South Bay July 2024 Webcases

Disclosures
July 29, 2024

Dr. Brooke Howitt has disclosed active financial relationships with Leica (consultant), Cartography Bioscience (advisory board member), and Santa Ana Bio (advisory board member). Dr. Sebastian Fernandez-Pol has disclosed active financial relationships with Leica (consultant) and Cartography Bioscience (advisory board member). South Bay Pathology Society has determined that none of the relationships of Drs. Howitt and Fernandez-Pol are relevant to the clinical diagnostic cases being discussed. 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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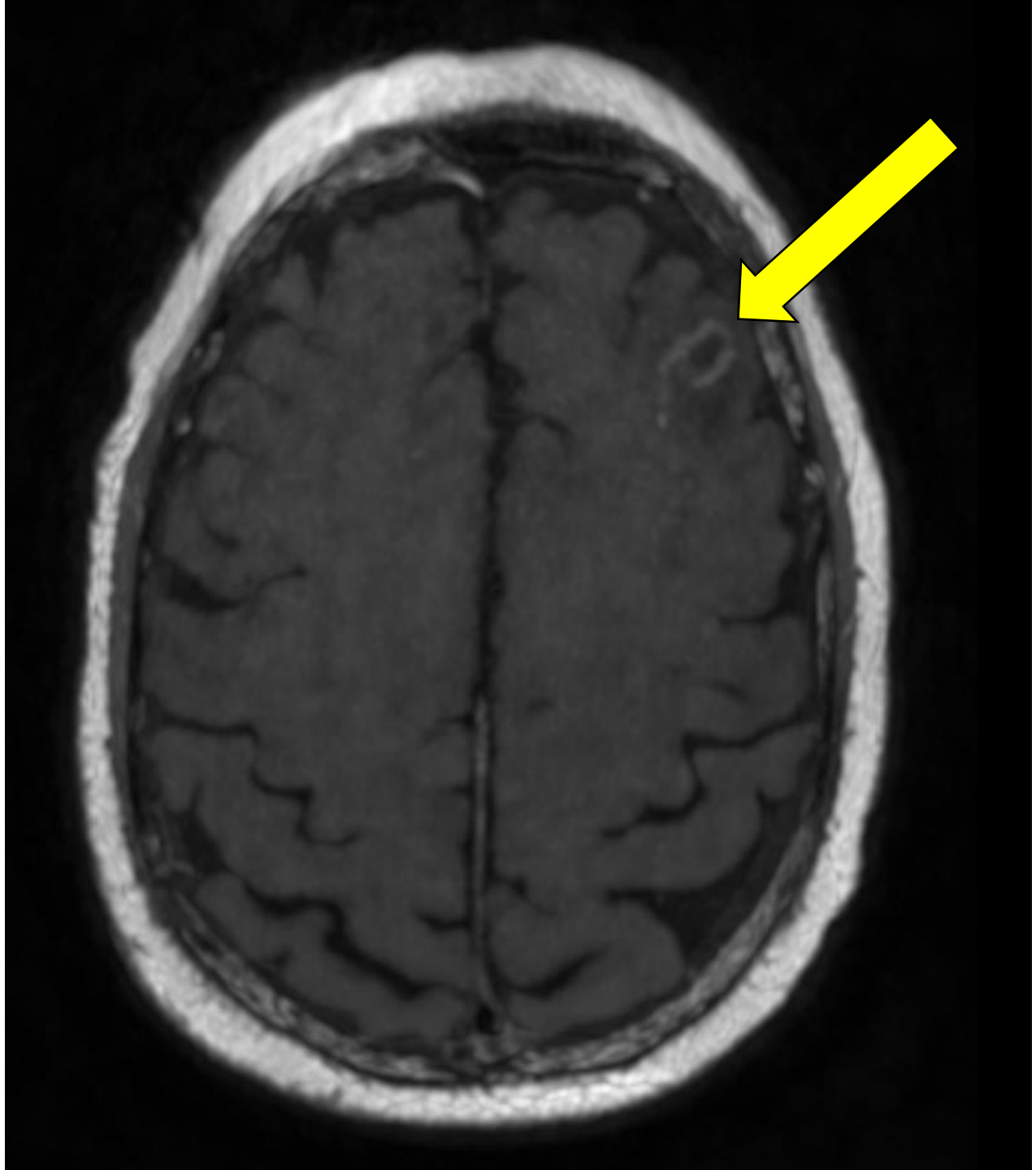
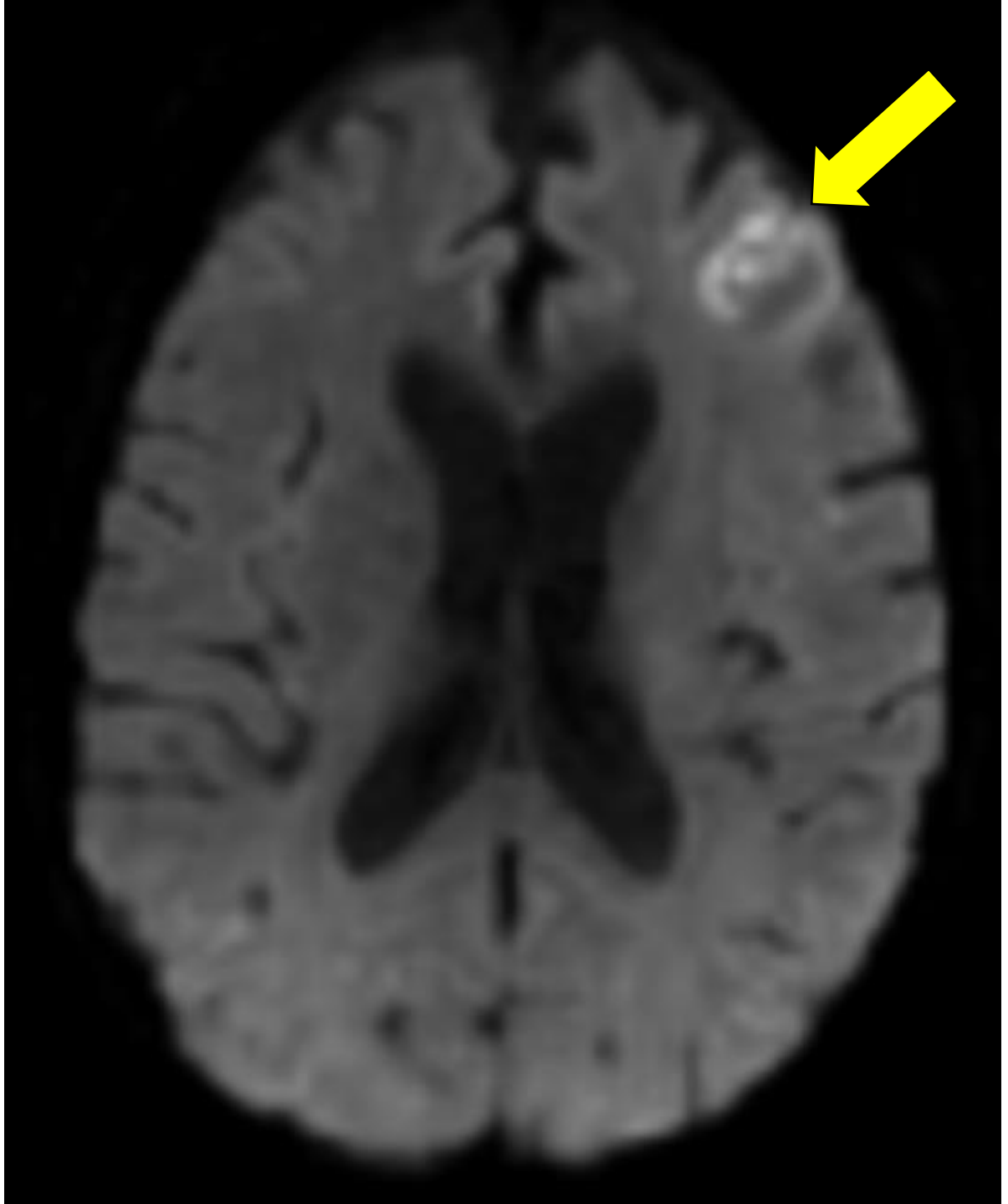
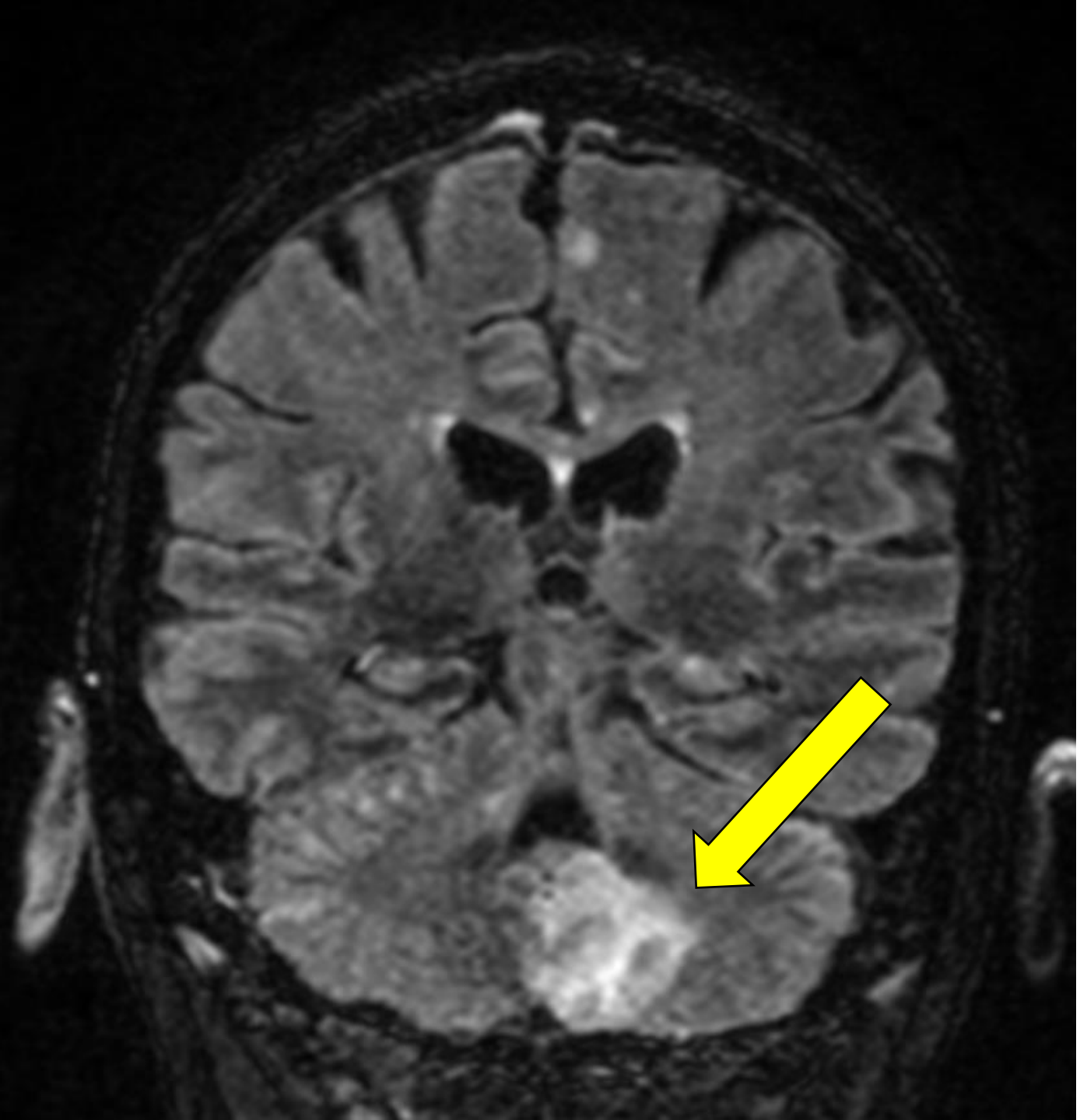
24-0701

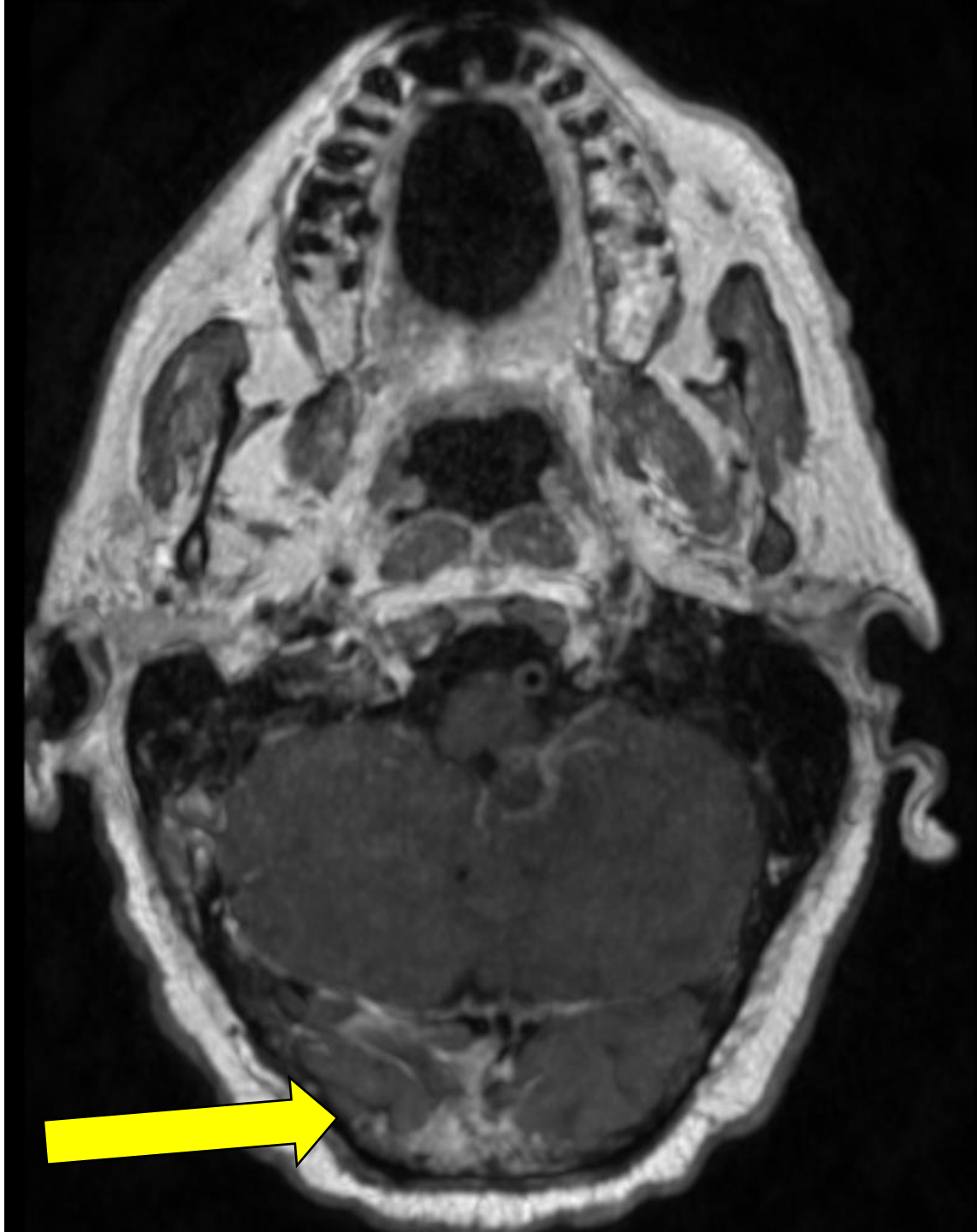
Adebola Adeniyi, Lisa Friedman, Sebastian Fernandez-Pol;
Stanford

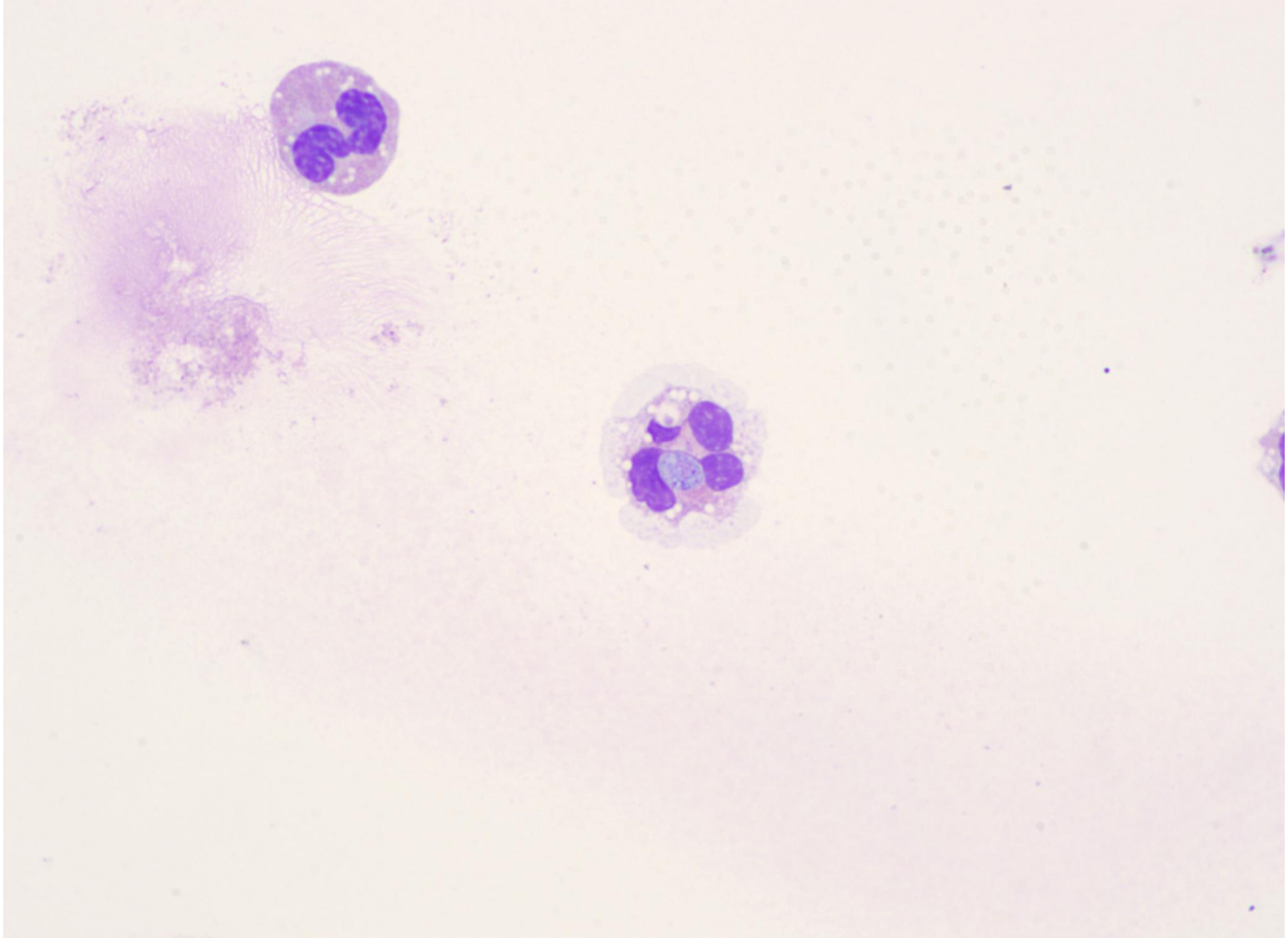
67Y male with PMHx of HTN, MM s/p auto transplant in 2020 with maintenance therapy c/b therapy-related B-ALL and t-MN s/p therapy, now admitted for haploidentical transplant on 4/23/24. Stroke code on 5/30 for AMS. MRI with enhancing left frontal and left cerebellar lesions. Neurocritical Care consulted for AMS and c/f meningoencephalitis vs malignancy.

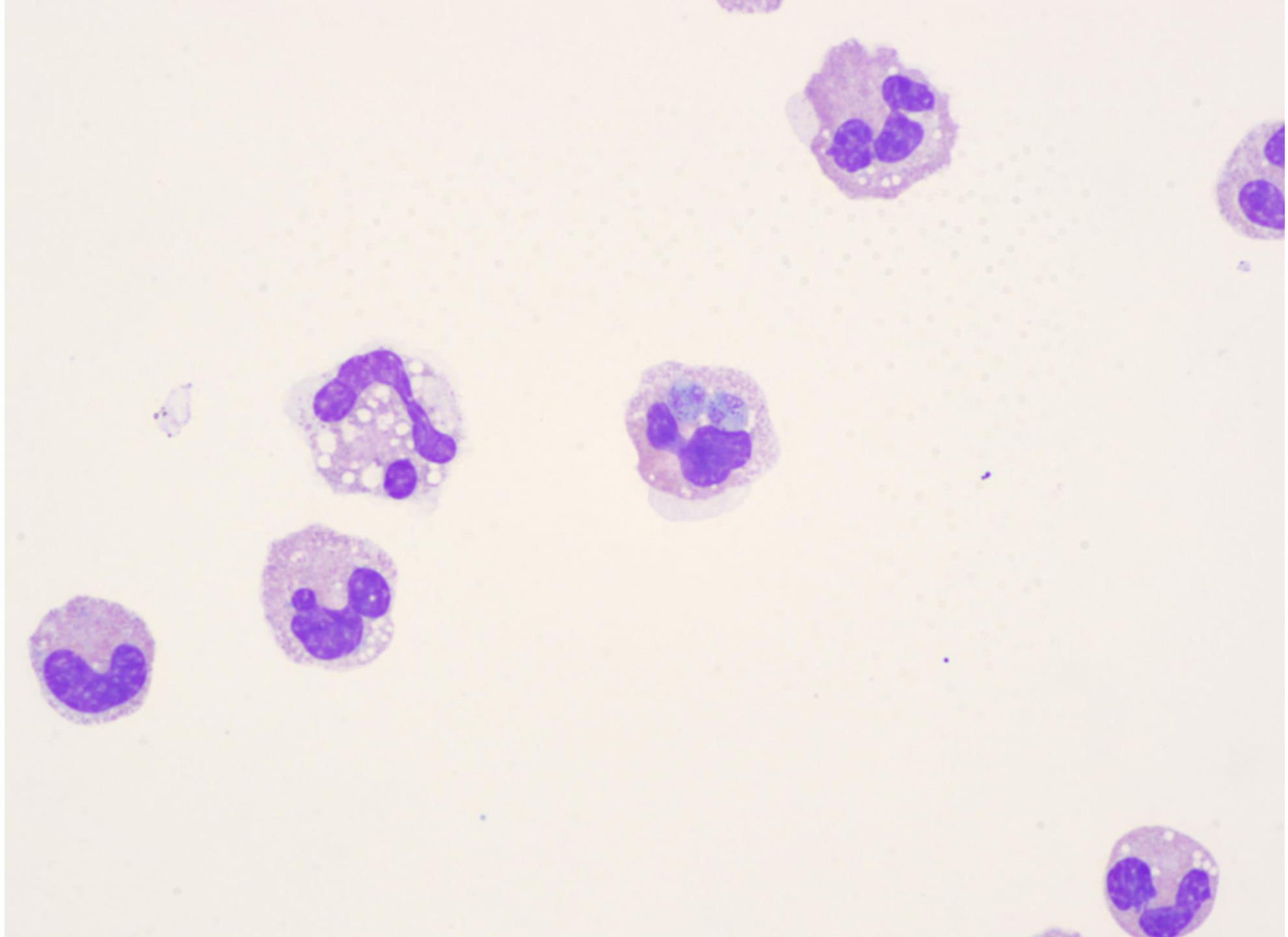




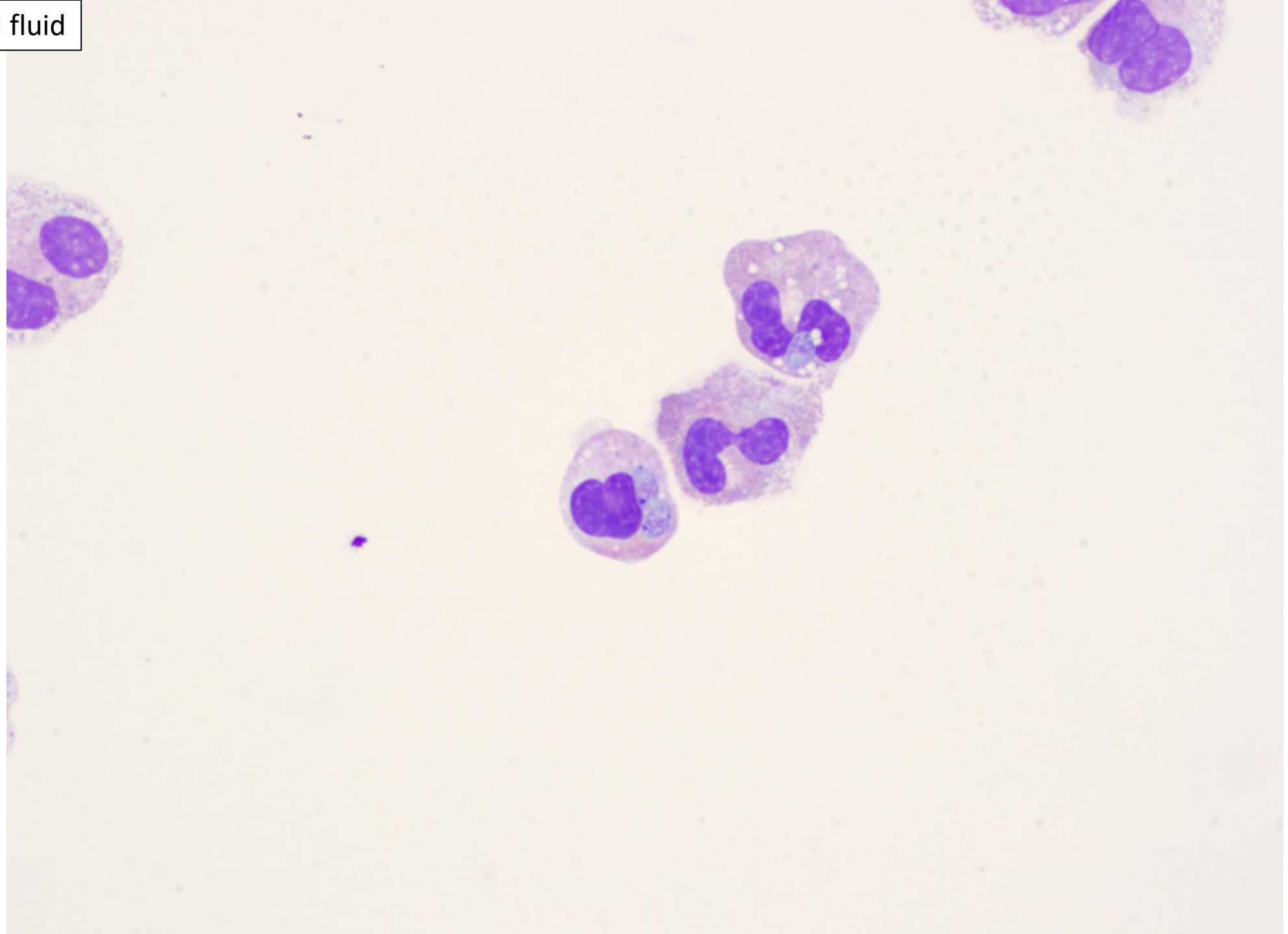




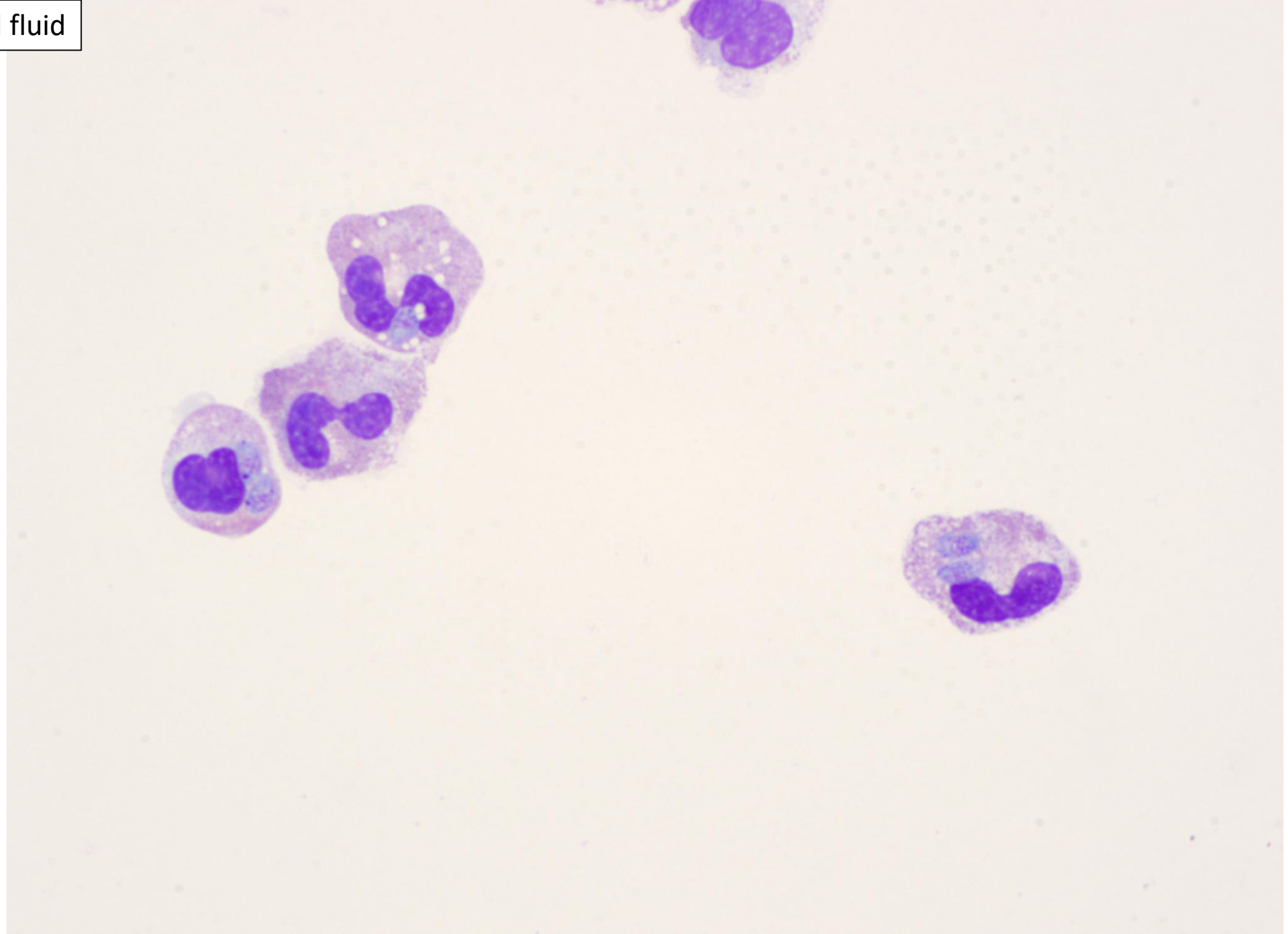




Cerebrospinal fluid

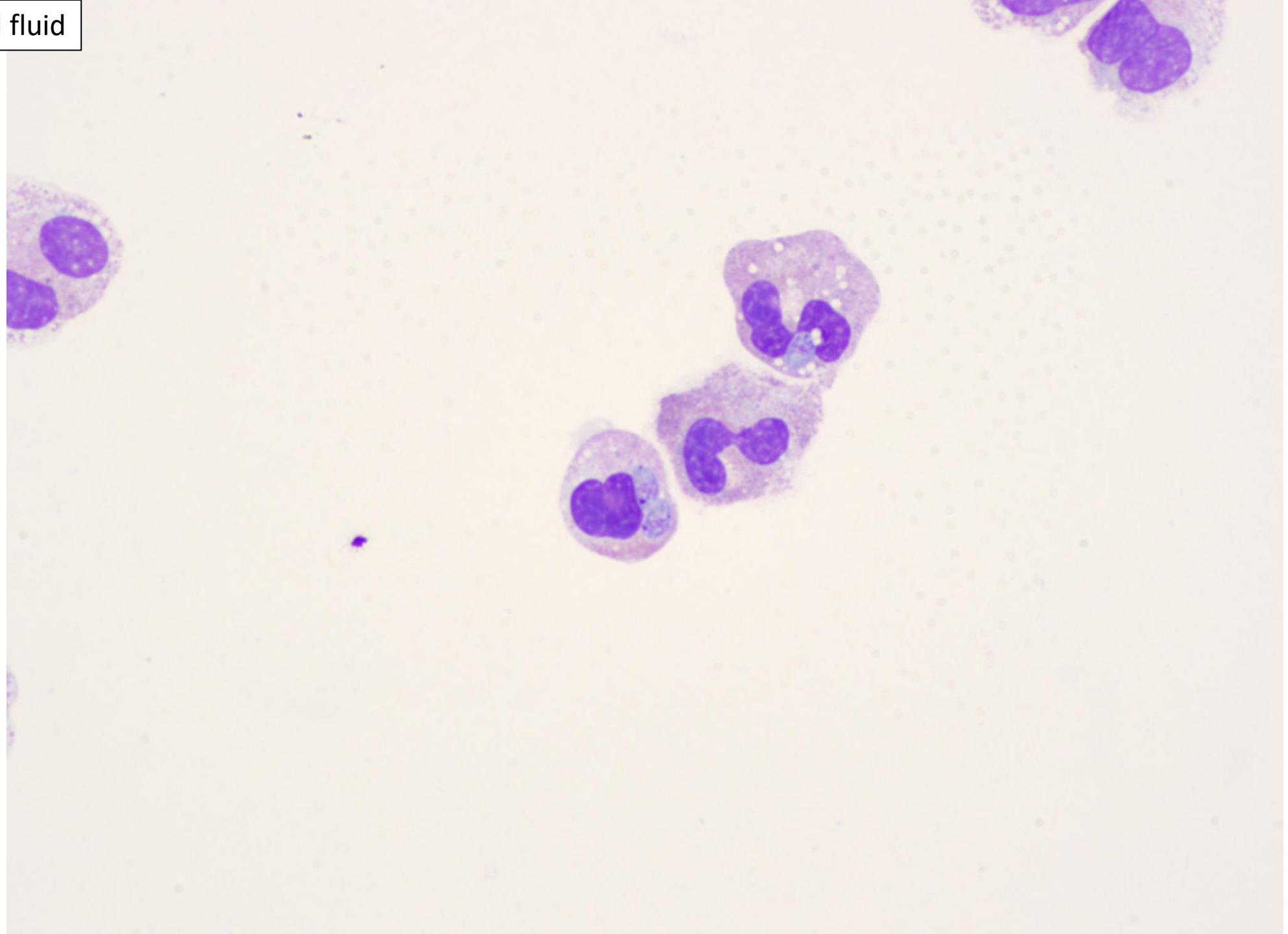


Cerebrospinal fluid



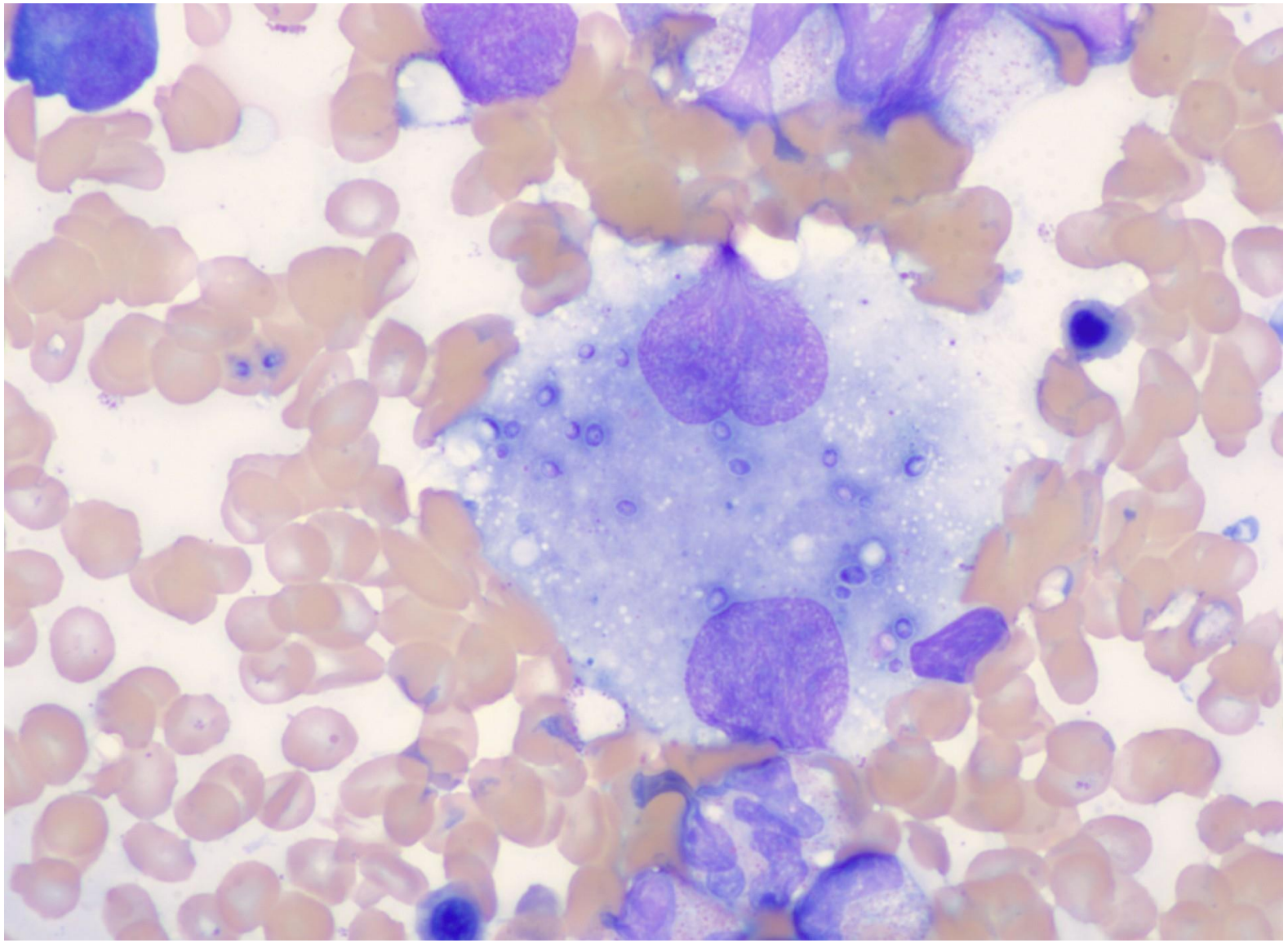
DIAGNOSIS?

Cerebrospinal fluid

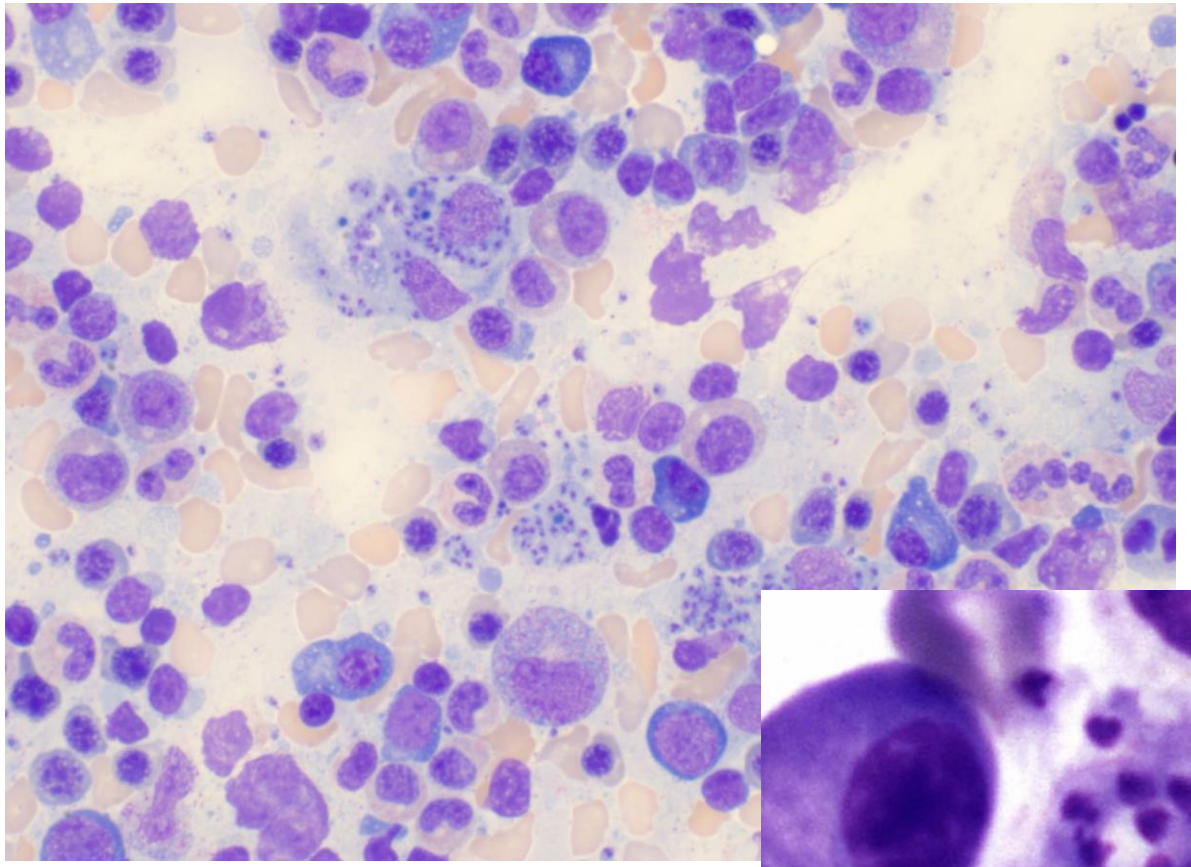


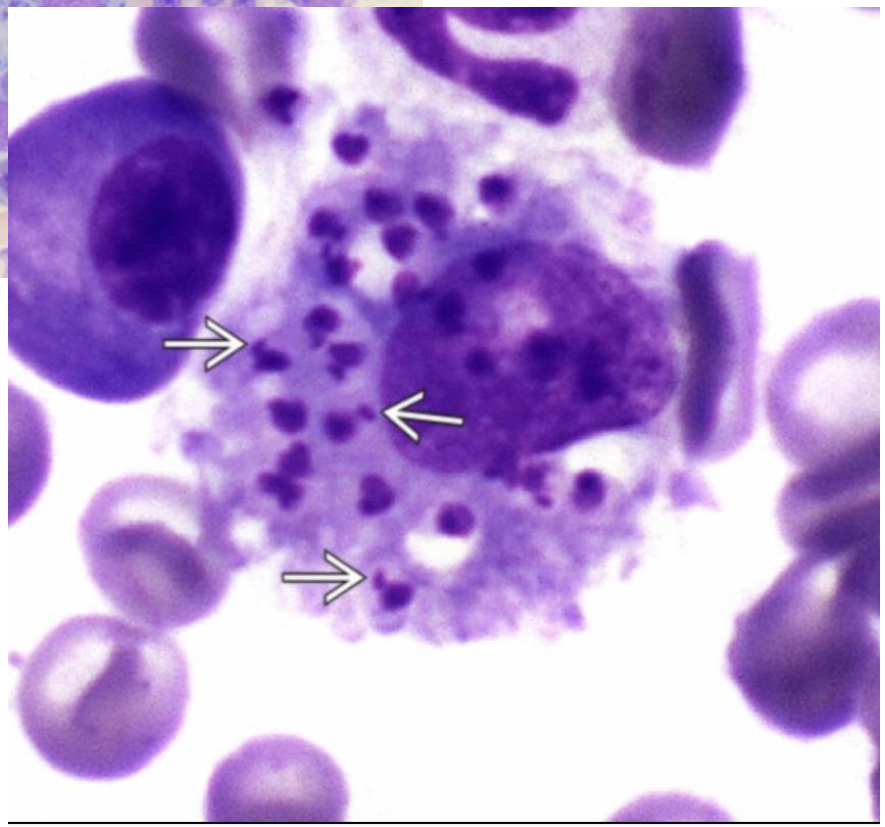
Differential diagnosis?

Histoplasma capsulatum



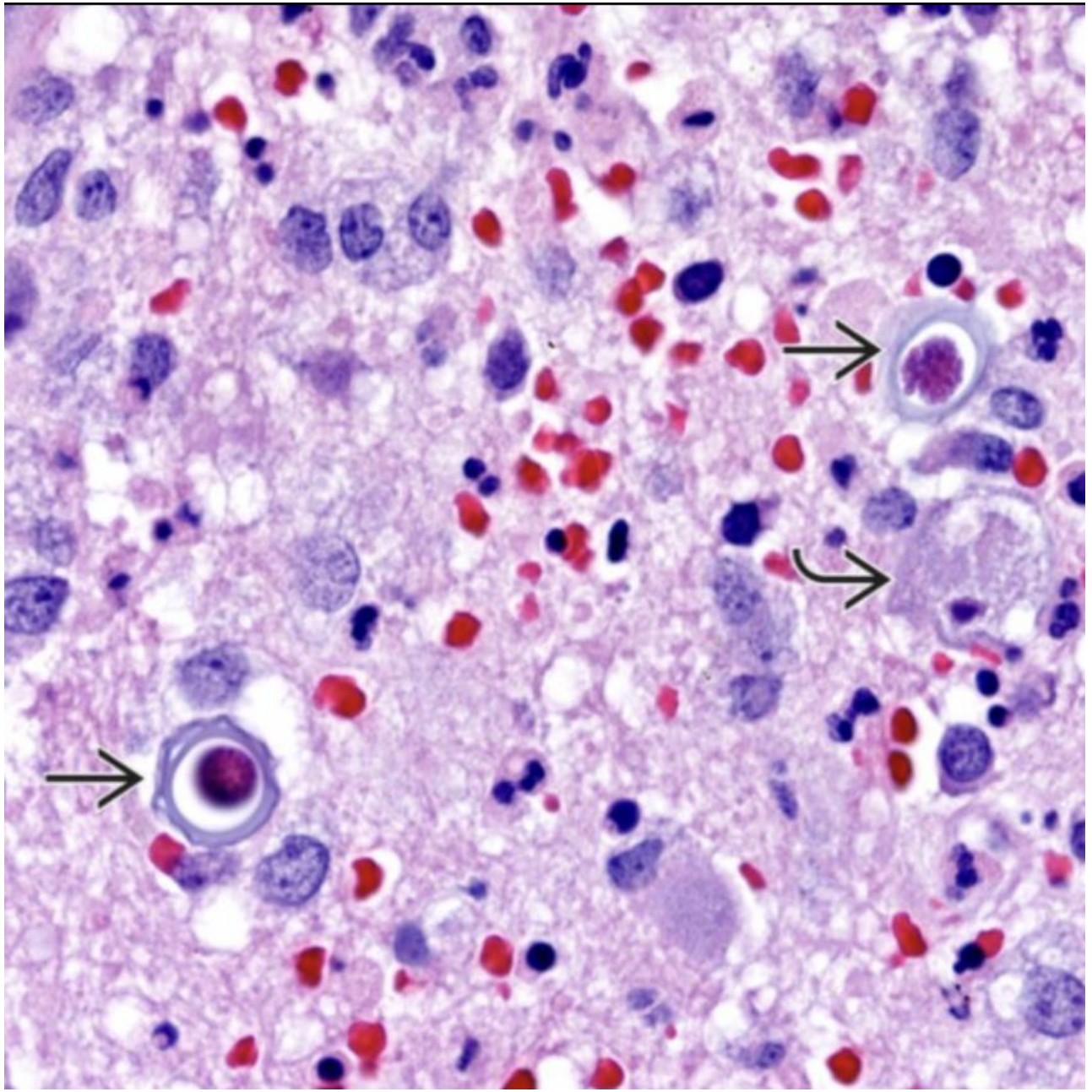
Leishmaniasis





Expert Path: Brian J. Hall, MD;Francisco Bravo, MD

Balamuthia mandrillaris



Expert Path: B. K. Kleinschmidt-DeMasters, MD;Melike Pekmezci, MD

Other considerations for the DDx….

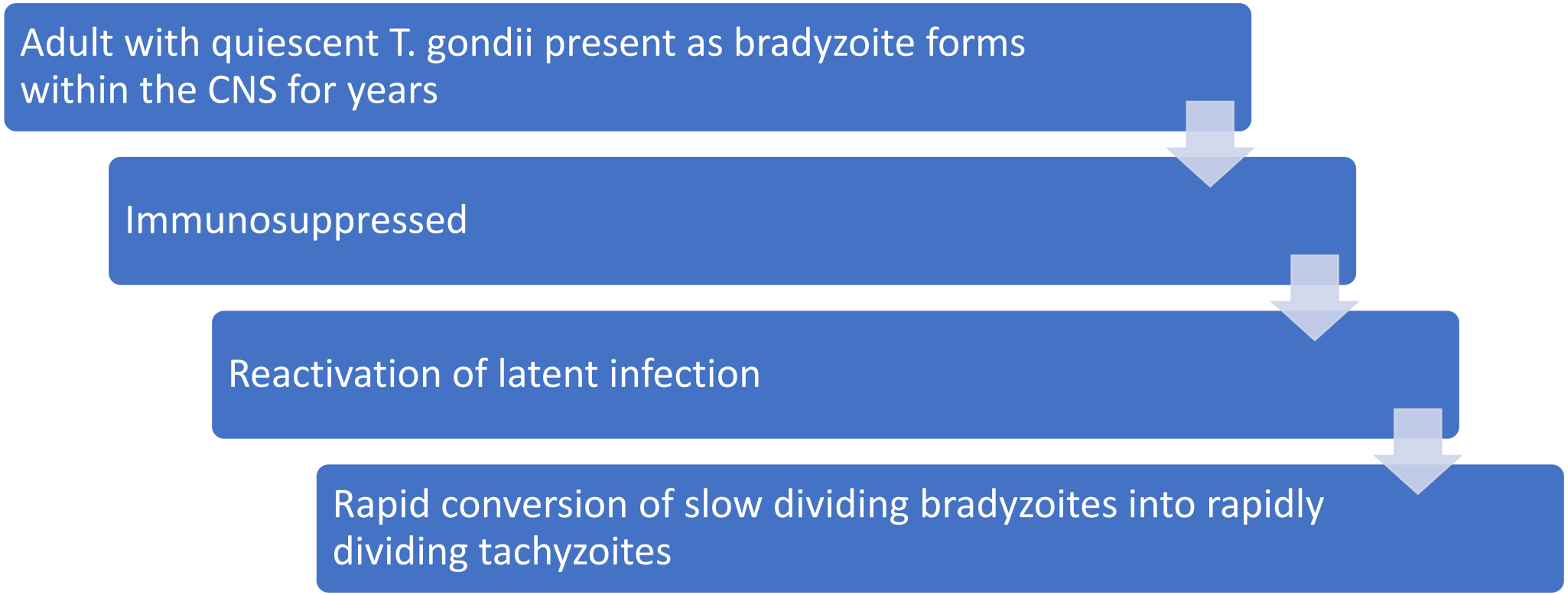
- *Cytomegalovirus*
- *Cryptococcus*
- A primary CNS lymphoma
- *Toxoplasmosis gondii*

Toxoplasmosis gondii within the CSF

- T. gondii detection within the CSF is exceedingly rare, with less than a handful of cases reported within the English literature
- This diagnosis is often difficult as anti-toxoplasmosis immunoglobulin antibodies can be low to undetectable in immunodeficient patients. Their absence does not necessarily exclude the diagnosis.
- A 12-year retrospective study from Cibas & Brogi located two out of 6,090 toxoplasmosis CSF (0.03%) specimens within the Brigham & Women's Hospital cytology records

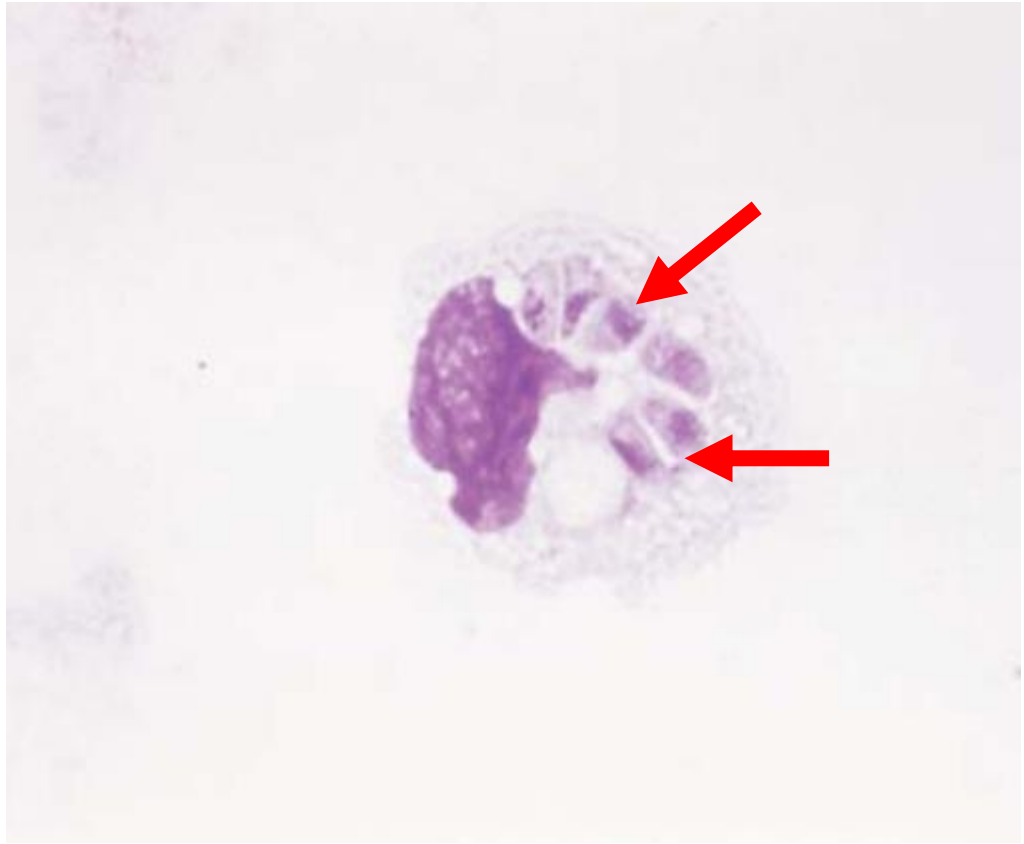
Brogi E, Cibas ES. Cytologic detection of Toxoplasma gondii tachyzoites in cerebrospinal fluid. Am J Clin Pathol. 2000 Dec;114(6):951-5. doi: 10.1309/2XQ7-A89R-RDXU-XXG1. PMID: 11338485.

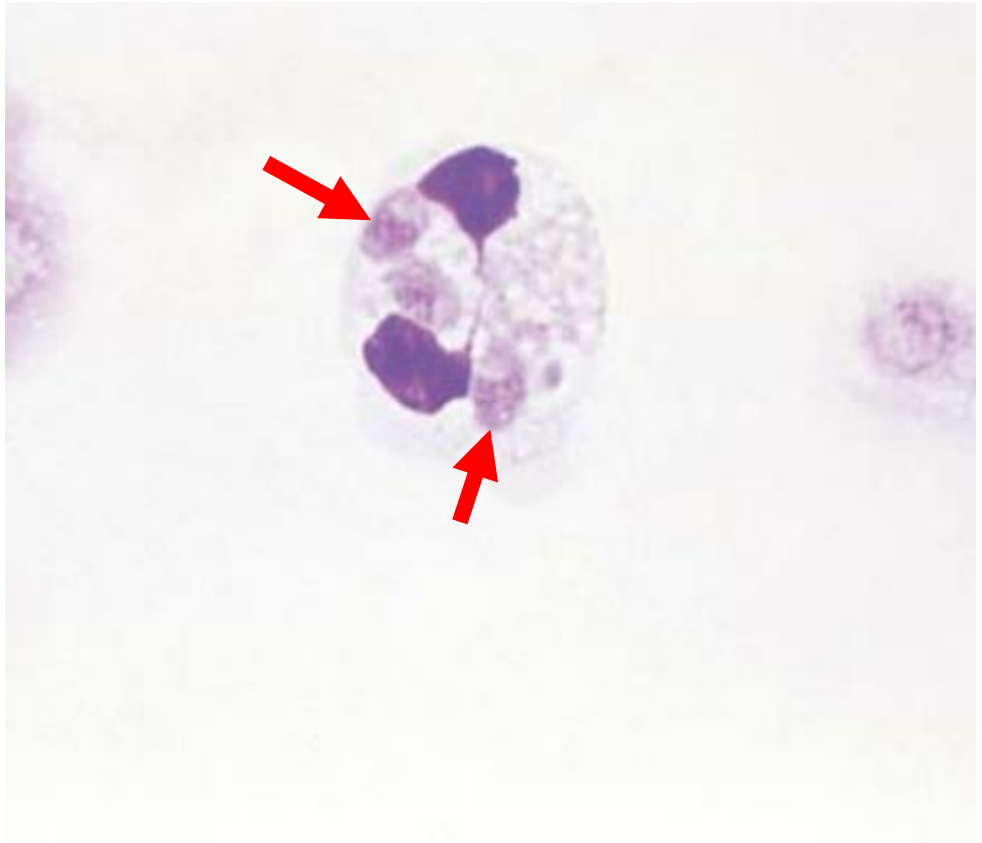
Toxoplasmosis gondii within the CSF: Life Cycle



S Al-Malki E. Toxoplasmosis: stages of the protozoan life cycle and risk assessment in humans and animals for an enhanced awareness and an improved socio-economic status. Saudi J Biol Sci. 2021 Jan;28(1):962-969. doi: 10.1016/j.sjbs.2020.11.007. Epub 2020 Nov 11. PMID: 33424388; PMCID: PMC7783816.

Toxoplasmosis gondii within the CSF: morphology





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Patient Follow Up

- The patient developed worsening mixed septic and cardiogenic shock and could not be stabilized despite multiple pressors and CPR
- The patient passed the day we received the lumbar puncture specimen
- Subsequently three days later, Toxoplasma PCR resulted as positive

Take away points

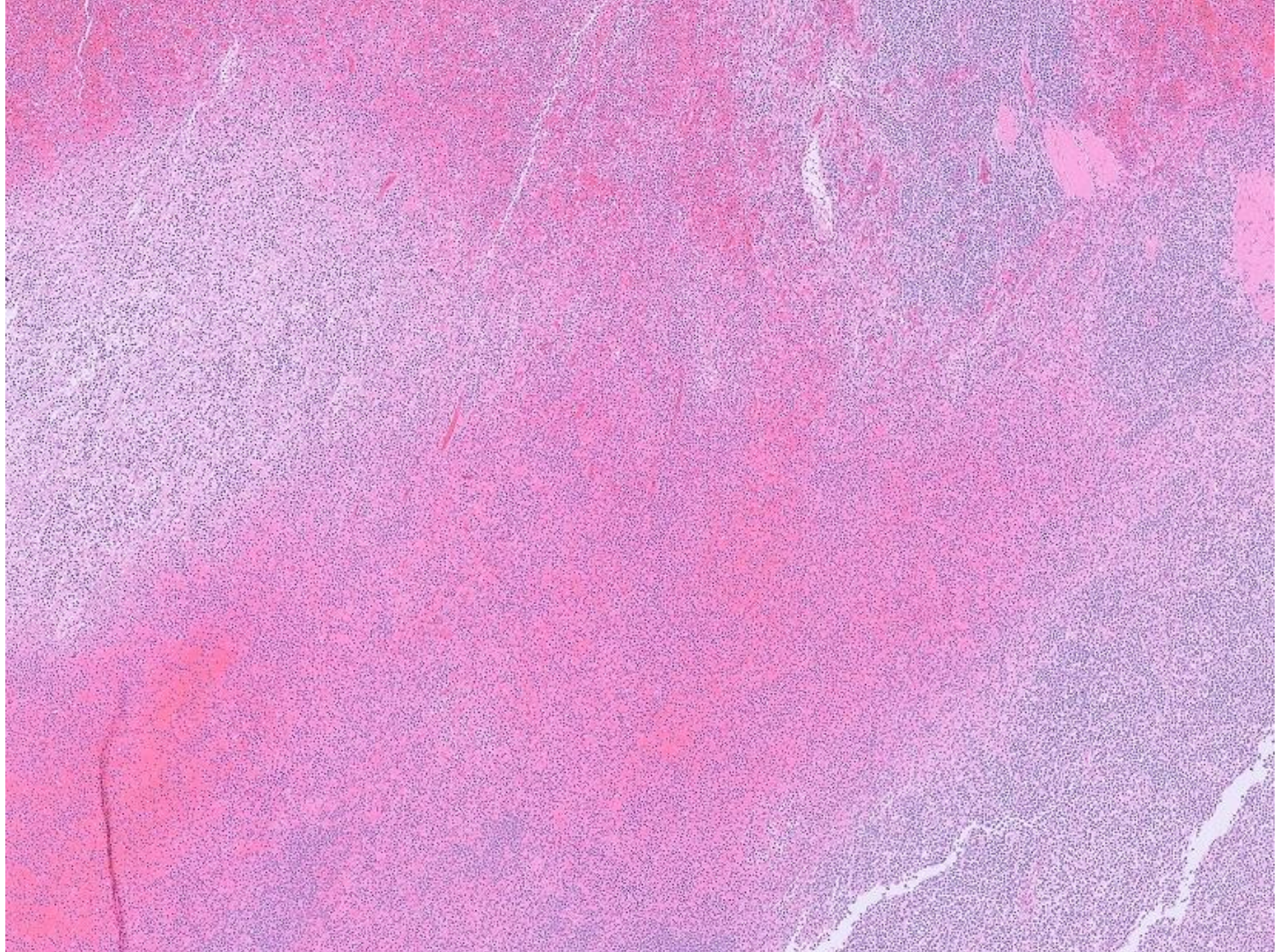
- It is extremely rare to detect T. gondii organisms within the CSF and its morphology within the CSF has not been well defined within the literature due to the lack of these cases
- The organism rests dormant as bradyzoites and when provided the right opportunity in an immunosuppressed individually, will reactivate into the tachyzoite form
- Clinicopathologic correlation is critical to determine a diagnosis quickly and begin treatment as soon as possible as patients have been known to rapidly decline

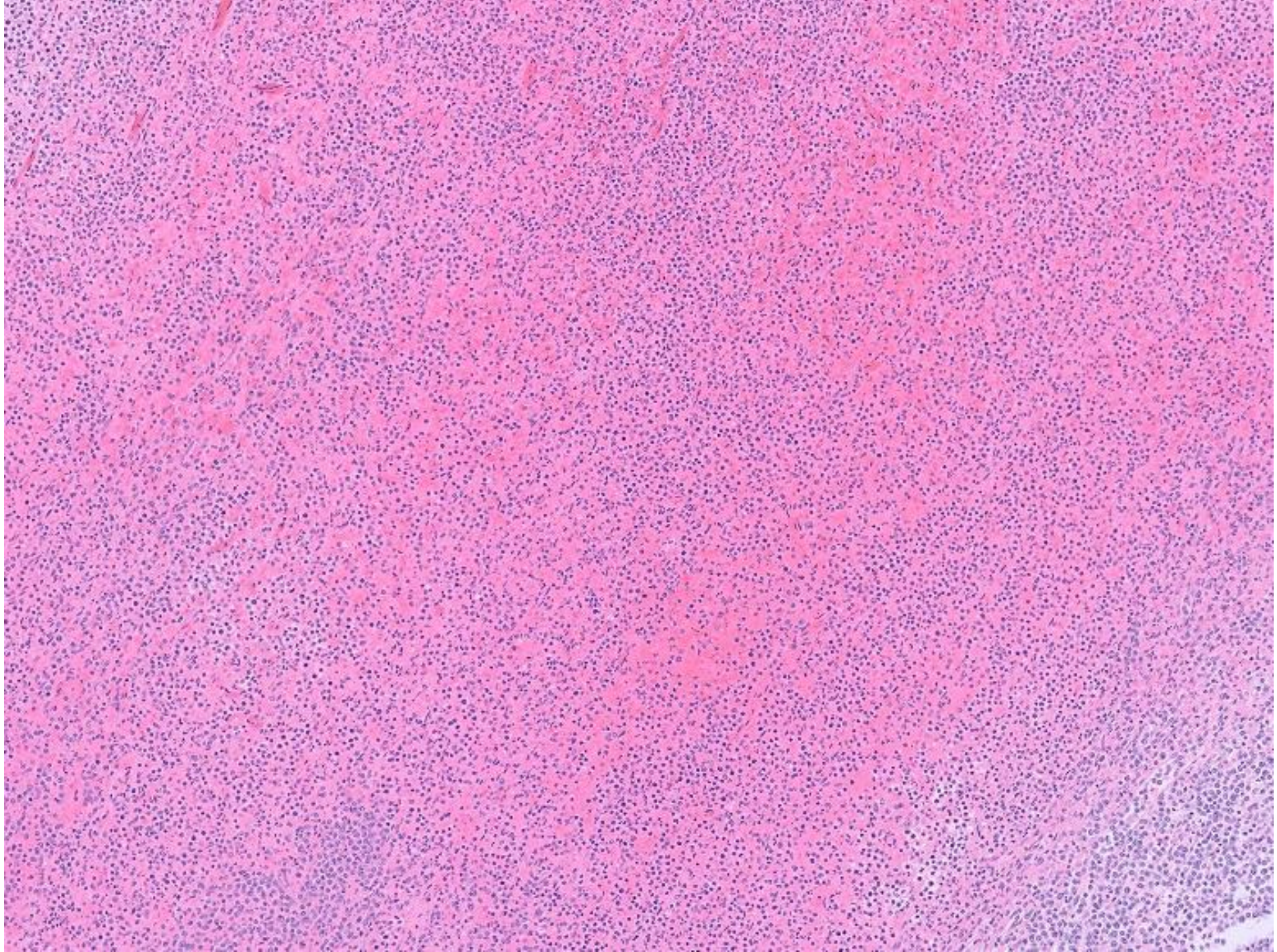
24-0702

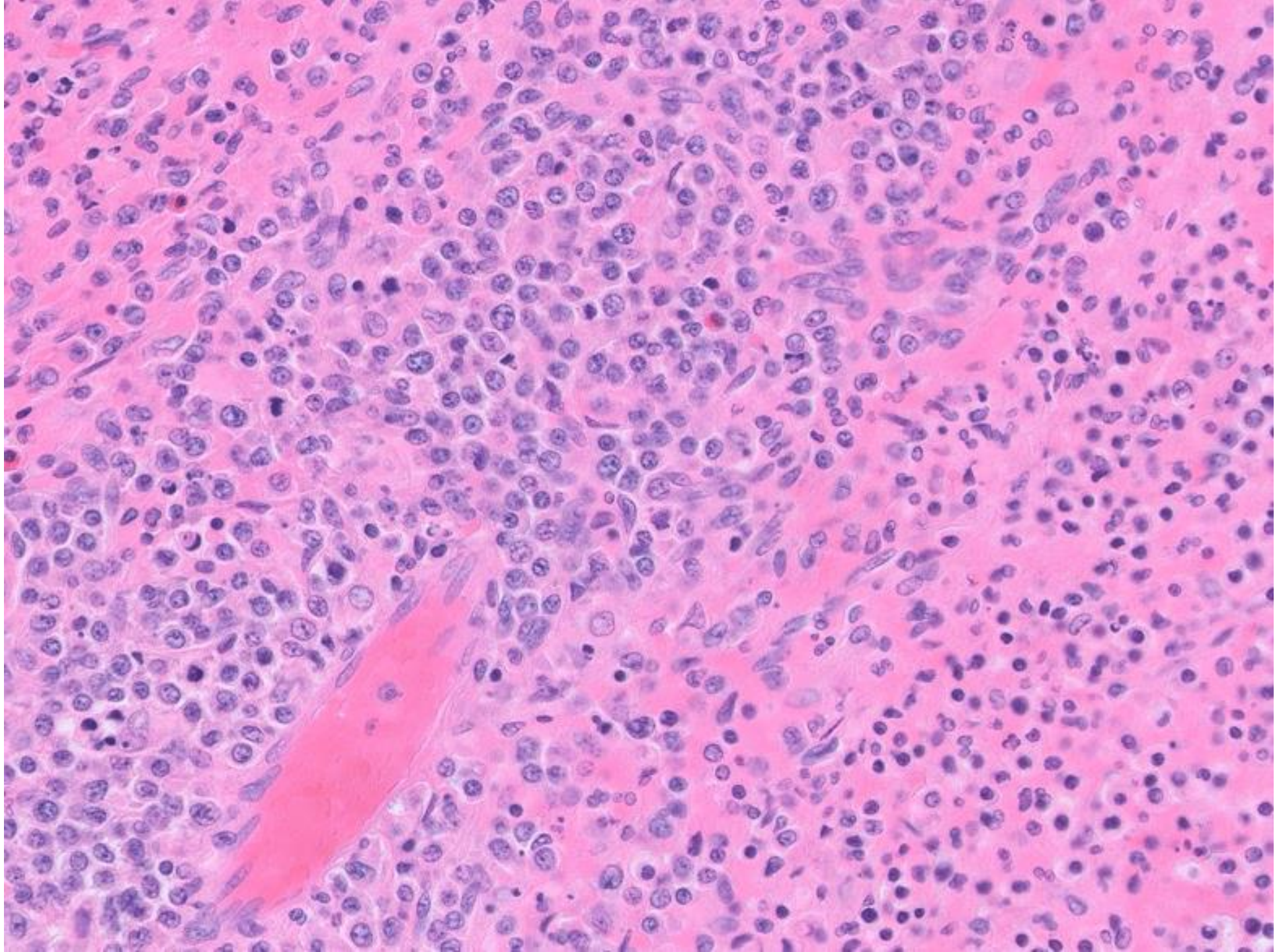
Andrew Xiao and Karthik Ganapathi; UCSF

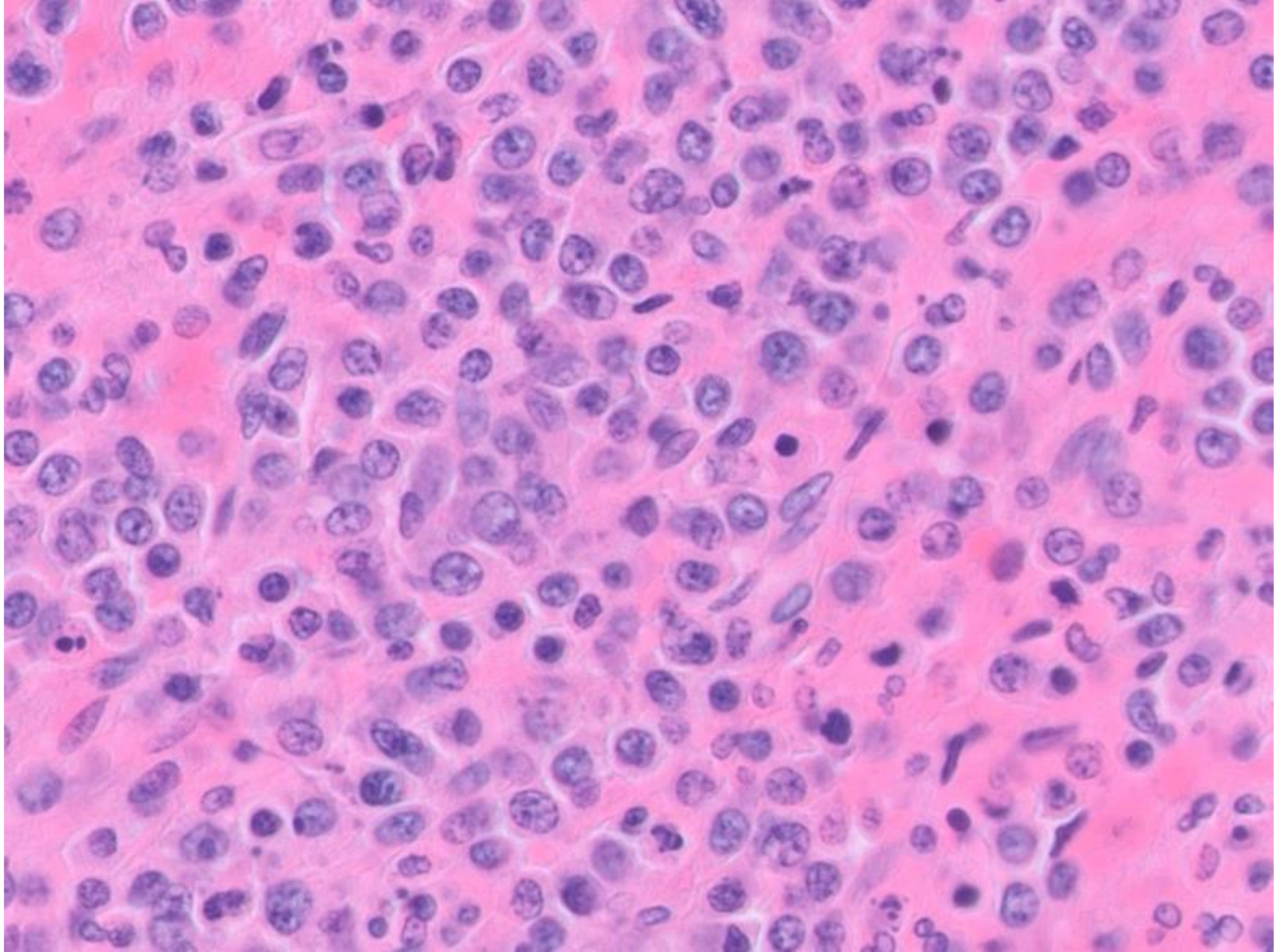
24 year old male with scrotal pain and was found to have thrombocytopenia, neutropenia, and massive splenomegaly on imaging.

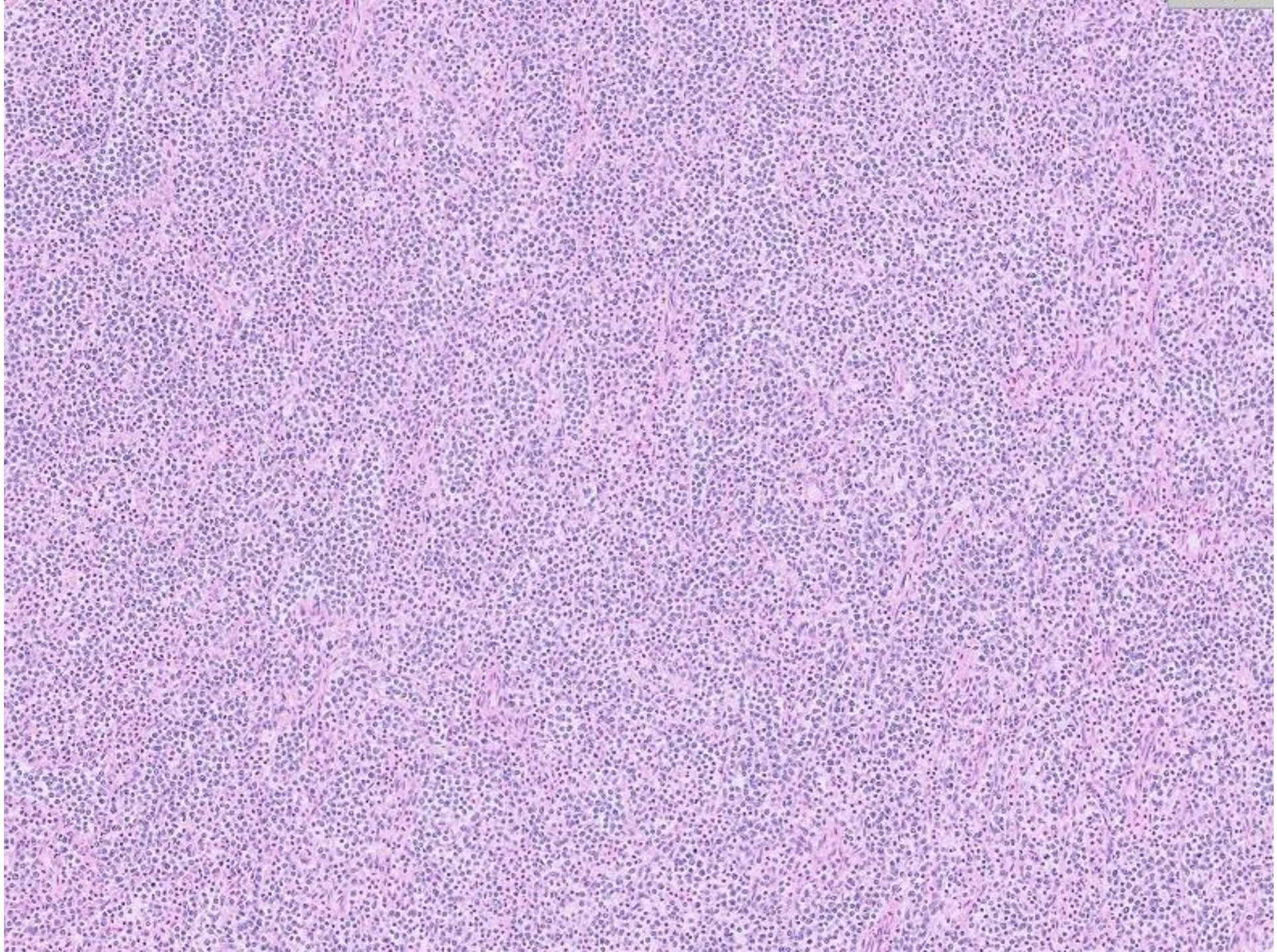
Spleen

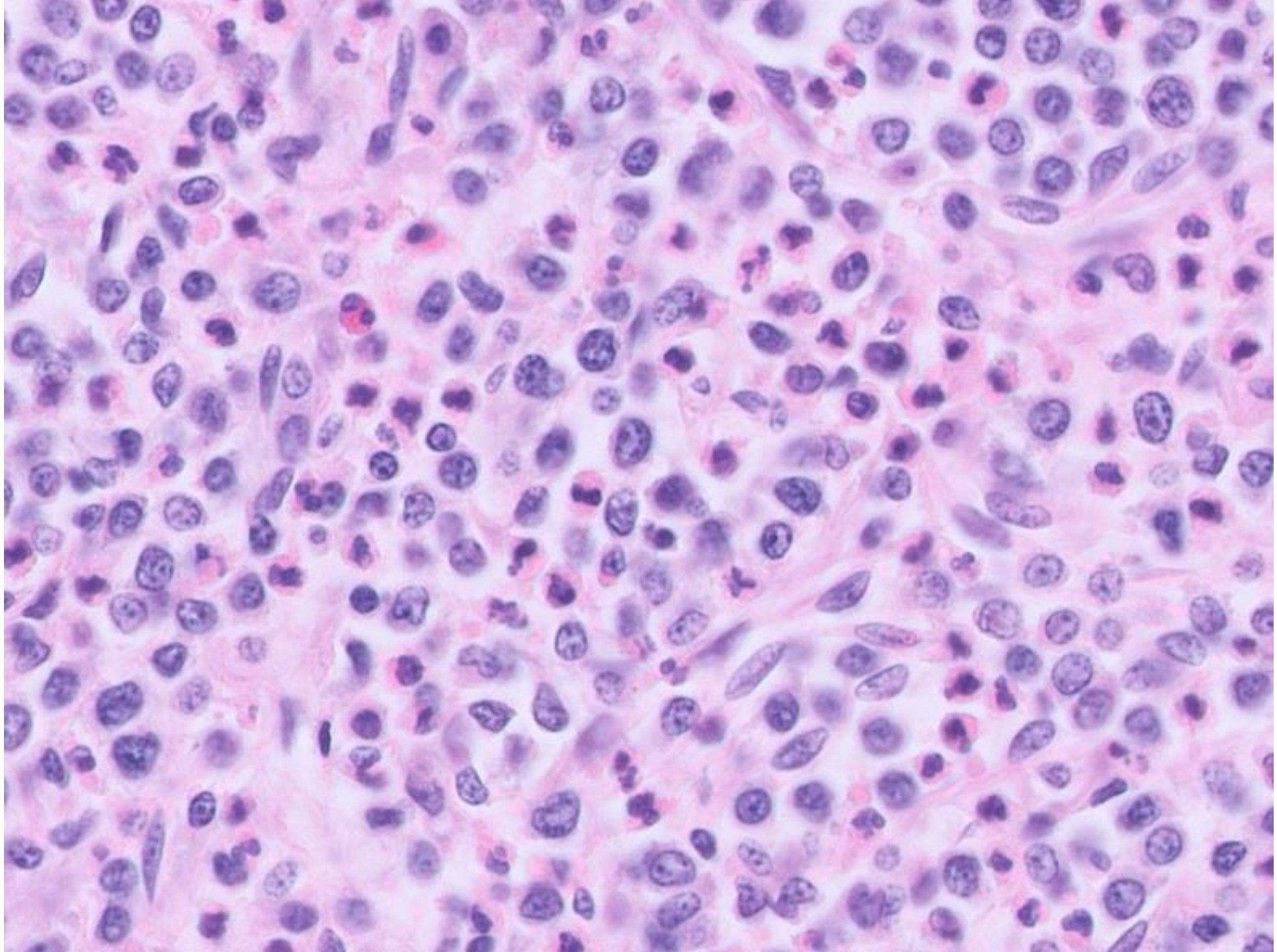




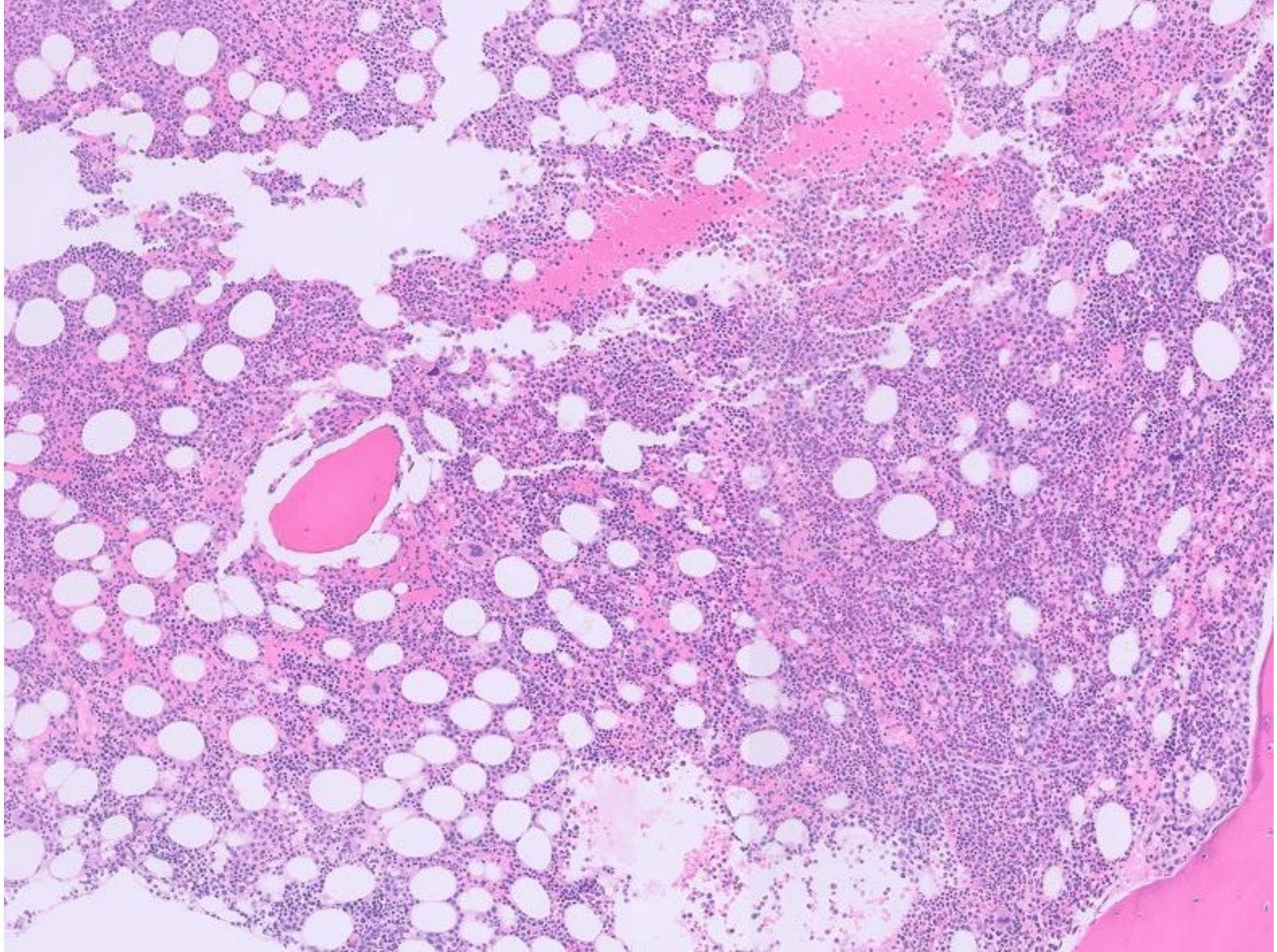


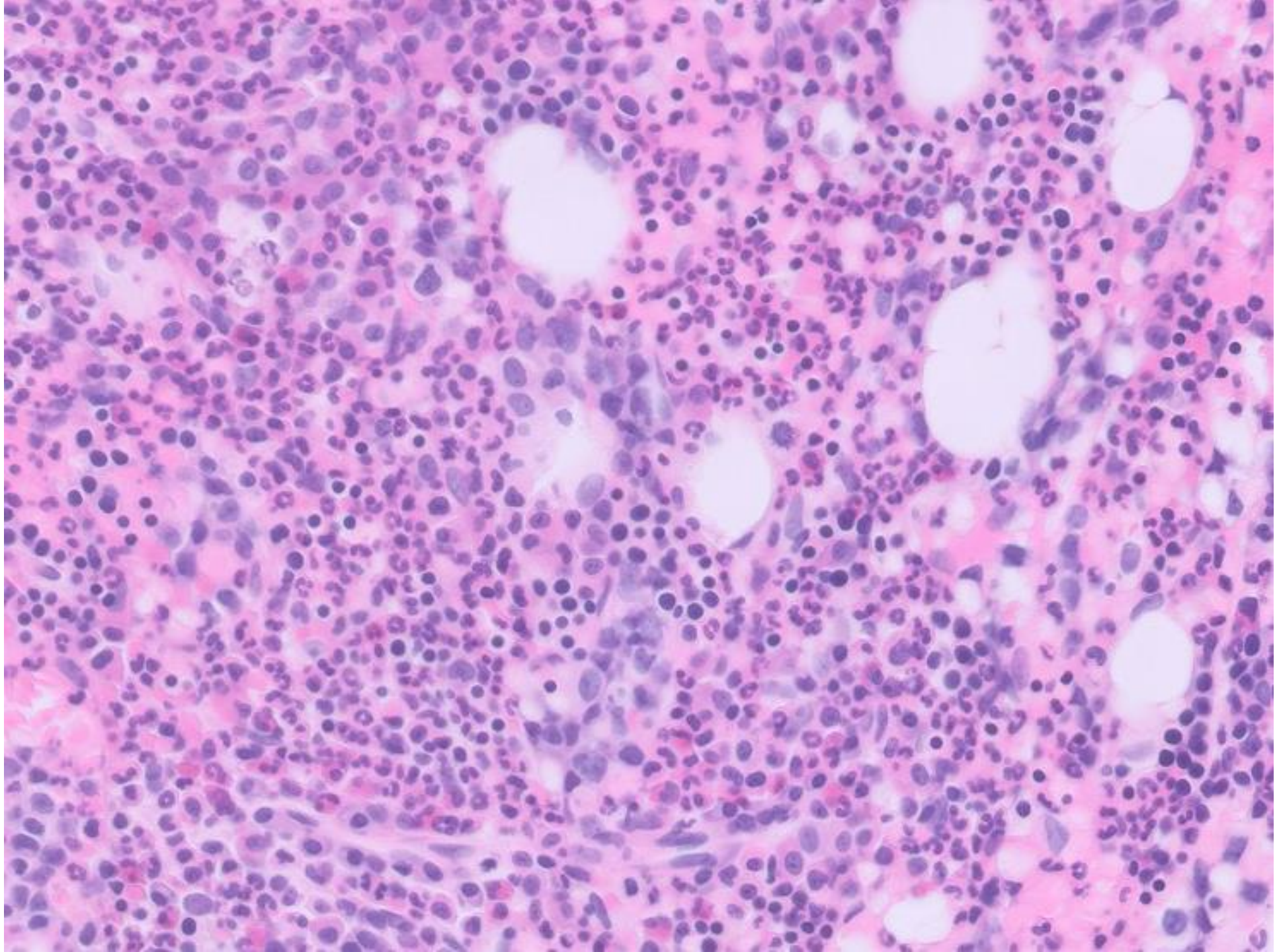


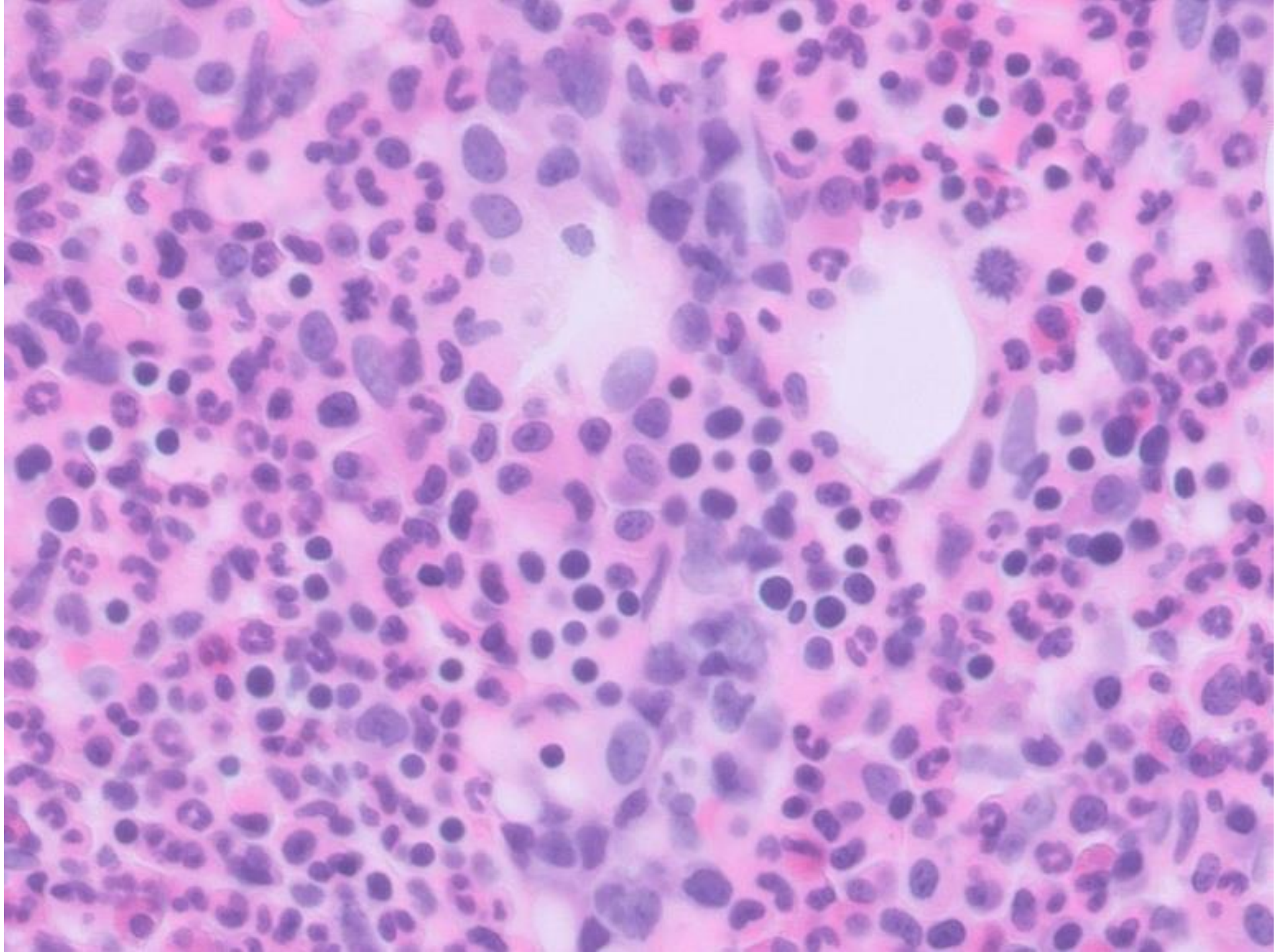




Bone Marrow







DIAGNOSIS?

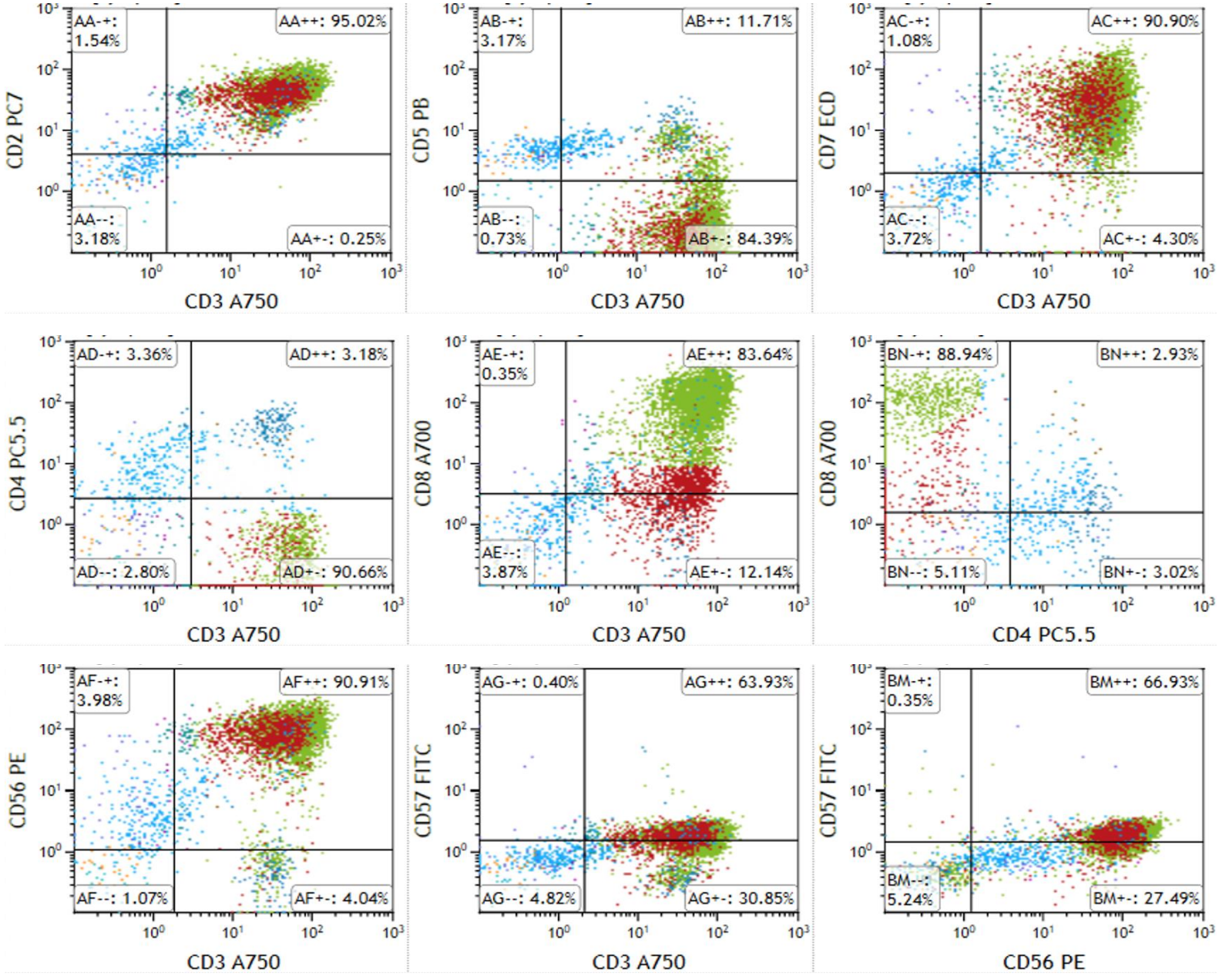
Withheld Clinical Information

- History of Crohn’s disease treated with azathioprine and infliximab
- Abnormal LFTs
  - D. Bilirubin 1.6 (normal: 0-0.3)
  - Alkaline Phosphatase 241 (normal: 40-125)
  - Others within normal (ALT, albumin, etc)
- LDH 685 (normal: 125-243)
- Hgb 7.3 (normal: 13.6-17.5)

Histology Recap

- Spleen
  - Effaced architecture
  - Atrophy of the white pulp
  - Red pulp:
    - “Large nodules”: red pulp sinuses & cords infiltrated by atypical lymphoid cells
    - Small-to-intermediate size
    - Irregular nuclear contours, open chromatin, inconspicuous nucleoli, and pale cytoplasm
- Bone Marrow
  - Normocellular (~80% cellularity) with background trilineage hematopoiesis
  - Intra-sinusoidal clusters of atypical lymphocytes
    - Small-to-intermediate size
    - Irregular nuclear contours, dense chromatin, inconspicuous nucleoli and pale cytoplasm

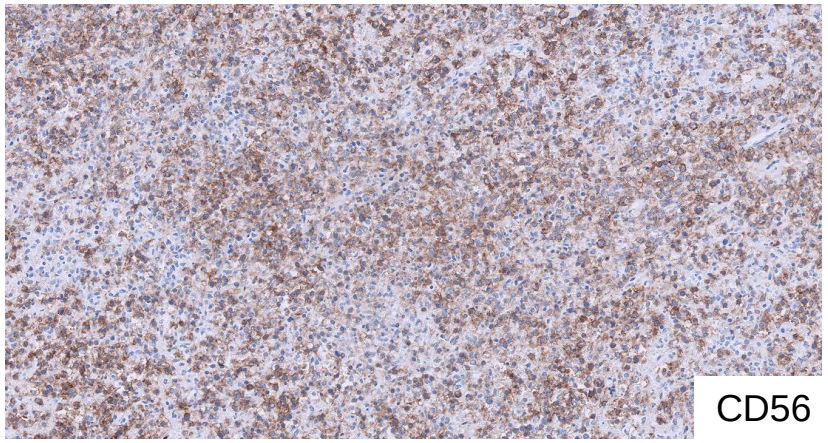
Flow Cytometry - Bone Marrow

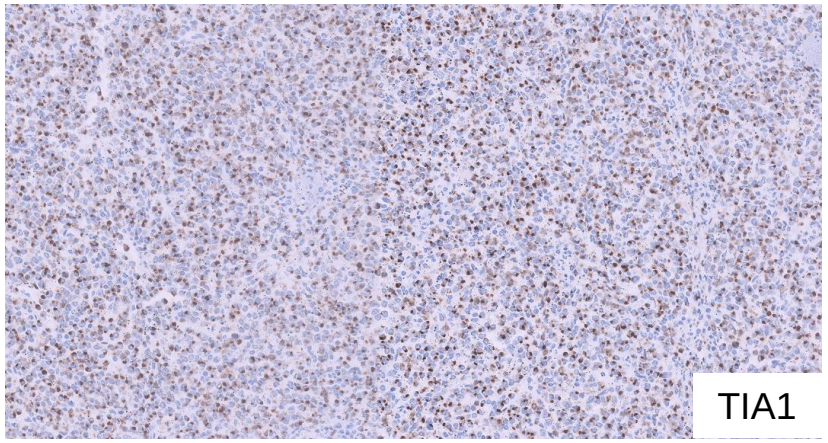


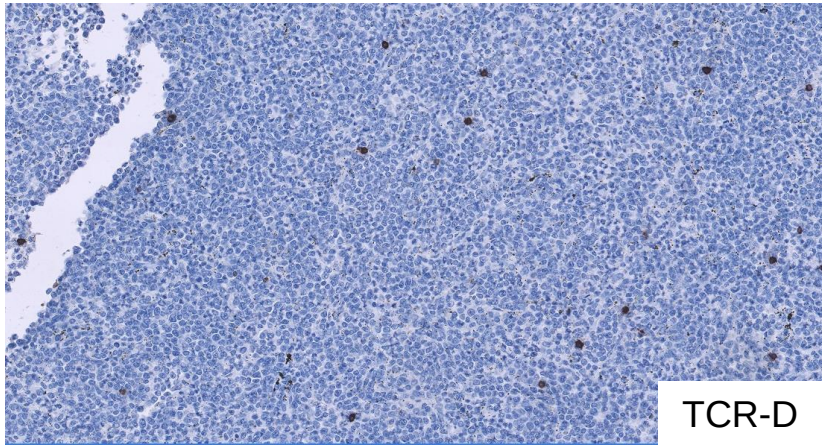
Flow Cytometry - Bone Marrow

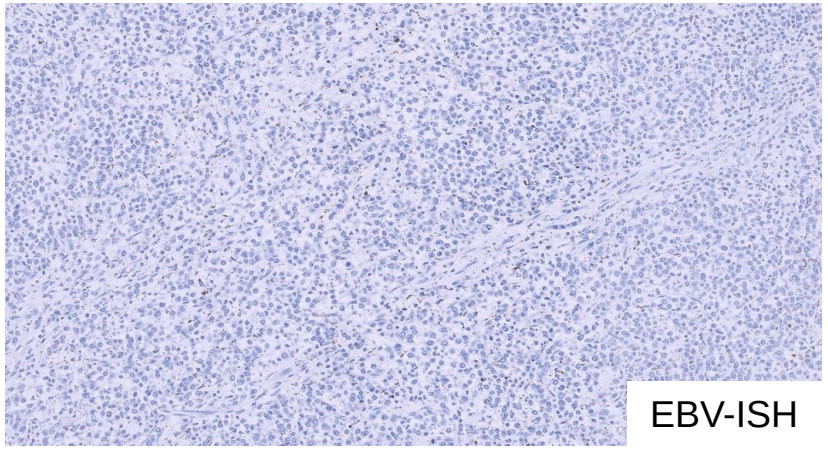
- Abnormal T-cell population with moderate side scatter and intermediate-to-high forward scatter
  - Positive for CD2, CD3, CD7, variable CD8, CD56, CD38
  - Negative for CD5, CD4, CD57

Immunohistochemistry - Spleen


CD56

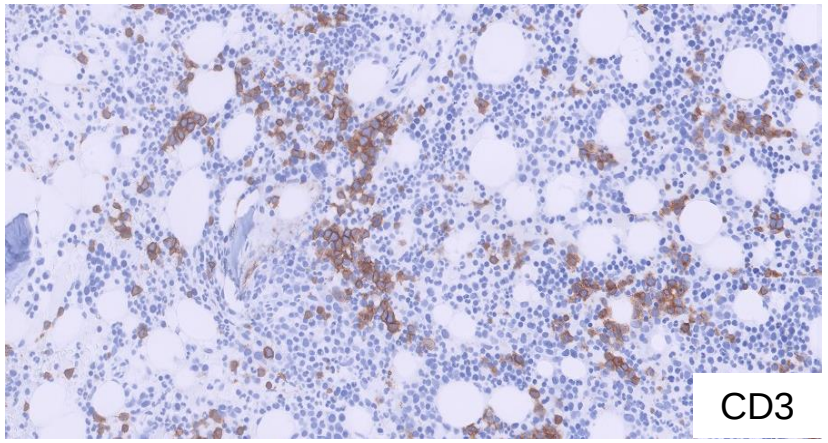

TIA1

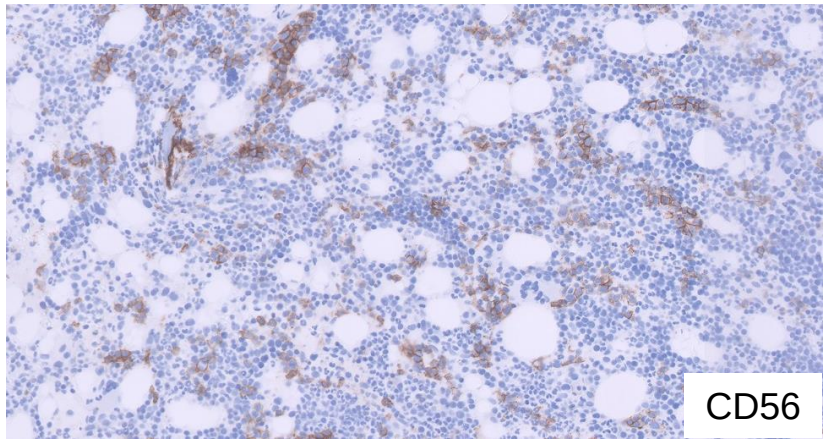

TCR-D

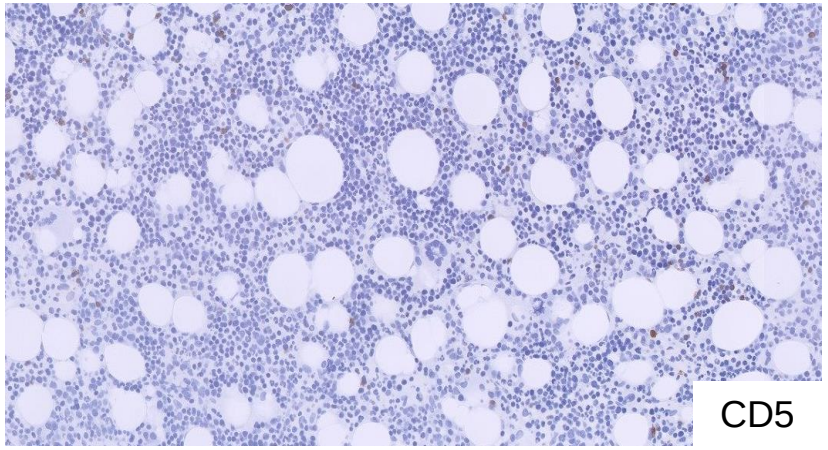

EBV-ISH

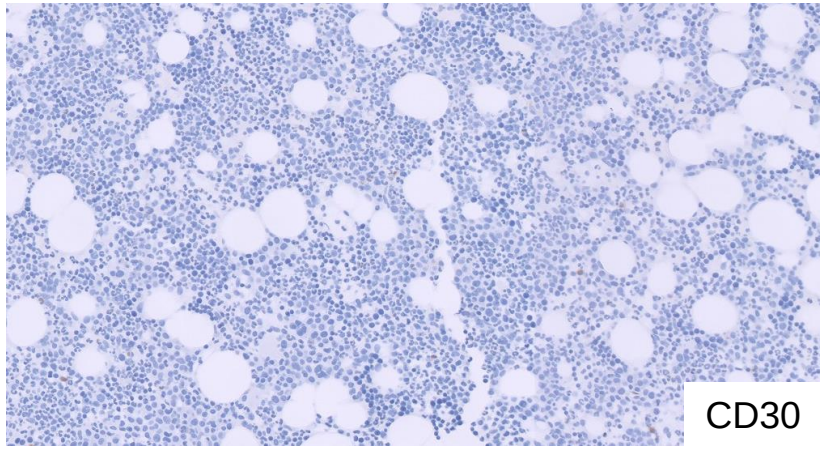
- Positive for CD3, CD8, CD56, TIA1, Granzyme B (subset), Perforin (subset)
- Negative for CD4, CD5, TCR-Delta, EBV-ISH

Immunohistochemistry – Bone Marrow


CD3


CD56


CD5


CD30

- Positive for CD3, CD8, CD56
- Negative for CD4, CD5, CD30, EBV-ISH

Differential Diagnosis

Diagnosis	Age (median/ mean), y	Common symptoms/ signs	Morphological findings	Immunohistochemical findings	Genomic findings
HSTCL	32	B symptoms, splenomegaly, cytopenia	Atypical small-intermediate T cells, sinusoidal pattern	$CD3^+$, $CD2^+$, $CD5^-$, $CD7^{+/-}$, $CD4^-/CD8^-$, $CD56^+$, $CD57^-$, EBV^-	i(7q), trisomy 8, *STAT3/STAT5B* mutation, CMG mutations
γδ T-LGL[41]	62	Neutropenia, anemia splenomegaly +/−	LGL, sinusoidal pattern	$CD3^+$, $CD2^+$, $CD5^-$/dim, $CD7^+$, $CD4^-/CD8^-$, $CD56^{+/-}$, $CD57^+$, EBV^-	*STAT3/STAT5B* aberrations
Aggressive NK-cell leukemia[42]	40	B symptoms, splenomegaly, cytopenia, lymphadenopathy +/−	Medium-large atypical lymphoid cells	Surface $CD3^-$, $CD2^+$, $CD5^-$, $CD56^+$, $CD16^+$, $CD57^-$, EBV^+	Del(6q), del(11q)
MEITL[66,67]	59	GI symptoms	Monomorphic medium-sized cells	$CD3^+$, $CD5^-$, $CD7^+$, $CD4^-$, $CD8^+$, $CD56^+$, $CD103^{+/-}$, cytotoxic markers$^+$, EBV^-	Gain in 8q24 (*MYC* gene), *STAT5B* mutation
CAEBV[45]	19	B symptoms, cytopenia, splenomegaly, lymphadenopathy	Small-intermediate T cells with no atypia	EBV^+ in T/NK cells (Asian population) or in B cells (Western population); no phenotypic abnormalities	Rare somatic mutations of perforin

Pro B, Allen P, Behdad A. Blood. 2020 Oct 29;136(18):2018-2026.

Cytogenetics – Bone Marrow

- Abnormal male karyotype
  - 46-48,XY,+7,i(7)(q10)x2,+8[3]/46,XY[38]
    - 2 copies of isochromosome of 7q
    - Gain of chromosomes 7 and 8

Targeted NGS analysis

- Pathogenic mutations in BCOR, GATA3, and STAG2

- Copy number changes compatible with isochromosome 7q
  - Copy gains: 7q
  - Copy losses: 7p

Final Diagnosis

Hepatosplenic T-cell lymphoma (HSTCL)

Hepatosplenic T-cell lymphoma

- Less than 5% of all peripheral T cell lymphoma cases
  - Proliferation of $\gamma\delta$ or $\alpha\beta$ TCR-expressing lymphocytes
- Majority of cases occur *de novo*
- 20% cases involve immunosuppression or immune dysregulation
  - Autoimmune disorders, inflammatory bowel disease (IBD), hematologic malignancies, and previous solid organ transplant
- Implicated IBD drugs: azathioprine, 6-mercaptopurine, infliximab

Pro B, Allen P, Behdad A. Blood. 2020 Oct 29;136(18):2018-2026.

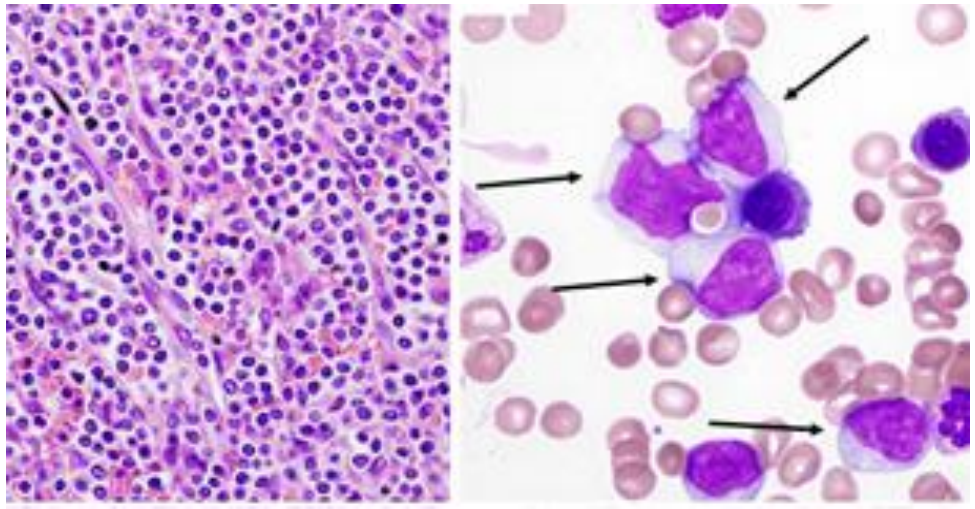
HSTCL: Clinical presentation

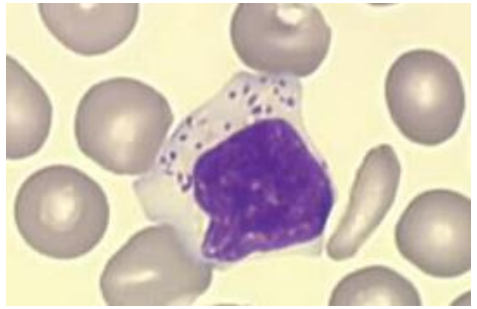
- Young adults
- Splenomegaly
- Thrombocytopenia
- ~20% of cases arise in immunosuppression or immune dysregulation (IBD, autoimmune disorders, etc)
- Commonly implicated agents
  - Azathioprine, 6-mercaptopurine, infliximab
  - Anti-TNF therapies

Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. Blood. 2020 Oct 29;136(18):2018-2026. doi: 10.1182/blood.2019004118. PMID: 32756940; PMCID: PMC7596851.

HSTCL: Morphology

- Lymphocytes are small to intermediate in size
- Irregular nuclear contours, mature chromatin, and inconspicuous nucleoli
- Moderate amount of cytoplasm
- No granules
  - vs T-cell large granular lymphocytic leukemia (azurophilic granules on blood smear)





Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: Blood. 2020 Oct 29;136(18):2018-2026
Lamy T, Moignet A, Loughran TP Jr. . Blood. 2017 Mar 2;129(9):1082-1094

HSTCL: Immunophenotype

- Typically CD4/CD8-double negative
  - CD8 may be expressed (as in this case)

- Positive: CD2, CD3, CD7, CD56 (usually)
  - $\gamma\delta$ TCR (majority, ~75%)
    - Most commonly derived from $\gamma\delta$1 subset
  - $\alpha\beta$ TCR (minority, ~20%)
    - More common in women & adults > 50
    - Worse prognosis

- Negative: CD5, CD1a, TdT, CD10, CD57

Pro B, Allen P, Behdad A. Blood. 2020 Oct 29;136(18):2018-2026

HSTCL: Genomic aberrations

- TCR β (TCRB) and γ (TCRG) genes rearranged
  - Molecular clonality studies do not define the T-cell subtype (αβ vs γδ) from which the lymphoma arose
  - TCRB was rearranged in all αβ and 62% of γδ HSTCLs
  - TCRG rearranged in all γδ and 75% of αβ HSTCLs
- Chromosomal abnormalities
  - Most common: Isochromosome 7q and trisomy 8
  - Other: 7q amplification, loss of Y chromosome, loss of chromosome 10q, gains in chromosome 1q

1. Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. Blood. 2020 Oct 29;136(18):2018-2026. doi: 10.1182/blood.2019004118. PMID: 32756940; PMCID: PMC7596851.
2. Travert M, Huang Y, de Leval L, Martin-Garcia N, Delfau-Larue MH, Berger F, Bosq J, Brière J, Soulier J, Macintyre E, Marafioti T, de Reyniès A, Gaulard P. Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. Blood. 2012 Jun 14;119(24):5795-806. doi: 10.1182/blood-2011-12-396150. Epub 2012 Apr 17. PMID: 22510872; PMCID: PMC3779008.

HSTCL: Genomic aberrations

- *SETD2*, *INO80*, *TET3*, *STAT5B*: almost exclusive to HSTL vs other PTCL
  - *SETD2*: most frequently silenced gene
    - Tumor suppressor gene in HSTL
    - Loss of function → increased proliferation
- *PIK3CD*, *UBR5*, *SMARCA2*: shared mutations observed in other B cell lymphomas
- Other mutations: *STAT3*, *ARID1B*, *EZH2*, *KRAS*, *TP53*
- *STAT5B*, *STAT3*, *PIK3CD* mutations
  - Constitutively activate downstream signaling
  - Cooperate to maintain proliferation pathways

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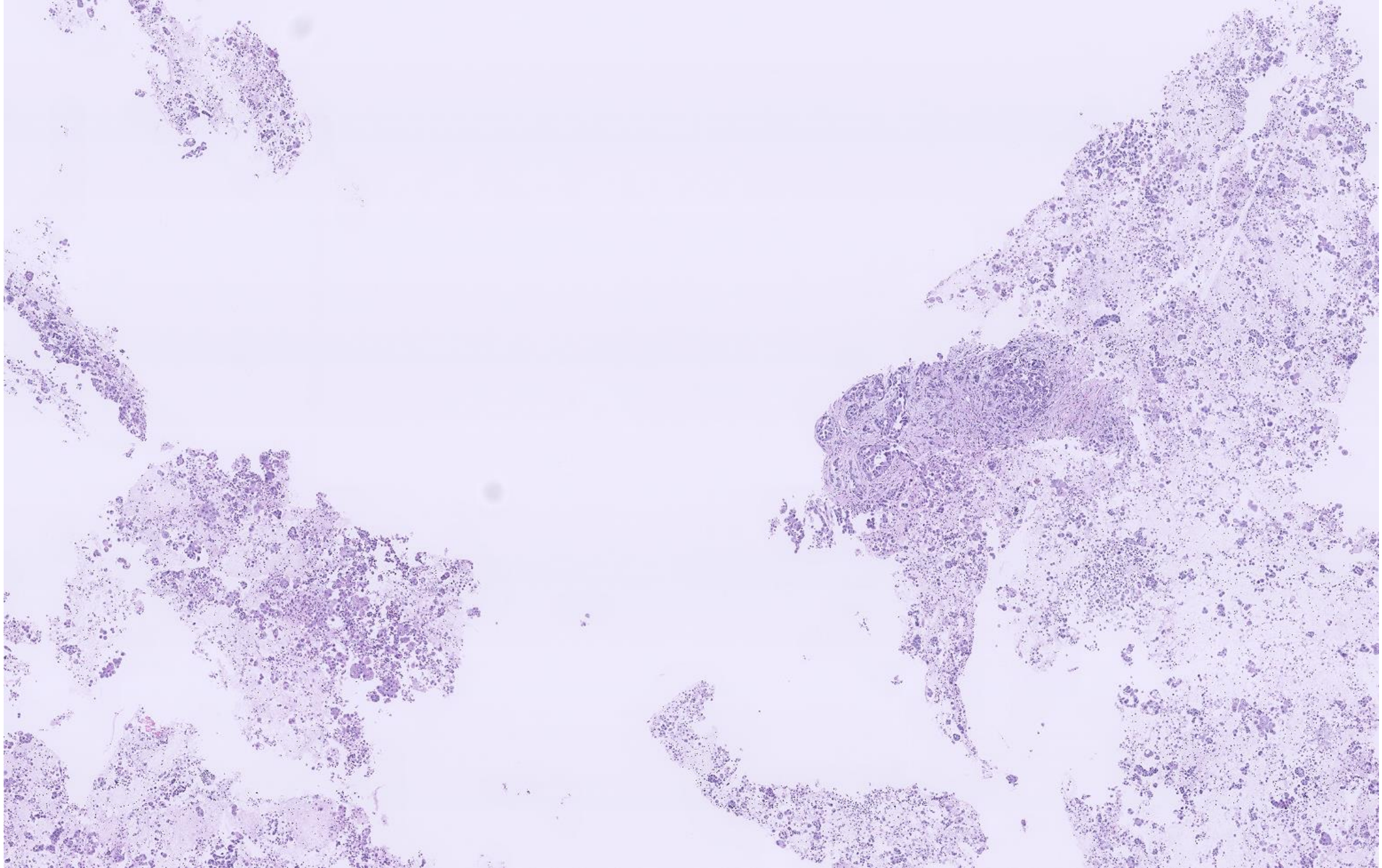
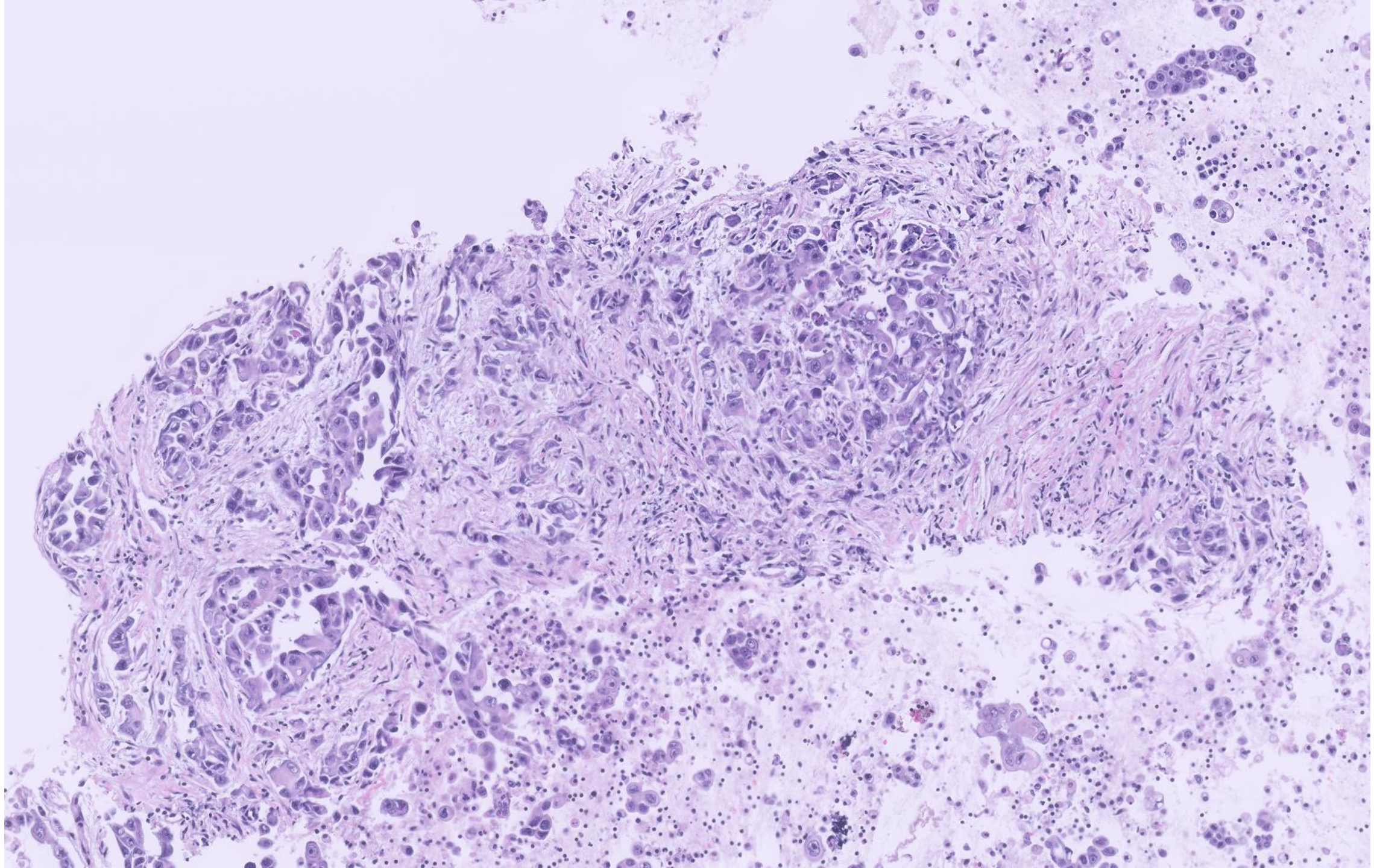
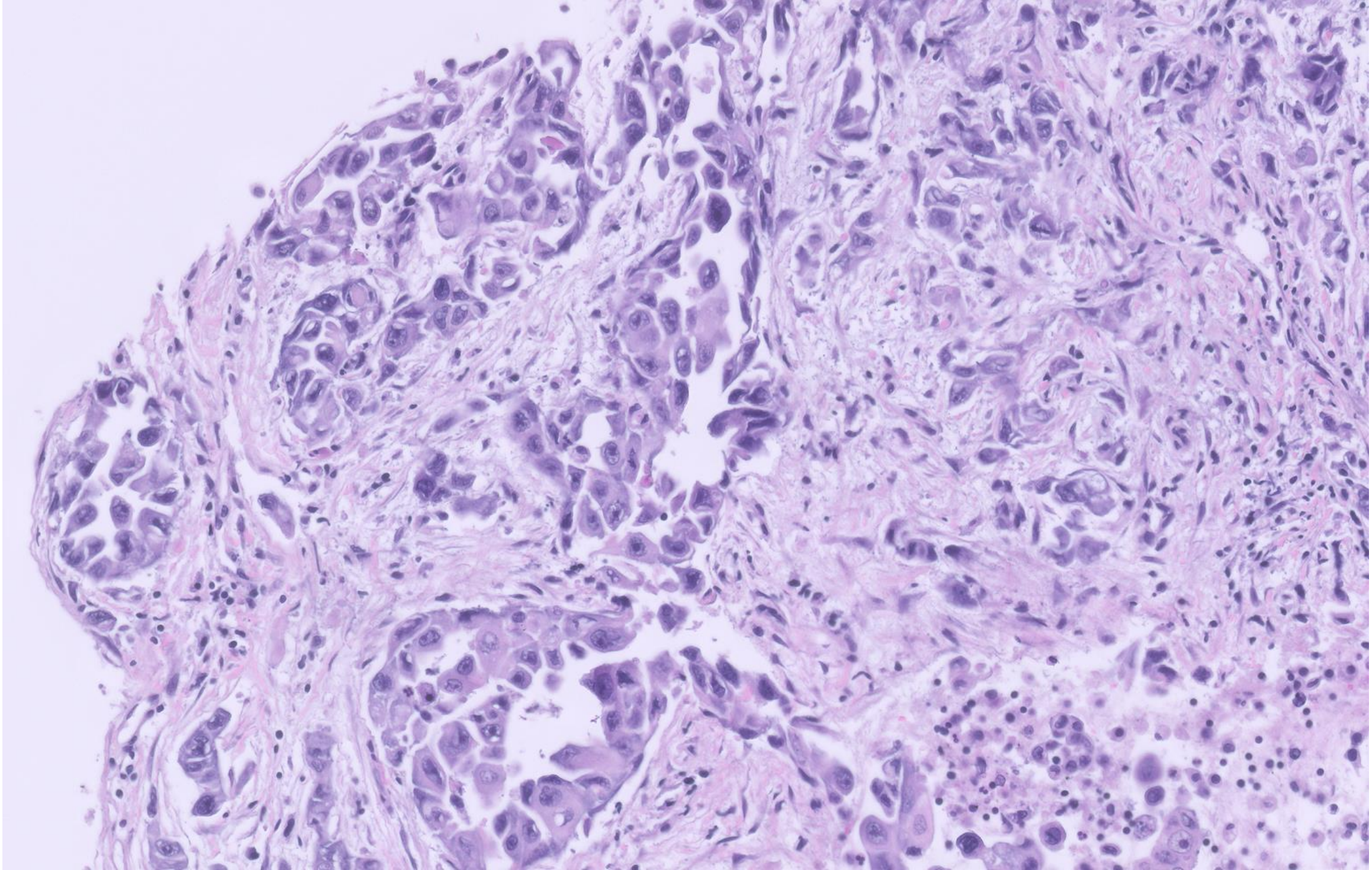
24-0703

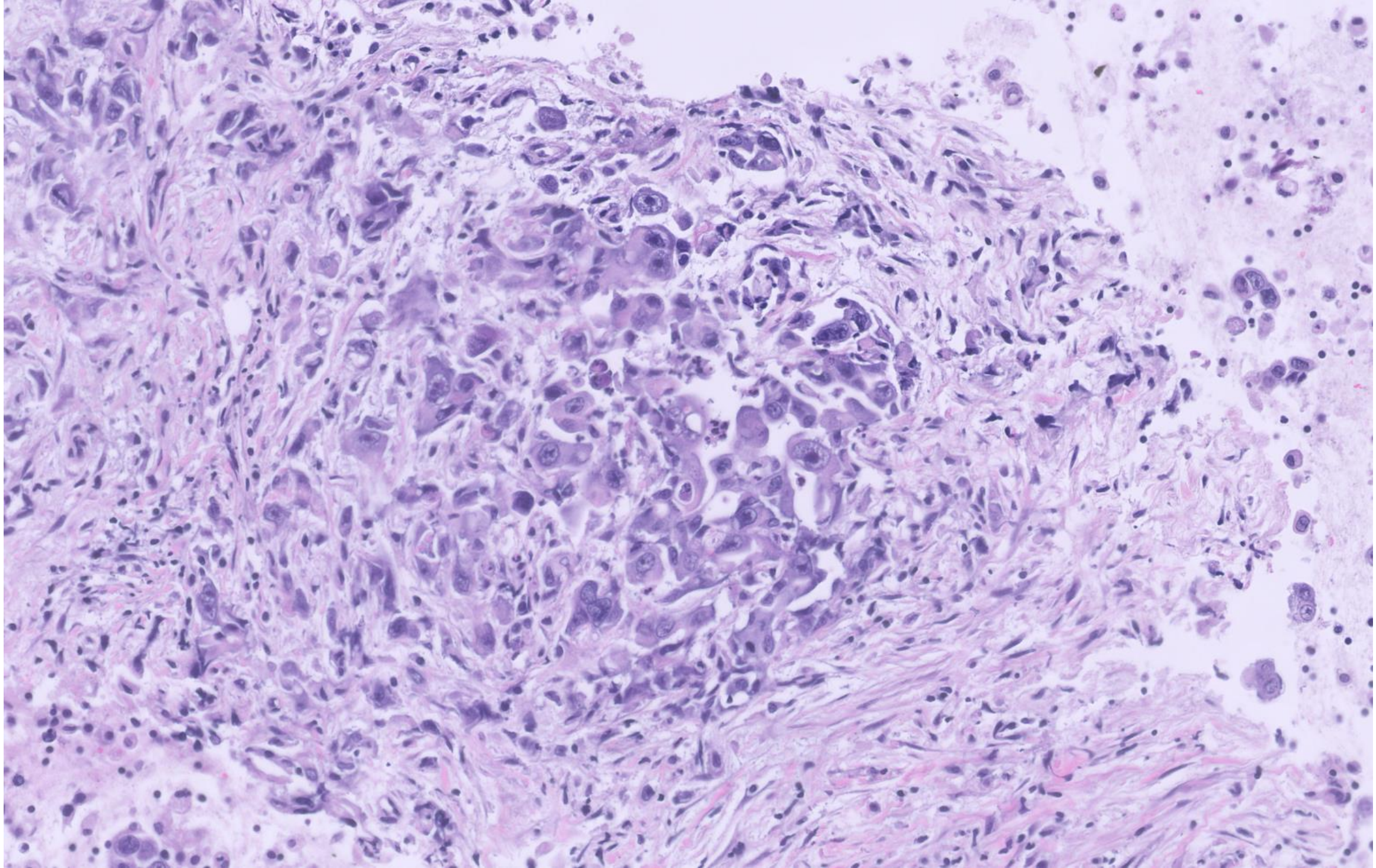
Douglas Wu, Ankur Sangoi; Stanford

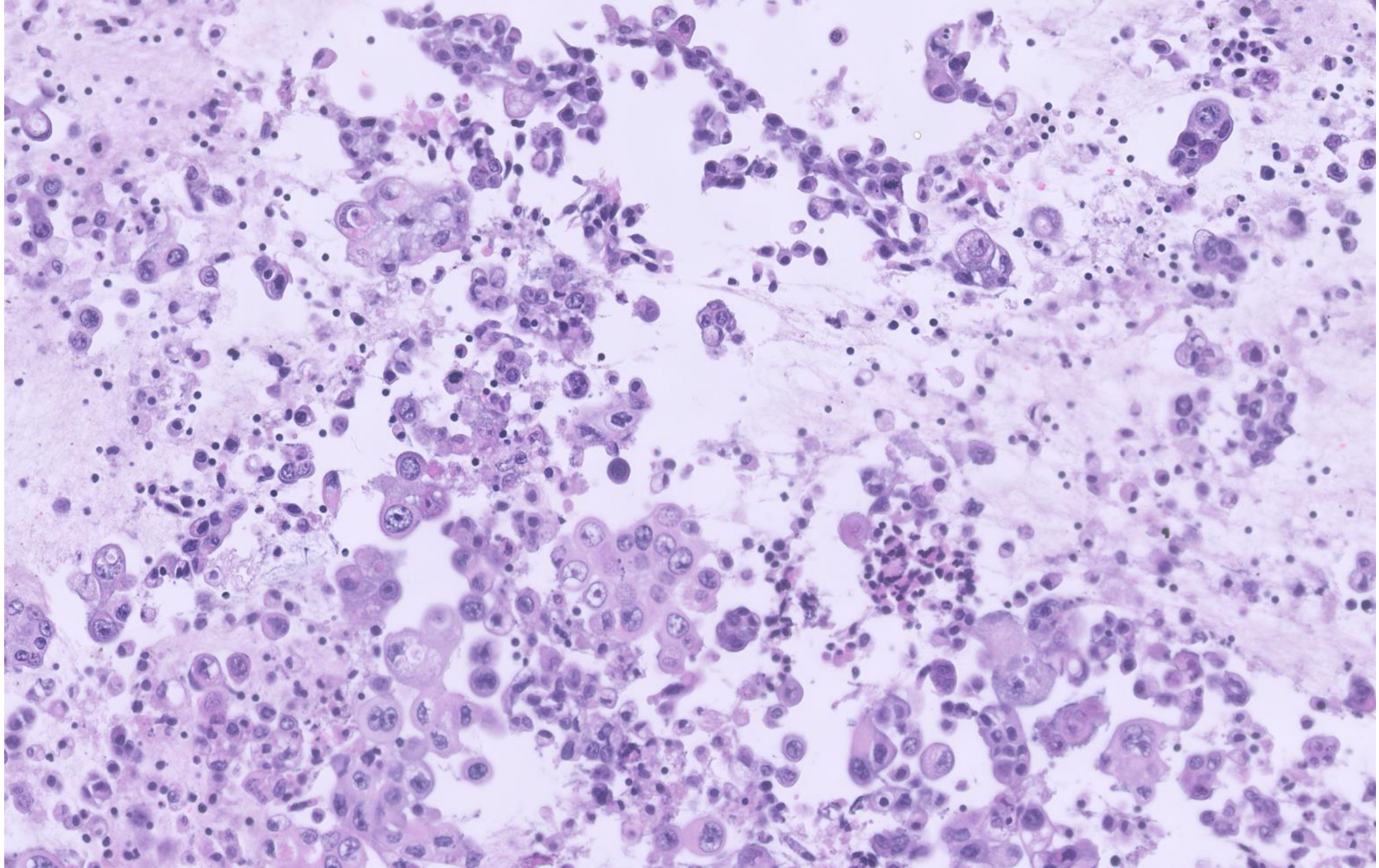
Teenage male who presented with a 5.5cm right kidney mass as well as mediastinal/hilar lymphadenopathy and multiple pulmonary nodules seen on imaging. A hilar lymph node was biopsied







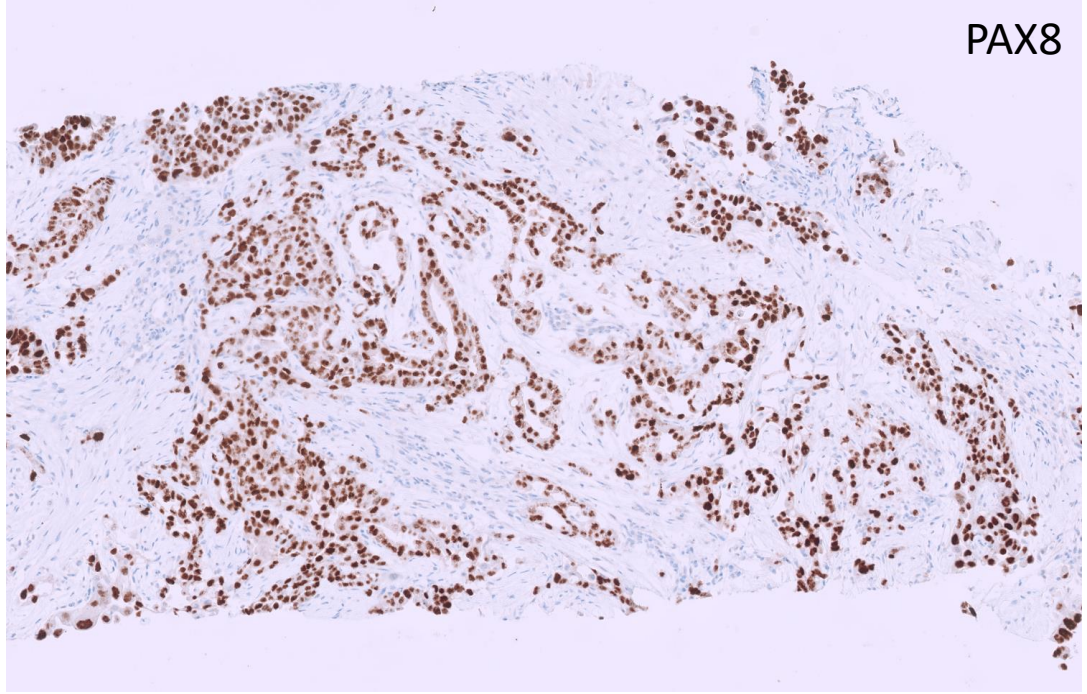




DIAGNOSIS?

Differential diagnosis

- Metastatic renal primary
  - High grade papillary renal cell carcinoma
  - FH deficient RCC
  - MITF family RCC
  - ALK mutated RCC
  - SMARCB1 deficient renal medullary carcinoma
- Poorly differentiated lung primary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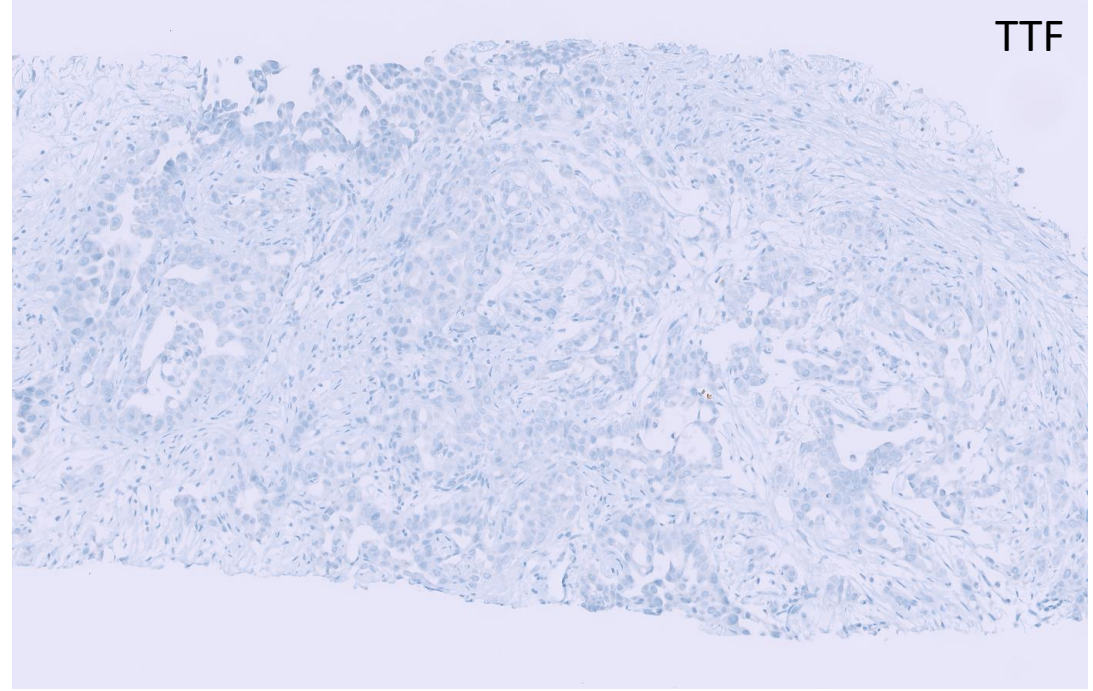
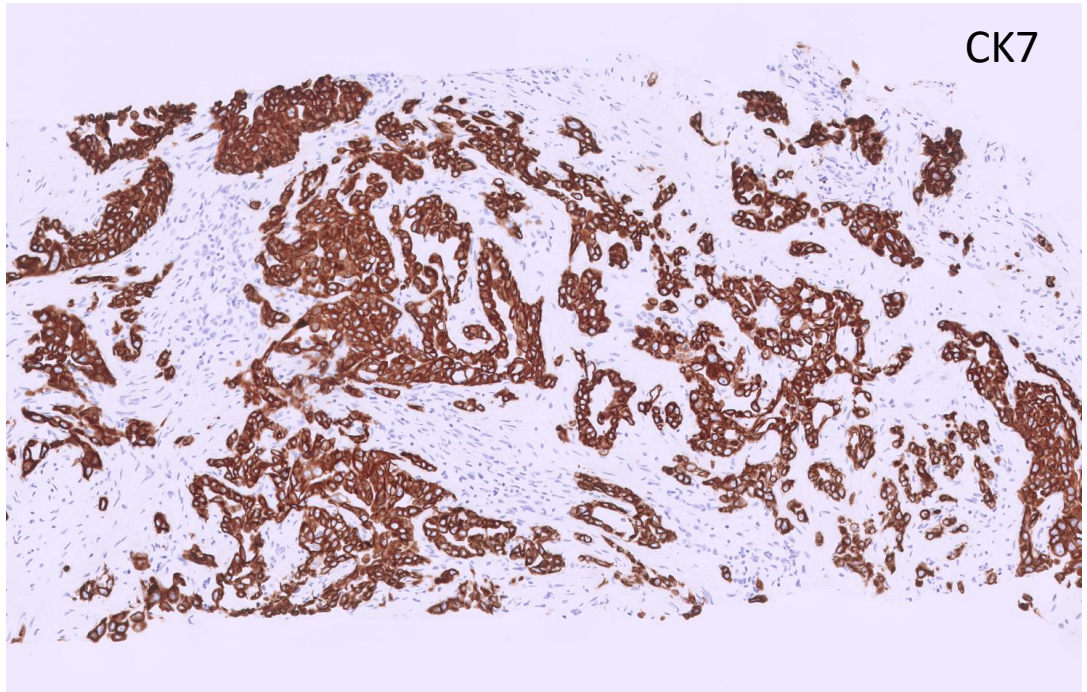
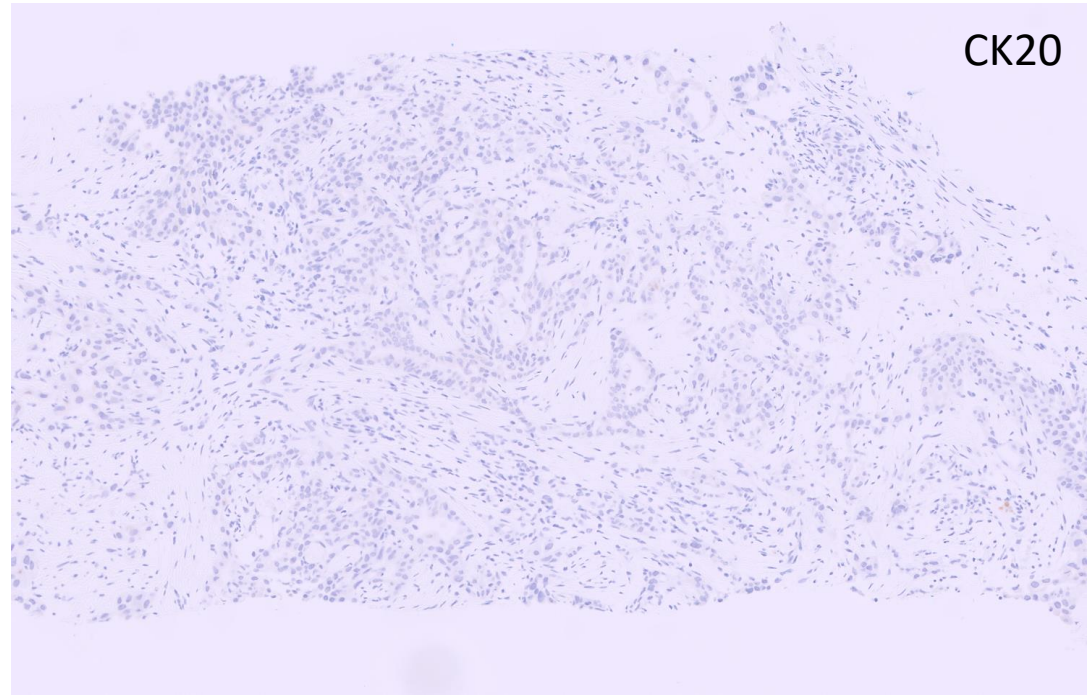

TTF


CK7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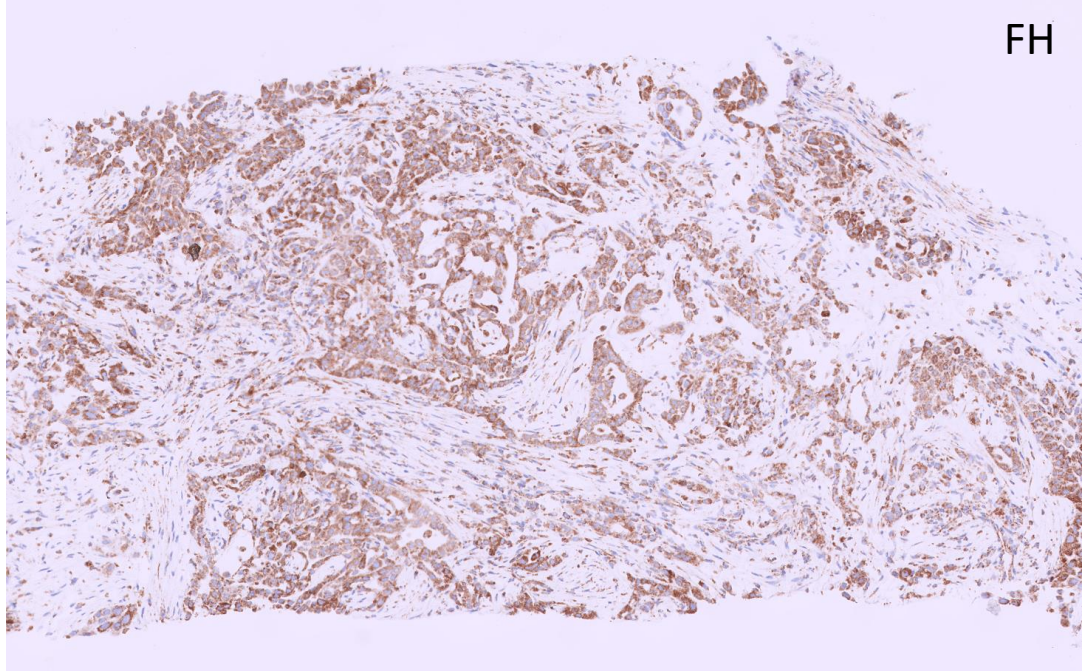
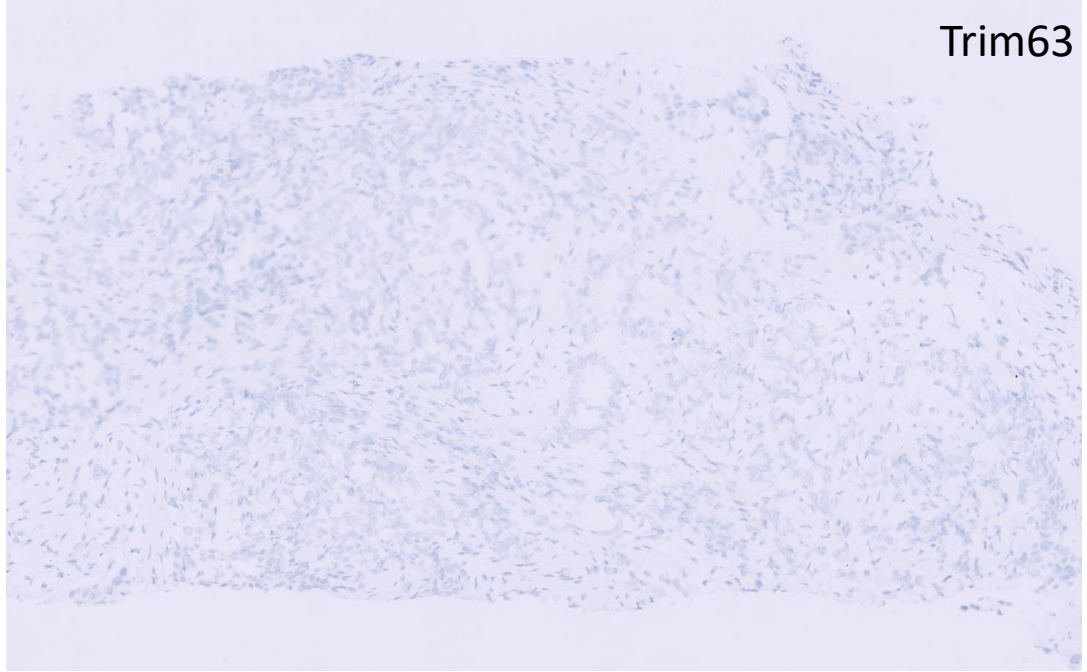
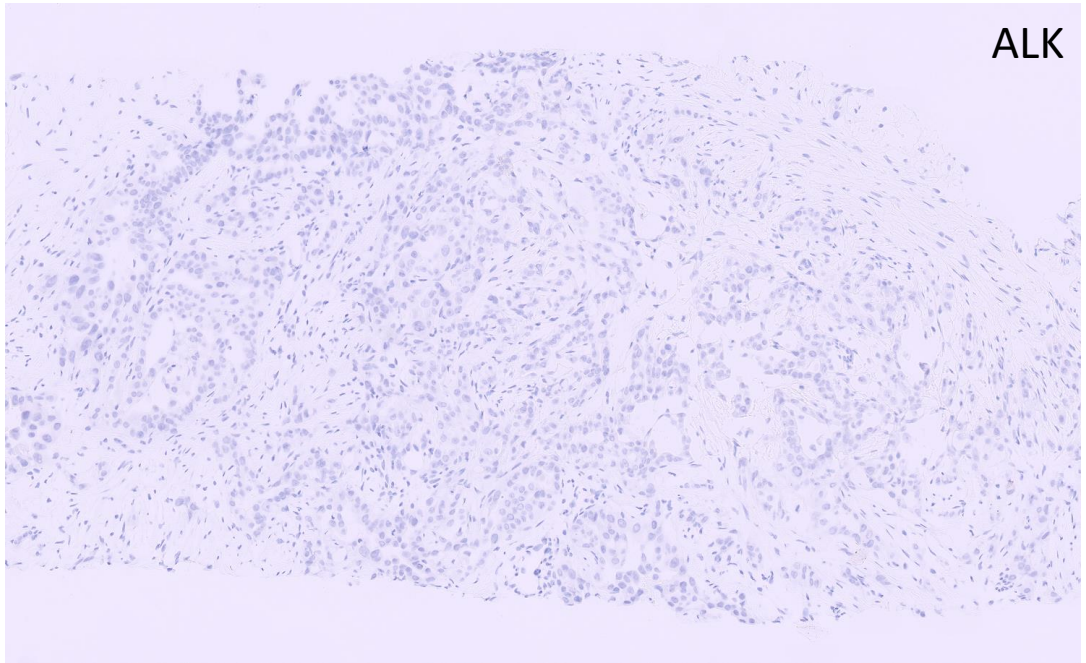
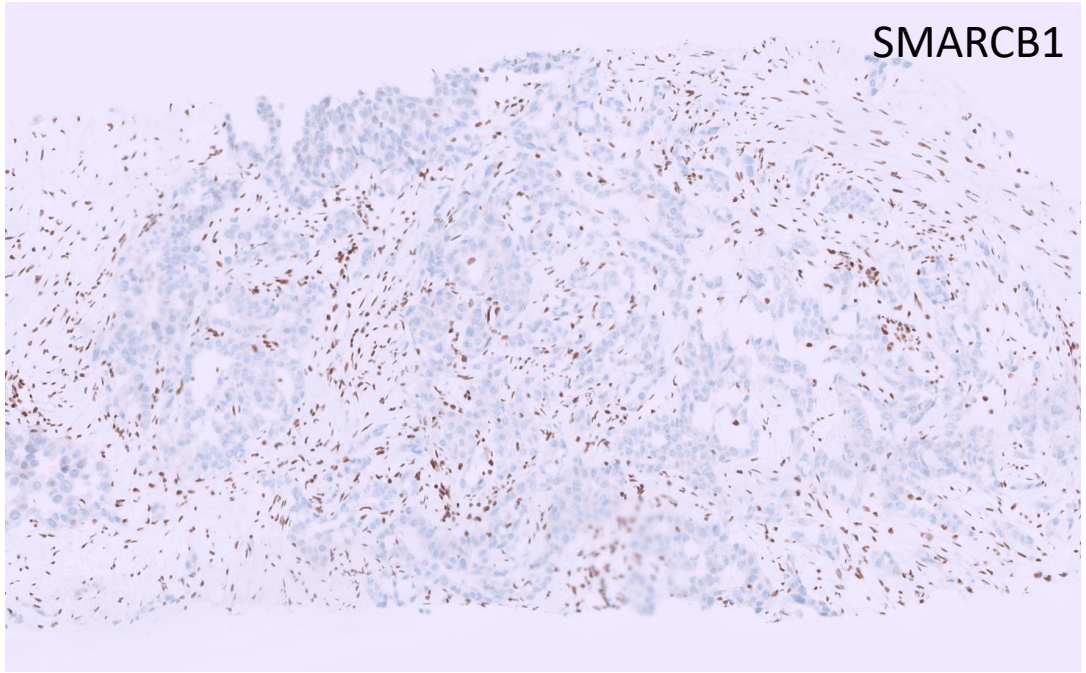
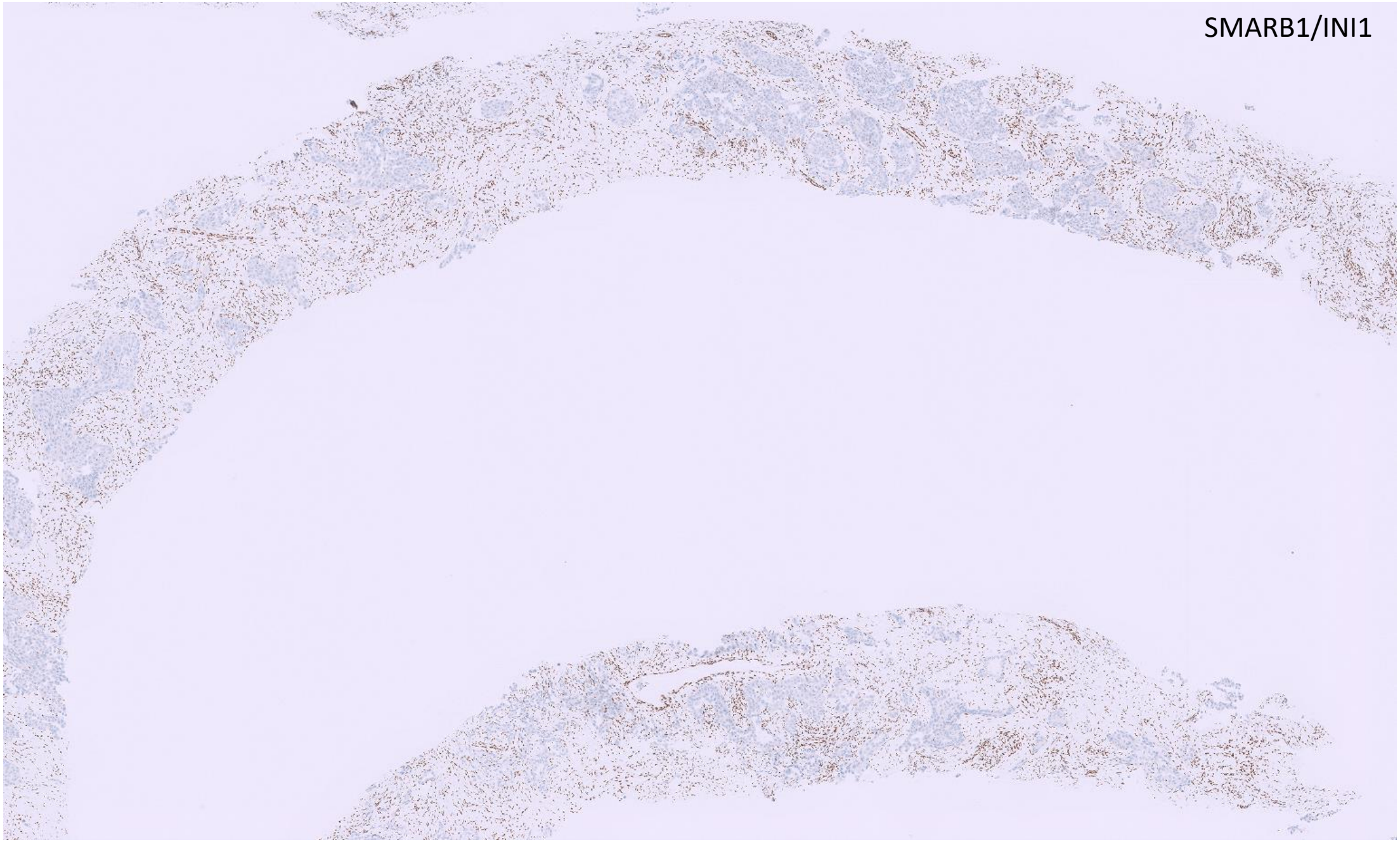

FH


Trim63


ALK


SMARCB1


SMARB1/INI1

SMARCB1 deficient renal medullary carcinoma

- Rare (<0.5%) pediatric renal tumor with poor prognosis (often metastatic at diagnosis with <3 year life expectancy)
- Most frequently seen in young African American patients with sickle cell or other hemoglobinopathies

- Histologically have high grade features (high mitotic rate, pleomorphism, rhabdoid features, infiltrative borders)
- Often seen infiltrating neutrophils and sickled erythrocytes in background

SMARCB1 deficient renal medullary carcinoma

- The 5th edition of the WHO reclassified renal medullary carcinomas to SMARCB1-deficient renal medullary carcinoma
  - Research showed that the previously named renal medullary carcinomas have uniform loss of SMARB1/INI1
- The renal medulla is hypoxic and hypertonic resulting in frequent DNA double strand breaks
  - Regional ischemia due to RBC sickling or other hemoglobinopathies may worsen this problem although it is possible to get SMARCB1 deficient RMC in patient without these diseases

- Of note, it is possible to get SMARCB1/INI1 loss in other RCC's (especially in RCCs with high grade/rhabdoid features) and also some bladder urothelial carcinomas
  - These should be classified under their primary type

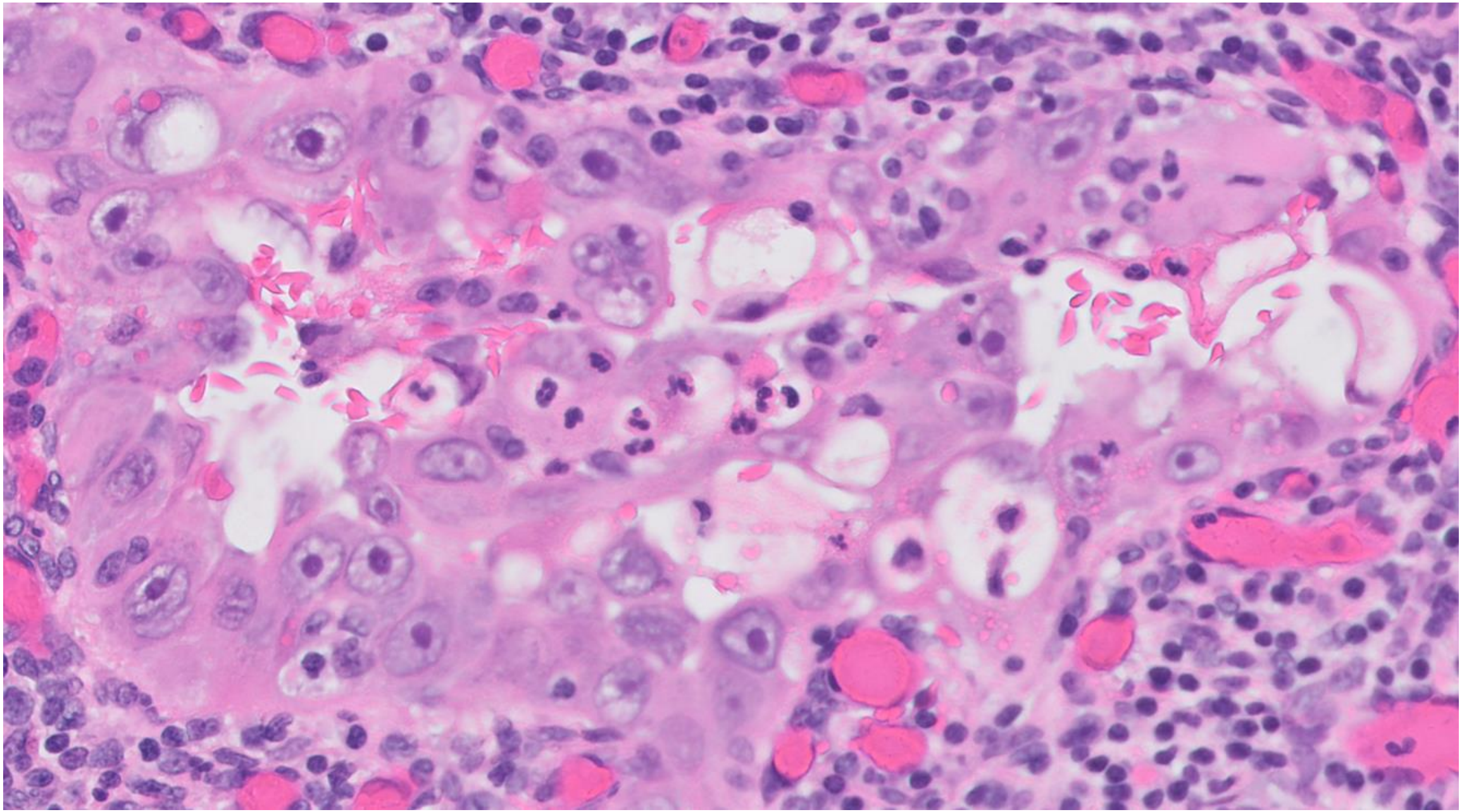
SMARCB1 NGS false negatives

- NGS can be falsely negative as allelic inactivation of SMARCB1 occurs in a large majority of cases either via concurrent hemizygous loss and translocation disrupting SMARCB1 or by homozygous loss

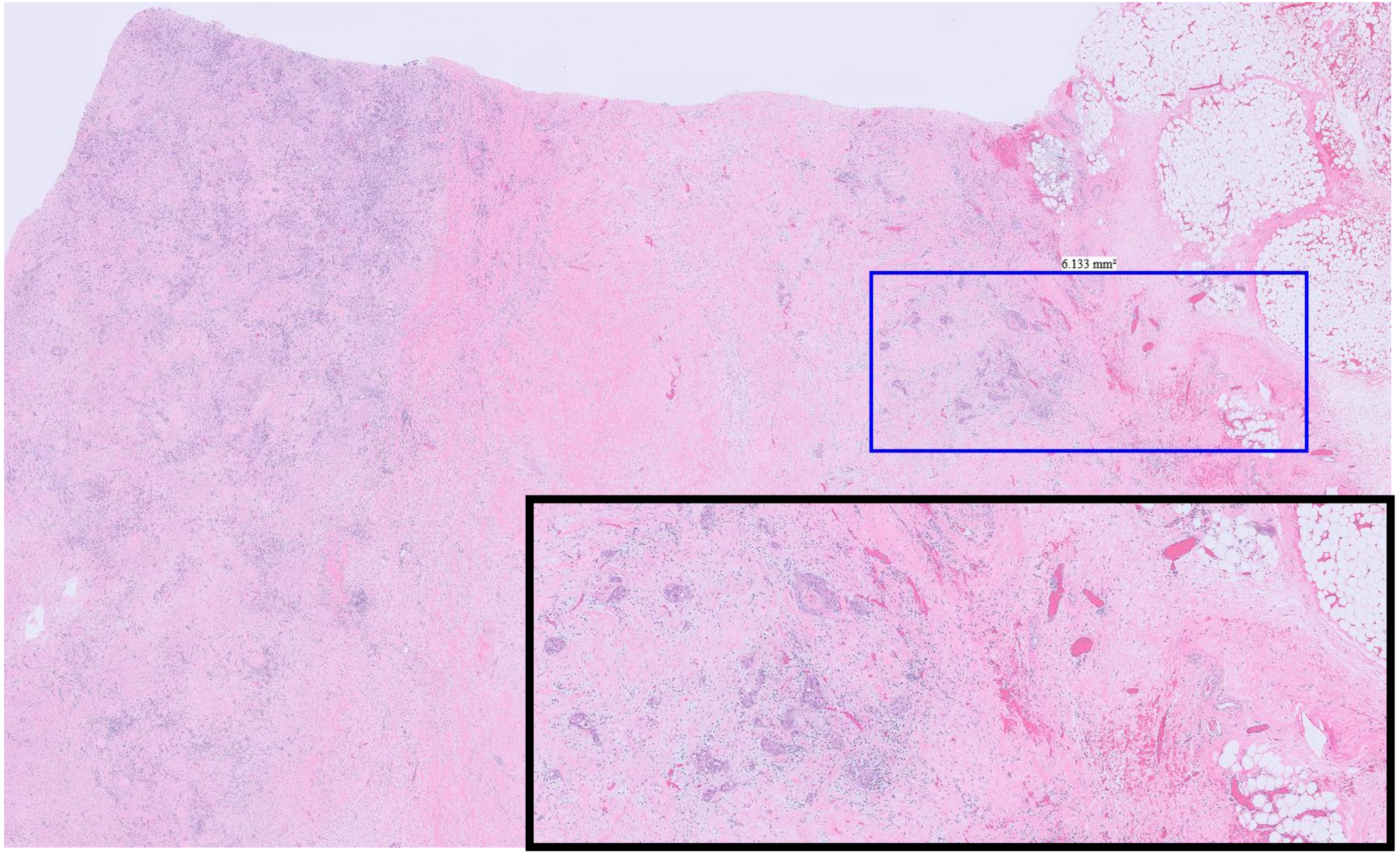
- In these patients, sickle cell/Hb testing is often recommended

Follow up

- Additional workup showed sickle cell trait
- Patient was treated with aggressive chemotherapy
- The kidney was resected for local control of primary tumor
  - >90% necrosis/tumor responses in kidney



Sickled RBCs and neutrophils in the final resection specimen



Tumor bed extends into perinephric fat, although viable tumor does not definitively invade into perinephric fat

Neoadjuvant chemotherapy in renal carcinoma

- There are no formal guidelines for how to handle neoadjuvant treated kidneys or how to report histological findings for renal tumors after treatment
- Neoadjuvant chemotherapy can complicate tumor staging, affecting tumor size and masking tumor extent
- One study recommends thorough and extensive sampling of the renal sinus and the perinephric fat to exclude the presence of microscopic extrarenal tumor involvement

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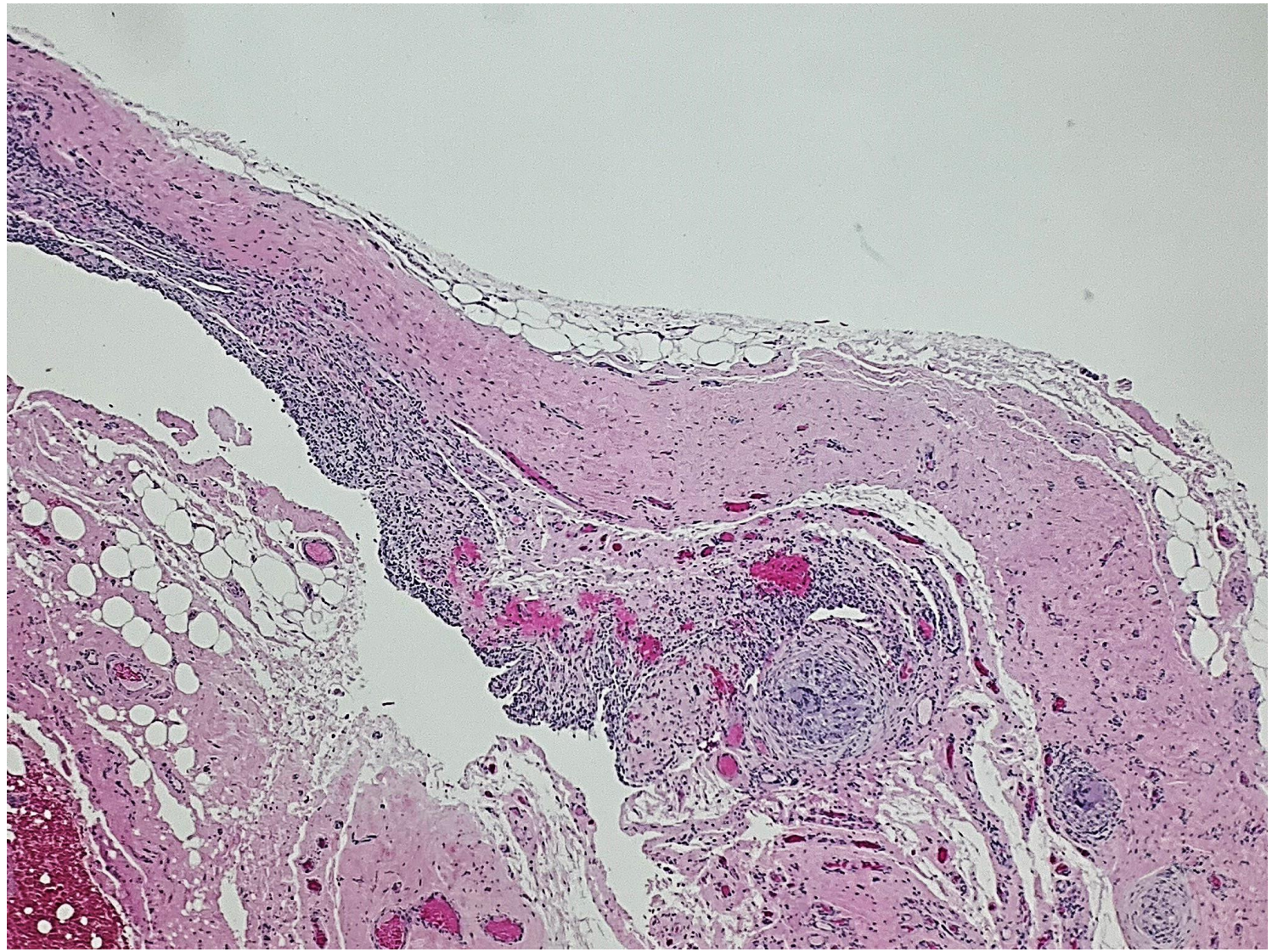
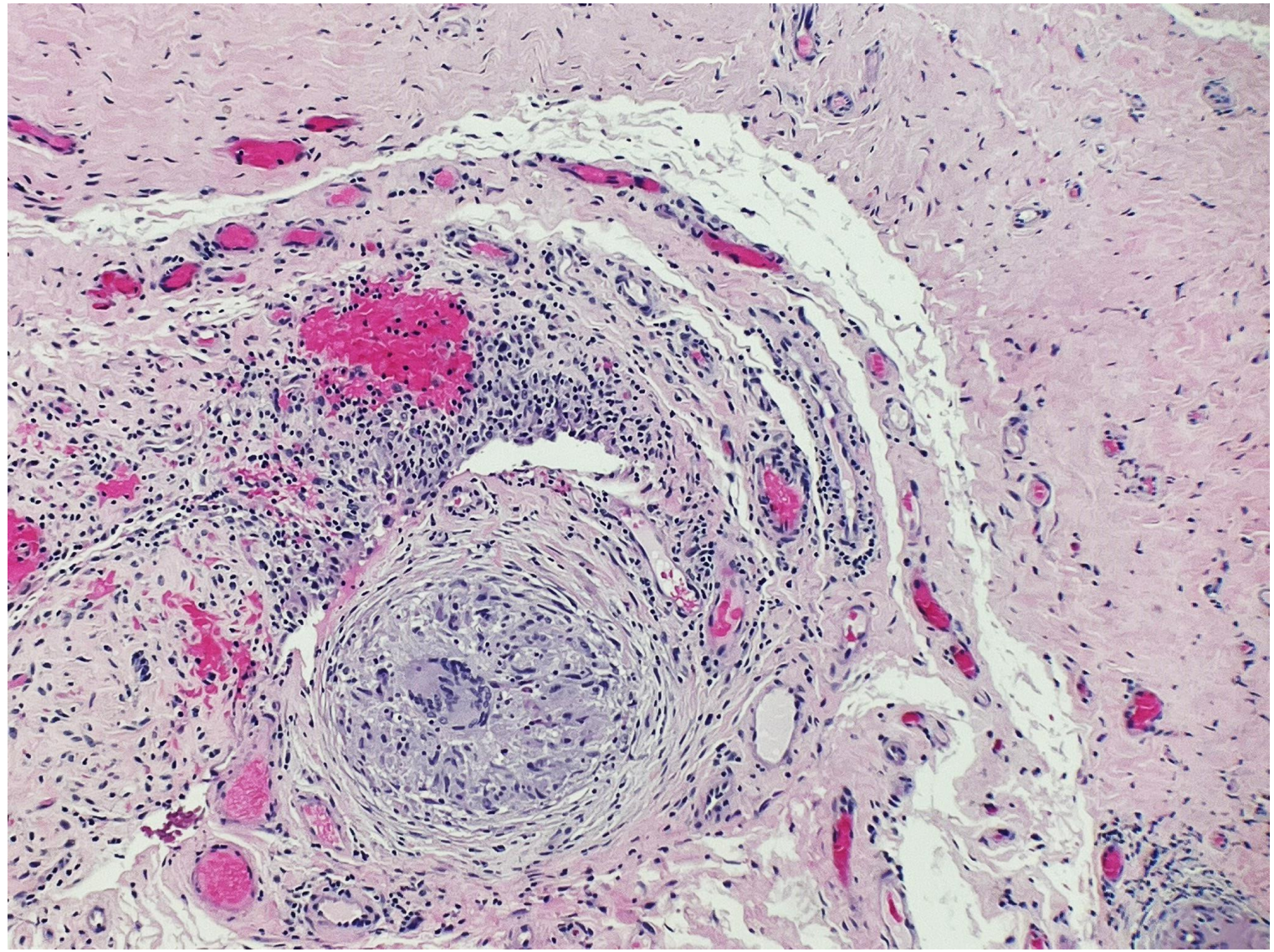
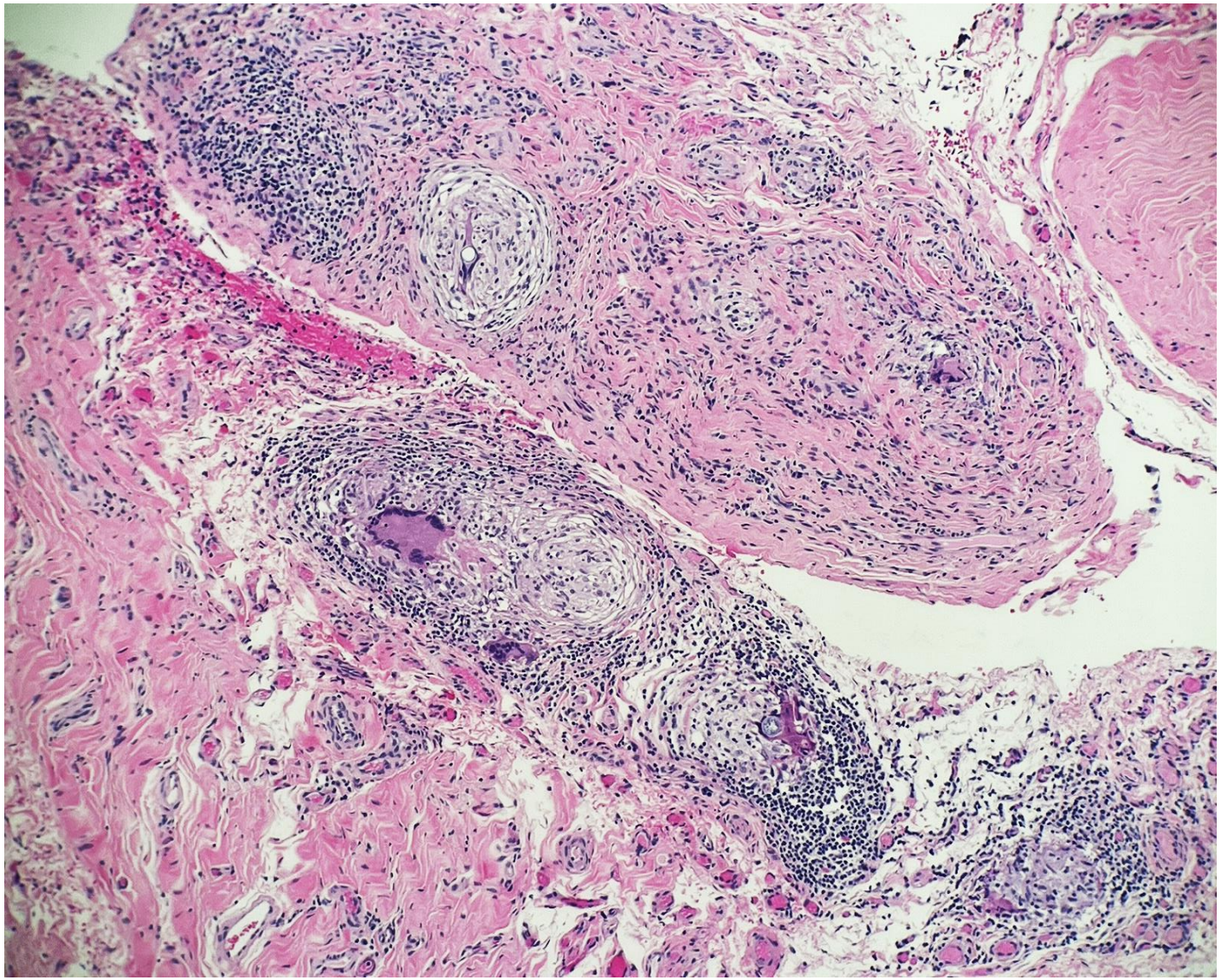
24-0704

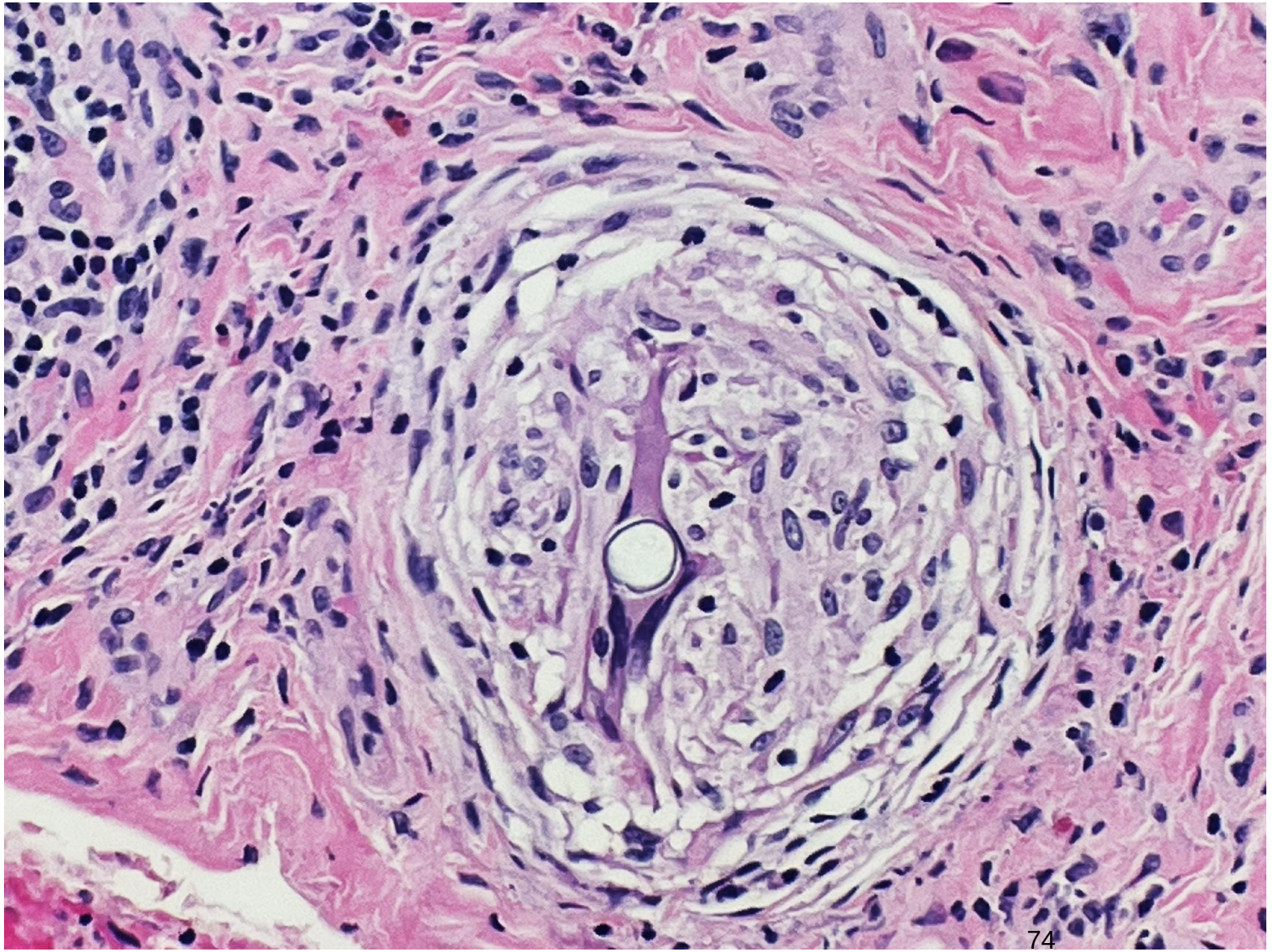
Harris Goodman

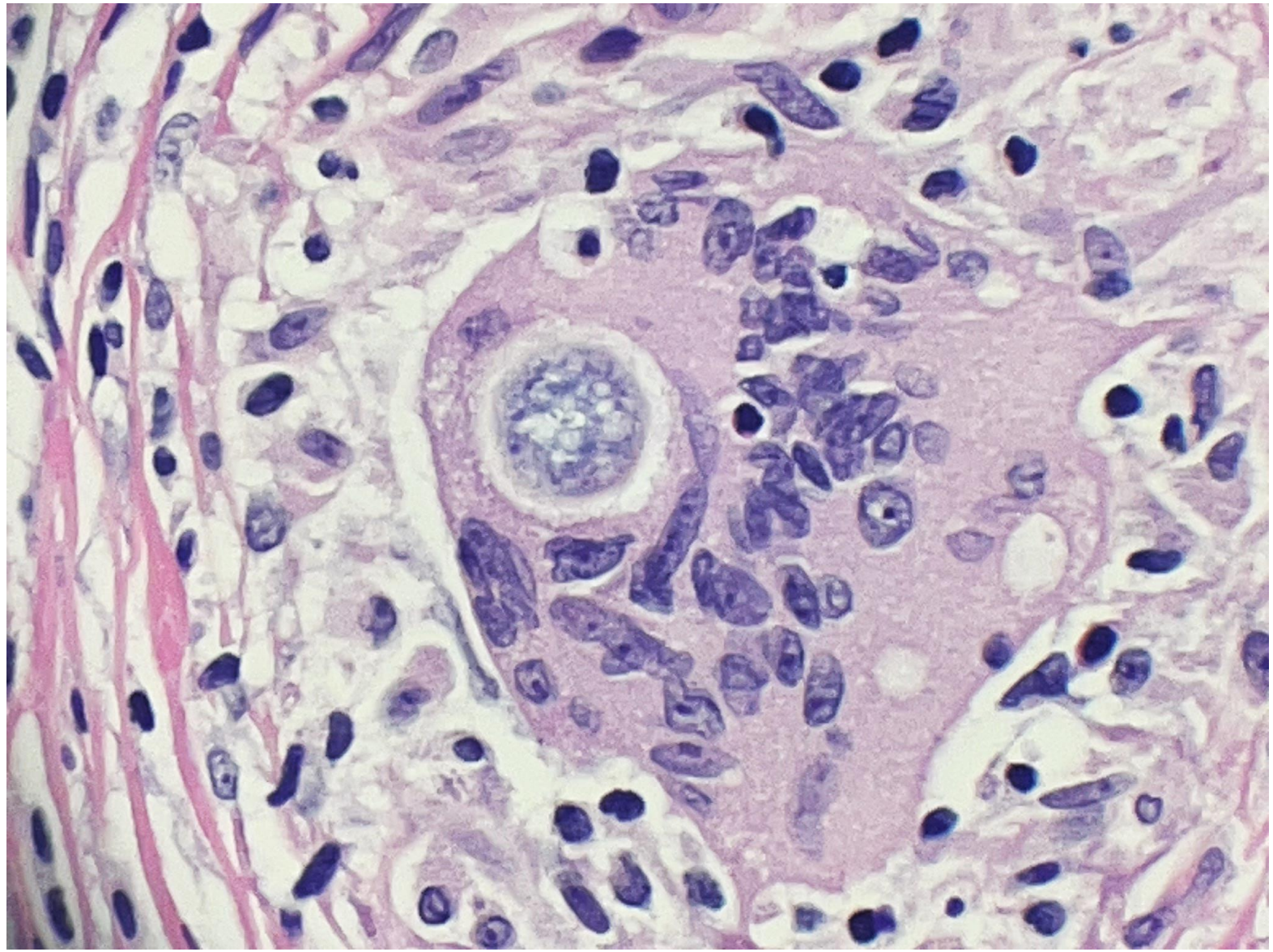
60-70 year old man with “symptomatic R inguinal hernia, PMHx significant for CAD s/p remote stent placement on DAPT. The hernia sac was dissected carefully off of the cord structures. A cord lipoma was noted and resected.”











DIAGNOSIS?

J Clin Pathol. 2013 Dec;66(12):1084-6. doi: 10.1136/jclinpath-2013-201734. Epub 2013 Jun 22.

Hernia sacs: is histological examination necessary?

Tao Wang [1], Rajkumar Vajpeyi

Affiliations + expand

PMID: 23794497 DOI: 10.1136/jclinpath-2013-201734

Abstract

The hernia sac is a common surgical pathology specimen which can occasionally yield unexpected diagnoses. The College of American Pathologists recommends microscopic examination of abdominal hernias, but leaves submission of inguinal hernias for histology to the discretion of the pathologist. To validate this approach at a tertiary care centre, we retrospectively reviewed 1426 hernia sacs derived from inguinal, femoral and abdominal wall hernias. The majority of pathologies noted were known to the clinician, including herniated bowel, lipomas and omentum. A malignancy was noted in three of 800 inguinal hernias and seven of 576 abdominal wall hernias; five of these lesions were not seen on gross examination. Other interesting findings in hernia sacs included appendices, endometriosis, a perivascular epithelioid cell tumour, and pseudomyxoma peritoneii. All hernia sacs should be examined grossly as most pathologies are grossly visible. The decision to submit inguinal hernias for histology may be left to the discretion of the pathologist, but abdominal and femoral hernias should be submitted for histology.

SBPS 24-0704

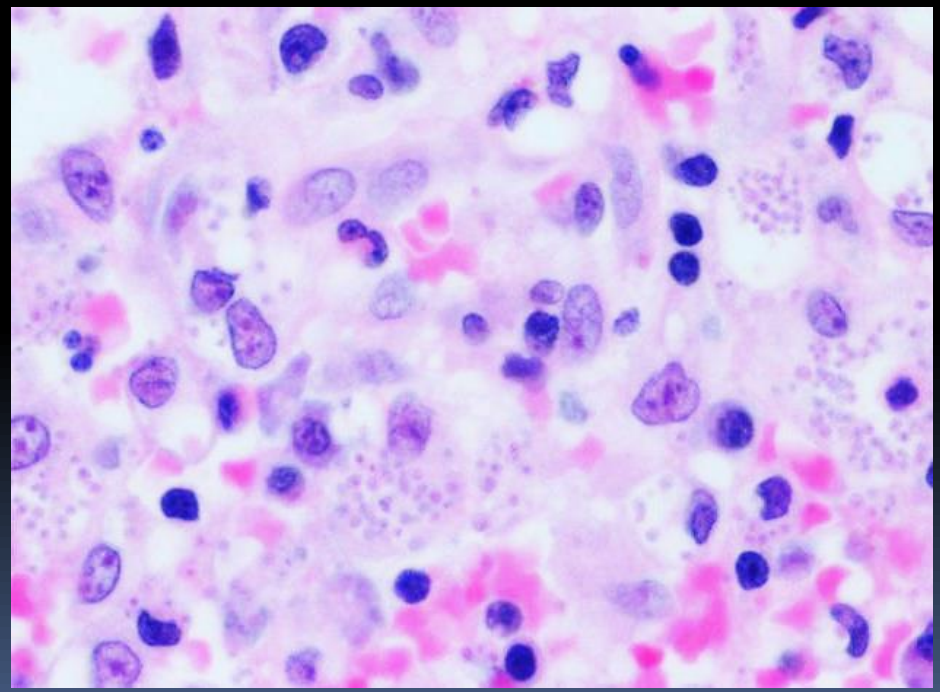
Differential diagnosis:

- Histoplasmosis
- Blastomycosis
- Cryptococcosis
- Coccidiodomycosis
- Paracoccidioidomycosis
- Foreign material

SBPS 24-0704

Differential diagnosis:

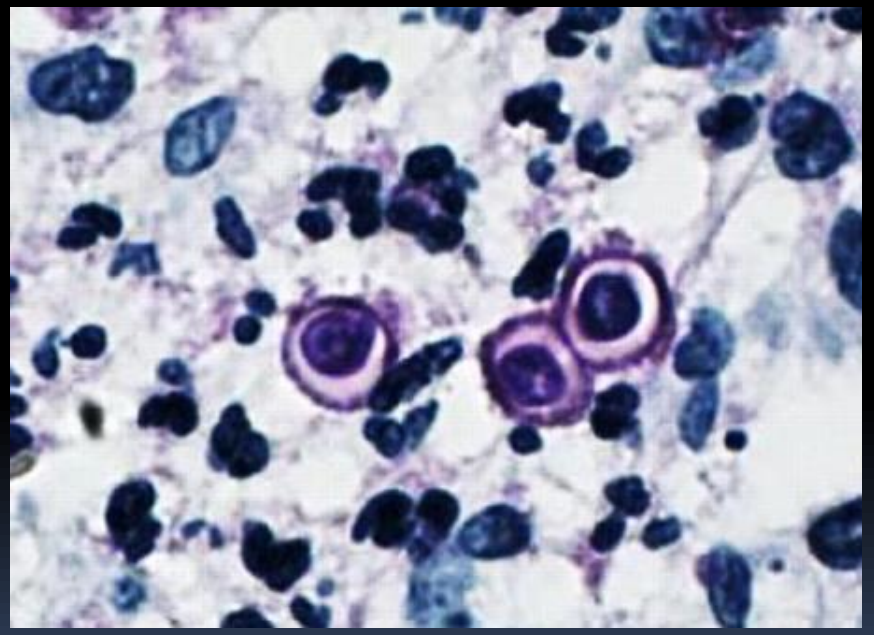
- Histoplasmosis
  - Endemic in the central and eastern U.S. (Ohio and Mississippi River valleys)
  - Small (2 - 5 microns) budding yeast within the histiocytes



SBPS 24-0704

Differential diagnosis:

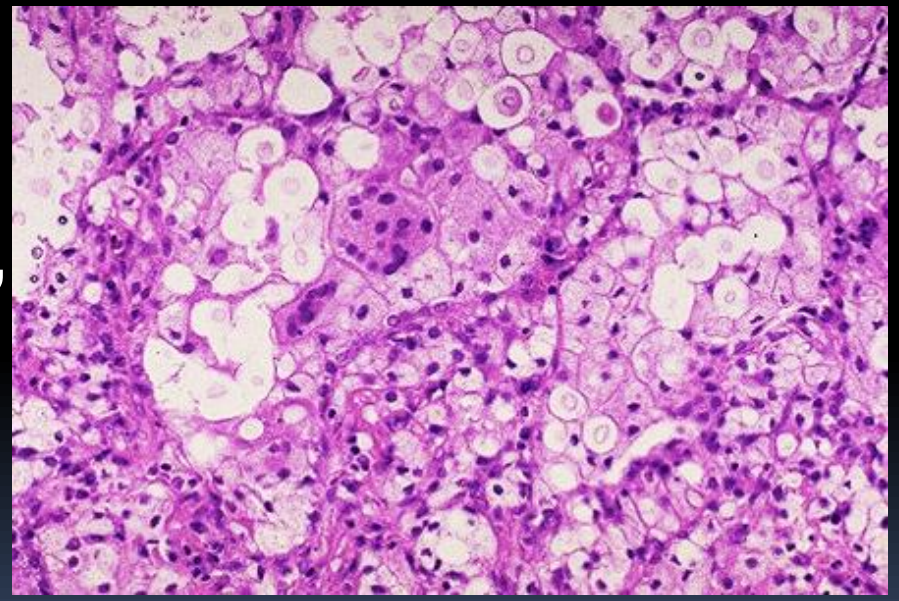
- Blastomycosis
  - Endemic in the eastern U.S. (Ohio, Mississippi River valleys, Great Lakes region)
  - Broad based budding yeast, smaller (8 - 15 microns) than Coccidioides sp.



SBPS 24-0704

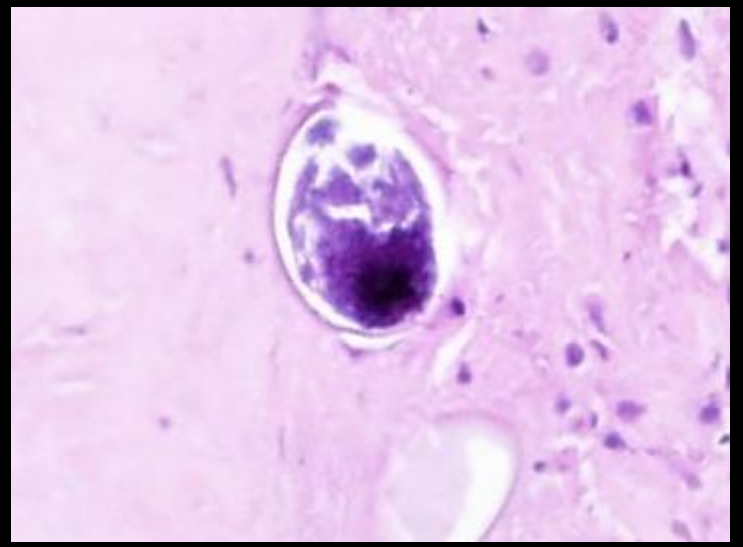
Differential diagnosis:

- Cryptococcosis
  - No specific endemic area
  - Round, medium sized (4 - 7 microns), yeast with thick mucoid capsule



SBPS 24-0704

Differential diagnosis:

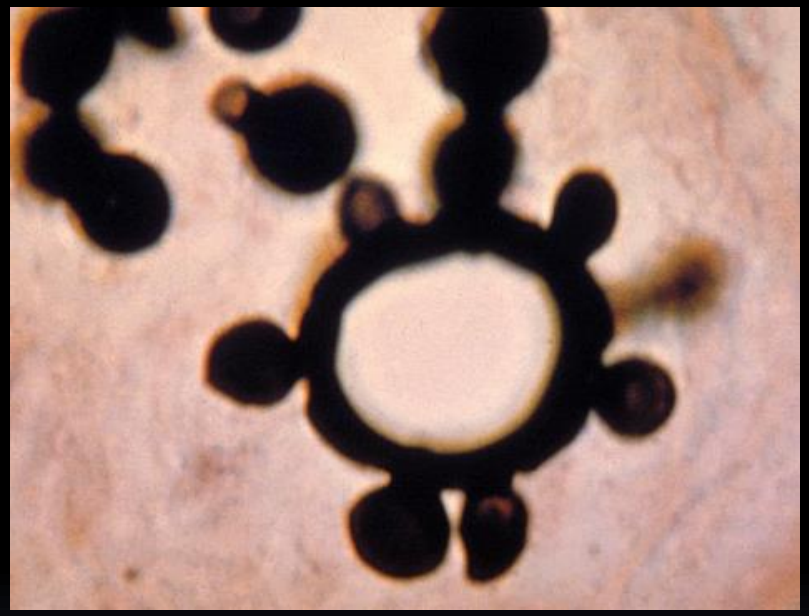


- Coccidiodomycosis
  - Southwest U.S.: California, Arizona, New Mexico, Texas, Central and South America: northern Mexico, Argentina, Brazil
  - Large (20 - 200 microns) thick walled spherules, with or without granular basophilic endospores (2 - 4 microns)

SBPS 24-0704

Differential diagnosis:

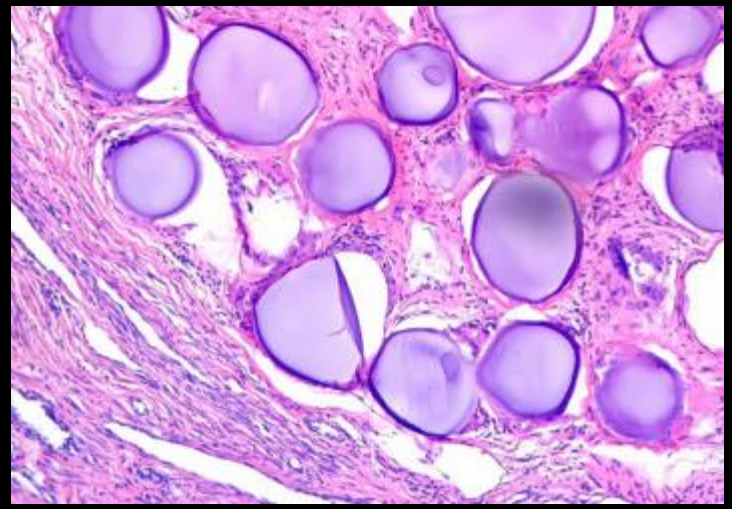
- Paracoccidioidomycosis
  - Endemic in South America
  - Large (10 - 60 microns) spherical yeast with circumferential budding, resembling mariner's wheel

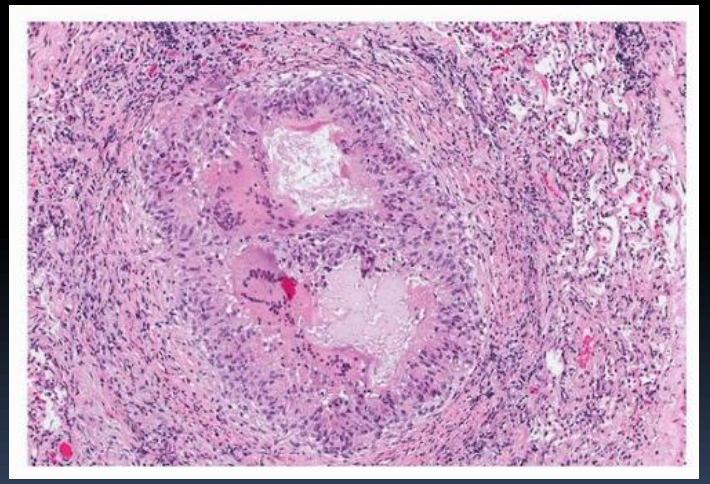


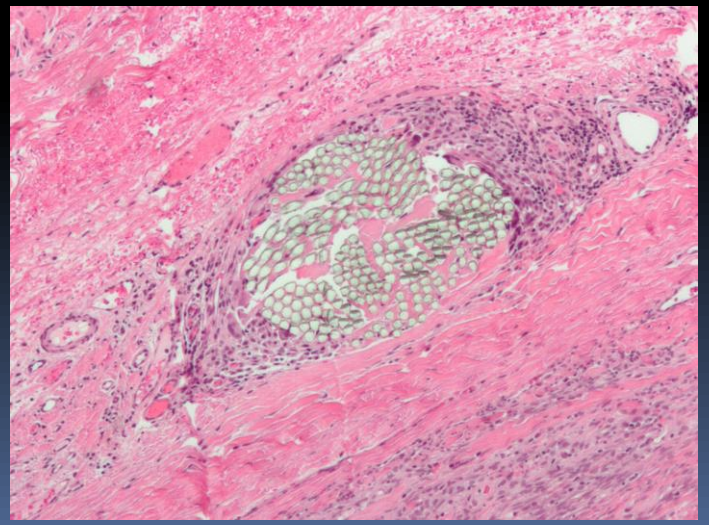
SBPS 24-0704

Differential diagnosis:

- Foreign material







SBPS 24-0704

CT of Chest:

Spiculated nodule of the anterior aspect of the superior segment of the right lower lobe, measuring 1.4 cm x 1.9 cm x 1.2 cm, abutting the major fissure. Tandem nodules superior and lateral to this dominant nodule may represent satellite nodules. This finding is most worrisome for primary neoplasm or metastatic disease. PET/CT scan and/or tissue sampling may be considered depending on probability of malignancy and associated comorbidities.

Prominent right suprahilar lymph node measures 2.2 cm x 1.6 cm. Enlarged left anterior costophrenic recess lymph node measures 1.6 cm x 1.2 cm. Given the setting, these findings are worrisome for metastasis.

SBPS 24-0704

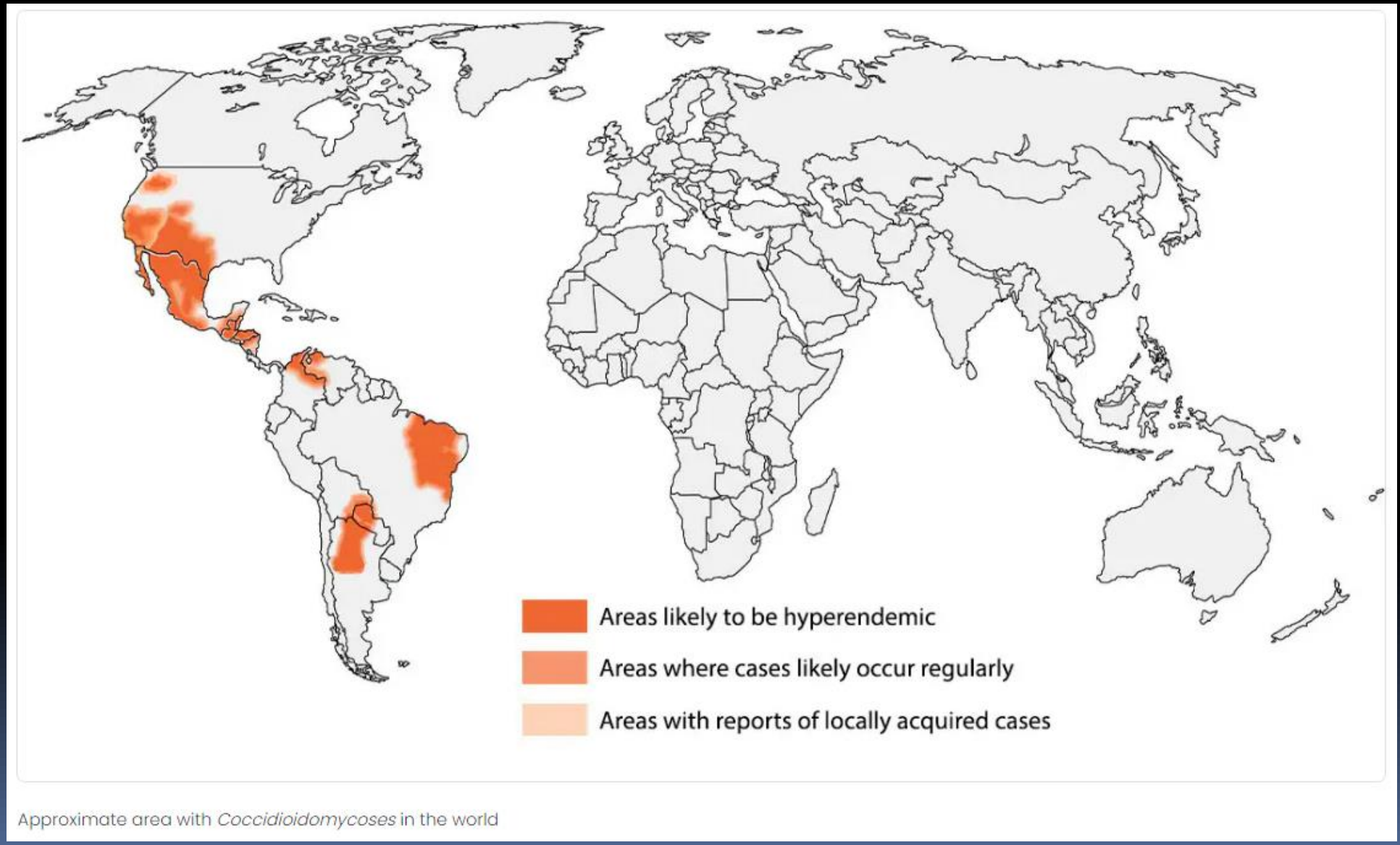
Coccidioides Antibody 1:32 ^

Comment: REFERENCE RANGE: <1:2

INTERPRETIVE CRITERIA:
<1:2 Antibody Not Detected
> or = 1:2 Antibody Detected

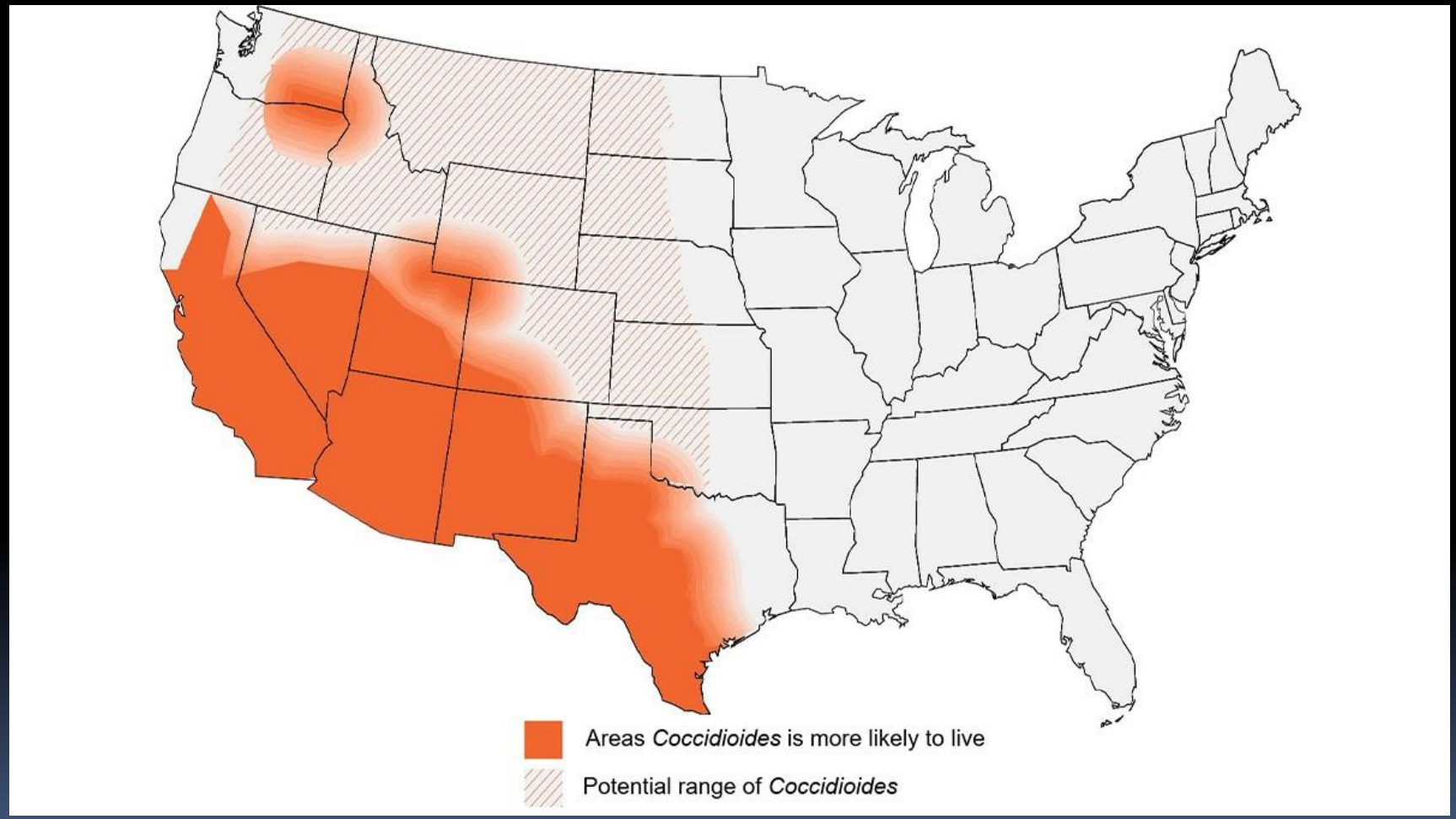
All serum titers > or = 1:2 should be considered evidence indicative of coccidioidomycosis, although titers of 1:2 and 1:4 should be confirmed by immunodiffusion testing. Titers exceeding 1:16 usually reflect disseminated disease. In general, higher titers are correlated with disease severity, and changes in serial titers are of prognostic value A negative CF test does not, however, rule out the diagnosis. Only 70% of patients with cavitary disease are positive, and only 30% of patients with nodular disease are positive.

SBPS 24-0704



Approximate area with *Coccidioidomycoses* in the world

SBPS 24-0704


Areas *Coccidioides* is more likely to live
Potential range of *Coccidioides*

SBPS 24-0704

About 40% of cases of Valley fever develop lung infection symptoms.

Infections are usually self-limiting but 5-10% develop complications. Disseminated disease is rare.

Serologic tests to detect IgM and IgG antibodies are the most common diagnostic tests.

Infections are usually treated with fluconazole or amphotericin B.

SBPS 24-0704

The CDC recommends ordering an enzyme immunoassay (EIA) antibody with immunodiffusion (ID) or complement fixation (CF) antibody test initially for coccidioidomycosis diagnosis. Initial testing with EIA or ID and CF may depend on availability and performance characteristics of test at facility. EIAs have a quicker turnaround time than ID and CF antibody testing.

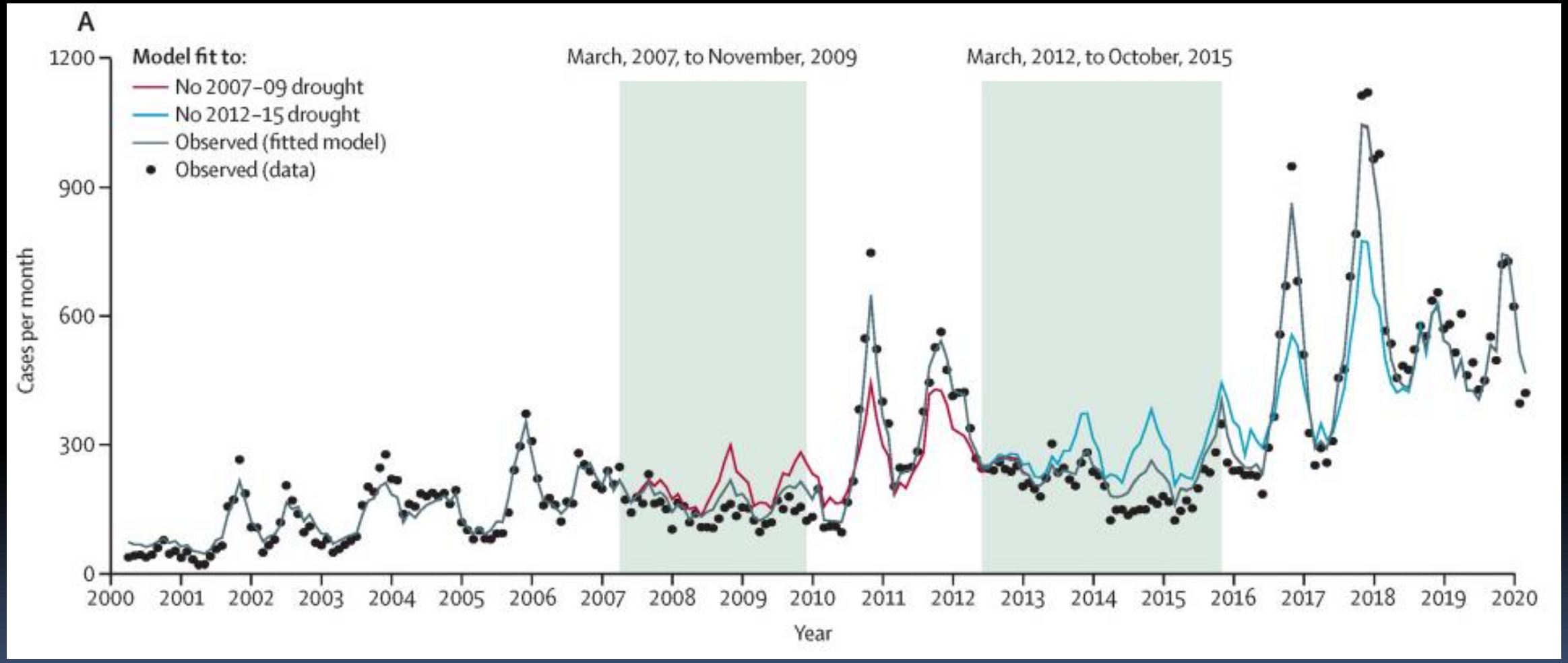
SBPS 24-0704

Effects of precipitation, heat, and drought on incidence and expansion of coccidioidomycosis in western USA: a longitudinal surveillance study

Jennifer R Head, PhD • Gail Sondermeyer-Cooksey, MPH • Alexandra K Heaney, PhD • Alexander T Yu, MD • Isabel Jones, PhD • Abinash Bhattachan, PhD • et al. Show all authors

Open Access • Published: October, 2022 • DOI: https://doi.org/10.1016/S2542-5196(22)00202-9 •

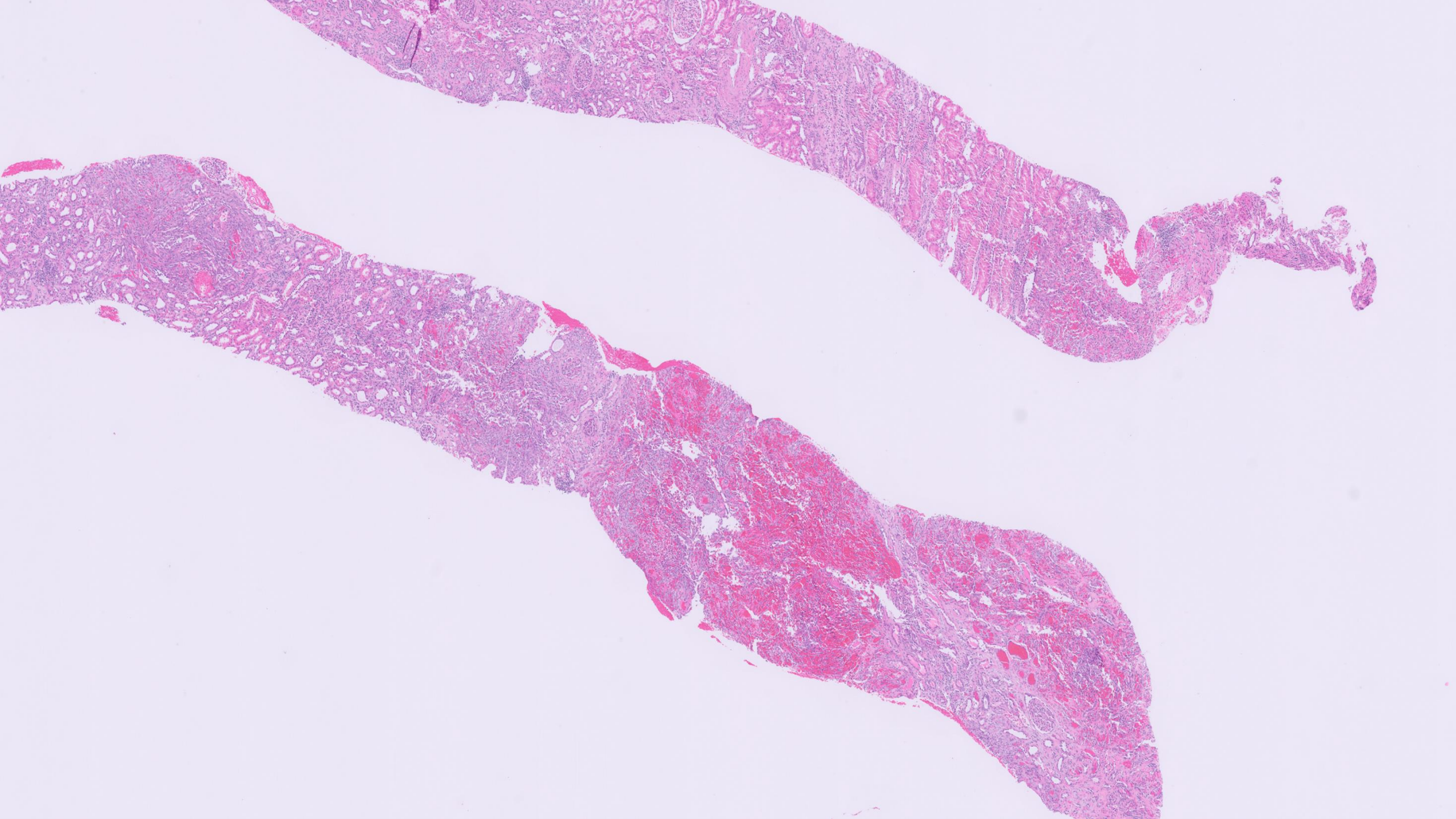
SBPS 24-0704

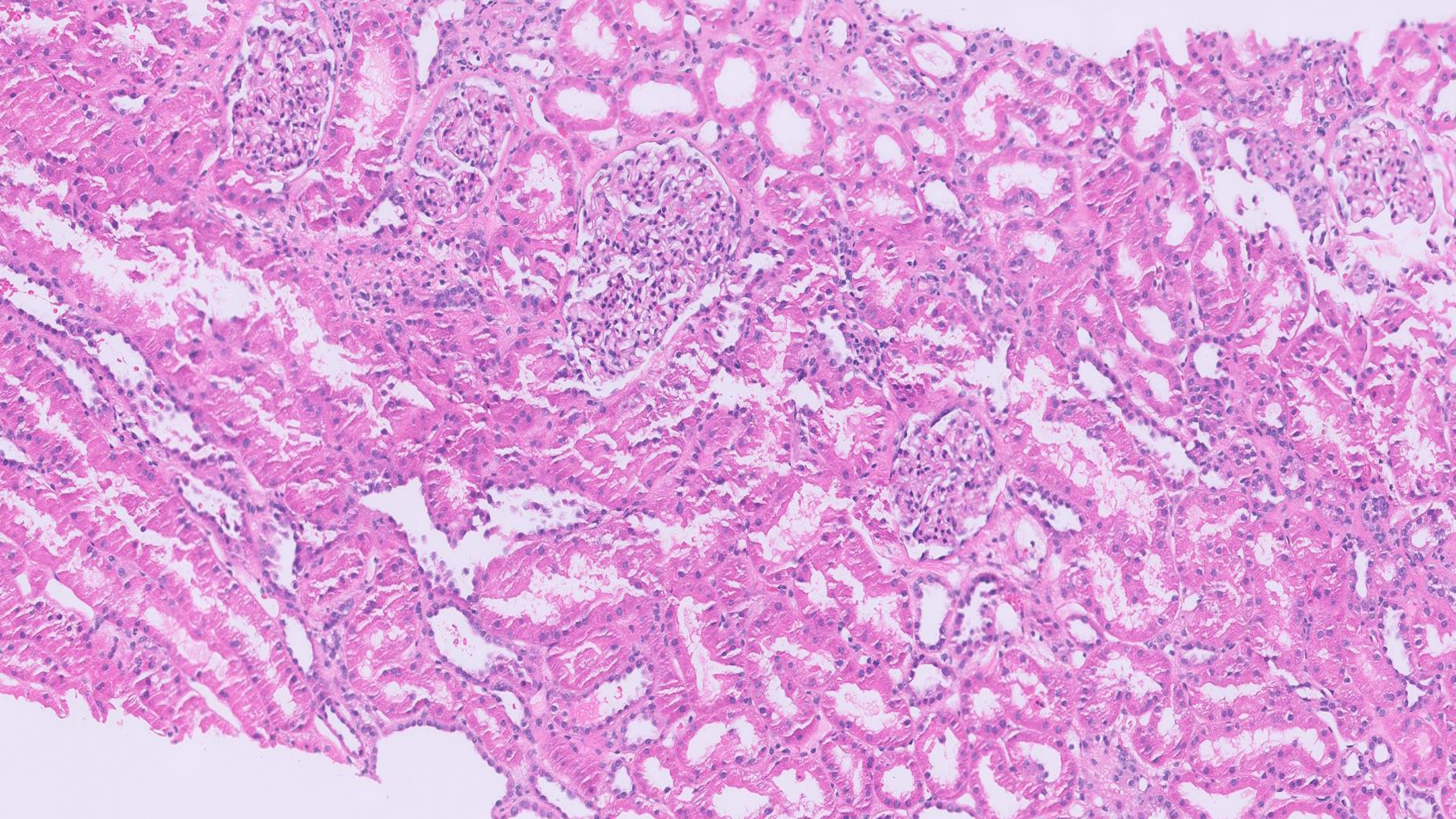

A
Model fit to:
No 2007–09 drought
No 2012–15 drought
Observed (fitted model)
Observed (data)
March, 2007, to November, 2009
March, 2012, to October, 2015
Cases per month
1200
900
600
300
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Year

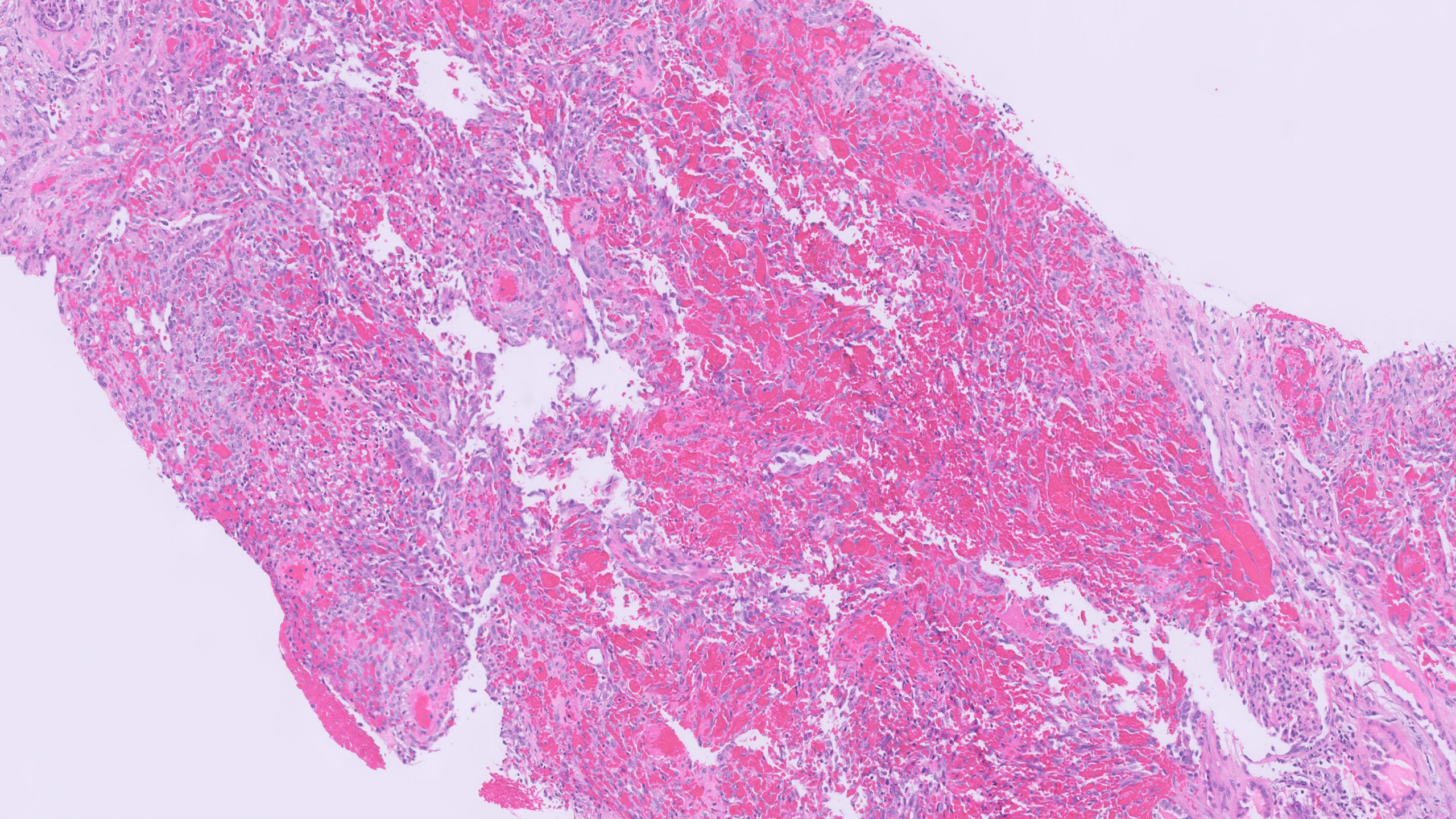
24-0705

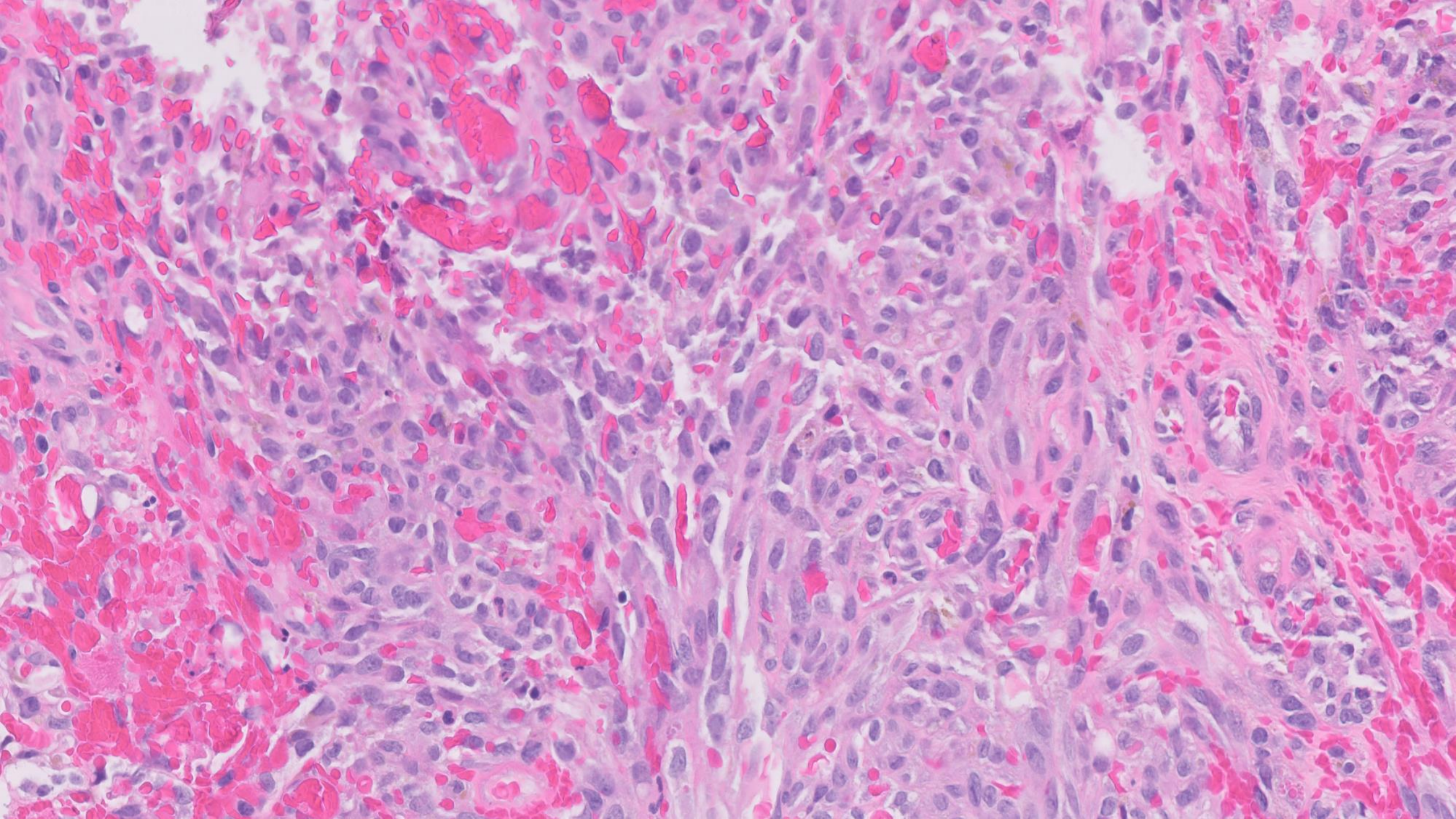
Cooper Rutland, MD (Stanford Surgical Pathology Fellow), Megan Troxell, Stanford, Lucy Han, MD (CPMC, Sutter Health)

39 year old male with history of kidney and pancreas transplant with a recent rise in creatinine.

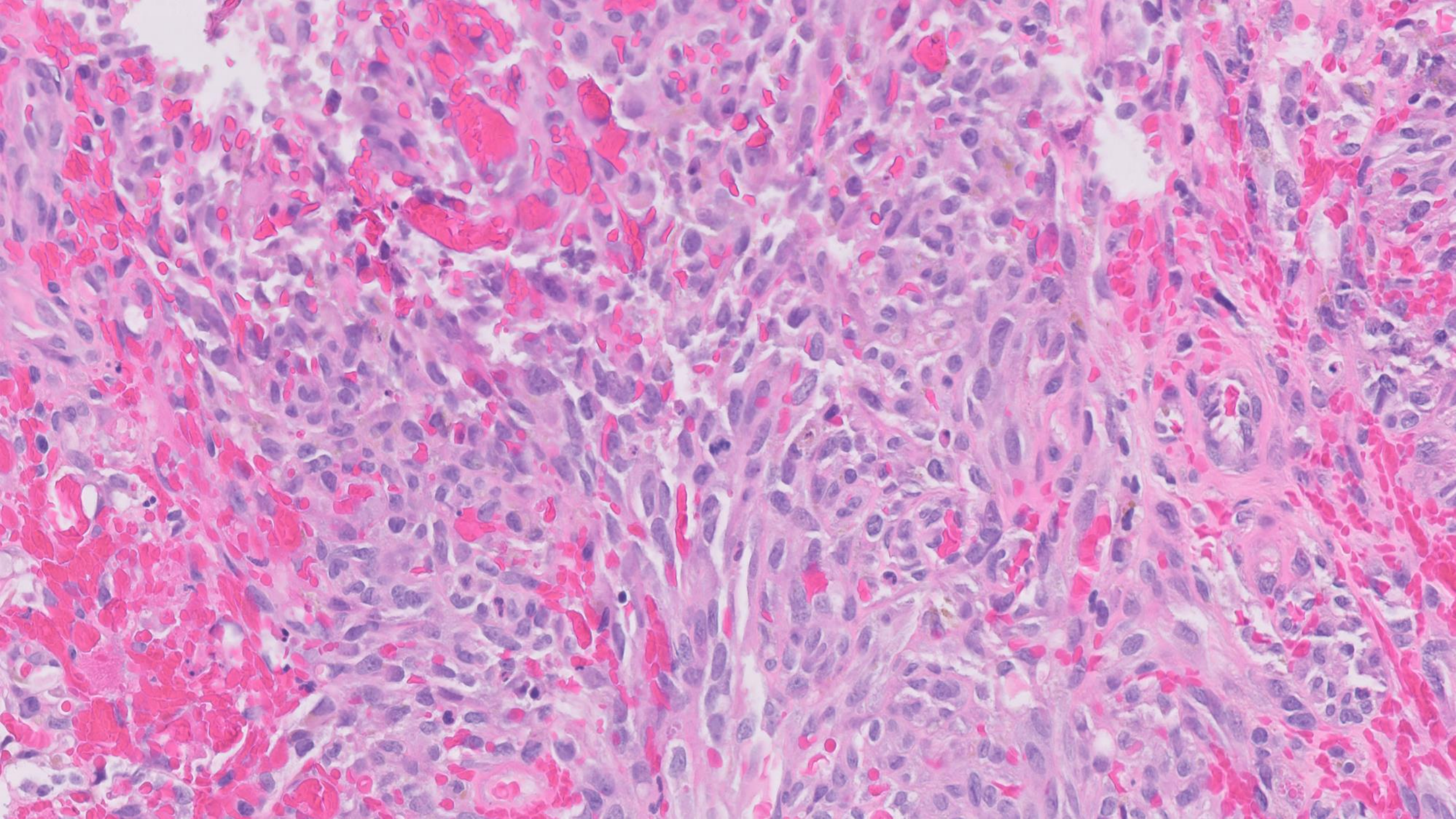








DIAGNOSIS?



Labs

WBC 0.8 (Abs neut 0.3, Abs lymph 0.3)

Plt 5

Hemoglobin 8.7

Cr 2.55 (up from 1.50, 2 months prior)

US Kidney Transplant

FINDINGS:

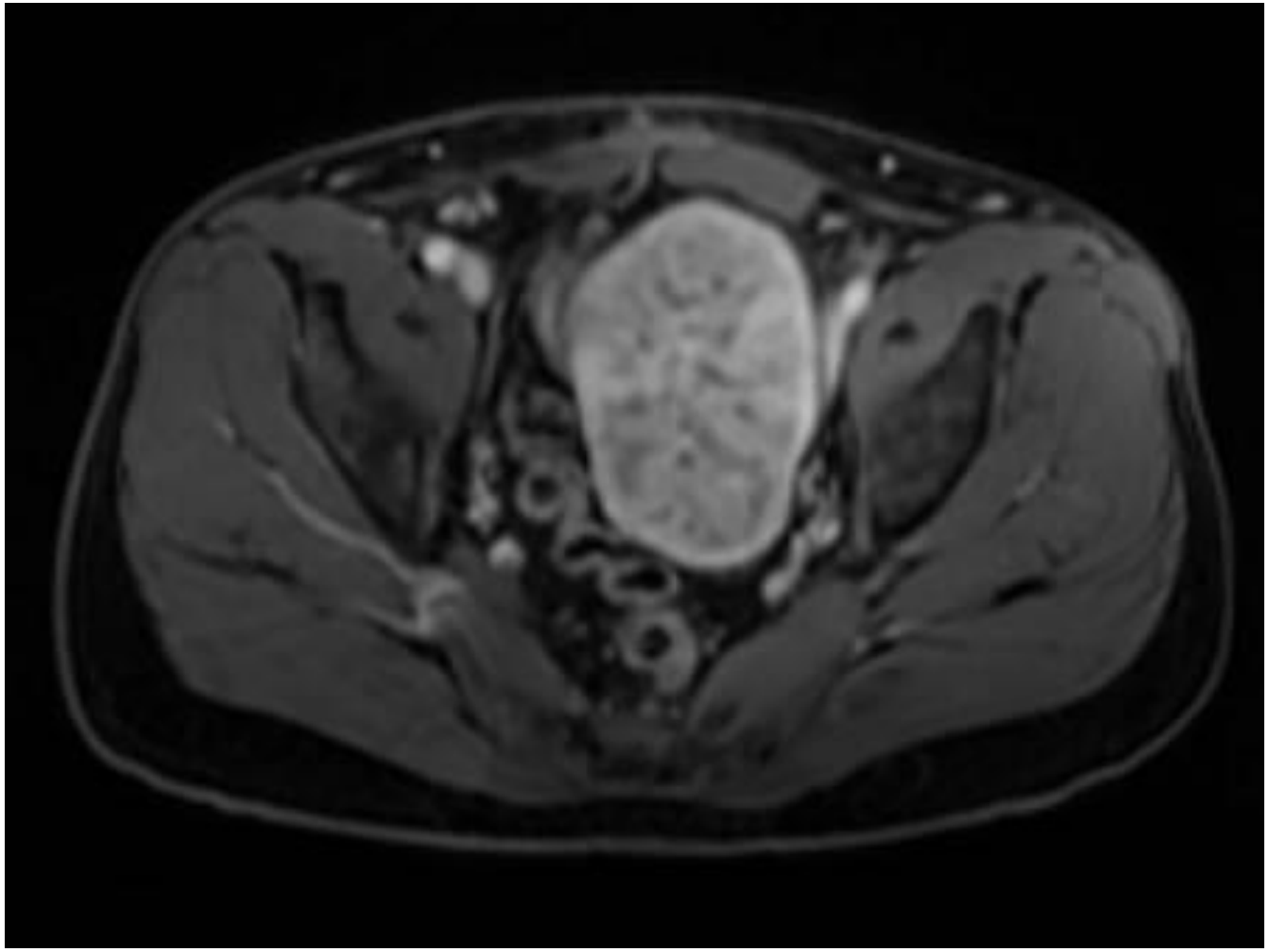
KIDNEY: Transplant kidney is identified within the left iliac fossa. Kidney demonstrates normal morphology with a length of 12.5 cm. Mild hydronephrosis with renal pelvis measuring 16 mm. Ureteral epithelial thickening at 3.4 mm.

FLUID COLLECTIONS: Small fluid collection at superior pole measuring 3.4 x 1.8 x 1.5 cm, similar to slightly increased in the prior.

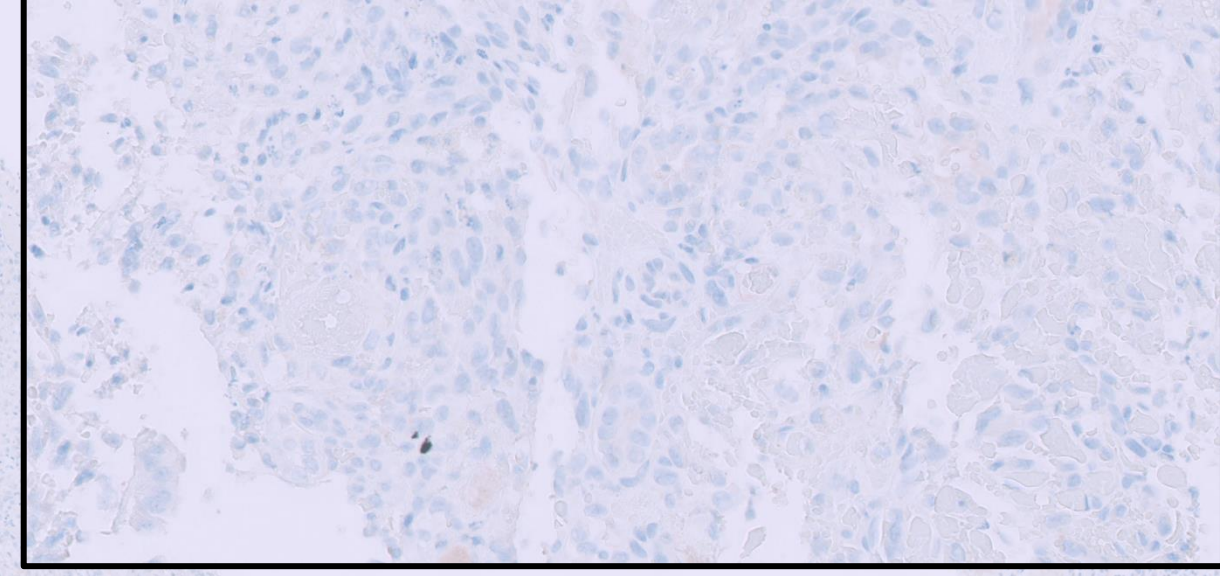
MRI Pelvis

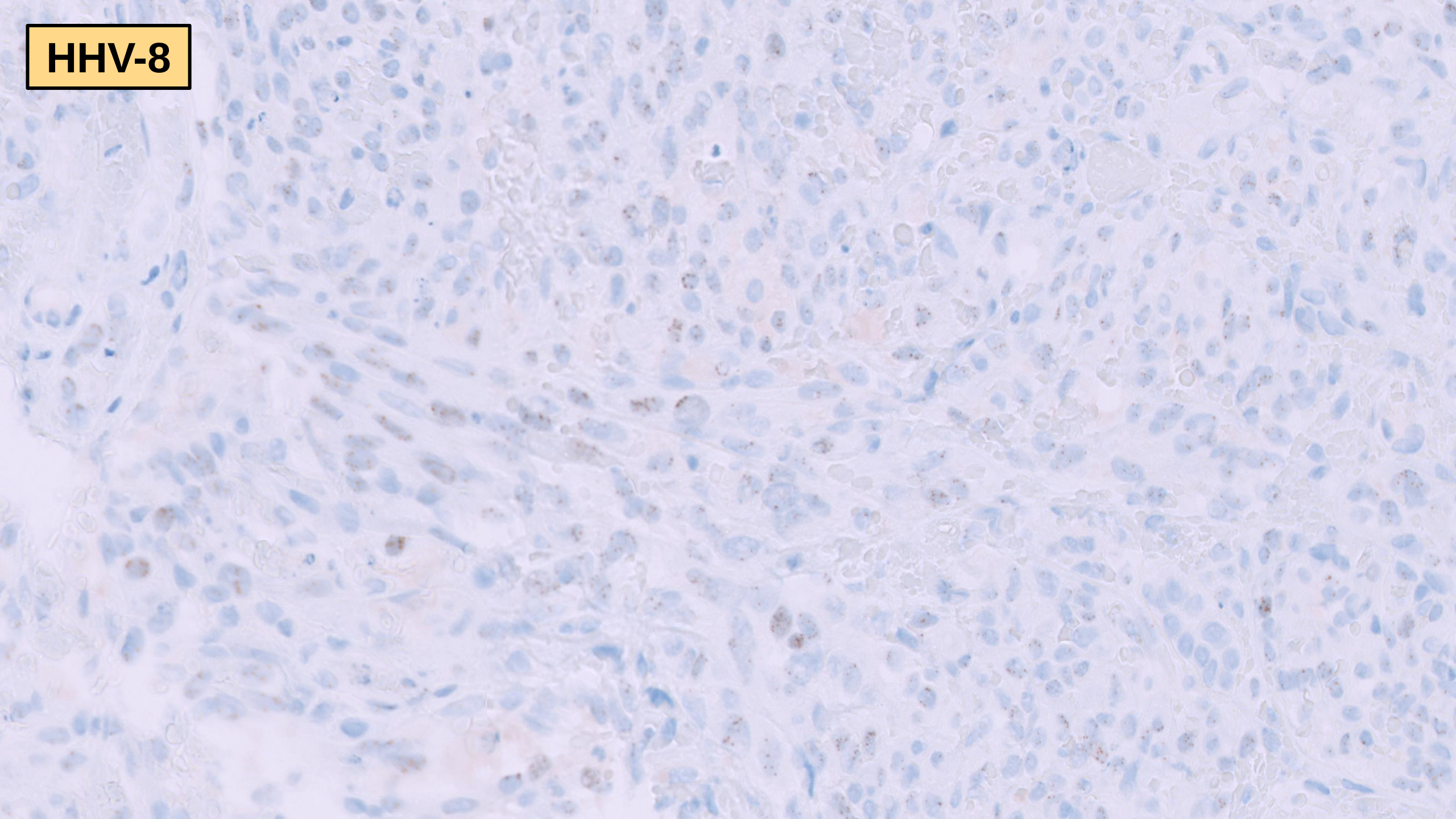
IMPRESSION:

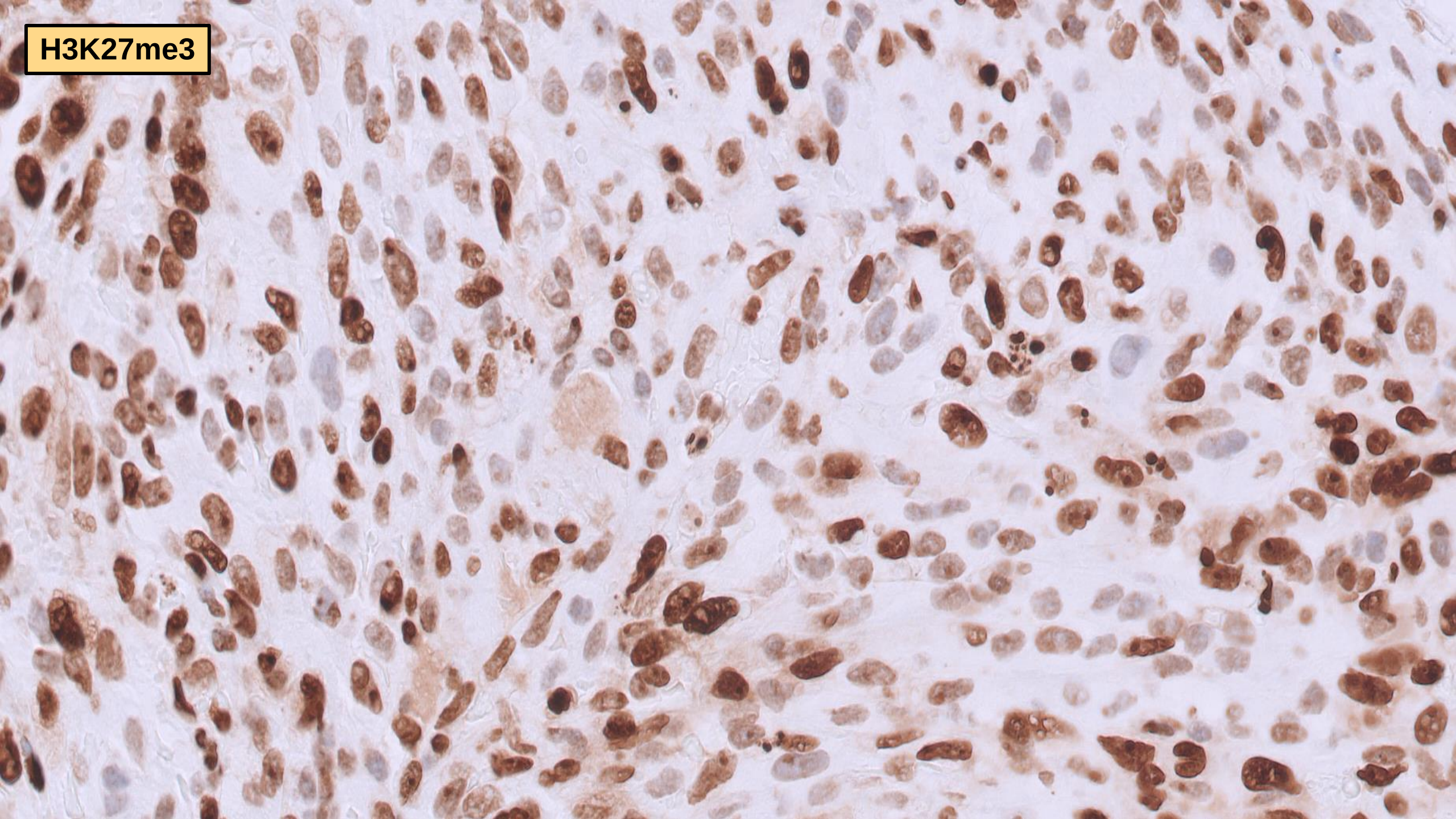
1. Abnormal enhancement pattern of transplant kidney without focal mass, suggesting a diffuse process. Considerations include a neoplastic process, bilateral nephritis, acute tubular necrosis, drug effect, or rejection, although the enhancement pattern is somewhat atypical for rejection…the findings could very well represent an infiltrative neoplasm.



CMV



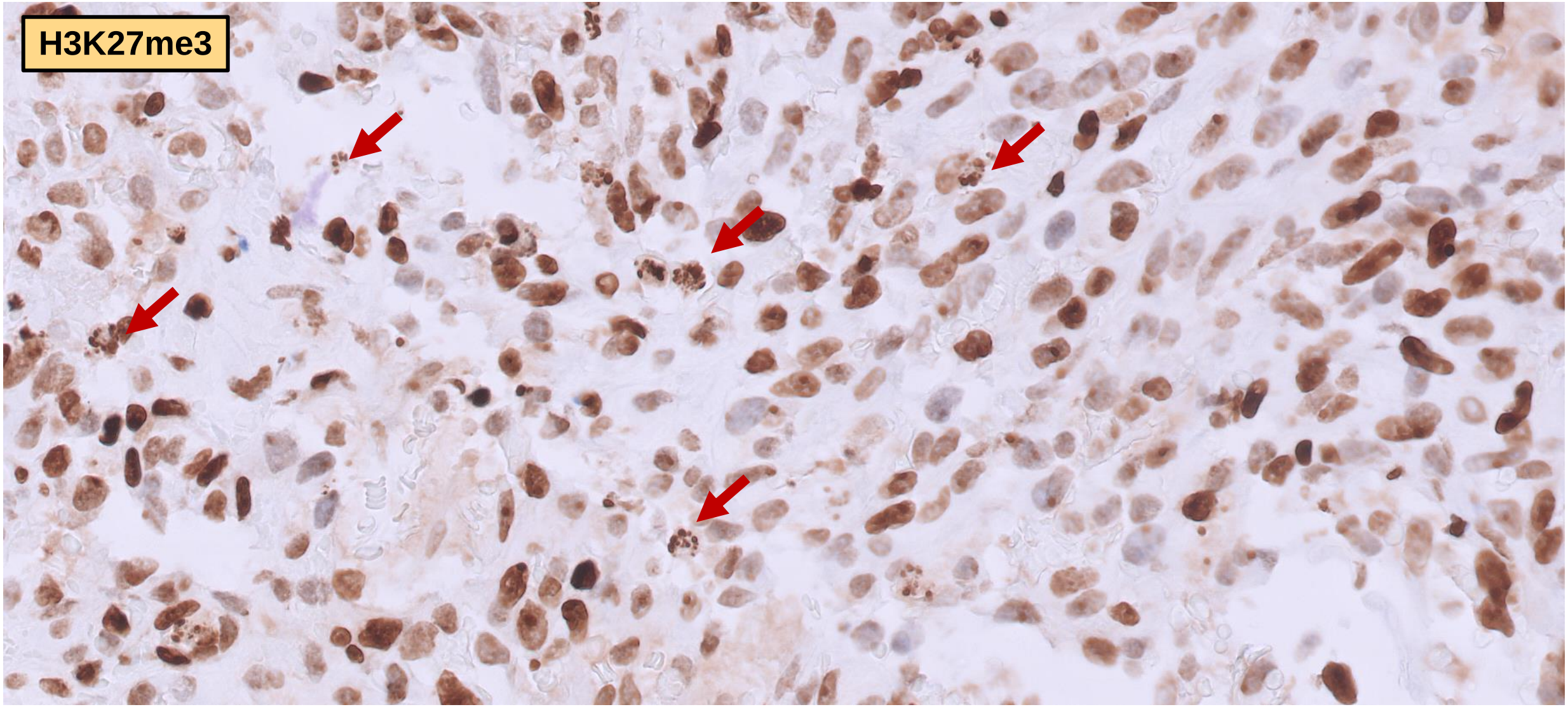

HHV-8

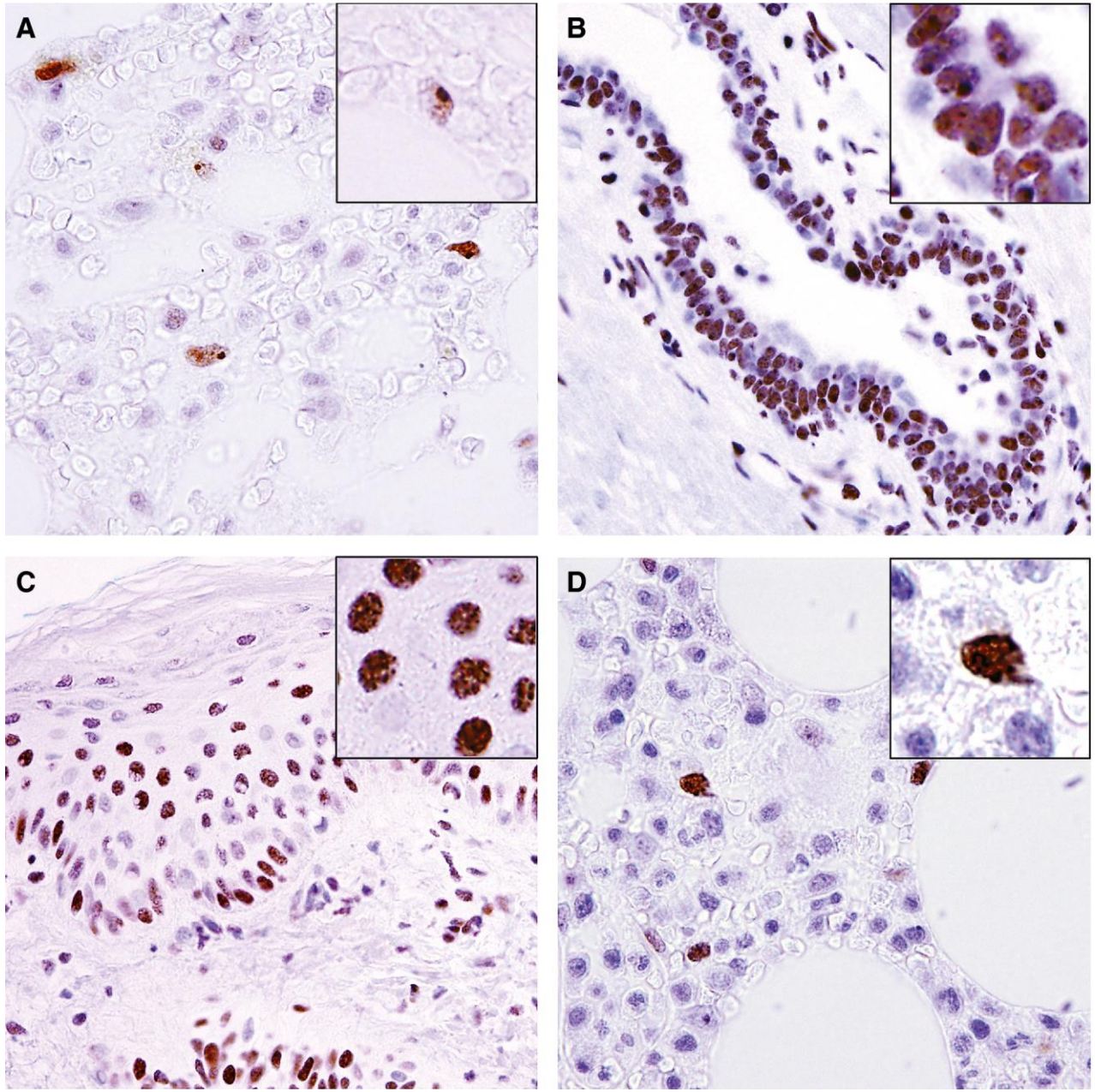

H3K27me3

39 year old *male*

A. Allograft kidney, left, core biopsy:

- **Kaposi sarcoma, involving renal parenchyma**





Histopathology

Correspondence | Full Access

H3K27me3 immunohistochemistry highlights the inactivated X chromosome (Xi) and predicts sex in non-neoplastic tissues

Inga-Marie Schaefer, Alissa Minkovsky, Jason L Hornick

In bone marrow from a male patient with chimerism after a bone marrow transplant from a female donor, the inactivated X chromosome is detectable in haematopoietic cells (**A**, inset). The inactivated X chromosome is present in breast tissue from a patient with Klinefelter syndrome (**B**, inset) but not in skin (**C**, inset) and bone marrow (**D**, inset) from two patients with Turner syndrome. Of note, staining in bone marrow is limited to a small subset of cells.

Kaposi Sarcoma

- Locally aggressive endothelial proliferation
- Cutaneous lesion >> Mucosal sites, lymph nodes, visceral organs
- Nodal and visceral disease can occur without mucocutaneous lesion

Kaposi Sarcoma—Etiologies/Subtypes

- Classic KS: reddish-purple/dark-brown macules, plaques; distal extremities; *indolent* with rare nodal and visceral involvement
- Endemic KS: localized to skin with protracted course; lymphadenopathic form rapidly aggressive and highly lethal.
- AIDS-associated KS: most aggressive; more frequent in advanced immunosuppression
- **Iatrogenic KS:** Uncommon; developing months-to-years after solid-organ transplant or immunosuppressive treatment

Iatrogenic Kaposi Sarcoma

- May resolve upon immunosuppression withdrawal
  - Course may be “unpredictable”

› Cancer. 1993 Sep 1;72(5):1779-83.
doi: 10.1002/1097-0142(19930901)72:5<1779::aid-cncr2820720543>3.0.co;2-m.

The appearance of Kaposi sarcoma during corticosteroid therapy

A Trattner [1], E Hodak, M David, M Sandbank

“Corticosteroids should be withdrawn to achieve clinical remission”

› J Am Acad Dermatol. 1998 Mar;38(3):429-37. doi: 10.1016/s0190-9622(98)70501-8.

Detection of human herpesvirus-8 DNA in Kaposi's sarcomas from iatrogenically immunosuppressed patients

P L Rady [1], E Hodak, A Yen, O Memar, A Trattner, M Feinmesser, M David, S D Hudnall, S K Tyring

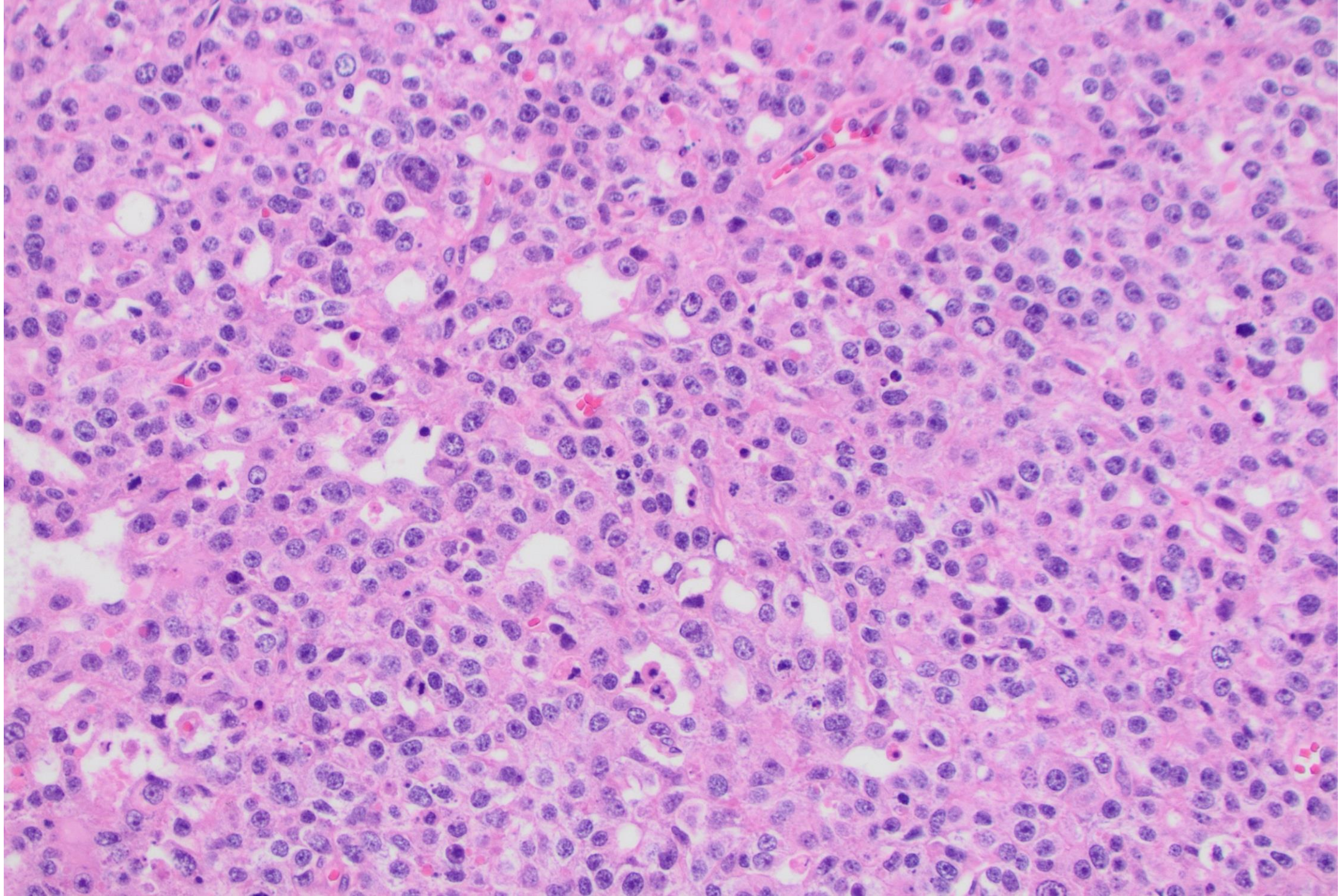
References

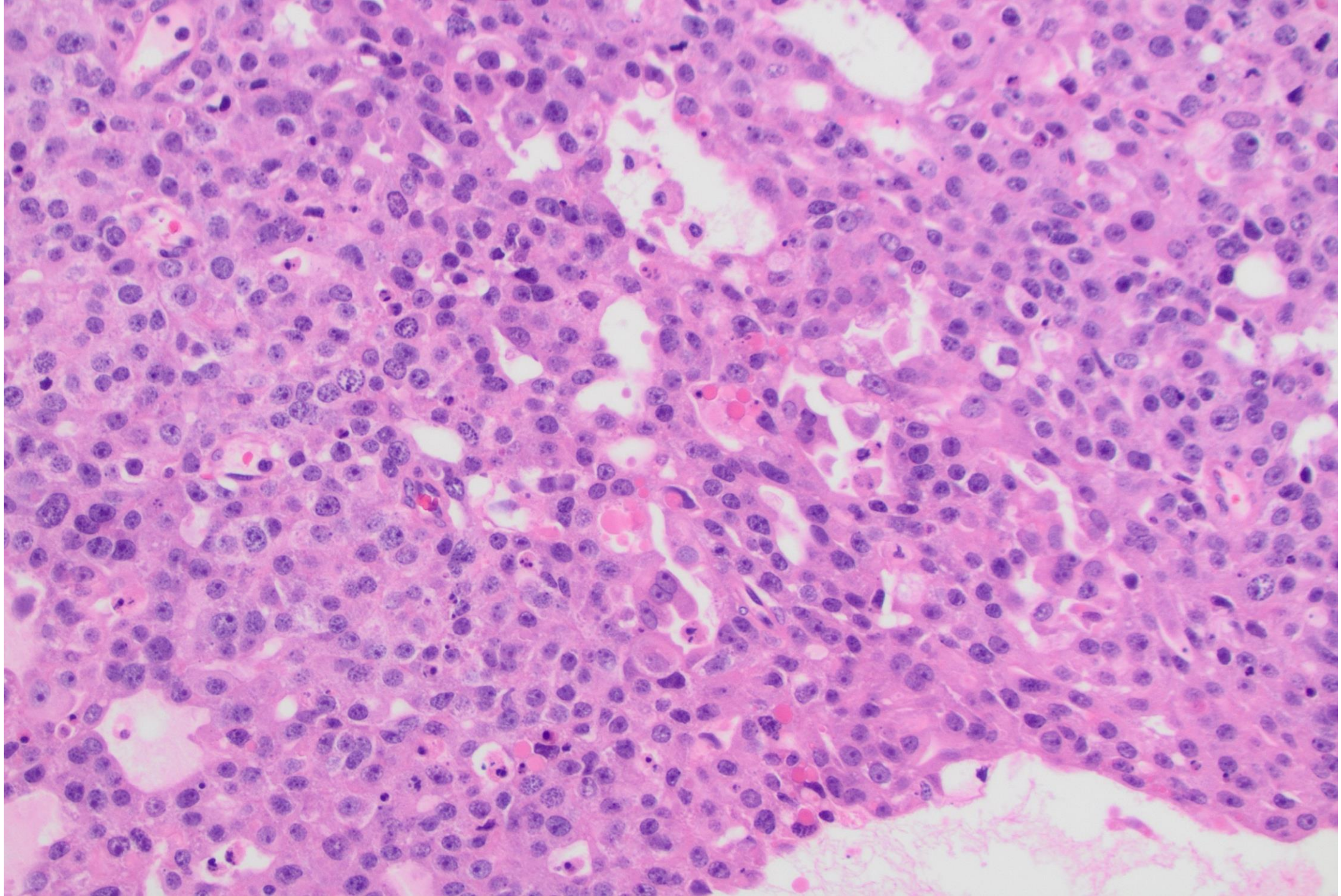
- Rady PL, Hodak E, Yen A, et al. Detection of human herpesvirus-8 DNA in Kaposi's sarcomas from iatrogenically immunosuppressed patients. J Am Acad Dermatol. 1998;38(3):429-437. doi:10.1016/s0190-9622(98)70501-8
- Schaefer IM, Minkovsky A, Hornick JL. H3K27me3 immunohistochemistry highlights the inactivated X chromosome (Xi) and predicts sex in non-neoplastic tissues. Histopathology. 2016;69(4):702-704. doi:10.1111/his.12972
- Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. Cancer. 1993;72(5):1779-1783. doi:10.1002/1097-0142(19930901)72:5<1779::aid-cncr2820720543>3.0.co;2-m
- WHO Classification of Tumors, 5th edition. “Kaposi Sarcoma”.

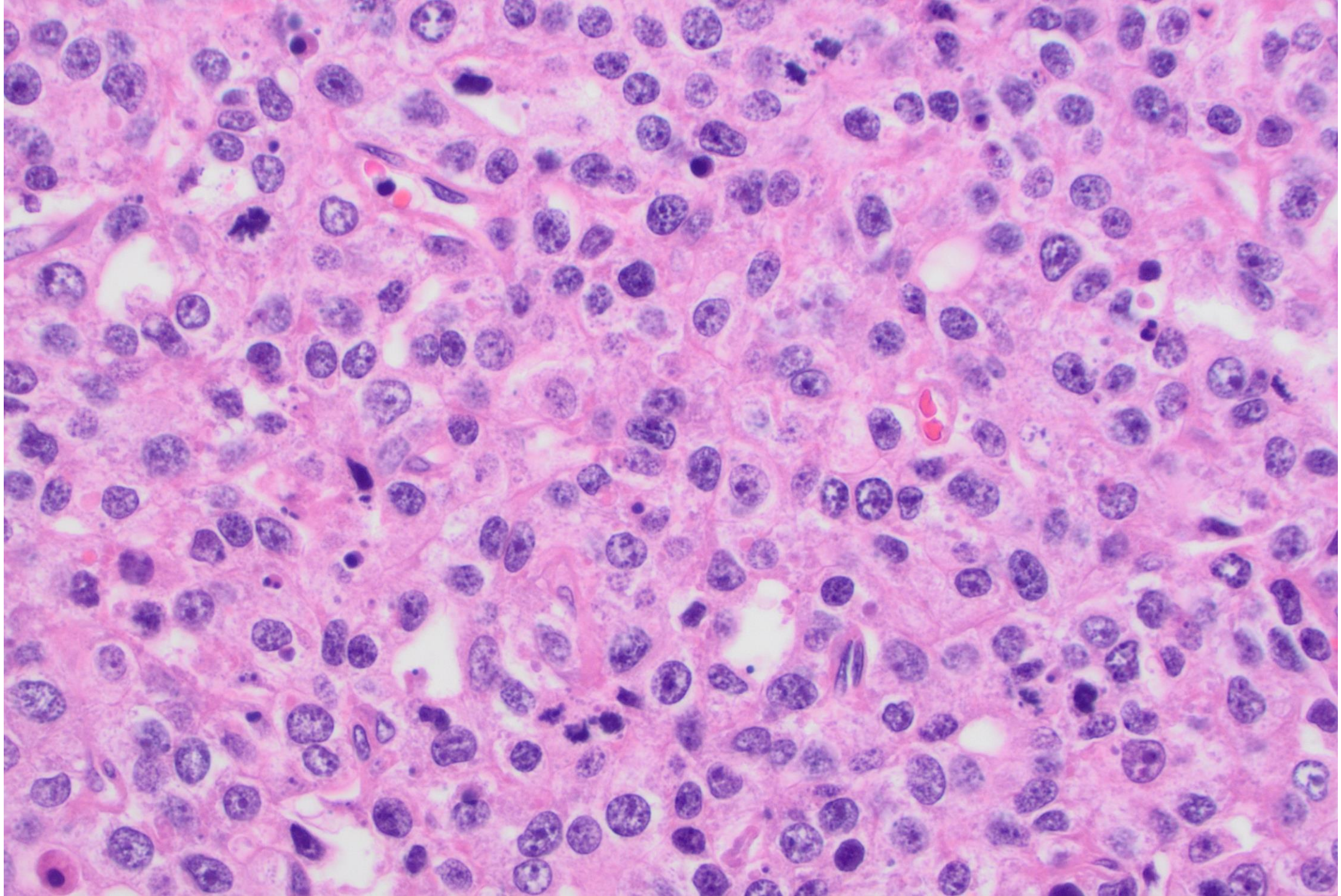
24-0706

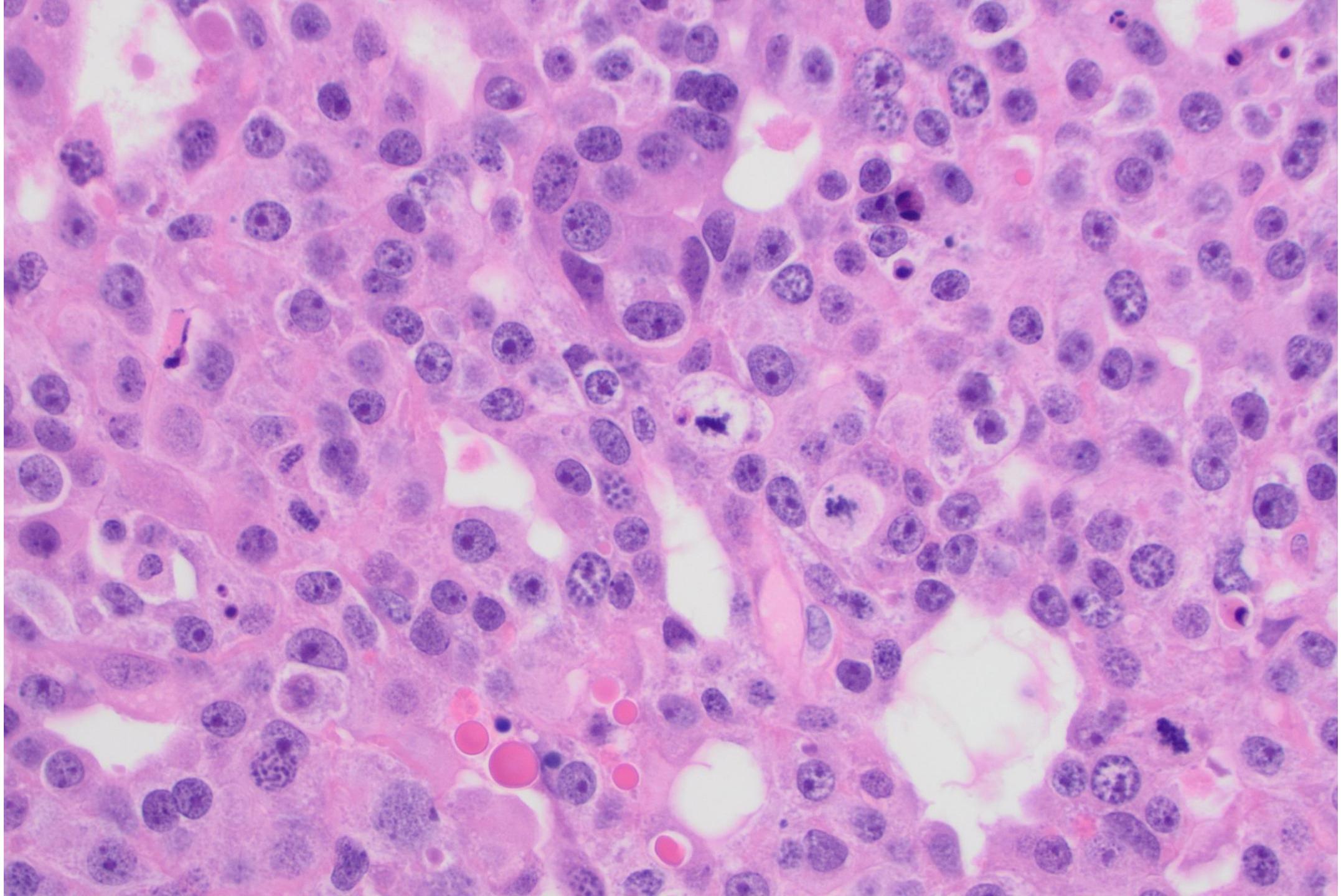
Greg Rumore; The Permanente Medical Group

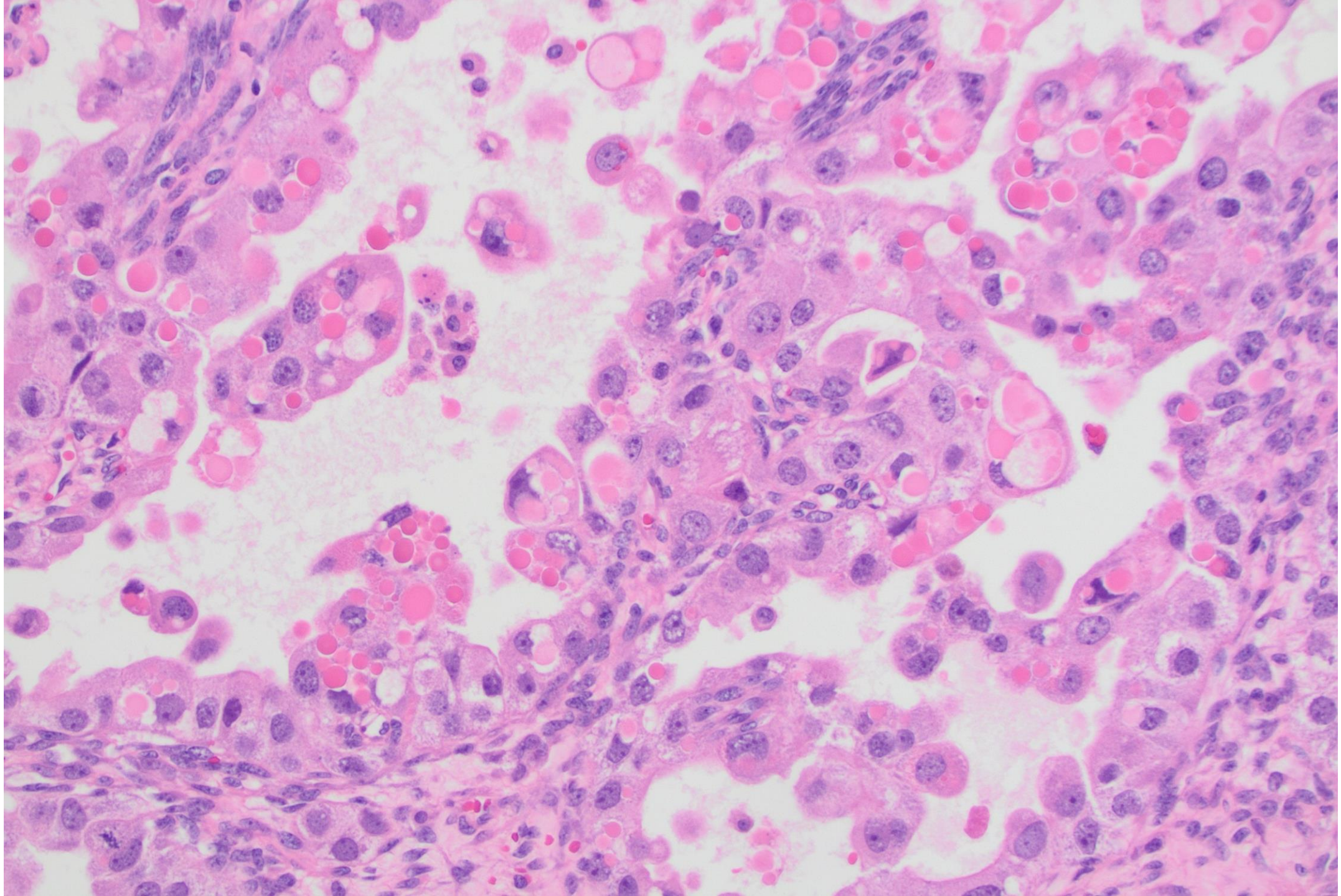
70ish woman with 22 cm R ovarian mass adherent to adjacent structures



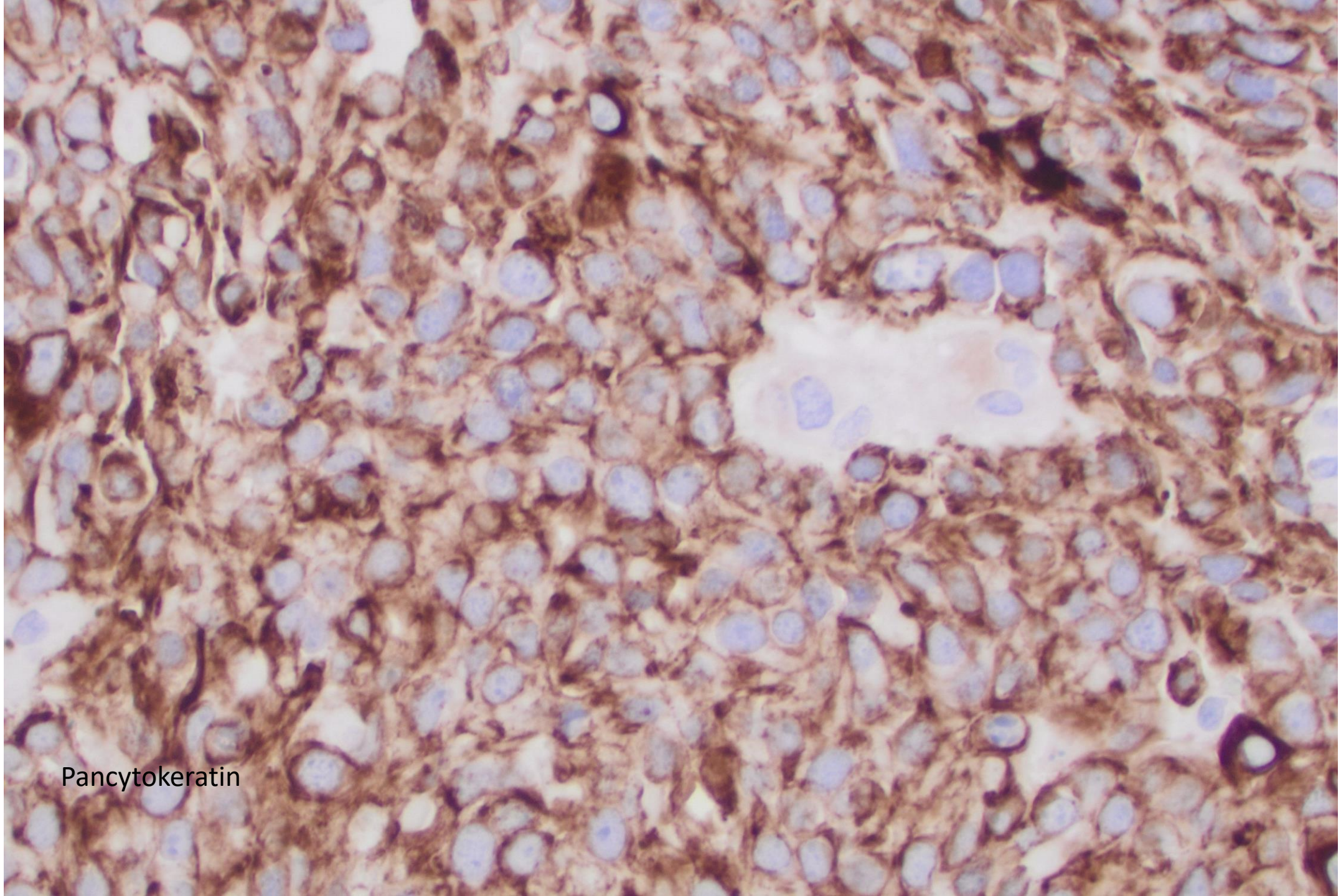








DIAGNOSIS?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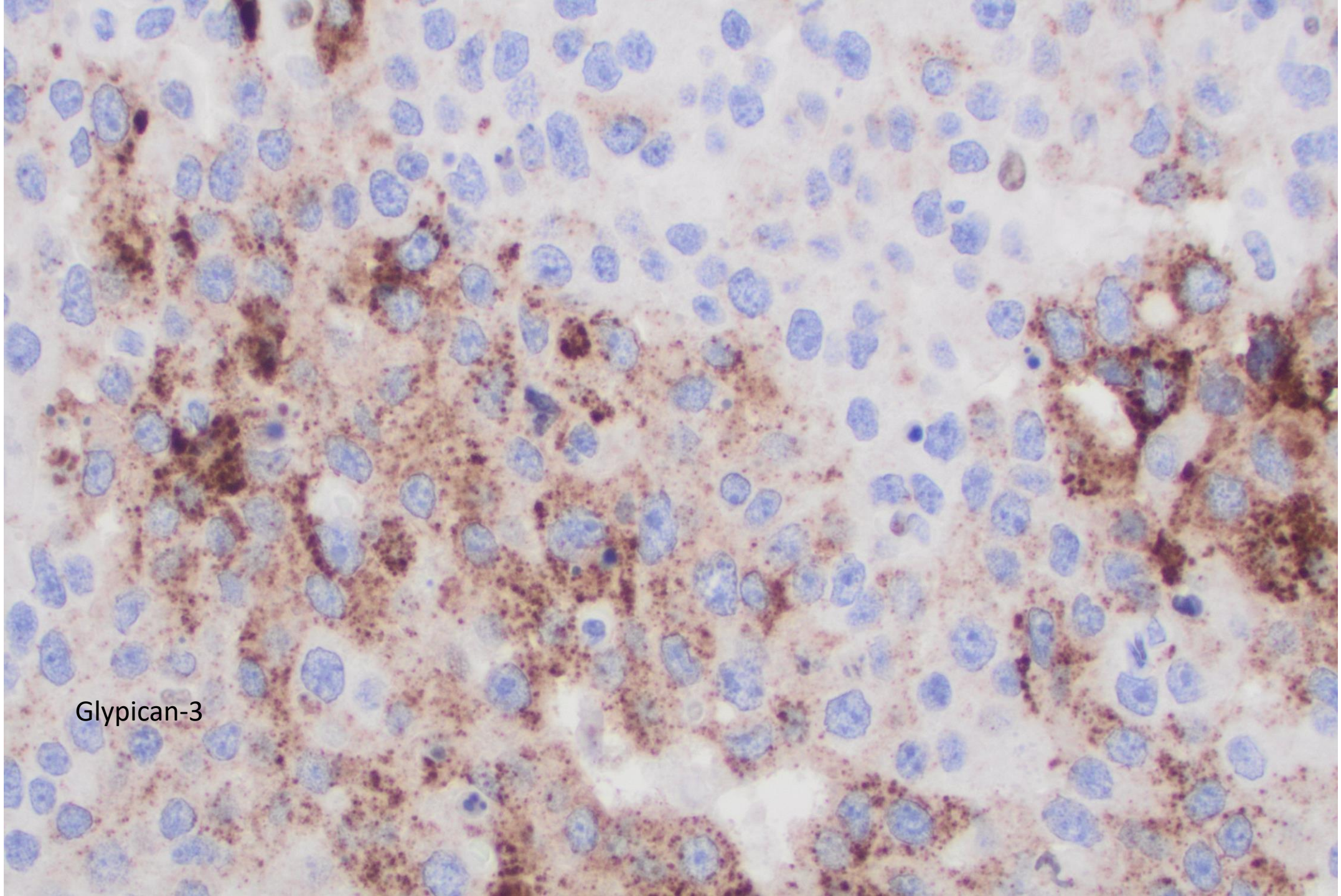
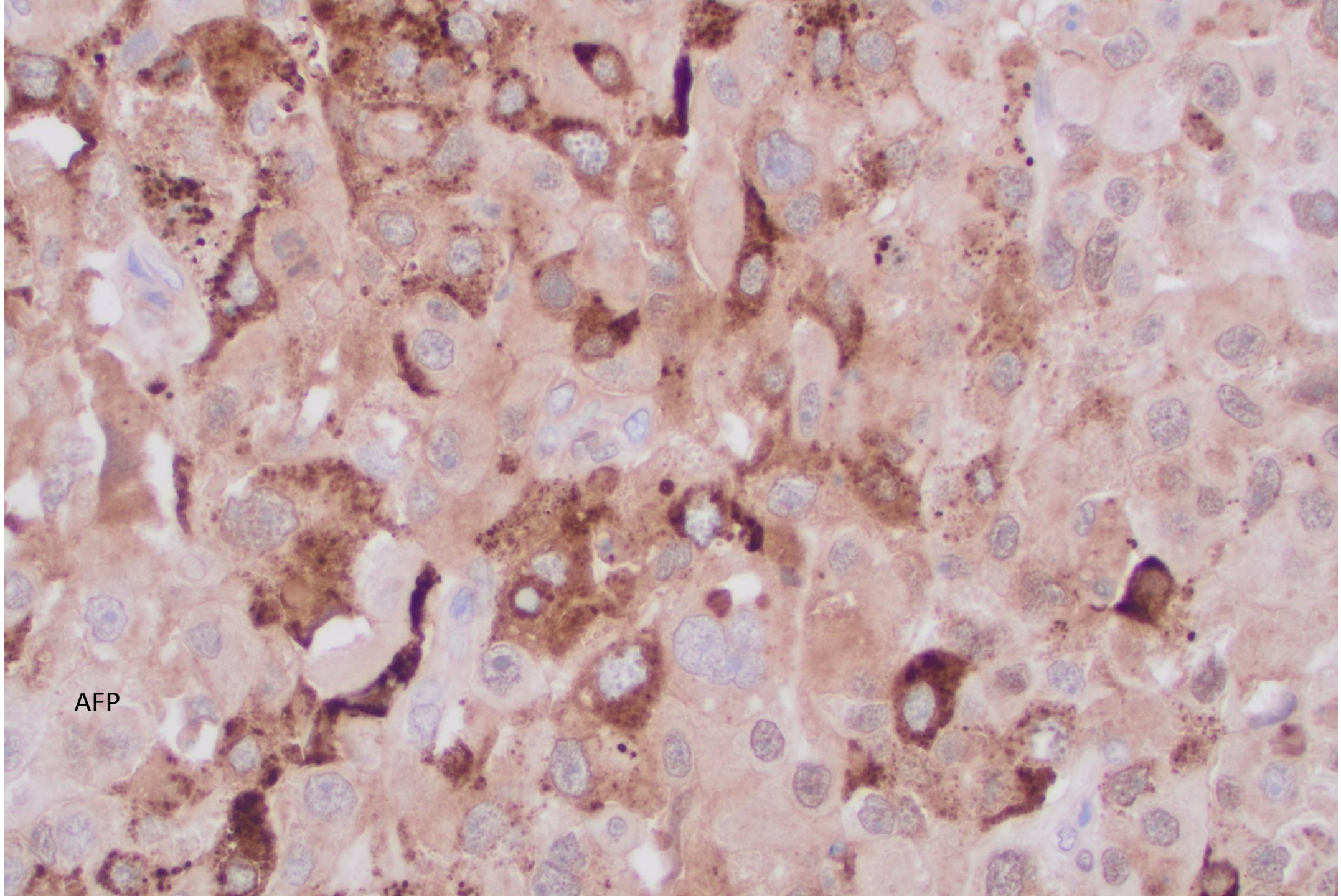
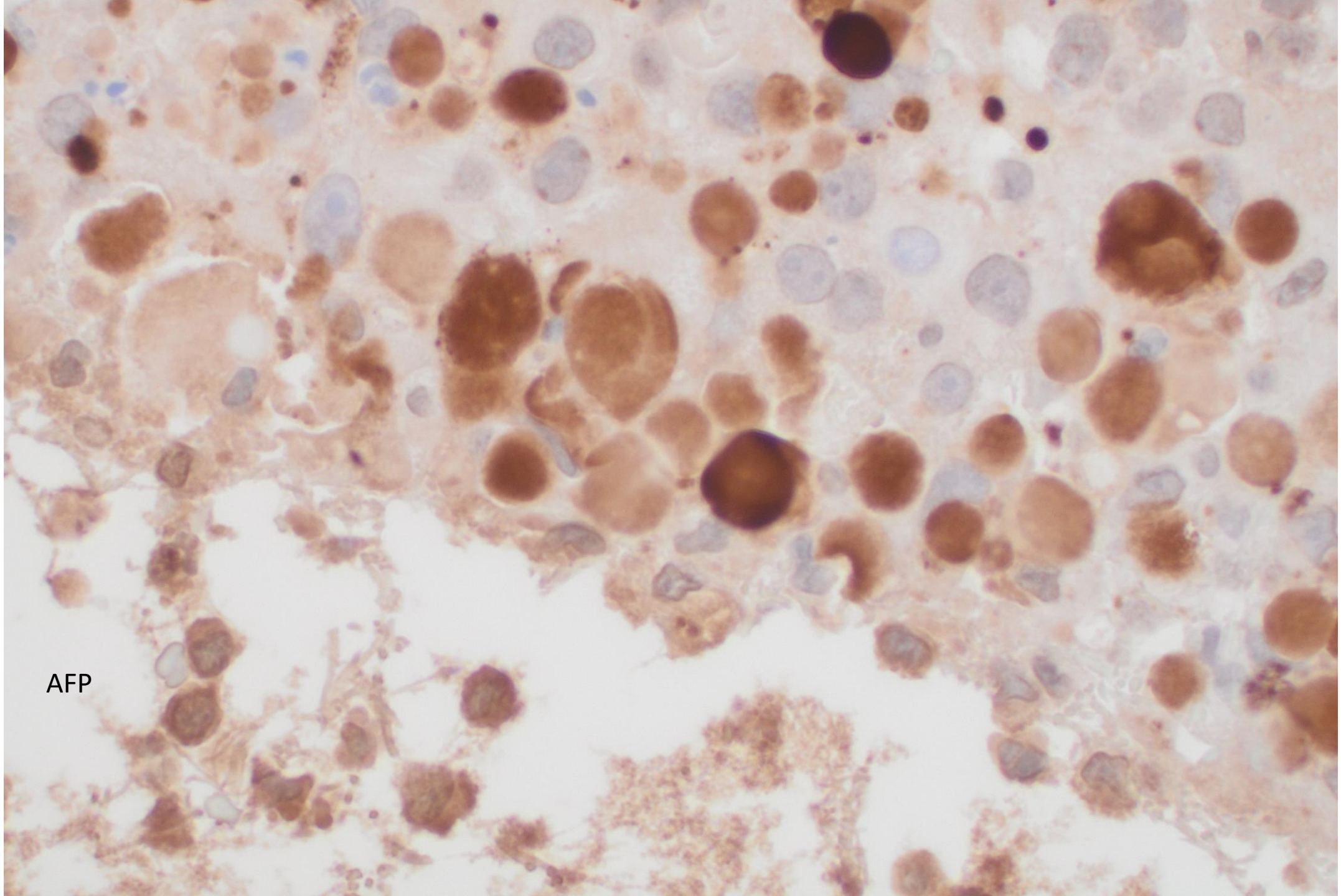

Glypican-3


AFP


AFP

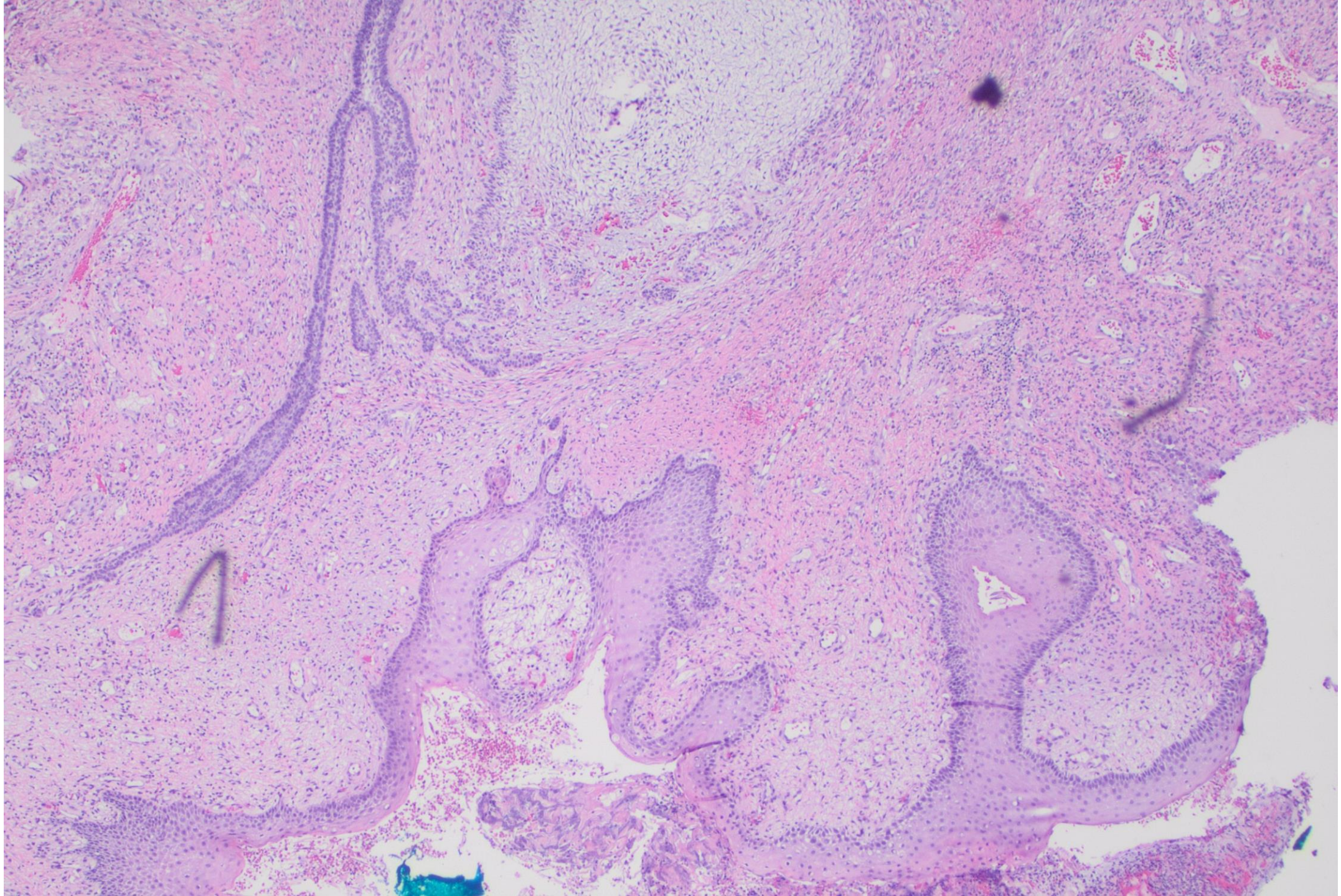
Hepatoid Carcinoma

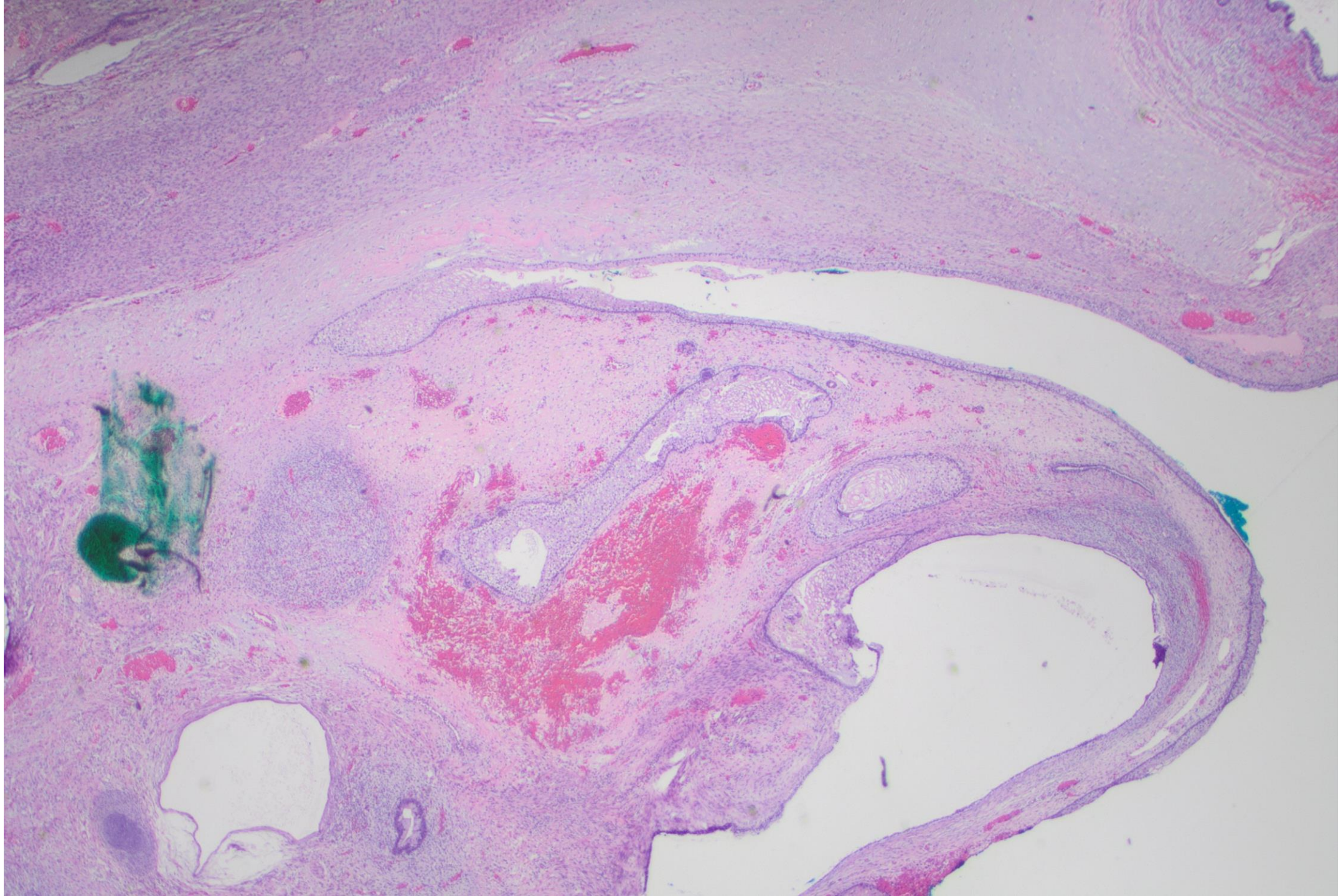
- Rare tumor seen in postmenopausal females
- Micro-resembles hepatocellular CA
- Sheets, trabeculae, and cords of cells with granular eos. cytoplasm
- Hyaline globules
- May have elevated serum AFP (this case peaked at 29K, 6 wks postop)
- May be associated with other surface epithelial CA's (esp. serous)
- Histologic DDX- metastatic HCC, hepatoid YST

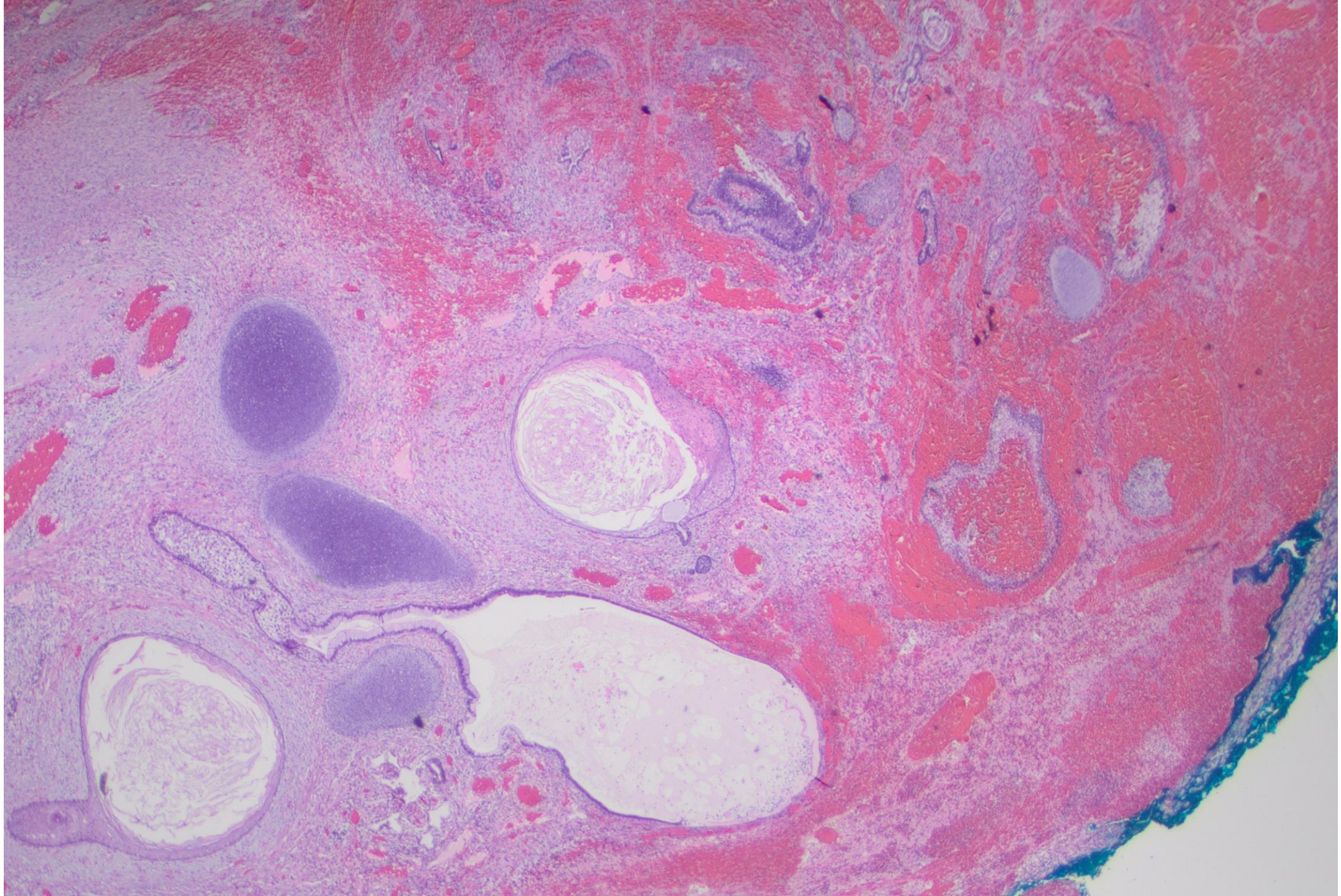
24-0707

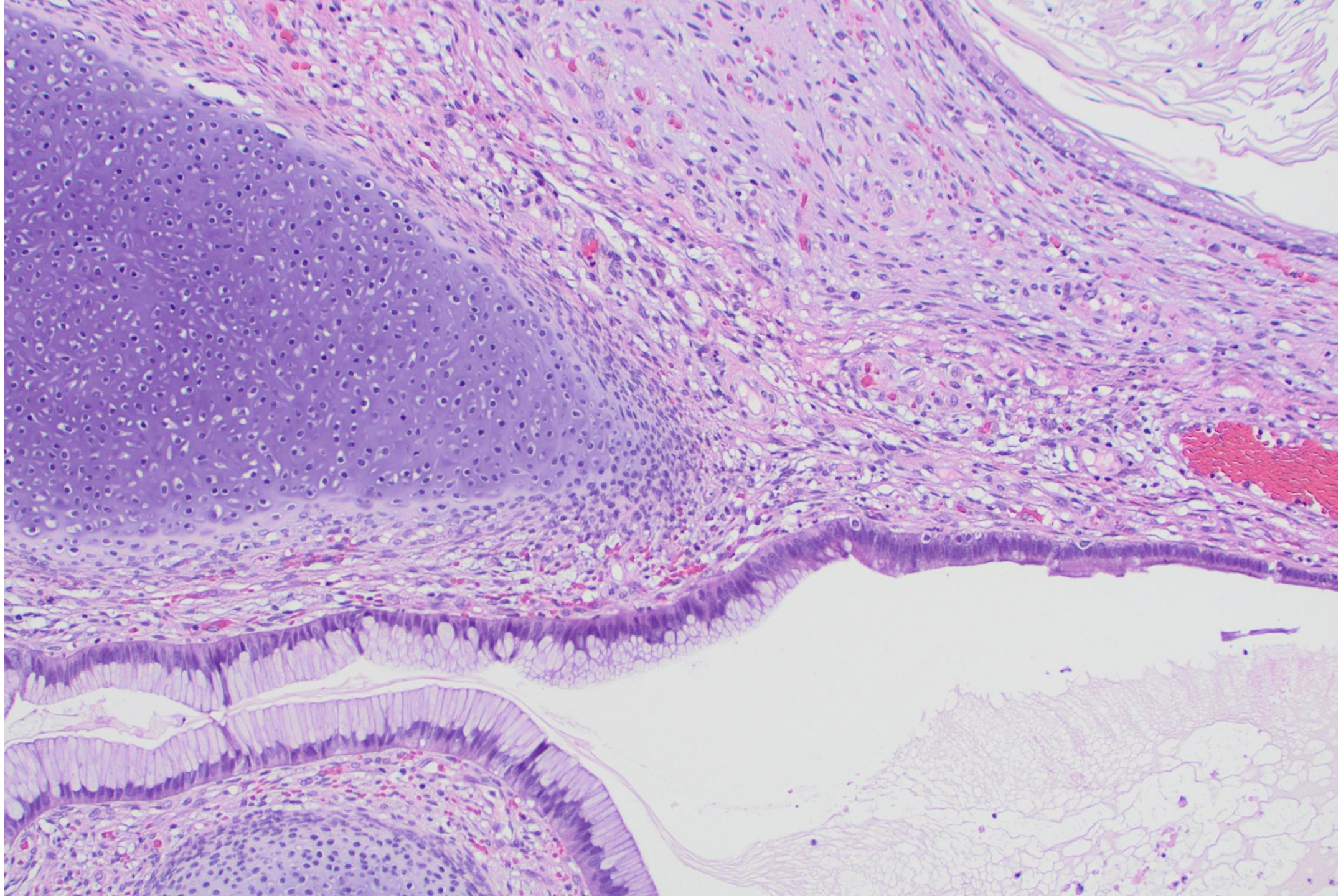
Greg Rumore; The Permanente Medical Group

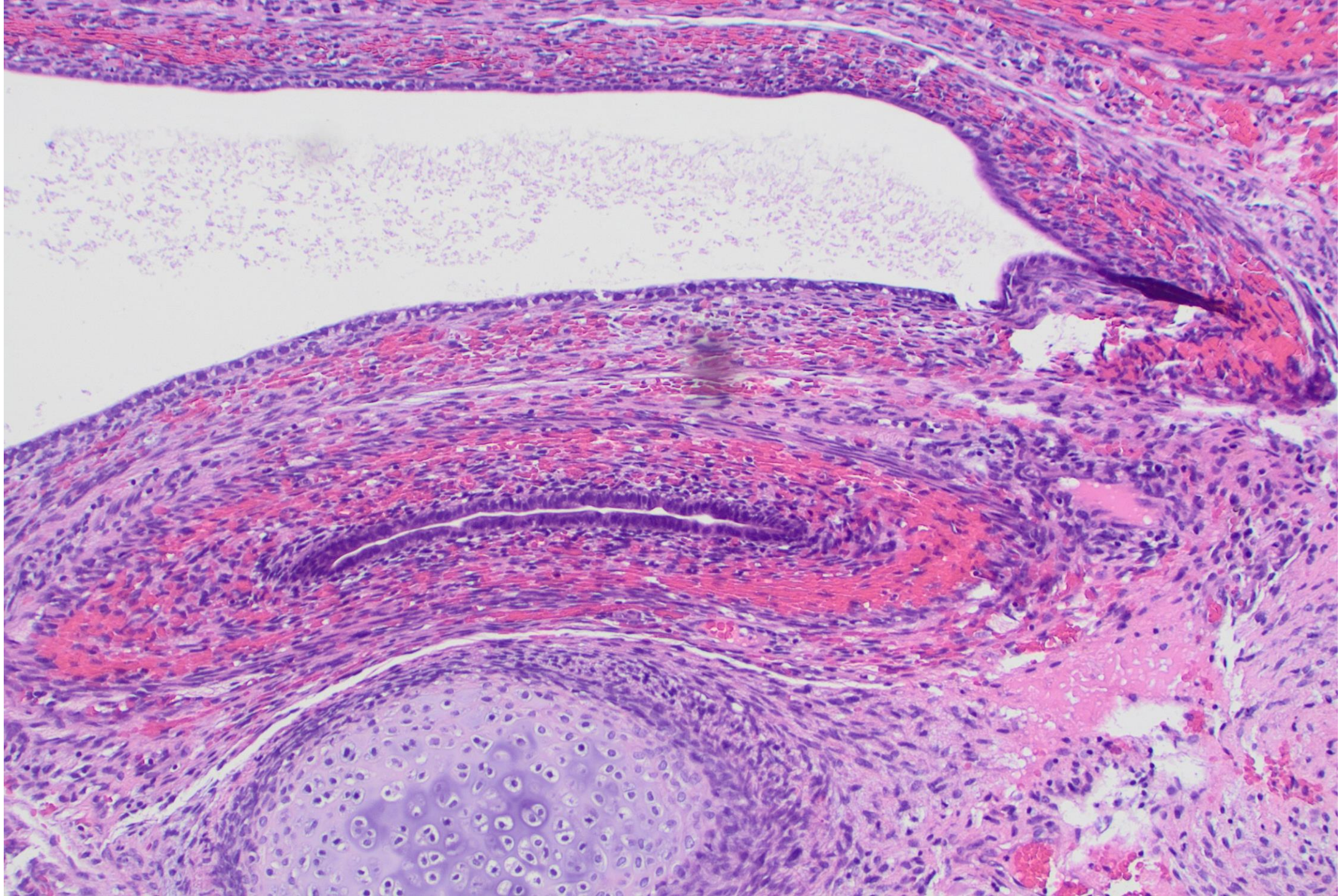
27 y.o. with prolonged heavy periods. U/S- endometrial and LUS polyps. Ovaries WNL.

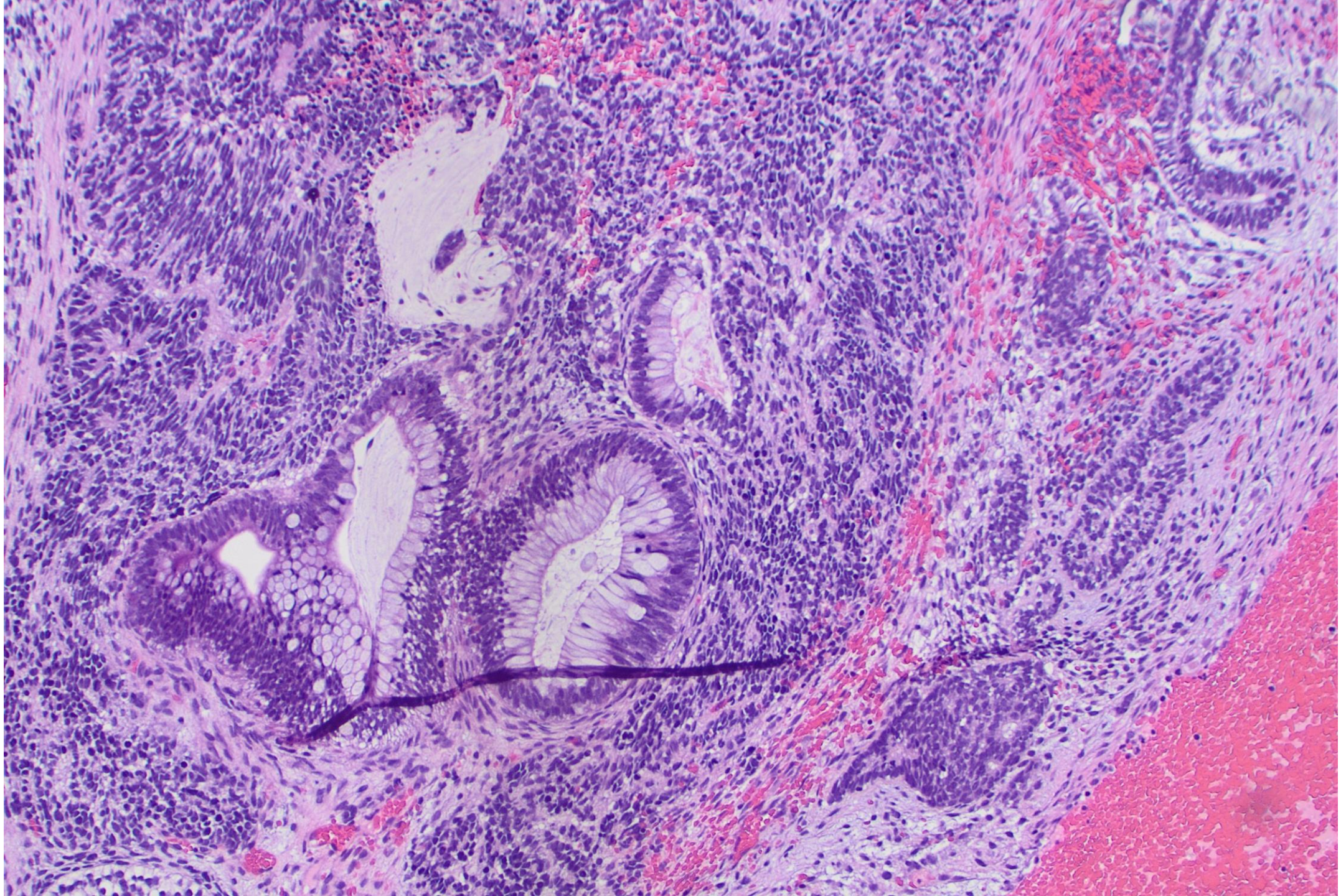


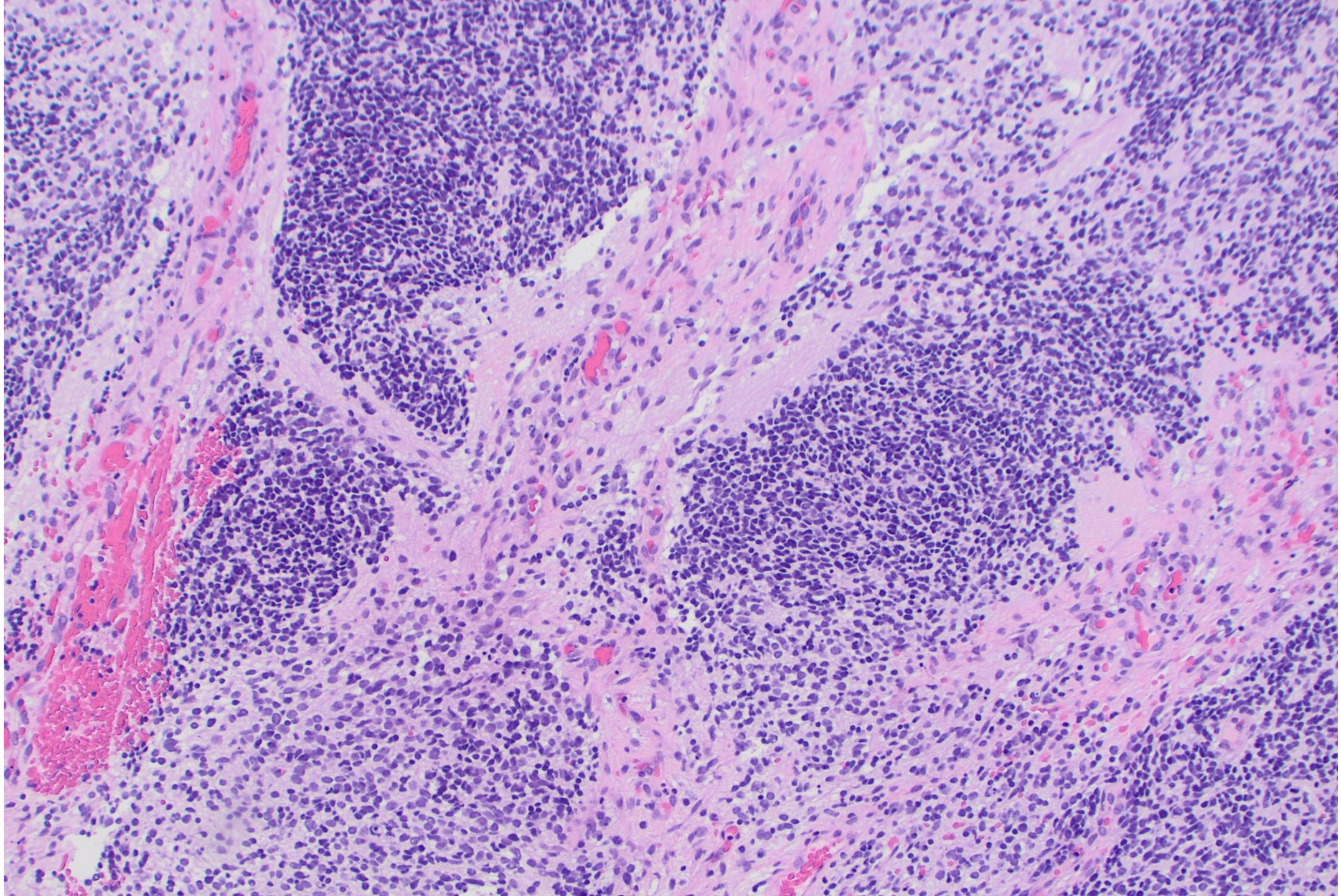


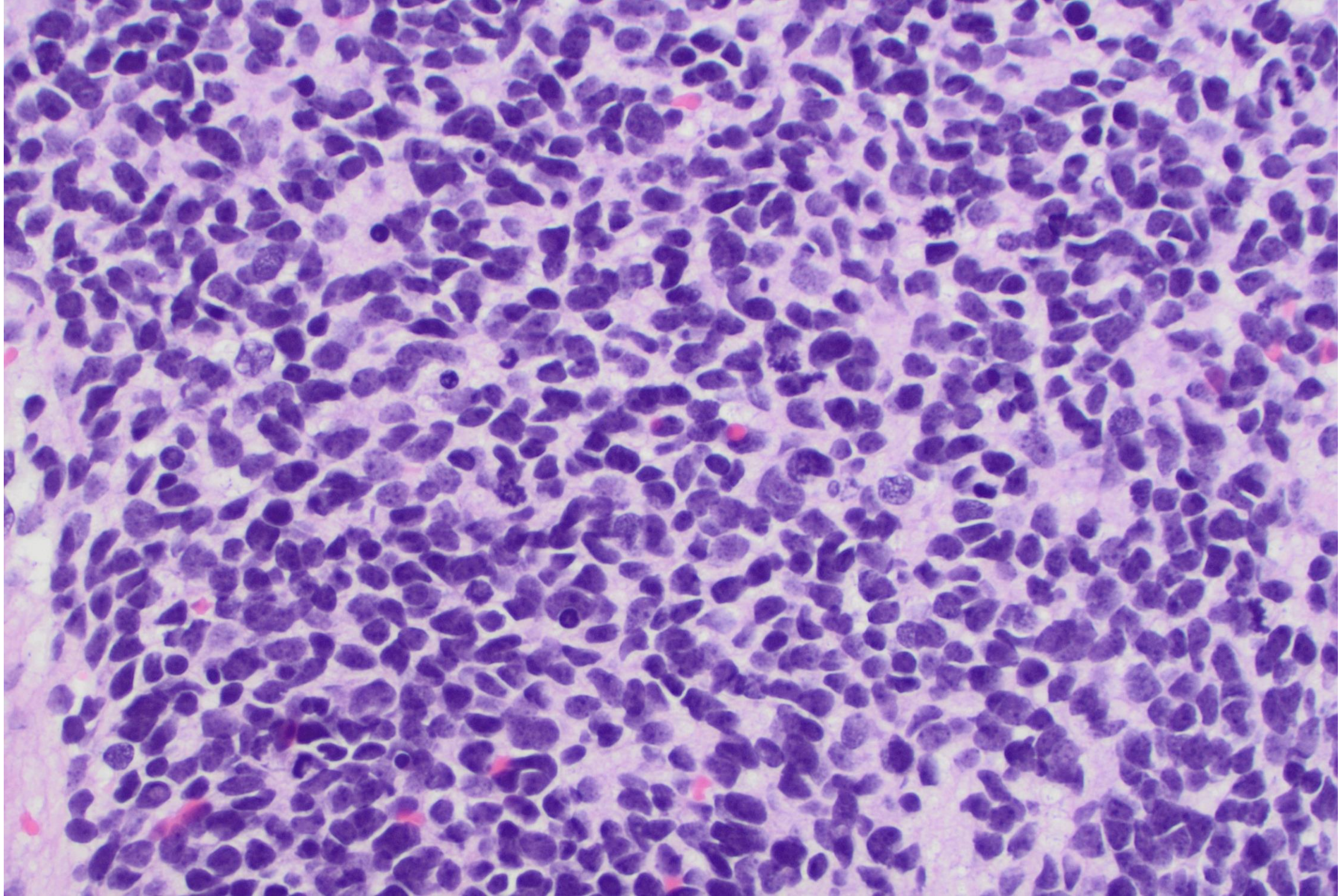


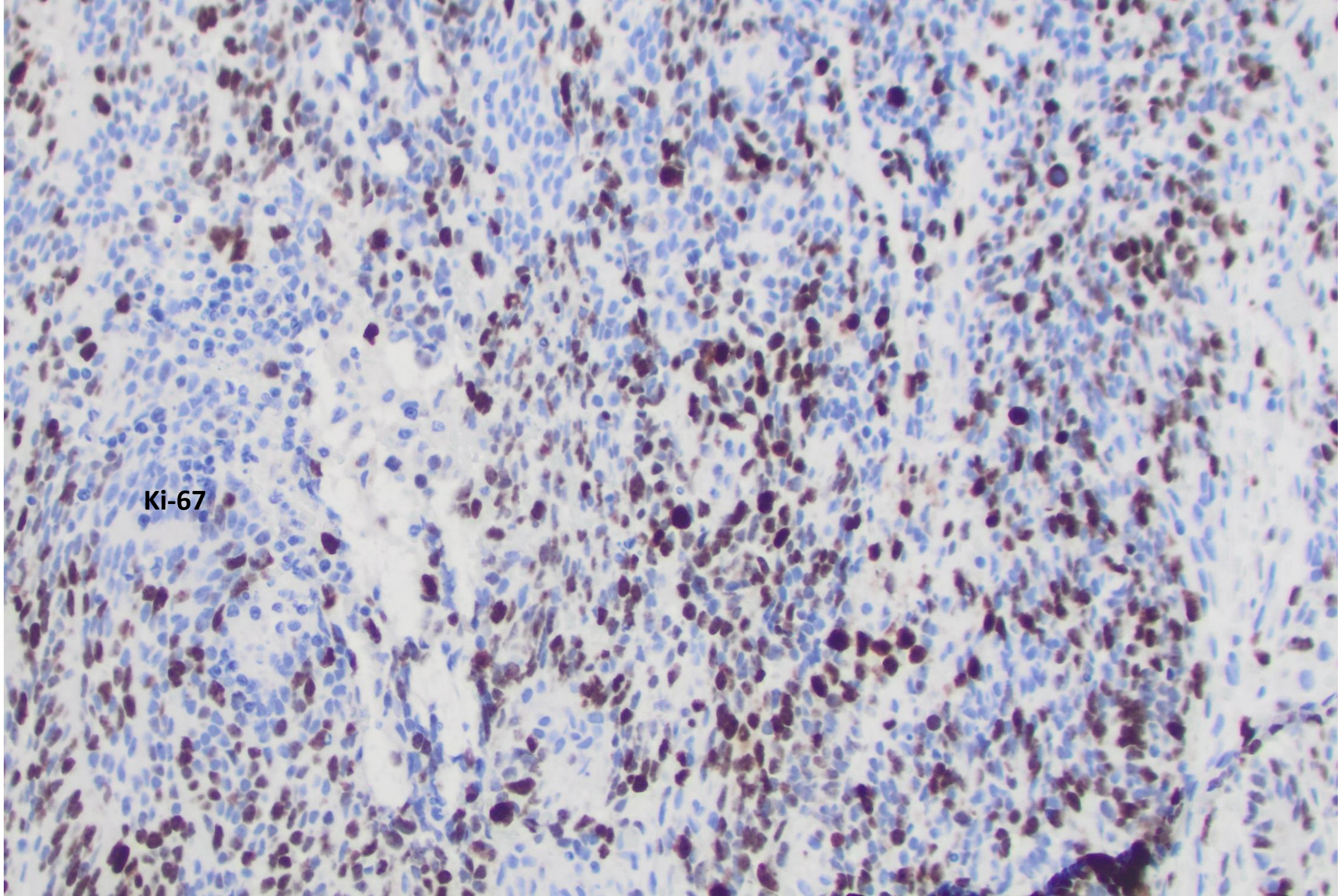











Ki-67

DIAGNOSIS?

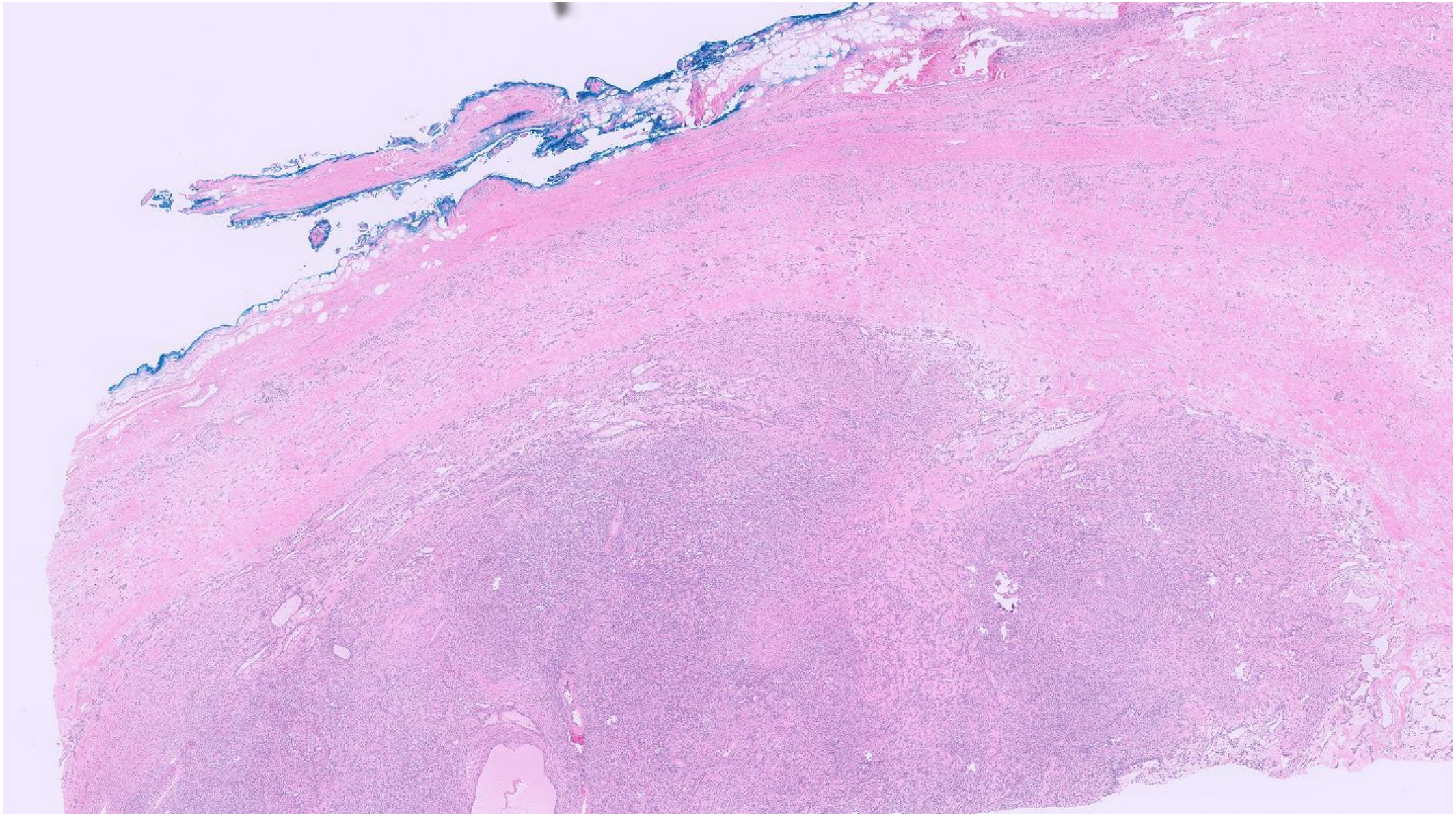
Polypoid Immature Teratoma, Gr.2

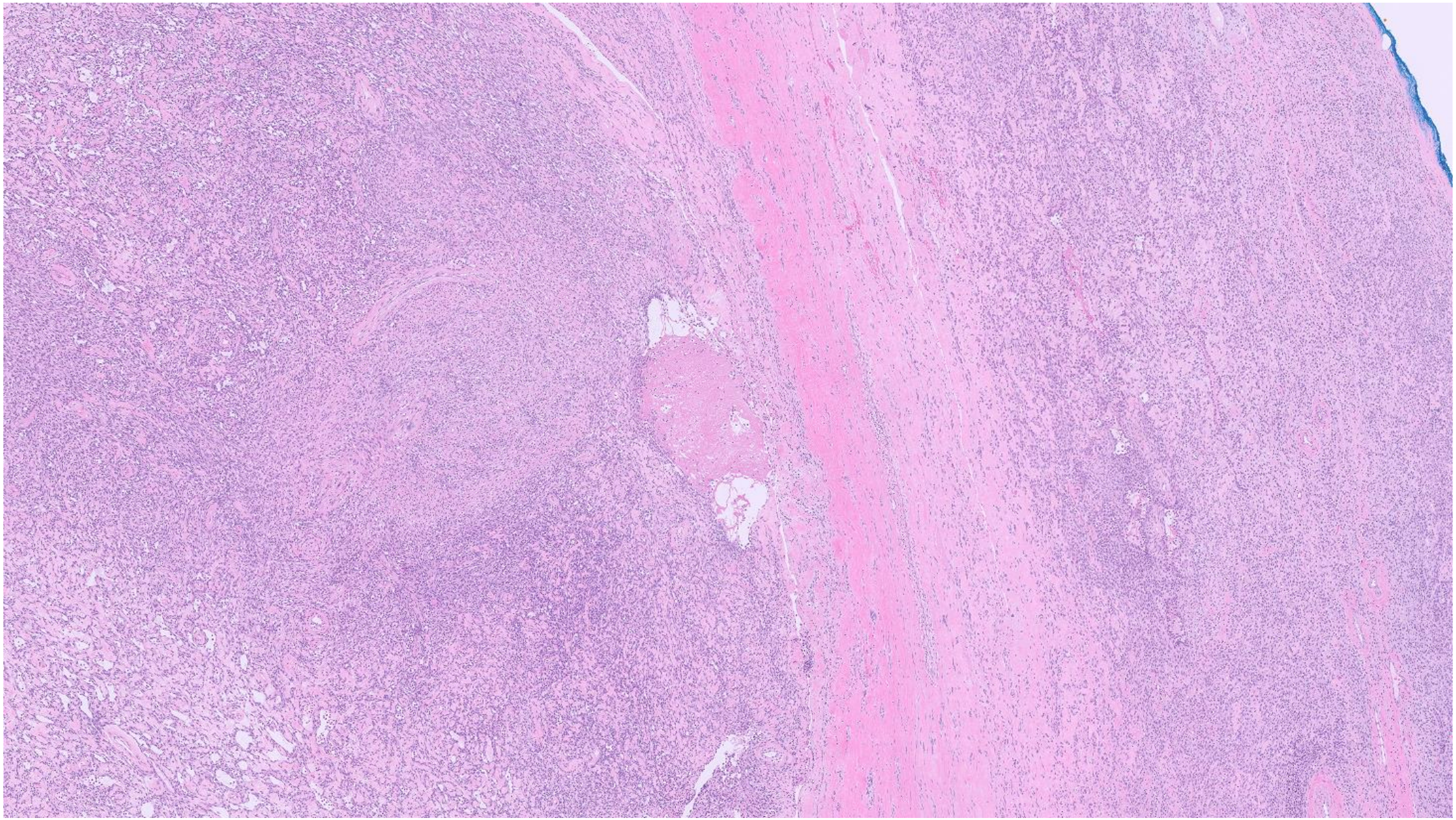
- At hysterectomy, involved omentum and cul de sac
- Very rare as primary tumor of endometrium/cervix
- Must exclude metastasis from ovary
- Same grading criteria as for ovary
- Likely arise from pluripotential stem cells or primordial germ cells

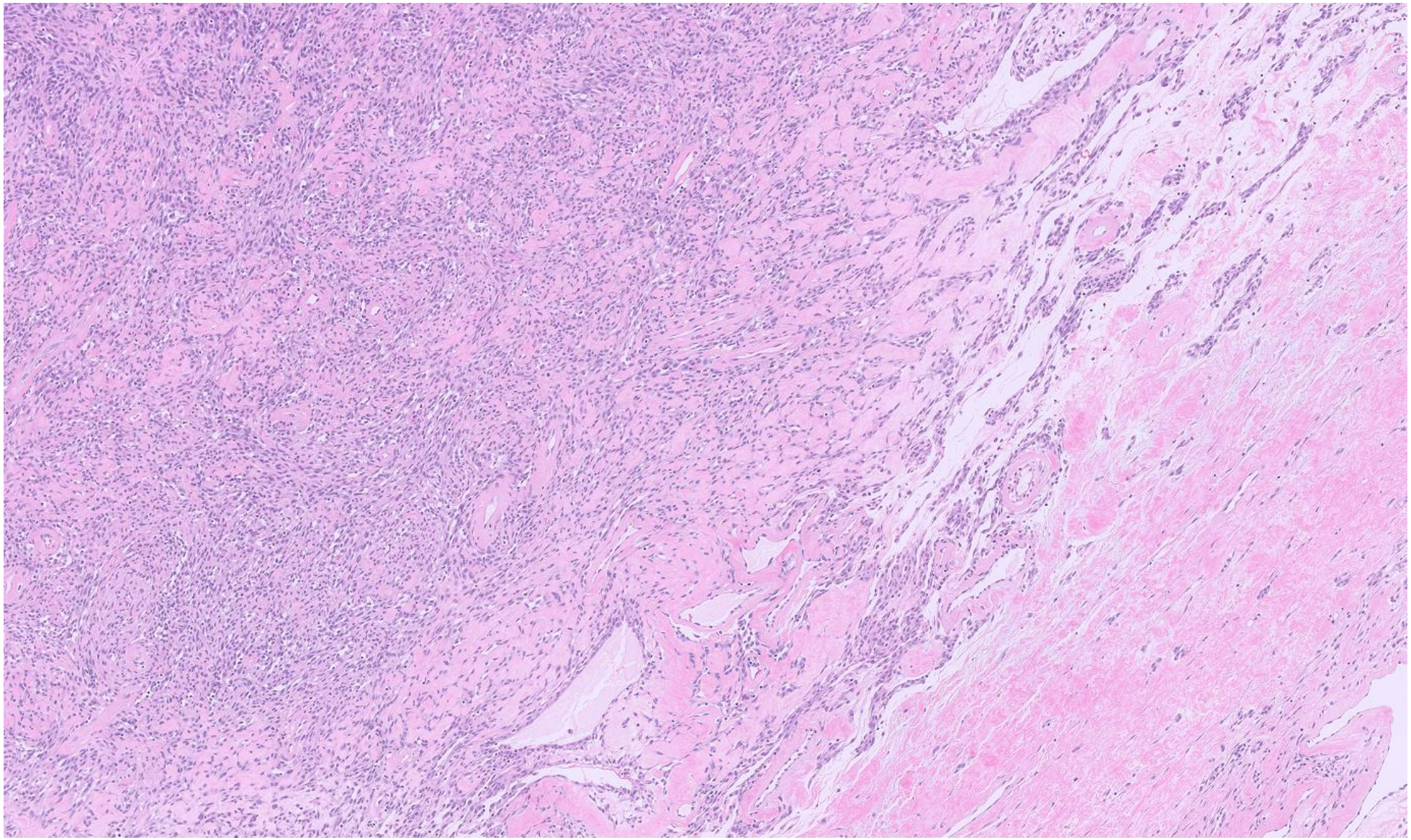
24-0708

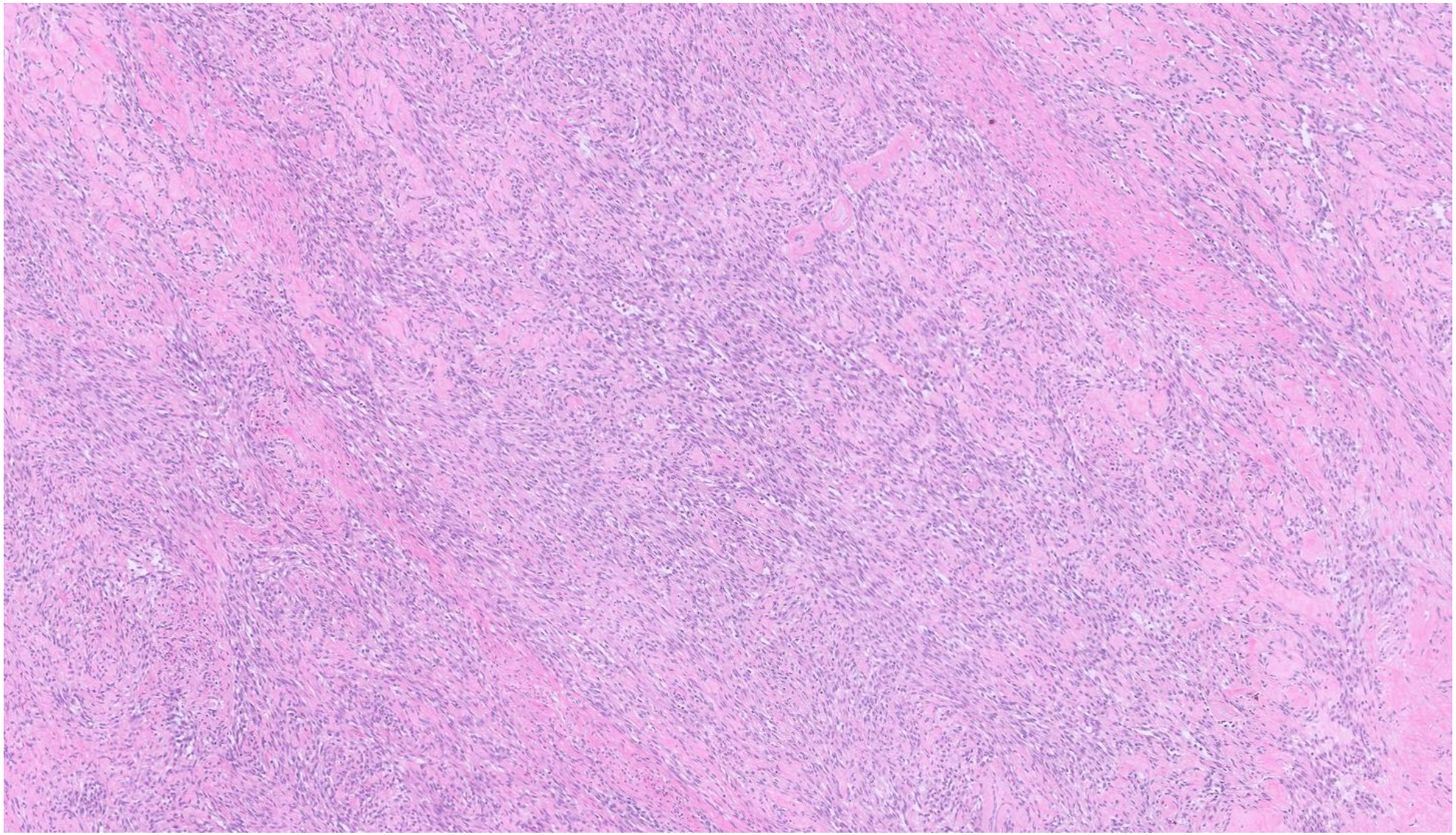
Sheren Younes, Brooke Howitt; Stanford

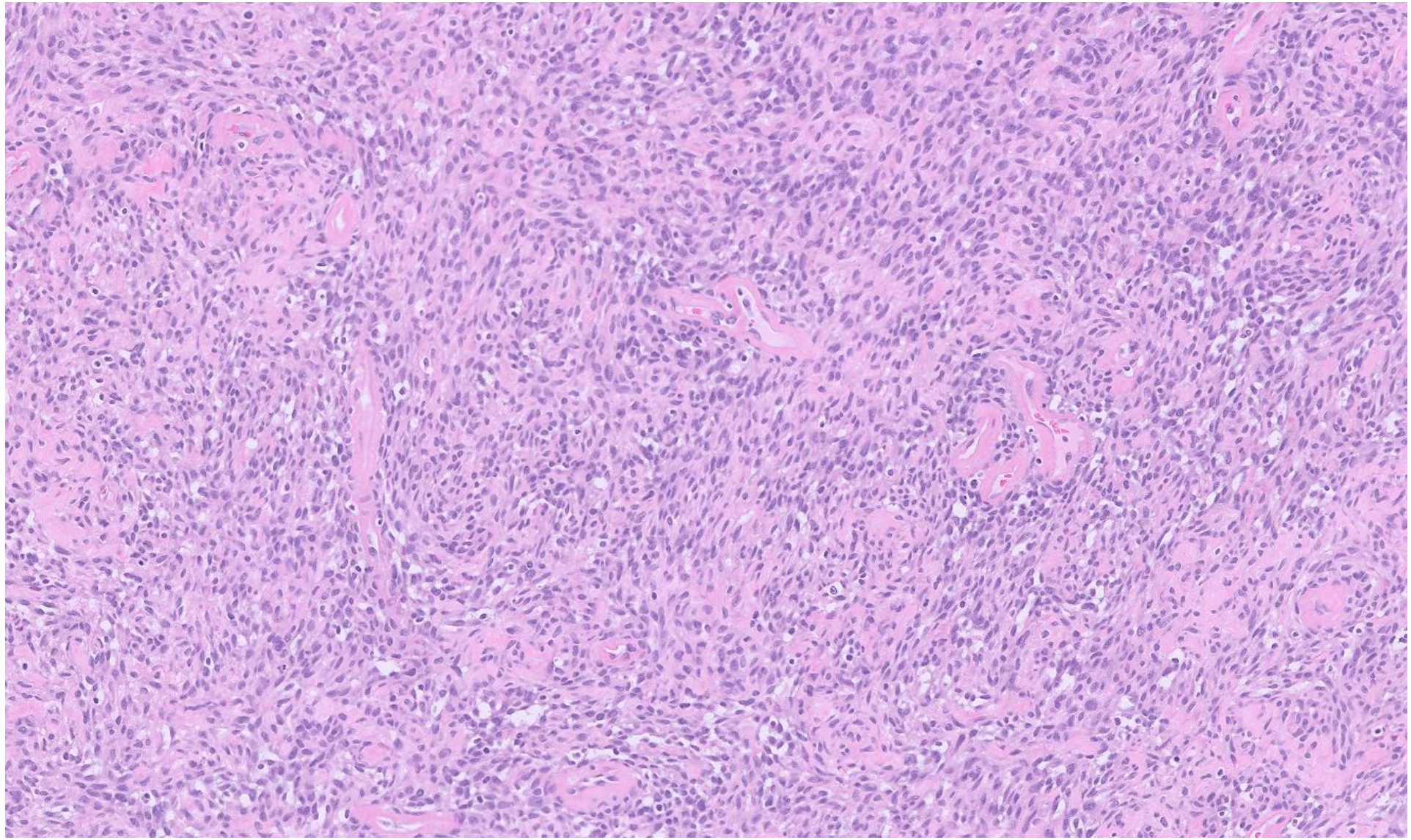
35-year-old female with a “brachial plexus” mass. She had a biopsy of the mass which was consistent with a bland spindle cell lesion and underwent surgical excision

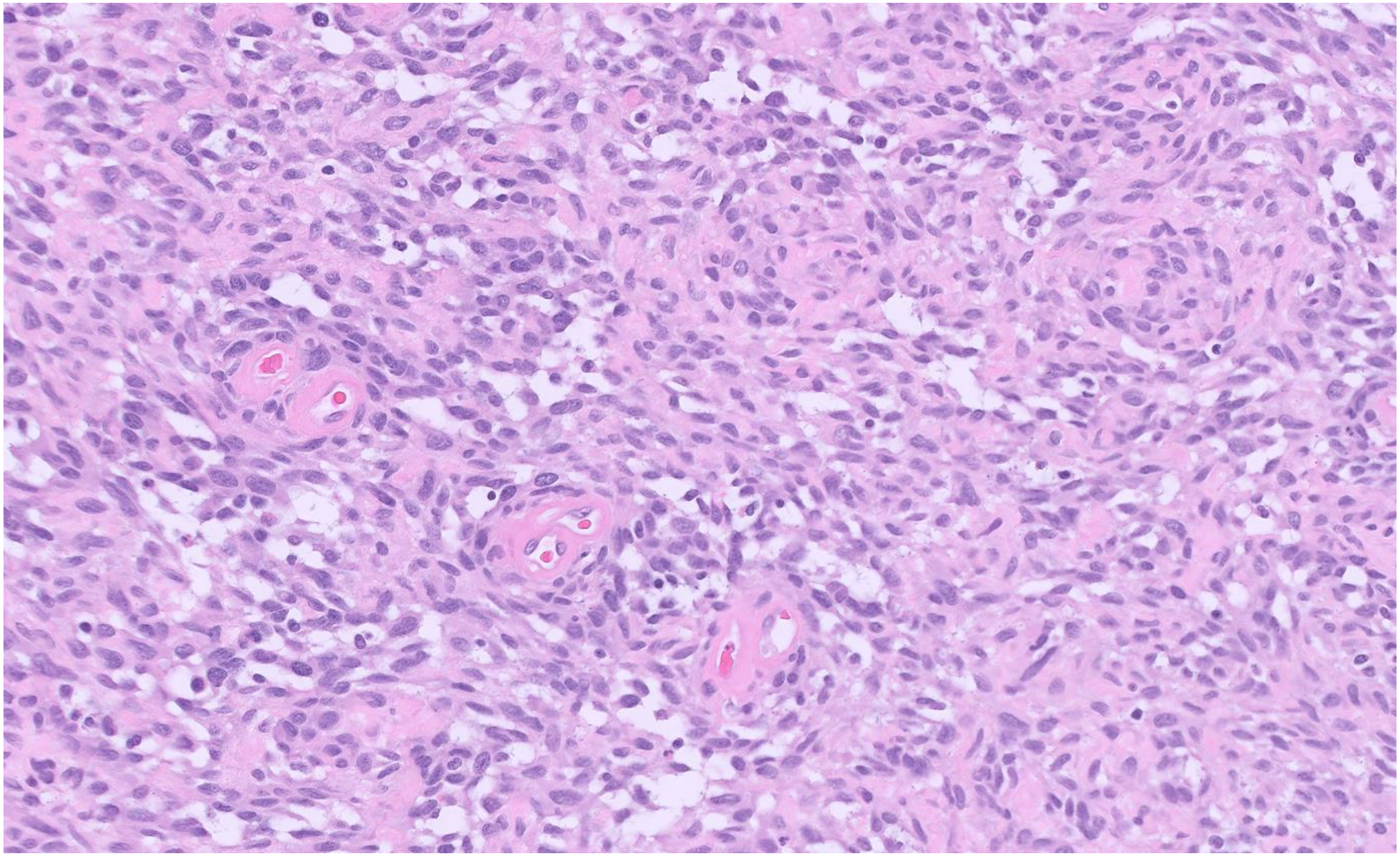


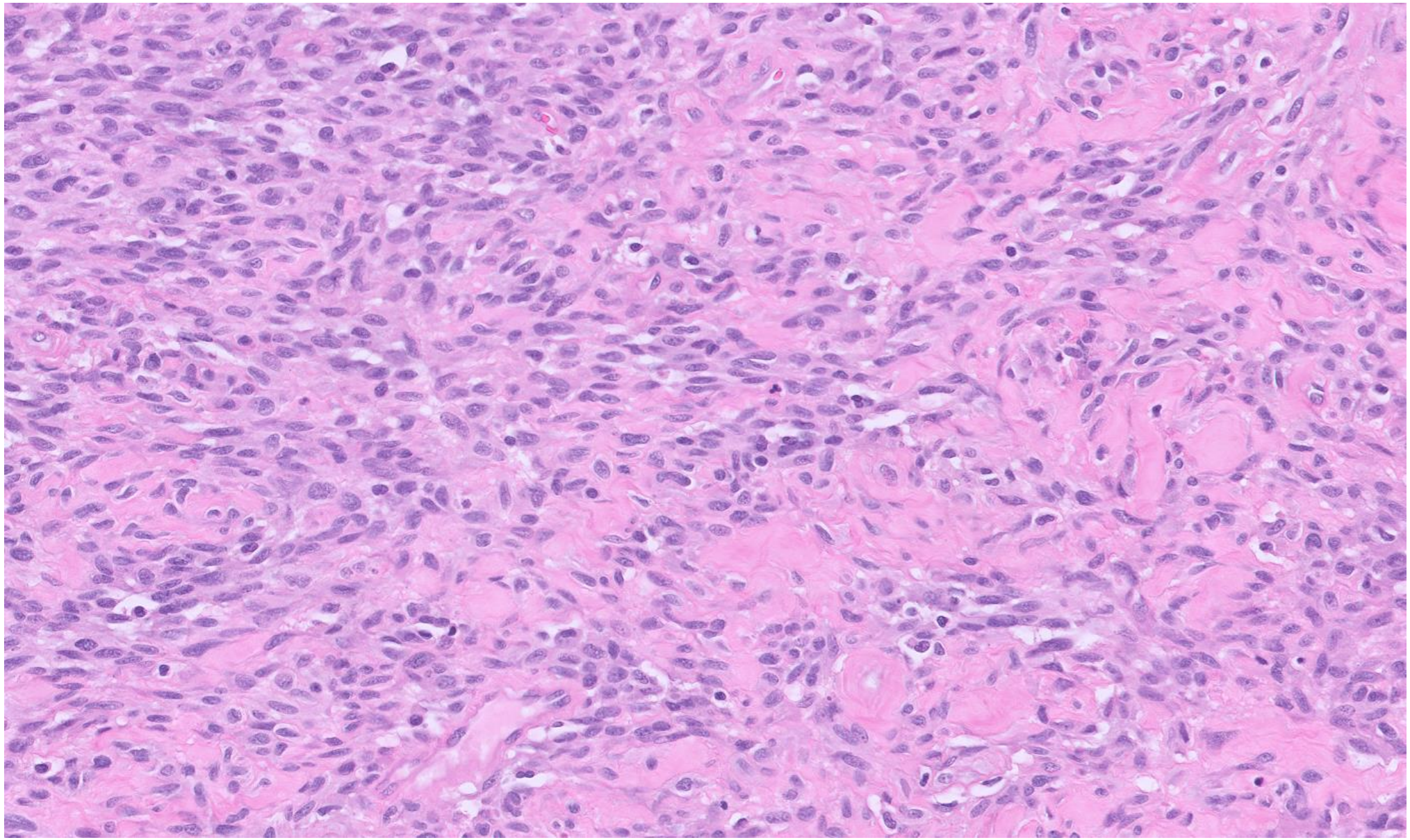


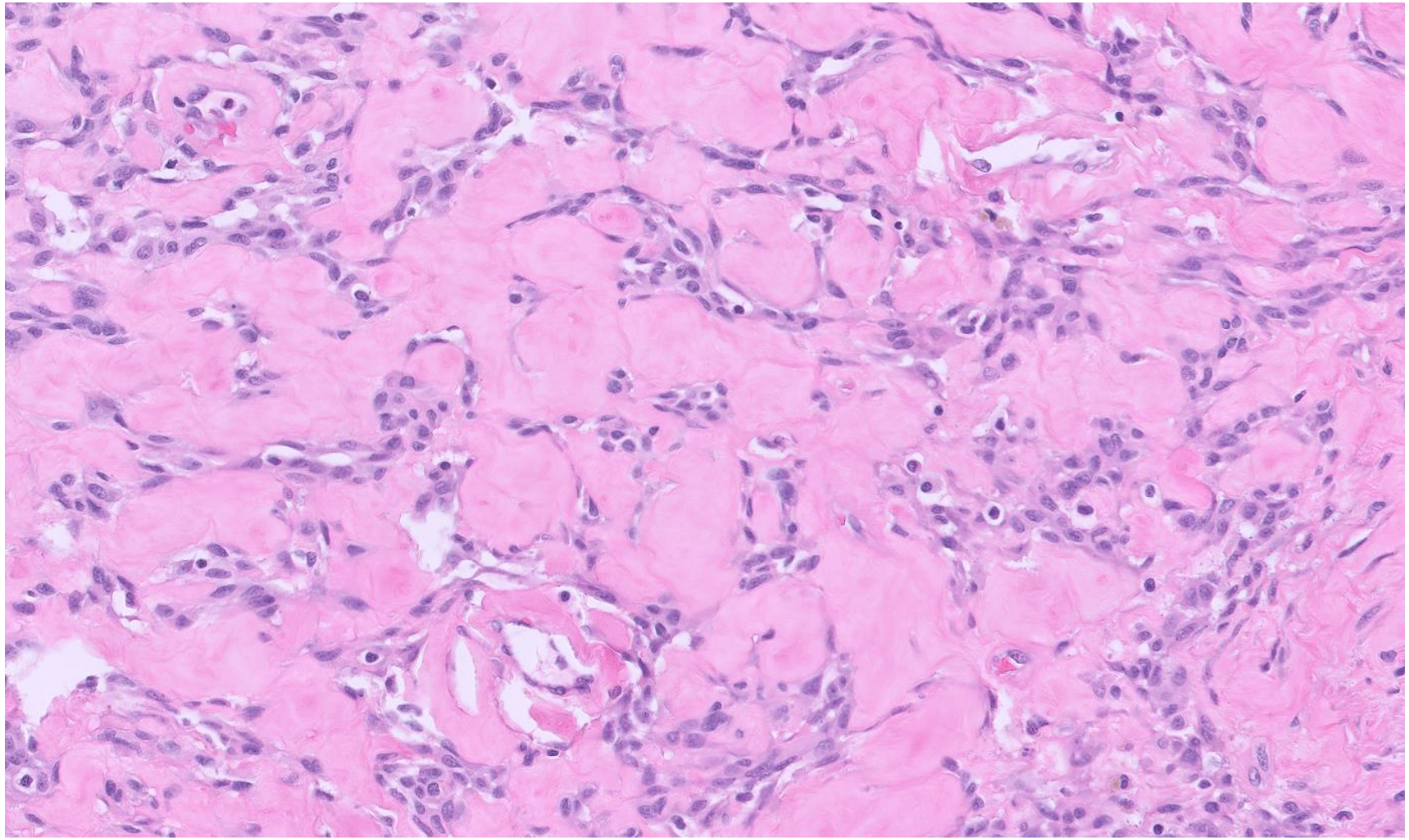


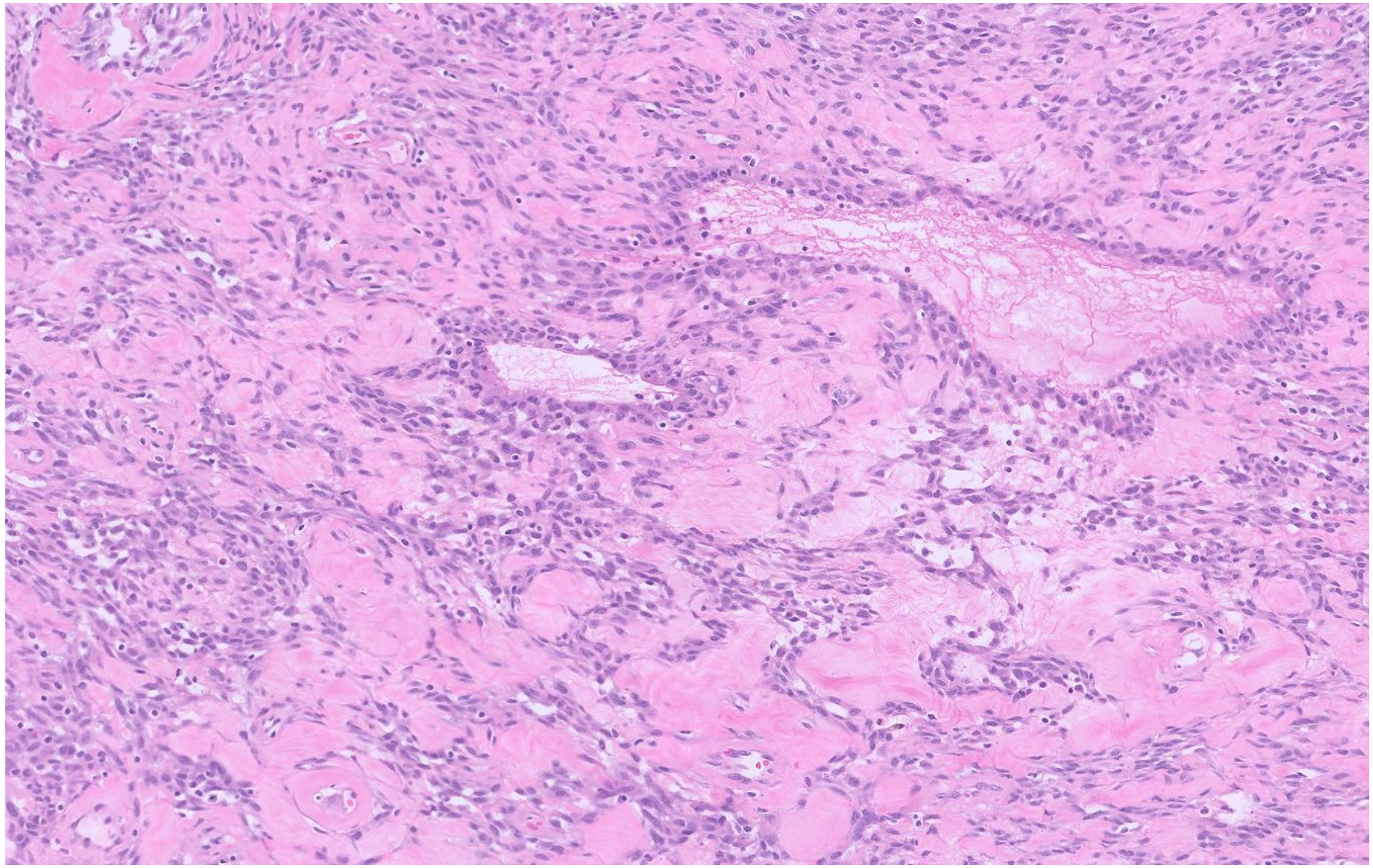


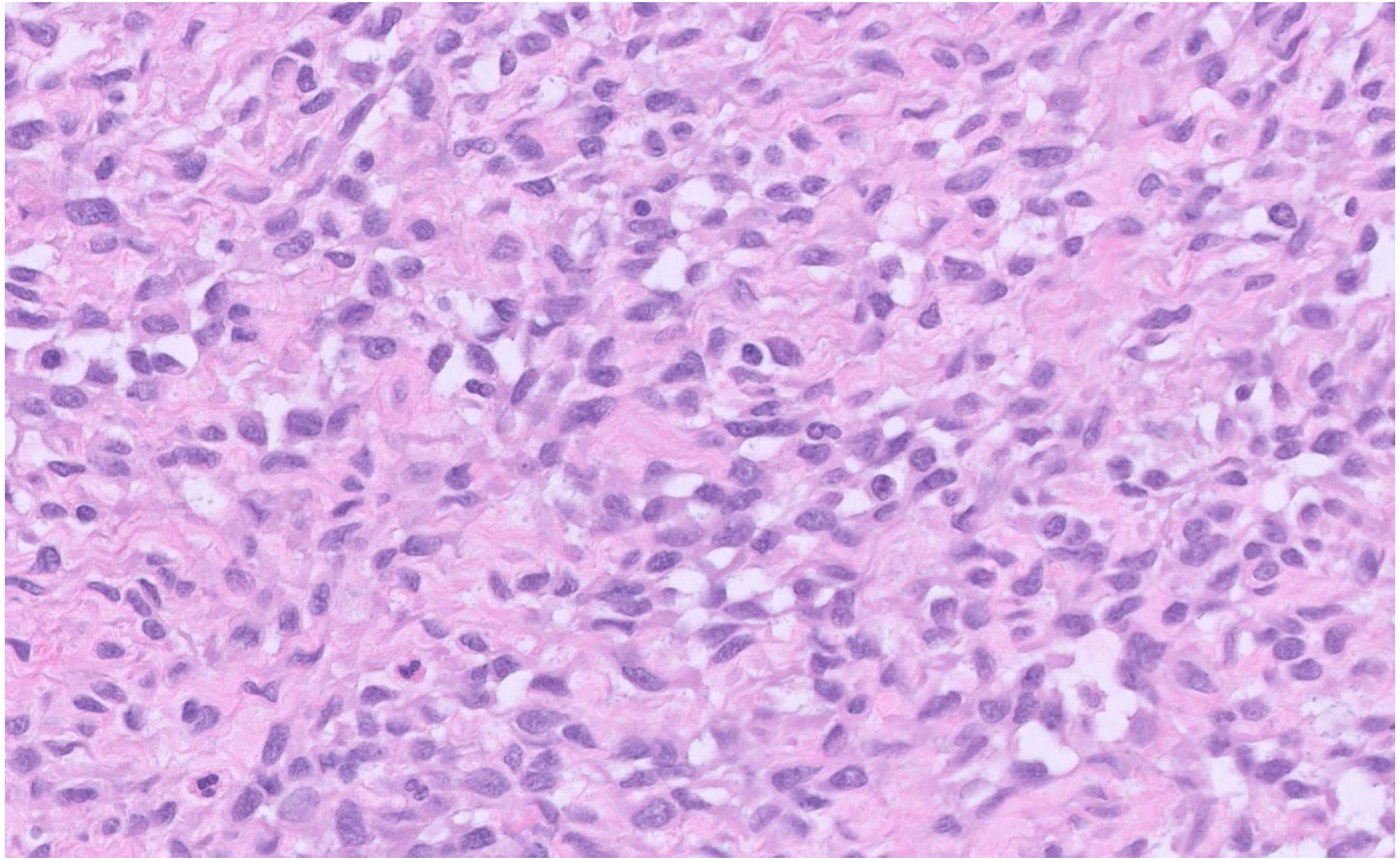


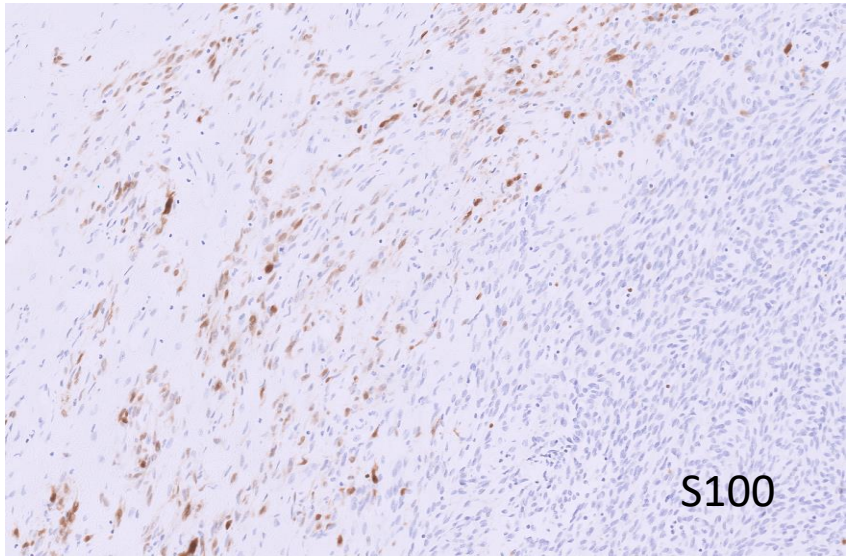








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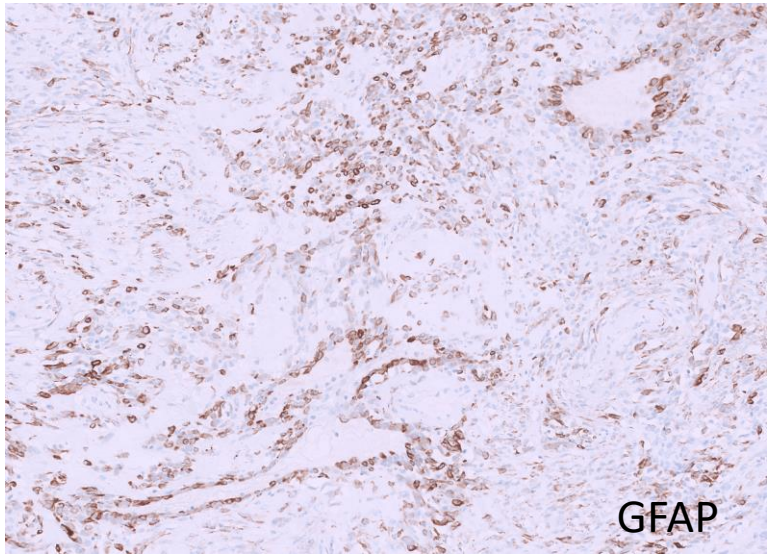
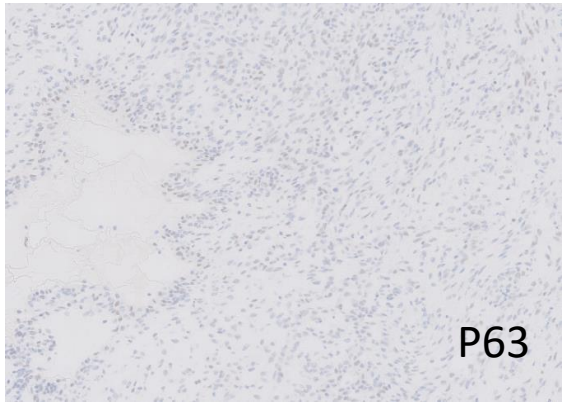

GFAP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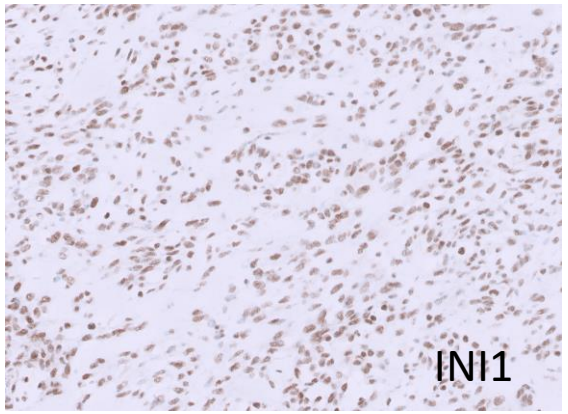
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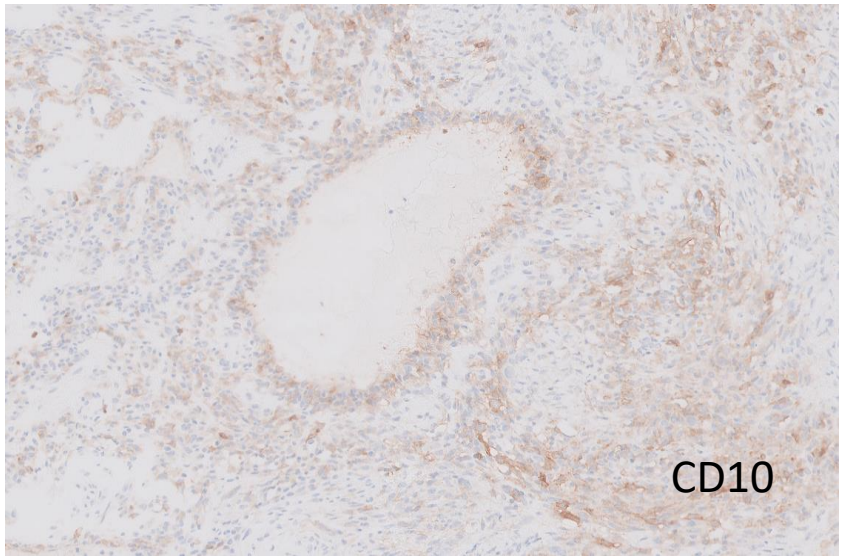
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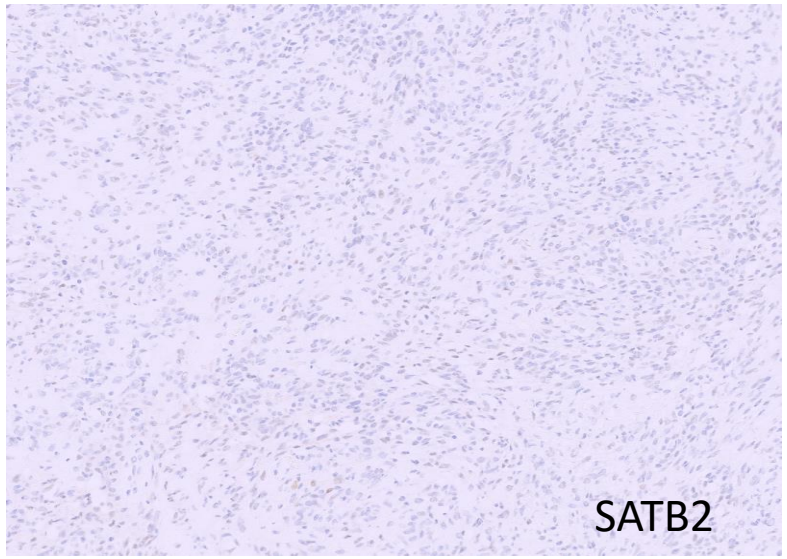
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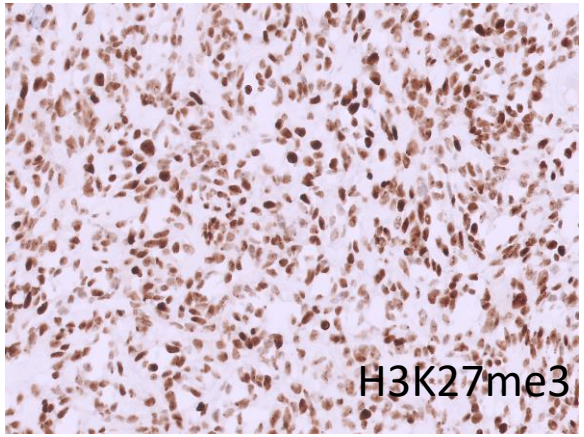
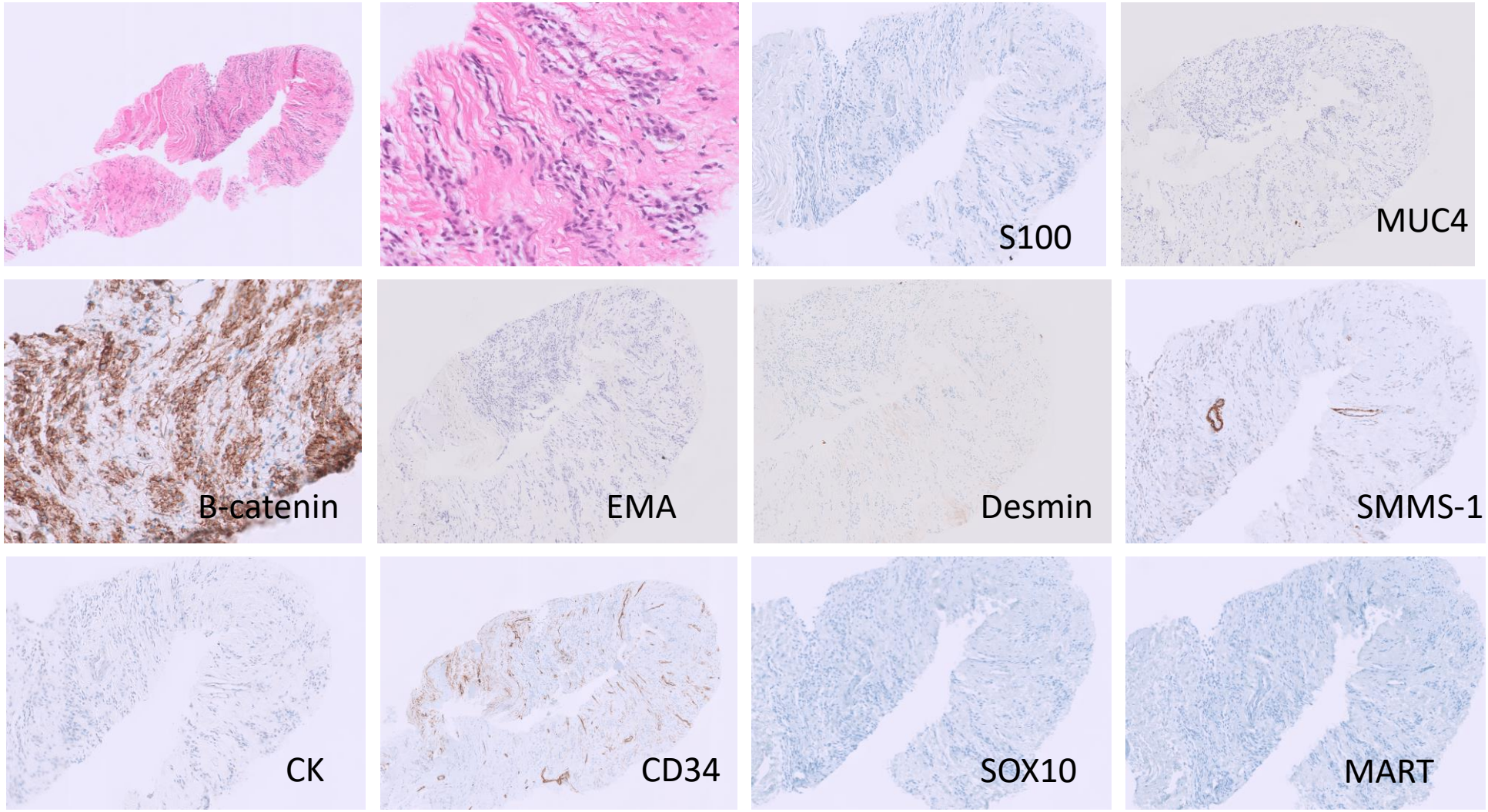

H3K27me3

Negative stains

- CKMIX
- EMA
- ERG
- CD34
- SOX10
- SMA

DIAGNOSIS?



Prior FNA

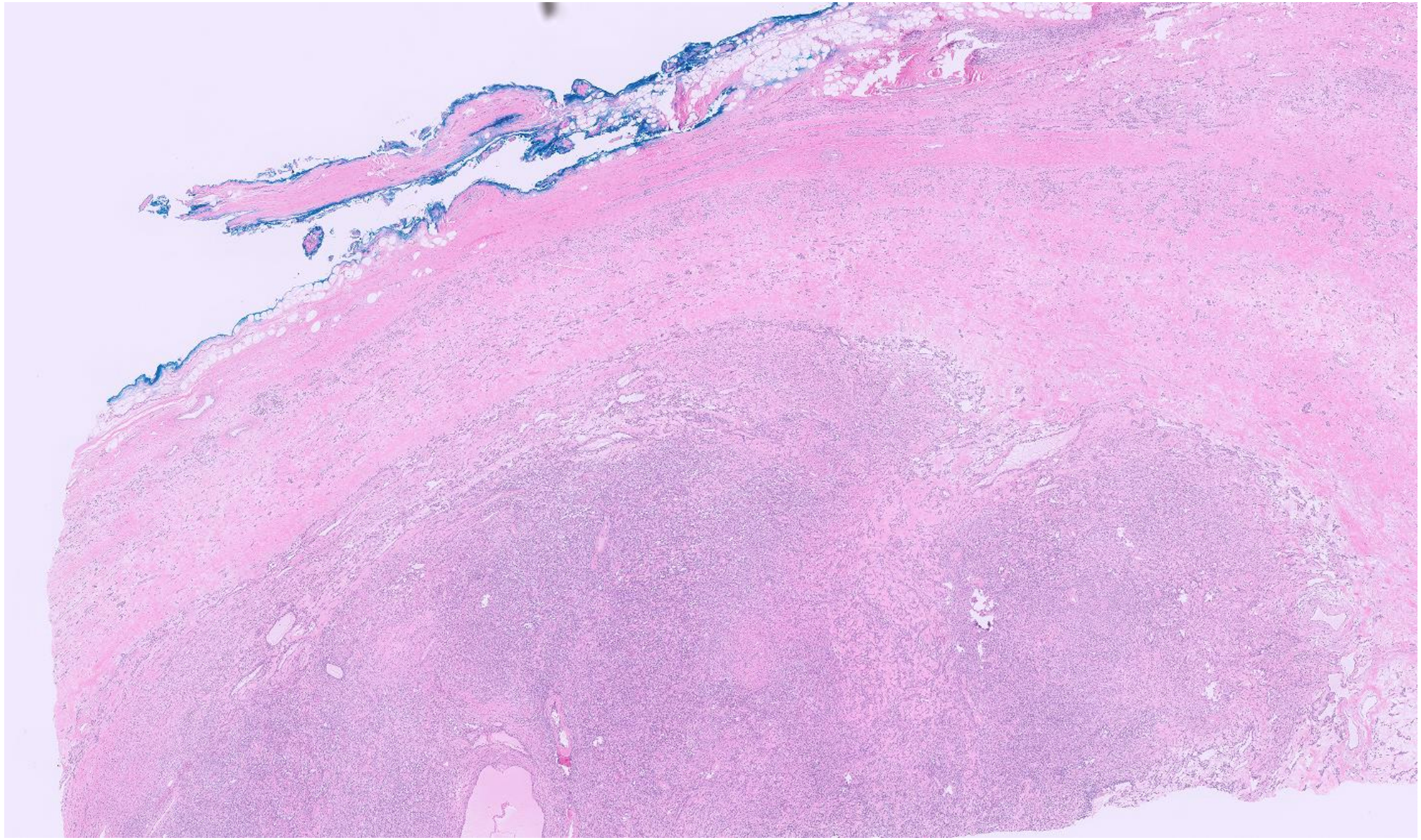
Soft Tissue, Left Inferior Neck, Ultrasound-Guided Biopsy

- **Bland spindle cell lesion**

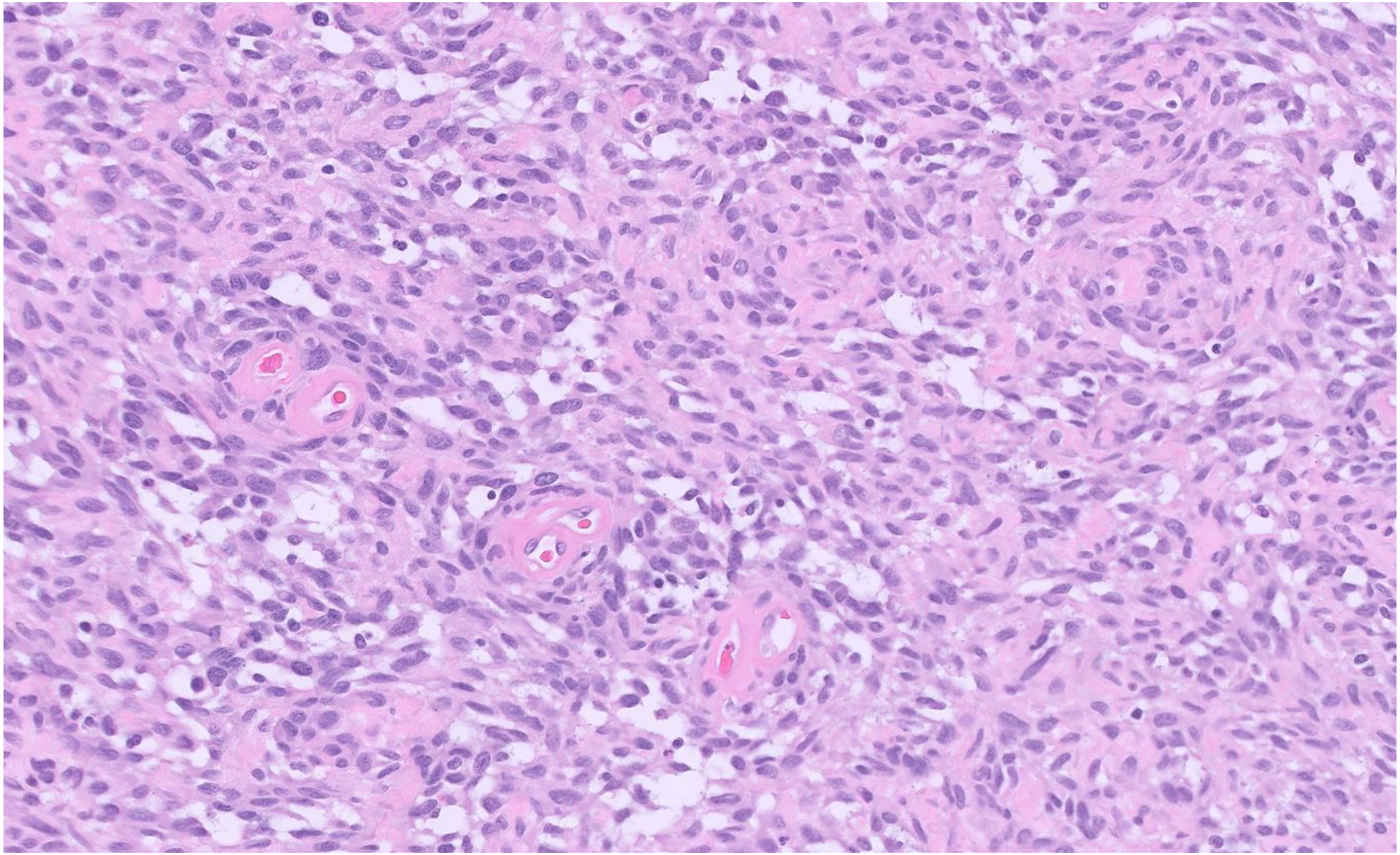
Infiltrative growth

Partially encapsulated

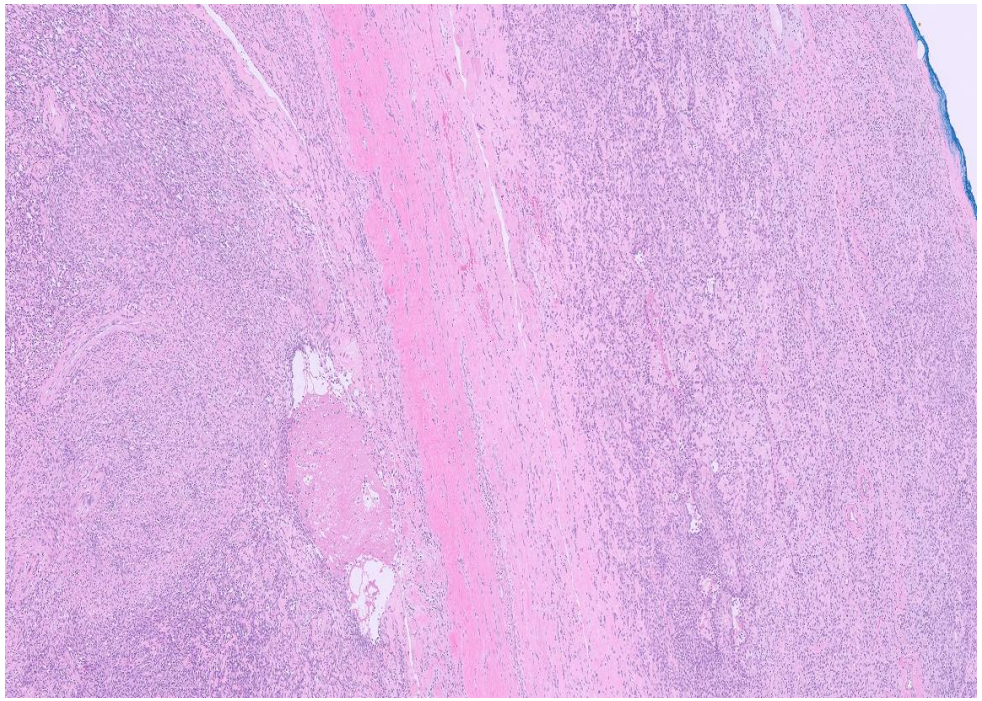
Variably cellular

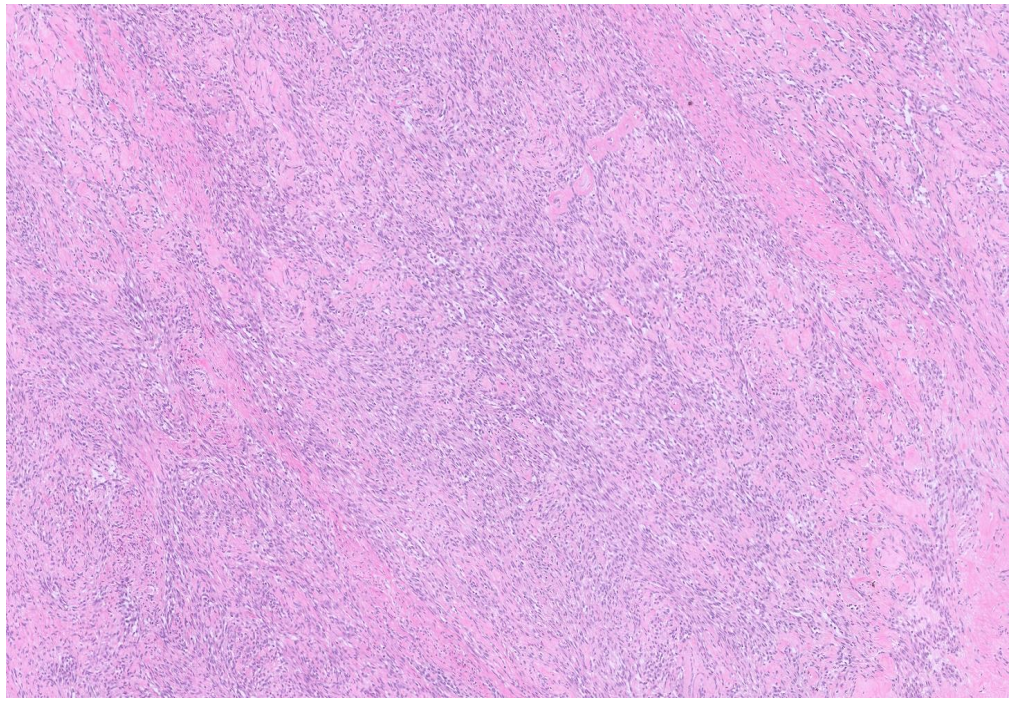


Hyalinized blood vessels

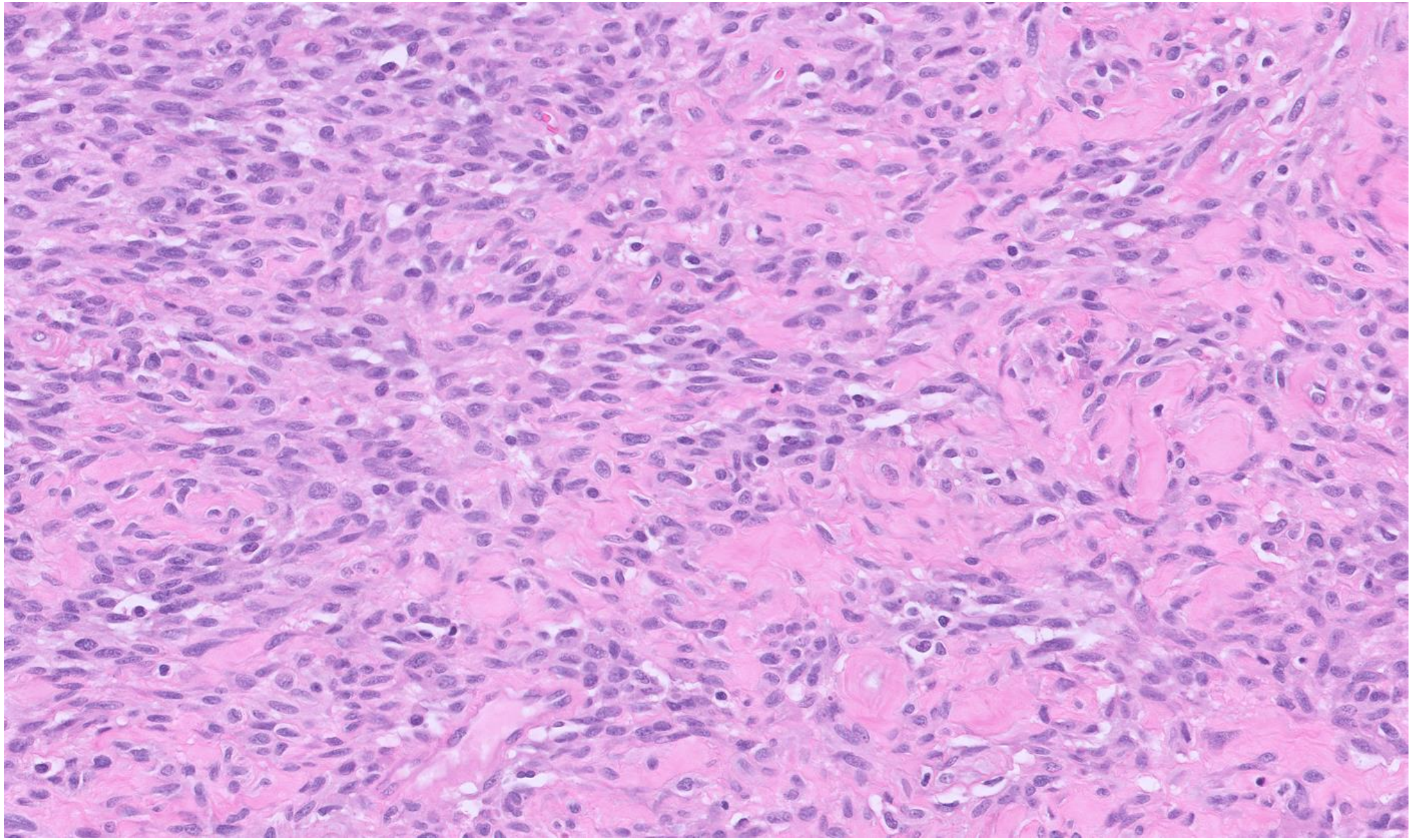


Fibrous septa

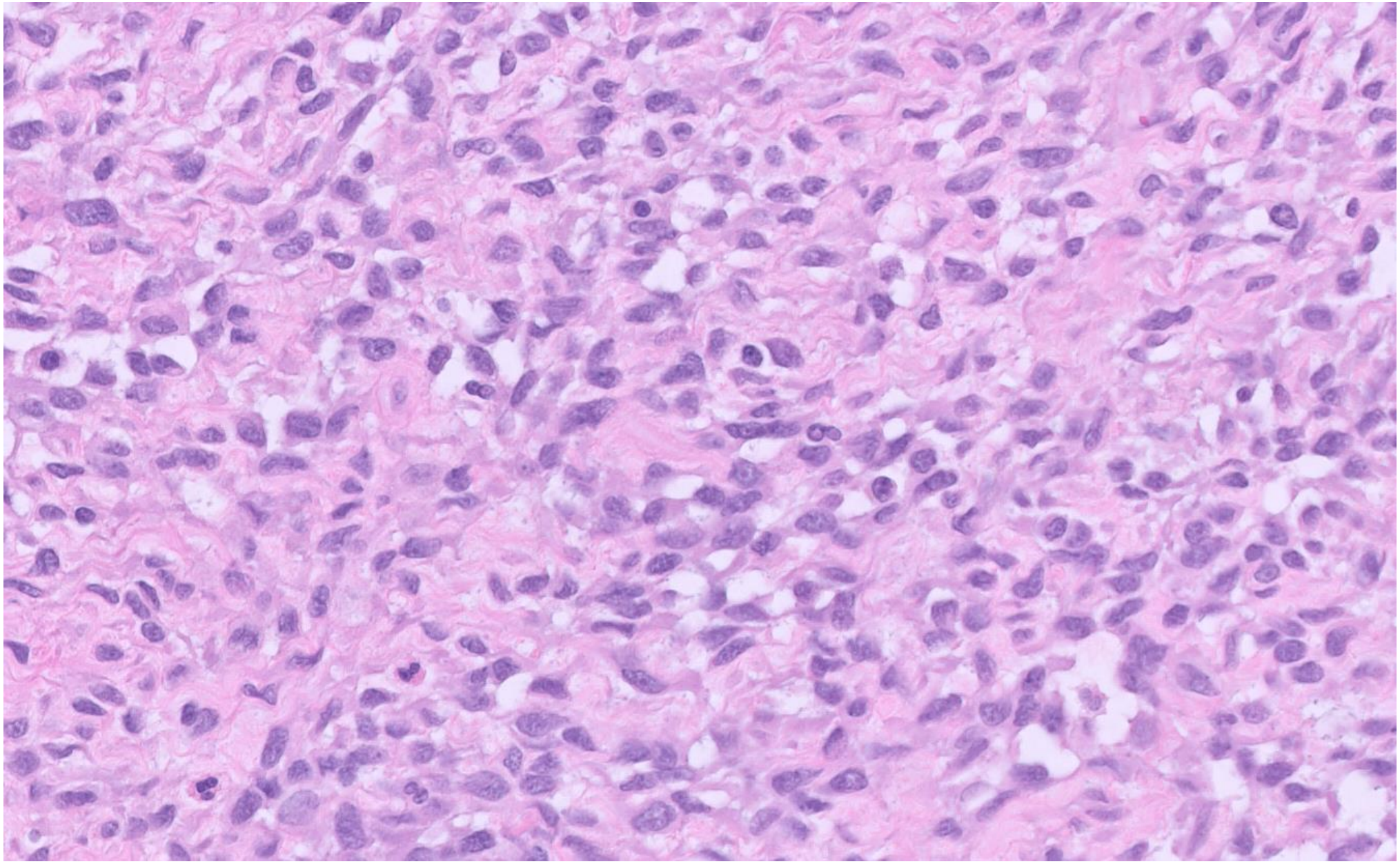




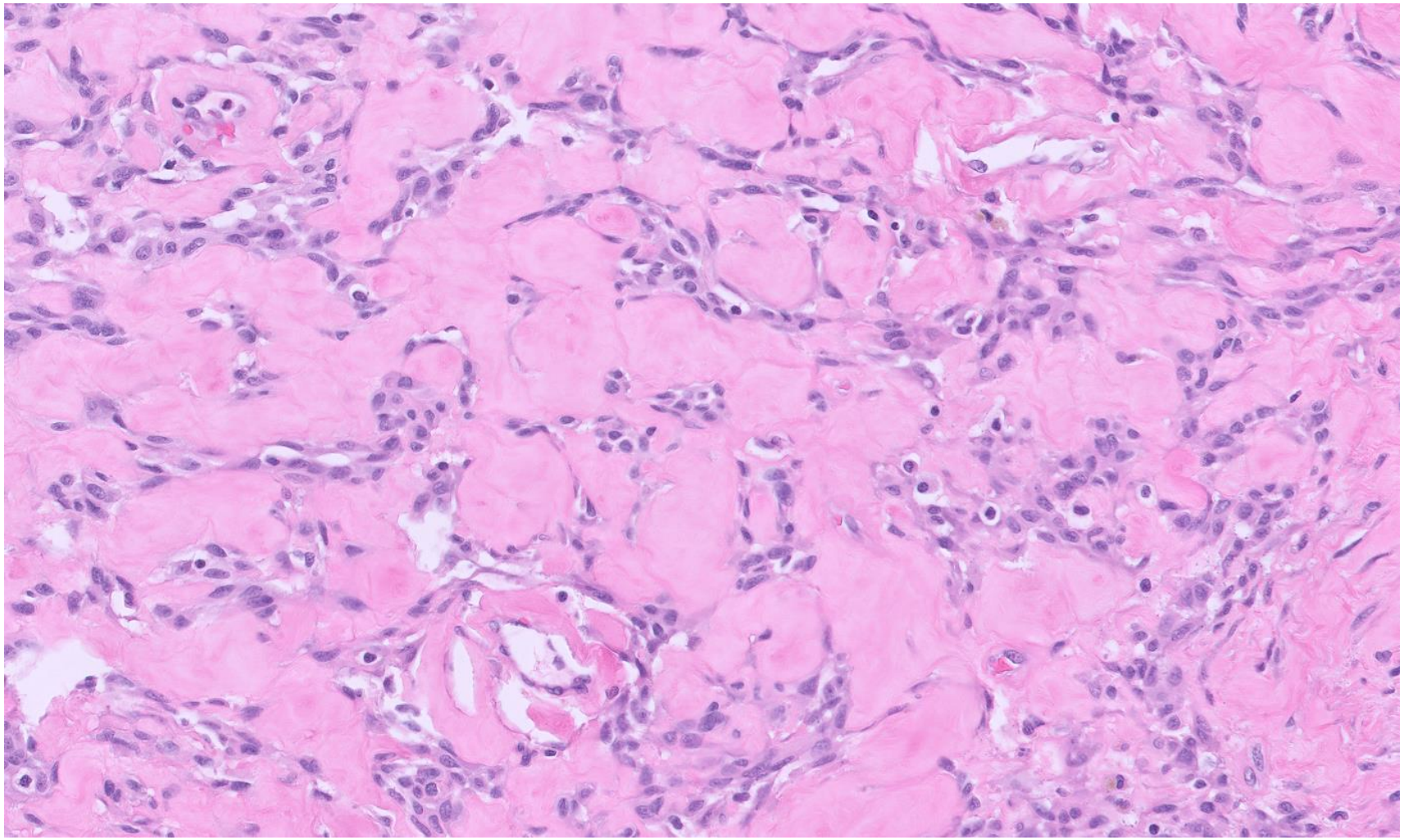
Uniform round-spindle cells



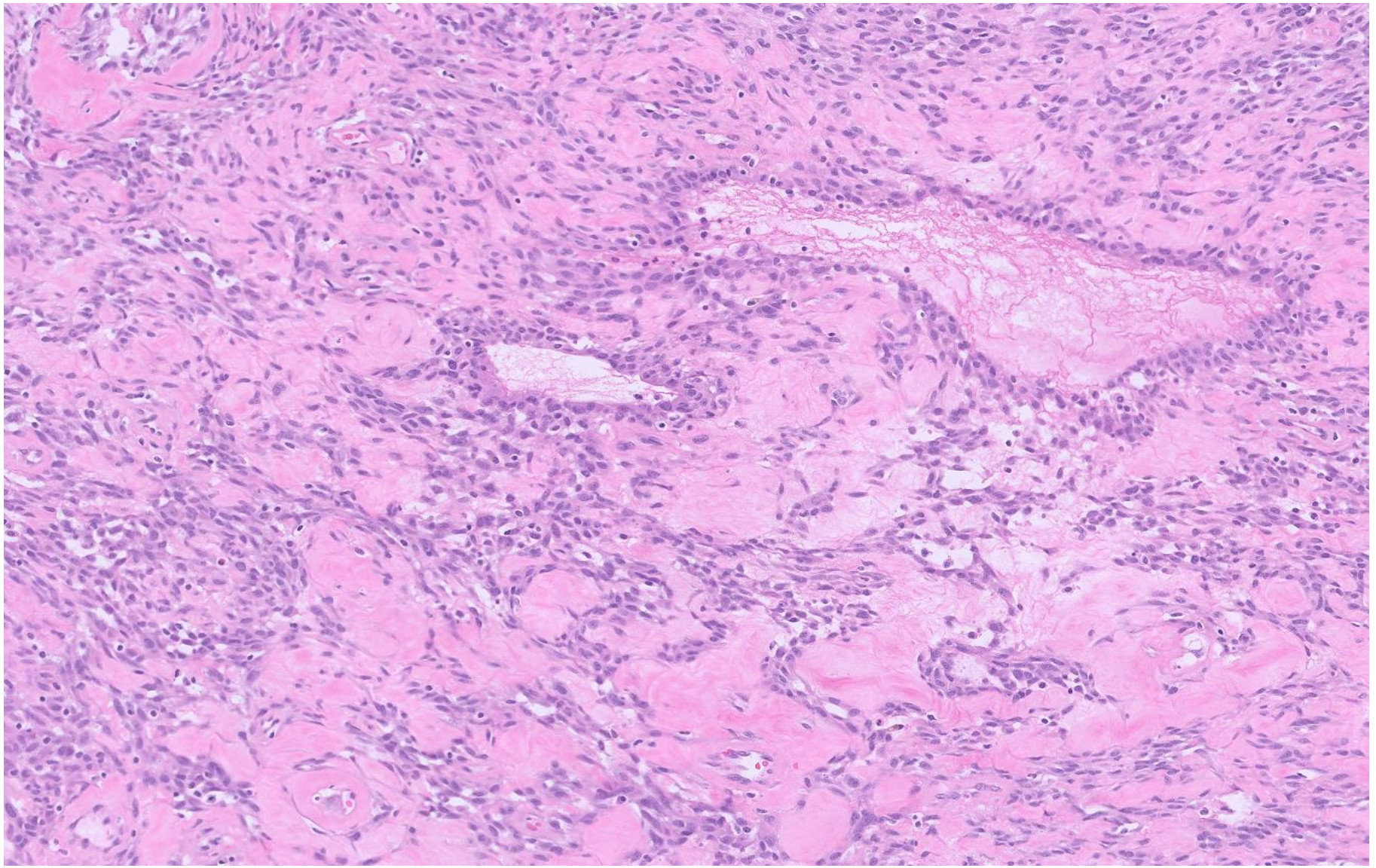
Uniform round-spindle cells

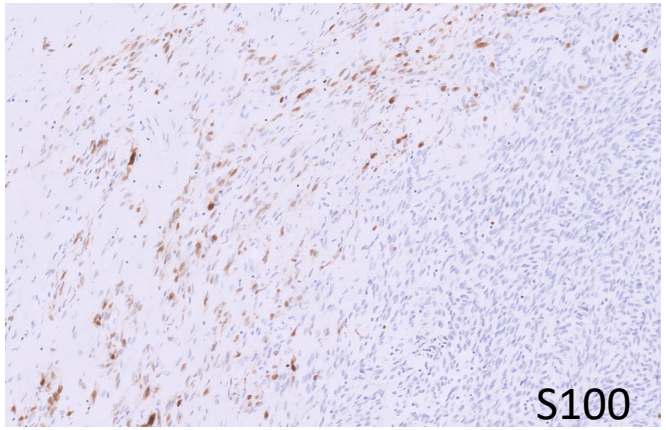


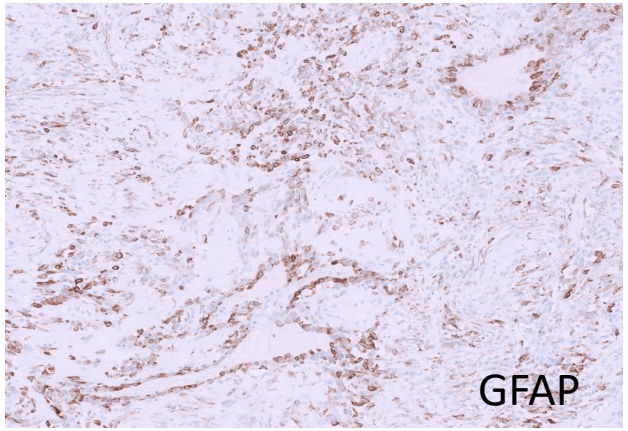
Collagen

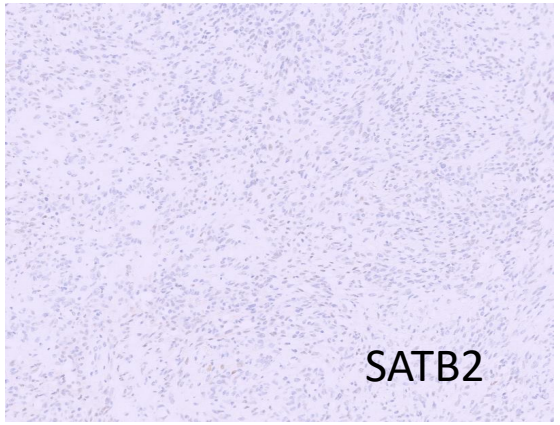


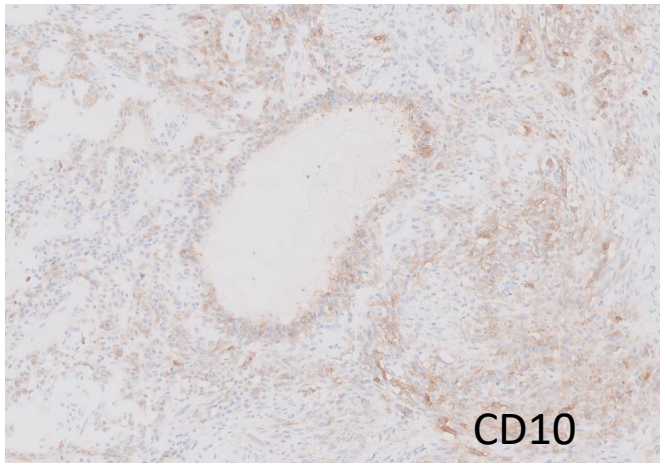
Microcystic spaces

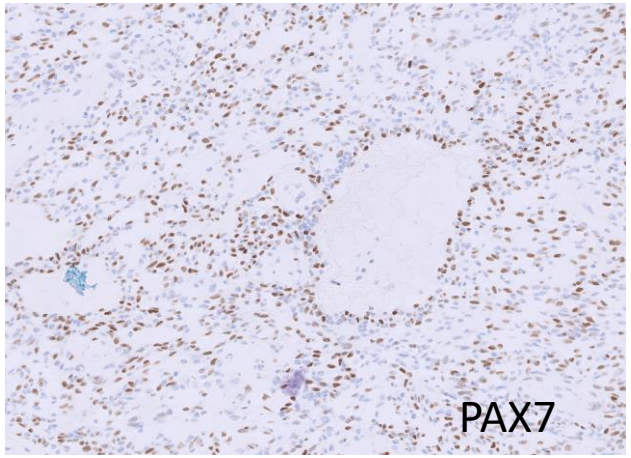


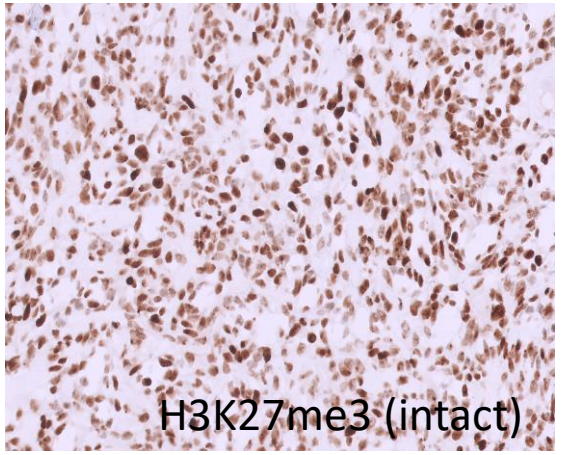


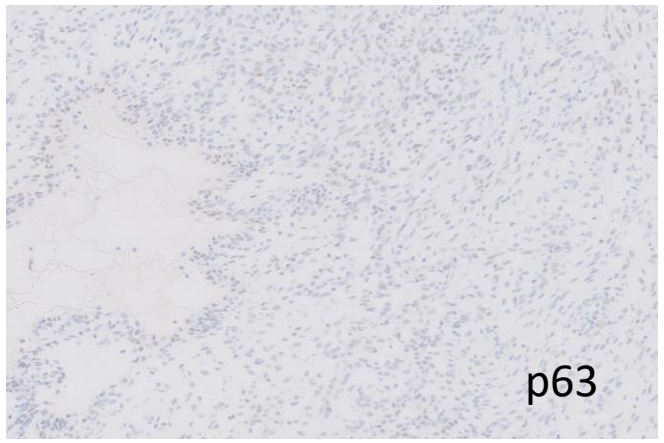


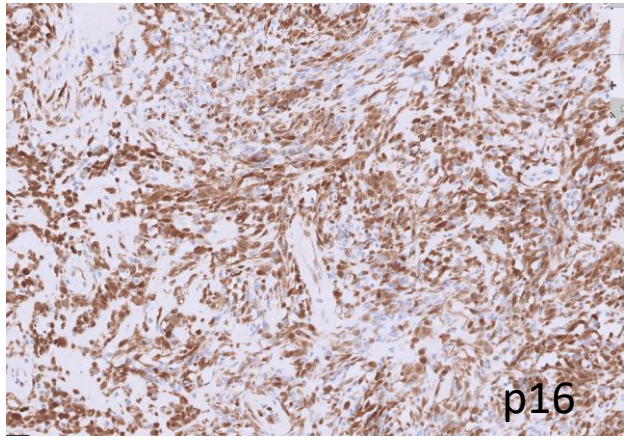


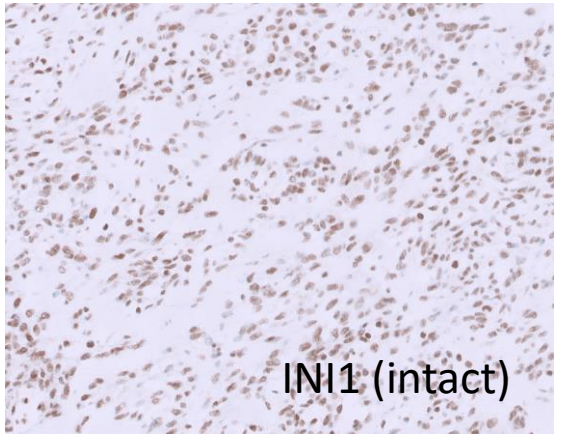












Positive stains

- CKMIX
- EMA
- ERG
- CD34
- SOX10
- SMA
- Myogenin
- myoD1

Negative stains

Desmin focally positive

Differential diagnosis

- **Myoepithelioma of Soft Tissue**
  - Myxoid stroma common and often abundant
  - EMA, keratin, S100, and SOX10 (+)
  - *EWSR1* rearrangements in 50% of cases, but no *EWSR1*::*PATZ1* fusion
- **Ossifying fibromyxoid tumor**
  - S100 (+)
  - *PHF1* fusions
- **Solitary Fibrous Tumor**
  - CD34 and STAT6 (+)
- **Synovial sarcoma**
  - Fasicular growth, keratin (+)
  - SS18::SSX fusion
- **Benign Peripheral Nerve Sheath Tumor**
  - S100 and SOX10 (+) (diffuse in schwannoma)
- **Malignant Peripheral Nerve Sheath Tumor**
  - Diffuse loss of nuclear H3K27me3
  - S100 and SOX10 (+)
- **Sarcoma With BCOR Alterations**
  - BCOR(+); S100 and desmin (-)
- **High-Grade Myxoid (Round Cell) Liposarcoma**
  - DDIT3(+) by IHC
  - S100, GFAP, and others (-)
- **CIC-Rearranged Sarcoma**
  - Prominent nucleoli and mitotic activity
  - Diffuse nuclear WT1(+) in most cases
  - S100 and desmin (-)
- **Rhabdomyosarcoma**
  - Embryonal, alveolar, and spindle cell/sclerosing types

Fusion STAMP-NGS

An *EWSR1::PATZ1* fusion that joins intron 8 of *EWSR1* and exon 1 of *PATZ1* is identified

Diagnosis

EWSR1::PATZ1 sarcoma, morphologically low-grade

EWSR1, the most common rearranged gene in ST tumors

- EWSR1 is member of the FET family of RNA-binding proteins
- First described in Ewing sarcoma, EWSR1-ETS fusion (Delattre et al., Nature. 1992)
- Found to be part of multiple fusion events for soft tissue and non-ST tumors, fusions
- Diverse benign and malignant tumors with mesenchymal, neuroectodermal, and epithelial/myoepithelial features
- Fusion gene analysis is the diagnostic gold standard in most of these tumors.

Round cell sarcoma with EWSR1-non-ETS fusions

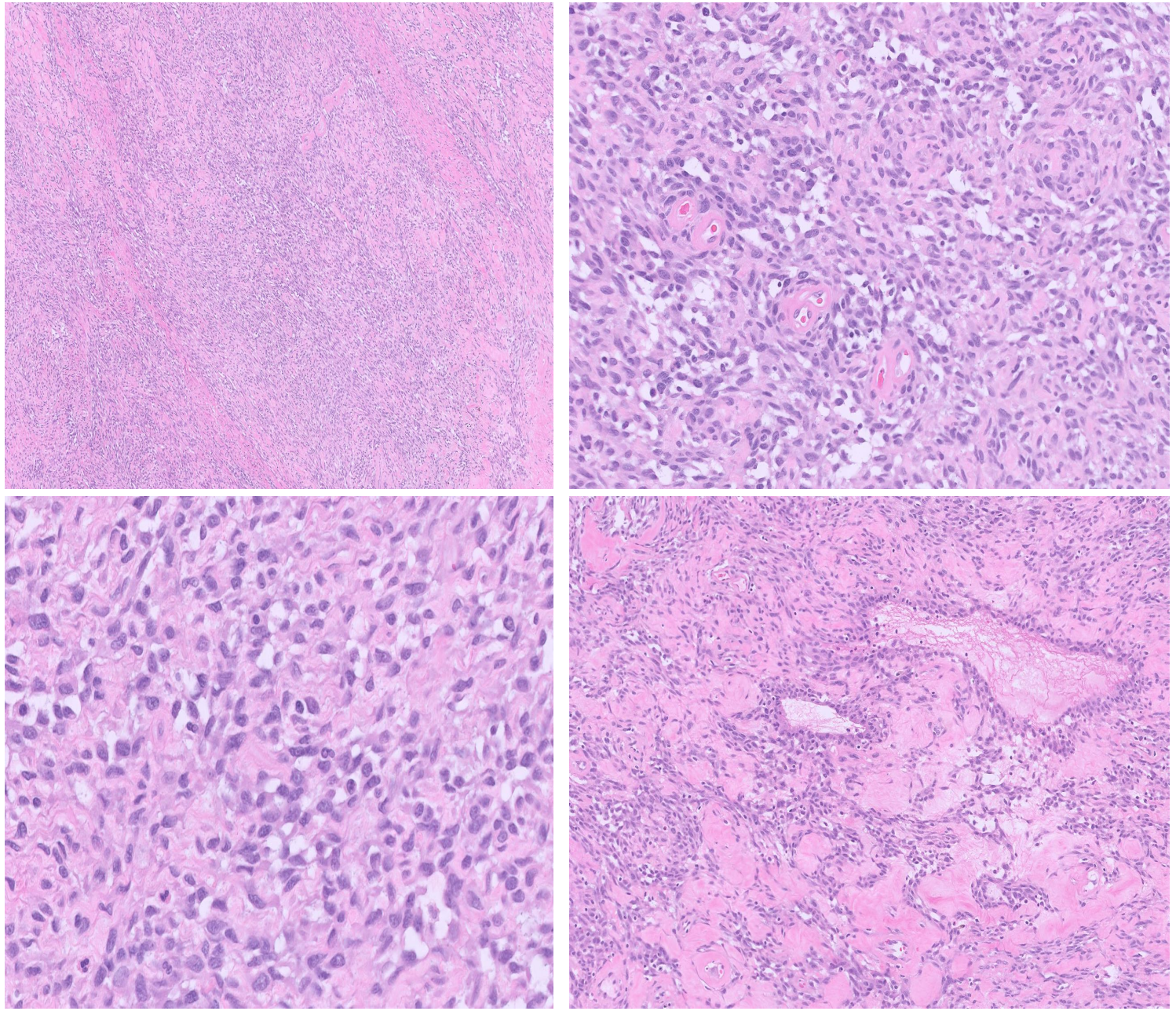
- *EWSR1::NFATC2* sarcomas, *EWSR1::PATZ1* sarcomas, and *EWSR1::SMAD3*-positive fibroblastic tumor (emerging)
- PATZ1 encodes a zinc finger protein with a Cys2-His2 motif with tumor suppressive functions involved in transcriptional regulation. PATZ1 resides ~2 Mb distance to *EWSR1* on chromosome 22, submicroscopic intrachromosomal paracentric inversion
- *EWSR1::PATZ1* fusions also define a clinically distinctive group of histologically polyphenotypic neuroepithelial/glioneuronal tumors of the central nervous, very rare renal cell carcinomas with follicular thyroid features.
- *EWSR1::PATZ1*–positive tumors of the central nervous system and kidney are morphologically and immunohistochemically distinct from their soft tissue counterparts.

EWSR1::PATZ1 sarcoma

- Rare
- Recently characterized group of round to spindle cell tumors
- Ranges from early childhood to the elderly, average in the fourth decade
- Anatomic sites vary, superficially and deep, mainly in the trunk (thorax, including lung; abdomen), rarely in the head and neck and extremities. Intracranial localization is reported.
- Variable size 0.3-11.3 cm
- Well-circumscribed or infiltrating
- Subset exhibit distant or locoregional metastases at time of diagnosis

EWSR1::PATZ1 sarcoma morphology

- Histology is striking variable
- Uniform, cytologically bland
- Round or ovoid to spindled cells
- Fibromyxoid matrix with prominent fibrous bands
- Pseudoalveolar/microcystic spaces
- A “polyphenotypic” immunohistochemical profile is common, with coexpression of skeletal muscle, epithelial, schwannian, and glial markers



EWSR1::PATZ1 sarcoma

- Michal et al. divided the tumors into two subgroups:
- Low-grade appearing tumors: the spindled, epithelioid, ovoid, and round cells are set in a hyaline stroma reminiscent of solitary fibrous tumors and myoepithelioma.
- Intermediate and high-grade appearing neoplasms resemble other small, blue round-cell tumors, e.g., ARMS, BCOR-, and CIC-rearranged sarcoma.
- Transition may occur from low-grade to high-grade morphology is yet unknown
- In contrast to NGS, FISH is not the method of choice for confirming the presence of the fusion gene due to the close proximity of the gene loci of *PATZ1* and *EWSR1* on chromosome 22q12
- Tumors can be aggressive or follow a more favorable course
- It is unclear if the above-mentioned morphological grading is prognostic for outcome; conflicting reports and opinions in the literature

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