South Bay Pathology Society

March Monthly Meeting

3/2/15

Disclosures
March 2, 2015

The following planners and faculty had no financial relationships with commercial interests to disclose:

Presenters:

Ben Buelow, MD, PhD

Thaddeus Mully, MD

Harris Goodman, MD

Gregg Manson, MD

Hannes Vogel, MD

Dave Bingham, MD

Mat Rumery, MD

Teri Longacre, MD

Sebastian Fernandez-Pol, MD

Eduardo Zambrano, MD

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Yaso Natkunam, MD

Activity Planners:

Kristin Jensen, MD

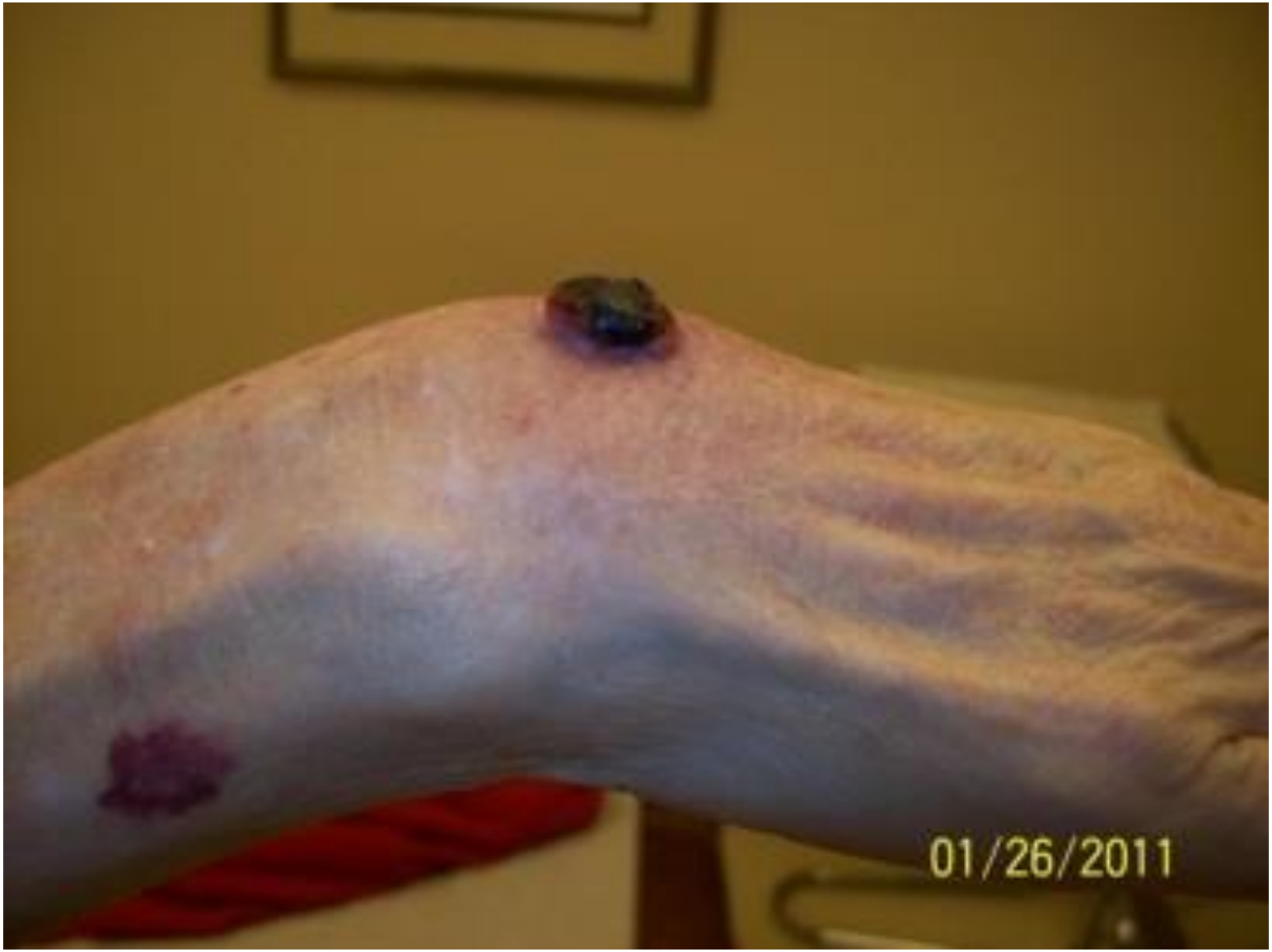
Ankur Sangoi, MD

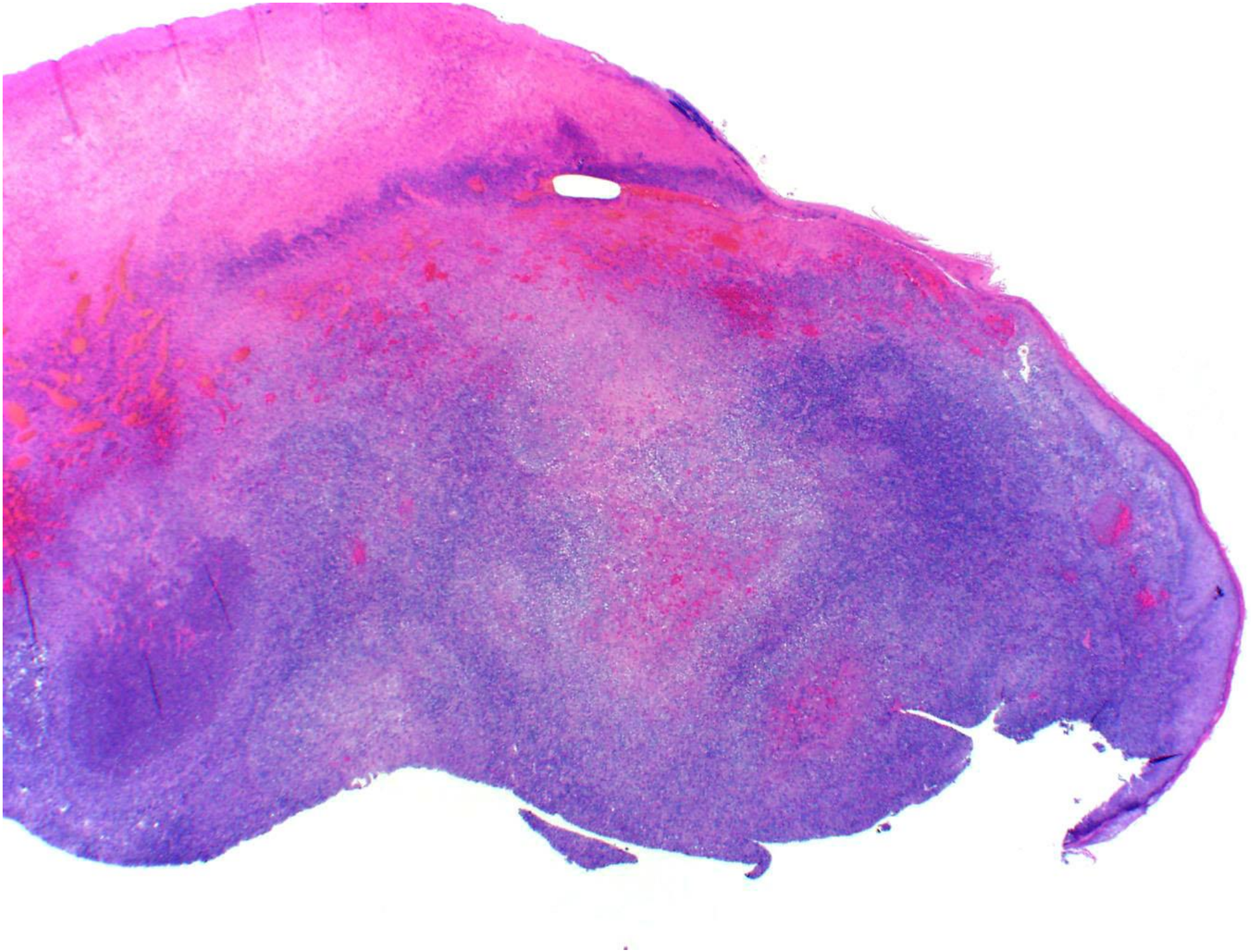
William Rogers, MD

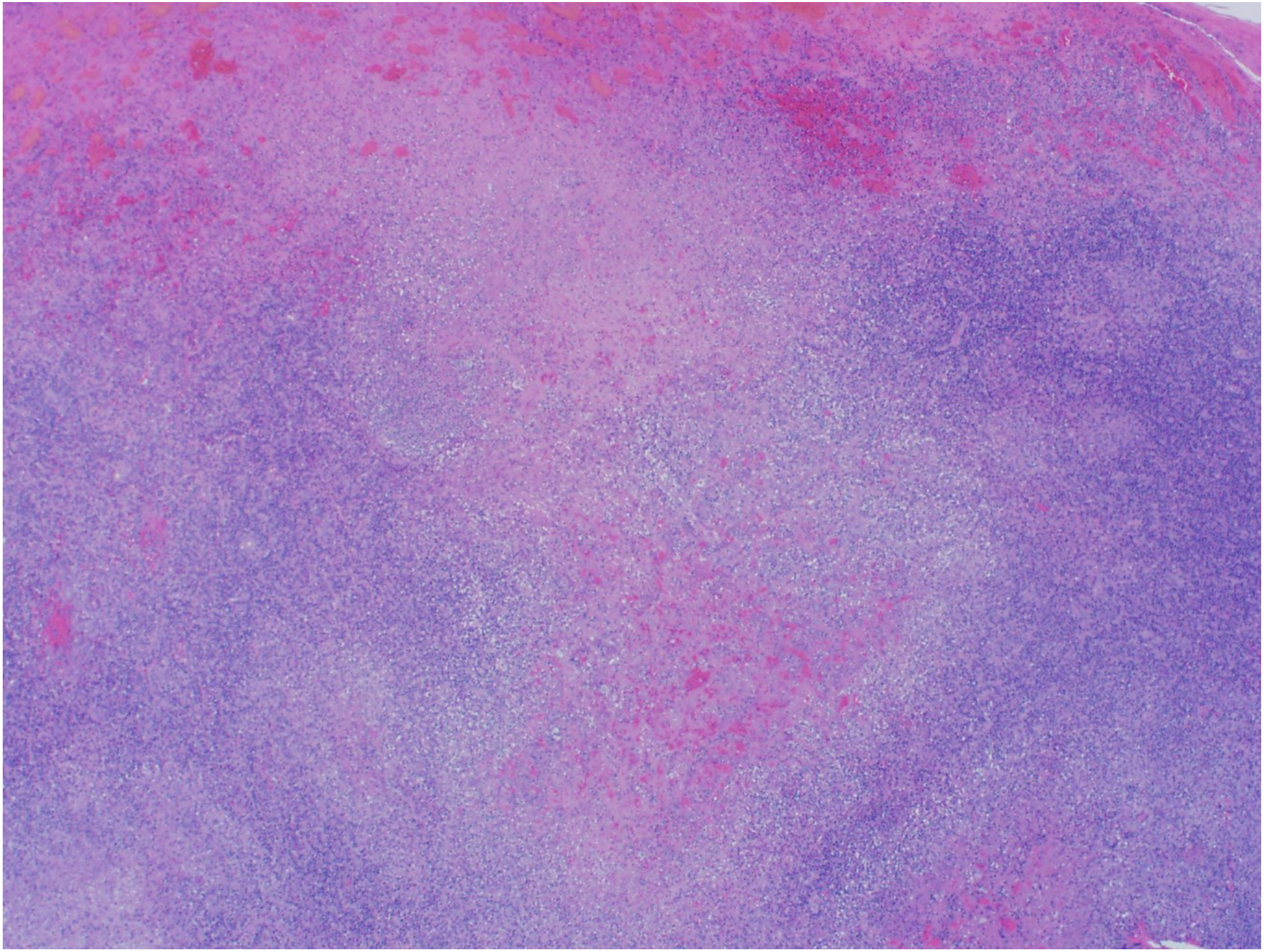
SB 5921

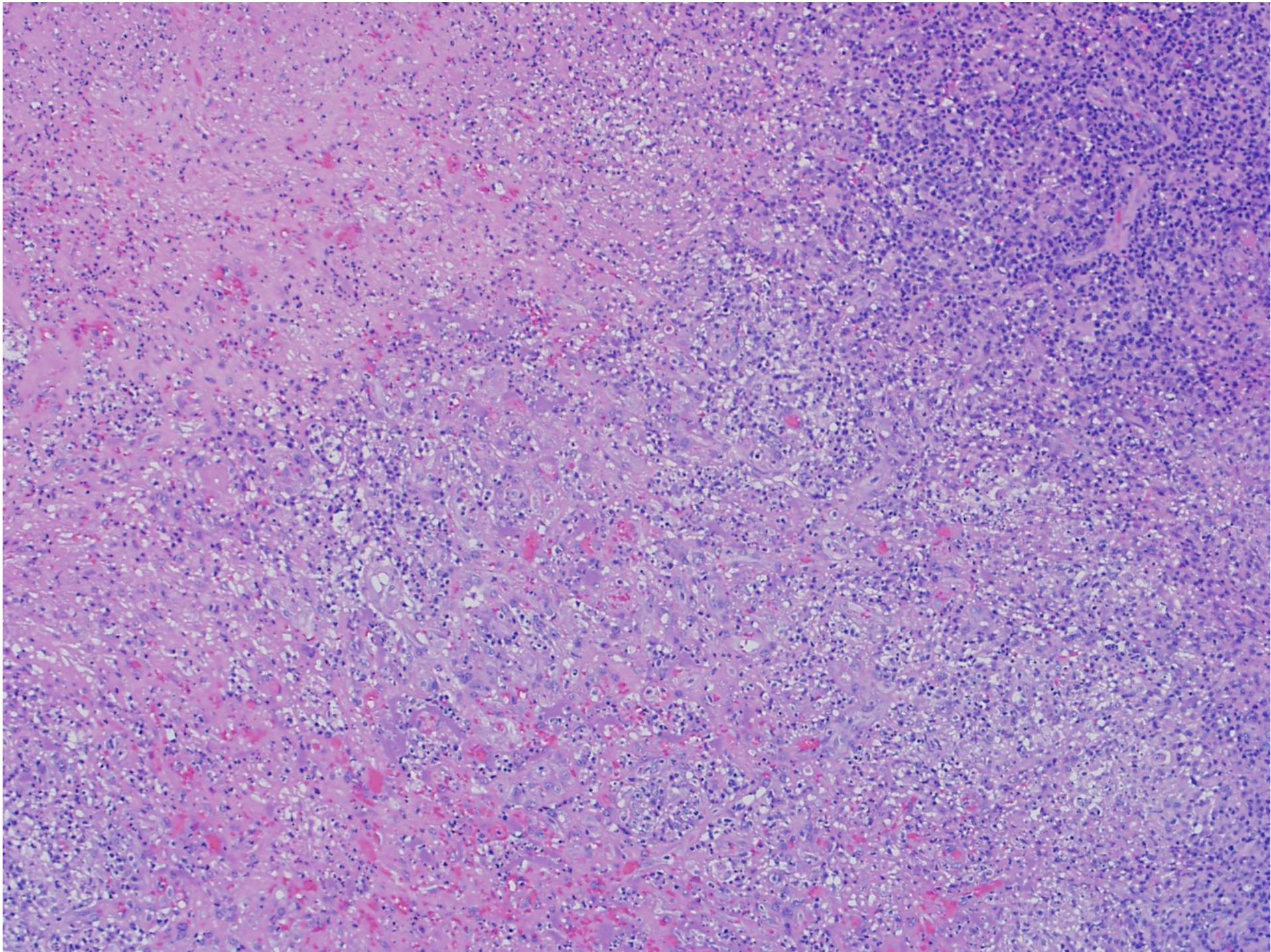
- 53-year-old HIV-negative female renal transplant patient on mycophenolate mofetil and tacrolimus with a history of episodes of graft rejection presented to dermatology clinic with a 3-month history of an enlarging purple nodule on her right wrist.

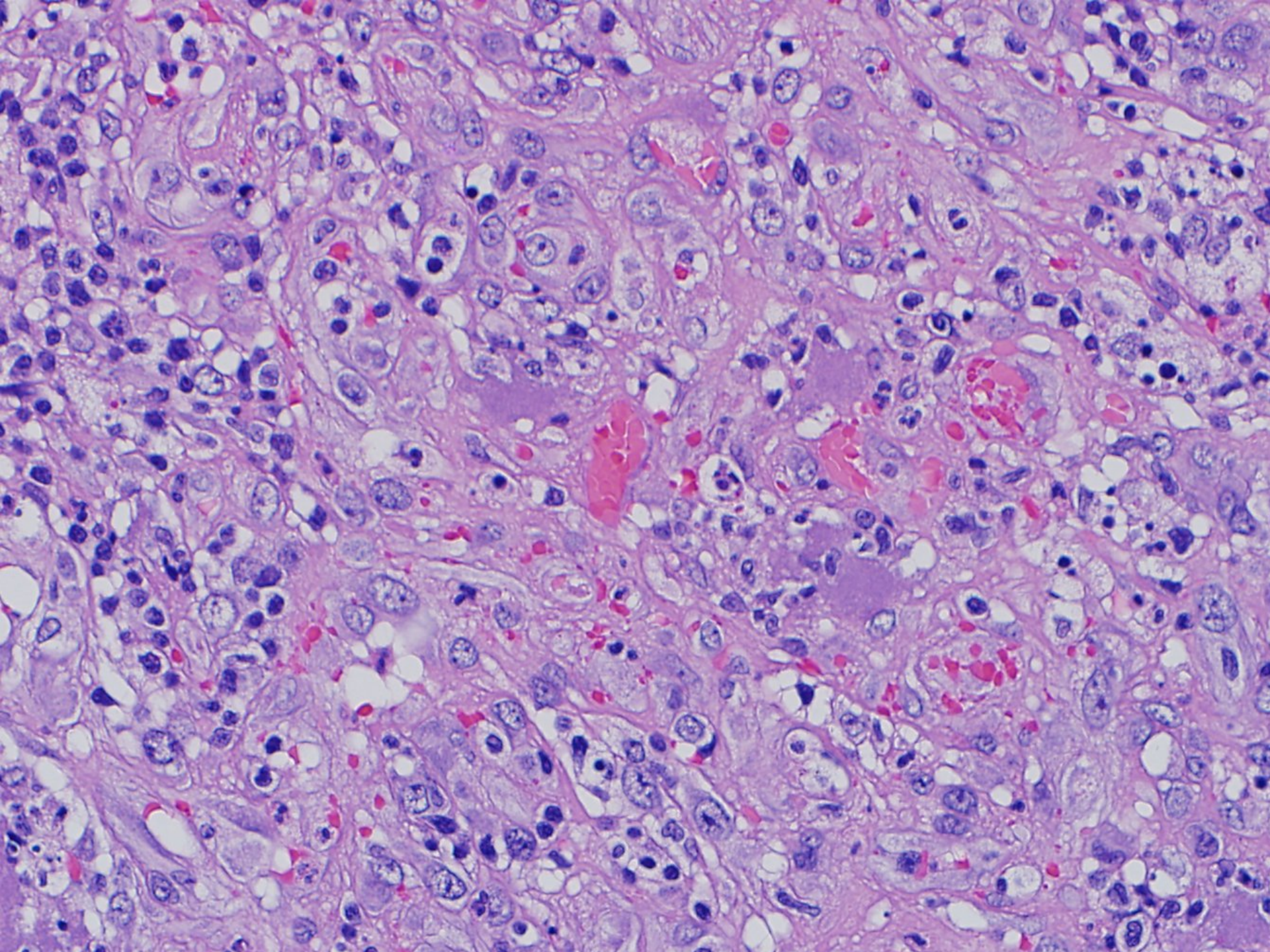
- Ben Buelow/Thaddeus Mully; UCSF


01/26/2011



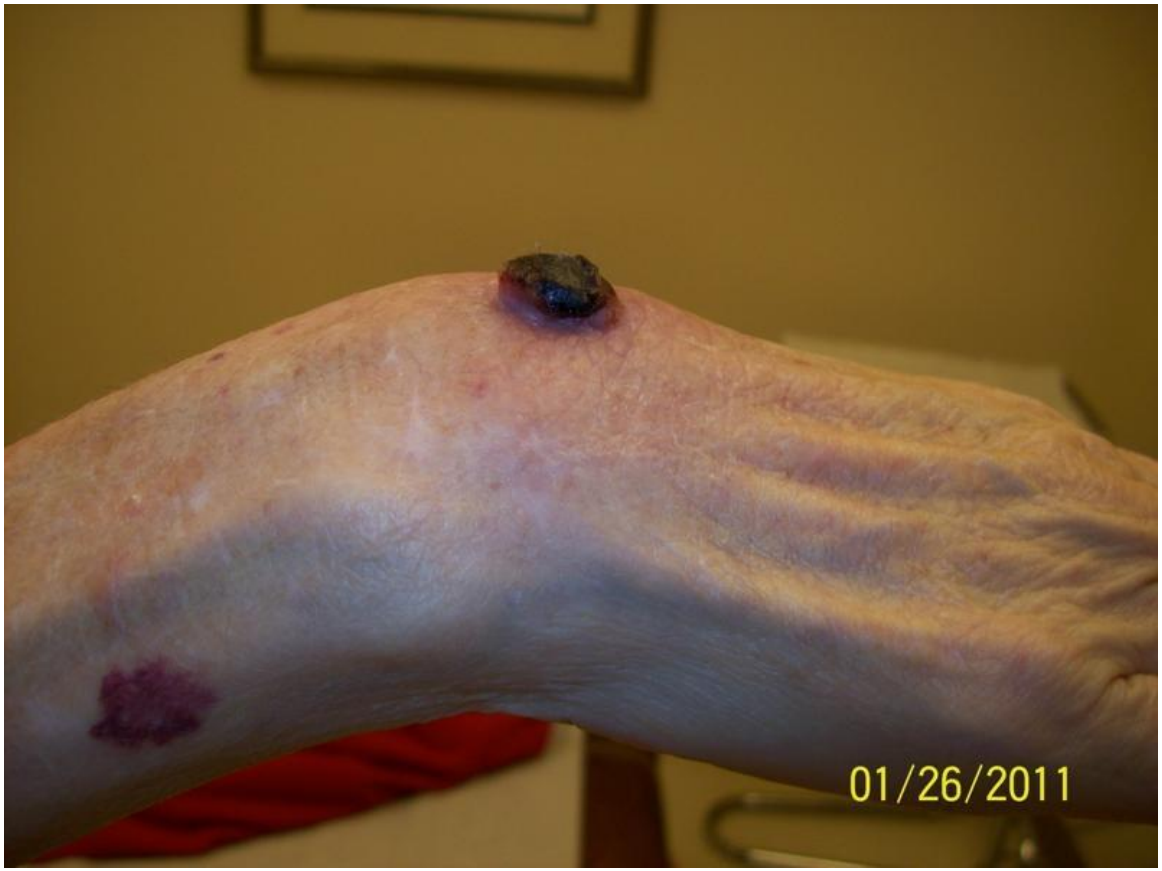






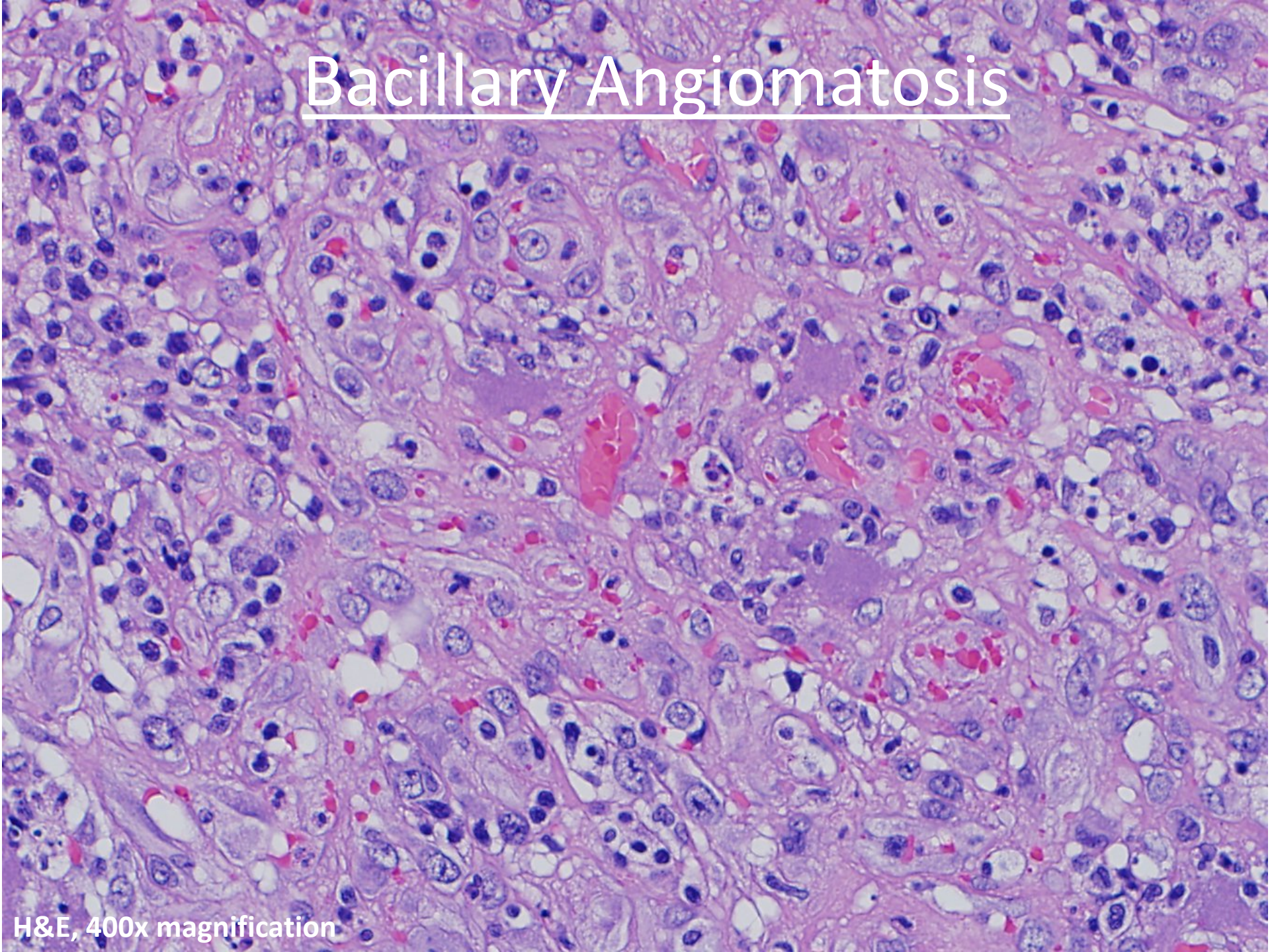
Diagnosis?

A 53 year old female renal-transplant patient with a wrist nodule

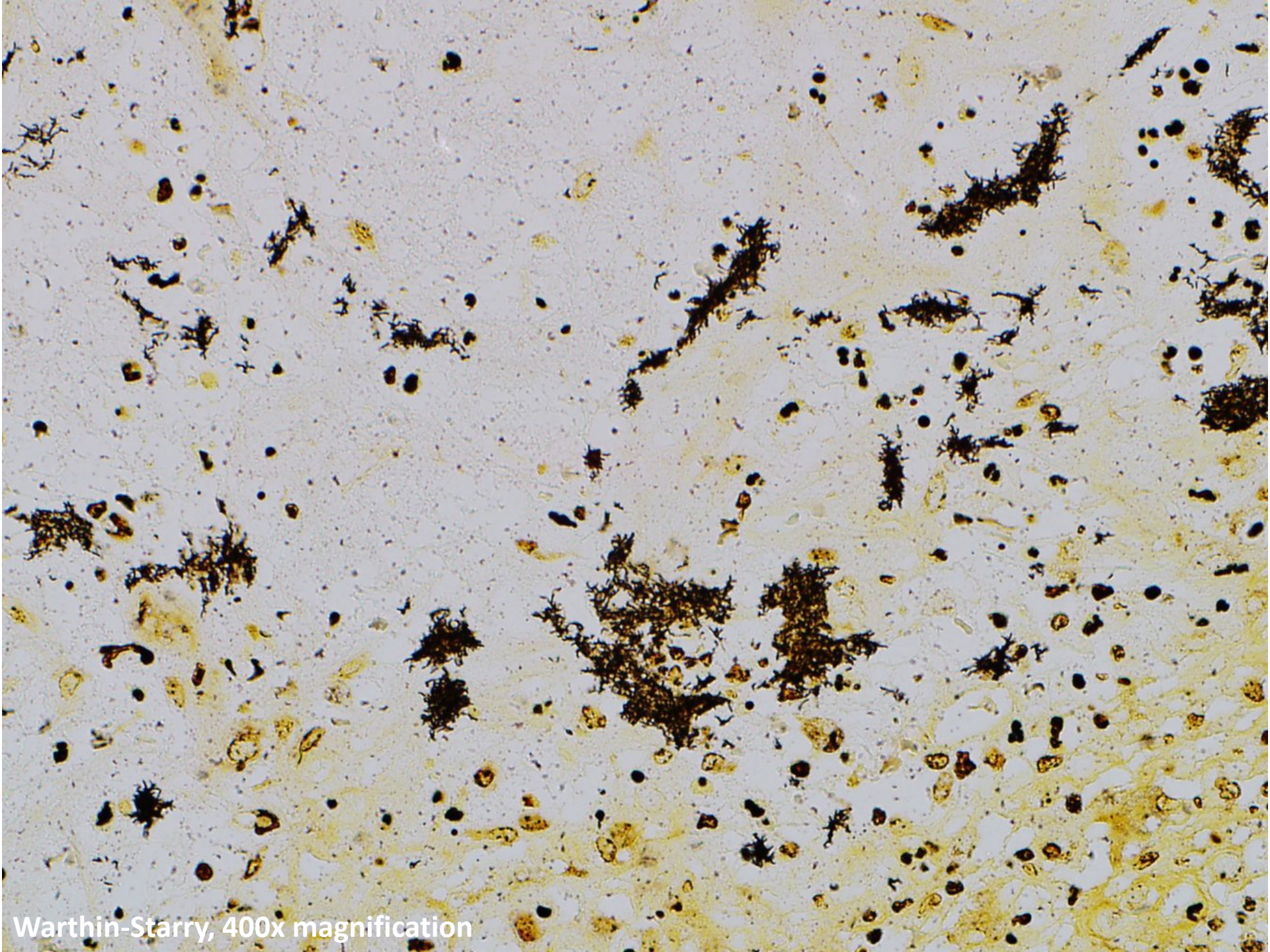


Ben Buelow, MD (PGY-4)
Thaddeus Mully, MD
UCSF Dermatopathology

Bacillary Angiomatosis

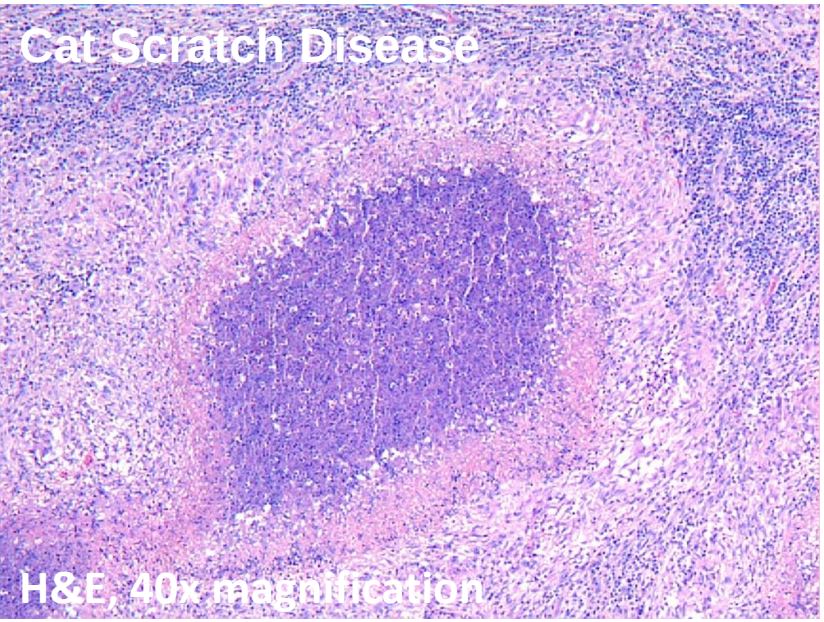


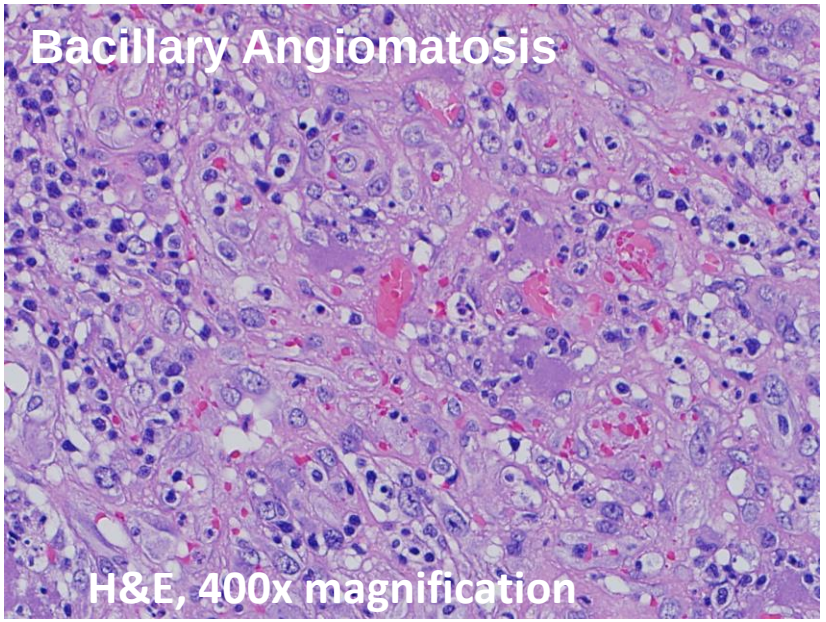
H&E, 400x magnification

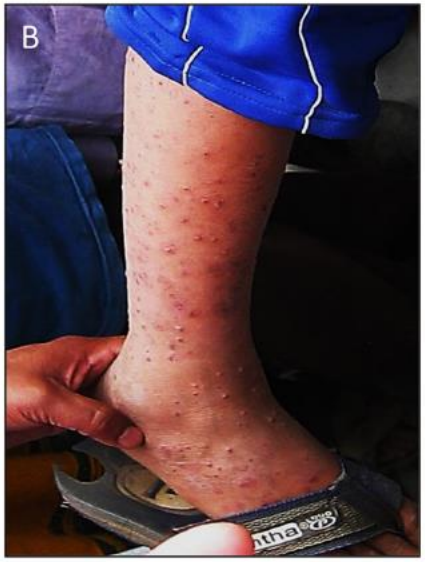


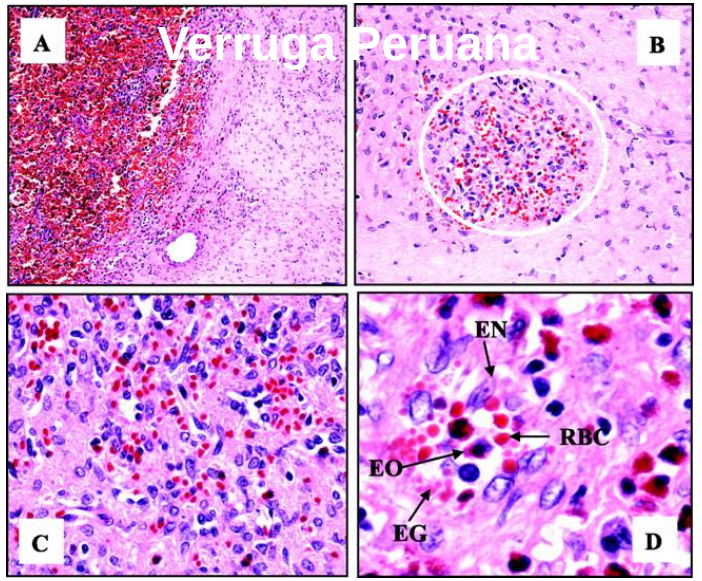
Warthin-Starry, 400x magnification

Bartonella infections: Demographics are Important!









Minnick et al. PLOS Negl Trop Dis, 2014
Lydy S L et al. J. Clin. Microbiol. 2008
Angelakis and Raoult, *Int J Antimicrob Agents*, 2014

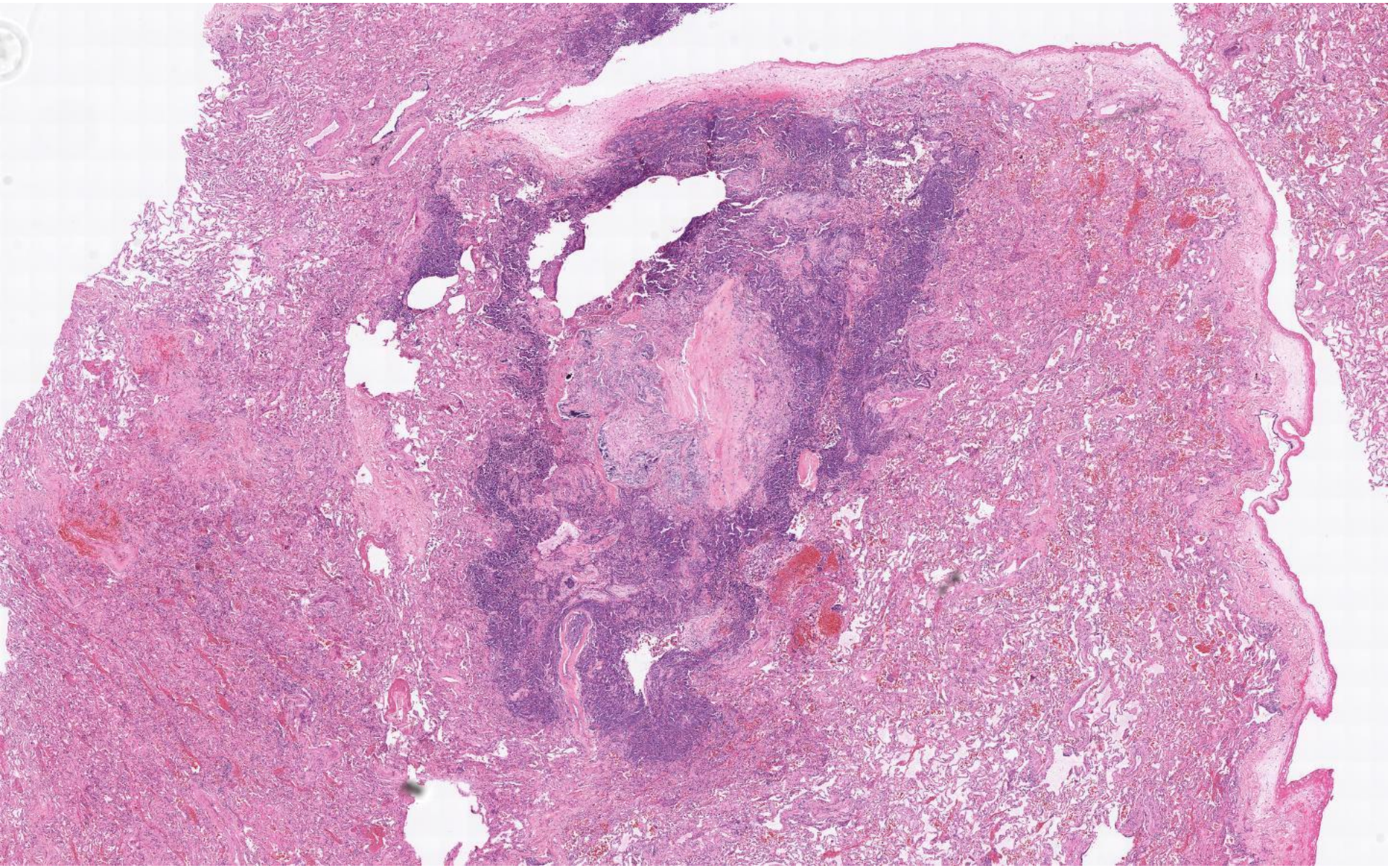
Bartonella henselae: Diagnosis

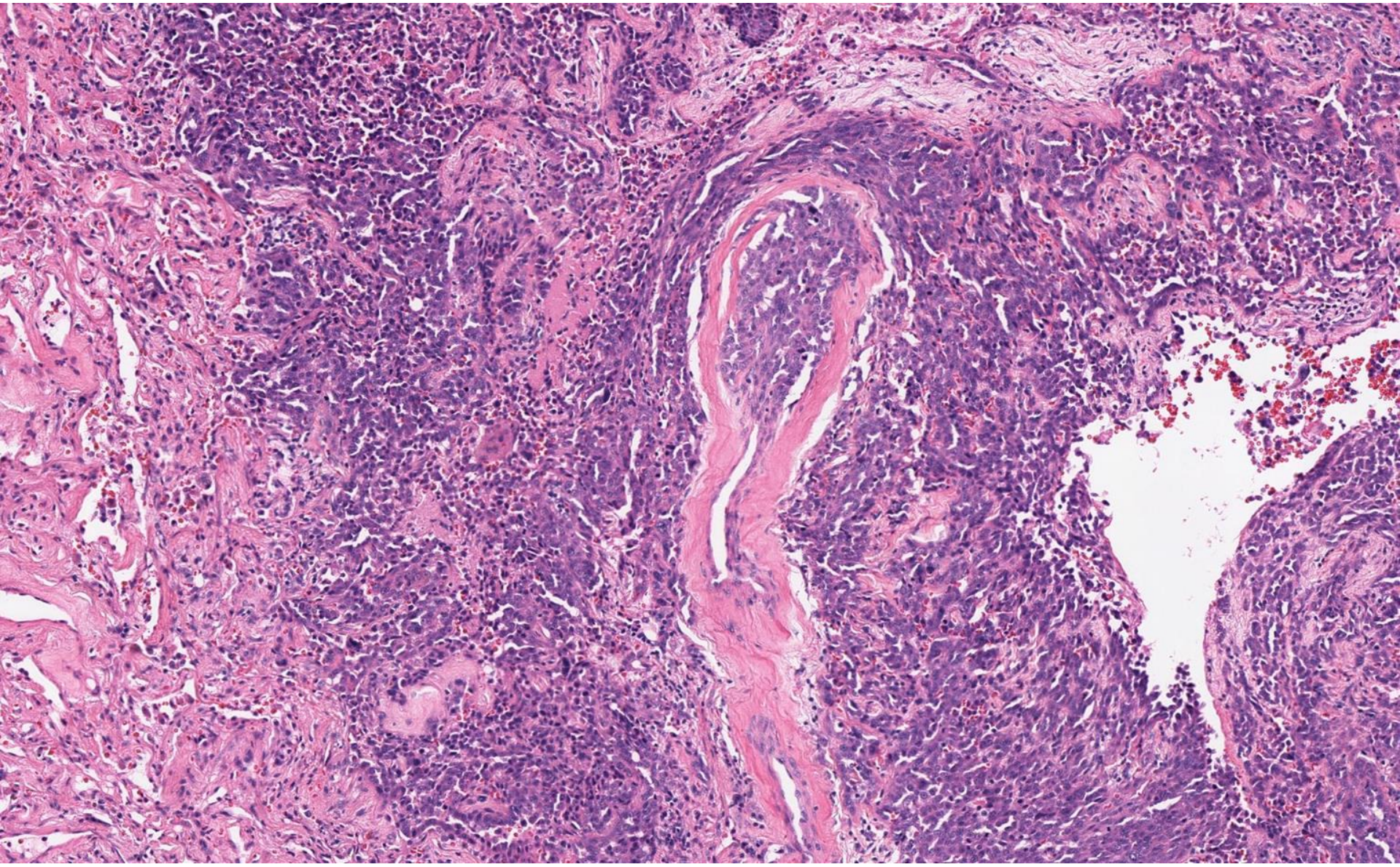
- Fastidious Gram-negative Rod
  - 7 days + to grow, if at all, but can be sensitive for infection (UCSF)
- Silver stain (Warthin-Starry)
- IgG/M titers 40-80% sensitive
  - Up to 4-6% of healthy controls are IgG-positive
- PCR is sensitive (80-100%, UW, Mayo)

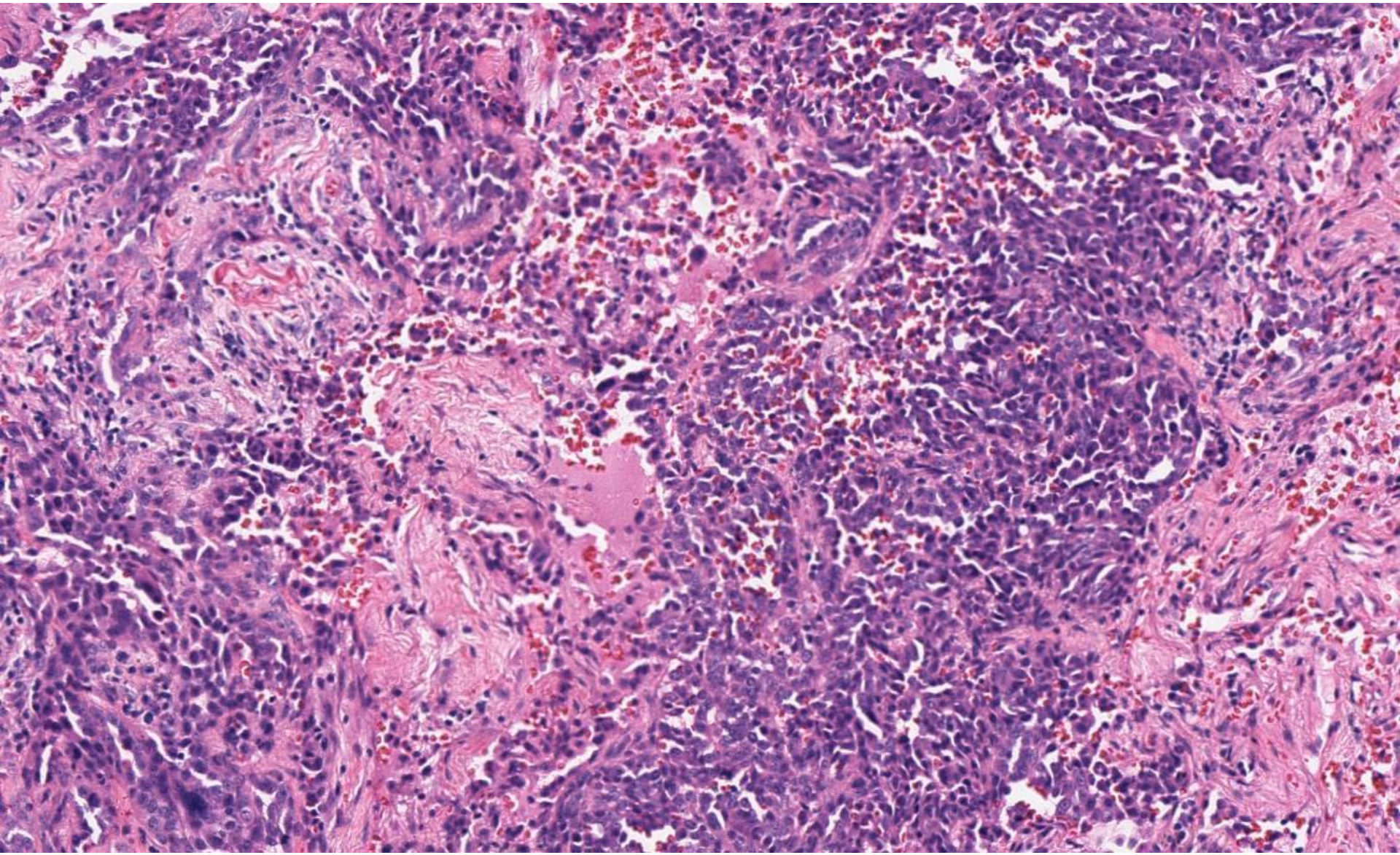
SB 5922

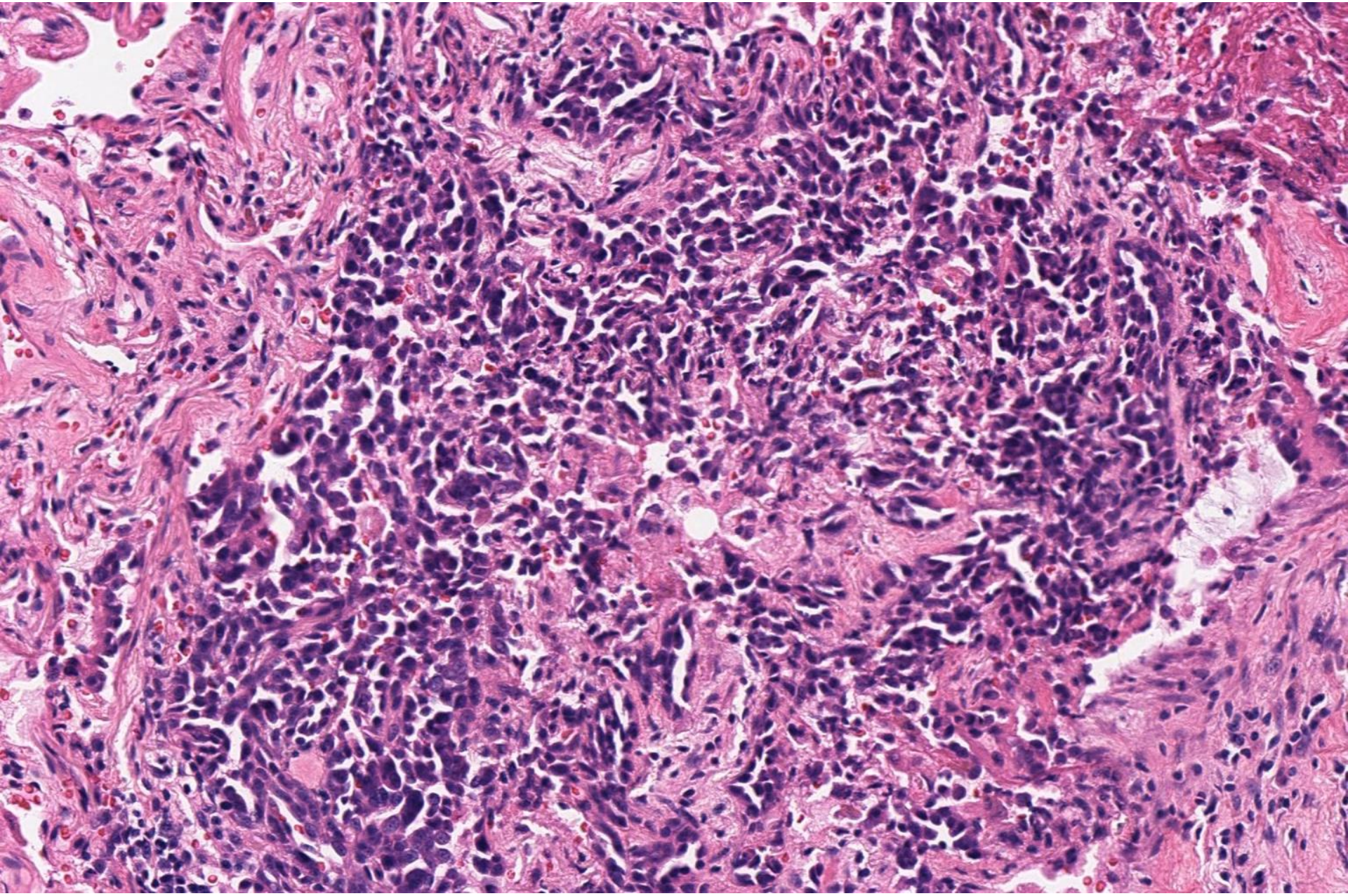
- 85-year-old female with spontaneous pneumothorax. Right wedge lung biopsy performed.

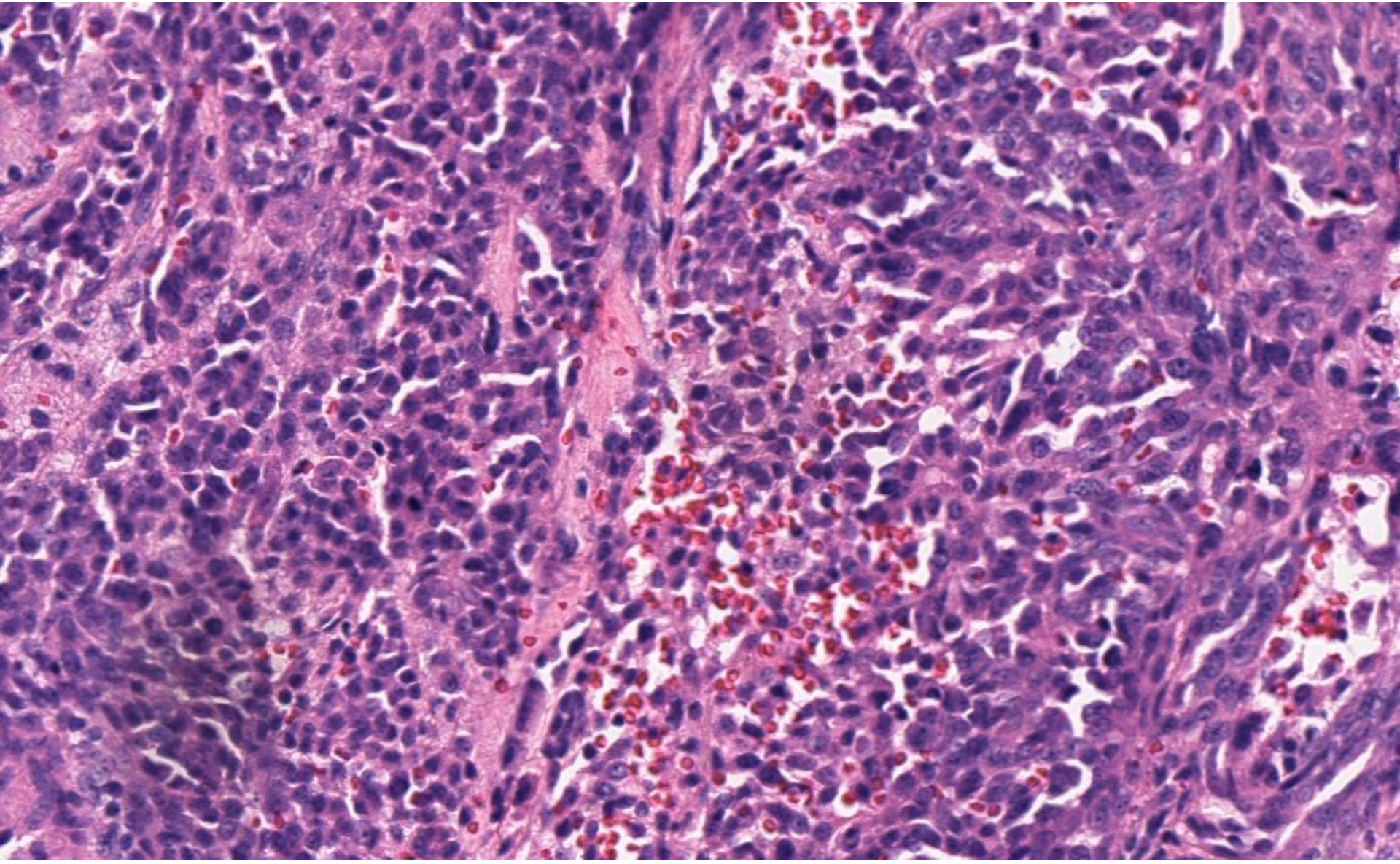
- Harris Goodman; Saint Francis Memorial Hospital







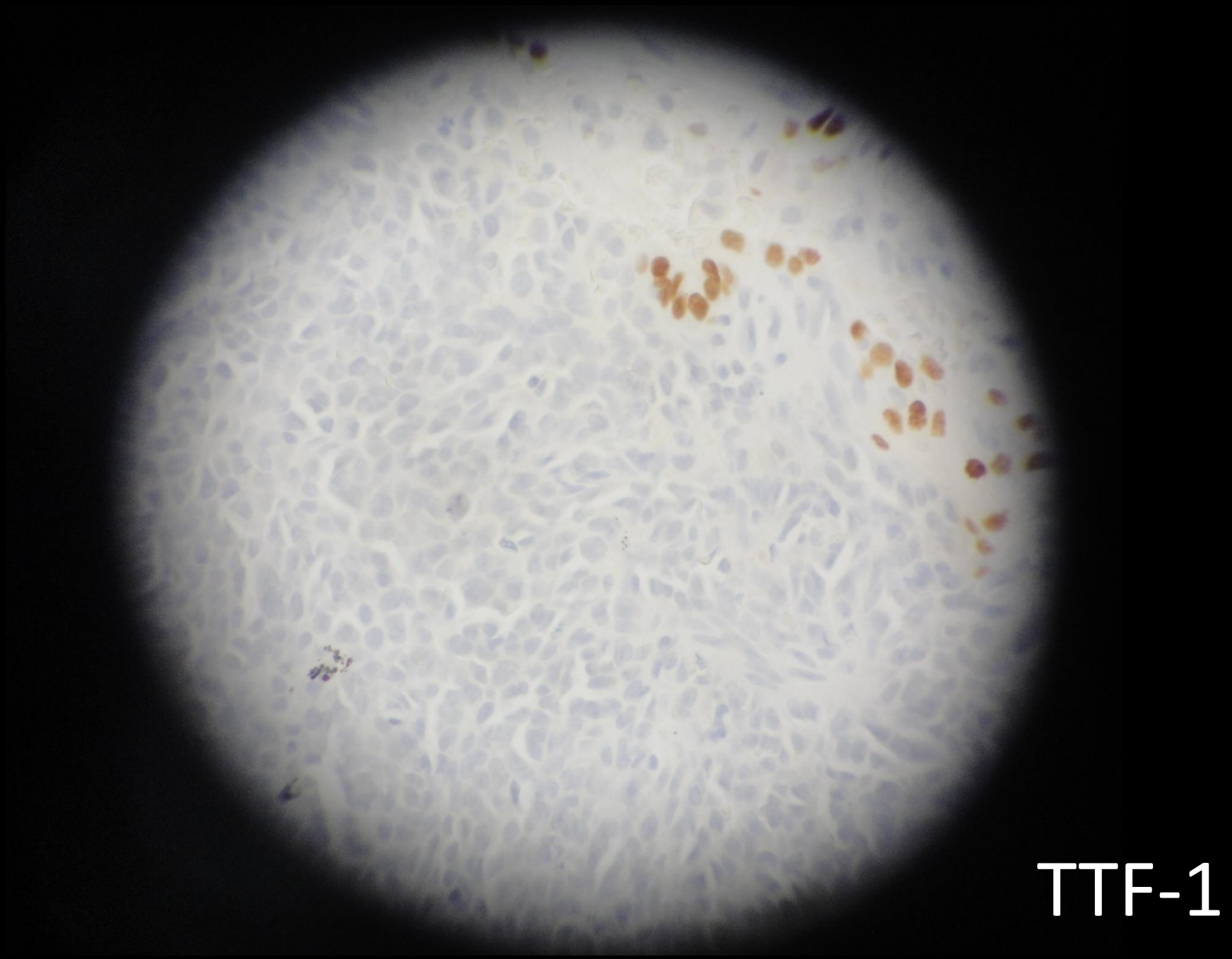


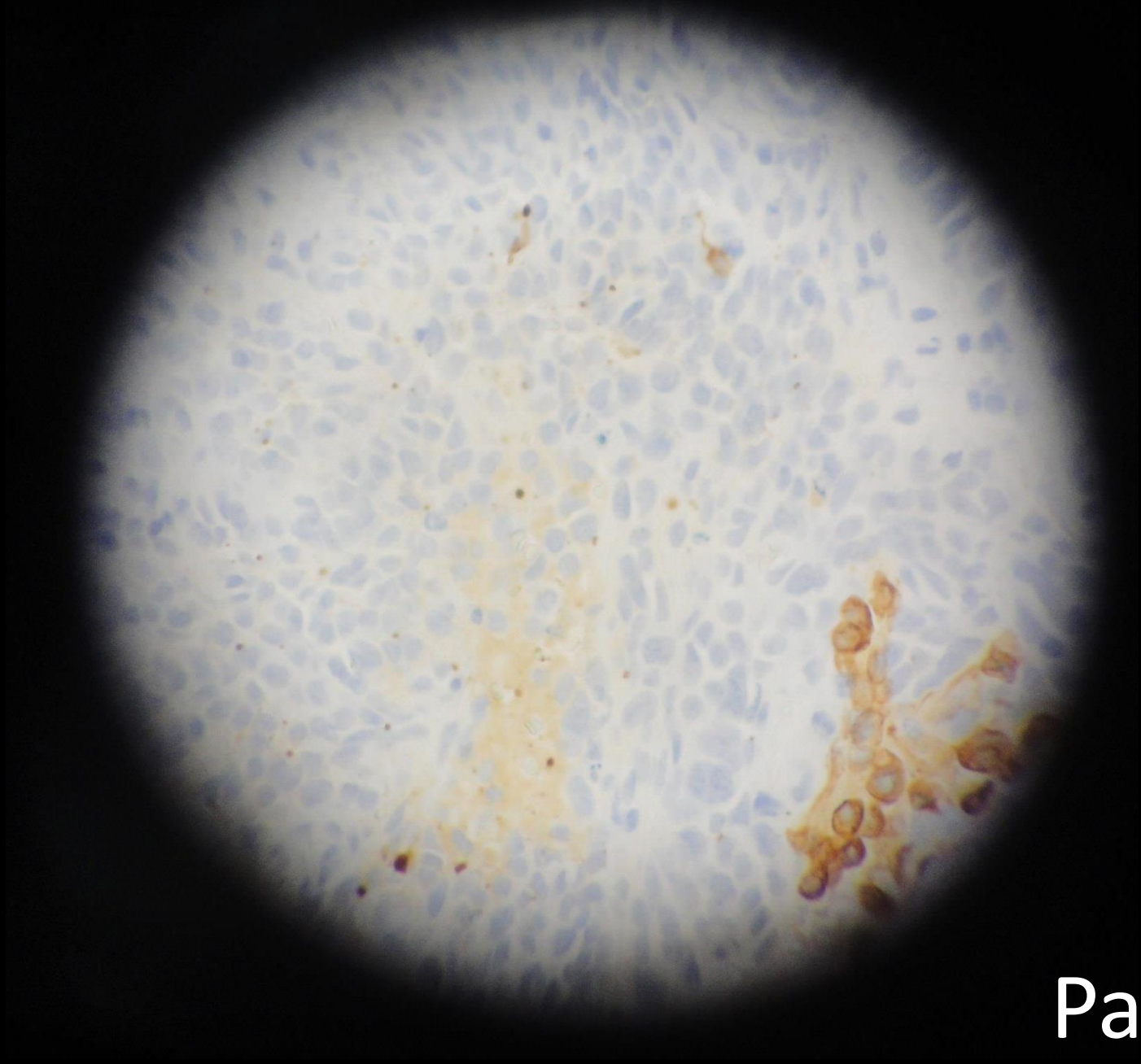


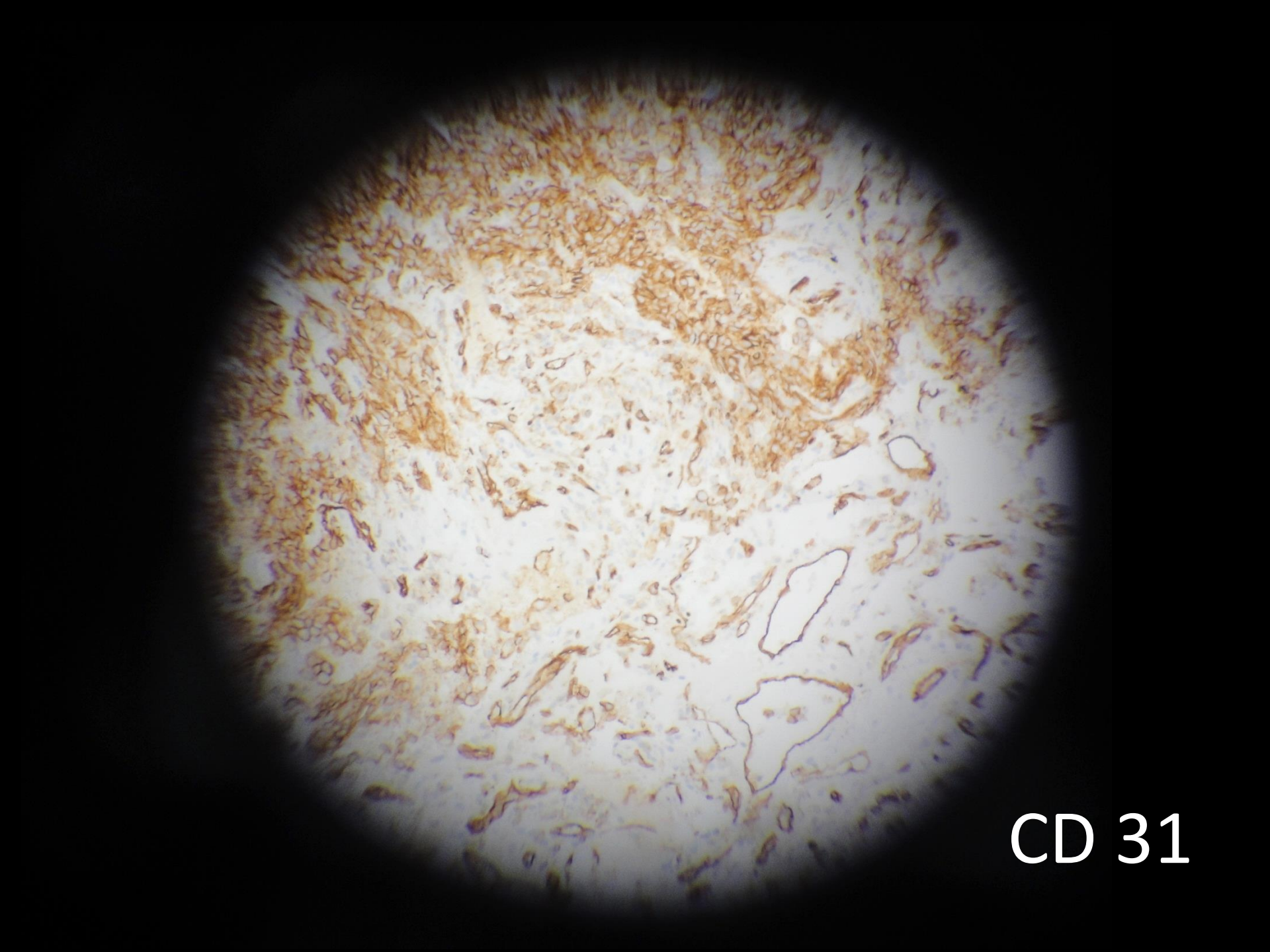
Diagnosis?

- Pre-Op Diagnosis:

  Spontaneous pneumothorax.


TTF-1


Pan-CK


CD 31

Diagnosis:

Angiosarcoma, metastatic.

- Pre-Op Diagnosis:

  Spontaneous pneumothorax.

  History of skin cancer

  (on scalp).

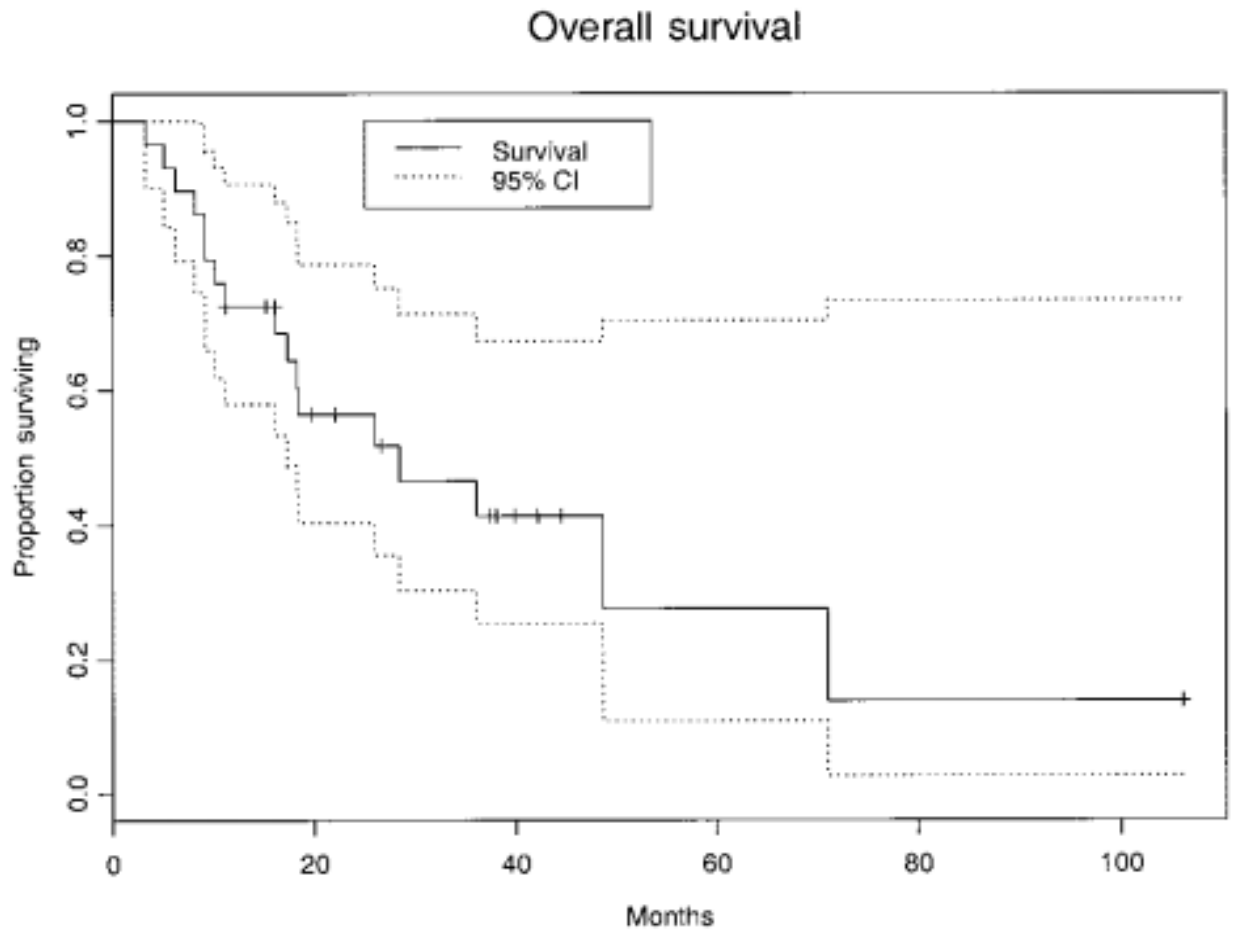


FIGURE 3. The median actuarial survival for patients with angiosarcoma of the scalp was 28.4 months. The 95% confidence intervals (95% CI) for the overall survival curve are relatively wide, suggesting that certain clinical or therapeutic variables may have a differential impact on survival.

Reference: Cancer 2003;98:1716 –26.

Metastatic angiosarcoma and spontaneous pneumothorax

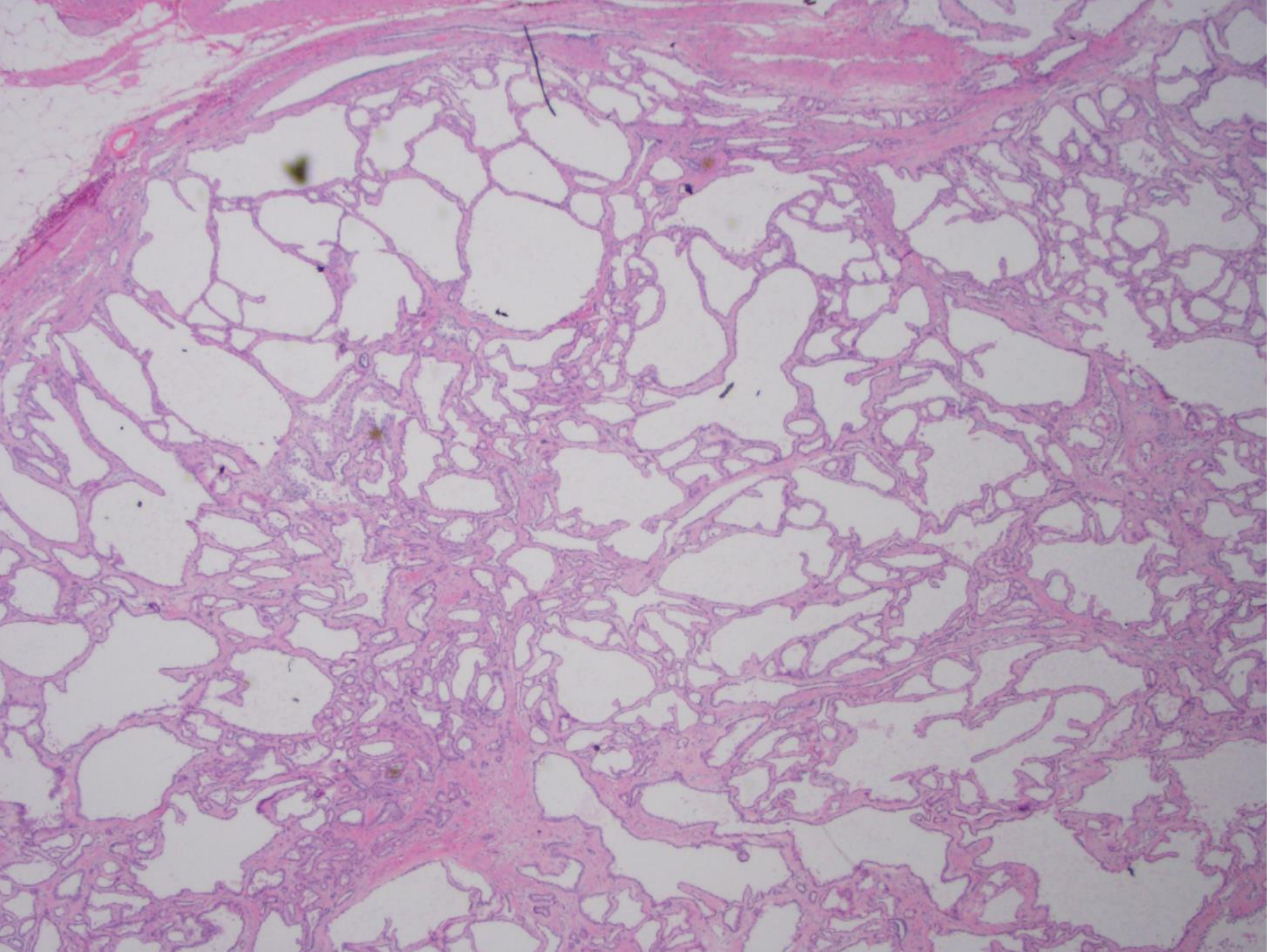
- Surg Today. 2006;36(10):919-22.
- **Simultaneous bilateral spontaneous pneumothorax secondary to metastatic angiosarcoma of the scalp: report of a case.**
- Sakurai H[1], Hada M, Miyashita Y, Tsukamoto K, Oyama T, Ashizawa I.

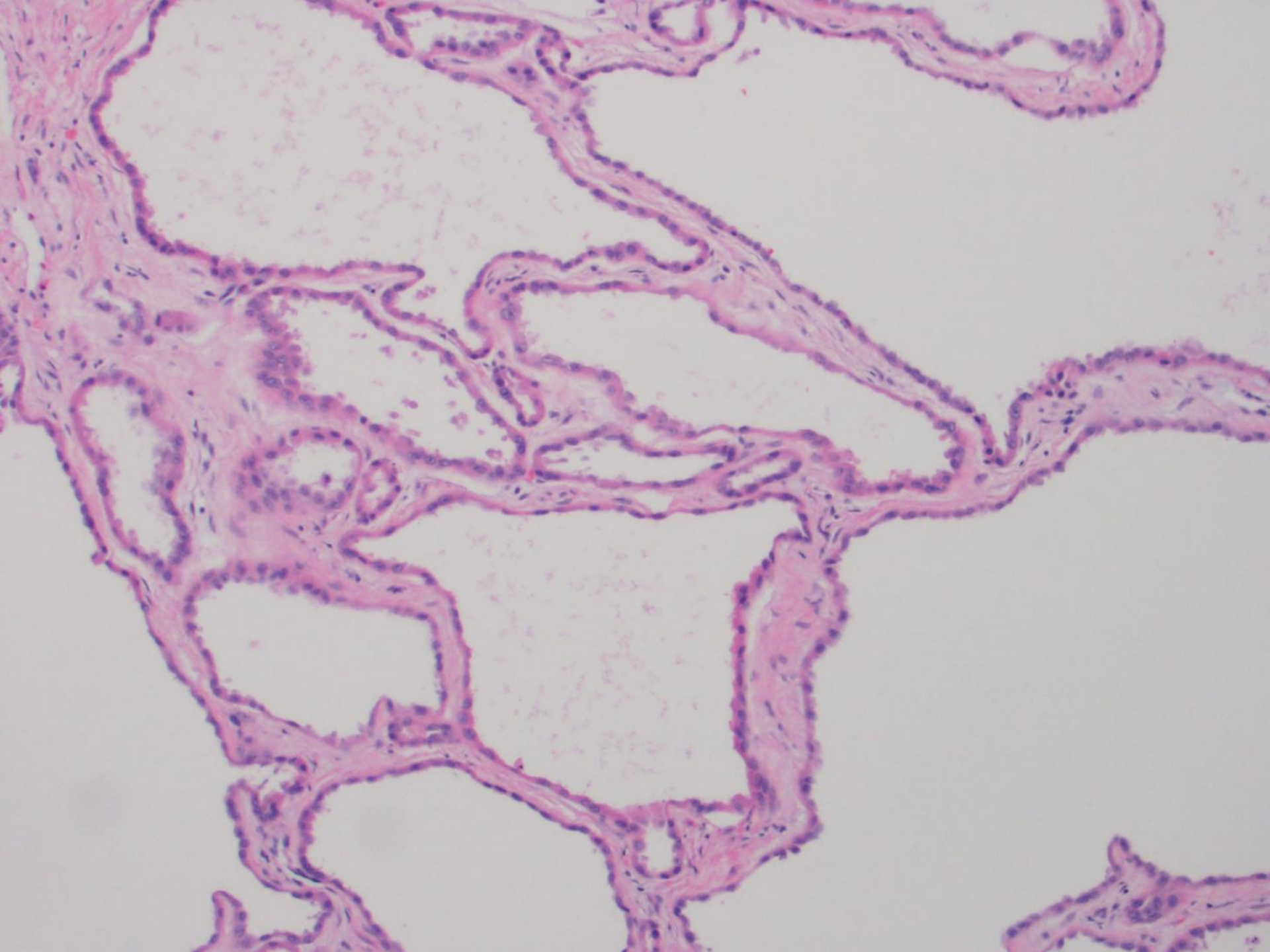
- J Formos Med Assoc. 2006 Mar;105(3):238-41.
- **Angiosarcoma with pulmonary metastasis presenting with spontaneous bilateral pneumothorax in an elderly man.**
- Chen W[1], Shih CS, Wang YT, Tseng GC, Hsu WH.

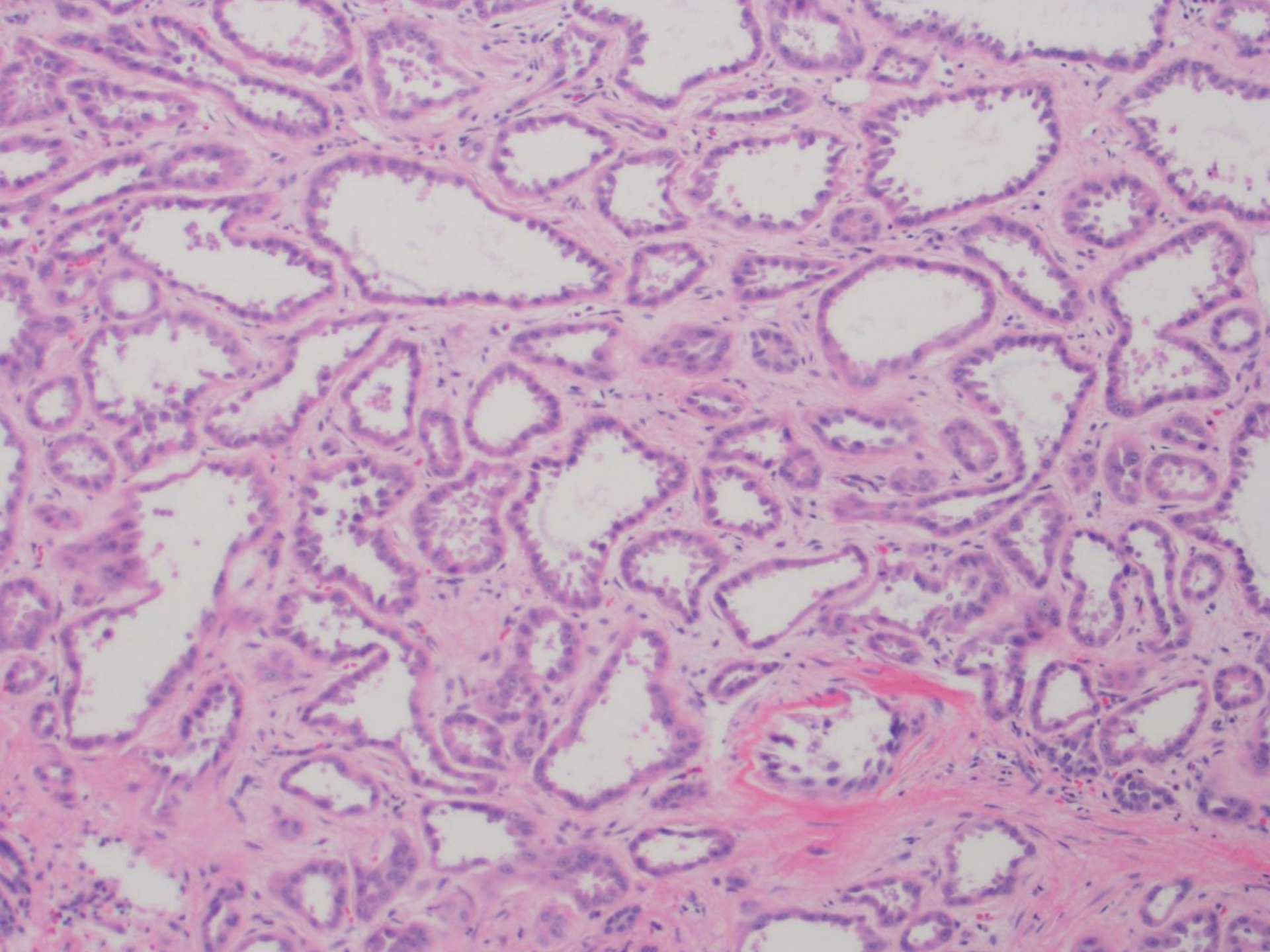
SB 5923

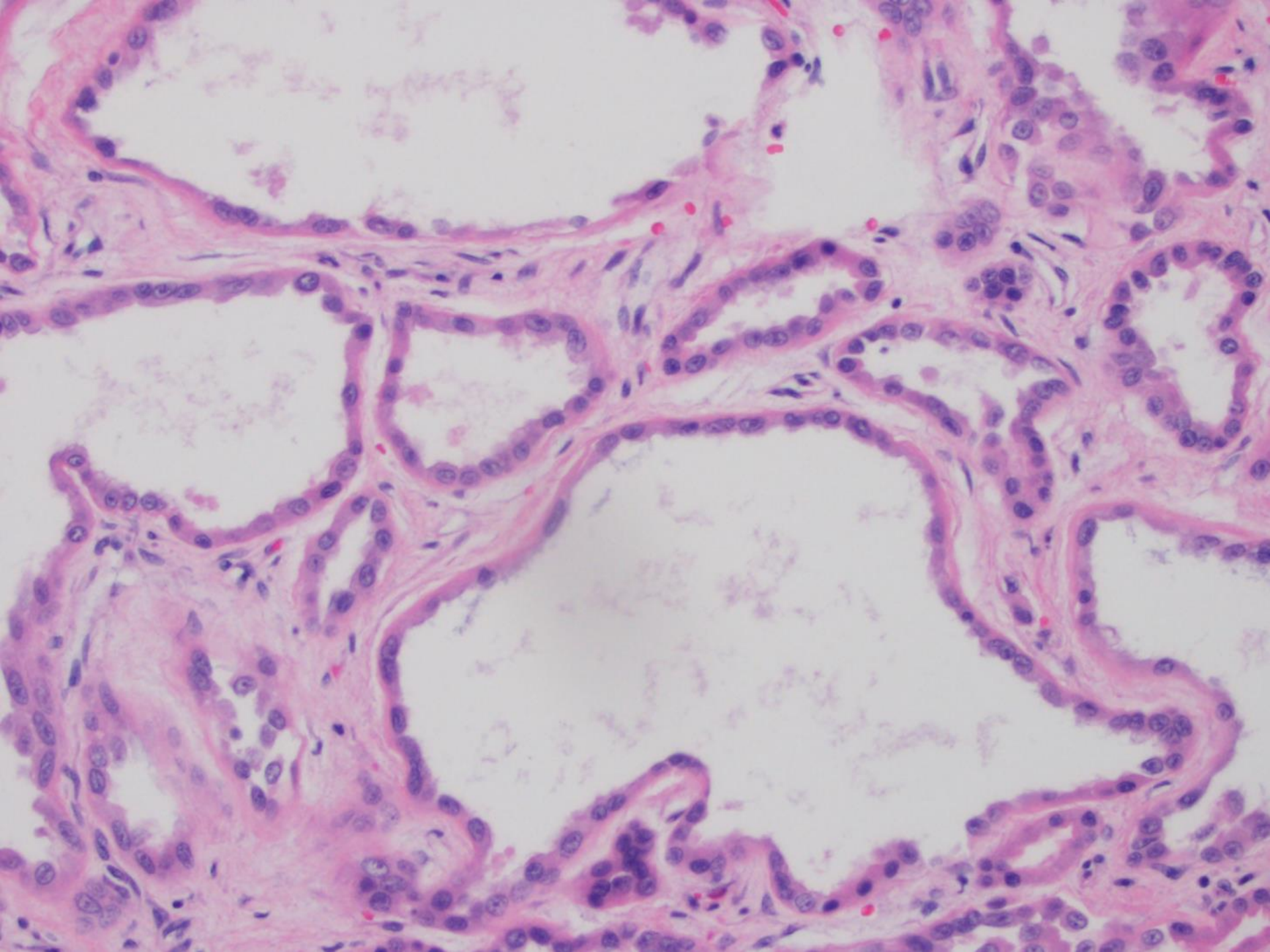
- Adult with 2cm well-circumscribed spongy grey-tan renal mass.

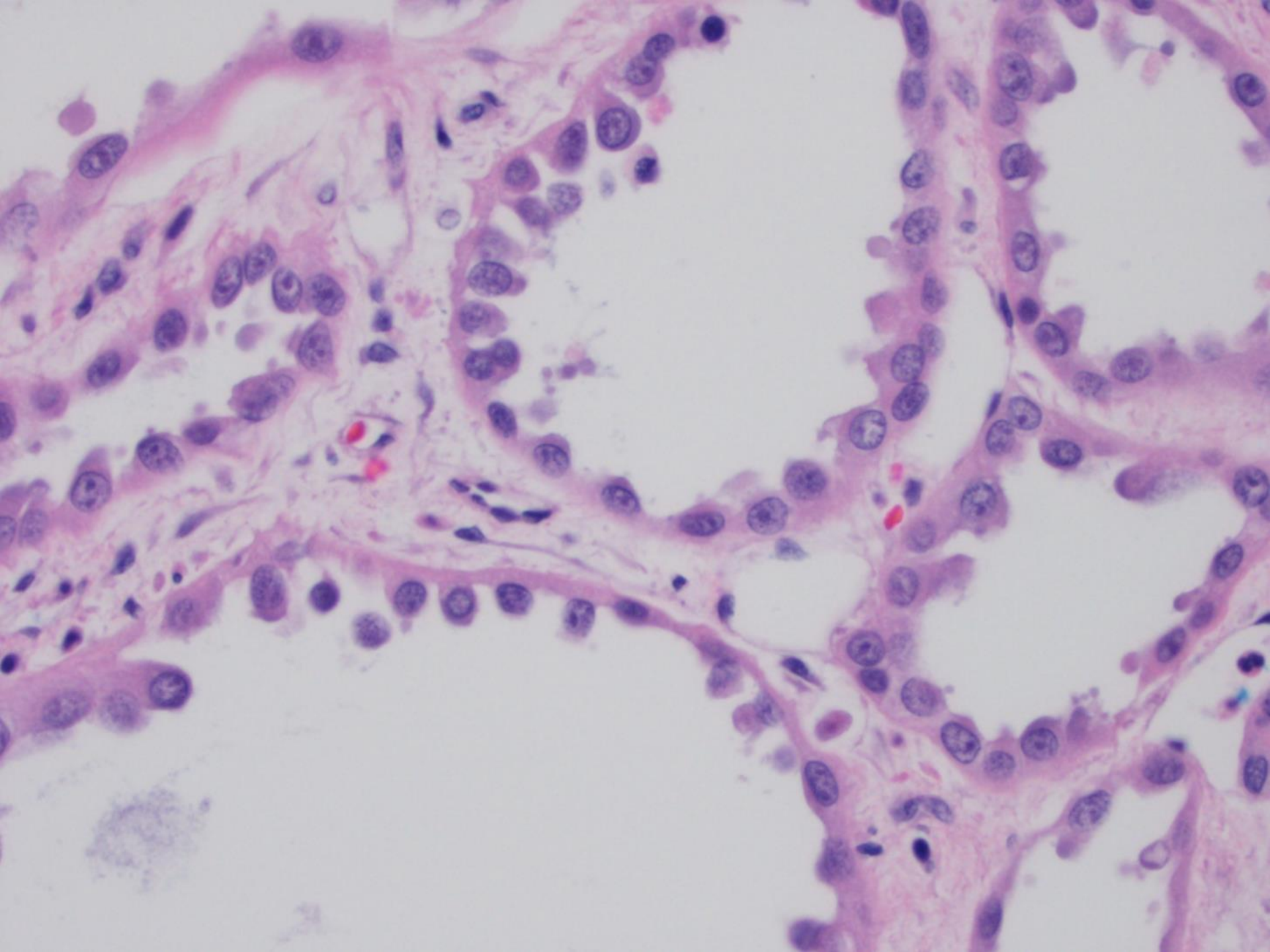
- Gregg Manson; Kaiser Walnut Creek











Diagnosis?

Tubulocystic Renal Cell Carcinoma

History

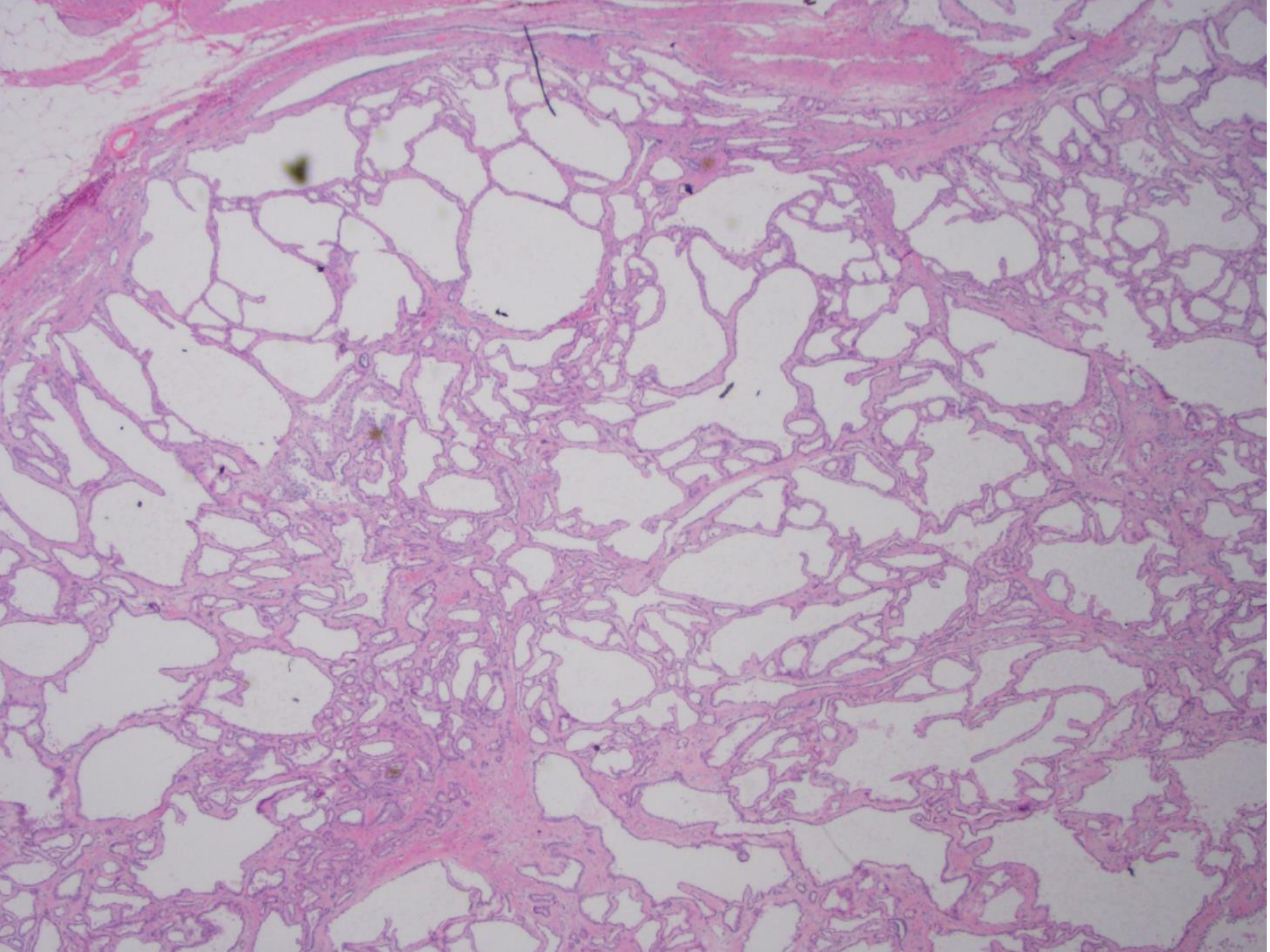
- 44 yo male with incidentally discovered 2 cm. left lower pole kidney mass
- Surgery on 3/14 – doing well US 10/14 unremarkable

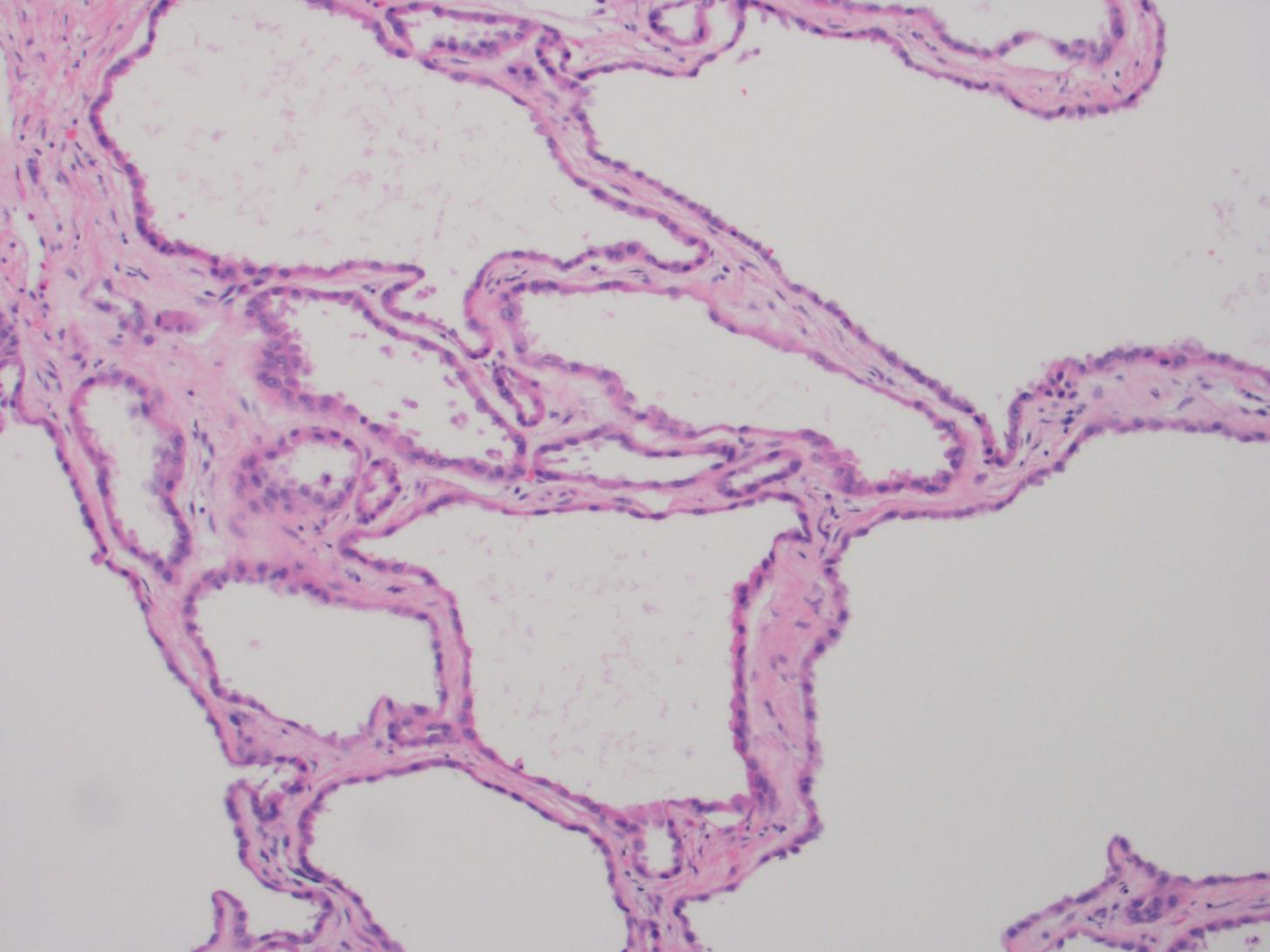
Gross

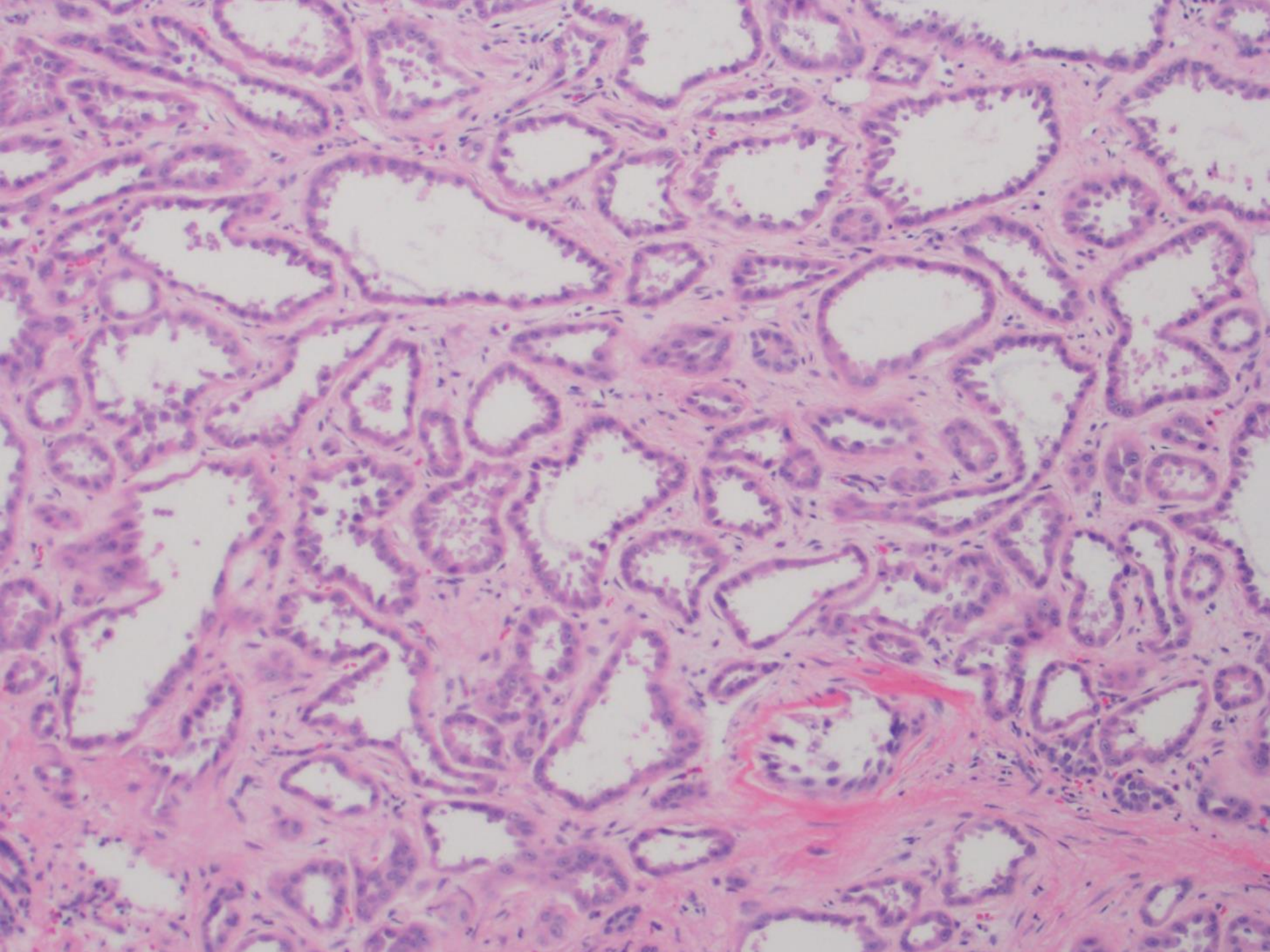
- 2.0 cm. well circumscribed spongy grey-tan mass

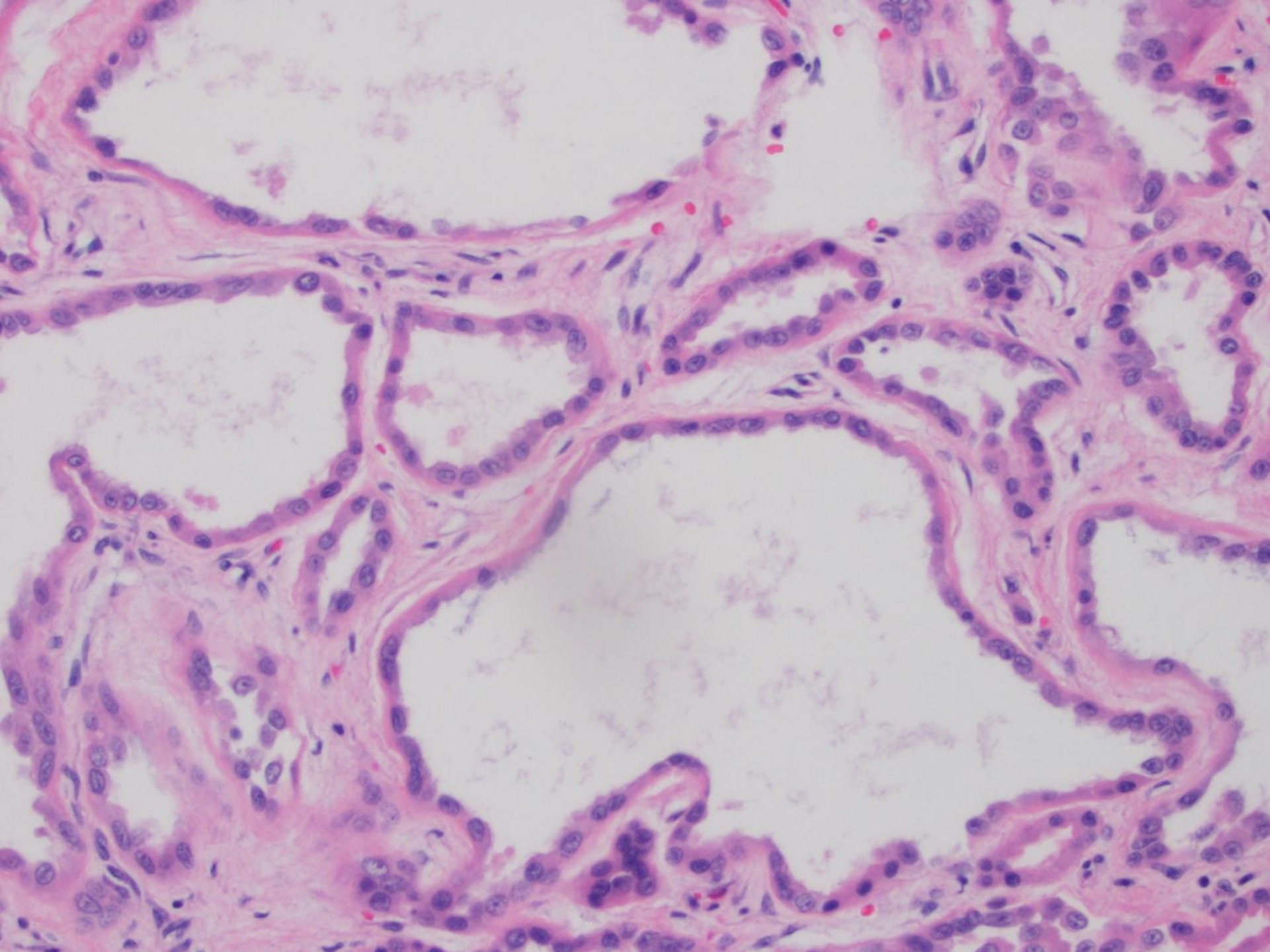
Histology

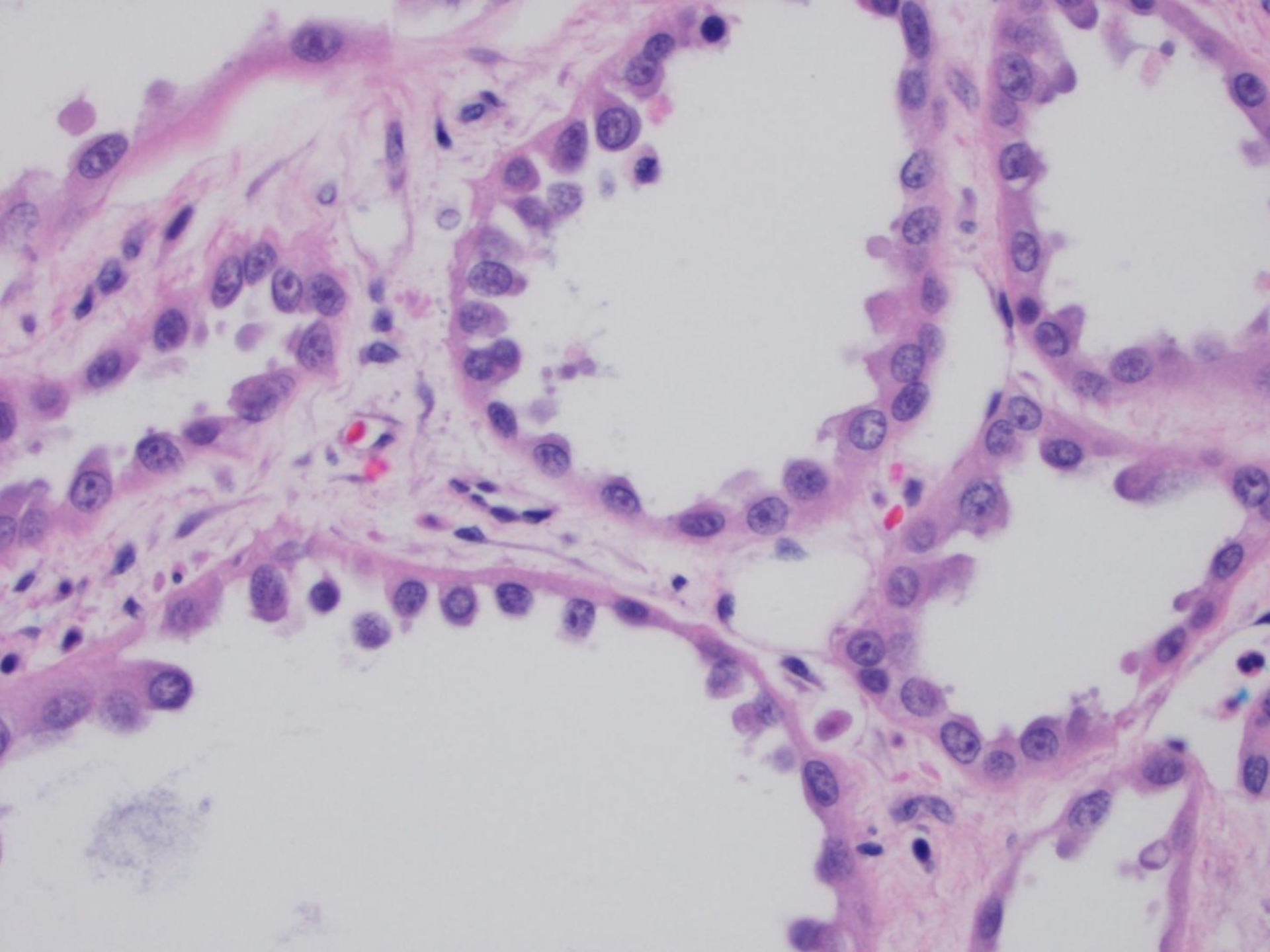
- Small to intermediate sized tubules admixed with cystically dilated tubules separated by fibrous stroma
- Lined by single layer of flat, “hobnail”, cuboidal to columnar cells with abundant eosinophilic cytoplasm, irregular nuclear membranes and occasional prominent nucleoli (Fuhrman nuclear grade does no prognostic value)
- Cellular stratification and papillations are uncommon and very focal
- IHC - +CK7,AMACR/CD10











DDX

- Multilocular cystic RCCA – Lined by clear cells(usually Fuhrman 1/2), cellular clusters in fibrous septae
- Cystic nephroma – female predominance, larger cysts, ovarian-type/desmoplastic stroma
- Collecting duct CA – Multinodular, extensive desmoplasia, solid/papillary/glandular, intratumoral inflammation

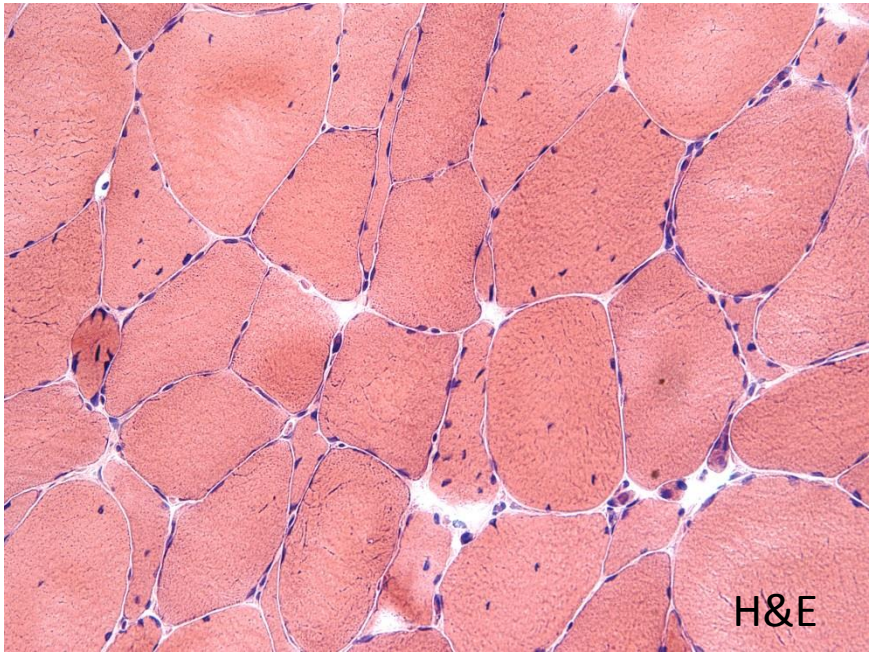
Clinical

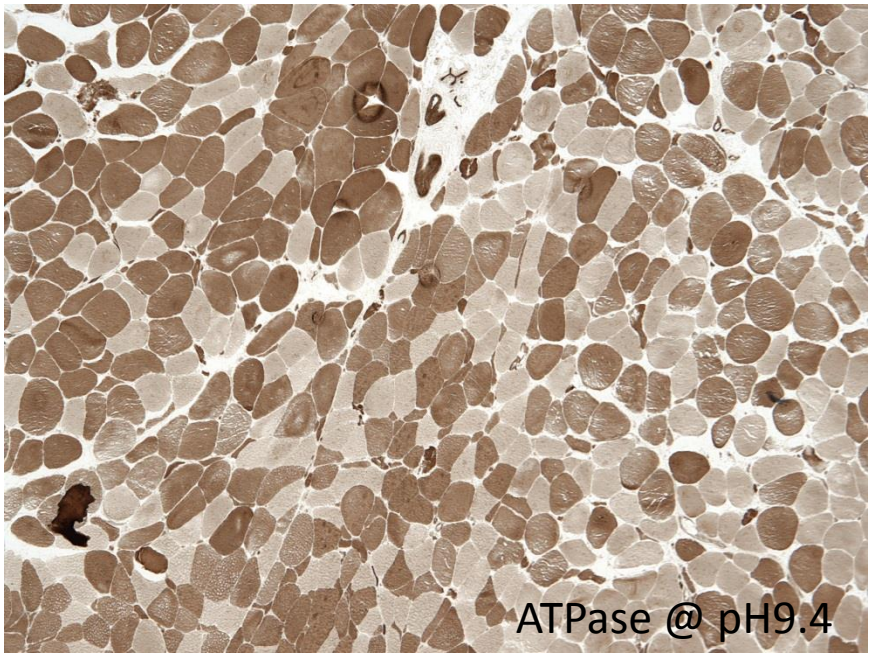
- Uncommon – 60 cases in literature
- Ages 34-94 (mean 60)
- Male:female 7:1
- Most asymptomatic
- Most low stage
- Disease progression in ~ 10%

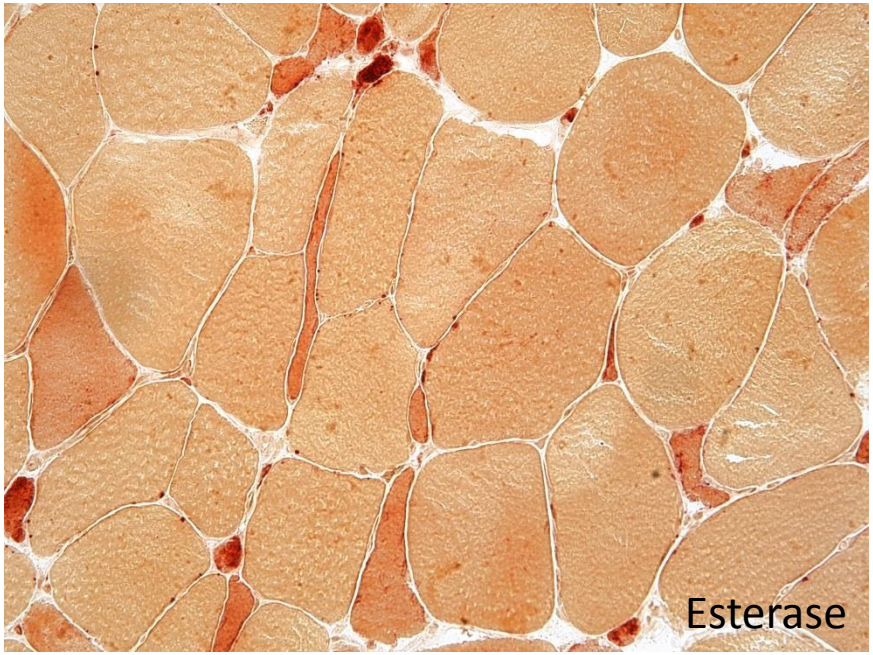
SB 5924

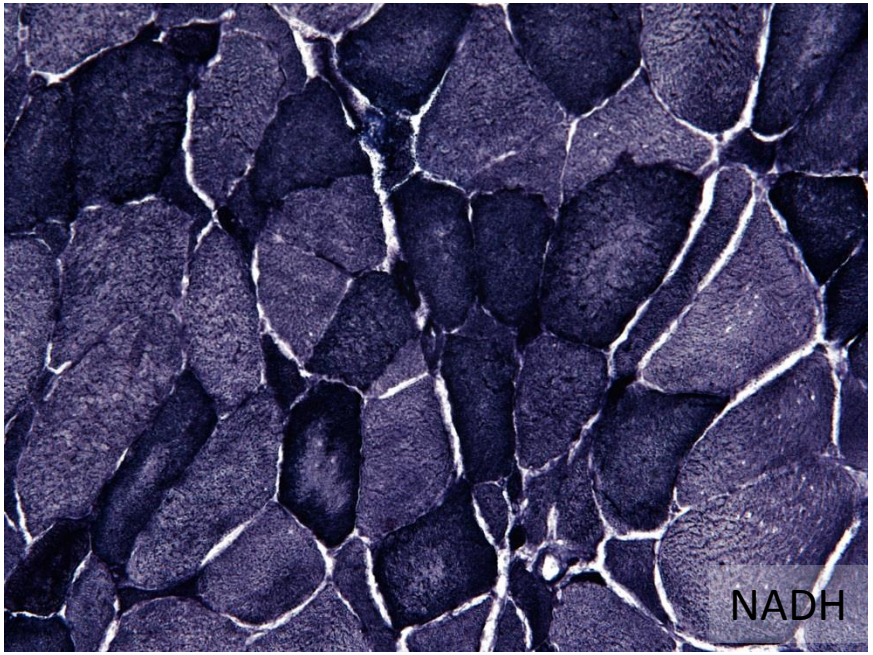
- 55 year-old male with presumed pituitary adenoma (1.6 cm hypo-enhancing mass in the left sella with infrasellar extension), hypothyroidism, hypogonadism, borderline thrombocytopenia/leukopenia, and muscle weakness reportedly compatible with a myotonic disorder. CK in the 600s. Left quadriceps muscle biopsy performed.

- Hannes Vogel; Stanford

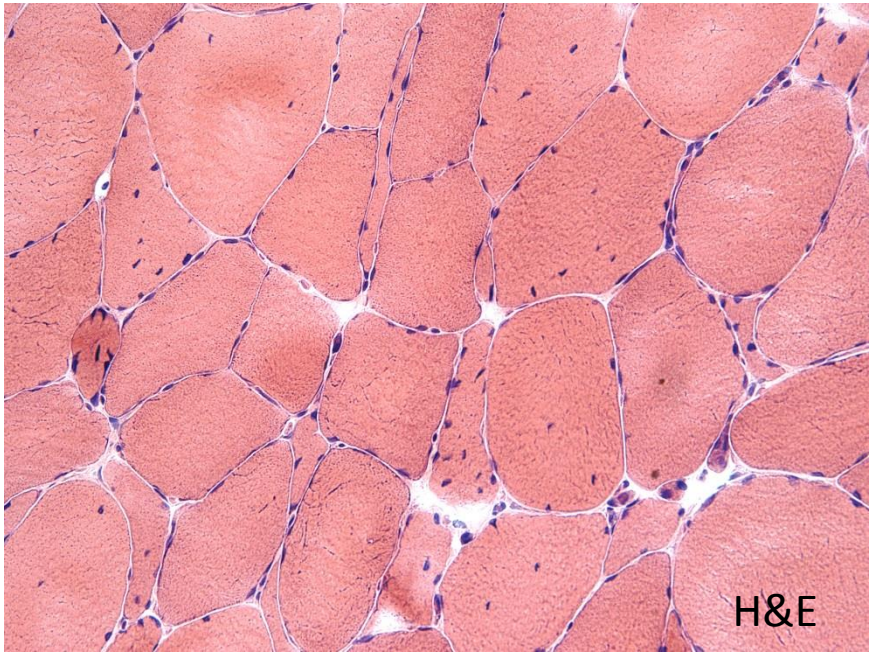

H&E


ATPase @ pH9.4


Esterase


NADH

Diagnosis?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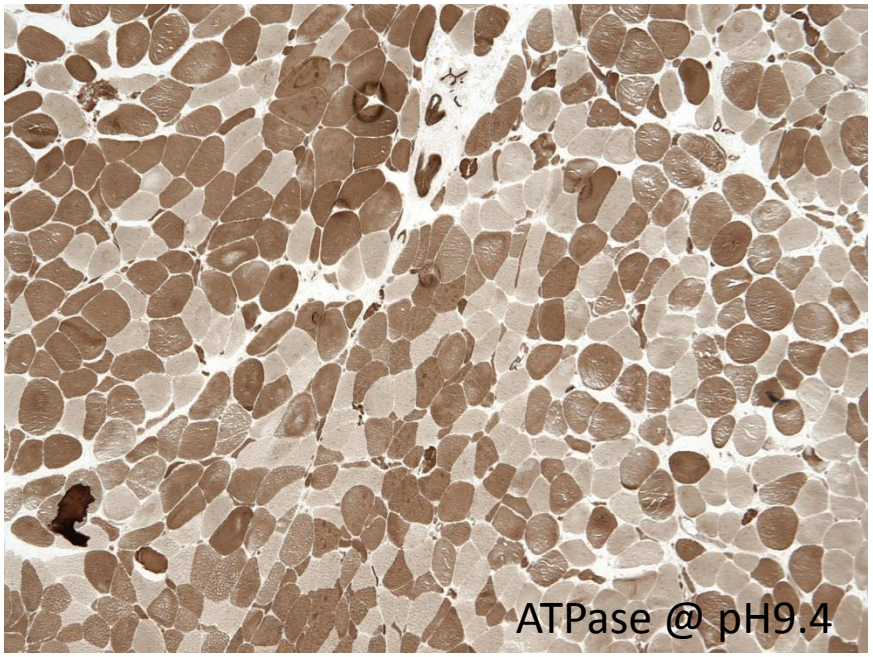
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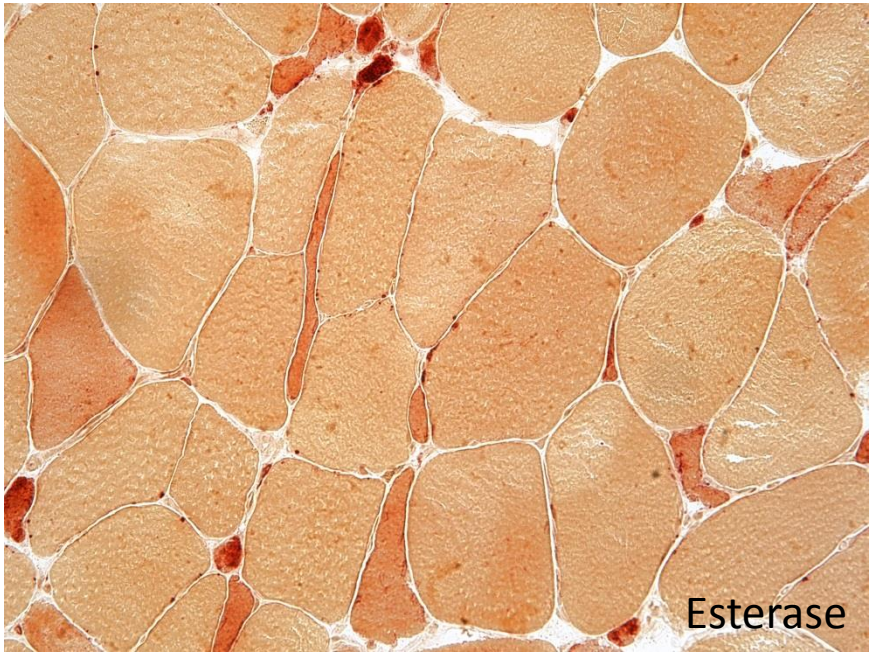
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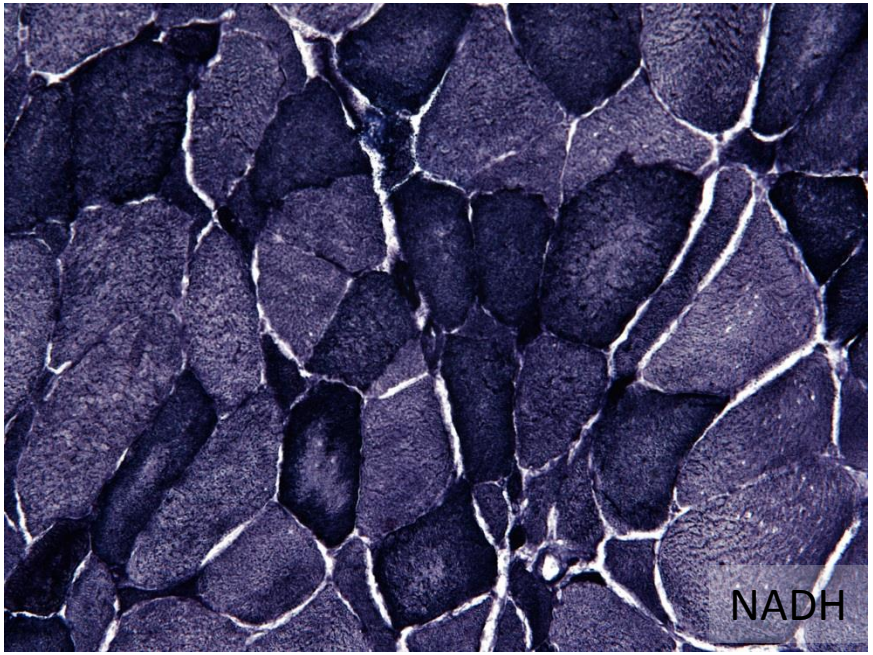

NADH

DIAGNOSIS:
MUSCLE, LEFT QUADRICEPS, BIOPSY
-- CHRONIC MYOPATHIC PROCESS (SEE COMMENT)

ZISKIN/BORN/DAY/VOGEL

COMMENT: Thank you for sending us this interesting case in consultation. The muscle biopsy shows features of a chronic myopathic process with many fibers showing numerous internally placed nuclei, frequent nuclear bag fibers, several acutely angulated esterase positive fibers, and many fibers showing acid phosphatase positive granules. In light of the reported history of elevated CK, hypogonadism, and clinical concern for a myotonic disorder, the biopsy findings are most suggestive of myotonic dystrophy type 2 (DM2) however DM1 cannot be completely excluded. Clinical correlation and genetic testing is recommended.

PATIENT IDENTIFICATION: [redacted] is a 56 y.o. male who was seen for a Genetics evaluation on 03/13/2014 due to recent diagnosis of Myotonic Dystrophy Type II (DM2) based on his clinical presentation and a muscle biopsy. Subsequent to that visit, testing for a panel of genes known to be associated with myotonia was sent. This panel included DMPK (DM1), ZNF9 (DM2), CLCN1 and SCN4.

RESULTS: Results of genetic testing show that [redacted] has a repeat expansion in ZNF9, a gene known to be associated with Myotonic Dystrophy Type II. The expansion in the patient is greater than 15,690 base pairs. This finding confirms the diagnosis of Myotonic Dystrophy Type II (DM2). It should be noted that the size of the repeat in this condition cannot be used in any way to predict the age of disease onset, rate of progression or severity. All other testing was negative. No mutations or repeat expansions were noted in DMPK, CLCN1, or SCN4.

- Myotonic dystrophy 2; DM2 *AKA* Dystrophia myotonica 2, Proximal myotonic myopathy; PROMM

- Caused by a (CCTG)*n* expansion in intron 1 of *ZNF9* in 3q21.3.

- Clinical features
  - Onset 8 to 60 years
  - Weakness: slowly progressive, proximal: legs > arms
  - Calf enlargement
  - Muscle pain or discomfort, variable from day-to-day
  - Myotonia
  - CNS: Clinical: Usually normal
    - Imaging: MRI: > 50% with white matter hyperintensity on T_2
- Systemic

  Cataracts: 100% over 20 years with slit lamp

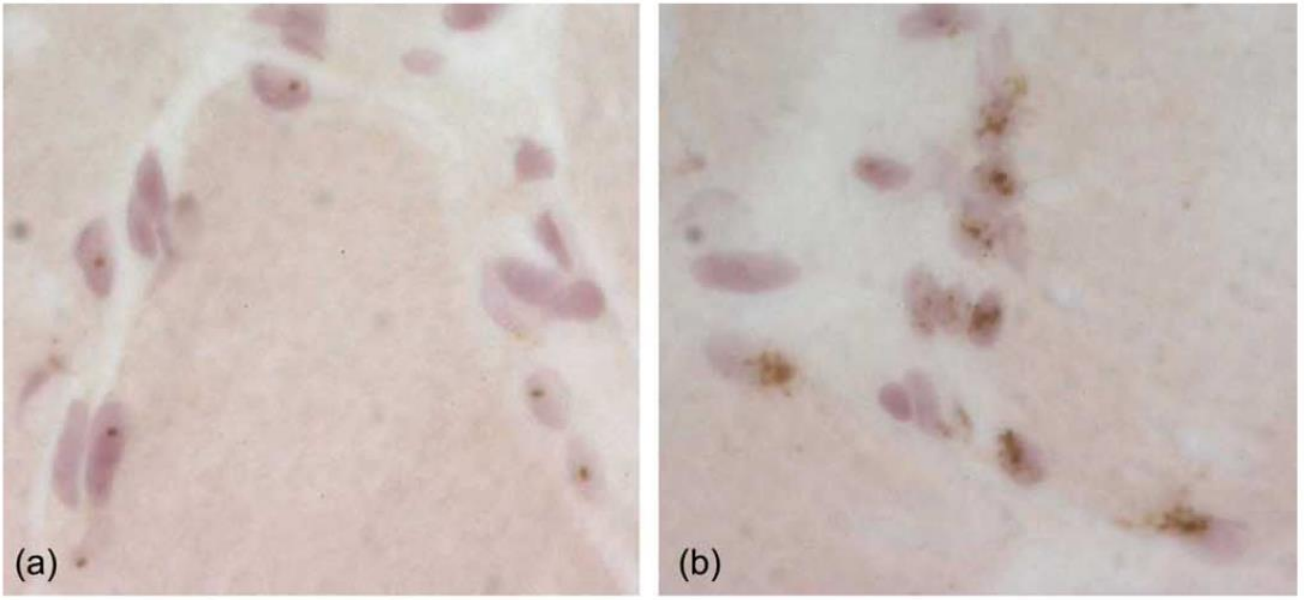
  Cardiac arrhythmias: 20%; Conduction defects

  Diabetes mellitus: 20%

  Hearing loss: 20%

  Fertility: Normal or Reduced

  Cardiovascular autonomic function: Normal



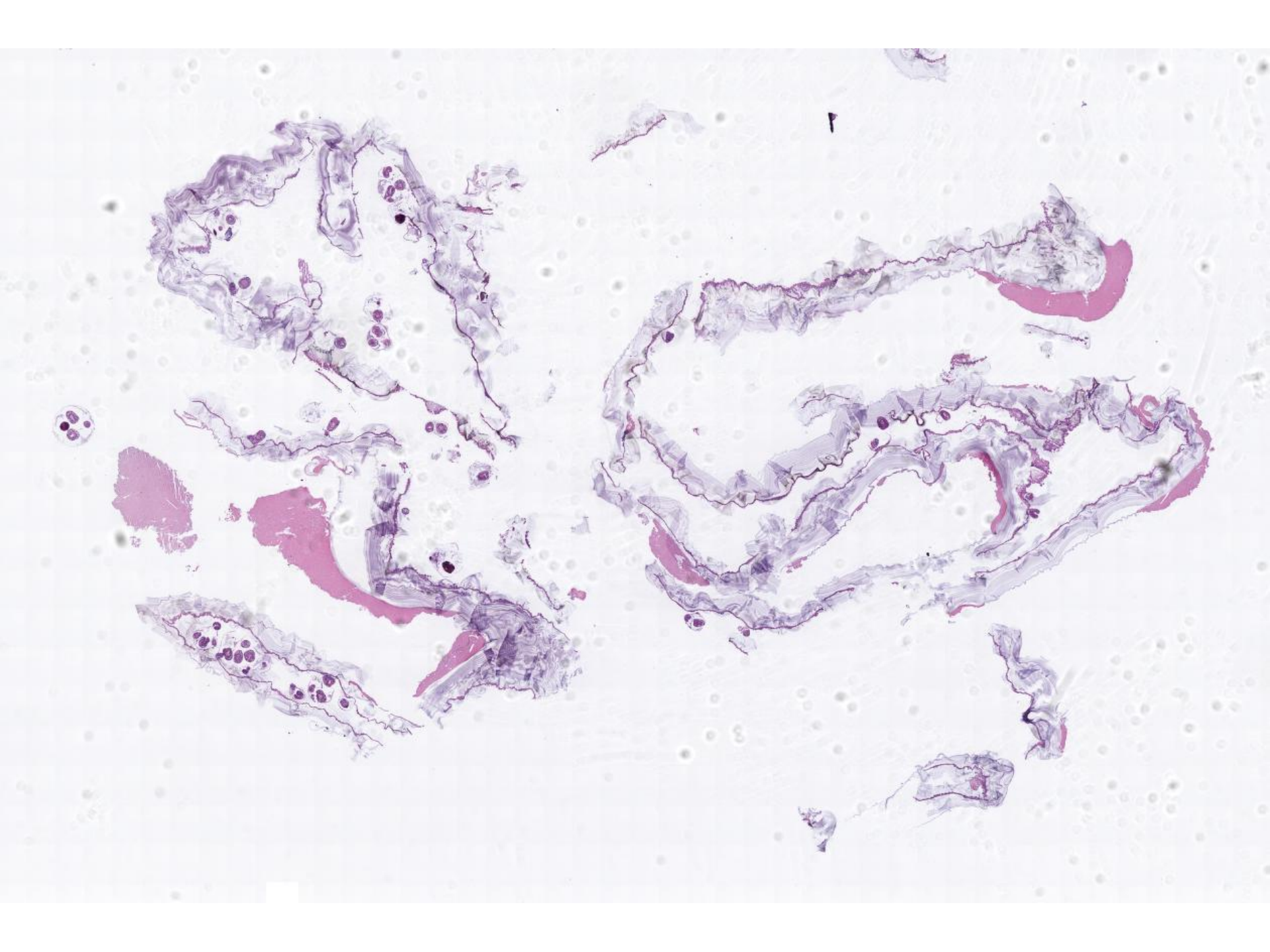
$(CCTG)_8$ sense oligonucleotide (a, DM2 patient frozen muscle)

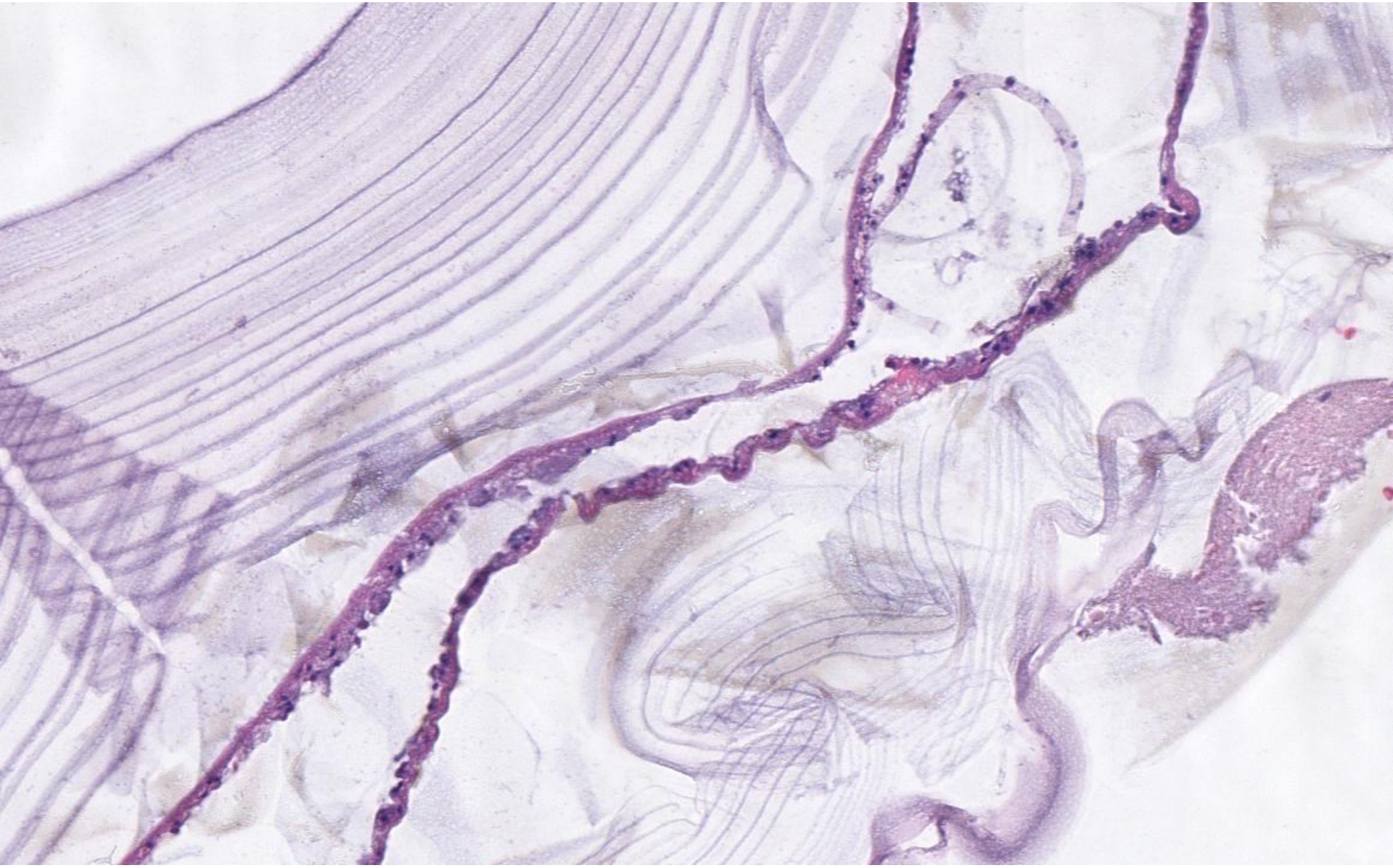
Ribonuclear inclusions containing accumulated mutant RNAs; $(CAGG)_8$ antisense oligonucleotide

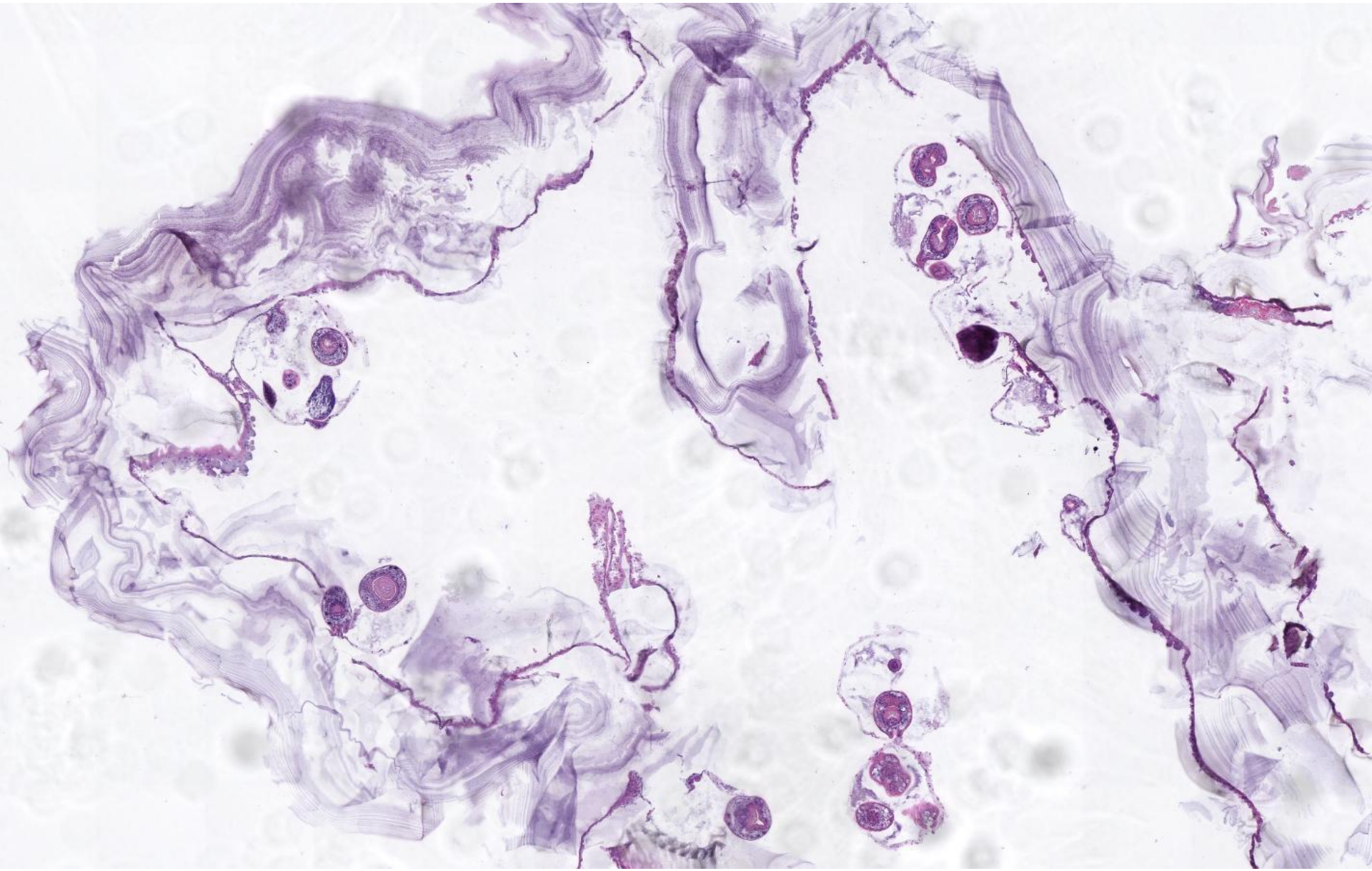
SB 5925

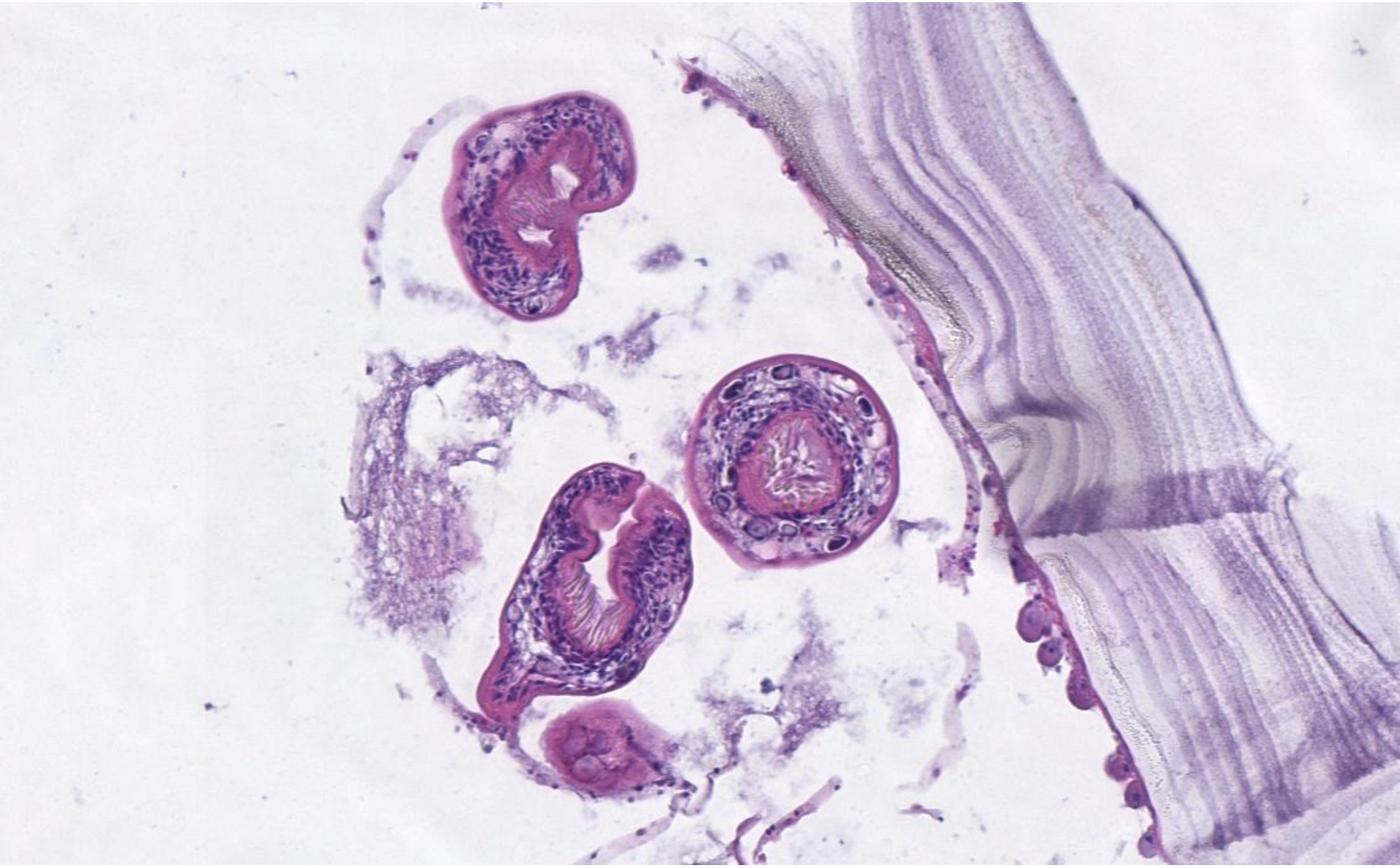
- 30-year-old female with liver mass.

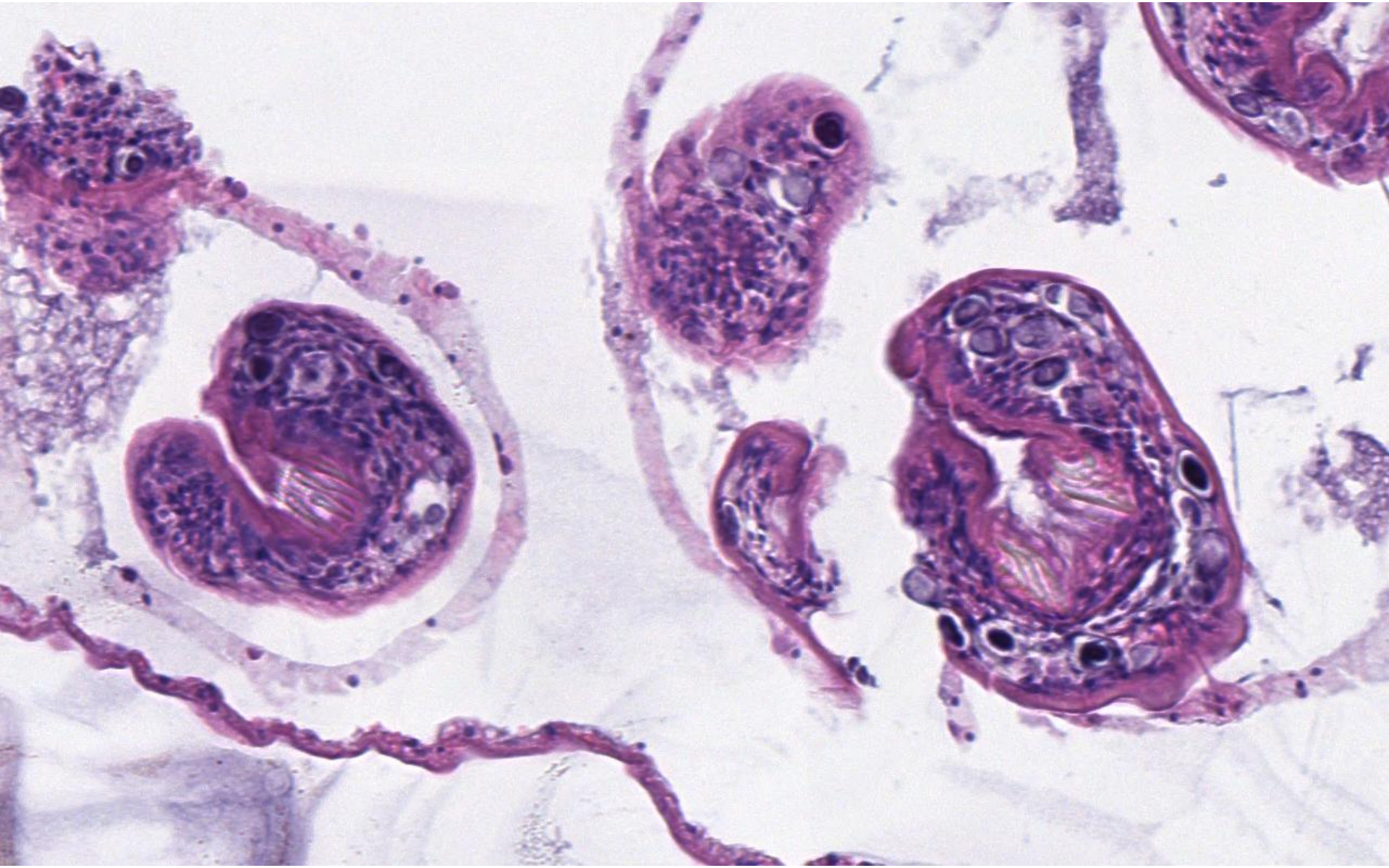
- Dave Bingham; Stanford



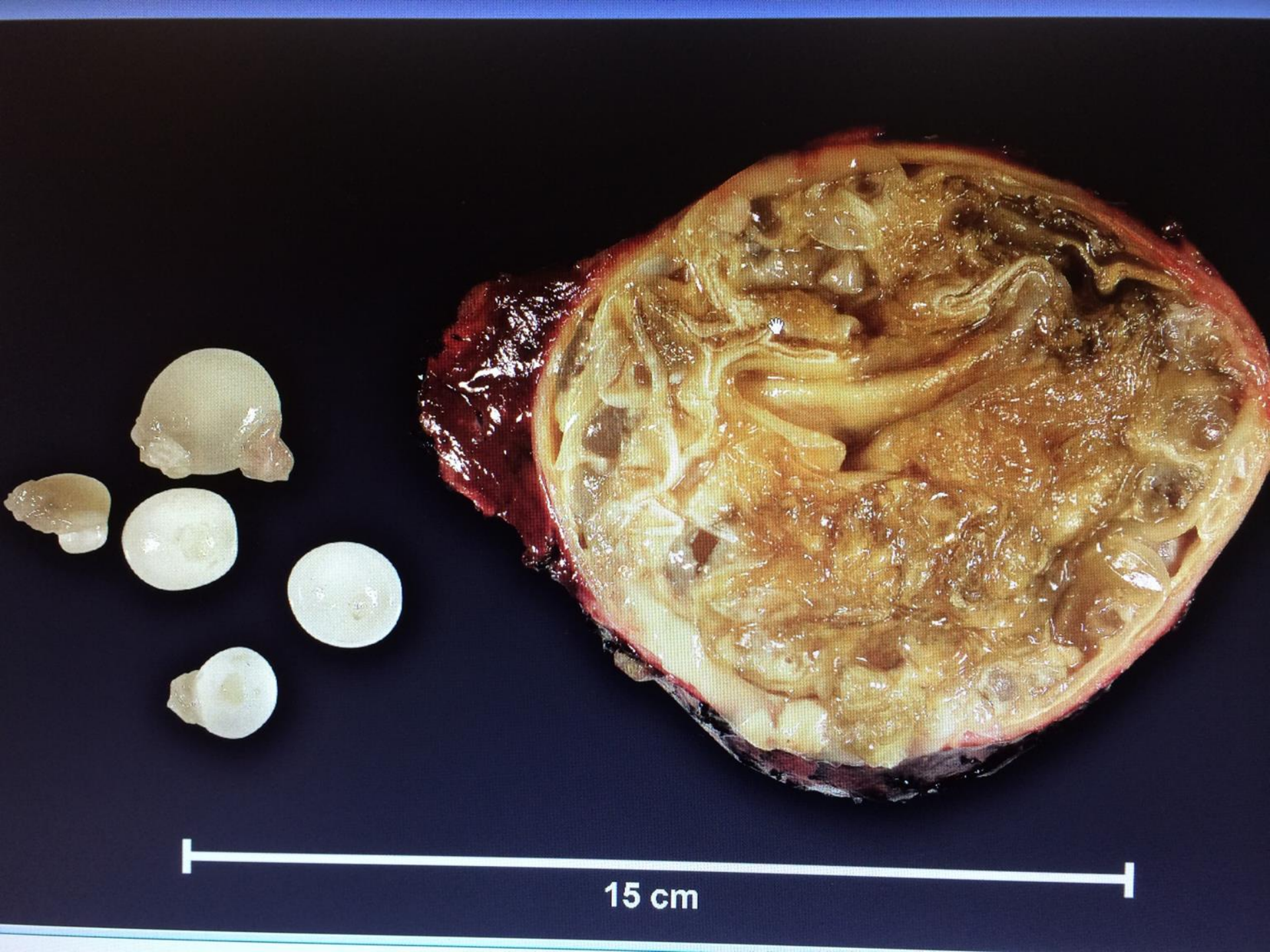


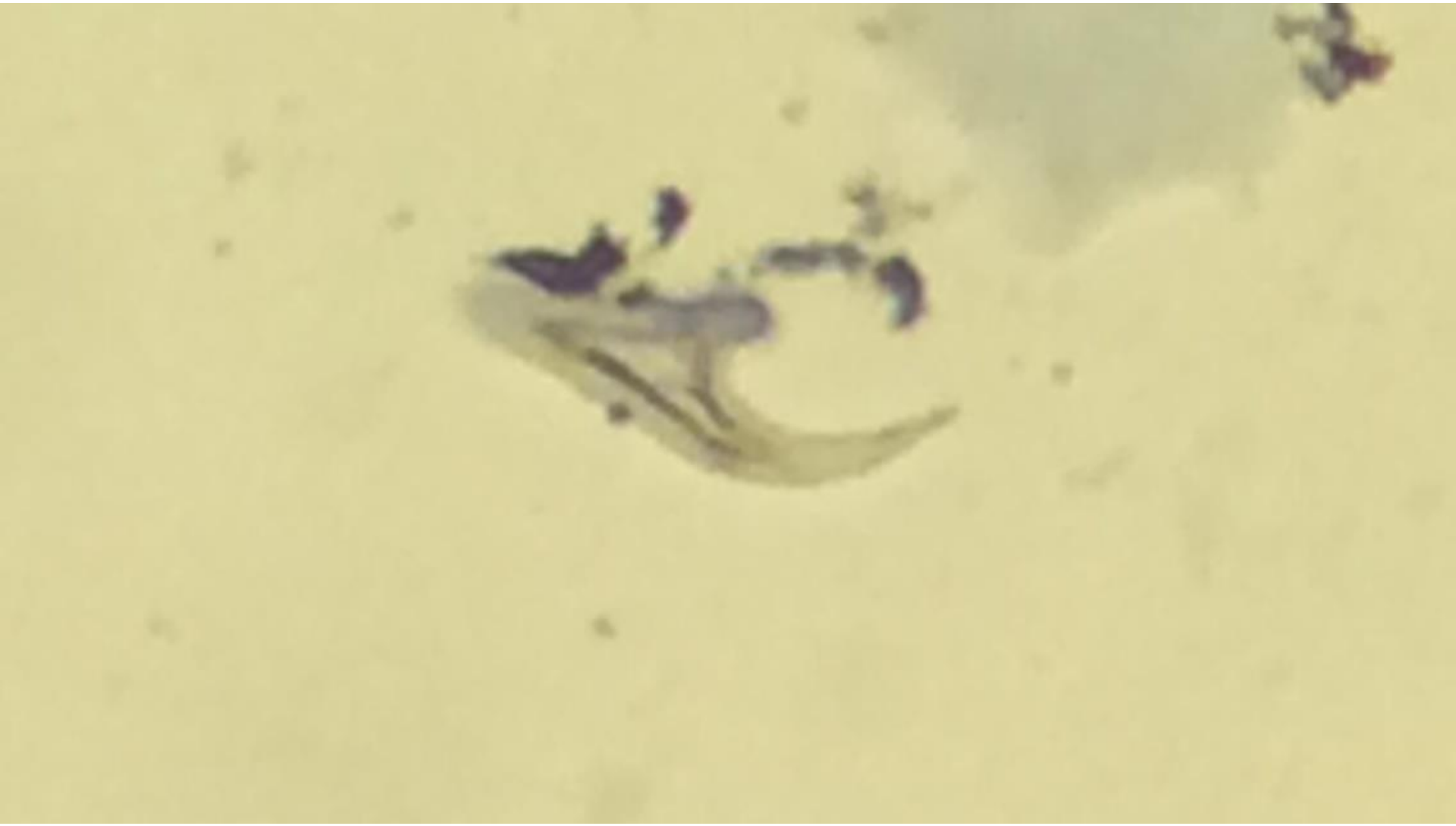


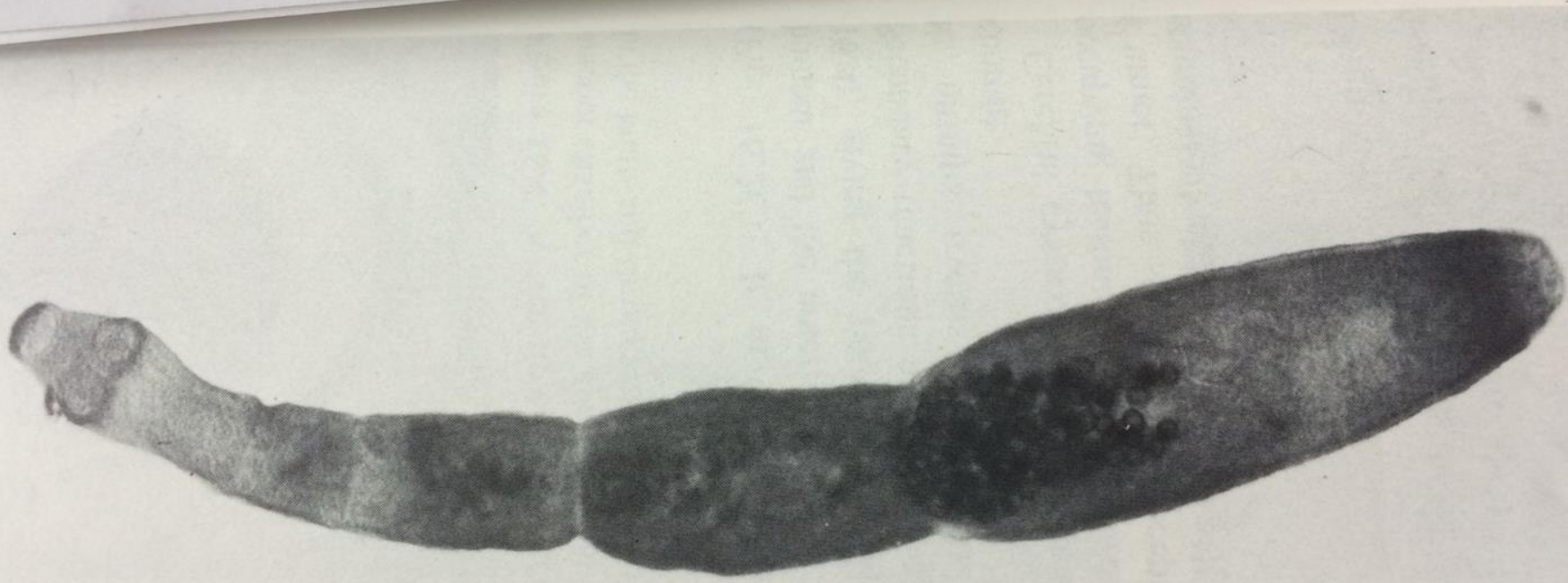


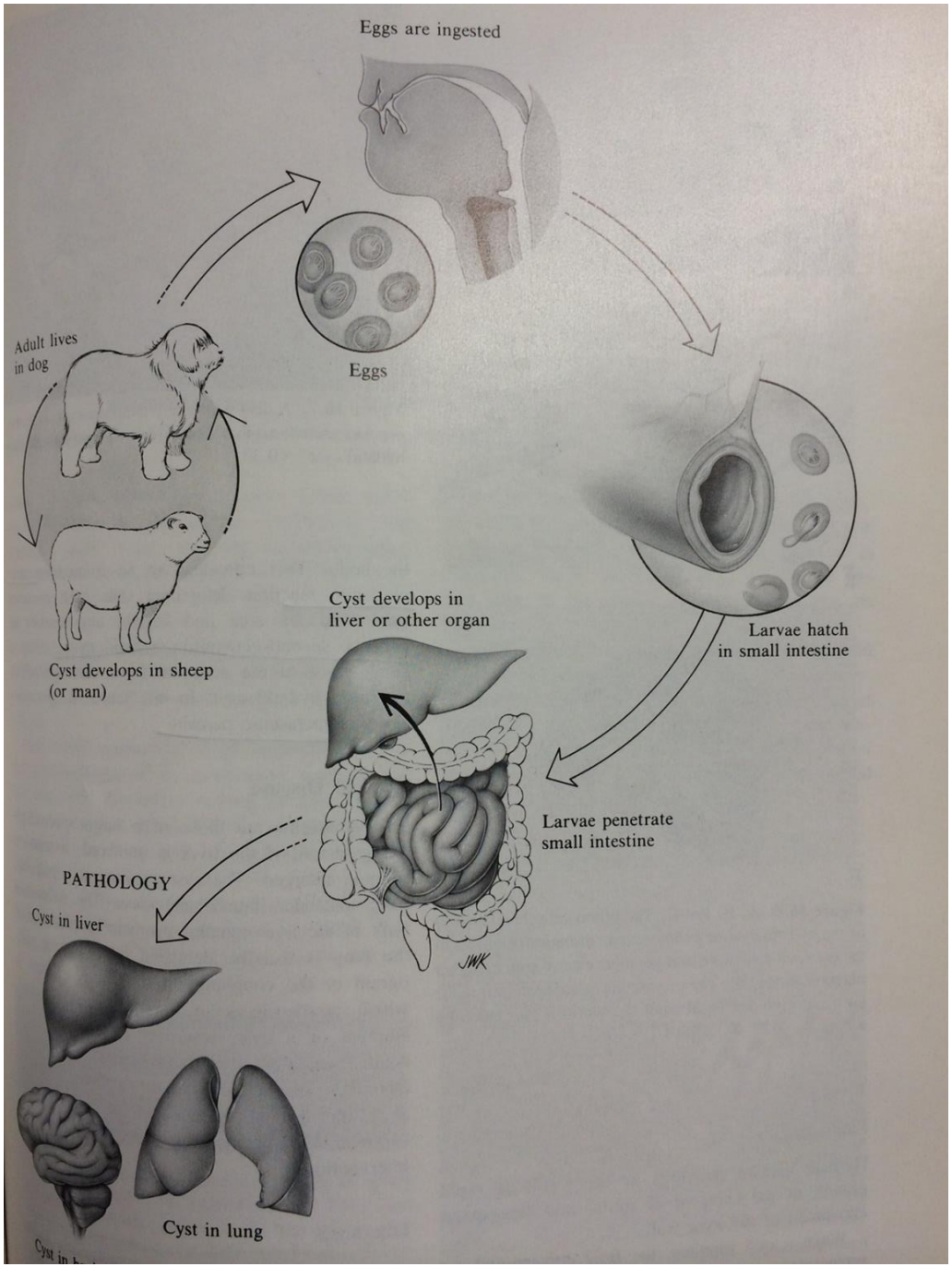


Diagnosis?


15 cm



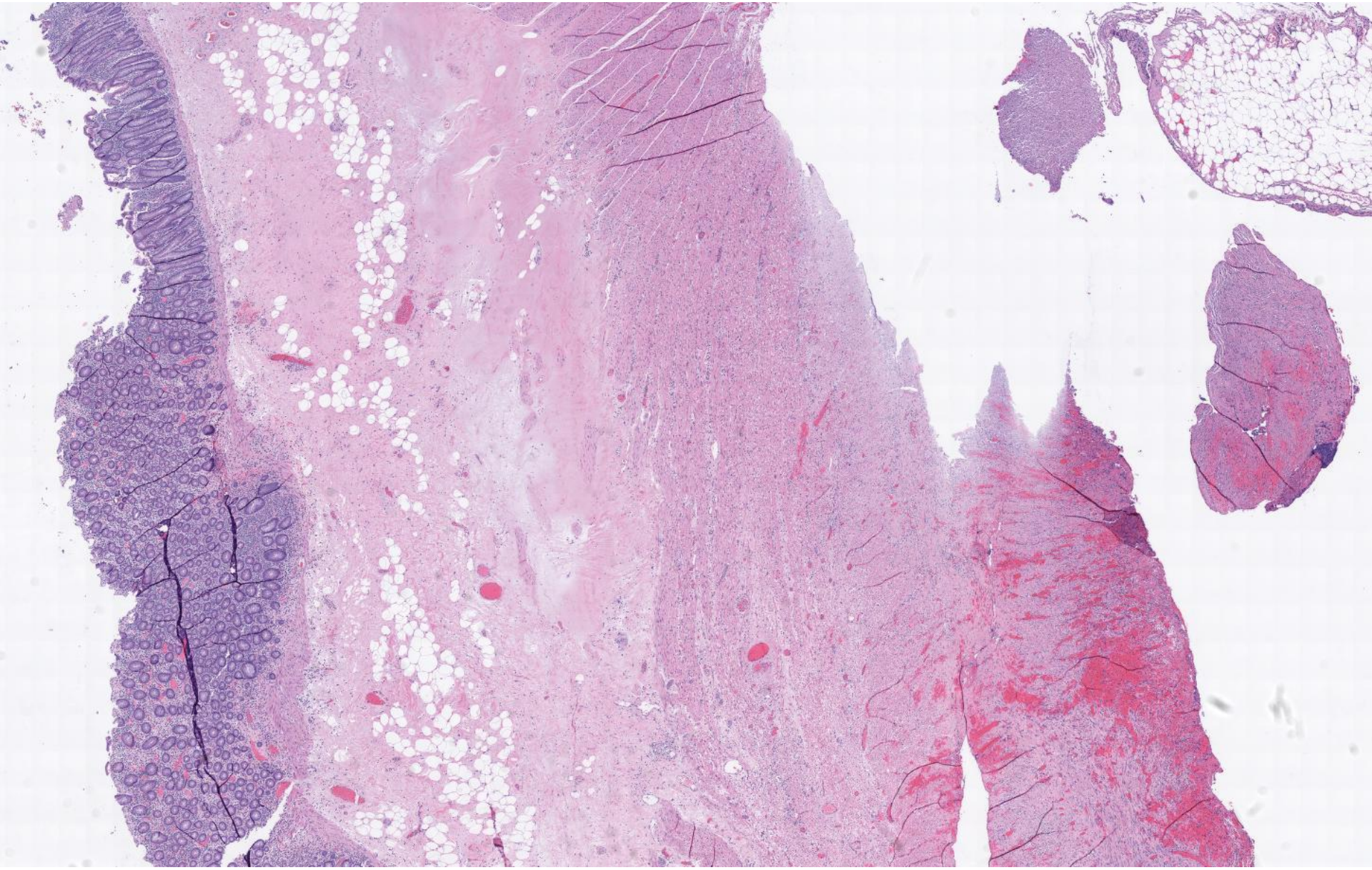


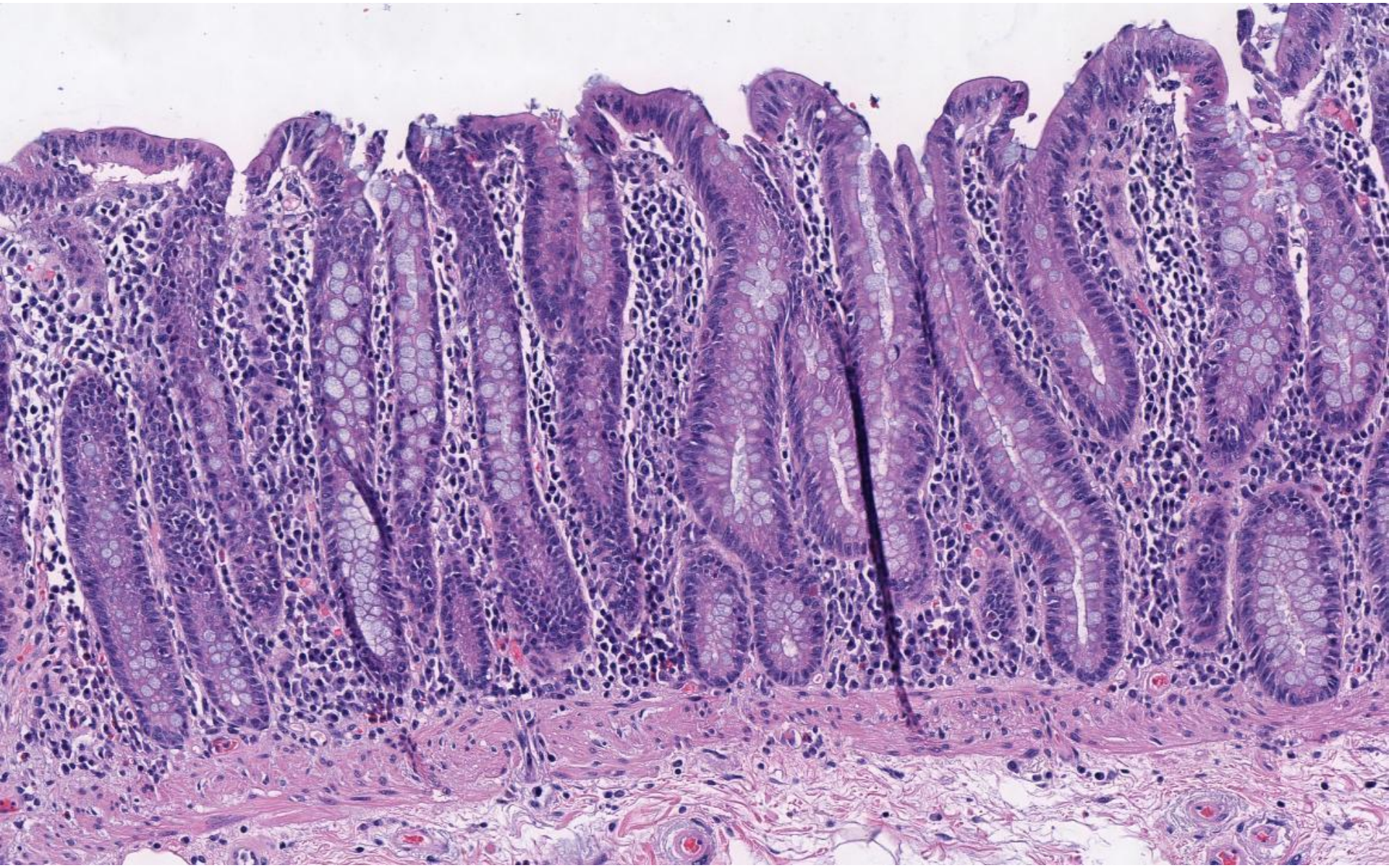

Eggs are ingested
Eggs
Adult lives in dog
Cyst develops in sheep (or man)
Larvae hatch in small intestine
Cyst develops in liver or other organ
Larvae penetrate small intestine
PATHOLOGY
Cyst in liver
Cyst in lung
JWK

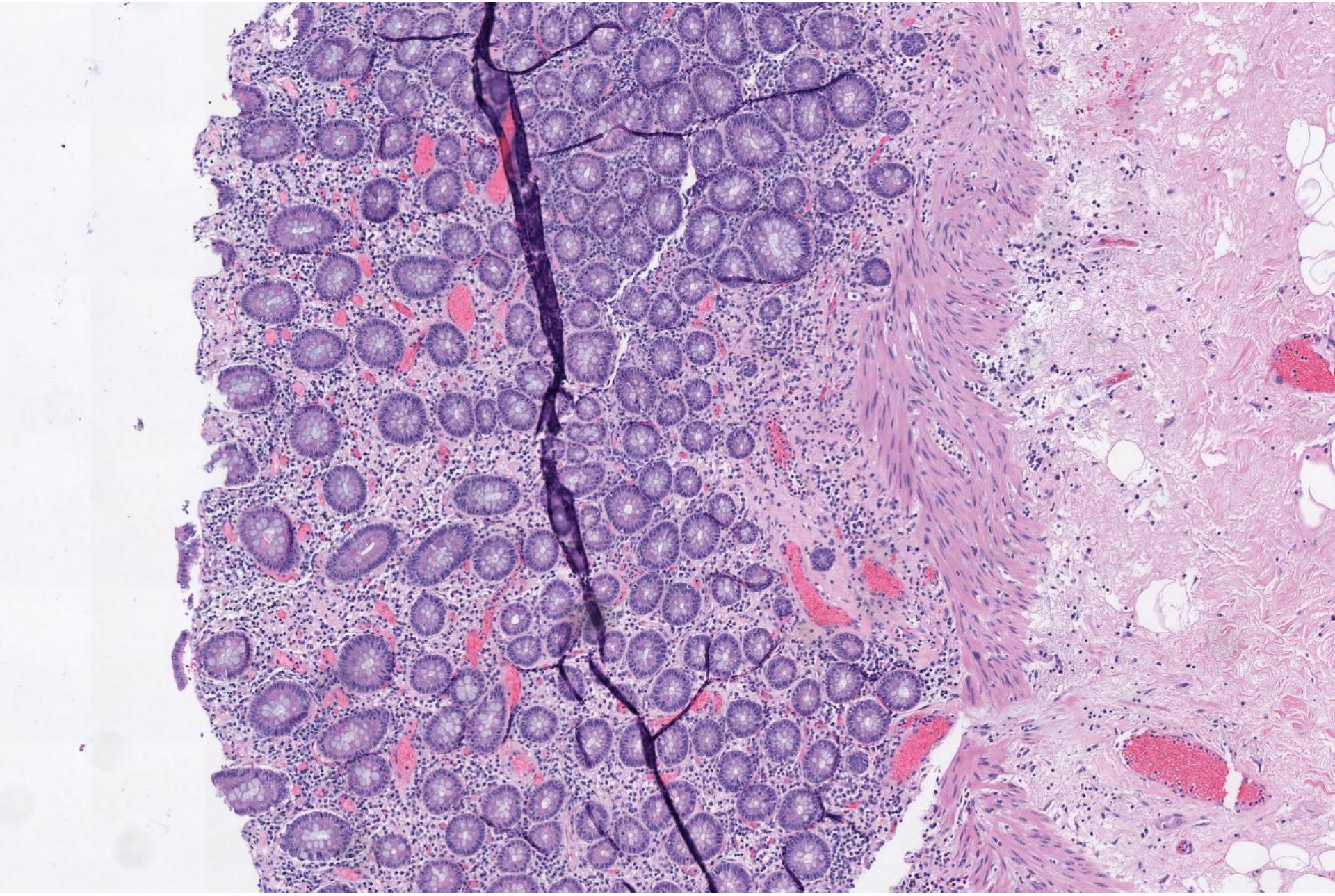
SB 5926

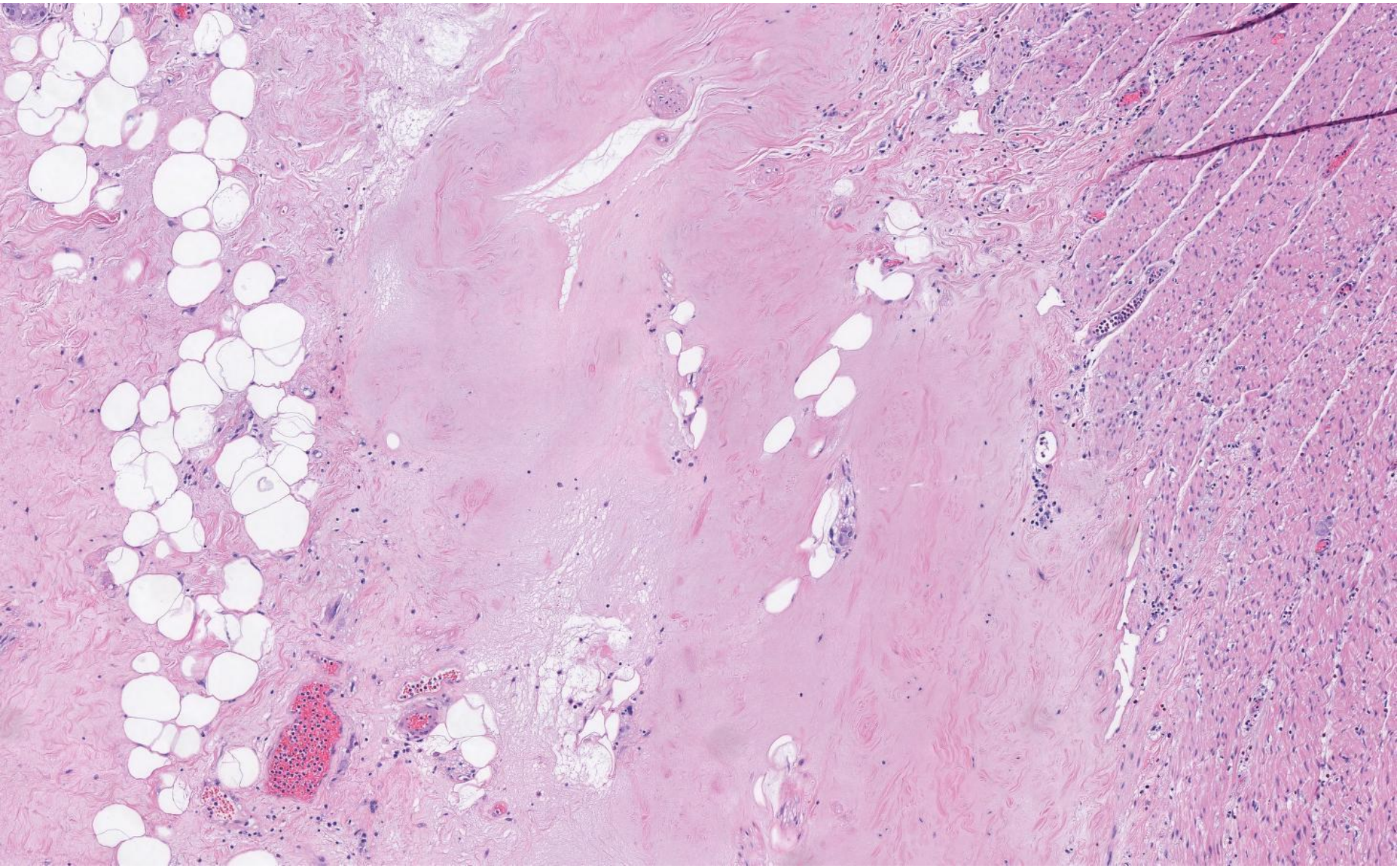
- 71-year-old female with bowel obstruction and a remote history of endometrial carcinoma.

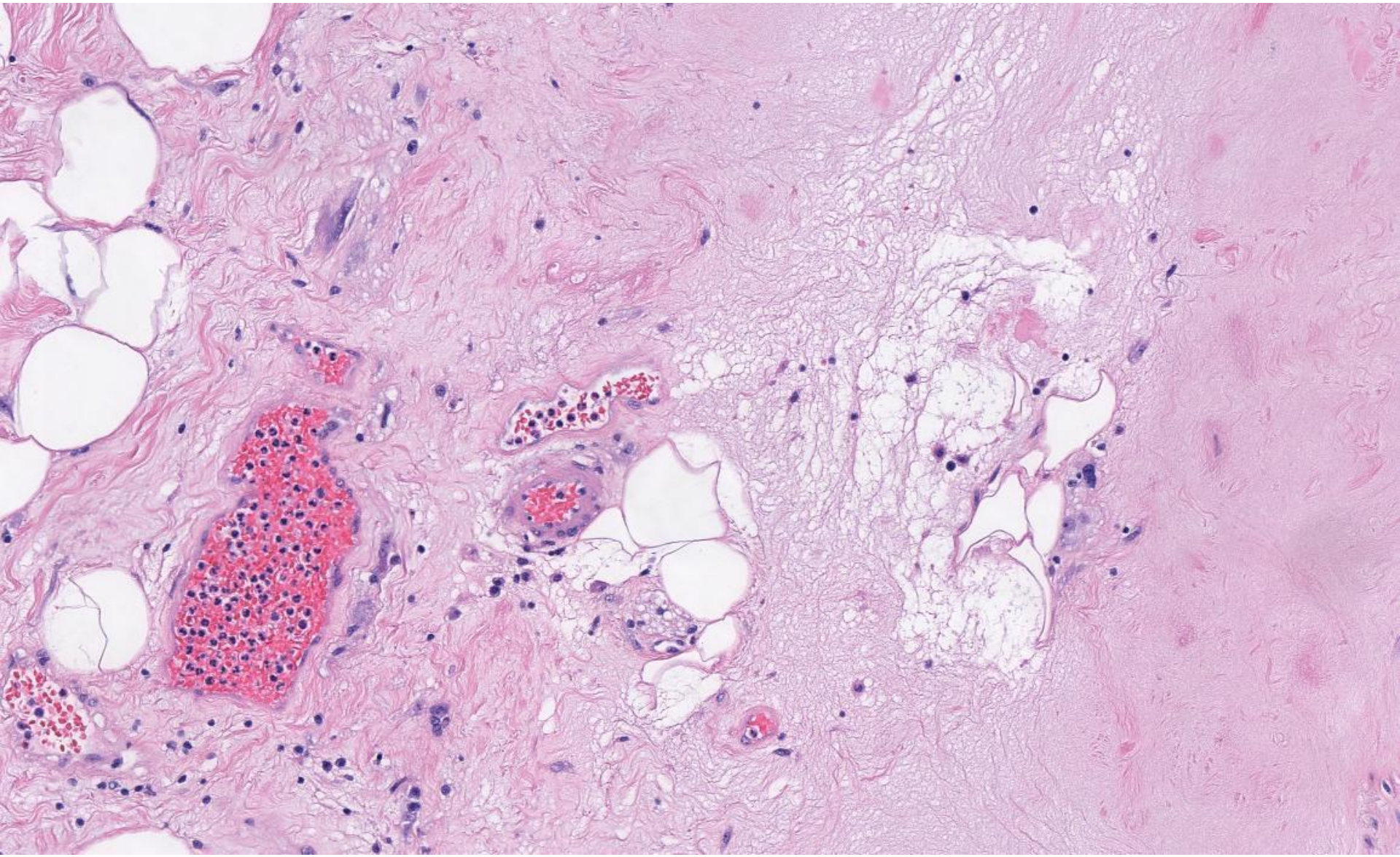
- Dave Bingham; Stanford

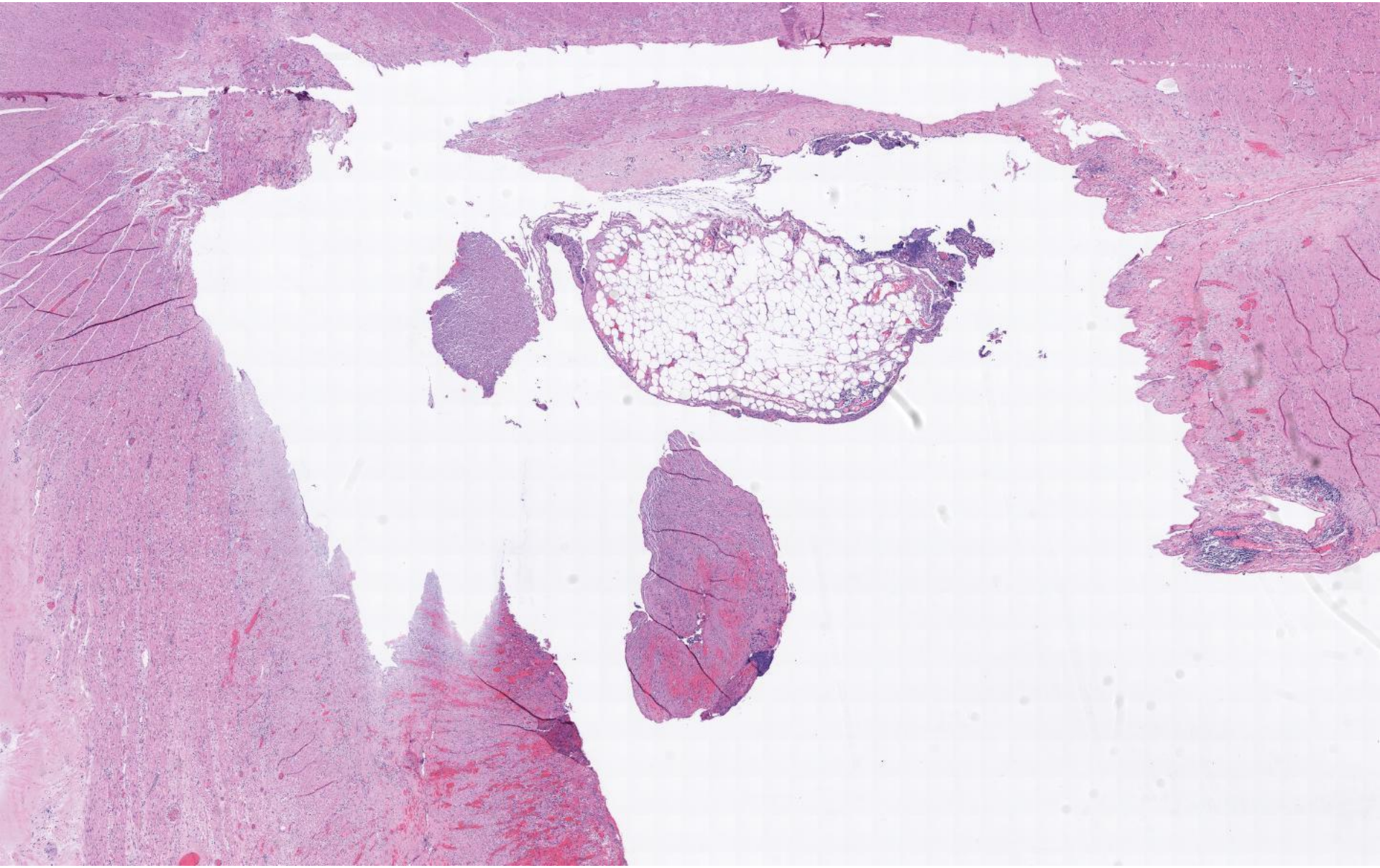


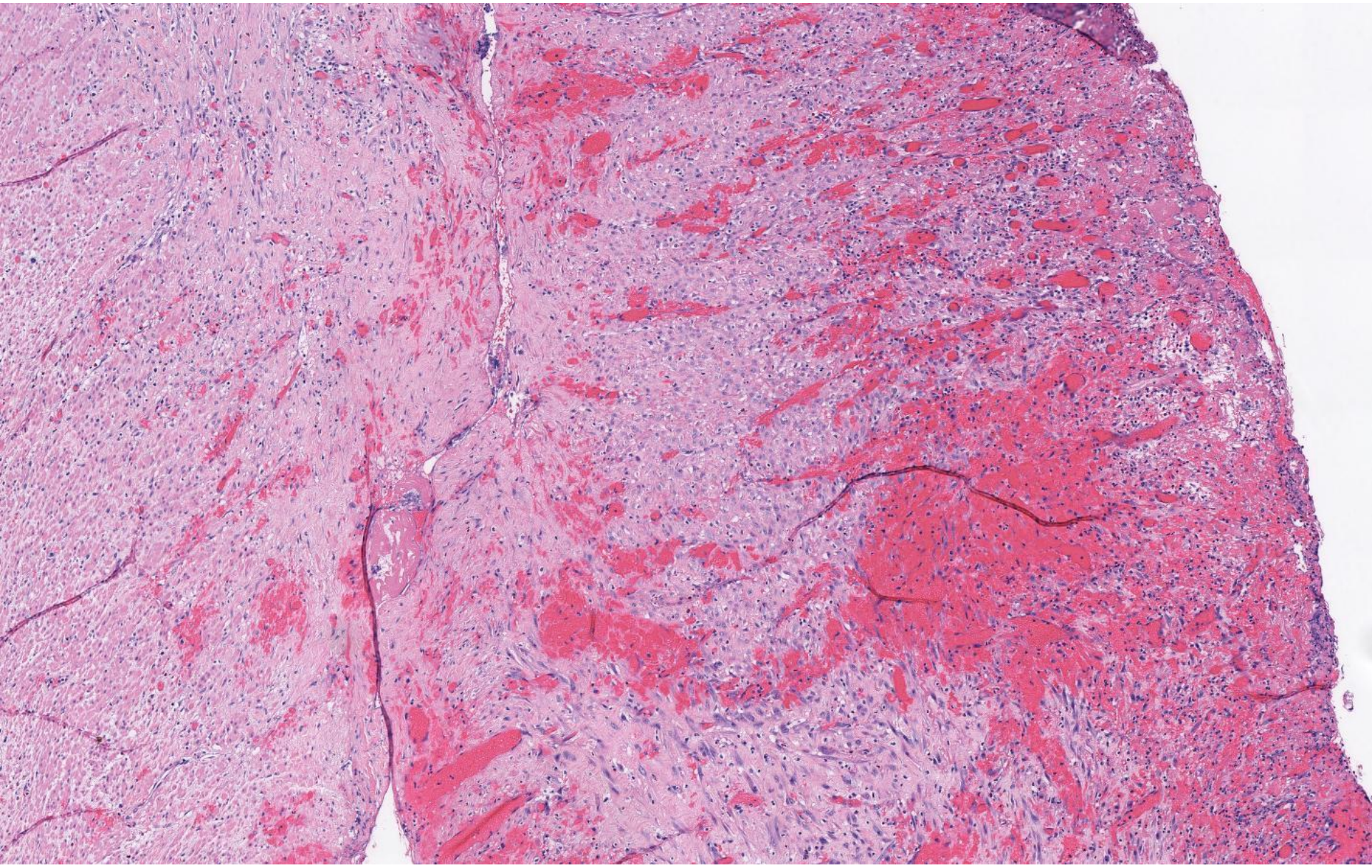












Diagnosis?

SB 5926

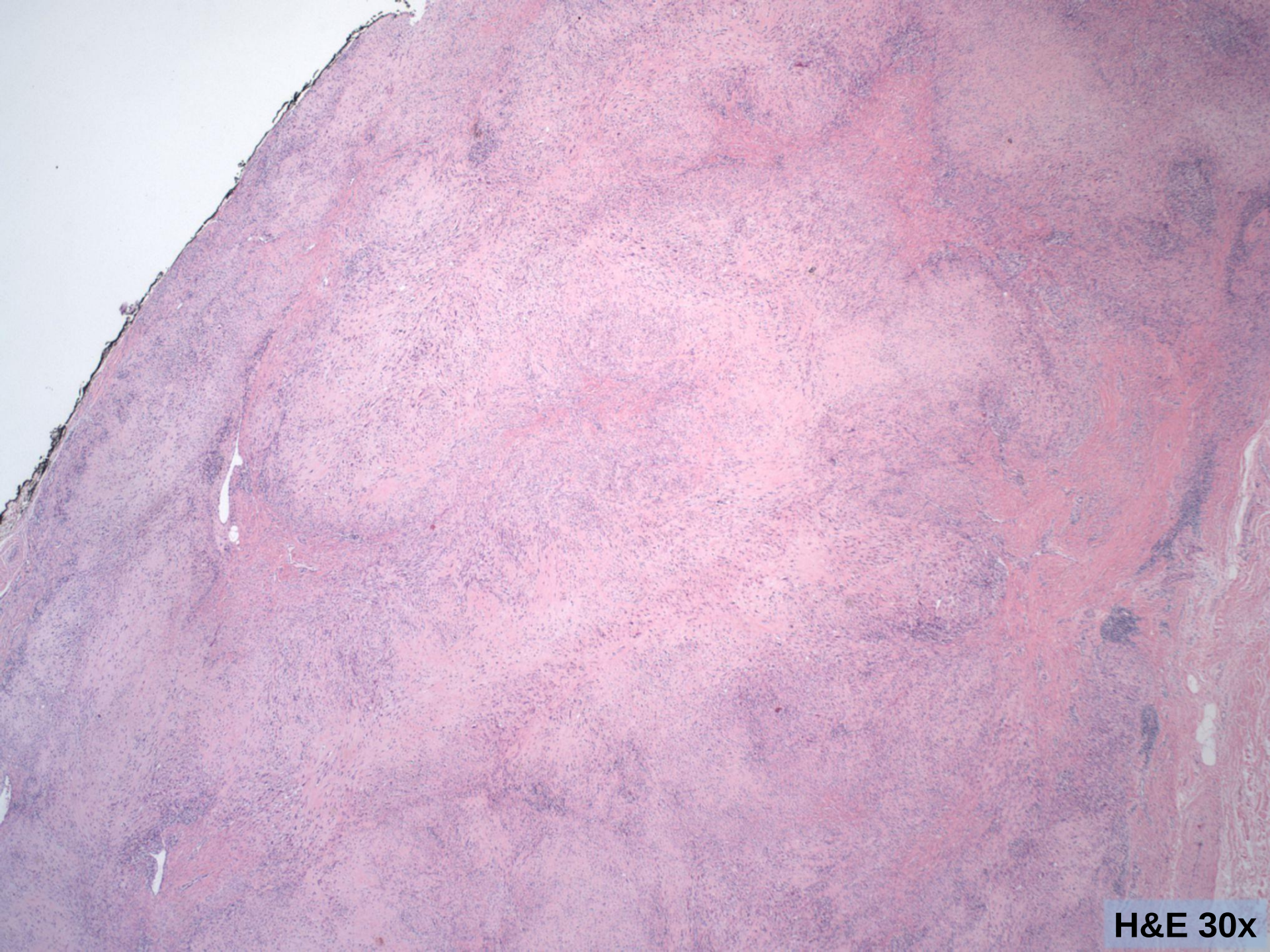
- 71-year-old female with bowel obstruction and a remote history of endometrial carcinoma.

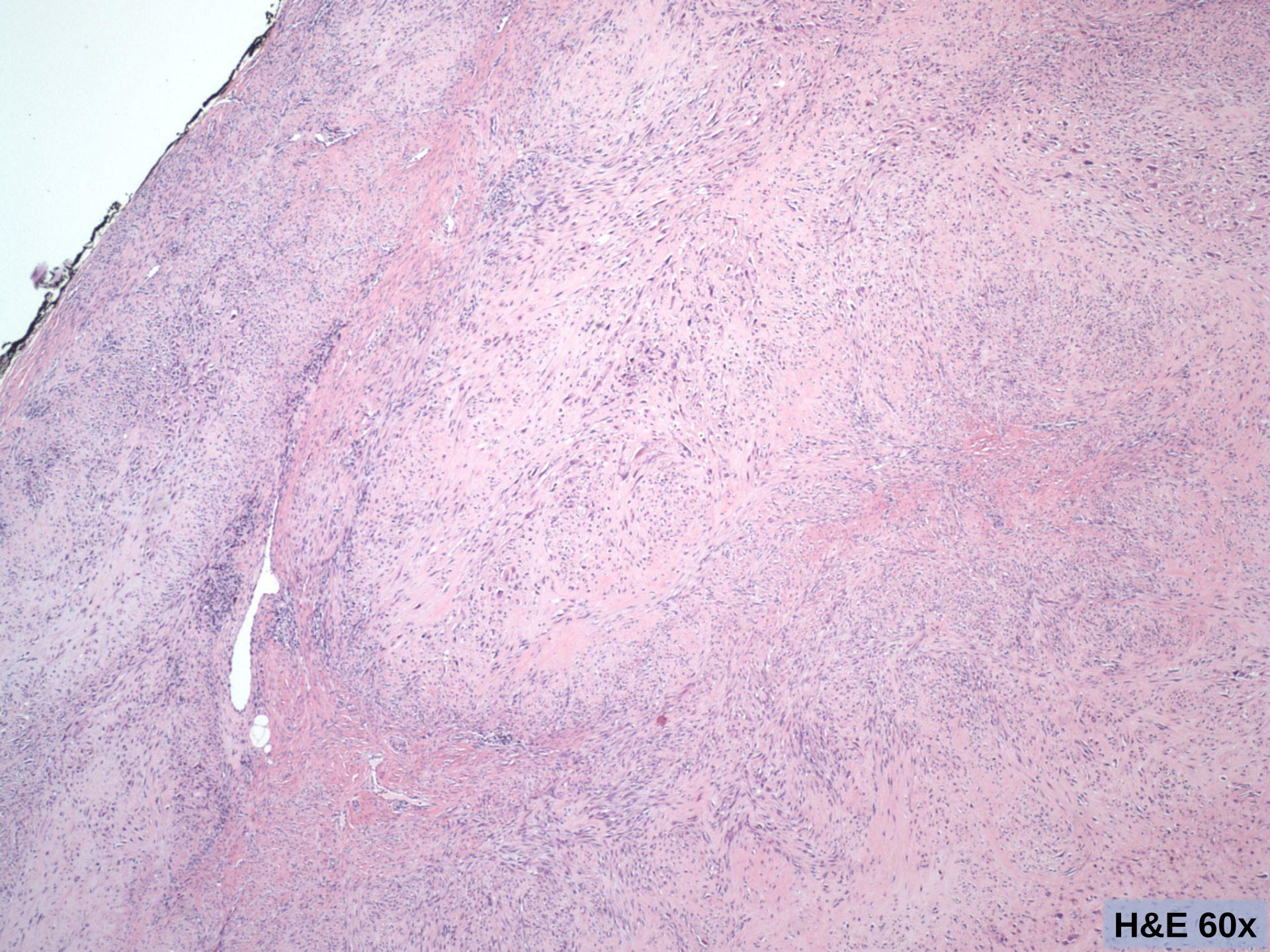
- Dave Bingham; Stanford

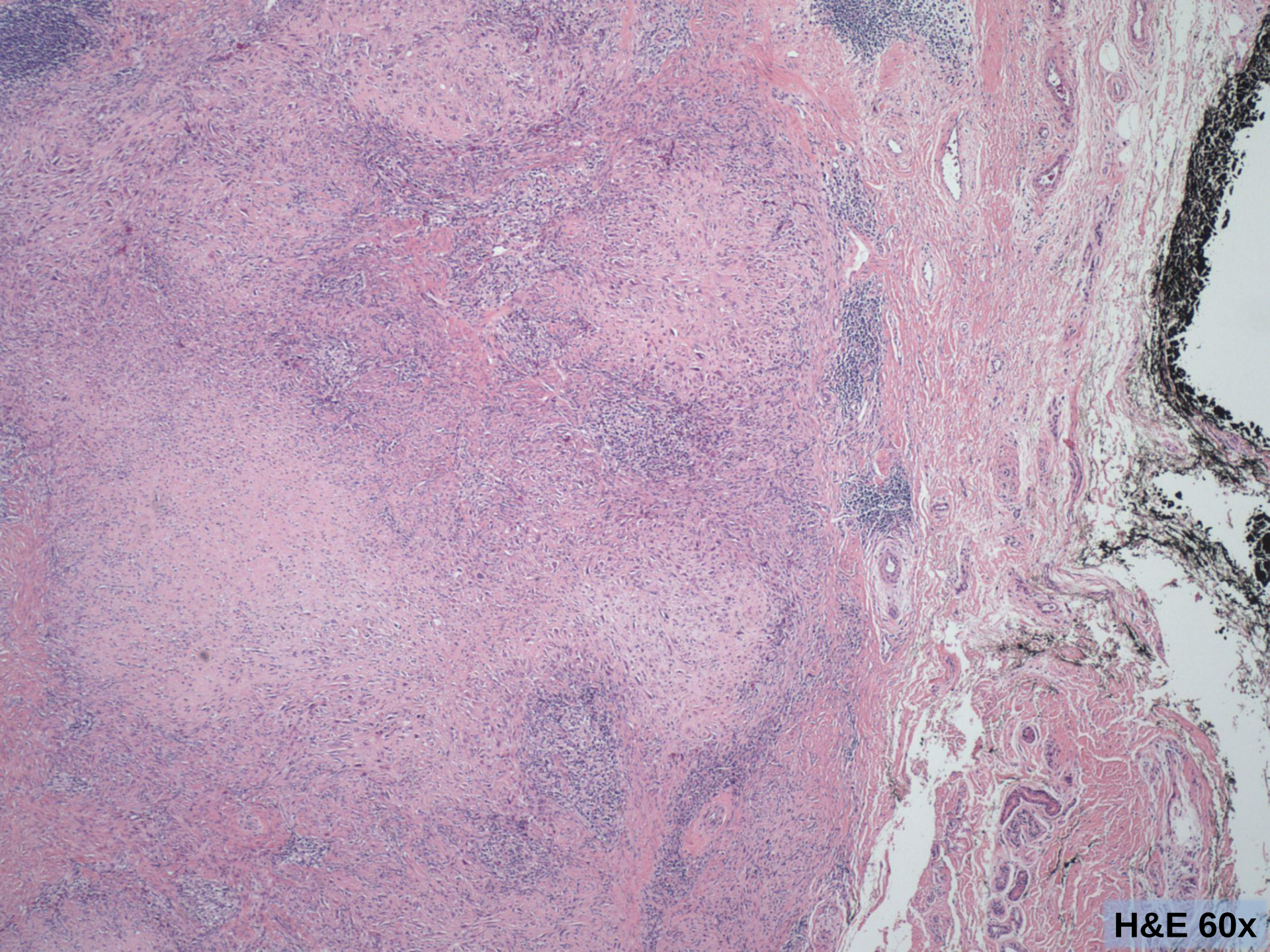
SB 5927

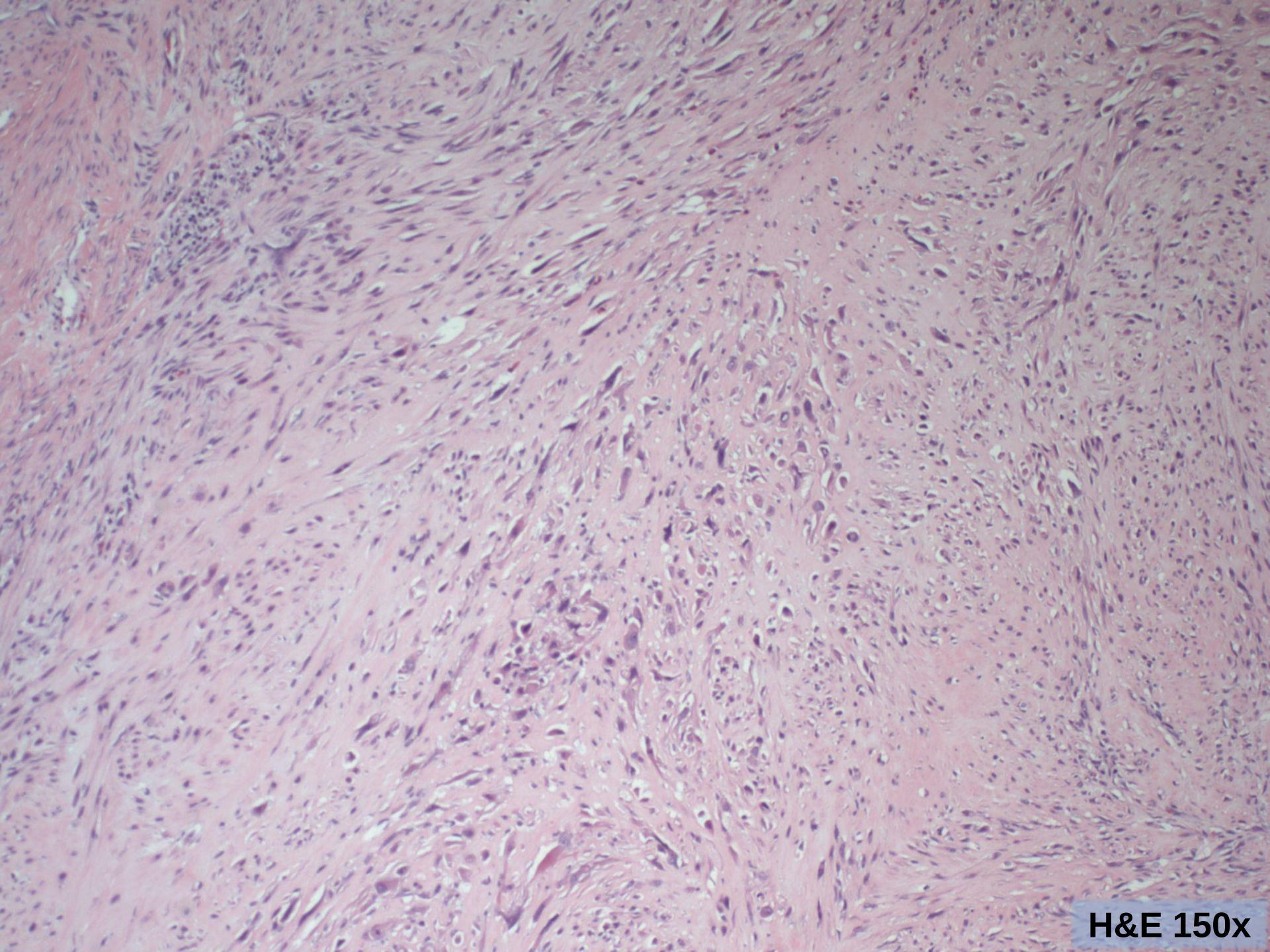
- 22-year-old male with subcutaneous mass on left knee.

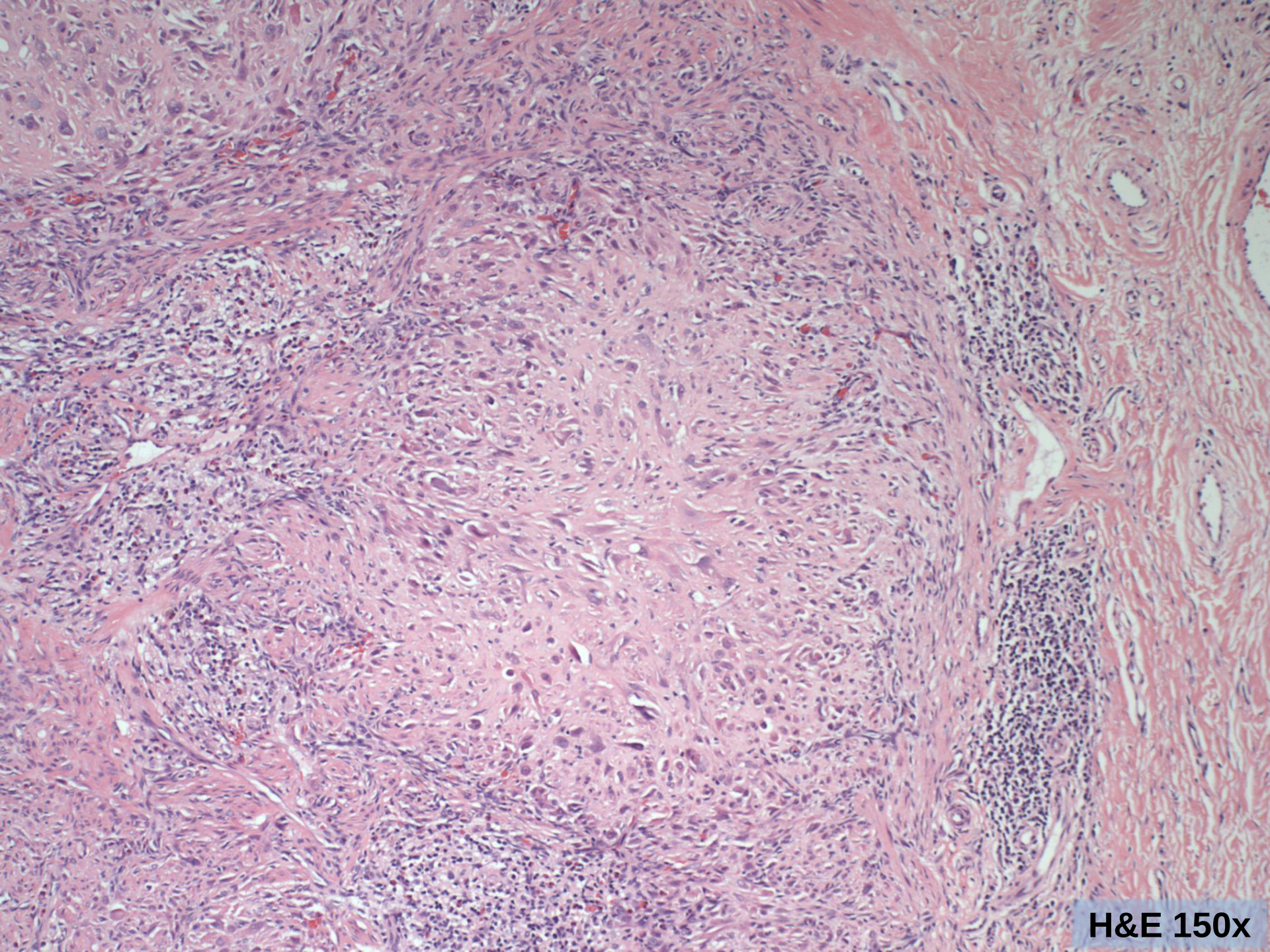
- Mat Rumery/Teri Longacre; Stanford


H&E 30x

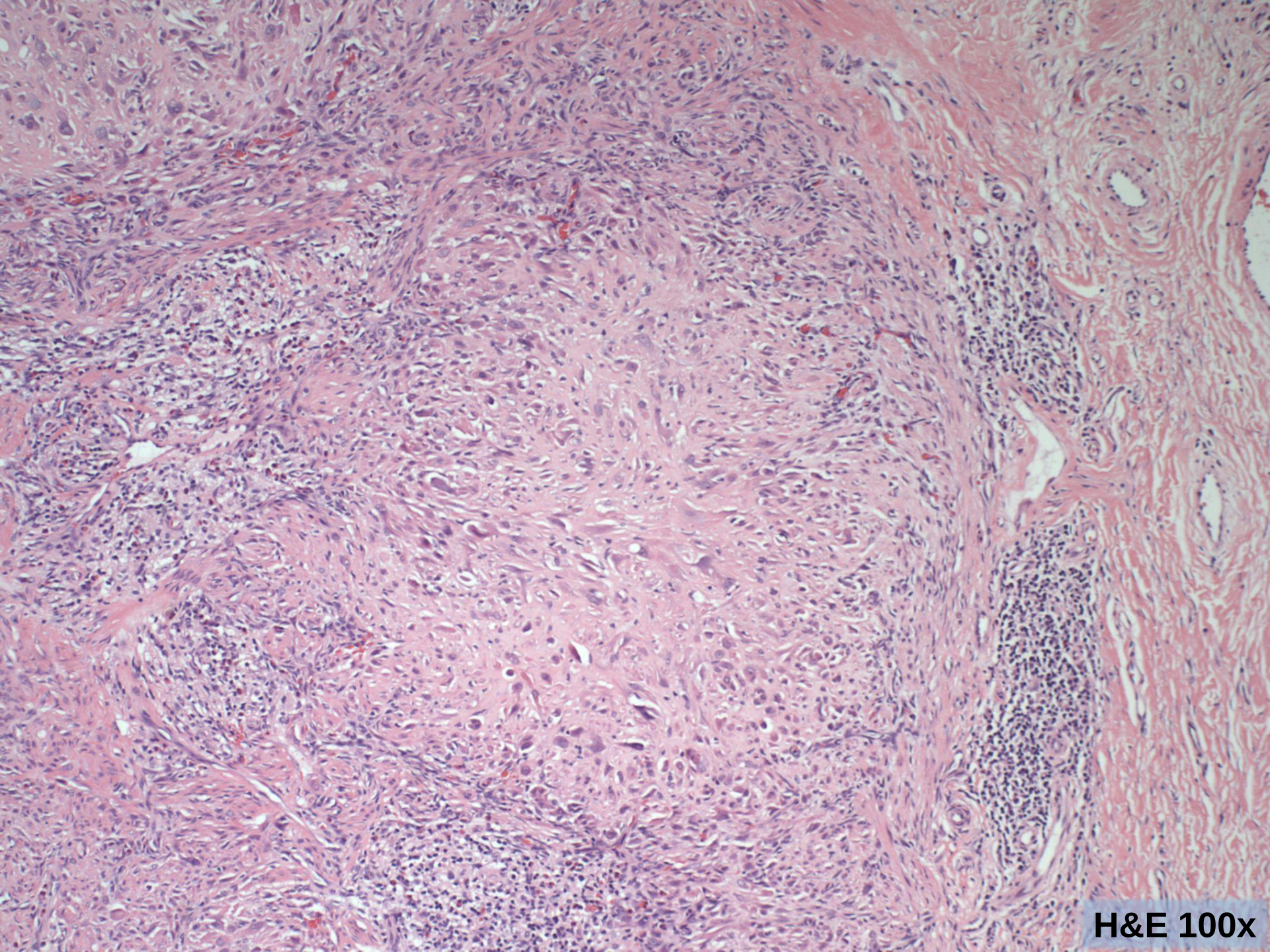

H&E 60x

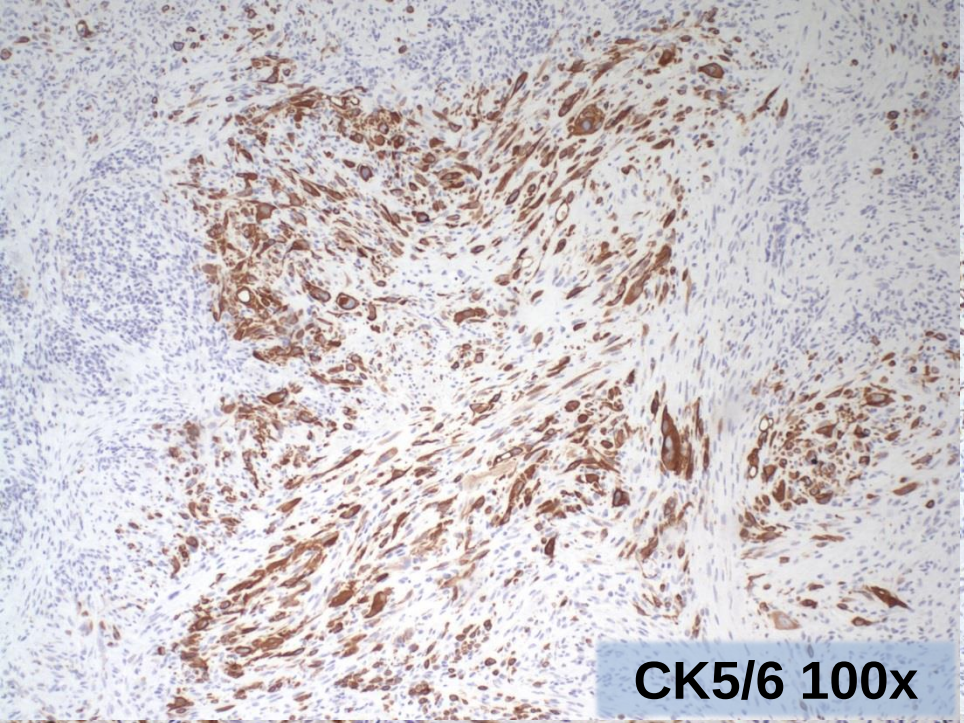

H&E 60x

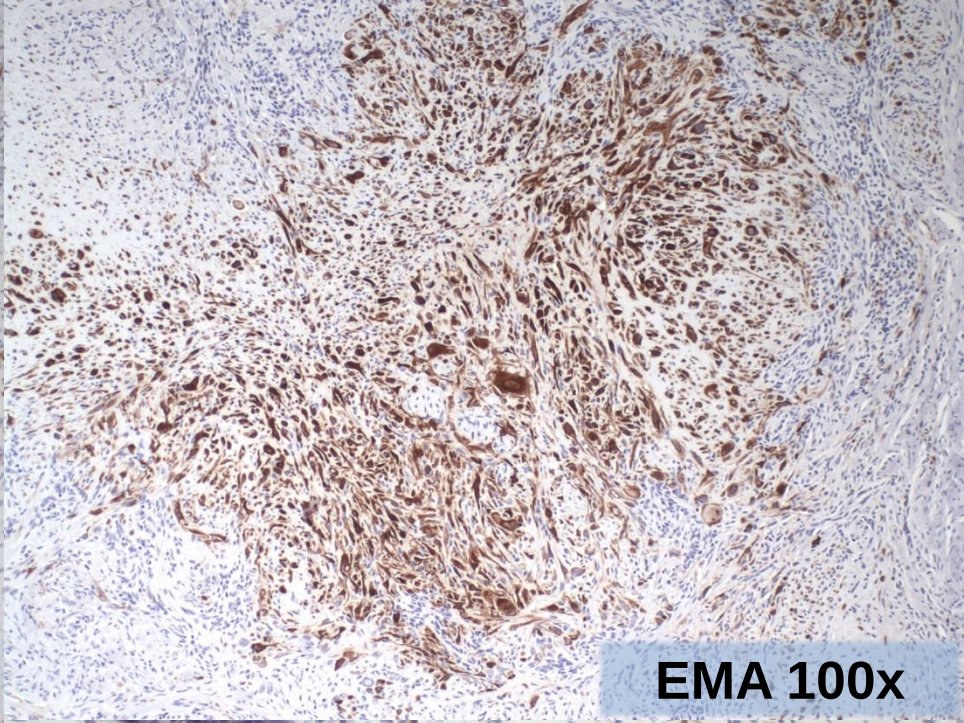

H&E 150x

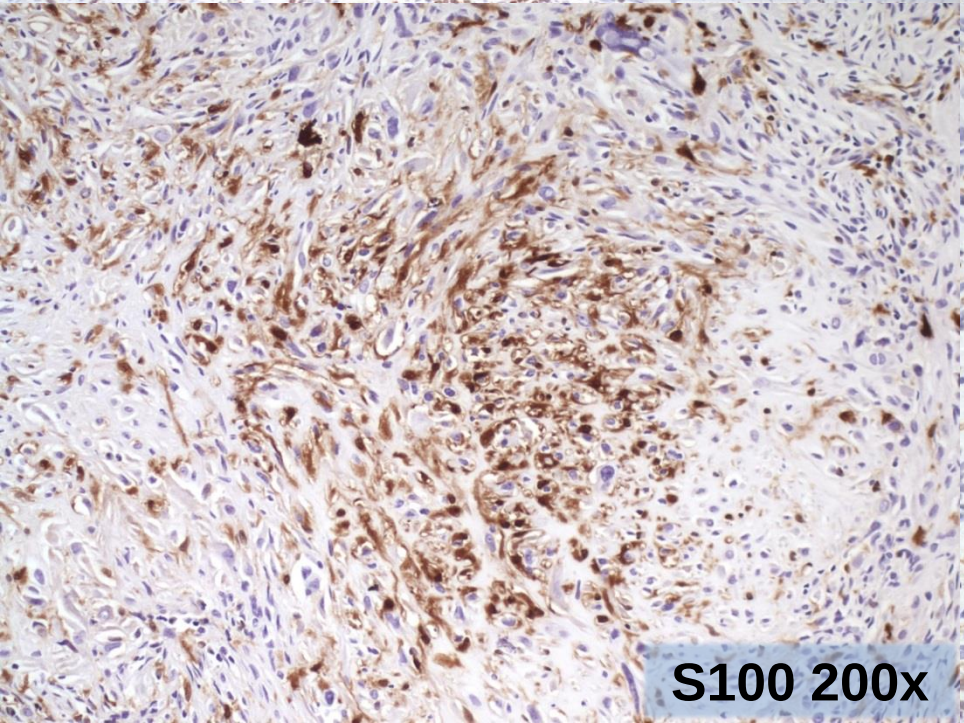

H&E 150x

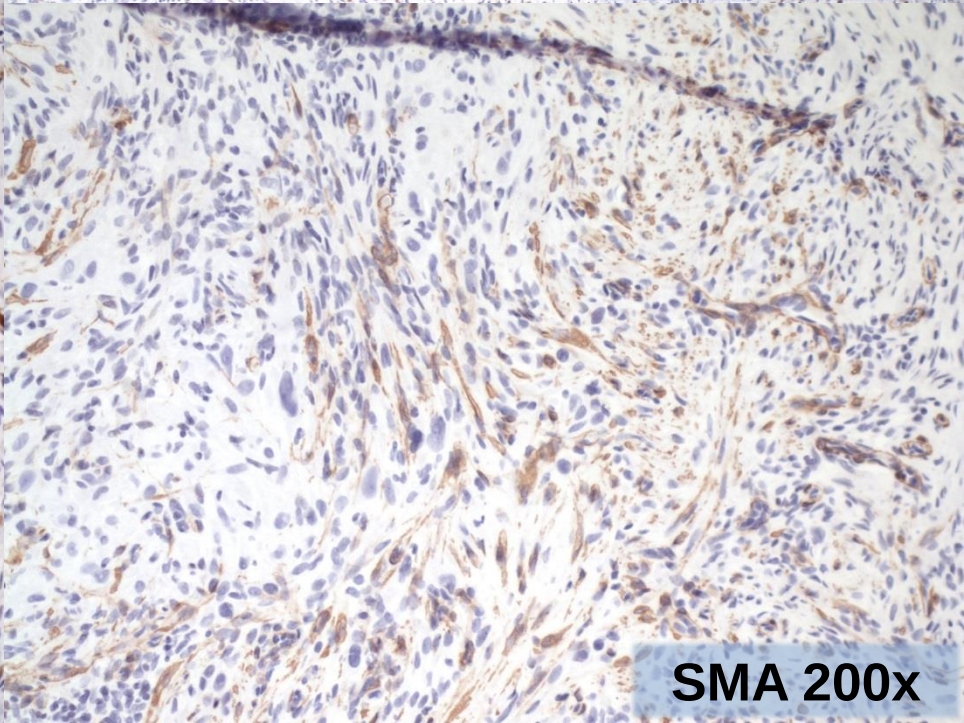
Diagnosis?


H&E 100x


CK5/6 100x


EMA 100x


S100 200x


SMA 200x

Diagnosis: Myoepithelioma

- AKA Mixed tumor of soft tissue or parachordoma
- Peak incidence 2nd-4th decade
- Slowly enlarging, painless mass
  - Thigh, groin, calf, upper arm, or forearm
  - 1-12 cm, well-circumscribed, yellow-white to tan

"Myoepithelioma/mixed tumor of soft tissue." in *Enzinger and Weiss's Soft Tissue Tumors.* Ed. Goldblum, J.R., Folpe, A.L., and Weiss, S.W. 6th ed. 2014.

Microscopic appearance

- Reticular appearance with cords of epithelioid, ovoid, or spindled cells
- Chondromyxoid to collagenized stroma
- Low mitotic rate (1/20 HPF)
- Malignant examples do occur
  - Coarse chromatin, prominent nucleoli, heterologous chondrosarcoma and osteosarcoma

Ancillary

- Immunohistochemistry
  - Cytokeratins
  - EMA
  - S100
  - Myoepithelial markers in 15-50%: muscle actins, GFAP, calponin, and p63
- Most commonly *EWSR1* gene rearrangements

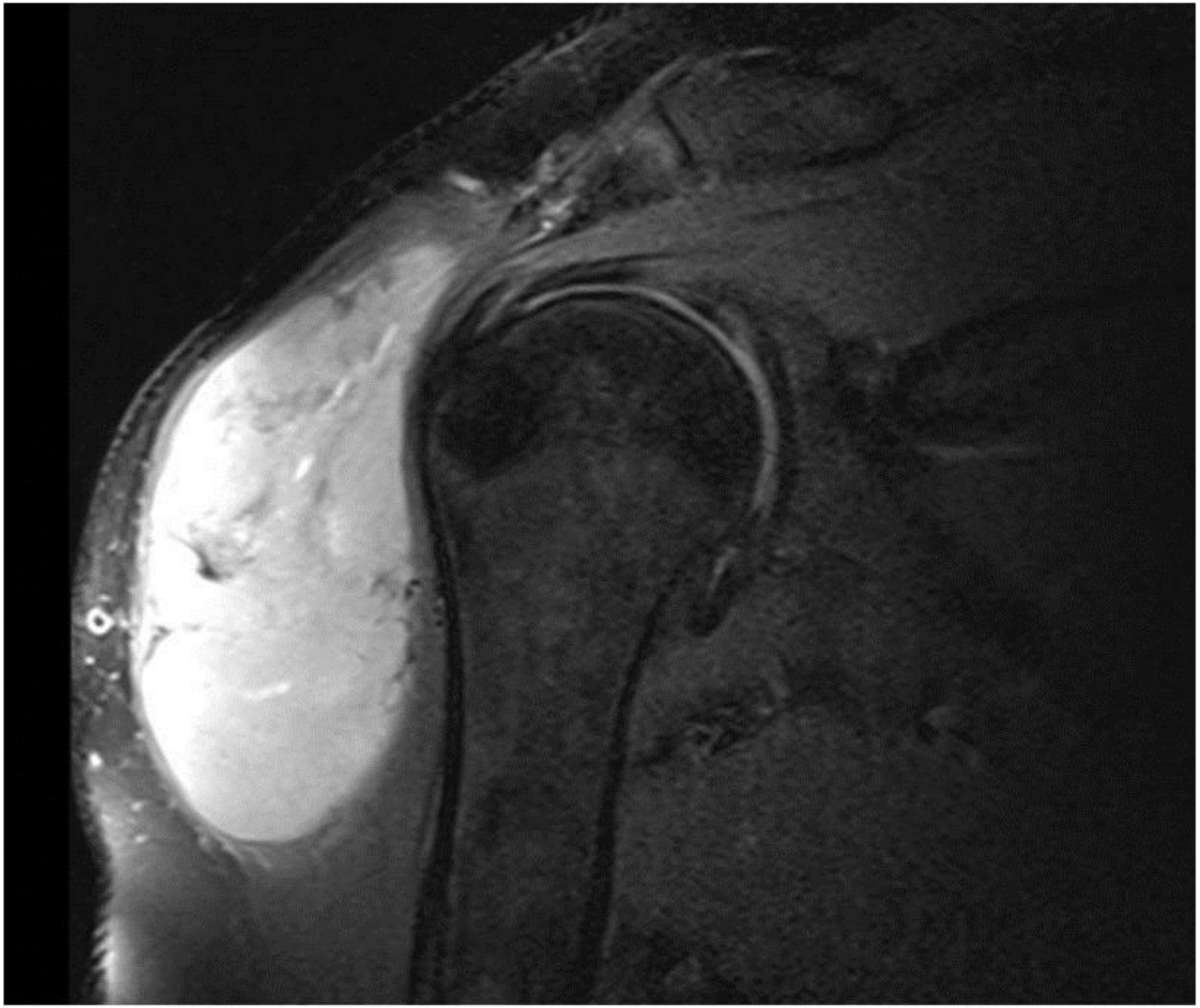
- DDx:
  - Extraskeletal chondromyxoid sarcoma
  - Ossifying fibromyxoid tumor
  - Extra-axial chordoma
- Outcome
  - Usually benign, but may locally recur (18%)
  - Malignant examples: recurrence (42%), metastasis (32%)

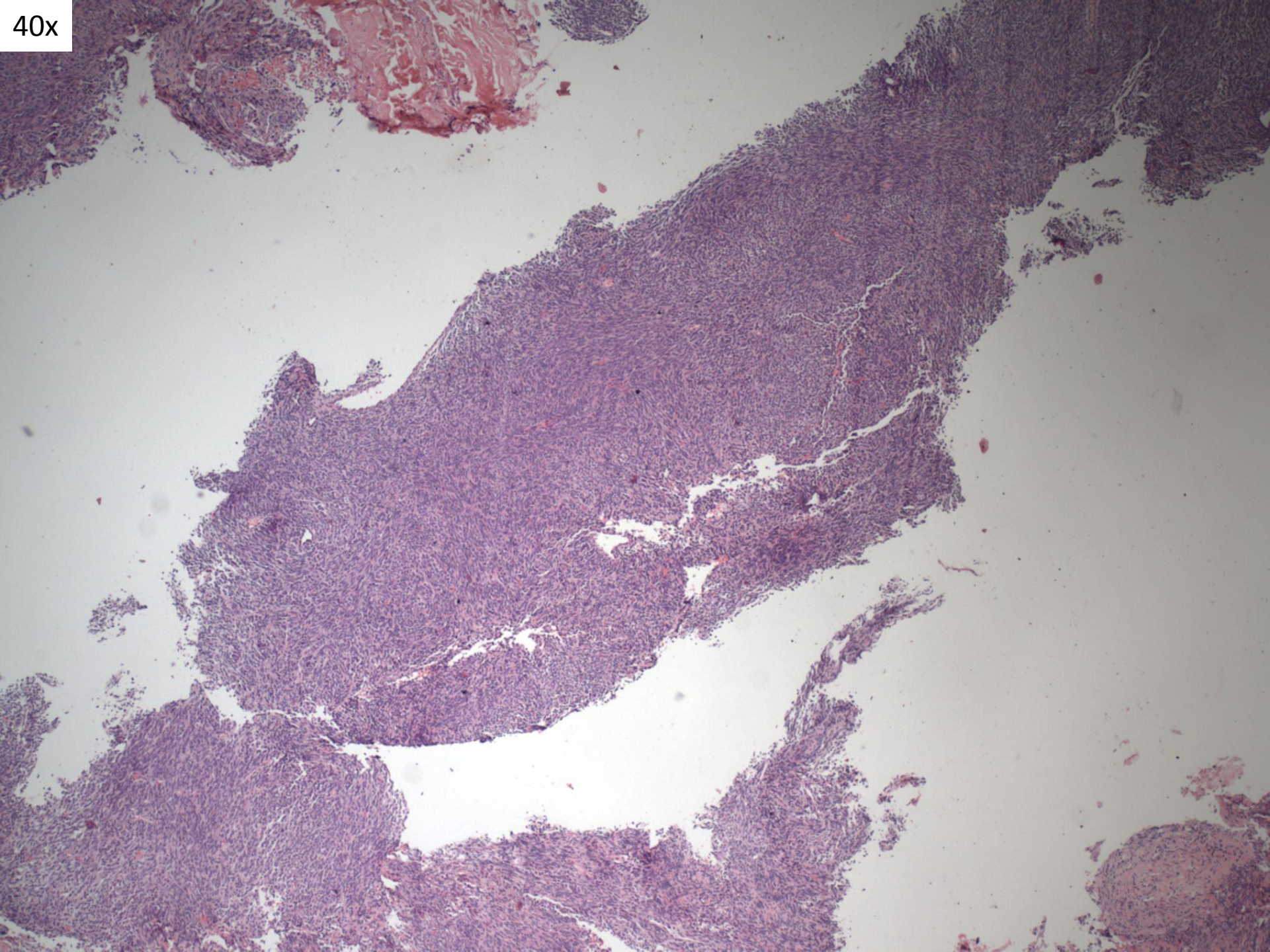
SB 5928

- 34-year-old male presenting with large mass on right shoulder after direct trauma to area 2 years ago. Non-tender, old shoulder ROM.

- Sebastian Fernandez-Pol/Eduardo Zambrano; Stanford

MRI

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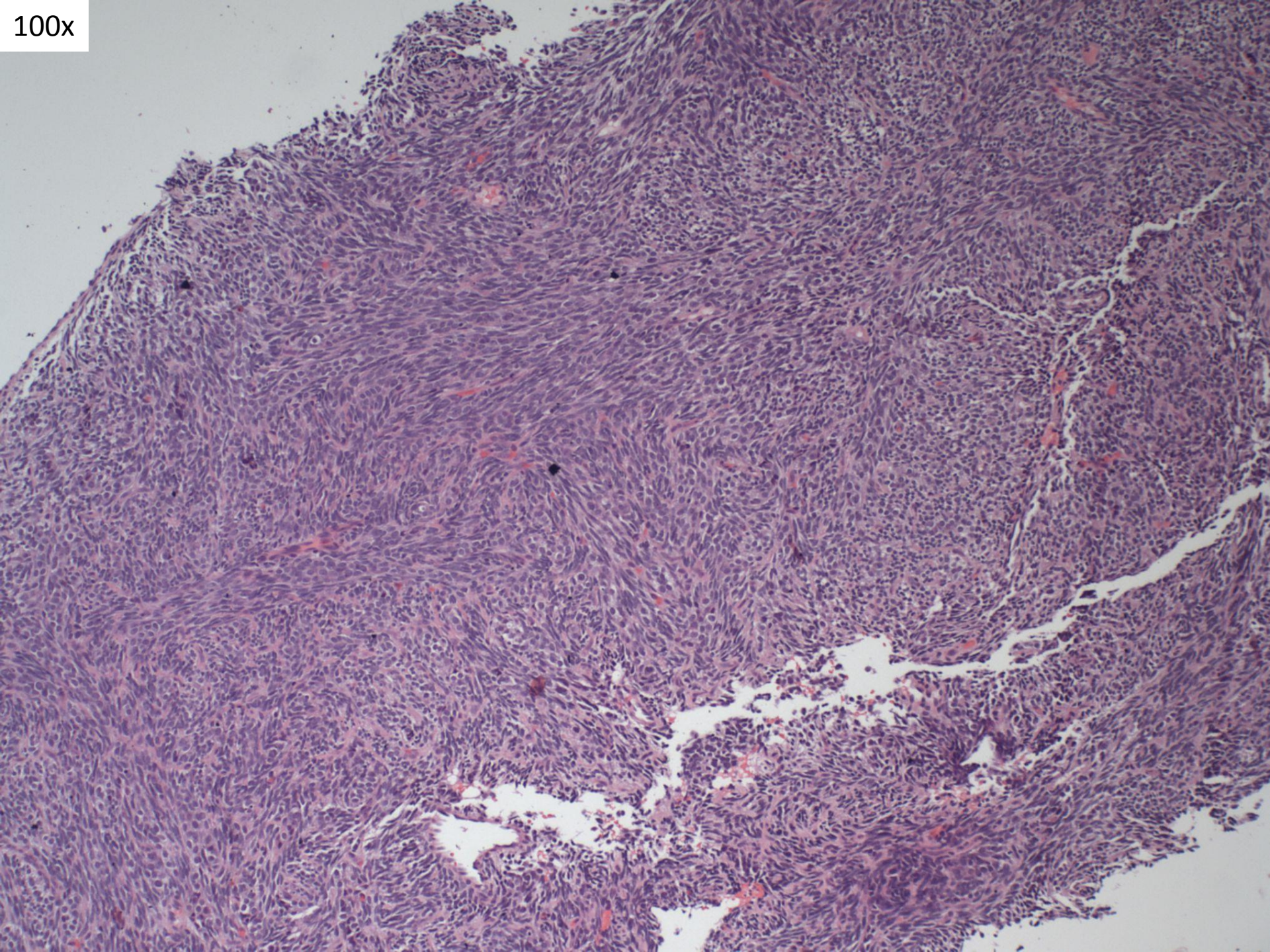
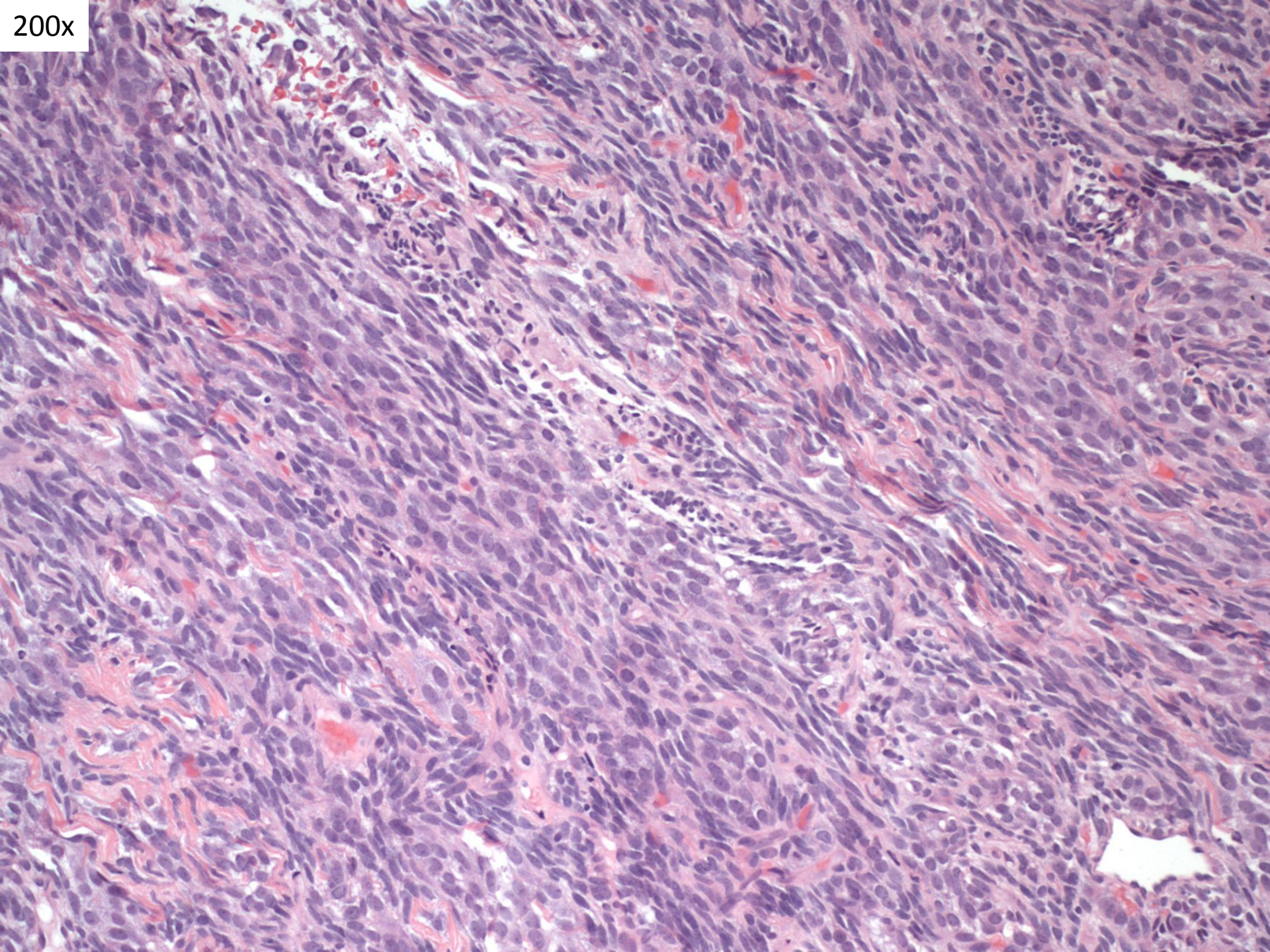

100x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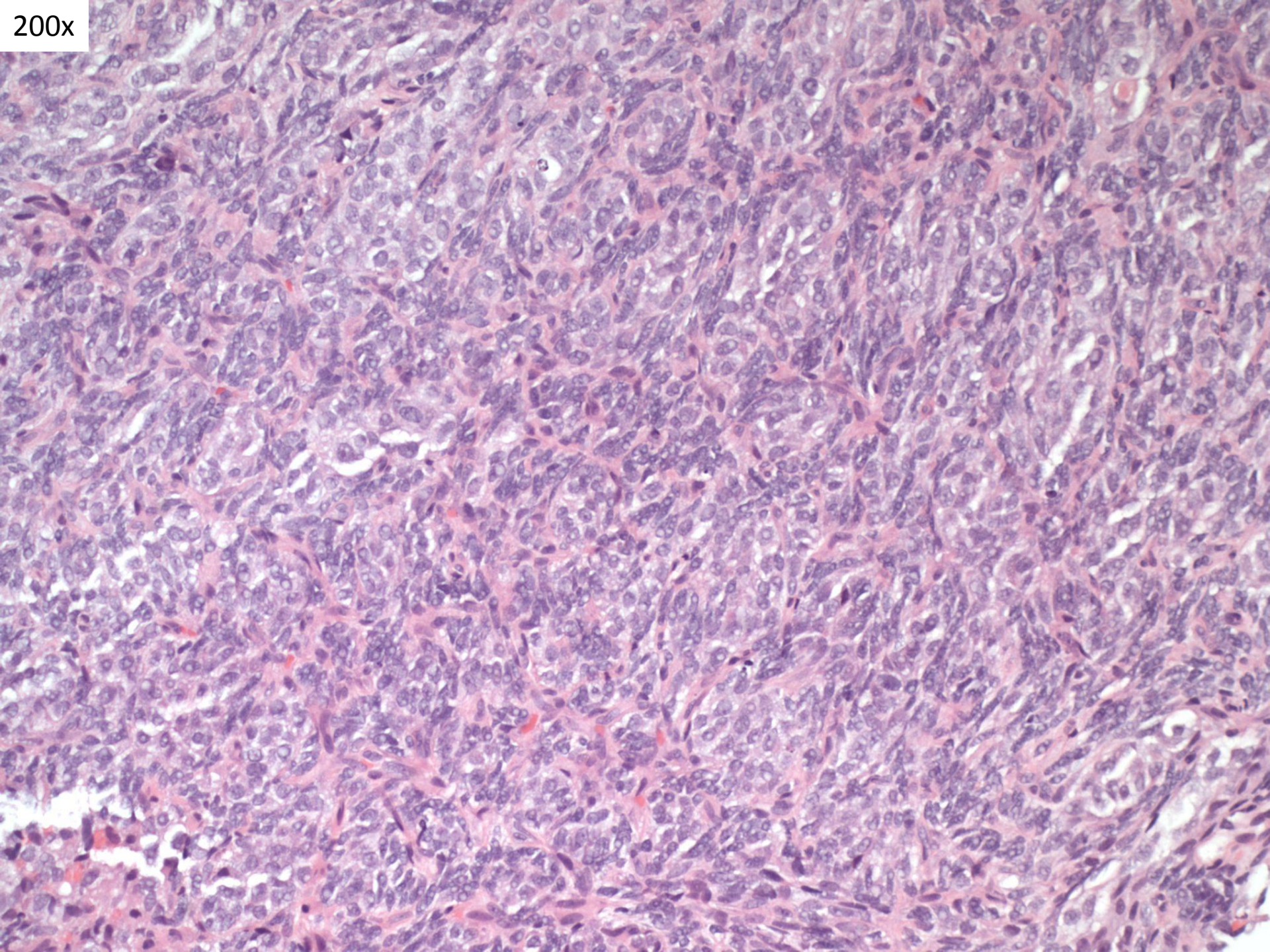
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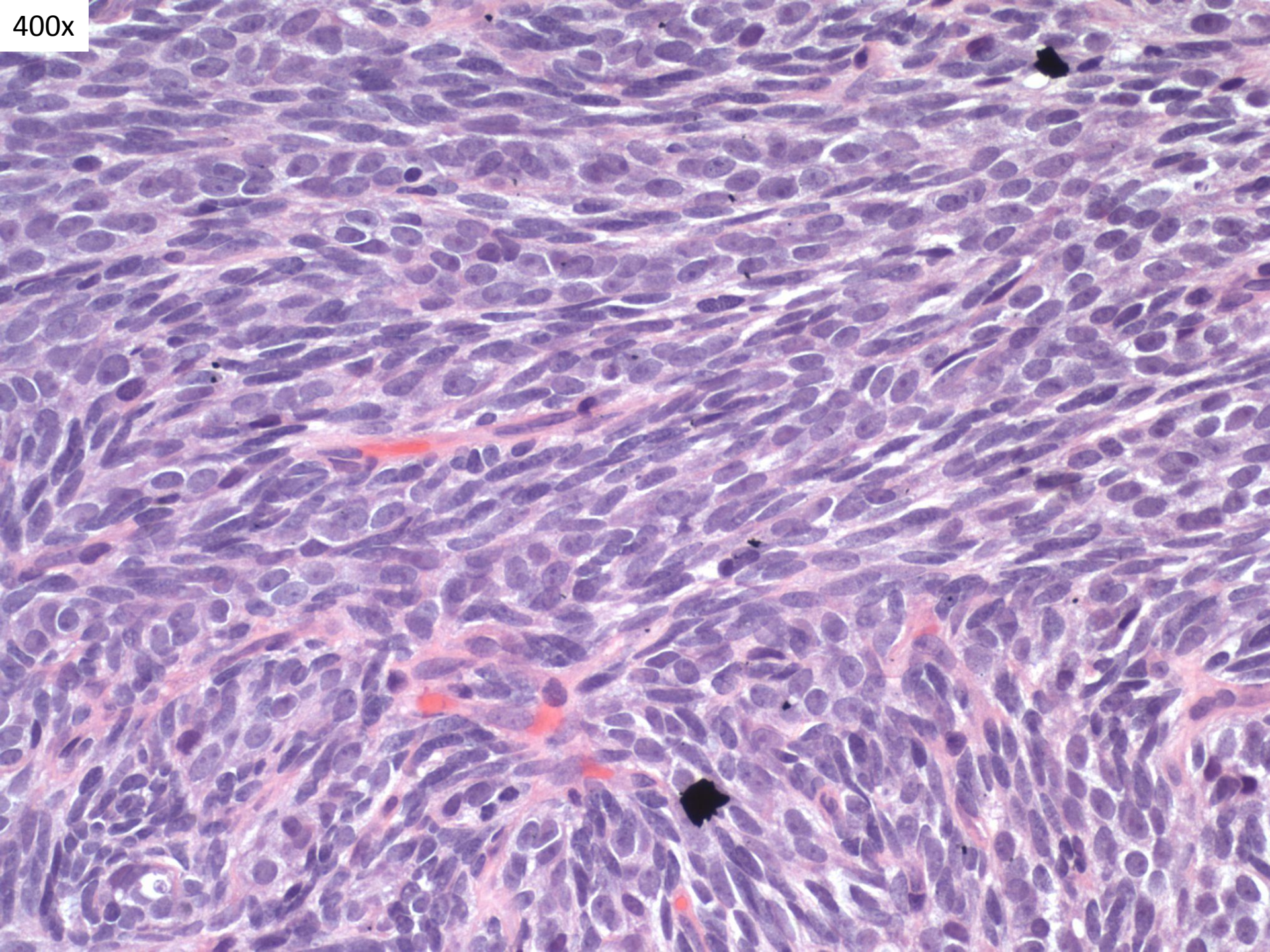
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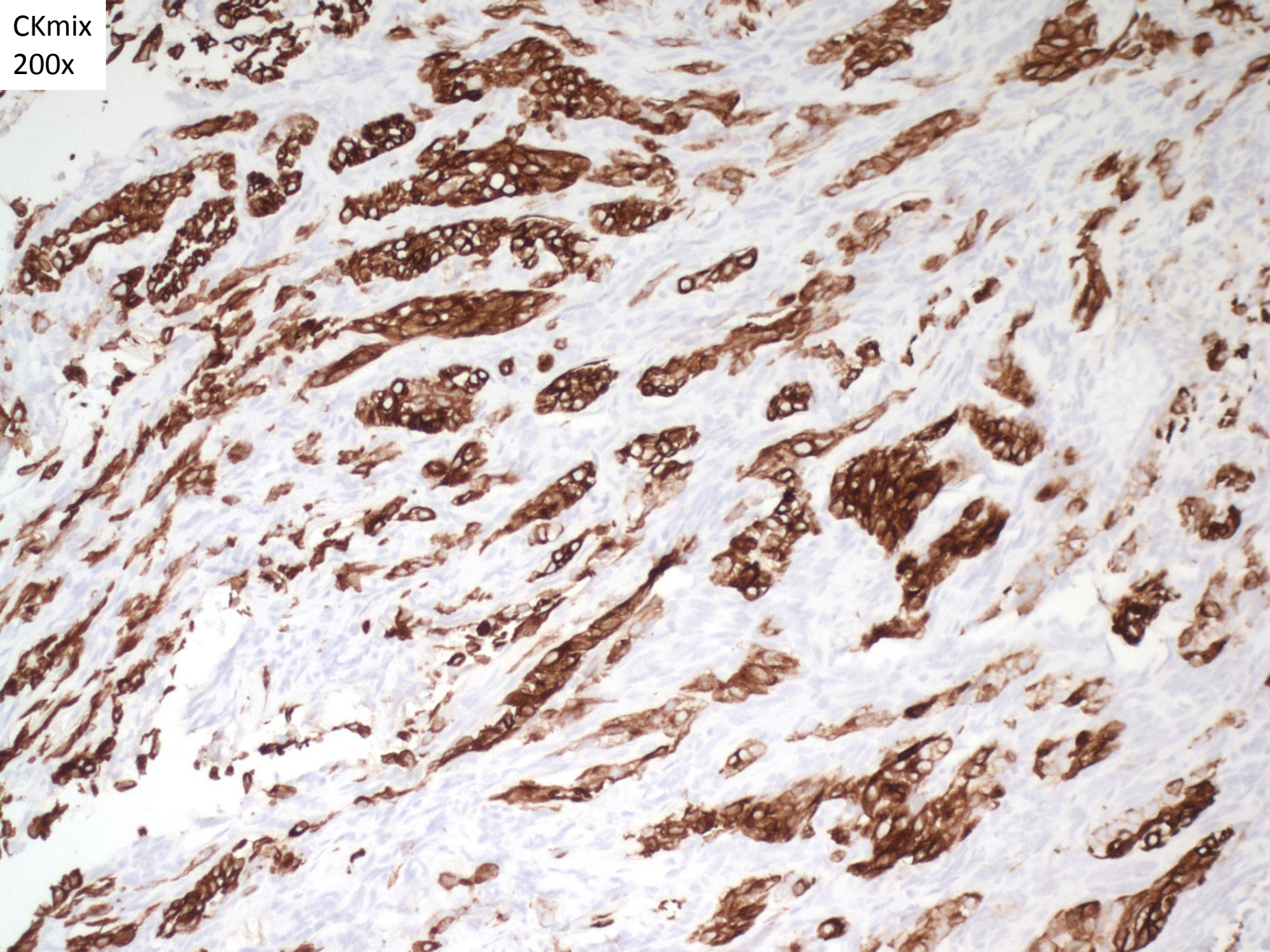
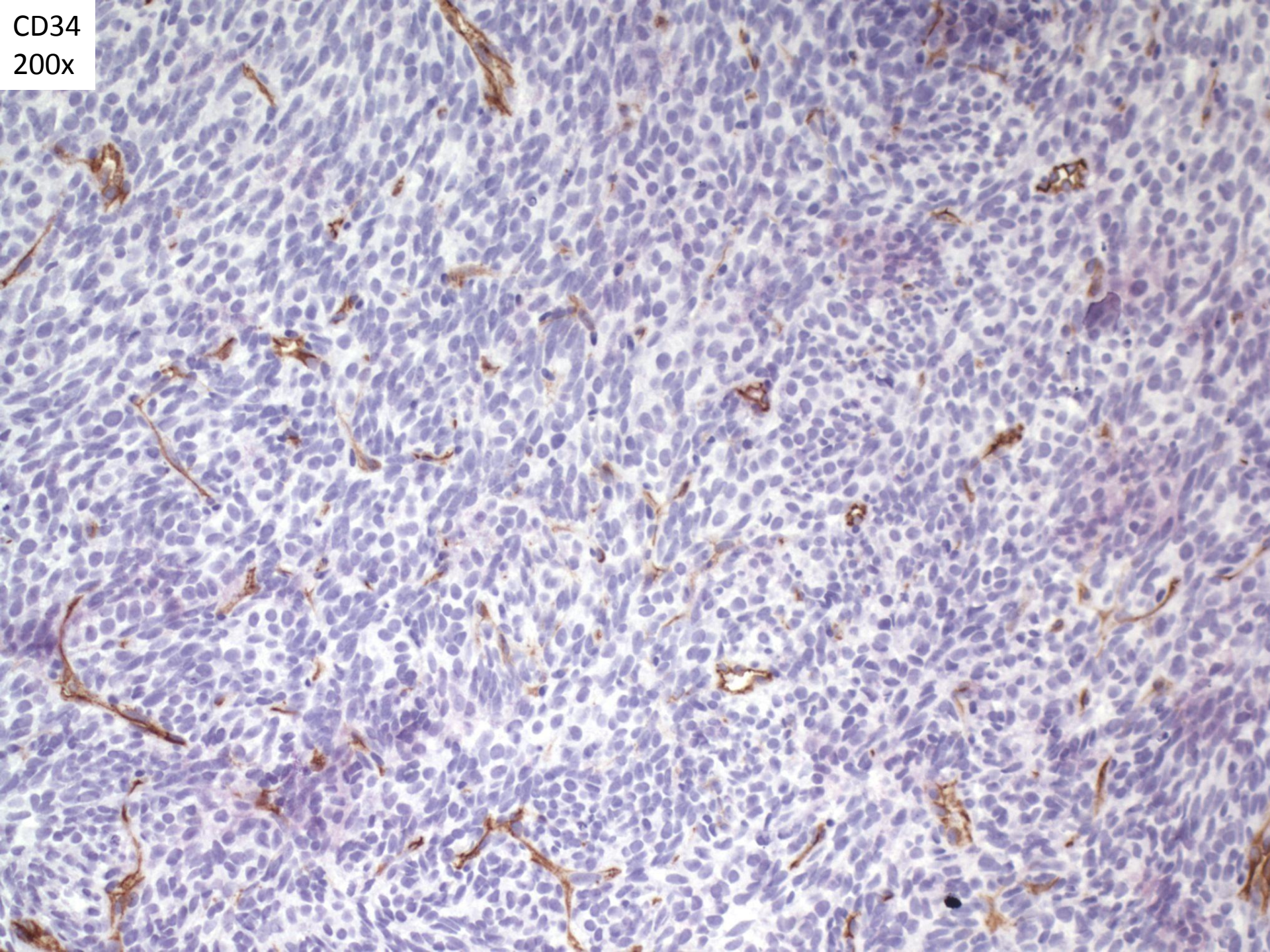
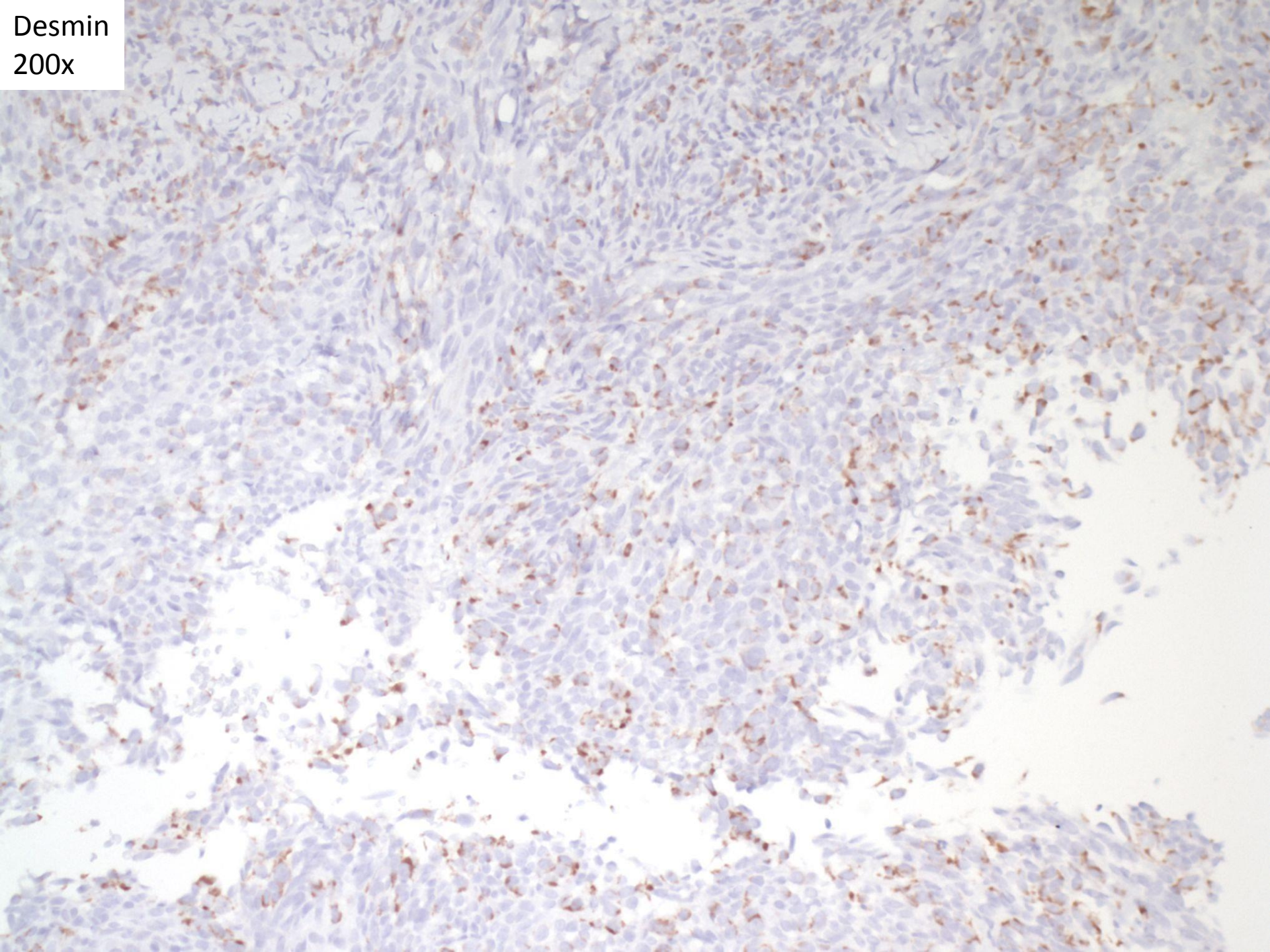
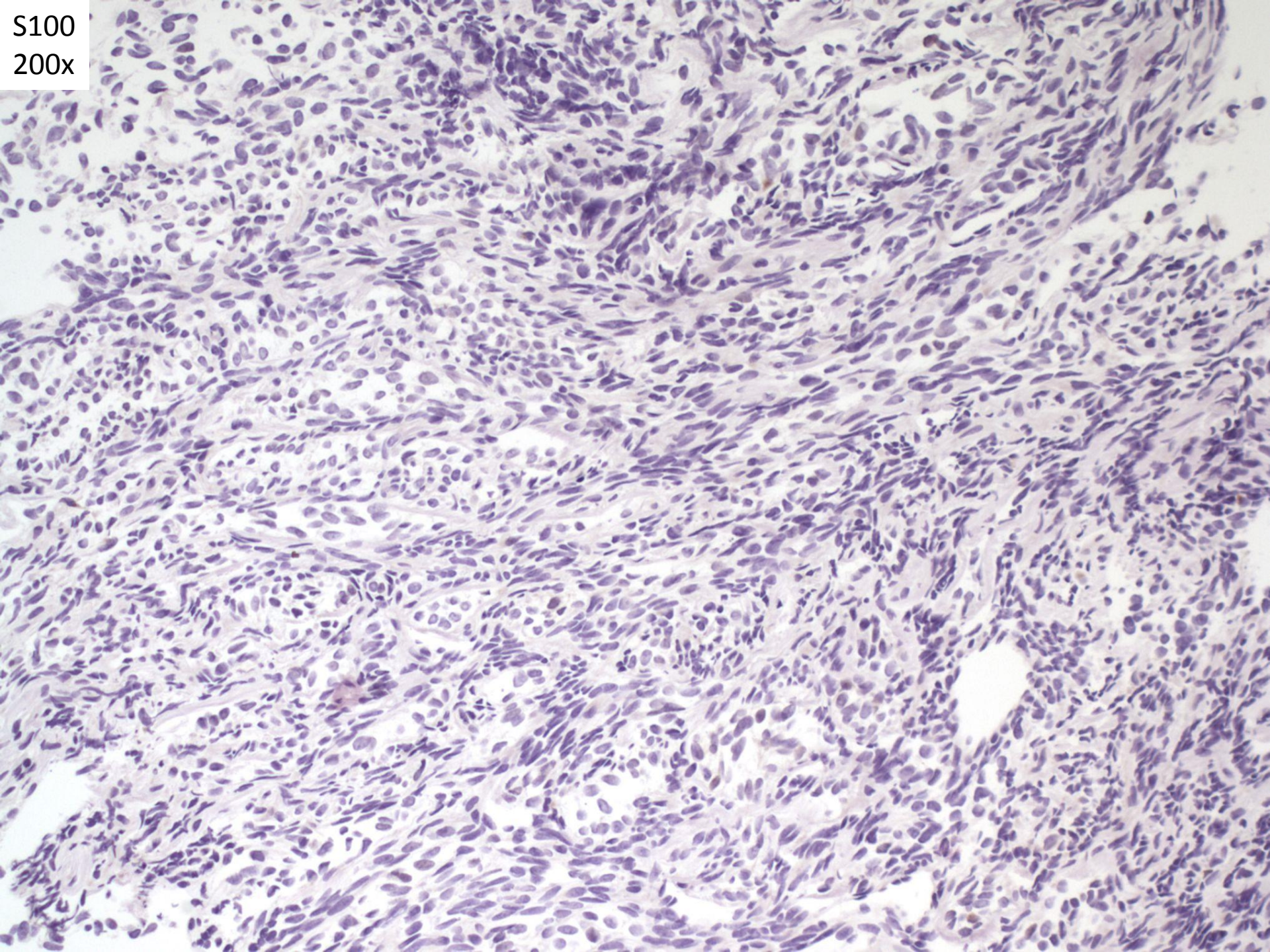

CKmix
200x


CD34
200x


Desmin
200x


S100
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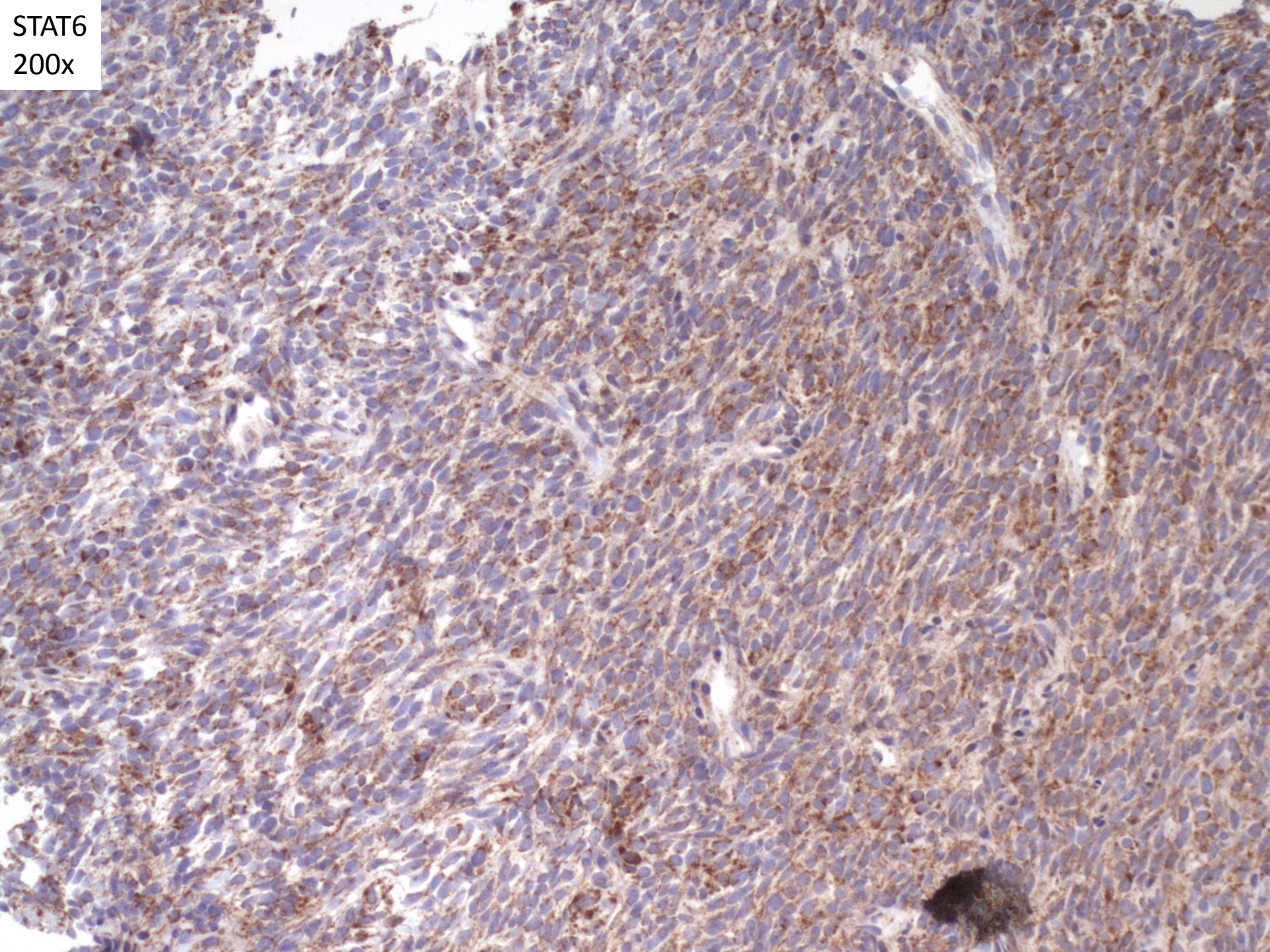

STAT6
200x

Diagnosis?

Differential diagnosis

- Solitary fibrous tumor
- Neural – MPNST
- Leiomyosarcoma
- Spindle cell rhabdomyosarcoma
- Dermatofibrosarcoma protuberans

Synovial sarcoma

- Malignant mesenchymal neoplasm with partial epithelial differentiation
- The monophasic spindle cell type is the commonest subtype of SS
- Defined by the presence of the **t(X;18)(p11.2;q11.2)** translocation, involving the **SS18 (formerly SYT)** gene on chromosome 18 and one of several synovial sarcoma X (SSX) genes on chromosome X (usually **SSX1 or SSX2**)

TLE1 is sensitive for SS but **not specific**

- TLE1 shows strong and diffuse nuclear staining in SS, with positive nuclear expression encountered in more than 90%
- TLE1 is positive in:
  - 15% to 30% of MPNST
  - 8% of SFT
  - 69% of malignant mesotheliomas
  - 33% of neurofibromas
  - 100% of schwannomas

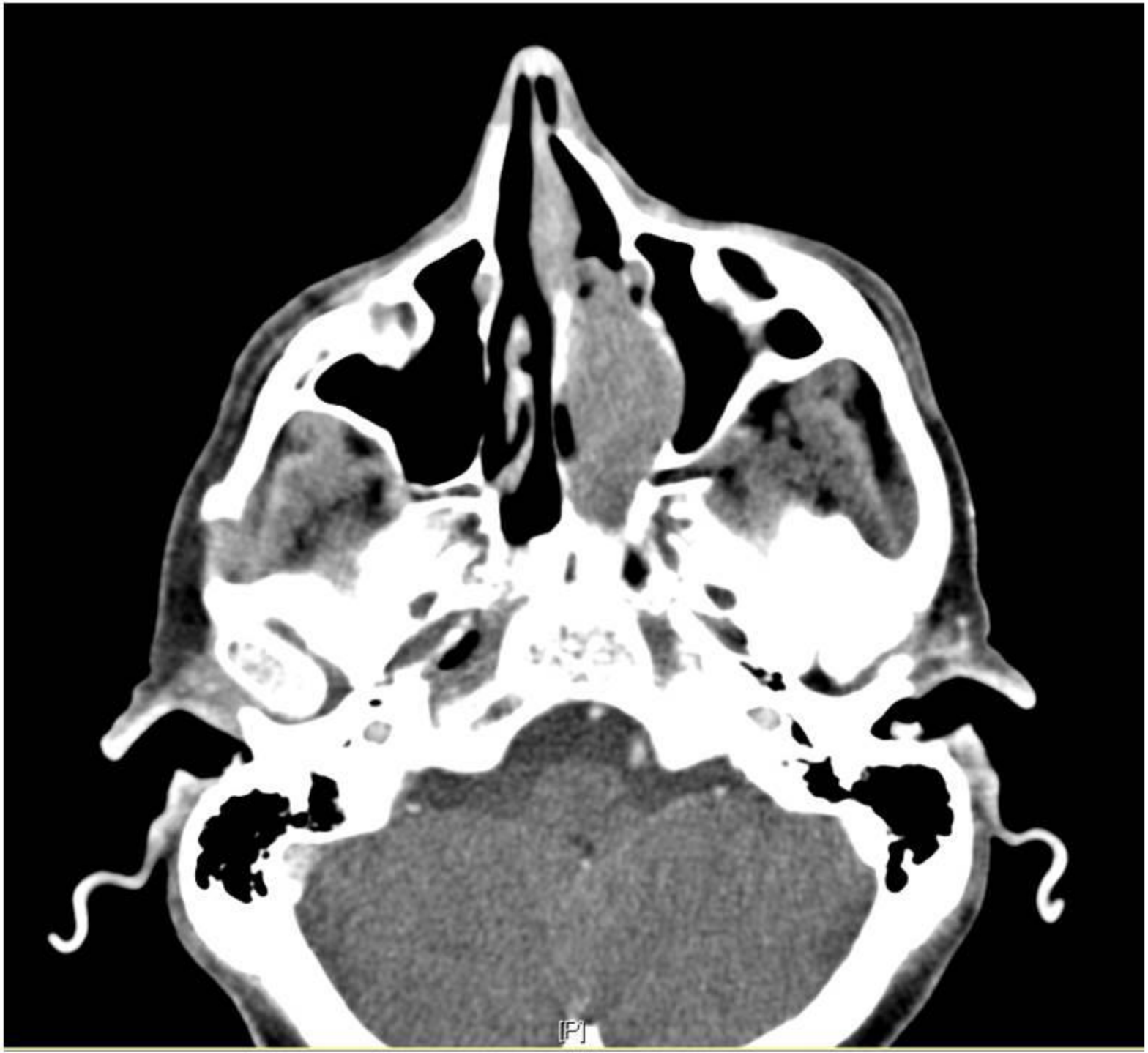
References

1. Thway and Fisher. **Synovial sarcoma: defining features and diagnostic evolution**, Annals of Diagnostic Pathology, 2014-12-01Z, Volume 18, Issue 6, Pages 369-380
2. Shi W, Indelicato DJ, Morris CG, Scarborough MT, Gibbs CP et al. (2013**) Long-term treatment outcomes for patients with synovial sarcoma: A 40-year experience at the University of Florida**. Am J Clin Oncol 36: 83-88.

SB 5929

- 63-year-old male with left nasal mass.

- Sebastian Fernandez-Pol/Eduardo Zambrano; Stanford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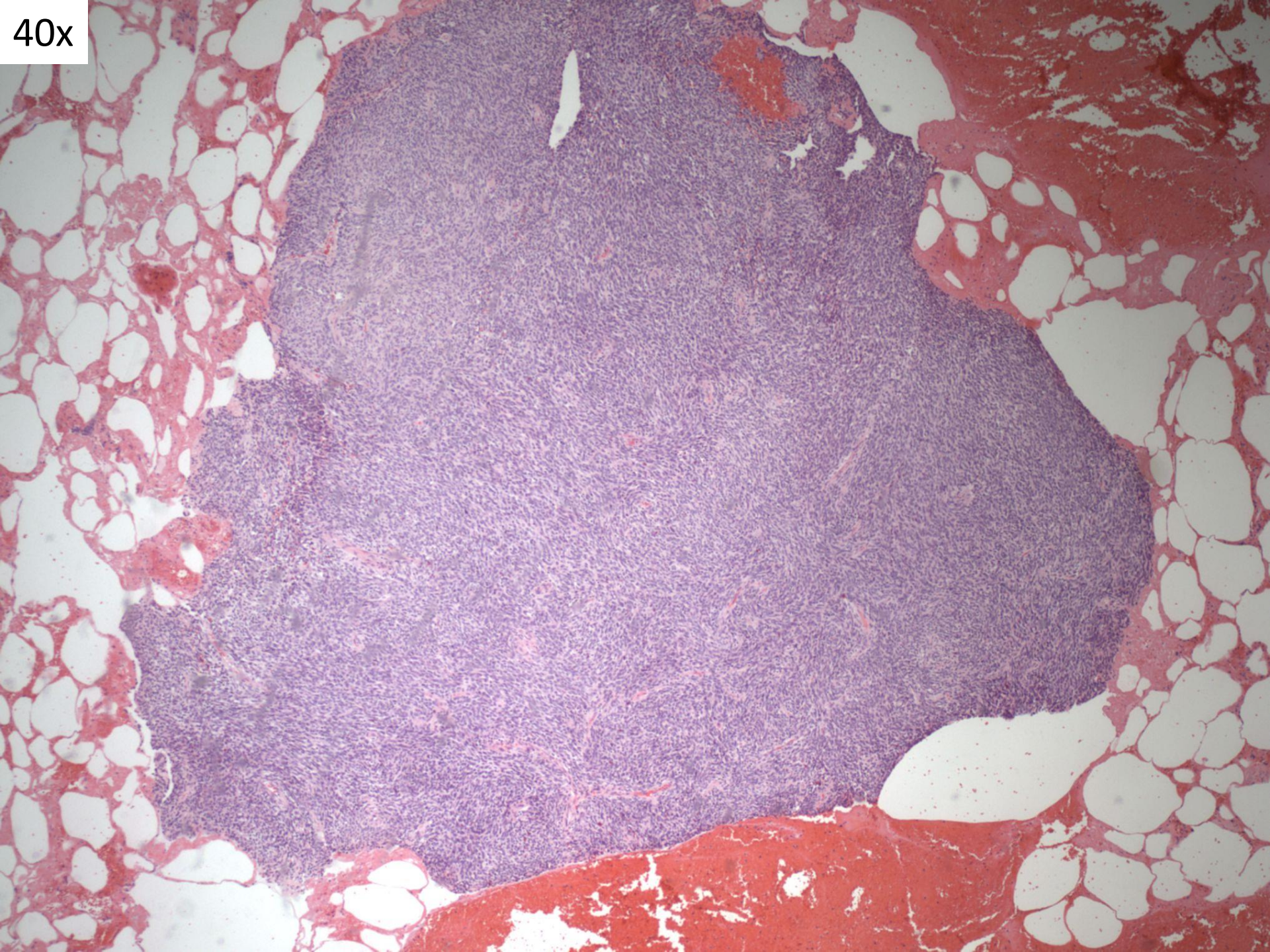
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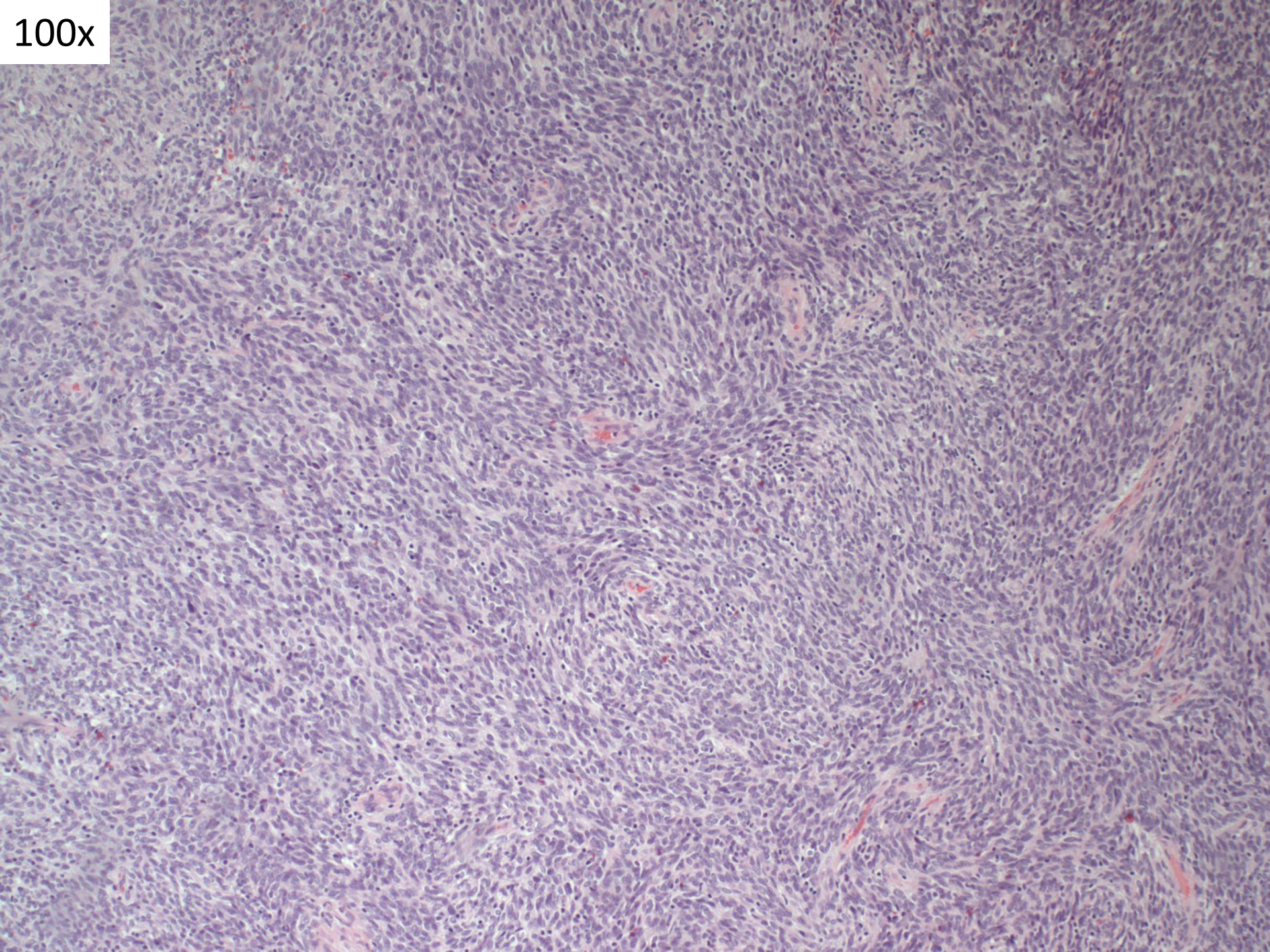
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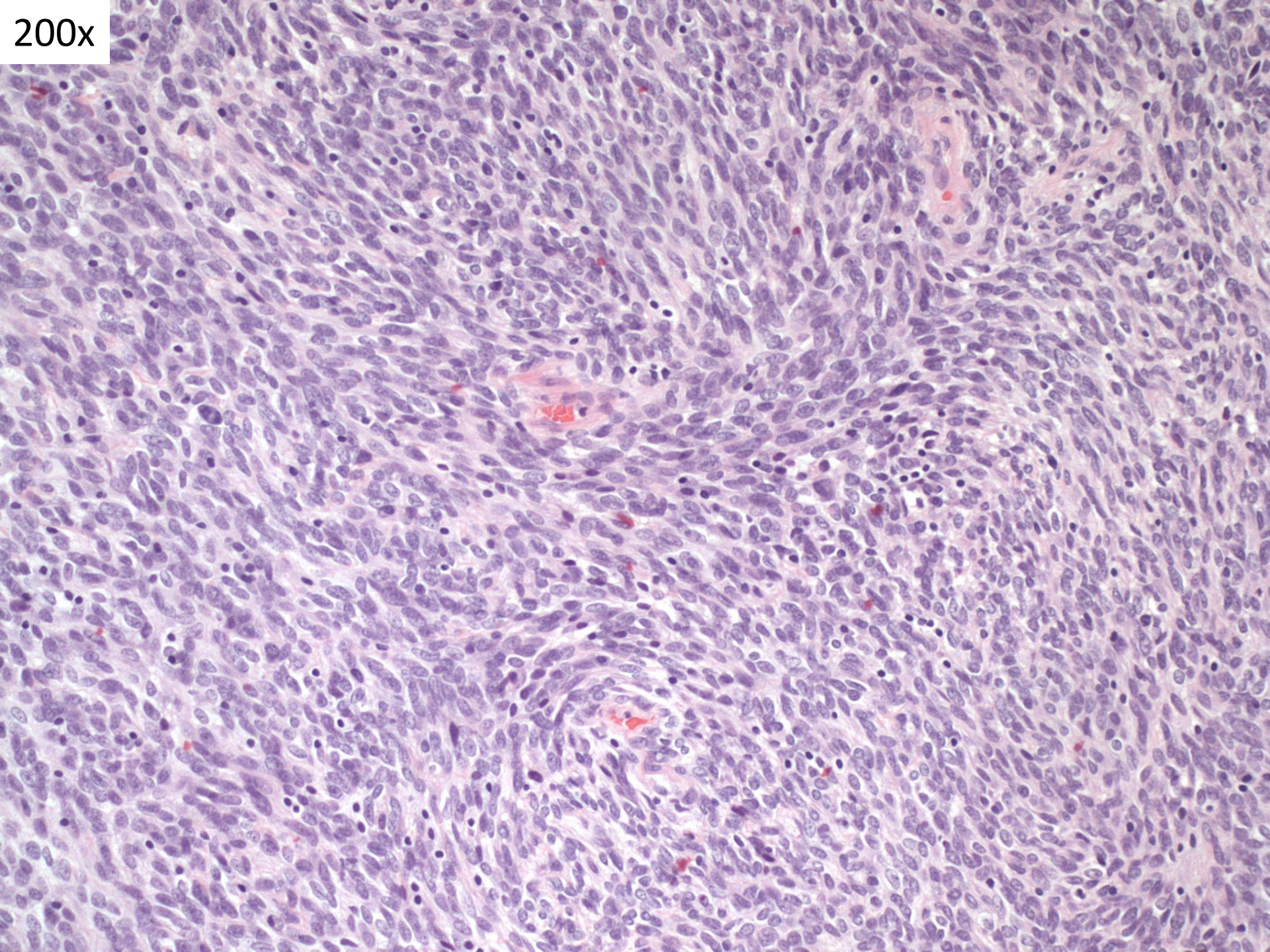
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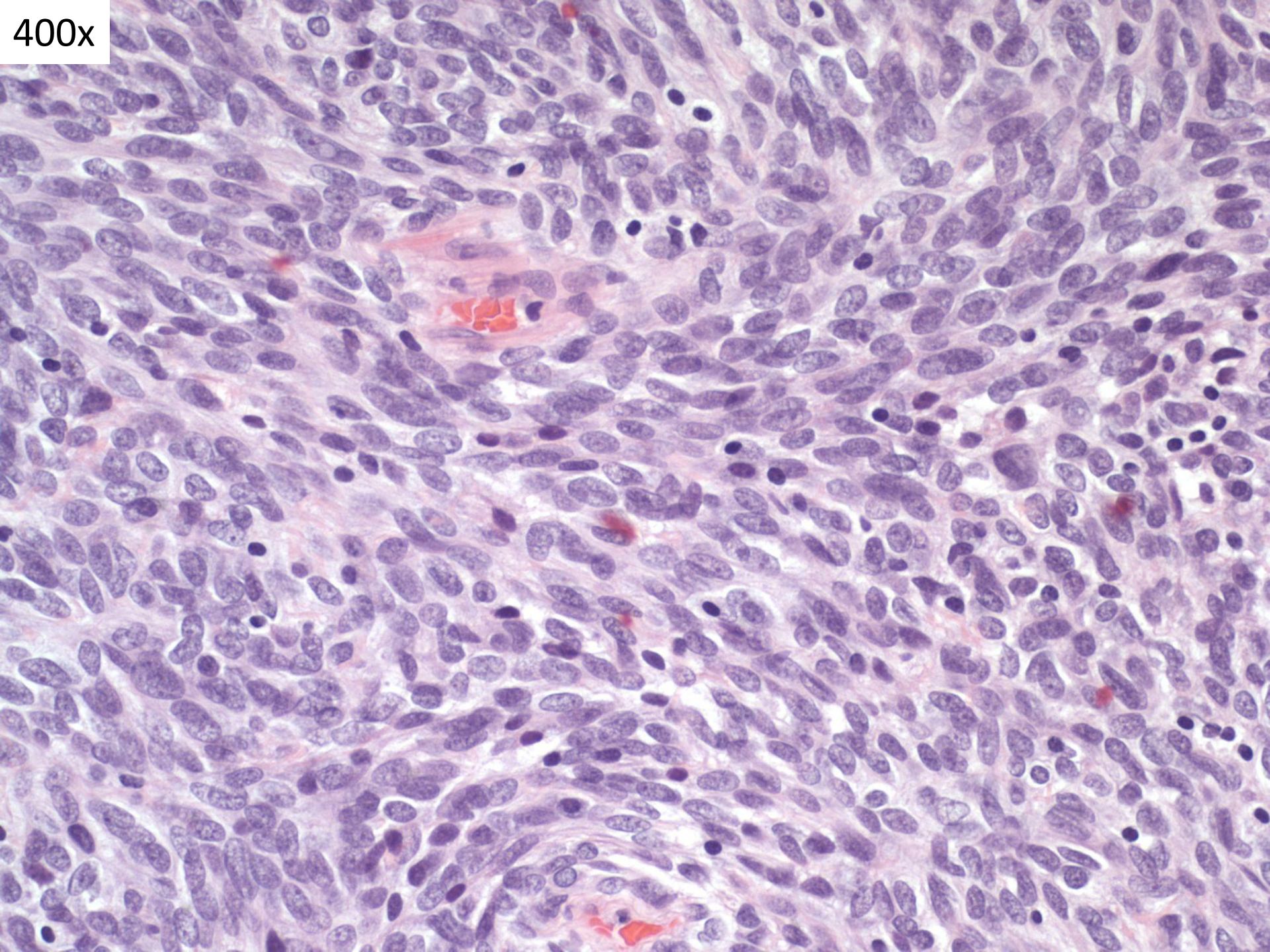
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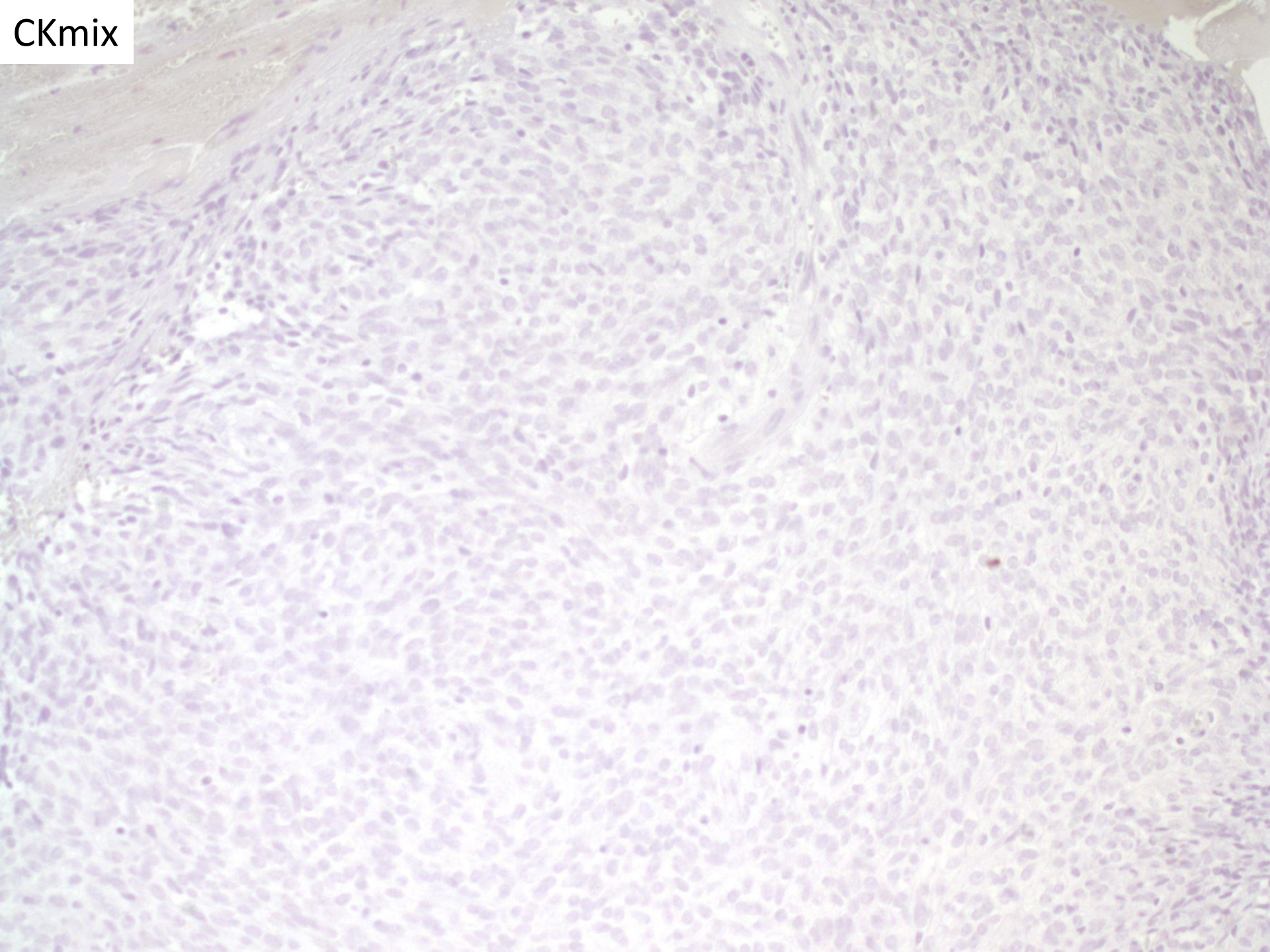
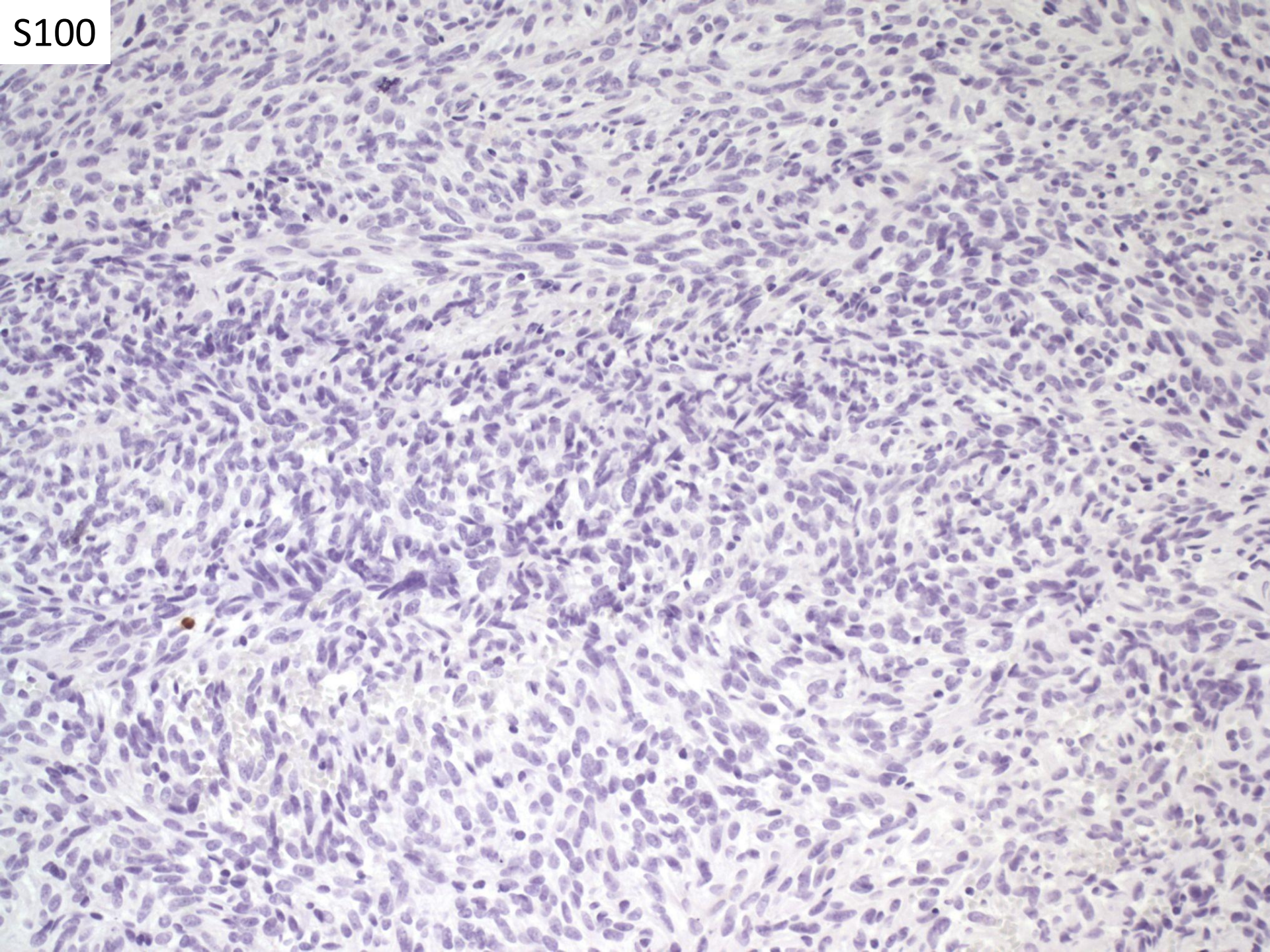
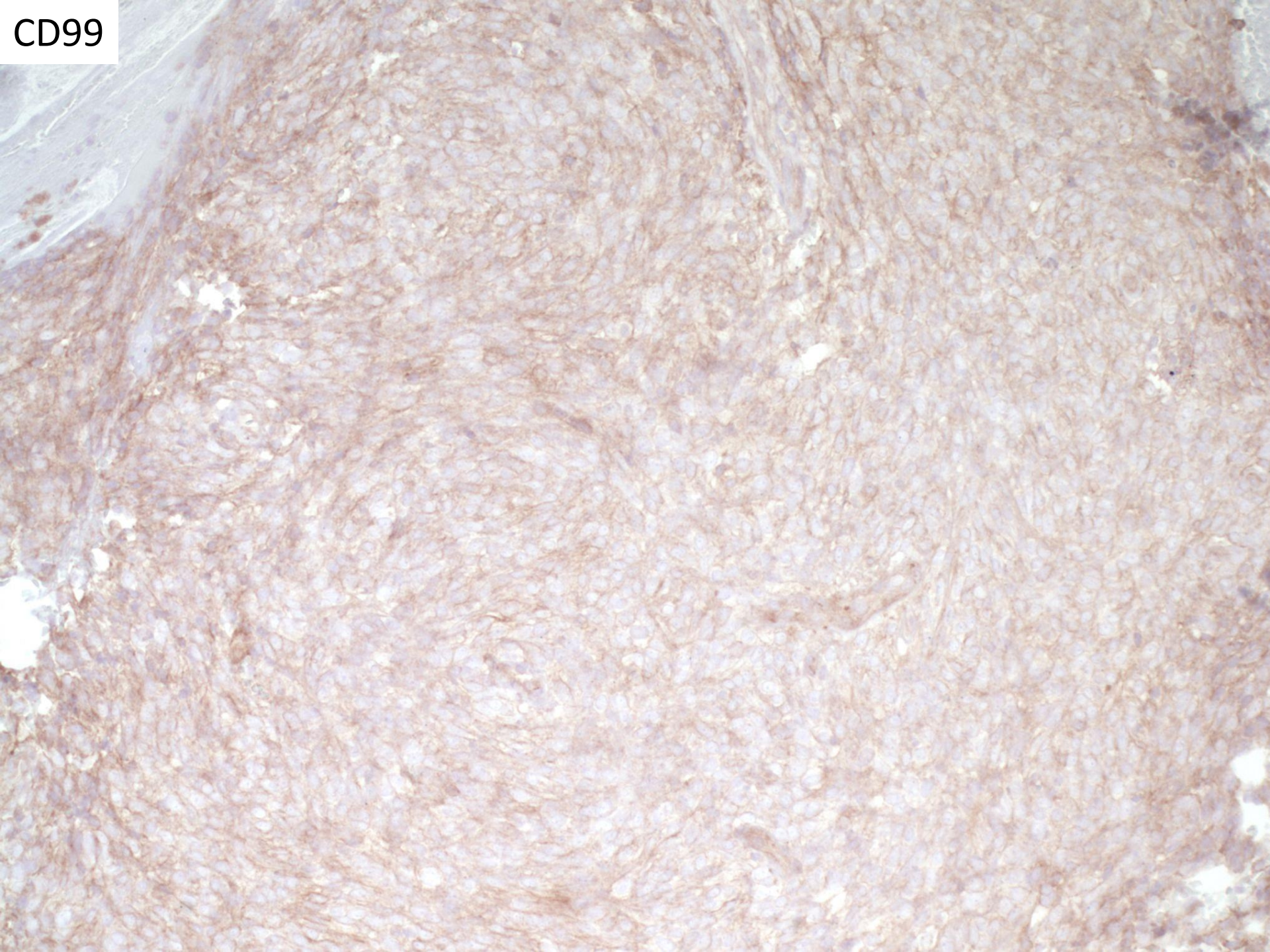
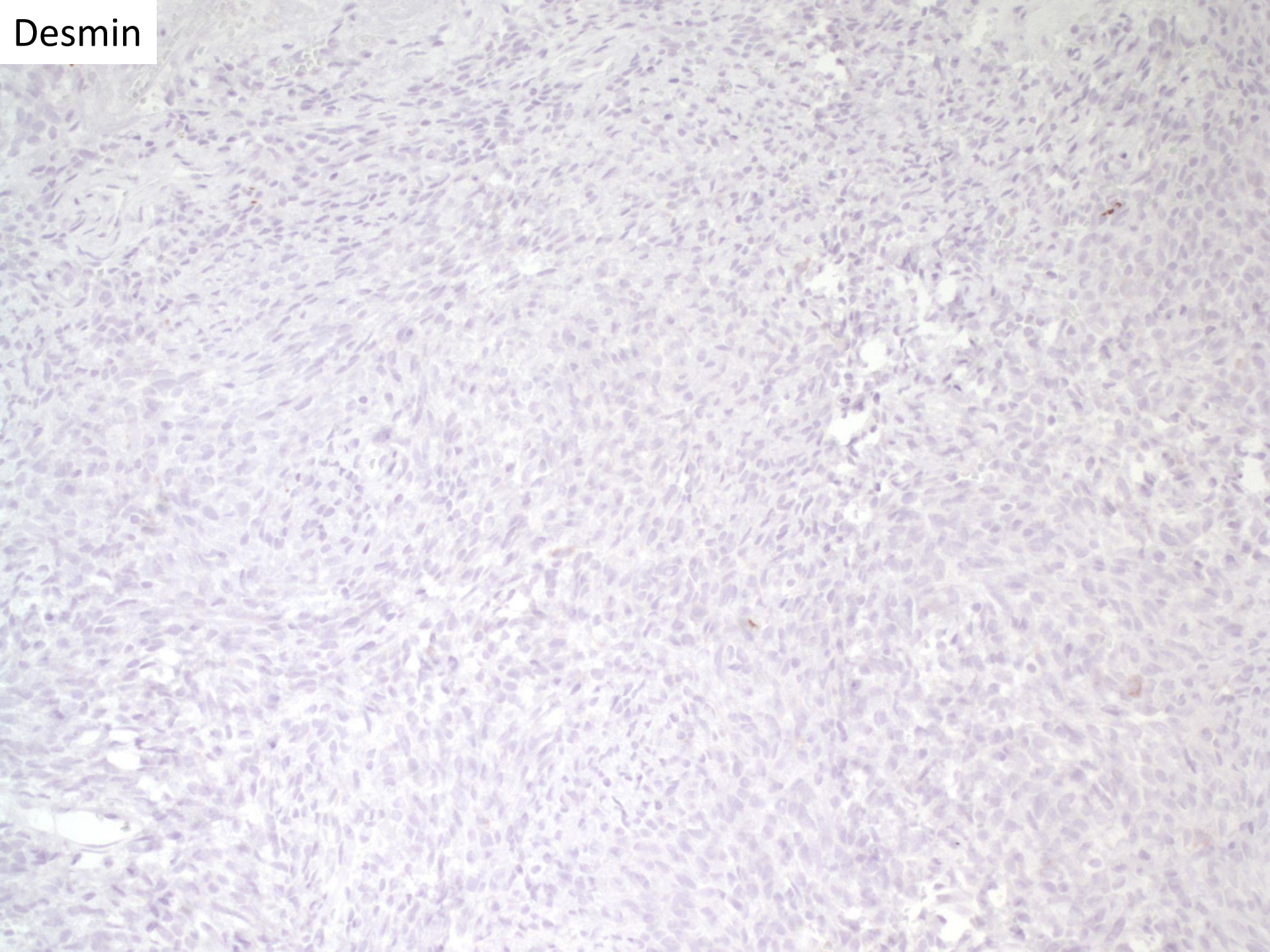

CKmix


S100


CD99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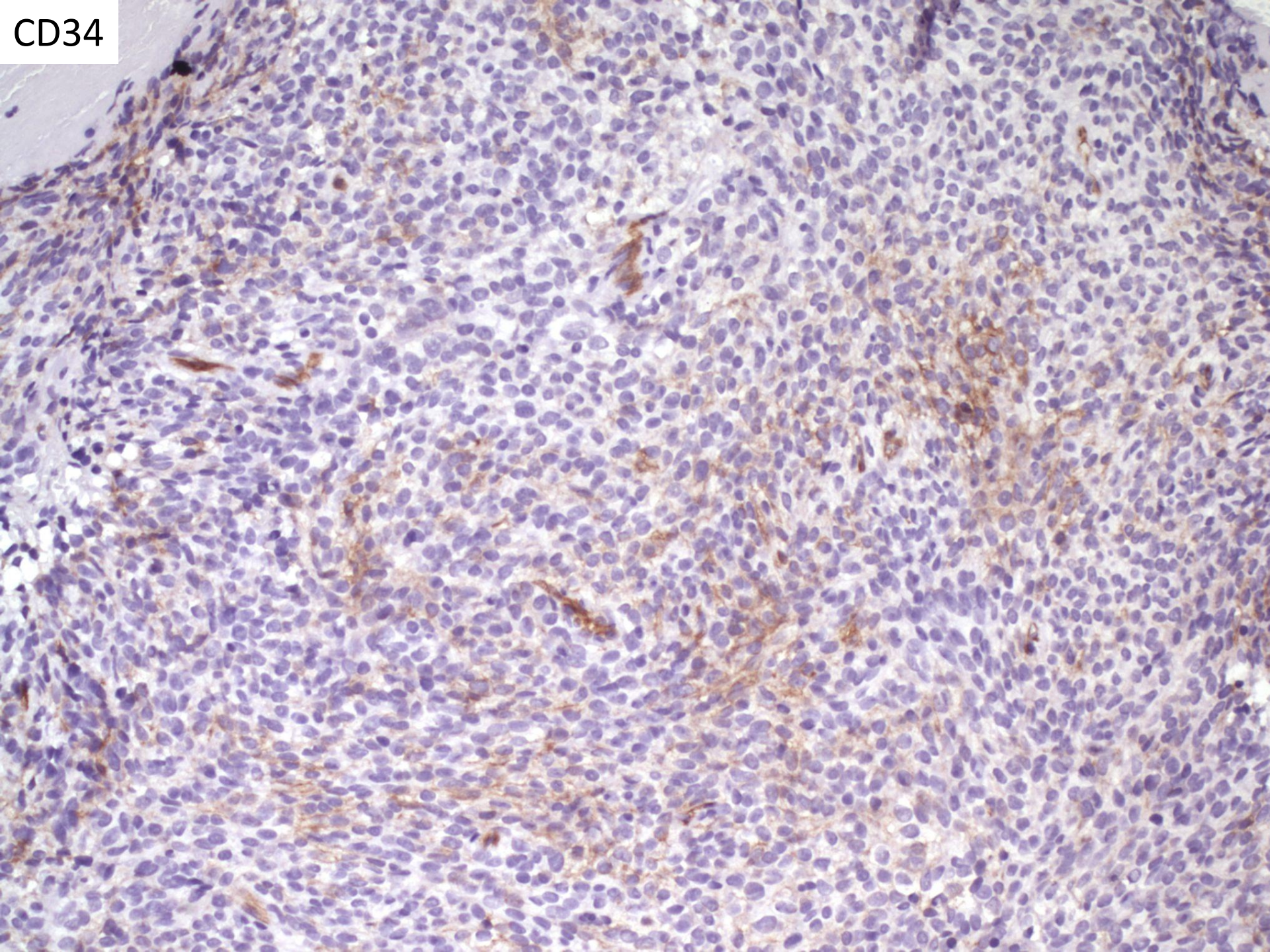
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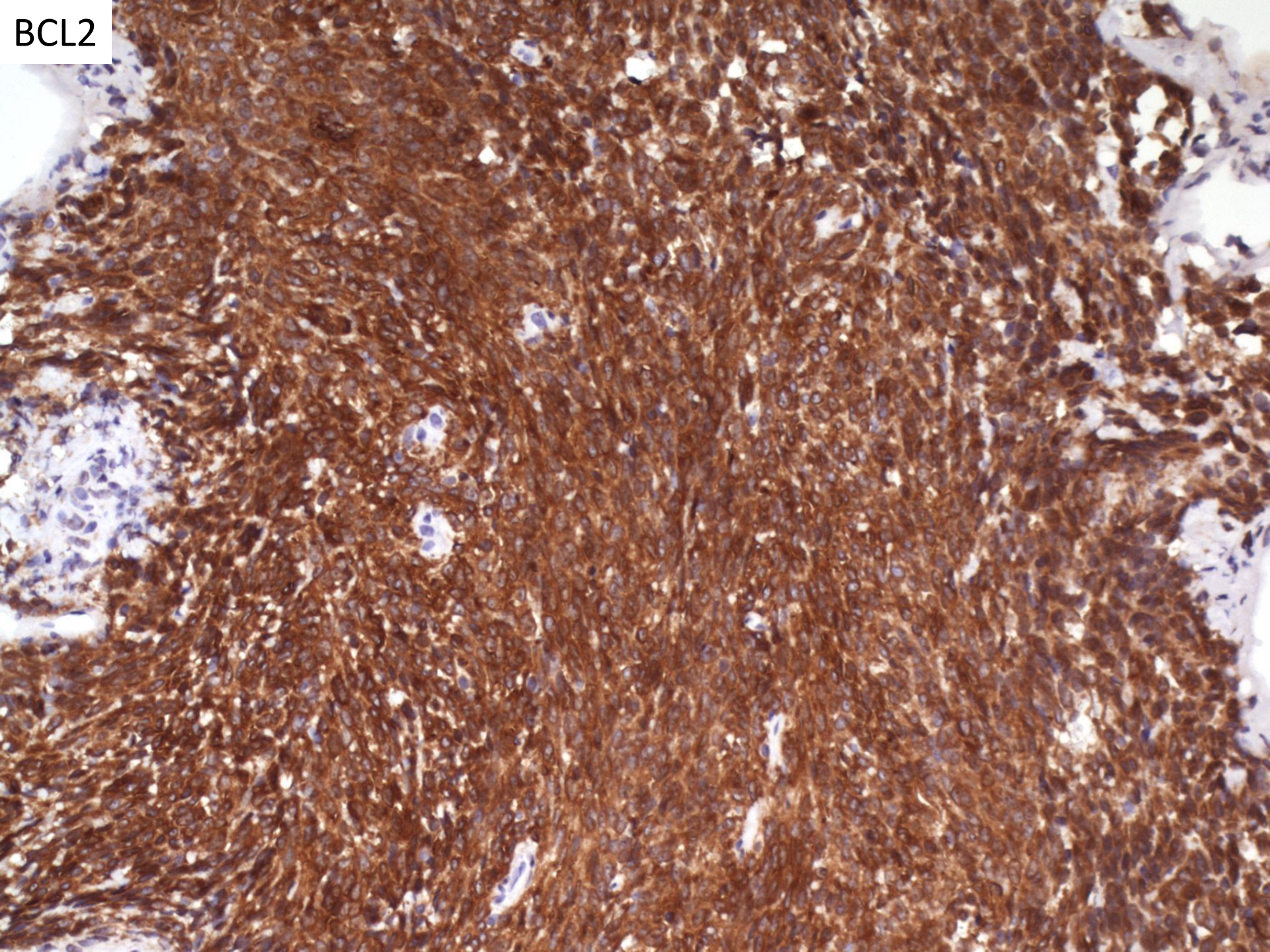
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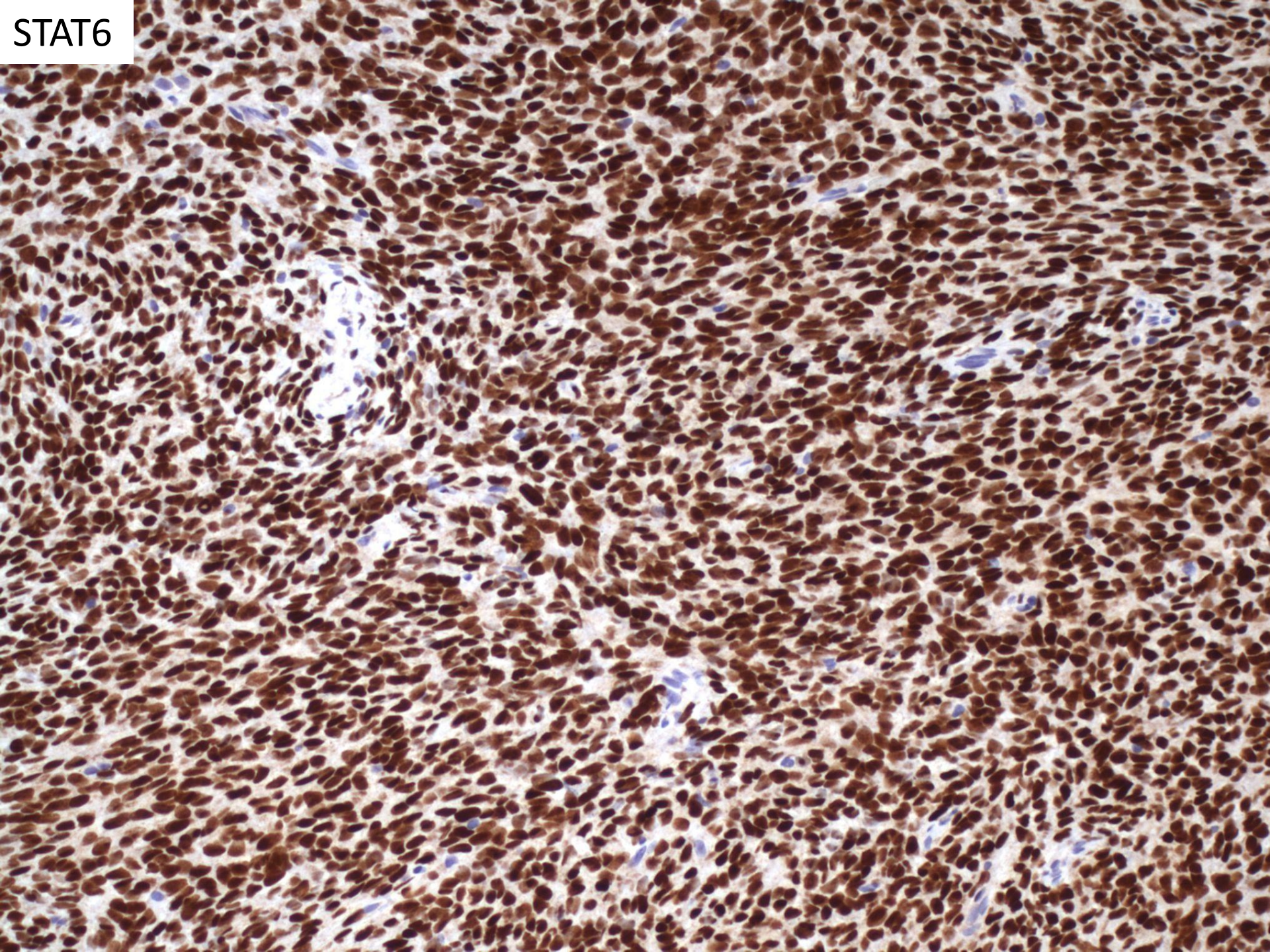
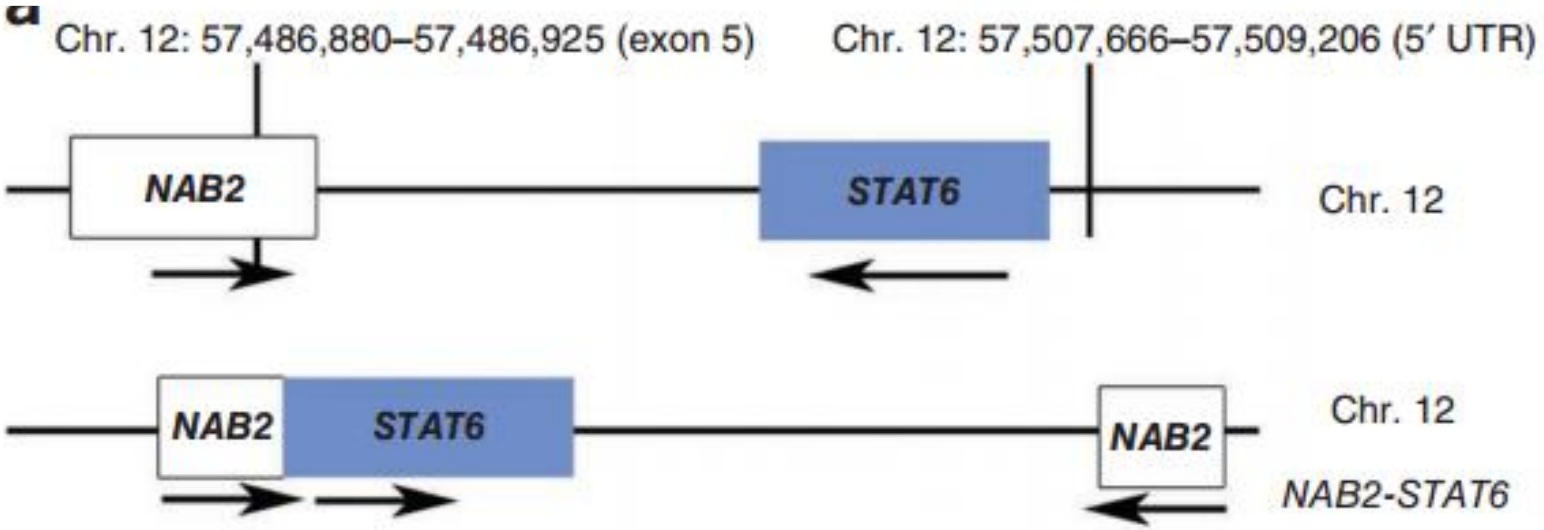

STAT6

Diagnosis?

Differential diagnosis

- Solitary fibrous tumor
- Synovial sarcoma
- Spindle cell carcinoma
- Leiomyosarcoma
- Neural – MPNST
- Spindle cell rhabdomyosarcoma

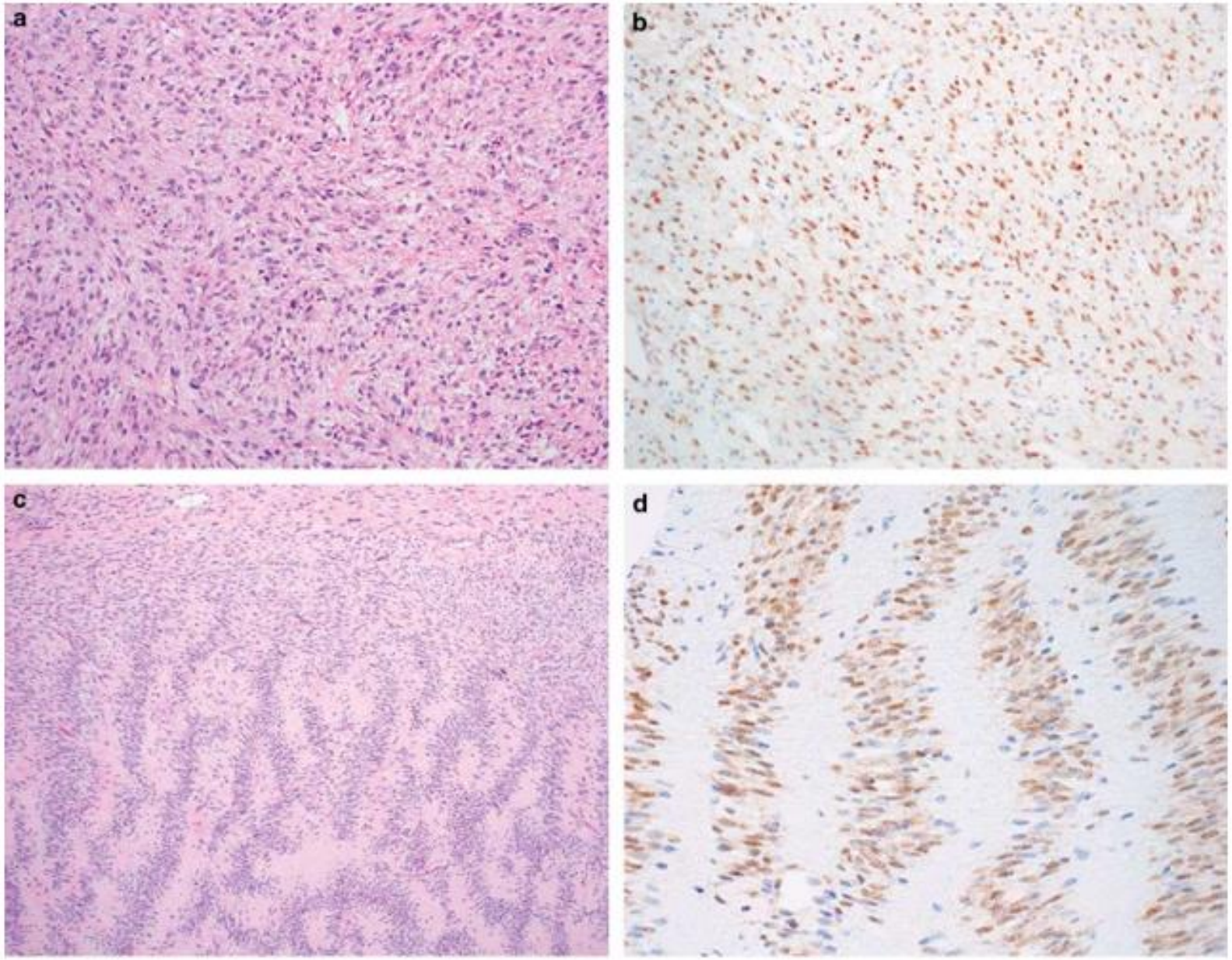
Solitary Fibrous Tumor (SFT)



1. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. **Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing.** Nat Genet. 2013;45:180-5.
2. Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D, McKenna A, Heinrich MC, Frank DA, Meyerson M. **Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors.** Nat Genet. 2013;45:131–2.

STAT6 is amplified in a subset of dedifferentiated liposarcoma

Leona A Doyle, Derrick Tao and Adrián Mariño-Enríquez



Summary

- STAT6 is sensitive and specific for SFT/hemangiopericytoma

- Beware that dedifferentiated liposarcoma may have spindle cells that express nuclear STAT6
  - Immunohistochemistry for MDM2 or CDK4
  - FISH for MDM2 amplification

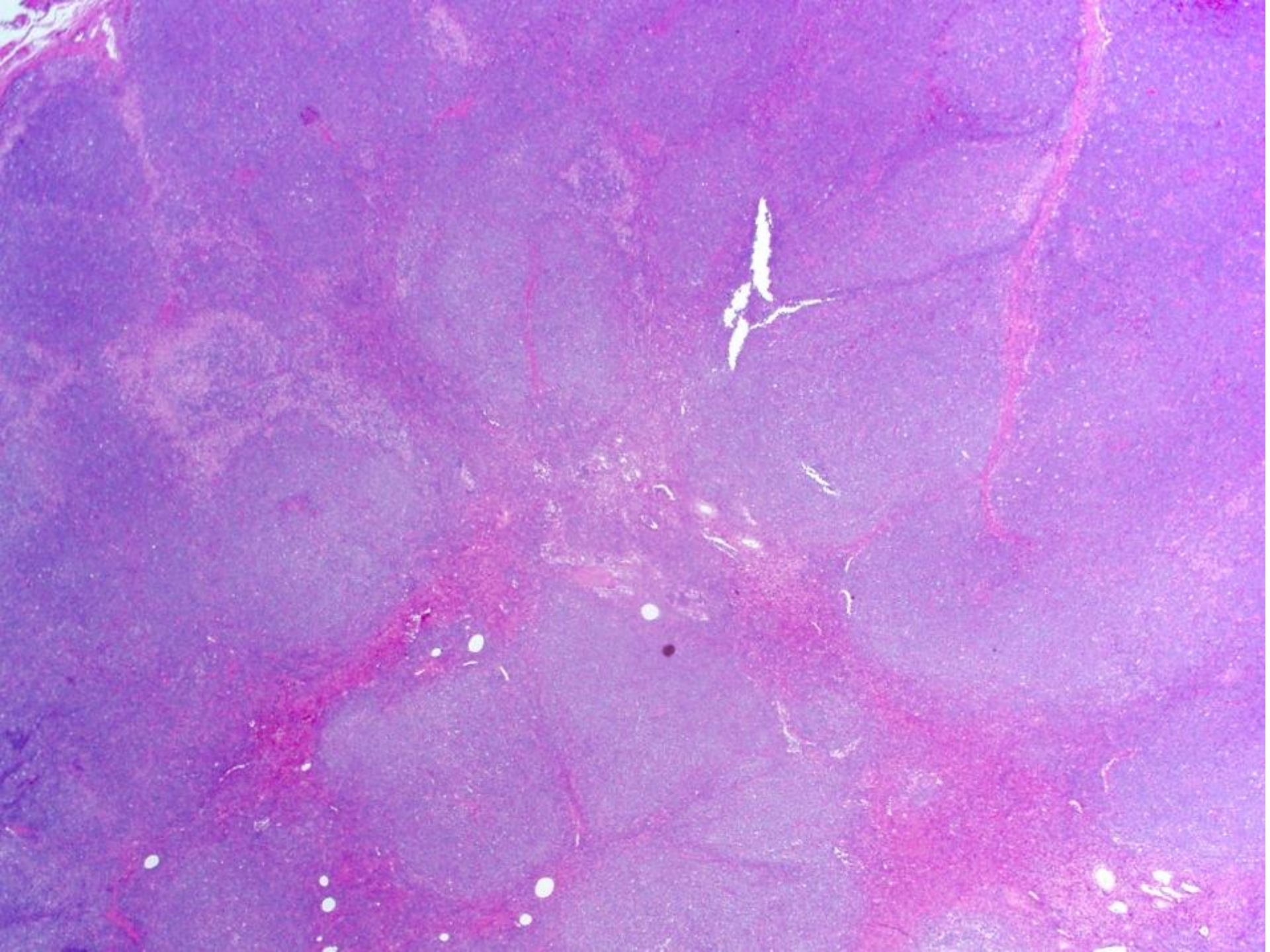
References

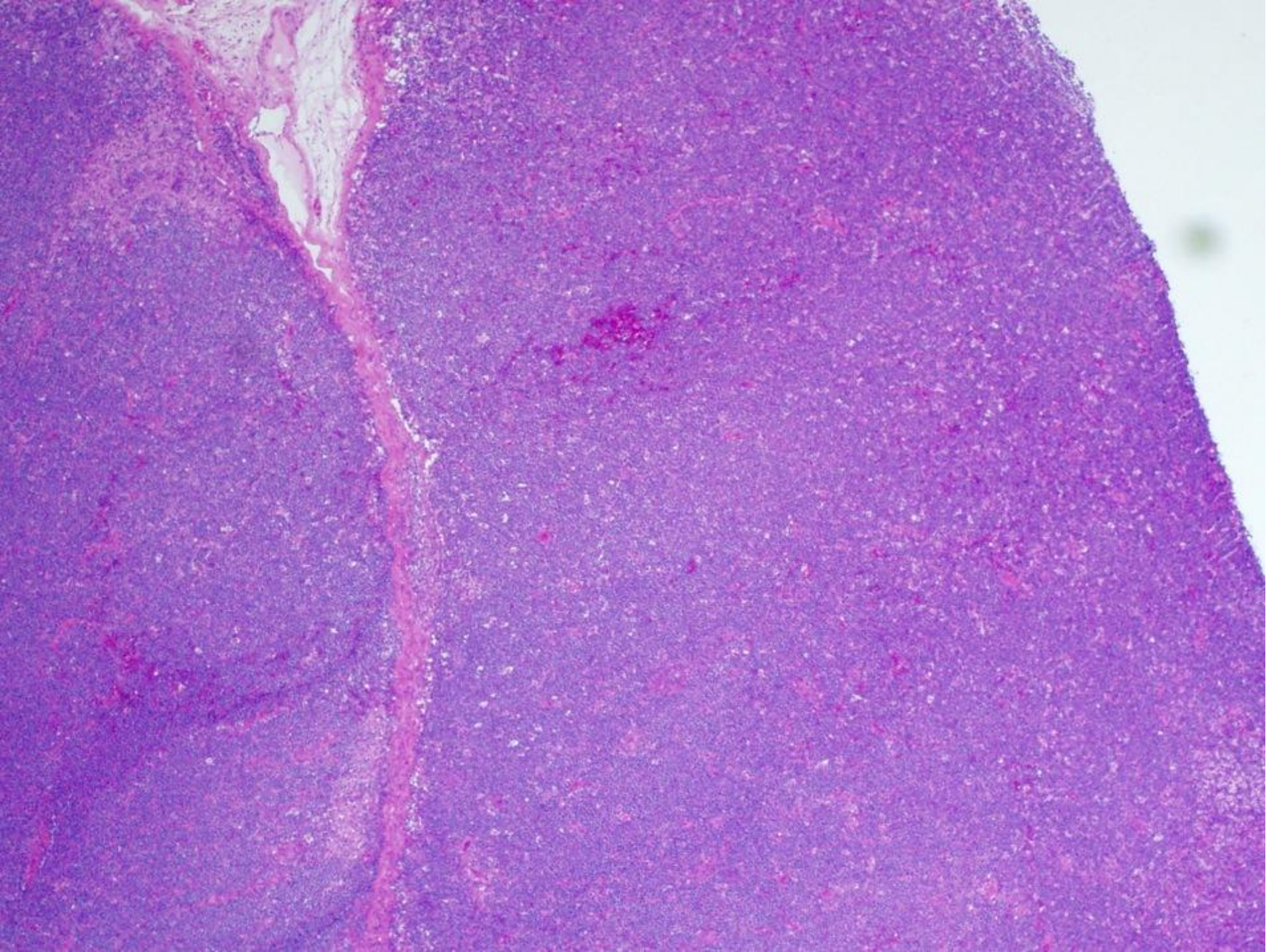
1. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. **Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing.** Nat Genet. 2013;45:180-5.
2. Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D, McKenna A, Heinrich MC, Frank DA, Meyerson M. **Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors.** Nat Genet. 2013;45:131–2.
3. Schweizer L, Koelsche C, Sahm F, Piro RM, Capper D, Reuss DE, Pusch S, Habel A, Meyer J, Göck T, Jones DT, Mawrin C, Schittenhelm J, Becker A, Heim S, Simon M, Herold-Mende C, Mechtersheimer G, Paulus W, König R, Wiestler OD, Pfister SM, von Deimling A. **Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein.** Acta Neuropathol. 2013;125:651–8.
4. Doyle LA, Tao D, Marino-Enriquez A. **STAT6 is amplified in a subset of dedifferentiated liposarcoma.Mod Pathol.** 2014;27:1231–1237. doi: 10.1038/modpathol.2013.247.

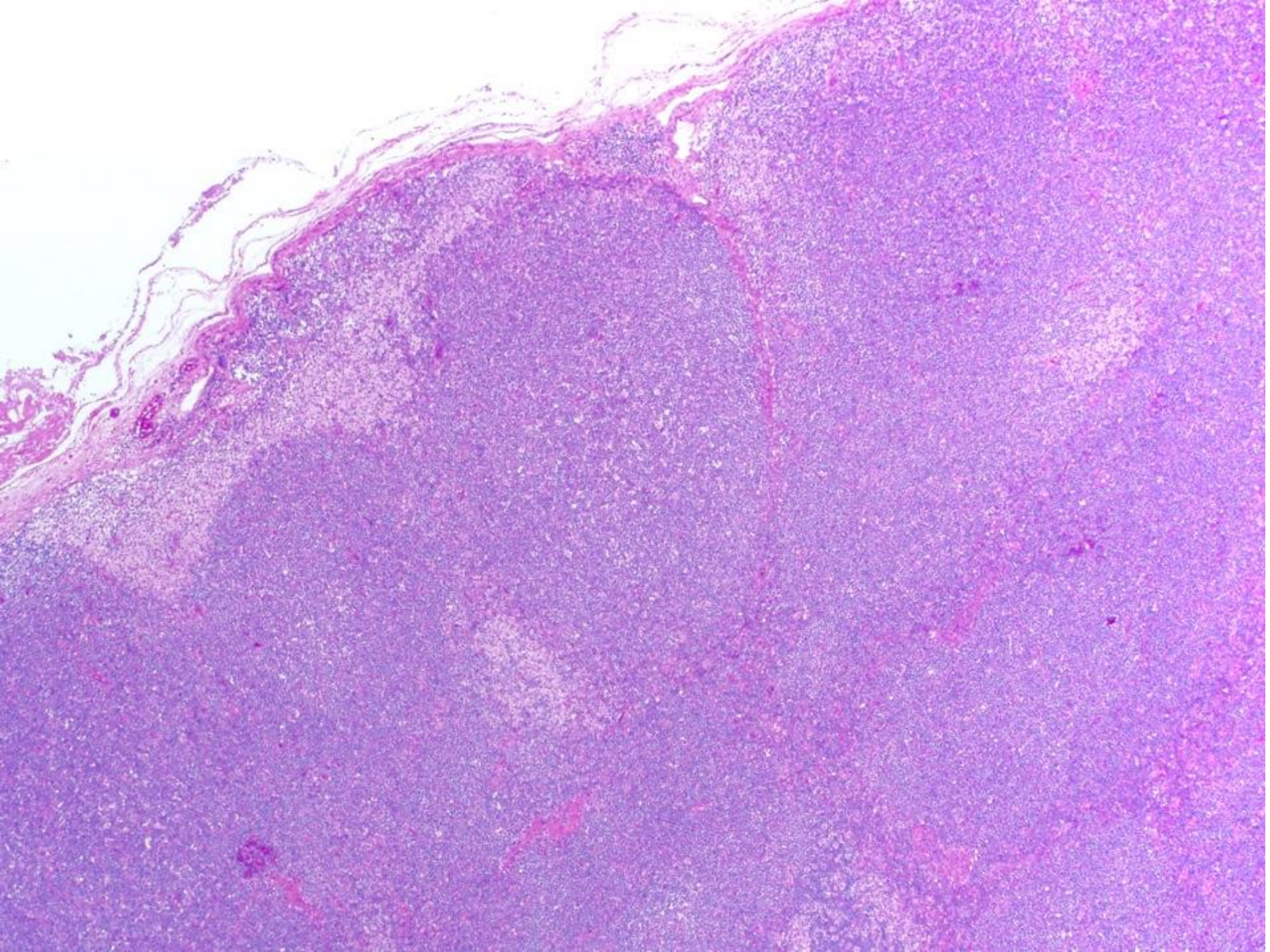
SB 5930

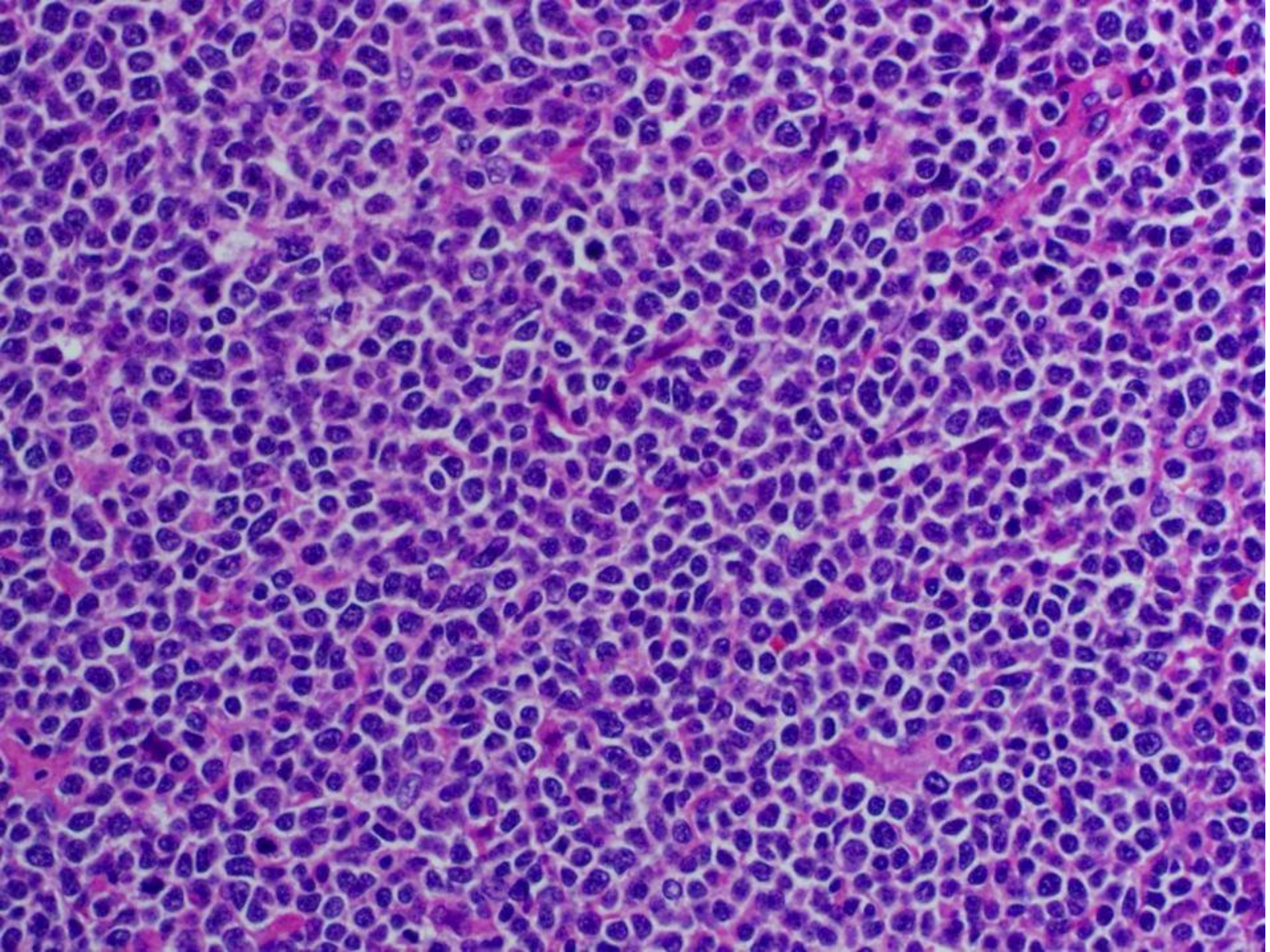
- 76-year-old male with inguinal lymphadenopathy. Concurrent flow cytometry showed a lambda-restricted population with bright CD45 and low SSC with expression of CD19, CD20, CD10, CD22, CD38, FMC7 and lacking CD23, CD103, and CD5.

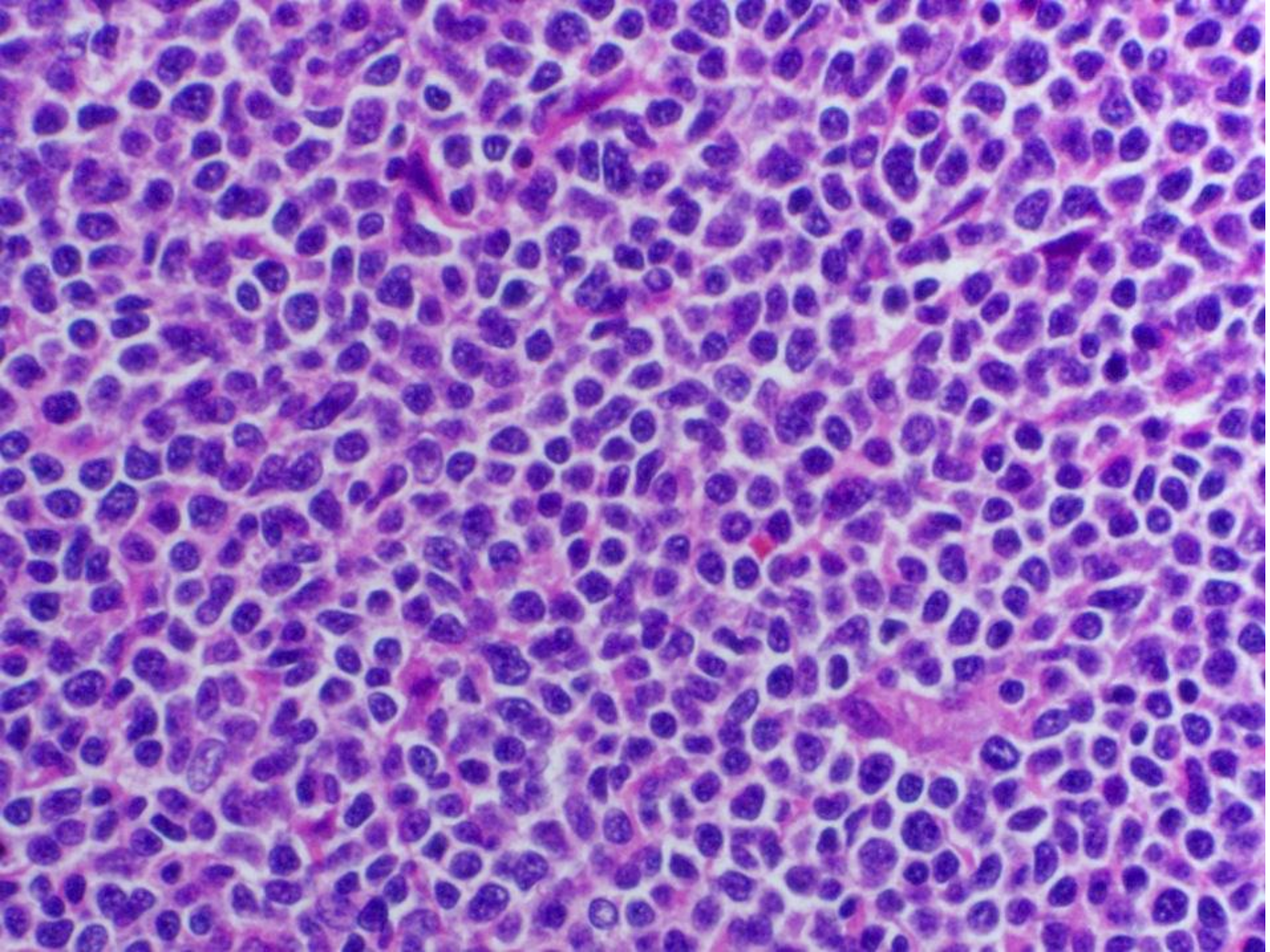
- Ryan Johnson/Yaso Natkunam; Stanford

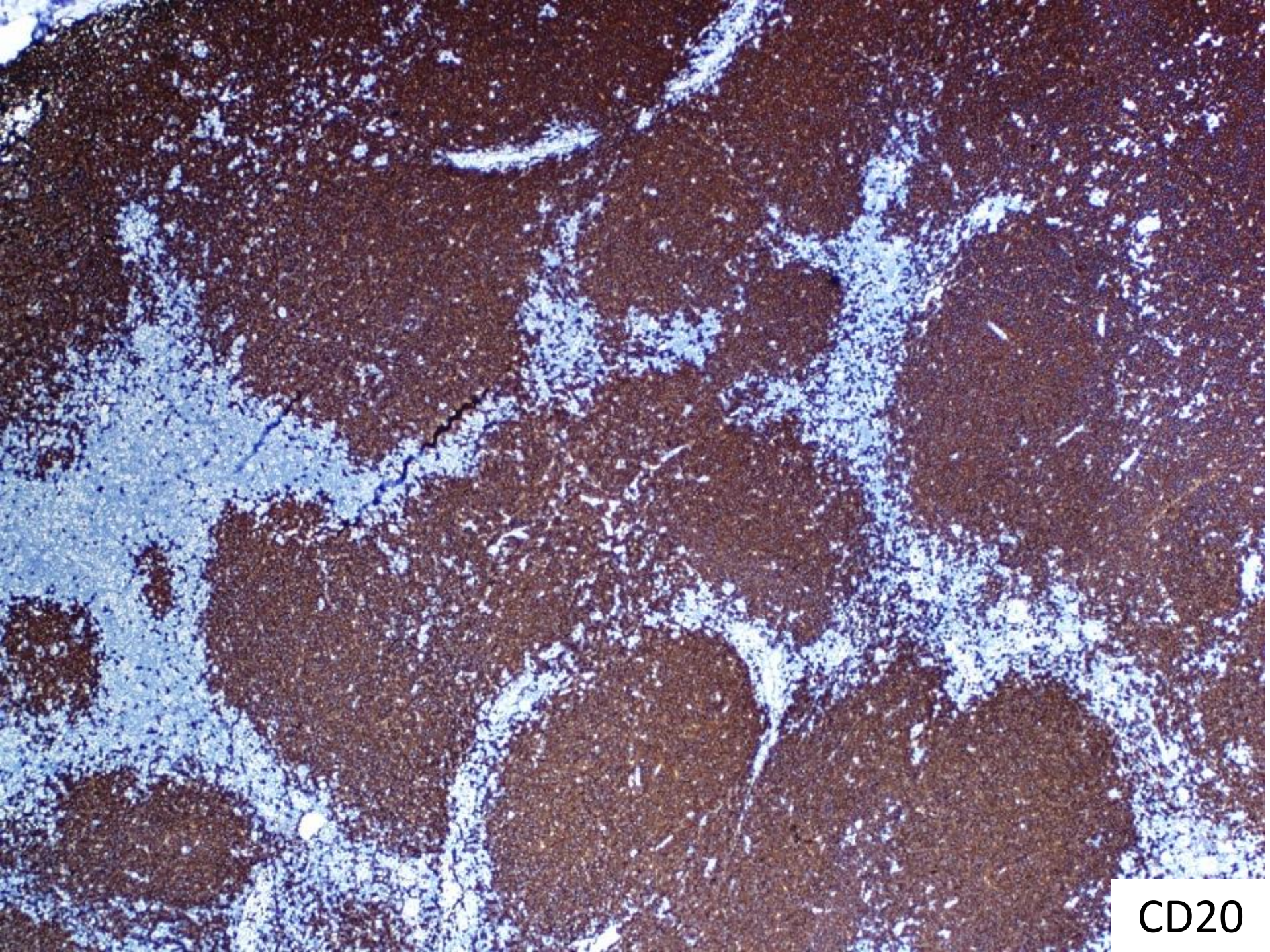


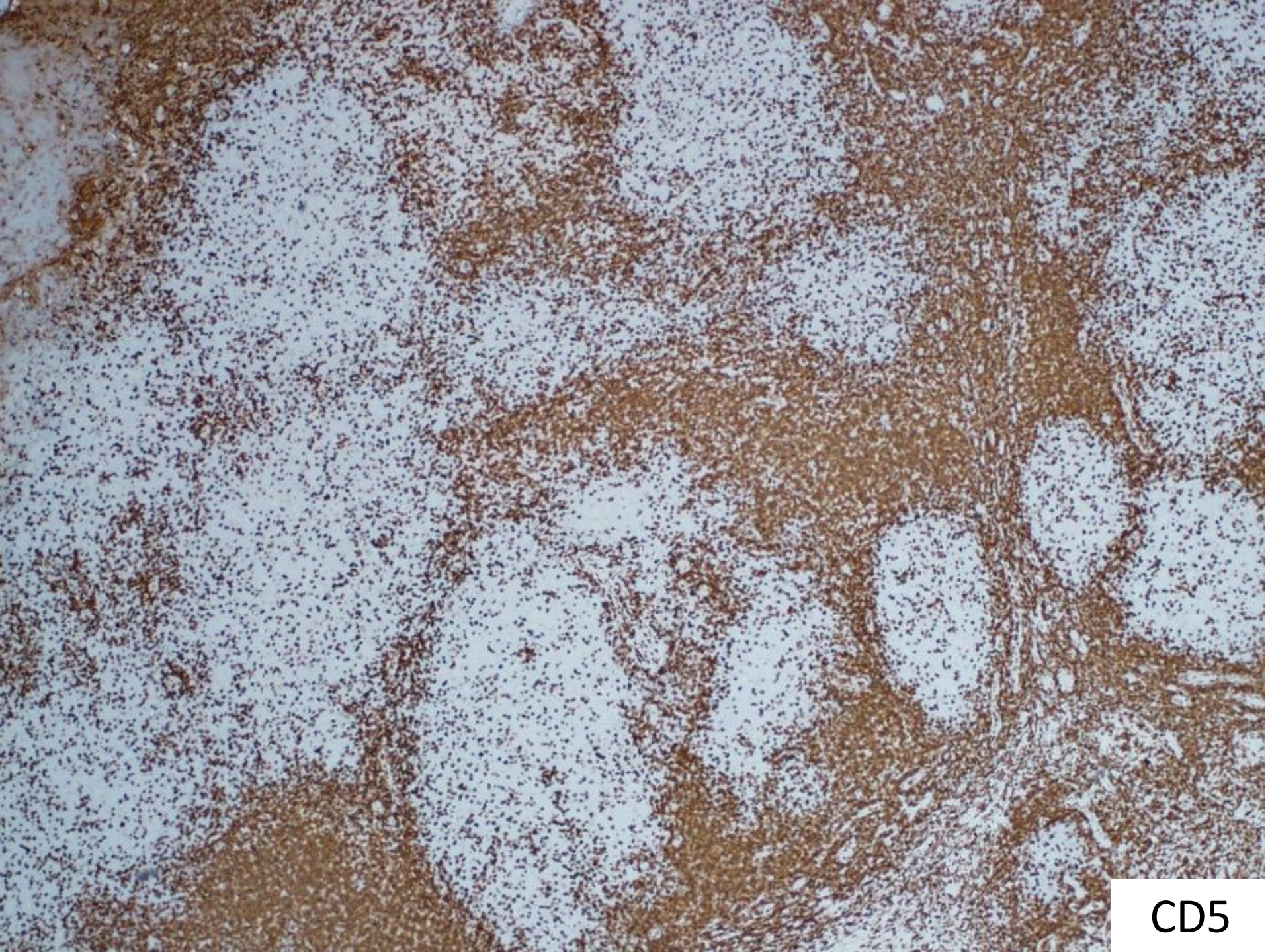




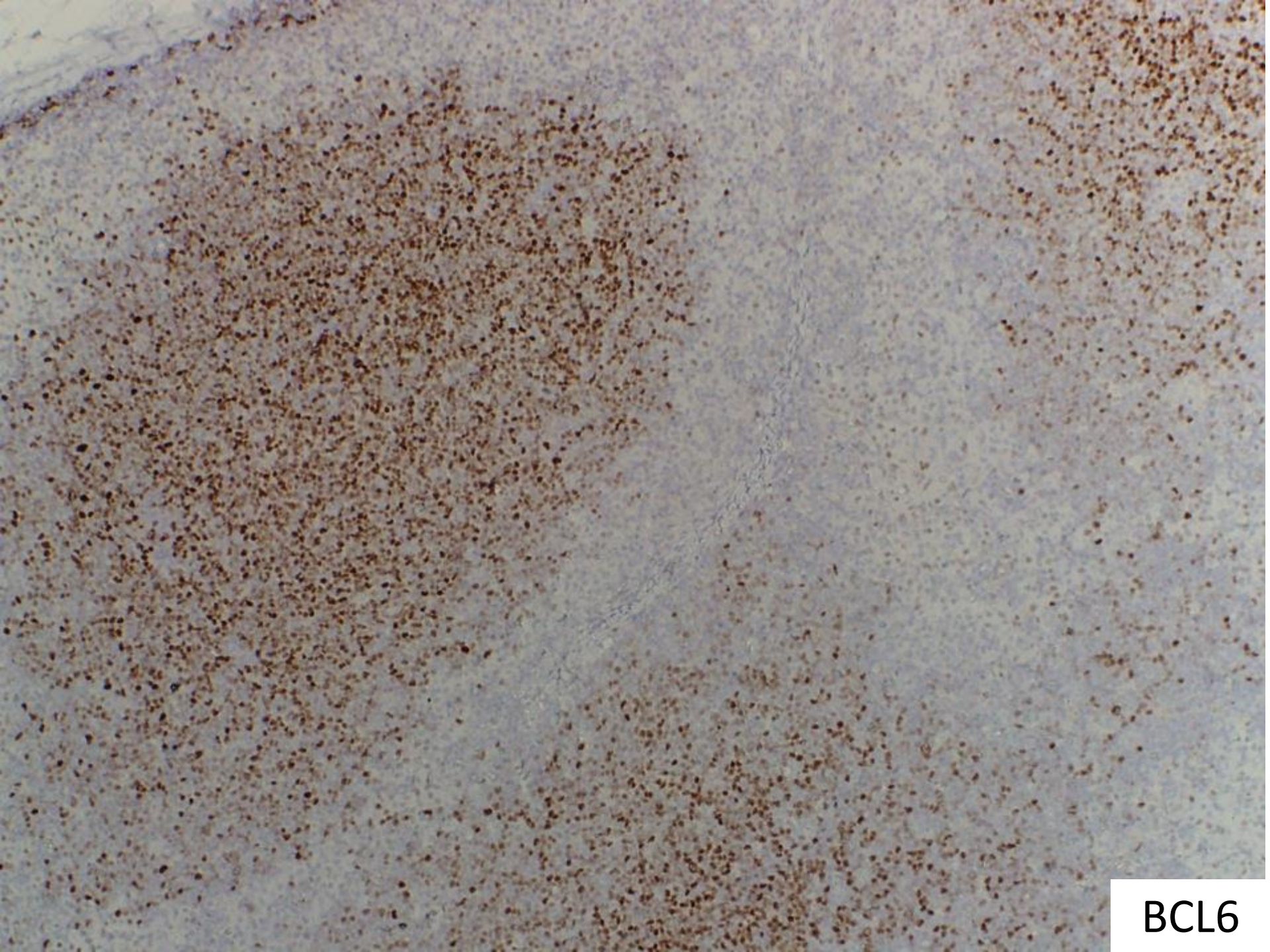


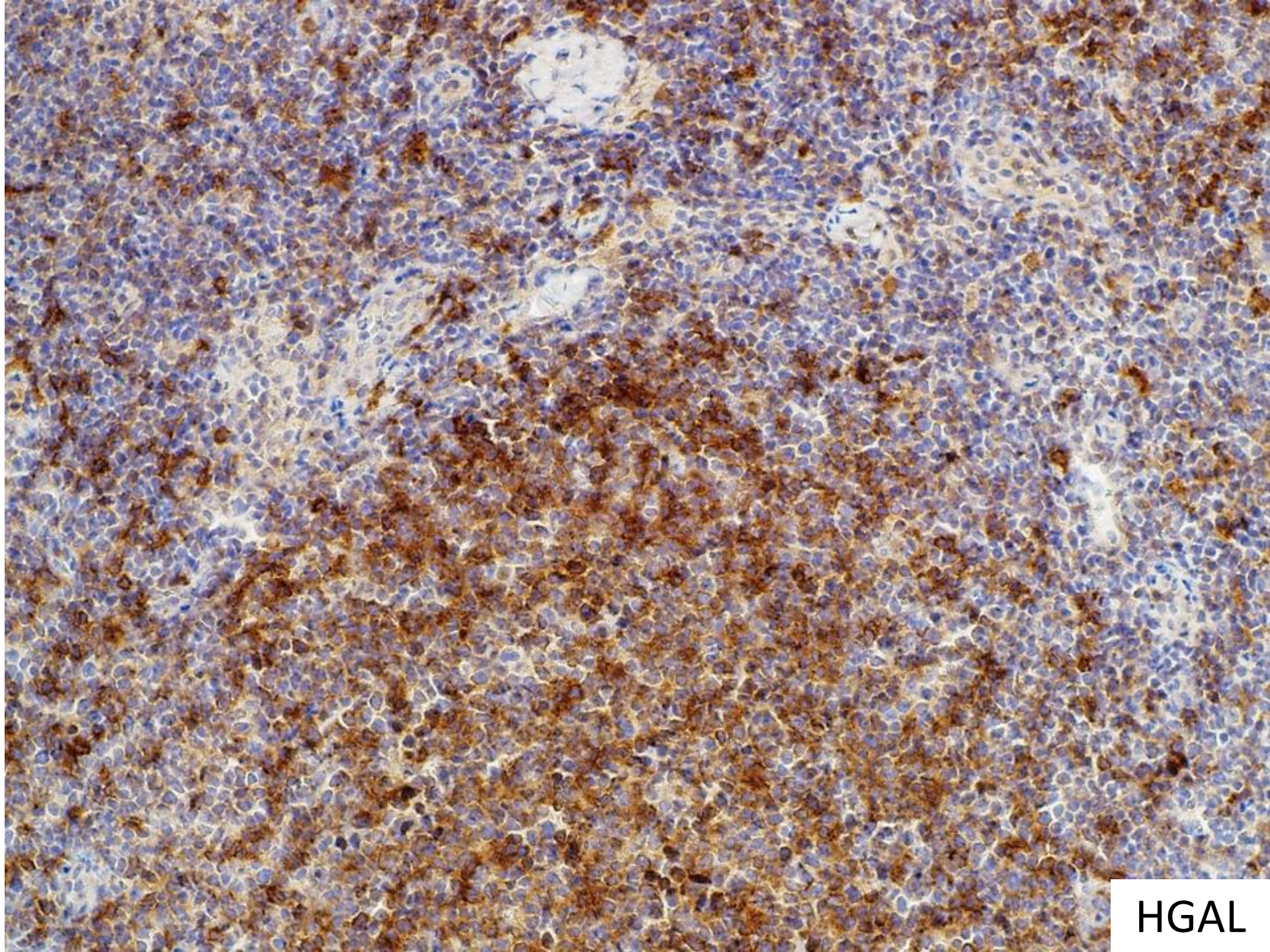


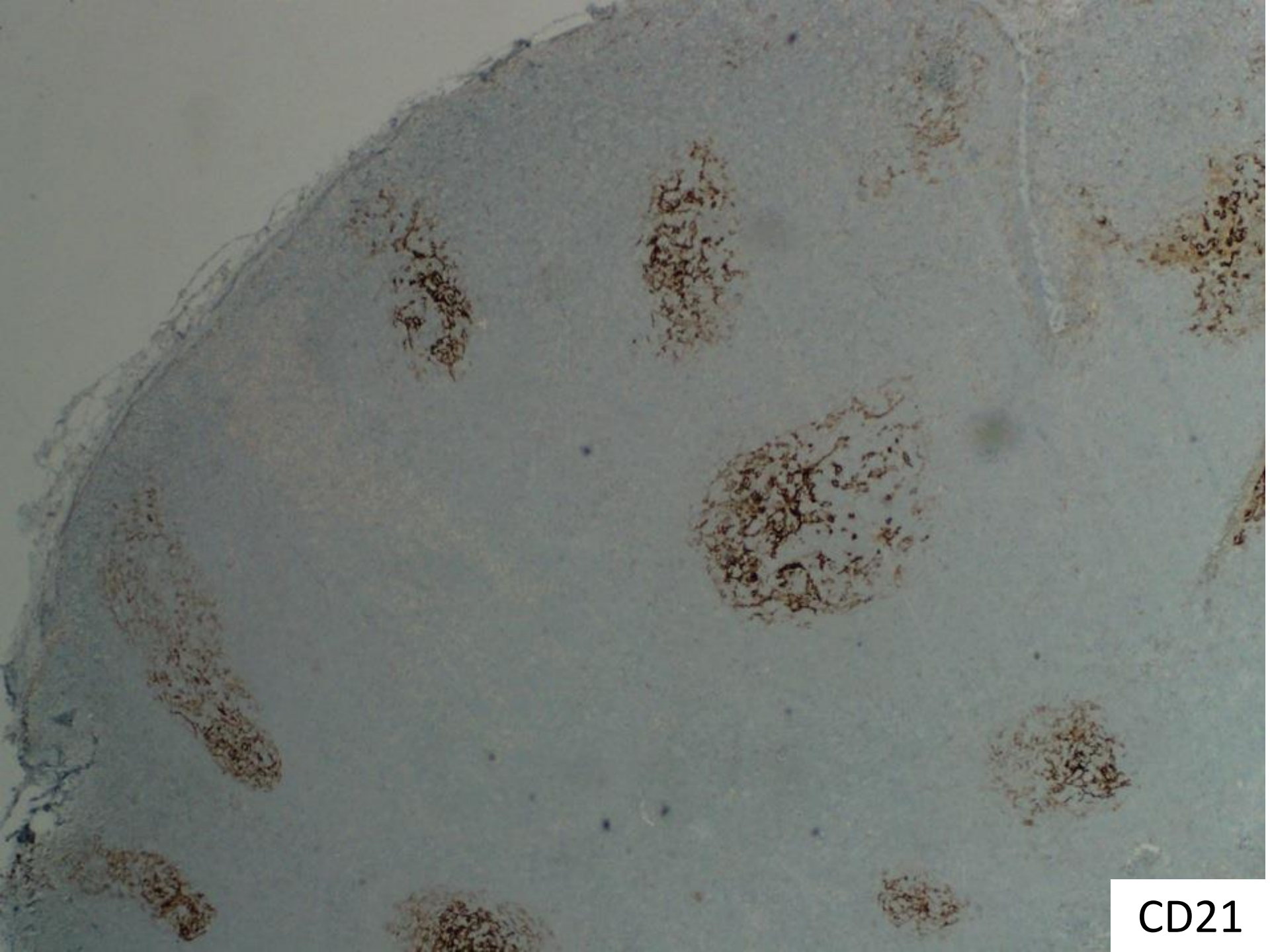

CD20


CD5


CD10


BCL6


HGAL


CD21

Diagnosis?

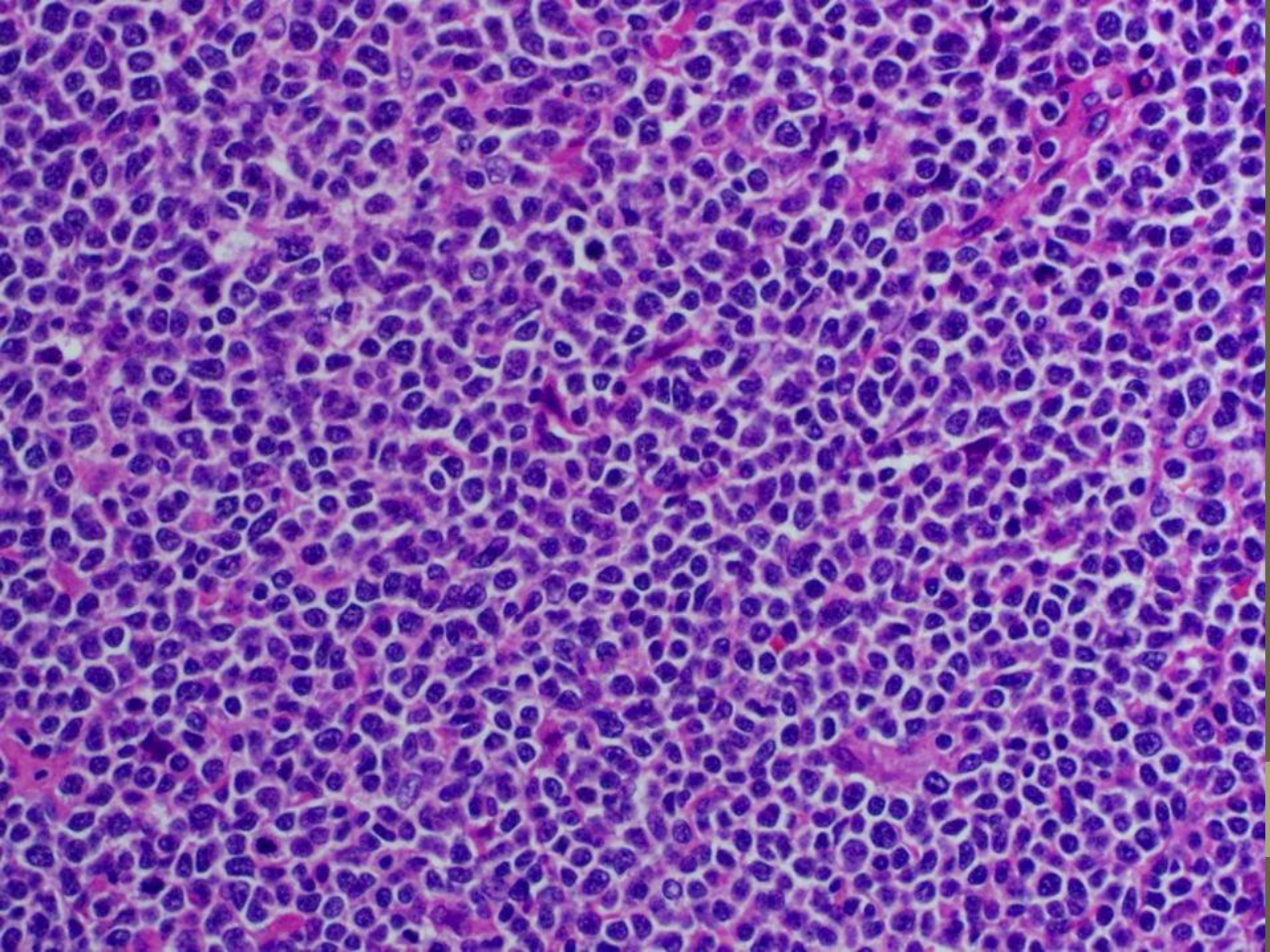
SB5930

Ryan Johnson, MD
Yasodha Natkunam MD, PhD
Stanford Health Care

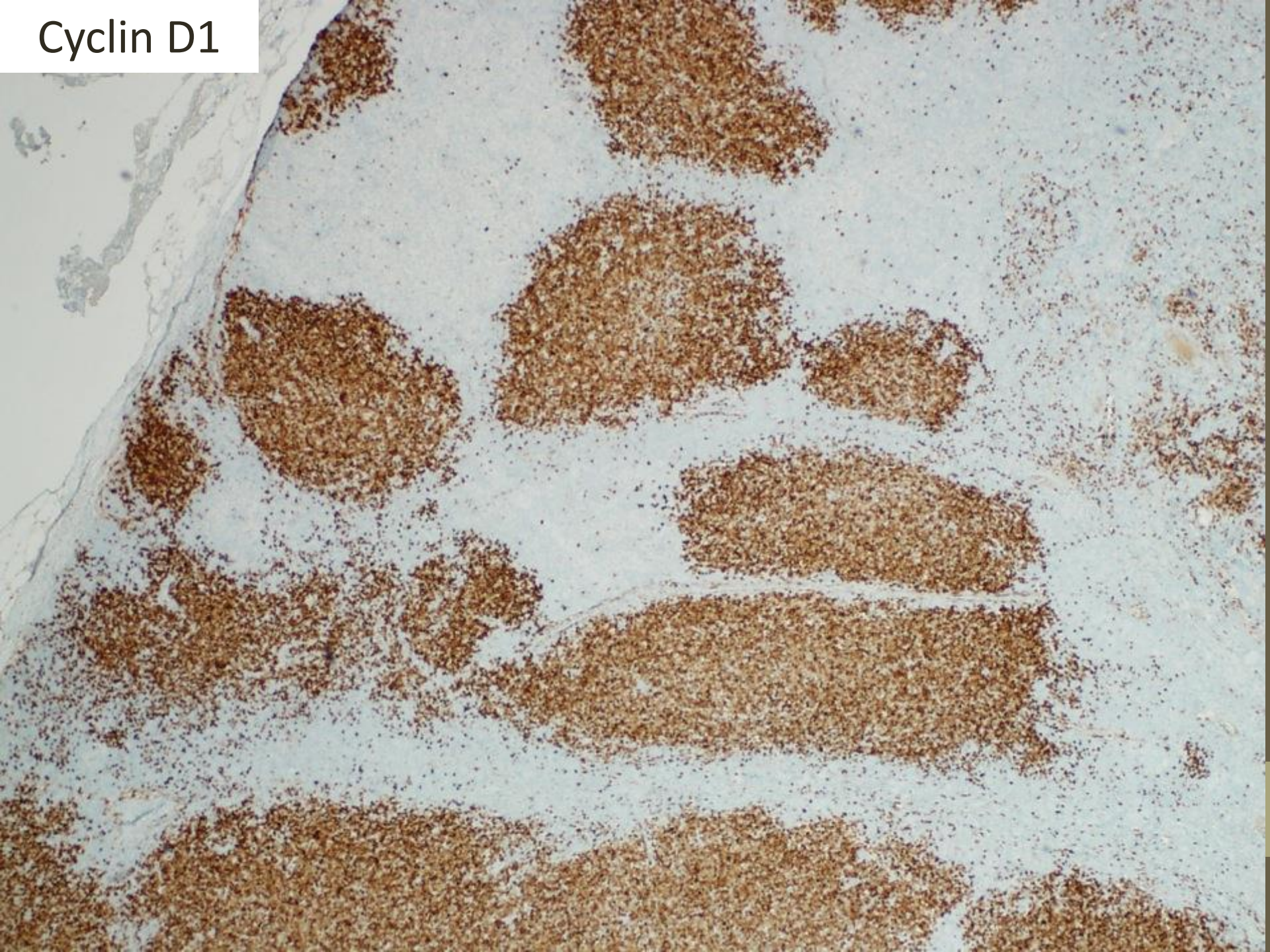
Clinical History

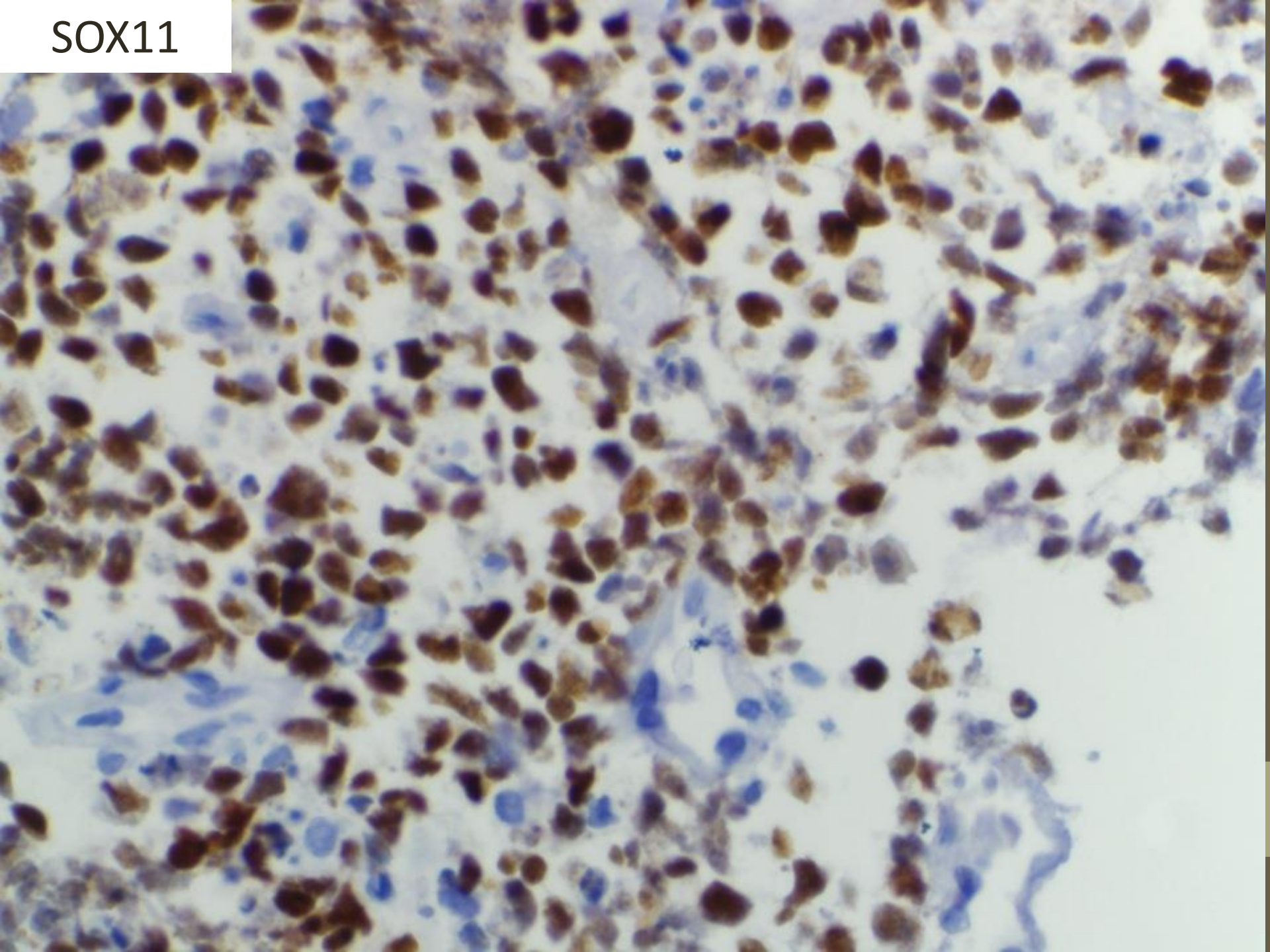
- The patient is a 76 year old male with inguinal lymphadenopathy.

- Concurrent flow cytometry showed a lambda restricted B-cell population with bright CD45 and low SSC with expression of CD19, CD20, CD10, CD22, CD38, FMC7, and lacking CD23, CD103 and CD5.




CD10


Cyclin D1

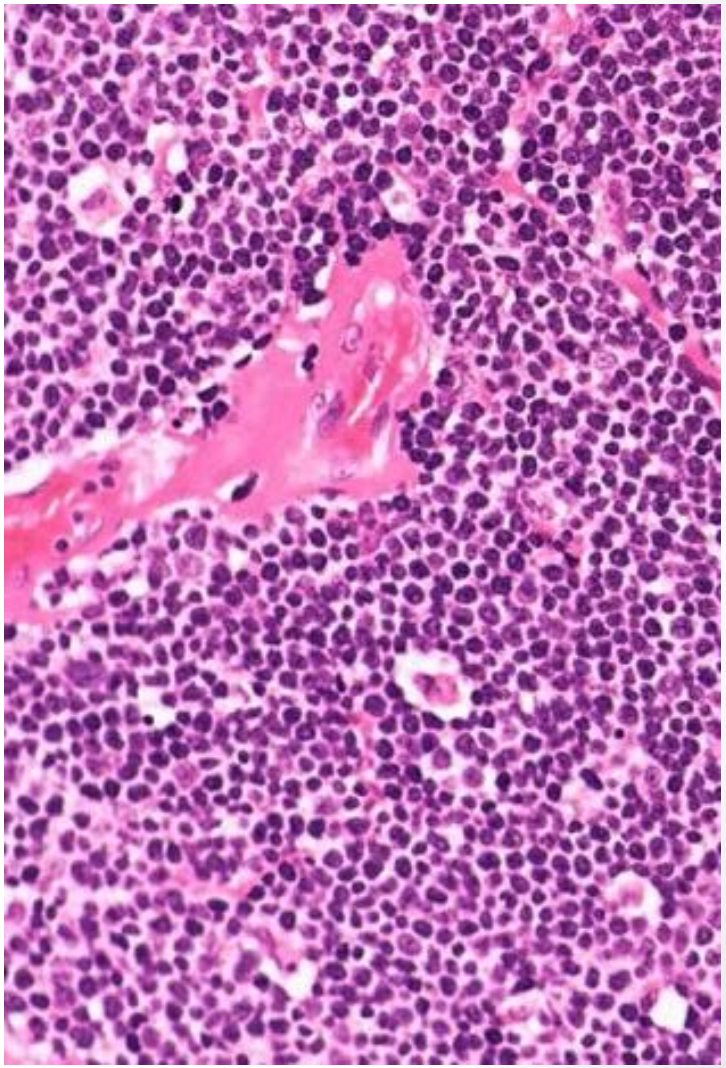

SOX11

Diagnosis:

- Mantle cell lymphoma
  - Aberrant expression of multiple ‘germinal center’ markers

Mantle cell lymphoma

- Small B-cell lymphoma generally +ve for t(11;14) CCND1/IGH
- Most cases express CD5
- Four morphologic variants:
  1) Classic
  2) Blastoid
  3) Pleomorphic
  4) marginal-zone like
- Can show mantle, nodular, or diffuse patterns
- Pink histiocytes and hyalinized vessels may help



Expression profile of MCL

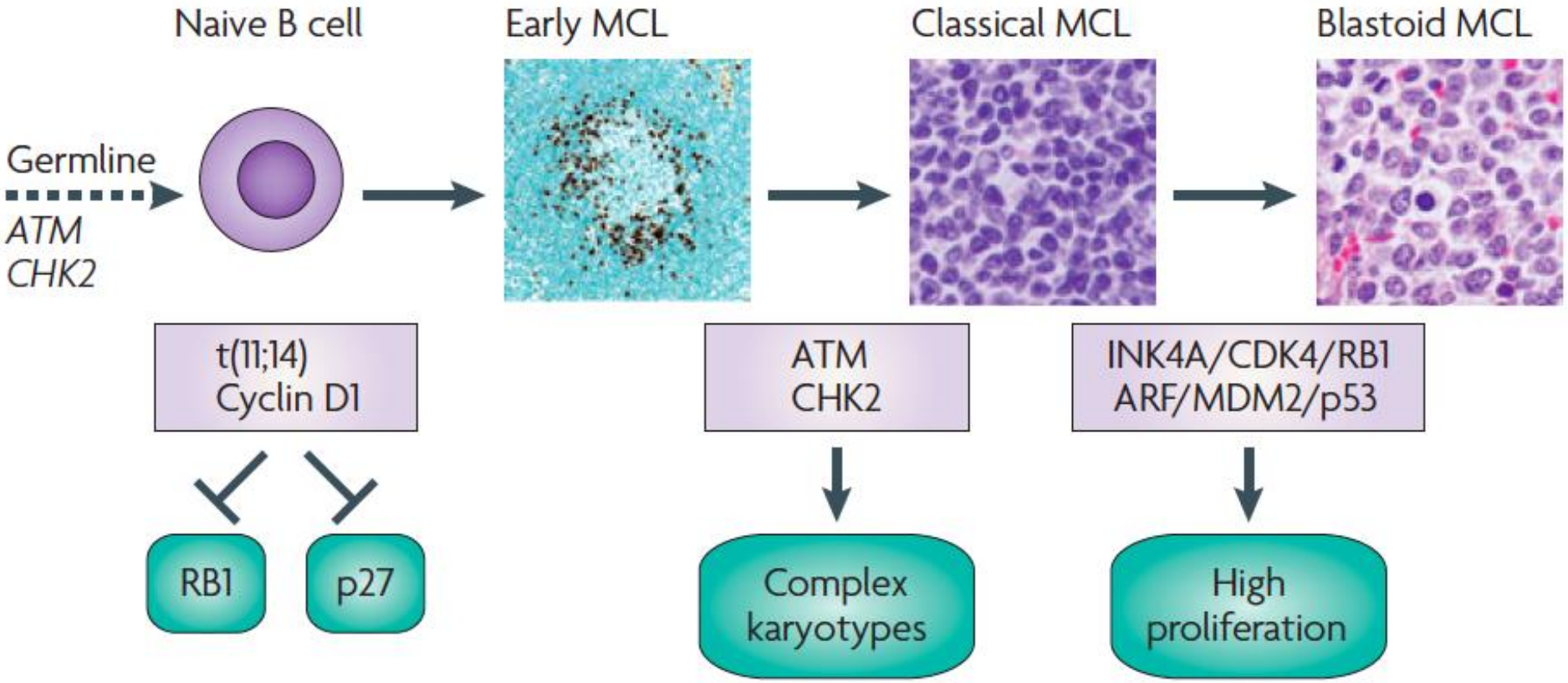
127 cases of MCL

- Male to female ~2.6:1
- Most showed classic morphology
- All had expression of BCL1
- Vast majority (96%) had CD5 expression
- 12% showed germinal center marker BCL6
- Most showed CD43 expression (common to most small B-cell lymphomas)

	N^{o} of cases	FISH positive	FISH negative
Female	35 (27.6%)	35	0
Male	92 (72.4%)	83	3
Mean Age	59 yo	59 yo	69 yo
Nodal	102 (80.3%)	94	3
Extranodal	25 (19.7%)	24	0
Classic morphology	113	110	3
Blastoid variant	11(9%)	11	0
Pleomorphic variant	2(1.5%)	2	0
Marginal-zone-like	1(0.75%)	1	0
CD20+	127	118	3
BCL-1 (cyclin D1)+	127	118	3
CD5+	122 (96%)	113	3
BCL-6+	15 (11.8%)	14	0
MUM1+	45 (35.4%)	44	1
CD43+	84 (66%)	79	2
Mean PI Ki-67	38.2	38	42
Total	127	118 (97.7%)	3 (2.3%)

Gualco G, et al. AIMM 2010 Mar;18(2):103-8.

Origin/progression

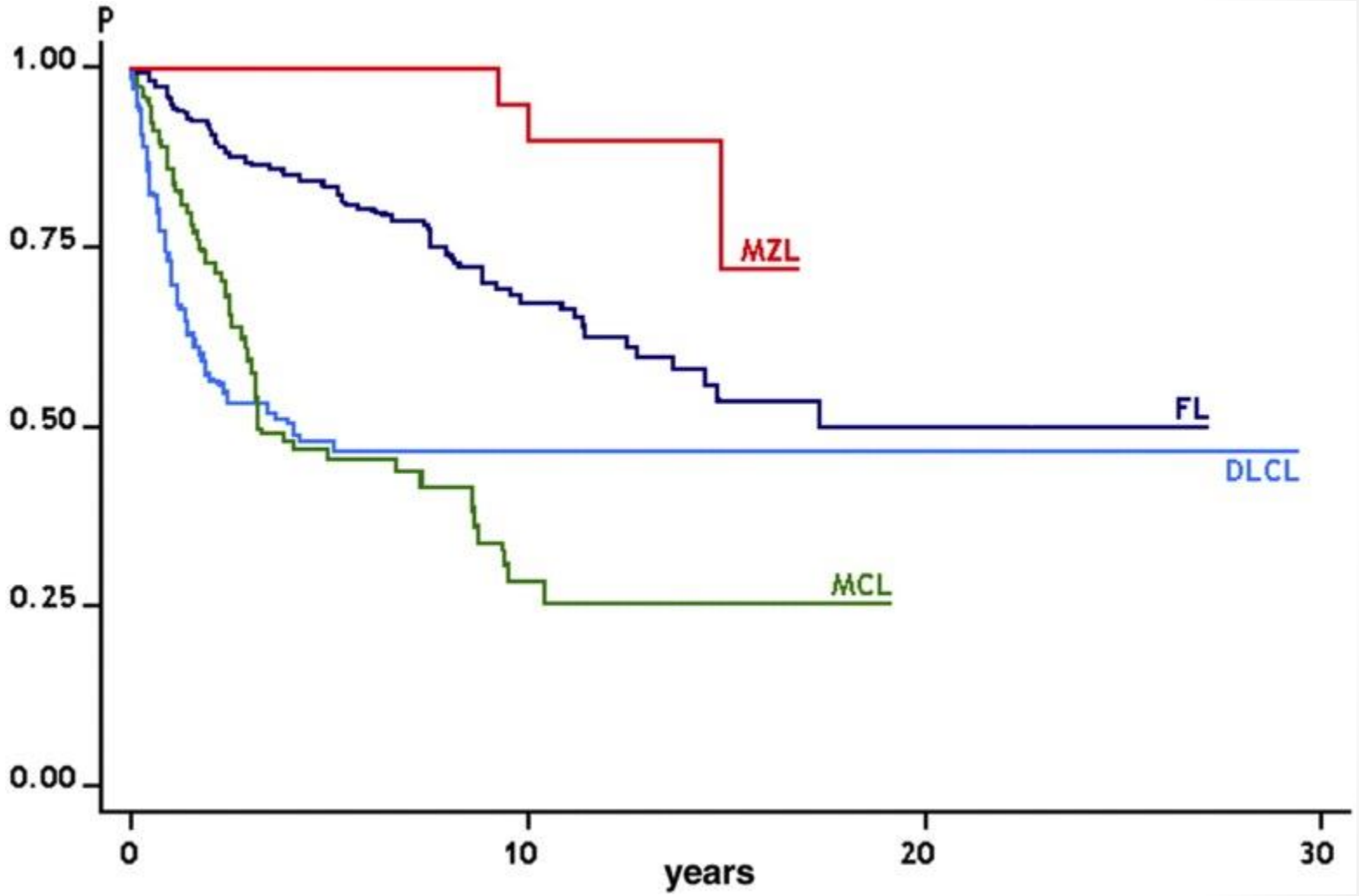


Jares P, et al. Nat Rev Cancer. 2007 Oct;7(10):750-62.

Why identify MCL?

- Most patients present with stage III or IV disease
- Don’t always respond to low grade lymphoma therapy
- Median survival worst among low grade B-cell lymphomas

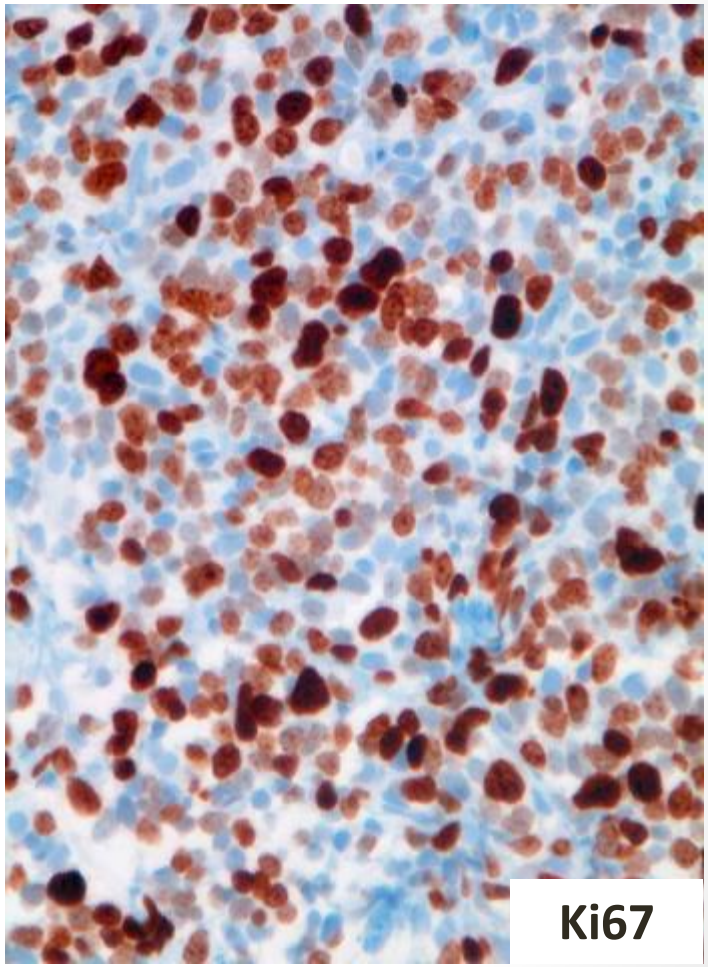
Cause-specific survival of the main B-cell lymphoma subtypes in the series of the Oncology Institute of Southern Switzerland, 1980-2006.



Michele Ghielmini, and Emanuele Zucca Blood 2009;114:1469-1476

Prognostic markers

- Morphology
  - Blastoid or pleomorphic thought to be adverse
- Proliferation rate (Ki67)
  - >30% or >40% thought to be adverse
- Subtype of MCL with PB, marrow, and spleen involvement but minimal LAD ('indolent MCL')



Take home points

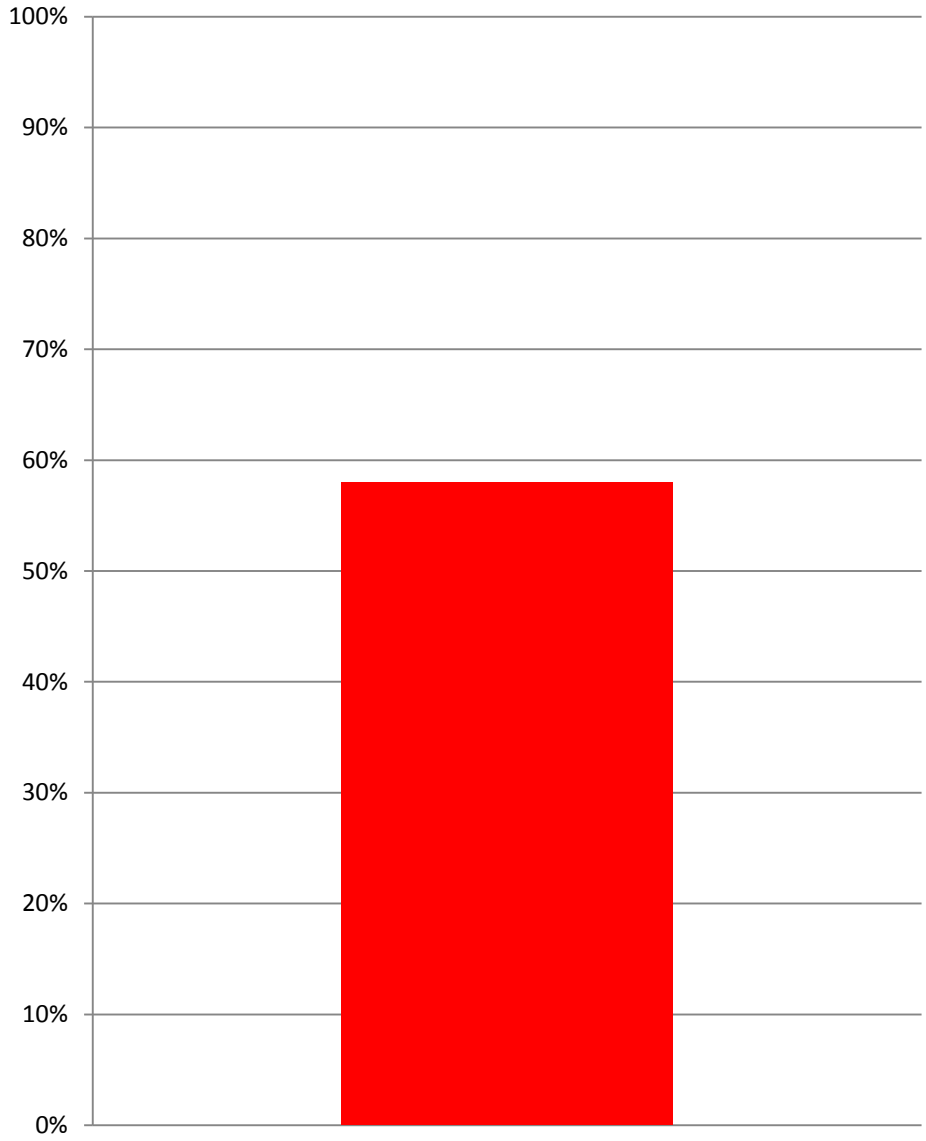
- Mantle cell lymphoma can lack CD5 and express markers associated with other small or large B-cell lymphomas
  - Utility in performing a BCL1 and/or SOX11 and/or send for FISH
- Mantle cell lymphoma as a whole demonstrates a more aggressive clinical course as compared with other low grade B-cell lymphomas
  - Some variation in clinical behavior in some subtypes
  - Perform a Ki67 on all cases to assess prognosis

Membership Dues

- 2014:
  - 107 memberships
- 2015:
  - YTD: 62 memberships
  - 4 new members!!!

PLEASE GET YOUR DUES PAID BY MARCH 31.

  - $50 late fee after March 31



The End

- Dean has CME certificates.