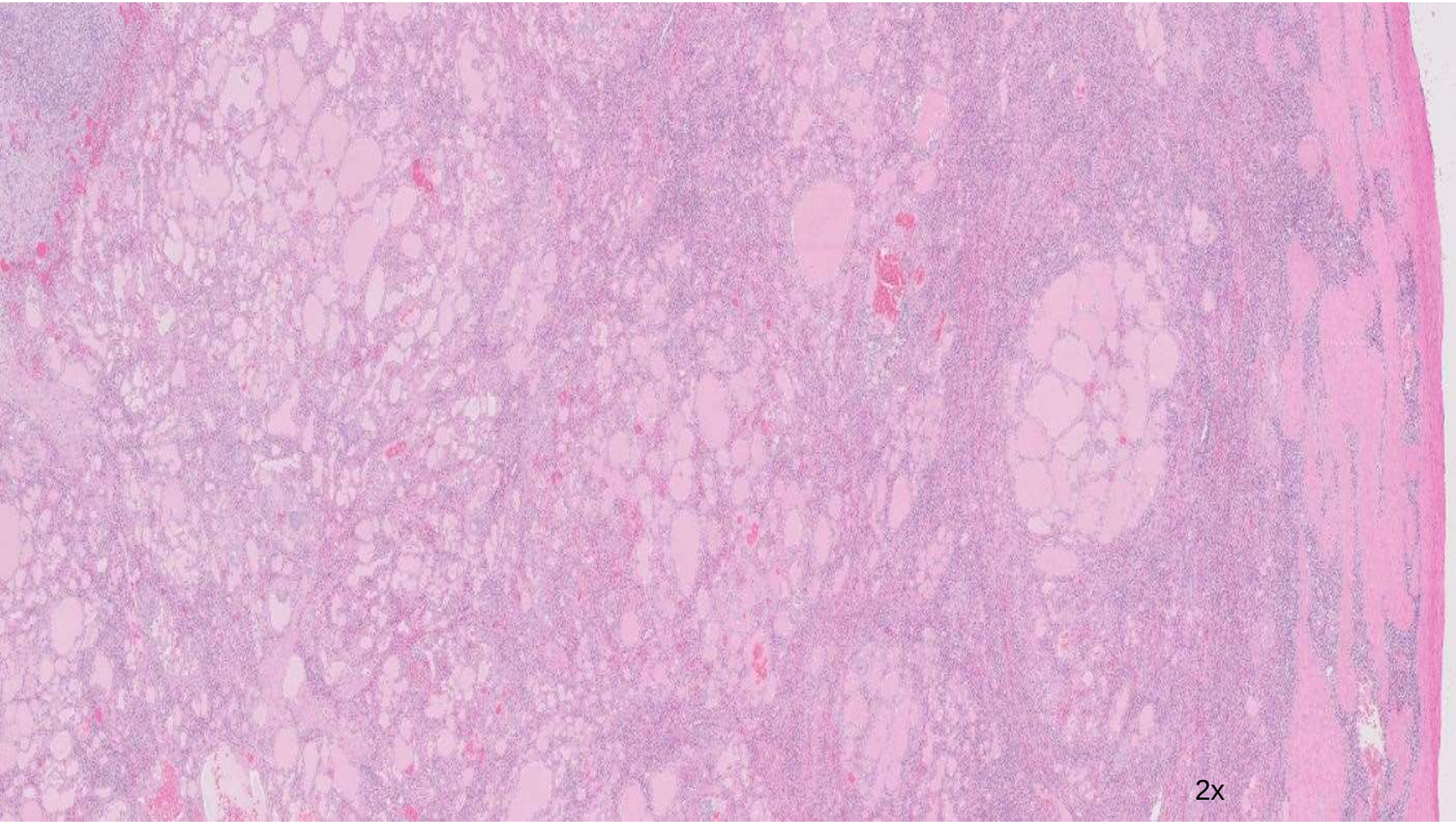
JUNE 2021 DIAGNOSIS LIST

21-0601: lymphangioma with papillary endothelial proliferation (spleen; hemepath)
21-0602: metastatic acinar cell carcinoma (hernia sac; GI path)
21-0603: mantle cell lymphoma, with extensive involvement by noncaseating granulomas (lymph node; hemepath)
21-0604: mantle cell lymphoma, CCND1/IGH translocation negative (lymph node; hemepath)
21-0605: hybrid sclerosing epithelioid fibrosarcoma/low grade fibromyxoid sarcoma (soft tissue; soft tissue path)
21-0606: plasmacytoid urothelial carcinoma (bladder; GU path)
21-0607: prostatic adenocarcinoma with mucinous features (prostate; GU path)
21-0608: papillary urothelial carcinoma with HSV (bladder; GU path+IDpath)

21-0601

Atif Saleem/Dita Gratzinger; Stanford

25-year-old F with 8.5cm splenic lesion detected incidentally during workup for diverticulitis.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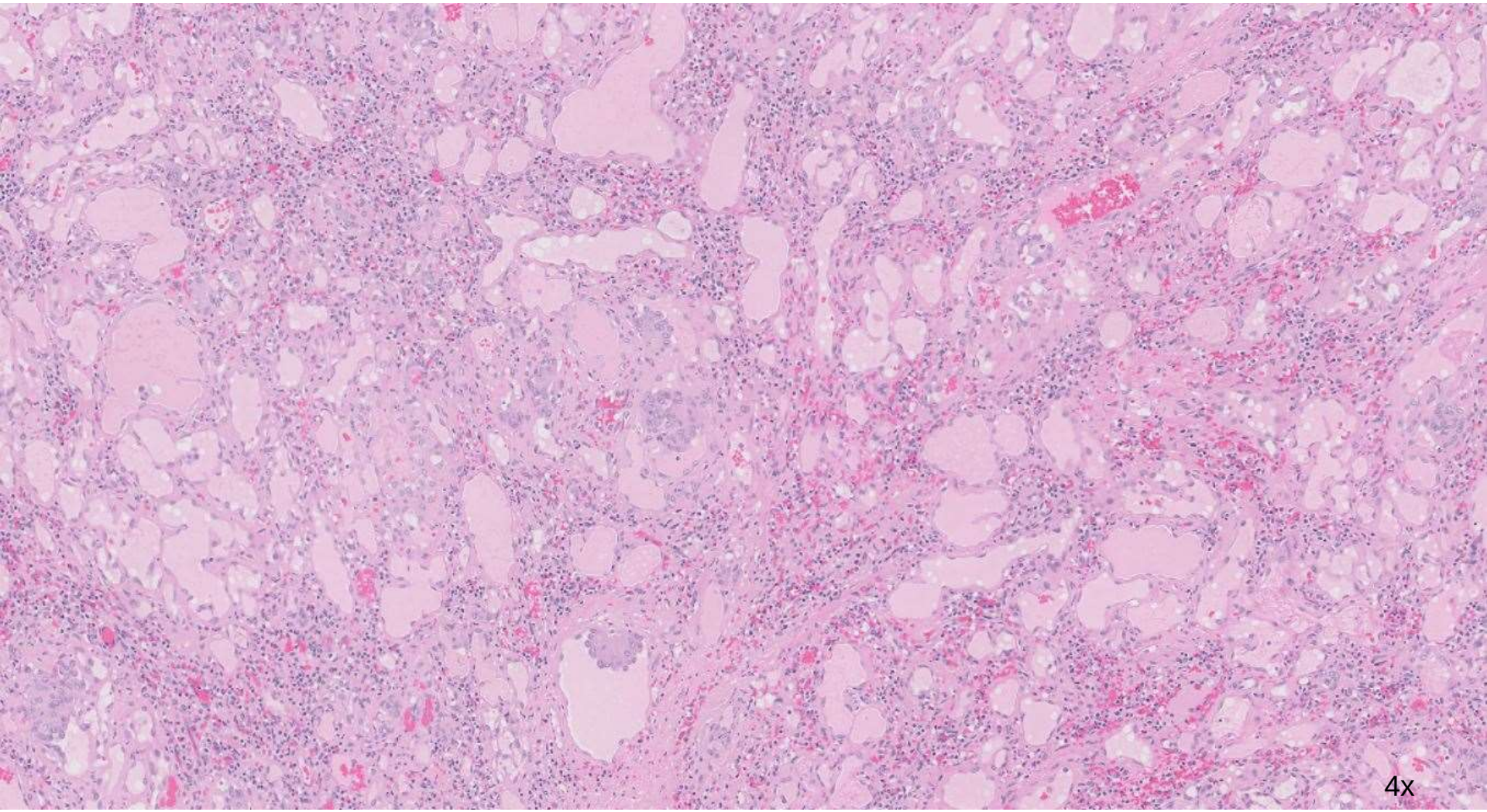
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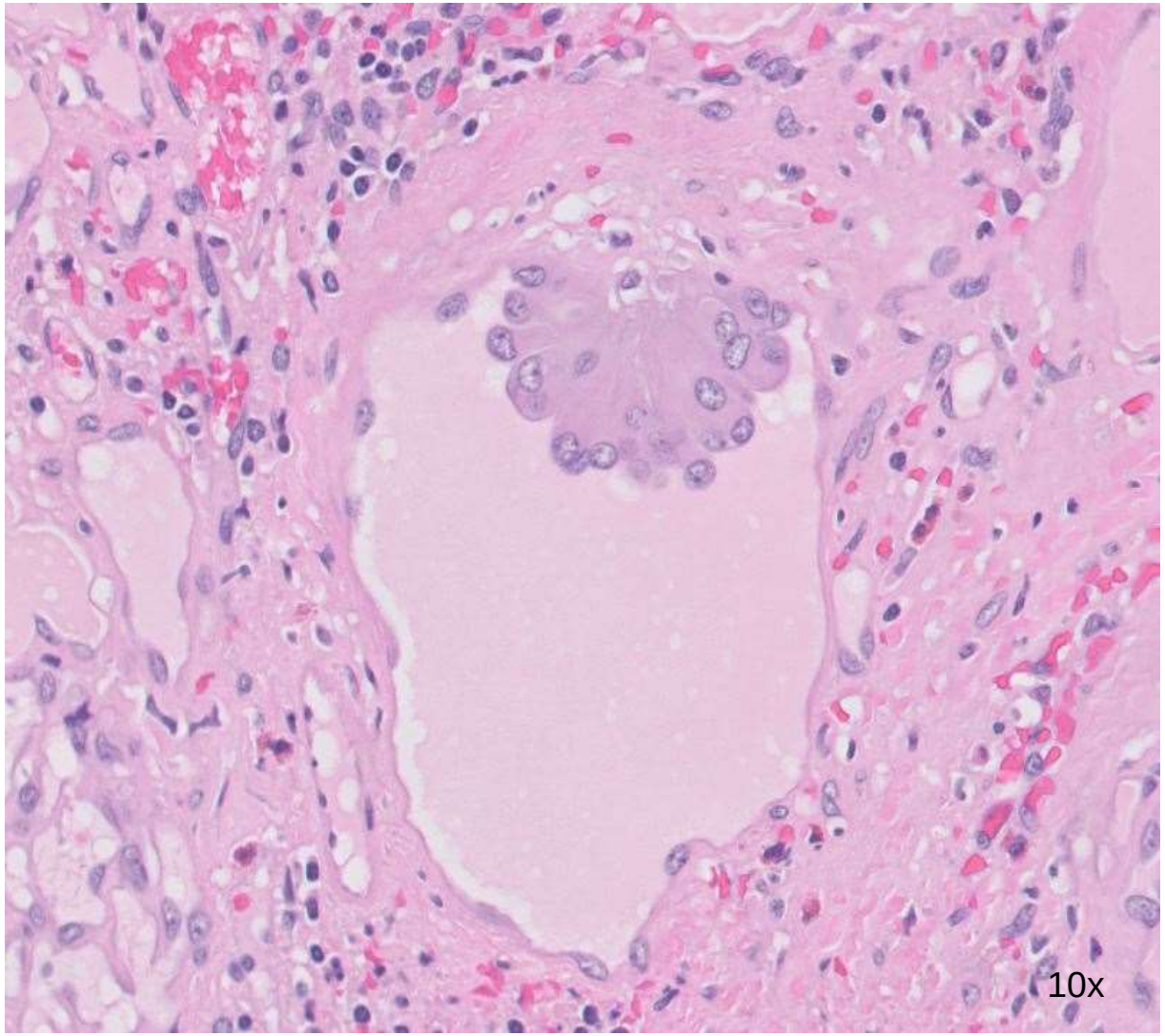
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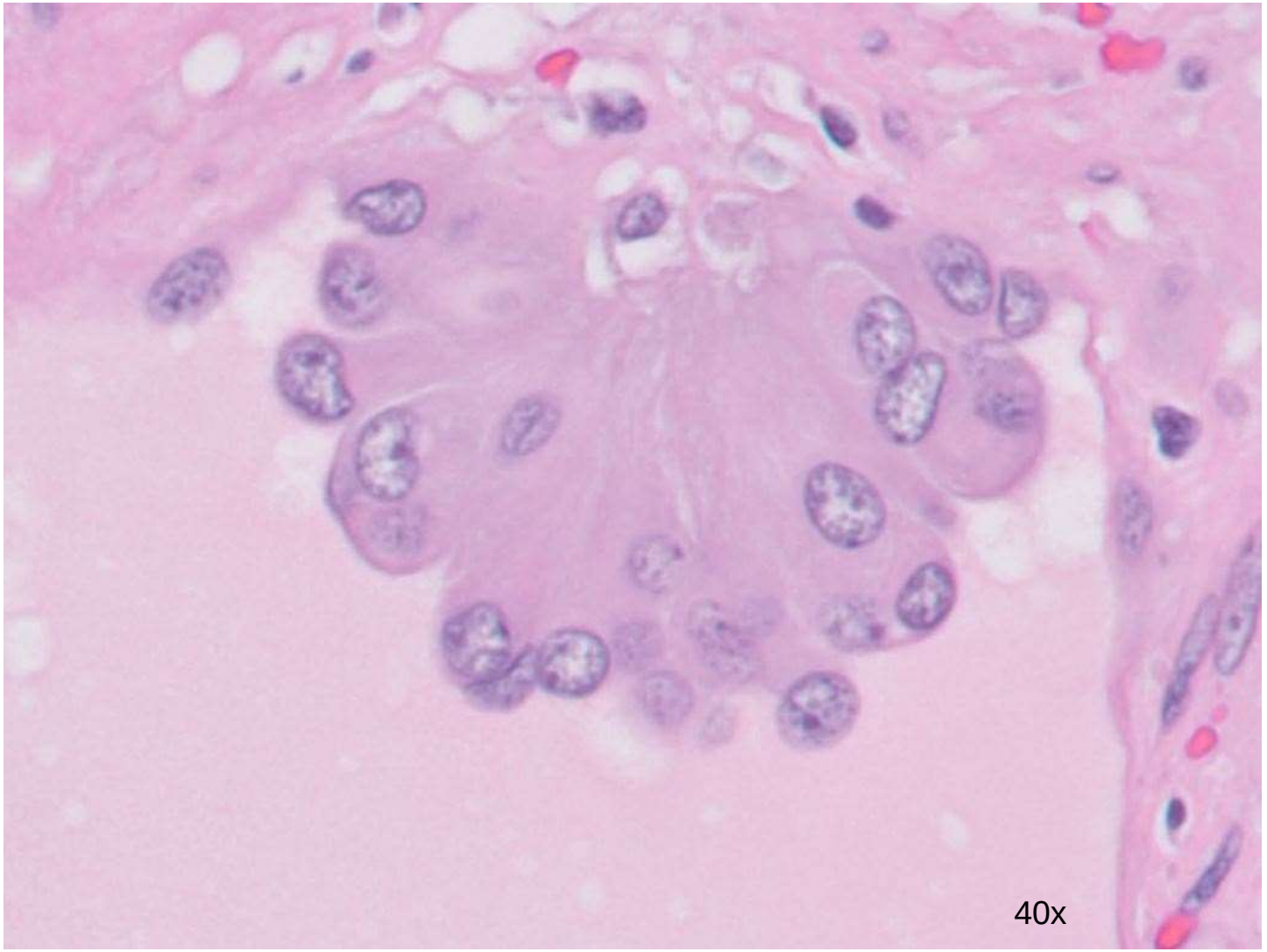
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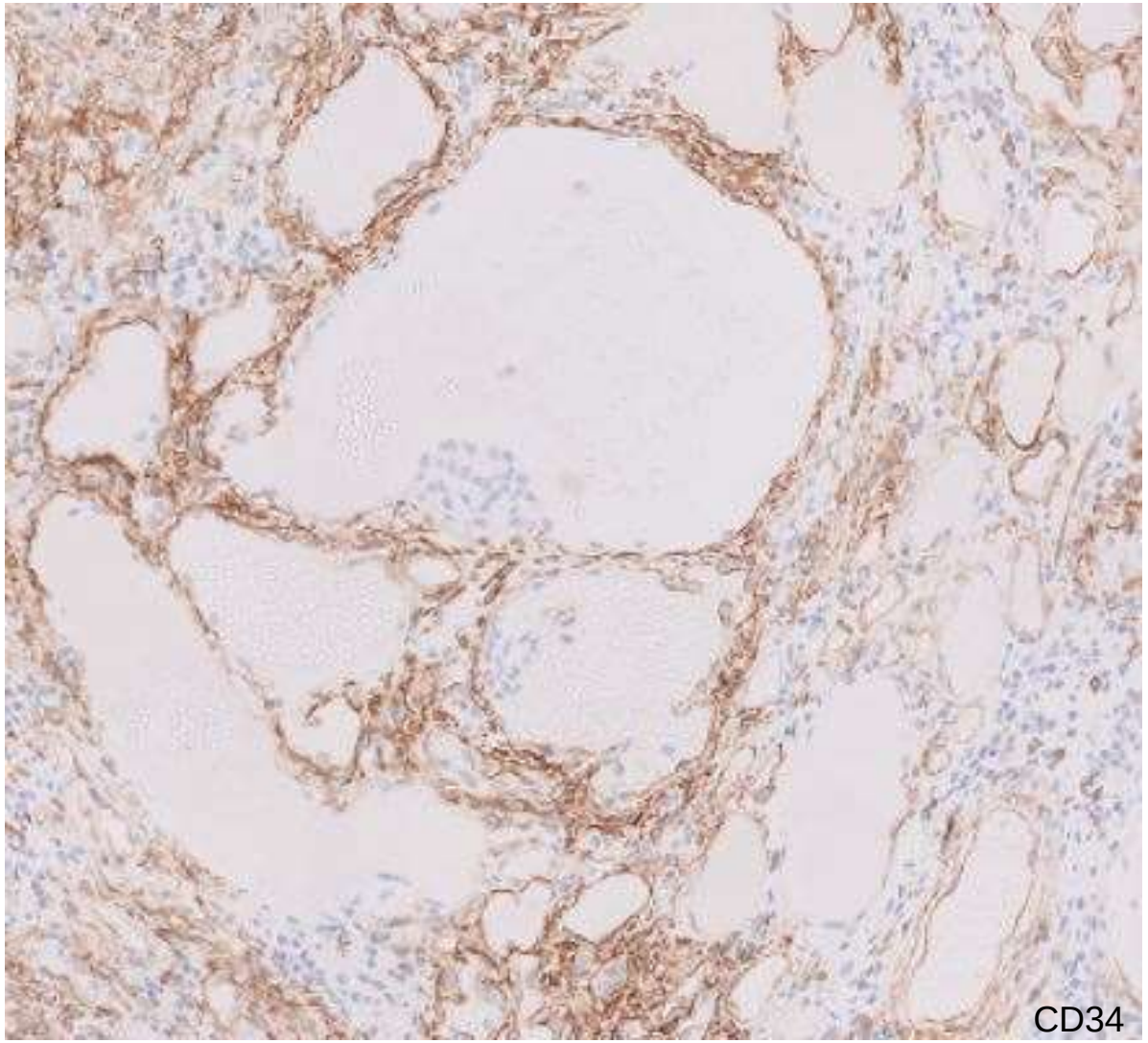
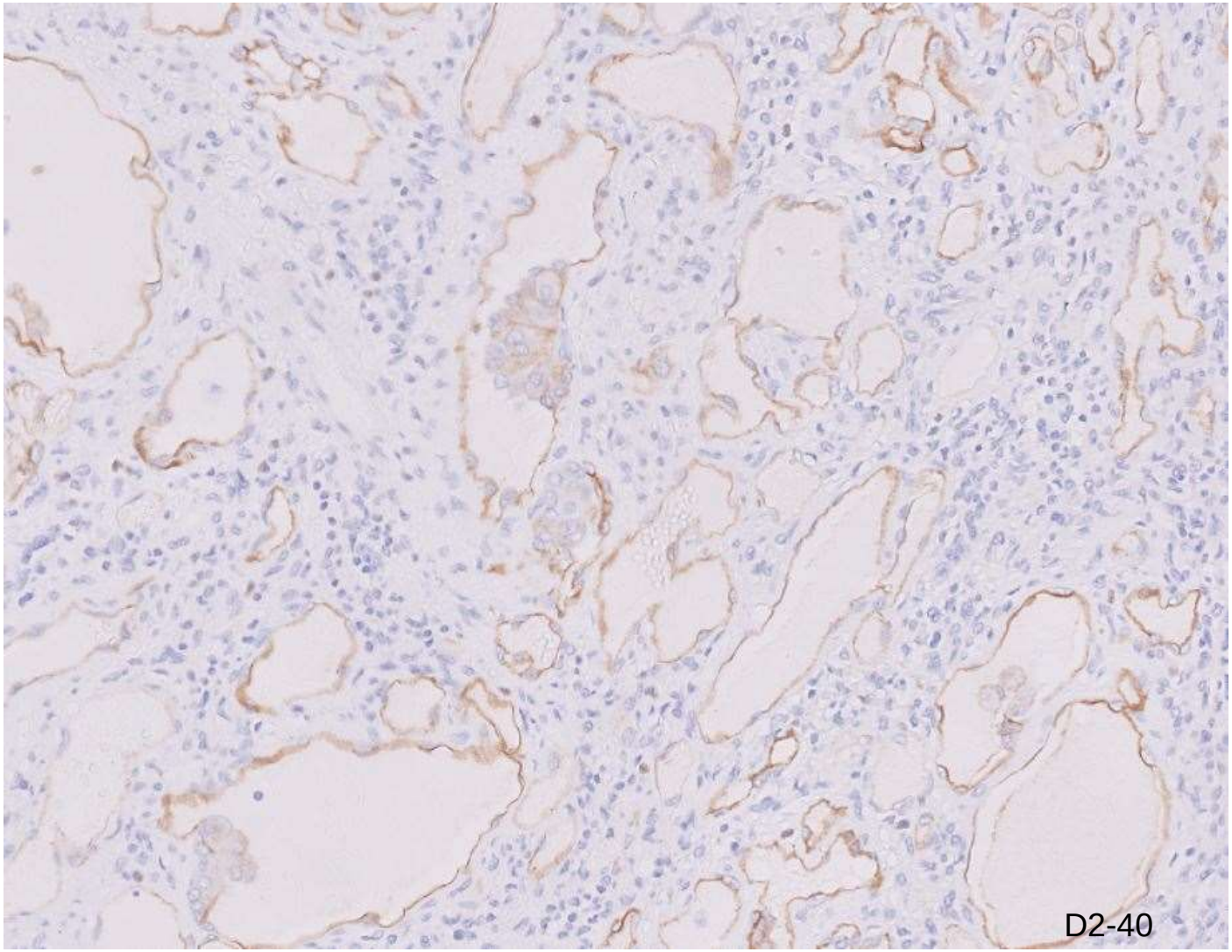
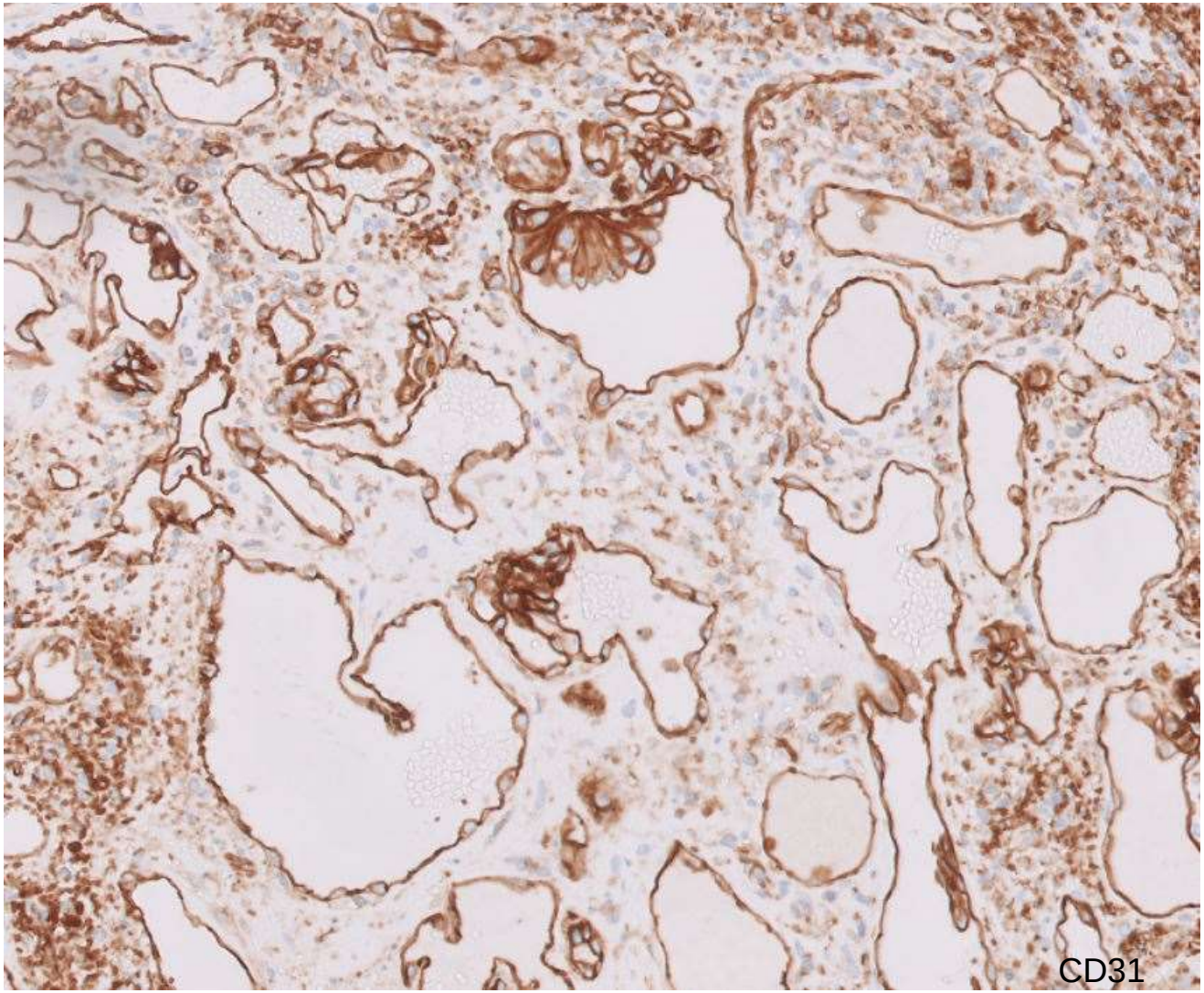

CD34


D2-40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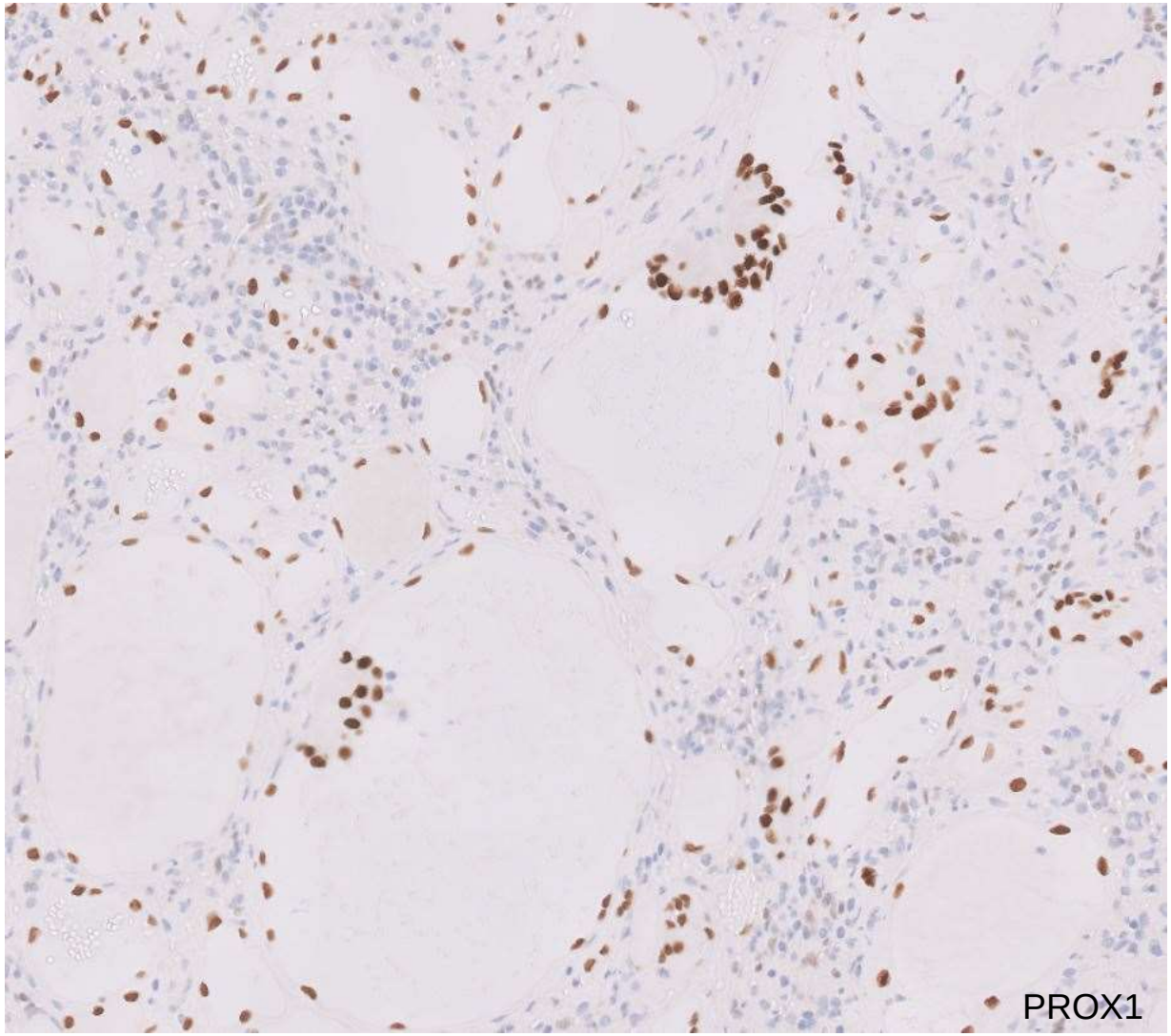
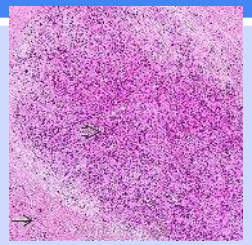
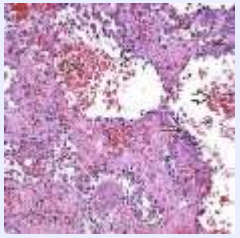
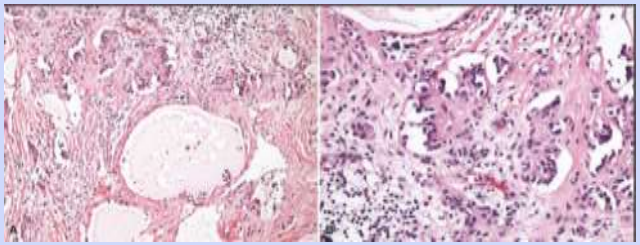
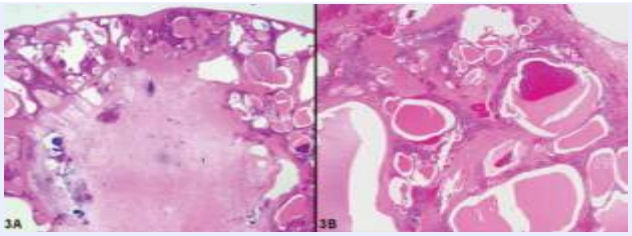

PROX1

Clinical and Gross Specimen Findings

- **25-year-old woman** with a multilobulated **splenic mass** found incidentally

- **Gross exam**: 400 grams, 11.0 x 8.2 x 6.0 cm **spleen** with an **8.5 x 7.0 x 5.5 cm ill-defined, red, slightly nodular mass with a central 2.0 x 1.1 x 0.7 cm pale-tan, white stellate scar** which abuts the smooth and intact splenic capsule

Differential Diagnosis	Features	Microscopic
Sclerosing angiomatoid nodular transformation (SANT)	• Usually incidentally detected, excellent prognosis • Single mass with central sclerosis • Angiomatoid nodules comprised of small vessels	
Littoral cell angioma	• Multiple lesions in spleen, excellent prognosis (rare cases of mets) • Multiple spongy vascular lesions • Irregular cystic vascular channels lined by tall + flat cells; can have papillary projections	
Papillary intralymphatic angioendothelioma (Dabska tumor)	• ~40% in adults, usually in superficial soft tissues, overall good prognosis • Ill-defined thickening with small cystic spaces (in soft tissues) • Cavernous, lymphatic-like spaces with intravascular papillae (“matchstick-like” appearance)	
Splenic Lymphangioma	• Mostly children, frequently involves multiple organs (lymphangiomatosis), favorable prognosis after resection • Solitary or multiple nodules, can have central scarring • Cystic structures, can have intraluminal papillary projections	

DIAGNOSIS:
SPLEEN, SPLENECTOMY
-- **SPLENIC LYMPHANGIOMA WITH PAPILLARY ENDOTHELIAL PROLIFERATION (SEE COMMENT)**

Splenic Lymphangioma

- **Etiology**: malformation of splenic lymphatic channels
- **Clinical**: children, **multiple organs involved in most cases** (systemic lymphangiomatosis), rare cases of transformation into malignant lymphangiosarcomas (**close follow up if atypical endothelial morphology)**, favorable prognosis after resection
- **Gross**: solitary or multiple nodules, can have central scarring
- **Micro**: **cystic** structures, can have intraluminal papillary projections
- **IHC**: positive for CD31, CD34, Factor VIII, **D2-40**, VEGFR3, **PROX1**

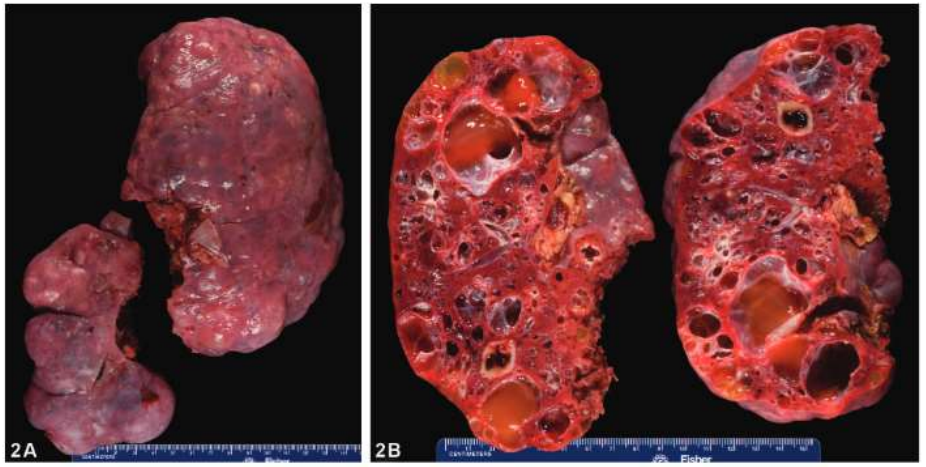
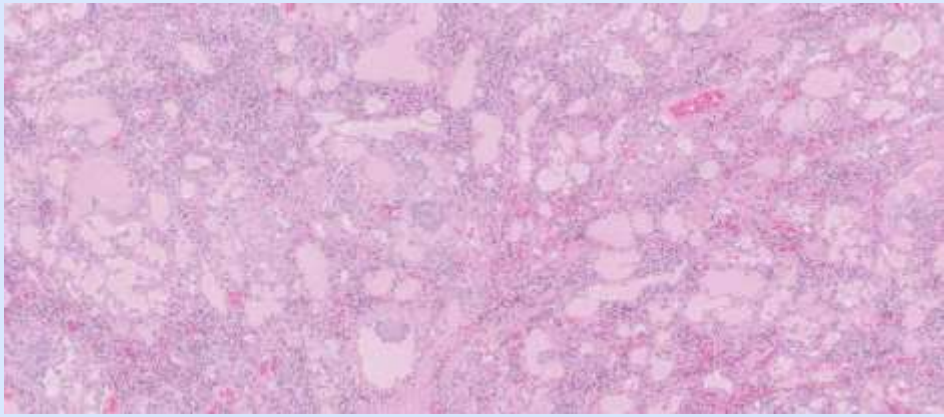


Figure 2. *A, Diffuse splenic lymphangiomatosis presenting with multiple nodules that involve the entire splenic parenchyma. B, Cross-sections reveal multiple cystic spaces of various diameters filled with serous fluid.*

Ioannidis et al. Archives of Pathology and Laboratory Medicine 139.2 (2015): 278-282.



Pathology International 2003; **53**: 483–488

Case Report

Splenic lymphangioma with papillary endothelial proliferation: A case report and review of the literature

Akiko Takayama,[1] Osamu Nakashima,[1] Keita Kobayashi[2] and Masamichi Kojiro[1]

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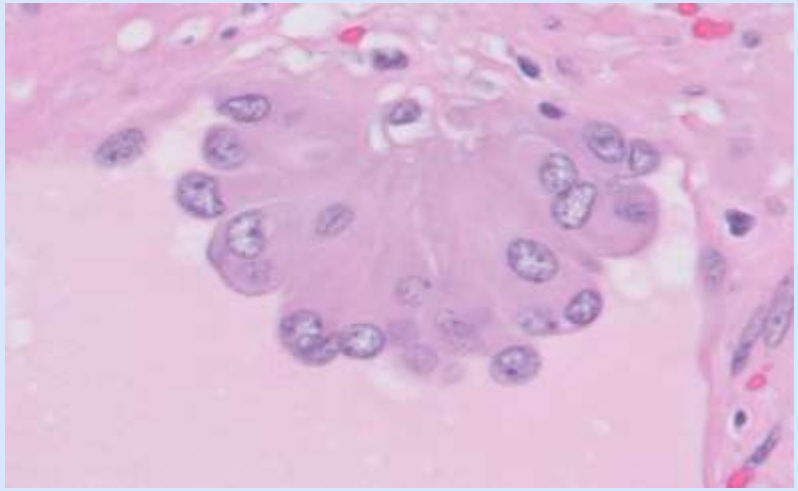


Summary

- Splenic lymphangiomas are commonly associated with **systemic lymphangiomatosis**
- Usually multiple cystic structures filled with eosinophilic amorphous proteinaceous material with **bland** appearing endothelial lining cells and papillae but in a minority of spaces
- Positive for lymphatic markers **D2-40**, **PROX1**
- Treatment of choice is **complete surgical resection**

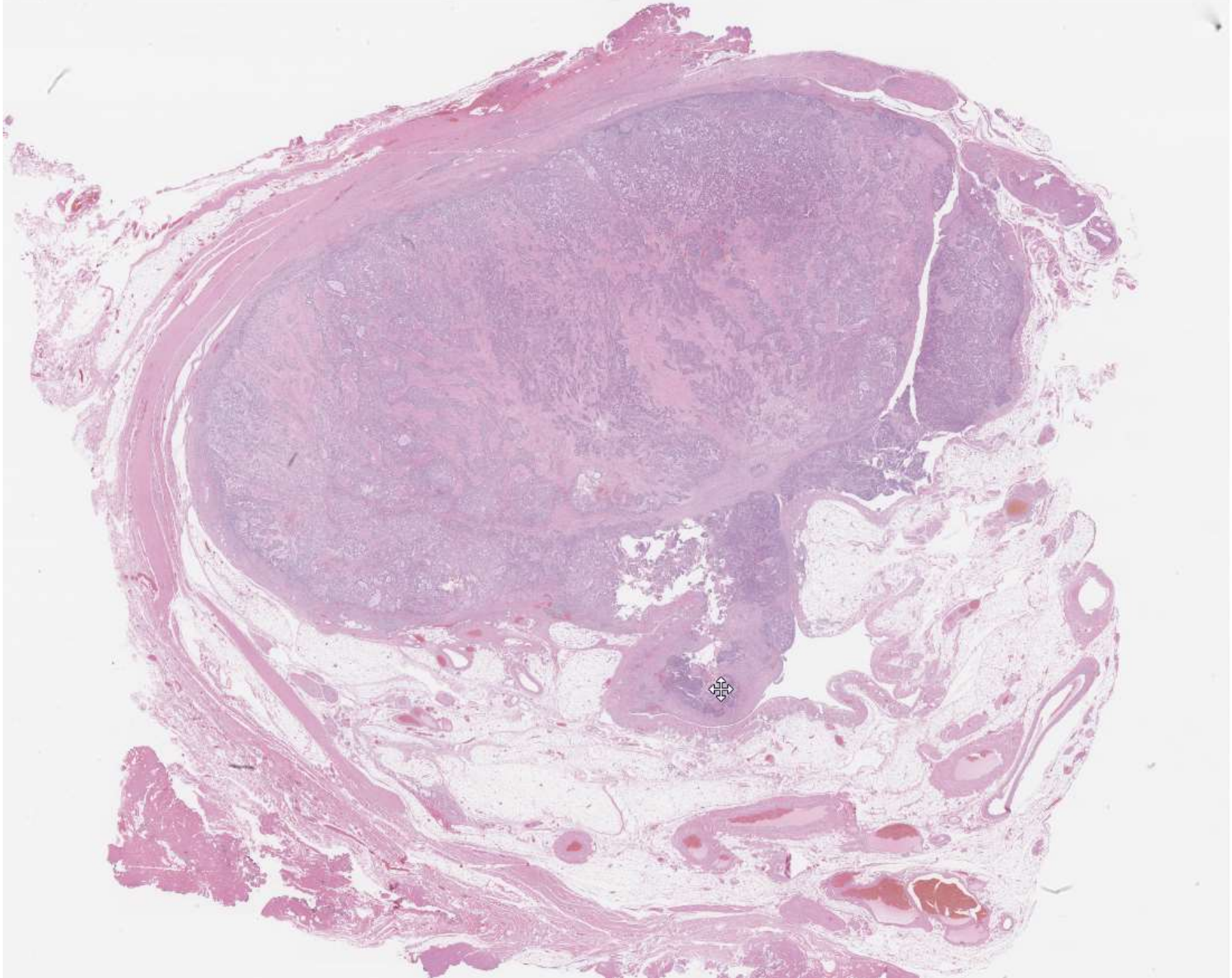
References

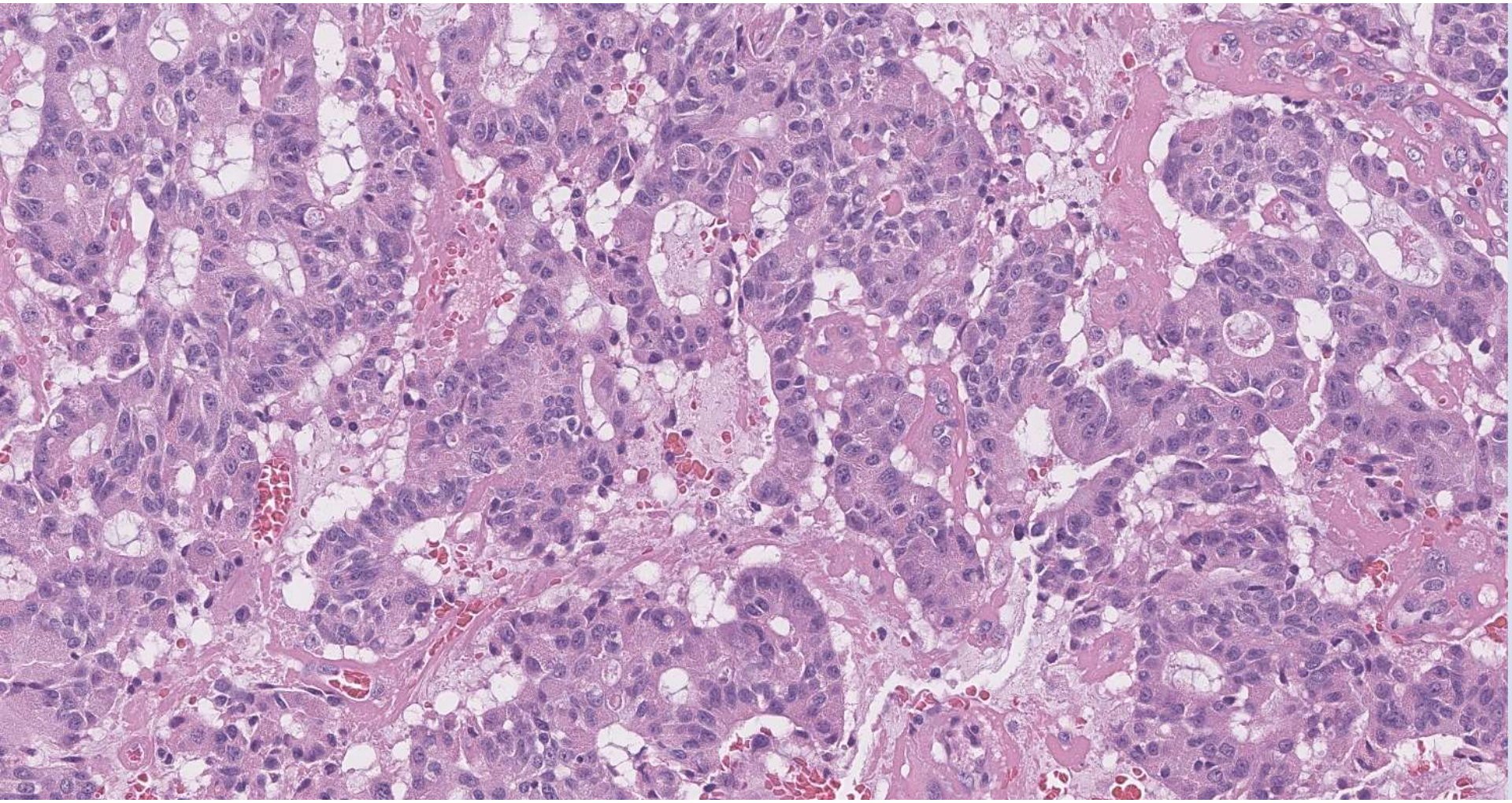
1. Abbott RM, Levy AD, Aguilera NS, Gorospe L, Thompson WM. From the archives of the AFIP: primary vascular neoplasms of the spleen: radiologic-pathologic correlation. Radiographics. 2004 Jul-Aug;24(4):1137-63. doi: 10.1148/rg.244045006. PMID: 15256634.
2. Takayama, Akiko, et al. "Splenic lymphangioma with papillary endothelial proliferation: a case report and review of the literature." Pathology international 53.7 (2003): 483-488.
3. Ioannidis, Ioannis, and Andrea G. Kahn. "Splenic lymphangioma." Archives of Pathology and Laboratory Medicine 139.2 (2015): 278-282.
4. Briana C. Gleason MD and Jason L. Hornick MD, PhD. Practical Soft Tissue Pathology: A Diagnostic Approach, 13, 341-390.
5. Experpath. (2013). Spleen. https://app.expertpath.com/tree/spleen/fa602573-8b23-4917-94c3-9a52b098daa0

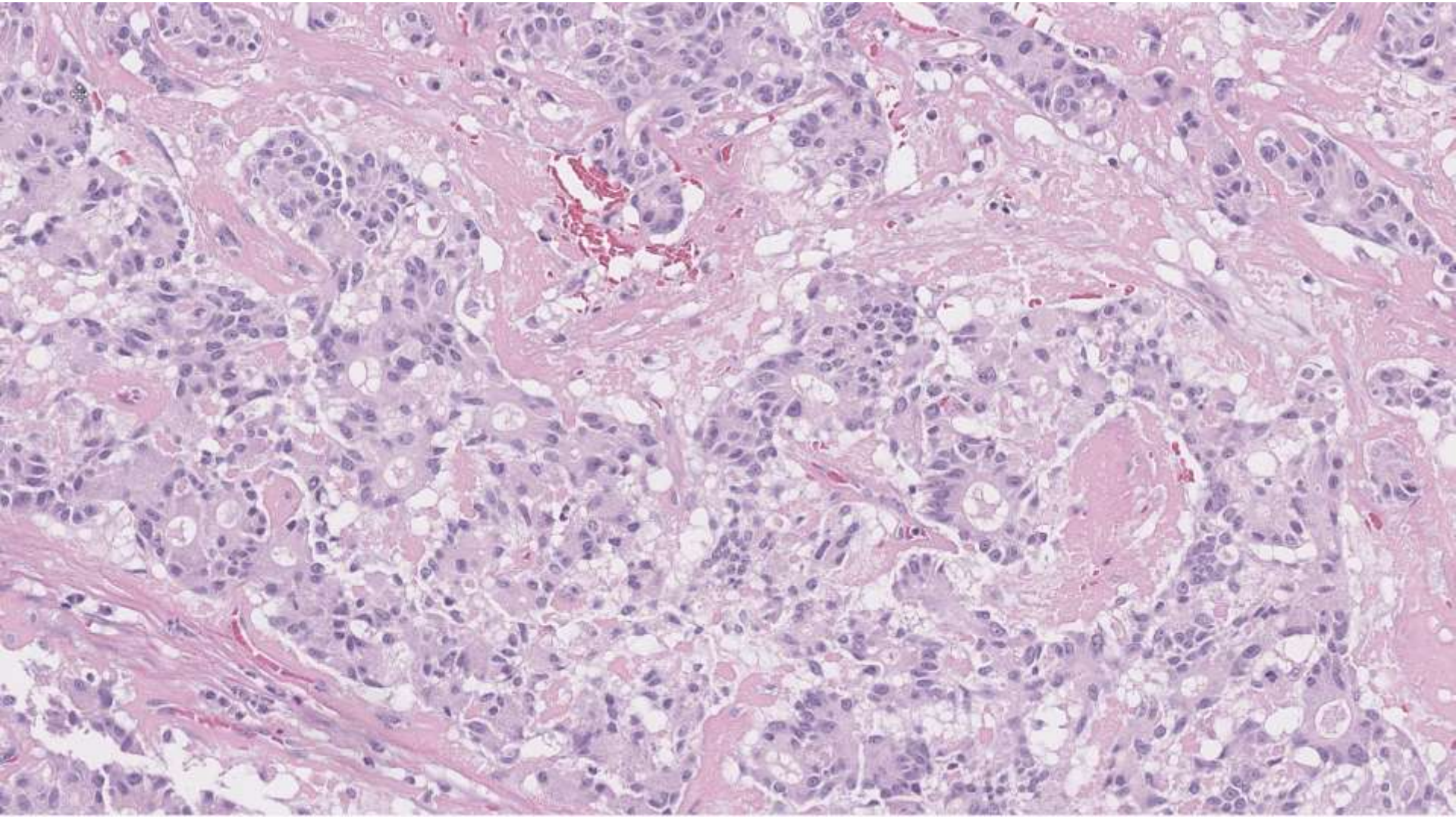
21-0602

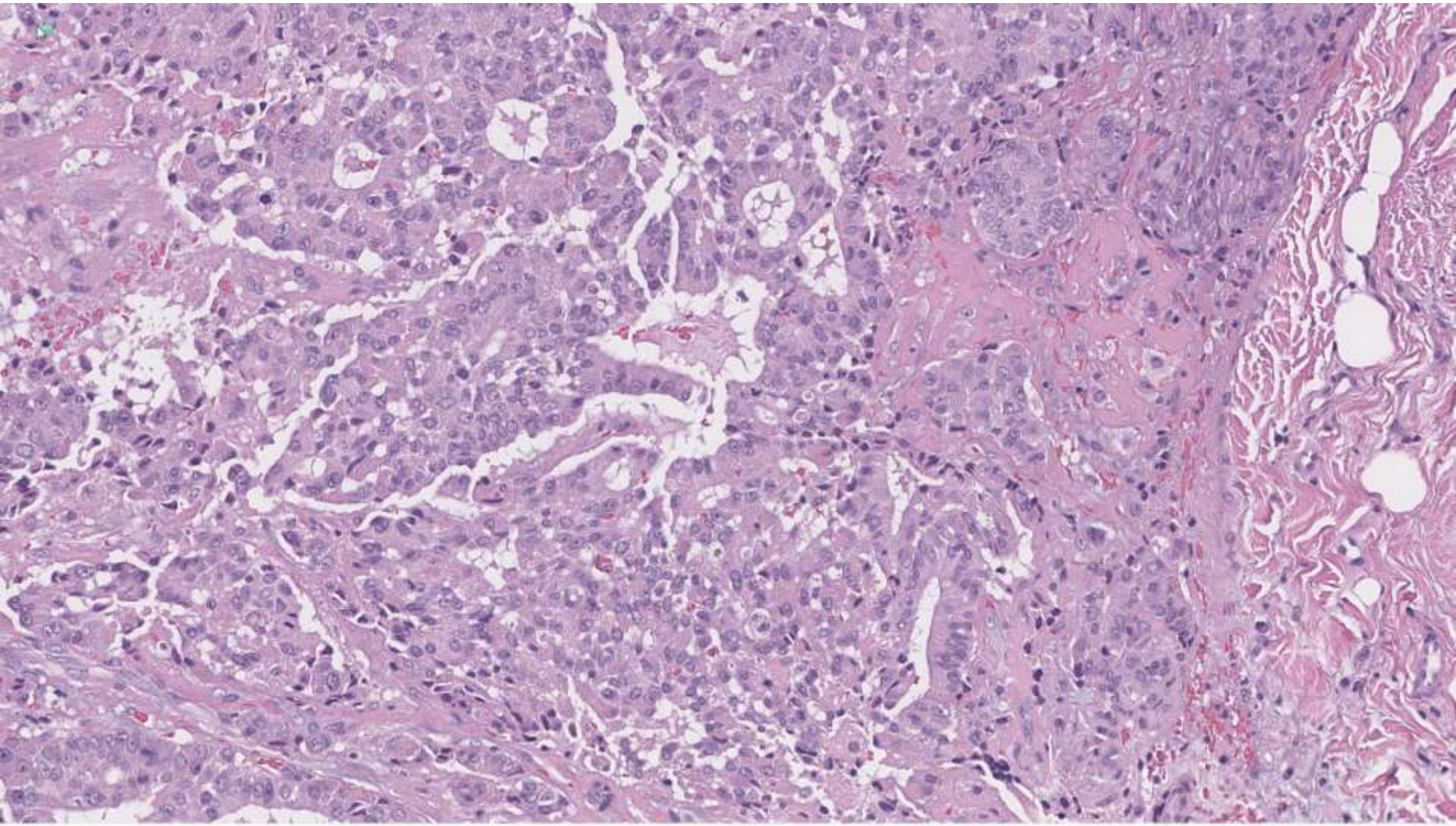
David Levin; Washington Hospital

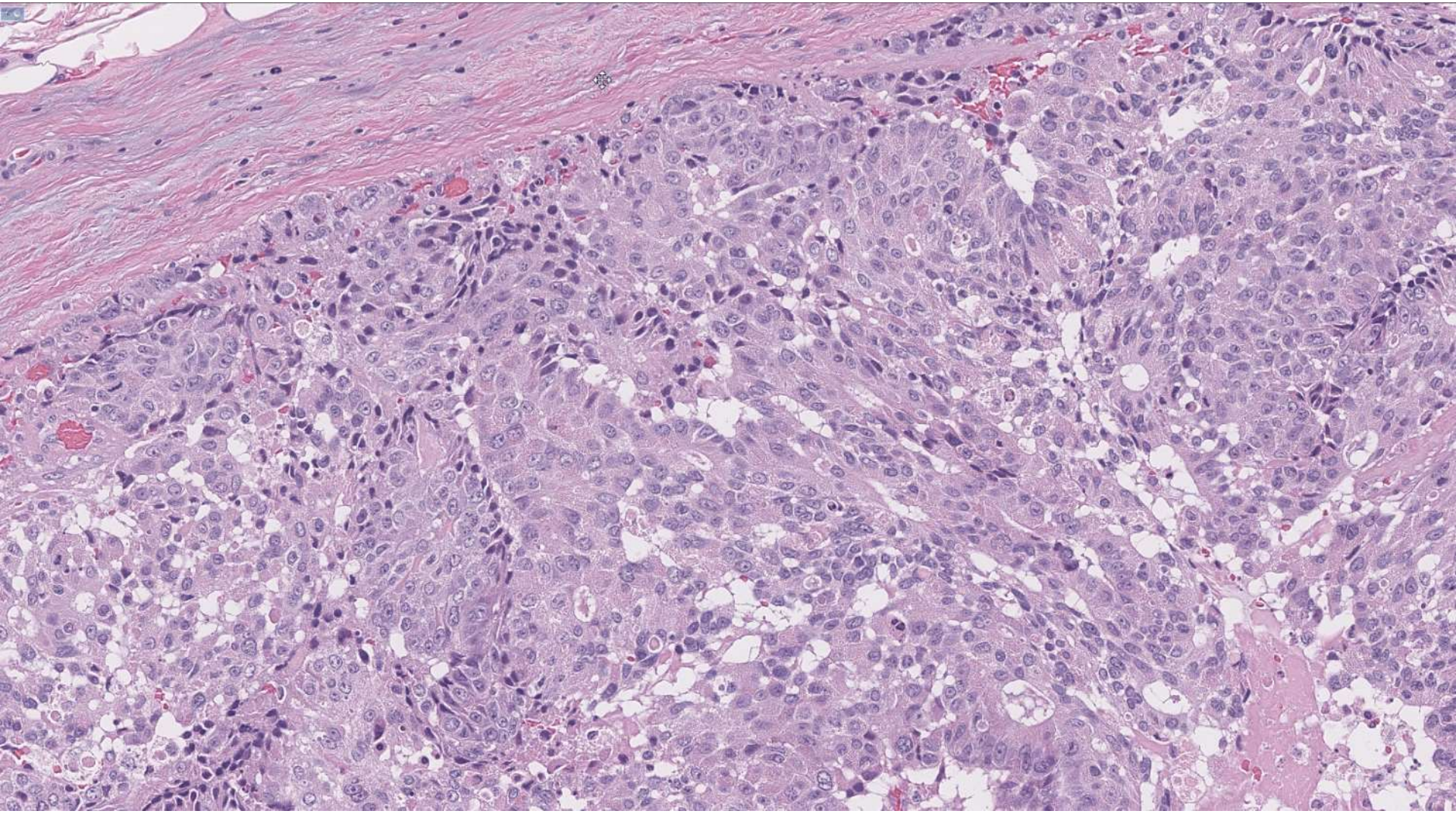
58-year-old F with chief complaint of umbilical pain for several months, underwent herniorrhaphy.

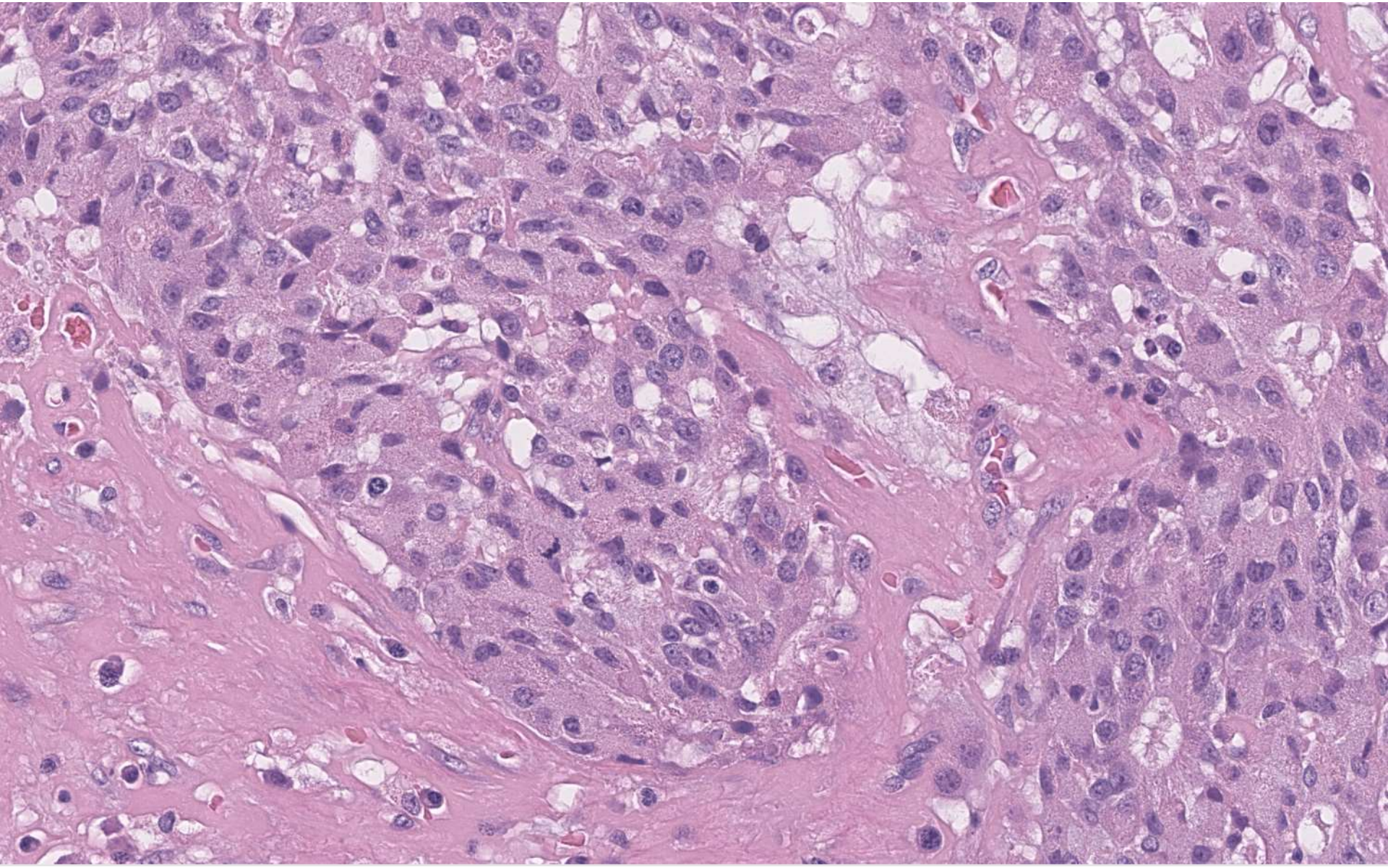


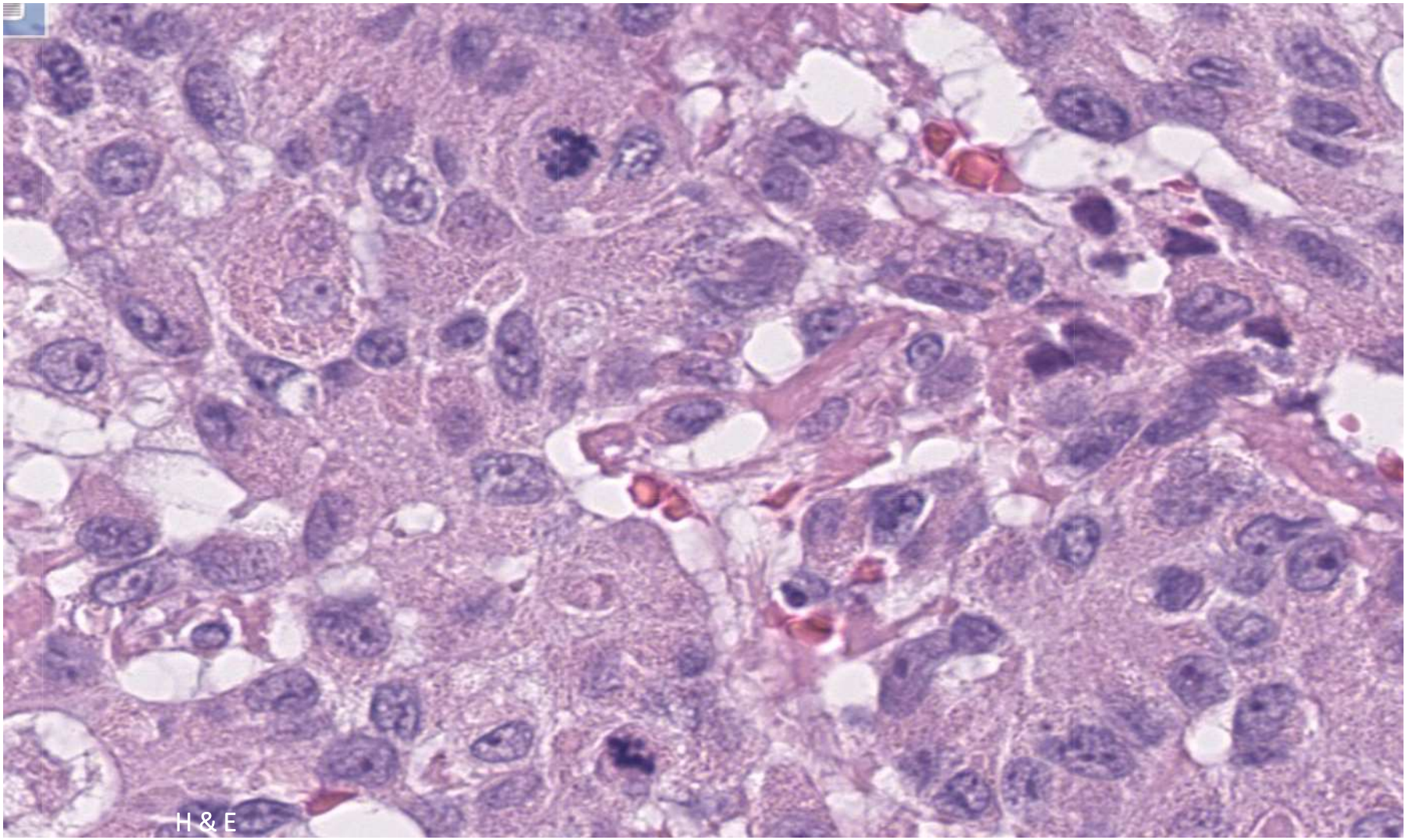








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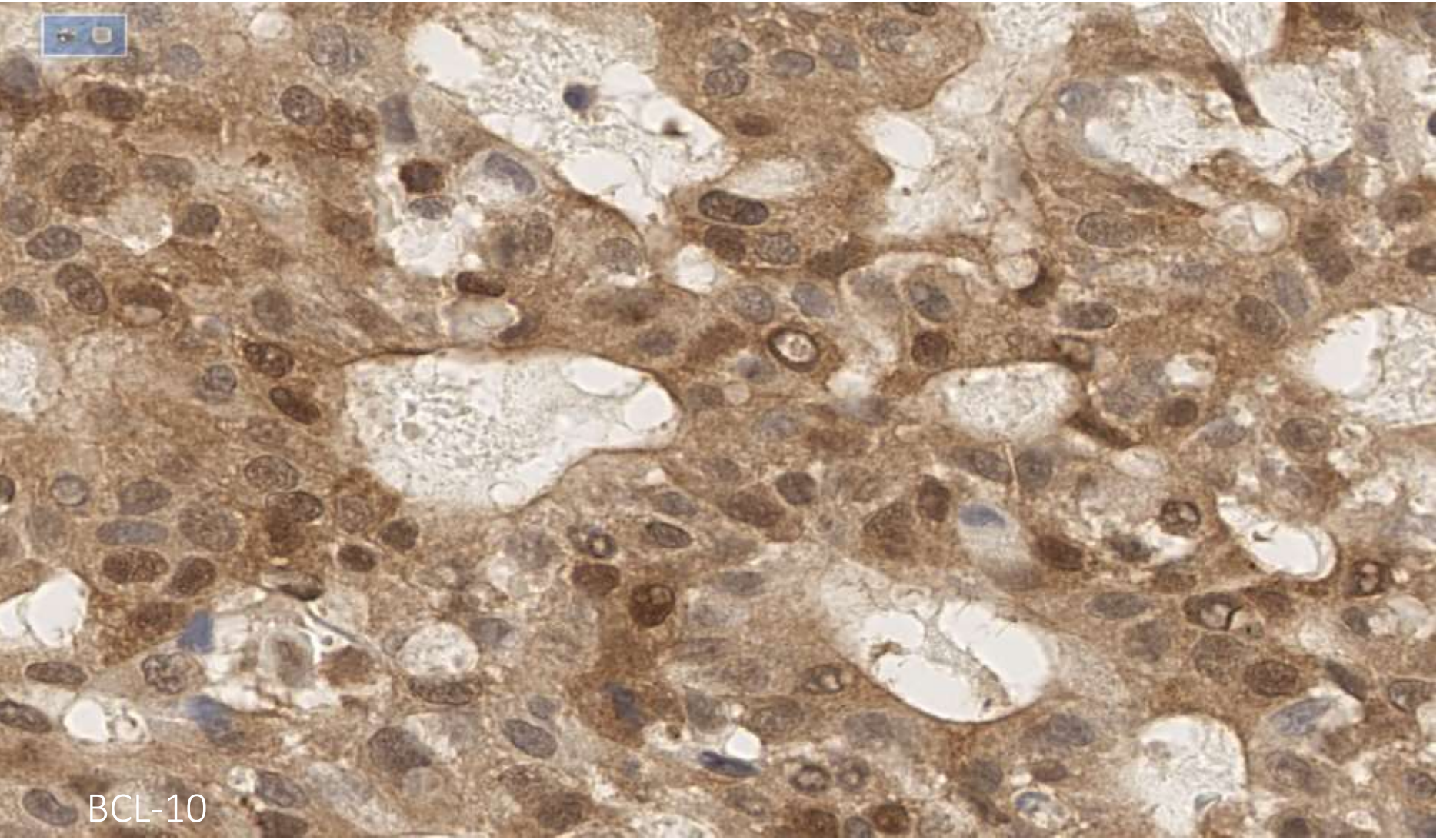
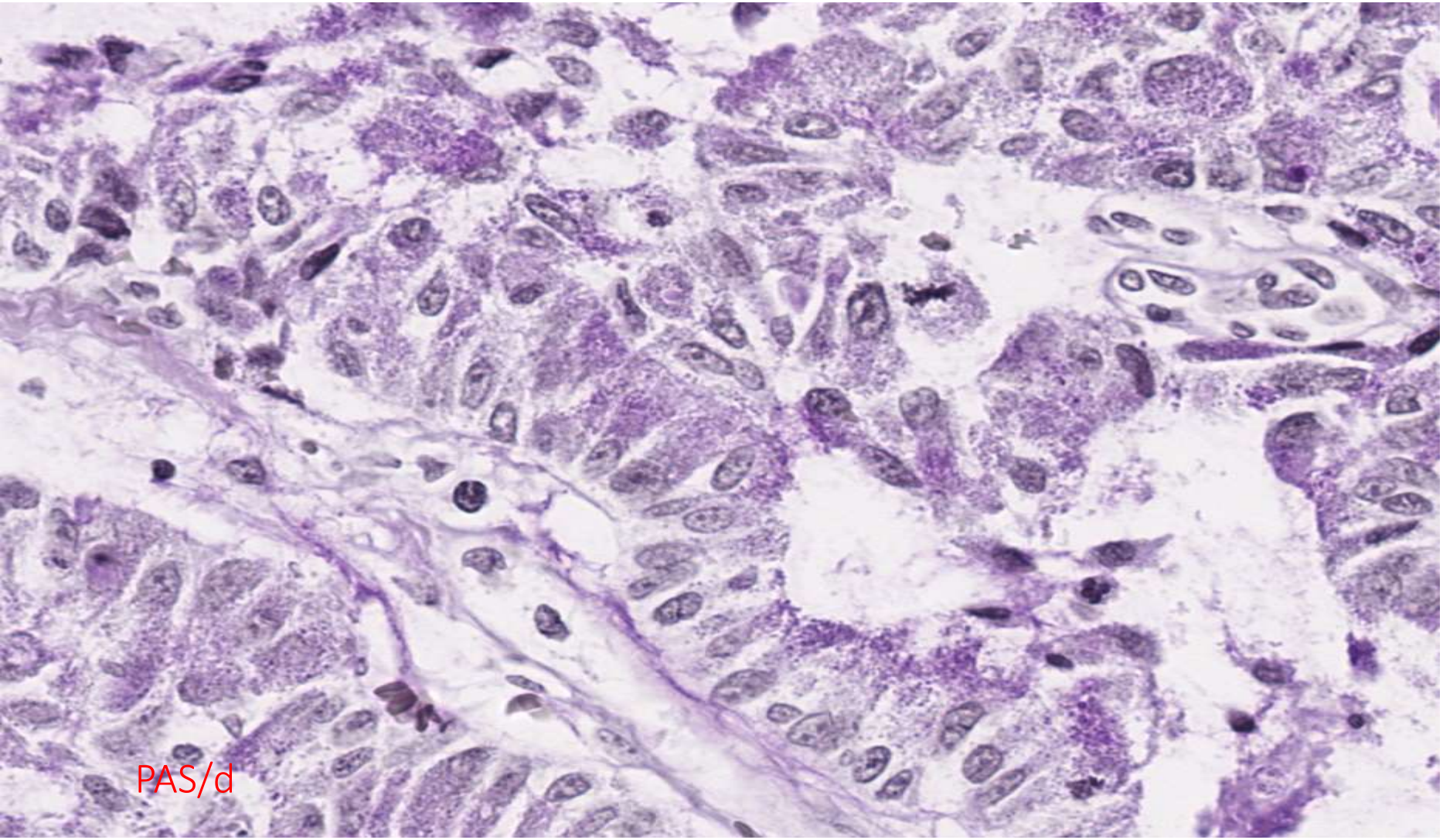

BCL-10


PAS/d

ACINAR CELL CARCINOMA

- DEFINITION
- cells with morphological resemblance to acinar cells and with evidence of pancreatic exocrine enzyme production • trypsin• chymotrypsin• BCL10

- CLINICAL FEATURES
- weight loss,
- abdominal pain,
- nausea and vomiting
- >50% have metastatic disease at presentation

- EPIDEMIOLOGY
- 1-2% of adult pancreatic neoplasms; and
- 15% of pediatric pancreatic neoplasms
- average age 59 years, range 20-88 years.
- ratio of Men:Women is 2:1.

ACINAR CELL CARCINOMA

- MACROSCOPIC
- large (8-10cm)
- well circumscribed,
- solid or with variably sized cysts (cystadenocarcinoma)

- MICROSCOPIC
- acinar, glandular, trabecular, and solid patterns.
- moderate amounts of Pas/d positive granular eosinophilic zymogen granules
- nuclei are usually uniform with a single prominent nucleolus.

Pancreatic Neoplasms with Acinar Differentiation: A Review of Pathologic and Molecular Features. Arch Pathol Lab Med. 2020;144:808–815

ACINAR CELL CARCINOMA

- PROGNOSIS
- median survival 19 months; 5-year survival rate of 25%.
- only stage has proven to be an independent prognostic factor in multivariate analysis

- DDx:
- mixed acinar carcinomas. > 30% of each line of differentiation. eg mixed acinar-neuroendocrine carcinoma, mixed acinar-ductal carcinoma
- Ductal adenocarcinoma
- Pancreatic endocrine tumor
- Solid pseudopapillary neoplasm
- Serous microcystic adenoma
- Serous oligocytstic adenoma
- Acinar cell cystadenoma
- Medullary carcinoma

ACINAR CELL CARCINOMA

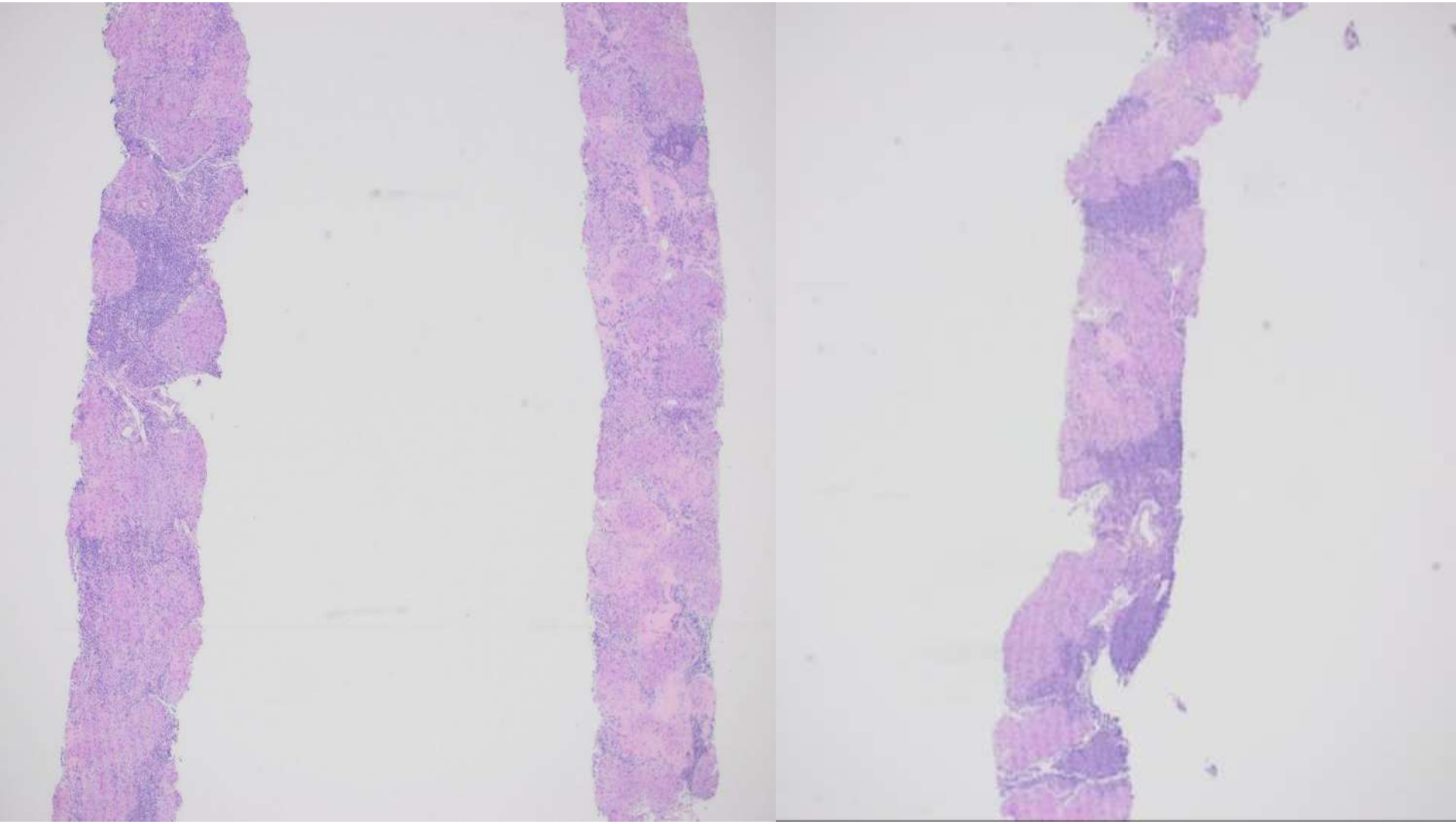
- References

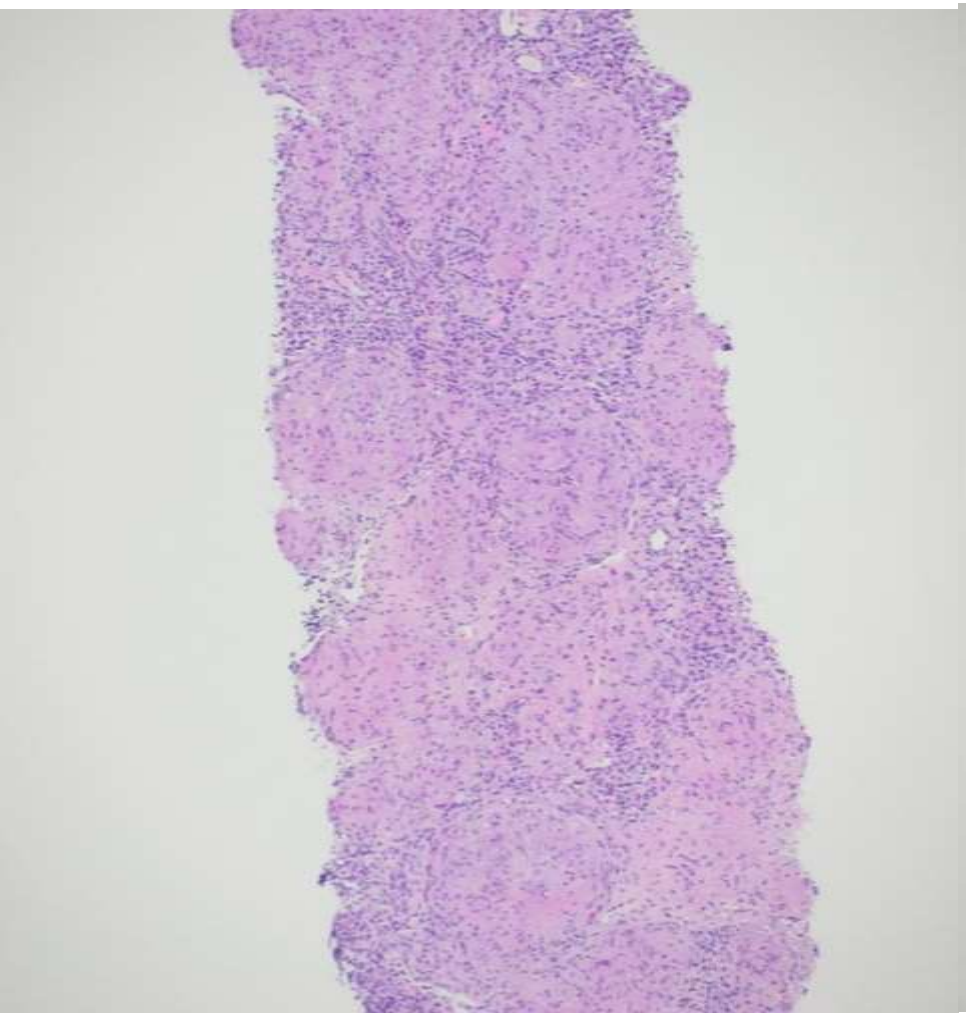
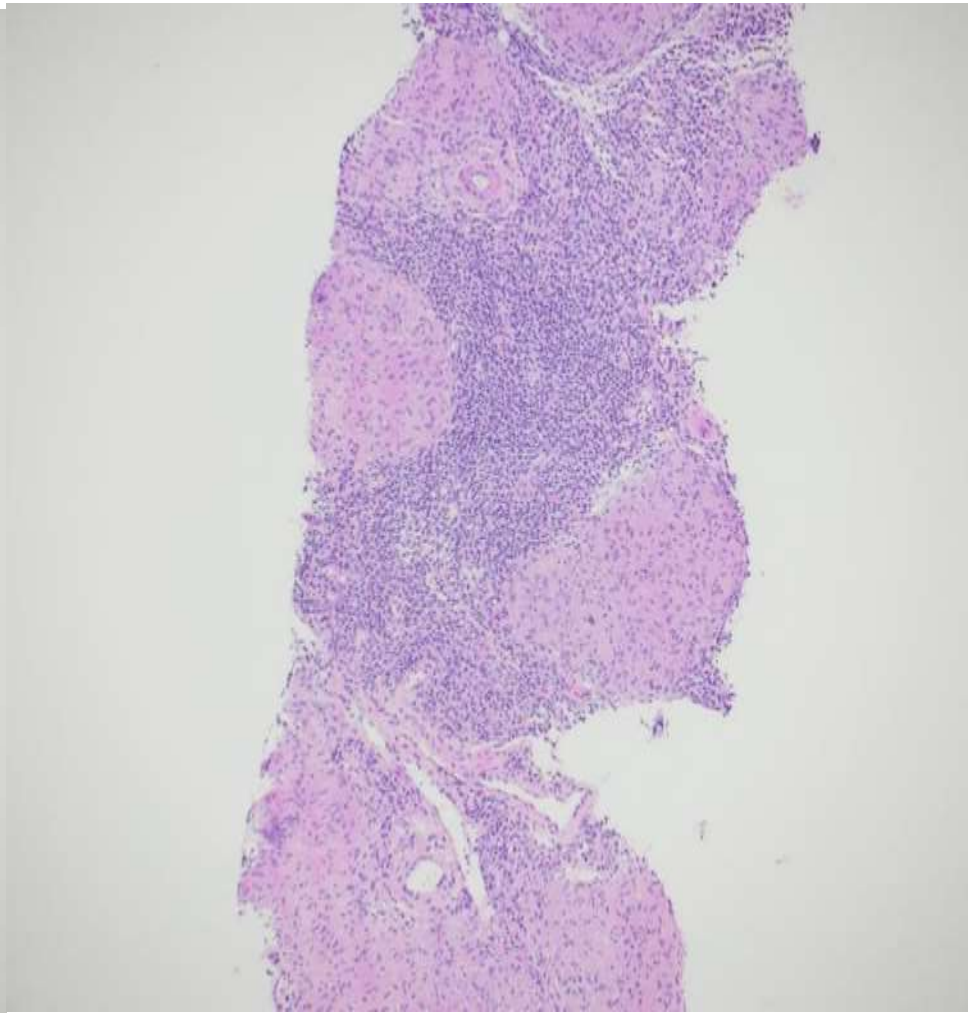
- WHO Classification of Tumours: Digestive System tumours (5th ed)
- Pancreatic Neoplasms with Acinar Differentiation: A Review of Pathologic and Molecular Features. Arch Pathol Lab Med. 2020;144:808–815

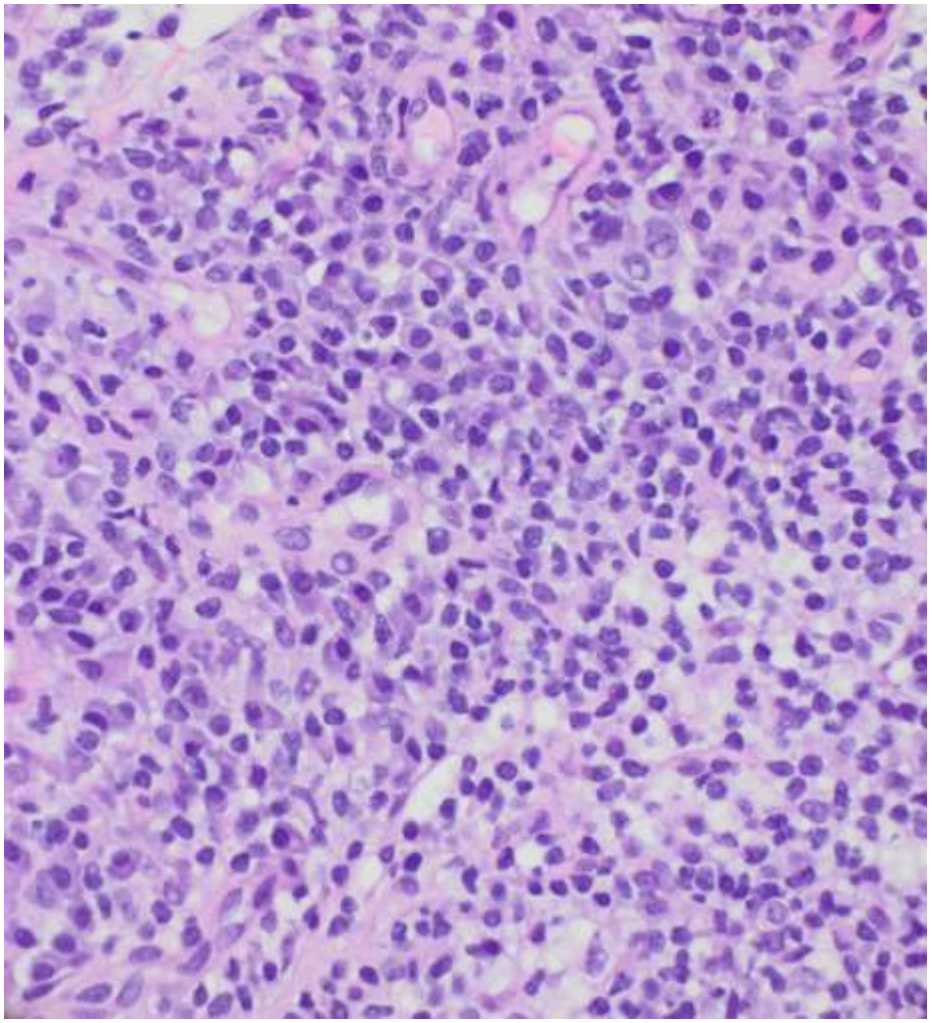
21-0603

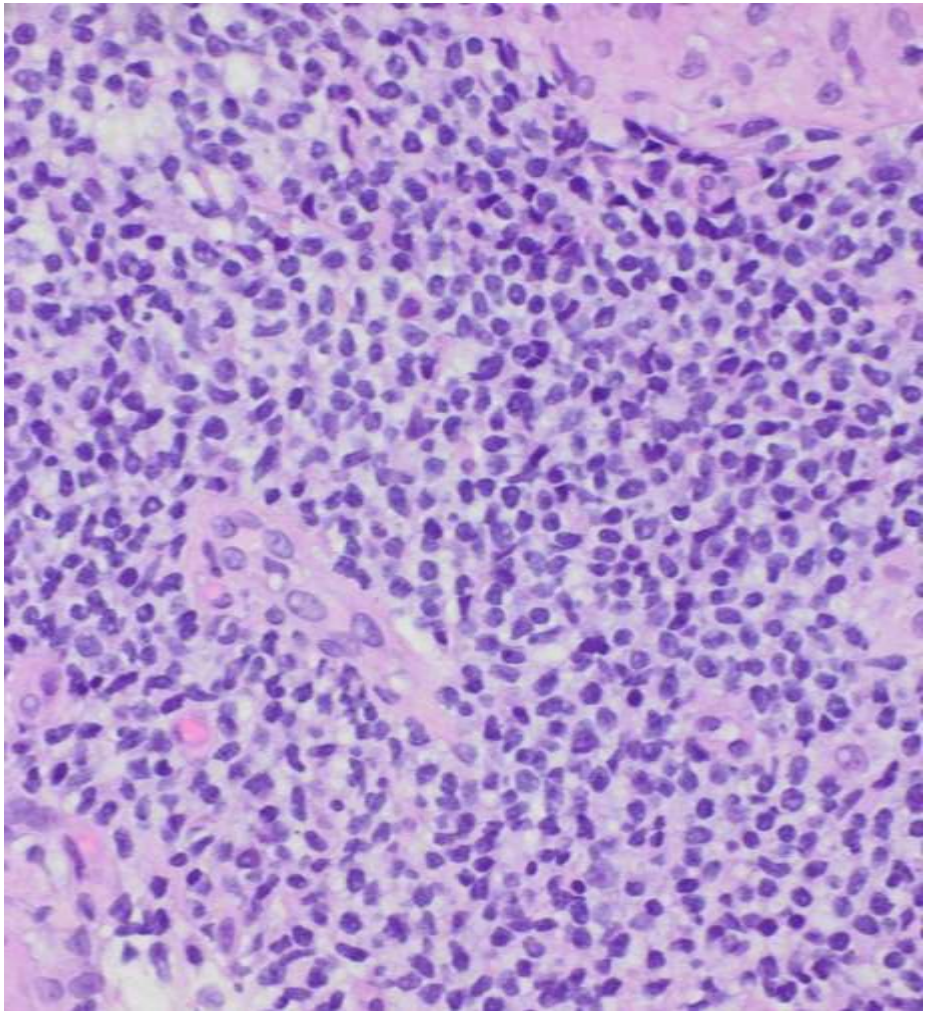
Natalya Hakim/Linlin Wang; UCSF

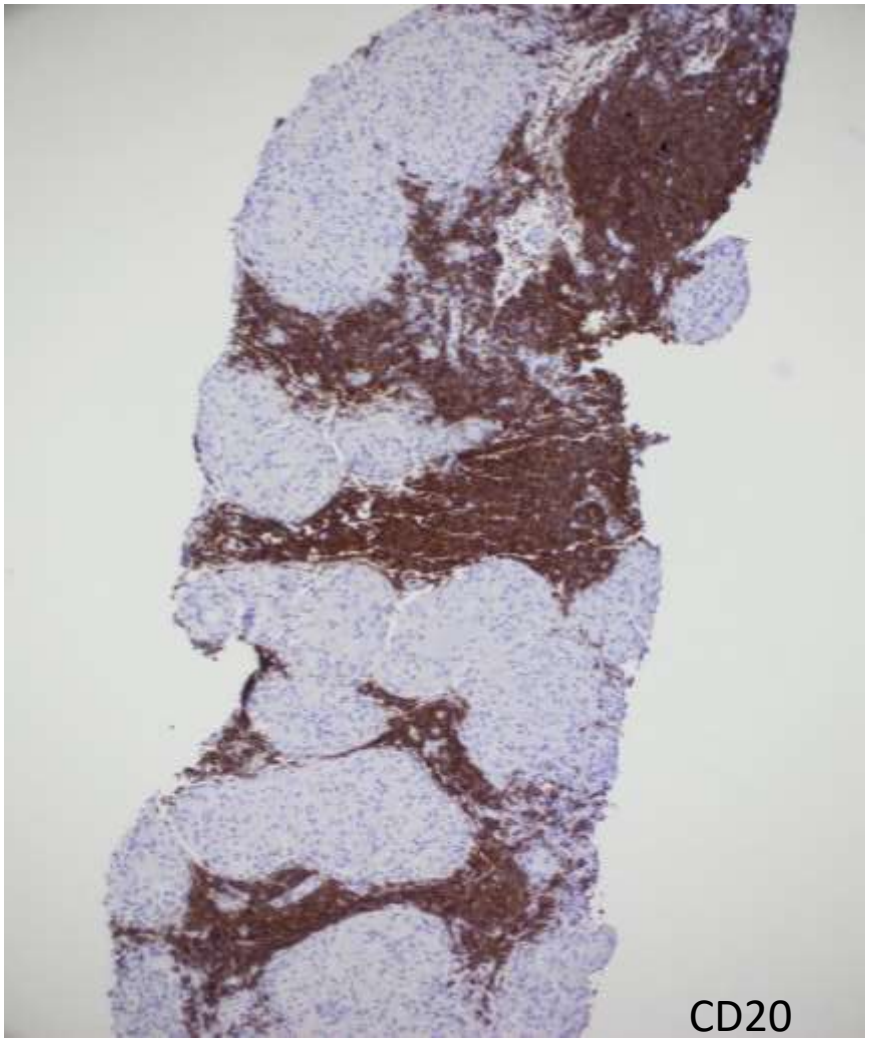
42-year-old M with SOB and mediastinal nodes. Clinical picture highly suspicious for sarcoidosis. Imaging studies show significant periportal and retroperitoneal adenopathy with left inguinal node enlargement, multiple bone lytic lesion in the pelvis and spine, splenomegaly with extensive nodular abnormalities, liver parenchyma with nodular pattern. Inguinal lymph node submitted.

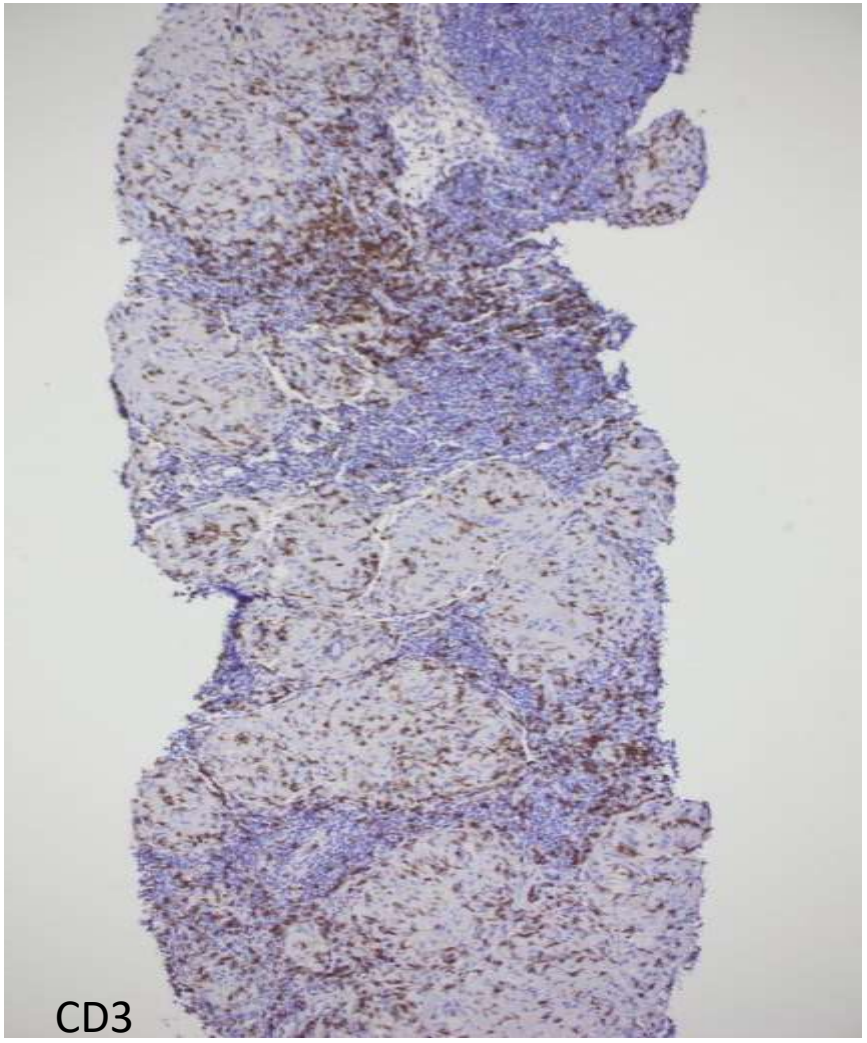







CD20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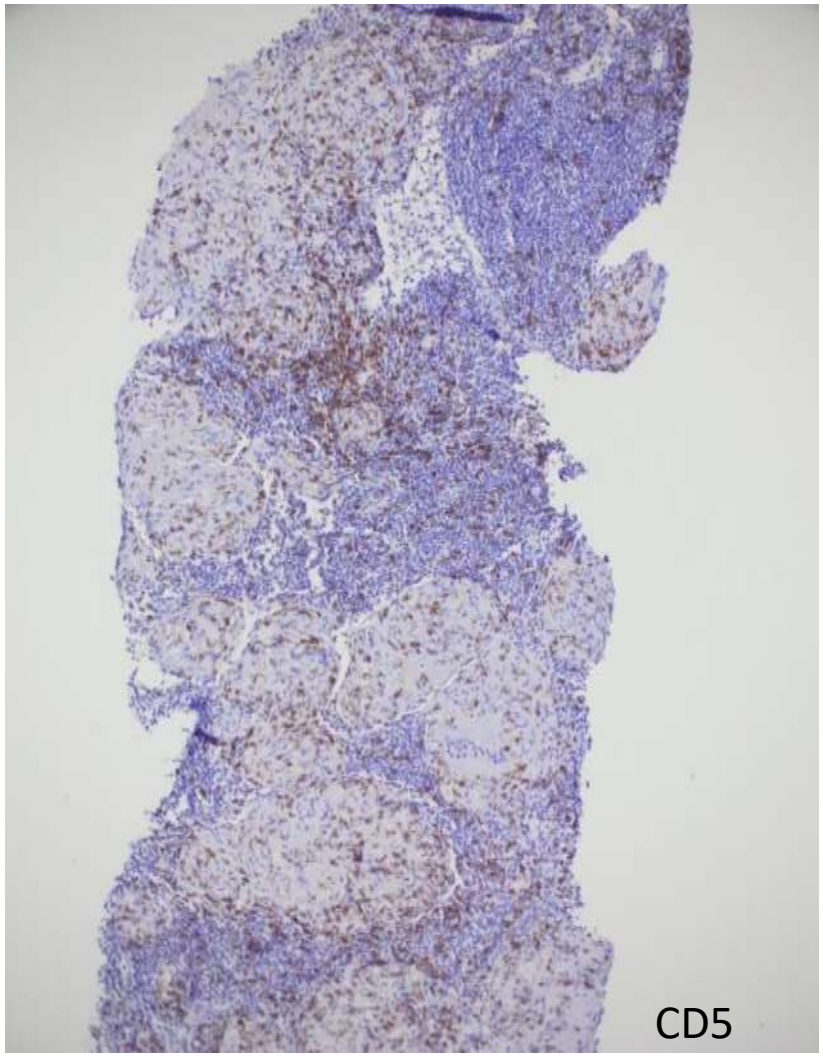
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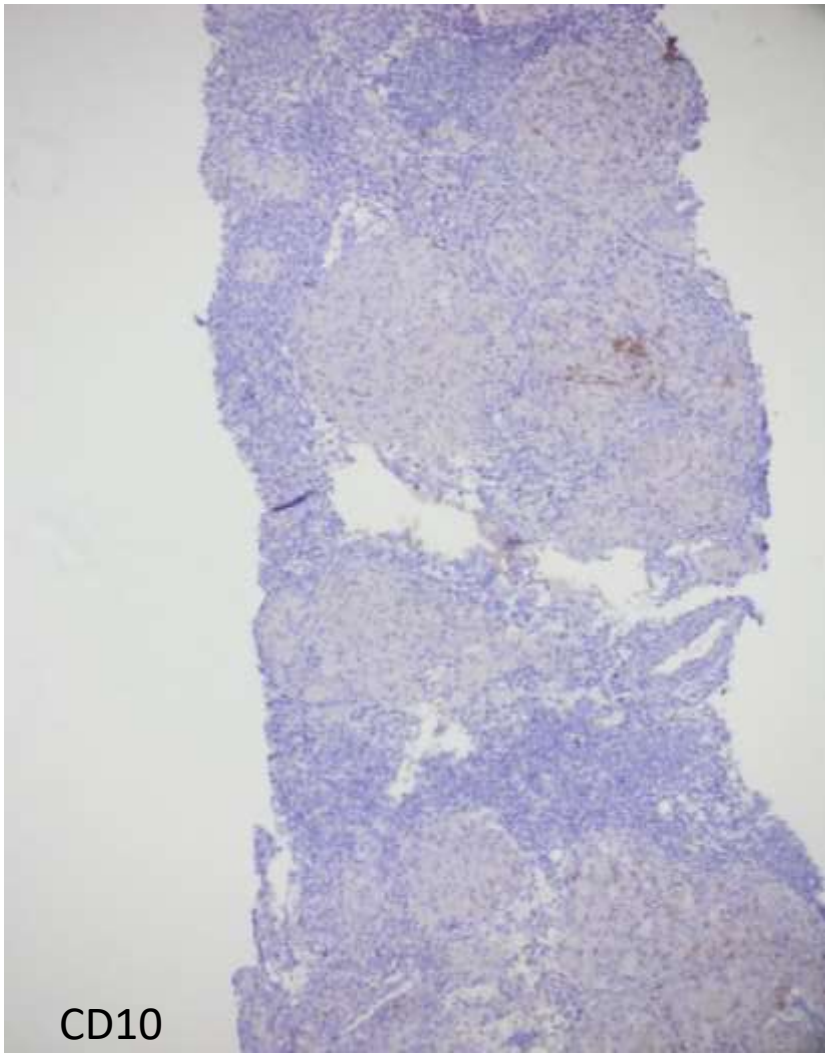
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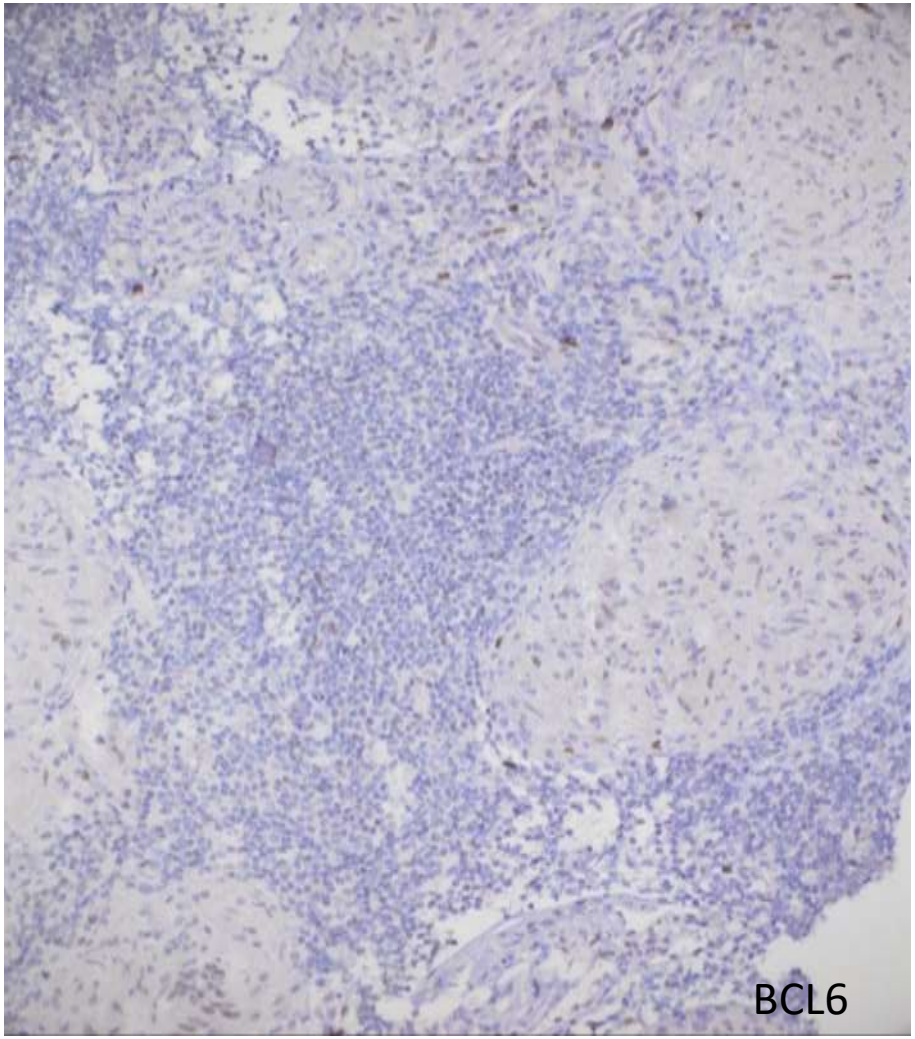
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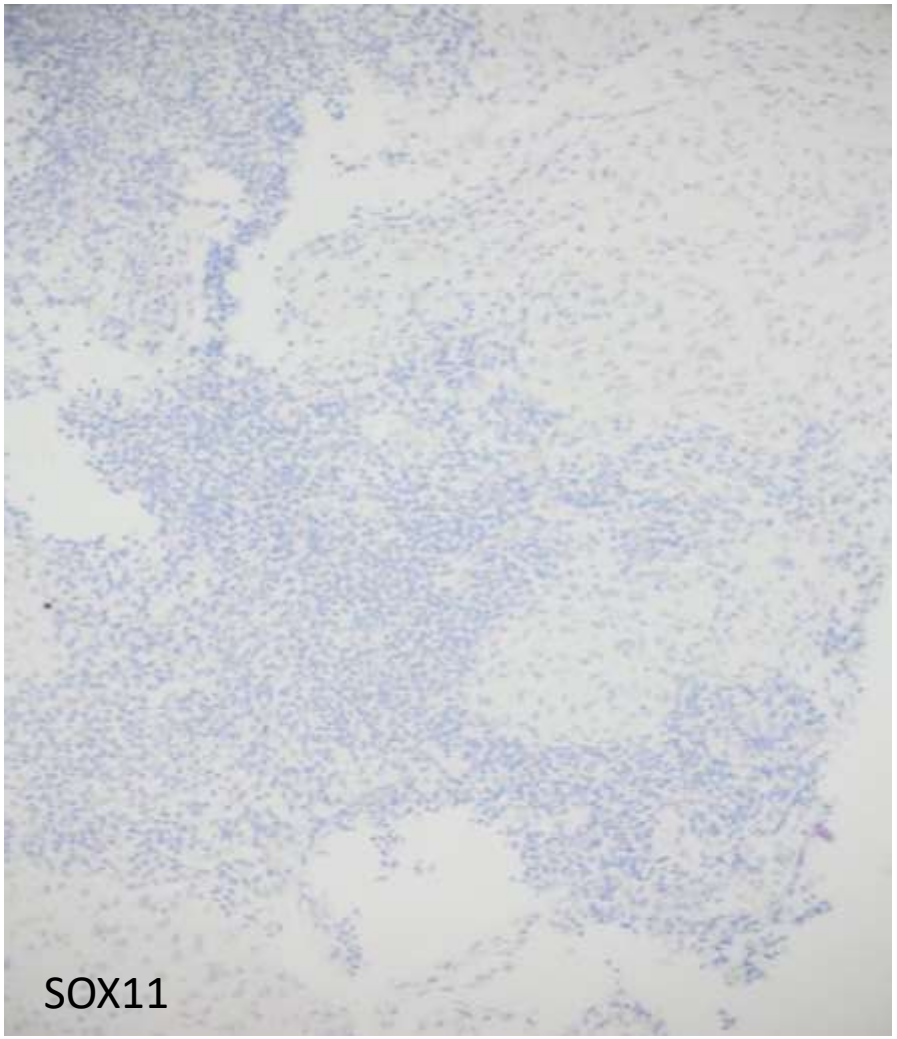
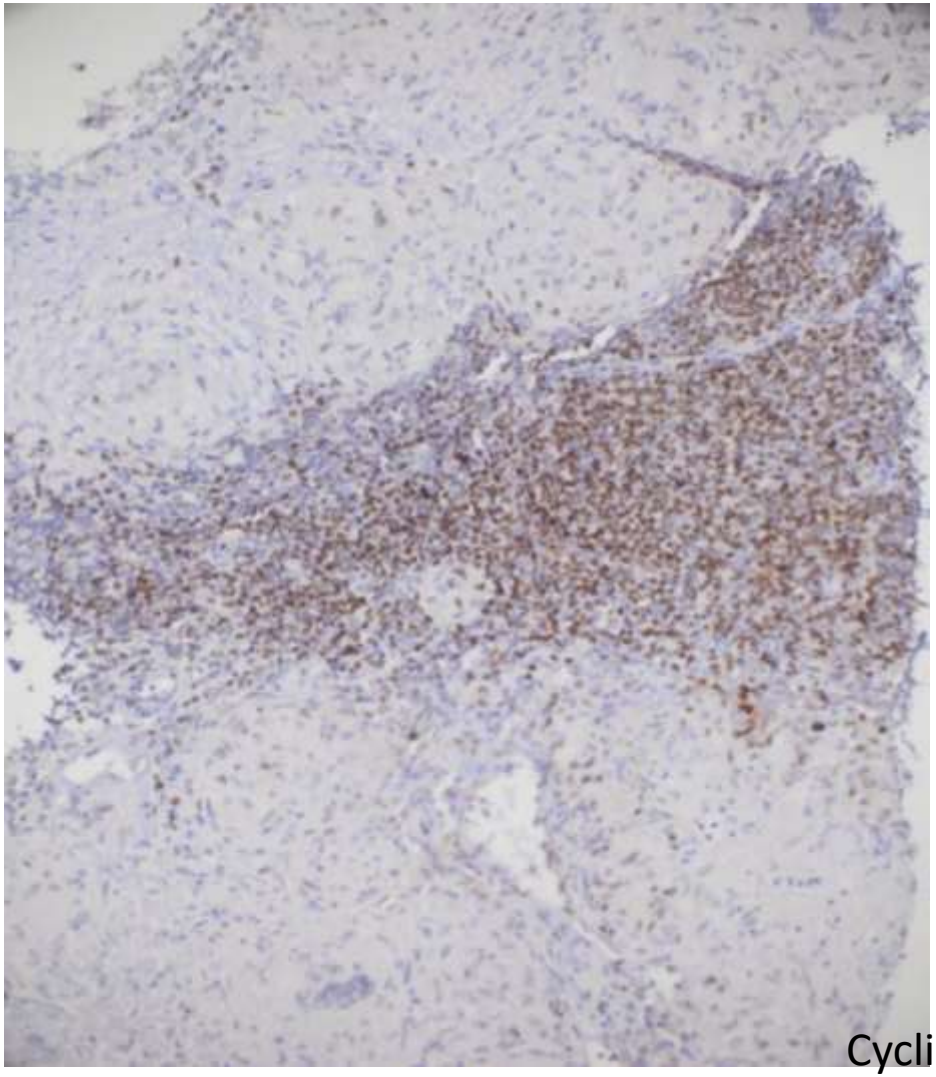
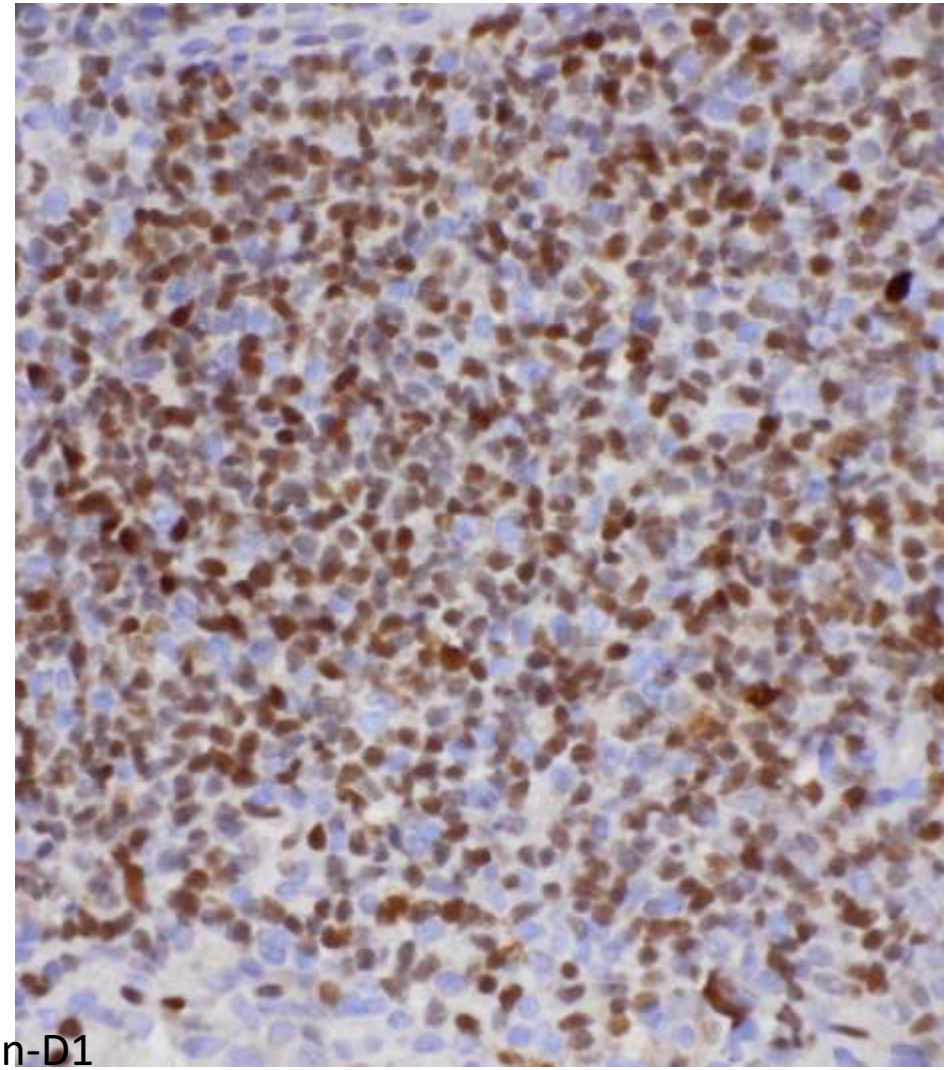

SOX11

Differential

- Small B-cell lymphoma, CD20+, CD10-/BCL6-, CD5-, SOX11-
- Flow cytometry studies show abnormal monoclonal lambda B-cell population, negative for CD10 and CD5.

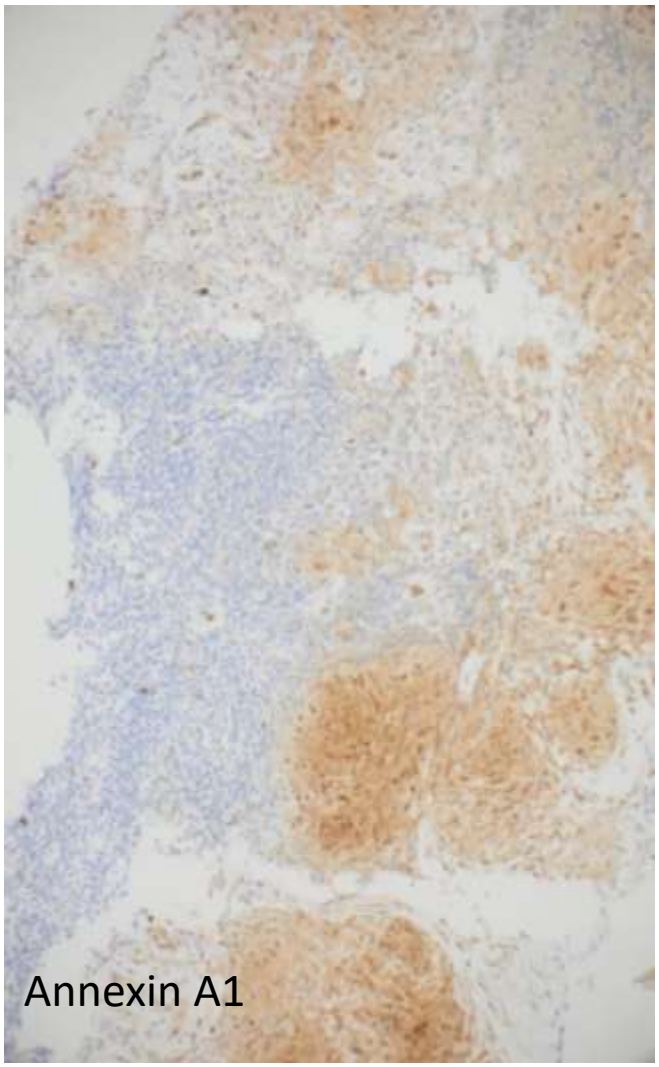


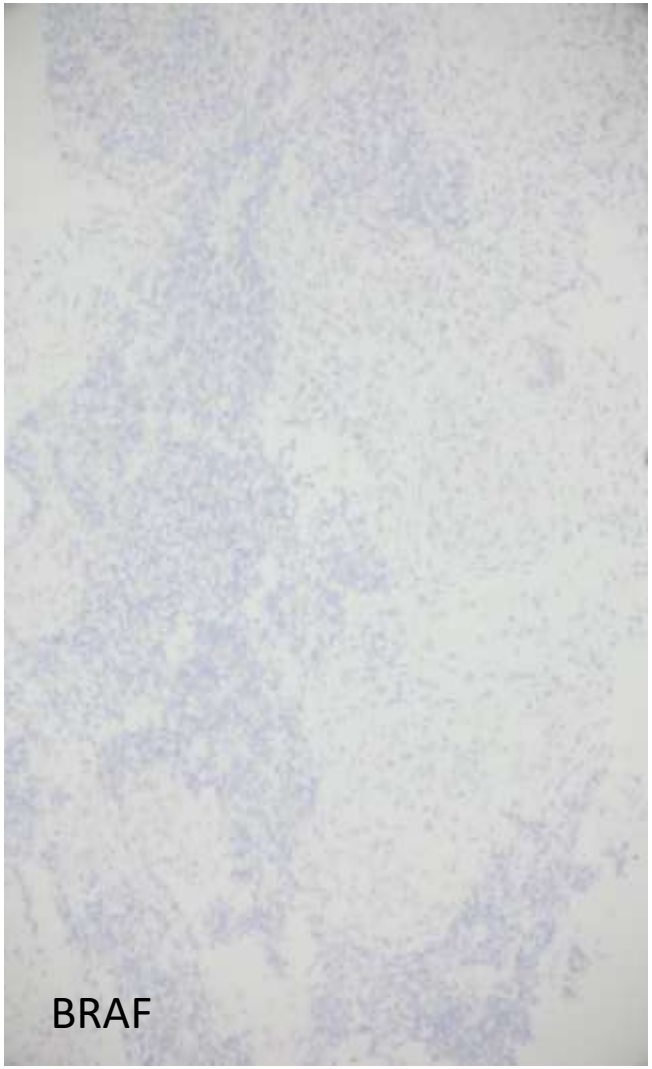


Cyclin-D1

Differential diagnosis of Cyclin $D1^{+}$/ $SOX11^{-}$ Lymphoma/Leukemia

- Subset of MCL (like nnMCL ASA leukemic variant)
- Hairy cell leukemia
- Plasma cell myeloma (25%, t(11;14) present)
- Chronic lymphocytic leukemia/ small lymphocytic leukemia (proliferation centers)


Annexin A1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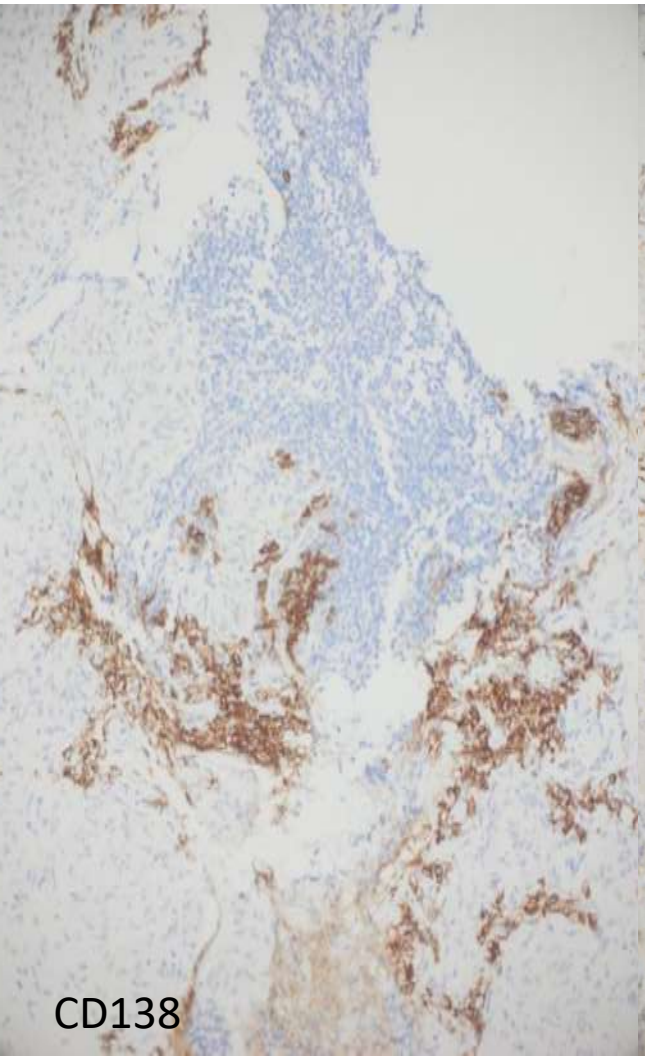
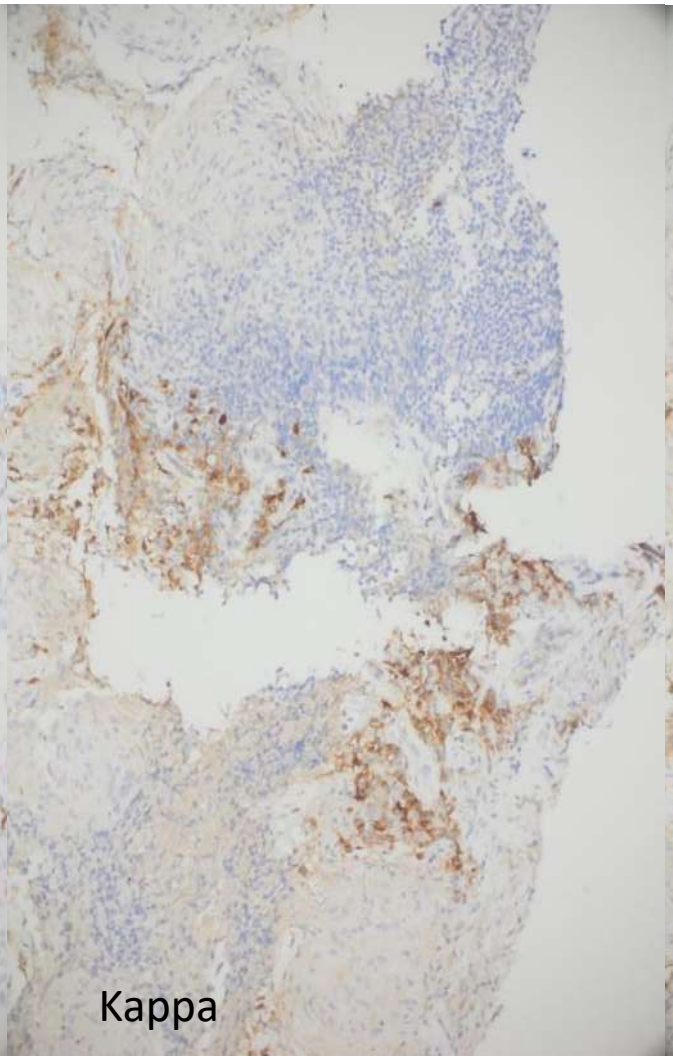
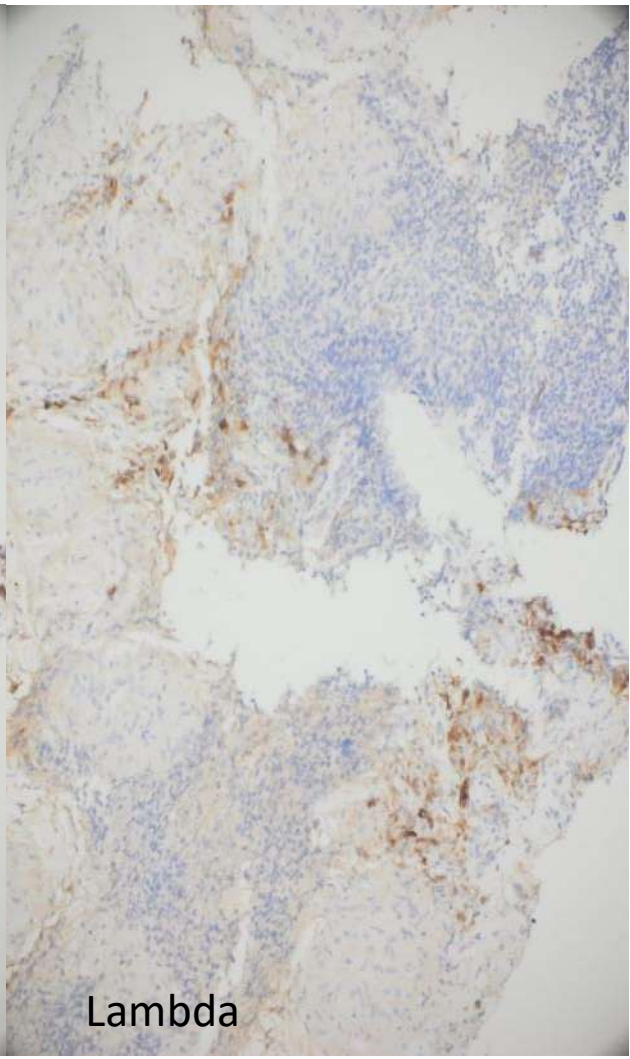
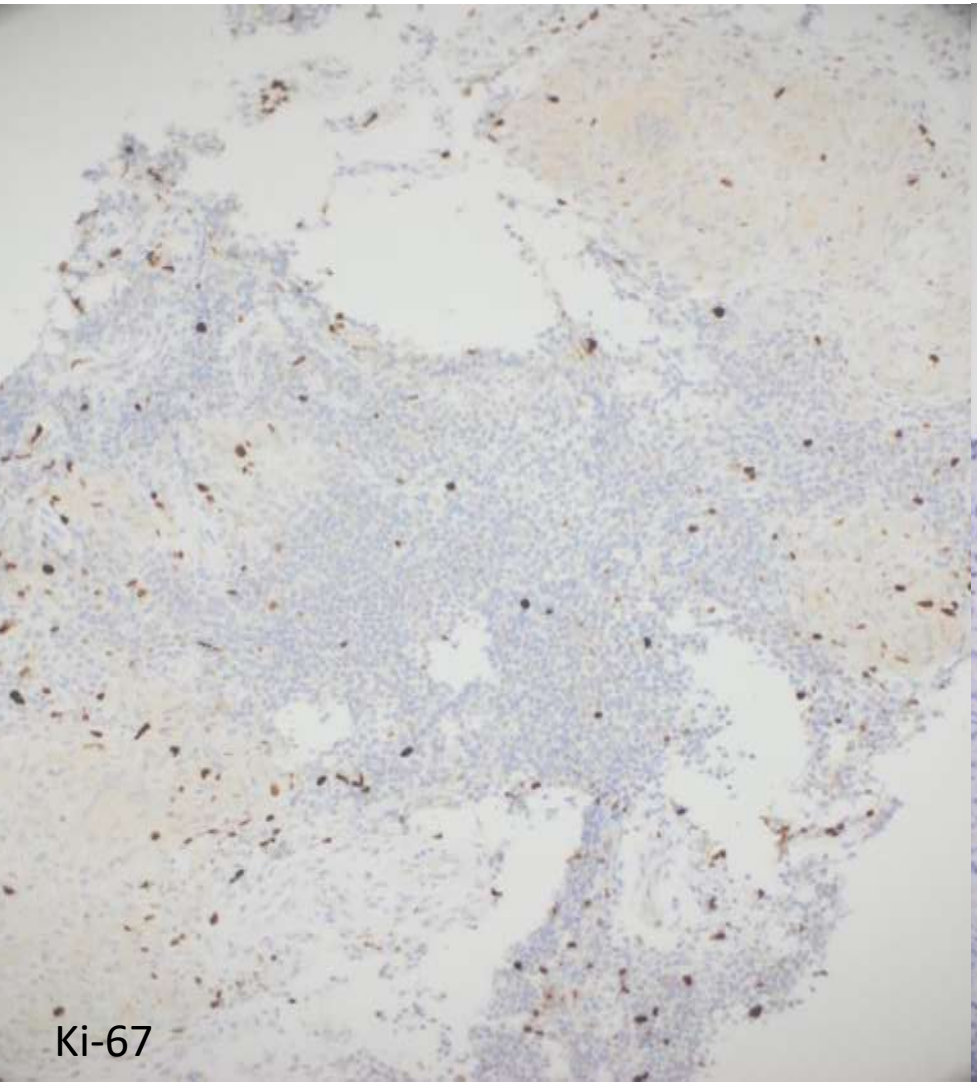
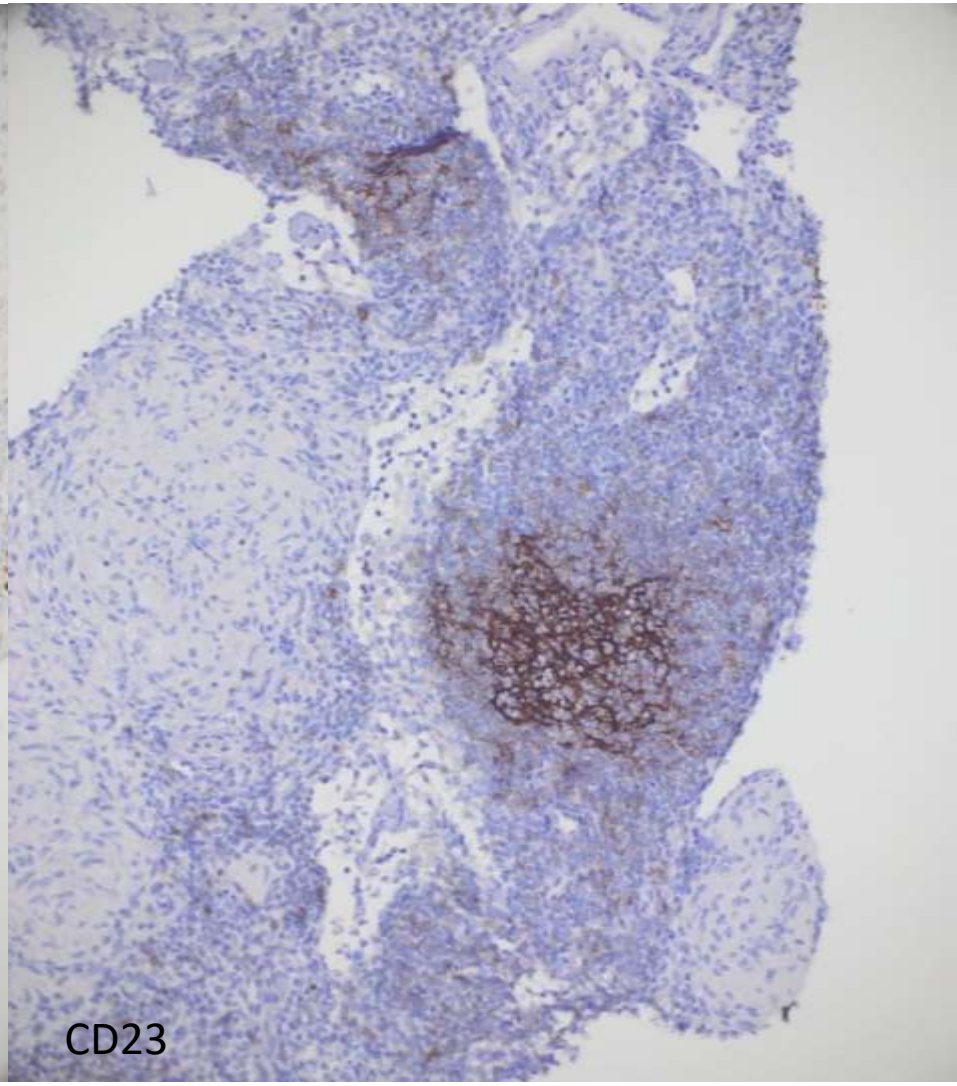

CD138


Kappa


Lambda


Ki-67


CD23

FISH studies

- CCND1/IGH gene fusion: Detected (64%)

FINAL DIAGNOSIS

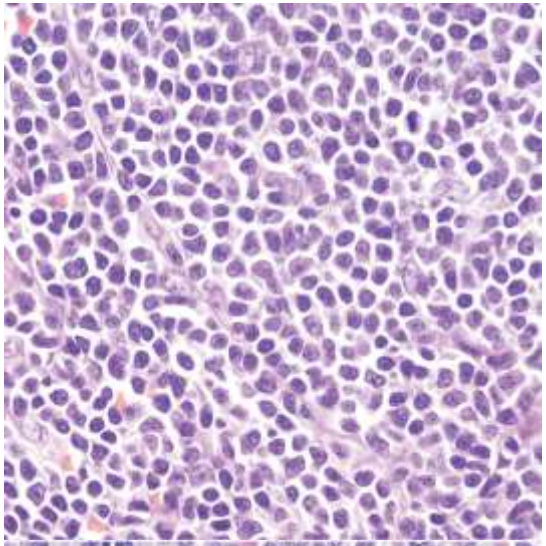
Left inguinal node, core biopsy:

- Mantle cell lymphoma.
- Extensive involvement by noncaseating granulomas.

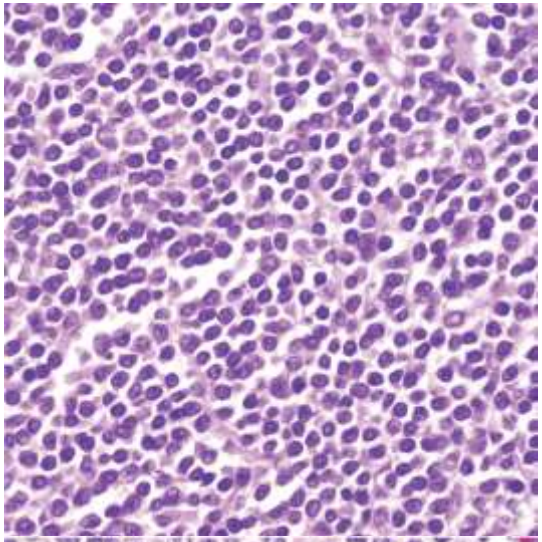
Mantle cell lymphoma (MCL)

- Comprises ~ 5 %of non-Hodgkin lymphomas
- Older men (median age 60, M:F >2:1)
- Can involve: LN, BM, PB (leukemic variant), spleen, gastrointestinal tract and other extra-nodal sites (CNS)
- Cytological variants: conventional, small cells, blastoid, and pleomorphic

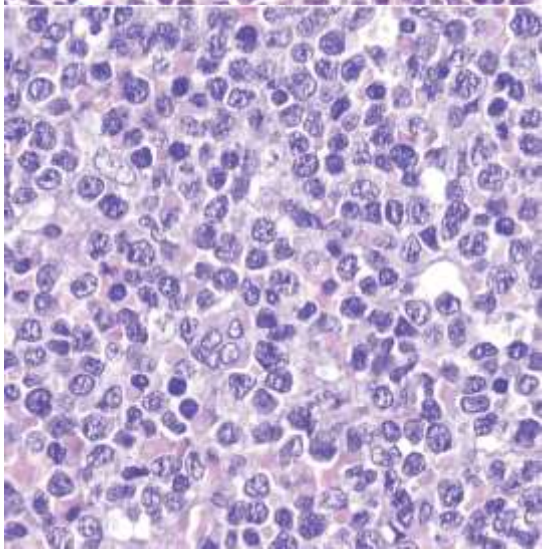
Conventional variant



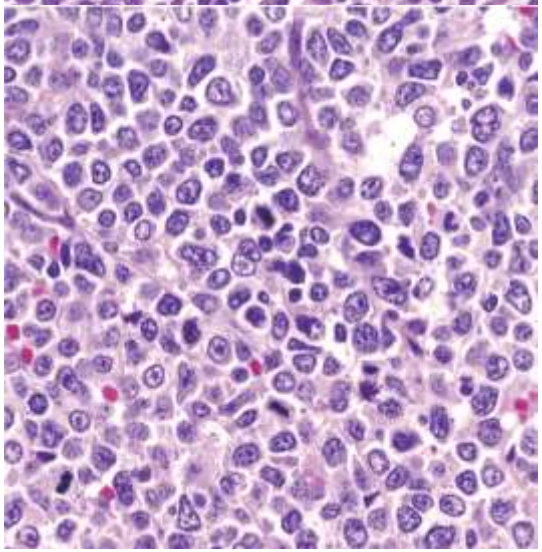
Small cell variant



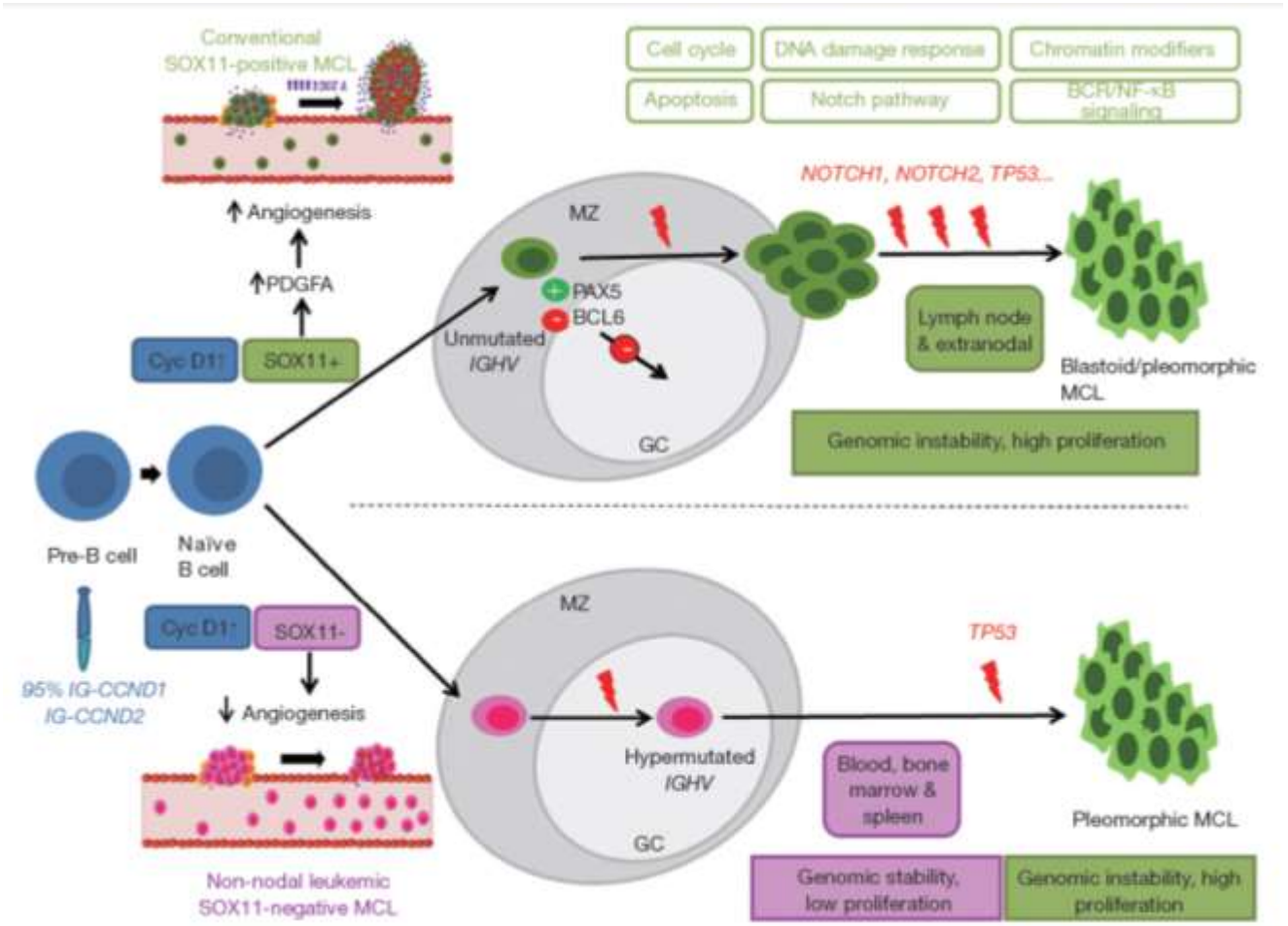
Blastoid variant



Pleomorphic variant



Both pathway resulted in more aggressive subtype when acquiring additional molecular alterations :
TP53, NOTCH1, NOTCH2



Veloza et al; Ann Lymphoma 2019;3:3

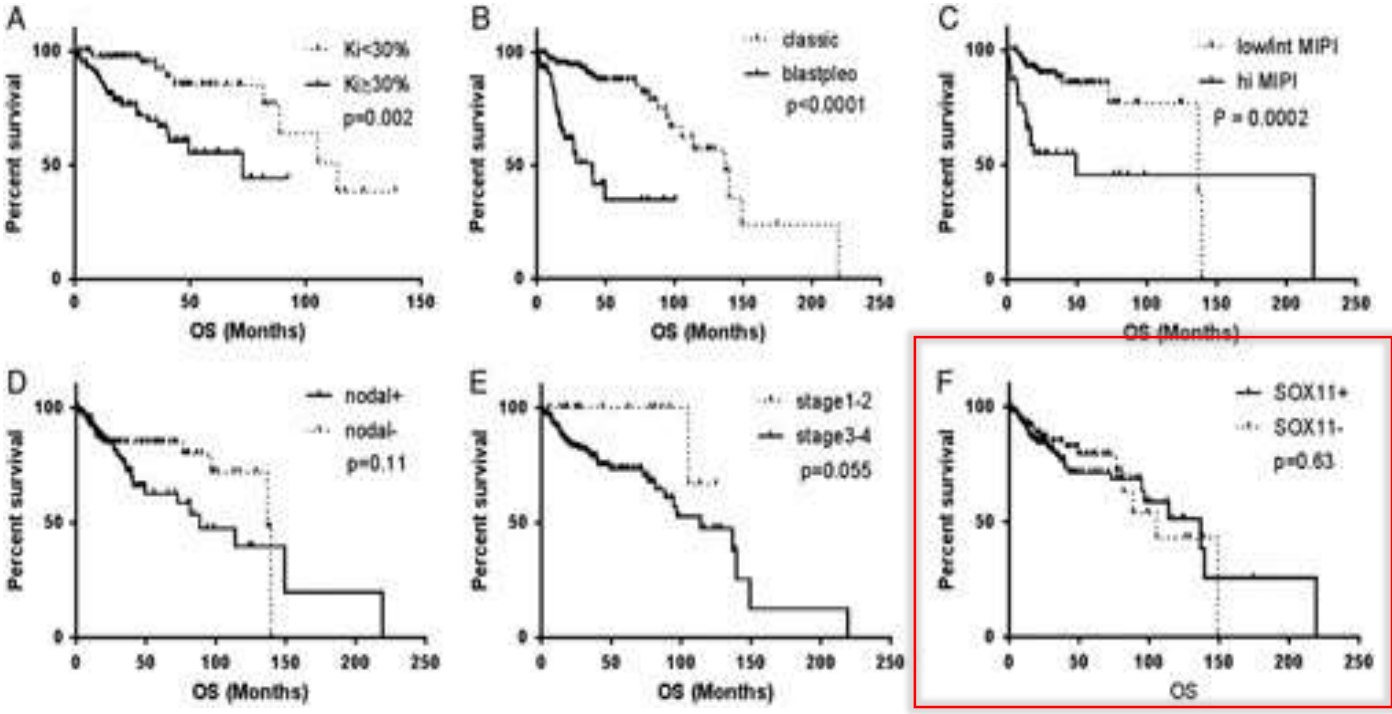
Going back to our case…..

- Cyclin $D1^{+}$/ $SOX11^{-}$
- Ki-67 <5%

- No leukemic presentation
- Generalized LAD
- Lytic bone lesions
- Additional genetic alterations?

Can SOX11 be used as independent prognostic indicator?

- Adverse outcome with:
  - Higher MCL International Prognostic Index (MIPI)
  - Higher Ki67
  - TP53
  - Blastoid/pleomorphic morphology
  - Nodal involvement
  - III/IV stage
  - SOX11 expression???



Jie et al. The American Journal of Surgical Pathology43(5):710-716, May 2019

Sarcoidosis

- Incidence and prevalence:
  - African American (AA)>White>Hispanic>Asian; F>M
- Genetic predisposition and environmental insult
- Lung skin, liver, extra-thoracic LN, bone marrow, eye …..)
- Aggressive clinical course in F and AA; extra-pulmonary disease in AA.
- Higher mortality: younger age, AA F

Hena KM, Front. Immunol, 2020

Take home massage

- MCL are heterogonous group with a spectrum of behavior from indolent to more aggressive
- Cyclin $D1^{+}$/ $SOX11^{-}$ are mostly nnMCL/Leukemic MCL with indolent behavior and mutated IGHV
- Cyclin $D1^{+}$/ $SOX11^{-}$ MCL with nodal (non-leukemic) can be seen (like our case):
  - Aggressive behavior after acquiring additional genetic alteration?
- SOX11 is not a prognostic indicator

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- Miao, Yuan; Lin, Pei; Saksena, Annapurna; Xu, Jie; Wang, Michael; Romaguera, Jorge; Yin, C. Cameron; Medeiros, L. Jeffrey; Li, Shaoying. *CD5-negative Mantle Cell Lymphoma- Clinicopathologic Correlations and Outcome in 58 Patients*. The American Journal of Surgical Pathology: August 2019 - Volume 43 - Issue 8 - p 1052-1060
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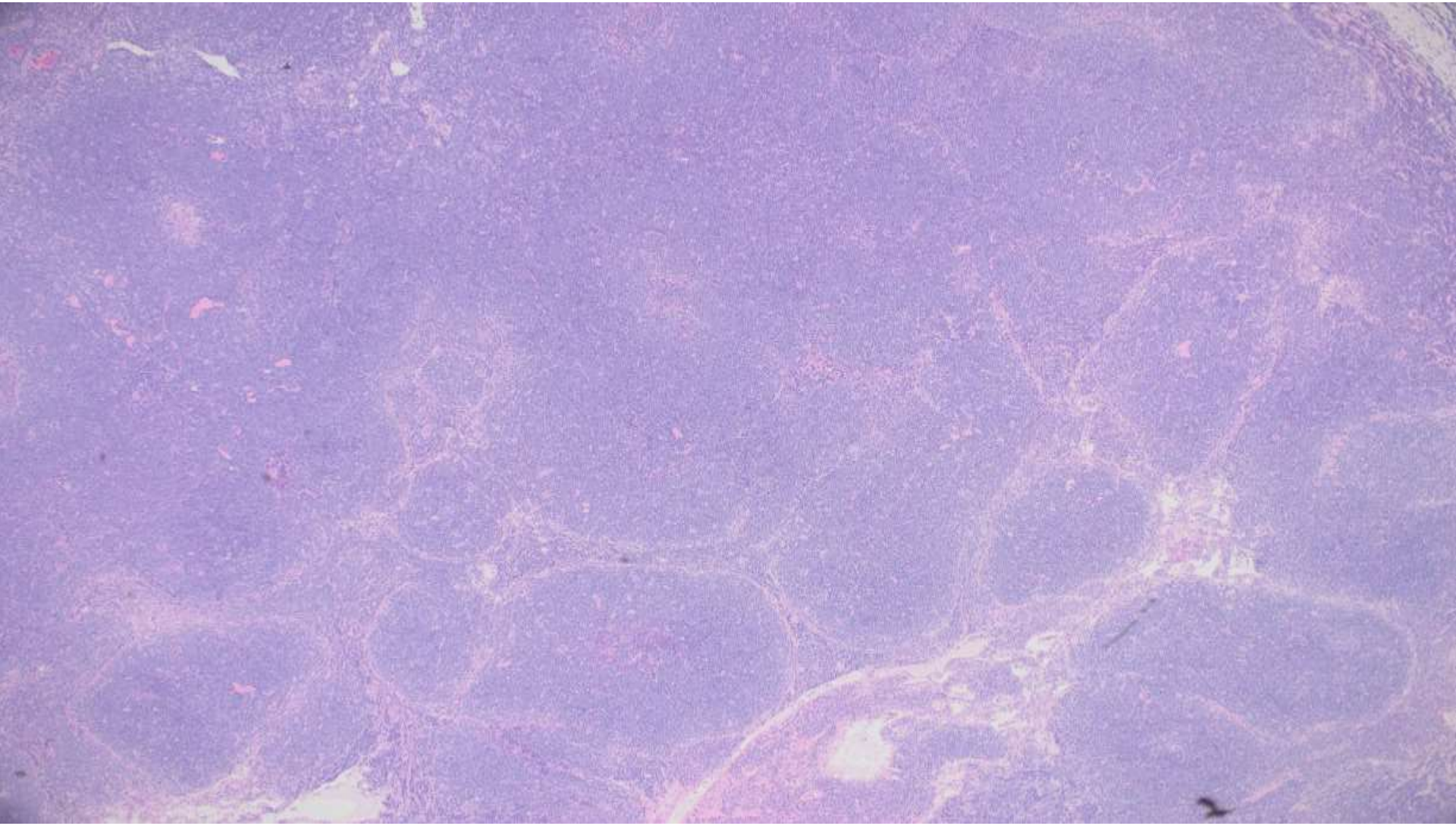
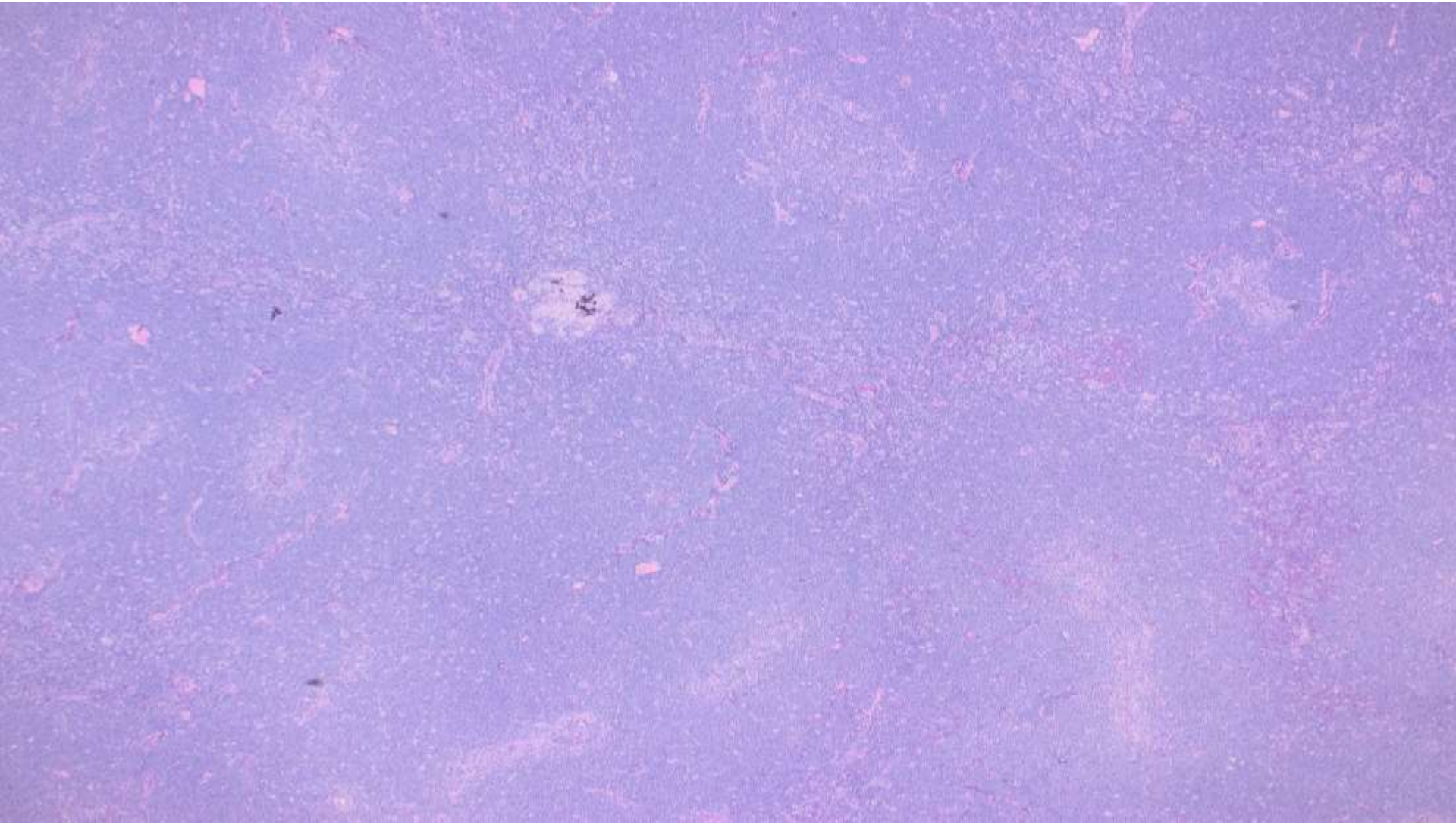
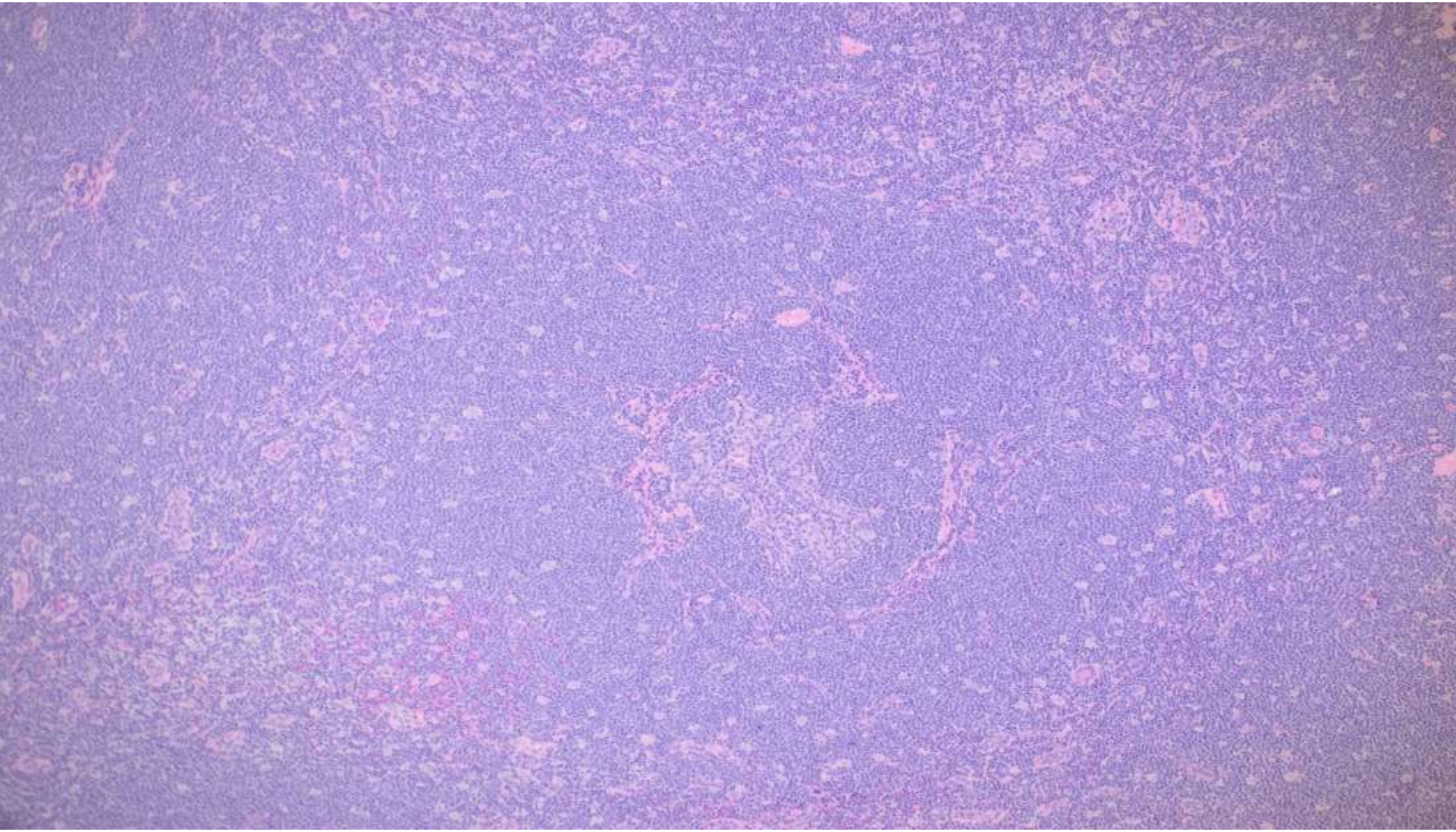
21-0604

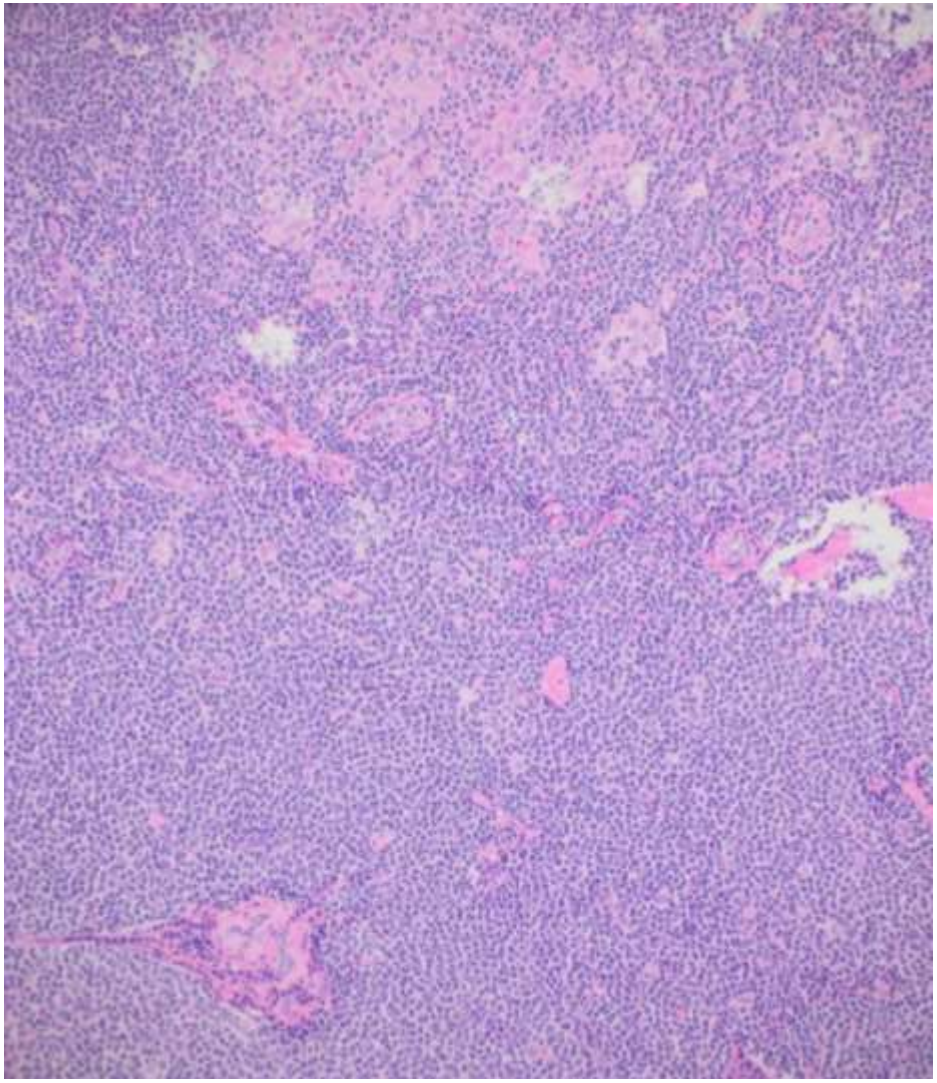
Natalya Hakim/Linlin Wang; UCSF

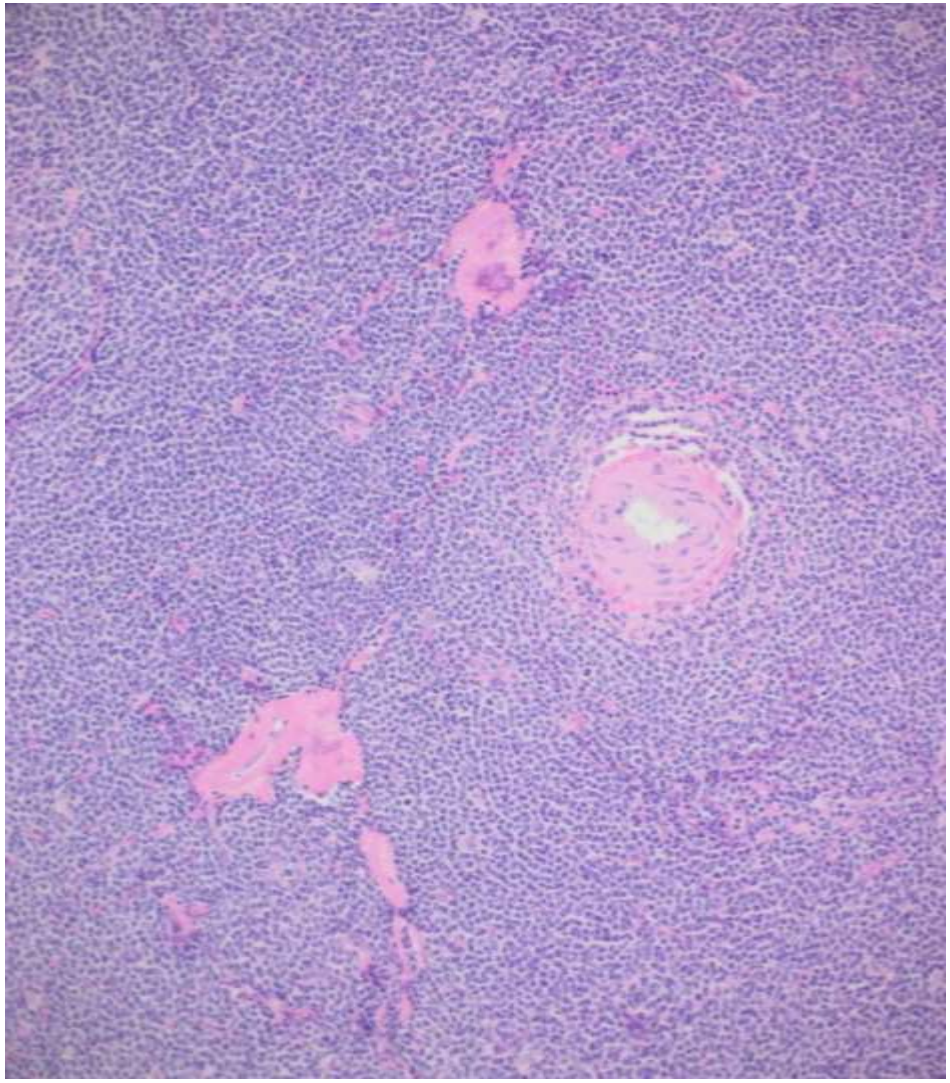
75-year-old F presented with progressive fatigue, weight loss and difficulty walking. Further physical exam and imaging studies showed extensive generalized lymphadenopathy and massive splenomegaly. Inguinal lymph node submitted.

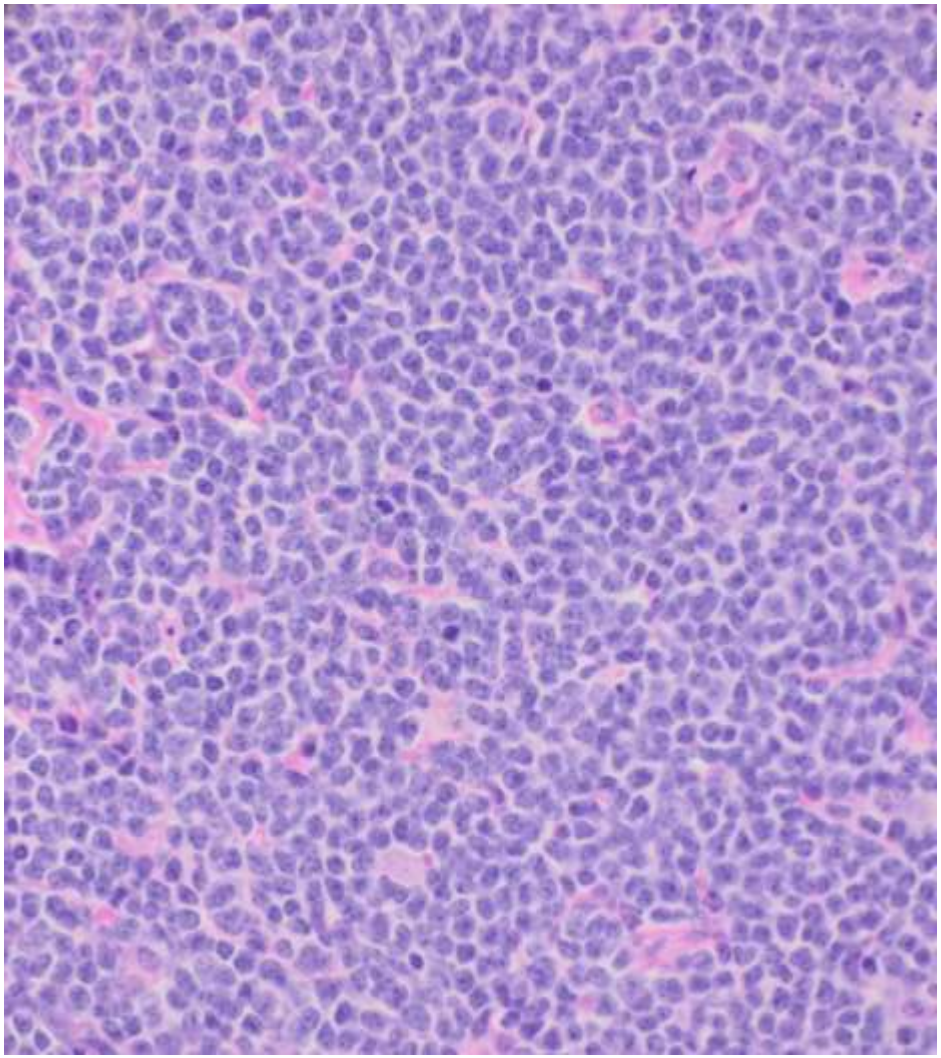
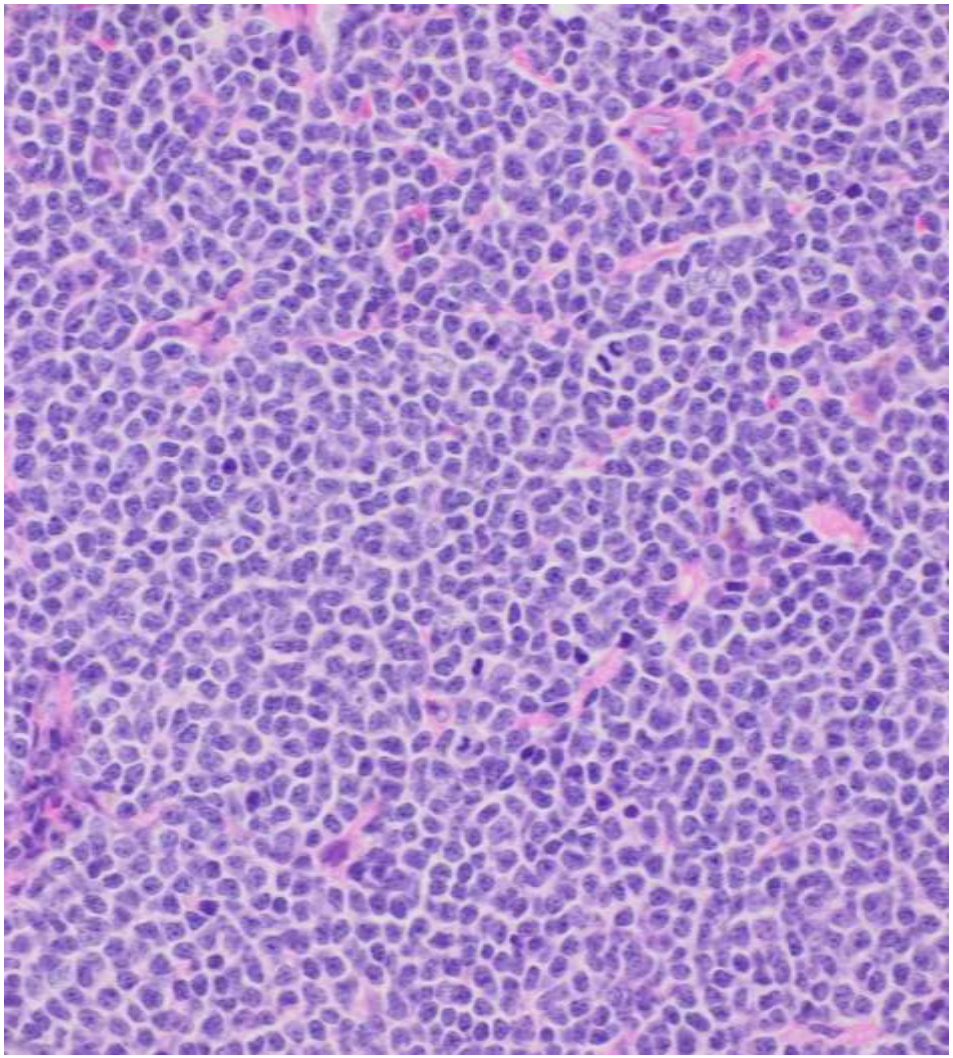


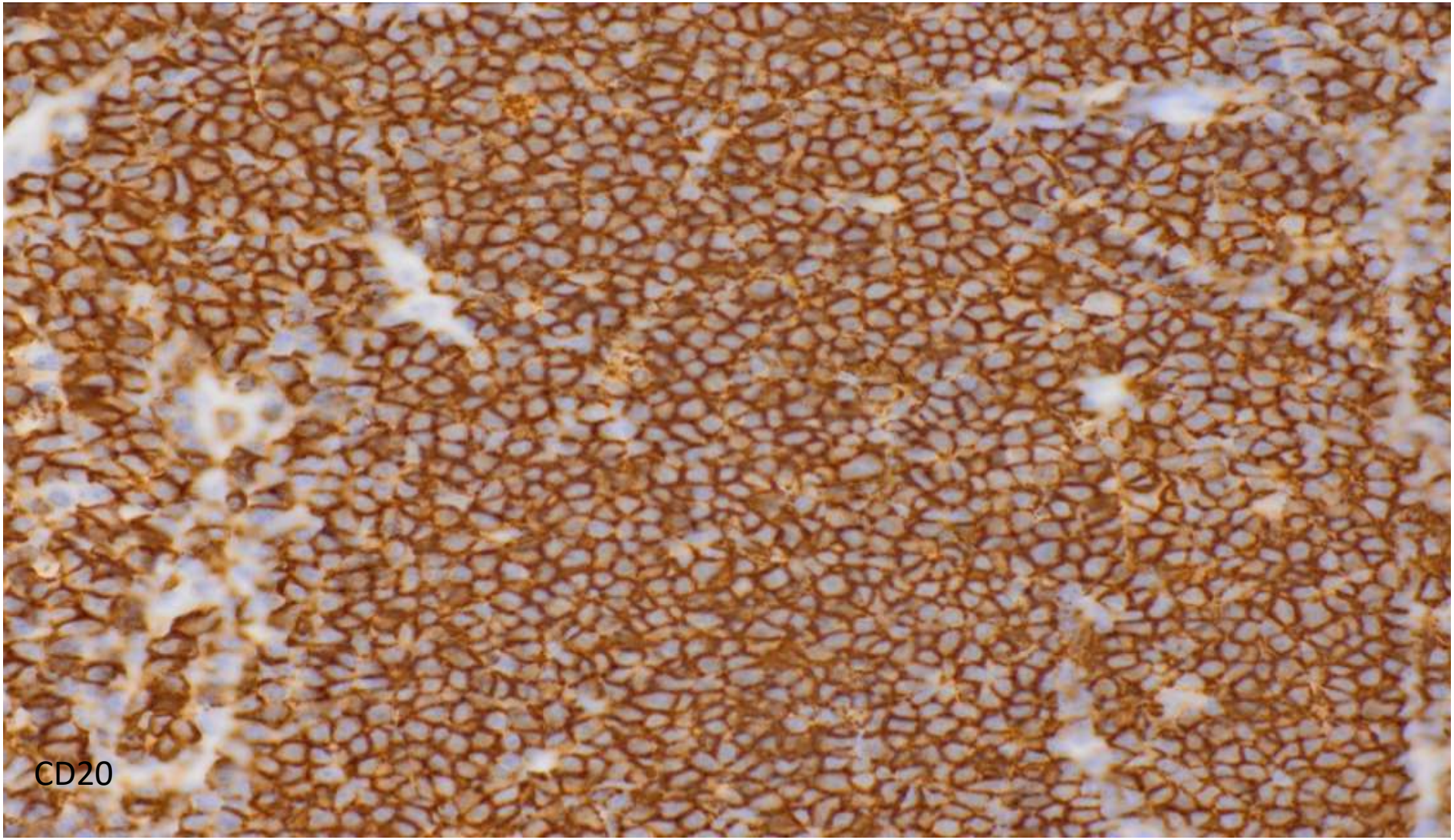


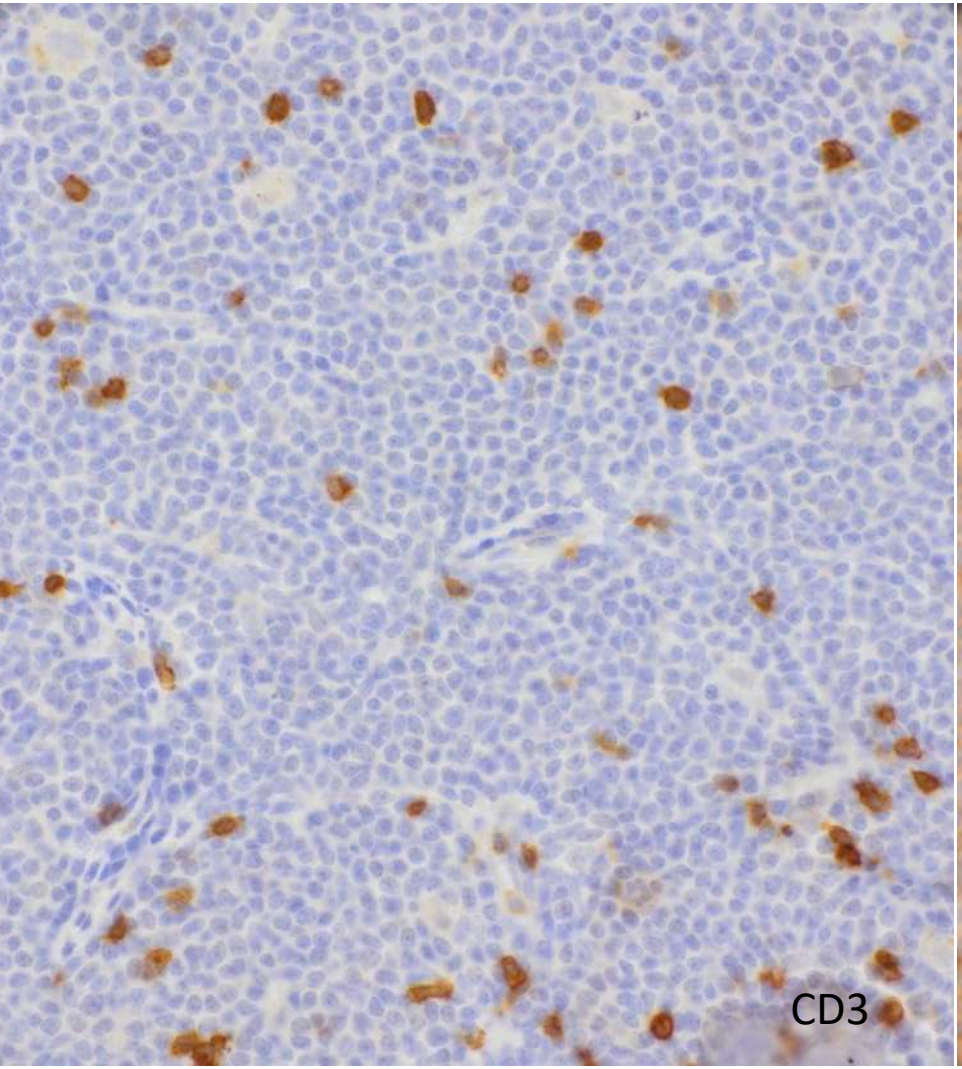


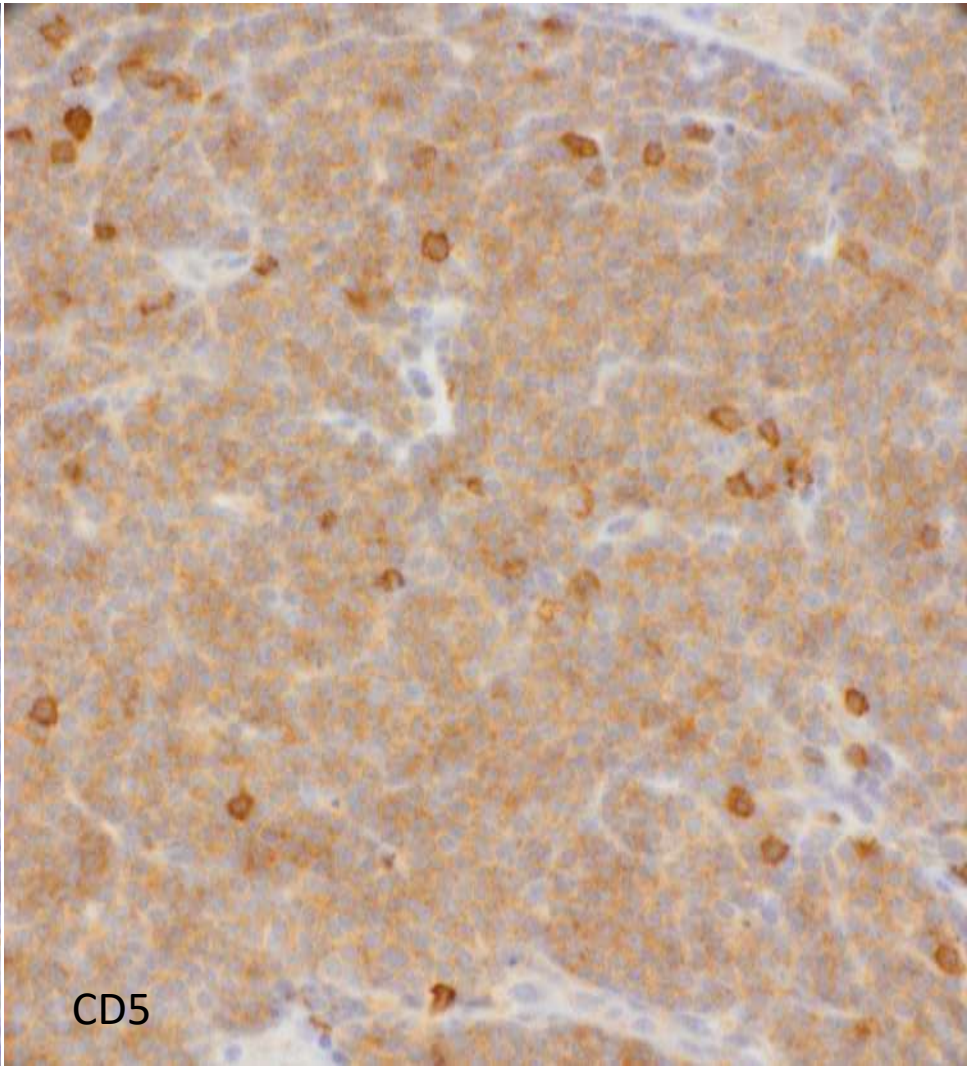


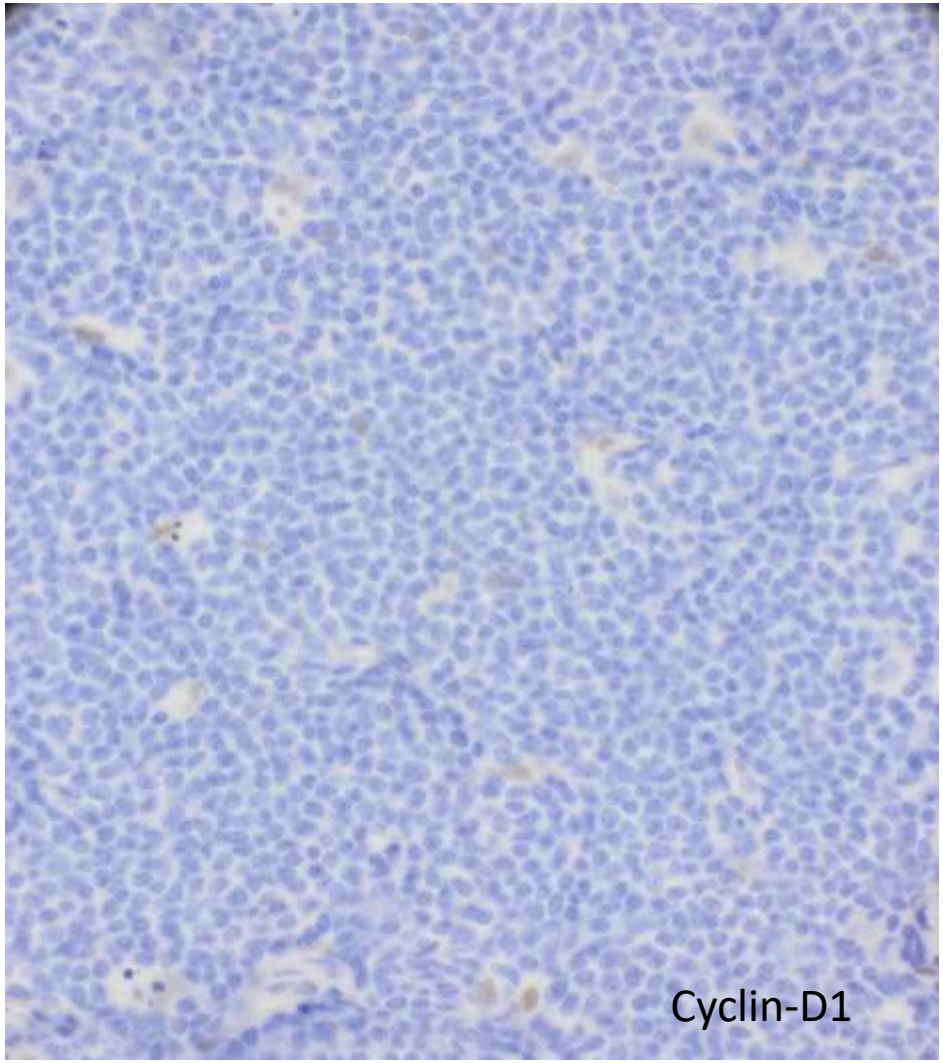


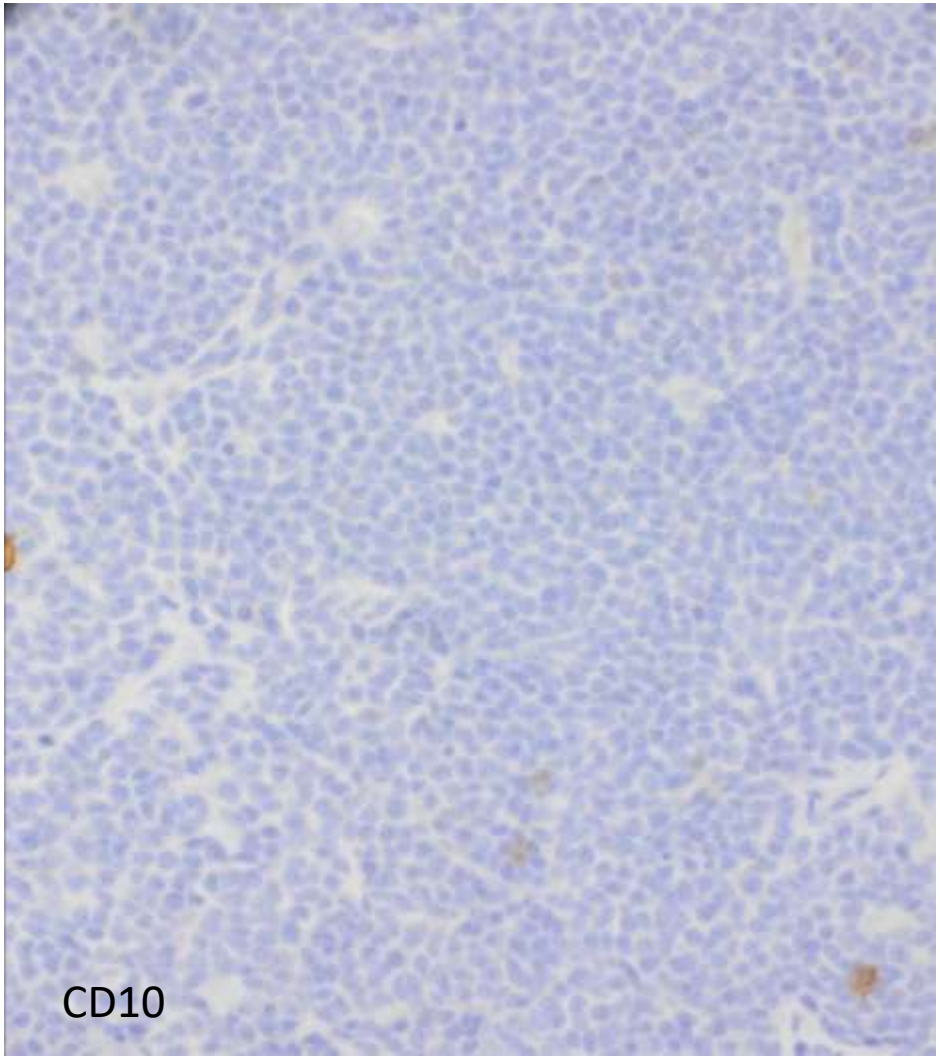



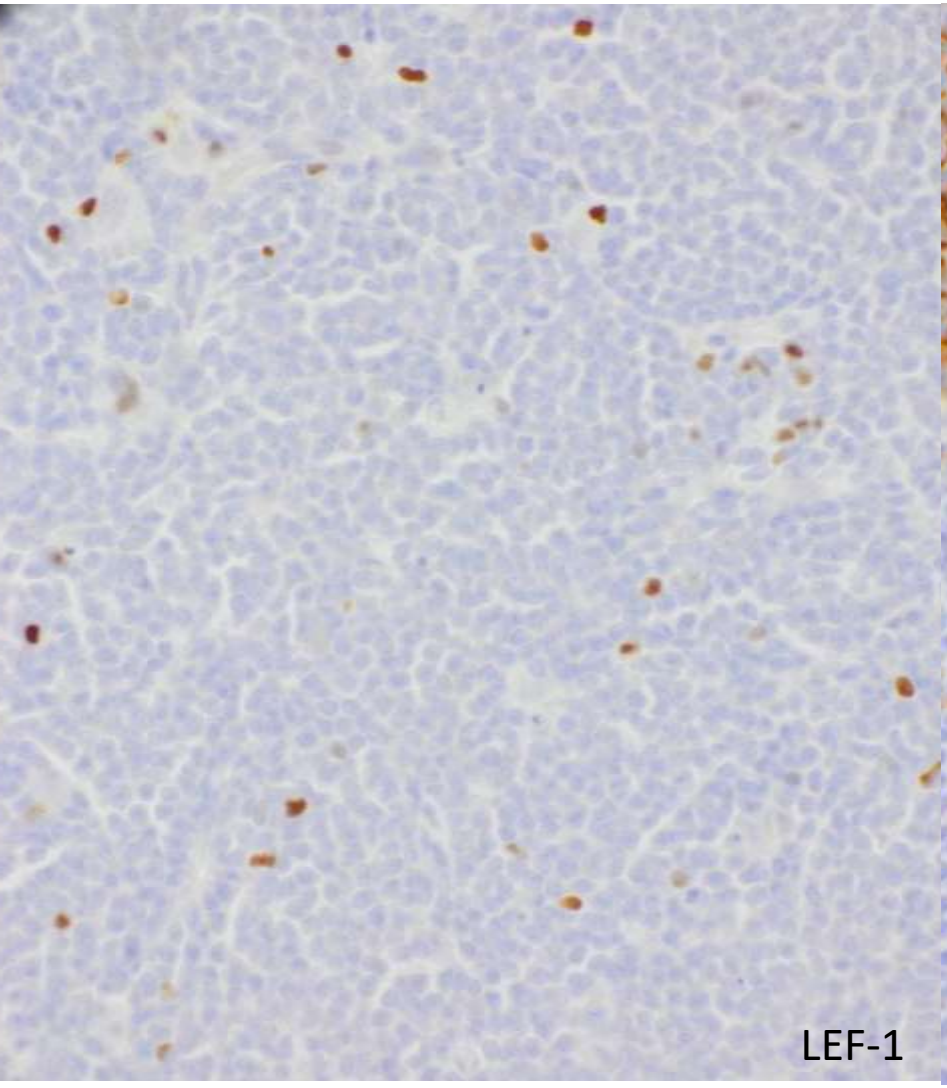

CD20

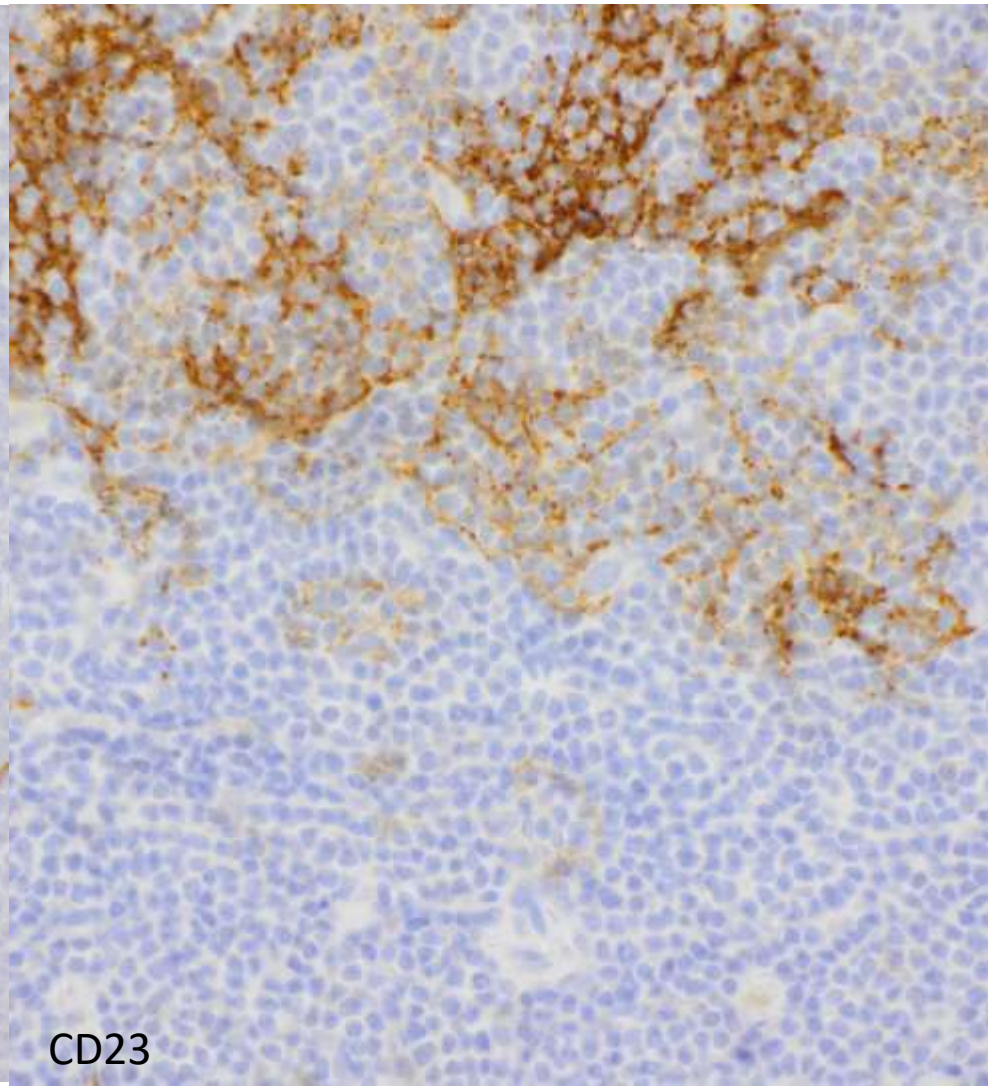

CD3


CD5


Cyclin-D1


CD10


LEF-1


CD23

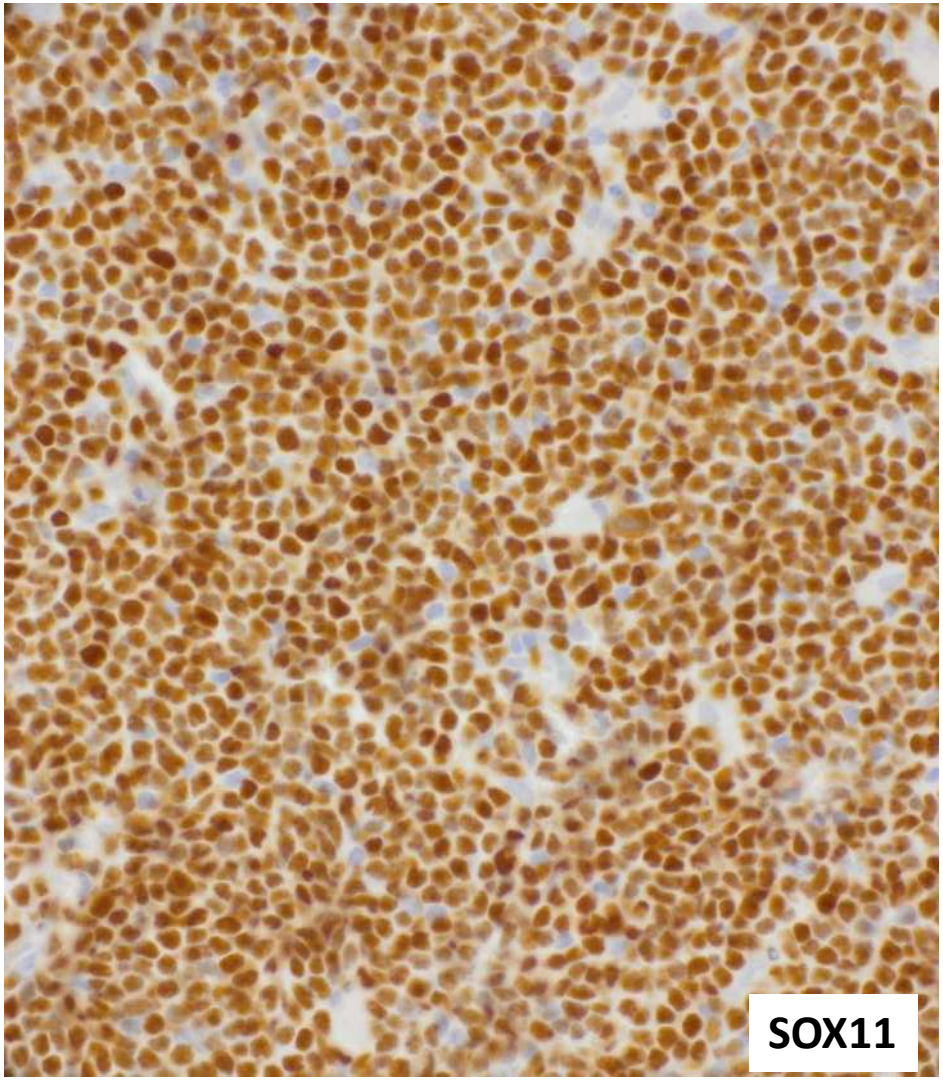
Flow cytometry

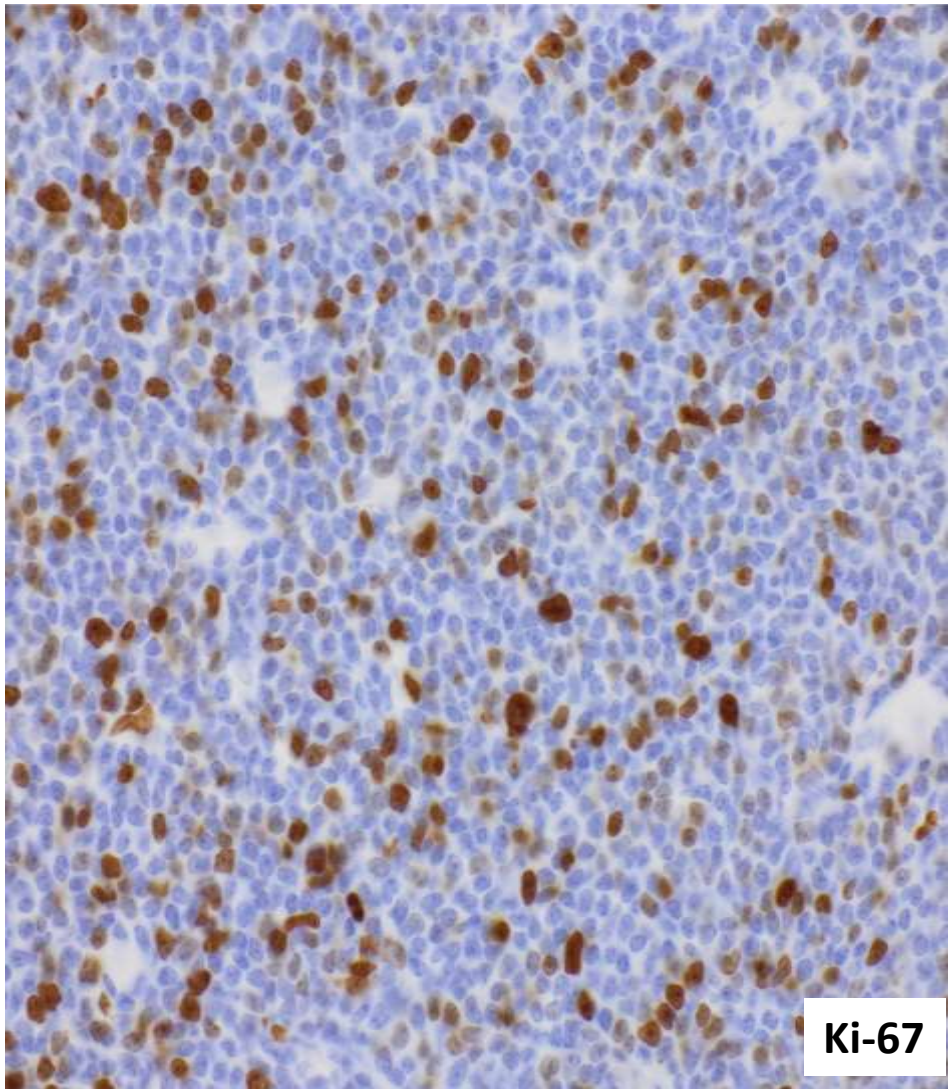
CD5-positive B-cell lymphoproliferative disorder.

Comment: The analysis identifies predominant population of abnormal, monotypic B cells that are small by forward scatter. They express low intensity CD5, CD19, CD20, minimal CD23, CD38, CD43, HLA-DR, FMC 7, lambda light chain restricted, and are negative with CD10.

Differential diagnosis

- Mantle cell lymphoma
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Follicular lymphoma (CD10 negative)


SOX11


Ki-67

Cytogenetics and Molecular studies

- Abnormal female karyotype: 46XX,t(2;11)(q33;q13)[2]/47,s1,+18[4]/46,XX[14]

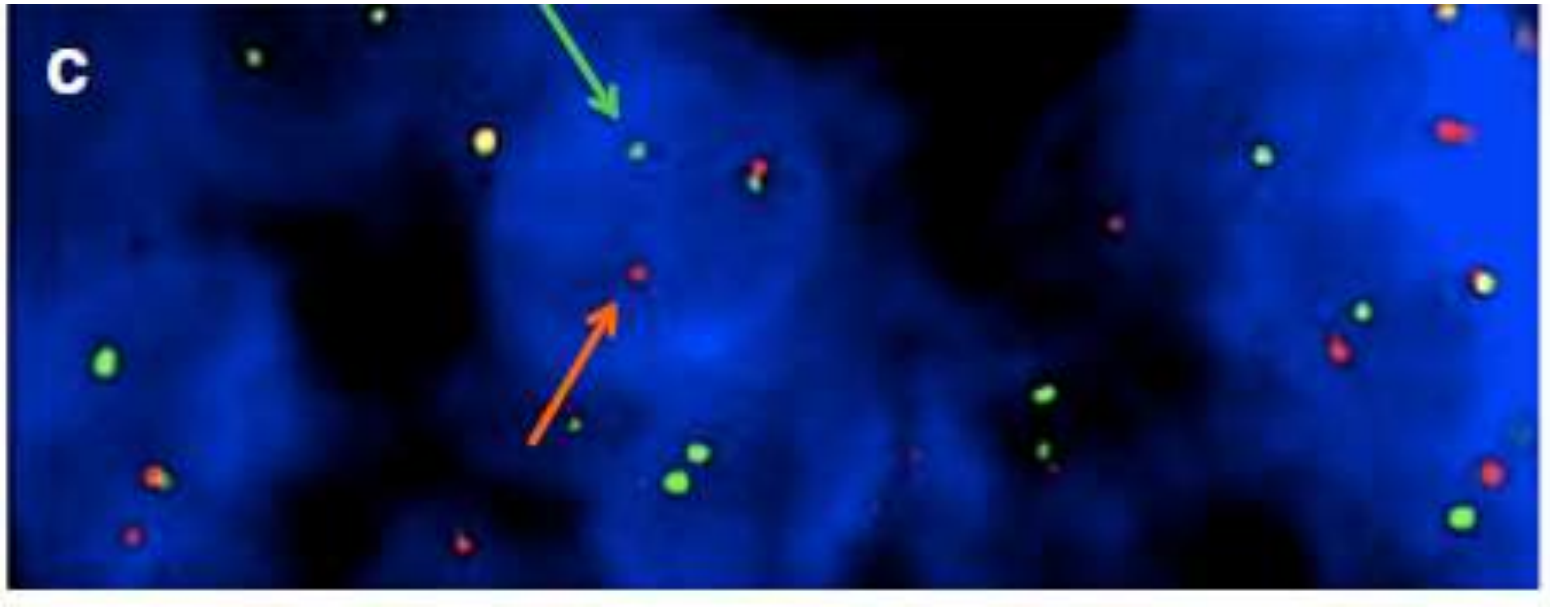
- CLL FISH panel: **Negative for CCND1/IGH translocation**. However, an extra copy of IGH was observed in 67.5% of nuclei indicating the presence of chromosome 14 abnormality (trisomy 14 or **translocation involving IGH and a gene other than CCND1**).

Final diagnosis

Lymph node, right inguinal, excisional biopsy:

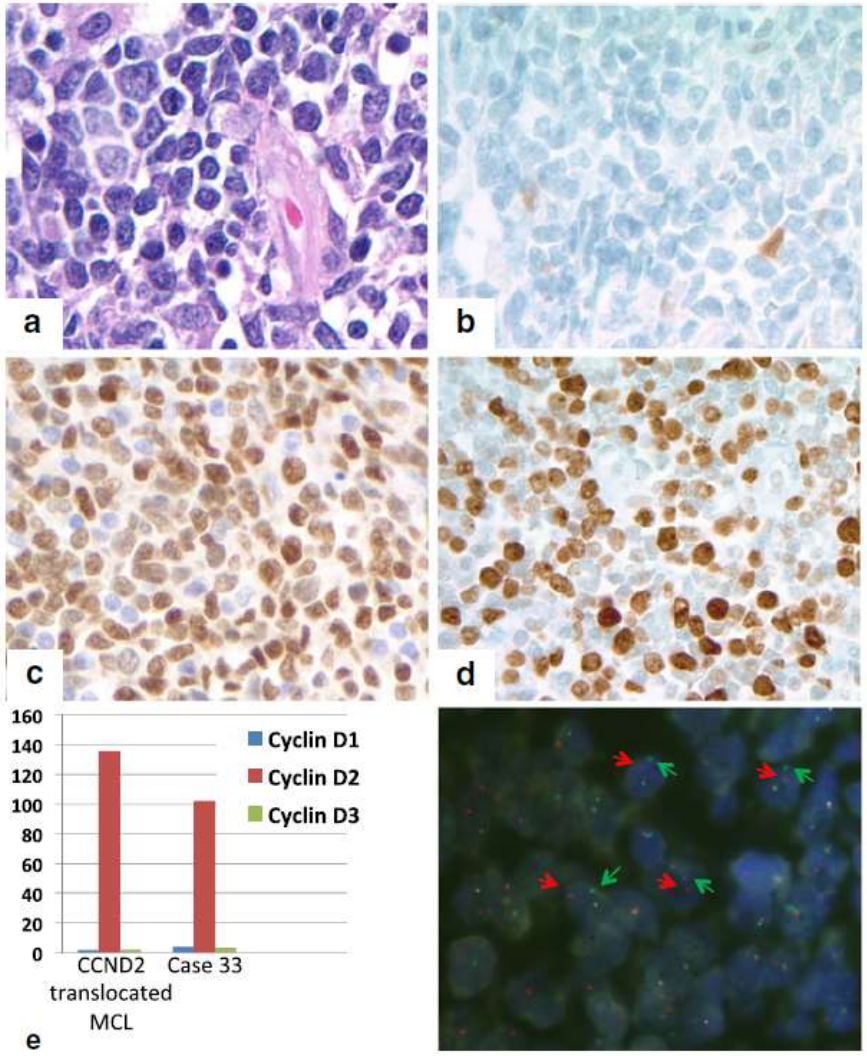
- Mantle cell lymphoma, CCND1/IGH translocation negative.

t(11;14) leading to cyclin D1 overexpression is the characteristic genetic alteration.



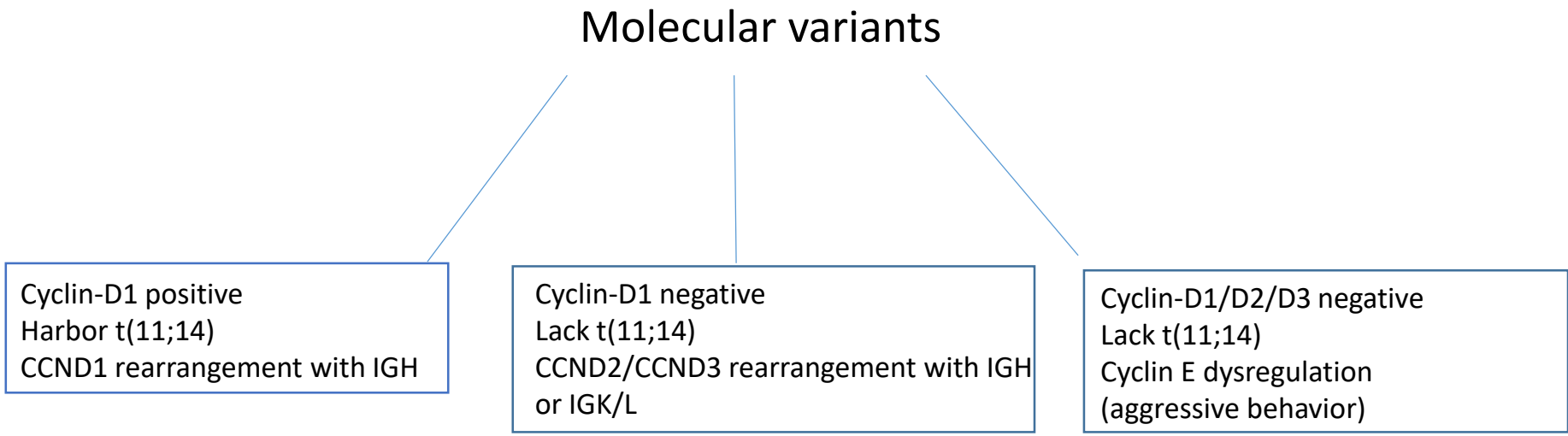
CCND1 FISH break-apart probes

Sander et al. Virchows Arch (2016) 468:245–257



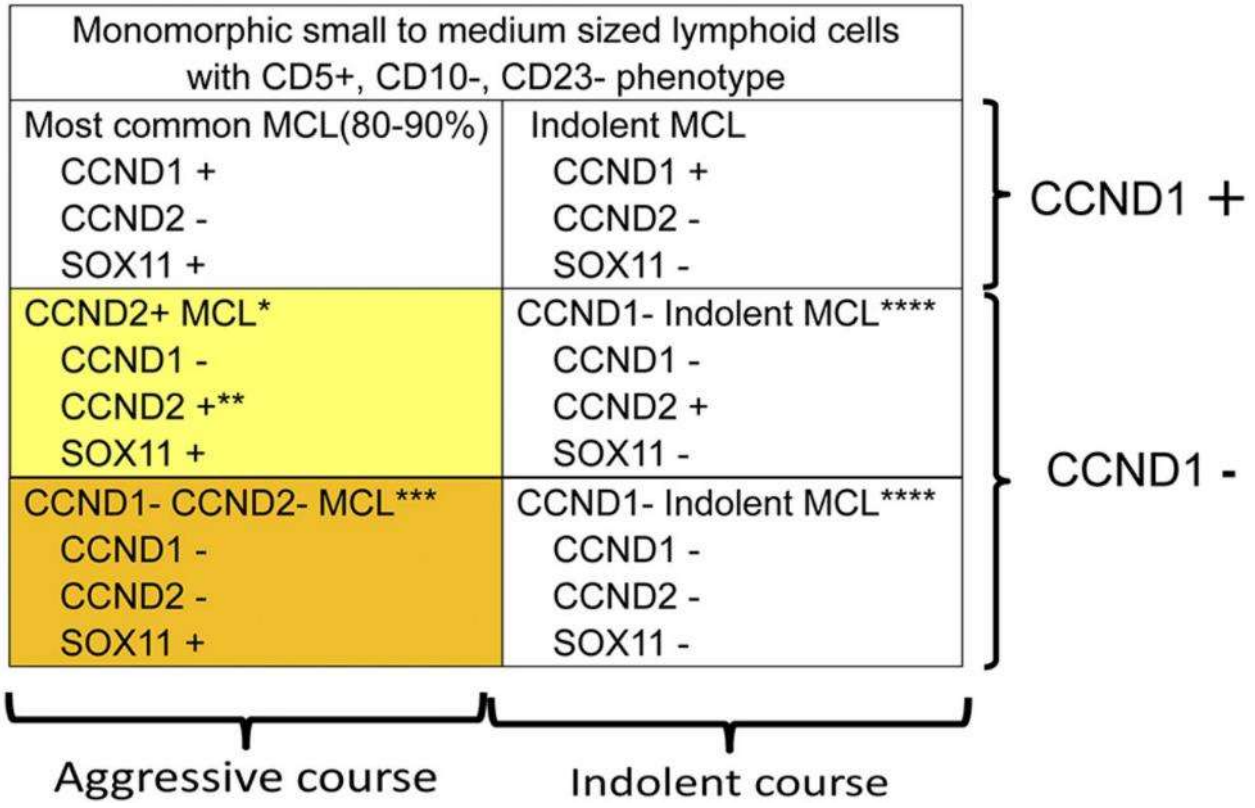
Sander et al. Virchows Arch (2016) 468:245–257

Genetic landscape



- 56 cyclin D1 neg MCL cases
- Inclusion criteria: morphology and phenotype consistent with MCL (CD5+ and CD23-), absence of cyclin D1 expression and t(11;14)(q13;q32), and SOX11 expression.
- Methods: FISH, NGS, and Gene-expression and copy-number analyses

MART´IN-GARCIA et al; Blood, 28 February 2019 | Vol 133, Number 9



Masao Seto, Cyclin D1-negative mantle cell lymphoma, Blood, 2013

How to diagnose?

- Morphology, morphology, morphology!!!!!
- SOX11 very useful marker to identify cyclin D1-negative MCL
- IHC for cyclin D2 and cyclin D3 not helpful (not specific and can be expressed in other lymphomas)
- Detection of CCND2/D3 by break apart FISH
- Quantitative analysis of CCND2 mRNA level is also reliable

Take home message

- Mantle cell lymphoma is a heterogeneous disease morphologically and genetically.
- CCND2, CCND3, CCNE1, CCNE2 are alternative alterations to CCND1 in MCL pathogenesis.
- Cyclin $D1^-$ and Cyclin $D1^+$ MCL share a common expression and genomic profile as well as clinical outcome.
- SOX11 is very reliable marker in cases of suspected cyclin D1-negative MCL.

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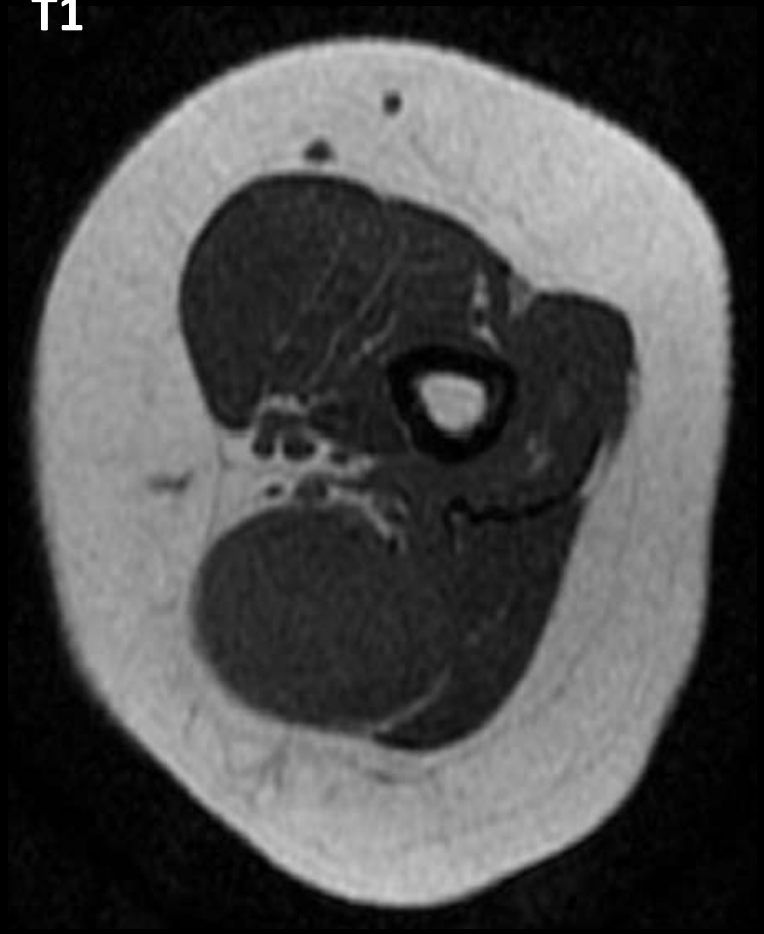
21-0605

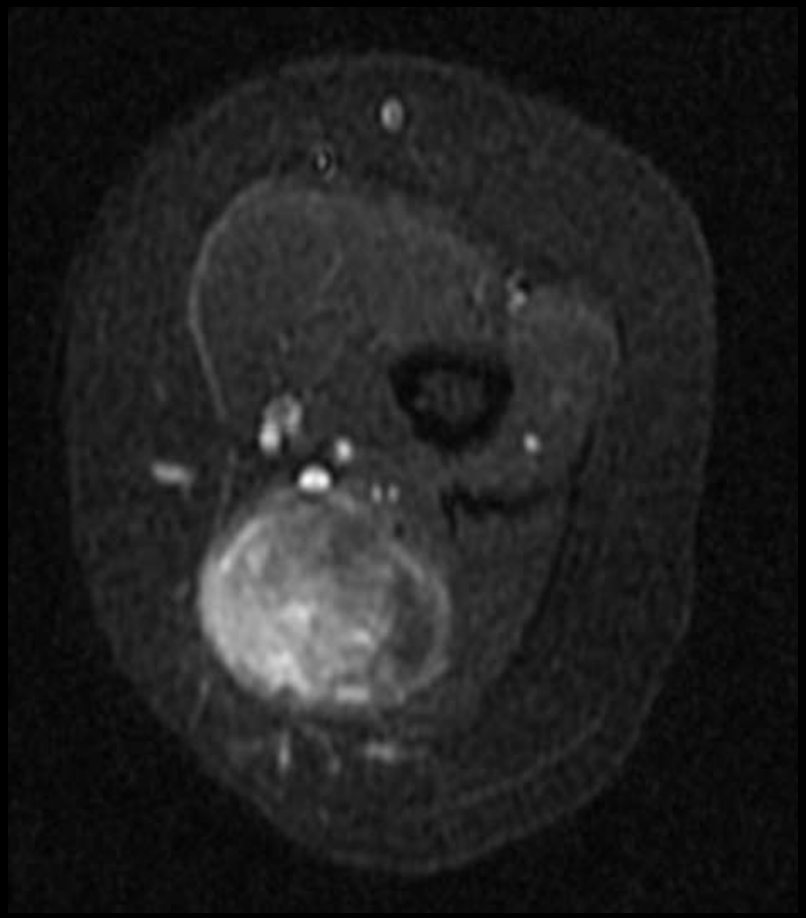
Jeff Cloutier/Brooke Howitt; Stanford

53-year-old F with left upper arm mass growing over 1 year.

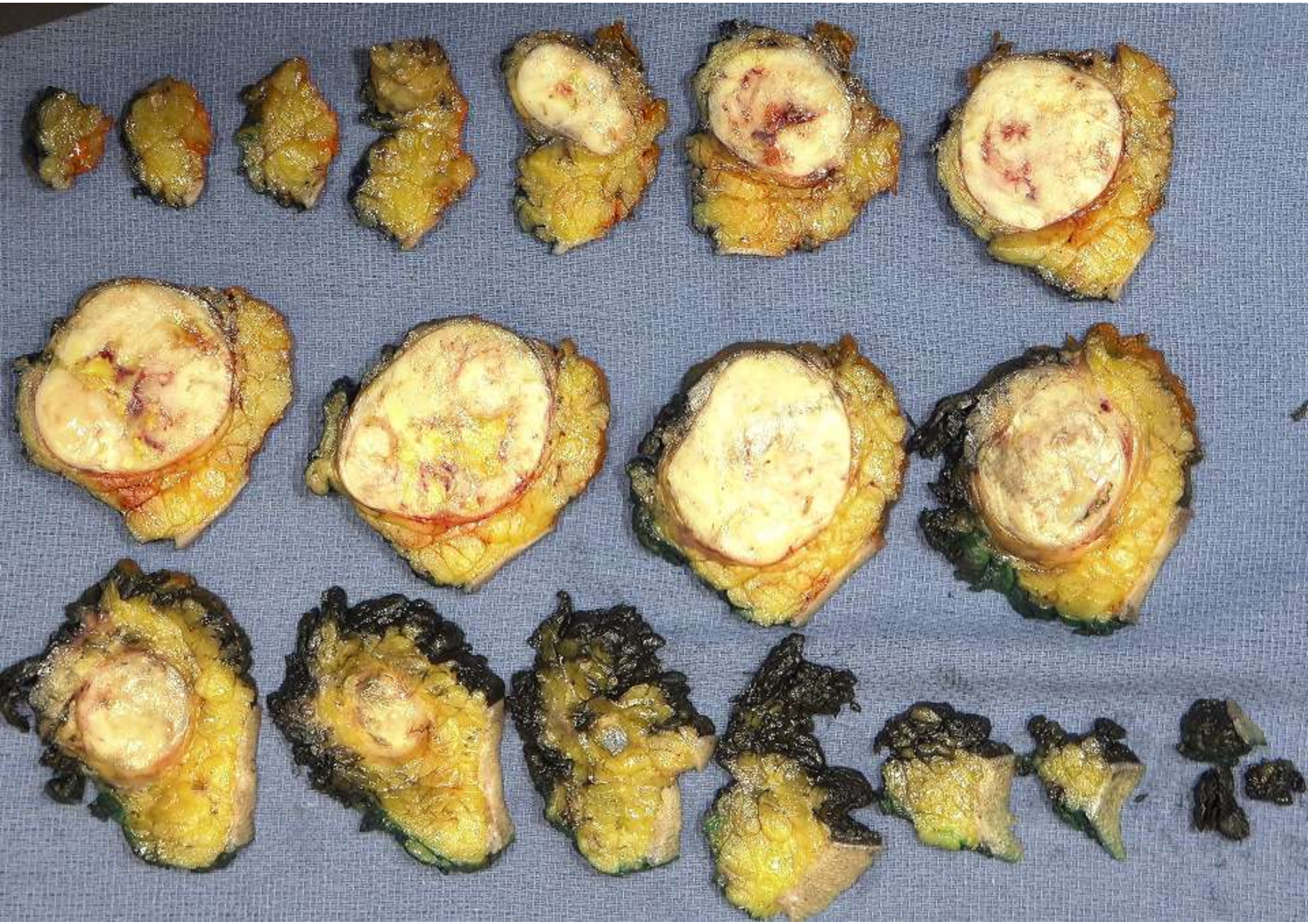
T1

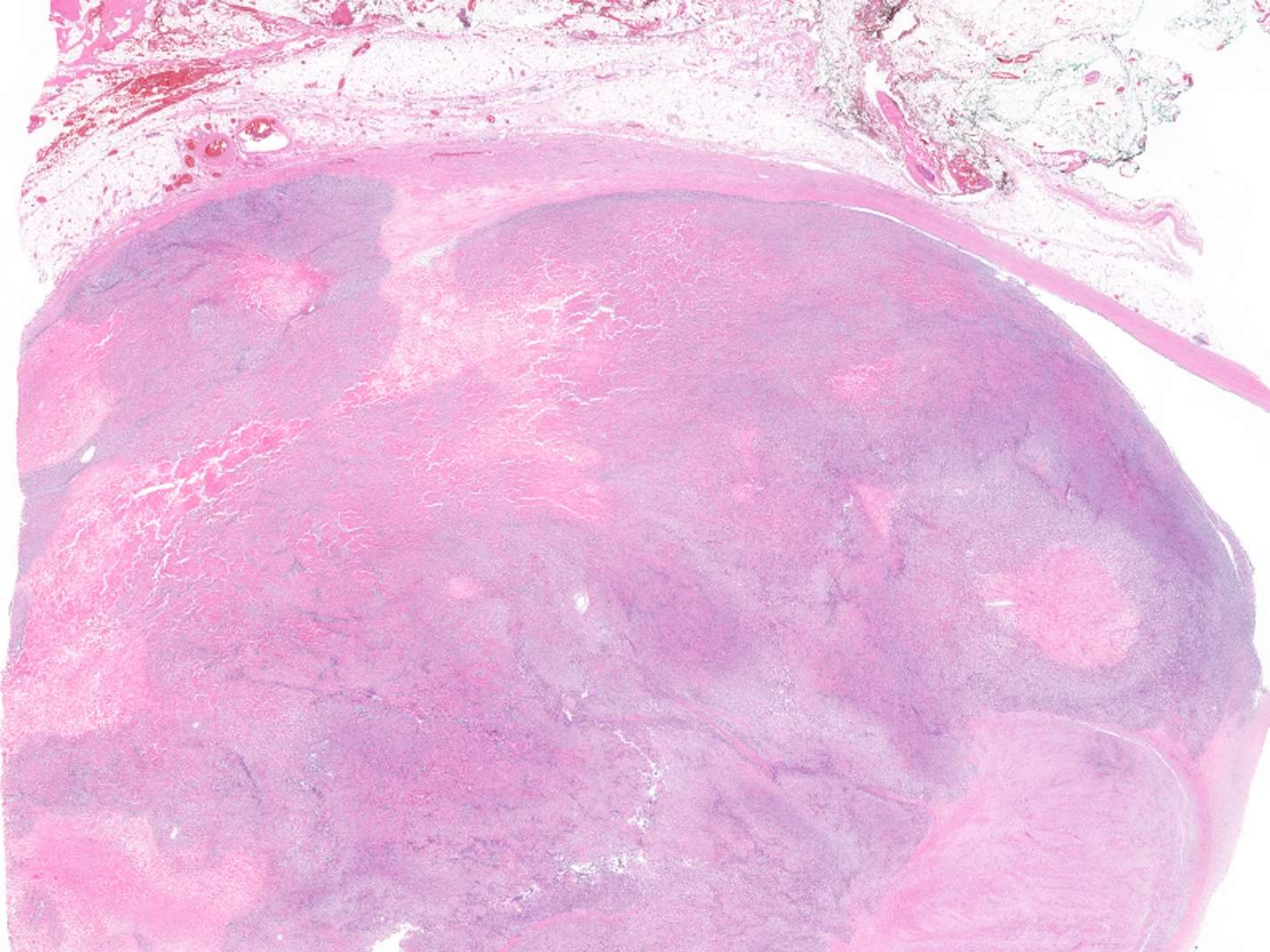


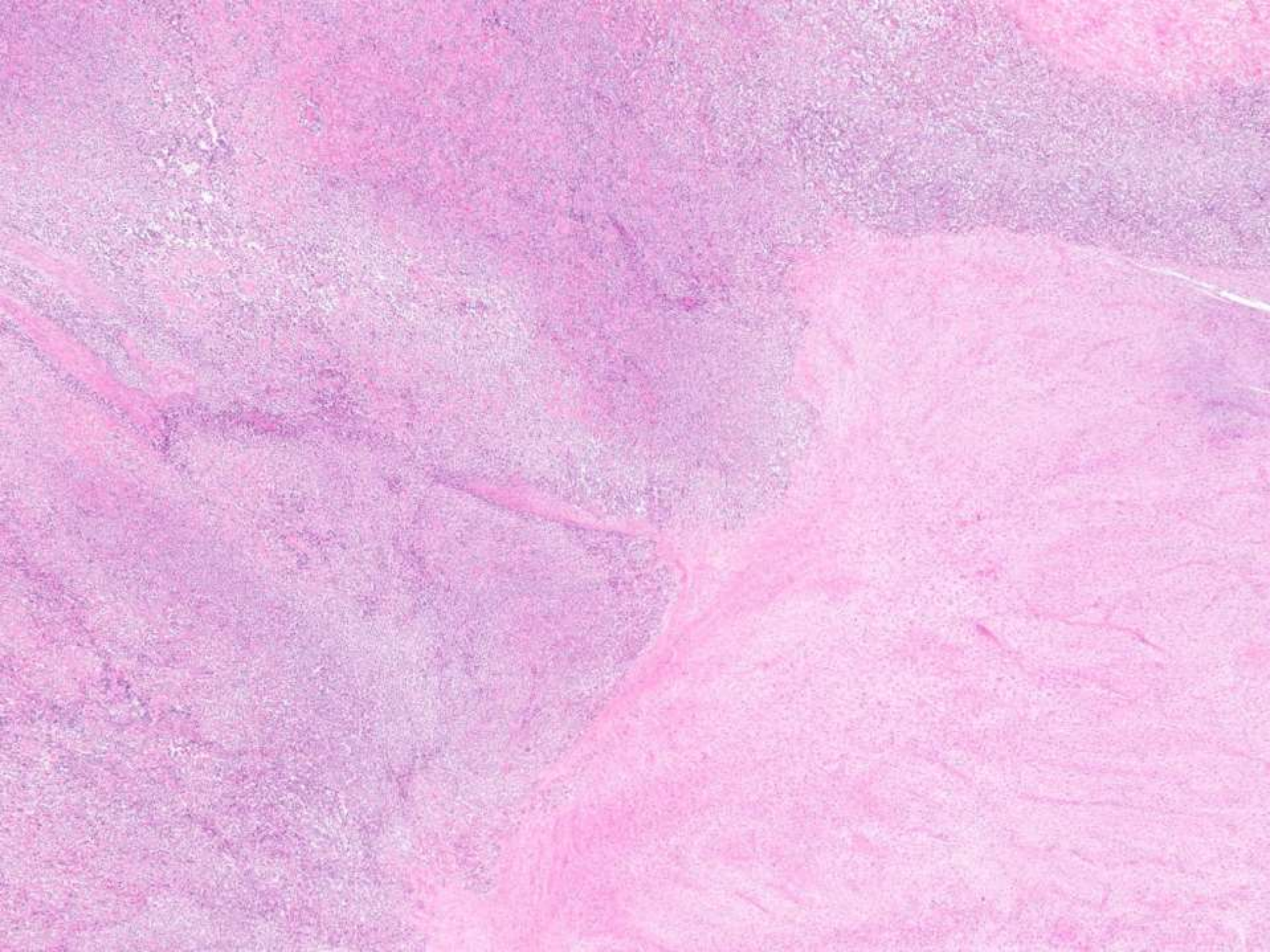
T2

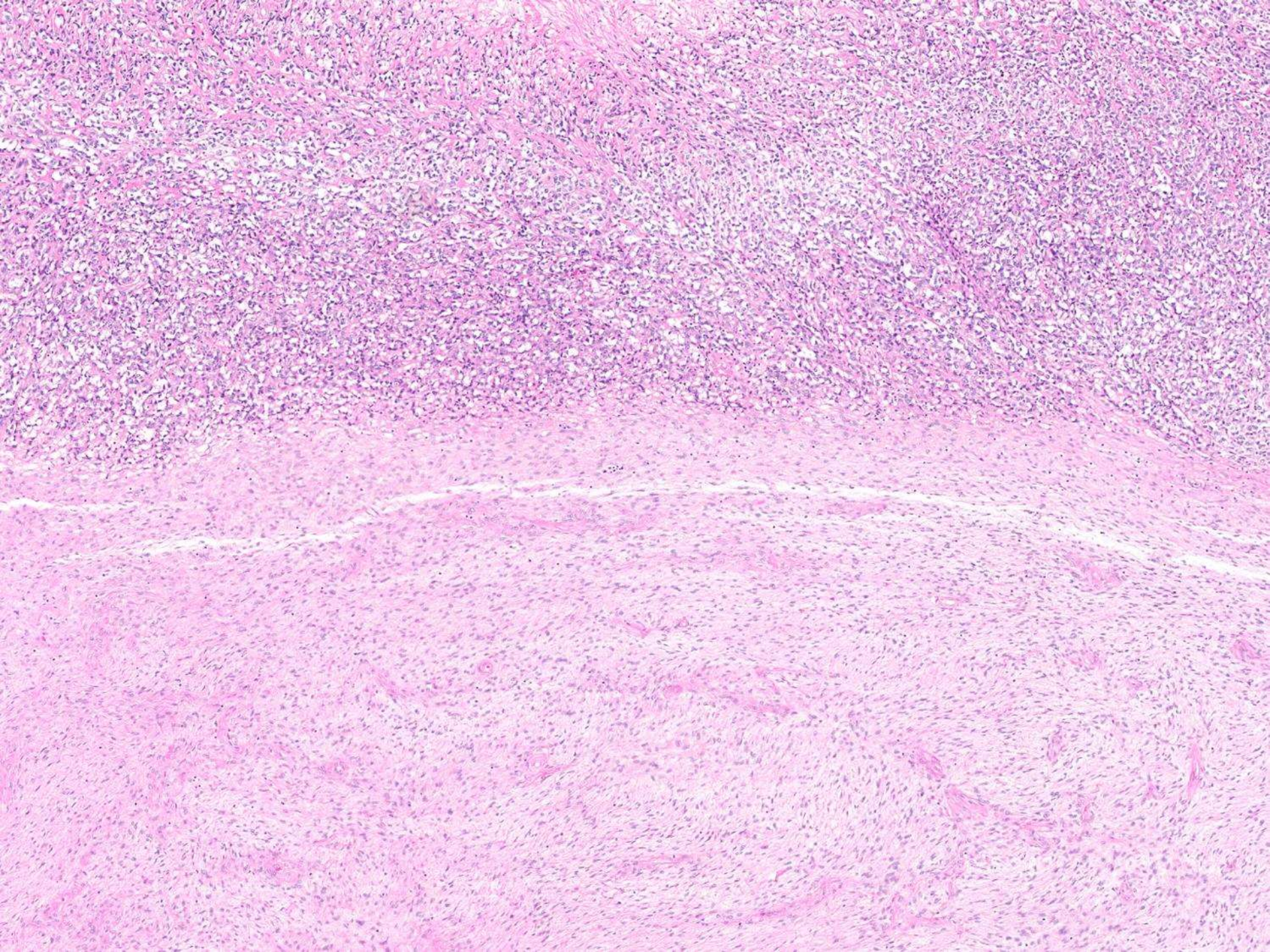


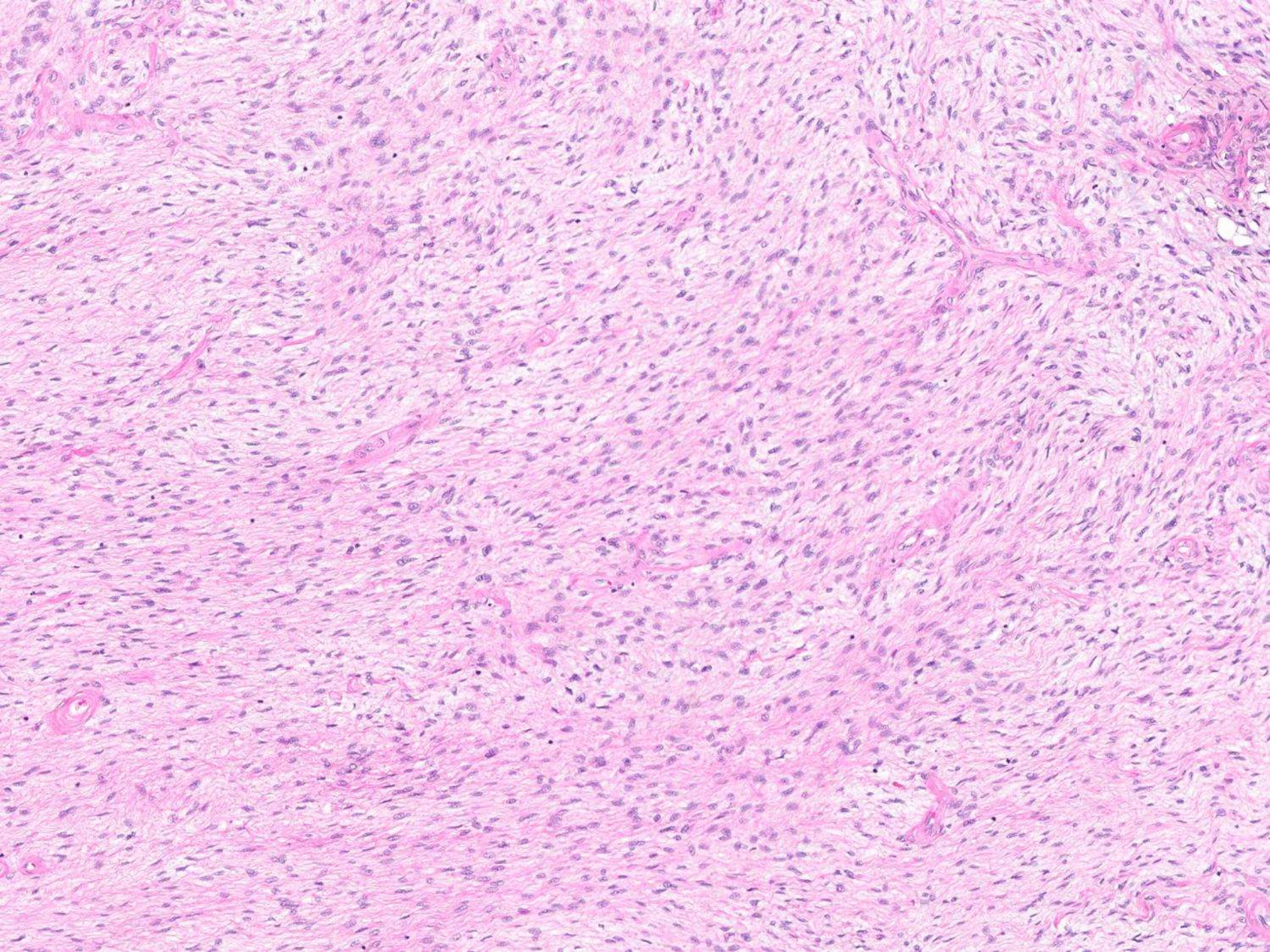
4cm subcutaneous mass abutting the triceps muscle

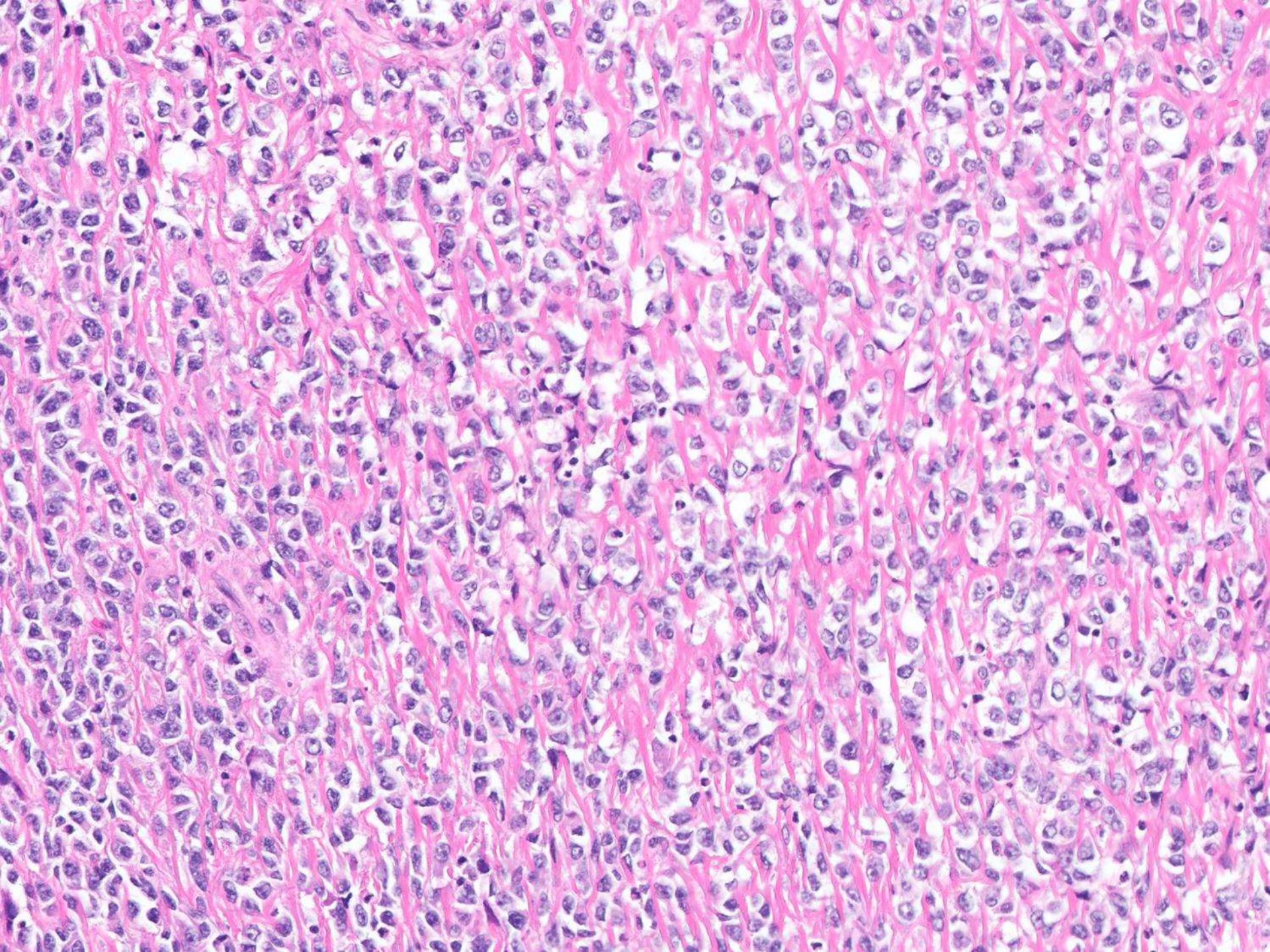


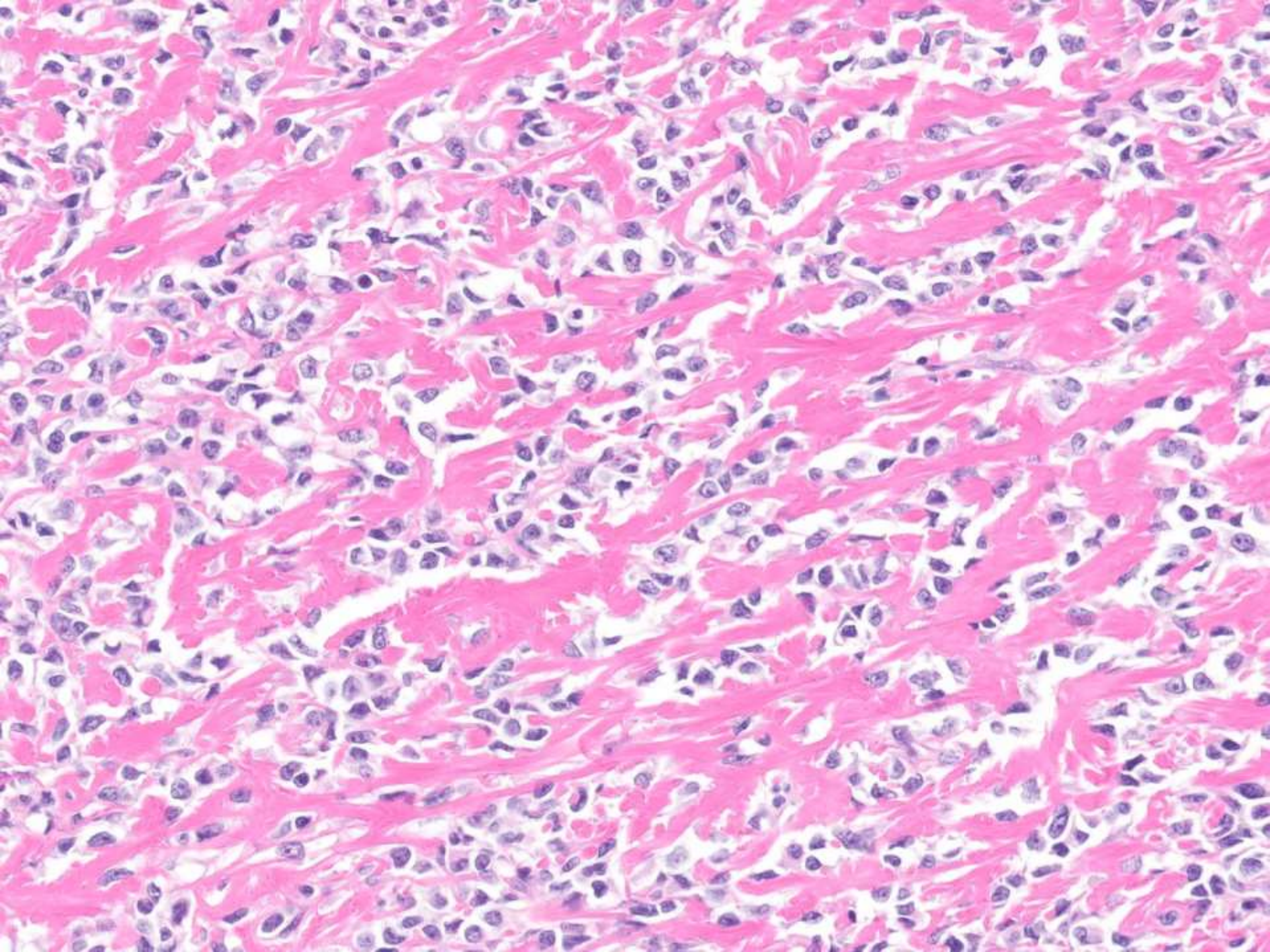


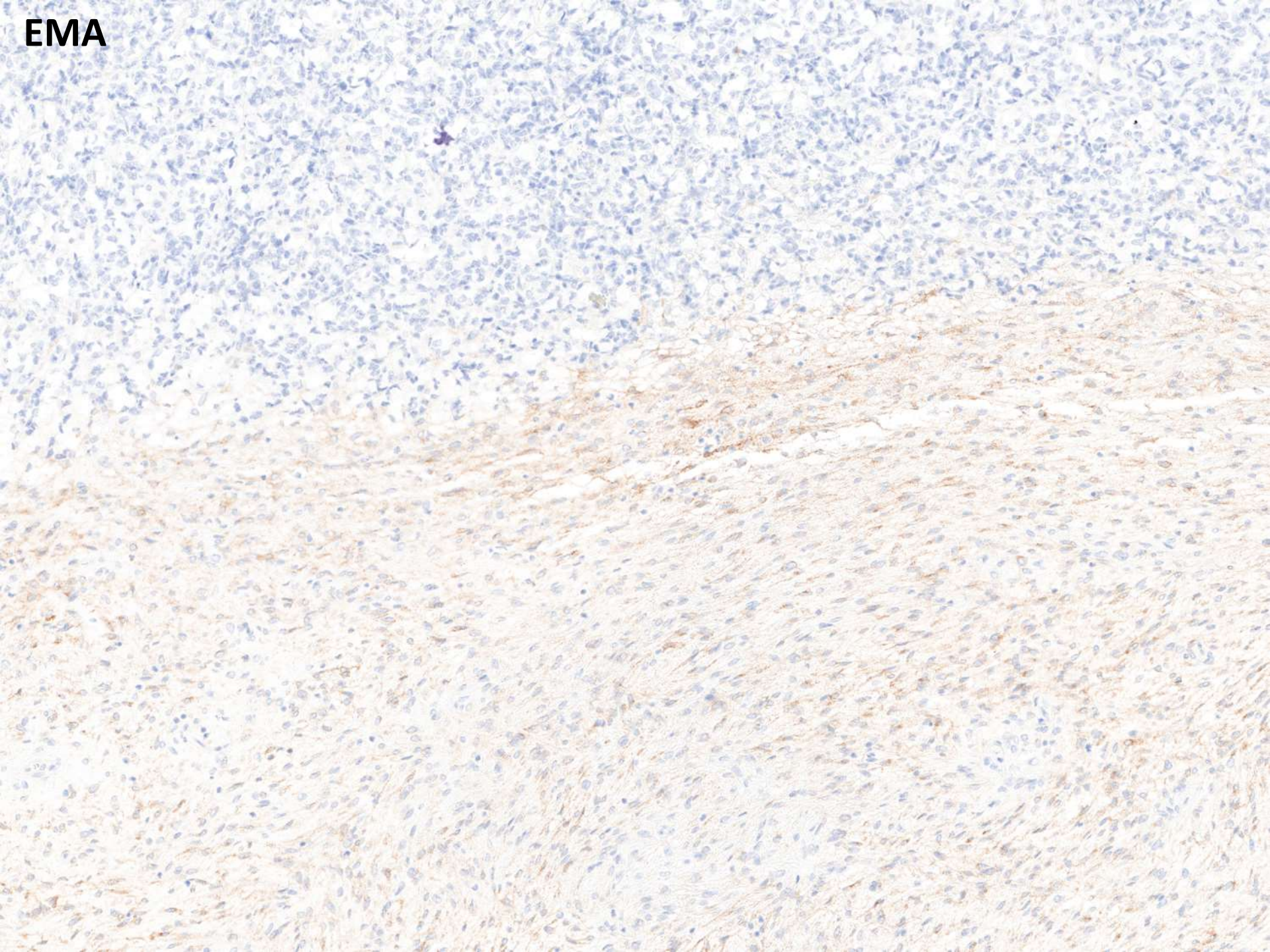








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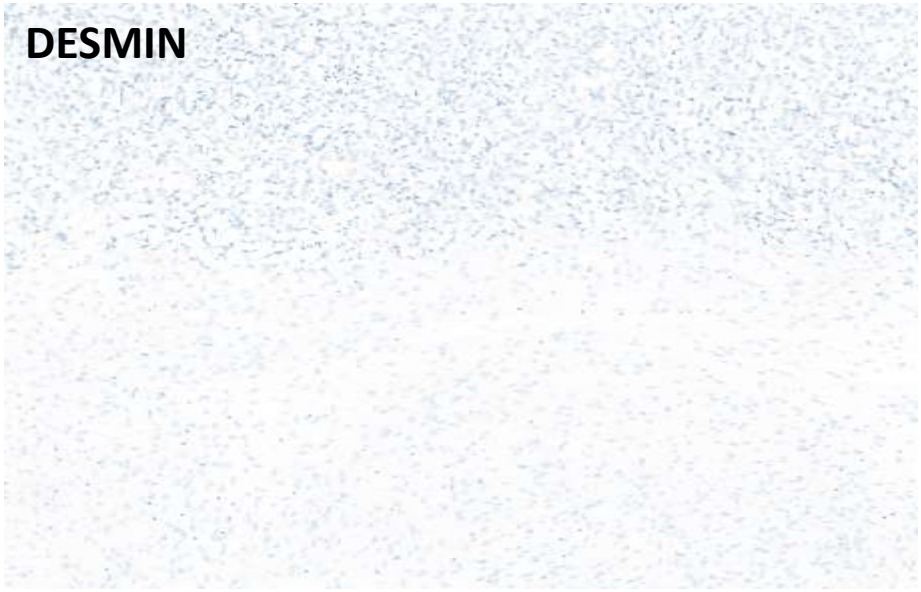
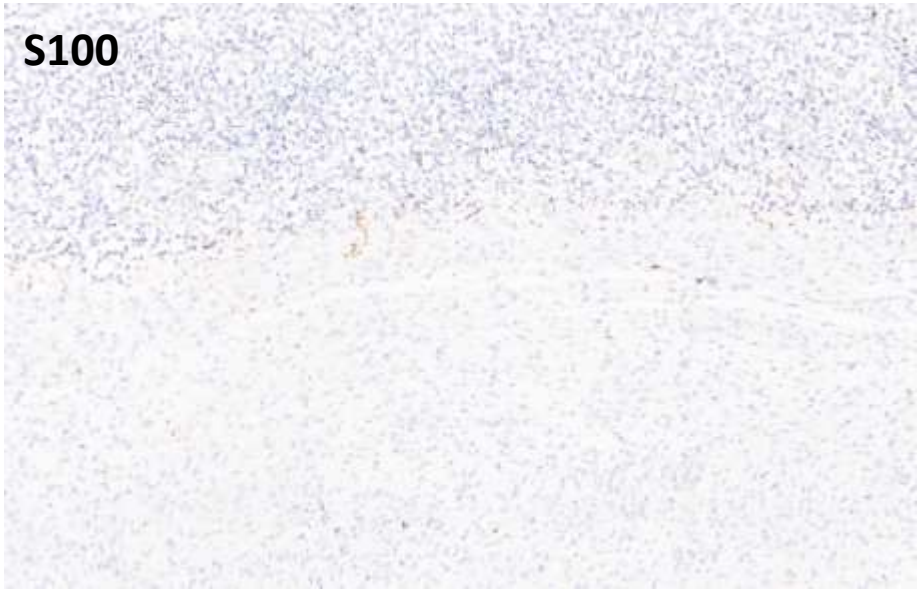
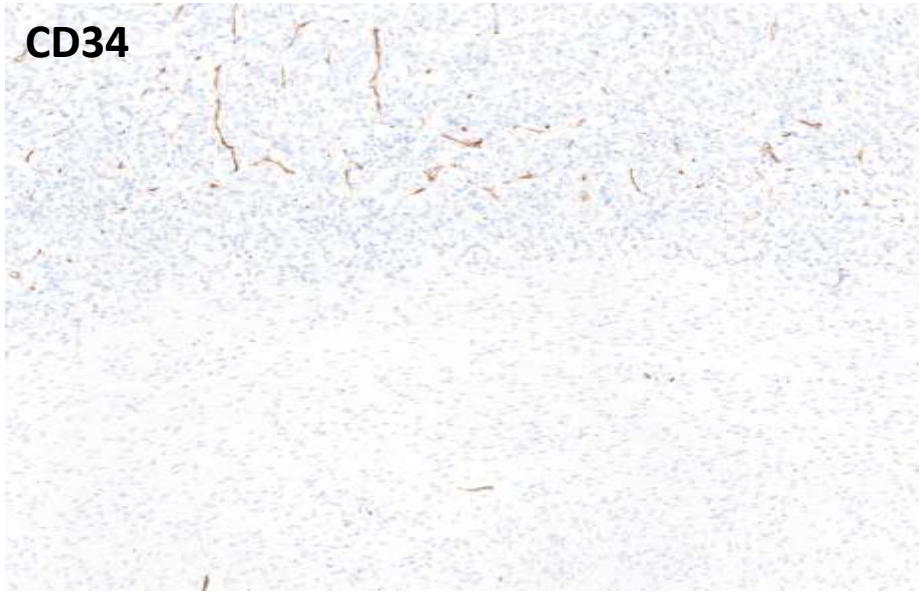
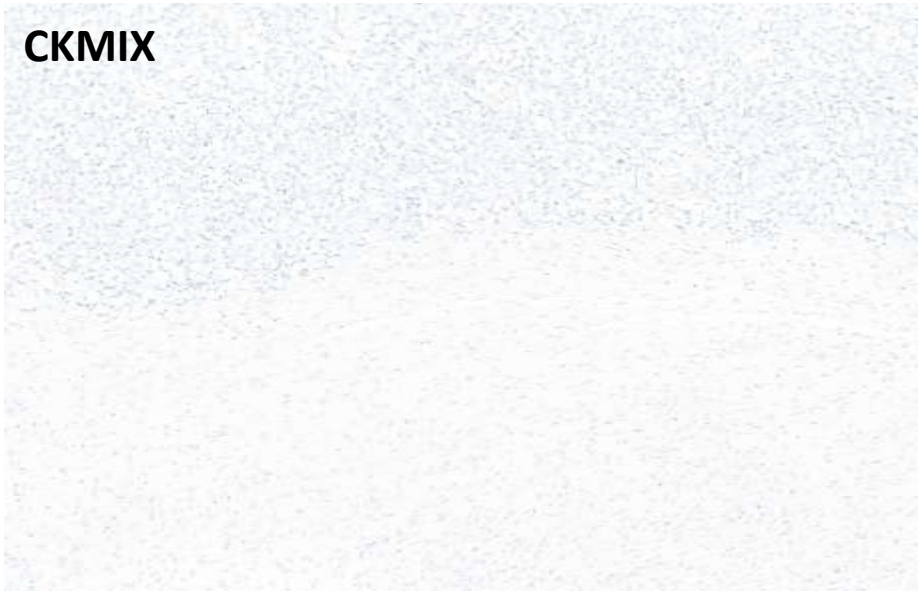

DESMIN

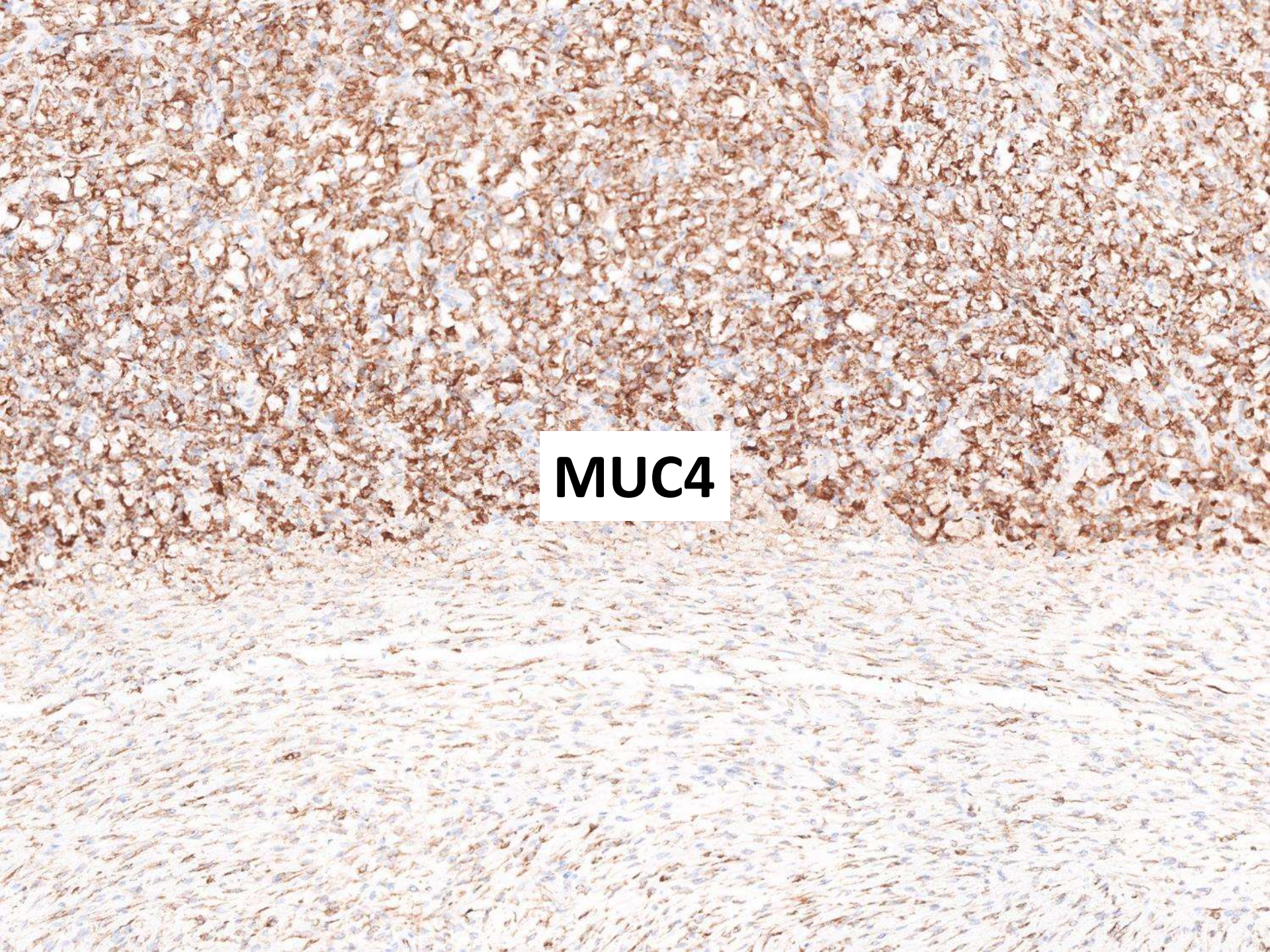

S100


CD34


CKMIX

Differential diagnosis

- Sclerosing epithelioid fibrosarcoma
- Low grade fibromyxoid sarcoma
- Perineurioma
- Desmoid fibromatosis
- Sclerosing rhabdomyosarcoma
- Ossifying fibromyxoid tumor


MUC4

DIAGNOSIS:
Hybrid sclerosing epithelioid fibrosarcoma/ low grade fibromyxoid sarcoma

Sclerosing epithelioid fibrosarcoma (SEF) and **low-grade fibromyxoid sarcoma (LGFMS**) are 2 distinct types of sarcoma, with a subset of cases showing overlapping morphologic, immunohistochemical, and genetic features.

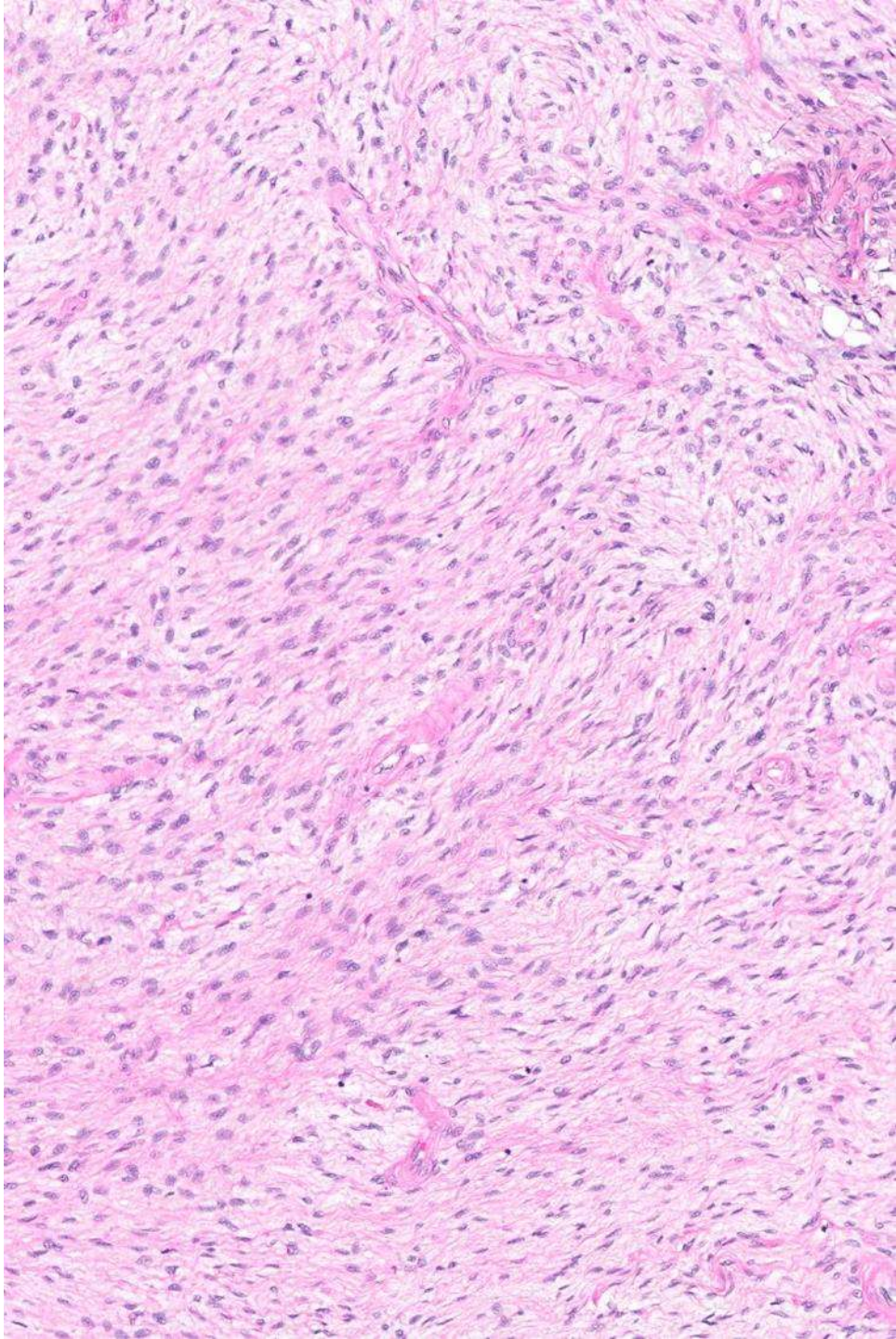
Low-grade fibromyxoid sarcoma (LGFMS)

- “Evans tumor”
- Wide age range (median 34 years)
- Equal sex distribution
- Proximal extremities, trunk, inguinal, head & neck
- Protracted clinical course:
  - Local recurrence (58% at 3.5 years)
  - Metastasis (45% at 5 years)
  - Mortality (42% at 15 years)

Evans HL. Am J Surg Pathol 2011

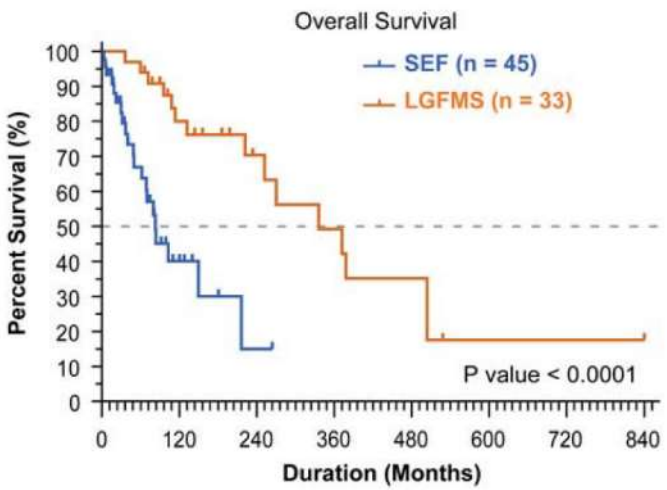
LGFMS

- Whorling fascicles of bland spindled cells, with contrasting hypocellular collagenous and cellular myxoid areas
- Prominent vascular network with arcades of thin-walled vessels
- MUC4+ (99%), EMA+
- ***FUS-CREBL2*** fusion
- Rare alternative fusions:
  - *FUS-CREBL1*
  - *EWSR1-CREB3L1*



Sclerosing epithelioid fibrosarcoma (SEF)

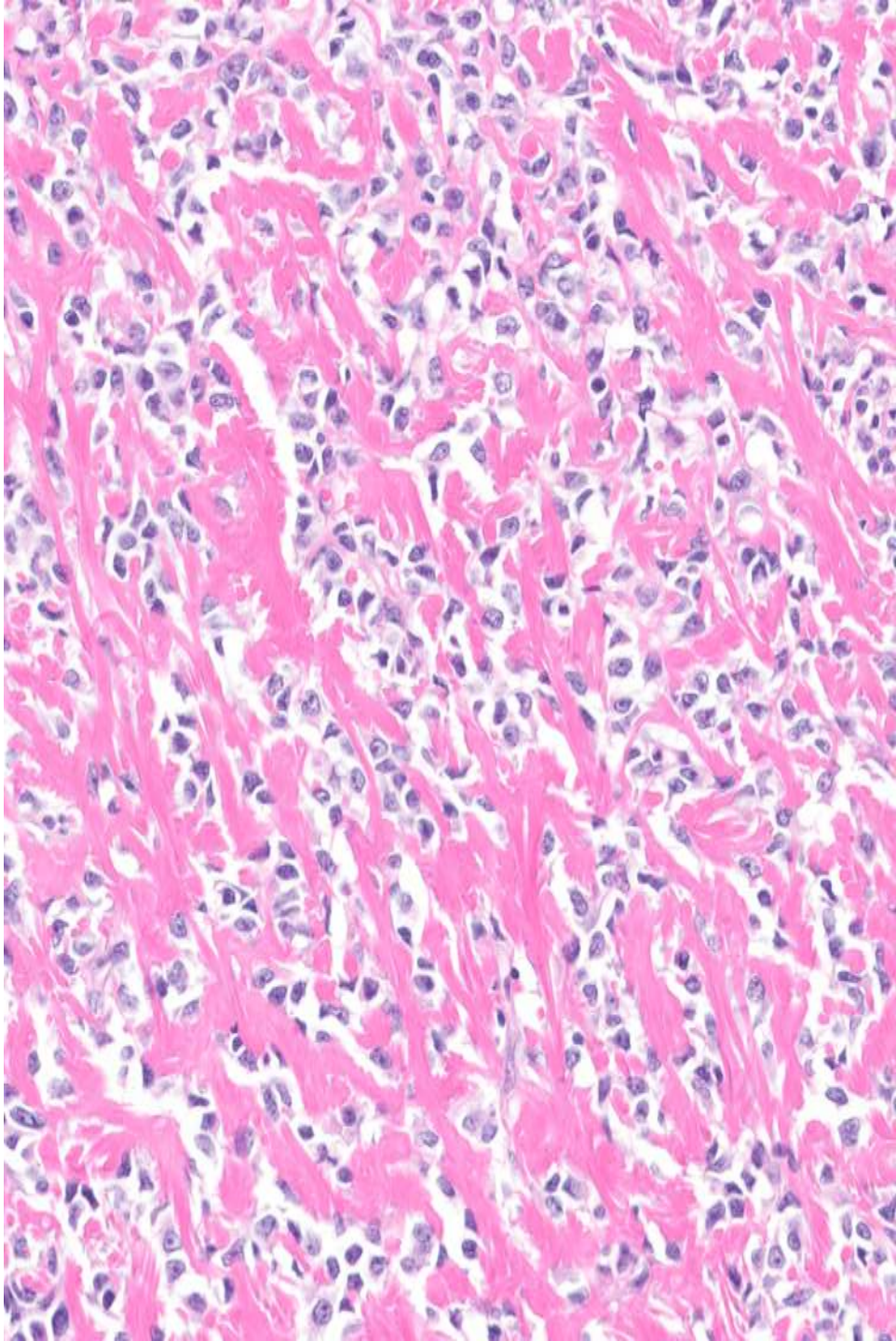
- Wide age range (median 45 years)
- Equal sex distribution (early studies suggested F>M)
- Lower extremity, intra-abdominal, chest wall/paraspinal, retroperitoneum, bone, head & neck
- Aggressive clinical behavior:
  - High rate of local recurrence (50%)
  - Metastasis (40-80%)
  - Mortality (25-57%)



Warmke and Meis. Am J Surg Pathol 2021

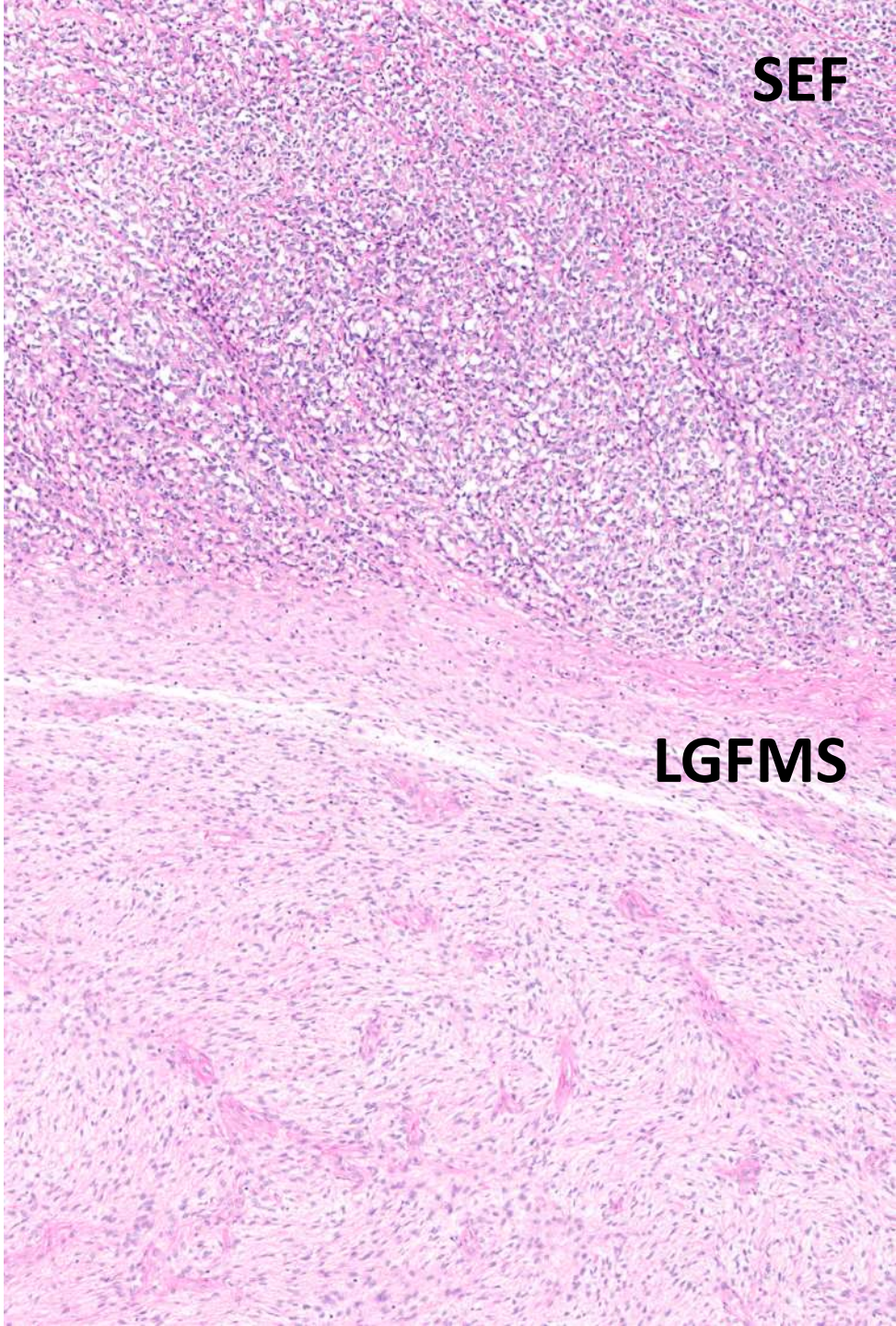
SEF

- Well-circumscribed, lobulated lesion (7-10 cm)
- Nests and cords of uniform small epithelioid cells embedded in sclerotic matrix
- MUC4+ (>80%), EMA+ (50%)
- ***EWSR1-CREB3L1*** fusion
- Rare alternative fusions:
  - *EWSR1-CREB3L2*
  - *FUS-CREB3L2*
  - *YAP1* and *KMT2A* rearrangements (MUC4-)



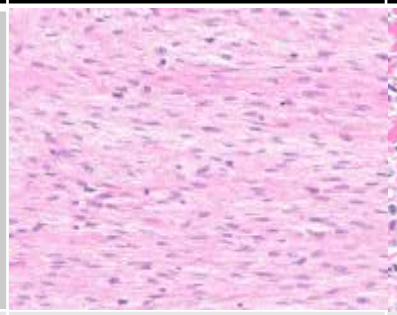
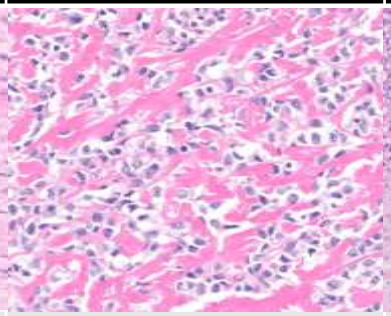
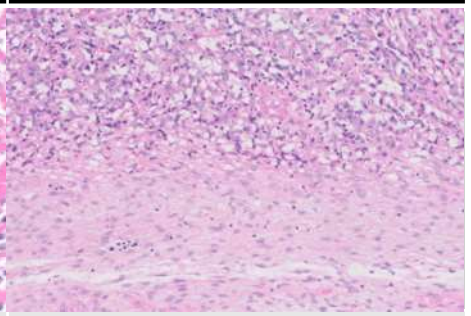
Hybrid SEF/LGFMS

- Admixed components of SEF and LGFMS
- Suggests biological relationship between 2 sarcoma types
- Similar mortality rate to SEF (37%)
- ***FUS-CREB3L2*** fusions (similar to LGFMS)



Prieto-Granada, Genes Chromosomes Cancer. 2015

The spectrum of SEF and LGFMS

	LGFMS	SEF	Hybrid LGFMS/SEF
Histology			
Genetics	***FUS-CREBL2*** *FUS-CREBL1* *EWSR1-CREB3L1*	***EWSR1-CREB3L1*** *EWSR1-CREB3L2* *FUS-CREB3L2* *YAP1* and *KMT2A* rearrangements	***FUS-CREB3L2***
Clinical behavior	Protracted course with recurrence and late metastasis/death	More aggressive with high risk of metastasis and mortality	Similar to SEF

A challenging diagnosis with many histologic mimics

LGFMS

- Desmoid-type fibromatosis *(MUC4-)*
- Soft tissue perineurioma *(MUC4-)*

SEF

- Poorly diff carcinomas, lobular carcinoma *(cytokeratin+)*
- Sclerosing lymphoma *(CD45+)*
- Sclerosing rhabdomyosarcoma *(desmin+)*
- Ossifying fibromyxoid tumor *(S100+, PHF1 fusion)*
- Osteosarcoma *(MUC4-)*
- Myoepithelial tumors *(S100+, SMA+, GFAP+)*

Several possible diagnostic pitfalls

- MUC4 is not 100% specific in this histopathologic differential
  - Positive in some myoepithelial tumors (can also have *EWSR1* fusion)
  - Positive in some ossifying fibromyxoid tumors
  - Expressed in numerous carcinomas

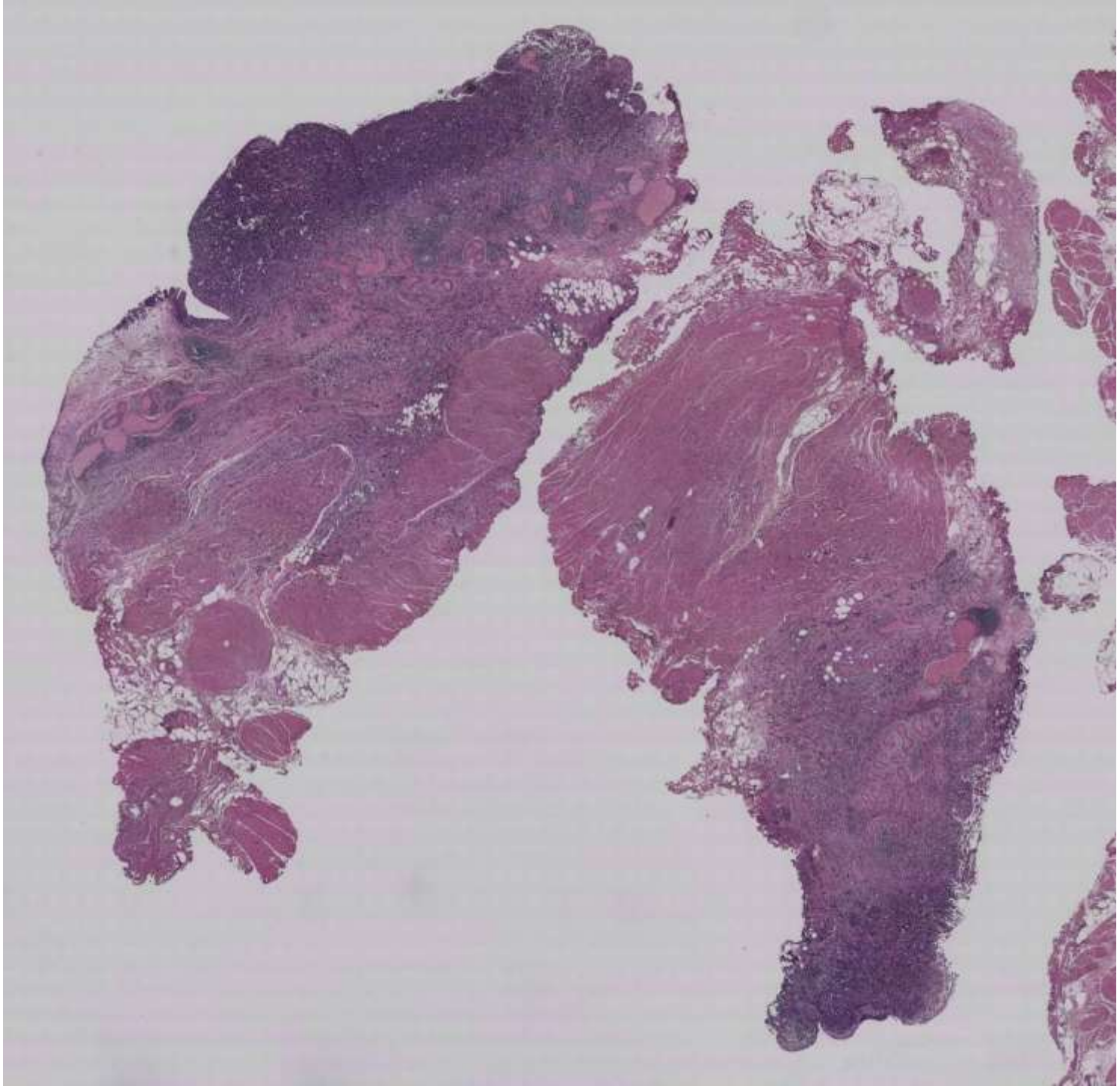
- Rare MUC4-neg LGFMS cases have been described (Prieto-Granda 2015, Linos 2014)

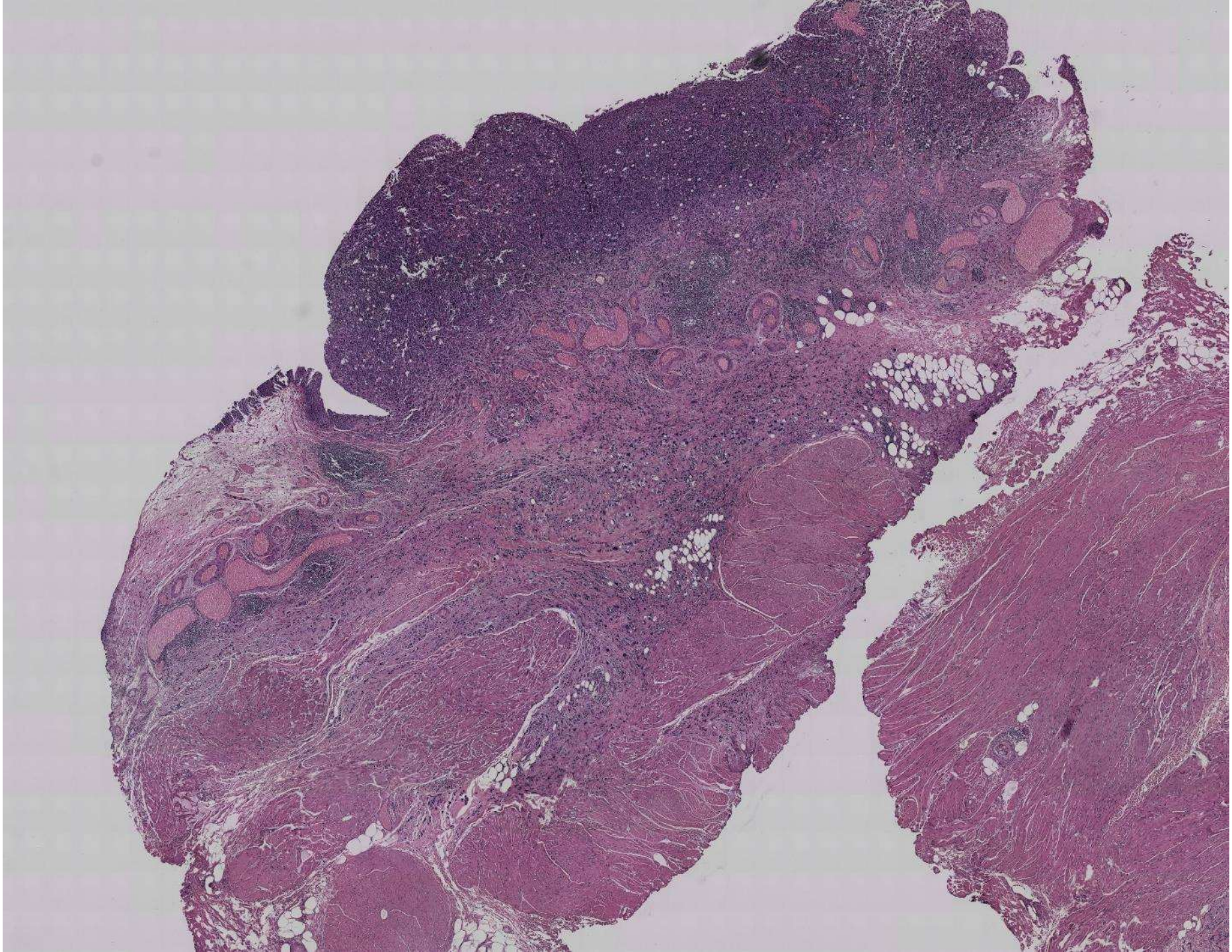
- Potential false negative FISH result, which can occur secondary to a cryptic rearrangement

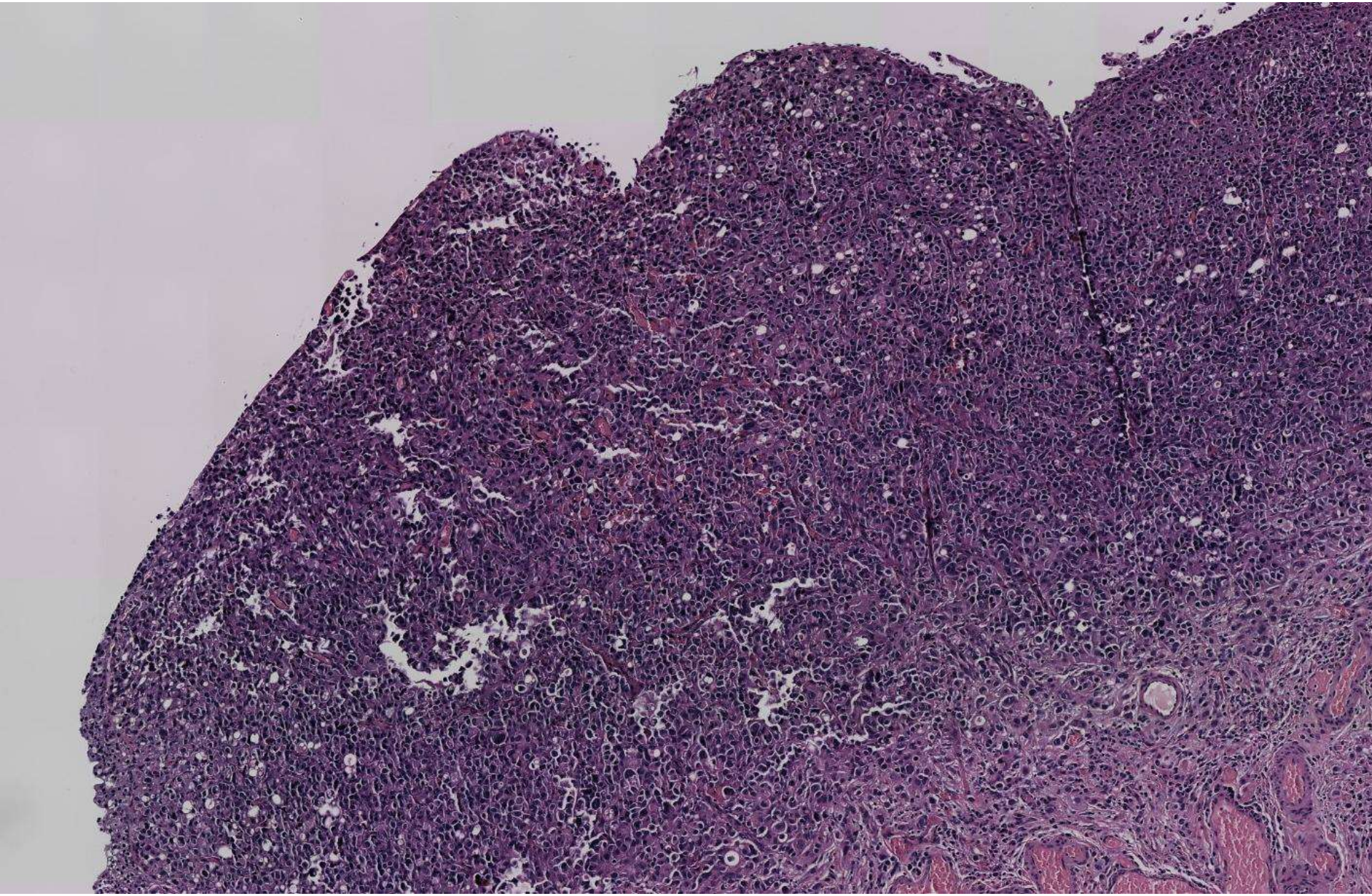
21-0606
scanned slide available!

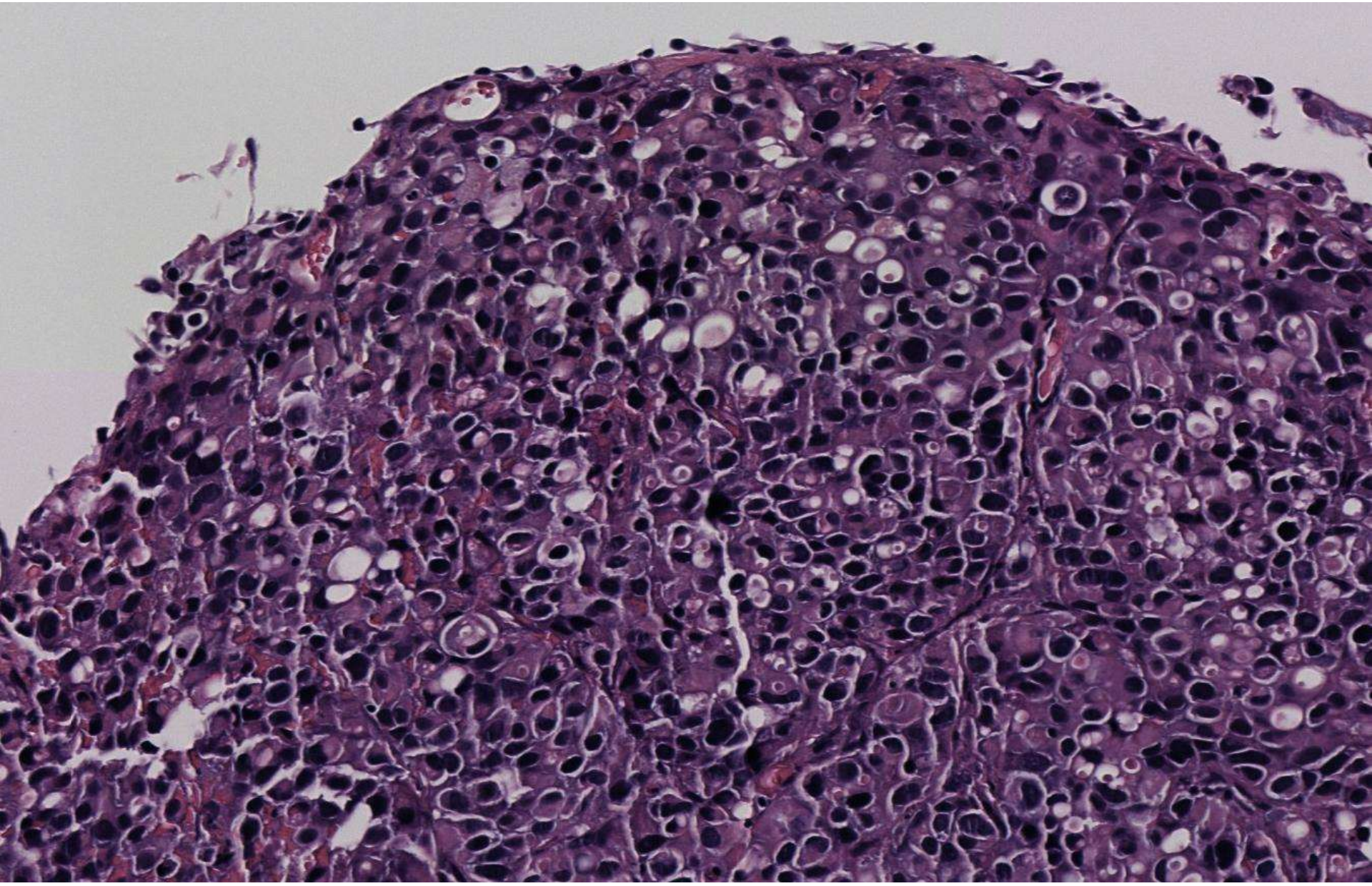
Ankur Sangoi; El Camino Hospital

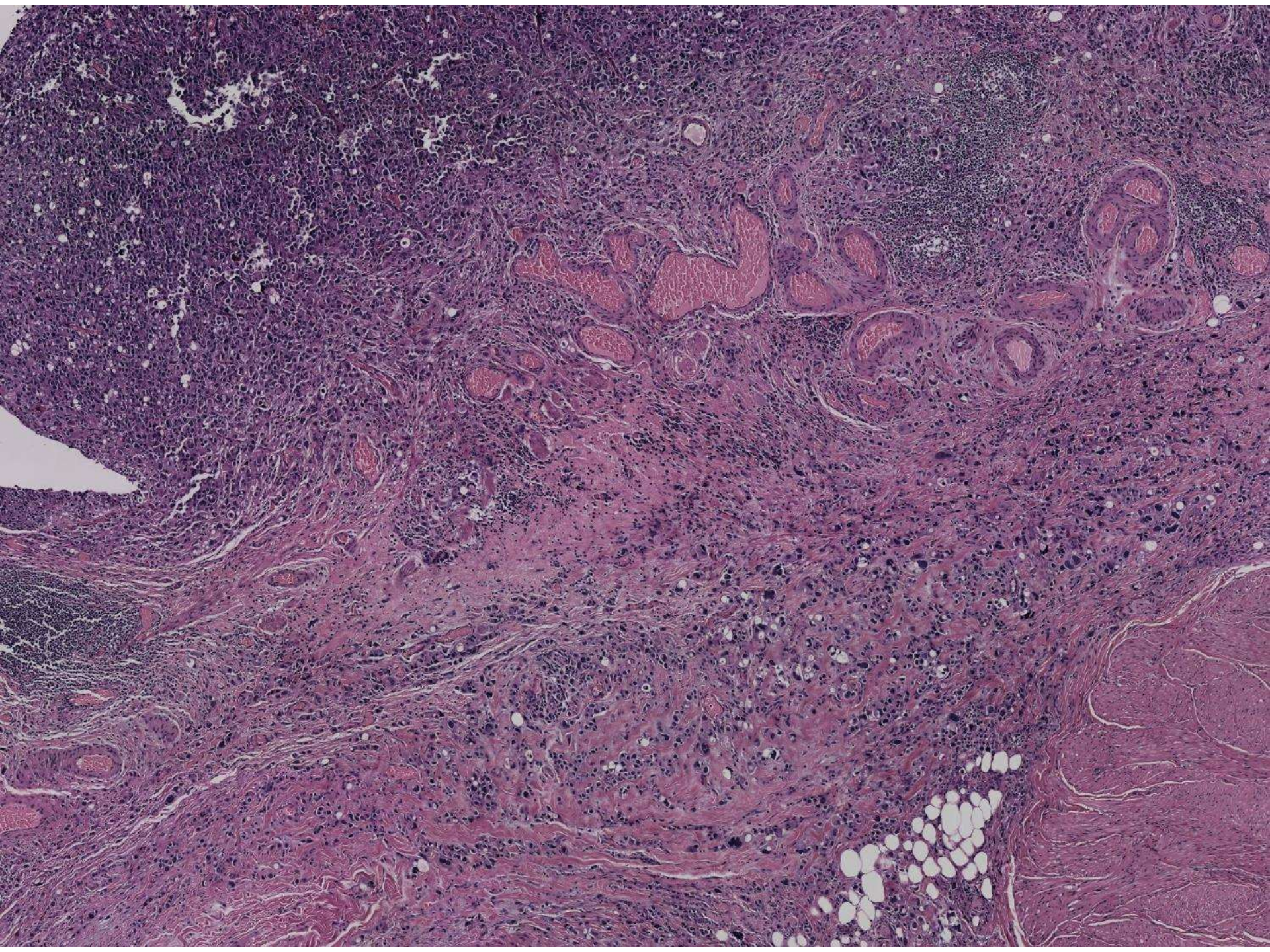
62-year-old M presents with hematuria, undergoes TURBT.

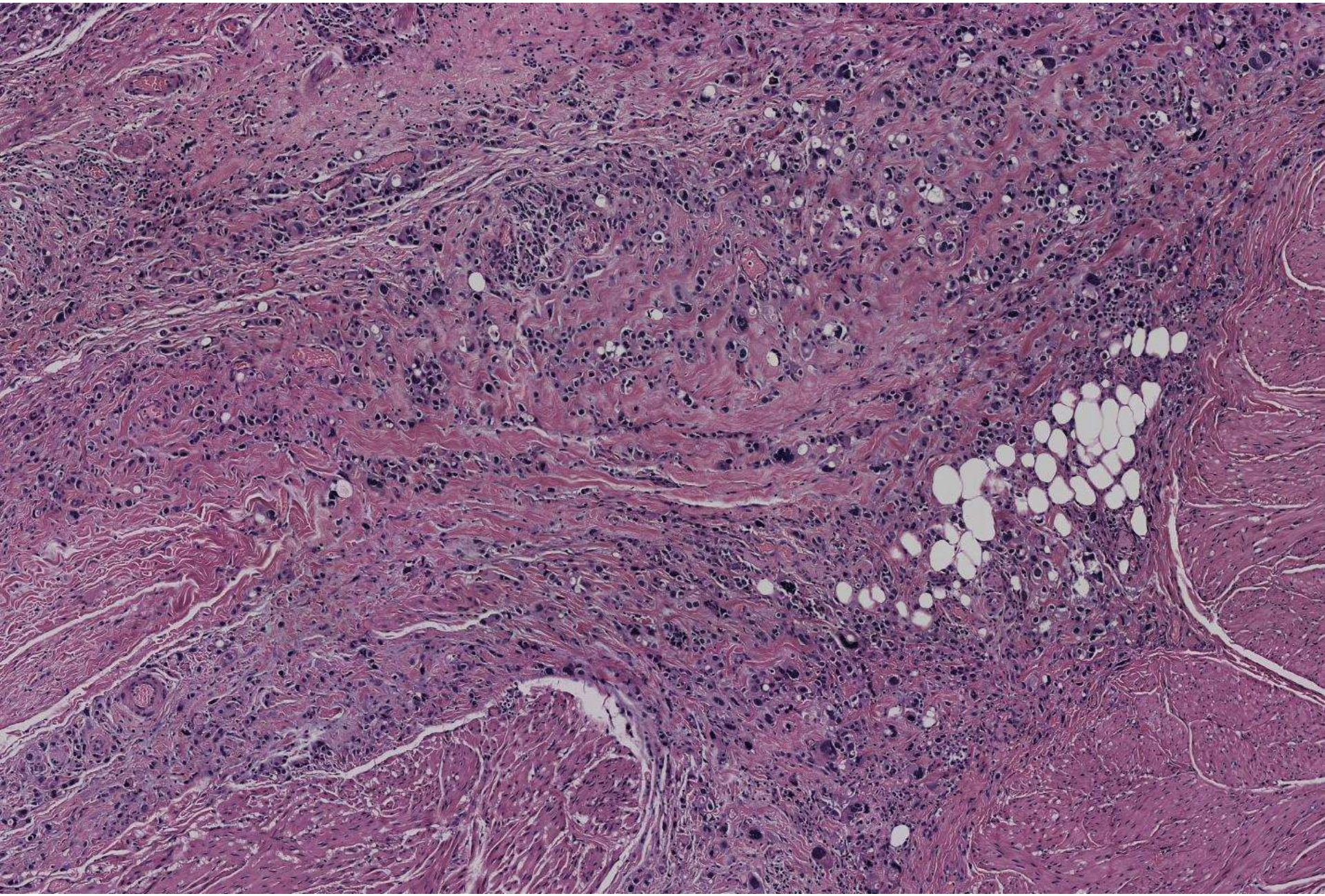


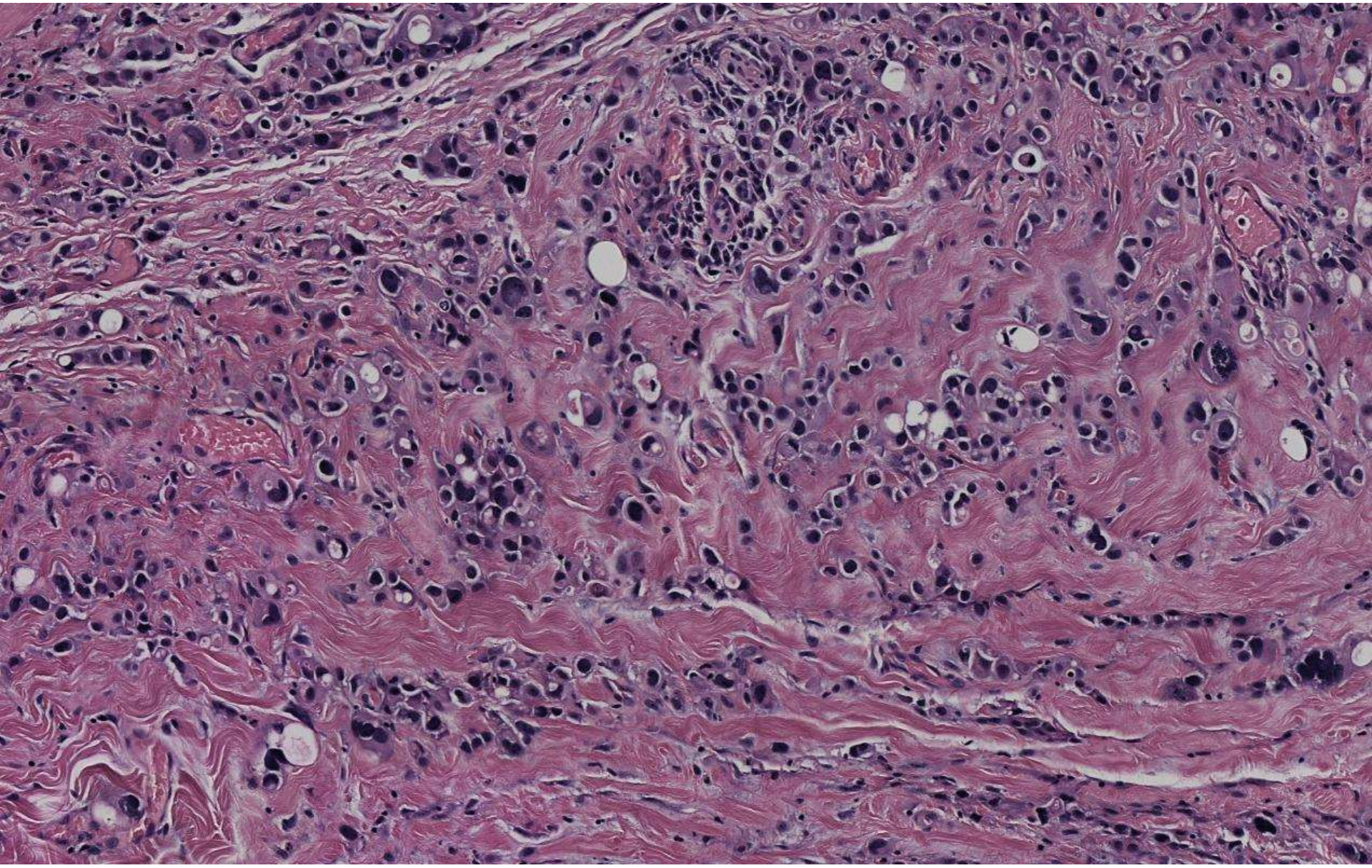


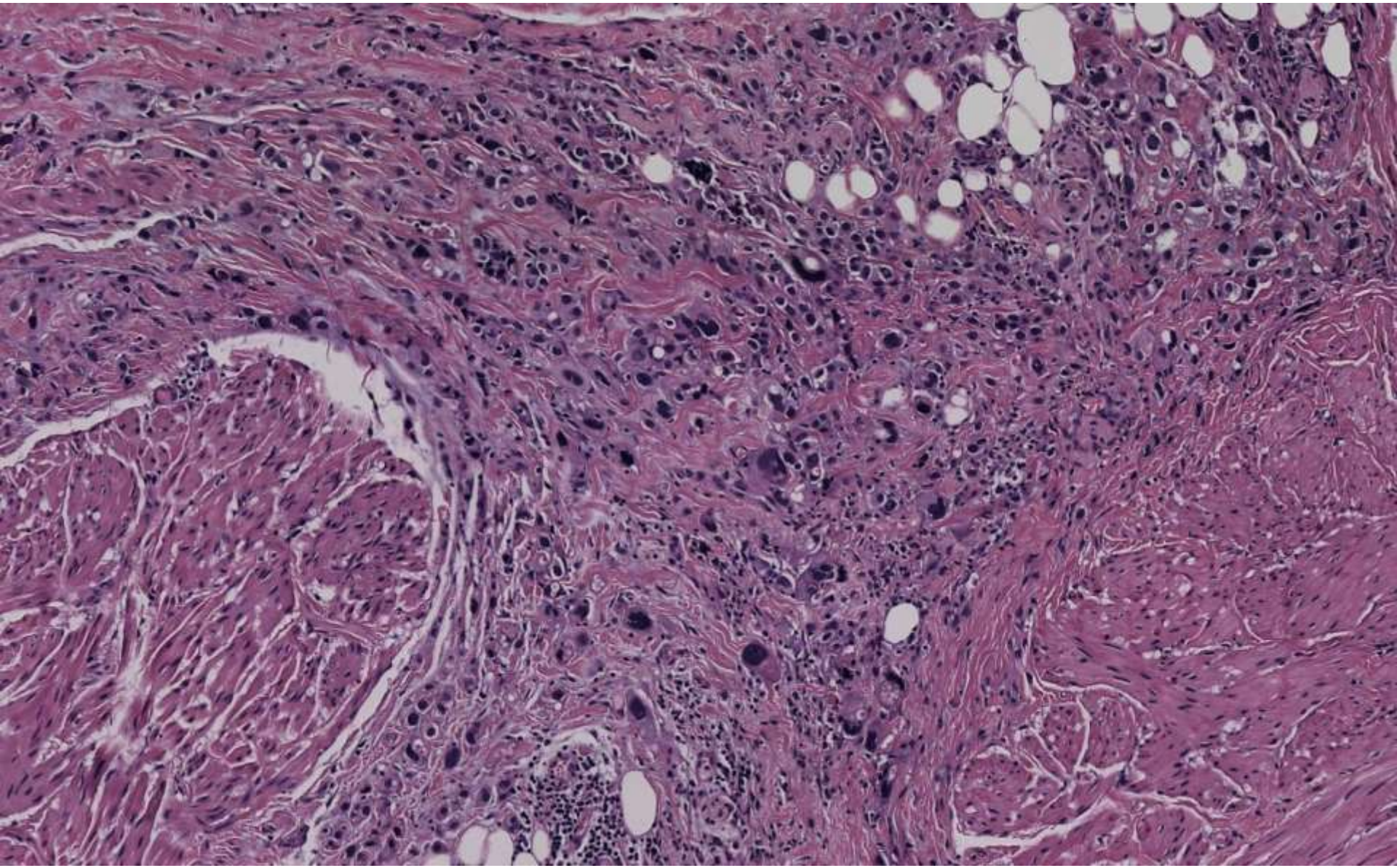


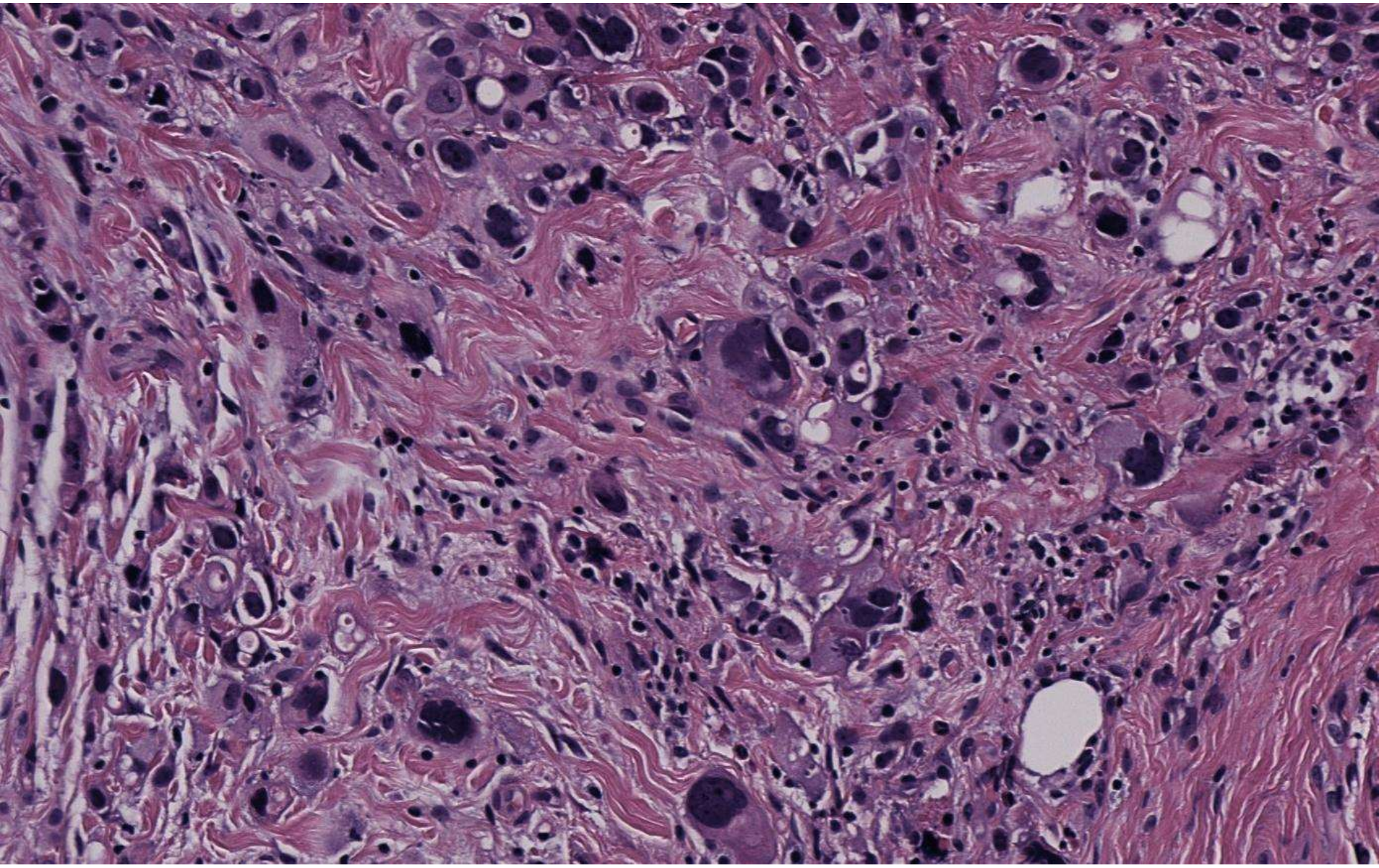






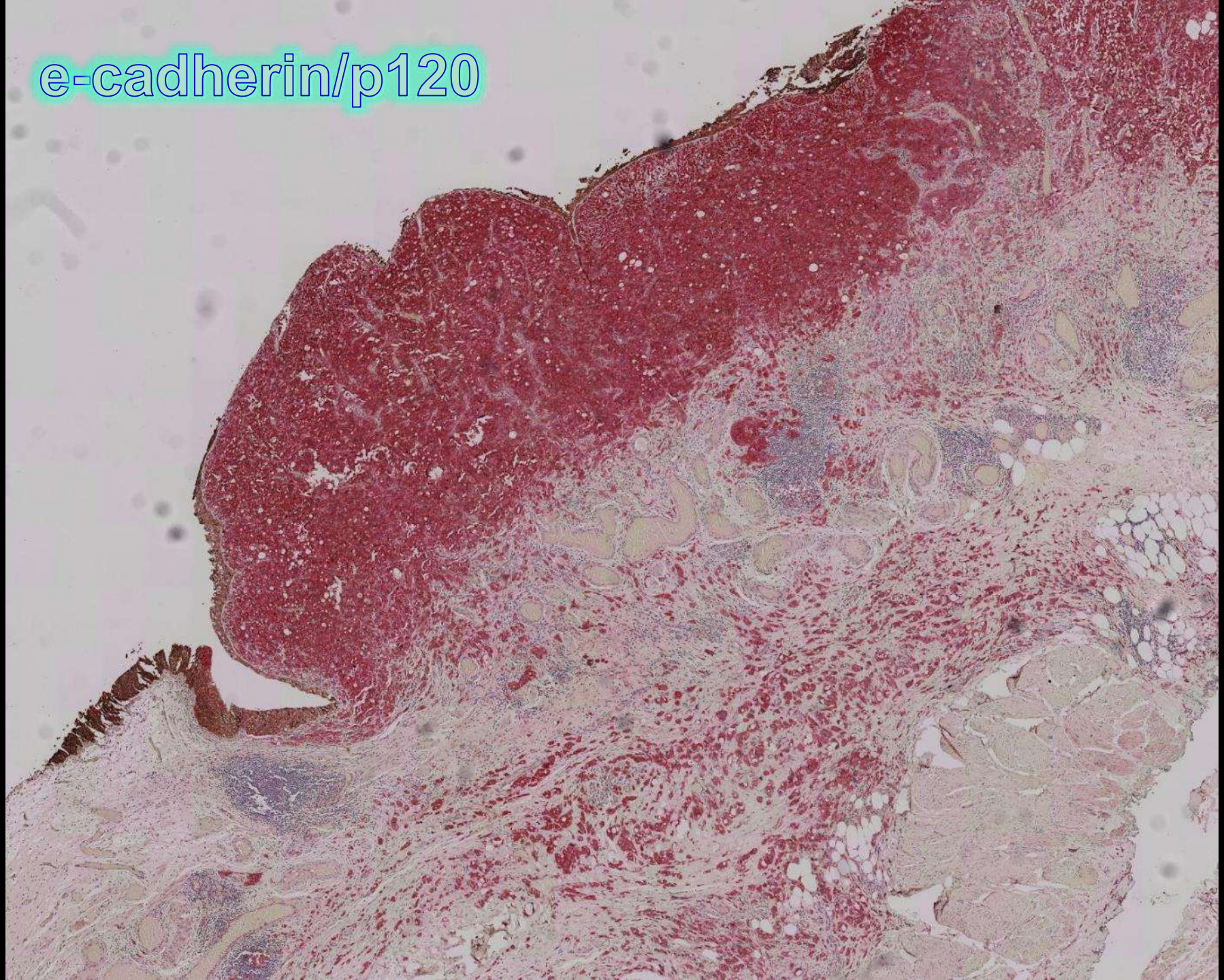


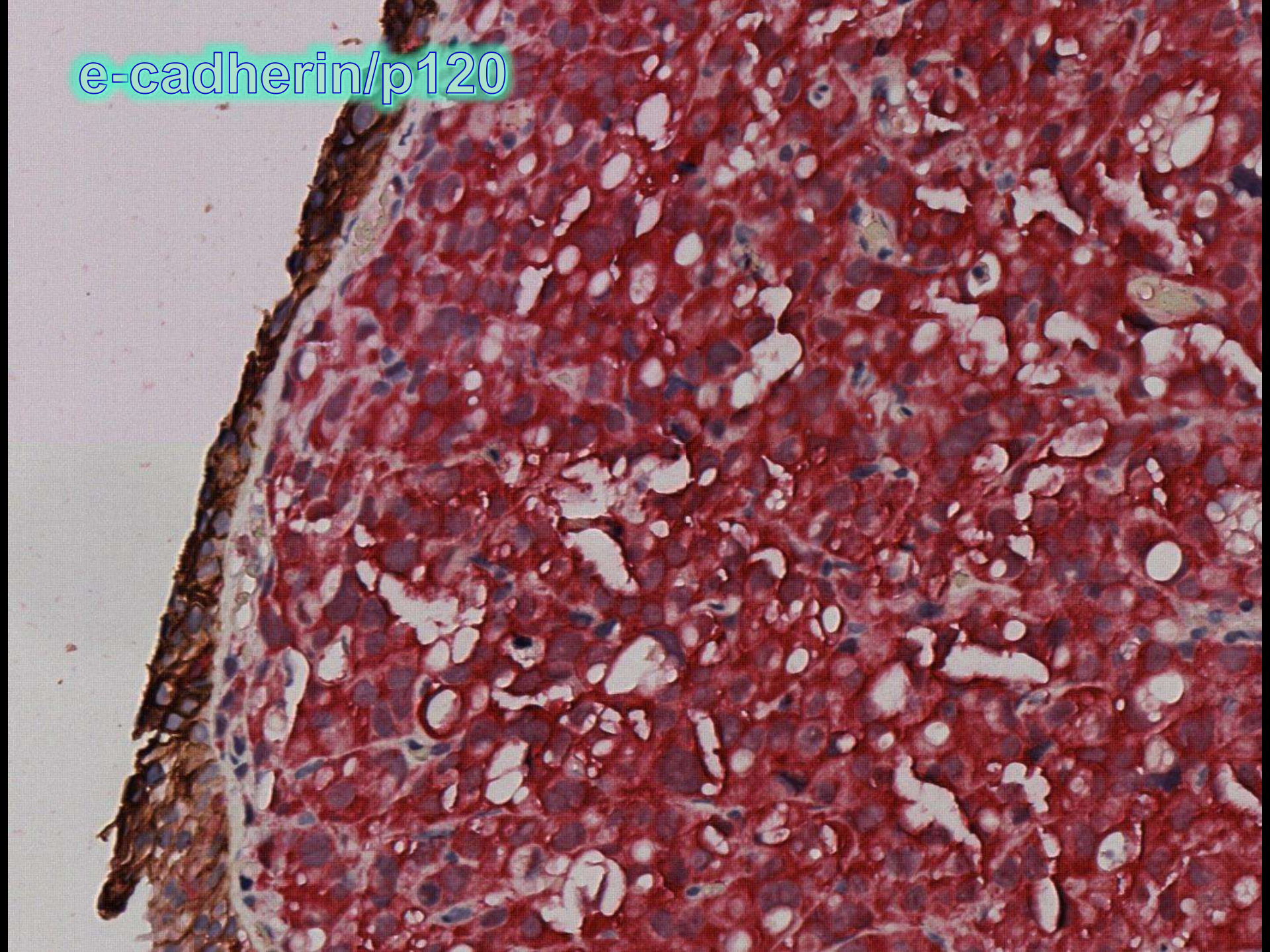




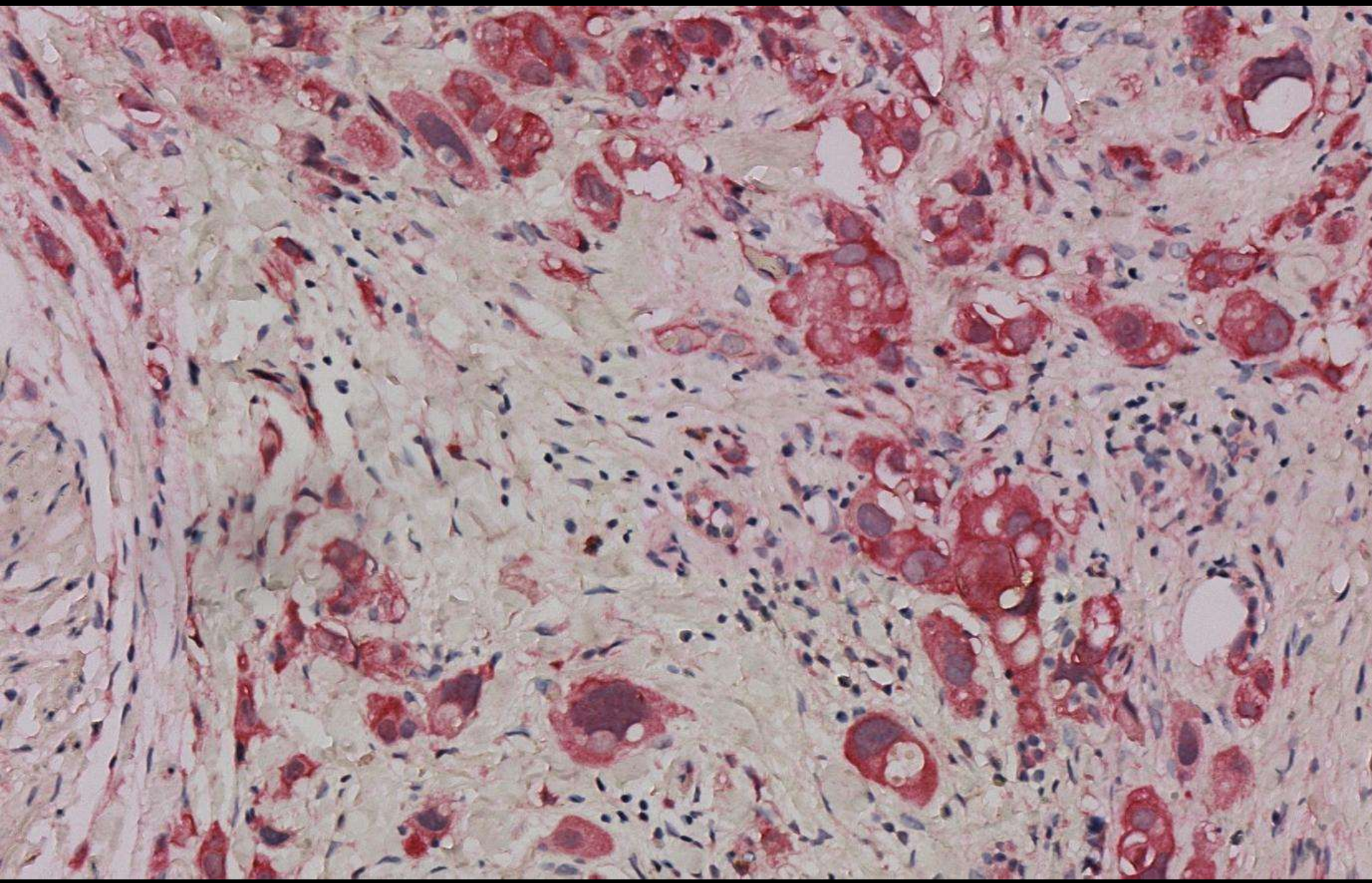
DDx

- Plasmacytoid urothelial carcinoma
- Urothelial carcinoma NOS
- Plasma cell neoplasm
- Lymphoma
- Melanoma
- Rhabdomyosarcoma
- Metastatic carcinoma
- Inflammation


e-cadherin/p120


e-cadherin/p120

e-cadherin/p120



Human Pathology (2020) 102, 54–59

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Original contribution

Invasive plasmacytoid urothelial carcinoma: A comparative study of E-cadherin and P120 catenin ☆

Ankur R. Sangoi MD, Pathologist [a,*], Emily Chan MD PhD, Pathologist [b], Bradley A. Stohr MD PhD, Pathologist [b], L. Priya Kunju MD, Pathologist [c]

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Keywords:
Bladder;
Carcinoma;
CDH1;
E-cadherin;
Plasmacytoid;
P120;
Urothelial

Summary Invasive plasmacytoid urothelial carcinomas (PUCs) are an uncommon aggressive variant, which often shows immunohistochemical loss of E-cadherin, underlying its distinct discohesive histology. The marker P120 (well described in breast pathology as being a diagnostic tool alongside E-cadherin for lobular neoplasia) has not been evaluated in PUCs. Biopsies, transurethral resections, and cystectomies of PUCs were collected, and whole-slide immunohistochemical analysis of E-cadherin and P120 was applied. A subset of cases were also tested for *CDH1* mutation. PUC cases were stratified into morphologic categories of classic, pleomorphic, or desmoplastic. For E-cadherin, 24 of 33 (73%) cases showed an abnormal staining pattern, consisting of complete absence of staining (17/24; 71%) or cytoplasmic staining (7/24; 29%). For P120, 24 of 33 (73%) cases showed an abnormal staining pattern, consisting of loss of membranous staining with cytoplasmic reactivity. Only 2 cases showed a discordant E-cadherin/P120 immunoprofile (94% concordance). Significant staining differences among the 3 morphologic categories were not found. *CDH1* mutation was found in 4 of 8 (50%) of cases, with 3 of 4 (75%) cases showing matched molecular/immunoprofile reactivity. No cases with *CDH1* mutation showed discordant pattern E-cadherin/P120 immunoreactivity. Our rate of aberrant E-cadherin immunoreactivity in PUCs (73%) is similar to a meta-analysis of published cases (74%). We also report an identical rate of aberrant P120 immunoreactivity in PUCs (73%). While PUC remains a histologic diagnosis, in a subset of cases showing a less appreciated pattern (such as desmoplastic) or confounding cytoplasmic E-cadherin reactivity, the utility of paired P120 staining may be a useful diagnostic tool.

Table 2 Immunohistochemical review of E-cadherin in plasmacytoid urothelial carcinomas.

Study	Cases with loss of membranous E-cadherin
Fritsche et al. [8]	5/5 (100%)
Keck et al. [9]	20/31 (65%)
Lim et al. [11]	4/4 (100%)
Keck et al. [10]	16/21 (76%)
Al-Ahmadie et al. [6]	31/31 (100%)
Fox et al. [7]	22/30 (73%)
Perrino et al. [12]	27/48 (57%)
Current	24/33 (73%)
Total	149/203 (73%)

p-120 Catenin is a Useful Diagnostic Biomarker for Distinguishing Plasmacytoid and Sarcomatoid Variants From Conventional Urothelial Carcinoma

Andres M. Acosta, MD; Justine Barletta, MD; Guru Sonpavde, MD; Stuart Schnitt, MD; Michelle S. Hirsch, MD, PhD

• *Context.*—Plasmacytoid urothelial carcinoma (PC-UC) is an aggressive variant of urothelial carcinoma (UC), characterized by loss of E-cadherin (E-Cad)–mediated intercellular adhesion. Loss of E-Cad by immunohistochemistry can help diagnosis PC-UC; however, sensitivity is limited. Expression of other cadherin-catenin adhesion complex members, that is, p-120 catenin (p-120) and β-catenin (B-Cat), which are diagnostically useful for lobular breast carcinoma, remains unknown in UC.

Objective.—To determine the utility of p-120 and B-Cat in conventional and variant UC.

Design.—E-cadherin, B-Cat, and p-120 immunohistochemistry was performed in 25 conventional UCs and 33 variant UCs, including 22 PC-UCs, 6 sarcomatoid UCs (SUCs), and 5 micropapillary UCs. Membranous staining for all biomarkers was considered normal; however, any cytoplasmic staining or an absence of staining was considered diagnostically abnormal. Next-generation sequencing was performed on 8 PC-UC cases.

Results.—E-cadherin, B-Cat, and p-120 showed membranous staining in all conventional and micropapillary UCs. In contrast, most PC-UCs were negative for E-Cad (17 of 22; 77%) with an additional 2 of 22 cases (9%) showing cytoplasmic with partial membranous staining. p-120 catenin demonstrated cytoplasmic or negative staining in 21 of 22 cases (95%). Most SUCs showed an absence of E-Cad (5 of 6; 83%) and cytoplasmic or negative p-120 in 5 of 6 cases (83%). Staining for B-Cat was also abnormal in a subset of PC-UCs and SUCs. Five PC-UC cases that harbored *CDH1* gene variants were p-120 cytoplasmic positive.

Conclusions.—p-120 catenin is a useful adjunct biomarker to E-Cad in the clinically important distinction of PC-UC and SUC from conventional UC. In particular, the combination of cytoplasmic p-120 and loss of E-Cad is strongly supportive of PC-UC and SUC.

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2020-0262-OA)

Table 3. Summary of Normal Versus Abnormal Immunostaining Results in Plasmacytoid Urothelial Carcinoma (PC-UC) and Sarcomatoid Urothelial Carcinoma (SUC)[a]

	PC-UC (n = 22)		SUC (n = 6)	
	Normal, No. (%)	Abnormal, No. (%)	Normal, No. (%)	Abnormal, No. (%)
E-Cad	3 (13.5)	19 (86.5)	1 (17)	5 (83)
B-Cat	6 (27.5)	16 (72.5)	4 (67)	2 (33)
p-120	1 (4.5)	21 (95.5)	1 (17)	5 (83)

Abbreviations: B-Cat, β-catenin; E-Cad, E-cadherin; p-120, p-120 catenin.

Plasmacytoid urothelial carcinoma

- classic category
  - small discohesive cells with eccentric nuclei, including well-formed signet ring cells, in linear or dispersed single cell pattern
- Pleomorphic category
  - cells with enlarged irregular nuclei
- Desmoplastic category
  - infiltrative tumor cells associated with marked stromal desmoplasia

Plasmacytoid urothelial carcinoma

- Loss of e-cadherin due to *CDH1* mutation or promotor hypermethylation
  - 84%; specific for this variant
- **No association with *CDH1* germline mutation**
- **Loss of e-cadherin IHC NOT specific**

Plasmacytoid urothelial carcinoma

- Aggressive variant, poor prognosis

Plasmacytoid Carcinoma of the Bladder: A Urothelial Carcinoma Variant With a Predilection for Intraperitoneal Spread

Roberto Rafael Ricardo-Gonzalez, Michael Nguyen, Neriman Gokden, Ankur R. Sangoi, Joseph C. Presti, Jr.* and Jesse K. McKenney†

From the Departments of Pathology (RRRG, MN, ARS, JKM) and Urology (JCP, JKM), Stanford University Medical Center, Stanford and Department of Pathology, El Camino Hospital (ARS), Mountain View, California, and Department of Pathology, University of Arkansas for Medical Sciences (NG), Little Rock, Arkansas

Submitted for publication July 7, 2011.
Study received institutional review board approval.
* Financial interest and/or other relationship with Progros DX and Myriad.
† Correspondence: Department of Pathology, Stanford University Medical Center, 300 Pasteur Dr., Room L235, Stanford, California 94305 (e-mail: jmck@stanford.edu).

For another article on a related topic see page 1071.

Purpose: Bladder plasmacytoid carcinoma is an invasive urothelial carcinoma subtype that is emphasized for its morphological overlap with plasma cells and metastatic carcinoma. Our experience suggests frequent intraperitoneal spread that is not typical of conventional urothelial carcinoma.
Materials and Methods: We identified cases of plasmacytoid urothelial carcinoma diagnosed on radical cystectomy. Patient age, gender, American Joint Committee on Cancer (7th edition) stage, metastatic spread/recurrence sites and clinical disease status at last followup were recorded.
Results: A total of 10 male and 5 female patients 42 to 81 years old were identified. One tumor was pT2, 11 pT3 and 3 pT4. Six of 15 patients (40%) presented with lymph node metastasis and 5 (33%) had intraperitoneal metastasis at cystectomy. These initial sites of metastatic spread included the prerectal space, ovary and vagina, ovary and fallopian tube, bowel serosa, and omentum and bowel serosa in 1 case each. Three patients had subsequent metastasis involving the prerectal space, pleural fluid and small bowel serosa, and bowel serosa in 1 each. Eight patients had followup information available, including 3 who died of disease, 3 with disease and 2 with no evidence of disease.
Conclusions: Of the patients 33% with the plasmacytoid variant of urothelial carcinoma presented with intraperitoneal disease spread and 20% had subsequent metastasis involving serosal surfaces. The possibility of noncontiguous intraperitoneal spread involving serosal surfaces should be recognized to ensure proper intraoperative staging and clinical followup for patients with plasmacytoid carcinoma.

THE JOURNAL OF UROLOGY®

Vol. 187, 852-855, March 2012

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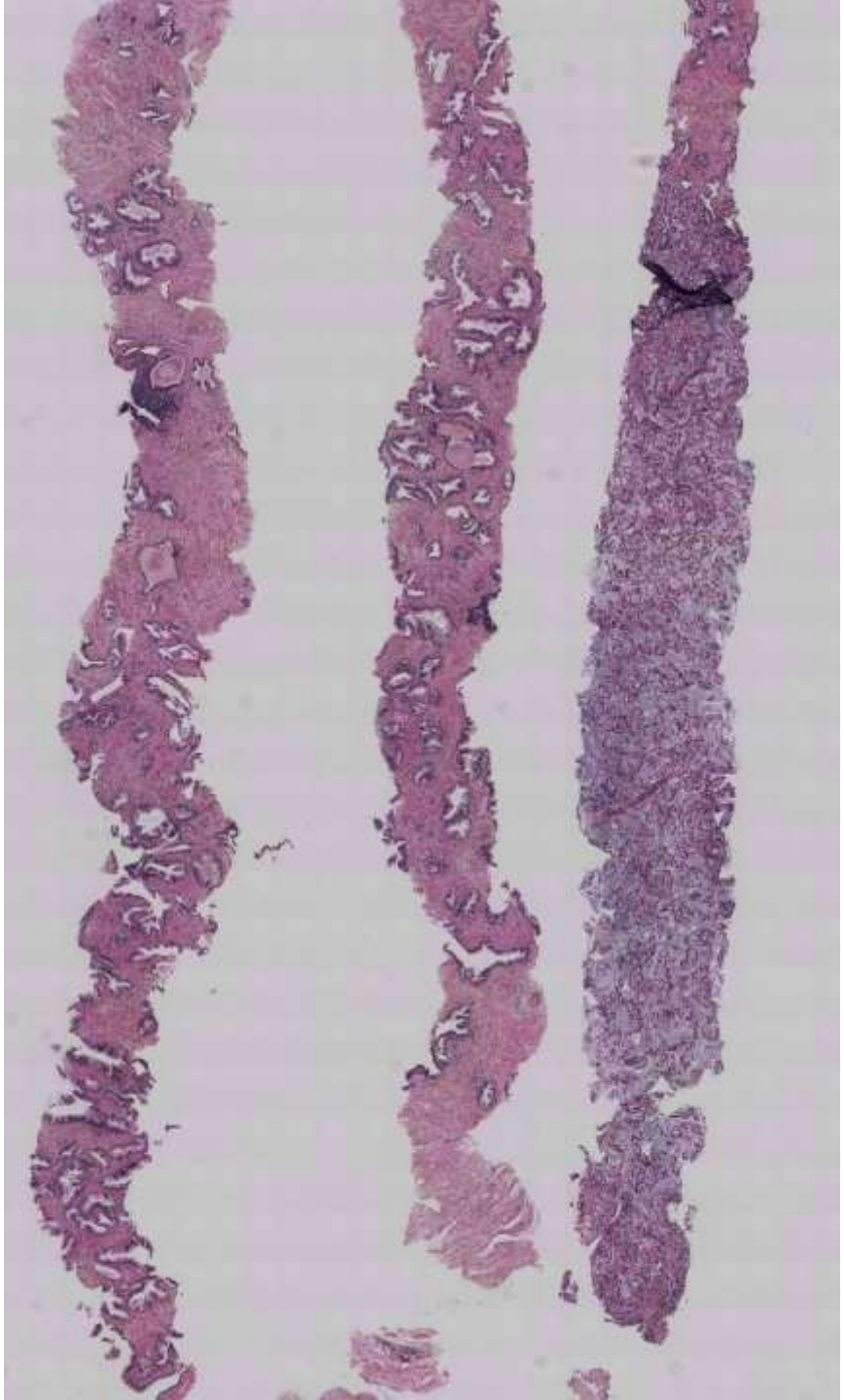
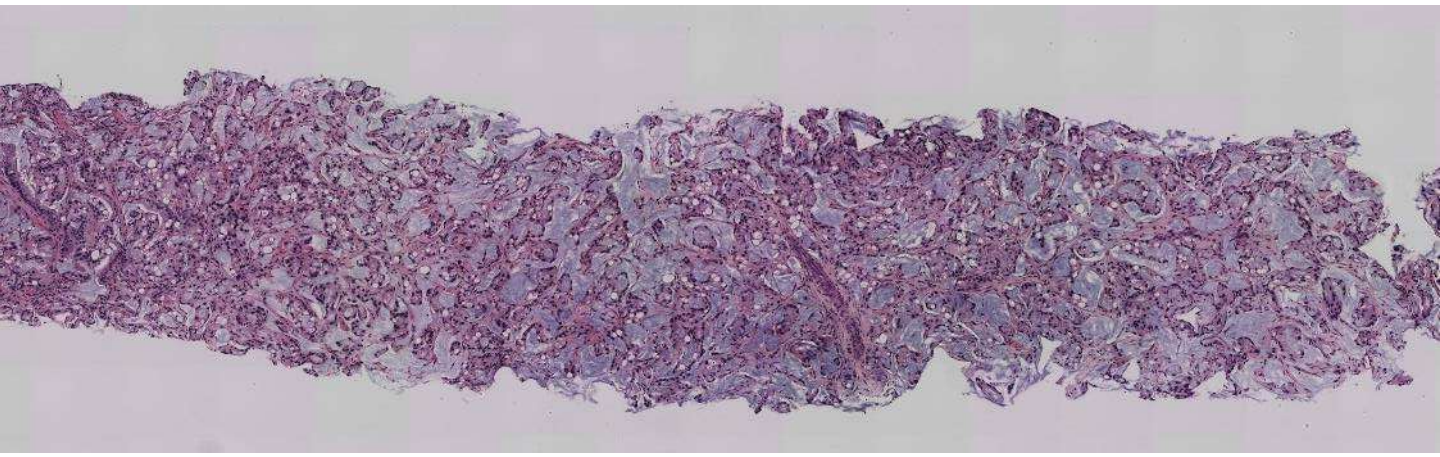
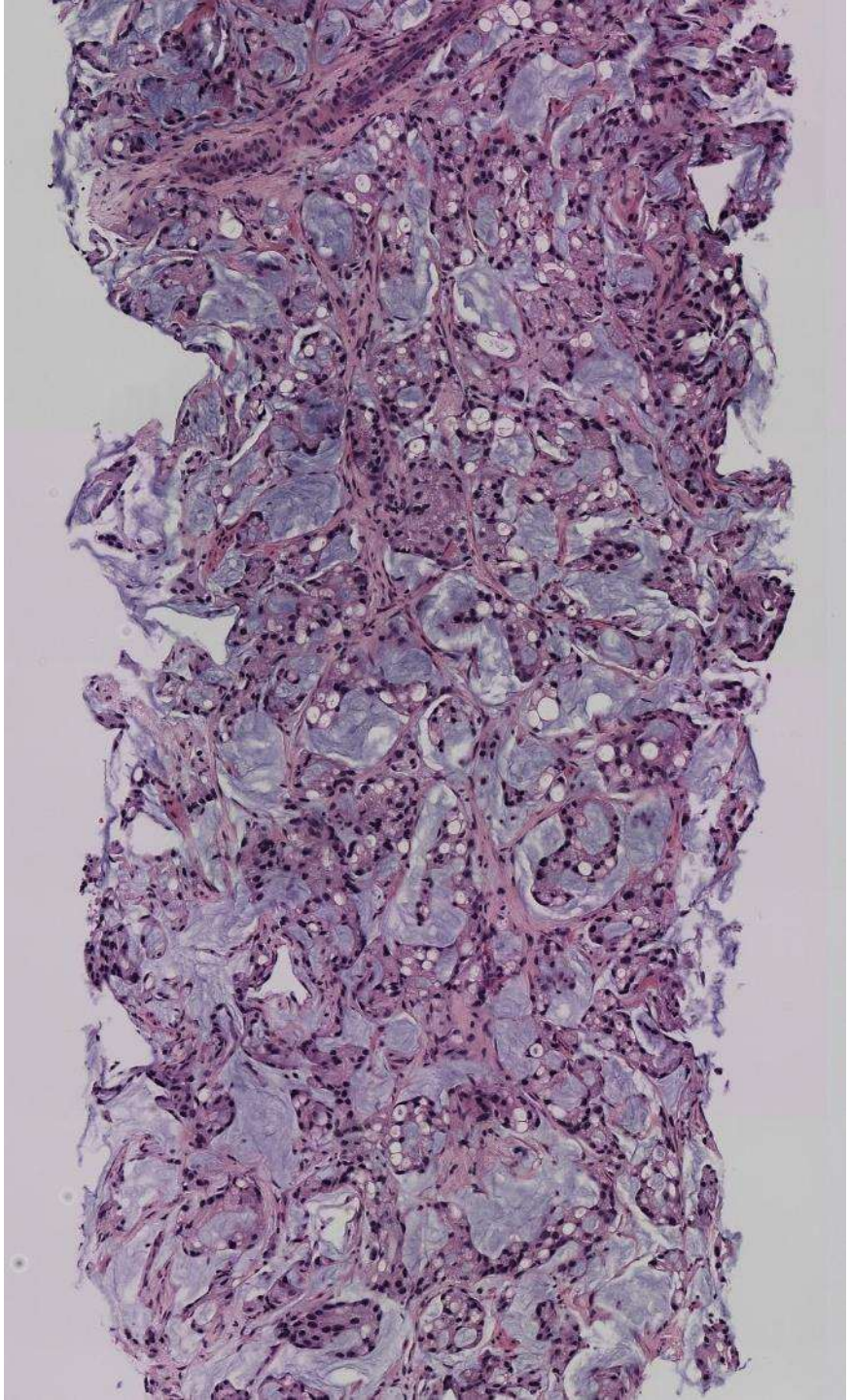
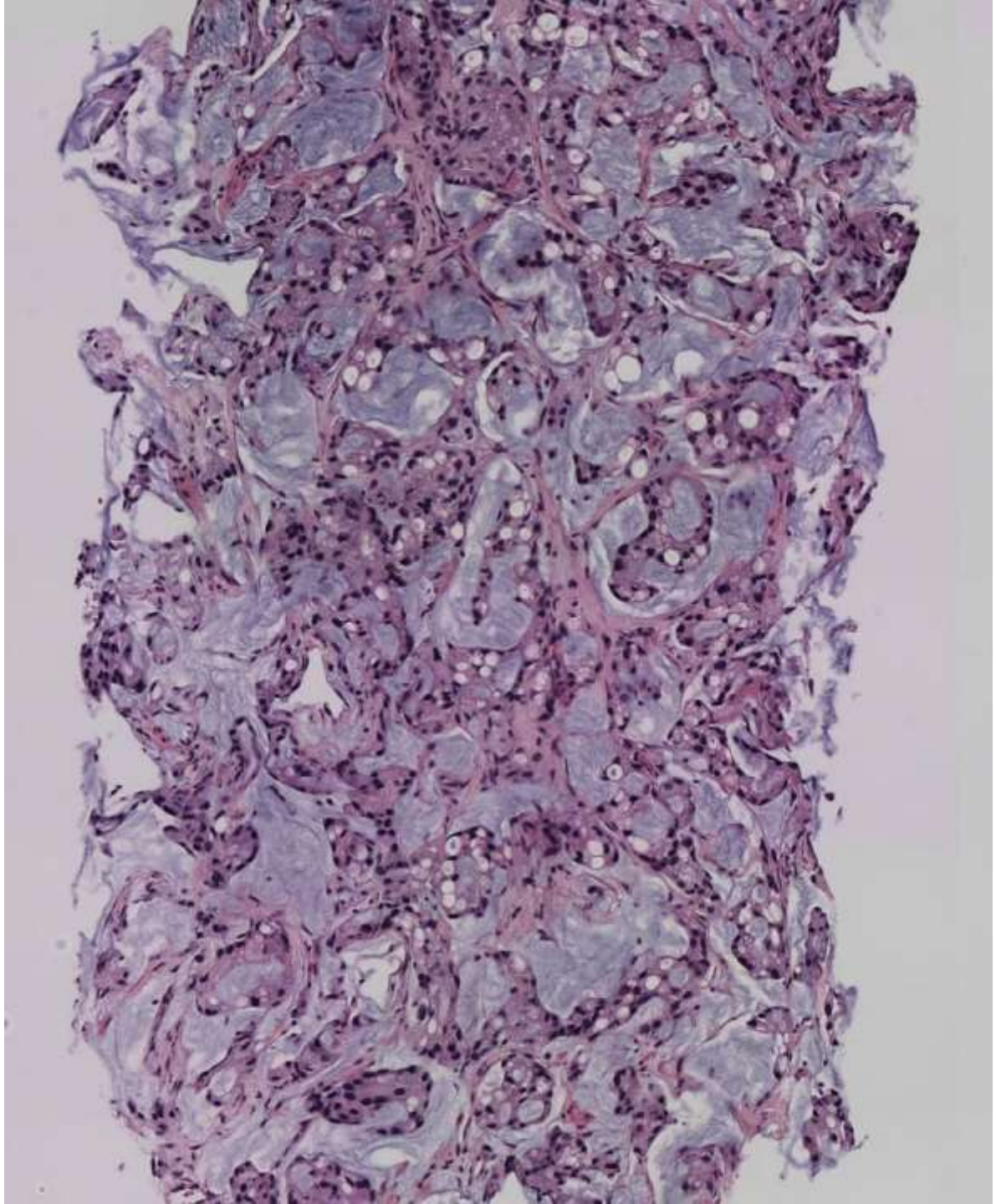
Ankur Sangoi; El Camino Hospital

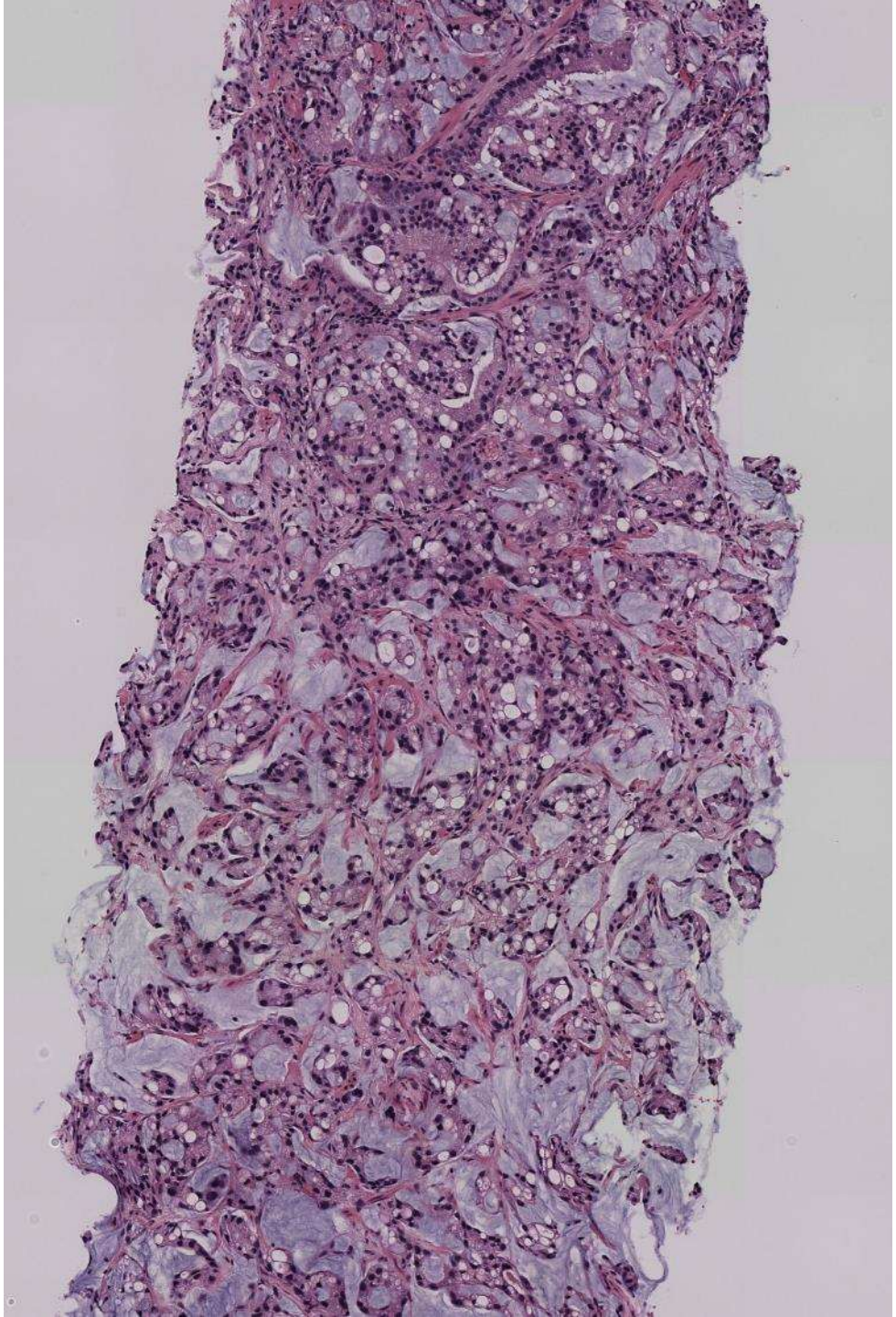
67-year-old M with elevated PSA, undergoes prostate biopsy.

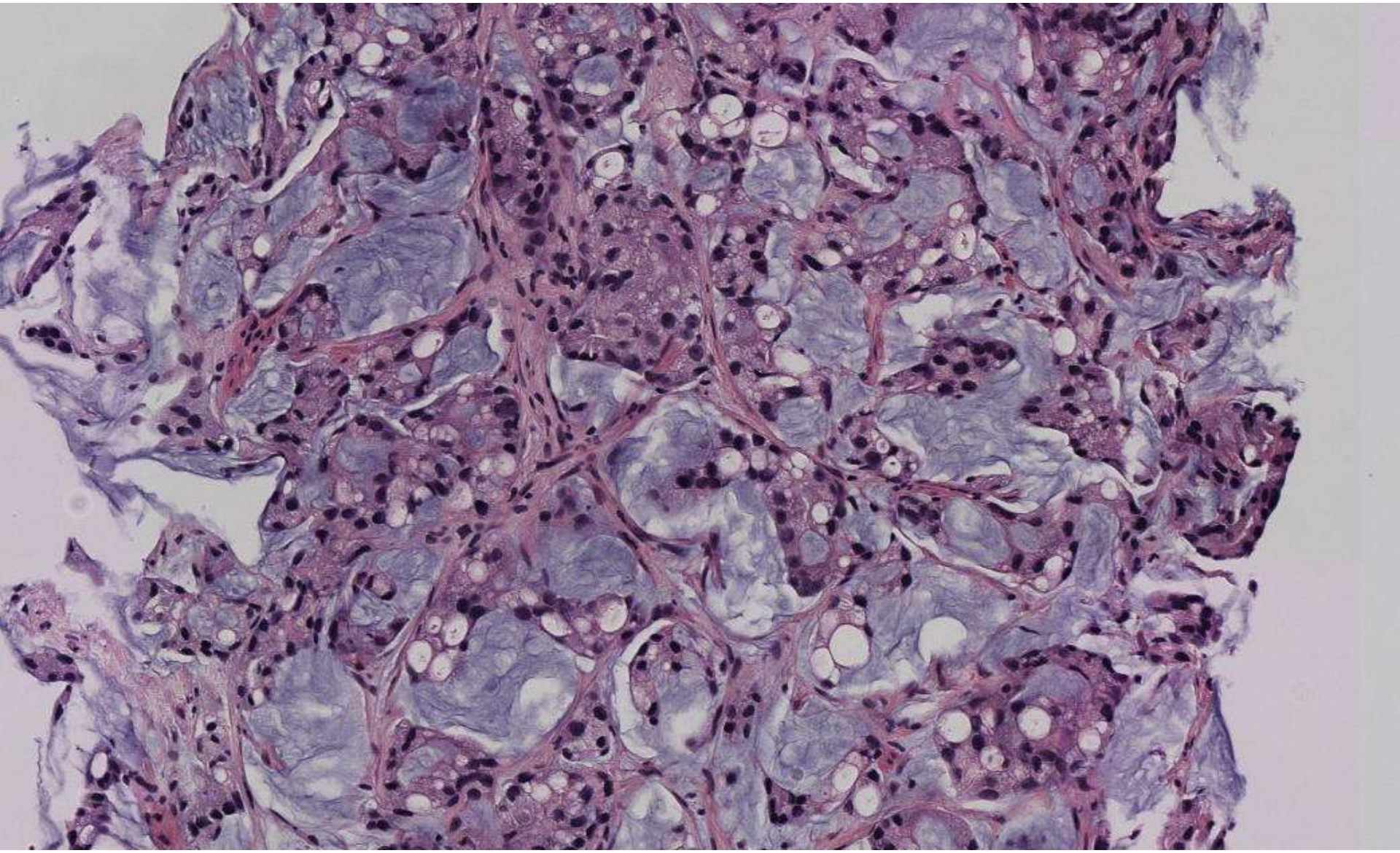


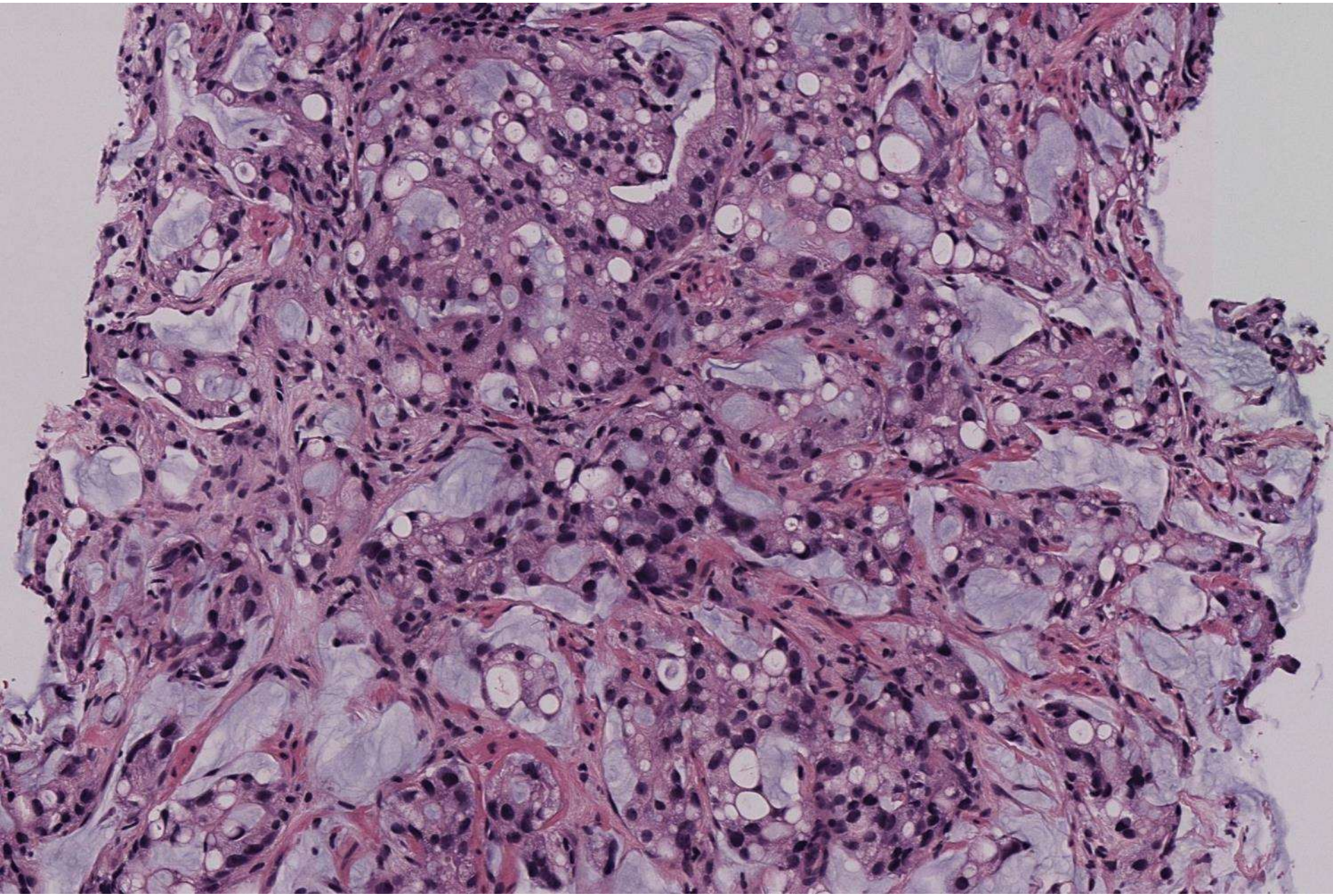












DDx

- Mucinous prostatic adenocarcinoma
- Prostatic adenocarcinoma with mucinous features
- Urothelial/urethral adenocarcinoma
- Metastasis/direction invasion
- Nephrogenic adenoma
- Mucinous metaplasia

Prostatic mucinous adenoca

- Intra and extracellular mucin must comprise 25%+ of tumor

- Grading:

Am J Surg Pathol • Volume 44, Number 8, August 2020

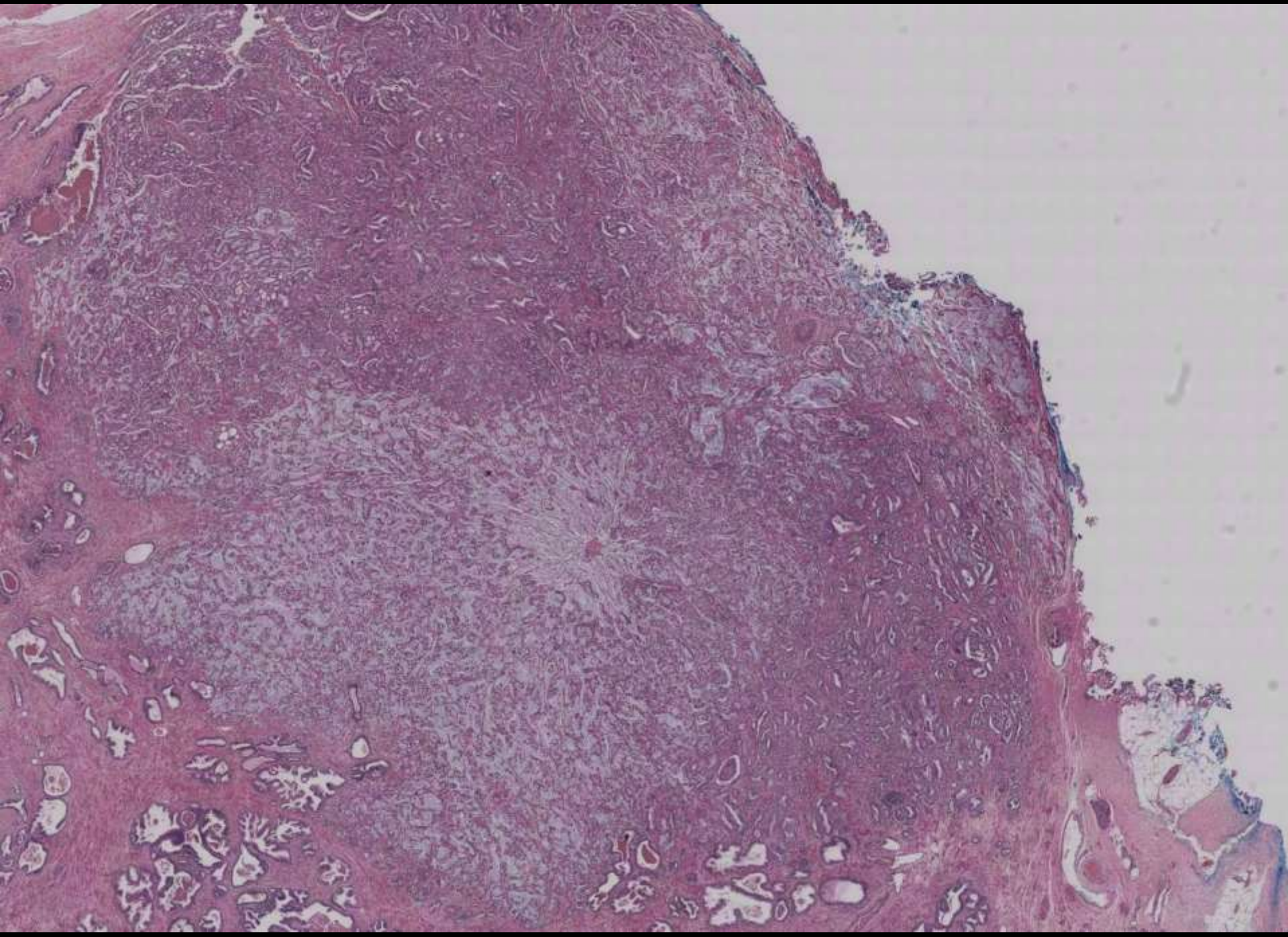
TABLE 1. ISUP 2014 Modifications to Growth Patterns and Grade Grouping of Prostatic Carcinoma[1]

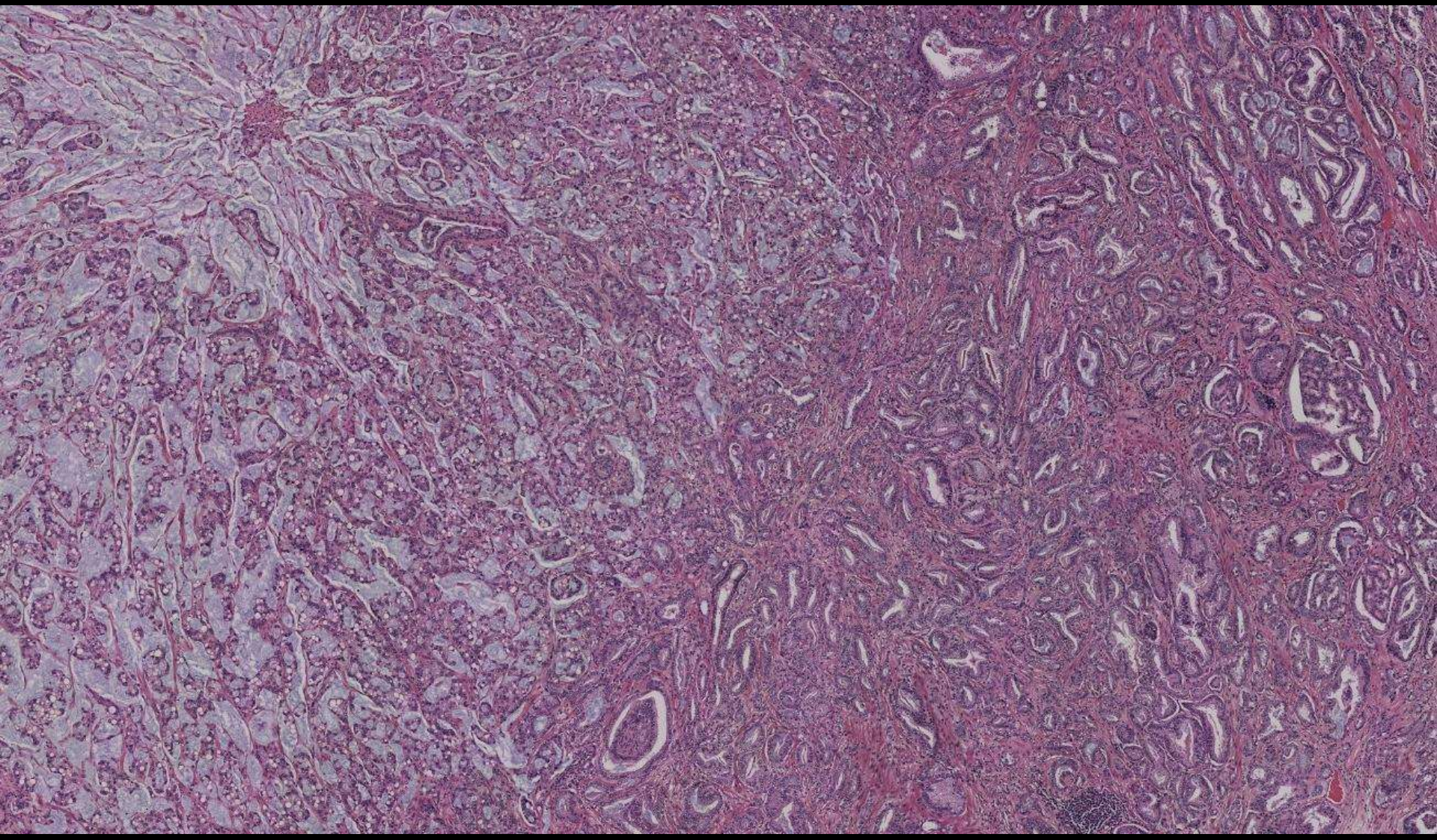
Assign cribriform glands as Gleason pattern 4, irrespective of size
Assign glomeruloid glands as Gleason pattern 4, irrespective of size
Grade mucinous carcinoma of the prostate based on its underlying growth pattern rather than grading them all as pattern 4
Do not assign a Gleason grade to IDC of the prostate without invasive carcinoma. Make a comment on its very strong association with aggressive prostate cancer
Use the 2014 modified 5-tier grading system[1] in conjunction with the Gleason system

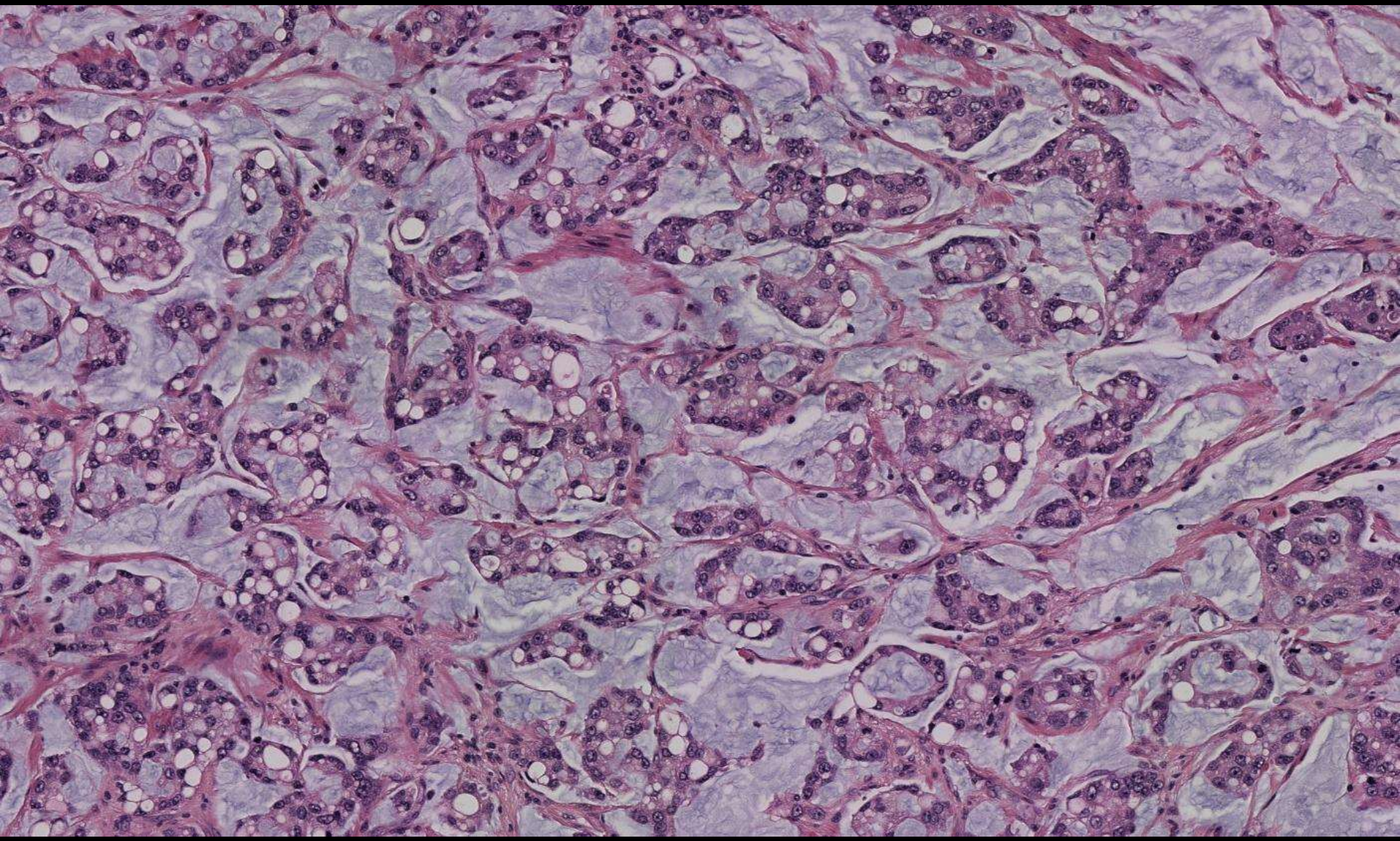
Sometimes easier said than done…

Dx for prostate bx

- Mucinous prostatic adenocarcinoma
- **Prostatic adenocarcinoma with mucinous features**
- Urothelial/urethral adenocarcinoma
- Metastasis/direction invasion
- Nephrogenic adenoma
- Mucinous metaplasia







Radical prostatectomy

- **Mucinous prostatic adenocarcinoma**

  Gleason grade 4+3 (Grade group 3)

  Margin positive

  pT2

  Follow-up: no recurrence/mets to date

MUCINOUS ADENOCARCINOMA OF THE PROSTATE DOES NOT CONFER POOR PROGNOSIS

BRIAN R. LANE, CRISTINA MAGI-GALLUZZI, ALWYN M. REUTHER, HOWARD S. LEVIN, MING ZHOU, AND ERIC A. KLEIN

ABSTRACT

Objectives. To report a series of patients with mucinous (colloid) adenocarcinoma (MC) at prostatectomy who were treated at a single institution from 1987 to 2005. MC is a rare form of prostate cancer reported in some cases to have a more aggressive clinical course than conventional adenocarcinoma (AC).

Methods. Radical prostatectomy specimens with mucinous features were identified from a database of 3613 consecutive patients. Each case was reviewed again by a single pathologist who confirmed the diagnosis of MC in 14 patients. MC was defined by the presence of pools of extracellular mucin in more than 25% of the tumor. Eighteen additional cases were identified in which the mucinous component occupied only a small portion of the tumor and were referred to as AC with focal mucin (AFM). The biochemical and overall survival of 26 patients with MC or AFM who had completed ≥6 months of follow-up was analyzed using Kaplan-Meier estimates.

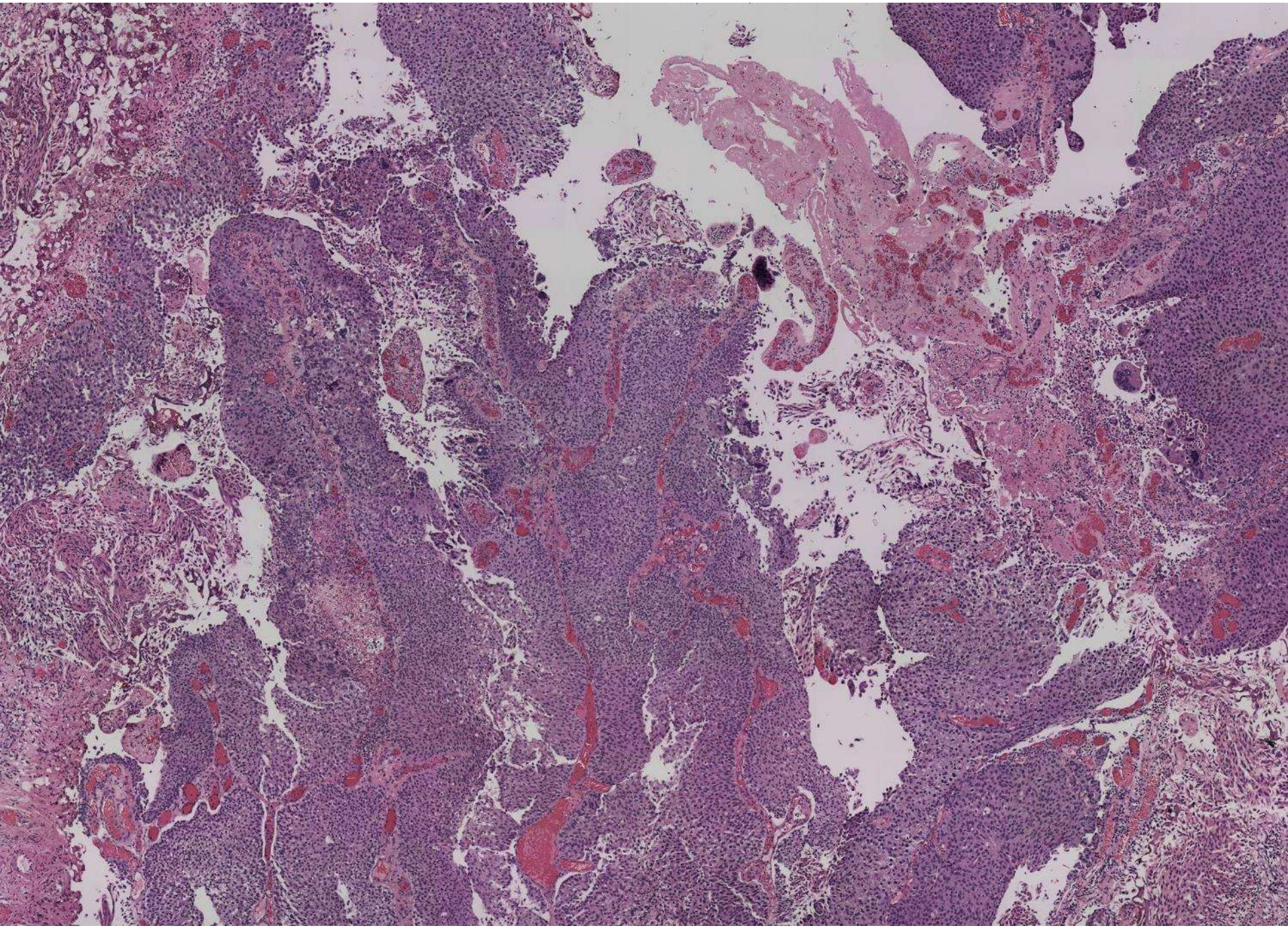
Results. No patients with MC or AFM died of disease, and 11 (91.7%) of 12 patients with MC and 9 (64.3%) of 14 patients with AFM were clinically and biochemically free of disease. No significant difference was found in biochemical recurrence or overall survival between those with MC or AFM and a matched group of patients with AC.

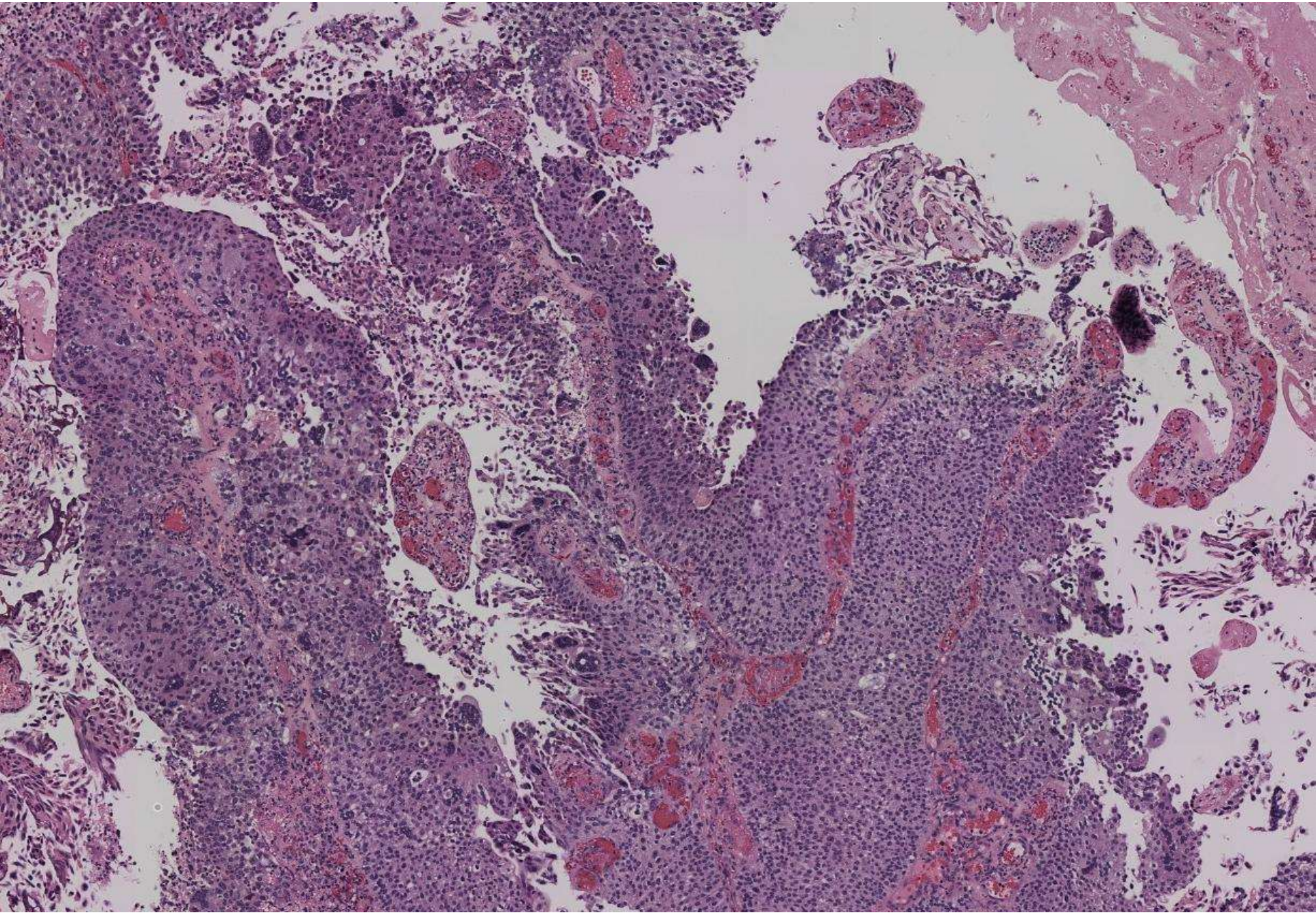
Conclusions. We report what we believe to be the largest published series of cases of MC (n = 14) with a median overall follow-up of 6.4 years. MC appears to behave clinically in a similar fashion to AC, with no statistically significant difference in biochemical failure or survival. UROLOGY **68**: 825–830, 2006.

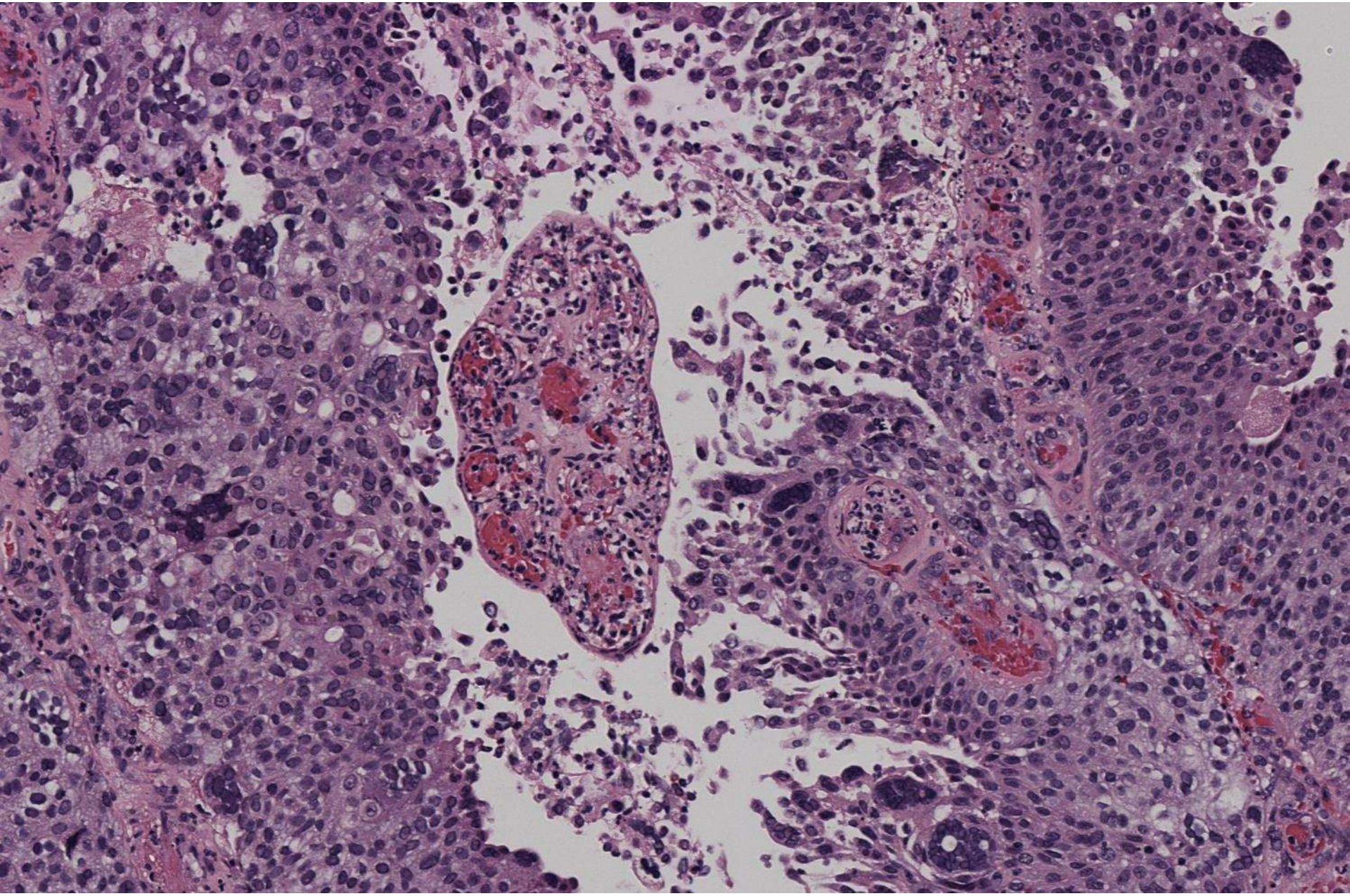
21-0608
scanned slide available!

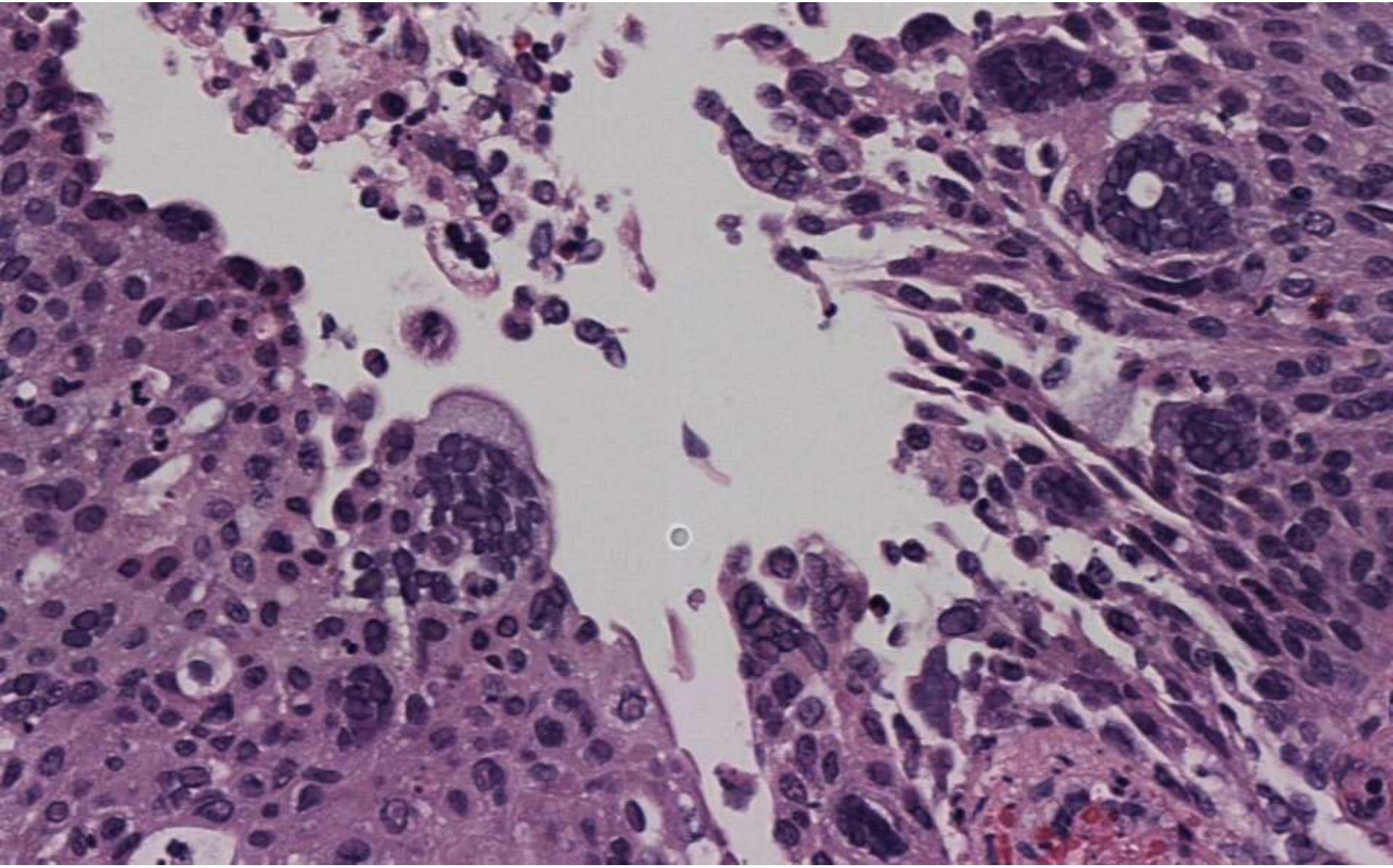
Ankur Sangoi; El Camino Hospital

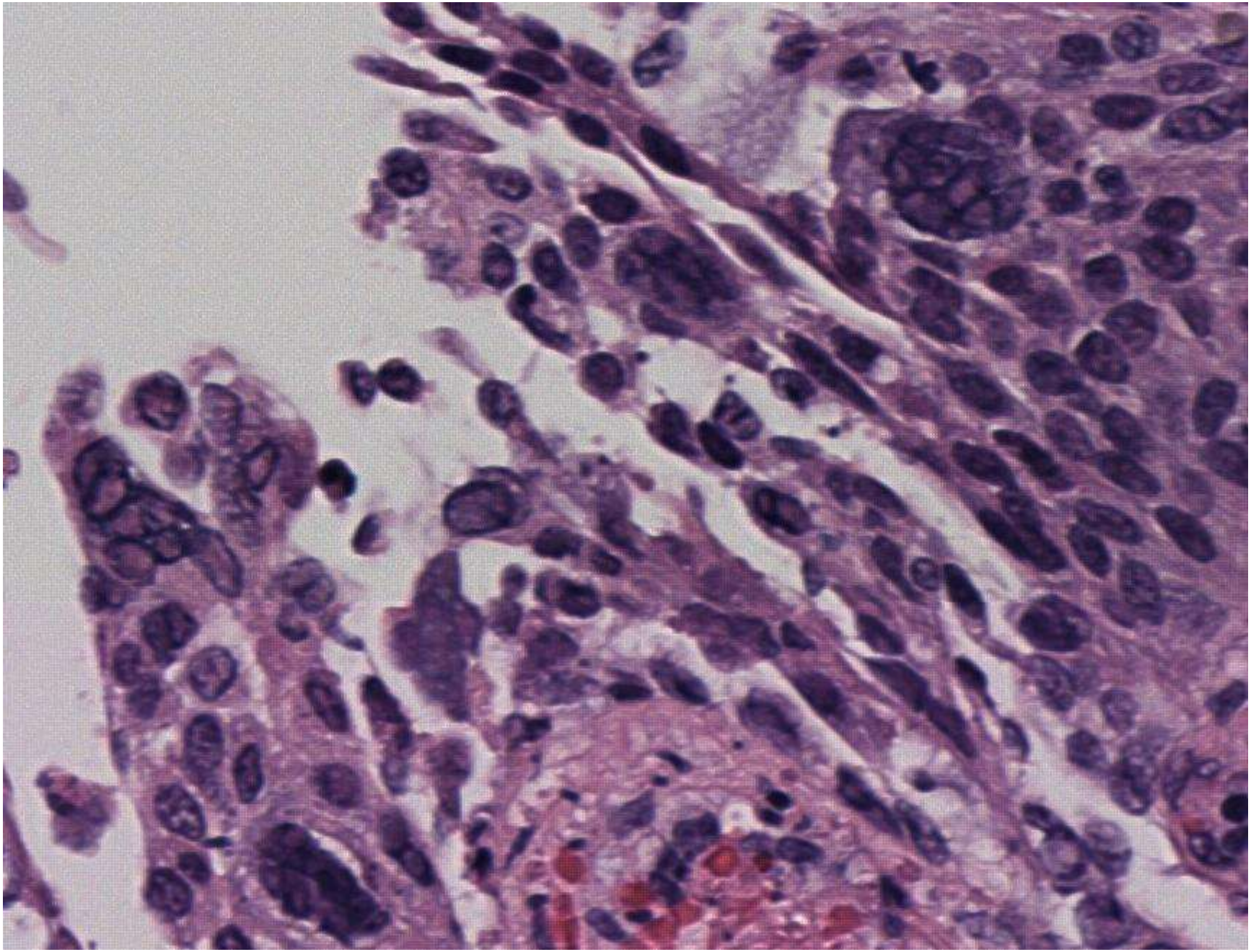
80-year-old F presents with hematuria, undergoes TURBT.

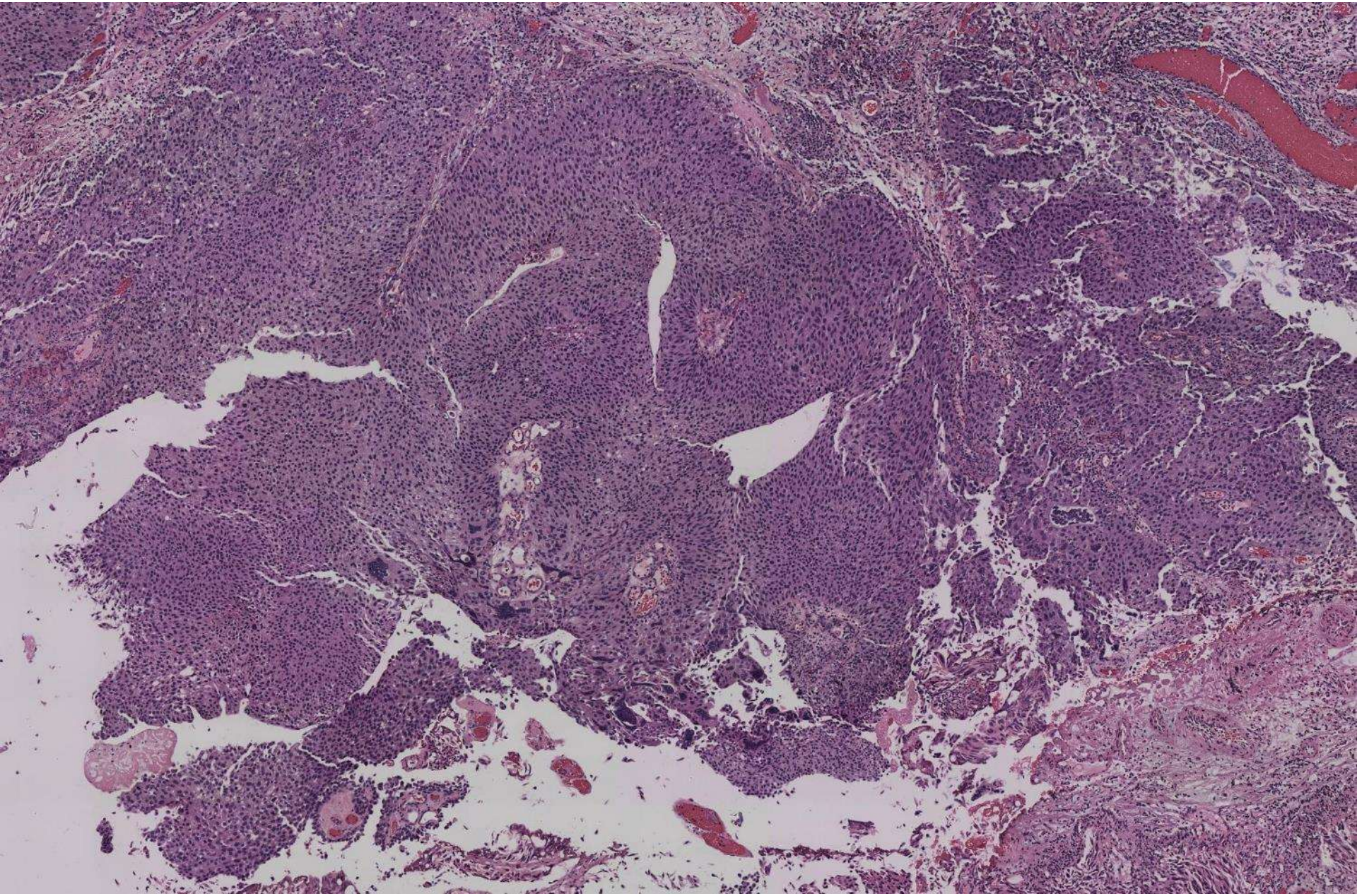


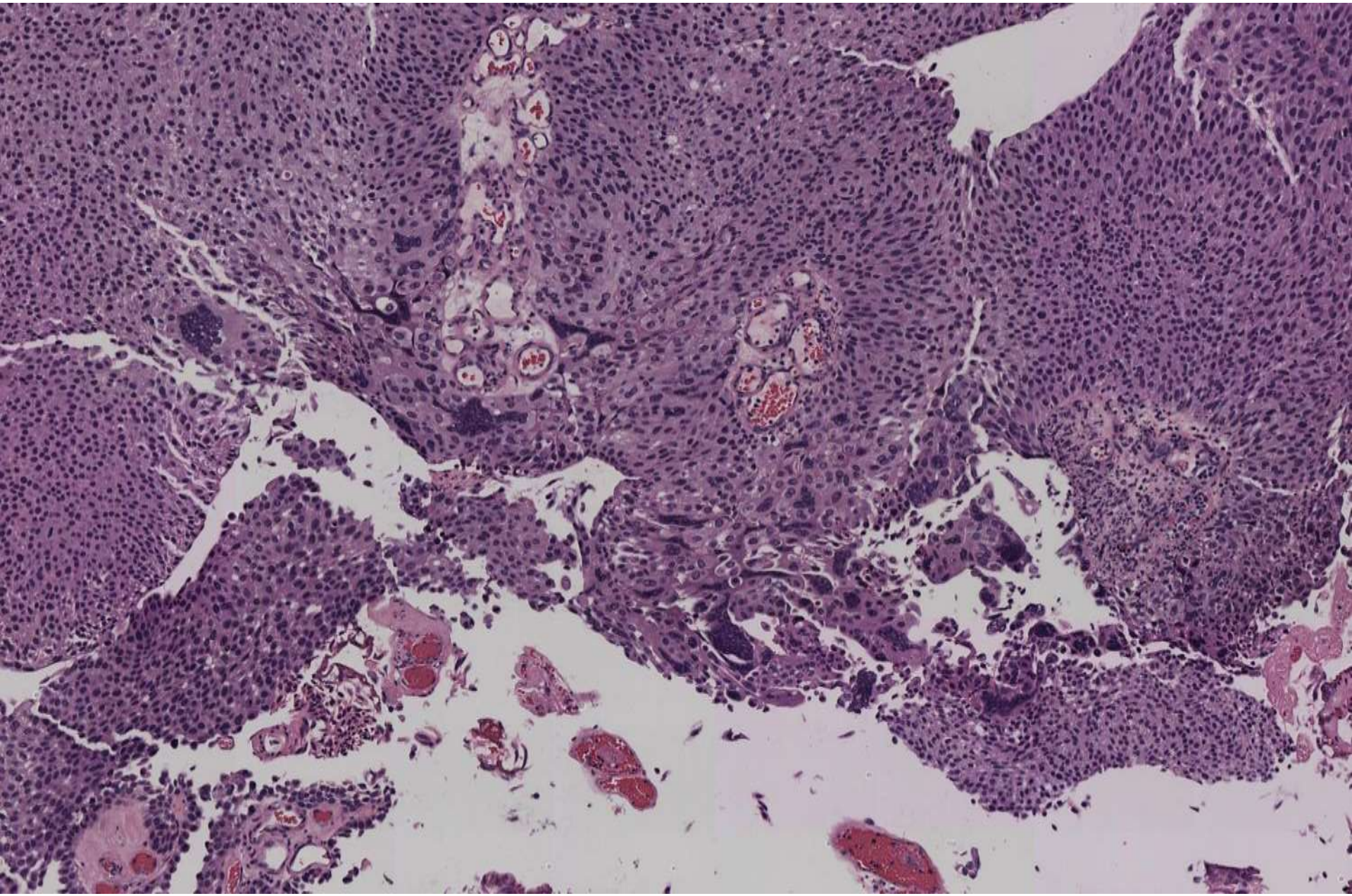


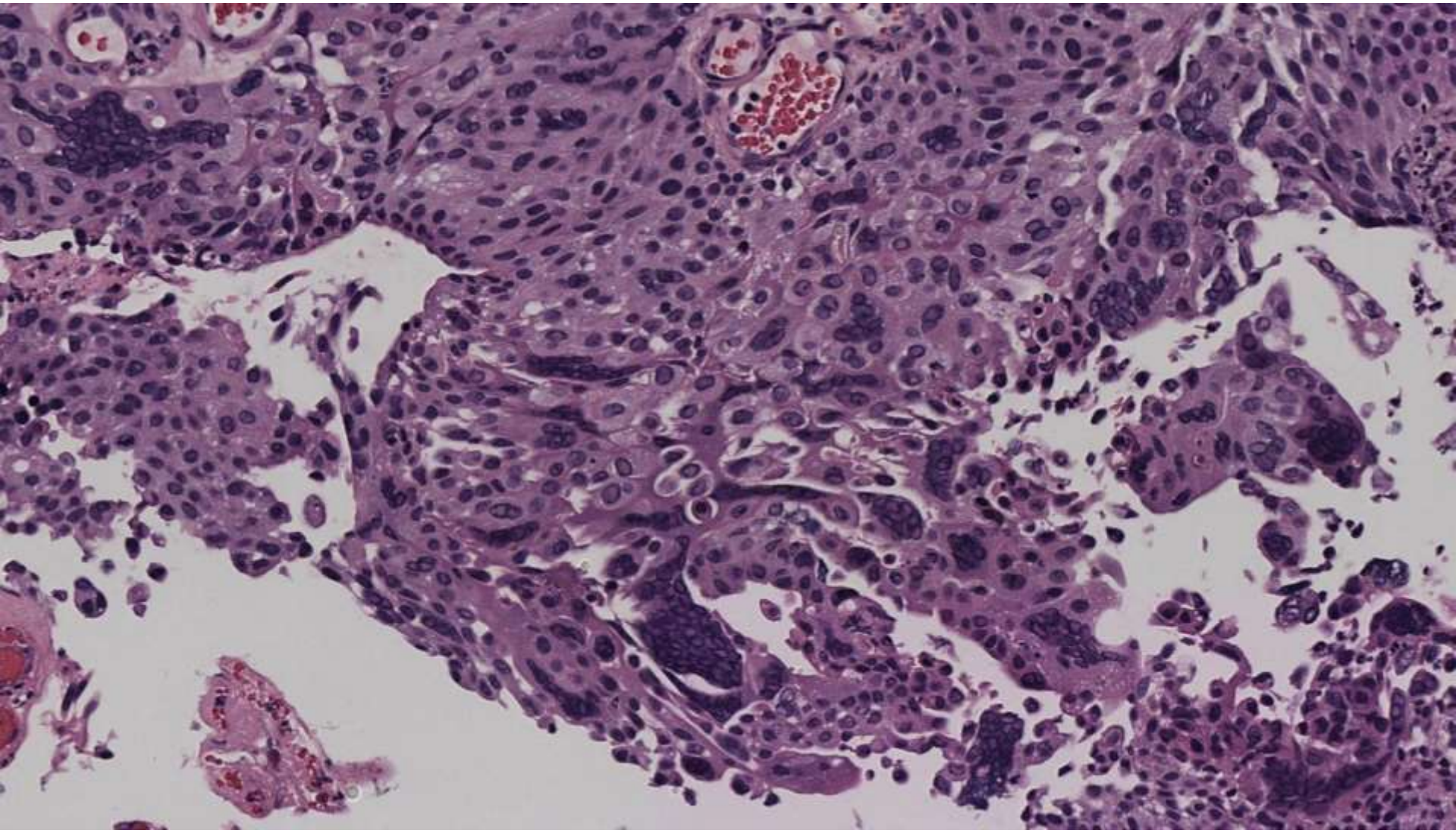


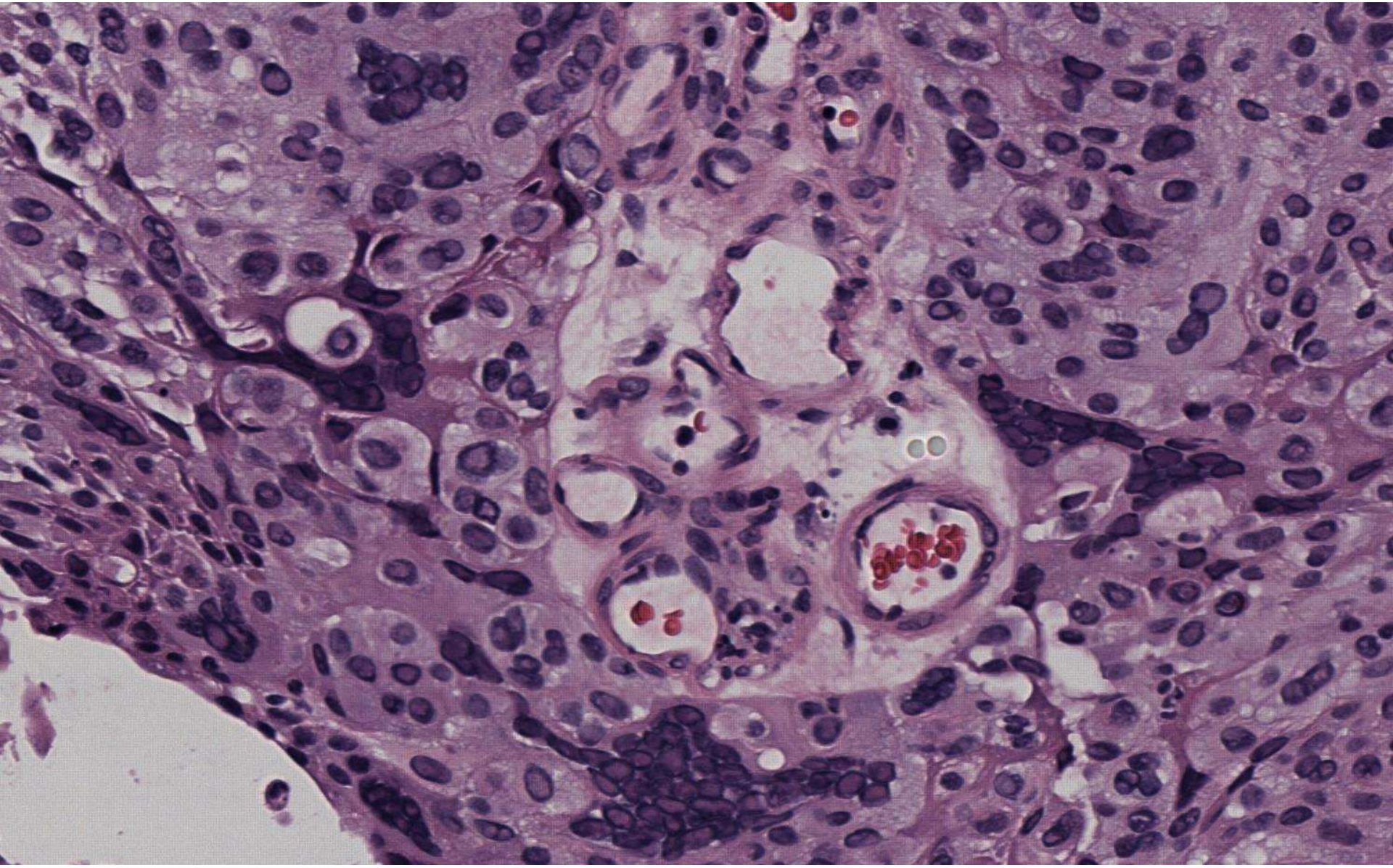


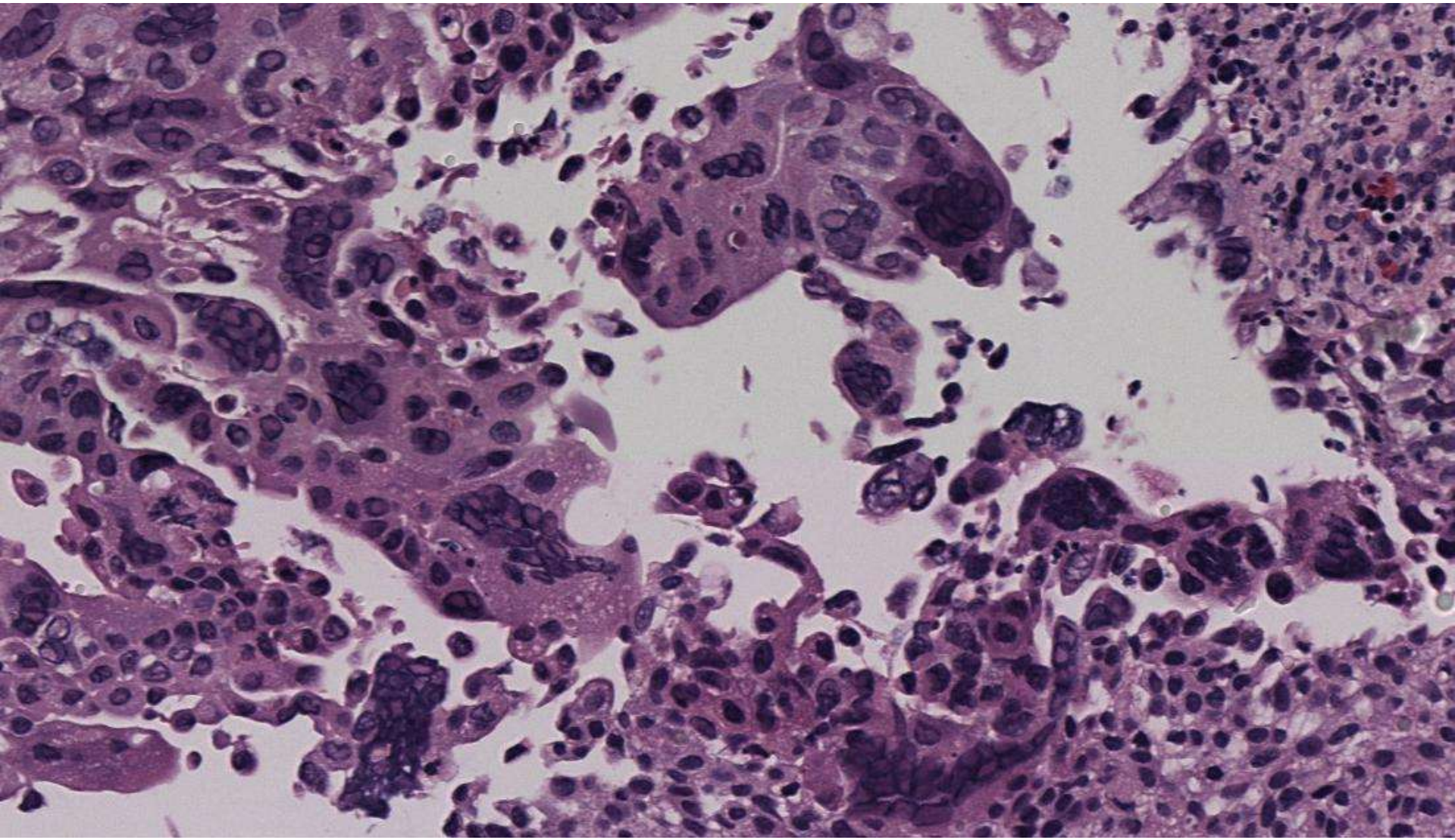


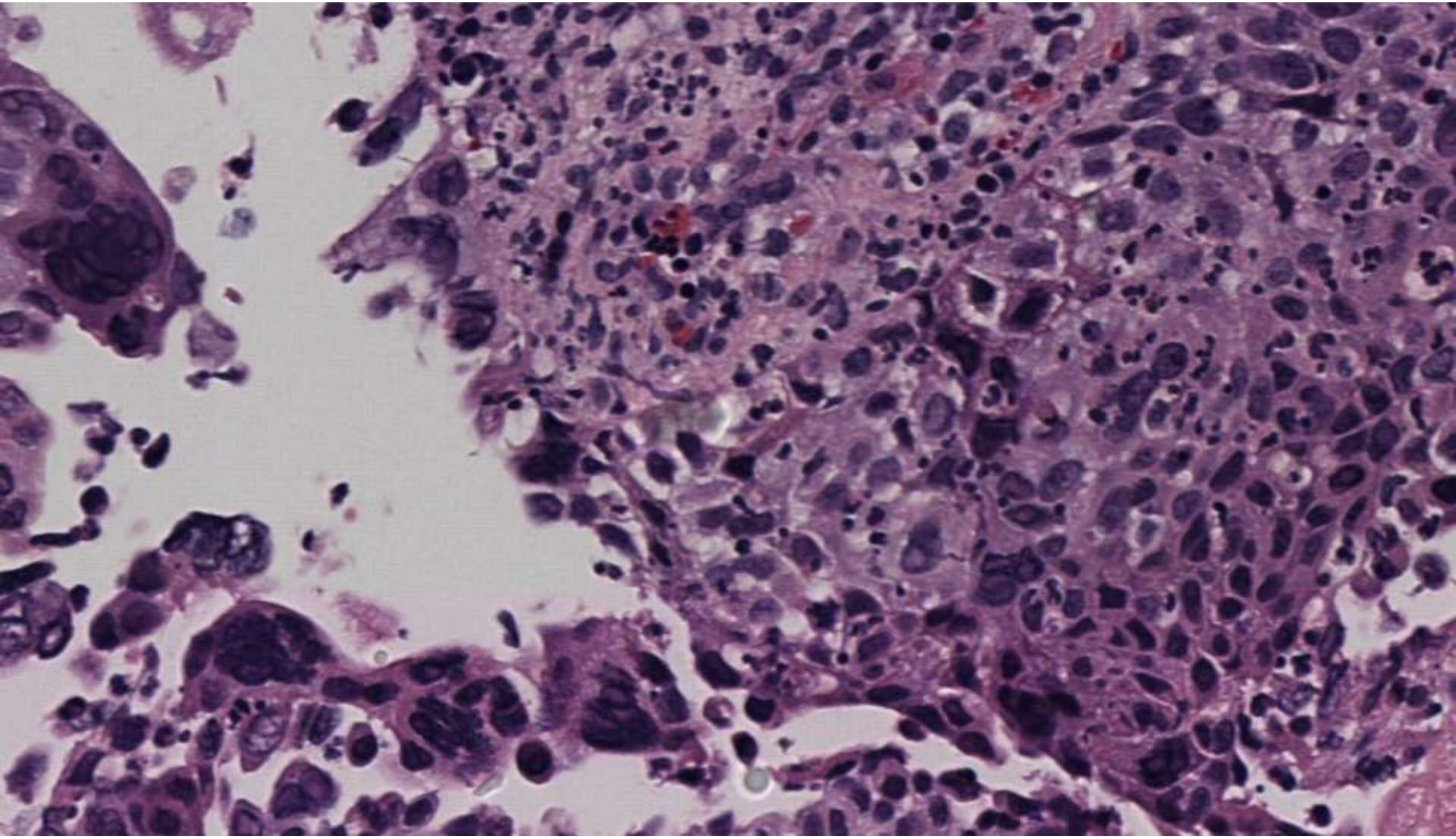








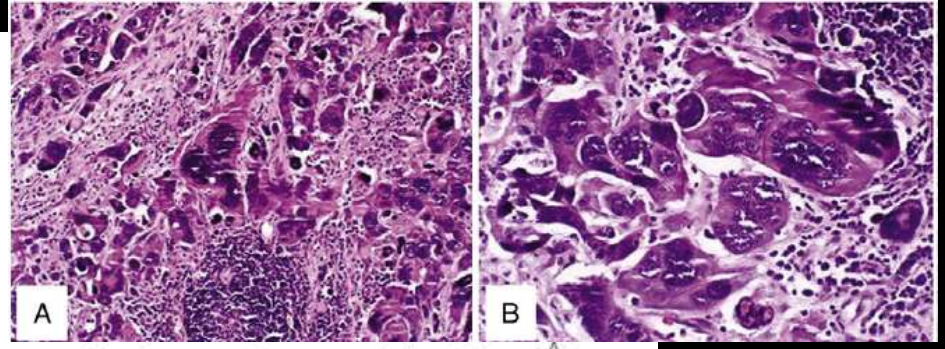




DDx

- Papillary urothelial carcinoma + HSV
- Pleomorphic giant cell variant urothelial carcinoma
- Urothelial carcinoma with trophoblastic differentiation

Human Pathology (2009) 40, 1461–1466



ELSEVIER

Original contribution

Pleomorphic giant cell carcinoma of the urinary bladder☆

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Keywords:
Bladder carcinoma;
Giant cell carcinoma;
Pleomorphic carcinoma

Summary In this report, we present the clinicopathologic features of 8 cases of the pleomorphic giant cell variant of urothelial carcinoma. This is a rare variant of bladder cancer recognized by the current World Health Organization classification of urologic tumors. The pleomorphic giant cell component varied from 20% to 100% of the tumor specimen; in 2 cases, the pleomorphic giant cell component composed greater than 50% of the tumor with 1 case showing pure pleomorphic giant cell carcinoma. The architectural pattern of the tumor varied from infiltrating pleomorphic tumor with bizarre giant cells to solid expansile nests with discohesive growth pattern; a hypocellular desmoplastic stromal response was present in 2 cases (25%) with single cells in sclerotic stroma. At histology, giant, bizarre, anaplastic cells with frequent typical or atypical mitotic figures were present in all cases. Seven mixed cases had concurrent conventional high-grade urothelial carcinoma; 2 cases presented features of micropapillary or lymphoepithelioma-like urothelial carcinoma. Variable size intracytoplasmic vacuoles were present in 2 cases. All patients had advanced-stage cancer (≥pT3), and 6 (75%) had lymph node metastases. Immunohistochemical staining demonstrated that both pleomorphic giant cell and associated conventional urothelial carcinoma were positive for cytokeratins 7, CAM 5.2 and AE1/AE3, and epithelial membrane antigen; P63, thrombomodulin, and uroplakin III were positive in 6, 3, and 2 cases, respectively. Follow-up information was available in all cases (range, 6-74 months; mean, 20 months). Five of the patients died of disease from 6 to 17 months, and 2 patients were alive with metastases at 11 and 19 months. One patient had no evidence of disease at 74 months. In summary, pleomorphic giant cell is an aggressive variant of urothelial carcinoma associated with poor prognosis that presents at an advanced clinical stage. In limited samples, it may be misdiagnosed as secondary carcinoma or sarcoma, a pitfall of paramount importance for its clinical management.

Urothelial Carcinomas With Trophoblastic Differentiation, Including Choriocarcinoma

Clinicopathologic Series of 16 Cases

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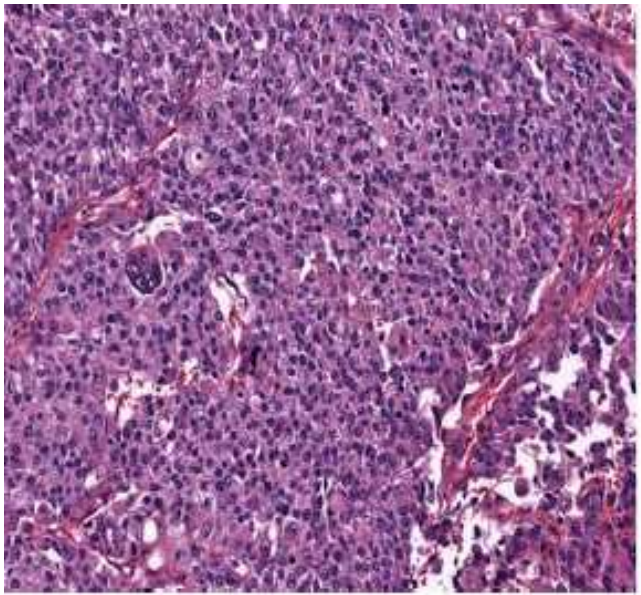
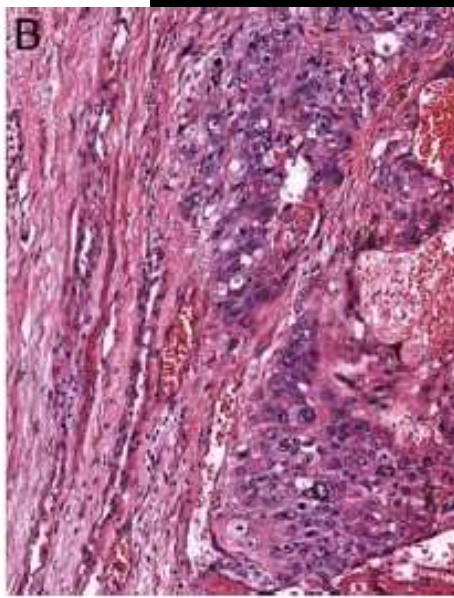
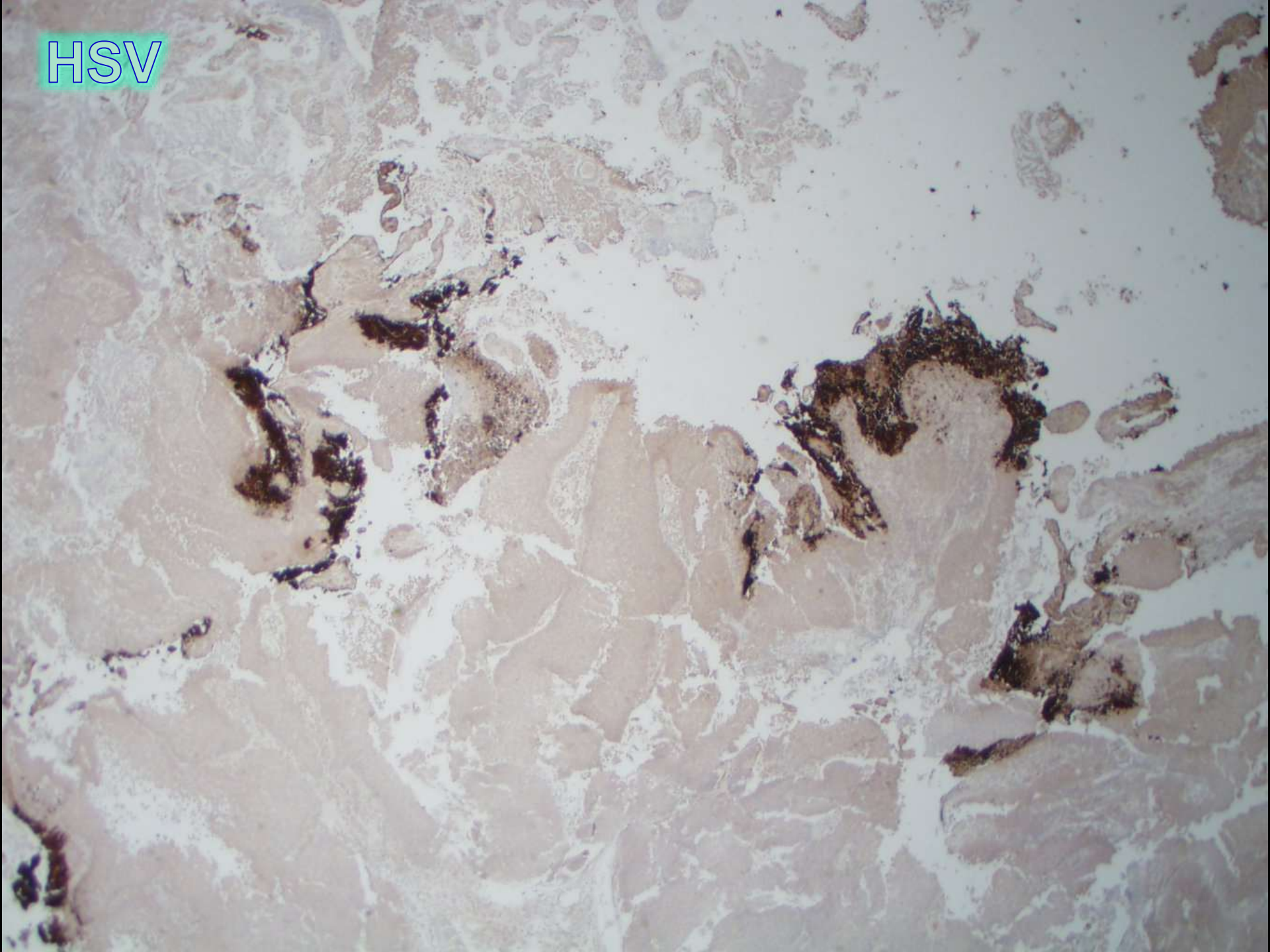
Abstract: Trophoblastic differentiation (including choriocarcinoma) arising in urothelial carcinoma has been described in numerous case reports, but never in a single series. We present a series of these tumors, describing the morphologic spectrum, applying traditional and novel immunohistochemical stains, and characterizing clinical follow-up. We identified 16 cases, arising predominantly in the bladder (N = 14), but also the ureter (N = 1) and prostatic urethra (N = 1). Six of our cases (38%) contained invasive urothelial carcinoma with admixed syncytiotrophoblasts, 8 cases (50%) consisted of invasive urothelial carcinoma with choriocarcinoma, 1 case (6%) showed urothelial carcinoma in situ with associated choriocarcinoma, and 1 case (6%) consisted of pure choriocarcinoma. Other subtypes of variant morphology were seen in 5 of our cases (31%) and included squamous, glandular, lipoid, chordoid/myxoid, and sarcomatoid features. Given the limited specificity of human chorionic gonadotropin immunohistochemistry, we also studied the expression of a novel specific trophoblastic marker, hydroxyl-δ-5-steroid dehydrogenase, as well as Sal-like protein 4. Human chorionic gonadotropin expression was seen in nearly all cases (93%) but was often not limited to the trophoblastic component, staining the urothelial component also in 85% of the cases. Expression of hydroxyl-δ-5-steroid dehydrogenase was more sensitive and more specific, staining 100% of the cases and limited to trophoblasts in all but 1 case. Sal-like protein 4 expression was variable, staining trophoblast in only 50% of cases and staining the urothelial carcinoma component in 43% of those positive cases. Most of our tumors presented at a high stage and were associated with poor clinical outcomes, with at least muscle-invasive disease (pT2) in 10 of the 14 bladder tumors (71%), perureteric fat invasion in the ureter tumor (pT3), distant metastases in 7 of 16 cases (44%) and death of disease in 3 of the 15 patients with follow-up (20%). Our study describes a series of urothelial carcinomas with trophoblastic differentiation, demonstrating the morphologic spectrum of this entity, its frequent association with other subtypes of variant morphology, its characteristic immunoprofile, and its aggressive clinical behavior.

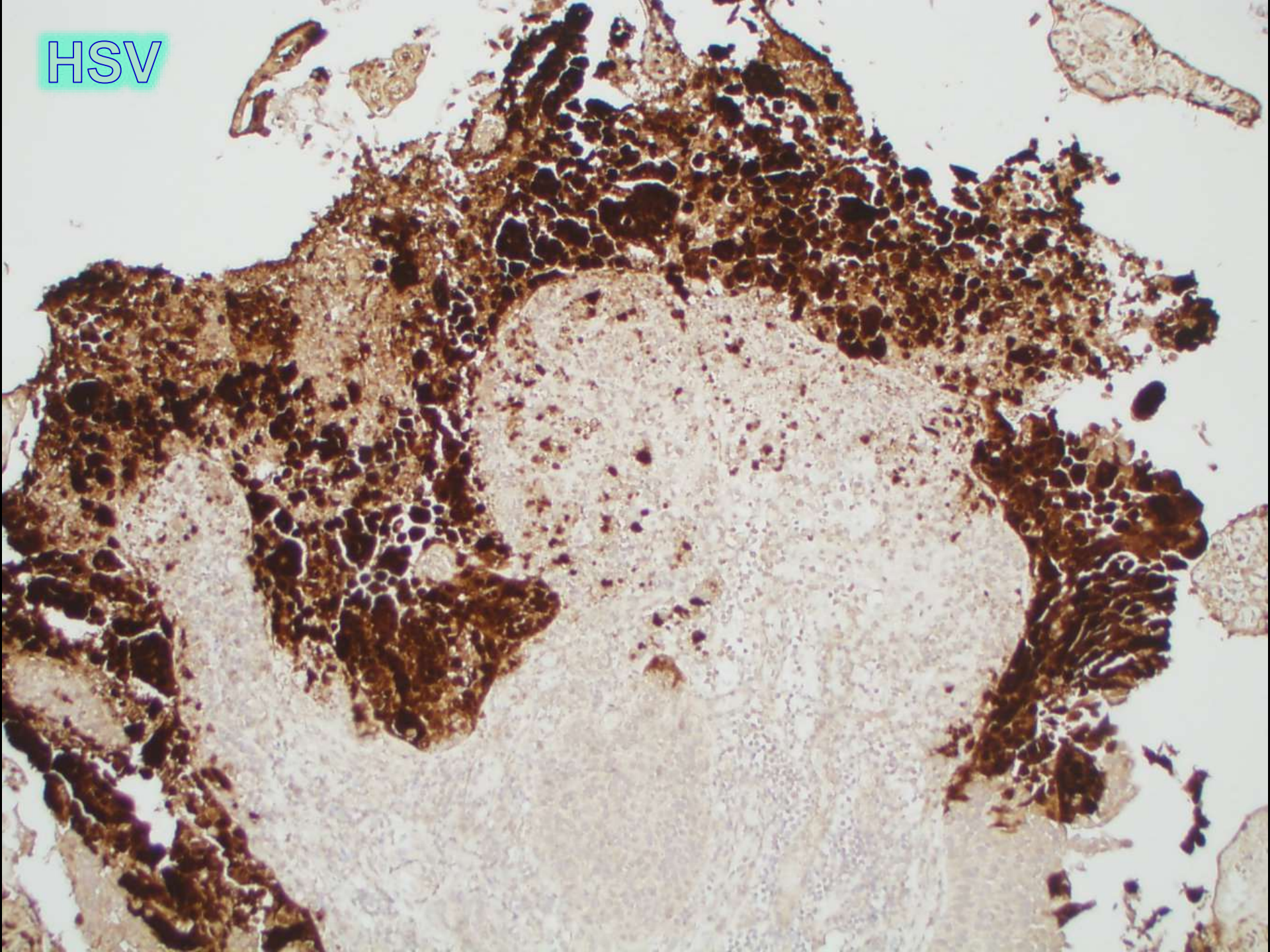
Key Words: choriocarcinoma, urothelial carcinoma, trophoblastic, bladder cancer

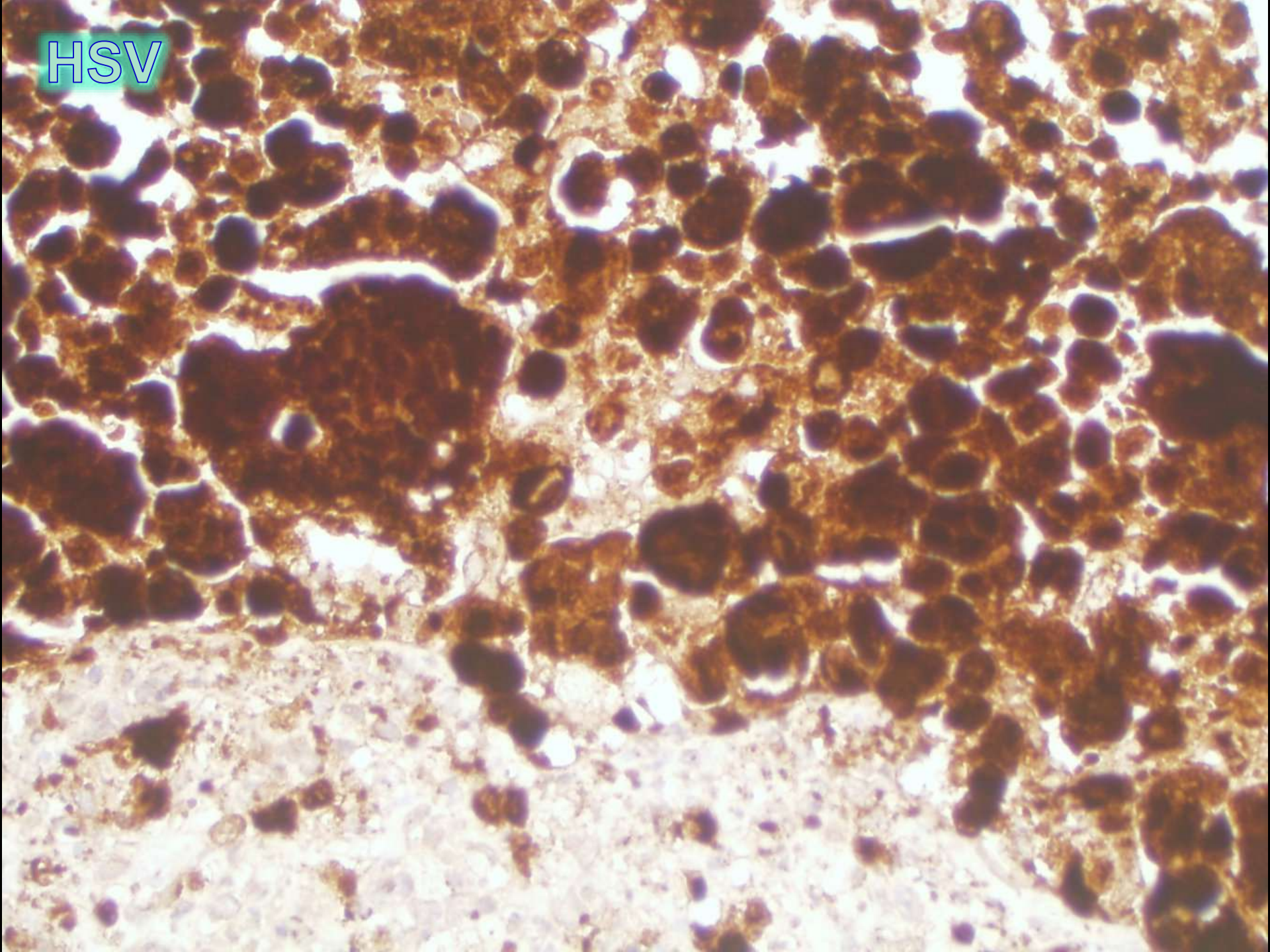
(*Am J Surg Pathol* 2020;44:1322–1330)






HSV


HSV


HSV

Dx

- **Papillary urothelial carcinoma + HSV**
- **Pleomorphic giant cell variant urothelial carcinoma**
- **Urothelial carcinoma with trophoblastic differentiation**

HSV infection & urothelial carcinoma

- **% association?**
  - 11% by IHC in one study
  - 33% by PCR in one study
- **no significant relationship between HSV and anatomical site, growth pattern or depth of invasion of UC,**
  - significantly higher in females than in males (shorter urethra as etiology?)

Virchows Arch (2004) 445:68–73
DOI 10.1007/s00428-004-1019-z

ORIGINAL ARTICLE

Naomi Kaku · Kenji Kashima · Tsutomu Daa ·
Iwao Nakayama · Shigeo Yokoyama

Herpes simplex infection in urothelial carcinoma

Received: 28 January 2004 / Accepted: 23 March 2004 / Published online: 20 May 2004

Abstract Herpes simplex virus (HSV), a member of the Herpesviridae family, is a very common pathogen that can infect any site in the body. Urothelial carcinoma (UC) is a common malignancy of the urinary tract. The possibility of HSV infection in cases of UC has attracted little attention. In this study, we investigated the possible presence of HSV in UC and non-neoplastic urothelium. We examined the incidence of HSV infection in 100 samples of UC from 78 patients and 50 samples of non-neoplastic urothelium from 50 autopsy cases using immunohistochemical staining and amplification of DNA using polymerase chain reaction (PCR). Infection by HSV was detected in 39 of the 100 samples of UC (35 of 78 patients) using immunohistochemical staining and/or PCR analysis, in marked contrast with 1 of 50 samples of non-neoplastic urothelium. There was no significant relationship between infection by HSV and anatomical site, growth pattern or depth of invasion of UC, but the frequency of HSV infection was significantly higher in females than in males. Our findings indicate that UCs become infected with HSV much more easily than non-neoplastic urothelium.

tral nervous system is
generally accepted that
ally, while HSV-2 is tr
genome of HSV conta
with the ability to trans
that suggests the possib
vivo [2, 6]. Indeed, HS
factor in the developme
[8, 12].

Urothelial carcinoma
90% of malignant neop
factors for UC include
smoking, exposure to c
certain artificial sweete
such as HSV, human
Barr virus, cytomegalov
reported to infect the u
by HSV in cases of UC
now, there were no
demonstrating the infec

In this study, we inv
HSV in UC and non-ne

Table 1 Infection with herpes simplex virus (HSV) of non-neoplastic urothelium and urothelial carcinoma. *IHC* immunohistochemical staining, *PCR* polymerase chain reaction, *HSV-1/-2 PCR* positive for HSV-1 and/or HSV-2 using PCR, *HSV IHC/PCR* positive for HSV using IHC and/or PCR. Note: one sample of non-neoplastic urothelium that gave positive result using PCR was obtained at autopsy from a case of HSV-associated hemophagocytic syndrome

	Number of cases	HSV IHC	HSV-1/-2 PCR	HSV IHC/PCR
		(%)	(%)	(%)
Non-neoplastic urothelium	50	0 (0)	1 (2.0)	1 (2.0)
Urothelial carcinoma	100	11 (11.0)	33 (33.0)	39 (39.0)