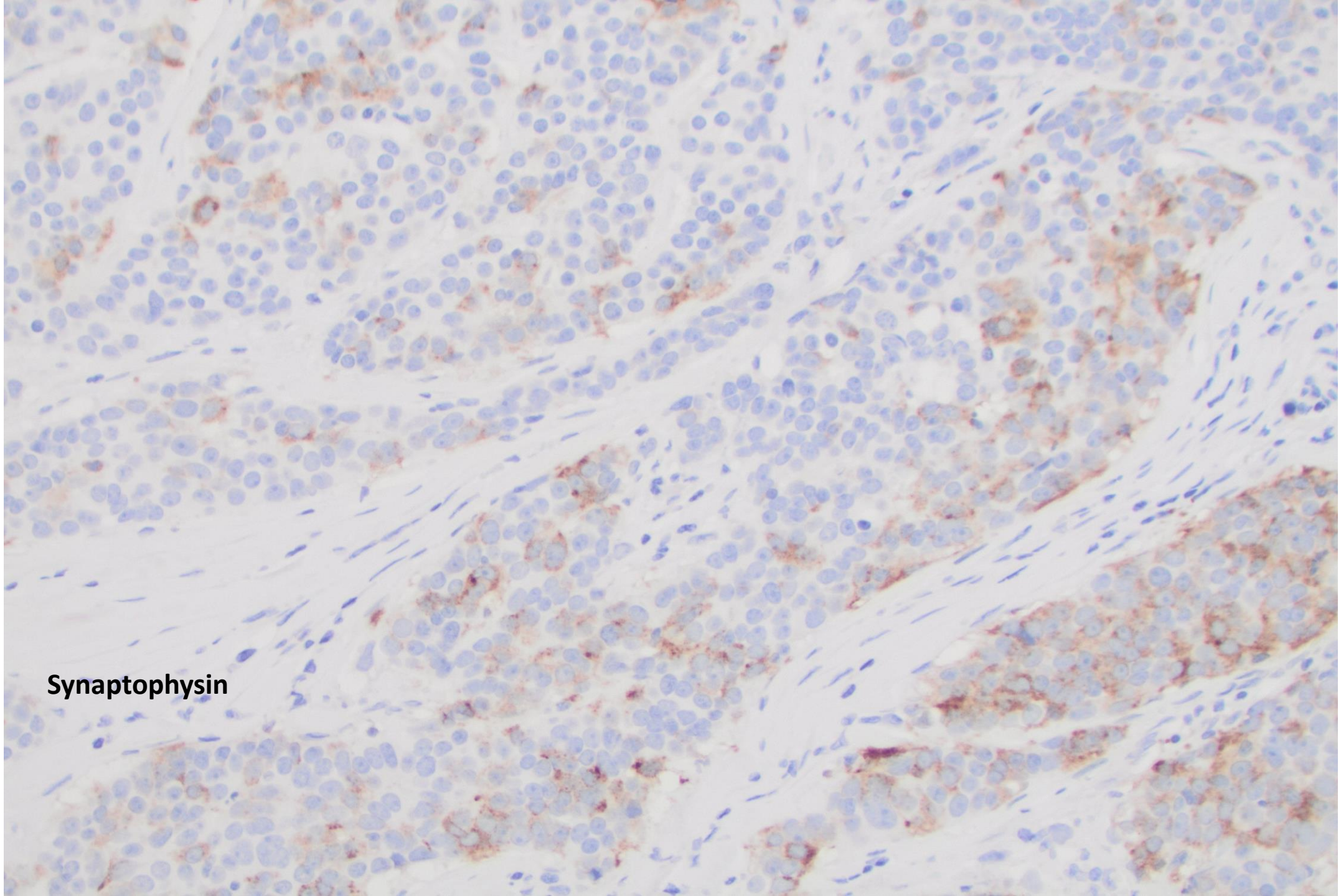
DIAGNOSIS?


p63


Pax-8


CD5


CD117


Synaptophysin

Intrathyroidal Thymic Carcinoma

- **CA**rcinoma **S**howing **T**hymus-**L**ike Differentiation (CASTLE)
- Thought to arise in intrathyroidal/perithyroidal thymic tissue
- Lower lobes affected
- Mean age 48.5 years; female predominance

Histologic features

- Highly infiltrative, unencapsulated
- Lobulated growth pattern with fibrous bands
- Squamoid features (non-keratinizing)
- May have lymphoepithelioma-like appearance
- Low mitotic rate (Proliferation rate=10-30%)
- No well differentiated thyroid CA component

Immunohistochemistry

- Positive: p40/p63, Pax-8, CD5 (epithelial cells), CD117 (no c-kit mutations), Synaptophysin/Chromogranin (scattered cells)
- Negative: Thyroglobulin, TTF-1, Calcitonin

Differential Diagnosis

- Anaplastic Thyroid Carcinoma
- Squamous Cell Carcinoma
- Poorly Differentiated Thyroid Carcinoma
- Medullary Thyroid Carcinoma
- Merkel Cell Carcinoma

Treatment and Prognosis

- Complete thyroidectomy, selective neck dissection, post-op RAD
- May respond to PDL-1 inhibitor
- Good prognosis-5 yr survival=90%, 10 yr= 82%
- Poor prognostic features- venous/perineural invasion, extrathyroidal extension, high proliferation rate
- Rare aggressive cases metastasize to brain, liver, lungs

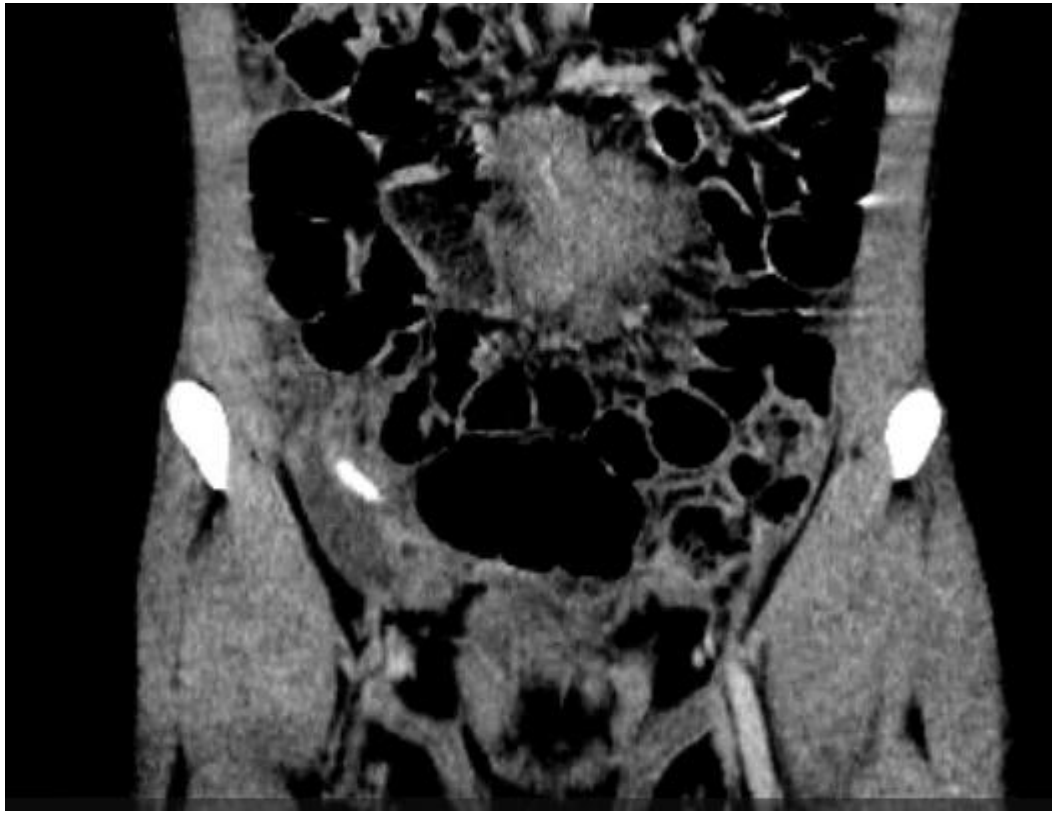
24-1007

Ruobin Wu; UCSF

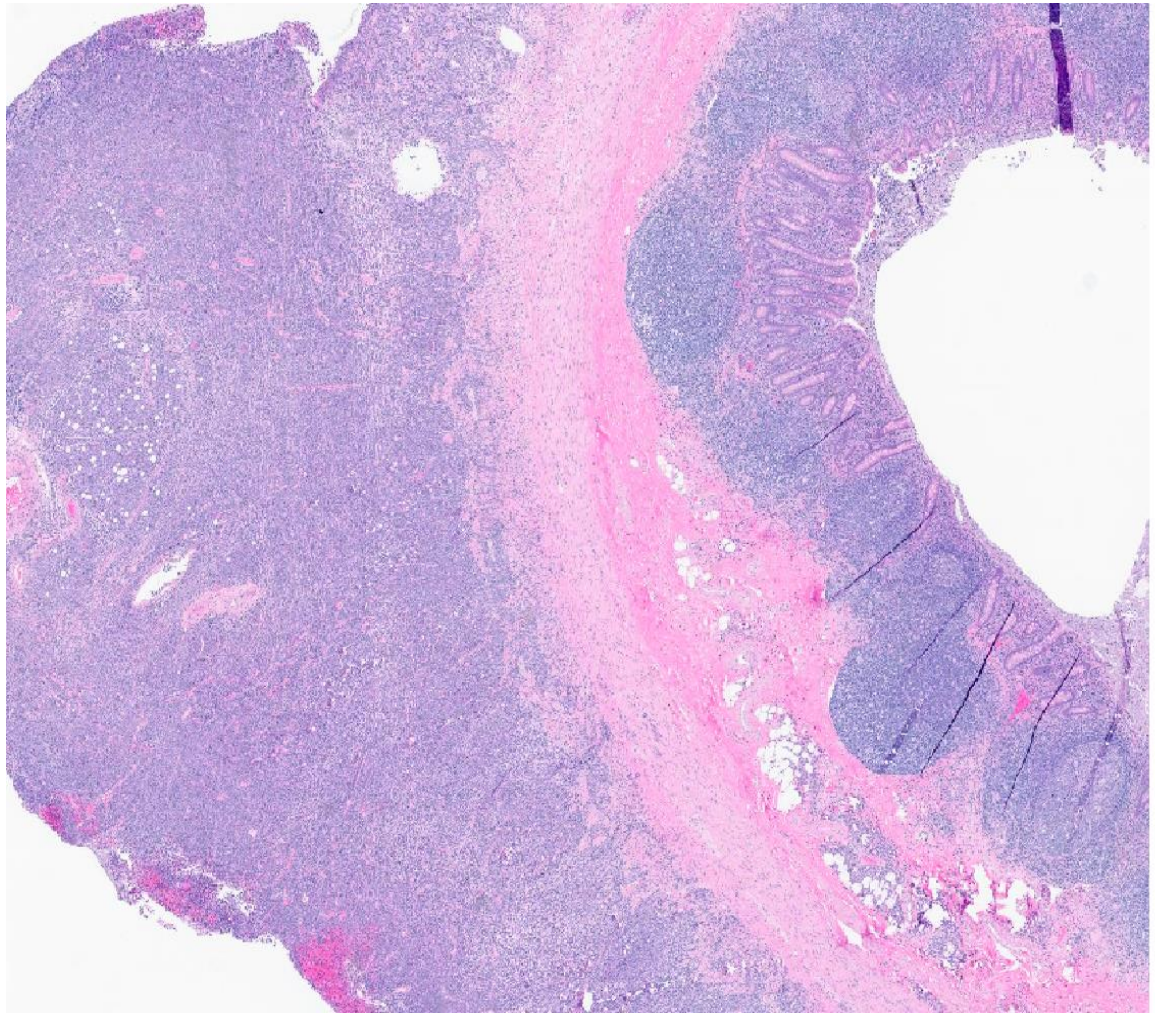
22-year-old patient with abdominal pain

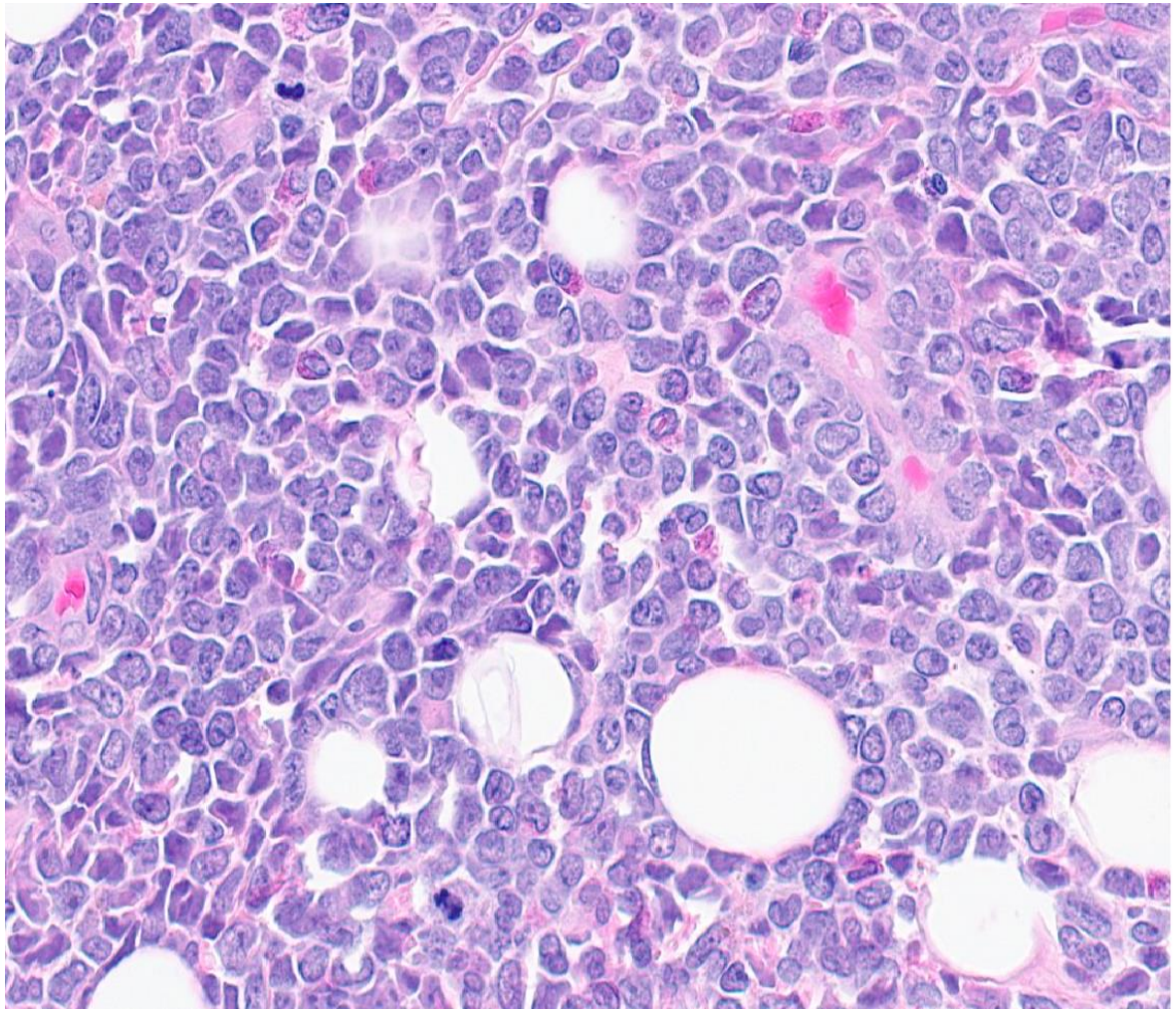
Case presentation

- 3/7/24 – Presented with abdominal pain, N/V
  - Imaging showed SBO
- 3/28/24 – Returns with diffuse lower abd pain, N/V, anorexia
  - CT concerning for appendicitis, periappendicits
- Appendectomy performed

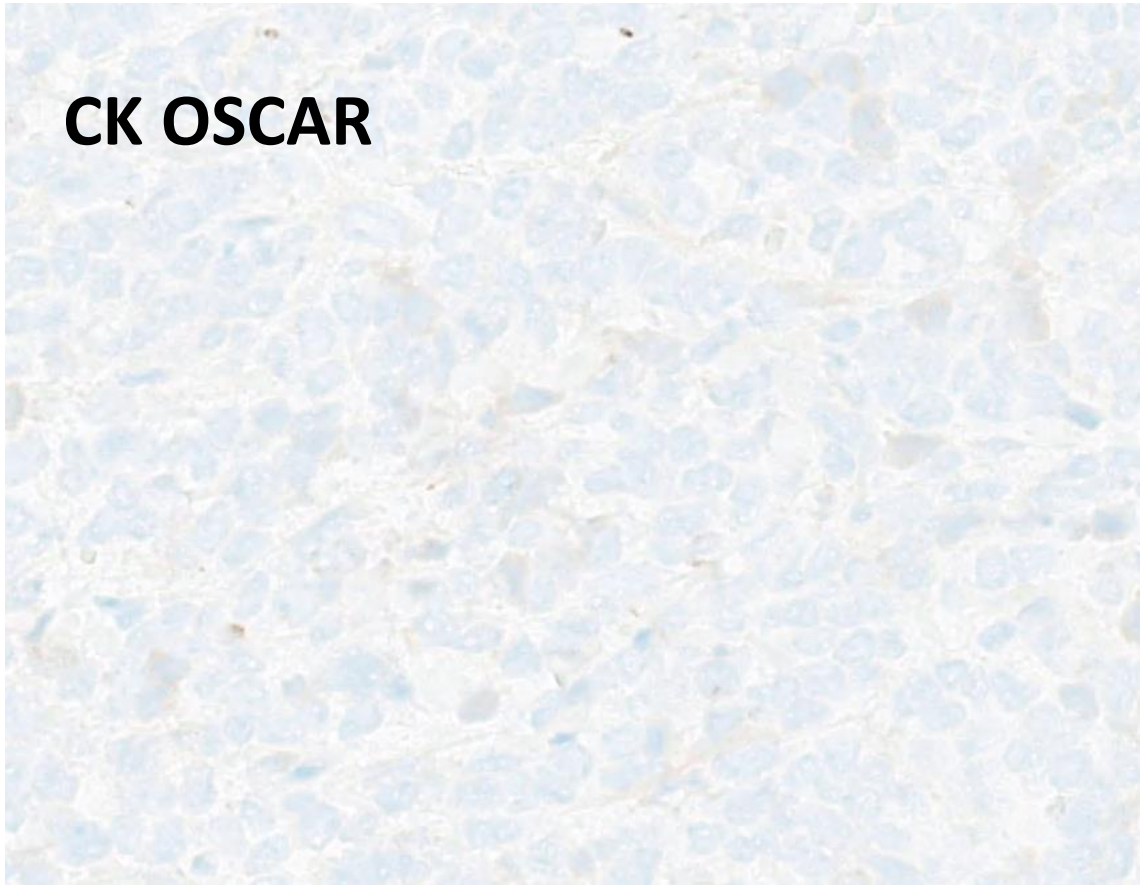


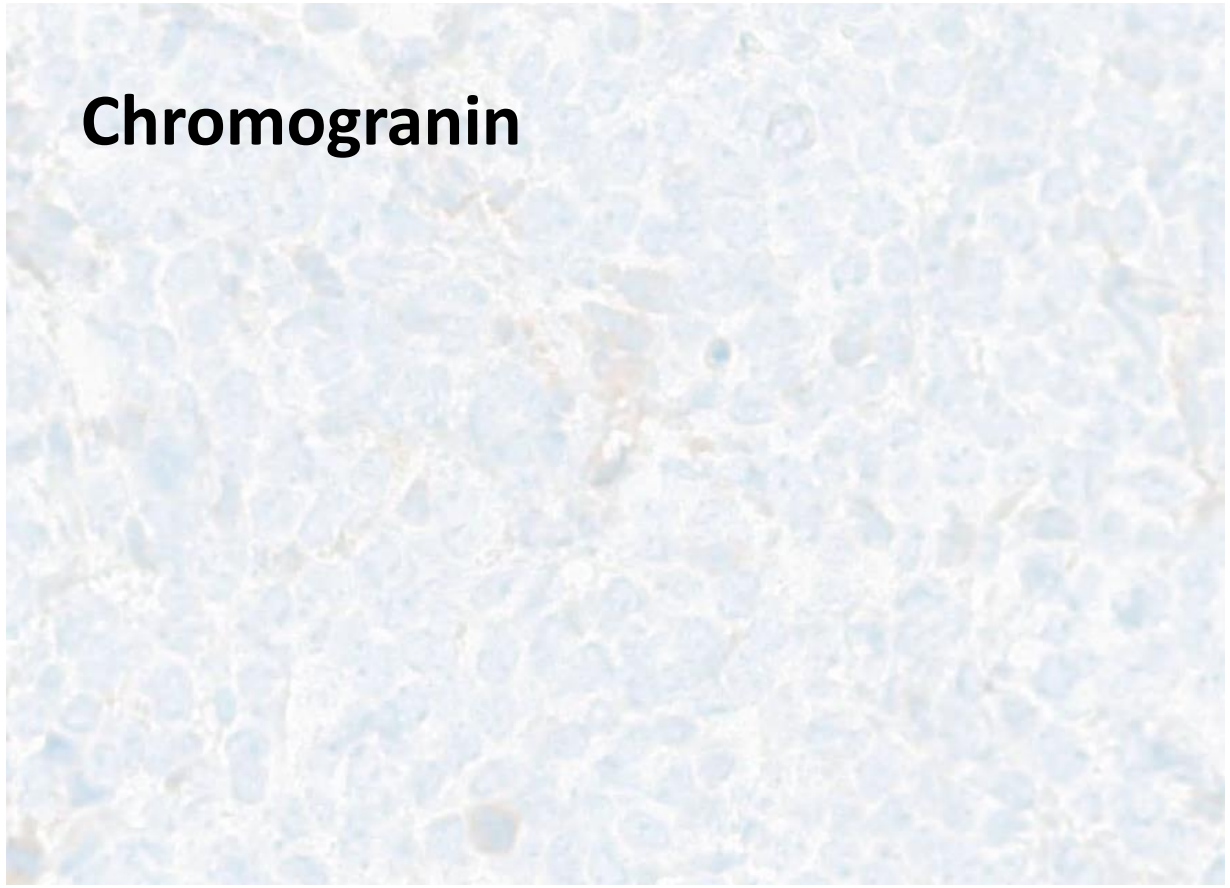
Appendix



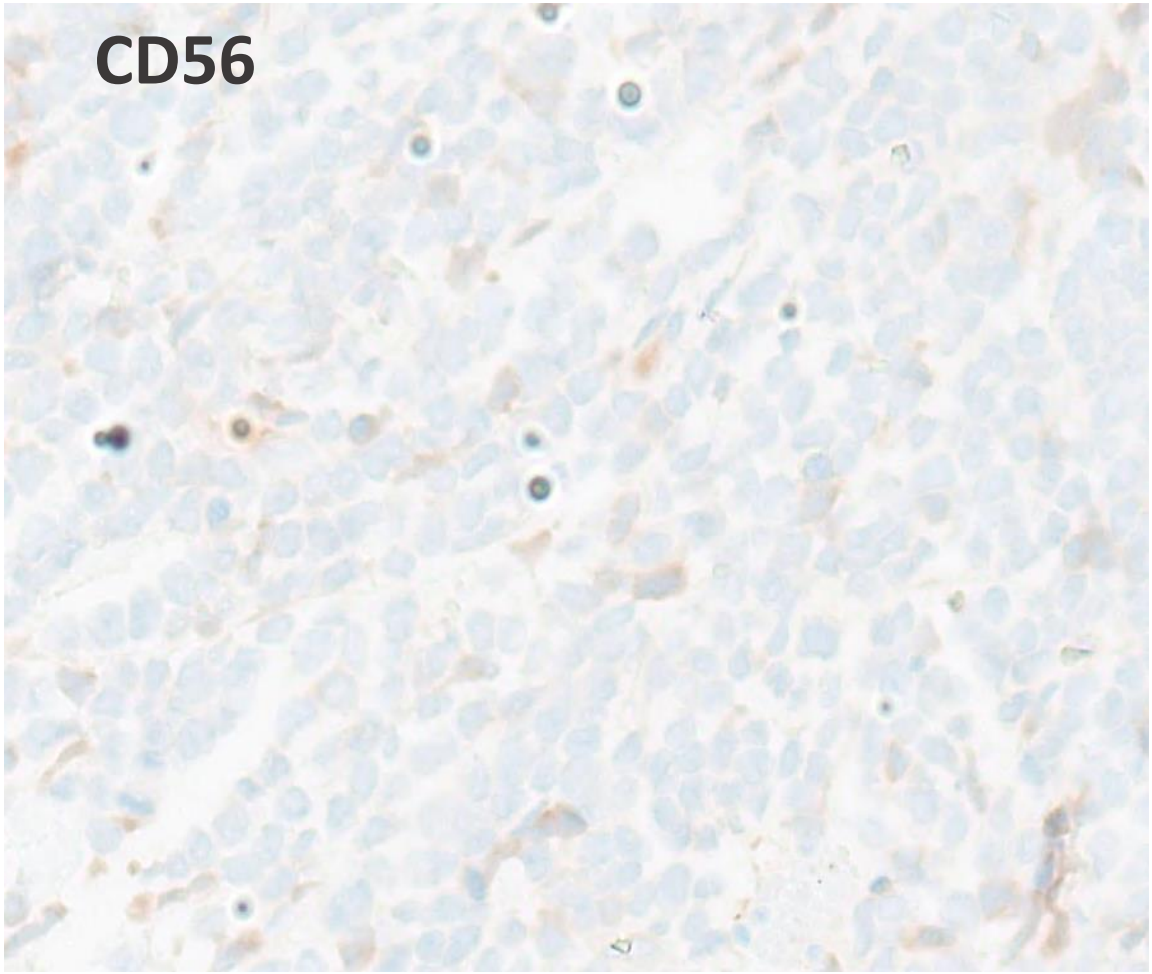


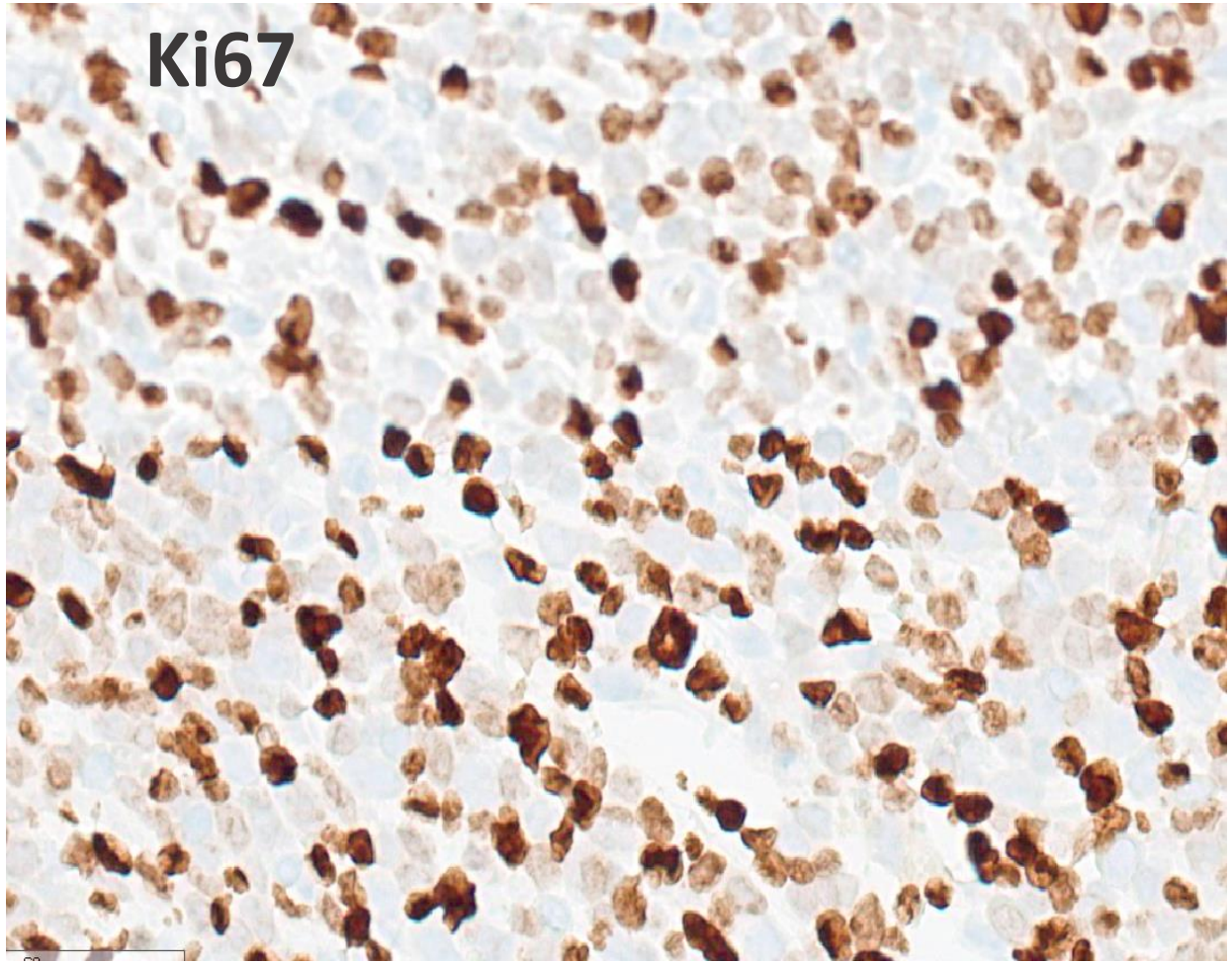
Appendix – IHC





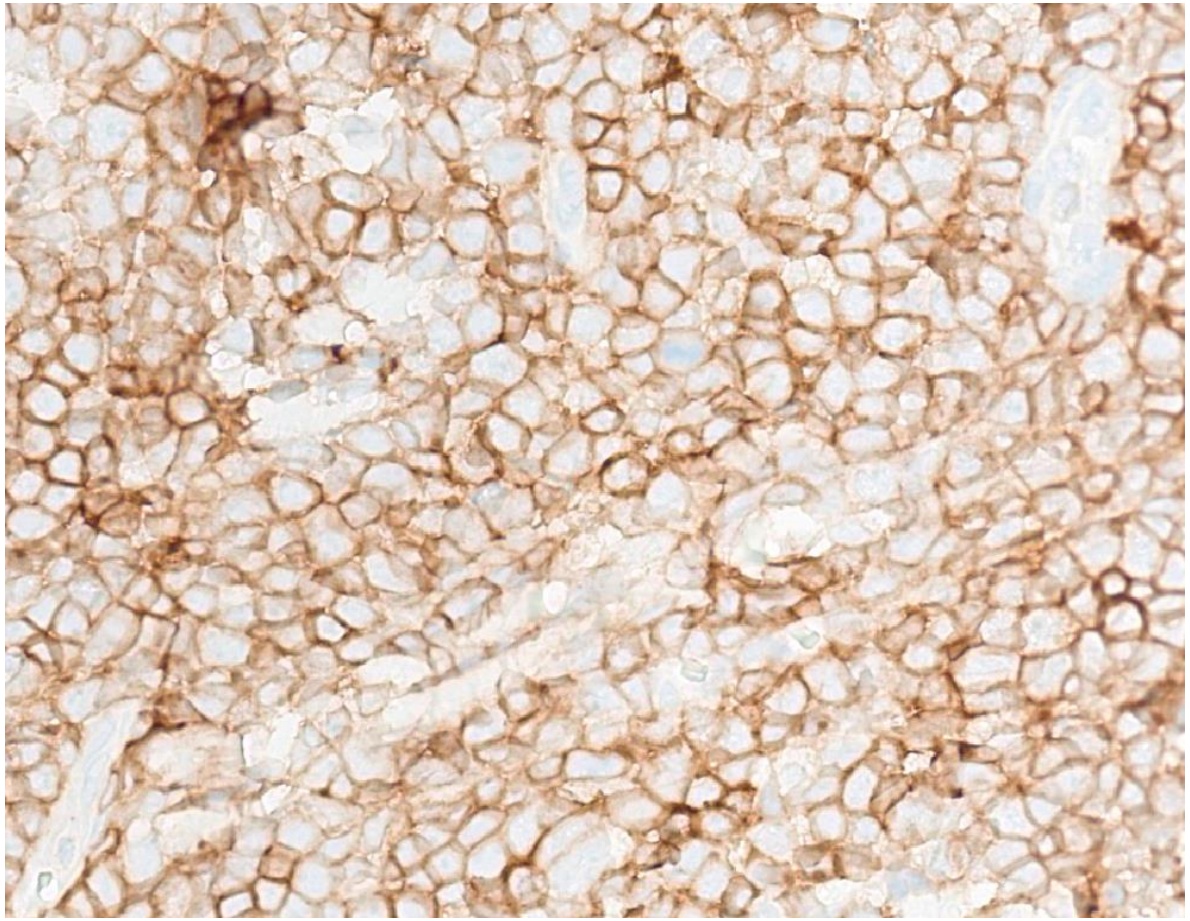
Appendix – IHC



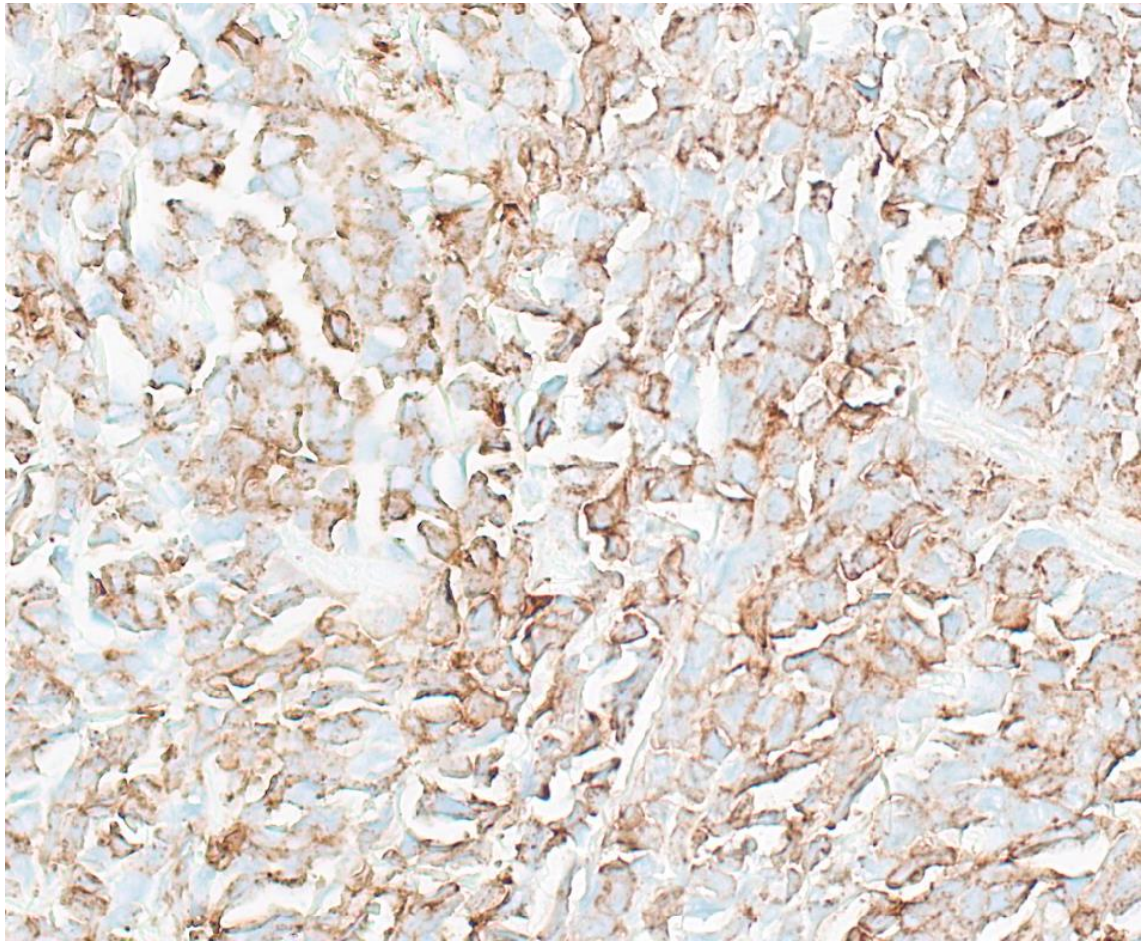


DIAGNOSIS?

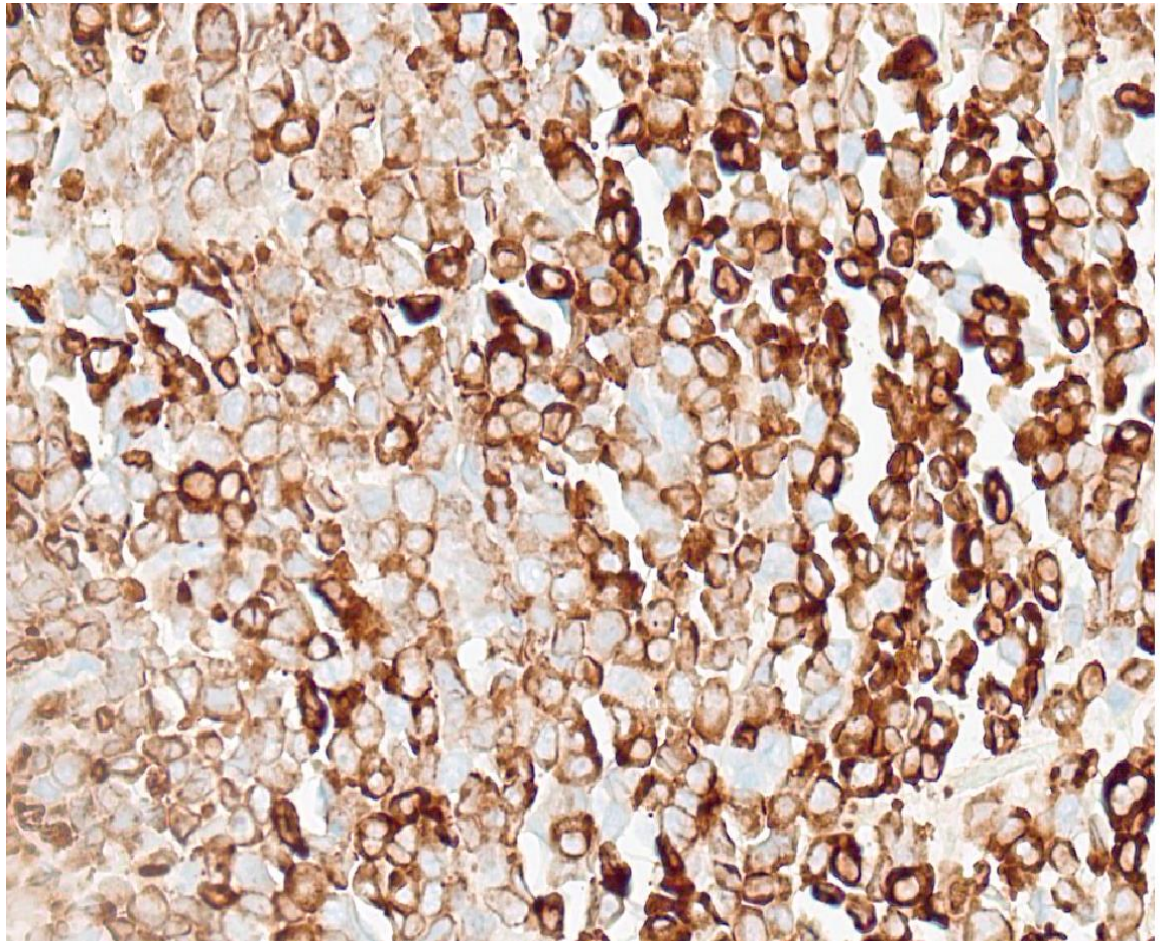
IHC – CD45



IHC (cont.)



CD34



MPO

Final diagnosis

Appendix, appendectomy:

- **Myeloid sarcoma**

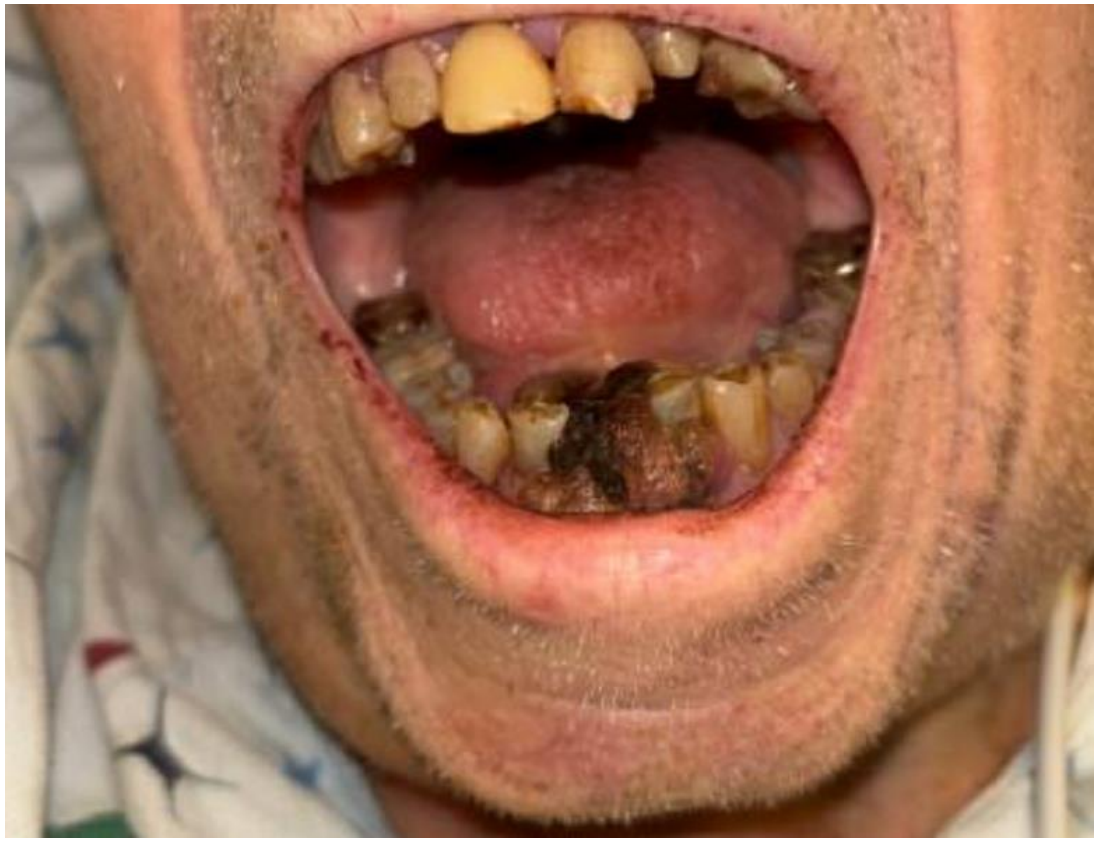
Follow-up bone marrow aspirate/biopsy:

- **Acute myeloid leukaemia with *CBFB::MYH11* fusion (WHO HAEM5)**
- **Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11* (ICC)**

24-1008

Vaishali Masatkar and Oscar Silva; Stanford

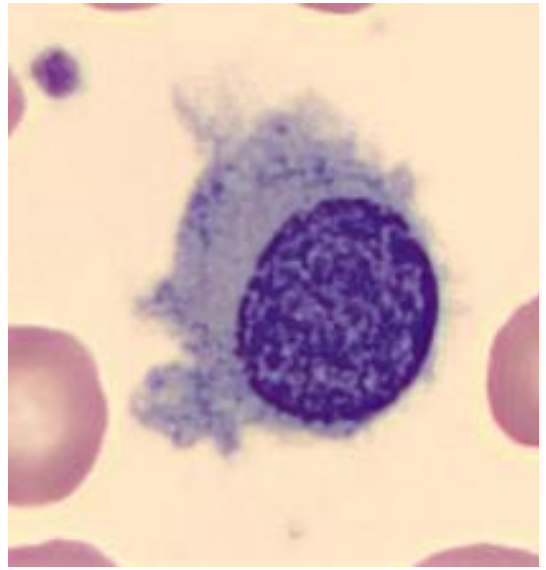
- 93-year-old male presented with pancytopenia and a rapidly growing oral mass
- Past medical history – DM, HTN, Colon Cancer, Hairy cell leukemia (diagnosed in July, 2023)
- Examination findings - soft tissue mass in midline anterior oral cavity arising from mandible at site of prior central incisor extraction; mass relatively soft, minimally tender, and partially necrotic on the posterior aspect.

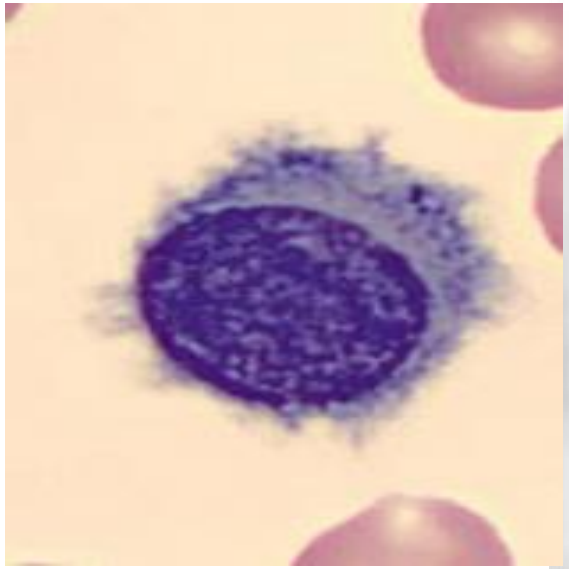


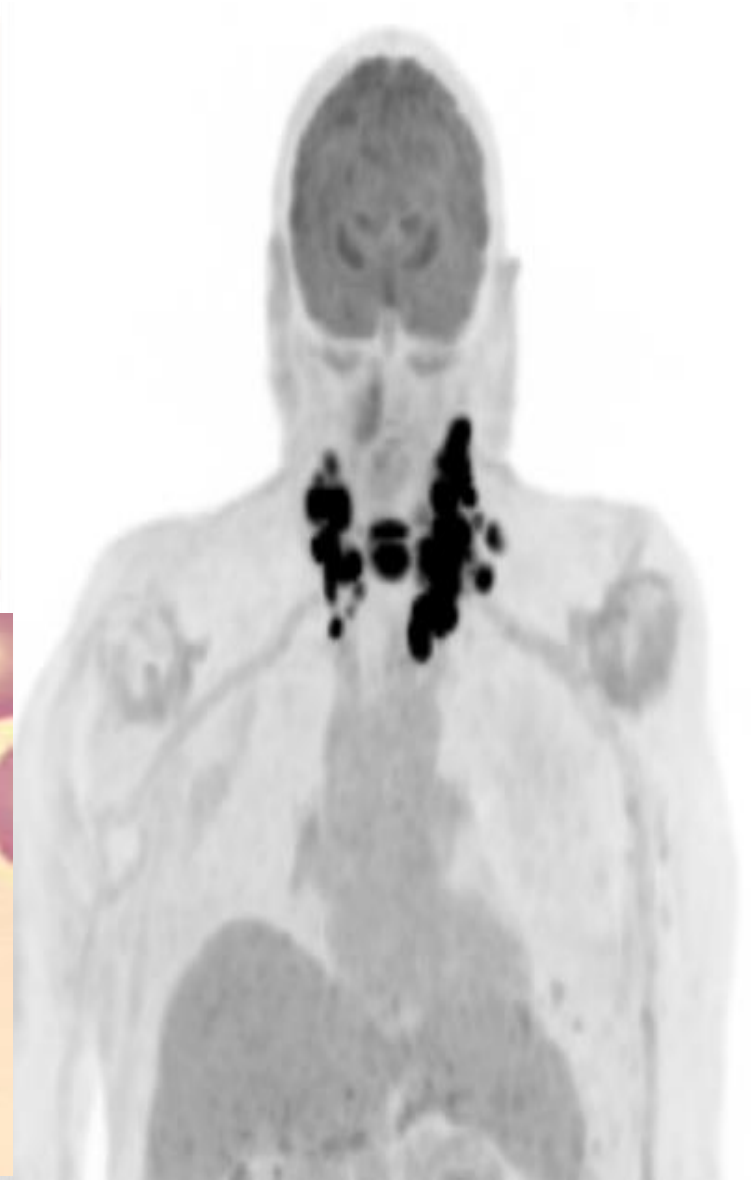
Case Presentation

- PET/CT –
  - Increase uptake in cervical, mediastinal and paraesophageal lymph nodes
  - Intense uptake in the mass involving the floor of the mouth and mandible at midline with associated lytic changes

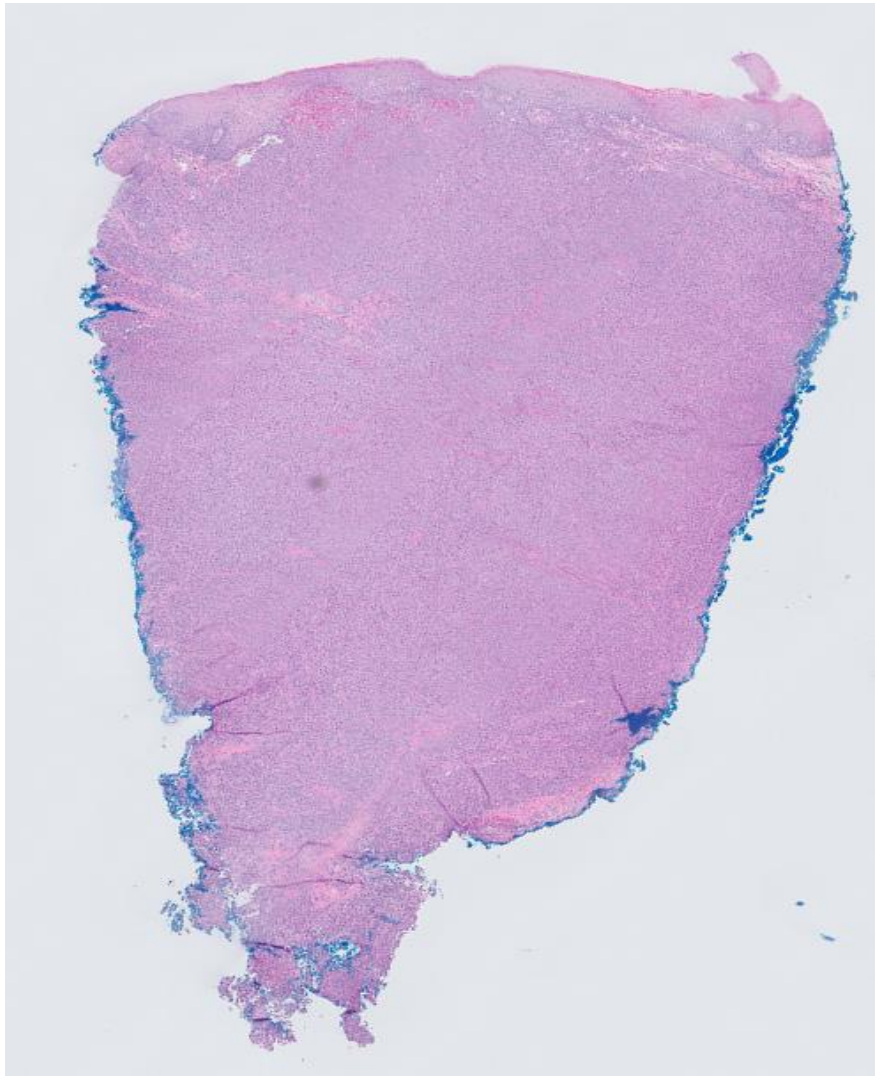
- Peripheral blood smear – Neoplastic cells with hairy projections
- Peripheral blood flow (Sept, 2024) - Kappa-restricted B-cell population (17% of CD45+ events) expressing CD19, CD20 (bright), CD22, CD25, CD103, CD123 and CD11c; negative for CD5 and CD10

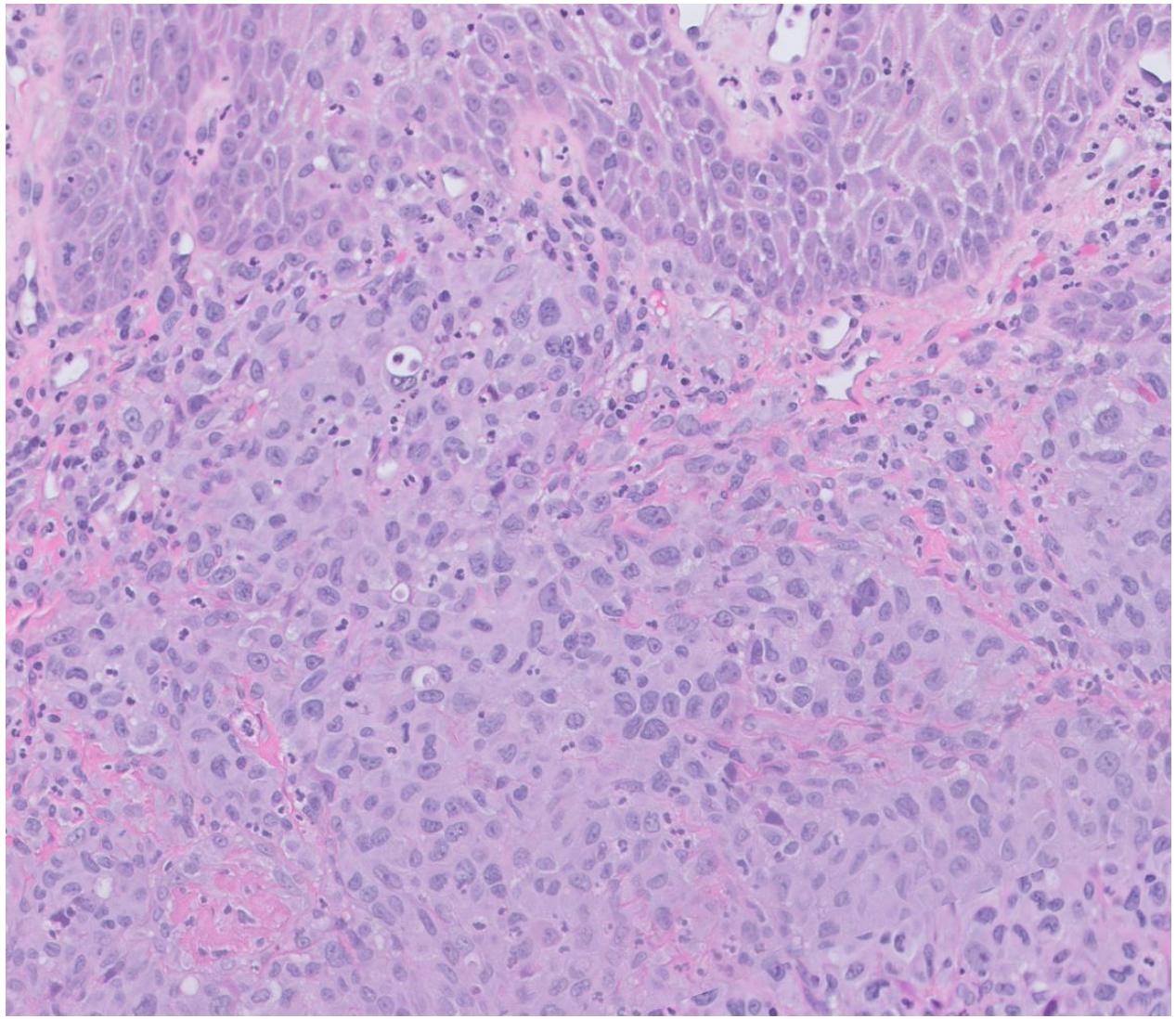






Oral Biopsy:





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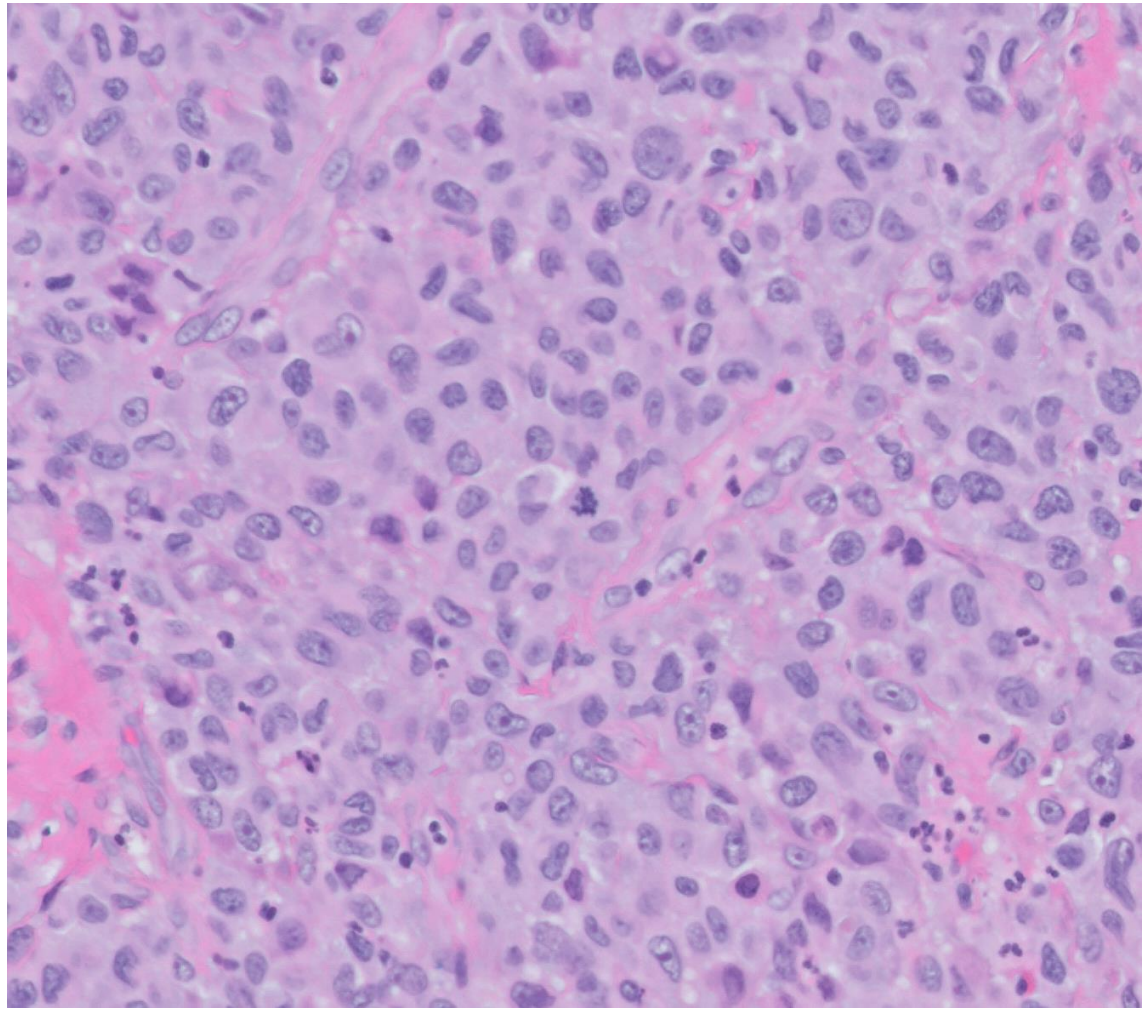
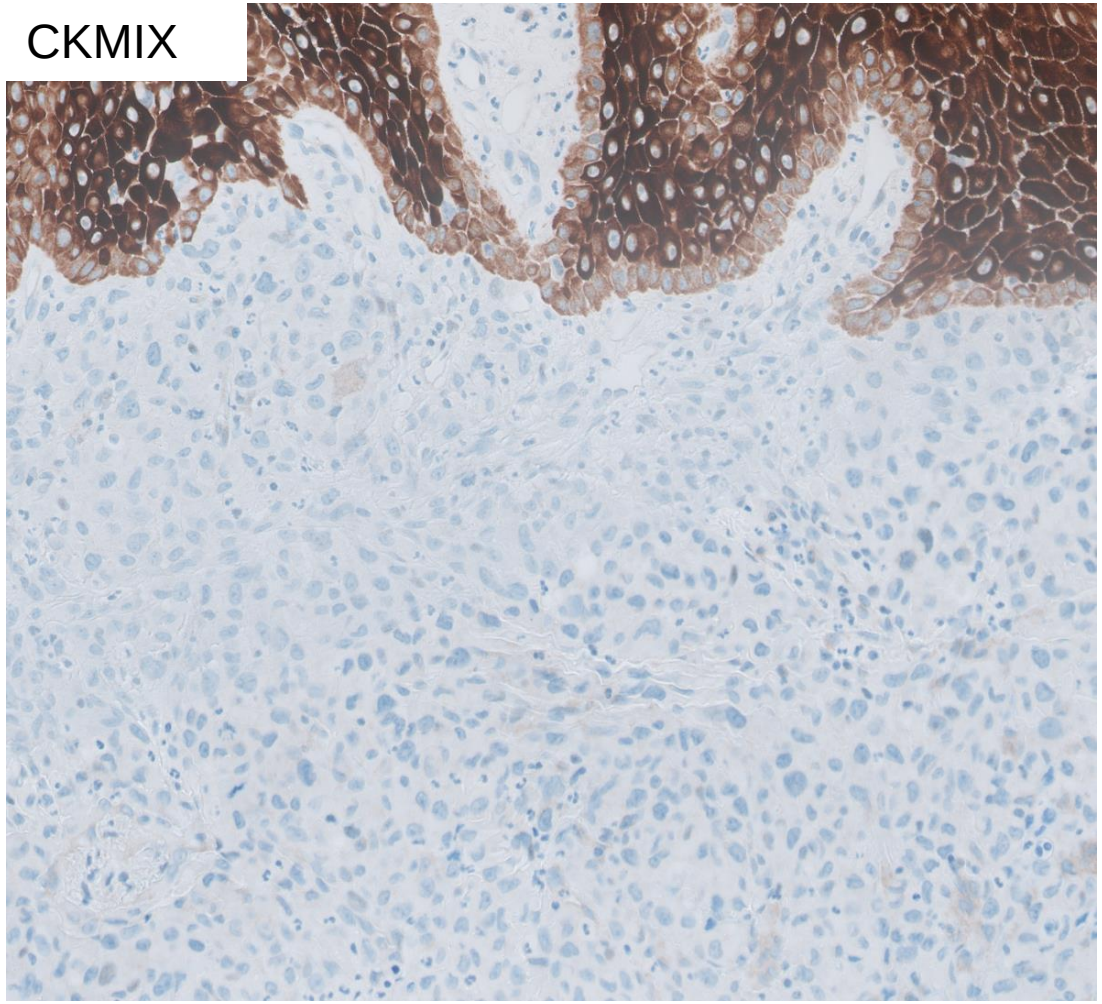
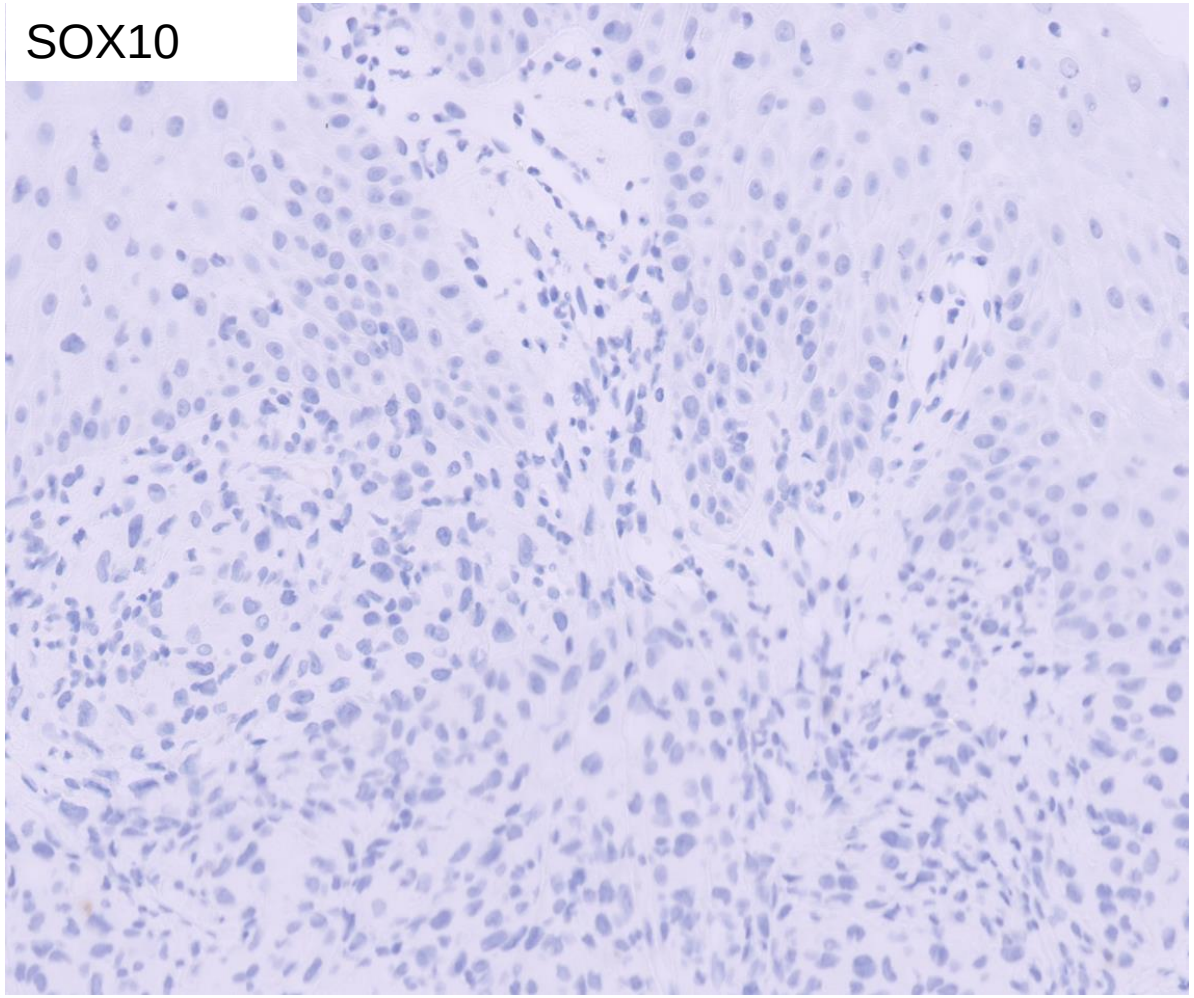


Oral Biopsy: *Immunohistochemistry*

CKMIX

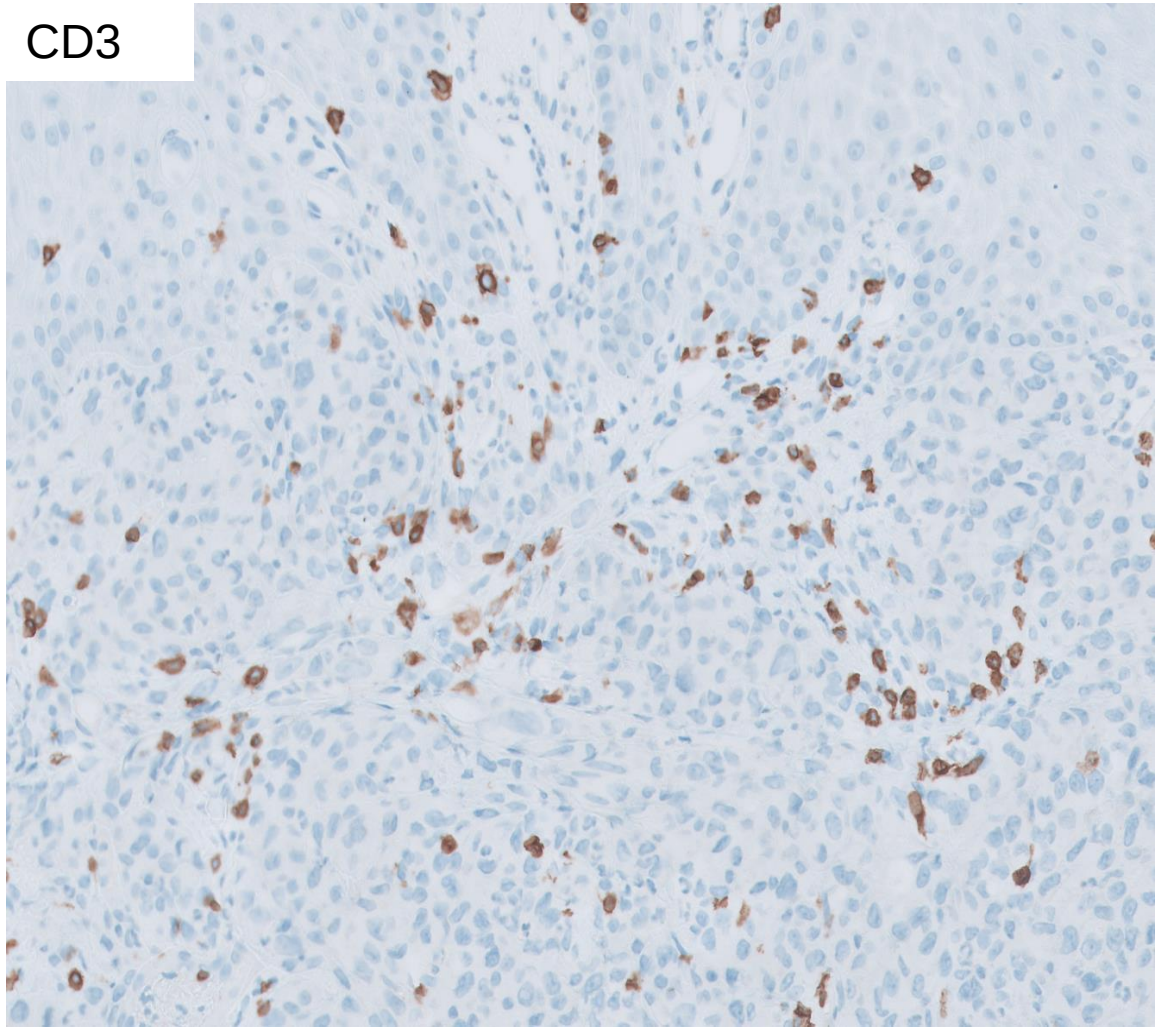


SOX10

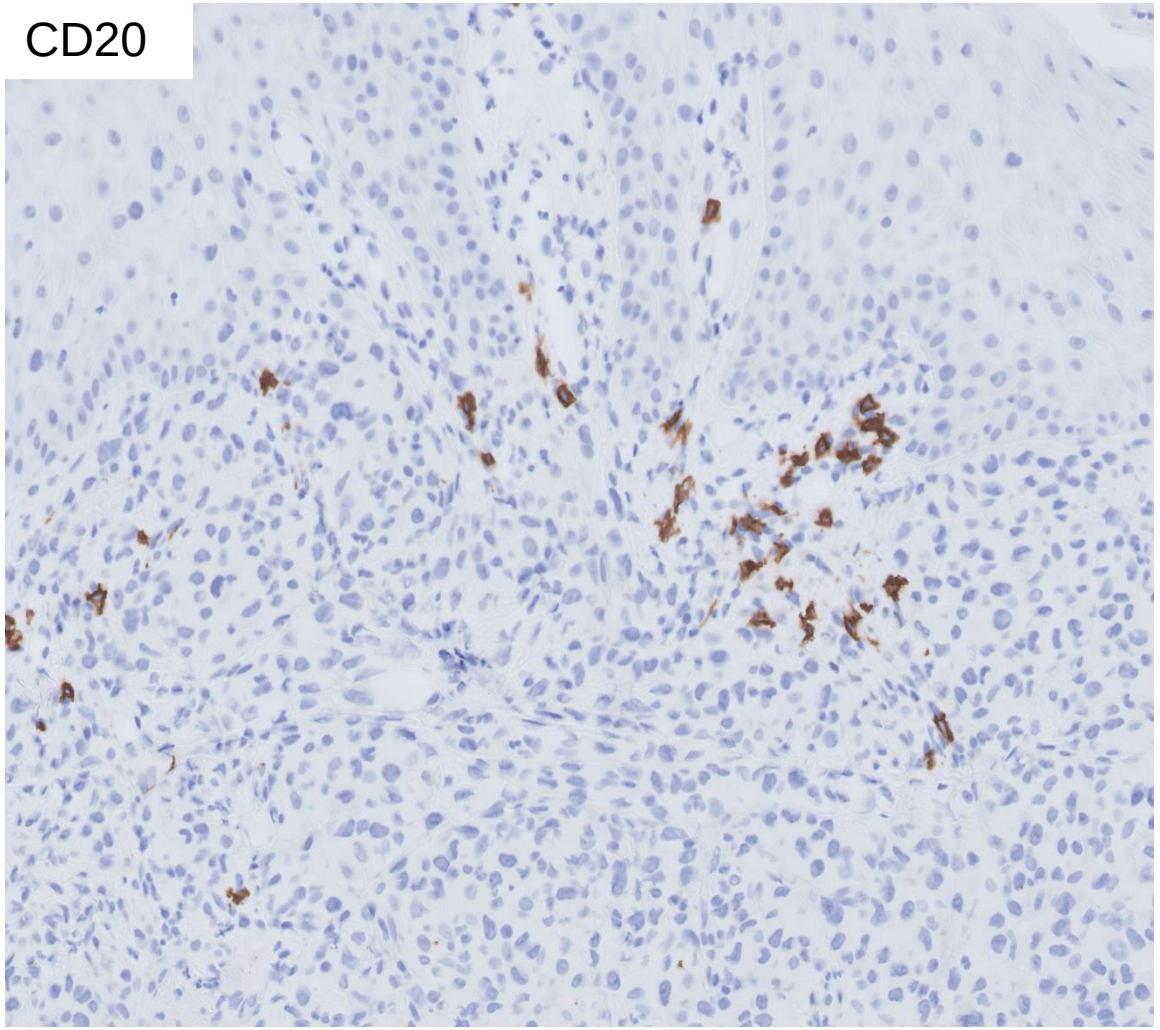


Oral Biopsy: *Immunohistochemistry*

CD3



CD20



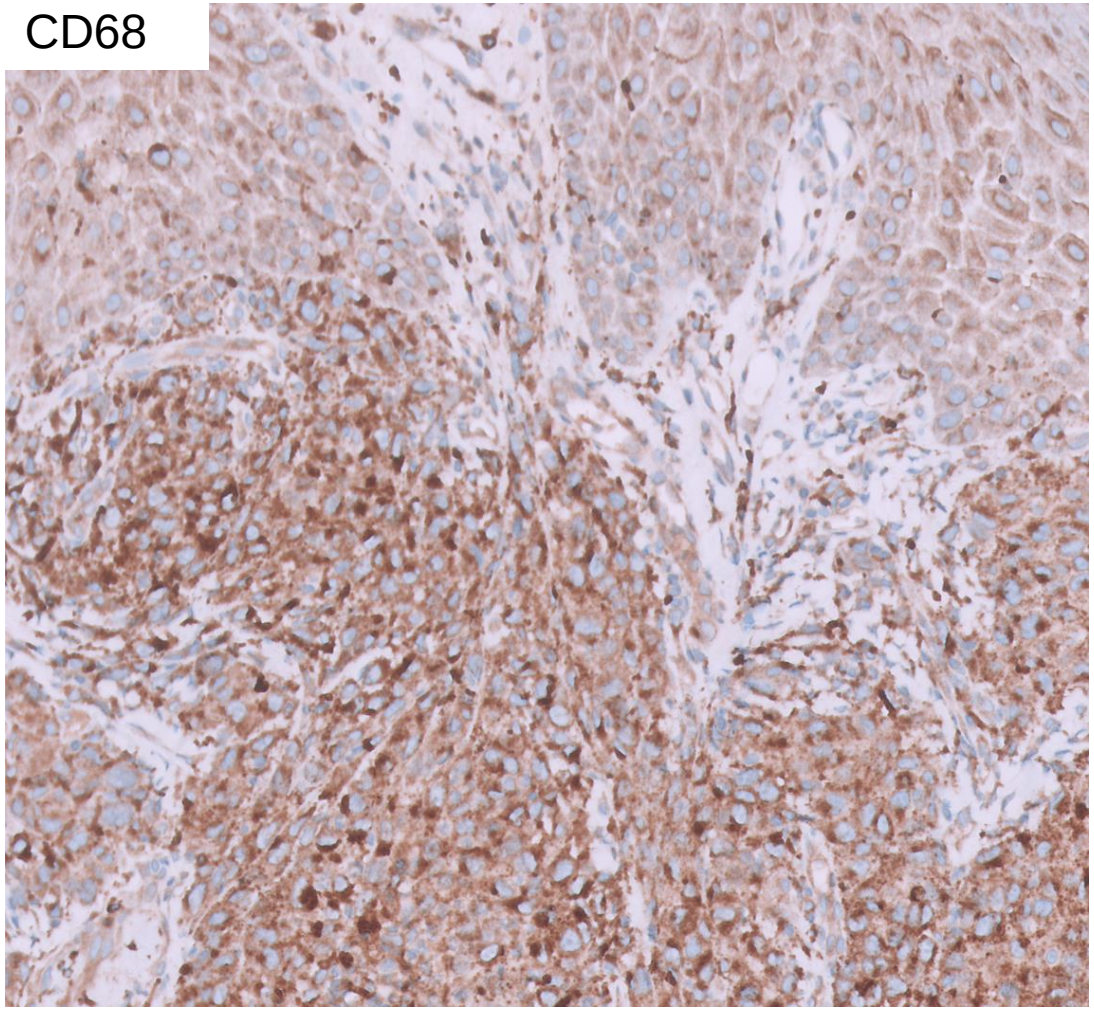
Oral Biopsy: *Immunohistochemistry*

Other negative markers:

p40, CD138, CD30, S100, CD1a, Langerin, CD34, CD117, IRF8, CD21, EBV-ish

Oral Biopsy: *Immunohistochemistry*

CD68



CD68
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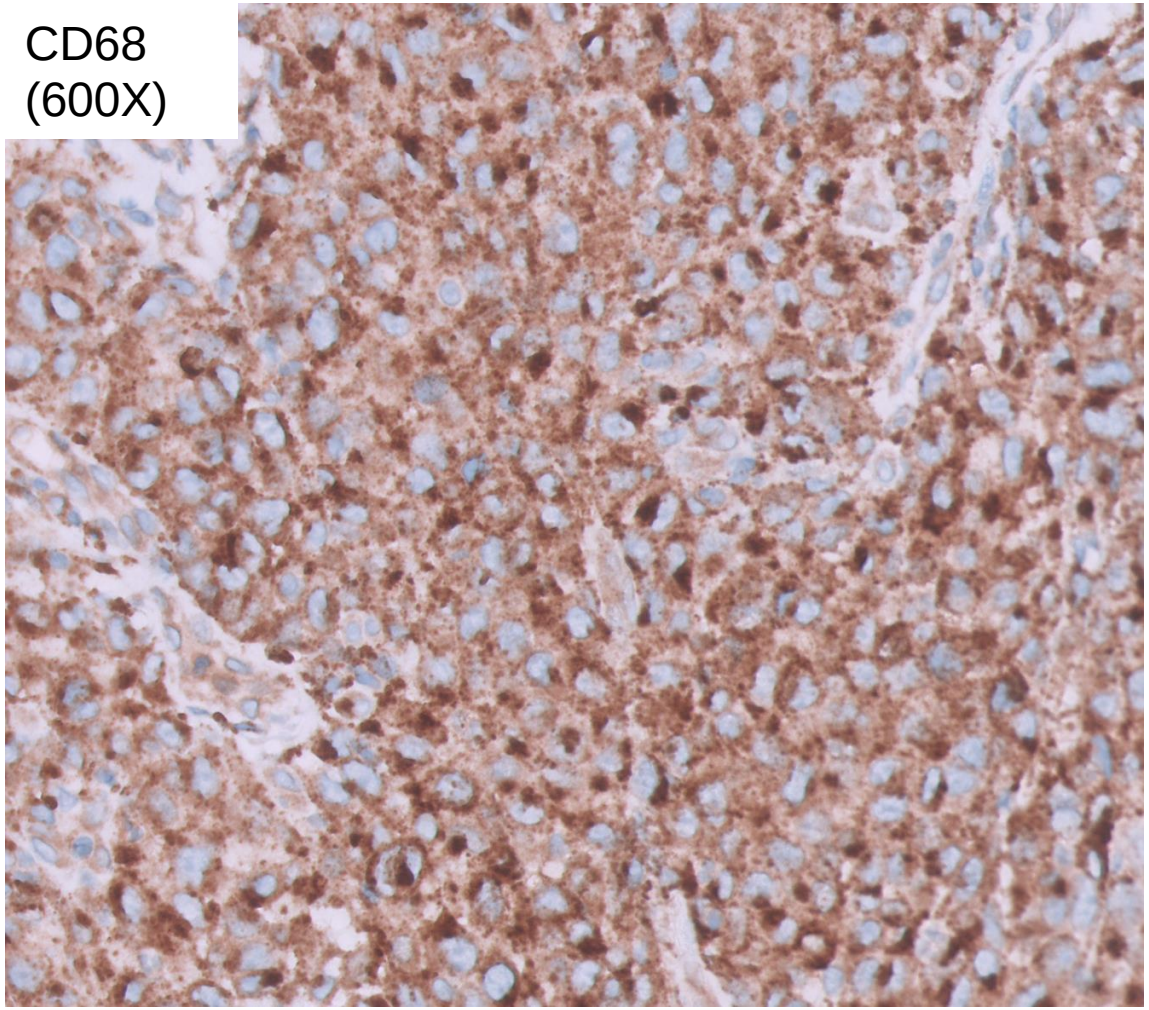
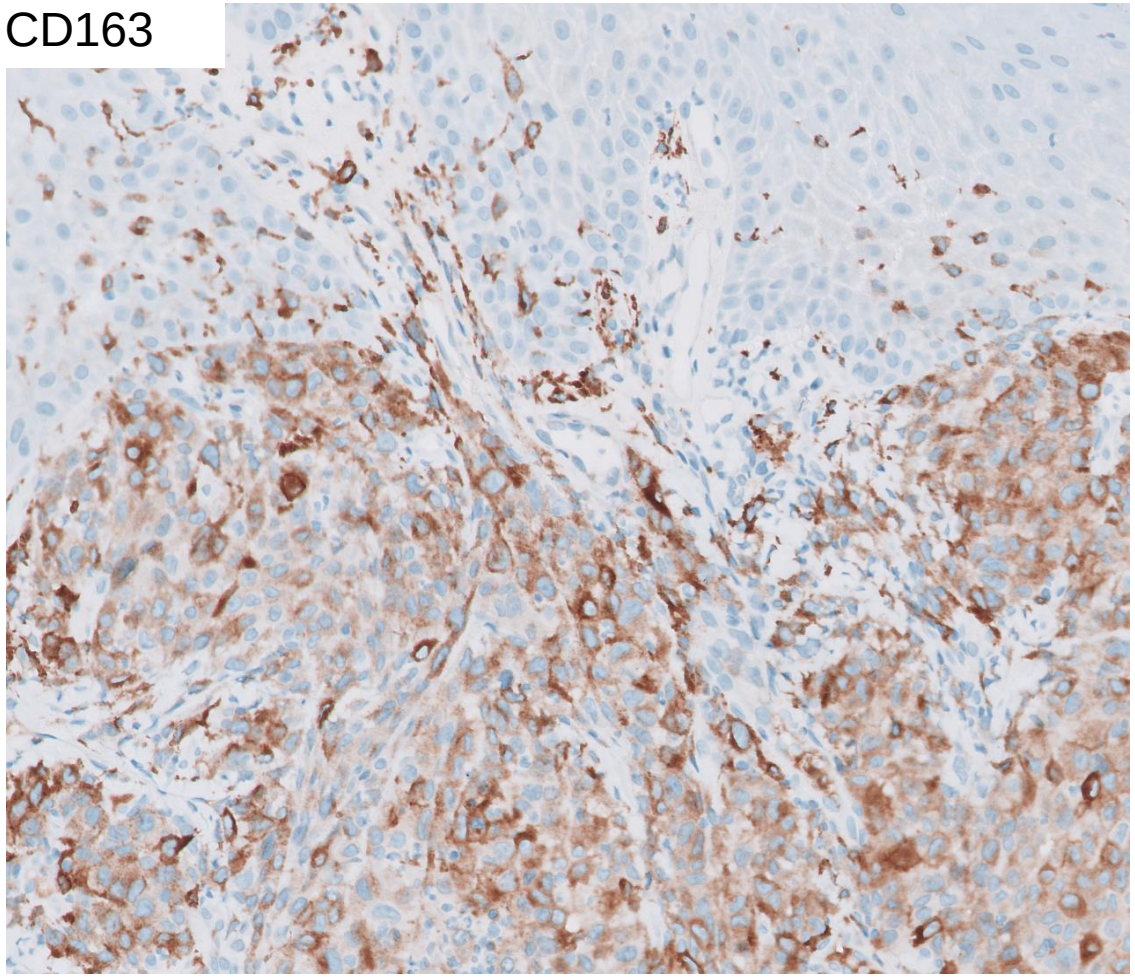


Oral Biopsy: *Immunohistochemistry*

CD163



CD163
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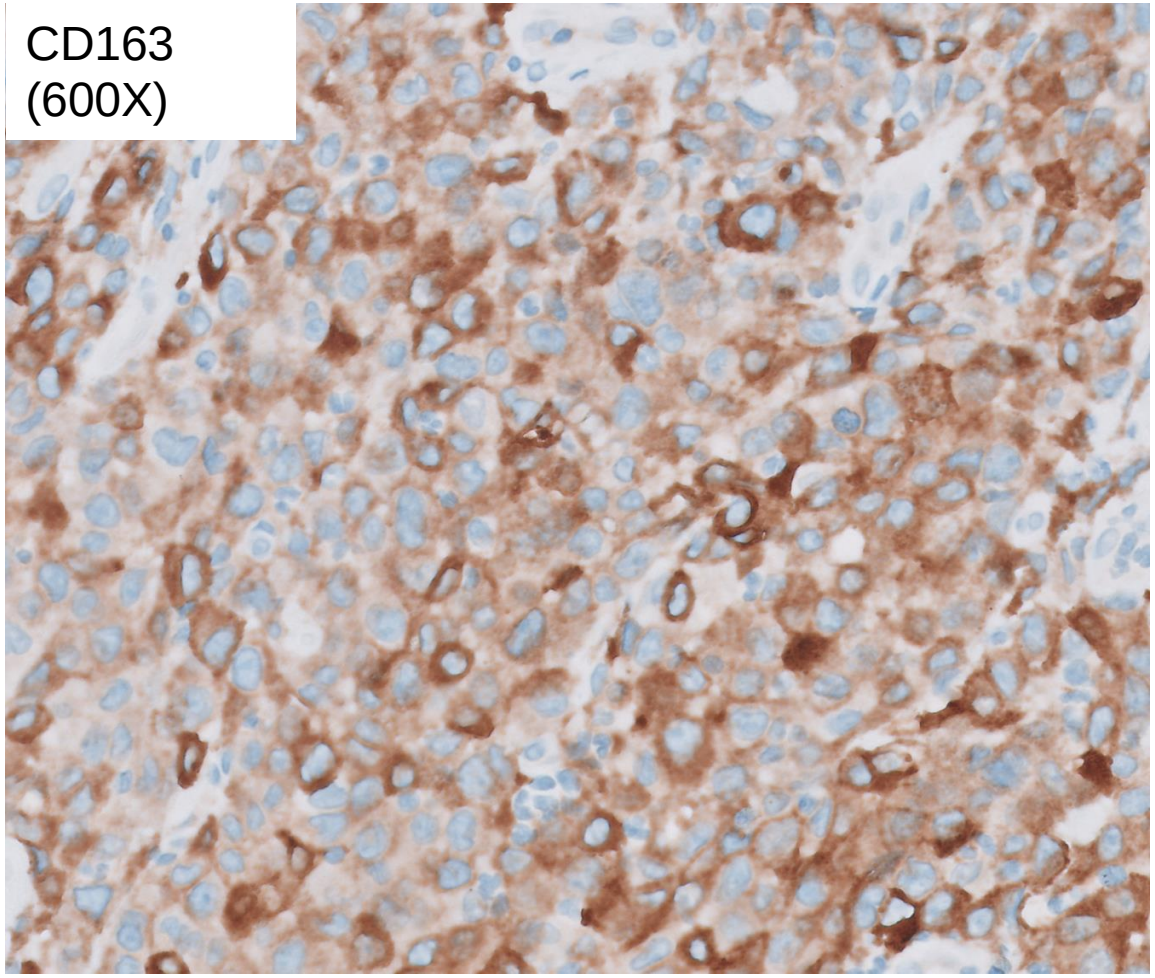
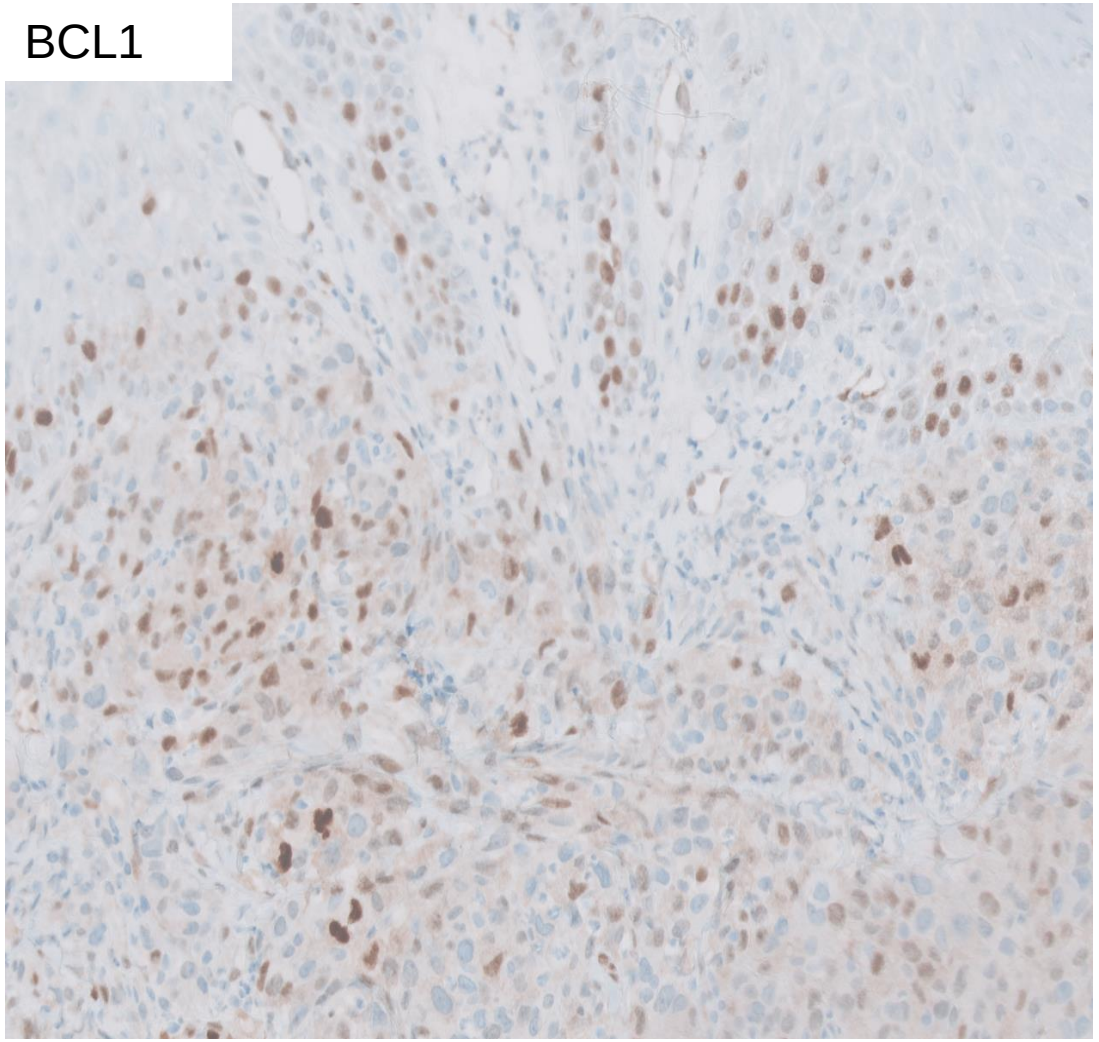


Oral Biopsy: *Immunohistochemistry*

BCL1



BCL1
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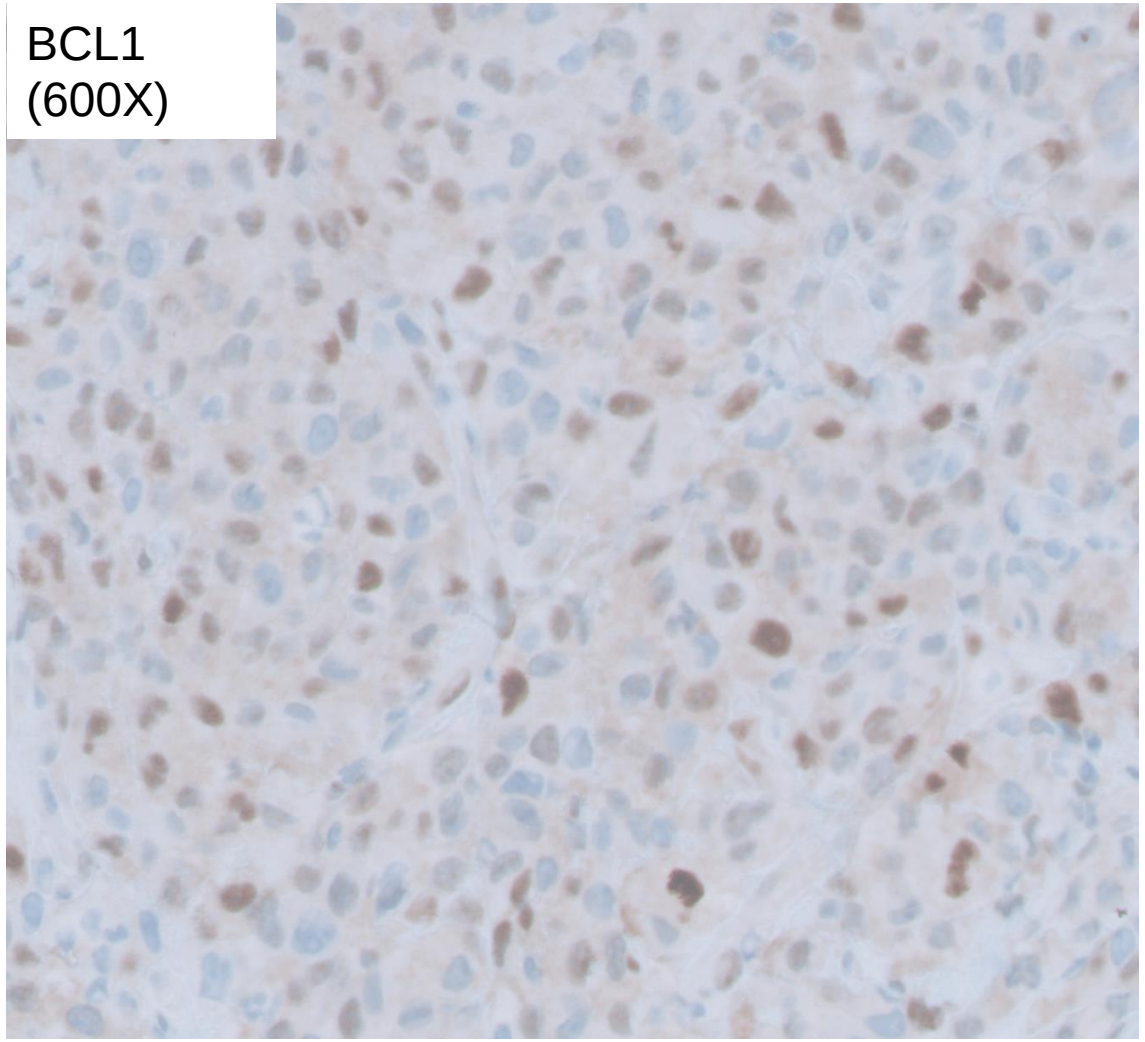
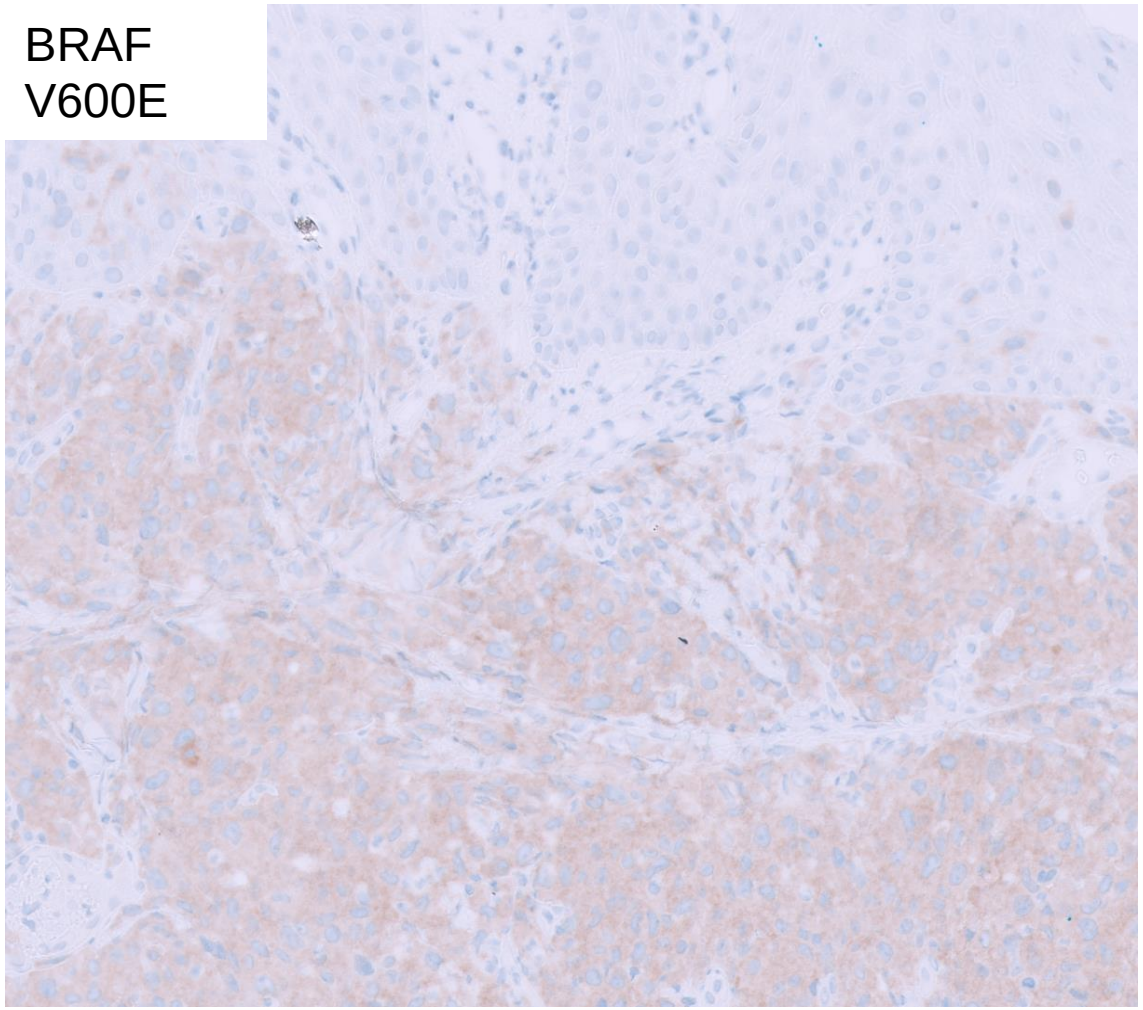
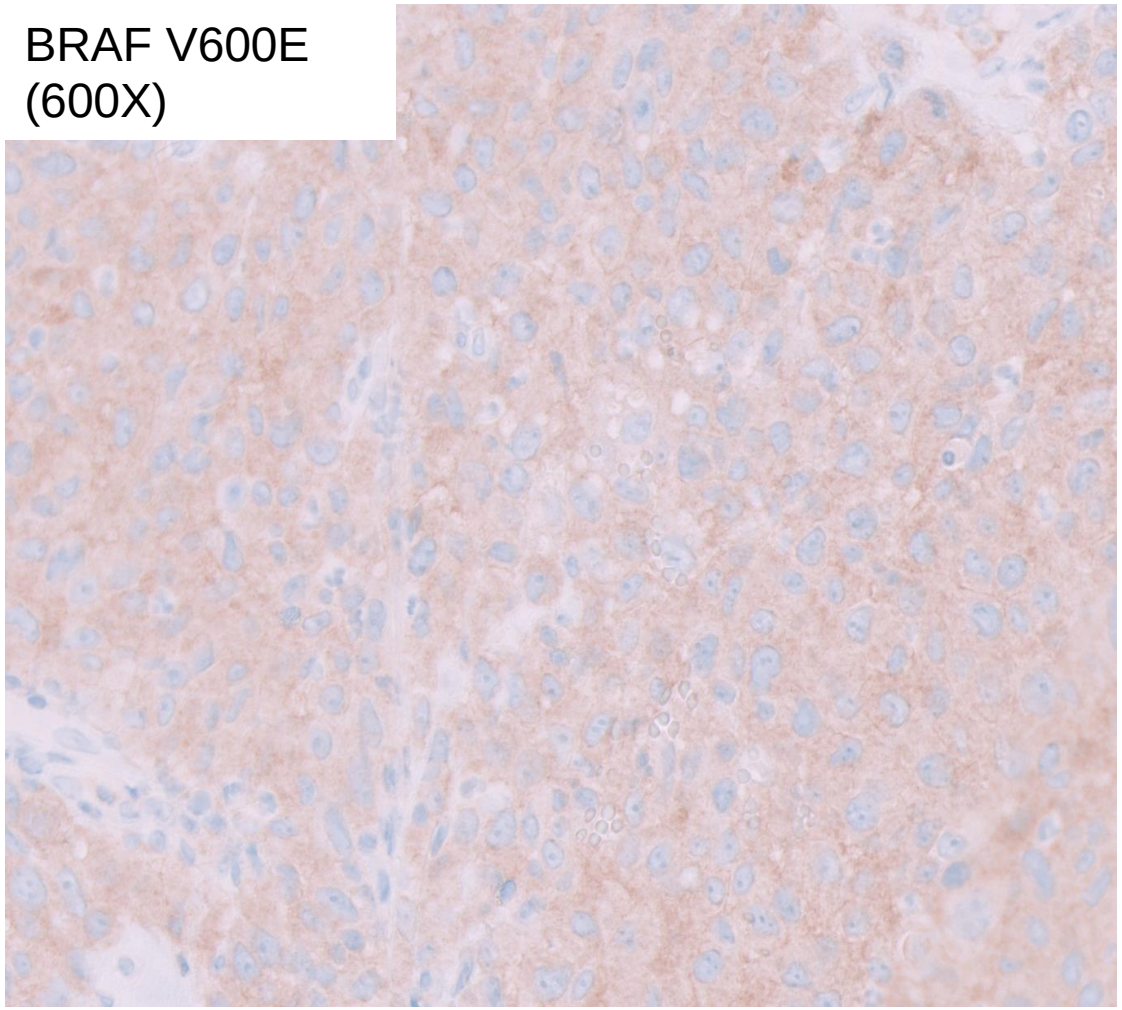


Oral Biopsy: *Immunohistochemistry*

BRAF V600E



BRAF V600E (600X)



DIAGNOSIS?

Histiocytic sarcoma (HS) transdifferentiated from Hairy cell leukemia (HCL)

- Most histiocytic/dendritic cell neoplasms arise de novo, but a subset of cases occur in association with or follow a lymphoma/leukemia
  - Express the same clonal markers as the associated or preceding lymphoma/leukemia

- Most commonly described with follicular lymphoma

- So far, only two cases of HS transdifferentiated from hairy cell leukemia have been described in the literature
  - BRAF V600E and clonal IgH mutation was identified in one case
  - In another case, in addition to BRAF V600E mutation, similar cytogenetic abnormalities were detected in both HCL and HS

- In our case –
  - BRAF V600E + on IHC
  - B cell clonality studies and HemeSTAMP are pending

Pathomechanisms – Cell lineage

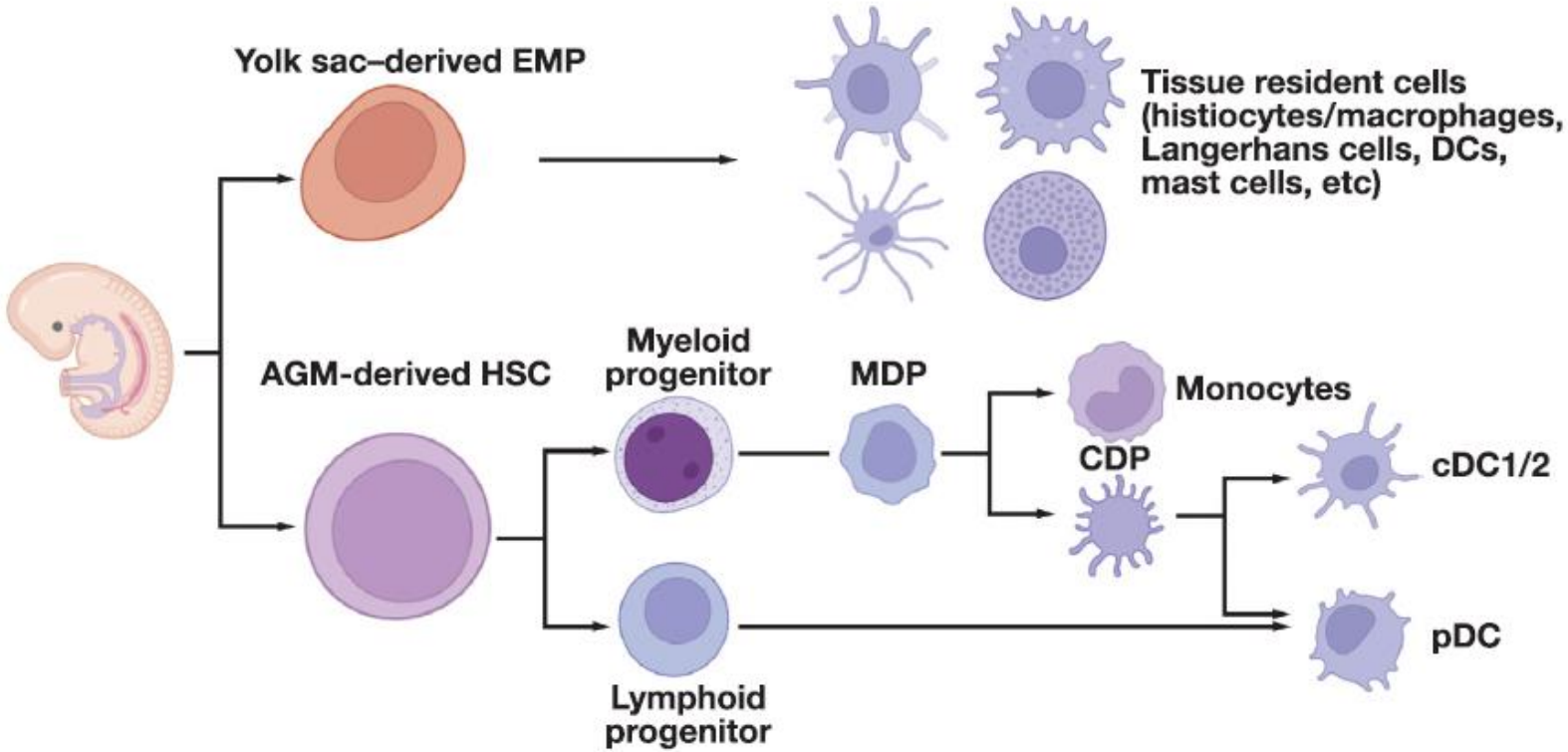


FIGURE 1 Cell of origin of histiocyte/monocyte/macrophage and dendritic cells (DCs). AGM, aorta-gonad-mesonephros; cDC, classic dendritic cell; CDP, common dendritic cell precursor; EMP, erythroid/myeloid precursor; HSC, hematopoietic stem cell; MDP, monocyte/dendritic cell precursor; pDC, plasmacytoid dendritic cell.

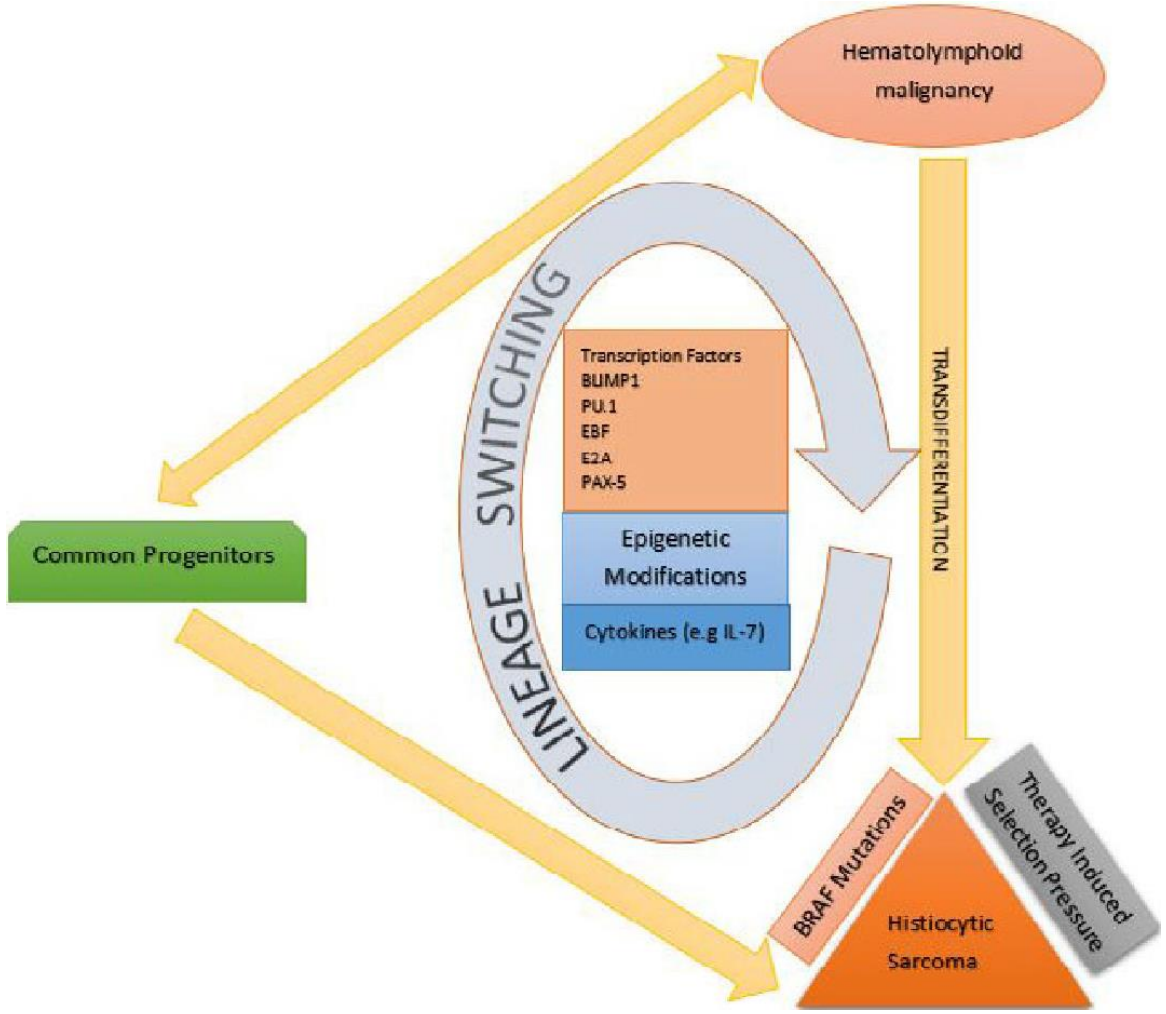
Pathomechanisms – proposed mechanisms

Three major putative mechanisms:

i. A direct transdifferentiation,

ii. A two-step process of transformation with first dedifferentiation of neoplastic B cells to early progenitors with subsequent redifferentiation, and

iii. A possible origin from a common neoplastic progenitor with differentiation along both B-cell and histiocytic/dendritic lineages at different times



Mutational profile of histiocytic/dendritic cell neoplasms associated with B-cell lymphoma

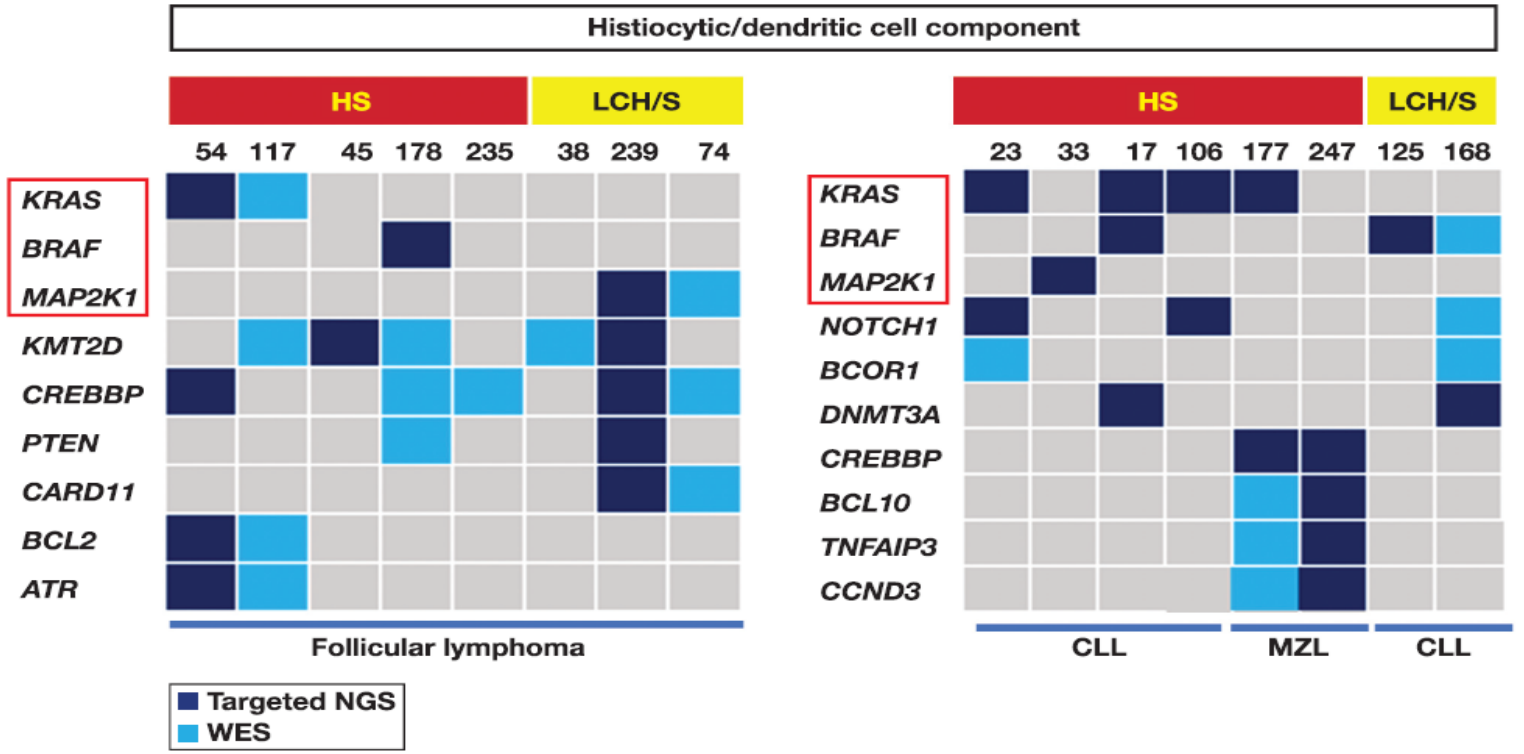


FIGURE 8 Mutational profile of histiocytic/dendritic cell neoplasms associated with B-cell lymphoma. CLL, chronic lymphocytic leukemia; HS, histiocytic sarcoma; LCH/S, Langerhans cell histiocytosis/sarcoma; MZL, marginal zone lymphoma; NGS, next-generation sequencing; WES, whole-exome sequencing.

Egan C et al. The mutational landscape of histiocytic sarcoma associated with lymphoid malignancy. Modern Pathology, 2021

Histiocytic Sarcoma

Clinical Presentation

- Nodal/ extranodal – GI (MC), spleen, soft tissue, skin, CNS
- Localized or disseminated
- Lymphadenopathy, skin lesions, GI obstruction, splenomegaly
- Fever, fatigue, night sweats, weight loss

Essential diagnostic criteria

- Tumor composed of non-cohesive large cells with abundant eosinophilic cytoplasm; variably pleomorphic neoplastic cells with reniform, grooved, or irregularly folded nuclei and distinct nucleoli;
  - positive immunostaining for two or more histiocytic markers;
  - negative for CD1a, CD207 (langerin), CD21, CD35

Pathogenesis

- Most frequent genomic alterations - mutations in MAPK pathway genes, including KRAS, NRAS, **BRAF**, MAP2K1, PTPN11, NF1, and CBL
- Clonal IG rearrangements, evidence of aberrant somatic hypermutation, and mutations typical of some B-cell lymphomas (e.g. CREBBP and KMT2D mutations) have been documented

Treatment and Prognosis

- Usually aggressive, with a high mortality rate
- Localized tumors have a more favorable outcome
- Our patient – BRAF inhibitor (Vemurafenib) and radiation to mass: 14 Gy in 4 fractions BID

Differential diagnosis based on histomorphology

- Malignant melanoma – MART-1, SOX10, S100
- Lymphoma (large B cell lymphoma and anaplastic large cell lymphoma) – CD45, CD20, Pax5, CD30
- Undifferentiated large cell carcinoma – CKMIX, p40
- Myeloid sarcoma – CD34, CD117, IRF8
- Other histiocytic/ dendritic cell neoplasm

TABLE 2 Proposed Algorithm of Lineage Assignment of Histiocytic/Dendritic Cell Neoplasms[a]

	LC and related neoplasm[b]					
IHC marker	LCH	LCS	Partial LC differentiation[d]	IDCT	HS	IDCS[c]
S100	+	+	+/−	+	+/−	+
CD1A	Strong and ≥50%	≥5%	+ (<5%)	Strong and ≥50%	−	−
Langerin	≥5%	−5%	+ (<5%)	−	−	−
Histiocytic markers[e]	+/−	+/−	+/−	+/−	+	−/+

References:

1. WHO 5th edition: Histiocytic/dendritic cell neoplasms: Introduction, Histiocytic Sarcoma, and Hairy cell leukemia
2. Ansari J et al. Histiocytic sarcoma as a secondary malignancy: pathobiology, diagnosis, and treatment. Eur J of Haematol. 2016.
3. Xiao W et al. B-cell lineage neoplasms transdifferentiating into histiocytic/dendritic cell neoplasms: diversity, differentiation lineage, genomic alterations, and therapy. Am J Clin Path. 2023.
4. Pal P et al. Molecular Mutations in Histiocytosis: A Comprehensive Survey of Genetic Alterations. Molecular Biotechnology. 2023.
5. Michonneau D et al. BRAF(V600E) mutation in a histiocytic sarcoma arising from hairy cell leukemia. J Clin Oncol. 2014.
6. Chai KL et al. BRAF-mutated hairy cell leukaemia with transdifferentiation to histiocytic sarcoma – A case report. Pathology. 2018.
7. Maitre E et al. Hairy cell leukaemia with unusual BRAF mutations. J Cell Mol Med. 2023.
8. Amador C et al. Transdifferentiation, phenotypic infidelity, progression, and transformation in T/NK-cell neoplasms: Report from the 2021 SH/EAHP Workshop. Am J Clin Pathol. 2023.
9. Yoon SO. Pathologic characteristics of histiocytic and dendritic cell neoplasms. Blood Research 2024.
10. Jonathan S. Genomic profiling of histiocytic sarcoma: new insights into pathogenesis and subclassification. Hematologica 2020.
11. Egan C. The mutational landscape of histiocytic sarcoma associated with lymphoid malignancy. Modern pathology. 2021.