South Bay April 2024

Disclosures
April 1, 2024

Dr. Greg Charville has disclosed a financial relationship as an advisory board member for Intuitive Surgical, Inc. The planners have determined that this relationship is not relevant to the clinical diagnostic (GI) case being presented. The remaining activity planners and faculty listed below have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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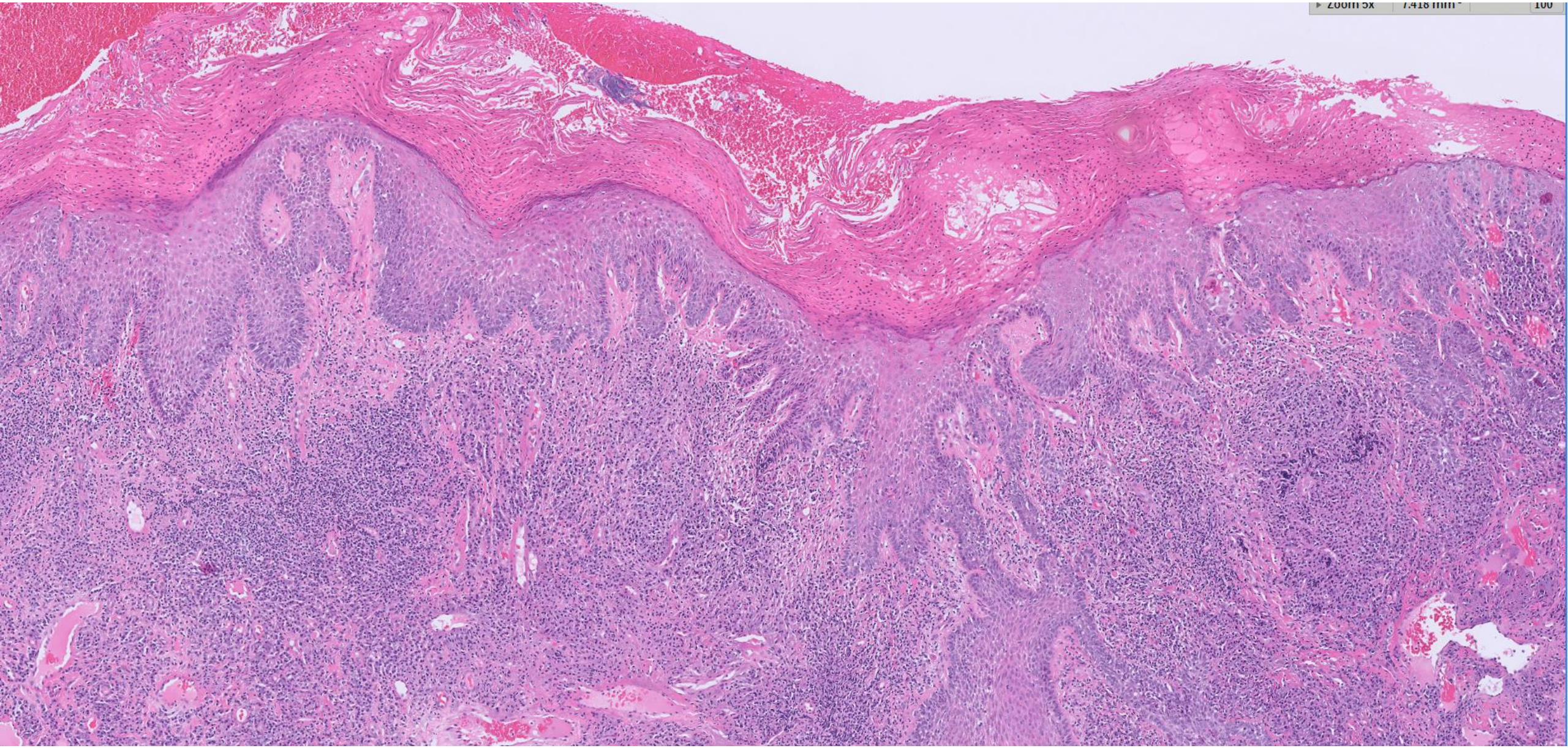
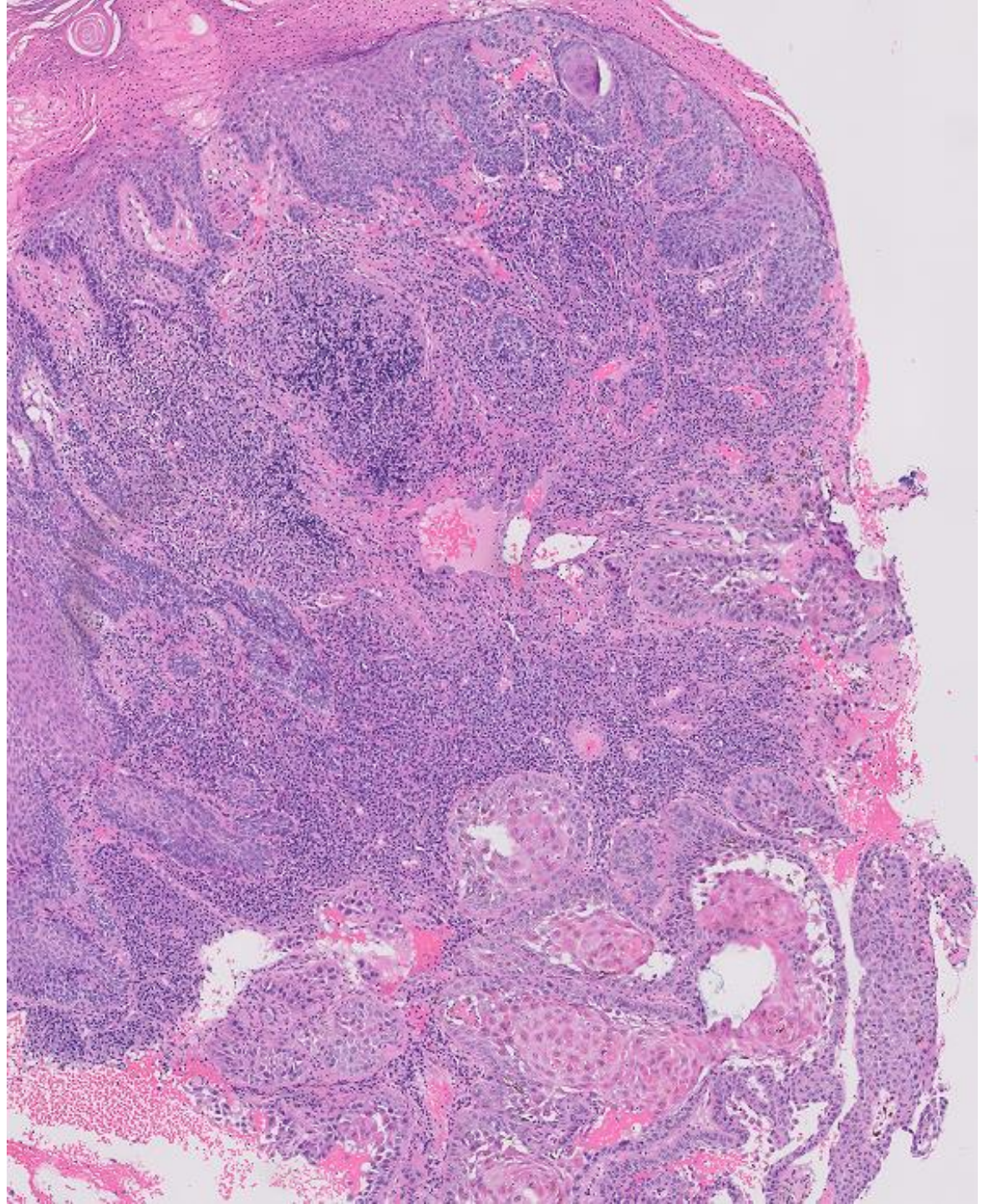
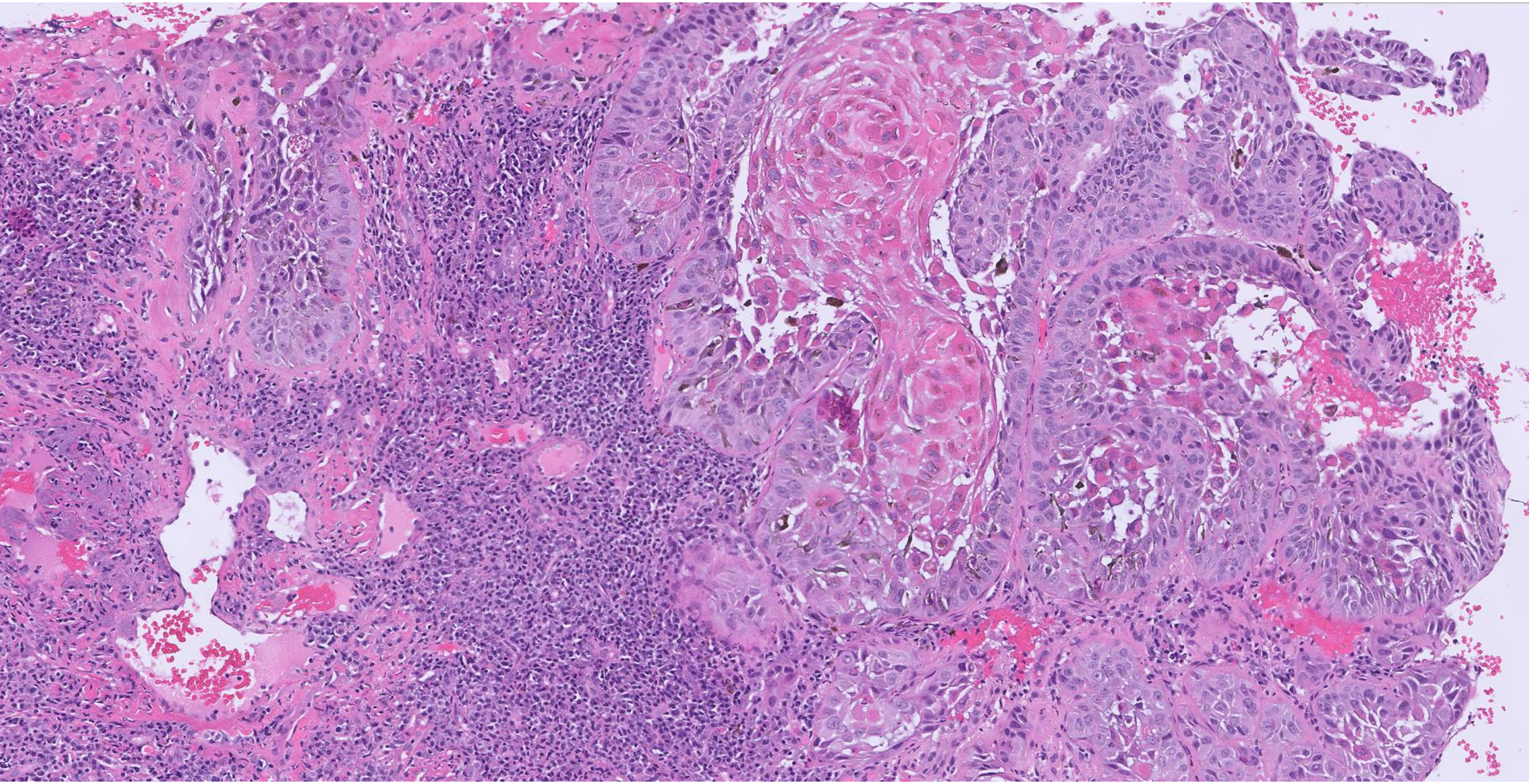
24-0401

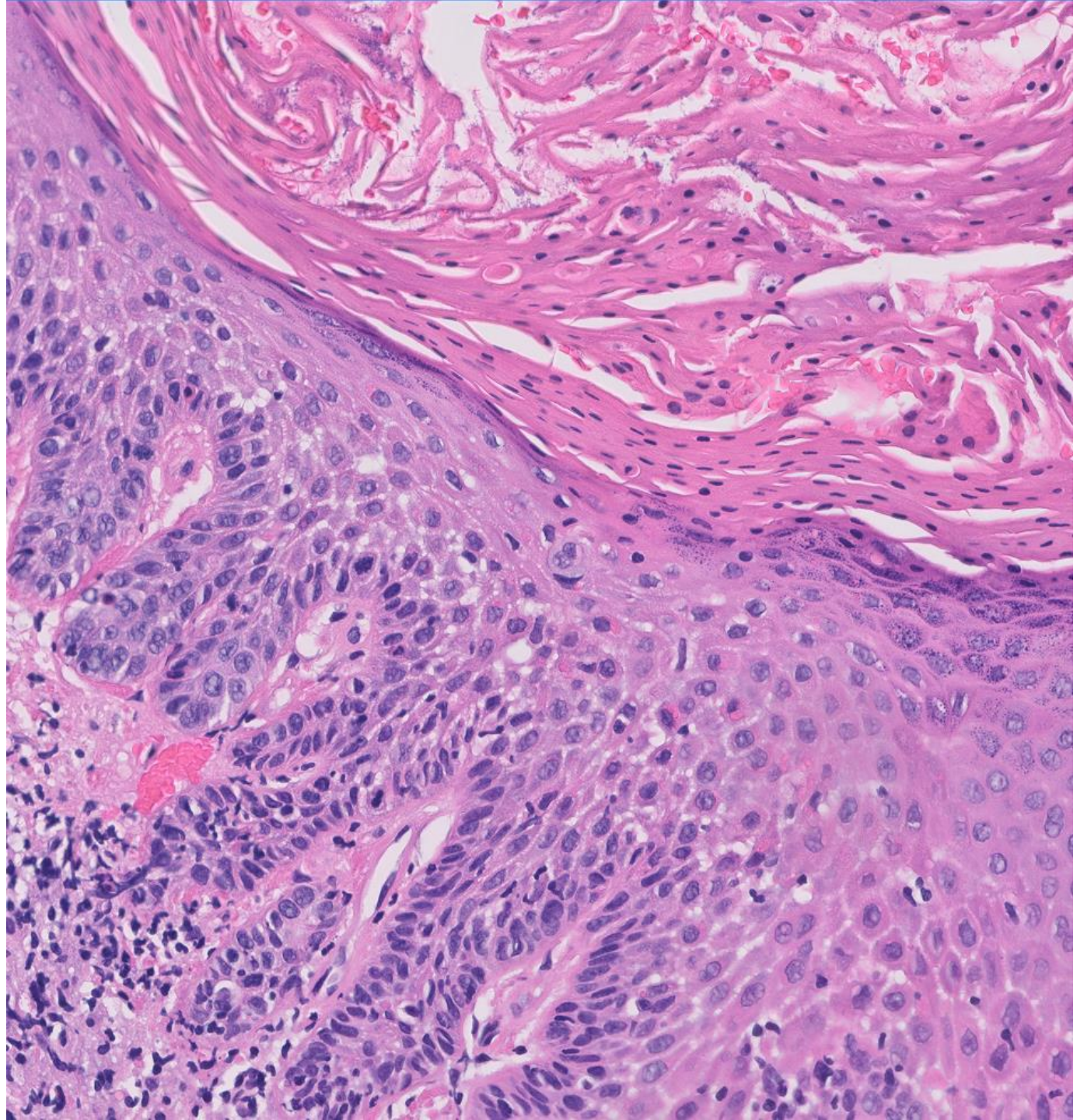
Ashley Monsrud and Brooke Howitt; Stanford

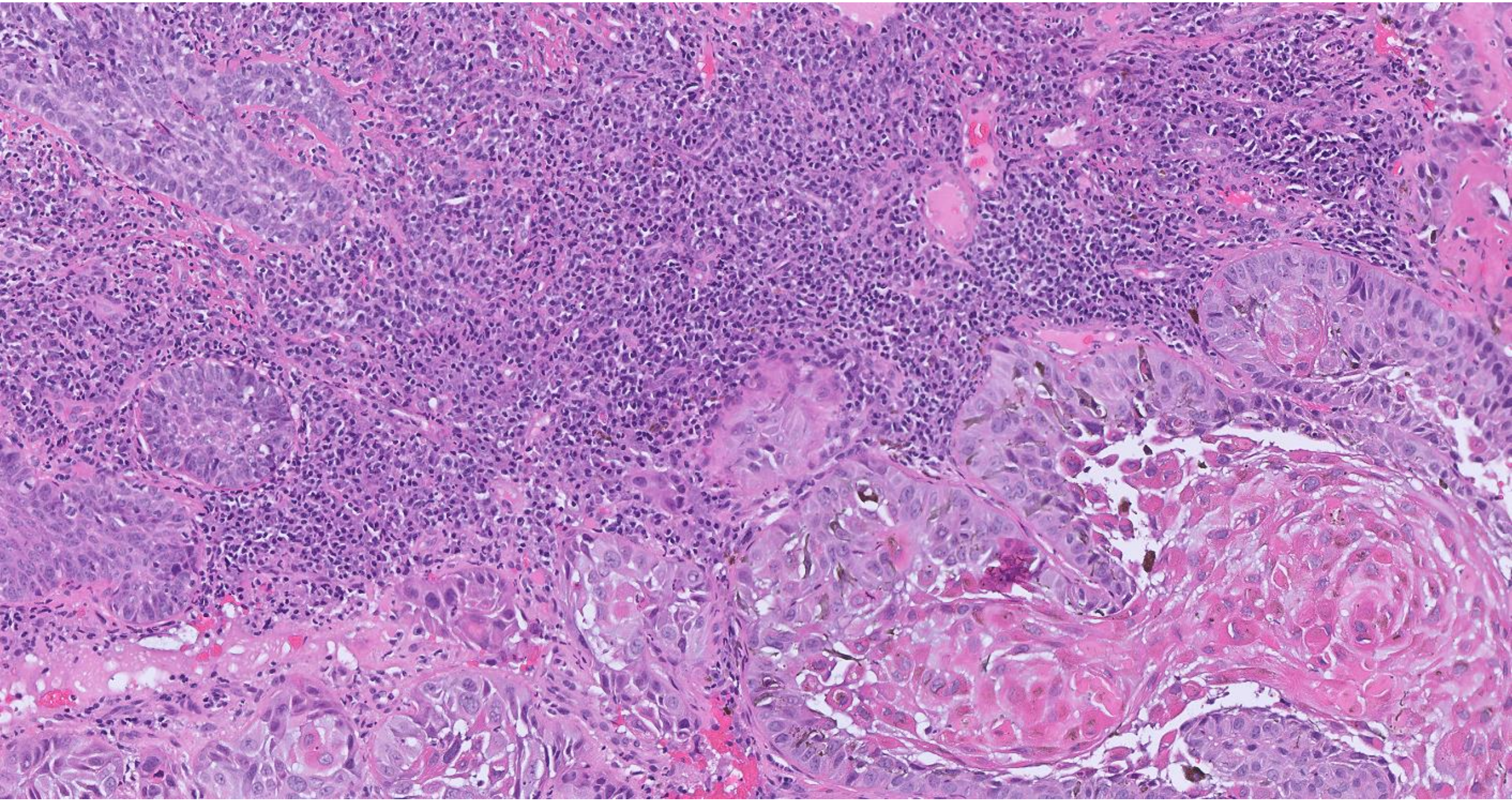
71-year-old female with a 4 cm vulvar mass

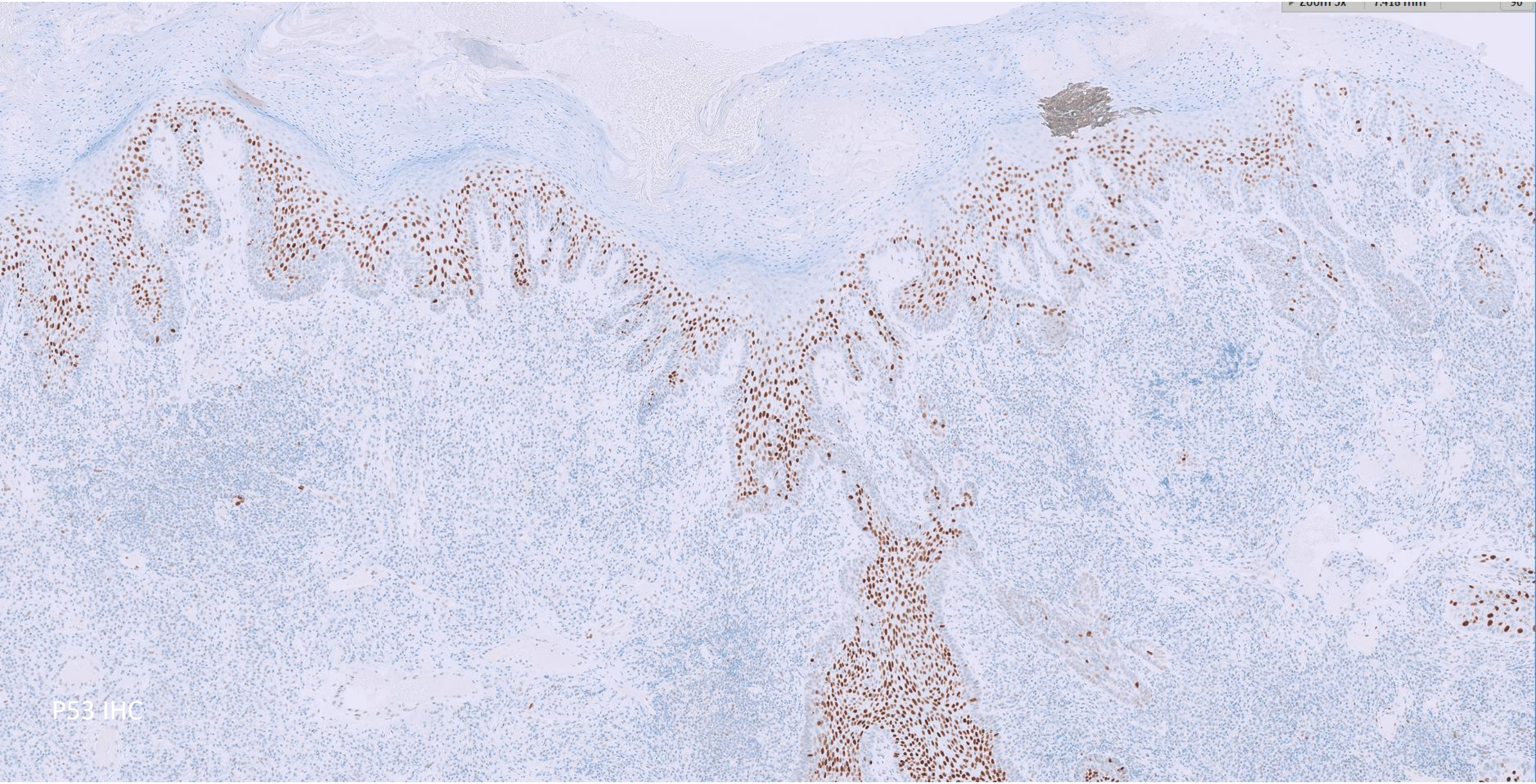






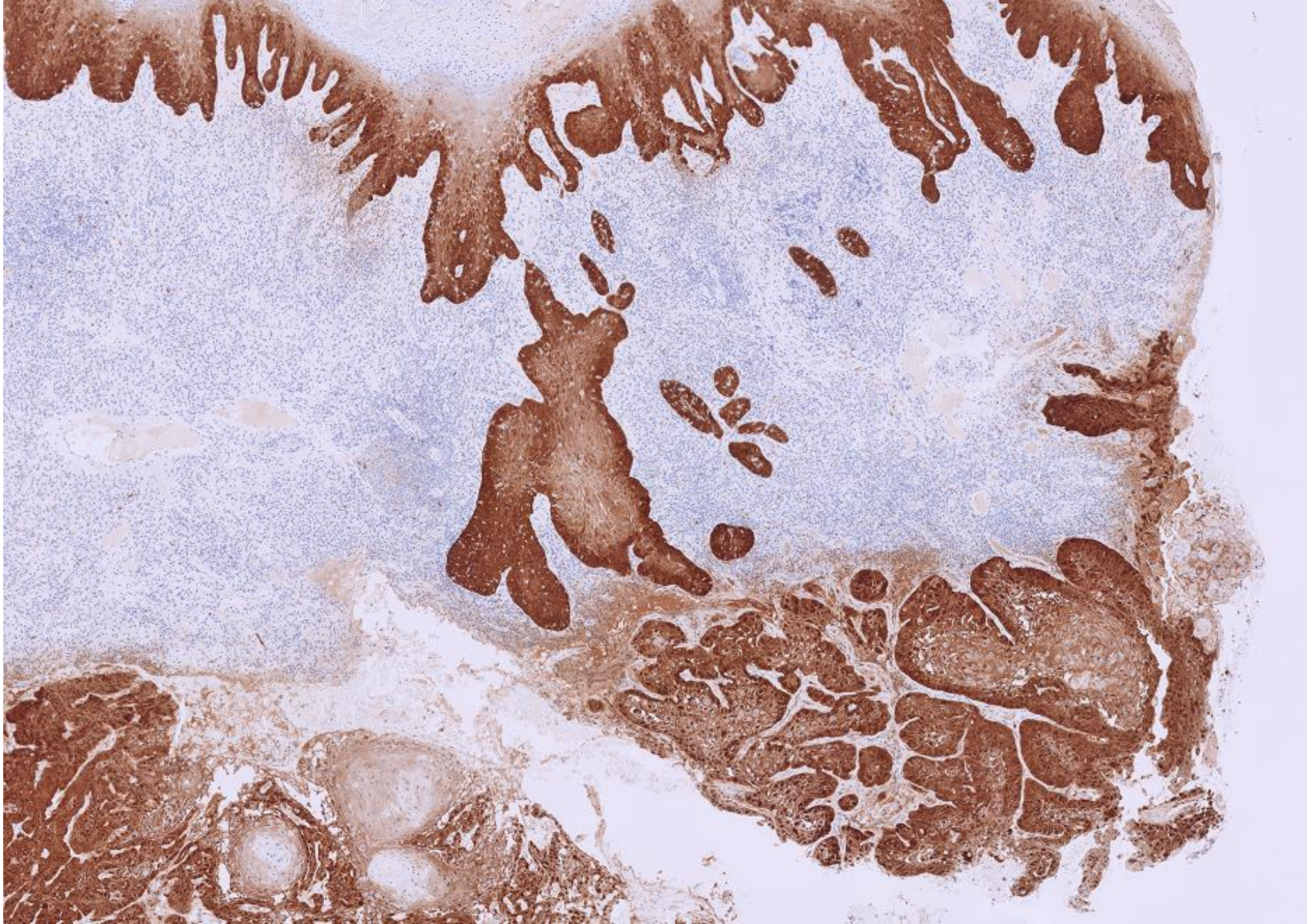


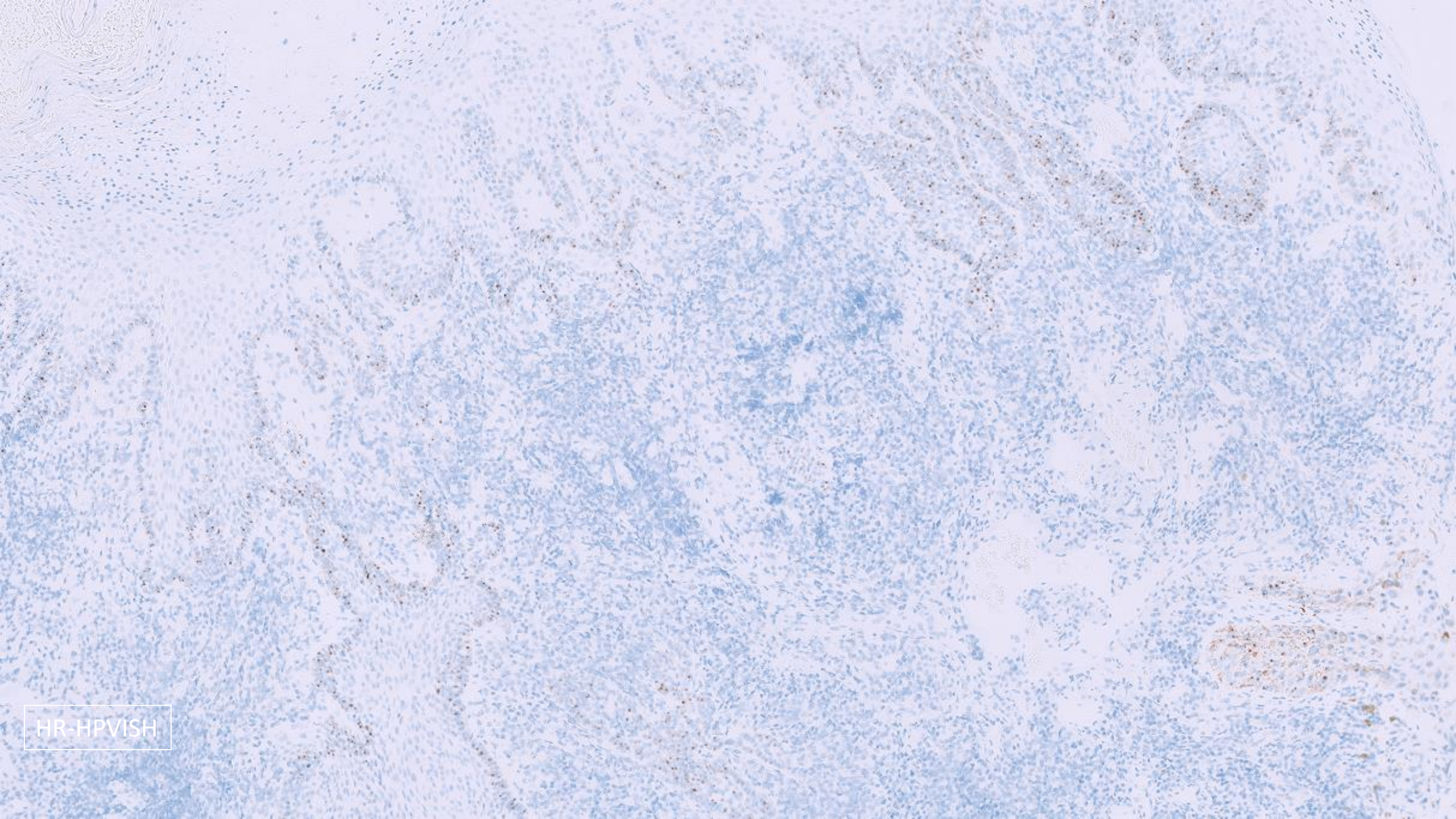



P53 IHC

DIAGNOSIS?

- P16 IHC

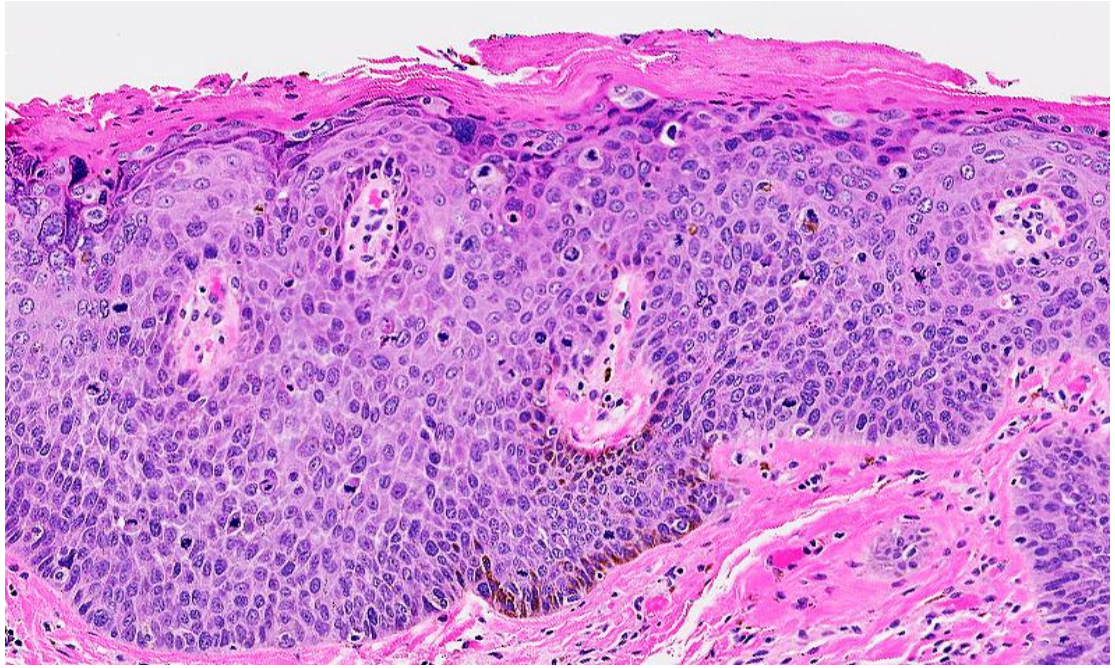



HR-HPVISH

Invasive squamous cell carcinoma, HPV-associated

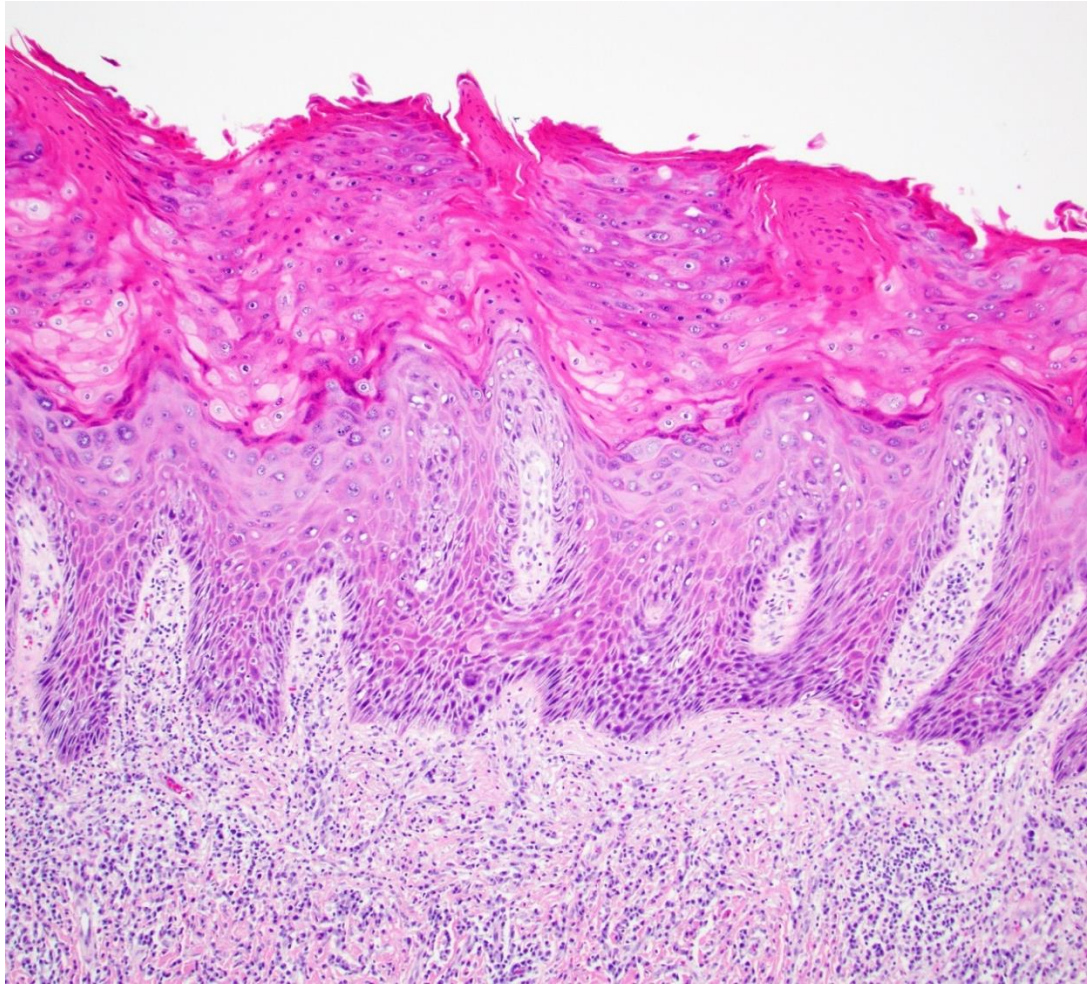
"Typical" morphology of HPV-associated precursors

- Cytological atypia with nuclear hyperchromasia
- High nuclear: cytoplasmic ratio
- Loss of maturation



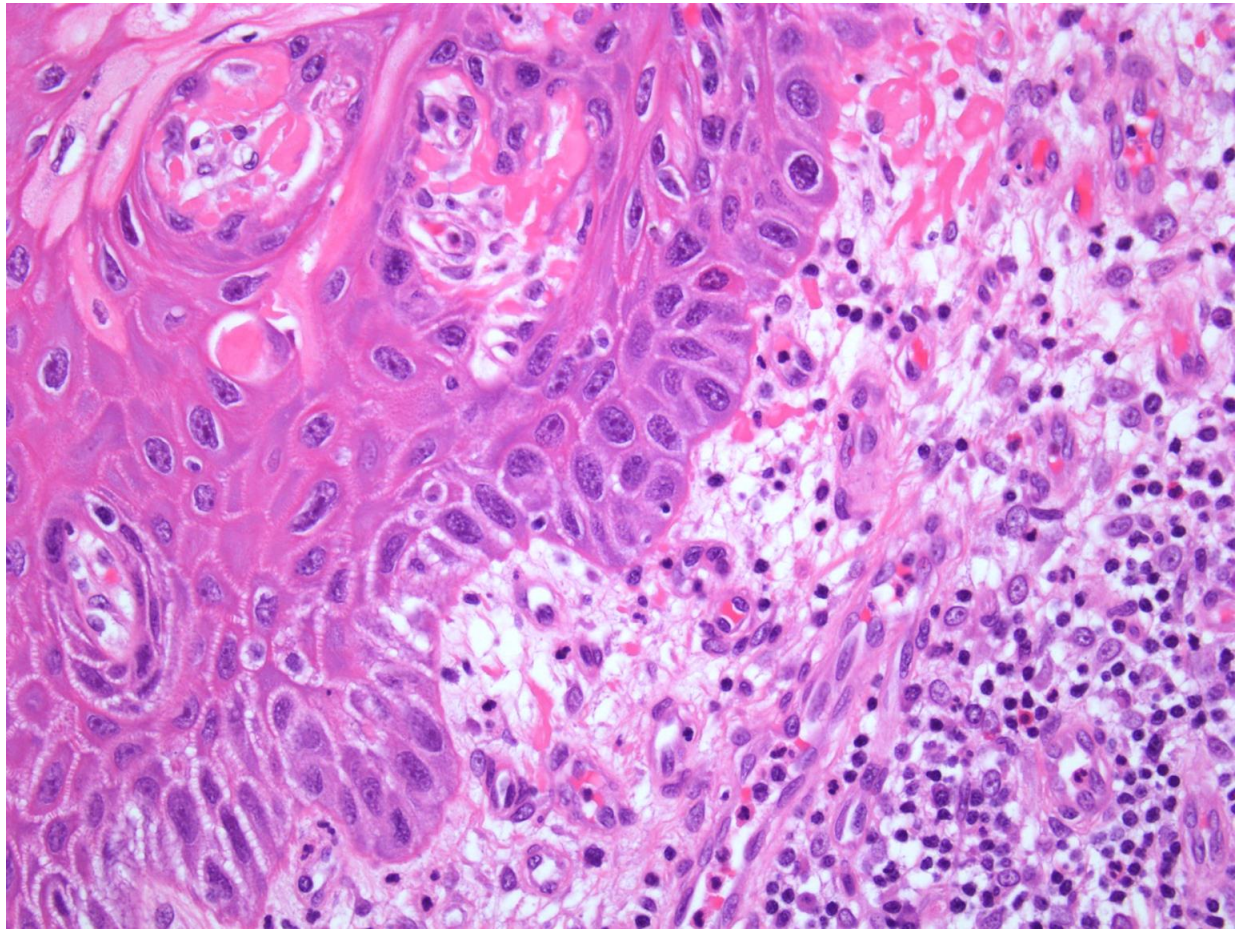
"Typical" morphology of differentiated VIN (dVIN): HPV-independent, p53mutant

- Typically thickened epithelium
- Elongated and/or fused rete ridges
- Prominent parakeratosis
- Dyskeratosis/abnormal keratinization



"Typical" morphology of differentiated VIN (dVIN): HPV-independent, p53mutant

- Prominent basal atypia:
  - Hyperchromasia
  - Nuclear enlargement
  - Prominent nucleoli
  - +/-atypical mitoses
- Prominent intercellular bridges in absence of inflammation



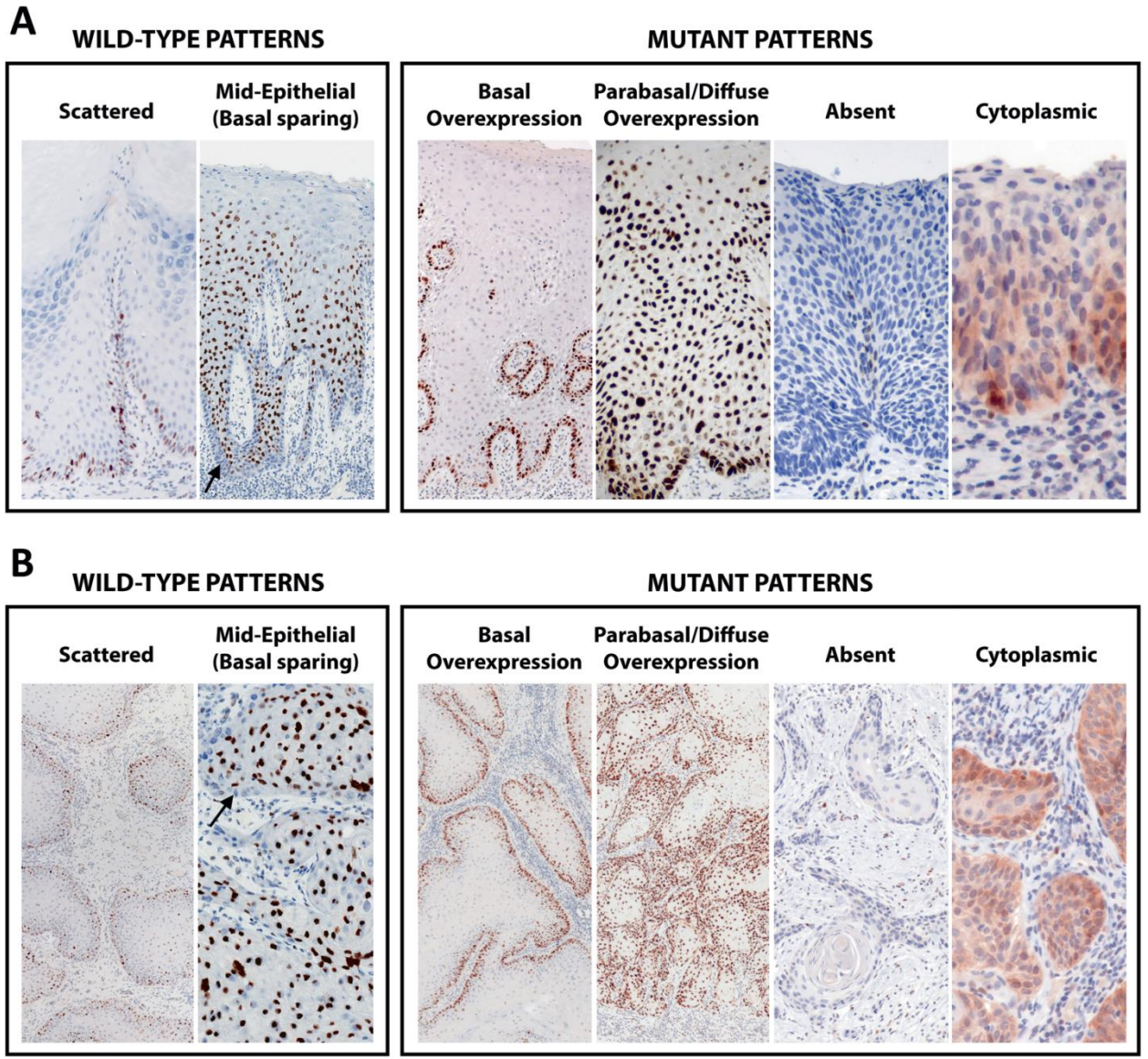
Interpretation of p53 in vulvar squamous lesions

- In the vulva, p53 staining pattern is evaluated in the basal layer (+/- extension into parabasal layer)
  - Overexpression pattern: Uniform, moderate to strong staining in basal layer (>70%), ideally with extension into parabasal layers
  - Null pattern: Complete absence of p53 staining in basal and parabasal layers

p53 interpretation in vulvar squamous lesions and cancers

In situ lesions

Invasive VSCC

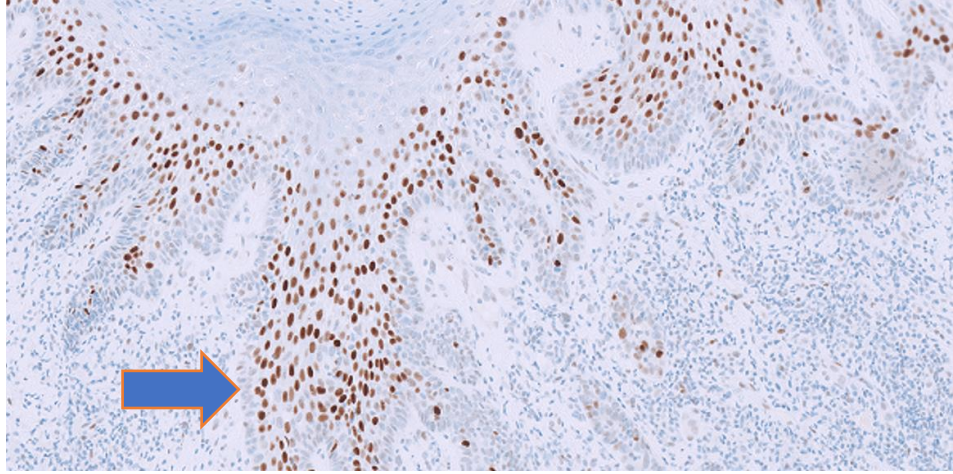


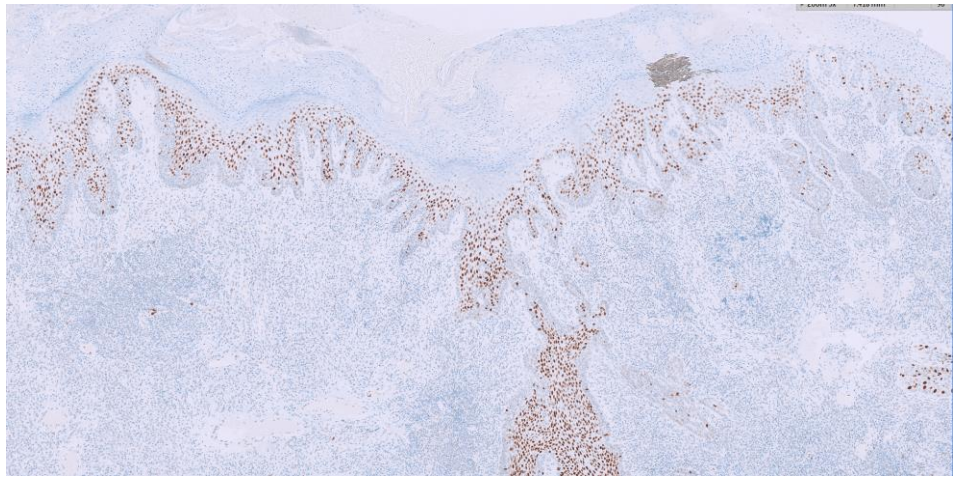
Tessier-Cloutier B et al. Mod Pathol. 2020 Aug;33(8):1595-1605.

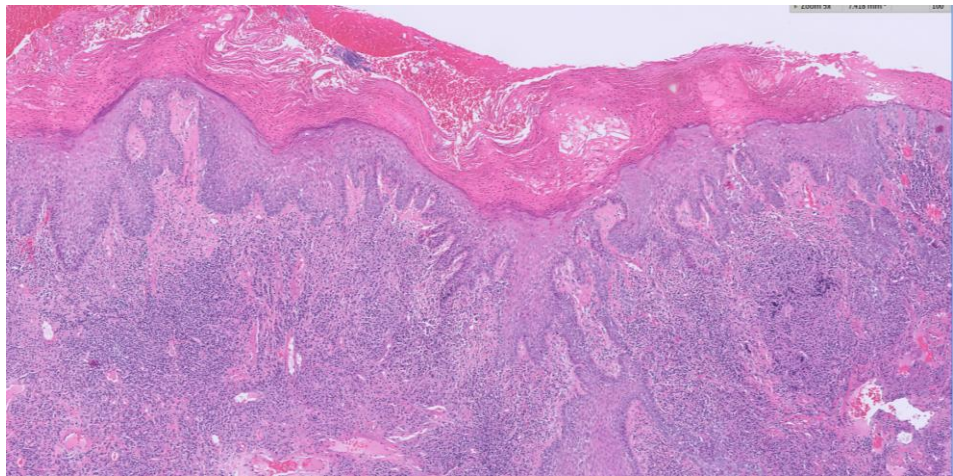
PITFALL

What type of pattern is this P53 staining in our case?

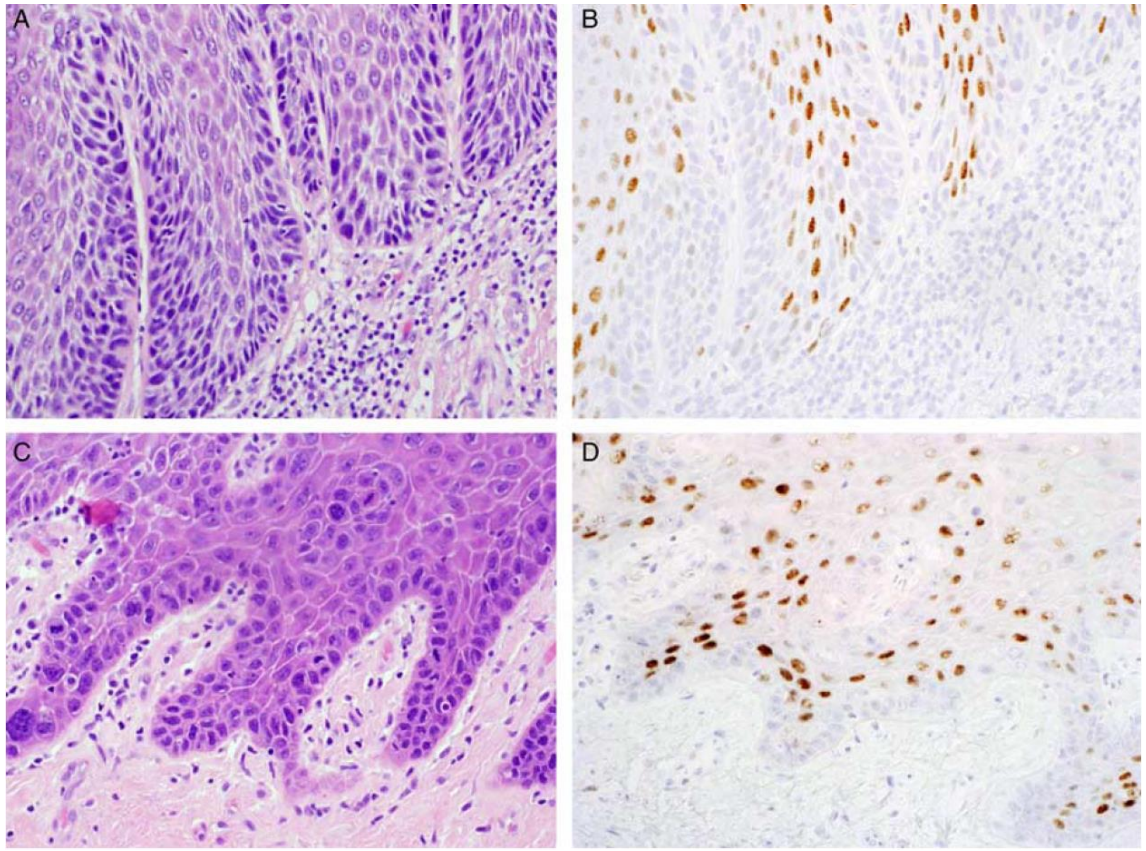
- Wild type pattern (basal sparing)







Moderate parabasal/mid-epithelial p53 positivity with sparing of the basal layer is seen in HPV-associated HSIL with LSC



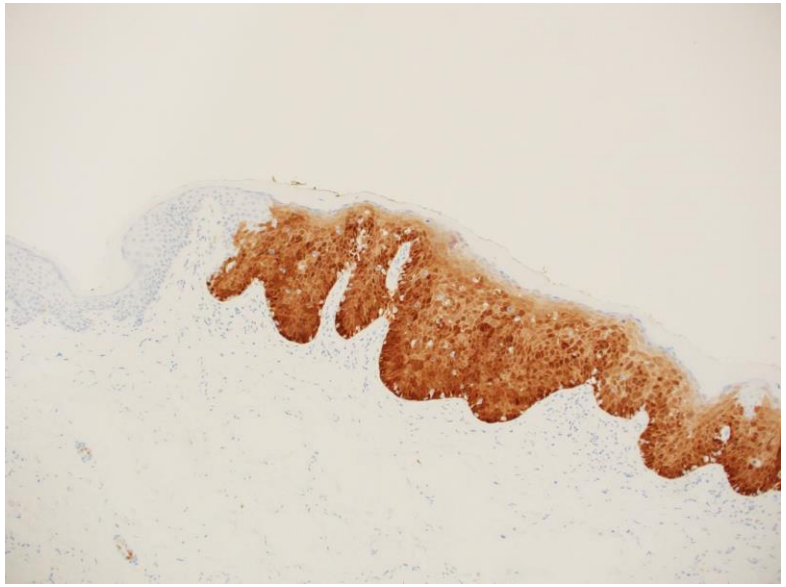
Original Article

Classic Vulvar Intraepithelial Neoplasia With Superimposed Lichen Simplex Chronicus: A Unique Variant Mimicking Differentiated Vulvar Intraepithelial Neoplasia

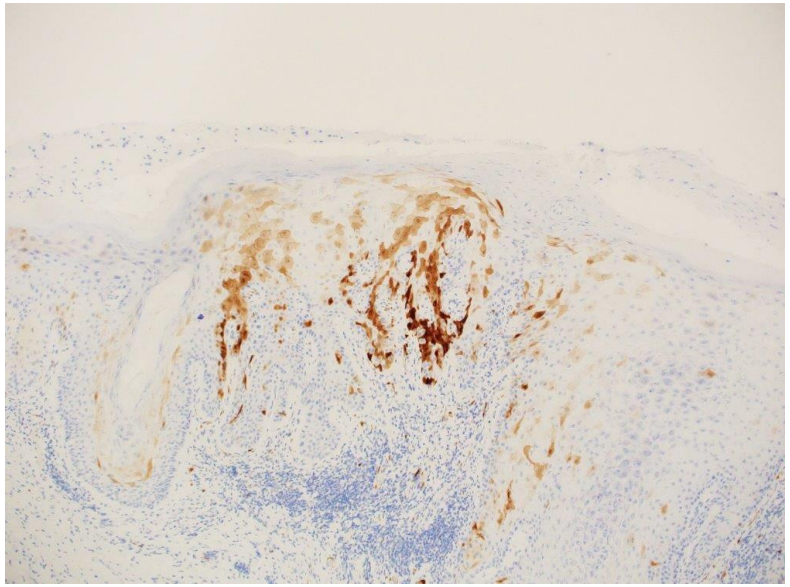
Jaclyn C. Watkins, M.D., M.S., Eric Yang, M.D., Ph.D., Christopher P. Crum, M.D., Michael Herfs, Ph.D., Tarik Gheit, Ph.D., Massimo Tommasino, Ph.D., and Marisa R. Nucci, M.D.

Interpretation of p16 in vulvar squamous lesions

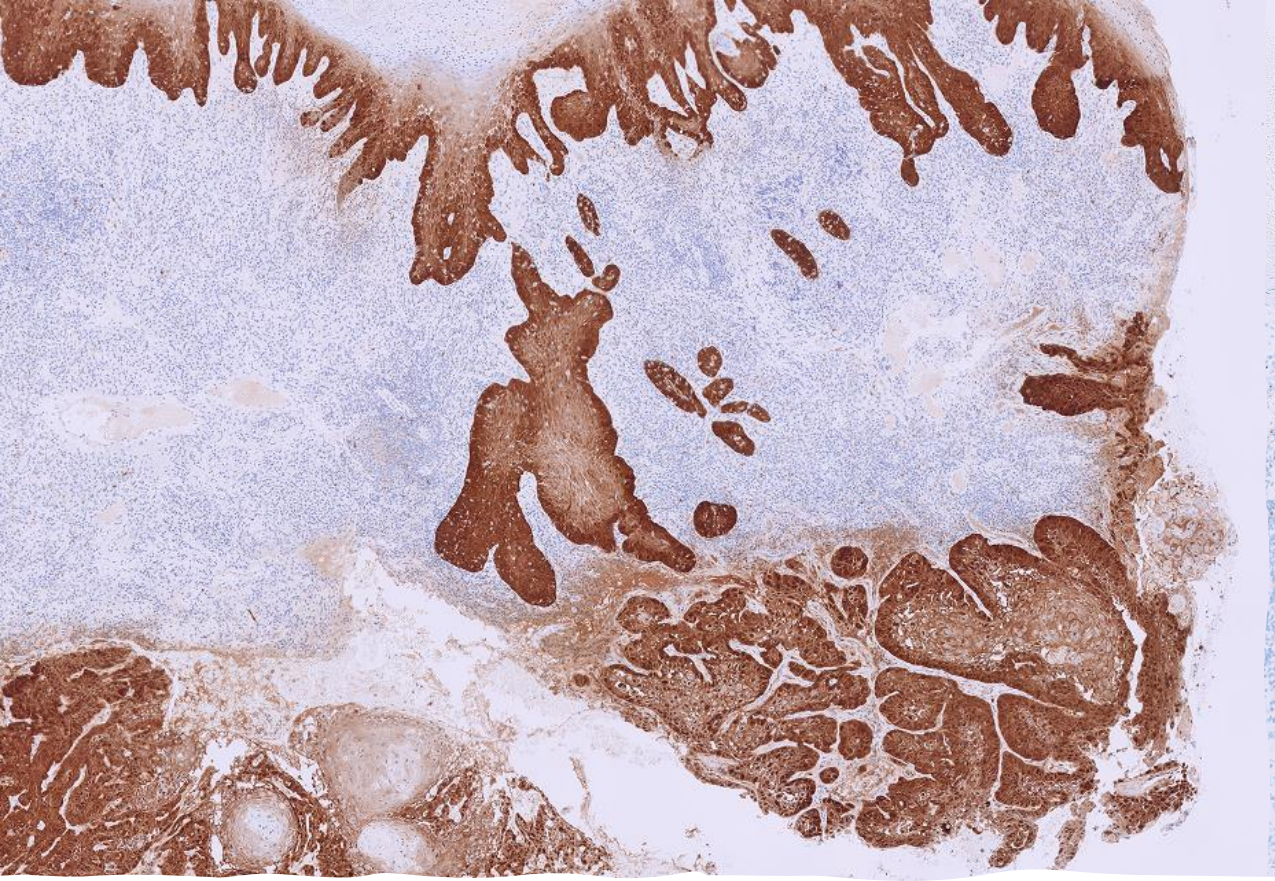
“Block” strong positivity: Strong positive cytoplasmic and nuclear p16 immunostaining of all basal epithelial cells, with variable extension into the superficial layers, often into 1/3 -2/3 of epithelial thickness

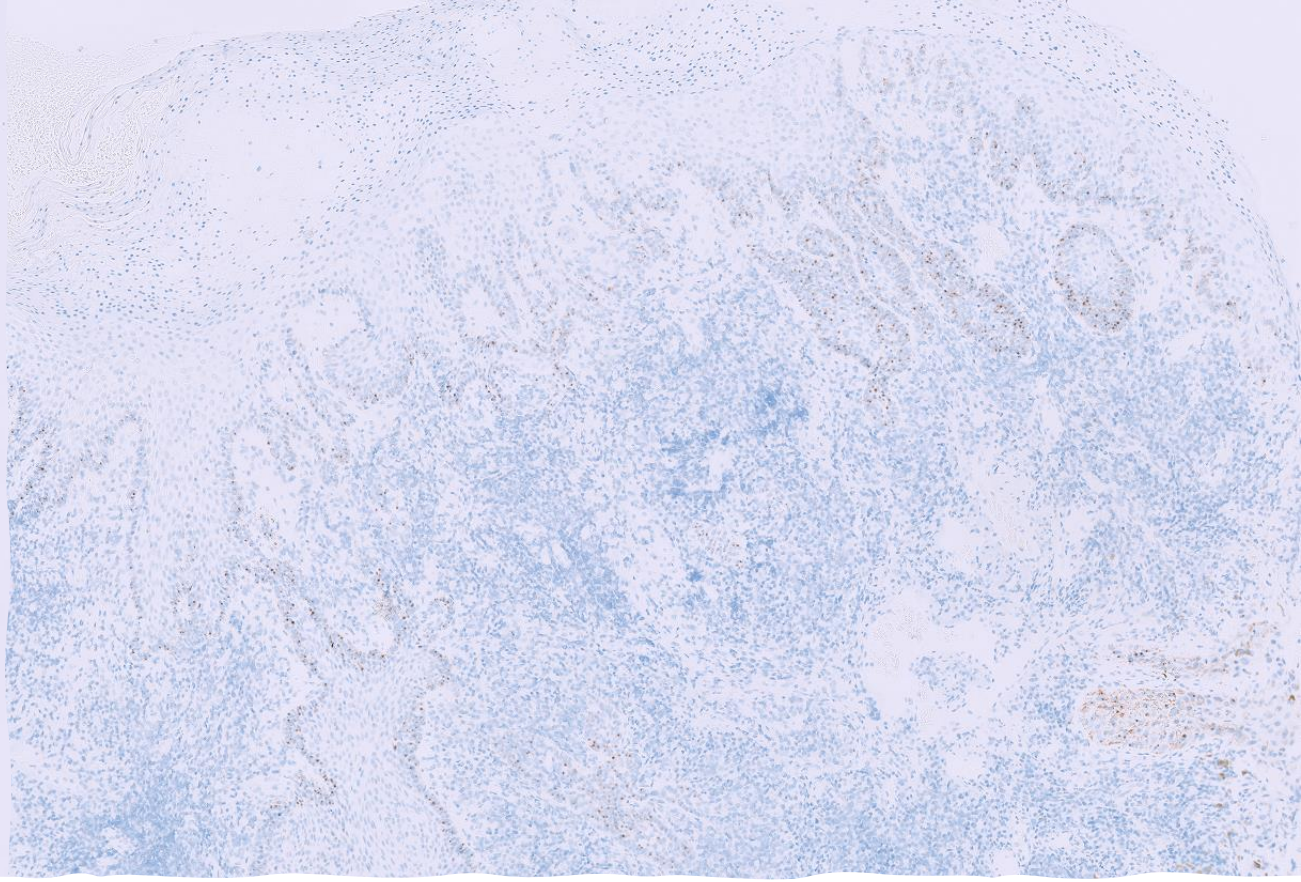


P16 positive examples



P16 negative example

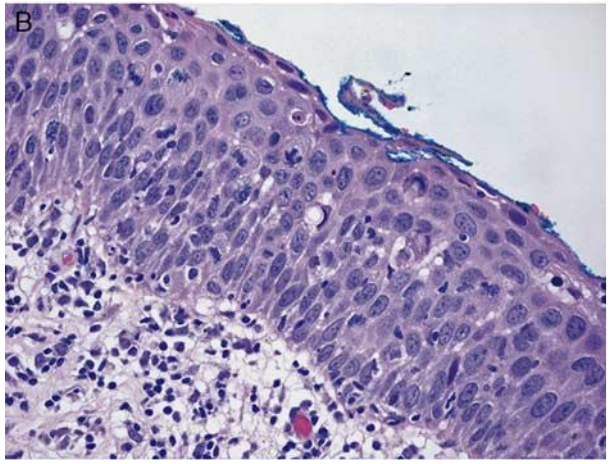


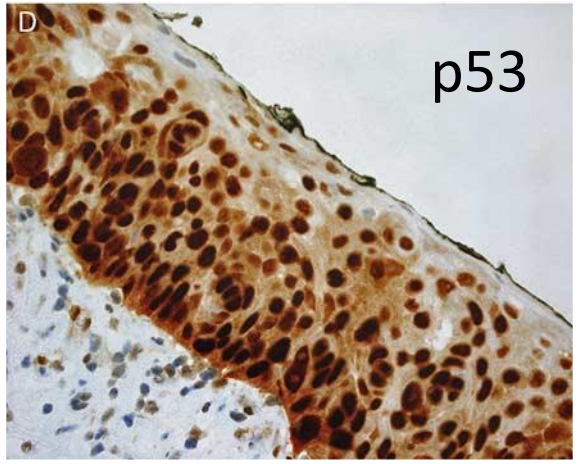


Our case demonstrating p16 block positivity and HR-HPVISH expression

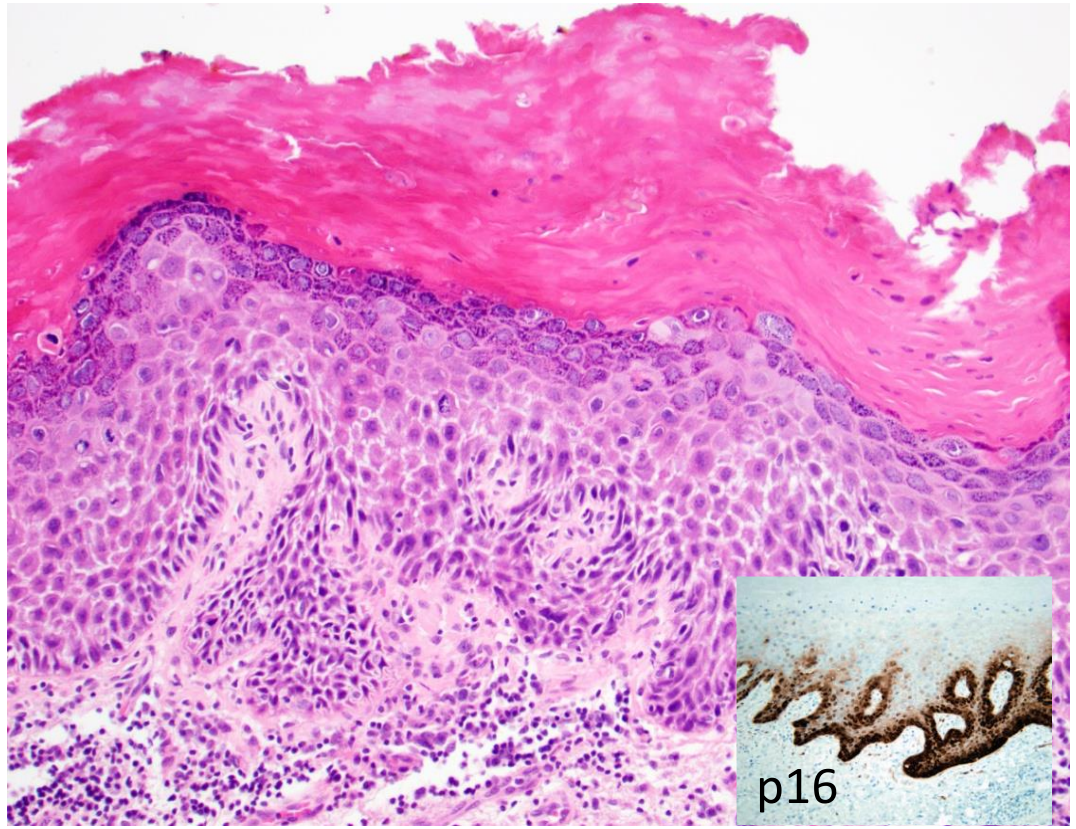
Morphologic overlap, pitfalls

dVIN





HSIL



Bigby et al, Int J Gynecol Pathol Vol. 35, No. 6, November 2016

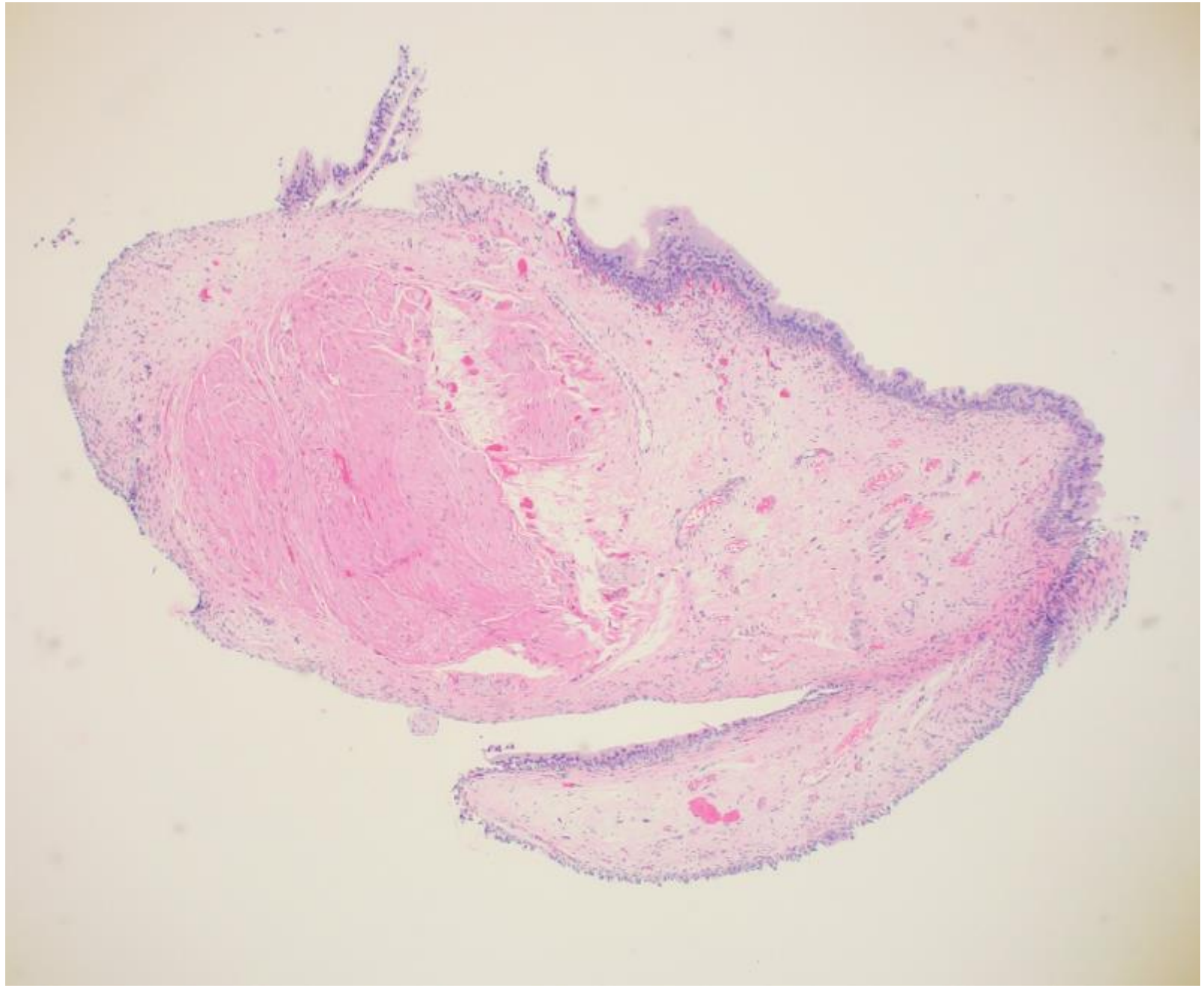
Take away points

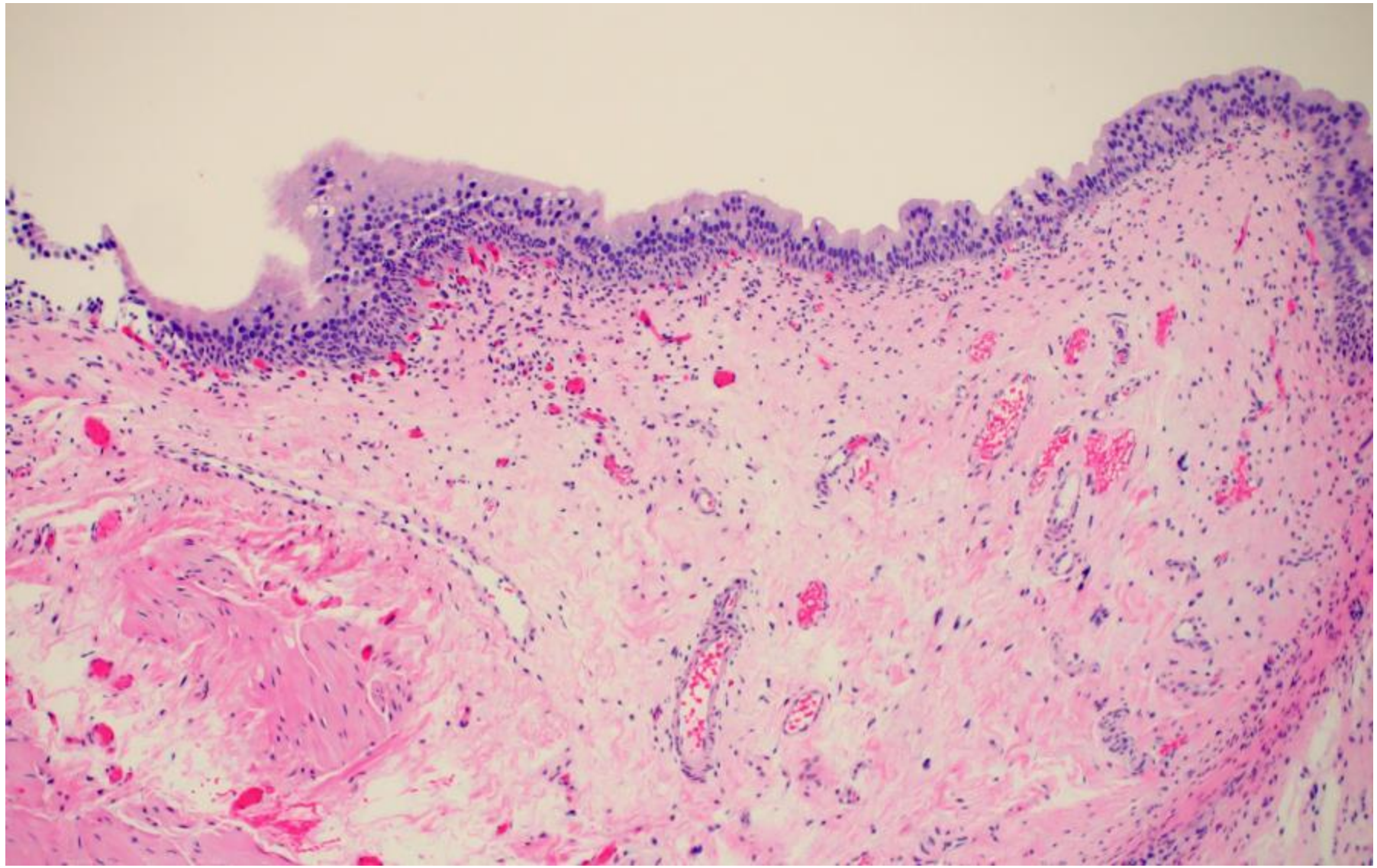
- Vulvar squamous lesions
  - Two broad groups:
    - HPV-associated
      - Typically younger patients
    - HPV-independent
      - Typically older/postmenopausal women, inflammatory dermatoses background; longstanding lichen sclerosus or lichen simplex chronicus
- Morphology can overlap!
  - USE IHCs (and interpret correctly*)
    - p16 (strong block positivity) +/- HPV testing
    - p53 (**basal layer uniformly moderate-strong diffuse staining** ideally with parabasal extension)

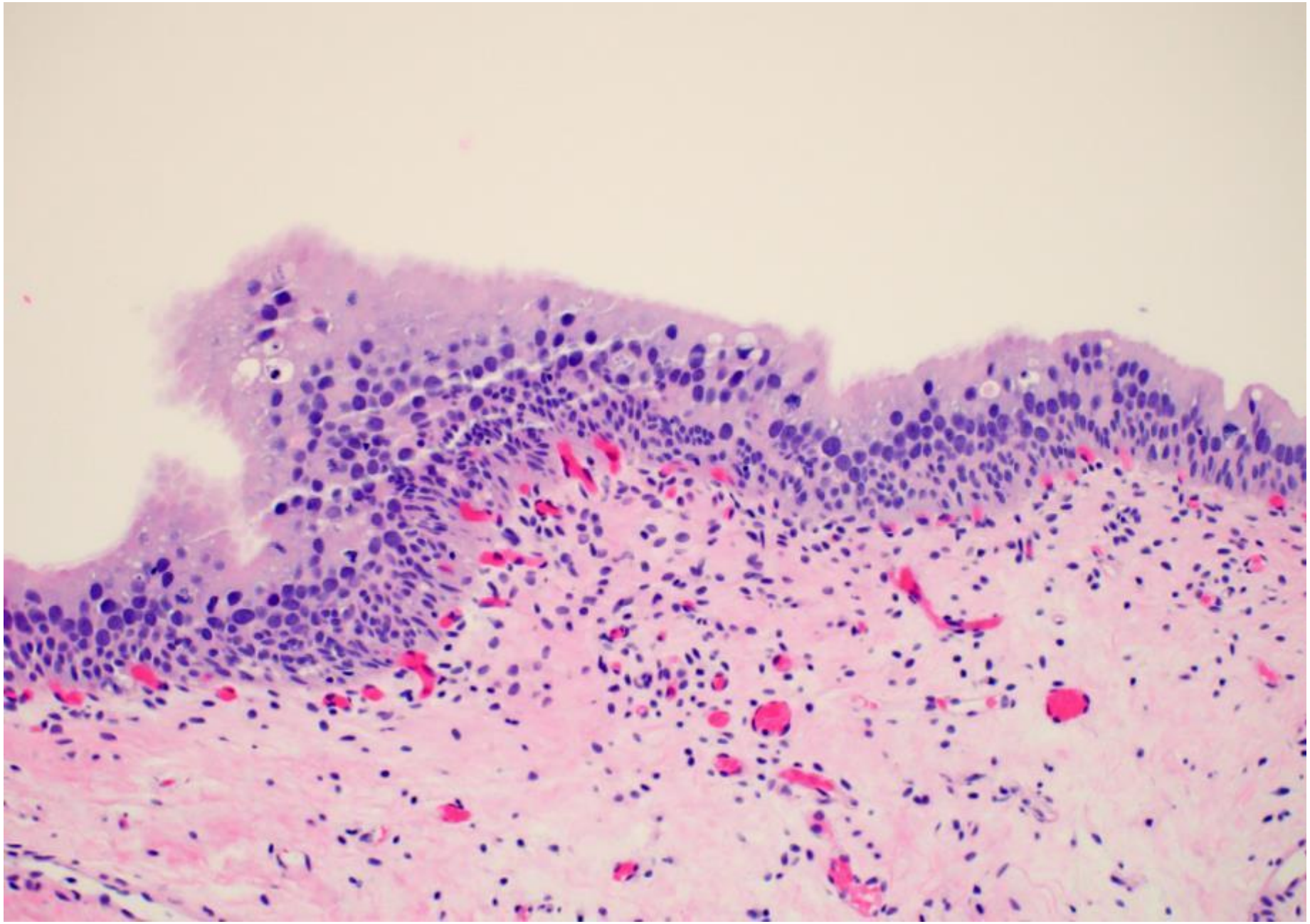
24-0402

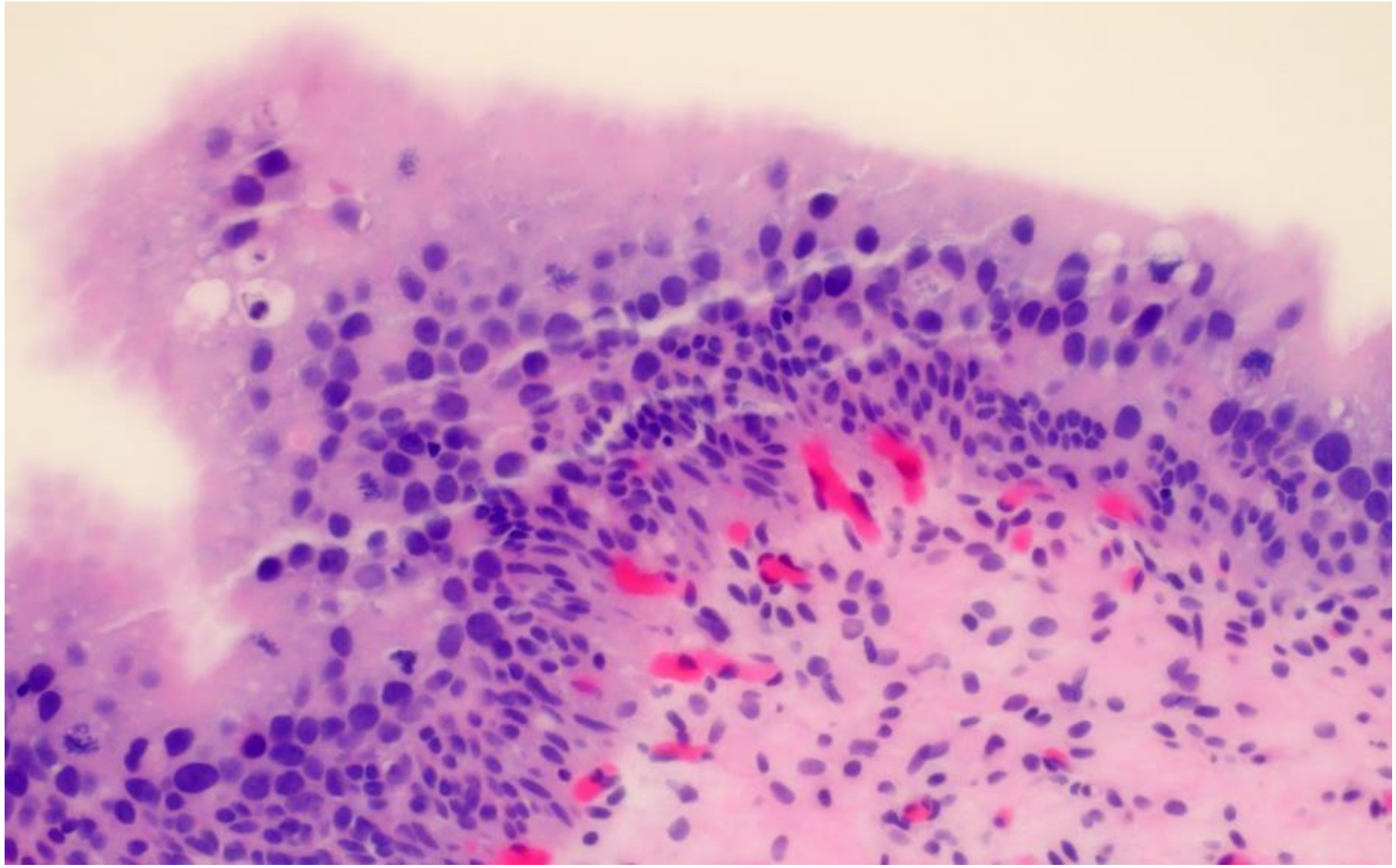
Emily Chan; case from her time at UCSF

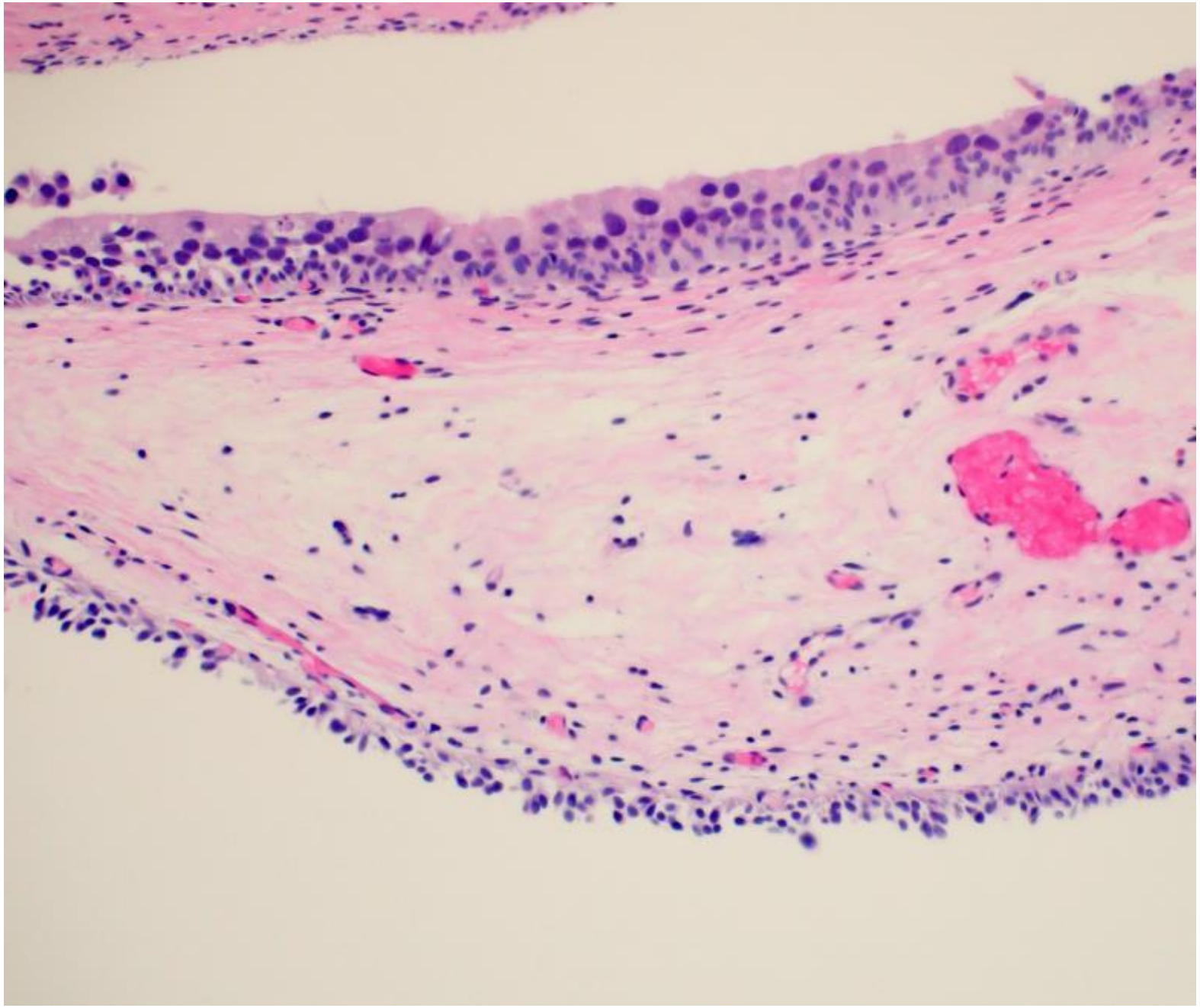
78-year-old man with microscopic hematuria and abnormal urine cytology. Cystoscopy shows no abnormal lesions random bladder biopsies





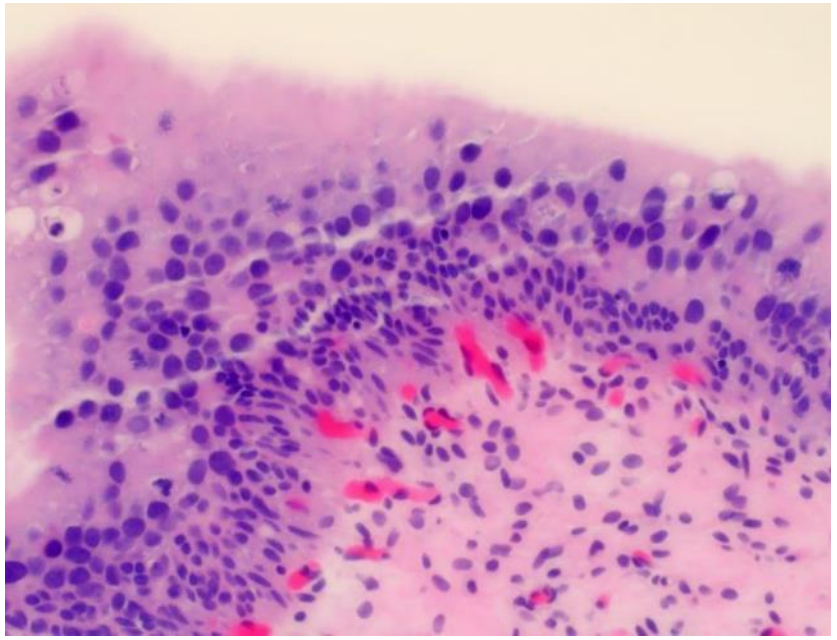






DIAGNOSIS?

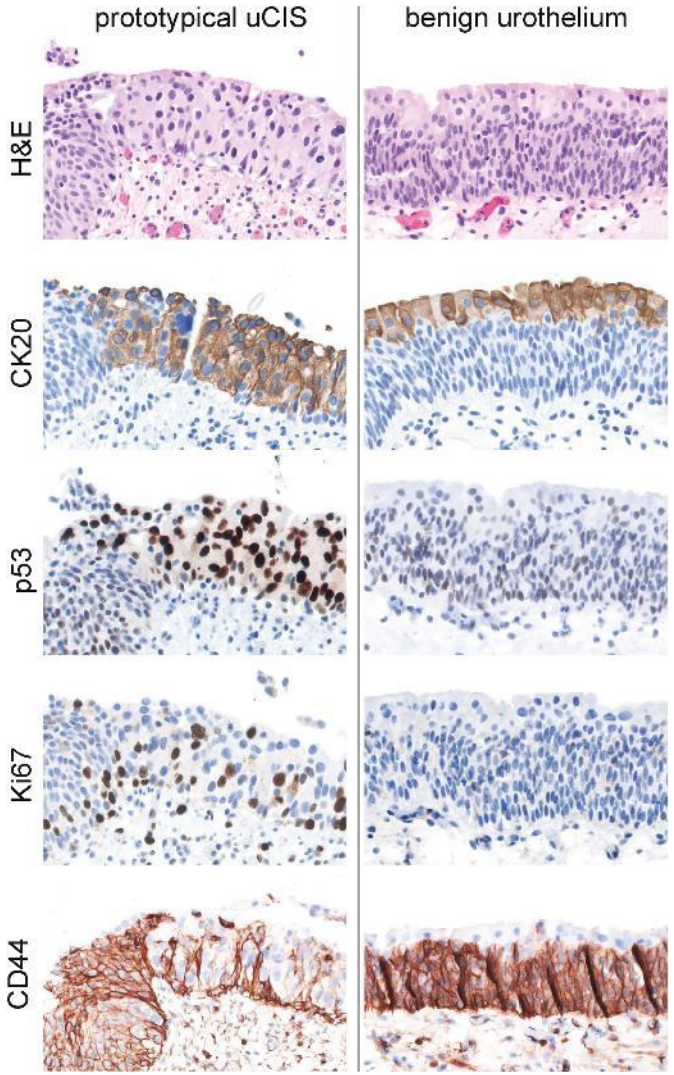
Differential Diagnosis



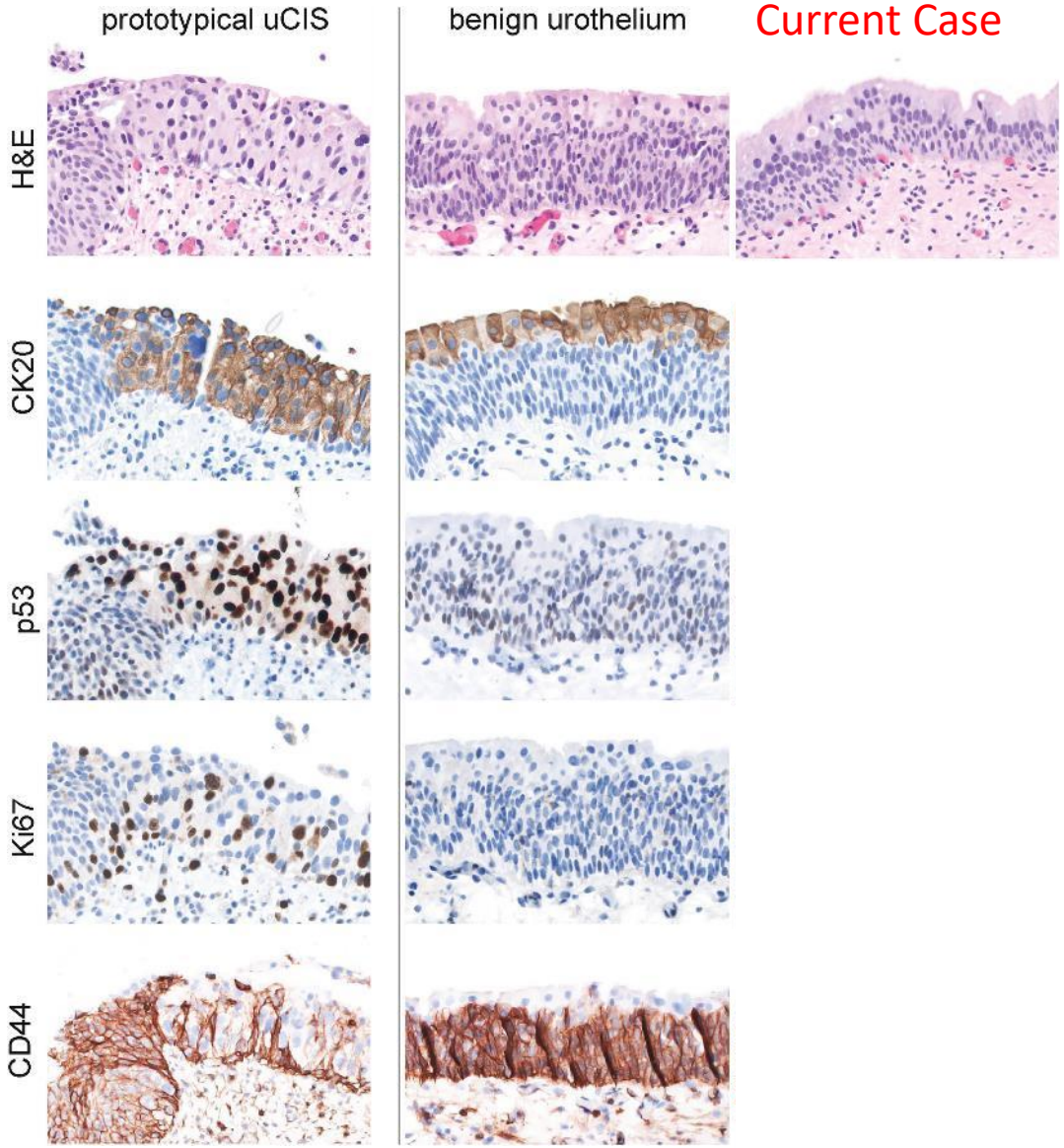
- Benign urothelium with bizarre umbrella cells/reactive urothelial atypia
- Glandular metaplasia (with/without dysplasia??)
- Urothelial carcinoma in situ – unusual pattern??

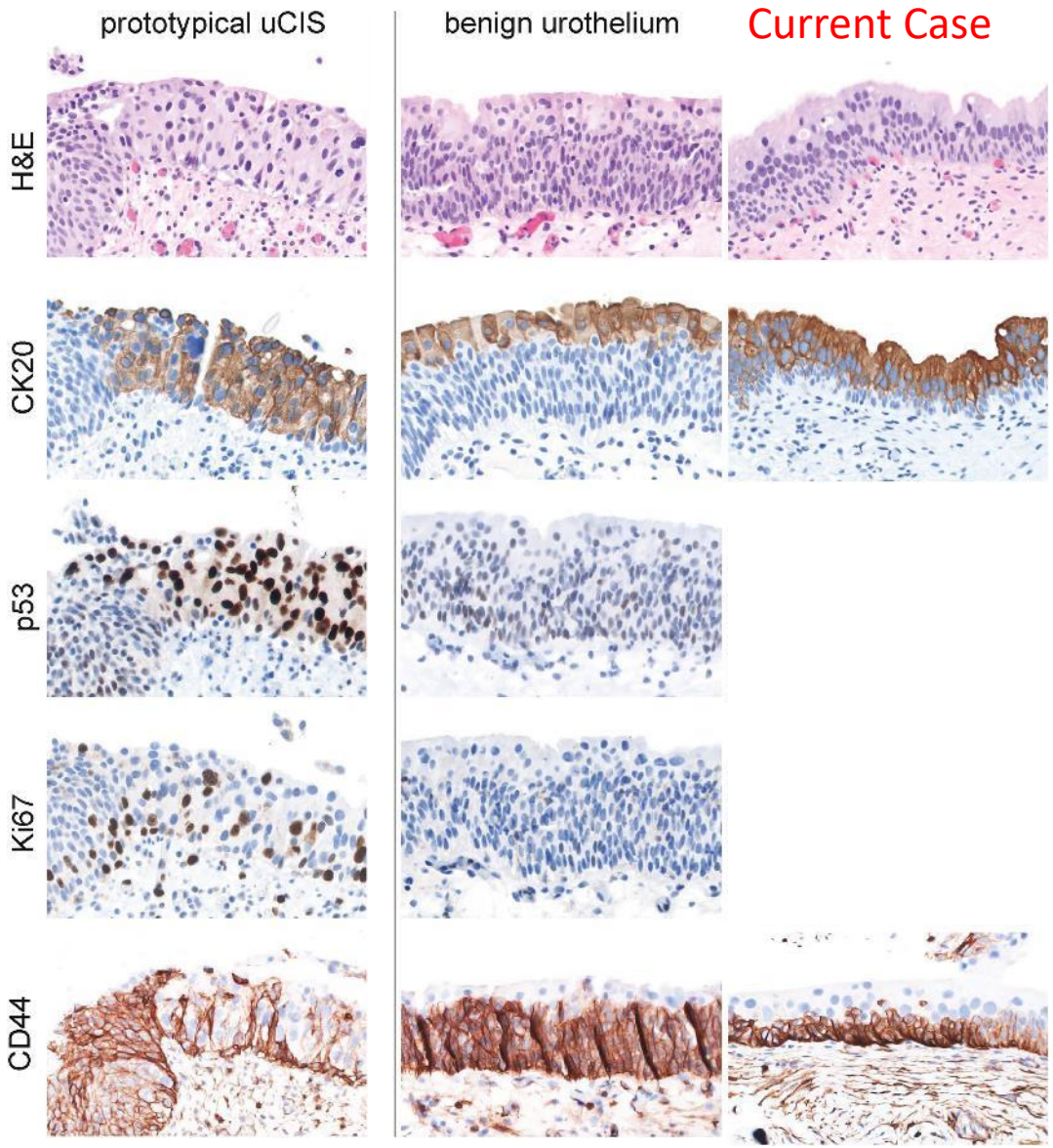
Credit to: Doruk Bahceci (Current Neuropath Fellow at UCSF)

“Useful” IHC for CIS vs reactive



CIS	**Benign/Reactive**
Full thickness	Umbrella cells only
Aberrant (diffuse strong or null)	Wildtype (variable staining)
Increased	Low
Negative	Full thickness sans umbrella cells


prototypical uCIS
benign urothelium
Current Case
H&E
CK20
p53
Ki67
CD44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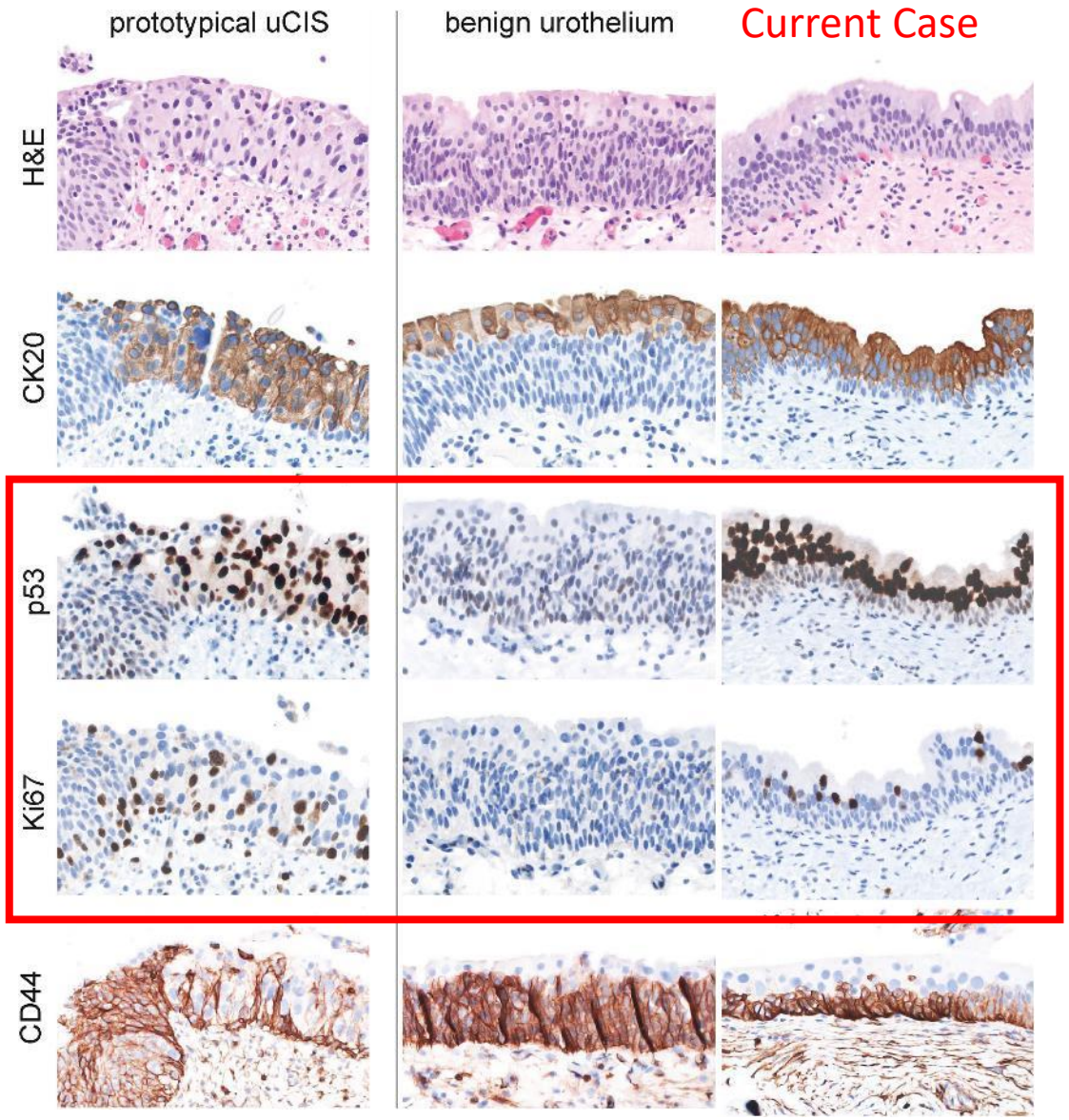

- UCSF500 NGS testing performed on the atypical urothelium revealed pathogenic mutations in *TERTp*, *TP53*, and *CDKN1a*

Final diagnosis: Urothelial atypia most compatible with urothelial carcinoma in situ

Human Pathology (2023) 136, 56–62

Human
PATHOLOGY
www.elsevier.com/locate/humpath

Original contribution

Urothelial carcinoma in situ with "*overriding*" features can evade detection by mimicking umbrella cells☆

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[b] *Robert J. Tomsich Institute of Pathology and Laboratory Medicine, Department of Pathology, Cleveland Clinic, Cleveland, OH, 44195, USA*
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Received 5 January 2023; revised 20 March 2023; accepted 24 March 2023

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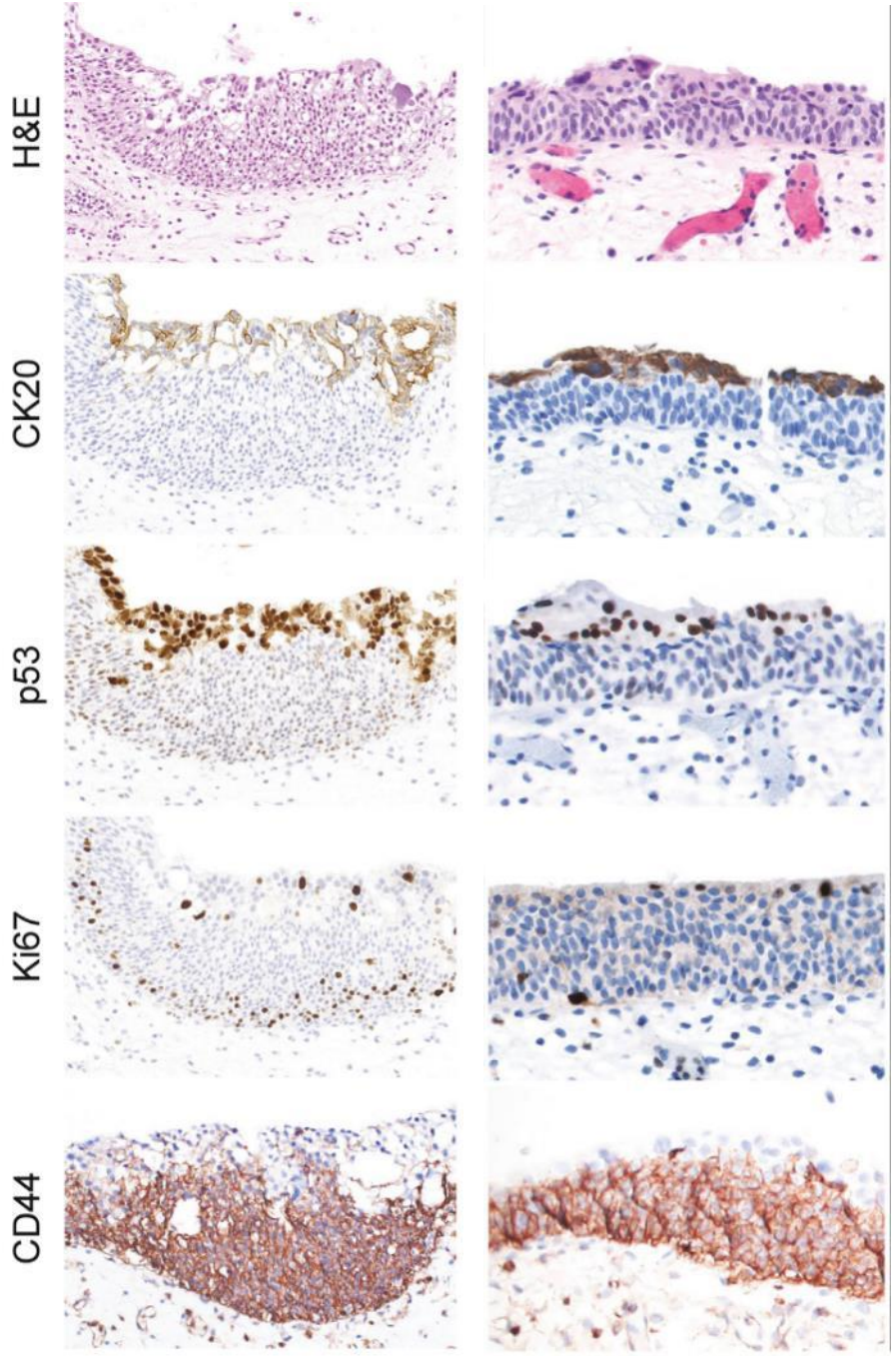


- Three cases described, the other two with more conventional CIS patterns adjacent/nearby

Bahceci D, Nguyen JK, Sangoi AR, Stohr BA, Chan E. Urothelial carcinoma in situ with "overriding" features can evade detection by mimicking umbrella cells. Hum Pathol. 2023 Jun;136:56-62. doi: 10.1016/j.humpath.2023.03.007. Epub 2023 Mar 29. PMID: 36997033.

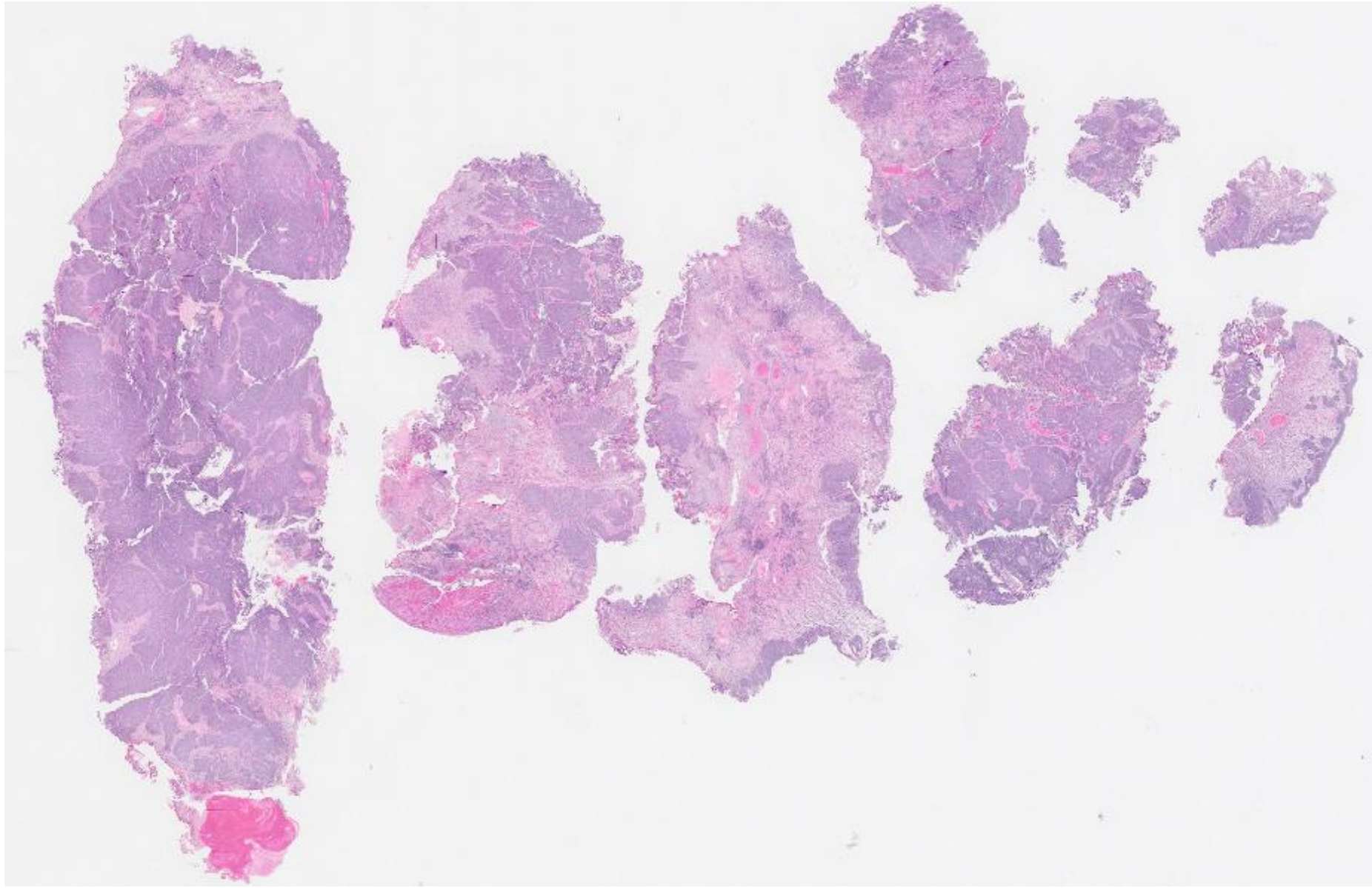
Take-home: Urothelial carcinoma in situ – “overriding” pattern

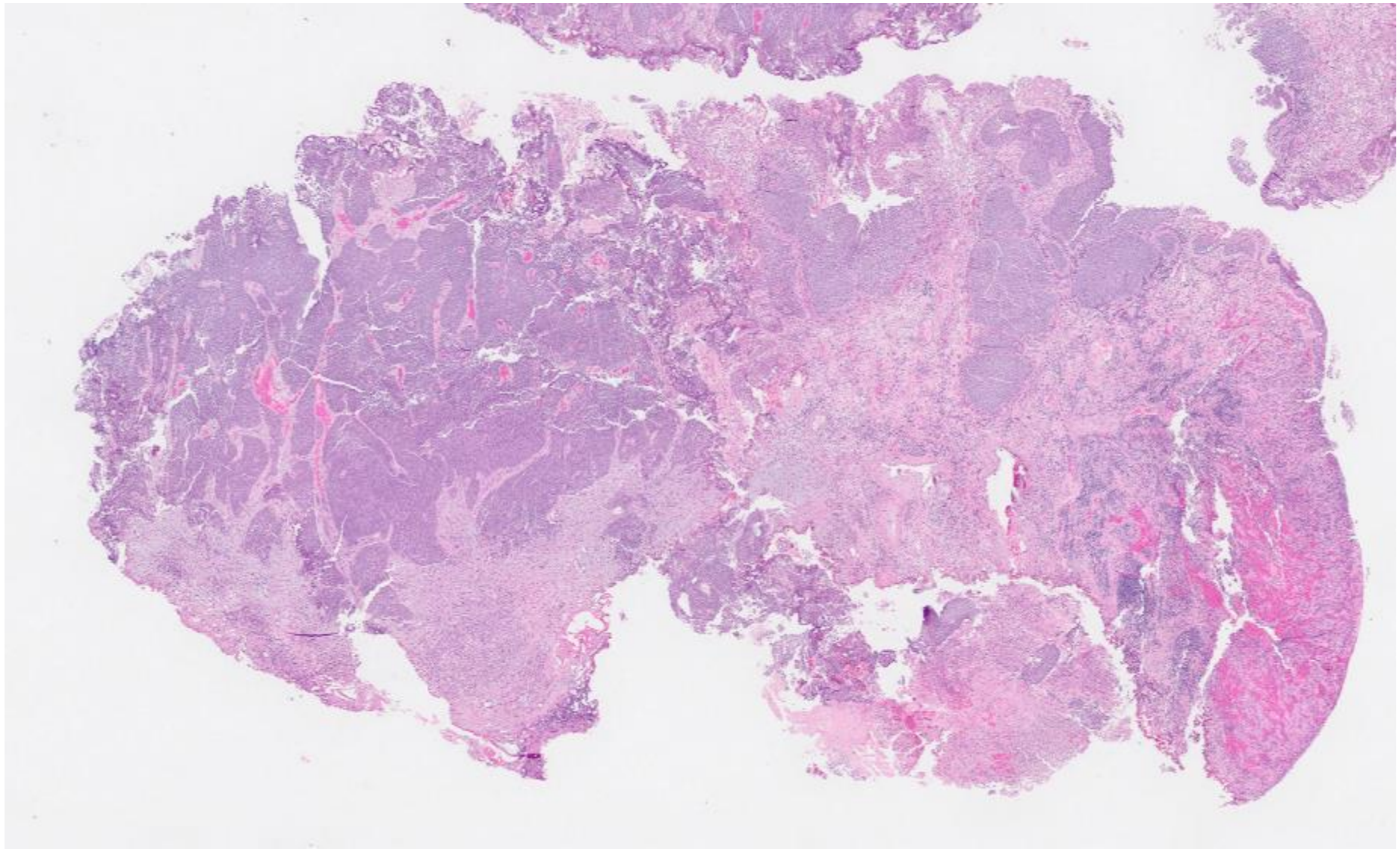
- Morphologic features can be subtle and “umbrella-like”
  - Look for dense eosinophilic cytoplasm, cytologic atypia (nuclear enlargement, hyperchromasia), and frequent mitotic activity)
- Aberrant p53 and increased Ki67 can be helpful
  - CK20 and CD44 will stain like umbrella cells
- In isolation, a diagnosis should be made with extreme caution
  - Consider “flat urothelial atypia of unknown significance”
  - Consider additional molecular testing

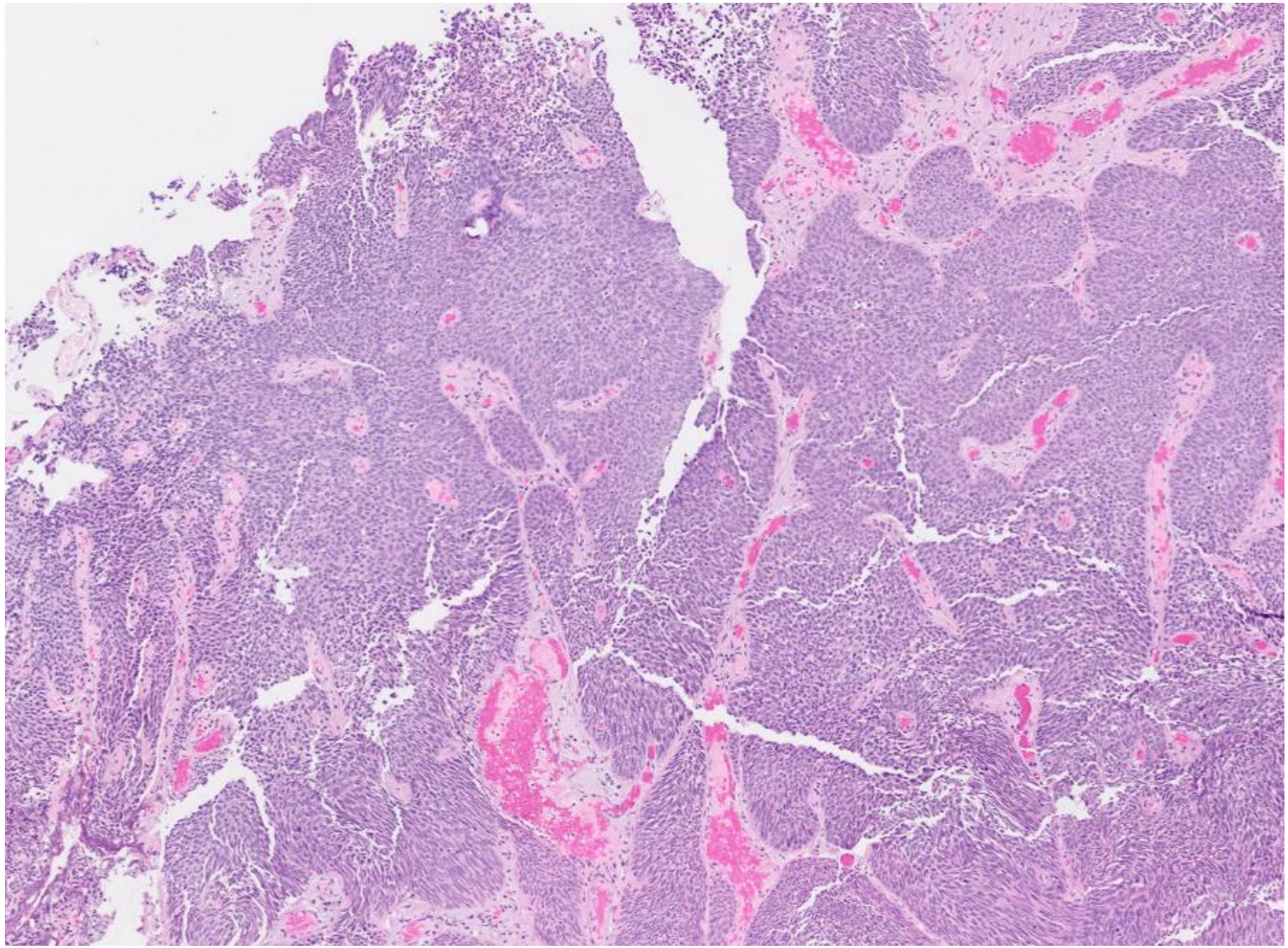
24-0403

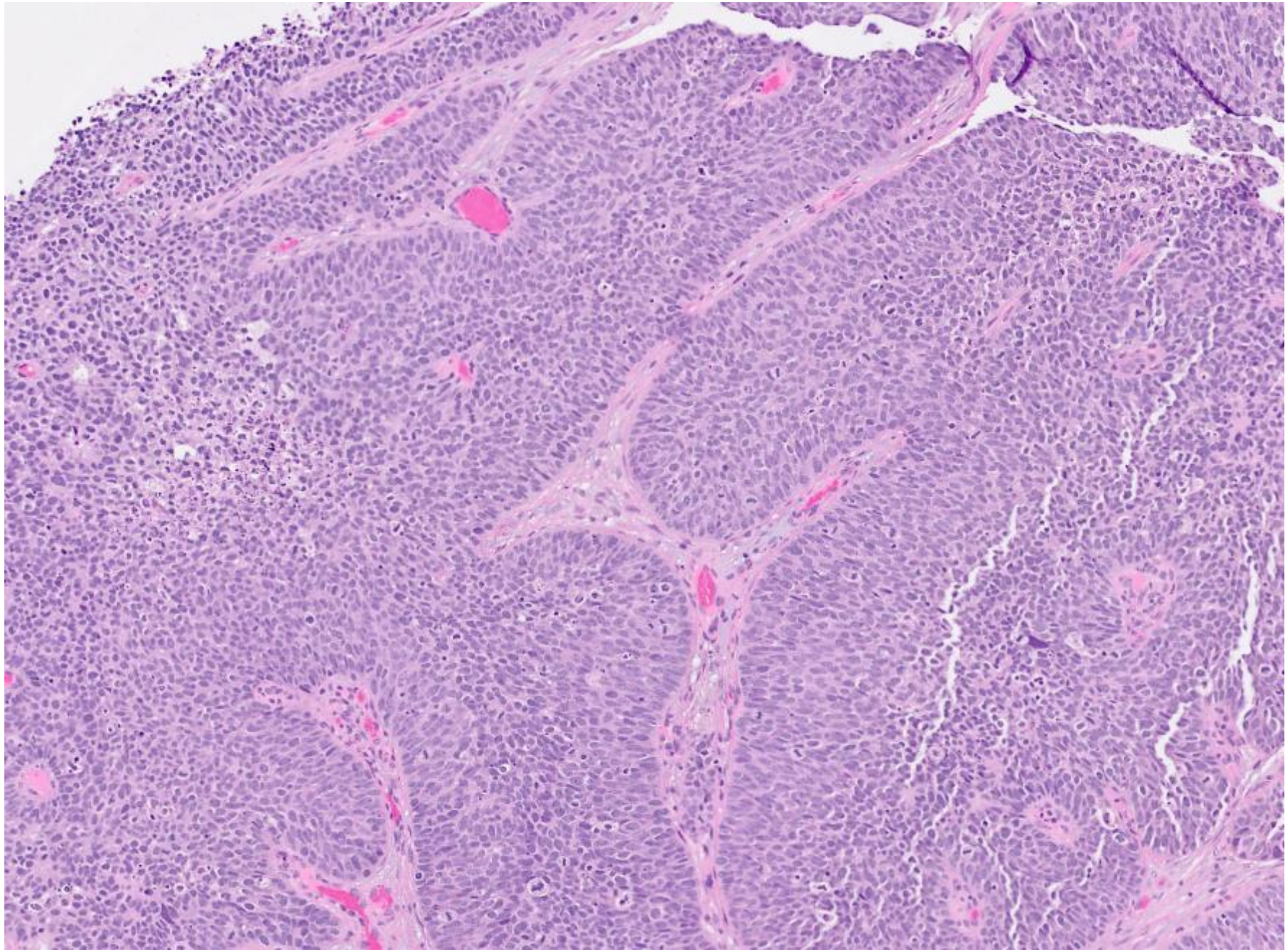
Emily Chan; Stanford

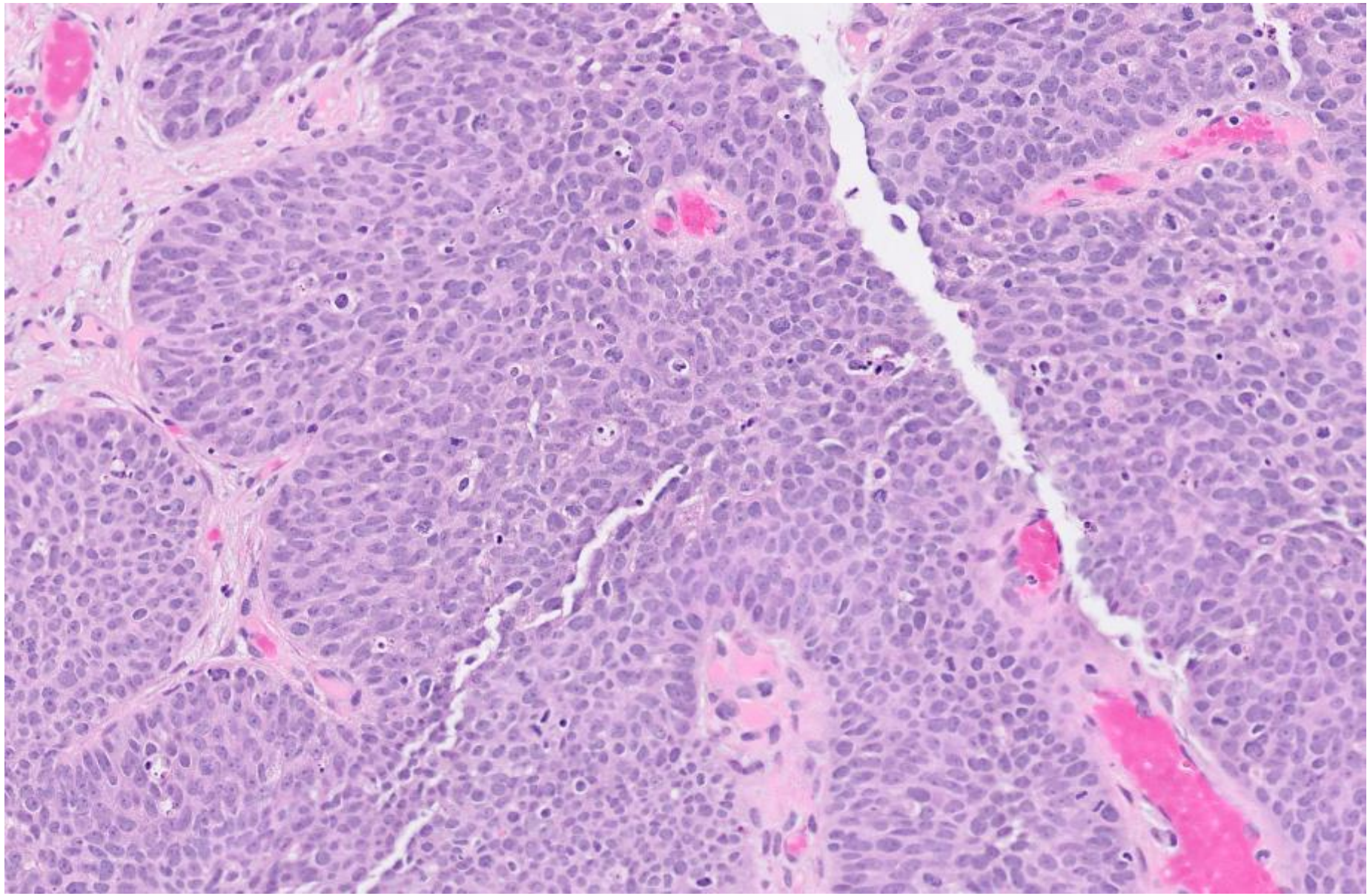
63 year-old woman with bulky urinary bladder posterior wall mass

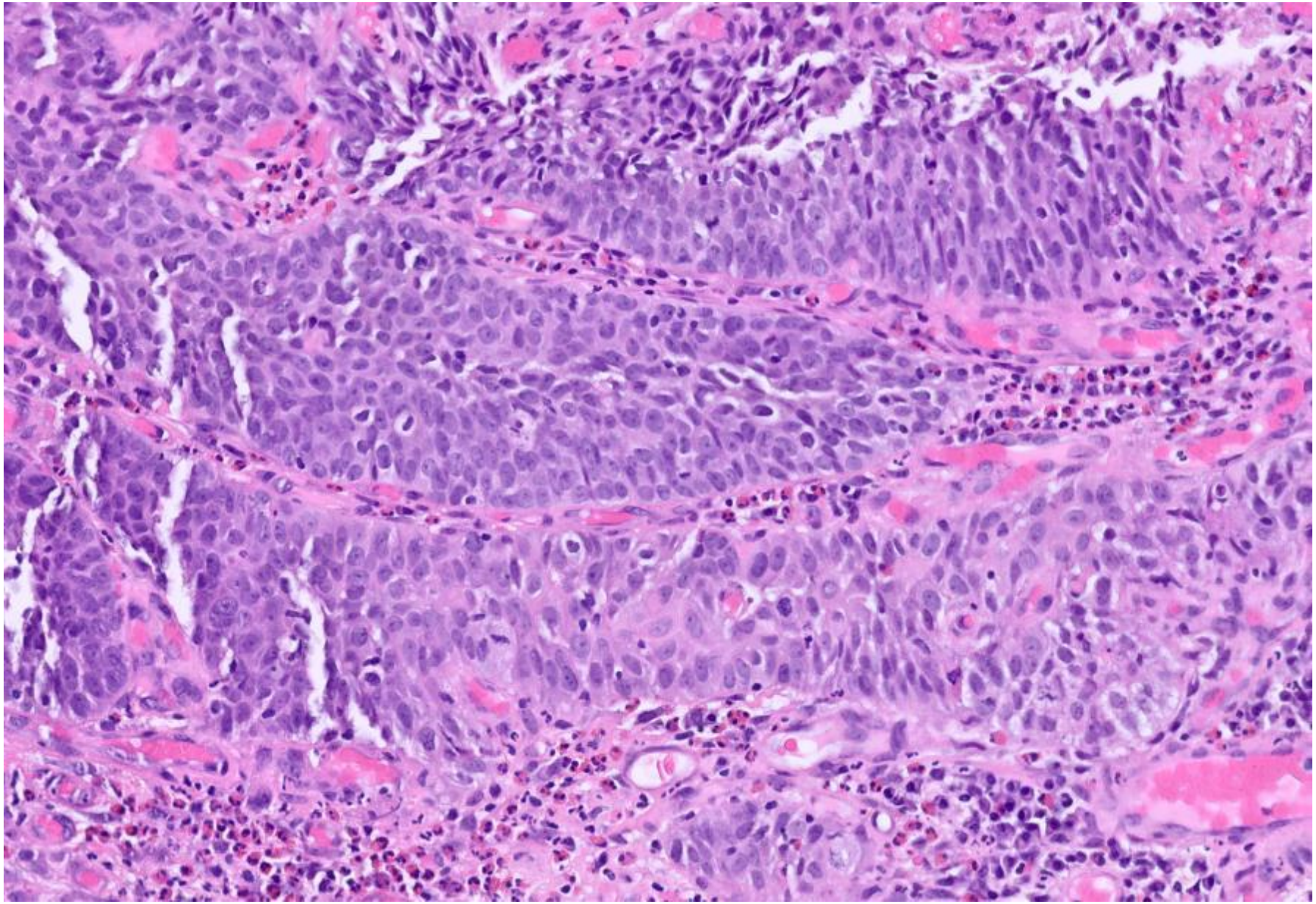






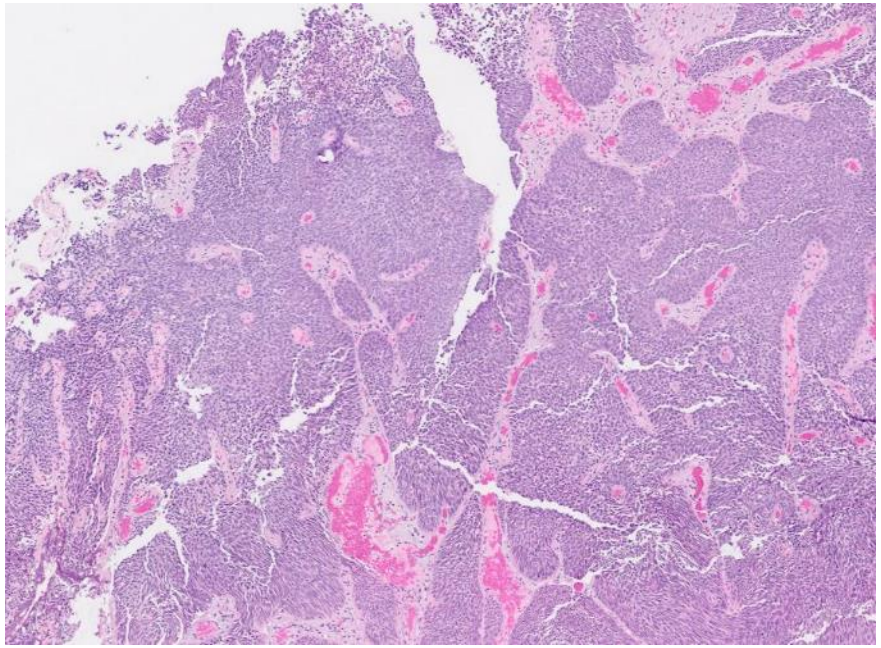






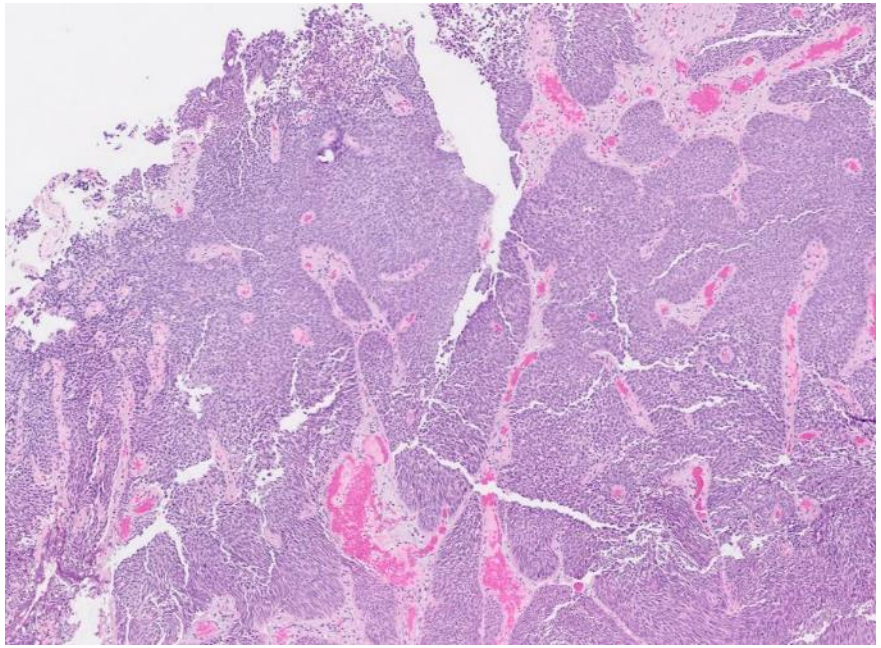
DIAGNOSIS?

Differential diagnosis



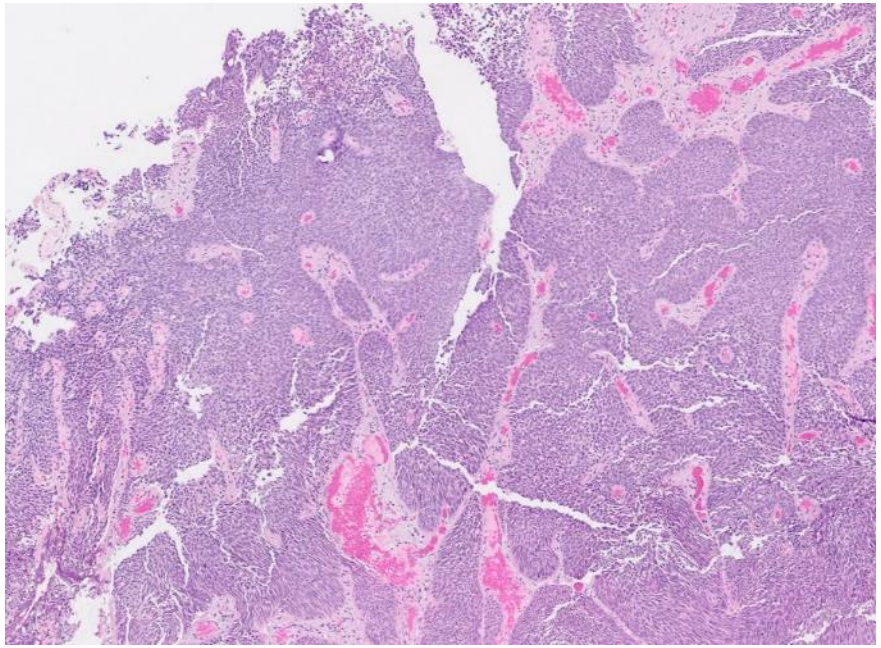
- Invasive high-grade papillary urothelial carcinoma
- BUT….

Differential diagnosis



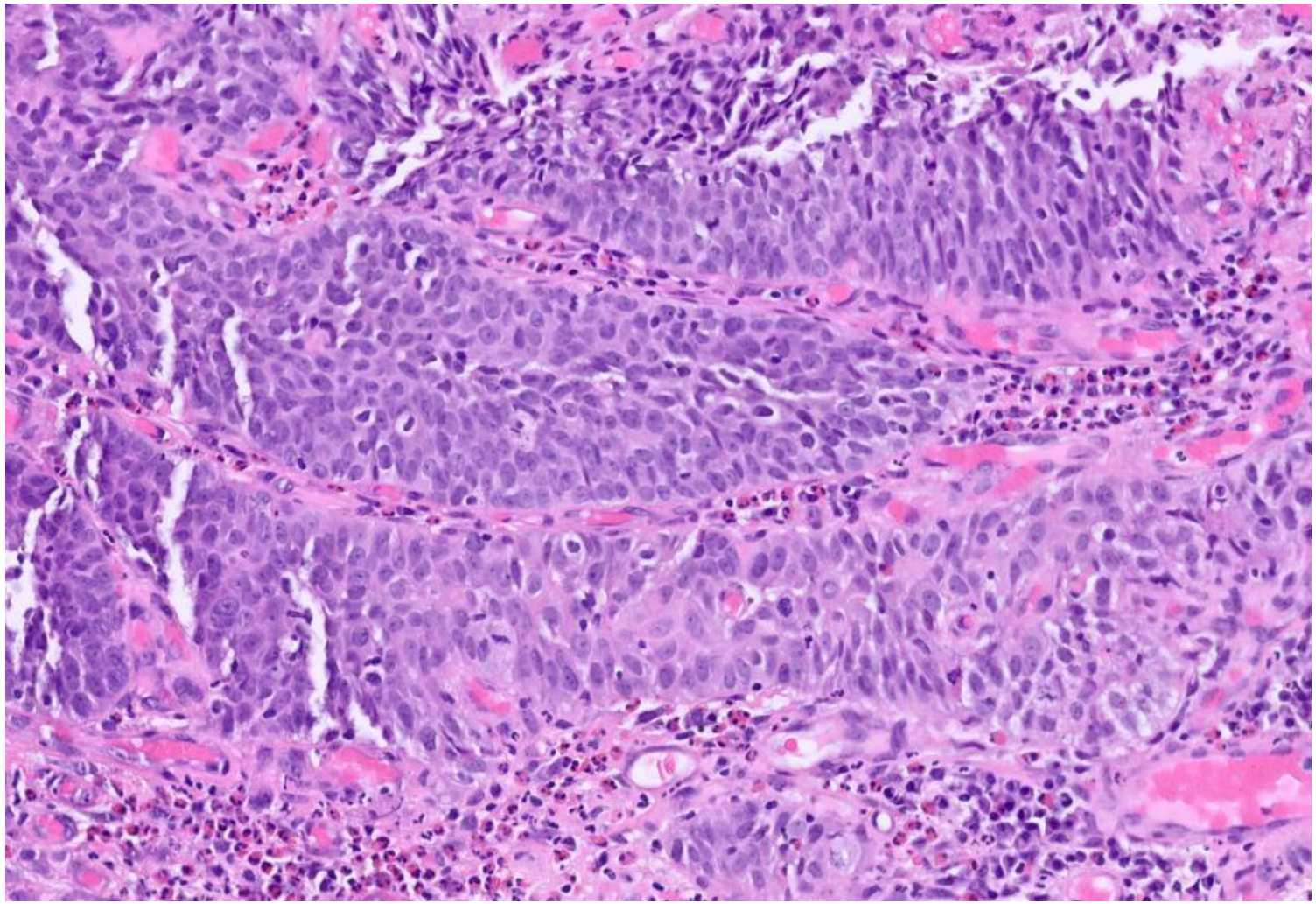
- Invasive high-grade papillary urothelial carcinoma
- BUT…. This is SouthBay!

Differential diagnosis

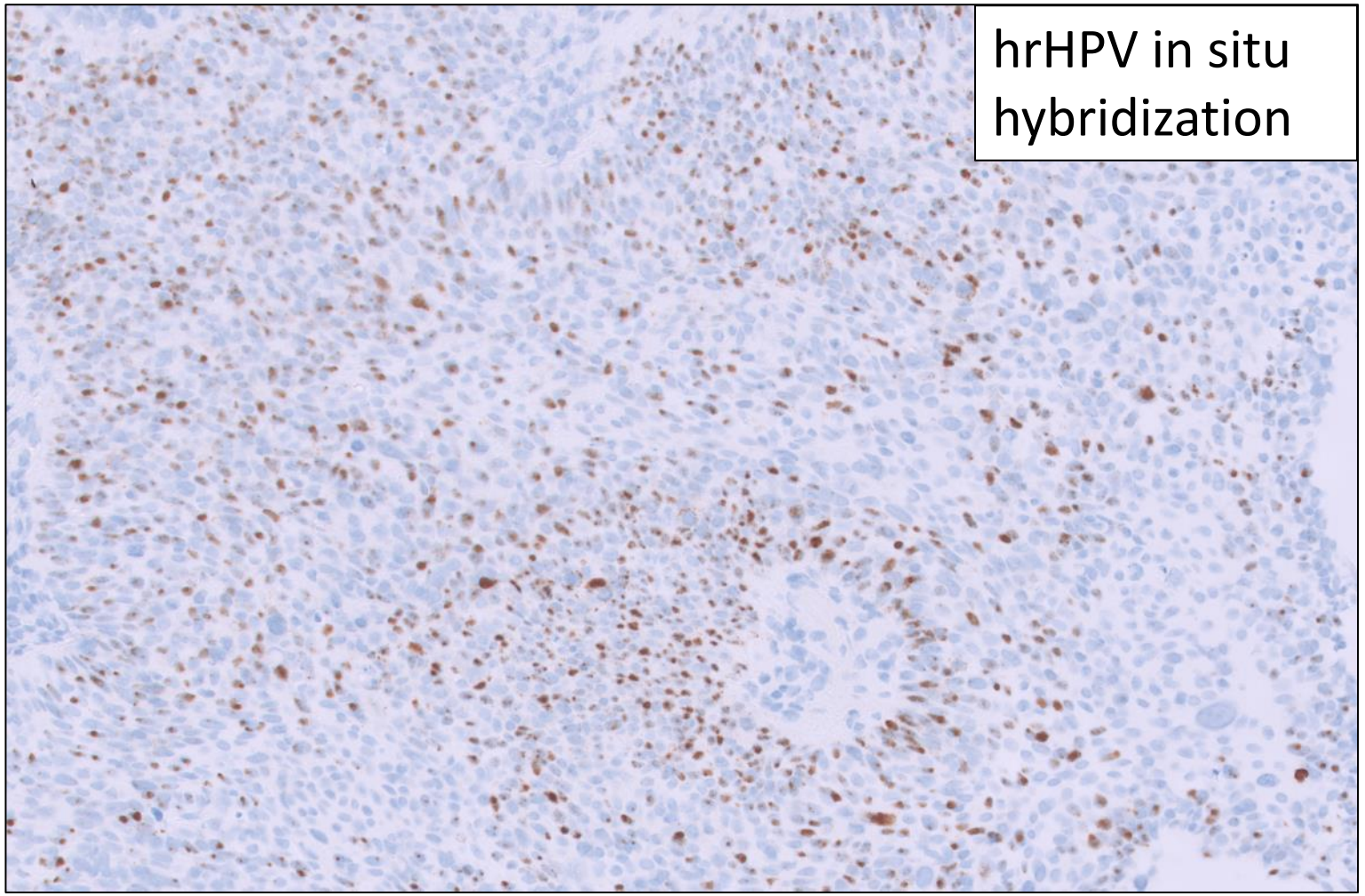


- Invasive high-grade papillary urothelial carcinoma
- Consider other possibilities:
  - Direct extension of a gyn tumor (or prostate if man)
  - Metastatic tumors mimicking high-grade urothelial carcinoma (e.g. melanoma, angiosarcoma, germ cell tumor, others…)

Morphology: basaloid with focal squamous??



Cystoscopy/imaging: “bulky posterior wall mass”



Diagnosis

- Invasive high-risk HPV positive carcinoma

Comment: Could represent HPV-associated squamous cell carcinoma arising from the gynecologic tract or primary HPV-associated carcinoma of the urinary bladder (rare)

MODERN PATHOLOGY (2012) 25, 1534–1542

Urothelial carcinoma with prominent squamous differentiation in the setting of neurogenic bladder: role of human papillomavirus infection

Elen B Blochin[1], Kay J Park[1], Satish K Tickoo, Victor E Reuter and Hikmat Al-Ahmadie

Memorial Sloan-Kettering Cancer Center, Department of Pathology, New York, NY, USA

- Reported on two cases of HPV-positive urothelial carcinomas of the urinary bladder with extensive squamous differentiation showing the typical basaloid, poorly differentiated morphology of HPV-associated tumors with no genital involvement
- Hypothesized that virus directly inoculated into bladder in process of catheterization of transferred by ascending infection associated with frequent catheterizations

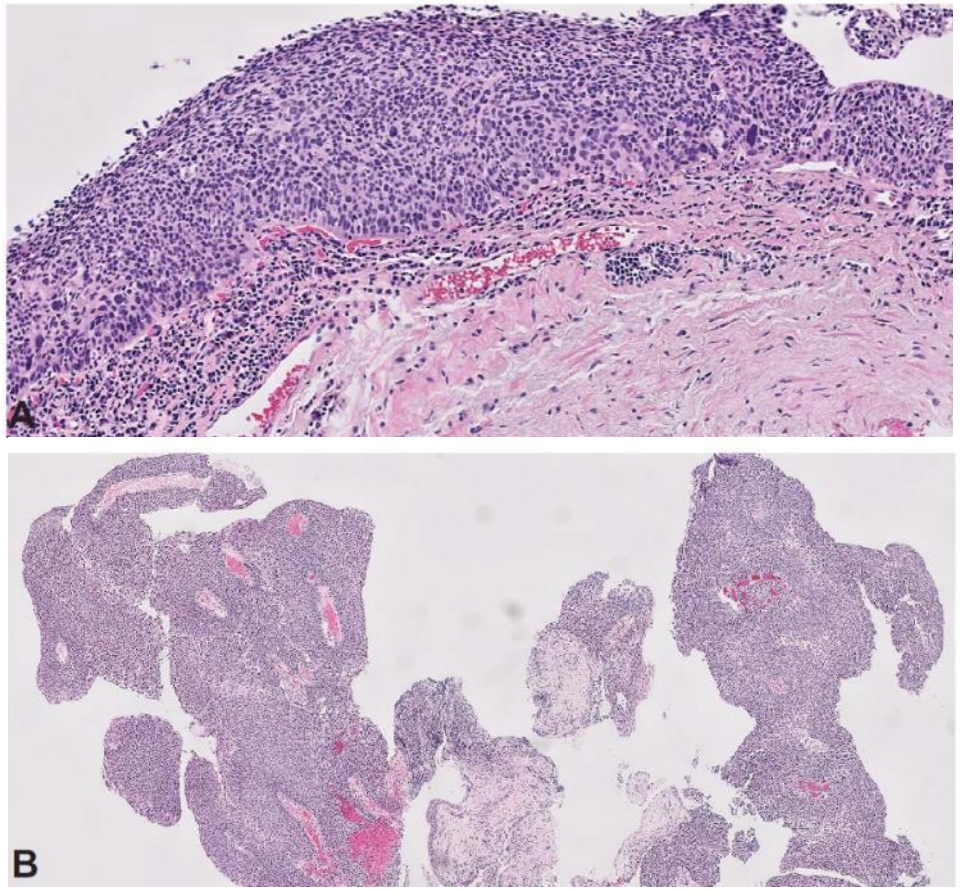
Arch Pathol Lab Med. 2024 Apr 1. doi: 10.5858/arpa.2023-0285-OA. Online ahead of print.

Clinicopathologic and Molecular Characterization of High-Risk Human Papillomavirus-Positive Carcinomas of the Urinary Tract

Neslihan Kayraklioglu [1], Bradley A Stohr [1], Emily Chan [1]

Affiliations + expand

PMID: 38555943 DOI: 10.5858/arpa.2023-0285-OA



- Mimics conventional high-grade urothelial carcinoma (UCa)
  - Typically shows basaloid or poorly differentiated morphology
  - Surface can be papillary or flat
  - Areas of more obvious squamous differentiation can be focal to absent

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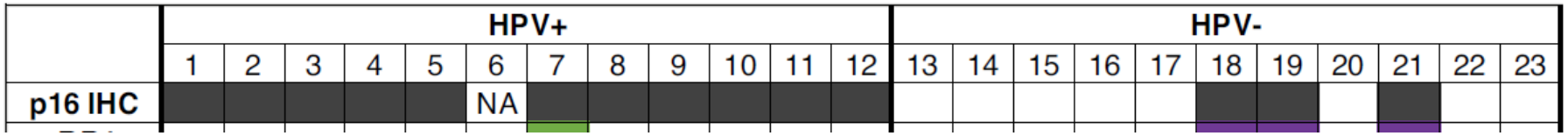
Table 2. Immunohistochemical Profile of HPV+ UTCs

Patient	Uroplakin	CK7	GATA3	p63	CK903	CK5/6
1	+/−	−	−	++	++	++
2	−	−	−	++	++	++
3	−	++	+/−	++	++	++
4	−	−	+/−	++	++	++
5	−	−	+/−	++	++	++
6	−	NA	+/−	++	NA	NA
7	−	++	++	++	++	++
8	−	−	+/−	++	++	++
9	−	−	+/−	++	++	++
10	−	−	−	++	++	++
11	−	++	−	++	++	++
12	−	++	+/−	++	++	++

Abbreviations: CK, cytokeratin; HPV, human papilloma virus; NA, not available; UTCs, urinary tract carcinomas; ++, strong/diffuse positive; +/−, weak/patchy positive; −, negative.

- Nonspecific immunoprofile (overlaps with UCa)
- P16 can be positive in HPV- tumors
  - Get hrHPV in situ hybridization (ISH)



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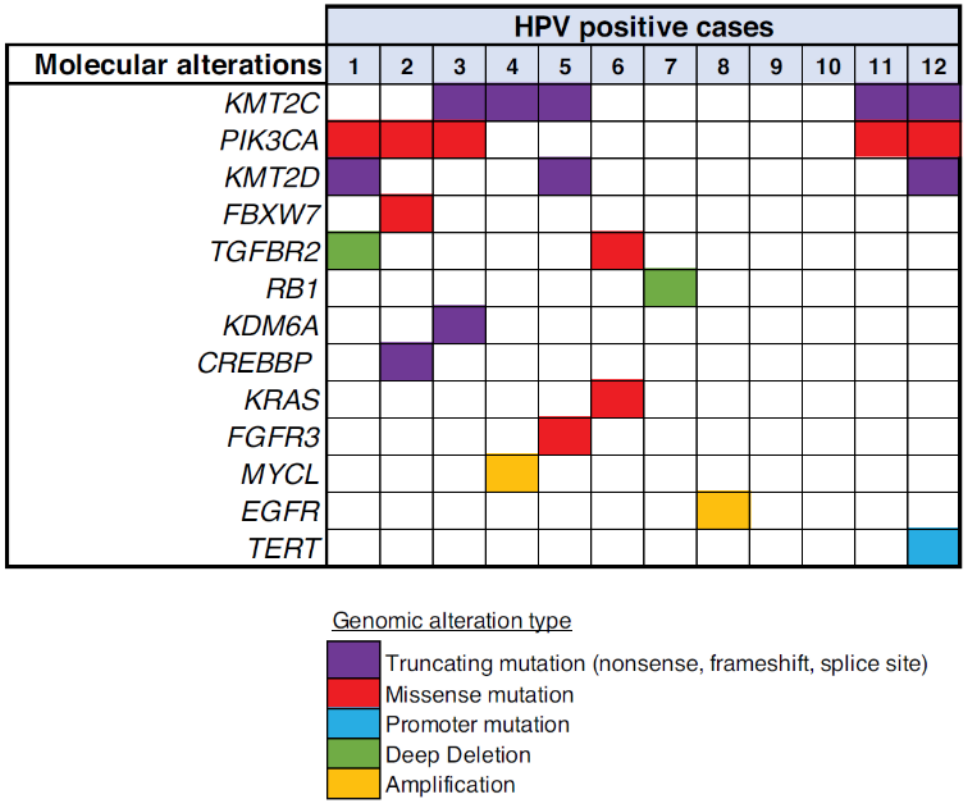


Characterization of HPV+ Urinary Tract Carcinomas—Kayraklioglu et al

- Molecular findings are more similar to HPV+ SCC of other sites than conventional UCa
  - Alterations in *TERTp, TP53* and *CDKN2A* rare
  - Suggesting treatment like HPV+ tumors rather than UCa, perhaps

Clinical follow-up

- Patient had prior remote history of hysterectomy for reportedly benign condition (pathology unknown)
- Patient had a prior initially called urothelial carcinoma
- Was ultimately switched from bladder regimen (EV + Pembro) to chemoRT for treatment as a locally advanced gynecologic primary as mass did involve vagina on imaging

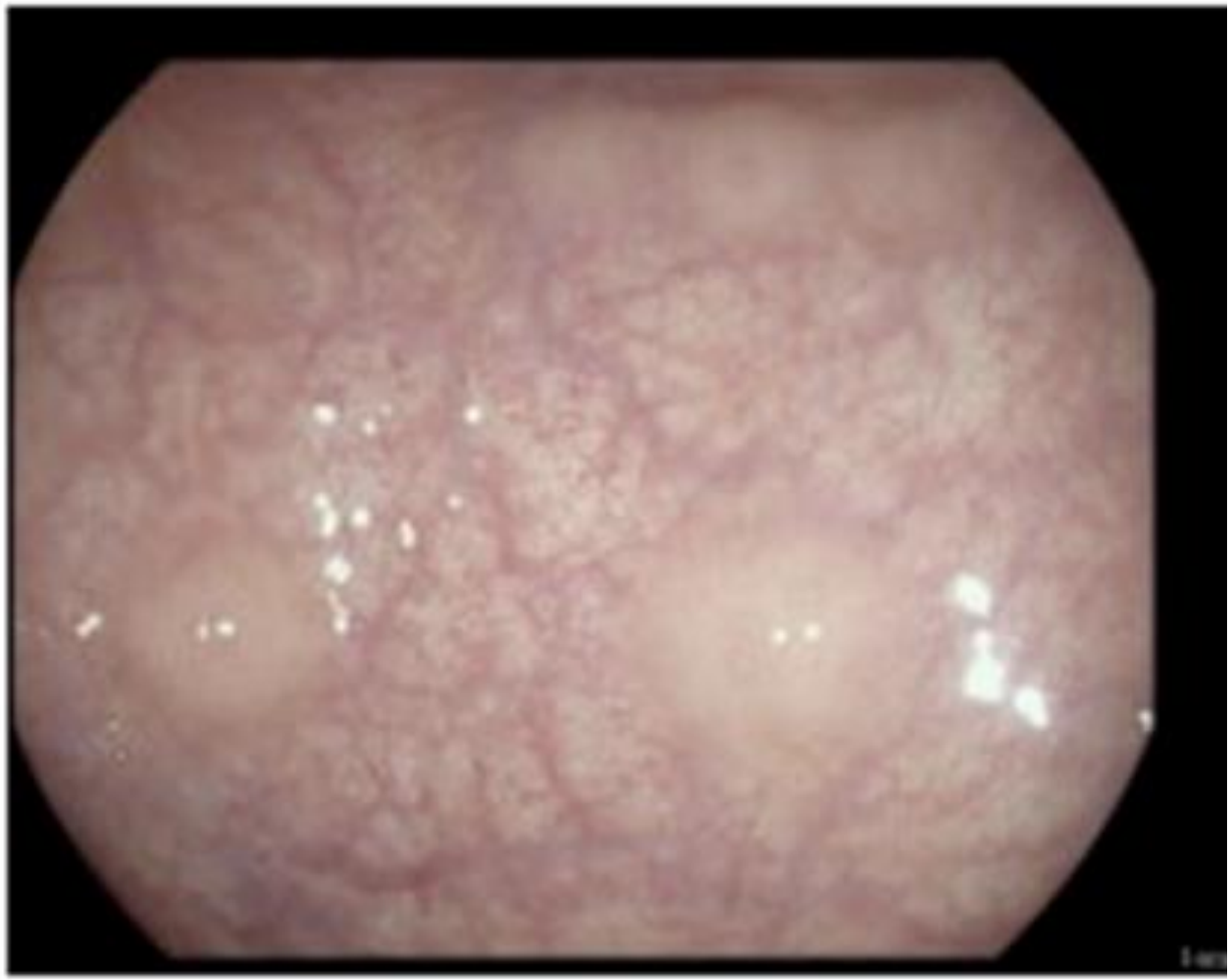
Take-home: HPV+ carcinomas involving the urinary bladder

- Can mimic conventional urothelial carcinoma
  - Different therapeutic regimen!
- Think about in a women with bulky posterior wall mass/any possible gyn involvement
- Think about if you see basaloid features with squamous differentiation (squamous can be focal)
- Get a hrHPV in situ hybridization to confirm
  - (p16 is sensitive but not specific)
- Can present as direct extension from gyn tract (more common) versus primary along the urinary tract (rare)

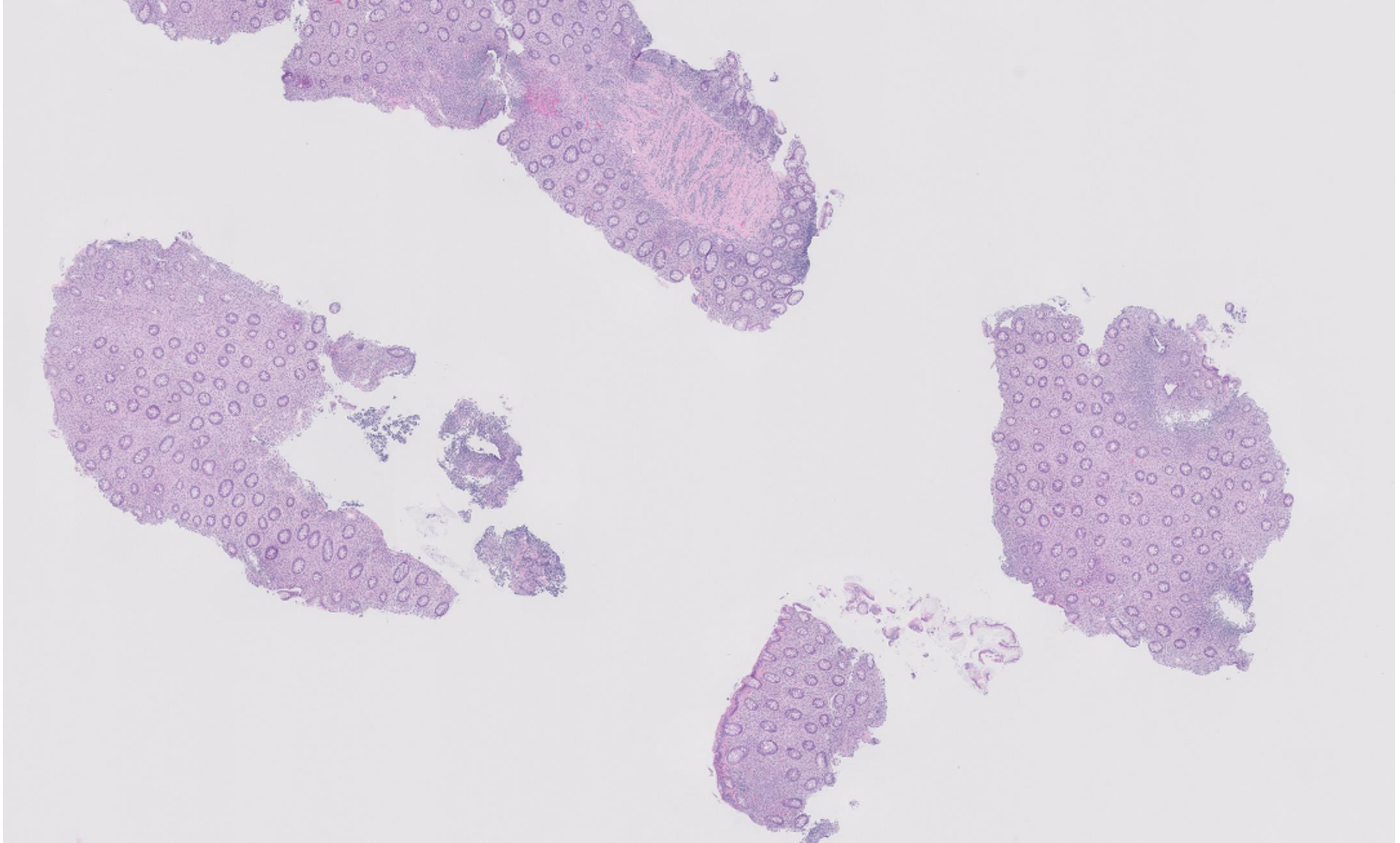
24-0404

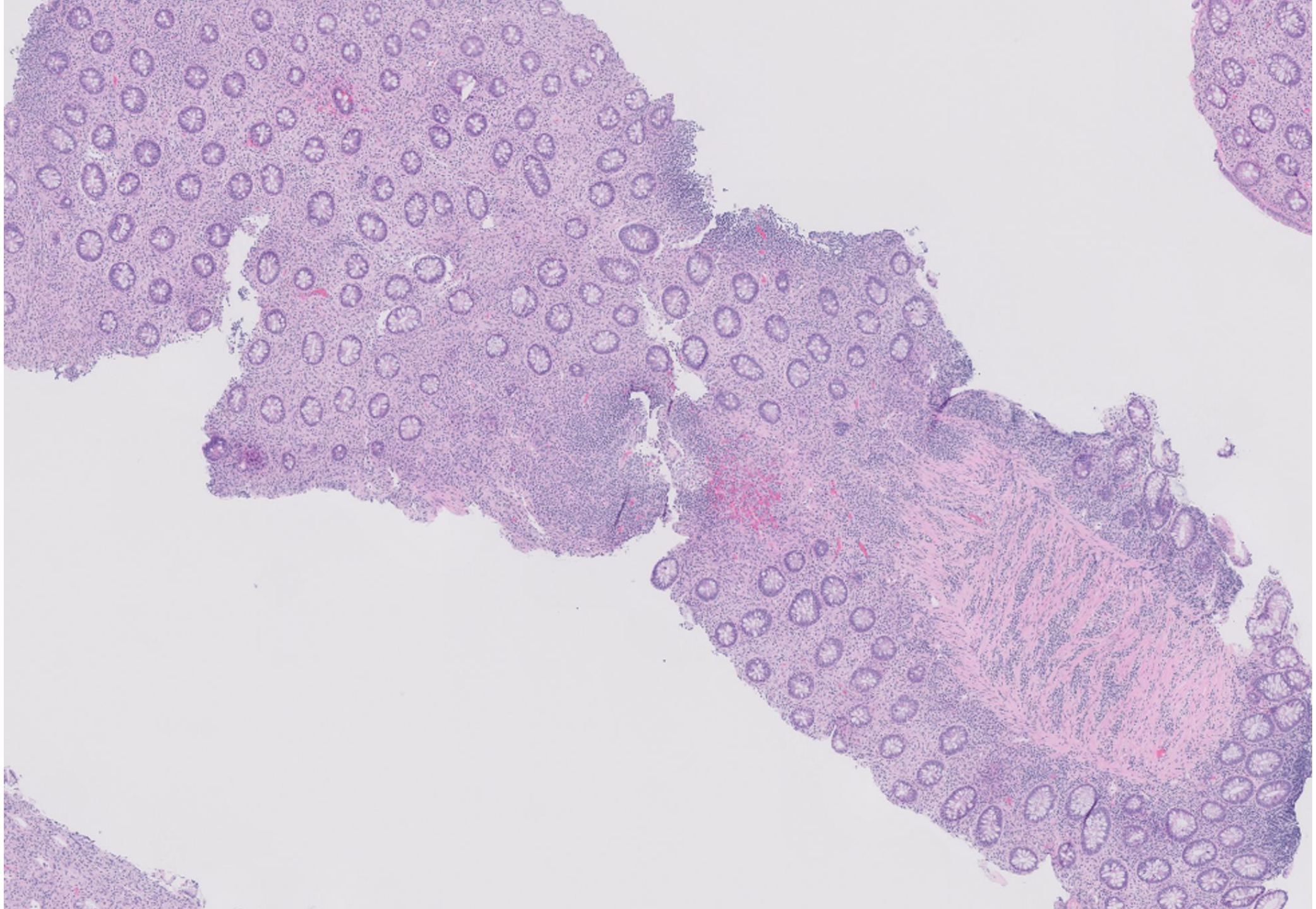
F. Goknur Akarca and Sarah Umetsu; UCSF

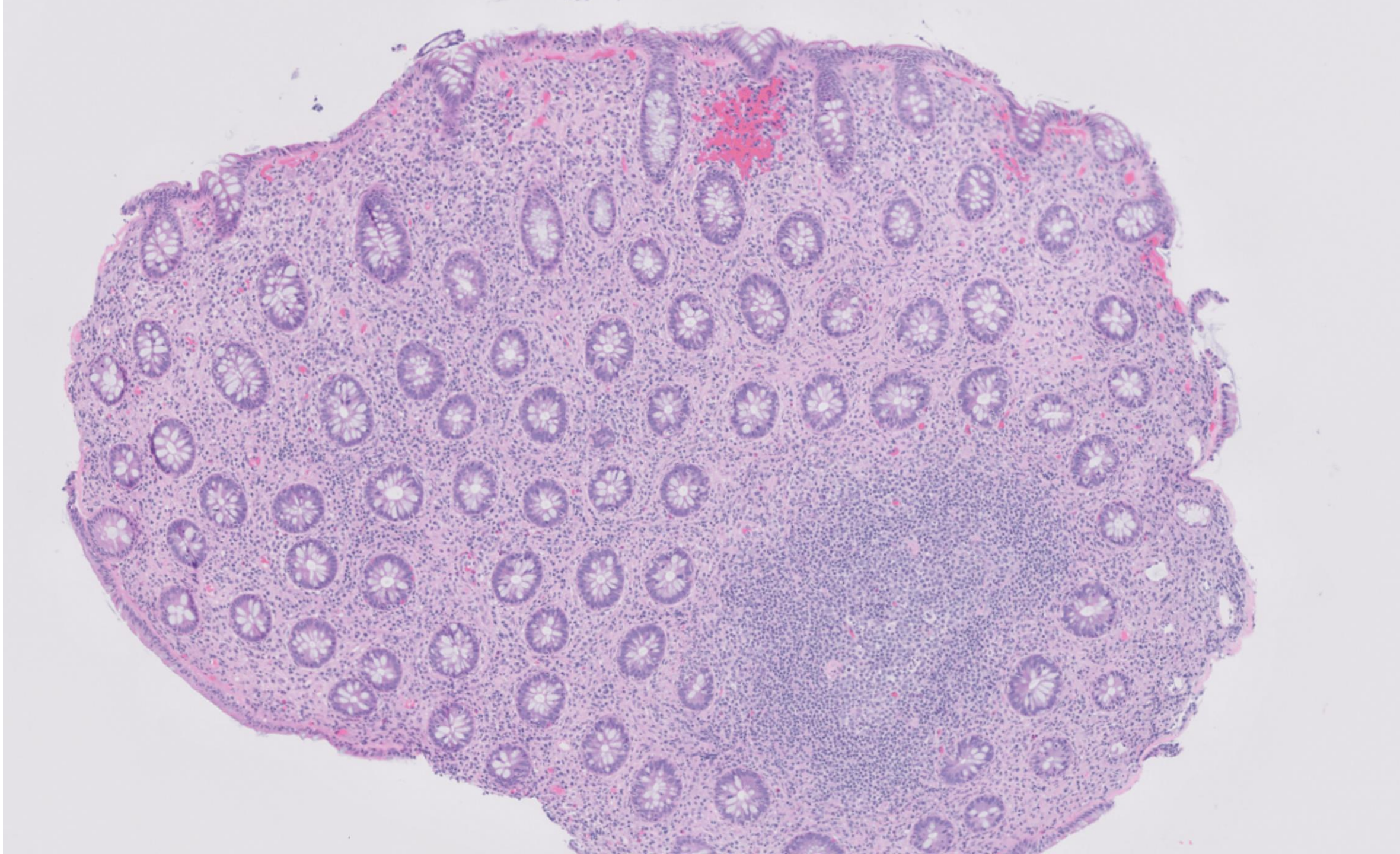
- 43 yo Male with clinically significant diarrhea; family history of Crohn’s disease
- Colonoscopy shows multiple well-circumscribed hypopigmented spots in the rectum

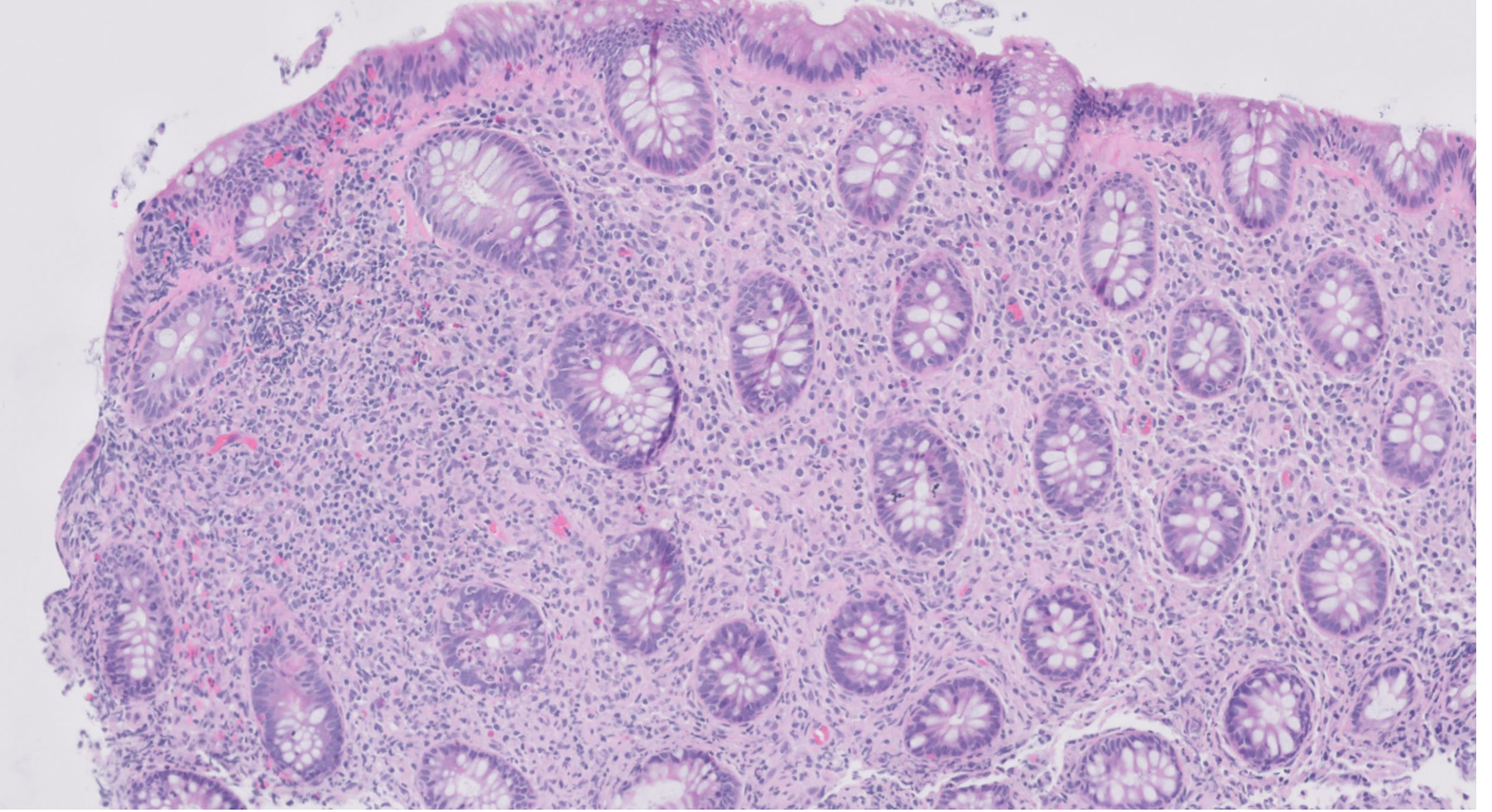


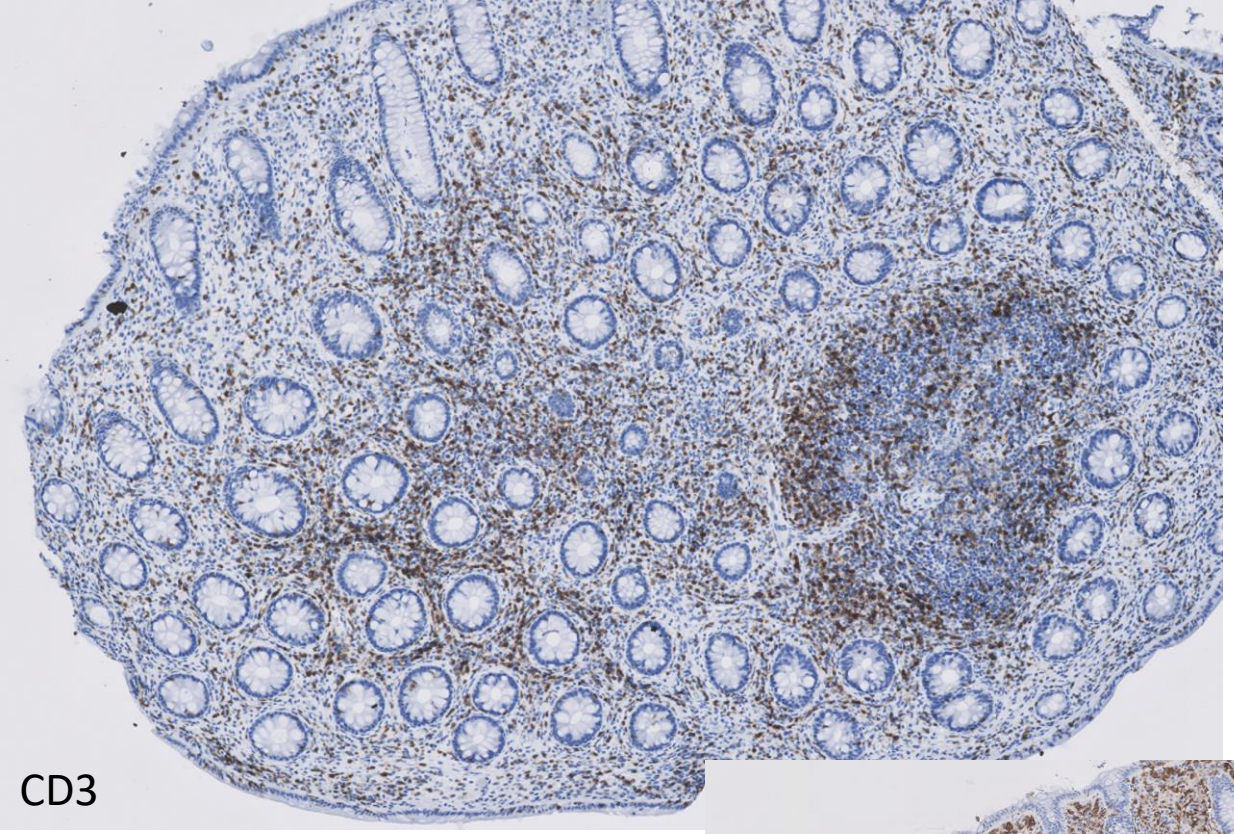
Multiple well-circumscribed, hypopigmented spots
(possibly suggestive of hyperplastic polyp per gastroenterologist)

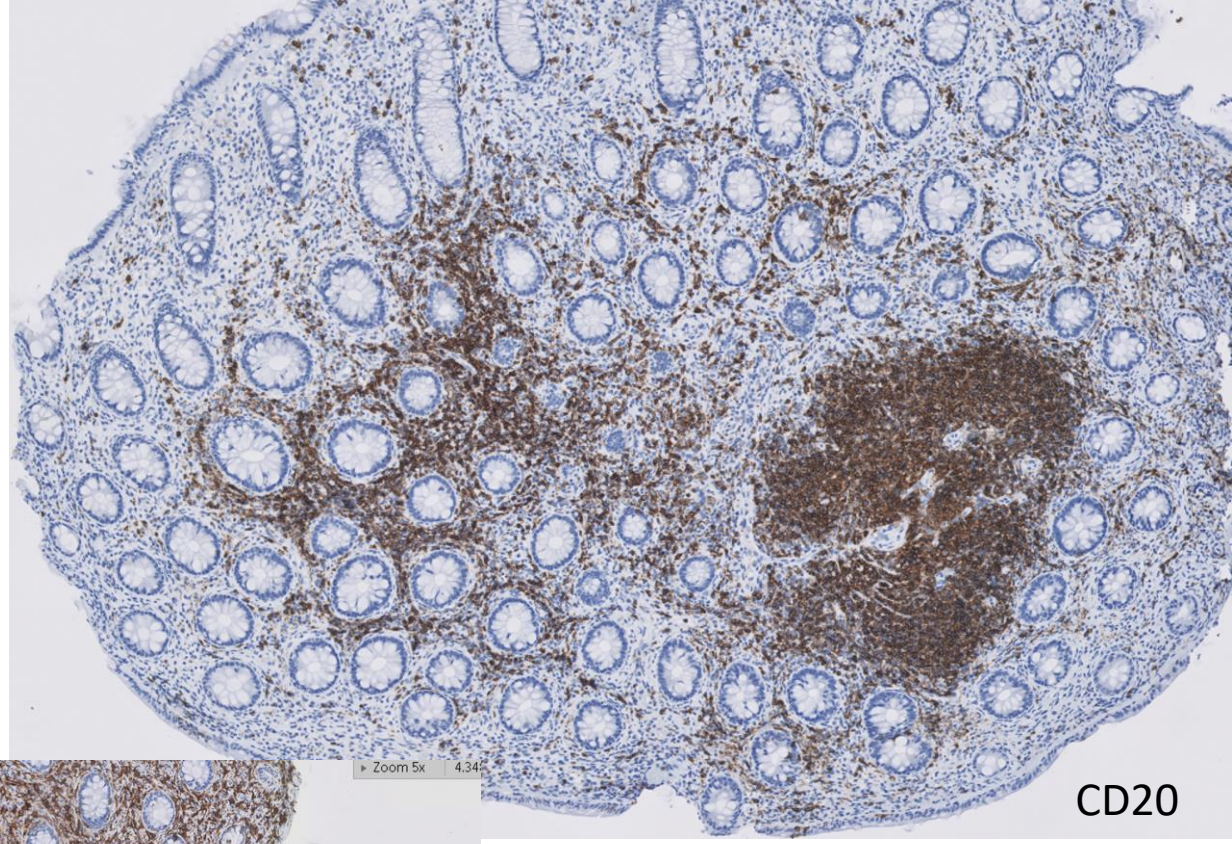


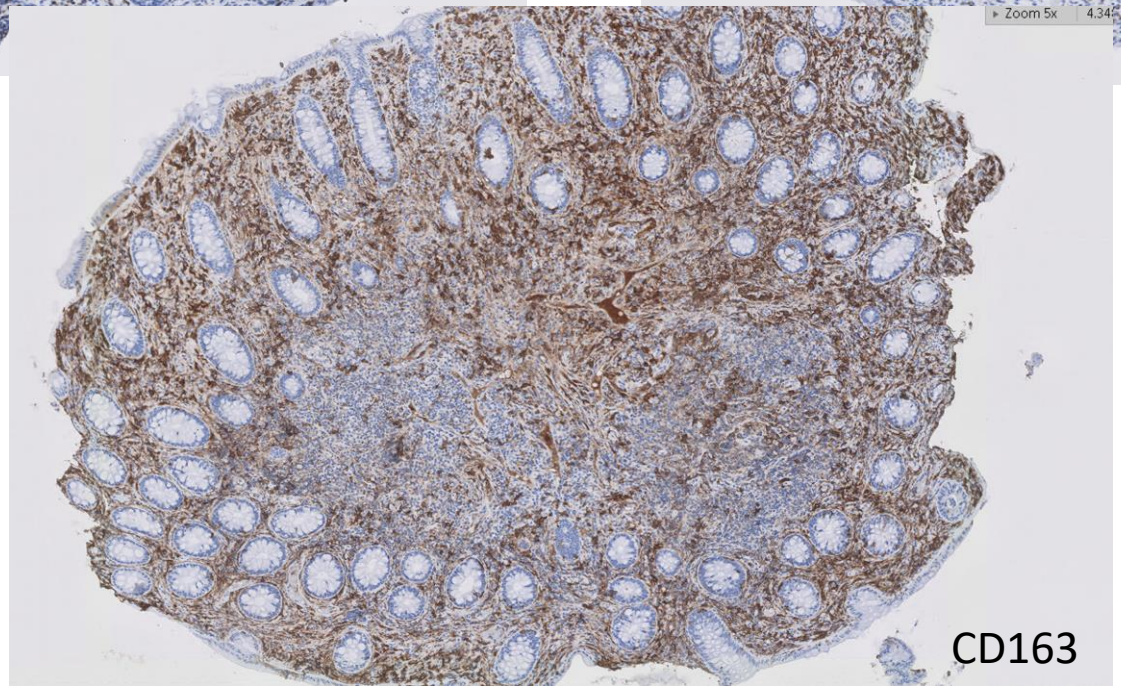







CD3

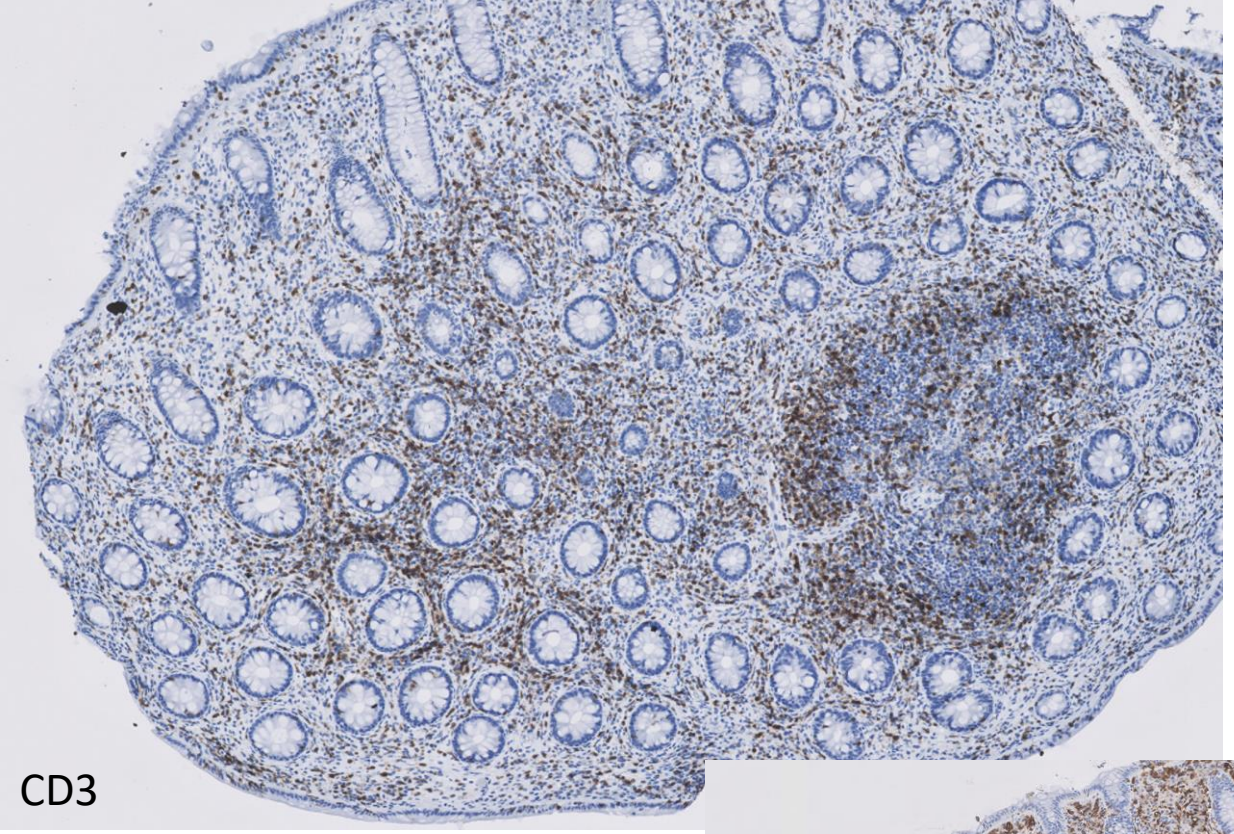

CD20

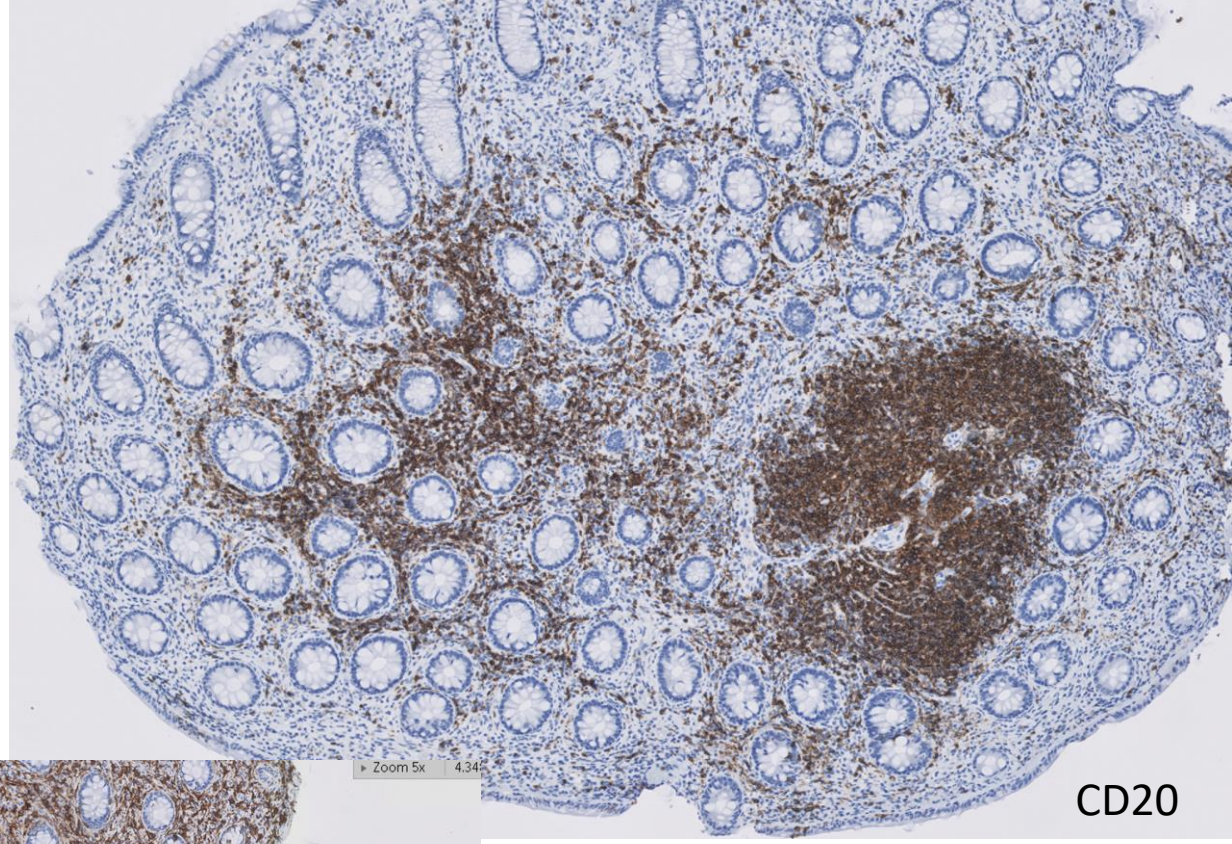

CD163

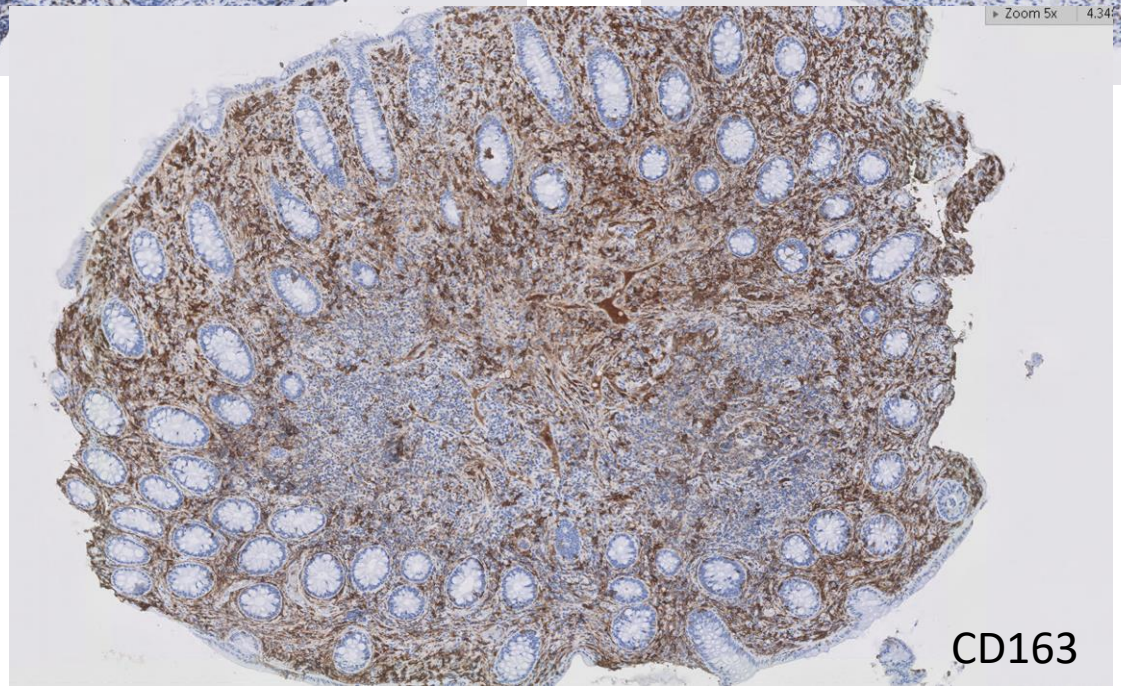
DIAGNOSIS?

Differential diagnoses

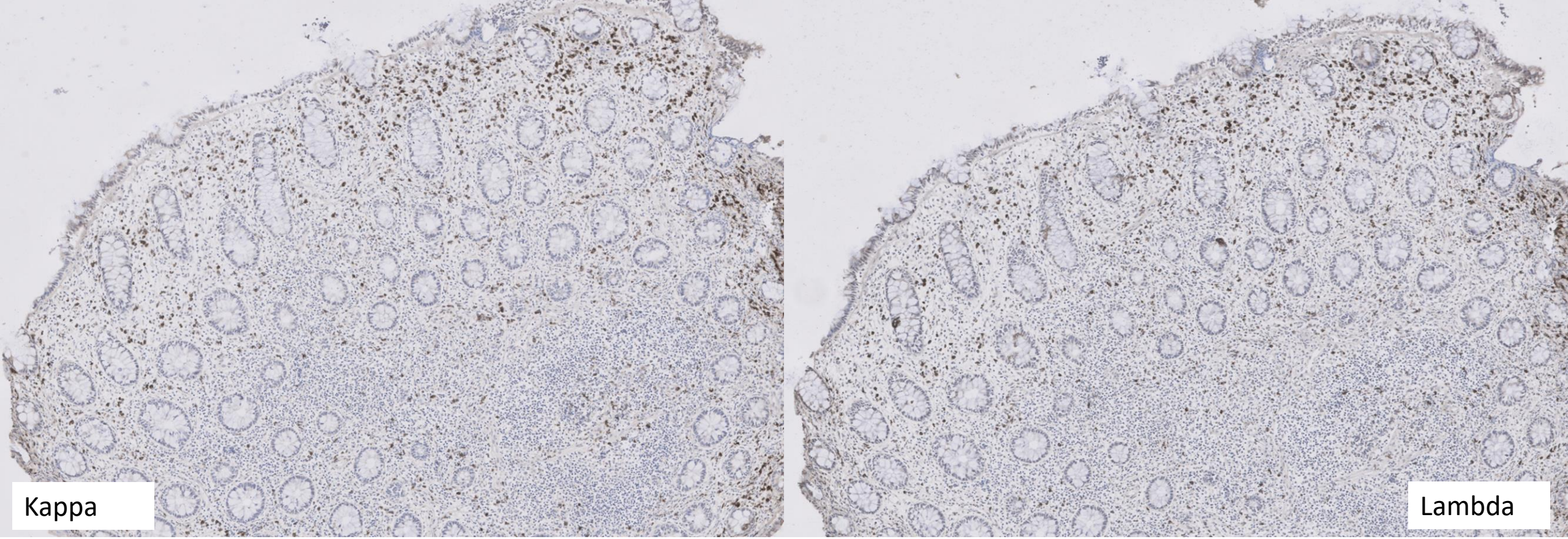
- Inflammatory bowel disease? - clinical history and crypt abscesses
- Hematopoietic disorder? - lymphoma, plasma cell neoplasm
- Infection? - tuberculosis, fungal microorganisms, *Treponema pallidum*


CD3


CD20


CD163

ADDITIONAL STAINS

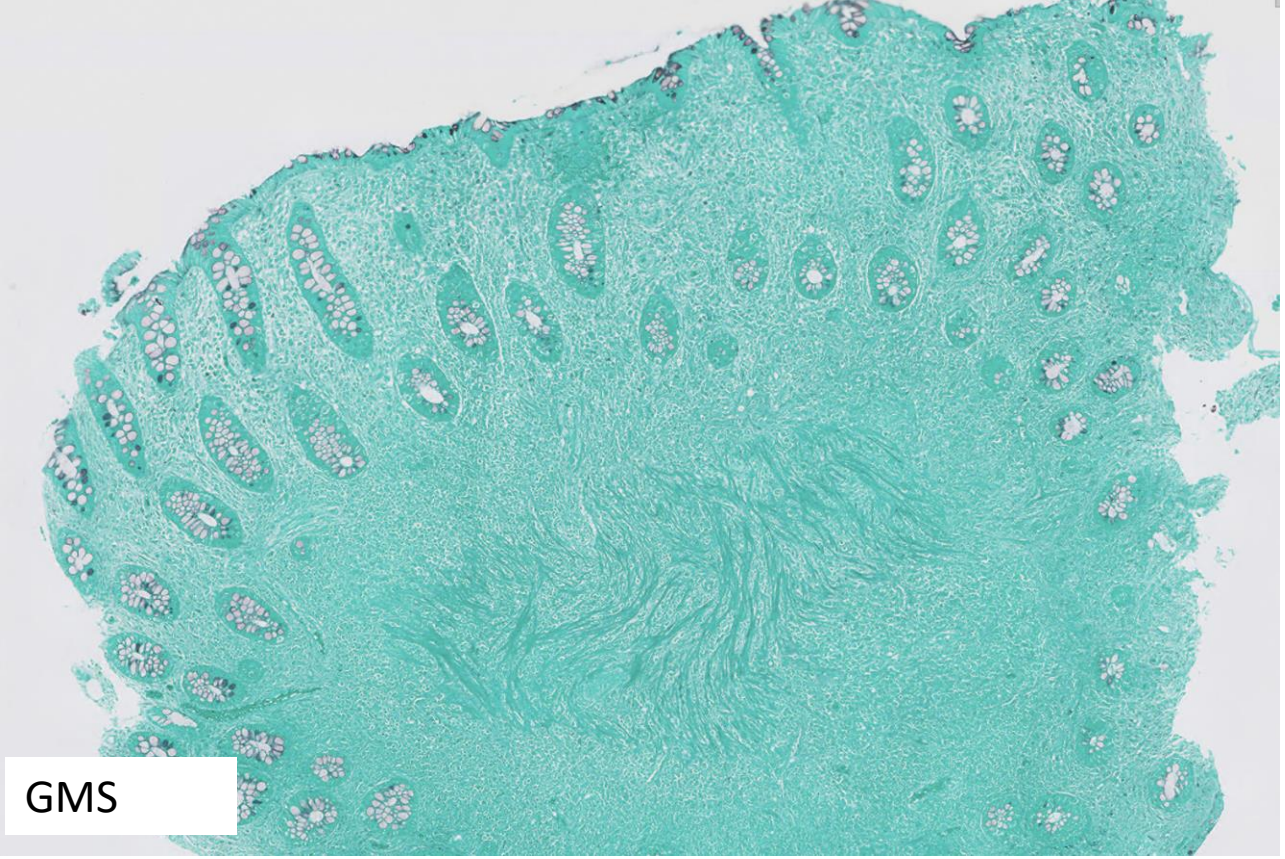


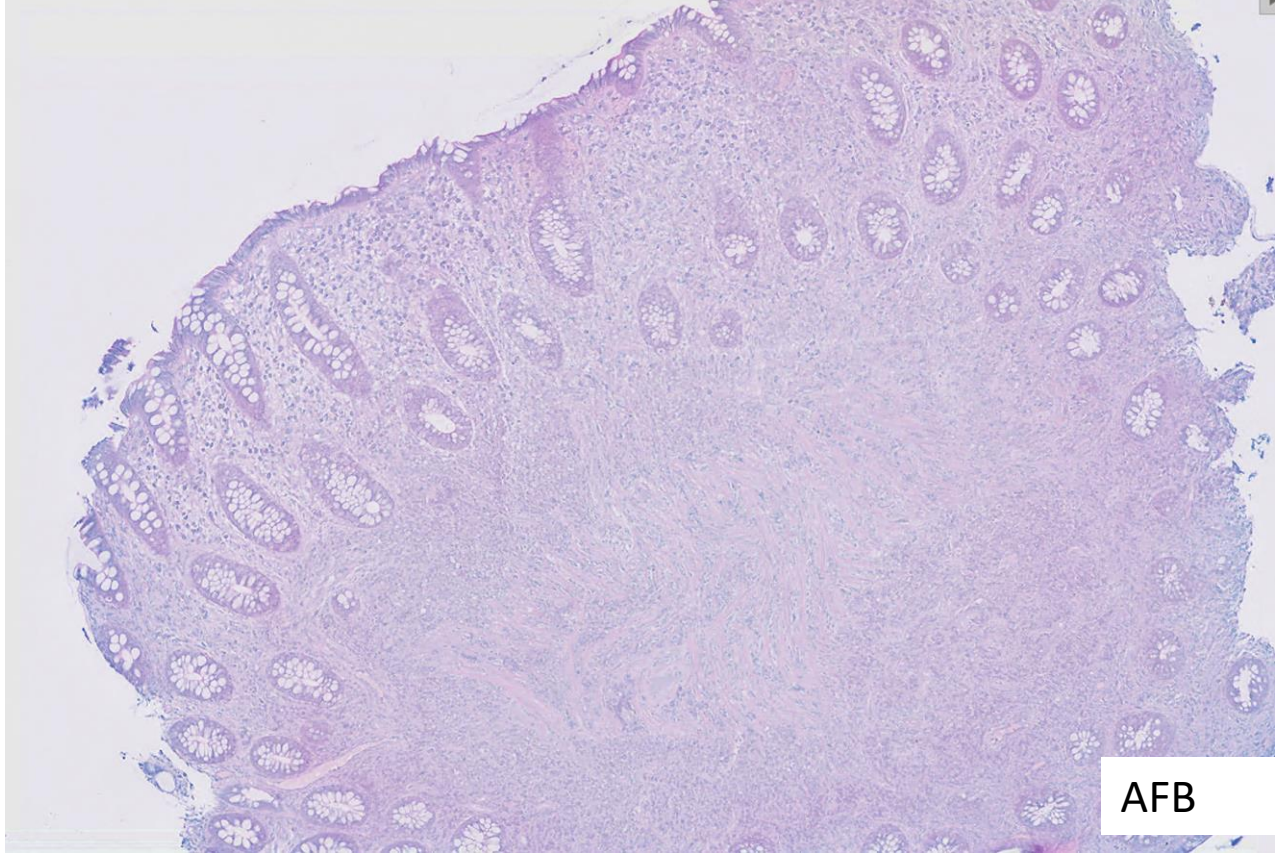
Polytypic staining with Kappa and Lambda-ISH

IHC – Contd.

Also, we did:

- Pankeratin: Negative in lamina propria.
- CD1a: Negative, argues against Langerhans cells.
- S100: Largely negative.
- CD68: Highlights numerous macrophages in the lamina propria.
- CD34: Negative.
- Alk: Negative.
- MPO: Negative.



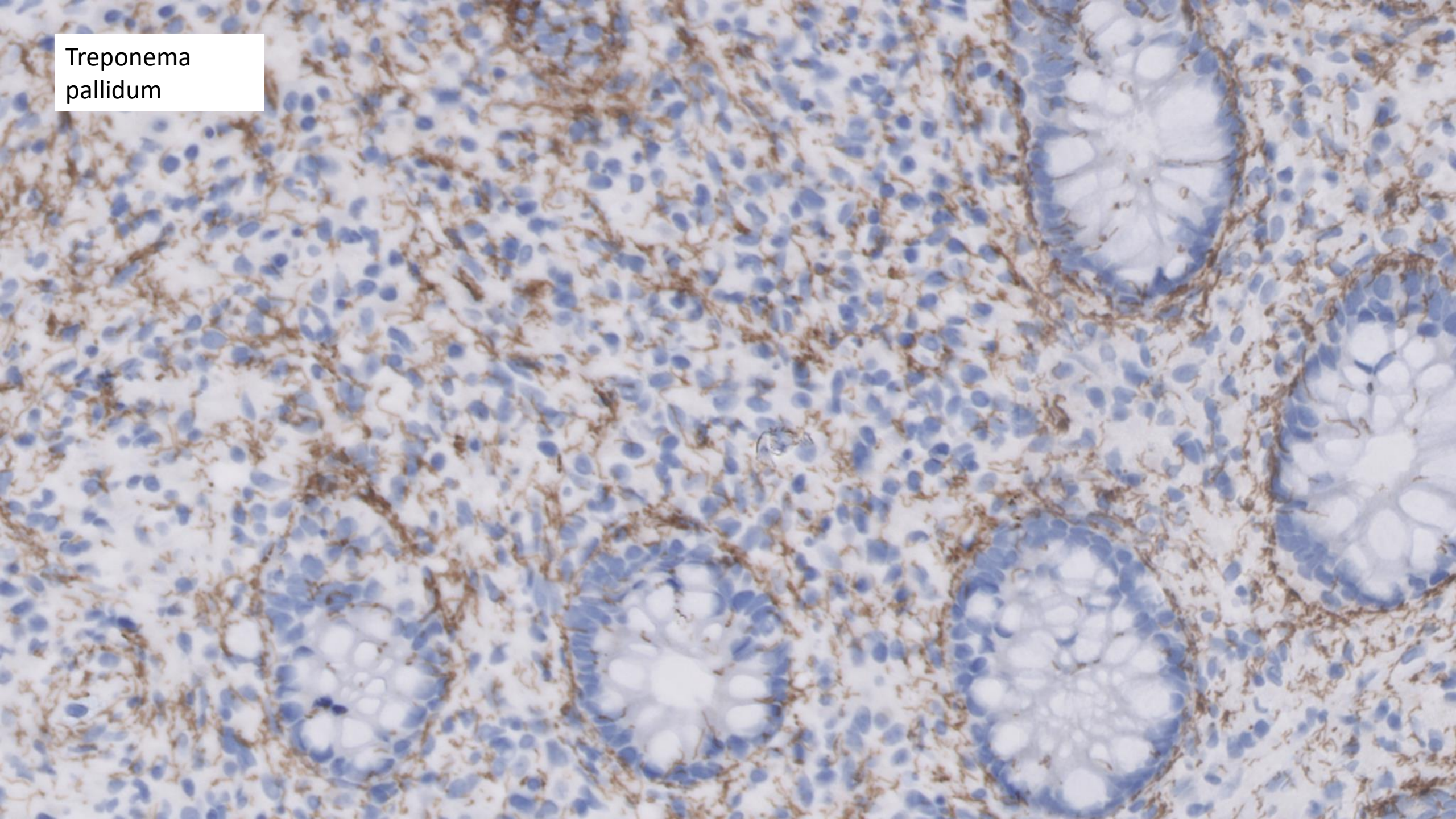


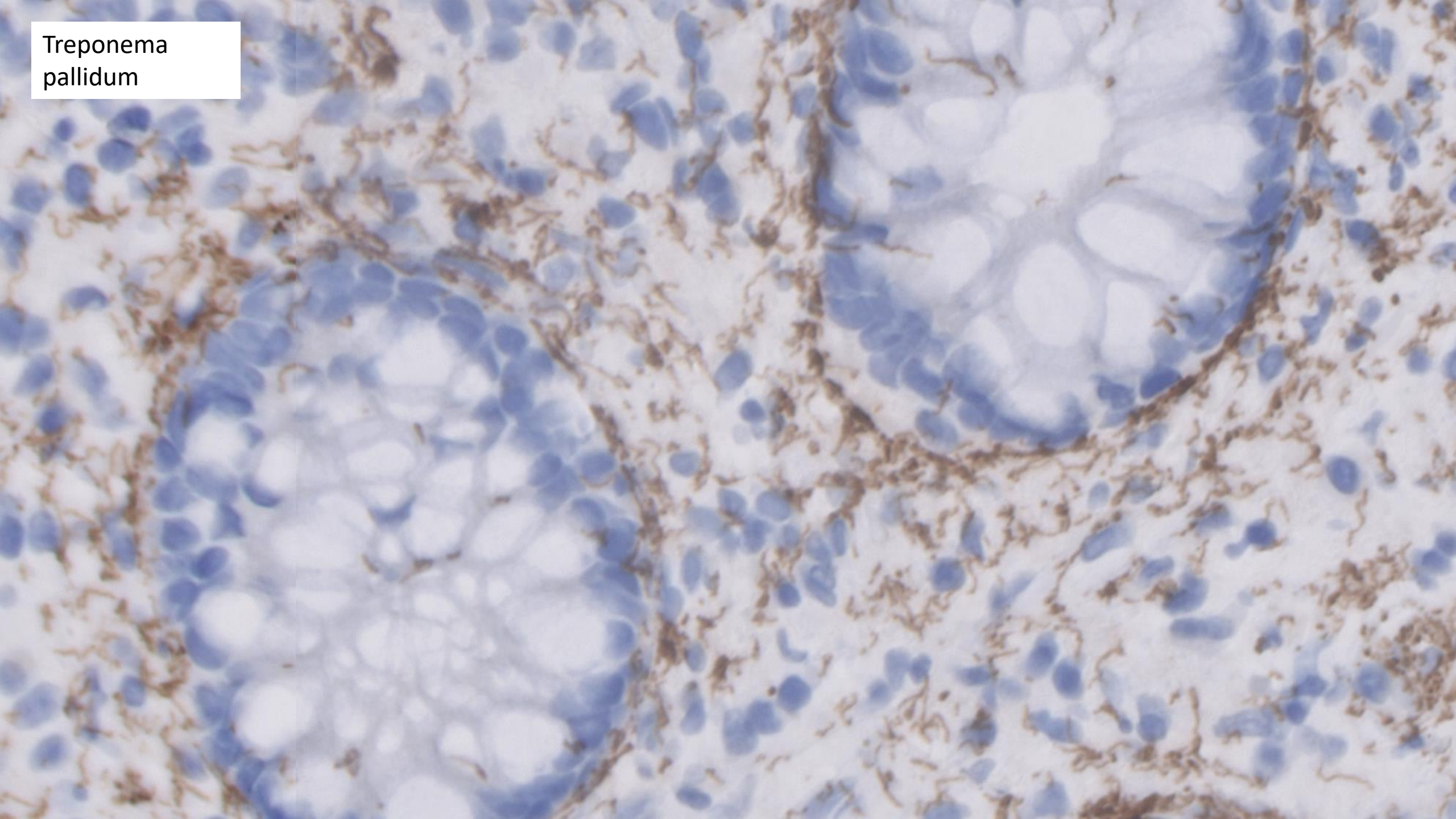
Both negative

What about *Treponema*?

- Negative RPR at an outside hospital!!!

SURPRISE ☺


Treponema
pallidum


Treponema
pallidum

What about *Treponema*?

- Post colonoscopy RPR and Treponemal antibody:

  POSITIVE!!!

Abundant Treponema pallidum organisms.

LAB TESTS:

Treponema Ab +

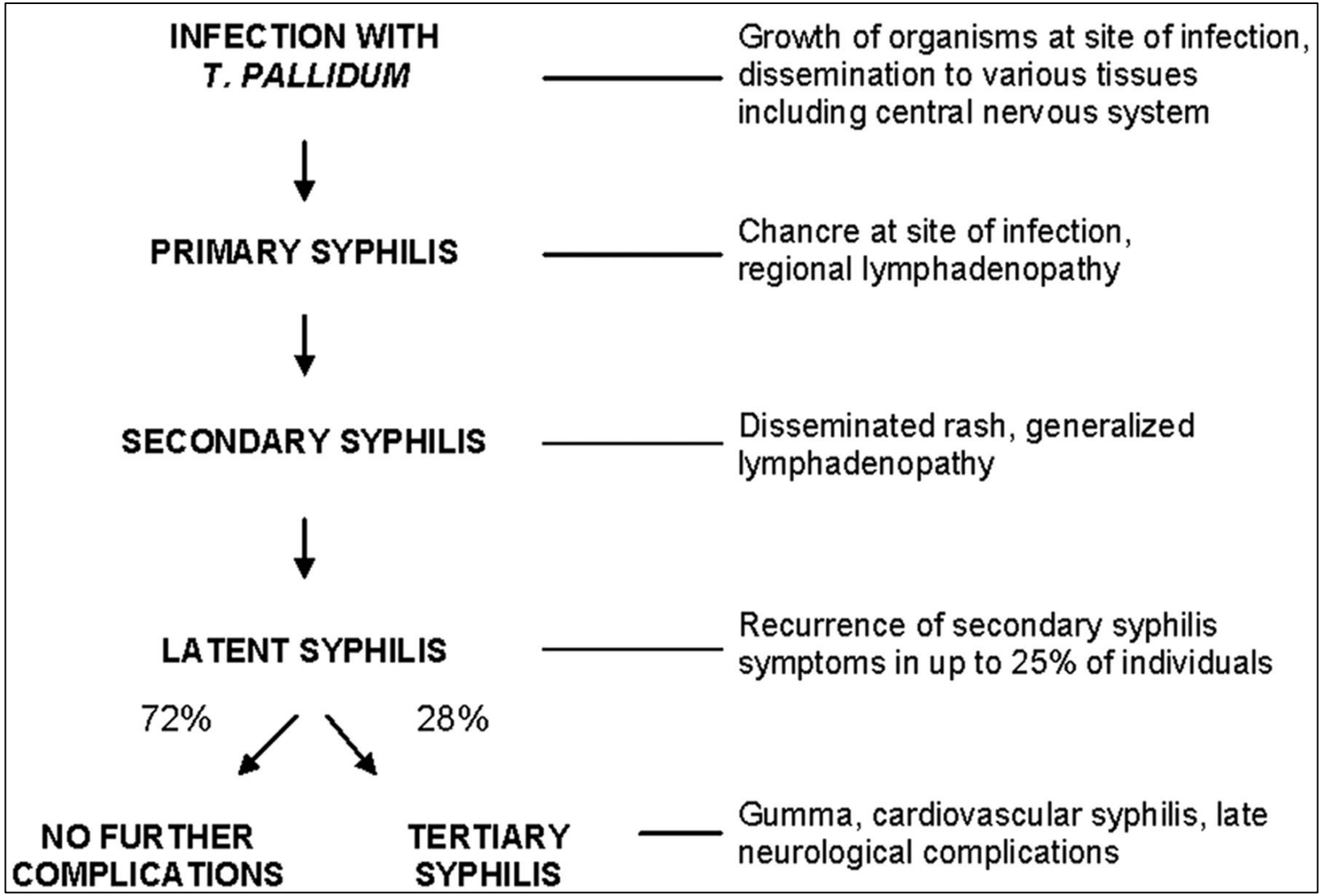
RPR titer 4+

FOLLOW-UP:
s/p 1 dose of penicillin-G IM as well as a course of metronidazole. His bowel frequency is improved.

- Primary syphilis can present as anorectal chancre, which is classically painless. Although anorectal chancre may be asymptomatic, it may present with itching, bleeding, rectal discharge, constipation, and tenesmus.

- In the secondary stage of syphilis, rectal mass, condyloma lata and/or mucous patches can be observed.

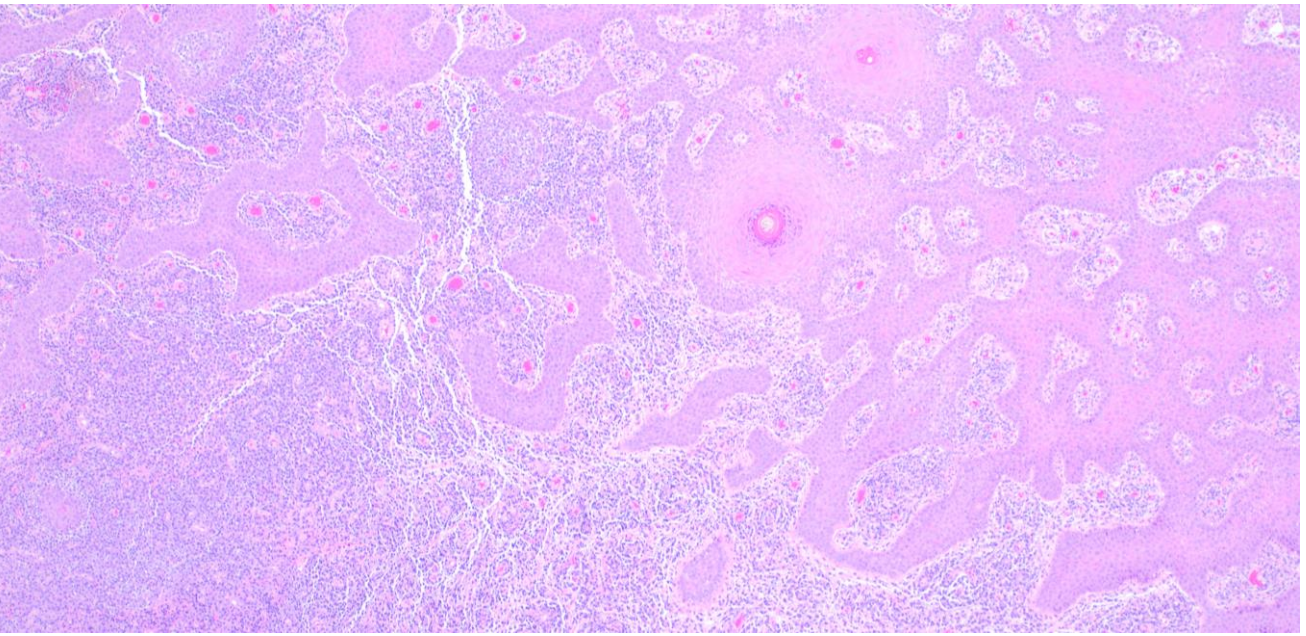
Natural history of untreated syphilis

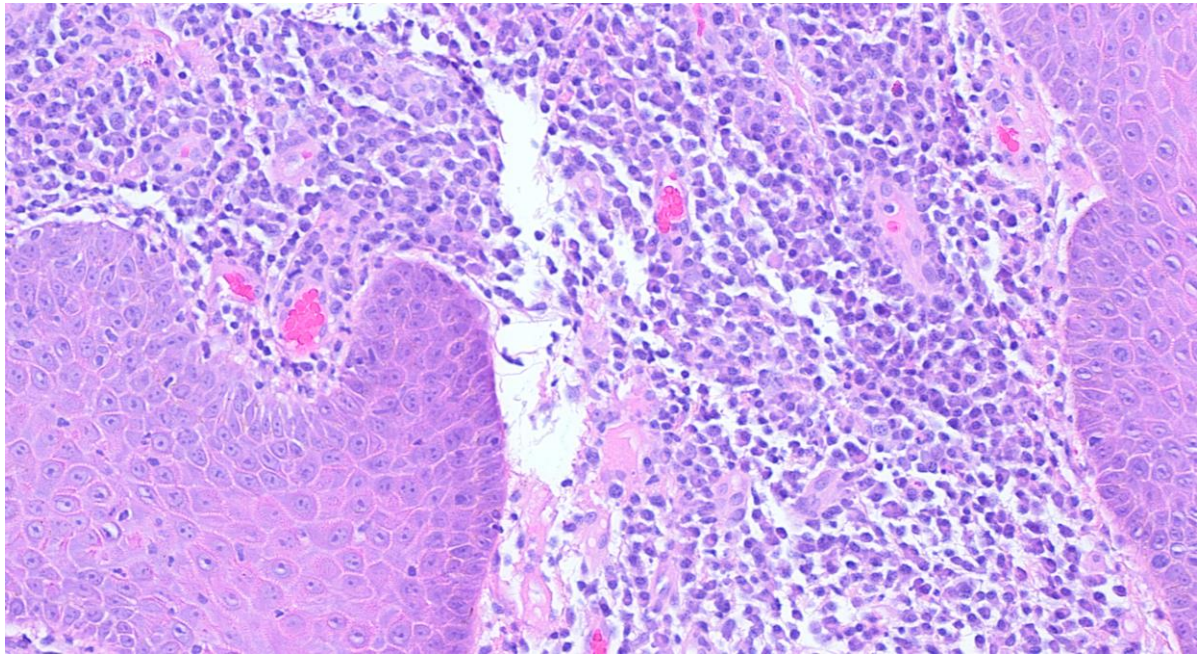


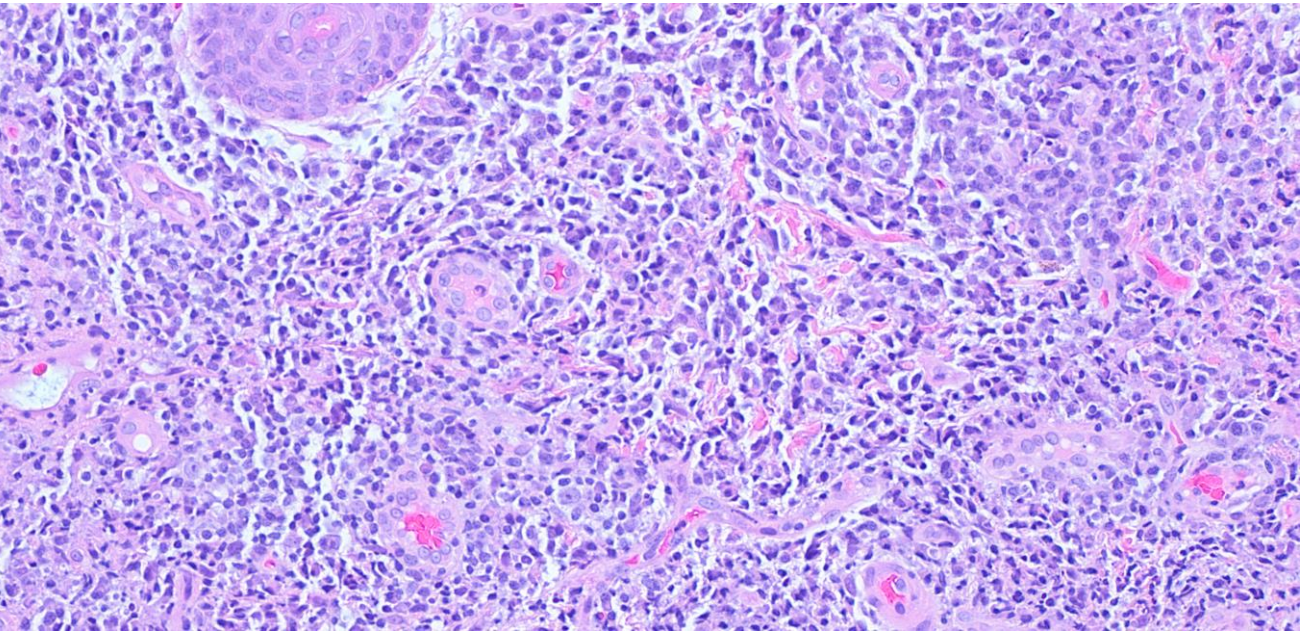
Rebecca E. LaFond and Sheila A. Lukehart. Biological Basis for Syphilis. Clin. Microbiol. Rev. 2006; 19(1):29-49

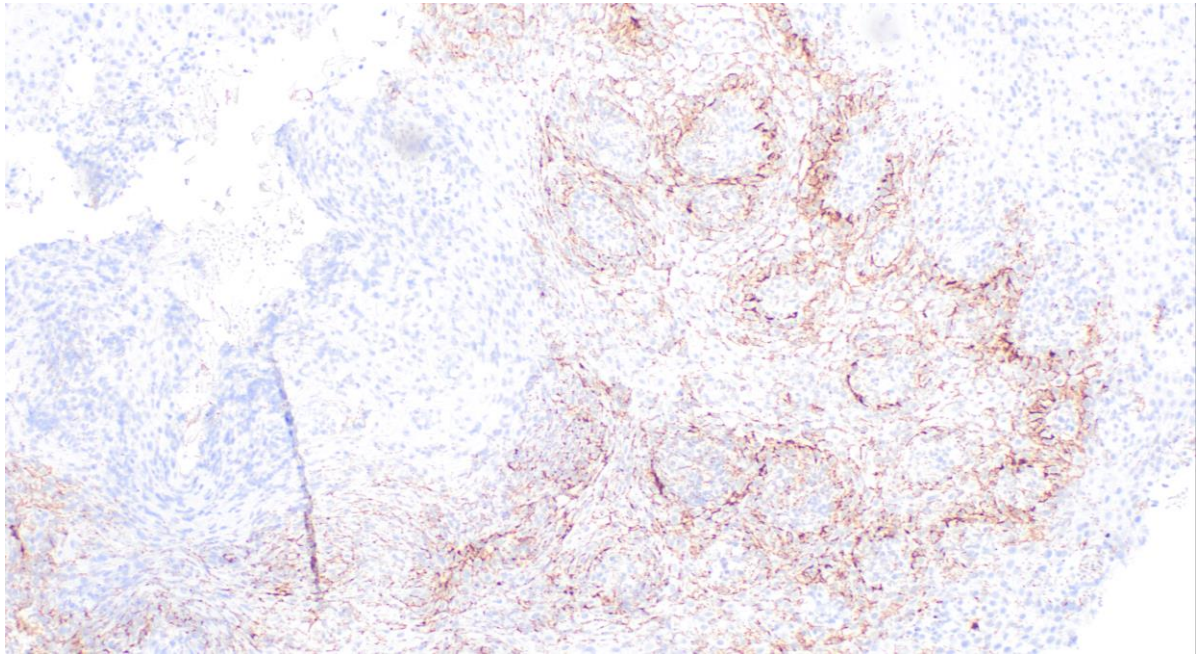
- Worldwide, an estimated 12 million new cases of syphilis occur each year.
- In the United States in 2022, 207,255 new cases were reported to the CDC in all stages
  - 80% increase since 2018
- The majority of cases are sexually transmitted
  - Transplacental infection leads to congenital syphilis
  - Infections transmitted through blood transfusion and accidental inoculation have occurred

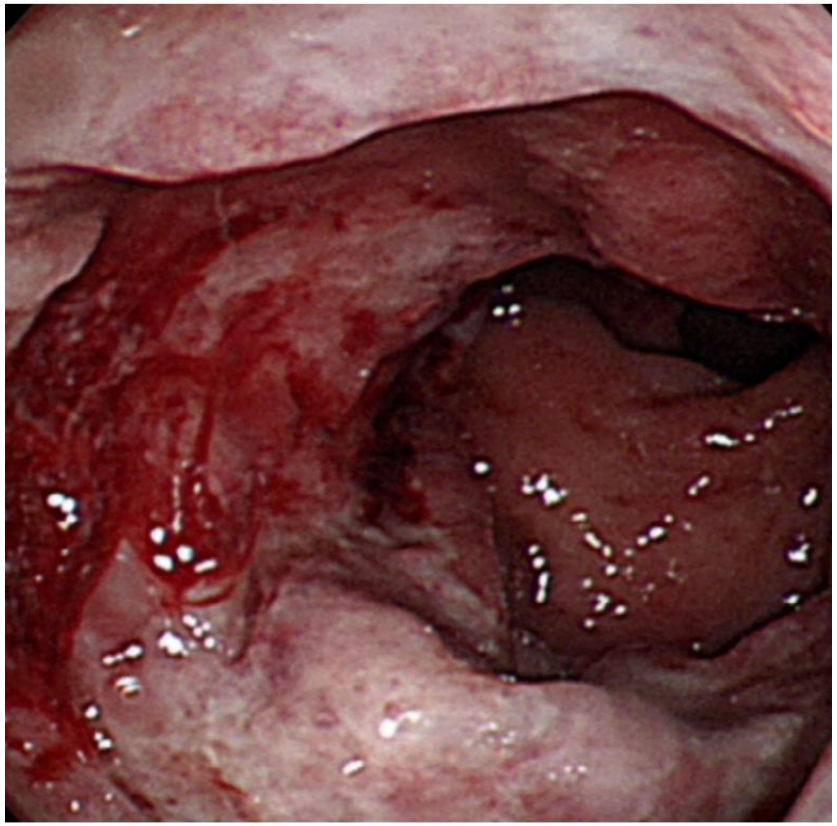
- Syphilitic lesions can be seen in anorectal region as anal canal ulcers, mucosal patches, anorectal inflammatory masses, and proctitis.
  - **Chancre:** has a prominent mononuclear cell infiltrate dominated by plasma cells with scattered histiocytes; also obliterative endarteritis with thickened small vessels due to proliferation of endothelial cells and fibroblasts
  - **Syphilis proctitis:** has a dense mononuclear cell infiltrate with conspicuous plasma cells, often with cryptitis and crypt abscesses; granulomas (usually small) and obliterative endarteritis may be present.

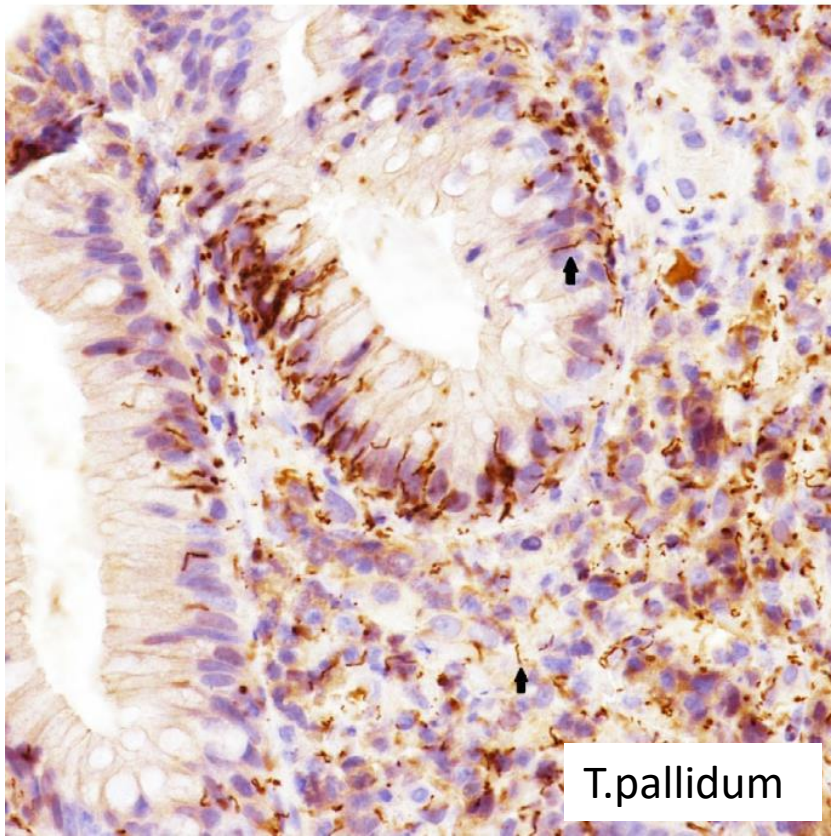


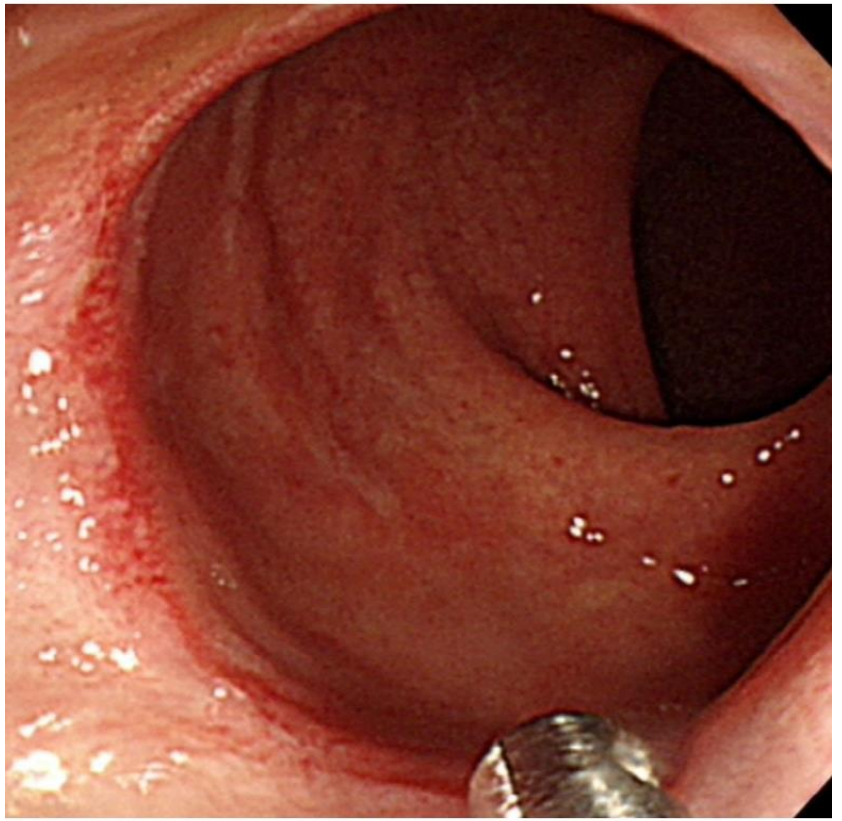












- 24, m, diarrhea
- Colonoscopy shows ulceration

Tian, Ming-Hung & Chang, Chen-Wang & Wu, Pao-Shu & Chen, Ming-Jen,. (2019). Diagnosis of syphilitic proctitis mimicking ulcerative colitis—A case report. Advances in Digestive Medicine. 7. 10.1002/aid2.13165.

Conclusion

- Syphilis should be considered in the differential diagnosis of anal canal ulcers, mucosal patches, anorectal inflammatory masses, and proctitis.
- Detailed clinical history!
- Recognition of the characteristic pattern of inflammation!
- Treponema pallidum staining can help avoid a missed diagnosis of syphilis.

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THANK YOU!

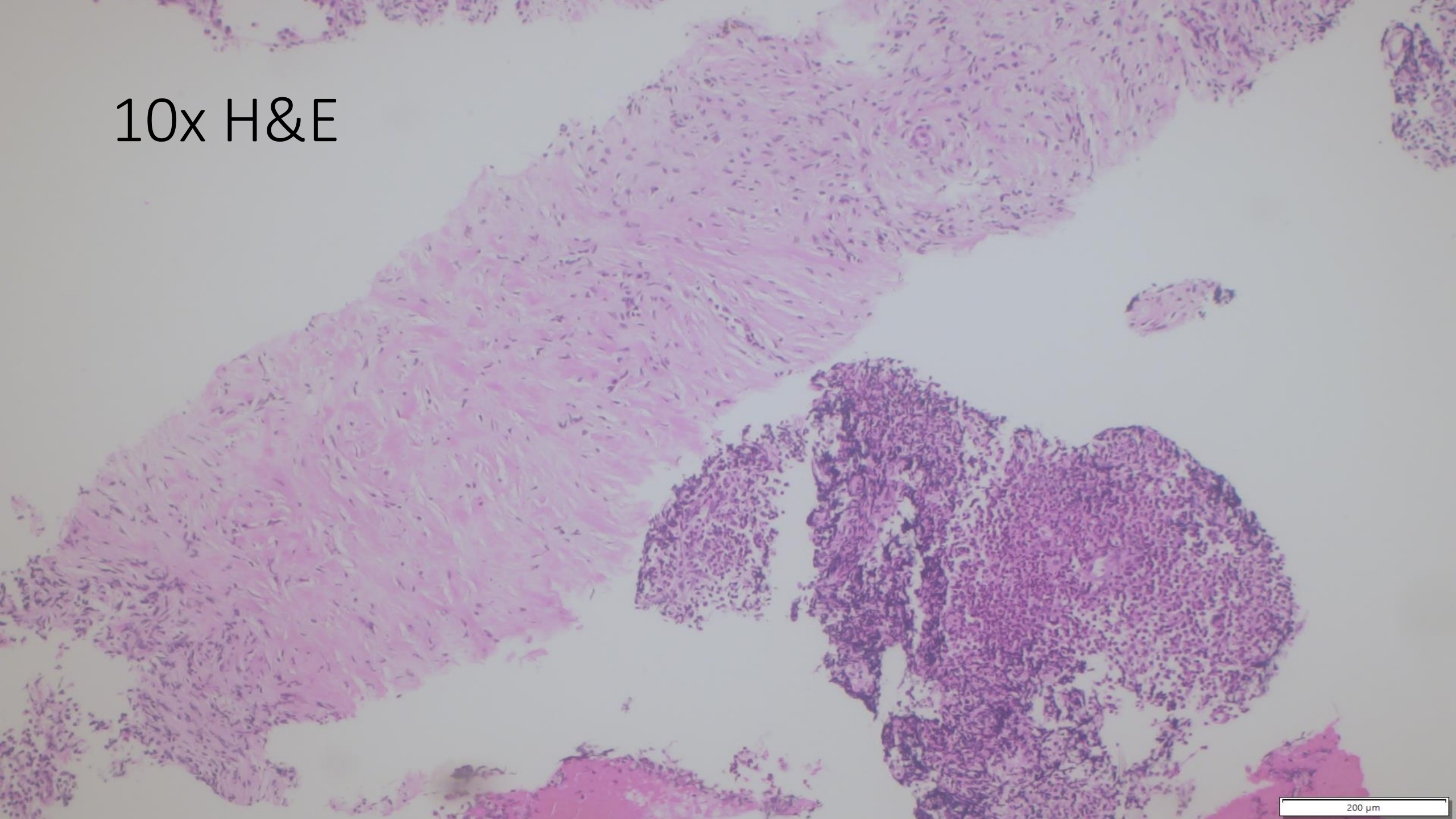
24-0405

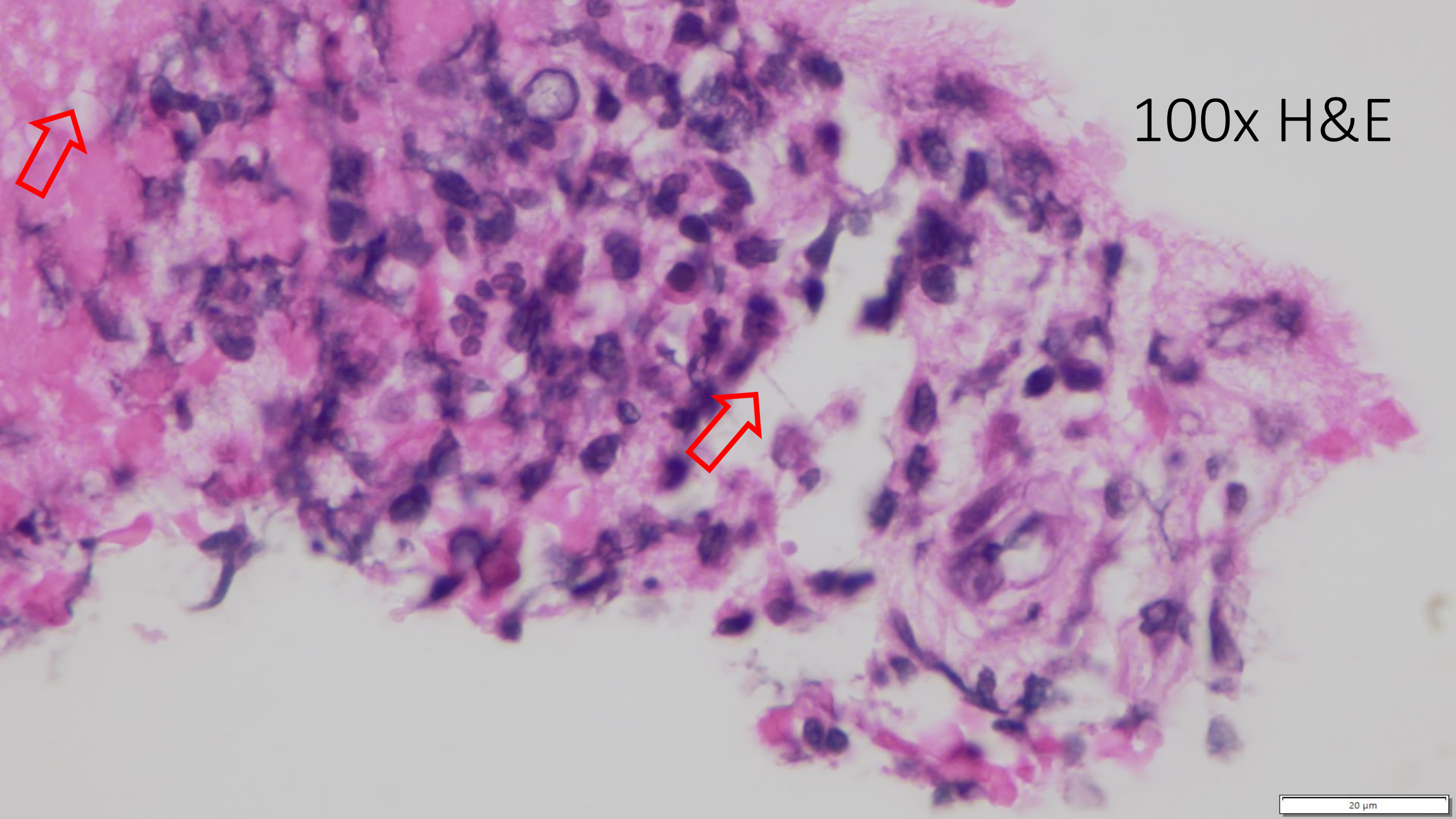
Iain Miller, MD, Patrick Mullane, MD, Kristin Jensen, MD; Stanford

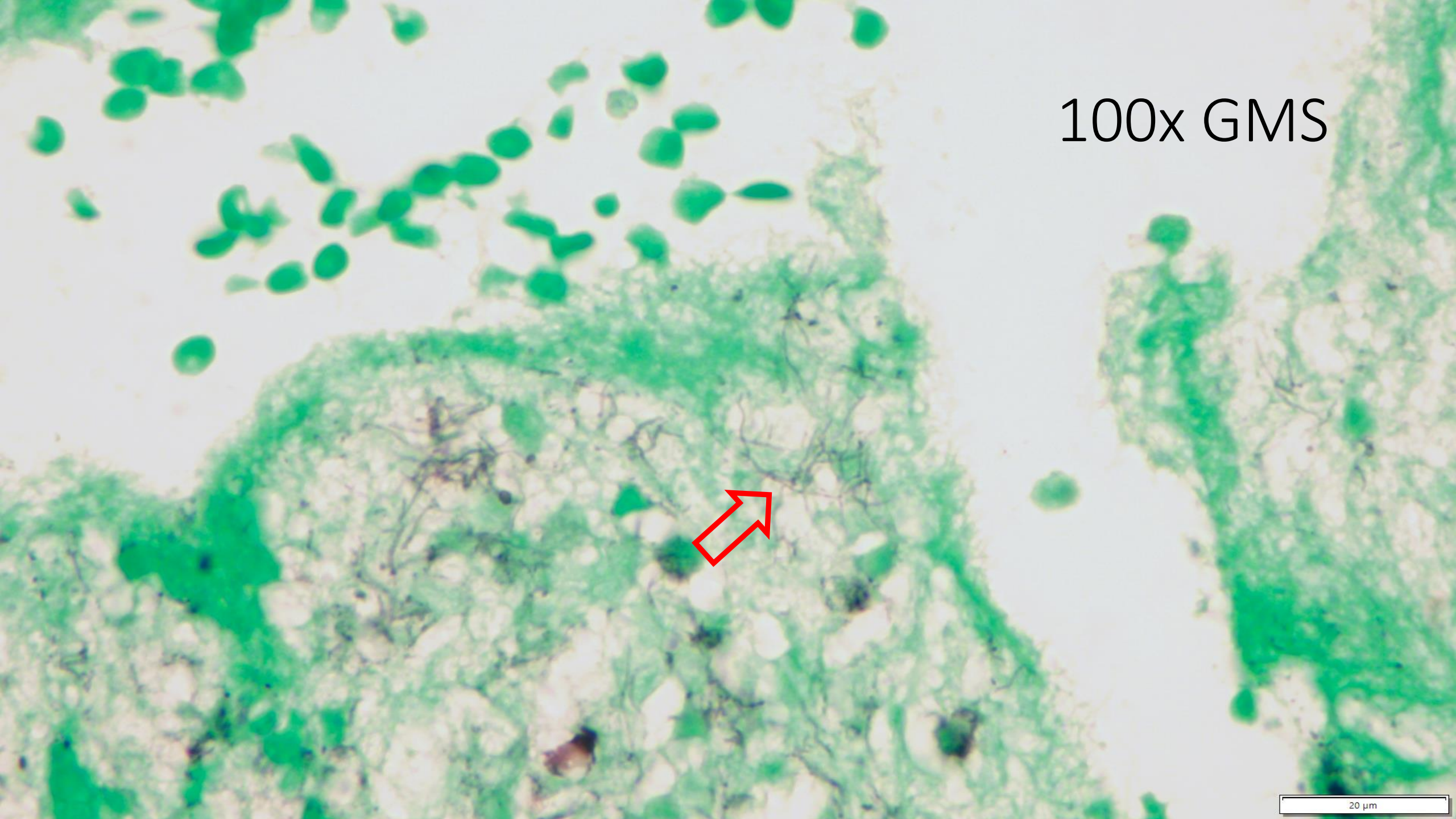
60-ish year-old male with history of prostate cancer (Gleason 4+3) status-post radiation (2019) and Lupron therapy, dilated cardiomyopathy, and pulmonary hypertension status-post heart transplant (3/2023). Patient with SARS-CoV-2 in 11/2023 and presents now with cough, fatigue, and chills.

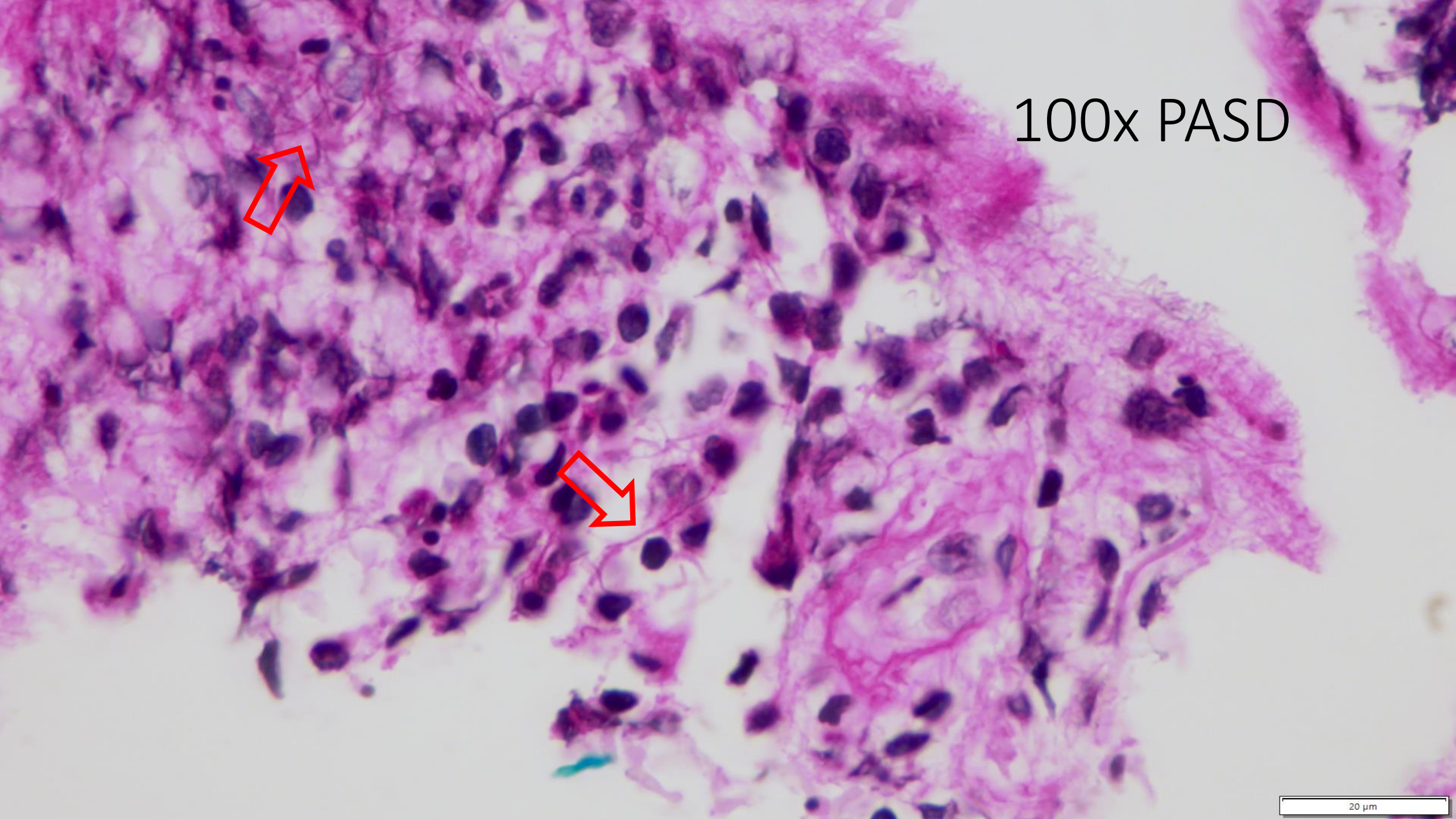
PET/CT significant for a 4.4 cm right apical lung mass concerning prostate cancer metastasis to the lung. Patient using CPAP at night for comfort for last 6-7 years.

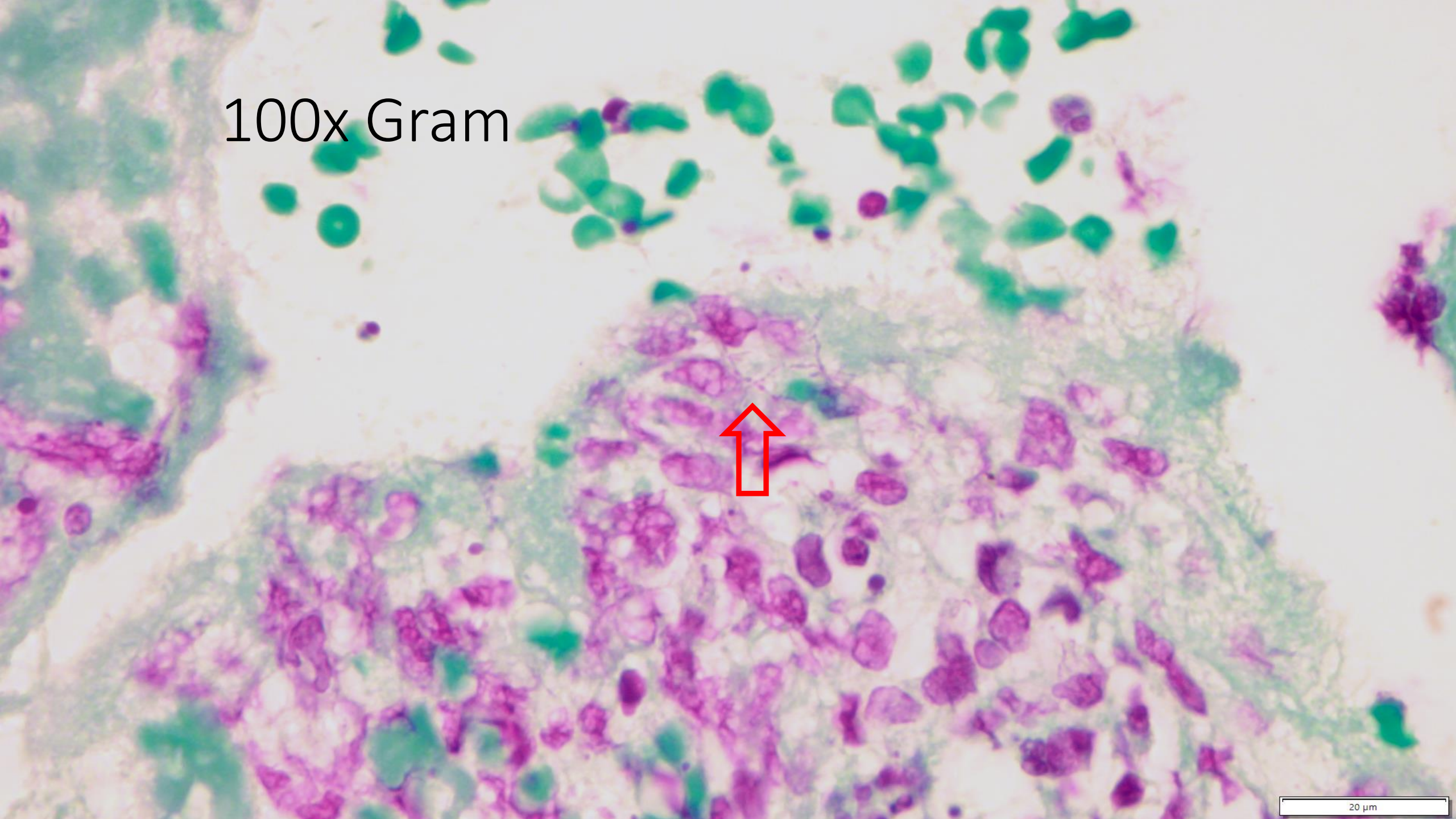
Lung, Right Apical Lesion: 10x Diff Quik

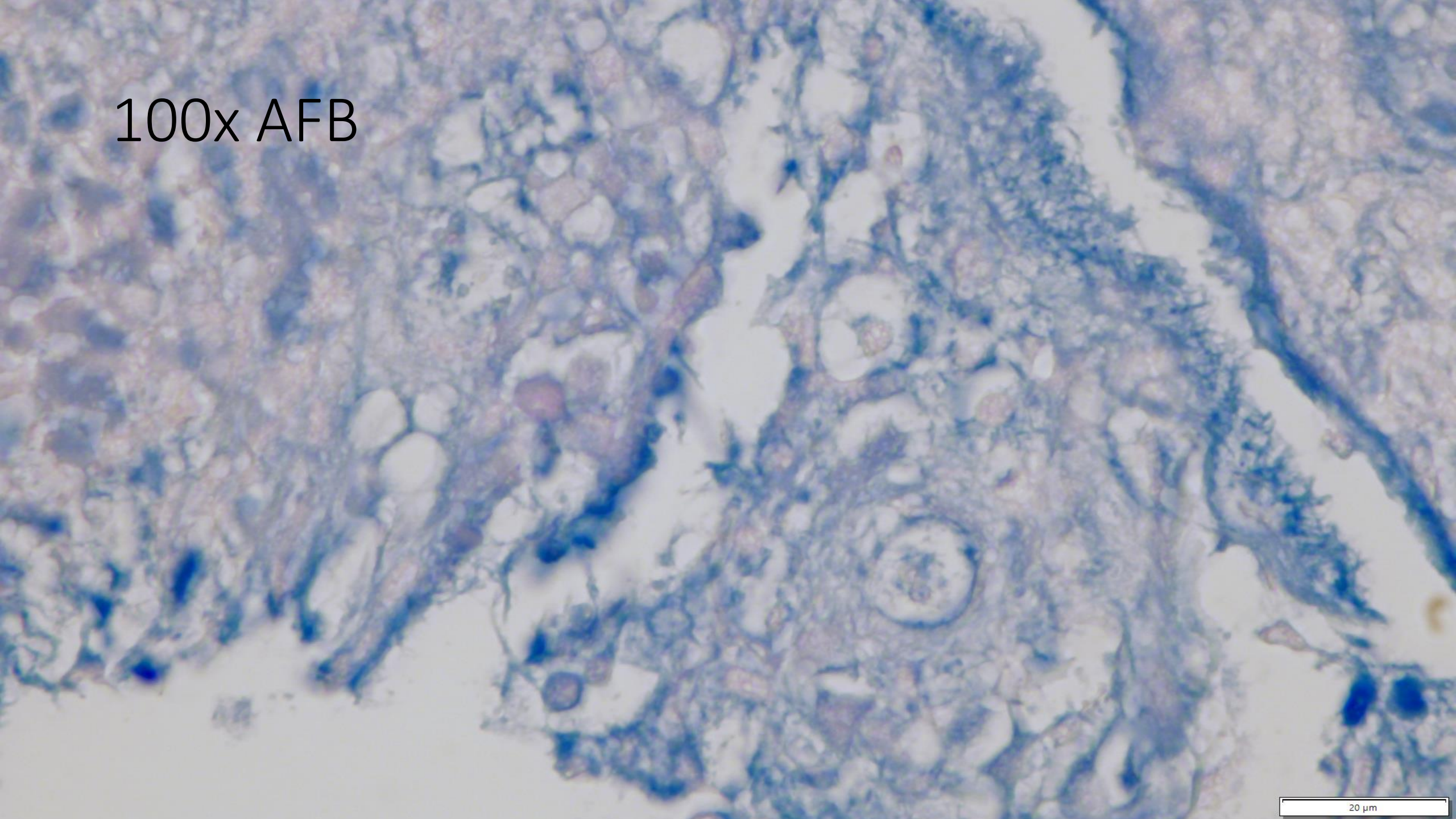

10x H&E
200 µm


100x H&E
20 µm


100x GMS
20 µm


100x PASD
20 µm


100x Gram
20 µm


100x AFB
20 µm

DIAGNOSIS?

Diagnosis:

Lung, Right Apical Lesion, CT-Guided Core Biopsy

- Lung parenchyma with fibrosis, acute and chronic inflammation, granulation tissue, and filamentous structures morphologically consistent with Nocardia spp. (see comment)
- Negative for malignancy

Comment: On GMS, PASD, and Gram stains, faint filamentous rods are identified, which are morphologically consistent with Nocardia spp. However, the differential additionally includes Actinomyces. The tissue block will be sent to Stanford for 16S rRNA bacterial sequencing and the results will be reported in an addendum.

Diagnosis:

Lung, Right Apical Lesion, CT-Guided Core Biopsy

- Lung parenchyma with fibrosis, acute and chronic inflammation, granulation tissue, and filamentous structures morphologically consistent with Nocardia spp. (see comment)
- Negative for malignancy

BACTERIAL ID BY SEQUENCING, SPECIMEN

Status: Final result Visible to patient: Yes (not seen)

Specimen Information: Lung, Right; Existing Patient Material

0 Result Notes

Bacterial ID	Nocardia species !
	-IDENTIFIED AS - Nocardia beijingensis
	The sensitivity and specificity of this assay are 97.7% and 100%, respectively, using culture as the reference method.

Comment: On GMS, PASD, and Gram stains, faint filamentous rods are identified, which are morphologically consistent with Nocardia spp. However, the differential additionally includes Actinomyces. The tissue block will be sent to Stanford for 16S rRNA bacterial sequencing and the results will be reported in an addendum.

Differential Diagnosis

Name	Nocardia	Actinomyces	Aspergillus
Histology	• Necrotizing pneumonia with granulohistiocytic inflammation	• Microabscesses • Polymorphous infiltrates of lymphocytes, histiocytes, plasma cells, giant cells, and fibrosis • Sulfur Granules	• Patchy eosinophilic pneumonia • Bronchocentric Granulomatosis • Chronic necrotizing aspergillosis • Etc…
Size (diameter)	• 0.5-1 μm	• 0.5-1 μm	• 2-10 μm
Gram	• Beaded (less) • Filamentous	• Beaded (more) • Filamentous	• Negative (but conidia are positive)
GMS PASD	• GMS: Positive • PASD: Variable	• GMS: Positive • PASD: Negative	• GMS: Positive • PASD: Positive
AFB Modified AFB	• AFB: Negative • Modified AFB: Positive	• AFB: Negative • Modified AFB: Negative	• AFB: Negative • Modified AFB: Negative

Potential Diagnostic Pitfalls

- Discounting GMS staining as background (false negative)
- Antibiotic effect can inflate bacteria (misdiagnosis as fungi)
- Misinterpreting PASD and GMS stains in absence of Gram stain (misdiagnosis as fungi)

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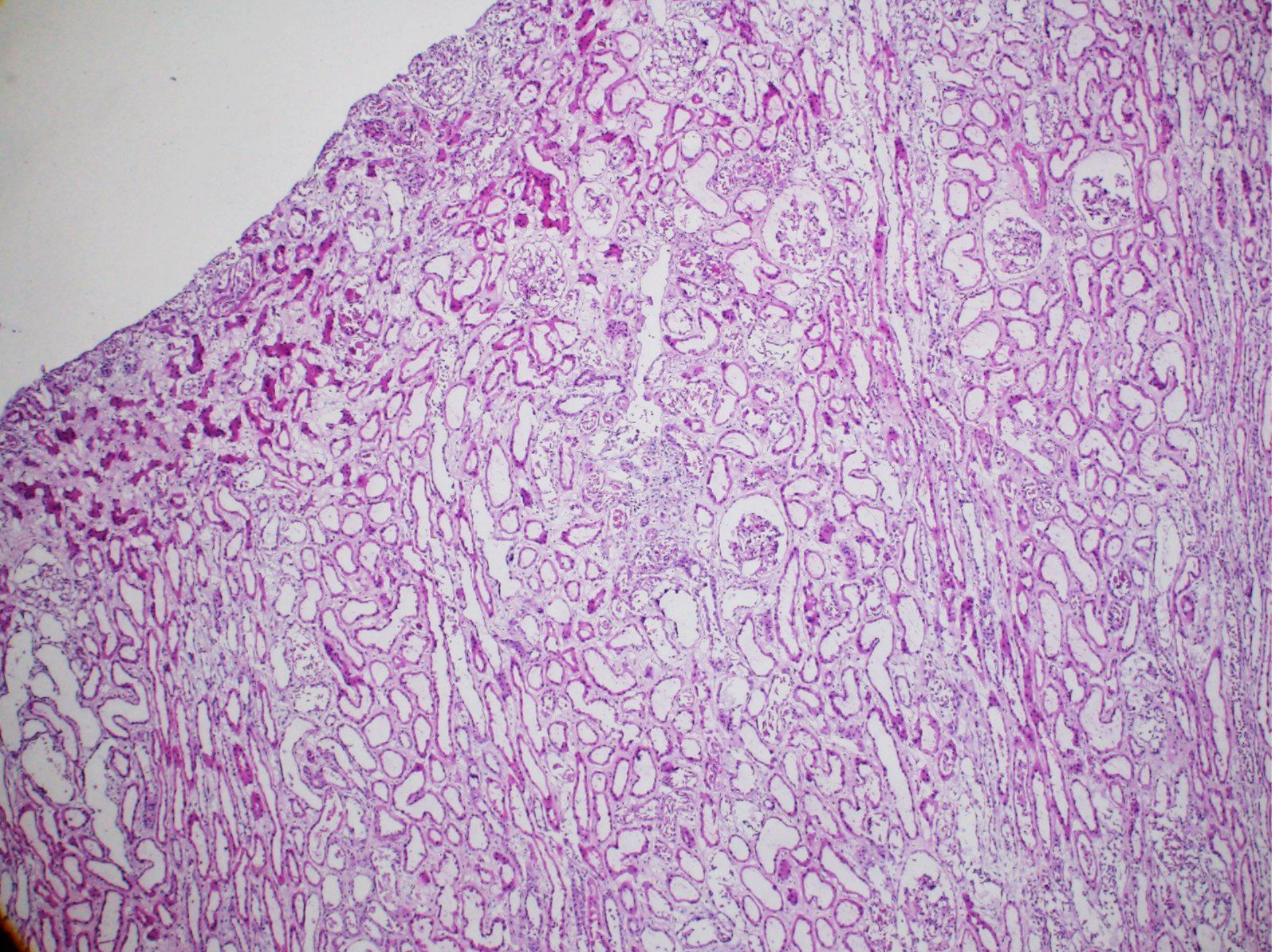
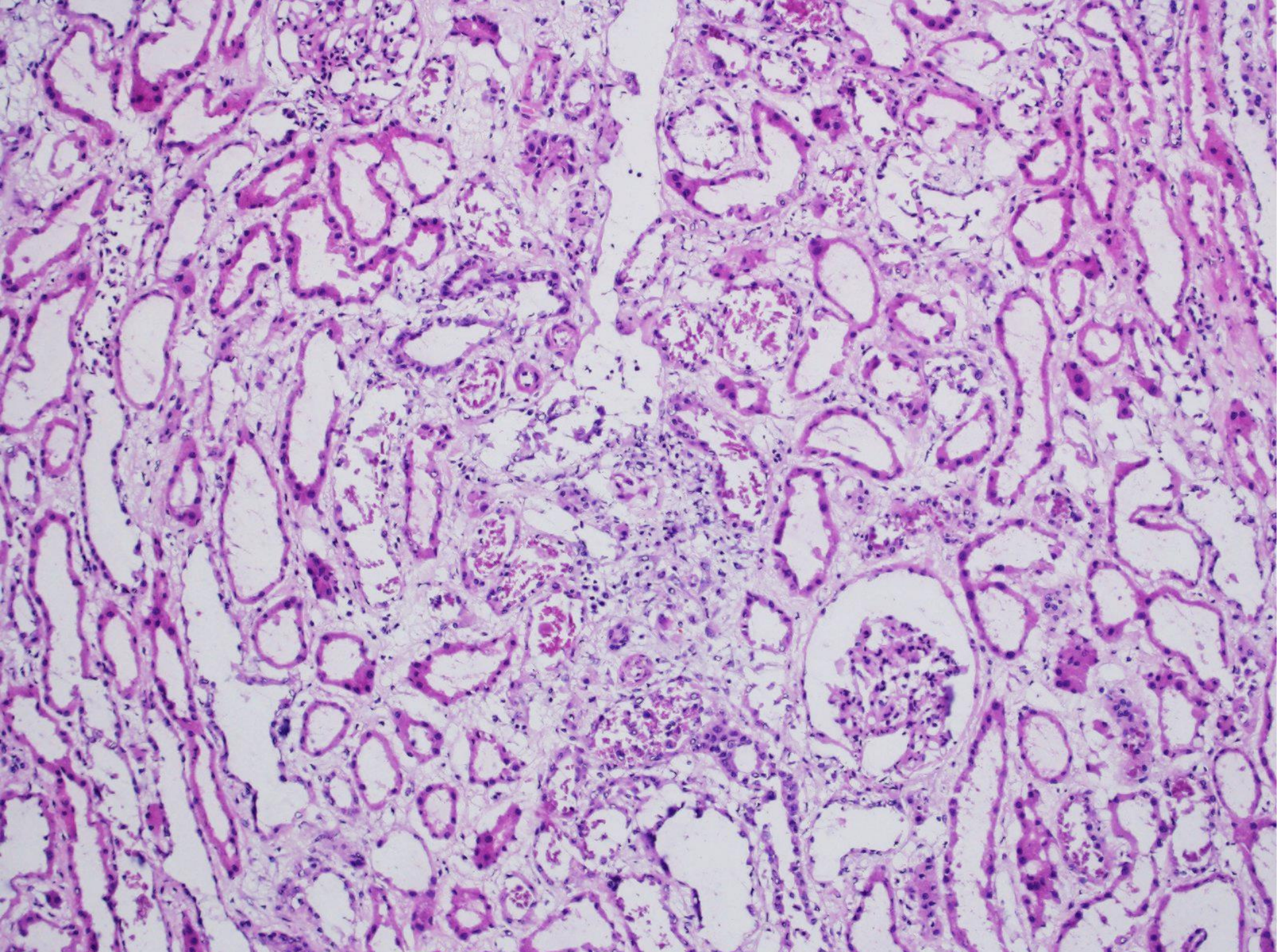
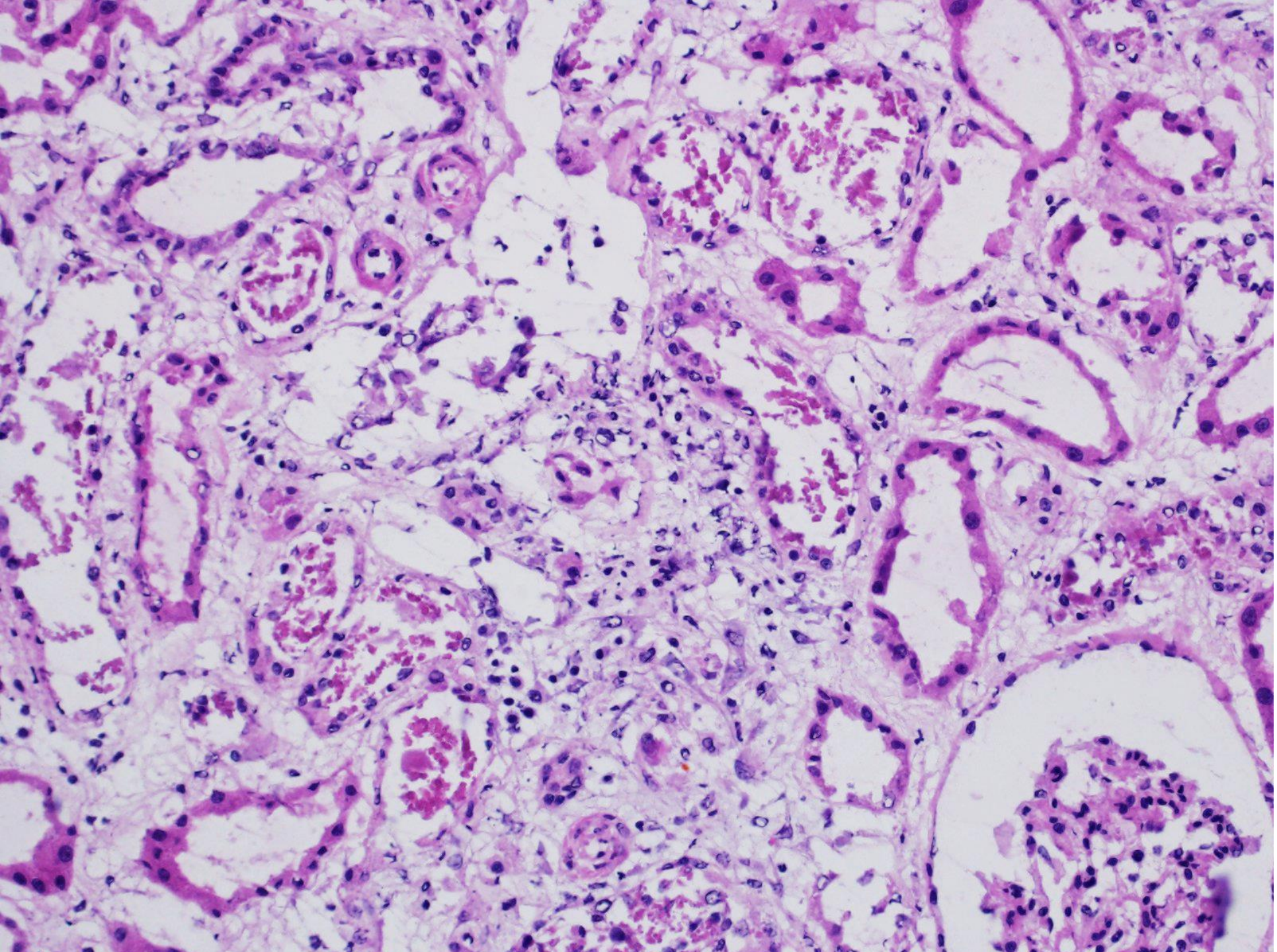
24-0406

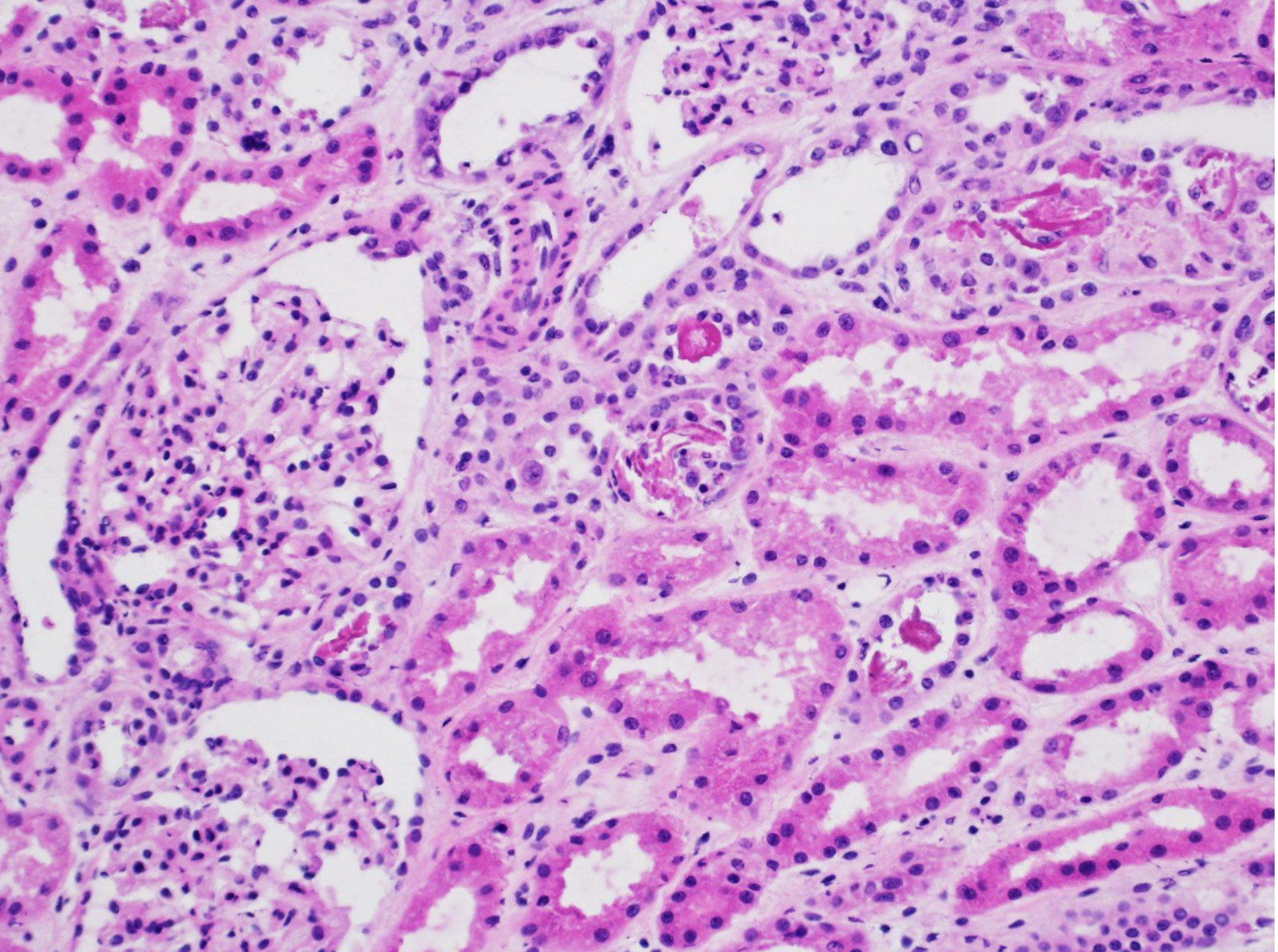
Megan Troxell; Stanford

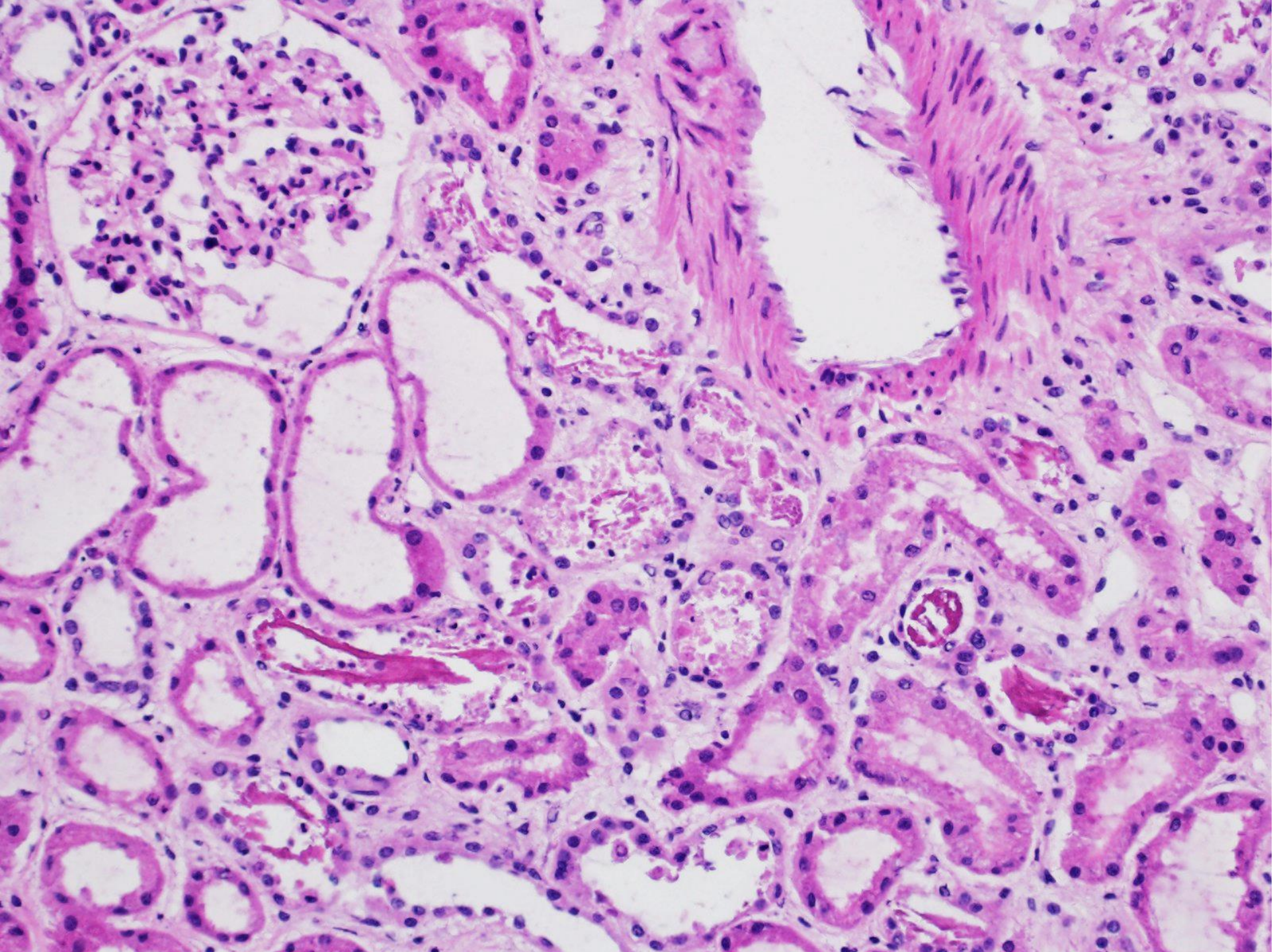
- Donor kidney frozen section (absolutely no history provided)



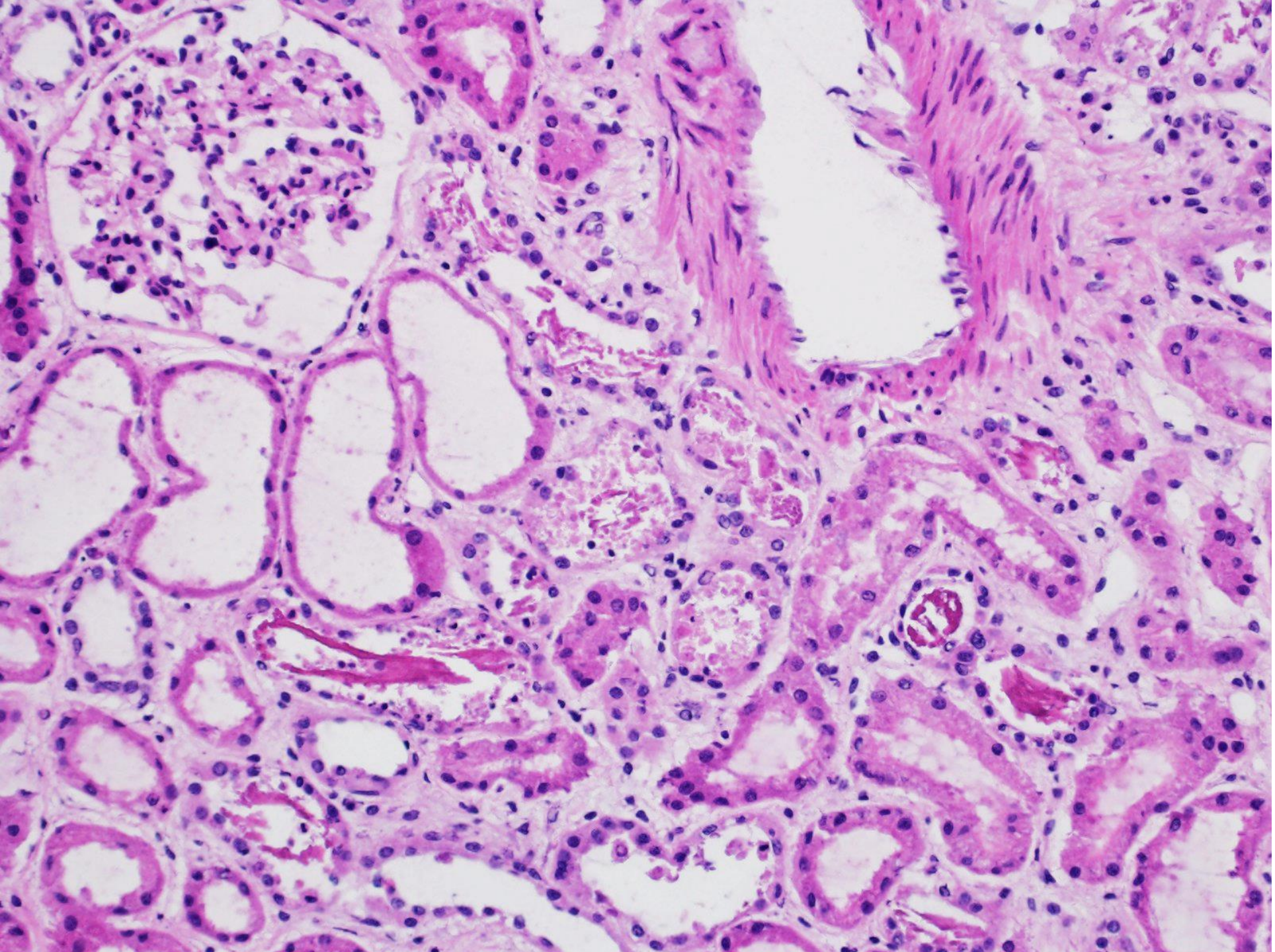






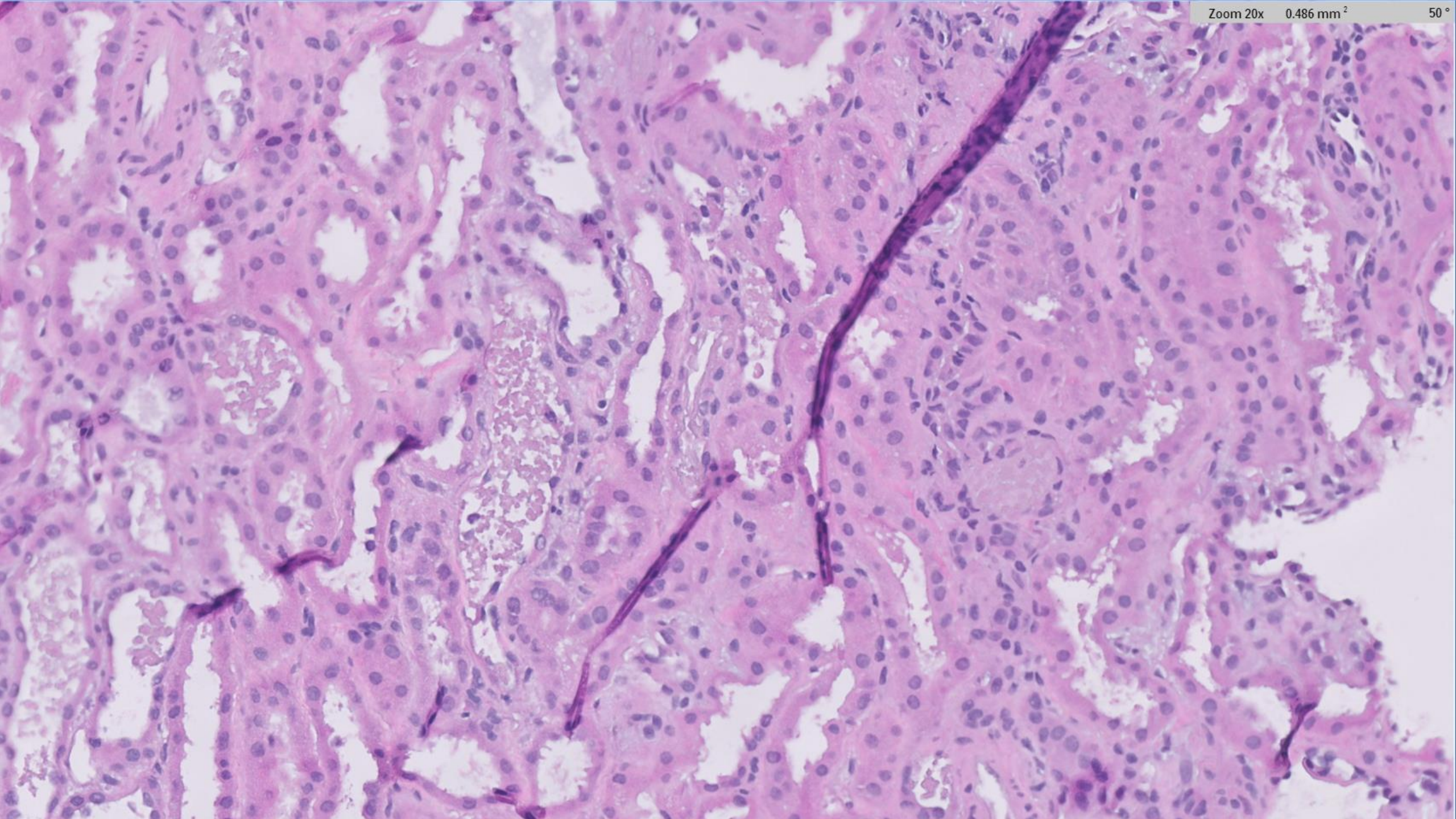


DIAGNOSIS?

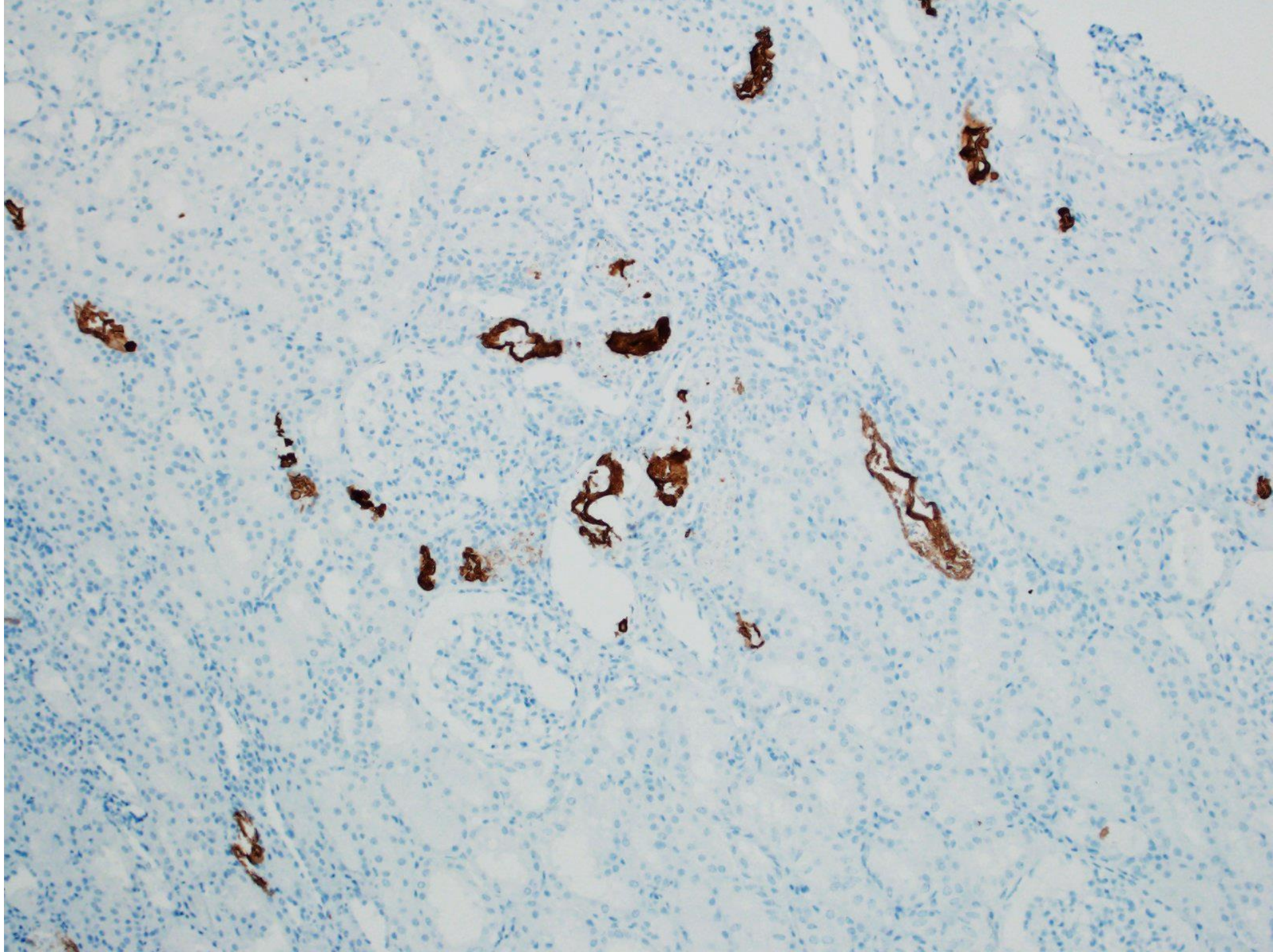


FS diagnosis:

- Global glomerulosclerosis: 0%
- IF/TA: <5%
- Artery/arteriolar narrowing: No
- Cortical necrosis: Absent
- Fibrin thrombi: Absent
- Other/comment: Extensive Acute Tubular Injury w/ Casts


Zoom 20x
0.486 mm ²
50 °

Myoglobin IHC

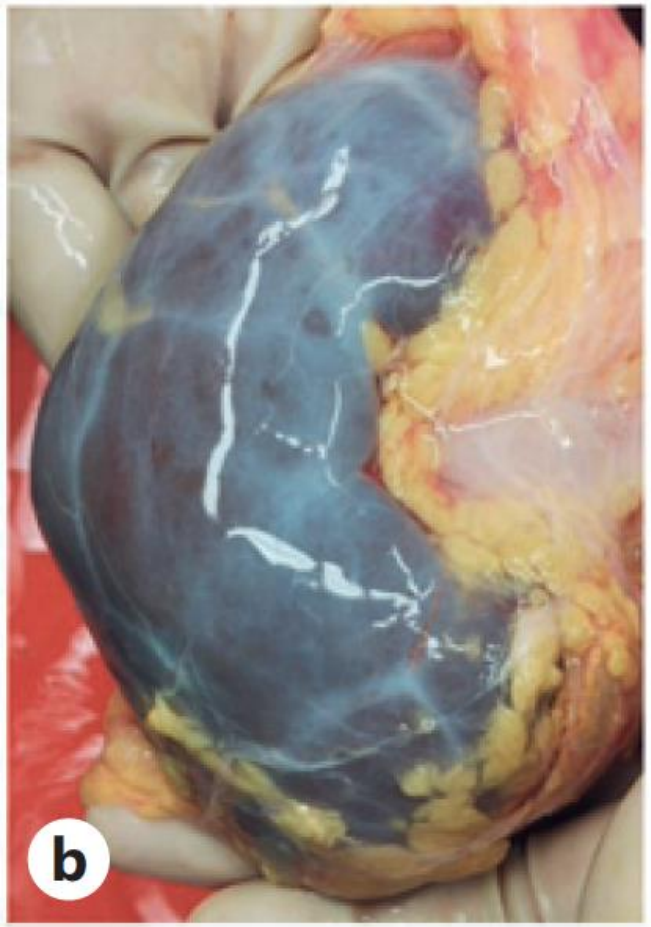


Final Diagnosis

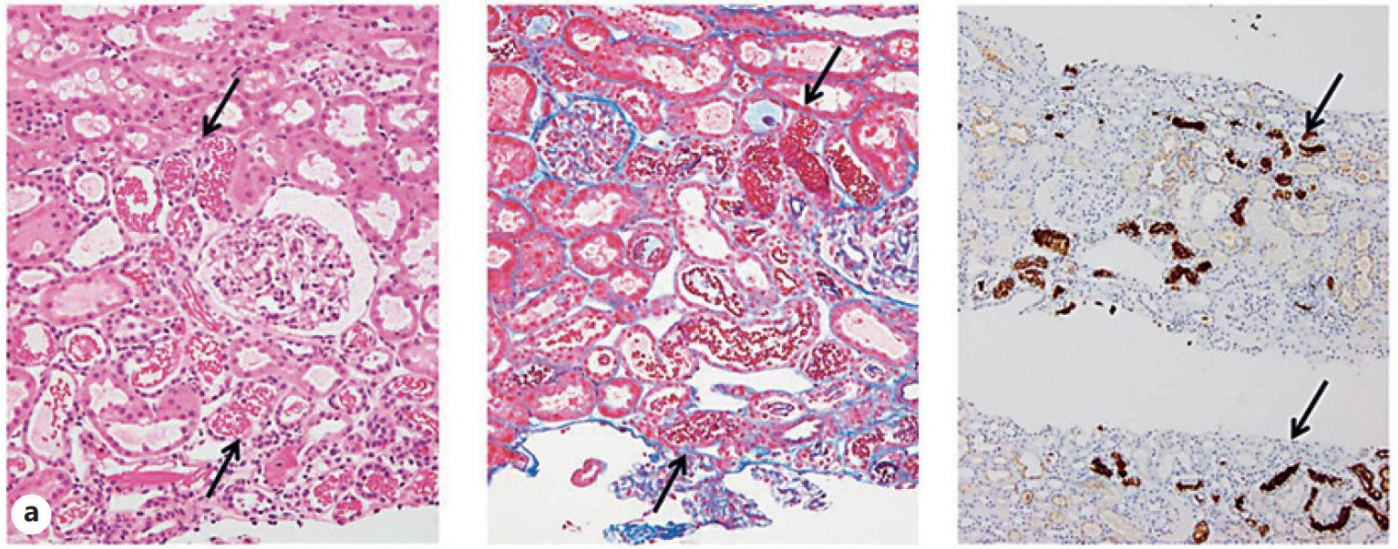
- Myoglobin Cast Nephropathy with Acute Tubular Injury

A Case of Kidney Transplantation from a Deceased Donor with Acute Kidney Injury due to Rhabdomyolysis

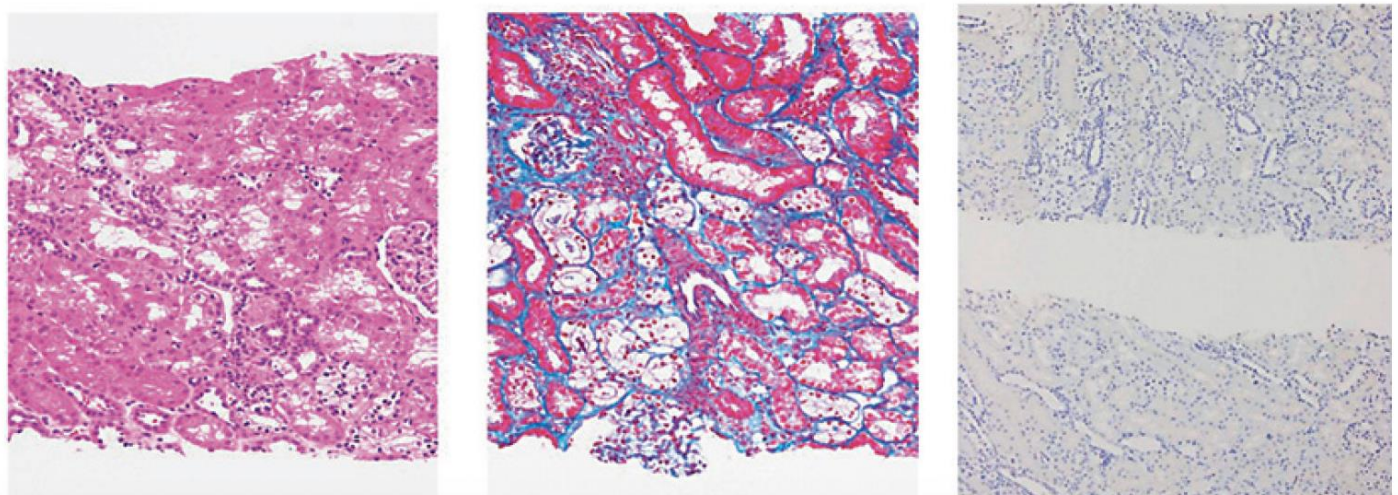
Takada et al. Nephron. 2023 Mar 24. doi: 10.1159/000530340



0-hour biopsy



Protocol biopsy at 1 months



- Esp. if very high CK
- Myoglobin toxicity esp: Volume depletion
  - Renal vasoconstriction
  - Urine acidification
- Treatment:
  - Hydration
  - Urine alkalinization??
  - Dialysis w/ usual criteria
- Alternatively, recipient derived
  - cyclosporine and HMG-CoA
  - cyclosporine and statin
  - rapamycin

Oliveira da Fonseca AJKD. 65(4):628-631.

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Kidney transplantation from donors with rhabdomyolysis and acute renal failure

Clinical Transplantation. 2017;31:e13021.

Chuan-bao Chen | Yi-tao Zheng | Jian Zhou | Ming Han | Xiao-ping Wang | Xiao-peng Yuan | Chang-xi Wang | Xiao-shun He

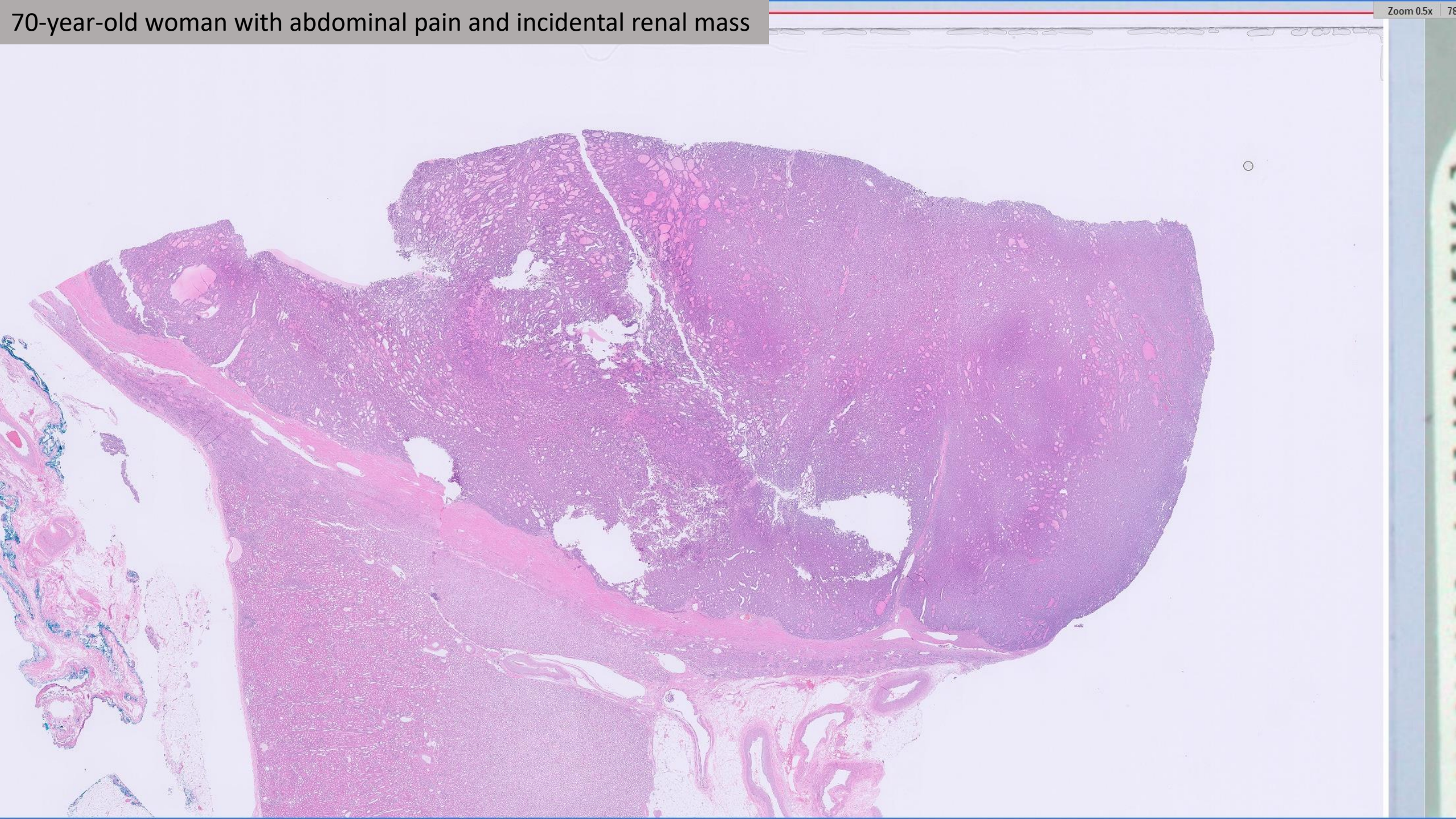
Transplant outcomes	Rhabdo (N=30)	Standard Criteria Donor (N=90)	
DGF	6 (23.3)	8 (8.9)	.11
Acute rejection	2 (6.7)	7 (7.8)	1.0
eGFR (mL/min/1.73 m^2)			
1 mo	52.1±14.4	62.7±13.8	<.01
6 mo	61.8±15.6	64.5±14.9	.45
12 mo	68.1±15.3	71.0±15.9	.42
24 mo	70.3±14.6	72.3±15.1	.60

24-0407

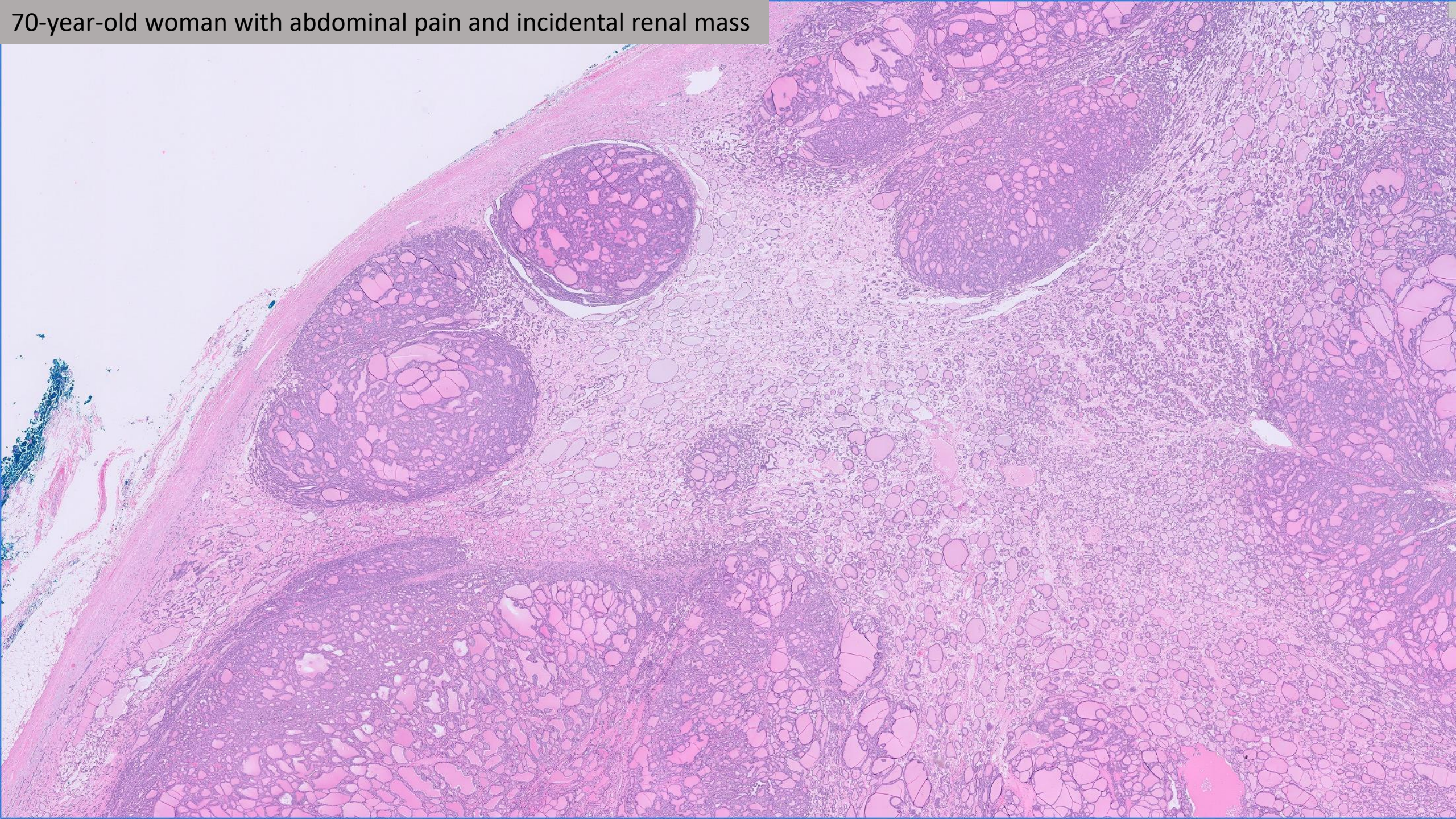
Tyler Jankowski and Ankur Sangoi; Stanford

70-year-old woman with abdominal pain and incidental renal mass.

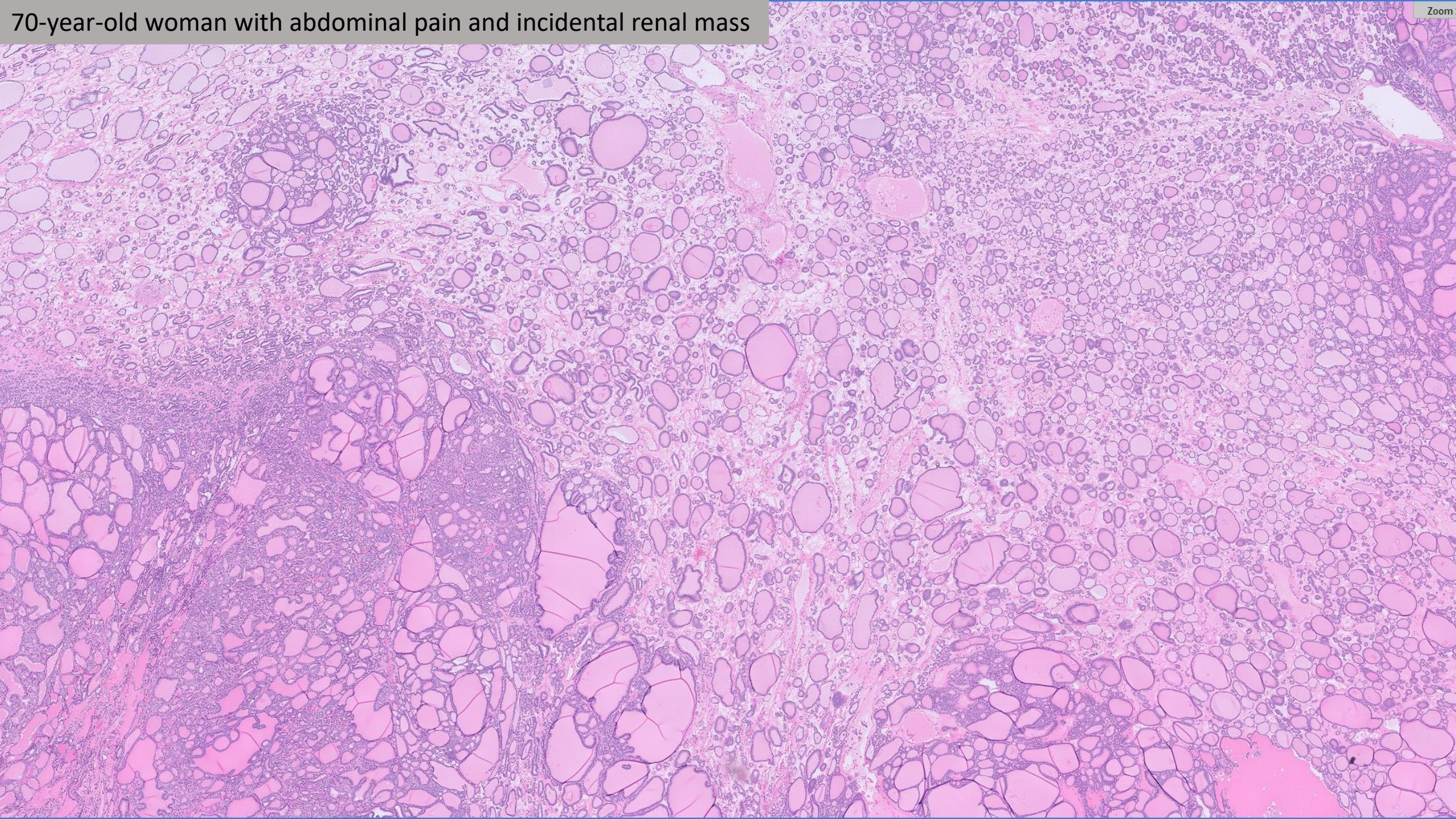
70-year-old woman with abdominal pain and incidental renal mass



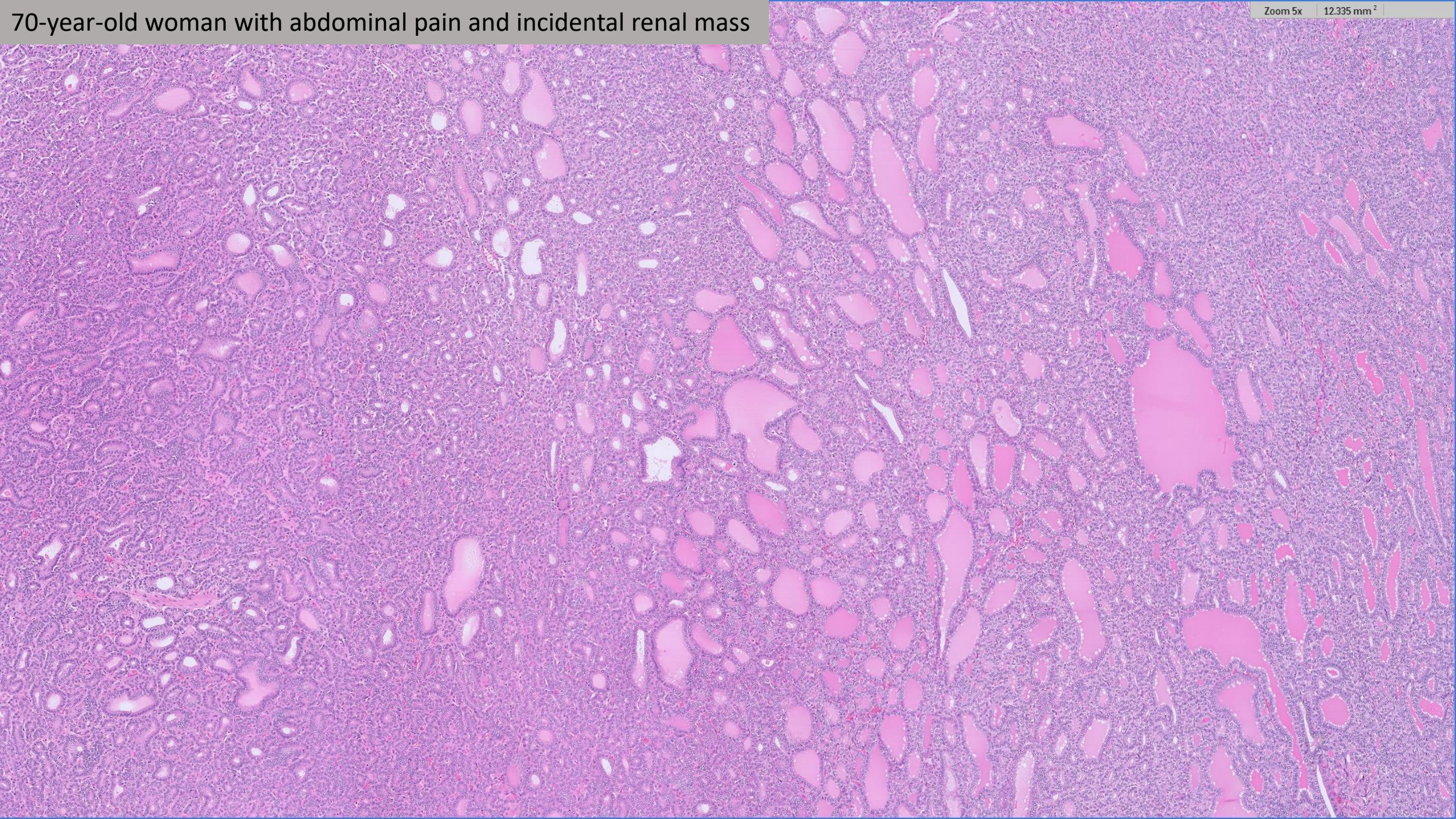
70-year-old woman with abdominal pain and incidental renal mass



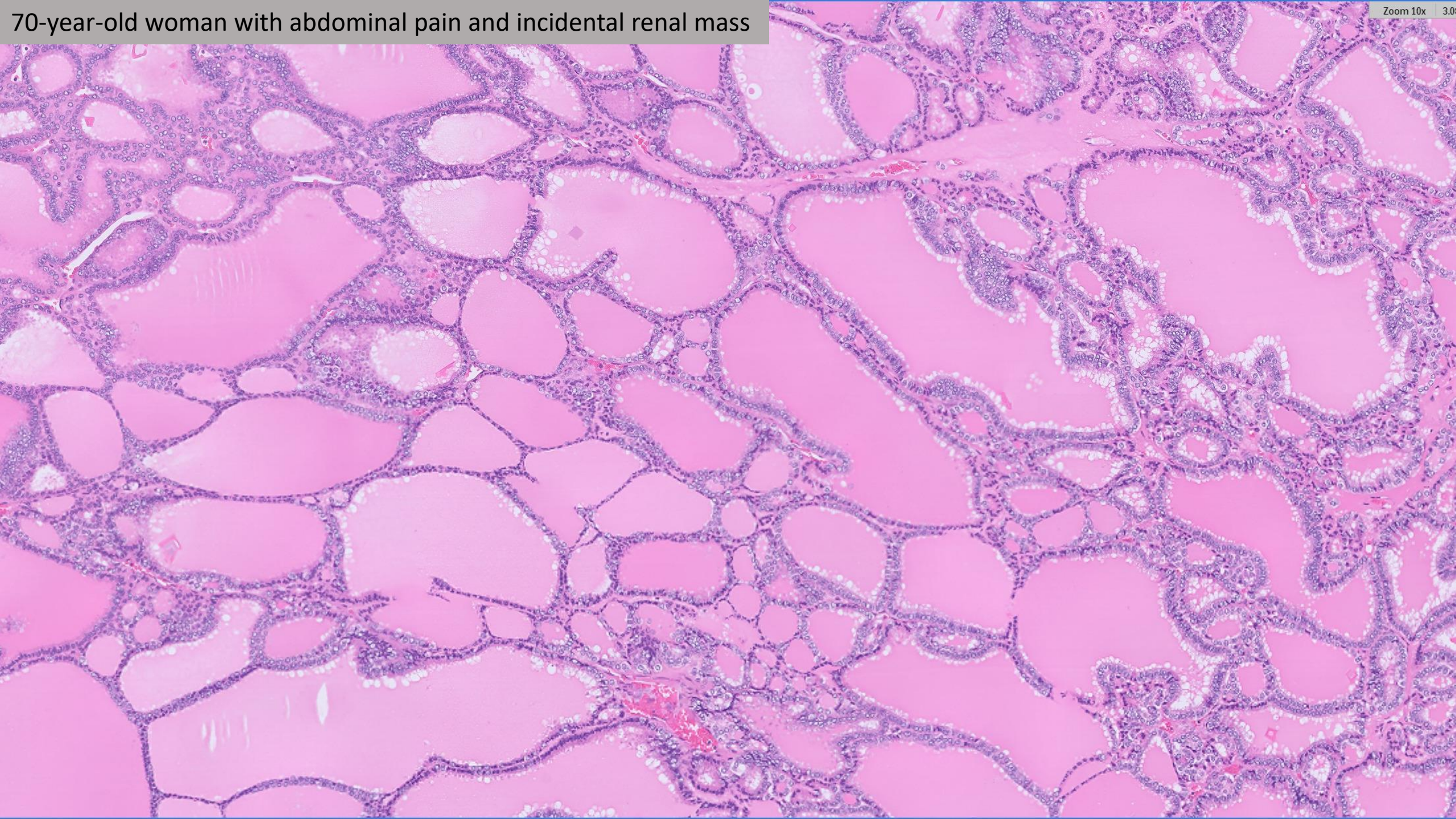
70-year-old woman with abdominal pain and incidental renal mass



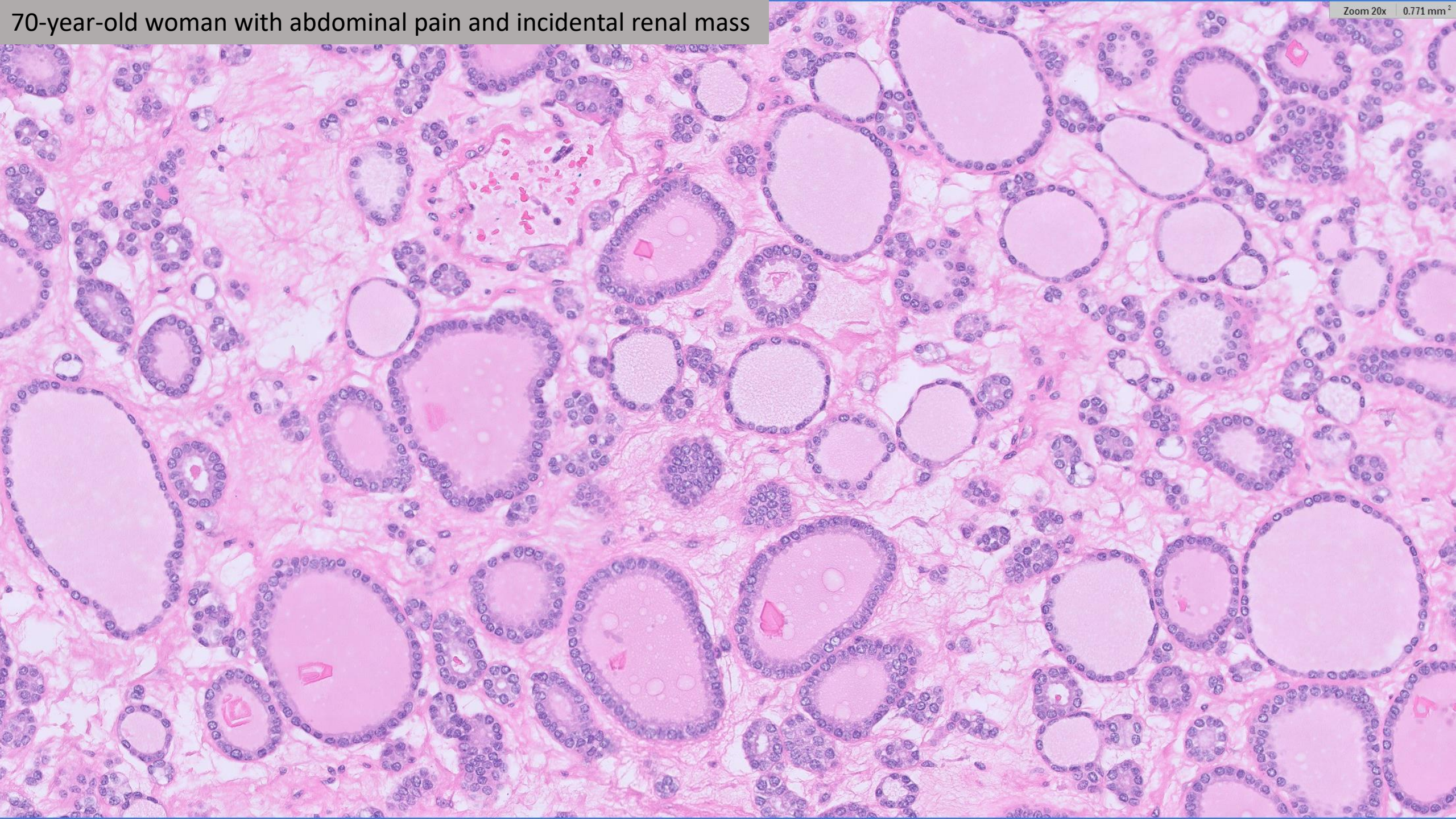
70-year-old woman with abdominal pain and incidental renal mass



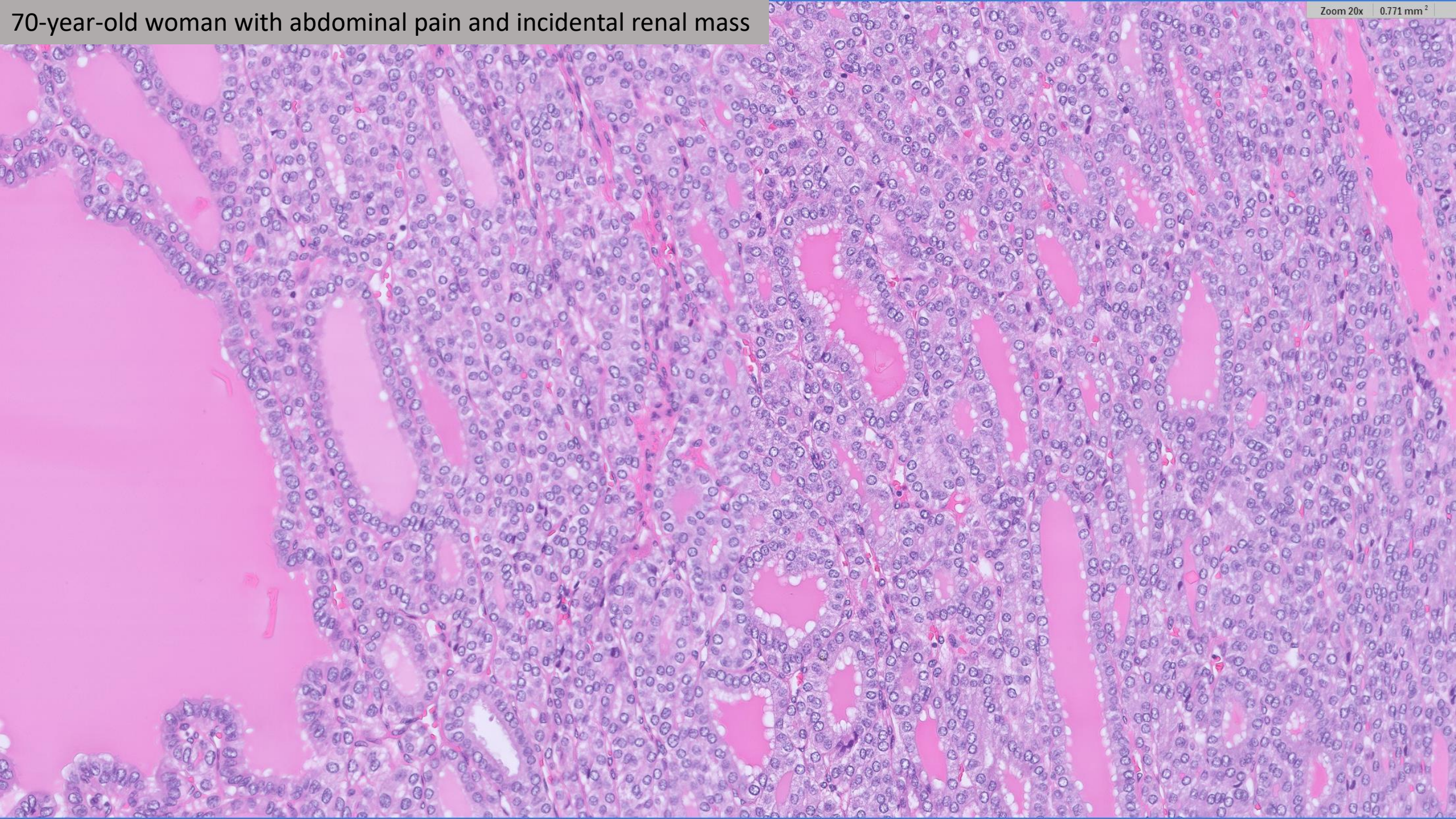
70-year-old woman with abdominal pain and incidental renal mass



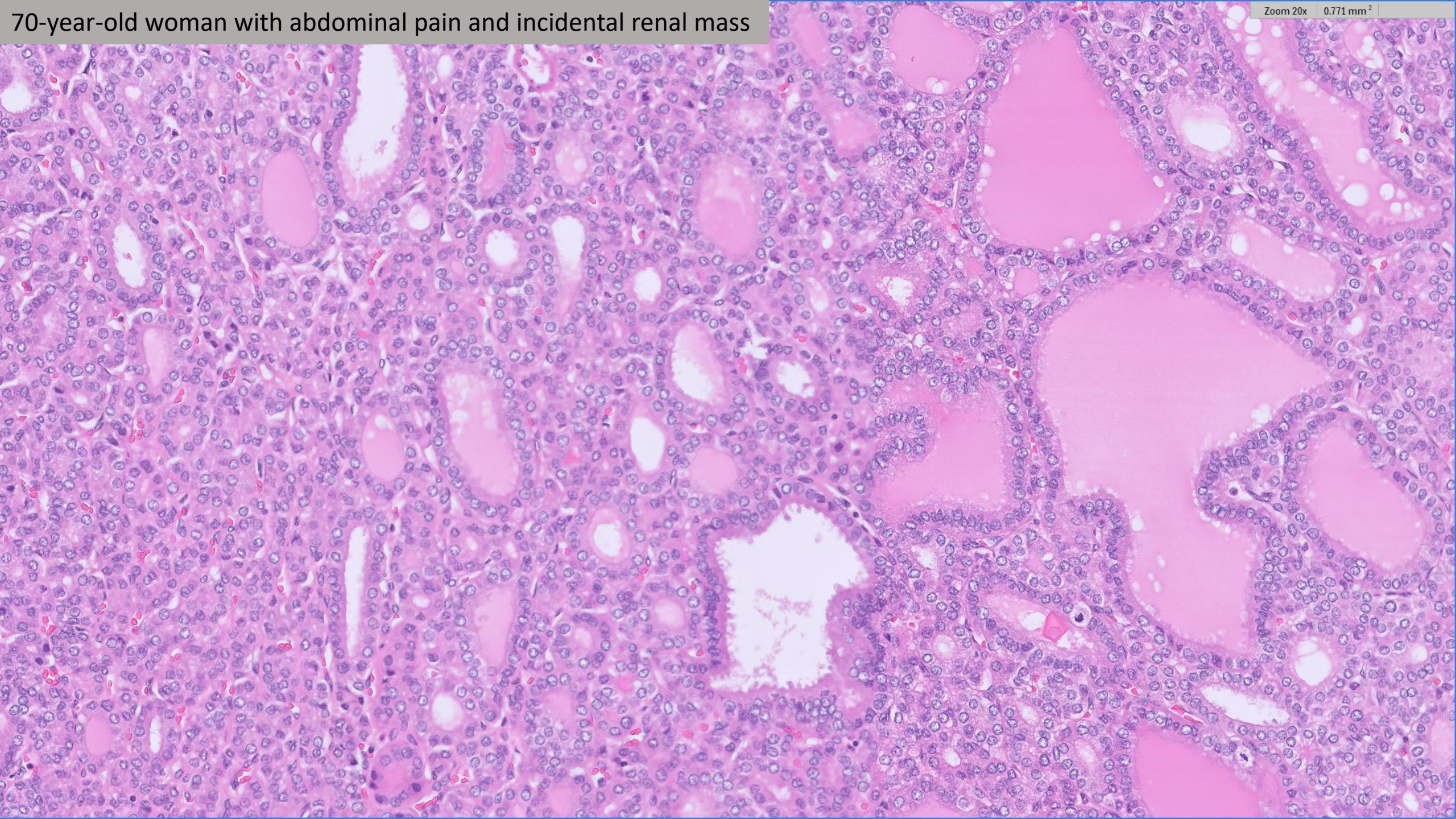
70-year-old woman with abdominal pain and incidental renal mass



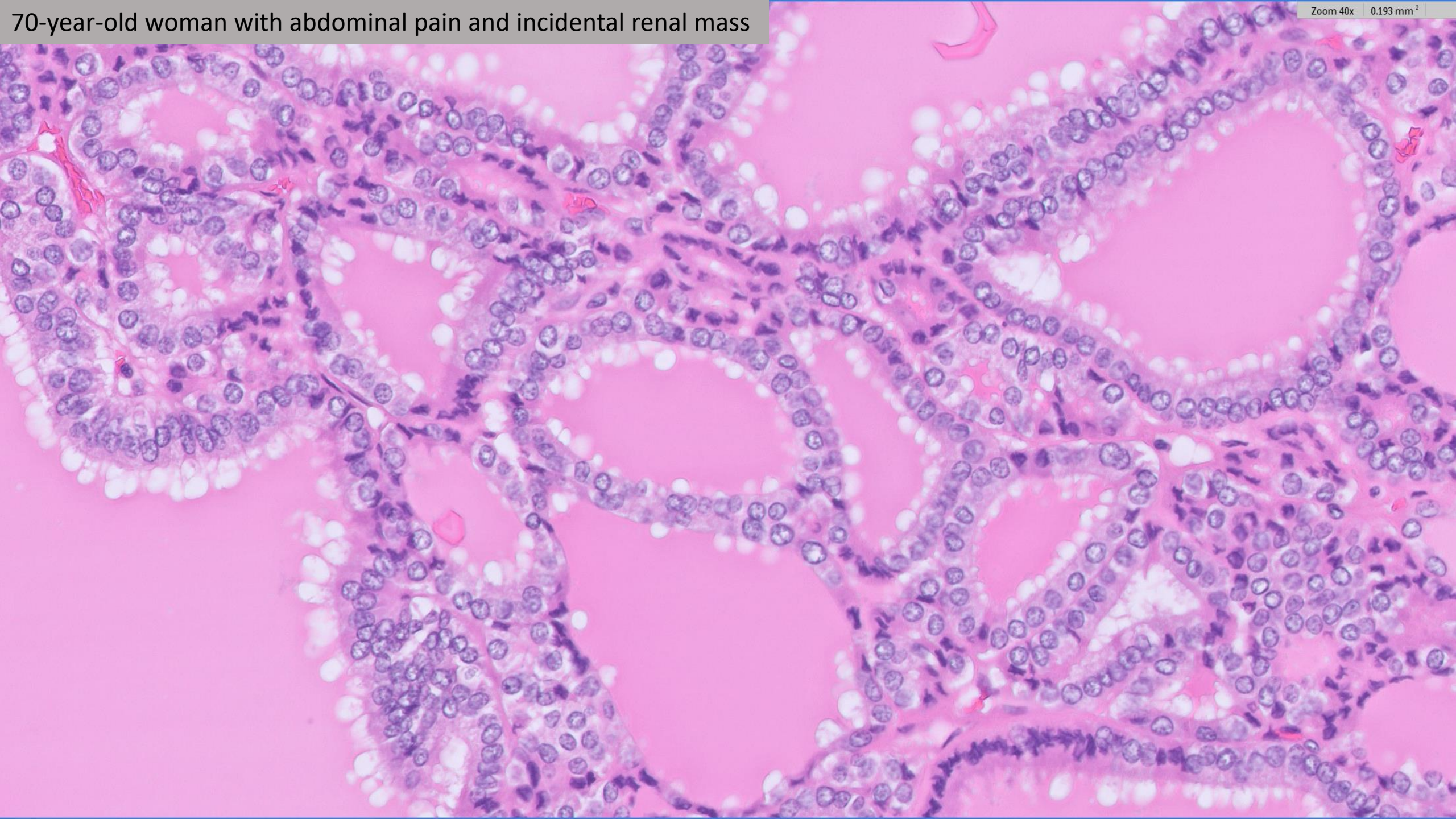
70-year-old woman with abdominal pain and incidental renal mass



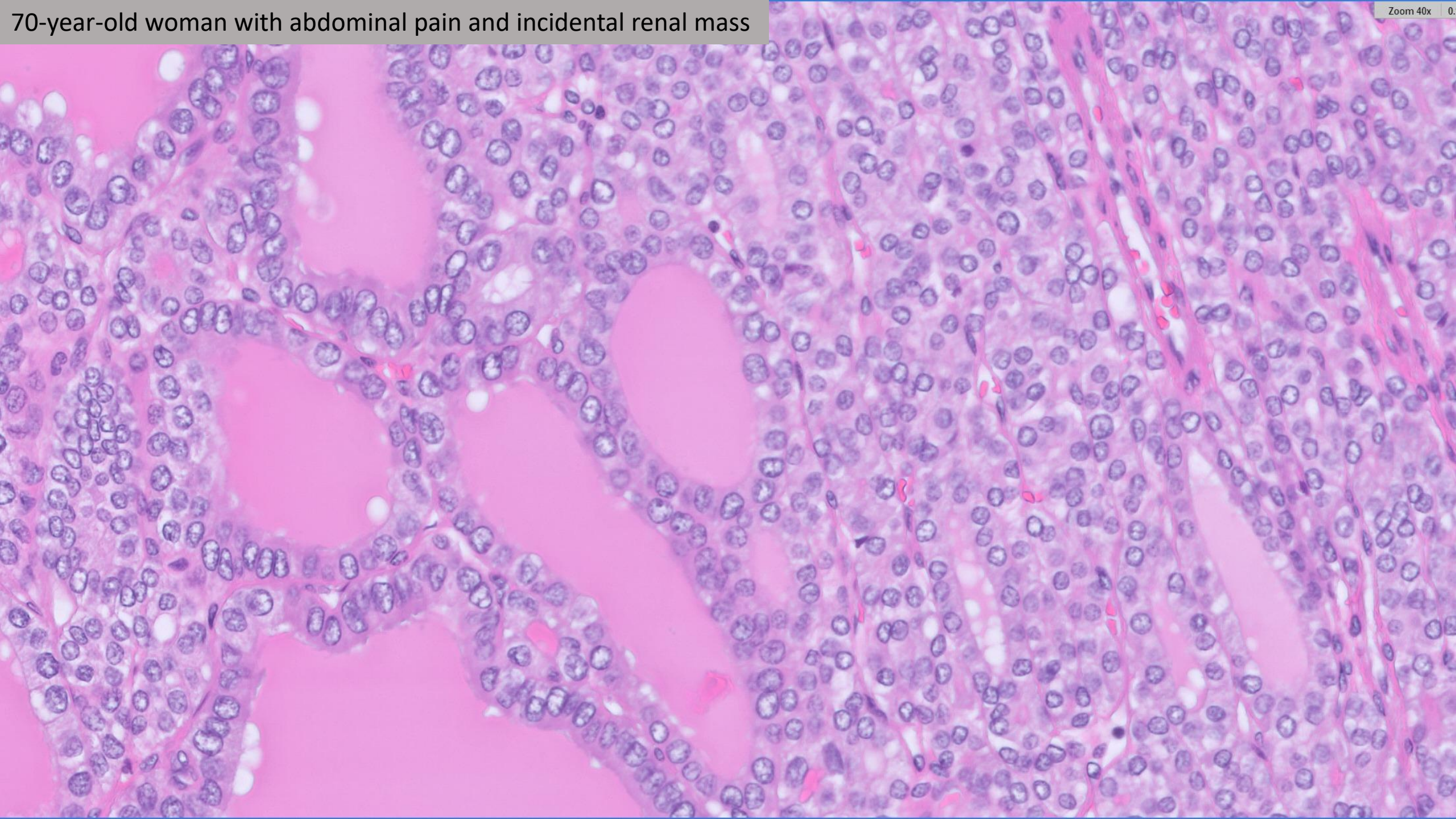
70-year-old woman with abdominal pain and incidental renal mass



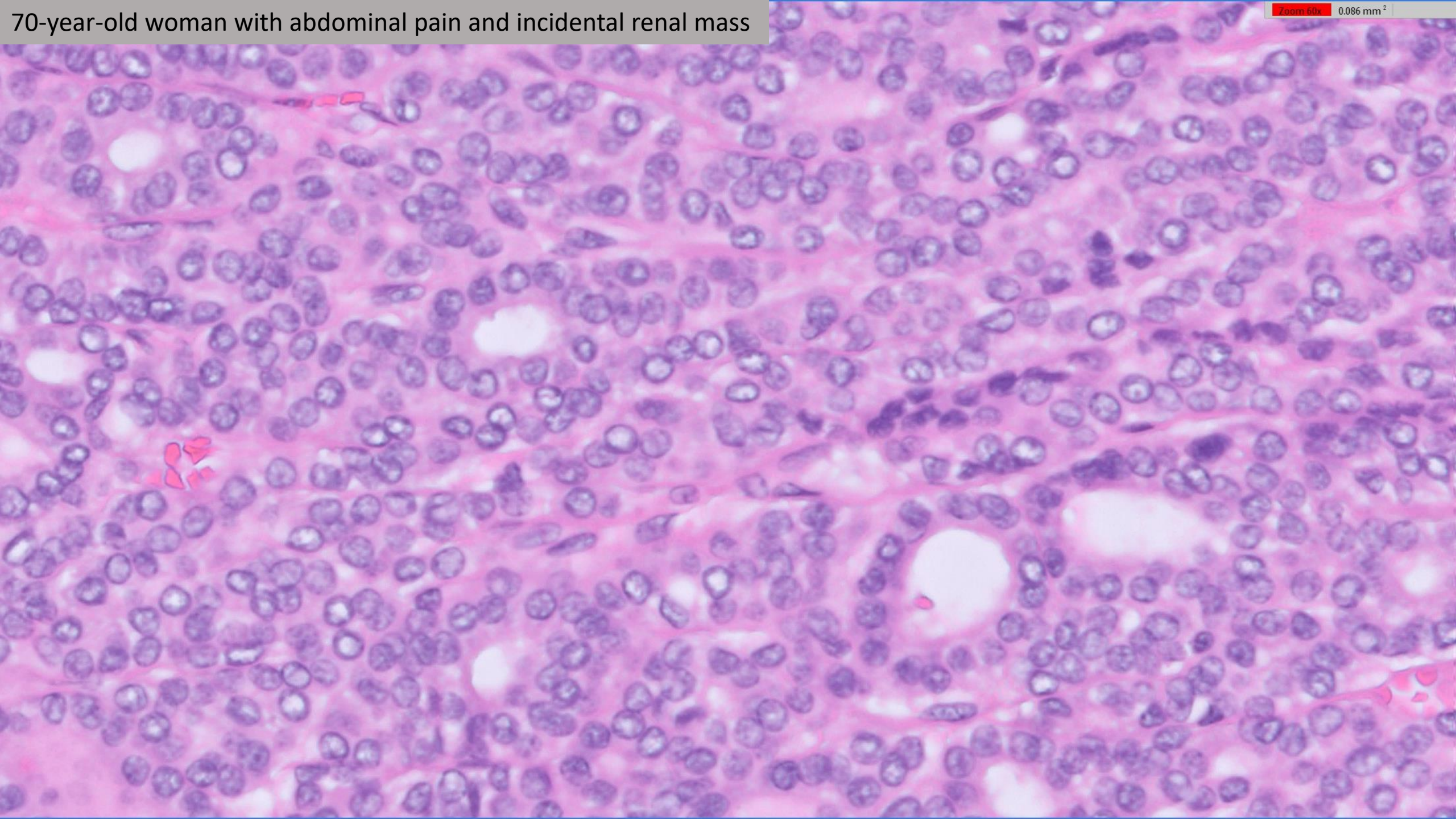
70-year-old woman with abdominal pain and incidental renal mass



70-year-old woman with abdominal pain and incidental renal mass



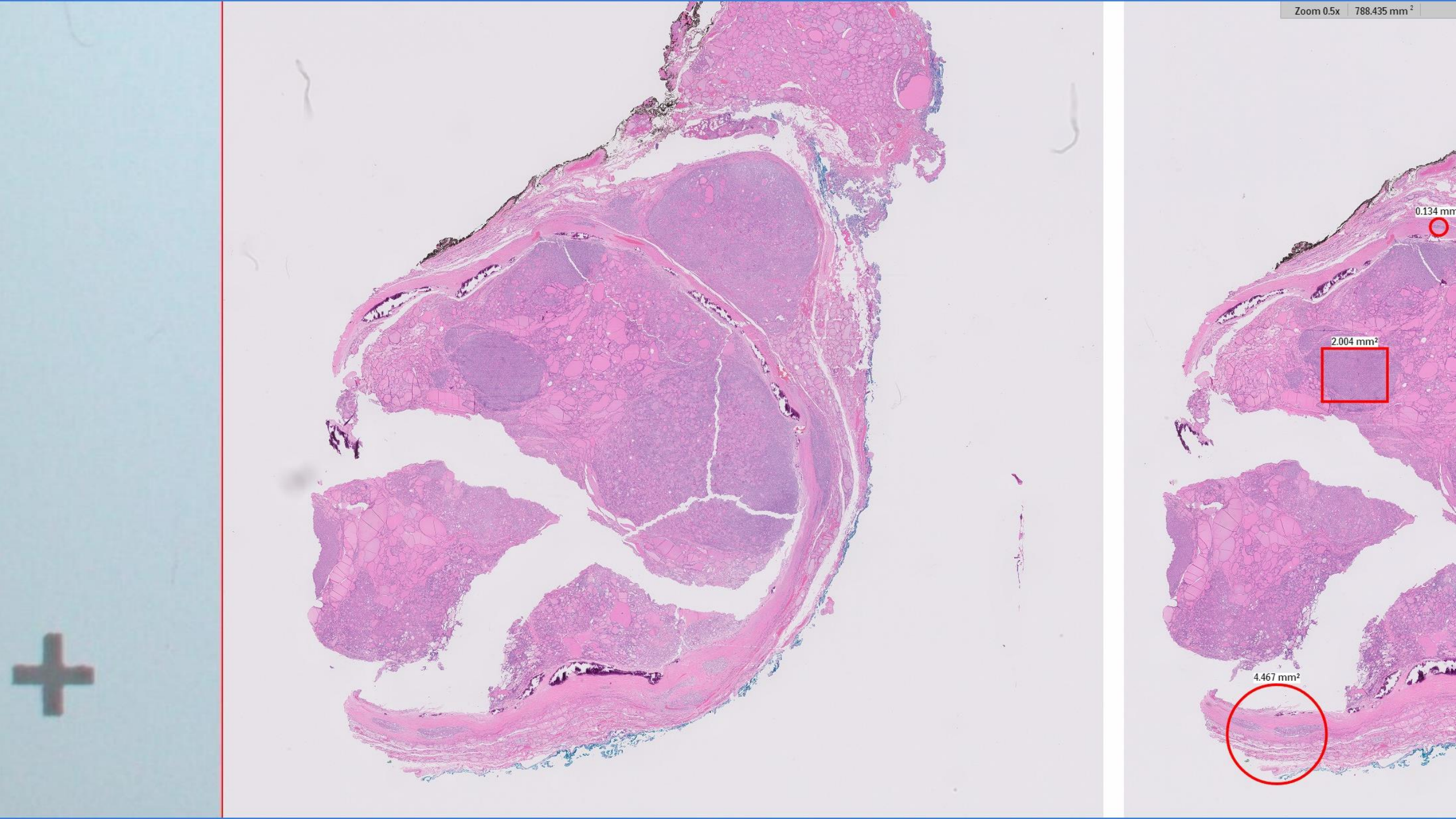
70-year-old woman with abdominal pain and incidental renal mass

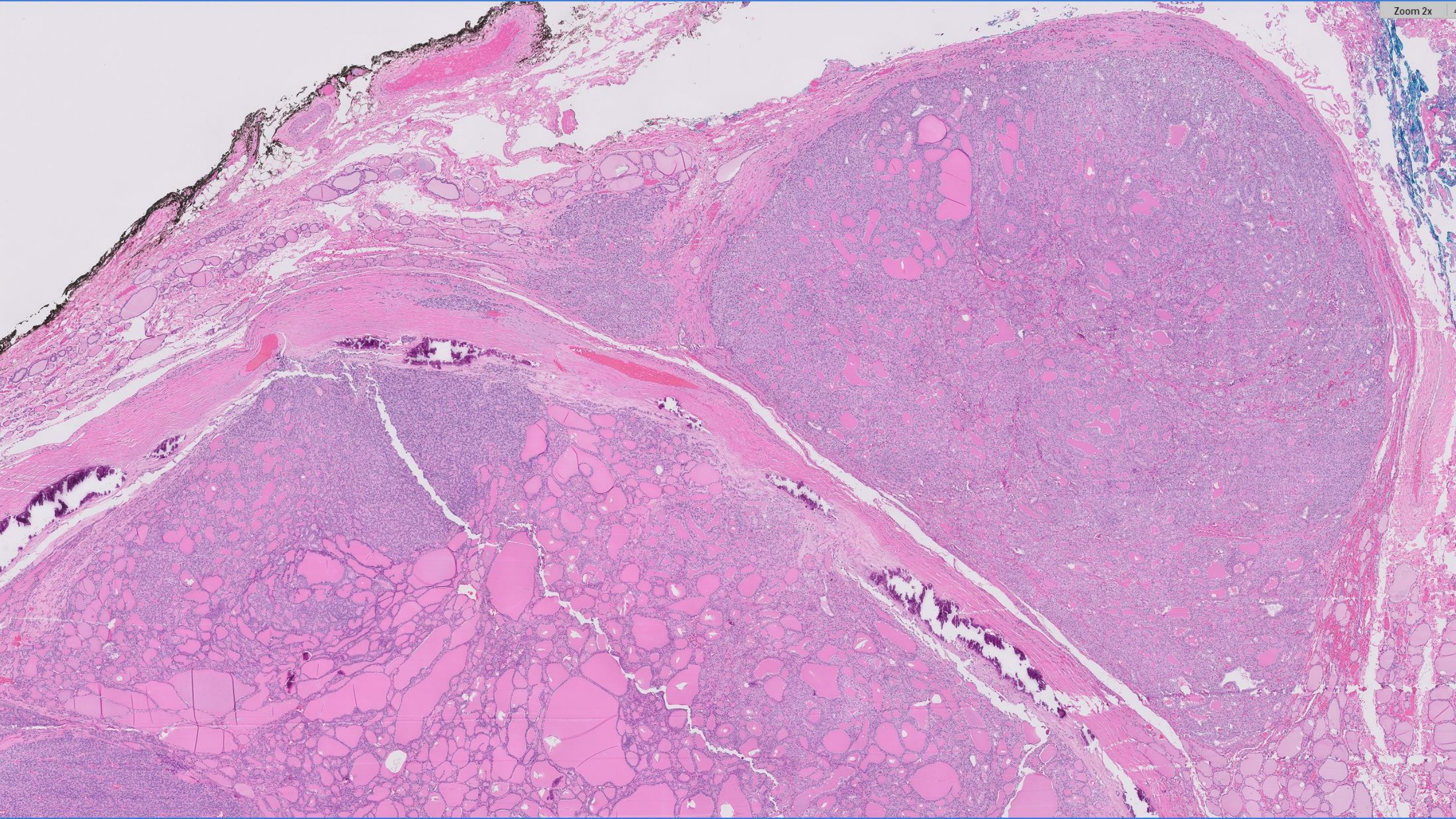


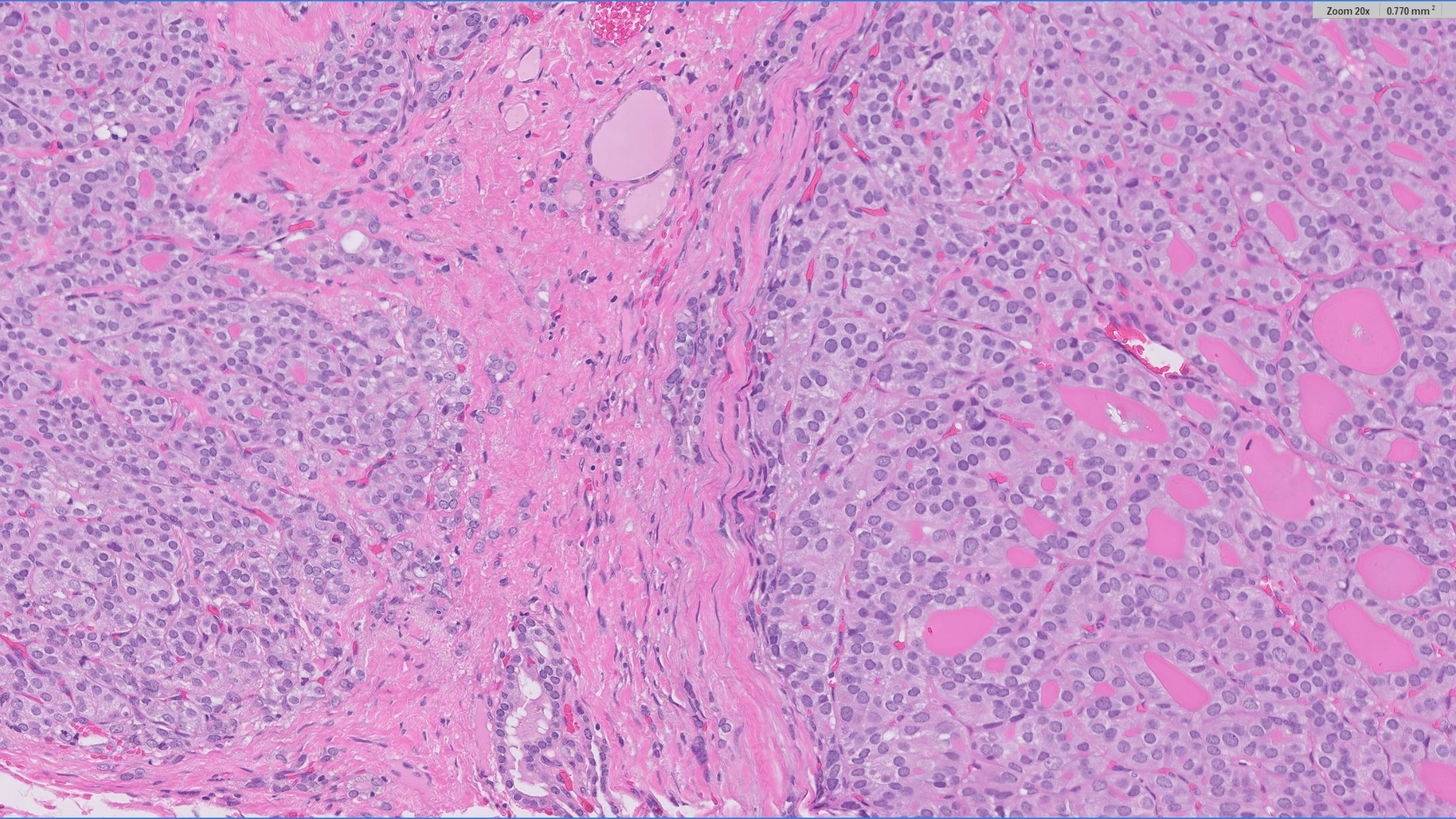
DIAGNOSIS?

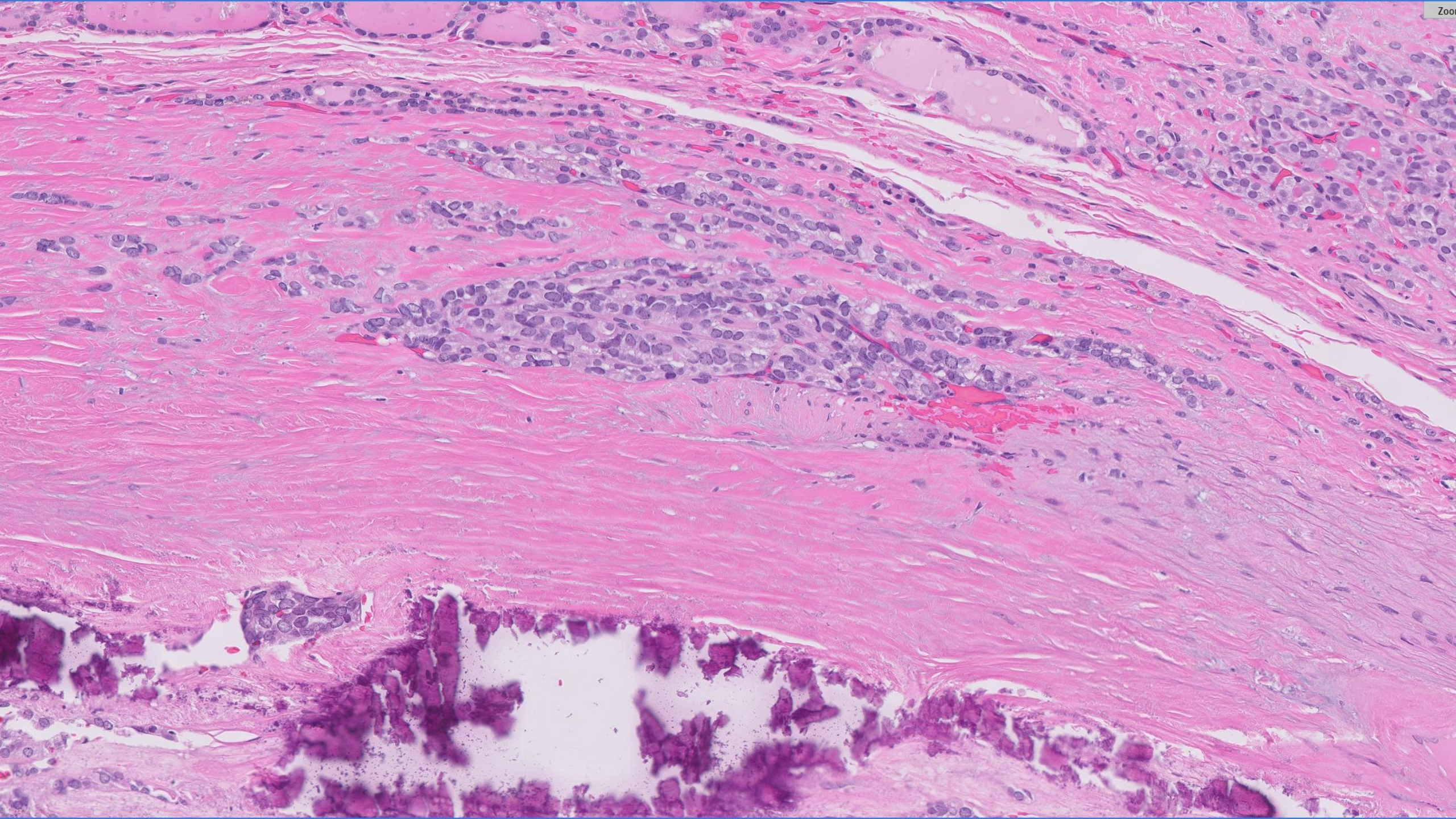
Final Diagnosis

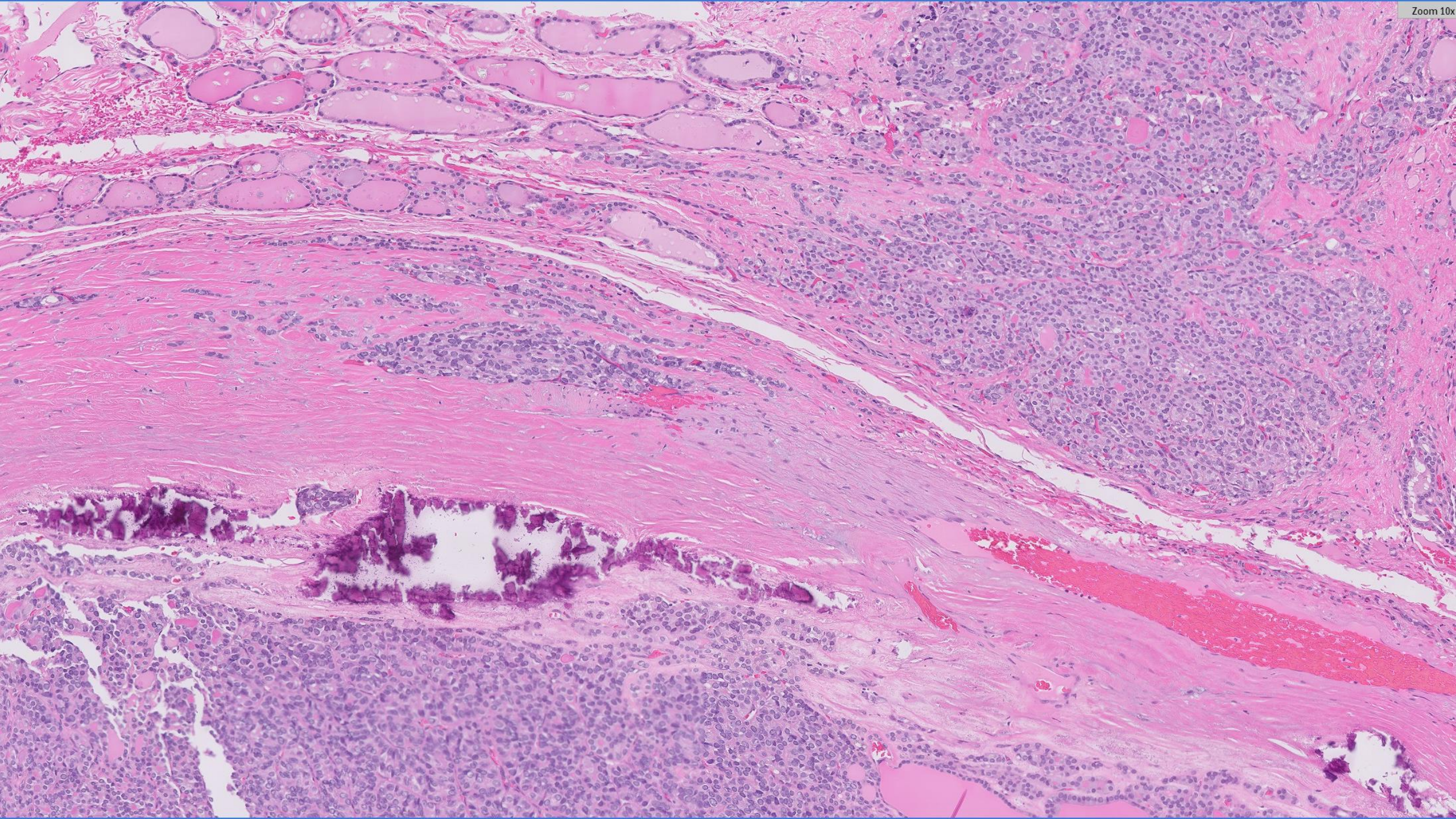
- Metastatic Papillary Thyroid Carcinoma

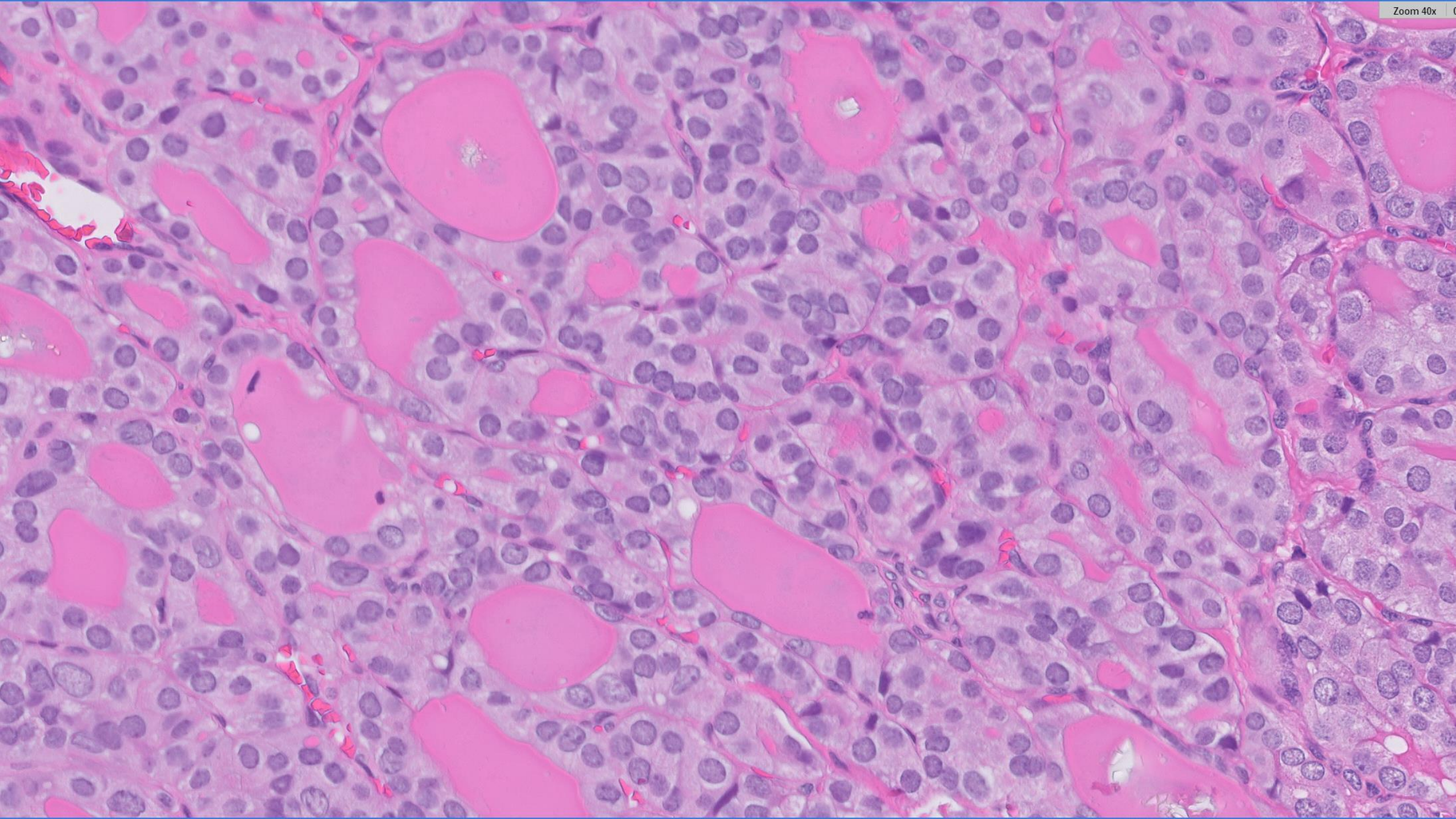

Zoom 0.5x
788.435 mm ²
0.134 mm
2.004 mm²
4.467 mm²


Zoom 2x


Zoom 20x
0.770 mm²




Zoom 10x


Zoom 40x

Discussion

- Metastatic PTC to the kidney is extremely rare
  - Less than 30-cases reported to date of primary PTC presenting as renal mass
    - Most are found at autopsy, but kidney represents fraction of sites discovered
      - Lungs, bone, lymph nodes more common
      - Can present as unilateral or bilateral masses
  - Of differentiated thyroid carcinomas metastatic to kidney- FTC most common
    - Likely due to propensity for vascular invasion
    - PTCs tend to be of higher grade (non-conventional) histologic sub-types
  - Differential diagnosis includes:
    - Other primary RCC (Oncocytoma, PRCC with tubular architecture), metanephric adenoma, changes of chronic kidney disease, and thyroid-like follicular carcinoma of the kidney

Discussion

- Primary thyroid-like follicular carcinoma of the kidney
  - Extremely rare variant of RCC (<10 cases reported in literature)
    - Well-circumscribed tumors with fibrous capsule and striking follicular architecture
    - Micro- and macro-follicles with inspissated colloid-like material
    - Round to oval nuclei with uniform chromatin and pinpoint nucleoli
    - Lack classic nuclear and architectural features of PTC (as seen in our case)
  - Indolent behavior (but 2 cases reported to have malignant potential)
  - IHC
    - Negative for classic thyroid markers (TTF-1 and thyroglobulin)
    - Also negative for classic RCC markers (RCC, CD10, WT1, Vimentin, Racemase)
    - Reportedly only PAX8 positive…
    - Molecularly different from primary thyroid tumors (do not harbor NRAS/HRAS or BRAF mutations): Recent proposition is an *EWSR1::PATZ1 fusion*

References

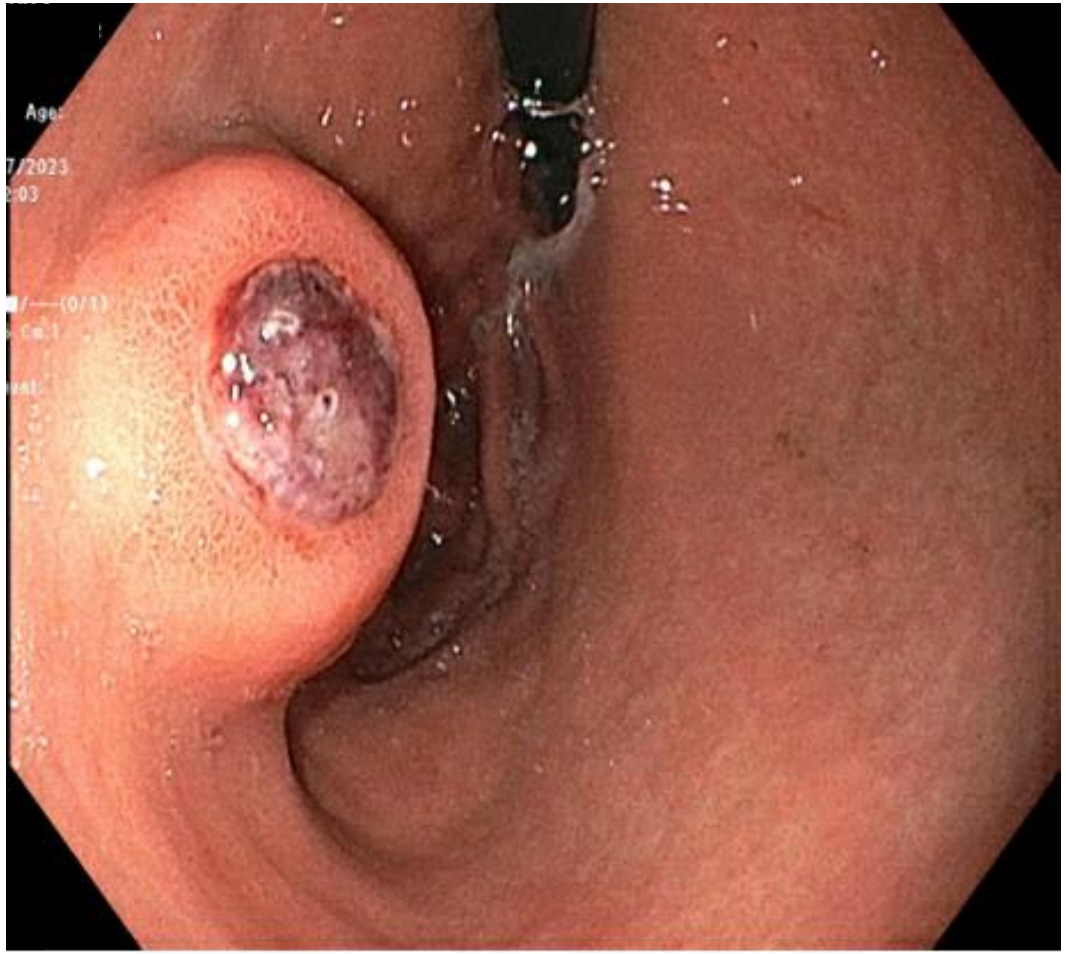
- Falzarano SM, Chute DJ, Magi-Galluzzi C. Metastatic papillary thyroid carcinoma to the kidney: report of two cases mimicking primary renal cell carcinoma and review of the literature. Pathology. 2013 Jan;45(1):89-93. doi: 10.1097/PAT.0b013e32835b5dcc. PMID: 23255036.
- Youssef B, Hanna K, Bowman A, Ardor GD, Alhaj AM, Nassar A. Metastatic Thyroid Carcinoma to the Kidneys Presenting Initially as Bilateral Renal Masses: A Rare Case Report and Literature Review. Int J Surg Pathol. 2023 Aug;31(5):795-800. doi: 10.1177/10668969221138860. Epub 2022 Nov 27. PMID: 36437643.
- Xie R, Tan D, Liu B, Han X, Jin X, Shen D, Zhou L, Shen J. Kidney cancer with thyroid metastasis combined with thyroid carcinoma, a case report. BMC Endocr Disord. 2023 Apr 27;23(1):95. doi: 10.1186/s12902-023-01332-3. PMID: 37106342; PMCID: PMC10134650.
- Thompson D, Hwang A, Waldorf B. Metastatic papillary thyroid carcinoma presenting as an isolated renal mass: Case report and review of the literature. Urol Case Rep. 2022 Apr 16;43:102087. doi: 10.1016/j.eucr.2022.102087. PMID: 35677474; PMCID: PMC9168477.

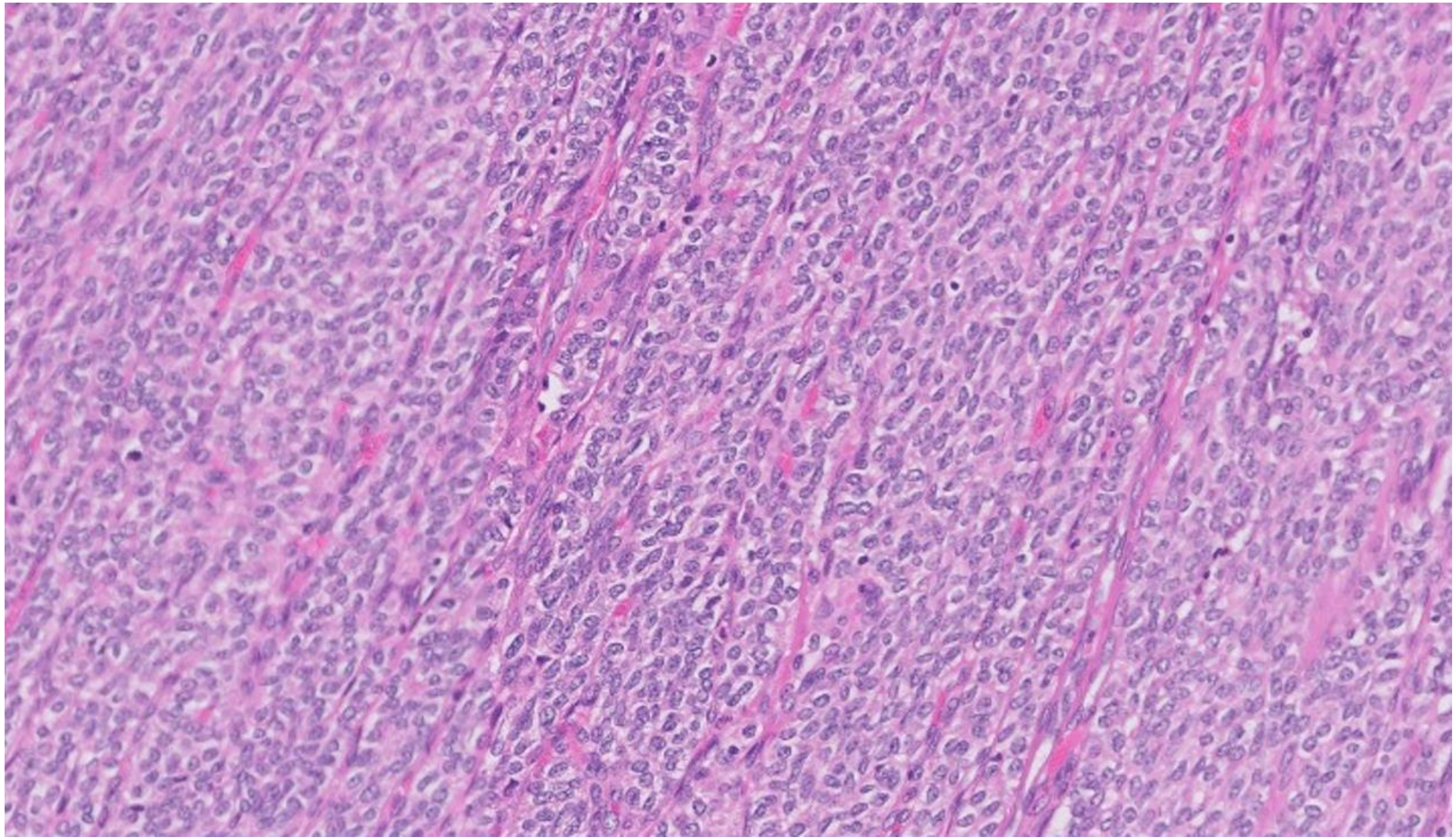
24-0408

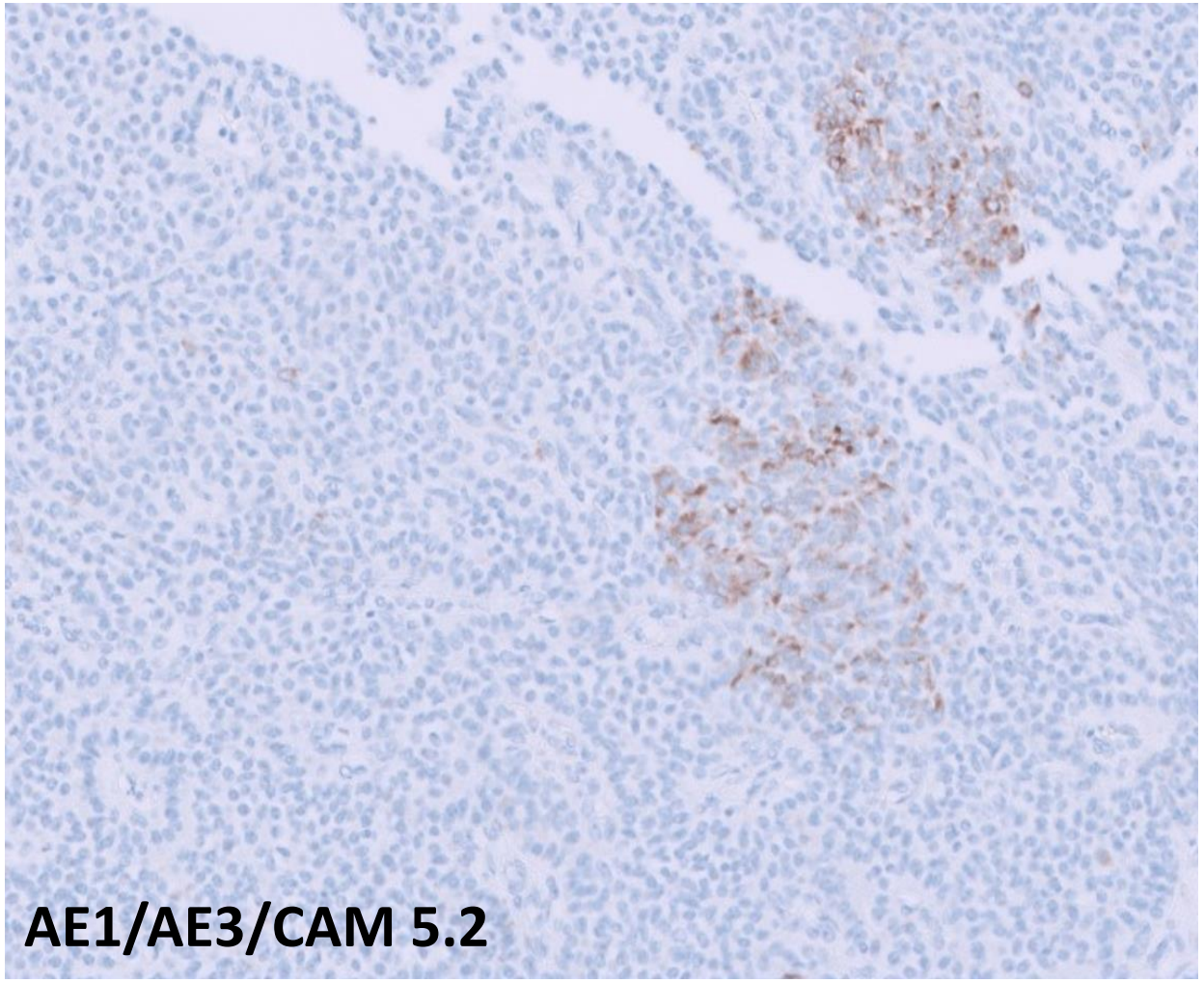
Oyewale Shiyanbola, Greg Charville and Cindy Wang; Stanford

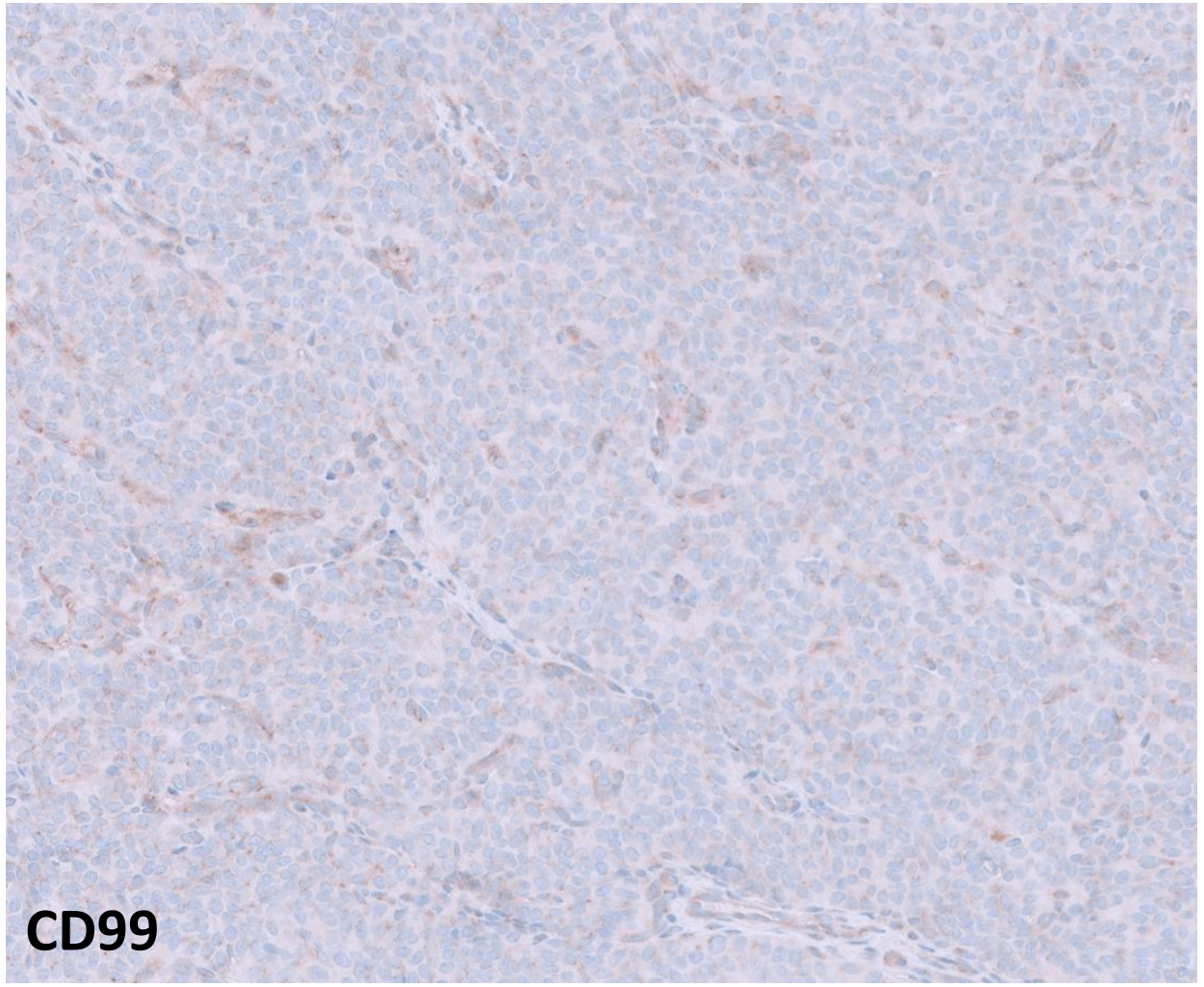
56-year-old male with type 2 diabetes mellitus, presenting to the emergency department for severe fatigue in the setting of recurrent dark stools

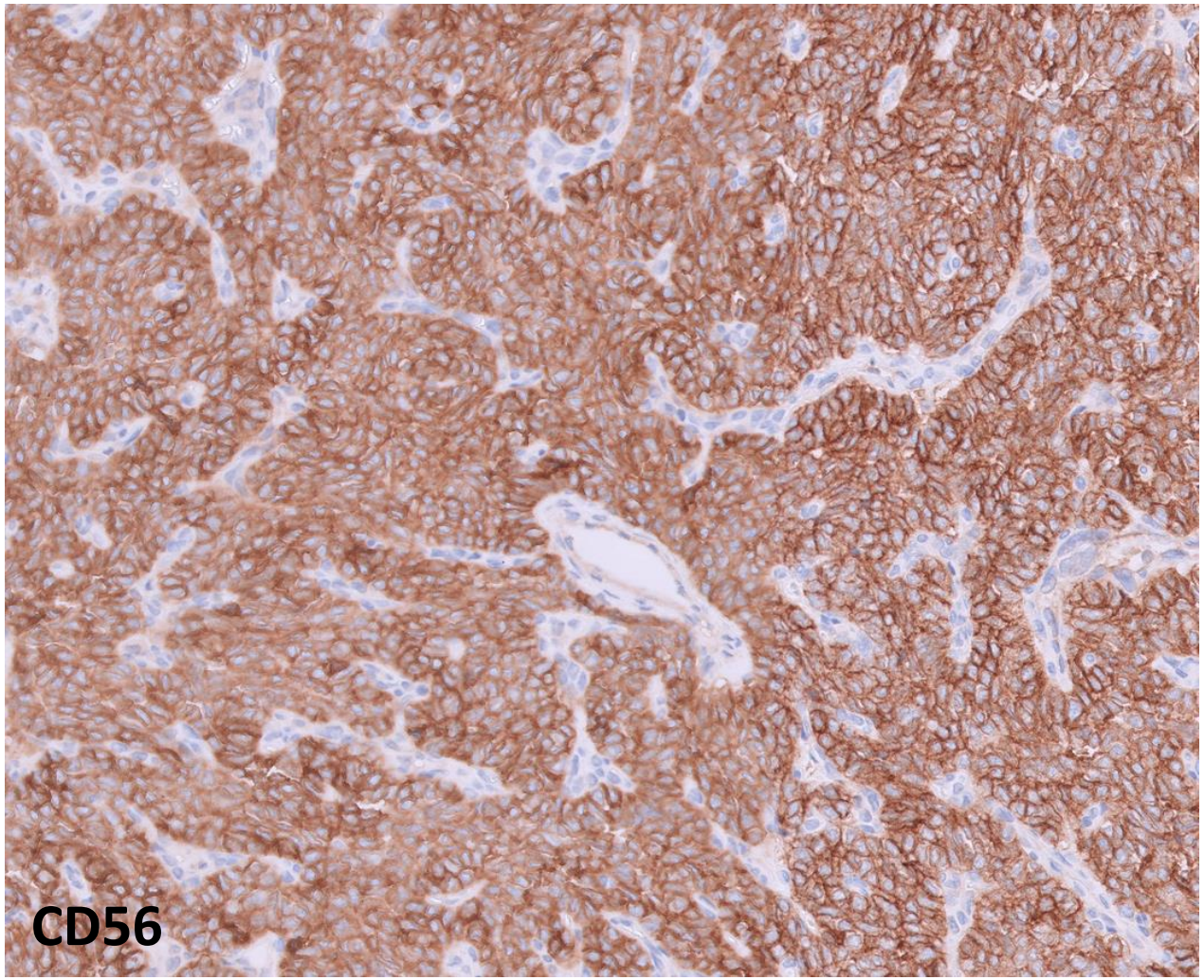
Upper GI Endoscopy

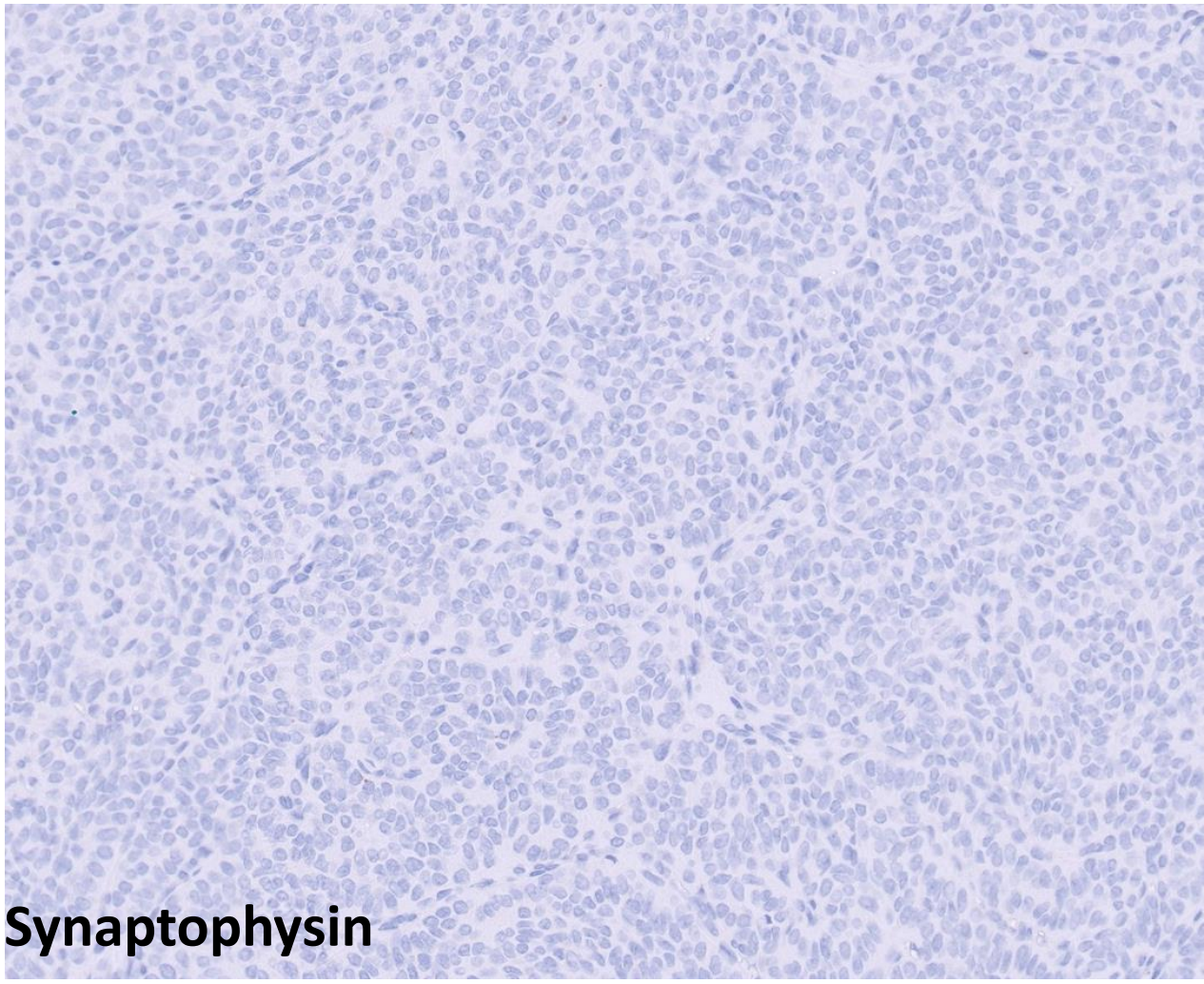





AE1/AE3/CAM 5.2


CD99


CD56


Synaptophysin

DIAGNOSIS?

Additional Negative Markers

- Smooth muscle markers (smooth muscle actin, P63) - pericytic tumor
- SS18-SSX, SSX CTERM - Synovial sarcoma
- HMB45 - PEComa, melanoma
- S100, SOX10 - cellular schwannoma, granular cell tumor
- CD117, DOG1 – gastrointestinal stromal tumor
- EMA, PAX8, CD34, CDX2

Diagnosis

- Atypical epithelioid and spindle cell neoplasm (suggestive of GLI1-altered soft tissue tumor)

Diagnosis

- Atypical epithelioid and spindle cell neoplasm

→ Targeted next generation sequencing assay for actionable fusion mutation panel (Fusion STAMP)

Diagnosis

- Atypical epithelioid and spindle cell neoplasm

→ Targeted next generation sequencing assay for actionable fusion mutation panel (Fusion STAMP)

→ *ACTB::GLI1* fusion

GLI1 altered Soft Tissue Tumors

Background

- Amplified in glioblastoma multiforme
- Has been described in various sites
- Oncogenetic mechanisms - amplification and fusion
- Currently described as “GLI1-altered soft tissue tumor” by WHO
- Fusions - *MALAT1::GLI1,* plexiform fibromyxoma and gastroblastoma in the stomach
- Fusion with *ACTB* – initially described as pericytoma with t[7;12] translocation

Tumor Behavior

- Variable – benign (Plexiform fibromyxoma)

  – malignant (*ACTB::GLI1*)

- Recently proposed - *GLI1*-altered mesenchymal tumor with malignant potential

GLI1-Altered Mesenchymal Tumors

Jeffrey M. Cloutier, MD, PhD[a,b], Darcy A. Kerr, MD[a,b,*]

KEYWORDS
• *GLI1* • Fusion • Amplified • Mesenchymal tumor • Glomoid neoplasm • Pericytoma

Surgical Pathology ■ (2023) ■–■
https://doi.org/10.1016/j.path.2023.06.004

Mod Pathol 37 (2024) 100386

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Journal homepage: https://modernpathology.org/

Research Article

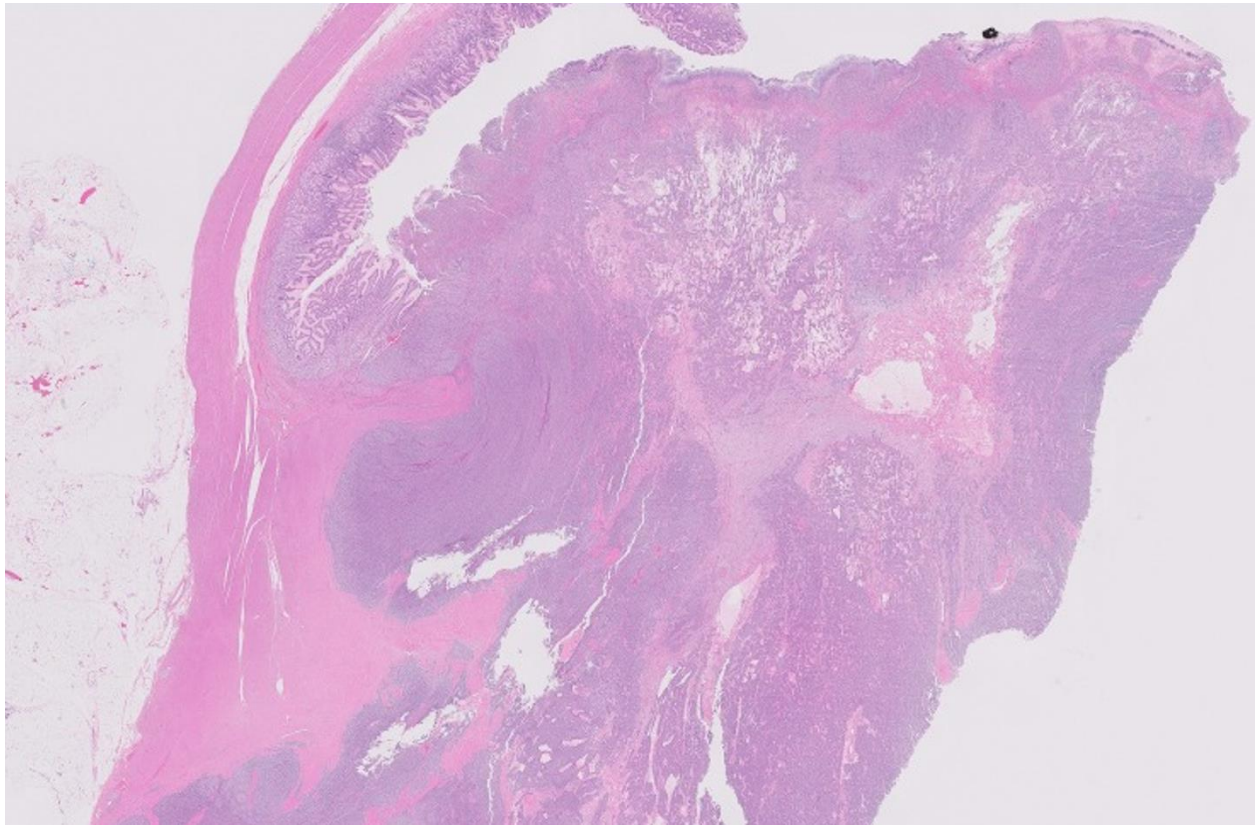
GLI1-Altered Mesenchymal Tumors With *ACTB* or *PTCH1* Fusion: A Molecular and Clinicopathologic Analysis

Darcy A. Kerr[a,b,*], Jeffrey M. Cloutier[c,d,e], Matthew Margolis[f], Douglas A. Mata[f], Nathalie J. Rodrigues Simoes[a], William C. Faquin[g], Dora Dias-Santagata[g], Shefali Chopra[h], Gregory W. Charville[i], Sintawat Wangsiricharoen[c], Alexander J. Lazar[c], Wei-Lien Wang[c], Andrew E. Rosenberg[j], Julie Y. Tse[f]

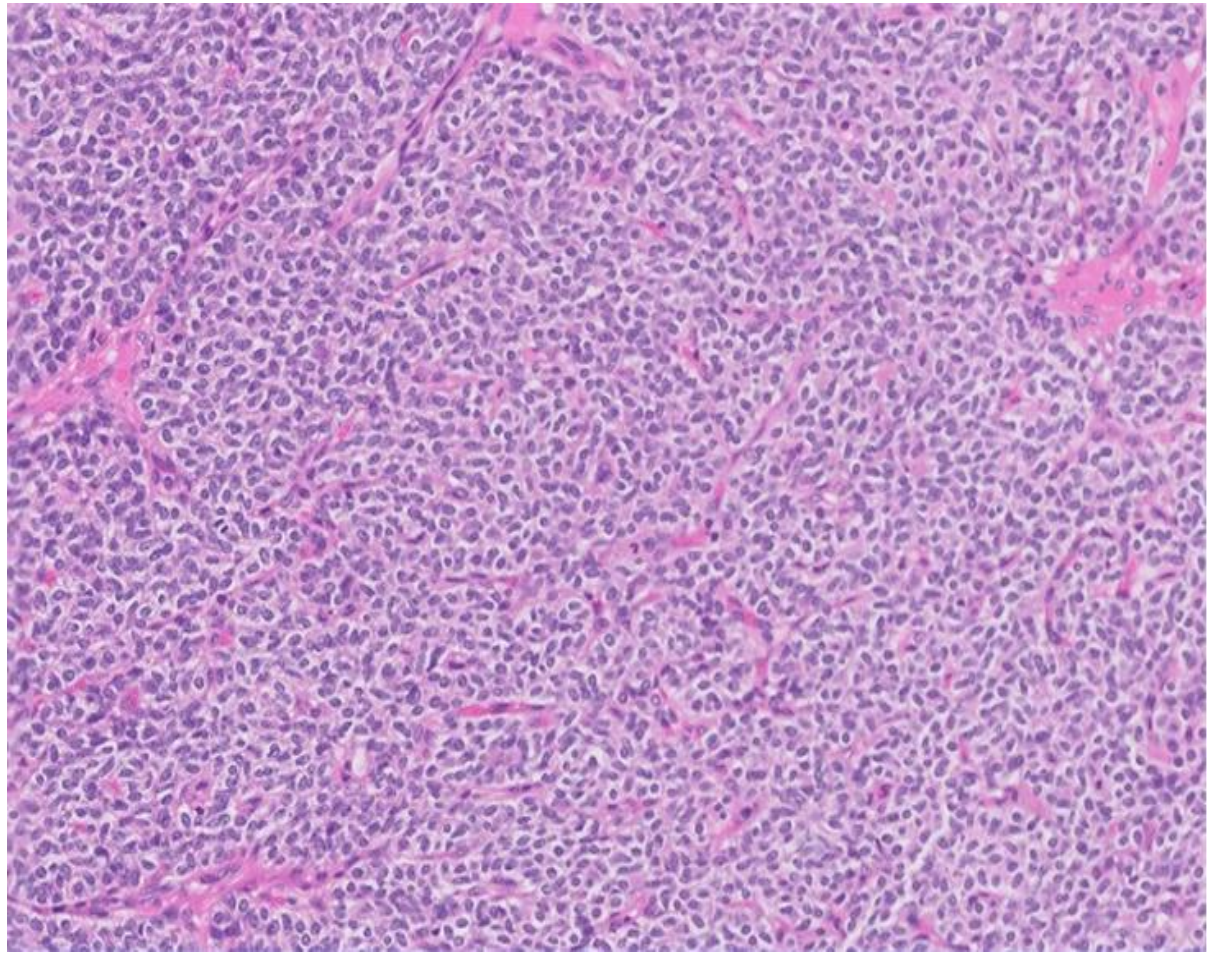
[a] *Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire;* [b] *Dartmouth Geisel School of Medicine, Hanover, New Hampshire;* [c] *Department of Pathology, MD Anderson Cancer Center, Houston, TX;* [d] *Now with Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon;* [e] *Now with Dartmouth Geisel School of Medicine, Hanover, New Hampshire;* [f] *Foundation Medicine, Inc., Cambridge, Massachusetts;* [g] *Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts;* [h] *Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, California;* [i] *Department of Pathology, Stanford University School of Medicine, Stanford, California;* [j] *Department of Pathology, University of Miami and Miller School of Medicine, Miami, Florida*

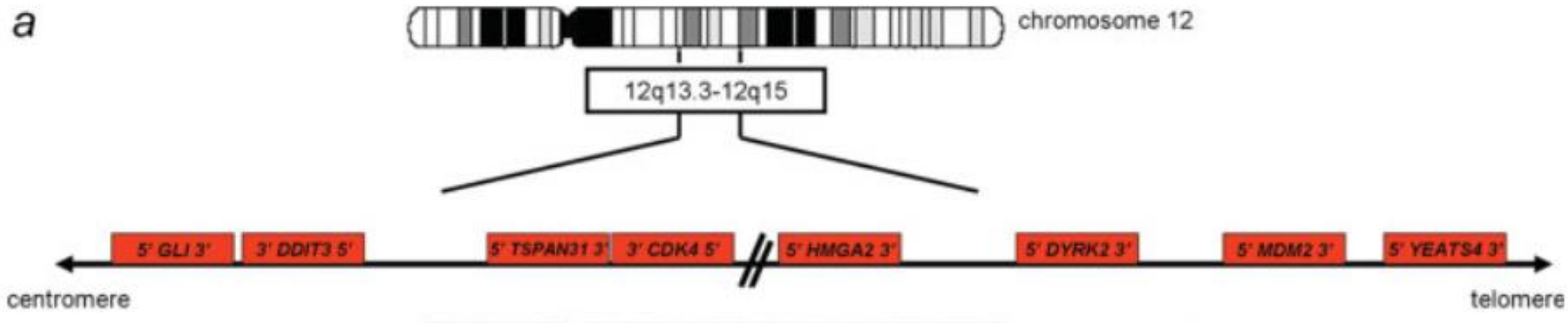
Morphology

- Relatively well-circumscribed, often infiltrating adjacent structures
- Multinodular, lobulated, or plexiform architecture with irregular fibrous septa



- Monomorphic cells, uniform nuclei, scant to moderate cytoplasm
- Monophasic, biphasic
- Variable nested architecture, delicate capillary network
- ± Tumor protrusion into vascular spaces/ lymphovascular invasion





Int J Cancer. 2008 May 15;122(10):2233-41

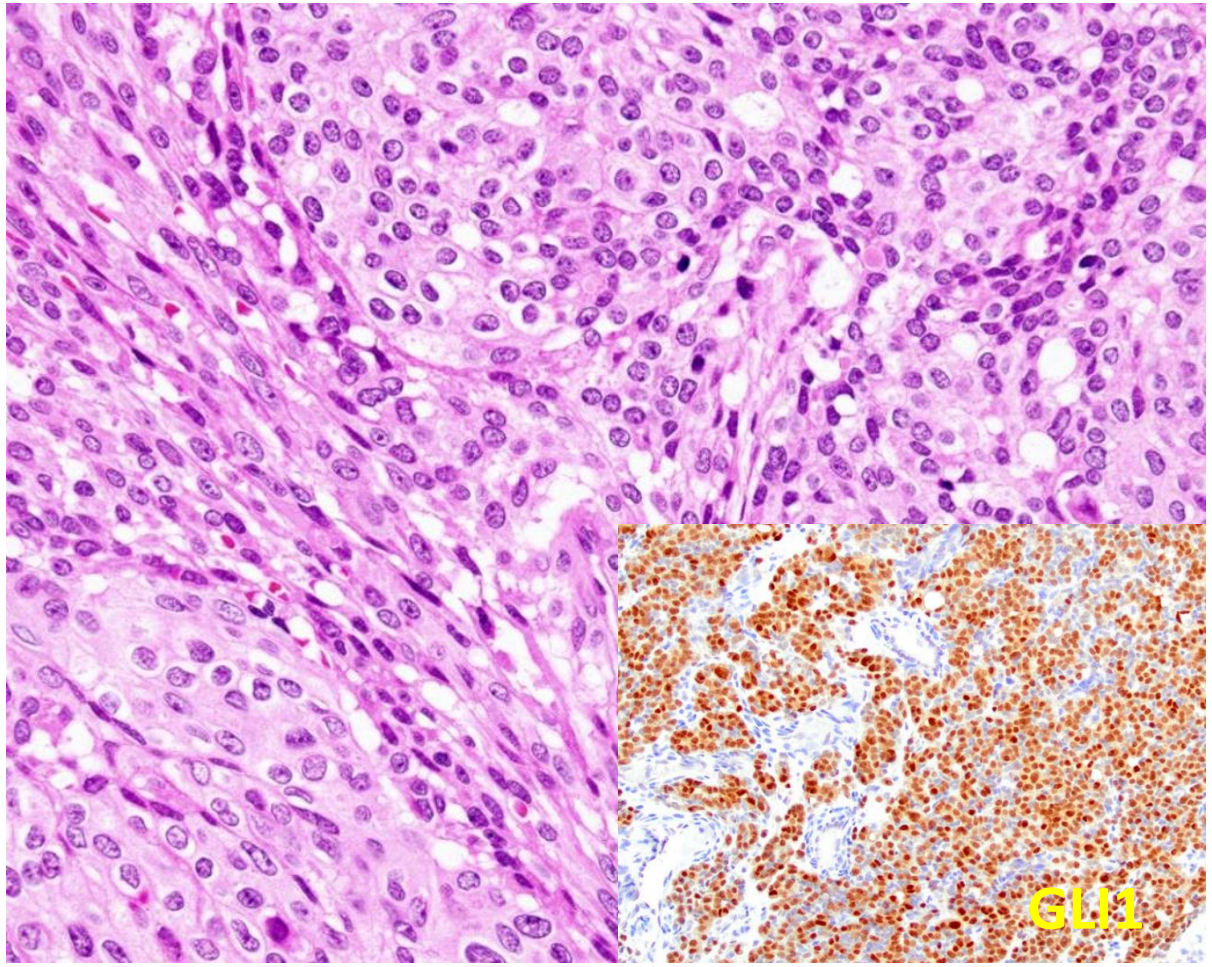
Immunohistochemistry

- Highly variable and non-specific
- Variable S100, CD56, and SMA expression
- Consistently SOX10(-)
- MDM2 and CDK4 (+) common in GLI1-amplified tumors
- STAT6(+) in minor subset
- Vascular, myoepithelial, myogenic epithelial markers (-/+)
- Most recent, GLI1 immunostain – >90% sensitivity and specificity

Differential Diagnosis

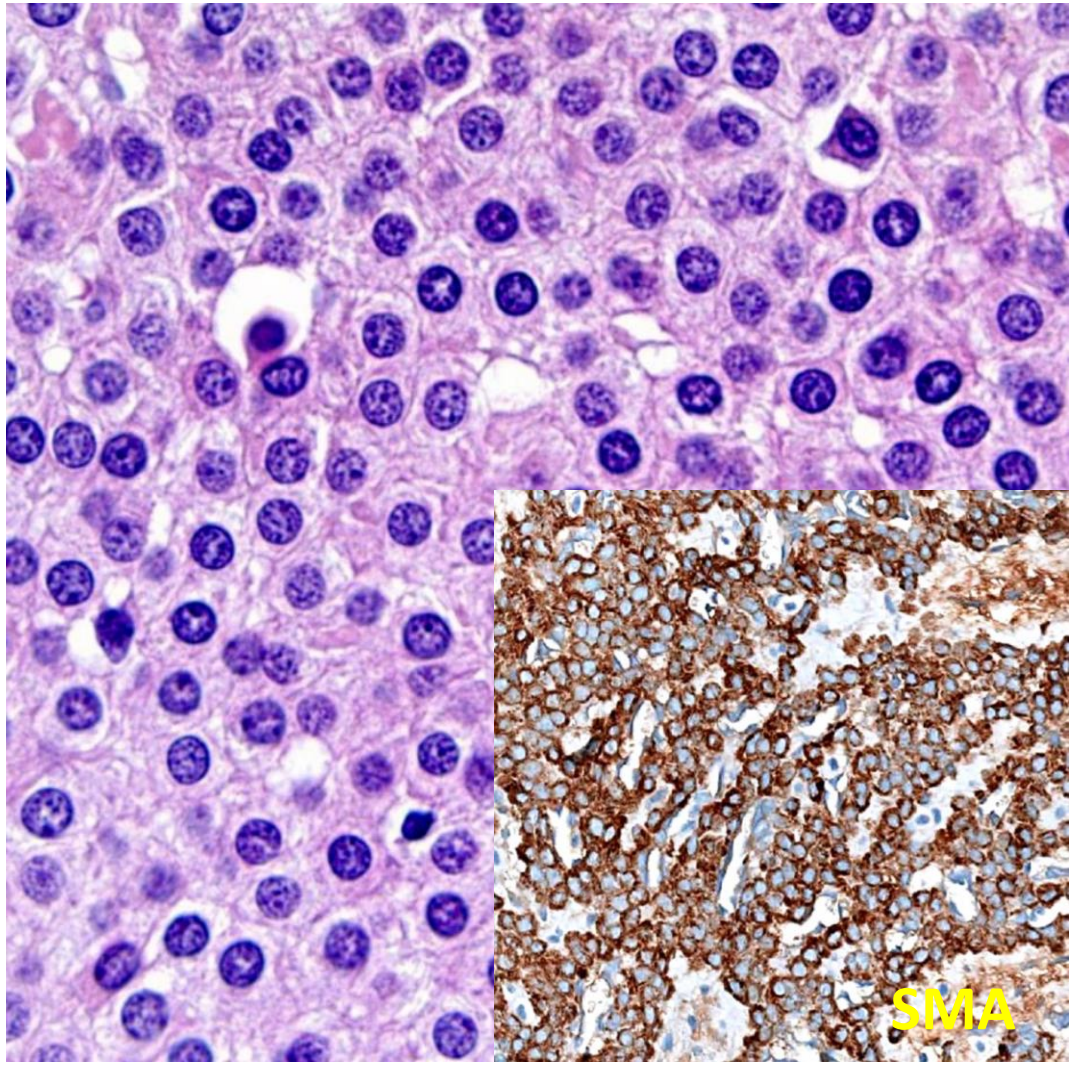
Gastroblastoma

- Biphasic tumor arising in gastric muscularis propria
- Uniform spindled and epithelial cells with nested architecture
- Focal labeling for CD56 and CD10
- *MALAT1-GLI1* gene fusion



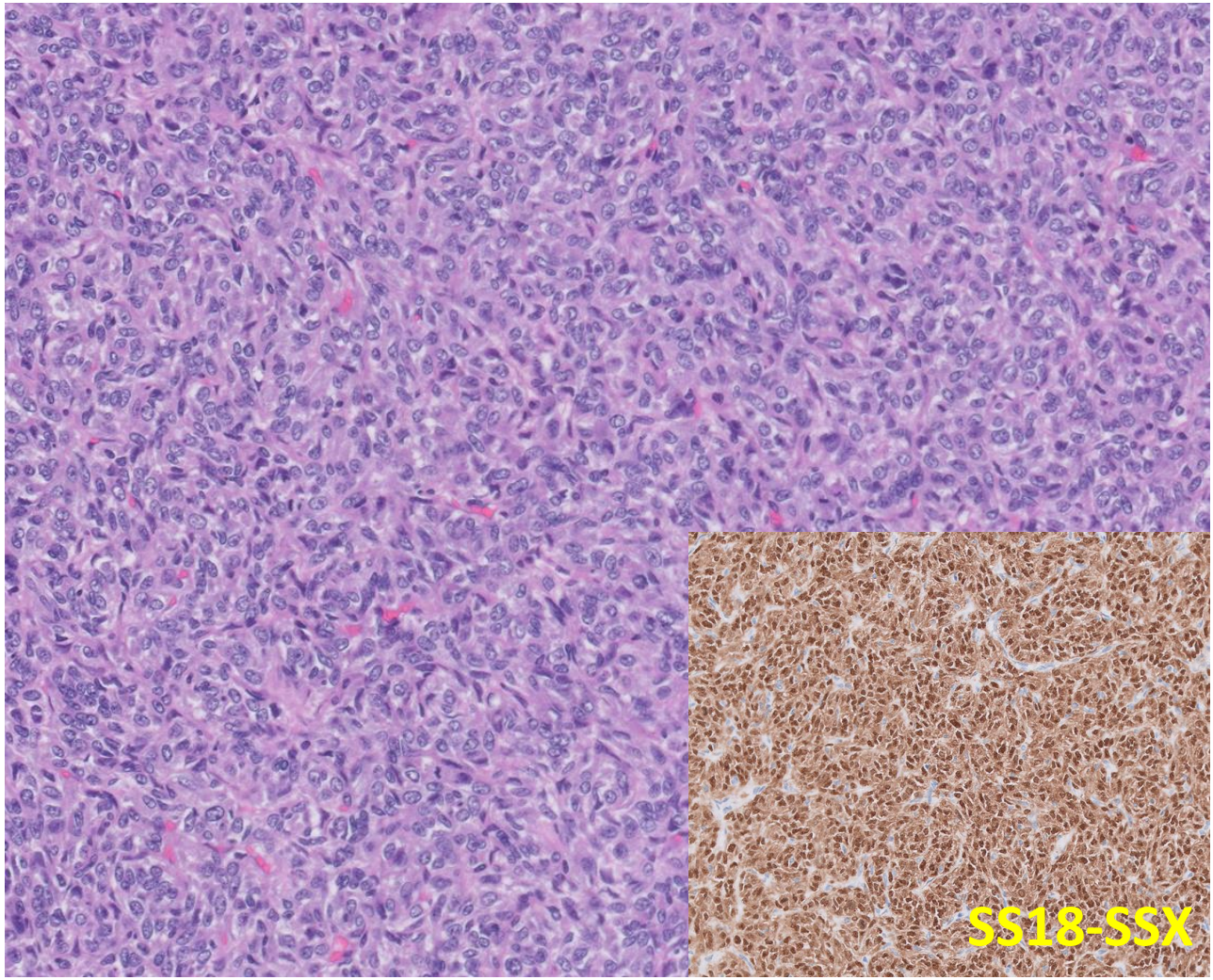
Glomus Tumor (and Variants)

- Perivascular mesenchymal neoplasm
- Rare in GI tract
- Stomach - most frequent site
- SMA and caldesmon (+)
- Desmin, S100, SOX10, and keratin (-)
- *NOTCH1/NOTCH2/NOTCH3* rearrangements



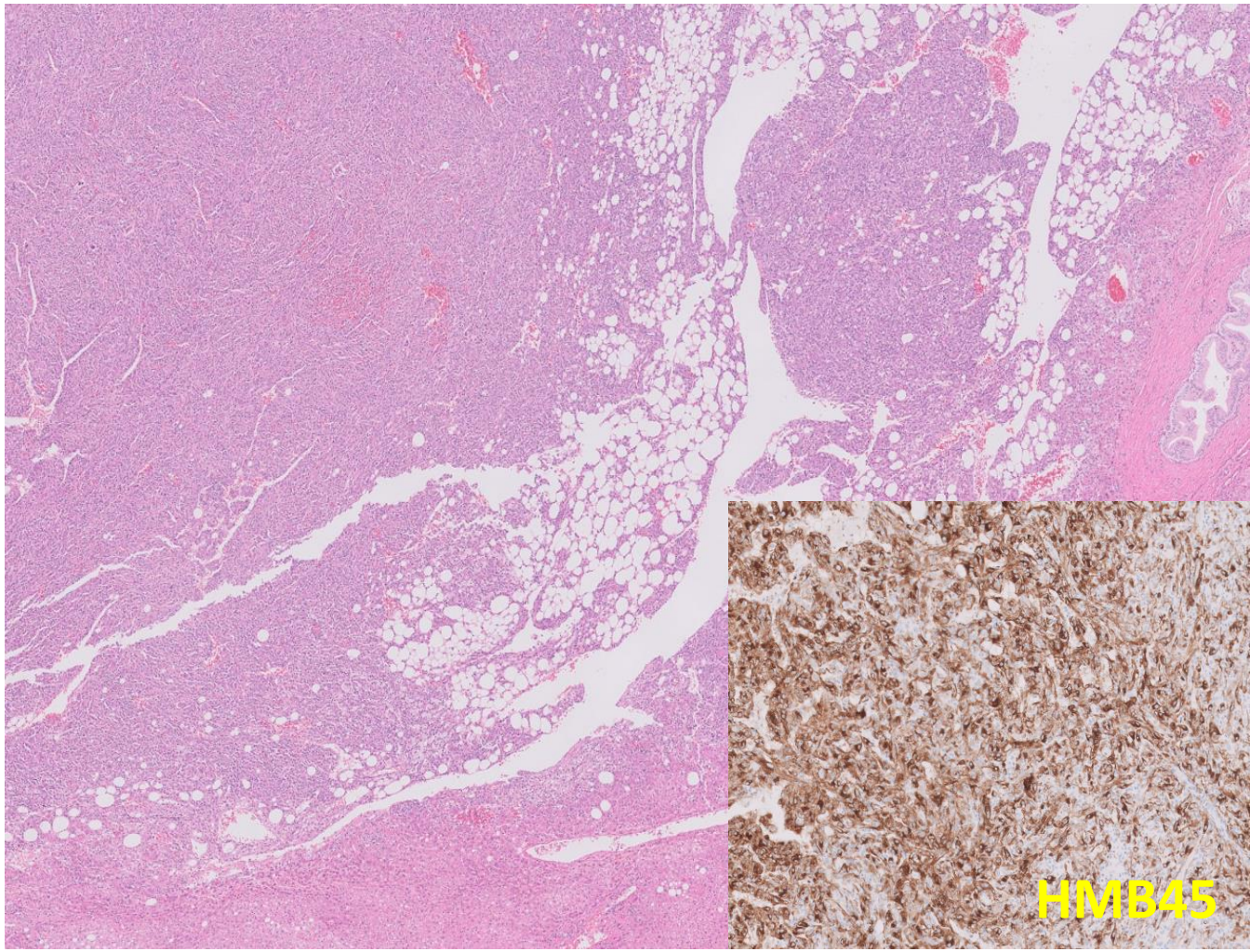
Synovial Sarcoma

- Monophasic, biphasic
- Stomach - most frequent gastrointestinal tract site
- ± EMA, Keratin expression
- Frequently BCL2 and CD99 (+)
- Focal S100
- H-caldesmon (-)
- SS18-SSX fusions studies (FISH or immunohistochemistry)

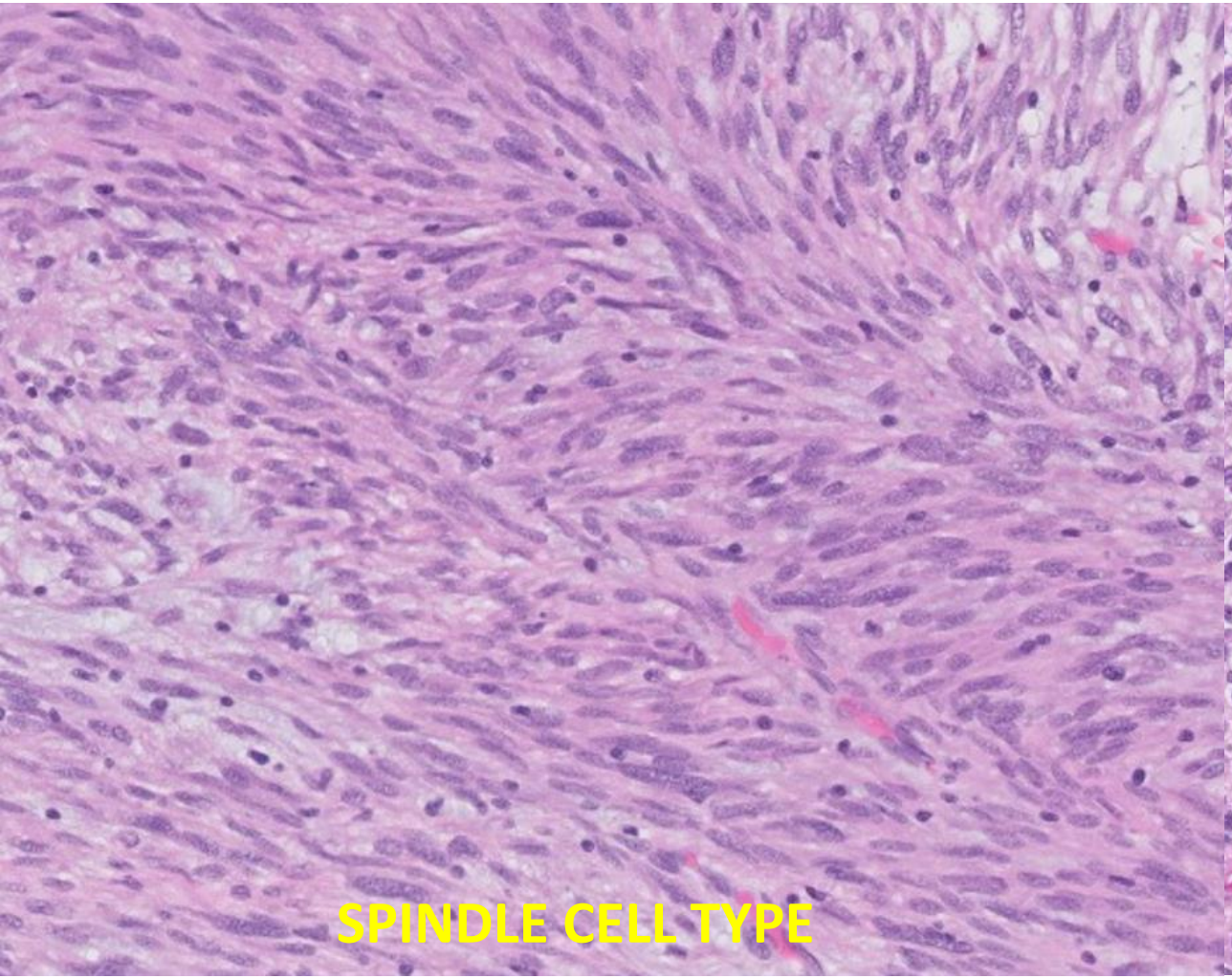


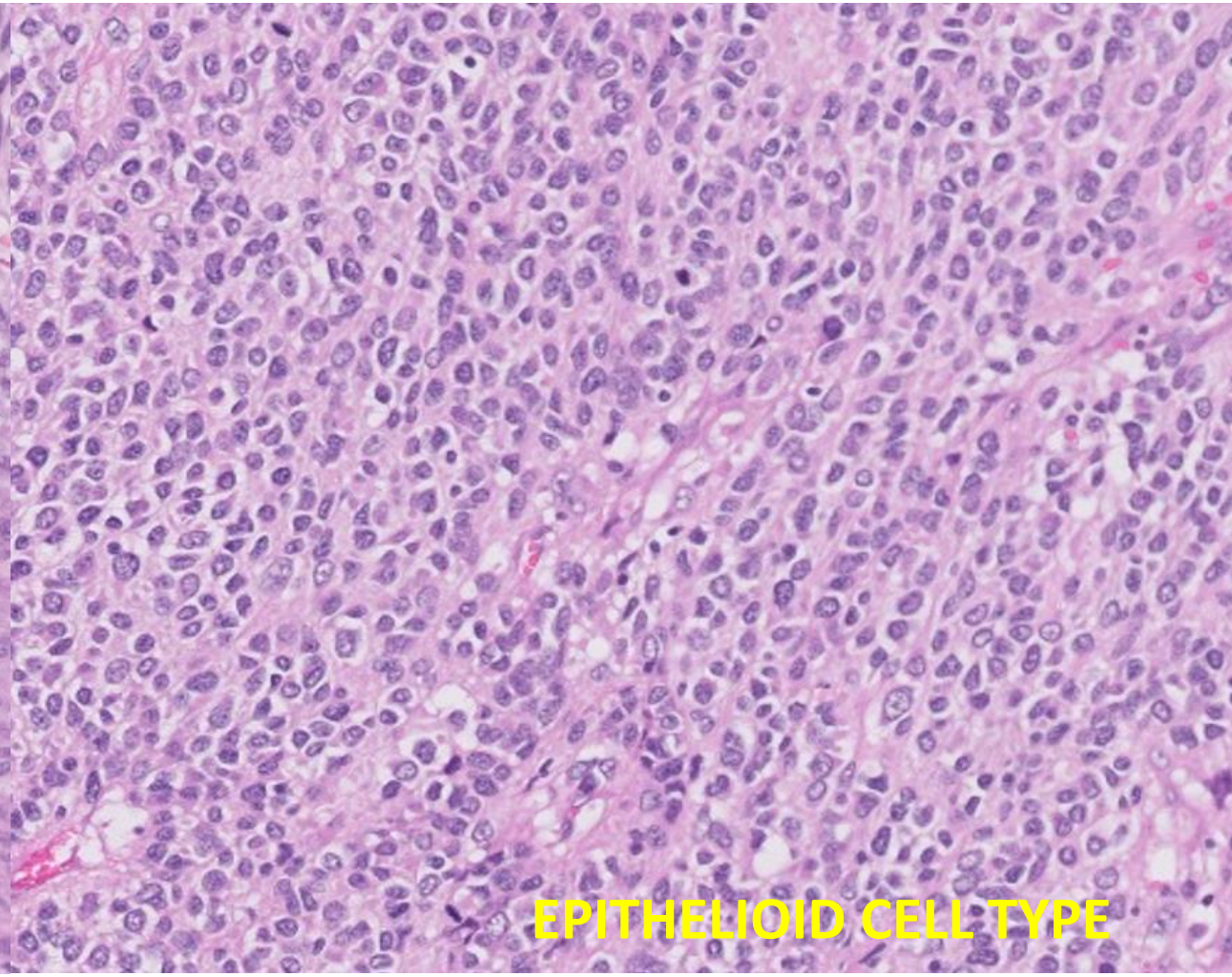
PEComa (including Angiomyolipoma)

- Nests, trabeculae, or sheets of epithelioid to spindled cells
- Intervening thin-walled vessels
- Variable stromal hyalinization or sclerosis
- Often with combined myomelanocytic immunophenotype



Gastrointestinal Stromal Tumor





Learning Points

GLI1 altered mesenchymal tumors

- Emerging group of neoplasms characterized by fusions or amplifications
- Rule them out
  - Monophasic and biphasic (often low-grade) neoplasms with non-specific immunophenotype
- Identification and determination
  - *GLI1* FISH probes
  - Next-generation DNA sequencing techniques: Solid Tumor mutation detection and fusion panels

Thank you

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