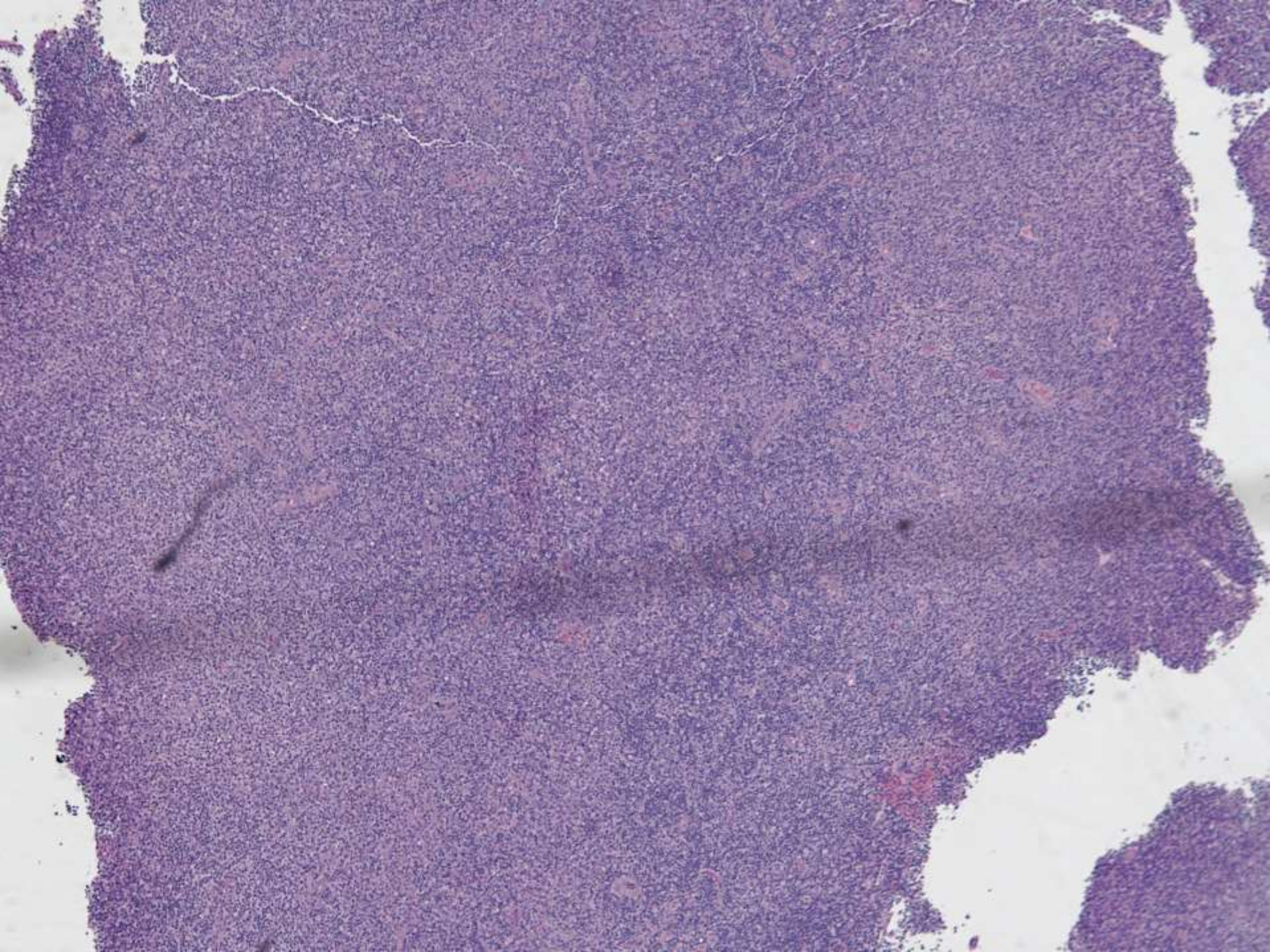
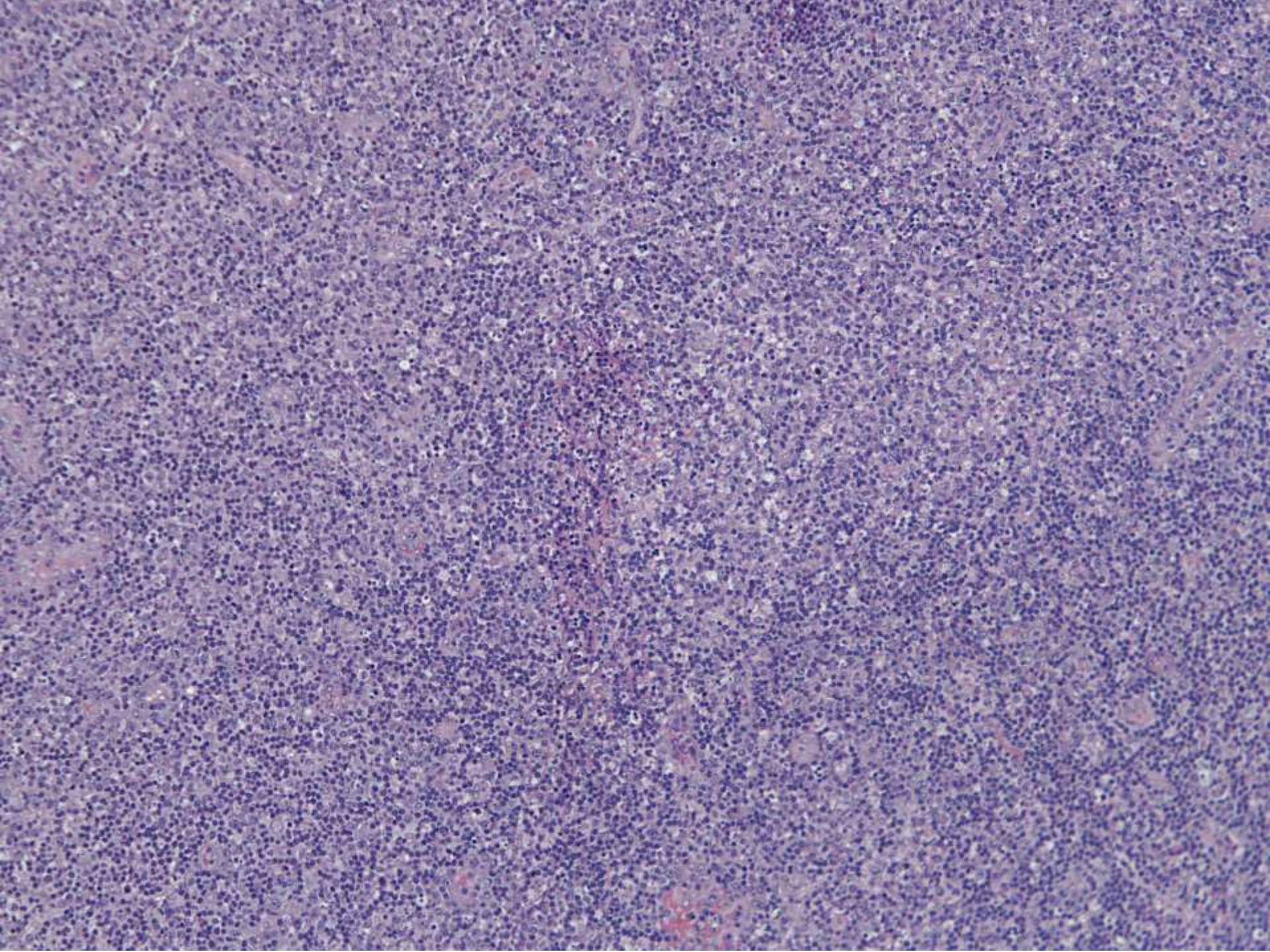
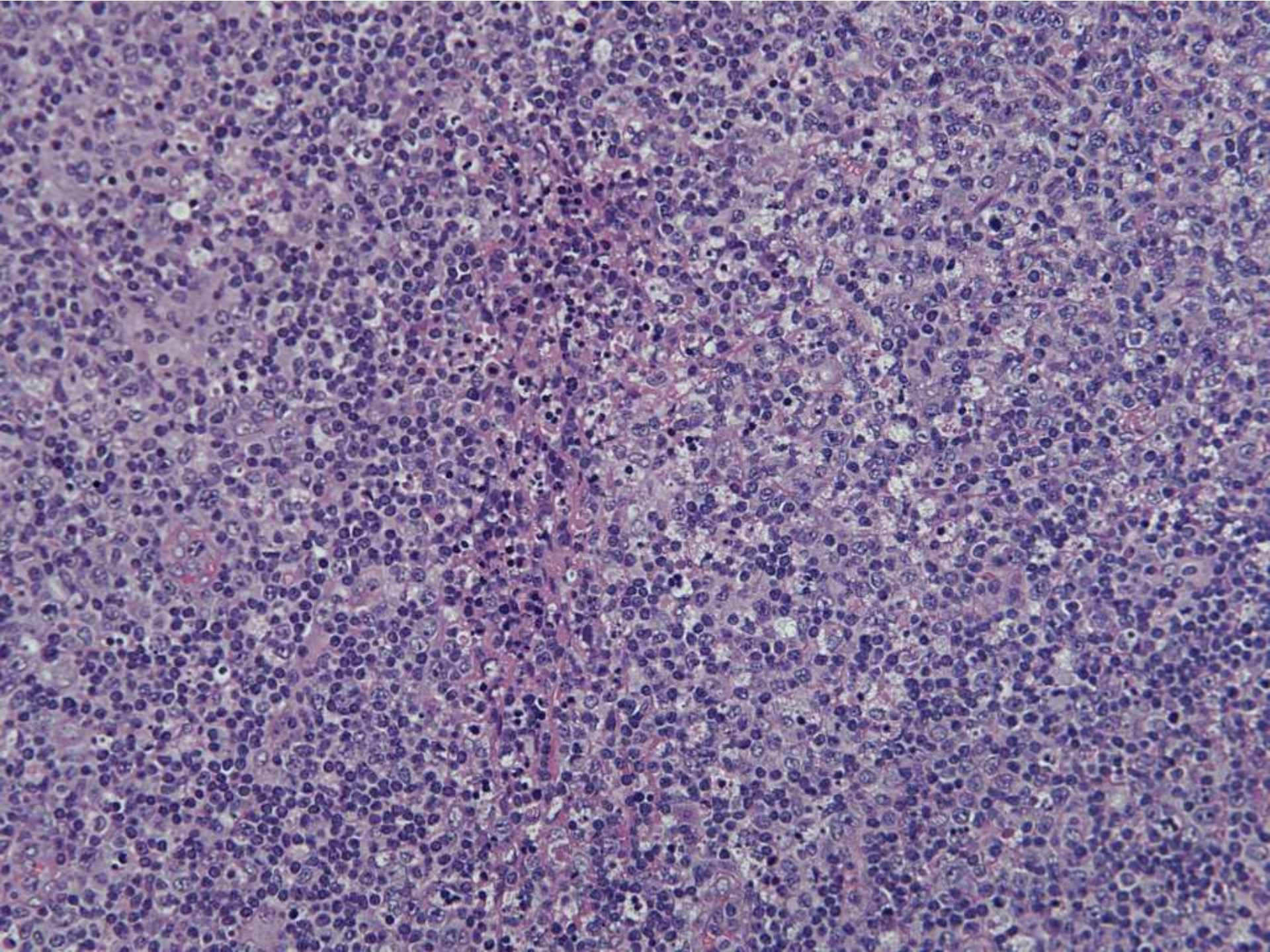
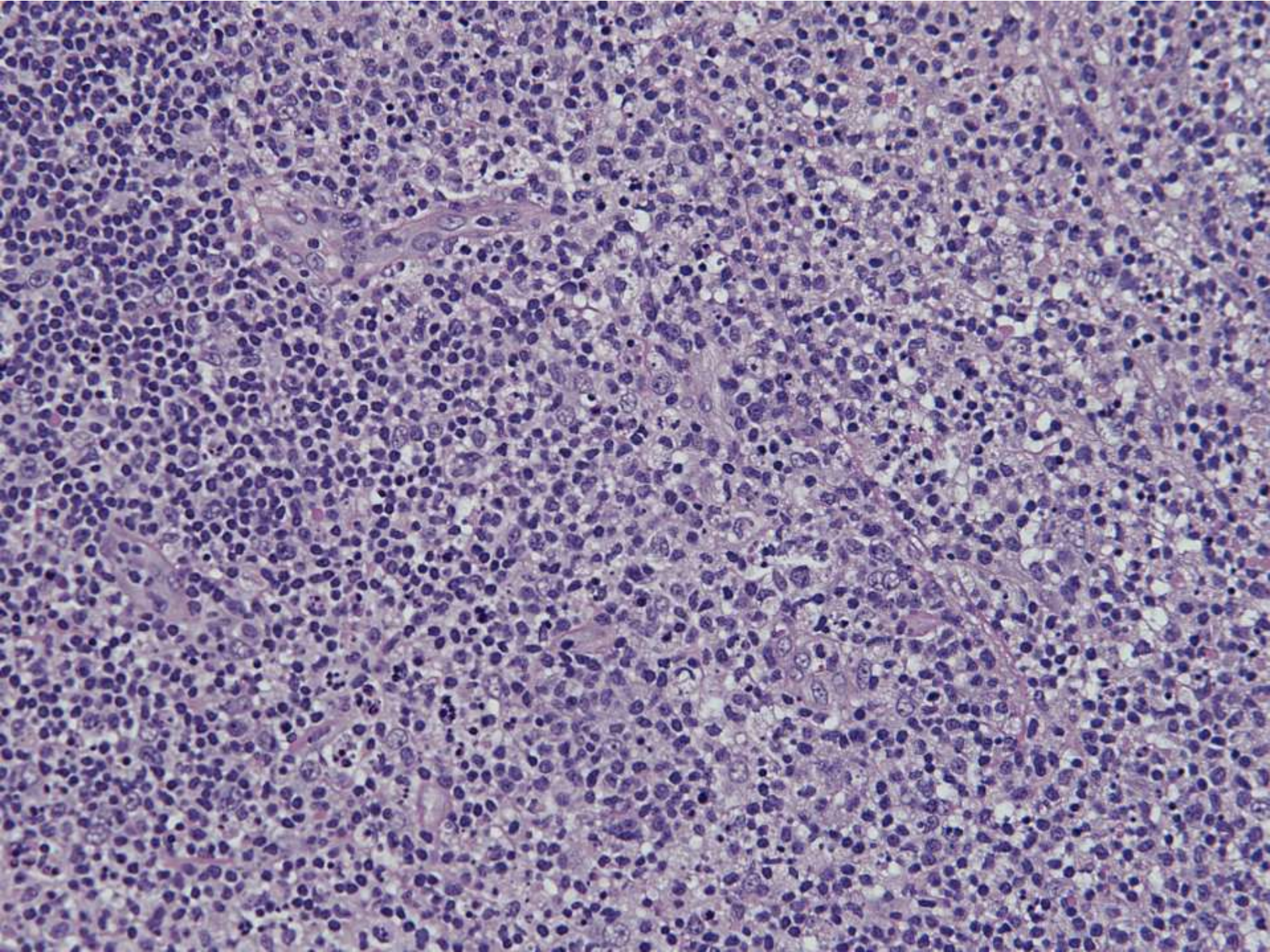
SB 6271
Sebastian Fernandez-Pol/Yaso Natkunam; Stanford

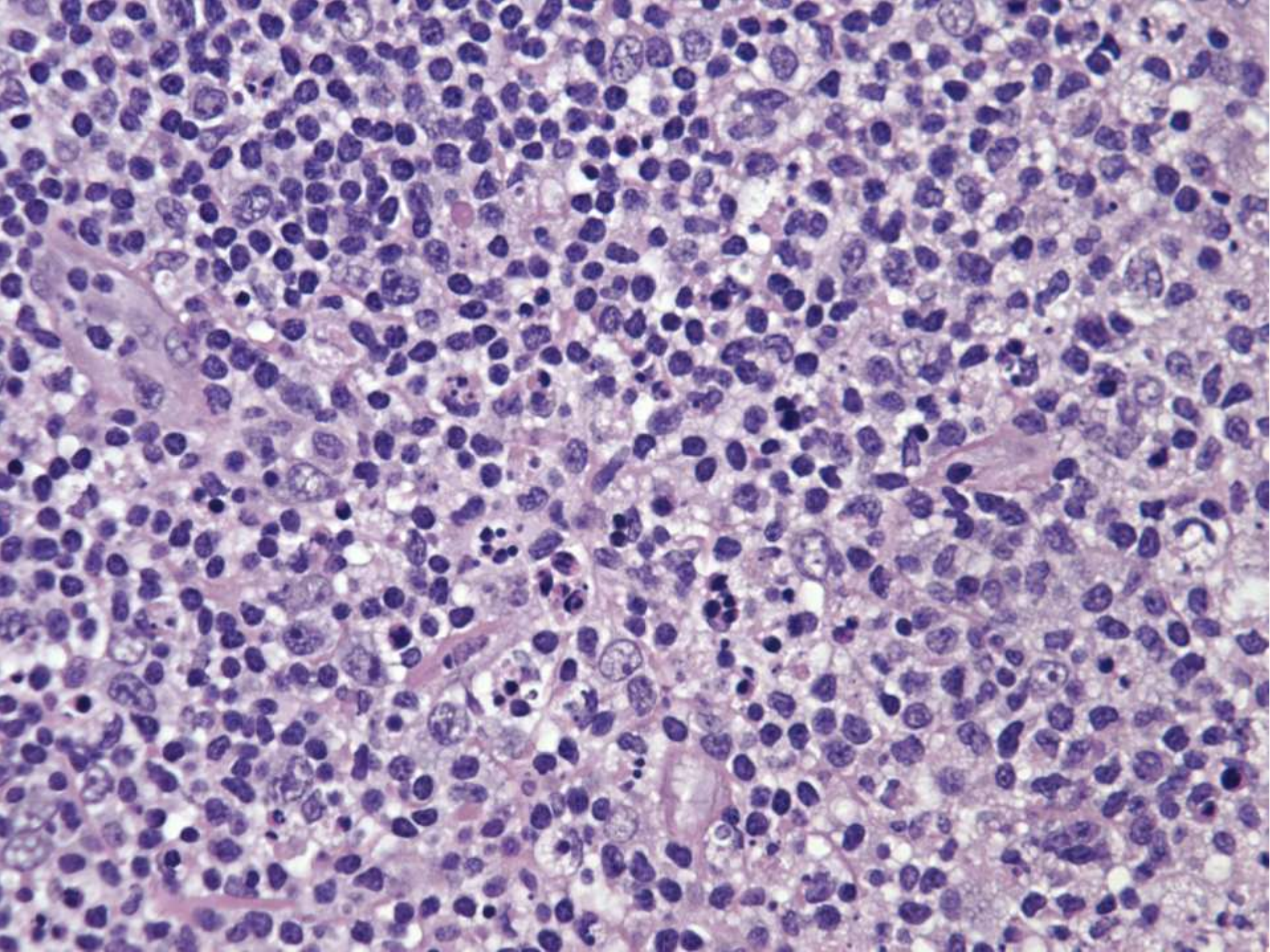
22-year-old man who reports recent history of night sweats, fatigue, and 3-4lb weight loss. Ultrasound imaging studies reported prominent lymph nodes up to 2.3cm. Right cervical LN.









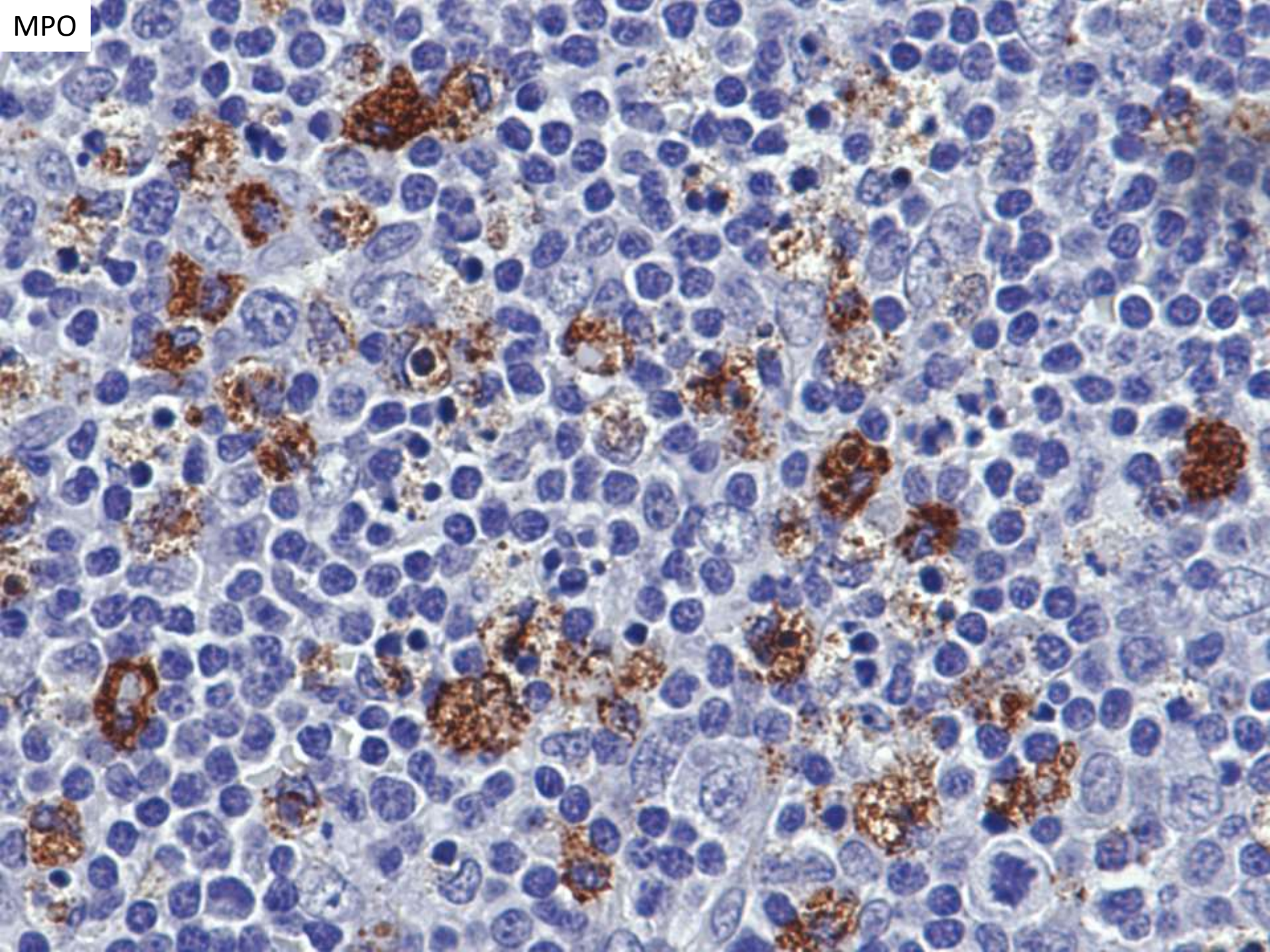


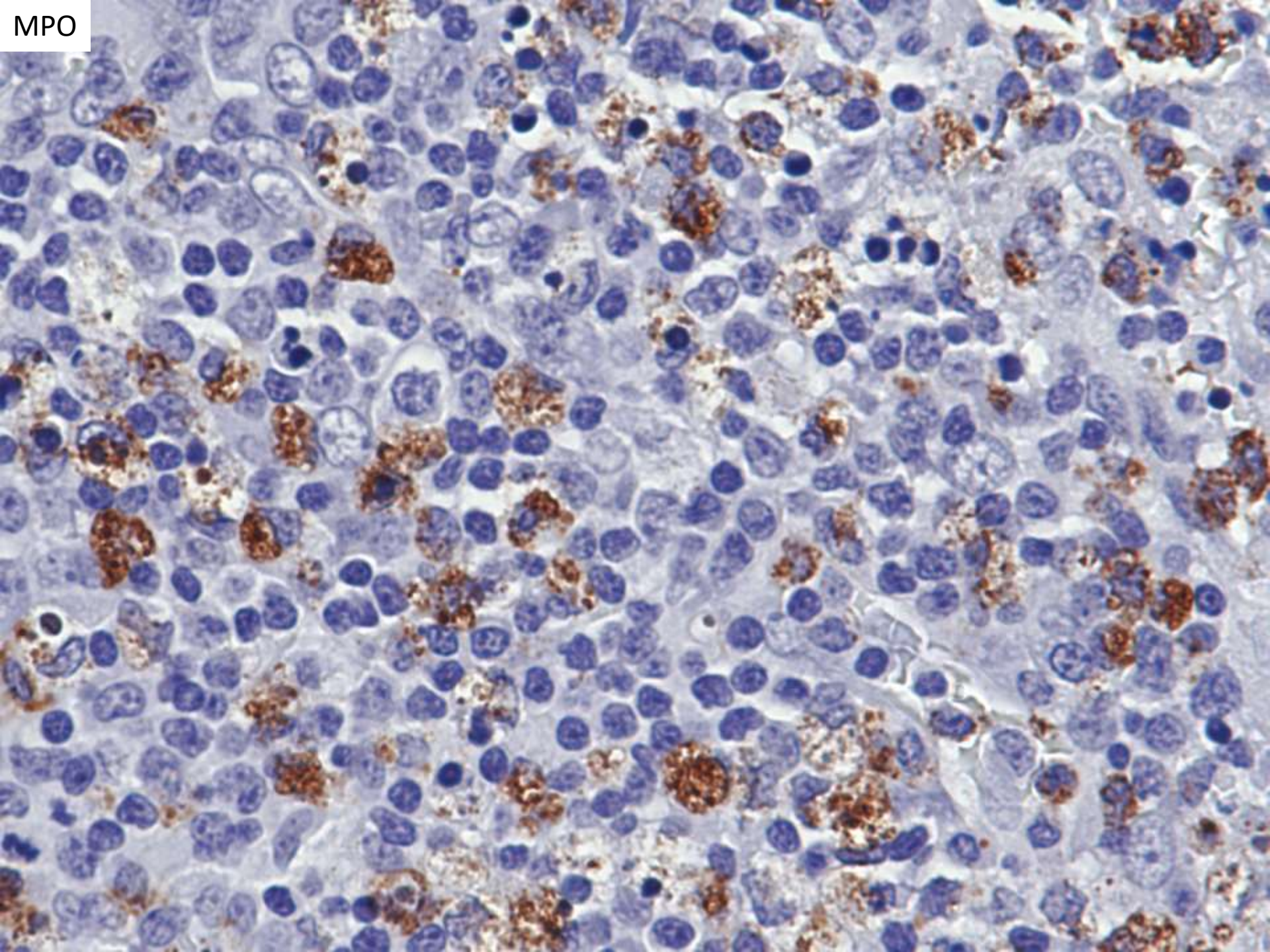
DIAGNOSIS?

Differential diagnosis

- T-cell lymphoma

- Necrotizing lymphadenitis
  - Herpes simplex (HSV)-associated lymphadenitis
  - Infections (fungal, mycobacterial)
  - Cat-scratch disease
  - Kikuchi-Fujimoto disease or histiocytic necrotizing lymphadenitis


MPO


MPO

Additional studies

- Negative viral stains:
  - EBER
  - CMV
  - HSV-1/2

- A corresponding flow cytometry study showed no aberrant T-cell antigen expression.

Kikuchi-Fujimoto disease histologic features

Morphology

- Can be classified into 3 evolving histologic phases:
  - Proliferative
    - Expanded paracortex with increases in various histiocytes and plasmacytoid dendritic cells
    - Admixed with variable number of lymphocytes and karyorrhectic nuclear debris
  - Necrotizing
    - Necrosis of any degree with proliferative features described above
  - Xanthomatous
    - When foamy histiocytes predominate
    - +/- necrosis

Kikuchi-Fujimoto disease histologic features

Immunohistochemistry

- Predominance of T cells (mostly CD8+) and histiocytes (MPO+ and CD68+)

- Relative large numbers of CD123+ plasmacytoid dendritic cells

Kikuchi-Fujimoto disease “typical” associations

- Presents in individuals under the age of 30
- Women are more frequently affected than men (4:1)
- Neutropenia and lymphocytosis in the peripheral blood occurs in 50% of patients
- *Many patients are of Asian descent??*
- *Laboratory testing is typically negative for ANA, dsDNA, and EBV??*
- *Necrotizing lymphadenitis without neutrophilic infiltration (in contrast to SLE lymphadenopathy)*

Medicine • Volume 93, Number 24, November 2014

Kikuchi-Fujimoto Disease

Retrospective Study of 91 Cases and Review of the Literature

*Guillaume Dumas, MD, *Virginie Prendki, MD, Julien Haroche, MD, PhD, Zahir Amoura, MD, PhD, Patrice Cacoub, MD, PhD, Lionel Galicier, MD, Olivier Meyer, MD, PhD, Christophe Rapp, MD, Christophe Deligny, MD, Bertrand Godeau, MD, PhD, Elisabeth Aslangul, MD, PhD, Olivier Lambotte, MD, PhD, Thomas Papo, MD, PhD, Jacques Pouchot, MD, PhD, Mohamed Hamidou, MD, PhD, Claude Bachmeyer, MD, Eric Hachulla, MD, PhD, Thierry Carmoi, MD, Robin Dhote, MD, Magdalena Gerin, MD, Arsene Mekinian, MD, Jérôme Stirnemann, MD, PhD, Fréderic Charlotte, MD, Dominique Farge, MD, PhD, Thierry Molina, MD, PhD, and *Olivier Fain, MD, PhD*

TABLE 4. Comparison of Kikuchi-Fujimoto disease manifestations between previous and present series

	Dumas et al.	Cheng et al.	Young Song et al.	Yu et al.	Kuo	Tsang et al.	Treilleux et al.	Kikuchi et al.	Dorfman et al.	Pileri et al.	Turner et al.
Reference	Present report	(11)	(58)	(85)	(46)	(79)	(78)	(38)	(16)	(60)	(81)
Year of publication	2014	2010	2009	2005	1995	1994	1991	1990	1988	1982	1982
Number of patients	91	195	102	58	79	75	11	276	108	27	30
Country	France	Taiwan	Korea	Taiwan	Taiwan	Hong-Kong	France	Japan	USA/other countries	Germany	USA
Age (yr)	30	24.6	26.7	24.9	26.8	25.5	23	26.9	30	26.6	28
Sex ratio M/F	1/3	1/2.6	1/3.6	1/1.76	1/1.1	1/2.75	1/2.7	1/1.56	1/4	1/2.85	1/9
Caucasian (%)	33	0	0	0	0	–	63.6	–	63	96	63
Afro-Caribbean (%)	31.9	0	0	0	0	–	36.4	–	5	–	0
Asian (%)	13.2	100	100	100	100	100	0	100	–	4	20
Localized nodes (%)	48	74.9	10.8	94.8	97	94.6	90	97.5	86	55.5	76.7
Generalized nodes (%)	52	23.1	3.9	5.2	1.3	5.3	–	11.3	12	22.2	23.3
Fever (%)	67	37.9	73.5	43	48.4	38.5	45.5	30.2	33	50	6.7
Night sweats (%)	43	5.6	8.8	2	–	–	36.4	–	6,5	–	3
Arthralgia (%)	34.1	2.6	6.9	3	–	–	27.3	–	3,7	–	–
Rash (%)	32.9	4.1	2	3	1.26	–	9	–	3,7	–	3.3
Hepato-splenomegaly (%)	14.8		–	3	–	–	–	–	8,3	28.5	10
Leucopenia (%)	34.9	23.1	53.5	29	42.9	45.5	18	58.3	20	25	16.7
ANA at diagnosis (%)	42.2	8.9	30.4[†]	–	2.5	6	–	–	7	–	–
Inflammatory syndrome (%)[*]	56.4	78.9	–	14	–	–	–	–	–	71	–
Corticosteroid Treatment (%)	31.9		12.7	7	–	–	–	–	–	–	–
Associated viral disease (%)	8.8	0	–	–	–		–	–	–	–	–
Recurrence (%)	17.6	7	20.6	0	3.3	3	18.2	4	5	–	–

ANA = Anti nuclear antibody.

[*] defined by elevated ESR or C-RP.

[†] data available in 46 patients.

TABLE 1. Baseline characteristics of Kikuchi-Fujimoto patients

	N (%) (n = 91)	NR*
Laboratory features		
Inflammatory syndrome (C-RP> 10 mg/l; ESR> 20mm)	44 (56.4)	13
Neutropenia (PNN< 1500/mm3)	28 (35)	8
Lymphopenia (< 1500/mm3)	53 (63.8)	8
Thrombocytopenia (<150 000/mm3)	12 (19)	28
Elevated liver enzymes (ALAT> 42U/l)	20 (24.4)	49
Increased LDH (>460UI/l)	44 (81.5)	37
ANA	33 (45.2)	18
Anti ds-DNA	11 (18)	30
Positive viral serology§	8 (8.8)	–
Treatment		
NSAIDs	6 (6.6)	–
Corticosteroids	29 (31.9)	–
Hydroxychloroquine	16 (17.6)	–
IVIG	3 (3.3)	–
Antibiotics	36 (39.6)	–
Outcome		
SLE	12 (13)	–
Recurrence	16 (20.7)	14

Abbreviations: ANA = Anti nuclear antibody; CRP = C-reactive protein; ds-DNA = double stranded DNA antibody; ESR = Erythrocyte sedimentation rate; IVIG = Intravenous Immunoglobulins; LDH = Lactate deshydrogenase; NSAIDs = non-steroidal anti-inflammatory drugs; SLE = Systemic Lupus Erythematosus.

* not recorded.

† Median (Q1-Q3).

‡ rheumatoid arthritis (1), Antiphospholipid syndrome (1), severe Raynaud's phenomenon (2), mixed connective (1), HIV(2), Sickle cells disease (2), end stage chronic kidney disease (1).

§ Epstein Barr Virus (EBV) = 4; Parvovirus B19 = 2, Human Herpes virus 6 (HHV6) = 1, Coxsackie A=1.

Clinico-pathologic differential diagnosis

- Kikuchi lymphadenopathy versus SLE-associated adenitis
  - Both share clinical and pathologic findings
  - Diagnosis of SLE can precede, follow, or coincide with the diagnosis of KFD

Clinical behavior

- The outcome is usually favorable
- Most patients show spontaneous resolution of the symptoms and lymphadenopathy within 1–4 months of the diagnosis
- Rare cases of fatal progression have been described

Take home points

- Do not make a diagnosis of T-cell lymphoma in a young patient before considering Kikuchi-Fujimoto disease
- Rule out infectious causes of necrotizing lymphadenitis (e.g. EBV, HSV, CMV, bacterial, fungal)
- Some histologic features are associated with Kikuchi over SLE, but even rigorously classified cases of Kikuchi are associated with a diagnosis of SLE
- Provide a differential diagnosis, recommend viral, ANA, and ds-DNA studies

References

- Gru AA, O'Malley DP. Autoimmune and medication-induced lymphadenopathies. Semin Diagn Pathol. 2018 Jan;35(1):34-43

- Dumas G, Prendki V, Haroche J, et al. Kikuchi-Fujimoto disease: retrospective study of 91 cases and review of the literature. Medicine (Baltimore) 93: 372-382, 2014

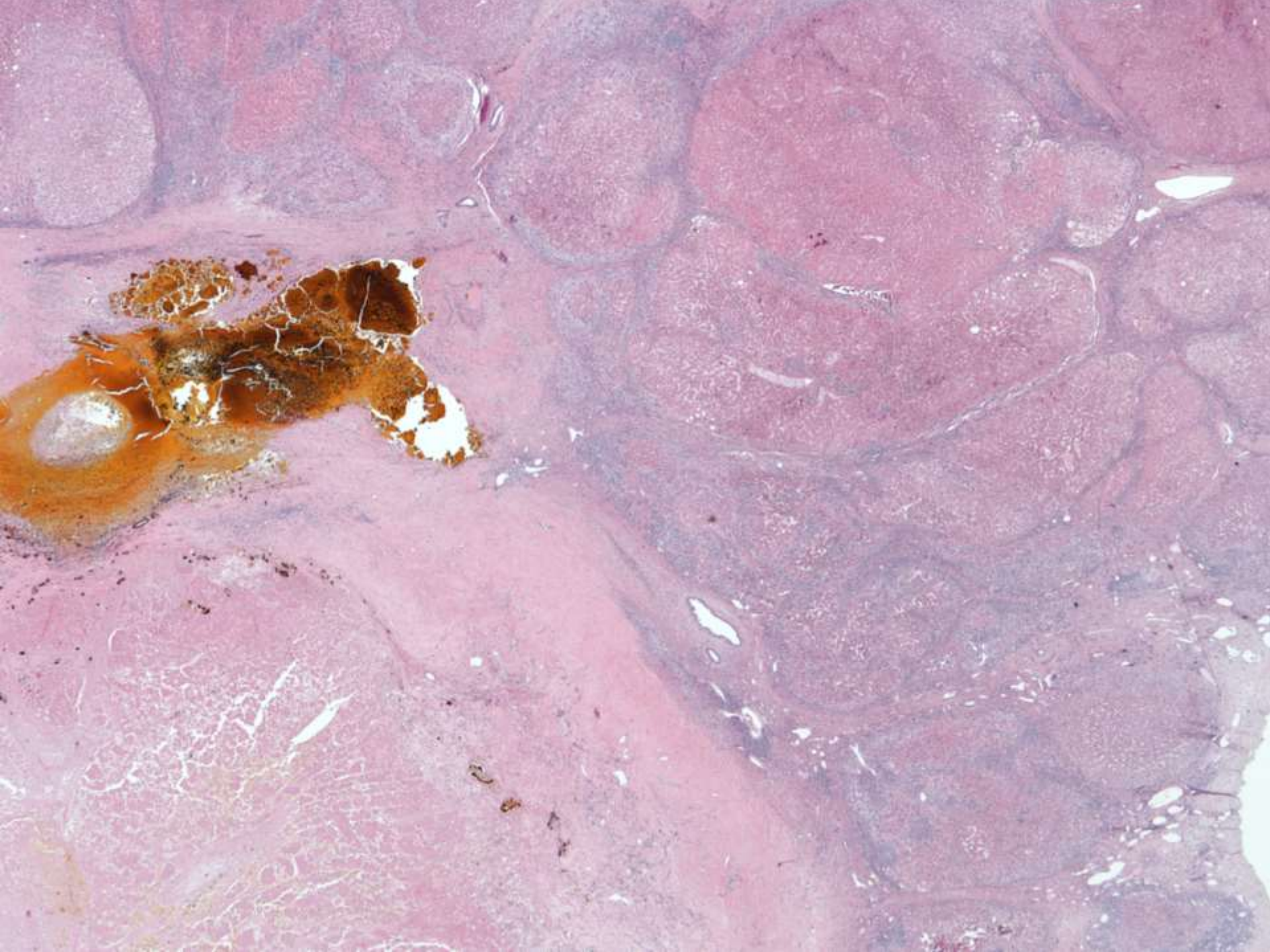
- Charles Blake Hutchinson and Endi Wang. Kikuchi-Fujimoto Disease Archives of Pathology & Laboratory Medicine 2010 134:2, 289-293

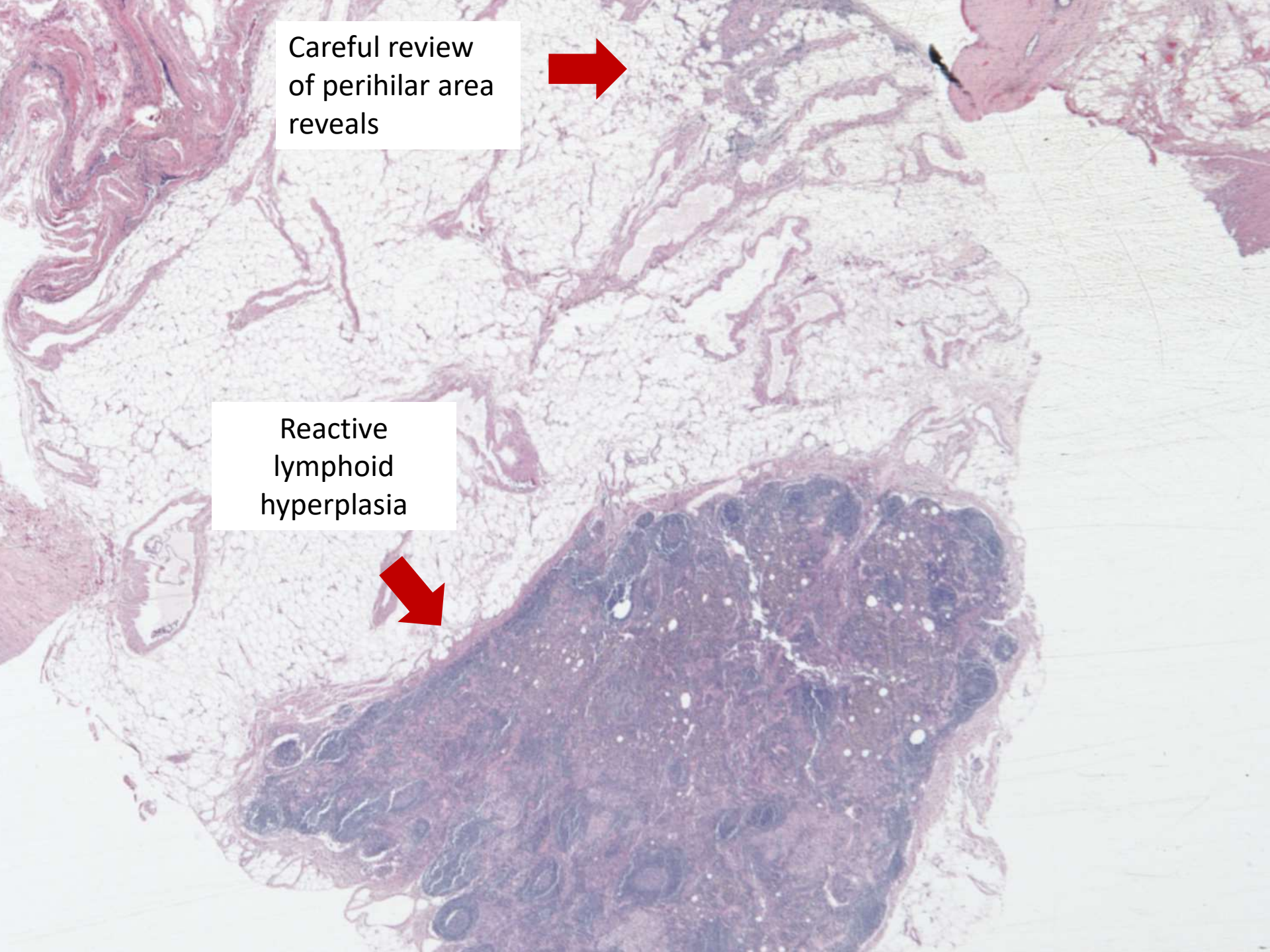
SB 6272
Josh Menke/John Higgins/Dita Gratzinger; Stanford

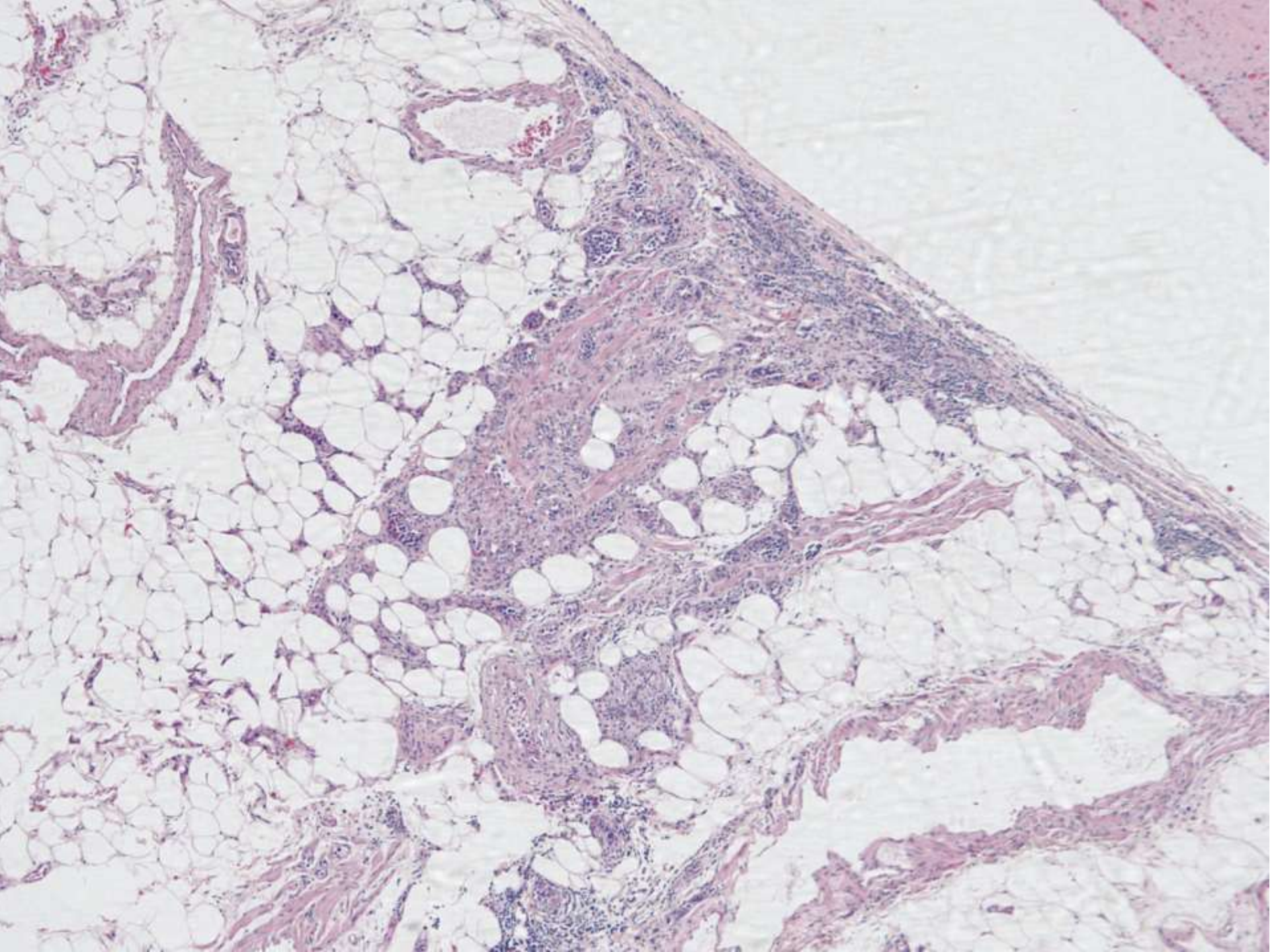
69-year-old man with cirrhosis secondary to hepatitis B and auto-immune hepatitis, complicated by hepatocellular carcinoma. Tissue submitted: explant liver.

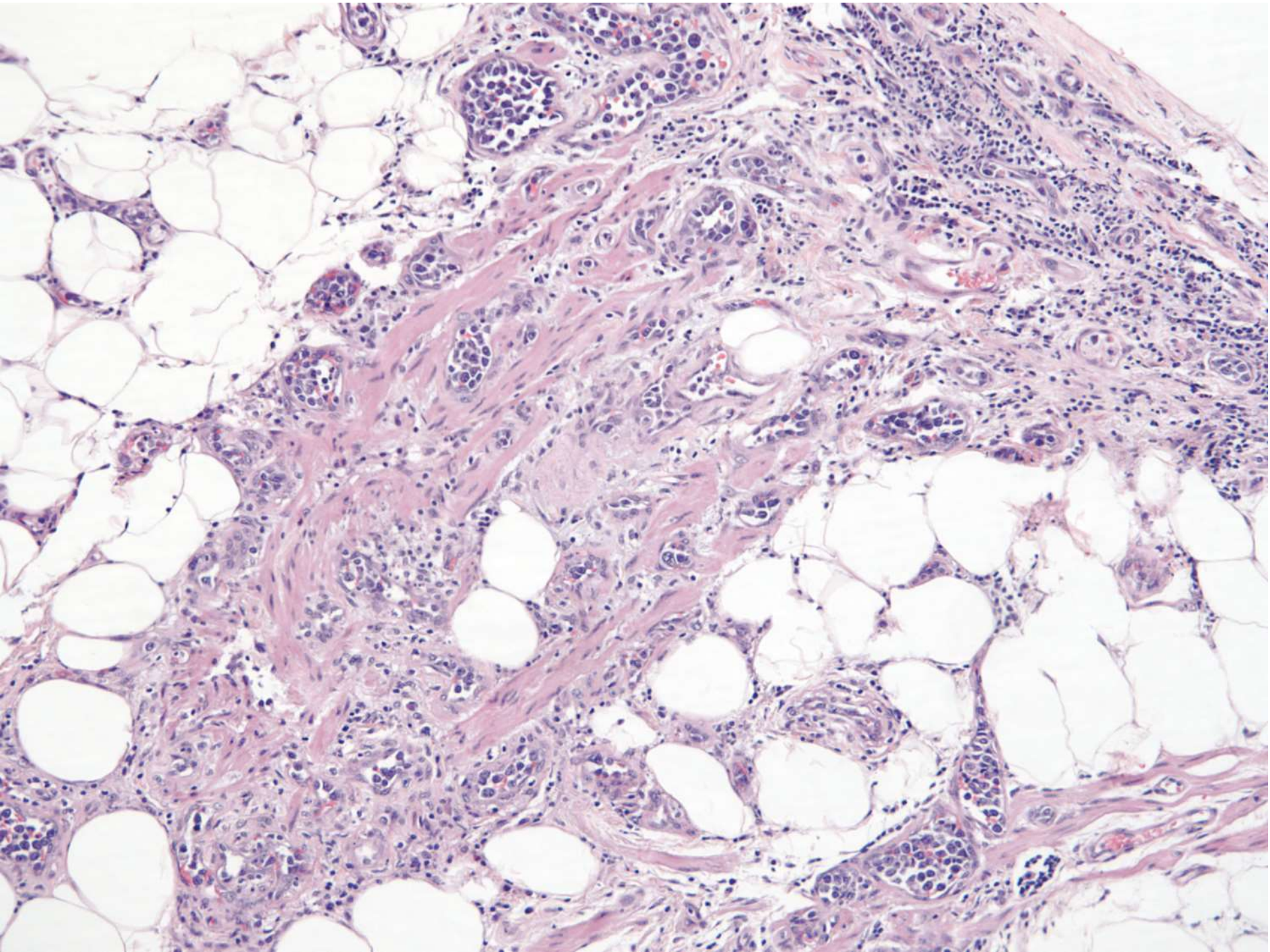
Clinical History

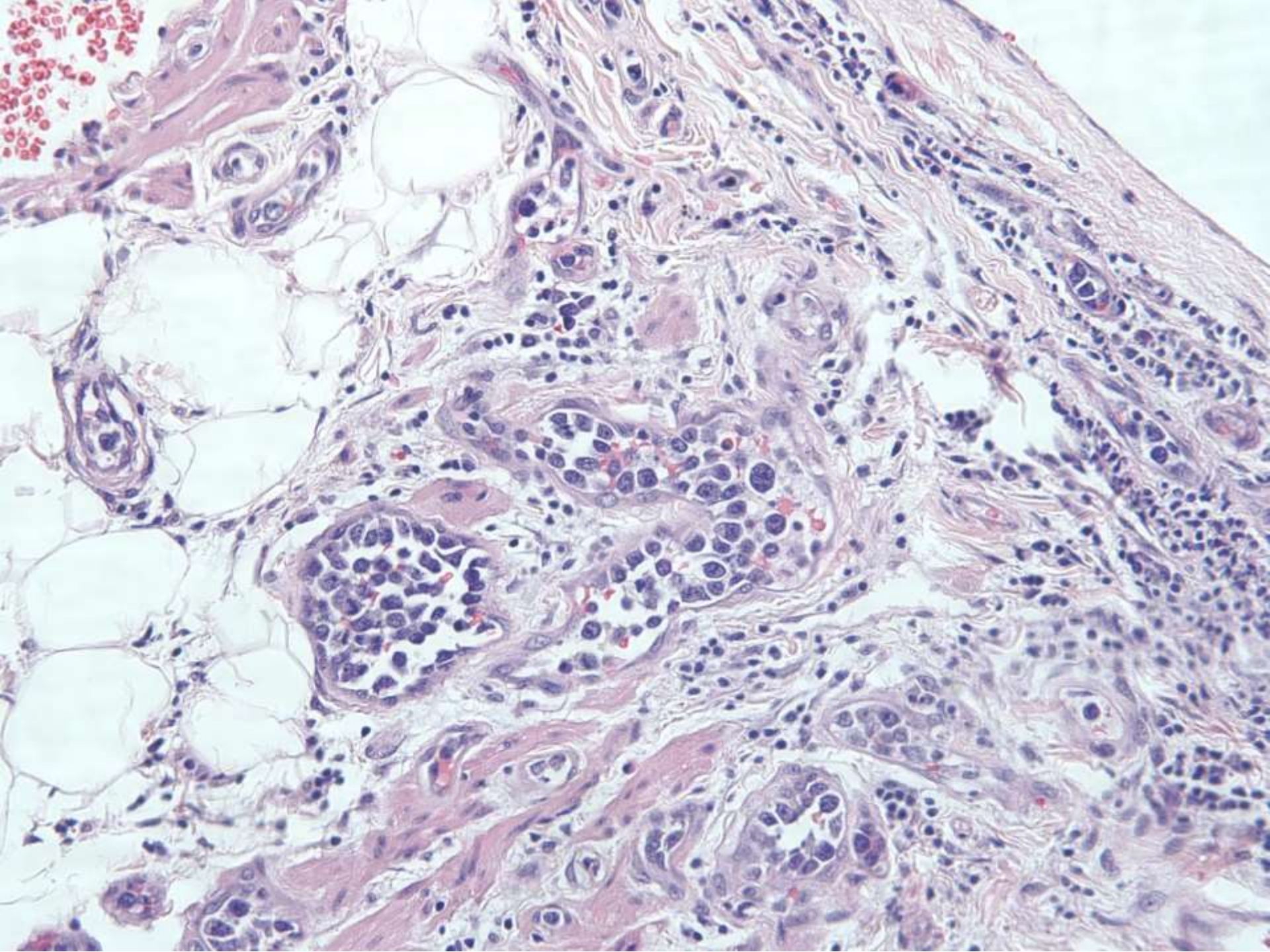
- 69 year old man with cirrhosis secondary to hepatitis B and autoimmune hepatitis, complicated by hepatocellular carcinoma
- Now status post liver transplant; native liver sampled for pathology review
- Native liver shows chronic hepatitis with grade 2 activity and stage 4 fibrosis

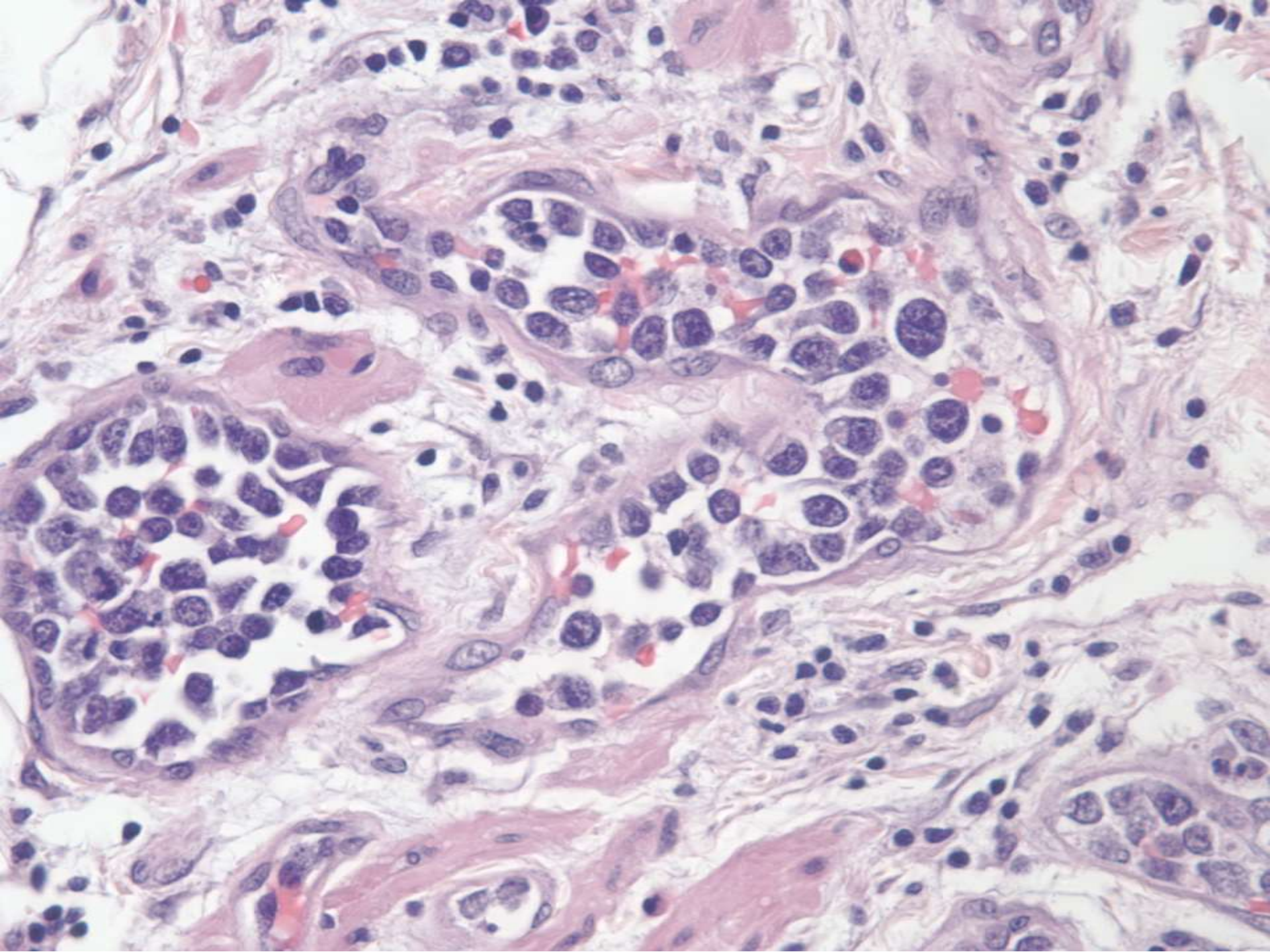



Careful review of perihilar area reveals
Reactive lymphoid hyperplasia









Differential Diagnosis?

DIAGNOSIS?

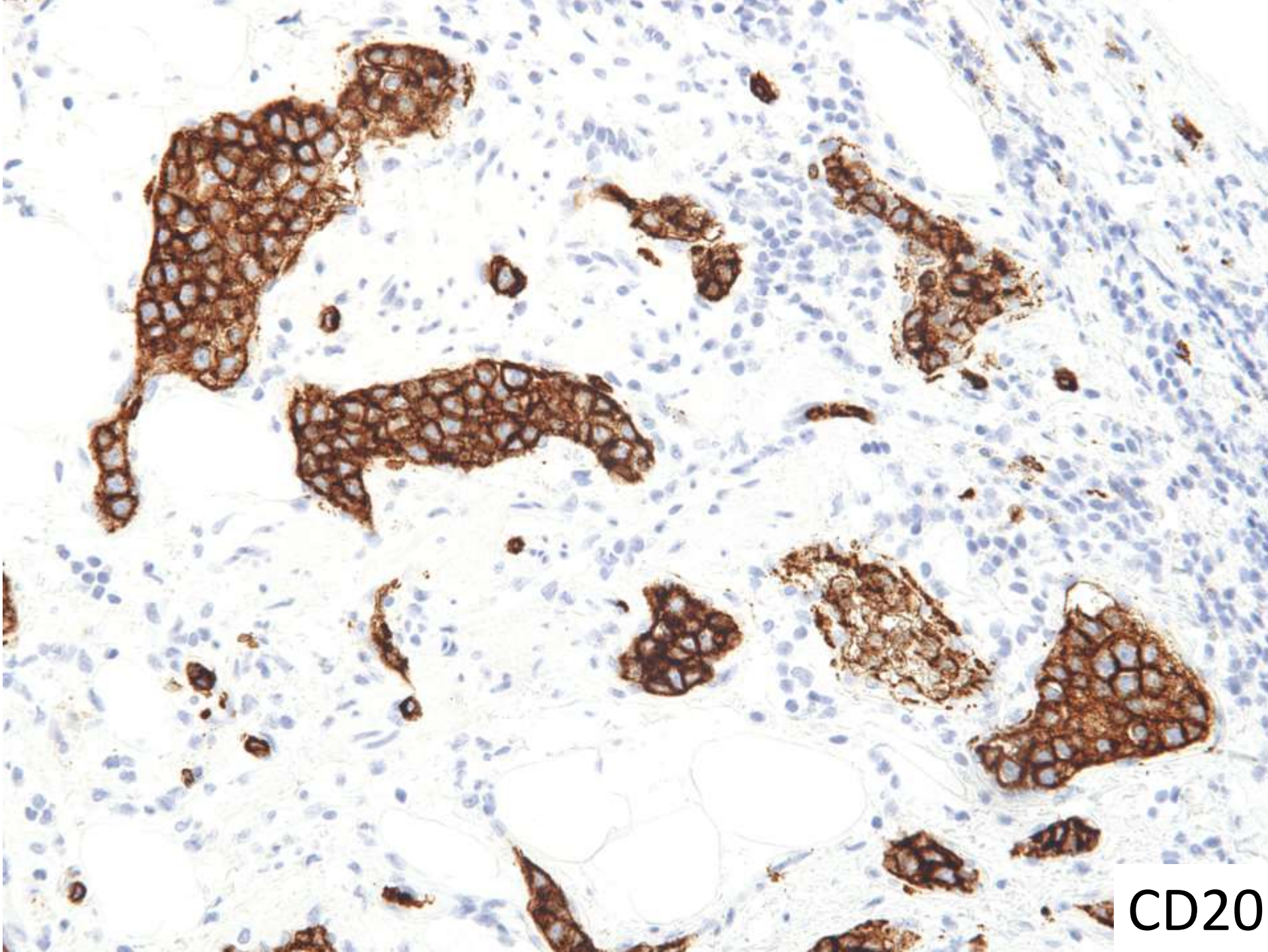
South Bay Case

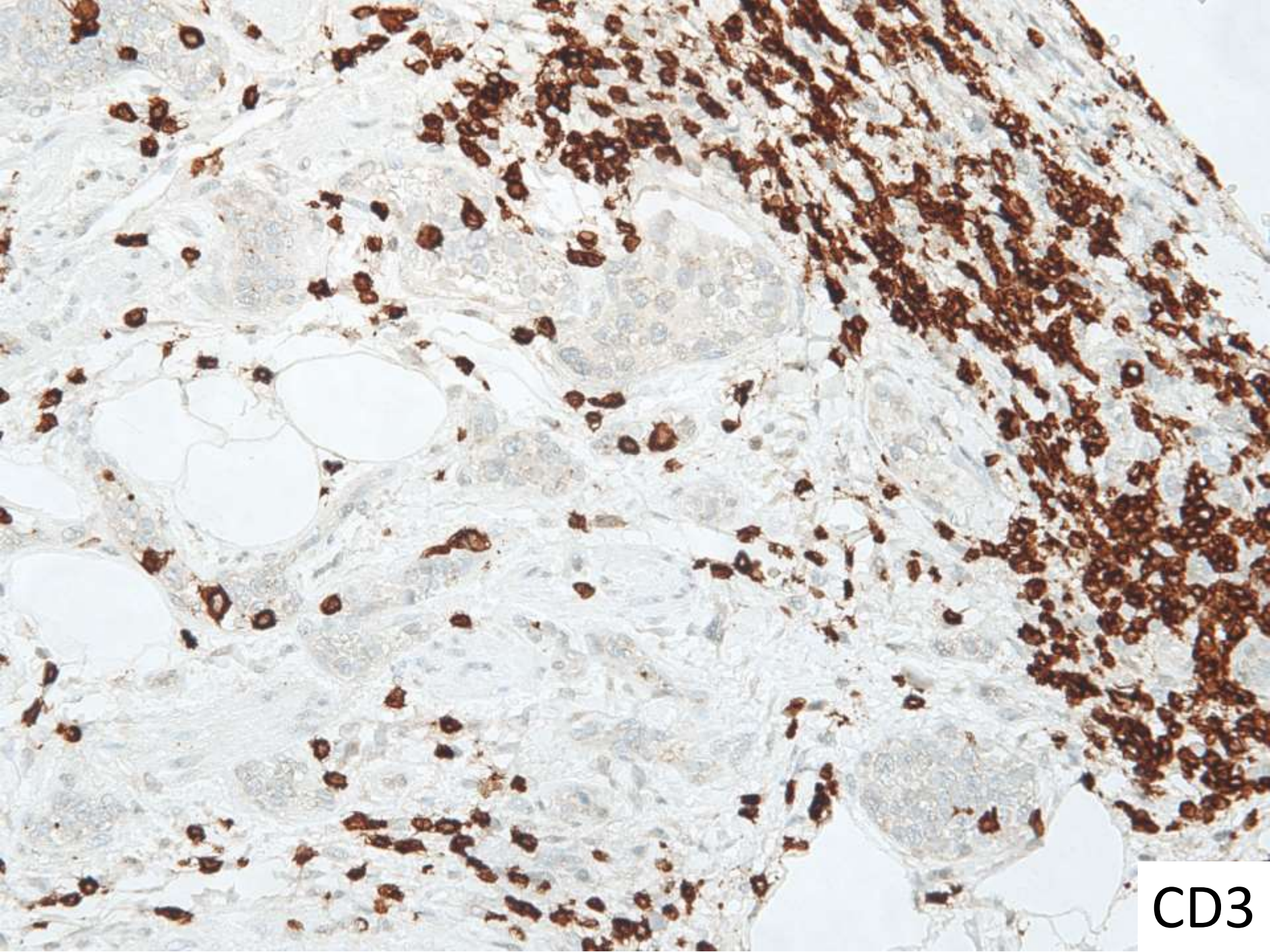
Joshua Menke
John Higgins
Dita Gratzinger

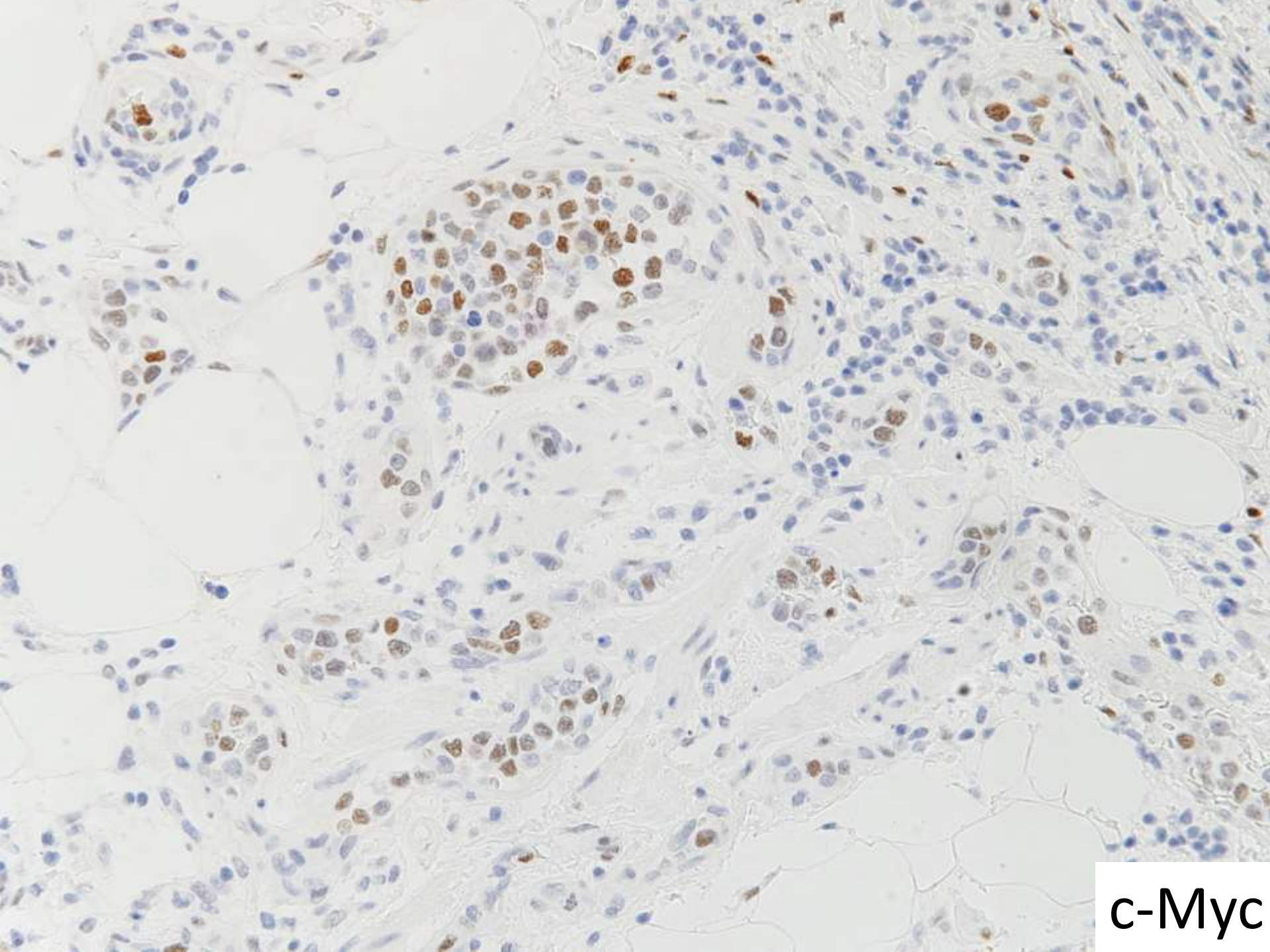
Stanford University

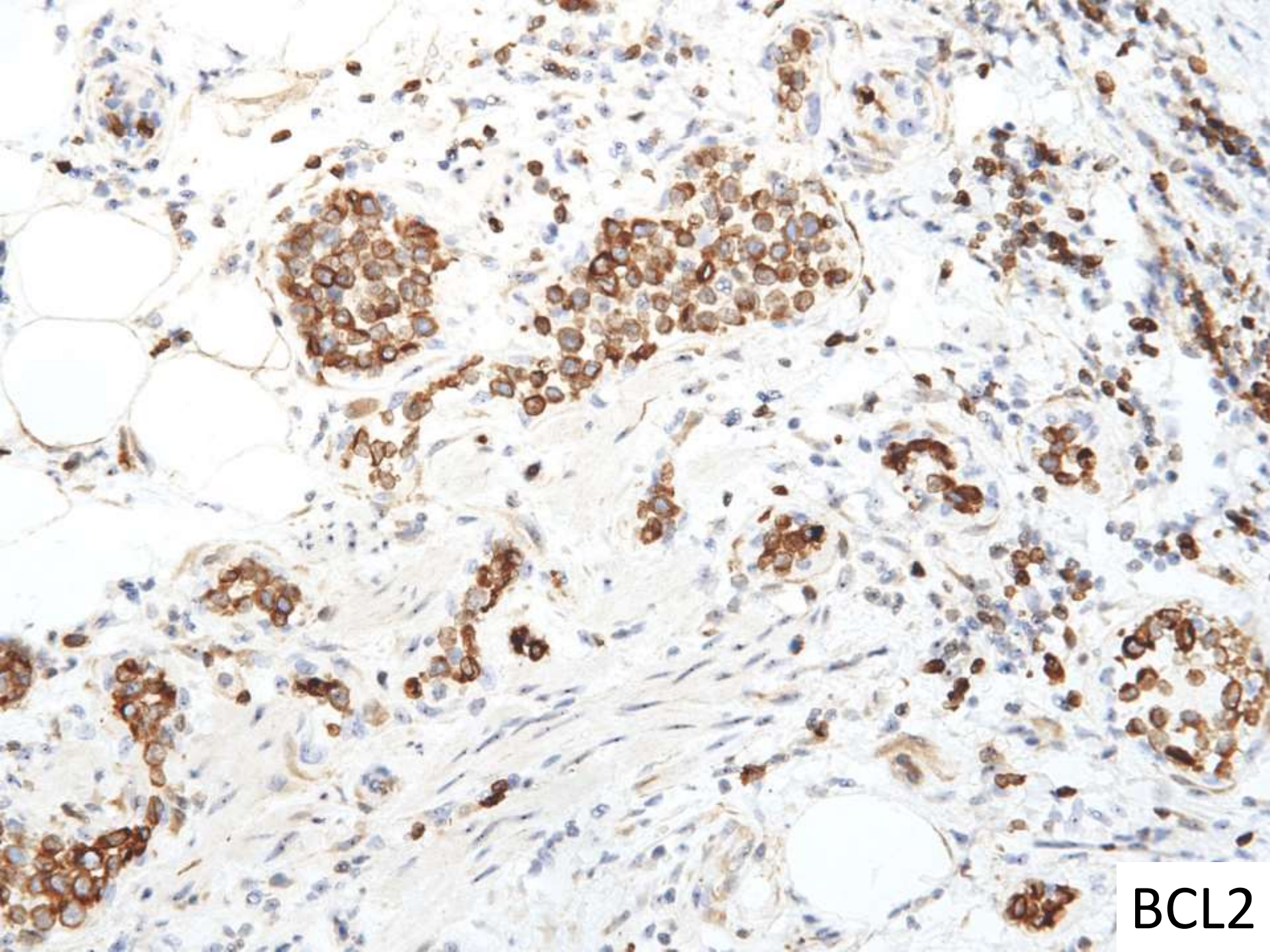
Differential Diagnosis

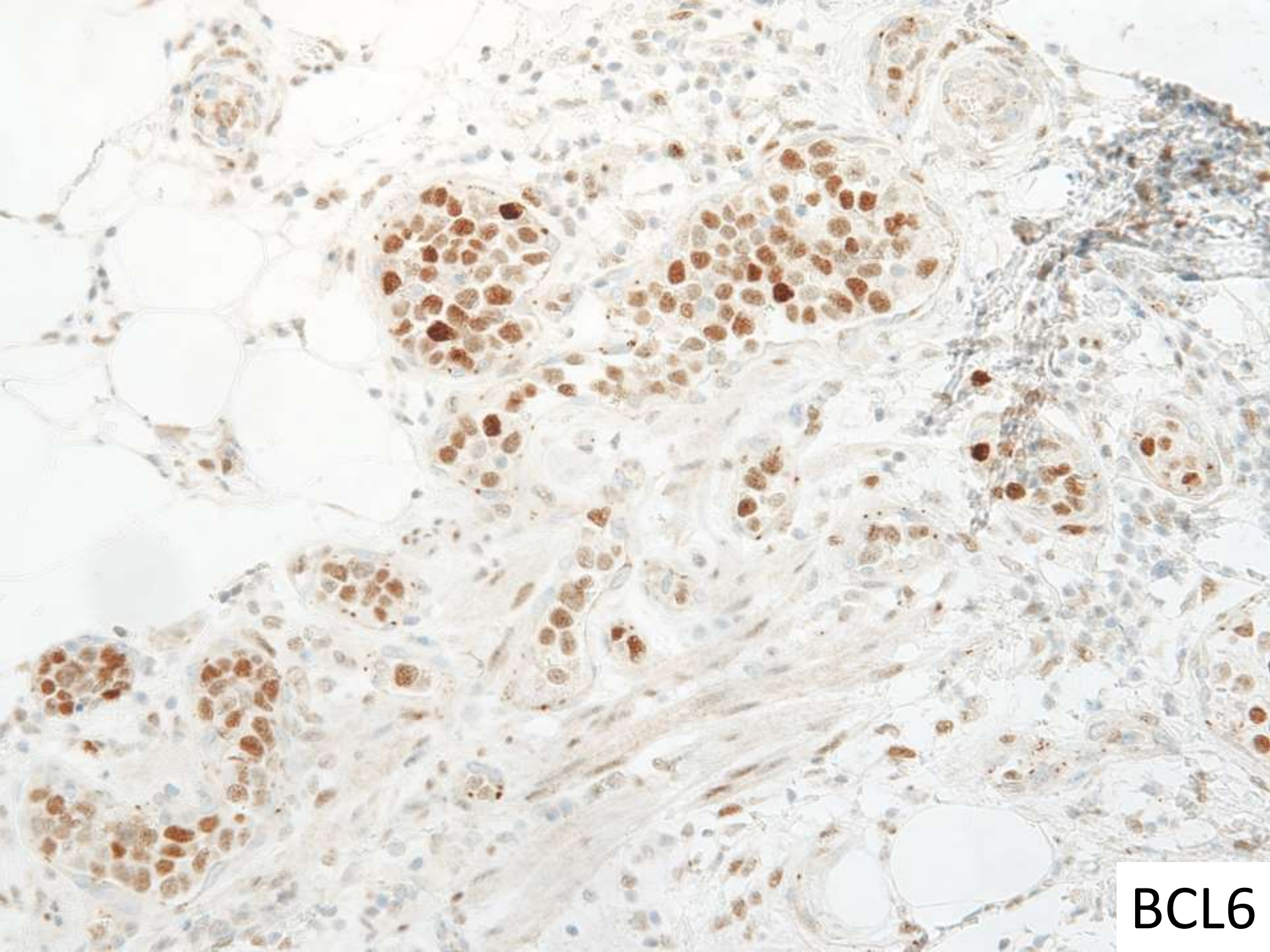
- Metastatic carcinoma (e.g. hepatocellular)
- Metastatic melanoma
- Intravascular lymphoma
- Reactive angioendotheliomatosis

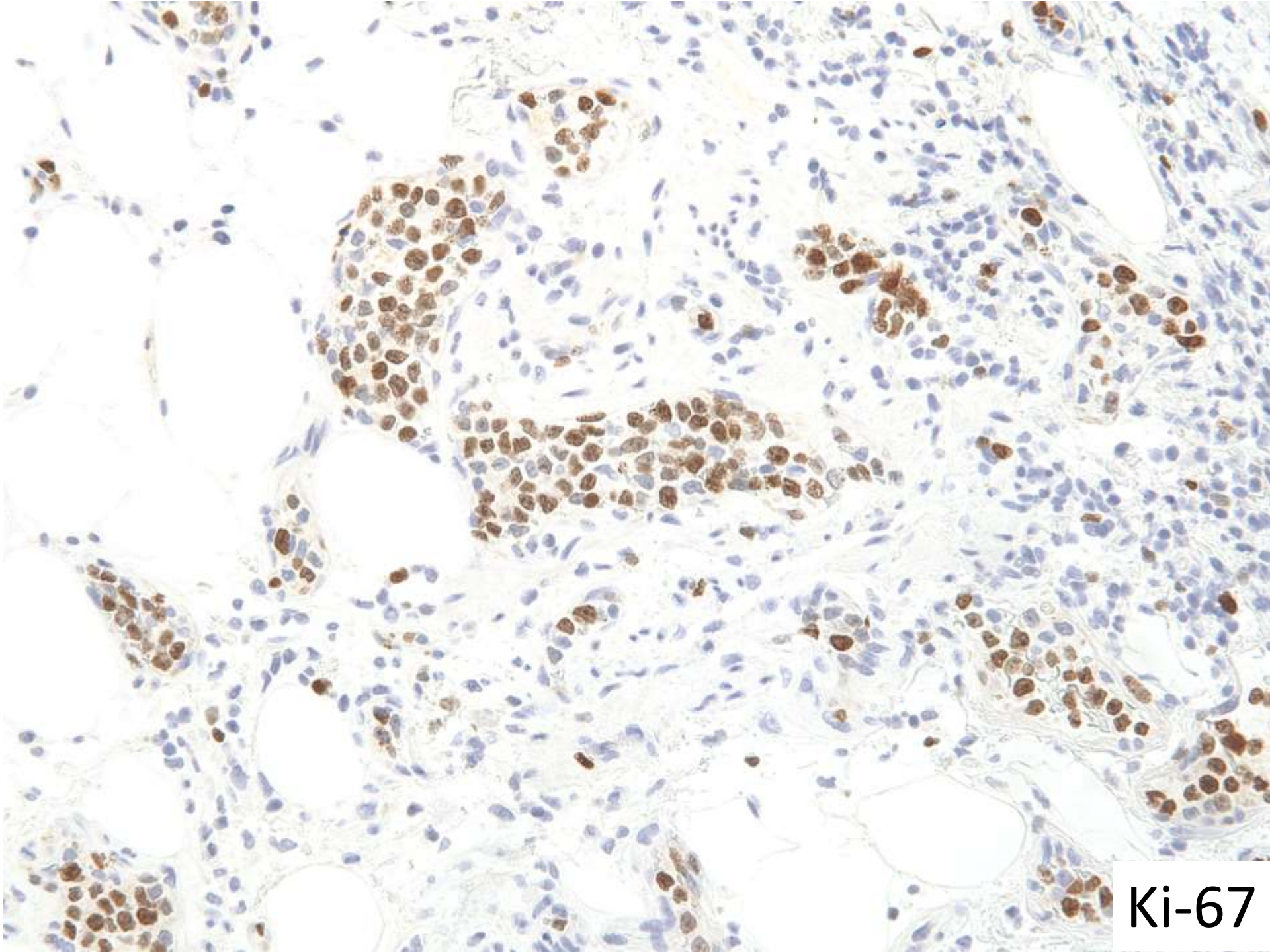

CD20

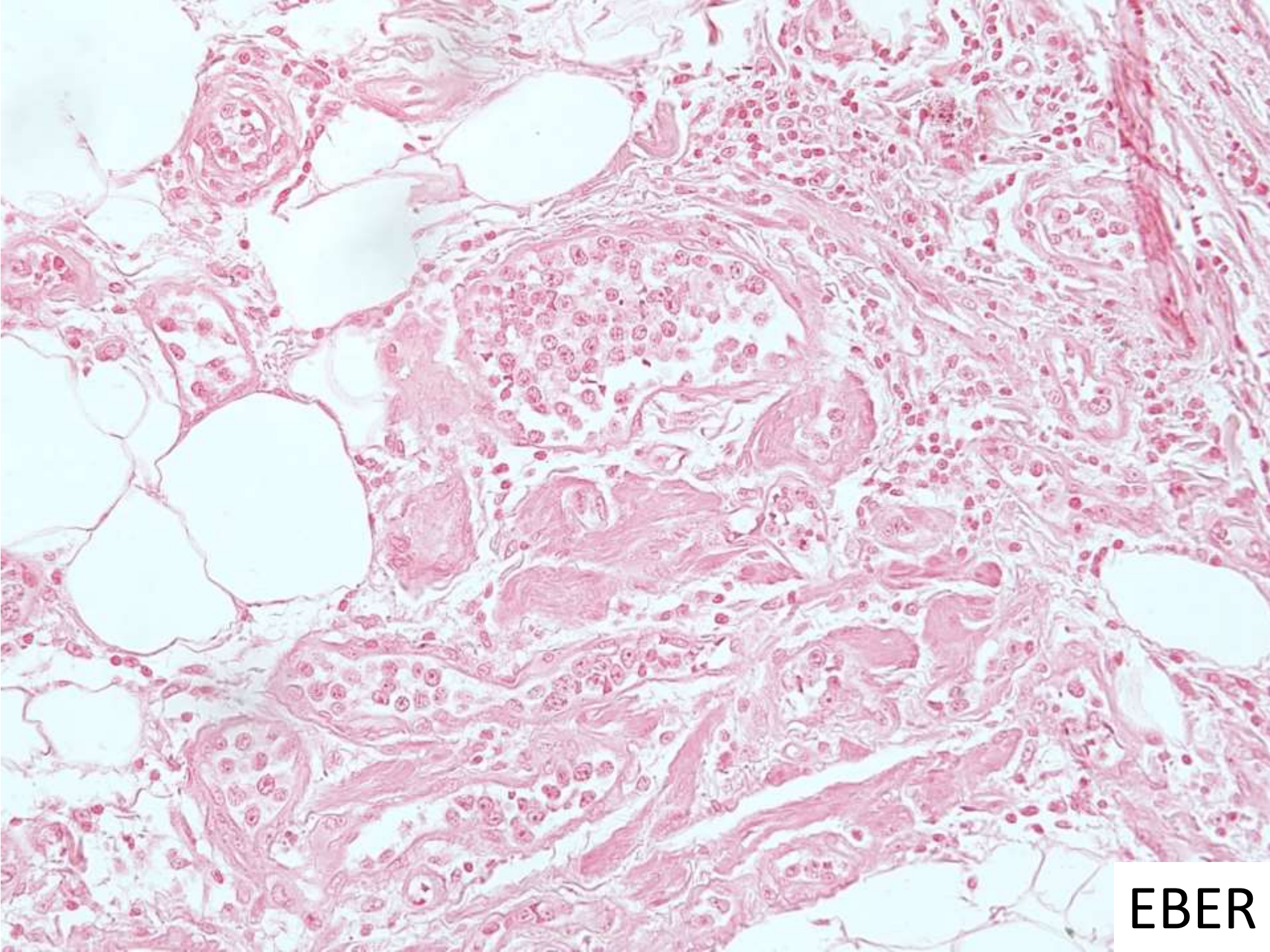

CD3


c-Myc


BCL2


BCL6


Ki-67


EBER

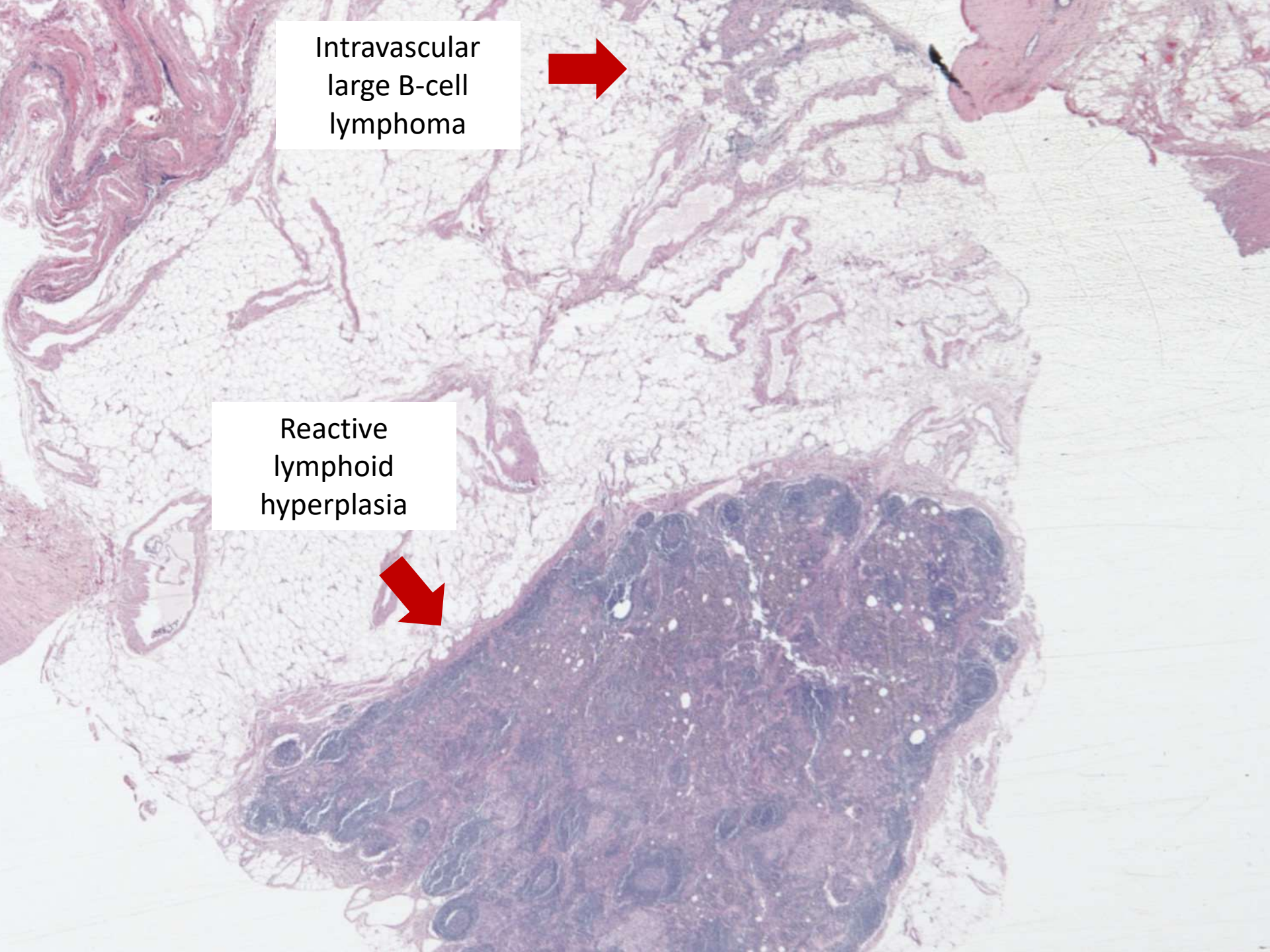
Additional immunostains

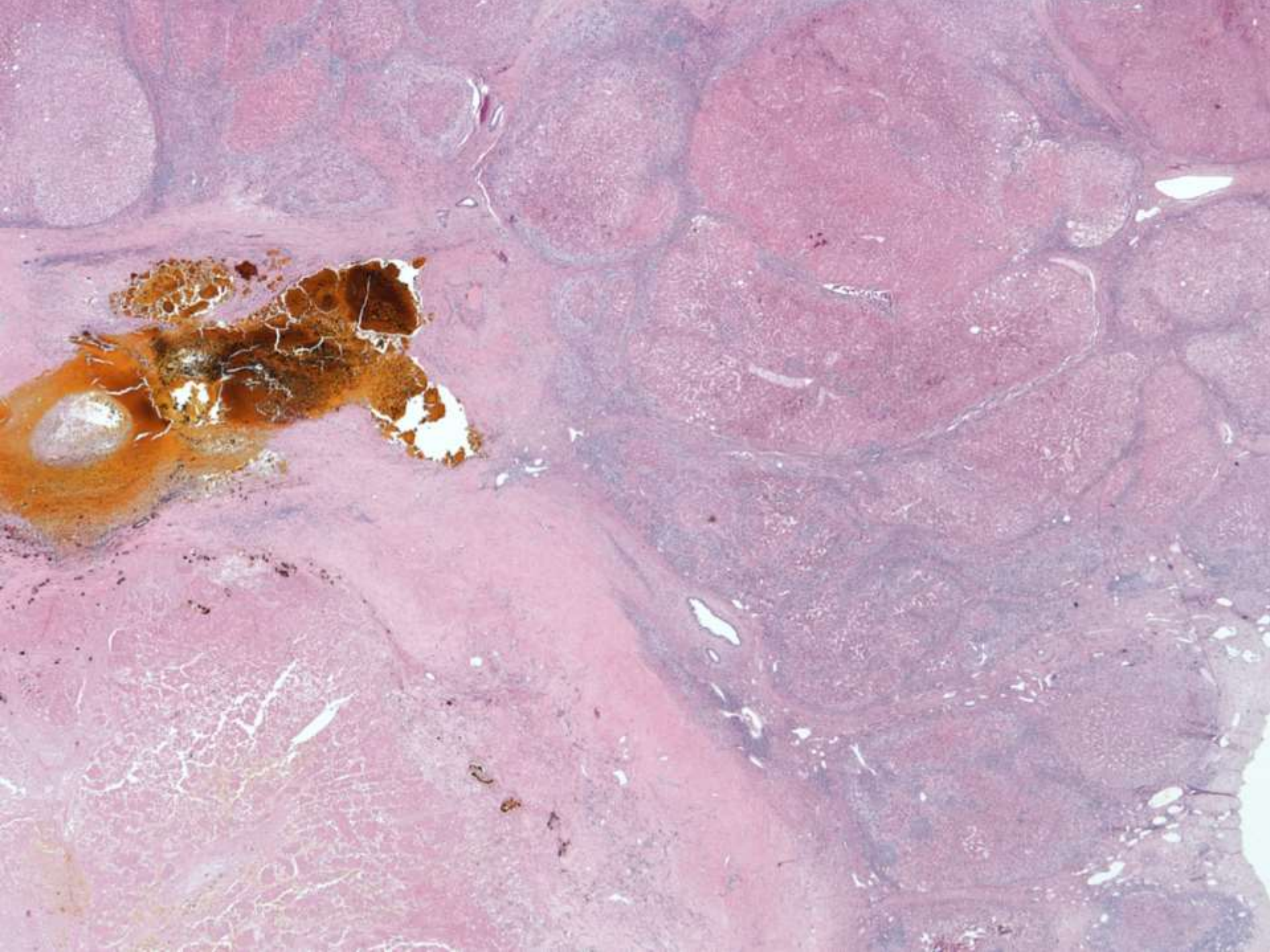
- MUM1 and CD10 both negative
- CD30 negative

Final Diagnosis

- Intravascular large B cell lymphoma in perihilar area of native liver explant*
- Chronic hepatitis with grade 2 activity and stage 4 fibrosis; negative for residual carcinoma
- One (1) lymph node with no tumor

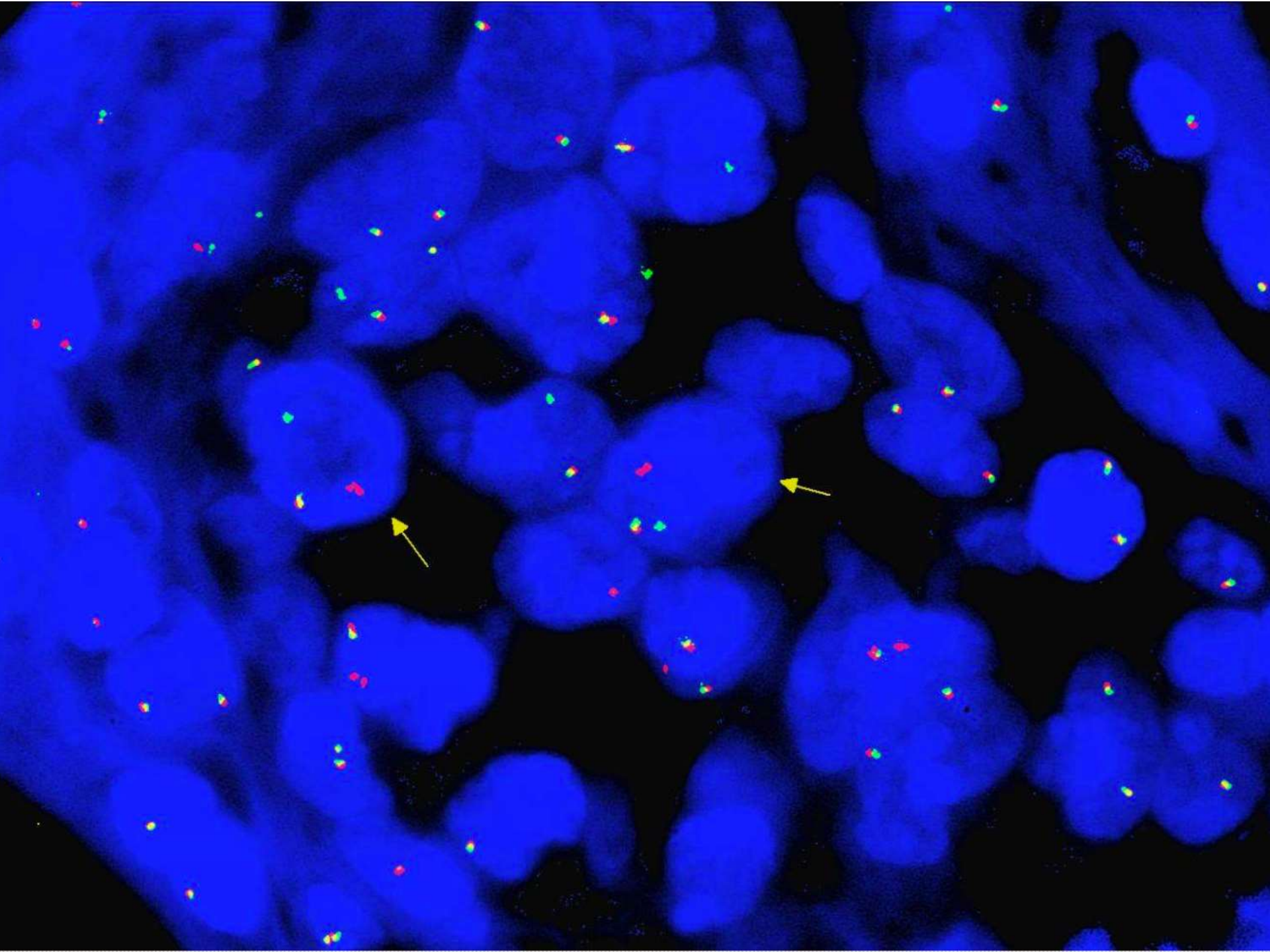
*No lymphoma was found in lymph node or native liver explant


Intravascular large B-cell lymphoma
Reactive lymphoid hyperplasia



Cytogenetics

- **FISH POSITIVE FOR *BCL6* REARRANGEMENT [48/200 nuclei]**
- **FISH NEGATIVE FOR *BCL2* AND *MYC* REARRANGEMENTS**



Follow up

- 6 months after liver transplant, liver biopsy showed evidence of acute rejection
- 6 weeks later, the patient passed away
- Postmortem cultures from multiple organs grew enterococcus
- No evidence of the patient's intravascular large B-cell lymphoma as noted on full body autopsy

Literature review

- Prior single case report describes a similar presentation: cirrhosis associated with hepatitis C; explanted liver showed involvement of small hilar vessels by IVLBCL; in this case non-germinal center type (CD10-, BCL6-)
  - However, adrenal biopsy showed diffuse large B-cell lymphoma with intravascular component

Roshal M, Till BG, Fromm JR, Cherian S. Intravascular large B cell lymphoma presenting in a liver explant. J Clin Pathol. 2008 Jul;61(7):877-8.

Discussion

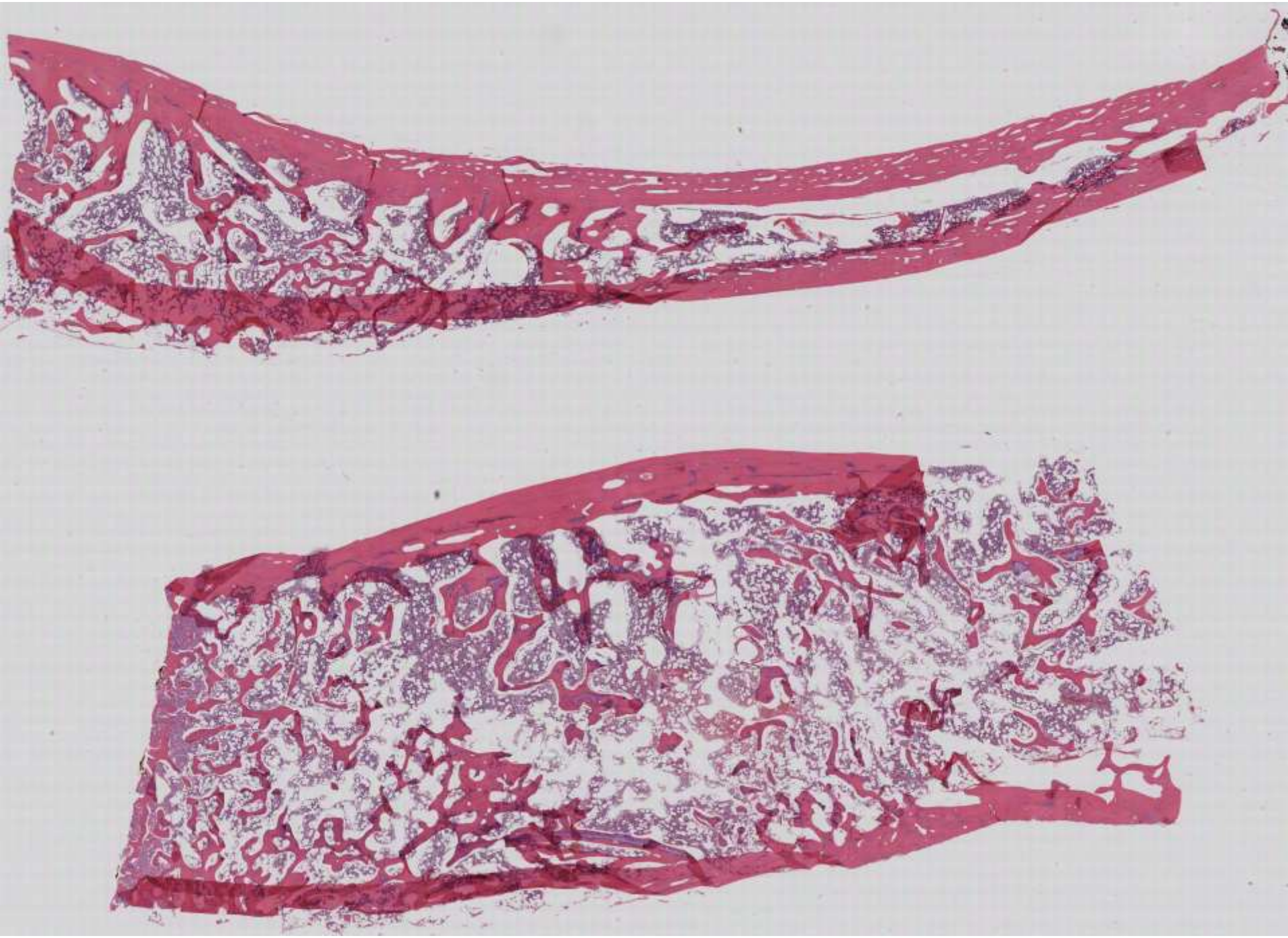
- Given the lack of systemic findings in an immunosuppressed patient after 6 months of follow-up, this also raises the question of whether bona fide IVLBCL can be a localized indolent phenomenon associated with local factors such as hepatitis-associated inflammation
- Various B-cell lymphomas have been associated with chronic hepatitis C infection, but not IVLBCL

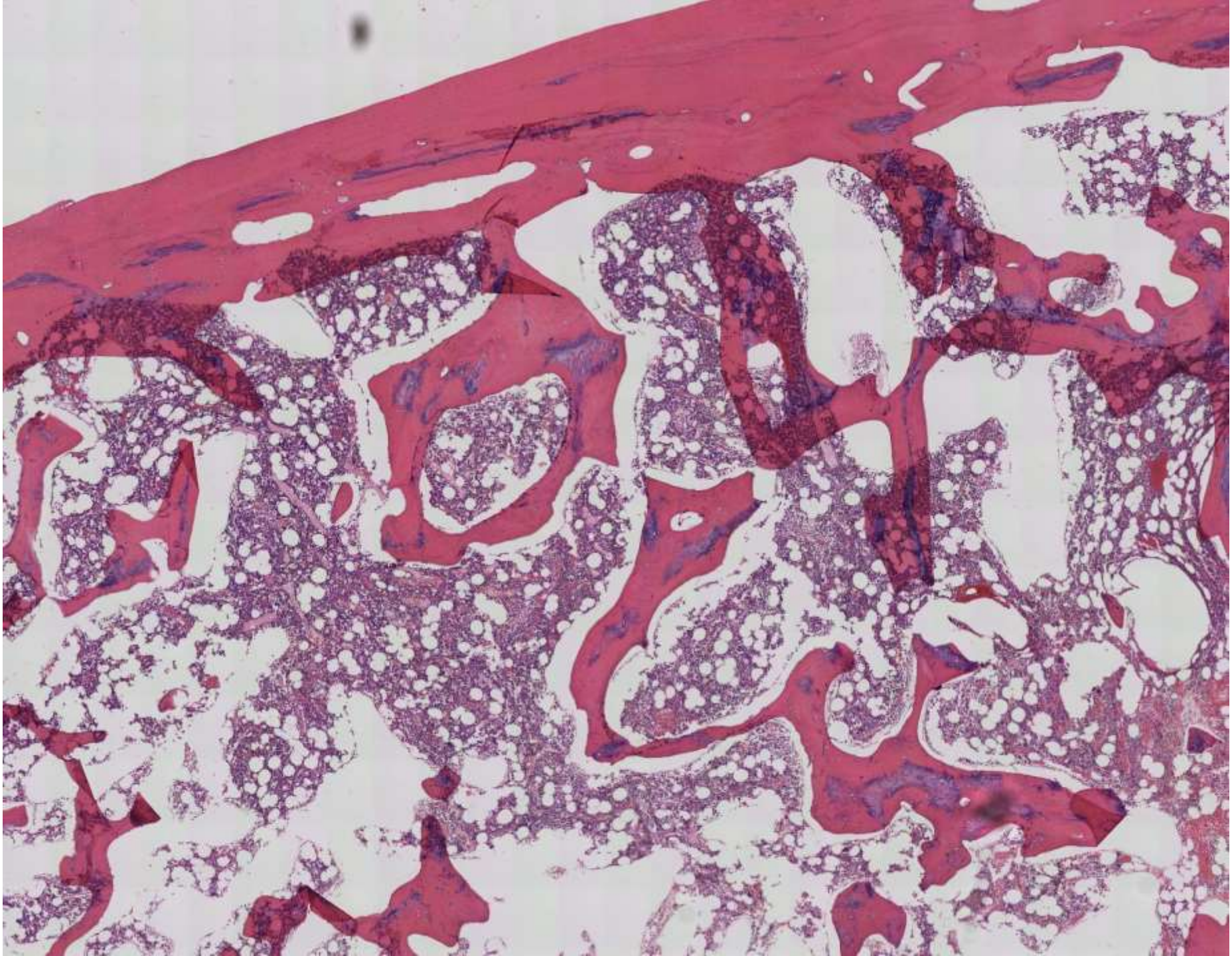
Viswanatha DS, Dogan A. Hepatitis C virus and lymphoma. J Clin Pathol. 2007 Dec;60(12):1378-83.

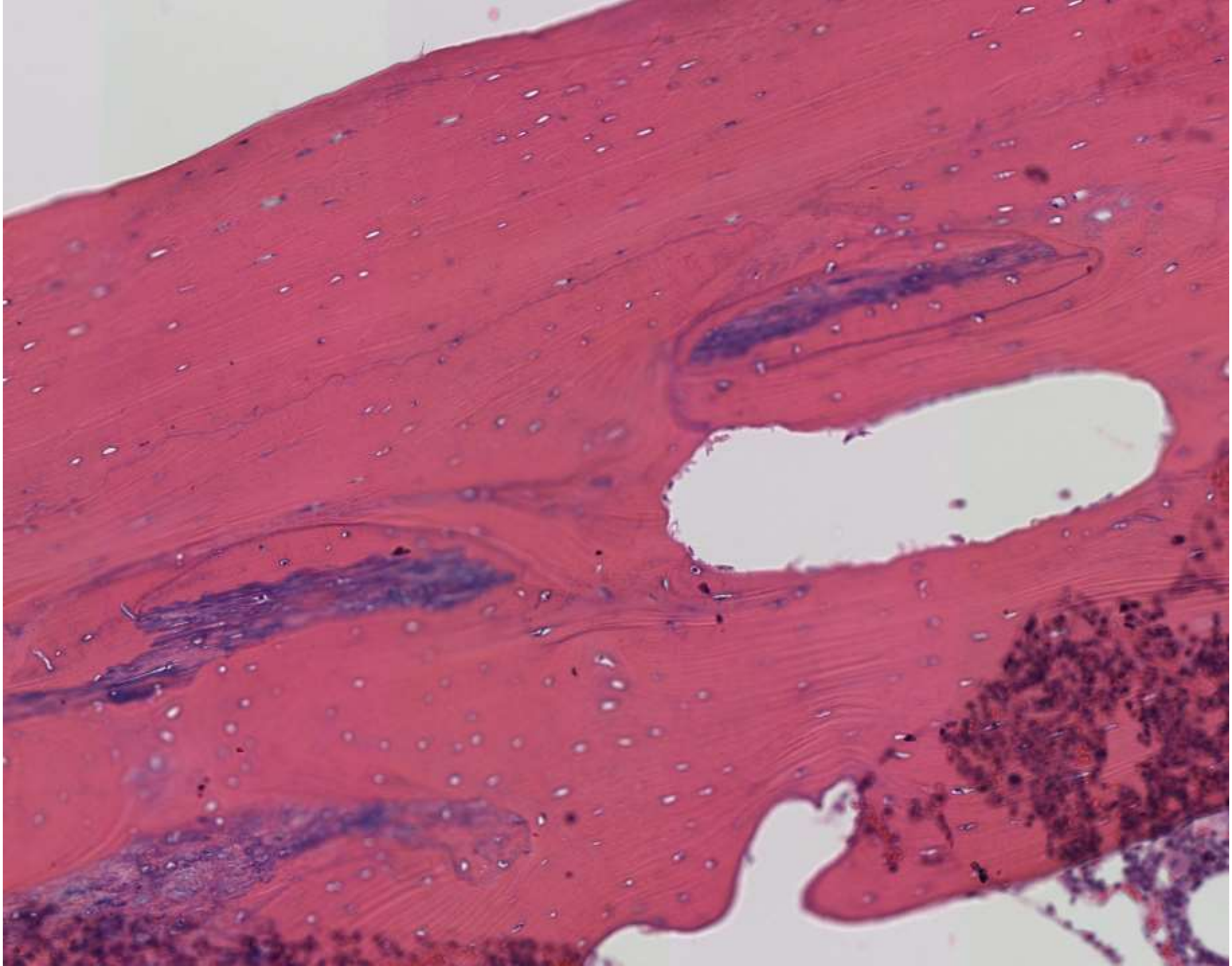
SB 6273

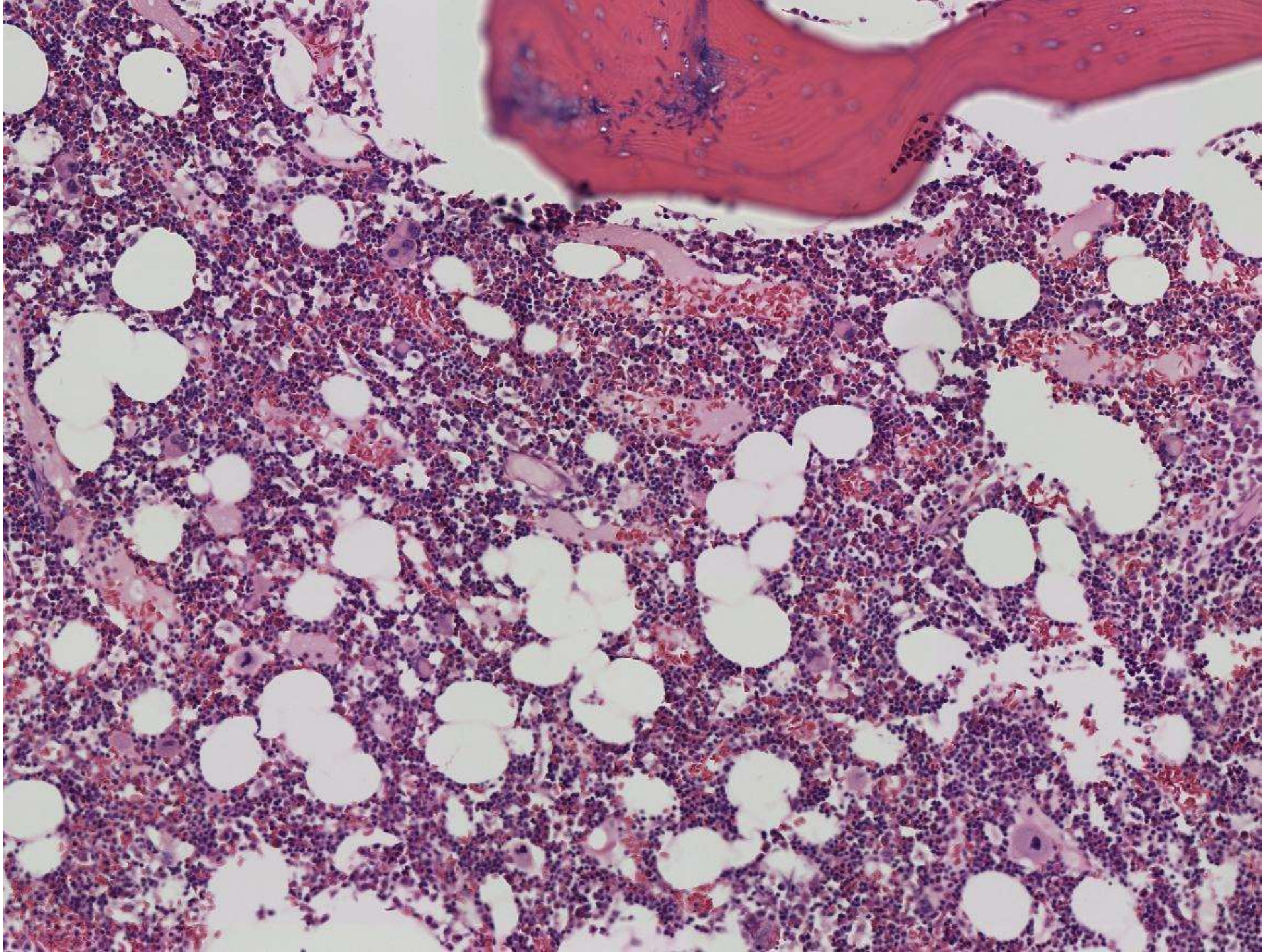
Eliah Shamir/Jessica Davis; UCSF

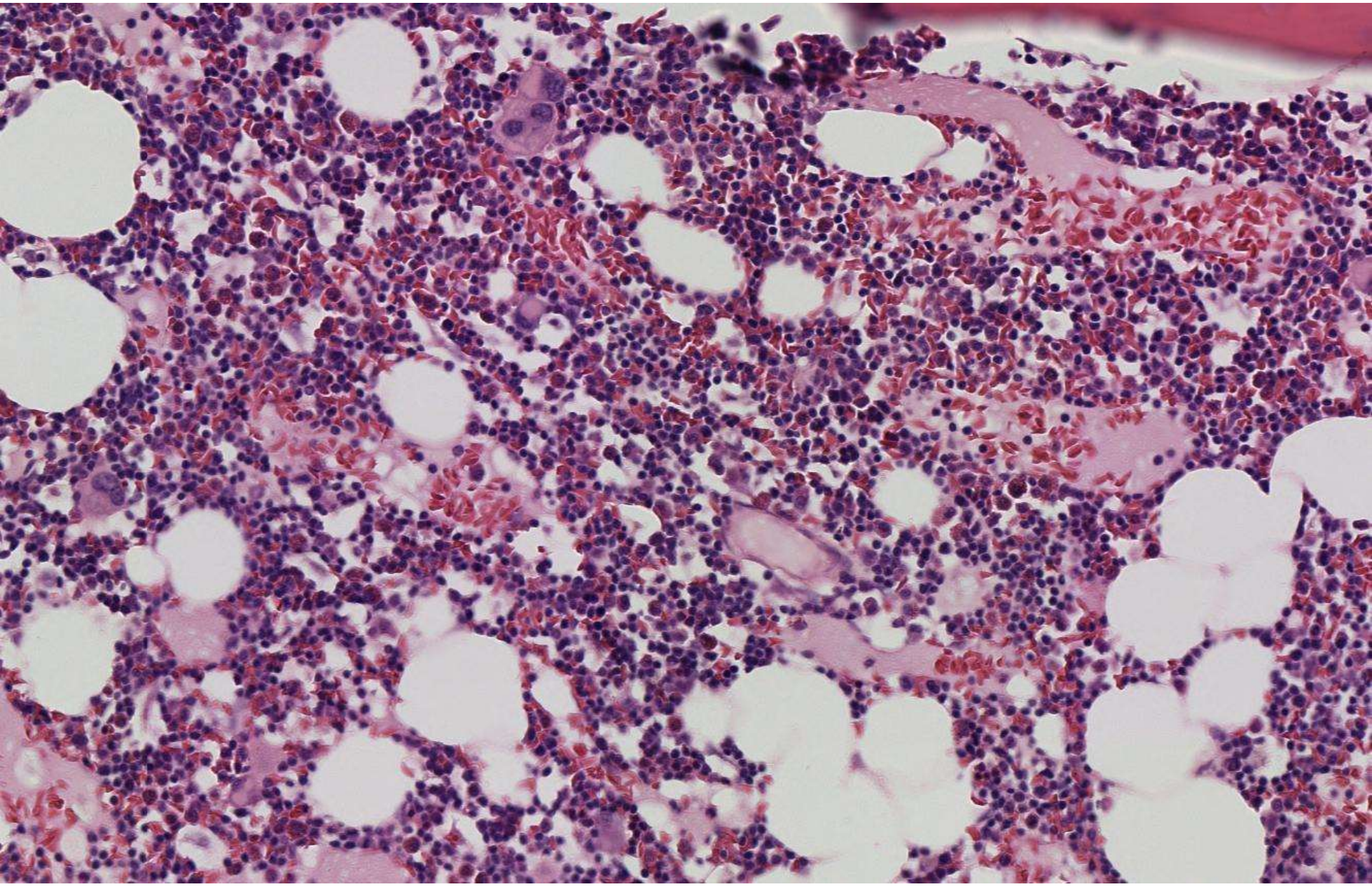
12-month-old girl presented with a prominence in left parietal bone that on CT appeared well-corticated with a smooth margin, radiographically suspicious for fibrous dysplasia.

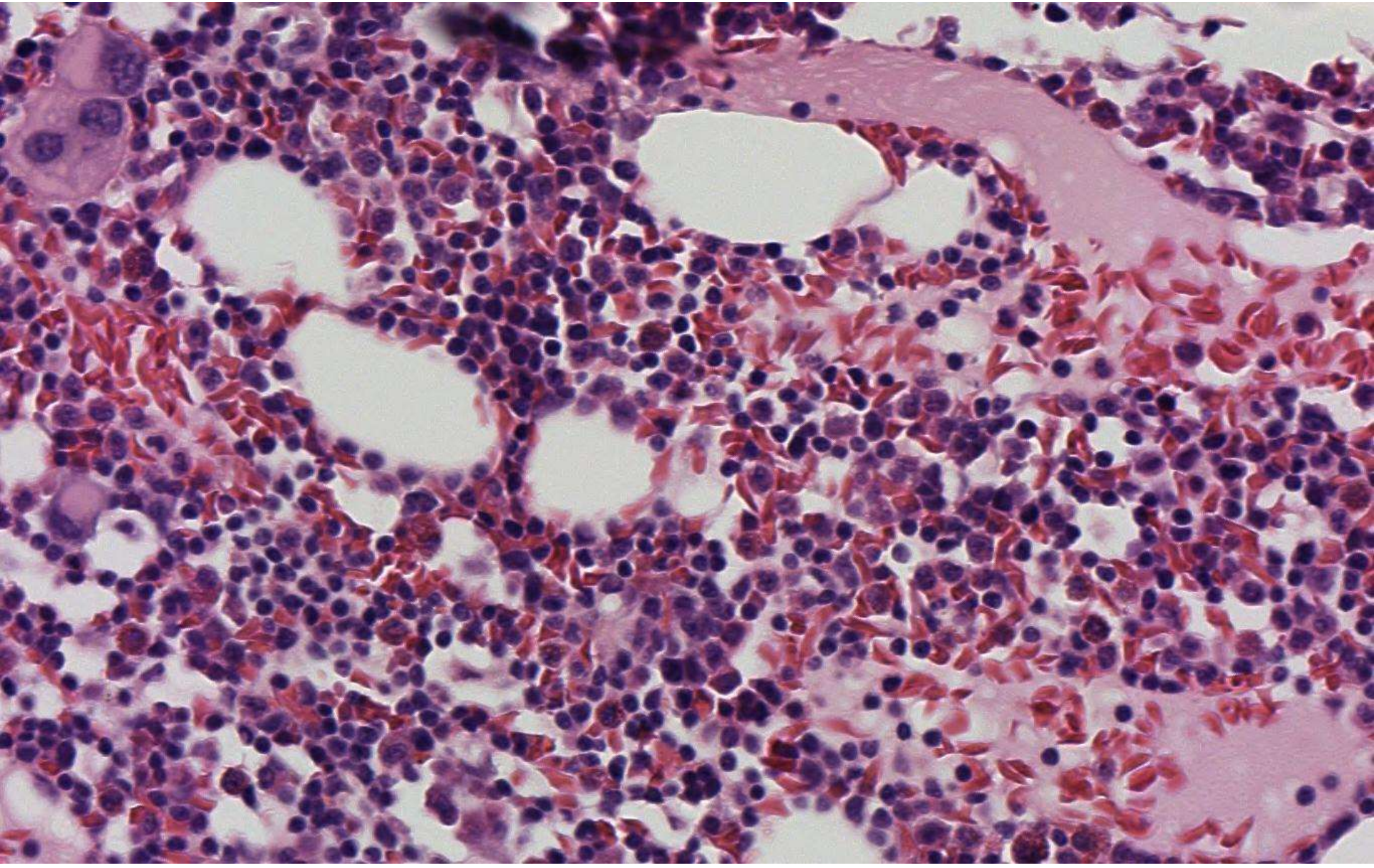


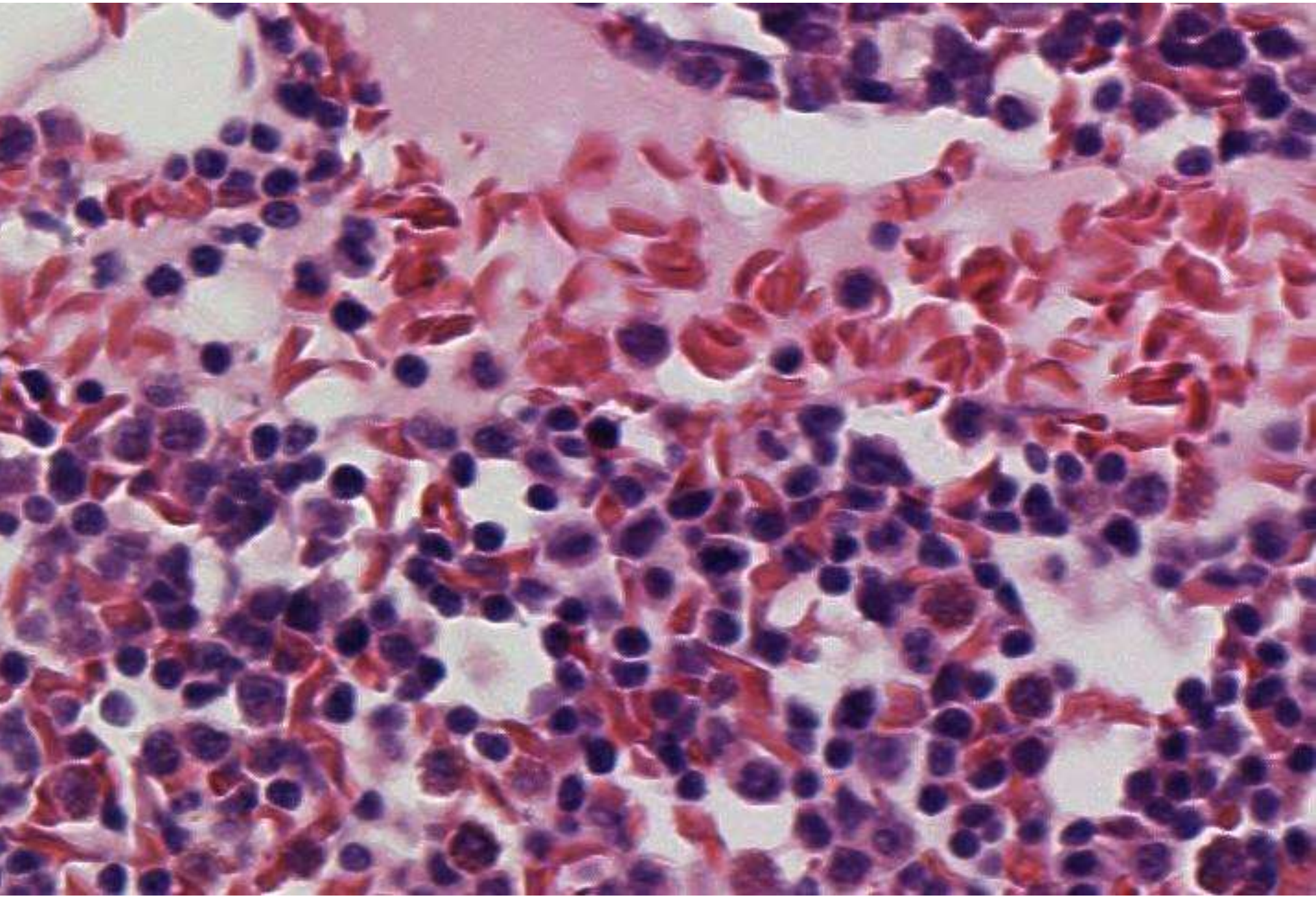










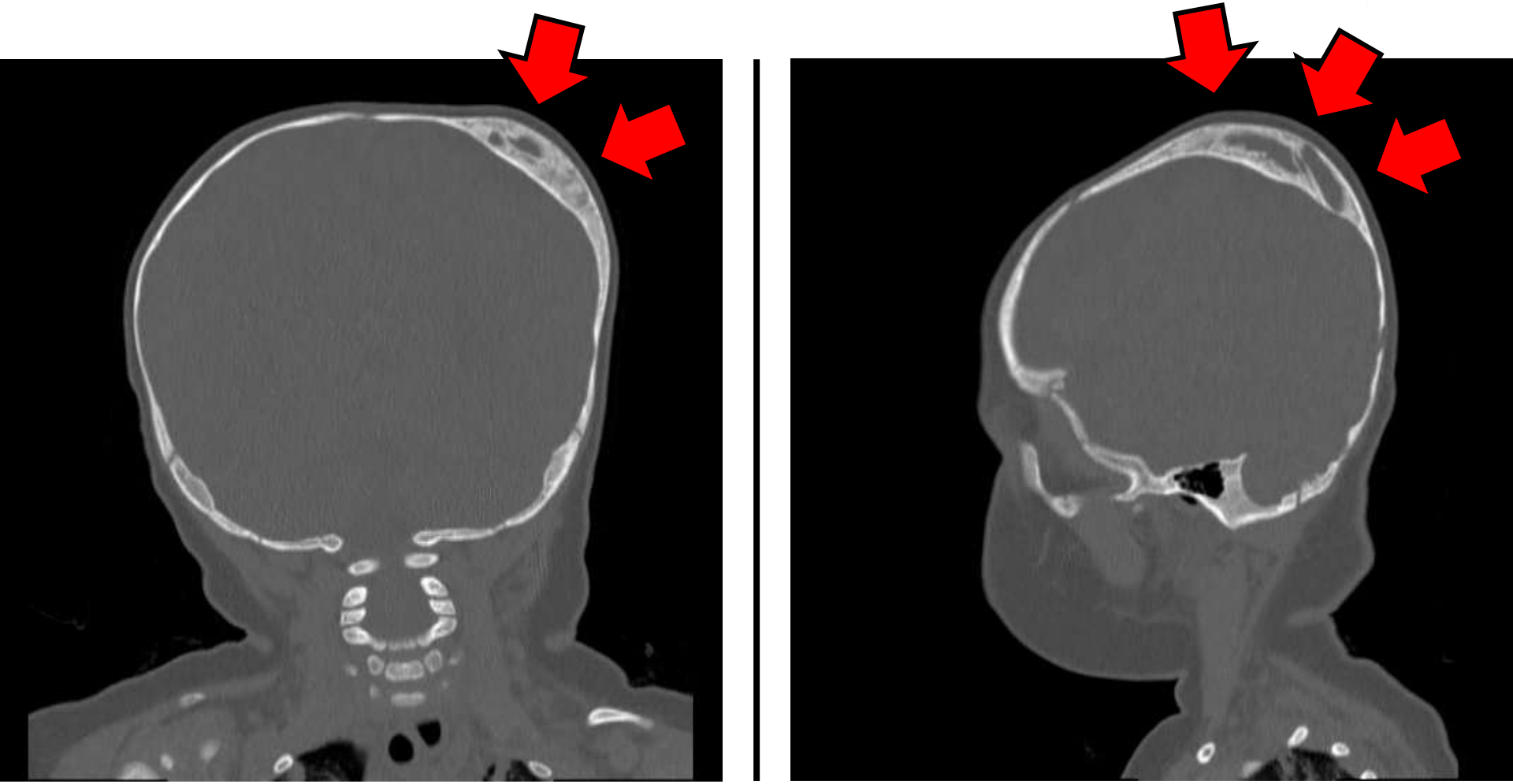


DIAGNOSIS?

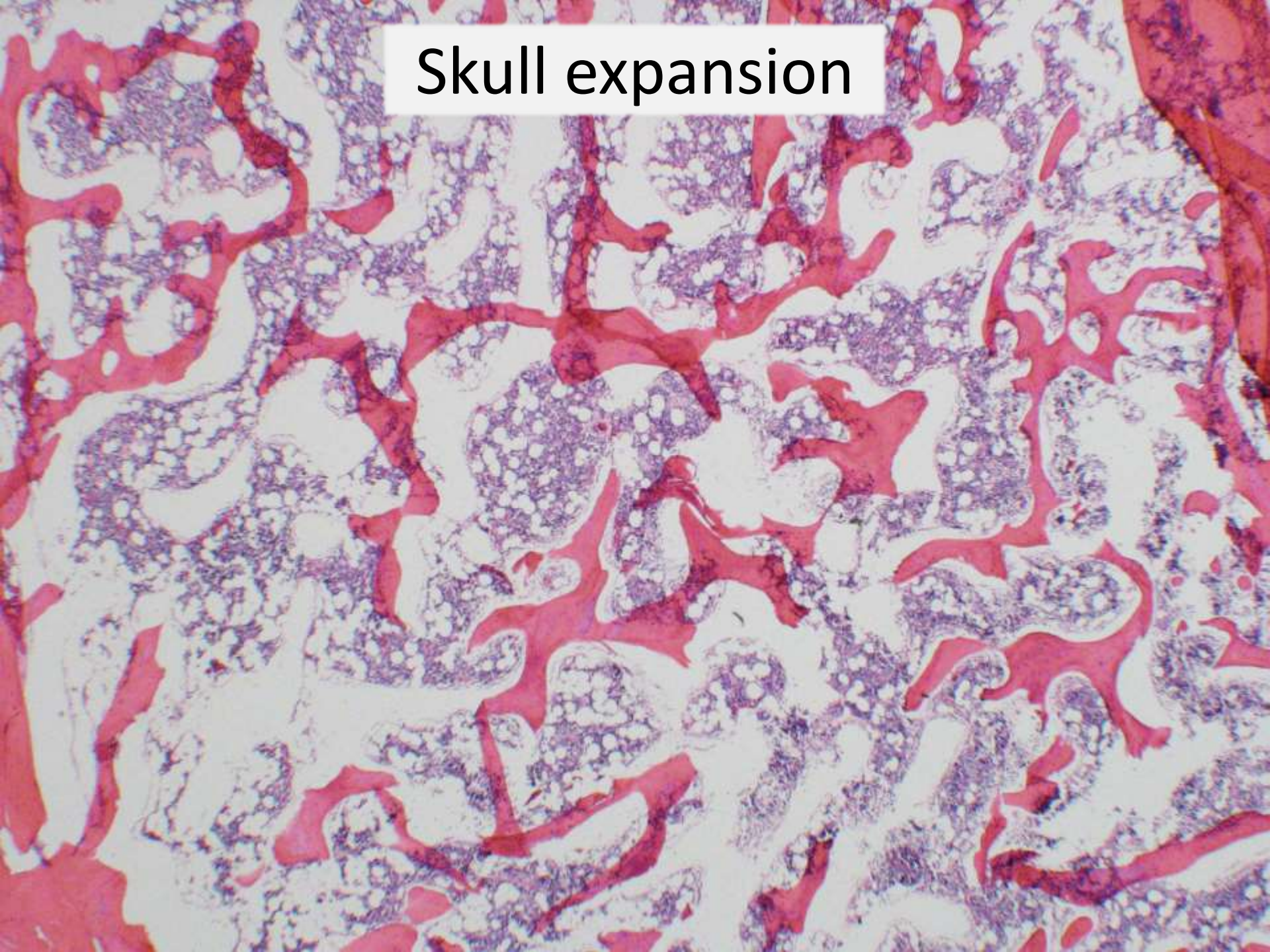
12-month-old girl with a prominence in the left parietal bone, radiographically suspicious for fibrous dysplasia

Dr. Eliah Shamir, PGY-2
Dr. Jessica Davis, Assistant Professor (OHSU)
Dr. Jeffry Simko, Professor
Department of Pathology, UCSF
South Bay Meeting
June 4, 2018

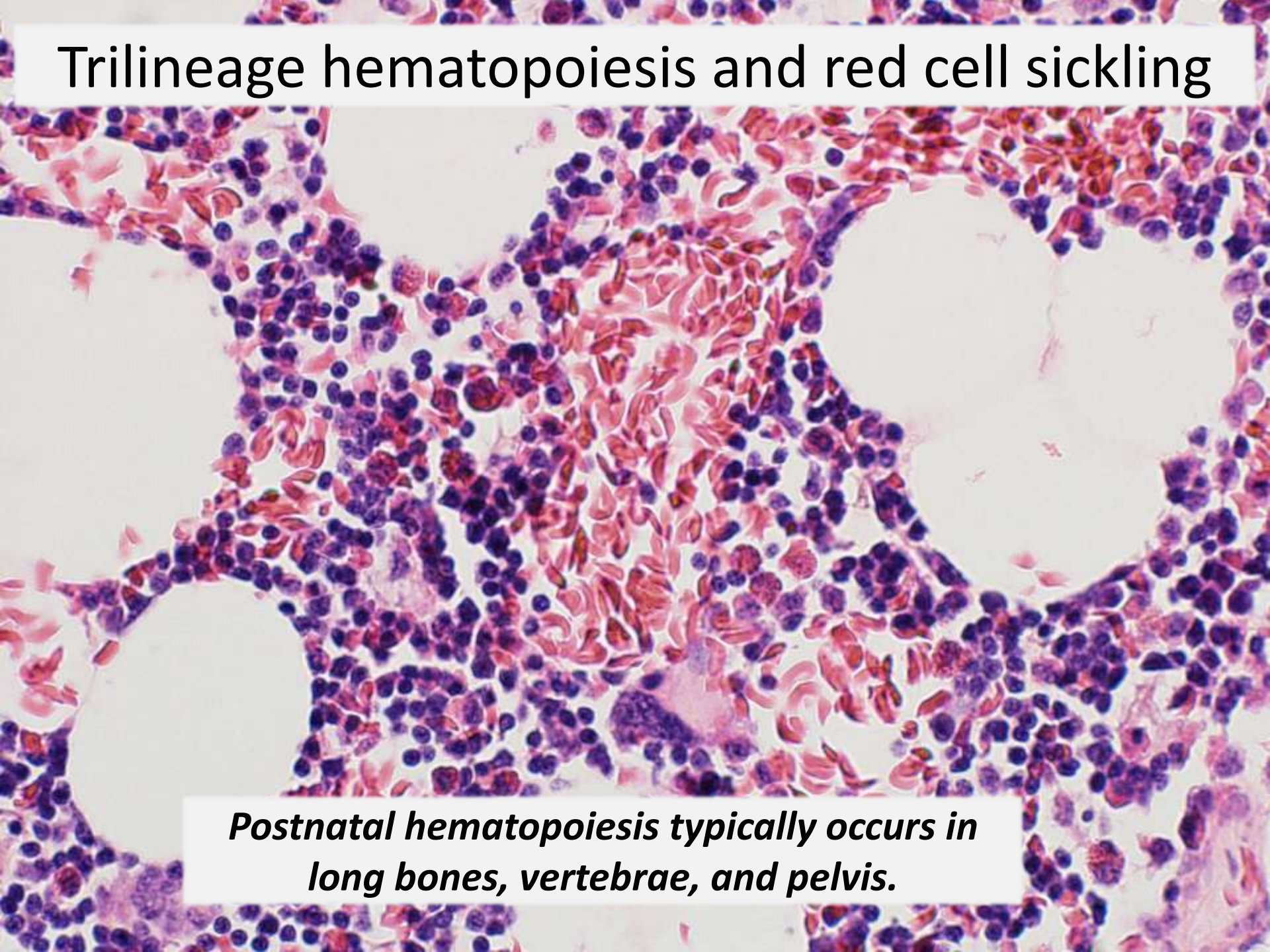
CT Maxillofacial without Contrast



Well-corticated skull thickening with ground-glass medullary space


Skull expansion

Trilineage hematopoiesis and red cell sickling



Postnatal hematopoiesis typically occurs in long bones, vertebrae, and pelvis.

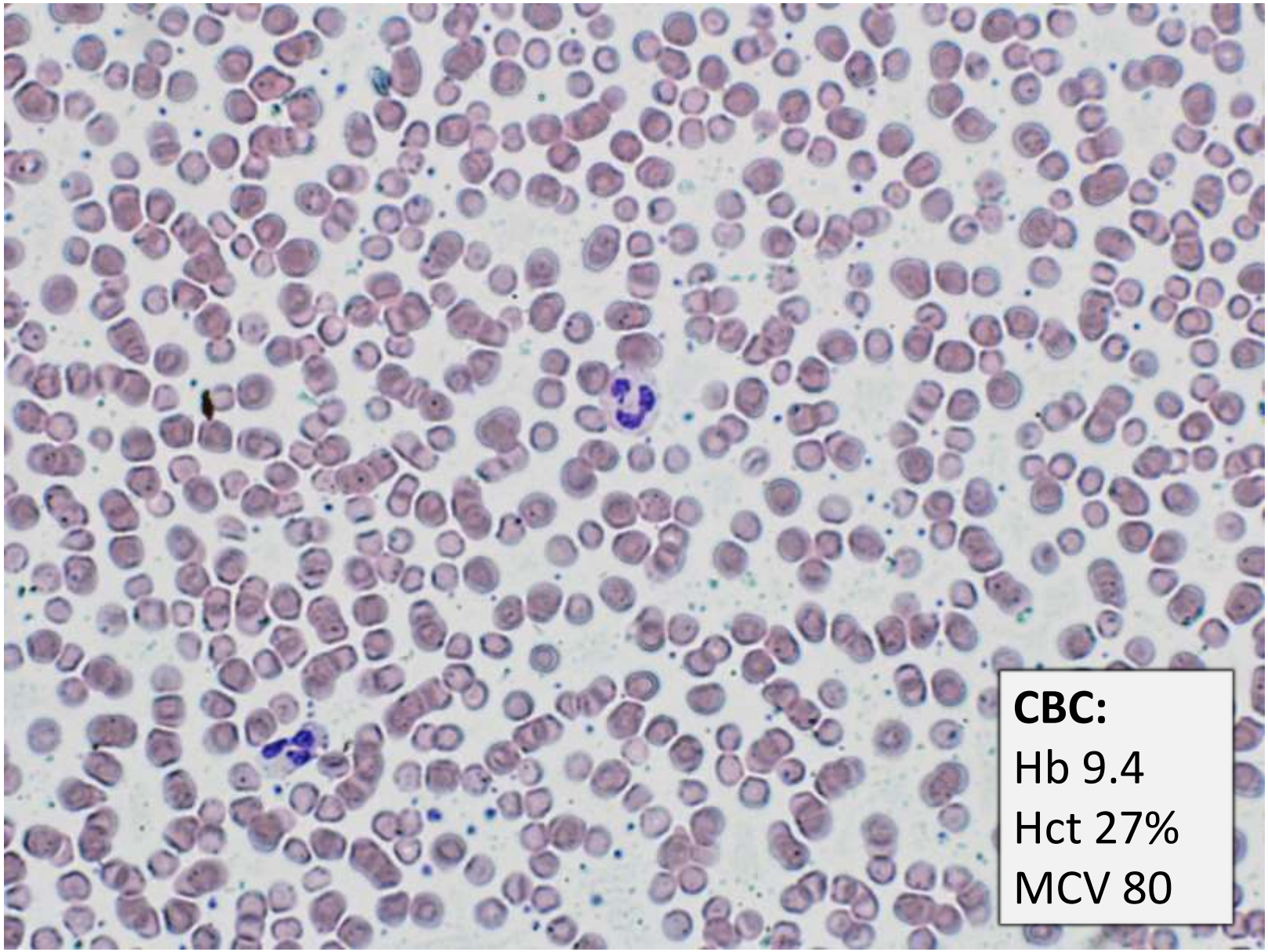
Diagnosis:

Extensive trilineage hematopoiesis with skull expansion and red cell sickling

Subsequent work-up:

- Salvadoran, no family history
- Mild normocytic anemia
- Hemoglobin electrophoresis: **Hb A/S = Sickle cell trait**
- Full sequencing: No mutations in alpha or beta globin genes

Peripheral smear



Differential diagnosis:

- Increased hematopoietic drive
  - Thalassemia syndromes (α and β)
  - Structural hemoglobin variants (HbS, HbE, HbC)
- Decreased marrow space / capacity
  - Leukemia/lymphoma
  - Myelodysplastic syndrome

Bone involvement in sickle cell disease

- Vaso-occlusive crises
- Osteomyelitis
- Stress fractures

Acute

Chronic ischemia/infarction
Bone marrow hyperplasia

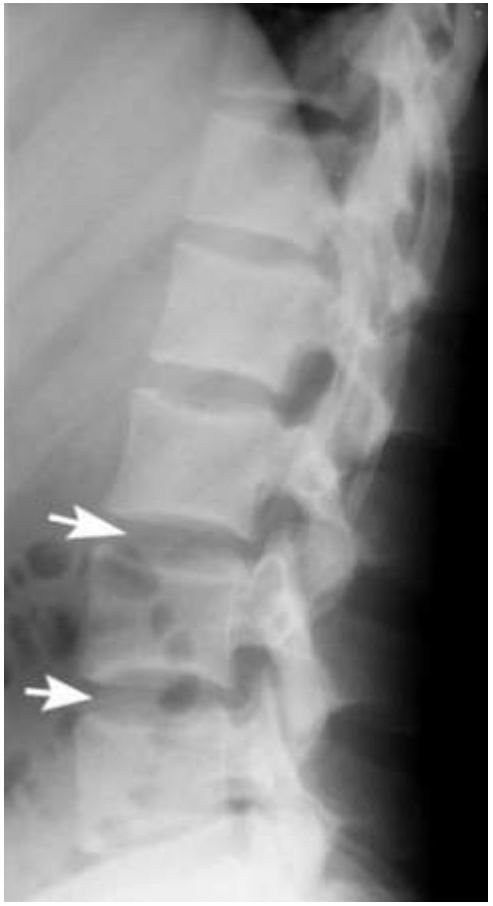
- Avascular necrosis (femoral/humoral head)
- Osteoporosis
- Impaired growth

Chronic

Ejindu et al, *RadioGraphics* 2007;27.
Almeida and Roberts, *BJH* 2005;129.

Intramedullary Marrow Hyperplasia

- Increased demand for erythropoiesis due to chronic red cell destruction
- Persistence of red marrow in all bones in infants
- Cortical thinning and medullary widening / expansion
- Coarsening of normal trabecular pattern in both long and flat bones

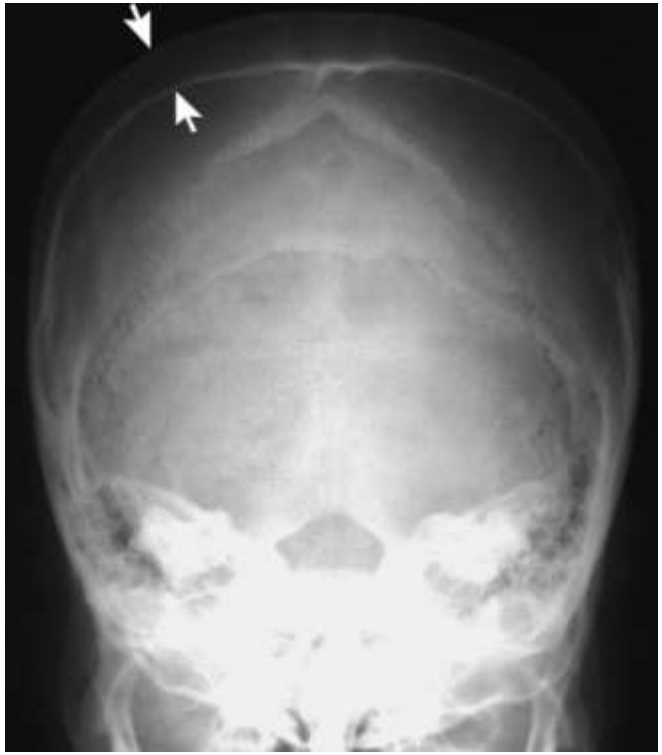


Biconcave "fish-mouth" deformity of vertebral bodies

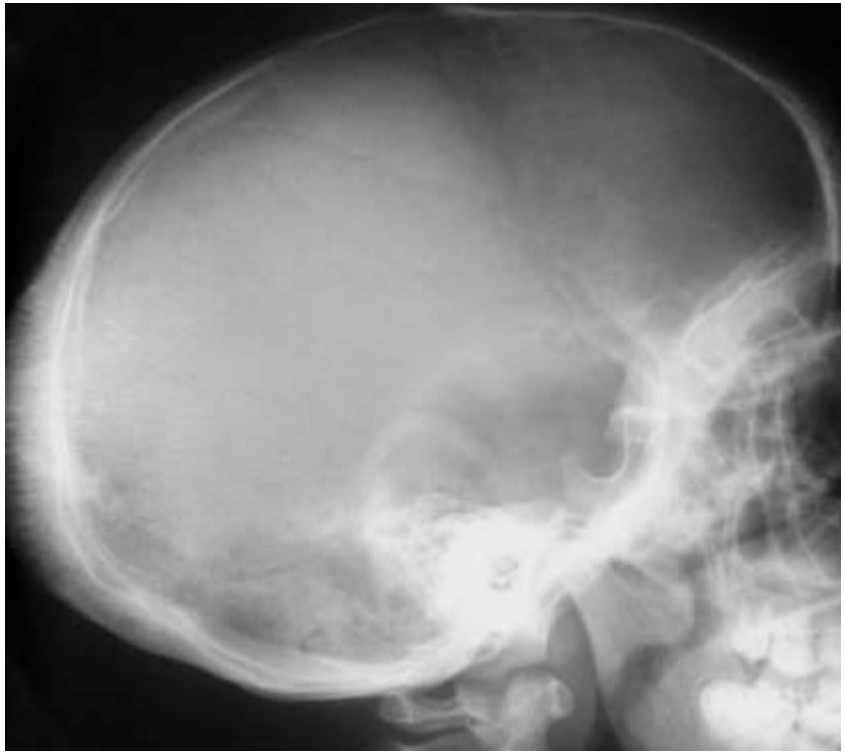
Ejindu et al, *RadioGraphics* 2007;27.
Almeida and Roberts, *BJH* 2005;129.

Intramedullary Marrow Hyperplasia

- Skull changes:



Widening of medullary cavity with thinning of inner and outer tables



Vertical “hair-on-end” striations due to new trabeculae

Ejindu et al, *RadioGraphics* 2007;27.

State Newborn Screening (NBS)

- Since 2006, detects sickle cell disease (SCD) and sickle cell trait (SCT)
  - Primary targets: Hb SS, SC, S-β thal

- **Goal**: Early detection improves health outcomes
  - Penicillin prophylaxis for *Strep pneumo*
  - Family education (e.g. reduce vaso-occlusive crises)
  - Genetic counseling / family planning

Hemoglobinopathies: Current Practices for Screening, Confirmation, and Follow-Up, APHL 2015

SCT-associated conditions

- Renal medullary carcinoma
- Hematuria
- Renal papillary necrosis
- Splenic infarction
- Exercise-related deaths
- Thromboembolic disease
- Pregnancy-related complications

Ojodu et al, *MMWR* 2014; 63(49).

Incidence of SCT based on NBS (2010)

- U.S. (44 states)
  - 15.5 per 1,000 newborns overall
  - 73.1 per 1,000 black newborns
  - 6.9 per 1,000 Hispanic newborns
- California
  - 8.2 per 1,000 newborns overall
  - 68.8 per 1,000 black newborns
  - 5.9 per 1,000 Hispanic newborns

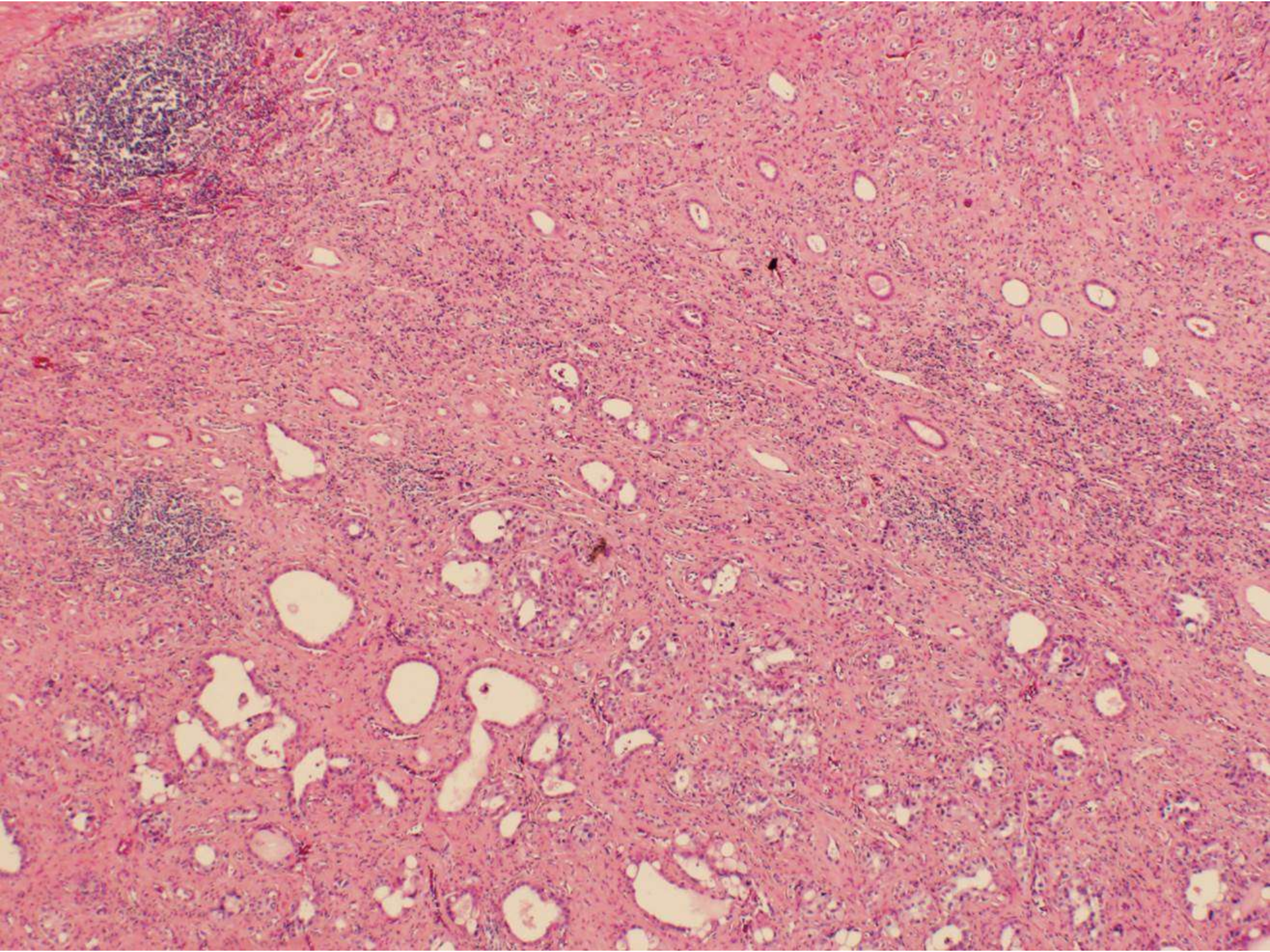
Ojodu et al, *MMWR* 2014; 63(49).

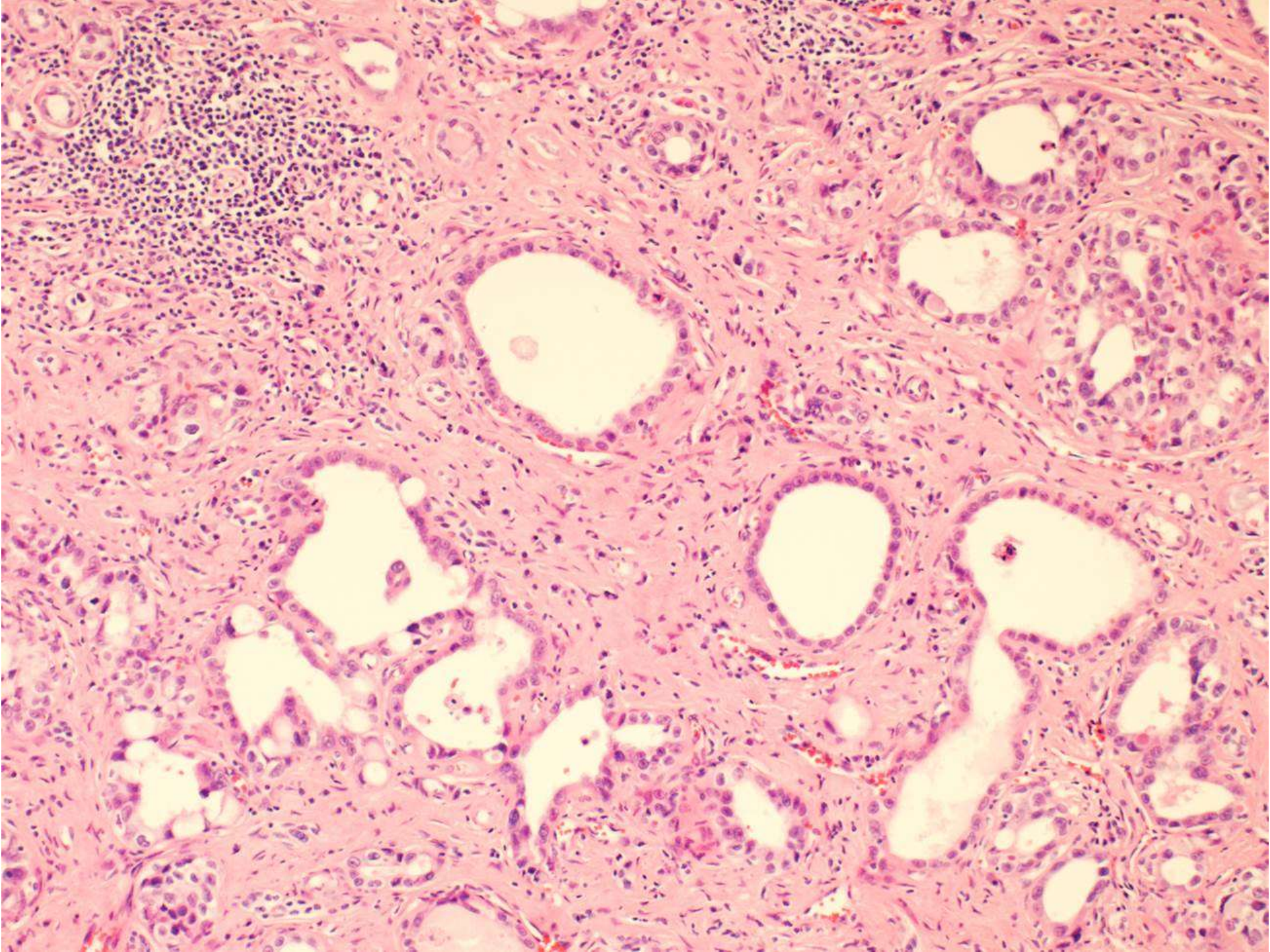
Take Home Points

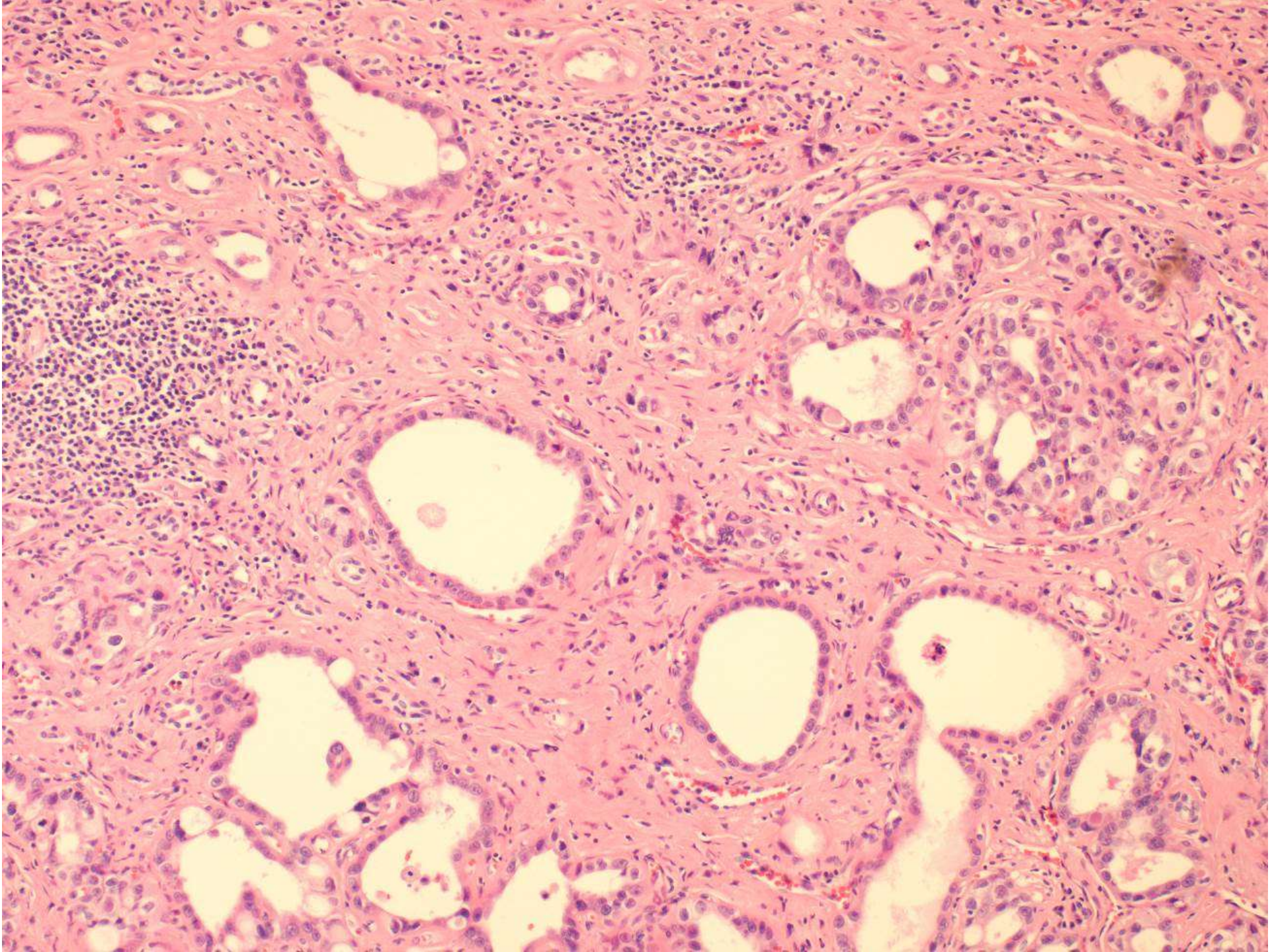
- Skull-based hematopoiesis in a child is unusual
- Consider congenital anemias
- Recommend further hematologic work-up
- Early detection benefits patients and families

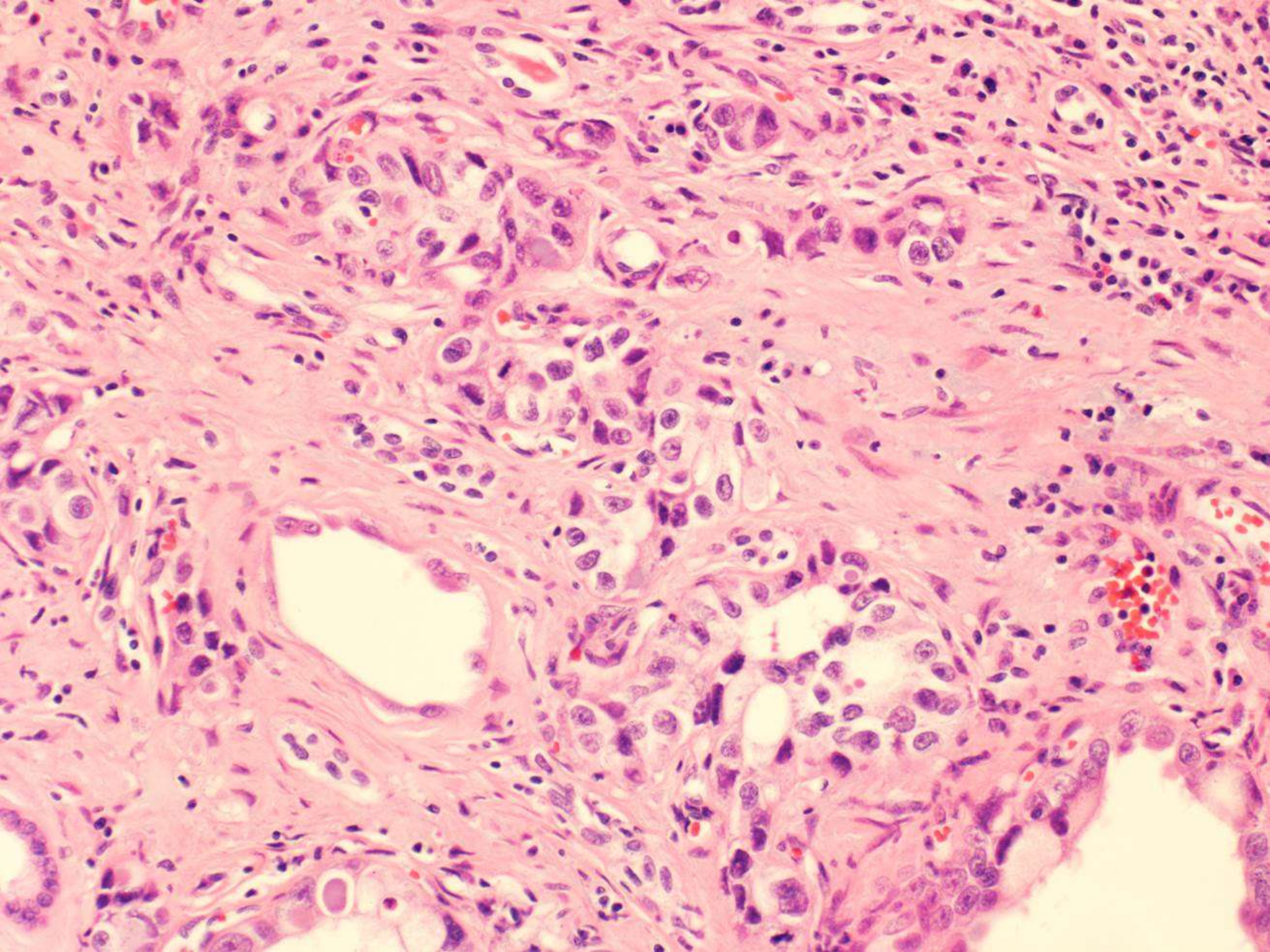
SB 6274
Anne Marie Amacher/Jeff Simko; UCSF

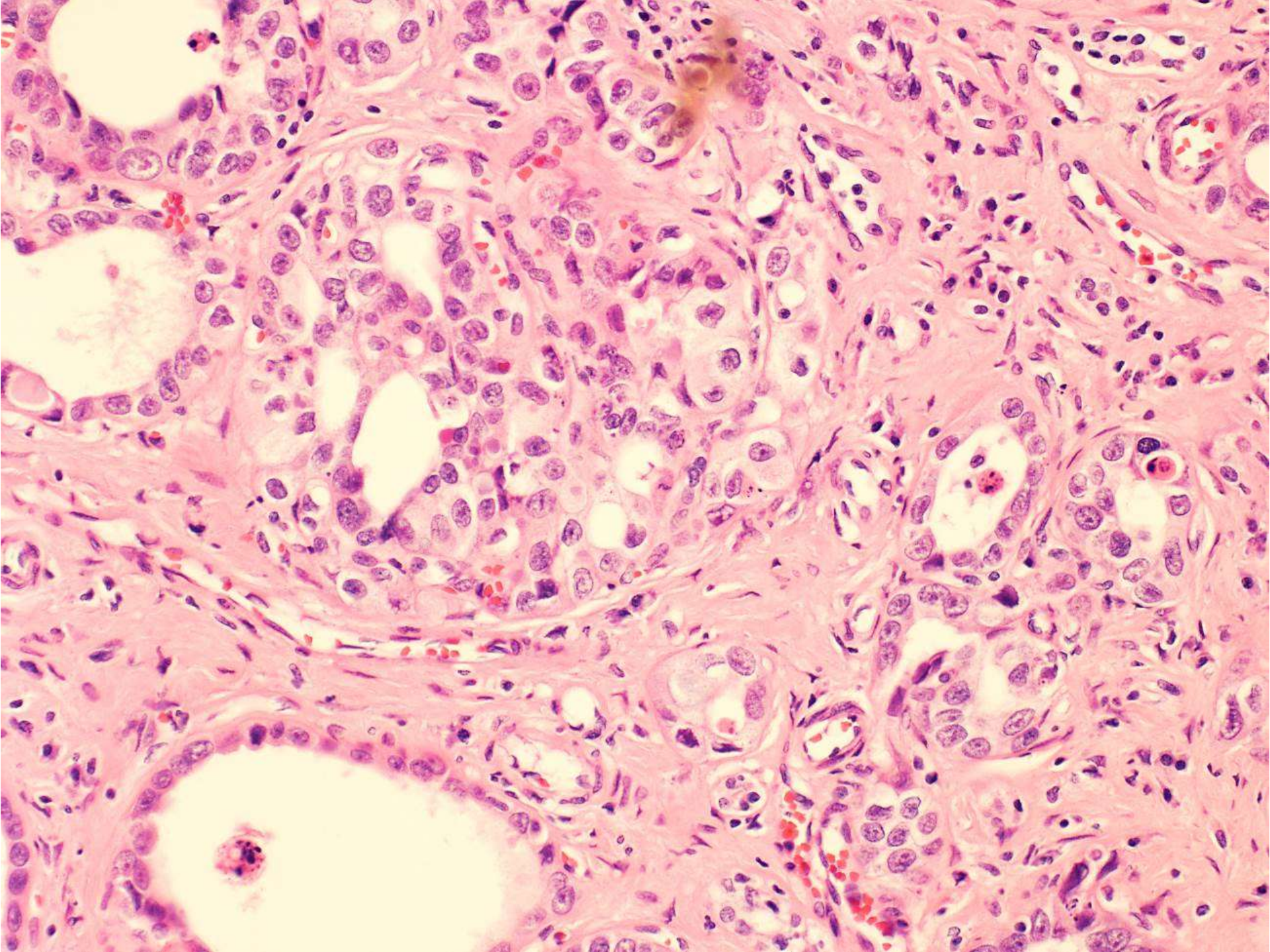
66-year-old man with kidney tumor measuring at least 5cm.

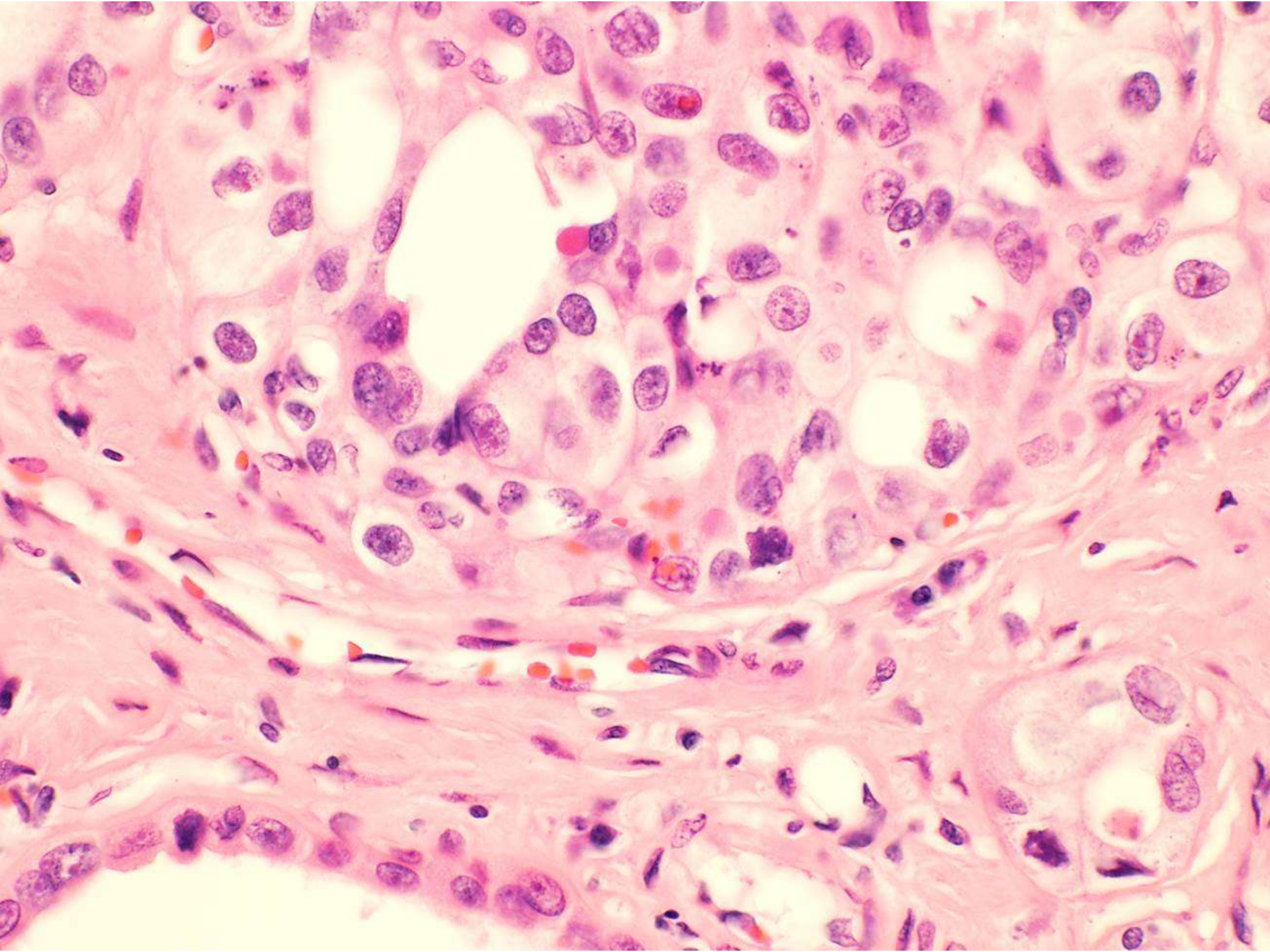


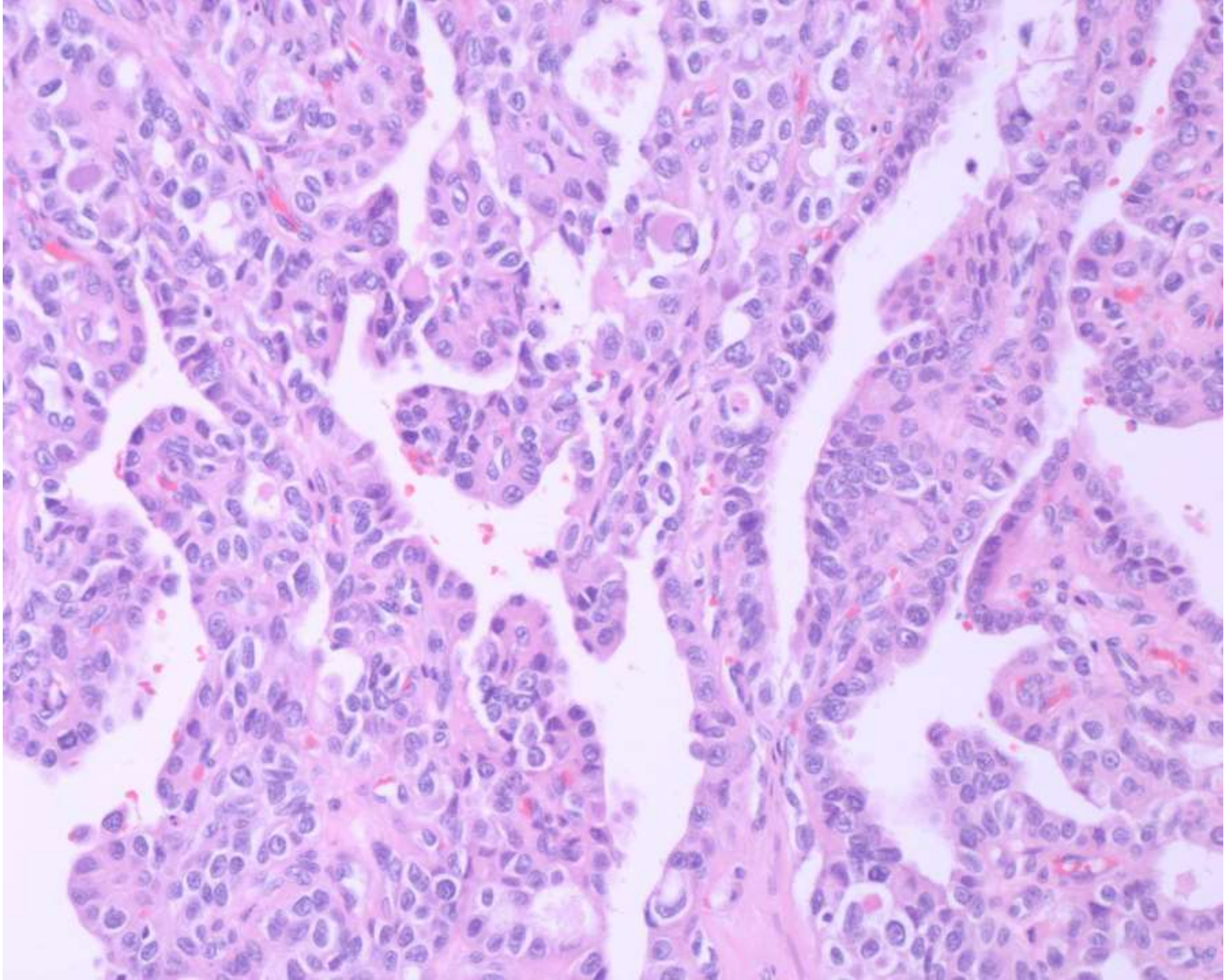


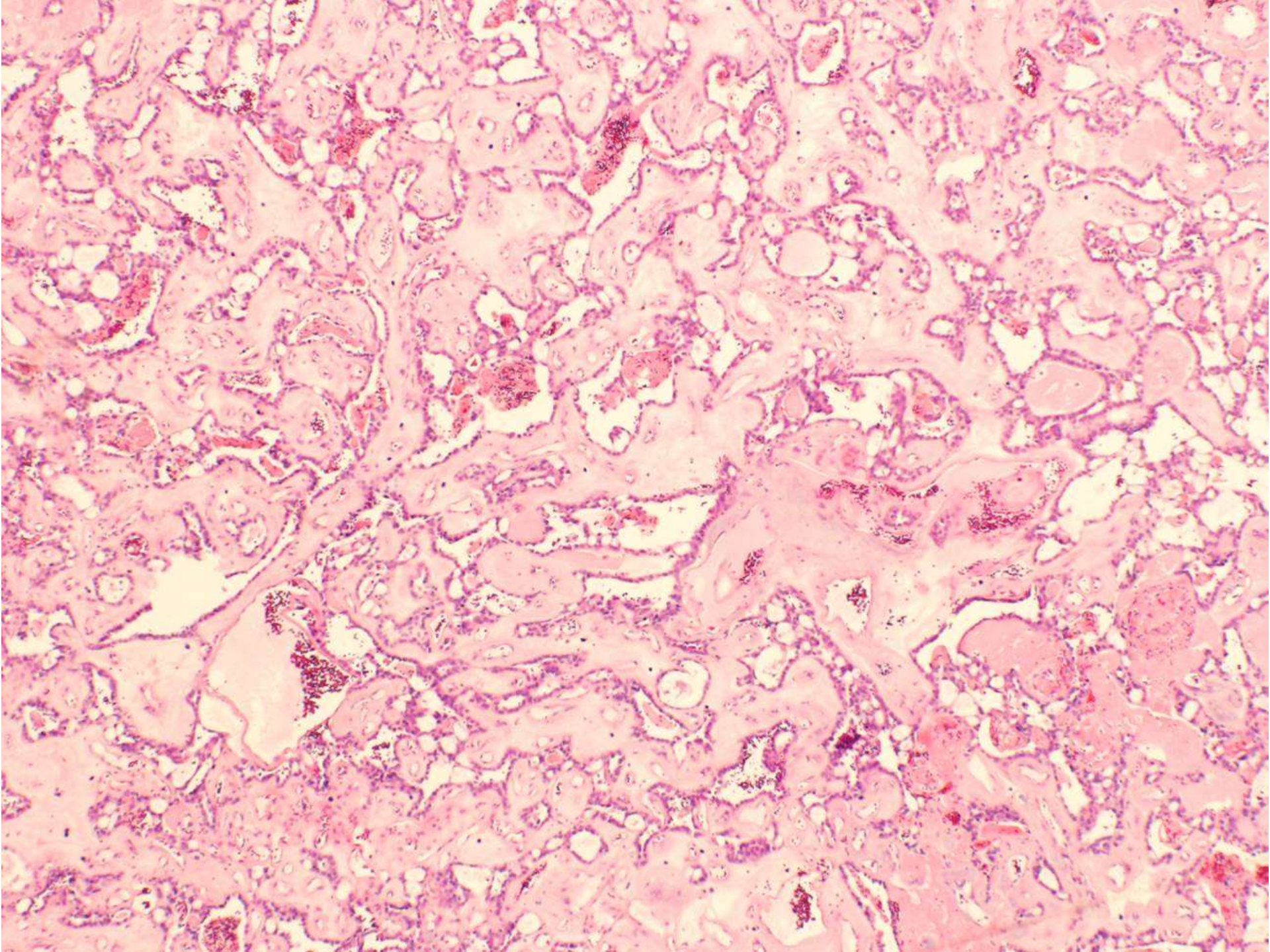


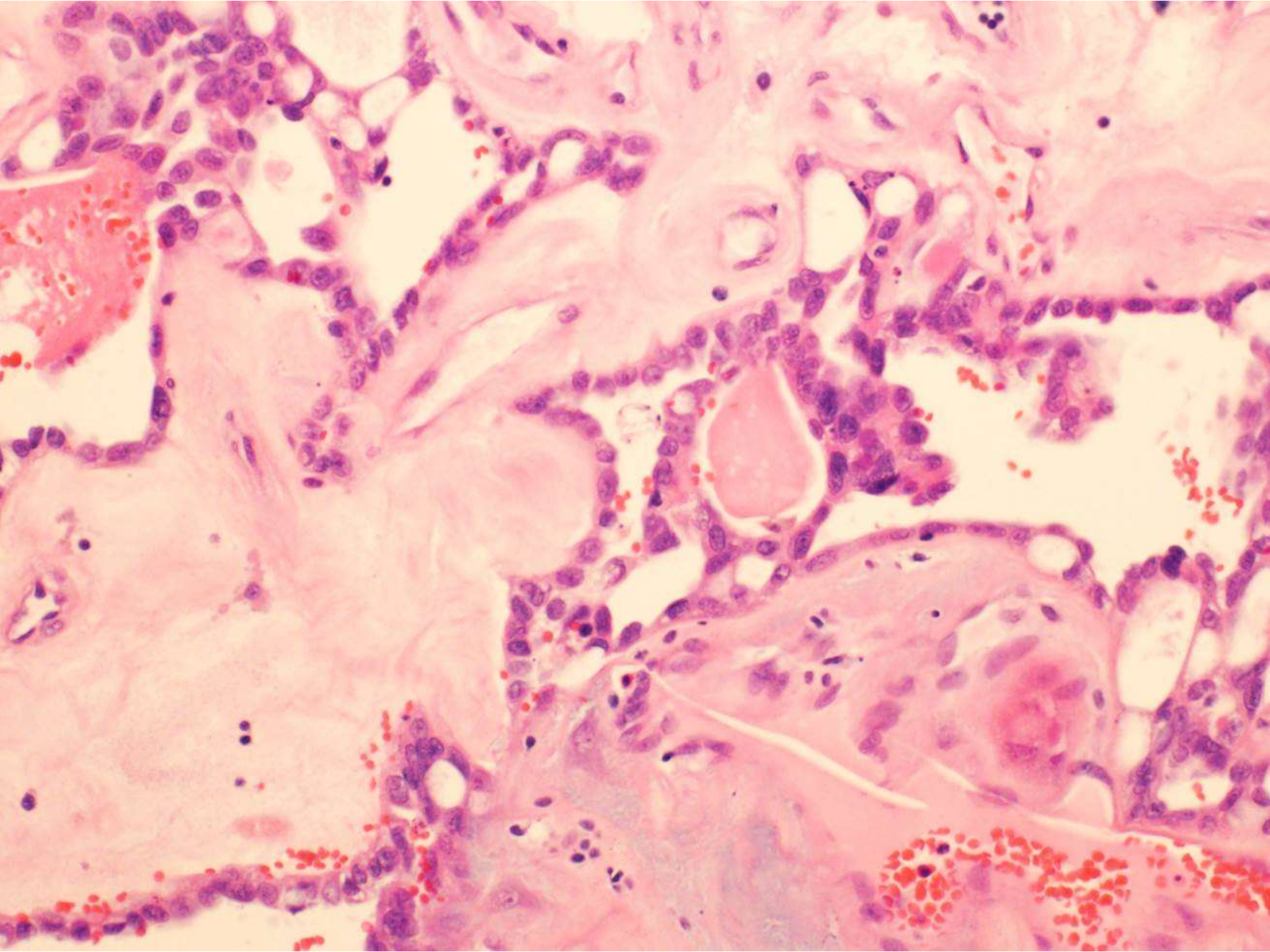












DIAGNOSIS?

66-year old man with a 5 cm unilateral renal mass reviewed at UCSF for a second opinion

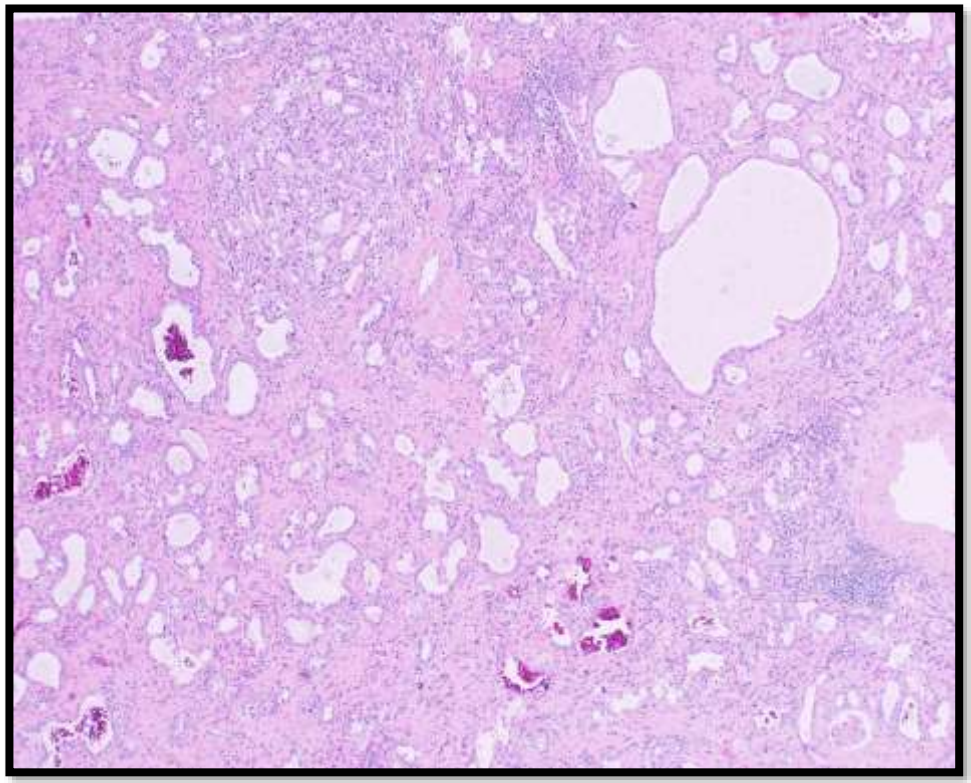
South Bay Meeting

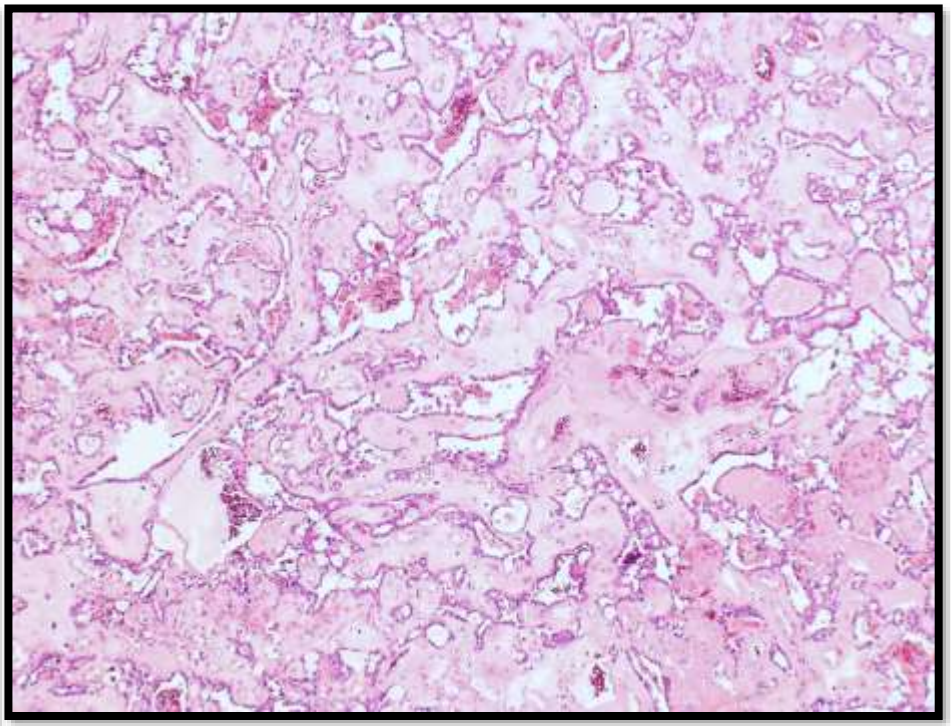
June 4, 2018

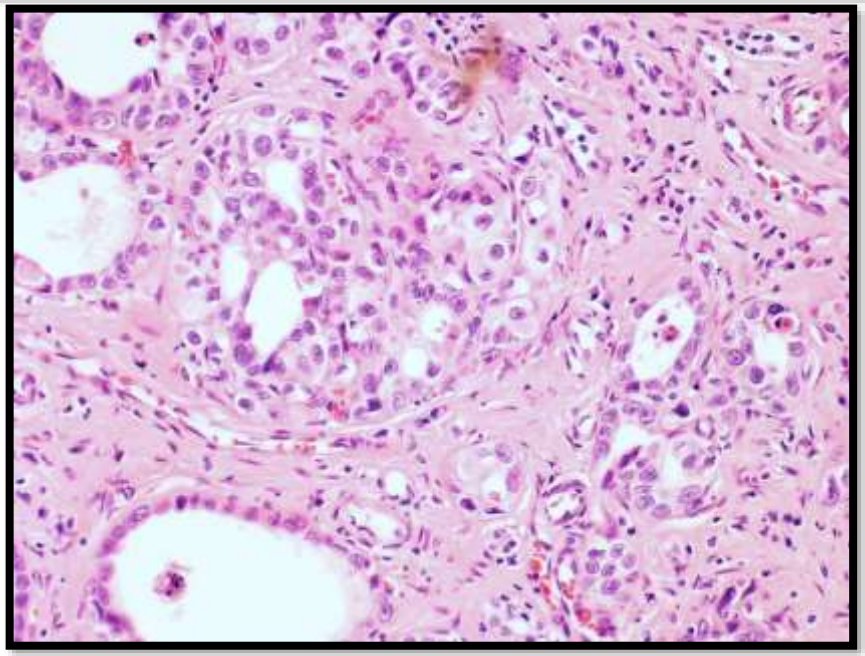
Anne Marie Amacher, Surgical Pathology Fellow, UCSF

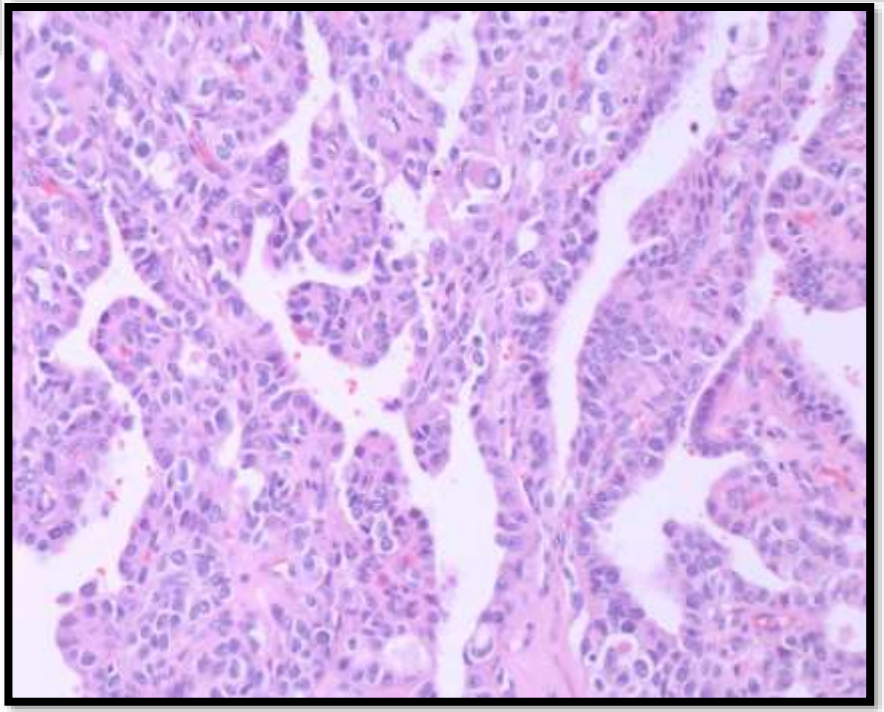
Dr. Jeff Simko, Professor, UCSF

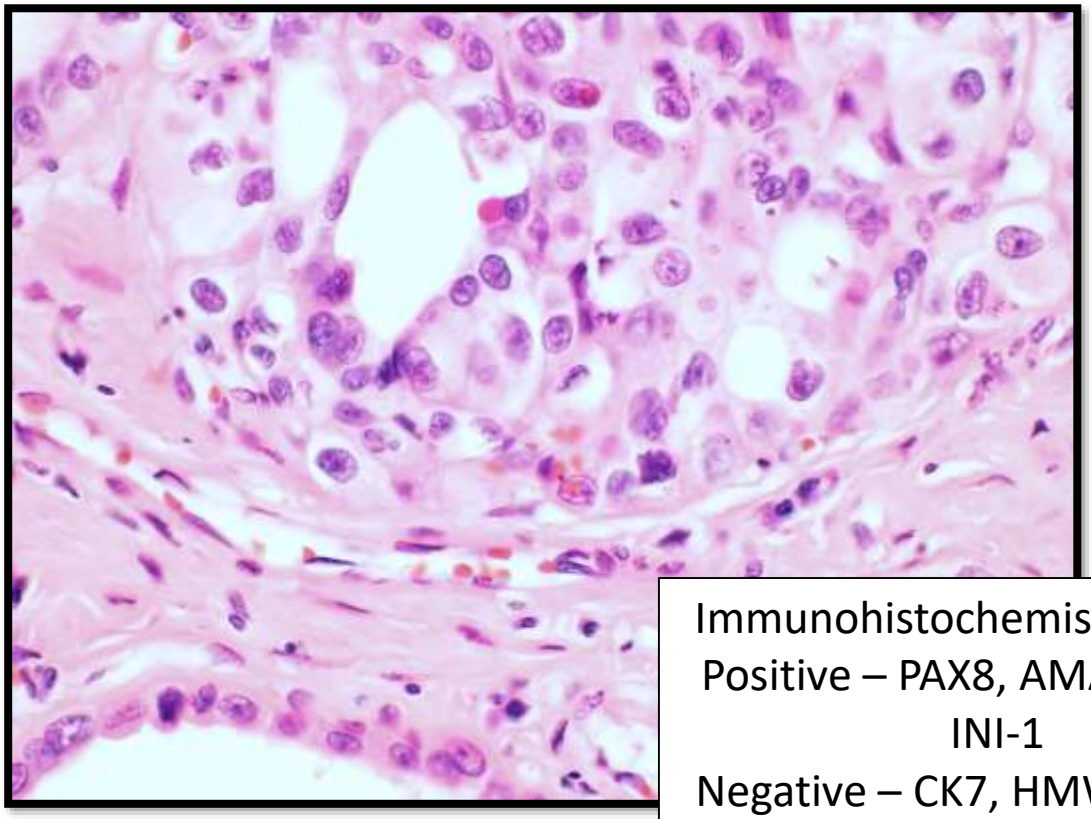
Dr. Shannon Mulholland, Saint Mary's Medical Center, SF

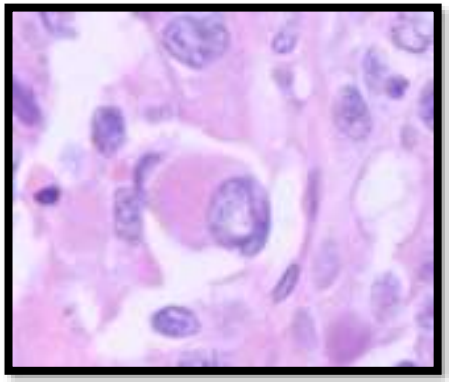




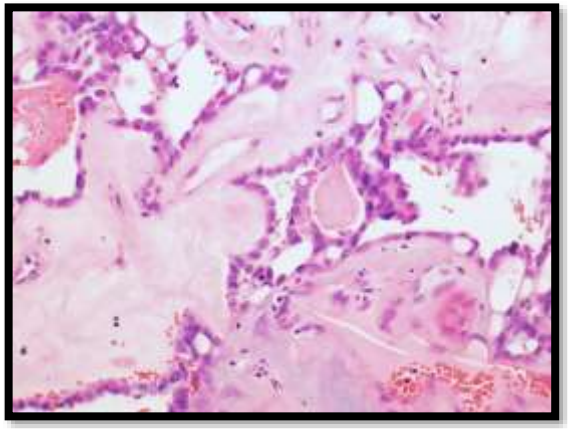


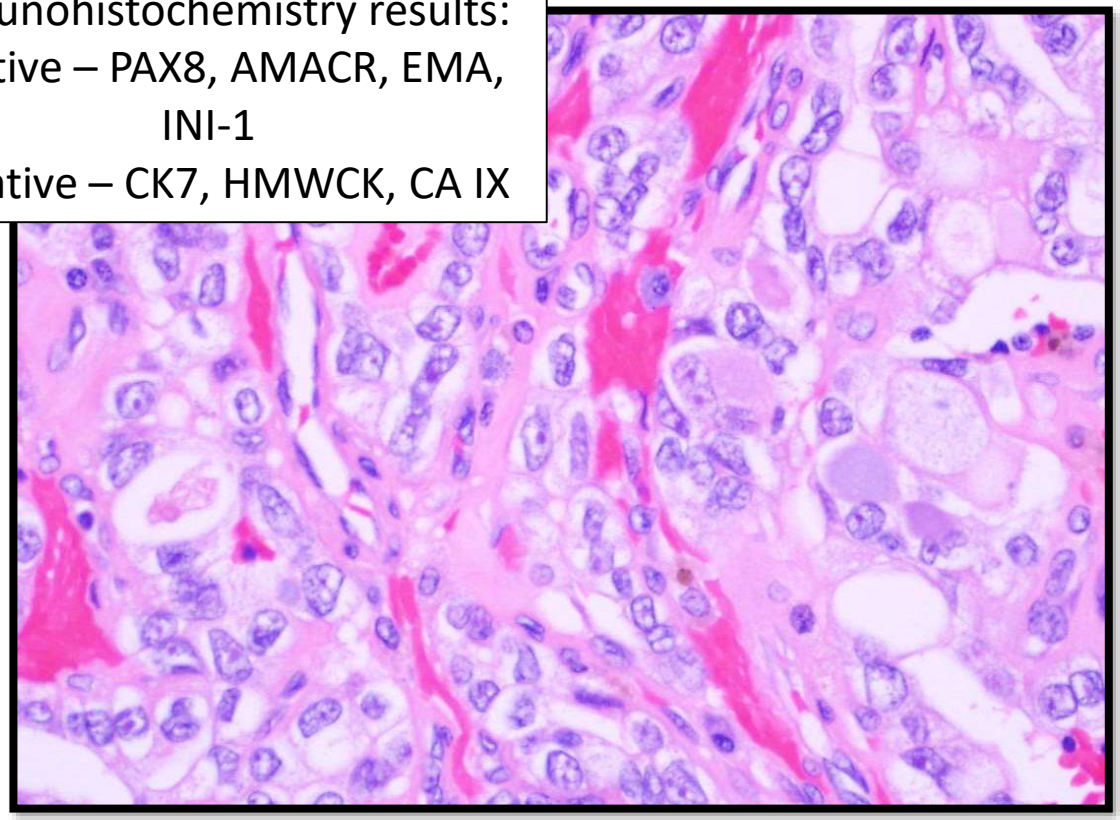






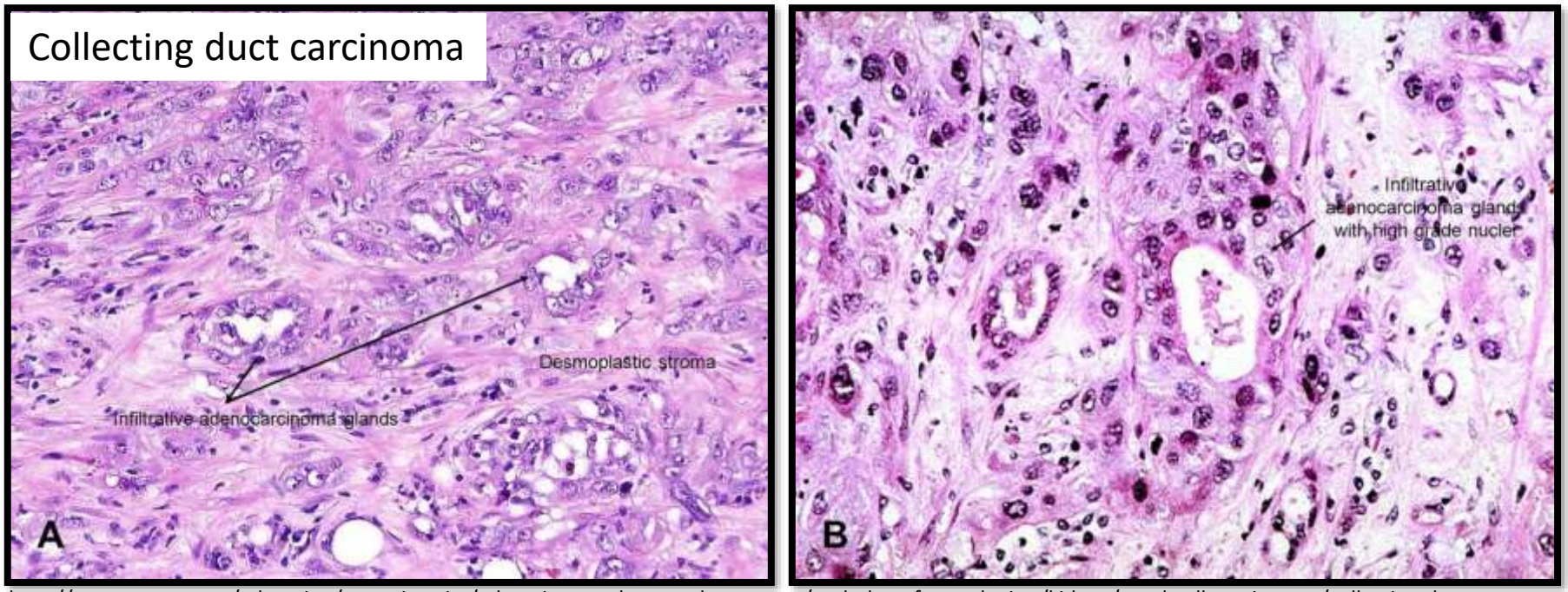
Immunohistochemistry results:
Positive – PAX8, AMACR, EMA, INI-1
Negative – CK7, HMWCK, CA IX





Differential diagnosis:

- Collecting duct carcinoma
  - HMWCK and CK7 were negative, which did not support this diagnosis
- Renal medullary carcinoma
  - Shows INI-1 loss, which occurs in ~15% of CDC; INI-1 retained in our case, no history of hemoglobinopathy, 66-year-old man
- Ohe C1, Smith SC, et al. Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase-deficient Renal Cell Carcinoma. Am J Surg Pathol. 2018 Mar;42(3):279-292.
- Other (new renal tumors frequently being described)



http://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/renal-cell-carcinomas/collecting-duct-carcinoma

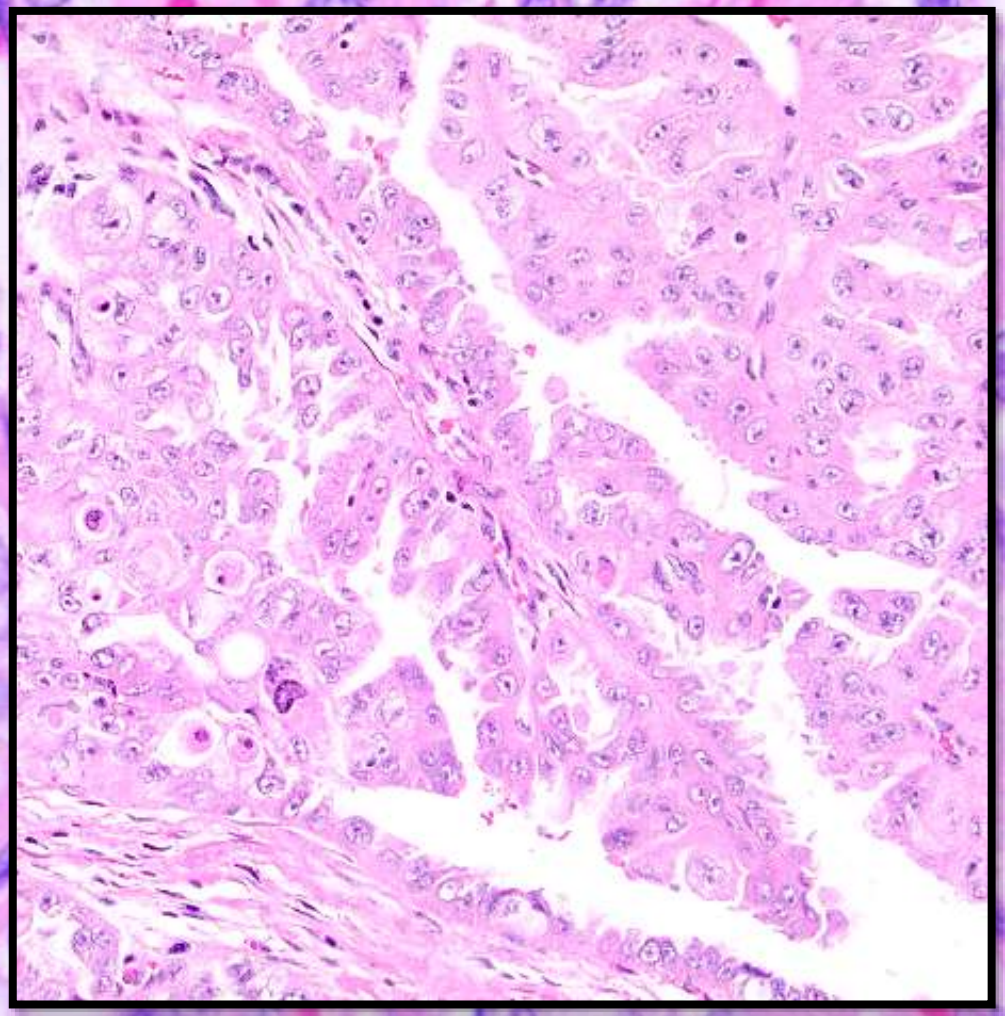
Diagnosis:

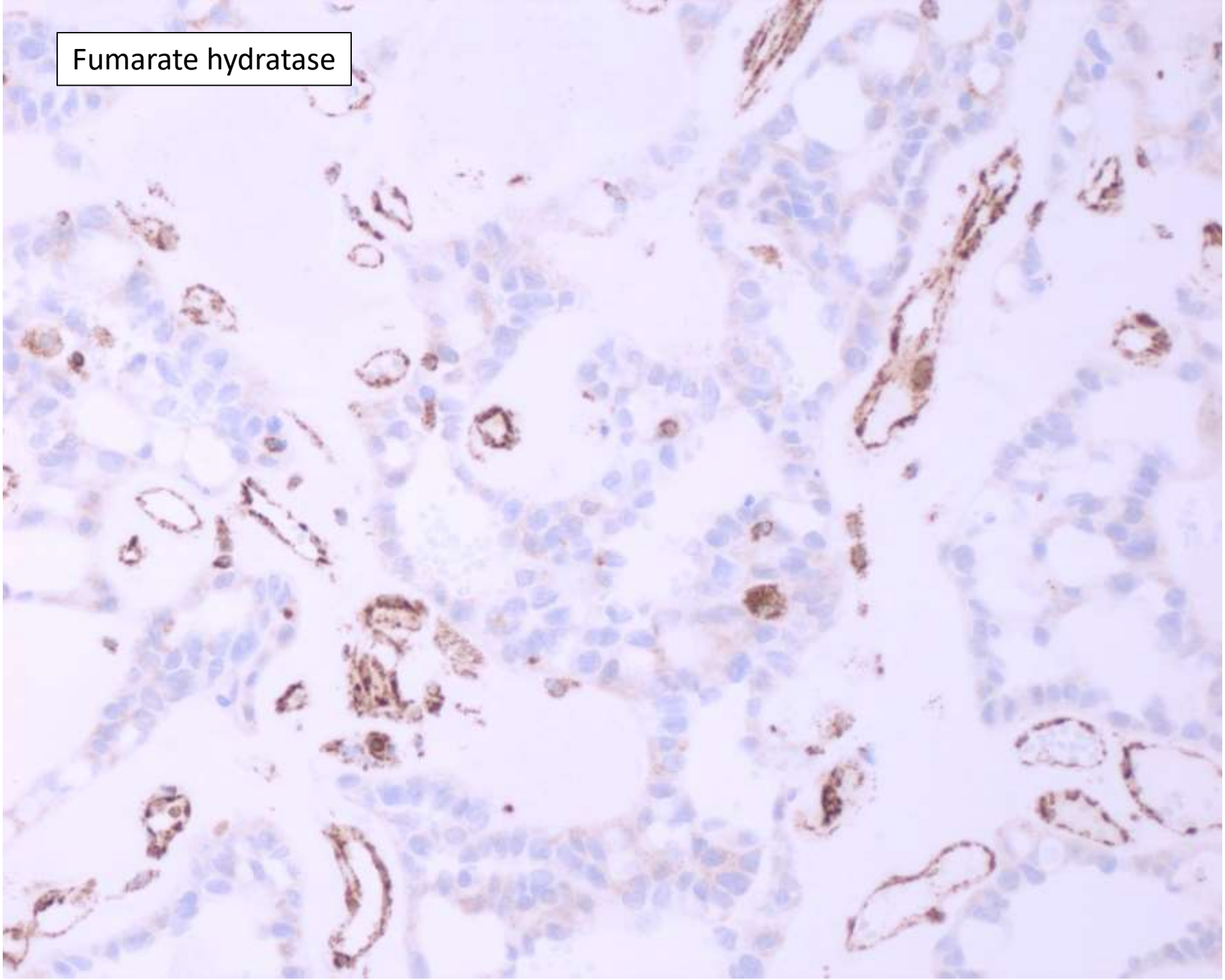
- Renal cell carcinoma, high grade unclassified
  - Favor collecting duct carcinoma, but IHC unusual, ? Other
  - Consider molecular testing if clinically indicated

- Molecular testing performed by Invitae: Sequenced 90 genes from saliva; positive for a **heterozygous mutation in the FH gene**: c.1157A>G (p.Gln386Arg)

- Amended diagnosis: Hereditary leiomyomatosis Renal Cell Carcinoma (HLRCC)
  - Additional family testing indicated

Focal prominent nucleoli with perinucleolar clearing




Fumarate hydratase

Hereditary Leiomyomatosis Renal Cell Carcinoma Syndrome (HLRCC)

- Inherited autosomal dominant disorder with germline *fumarate hydratase* (*FH*) mutations and a “second-hit” of the remaining *FH* allele
- Increased risk of cutaneous and uterine leiomyomas and renal cancer and cystic lesions
- Aggressive, usually cortical tumor, often with metastasis at presentation and death due to disease in less than 5 years
- Tumors demonstrate a spectrum of architecture patterns with prominent eosinophilic nucleolus with perinucleolar halo, which may be focal

Classifying high grade RCCs

- Many new entities
- Morphologic overlap in high grade RCCs and difficulty in classification (e.g., 100% sarcomatoid tumor)
- May or may not be important to have exact diagnosis:
  - Tumor all out: May be finished with treatment / cured
  - Oncologists starting to give adjuvant and targeted therapies, may be particularly relevant in high grade tumors
  - Hereditary tumor types; need family members tested

nature COMMUNICATIONS

ARTICLE

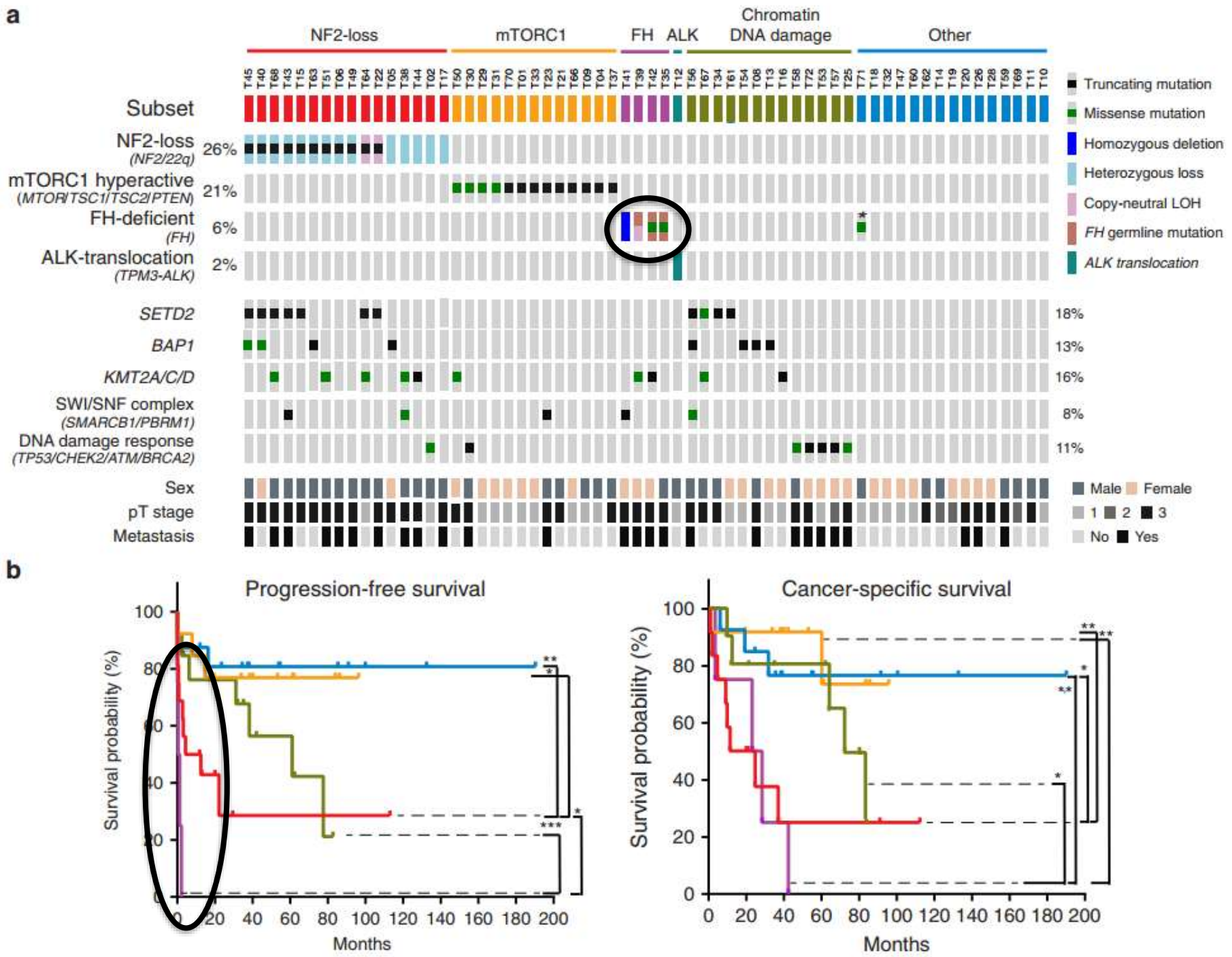
Received 28 Mar 2016 | Accepted 5 Sep 2016 | Published 7 Oct 2016

DOI: 10.1038/ncomms13131 OPEN

Molecular analysis of aggressive renal cell carcinoma with unclassified histology reveals distinct subsets

Ying-Bei Chen[1], Jianing Xu[2], Anders Jacobsen Skanderup[3,†], Yiyu Dong[2], A. Rose Brannon[1], Lu Wang[1], Helen H. Won[1], Patricia I. Wang[2], Gouri J. Nanjangud[4], Achim A. Jungbluth[1], Wei Li[5], Virginia Ojeda[5], A. Ari Hakimi[6], Martin H. Voss[7], Nikolaus Schultz[3], Robert J. Motzer[7], Paul Russo[6], Emily H. Cheng[1,2], Filippo G. Giancotti[5,†], William Lee[3,8], Michael F. Berger[1,2], Satish K. Tickoo[1], Victor E. Reuter[1] & James J. Hsieh[2,7,9]

- 62 hig
- Targe RNA seque
- Identi in 29 genes


a
NF2-loss
mTORC1
FH
ALK
Chromatin DNA damage
Other
Subset
NF2-loss (NF2/22q) 26%
mTORC1 hyperactive (MTOR/TSC1/TSC2/PTEN) 21%
FH-deficient (FH) 6%
ALK-translocation (TPM3-ALK) 2%
SETD2 18%
BAP1 13%
KMT2A/C/D 16%
SWI/SNF complex (SMARCB1/PBRM1) 8%
DNA damage response (TP53/CHEK2/ATM/BRCA2) 11%
Sex
pT stage
Metastasis
Truncating mutation
Missense mutation
Homozygous deletion
Heterozygous loss
Copy-neutral LOH
FH germline mutation
ALK translocation
Male Female
1 2 3
No Yes
b
Progression-free survival
Cancer-specific survival
Survival probability (%)
Months

High grade case without classic features

- Best diagnosis may be RCC, high grade unclassified type, consider molecular testing
- Tumors with focal clear cell differentiation can be diagnosed as clear cell RCC
- Molecular testing may be needed in RCC, high grade unclassified type, to provide:
  - Adjuvant and targeted therapy
  - Hereditary information to family members
- Important to consider clinical context

References

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- Carter CS, et al. Immunohistochemical Characterization of Fumarate Hydratase (FH) and Succinate Dehydrogenase (SDH) in Cutaneous Leiomyomas for Detection of Familial Cancer Syndromes. Am J Surg Pathol. 2017 Jun;41(6):801-809.
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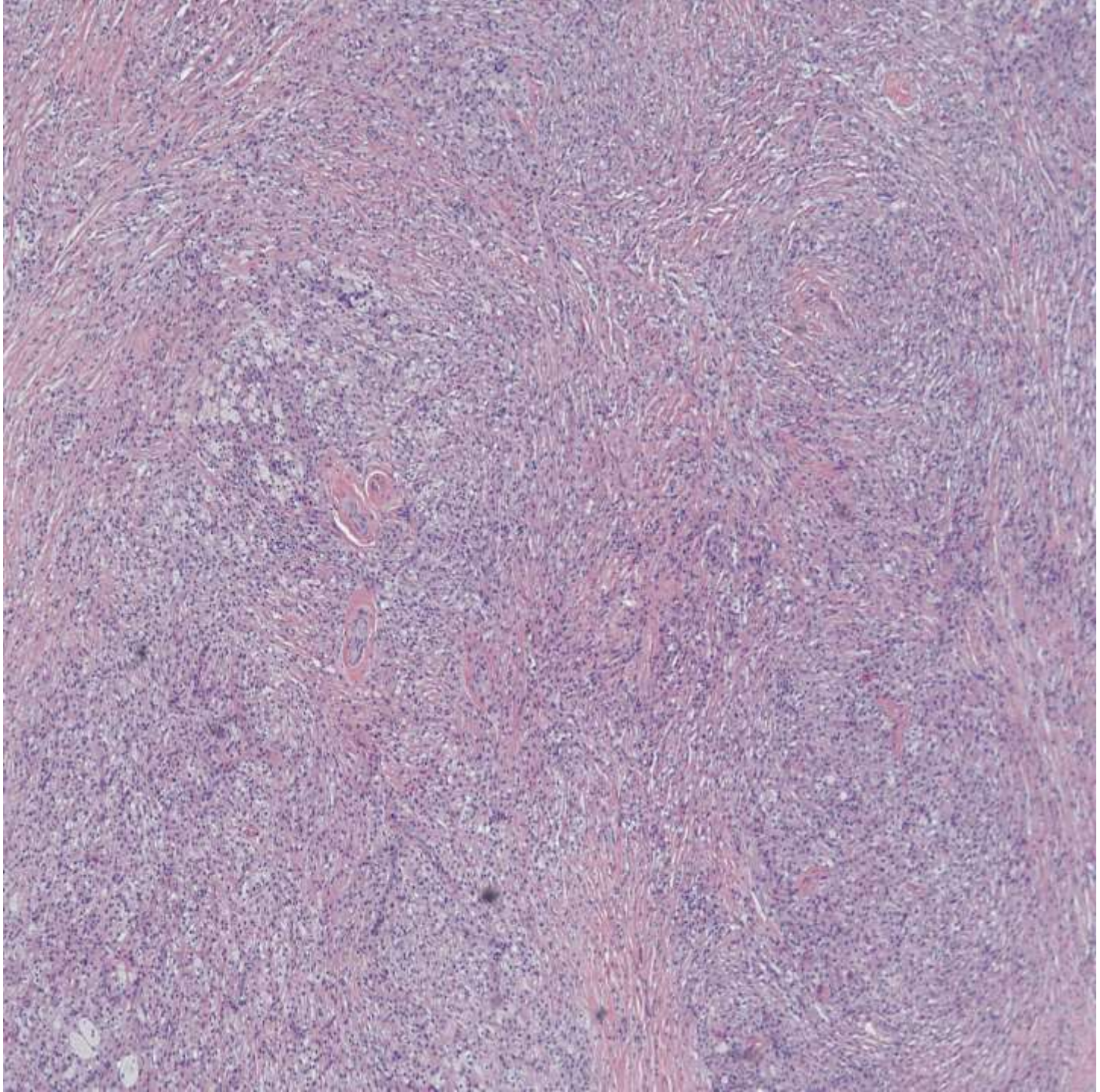
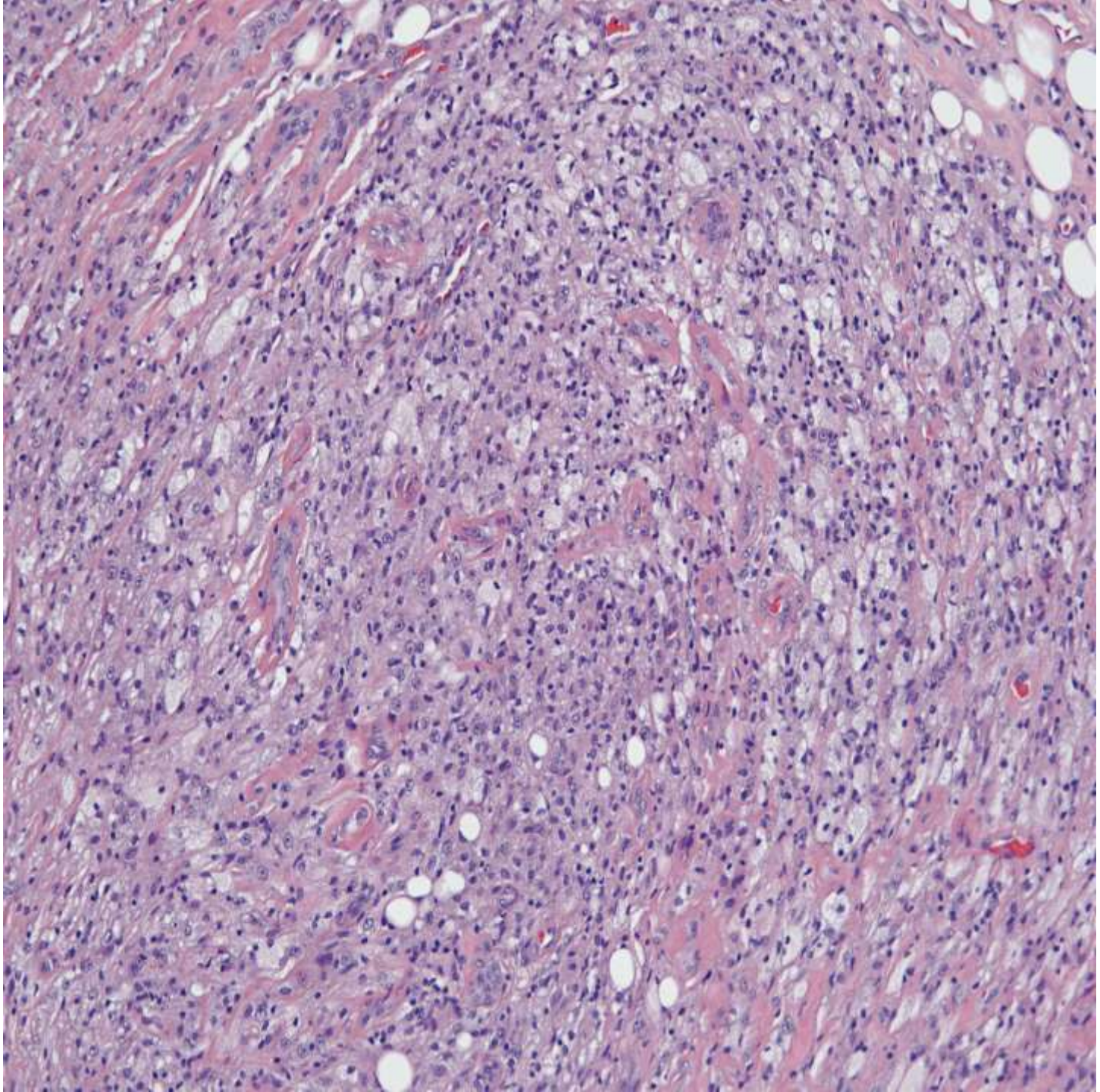
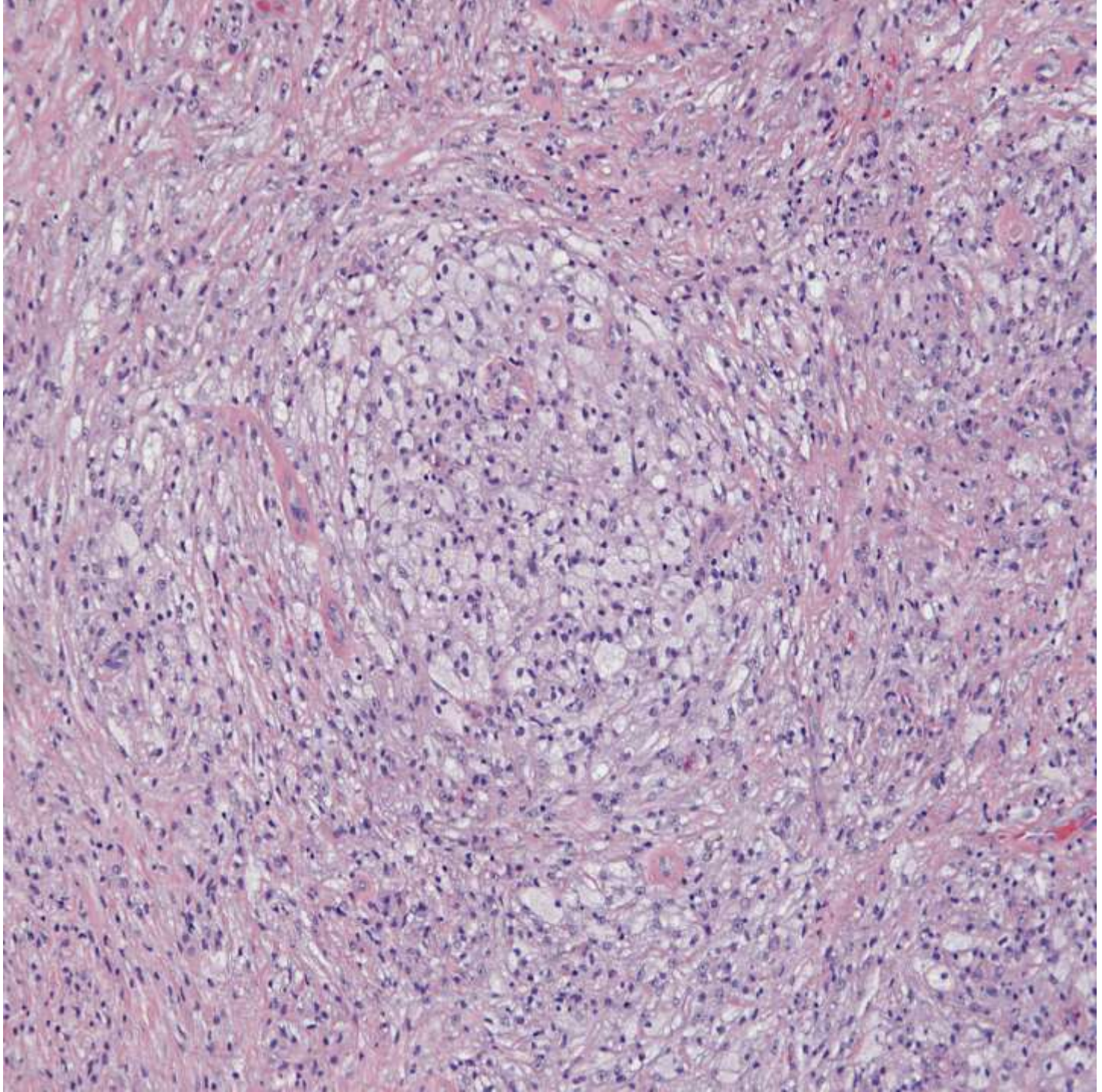
- Ohe C1, Smith SC, et al. Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase-deficient Renal Cell Carcinoma. Am J Surg Pathol. 2018 Mar;42(3):279-292.
- Chen YB, et al. Molecular analysis of aggressive renal cell carcinoma with unclassified histology reveals distinct subsets. Nat Commun. 2016 Oct 7;7:13131.
- Figlin RA, et al. Adjuvant therapy in renal cell carcinoma: does higher risk for recurrence improve the chance for success? Ann Oncol. 2018 Feb 1;29(2):324-331.
- https://www.cancer.gov/about-cancer/treatment/clinical-trials/kidney-cancer

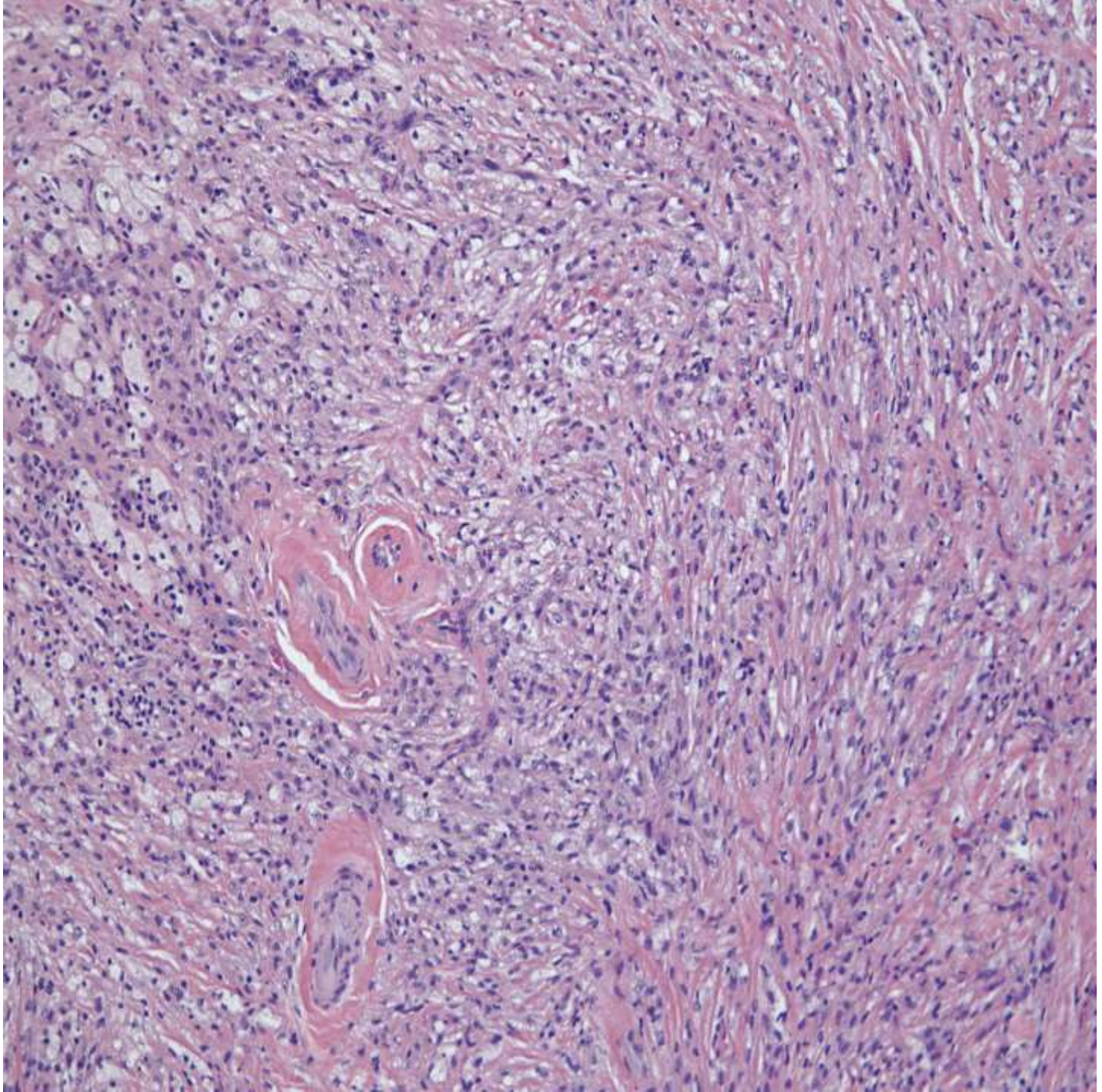
SB 6275
Sebastian Fernandez-Pol/Lisa McGinnis/Yaso Natkunam; Stanford

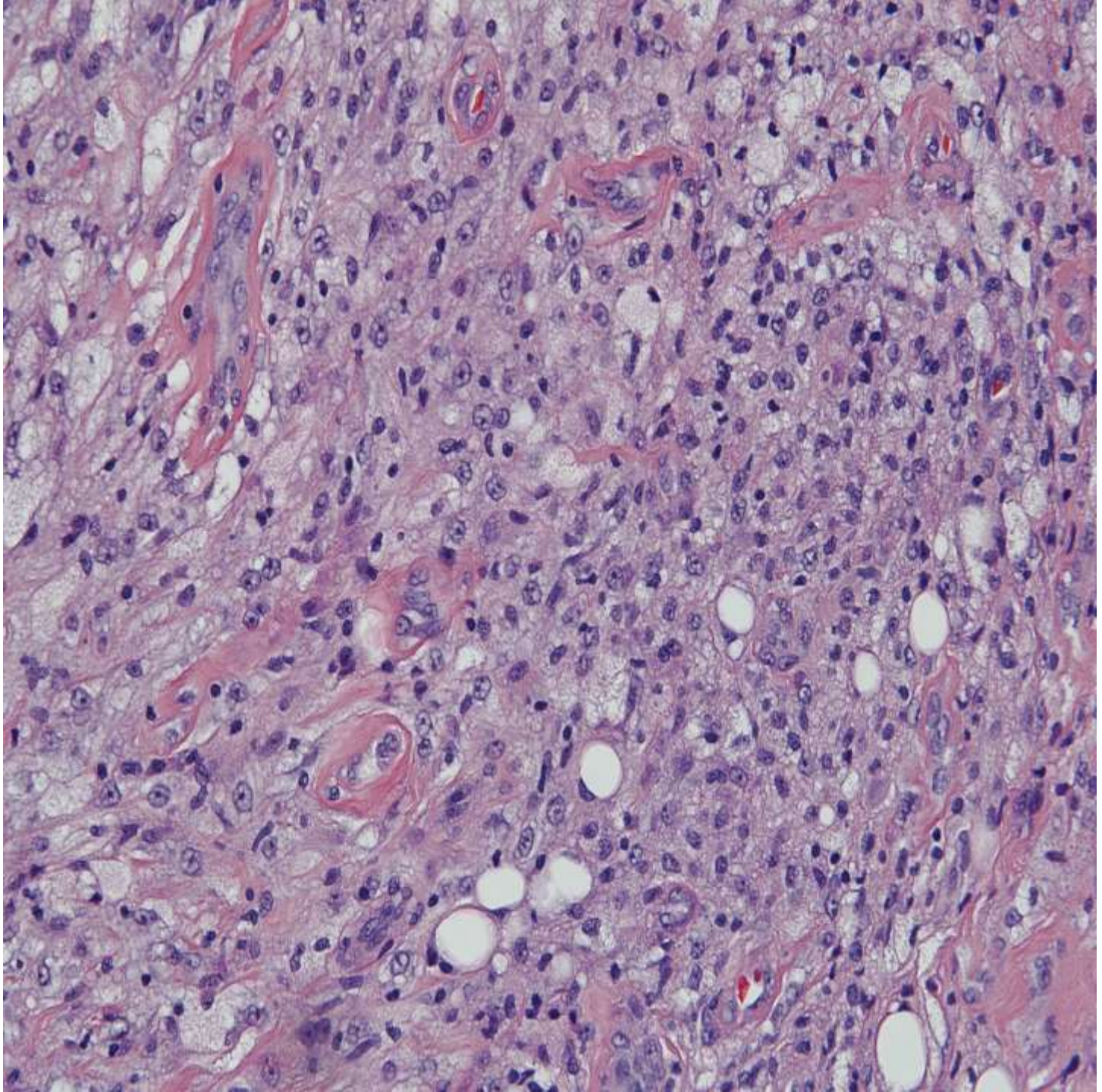
54-year-old woman with history of CALR-mutated essential thrombocytosis and right orbital mass.

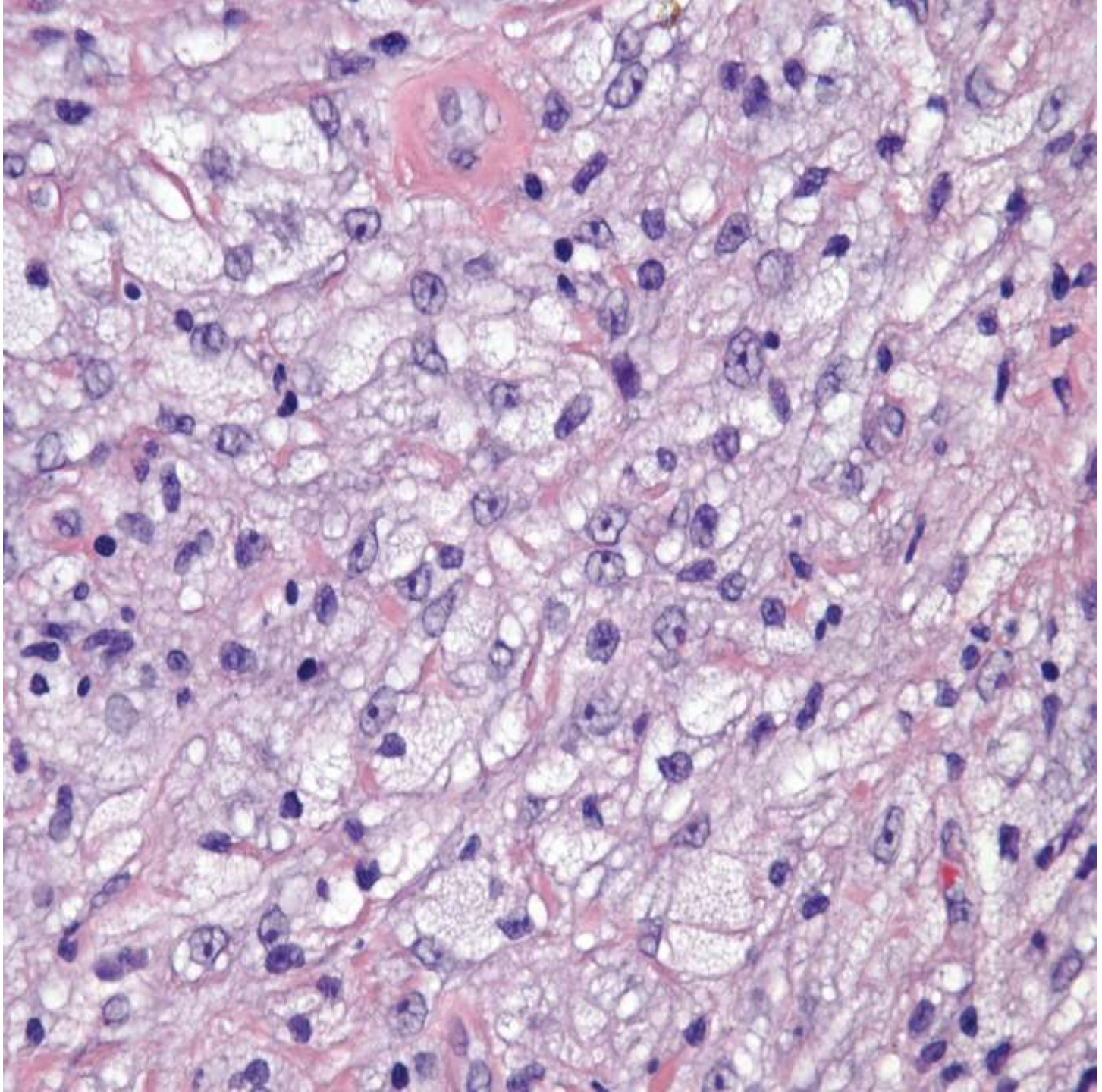






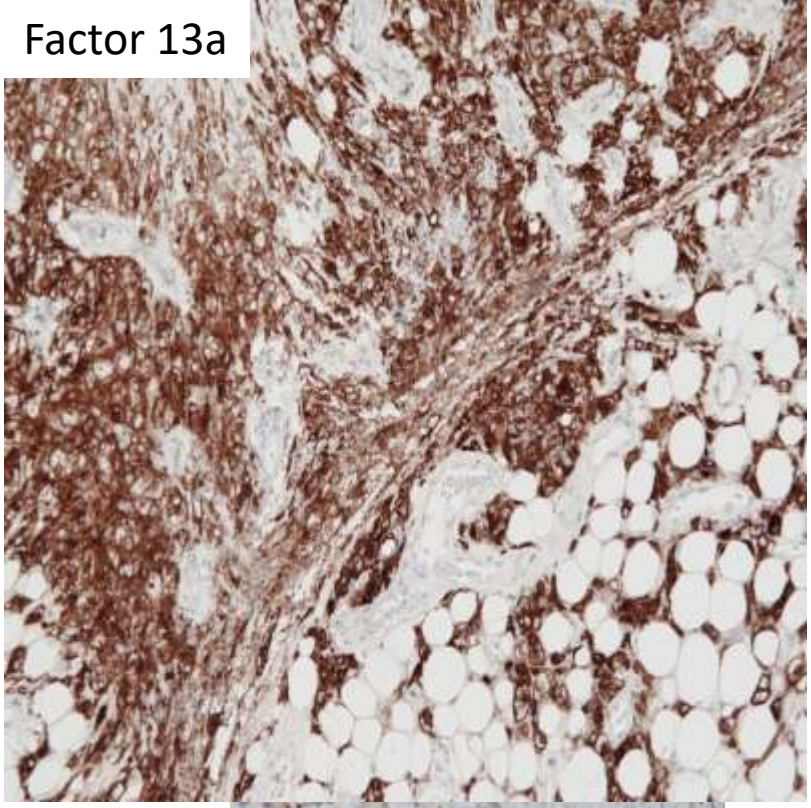




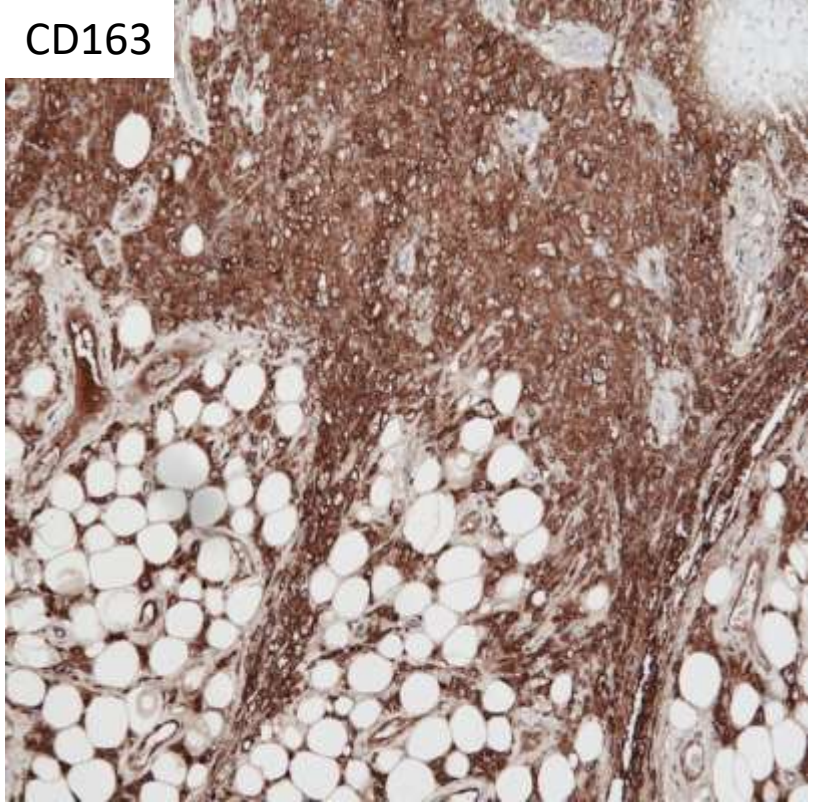


DIAGNOSIS?

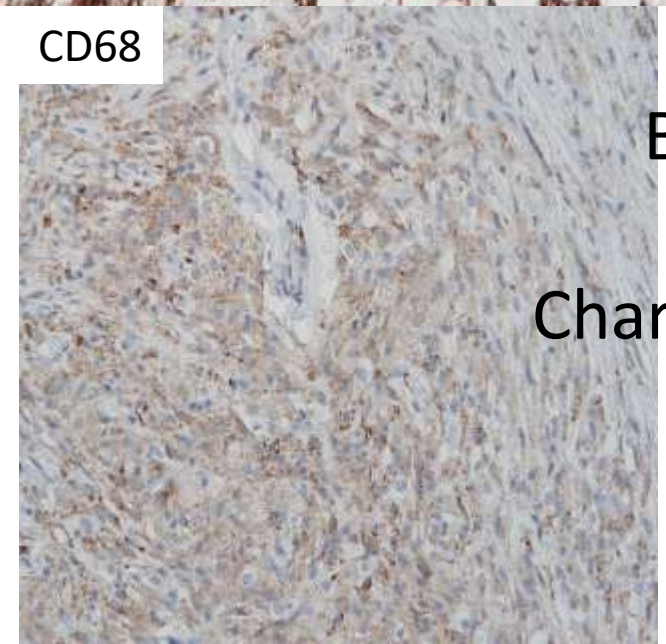
Factor 13a



CD163



CD68



BRAF V600E mutation was detected

+

Characteristic clinical/radiographic feat

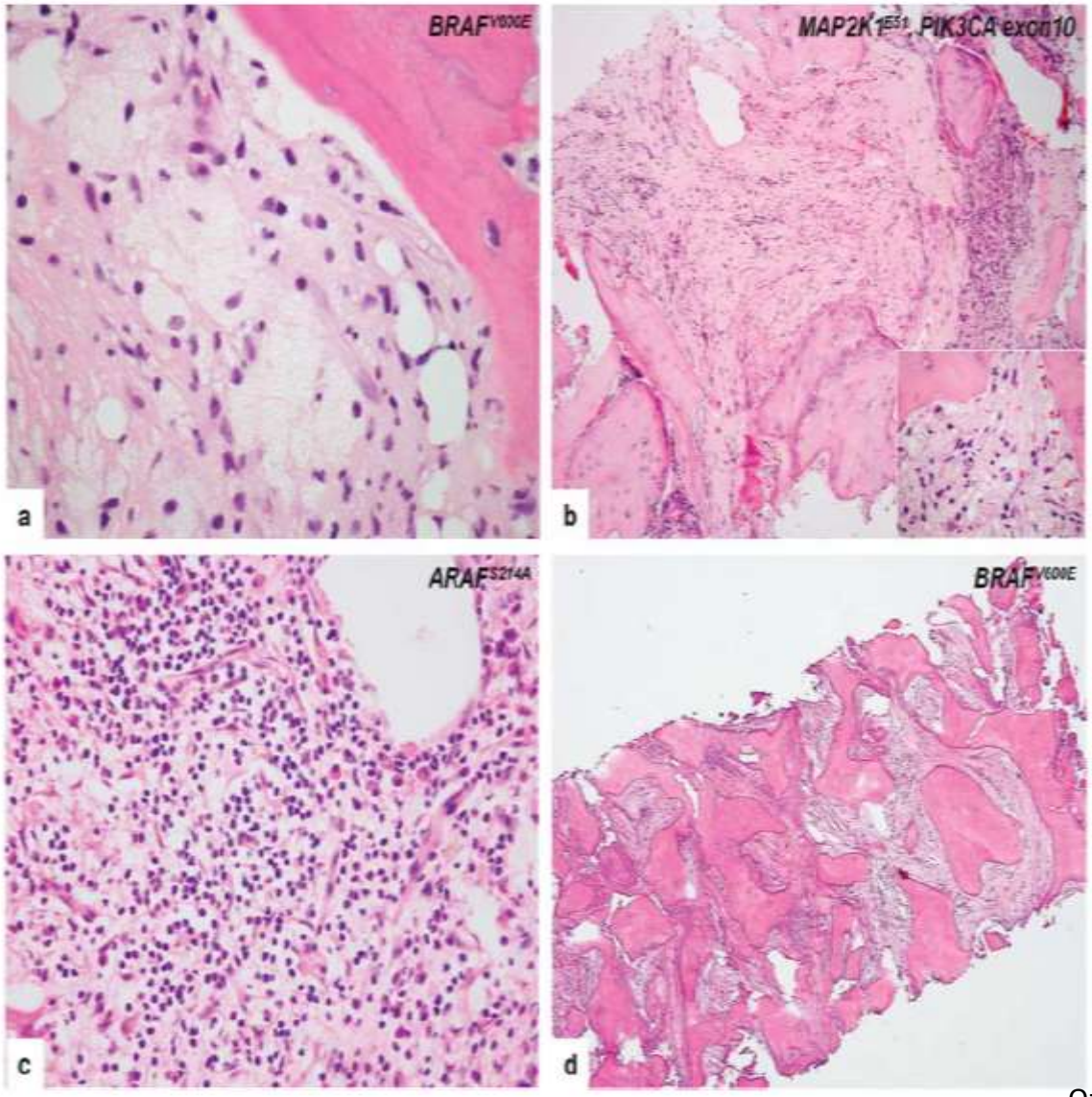
⬇

Erdheim-Chester disease

Additional clinical information

- Extensive multiorgan involvement
- Neurologic symptoms
  - Loss of balance, blurred vision, and aphasia

Histologically variable – Intraosseous lesions



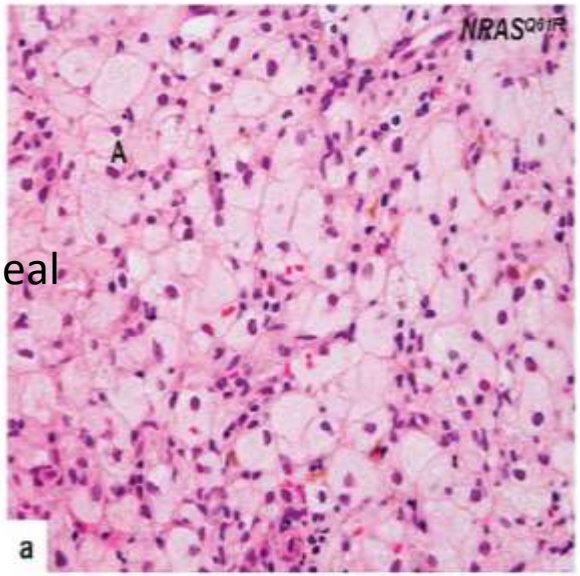
Dense lymphoplasmacytic infiltrate

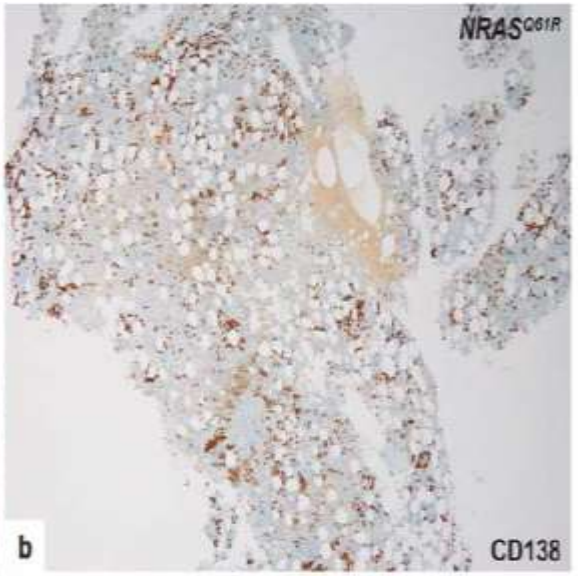
Prominent fibrosis and osteosclerosis

Ozkaya et al, Mod Pathol. 2017

Histologically variable

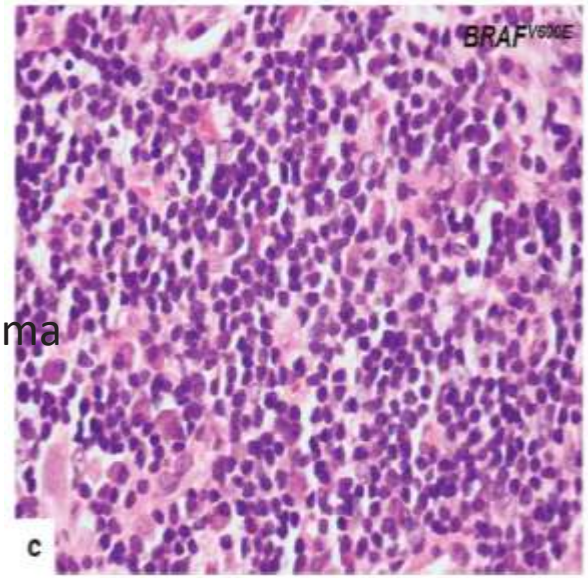
Retroperitoneal

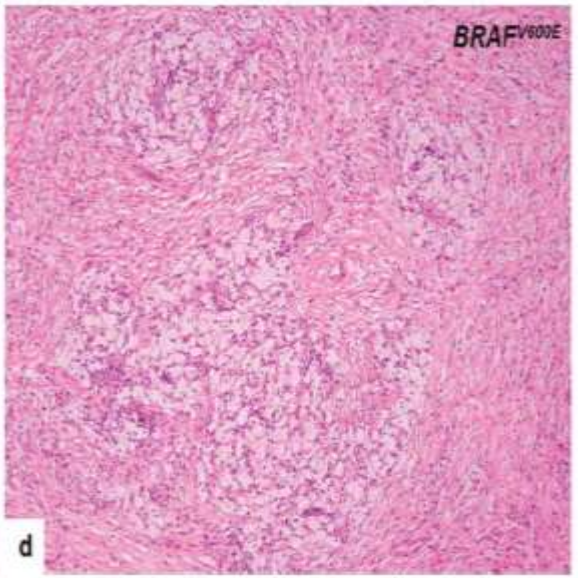




Retroperitoneal

Orbital
DDx lymphoma



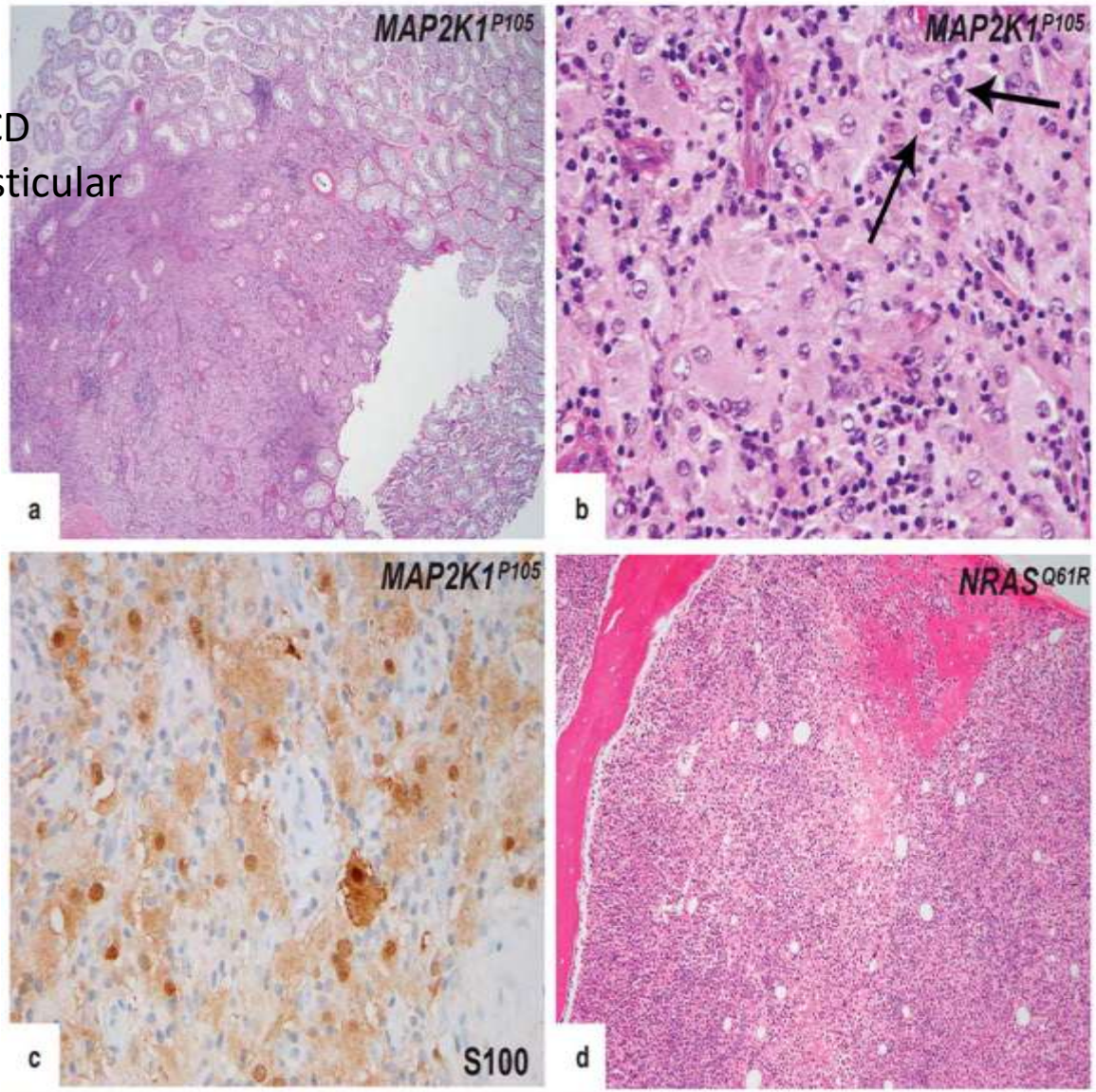


Orbital

Özkaya et al, Mod Pathol. 2017

Histologically variable: Rosai-Dorfman

2 patients with ECD
Elsewhere had testicular Rosai-Dorfman



Concomitant CMM

Özkaya et al, Mod Pathol. 2017

Immunohistochemistry

- All specimens were positive for one or more of the histiocytic markers:
  - **CD68, CD163, or FXIIIa**

- **S100 was positive** in 12/40 (30%) cases of Erdheim–Chester disease samples (brain and testis biopsies were excluded)

- All of the specimens were completely **negative for CD1a** (except the case with concomitant Langerhans cell histiocytosis infiltration)

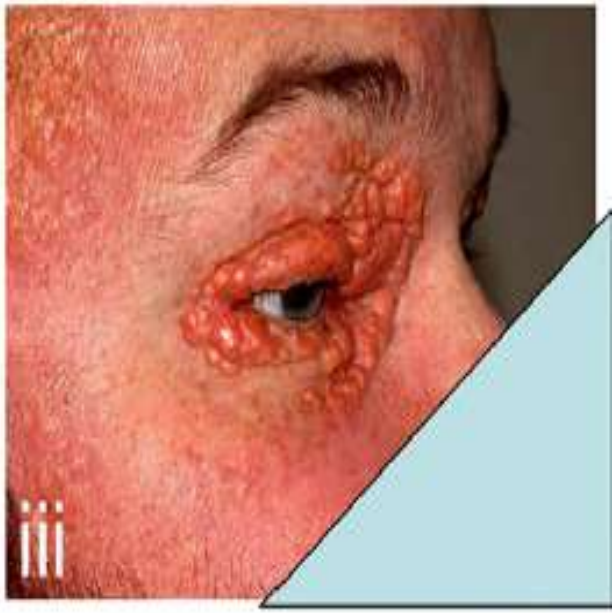
Ozkaya et al, Mod Pathol. 2017

Histologic differential diagnosis

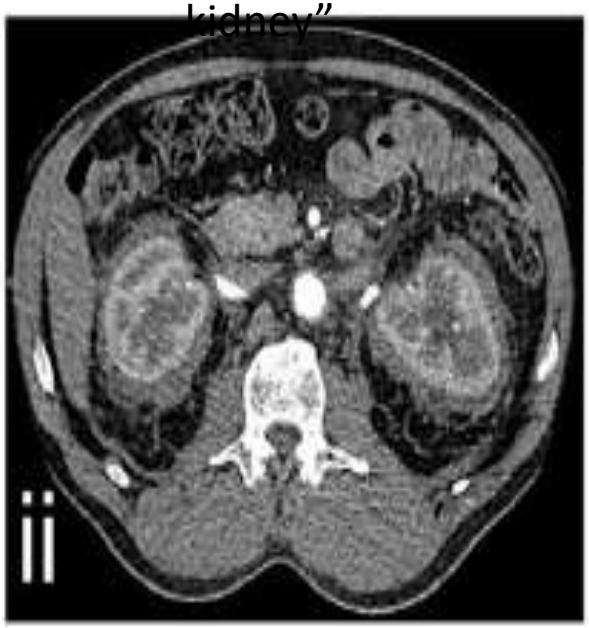
- Xanthogranulomatous inflammation
- Histiocytic disorders
  - Erdheim-Chester Disease
  - Disseminated xanthogranuloma
  - Langerhan cell histiocytosis
  - Rosai-Dorfman
- Benign fibrous histiocytoma of bone (fibrous xanthoma or xanthofibroma, nonossifying fibroma)
- Fibrous dysplasia with xanthomatous reaction secondary to hemorrhage
- Dense lymphoplasmacytic infiltrate:
  - IgG4-related sclerosing disease
  - Lymphoma (e.g. extranodal marginal zone lymphoma)
  - Rosai-Dorfman

Erdheim-Chester disease: clinical and radiographic findings

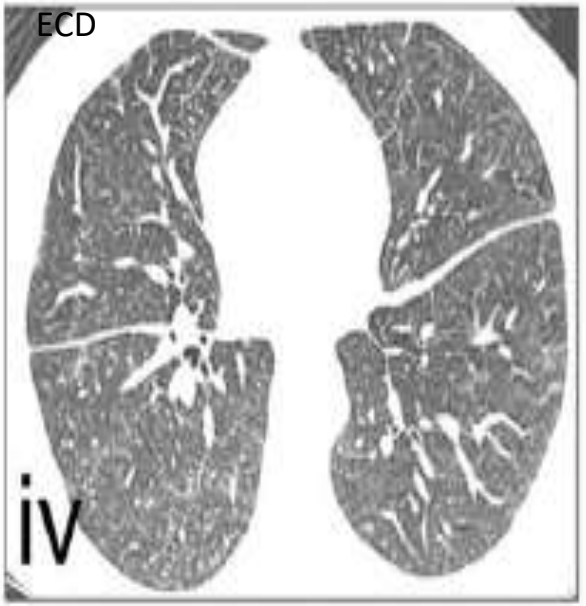
Xanthelasma of ECD



"Hairy kidney"

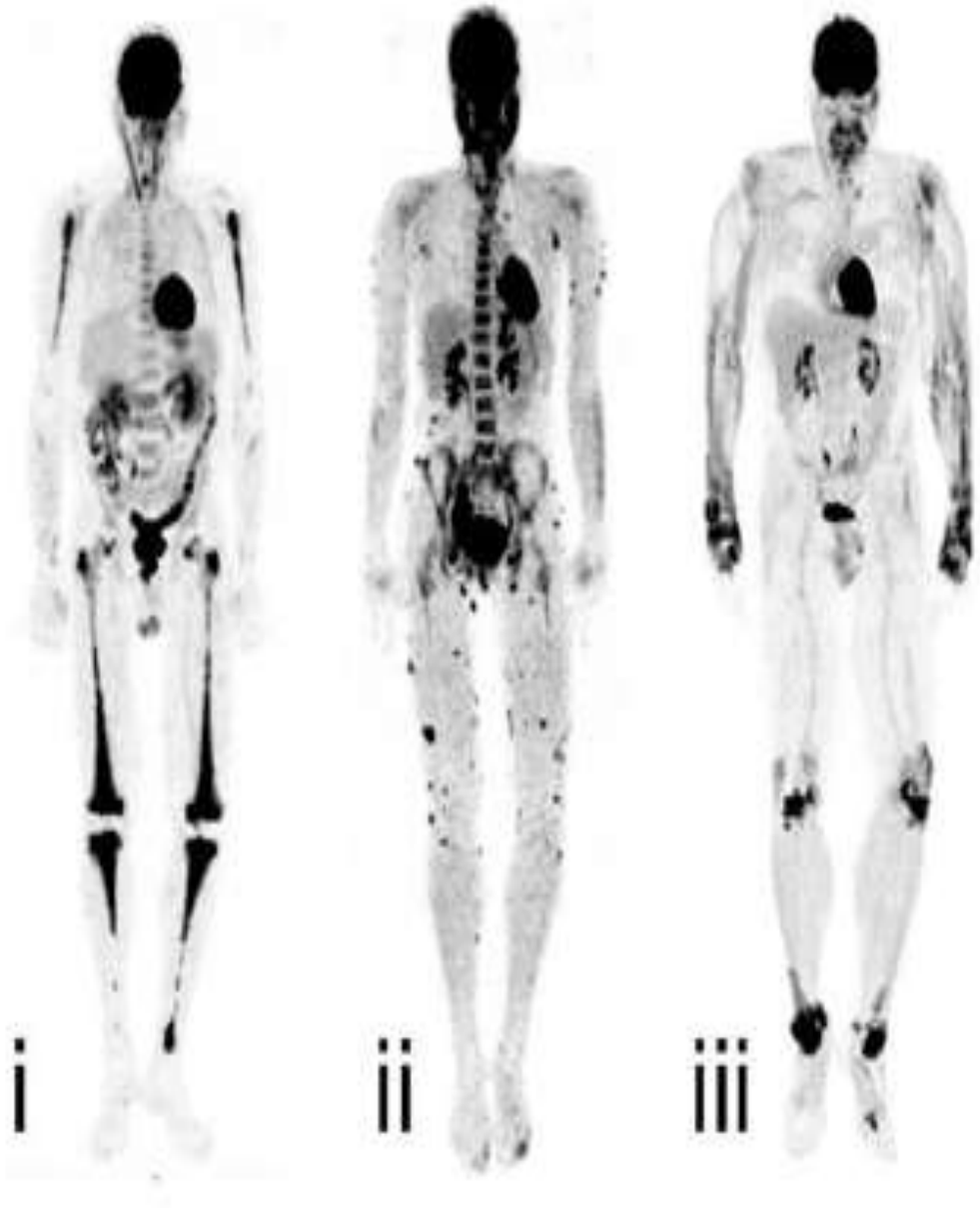


Micronodular ground-glass opacities and thickening of interlobular pulmonary septa in ECD

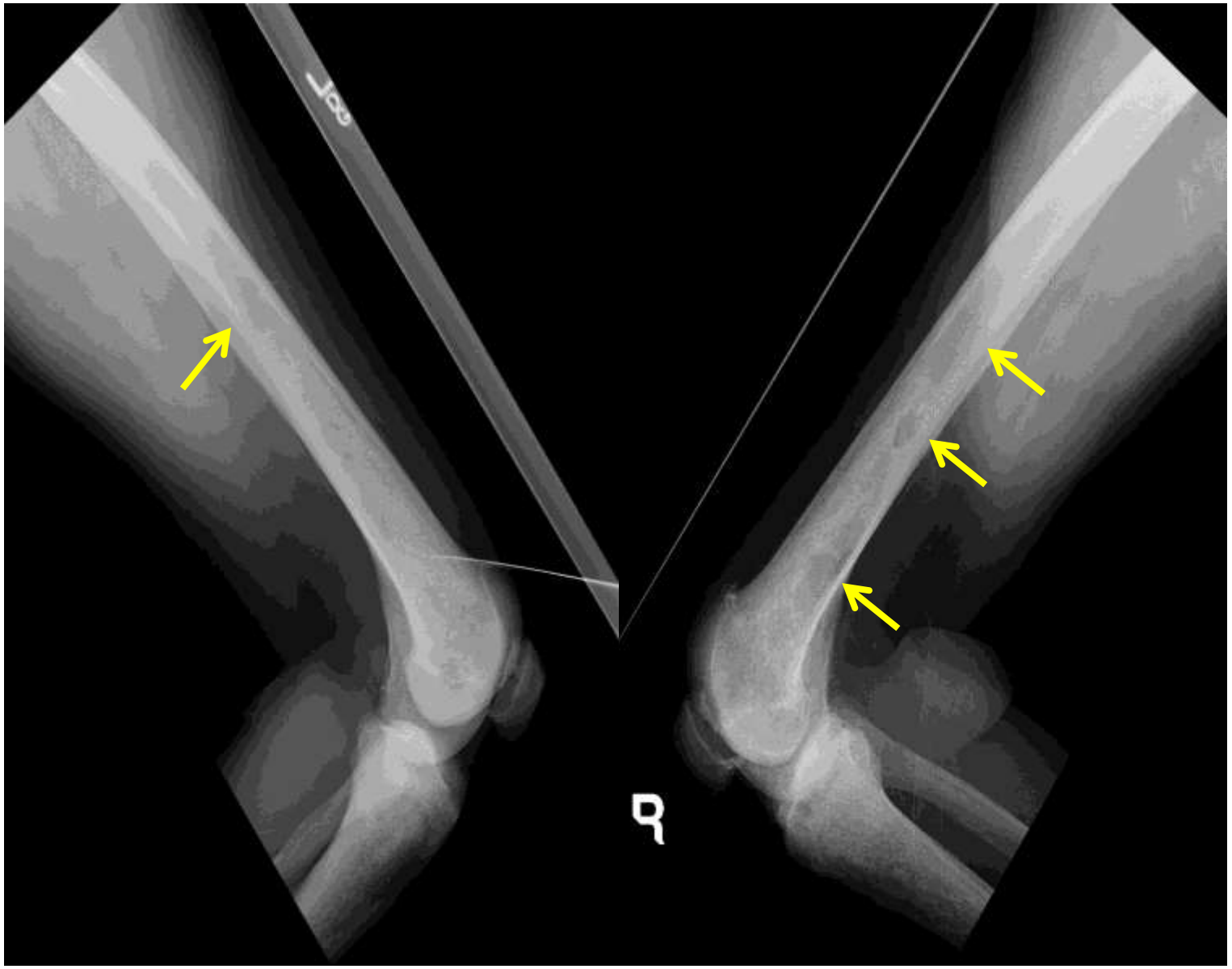


Emile et al, Blood. 2016

Erdheim-Chester disease Rosai-Dorfman Xanthoma disseminatum



18F-labeled fluorodeoxyglucose (PET) Emile et al, Blood. 2016


R

Relationship between Erdheim-Chester and Langerhan cell histiocytosis??

- Nearly 20% of patients with Erdheim-Chester disease (ECD) also have LC histiocytosis (LCH) lesions
- Both diseases have clonal mutations involving genes of the MAPK pathway in >80% of cases
- Clinical features can be similar (diabetes insipidus and/or neurodegenerative disease)
- *Justification for "L" group with LCH, ECD, and extracutaneous JXG*

Hervier B, Haroche J, Arnaud L, et al; French Histiocytoses Study Group. Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood. 2014;124(7):1119-1126.

Relationship to concurrent myeloid neoplasms?

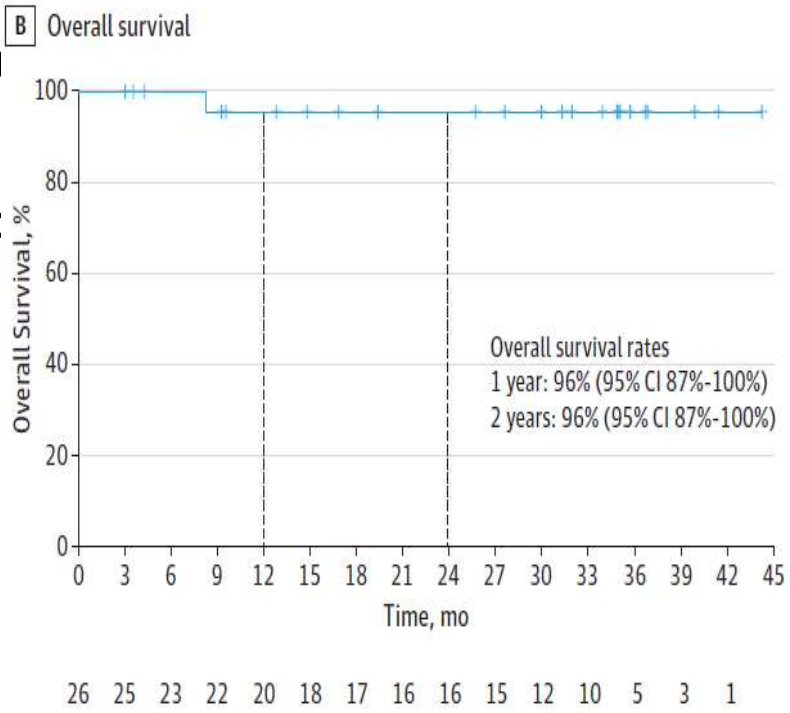
- Myeloid neoplasms can be seen in the course of Erdheim–Chester disease - 15% (6/42) of one case cohort
  - Chronic myelomonocytic leukemia (4 patients)
  - JAK2+ unclassified myeloproliferative neoplasm (1 patient)
  - Myelodysplastic syndrome with excess blasts-1 (1 patient)
  - Two marrows with reactive changes

- Peripheral blood monocytes harboring the same mutations as pathological histiocytes have been reported in both diseases

Ozkaya et al, Mod Pathol. 2017

Treatments

- **Vemurafenib (BRAF V600E inhib**
- Interferon alpha
- Anakinra (IL1Ra) and/or targetec
- Methotrexate
- Cytarabine
- Imatinib
- 6-mercaptopurine
- Mycophenolate
- Clofarabine
- Vinblastine/prednisone
- Cladribine



Ozkaya et al, Mod Pathol. 2017
Diamond et al,JAMA Oncol. 2018

Erdheim-Chester Disease: Take home points

- Consider Erdheim-Chester disease when evaluating cytologically bland fibrotic lesions (Ddx IgG4-related sclerosing disease)
- Diagnosis relies on combination of morphology, immunophenotype, molecular, clinical, and radiographic correlation
- Immunophenotypically distinct from Langherhan cell histiocytosis but may be related (similar spectrum of MAPK pathway mutations)
- Associated with Rosai-Dorfman in the testis
- Concurrent myeloid neoplasms in a subset

References

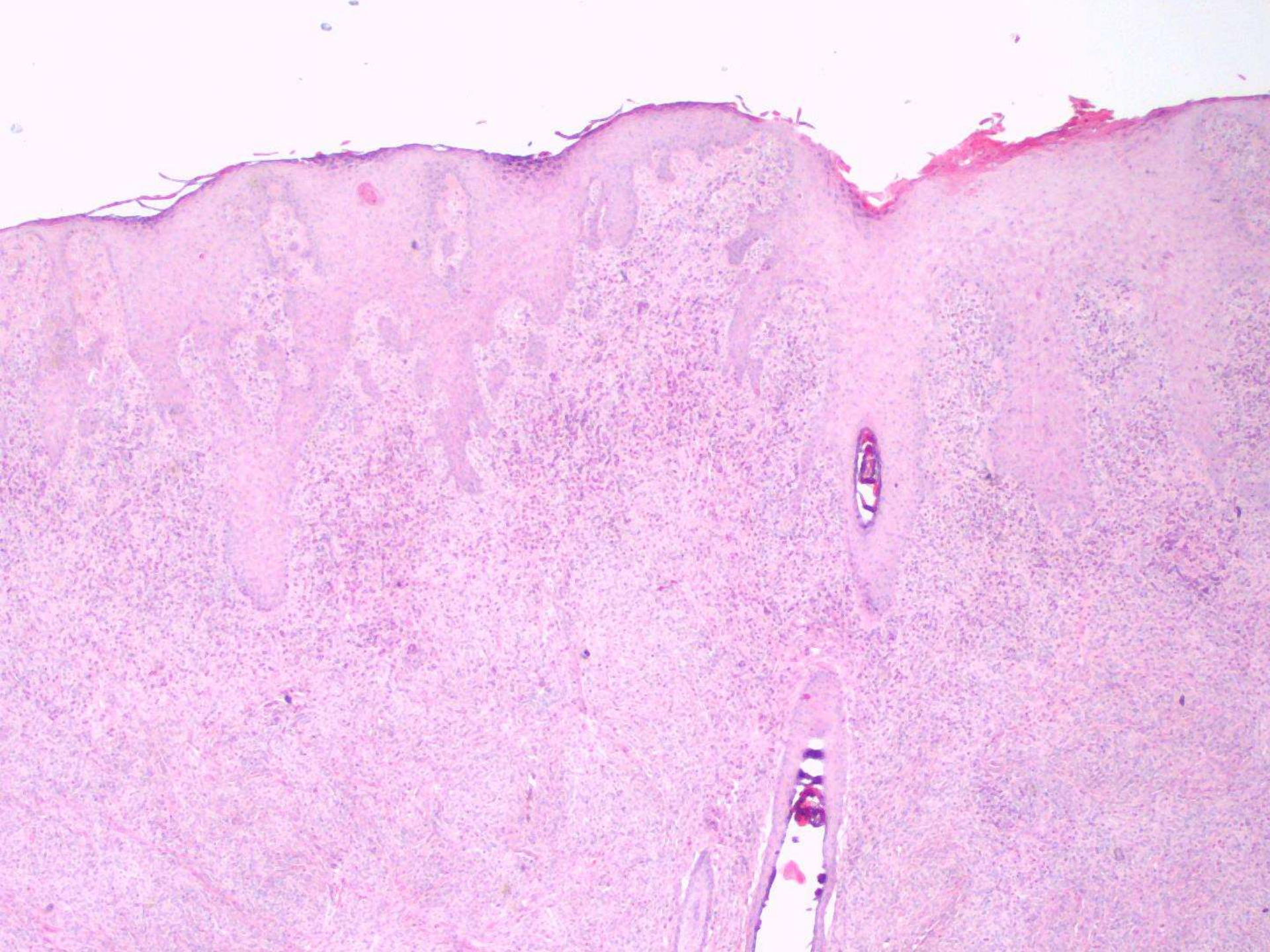
- Emile J.F., Abla O., Fraitag S. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127:2672–2681.
- Ozkaya Neval, Rosenblum Marc K., Durham Benjamin H. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. Mod Pathol. 2017:1–17.
- Diamond EL, Subbiah V, Lockhart AC, Blay JY, Puzanov I, Chau I, Raje NS, Wolf J, Erinjeri JP, Torrisi J, Lacouture M, Elez E, Martinez-Valle F, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol. 2018;4:384–388.

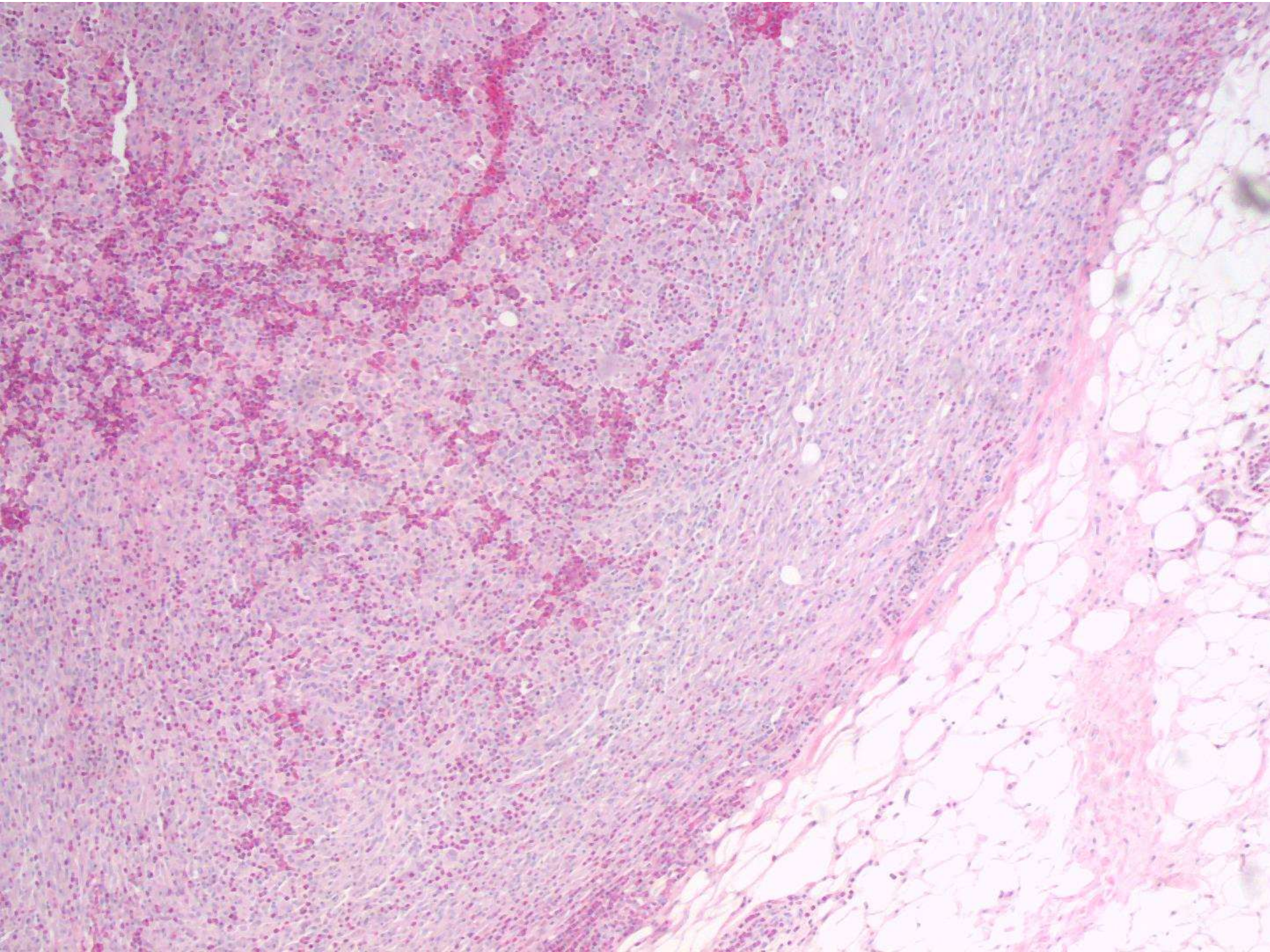
SB 6276
Josh Menke/Roger Warnke; Stanford

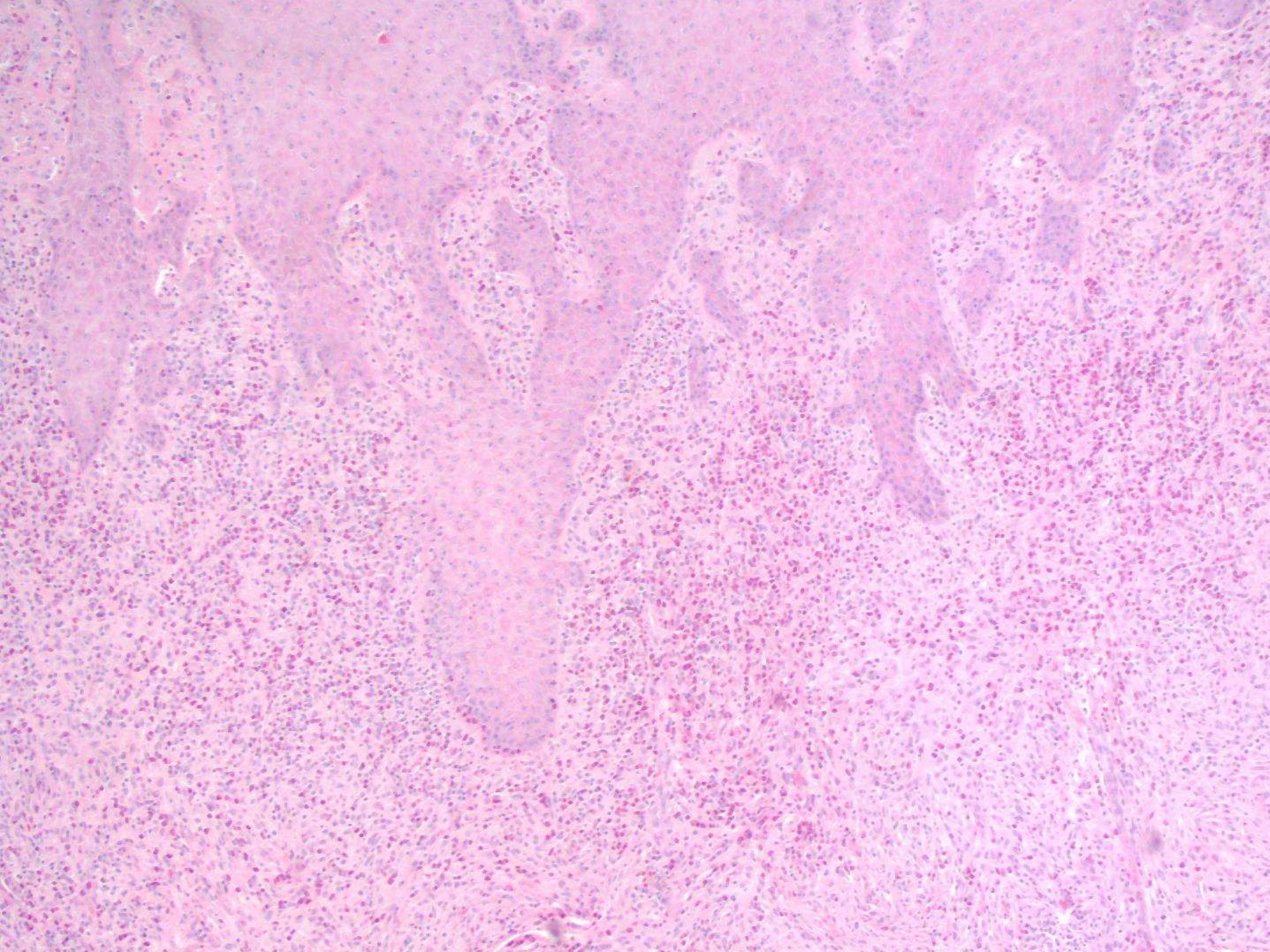
2-year-old girl with 2cm firm, mobile, flesh-colored mass at superior portion of right posterior neck at scalp base. Mass has been expanding over 4 months and was non-pulsatile.

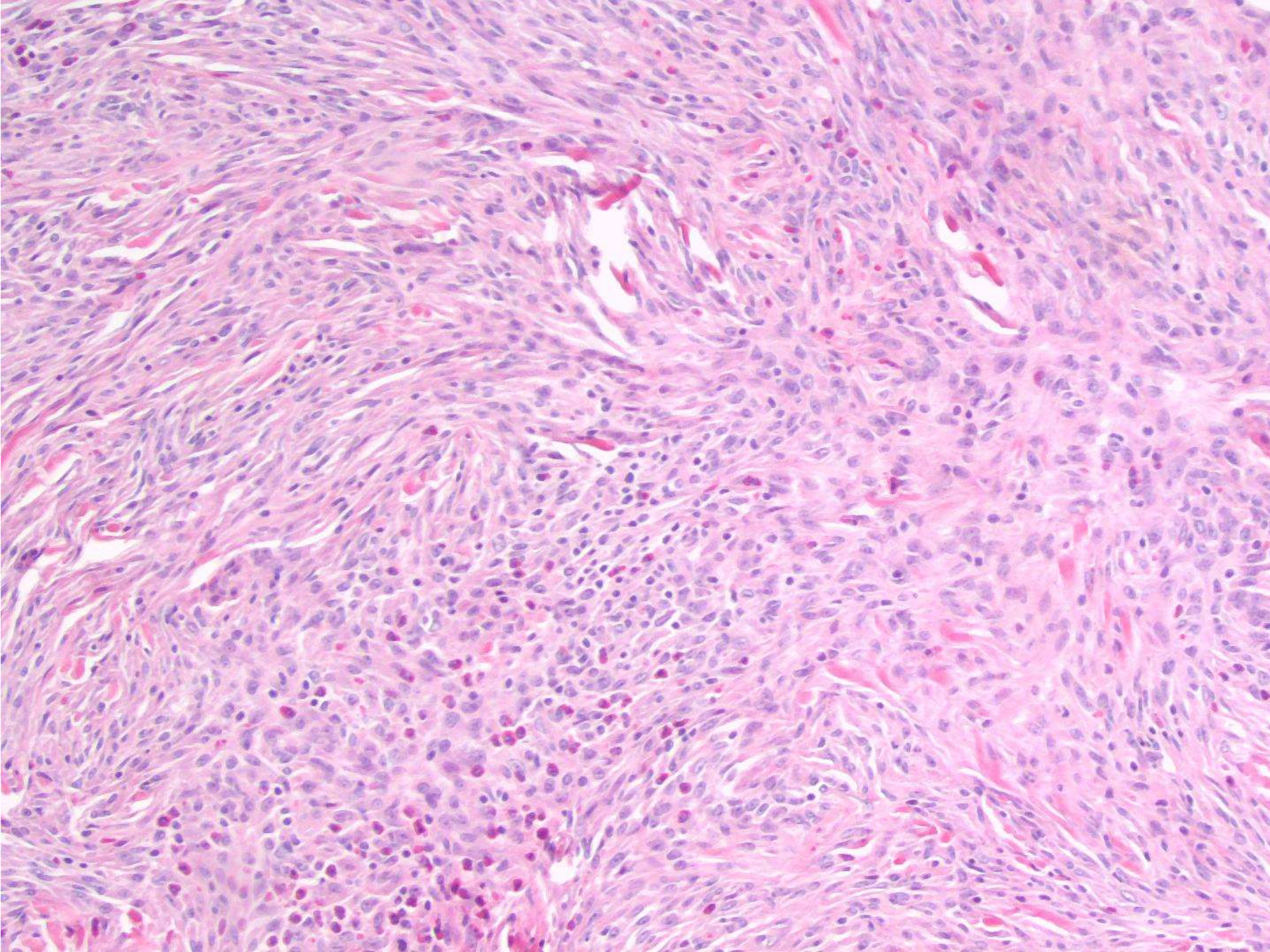
History

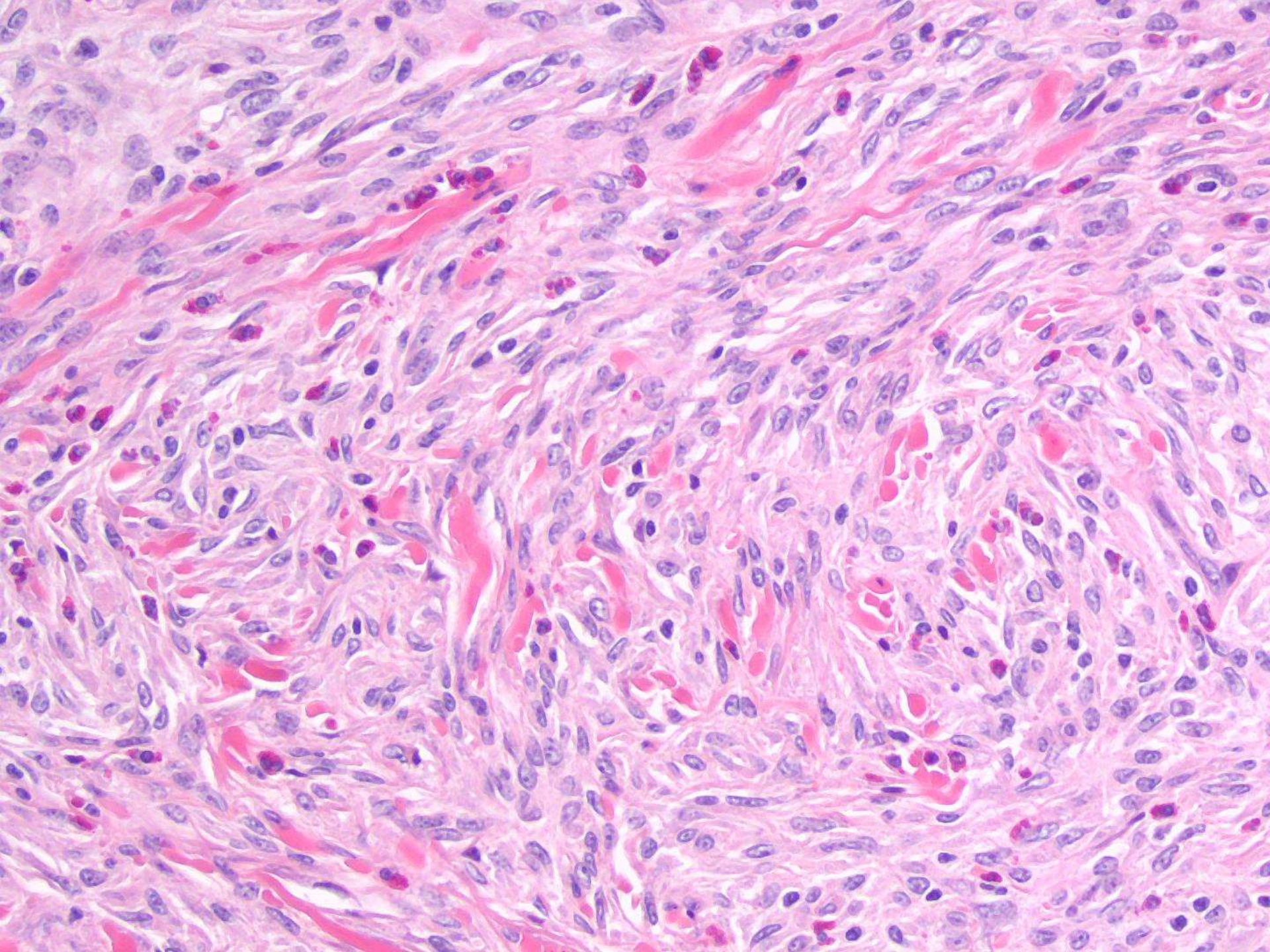
- 2 year old female with a 2 cm firm, mobile, flesh colored mass at the junction of the right posterior neck and base of the scalp
- The mass had been expanding over a 4 month period and was non-pulsatile
- No U/S or imaging was done

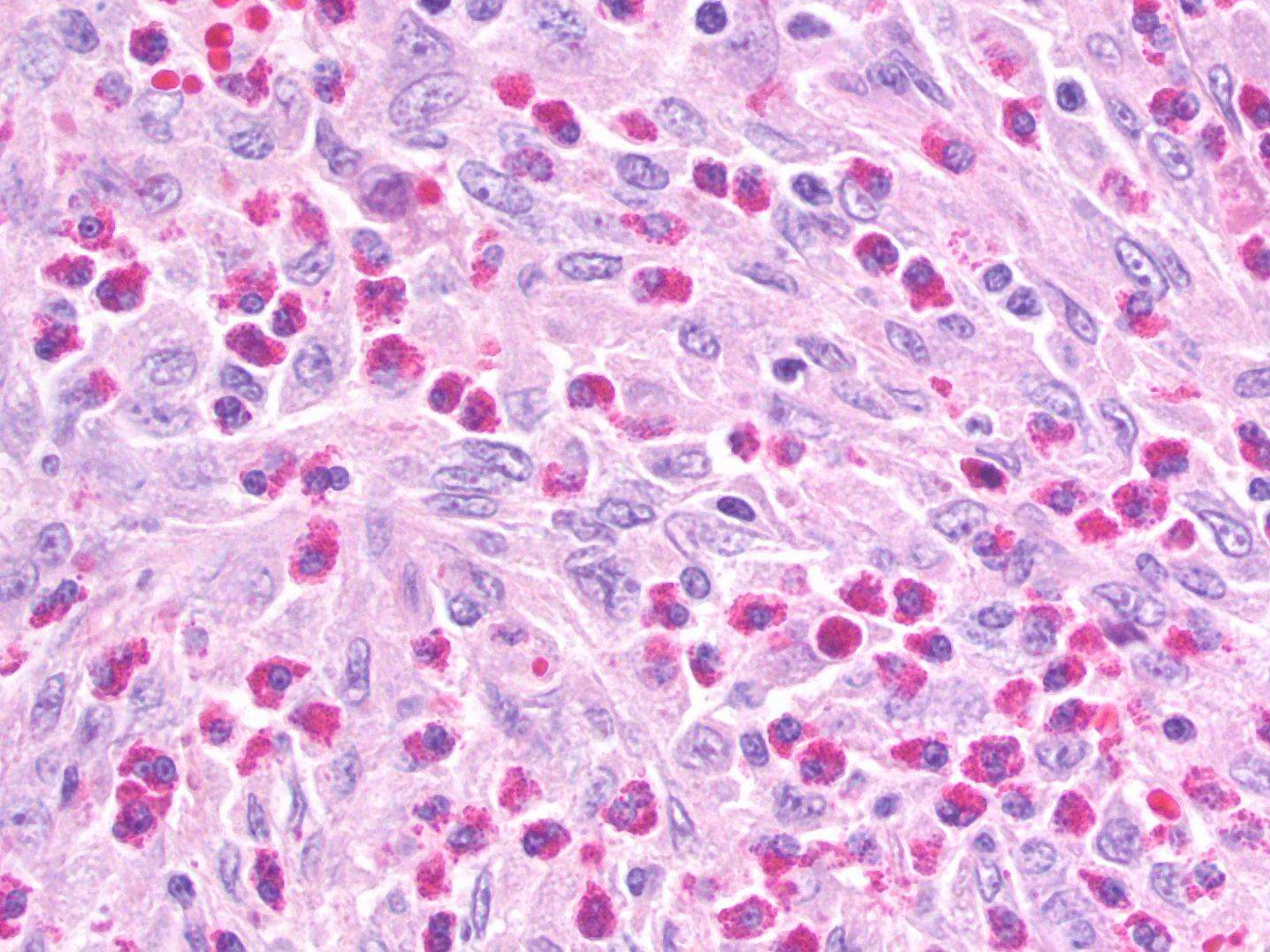


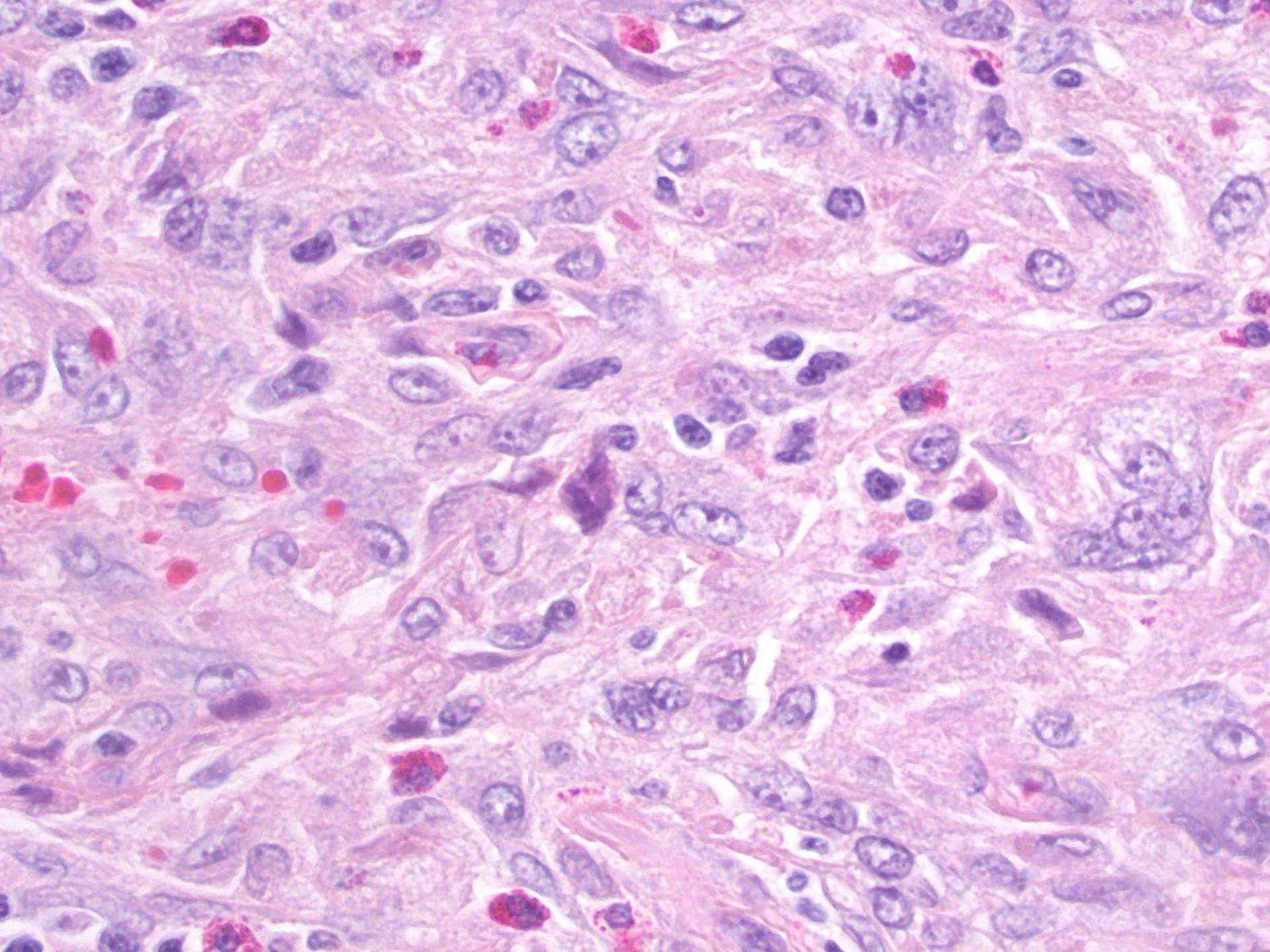


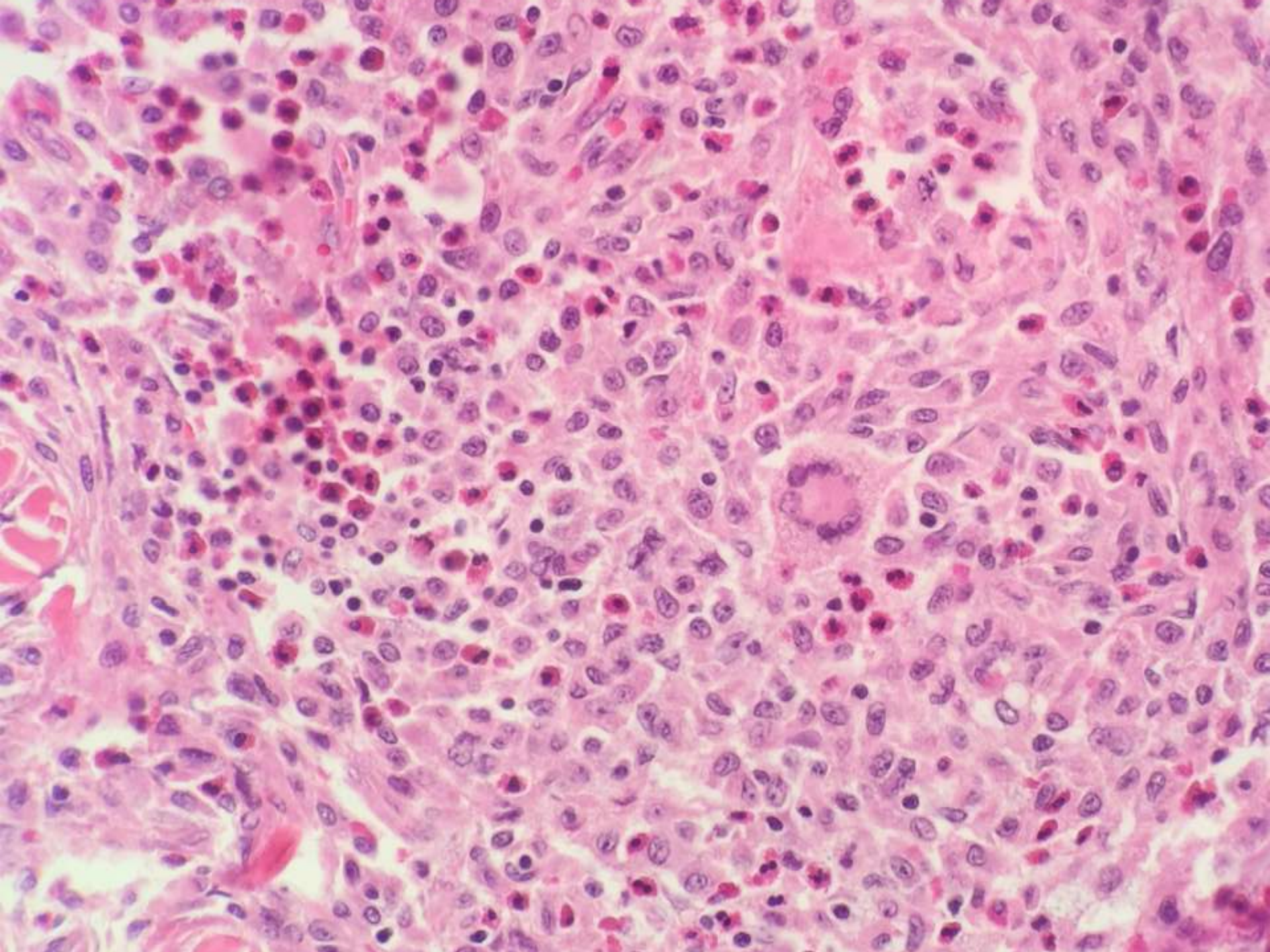












Differential diagnosis?

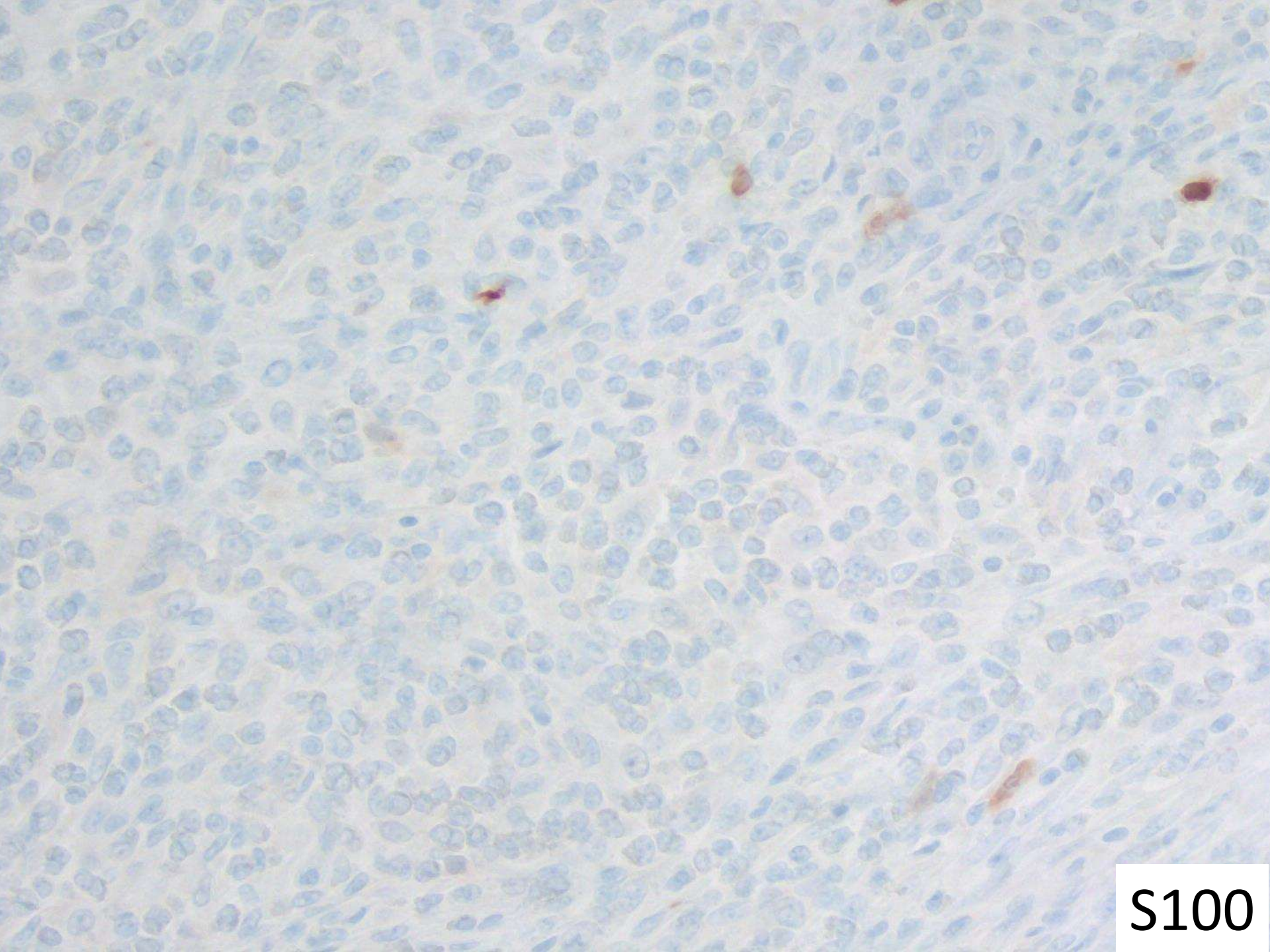
DIAGNOSIS?

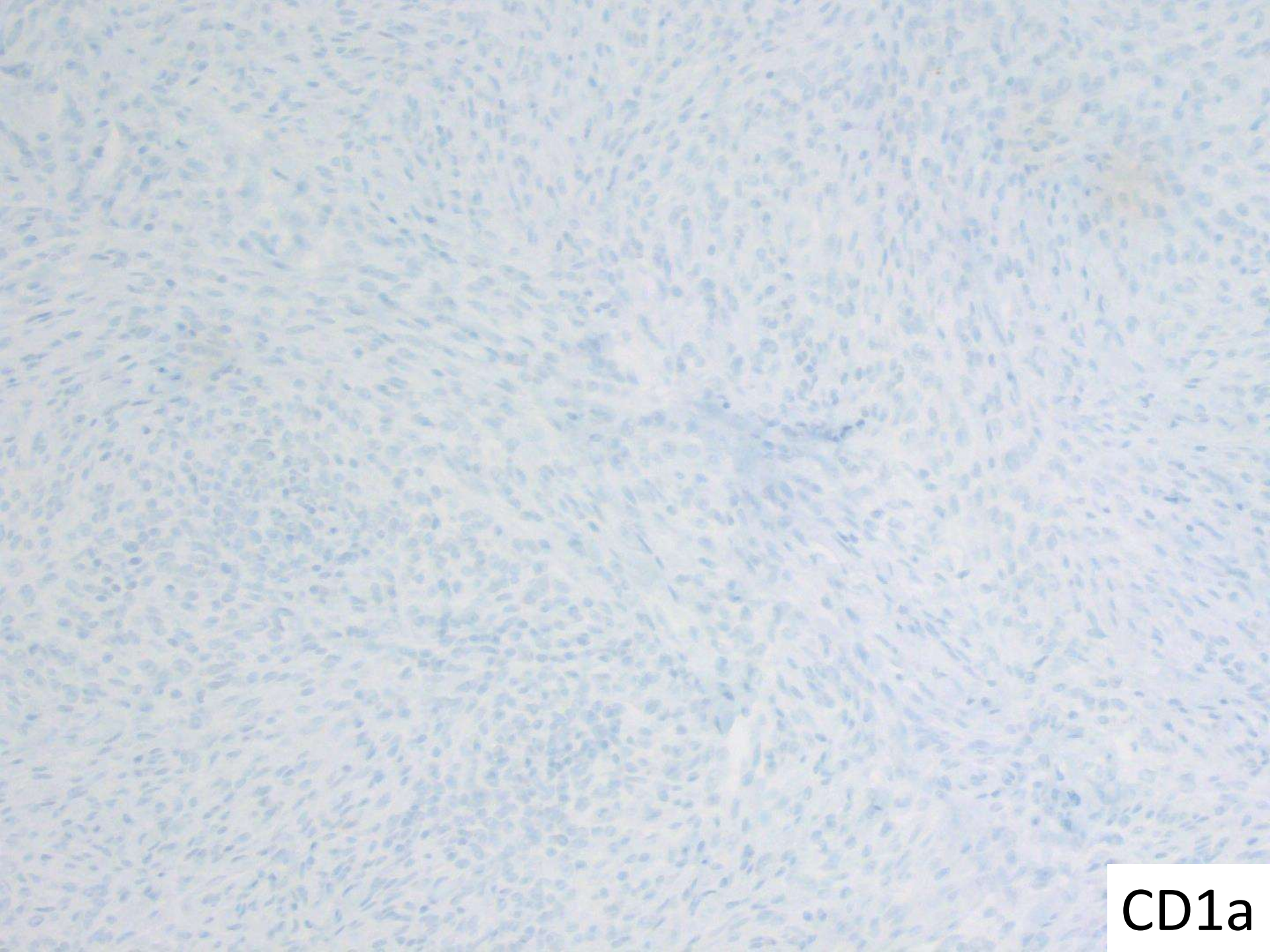
South Bay Case

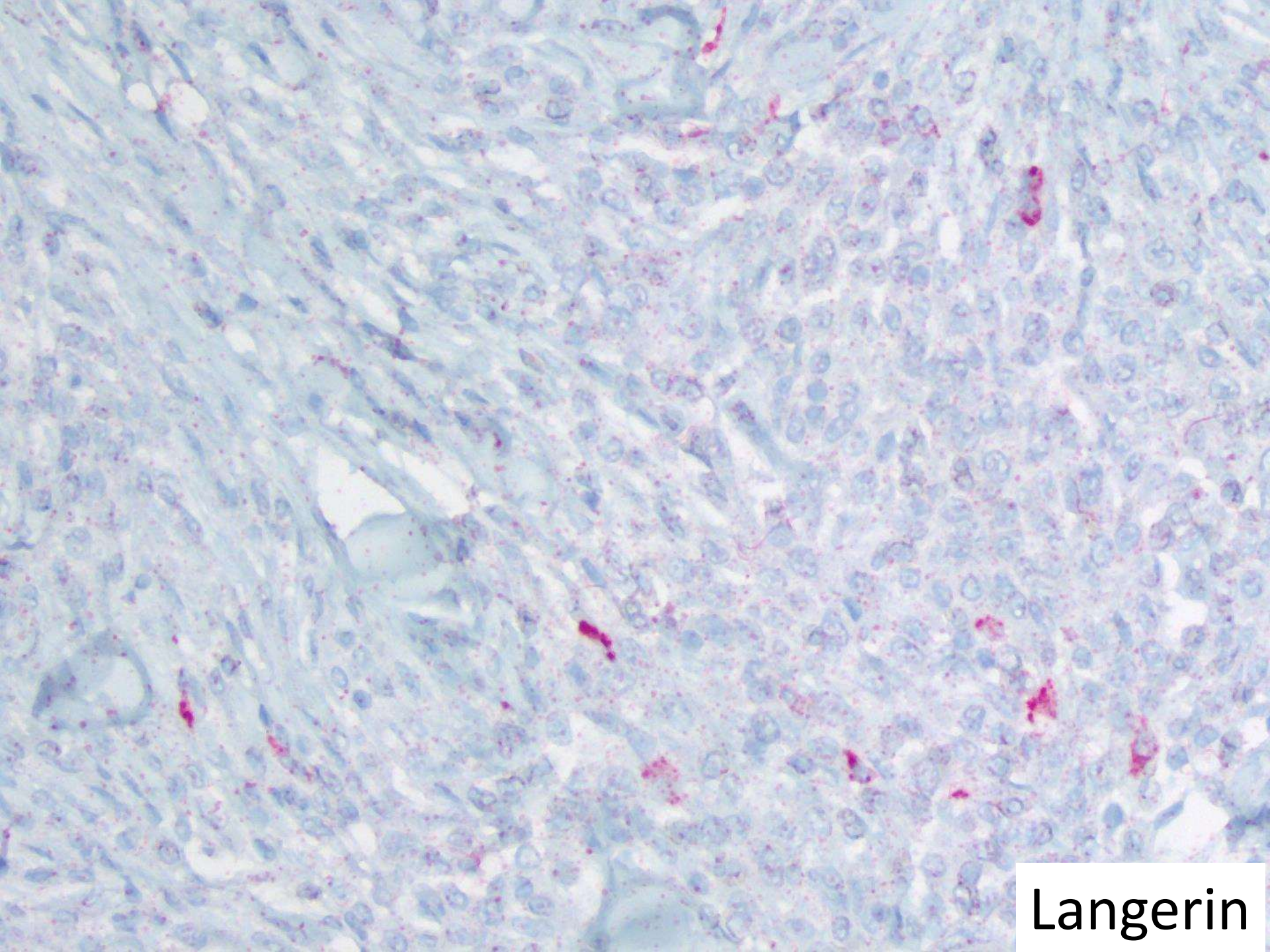
Joshua Menke
Derek Allison

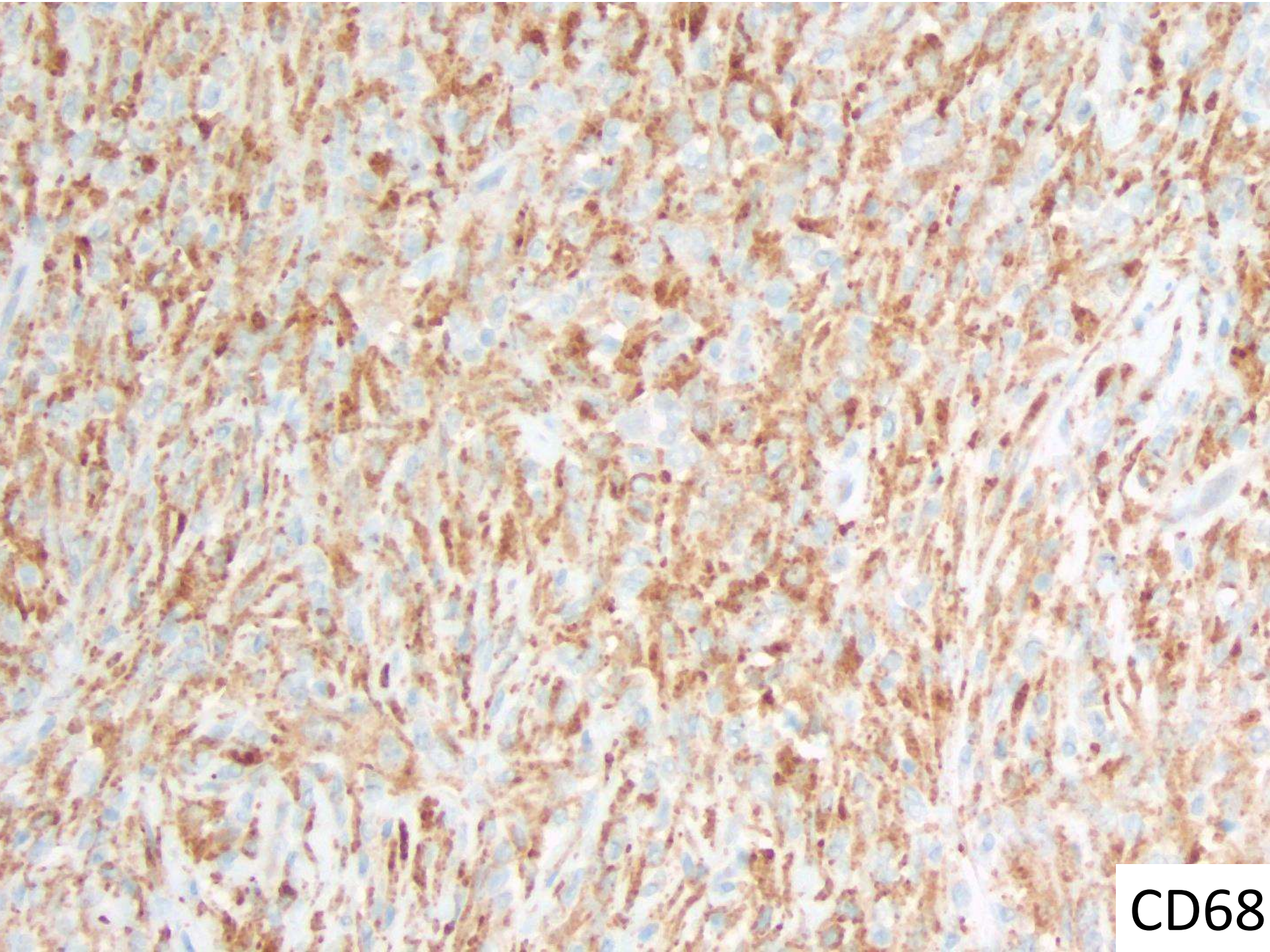
Differential Diagnosis

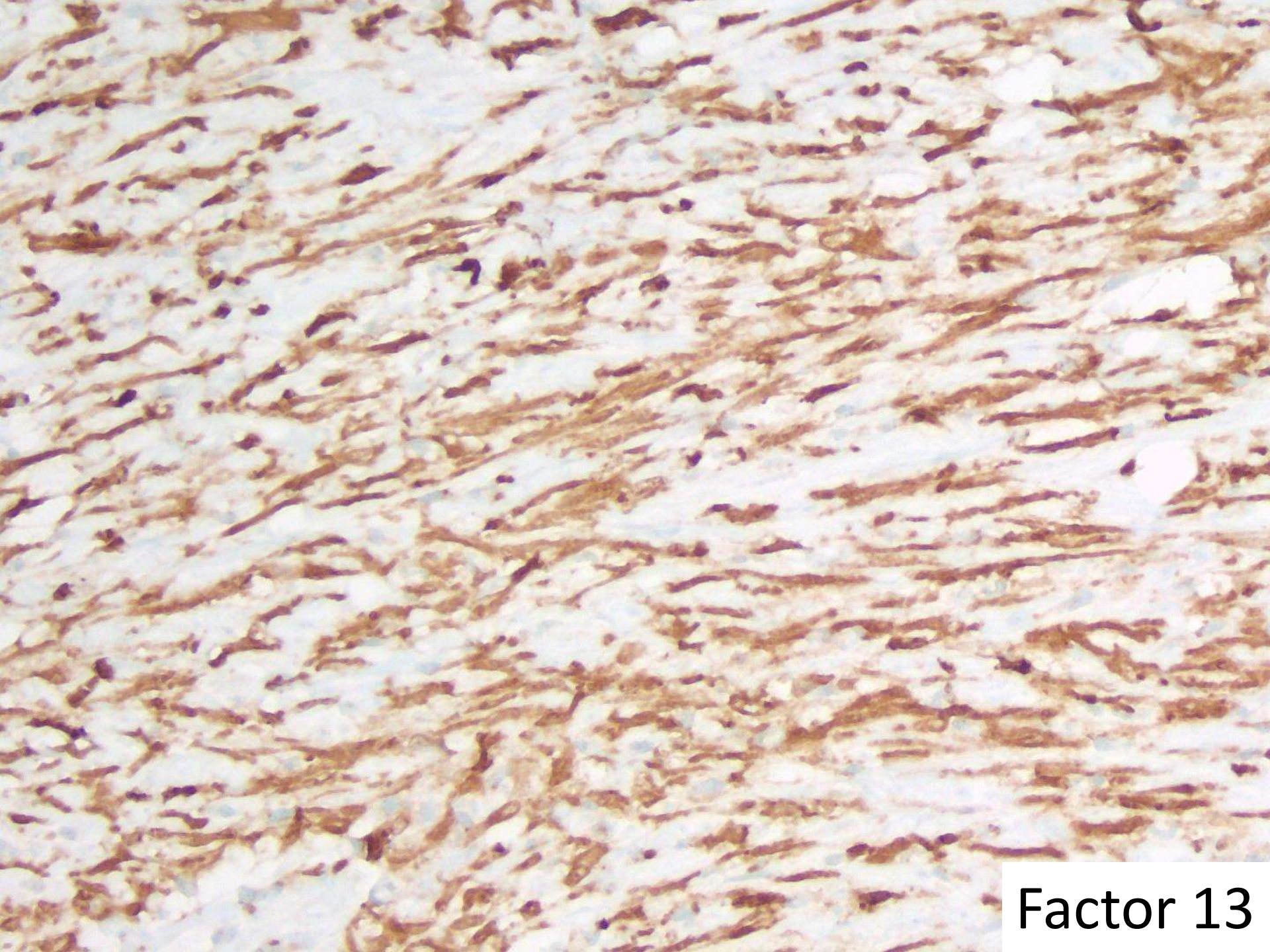
- Langerhans histiocytosis
- Non-Langerhans histiocytoses
  - Erdheim-Chester disease
  - Juvenile xanthogranuloma
  - Rosai-Dorfman disease
- Xanthogranulomatous inflammation
- Benign fibrous histiocytoma, xanthoma


S100


CD1a


Langerin


CD68


Factor 13

Final Diagnosis

- Juvenile Xanthogranuloma (JXG)

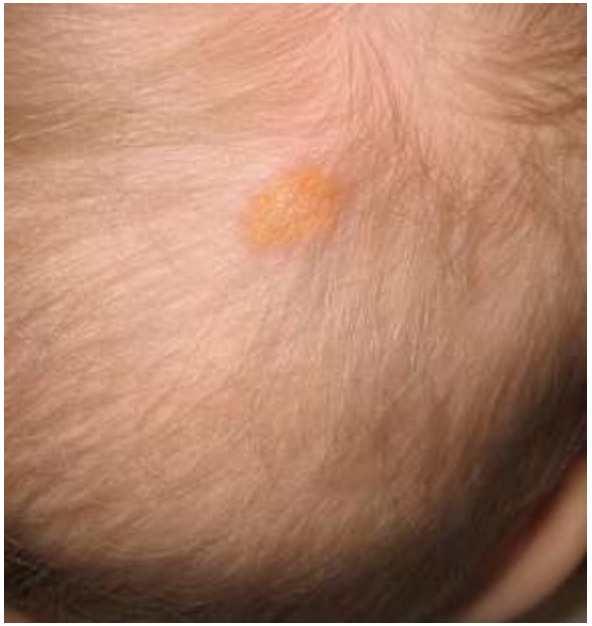
Clinical features

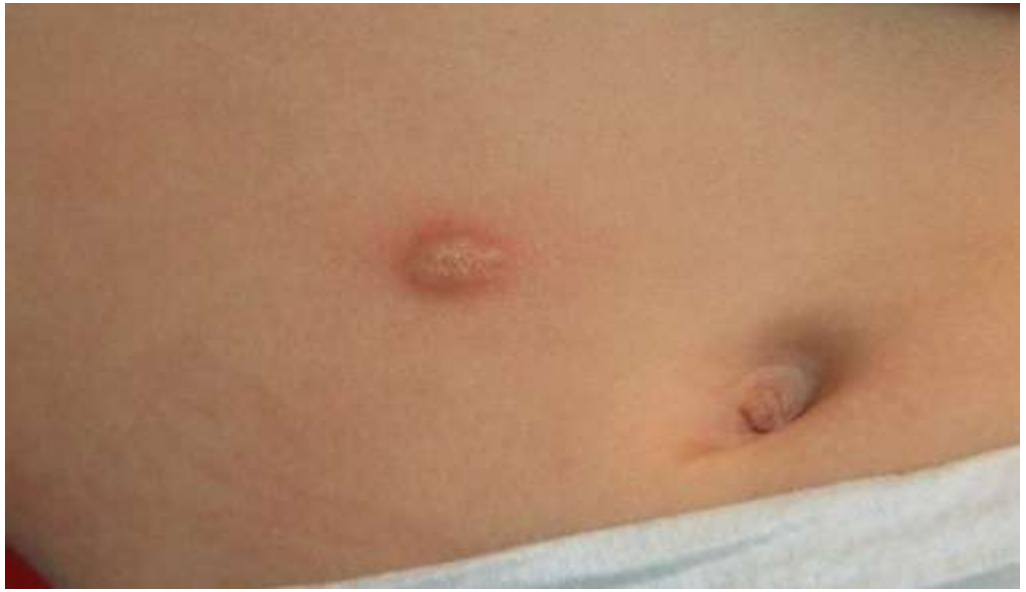
- Rare; 0.5% incidence in Kiel tumor registry[1]
- Usually infants, median age 5 months
- Solitary cutaneous lesion in 67-80% of cases[1-2]
  - Solitary subcutaneous or deep tissue in 10-16%[2]
  - Multiple cutaneous/visceral lesions in 4-5%[1-2]
- May spontaneously regress, excision is often curative; 7% recurrence rate
- Rare systemic cases require chemotherapy

[1]Janssen D. Am J Surg Pathol. 2005; [2]Dehner LP. Am J Surg Pathol. 2003.

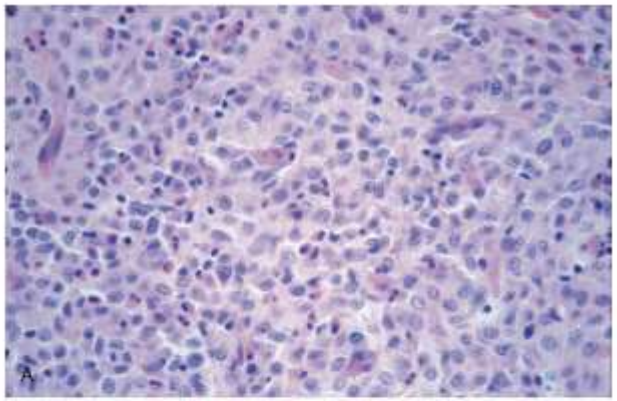
Exam findings

- Head and trunk most common sites
- Yellow to brown papule, usually <2 cm
- Majority solitary





Morphologic spectrum



- **Early JXG:** dense monomorphic histiocytic infiltration without lipidization and scattered eosinophils (DDx LCH)

Immunophenotype

- CD68, lysozyme, and factor 13 positive
  - Same immunophenotype as Erdheim-Chester and disseminated JXG cases are difficult to distinguish
    - However, no *BRAF V600E* or *MAP2K1* mutations
- S100, CD1a, Langerin are negative
  - Differs from LCH

Molecular phenotype

- Poorly characterized to date
- Whole exome sequencing study showed 17 somatic mutations in 4 JXG lesions (median 4 per case), and no *BRAF V600E* mutations
  - *PI3KCD* p.E368K mutation identified in 1 patient
  - Germline *NF1* splice site mutation was found in another patient with neurofibromatosis type 1 [1]

[1]Chakraborty R. Blood. 2014

Follow up

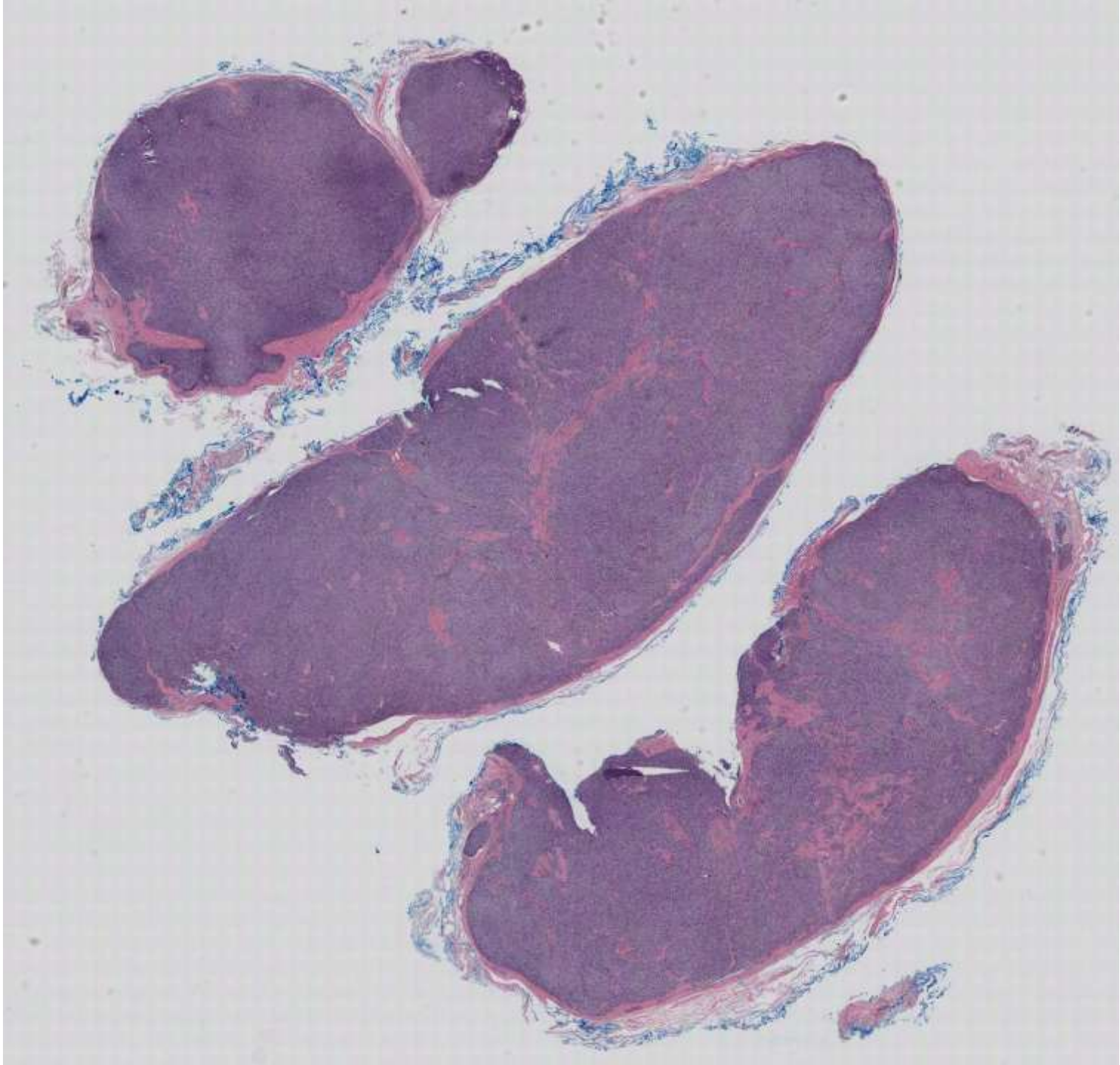
- Patient is now 5 years old and has not recurred

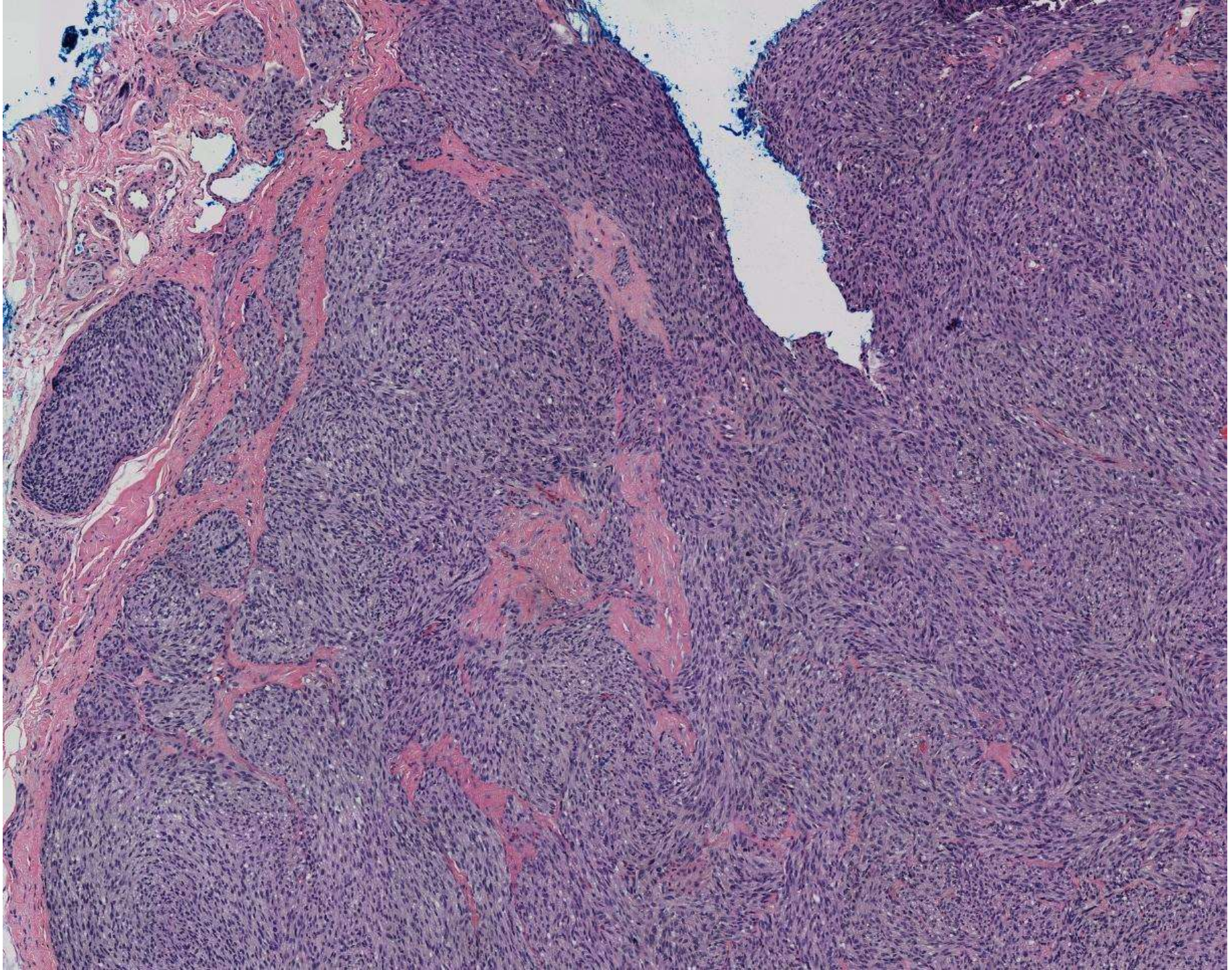
Conclusions

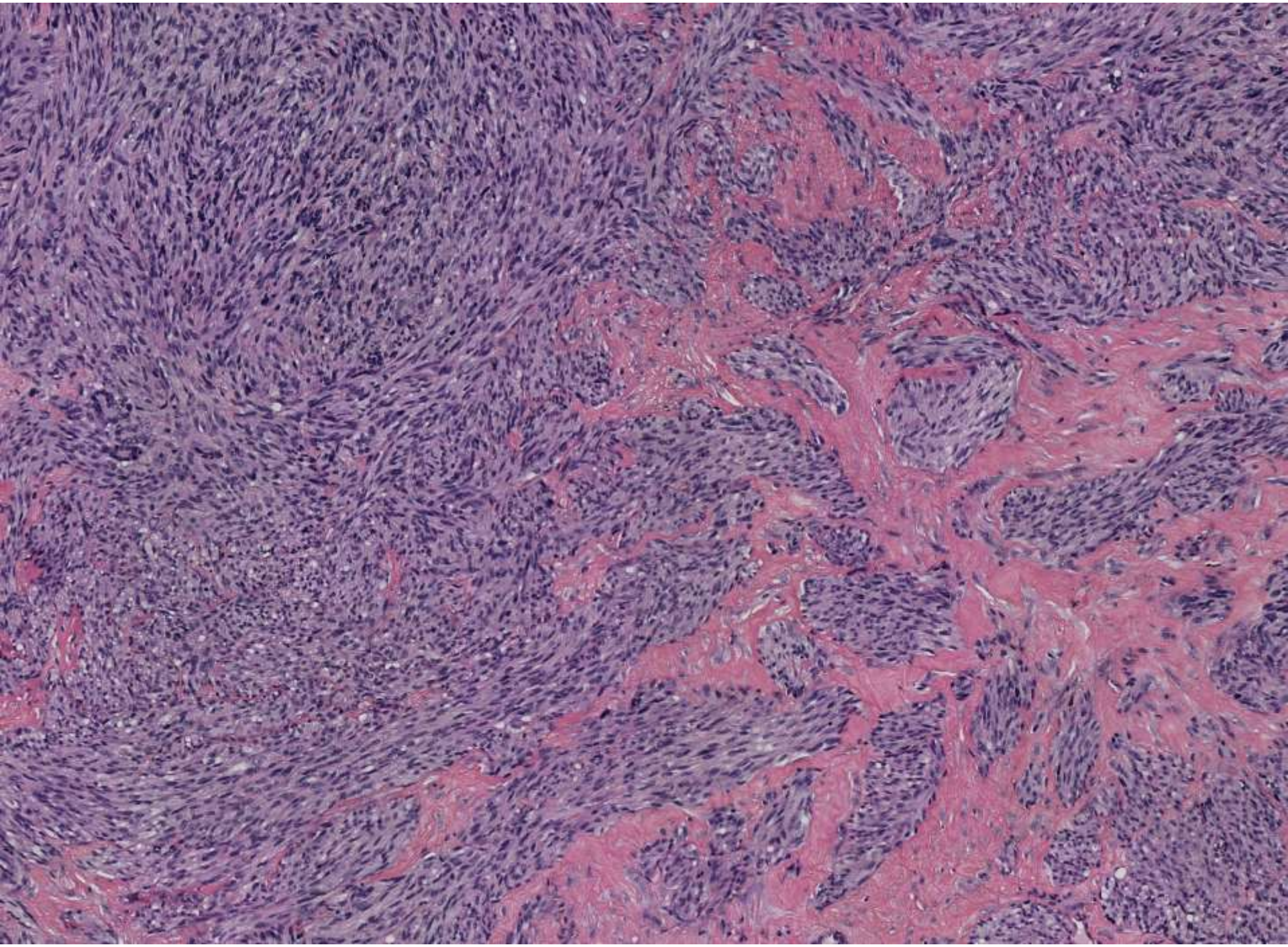
- JXG is rare and usually occurs as solitary cutaneous papule in head or trunk of infant
- Morphologic spectrum of JXG varies with age of lesion and can overlap with LCH
- Immunoprofile is same as ECD, but no *BRAF V600E* or *MAP2K1* mutations
- More molecular studies of JXG are needed

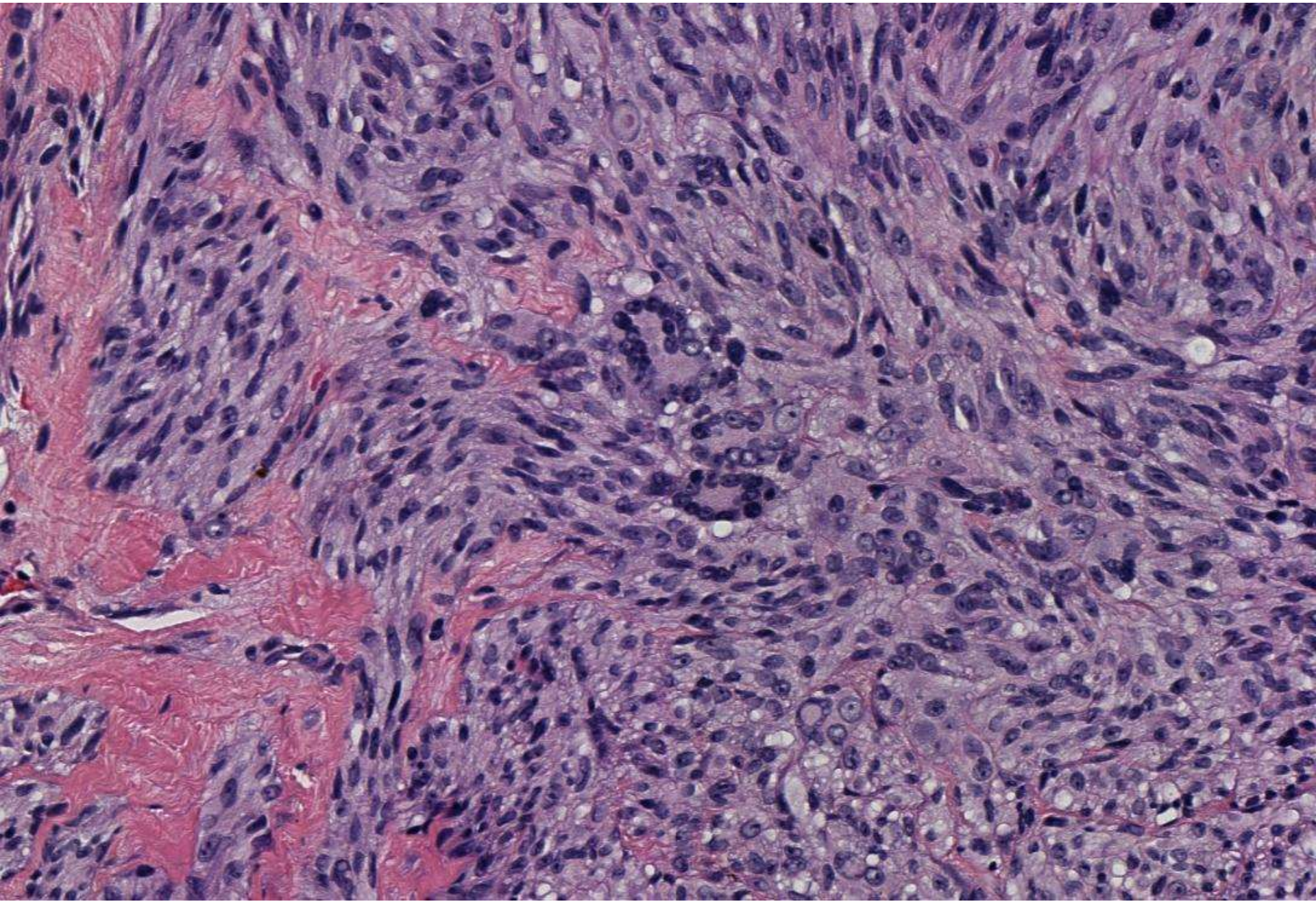
SB 6277
Keith Duncan; Mills-Peninsula Hospital

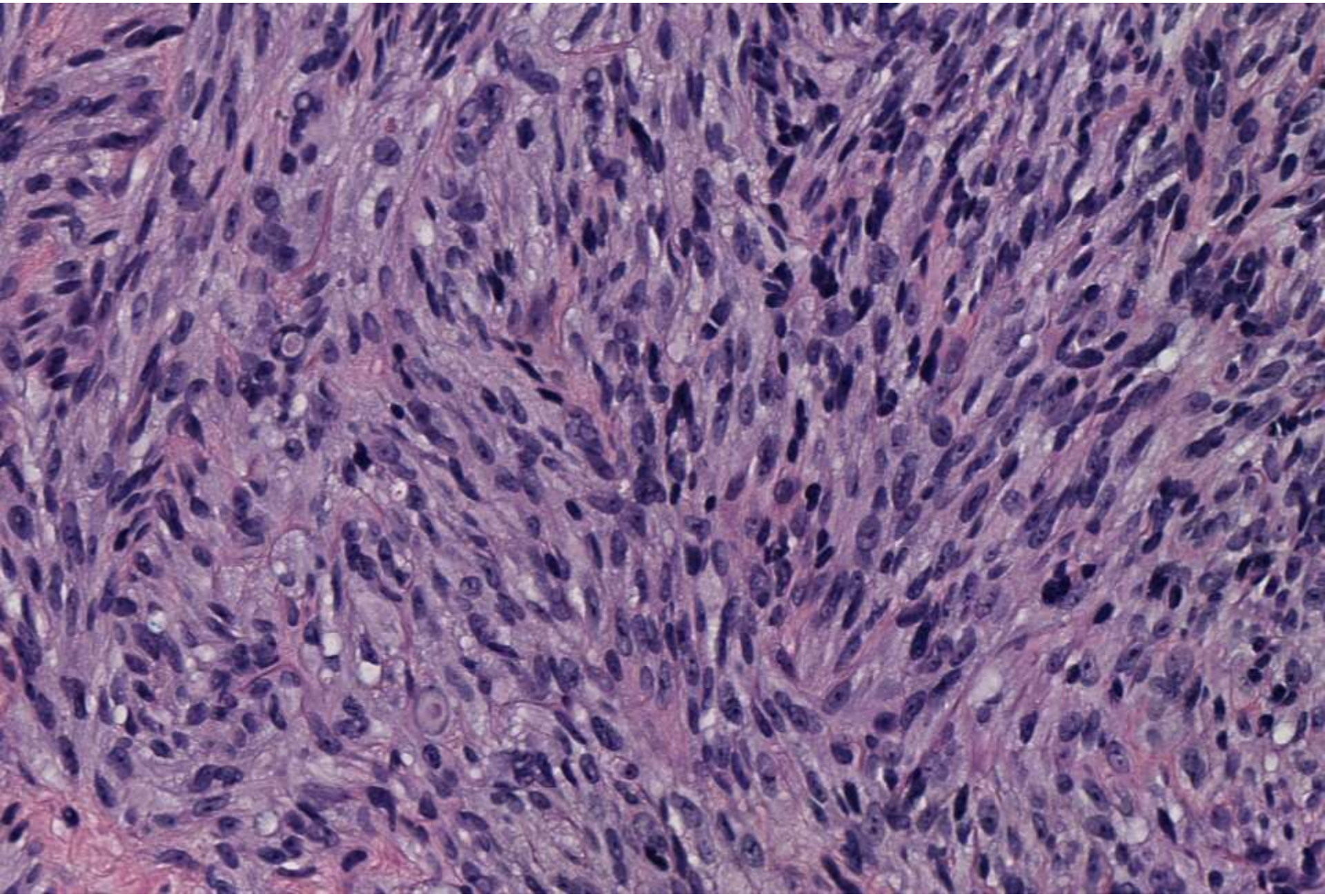
72-year-old woman with right small finger mass, proximal interphalangeal mass, suspect giant cell tumor.

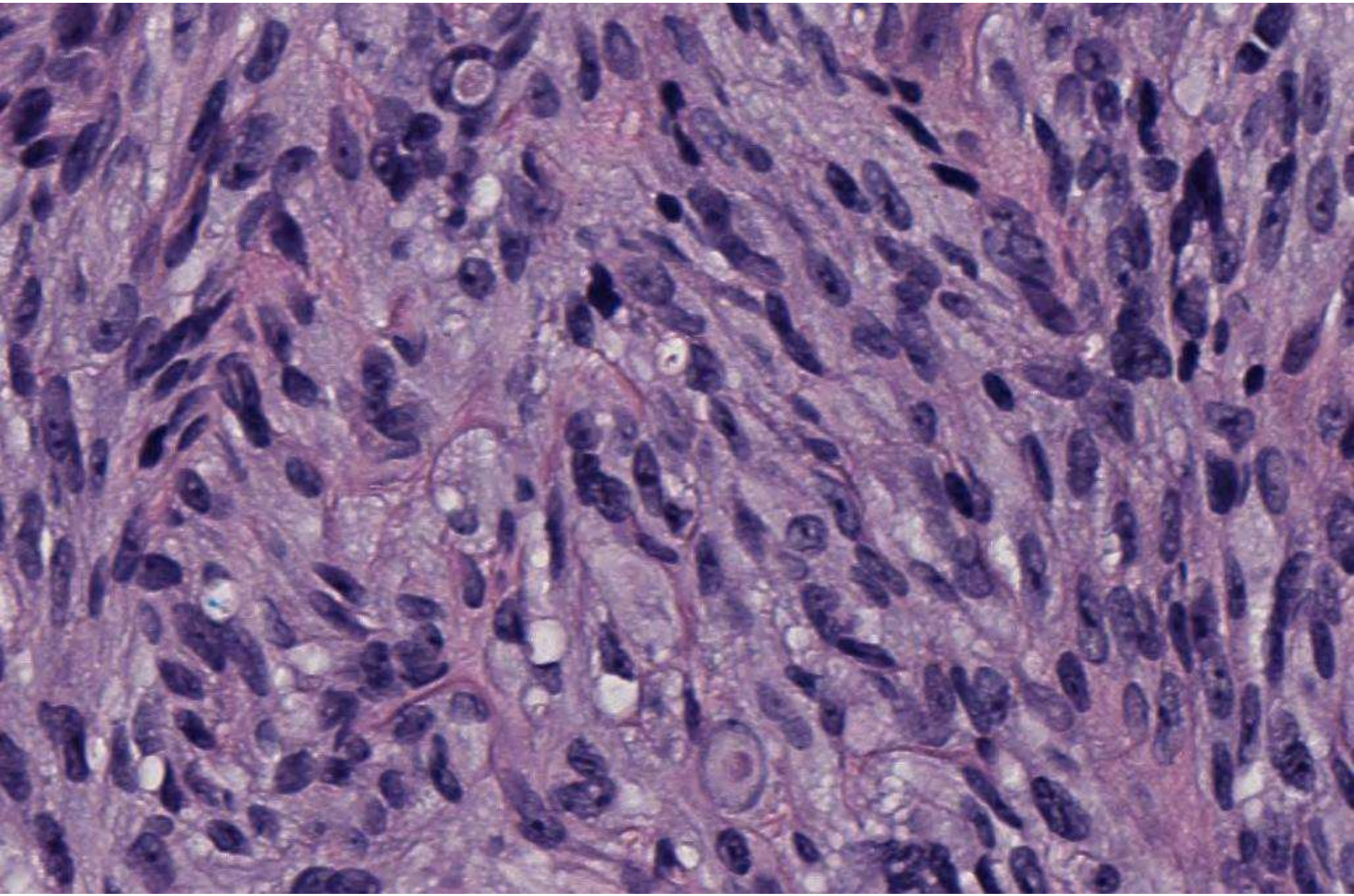


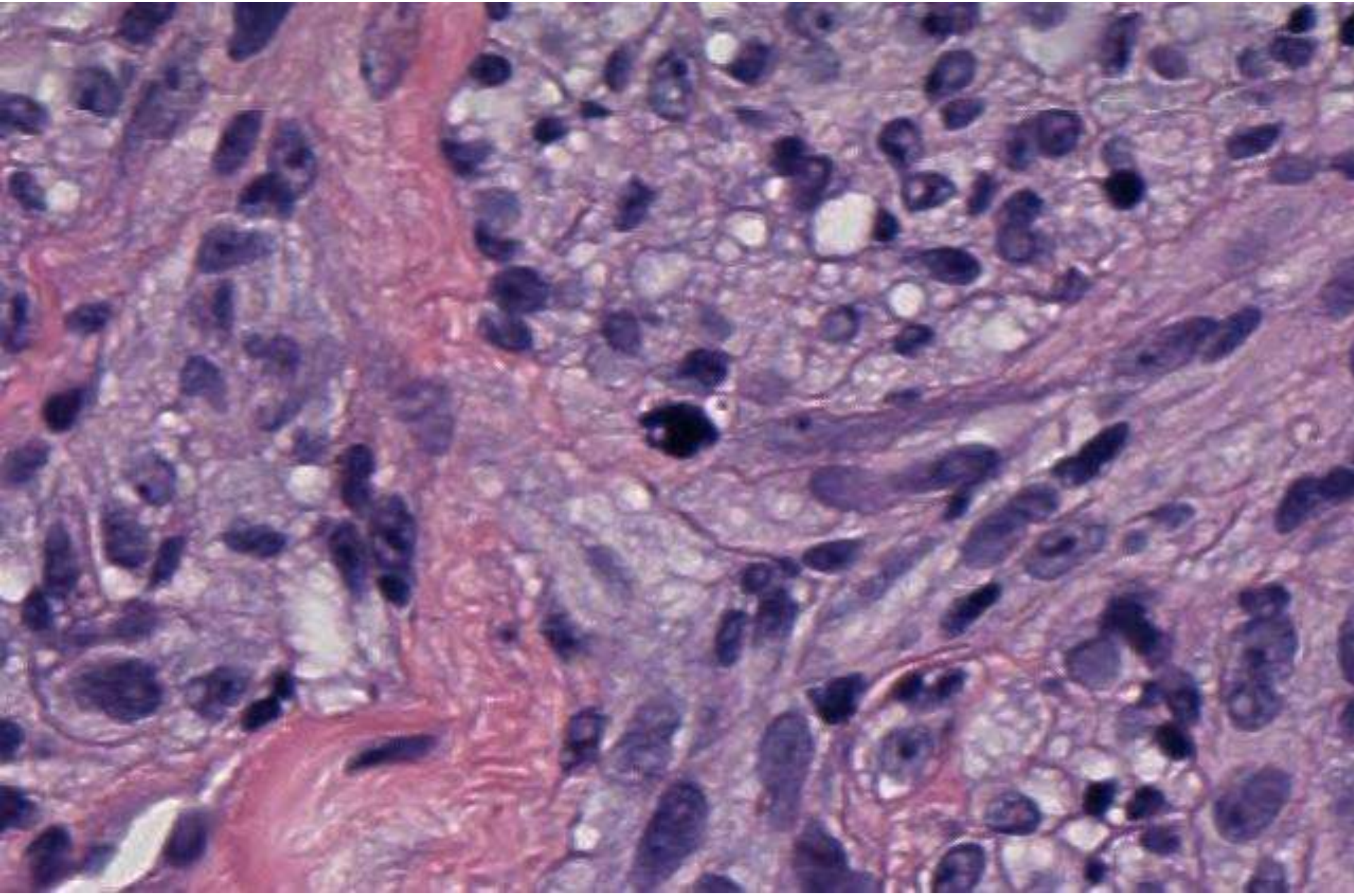












DIAGNOSIS?

MELANOMA OF SOFT PARTS

Rare soft tissue tumor, presents as slow growing mass intimately associated with tendon or aponeuroses, with predilection for foot & ankle affecting primarily young adults

To be distinguished from clear cell sarcoma of kidney, unrelated

MELANOMA OF SOFT PARTS

- **Micro:**
- Nests or short fascicles of spindled or epithelioid cells with clear to granular eosinophilic cytoplasm separated by fibrous septa; surrounds normal epithelial elements
- Also multinucleated giant cells, variable melanin

Positive stains

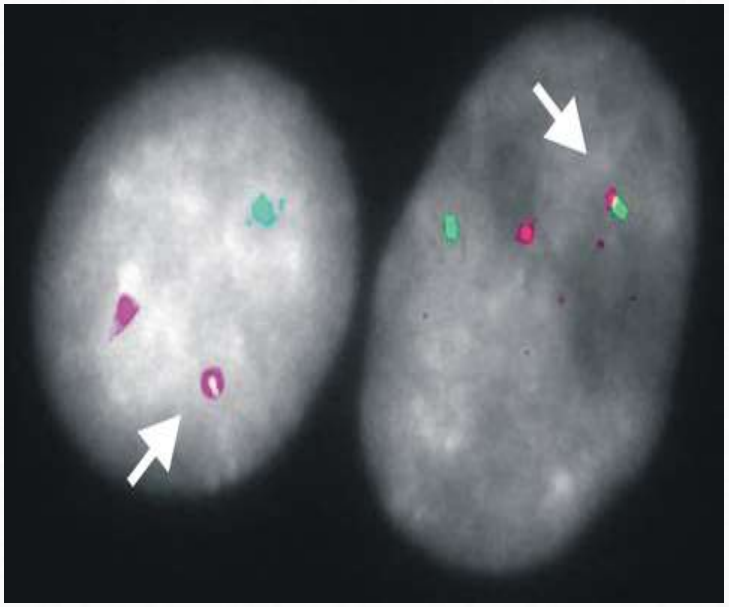
- S100, HMB45

Negative stains

Keratin, CD99

Molecular / cytogenetics

t(12;22)(q13;q12), EWS / ATF1 gene region rearrangement in > 95%



Dual colour in situ hybridisation the EWS cosmid G9 (green) and the ATF1 CCS2.2 cosmid (red) demonstrating a juxtaposition of 5' EWS to 3' ATF1 sequences, indicating the presence of a EWS/ATF1 genomic fusion (arrowheads)

Differential diagnosis:

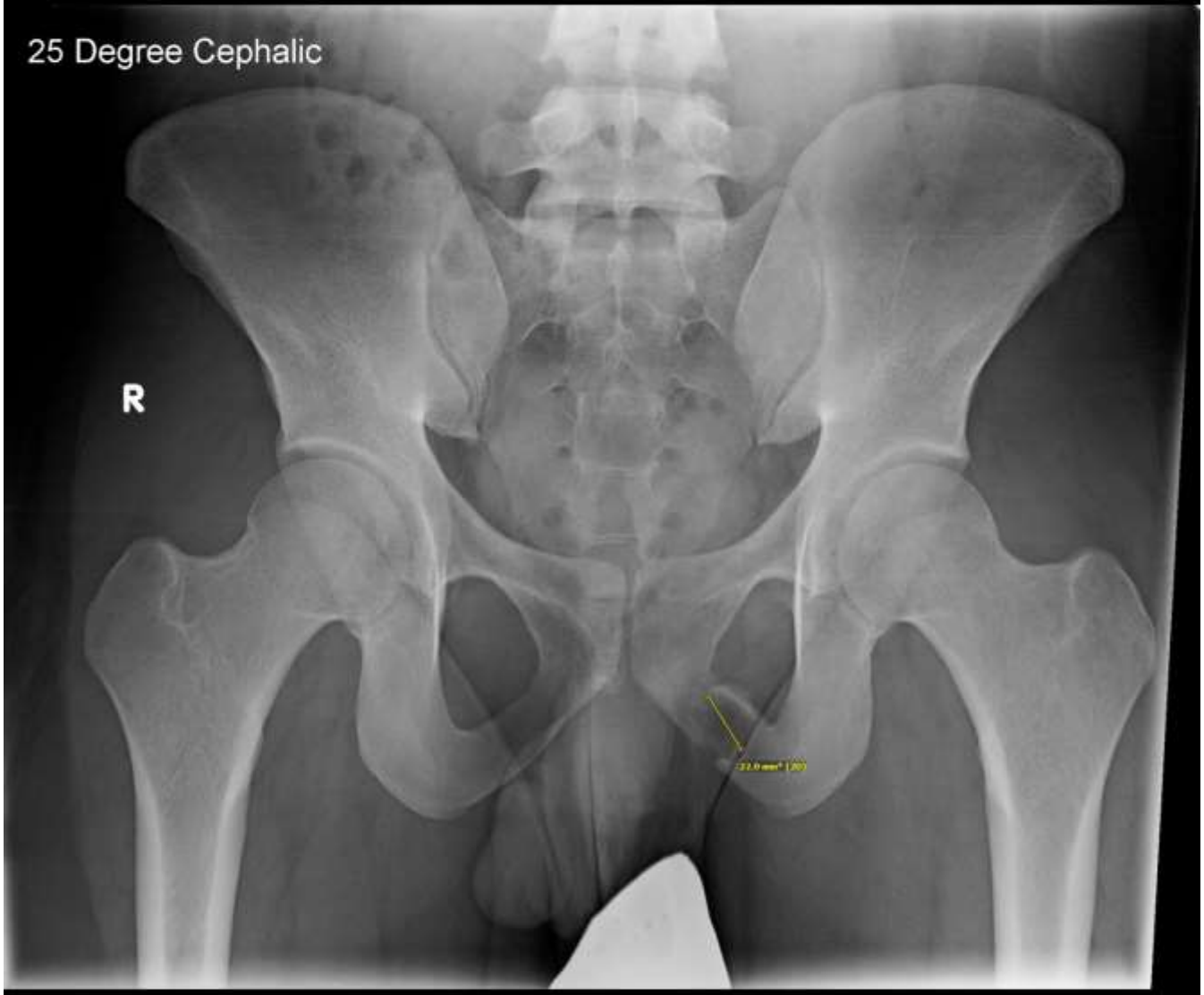
- **Clear cell sarcoma**: very young children, similar histology but nests are formed by vascular structures, S100-, HMB45-, different translocation

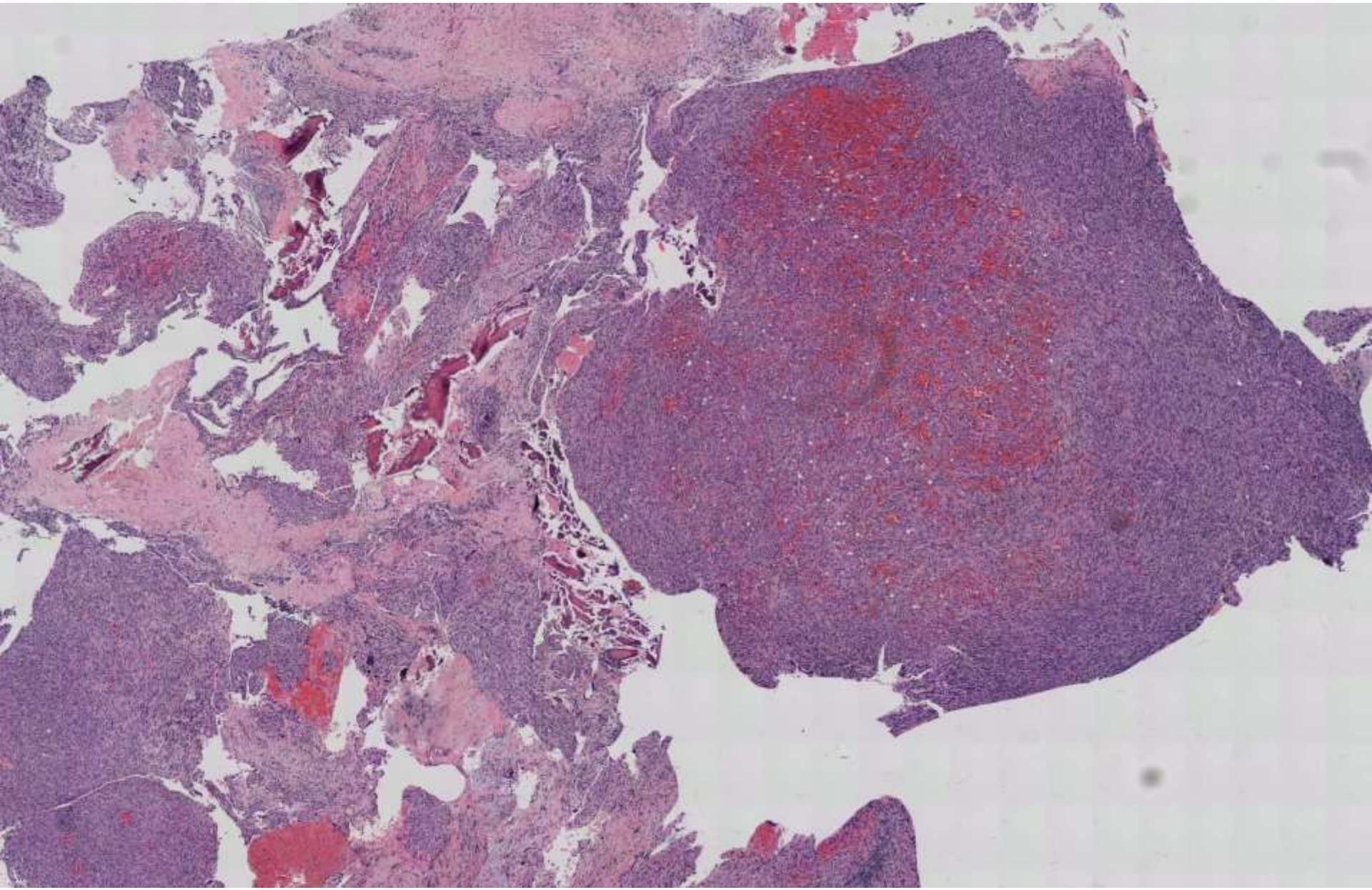
- **Wilms' tumor**: usually triphasic, no dominant nesting pattern, negative for melanocytic markers

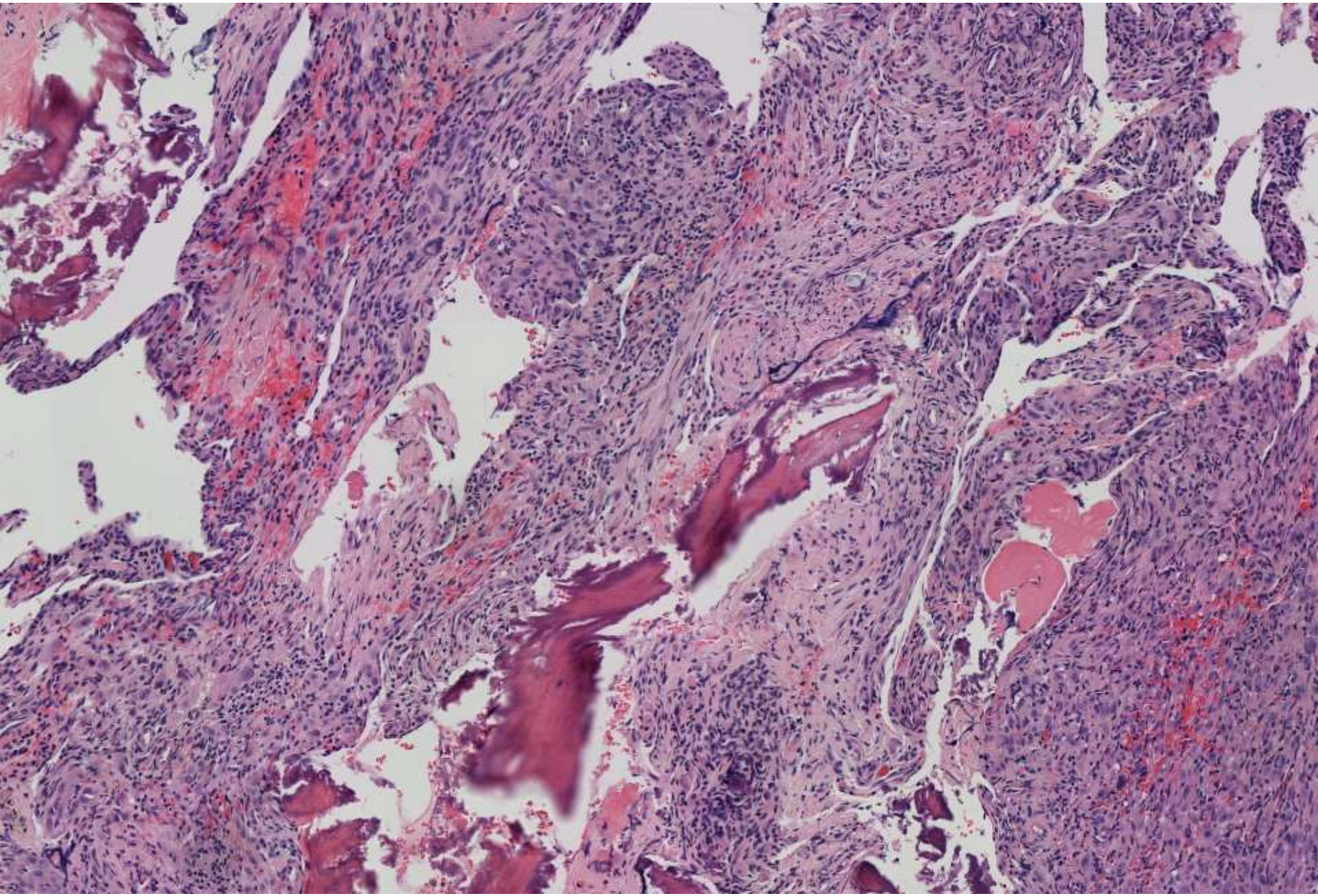
SB 6278

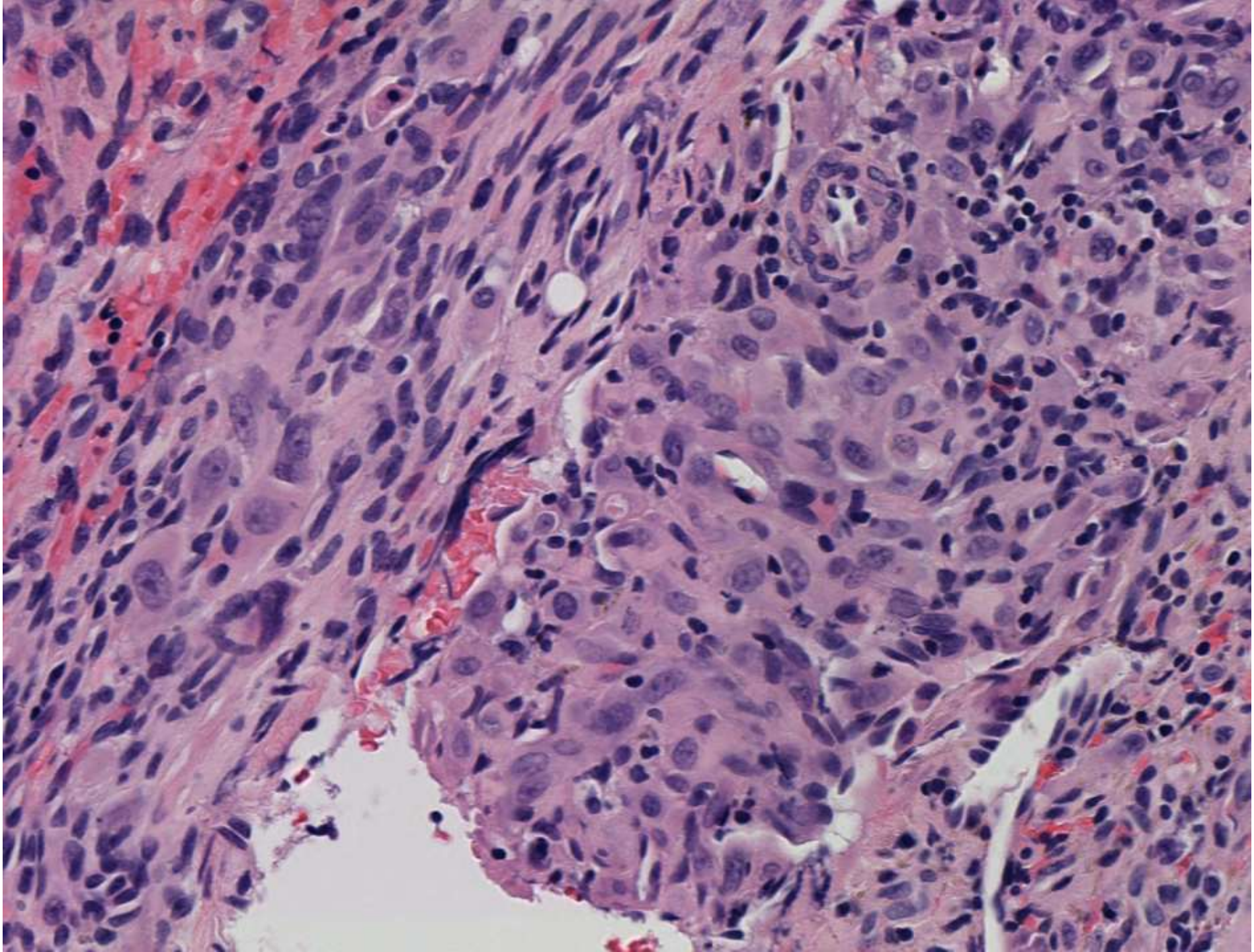
Yue Peng/Soo-Jin Cho/Charles Zaloudek; UCSF

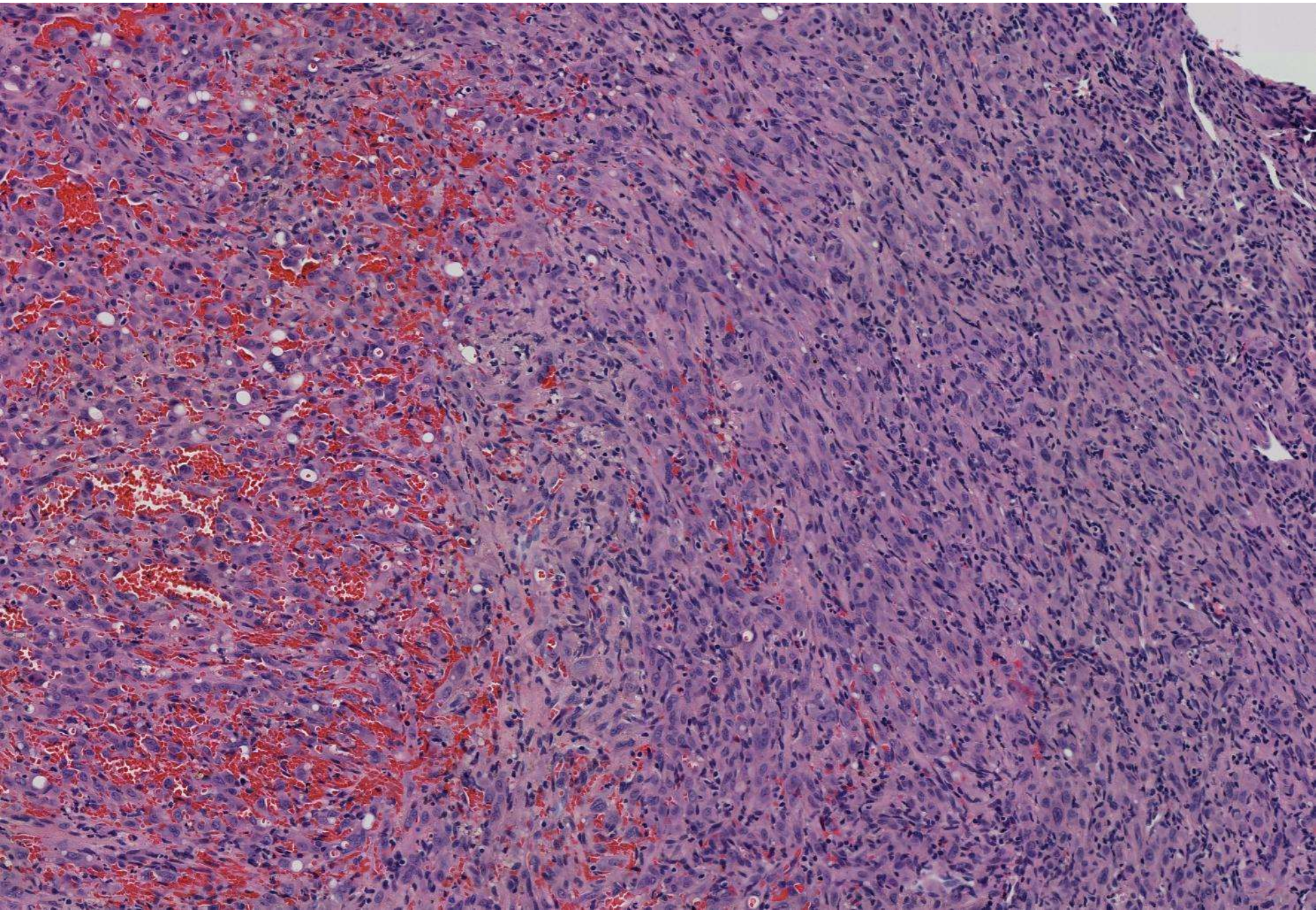
22-year-old man with groin/perineal pain for a year, relieved by NSAIDs. MRI described a left inferior pubic ramus lytic lesion (2cm), and X-ray didn't identify significant periosteal reaction around the lesion. He underwent open biopsy of lesion.

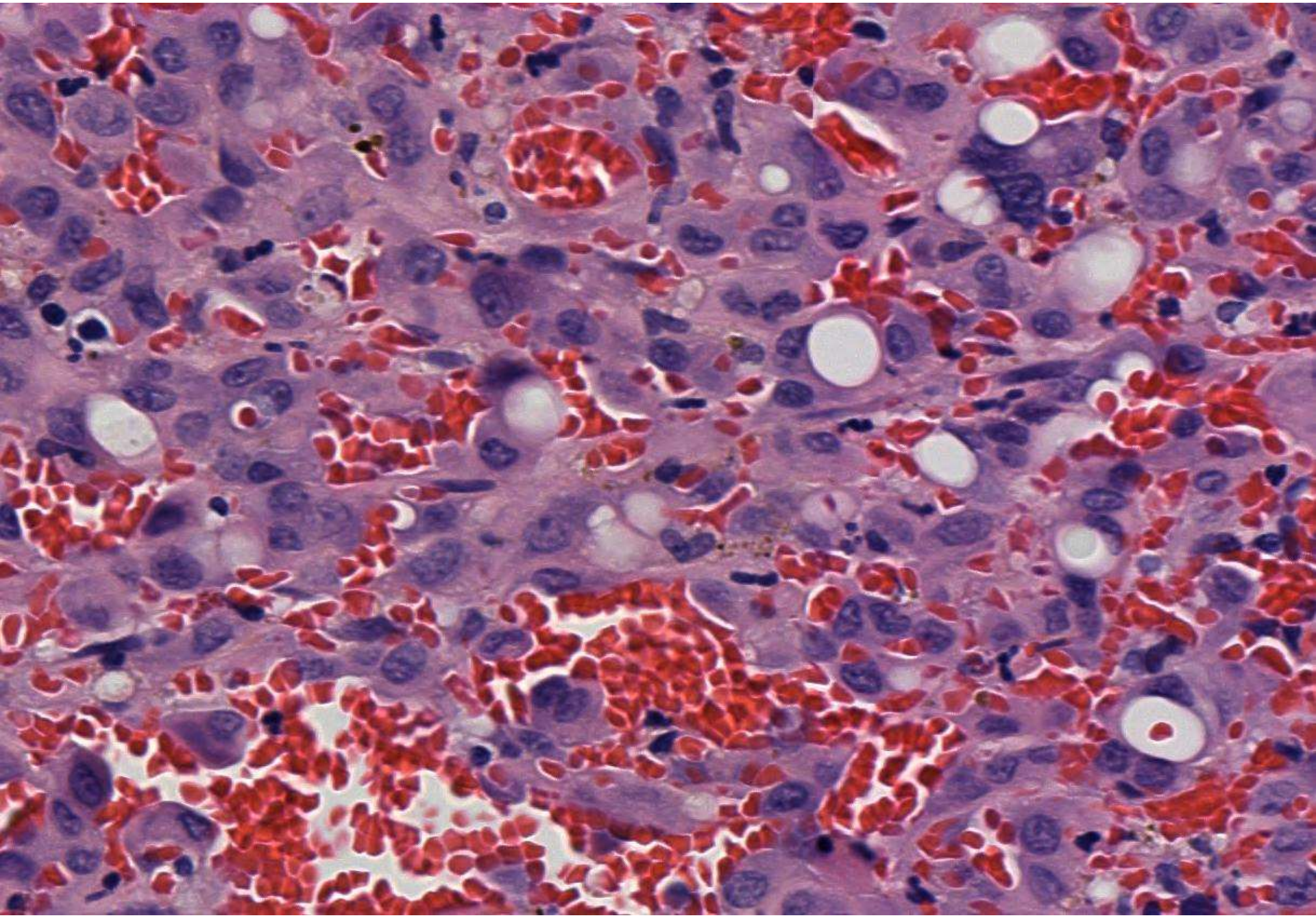

25 Degree Cephalic
R

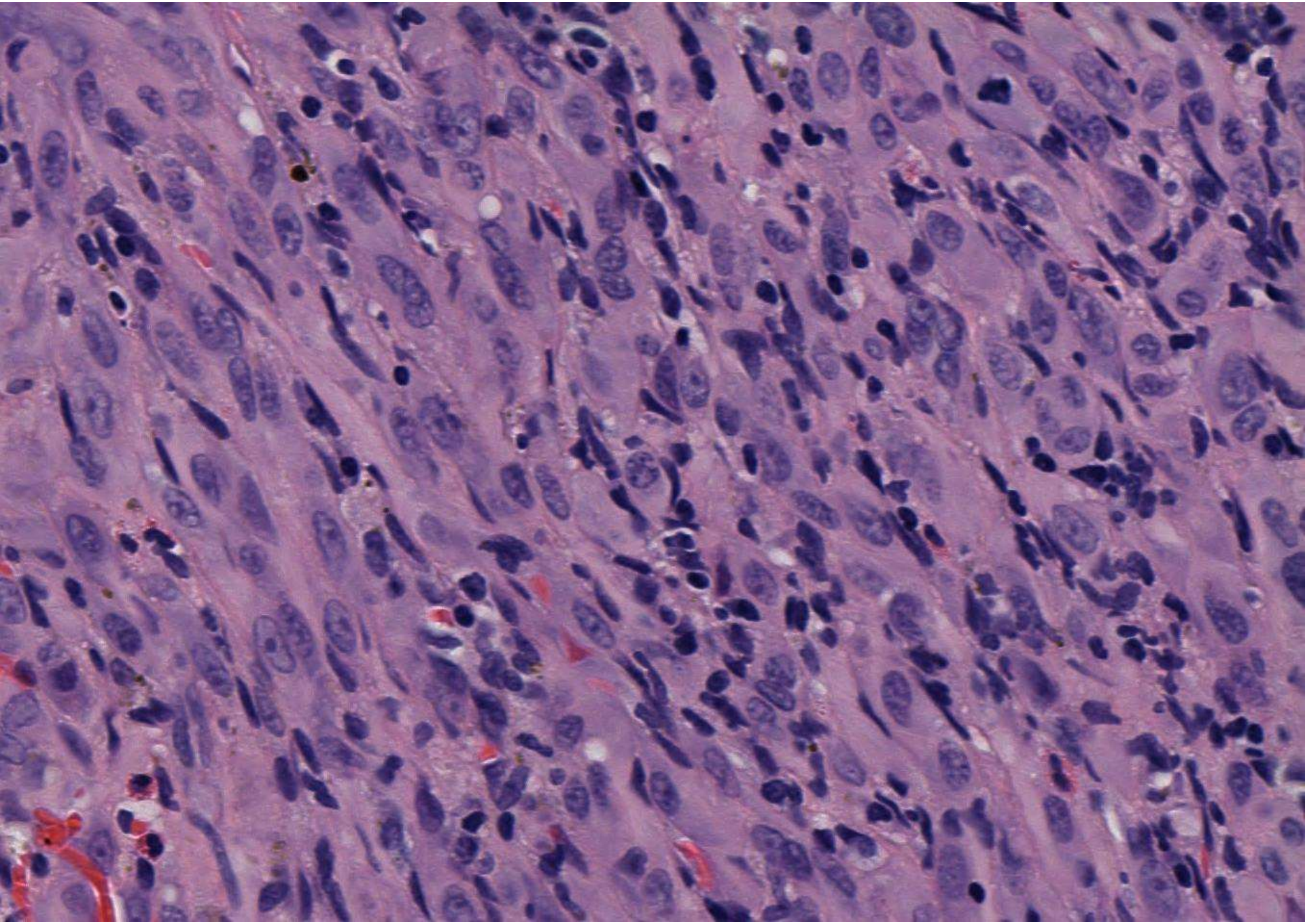








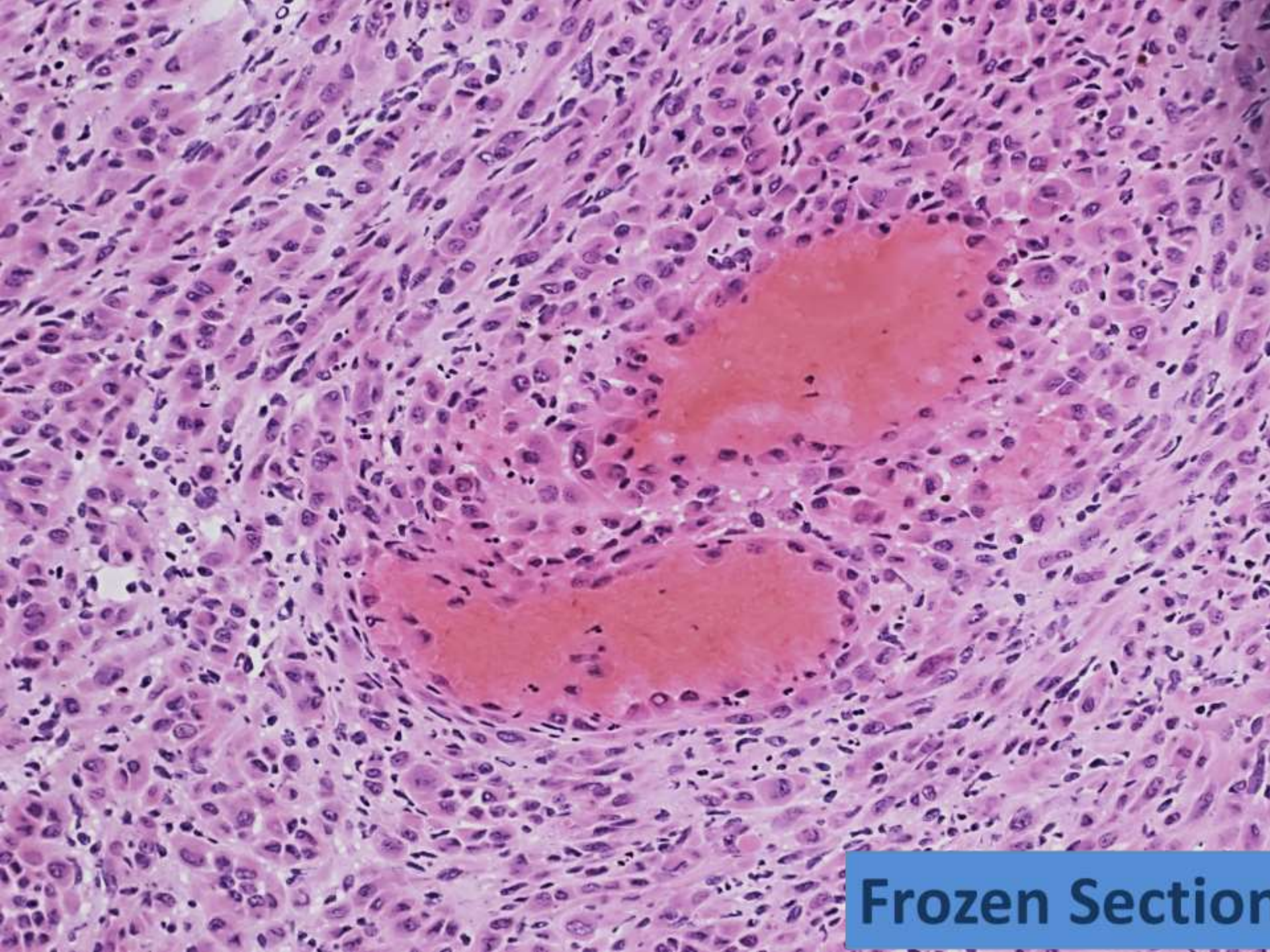


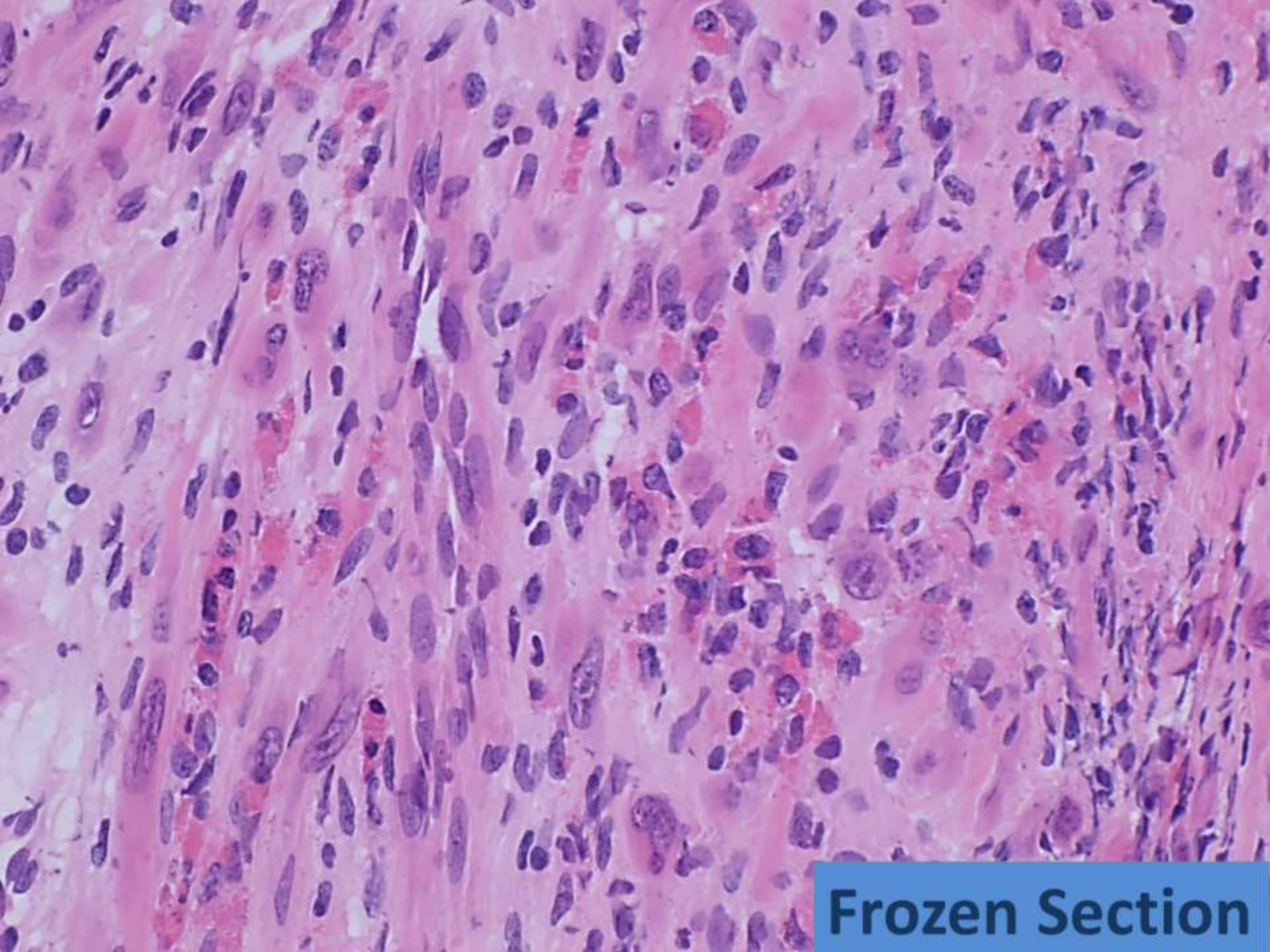


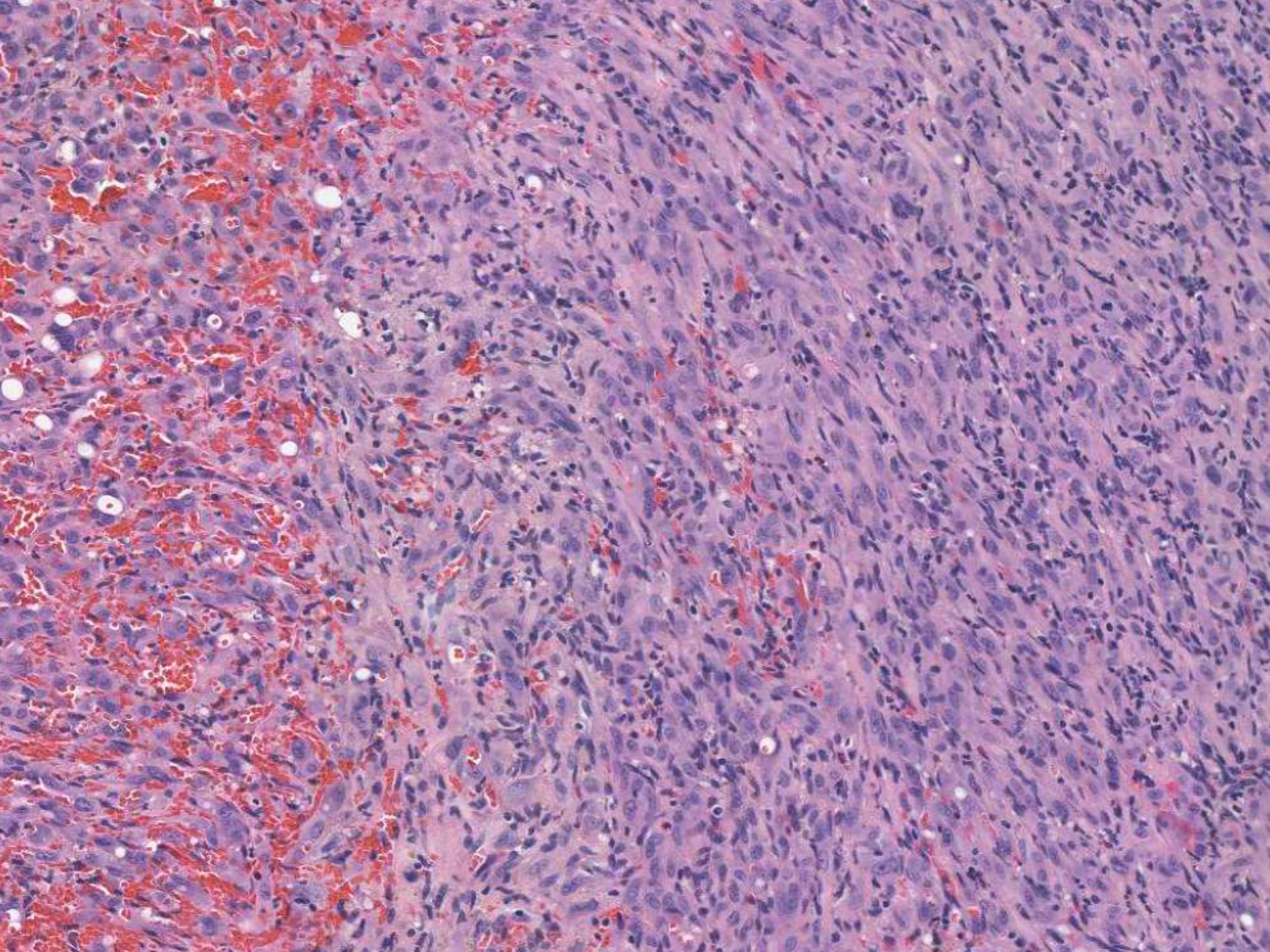
DIAGNOSIS?

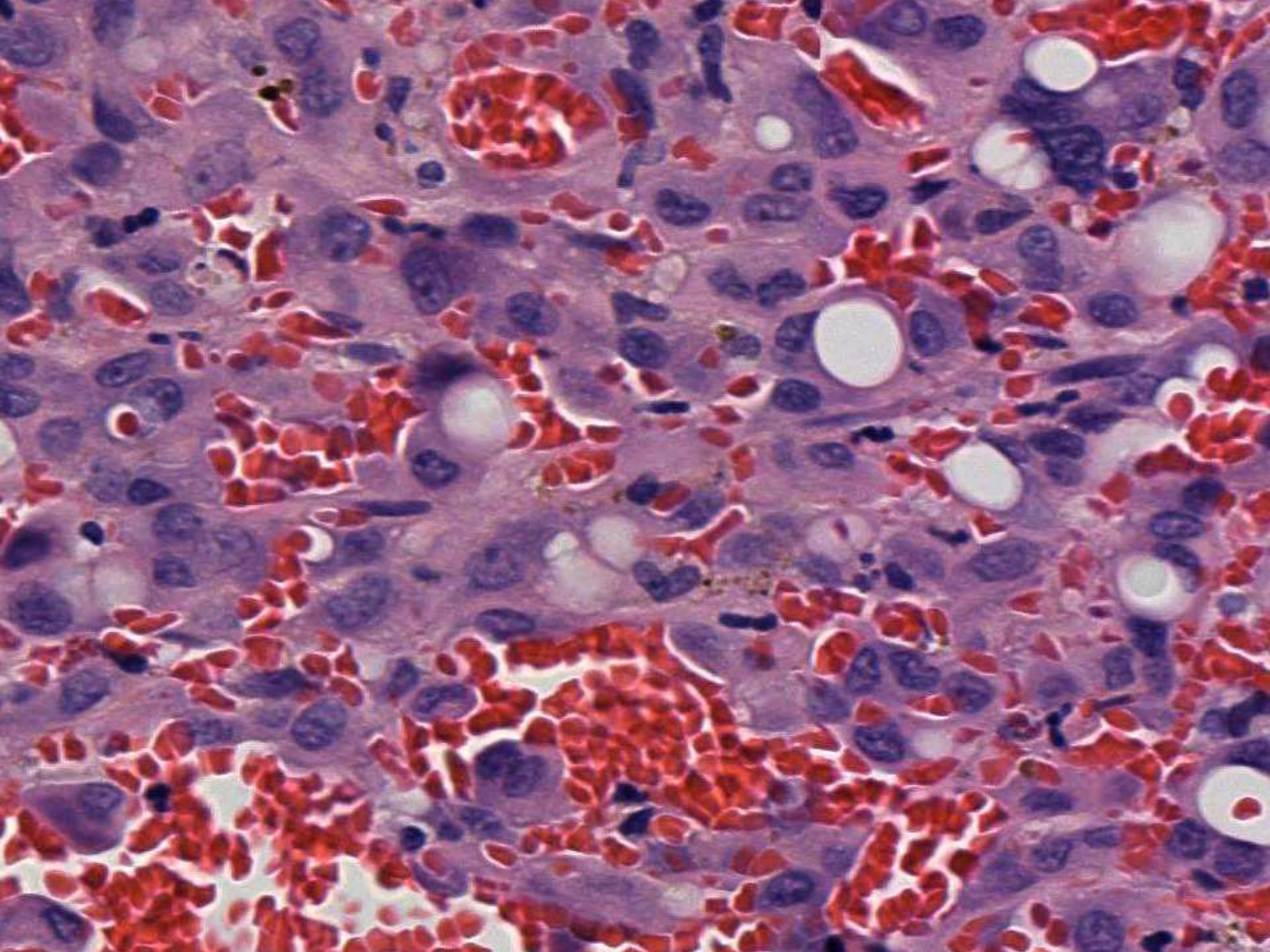
SB 6278

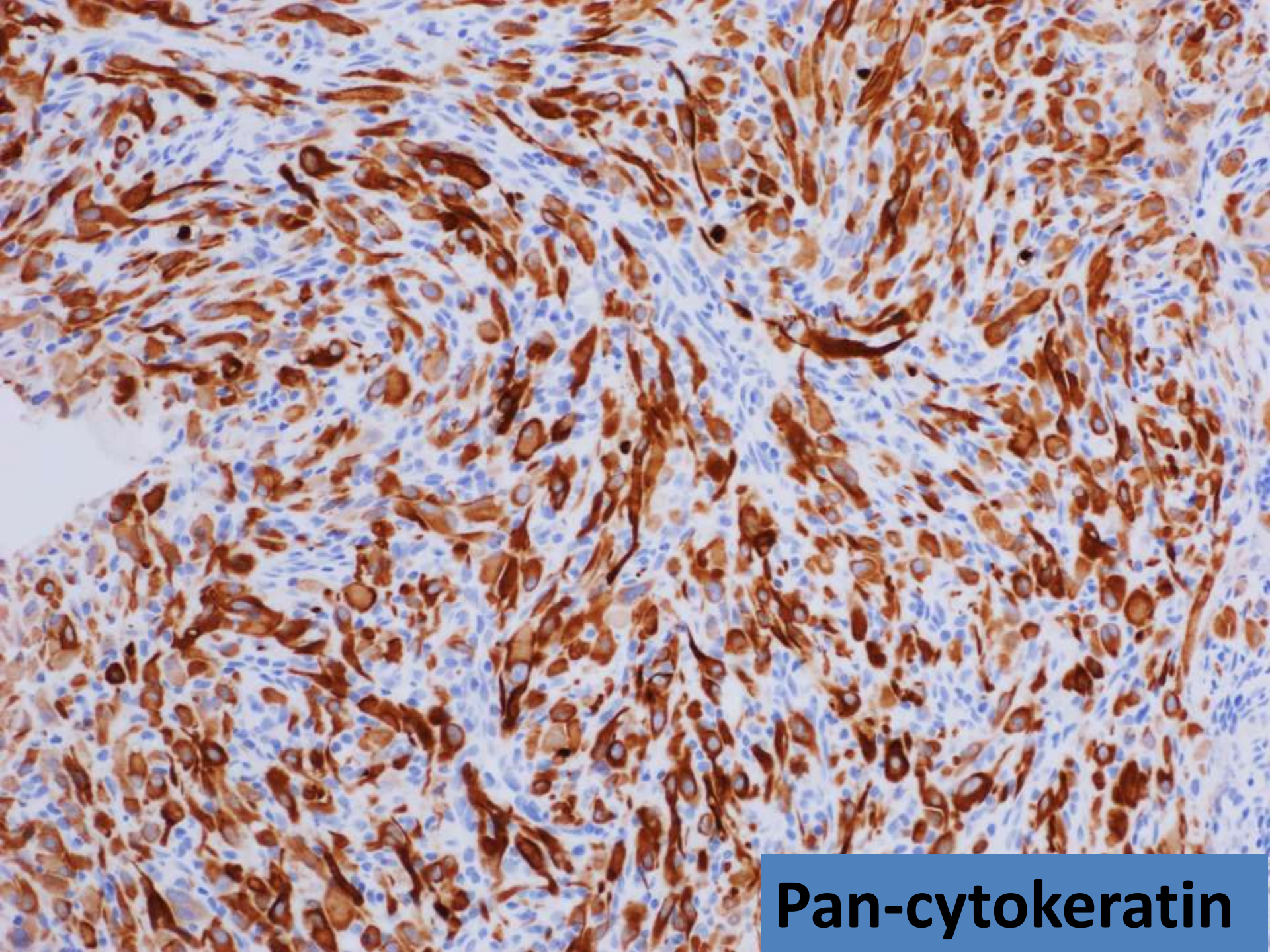
Dr. Yue Peng, Surgical Pathology Fellow
Dr. Soo-Jin Cho, Assistant Professor
Dr. Charles Zaloudek, Professor
Department of Pathology
UCSF
South Bay Meeting June 4, 2018

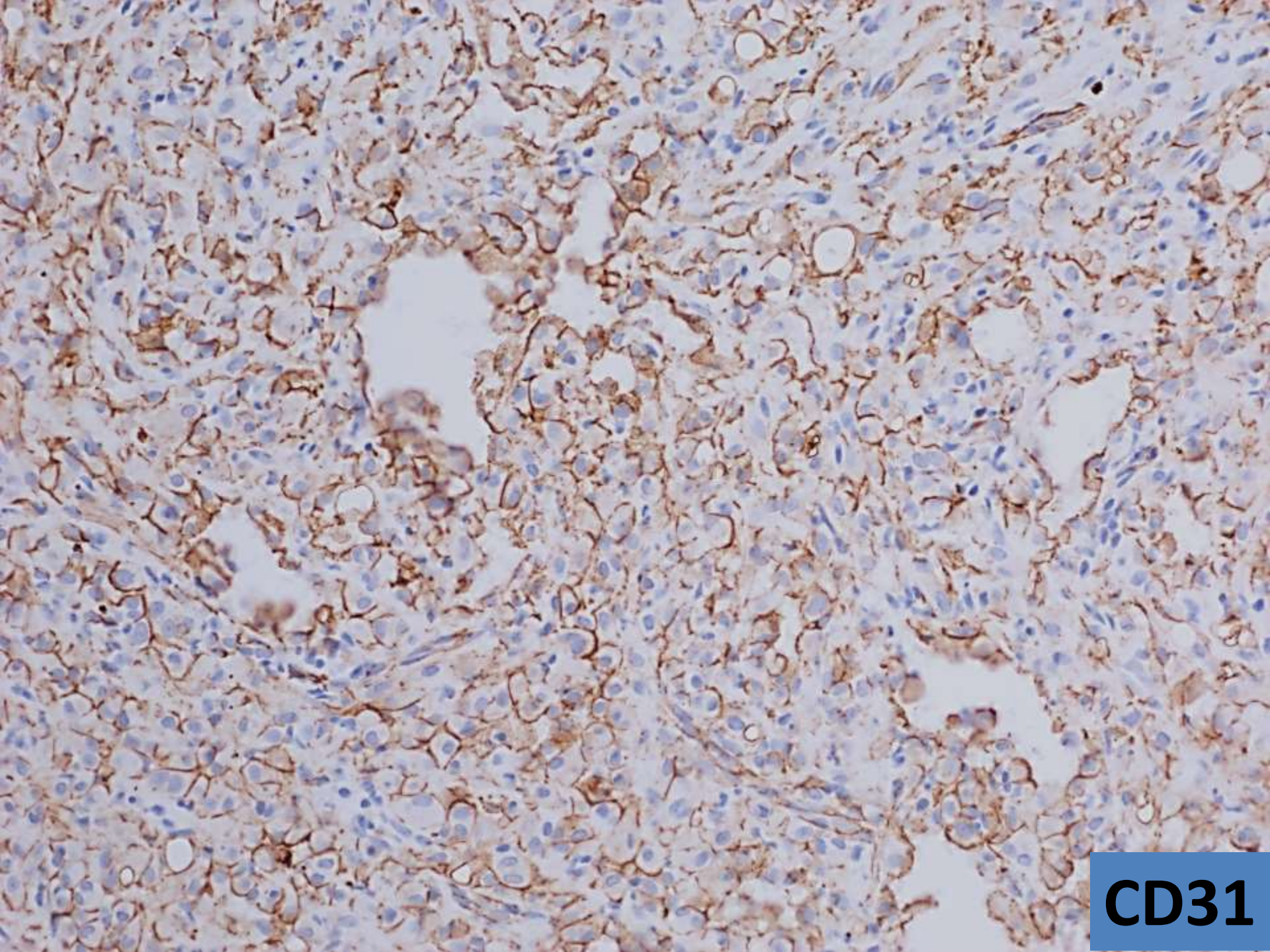

Frozen Section

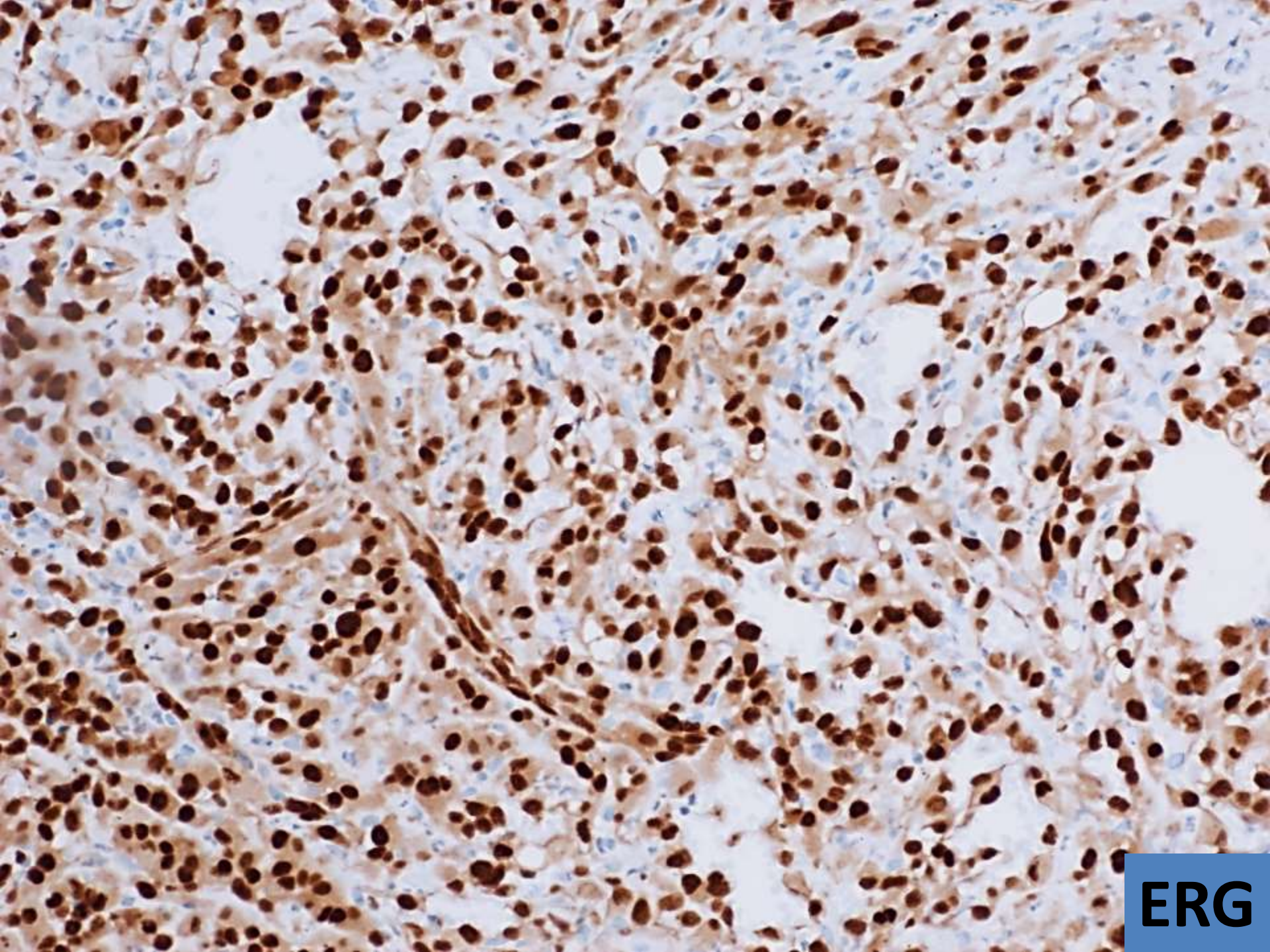

Frozen Section






Pan-cytokeratin

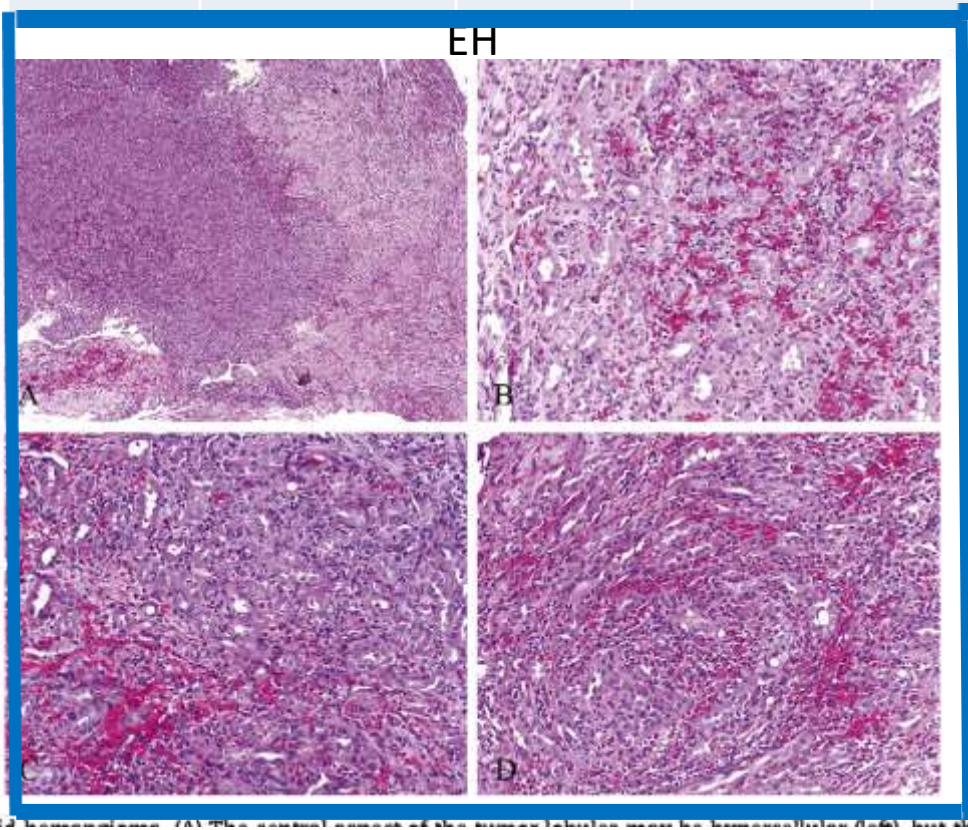

CD31

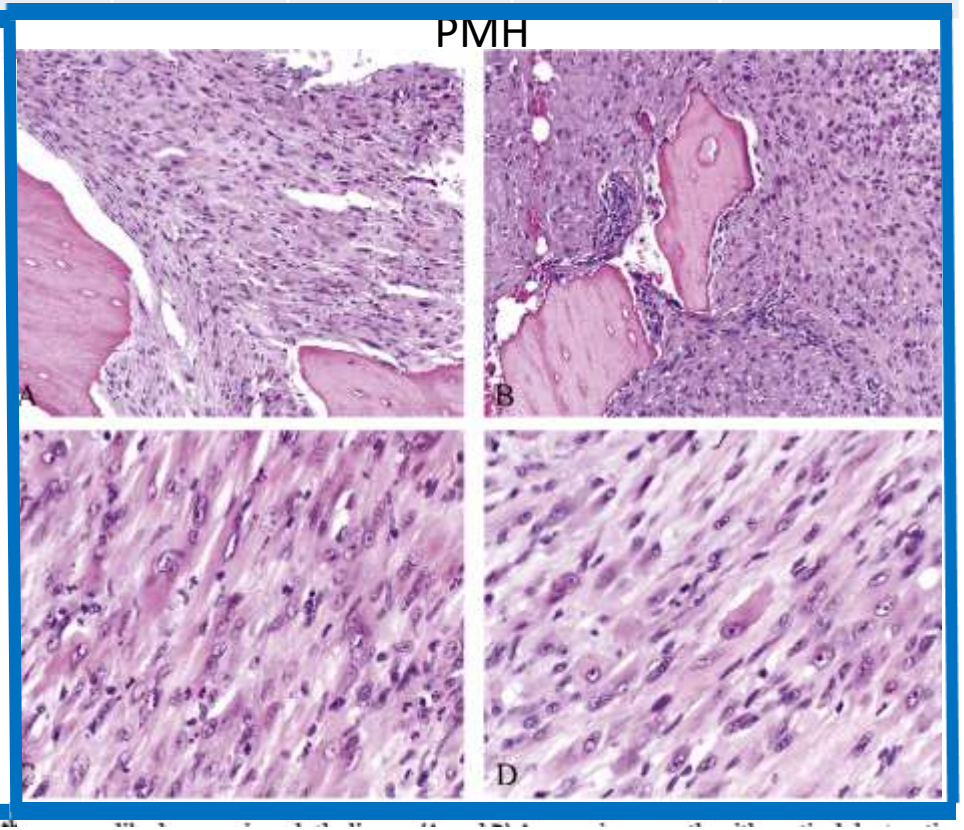

ERG

Epithelioid vascular neoplasms (CK+/CD31, ERG+)

	Incidence	Bones involved	Recurrence	Metastasis and/or death	Grade
Epithelioid hemangioma (EH)	Uncommon	Long tubular bones, distal lower extremities	10%	Rare LN metastases; death from the disease never been reported	Benign
Pseudomyogenic hemangioendothelioma (PMH)	Rare, multicentric	Arises in skin and soft tissue	60%	Very rare (loco-regional)	Benign/low grade
Epithelioid hemangioendothelioma (EHE)	Rare	long and short tubular bones of the extremities, pelvis, rib, vertebral	-	20%, 5-year survival 73%	Low to intermediate grade
Epithelioid angiosarcoma (EA)	Rare	long and short tubular bones of the extremities, pelvis, axial	-	1- and 5- year survival rates are ~55% and 33%;	High grade

Tumor	Aggressive growth	Solid sheets	Vascular Channels	Blister cells	Atypia	Mitoses	Necrosis	Molecular
EH	Yes (locally)	±	Yes	±	Mild	<1/10	Rare	FOSB (54%)
PMH	Yes (locally)	Yes	No	No	Mild	<1/10	<20%	FOSB (96%)

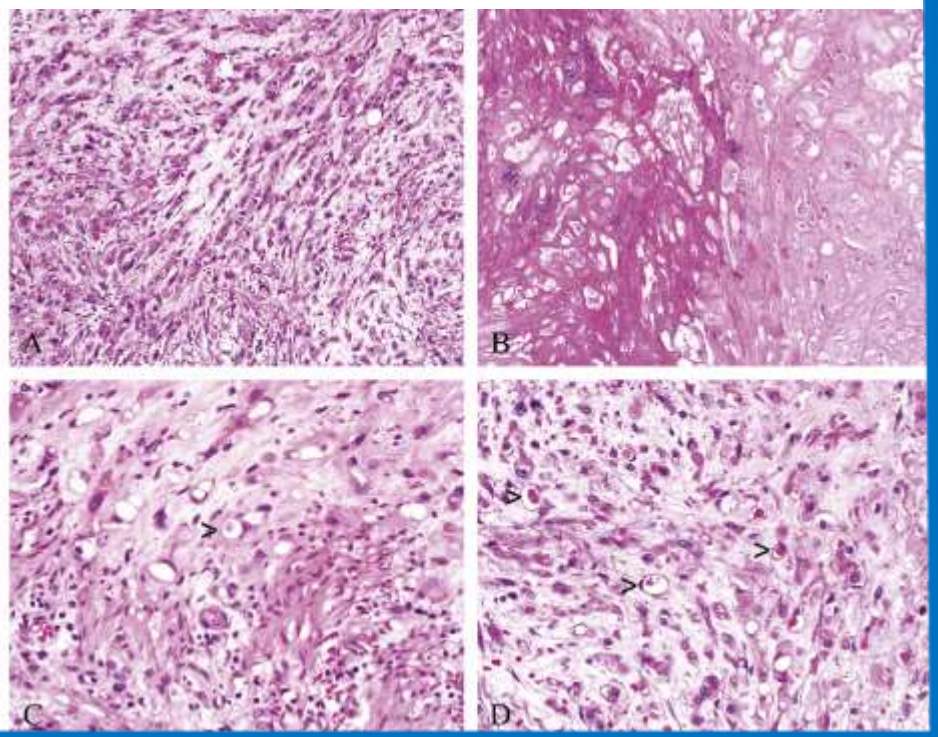




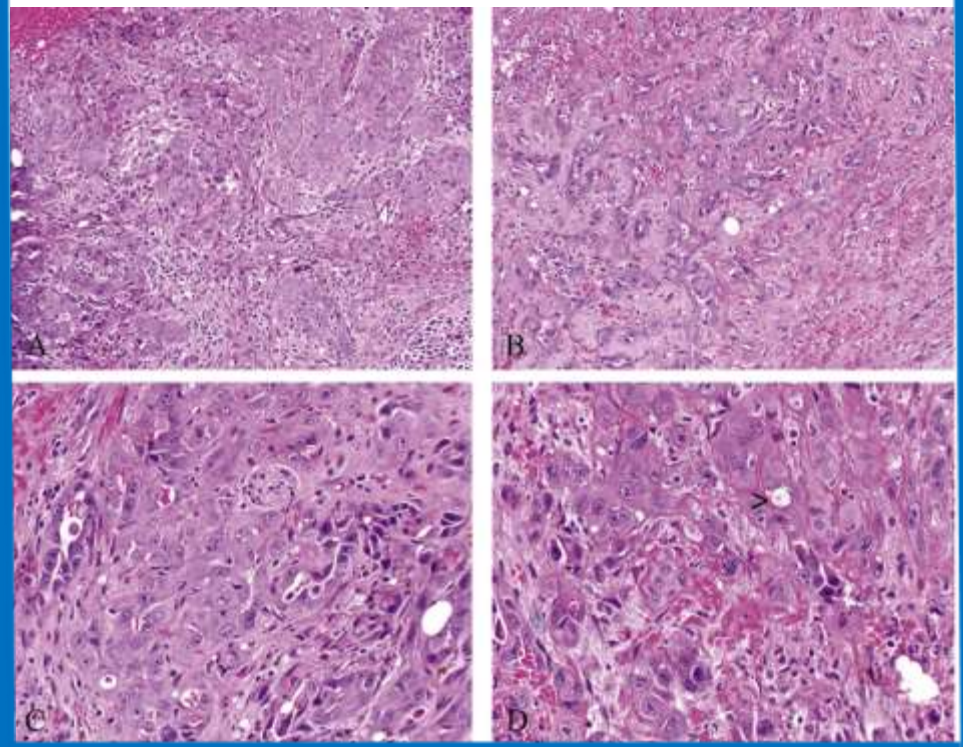
Hart J, Edgar MA, Gardner JM. 2014 Jan;31(1):30-8.

Tumor	Aggressive growth	Solid sheets	Vascular Channels	Blister cells	Atypia	Mitoses	Necrosis	Molecular
EHE	±	No	No	Yes	Mod	<3/10	<20%	CAMTA-1/ TFE3
EA	Yes	Yes	Yes	±	Severe	Many	Yes	

EHE



AS



Hart J, Edgar MA, Gardner JM. 2014 Jan;31(1):30-8.

DIAGNOSIS

Left ischium, biopsy: Epithelioid vascular neoplasm, EH vs. PMH.

The main differential diagnosis includes epithelioid hemangioma (EH) and pseudomyogenic hemangioendothelioma (PMH; otherwise known as epithelioid sarcoma-like hemangioendothelioma). Given the presence of well-developed vascular channels and predominantly epithelioid morphology, along with the focal eosinophilic infiltrate, EH is favored, but PMH cannot be excluded.

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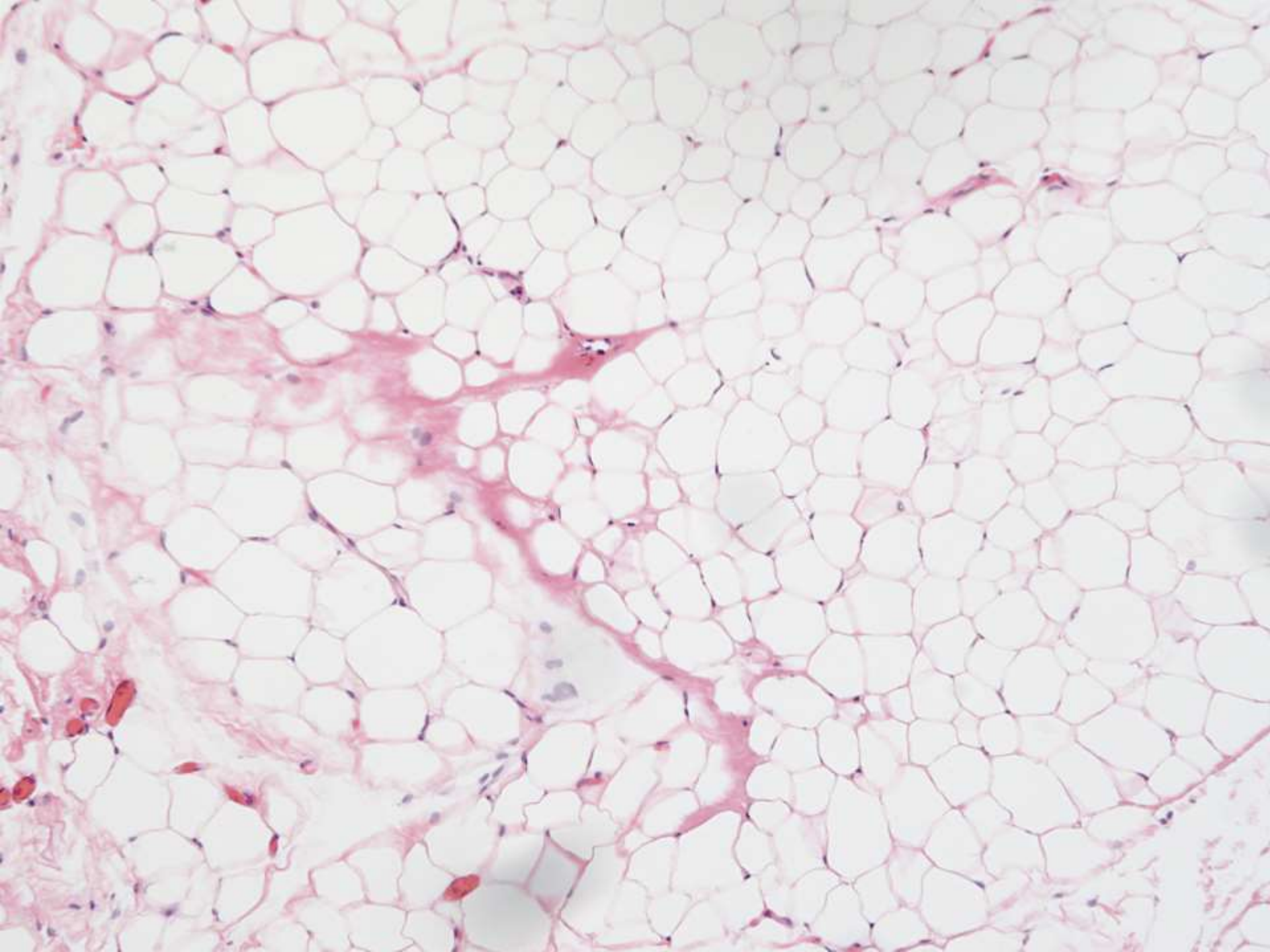
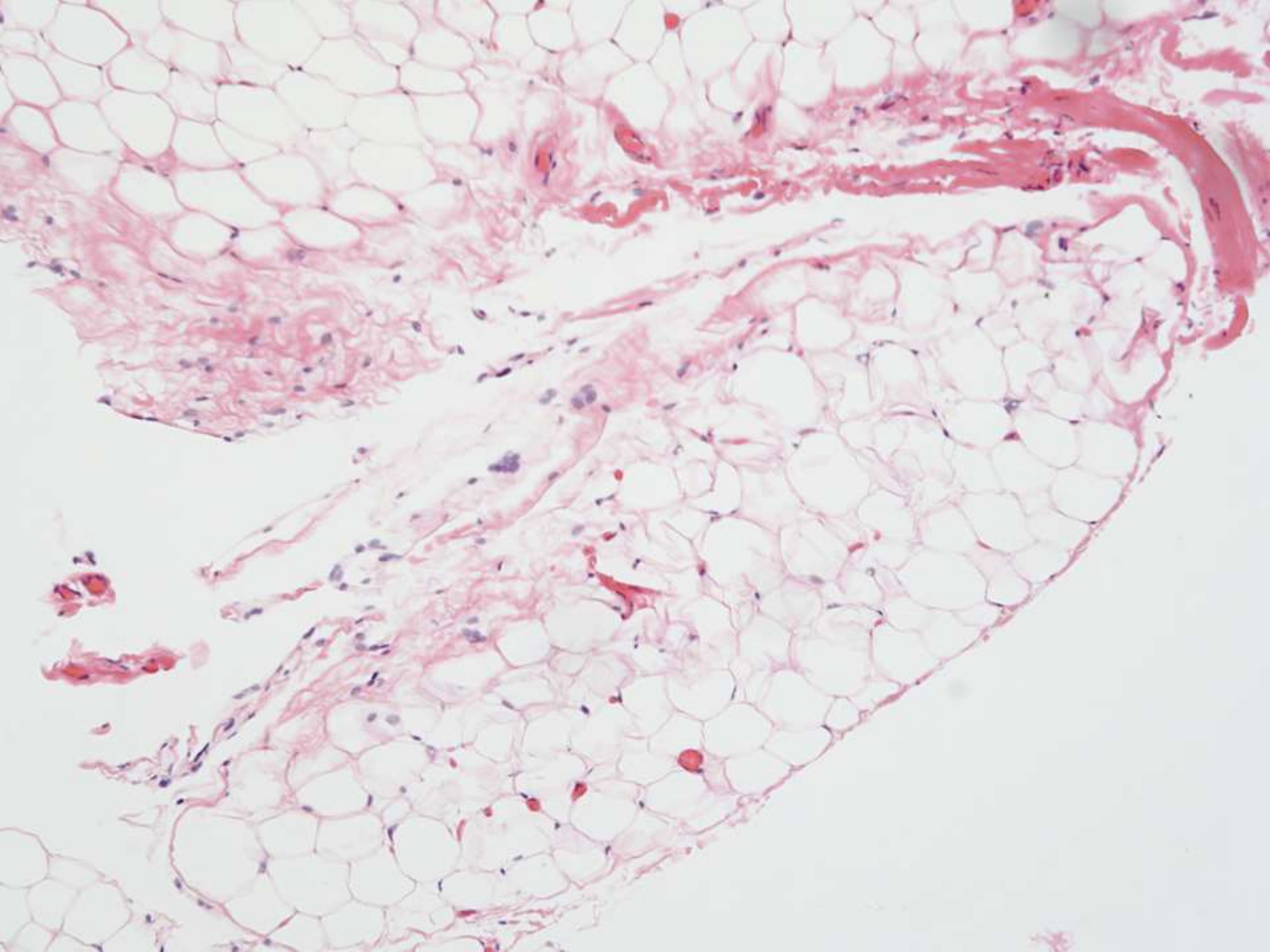
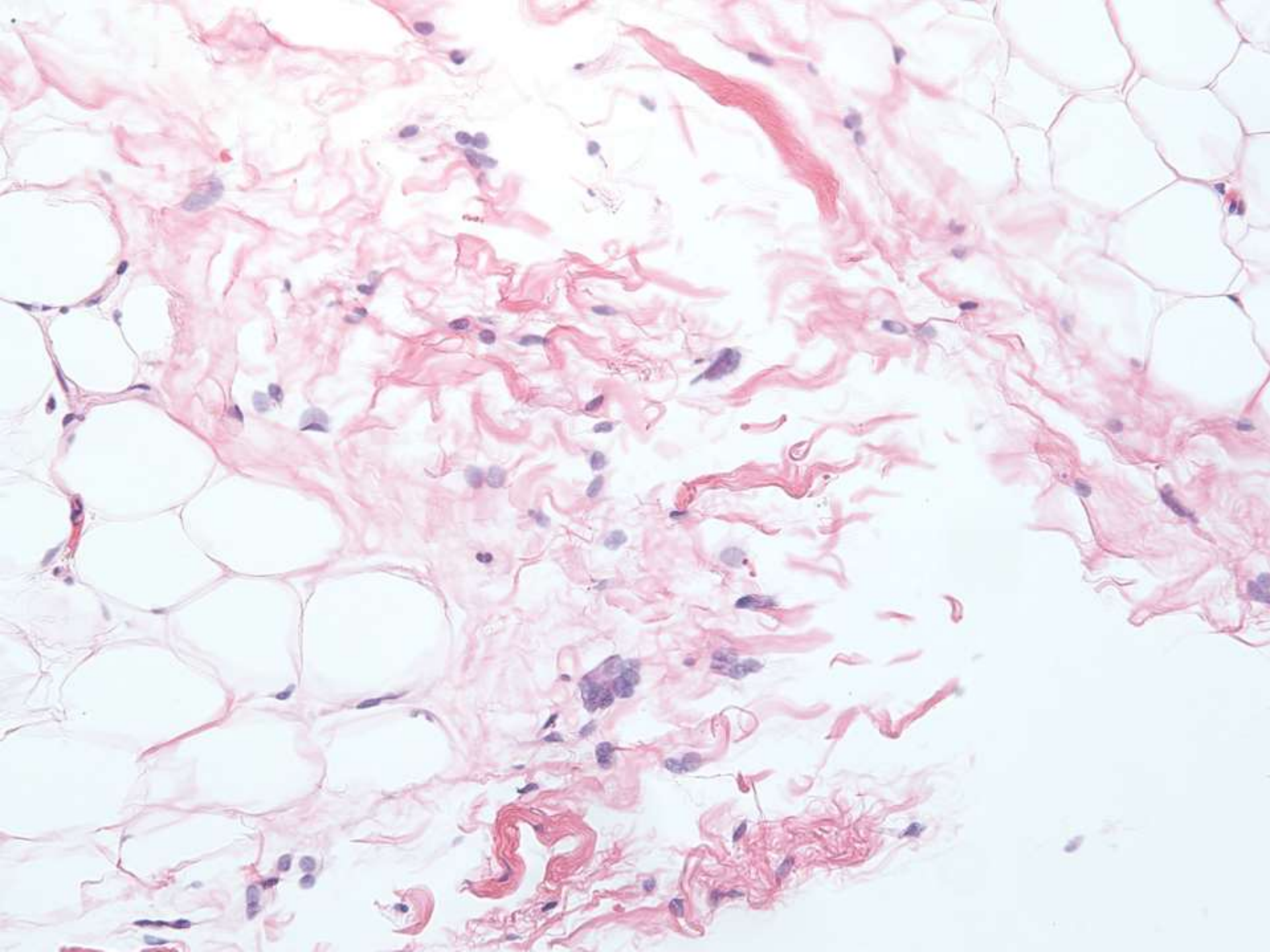
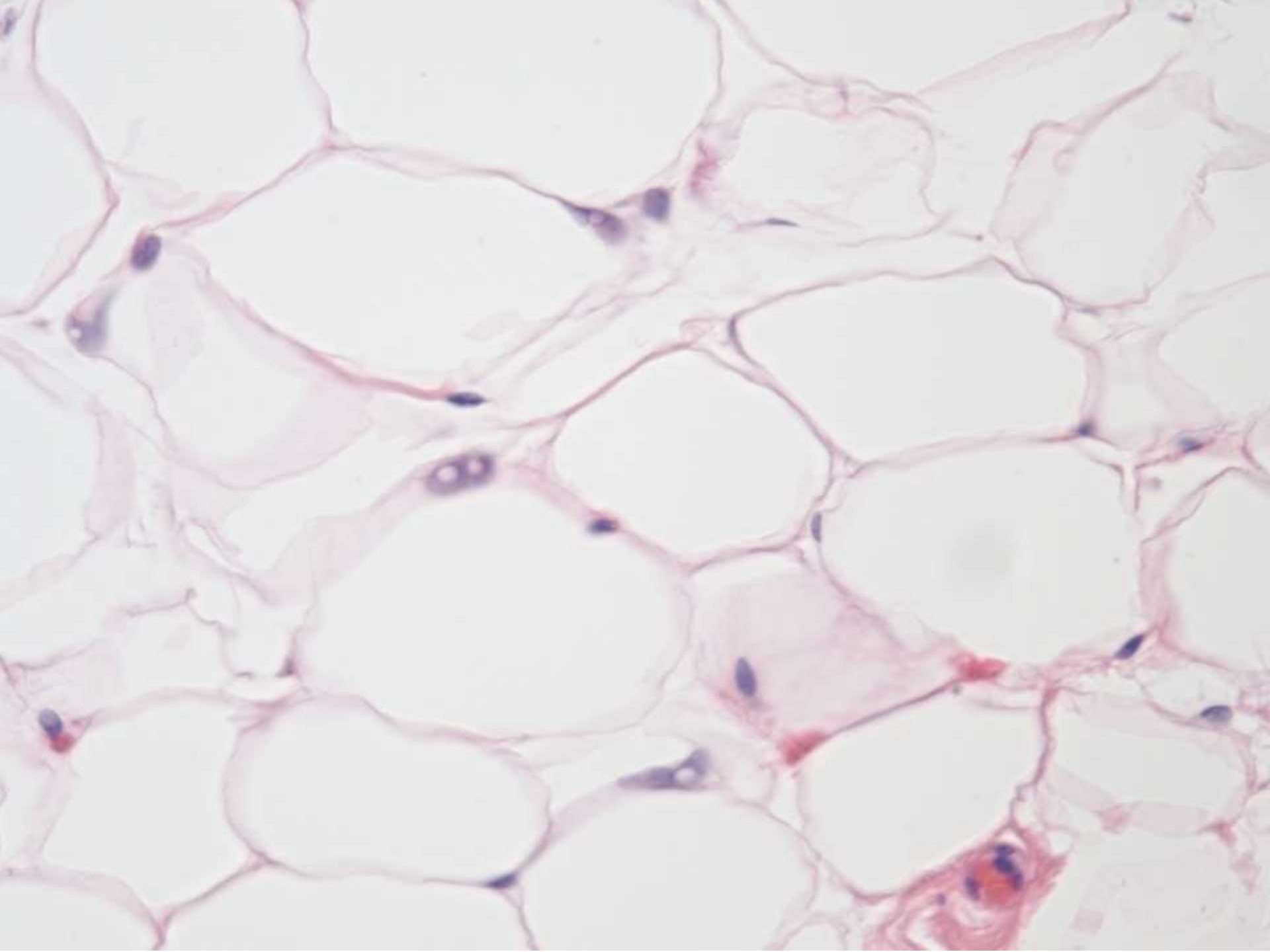
SB 6279
Vivek Charu/Christine Louie; VA Palo Alto

60-year-old man with several year history of bilateral temporal orbital masses.









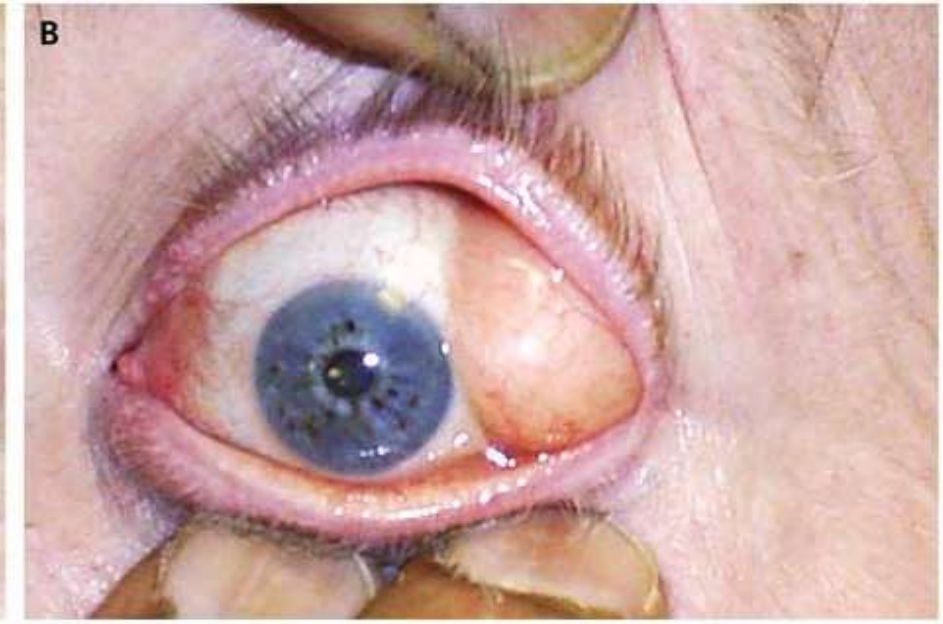
DIAGNOSIS?

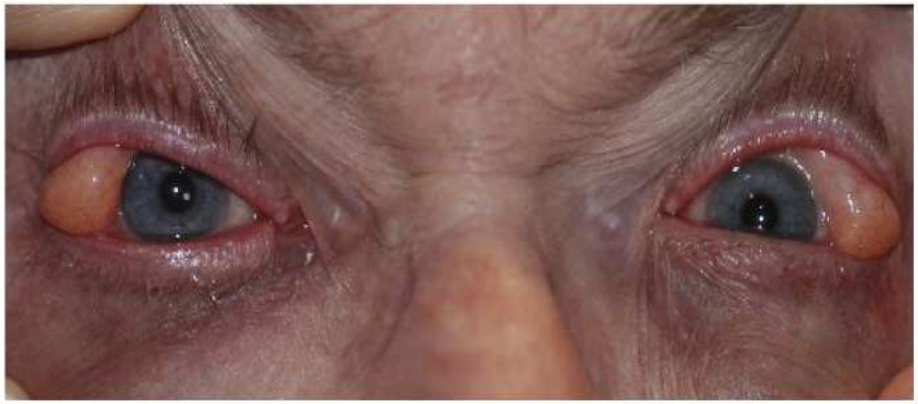
60M with several year history of bilateral temporal orbital masses

Vivek Charu and Christine Louie

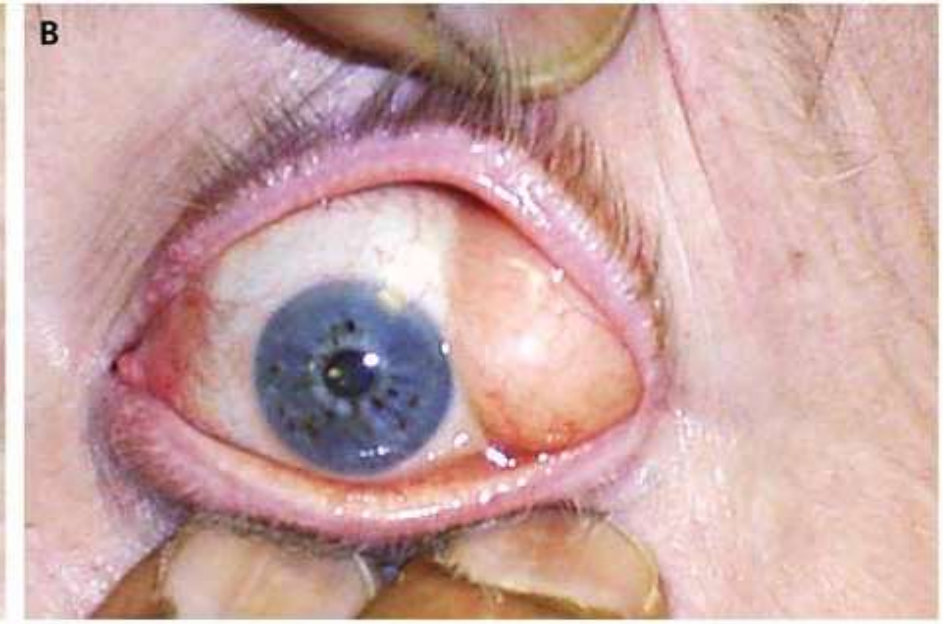
VA Palo Alto

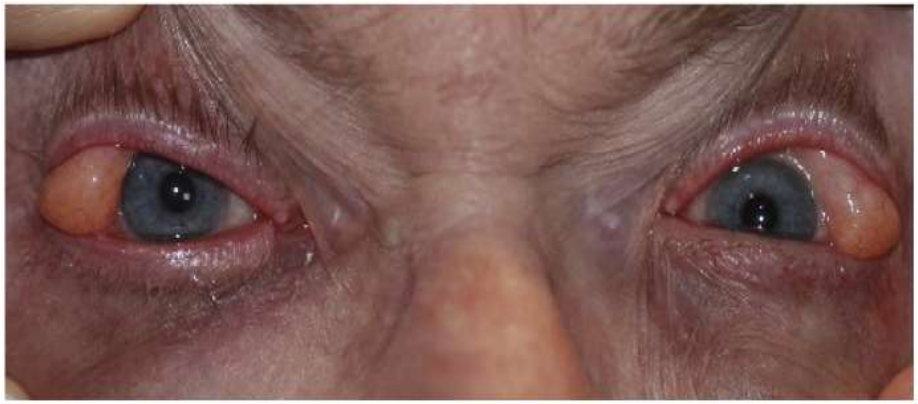
June 2018

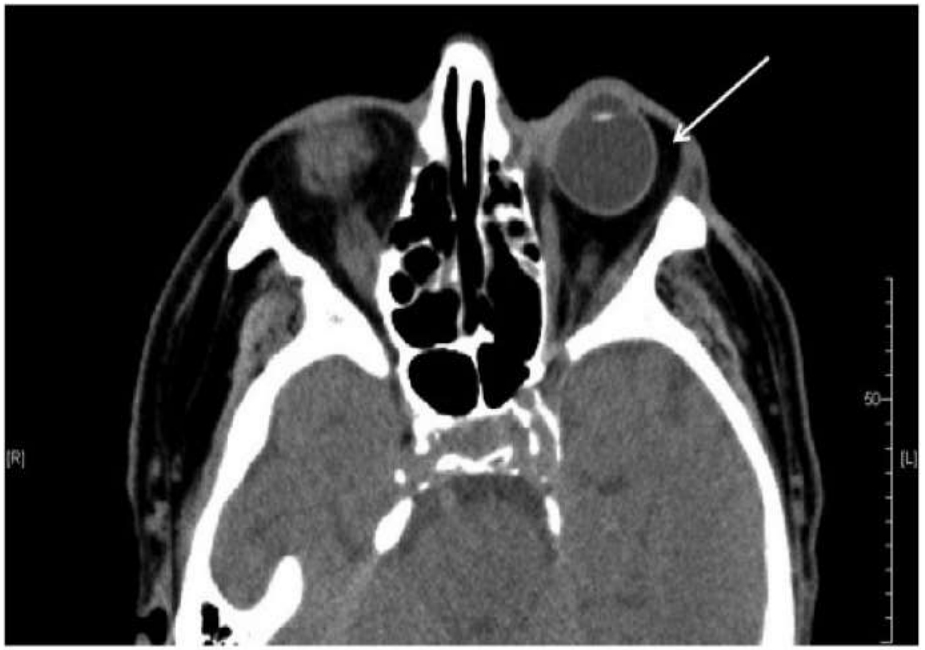




Masoud NEJM, 2007
Skorin et al. Optometry and visual science, 2014







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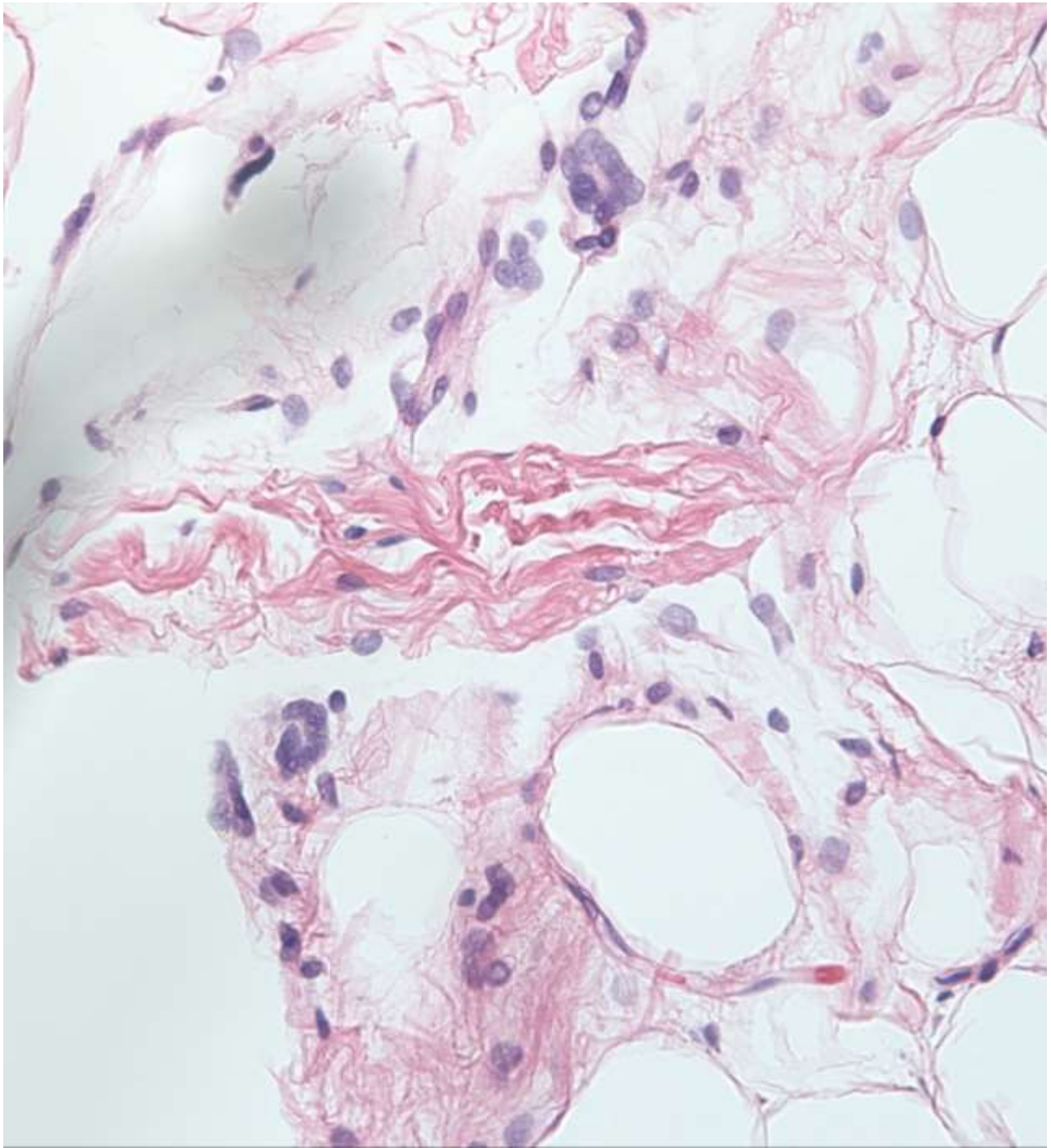


DDx:

Pleomorphic Lipoma

Atypical lipomatous tumor

Subconjunctival herniated orbital fat

DDx:

Pleomorphic Lipoma

- Soft tissues of back/shoulder
- Variably myxoid stroma
- Wire-like collagen
- Bland spindle cell proliferation

Atypical lipomatous tumor

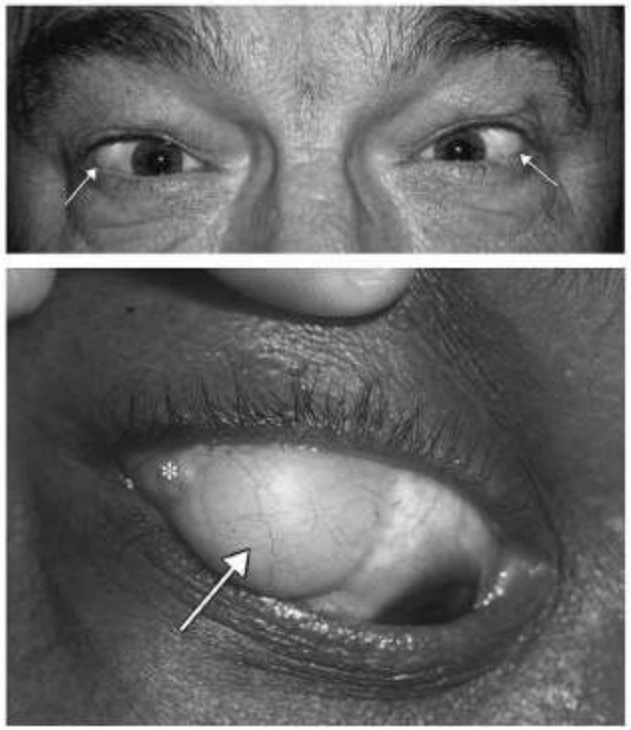
- Rarely involves the orbit
- Enlarged hyperchromatic cells within fibrous septae
- MDM2 amplification

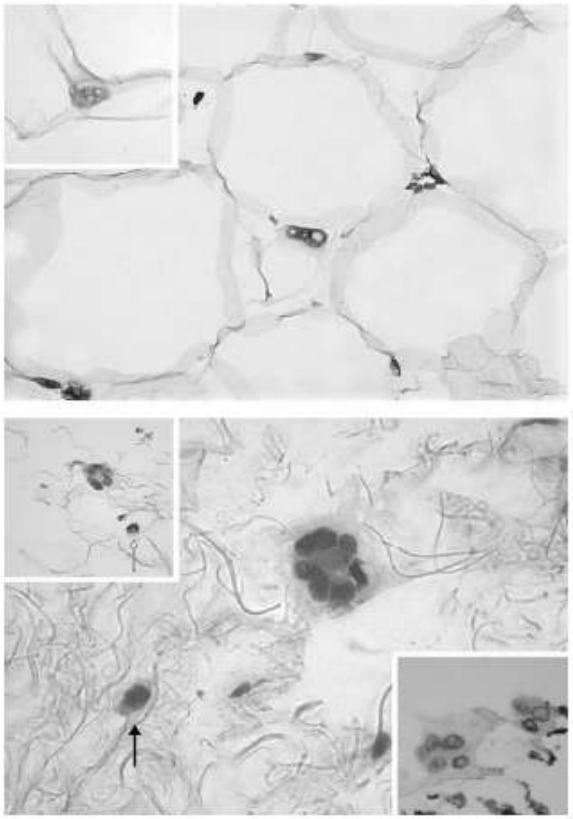
Subconjunctival herniated orbital fat

- Mature fat, often bilateral
- Fibrous septae lacking hyperchromatic cells
- Intranuclear vacuoles, multinucleated cells

Subconjunctival Herniated Orbital Fat: A Benign Adipocytic Lesion That may Mimic Pleomorphic Lipoma and Atypical Lipomatous Tumor

Ingo Schmack, MD,† Rajiv M. Patel, MD,‡ Andrew L. Folpe, MD,‡ Ted Wojno, MD,† Renzo A. Zaldivar, MD,† Bonnie Balzer, MD,‡ Shin J. Kang, MD, PhD,† Sharon W. Weiss, MD,‡ and Hans E. Grossniklaus, MD**





AJSP, 2007

Subconjunctival Herniated Orbital Fat

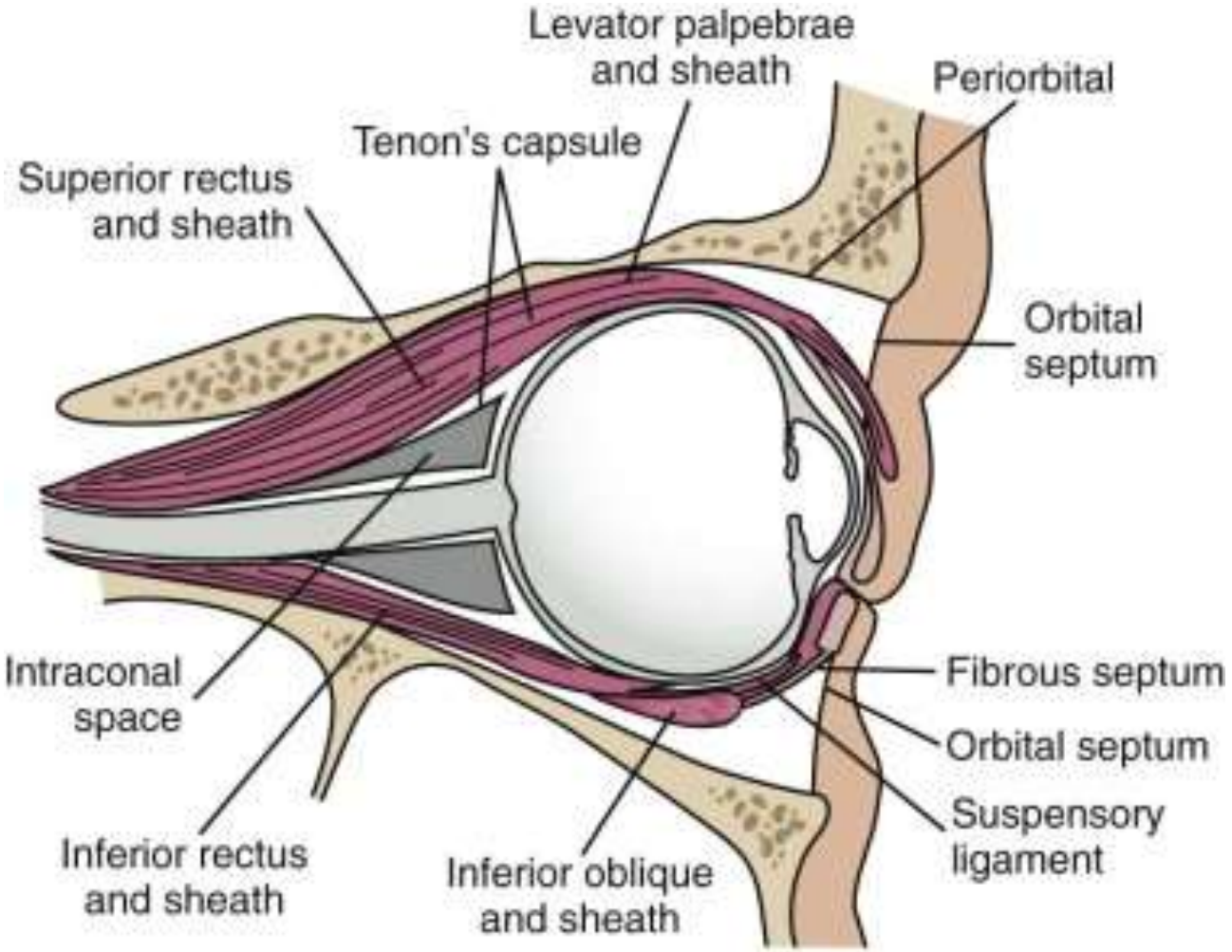
1. Mature fat (often bilateral, as in this patient); elderly, obese men

2. Fibrous septae lacking hyperchromatic cells

3. Adipocytes with intranuclear vacuoles (**Lochkern cells**; CD34, S100, vimentin +)

4. Multinucleated giant cells with wreathlike configuration of normochromatic nuclei (**Floret cells**; CD34+)

5. Varying numbers of histiocytes, lymphocytes, plasma cells and mast cells



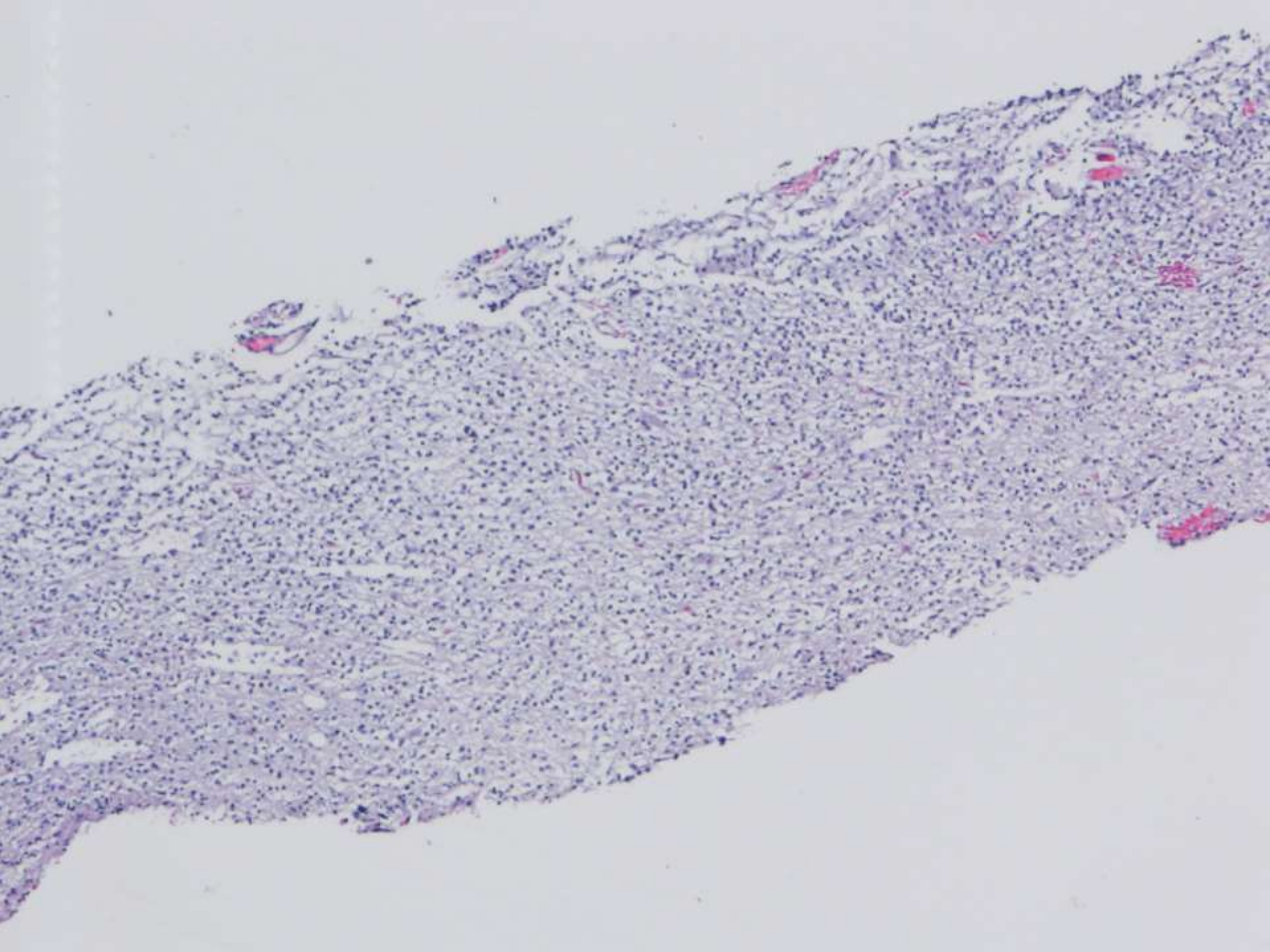
Hernatiation of **intraconal** fat due to laxity in Tenon's capsule

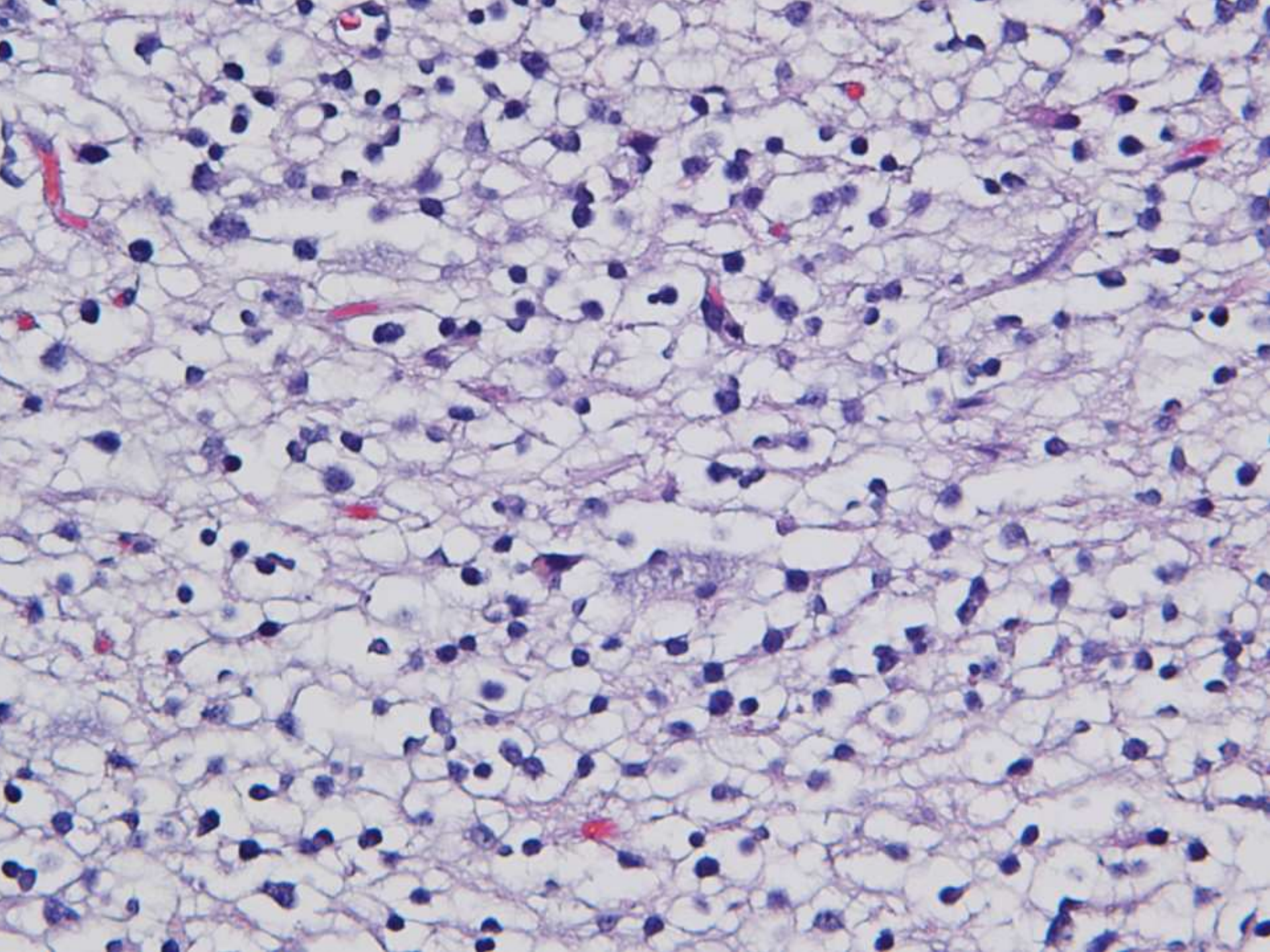
Thank you!

SB 6280
Jonathan Lavezo/Donald Born; Stanford

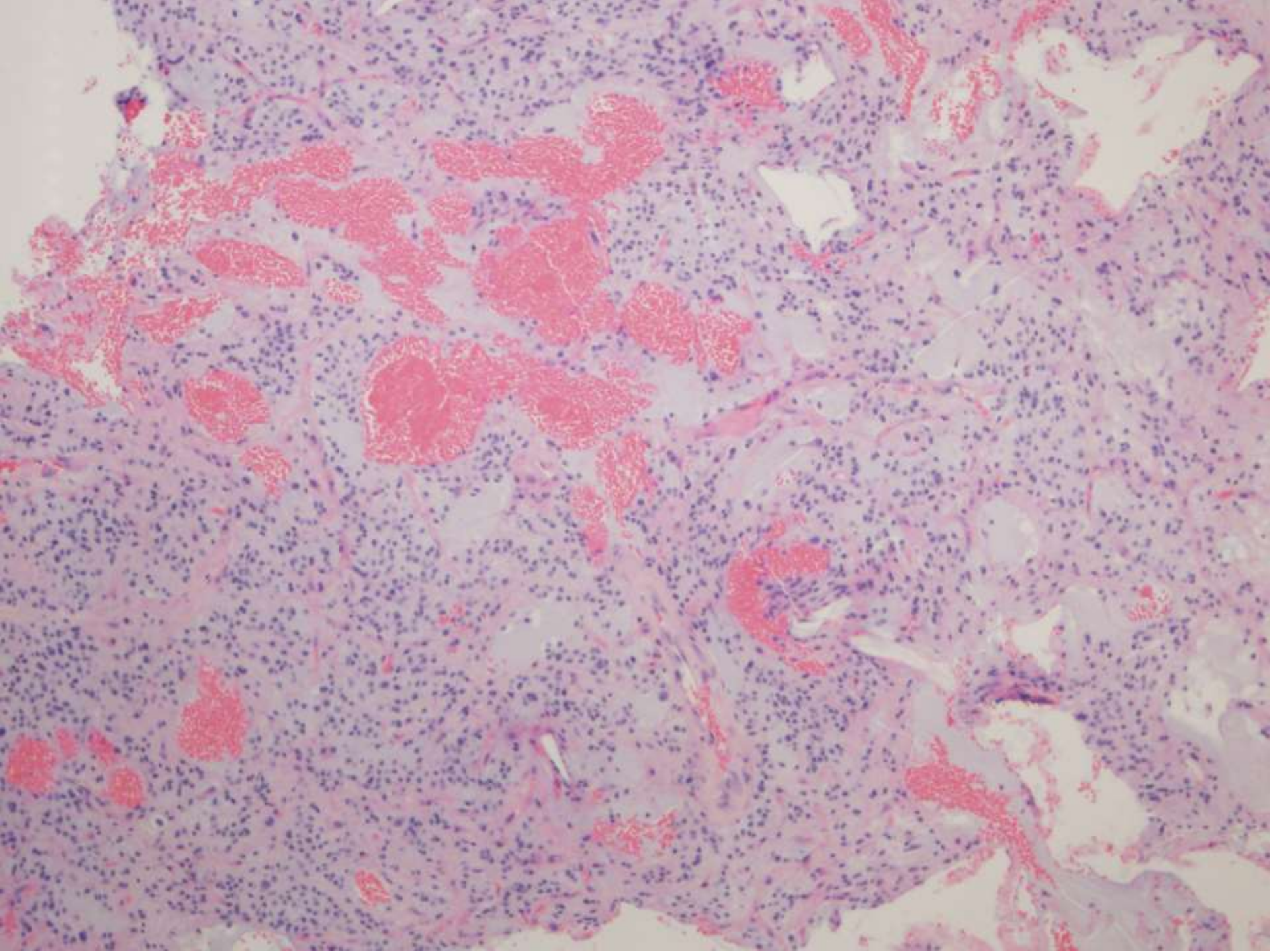
57-year-old woman with bilateral temporal lobe lesions. Left-side is 5.5cm T2 hyperintense w/o contrast enhancement. Right-side is 1.8cm T2 hyperintense lesion that on repeat imaging showed rim-enhancement.

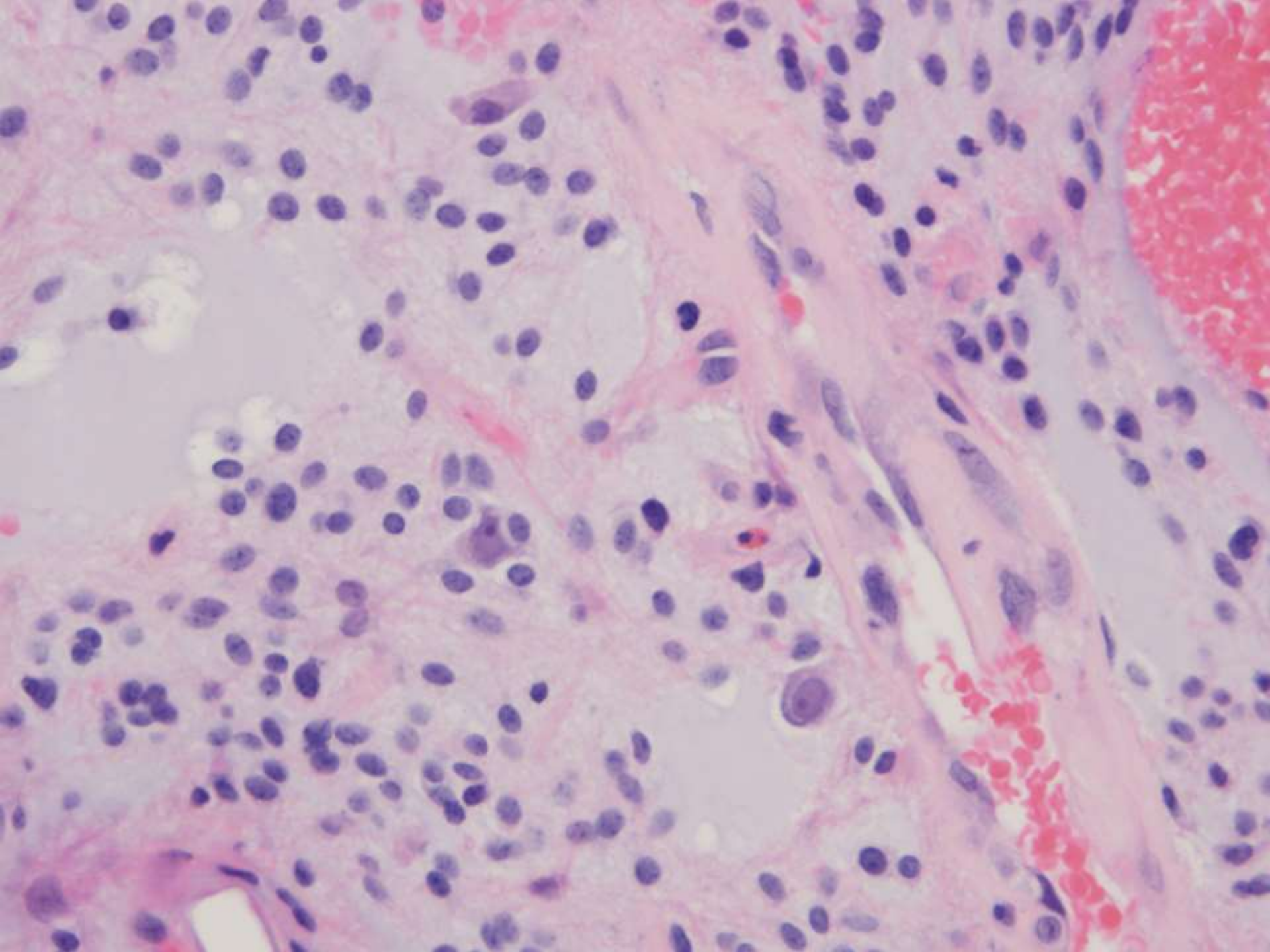
Left Temporal Lobe, Biopsy - 2017

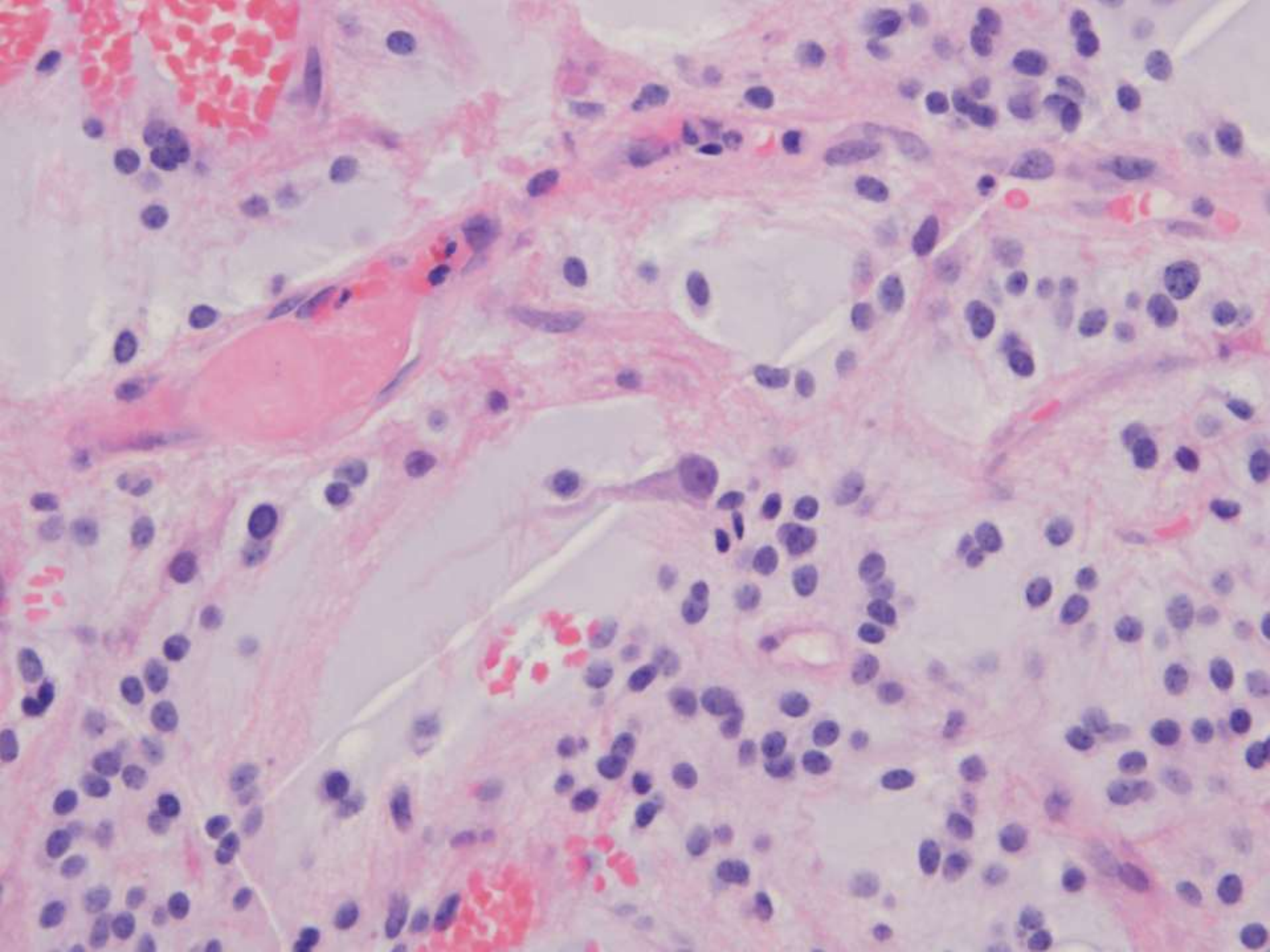




Right Temporal Lobe, Resection - 2018







DIAGNOSIS?

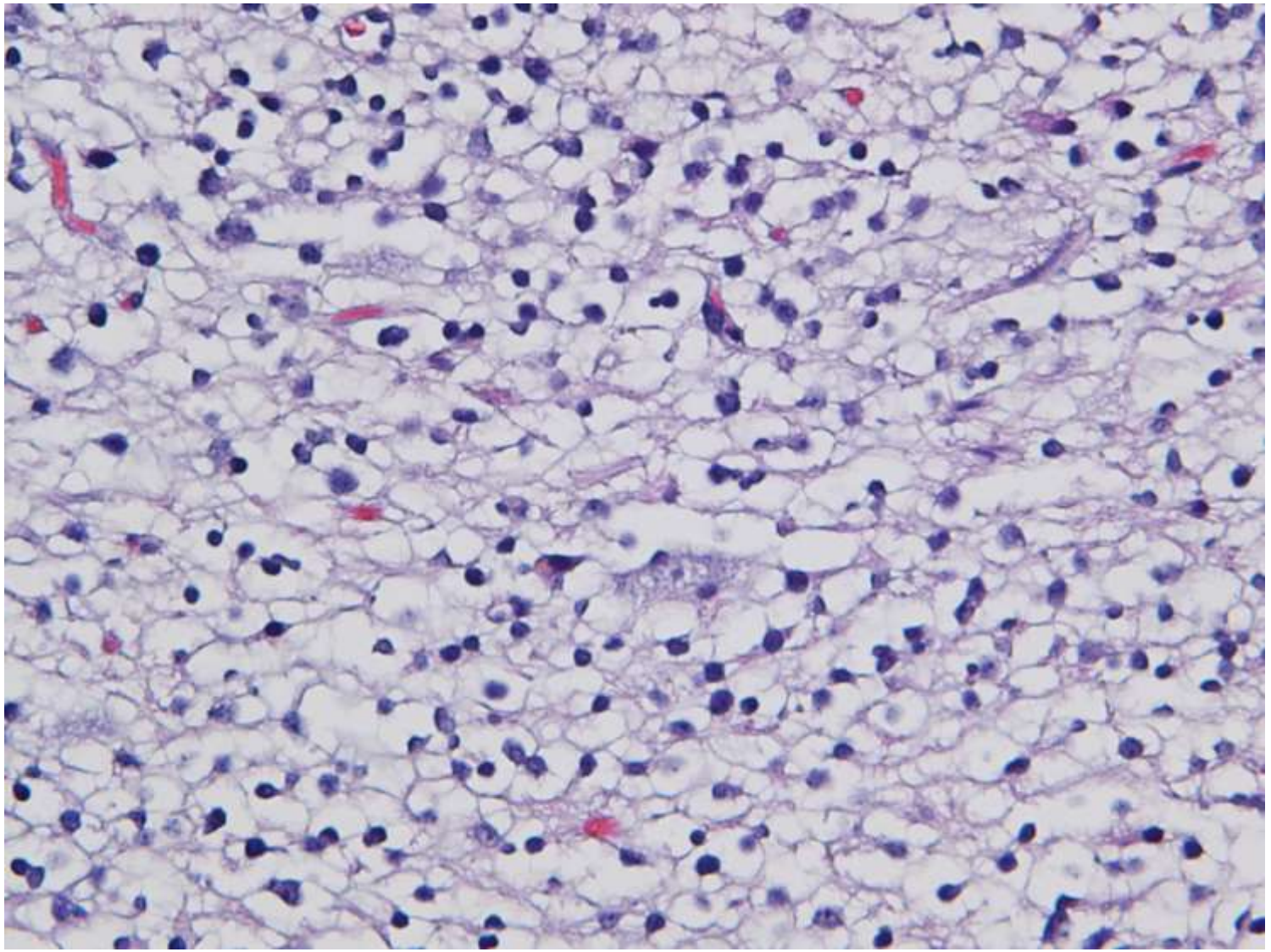
The patient is a 57 year-old woman with bilateral temporal lobe lesions. Left side is 5.5 cm T2 hyperintense without contrast enhancement. Right side is 1.8cm T2 hyperintense lesion that on repeat imaging showed rim-enhancement.

Jonathan Lavezo/Donald Born

Stanford University

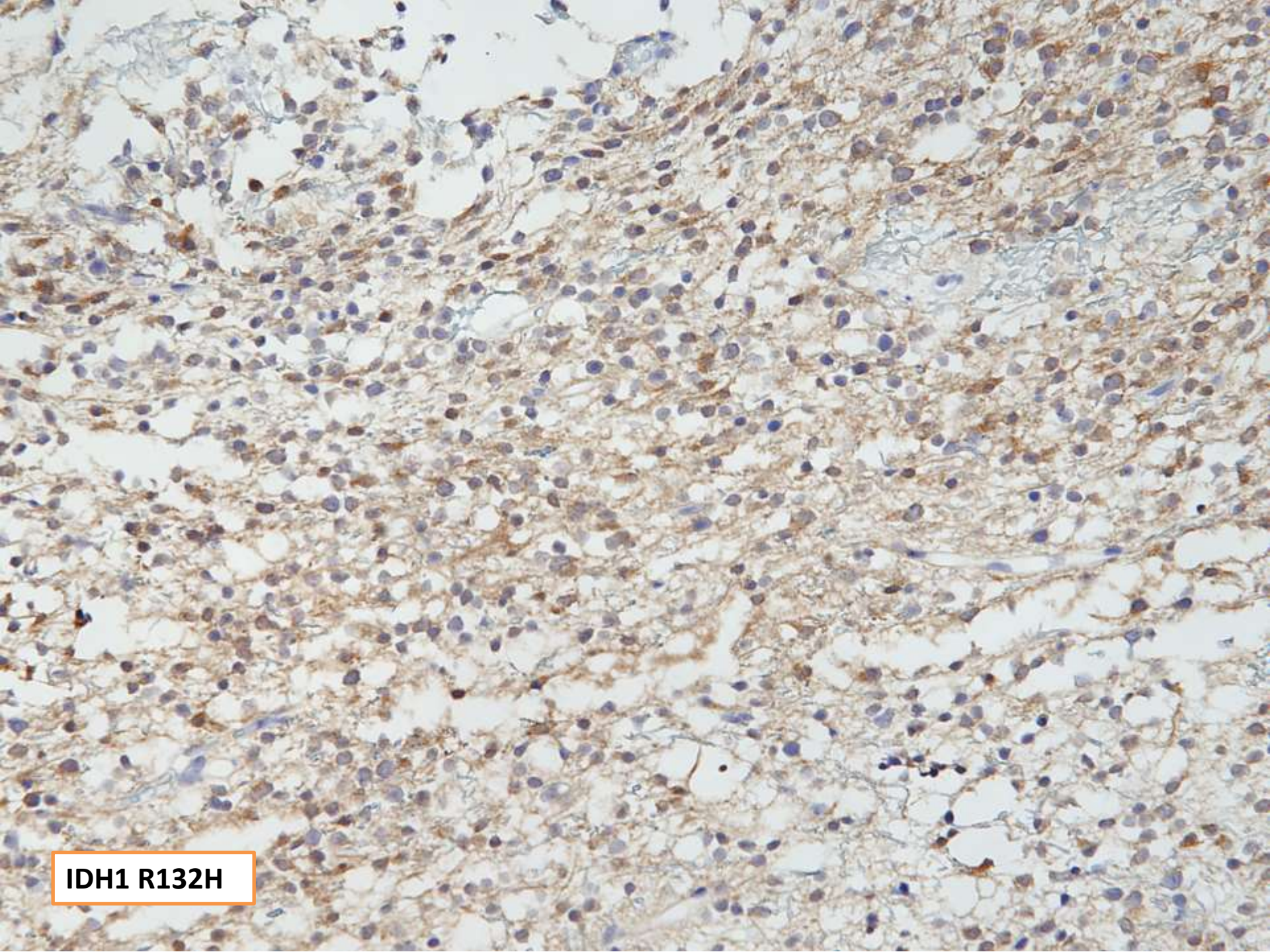
Department of Neuropathology

Left Temporal Lobe, Biopsy - 2017

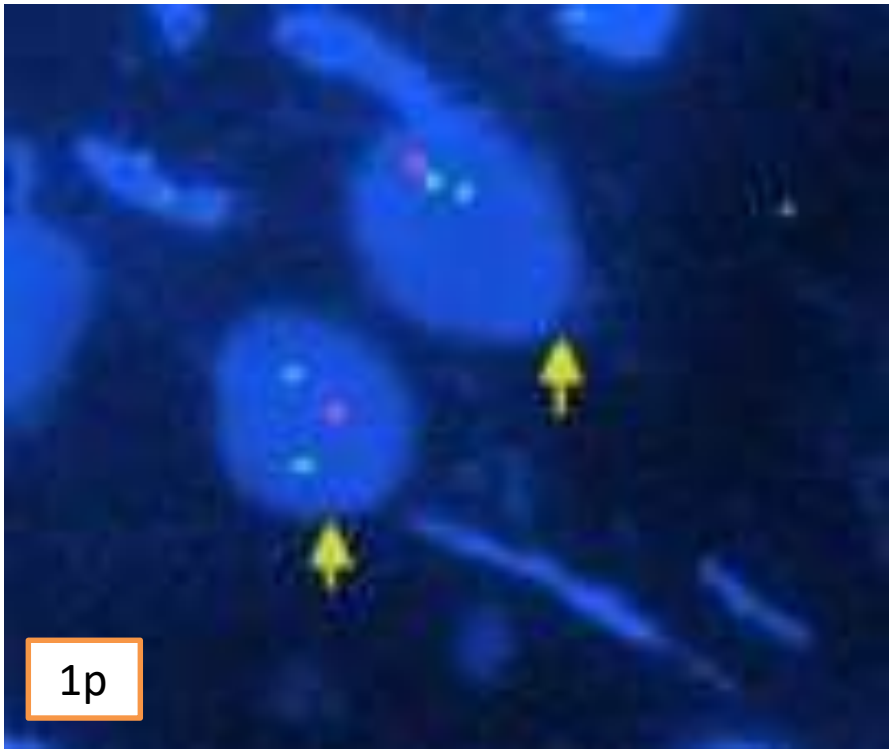


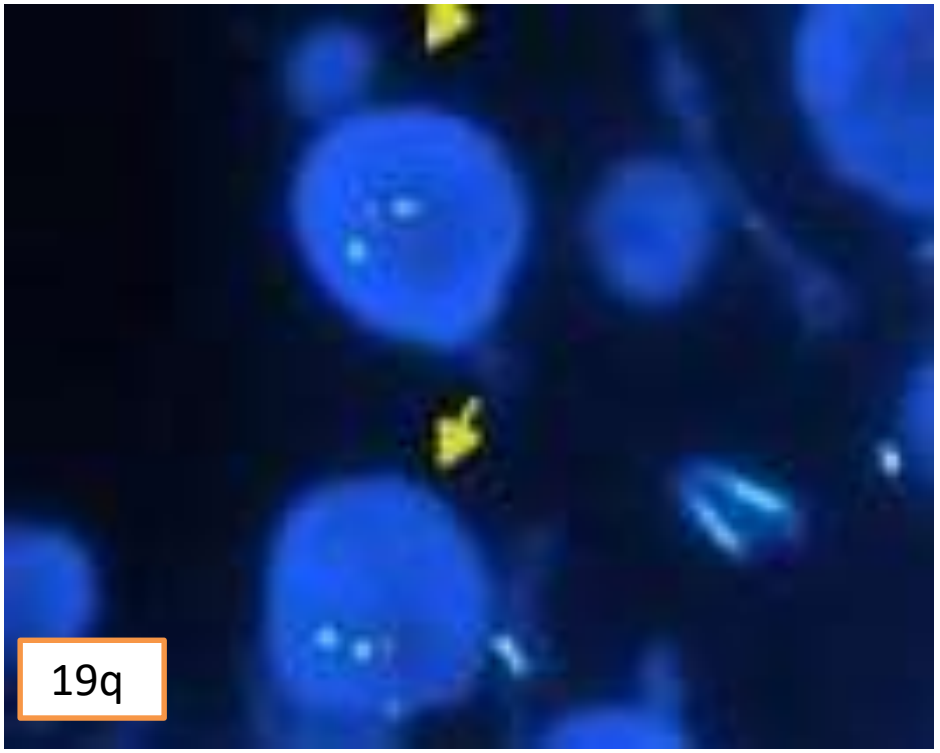
DDX

- Macrophage-rich processes (demyelinating diseases or cerebral infarctions)
- Oligodendroglioma
- Diffuse astrocytoma
- Clear cell ependymoma
- Neurocytoma
- Dysembryoplastic neuroepithelial tumor
- Pilocytic astrocytoma
- Diffuse leptomeningeal glioneuronal tumor
- Hemangioblastoma
- Clear cell meningioma
- Metastatic clear cell RCC


IDH1 R132H

FISH





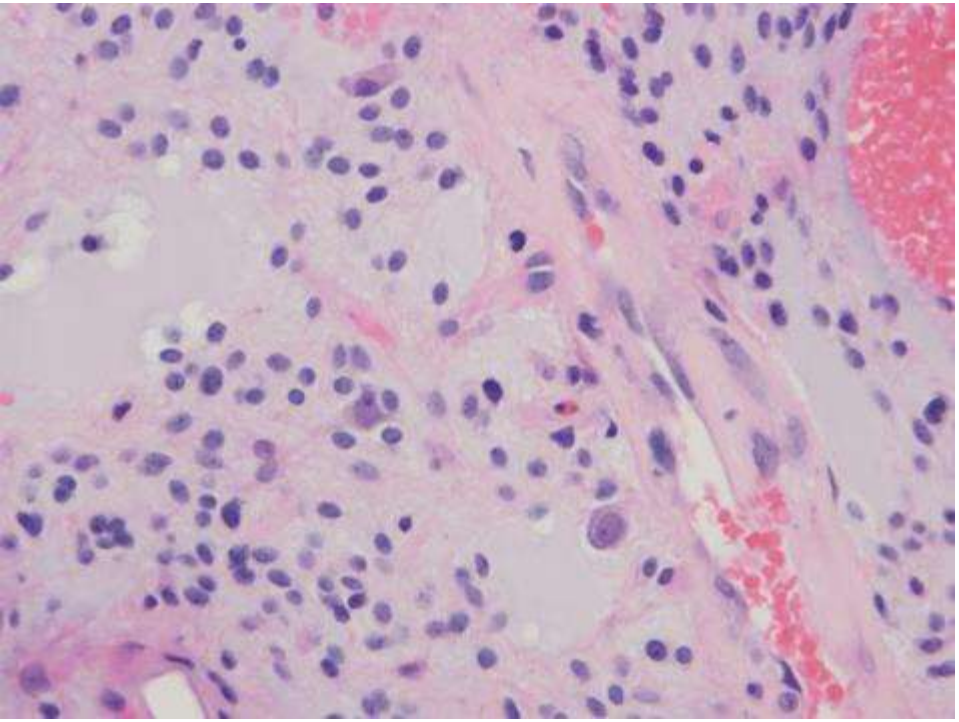
Oligodendroglioma, IDH-mutant and 1p/19q co-deleted, WHO grade II

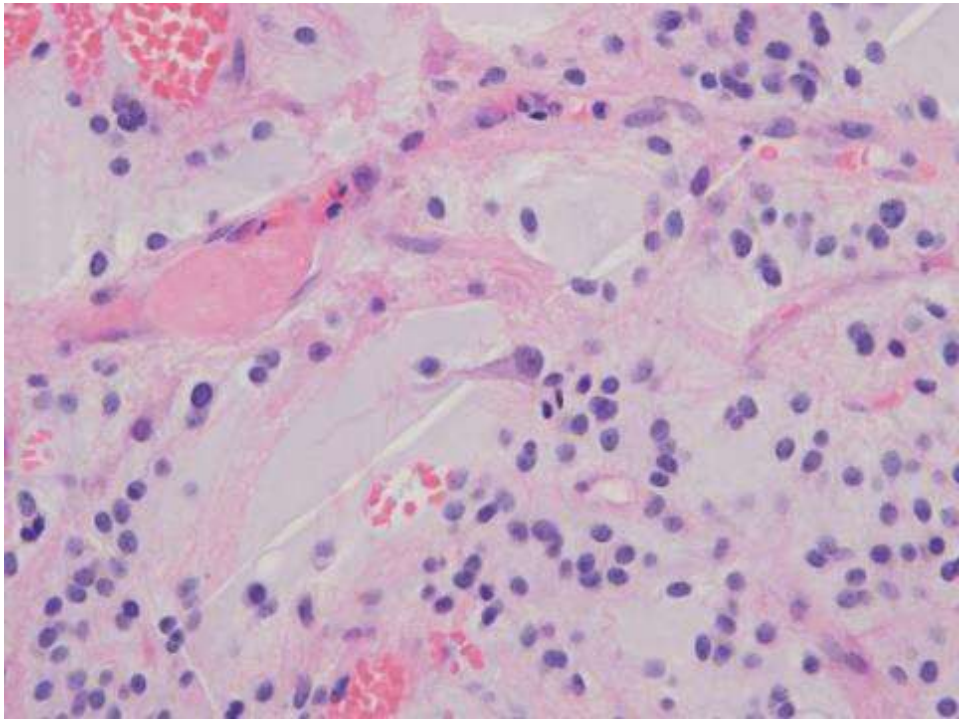
- Molecularly defined diffusely infiltrating, slow-growing glial neoplasm
- Peak incidence in patients 35-44 years of age
- Cerebral predilection with >50% of cases in the frontal lobe
- Initial presentation is most often seizures (2/3rds)

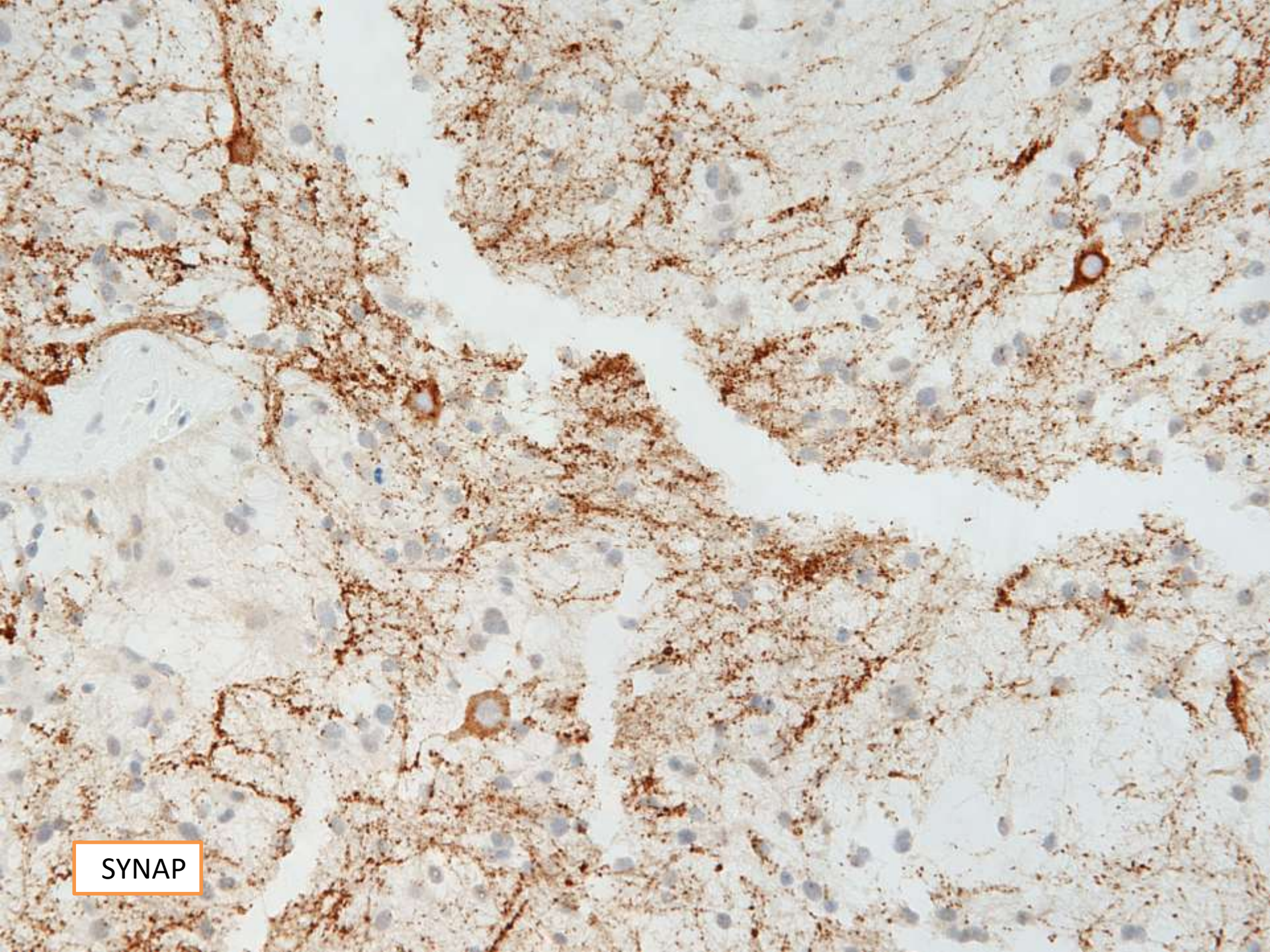
Oligodendroglioma cont.

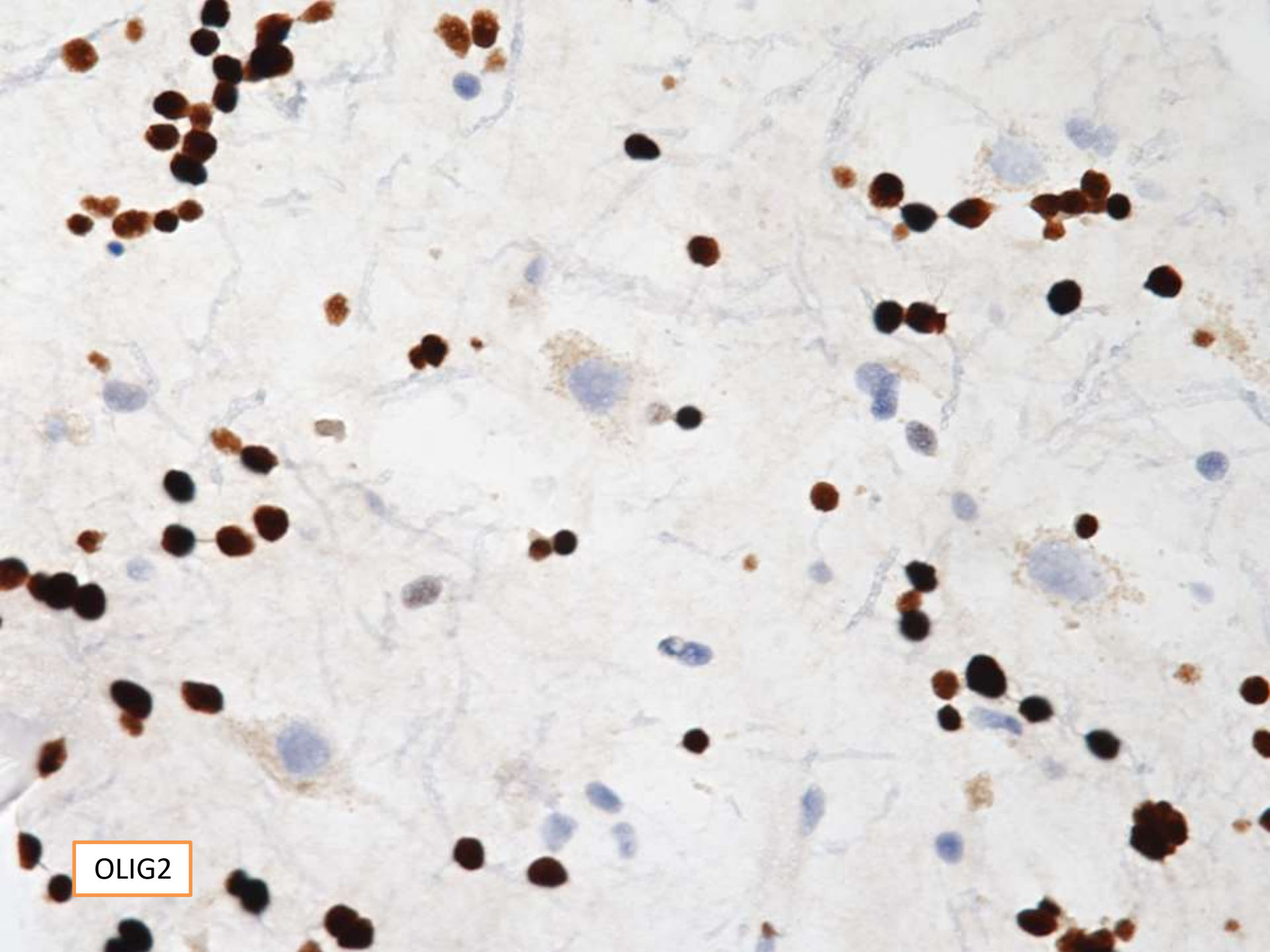
- Imaging is usually T2-hyperintense well-demarcated mass lesions in the cortex and subcortical white matter.
- Contrast enhancement in >70% of WHO grade III anaplastic oligodendrogliomas
- Rare cases of oligodendroglial gliomatosis cerebri

Right Temporal Lobe, Resection - 2018



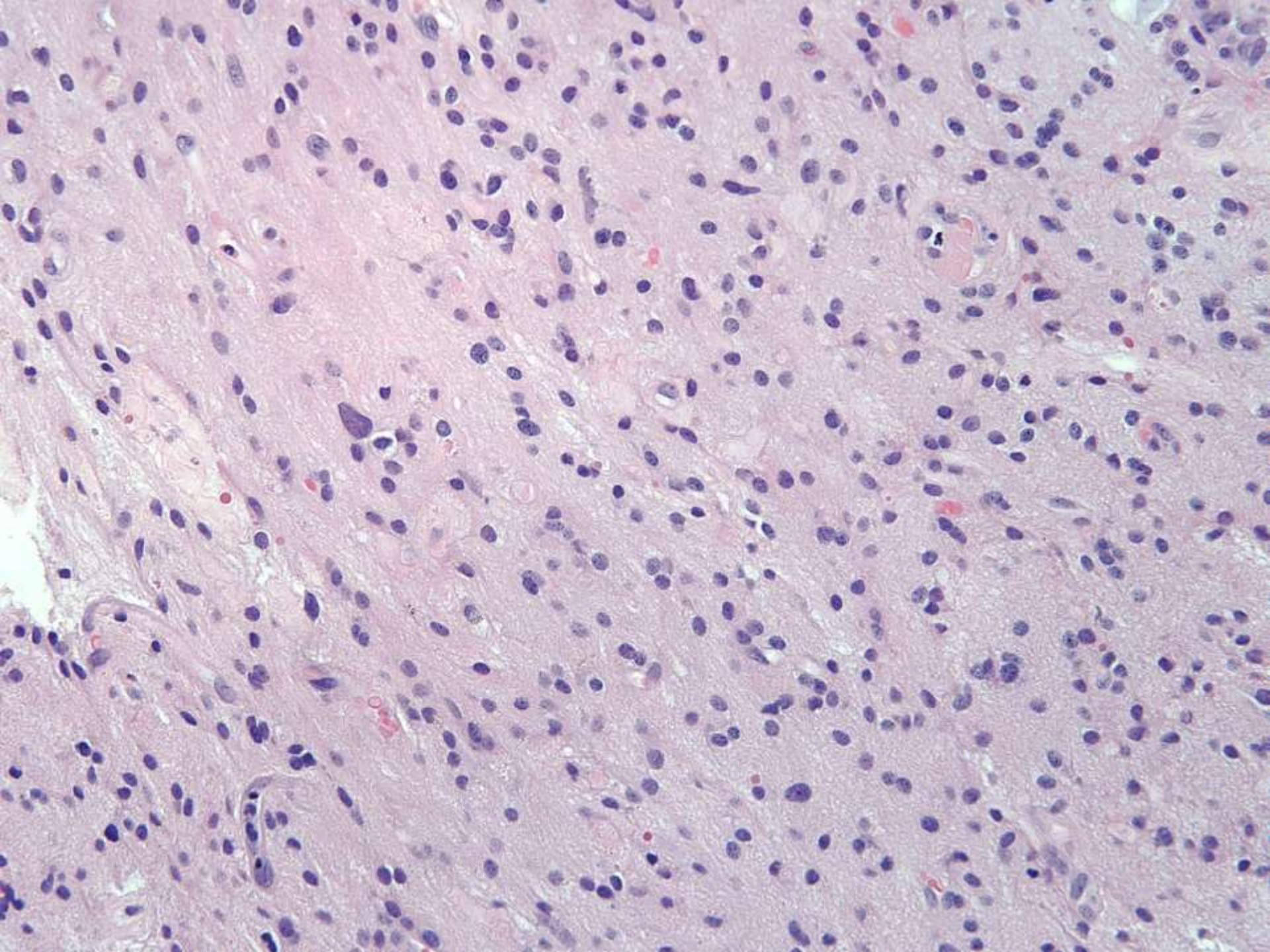


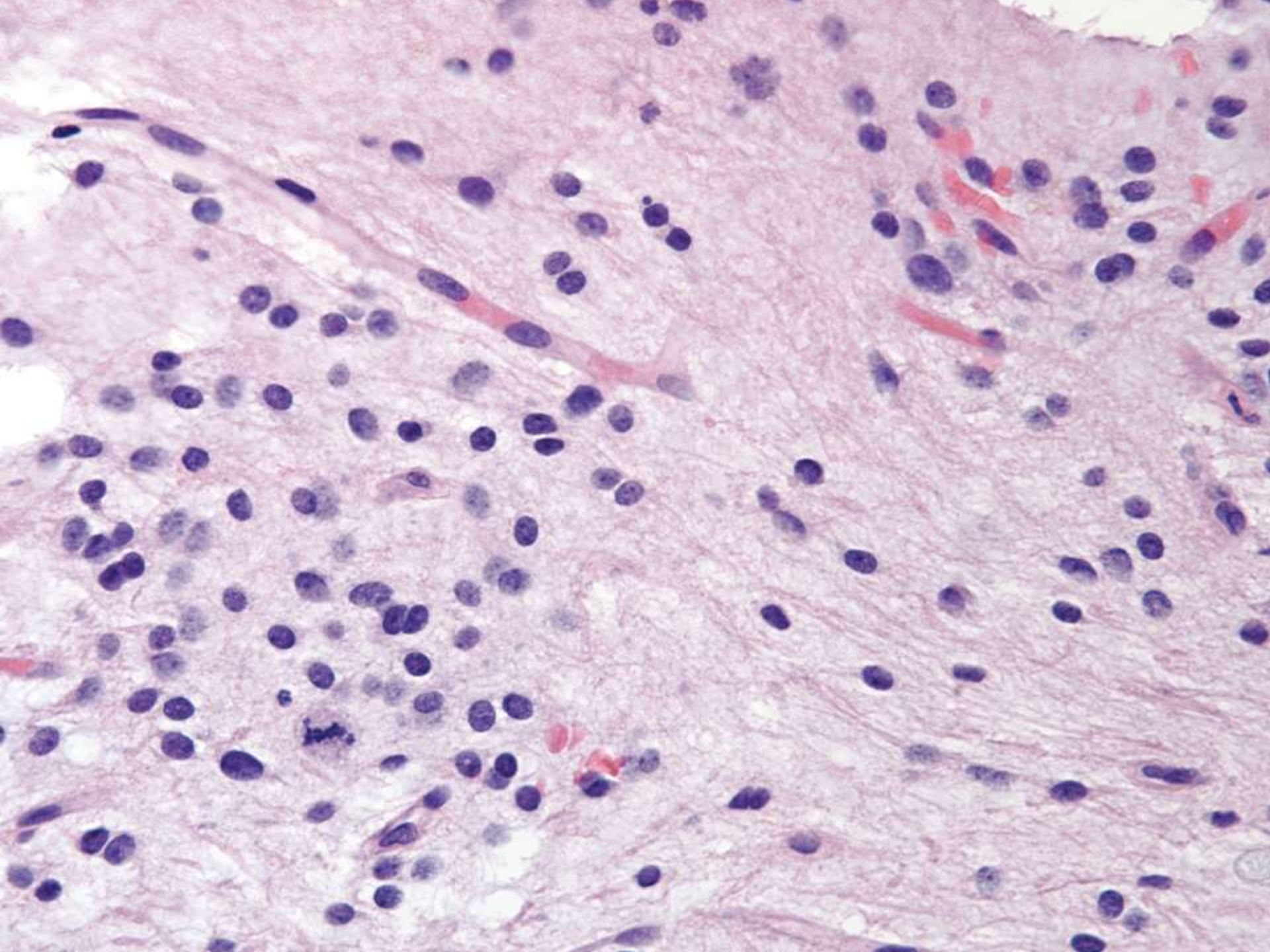

SYNAP

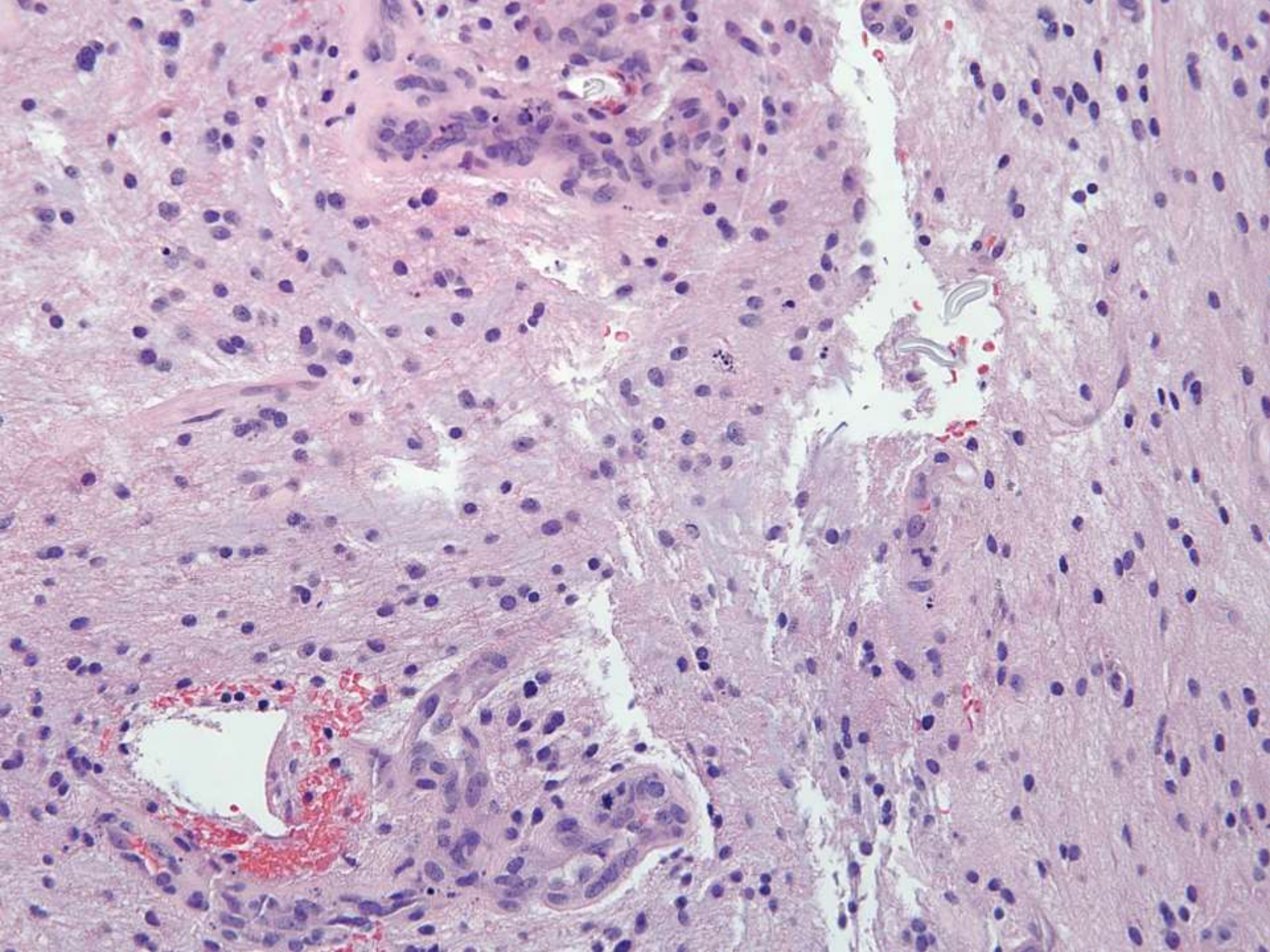

OLIG2

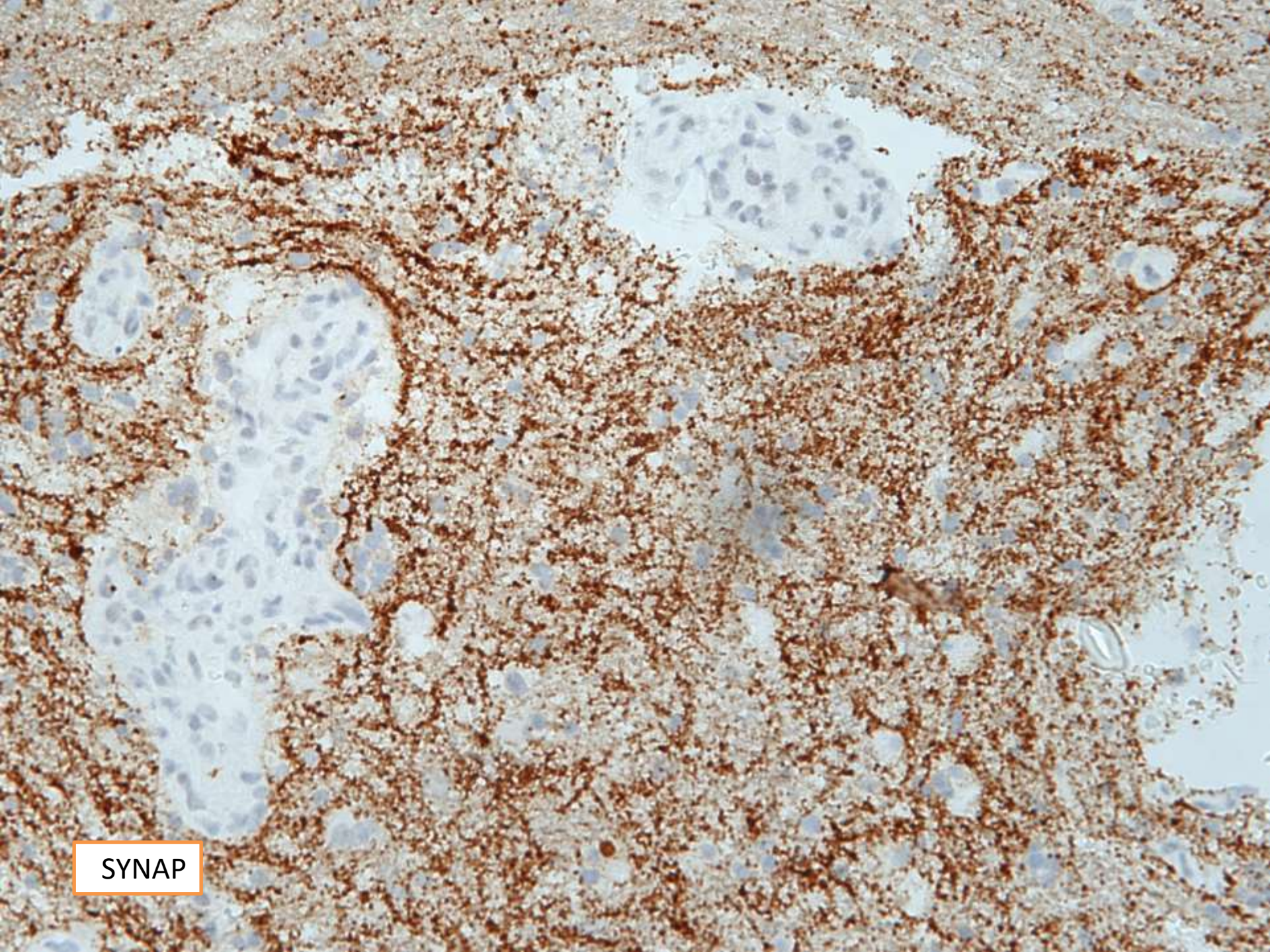
Dysembryoplastic Neuroepithelial Tumor, WHO grade I

- Benign glioneuronal neoplasm characterized by columns composed of bundles of axons oriented perpendicular to the cortical surface
- Columns lined by oligodendroglial-like cells embedded in a mucoid matrix and interspersed with floating neurons
- Complex variants of DNT contain glial tumor components associated with specific glioneuronal element.








SYNAP

DNT Complex Form

- Glial component can be variable in location, amount and morphology (astrocytic and oligodendroglial-like)
- Architecturally is typically nodular but may be diffuse
- Often mimic pilocytic astrocytoma
- May show nuclear atypia, rare mitoses, or microvascular-like proliferation and ischemic necorsis

DN(E)T

- Lack mutations in IDH1/IDH2 and 1p/19q co-deletion
- GFAP and MAP2 helpful in differentiating DNT from Oligodendroglioma
  - DNT lack GFAP positivity in oligodendroglia-like cells
  - Oligodendroglioma shows strong ring-shaped cytoplasmic staining for MAP-2

Follow-up

- Treated with chemotherapy and radiation post left frontal biopsy
- Right temporal lesion was resected because it was changing/growing by imaging
- Radiology on 3/27/2018
  - Stable left frontal hyperintense flair signal lesion
  - Post surgical changes of right temporal resection