



Ants in the Pants: Infectious and Inflammatory Lesions of the GU Tract

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Learning Objectives

- Identify infection associated malignancy and implications in the GU tract
- Introduce novel/emerging cause of injury to the bladder in at-risk patient demographics
- Review epidemiologic data and “unusual / non-classical” presentations of a common GU infection.
- Updates on the impact of novel IHC in disease detection
 - Understand potential profound treatment implications
- Compare inflammatory lesions mimicking renal tumors – and tumors inciting inflammatory response.

Outline

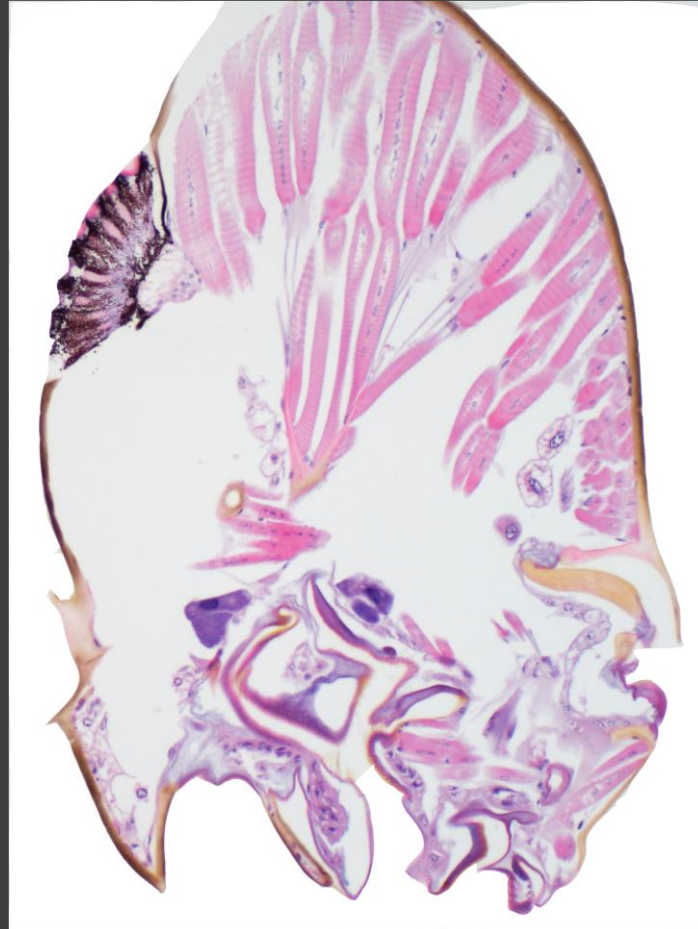
- Case Based Review With Discussion
 - 5 Cases + 1 Bonus Case

Case 0

- 70M – Routine screening colonoscopy.

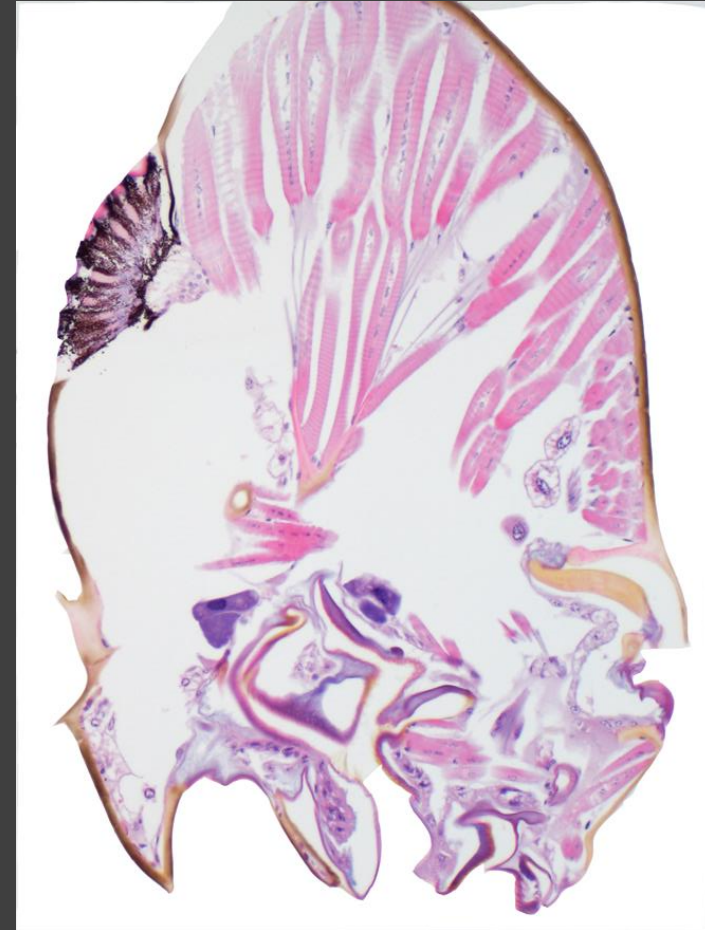
Case 0

70M – Routine screening colonoscopy –
“Mass” in cecum.




Case 0 – Ants in the Cecum

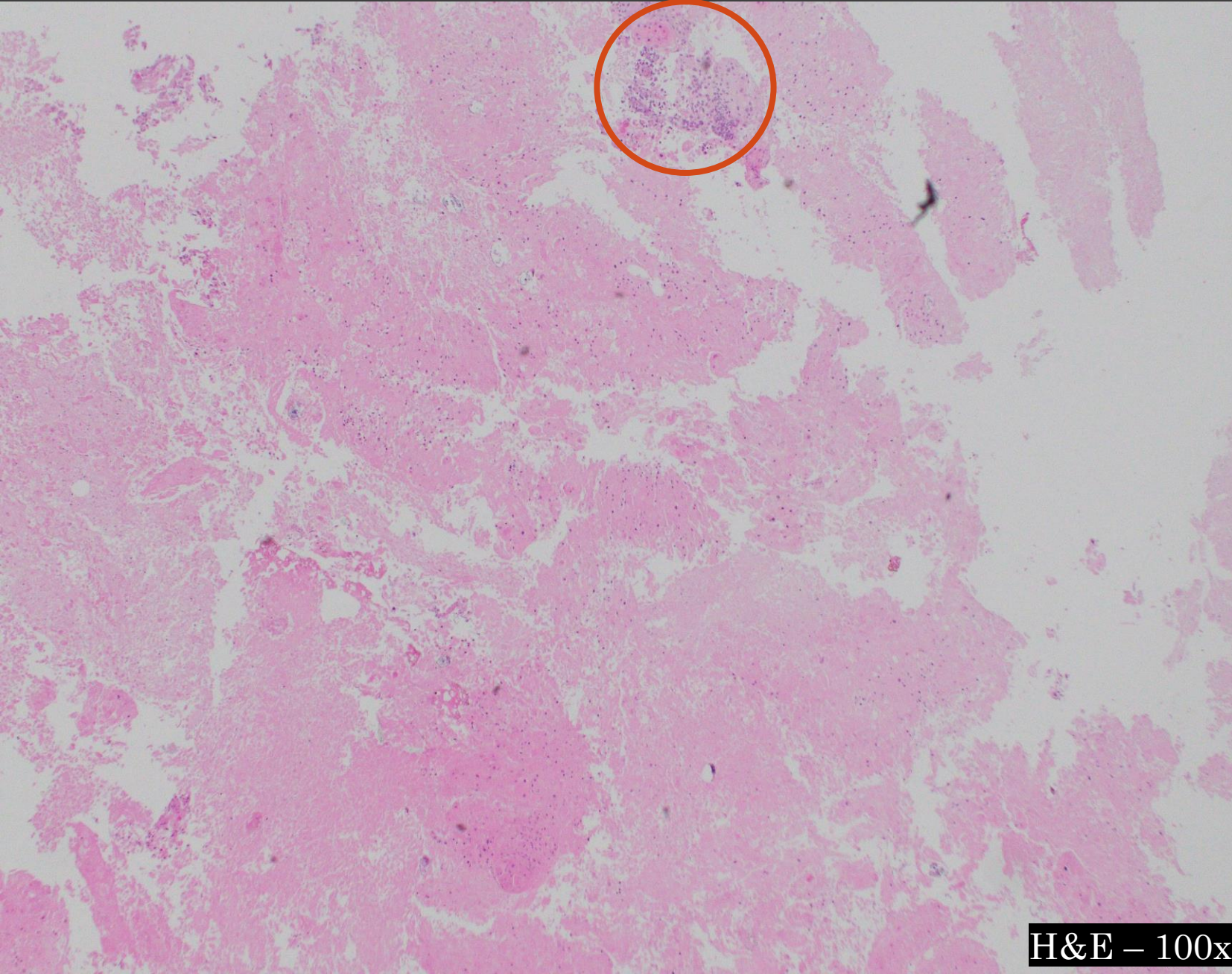
- 70M – Routine screening colonoscopy.
- On follow-up: “Recently eaten fresh fruit with insect holes”



Case 1

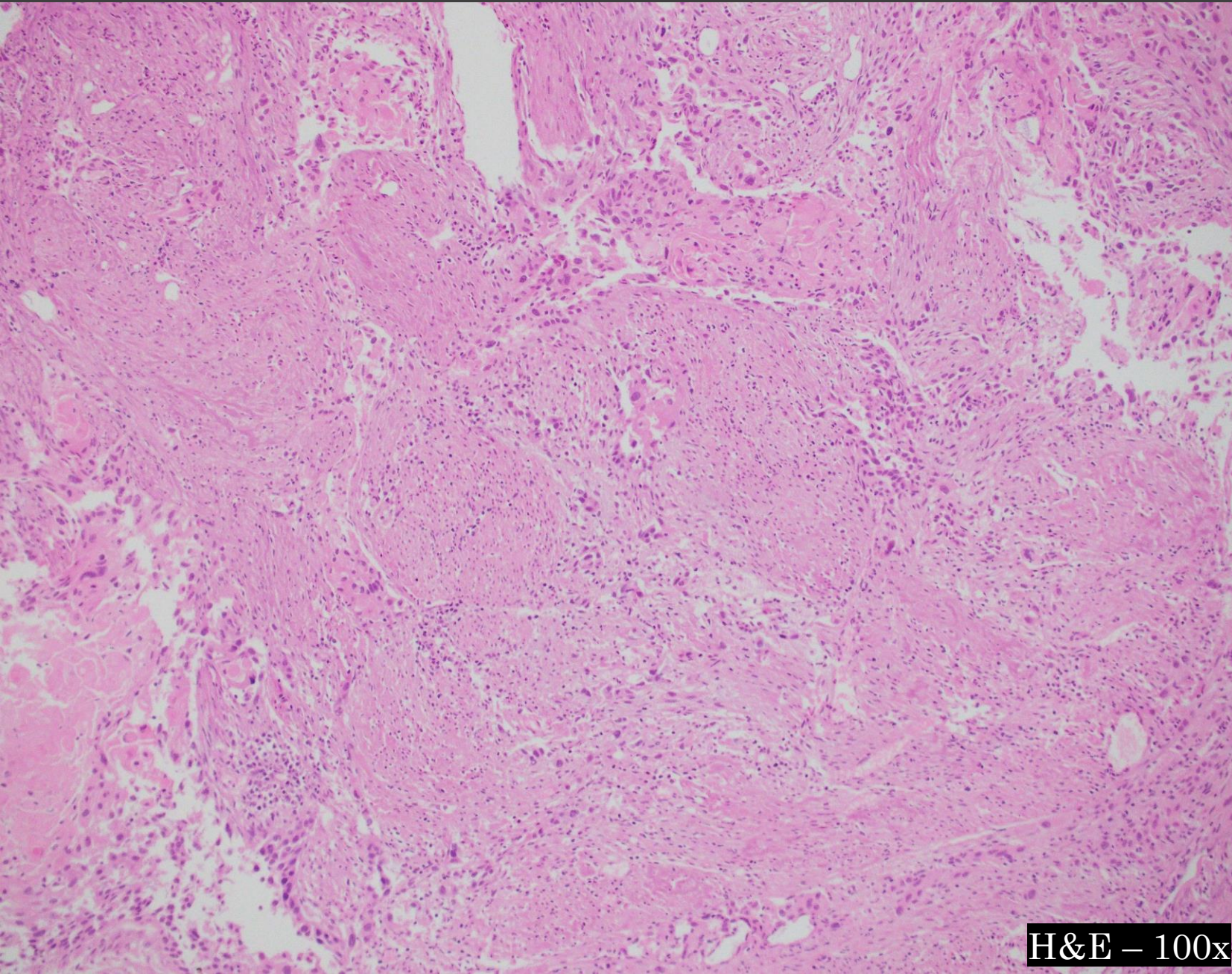
- 56 F presented to ED with right leg pain.
- ED Labs – Hypercalcemia and AKI
- ED CT – Scattered calcification of the bladder with intravesical debris and bilateral ureteral obstruction with hydronephrosis.
- Critical component of history omitted.
-  TURBT (and subsequent nephrostomy tube placement for ureteral obstruction).

Case 1



- Markedly necrotic (60-70%) TURBT sample with scattered calcified debris
- Focal areas suggestive of squamous metaplasia

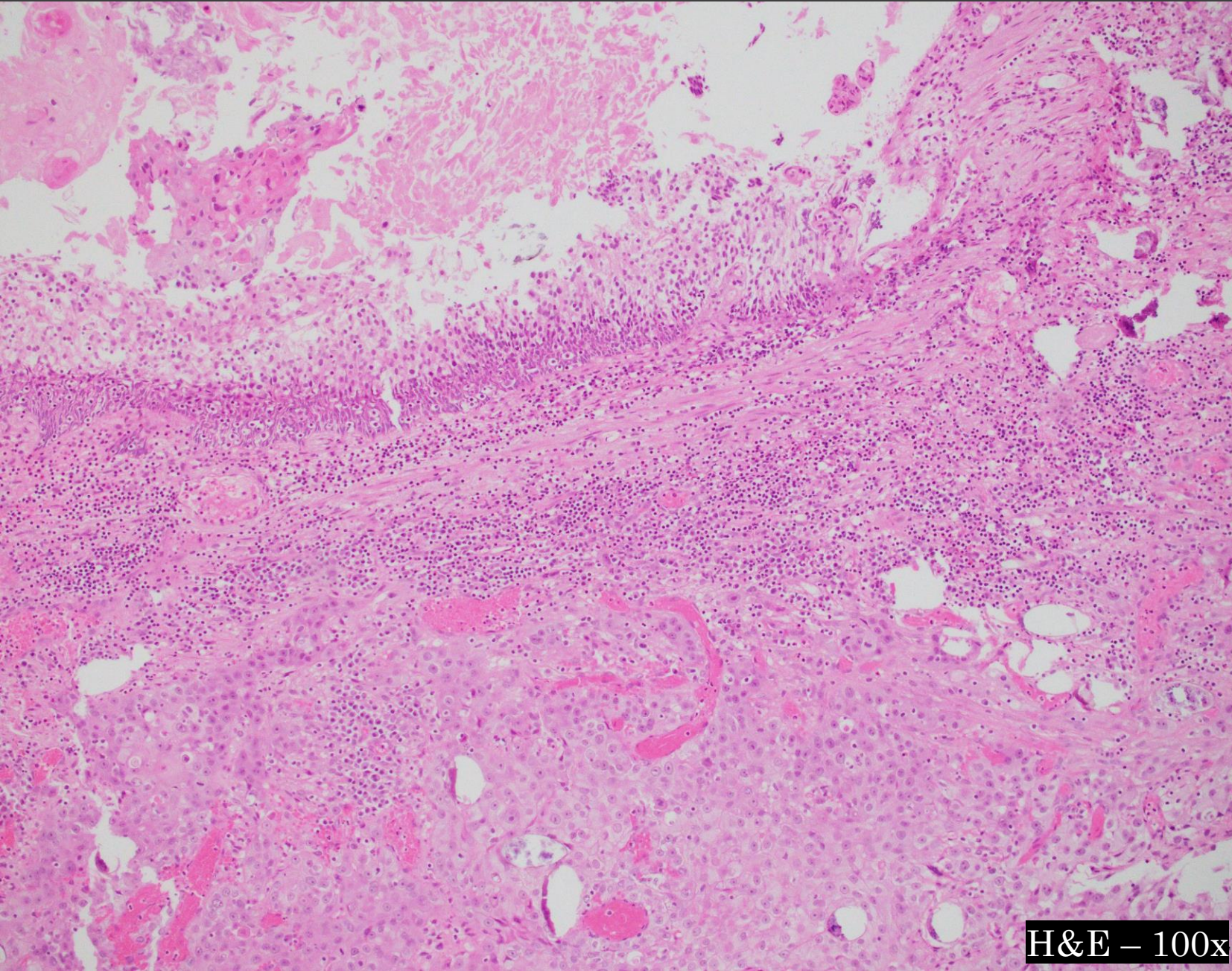
Case 1



- Foci of preserved muscularis propria (MP) with deeply invasive carcinoma.
- Carcinoma demonstrates squamous features

H&E – 100x

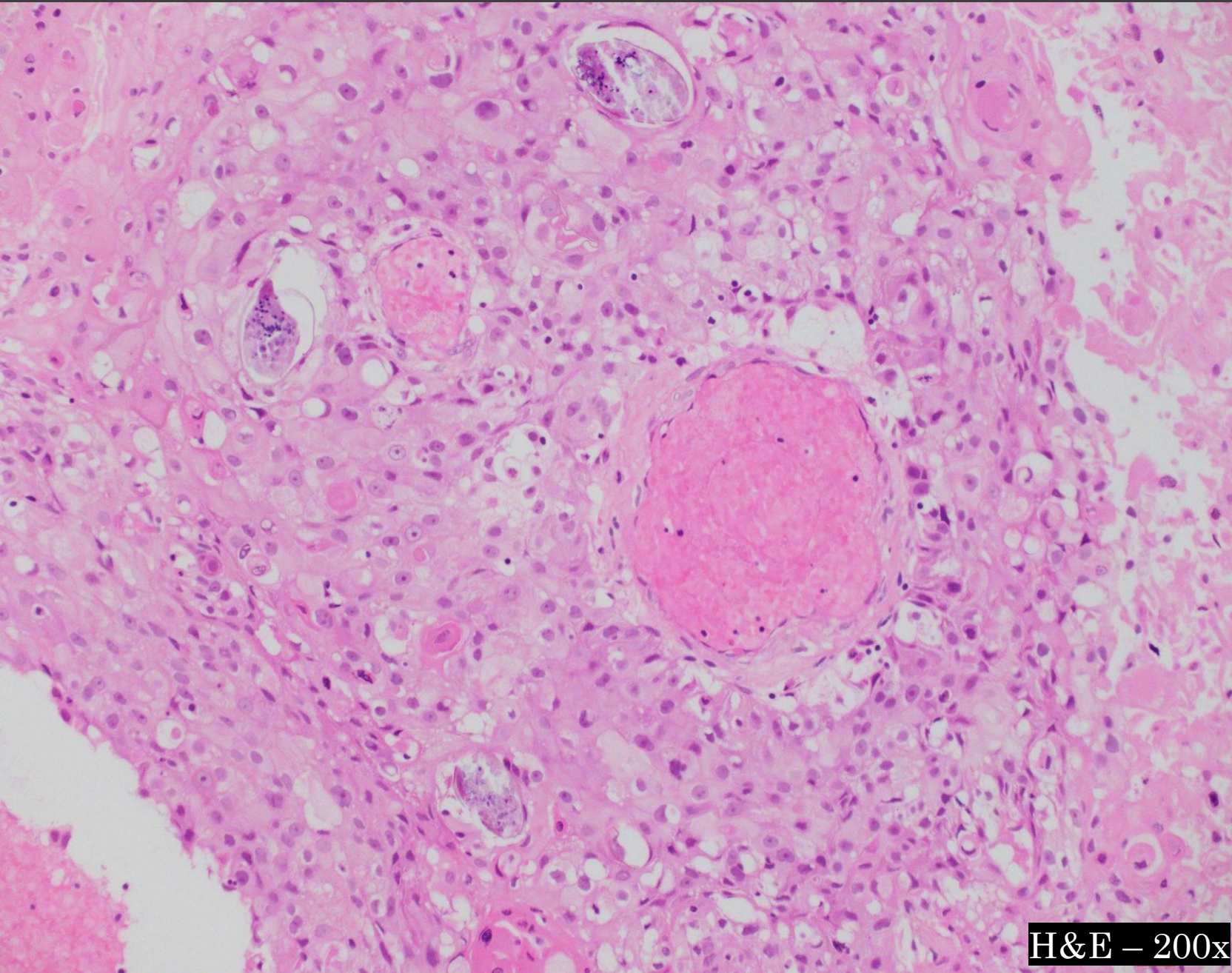
Case 1



H&E – 100x

- Bland overlying urothelium, underlying invasive carcinoma with squamous features.
- Ovoid calcifications with internal complexity

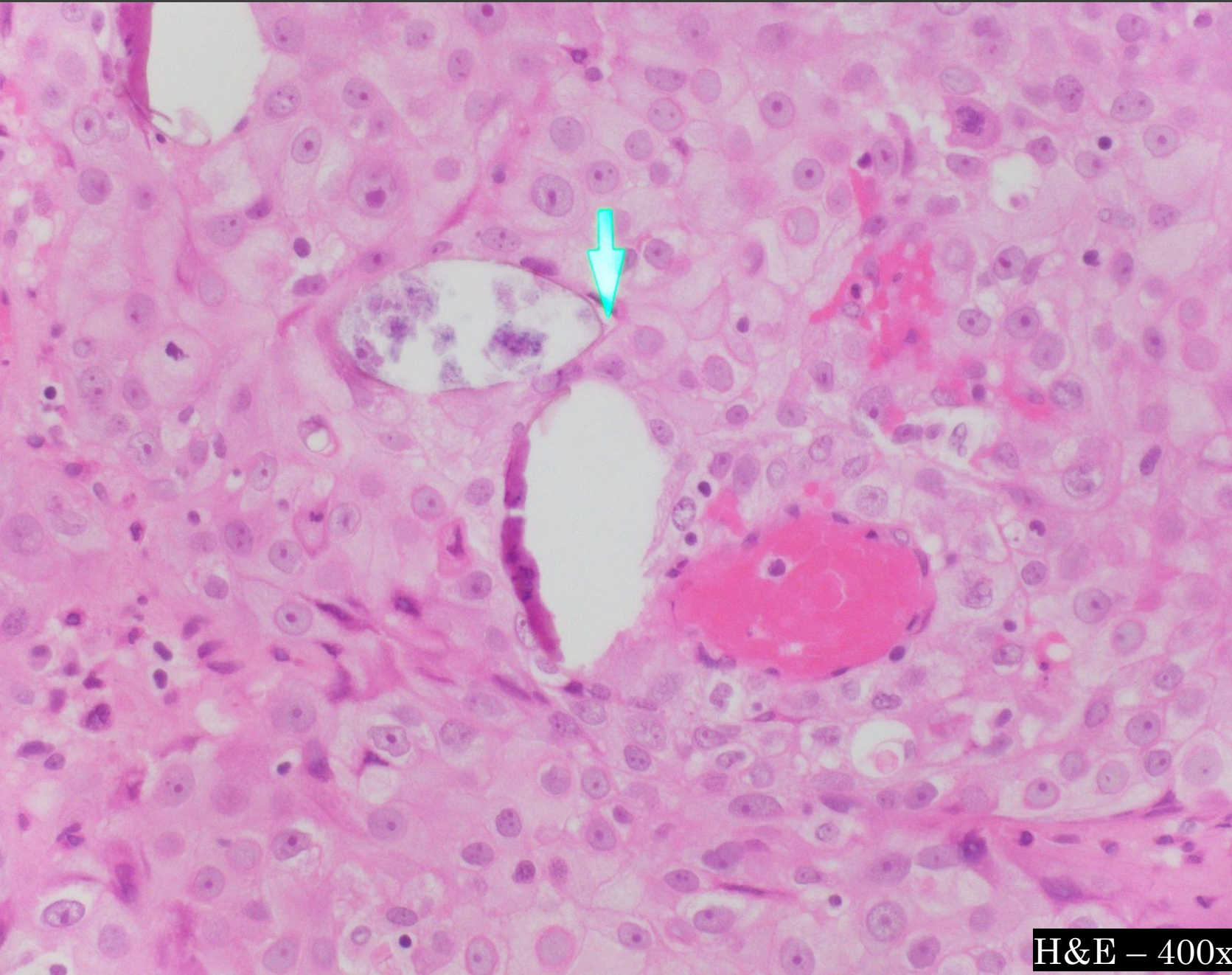
Case 1



H&E – 200x

- Squamous carcinoma is associated with ovoid calcifications with internal complexity.

Case 1



- Calcified ovoid structures - subtle terminal spine at narrow apex of the oval

H&E - 400x

Schistosoma haematobium associated squamous cell carcinoma of the urinary bladder.

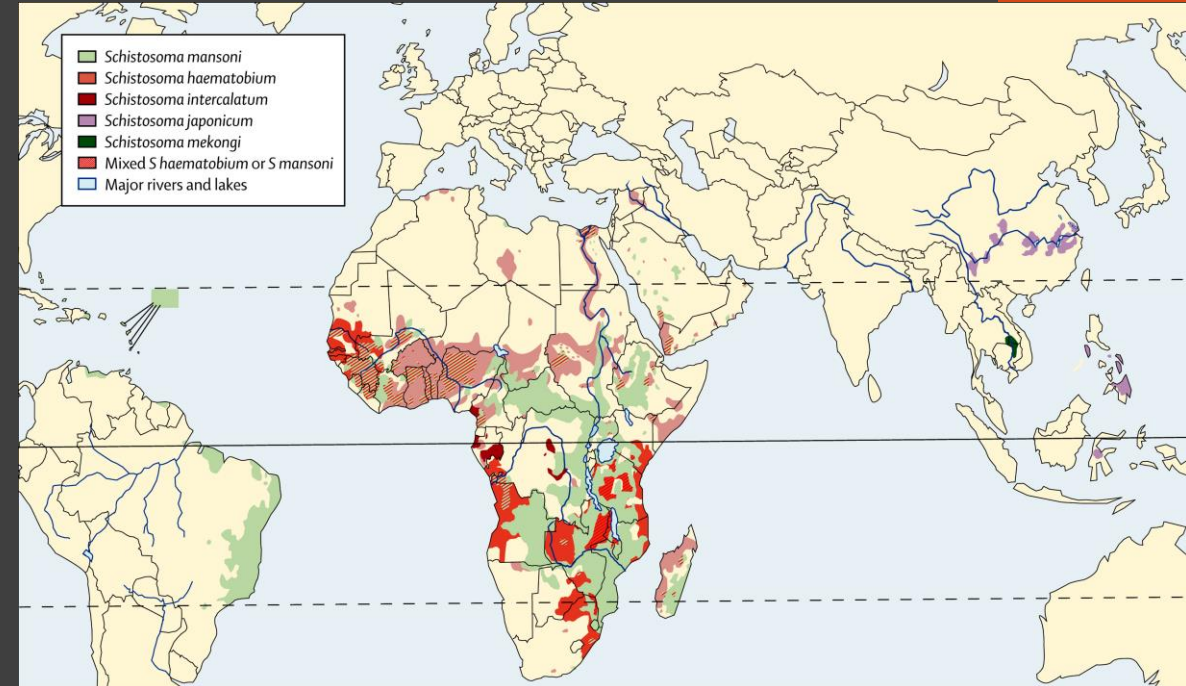
- Urinary Bladder, TURBT:
 - Invasive squamous cell carcinoma, moderately differentiated, arising in a background of schistosomiasis.
 - Muscularis propria invasion present (at least pT2).
 - Lymphovascular invasion present.
 - Perineural invasion present.

- Critical history omitted by the ED -- picked up by our urologists...

- Where was this patient likely from?

Case 1 – Schistosoma haematobium associated squamous cell carcinoma of the urinary bladder.

- Recent immigrant from Somalia.
- Schistosoma haematobium: Urogenital trematode
 - Endemic in essentially all of Africa and locally in parts of Middle East.
- Egypt: 40-50% of population is infected.
 - Failed Eradication 1950s-1980's (Sponsored by WHO)
- Egypt and Sudan: 33.7% of bladder cancers have identifiable Schistosoma as cause.
- Wading//Bathing in fresh water.
 - Schistosoma haematobium is capable of penetrating intact skin!
- Chronic infection a known risk for squamous cell carcinoma of bladder.
- Very rare in the US – increasing incidence.



Case 1 – Schistosoma haematobium associated squamous cell carcinoma of the urinary bladder.

	Urothelial (Transitional) Carcinoma	Schisto-associated squamous cell carcinoma	Non-Schisto associated squamous cell carcinoma
Geographic Distribution	Industrialized Countries	Shisto-endemic Areas	Rare in both
Age	50s-70s	20s-40s	50s-70s
Risk Factors	Smoking, Dyes, Toxic chemical exposure (occupational)	Chronic irritation secondary to Schistosoma h.	Chronic irritation associated with stasis (indwelling catheters, paraplegia, calculi)
Clinical Stage at Presentation	Localized	Advanced	Advanced
Histologic Differentiation	Urothelial	Squamous with associated eggs	Squamous
Precursor Lesions	Urothelial carcinoma in situ or non-invasive papillary UC	Squamous Metaplasia	Squamous Metaplasia
Chemo-Rads Response	Fair	Poor	Poor
Prognosis	Good-Fair	Poor	Poor
Nodal Involvement	16-45%	16-25%	22-23%

Case Follow-Up:

- Imaging: Innumerable metastatic sites including bone (ED: leg pain).
- Treated with praziquantel for 3 days.
- Refused all further treatment – surgery, chemotherapy, and immunotherapy.
- Died of disease ~5 months after diagnosis.

Case 1 – Schistosoma haematobium associated squamous cell carcinoma of the urinary bladder.

Case 1 Take Home Points

Schistosoma h. infection increases risk of squamous cell carcinoma of the bladder.

Strong geographic and or travel history.

Schisto-associated squamous carcinoma typically presents with higher stage, younger patients, with poor prognosis as compared to urothelial carcinoma.

Case 2

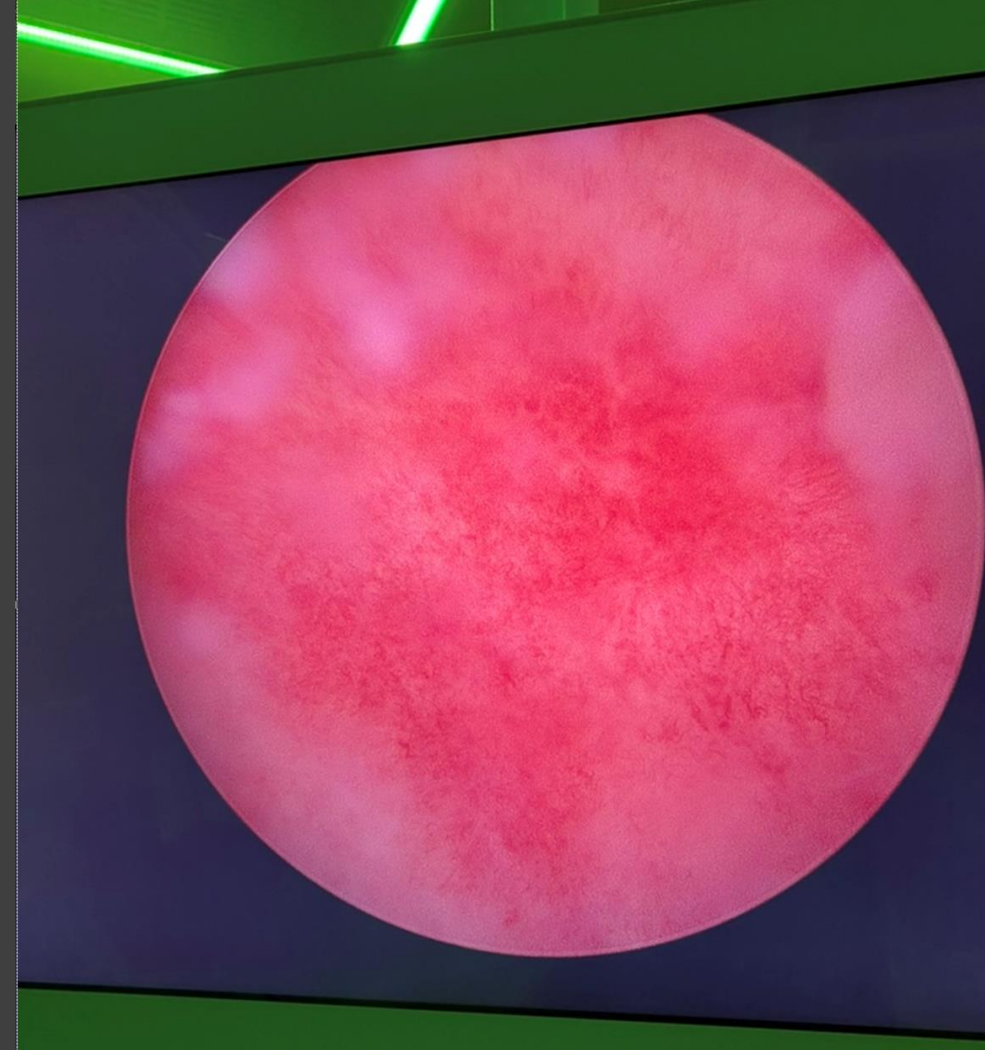
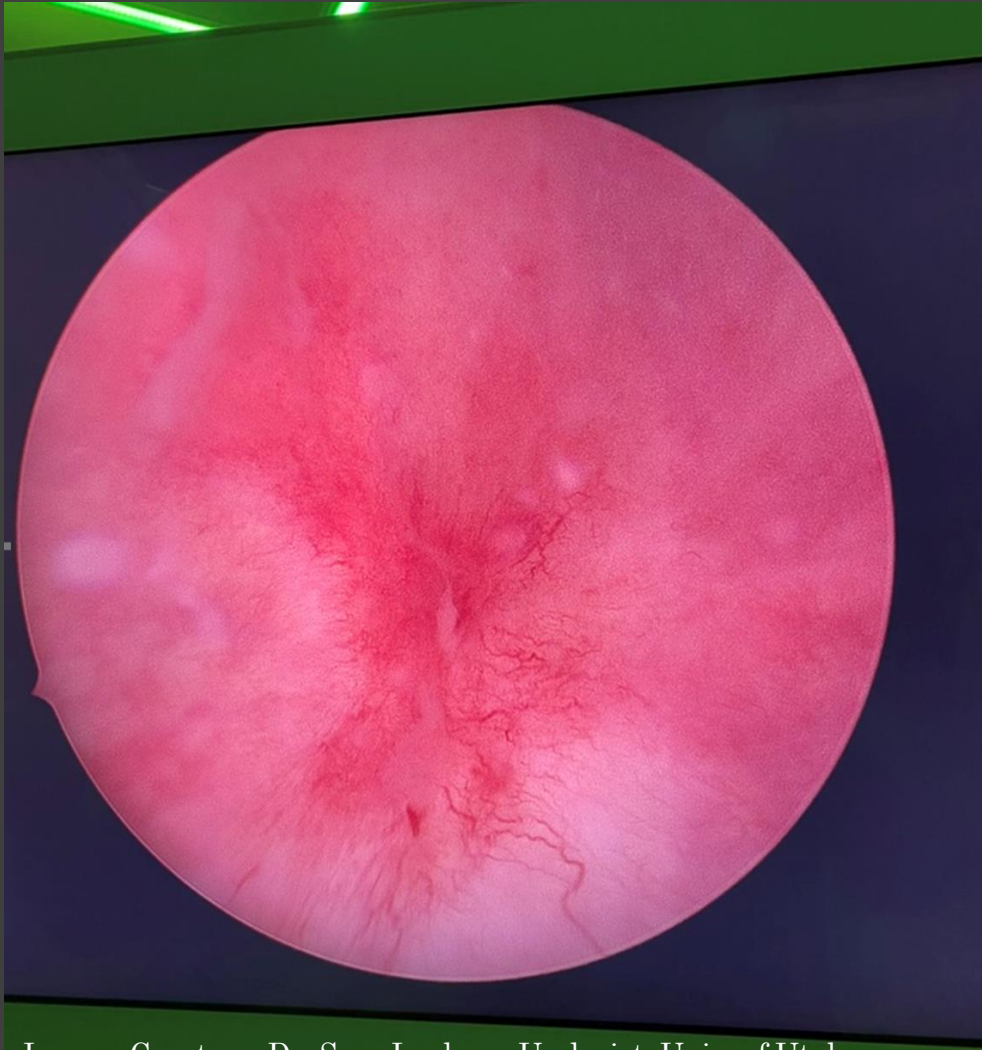
- 28 M - recurrent hematuria, bladder pain on voiding. Insidious onset, increased after attending 4-day outdoor musical festival 15 months ago.
- UA – 3+ RBCs, 1+ WBCs, +/- Leuk. Esterase
- Urine Culture: Negative, repeatedly
- STI screening: Negative, repeatedly
- Imaging: Asymmetrically thickened bladder wall, no mass lesions.
- Critical component of history omitted.

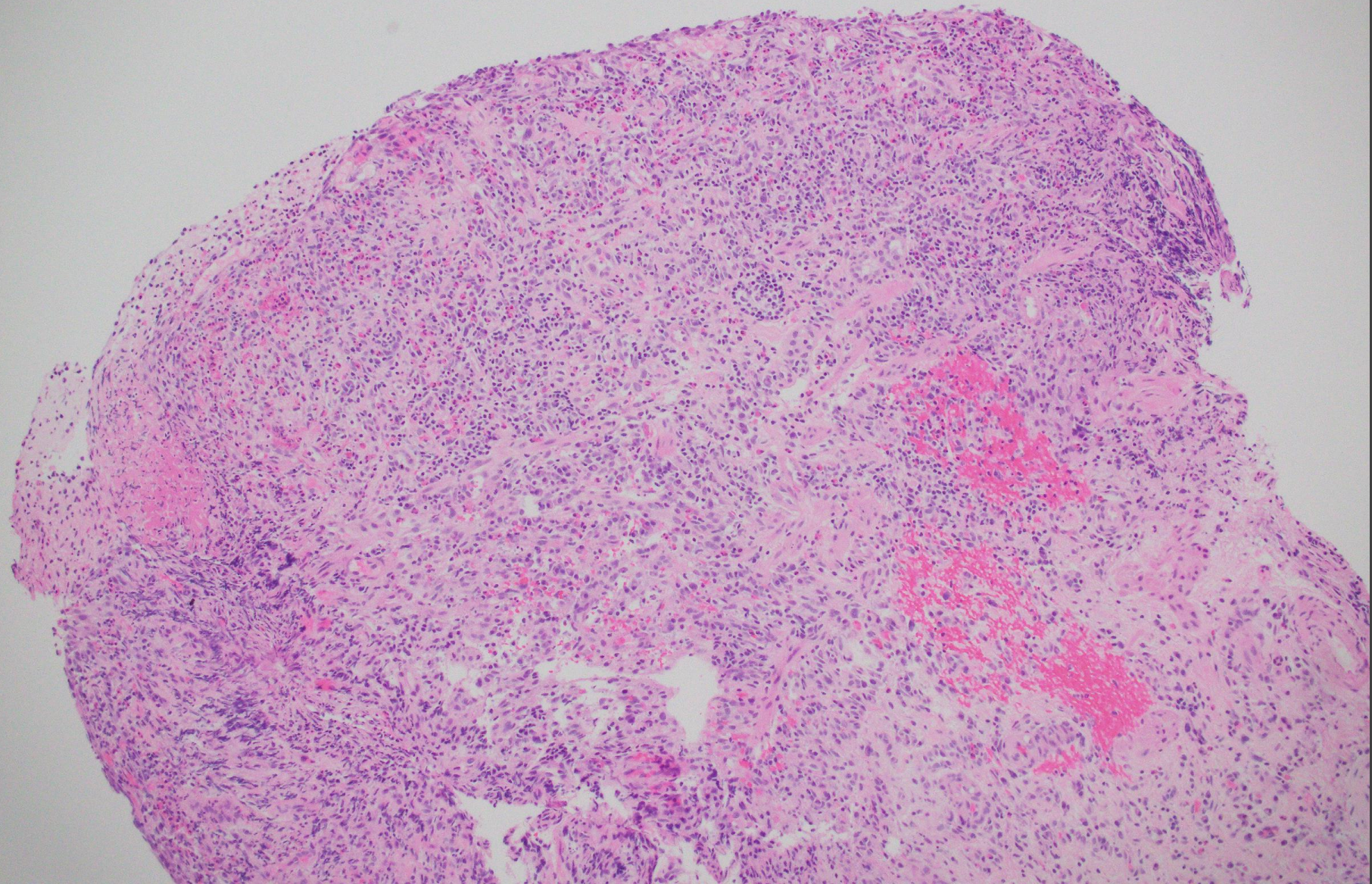
- Recalcitrant to antibiotic therapy for presumptive UTI in negative culture setting.

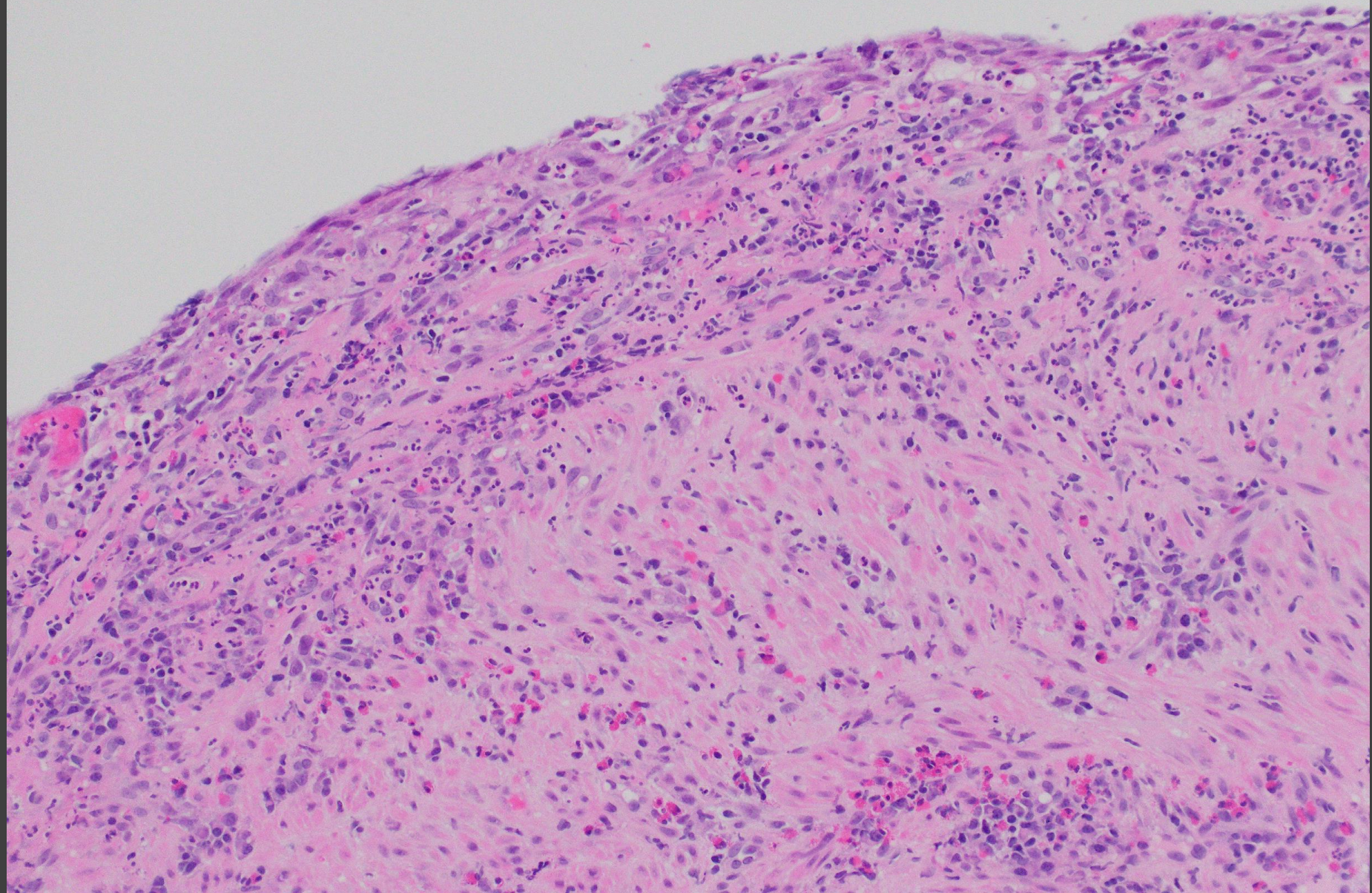
 • Cystoscopy and Biopsy.

Case 2

Cystoscopy: Diffusely erythematous mucosa with ulceration and bleeding.
No mass lesion.



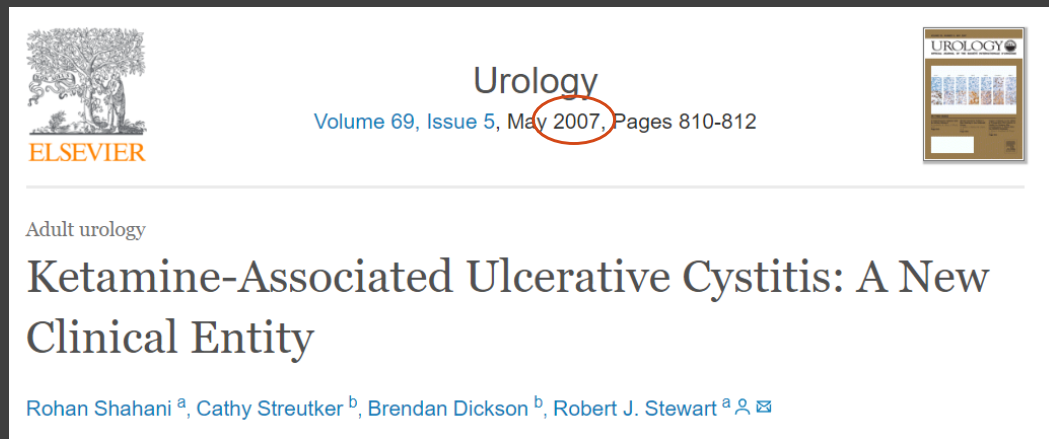




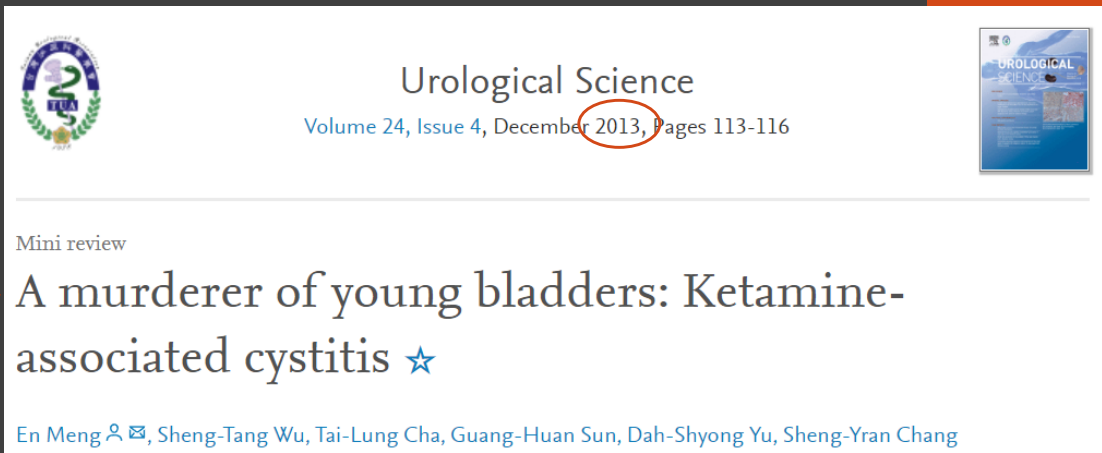
Case 2 – Ketamine associated ulcerative cystitis (Ketamine Cystitis)

- Ketamine: Dissociative anesthetic and hallucinogen.
 - NMDA Antagonist; “Horse Tranquilizer”, “Vitamin K”, “Special K”
 - Short acting high, large dose required
 - Addicts: Multiple grams / day.
 - (Dosage IV Anesthesia: 1-1.5 mg/kg (~100 mg))
 - Tolerance established quickly → Increasing doses required
 - Frequent drug of abuse in UK and Canada.
 - USA: Increasing Incidence– up to 0.9% of the US population has used ketamine recreationally (2019).
 - Heavy use / Abuse: Severe irritative voiding symptoms, pelvic pain, hematuria, mucosal sloughing.
 - Still unclear etiology? – direct toxic effect (or metabolites), breakdown of epithelial-urine barrier, direct stimulation/induction of fibrosis.





6 years



- Significant overlap with “Interstitial Cystitis”
 - Symptoms
 - Cystoscopy
 - Histologic Findings
 - Urothelial ulceration and underlying granulation tissue.
 - Fibrosis of lamina propria (chronic) – leading to contracture
 - Increased inflammatory infiltrate – neutrophils, eosinophils, and mast cells.
 - Reactive urothelial atypia
 - No cases of associated carcinoma (*yet?)
- Responds quickly and nearly universally to cessation of drug use.
- Duration and frequency of use directly correlates with symptoms and injury.
- Chronic use may lead to scarring, fibrosis, and bladder contracture – Partial/simple cystectomy.

Case 2 – Ketamine associated ulcerative cystitis (Ketamine Cystitis)

Case 2

Take Home Points

Ketamine is a rare (but rapidly increasing) drug of abuse in the USA.

Ketamine causes severe damage to urothelium with potential for fibrosis and permanent damage requiring corrective surgery.

Ketamine cystitis should be considered clinically in cases resembling “interstitial cystitis” in the appropriate patient demographic.

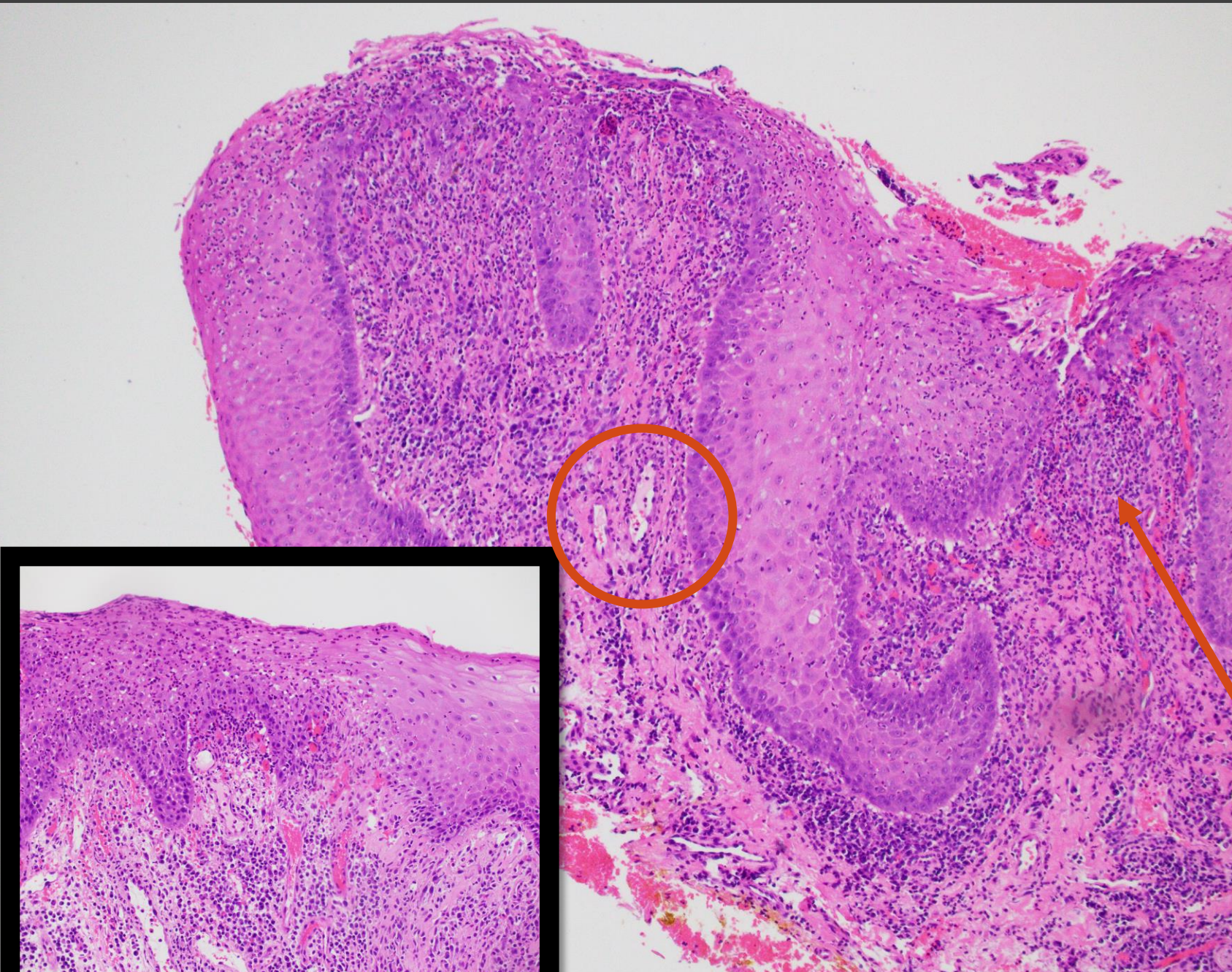
Case 3

- 25 M - Painless ulcer on glans penis for 2.5 weeks, recent (1-2 days) red blotchy rash on palms/hands.
- Urine Culture: Negative
- STI screening: **Positive**
- Critical component of history omitted.

→ • ... Biopsy

Glans Penis:

- Acanthosis and Psoriasiform epithelial hyperplasia
- Ulcer with epidermal PMNs
- Dense lymphoplasmacytic infiltrate.
- Endothelial swelling
- Vasculitis: Obliterative endarteritis



Comparative analysis of immunohistochemistry, polymerase chain reaction and focus-floating microscopy for the detection of *Treponema pallidum* in mucocutaneous lesions of primary, secondary and tertiary syphilis

H Müller[†], K Eisendle, W Bräuninger, H Kutzner, L Cerroni, B Zelger

Comparative Study > J Cutan Pathol. 2004 Oct;31(9):595-9.

doi: 10.1111/j.0303-6987.2004.00236.x.

Secondary syphilis: a histologic and immunohistochemical evaluation

Mai P Hoang[†], Whitney A High, Kyle H Molberg

Spirochetes in BOTH epidermis and dermal-epidermal junction.

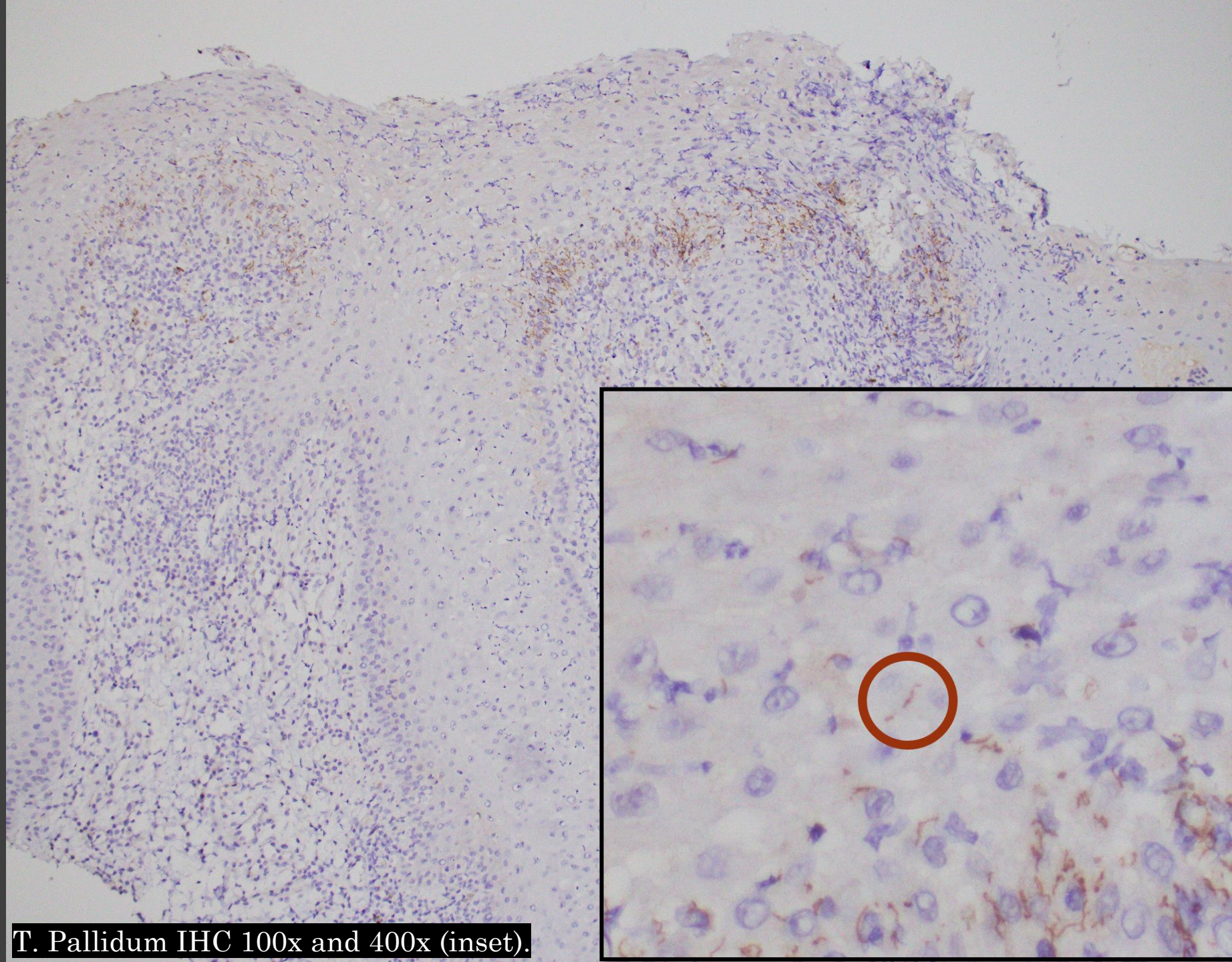
Classic spiral-form spirochete morphology appreciated at 400x.

Detection Sensitivity

T. Pall IHC:	71% (49-92%)
Silver Stains:	0-41%
NAAT:	50-87%

IHC Detection Rate Varies Based on Clinical Stage :

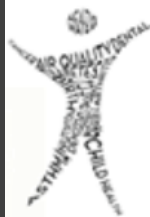
Primary:	67%
Secondary:	55%
Tertiary:	13%



T. Pallidum IHC 100x and 400x (inset).

Case 3 - Syphilis

- Prevalence rapidly increasing in US (and UT) for the past decade.
- Classically a genital disease - increasingly found in other sites at our institution with utilization of T. Pallidum IHC (ARUP 2019).



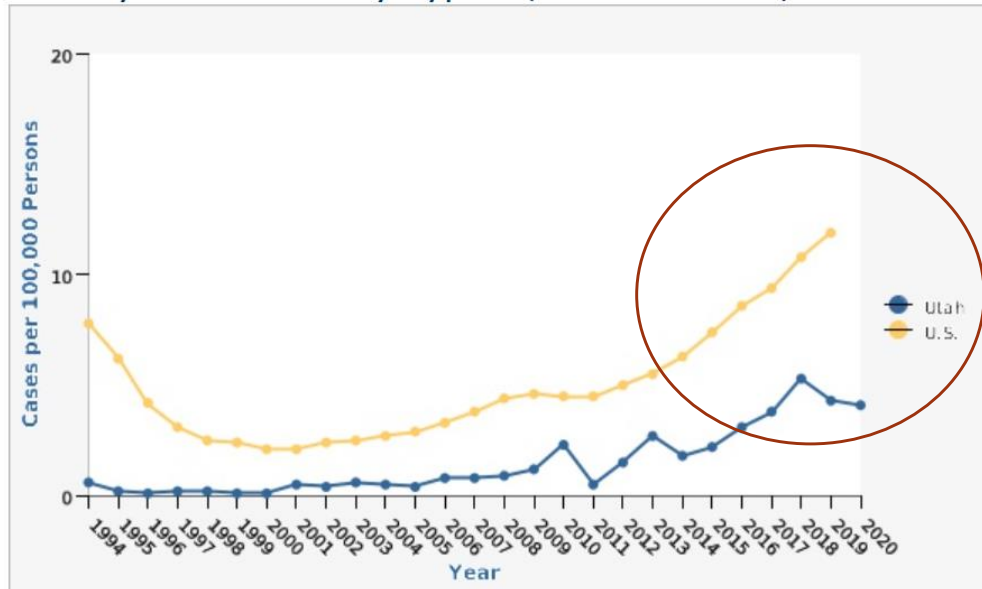
Public Health Indicator Based Information System (IBIS)

Utah's Public Health Data Resource

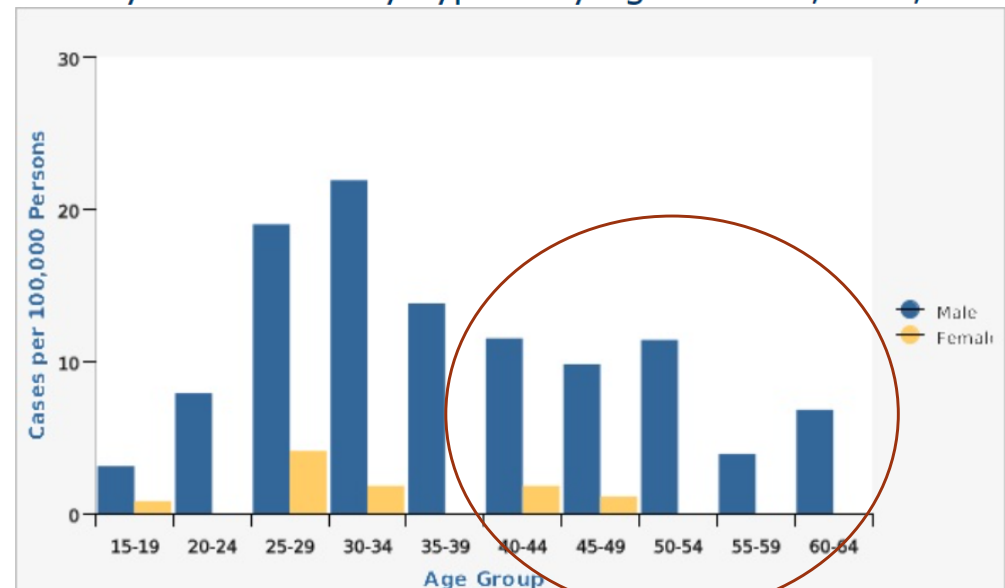
Path: [IBIS-PH](#) » [health indicators](#) » [index](#) » [report](#)



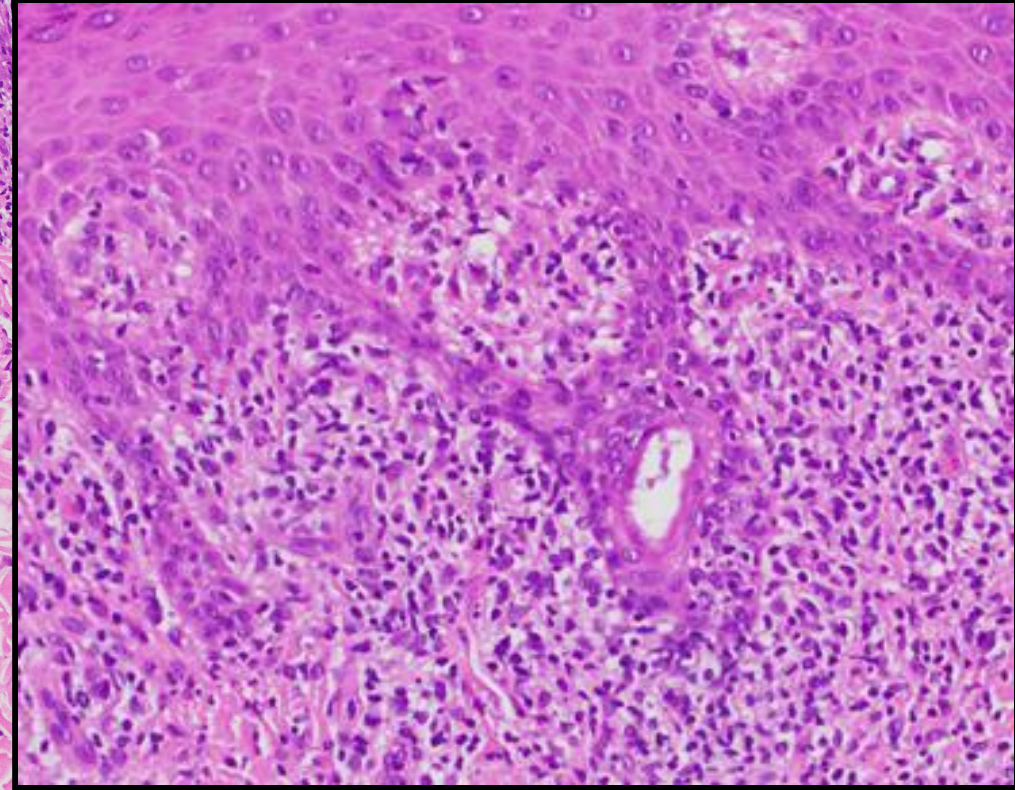
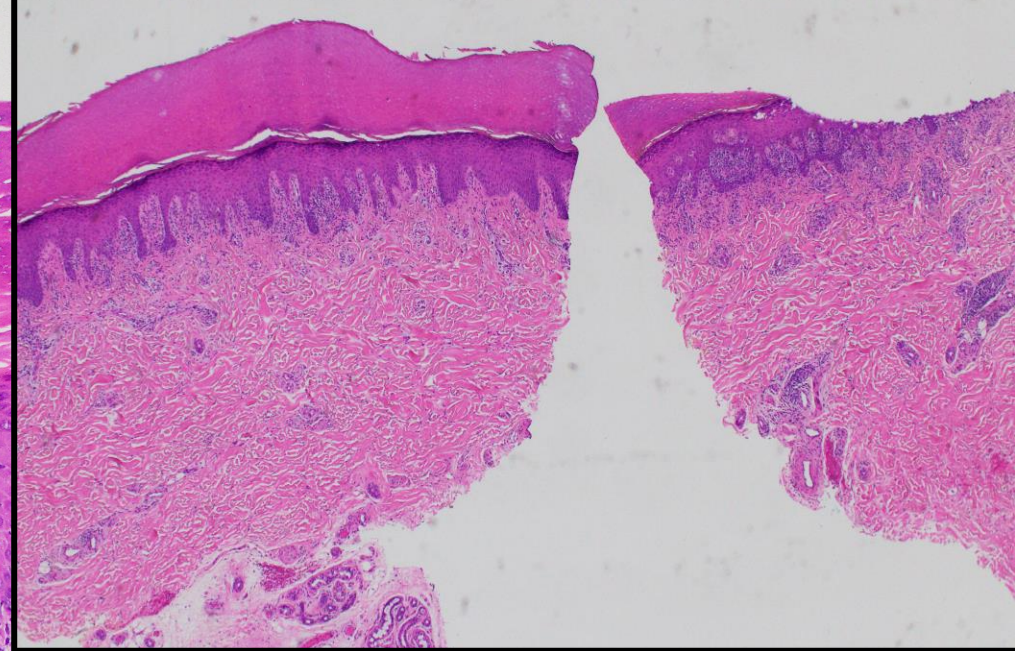
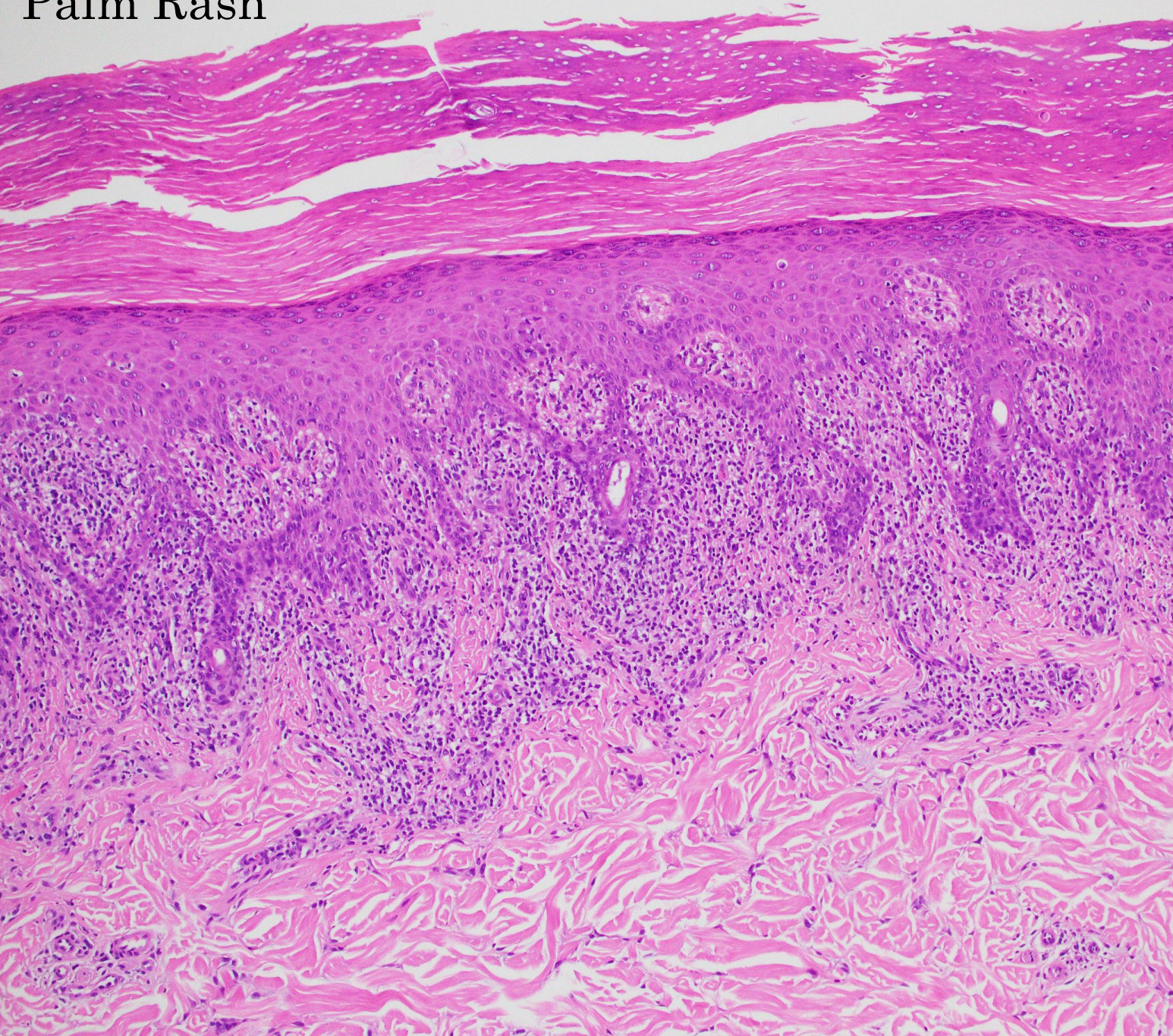
Primary and Secondary Syphilis, Utah and U.S., 1994-2020



Primary and Secondary Syphilis by Age and Sex, Utah, 2020

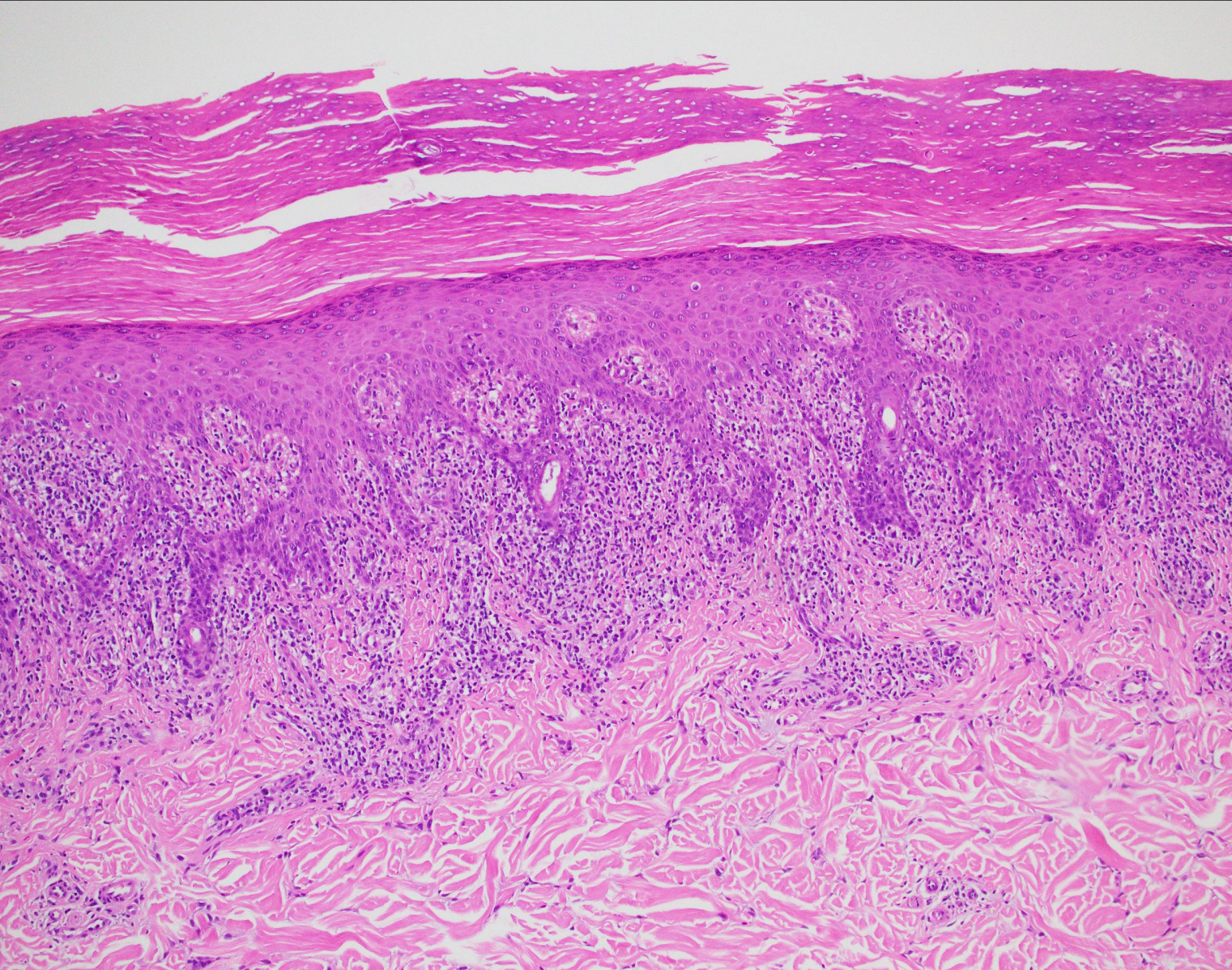


Palm Rash



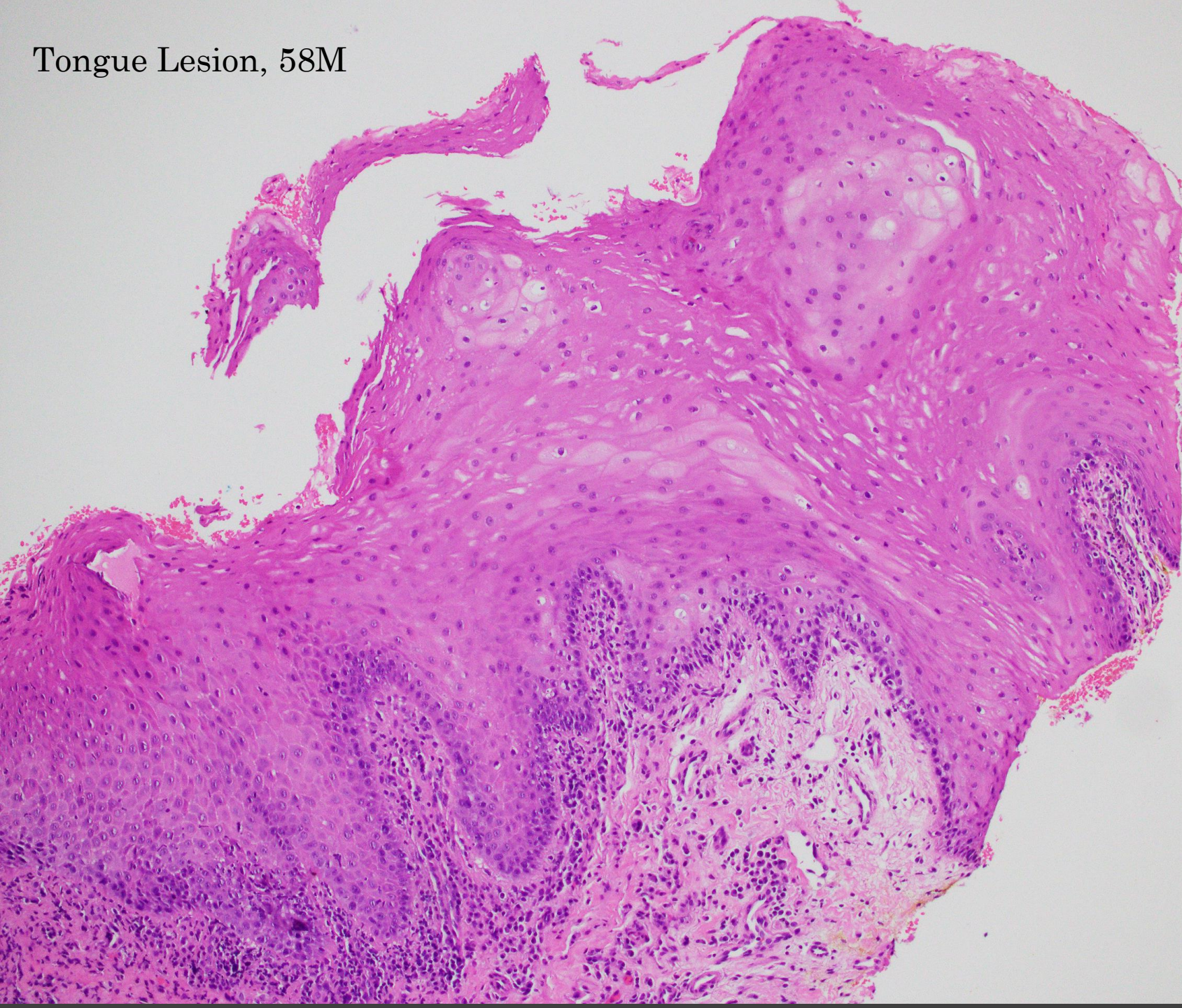
Case 3 – Syphilis (Secondary)

Palm Rash – Secondary syphilis (biopsied concurrently with penile lesion)



- Acral skin without ulceration
- No/minimal epidermal involvement
- Significantly less inflammation
 - Lymphocytes – lichenoid distribution with interface change
 - (DDx: Mycosis Fungoides, Lichenoid Drug Reaction)
- Noticeably reduced amount of plasma cells
 - Plasma cells absent in 30-40% of secondary syphilis

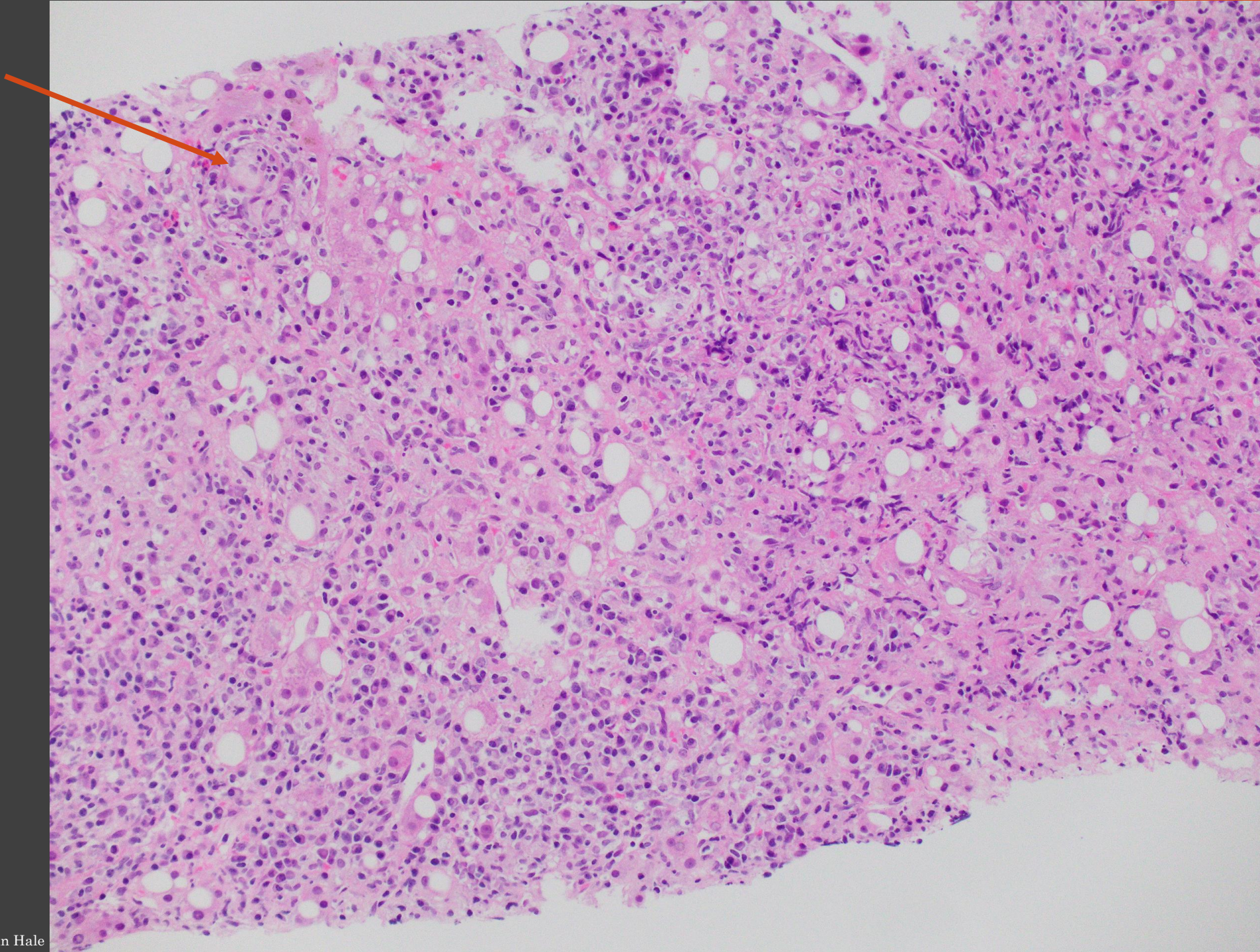
Tongue Lesion, 58M

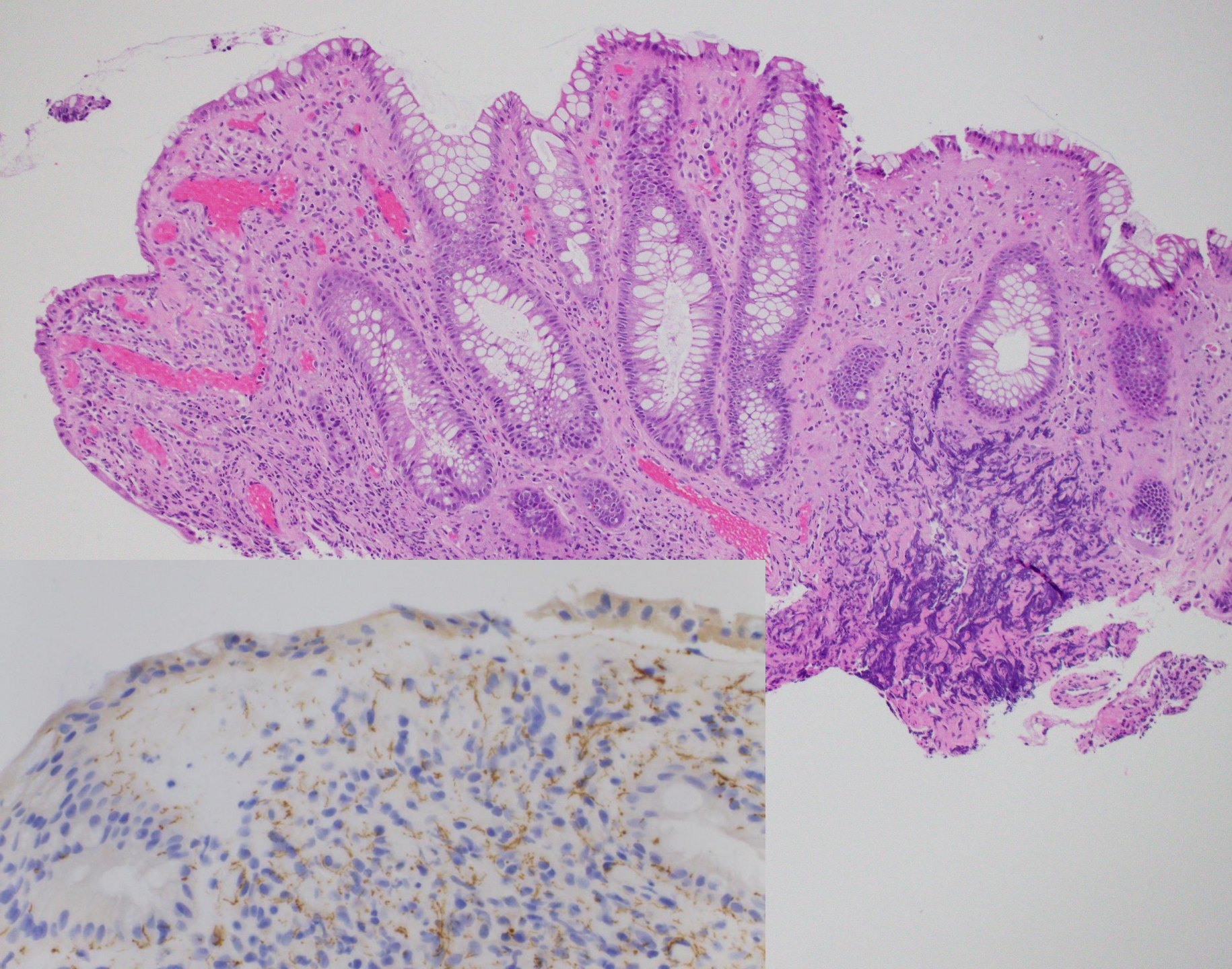


**Case 3:
Syphilis**

Case 3: Syphilis

- Targeted Liver Biopsy,
62M





Case 3: Syphilis

Surveillance
Colonoscopy for IBD,
63M

Case 3 – Syphilis

T. Pallidum IHC (ARUP 2019):
(~1 / 8,000 General Surg Path Cases)

Case 3 Take Home Points

Syphilis continues to rapidly increase in the general population.

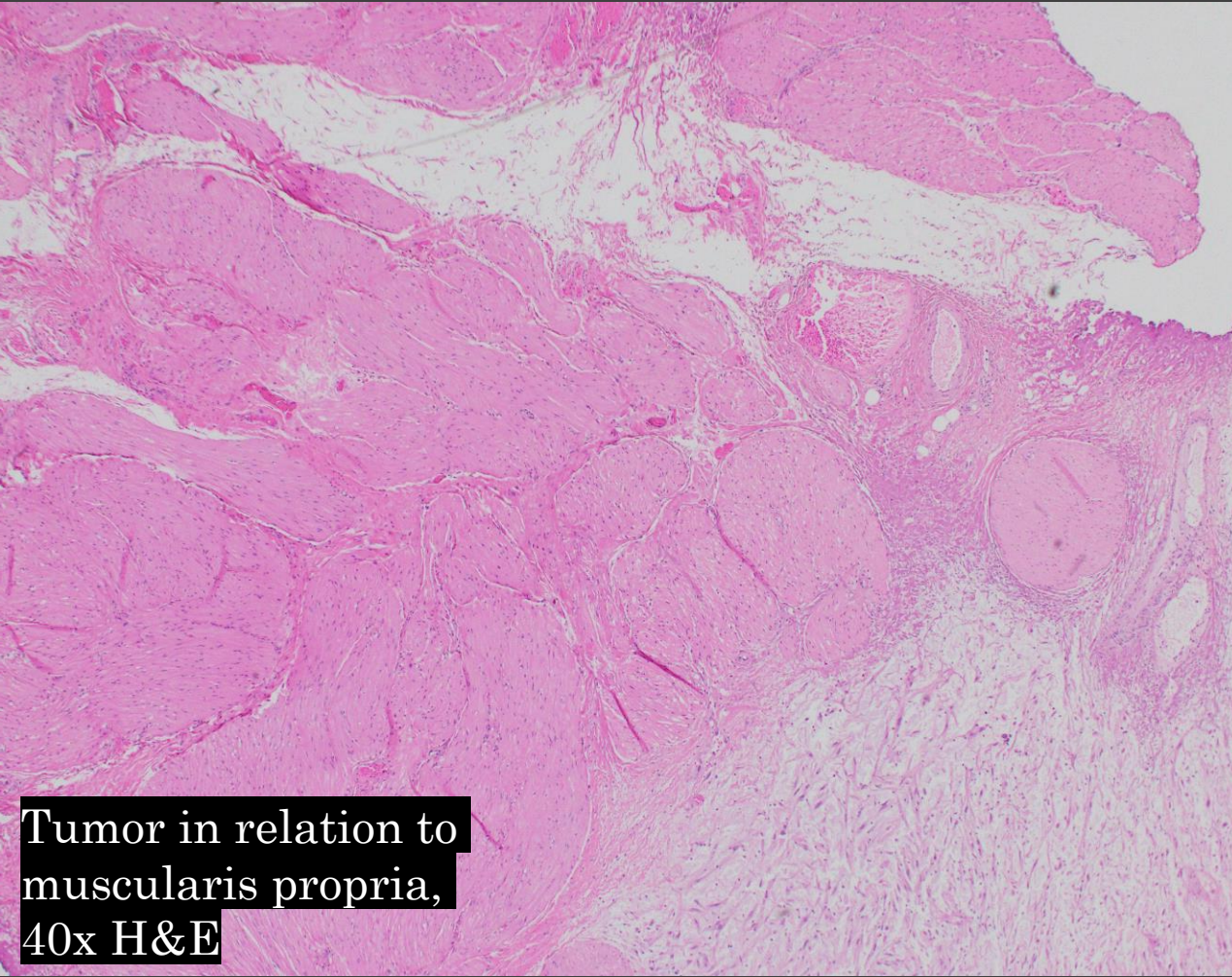
Syphilis while typically clinically recognized and not biopsied in classical genital sites – may be easily overlooked in “non-traditional” locations.

The same histologic features of primary genital syphilis are also present in “non-traditional” sites.

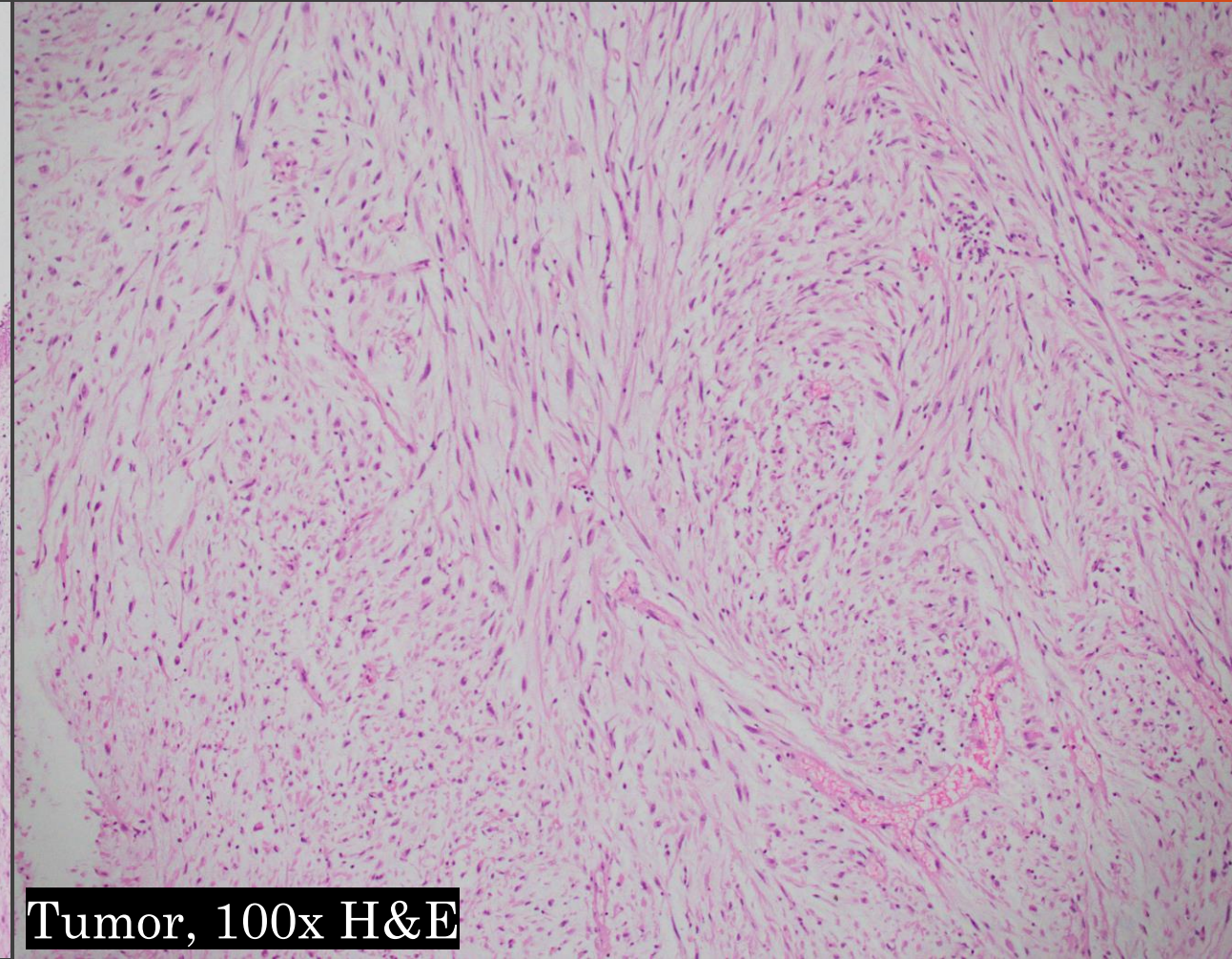
Case 4

- 63F - Pelvic pain
- MRI: 2.7 cm enhancing bladder mass (right posterolateral) with extension into surrounding fat.
- TURBT

Case 4



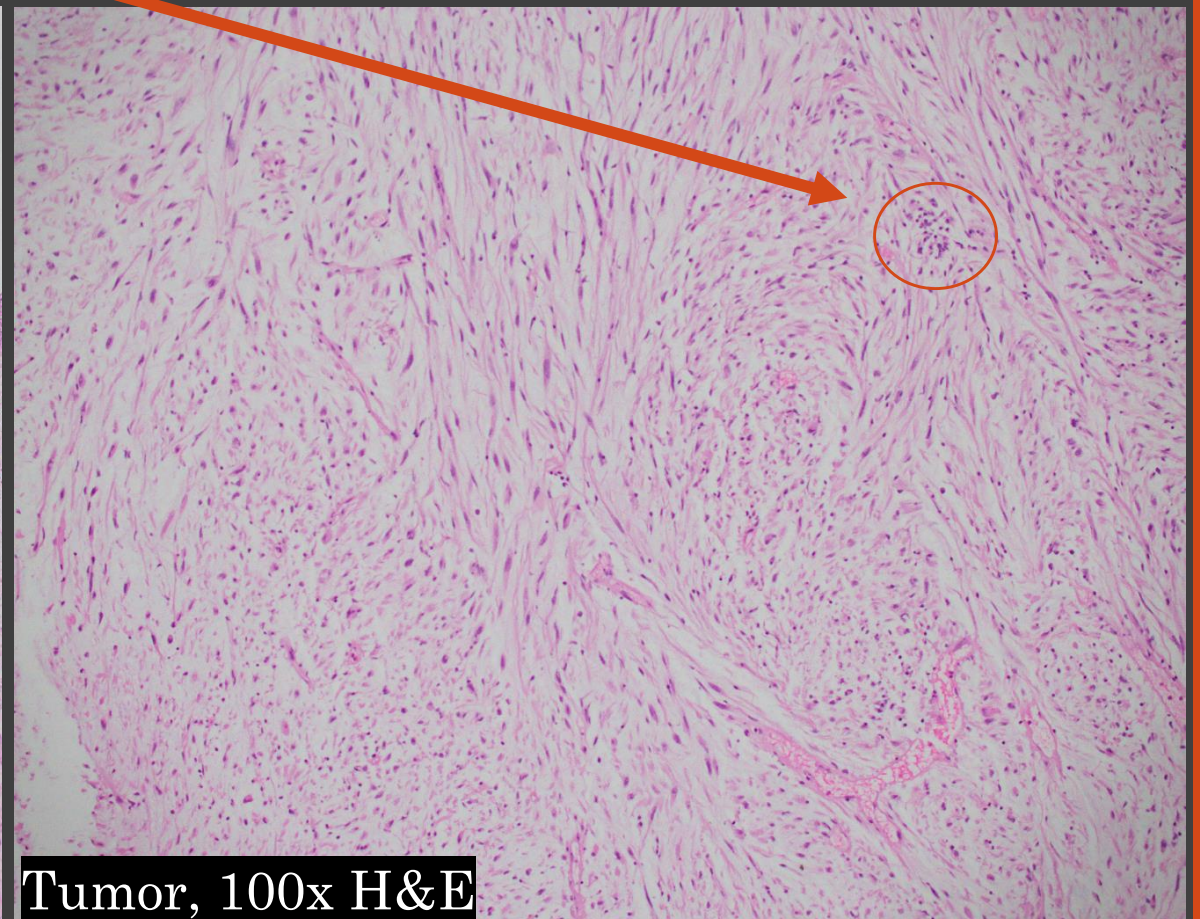
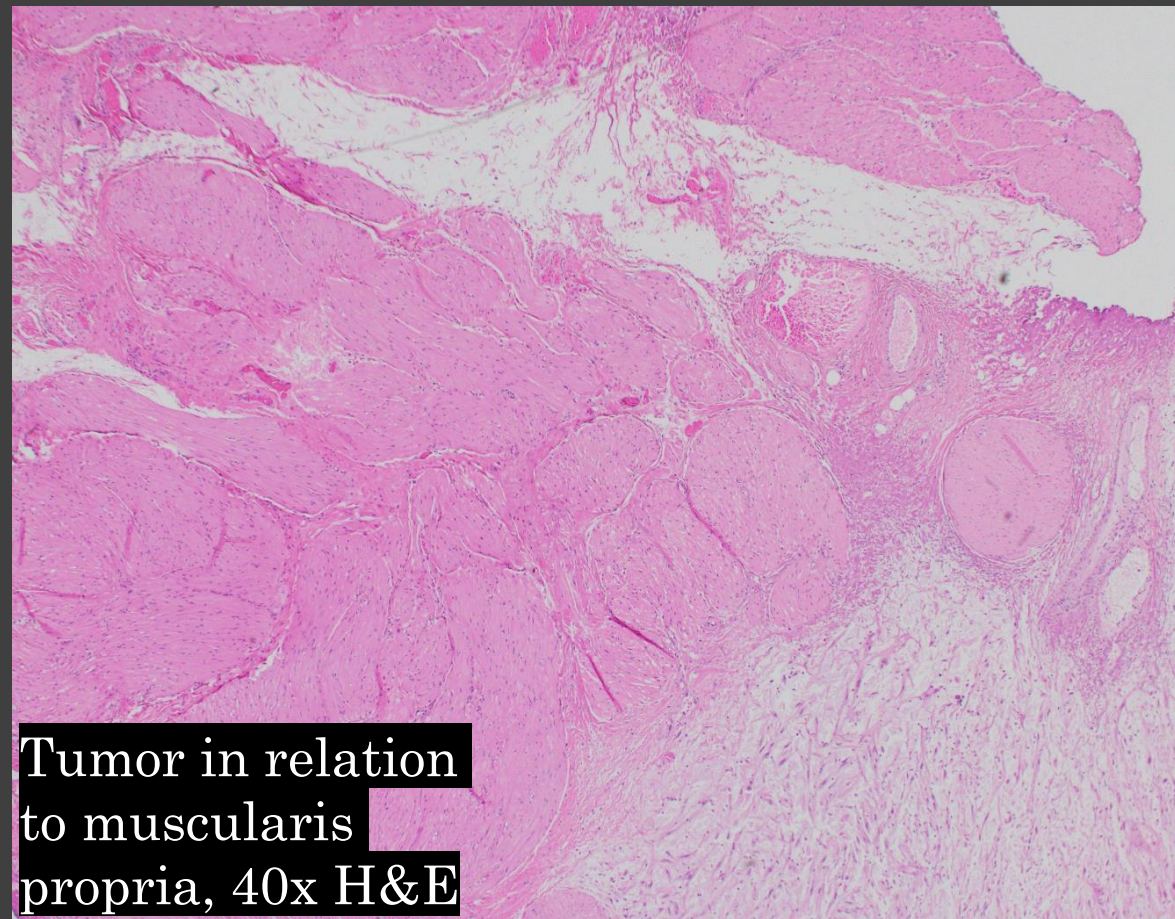
Tumor in relation to muscularis propria, 40x H&E

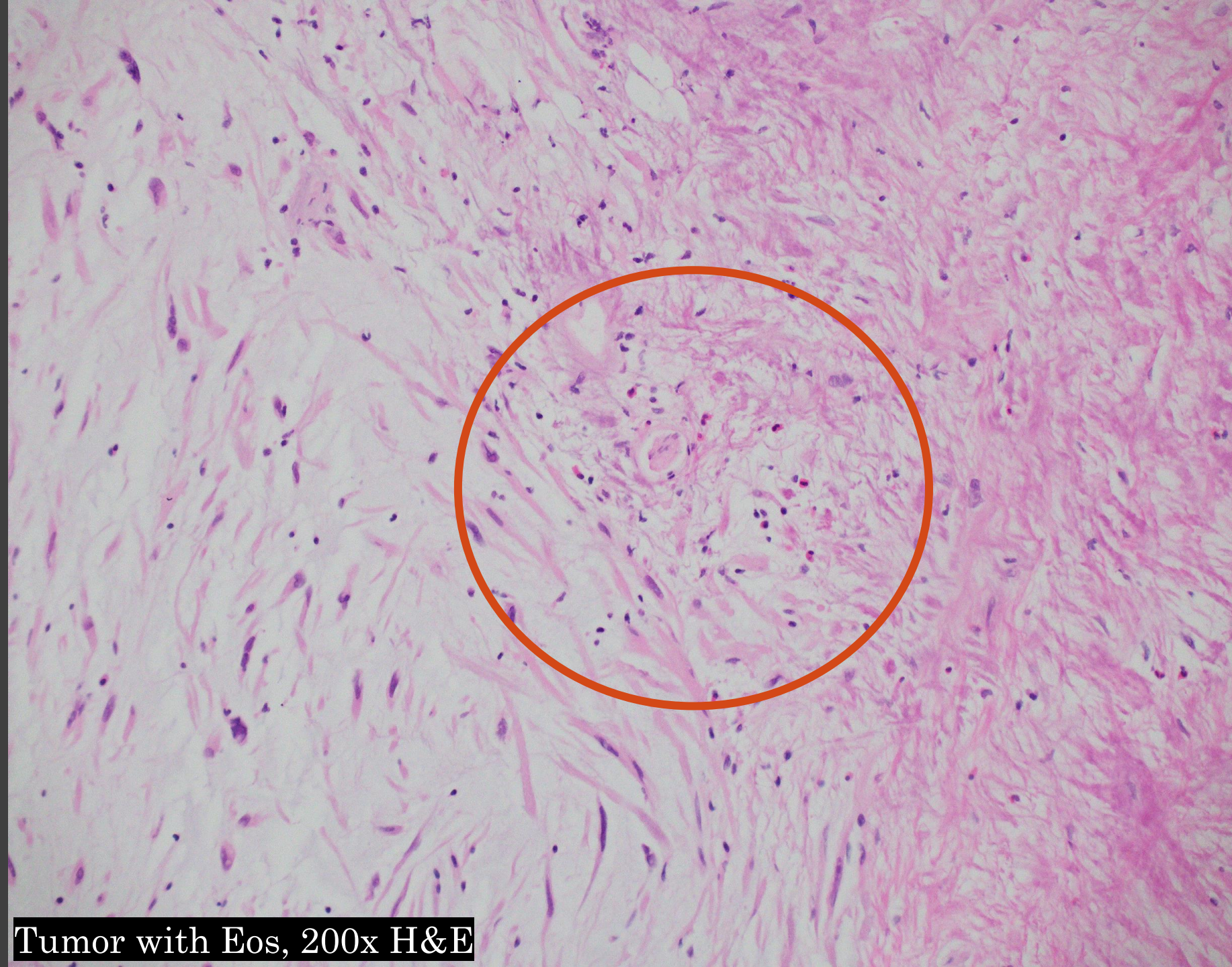


Tumor, 100x H&E

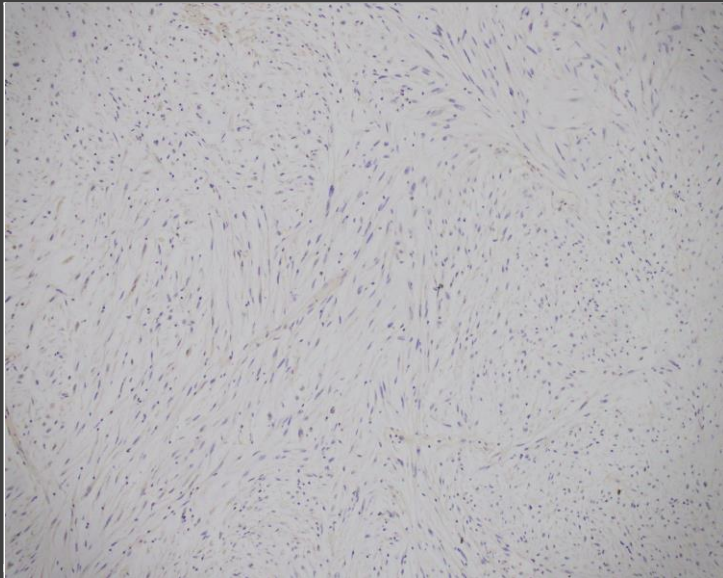
Case 4

Thin, delicate, spindled/fusiform morphology, elongated cytoplasmic processes, focal rare inflammatory (lymphocyte) aggregates.

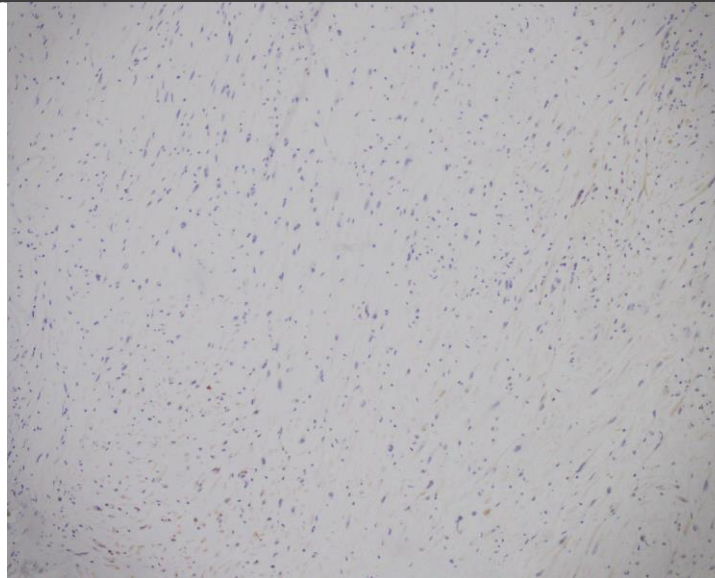




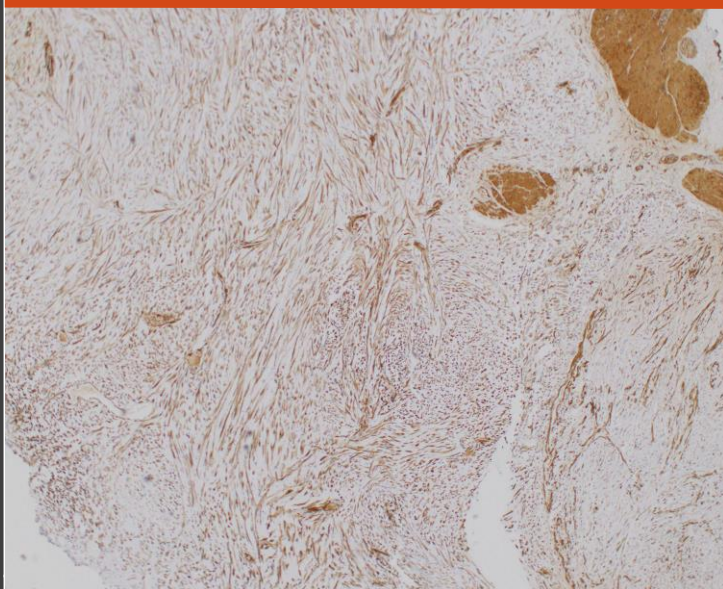
Tumor with Eos, 200x H&E



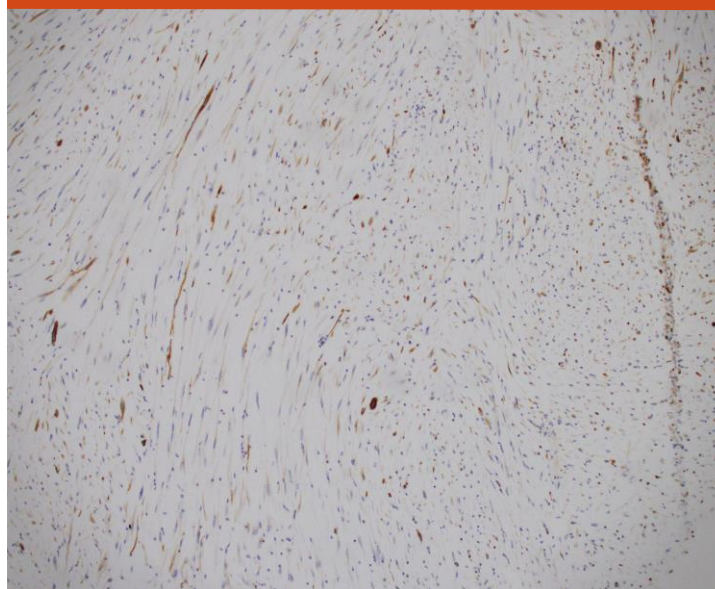
HMW CK (K903): Negative



p63: Negative



SMA: Diffusely Strong Positive



Desmin: Variably Positive

Case 4 – ALK+ Inflammatory Myofibroblastic Tumor (IMT)

Suspicious/Equivocal ALK IHC



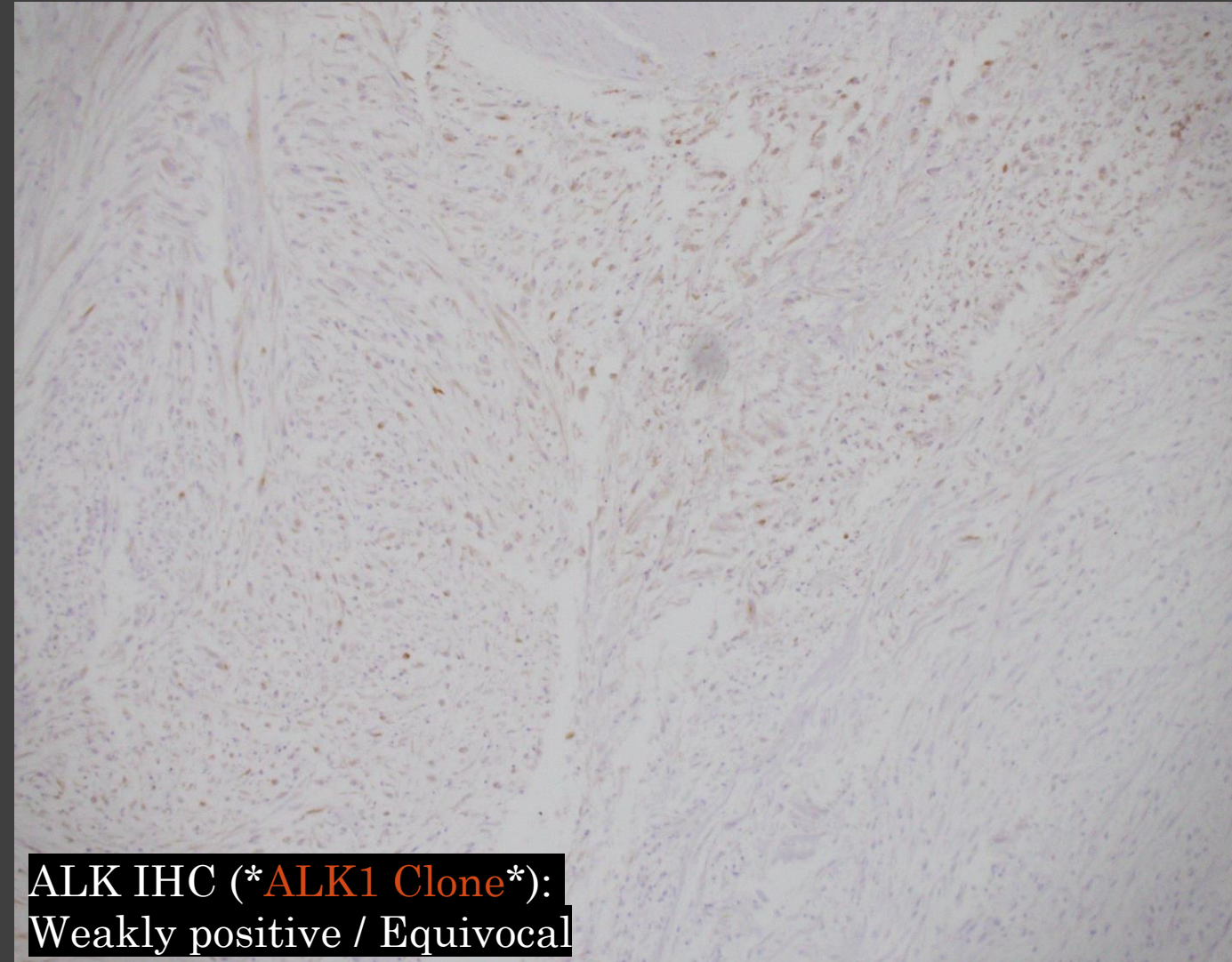
FISH Testing

ALK FISH:

Positive for ALK Rearrangement (ABNORMAL)

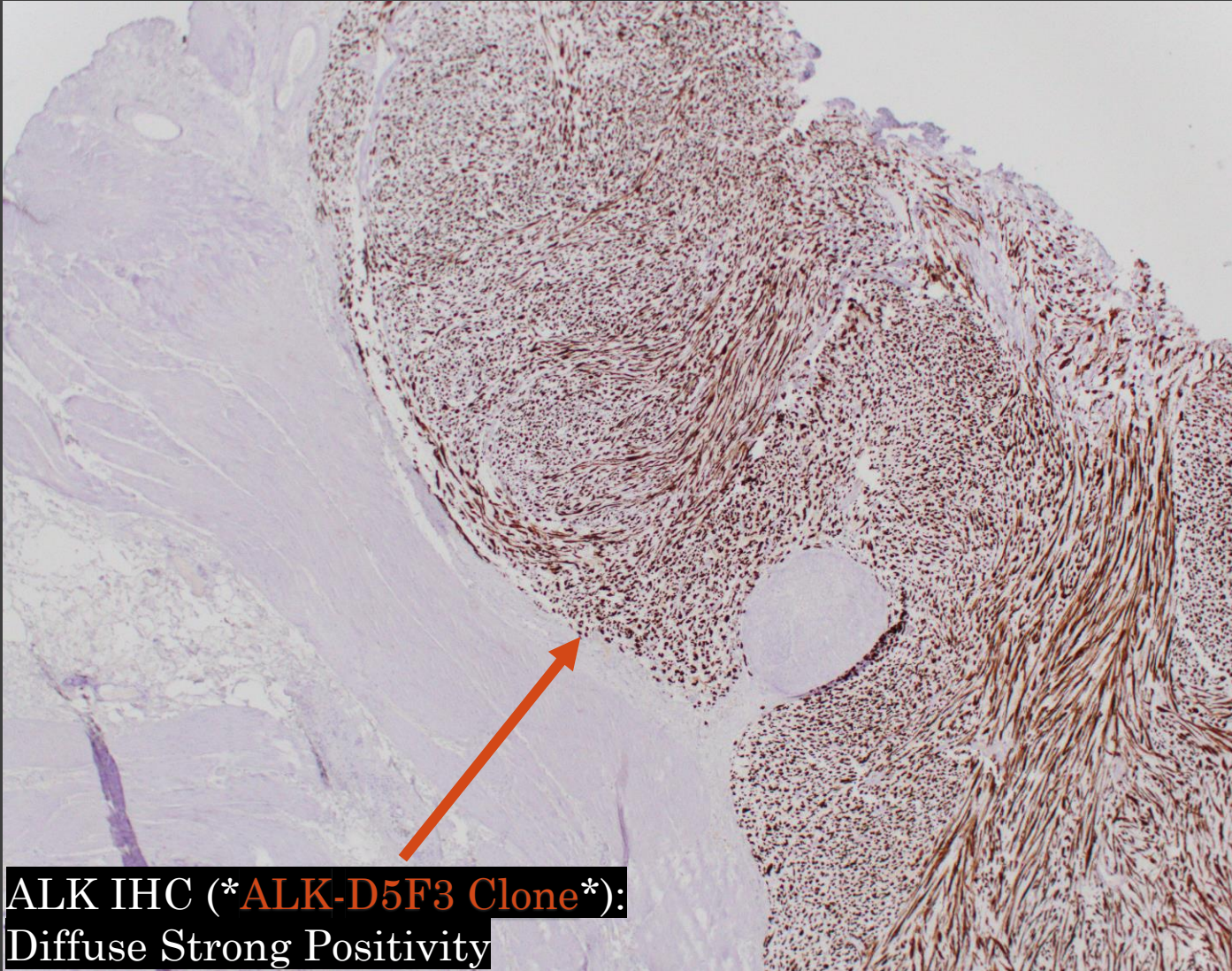
Important Notes About ALK IHC:

- ALK1 IHC – Developed for Anaplastic Large Cell Lymphoma (ALCL).
- Significantly reduced ALK expression in solid tumors compared comparison to ALCL.
- ALK1 IHC – is not recommended for solid tumor analysis.
 - Sensitivity (Lung): 67%
 - Specificity (Lung): 91-99%
- ALK-D5F3 Clone has significantly better sensitivity and is comparable to FISH assays
 - Sensitivity: 97% (FISH = ground truth)
 - Specificity: >99%



ALK IHC (*ALK1 Clone*):
Weakly positive / Equivocal

Case 4 – ALK+ Inflammatory Myofibroblastic Tumor (IMT)



Suspicious/Equivocal ALK IHC



FISH Testing

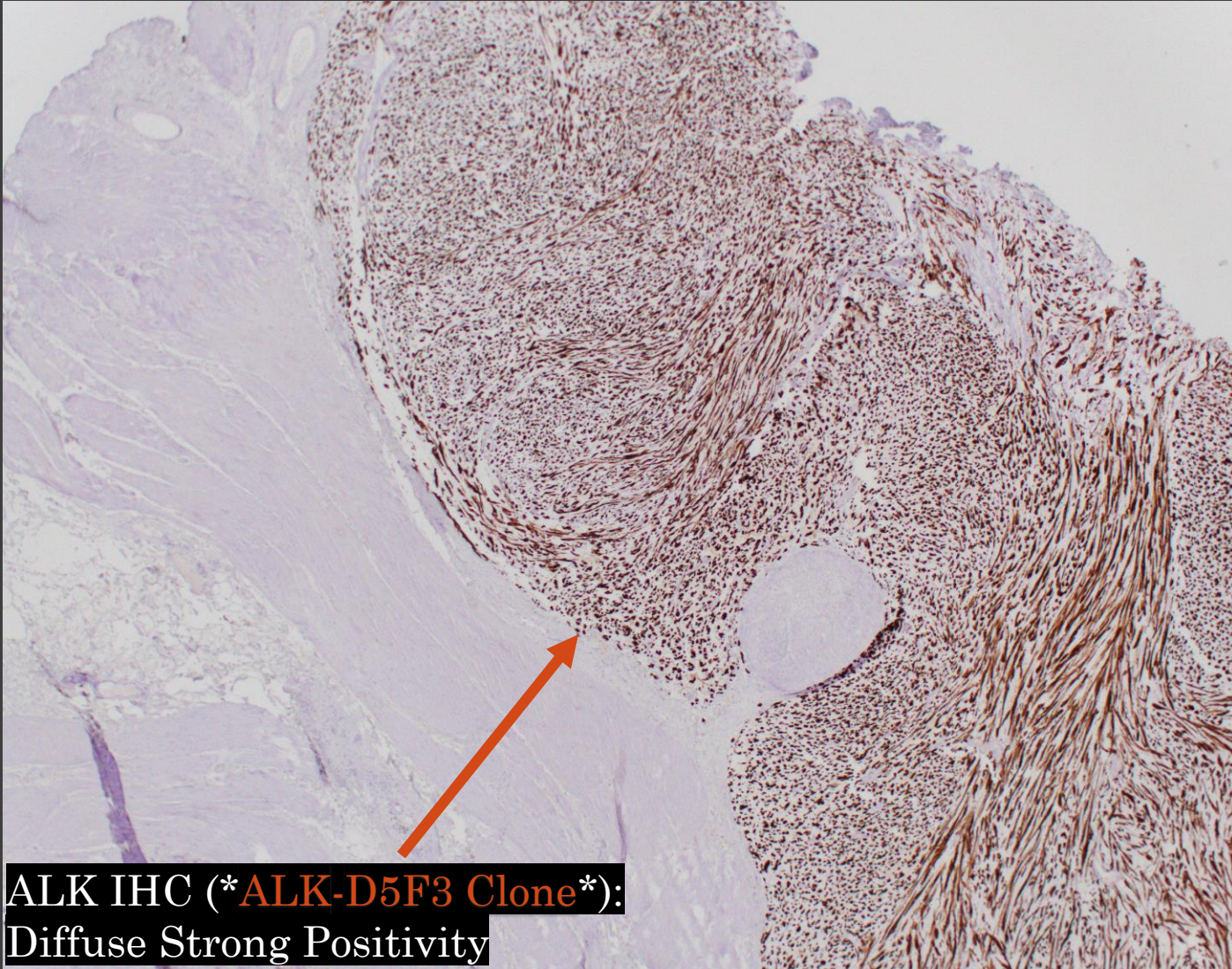
ALK FISH:

Positive for ALK Rearrangement (ABNORMAL)

An Important Note About ALK IHC:

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 - Specificity: >99%

Case 4 – ALK+ Inflammatory Myofibroblastic Tumor (IMT)



- IMT – Mesenchymal (Myofibroblastic) neoplasm with “Intermediate malignant potential”
- Only 40-50% of IMT’s are ALK+
 - Narrows differential when positive.
 - Not contributory when negative.
 - NOT required for diagnosis of IMT if morphology and IHC profile is otherwise fitting

Case 4 – ALK+ IMT

- Omitted History:
 - 2017
 - Endometrial Biopsy: “High-grade sarcoma”
 - Radical Hysterectomy and BSO: “High-grade Spindle Cell Sarcoma”
 - Docetaxel/gemcitabine
 - 2019
 - Imaging and Pathology Confirmation – “Recurrent Spindle Cell Sarcoma”
 - + Pelvic XRT
 - 2020
 - Mass growing through XRT
 - TURBT ALK+ IMT
 - Patient prescribed oral Alectinib (ALK inhibitor) BID
 - Current
 - Disease free without recurrence (daily maintenance Alectinib).

Case 4 – Inflammatory Myofibroblastic Tumor (ALK+)

Case 4 Take Home Points

IMT should always be in differential for spindle cell tumors in the bladder (and throughout the pelvis)

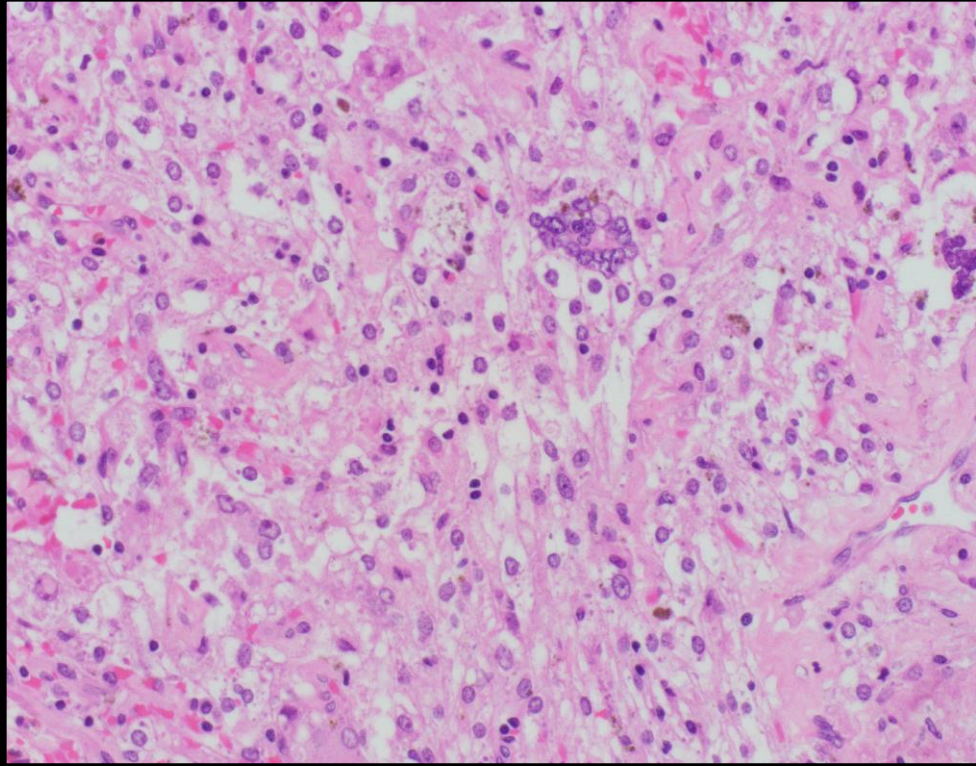
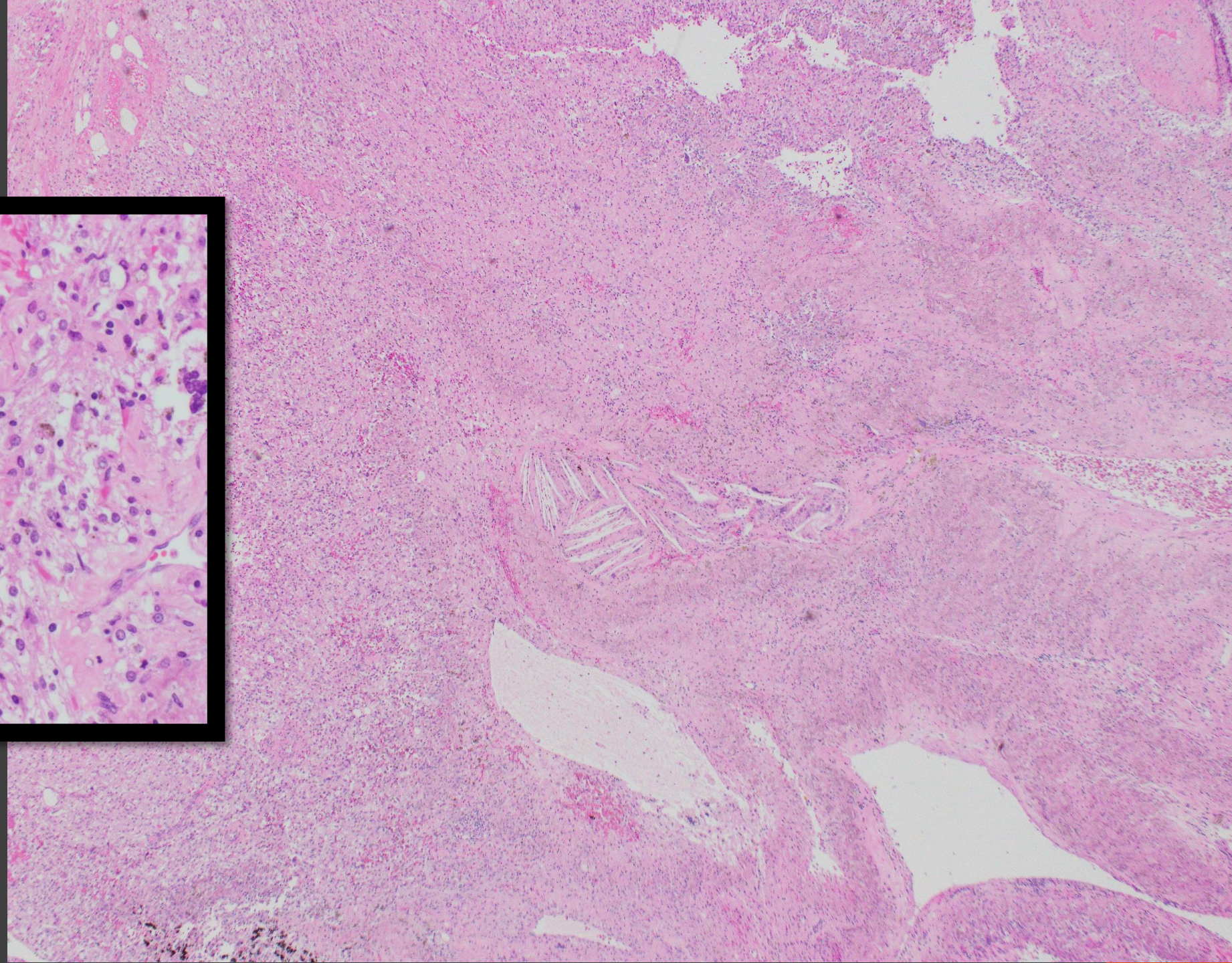
IMT's are ALK+ in only 40-50% of cases.

ALK D5F3 clone is markedly superior to ALK1 clone for solid tumor testing of ALK status by IHC.

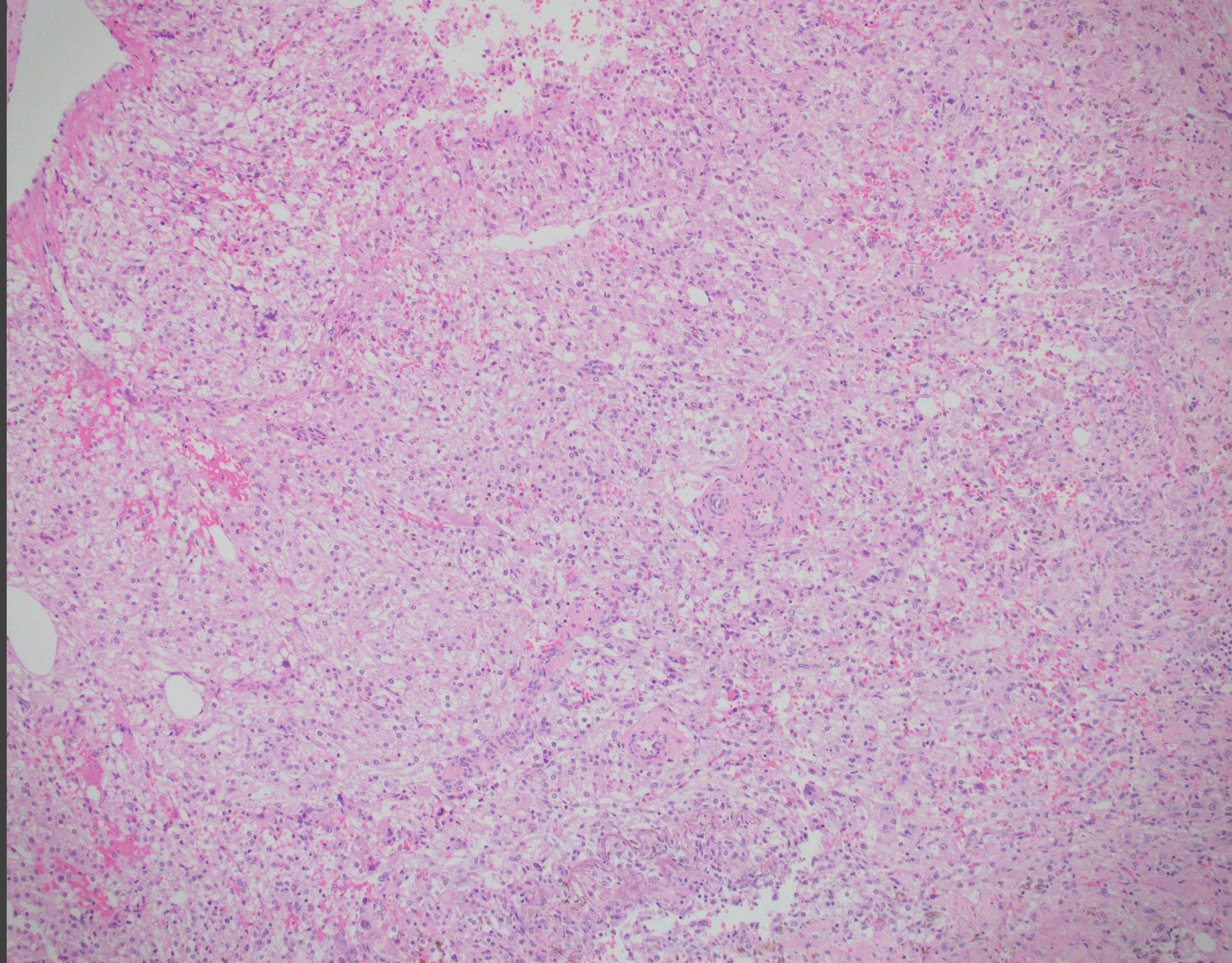
Case 5

- 59F, Current Smoker, Cirrhotic.
- Recently: 5.0 cm Cecal Polypectomy
 - Cecum: Invasive Adenocarcinoma, Moderately Differentiated, Invading Submucosa (pT1).
- Imaging: Incidental 3.7 cm left kidney mass found on workup for new colon cancer diagnosis.
- Surgery:
 - Hemicolectomy
 - Partial Nephrectomy

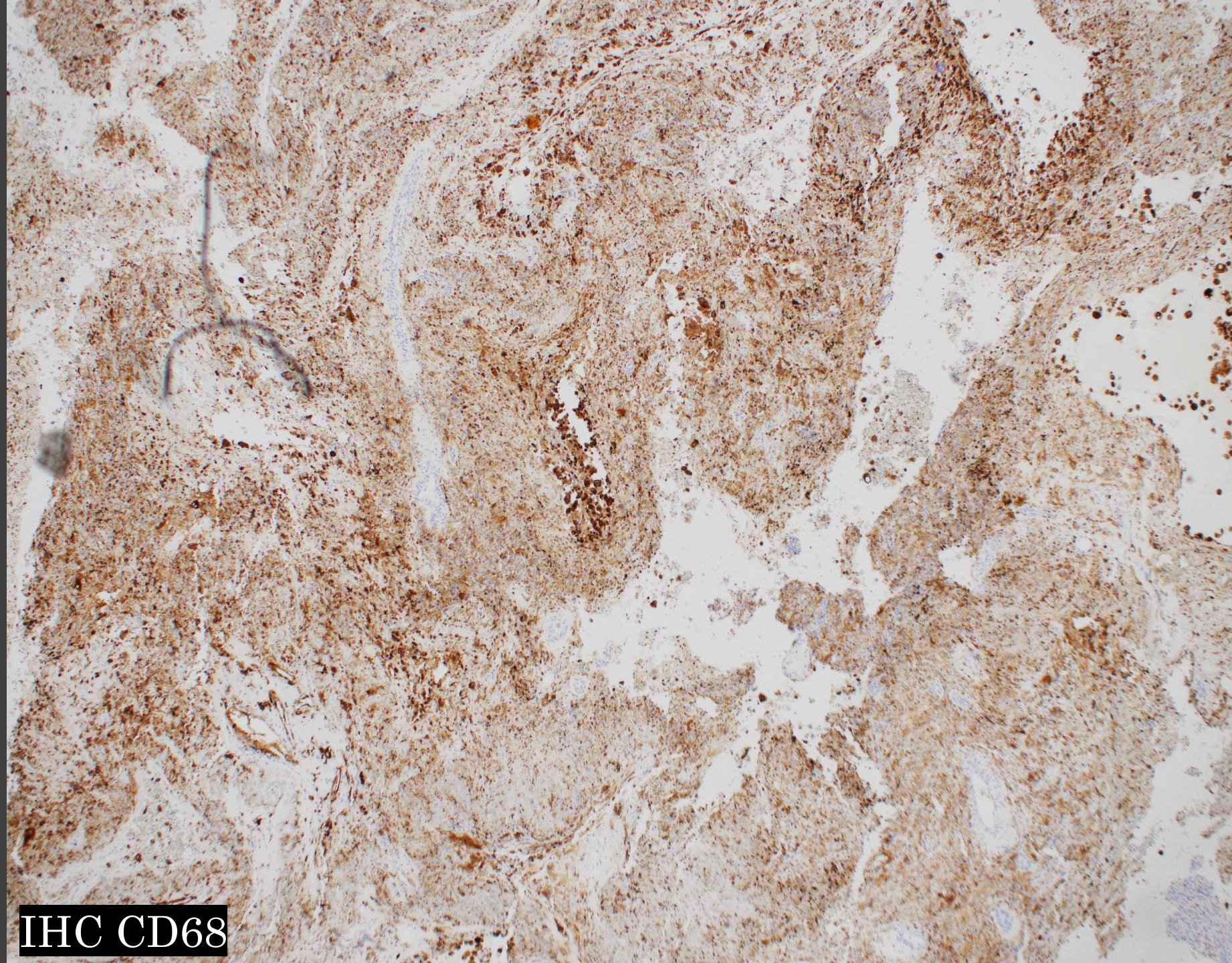
Case 5



Case 5



Case 5

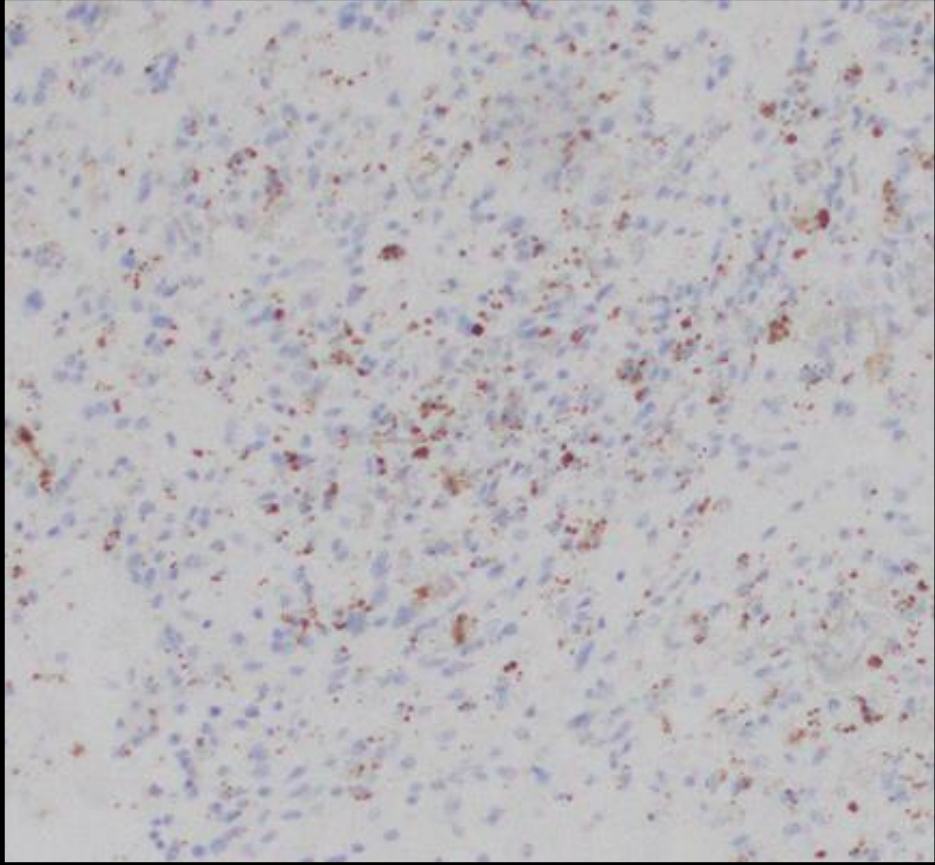
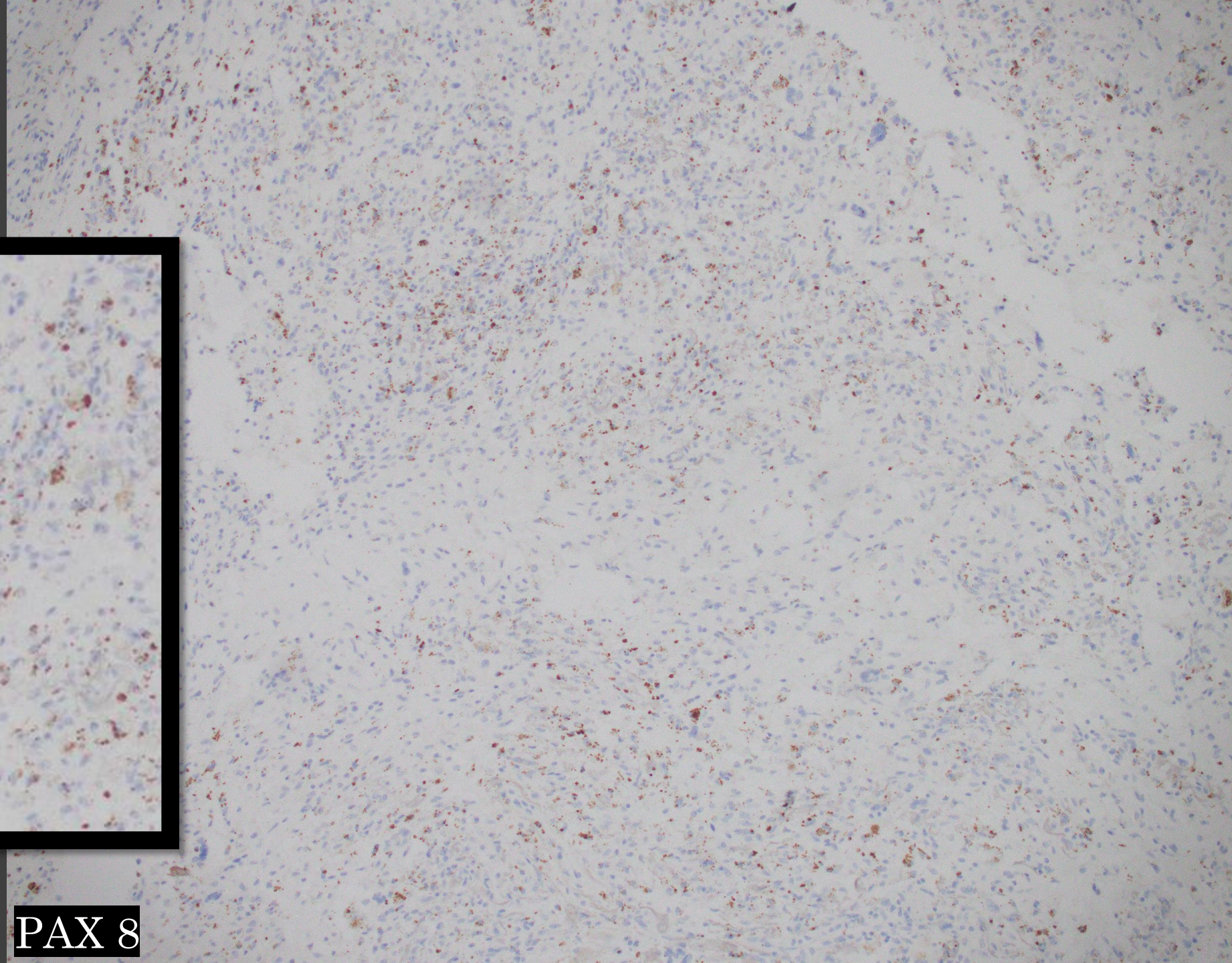


IHC CD68

Case 5

CA-IX

Case 5



PAX 8

Case 5

Nephrectomy: Expansile histiocytic inflammation, compatible with xanthogranulomatous pyelonephritis.

- Sheets of foamy histiocytes with parenchymal replacement
- F>M (2:1) – Related to UTI (E. Coli, Proteus, among others)
- Frequent associated renal calculi - may serve as nidus for infection or calyceal injury

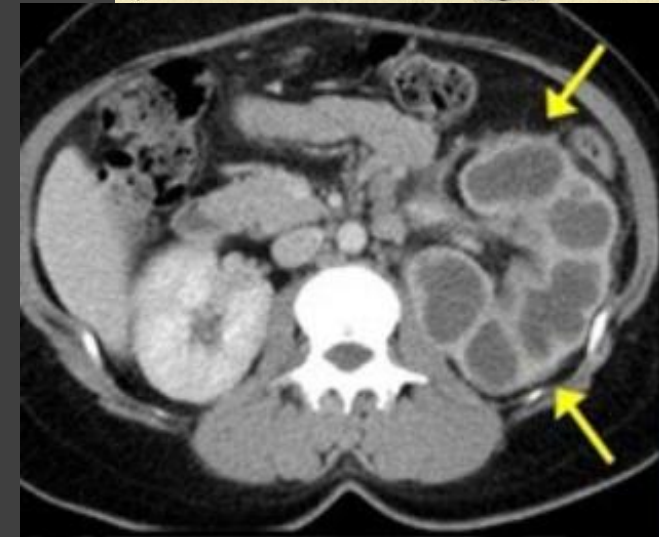
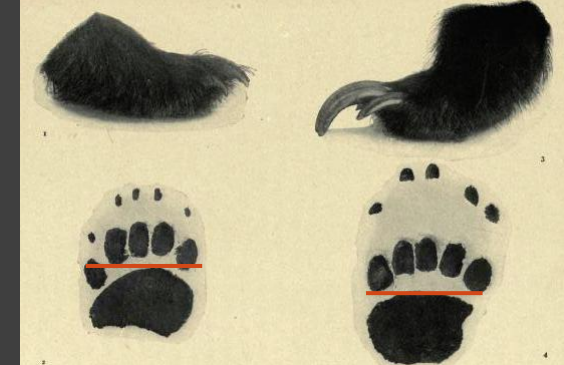
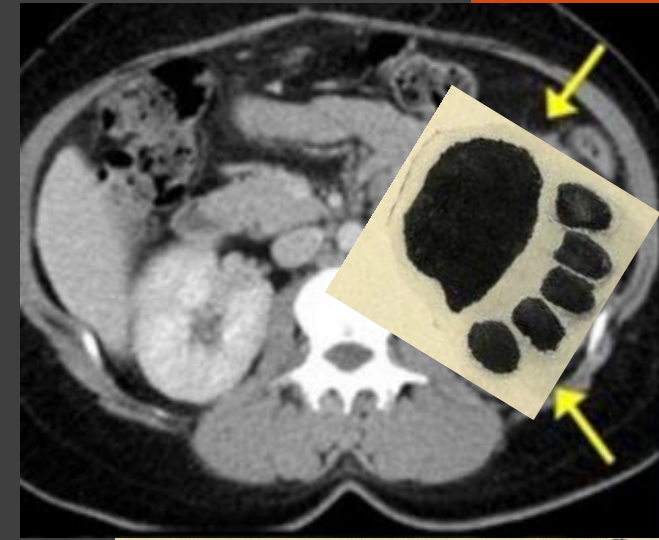
Case 5

Nephrectomy: Expansile histiocytic inflammation, compatible with xanthogranulomatous pyelonephritis.

Tumor Board Imaging Review:
Radiologist: “Not at all compatible with XGP”

Radiologic Findings in XGP

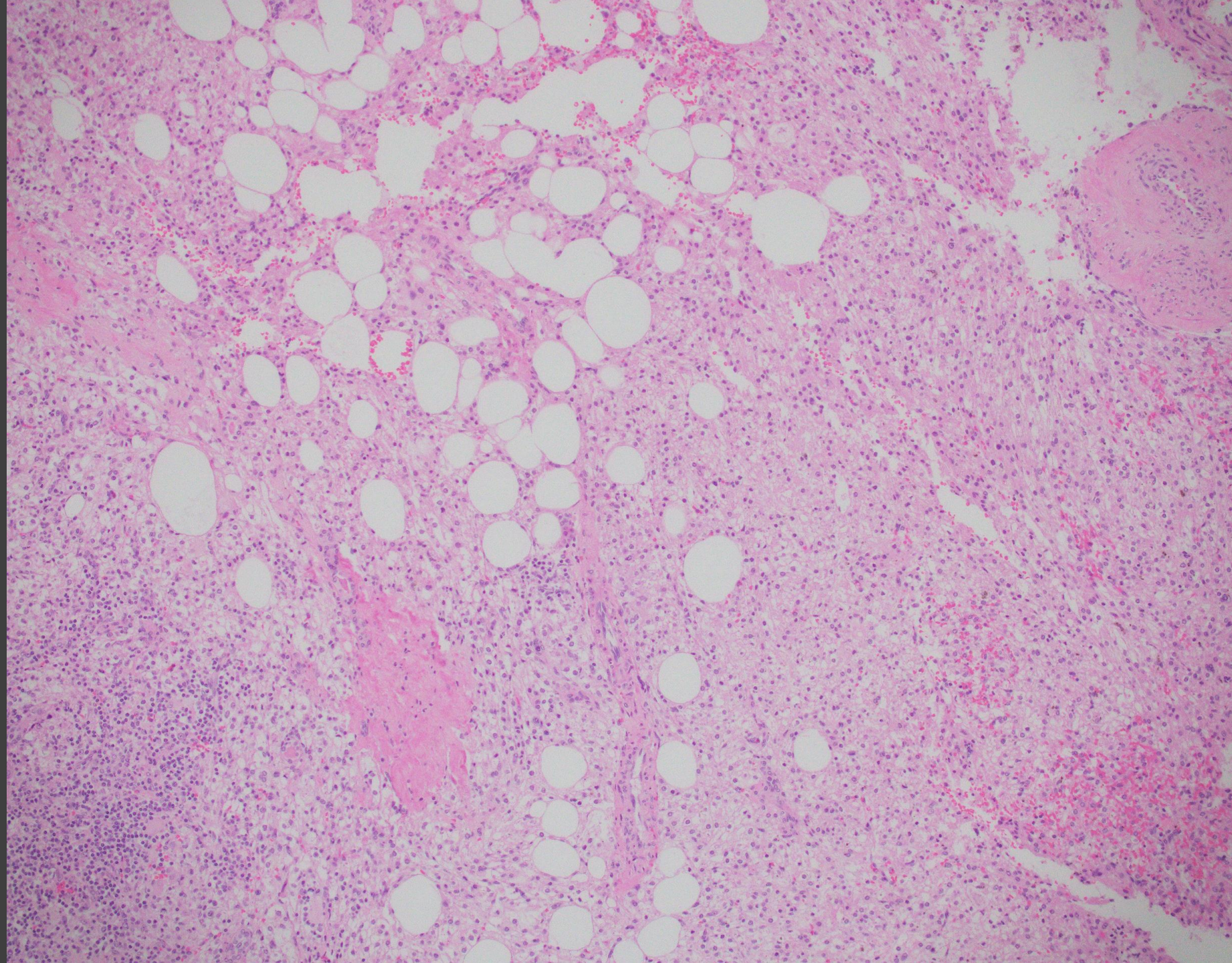
- Lost renal outline with perinephric fat stranding
- “Bear paw sign” – dilated calyces



Case 5

Re-review:

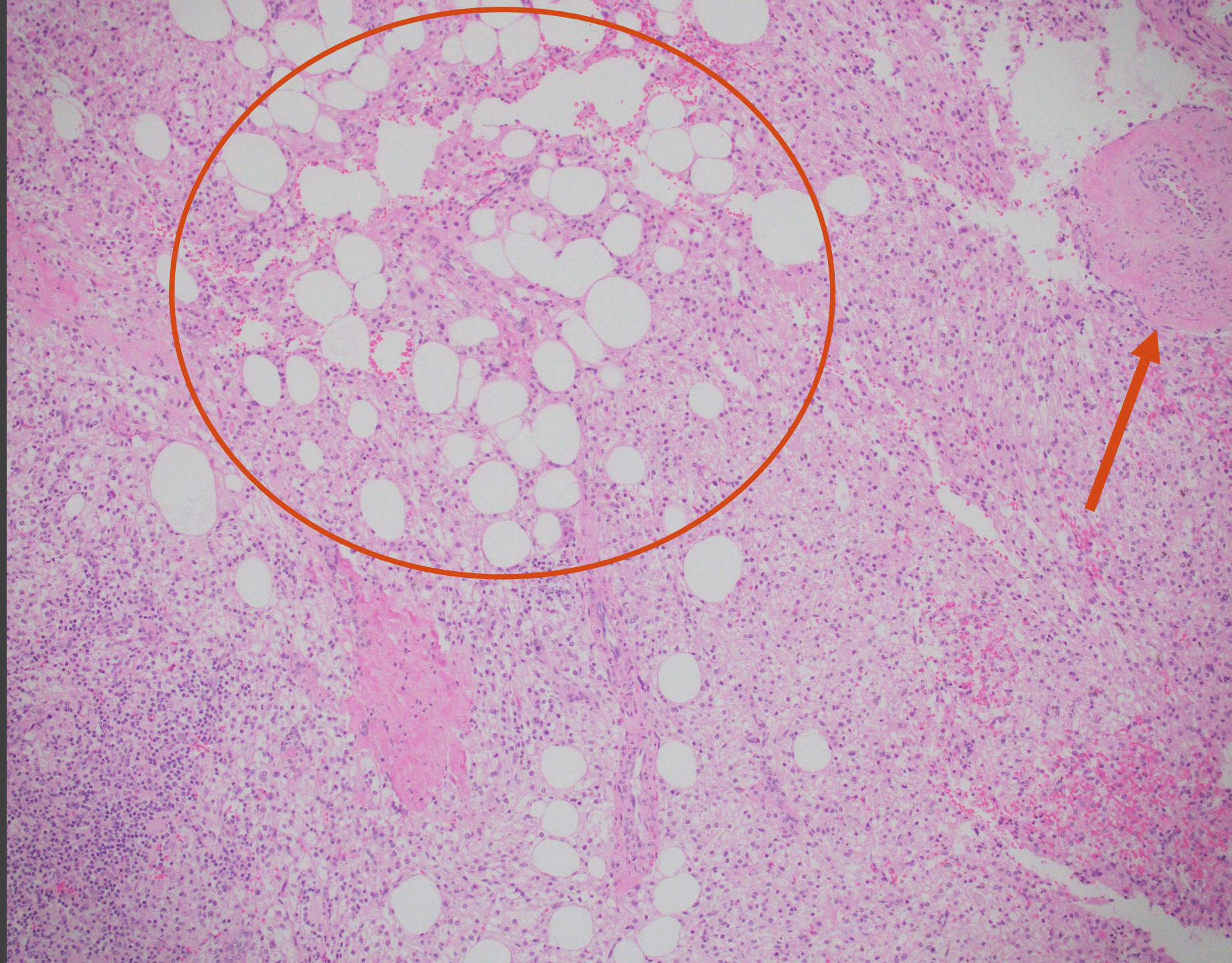
Diagnostic focus
found

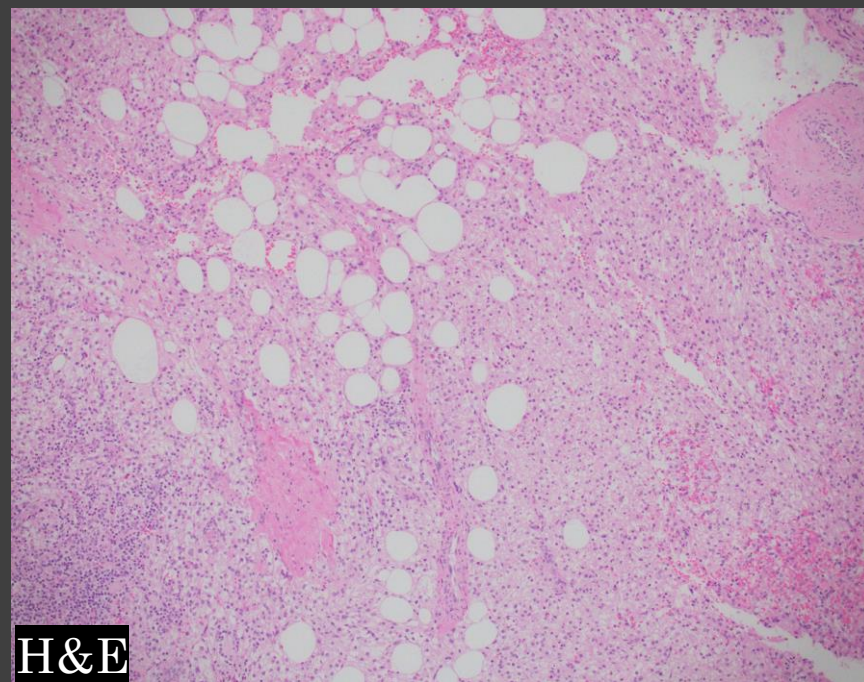
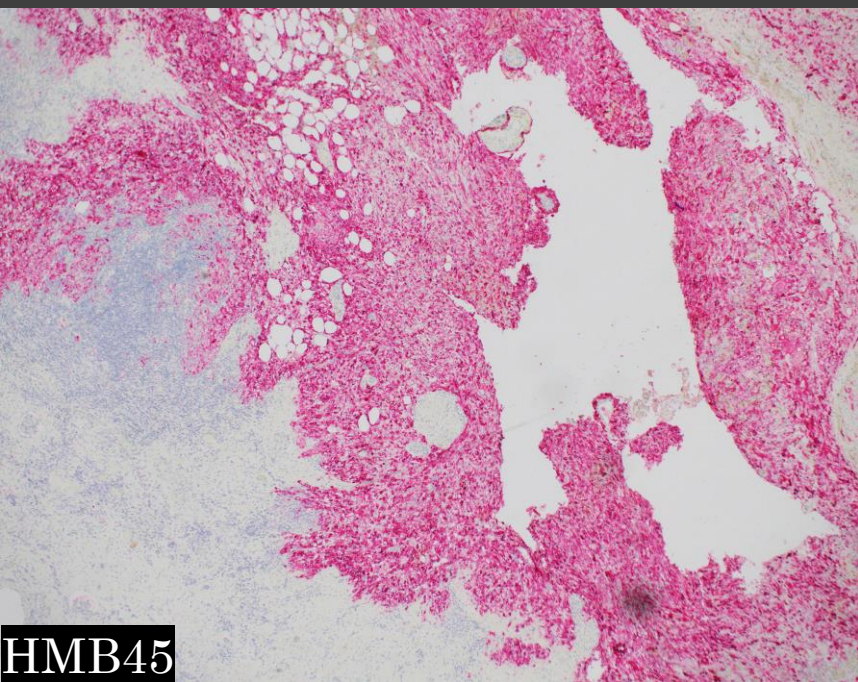
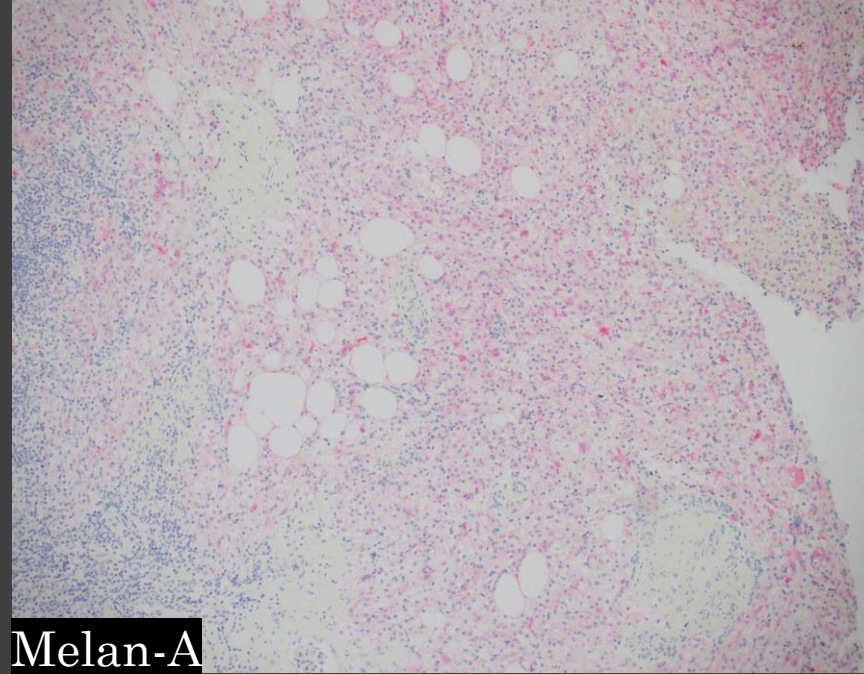
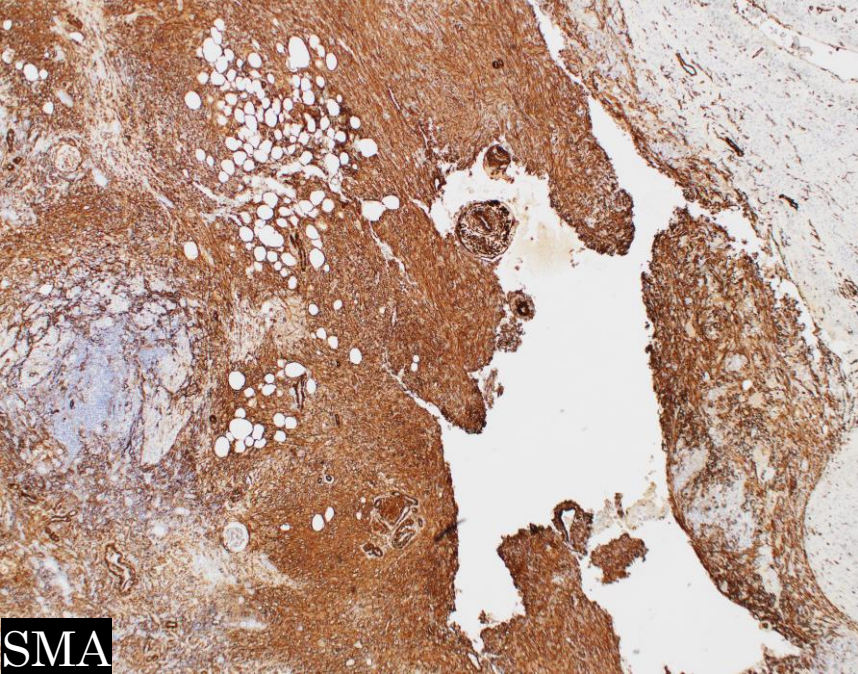


Case 5

Re-review:

- Intra-renal fat
- Thick-walled vessel with spiral-form “cart-wheel like” appearance
- Background of expansile histiocytic inflammation





Case 5

Corrected Diagnosis

Nephrectomy: Angiomyolipoma with expansile histiocytic inflammation, suggestive of prior hemorrhage.

Angiomyolipoma

WHO:

- Most frequent complication of AML – Hemorrhage
- XPG may be confused for previously hemorrhagic tumors of any type
- Tumor may be completely obscured in extreme cases.

Case 5 – Angiomyolipoma with hemorrhage masquerading as XPG

Case 5

Take Home Points

XPG has classic clinical and radiologic findings (infection, fat stranding, “bear paw sign”)

Angiomyolipoma is a benign tumor prone to hemorrhage.

Severe hemorrhage in any renal tumor may mimic XPG.

Sources

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Questions?

