NOV 2022 DIAGNOSIS LIST

22-1101: cutaneous melanocytic tumor with CRTC1::TRIM11 fusion (soft tissue; soft tissue path)
22-1102: hepatocytes with intracellular crystalline deposition (liver; liver path)
22-1103: papillary squamous cell carcinoma, low risk HPV associated (cervix; GYN path)
22-1104: anaplastic large cell lymphoma (LN; hemepath)
22-1105: segmental overgrowth (PIK3CA mutation) (soft tissue; peds&soft tissue path)
22-1106: sialadenitis (amylase crystals); (soft tissue; cytopath)
22-1107: benign cortical cyst/decortication (kidney; GU path)
22-1108: pT2M1a (testis; GU path)

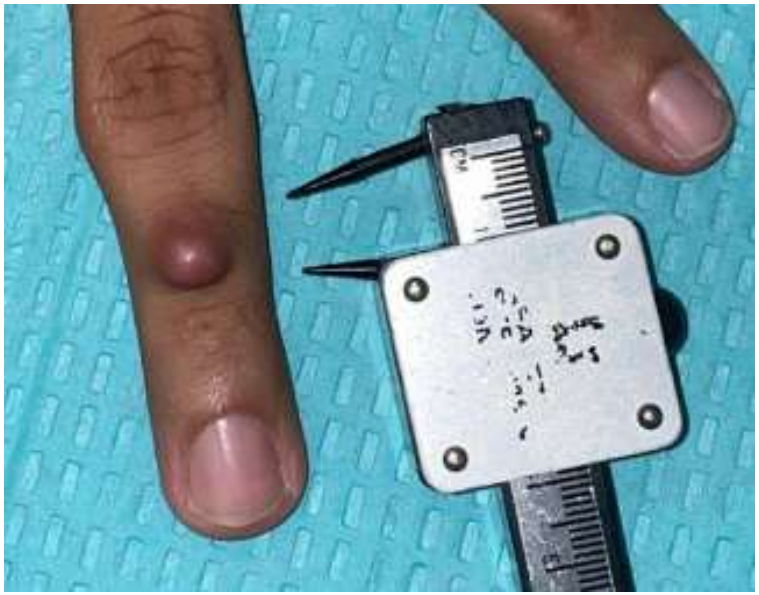
22-1101

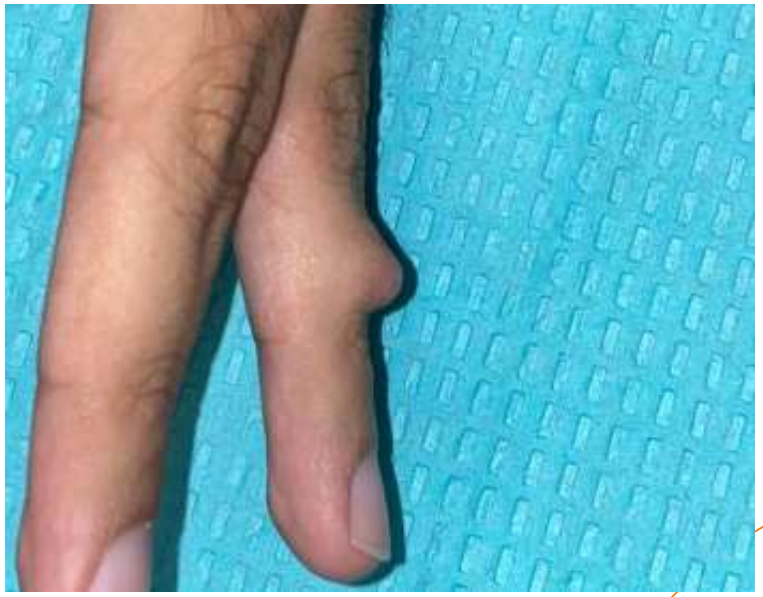
Bonnie Balzer; Cedars-Sinai

Previously-healthy 20ish M presents with 1.2cm painless growing exophytic mass on left 4th finger, first noticed 1.5 years prior.

Case presentation

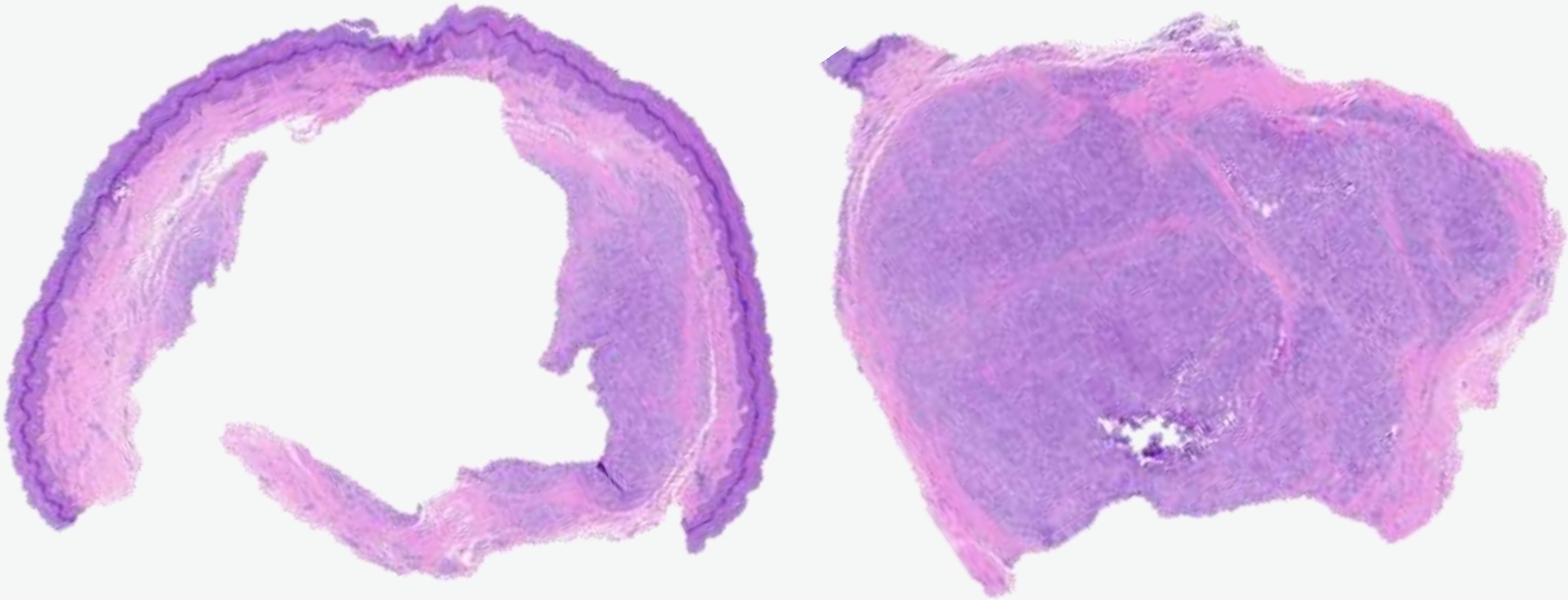
A previously healthy 20ish male presented with a 1.2 cm painless growing exophytic mass on his left fourth finger, first noticed 1.5 years prior.

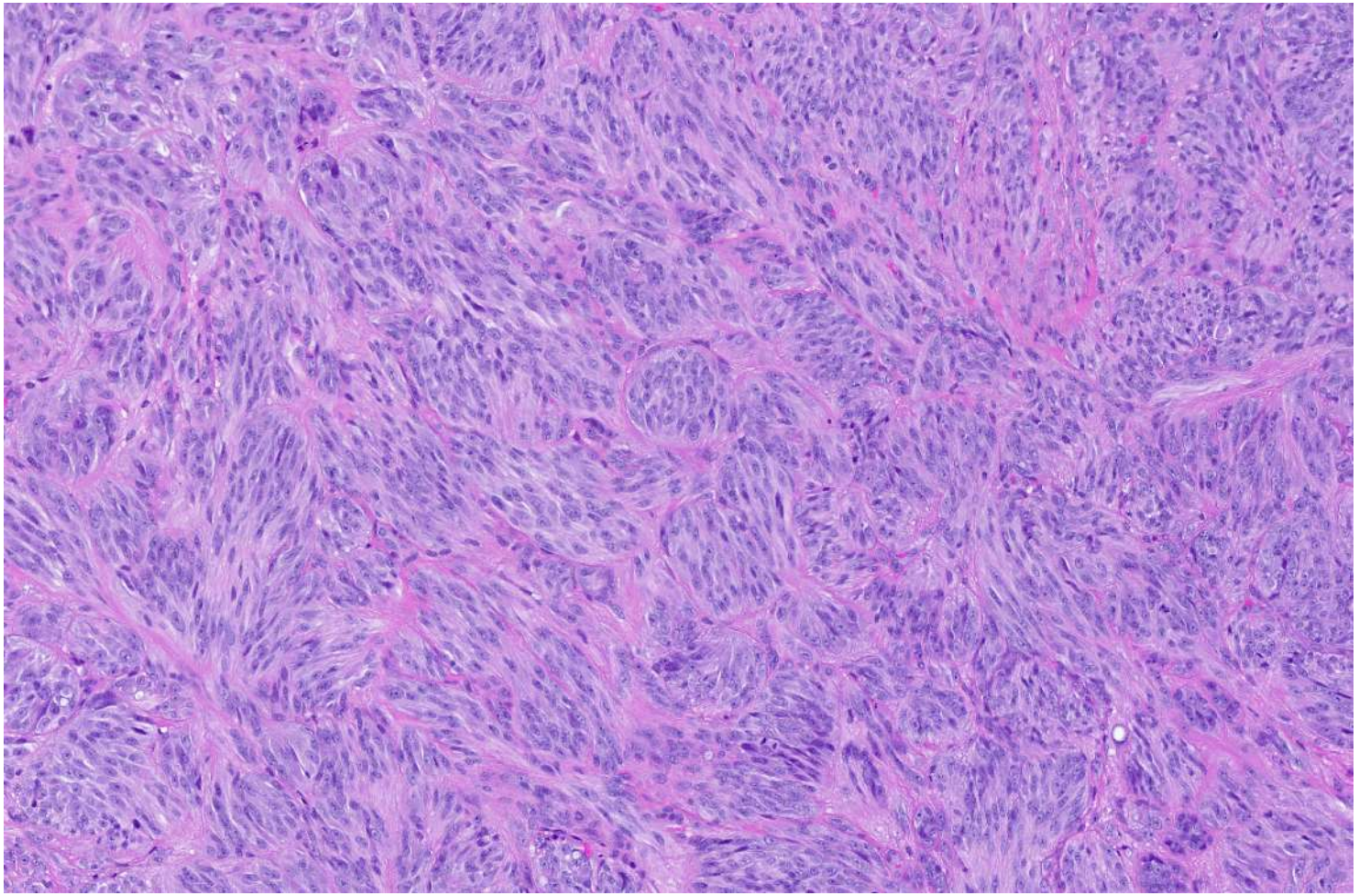




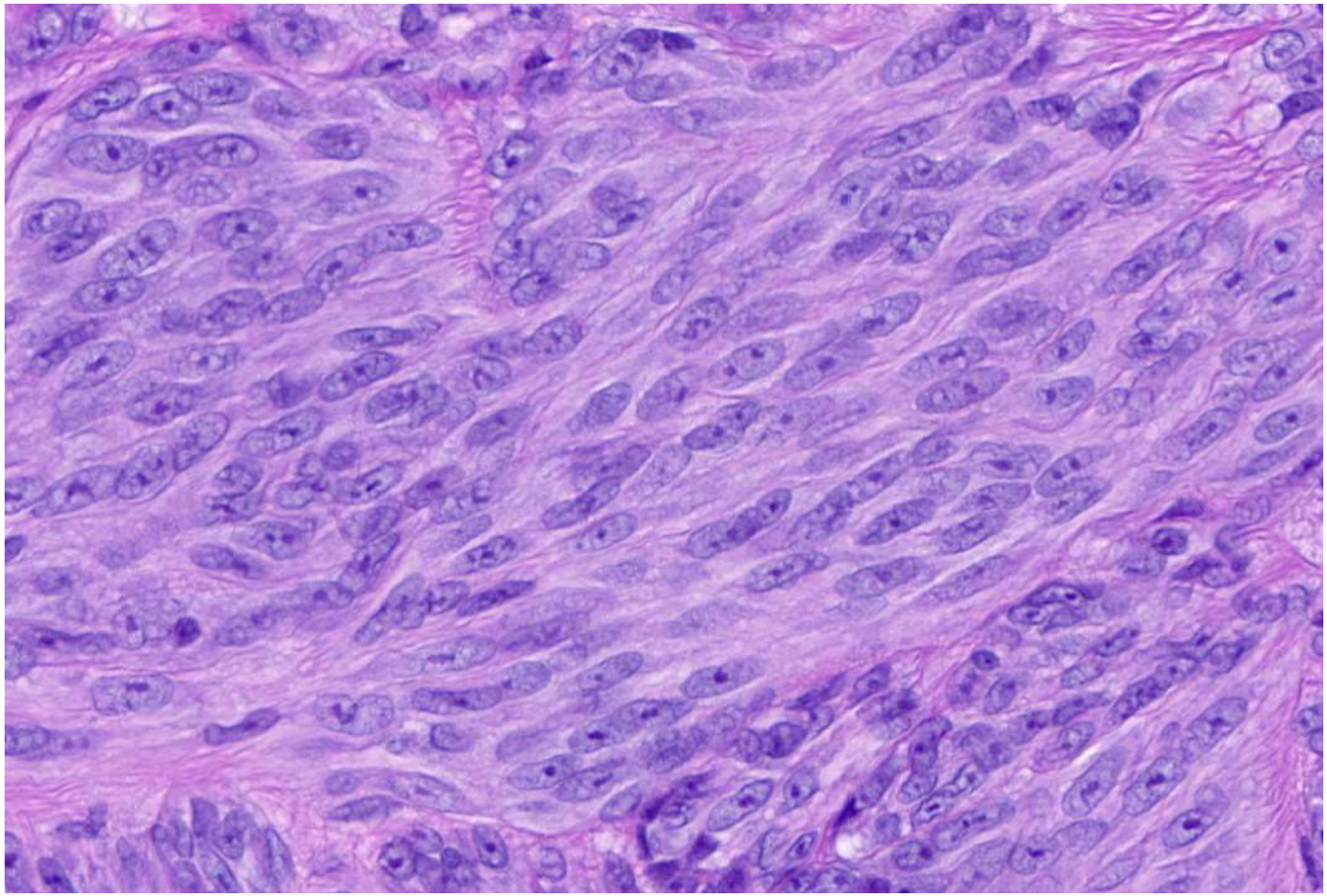
Cedars Sinai

Excisional biopsy: a 1.2-cm white firm soft tissue fragment with overlying skin.

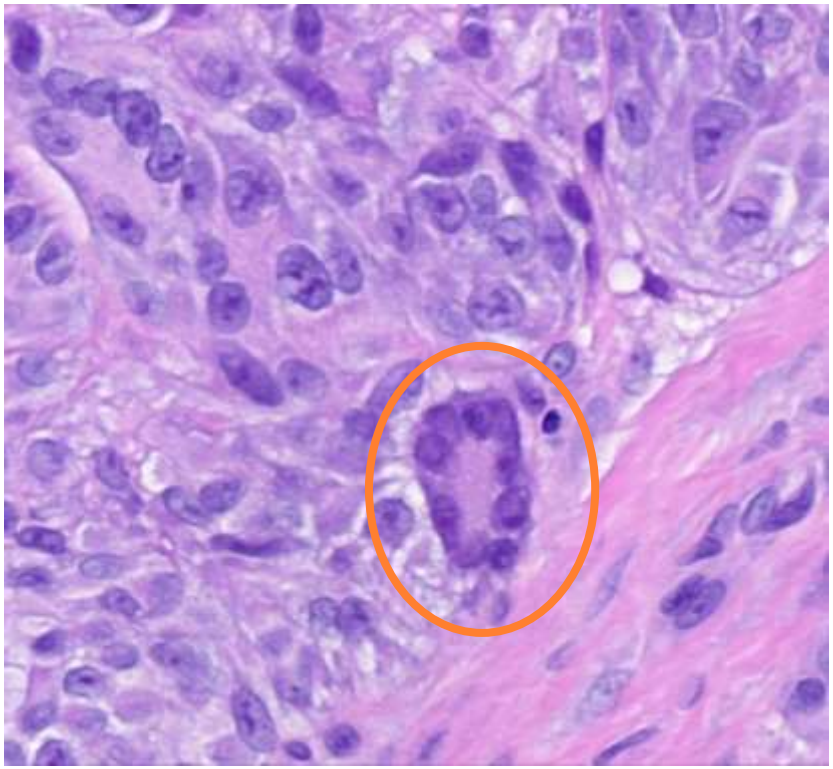


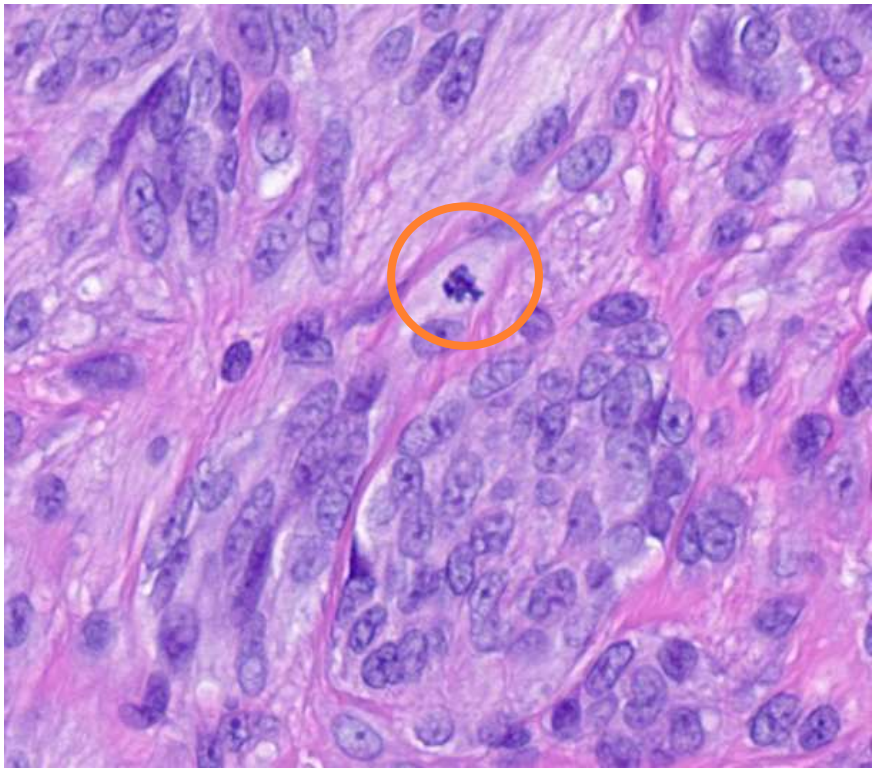


Cedars Sinai

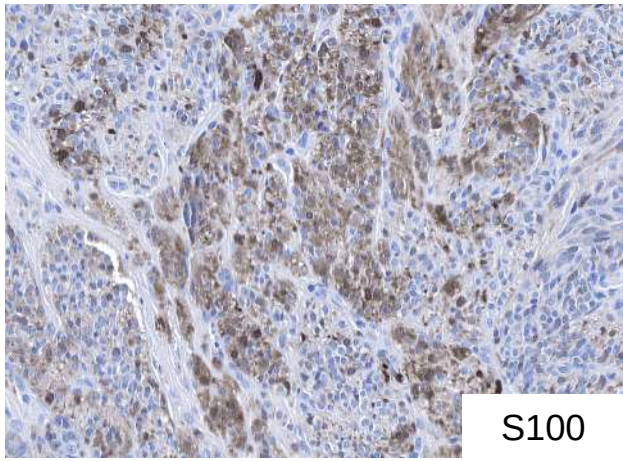


Cedars Sinai





Cedars Sinai



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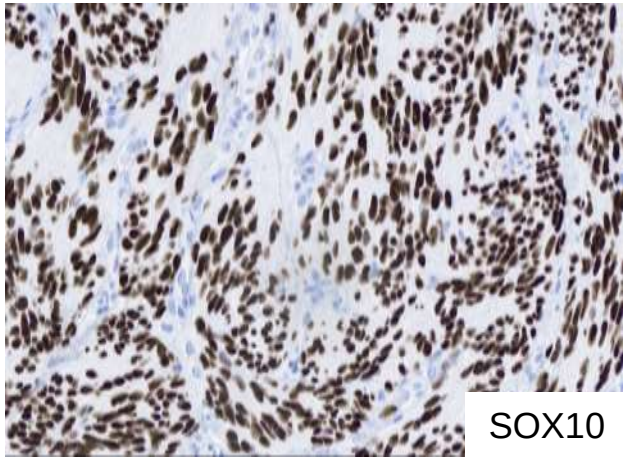
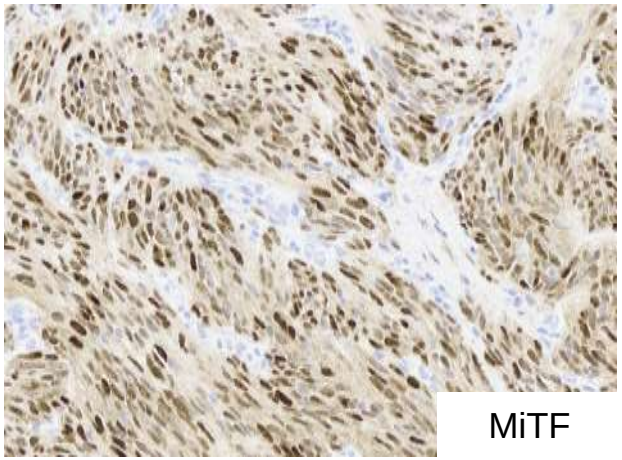
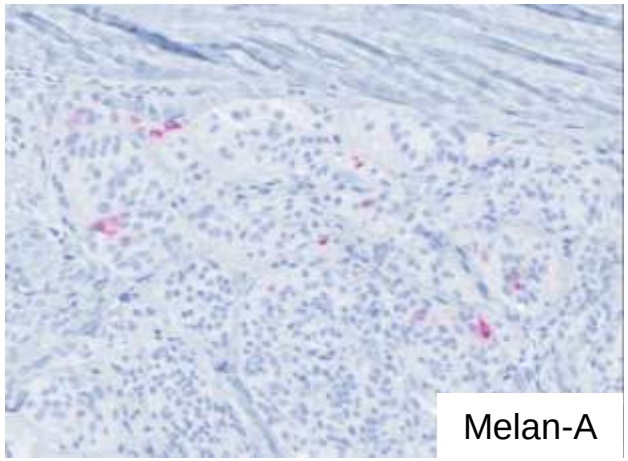


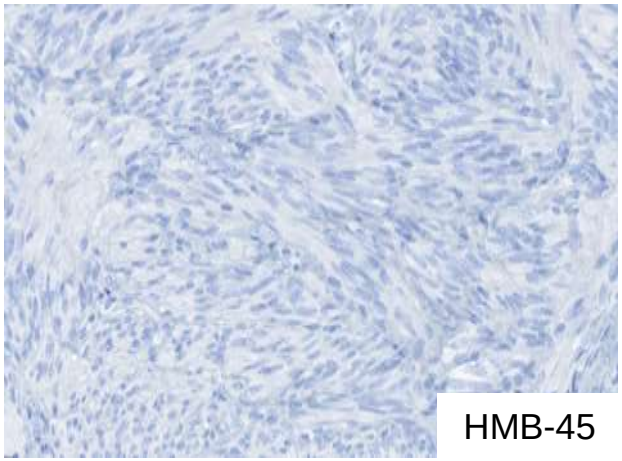
SOX10



MiTF

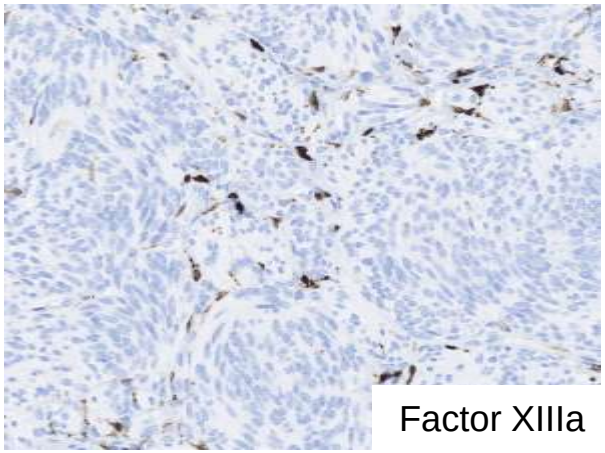


Melan-A

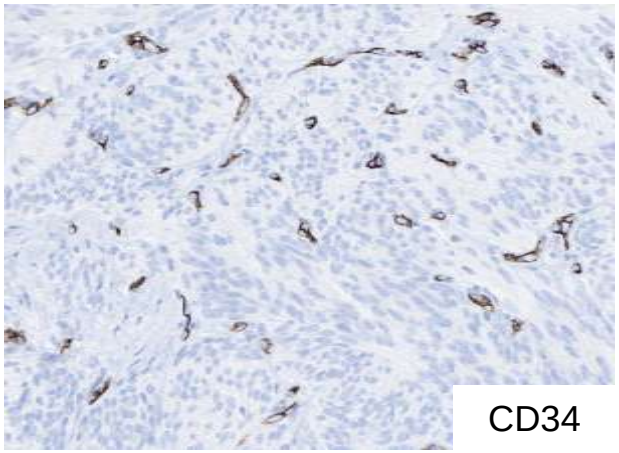


HMB-45

Cedars Sinai



Factor XIIIa



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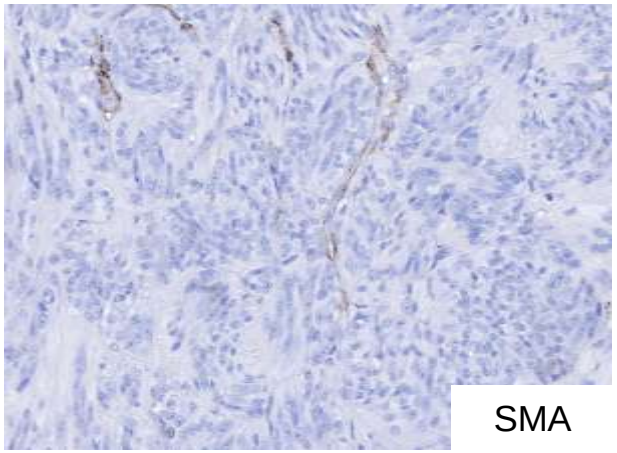

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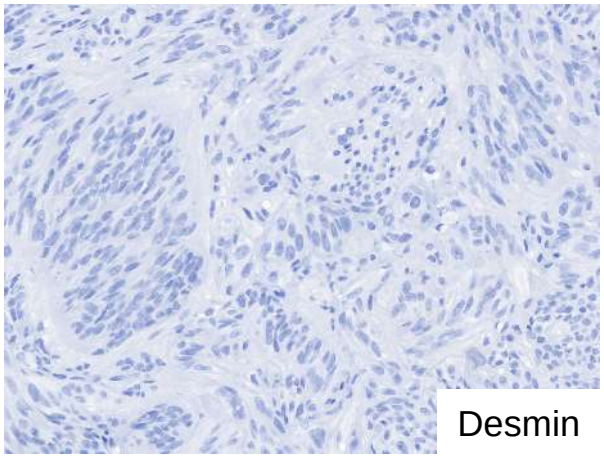
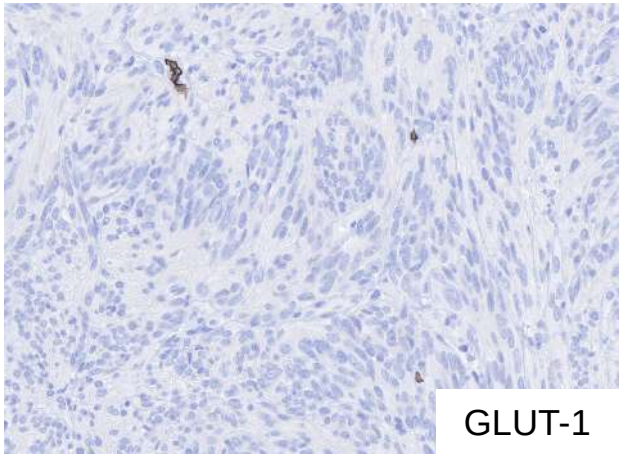
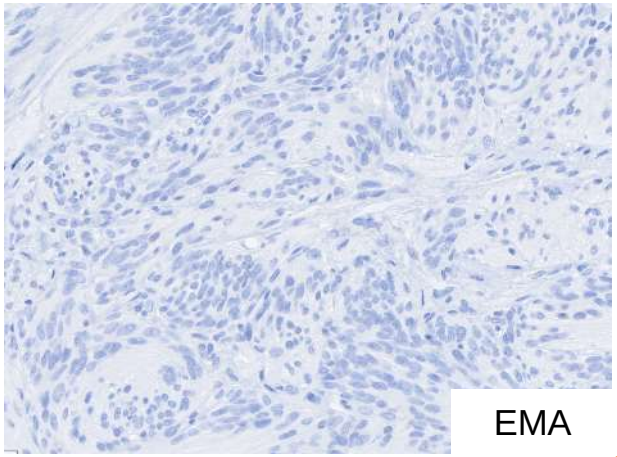


Desmin



GLUT-1



EMA

Cedars Sinai

Differential diagnosis

- **Melanocytic neoplasms:**
  - **Melanocytomas** (including those with specific gene rearrangements)
    - **Cutaneous melanocytic tumor with *CRTC1::TRIM11* fusion**
    - **Clear cell tumor with melanocytic differentiation and *MITF* gene rearrangement**
  - **Melanoma**, primary and/or metastatic
  - **Amelanotic cellular blue nevus**
- **Cutaneous clear cell sarcoma of soft tissue,** primary and/or metastatic
- **Nerve sheath tumors**
- **Soft tissue tumors with fibroblastic/fibrohistiocytic or myoid differentiation**

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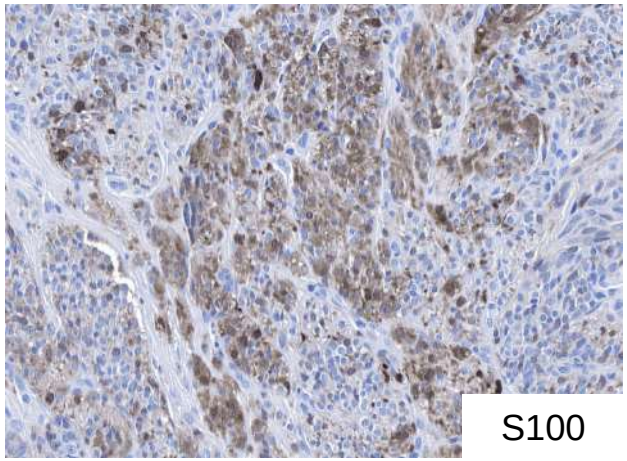

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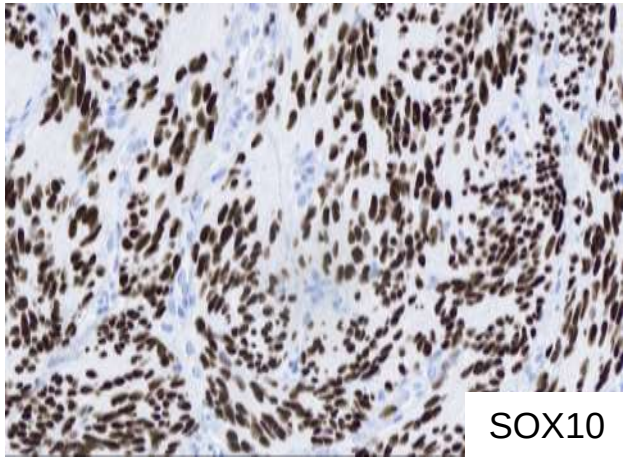
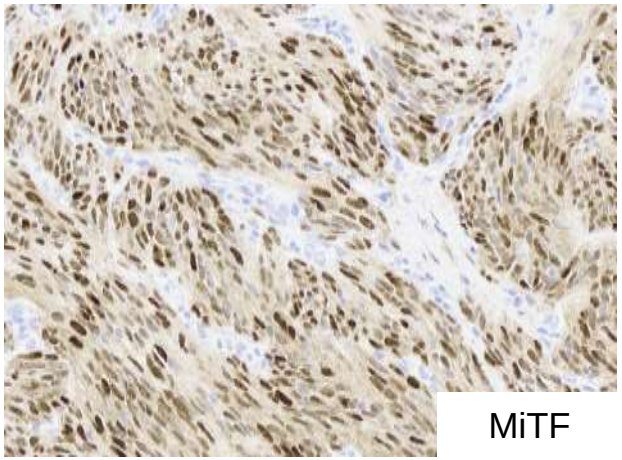


SOX10



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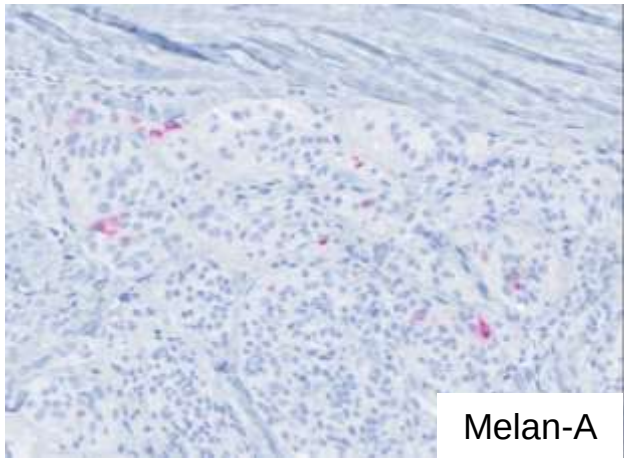

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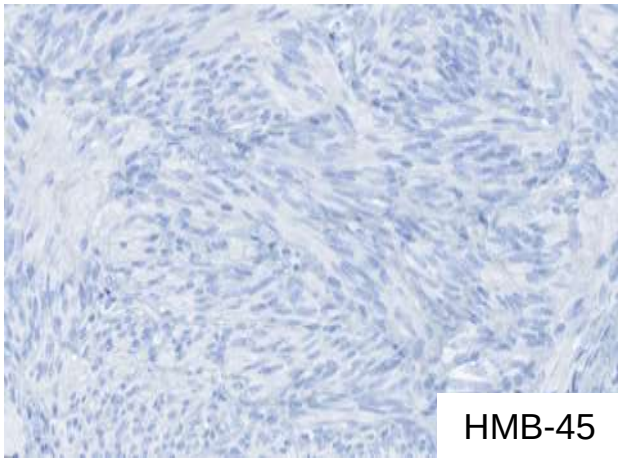
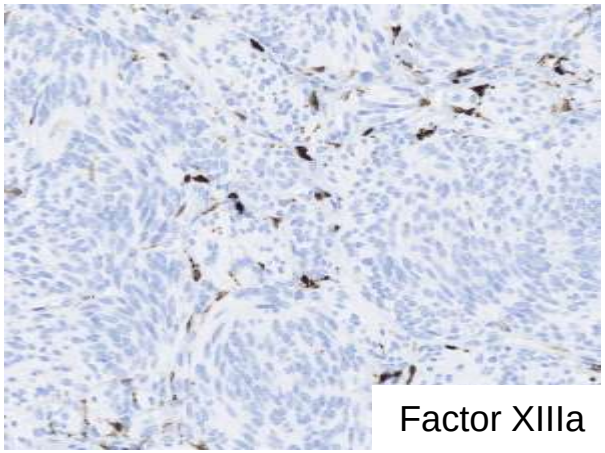


HMB-45

Cedars Sinai



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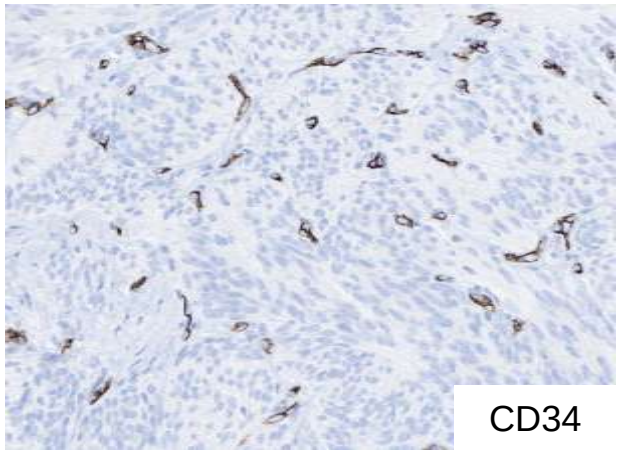

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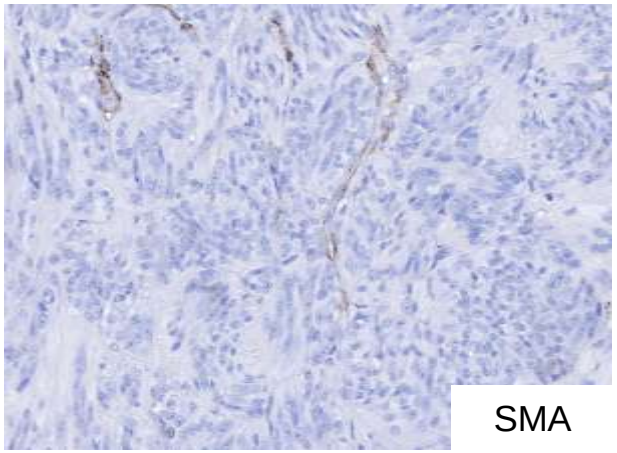
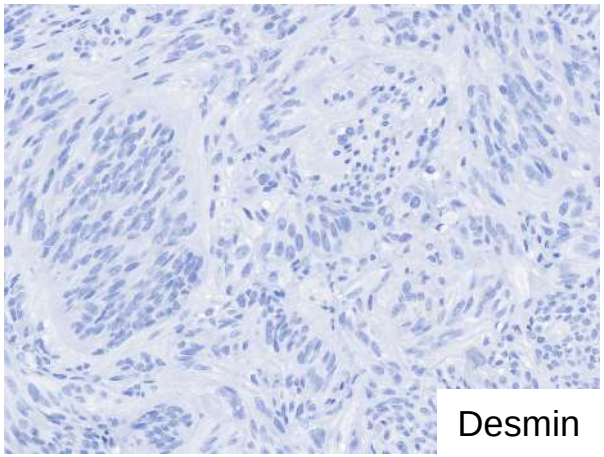
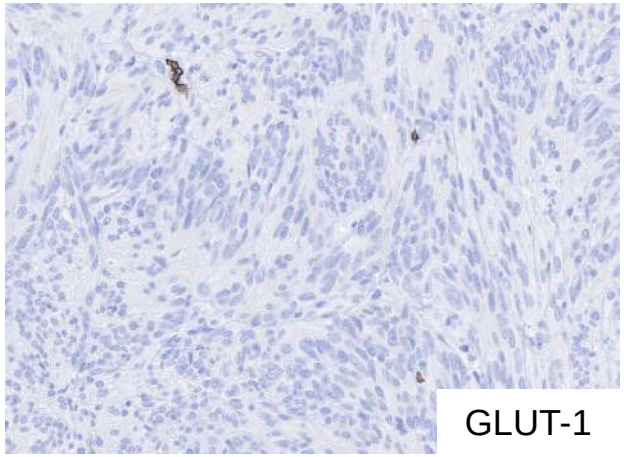


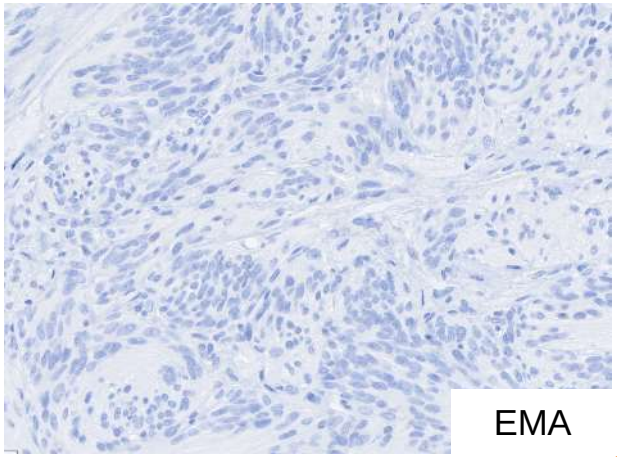
SMA



Desmin



GLUT-1



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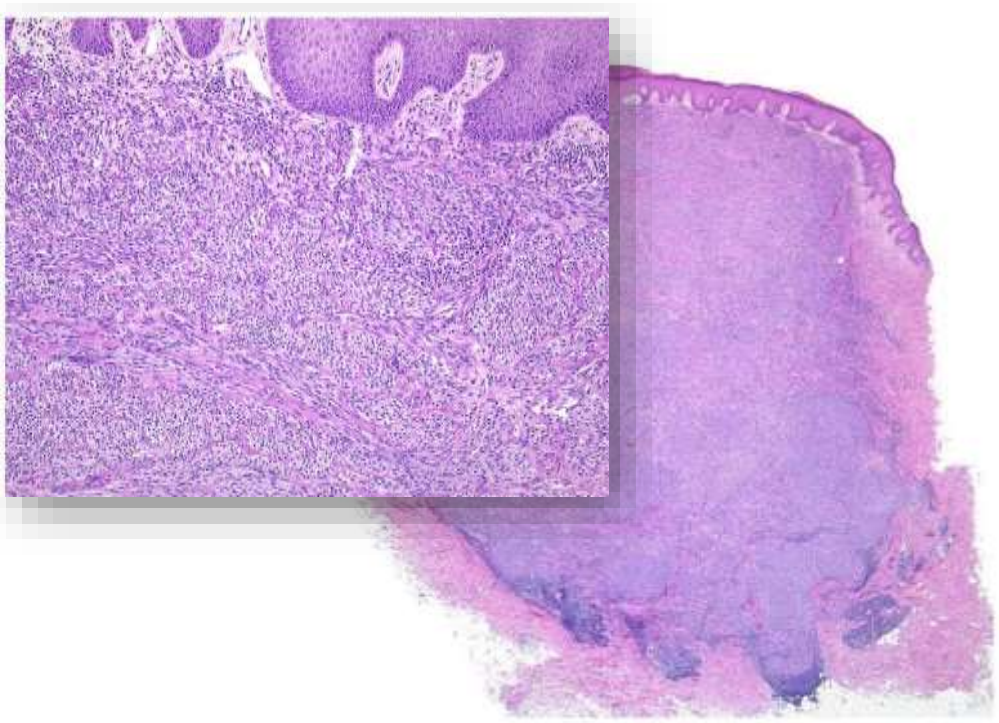
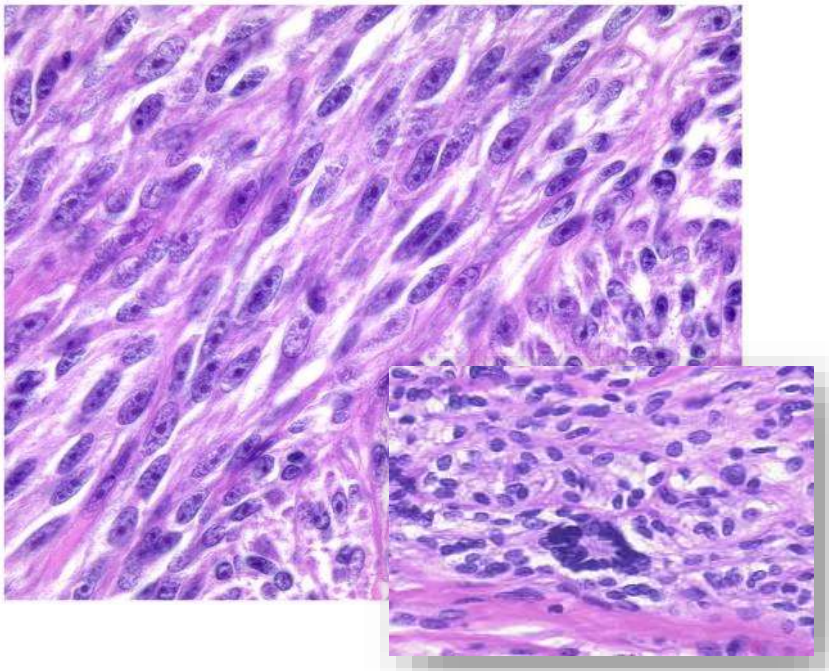
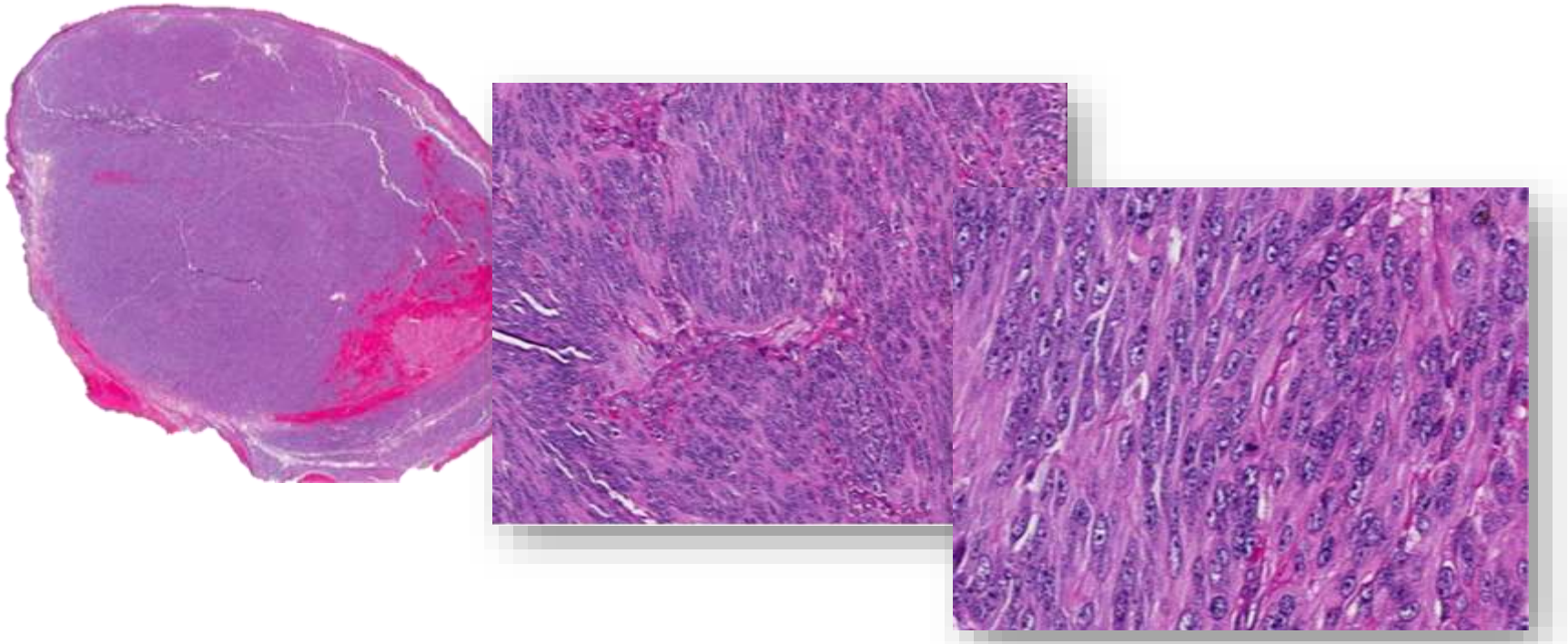
Cutaneous clear cell sarcoma of soft tissue





Hantschke M et al., Am J Surg Pathol. 2010 Feb;34(2):216-22.

Cutaneous melanocytic tumor with *CRTC1::TRIM11* fusion



Ko JS et al, J Cutan Pathol. 2019 Nov;46(11):810-818.

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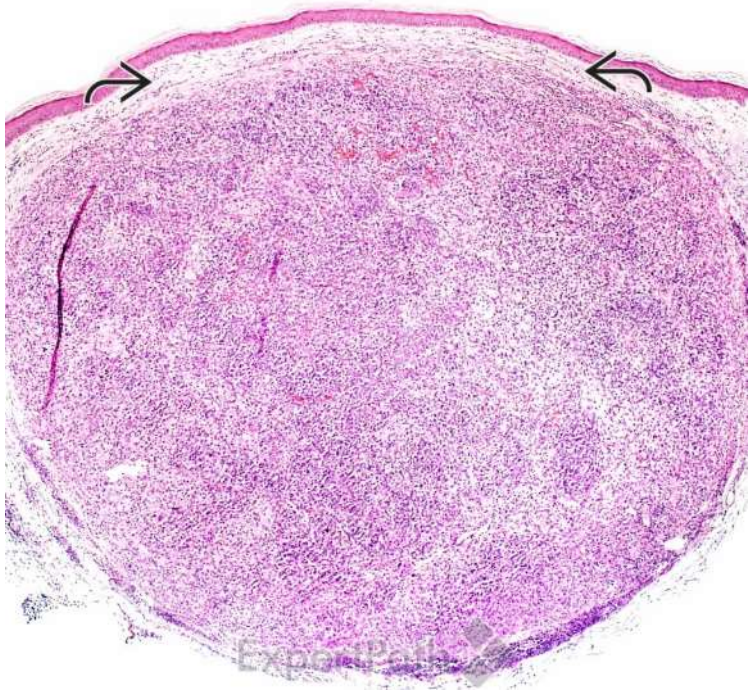
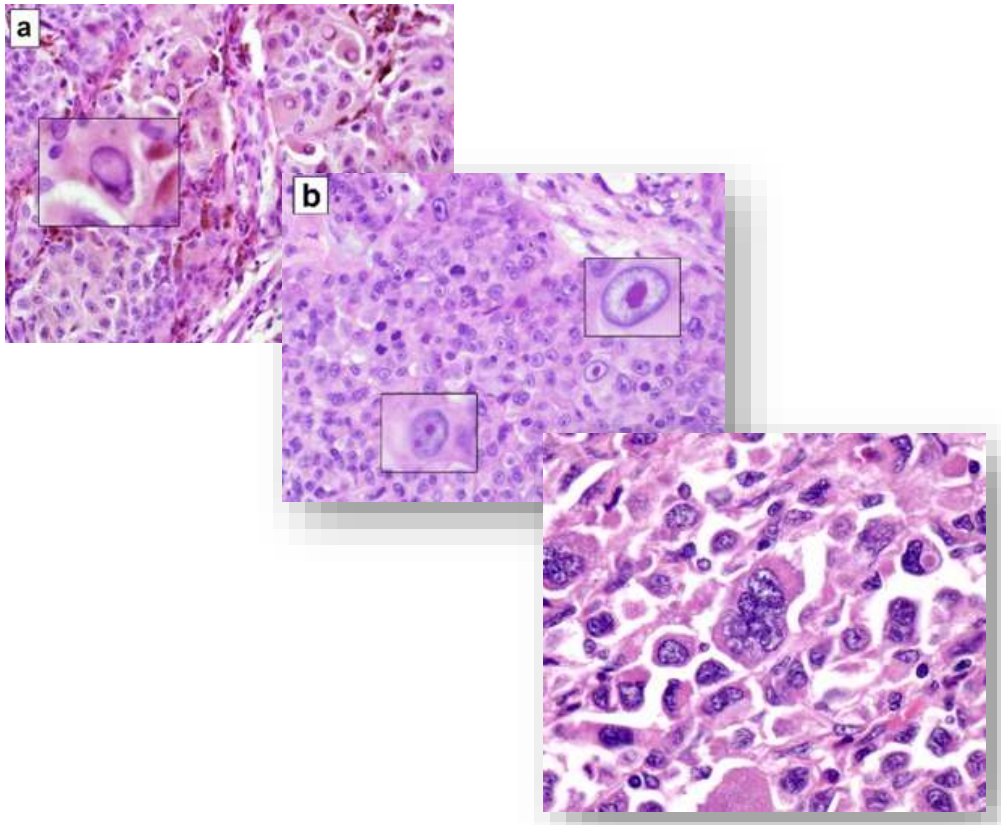
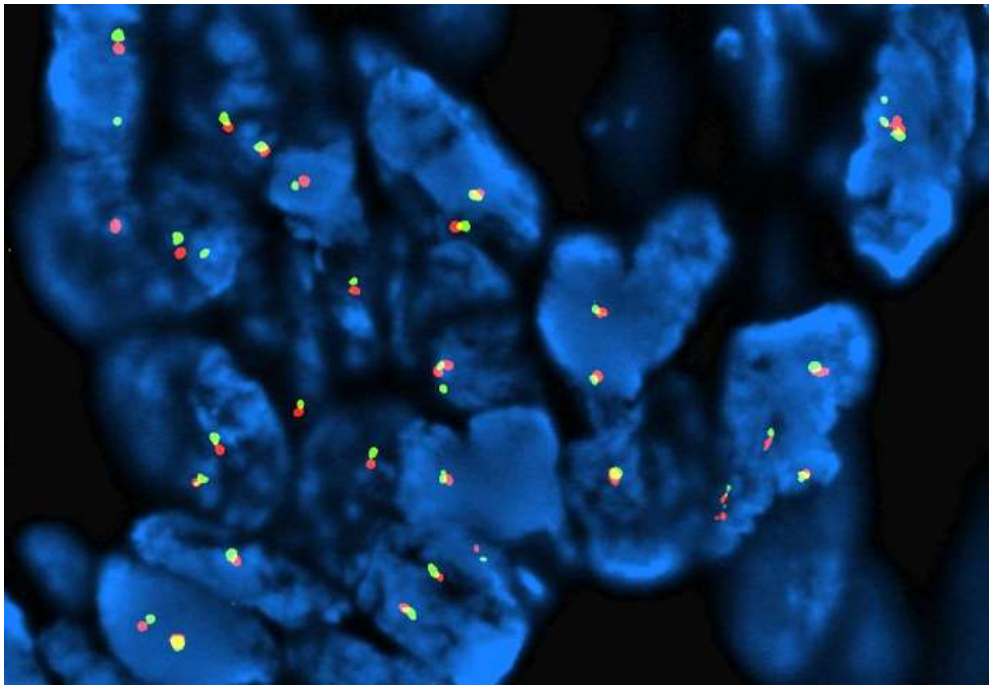
Dermal melanoma



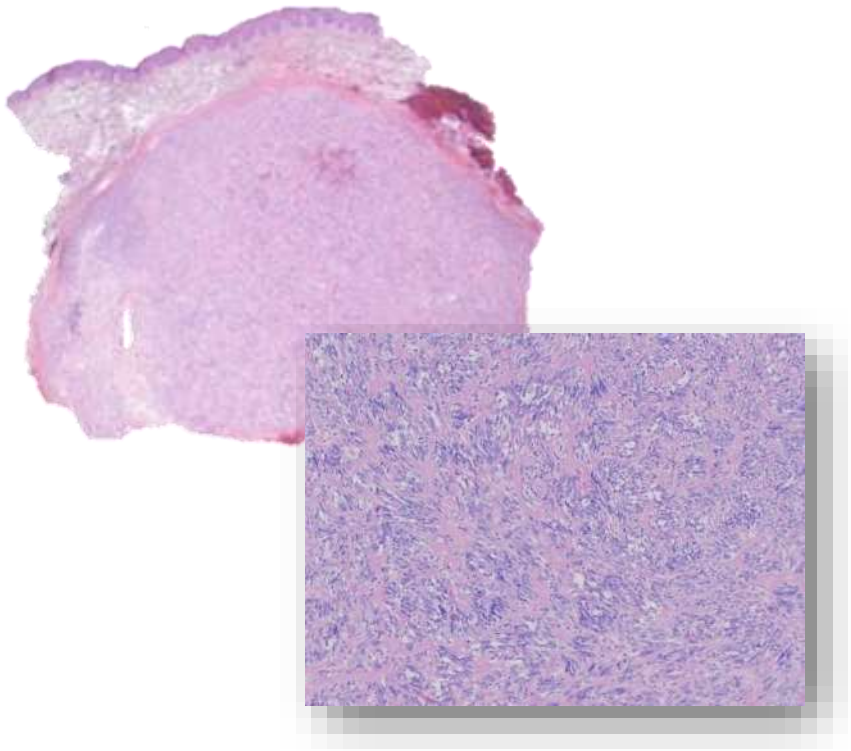


Donizy P et al. Diagn Pathol. 2017 Dec 29;12(1):88.
Expertpath

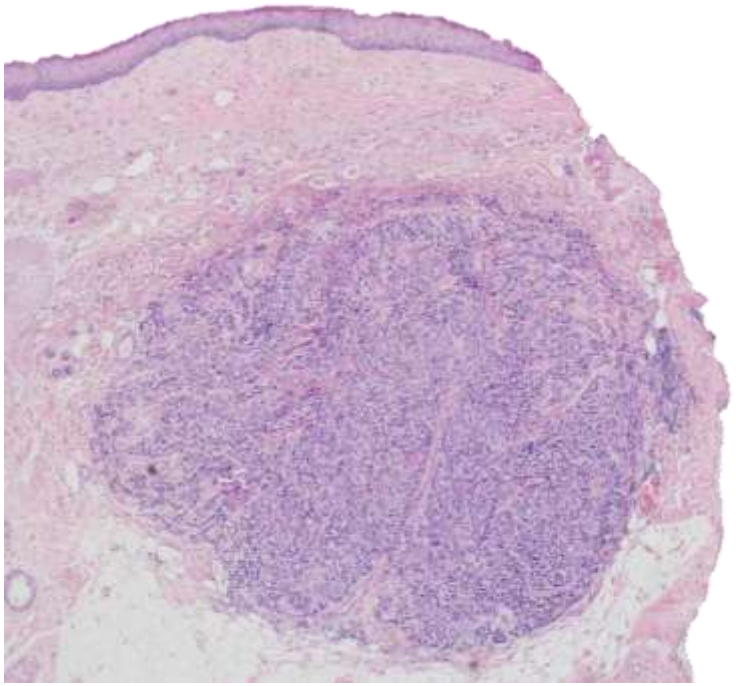
Back to the case …
EWSR1 – Break Apart FISH



Cutaneous melanocytic tumor with CRTC1-TRIM11 fusion



Dermal melanoma



Parra O et al, J Cutan Pathol. 2021 Jul;48(7):915-924.
Scolyer RA et al, Mod Pathol. 2020 Jan;33(Suppl 1):15-24.

NGS fusion panel

Solid Tumor Gene Fusion NGS Panel (SRCNGS) – 58 Genes

ALK	*CSF1*	*FUS*	*NCOA1*	*NTRK1*
BCOR	*EPC1*	*GLI1*	*NCOA2*	*NTRK2*
BRAF	*ETV6*	*HMGA2*	*NCOA3*	*NTRK3*
CAMTA1	*EWSR1*	*JAZF1*	*NOTCH1*	*NUTM1*
CCNB3	*FOS*	*MEAF6*	*NOTCH2*	*PAX3*
CIC	*FOSB*	*MKL2*	*NOTCH3*	*PAX7*
CRTC1	*FOXO1*	*MYB*	*NR4A3*	*PDGFB*
PDGFD	*RAF1*	*STAT6*	*TRIM11*	
PGR	*RELA*	*TAF15*	*USP6*	
PHF1	*RET*	*TCF12*	*WWTR1*	
PLAG1	*ROS1*	*TFE3*	*YAP1*	
PRDM10	*SRF*	*TFEB*	*YWHAE*	
PRKD1	*SS18*	*TFG*		

Positive *CRTC1::TRIM11* fusion

Cedars Sinai

Final diagnosis

- **Cutaneous melanocytic tumor with *CRTC1::TRIM11* fusion**

Am J Surg Pathol. 2018 Mar;42(3):382-391. doi: 10.1097/PAS.0000000000000996.

Cutaneous Melanocytoma With CRTC1–TRIM11 Fusion: Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier [1], Emilie Perron [1 2 3], Daniel Pissaloux [1], Marie Karanian [1], Veronique Haddad [1], Laurent Alberti [1], Arnaud de la Fouchardière [1]

Affiliations + expand

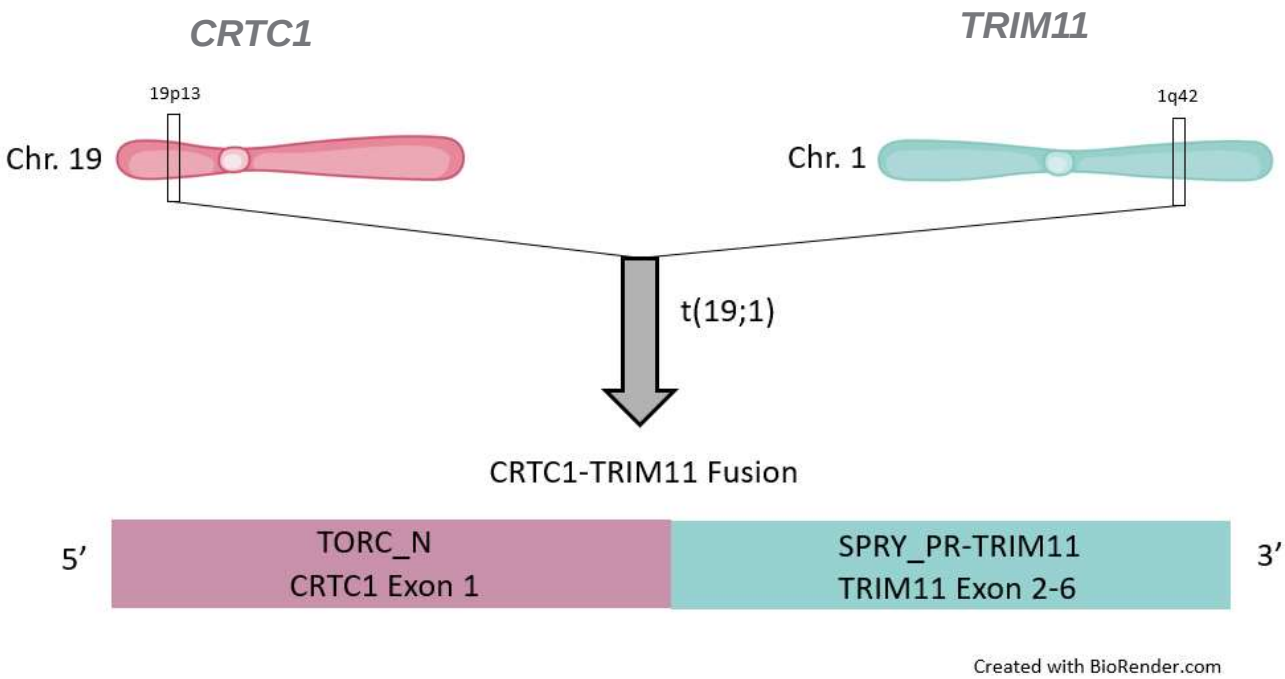
PMID: 29240581 DOI: 10.1097/PAS.0000000000000996

- **13 cases reported in the literature to date**
- **12 of 13 cases had an indolent clinical course with:**
  - 10 complete excision, 1 incomplete excision, and 1 unknown
  - No recurrence or metastasis (average follow-up 21 months)
- **One patient experienced local recurrences and metastasis 13 years after initial resection**

Cedars Sinai

Parra O et al, Biology (Basel). 2021 Dec 7;10(12):1286.
Parra O et al, J Cutan Pathol. 2021 Jul;48(7):915-924.

Schematic diagram of *CRTC1::TRIM11* fusion



Parra O et al., J Cutan Pathol. 2021 Jul;48(7):915-924.
Wang X et al., J Exp Clin Cancer Res. 2016 Jun 21;35(1):100.
Chen J et al., BMC Cancer. 2015 Oct 26;15:803.

Cedars Sinai

References

Papke DJ Jr et al., Histopathology. 2022 Jan;80(1):216-232.

Parra O et al., Biology (Basel). 2021 Dec 7;10(12):1286.

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De la Fouchardiere et al., *Virchows Archiv*, *479*(4), 841-846.

Scolyer RA et al., Mod Pathol. 2020 Jan;33(Suppl 1):15-24

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Kashima J et al., Pathol Int. 2019 Aug;69(8):496-501.

Bontoux C et al., Am J Surg Pathol. 2019 Jun;43(6):861-863.

Cellier L et al., Am J Surg Pathol. 2018 Mar;42(3):382-391.

Hantschke M et al., Am J Surg Pathol. 2010 Feb;34(2):216-22.

Chen Y et al., Clin Res Hepatol Gastroenterol. 2017 Mar;41(2):190-196.

Sidiropoulos M et al., J Am Acad Dermatol. 2014 Dec;71(6):1083-92.

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Donizy P et al. Diagn Pathol. 2017 Dec 29;12(1):88.

Hida Y et al., J Dermatol. 2009 Jun;36(6):346-52.

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Feasel PC et al., J Cutan Pathol. 2016 Oct;43(10):838-46.

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Zamir H et al., J Cutan Med Surg. 2021 Jan-Feb;25(1):53-58.

Harris CG et al., Eur J Surg Oncol. 2020 Nov;46(11):2131-2139.

Chacón Met al., Cancers (Basel). 2020 Aug 21;12(9):2362.

Wang X et al., J Exp Clin Cancer Res. 2016 Jun 21;35(1):100.

Ferrara G et al., Front Oncol. 2021 Jul 2;11:675296.

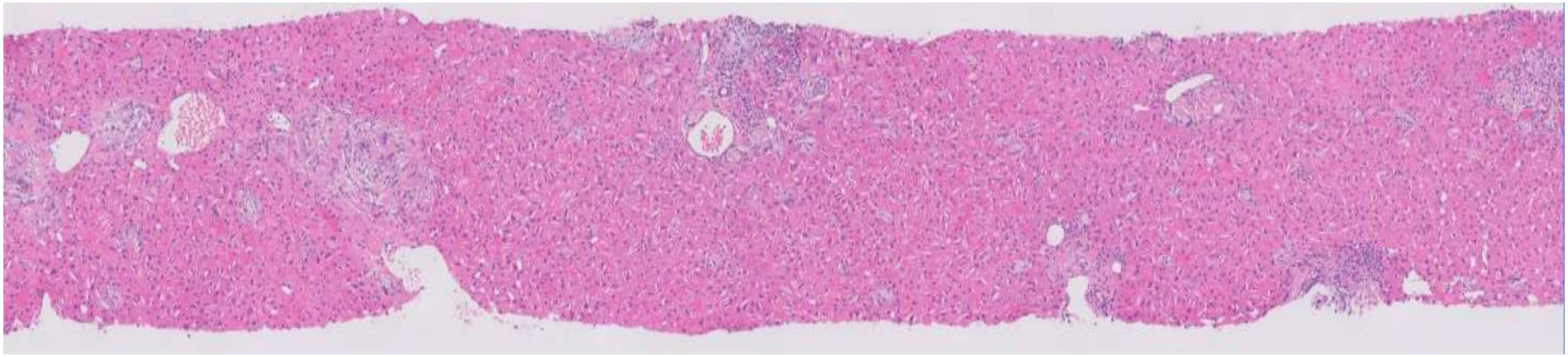
Chen J et al., BMC Cancer. 2015 Oct 26;15:803.

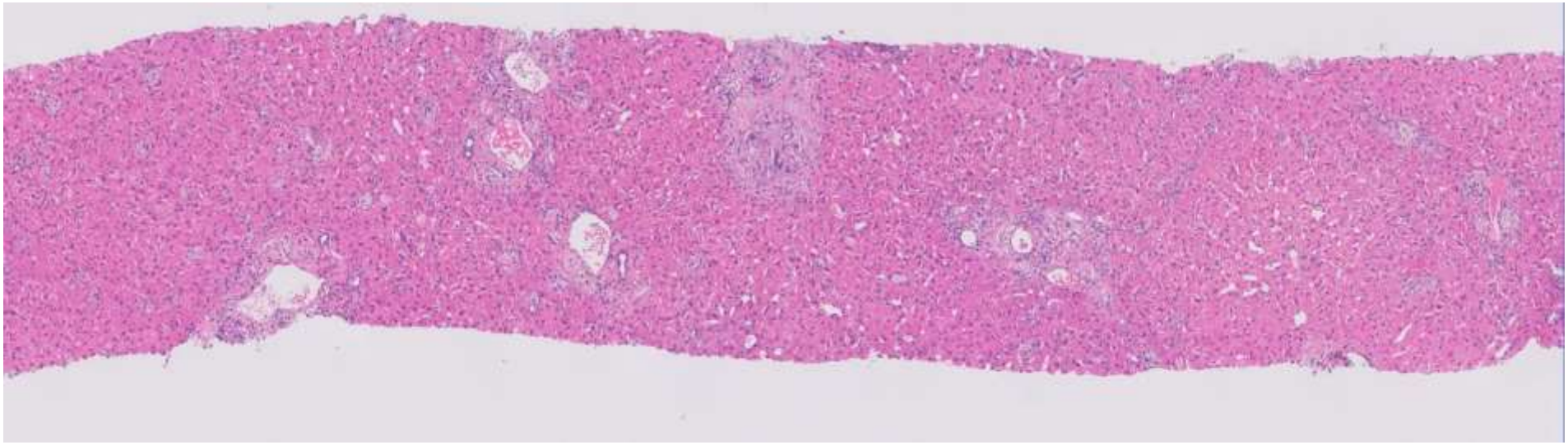
Cedars Sinai

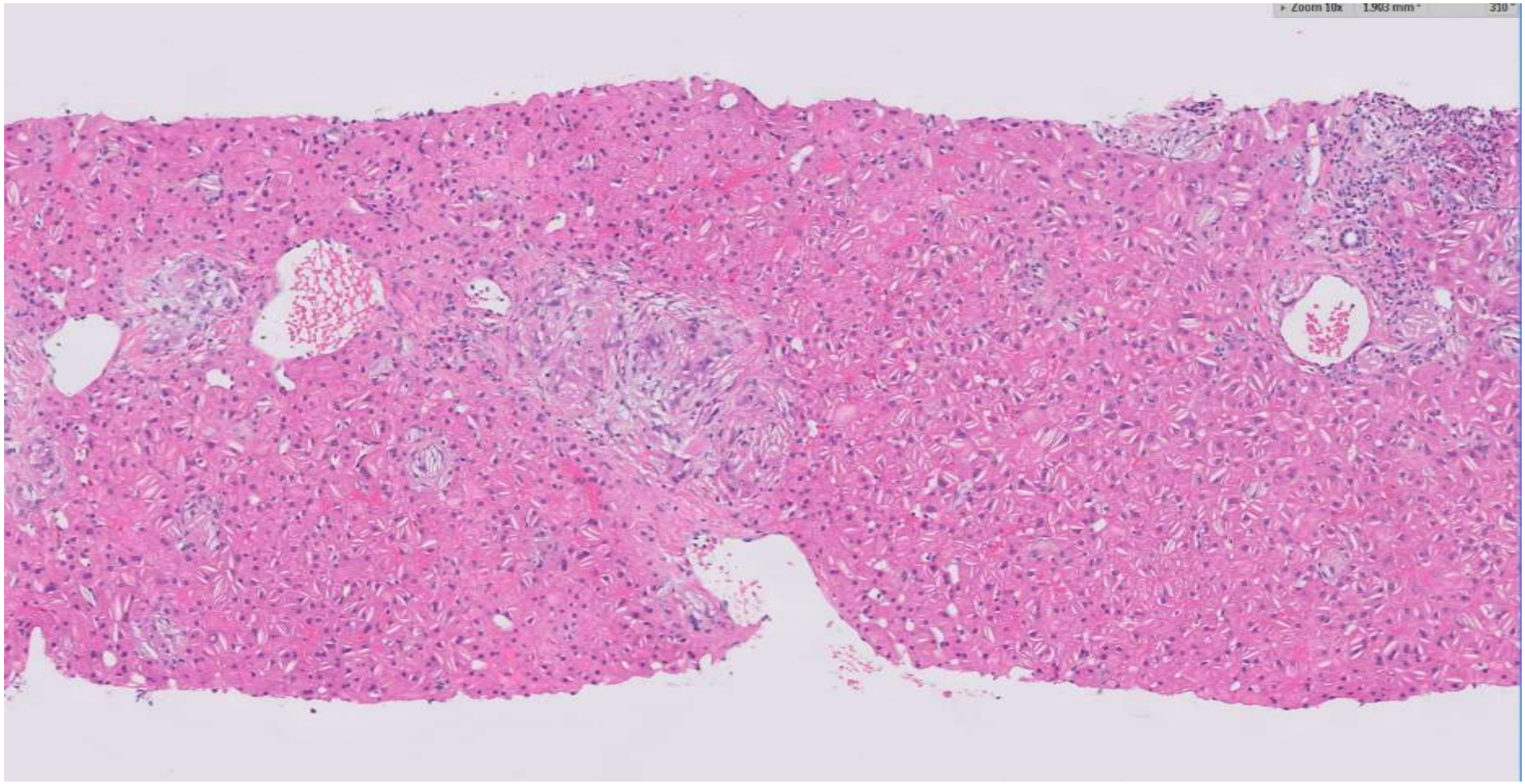
22-1102

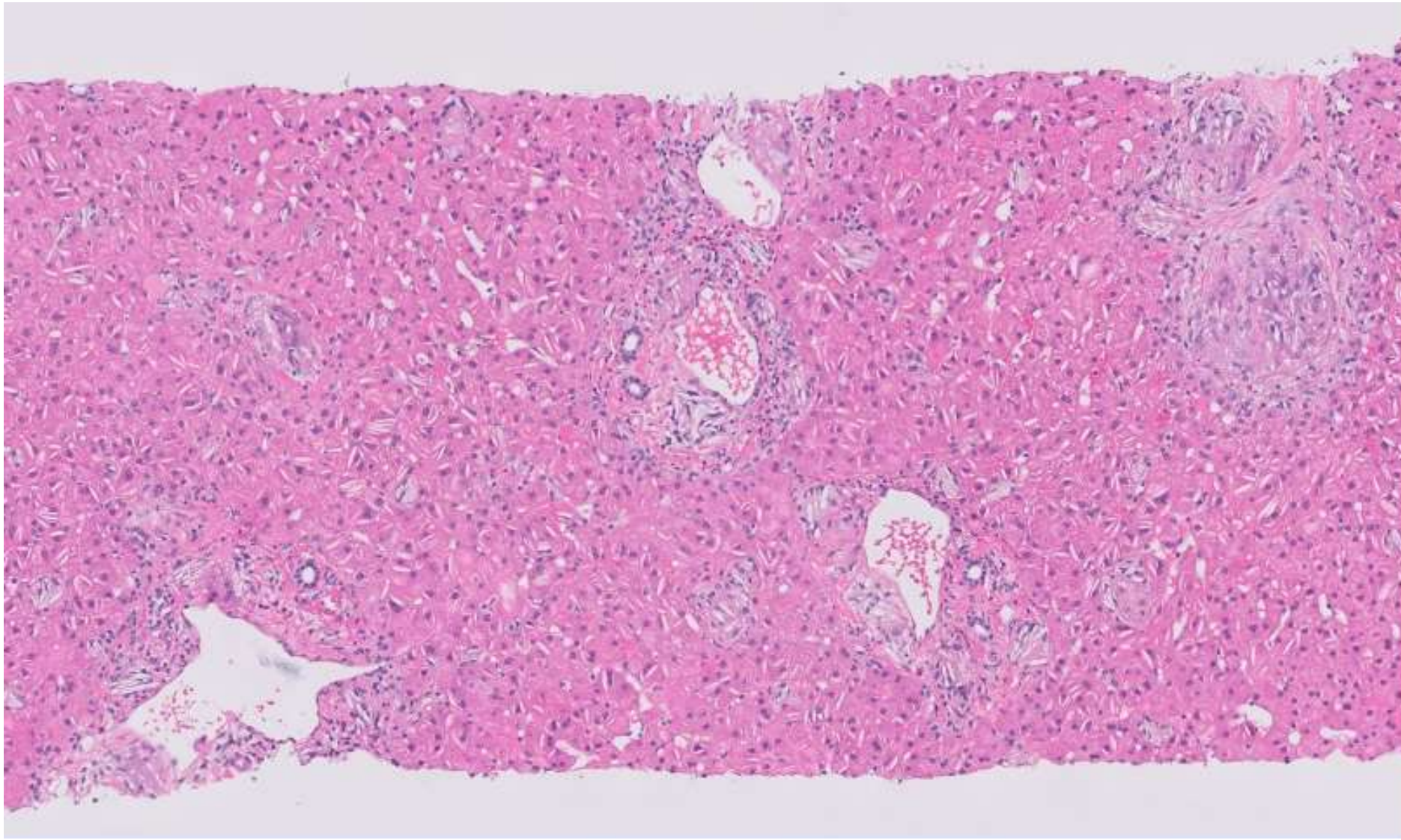
Jeenal Gordhandas/Serena Tan; Stanford

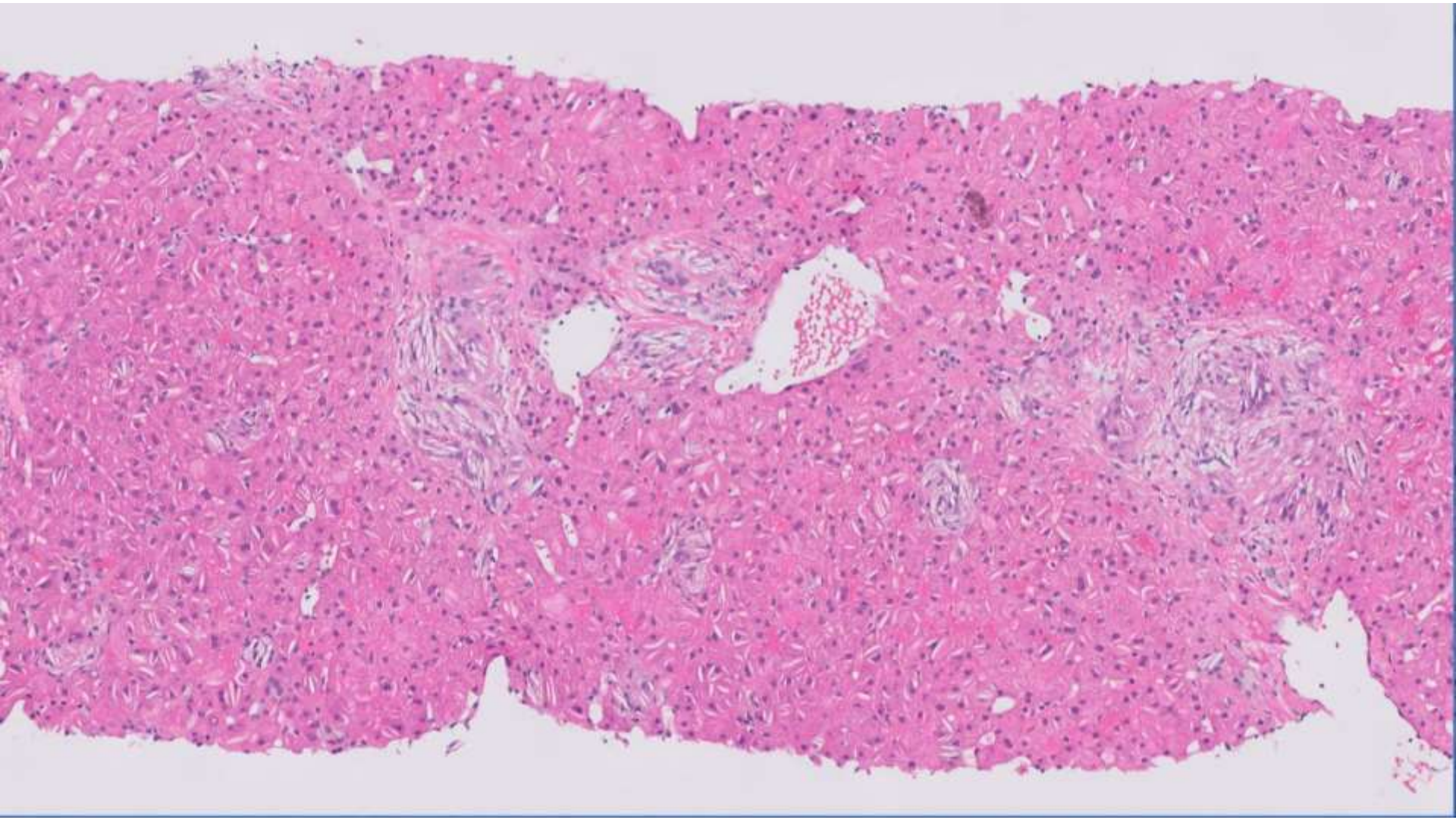
20ish M with a clinical history of hyperlipidemia, fatty liver now with elevated LFTs (AST-116, ALT-347, Alk Phos-76, Tbili-1.1, BMI 21)

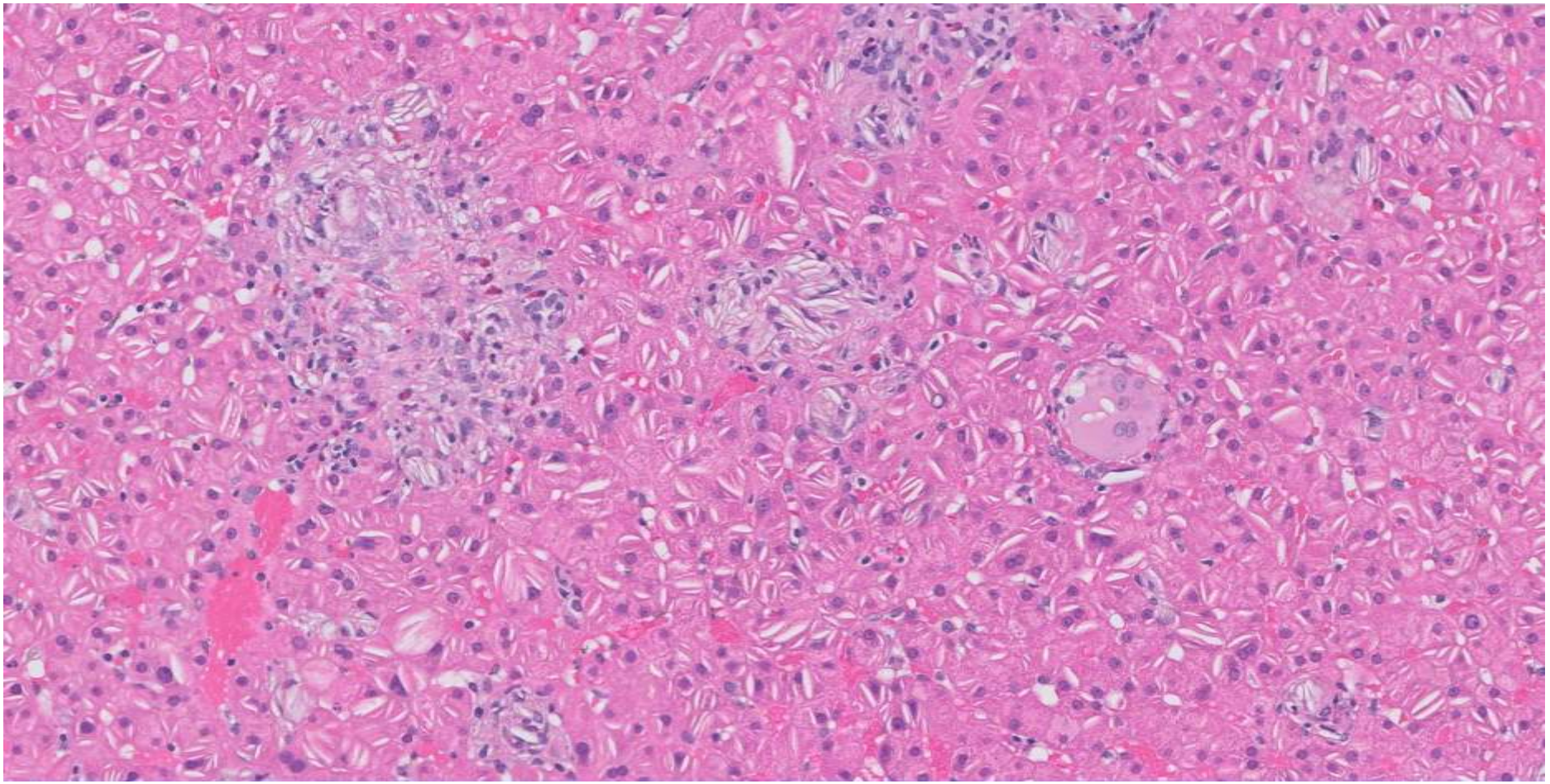


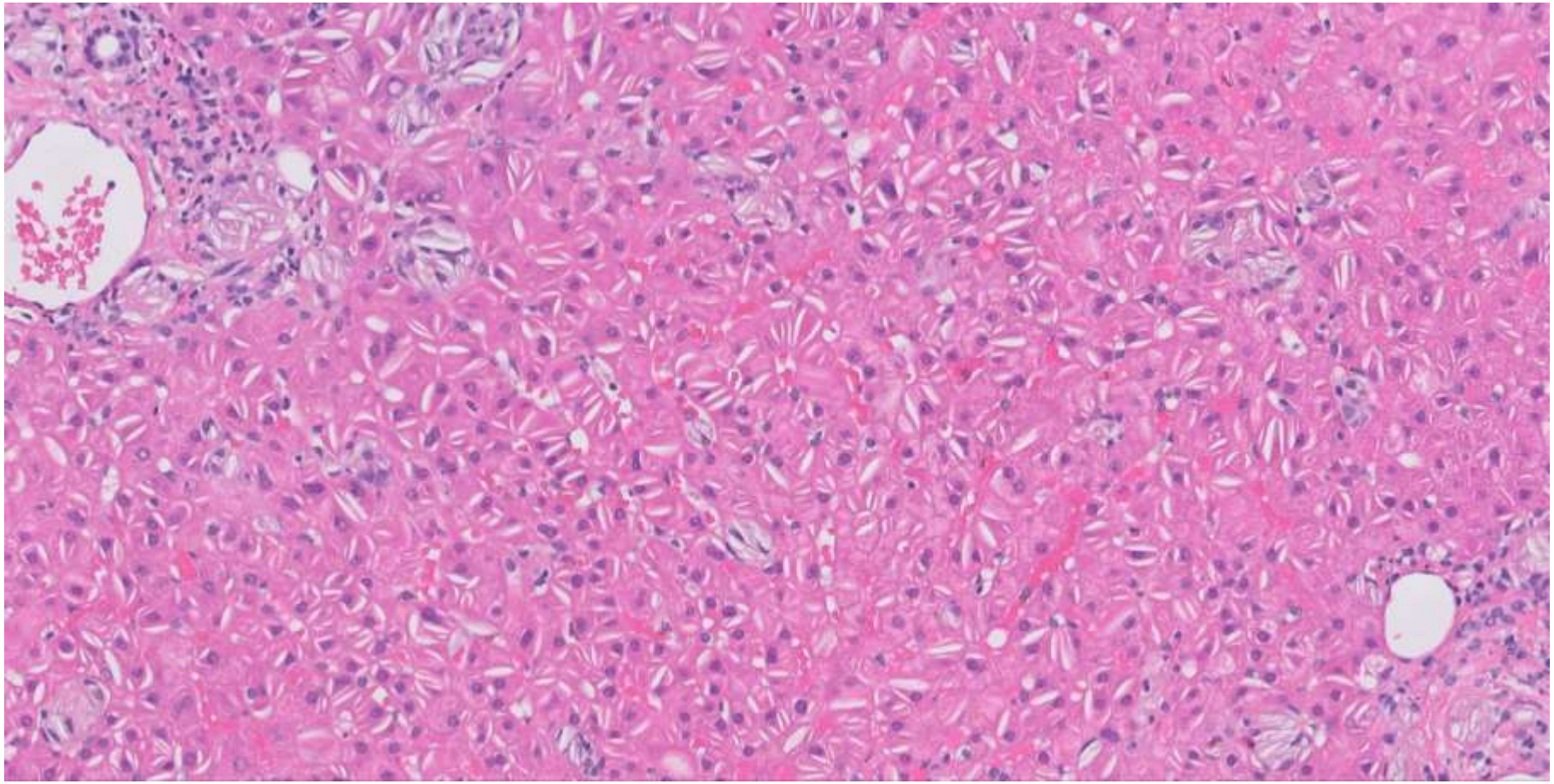


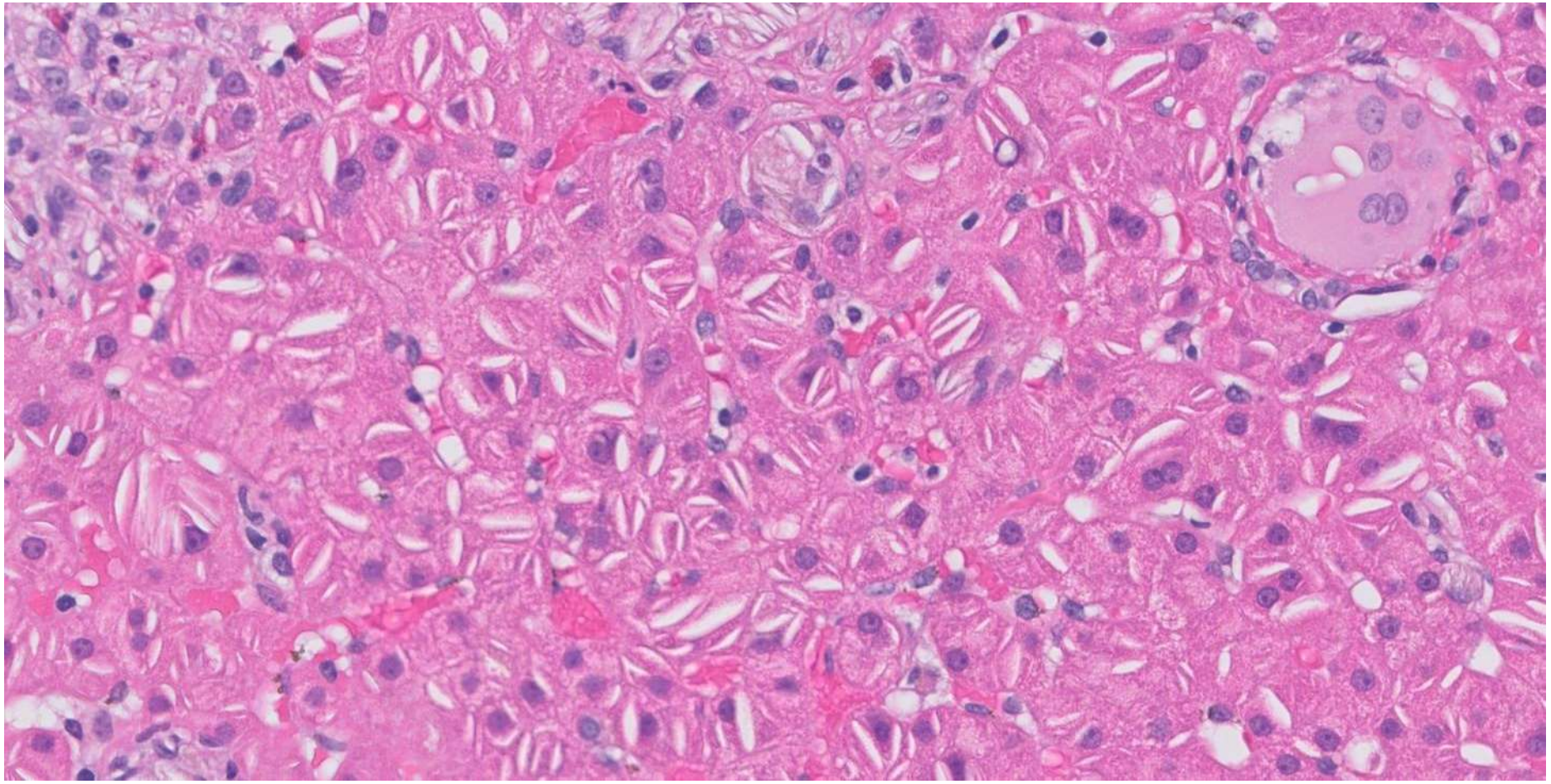

Zoom 10x







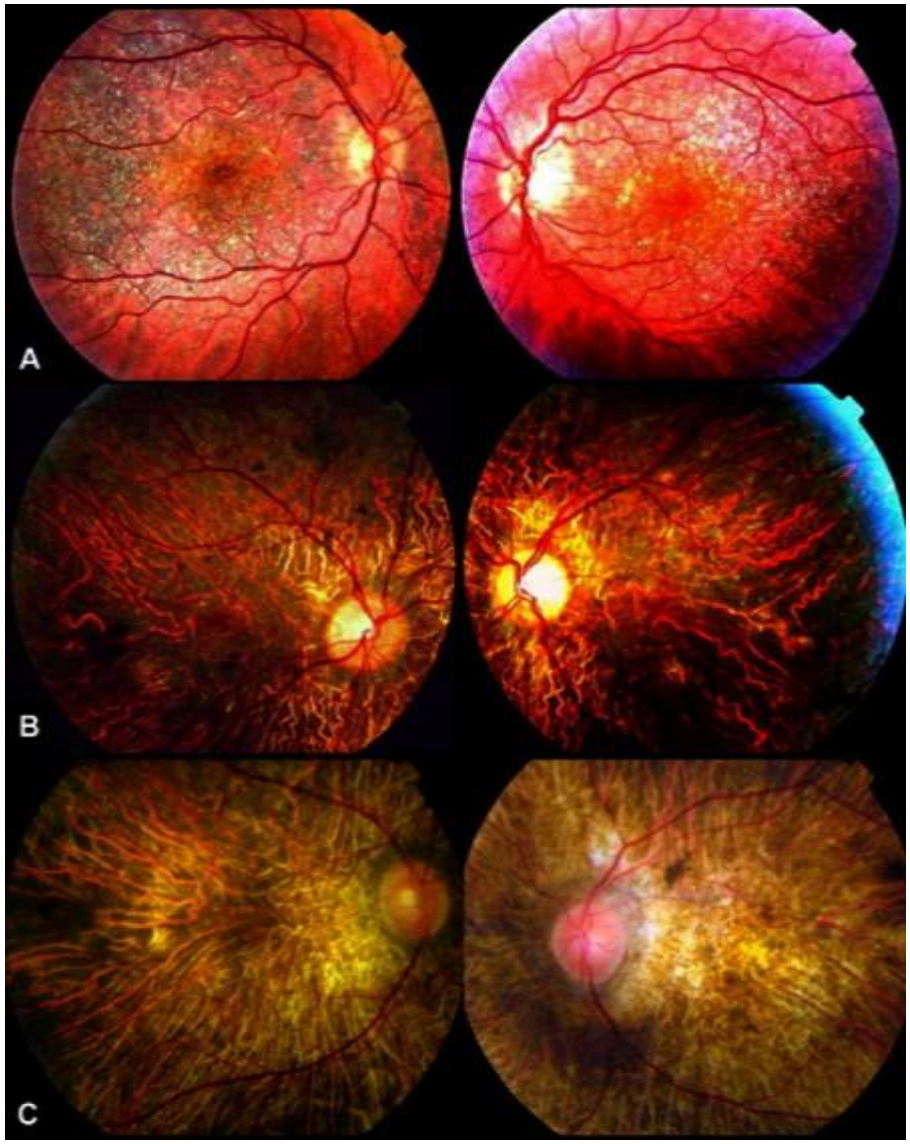




Differential diagnosis

- Unusual Steatohepatitis
- Storage disease
- Processing artifact
- Drug effect

Bietti's Crystalline Dystrophy



Characterized by:

- Numerous tiny glistening yellow-white crystals at posterior pole of retina and corneoscleral limbus
- Atrophy of retinal pigment epithelium
- Pigment clumps
- Choroidal sclerosis

Garcia- Garcia et al, 2019.

Bietti's Crystalline Dystrophy

- Described by Bietti in 1937
- Autosomal recessive, biallelic mutations in CYP4V2 gene of cytochrome p450 family of genes
- Prevalence of 1 in 67,000 individuals
- High incidence in East Asia – China, Japan, Korea
- Decreased vision (2nd-4th decade), progression to legal blindness (5th or 6th decade)

Bietti's Crystalline Dystrophy

- Abnormally high triglycerides and free cholesterol levels in cultivated patient cells --> may deposit as crystals --> lysosomal dysfunction + impaired autophagy --> cell damage --> cell death
- No proven mechanism to relate CYP4V2 function to free cholesterol accumulation

- Gene expression of CYP42V in retinal pigment epithelium, other layers of retina, corneal epithelium, heart, lung, **liver**, pancreas, kidney, brain, skeletal muscle, placenta
- No functional impairment in non-ocular tissues – missing histologic characterization in other tissues

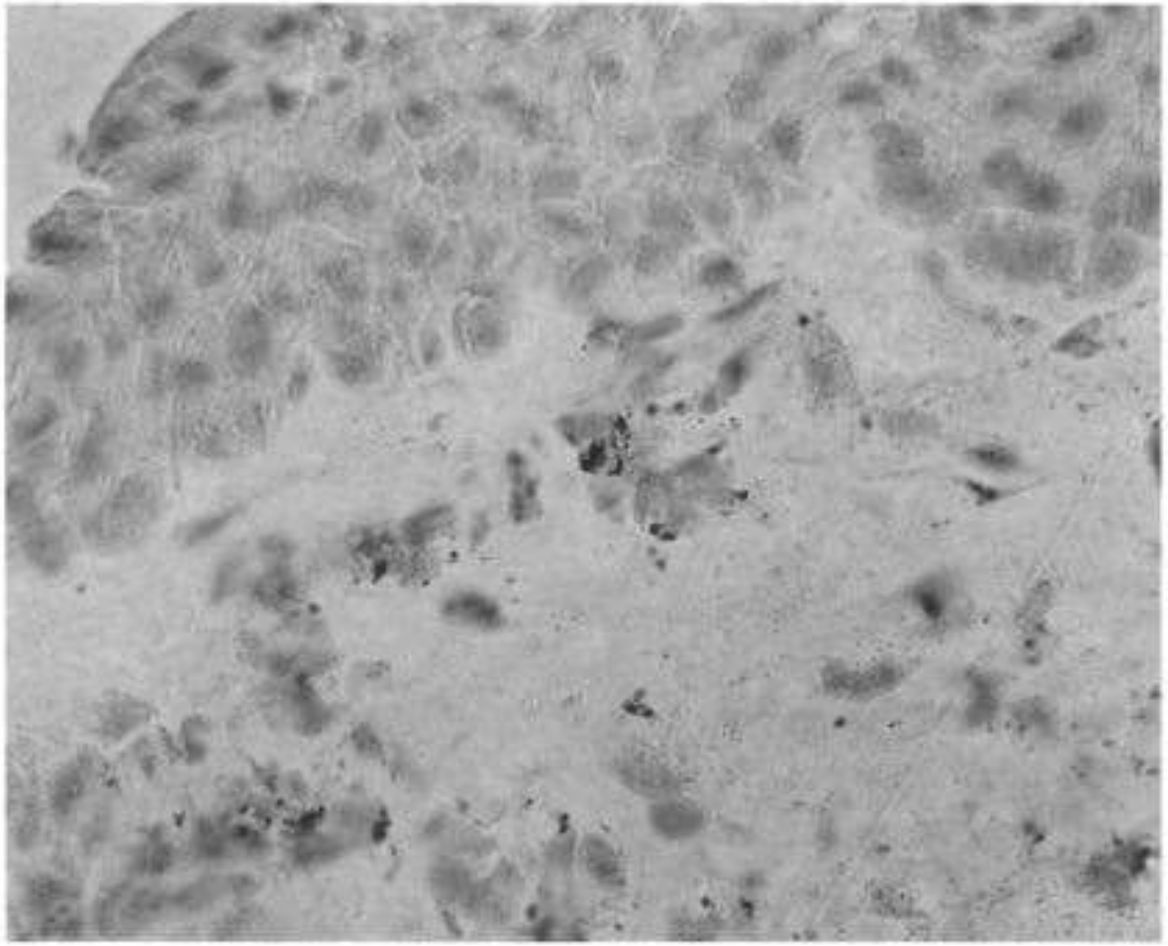


FIGURE 5
Case I. Photomicrograph of conjunctival biopsy stained with oil red 0 showing lipid material within the fibroblasts of the substantia propria × 800.

Welch, 1977

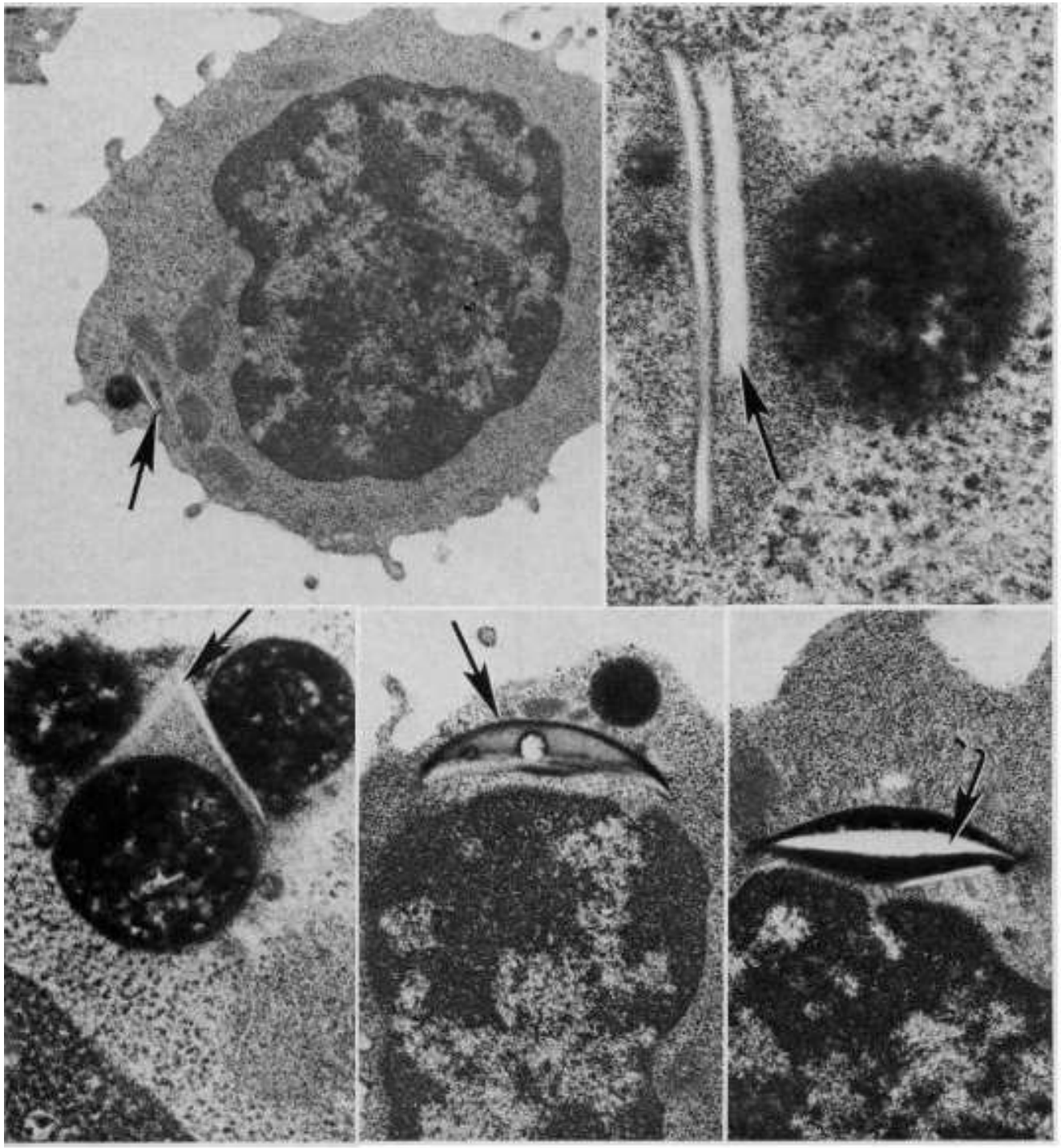


Fig 10.—Case 1. Ultrastructural appearance of crystalline spaces (arrows) variably combined with granular and osmiophilic material in peripheral blood lymphocytes (top left, ×13 000; top right, ×110 000; bottom left, ×44 000; bottom center, ×20 000; bottom right, ×22 000).

Wison et all, 1989

LIVER, NATIVE, BIOPSY

Dx: HEPATOCYTES WITH INTRACELLULAR CRYSTALLINE DEPOSITION (SEE COMMENT)

Comment: (it is possible these findings represent hepatic manifestation of this crystalline dystrophy... superimposed drug effect?)

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22-1103

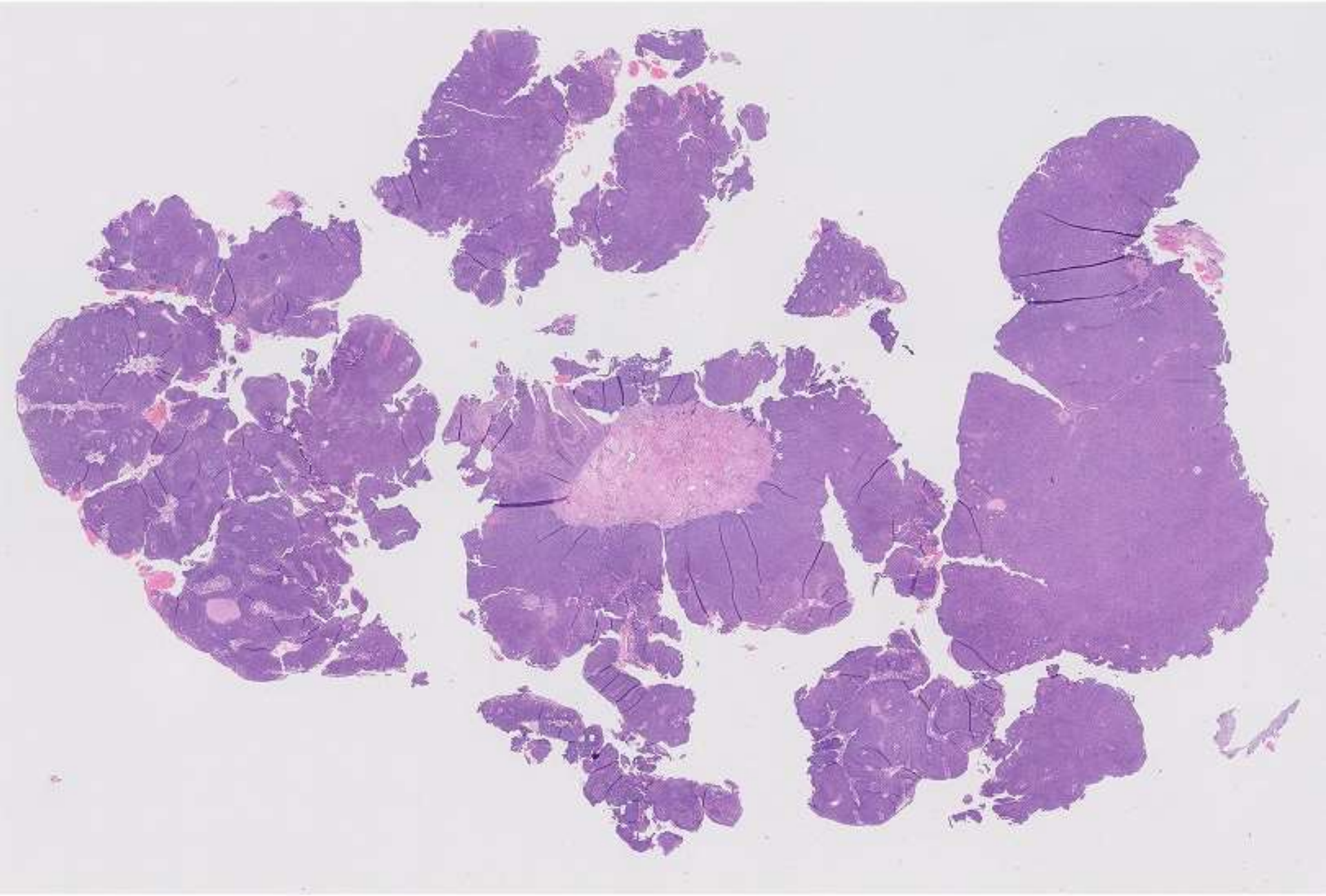
Xiaoming Zhang/Brooke Howitt; Stanford

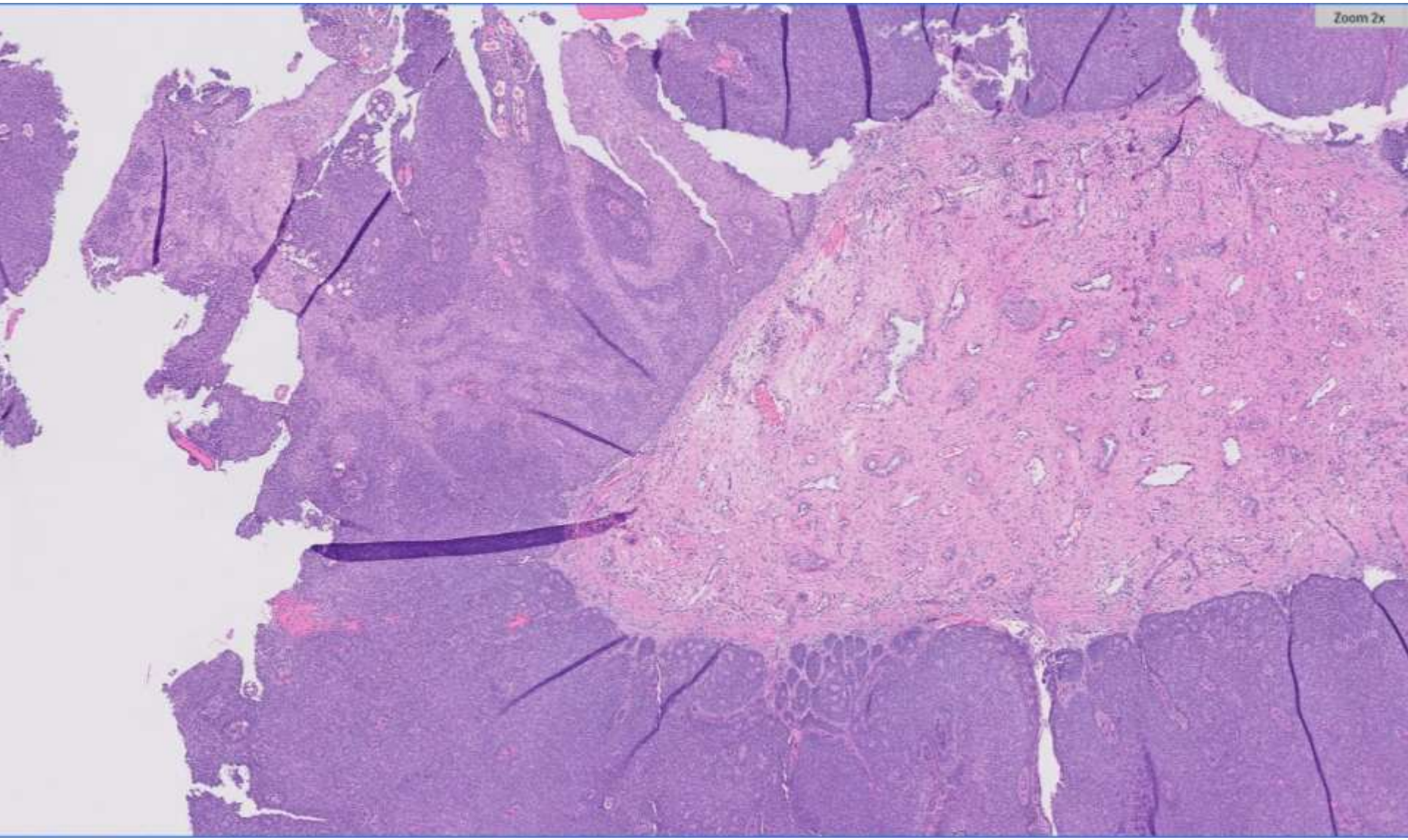
40ish F with cervical polyp who underwent polypectomy.

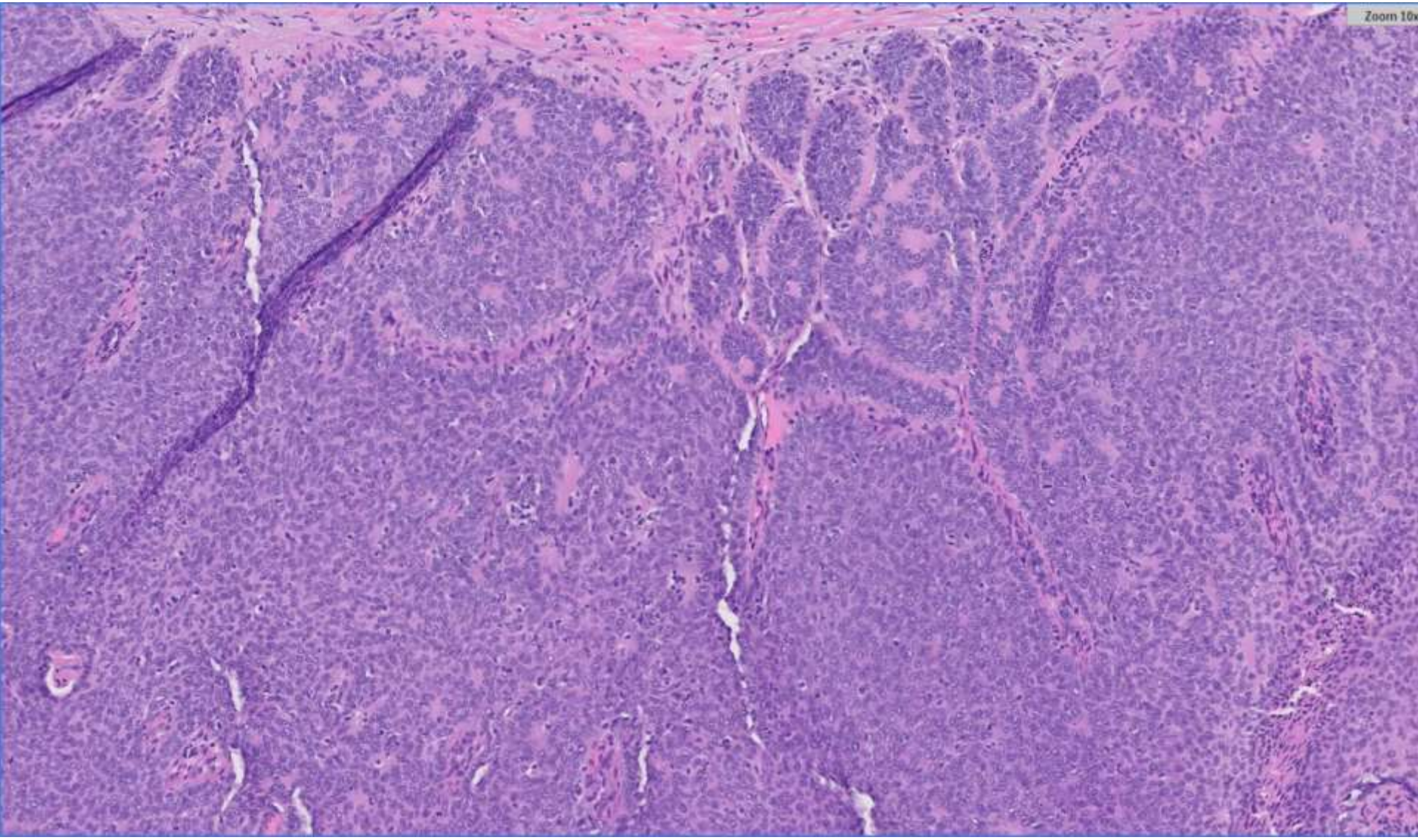
Xiaoming Zhang/Brooke Howitt; Stanford

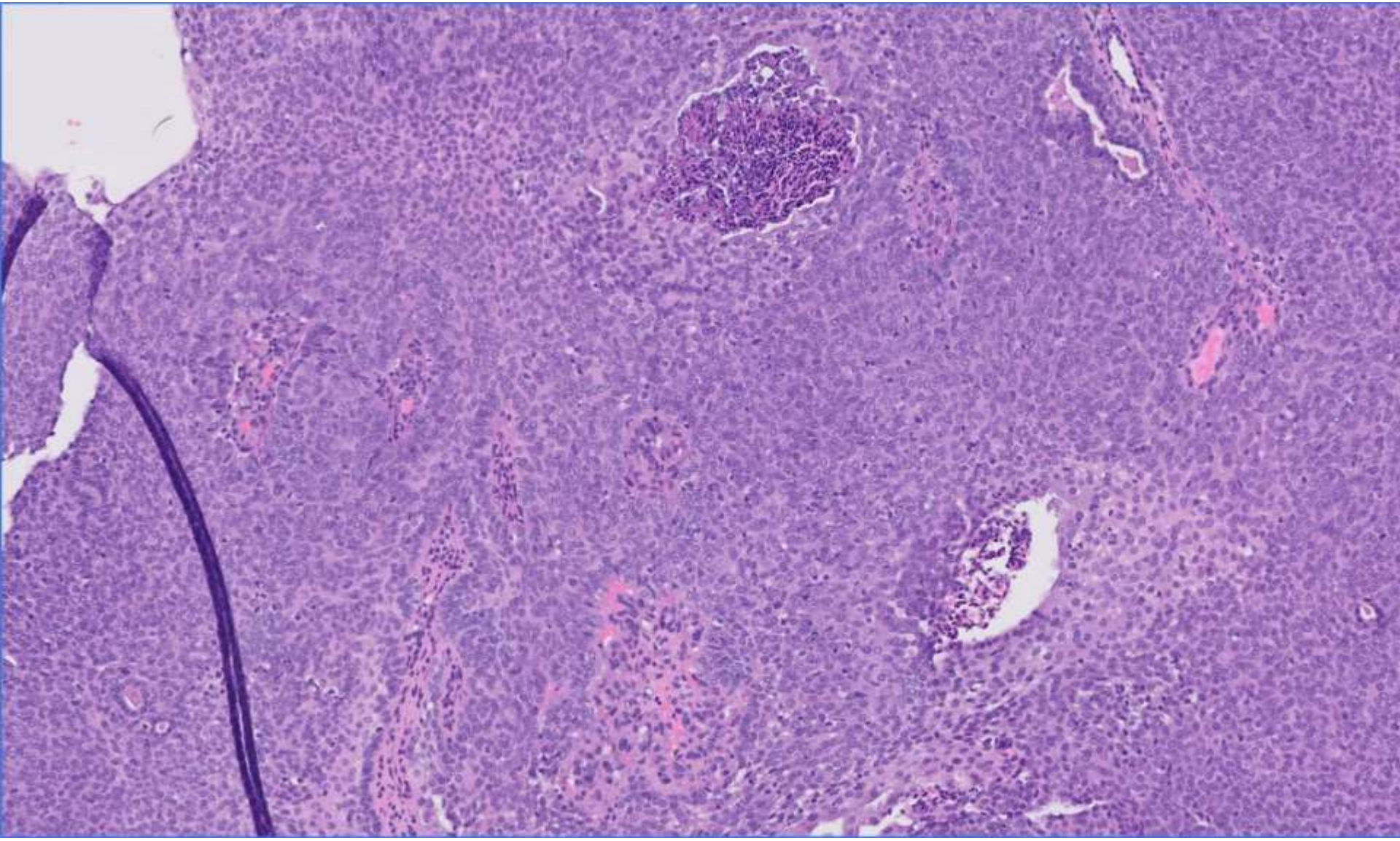
40ish F with a cervical polyp who underwent polypectomy

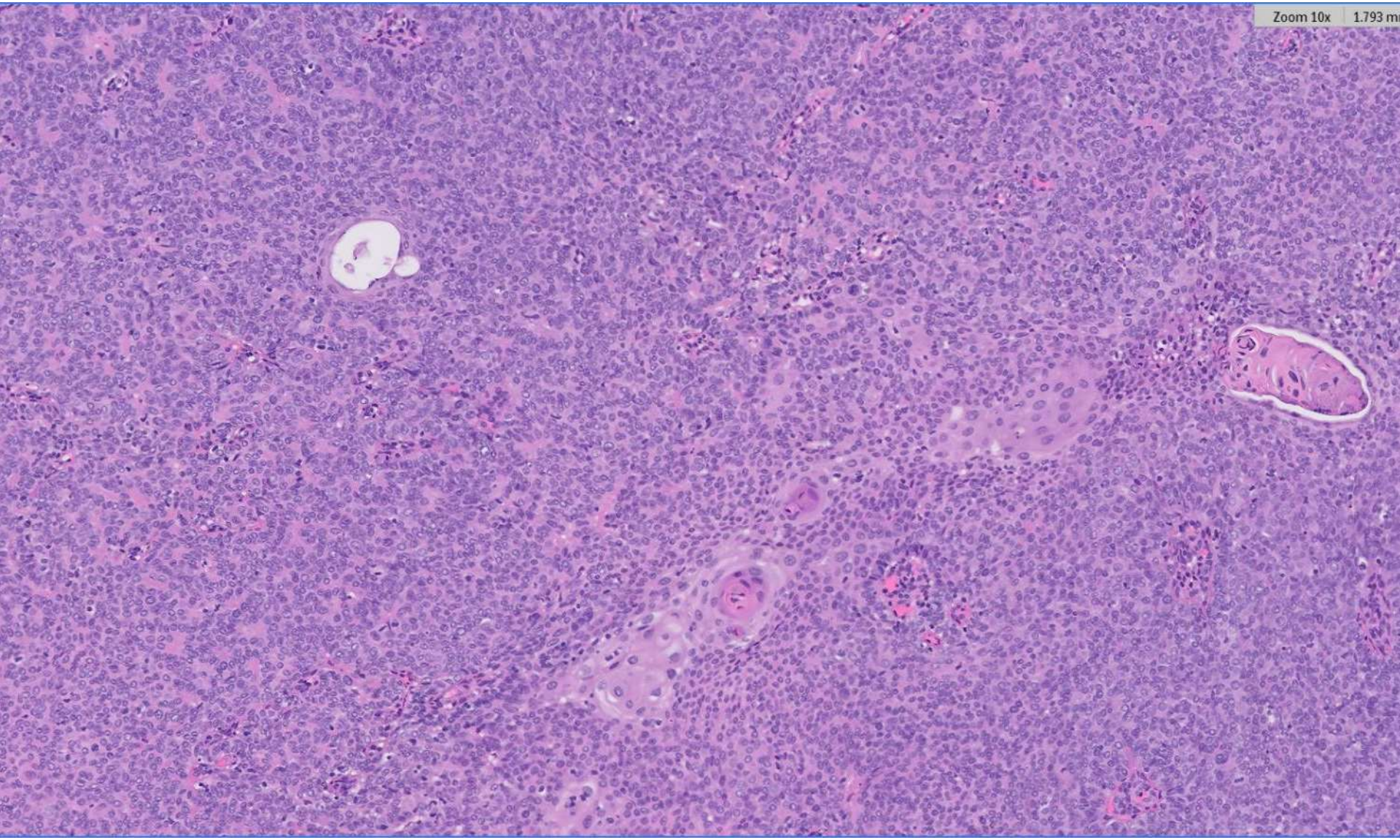
(consult case provided courtesy of Dr. Shawn Emery, Yosemite Pathology in Modesto, CA)

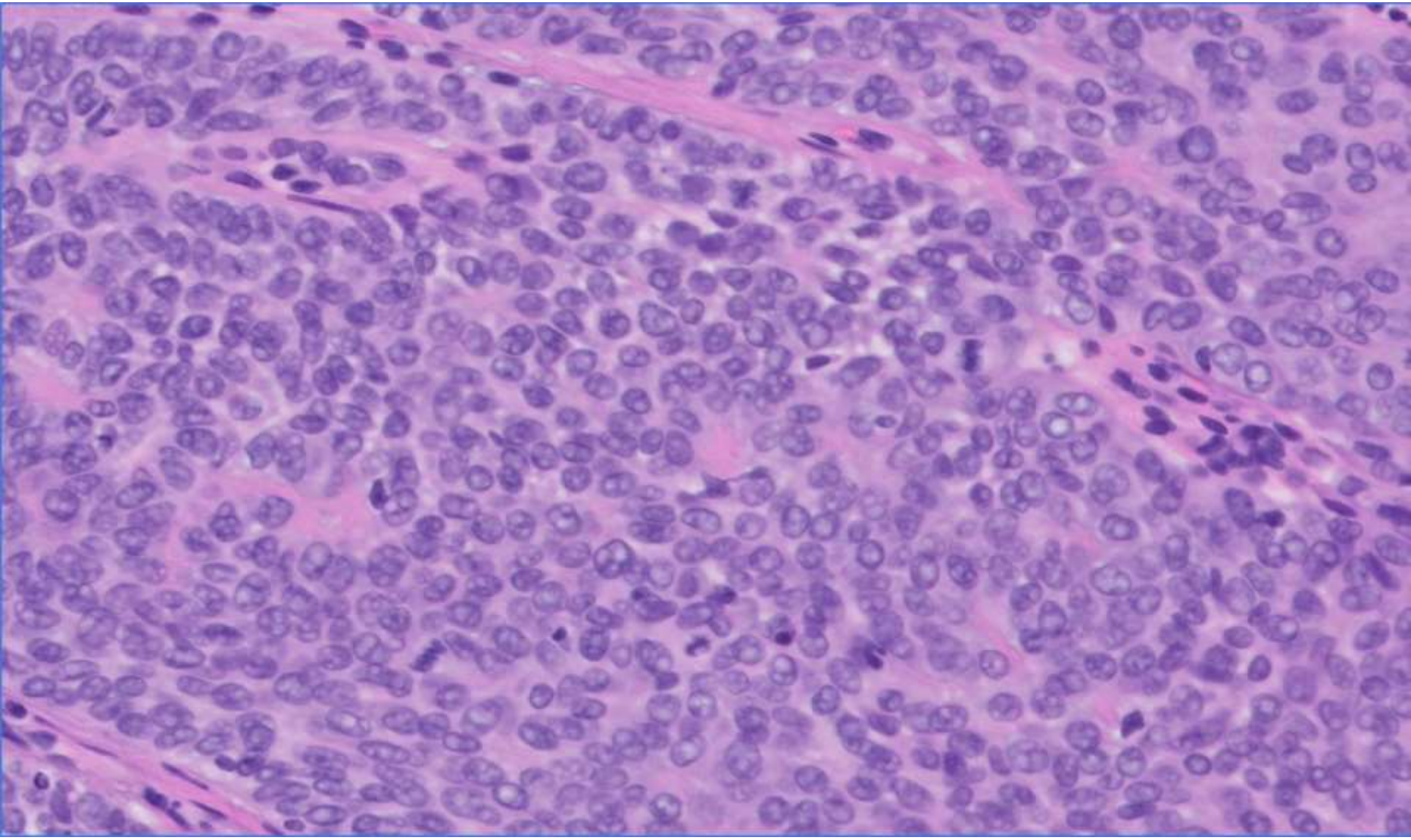


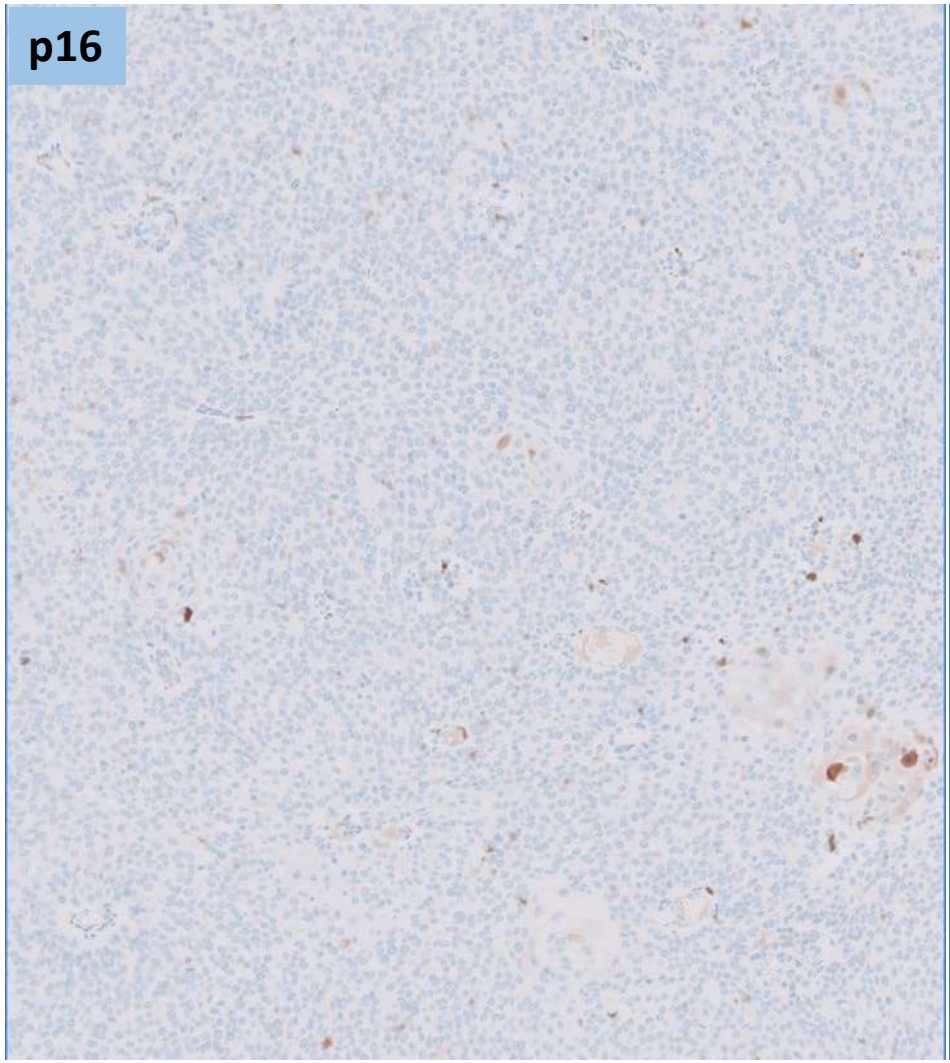

Zoom 2x

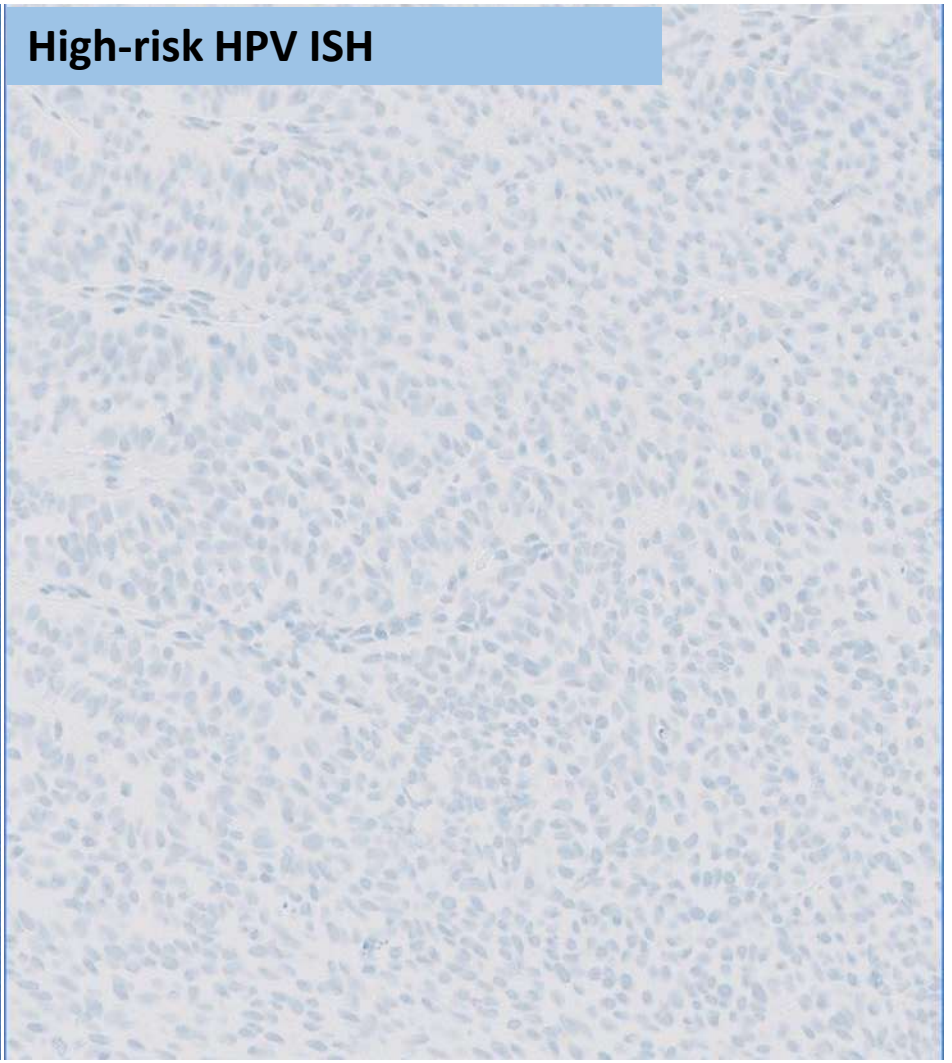

Zoom 10x

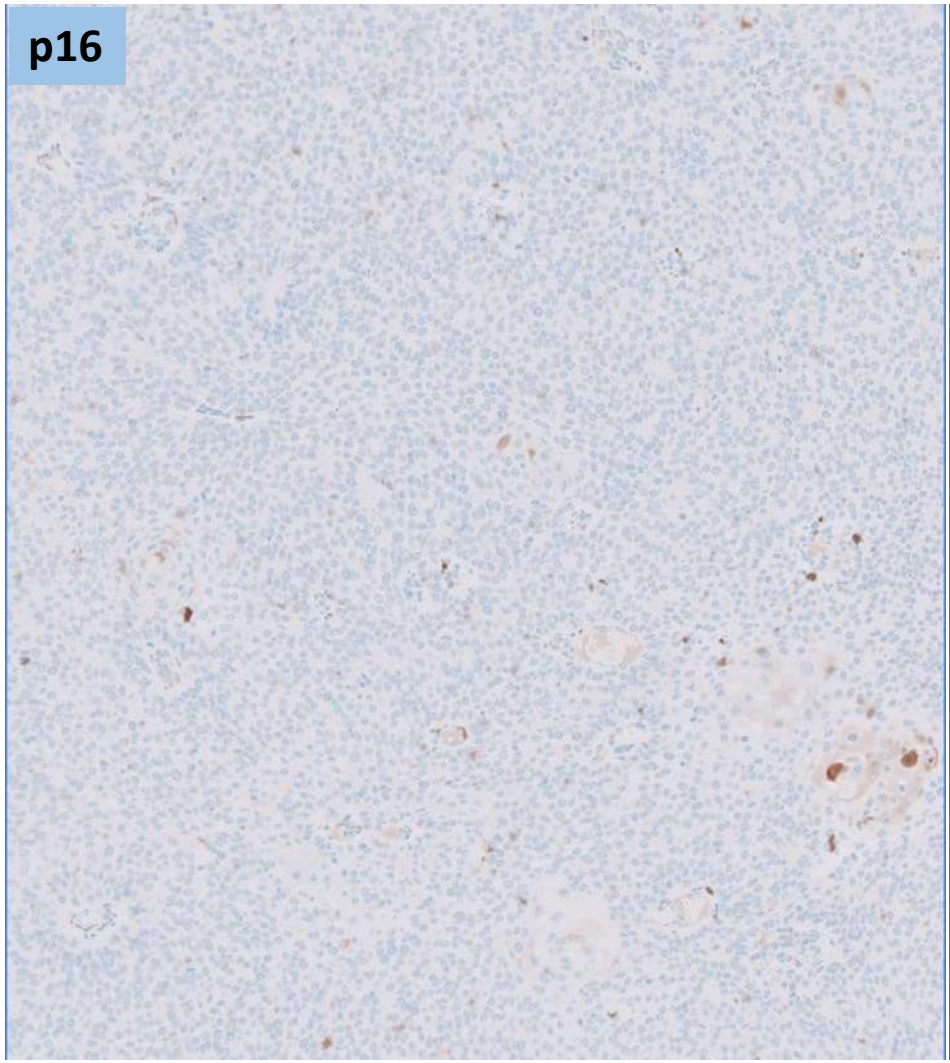


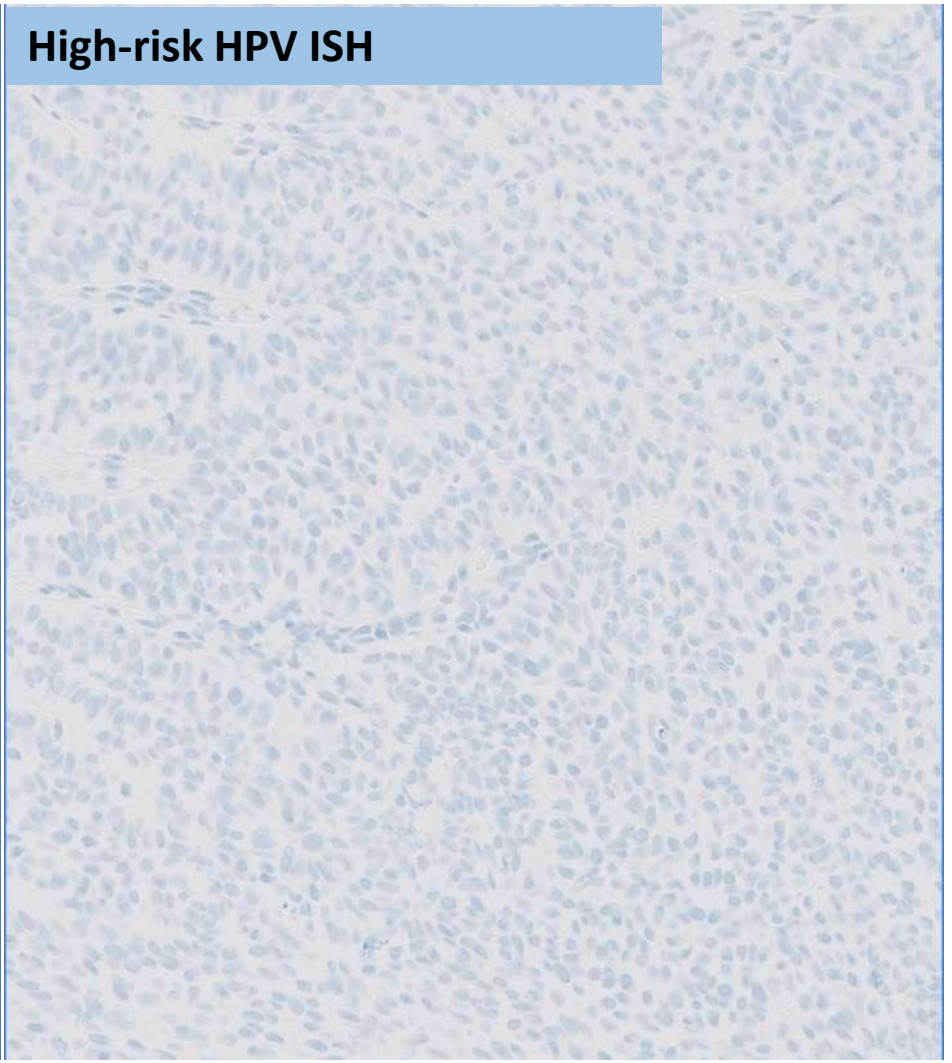

Zoom 10x
1.793 m

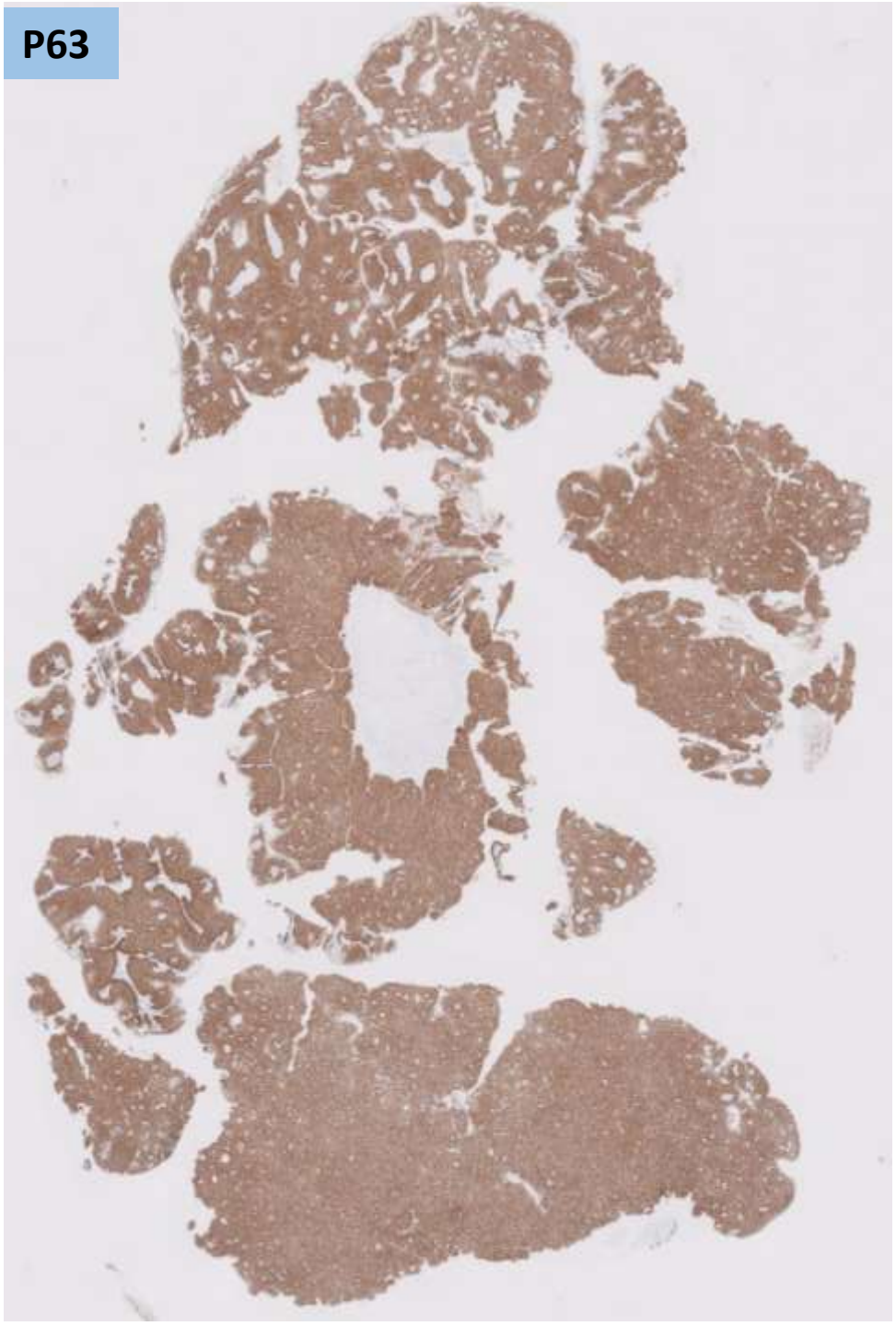


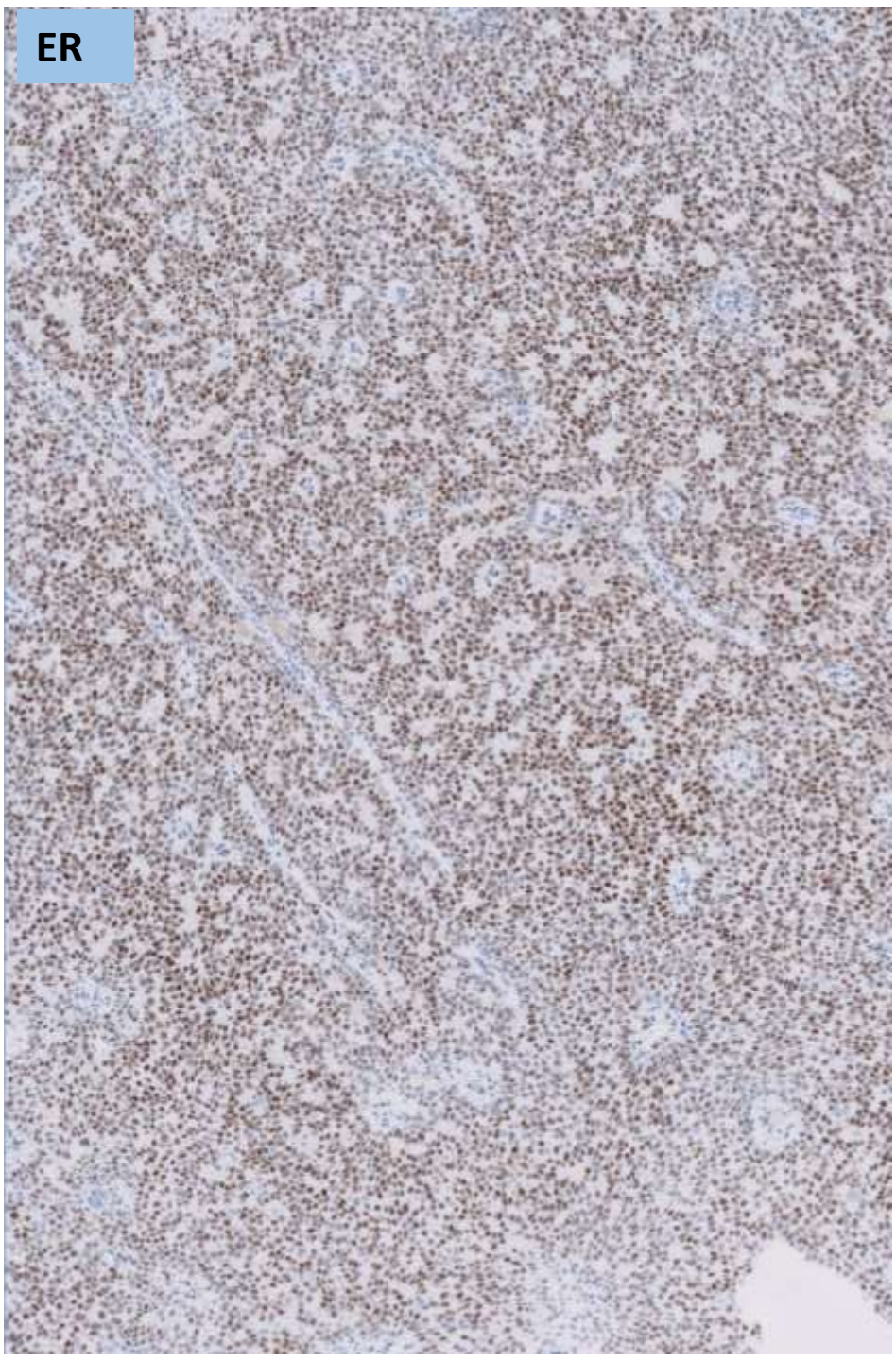

p16


High-risk HPV ISH


p16


High-risk HPV ISH


P63


ER

Differential diagnosis

- **Endometrial endometrioid carcinoma with extensive squamous differentiation involving cervix**
  - However, in this case:
    - PTEN intact, MMR intact, Beta-catenin: membranous staining
    - Unremarkable endometrium on US
- **Neuroendocrine tumor**
  - However, in this case: INSM1 –, synaptophysin –
- **Adenoid cystic carcinoma**
  - However, in this case: SOX10 –, MYB (ISH) –, ER+
- **NUT midline carcinoma**
  - However, in this case: NUT IHC –
- **Squamous cell carcinoma**
  - Diffuse and strong p63
  - p16 and high-risk HPV negative, but…
- **Giant condyloma, HSIL**
  - However, in this case:
    - No koilocytosis
    - Degree of proliferation, cytologic atypia, complex papillae/architecture, brisk mitotic activity – too much for condyloma
    - Features c/w exophytic-type invasion

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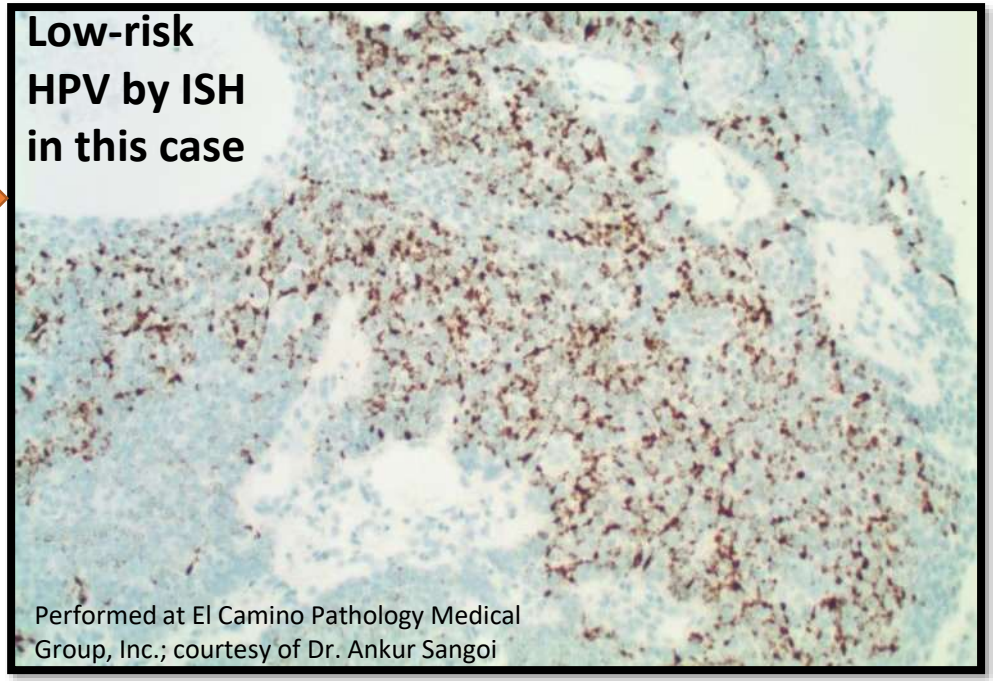


Final diagnosis

Papillary squamous cell carcinoma, low-risk HPV-associated

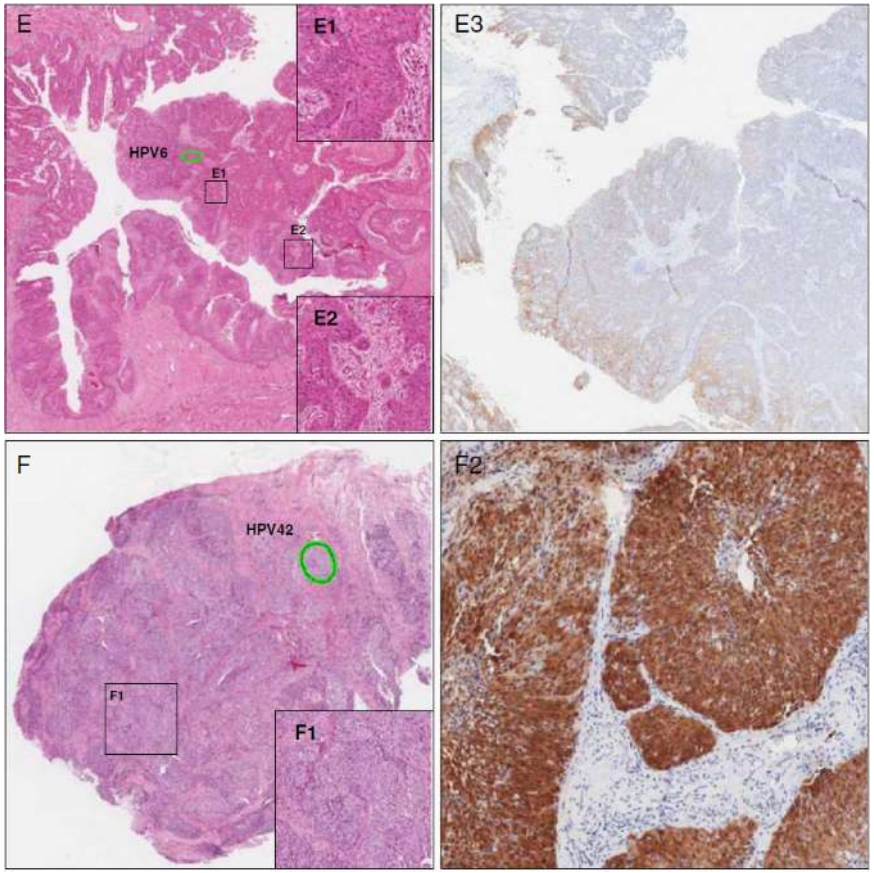
Am J Surg Pathol. 2013 Sep;37(9):1299-310. doi: 10.1097/PAS.0b013e31828b6be4.

The occasional role of low-risk human papillomaviruses 6, 11, 42, 44, and 70 in anogenital carcinoma defined by laser capture microdissection/PCR methodology: results from a global study

Núria Guimerà [1], Belén Lloveras, Jan Lindeman, Laia Alemany, Miekel van de Sandt, Maria Alejo, Gustavo Hernandez-Suarez, Ignacio G Bravo, Anco Molijn, David Jenkins, Antonio Cubilla, Nubia Muñoz, Silvia de Sanjose, Francesc Xavier Bosch, Wim Quint, RIS HPV TTHPV VVAPO study groups

- A global study of 13,328 anogenital carcinomas, **46** LR-HPV associated SCC were identified
  - **21 (46%) cervical**
  - 1 (2%) vaginal
  - 5 (11%) vulval
  - 4 99%) anal
  - 15 (33%) penile

- **Two distinctive patterns:**
  - HPV 6/11:
    - Papillary, warty or warty-basaloid, squamous, or transitional histology
    - Little or no p16 expression
    - Young age
  - HPV 70/42:
    - Typical SCC
    - Diffuse p16 expression
    - Older age



International Journal of Gynecological Pathology
38:493–497, Lippincott Williams & Wilkins, Baltimore

Original Article

HPV 6-associated HSIL/Squamous Carcinoma in the Anogenital Tract

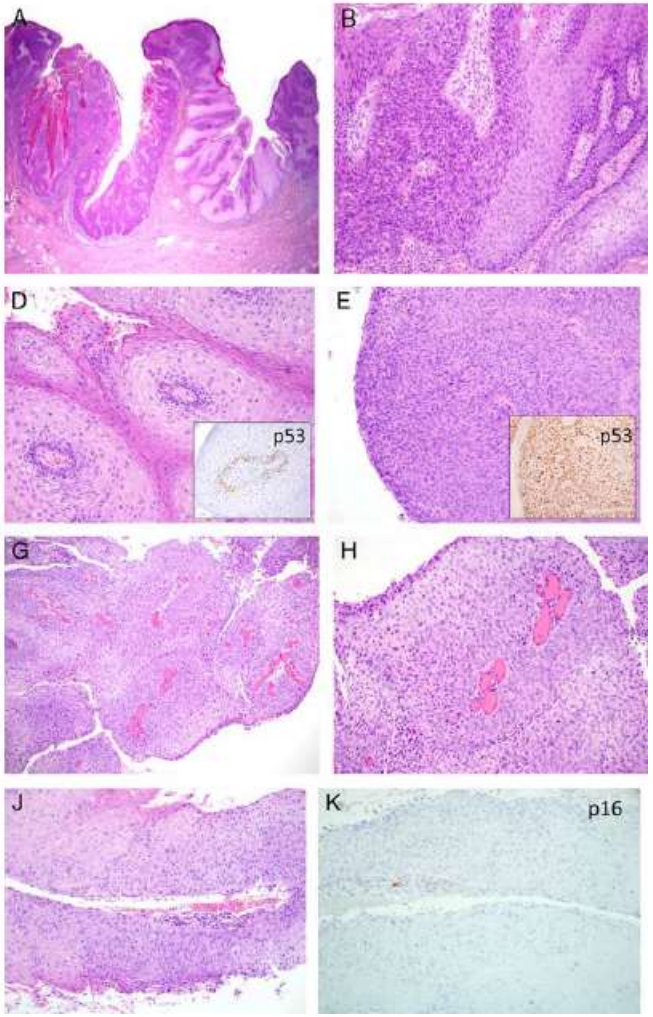
Martina Z. Liu, M.D., Yin P. Hung, M.D., Ph.D., Eric C. Huang, M.D., Ph.D., Brooke E. Howitt, M.D., Marisa R. Nucci, M.D., and Christopher P. Crum, M.D.

TABLE 2. *Histology and immunohistochemistry*

Case	Histology	p16	p53
1	Anal condyloma with contiguous HSIL	Neg	+++ (HSIL)*
2	Biphasic low–grade and high-grade papillary SIL with microinvasion and LN metastasis	Neg	+++ (HSIL and invasive SCC)
3	Papillary SIL with superficial invasion	Neg	+
4	Fragments of papillary SIL	Neg	++

*Also contained a deleterious *Tp53* mutation (see text).

+indicates weak; ++, moderate or focally strong; +++, Strong and diffuse; HSIL, high-grade squamous intraepithelial lesion; ND, not done; Neg, negative; SCC, squamous cell carcinoma; SIL, squamous intraepithelial lesion.



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Gynecologic Oncology 90 (2003) 657–661

www.elsevier.com/locate/ygyno

Papillary squamous cell carcinoma of the uterine cervix: an immunophenotypic appraisal of 12 cases

Ramin Mirhashemi, M.D.,[a,*] Parvin Ganjei-Azar, M.D.,[b] Mehrdad Nadji, M.D.,[b] Nicholas Lambrou, M.D.,[c] Fikret Atamdede, M.D.,[a] and Hervy E. Averette, M.D.[c]

[a] *Harbor–UCLA Medical Center, David Geffen School of Medicine, Department of Obstetrics and Gynecology, Box 3, 1000 W. Carson St., Torrance, CA 90502, USA*

[b] *Department of Pathology, University of Miami School of Medicine, 1611 N.W. 12th Avenue, Miami, FL 33136, USA*

[c] *Department of Obstetrics and Gynecology, University of Miami School of Medicine, 1475 N.W. 12th Avenue, Suite 3500, Miami, FL 33136, USA*

Received 21 February 2003

Table 1
Patient characteristics, treatment details, and follow-up

Patient	Age (years)	Race	FIGO stage	Presenting symptom	Initial TX	LVSI	+LN	Parametrial margins	Follow-up (months)
1	45	W	IA2	Abnml Pap (CINIII)	RAH/LND	N	N	N	NED;84
2	35	H	IB1	Postcoital bleeding	RAH/LND	N	N	N	NED;16
3	36	W	IB2	Metrorrhagia	Staging Lap/XRT	N	Y(gross + obturator)	N/A	NED;20
4	36	B	IIIA	Metrorrhagia	Staging Lap/XRT	N	N	N/A	Alive with Dz;22
5	37	B	IB1	Metrorrhagia	RAH/LND	N	N	N	NED;18
6	38	H	IB1	Abnml Pap (CIS)	RAH/LND	Y	N	N	NED;33
7	42	H	IB1	Postcoital bleeding	RAH/LND	N	N	N	NED;24
8	45	H	IB1	Abnml Pap (CIS)	RAH/LND	N	N	N	NED;23
9	57	W	IB1	Postmenop bleeding	RAH/LND	N	N	N	Dead w/Dz 39/Psoas recurrence GOG 169
10	67	B	IA1	Abnml Pap (CIS)	TAH/BSO	N	N/A	N	NED;29
11	70	W	IB1	Postmenop bleeding	XRT (EXT-5040cGy ICR-3600cGy)	N/A	N/A	N/A	NED;76
12	74	W	IA2	Abnml Pap	RAH/	N	N	N	NED;26

Only high-risk HPV were investigated

Table 2
Biologic characteristics of papillary squamous cell carcinoma of the uterine cervix

Patient	HPV status (hybrid capture)	HPV status (PCR)	p53 immunostaining	Ki-67 immunostaining
1	NEG	NEG	0	3+
2	NEG	NEG	0	2+
3	NEG	POS	0	3+
4	NEG	POS	+	3+
5	NEG	NEG	0	3+
6	NEG	POS	0	3+
7	NEG	POS	0	2+
8	NEG	NEG	0	2+
9	NEG	POS	+	3+
10	NEG	NEG	0	2+
11	NEG	POS	+	3+
12	NEG	NEG	0	3+

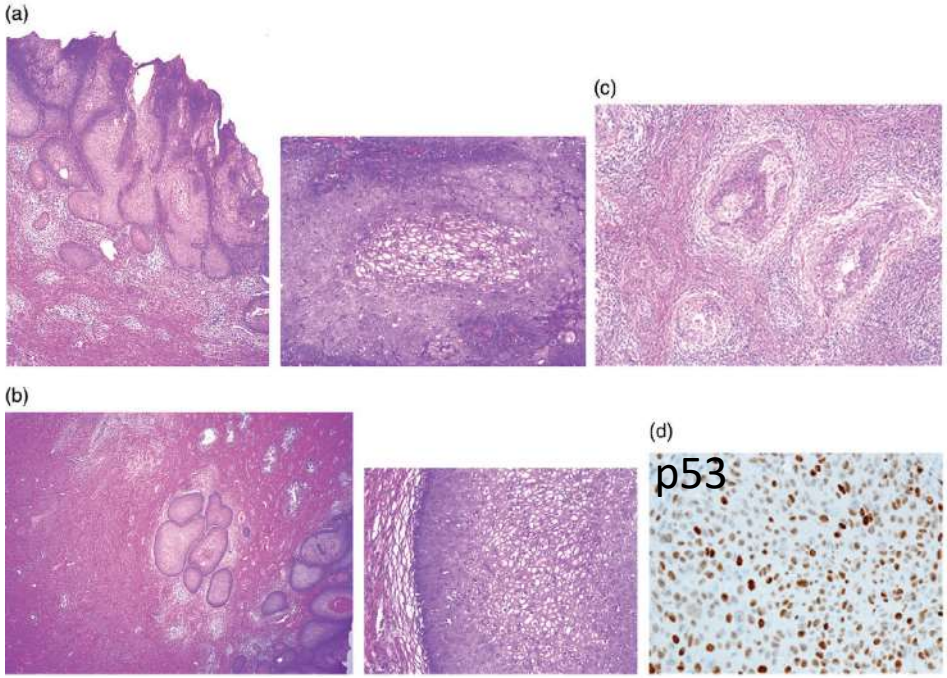
THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13553 J. Obstet. Gynaecol. Res. Vol. 44, No. 3: 583–587, March 2018

Case of rapidly progressing condylomatous squamous cell carcinoma of the uterine cervix associated with low-risk human papillomavirus type 6

Miho Masuda[1], Kaoru Abiko[1], Sachiko Minamiguchi[2], Ryusuke Murakami[1], Tsukasa Baba[1] and Ikuo Konishi[1]

Departments of [1]Gynecology and Obstetrics and [2]Diagnostic Pathology, Kyoto University Graduate School of Medicine, Kyoto, Japan



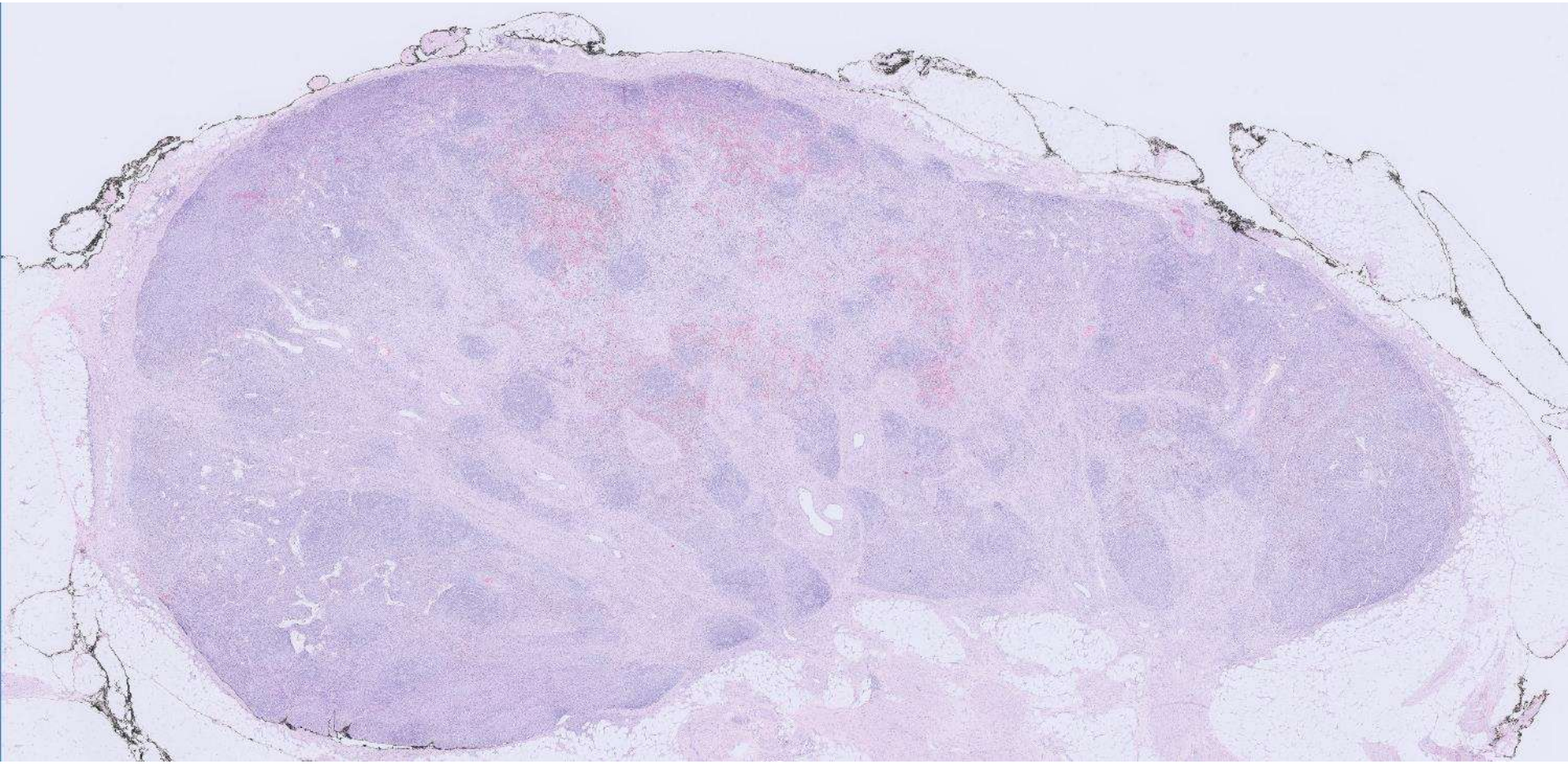
Take home points

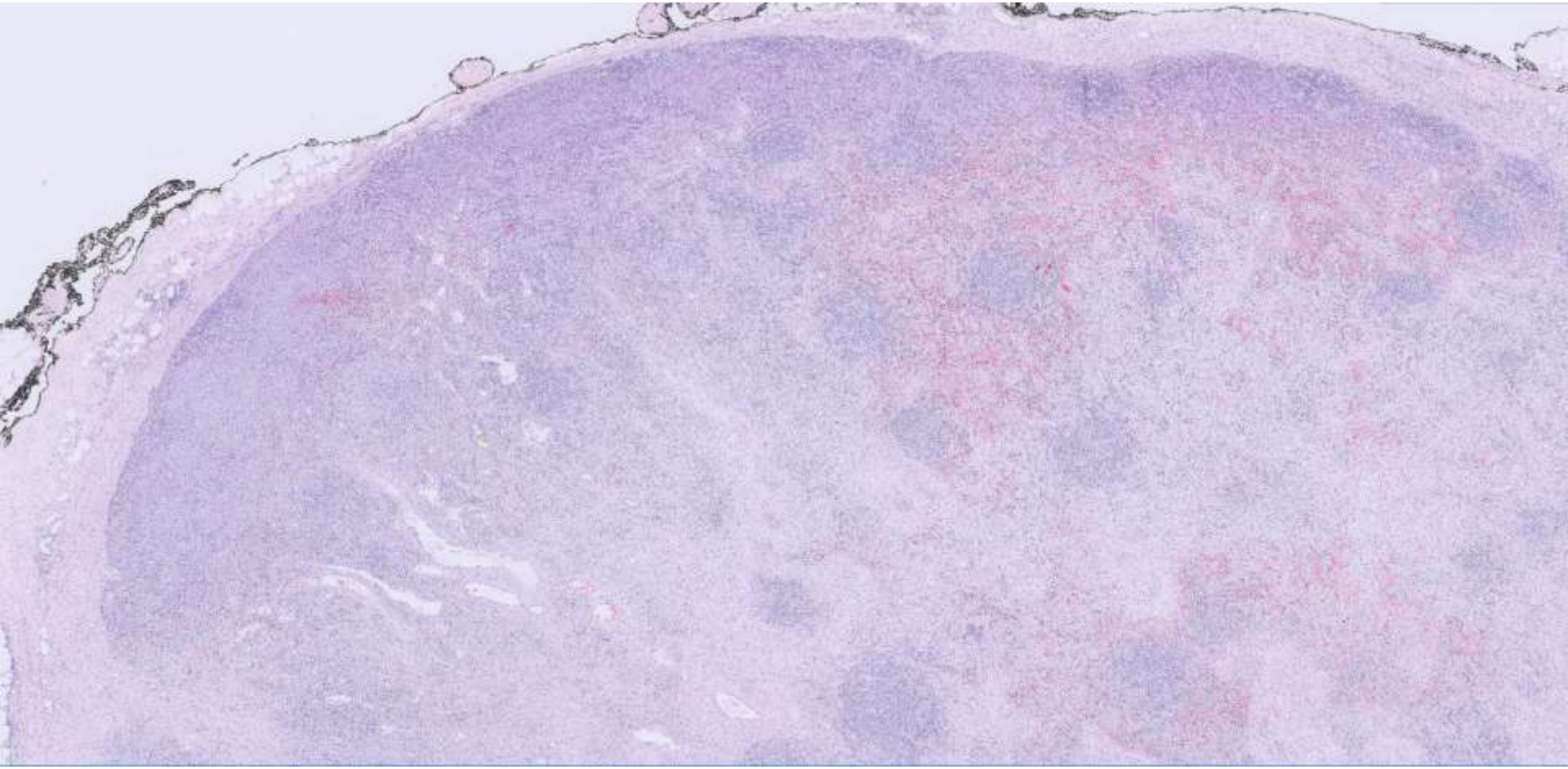
- Very rarely, low-risk HPV genotypes have been identified as the sole cause of cervical SCC
- HPV 6/11 associated SCC often show papillary appearance
- Clinical behavior of low-risk HPV associated SCC is unclear, but could be aggressive

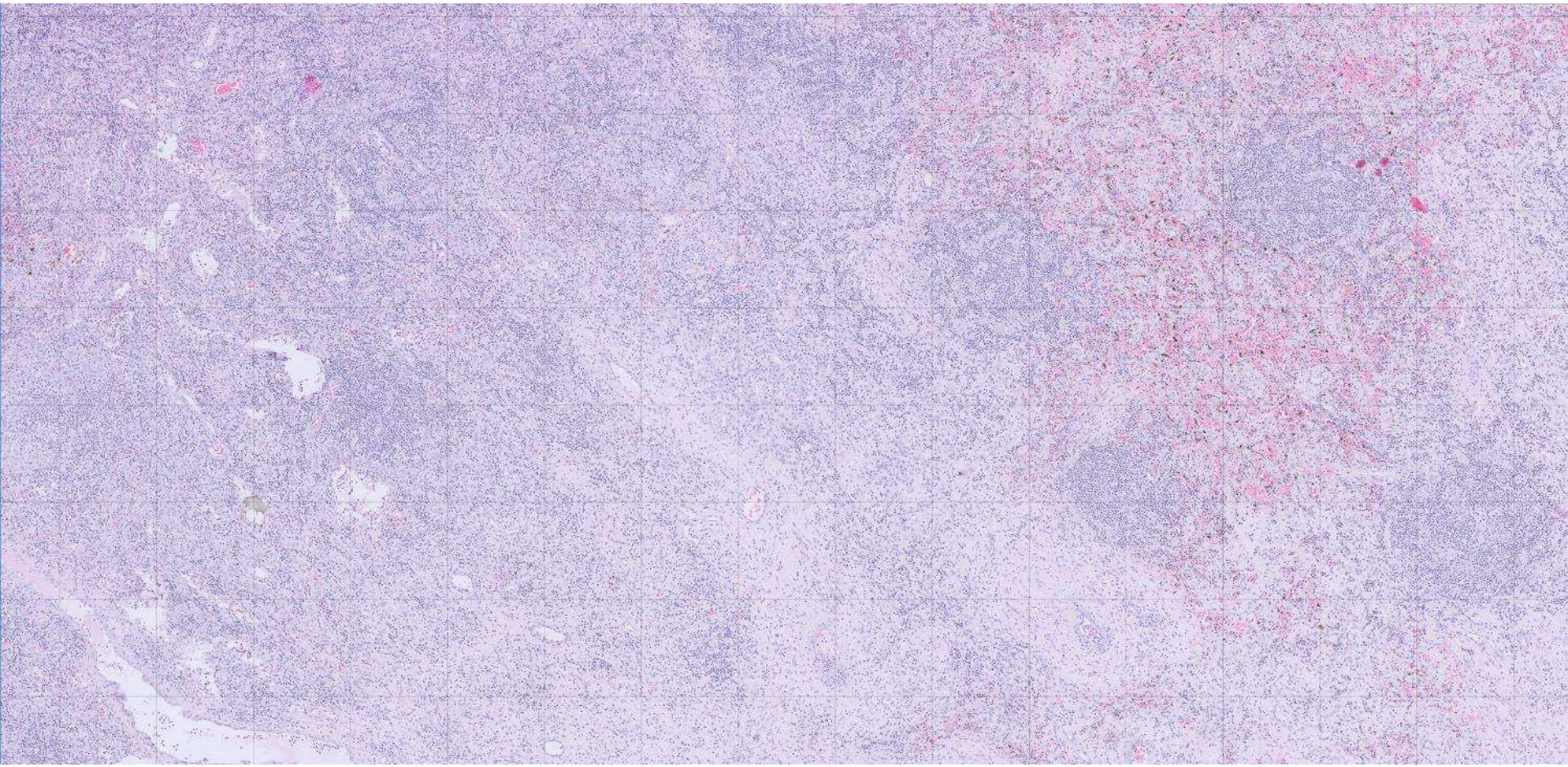
22-1104

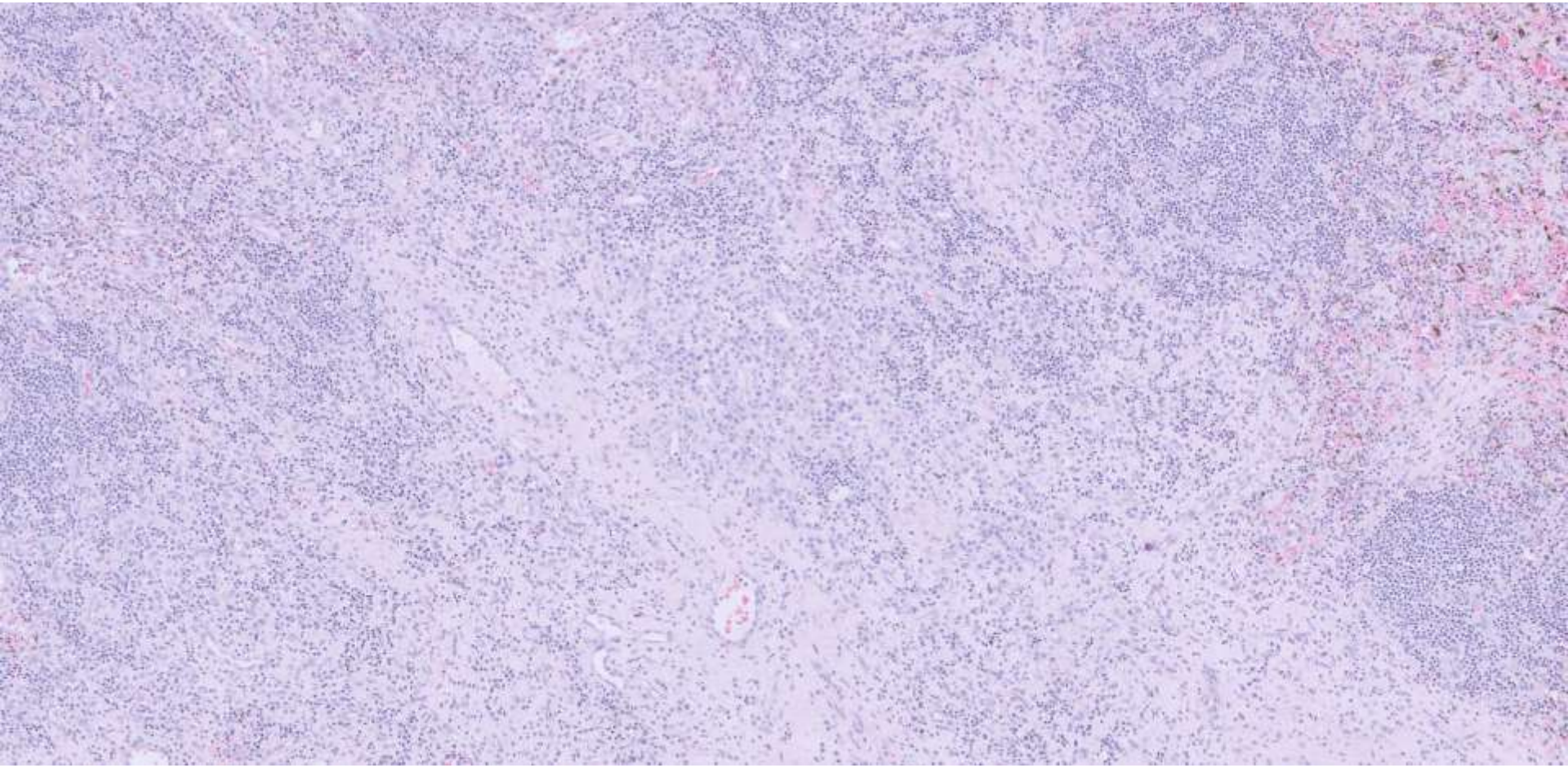
Jason Kurzer; Stanford

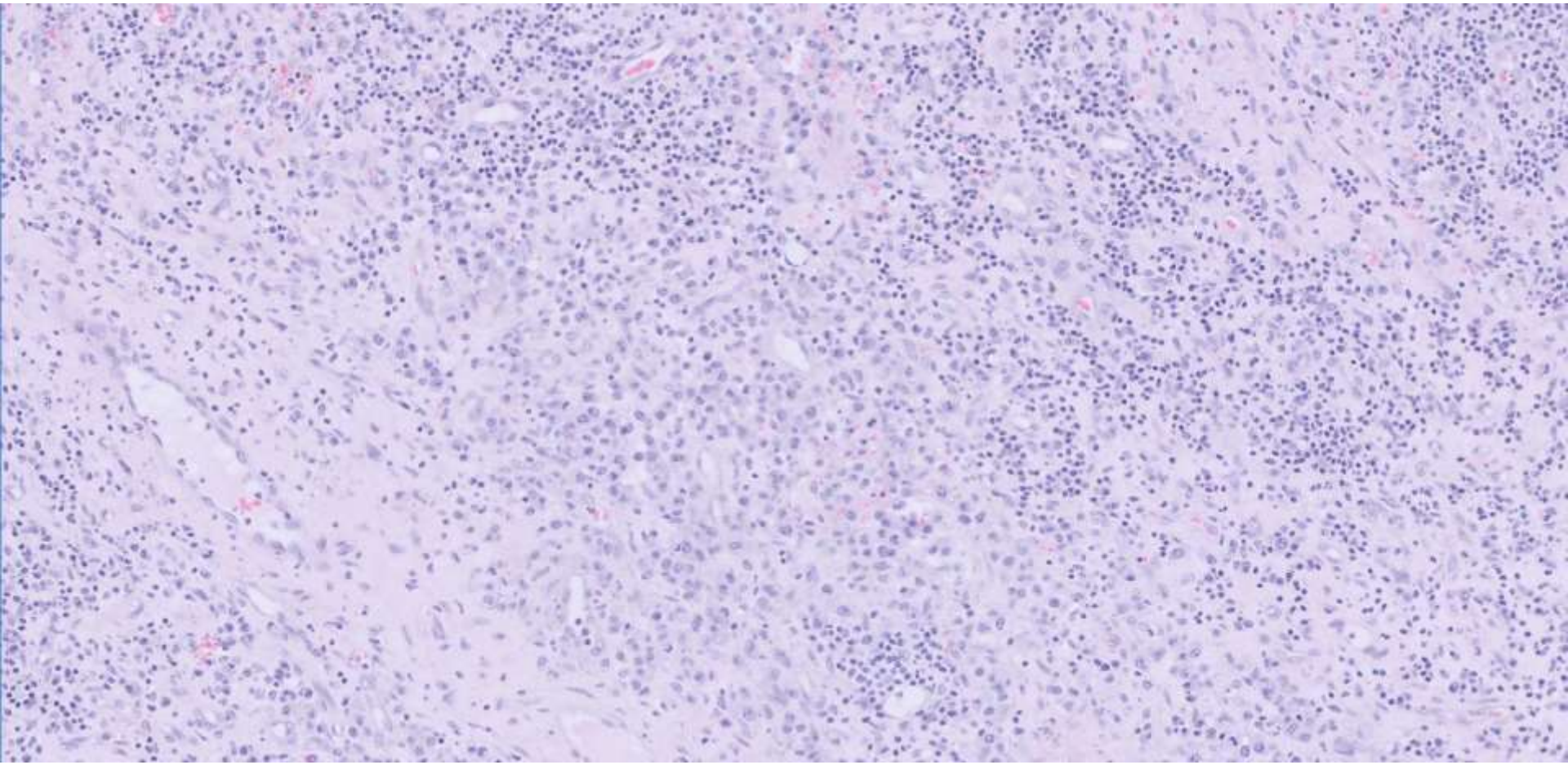
50ish F presents with shortness of breath, hip pain, and headache. CT scan of the abdomen showed adenopathy in the right inguinal, pelvic area, retroperitoneal area, upper abdomen, and pericardial regions. There was also mediastinal and supraclavicular lymphadenopathy.

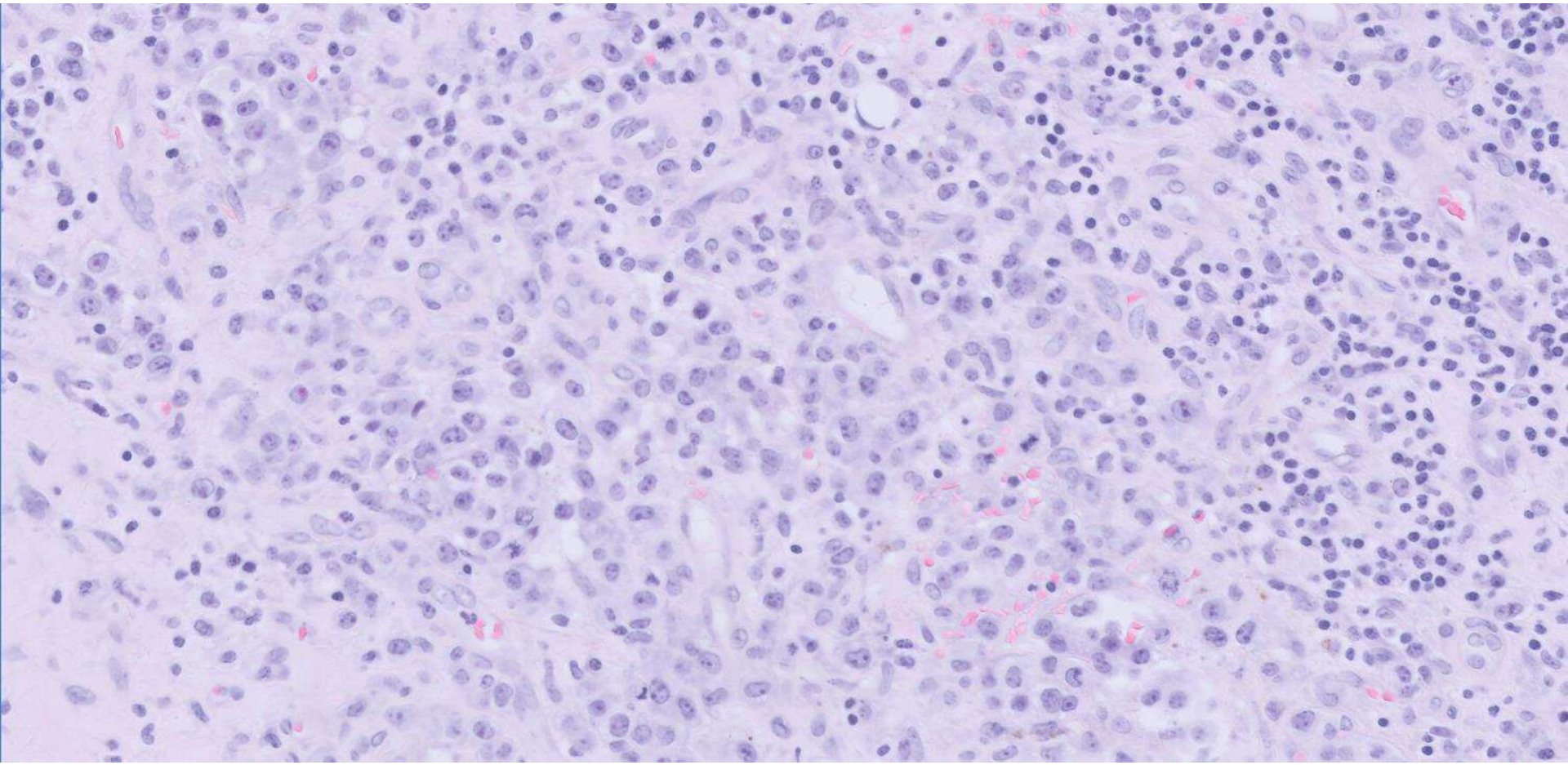


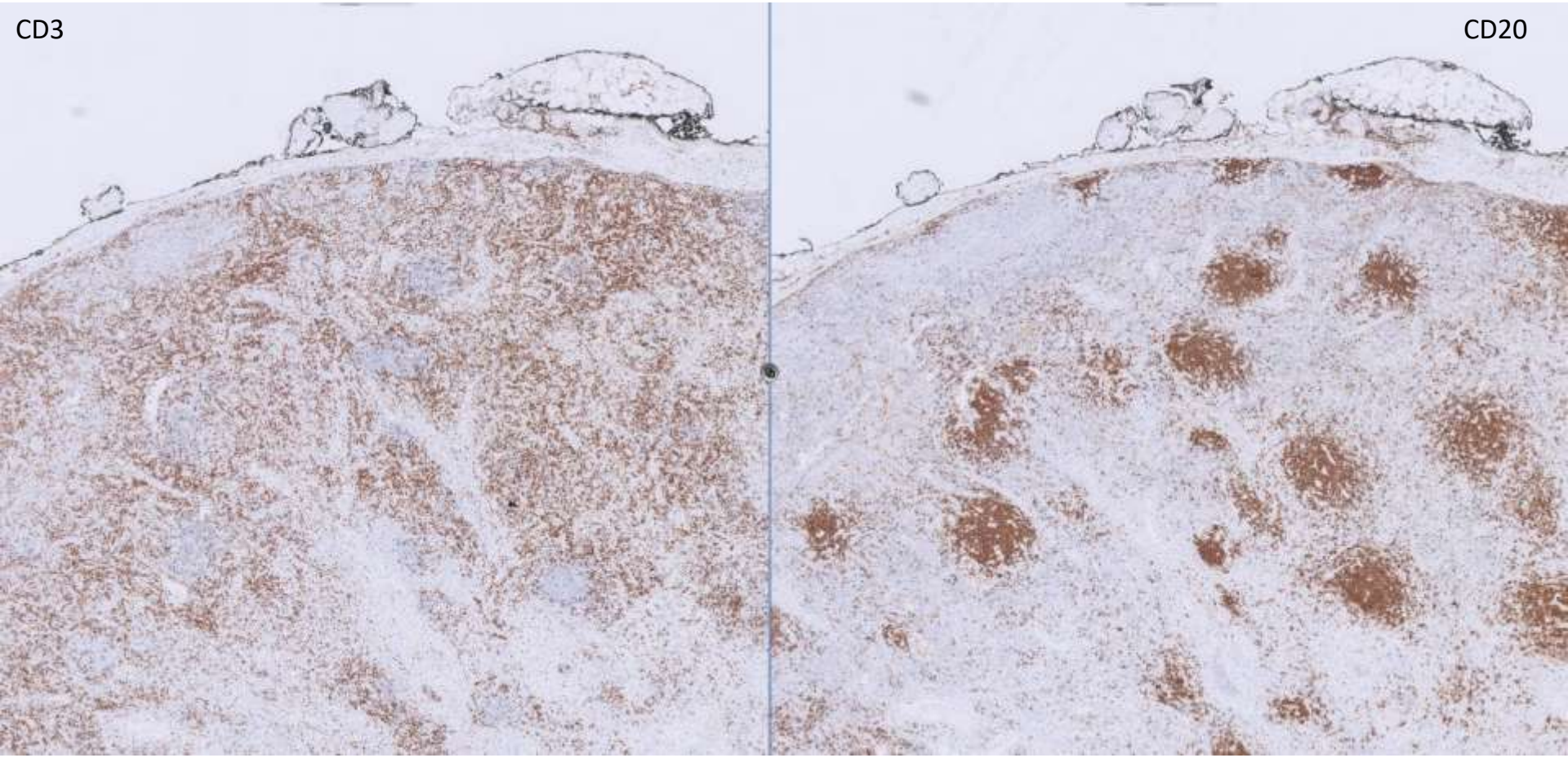


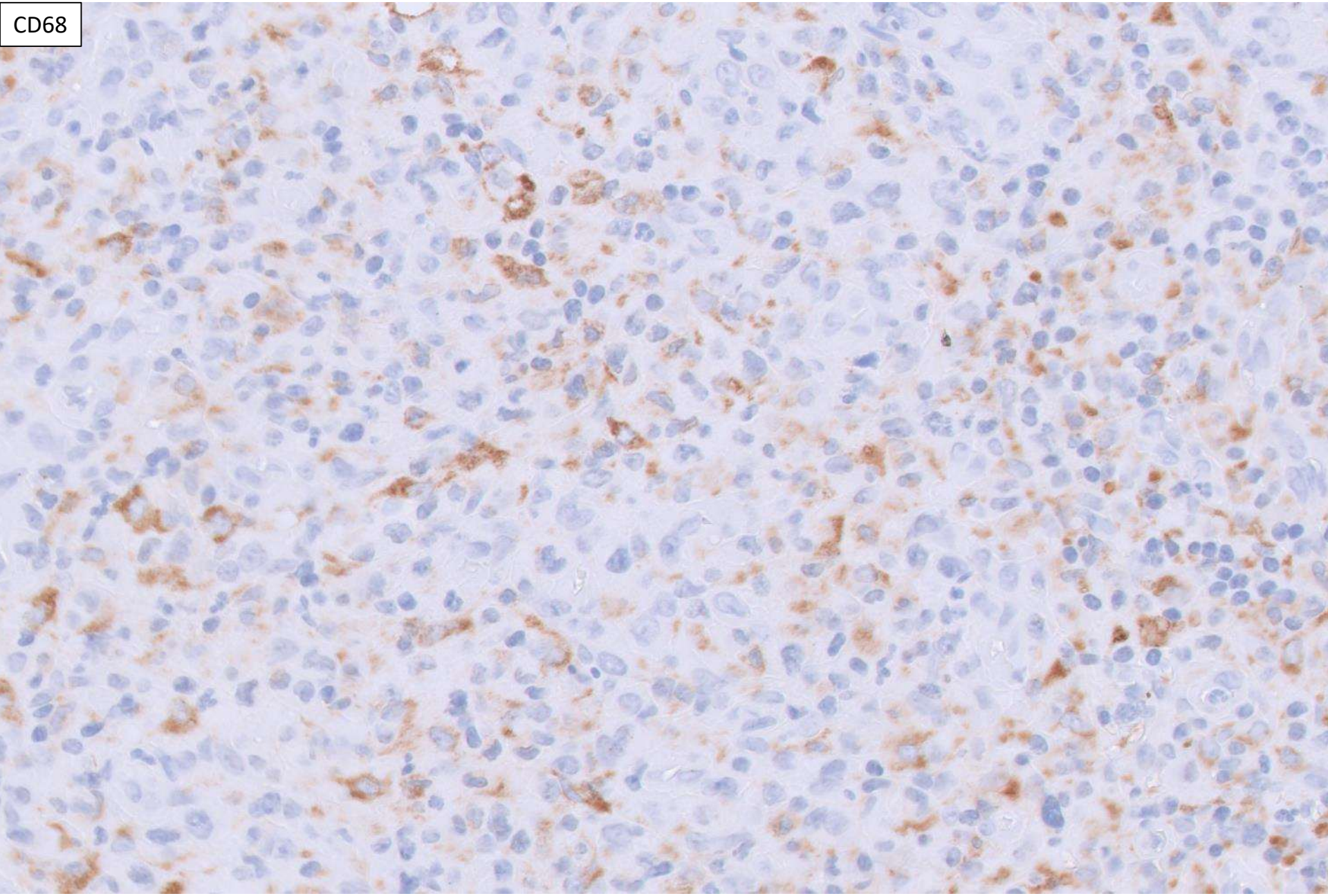









CD3
CD20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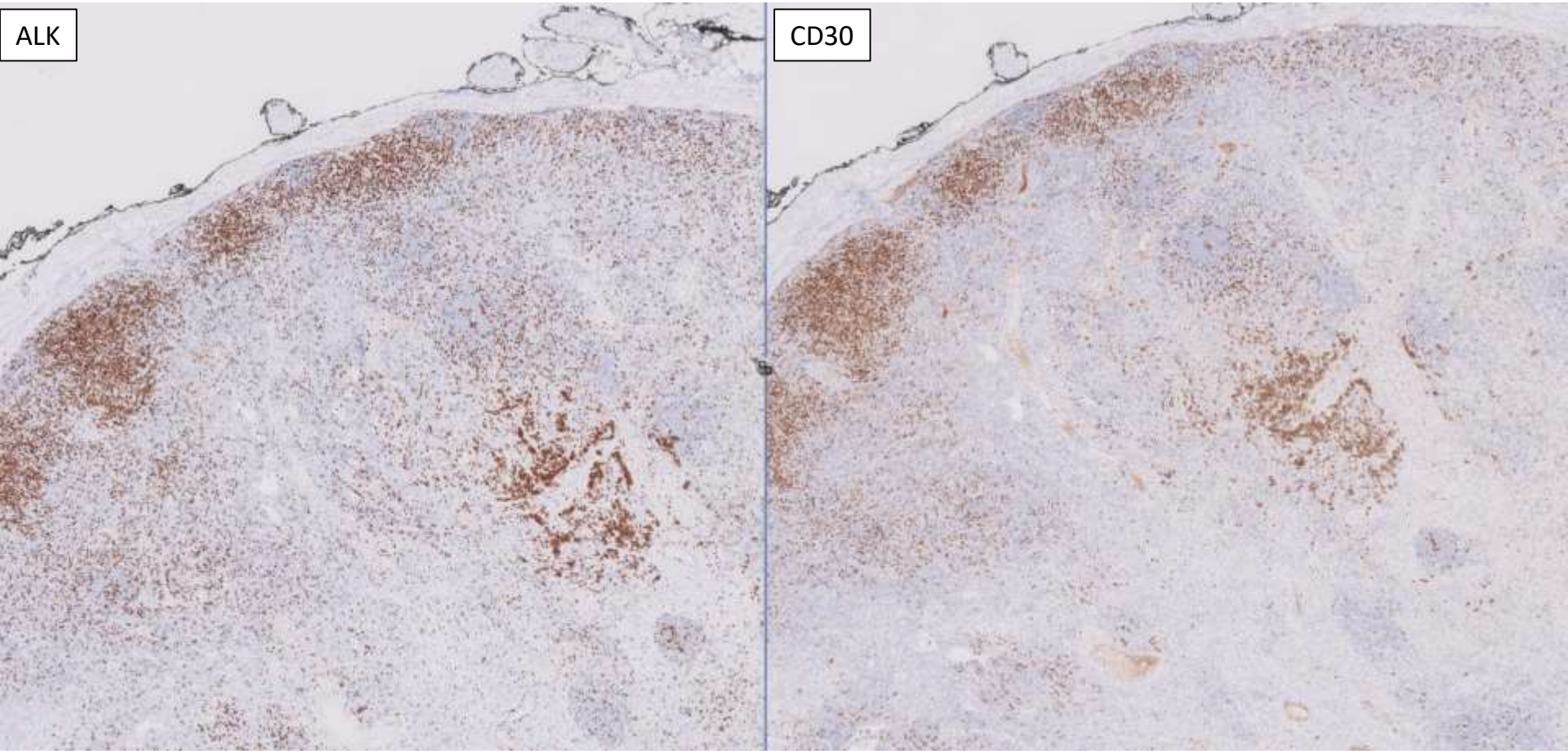
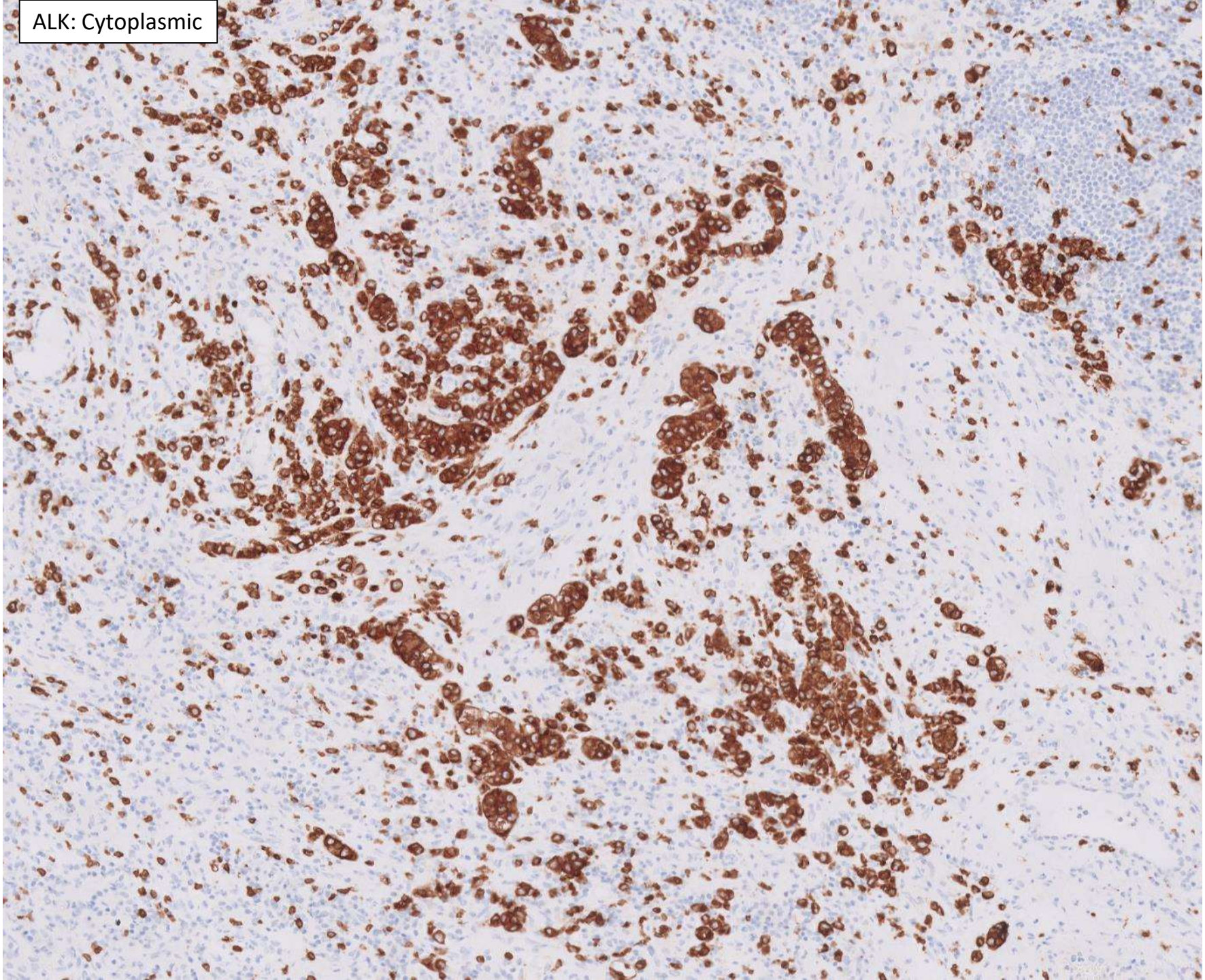
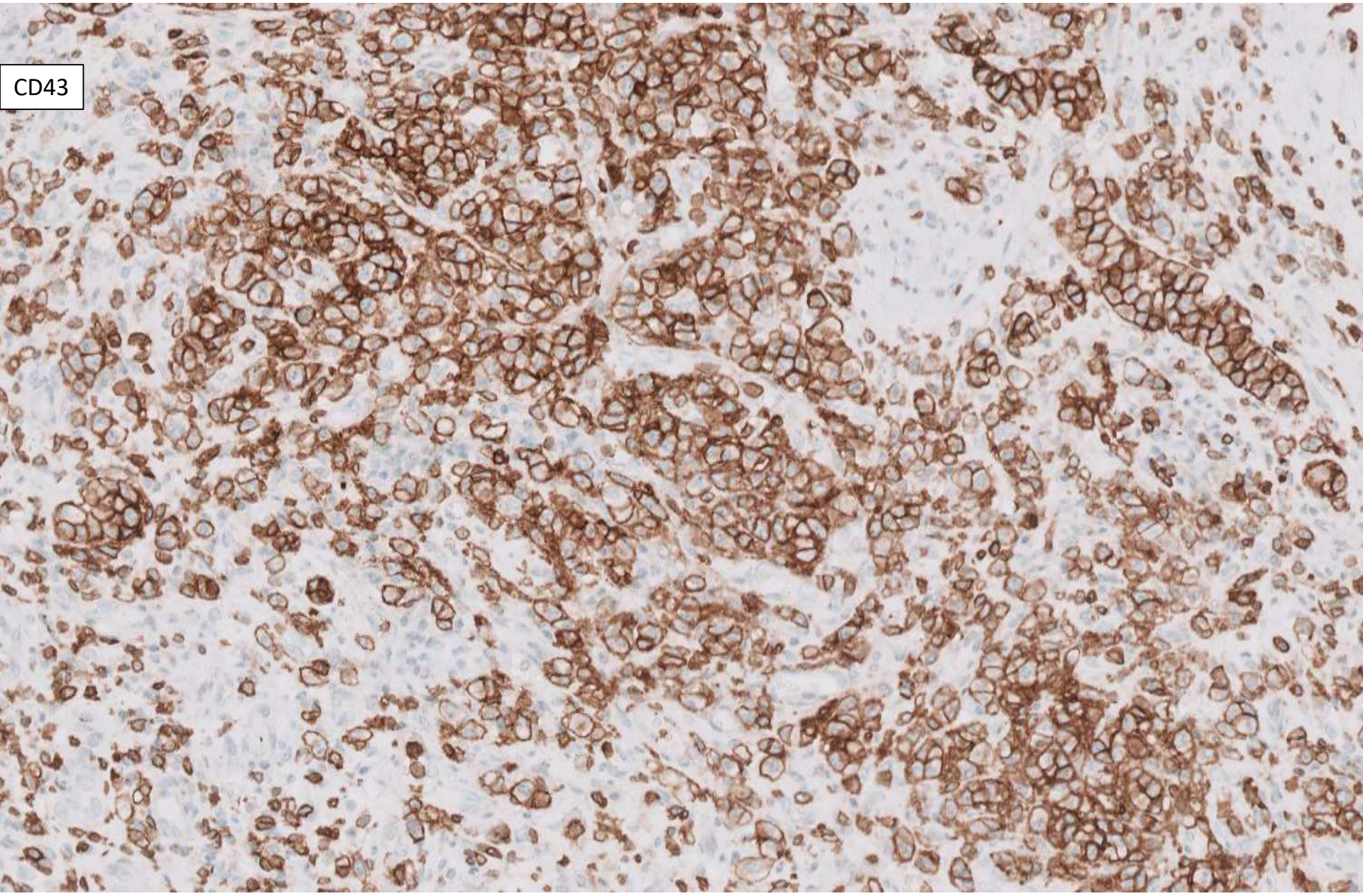
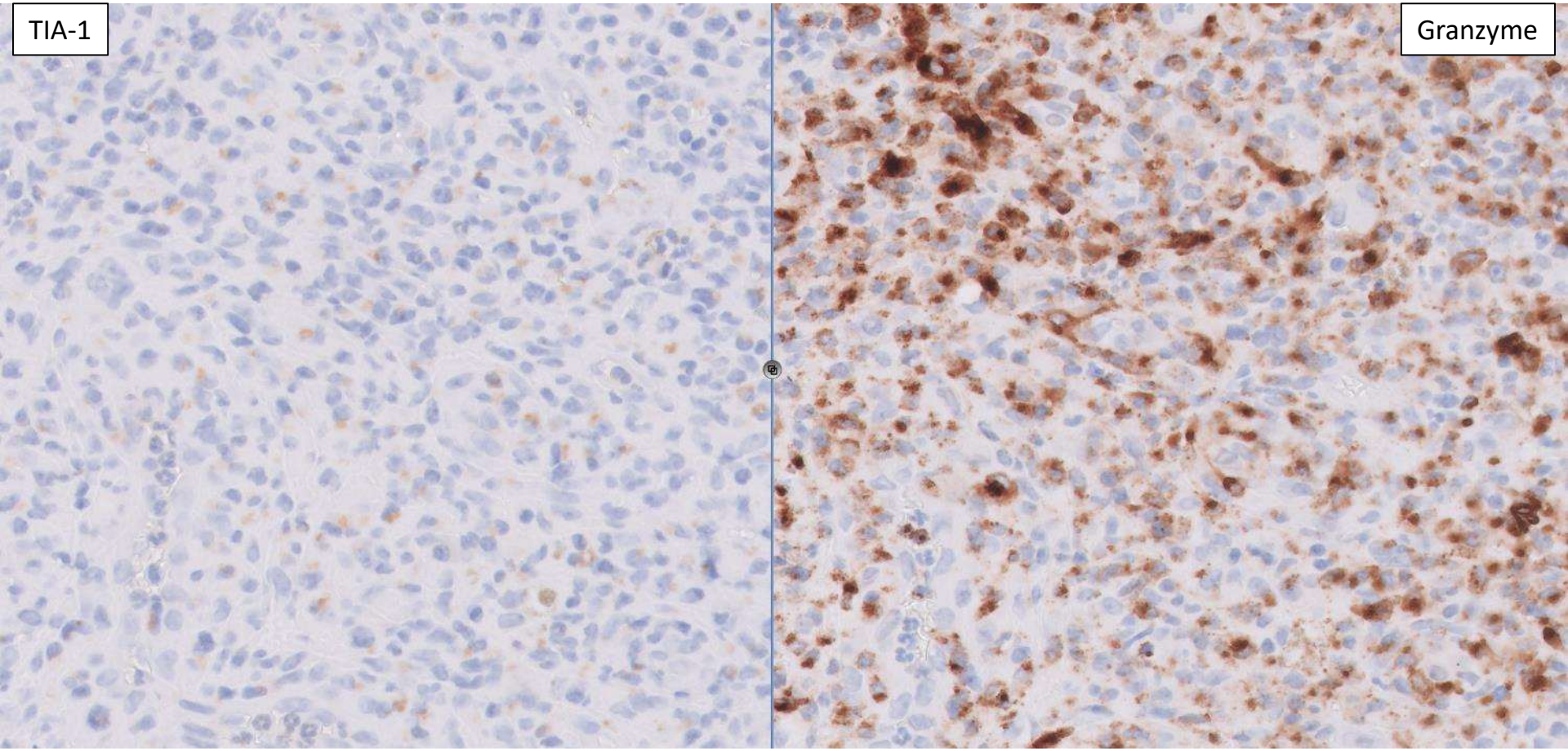
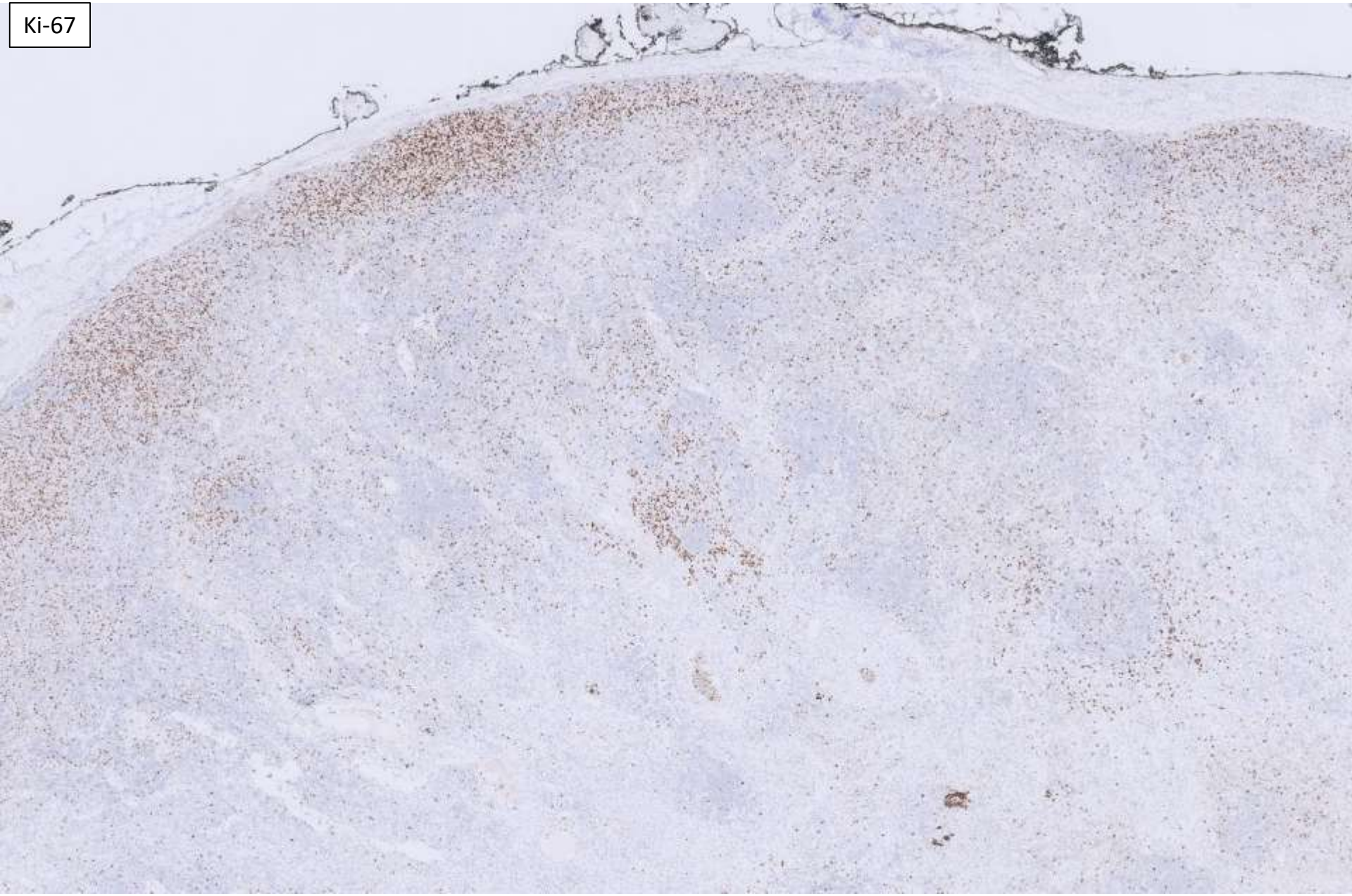

ALK
CD30

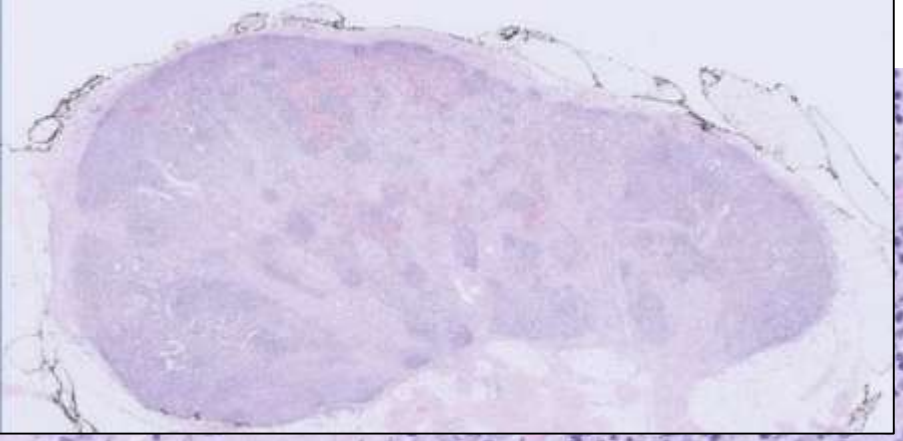

ALK: Cytoplasmic


CD43


TIA-1
Granzyme


Ki-67

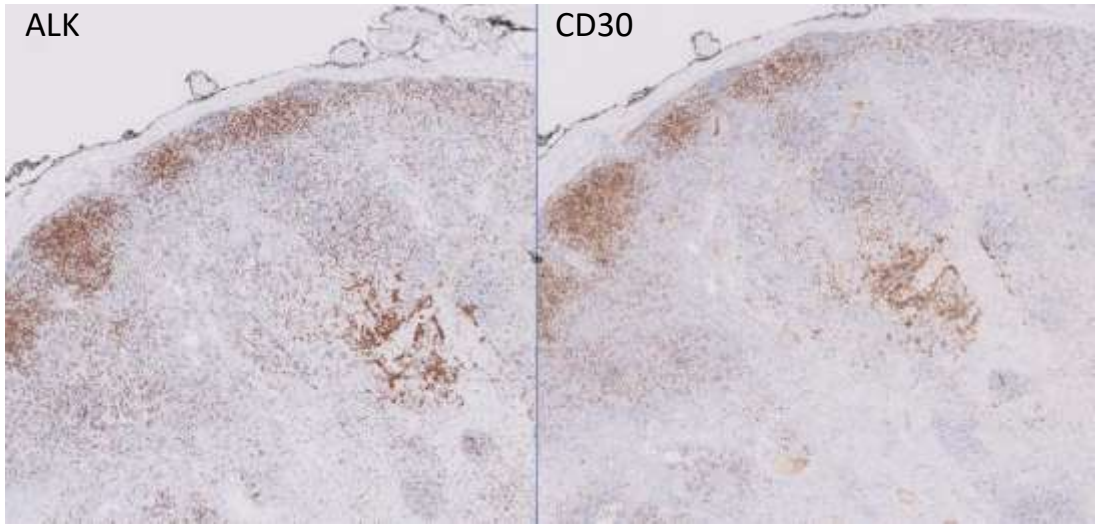
ALK+ Anaplastic Large Cell Lymphoma




ALK

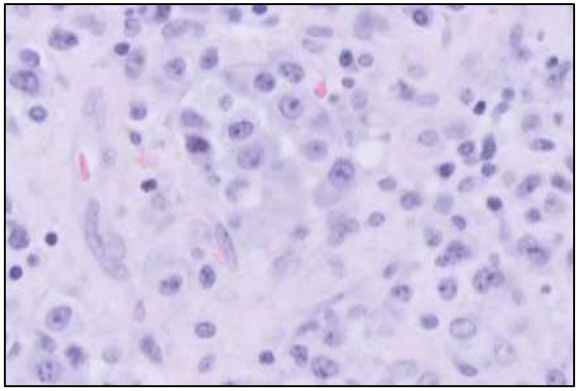
ALK-Positive Anaplastic Large Cell Lymphoma

- WHO Definition: CD30-positive mature T-cell lymphoma with aberrant expression of the Anaplastic Lymphoma Kinase (ALK) protein secondary to rearrangements of the *ALK* gene
- 10-15% of pediatric and adolescent NHL; median age of 34 years
  - Usually presents with systemic symptoms and in advanced stage
- Usually nodal:
  - Paracortical
  - Sinusoidal
  - Perifollicular
  - Intravascular
  - Diffuse



ALK-Positive Anaplastic Large Cell Lymphoma

- Histology / cytology:
  - “Hallmark Cells”: eccentrically-placed, large, horse-shoe shaped nuclei with multiple nucleoli with abundant amphophilic cytoplasm.
- Morphologic Patterns
  - Common (60% of cases)
  - Lymphohistiocytic
  - Small Cell
  - Hodgkin-like
  - Composite



Neoplasms with ALK Abnormalities

- Anaplastic Large Cell lymphoma
  - 70-80% NPM-ALK t(2;5)(p23;q35): Shows both **nuclear and cytoplasmic** ALK staining
  - Other translocation partners (e.g., TPM3, TPM4, TFG, ATIC, CLTC, MSN, ALO017, MYH9): more likely to be strictly **cytoplasmic**
- ALK+ Large B-cell lymphoma: A diffuse large B-cell lymphoma with plasmablastic immunophenotype
  - Translocation partners (e.g., CLTC, SQSTM1, NPM1, RANBP2, EML4, GORASP2, SEC31A)
  - Some plasmacytomas
  - Should be positive for CD138, MUM1, EMA, BOB.1, OCT-2
    - Might be positive for CD4 or CD43
    - Usually negative for PAX5, CD79a, CD30
- Inflammatory Myofibroblastic Tumor: Mesenchymal neoplasm with spindled myofibroblastic and fibroblastic cells and an inflammatory infiltrate
  - Translocation partners (e.g., IGFBP5, TPM3, TPM4, CLTC, CARS, ATIC, RANBP2)
- Epithelioid Fibrous Histiocytoma: Benign cutaneous neoplasm composed of epithelioid cells
  - Translocation of *SQSTM1-ALK* or *VCL-ALK*
- Carcinoma: NSCLC, Esophageal, Renal Cell, Renal Medullary, Breast, Colon, Neuroblastoma, Thyroid
- ALK+ Histiocytosis: Histiocytic neoplasm, usually with *KIF5B-ALK* rearrangements
  - Multisystem with systemic hematopoietic involvement: Infants with multisystemic disease (liver, spleen, marrow)
  - Multisystem, others: Older patients with multisystemic disease (two or more) – central and peripheral nervous system, bone, skin, lung
  - Patients with single system disease: CNS PNS, skin, breast, soft tissue
  - Positive for Histiocytic markers
  - Negative for CD30; Ki-67 typically low to moderate

Workup

- Immunohistochemistry:
  - Strong uniform expression of CD30
    - Helpful to include CD30 in one's arsenal of screening stains
  - ALK: Usually cytoplasmic and nuclear
  - Loss of T-cell associated antigens
    - CD3 negative in >75% of cases
    - CD2 and/or CD4 may be positive
    - CD43 and CD45RO
  - Cytotoxic markers
    - TIA-1
    - Granzyme B
    - Perforin
- If morphologically/immunophenotypically compatible with anaplastic large cell lymphoma, but ALK is negative:
  - *DUSP22* rearrangement (LEF1 expression, strong >75% of tumor cells)
  - *TP63* rearrangement (can stain for TP63)

Treatment and Prognosis

- ALK+ ALCL or possibly *DUSP22r*: Usually Brentuximab vedotin (anti-CD30) + cyclophosphamide, doxorubicin and prednisone (BV-CHP) x 6 cycles
  - Superior PFS to CHOP: 5/49 vs 16/49
  - Superior OS to CHOP: 4/49 vs 10/49
    - Side note: this study of BV-CHP on CD30+ T-cell lymphomas used 10% CD30+ cells as a cutoff

References

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2. Minoo P, et al. “ALK-immunoreactive neoplasms.” *Int J Clin Exp Pathol*. 2012; 5(5): 397-410.
3. Horwitz S, et al. “Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomized, phase 3 trial.” *Lancet*. 2019; 393(10168): 229-240.

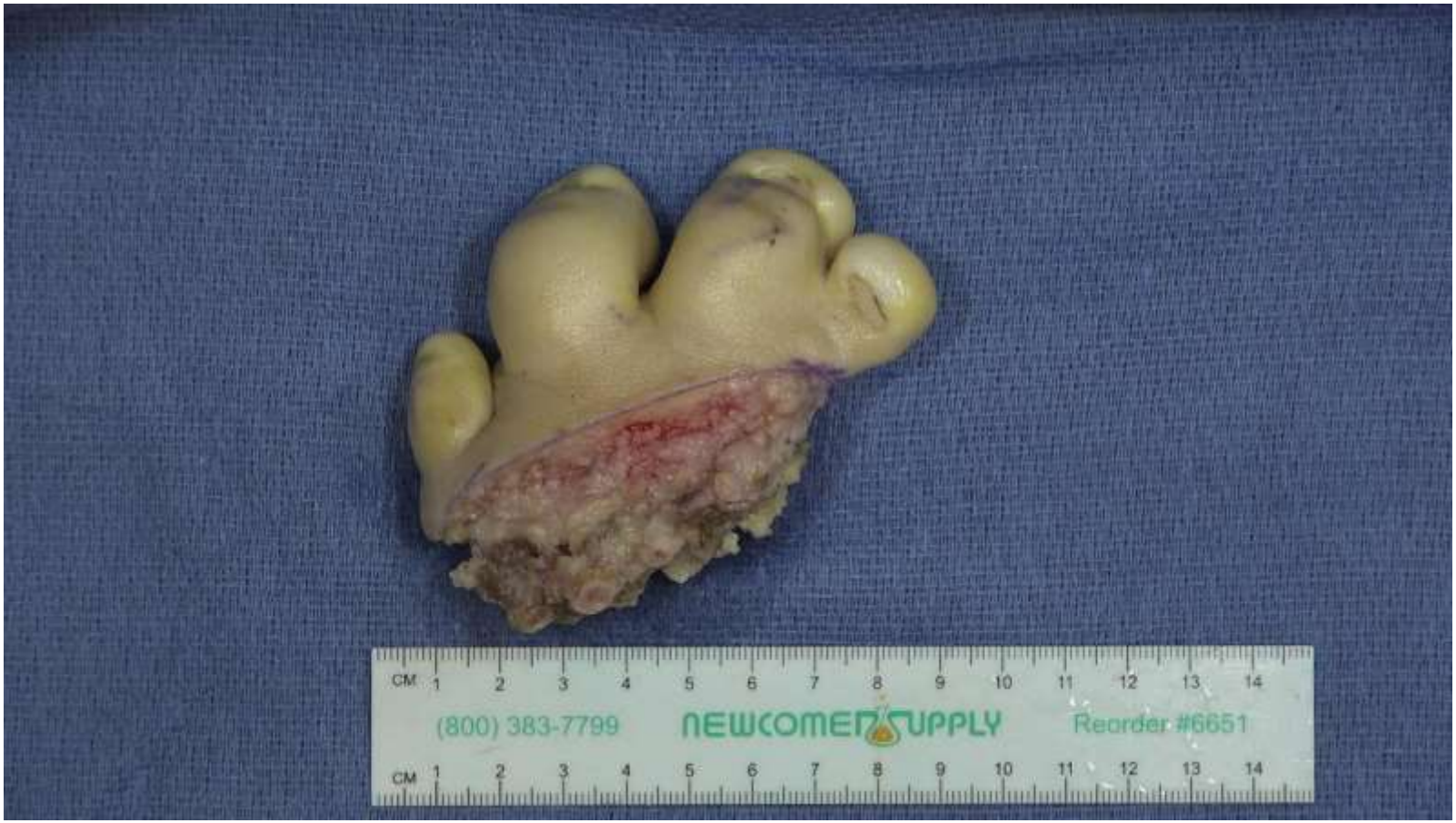
22-1105

Jiajie “George” Lu/Serena Tan; Stanford

Young infant female with macrodactyly of her left 2nd, 3rd, and 4th toes. She undergoes left foot amputation.

Clinical History

Two-year-old female with a partial amputation of the left foot. Gross description: “the 2nd, 3rd, and 4th toes with attached surrounding soft tissue appear enlarged and bulging.”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(800) 383-7799
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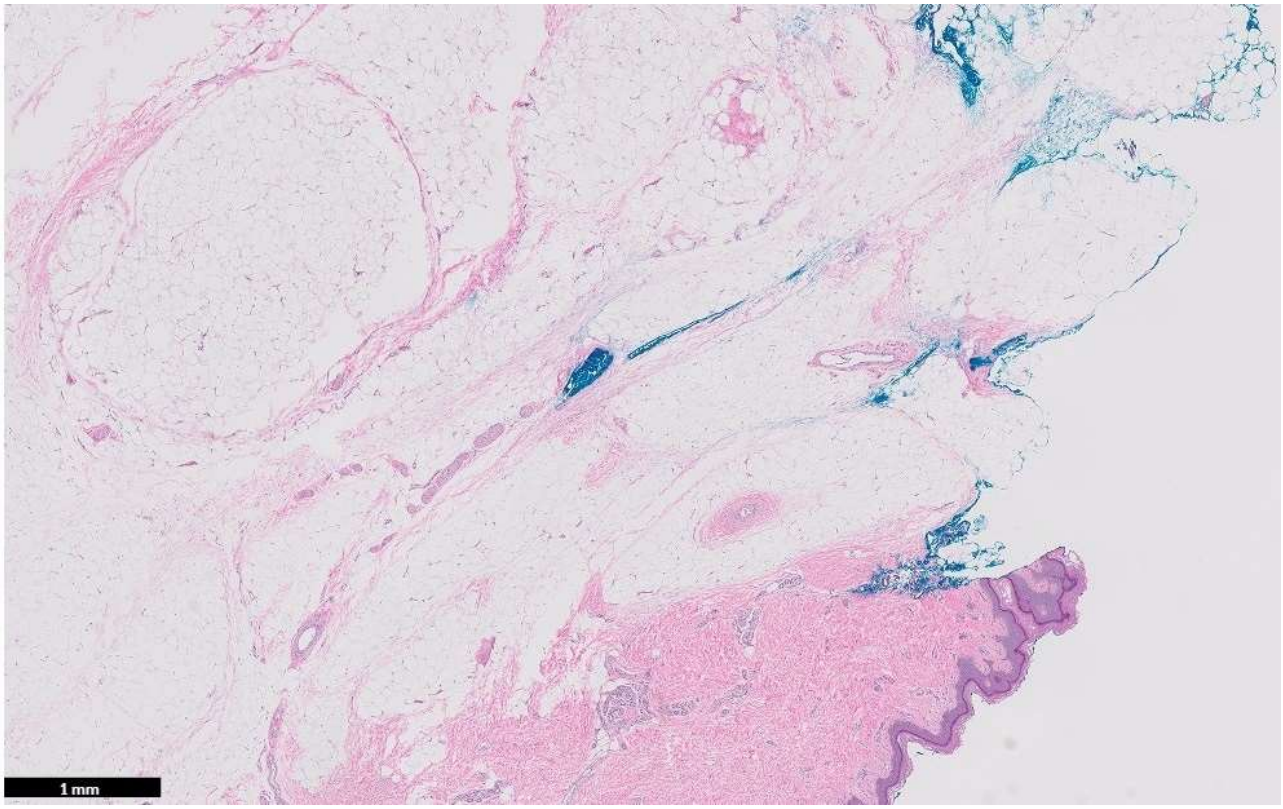
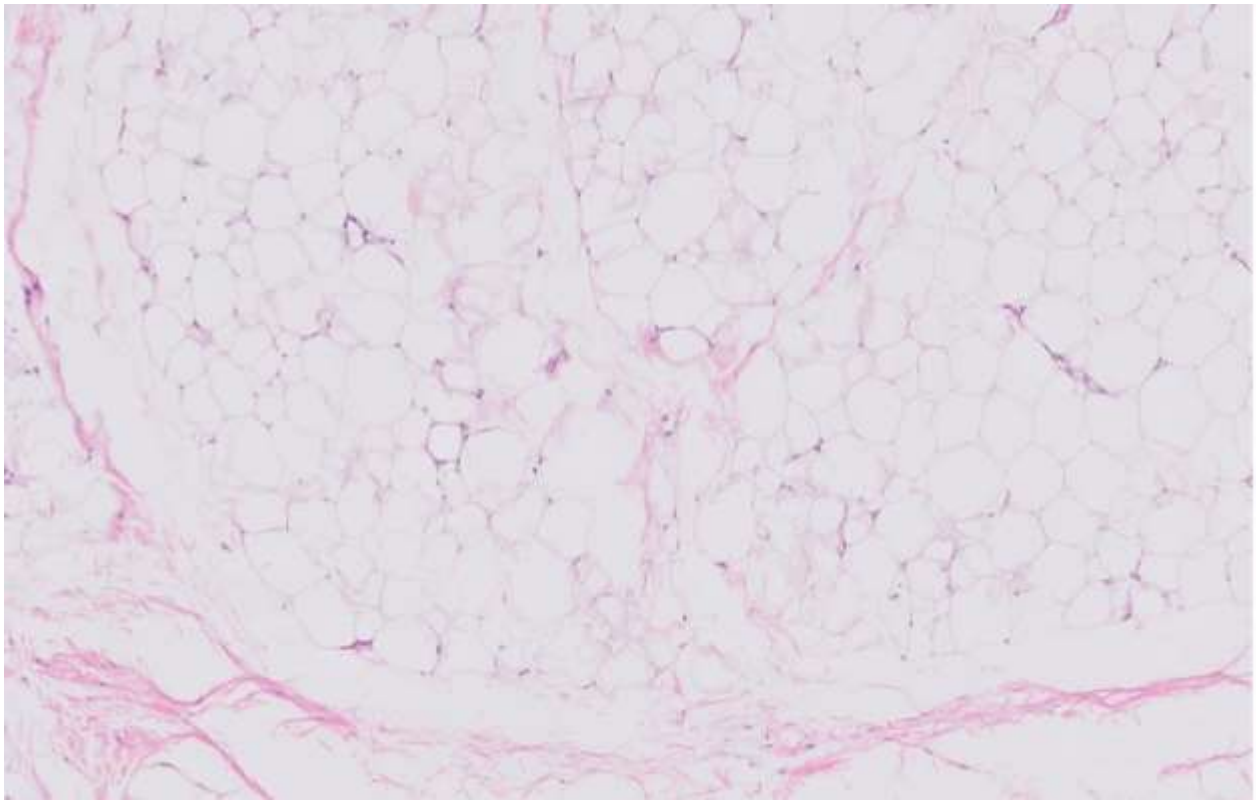
2nd toe, skin with soft tissue and resection margin



3rd toe soft tissue



Diagnosis

A. FOOT, LEFT, TRANSMETATARSAL AMPUTATION
-- CONSISTENT WITH SEGMENTAL OVERGROWTH (SEE COMMENT)

COMMENT: Gross examination reveals marked enlargement of the 2nd-4th toes and is consistent with the clinical history of macrodactyly of the 2nd, 3rd and 4th toes in the setting of overgrowth. Histologic sections of the underlying soft tissue show predominantly lipomatous overgrowth in the vicinity of the 2nd-4th toes. The bone at the specimen edge appear unremarkable.

Next Generation Sequencing showed a ***PIK3CA* mutation E545K, gain-of-function**

PIK3CA Overgrowth Syndrome

- Group of genetic disorders that lead to overgrowth of various body parts due to mutations in the *PIK3CA* gene
- Many named syndromes fall under this umbrella, with overlapping phenotypes
- *PIK3CA* mutation:
  - Gain of function *PIK3CA* leads to increased cell growth and division, especially in bone, soft tissue, and blood vessels.
  - Acquired somatic mutation. Germline *PIK3CA* mutation is embryonic lethal.
  - Usually mosaic: only certain body parts acquire the mutation.

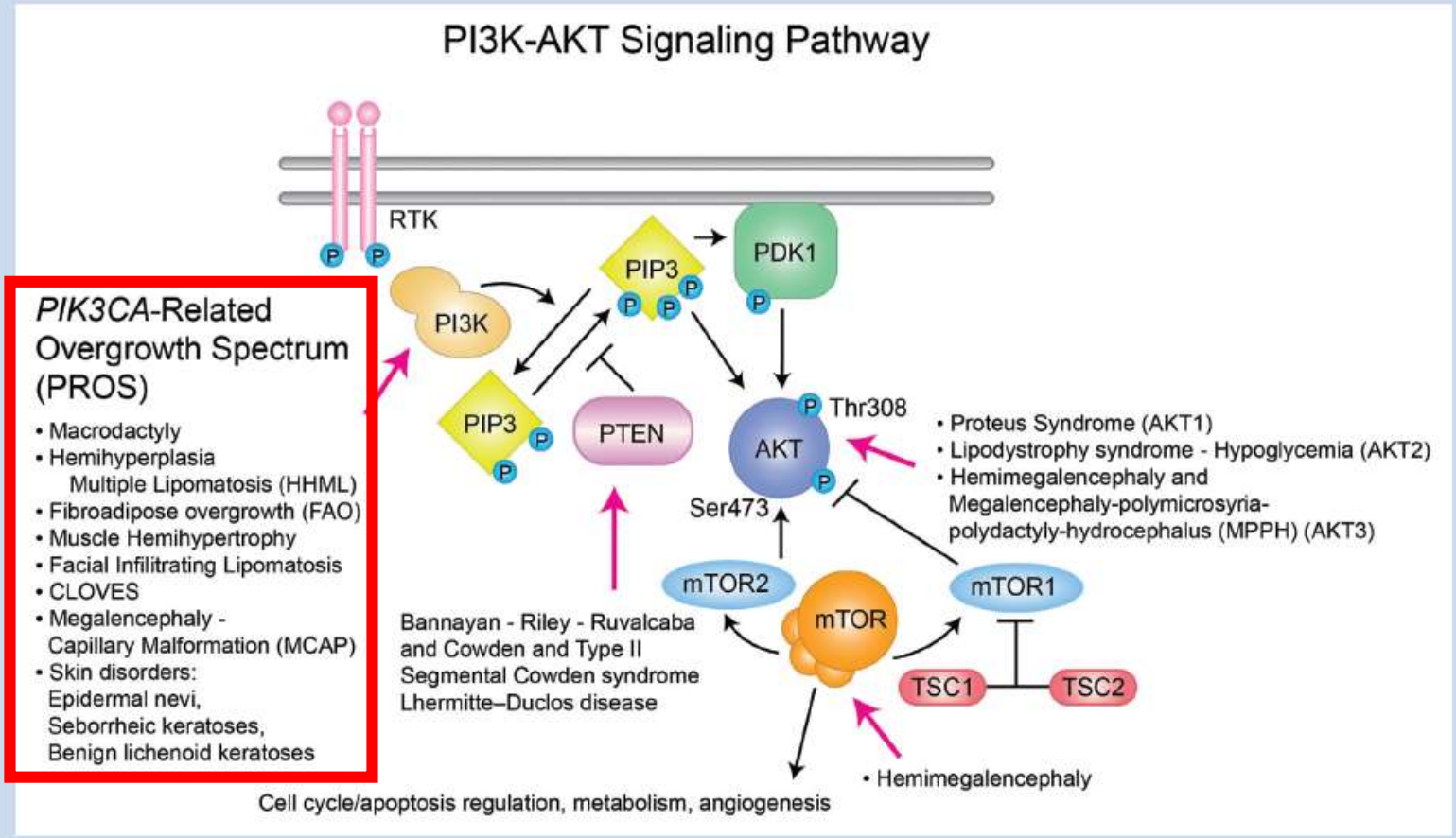


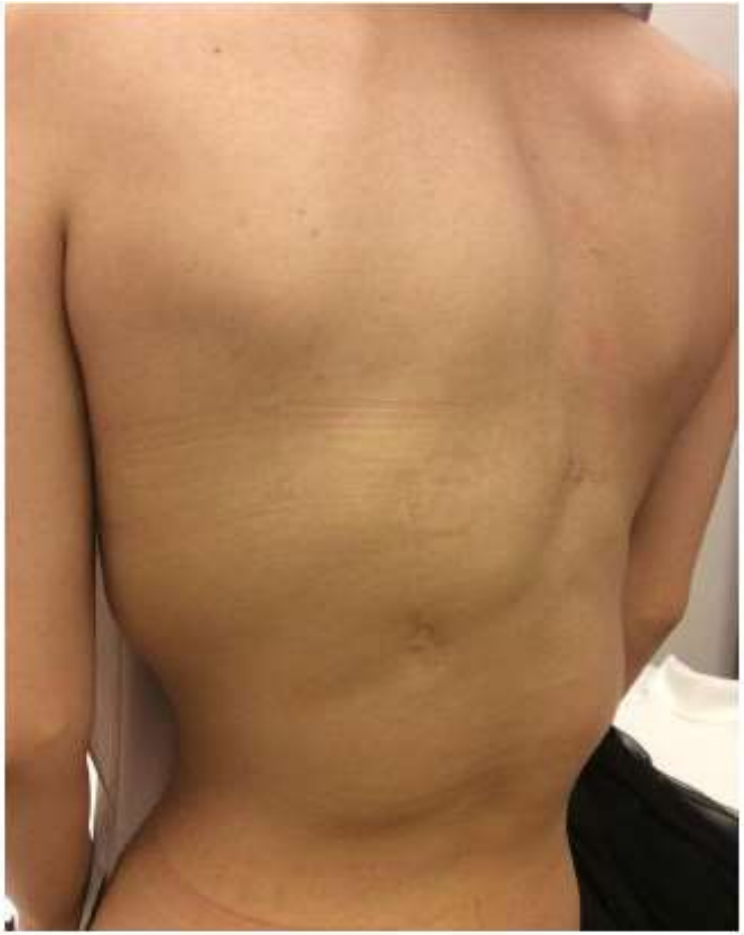
FIG. 1. PI3K-AKT Pathway and associated clinical overgrowth disorders.

Keppler-Noreuil KM et al. Am J Med Genet Part A 2015; 167: 287-295.

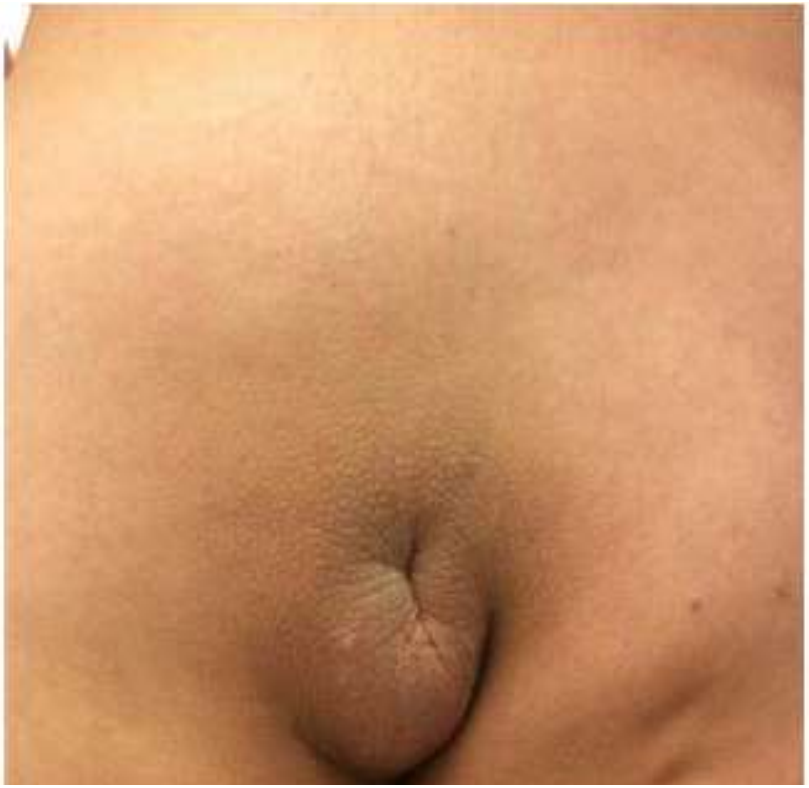
Example: CLOVES Syndrome

- Rare, sporadic (non-hereditary) mosaic overgrowth syndrome, first described in 2007
- Congenital Lipomatous Overgrowth
  - Lipomatous masses, asymmetric hemihypertrophy of trunk
  - Often covered with vascular malformations
- Vascular malformations
  - Solitary or multiple, localized or diffuse, superficial or deep, low- or high-flow
  - Capillary, venous, lymphatic, AV malformations
- Epidermal Nevi
  - Neck, abdomen, flank, limbs
- Spinal (scoliosis) and/or skeletal anomalies

Clinical, Cosmetic and Investigational Dermatology 2022; 15: 621-630

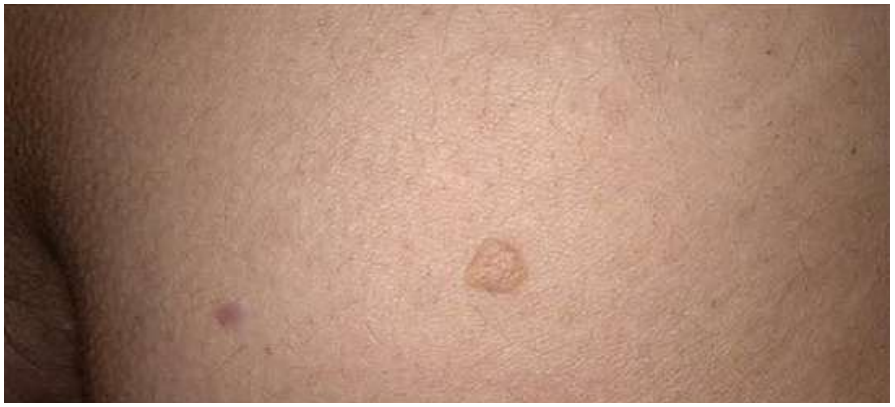


Left sided tumefaction and scoliosis

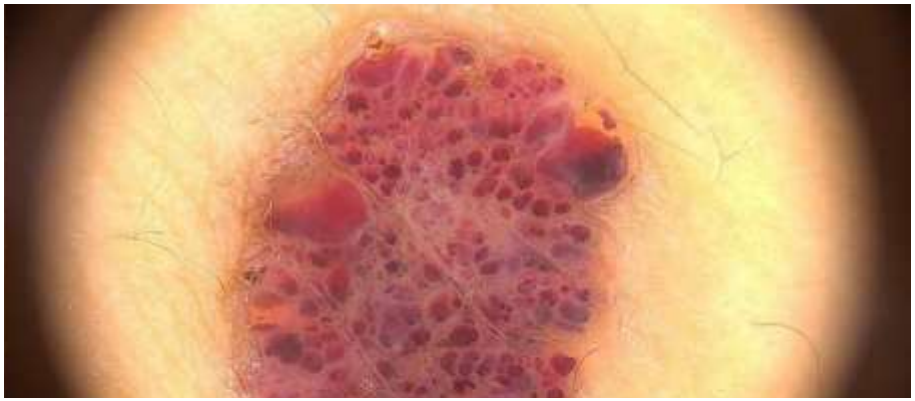


Sacral midline lipomatous mass

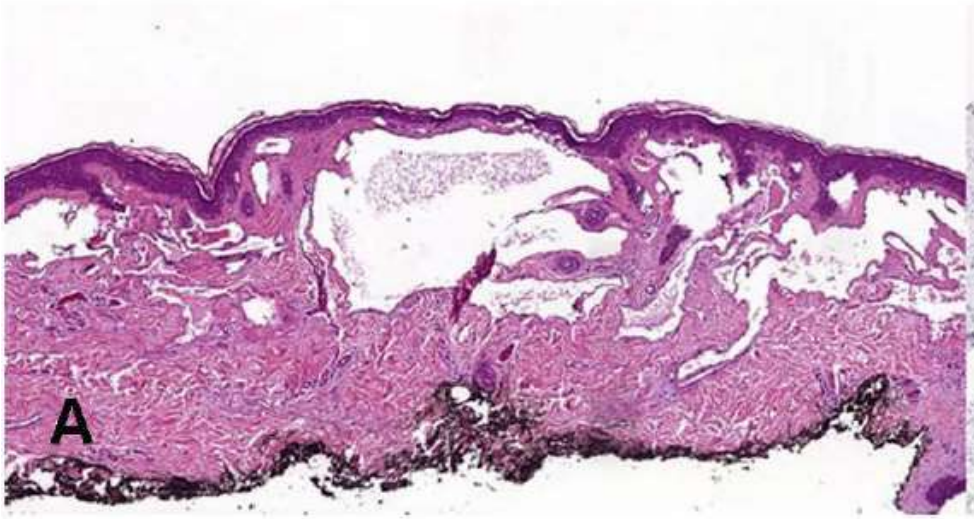
Clinical, Cosmetic and Investigational Dermatology 2022; 15: 621-630

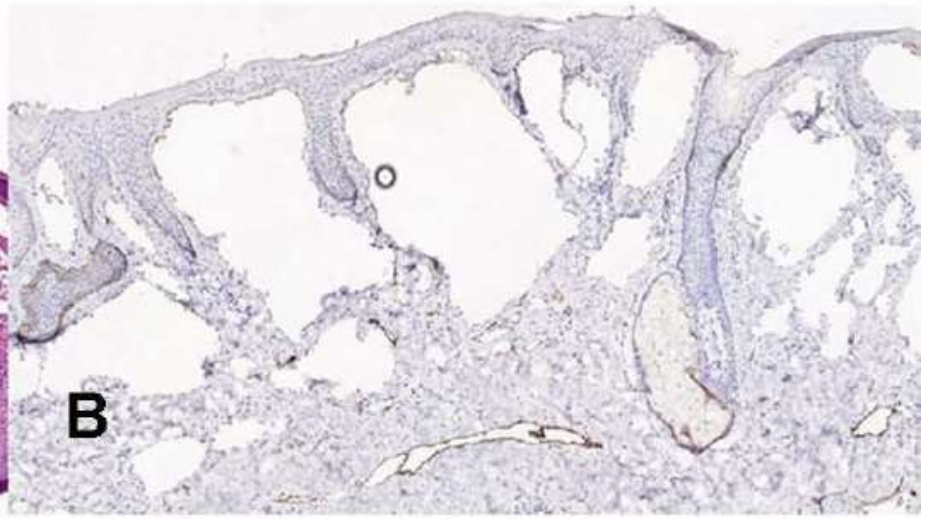


Translucent blister with clear fluid, indicating



Mixed capillary and lymphatic tumor





Dilated lymphatic channels within the upper dermis, positive for D2-40.

Clinical, Cosmetic and Investigational Dermatology 2022; 15: 621-630

Other Examples

- CLAPO[1]
  - Capillary malformation of lower lip
  - Lymphatic malformation on face/neck
  - Asymmetry
  - Partial/generalized Overgrowth
- Klippel-Trenauny Syndrome[2]
  - Capillary malformation on limb
  - Fused toes/fingers
  - Vascular malformations of stomach, rectum, liver, bladder, kidneys, lungs
  - Hypertrophy of a limb

1. Genet Med 2018; 20: 882-889.
2. J Vasc Surg Venous Lymphat Disord. 2017; 5: 587-595.

Example: Klippel Tremauney

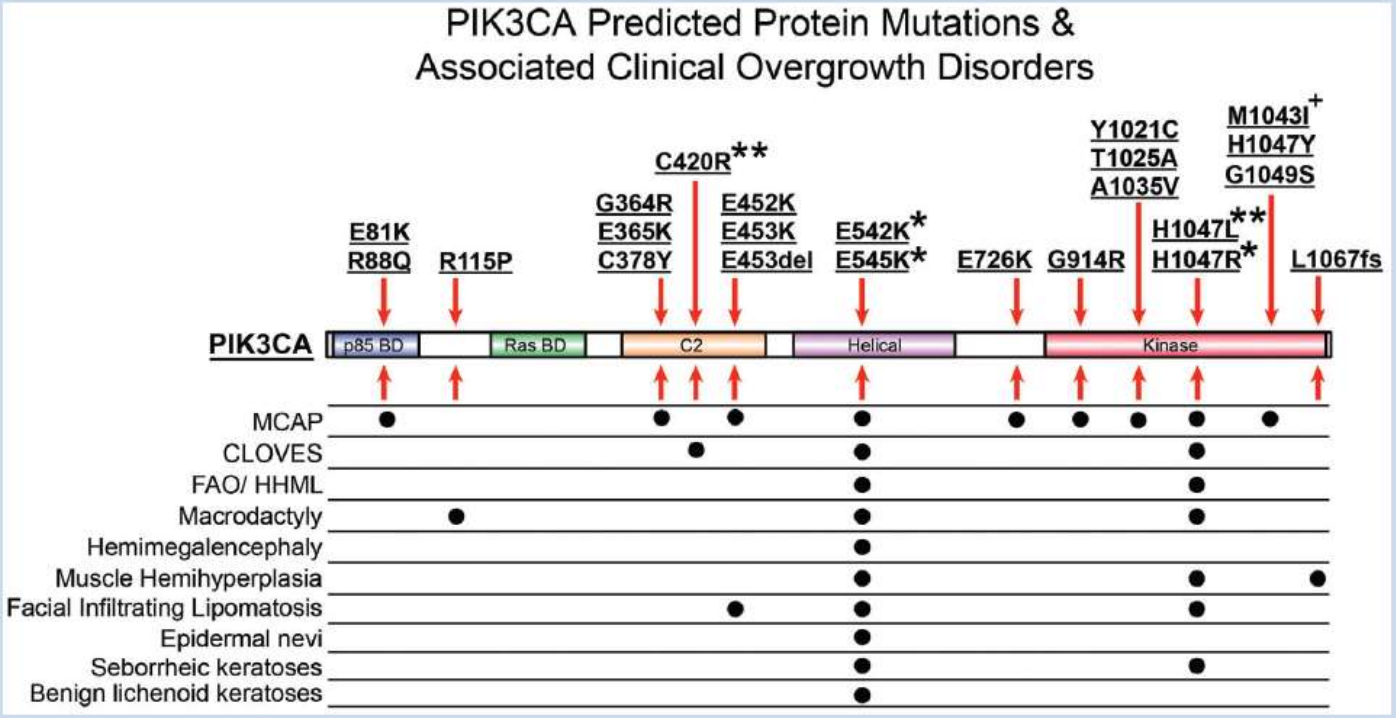


FIG. 2. *PIK3CA*-Related Overgrowth Spectrum (PROS). PIK3CA predicted protein mutations and associated clinical overgrowth disorders discovered to date. Oncogenic potency: *Hot spot mutations, **Strong mutations, and +Intermediate [Gymnopoulos et al., 2007].

Keppler-Noreuil KM et al. Am J Med Genet Part A 2015; 167: 287-295.

PIK3CA in Malignancy[1]

- Frequently mutated in various malignancies
  - 30% of breast cancers (more commonly in ER/PR positive and HER2 positive)
  - 25% of endometrial cancers
  - 10-30% colorectal carcinomas
  - 15% head and neck cancers
  - 10% squamous non-small cell lung cancers
  - Amplifications are also common
- PI3K inhibitors have undergone trials, however had notable to severe side effects
- PROS patients can develop Wilms tumor, but do not appear to have increased epithelial cancer risk[2]

1. Trends Mol Med. 2018; 24: 856-870.
2. Semin Cancer Biol. 2019; 59: 36-49.

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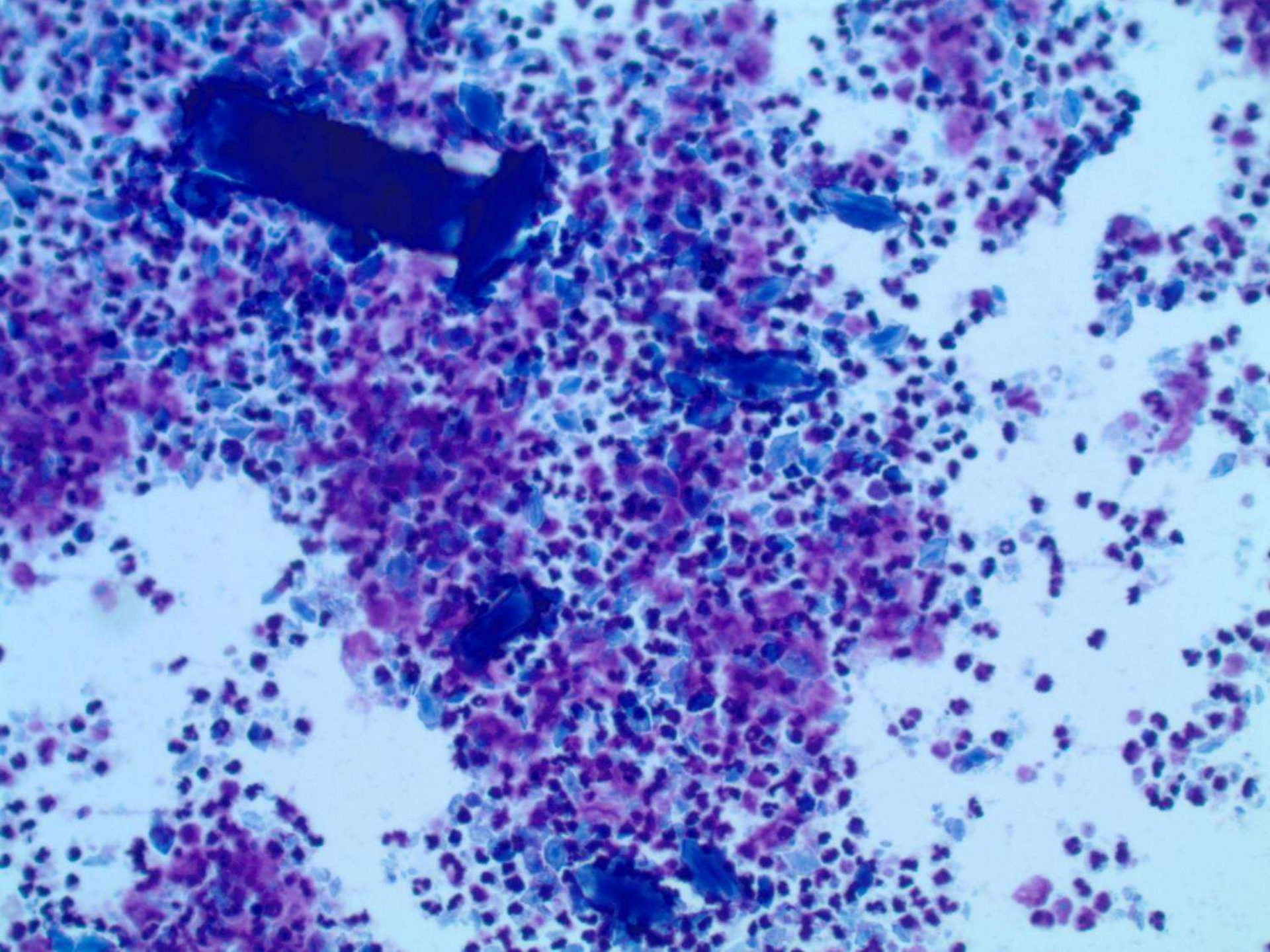
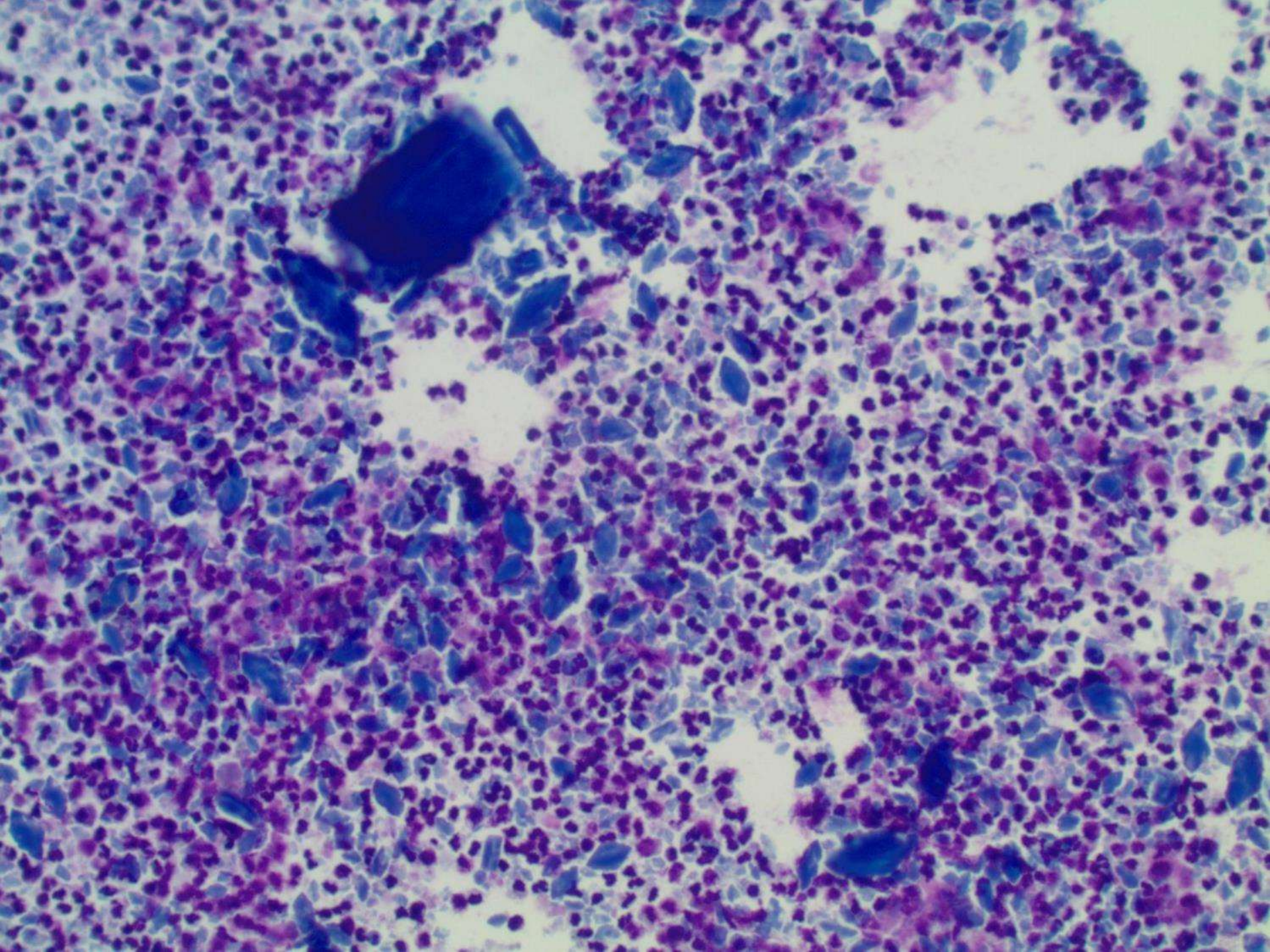
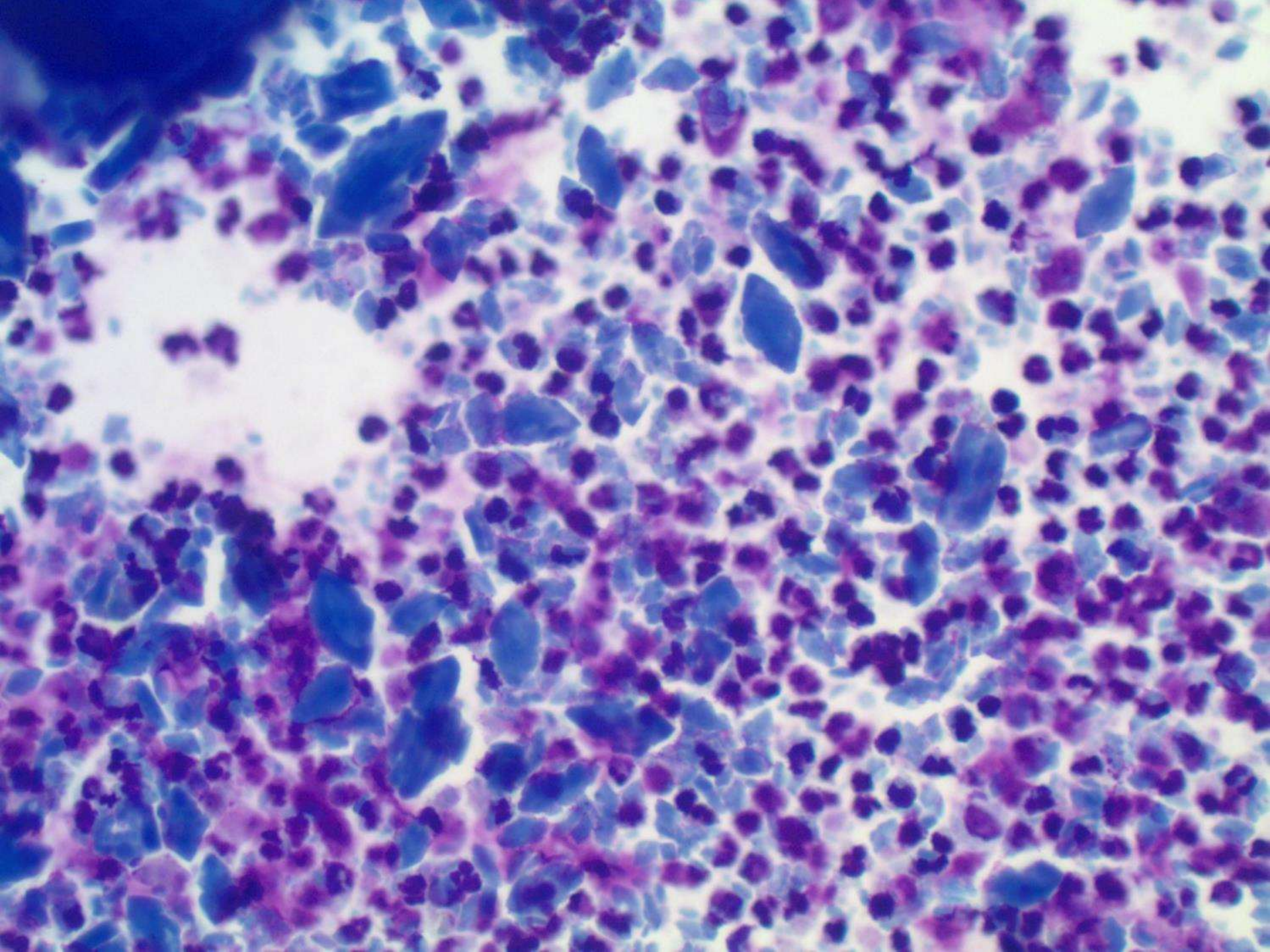
22-1106

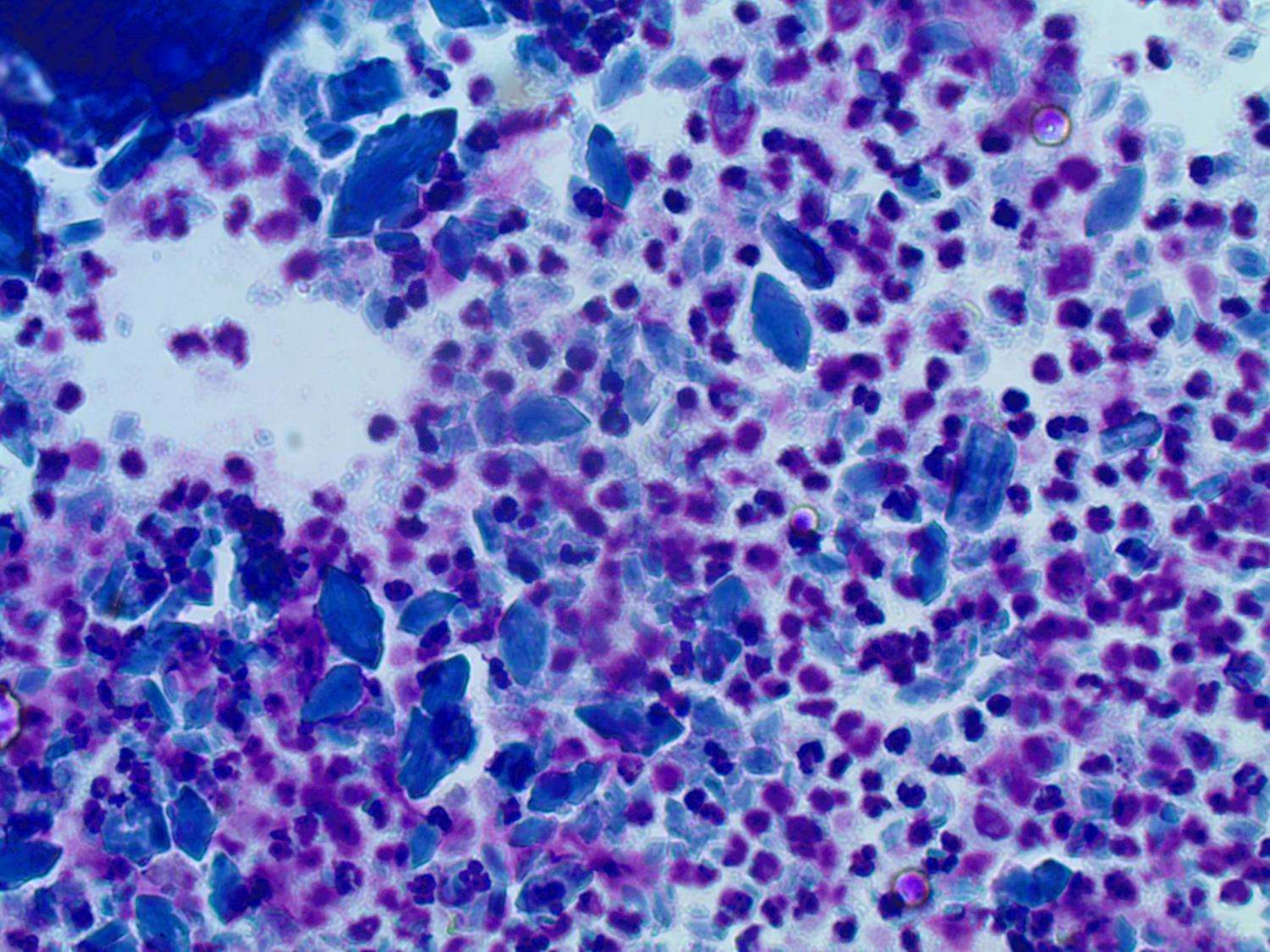
Ankur Sangoi; El Camino Hospital

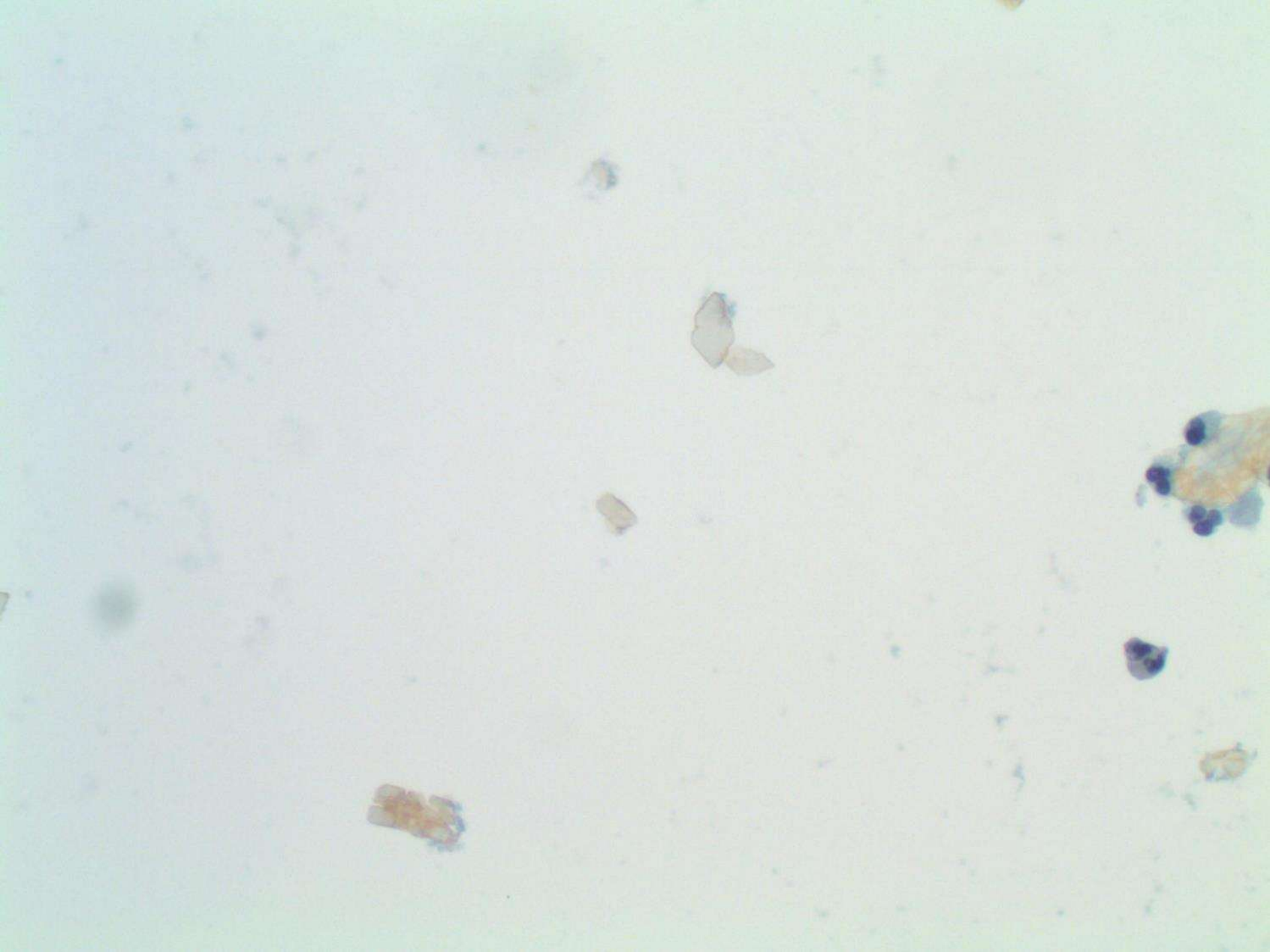
90ish F with neck mass. FNA performed. Probable diagnosis?

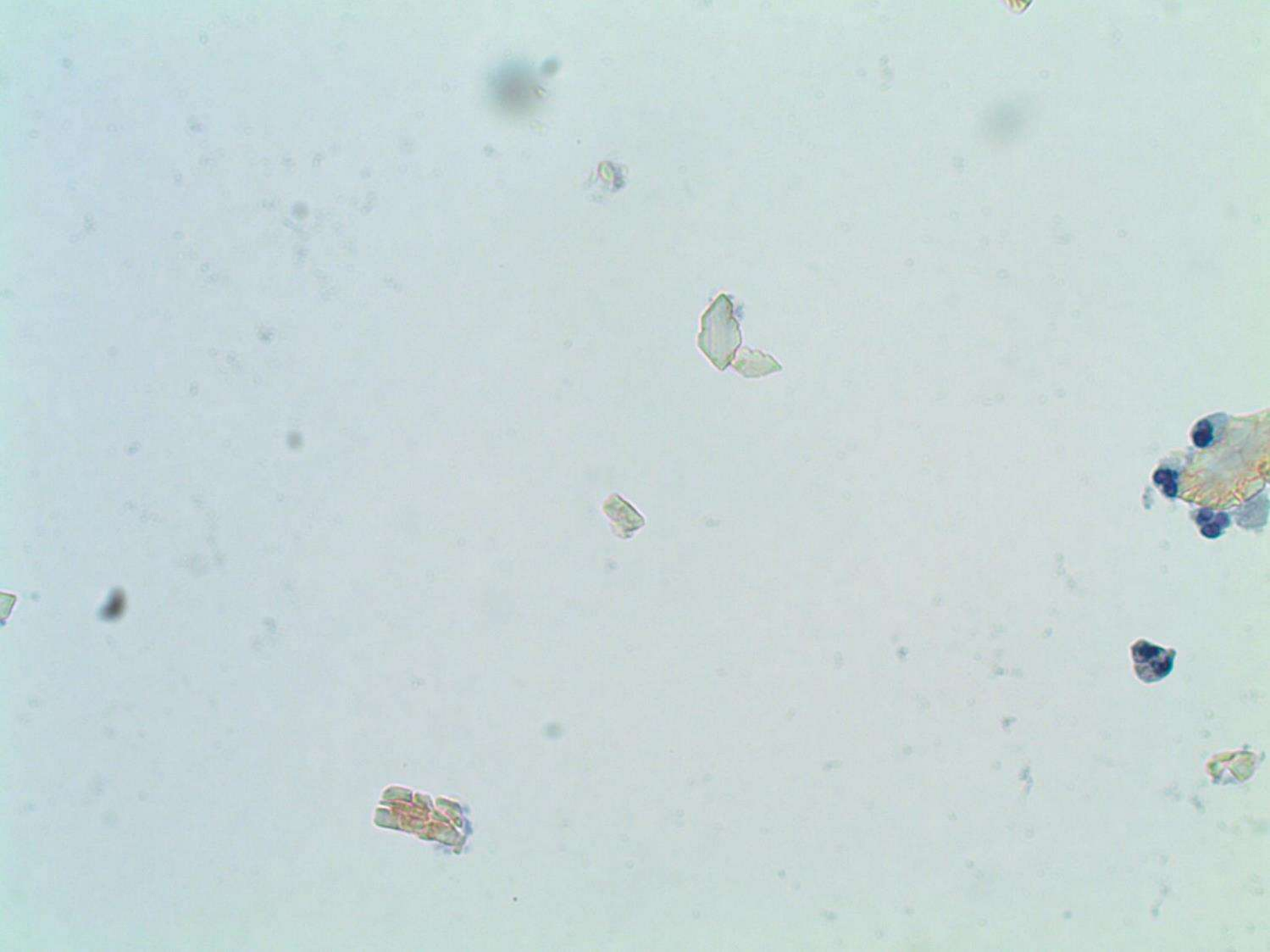


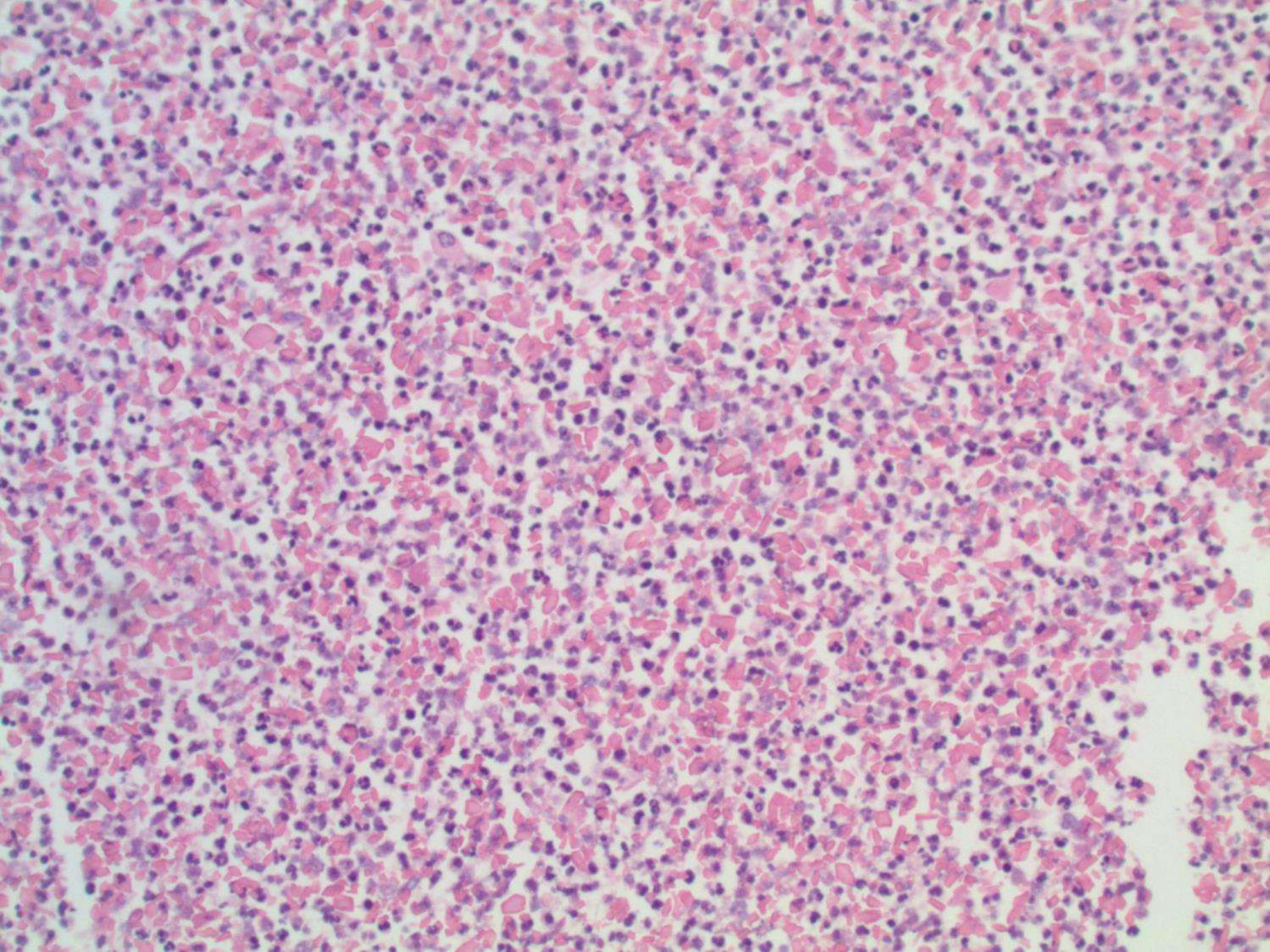


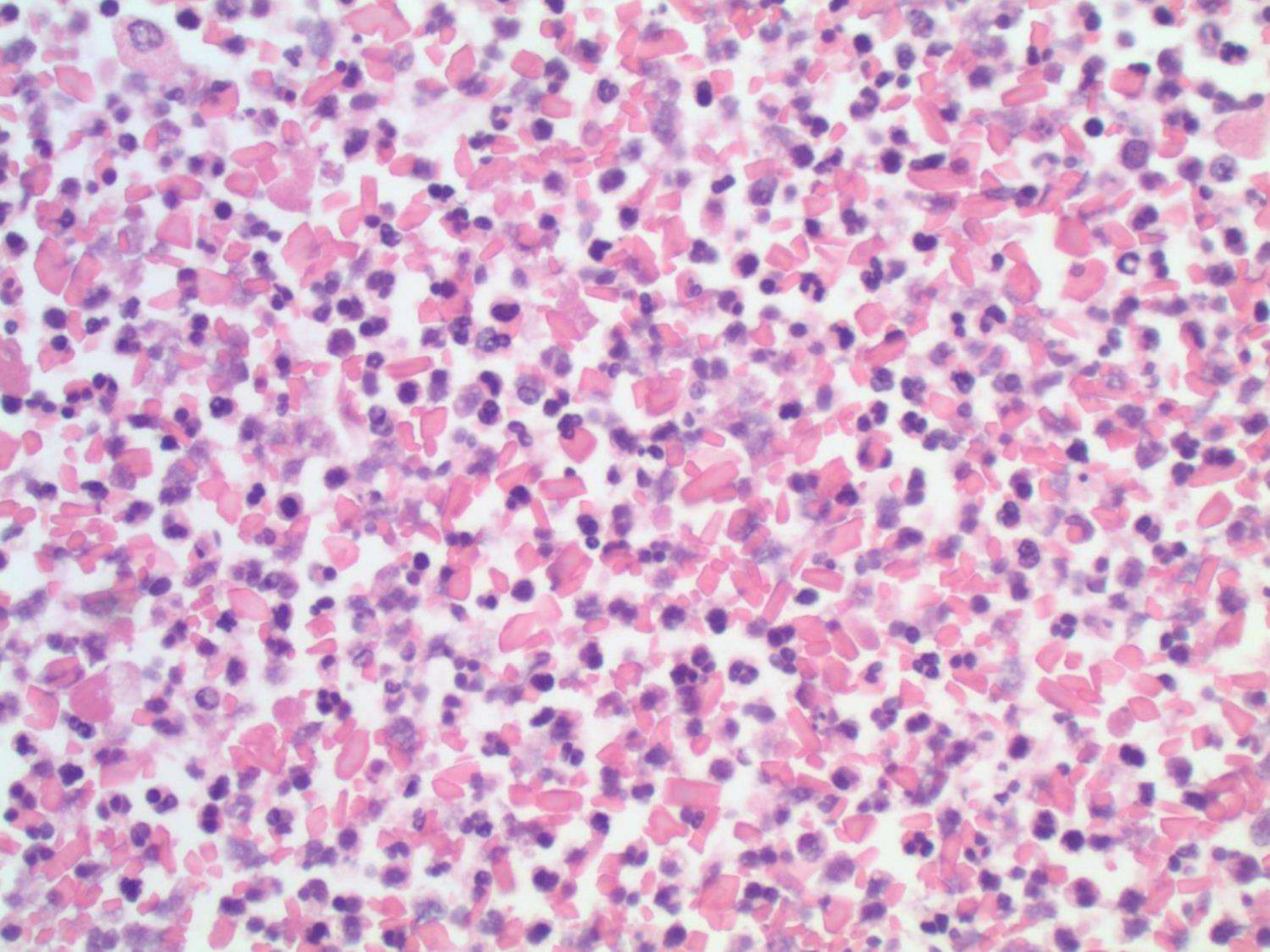












DDx

- **Abscess, NOS**
- **Abscess + amylase crystals**
  - s/o sialoadenitis
- **Abscess + tyrosine crystals**
  - s/o salivary gland neoplasm

Review Article

Crystals and crystalloids in cytopathology: Incidence and importance

Vanda F. Torous, MD[1]; Leslie G. Dodd, MD[2]; Patrick J. McIntire, MD[3]; and Xiaoyin Sara Jiang, MD[4]

Many crystals and crystal- like structures may be encountered in cytopathology practice and can represent both beautiful novelties and diagnostic aids. The authors present an organ- specific review of the published literature on crystals combined with personal experiences. The purpose is not only to serve as a reference guide by highlighting the clinical and morpho-logic features of crystals, crystalloids, and crystal- like structures but also to review their significance and to offer reporting strategies in cases that bear management implications. ***Cancer Cytopathol* 2022;130:759-770**. *© 2022 American Cancer Society.*

DIAGNOSIS

- **Abscess + amylase crystals**
  - s/o sialoadenitis

  (turns out: “neck” FNA actually from submandibular gland area)

SALIVARY GLAND CRYSTALS

- **Amylase**
  - Needle-like, rhomboid
  - Orange on Pap, blue on DQ
  - Often associated with cystic lesions
    - Usually non-neoplastic
      - Duct obstruction, sialadenitis, cysts
    - Have been assoc w/Warthin tumor
      - Benign!

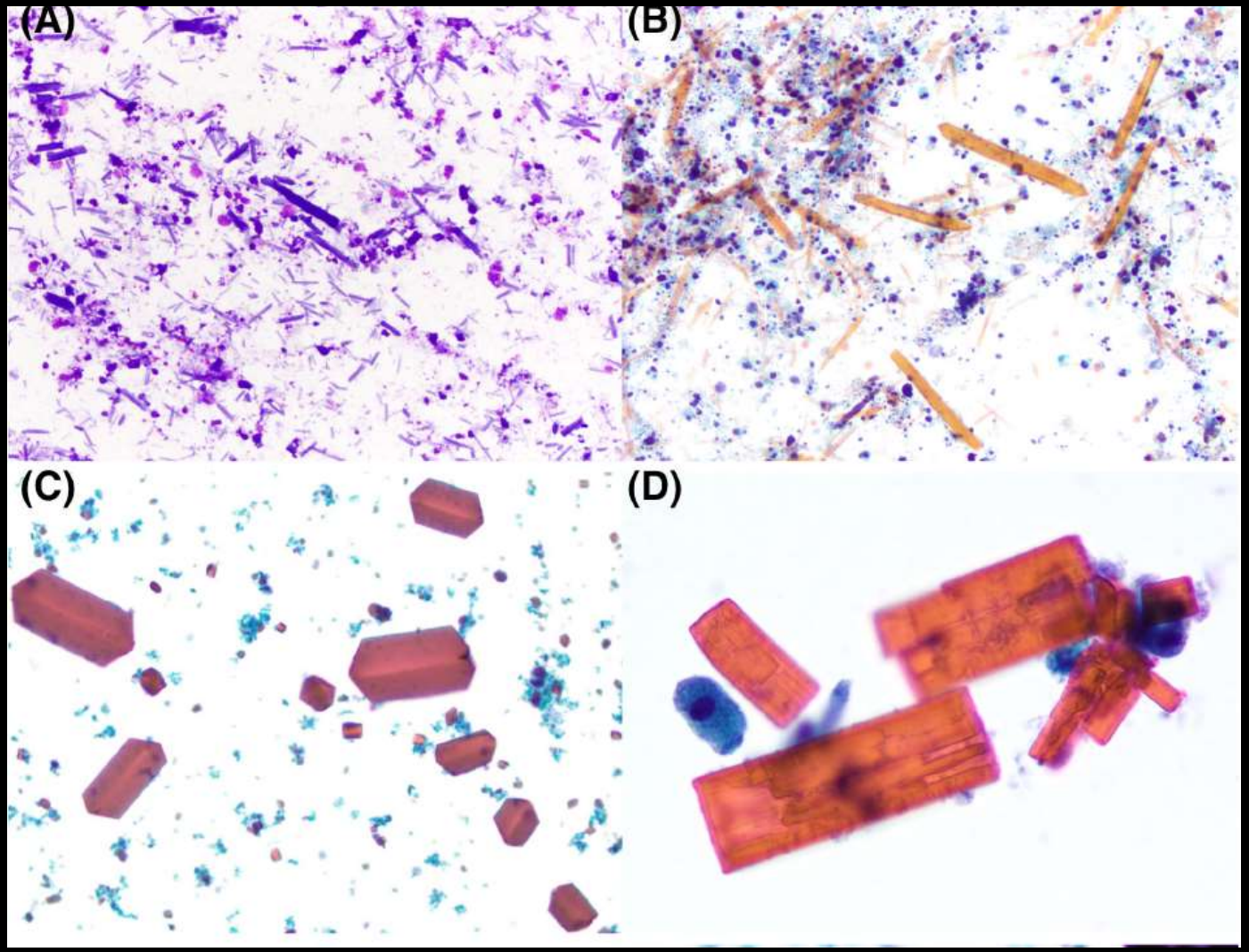


Figure 1. Examples of amylase crystalloids identified on (A) Diff Quik-stained air-dried aspirate smears, (B) Papanicolaou (Pap)-stained alcohol fixed aspirate smears, and Pap-stained liquid-based preparations including (C) SurePath and (D) ThinPrep. Amylase crystalloids appear deep blue on Romanowsky type stains such as Diff Quik and appear orange on Pap-stained preparations.

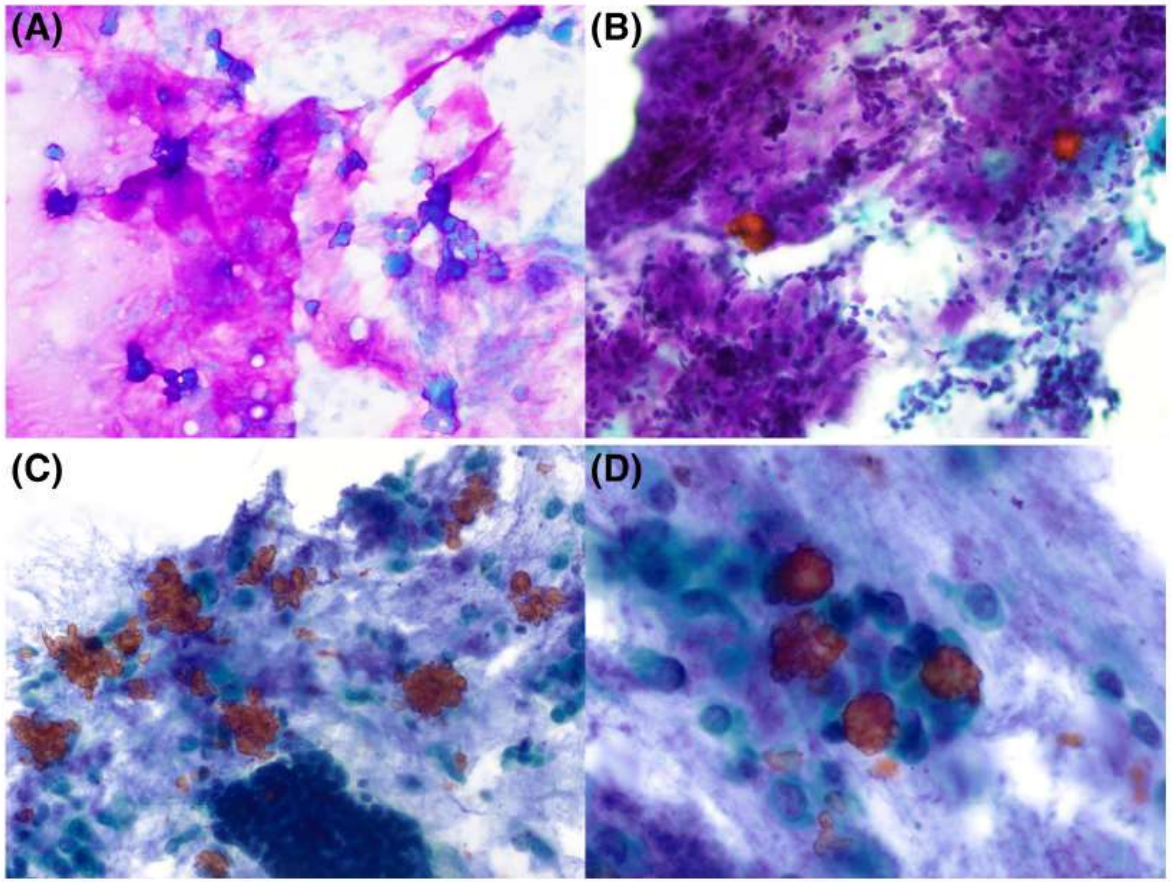


Figure 3. Tyrosine crystalloids identified on Diff Quik stained air-dried aspirate smear (A) and Papanicolaou (Pap)-stained alcohol fixed aspirate smears (B-D). Tyrosine crystalloids appear deep blue on Romanowsky type stains and orange on Pap-stained preparations. They have a floret appearance and are usually associated with neoplastic processes (pleomorphic adenoma in each of the pictured cases).

SALIVARY GLAND CRYSTALS

- **Tyrosine**
  - Floret or rosette-like
  - Orange on Pap, basophilic on DQ
  - Often associated with stromal elements of neoplastic processes
    - Usually benign tumors (typically PA)
    - But can occur in malignancy

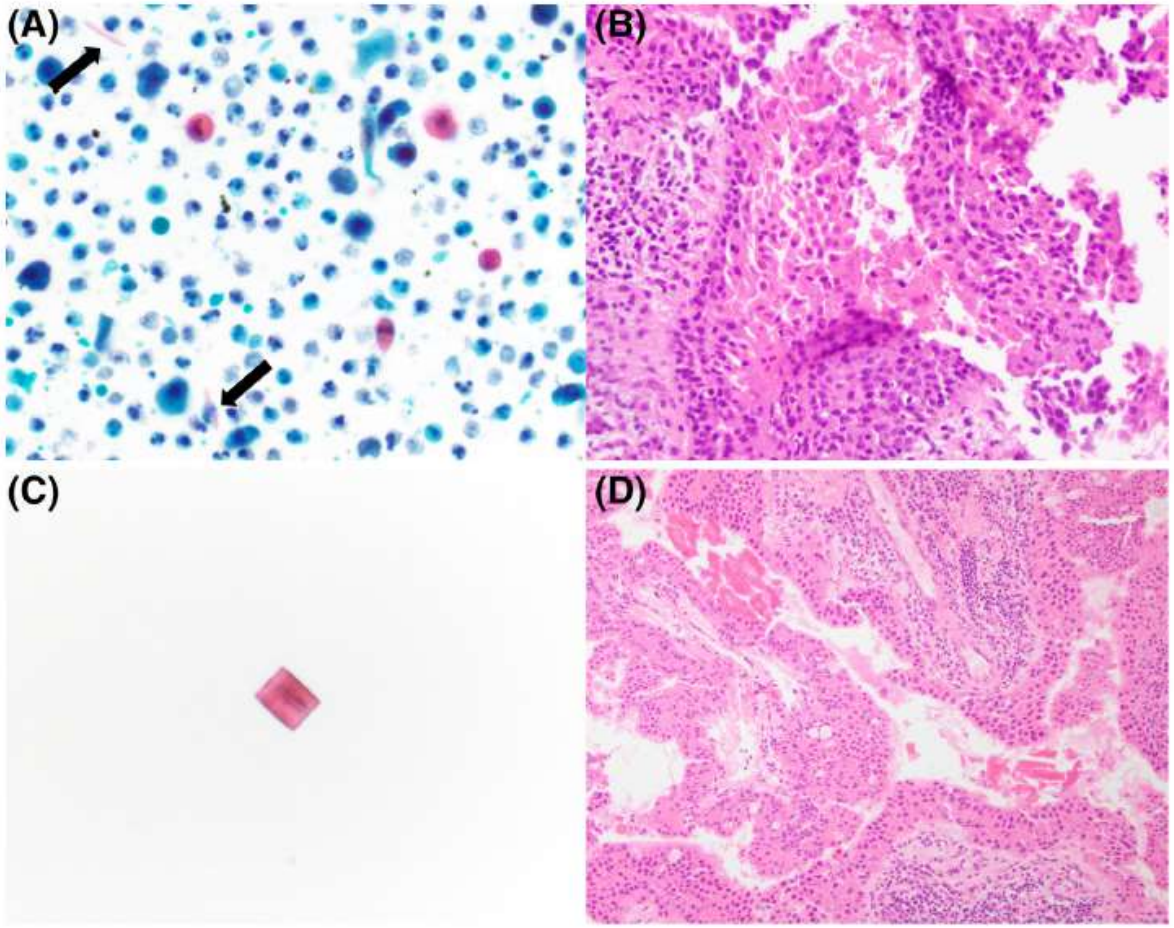


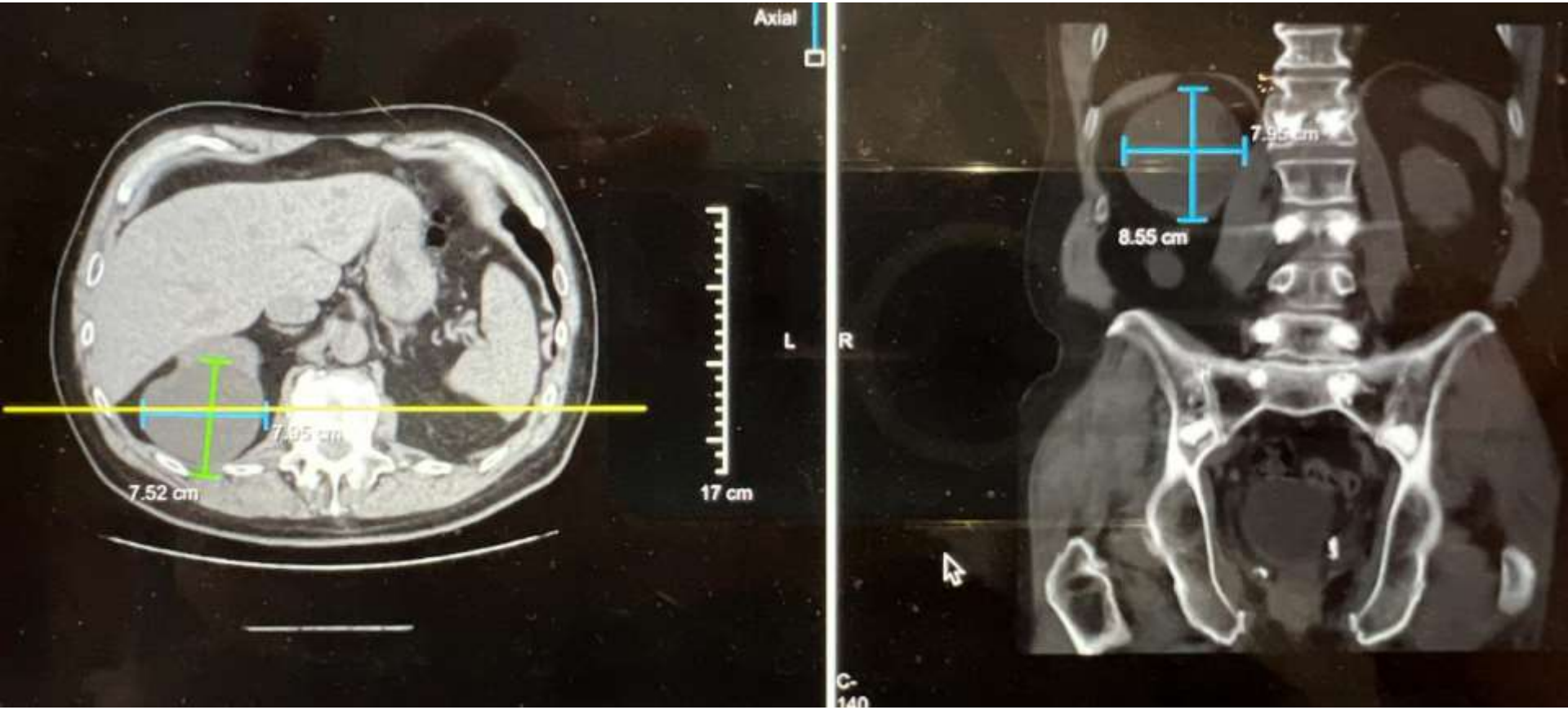
Figure 2. (A and B) Identification of amylase crystalloids (arrows) can be a helpful clue when concerning findings such as atypical squamoid cells are present and caution should be exercised as they have only been found to be associated with benign nonneoplastic and benign neoplastic lesions to date. This case was from a Warthin tumor with squamous metaplasia. (C and D) When amylase crystalloids are found in a background of inflammation and without epithelial cells to suggest a neoplastic process, a category of nonneoplastic rather than nondiagnostic is most appropriate. In cases where the material overall is scant but amylase crystalloids are present, notation of this finding may be helpful in preventing additional unnecessary procedures as they have been found in association with only benign lesions. Clinical correlation is needed as they may be associated with benign neoplasms, and specifically Warthin tumor. In this case, the fine-needle aspiration was extremely scant and only showed rare amylase crystalloids. The follow-up excision showed a Warthin tumor with abundant amylase crystalloids.

TAKE HOME POINTS

- **Finding amylase crystals is reassuring of benign process**
  - Benign non-neoplastic condition
  - Benign neoplastic lesion
  - Especially helpful if background atypical squamoid cells present
- **Can turn a “nondiagnostic” case to “nonneoplastic”!**

22-1107

80ish M with 8cm cystic renal mass. DDx and procedure off the gross specimen?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17 cm
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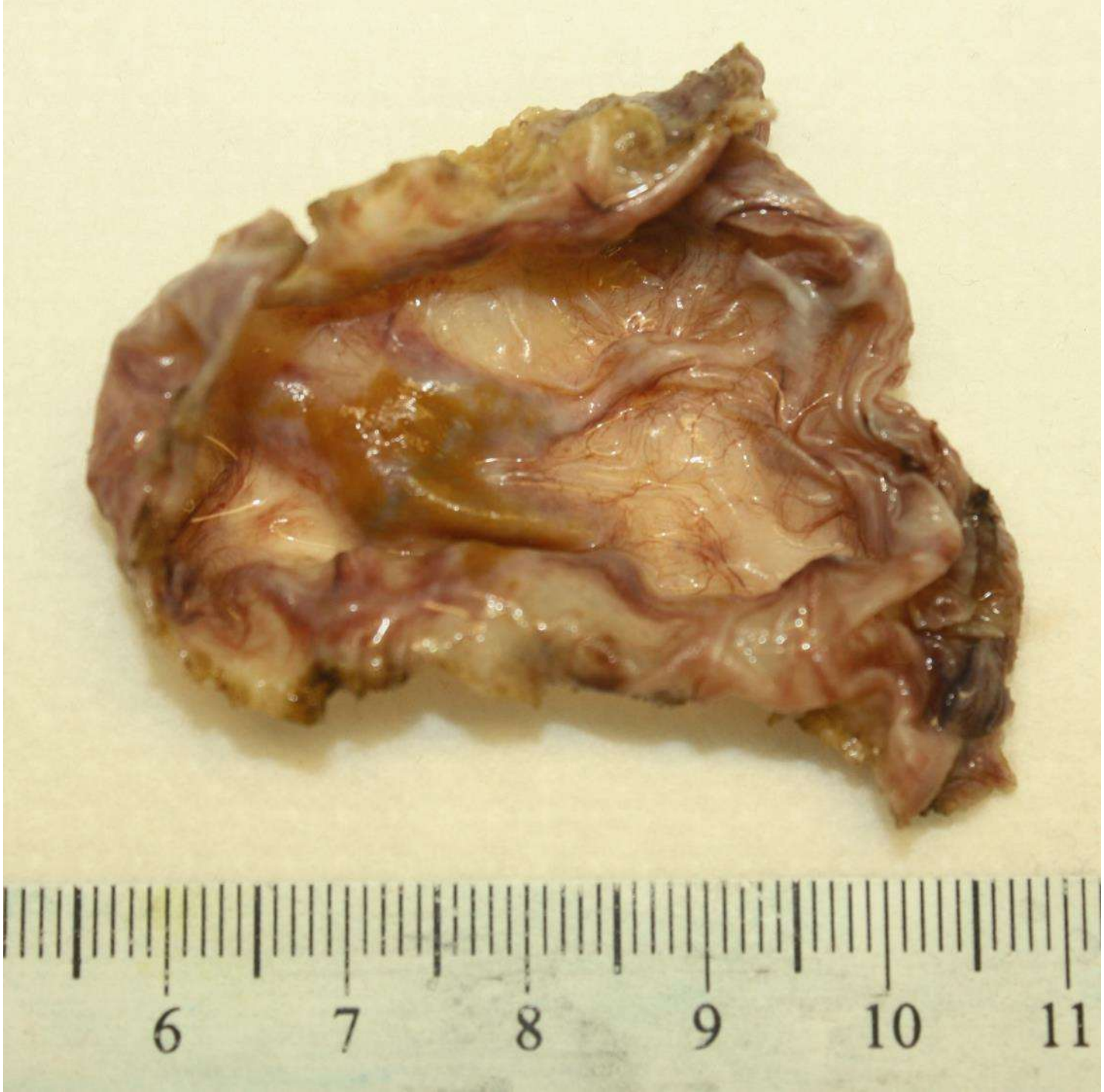
R
8.55 cm
C-
140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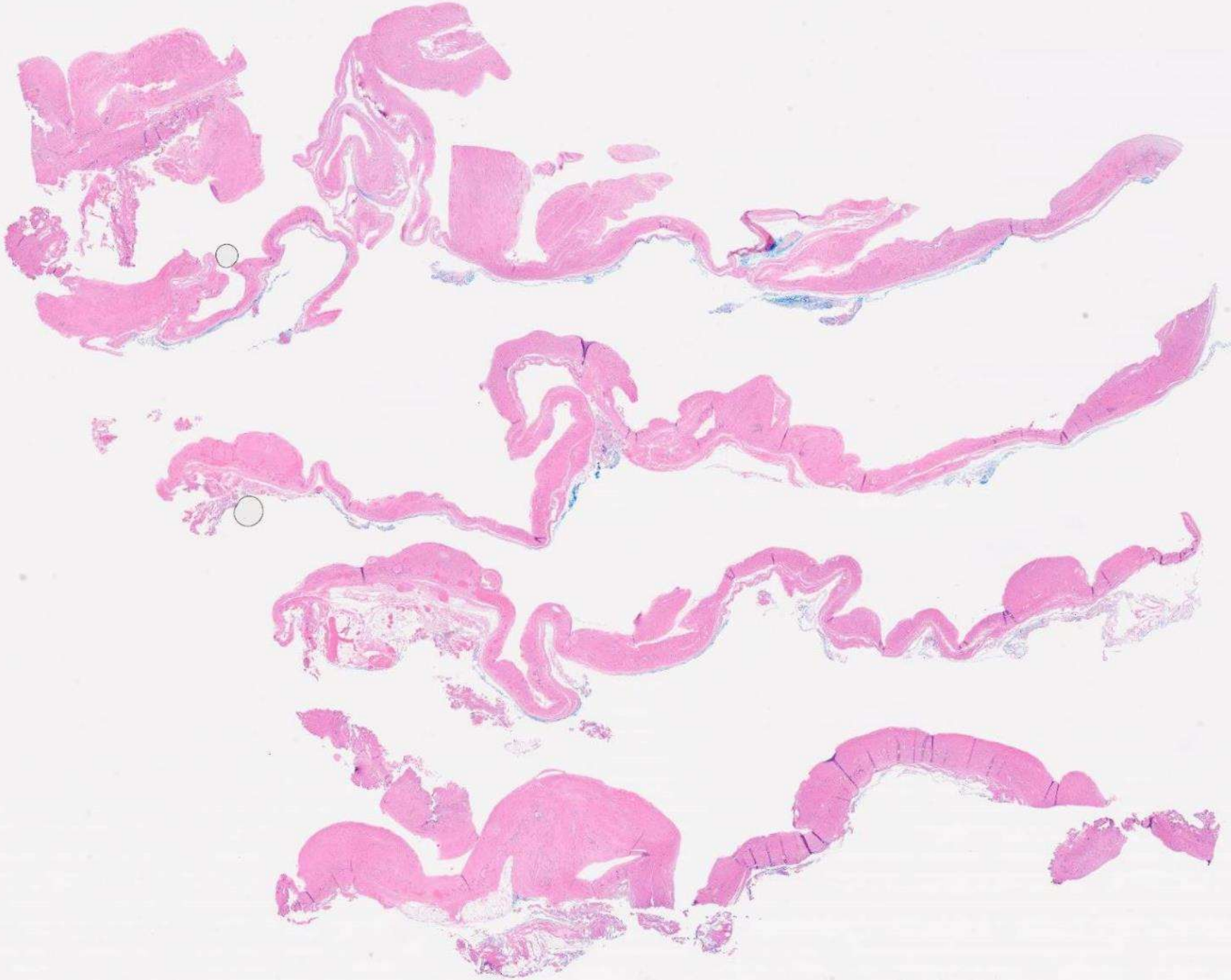
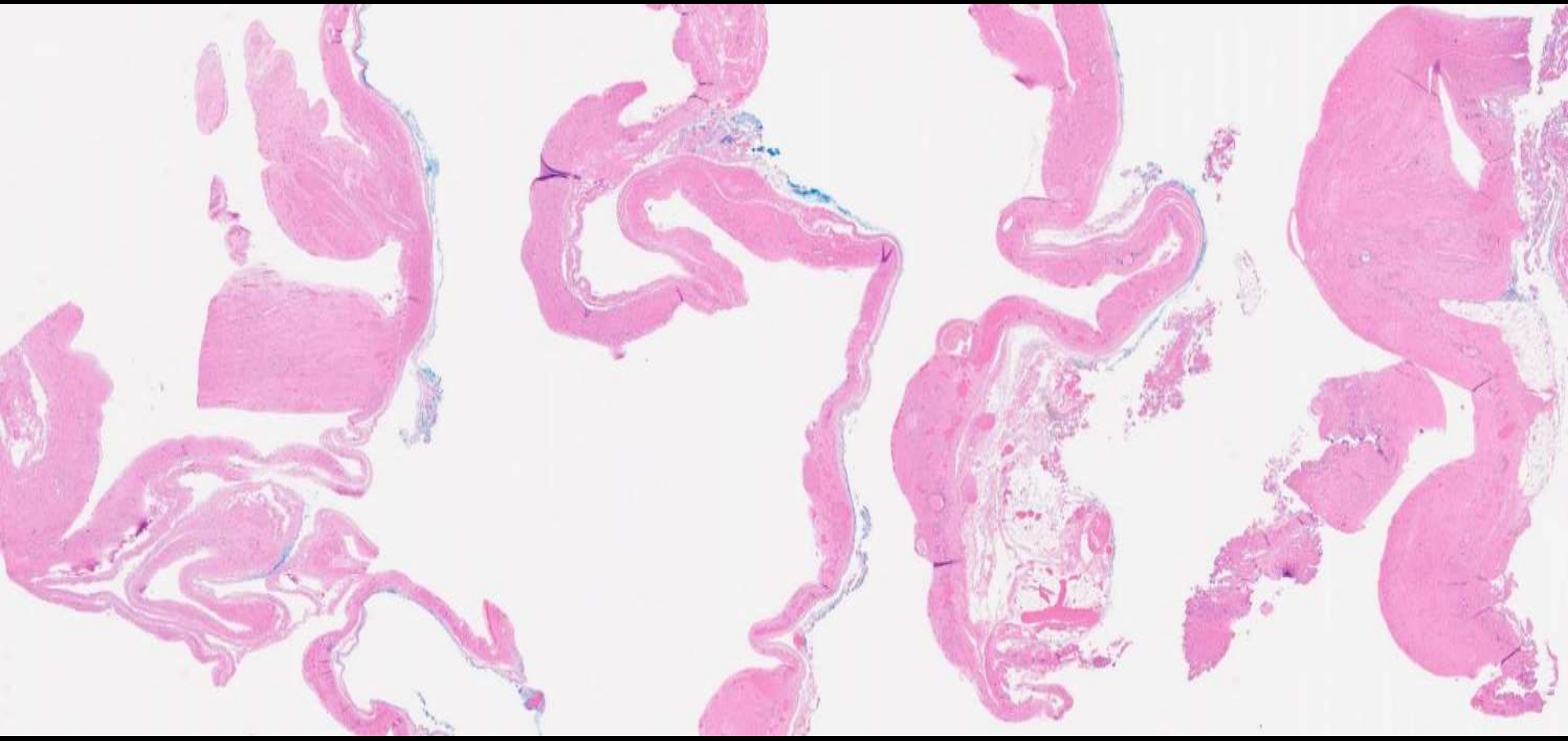
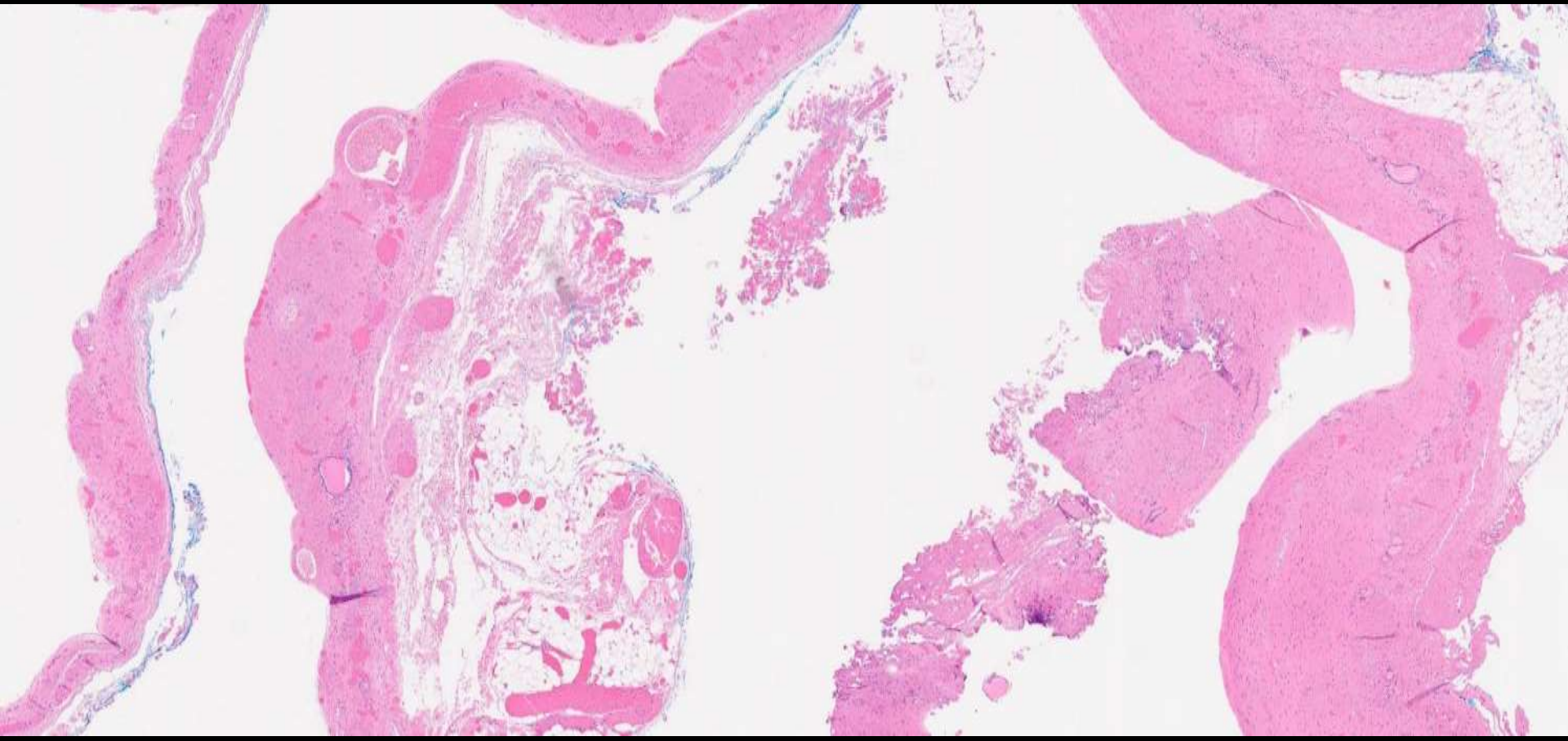
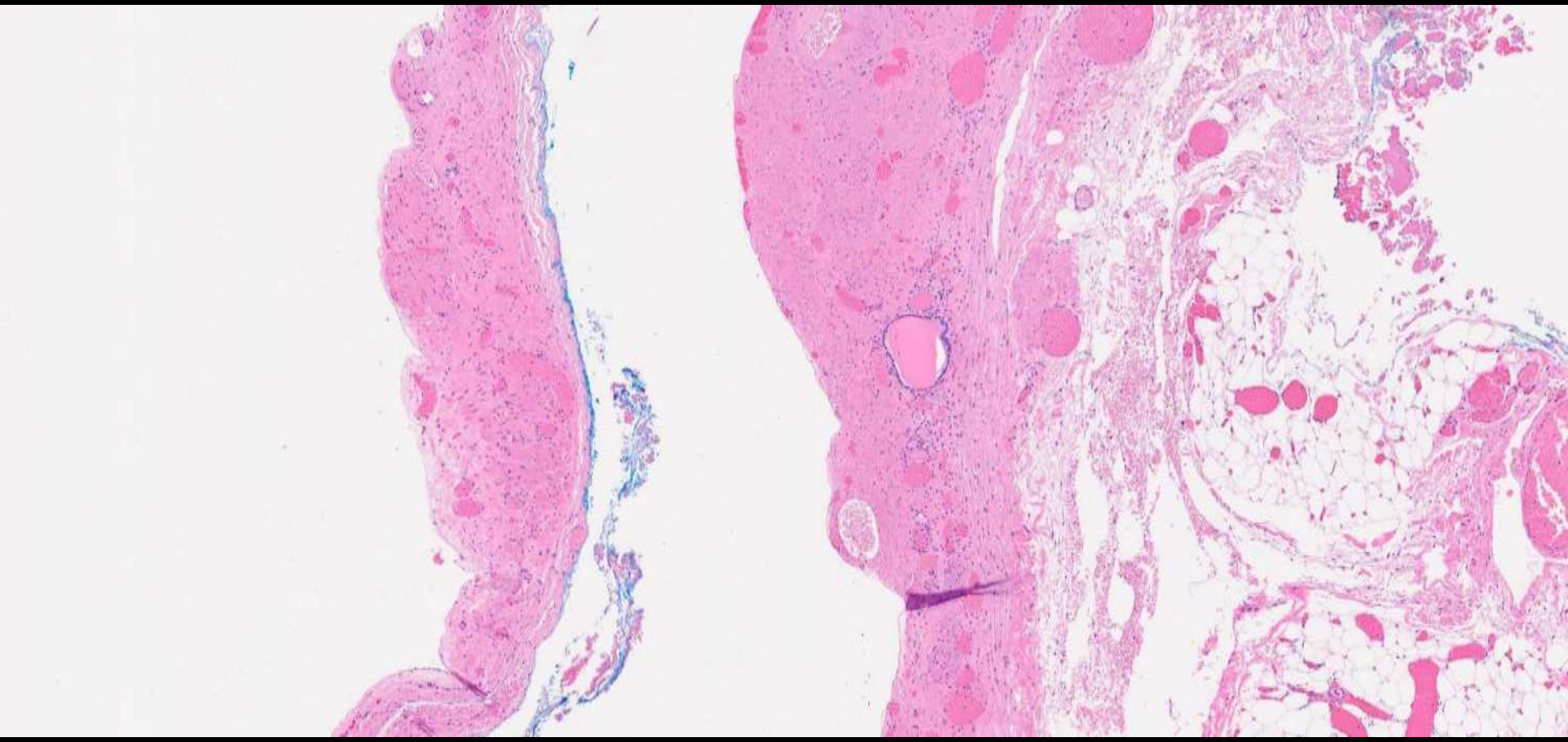
DDx

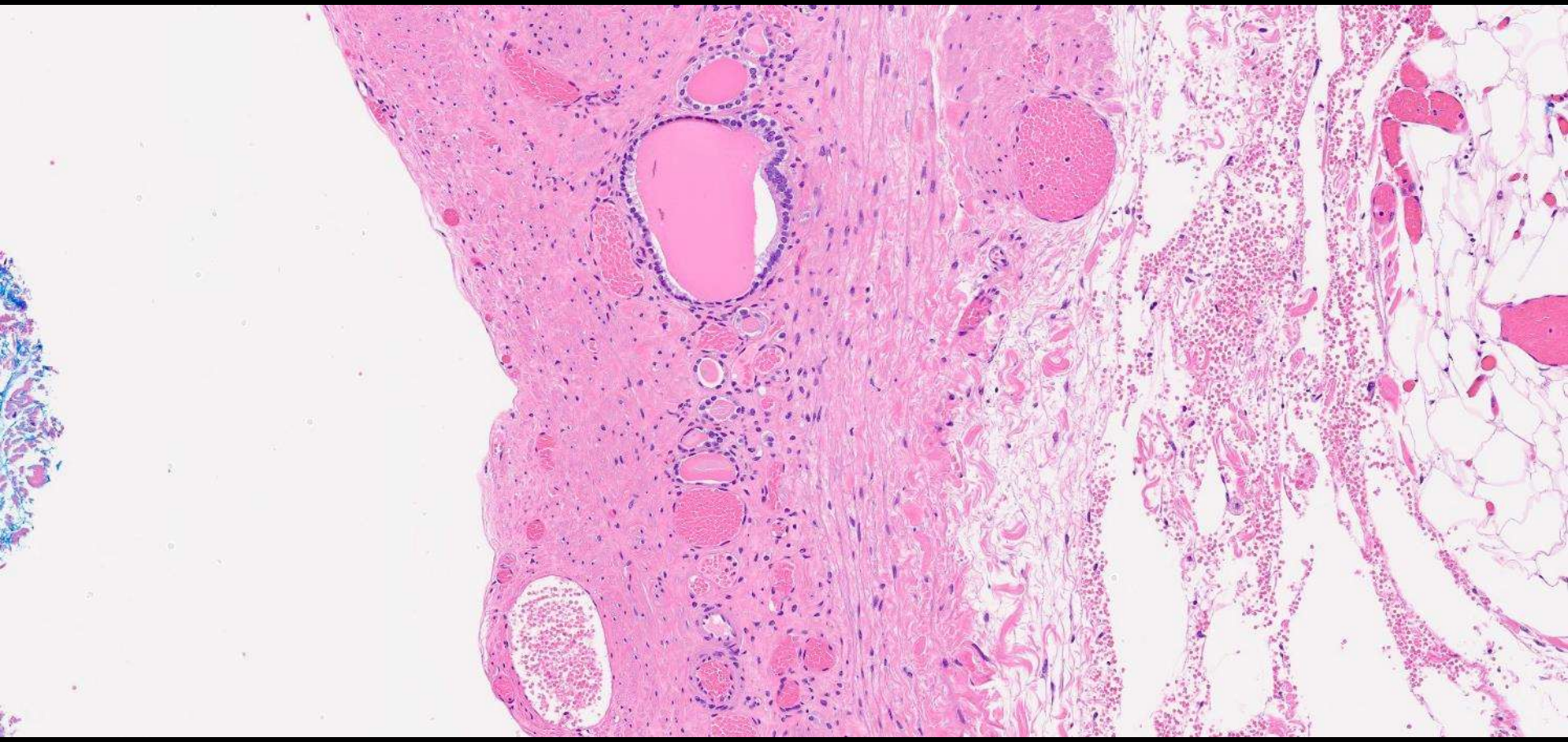
- **Benign cortical cyst**
- **Cystic renal neoplasm**
  - Atypical renal cyst
  - Clear RCC with cystic change
  - MRNLMP
  - Cystic nephroma/MEST







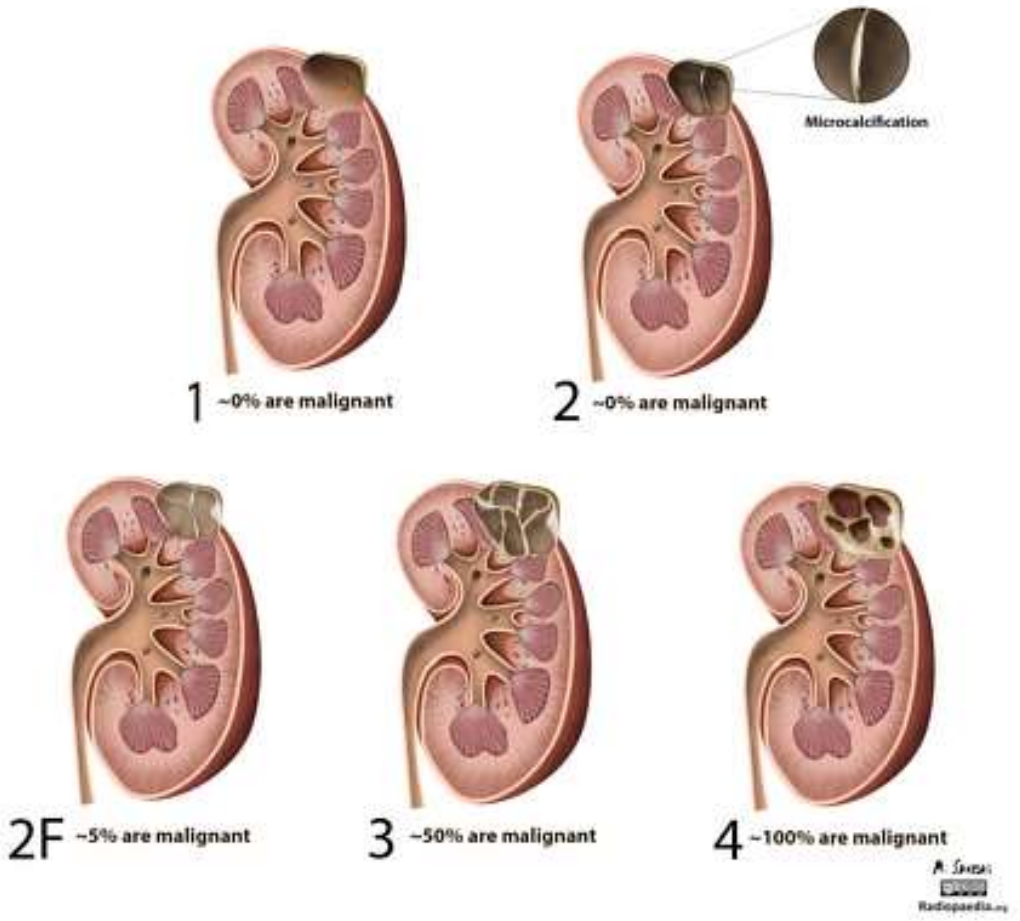




DIAGNOSIS

- **Kidney, [laterality], decortication:**
  - Consistent with benign cortical cyst

Bosniak classification of renal cysts



Bosniak Renal Cyst Classification System

I
- **Simple cyst** with a hairline-thin wall.
- No septa, calcifications, or solid components.
- Water attenuation, no enhancement.

II
- **Septa**: few hairline-thin in which not measurable enhancement may be appreciated.
- **Calcification**: fine or a short segment of slightly thickened may be present in the wall or septa.
- **High-attenuation**: uniform in lesions (< 3cm) that are sharply marginated and do not enhance.

IIF
- **Septa**:multiple hairline-thin in which not measurable enhancement of septum or wall is appreciated.
- **Minimal thickening of wall or septa**, which may contain calcification, that may be thick and nodular, but no measurable contrast enhancement.
- No enhancing soft-tissue components.
- **Intrarenal:** totally intrarenal nonenhancing high-attenuating renal lesions > 3 cm

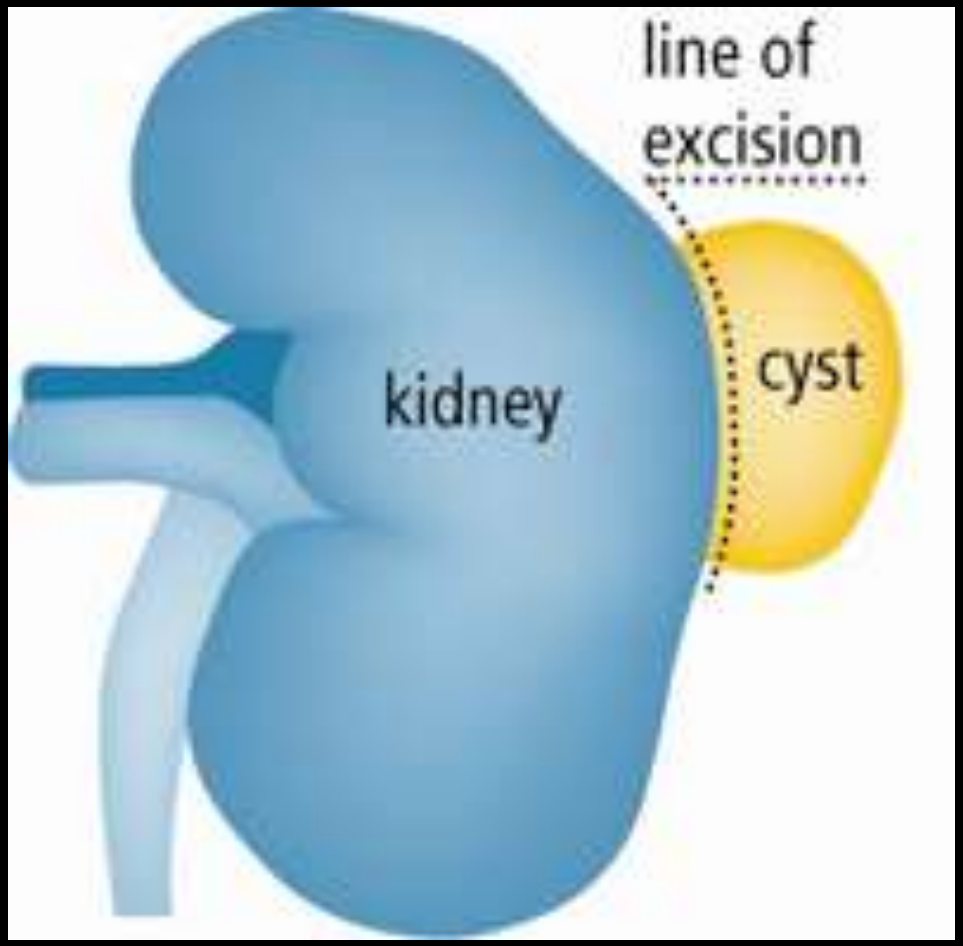
III
- **Measurable enhancement**

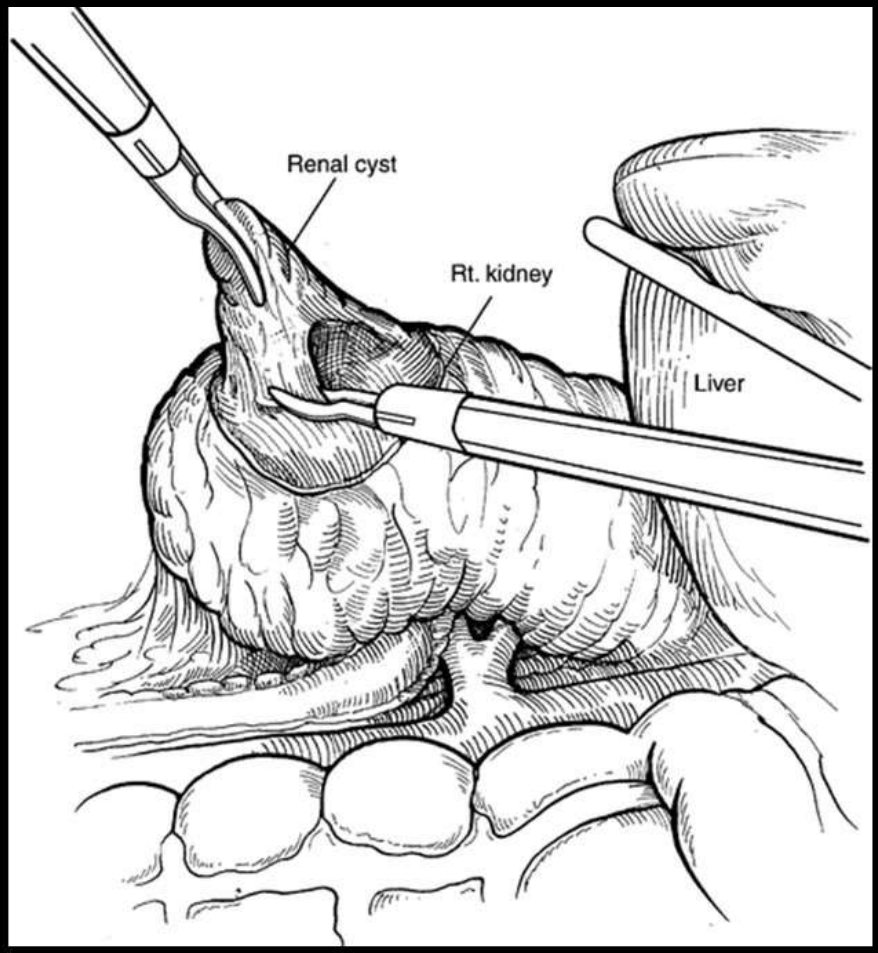
Cystic mass with thickened irregular or smooth walls or septa in which measurable enhancement is present

IV
- **Enhancing soft-tissue components**

Clearly malignant cystic masses that can have all of the criteria of category III but also contain distinct enhancing soft-tissue components independent of the wall or septa

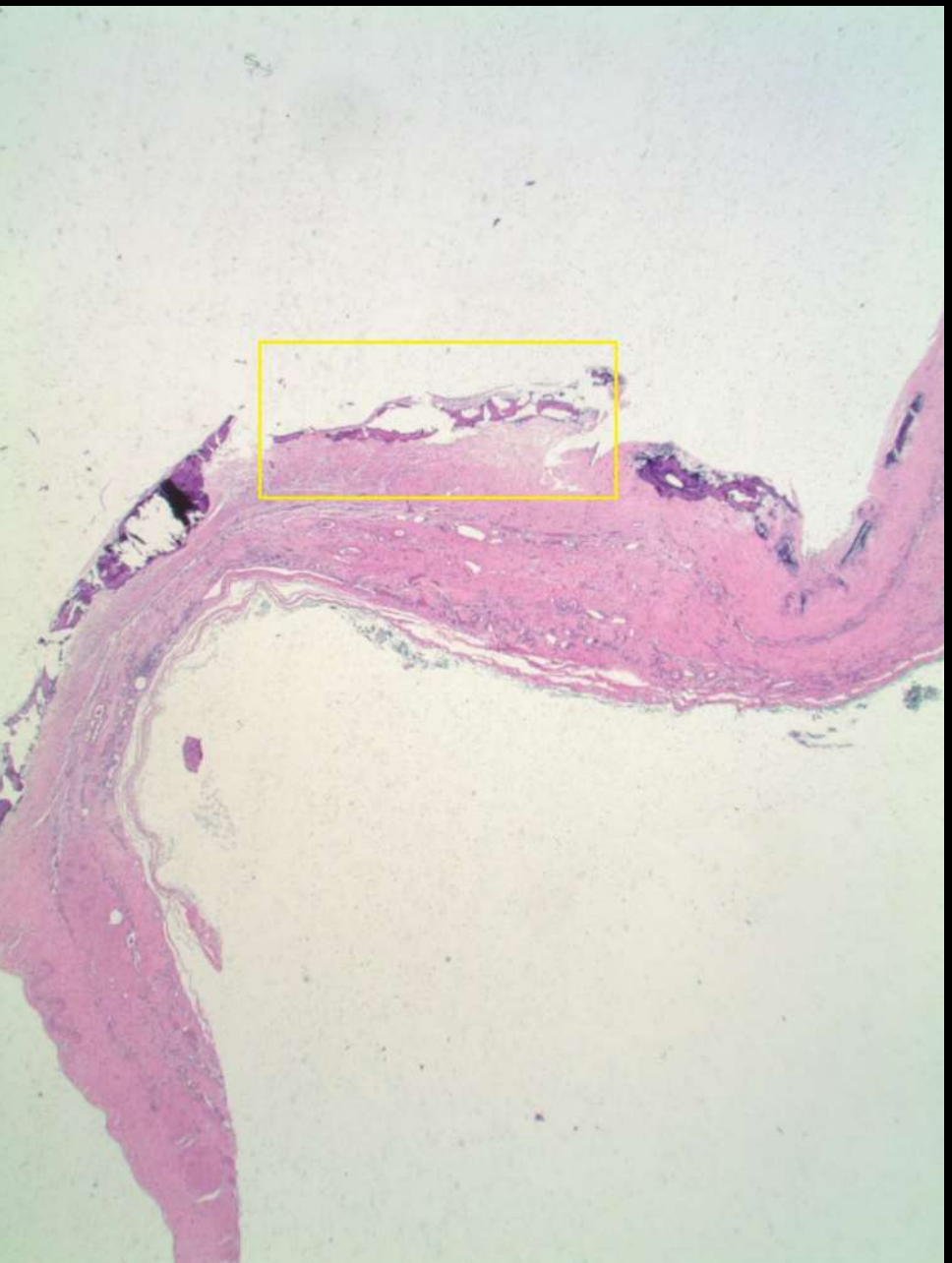
Decortication procedure

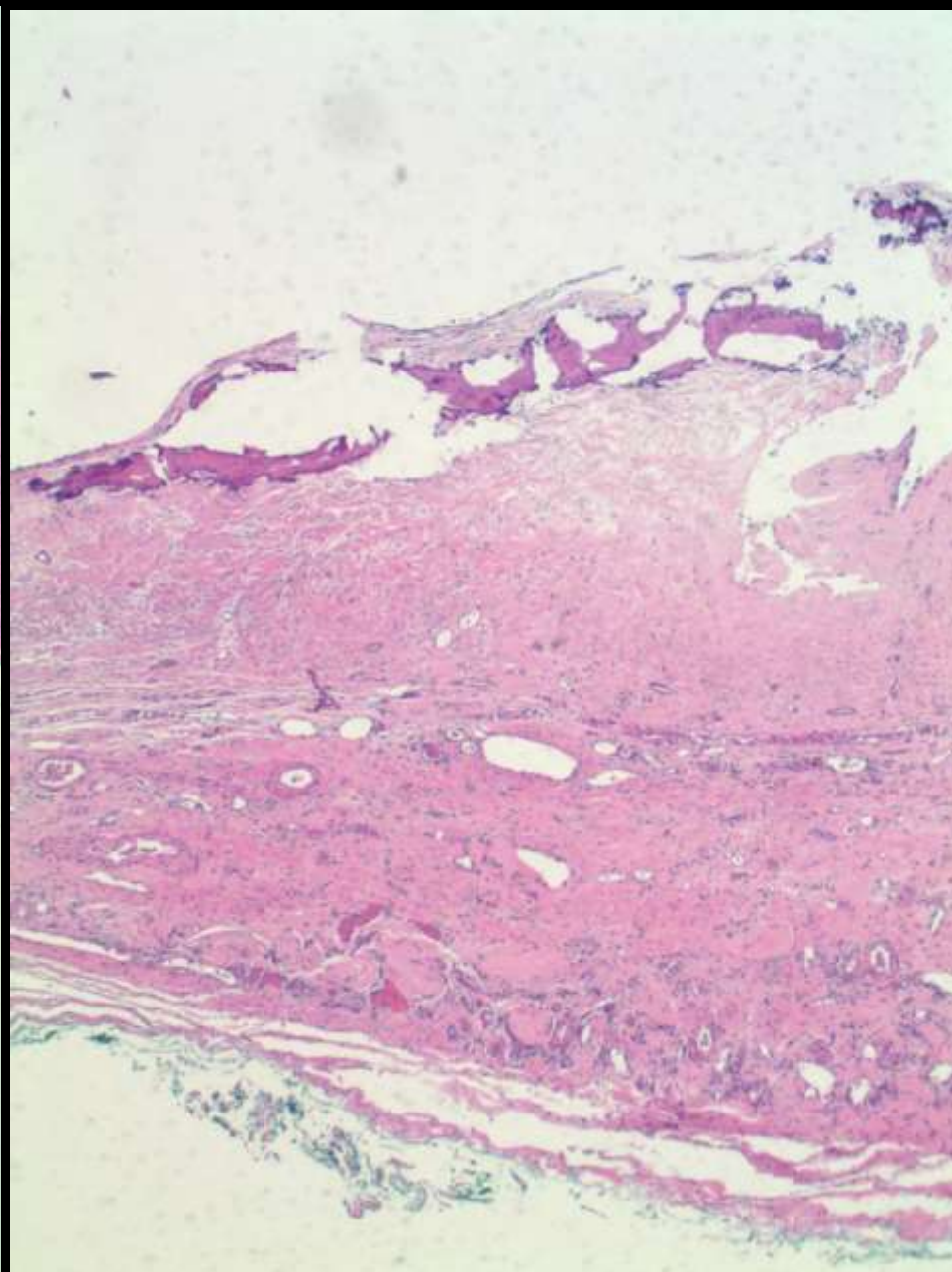




https://link.springer.com/chapter/10.1007/978-1-60327-820-1_5

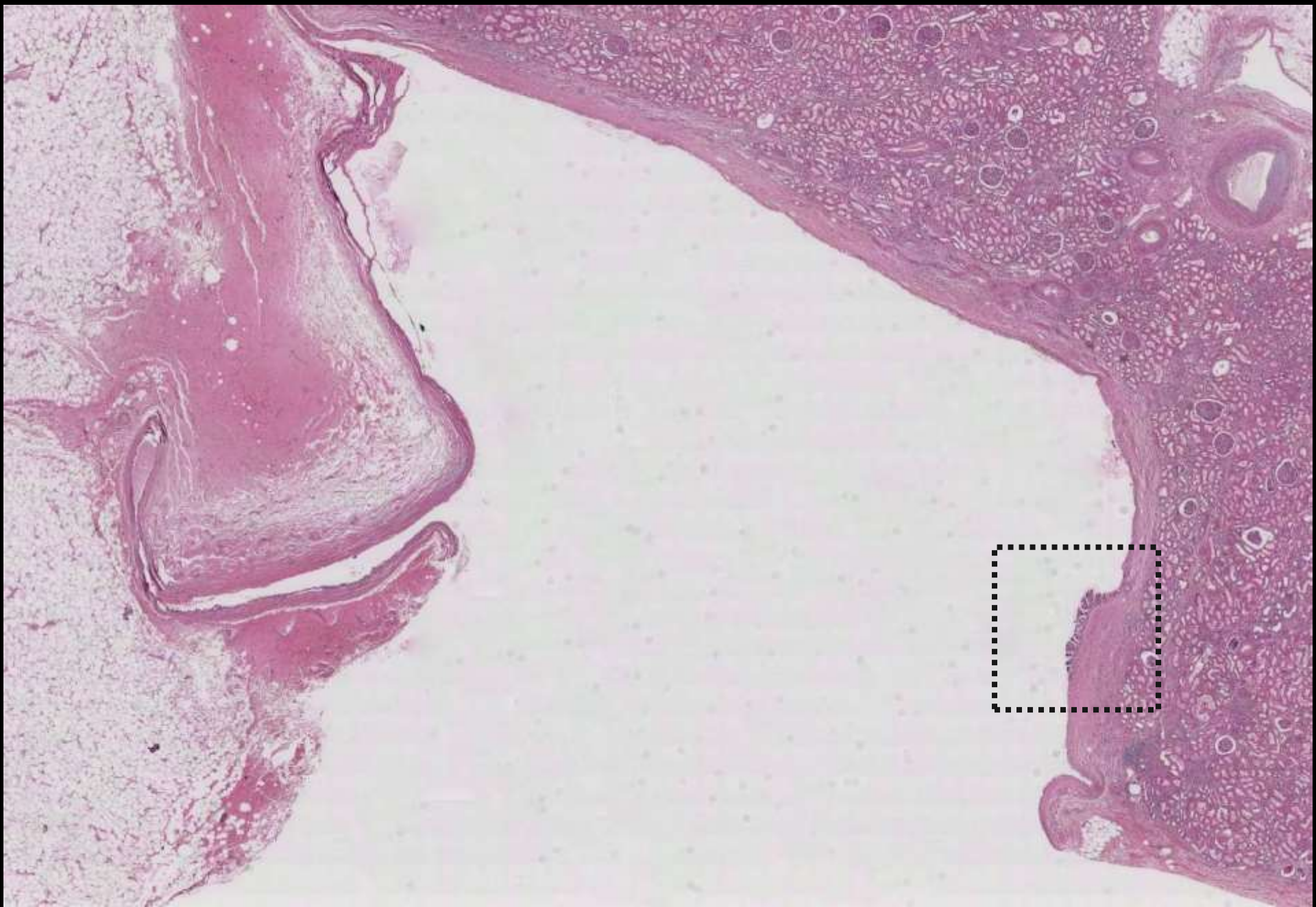
Sometimes cyst wall can get BONEfide calcs



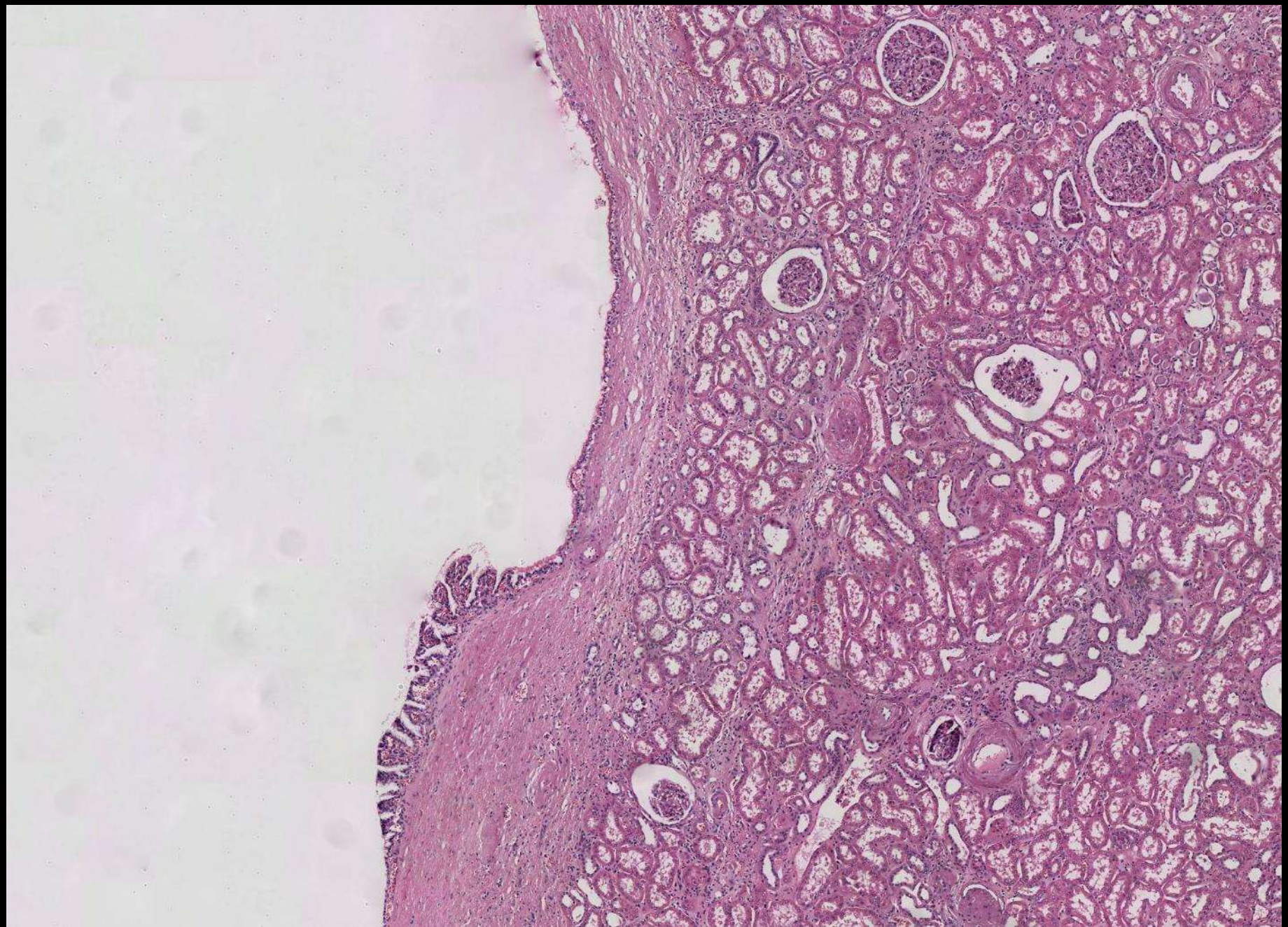


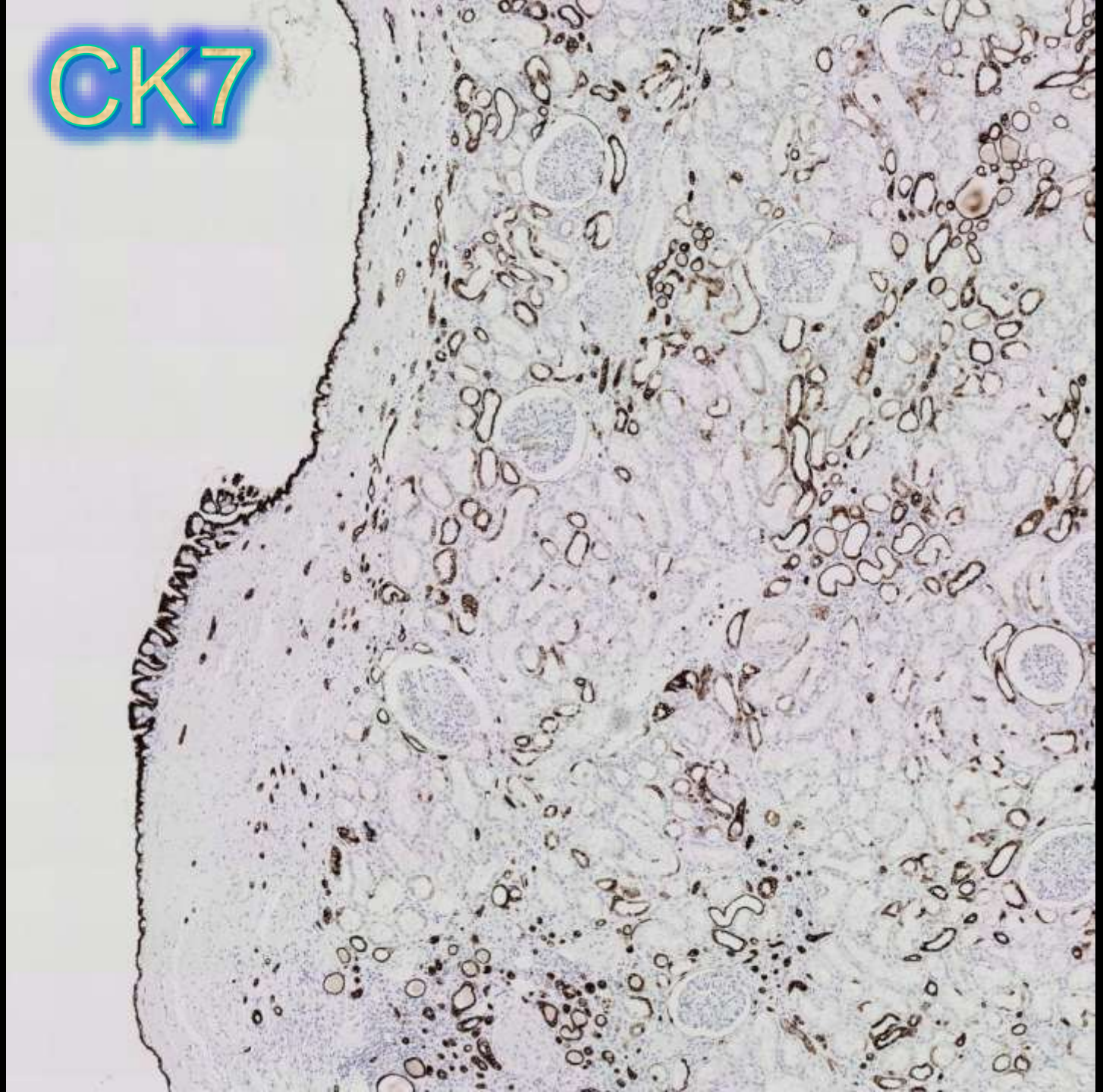
IHC?

atypical renal cyst

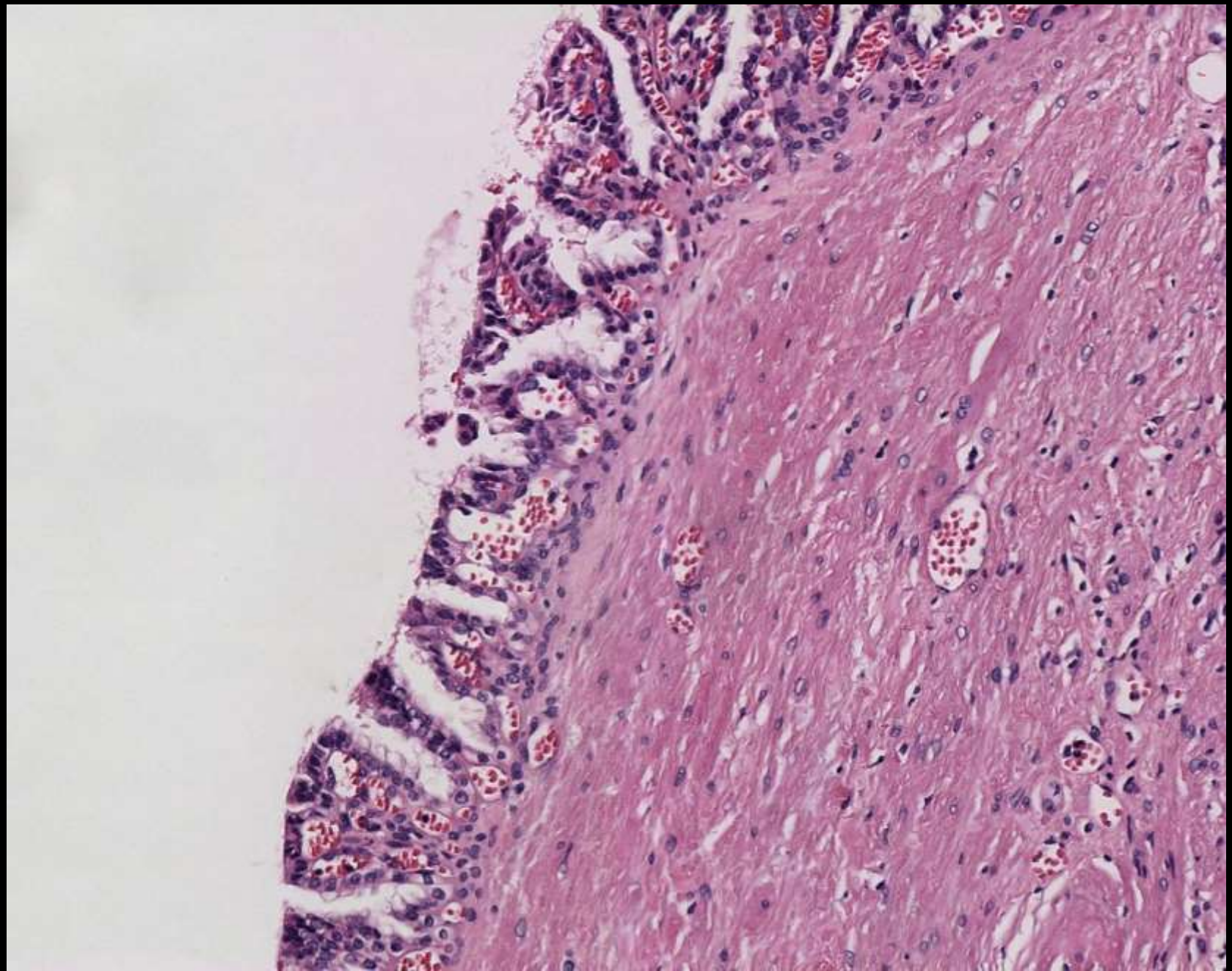


atypical renal cyst




CK7

atypical renal cyst



TAKE HOME POINTS

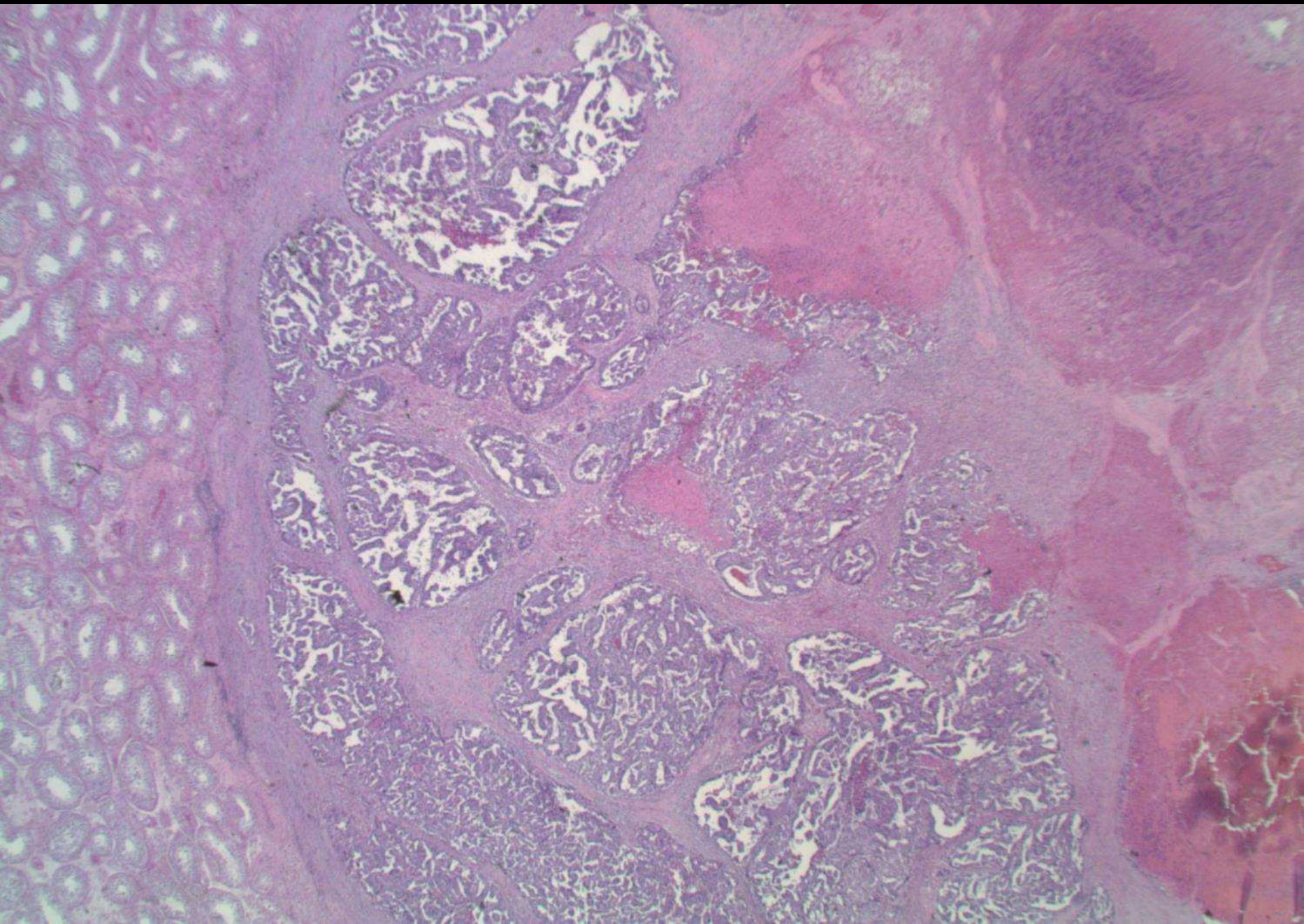
- **Beware of increasing prevalence of renal cyst decortications**
  - Can also be done at time of partial nephrectomy on other low Bosniak cysts

22-1108

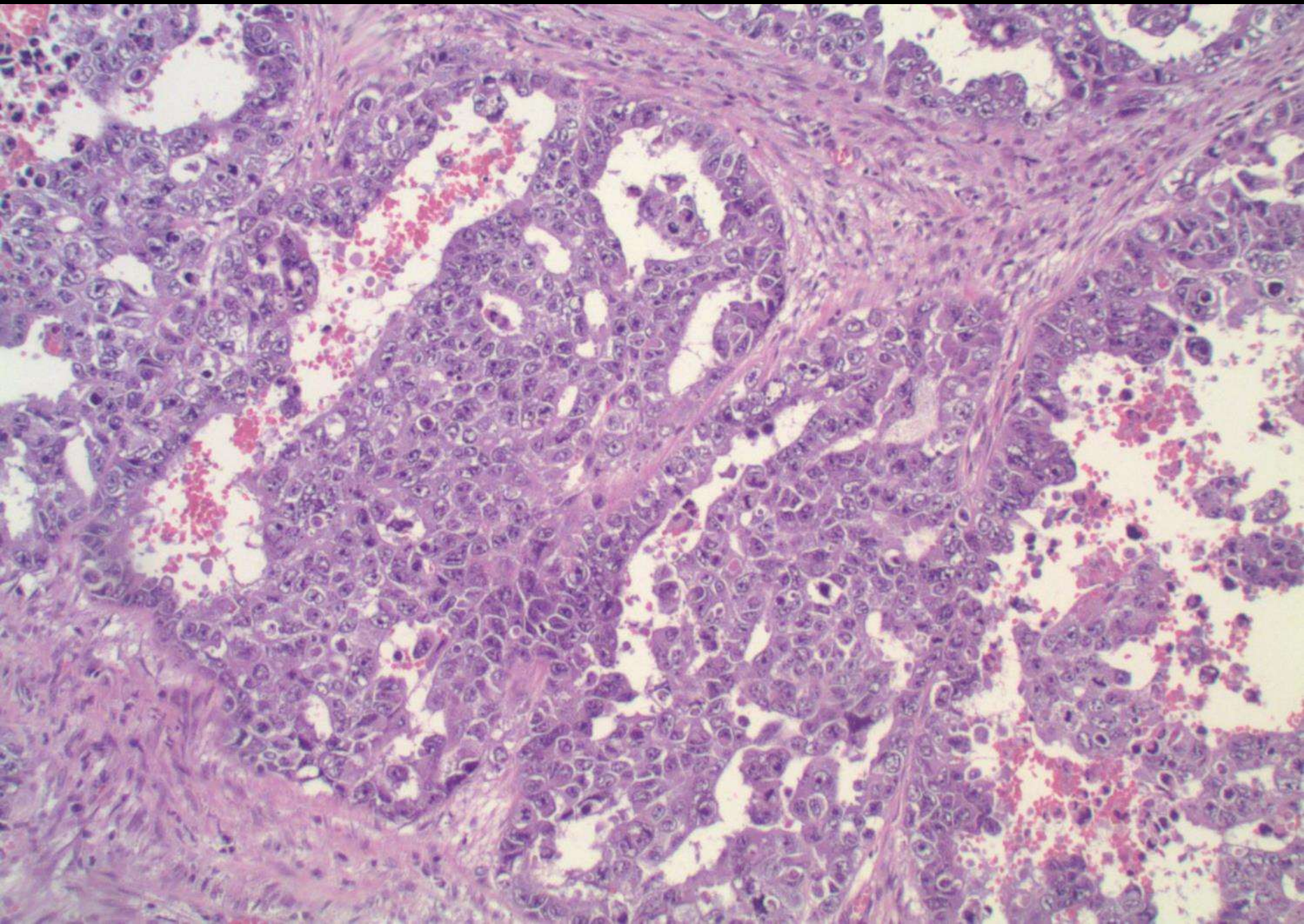
Ankur Sangoi; El Camino Hospital

20ish M with germ cell tumor, radical orchiectomy performed. Other sections show hilar soft tissue involvement and LVI. Section of spermatic cord shown. What is the pathologic stage?

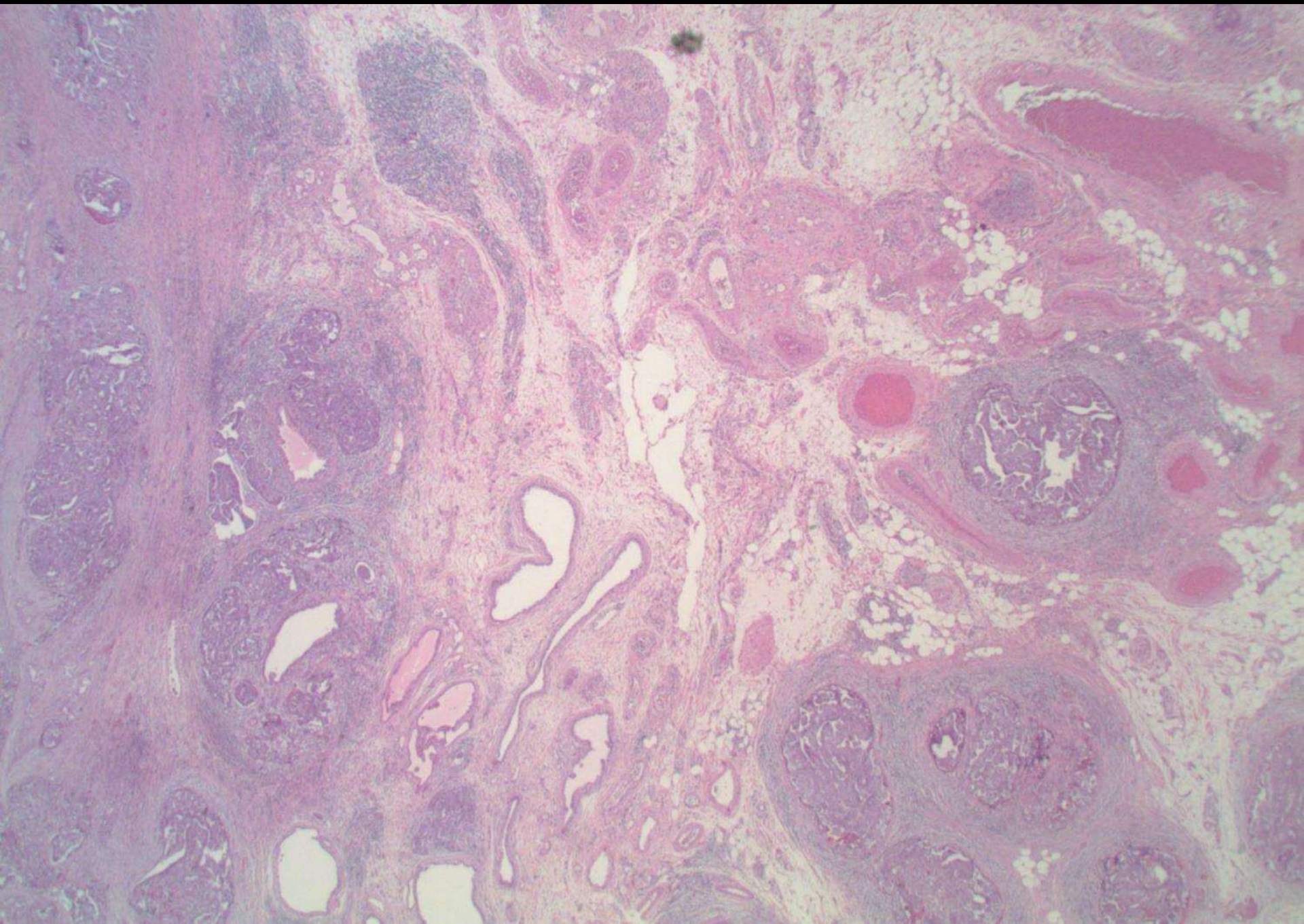
central tumor



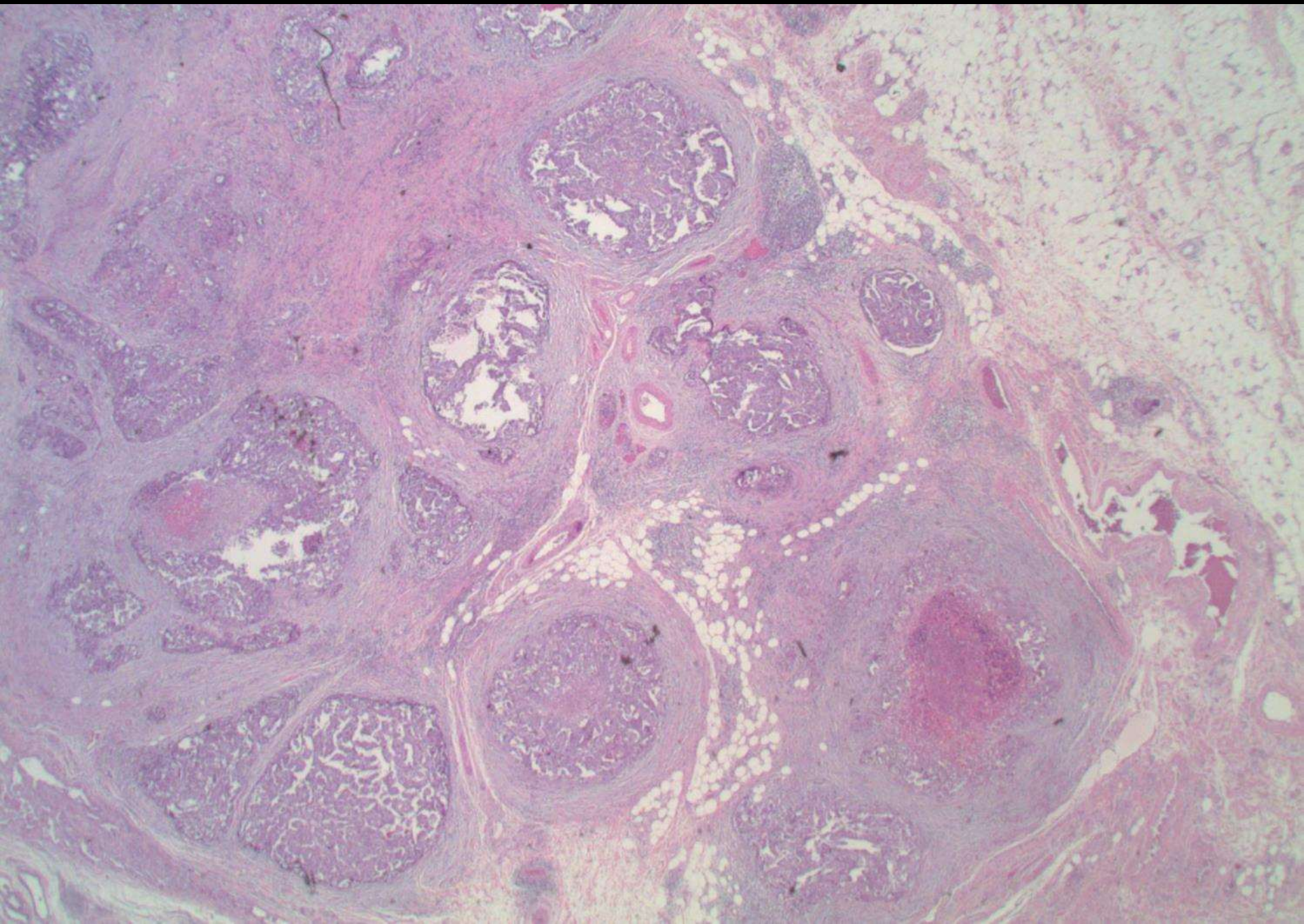
central tumor



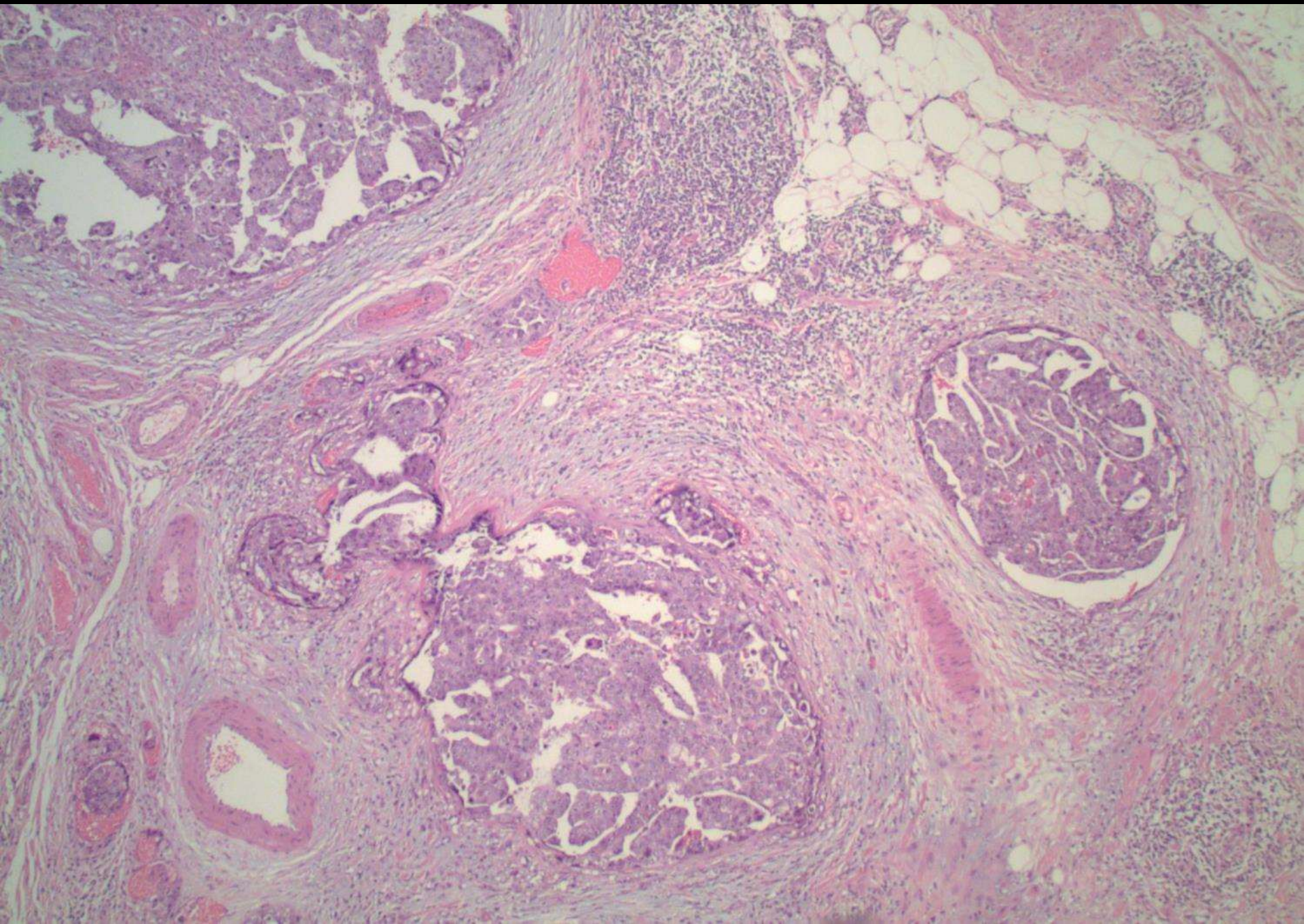
tumor to hilum



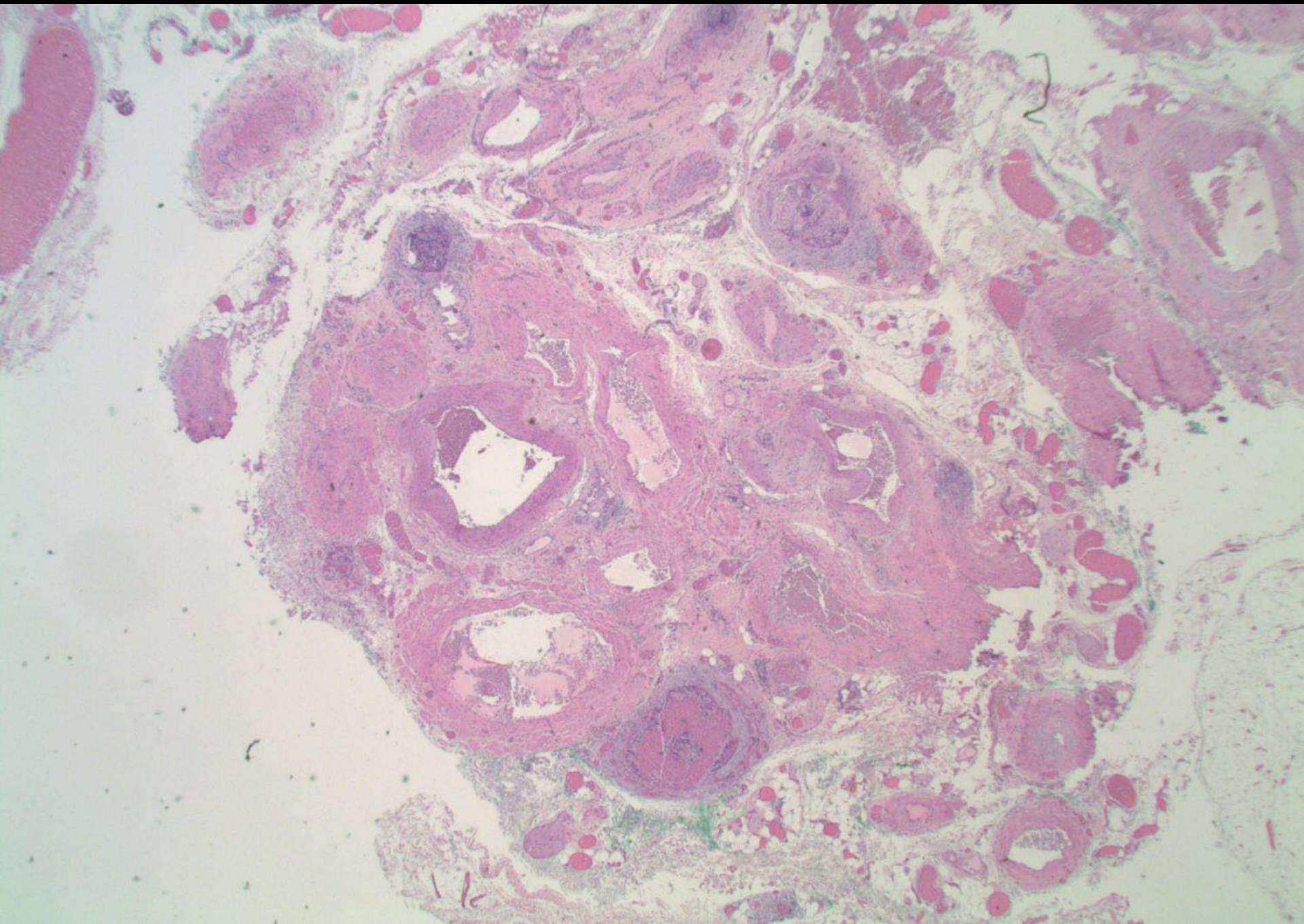
tumor to hilum



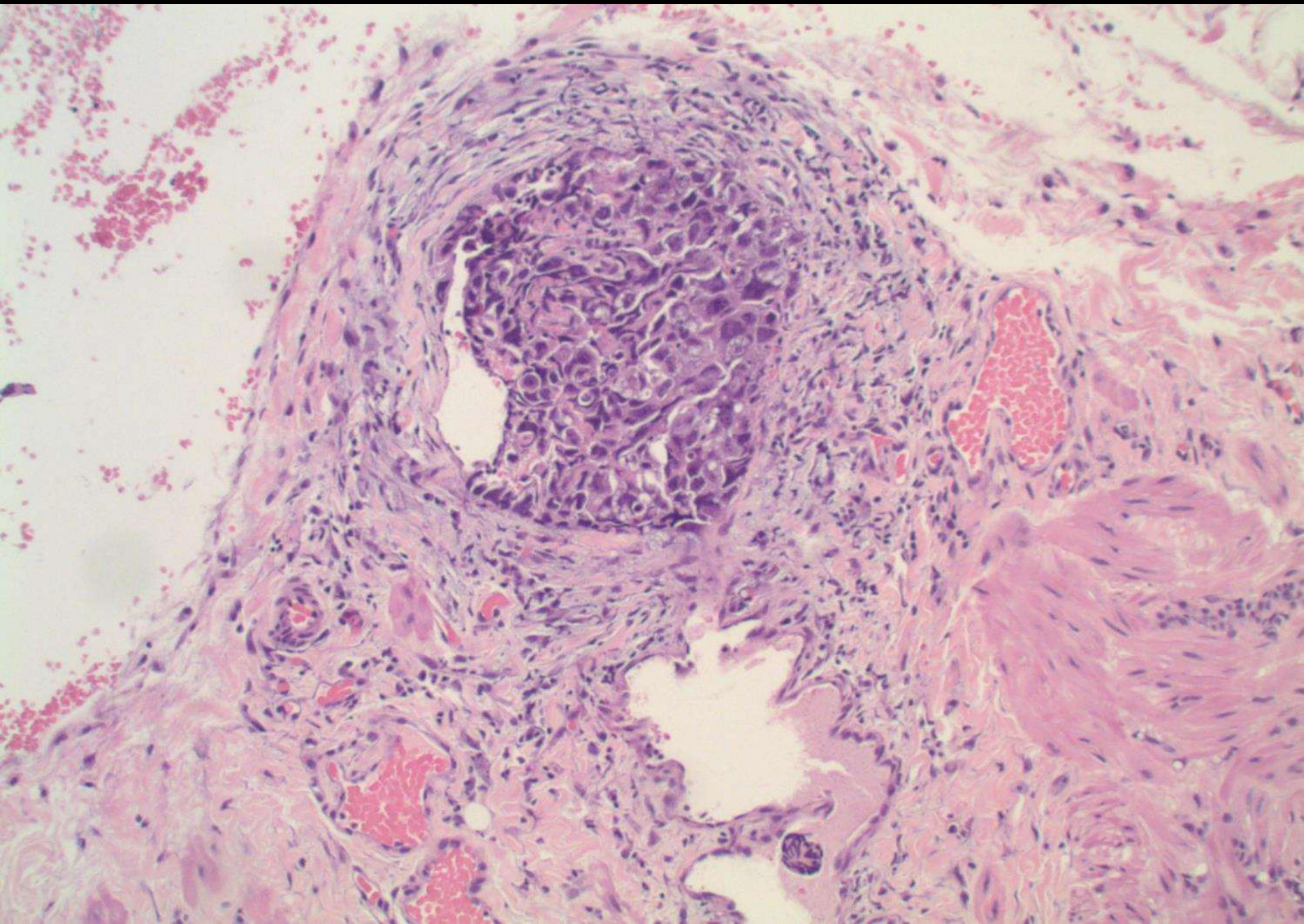
tumor to hilum



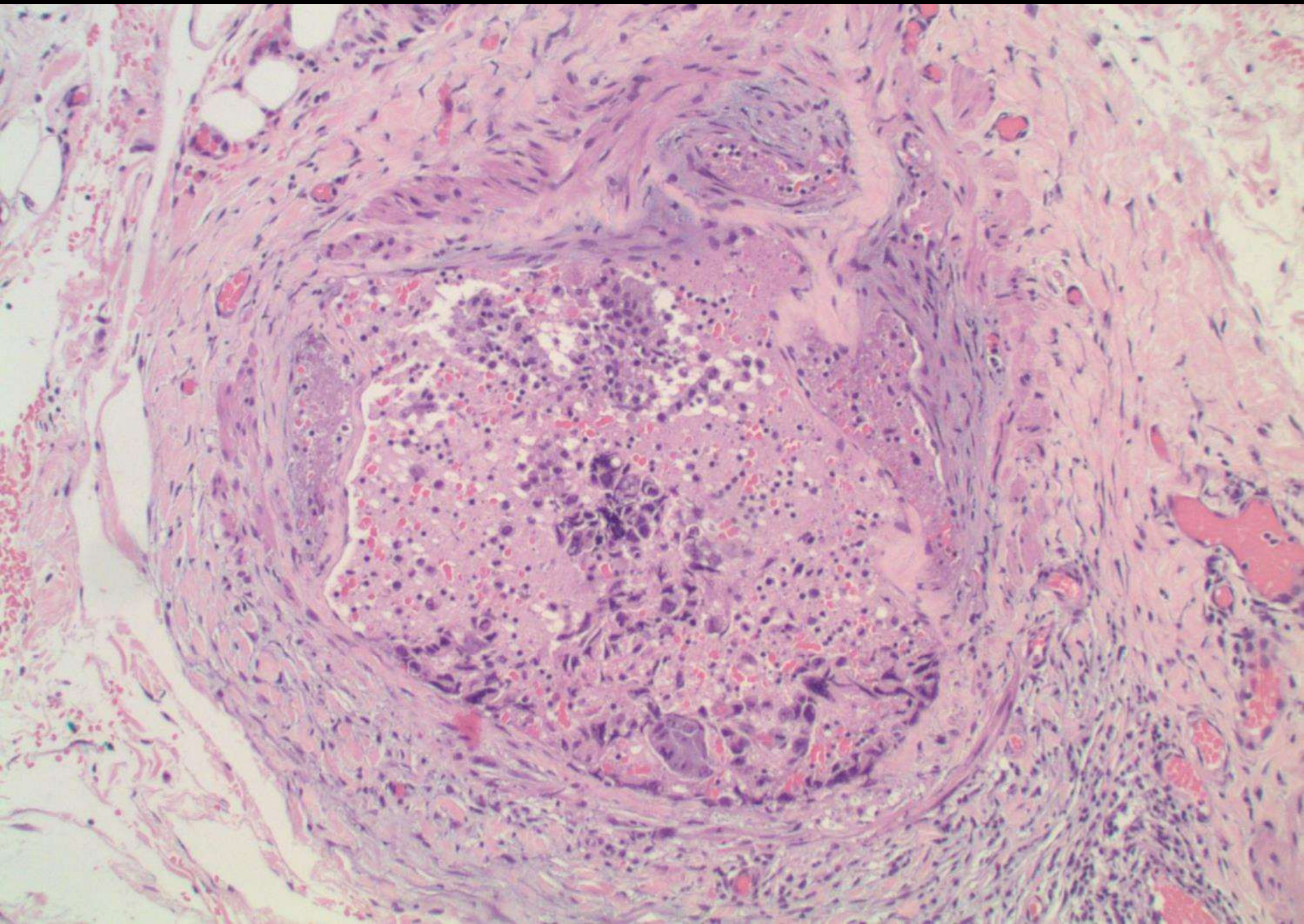
spermatic cord



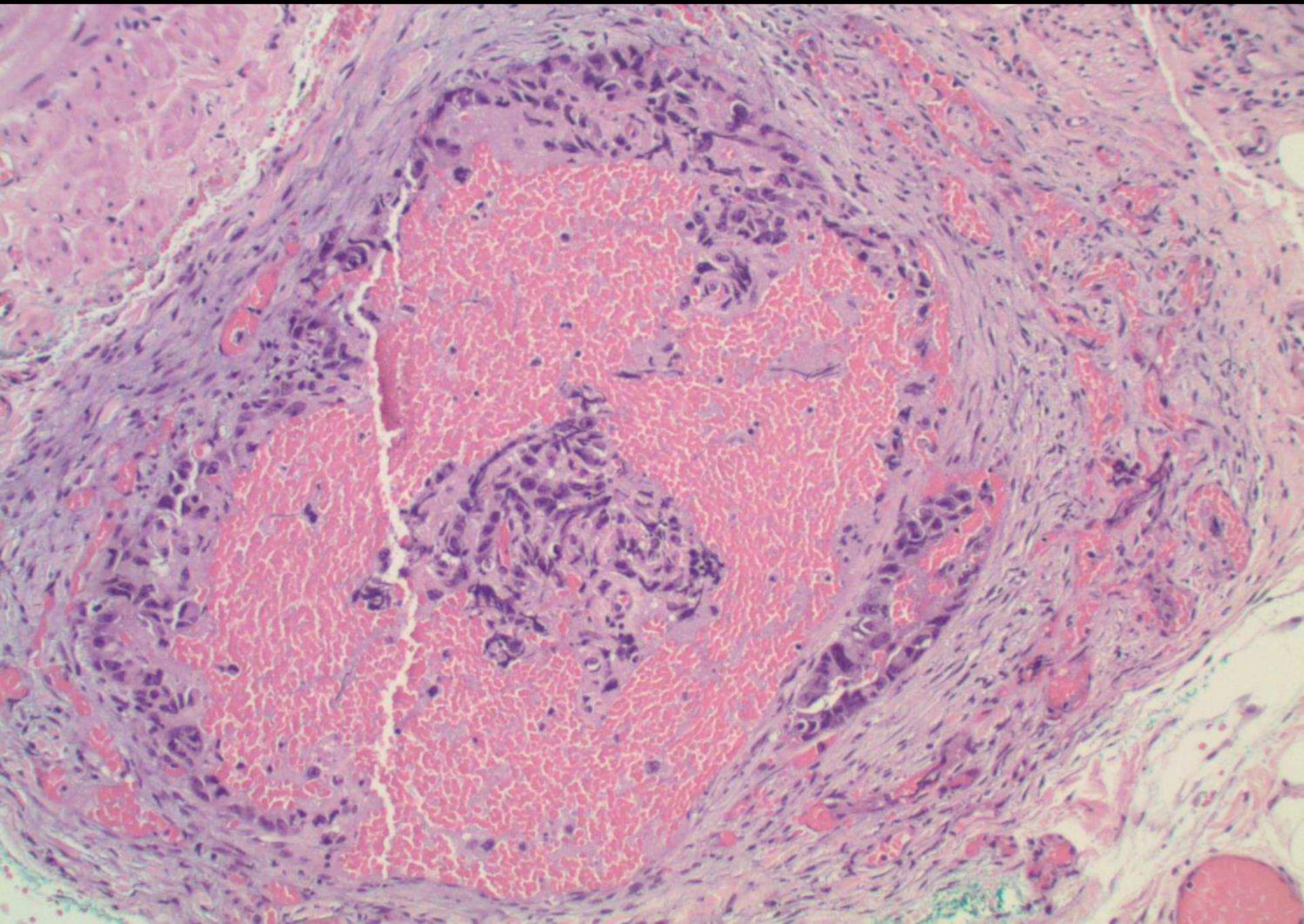
spermatic cord



spermatic cord



spermatic cord



Pathologic stage?

- pT2Mx
- pT2M1
- pT3Mx
- pT3M1
- pT4Mx
- pT4M1

AJCC 8th ed TNM staging for testicular cancer

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Germ cell neoplasia in situ
T1	Tumor limited to testis (including rete testis invasion) without LVI
T1a[a]	Tumor smaller than 3 cm
T1b[a]	Tumor 3 cm or larger
T2	Tumor limited to testis (including rete testis invasion) with LVI or Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without LVI
T3	Tumor directly invading spermatic cord soft tissue with or without LVI
T4	Tumor invading scrotum with or without LVI

M	Distant metastasis
M0	No distant metastasis
M1	Distant metastases or discontinuous involvement of spermatic cord soft tissue
M1a	Nonretroperitoneal nodal or pulmonary metastases
M1b	Nonpulmonary visceral metastases

Pathologic stage?

- **pT2Mx**
- **pT2M1**
- **pT3Mx**
- **pT3M1**
- **pT4Mx**
- **pT4M1**

THE REAL ISSUES:

- **Is spermatic cord involvement continuous or discontinuous?**

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  → Discontinuous here

Pathologic stage?

- **pT2Mx**
- **pT2M1**
- **pT3Mx**
- **pT3M1**
- **pT4Mx**
- **pT4M1**

THE REAL ISSUES:

- **Is spermatic cord involvement continuous or discontinuous?**
  → Discontinuous here
- **Is spermatic cord involvement purely LVI or extension into adj soft tissue?**

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- **Should discontinuous spermatic cord involvement be considered metastatic or just pT2Mx?**

Pathologic stage?

- **pT2Mx**
- **pT2M1**
- **pT3Mx**
- **pT3M1**
- **pT4Mx**
- **pT4M1**

THE REAL ISSUES:

- **Is spermatic cord involvement continuous or discontinuous?**
  → Discontinuous here
- **Is spermatic cord involvement purely LVI or extension into adj soft tissue?**
  → IHC showed LVI + extravascular invasion
- **Should discontinuous spermatic cord involvement be considered metastatic or just pT2Mx?**
  → Best considered as pT2M1 in this case

Testicular Germ-Cell Tumors with Spermatic Cord Involvement: A Retrospective International Multi-Institutional Experience

Maria Del Carmen Rodriguez Pena[1,17], Sofia Canete-Portillo[1,17], Ali Amin[2], Manju Aron[3], Piergiuseppe Colombo[4], Roni Cox[5], Dilek Ertoy Baydar[6], Ivan Gallegos[7], Francesca Khani[8], Květoslava Michalova[9], Roberta Lucianò[10], Hiroshi Miyamoto[11], Adeboye O. Osunkoya[12], Maria Rosaria Raspollini[13], Diego F. Sánchez[14], Federico Scarfo[10], Jeffrey S. So[15], Debra L. Zynger[16], Shi Wei[1], George J. Netto[1] and Cristina Magi-Galluzzi[1]✉

The 8th Edition of the American Joint Committee on Cancer (AJCC) Staging Manual designates discontinuous involvement of spermatic cord soft tissue by testicular germ cell tumors as a metastatic deposit. We conducted a retrospective international multi-institutional study to validate the current recommendations. Thirty-three (72%) nonseminomatous and 13 (28%) seminomatous testicular germ cell tumors were collected from 15 institutions in America, Europe, and Asia. Testicular tumor size ranged from 1.3 to 18.0 cm (mean: 6.1). Cases were classified as discontinuous involvement of spermatic cord soft tissue ($n = 26$), continuous cord involvement ($n = 17$), or cord lymphovascular invasion ($n = 3$). The mean follow-up was 39 months. Clinical stage for discontinuous involvement of spermatic cord soft-tissue patients was I (local disease) in 2/24 (8%), II (regional disease) in 6/24 (25%), and III (distant disease) in 16/24 (67%) cases; 16 (67%) patients presented with distant metastasis. Clinical stage for continuous cord involvement patients was I in 9/17 (53%), II in 4/17 (23%), and III in 4/17 (23%); 4 (23%) patients presented with distant metastasis. Disease progression was seen in 4 patients with discontinuous involvement of spermatic cord soft tissue and 5 with continuous cord-involvement ($p = 0.699$). When comparing discontinuous and continuous cord involvement, a significant difference was found in cord margin status ($p = 0.044$), spermatic cord tumor size ($p = 0.016$), lymph-node involvement ($p = 0.037$), distant metastasis ($p = 0.010$), individual clinical stage ($p = 0.003$), and nonadvanced vs. advanced disease ($p = 0.003$) at presentation. In multivariate analysis, after adjusting for age, histology, testicular tumor size, percent of embryonal carcinoma, lymphovascular invasion, and cord margin status, discontinuous involvement of spermatic cord soft tissue was significantly associated ($p = 0.011$) with advanced clinical stage at presentation. Our findings support the designation of metastatic disease for discontinuous involvement of spermatic cord soft tissue, as introduced by the 8th edition of the AJCC staging.

Modern Pathology (2022) 35:249–255; https://doi.org/10.1038/s41379-021-00912-9

Modern Pathology (2022) 35:249 – 255

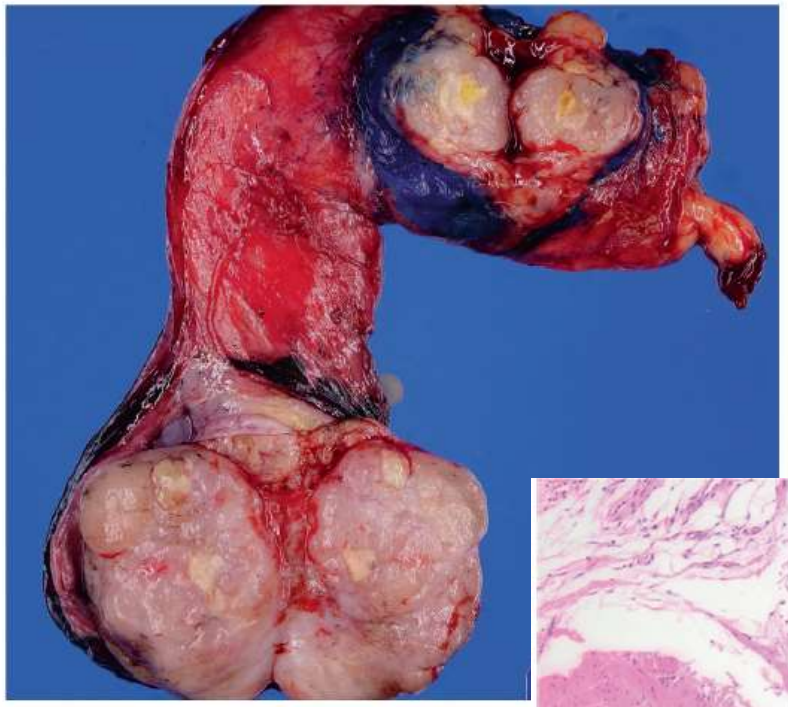
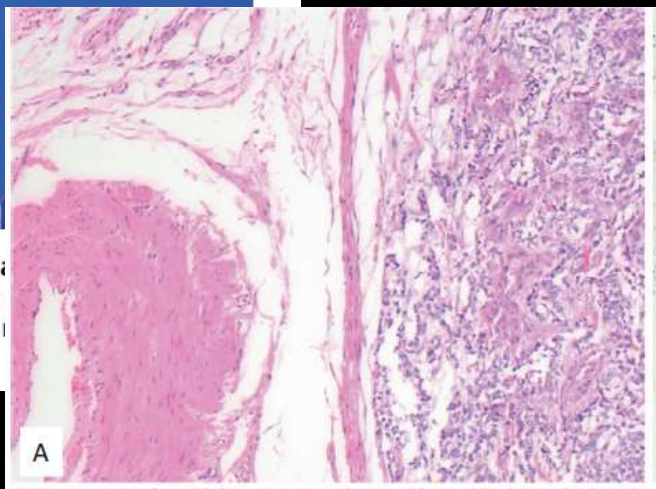
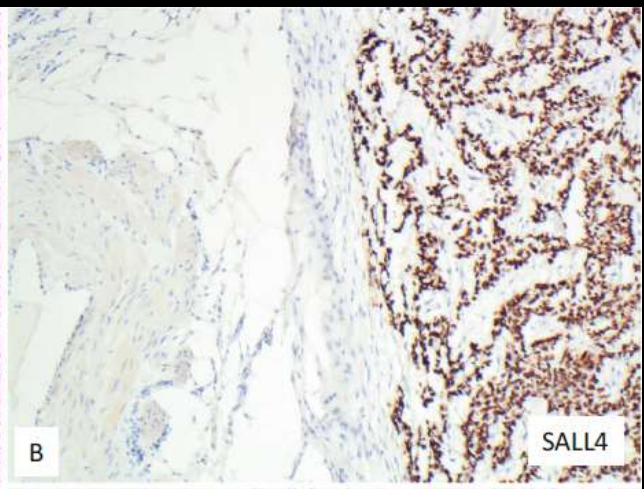
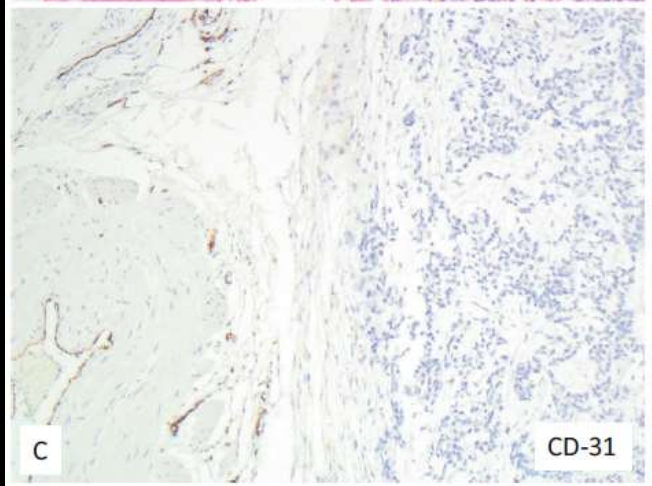
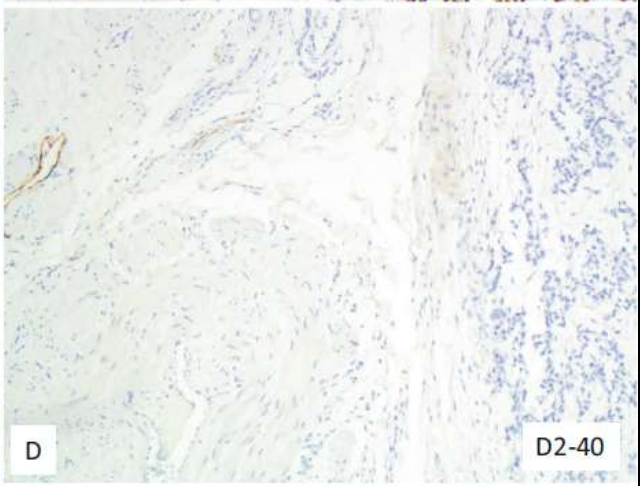


Fig. 1 Discontinuous involvement of sperma
white-tan tumor nodule with small areas
proximal spermatic cord in a discontinuous
tumor (courtesy of Dr. Debra Zynger).









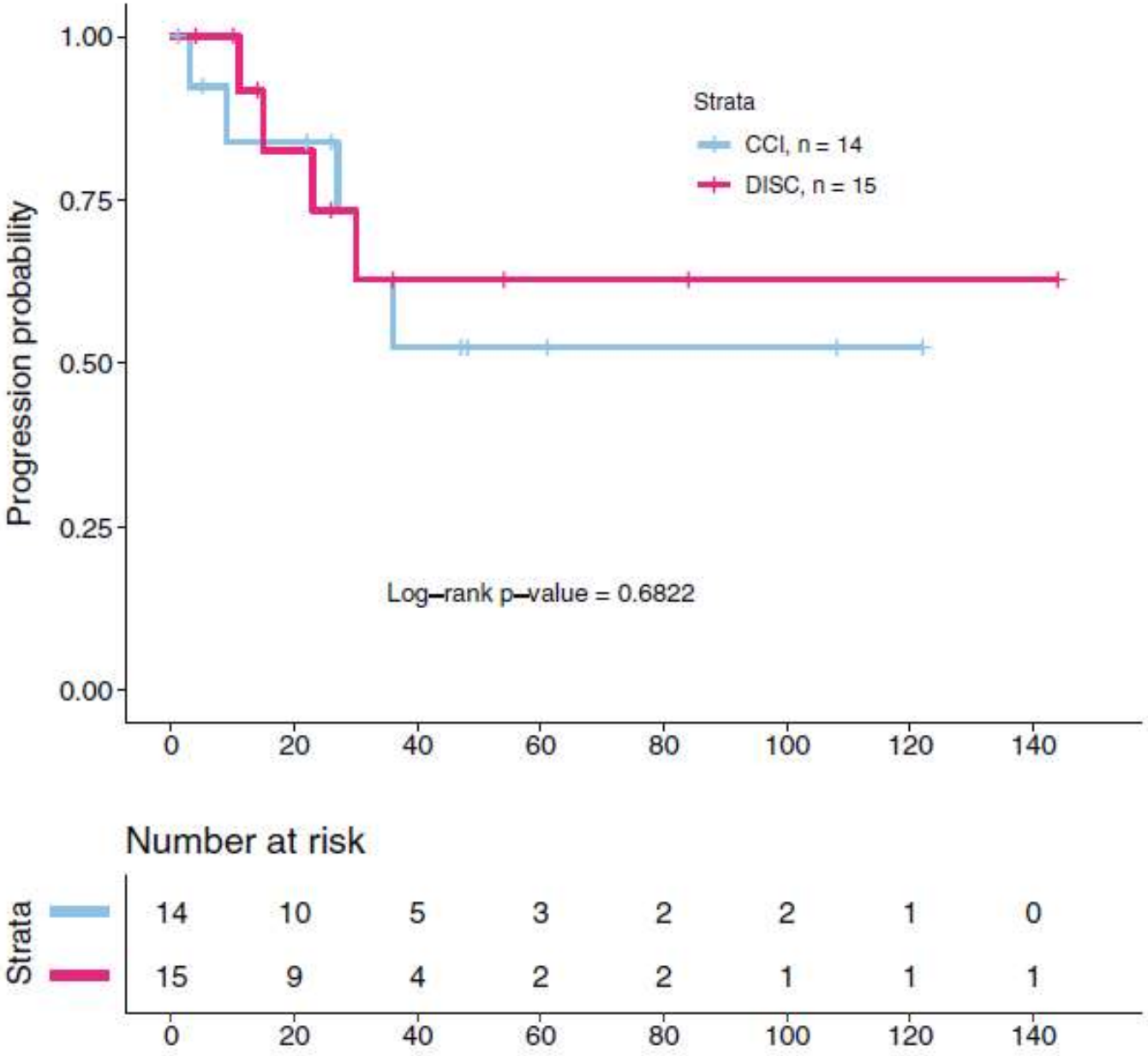


Fig. 3 Kaplan–Meier curve. Disease progression by tumors with cord involvement.