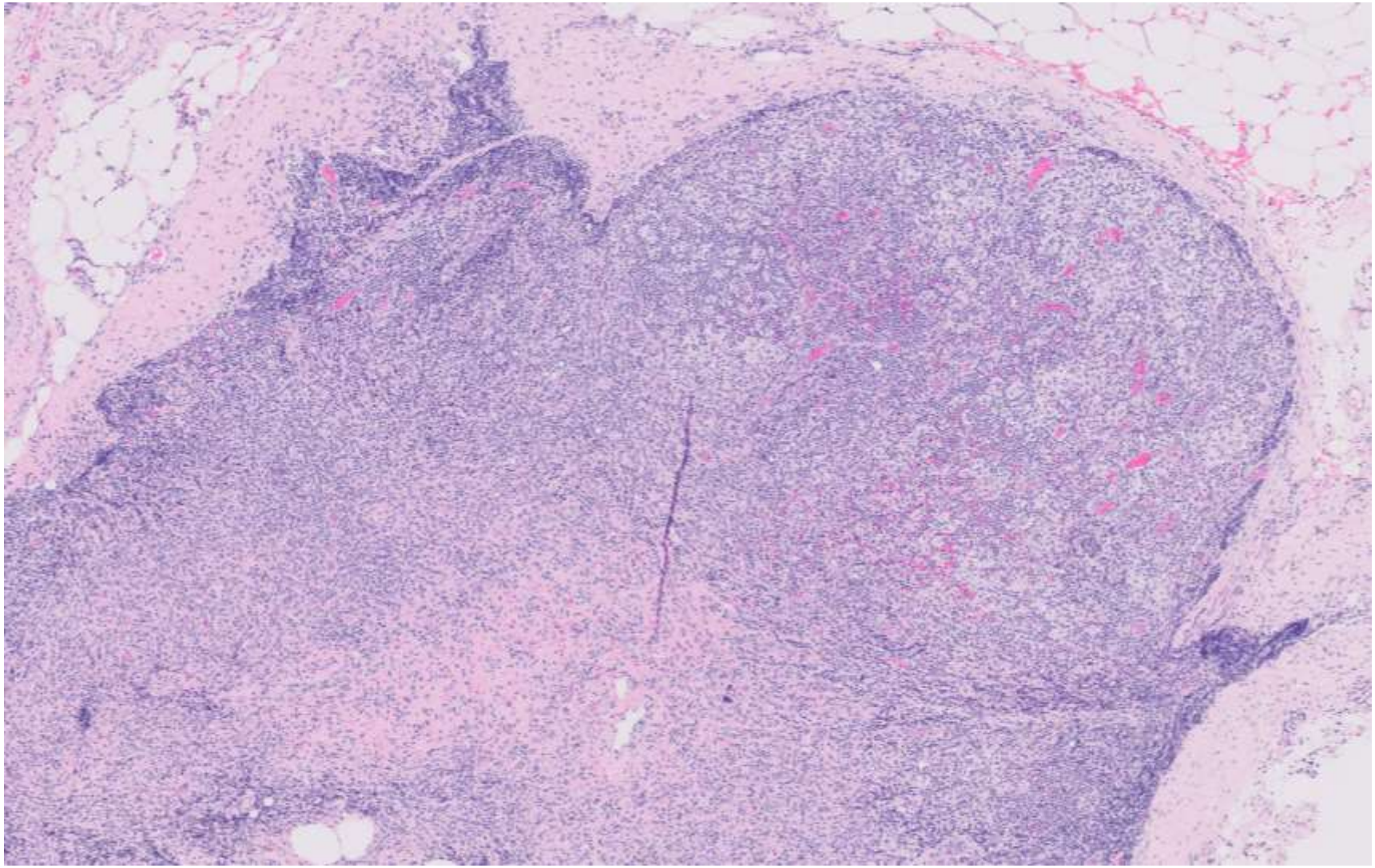
AUG 2022 DIAGNOSIS LIST

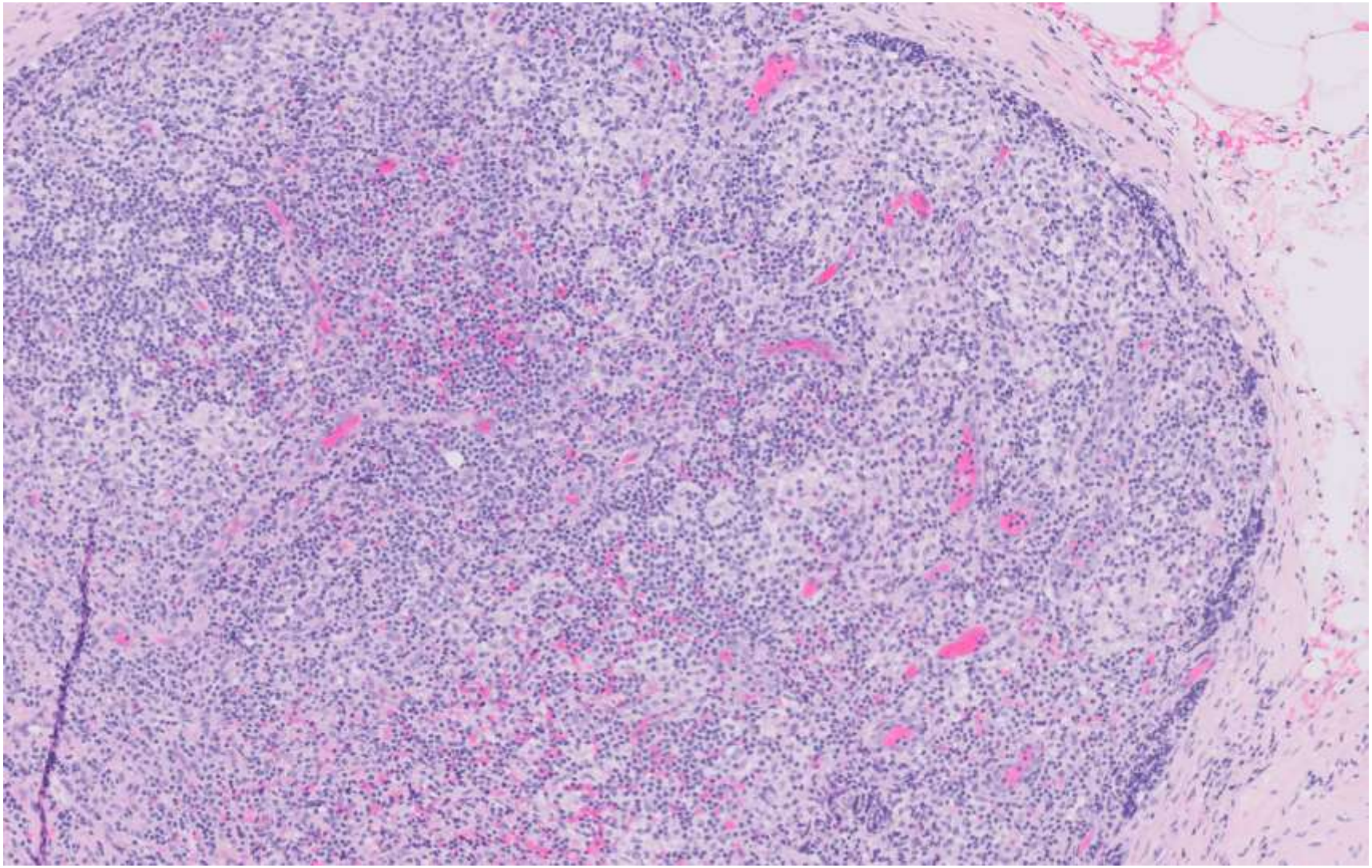
22-0801: Dermatopathic lymphadenitis and proliferation of CD30+ dendritic cells/Langherhans cells [lymph node; heme path]
22-0802: epithelioid sarcoma, proximal type [soft tissue; soft tissue path]
22-0803: peripheral T-cell lymphoma with T follicular helper phenotype and associated EBV-positive Hodgkin/Reed-Sternberg-like cells (lymh node; heme path)
22-0804: splenic marginal zone lymphoma [lymph node; heme path]
22-0805: heterotopic placental nodule [placenta; GYN path]
22-0806: pneutomatosis-like mature teratoma [ovary; GYN path]
22-0807: adenomatoid tumor [gallbladder; GI path]
22-0808: “shoulder” lesion of non-invasive urothelial carcinoma [bladder; GU path]

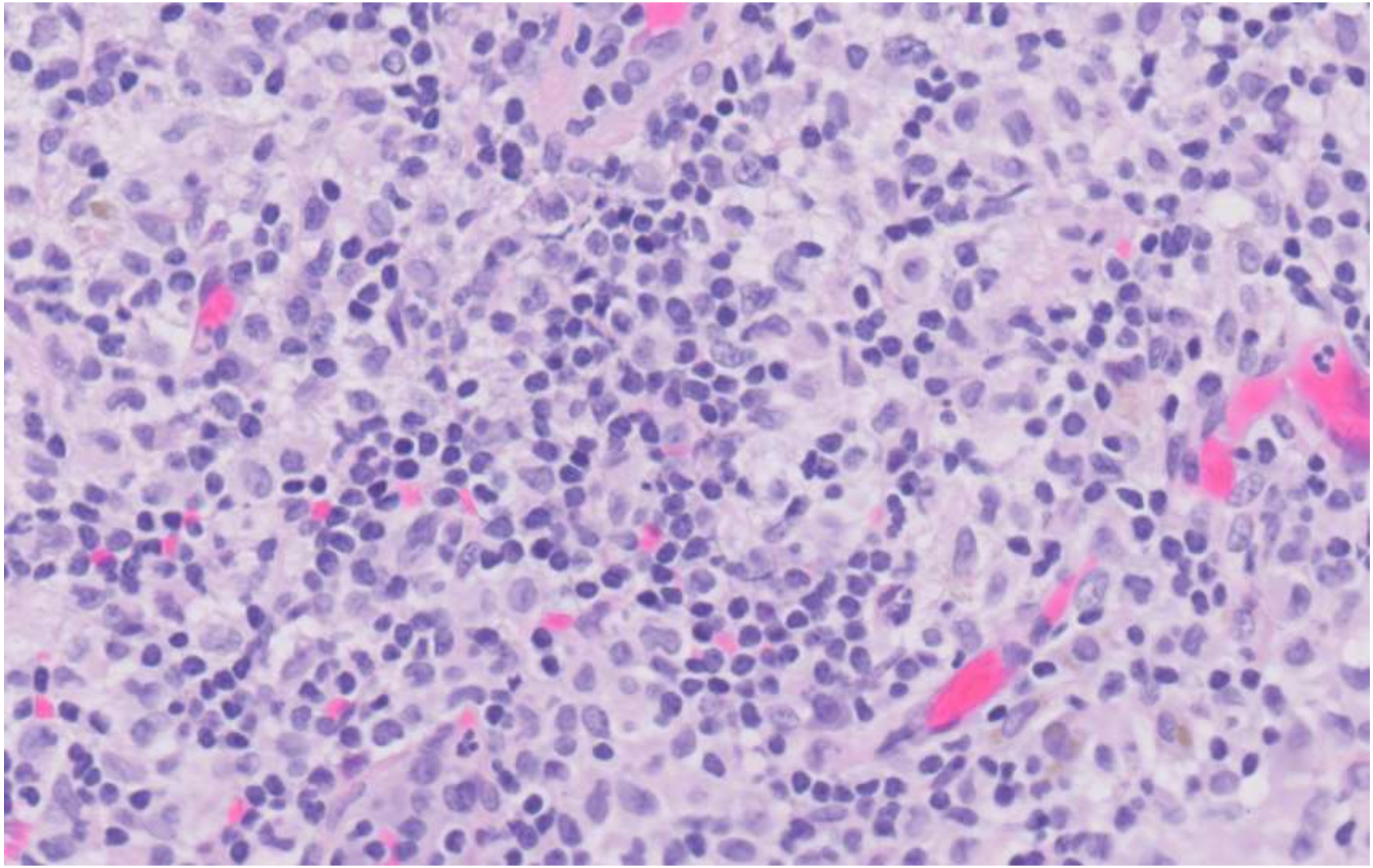
22-0801

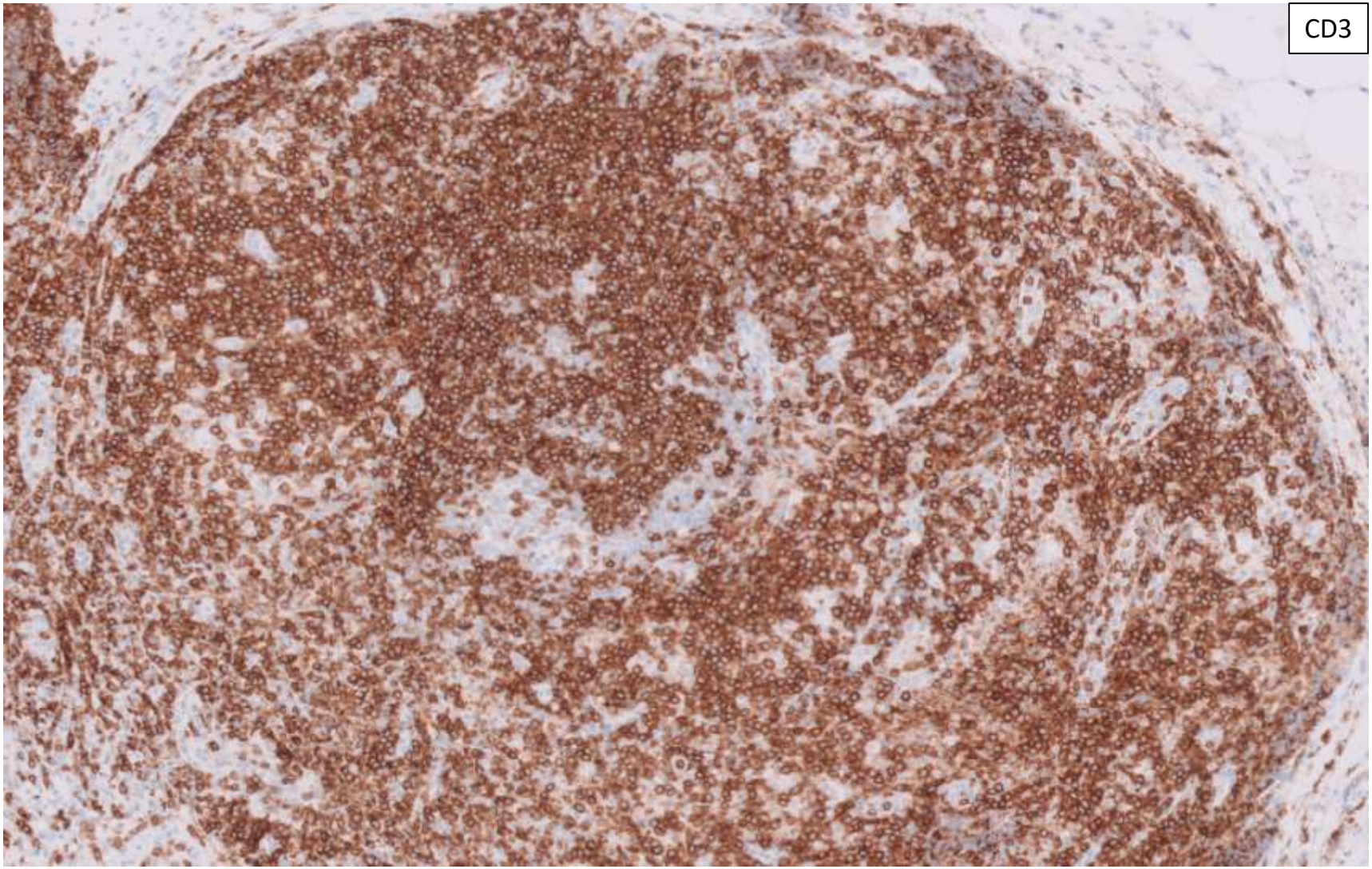
Marietya Lauw/George Xu; Stanford

70ish F with inguinal lymphadenopathy. Flow cytometry detected no immunophenotypic abnormalities. Right groin lymph node submitted.





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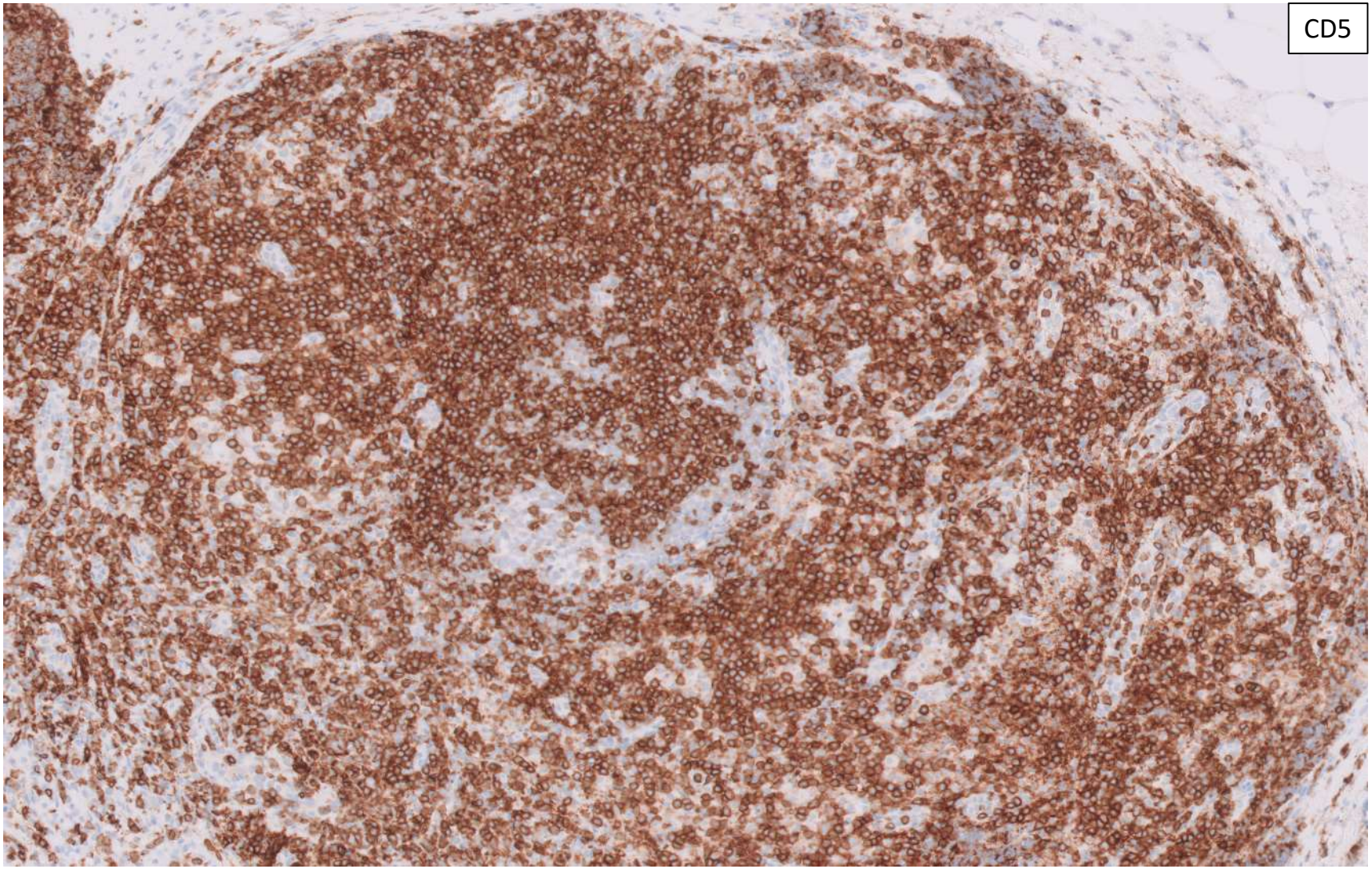
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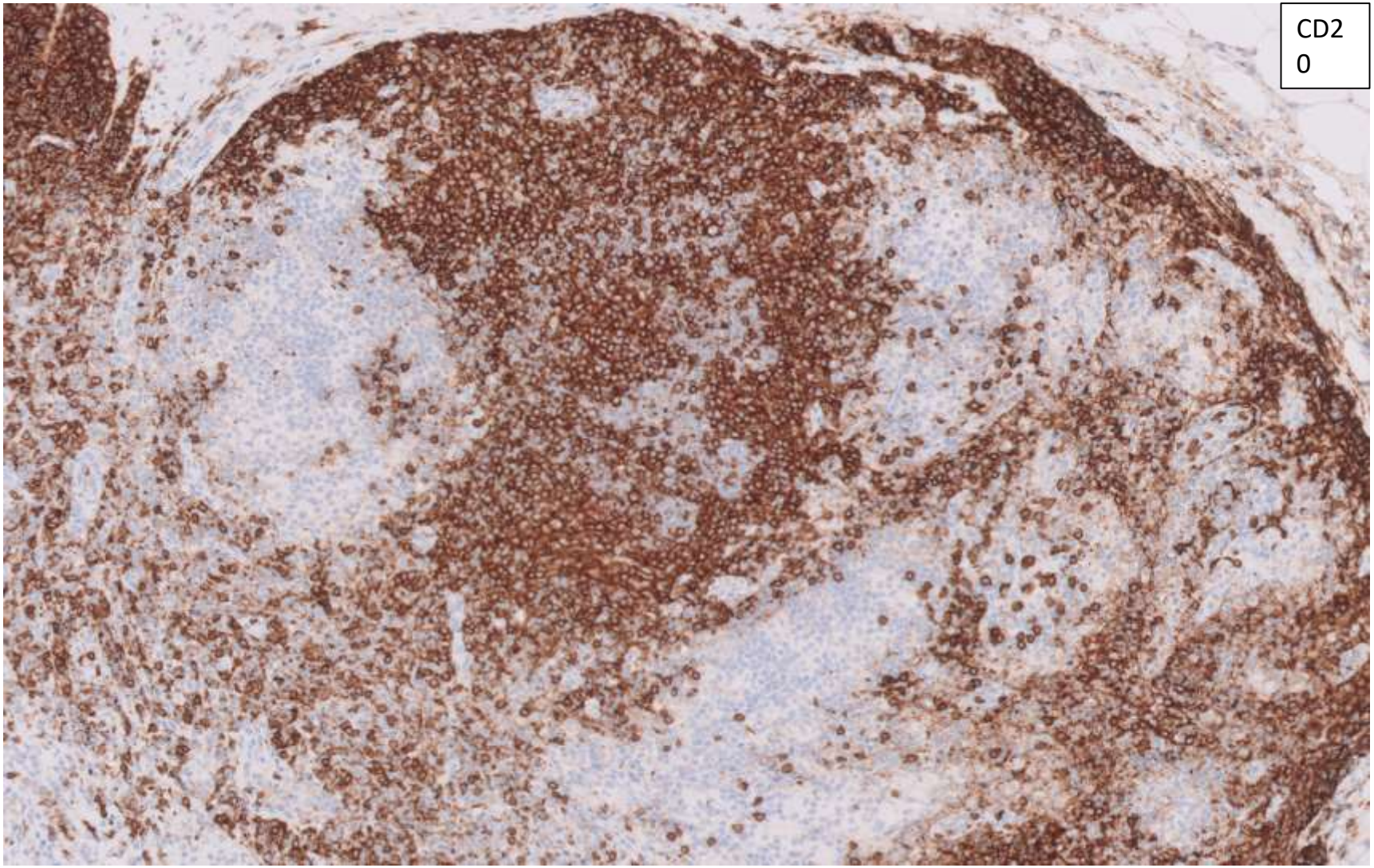
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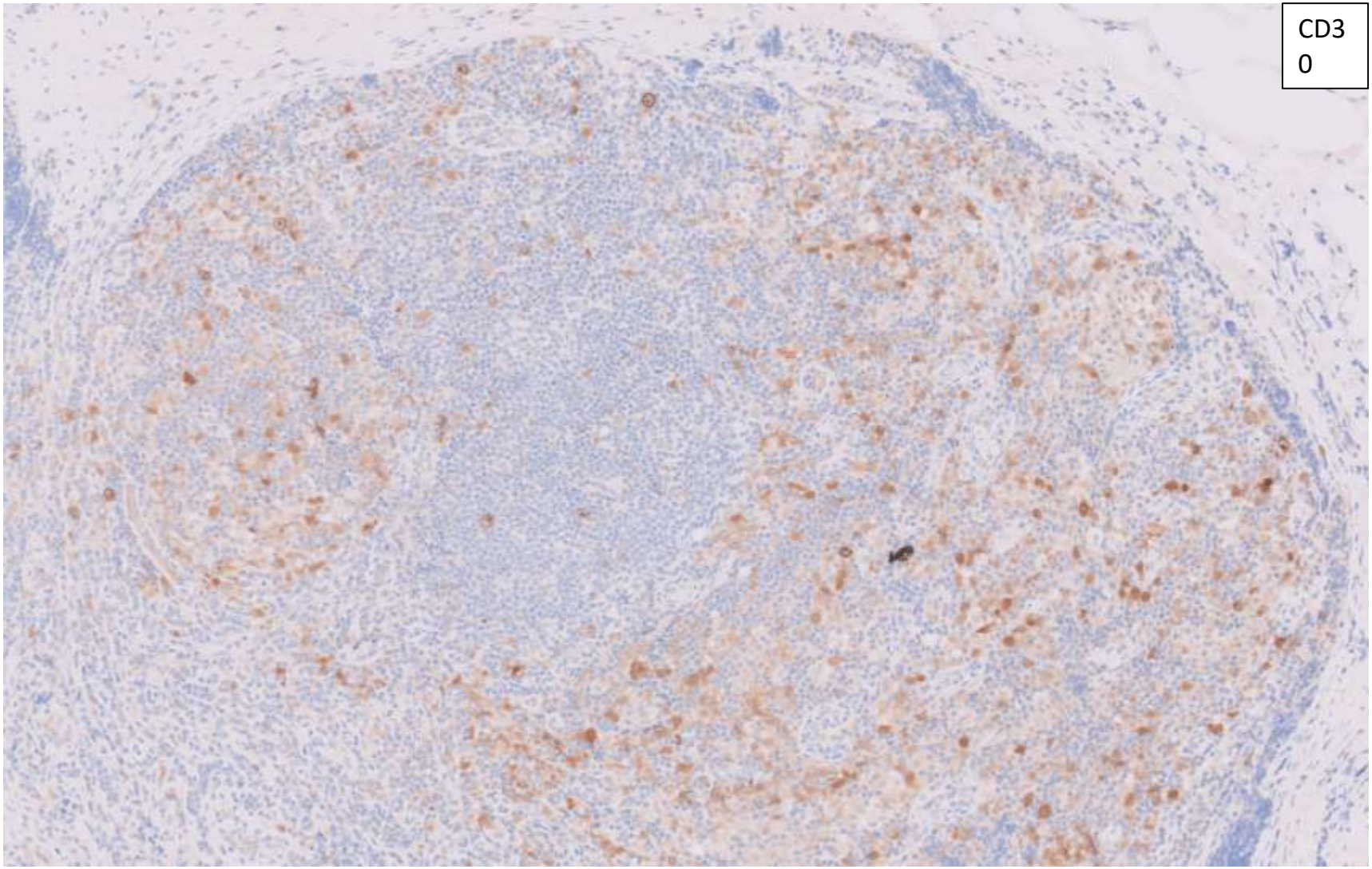
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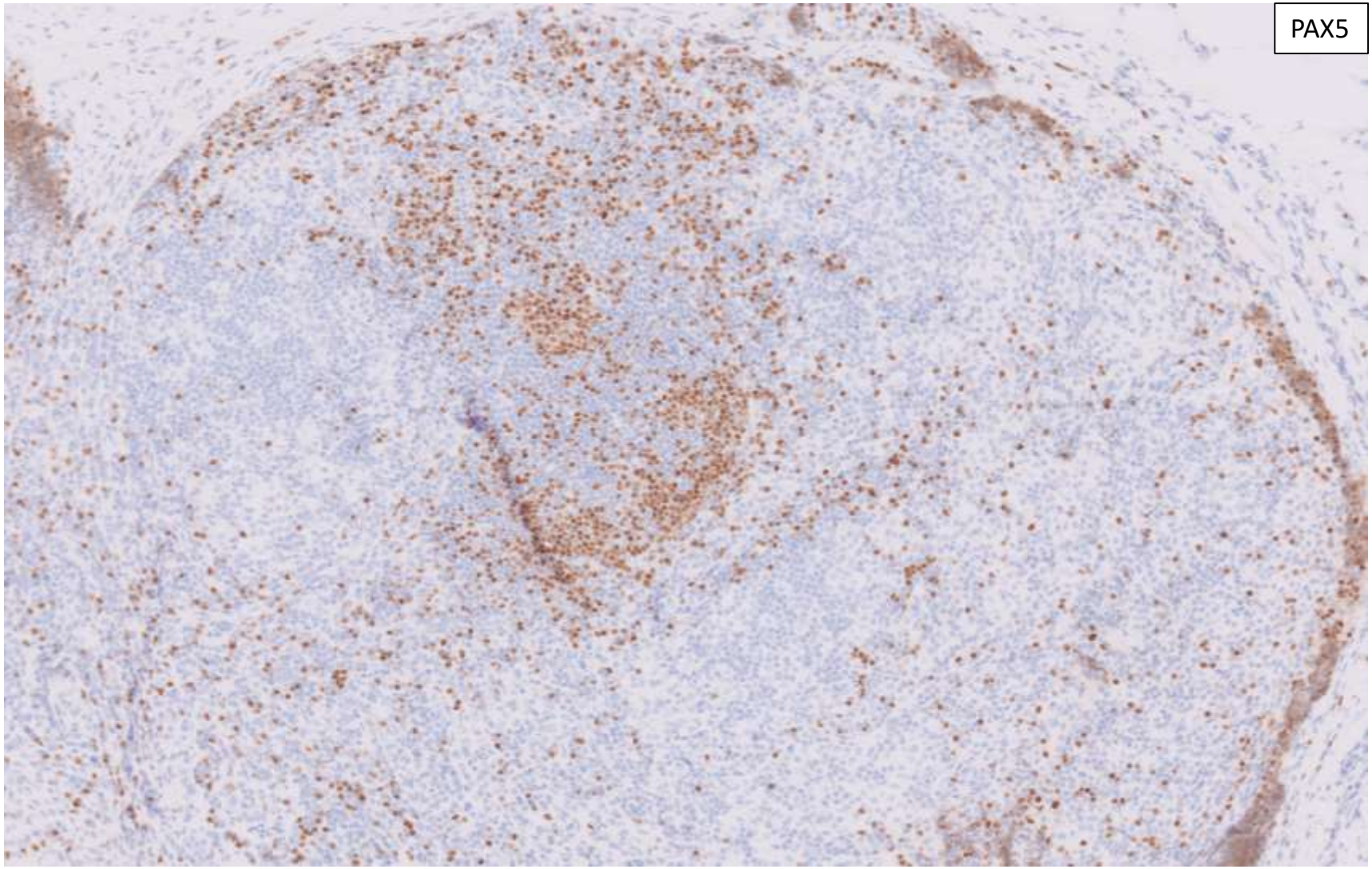
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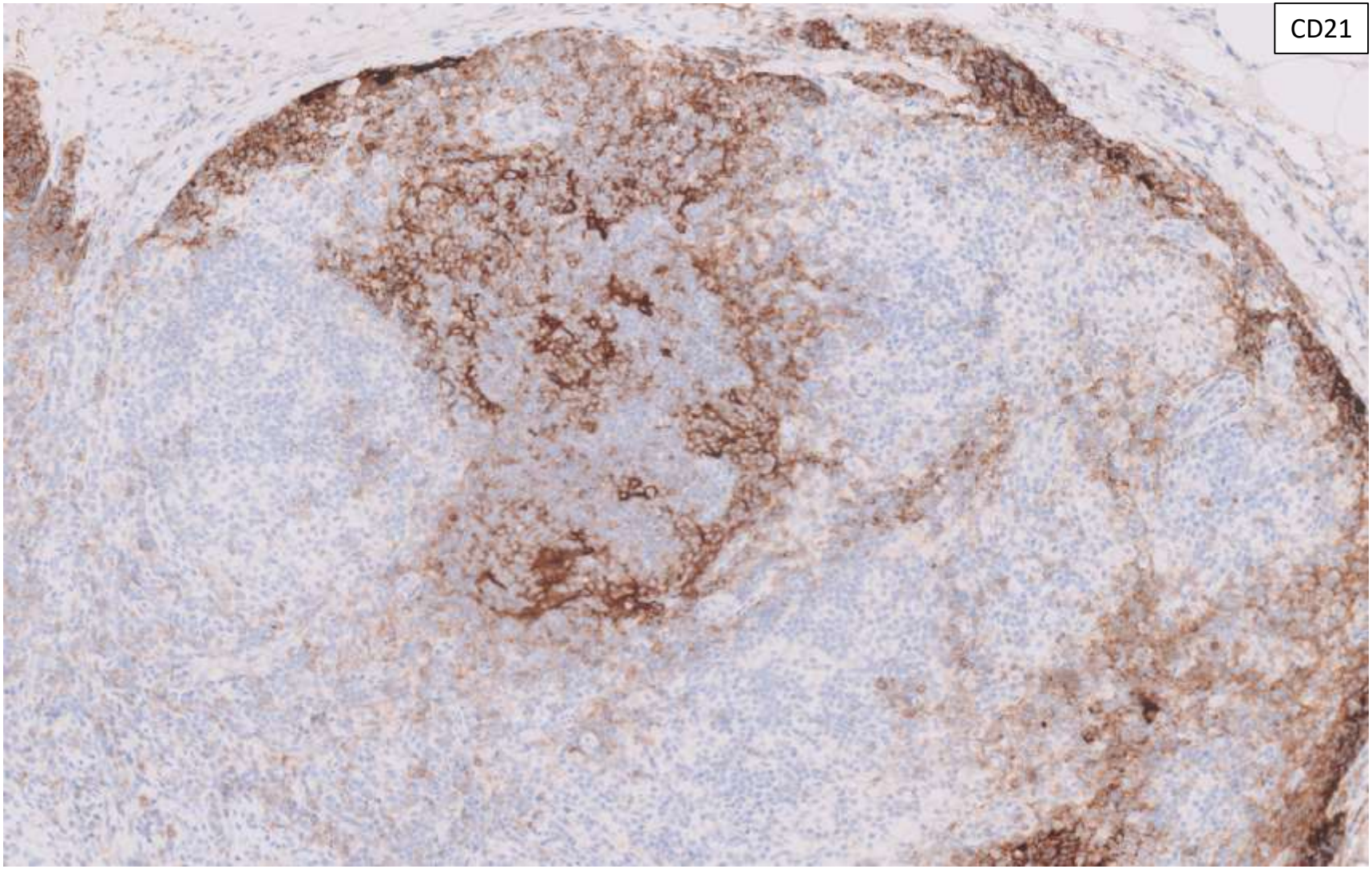
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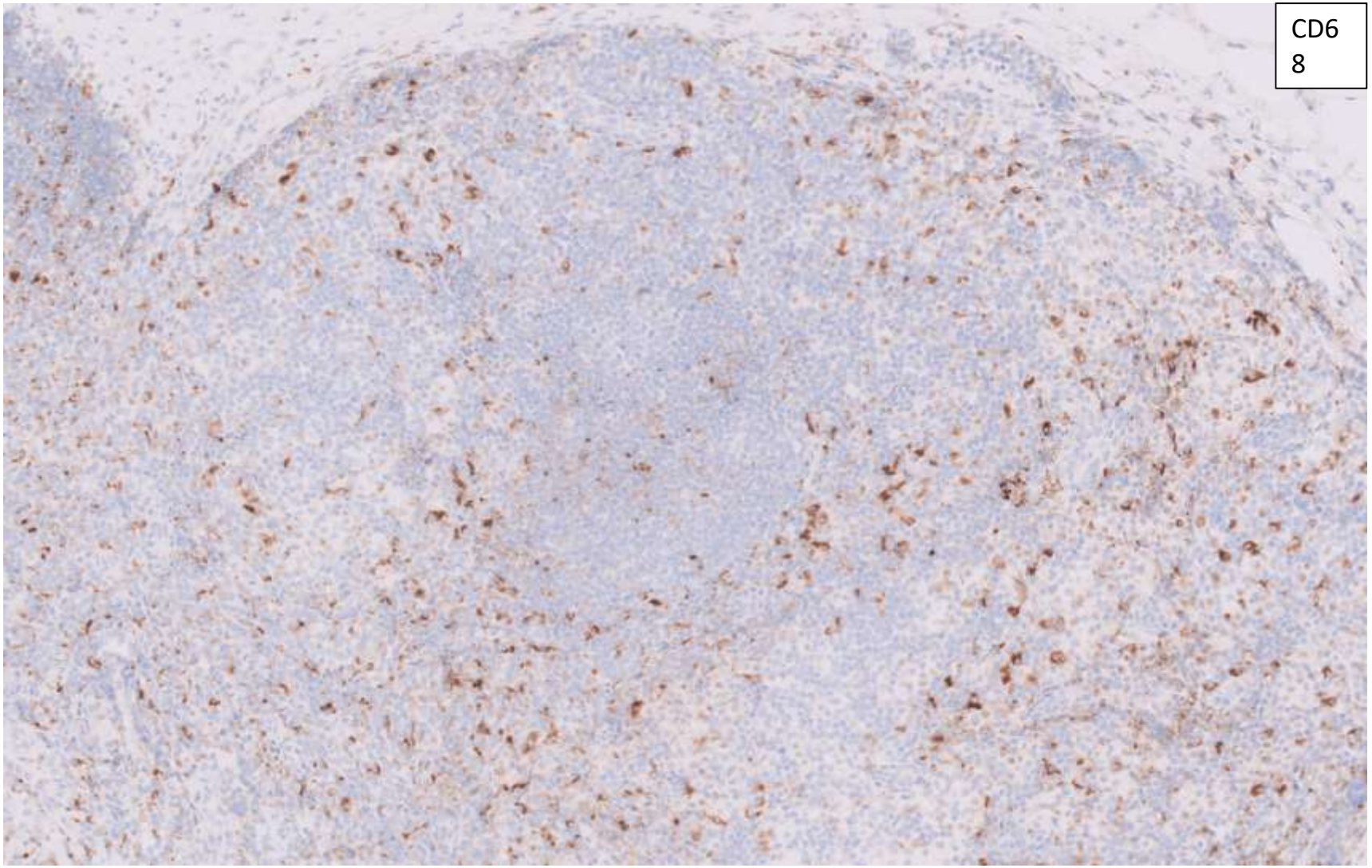
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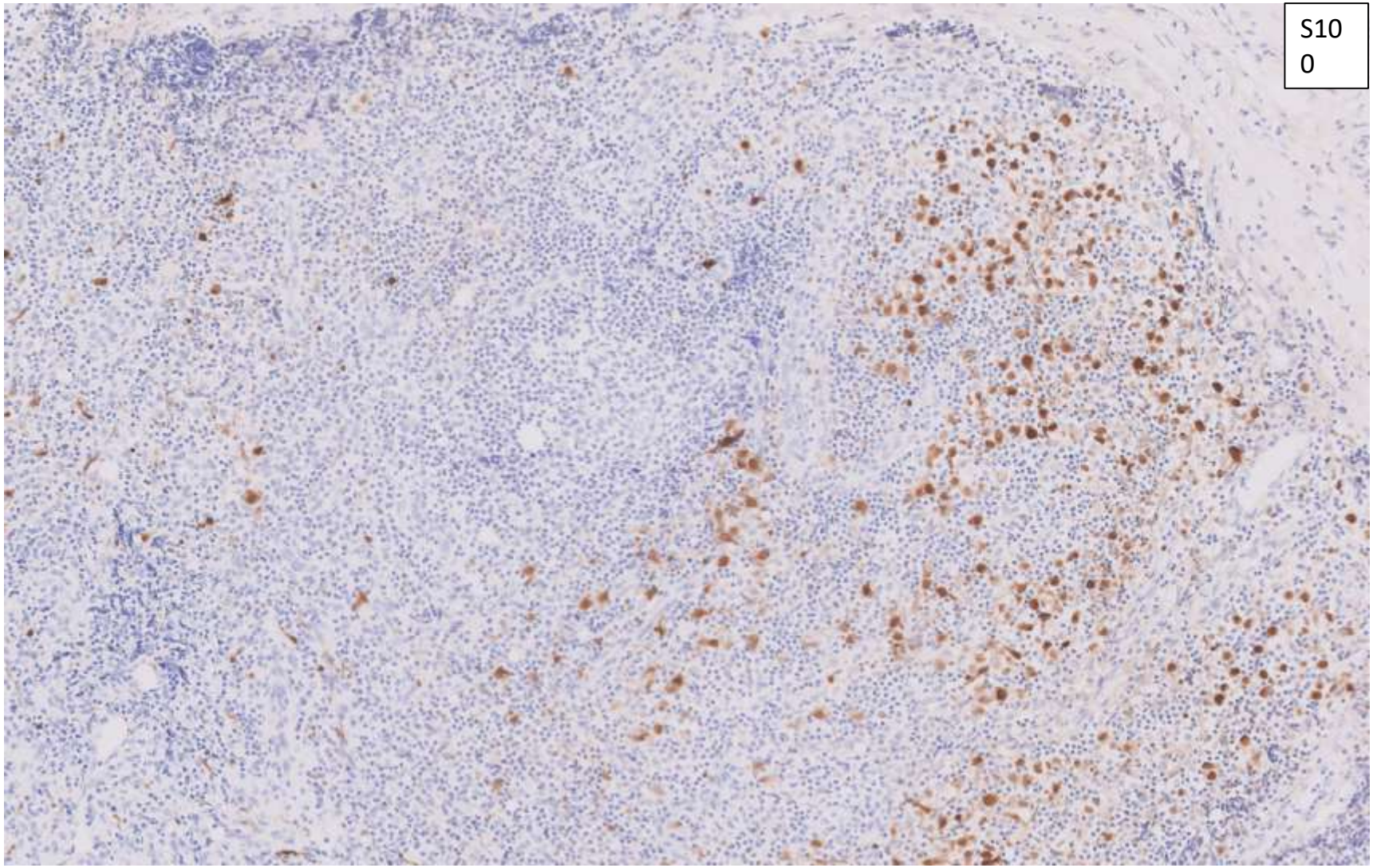
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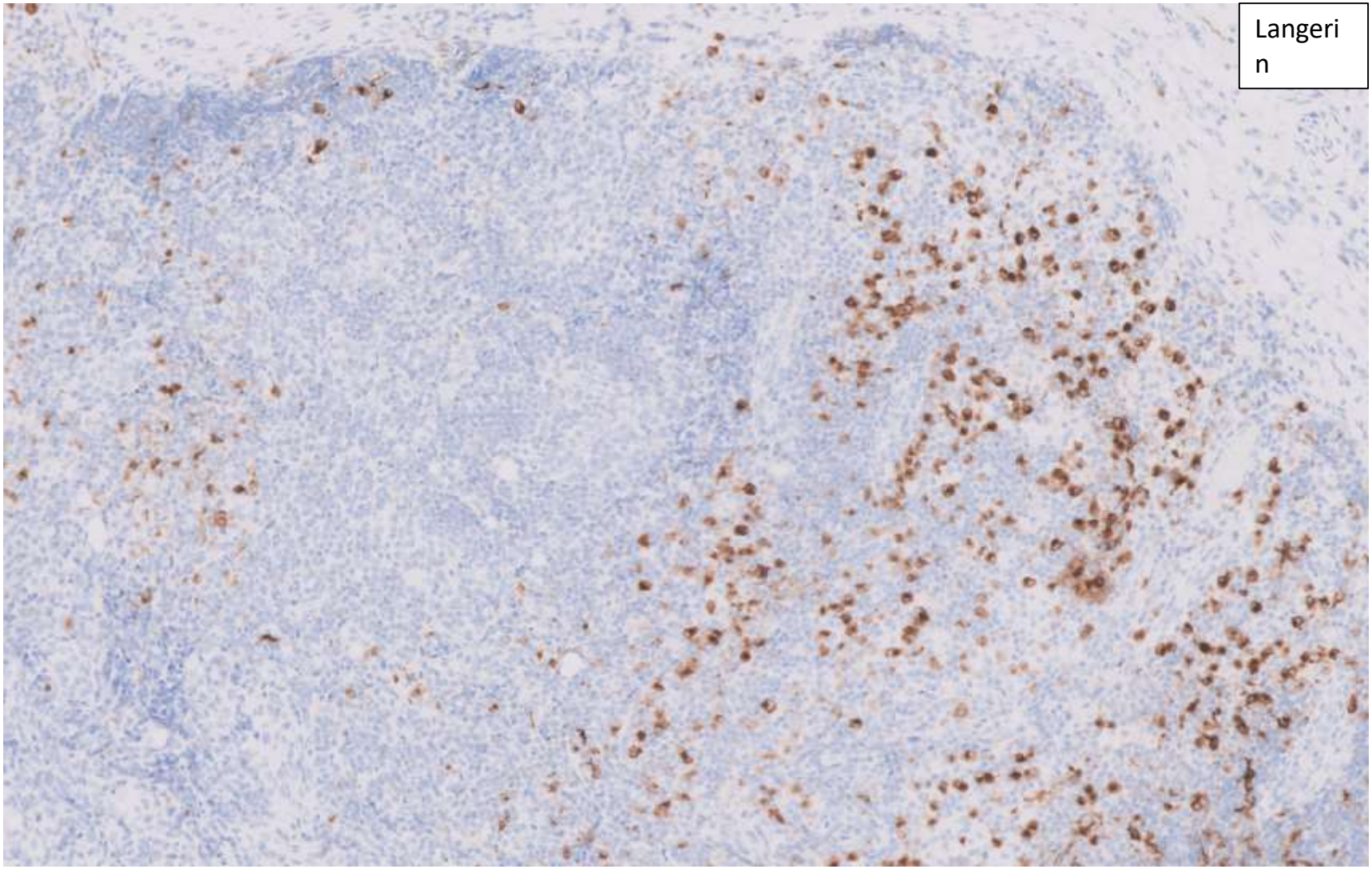
Langeri
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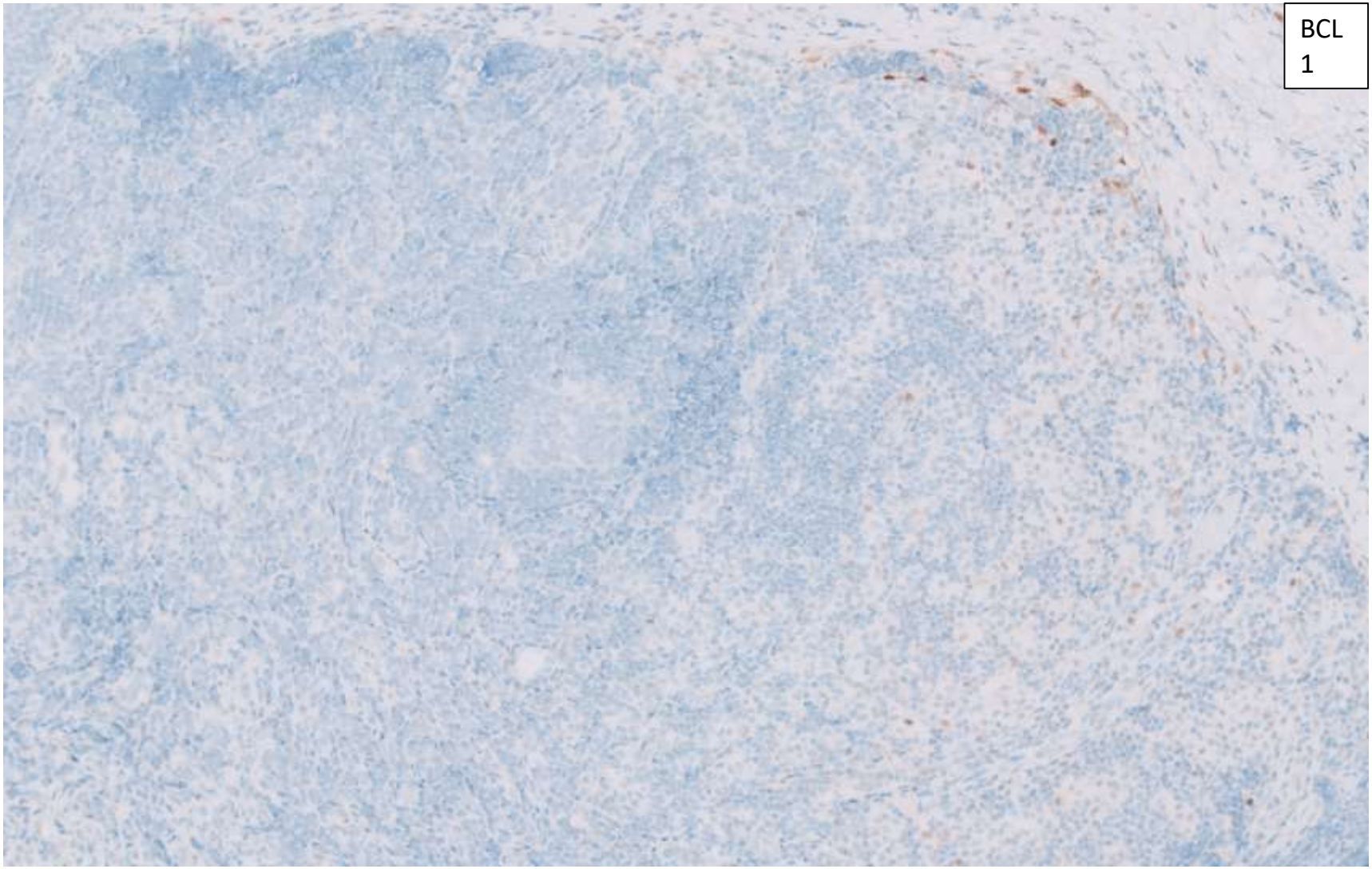
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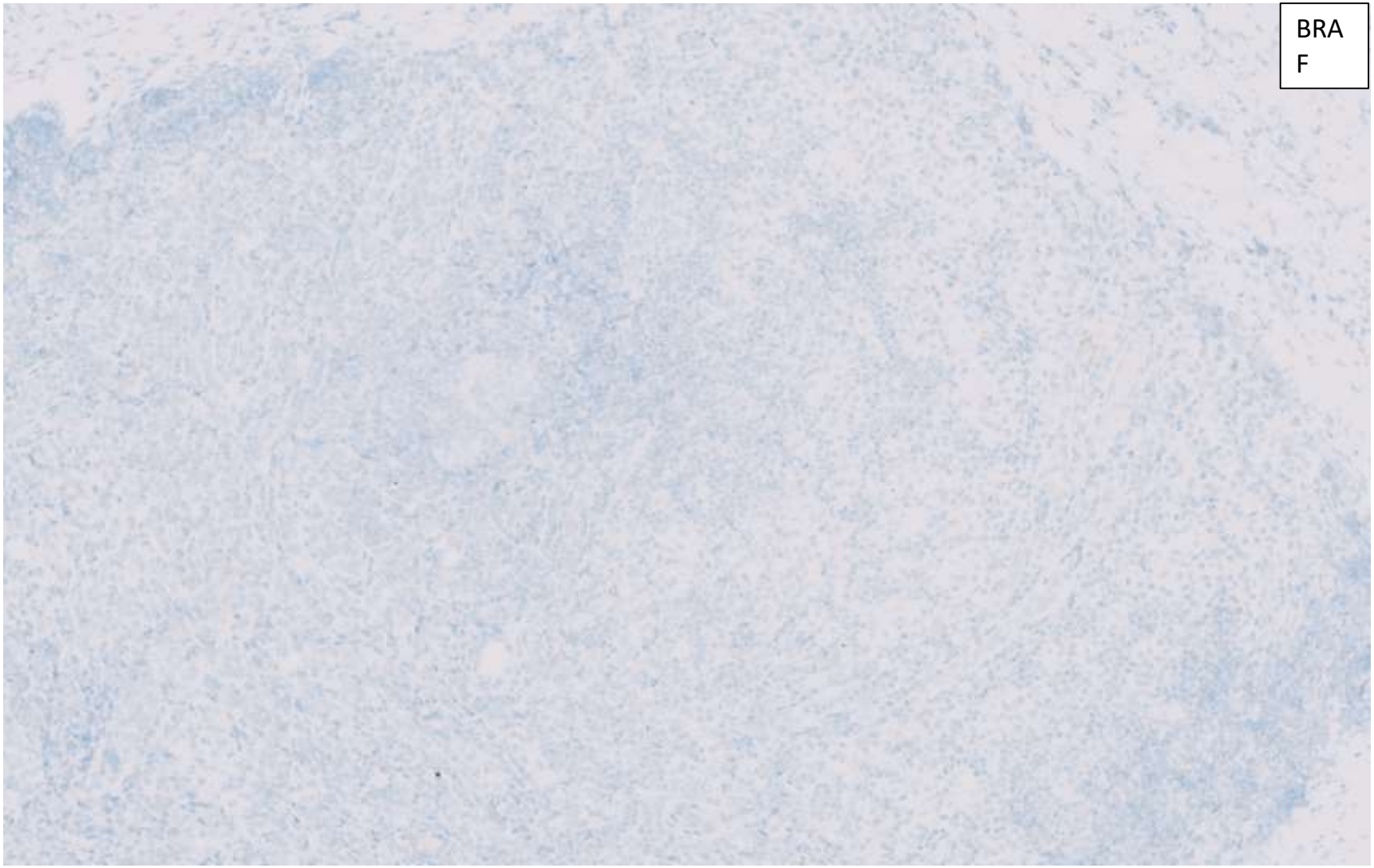
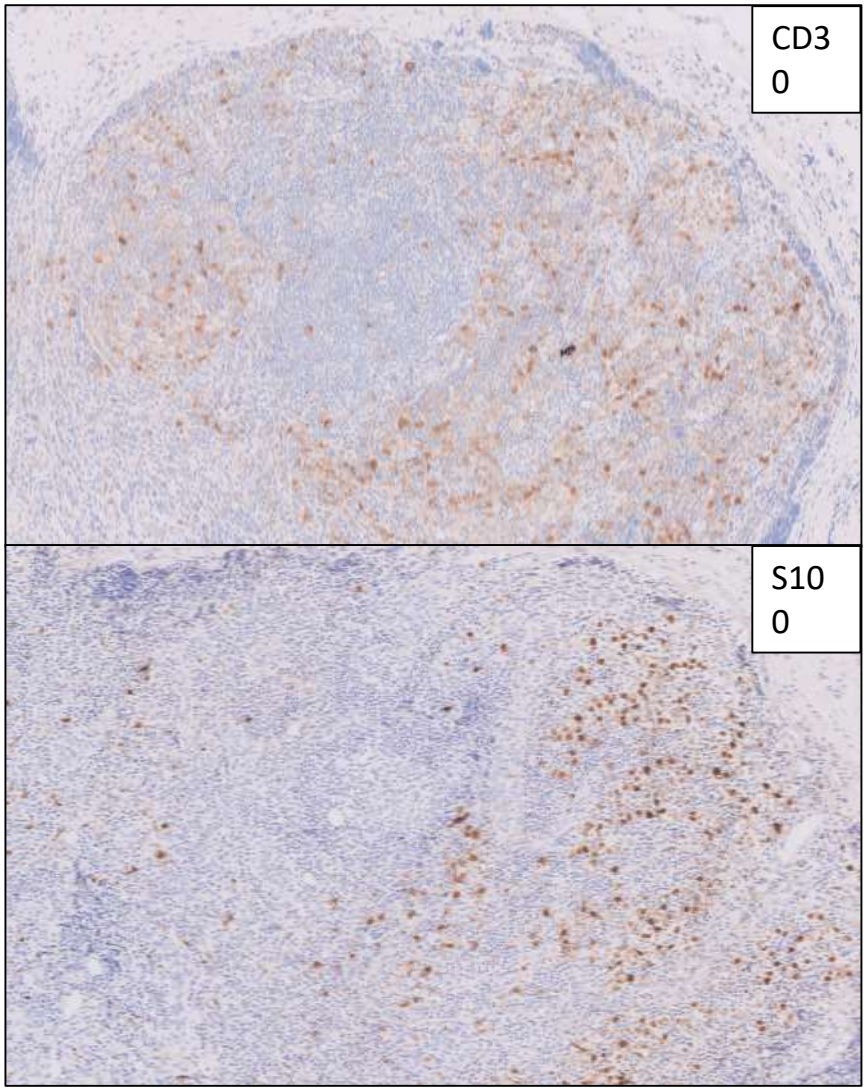

BRA
F

Differential diagnosis

- T-cell lymphoma (e.g. involvement by cutaneous CD30-positive T-cell lymphoma, ALCL)
- Classic Hodgkin lymphoma
- Dermatopathic lymphadenitis with proliferation of CD30+ Langerhans cells/dendritic cells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S10
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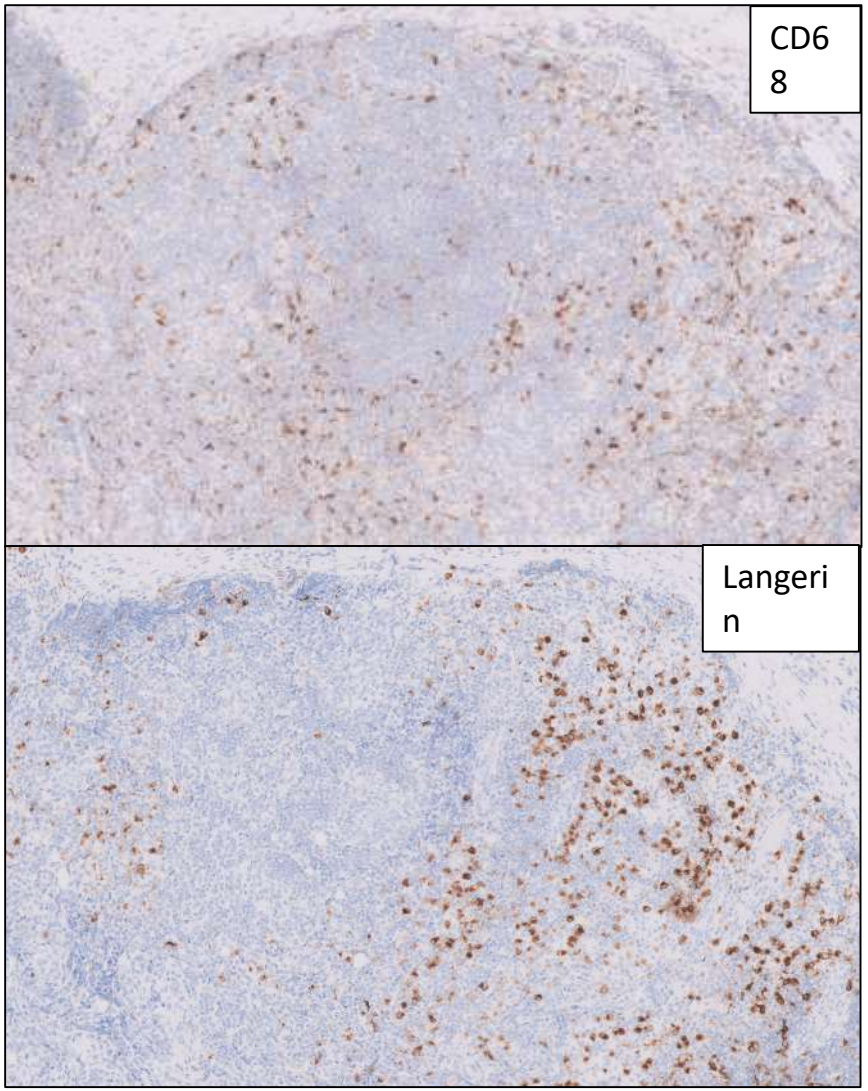
CD6
8
Langeri
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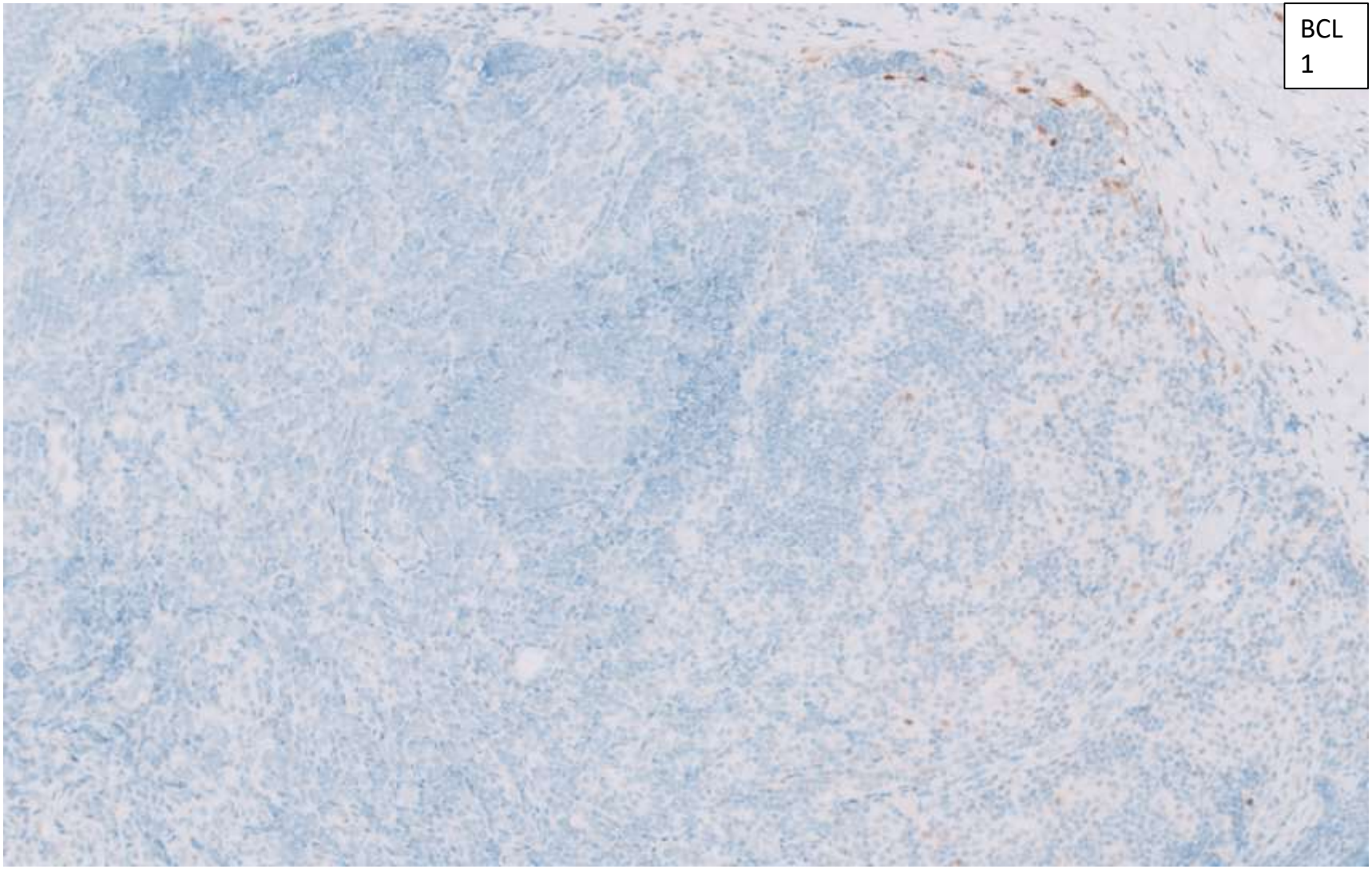
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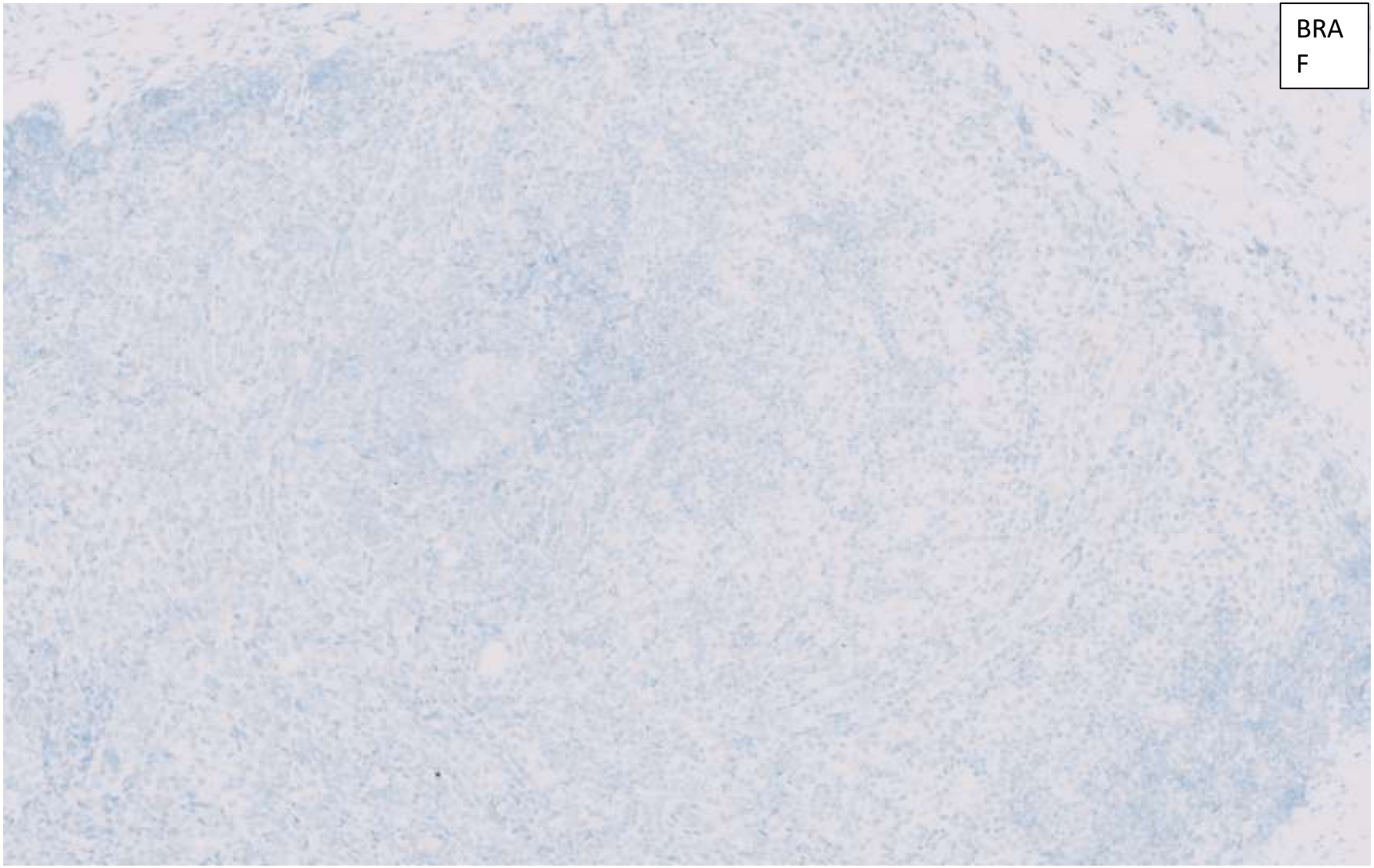

BRA
F

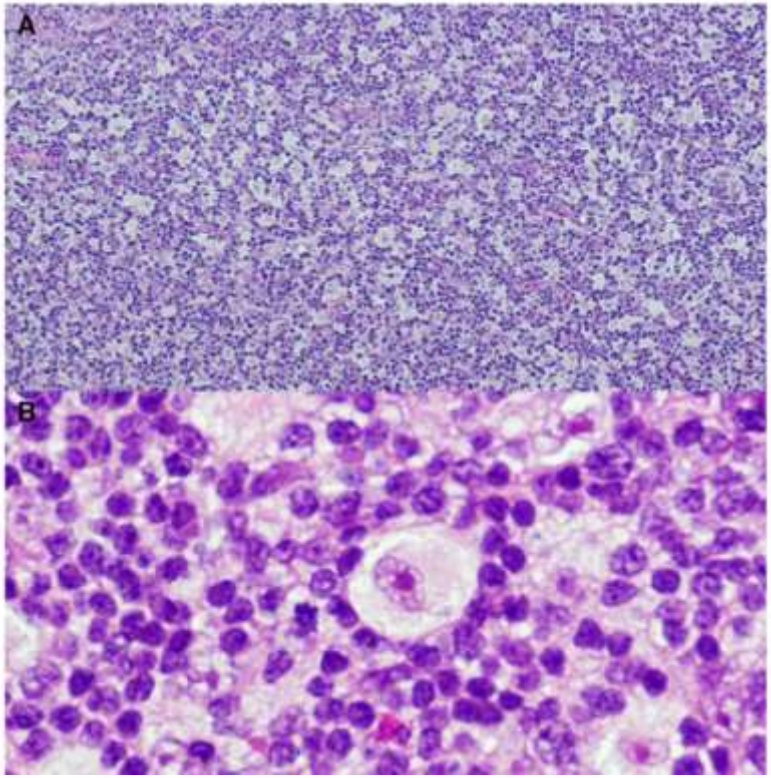
Differential diagnosis

- T-cell lymphoma (e.g. involvement by cutaneous CD30-positive T-cell lymphoma, ALCL)
- Classic Hodgkin lymphoma
- **Dermatopathic lymphadenitis with proliferation of CD30+ Langerhans cells/dendritic cells**

Lymphoid Hyperplasia with Atypical Dendritic/Langerhans Cell Proliferation Mimicking Hodgkin Lymphoma

Morphology:

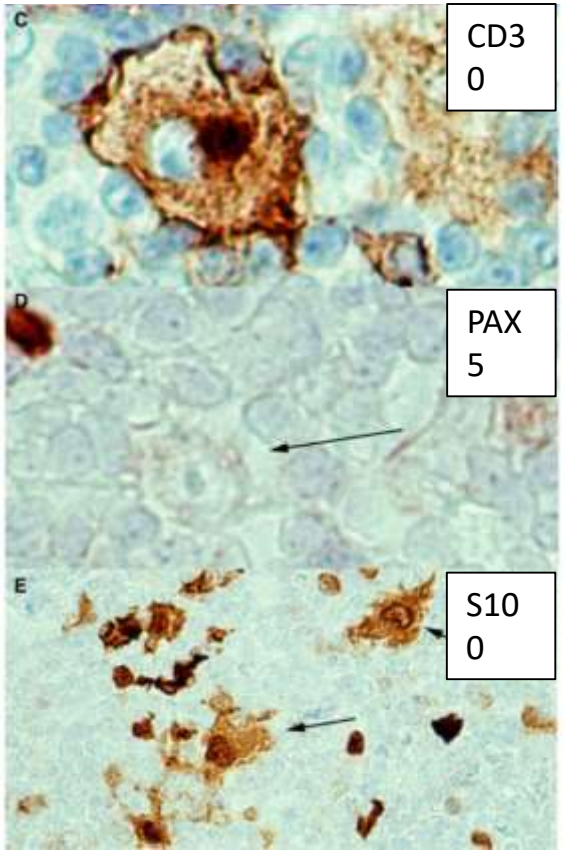
- Diffuse paracortical expansion with small lymphocytes, eosinophils, histiocytes, immunoblasts, and plasma cells, and admixed scattered large cells with abundant pale eosinophilic cytoplasm and focal emperipolesis
- The atypical cells had irregular, sometimes lobulated nuclei, with finely dispersed chromatin, and variably prominent nucleoli



Jayalakshmi et al. 2019 Apr; 74(5): 797–799.

Lymphoid Hyperplasia with Atypical Dendritic/Langerhans Cell Proliferation Mimicking Hodgkin Lymphoma

- IHC:
  - Positive: S100 and CD30
  - Negative: CD15, CD23, PAX5, and EBER
- Not histiocytic or dendritic neoplasm:
  - Atypical cells are widely scattered
  - Negative for mutated BRAF and BCL1



Jayalakshmi et al. 2019 Apr; 74(5): 797–799.

Take home message

- On rare occasions, CD30 expression can be seen in reactive Langerhans cells/dendritic cells
- IHC will help in the differential diagnosis of reactive versus lymphoma

References

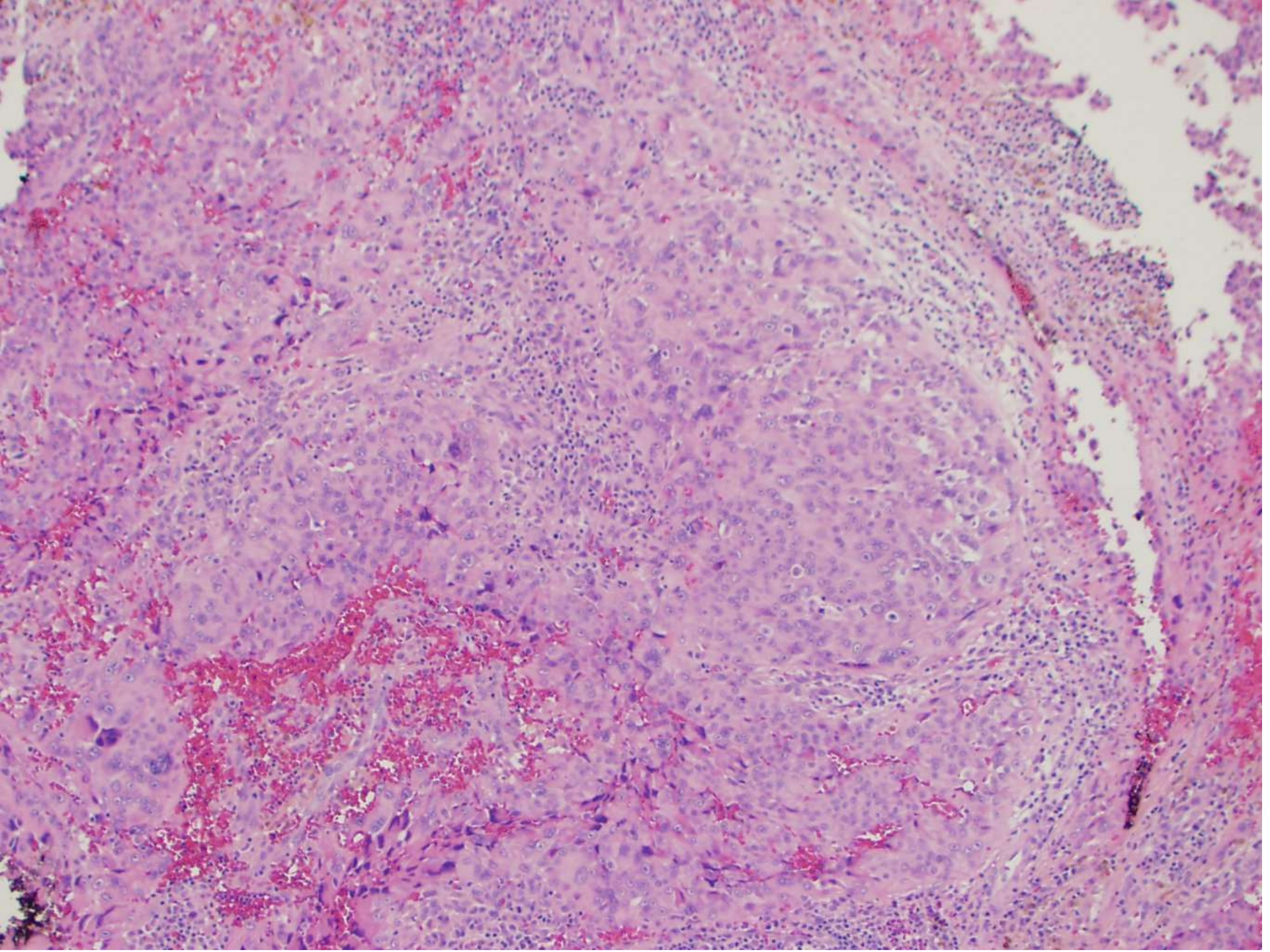
1. Jayalakshmi P Balakrishna, Mark Raffeld, Elaine S Jaffe, and Stefania Pittaluga. Lymphoid hyperplasia with atypical dendritic/Langerhans cell proliferation mimicking Hodgkin lymphoma. Histopathology. 2019 Apr; 74(5): 797–799. PMID: 30565719

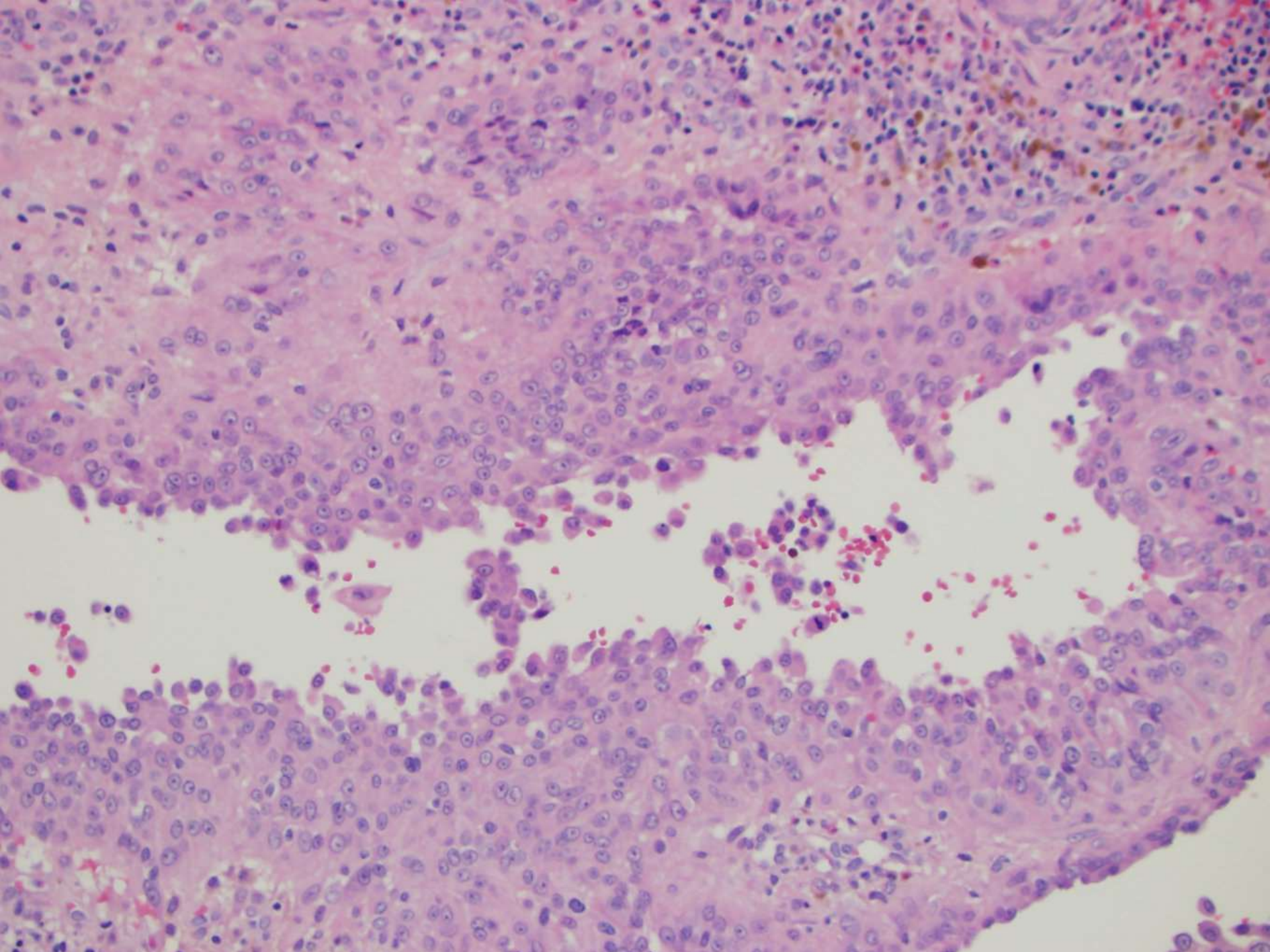
2. Andreesen R, Brugger W, Löhr GW, Bross KJ. Human macrophages can express the Hodgkin's cell-associated antigen Ki-1 (CD30). Am J Pathol. 1989 Jan;134(1):187-92. PMID: 2536522; PMCID: PMC1879544.

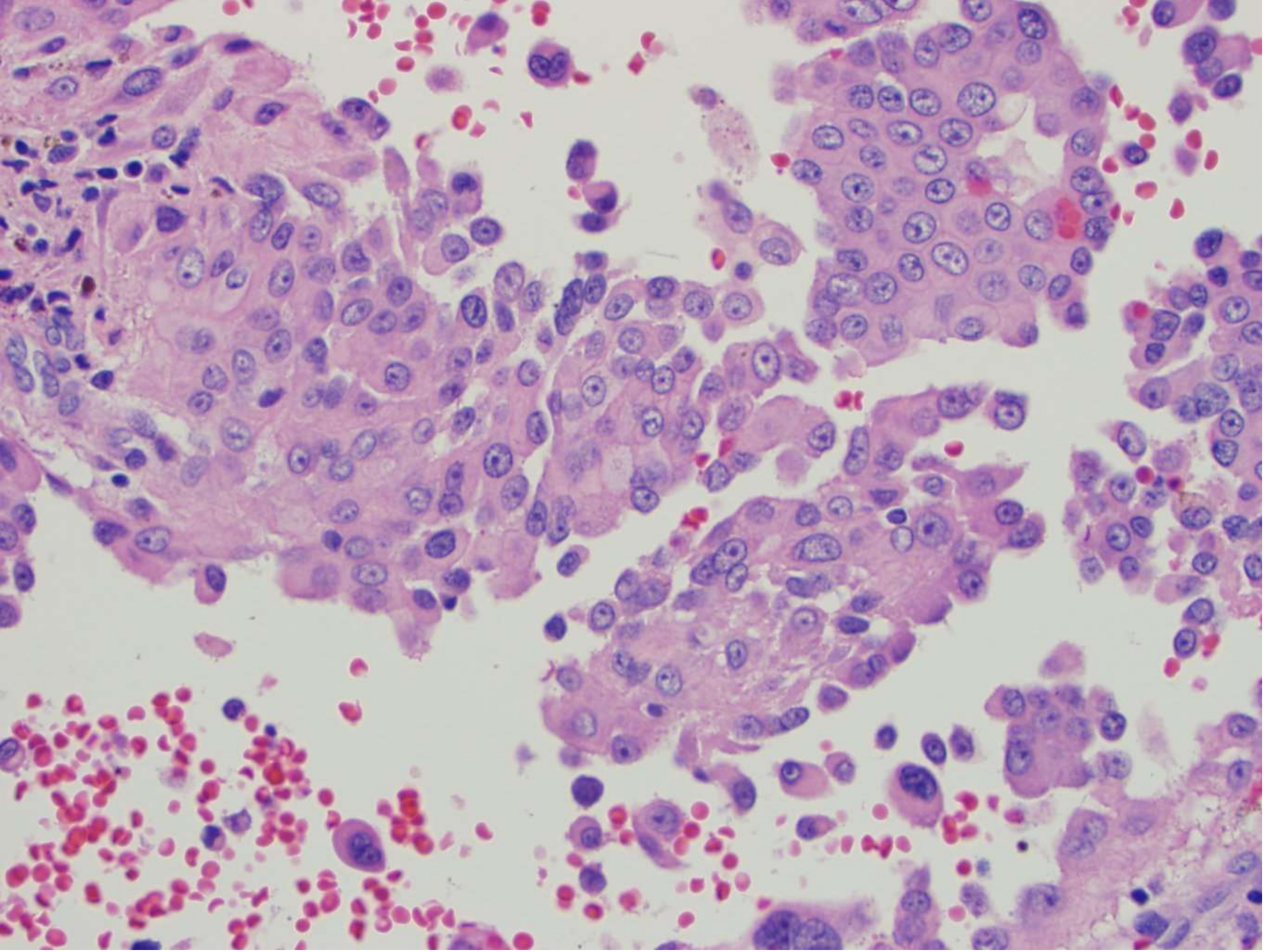
22-0802

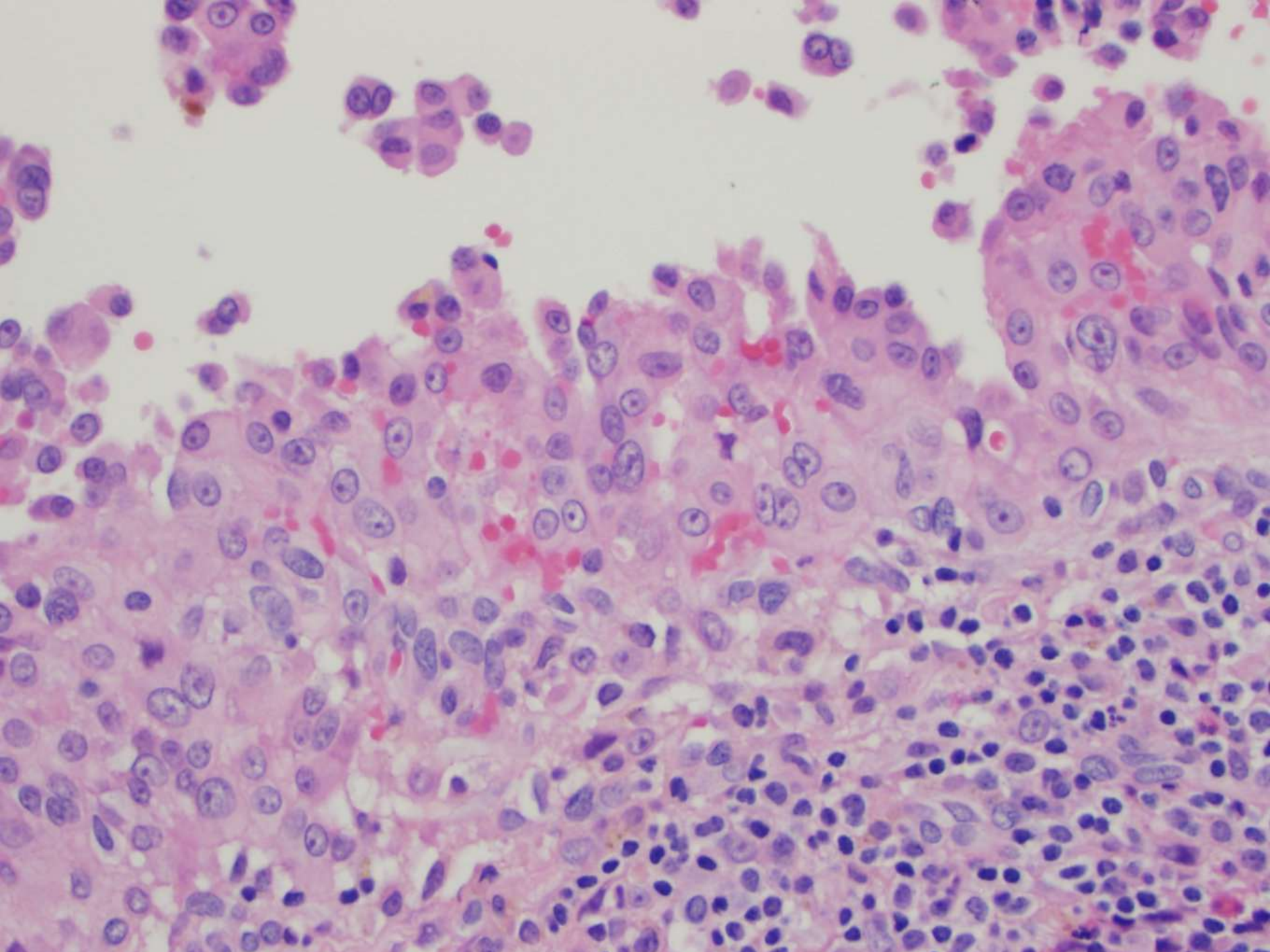
Greg Rumore; Kaiser Diablo

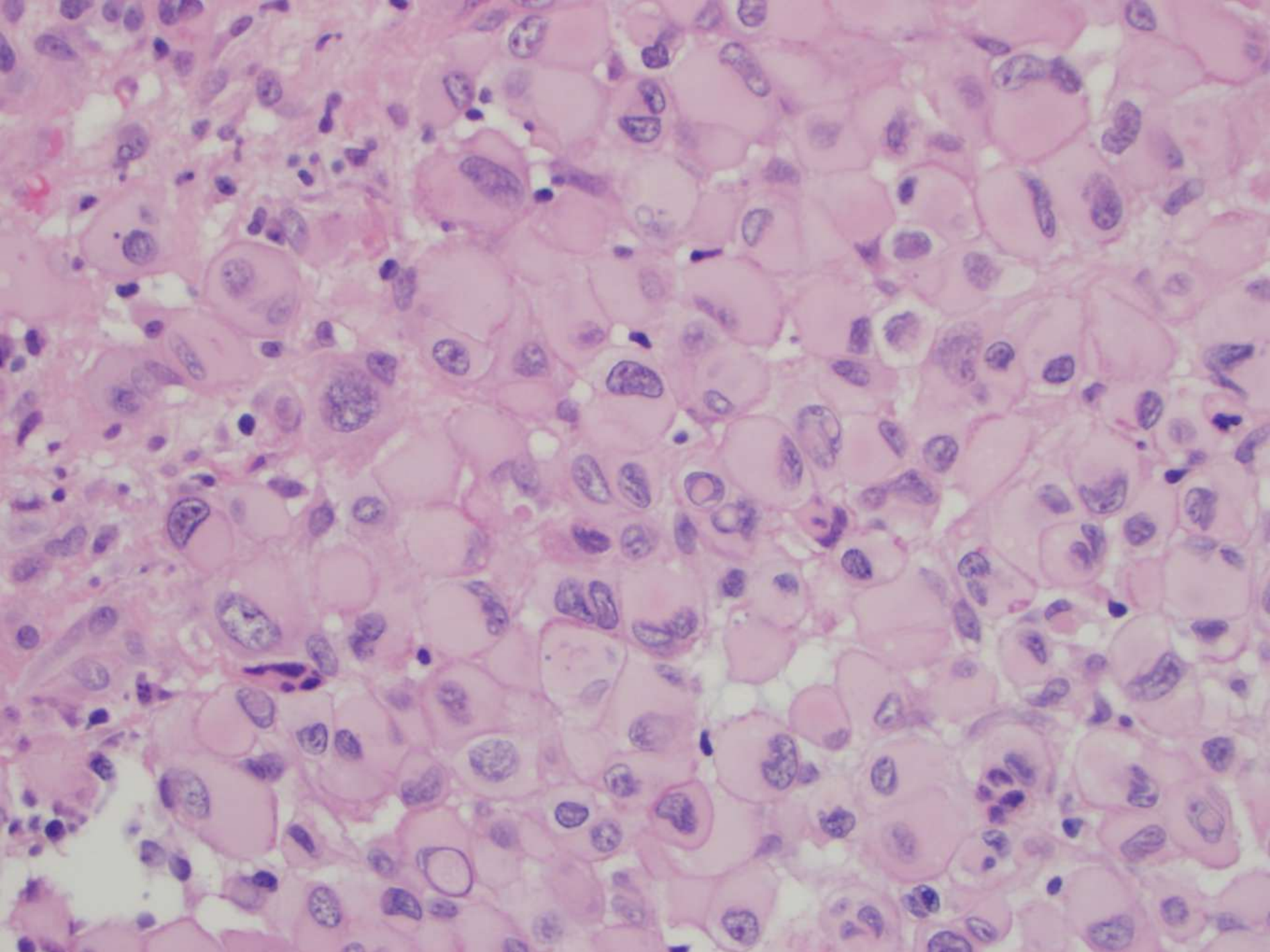
20ish F with vulvar cyst/mass.

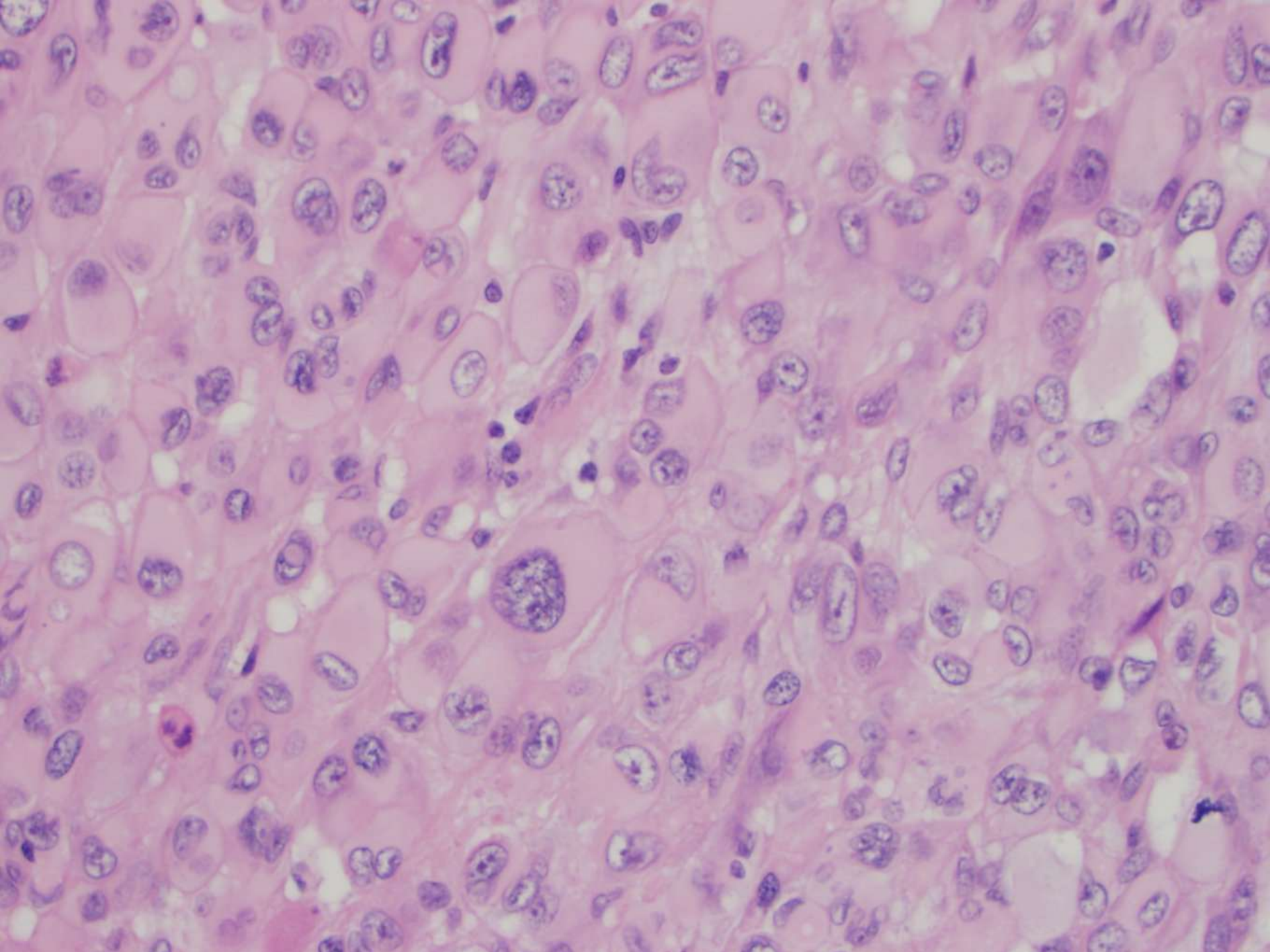


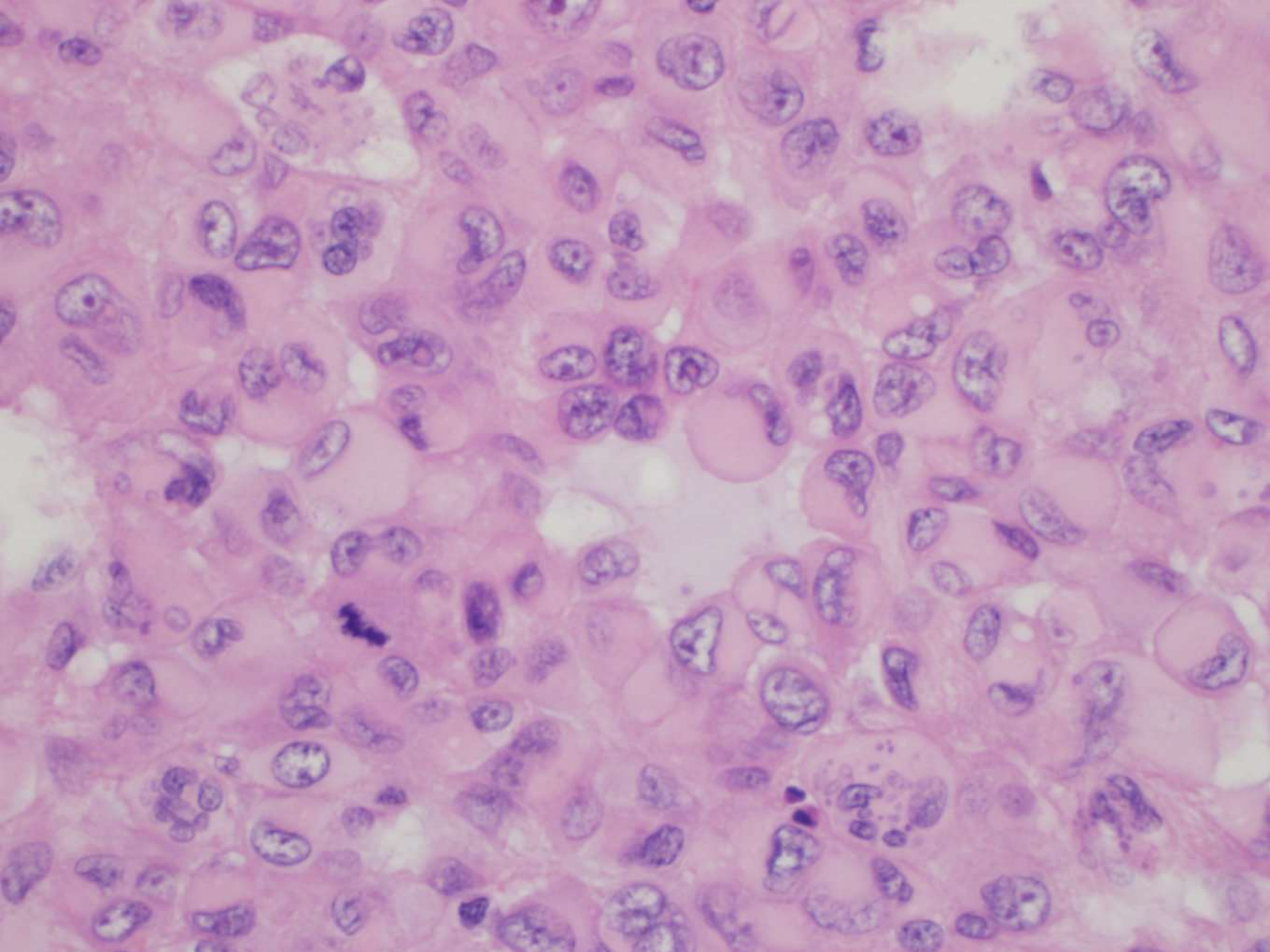




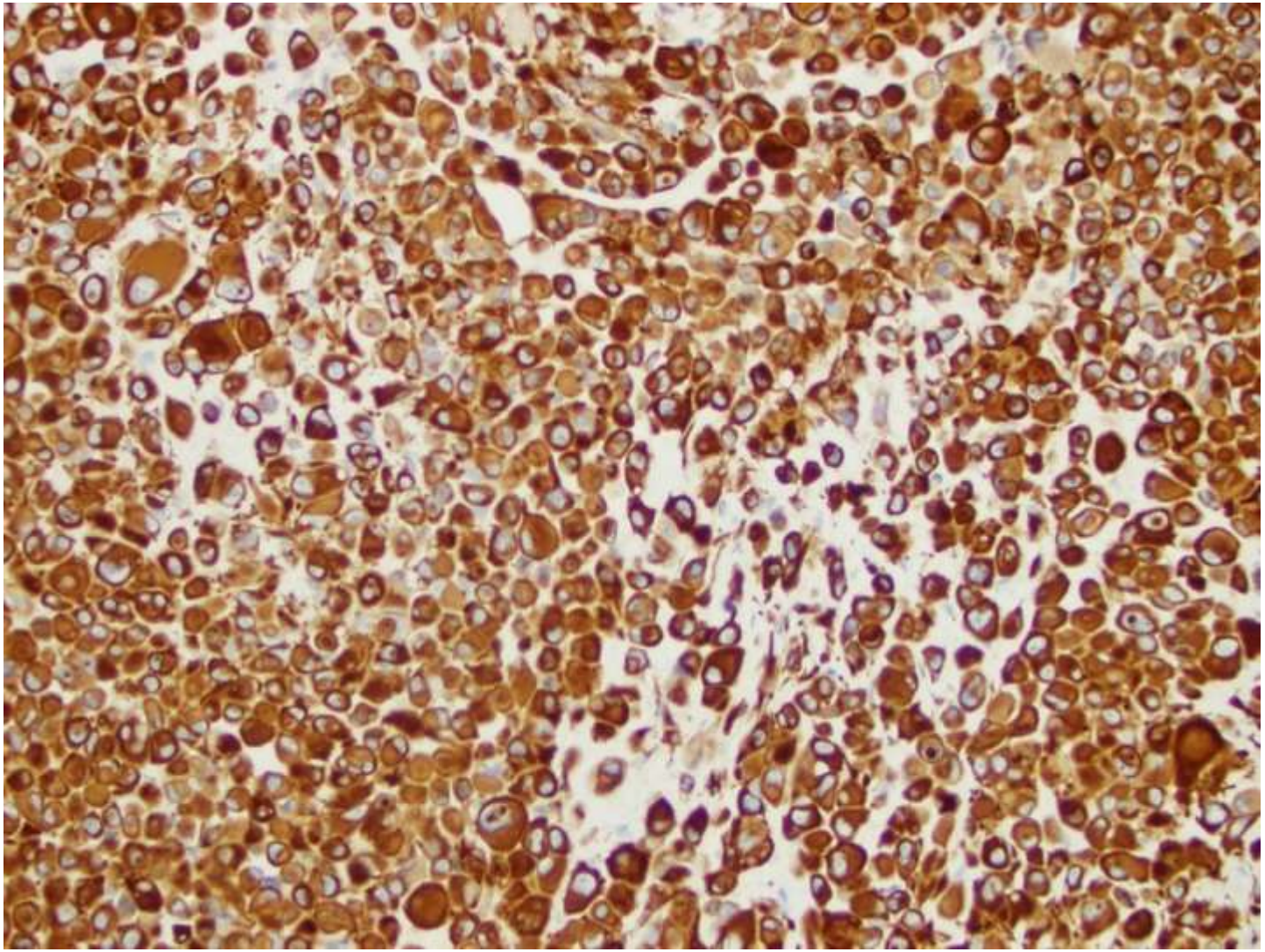




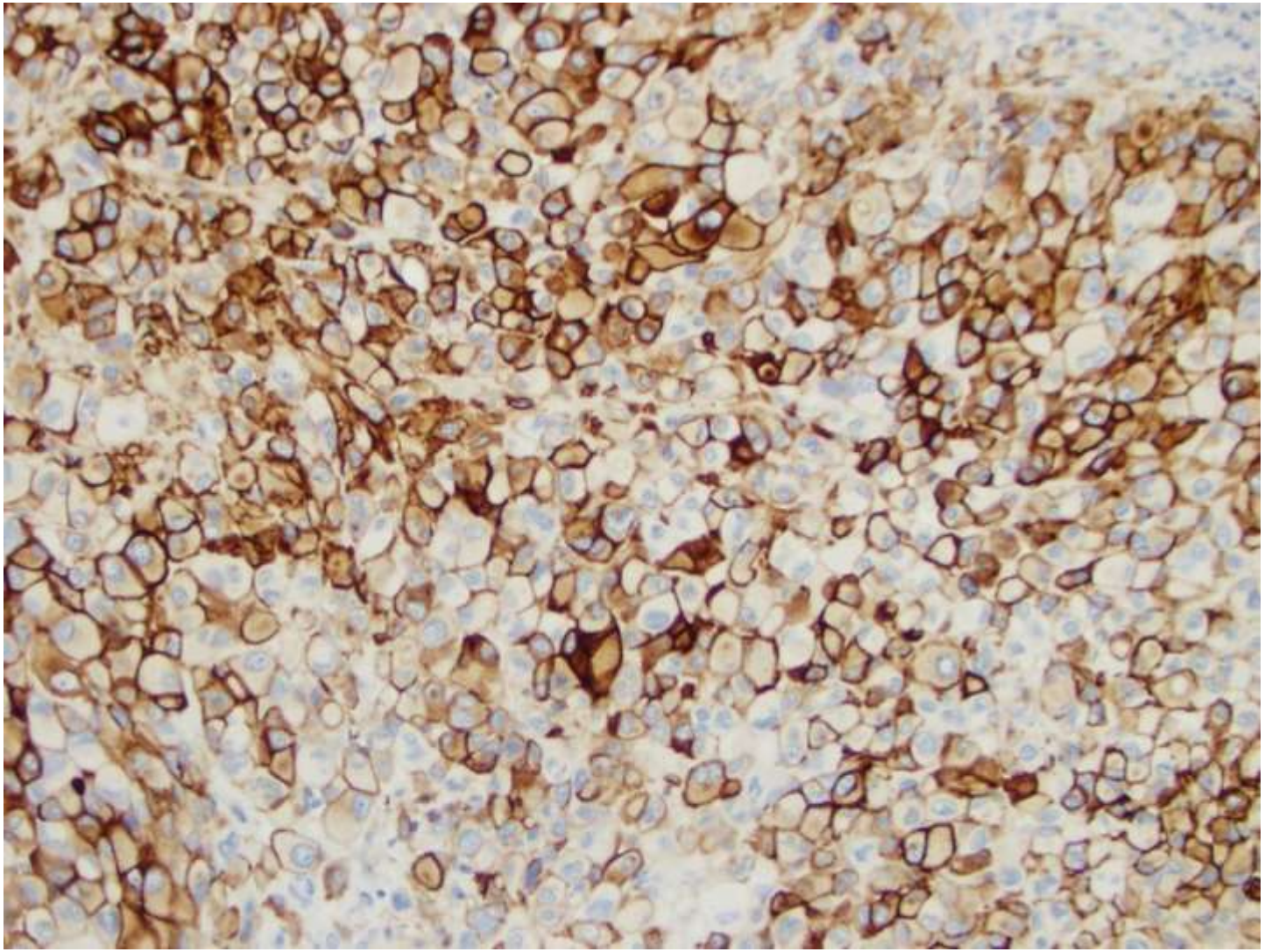




PANCYTOKERATIN



EMA



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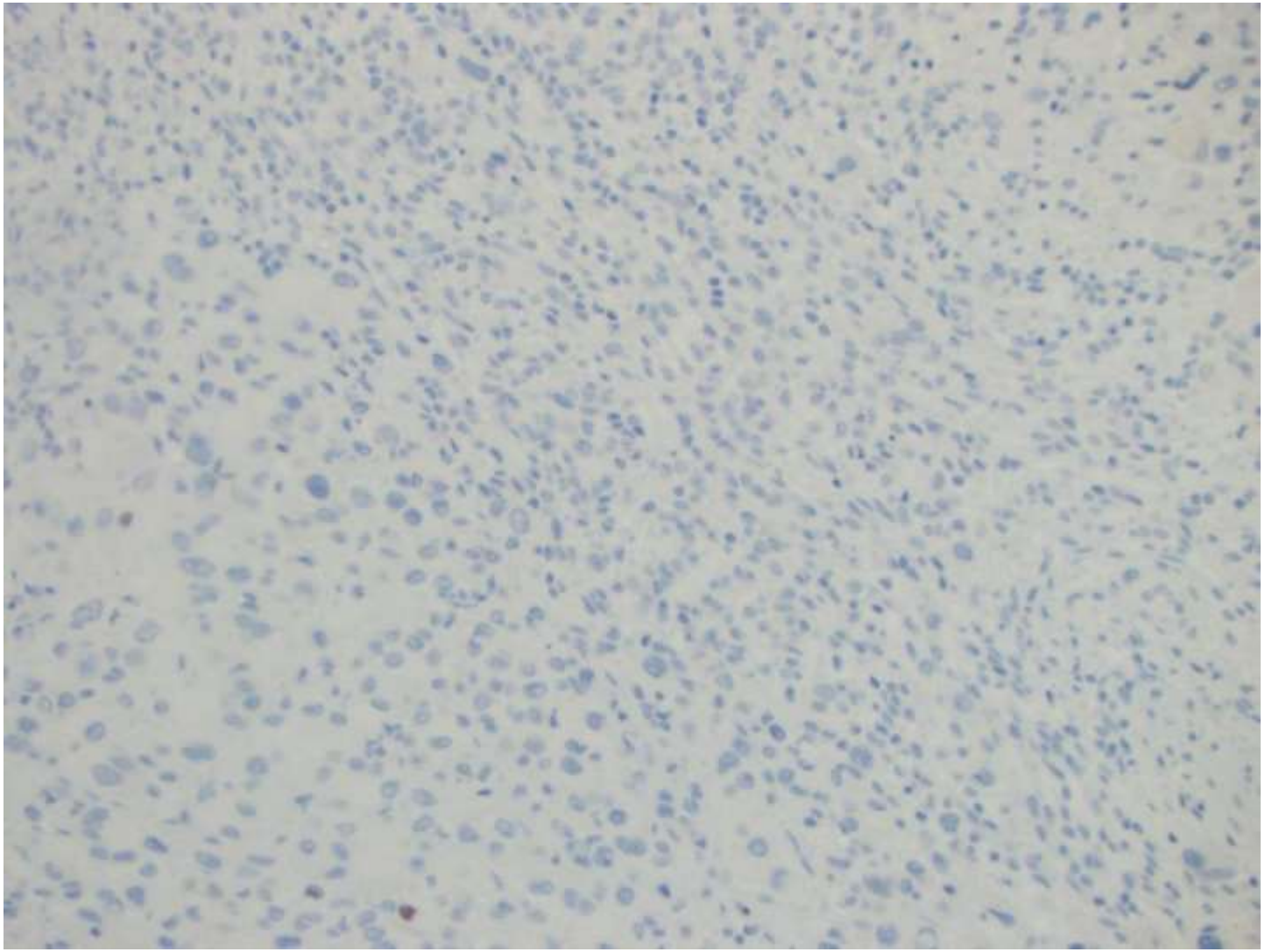
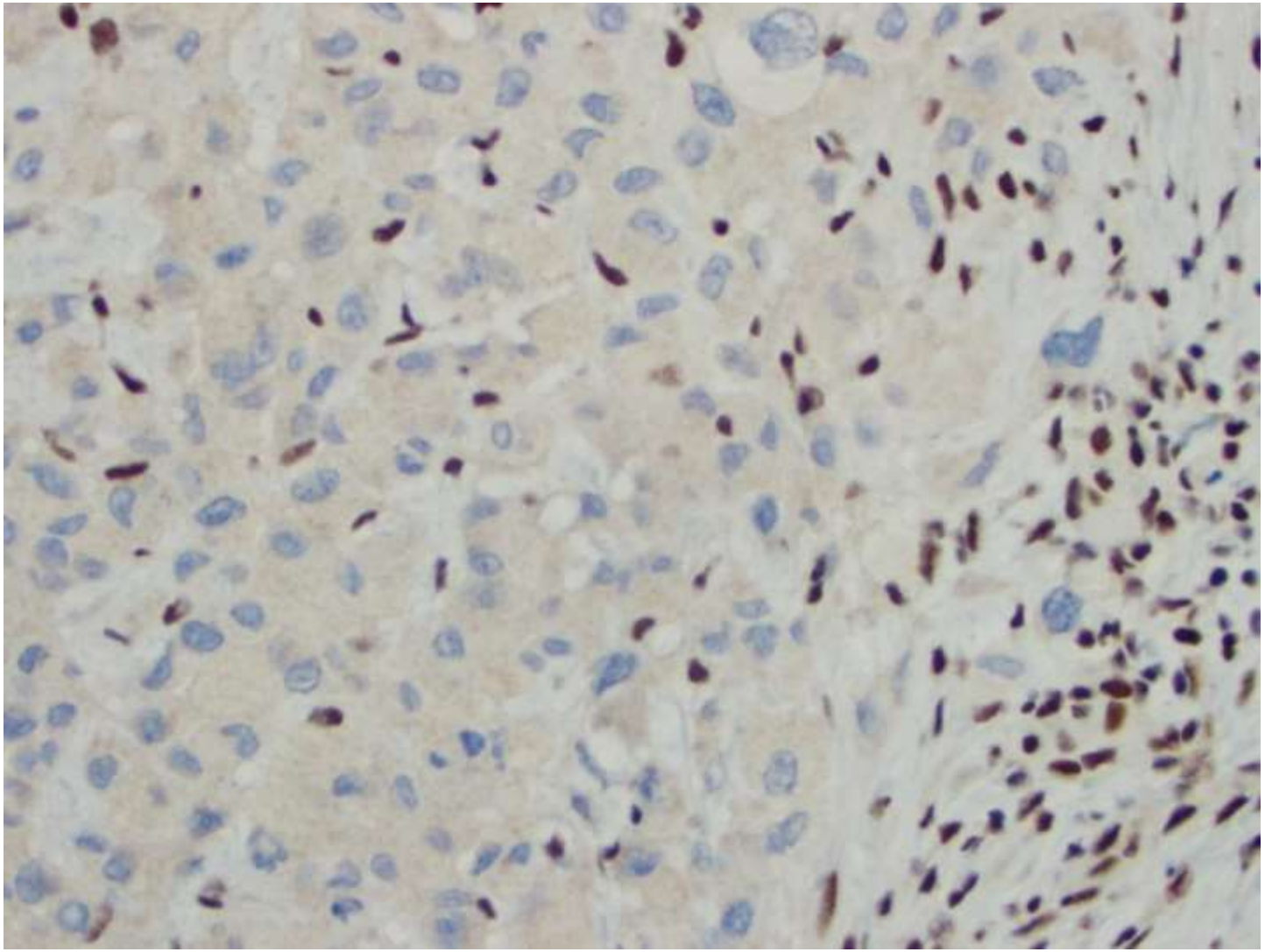


INI-1



Epithelioid Sarcoma, Proximal Type

- Reproductive age group
- SubQ or deep soft tissue mass
- Epithelioid/rhabdoid features
- Marked cytologic atypia
- Necrosis common, but lack granulomatous pattern of usual ES
- Cytokeratin+, EMA+, INI-1-neg
- More aggressive than usual ES-50% fatal
- DDX-SCCA, MERT, Melanoma, other sarcomas with epith features

22-0803

Alexandra Chang-Graham/Joshua Menke; Stanford

60ish F with h/o “atypical Hodgkin lymphoma” with recurrence two years after standard classic Hodgkin lymphoma therapy (ABVD). Lymph node submitted.

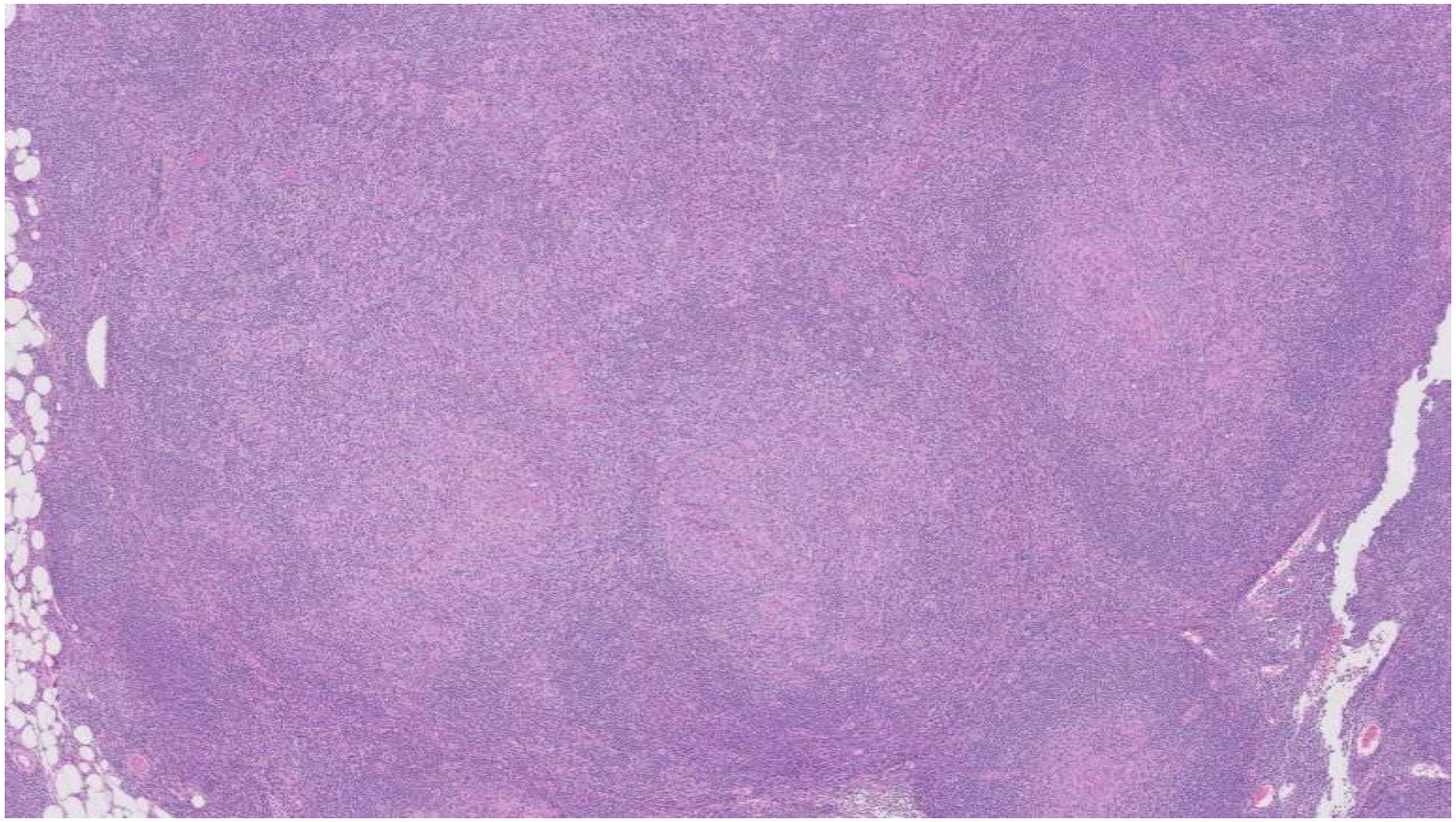
60ish F with "atypical Hodgkin lymphoma" and recurrent adenopathy

Alex Chang-Graham, Sebastian Fernandez-Pol, Joshua Menke

Stanford University

South Bay

Clinical History: Elderly woman presenting with a history of "atypical Hodgkin lymphoma" s/p 2 cycles of ABVD and 5 cycles of AVD, now with recurrent adenopathy above and below the diaphragm. Right inguinal lymph node excisional biopsy was performed.



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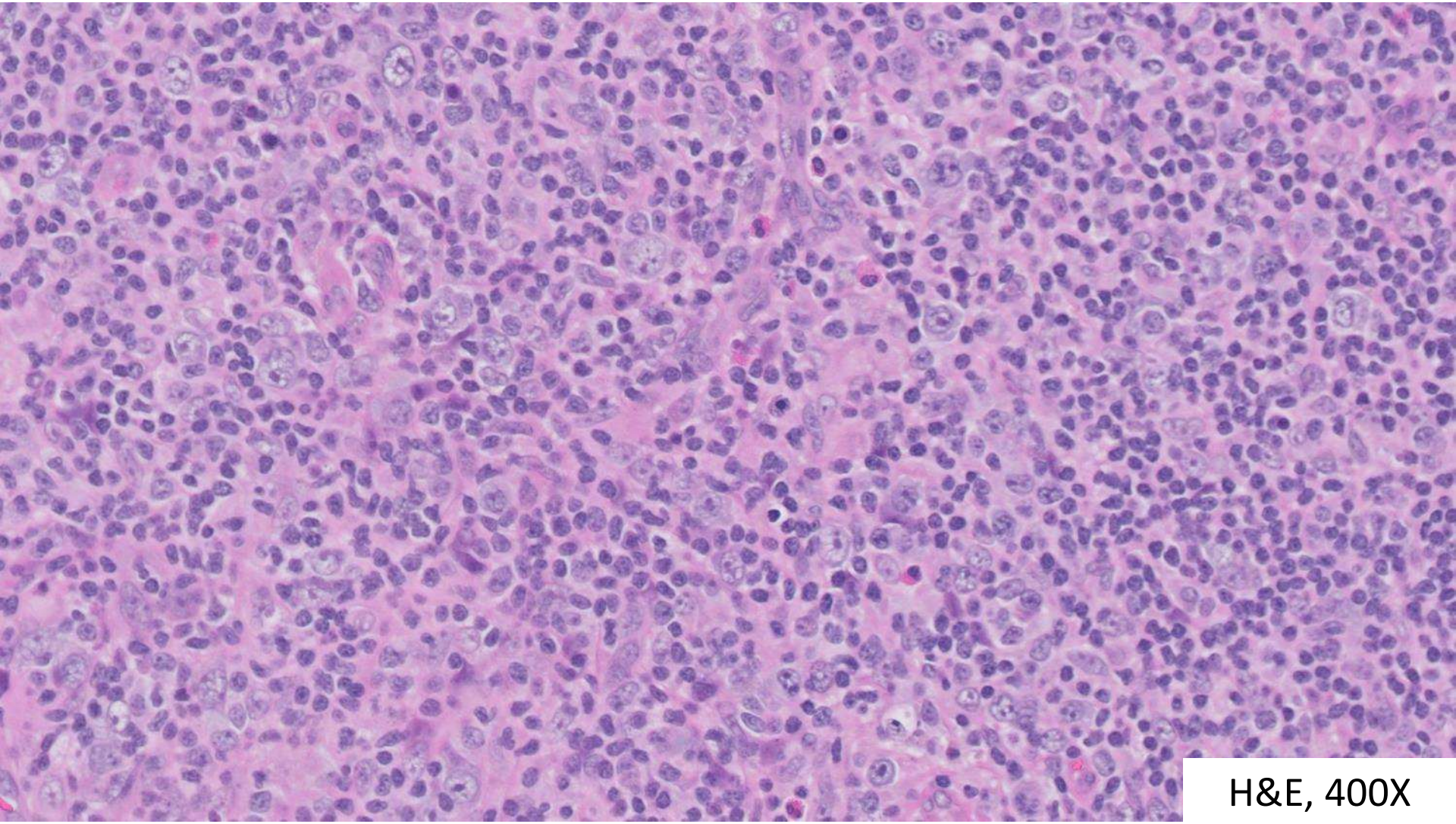

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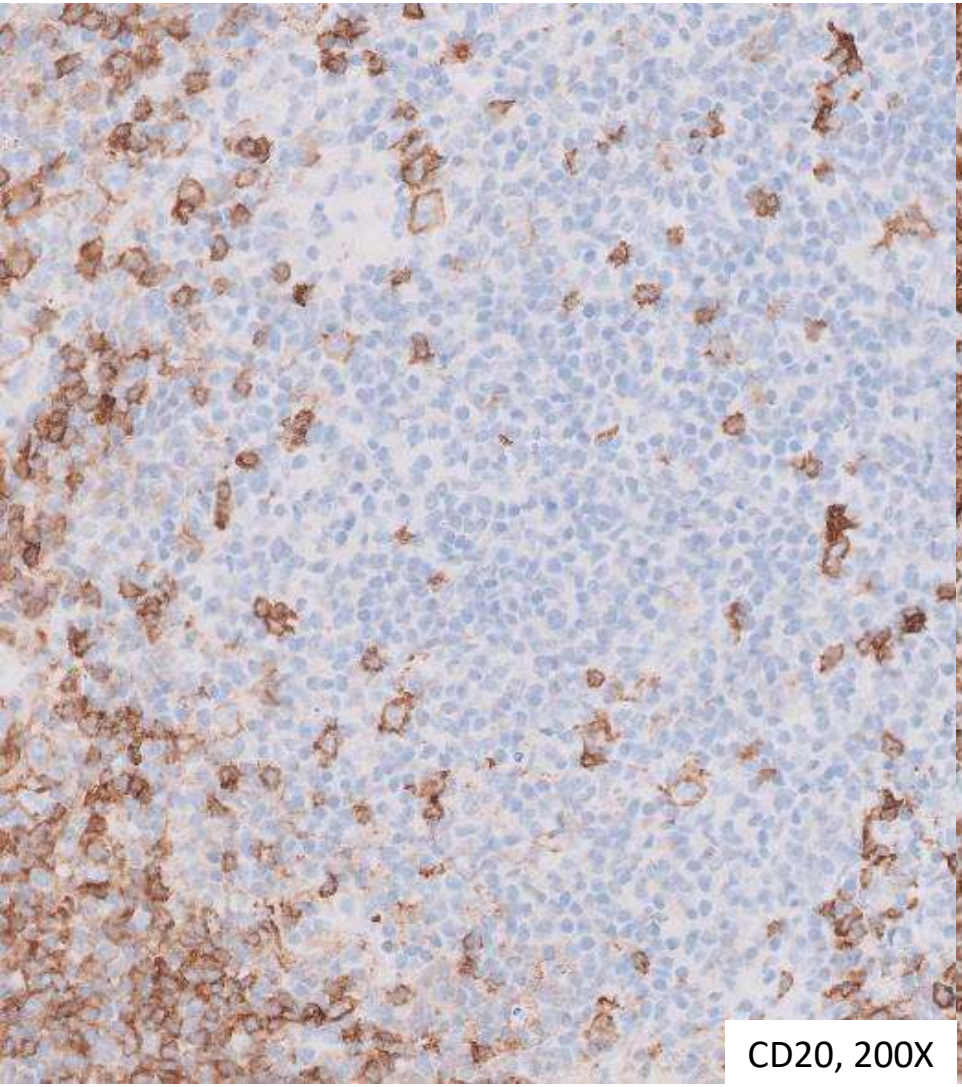

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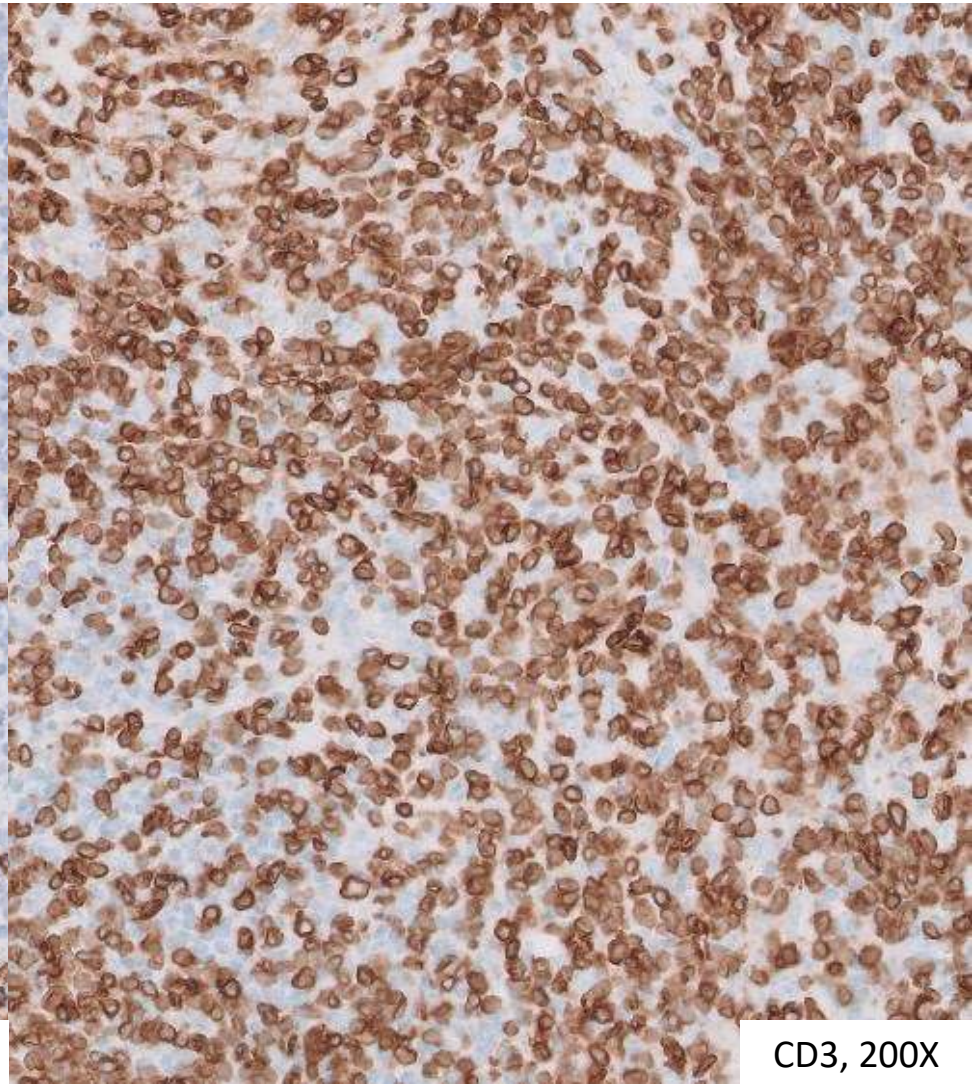

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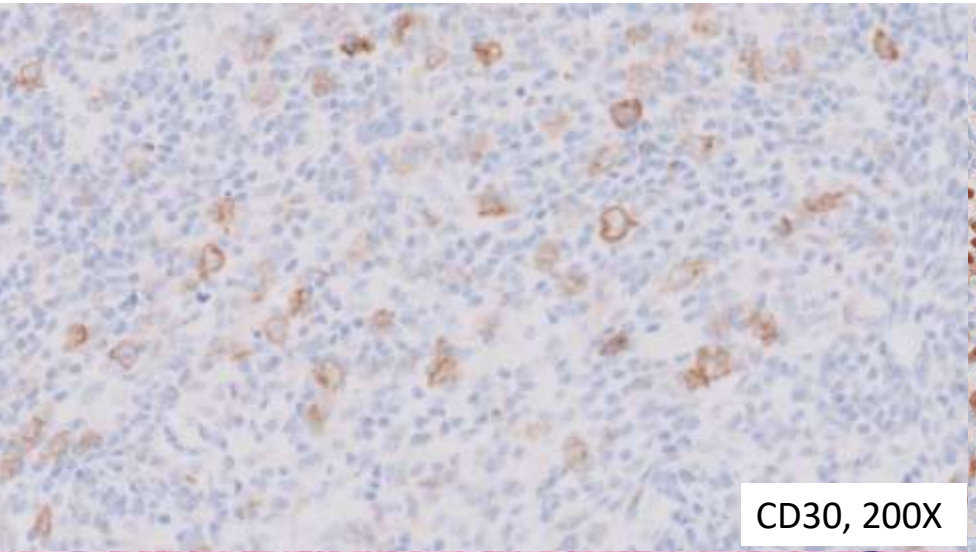

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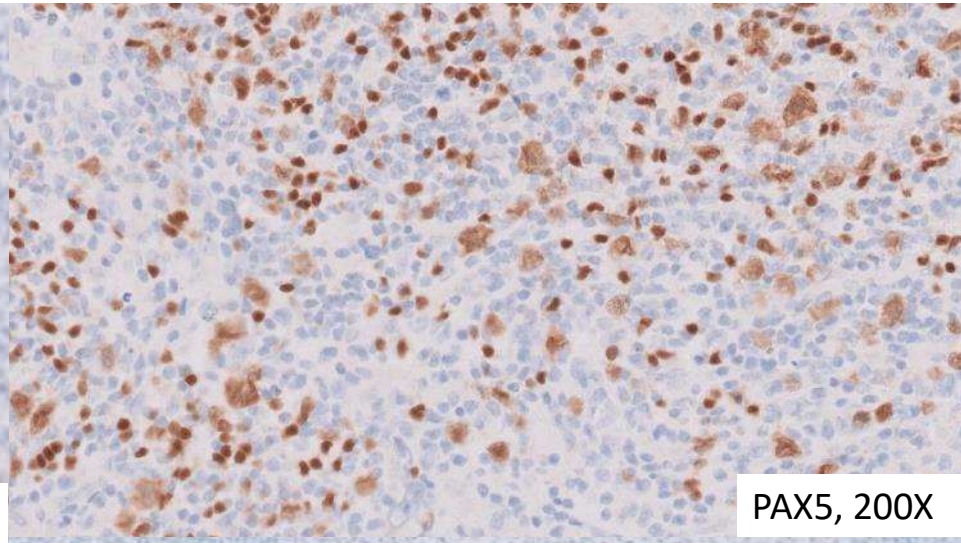

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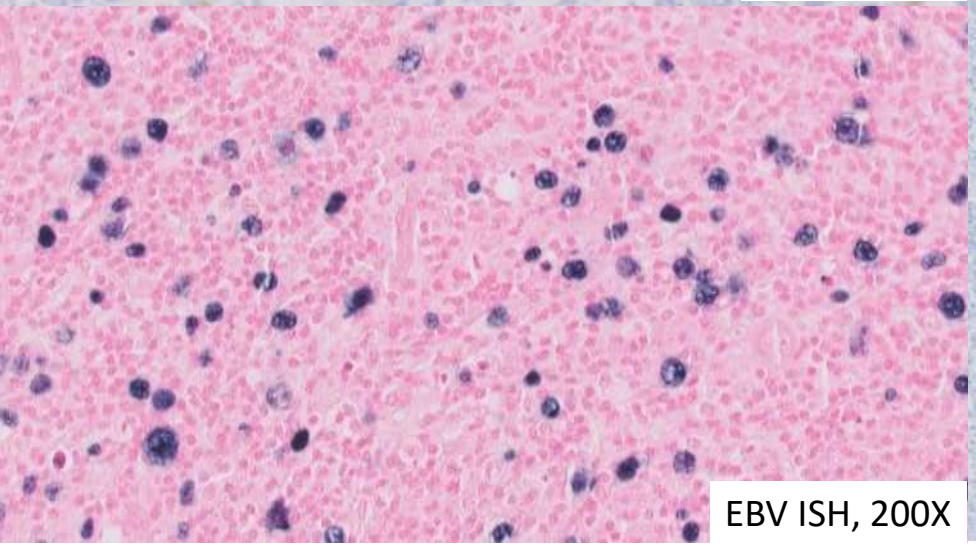
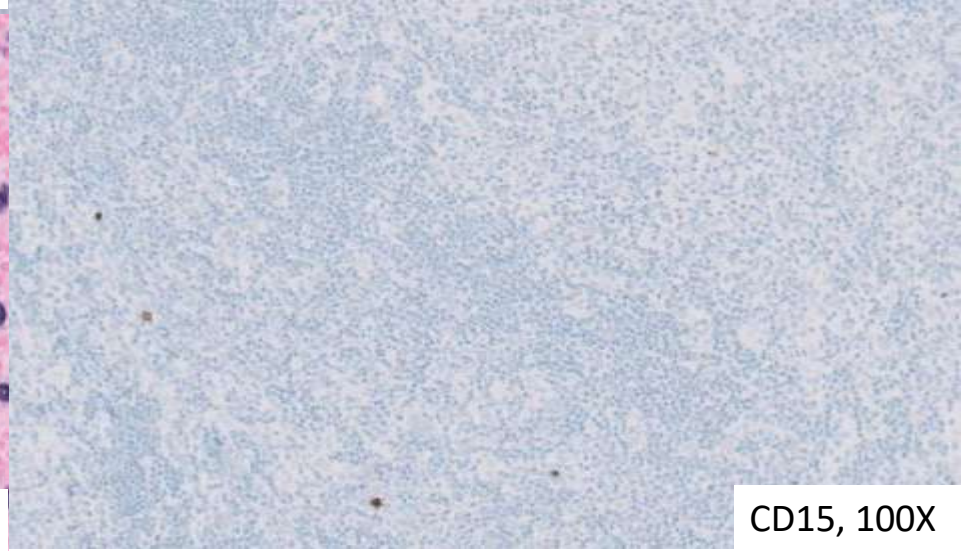


EBV ISH, 200X



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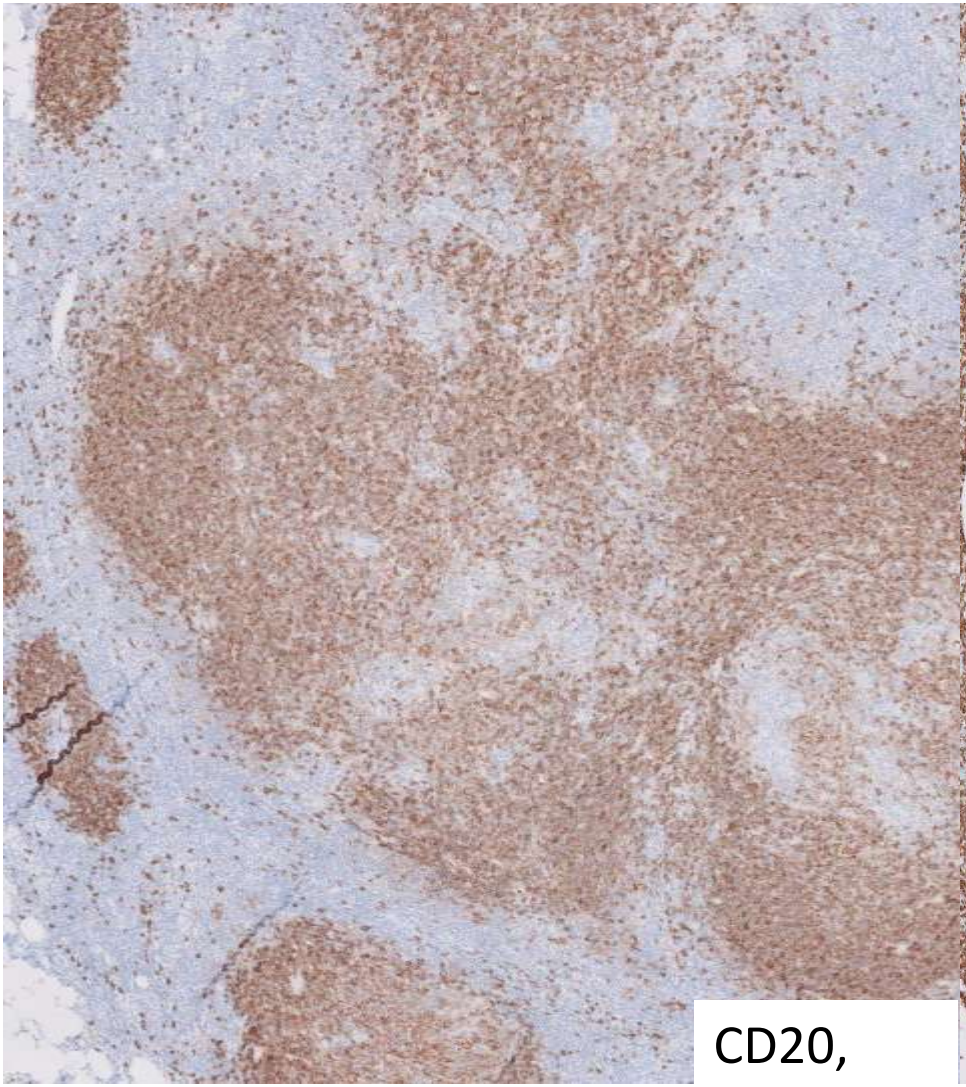

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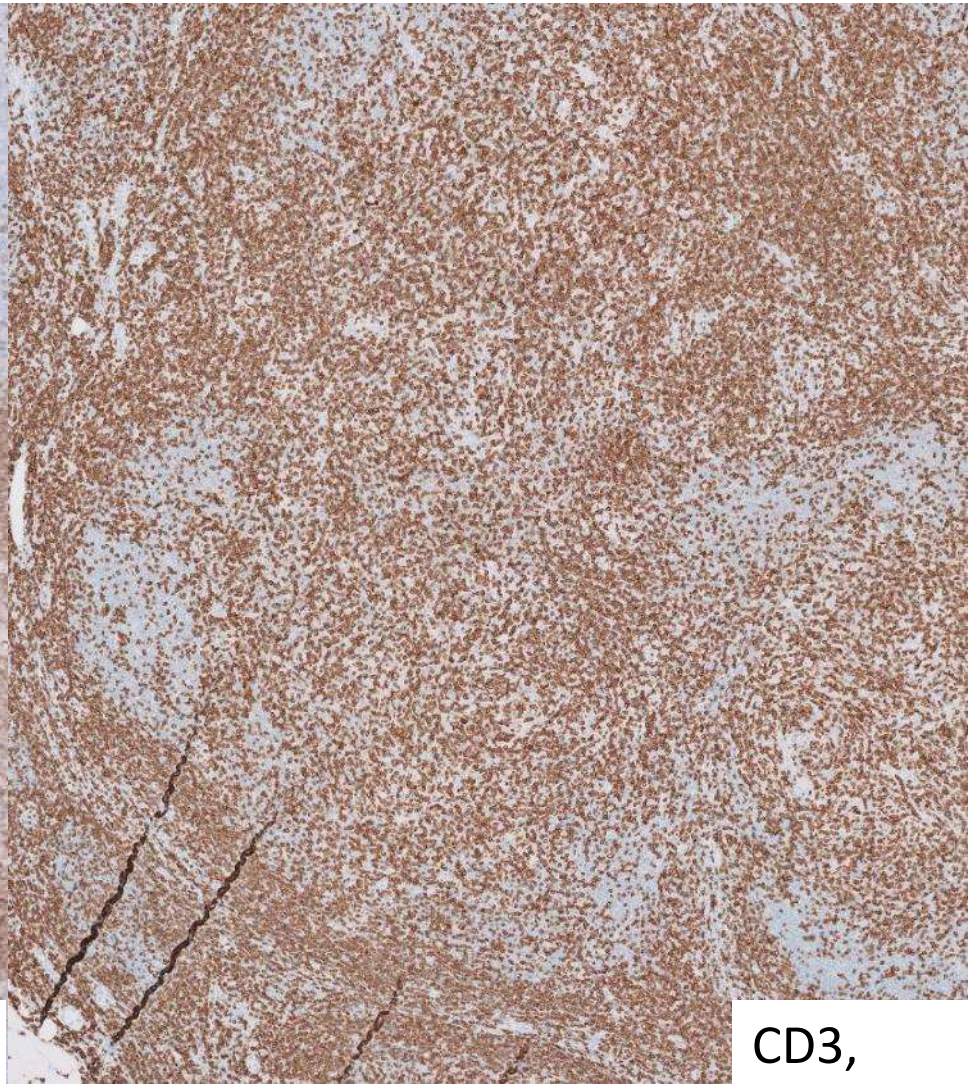
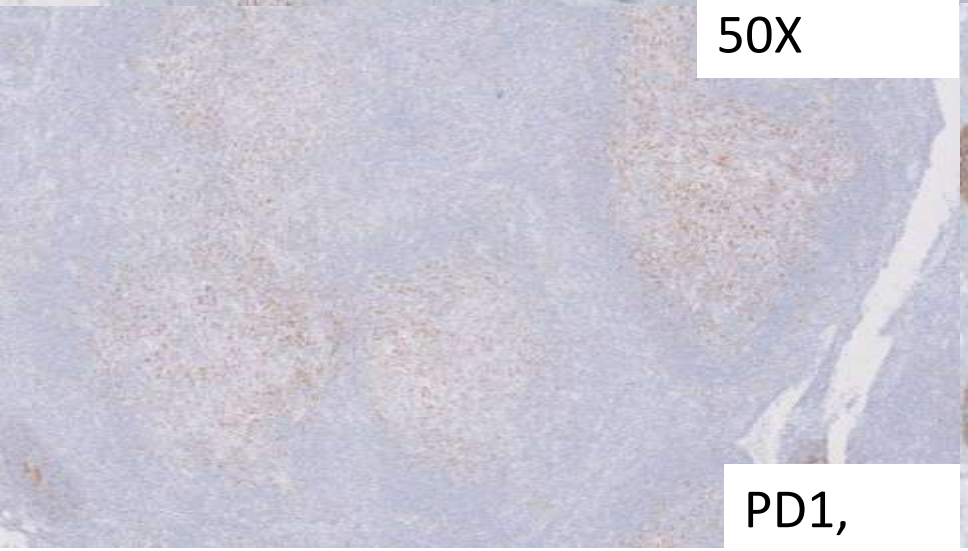


CD3, 50X

BCL6,
50X

ICOS,
50X



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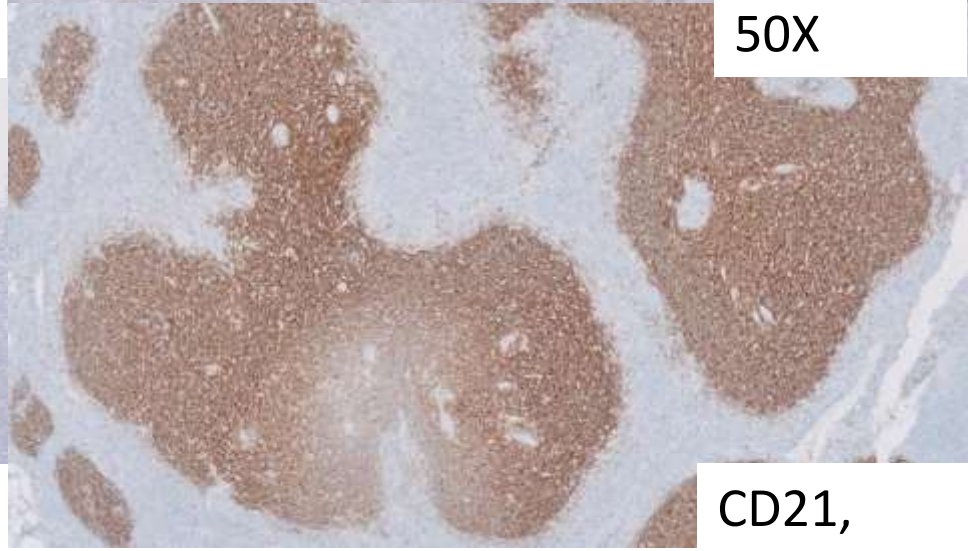

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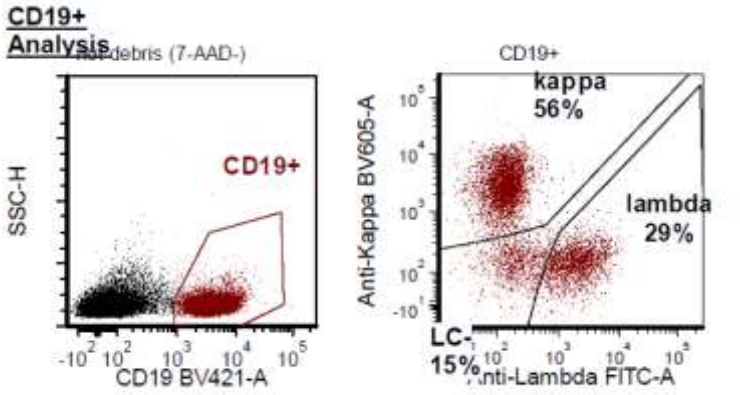
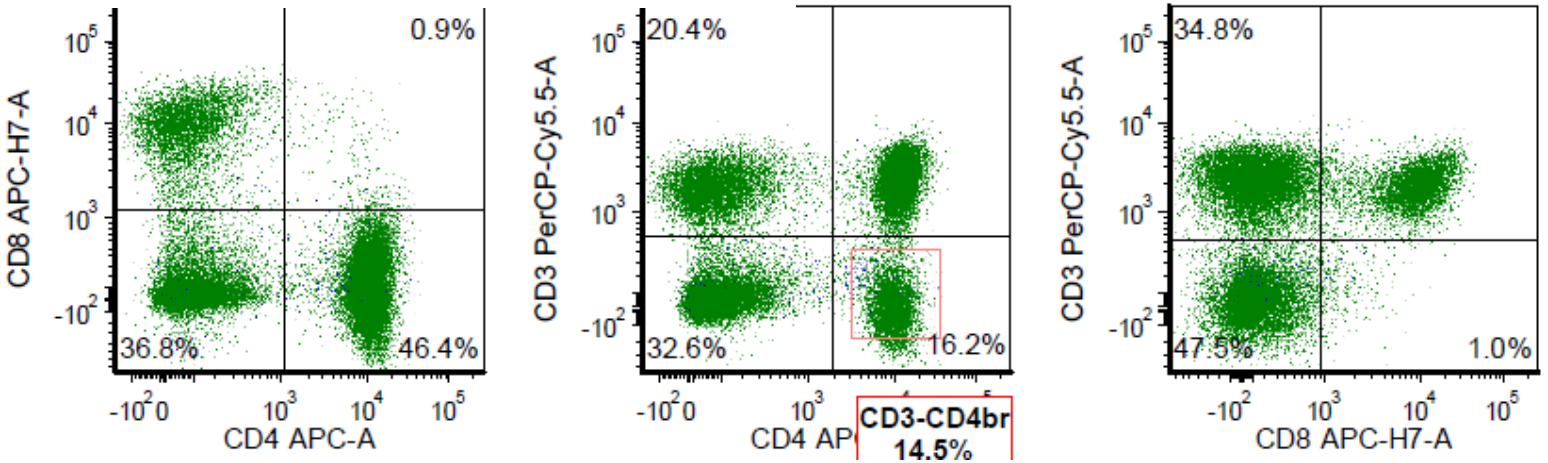
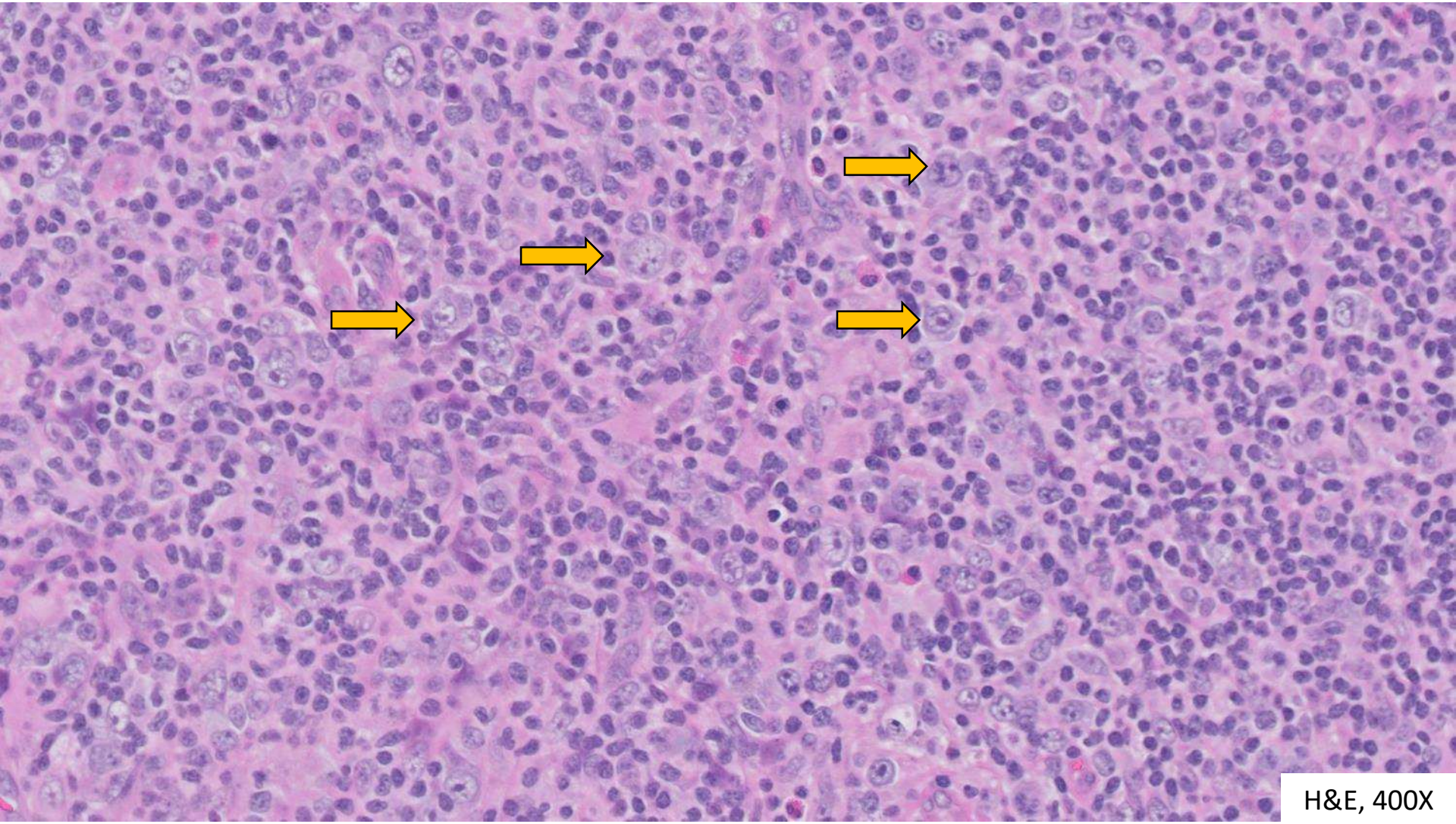
Flow cytometry



	% of viable	κ/λ ratio
CD19+	26.4	1.9 : 1
CD10+CD19+	0.2	2.1 : 1
CD5+CD19+	1.4	2.1 : 1
CD20+	26.9	2 : 1
CD22+	26.0	1.9 : 1





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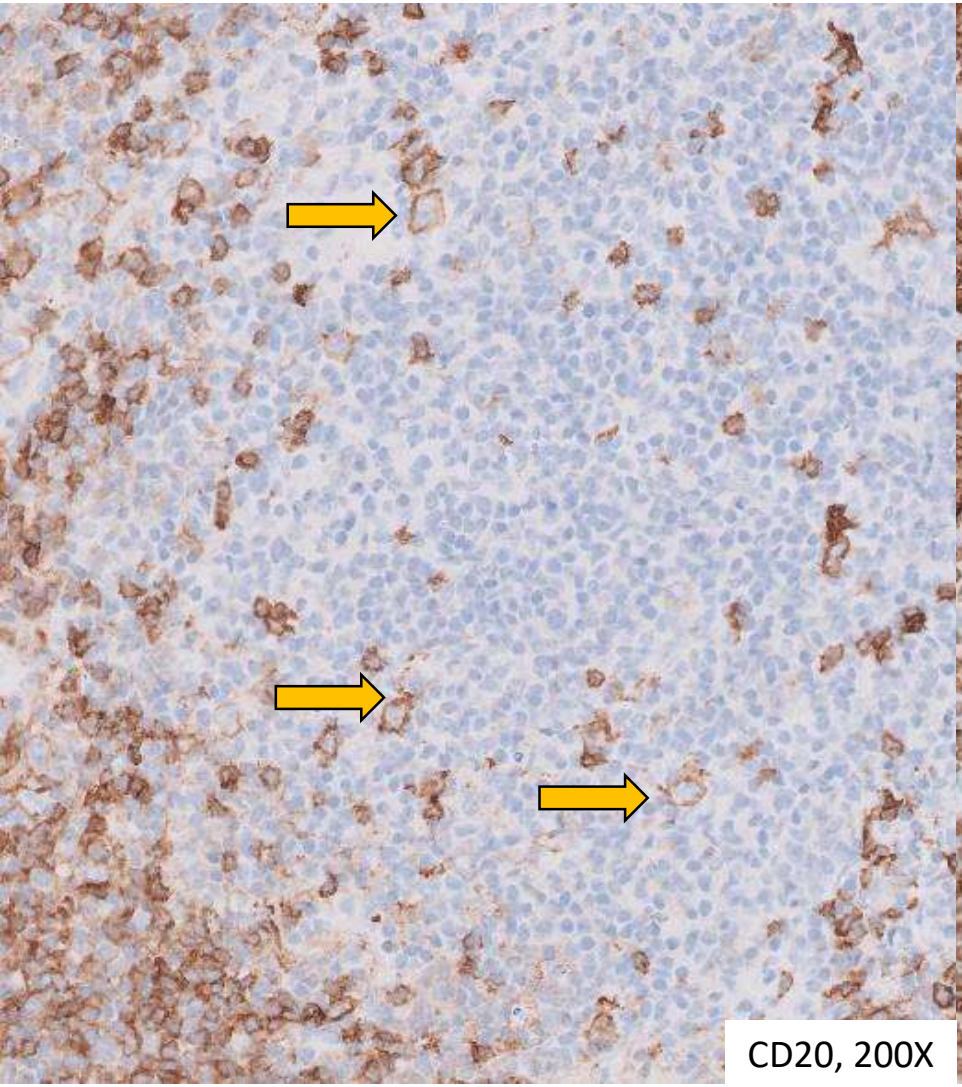

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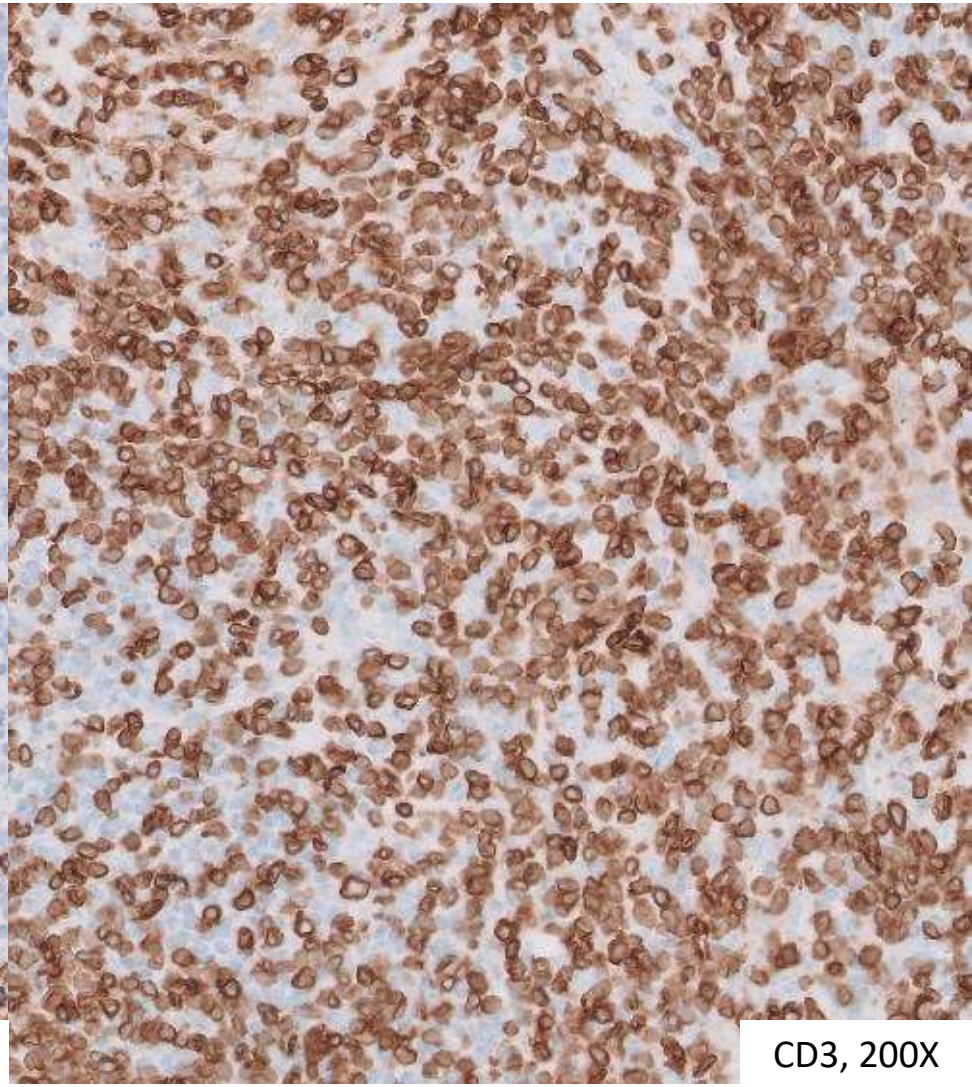

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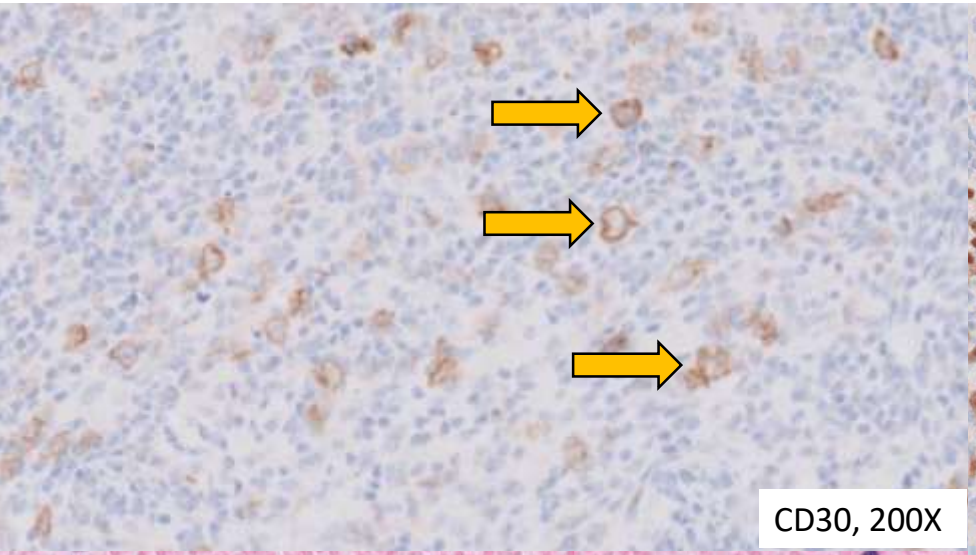

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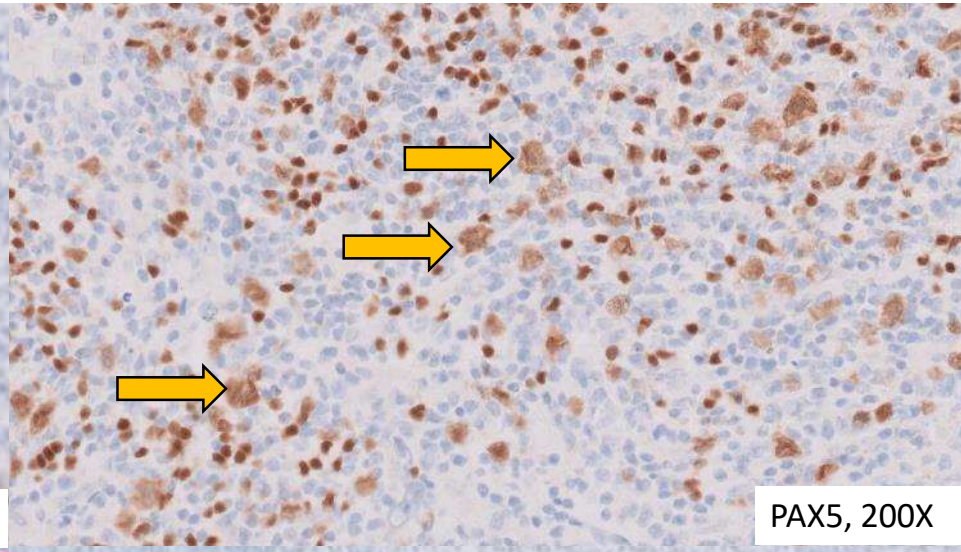
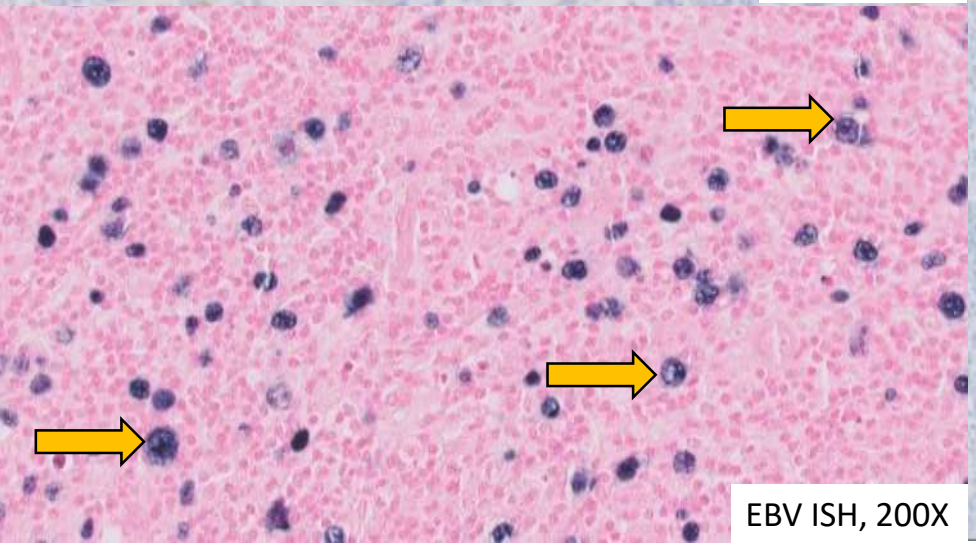
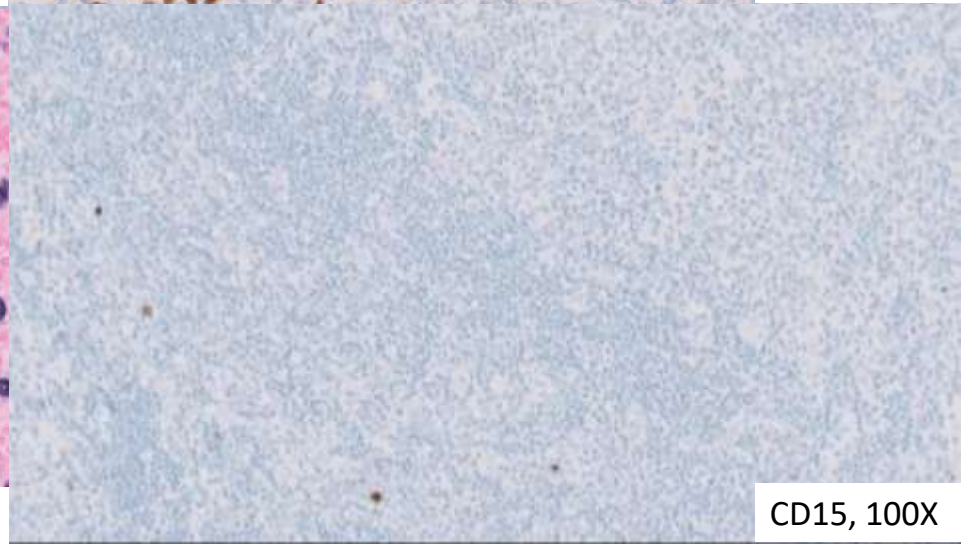


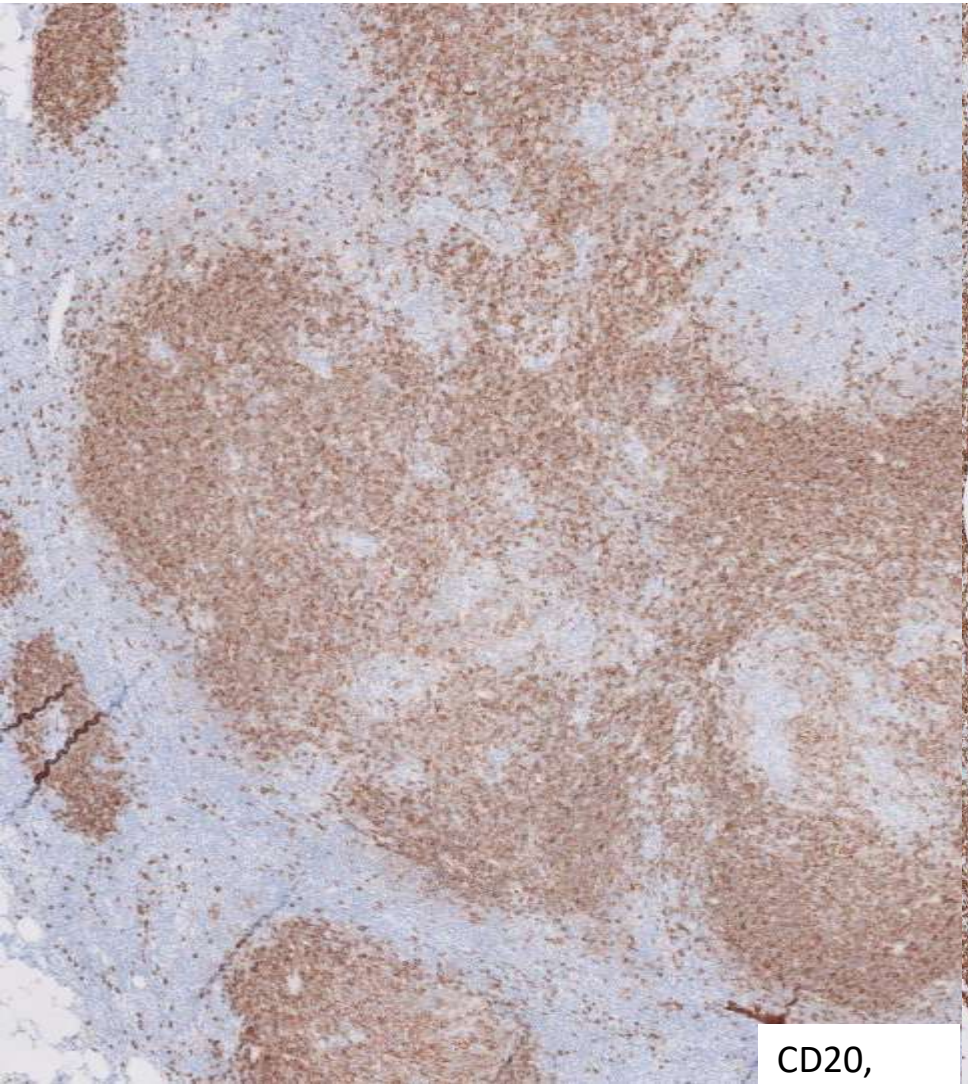
PAX5, 200X



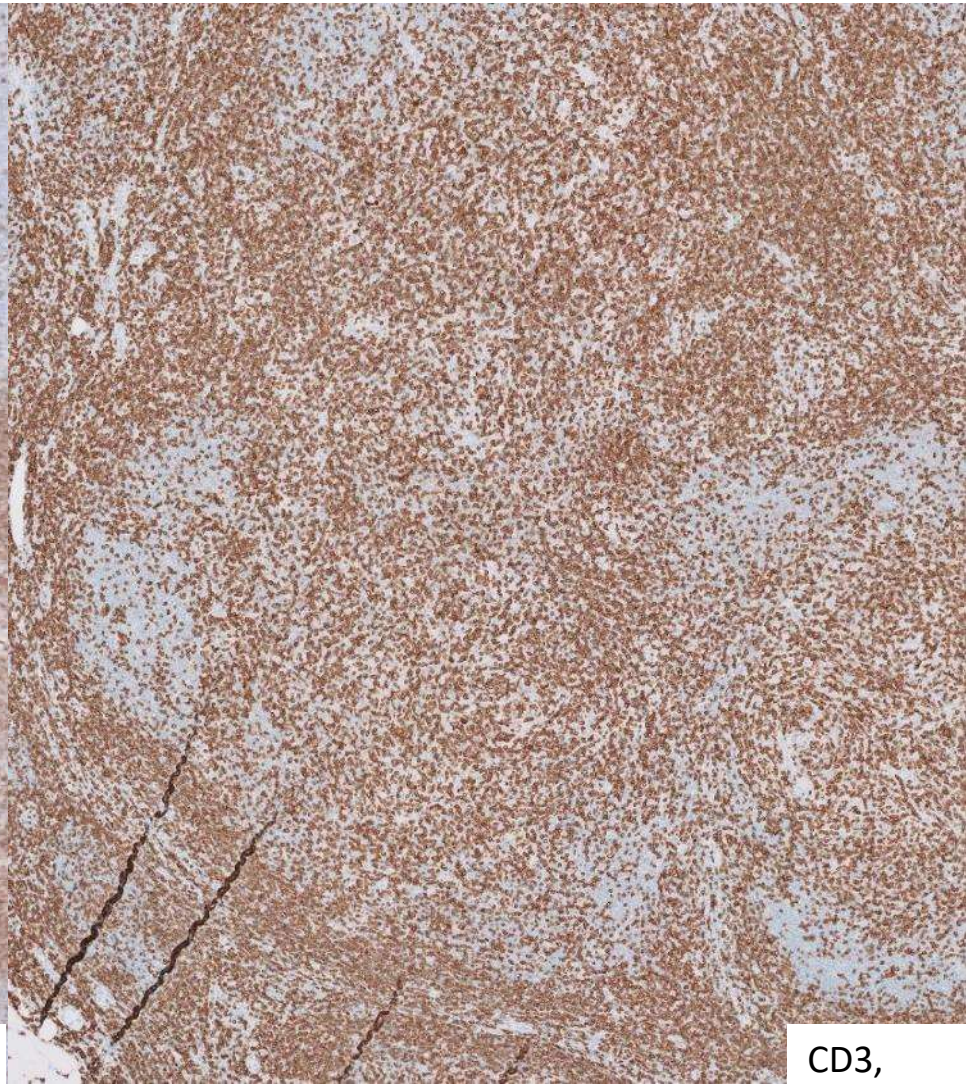
EBV ISH, 200X



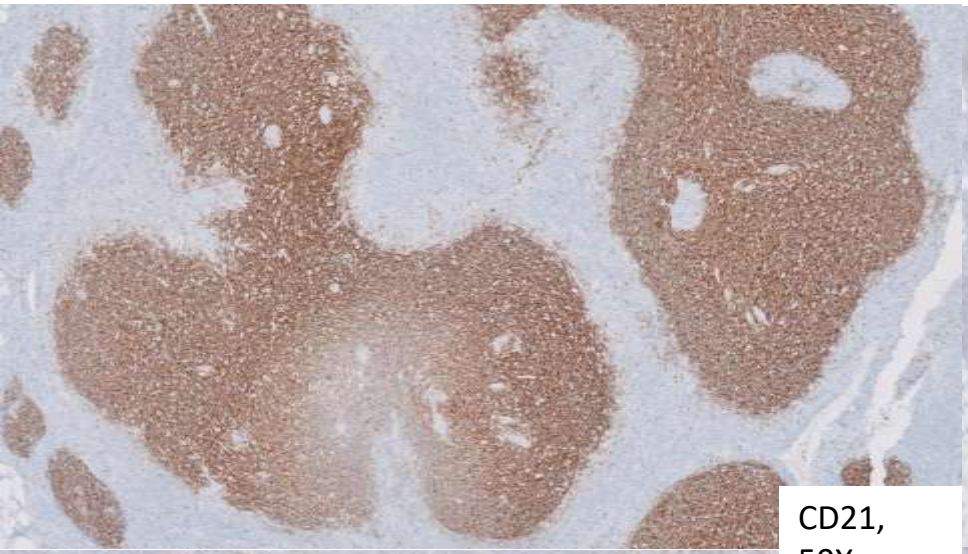
CD15, 100X



CD20, 50X



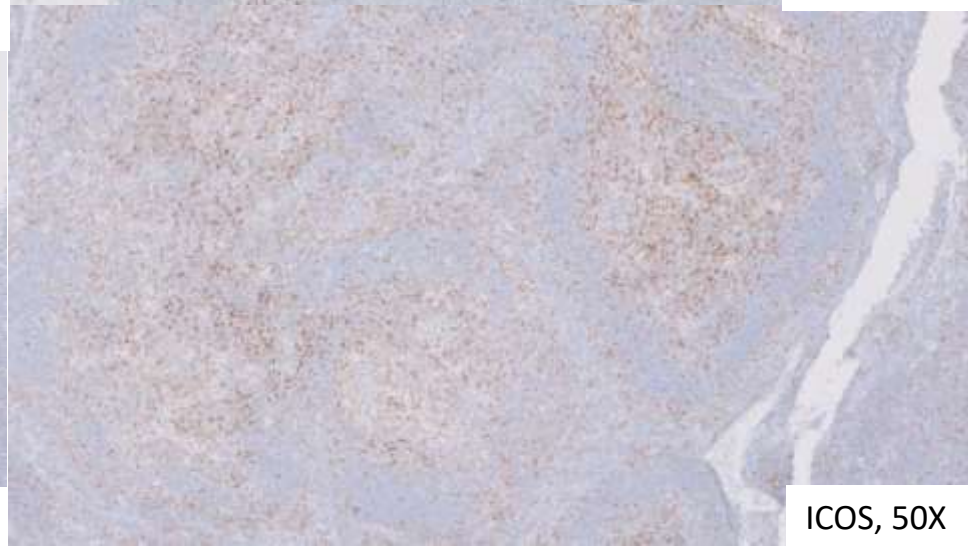
CD3, 50X



CD21, 50X

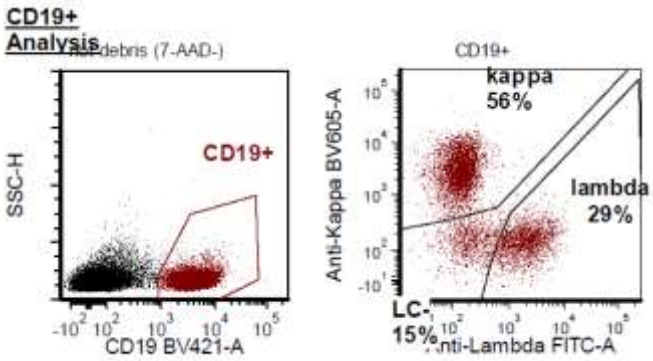
BCL6, 50X

PD1, 50X



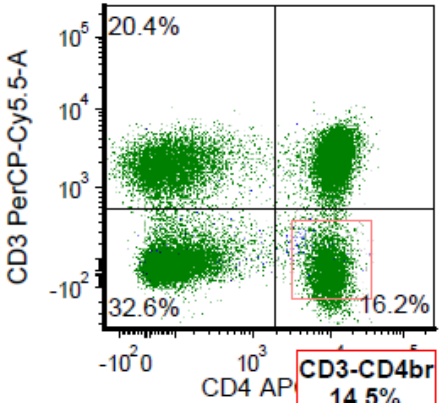
ICOS, 50X

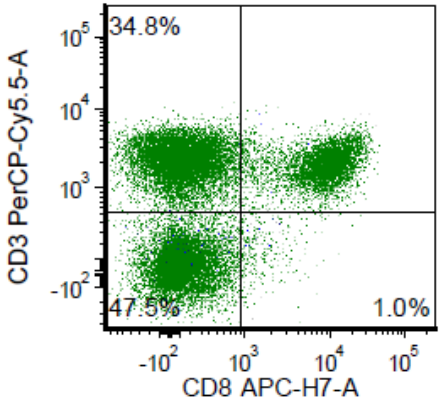
Flow cytometry

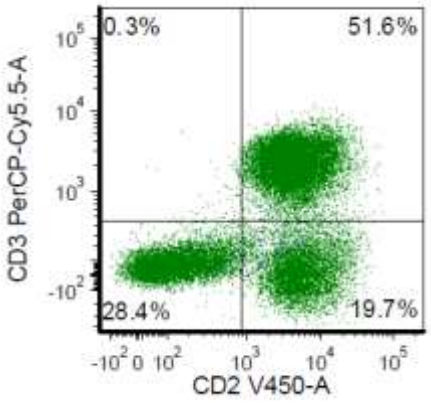


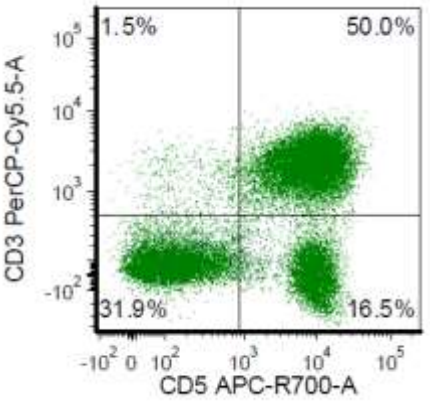
	% of viable	κ/λ ratio
CD19+	26.4	1.9 : 1
CD10+CD19+	0.2	2.1 : 1
CD5+CD19+	1.4	2.1 : 1
CD20+	26.9	2 : 1
CD22+	26.0	1.9 : 1

- Polytypic B-cells
- Atypical T-cell population (16% of lymphocytes) expressing CD5, CD4, CD2, CD43, CD200 (partial), and CD10 (subset) and lacking sCD3, CD7, CD8, CD56, CD20







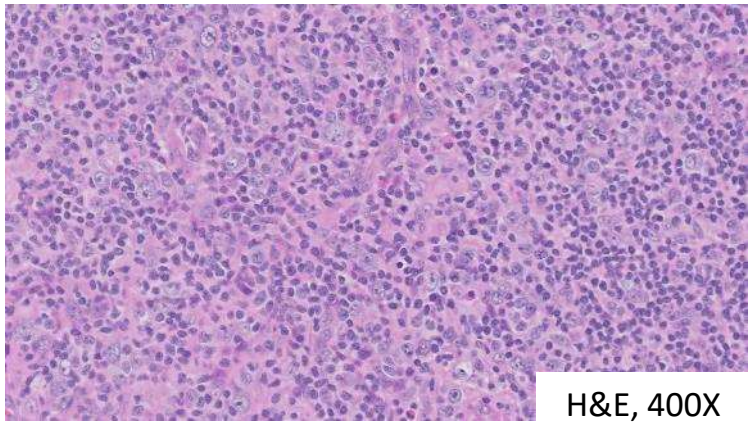


Next generation sequencing (NGS) results support a T cell neoplastic process

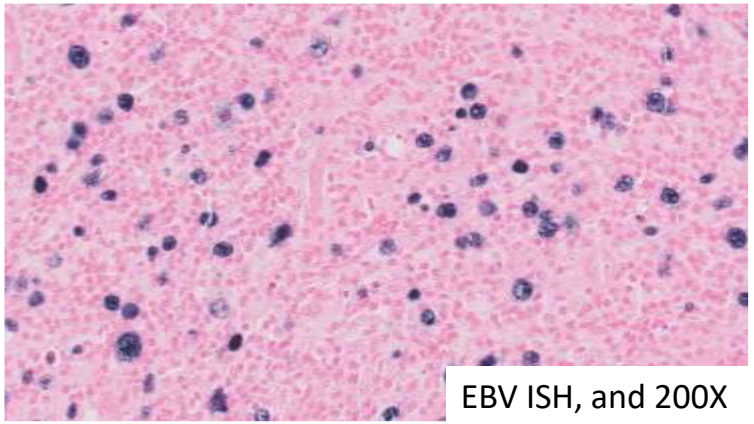
- NGS clonality studies:
  - Clonal TCR gamma (TRG) and clonal TCR beta (TRB) rearrangements identified
  - No clonal immunoglobulin gene rearrangement
- 164 gene heme-specific NGS panel (Heme-STAMP) shows pathogenic mutations in:
  - *TET2* R1261G with a variant allele fraction of 54%
  - *SH2B3* S303FS with a variant allele fraction of 2%

Diagnosis: Nodal T follicular helper cell lymphoma and associated EBV-positive Hodgkin/Reed-Sternberg-like cells

- Nodal TCL with TFH-phenotype is rare, about 1/4 of TFH-origin lymphomas
- Median age > 60 y/o, no sex predominance
- Similar overall survival (5-year, 60%) as the angioimmunoblastic type
- First-line chemo is often CHOP/CHOEP
- EBV-positive B cell lymphoproliferation is a common co-occurrence



H&E, 400X



EBV ISH, and 200X

Interesting features of this case

- Nodal TFH cell lymphomas with Hodgkin/Reed-Sternberg-like cells have features that closely overlap with classic Hodgkin lymphoma
  - small volume core biopsy was enriched for Hodgkin/Reed-Sternberg-like cells
  - flow was not performed on the original case
  - led to the wrong diagnosis and improper therapy for about 3 years
- *TET2* mutation
  - present in 47-86% of peripheral T-cell lymphomas
  - have only rarely been reported in classic Hodgkin lymphoma

References

- Lemonnier F, Couronné L, Parrens M, *et al*. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood*. 2012;120(7):1466-1469. doi:10.1182/blood-2012-02-408542

- Venanzi A, Marra A, Schiavoni G, *et al*. Dissecting Clonal Hematopoiesis in Tissues of Classical Hodgkin Lymphoma Patients. *Blood Cancer Discov*. 2021;2(3):216-225. doi:10.1158/2643-3230.BCD-20-0203

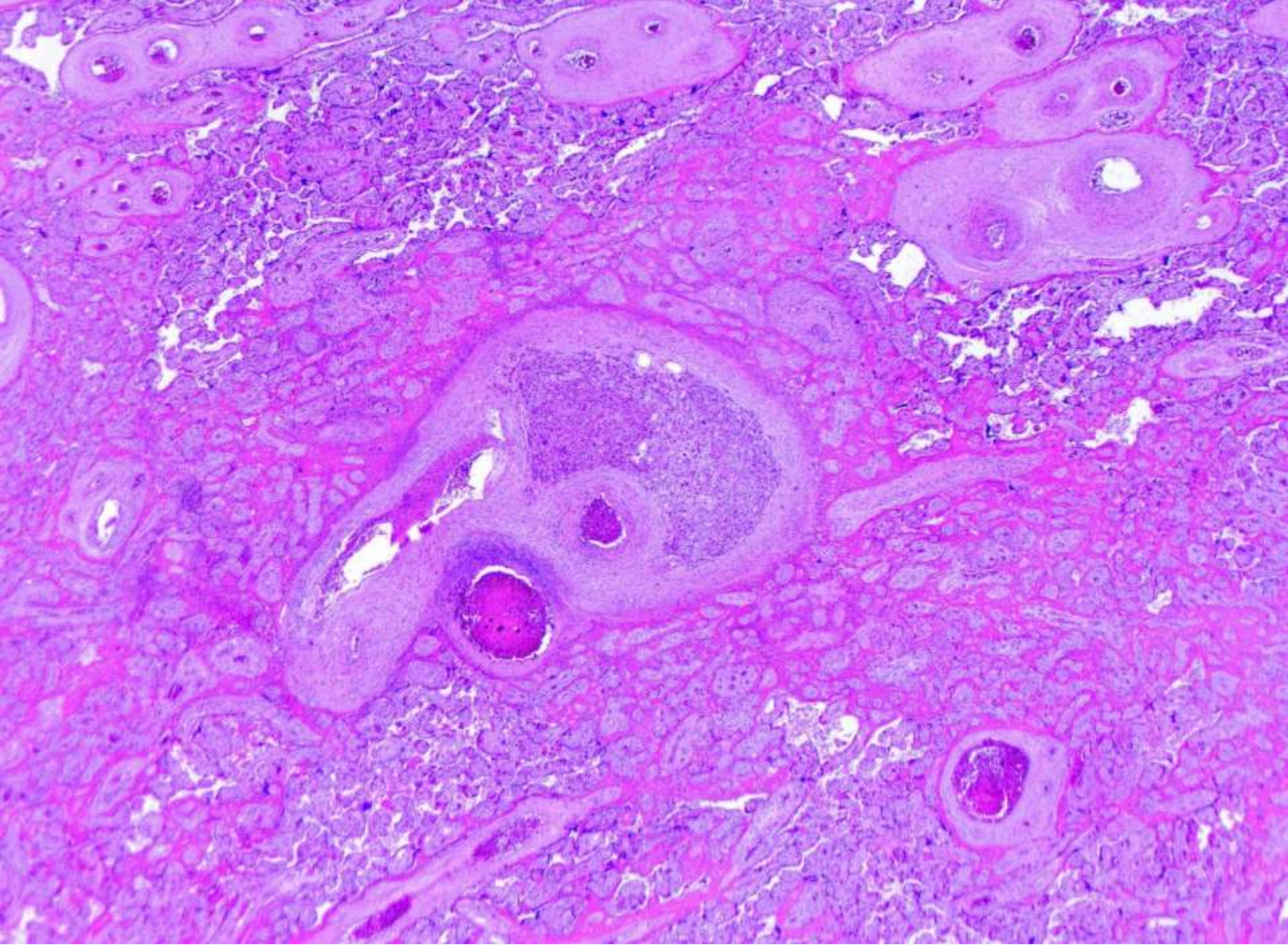
- Yoon, S.E., Cho, J., Kim, Y.J. *et al.* Comprehensive analysis of clinical, pathological, and genomic characteristics of follicular helper T-cell derived lymphomas. *Exp Hematol Oncol* **10,** 33 (2021). https://doi.org/10.1186/s40164-021-00224-3

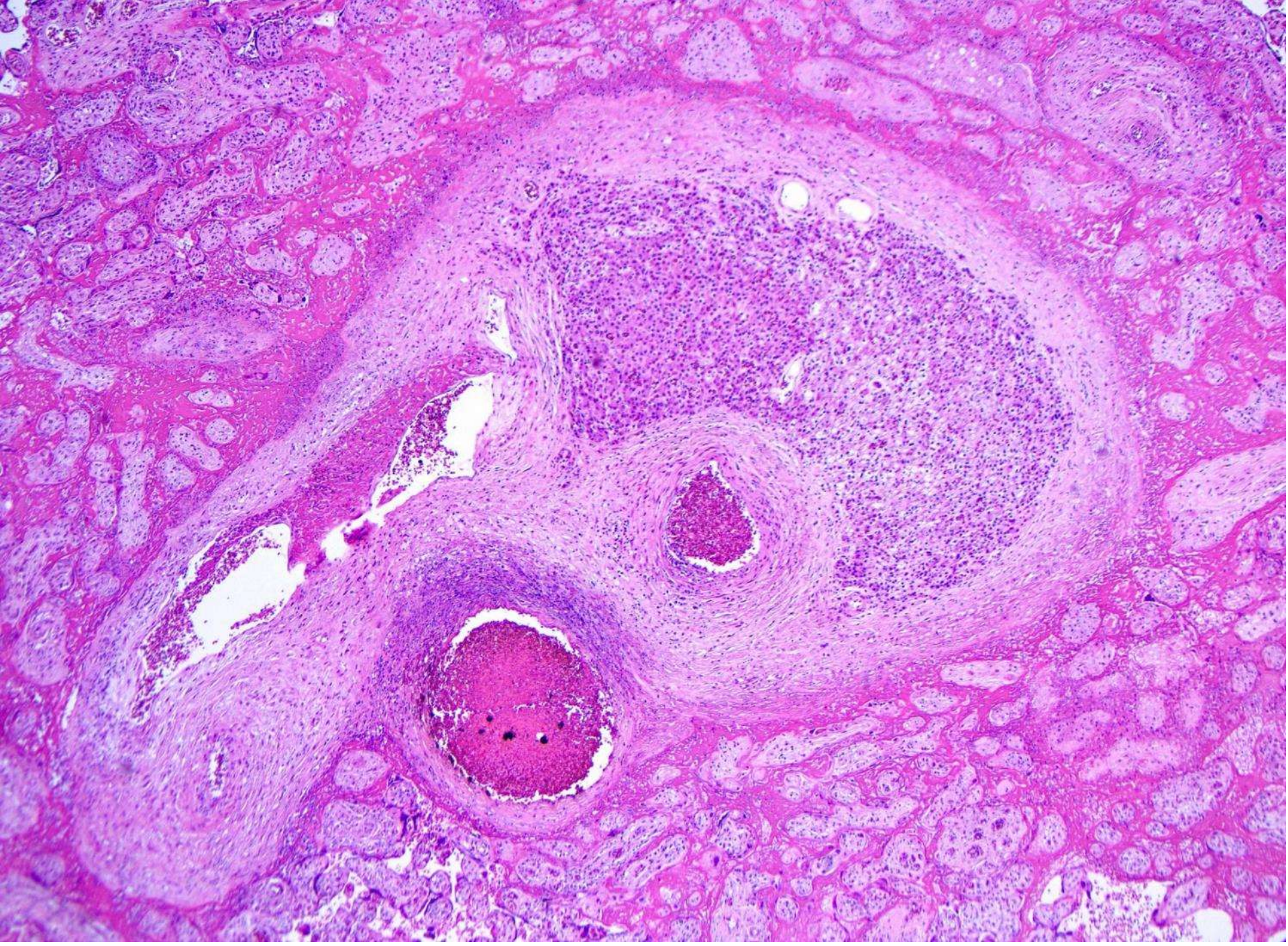
22-0804
Direct link to scanned slide:

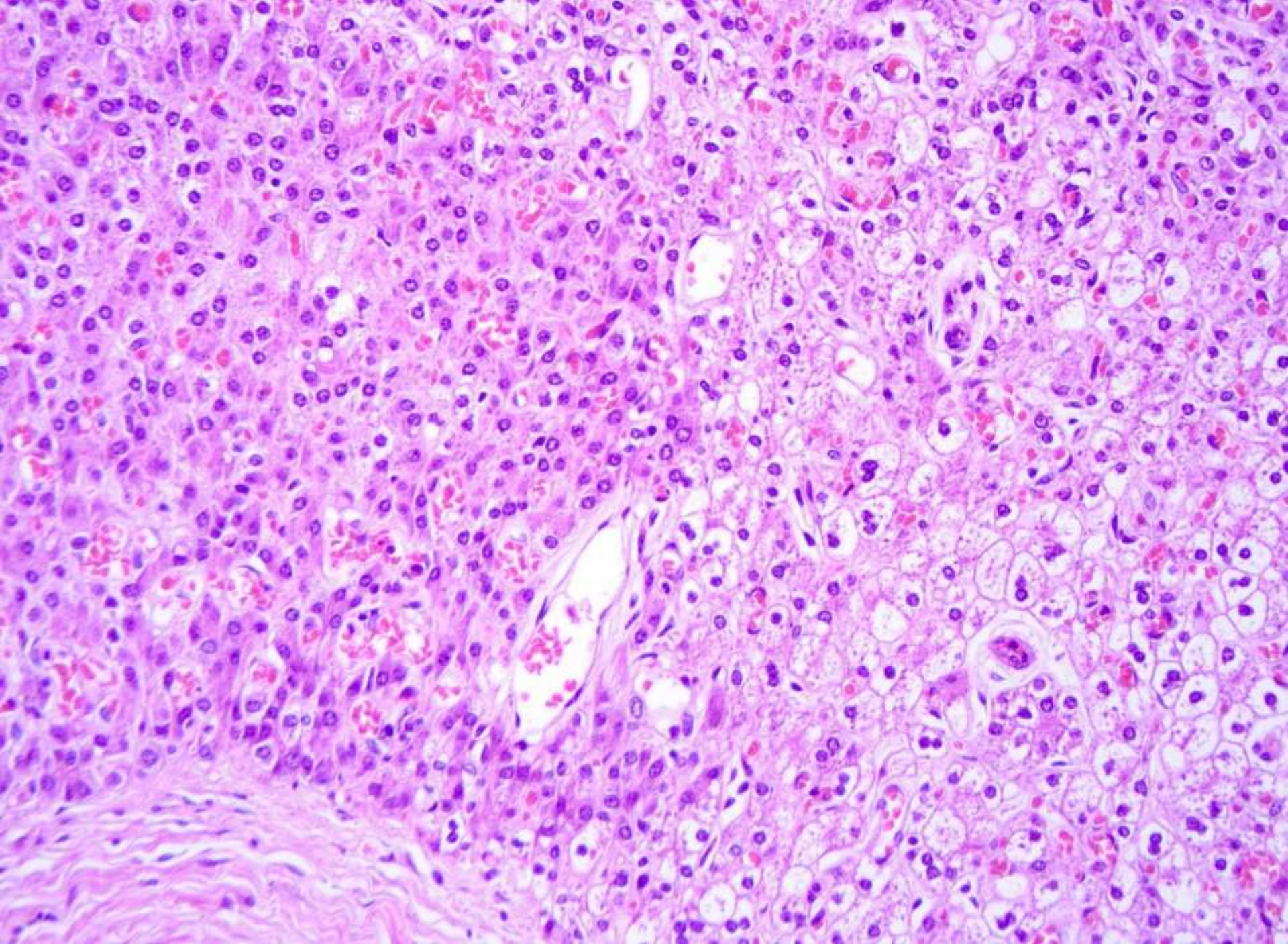
https://pathpresenter.net/public/display?token=3221eb31

Lucas Massoth; El Camino Hospital

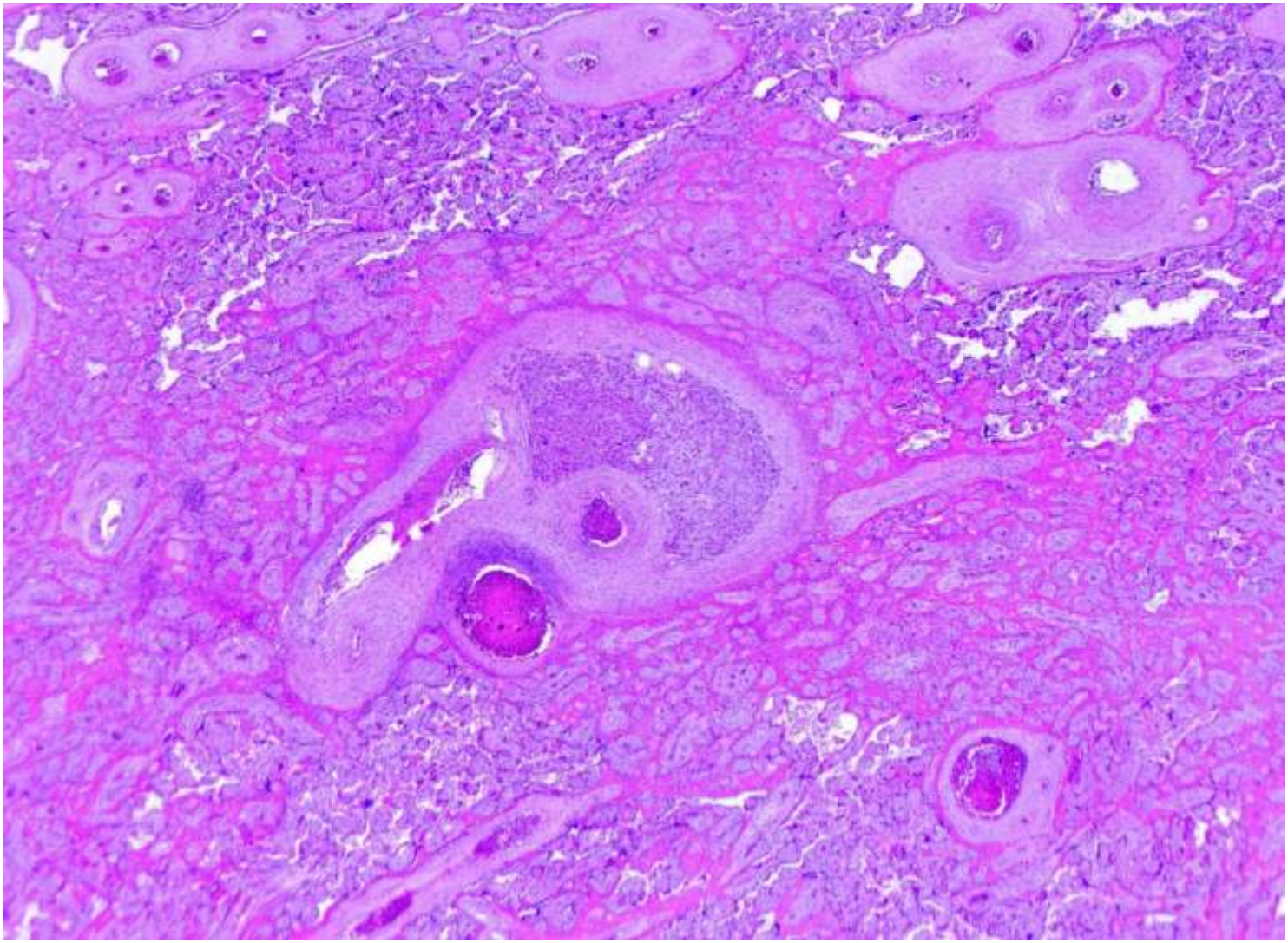
30ish F presents at 39 weeks in labor. Cesarean section performed due to failure to progress and fetal intolerance to labor. Thick meconium was noted at delivery. Section of placental disc.

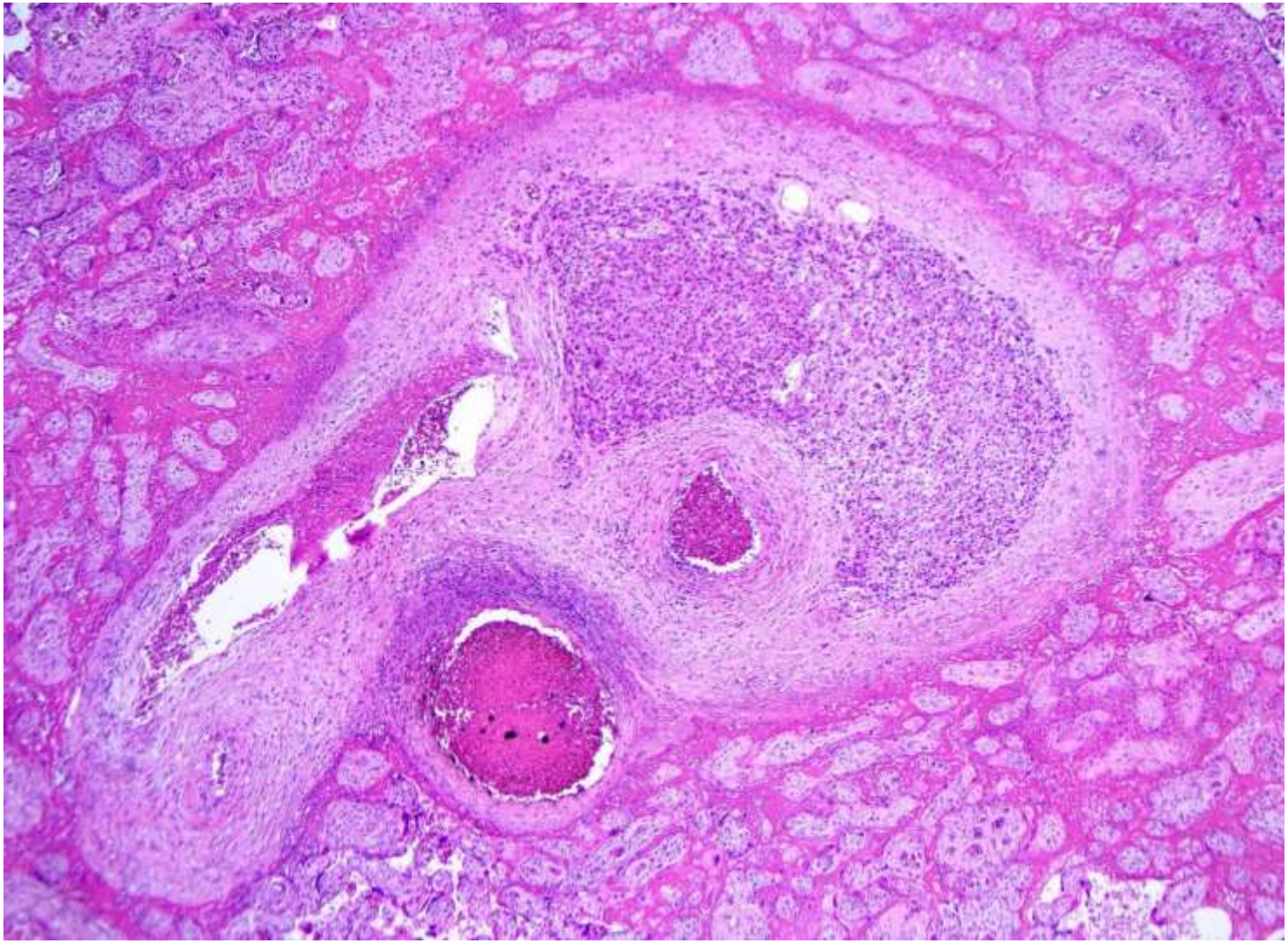


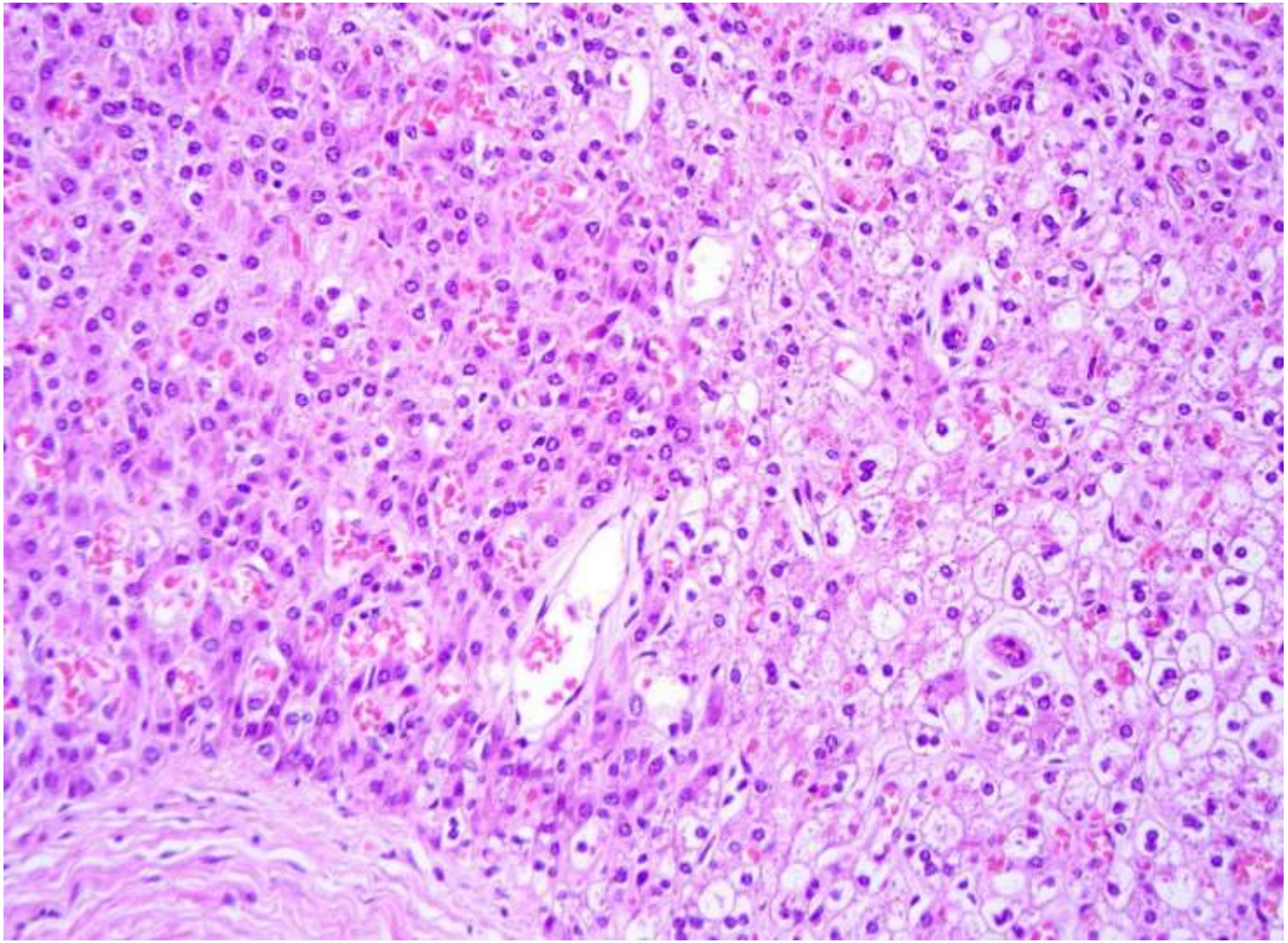




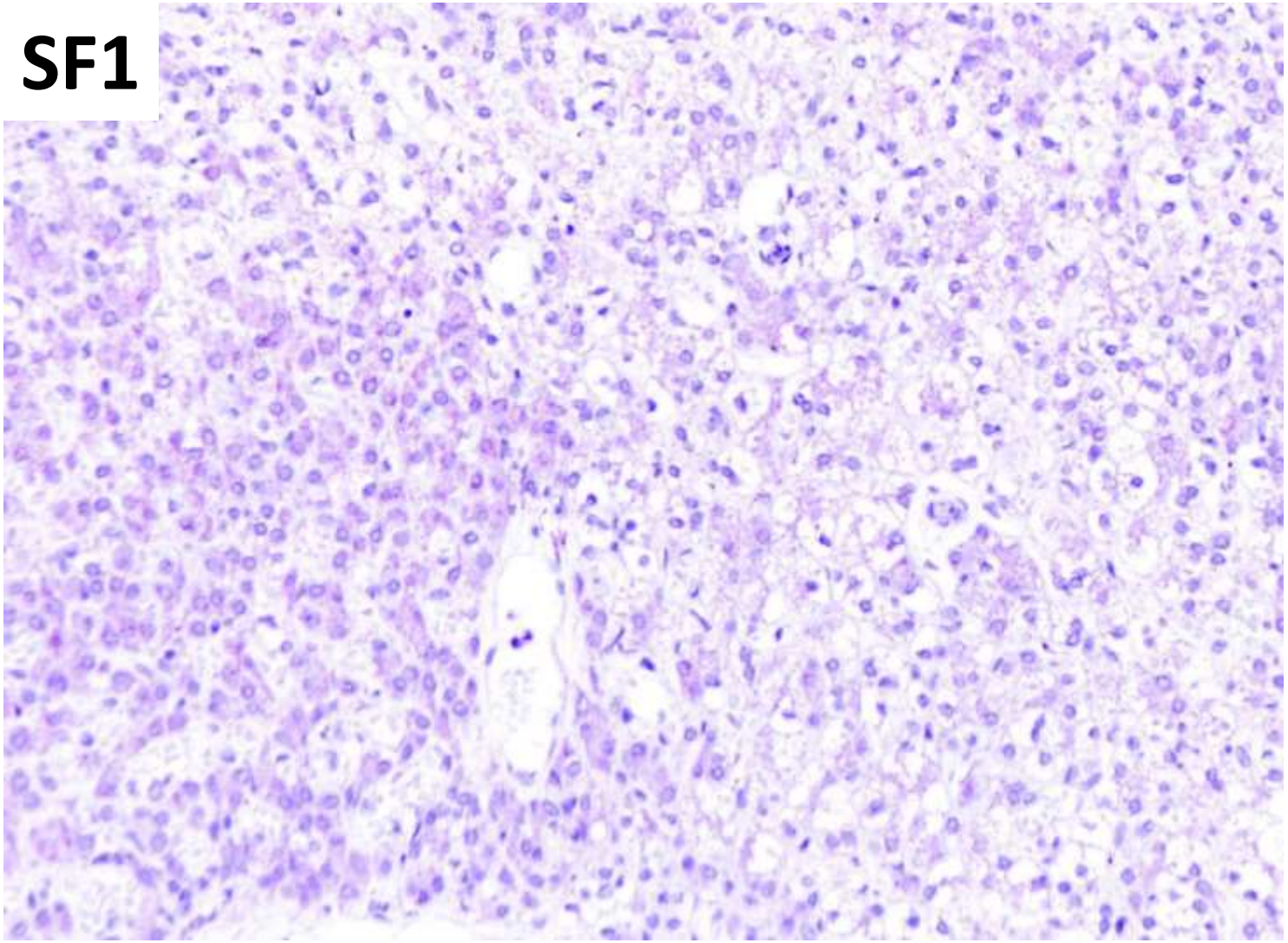
DIAGNOSIS?



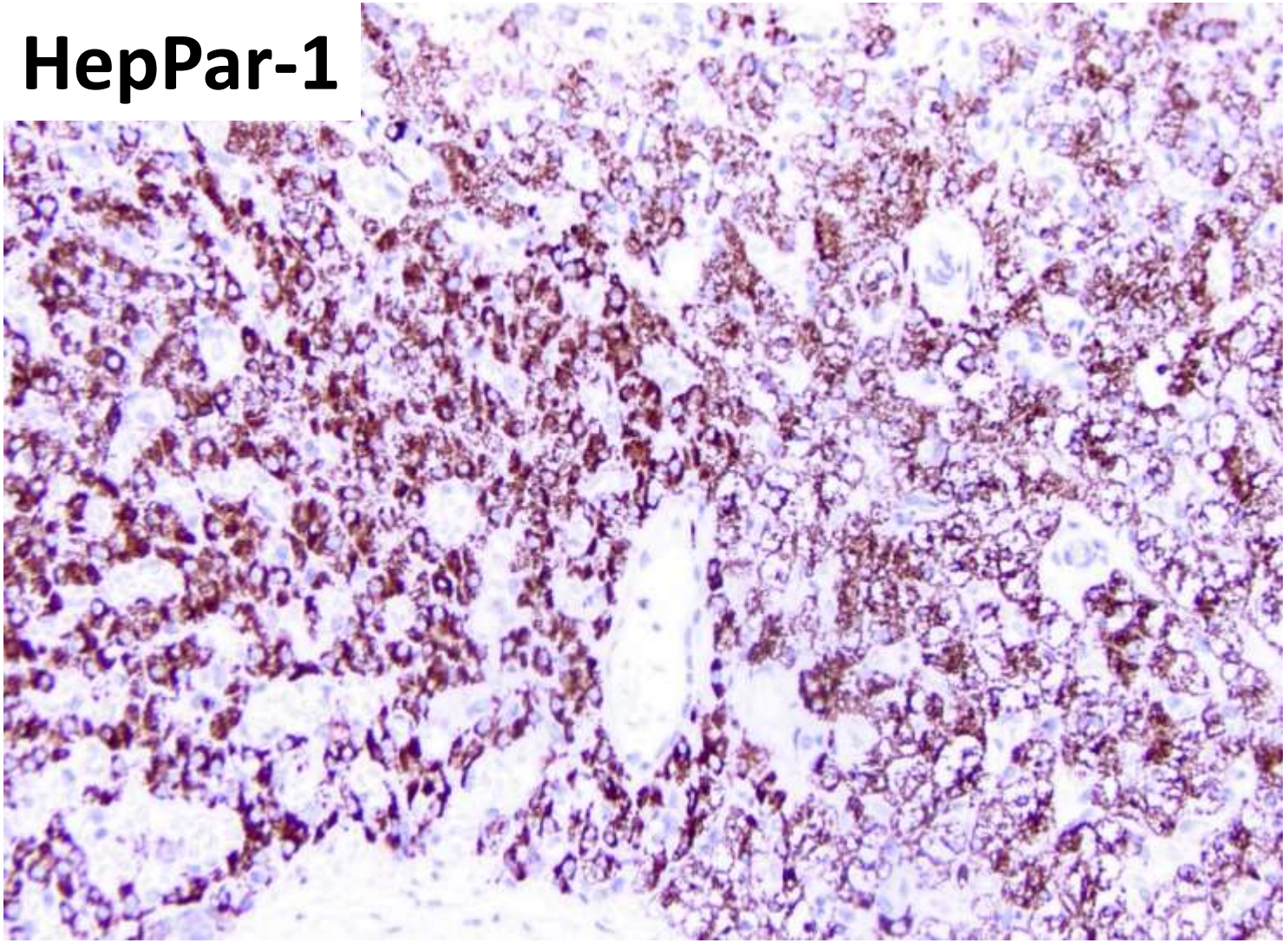




SF1



HepPar-1



Original Investigation

Heterotopic Nodules in the Placenta, an Immunohistochemical Re-evaluation of the Diagnosis of Adrenocortical Heterotopia

Pediatric and Developmental Pathology
2021, Vol. 24(1) 27–33

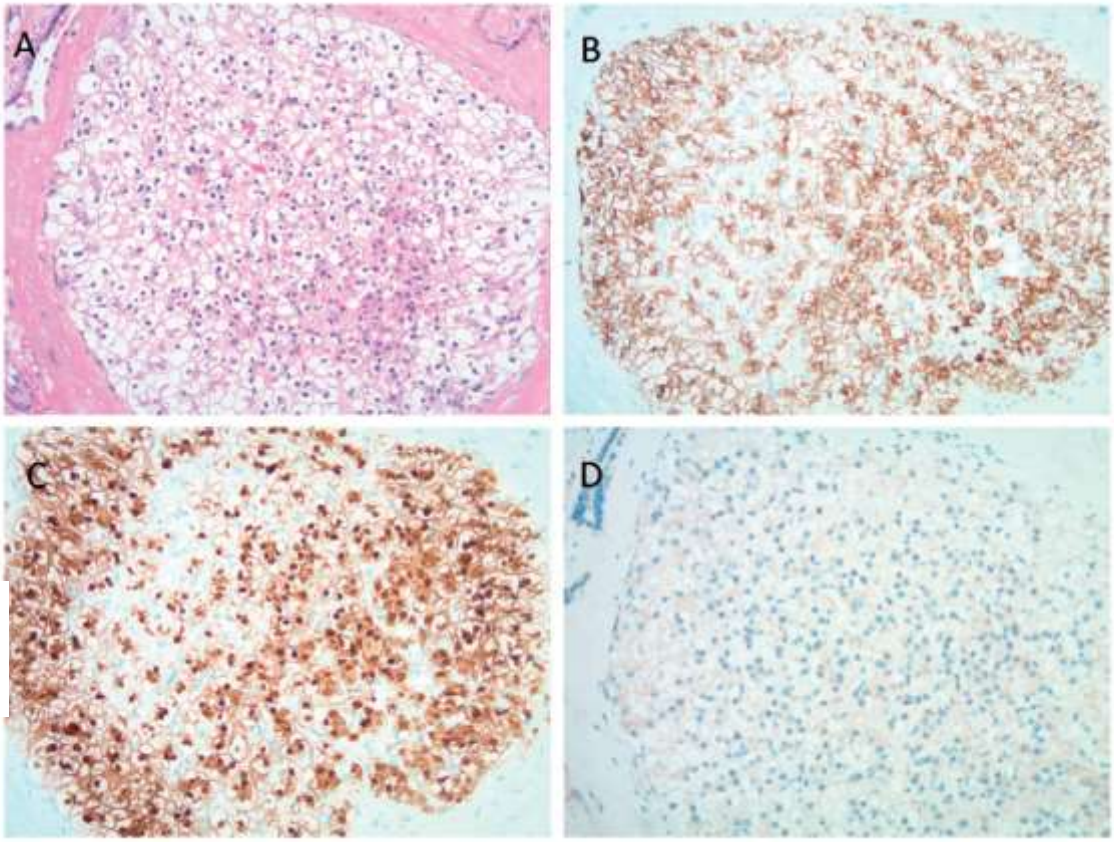
DOI: 10.1177/1093526620953361
journals.sagepub.com/home/pdp
SAGE

Amy Heerema-McKenney[1], Laura Rabinowitz[1], Robert Bendon[2], Frido Bruehl[1], Alexander Blank[1], and Halit Pinar[3]

Rare nodules of heterotopic adrenocortical and hepatic tissue are reported in placenta

- **Hepatic tissue: considered related to yolk sac primordia**
- **Adrenocortical tissue: presence more perplexing**
  - **Clear cell morphology ~ adrenal cortex of the adult; fetal adrenal gland lacks clear cells**

H&E



HepPar-1

Arginase

SF1

Methods: stained 9 placental nodules consistent with "adrenocortical" heterotopia of the placenta

Results:

- **Steroid factor-1 (SF-1) negative**
- **HepPar-1 and Arginase-1 positive**
- **PAS positive: suggests glycogen accumulation → clear cytoplasm.**

Conclusion:

- **Adrenocortical heterotopia in the placenta is a misnomer as the nodules show hepatic differentiation.**

FINAL DIAGNOSIS in our case: Hepatic Heterotopia

22-0805

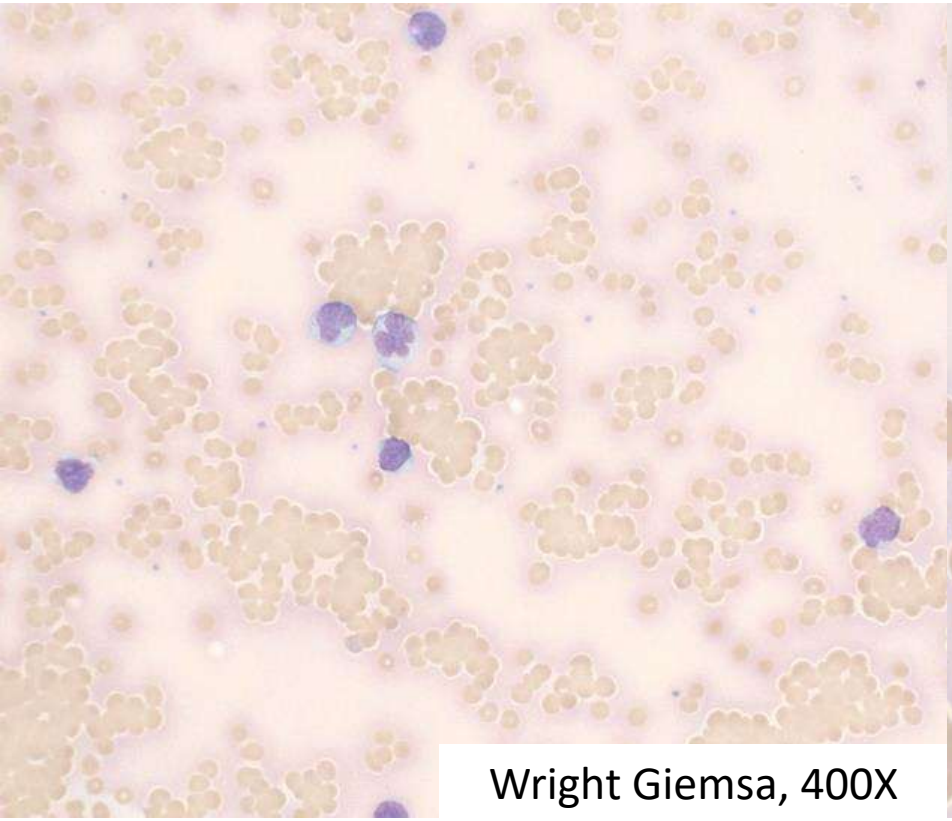
Nivaz Brar/Joshua Menke; Stanford

70ish F with lymphadenopathy and splenomegaly.
Bone marrow & lymph node submitted.

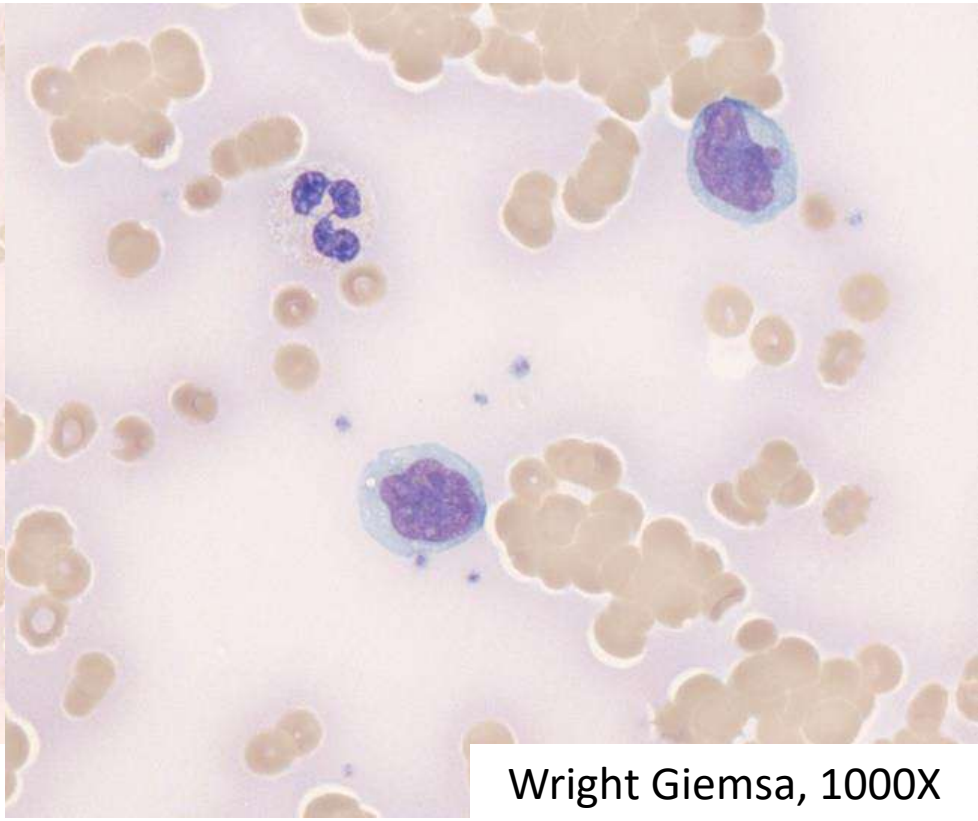
Clinical history

- 70ish F with a reported history of chronic lymphocytic leukemia diagnosed in another country
- Patient has anemia with prominent RBC agglutination, neutropenia, and thrombocytopenia
- PET-CT shows massive splenomegaly (20 cm in vertical axis), mildly enlarged hypermetabolic lymph nodes above and below the diaphragm, and moderate uptake throughout the marrow

Peripheral blood smear shows RBC agglutination and atypical lymphoid cells



Wright Giemsa, 400X



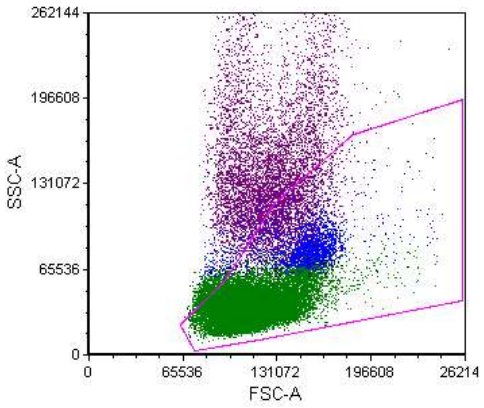
Wright Giemsa, 1000X

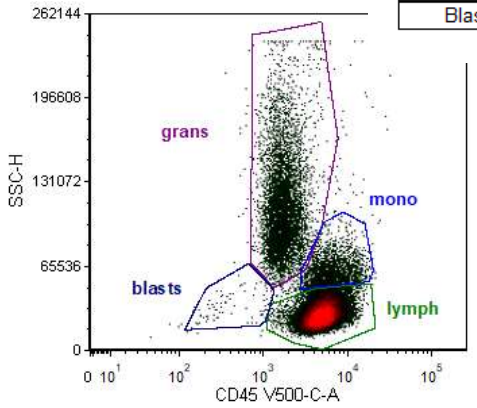
Peripheral blood flow

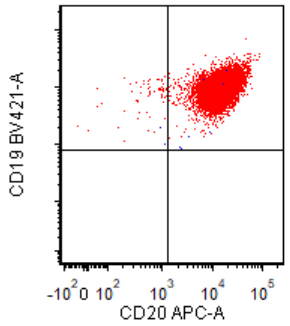
Differential:

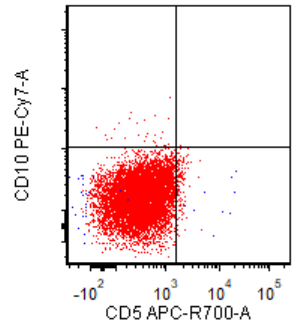
	% not debris	%CD45+
Lymphocytes	75.0	75.1
Granulocytes	17.3	17.3
Monocyte	6.7	6.7
Blasts	0.2	0.1

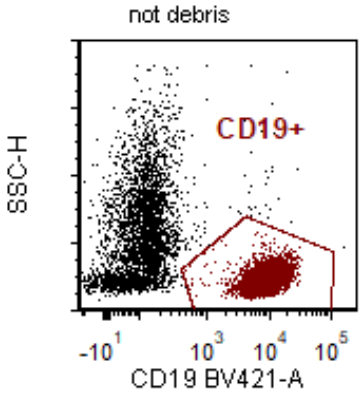
Abnl B	62.04% of CD45+ 61.96% of not debris (24453 events)

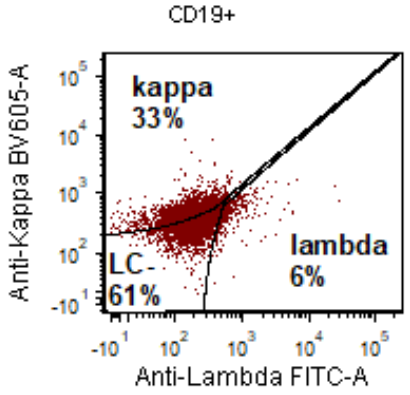


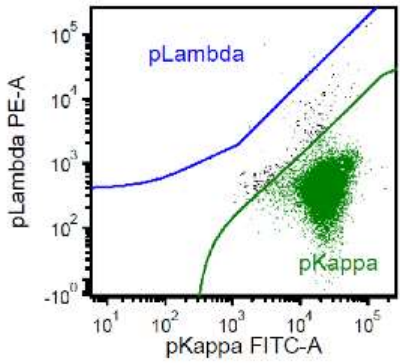


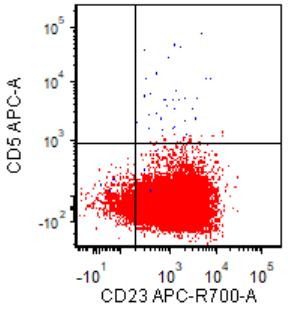


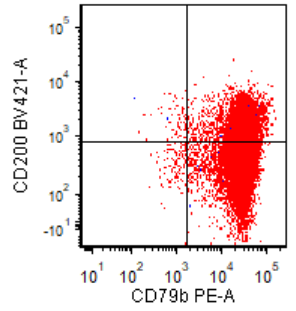




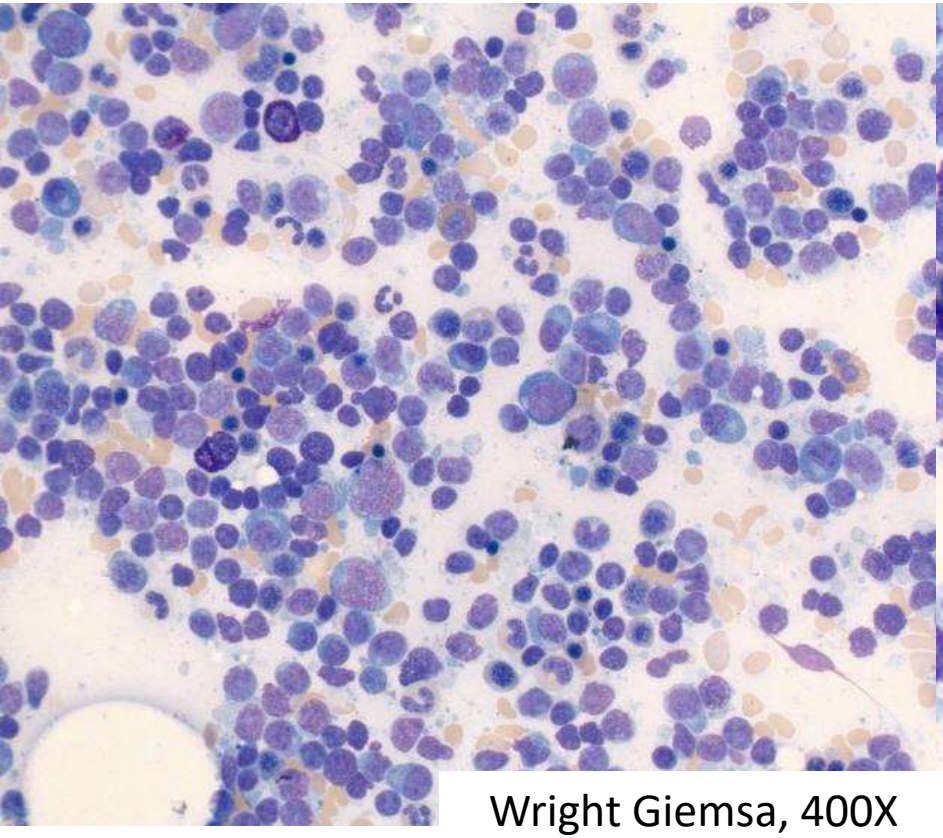




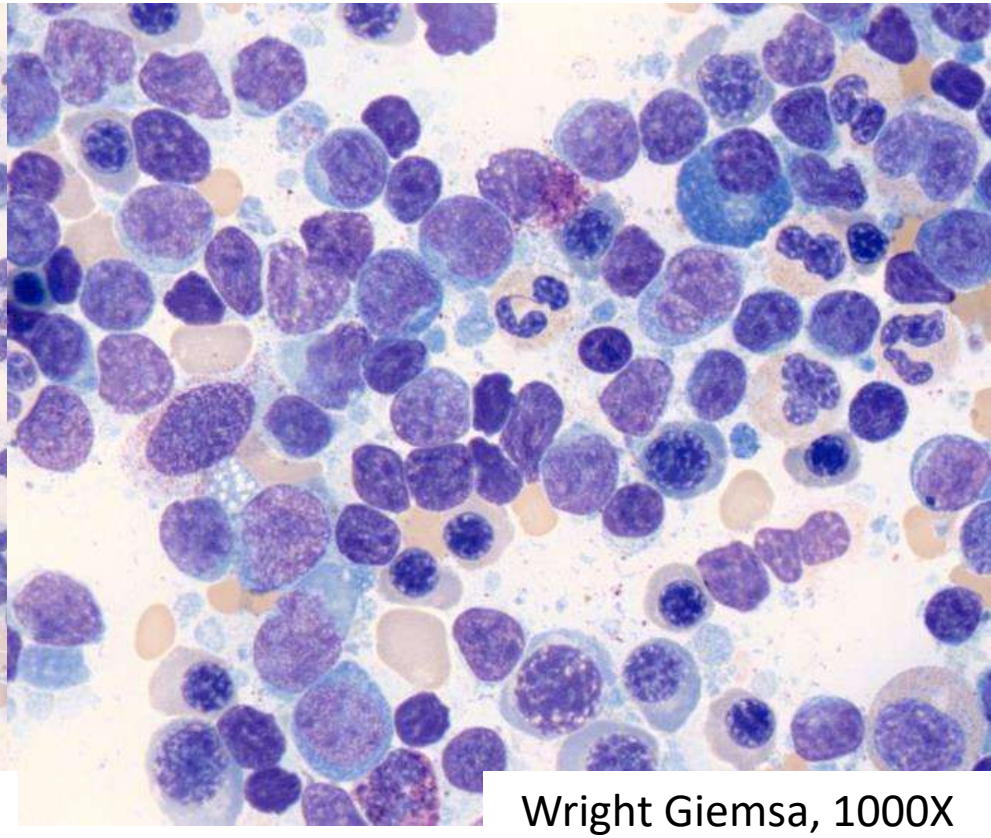




Bone marrow aspirate

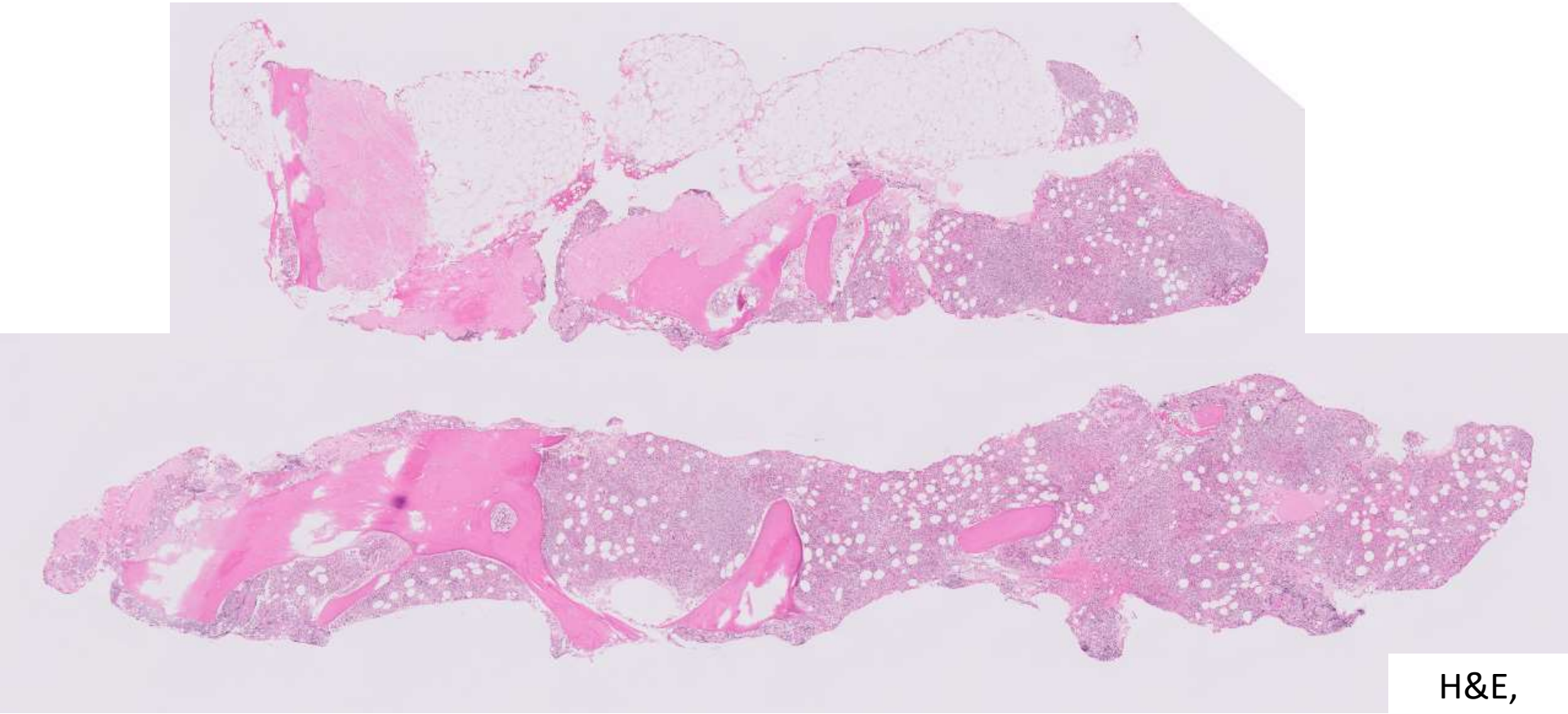


Wright Giemsa, 400X

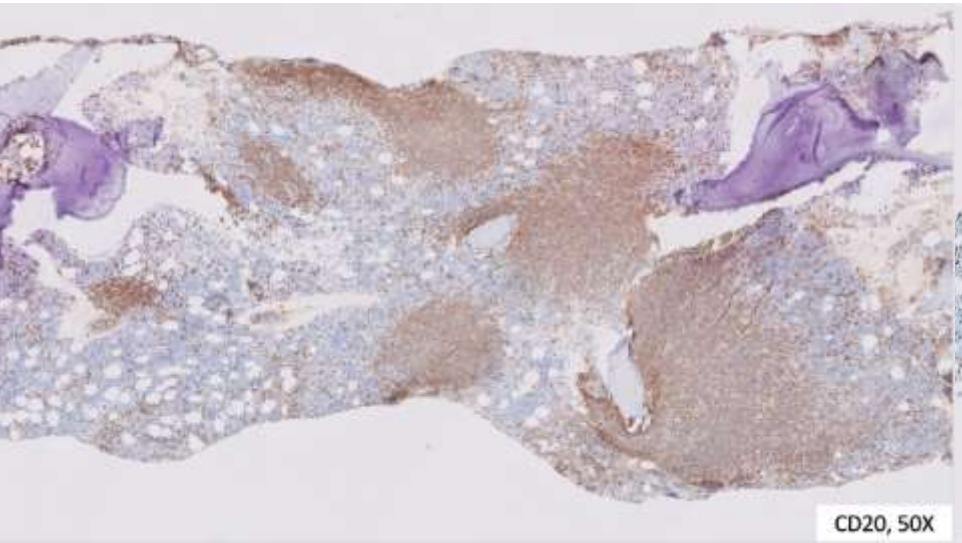


Wright Giemsa, 1000X

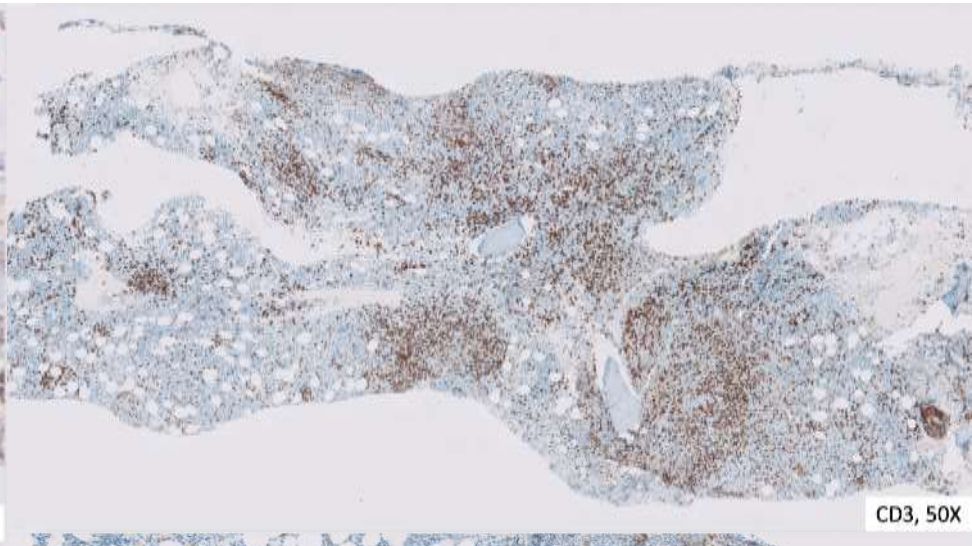
Bone marrow core biopsy



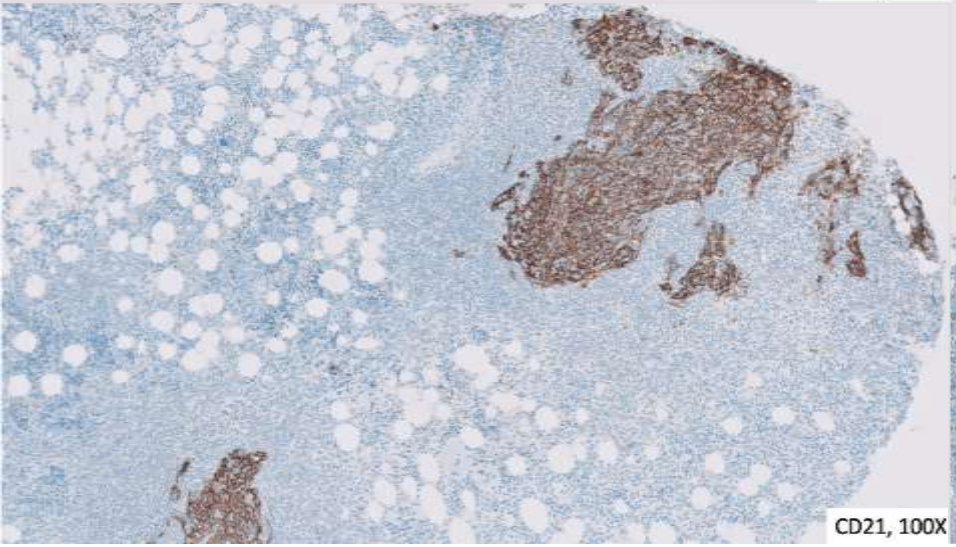
H&E,
10X



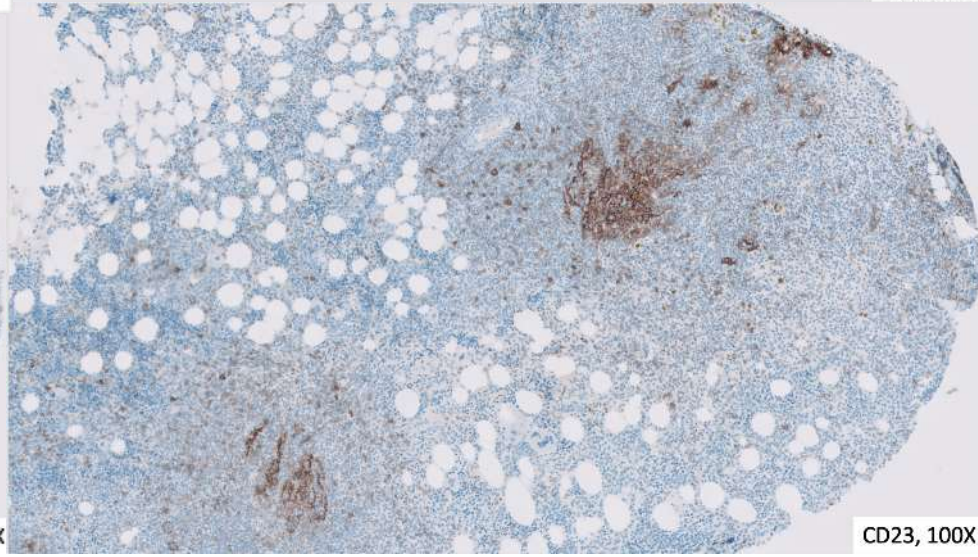
CD20, 50X



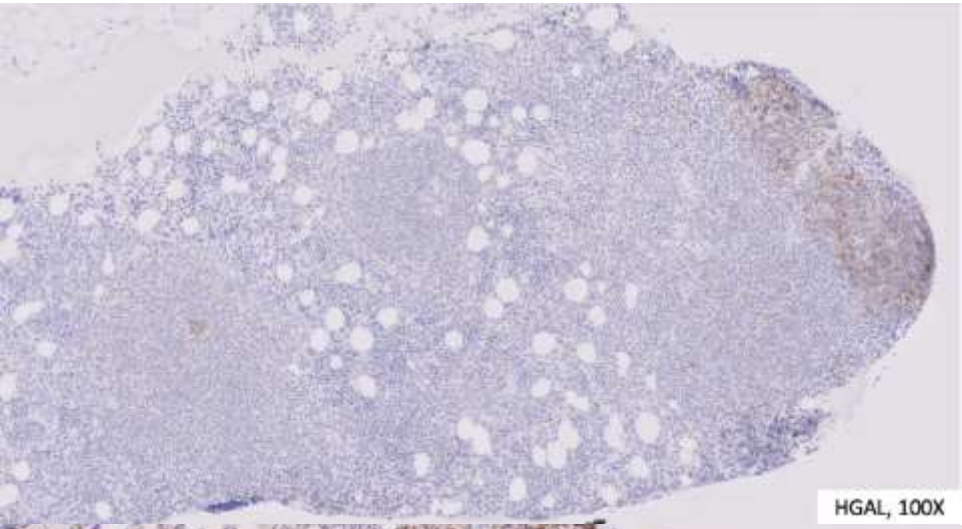
CD3, 50X



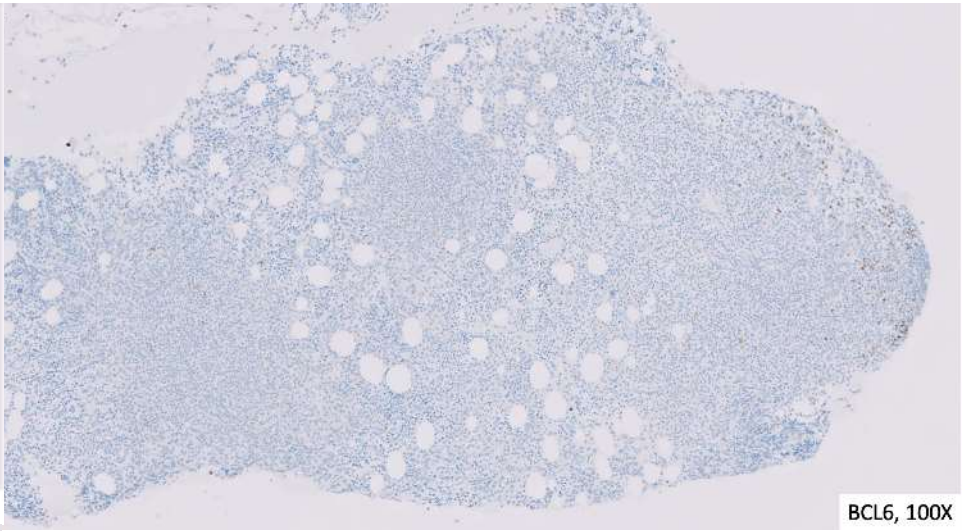
CD21, 100X



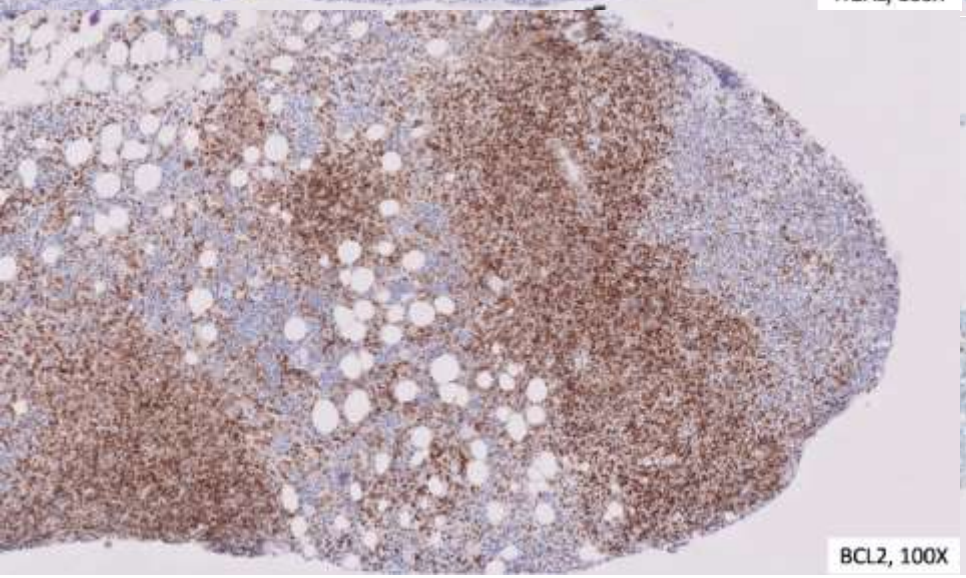
CD23, 100X



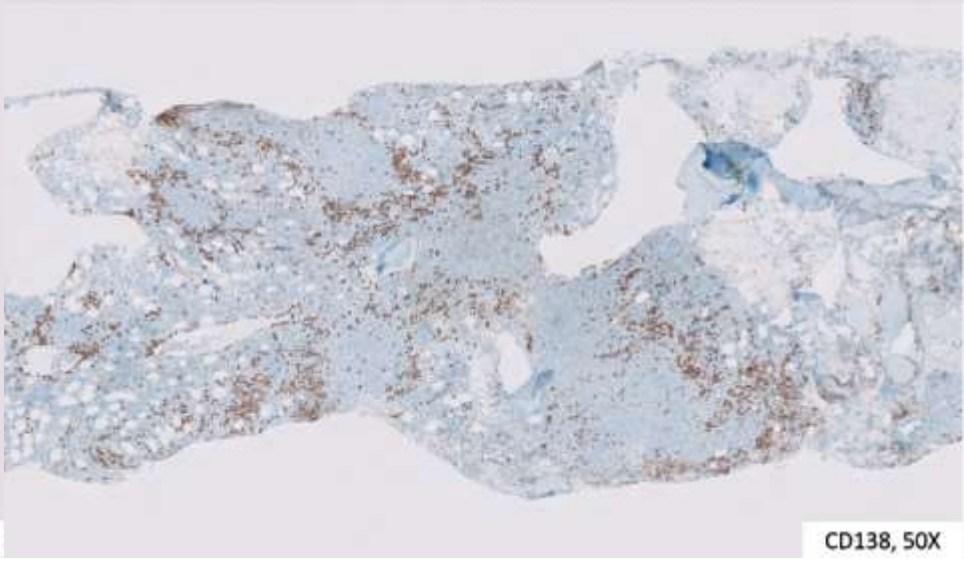
HGAL, 100X



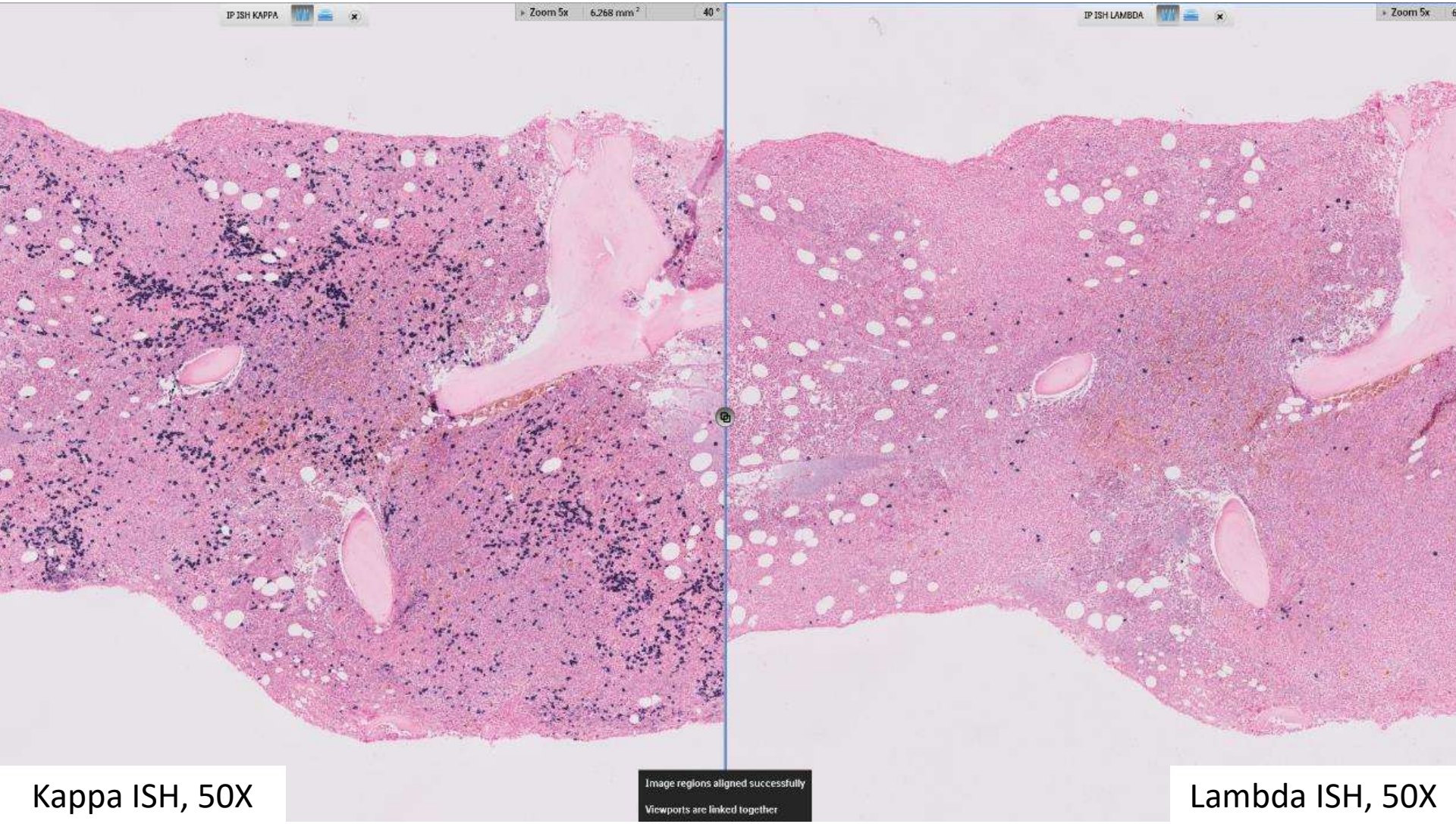
BCL6, 100X



BCL2, 100X

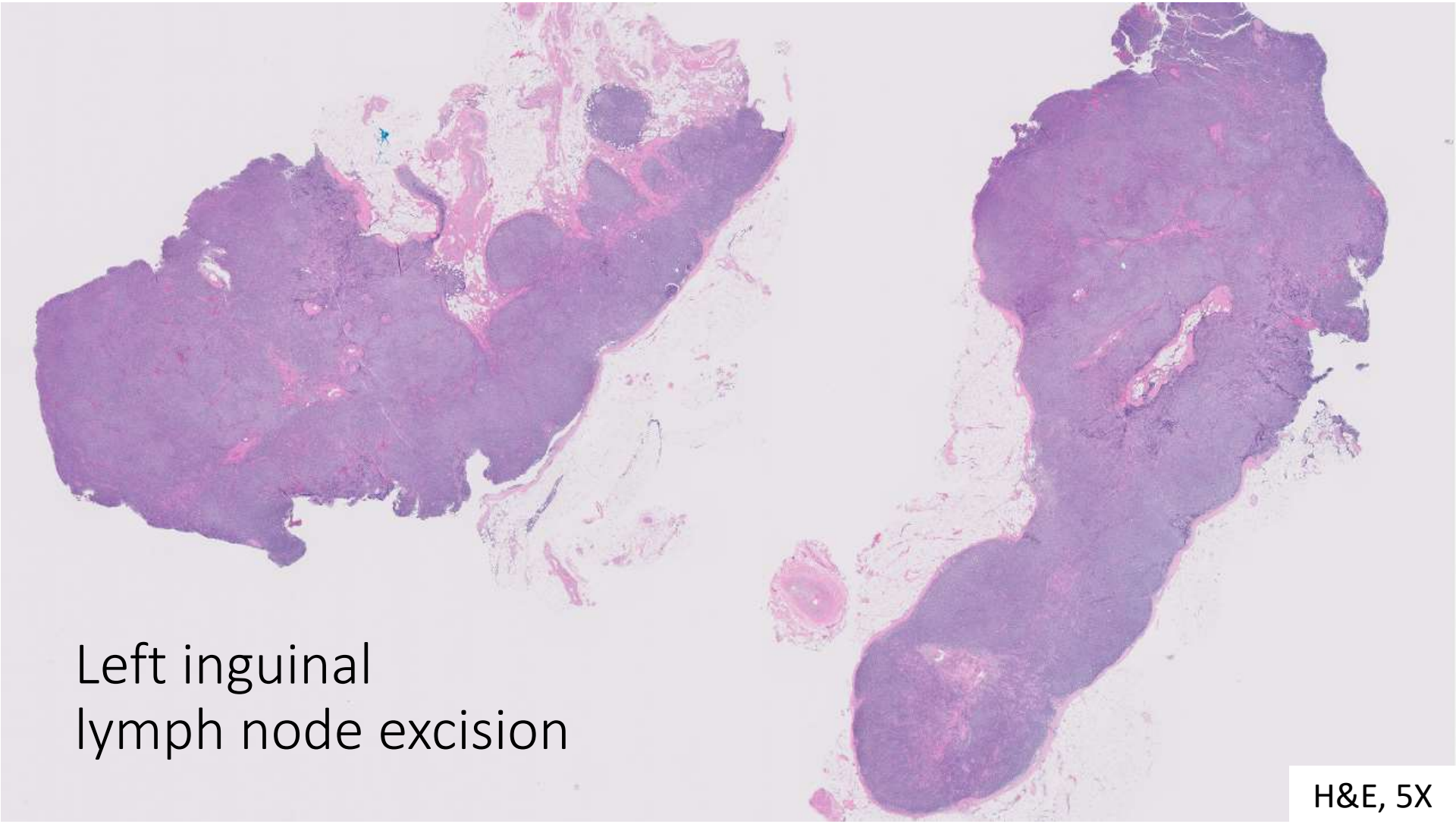


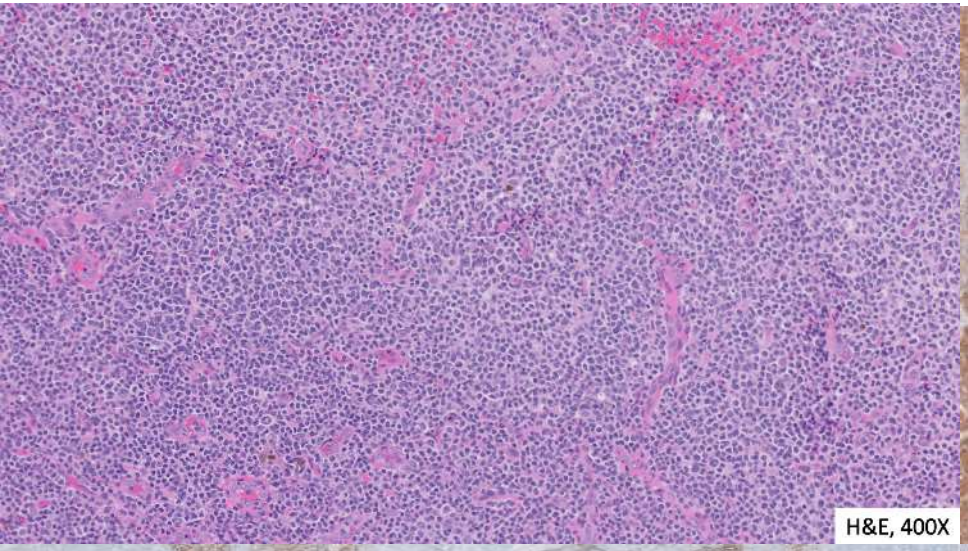
CD138, 50X

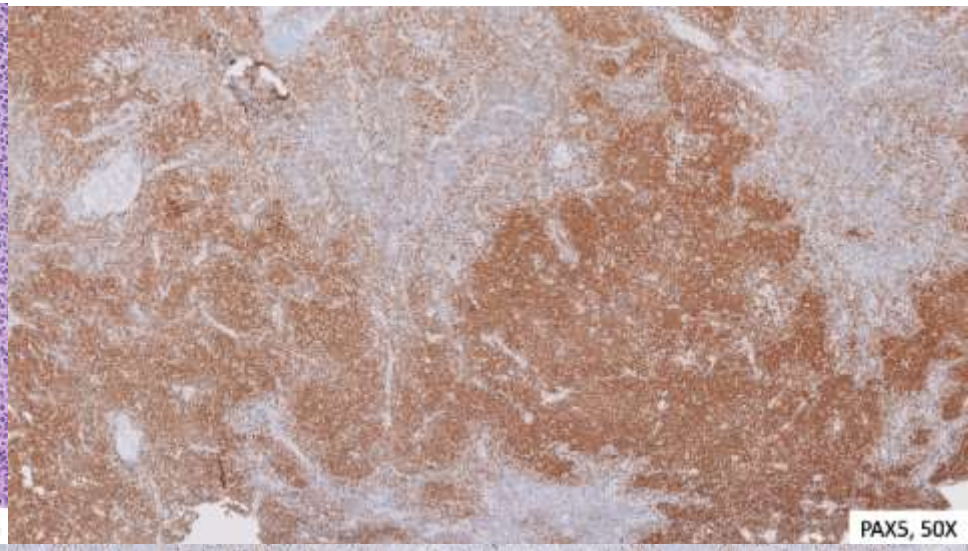


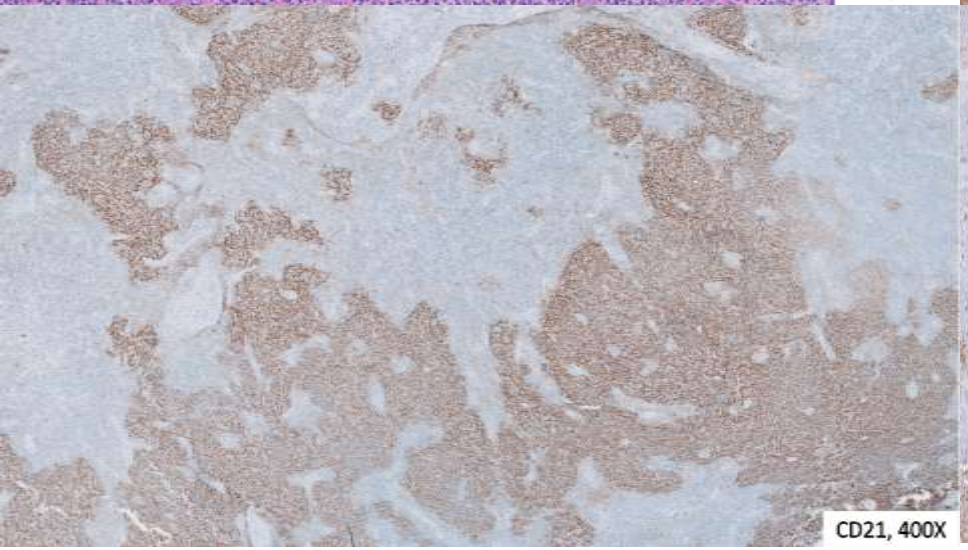
Kappa ISH, 50X

Lambda ISH, 50X


Left inguinal
lymph node excision
H&E, 5X


H&E, 400X


PAX5, 50X


CD21, 400X


Ki-67, 400X

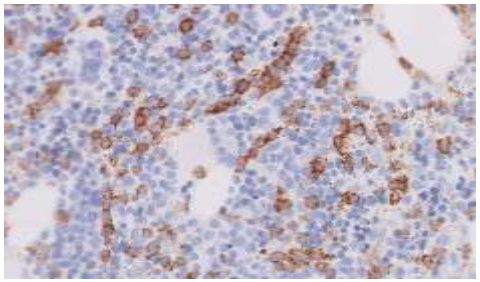
Differential Diagnosis

- Polyclonal B-cell lymphocytosis
- Hair cell leukemia
- Splenic marginal zone lymphoma
- Chronic lymphocytic leukemia

Diagnosis

- Marginal zone lymphoma (likely splenic) with activating NFKB2 3’ deletion

Splenic marginal zone lymphoma



- B-cell lymphoma comprising 1-2% of all lymphoma and median age of 65 years old*
- Most common sign is splenomegaly. Anemia, thrombocytopenia and/or autoimmune conditions may also be present.
  - Frequent sites: bone marrow (nearly 100% of cases), peripheral blood (68-57%, lymphocytes with or without villous projections), liver (33%), abdominal lymphadenopathy (25%) and less commonly peripheral lymphadenopathy (17%)*
- Histology: micronodular lymphoid infiltrate with biphasic follicle appearance and diffuse red pulp (spleen); intertrabecular and intrasinusoidal (marrow)
- IHC: CD20+, CD79a+, CD5-, CD10-, CD23-, BCL6-, LEF1-, BCL1-, annexin A1-, IgD+
- Indolent with overall 5-year median survival 65-78%, although the prognosis is poor if associated with *TP53* mutations, 7q deletion, absence of *IgVH* somatic mutation.
- Differential: Nodal or non-nodal marginal zone lymphoma, hairy cell leukemia, chronic lymphocytic leukemia, follicular lymphoma

*Piris and Mollejo. “Splenic Marginal-Zone Lymphoma and Other Small B-Cell Neoplasms in the Spleen” in *Hematopathology*, ed. Jaffe. (2016), 309-319.

Molecular findings: novel NFKB2 3’ activating deletion

- Pathogenic *NFKB2* 3’ activating exonic deletion
  - Caused by a 38 kp deletion between *NFKB2* exon 18 and a downstream intergenic region, resulting in deletion of portion of exon 18 and all of exons 19-23 of *NFKB2*
  - Prior study has shown this results in a truncated NFKB2 protein and an oncogenic gain of function with downstream activation of non-canonical NF-kappaB signaling.
  - Not previously described in marginal zone lymphoma
- Two variants in EP300 of uncertain significance, although one of the *EP300* variants was immediately adjacent to a hotspot and suspicious for pathogenicity.
- No MYD88 mutation was detected.

Discussion

- Pathogenesis of SMZL are not well understood, possibly related to infectious agents (*Hep C, C. jejuni, B. burgdorferi, C. psittaci*)
- *NFKB2* 3' activating deletions have been described in cutaneous T-cell lymphomas and diffuse large B-cell lymphoma, but not in marginal zone lymphoma
- *NFKB2* signaling pathway activation is common across the spectrum of marginal zone lymphomas, nodal, extranodal, and splenic.
  - More than 30% of SMZLs have NF-κB activation and approximately 15% are seen with *TP53* mutation
- NGS is not routinely performed in small B-cell lymphomas currently, but this case raises questions about the methods and need for routine detection of structural variants.

References (Pubmed Identifications)

- 7651435, 21881048, 22435566, 26192916, 17548614, 17119127
- WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue (Medicine) 4th Edition. 2017.
- Piris and Mollejo. “Splenic Marginal-Zone Lymphoma and Other Small B-Cell Neoplasms in the Spleen” in *Hematopathology*, ed. Jaffe. (2016), 309-319.

22-0806

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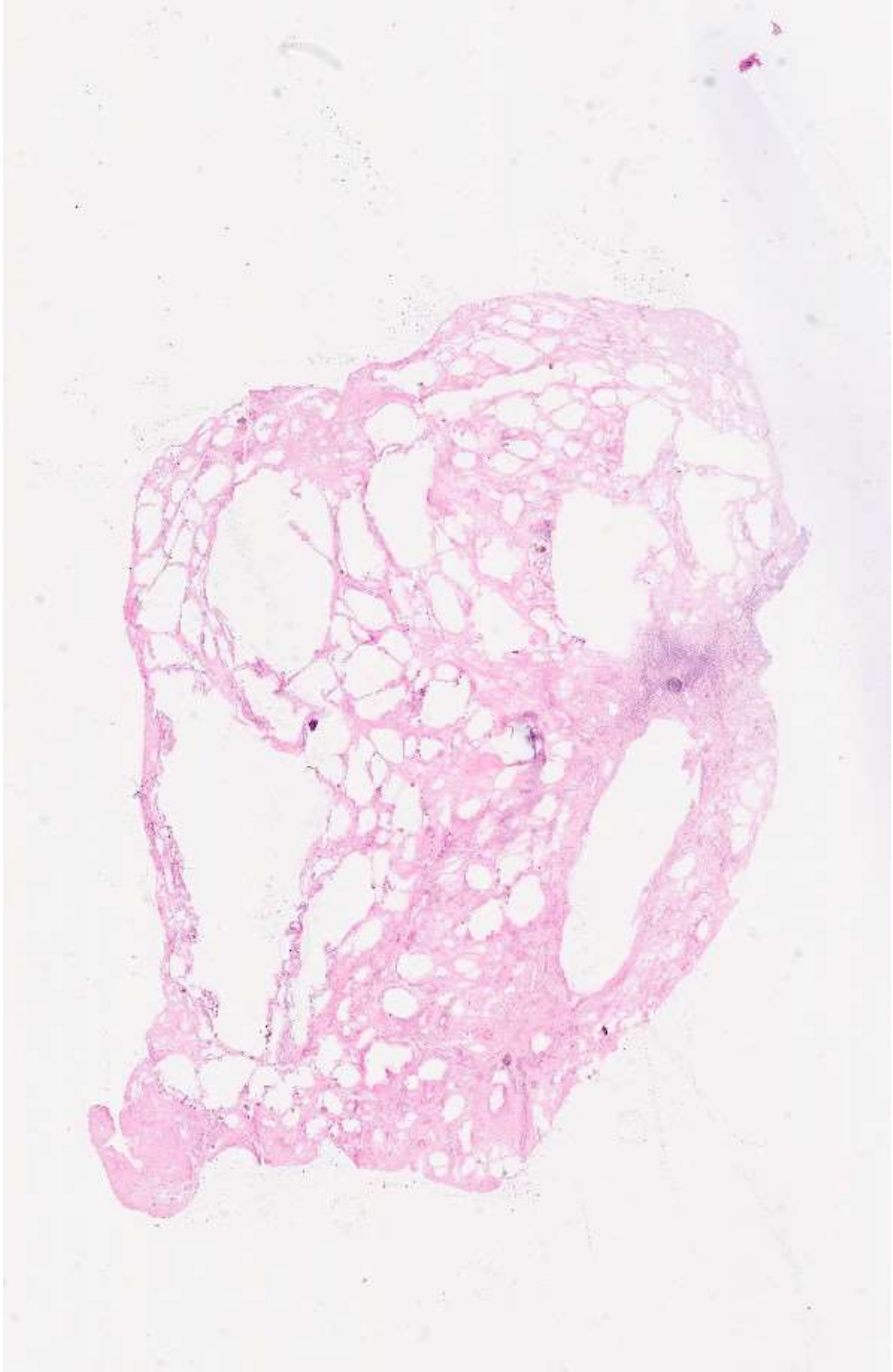
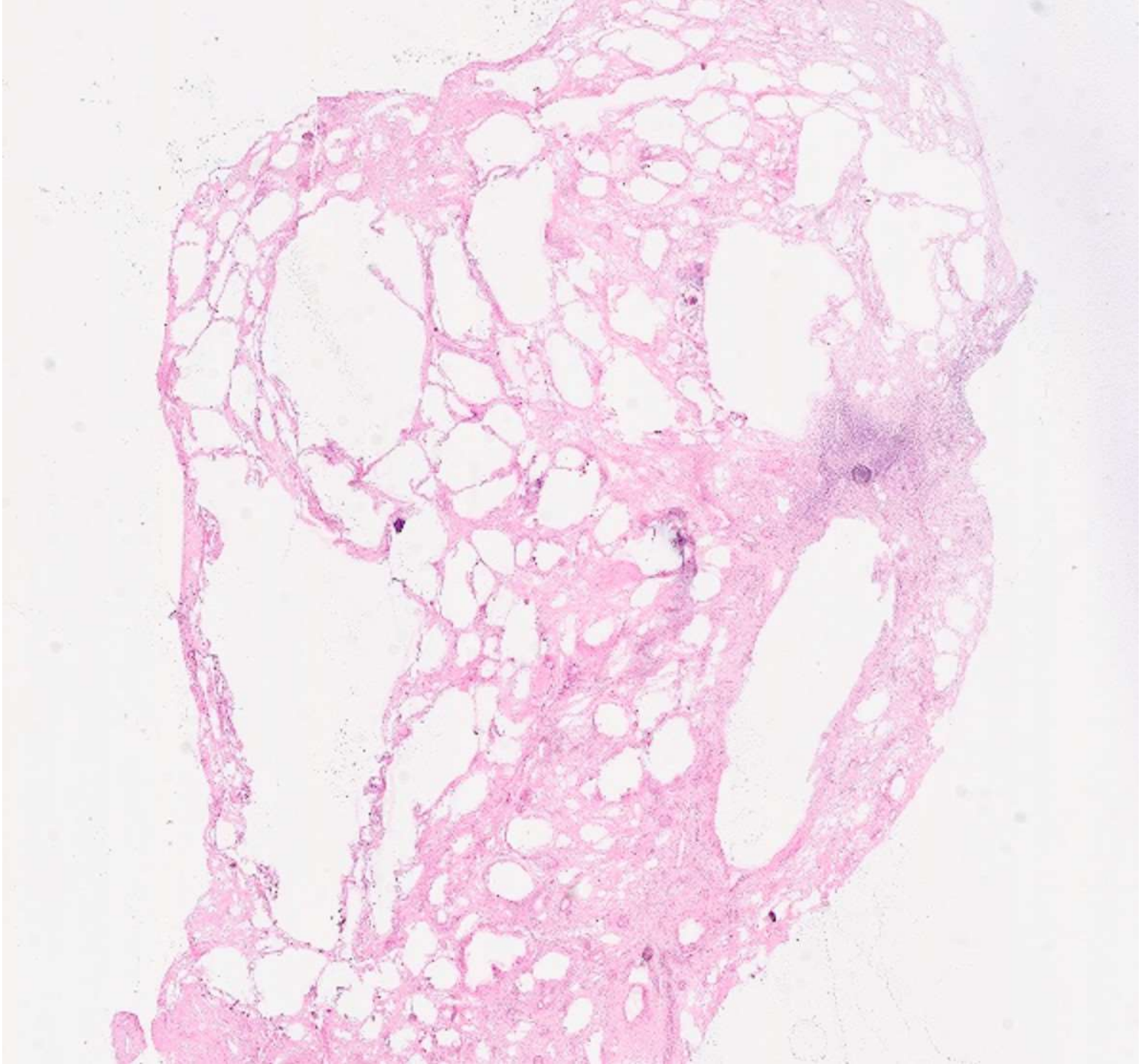
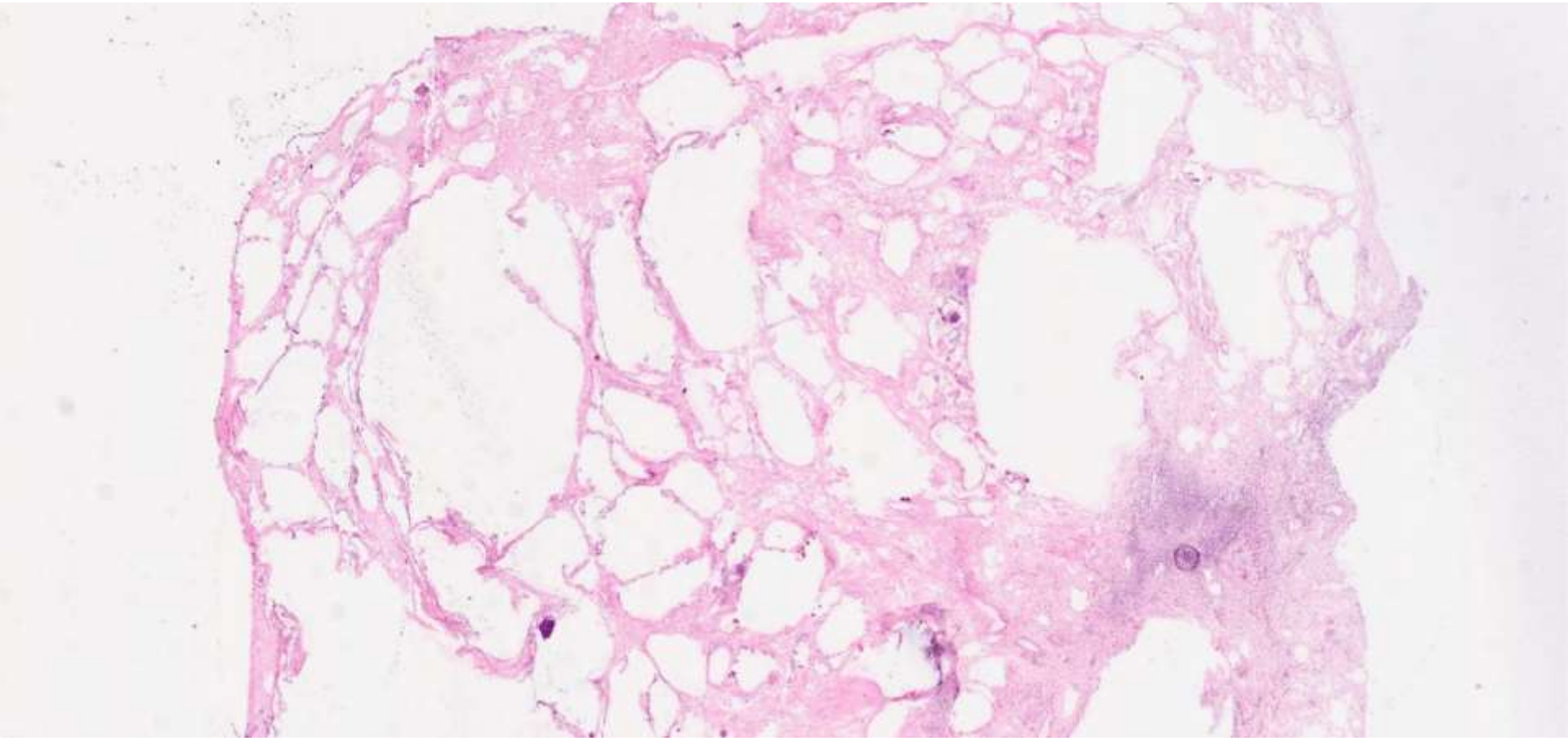
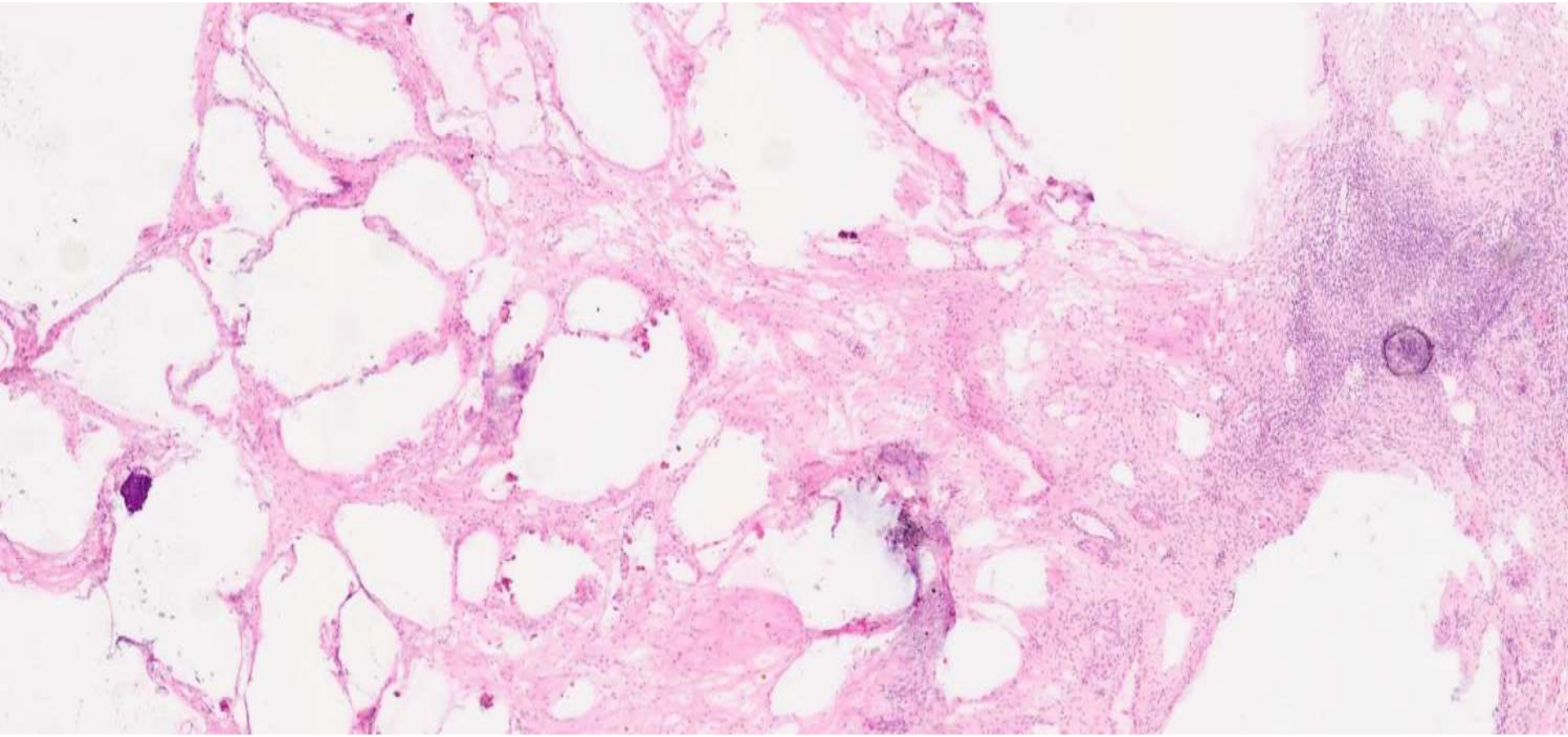
Ankur Sangoi; El Camino Hospital

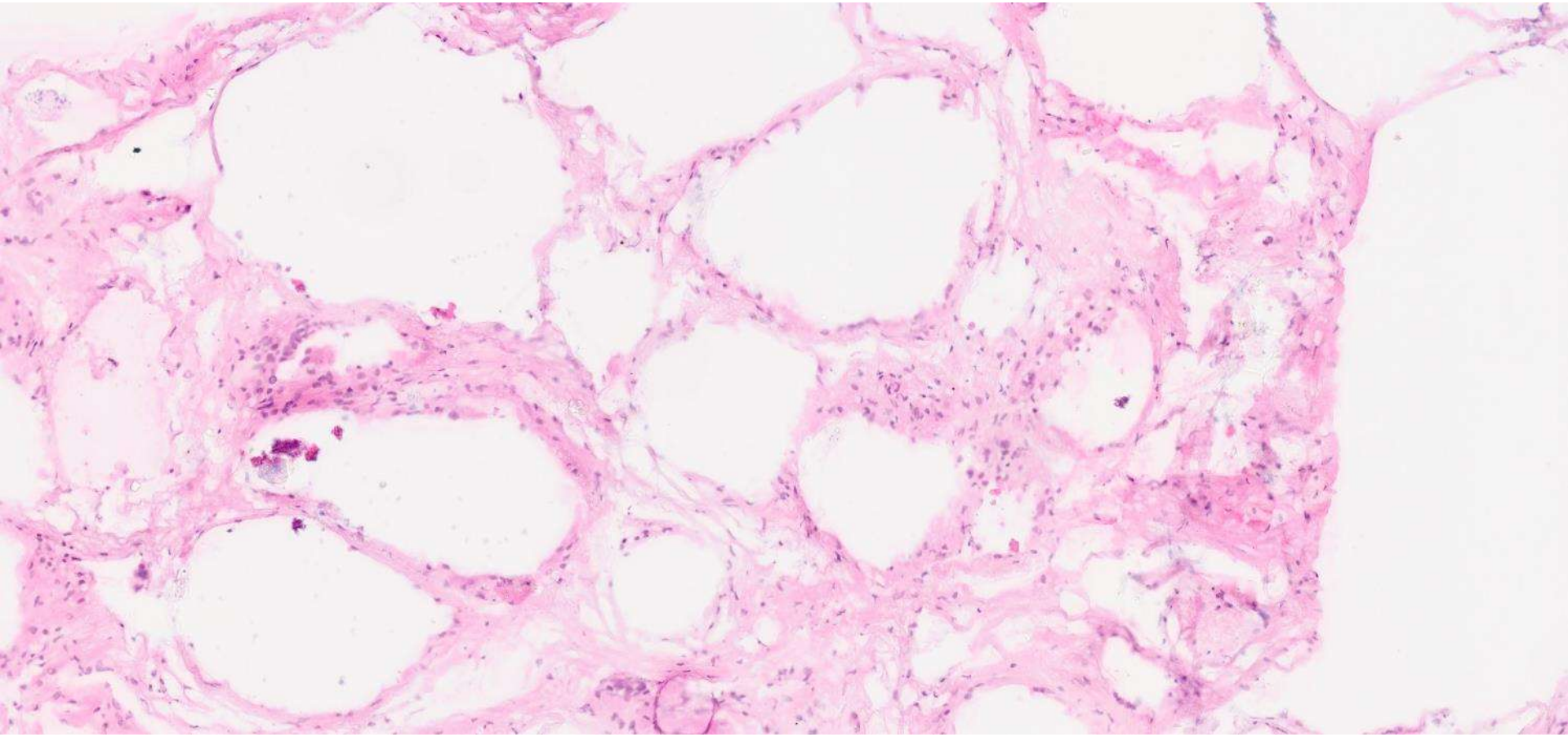
Teenage girl presents with left ovarian cystic mass, frozen section of left ovarian cyst submitted.

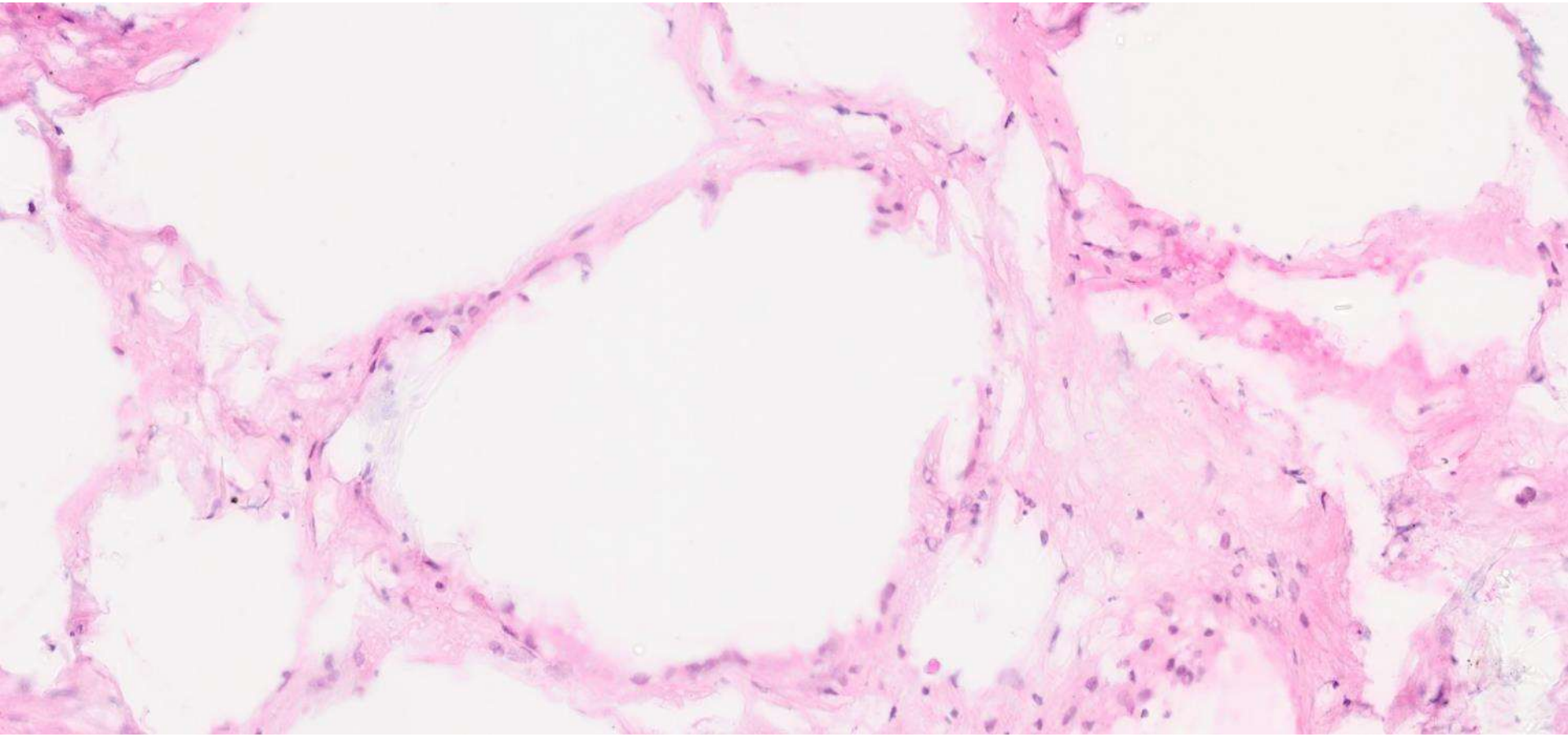


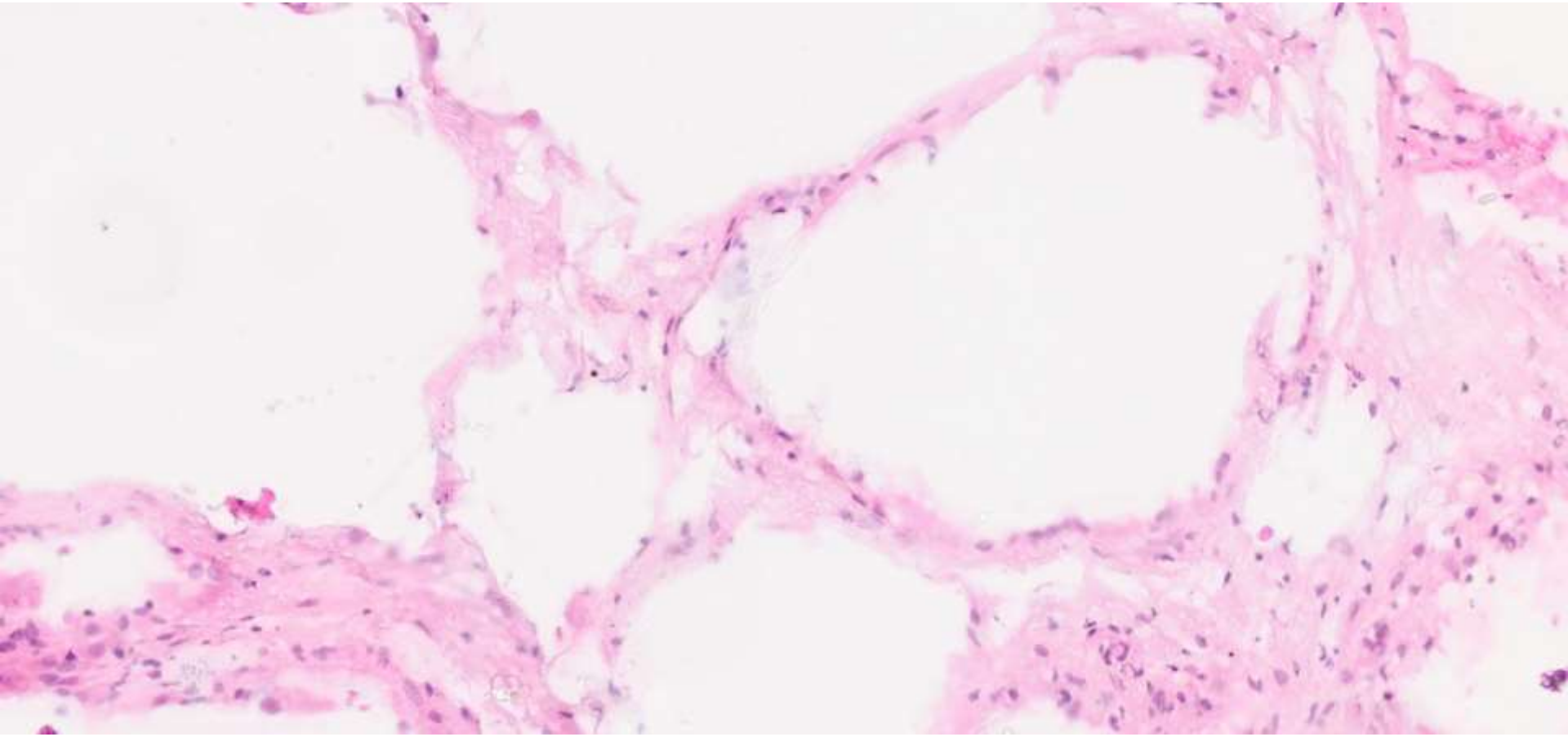






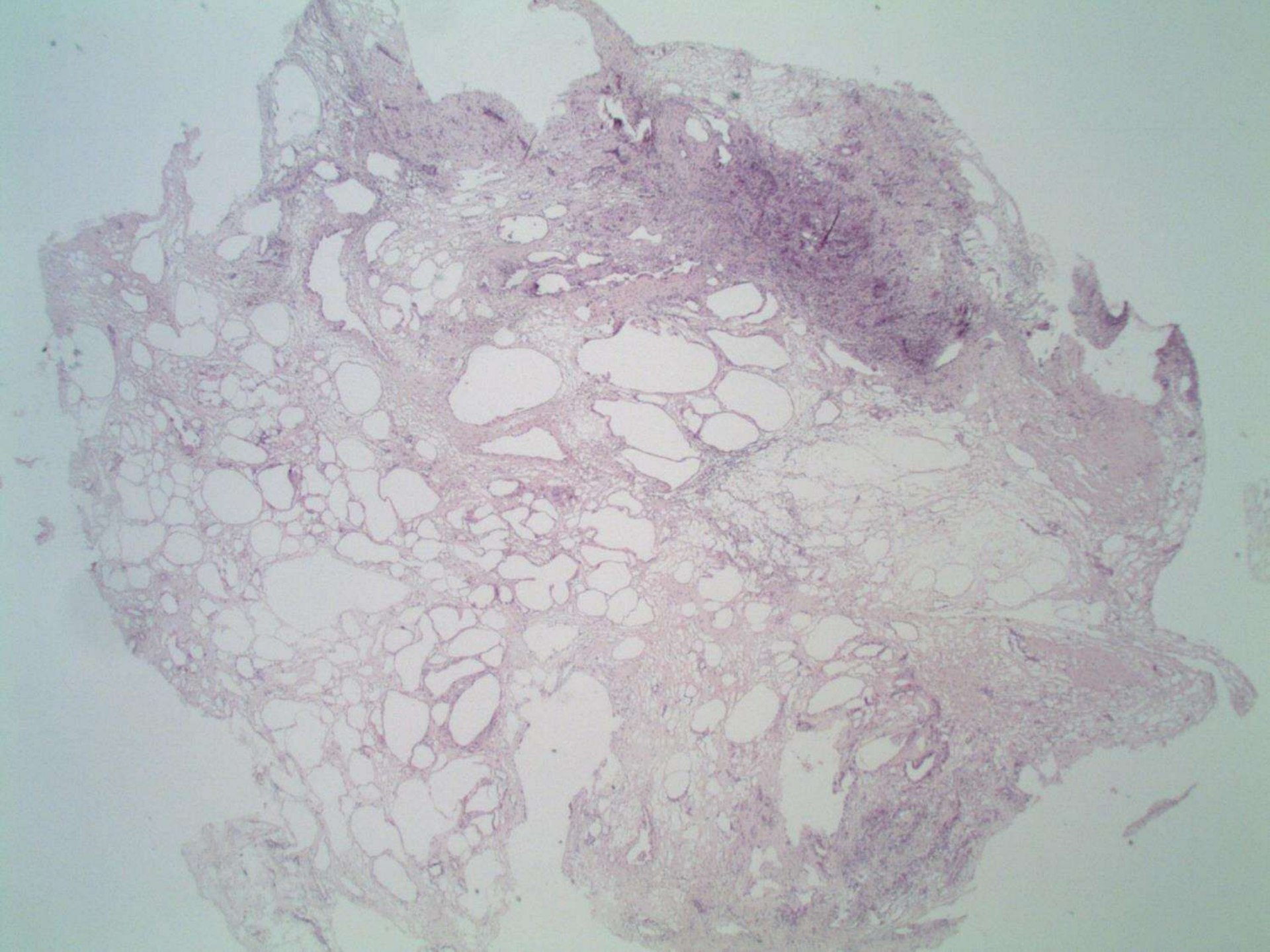


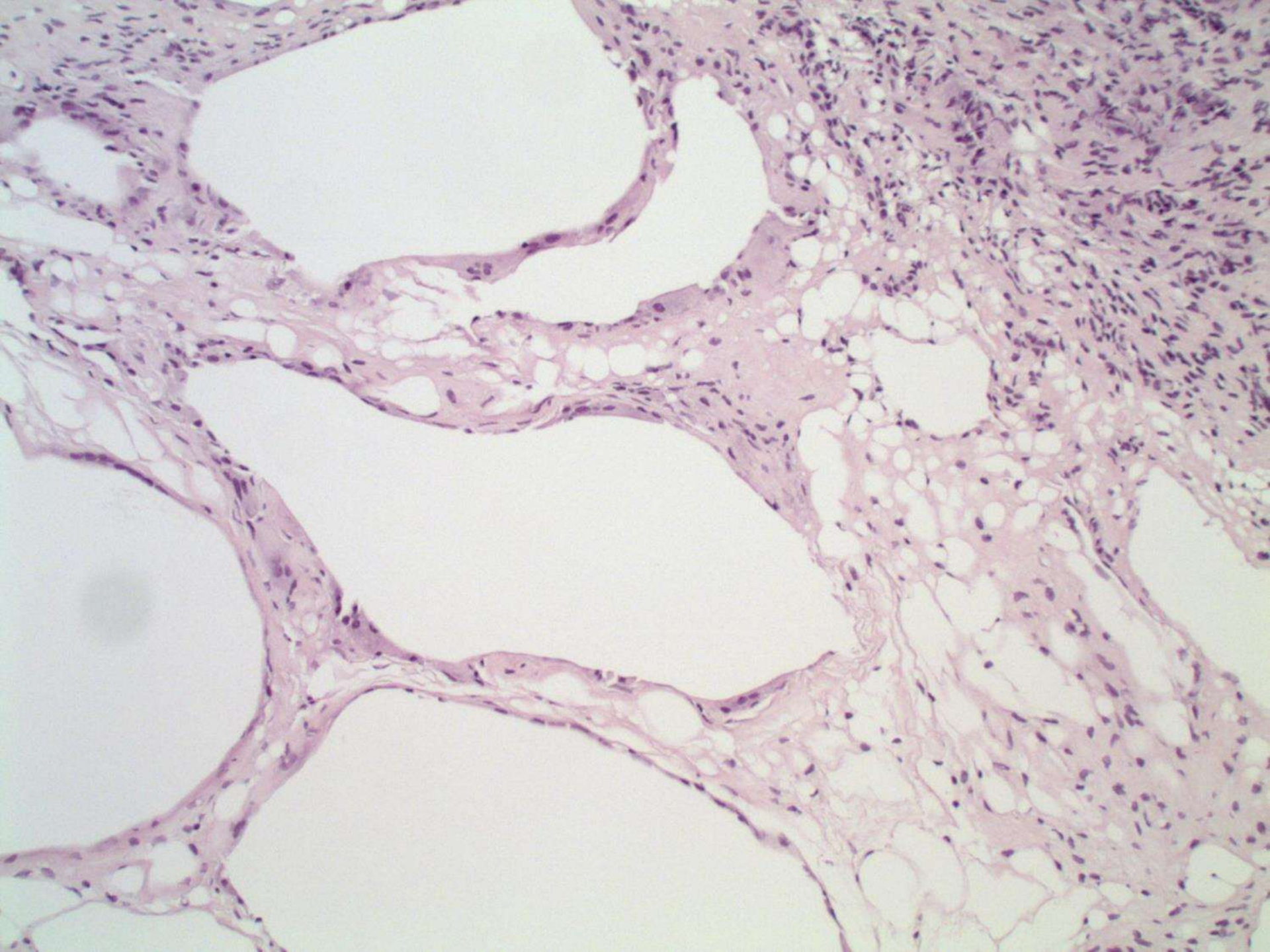


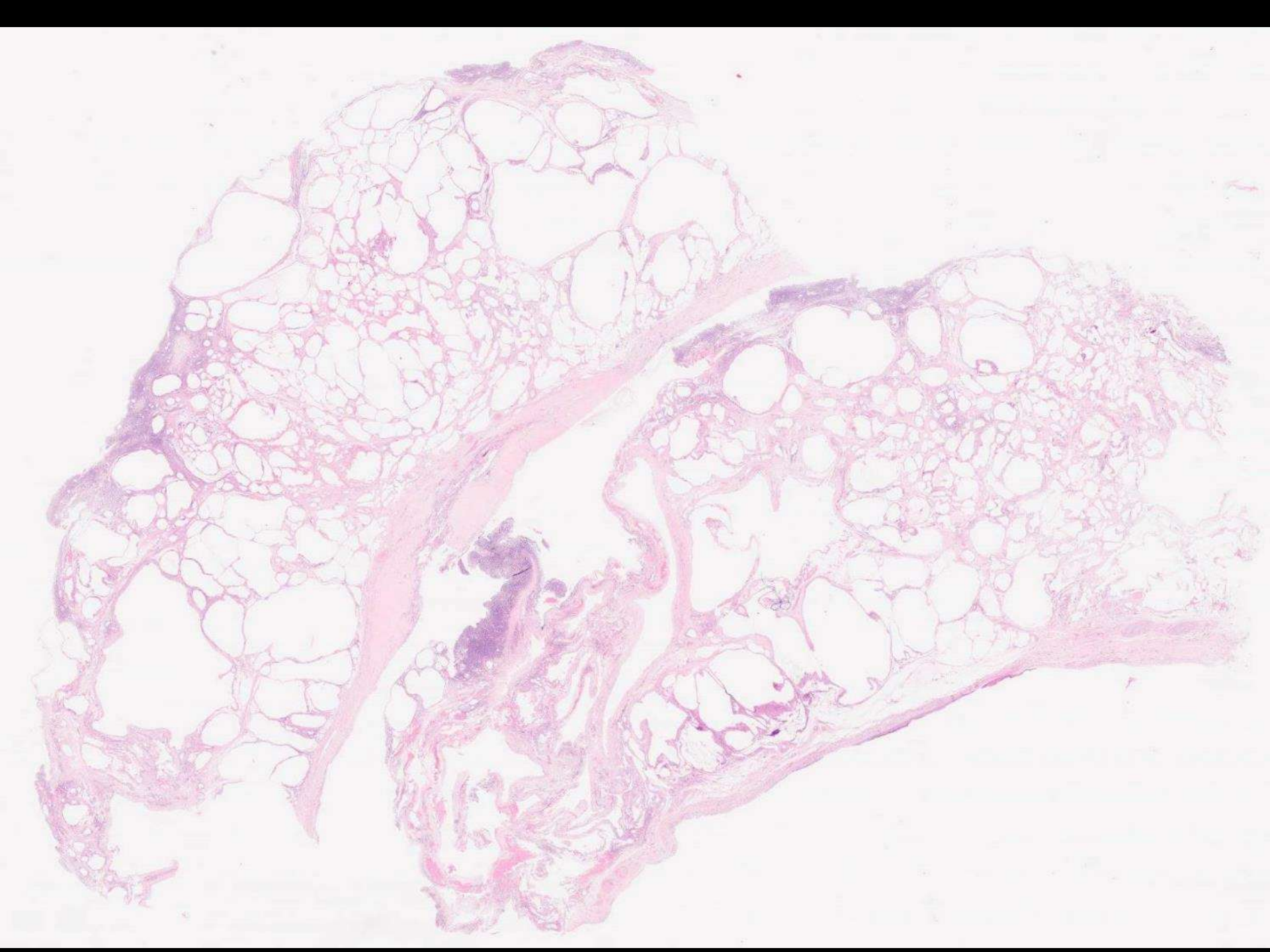


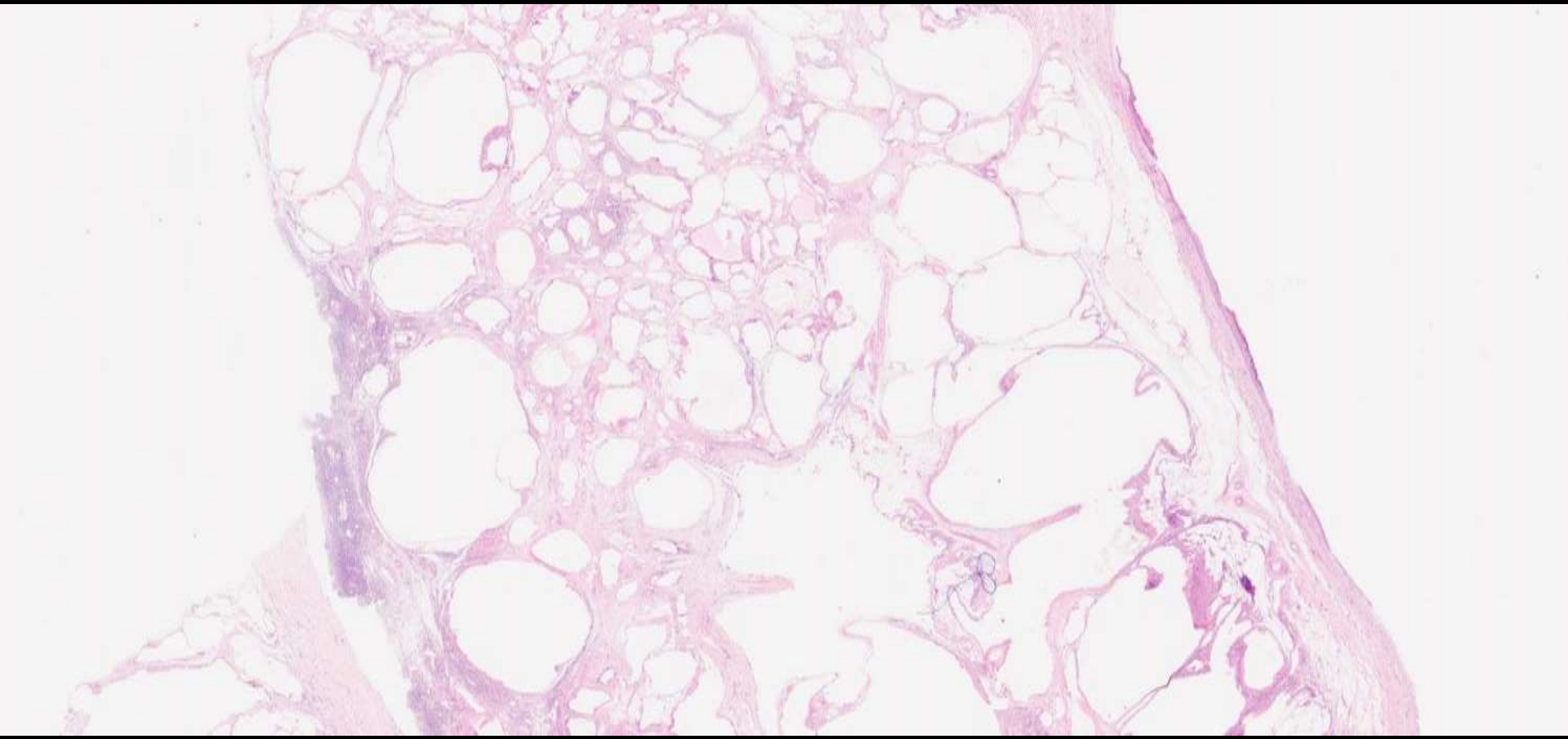
DDx

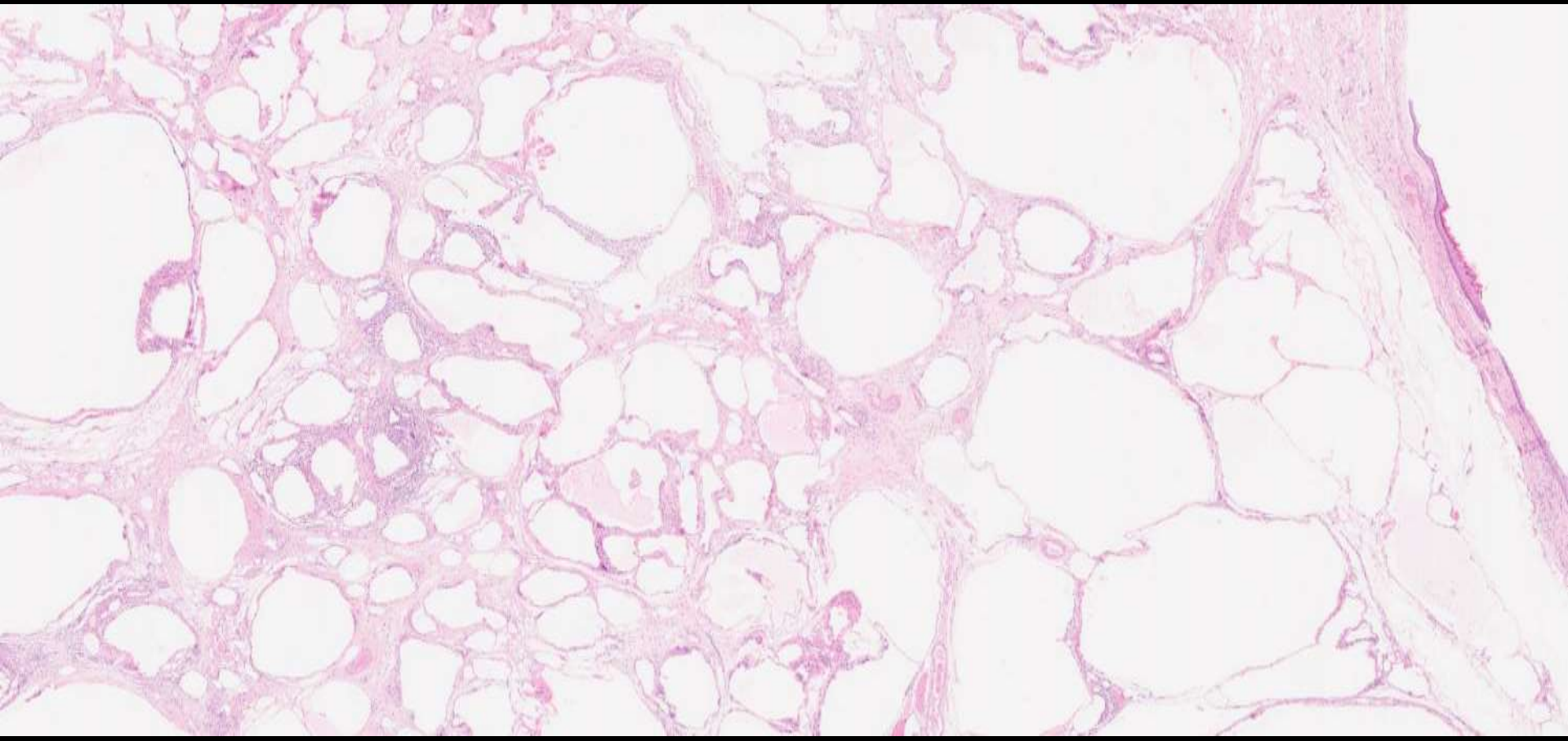
- Adenomatoid tumor
- Lymphangioma
- Mesothelial cysts
- Biopsy site changes (if prior procedure)
- teratoma

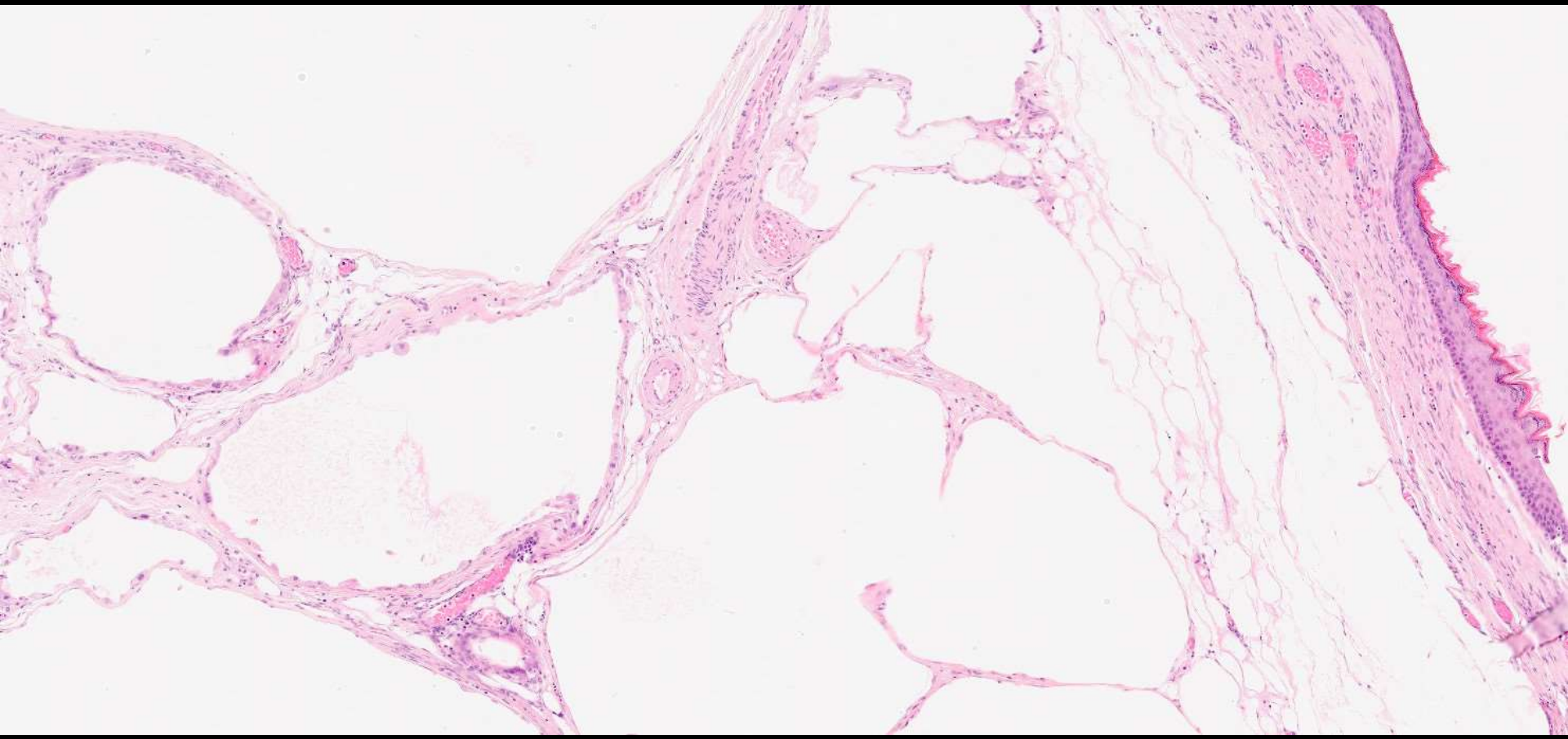


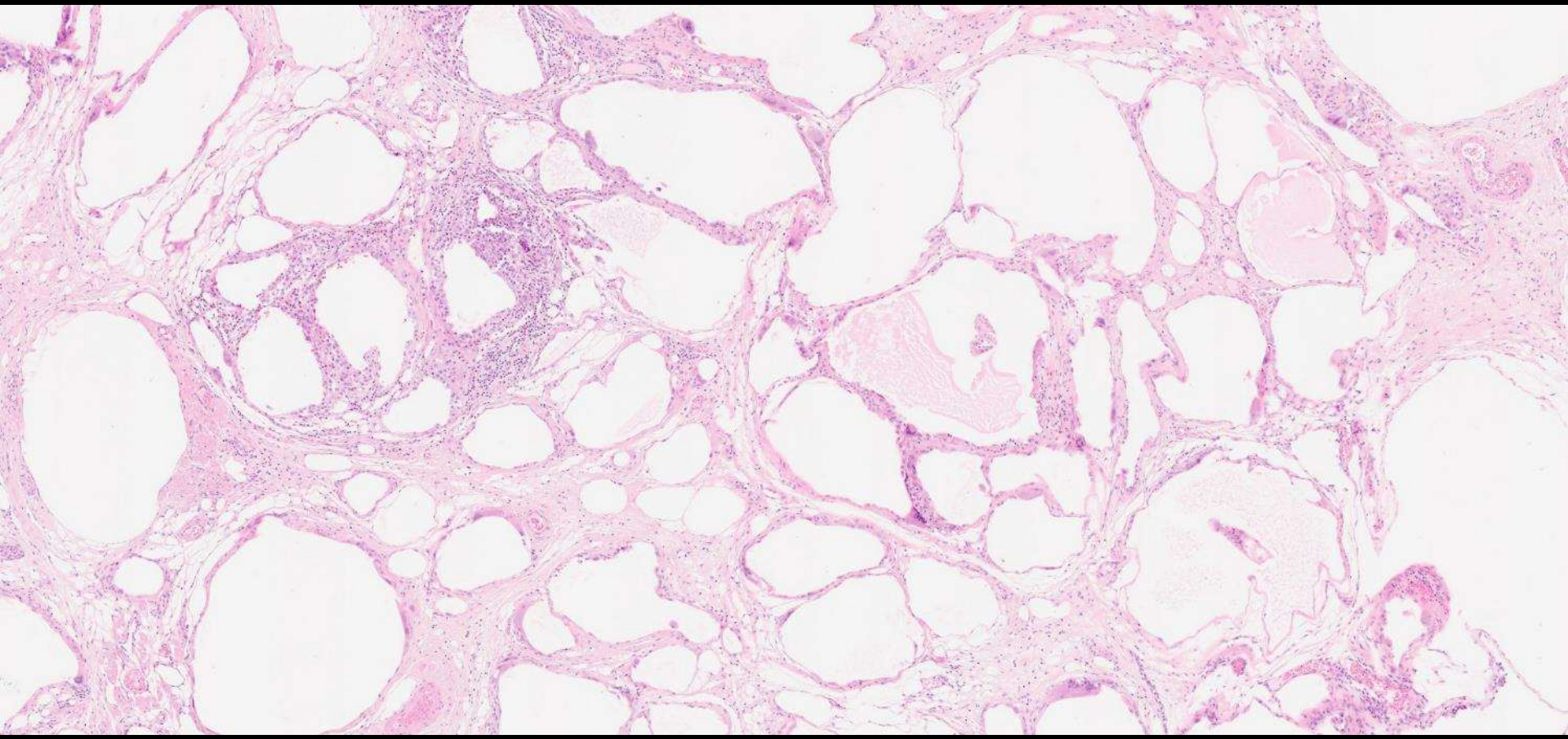


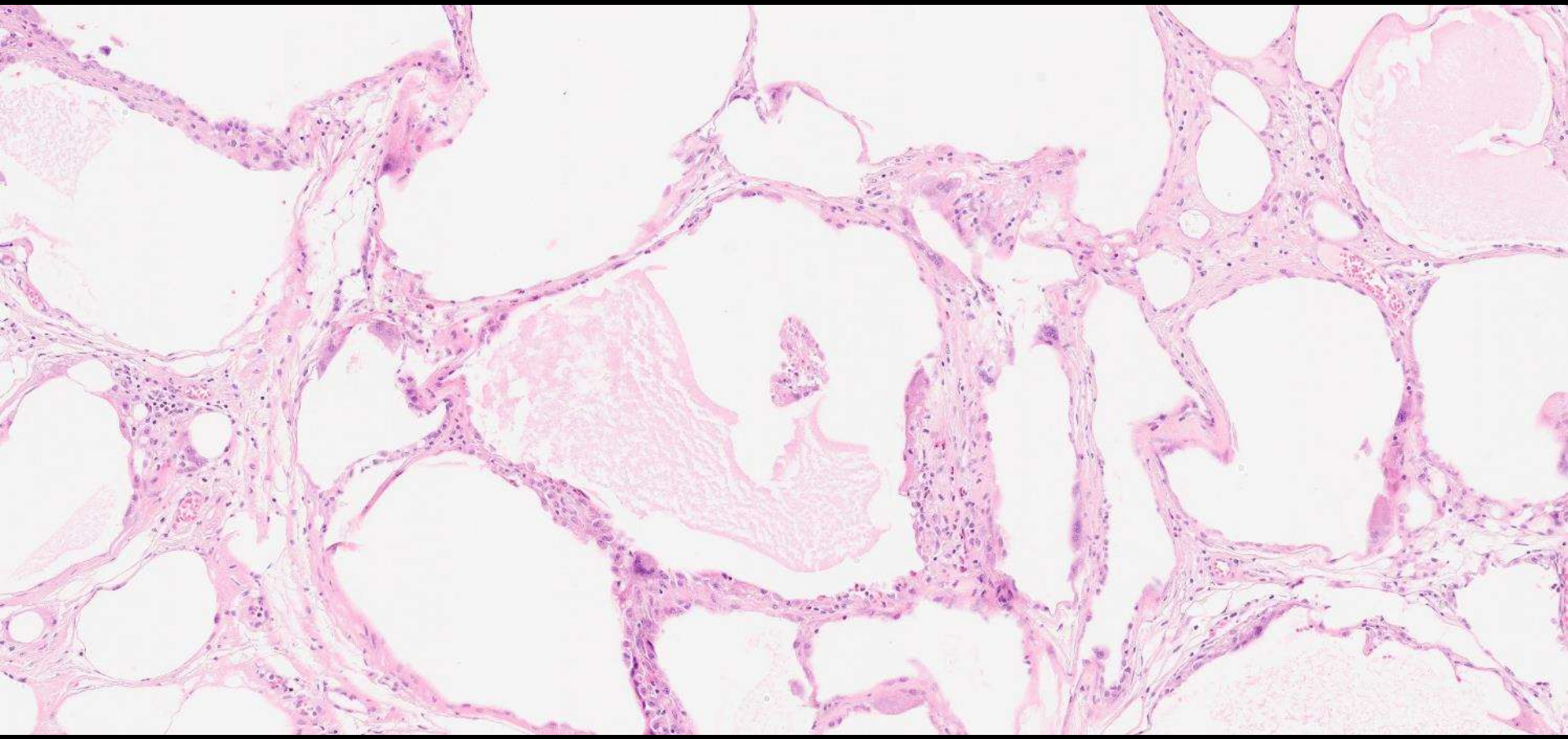


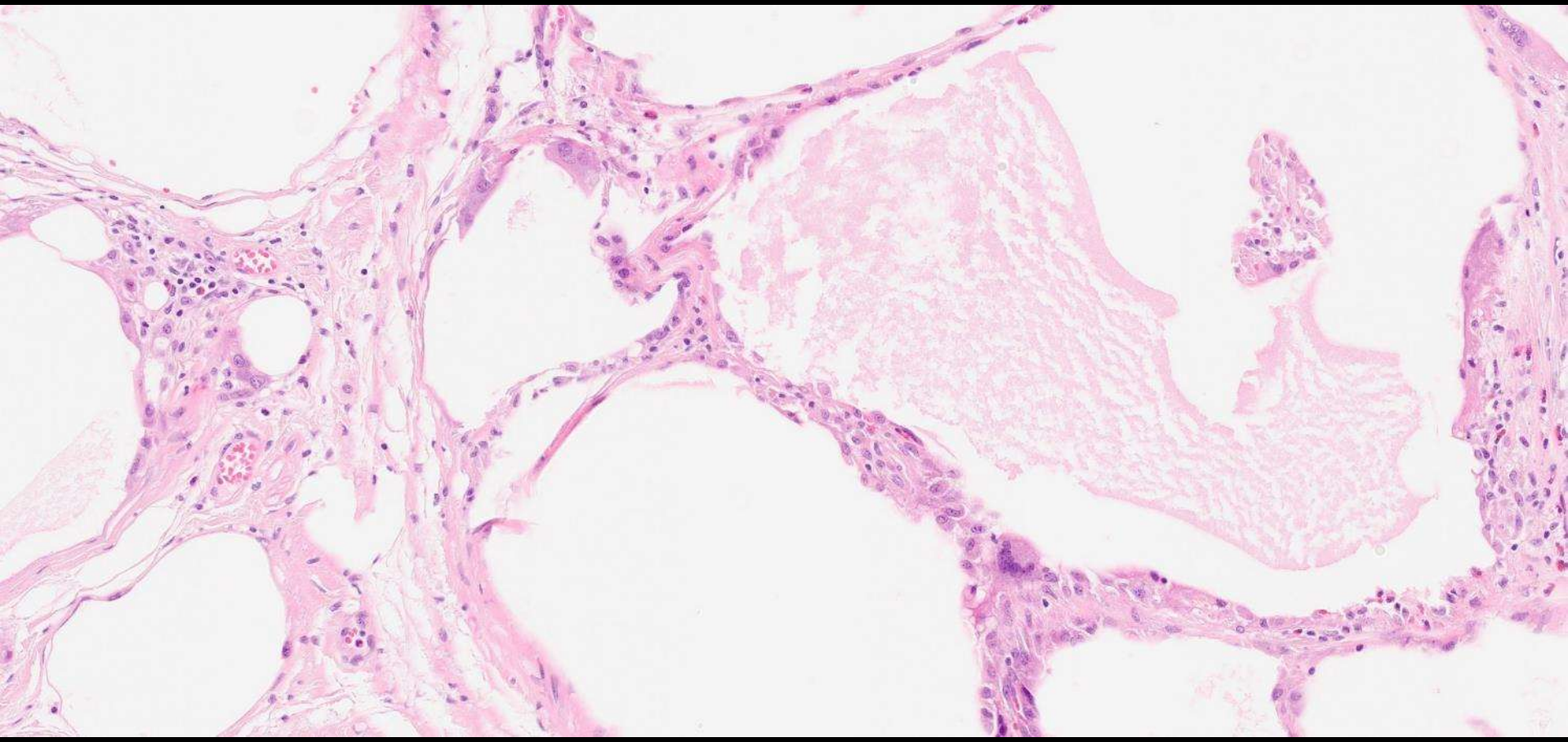












Dx

- **Mature teratoma**
  - Comment: pneumatosis-like features

Brief report

Pneumatosis cystoides-like appearances in a mature cystic teratoma of the ovary

G.MAUDSLEY & H.D.ZAKHOUR
Histopathology Department, Arrowe Park Hospital, Wirral, UK

Accepted for publication 26 July 1988

A case of mature ovarian teratoma is described showing appearances not unlike those seen in pneumatosis cystoides intestinalis, posing intriguing problems in its explanation.

Keywords: gas cysts, ovarian teratoma, pneumatosis cystoides intestinalis

Introduction

Pneumatosis cystoides intestinalis is the curious condition, first described by DuVernoi in 1730, in which multiple gas-filled cysts are present in the gastrointestinal tract. The cysts have also been described outwith the latter, in the gastrohepatic ligament, mesentery, mesocolon, omentum and lymph nodes (cited by Koss 1952). Similarities with emphysematous vaginitis and emphysematous cystitis have also been noted. The source, route of entry and persistence of the gas have been debated (Koss 1952, Doub & Shea 1960, Keyting *et al.* 1961, Yale Balish & Wu 1974).

Case report

55 × 50 × 35 mm with a 30 mm diameter hole at one end, were received in formalin. The average wall thickness was 4 mm, but with small peripheral cysts (Figure 1) measuring up to 10 mm diameter, some containing bright yellow fluid, some apparently empty. The main cavity contained yellow fatty material admixed with hairs.

Microscopic examination showed skin with pilosebaceous follicles, respiratory epithelium, gastrointestinal mucosa, smooth muscle, cartilage, fibrous tissue and small very inconspicuous islands of adipose tissue (Figure 2). Closely packed cystic spaces were present (Figure 3) measuring from less than 0.1 mm up to approximately 6.5 mm maximum dimension, and lined by flattened cuboidal cells, macrophages and multinucleate foreign body-type giant cells in a discontinuous fashion. These were focally positive immunohistochemically for α_1-antitrypsin and α_1-antichymotrypsin (Dako) but were negative for epithelial membrane antigen, keratin, cytokeratin and lysozyme (Dako) and with *Ulex europaeus* (Lec Lab). These cells were not significantly foamy, and adipose tissue was not detectable amongst

International Journal of Gynecological Pathology
27:531–533, Lippincott Williams & Wilkins, Baltimore

Case Report

Pneumatosis Ovarii (Emphysematous Changes in the Ovary): A Case Report

Yinong Wang, M.D., Ernest A. Topran, M.D., and Fattaneh Tavassoli, M.D.

Summary: Emphysematous changes in the ovary have not been described previously, although a similar process in the vagina, vaginitis emphysematosa, has been well described in the literature. We present a case with emphysematous changes in the ovary of a 38-year-old woman. Patient presented with a right ovarian cyst. Histologically, in addition to the cystic follicles, a portion of the ovary had numerous cystic spaces lined by histiocytes and giant cells resembling alterations previously noted vaginitis emphysematosum. **Key Words:** Emphysematosa—Ovary—Vaginitis—Cystitis.

> Pathologica. 1994 Feb;86(1):43-6.

Sieve-like areas in mature cystic teratomas of the ovary. A histochemical and immunohistochemical study of 7 cases

V Canzonieri [1], R Volpe, A Gloghini, A Carbone

Affiliations + expand

PMID: 8072800

Abstract

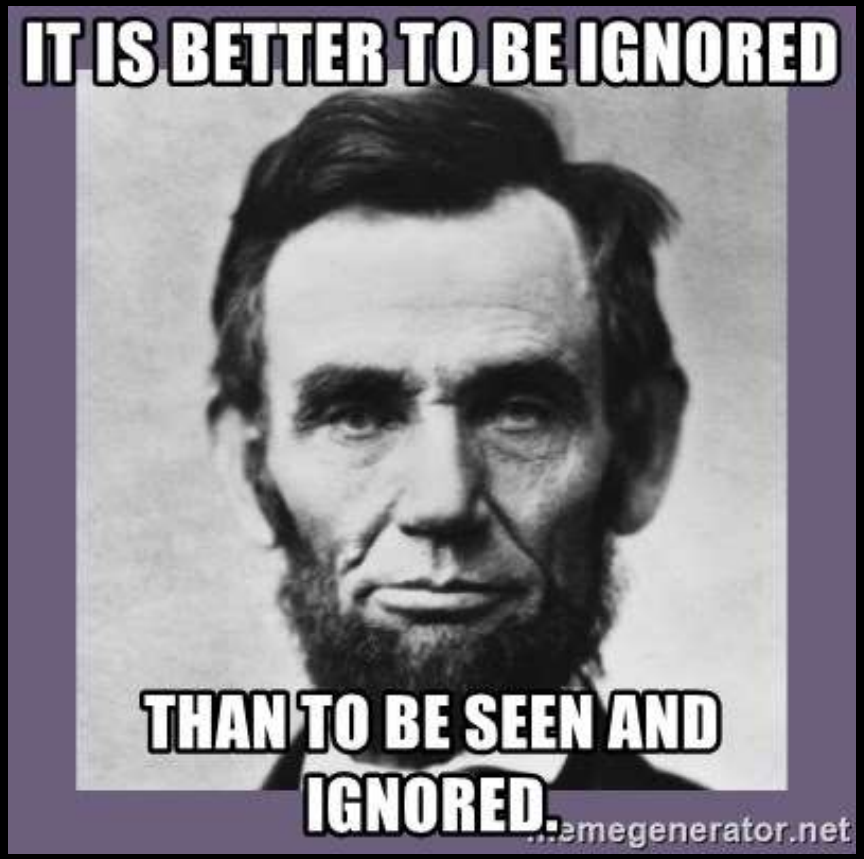
The authors describe histologic and immunohistologic features of seven cases of ovarian mature teratomas showing multiple cysts, optically empty, in their walls. These cysts have been detected in 7 out of 31 cases of ovarian teratomas observed from 1985 to 1991 (incidence rate 22%); they measured from less than 0.1 mm up to 5 mm in their largest size, and were lined by flattened cuboidal cell, histiocytes and multinucleate foreign body-type giant cells. Masson trichrome stain revealed a fibrous framework around them. Immunohistochemical stains provided evidence of both macrophagic and endothelial nature of the lining cells of the cysts because of their cytoplasmic positivity for KP1, KIM 6 and, though focally, for FVIII-related antigen. Ovarian teratomas exhibiting such aspects, defined as pneumatosis cystoides-like appearances or multicystic structures, have been previously described. These peculiar morphologic finding are reported in gynecological literature under the heading of sieve-like areas but, generally, little information about the mechanisms of their constitution is available. Etiopathogenic hypotheses are hereafter considered and discussed. The present findings suggest that these multicystic spaces may be the result of a granulomatous lipophagic reaction due to extravasated material (such as lipids or sebum) and/or of a dilatation of lymphatics vessels.

pneumatosis-like changes in mature teratoma

- **Cleared fat vs fat necrosis/lipogranulomatosis reaction from skin appendages**
- **Oil red O positive inside cysts**
  - Best done on unprocessed tissue
- **Lymphovascular or mesothelial IHC negative**

pneumatosis-like changes in mature teratoma

- **Probably under-reported b/c focal when present**
- **Important to consider**
  - esp on frozen!



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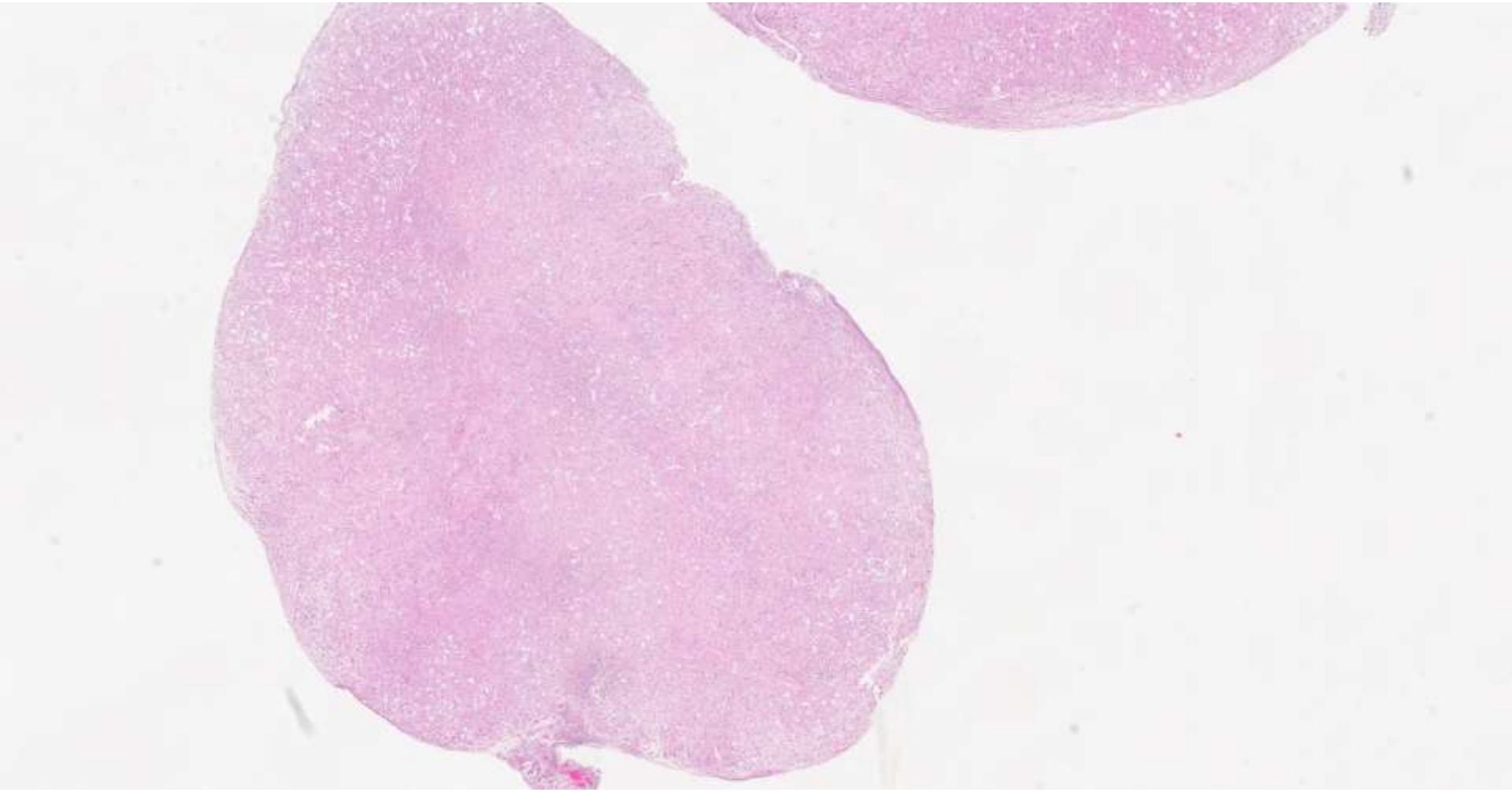
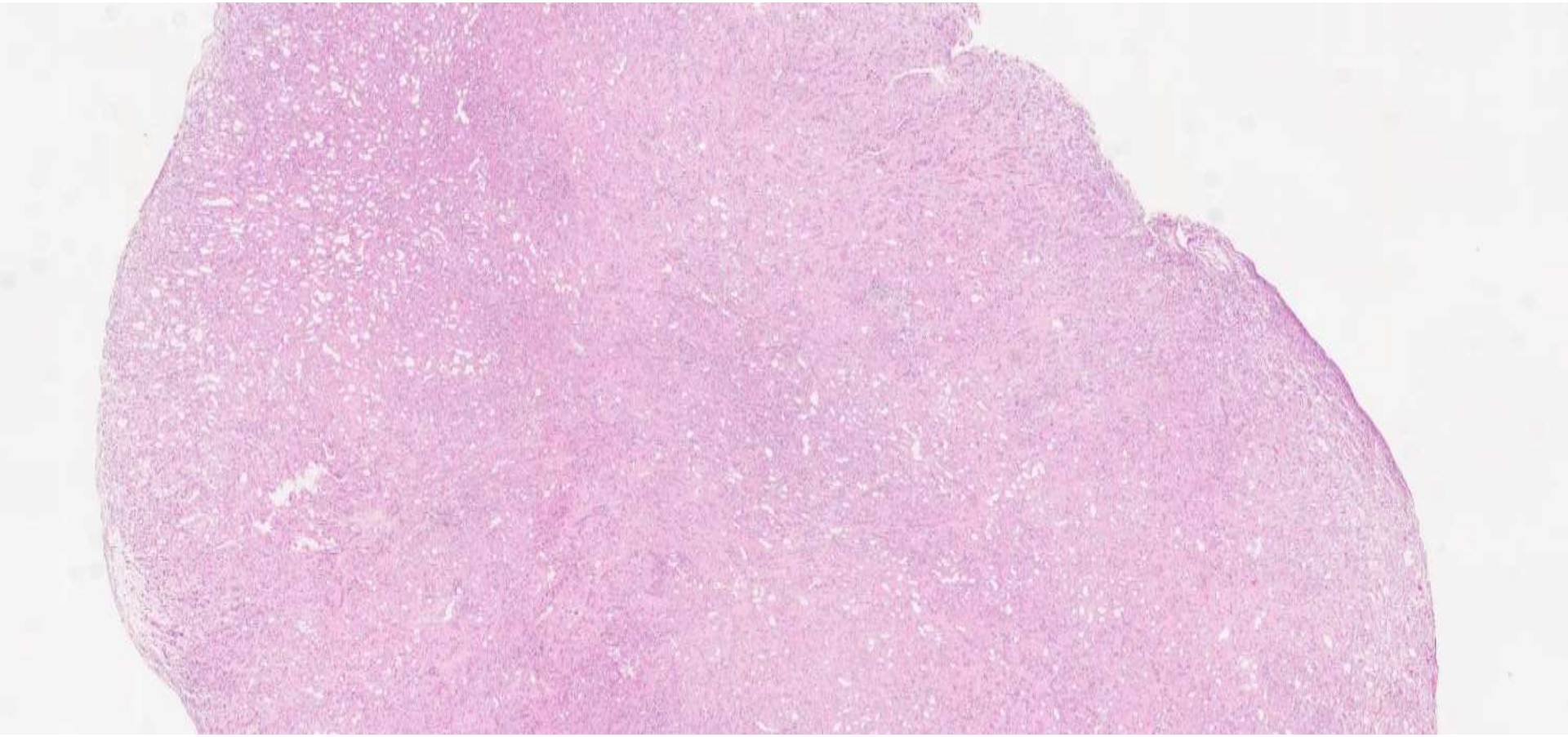
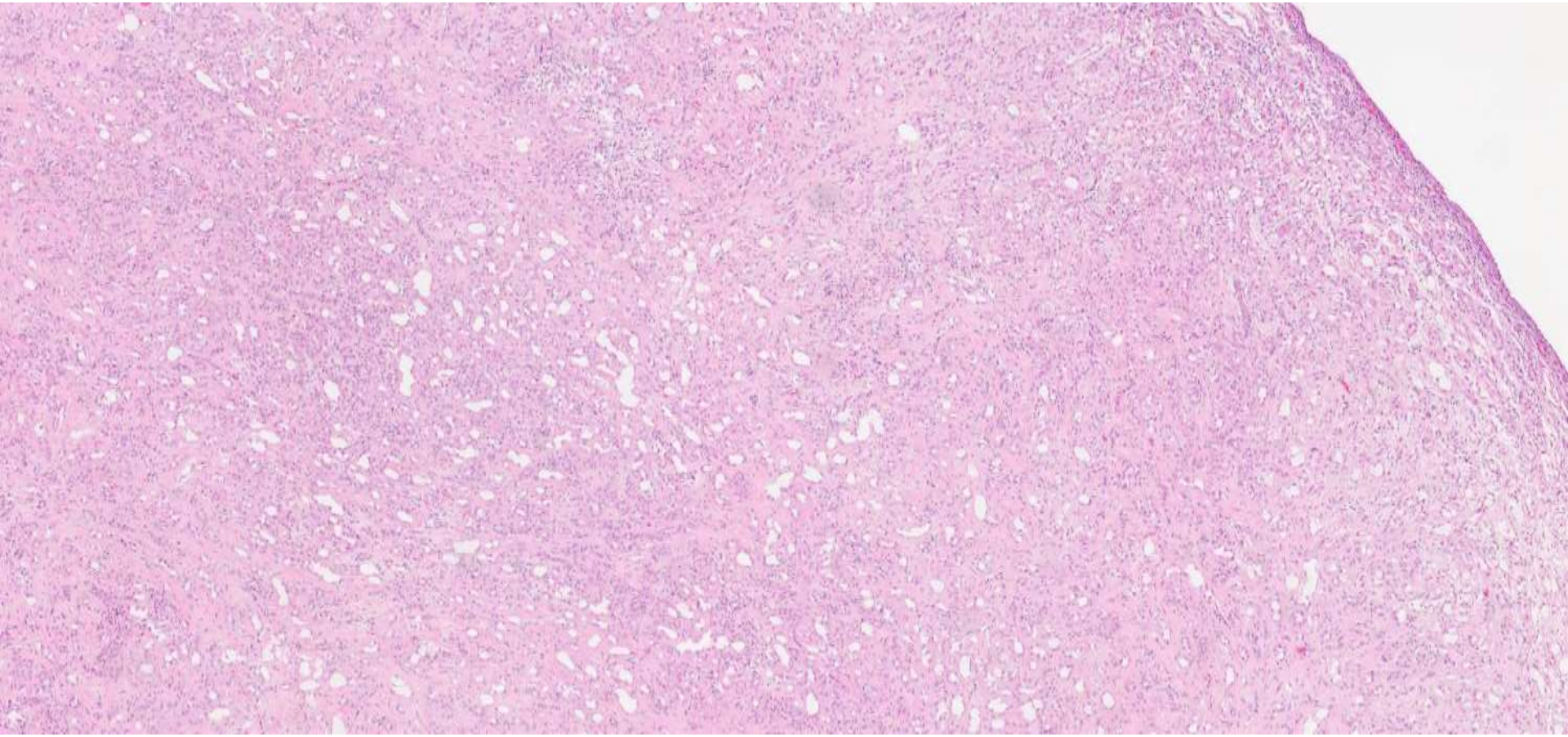
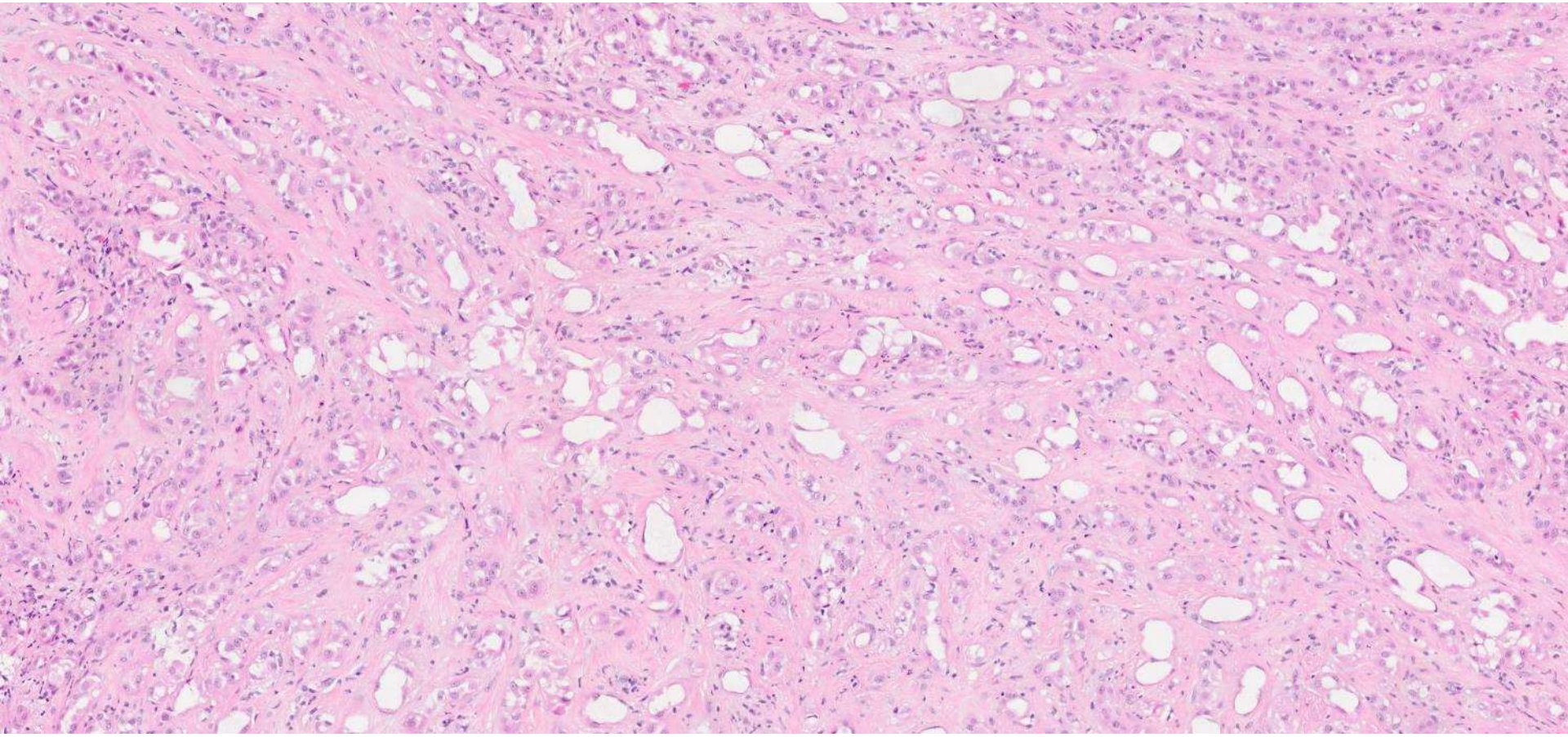
Ankur Sangoi; El Camino Hospital

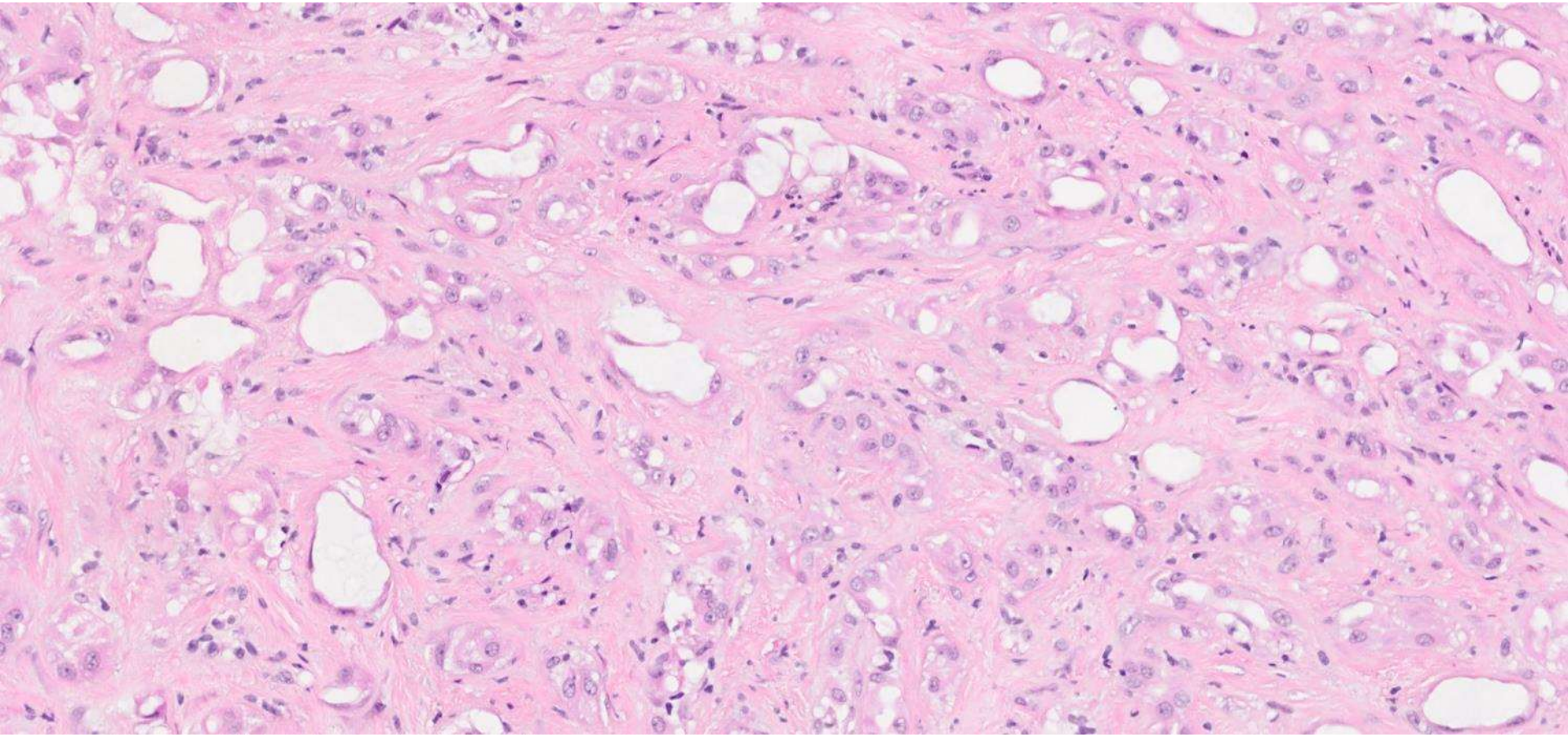
Middle-aged Indian F presents with abdominal pain, found to have acute cholecystitis and gallstones. Cholecystectomy and “pericholecystic lymph node” excision performed.

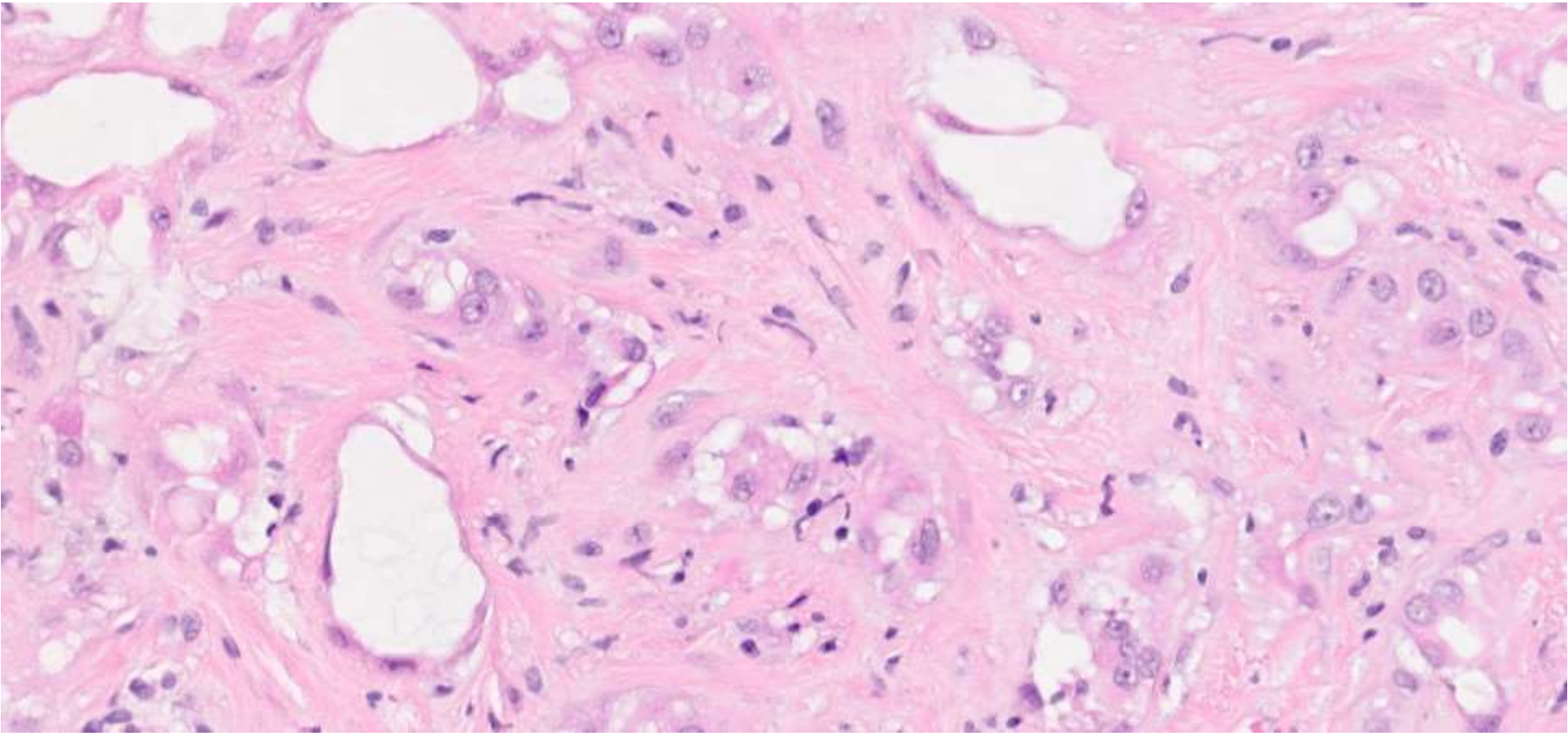












DDx

BENIGN

- Lymphangioma
- Multilocular peritoneal inclusion cyst
- Adenomatoid tumor
- Biopsy site changes (if prior procedure)

MALIGNANT

- Adenocarcinoma
- Mesothelioma (localized type)

ADD'L IHC NOT SHOWN

Lesional cells:

Calretinin +

WT1 +

D2-40+

BAP1 retained

Final Dx

Adenomatoid tumor

Adenomatoid Tumor: A Review of Pathology With Focus on Unusual Presentations and Sites, Histogenesis, Differential Diagnosis, and Molecular and Clinical Aspects With a Historic Overview of Its Description

Georgia Karpathiou, MD, BSc, PhD, Kenzo Hiroshima, MD, PhD,†‡ and Michel Peoc'h, MD, PhD**

Abstract: Adenomatoid tumors have been described almost a century ago, and their nature has been the subject of debate for decades. They are tumors of mesothelial origin usually involving the uterus, the Fallopian tubes, and the paratesticular region. Adenomatoid tumors of the adrenal gland, the liver, the extragenital peritoneum, the pleura, and the mediastinum have been rarely reported. They are usually small incidental findings, but large, multicystic and papillary tumors, as well as multiple tumors have been described. Their pathogenesis is related to immunosuppression and to *TRAF7* mutations. Despite being benign tumors, there are several macroscopic or clinical aspects that could raise diagnostic difficulties. The aim of this review was to describe the microscopic and macroscopic aspects of adenomatoid tumor with a special focus on its differential diagnosis and pathogenesis and the possible link of adenomatoid tumor with other mesothelial lesions, such as the well-differentiated papillary mesothelioma and the benign multicystic mesothelioma, also known as multilocular peritoneal cysts.

Key Words: mesothelial, mesothelioma, TRAF, L1CAM, pleura, peritoneum, uterus, genital tract

(*Adv Anat Pathol* 2020;27:394–407)

and the serosal surface of the uterus, showing morphologic similarities with tumors previously reported under various names. The authors first proposed the name "adenomatoid tumor" a term found "morphologically correct and genetically neutral," as they considered that "the primary unit of the tumor is epithelial in nature and it tends to form gland-like spaces, but the genesis of the tumor is obscure."[1] The term rapidly gained acceptance, and it is used until today. Before the term proposed by Golden and Ash, other authors did describe a similar tumor, under various names, as reviewed by Golden and Ash[1]: lymphangioma,[2] mixed leiomyoma and lymphangioma,[3,4] adenoma,[5,6] or low-grade adenocarcinoma.[7] The first description of this tumor seems to belong to Leighton in 1912 (reviewed by de Klerk and Nime[8]) who considered them lymphangiomas of the female genital tract.[9] The mesothelial origin of the adenomatoid tumor was correctly proposed for the first time by Masson et al,[10] suggesting derivation from pelvic serosa, and describing brush borders and supranuclear diplosomes with flagella (as cited by Ferenczy et al[11]) and supported by

Adenomatoid tumor: sites

- Typically seen in GYN & GU tract
- Have been reported in adrenals, peritoneum, liver, pleura, mediastinum
- CAUTION: be aware of “adenomatoid” patterns of mesothelioma!

Adenomatoid tumor: morphology

- **Can appear infiltrative!**
  - Vacuolated, signet like-cells, “thin-bridging” strands
- **Lymphoid aggregates typically seen in GU (not GYN) tract sites**

RIP:
Dr. Ondrej Hes

Hes et al

Annals of
DIAGNOSTIC
PATHOLOGY

VOL 7, NO 5 OCTOBER 2003

ORIGINAL ARTICLES

Thread-Like Bridging Strands: A Morphologic Feature Present in all Adenomatoid Tumors

Ondrej Hes, MD, PhD, Delia M. Perez-Montiel, MD, Isabel Alvarado Cabrero, MD, Michal Zamecnik, MD, Miroslav Podhola, MD, Miroslav Sulc, MD, Milan Hora, MD, PhD, Petr Mukensnabl, MD, Radim Zalud, MD, Ondrej Ondic, MD, and Michal Michal, MD

Adenomatoid tumor (AT) is a benign, relatively rare neoplasm occurring primarily in the genital tract of both genders. Histologically, ATs were composed of fibrous tissue, which are separated by numerous slit-like and pseudotubular spaces. Peculiar "thread-like bridging strands" (TBS) crossing the pseudotubular spaces are typical morphologic feature. In this study, the frequency of occurrence of these TBS within a large series of ATs in various organs was examined. Sixty-nine cases were included in our study. Twenty-eight cases occurred in women, 41 cases in men. Tumors were located in the myometrium, fallopian tube, ovary, epididymis, tunica albuginea, and testicular parenchyma. Tumor size ranged from 0.8 to 8.2 cm (mean, 2.7 cm). TBS were found in 100% of cases. Presence of thin intraluminal TBS within ATs was a constant morphologic feature independently on gender and localization of the lesions. Ultrastructurally, they were always formed by apposition of attenuated cytoplasm of two adjacent mesothelial cells. In our opinion, TBS are morphologically very specific for ATs and we are not aware of any other epithelial structure in any organ demonstrating as appearance similar to these TBS of ATs.
Ann Diagn Pathol 7: 273-277, 2003.

Index Words: Adenomatoid tumor, morphology, strands

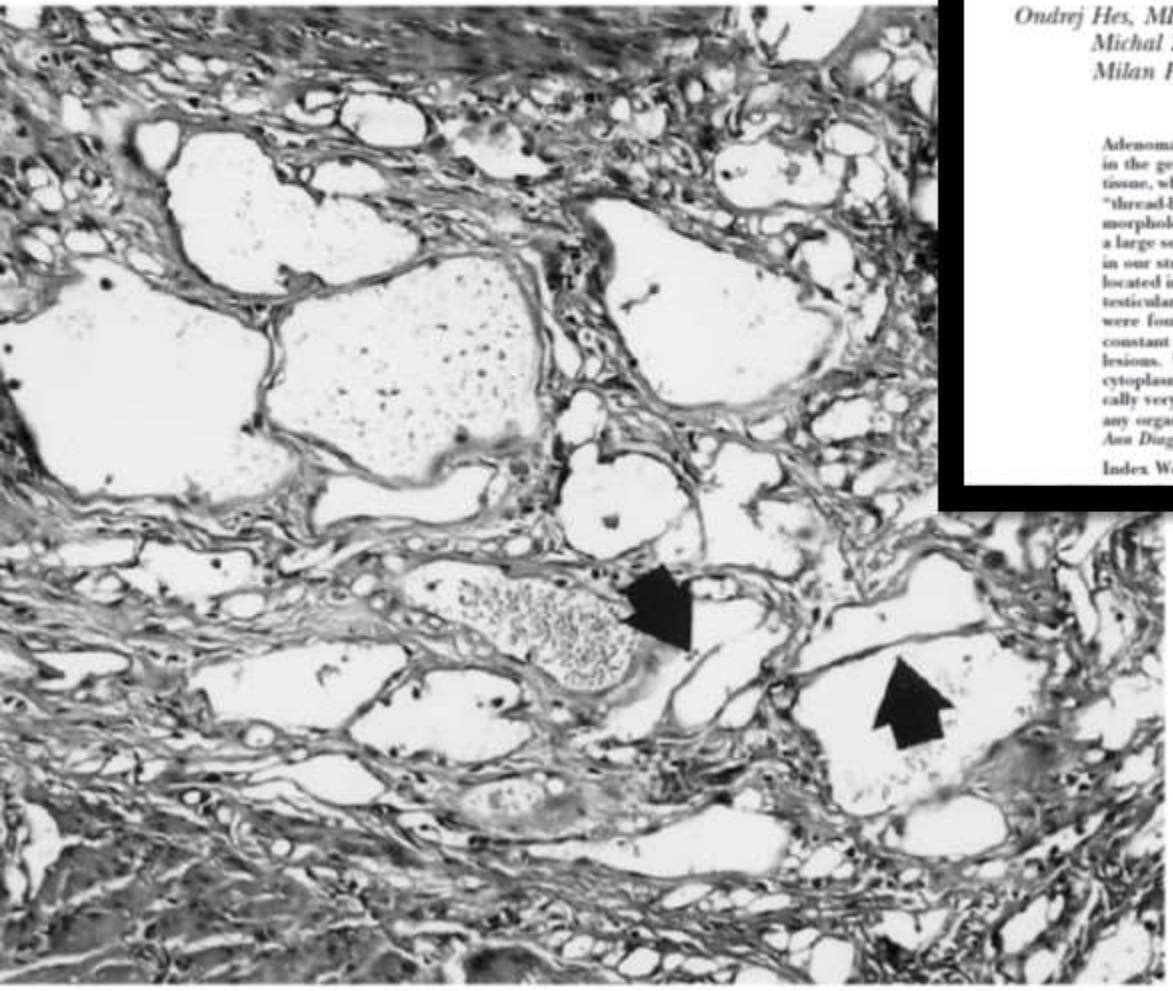


Figure 1. Thread-like bridging strands (arrows) are typical feature of ATs.

Adenomatoid tumor: IHC

- Keratin positive
- CD31 negative, PAX8 negative
- + for mesothelial markers (D2-40, calretinin, WT1, HBME1)
- Can be GATA3+ and BerEp4+
- BAP1 retained

Adenomatoid tumors of the female and male genital tracts: a clinicopathological and immunohistochemical study of 44 cases

Ankur R Sangoi, Jesse K McKenney, Erich J Schwartz, Robert V Rouse and Teri A Longacre

Department of Pathology, Stanford University, Stanford, CA, USA

Adenomatoid tumors of the female and male genital tracts are well characterized as mesothelial in origin, but a detailed histological and immunohistochemical analysis comparing both traditional and newer mesothelial markers across gender and site has not been formally conducted. A variety of morphologic features previously described as characteristic of adenomatoid tumors were evaluated in 44 adenomatoid tumors from the male and female genital tracts. Immunohistochemical analysis with pankeratin (AE1/CAM5.2), WT-1, calretinin, CK5/6, D2-40, and caldesmon was also performed. The extent and intensity of staining were scored semiquantitatively on one representative section per case and mean value for each parameter was calculated. All ($n=44$) the adenomatoid tumors from both the female and male genital tracts demonstrated a distinctive thread-like bridging strand pattern. Lymphoid aggregates were seen in all 12 adenomatoid tumors of male patients, but in only 4 of 32 (13%) tumors in female patients ($P<0.0001$). The remaining morphologic features were variably present with no clear sex predilection. Pankeratin, calretinin, and D2-40 reactivity were identified in all female ($n=32$) and male ($n=12$) genital tract adenomatoid tumors. Adenomatoid tumors expressed WT-1 in 11/12 (92%) male patients and in 31/32 (97%) female patients. In male patients, reactivity for CK5/6 and caldesmon was found in 1/12 (8%) and 0/12 (0%) adenomatoid tumors (respectively), whereas reactivity in female patients was found in 5/32 (16%) and 1/32 (3%); respectively. Female tumors differ from their male counterparts by the frequent absence of lymphoid aggregates and the presence of a circumscribed margin when occurring in the fallopian tube. Of the putative mesothelial markers evaluated, calretinin, D2-40, and WT-1 show a similar immunoprofile and have a higher sensitivity than CK5/6 and caldesmon in genital tract adenomatoid tumors. However, the presence of additional, often strong expression of WT-1 in normal tissues of the female genital tract limits the utility of WT-1 in this setting.

Modern Pathology (2009) **22,** 1228–1235; doi:10.1038/modpathol.2009.90; published online 19 June 2009

Keywords: adenomatoid tumor; genital tract; calretinin; D2-40; WT-1; caldesmon

Adenomatoid tumor: molecular

- **TRAF7 mutation present**
  - Also present in well-diff papillary mesothelioma
  - Absent in malignant mesothelioma

Adenomatoid tumors of the male and female genital tract are defined by *TRAF7* mutations that drive aberrant NF-kB pathway activation

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Adenomatoid tumors are the most common neoplasm of the epididymis, and histologically similar adenomatoid tumors also commonly arise in the uterus and fallopian tube. To investigate the molecular pathogenesis of these tumors, we performed genomic profiling on a cohort of 31 adenomatoid tumors of the male and female genital tracts. We identified that all tumors harbored somatic missense mutations in the *TRAF7* gene, which encodes an E3 ubiquitin ligase belonging to the family of tumor necrosis factor receptor-associated factors (TRAFs). These mutations all clustered into one of five recurrent hotspots within the WD40 repeat domains at the C-terminus of the protein. Functional studies *in vitro* revealed that expression of mutant but not wild-type *TRAF7* led to increased phosphorylation of nuclear factor-kappa B (NF-kB) and increased expression of L1 cell adhesion molecule (L1CAM), a marker of NF-kB pathway activation. Immunohistochemistry demonstrated robust L1CAM expression in adenomatoid tumors that was absent in normal mesothelial cells, malignant peritoneal mesotheliomas and multilocular peritoneal inclusion cysts. Together, these studies demonstrate that adenomatoid tumors of the male and female genital tract are genetically defined by *TRAF7* mutation that drives aberrant NF-kB pathway activation.

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"Damn it, cilantro ruins everything."

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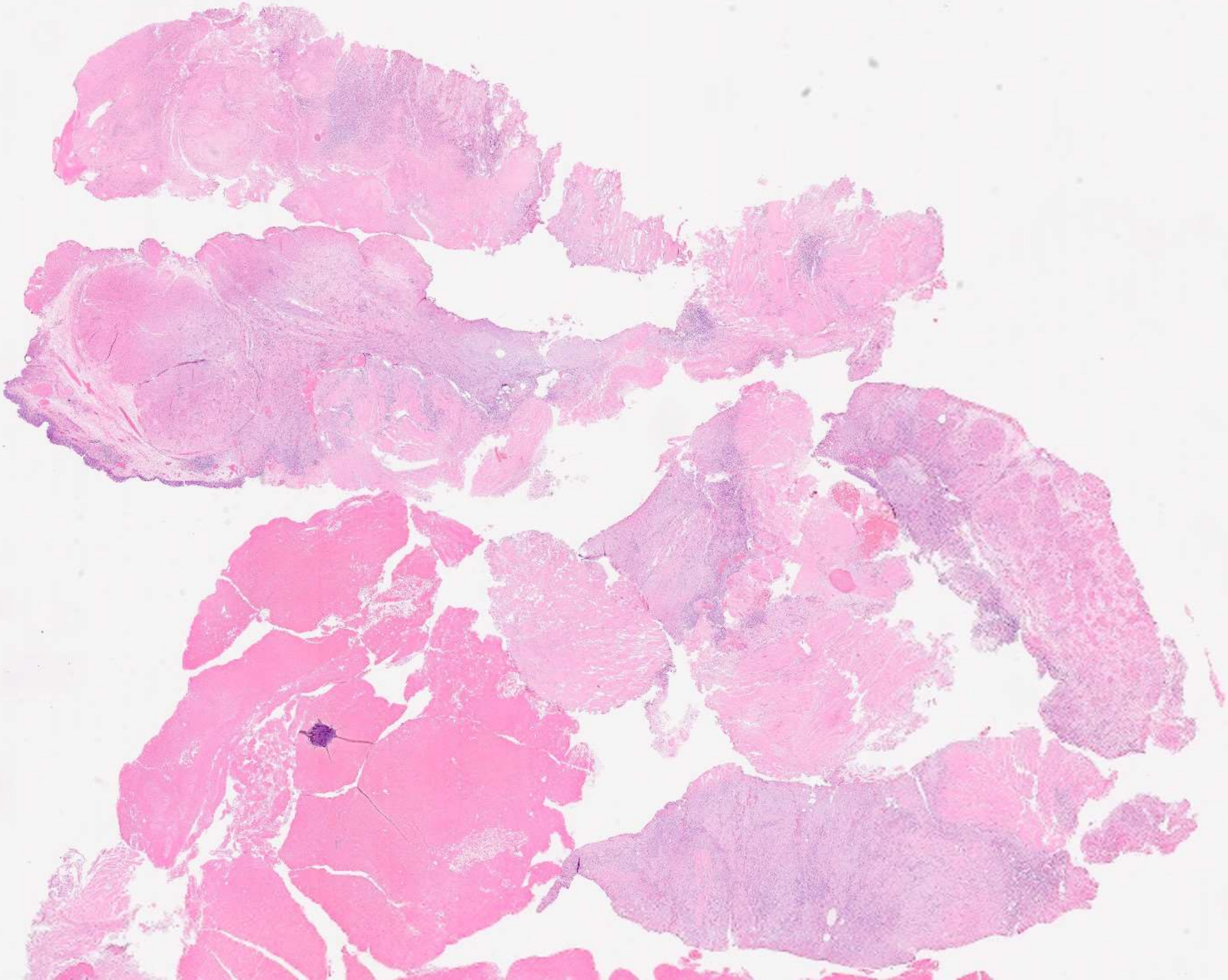
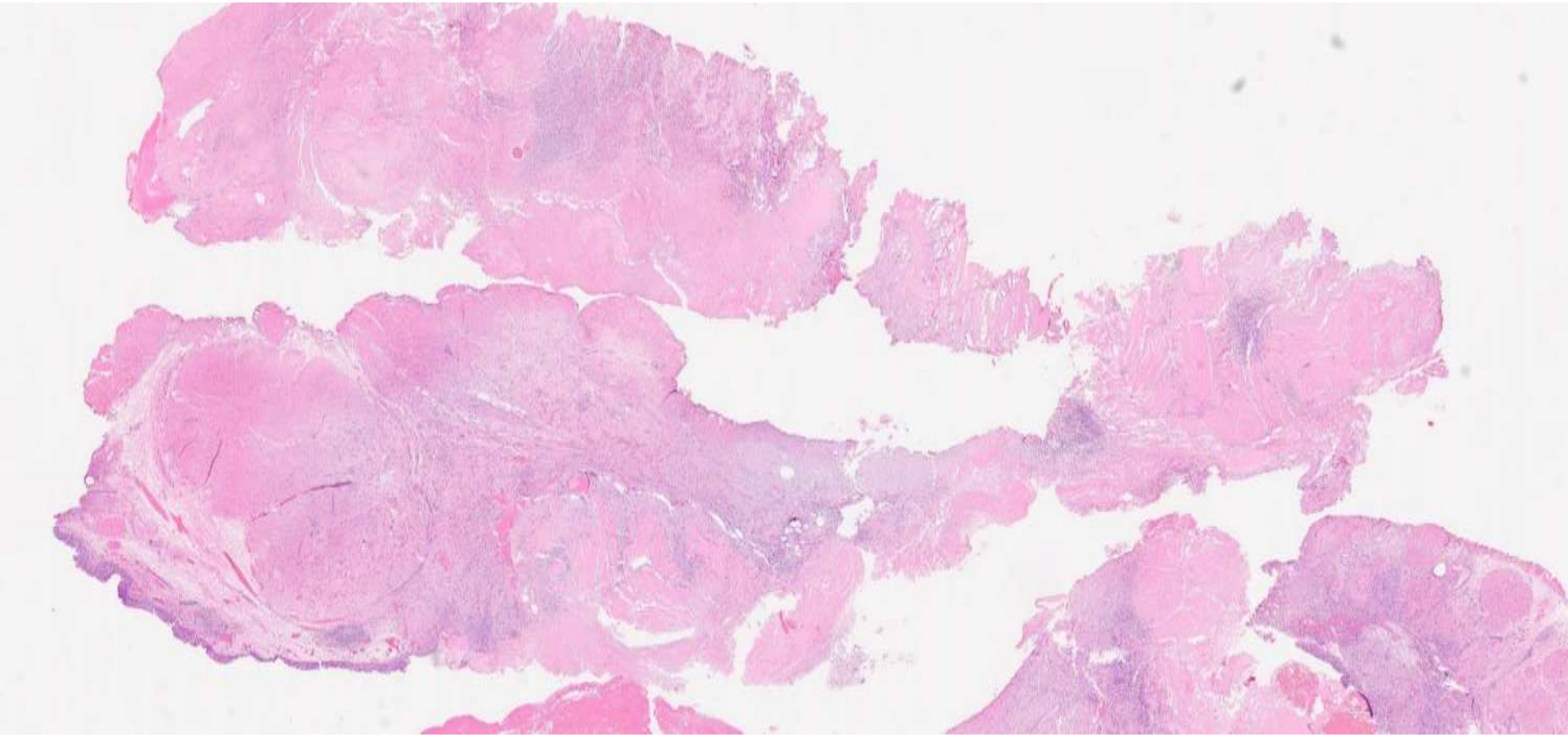
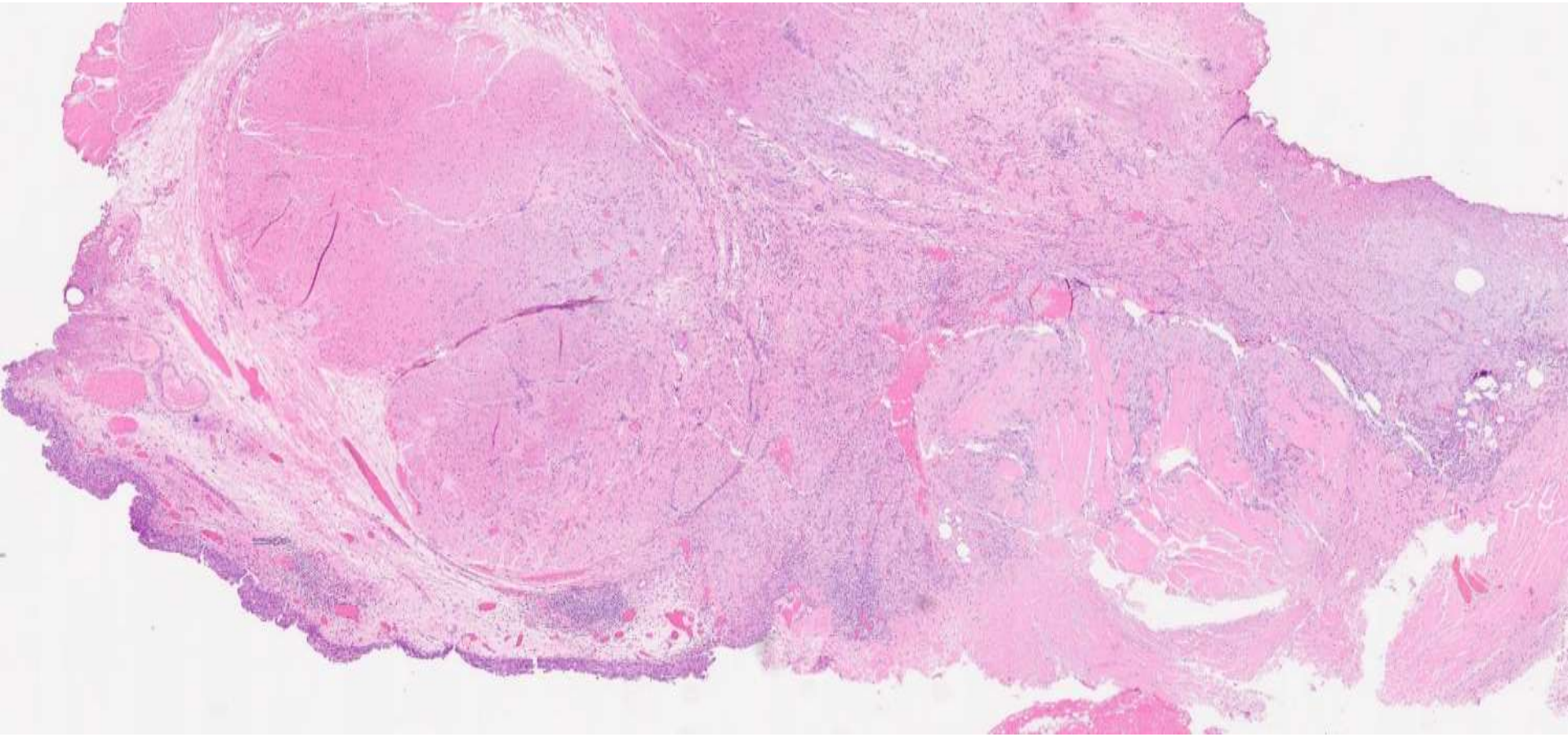
Direct link to scanned slide:
https://pathpresenter.net/public/display?token=7655283d

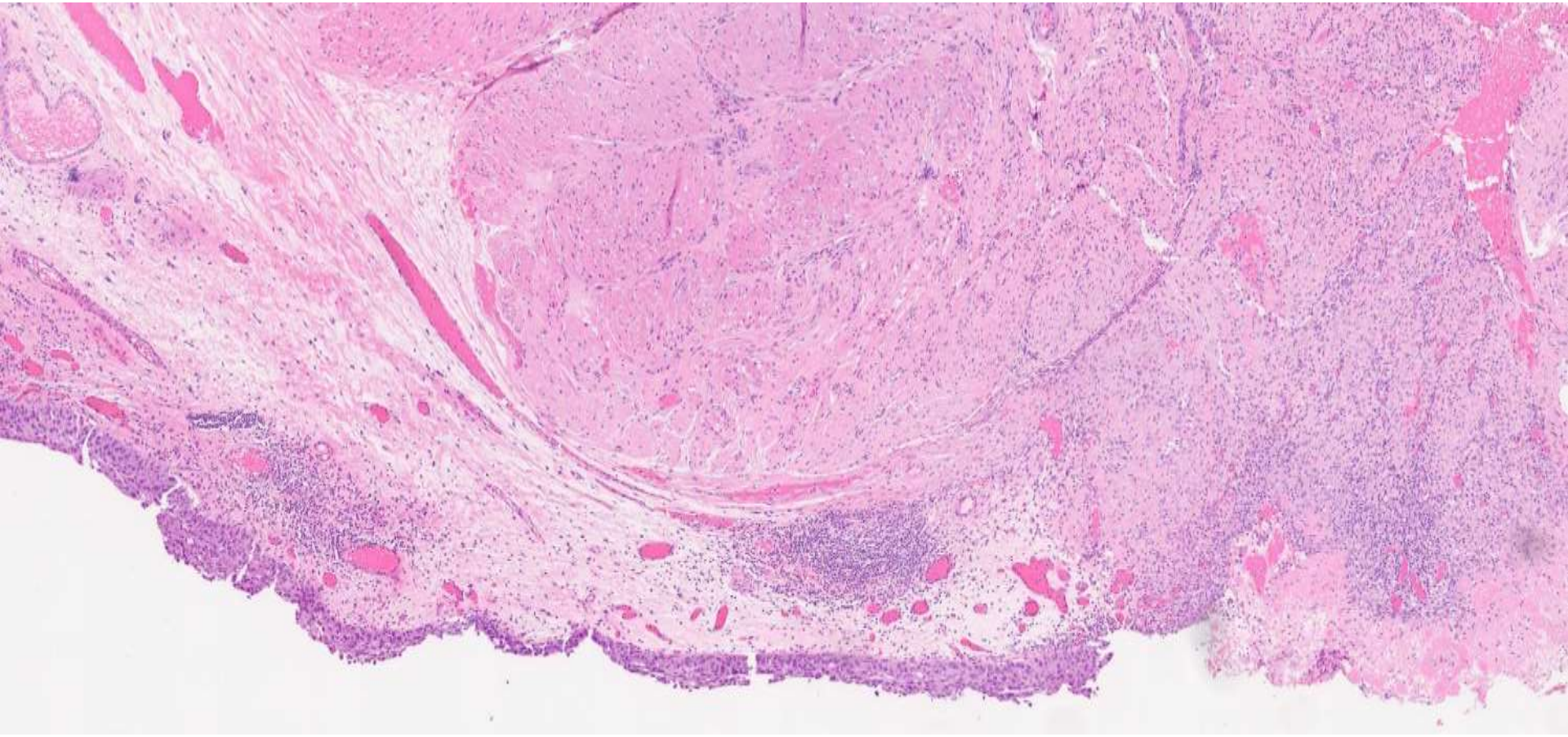
Ankur Sangoi; El Camino Hospital

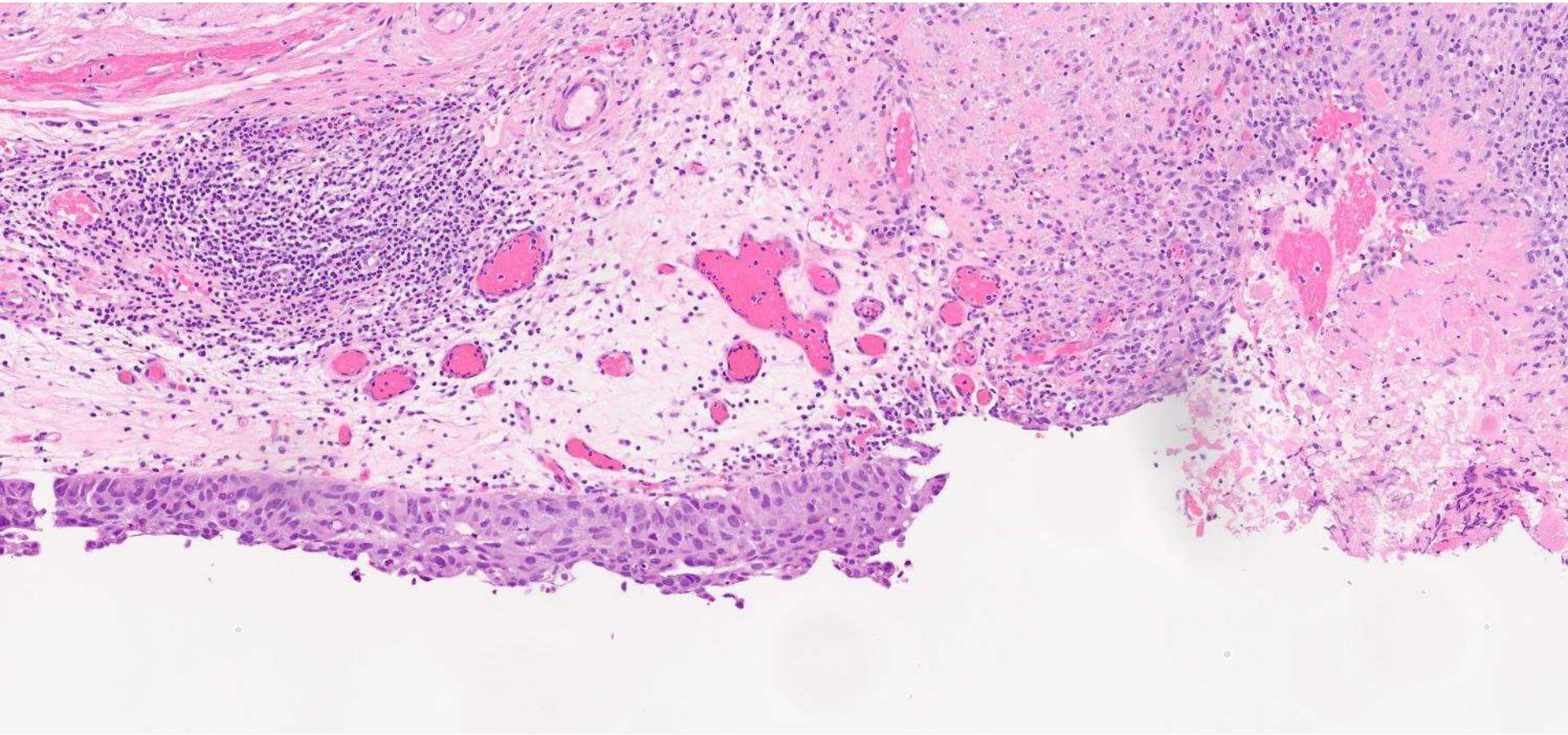
70ish M, TURBT.

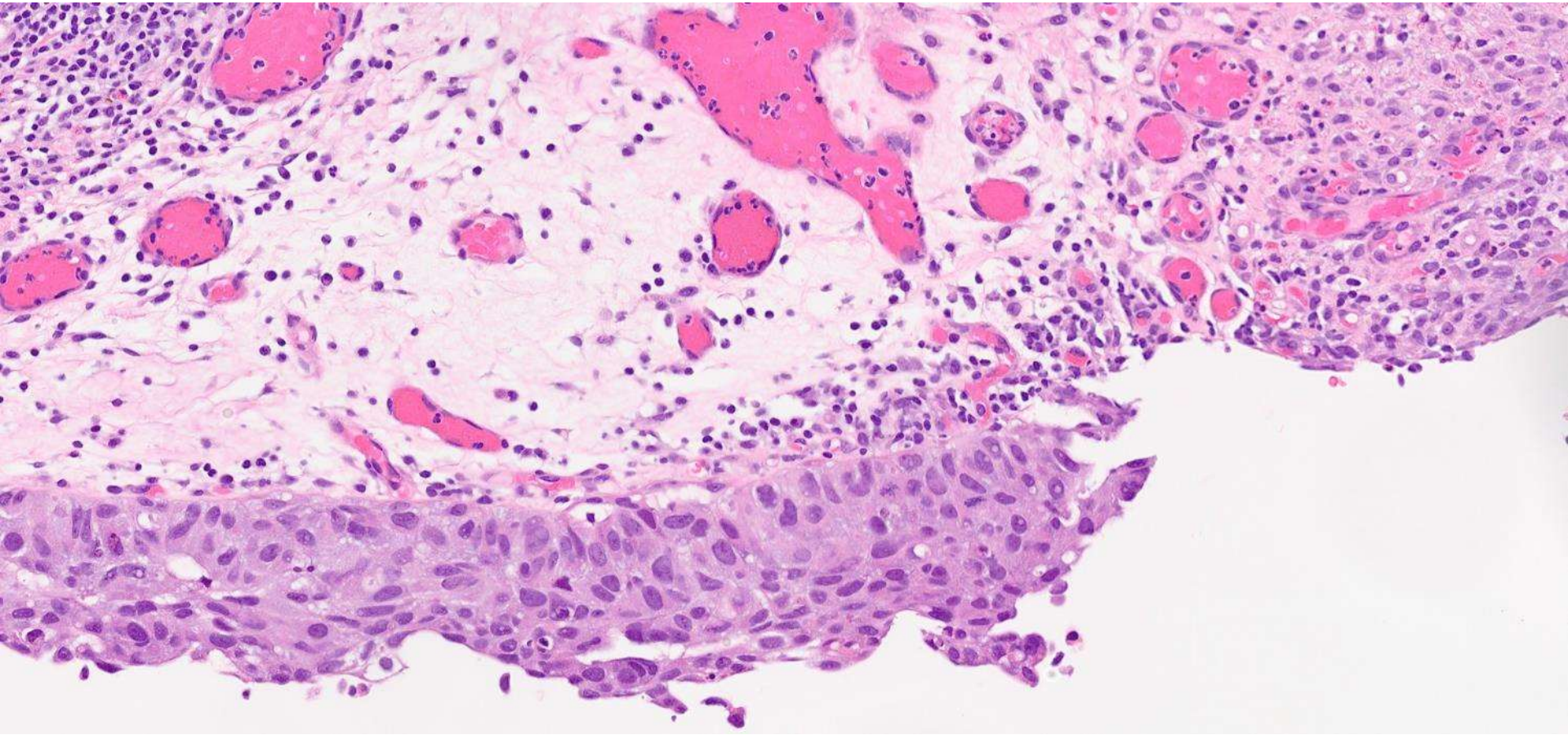


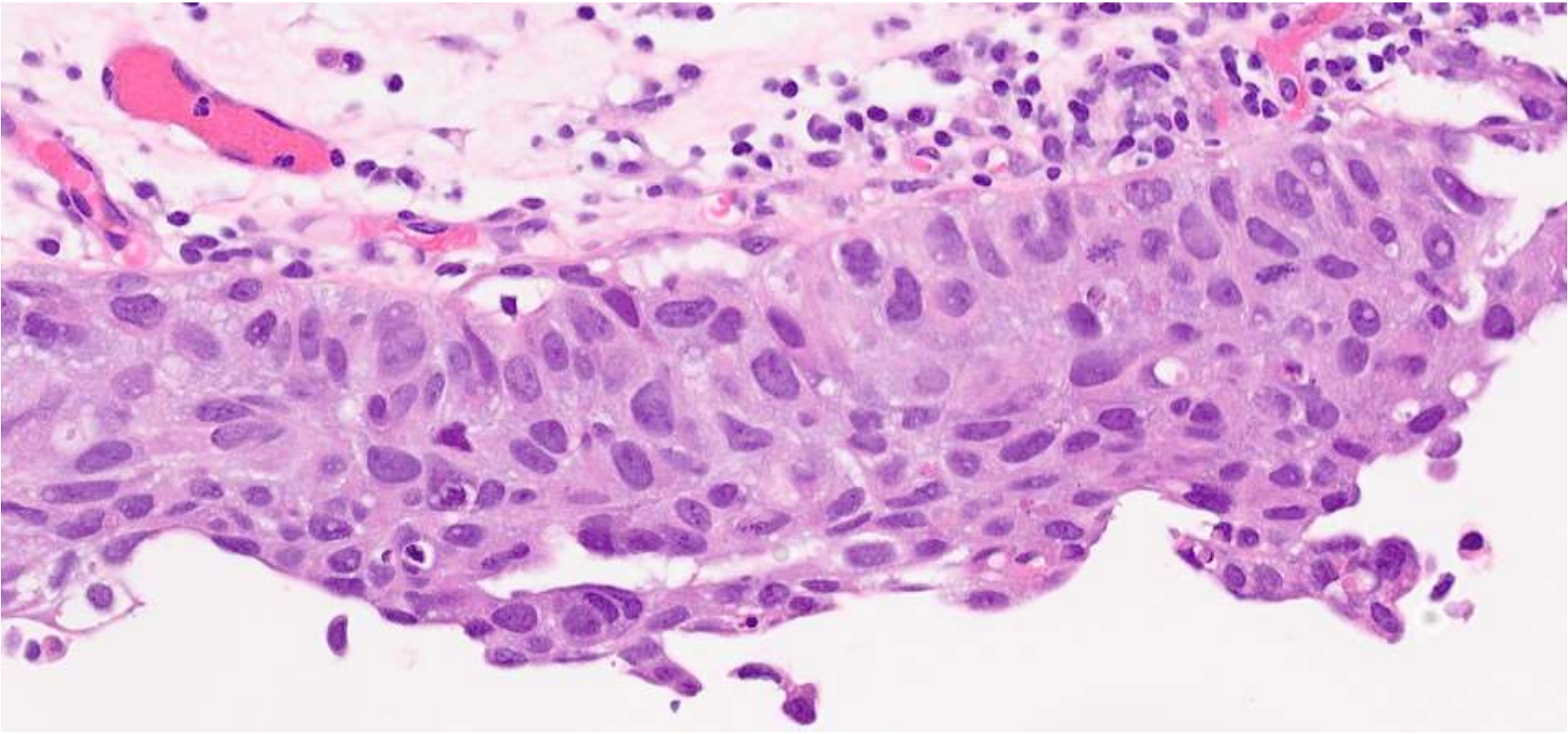












DDx

- Urothelial carcinoma in situ
- “non-papillary” pTa papillary urothelial carcinoma
- “shoulder” lesion of a prior pTa papillary urothelial carcinoma

(my) Dx & approach:

- **“shoulder” lesion of prior pTa PUC**

  = (c/w residual high grade pTa PUC)

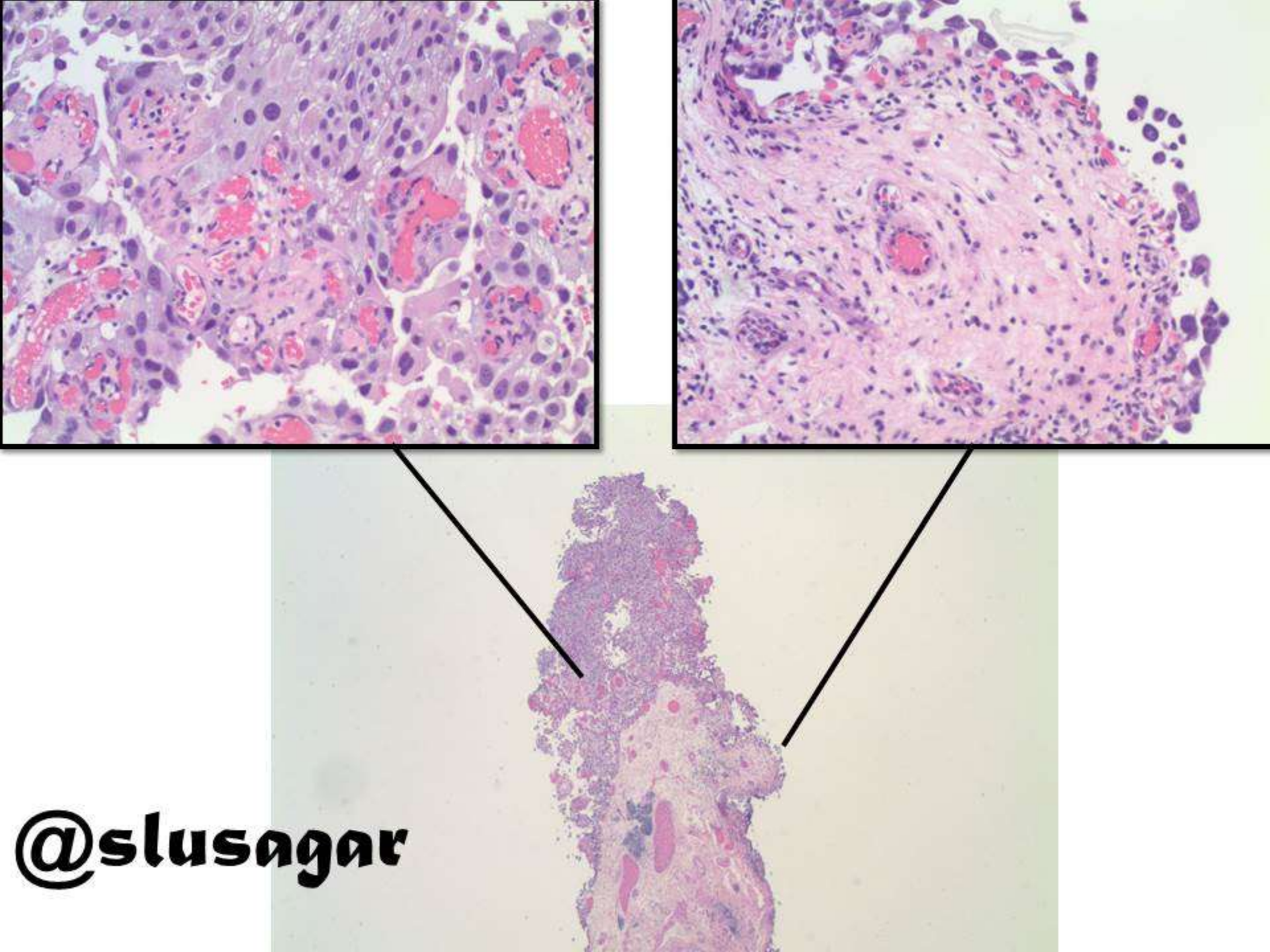
  → Biopsy site changes noted

  - Patient had prior pTa PUC on TURBT

Non-invasive “shoulder” lesions

- sometimes the lateral edges of the tumor/base appear flattened without fibrovascular cores
  - I consider these "*shoulder*" lesions of the main tumor & don't call urothelial CIS
- I typically don’t call CIS AND PUC within same specimen
  - Unless urologists says bx done of separate flat + papillary areas in same specimen jar

Non-invasive “shoulder” lesions


@slusagar

984 Urothelial Carcinoma in Situ Versus Early High-Grade Papillary Urothelial Carcinoma: A Survey of Pathologist and Urologist Interpretations

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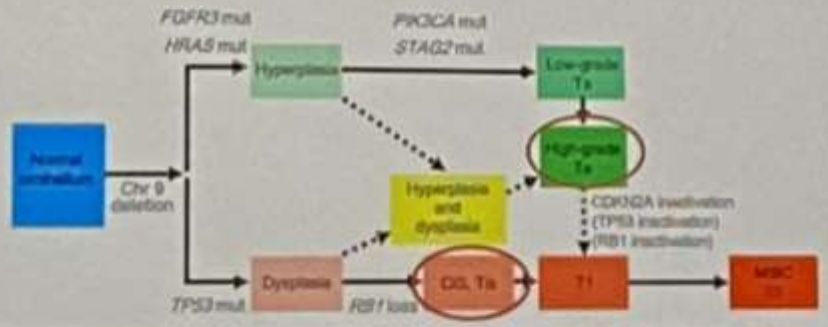
Background: Urothelial carcinoma in situ (CIS) "with early papillary formations" has been proposed as a term for incipient high-grade papillary urothelial carcinoma (PUC). However, confusion may arise between true CIS and lateral flat spread of PUC. It remains unclear how pathologists and urologists interpret this scenario.

Design: Web surveys were circulated to pathologists and urologists. Pathologists were divided into 3 groups: P1 = 28 invited academic genitourinary (GU) pathologists, P2 = 17 pathologists recruited online with self-reported GU focus, and P3 = 23 pathologists self-reported as non-GU specialists. Urologists yielded 32 responses (25 self-reported cancer specialists).

Results: P1 noted reporting CIS in the same specimen (but different tissue fragment) as PUC (57%) "regularly," compared to P2 (41%) or P3 (17%), and "regularly" diagnosed CIS in a specimen clinically labeled as "tumor" (61% vs 47% vs 22%). Pagetoid spread was considered to favor CIS predominantly by P1 (61% vs 35% vs 22%). All groups (65-76%) tended to consider previous PUC history before making a diagnosis. Cytokeratin 20 was the most used immunostain (83-95%), followed by p53 (63-100%). MIB-1 was least preferred by P1 (29% vs 67% vs 56%). Only 24-36% interpret negative p53 staining as null mutant, highest in P1. Case image interpretation as pure CIS was higher in P3 compared to P1 and P2 for 4/5 cases, who gave more descriptive or mixed diagnoses. Urologists felt that the term "lateral spread/shoulder" was unclear (75%) and preferred either "early" PUC (44%) or PUC with "early growth" (44%) mentioned in a note. Some urologists (47%) felt pagetoid spread could affect treatment, and 63% would like it documented. Over half (59%) of urologists considered CIS in the "base of tumor" to be part of the tumor; however, 71% of the non-cancer specialists (n=7), interpreted this as a second diagnosis. Half (53%) of urologists felt that reporting CIS instead of lateral spread of PUC would change management.

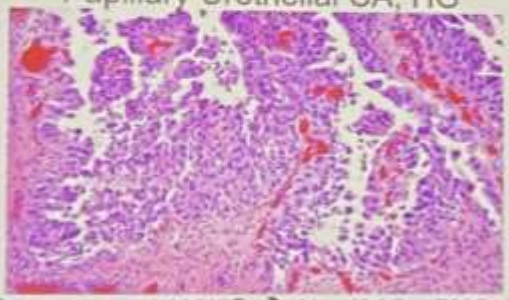
Conclusions: Interpretation and documentation of flat lesions (CIS and early PUC) lack consensus among pathologists, and may benefit from distinctive terminology, such as "CIS" and "non-invasive high-grade urothelial carcinoma". Moreover, the distinction between CIS and early PUC is not always clear to urologists and can influence management.

- Different morphology and IHC in a subset of cases
- Important to know if the is bx is deep or subsequent to a papillary tumor versus a de novo flat or random bx
- Molecular profile may differ, at least initially (FGFR3 and TP53/RB1 pathway alterations)
- Affects pt risk stratification and research cohorts

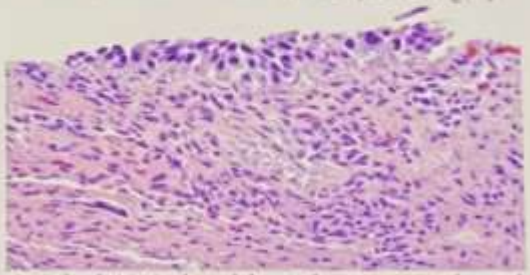


Case with multiple parts:

Part A – Tumor
Papillary Urothelial CA, HG



Part B – Base of Tumor
Non-Invasive UCA, HG (not UCIS)



?Concurrent UCIS? → No, IMO - PUC, High Grade (UCIS should not be a secondary dx)

Dr. M Hirsch, USCAP 2022 GUPS society

TAKE HOME POINTS

- **When encounting “CIS” looking area with background bx site changes:**
  - Inquire about prior TURBT & Dx
  - Consider “shoulder” lesion” of prior PUC
  - Know how your urologists handle secondary Dx of CIS