



Occasional and Rare Lesions of the Urinary Tract

Park City AP Annual Update

February 2023

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Disclosures

- None

Objectives:

Describe and Recognize occasional and uncommon primary and secondary lesions of the urinary tract (urethra, bladder, ureter)

Selected use of ancillary testing in the workup of unusual morphologic features

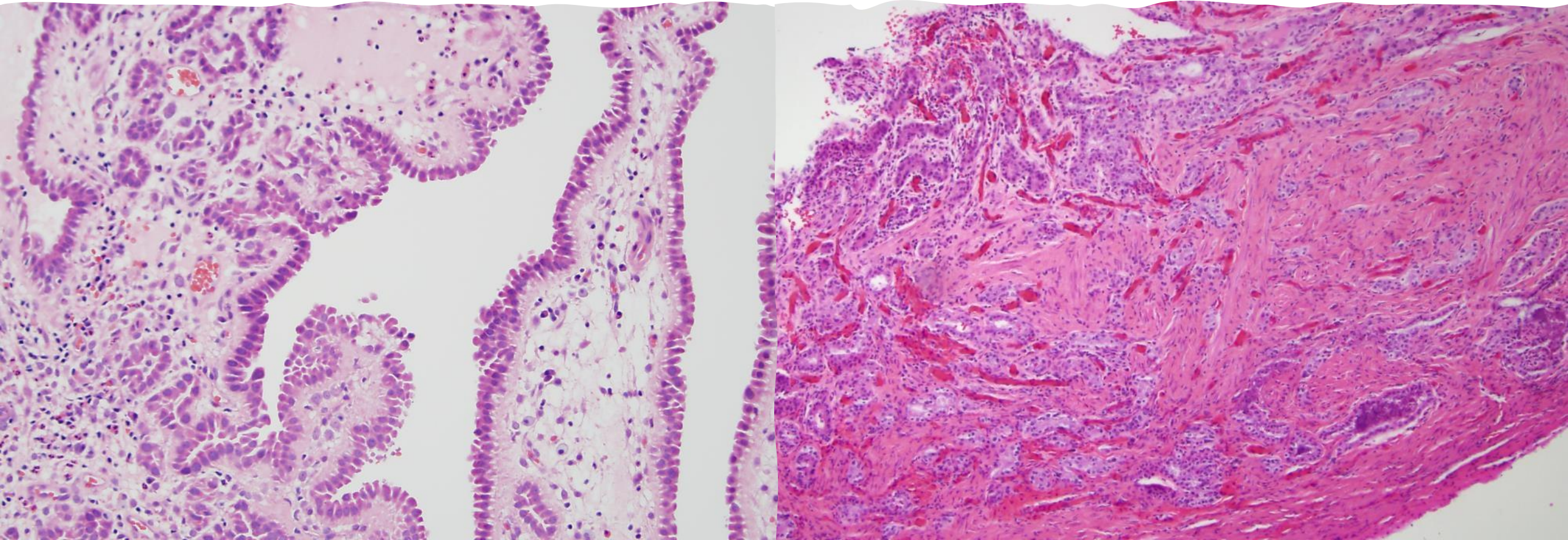
Gland forming

Epithelioid / poorly differentiated

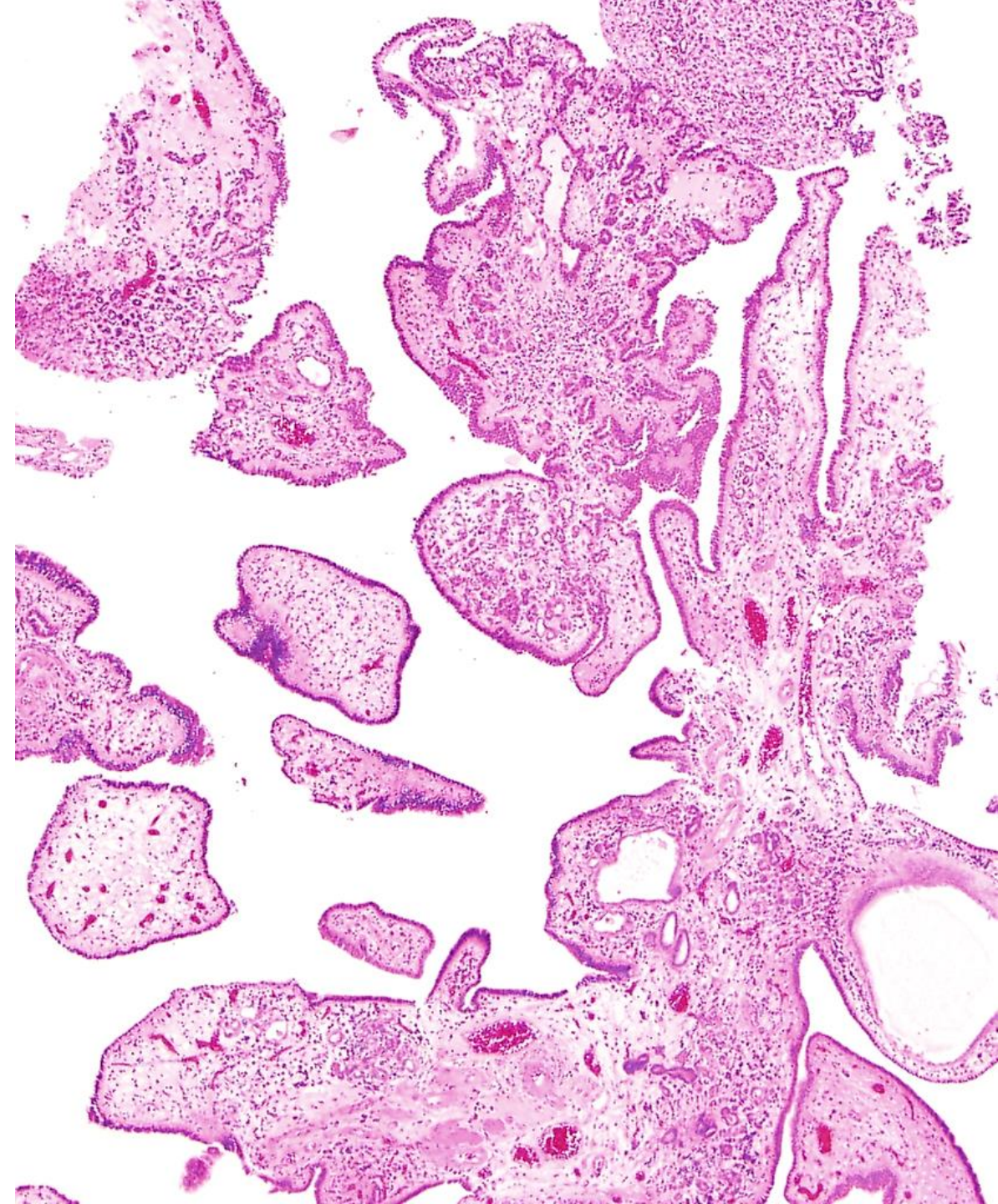
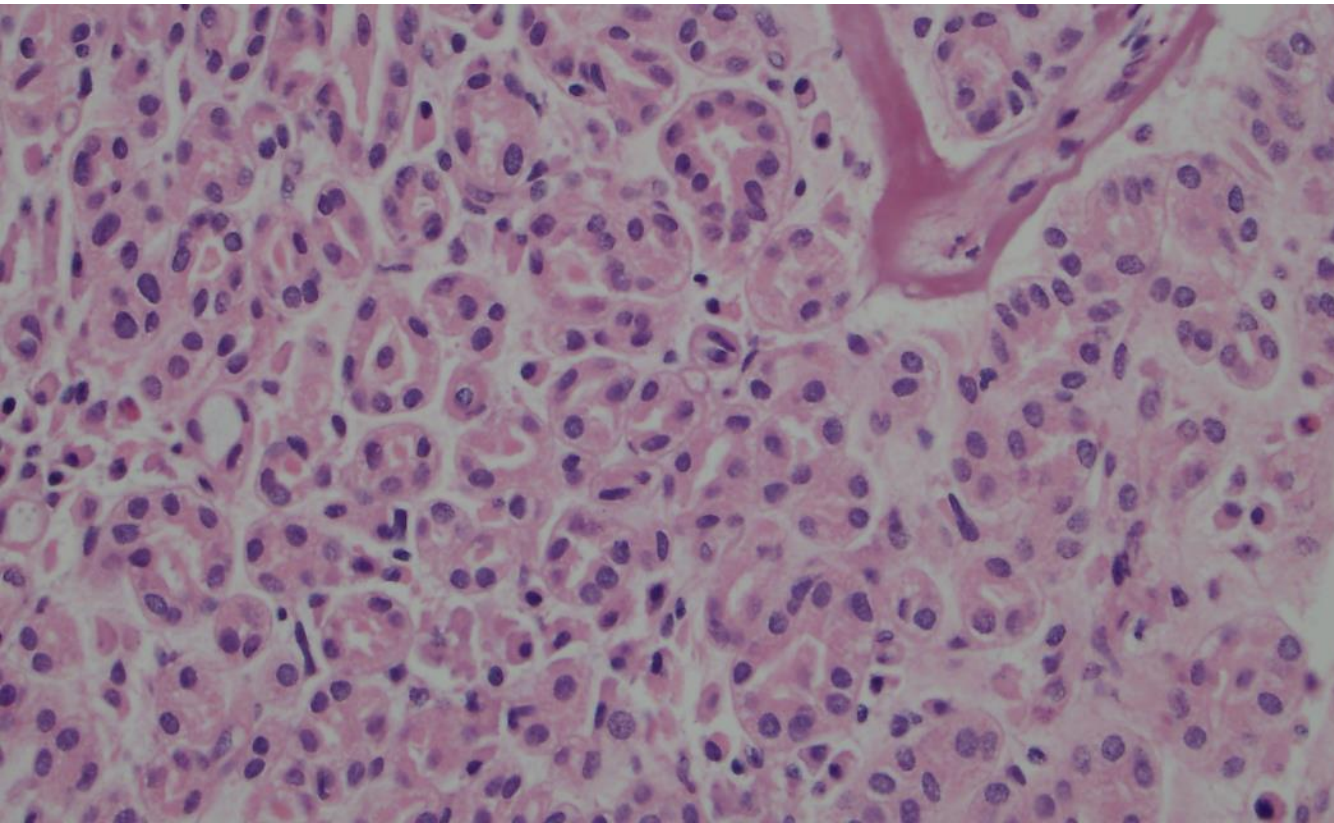
Mesenchymal

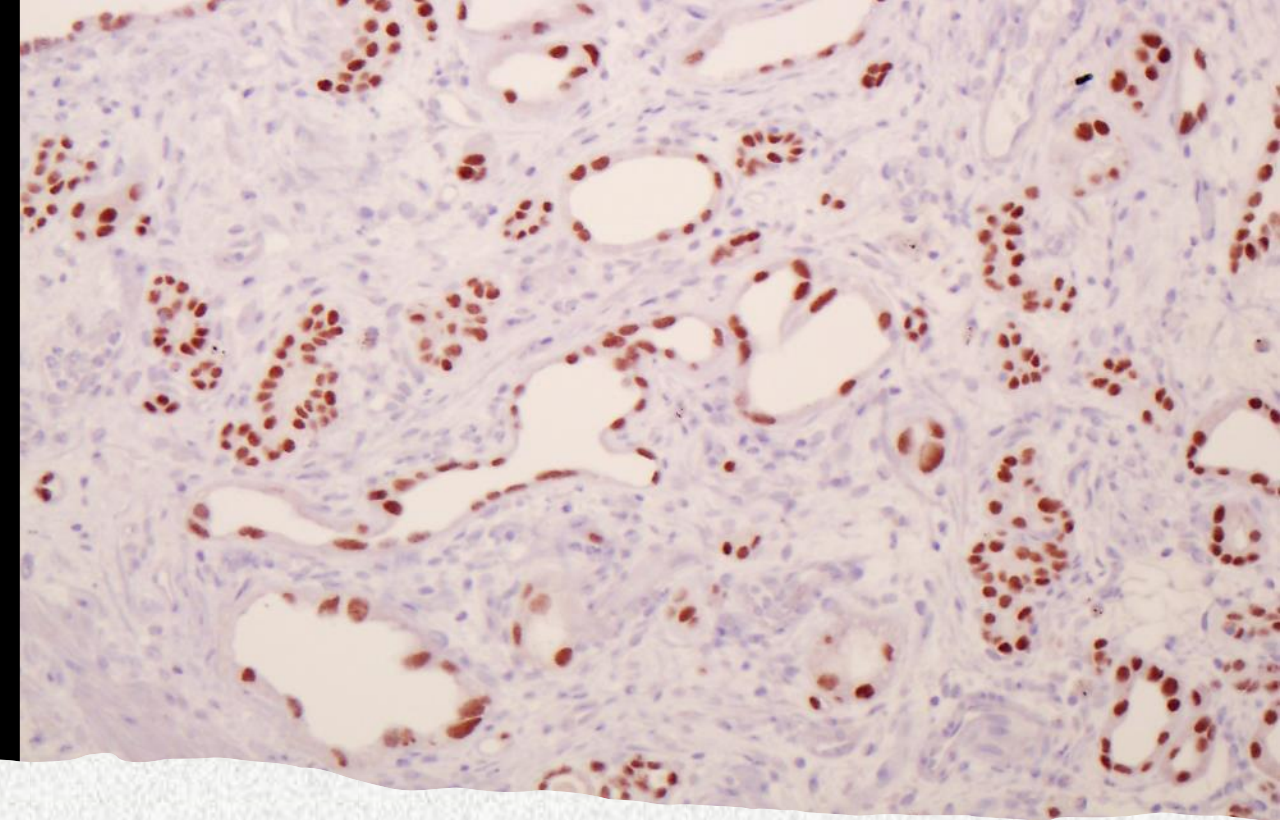
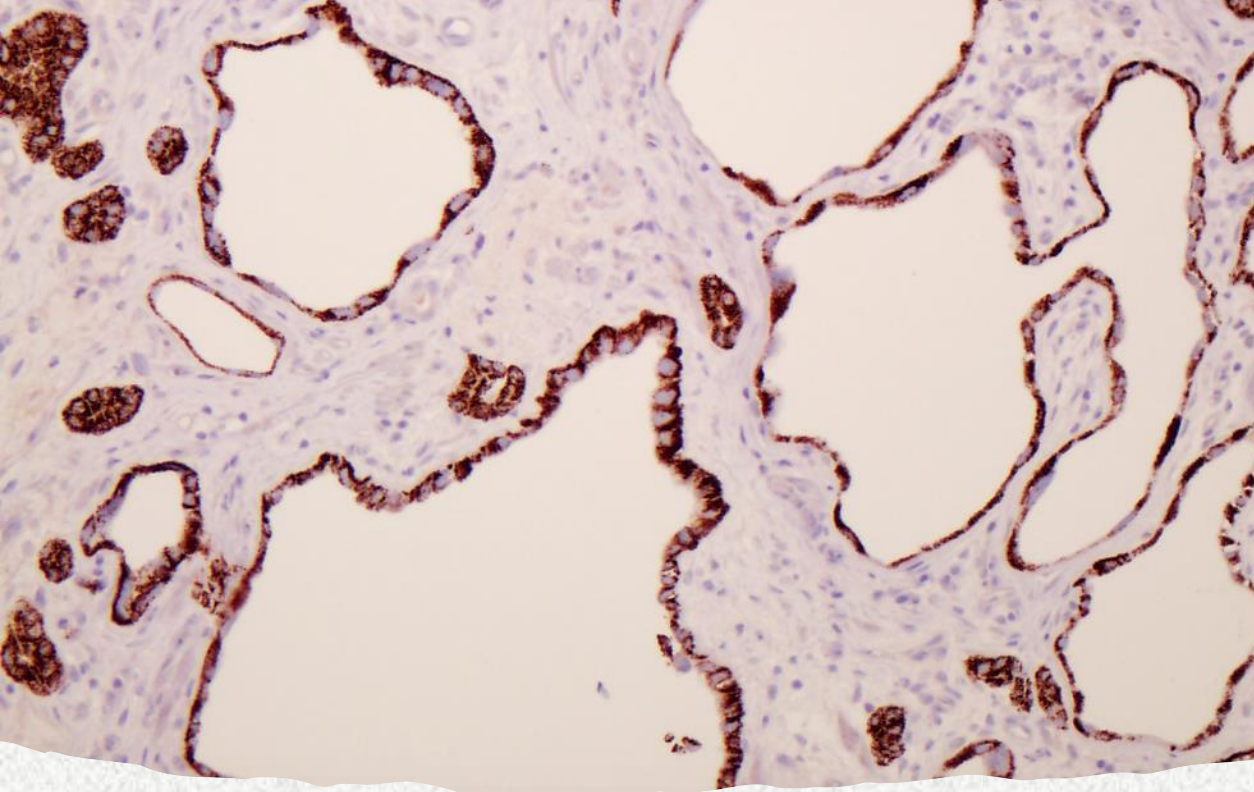
Bonus Cases

- 43-year-old female recurrent UTI's
- 38-year-old female renal transplant



- 62 year old man with BPH and bladder stones





P504s and pax8

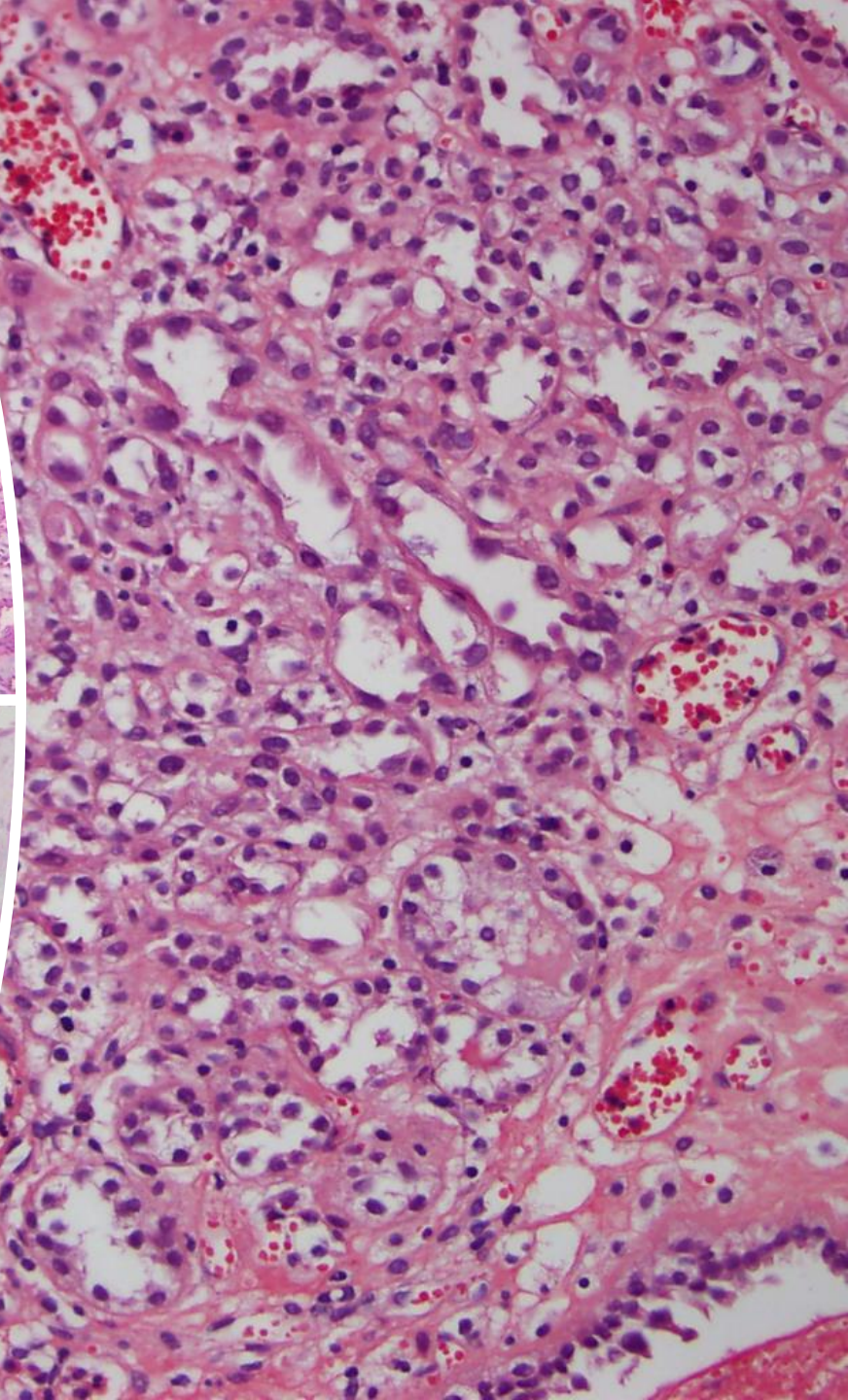
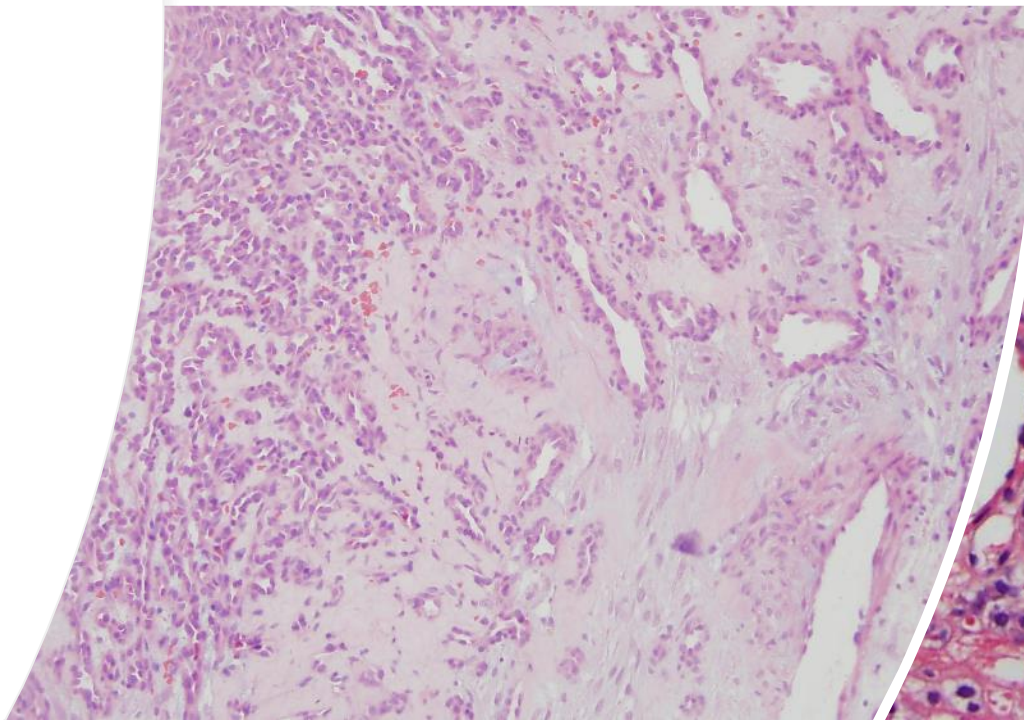
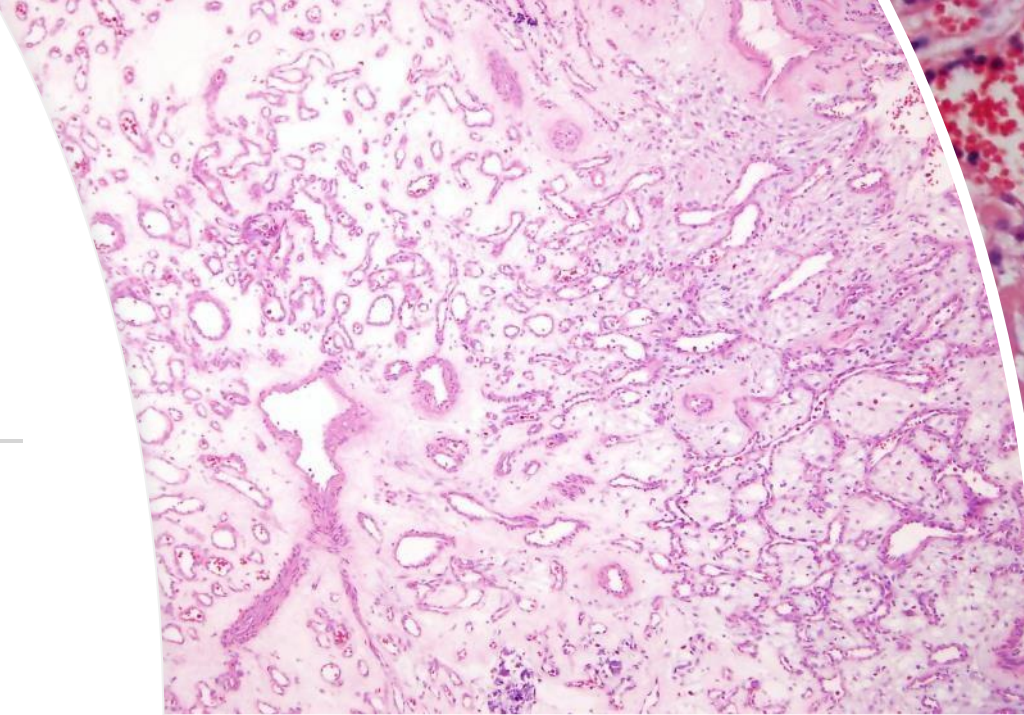
- Nephrogenic Adenoma / Metaplasia
- Some may express PSA/PAP (focal) or GATA3
- Napsin-A usually positive (may be negative in fibromyxoid variant)

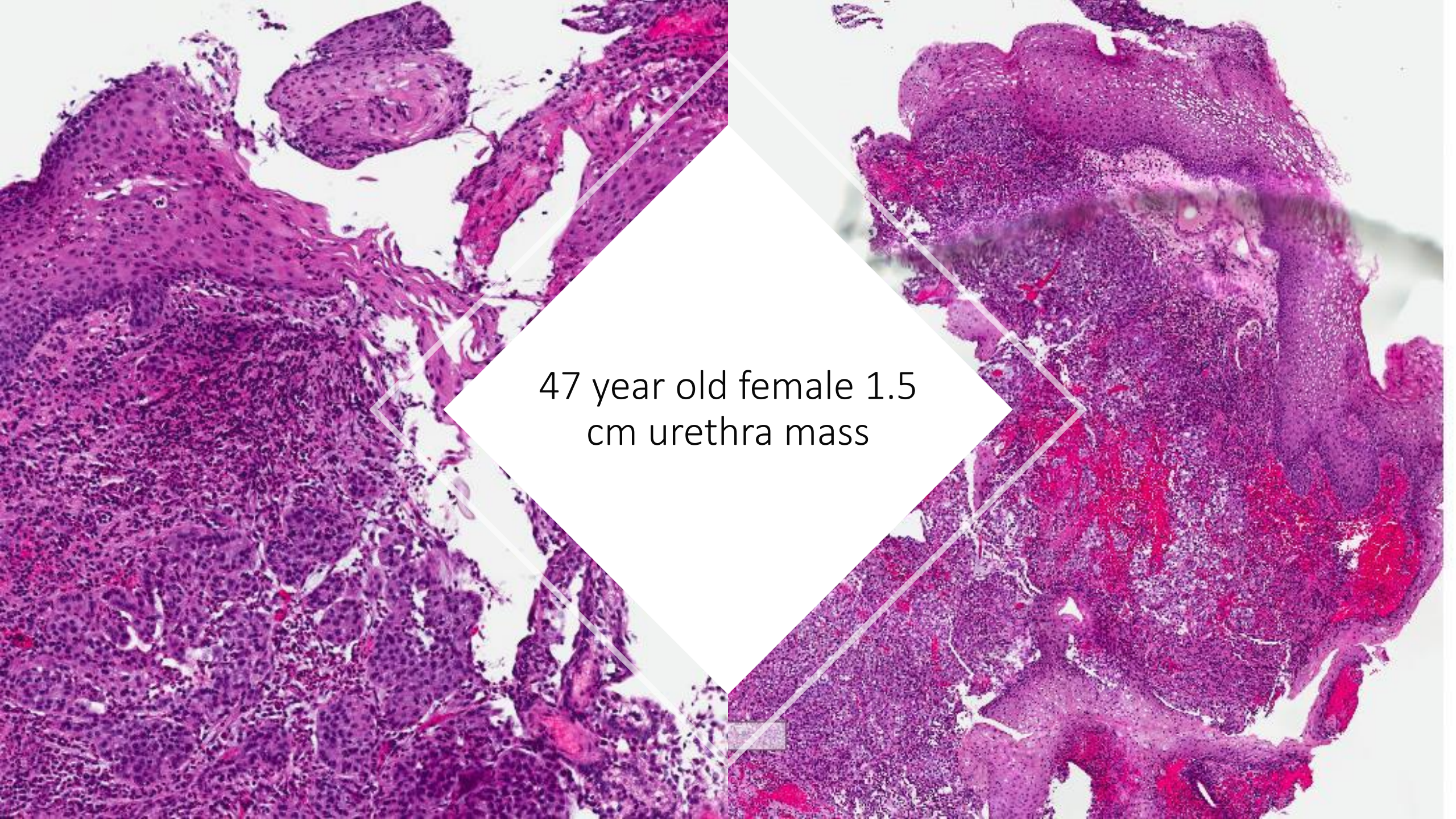
Sharifai N et al. Napsin A is a highly sensitive marker for nephrogenic adenoma: an immunohistochemical study with a specificity test in genitourinary tumors. *Hum Pathol.* 2020

Li L et al. Fibromyxoid Nephrogenic Adenoma: A Series of 43 Cases Reassessing Predisposing Conditions, Clinical Presentation, and Morphology. *Am J Surg Pathol.* 2023 Jan

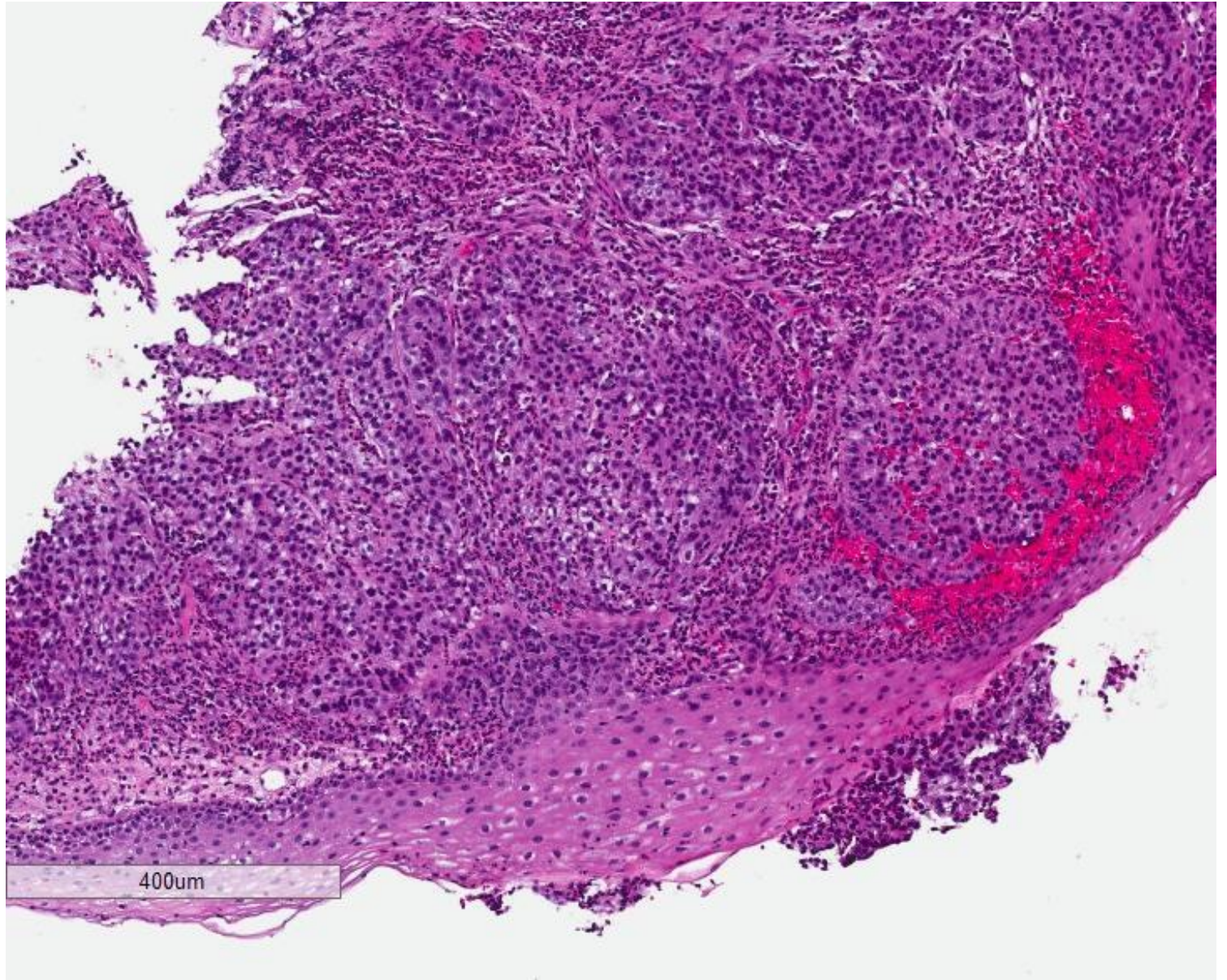
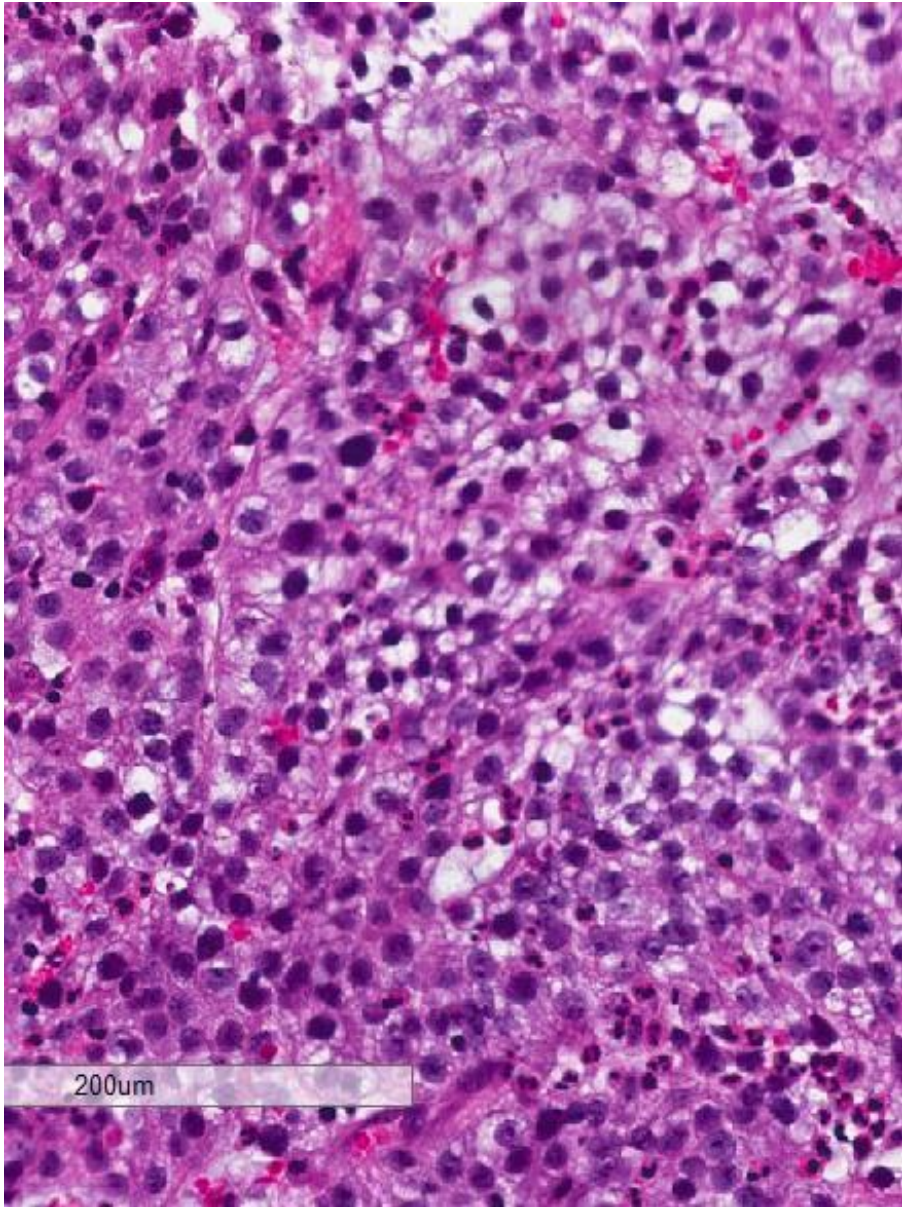
Differential Diagnosis

- Urothelial carcinoma w/ papillary architecture or CIS, glandular differentiation, tubular or microcystic pattern
- Prostatic adenocarcinoma
- Clear cell adenocarcinoma of urinary tract
 - May have very “bland” appearing cells and evaluation of muscularis is needed.



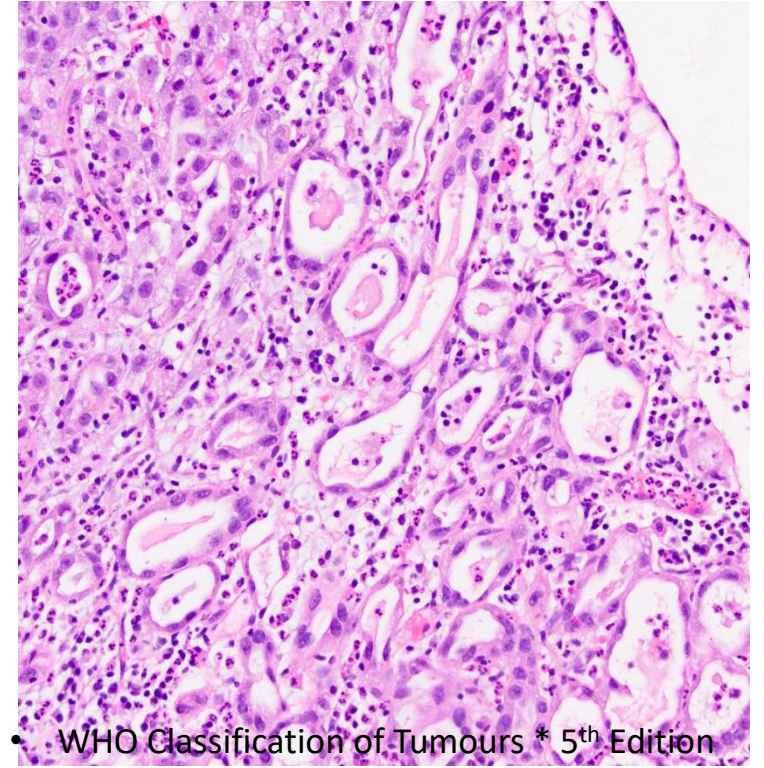
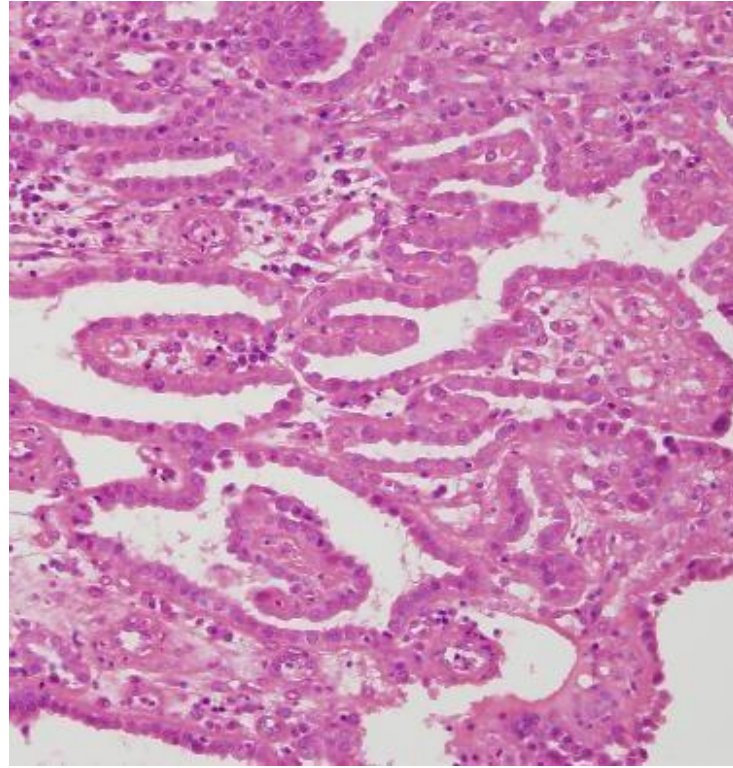
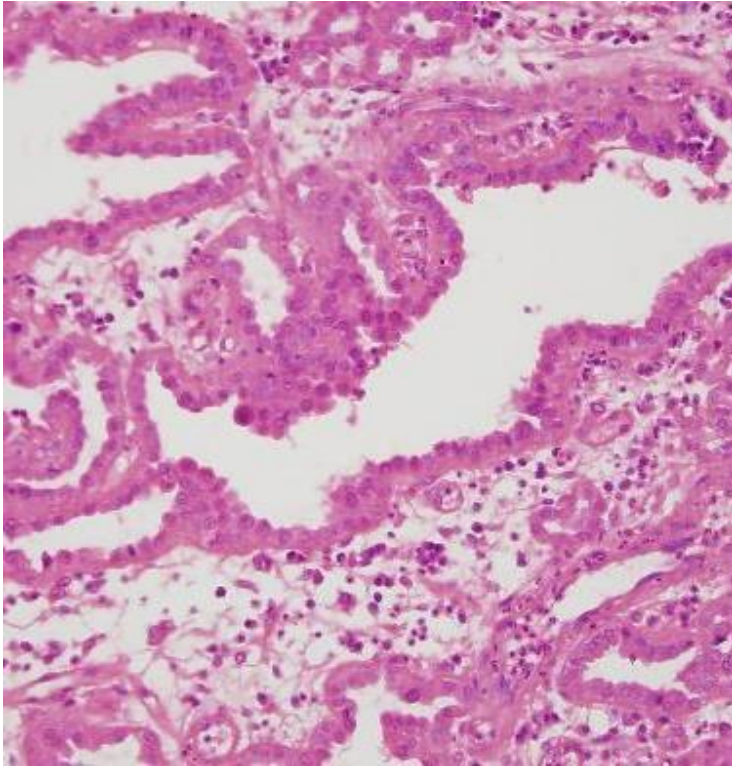


47 year old female 1.5
cm urethra mass



Differential Diagnosis

- Broad differential
 - Urothelial carcinoma with clear cell features
 - Metastatic renal cell carcinoma
 - Clear cell adenocarcinoma
 - Primary urinary tract
 - Secondary gynecologic tract
- Initial IHC workup:
 - Positive: Pax8, GATA3, CK20, CD10, CK7
 - Negative: Uroplakin II, p63, RCC
- **Diagnosis: Clear Cell Adenocarcinoma**



• WHO Classification of Tumours * 5th Edition

Clear Cell Adenocarcinoma with Nephrogenic Adenoma Like Features

- * Architecture is variable and may be papillary, tubulopapillary, cystic or microcystic, nested or solid
- * Hobnail, attenuated, or cuboidal cells with eosinophilic to clear cytoplasm

Clear Cell Adenocarcinoma of the Urinary Tract

- Urethra most common location followed by bladder
- Predominance in females (1:4)
- Essential in biopsy or TURBT to examine muscularis propria b/c of significant morphologic overlap
- Clear cell adenocarcinoma arising in urothelial carcinoma can occur
- Most often PAX8, CK7 p504s, HNF1-beta, and Napsin-A (+)
 - **GATA3 variable**
 - (-)p63, ER, PR, 34betaE12
 - Limited sequencing data: ARID1a, KRAS, PIK3CA, TP53

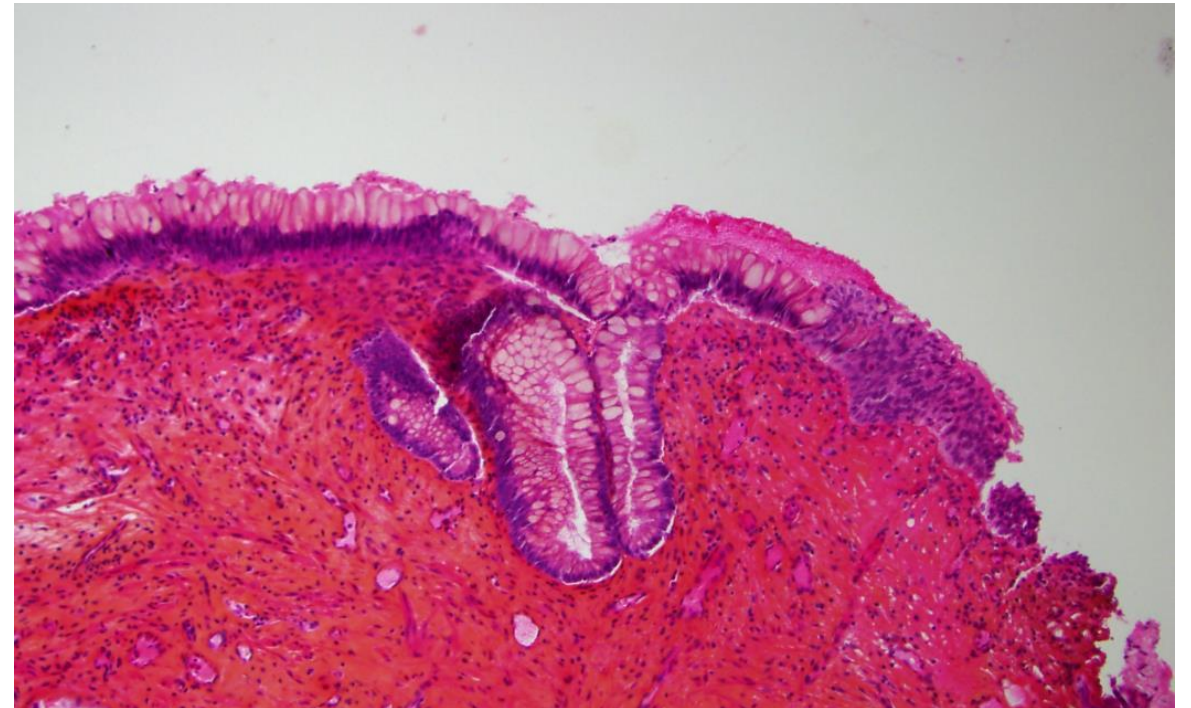
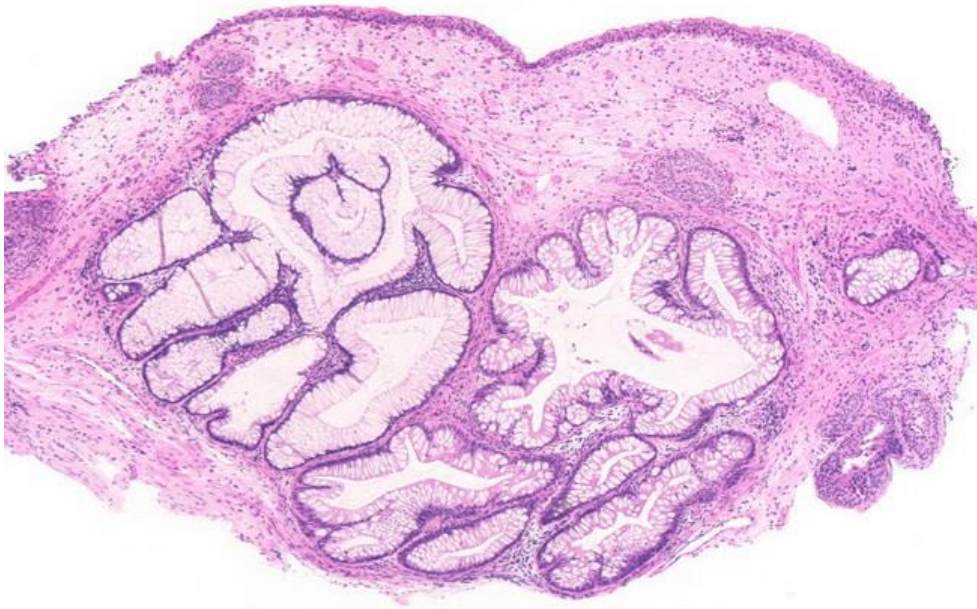
• Akgul M et al. GATA3 expression in clear cell adenocarcinoma of the lower urinary tract: a potential diagnostic pitfall. *Diagn Pathol.* 2022

• Lin CY et al. Molecular profiling of clear cell adenocarcinoma of the urinary tract. *Virchows Arch.* 2019

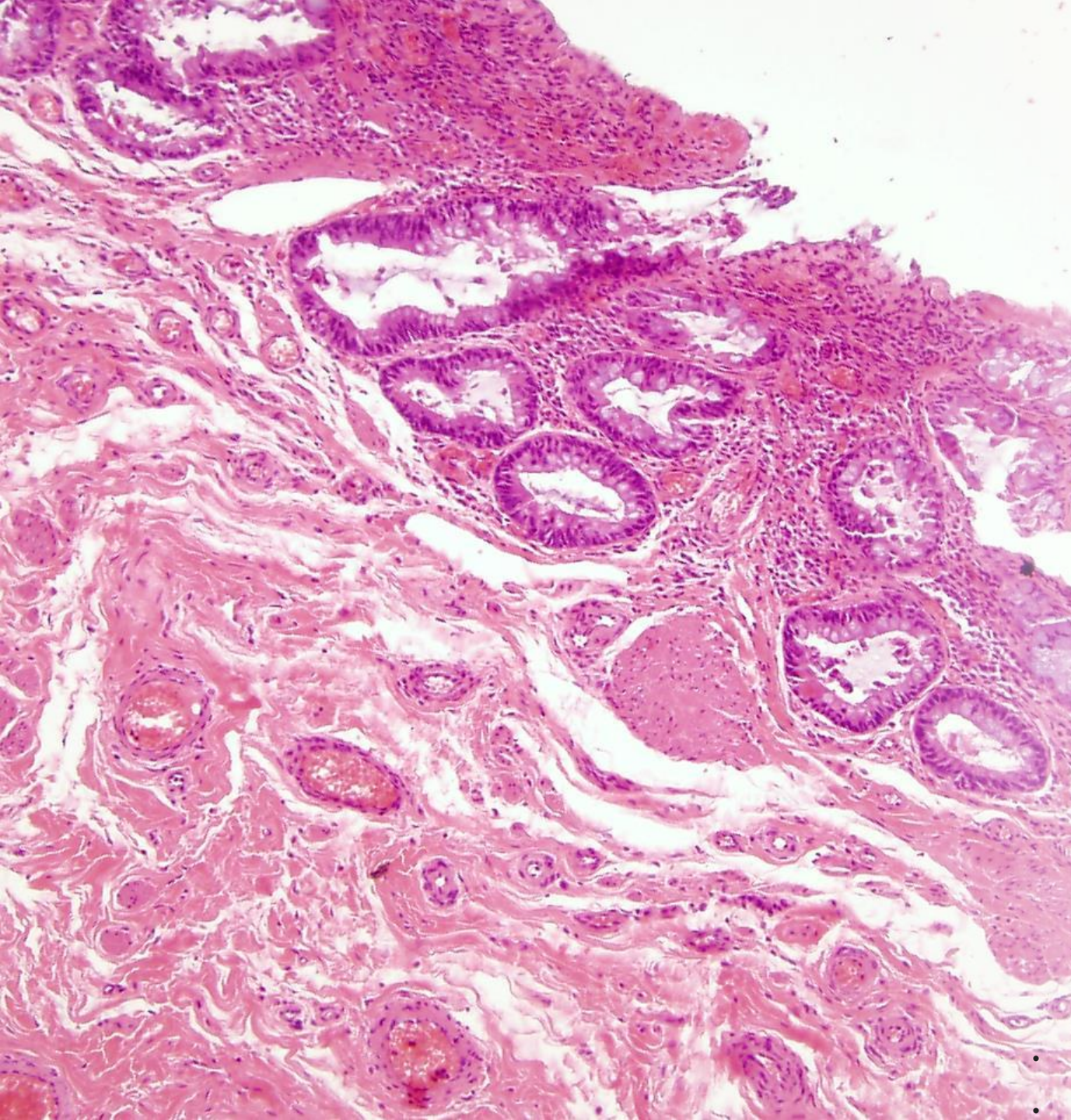
Intestinal metaplasia / Cystitis glandularis

- Intestinal metaplasia and cystitis glandularis are relatively common findings in AP urinary tract specimens
- Continued ongoing debate if/when intestinal metaplasia is associated with risk for malignant transformation - as a general rule incidental IM confers no significant increased risk

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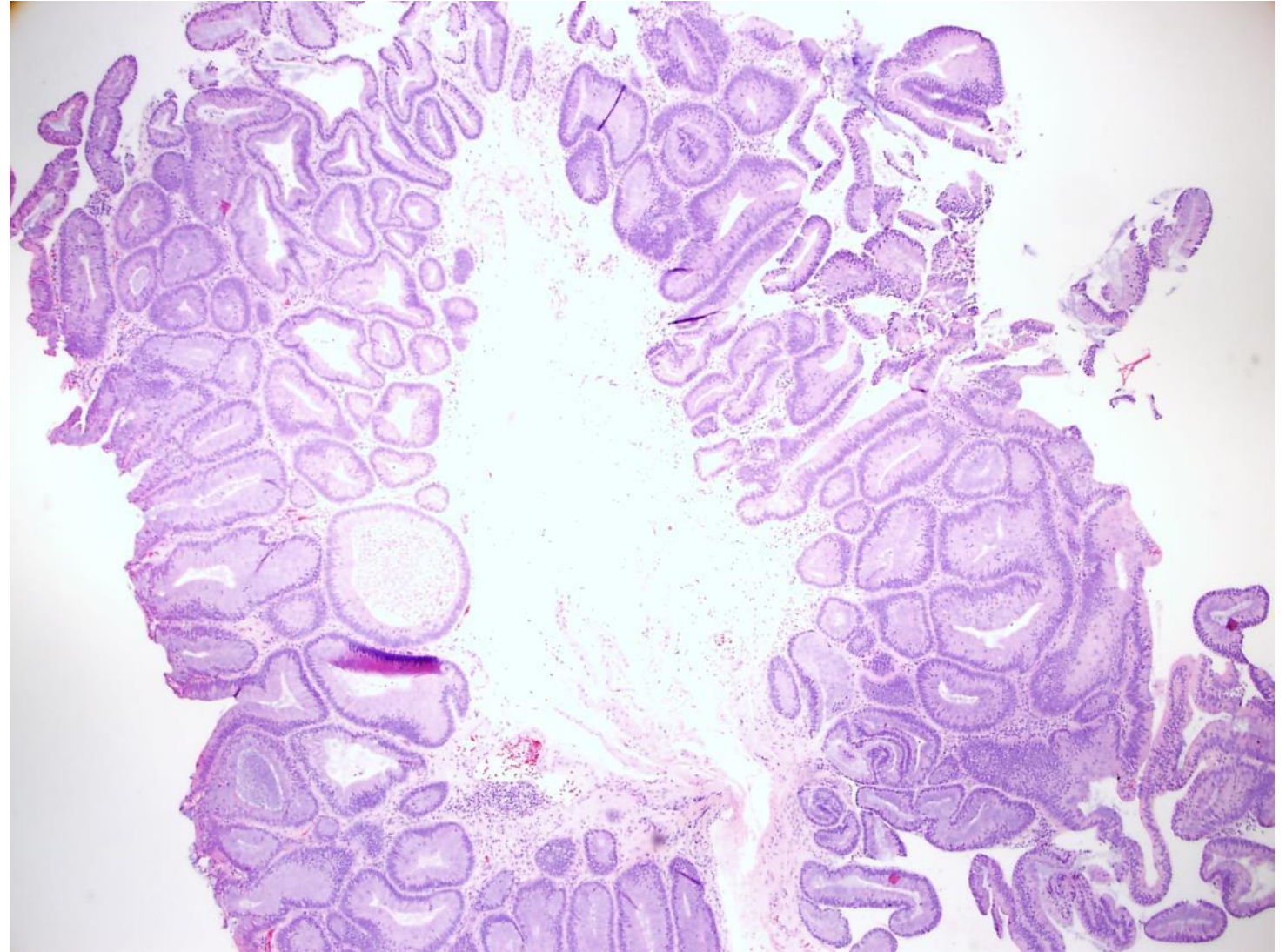
When does it matter?



- Known associations with increased risk are numerous but uncommon
- Bladder Exstrophy
 - Rare (1:30,000-50,000 births USA)
 - Increased risk of neoplasia (adenocarcinoma, squamous cell carcinoma, and rarely urothelial carcinoma)

- Siffel C et al. Bladder Exstrophy: An epidemiologic Study From the International Clearinghouse for Birth Defects Surveillance and Research 2011
- Smeulders N, Woodhouse CR. Neoplasia in adult exstrophy patients 2001

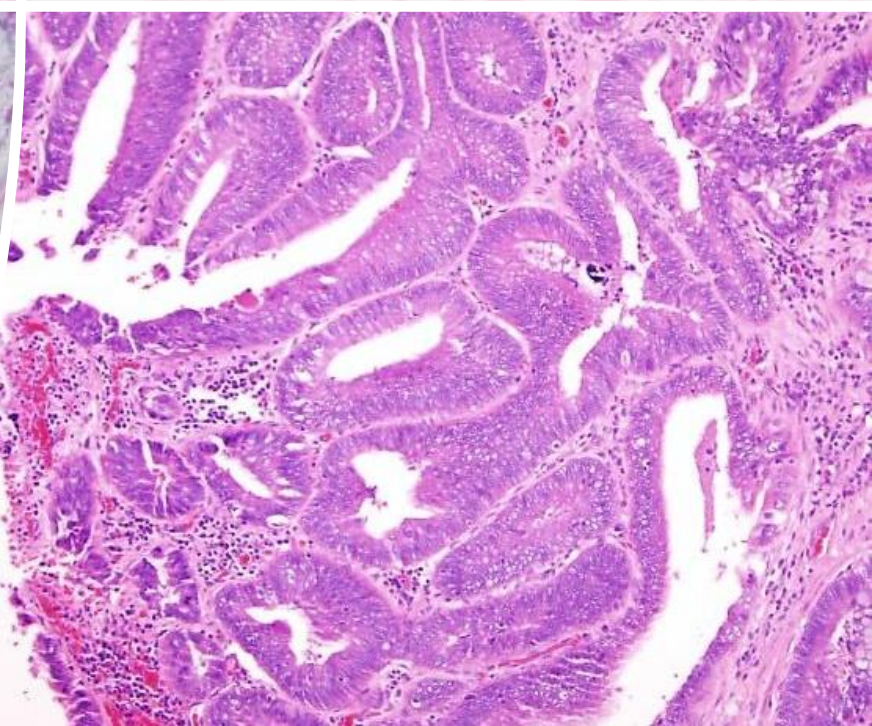
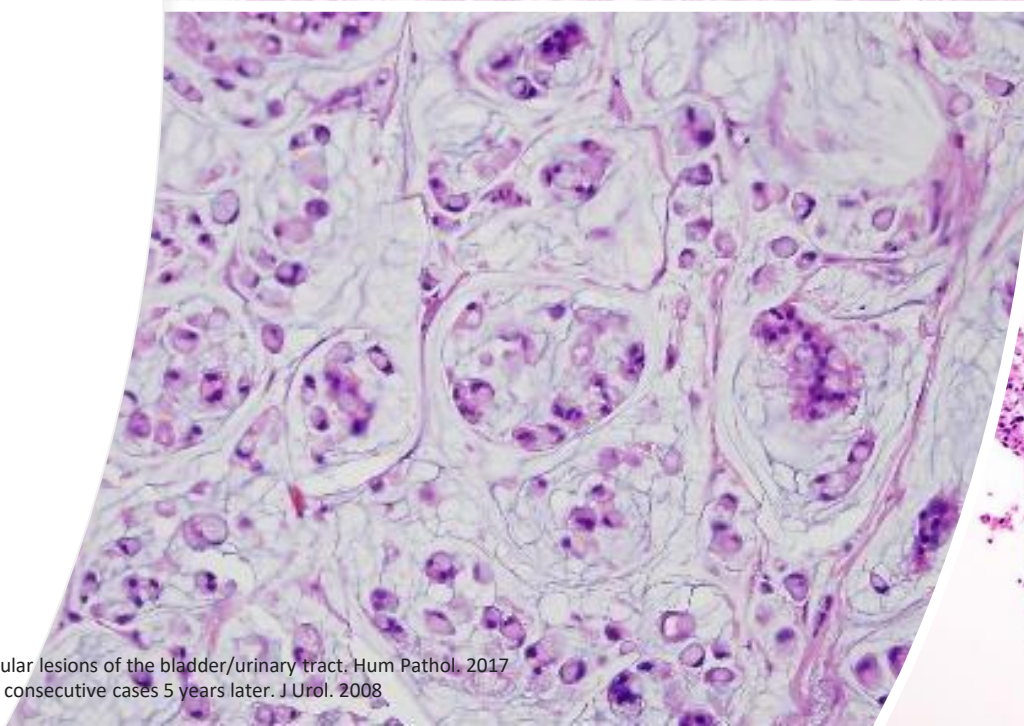
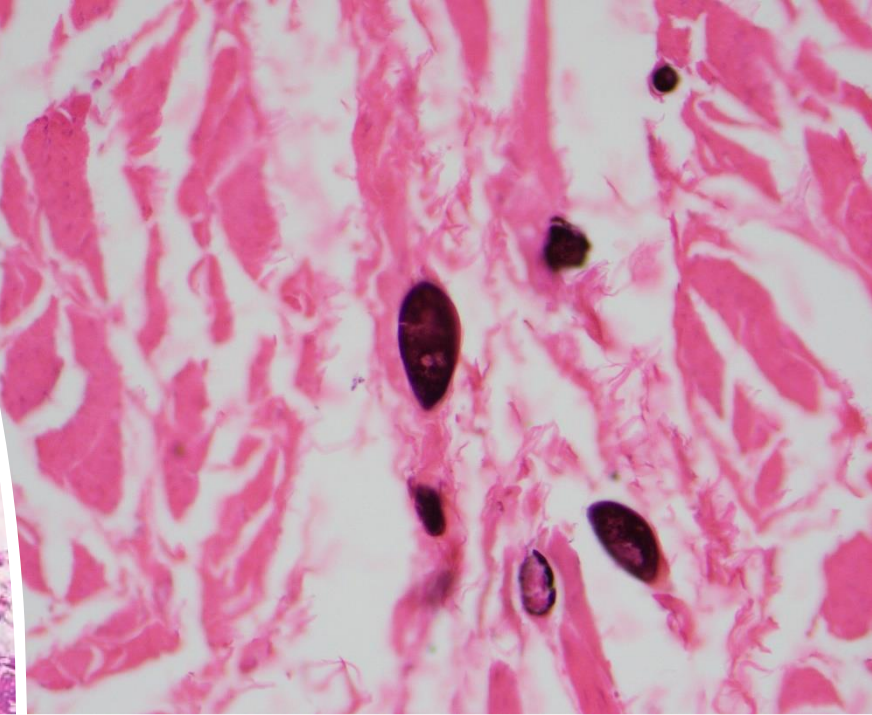
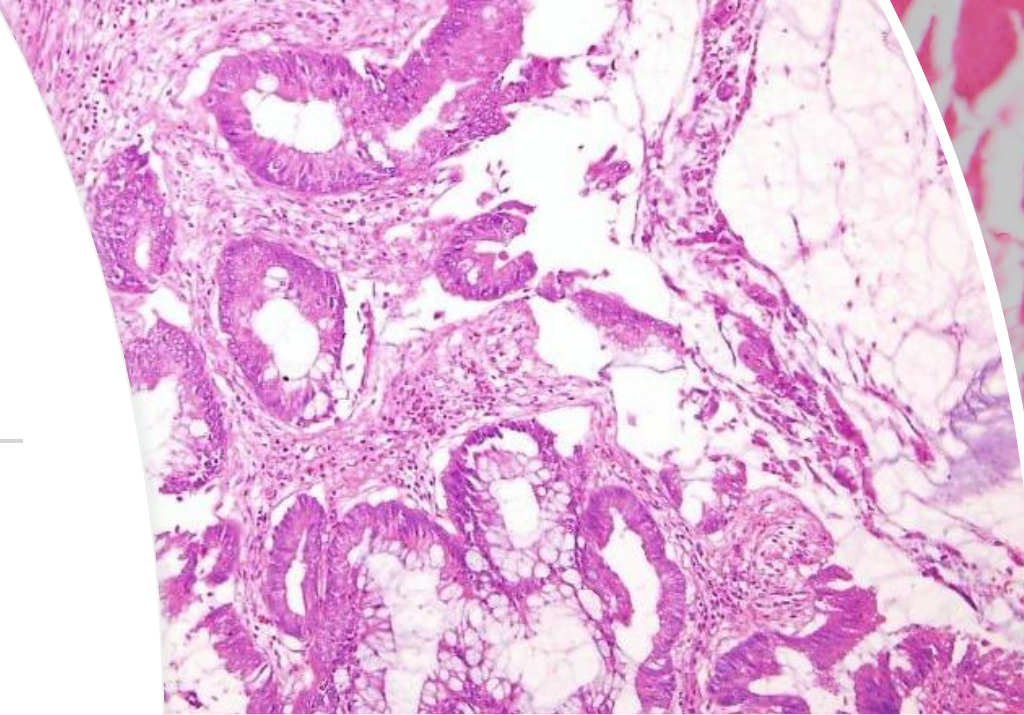
- 3.7 cm solitary anterior bladder mass
- Villous adenoma
 - Typical IHC staining demonstrates enteric phenotype
 - Submit entire lesion to evaluate for AIS / invasive adenocarcinoma – up to 1/3 have concurrent AIS/invasive adenocarcinoma
 - Exclusion of UC with extensive glandular differentiation or urachal primary

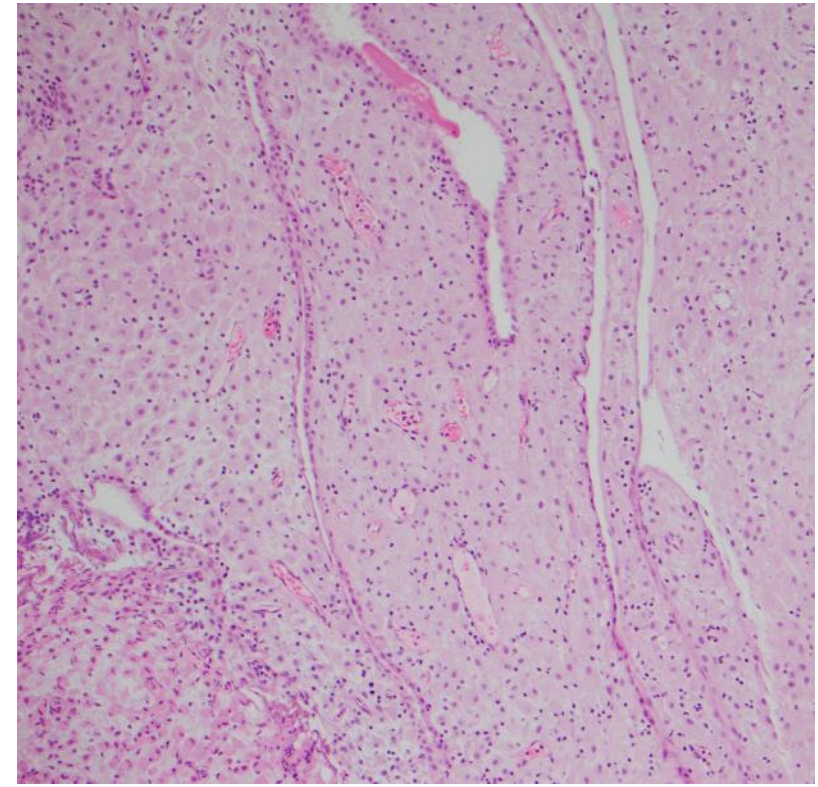
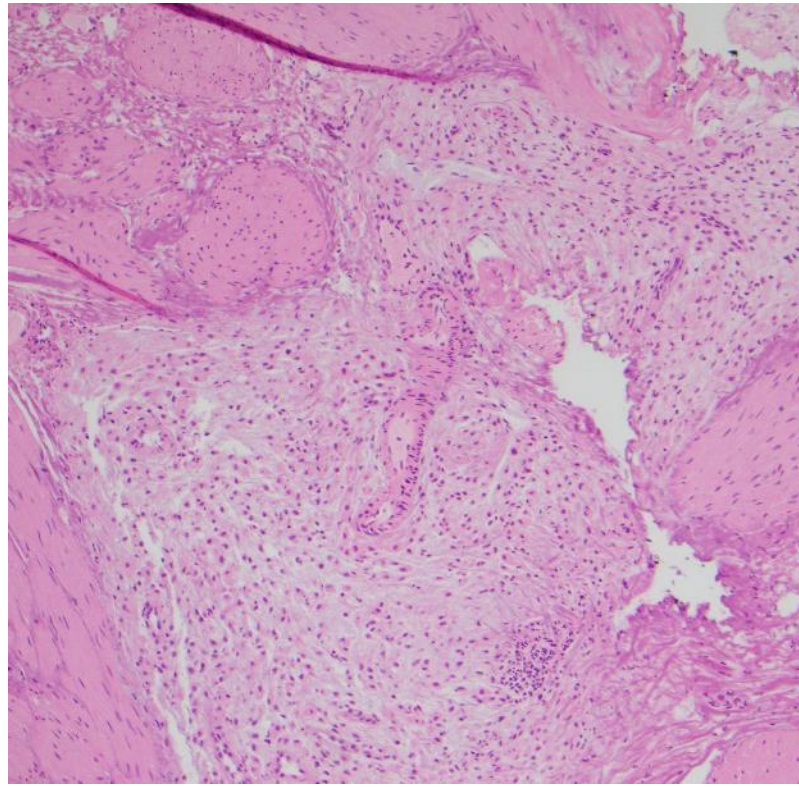
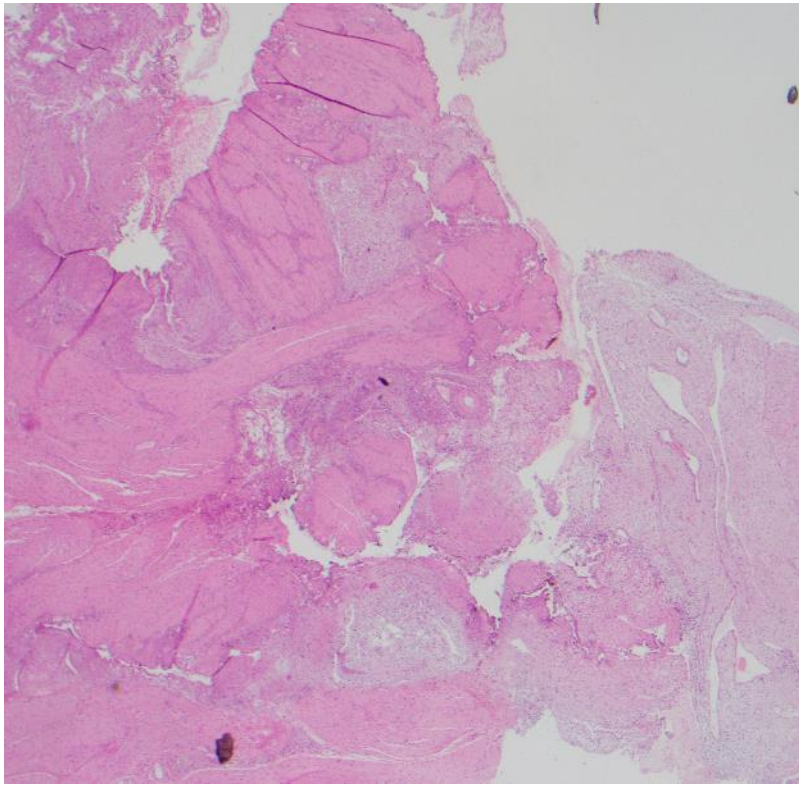


Cheng L et al. Villous adenoma of the urinary tract: a report of 23 cases, including 8 with coexistent adenocarcinoma. *Am J Surg Pathol.* 1999 Jul;23(7)

Adenocarcinoma NOS

- <2% of malignant bladder tumors
- Risk factors: bladder exstrophy, augmentation, chronic inflammation/irritation, neurogenic bladder, *Schistosoma haematobium*
- More than half present with advanced stage disease
- Metastatic disease / Direct invasion more common than primary
 - GYN/upperGI/lowerGI
 - Little help from molecular or immunohistochemical staining – CPC needed with imaging and surgical impression





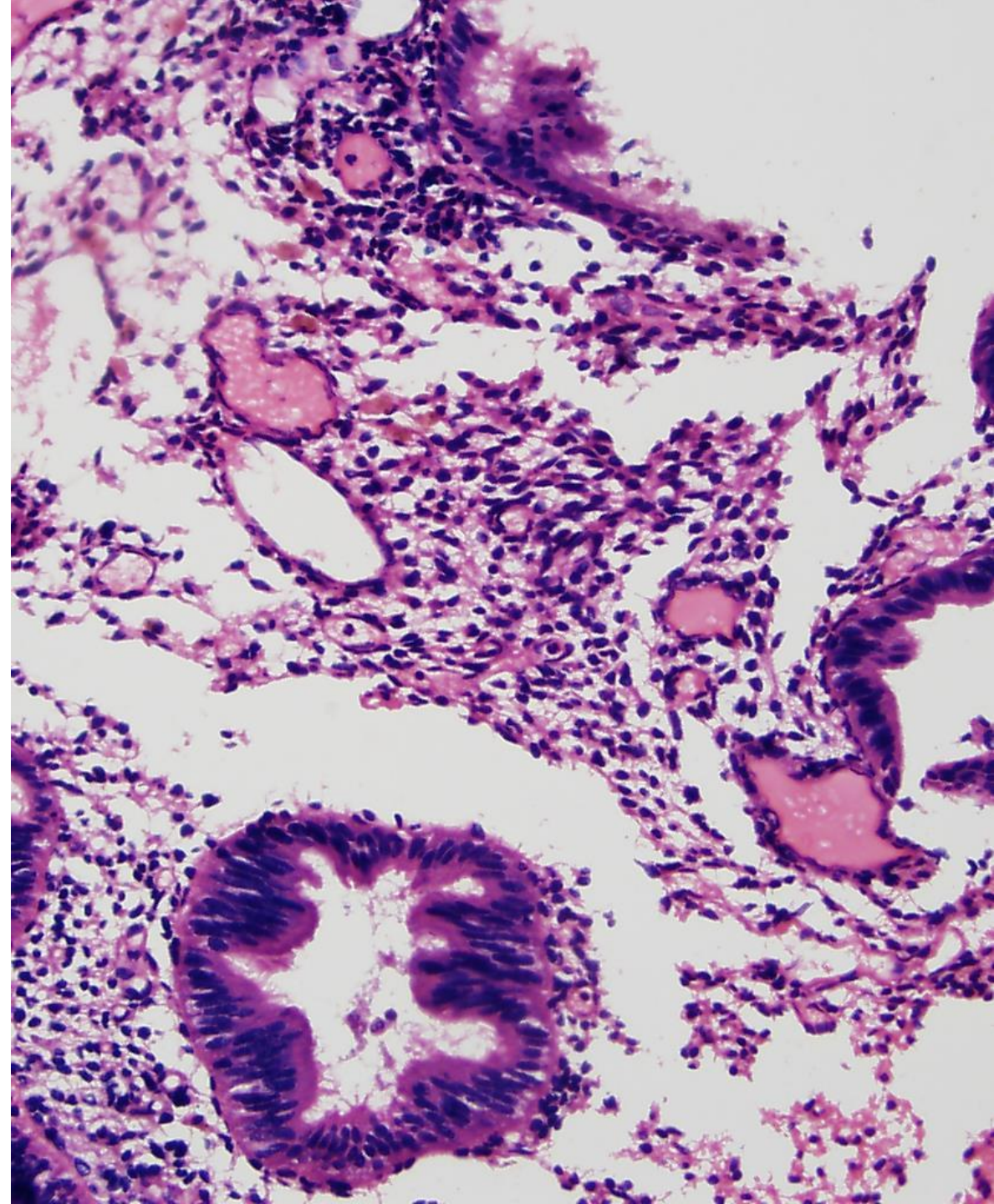
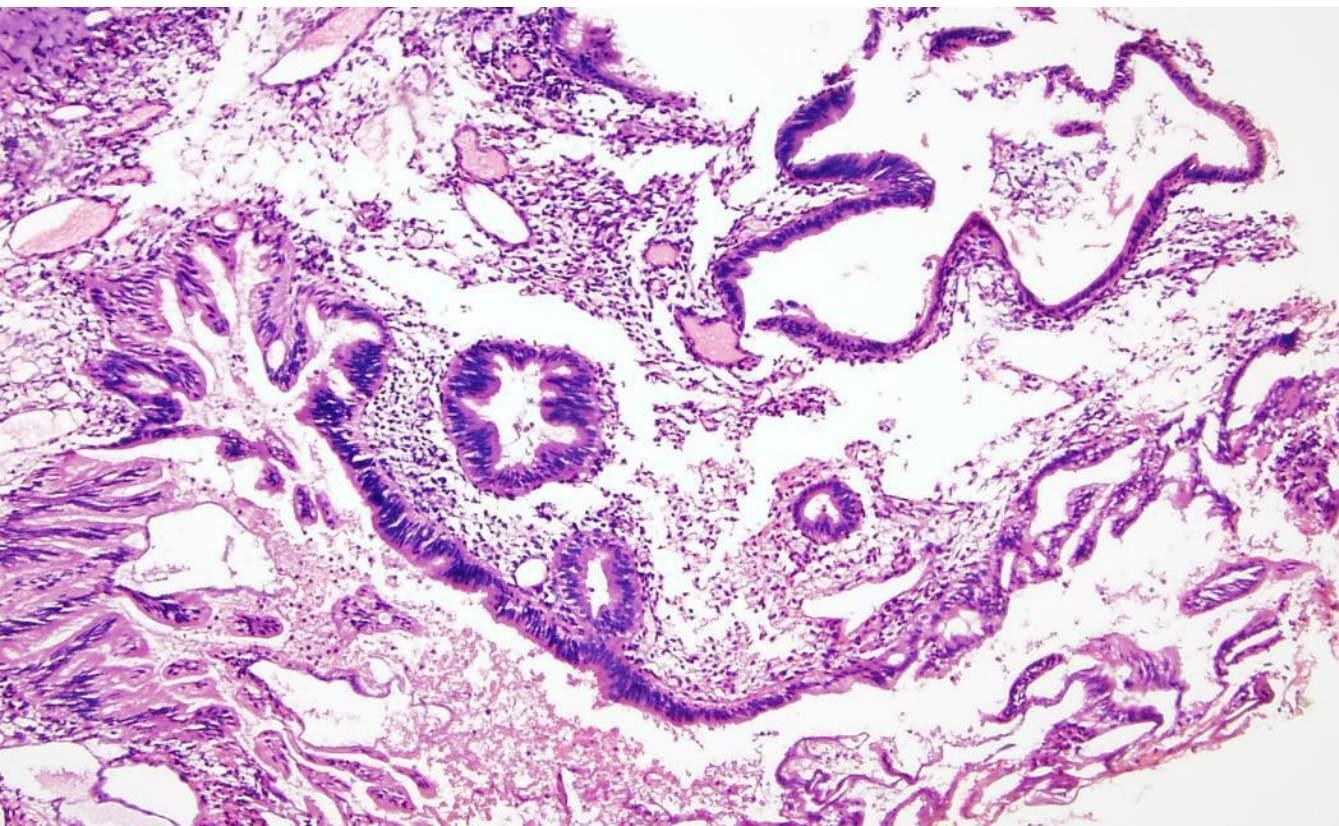
34 y.o. female large papillary bladder mass

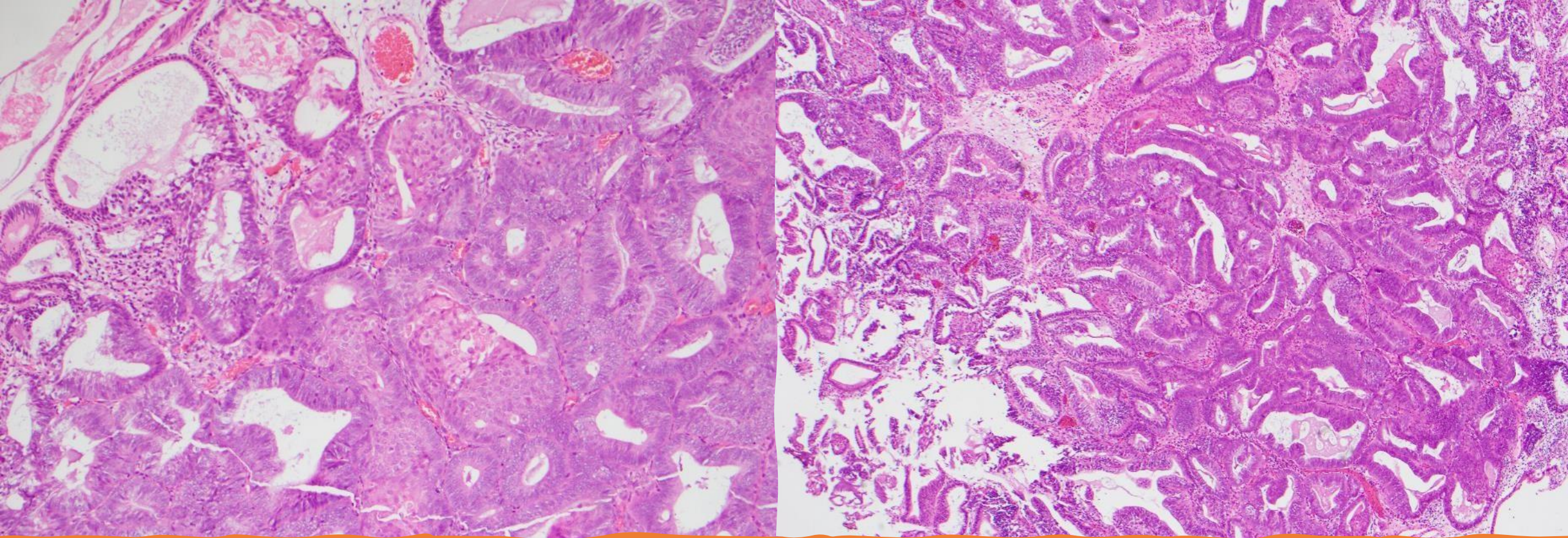
Clinical / imaging suspicion of locally advanced bladder tumor in pregnant patient

Diagnosis: Endometriosis

46 year old
female bladder
mass

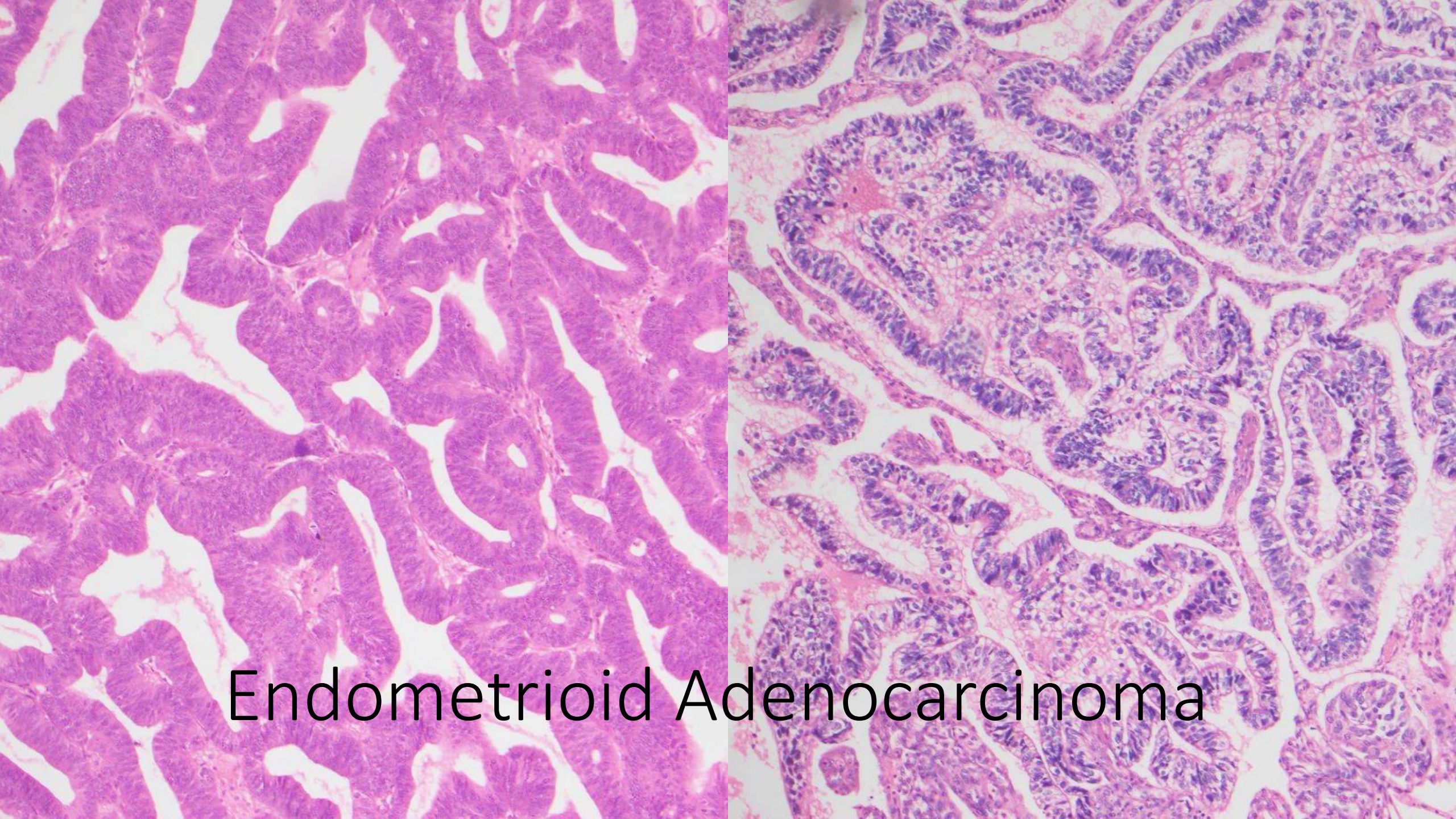
- Endometriosis



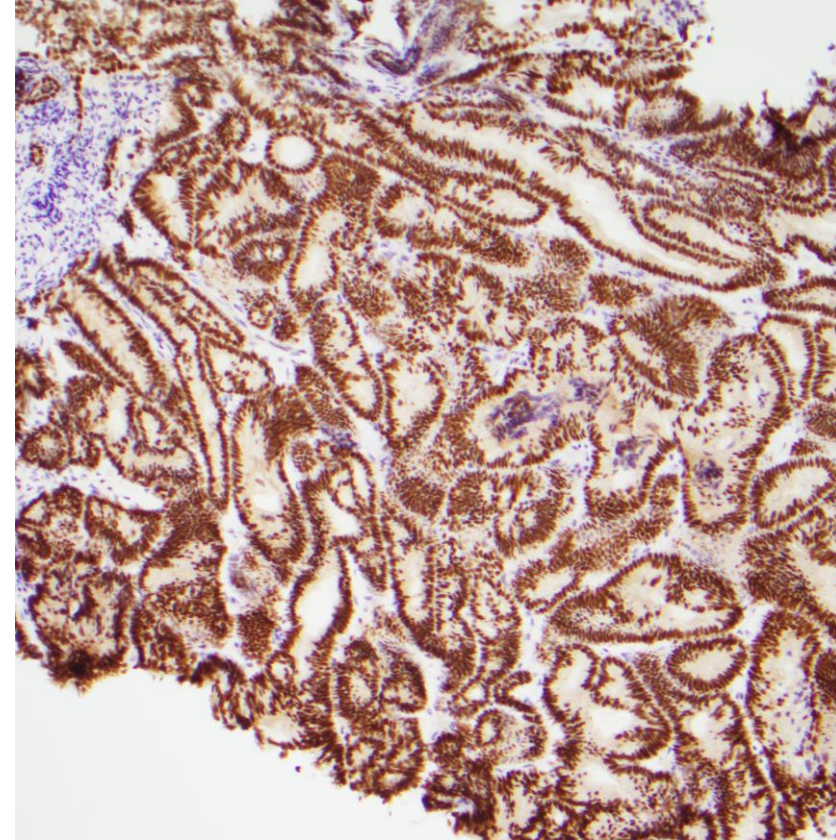
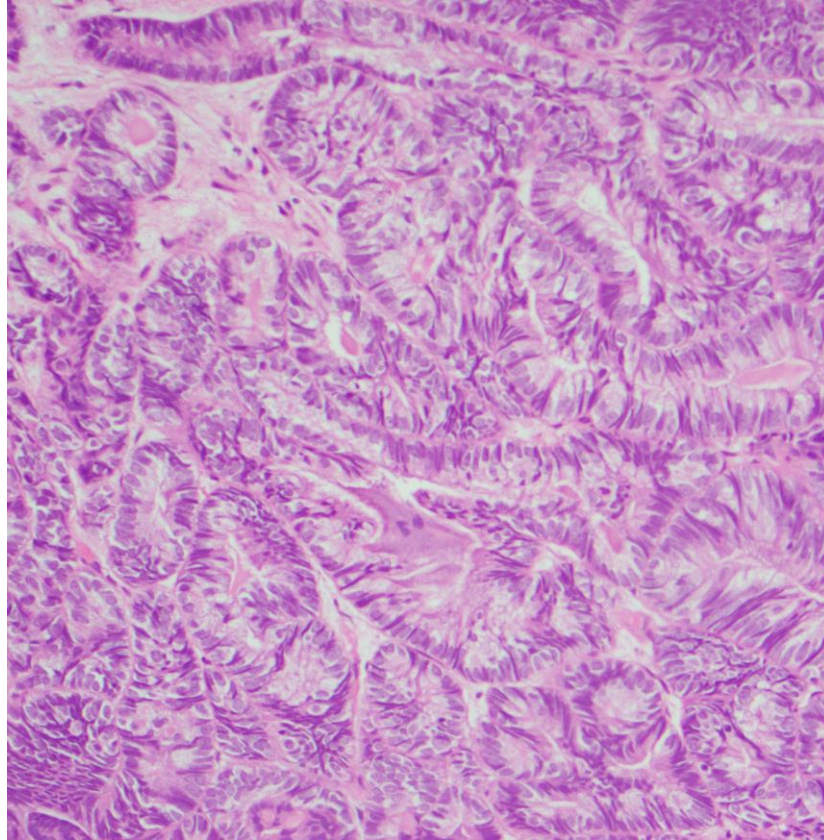
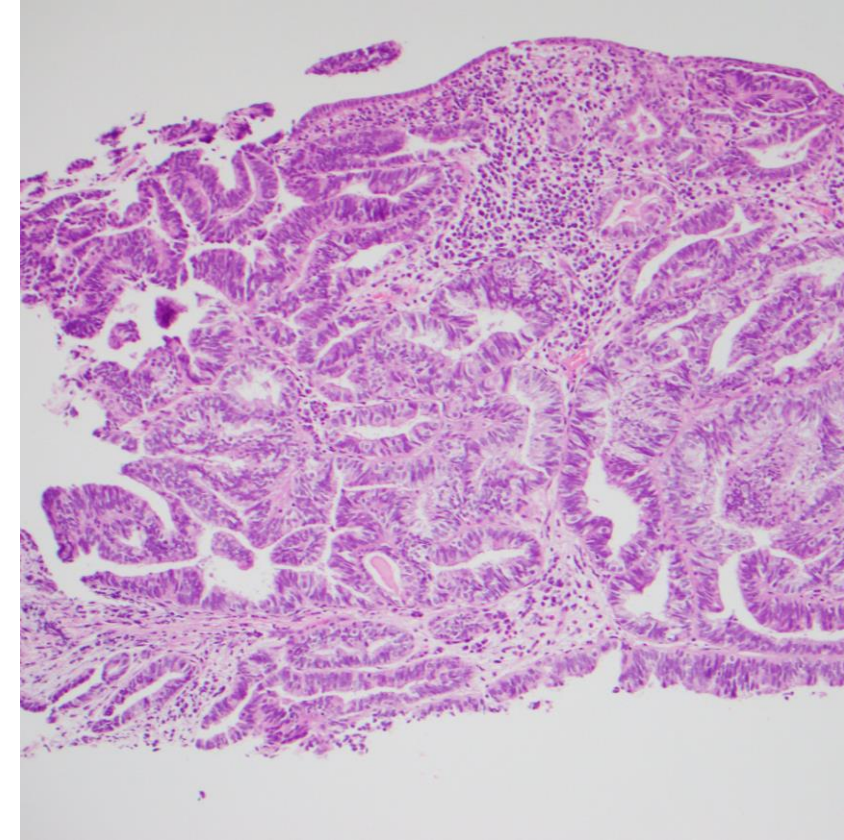


79 yo female with hematuria and large bladder mass

- Presence of Squamous Morular Metaplasia when present is a great clue to Endometrioid Adenocarcinoma
- IHC: ER, PR, Pax8 (+) with concurrent negative urothelial and GI markers
- Very rare primary endometrioid adenocarcinoma has been described – most often in setting of endometriosis



Endometrioid Adenocarcinoma

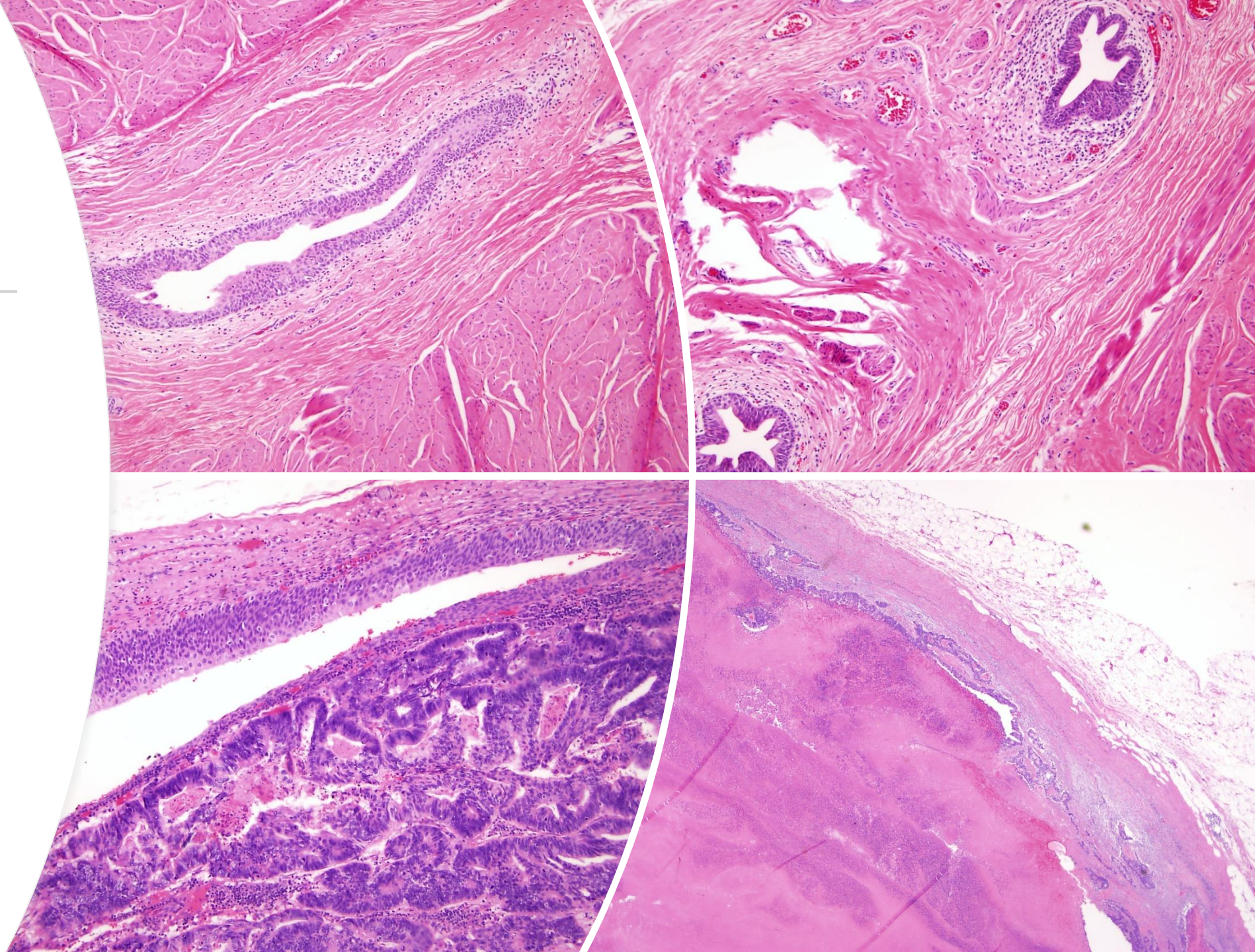


88 year old 4 cm right ureter mass

- PAX8, ER, PR, CK7 Positive
- Endometrioid adenocarcinoma with tubular differentiation
- Possible origin: endometriosis, endometrium, ovary

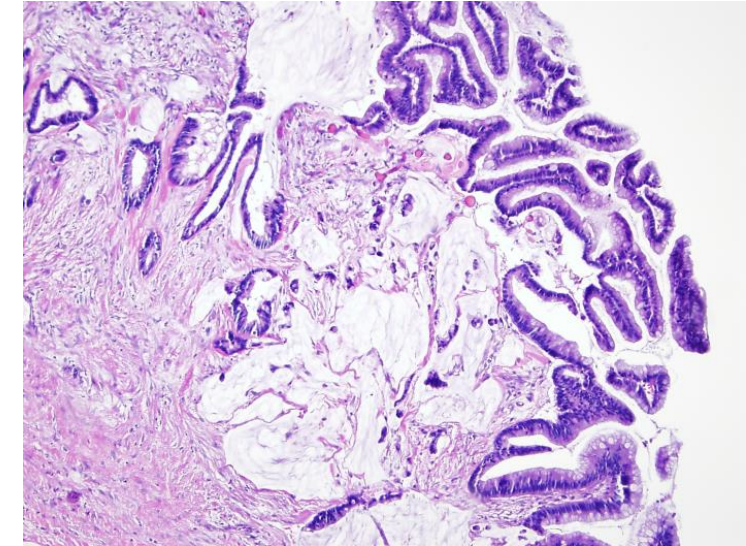
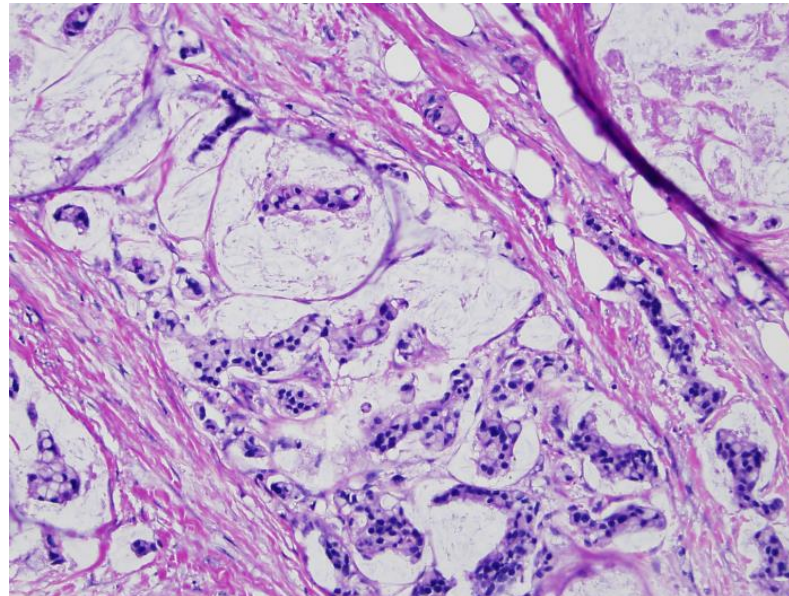
Urachal Remnants and Carcinoma

- 52 year old male with hematuria and 4 cm bladder dome mass

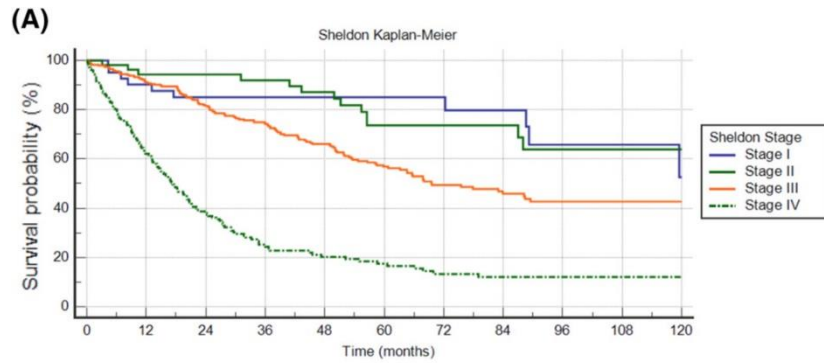


Urachal Carcinomas

- Vast majority are adenocarcinoma (85-90% mucinous, non-mucinous, signet ring cell) with rare urothelial carcinoma (10%) and very rare squamous cell carcinoma (1-2%)
- Multiple staging systems (Mayo, Ontario, Sheldon, recent novel TNM)

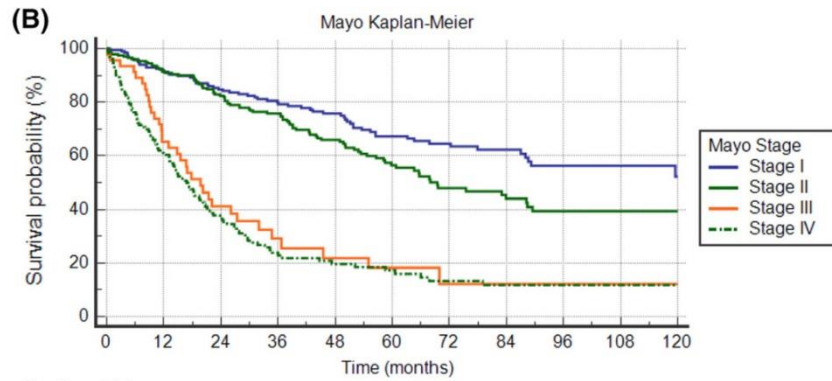


- Dursun F et al. Clinical outcomes and patterns of population-based management of urachal carcinoma of the bladder: An analysis of the National Cancer Database. *Cancer Med.* 2022
- Dhillon J, Liang Y, Kamat AM, Siefker-Radtke A, Dinney CP, Czerniak B, Guo CC. Urachal carcinoma: a pathologic and clinical study of 46 cases. *Hum Pathol.* 2015
- Limonnik V et al, Samiei A, Abel S, Wegner RE, Vemana G, Mao SS. Urachal carcinoma: A novel staging system utilizing the National Cancer Database. *Cancer Med.* 2022



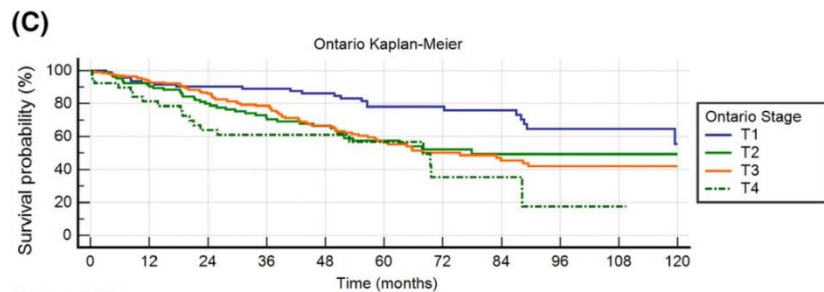
Number at risk

Stage	0	12	24	36	48	60	72	84	96	108	120
Stage: 1	43	35	33	26	23	20	16	13	8	7	4
Stage: 2	57	47	41	38	34	26	21	15	9	6	2
Stage: 3	349	294	242	185	142	96	66	48	31	24	16
Stage: 4	177	107	61	31	23	18	11	9	8	7	7



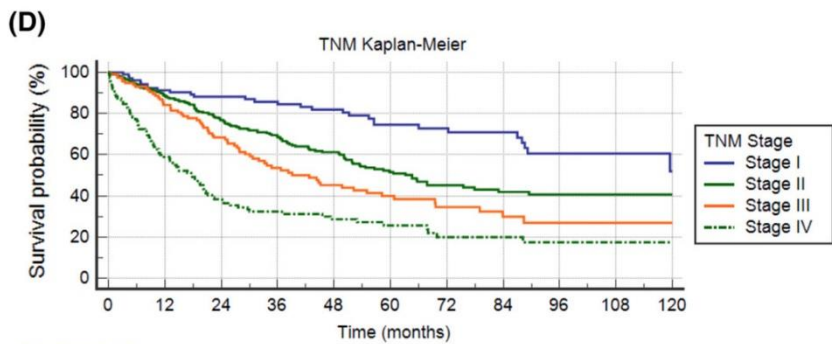
Number at risk

Stage	0	12	24	36	48	60	72	84	96	108	120
Stage I	209	174	147	121	102	80	61	44	28	22	13
Stage II	240	202	169	128	97	62	42	32	20	15	9
Stage III	46	30	16	8	6	5	2	2	2	2	2
Stage IV	131	77	45	23	17	13	9	7	6	5	5



Number at risk

T	0	12	24	36	48	60	72	84	96	108	120
T1	100	82	74	64	57	46	37	28	17	13	6
T2	110	92	73	57	45	34	24	16	11	9	7
T3	201	173	147	110	81	53	38	29	19	14	9
T4	40	29	22	18	16	9	5	3	1	1	0



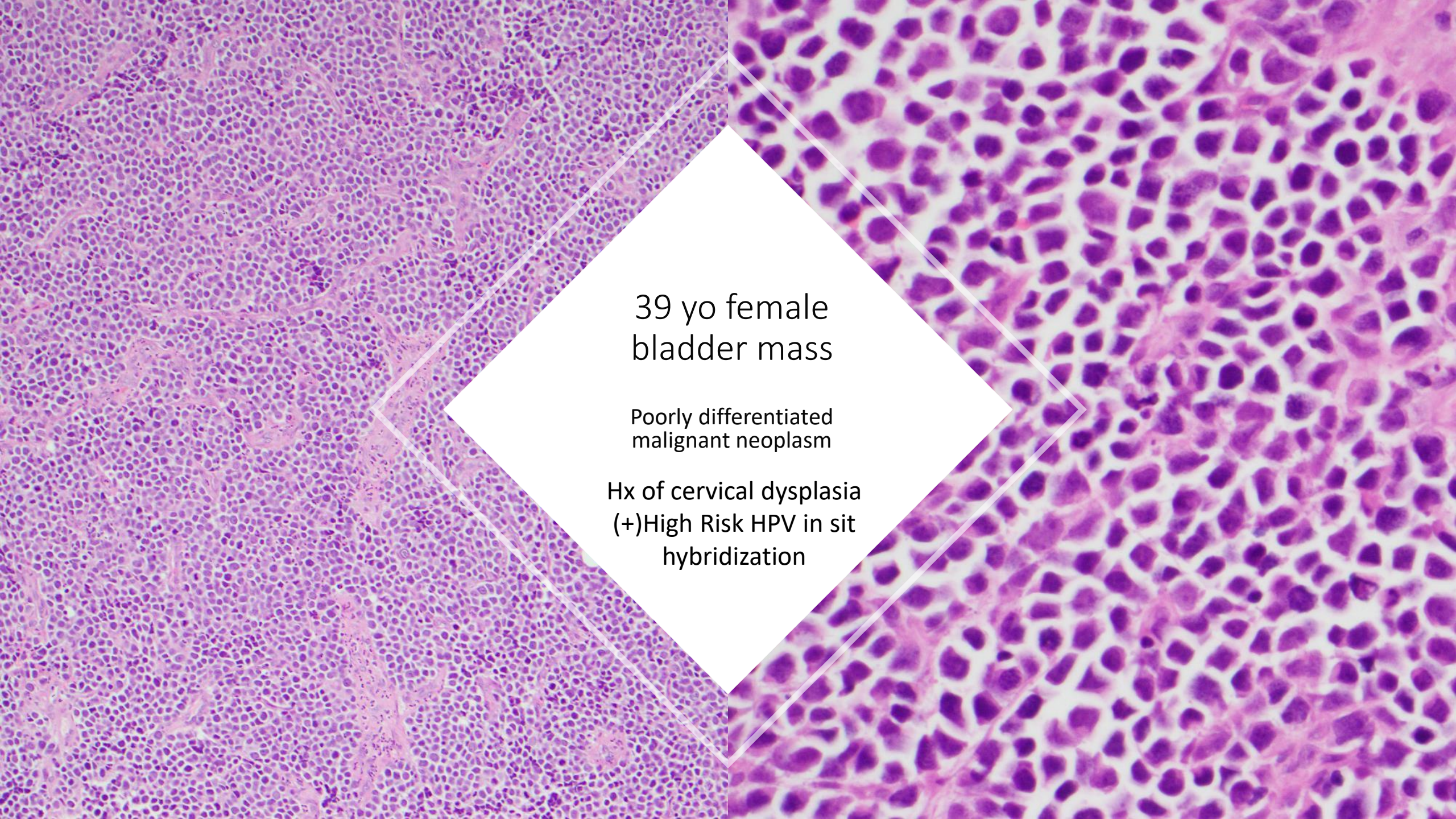
Number at risk

Stage	0	12	24	36	48	60	72	84	96	108	120
Stage I	110	90	78	66	59	48	38	29	18	13	6
Stage II	288	238	189	140	103	71	49	35	23	18	14
Stage III	116	94	71	45	38	26	17	12	9	7	4
Stage IV	112	61	39	29	22	15	10	9	6	6	5



Unusual Morphologic Features (Poorly Differentiated, Epithelioid, Mesenchymal)

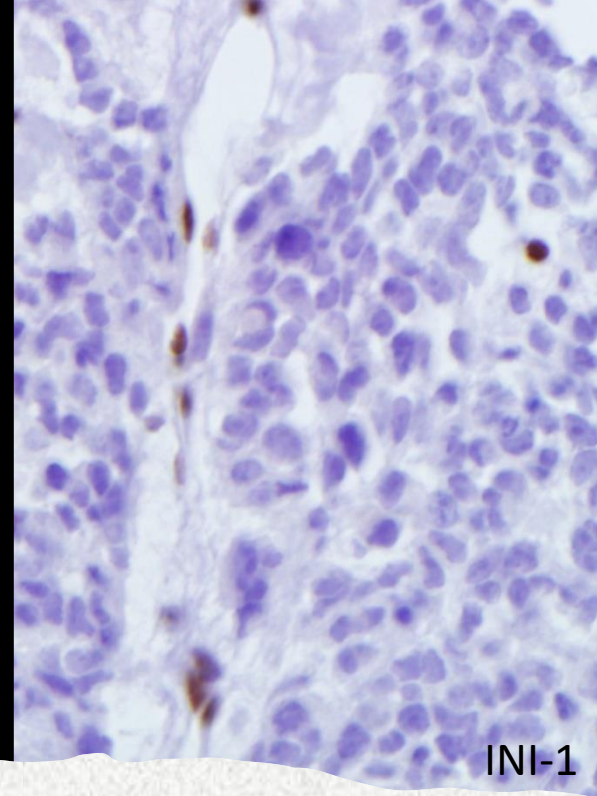
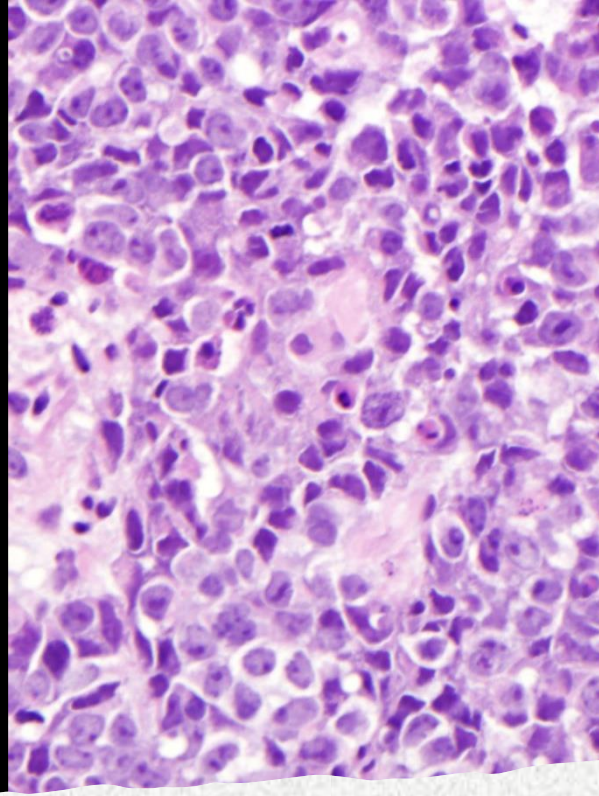
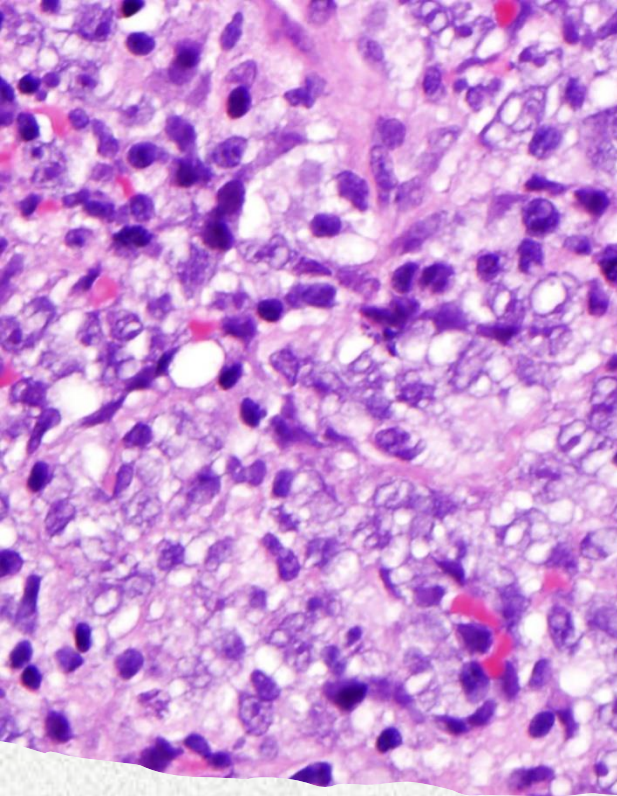
- Is there a previous oncologic history or known risk factors for neoplasia?
- Is this poorly differentiated UC, or UC with divergent differentiation?
- Could this be a secondary malignancy – namely prostate, cervical, colorectal, or uterine? Is urachal carcinoma anatomically feasible?
- IHC studies or HPV ISH? molecular testing (FISH, NGS)?

The image shows a histological section of bladder tissue stained with hematoxylin and eosin (H&E). The tissue exhibits a dense population of cells with hyperchromatic nuclei and a loss of normal architecture, consistent with a malignant neoplasm. A white diamond-shaped overlay is centered on the image, containing text that provides clinical and pathological context. The background tissue shows a transition from a more organized structure on the left to a highly cellular, disorganized area on the right.

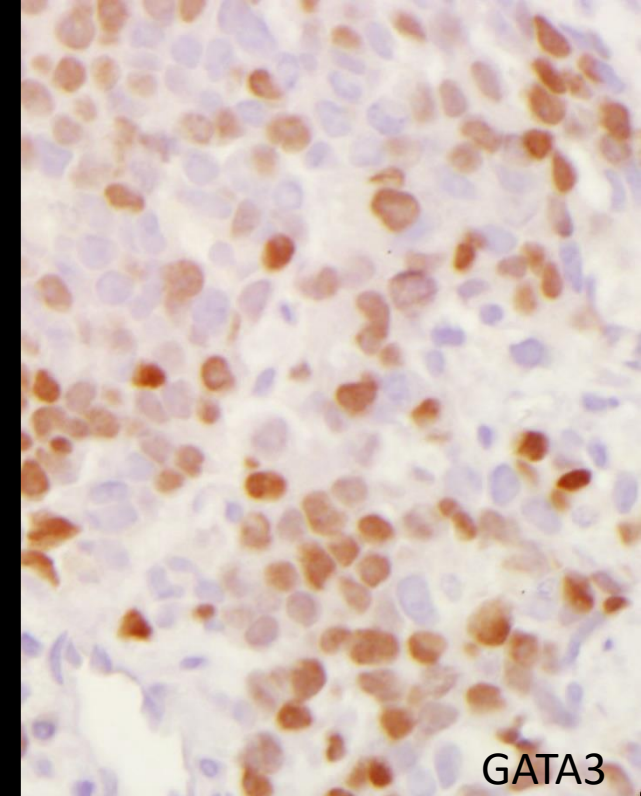
39 yo female
bladder mass

Poorly differentiated
malignant neoplasm

Hx of cervical dysplasia
(+)High Risk HPV in sit
hybridization



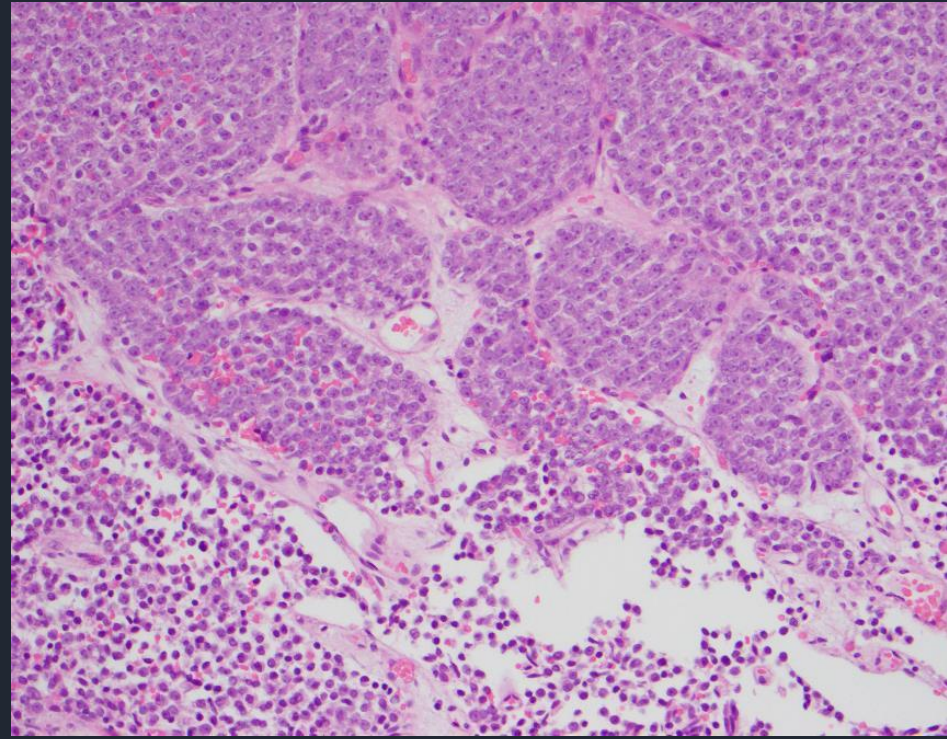
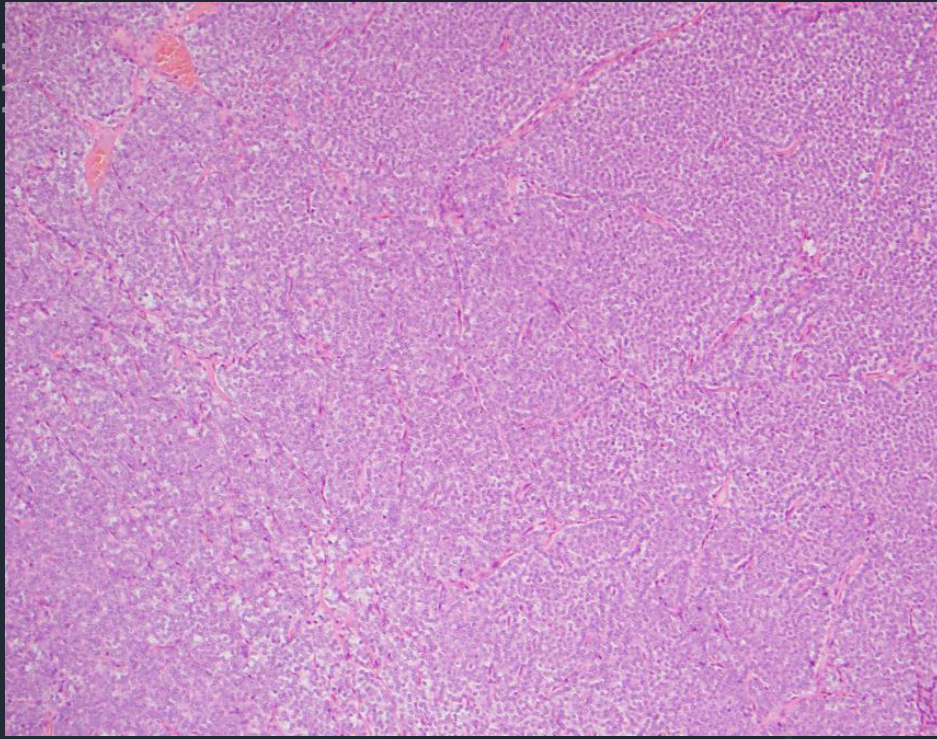
INI-1



GATA3

- 38 year old female with mid ureter obstruction and mass

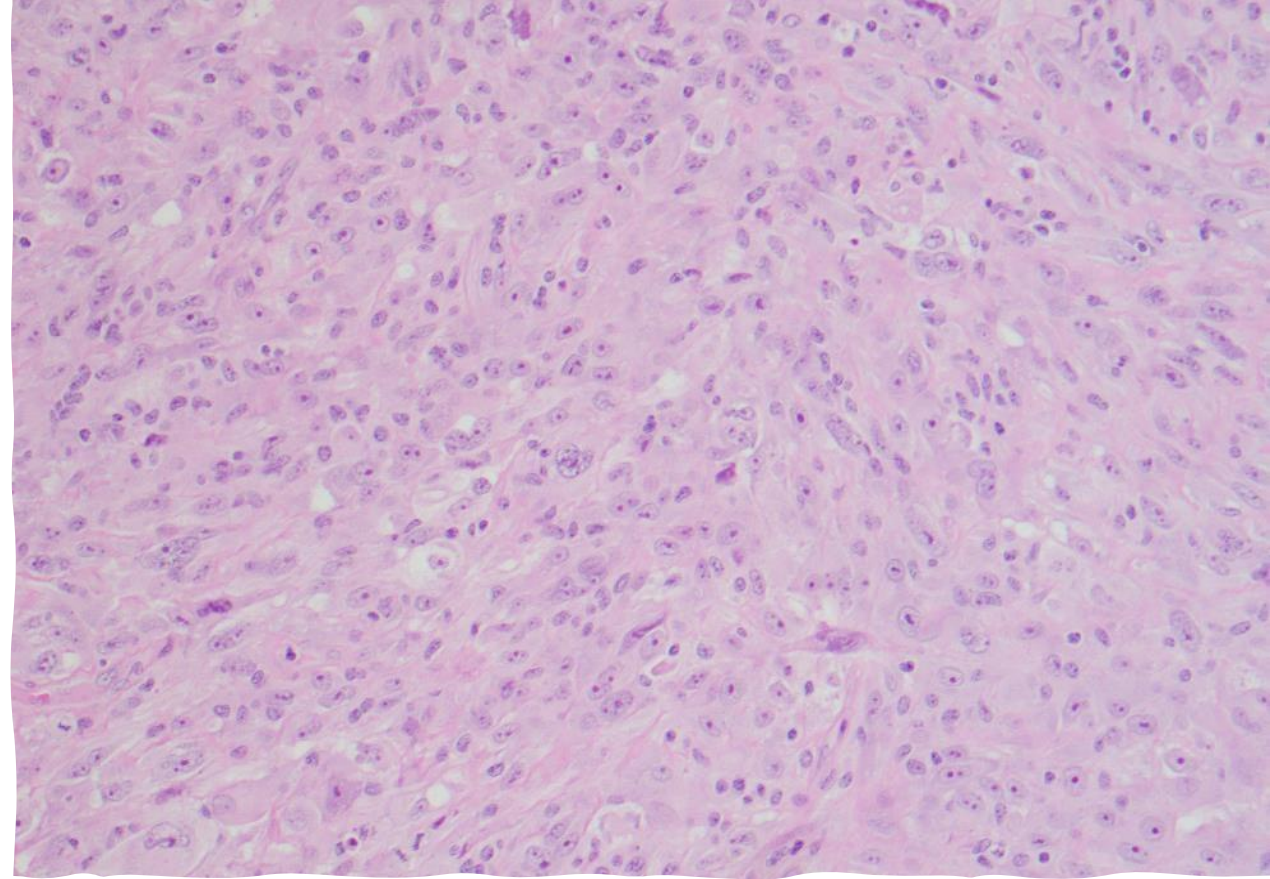
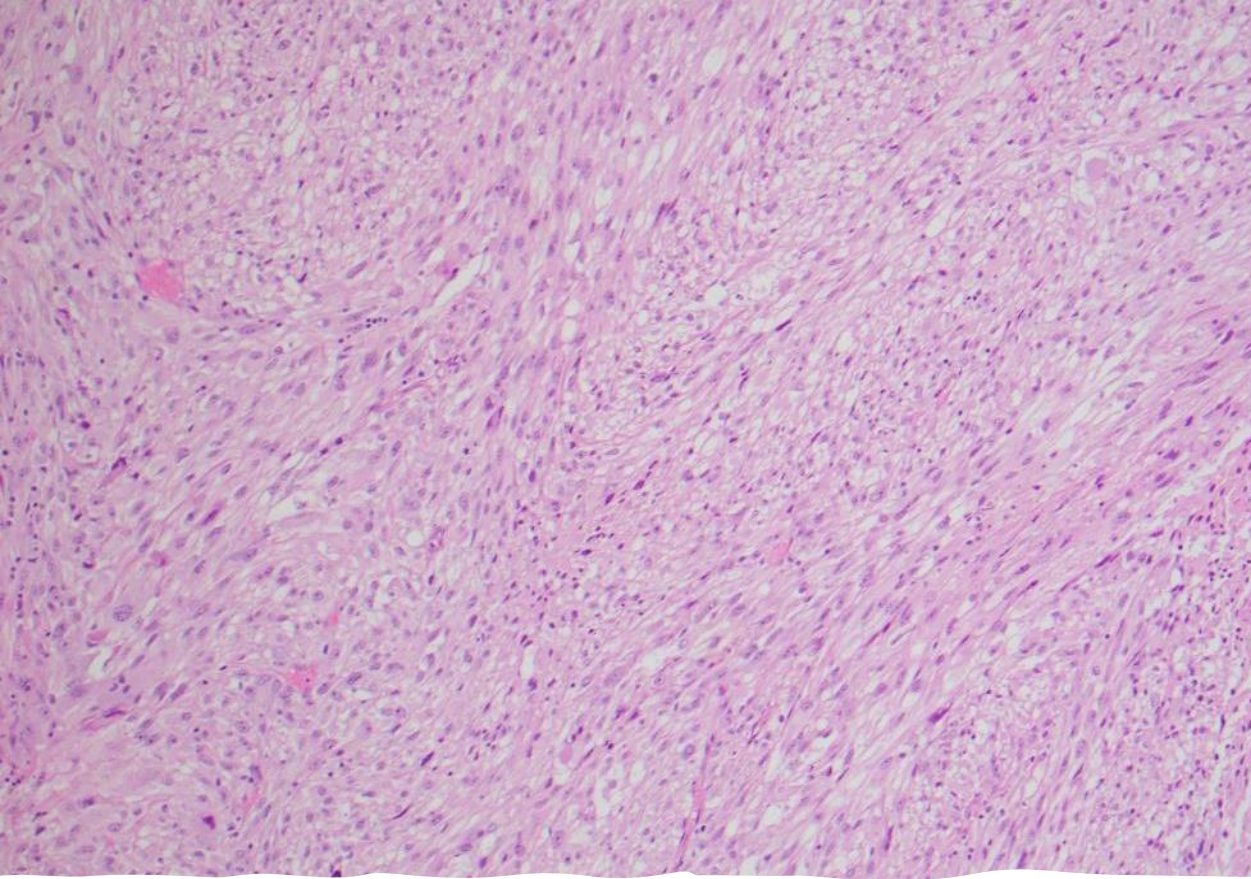
Ancillary testing: focal Cam5.2, focal weak GATA3, focal CD56
(-) CIC-DUX and EWSR FISH



68 year old male with
difficulty urinating and
mass at bulbar urethra

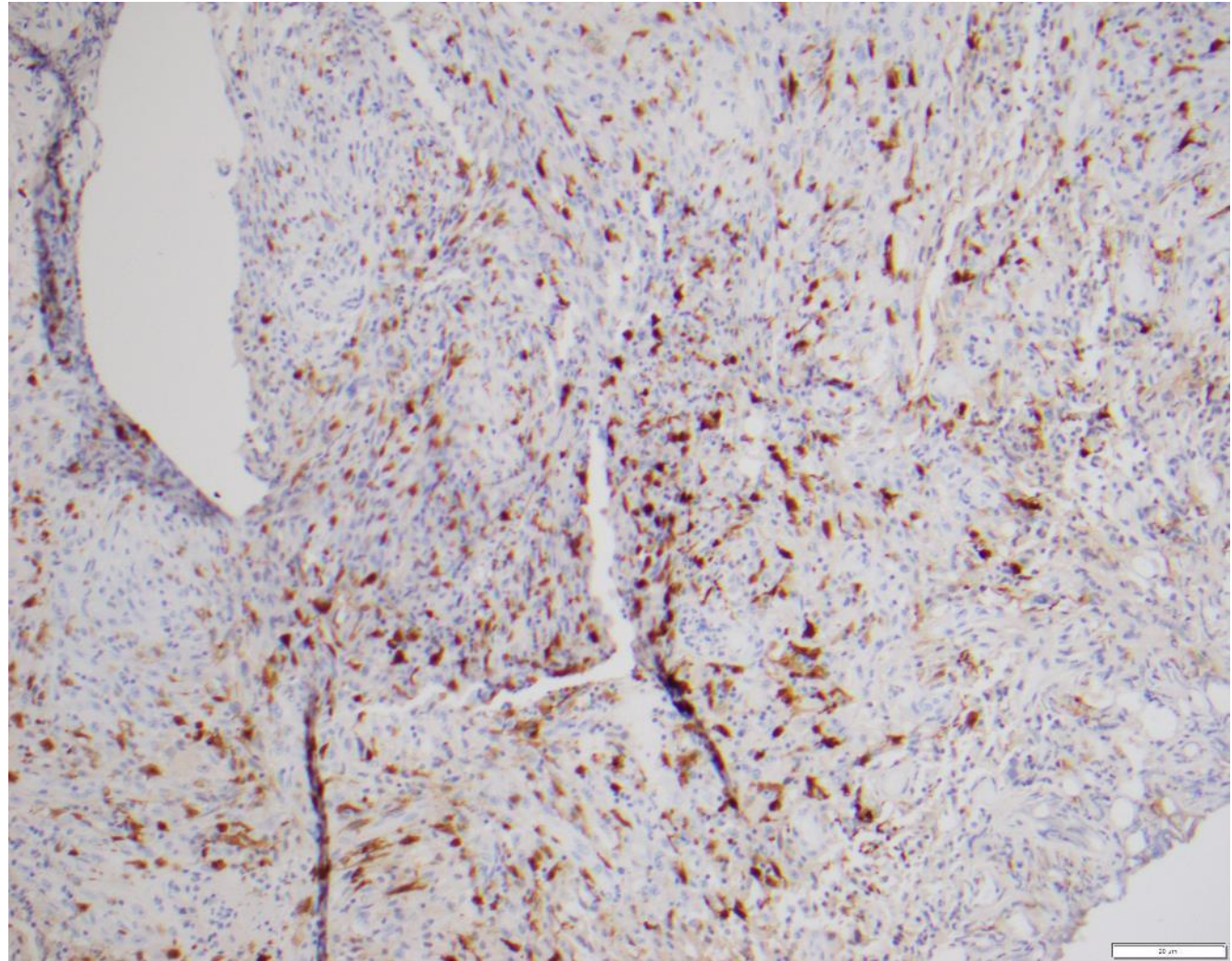
IHC: Urothelial markers (-)
NKX3.1 and p501s (+)
Neuroendocrine markers patchy (+)

Diagnosis: Prostatic Adenocarcinoma with
neuroendocrine features



- 60 Year Old Male with hematuria and large bladder mass
- Epithelial markers and muscle markers negative

S100

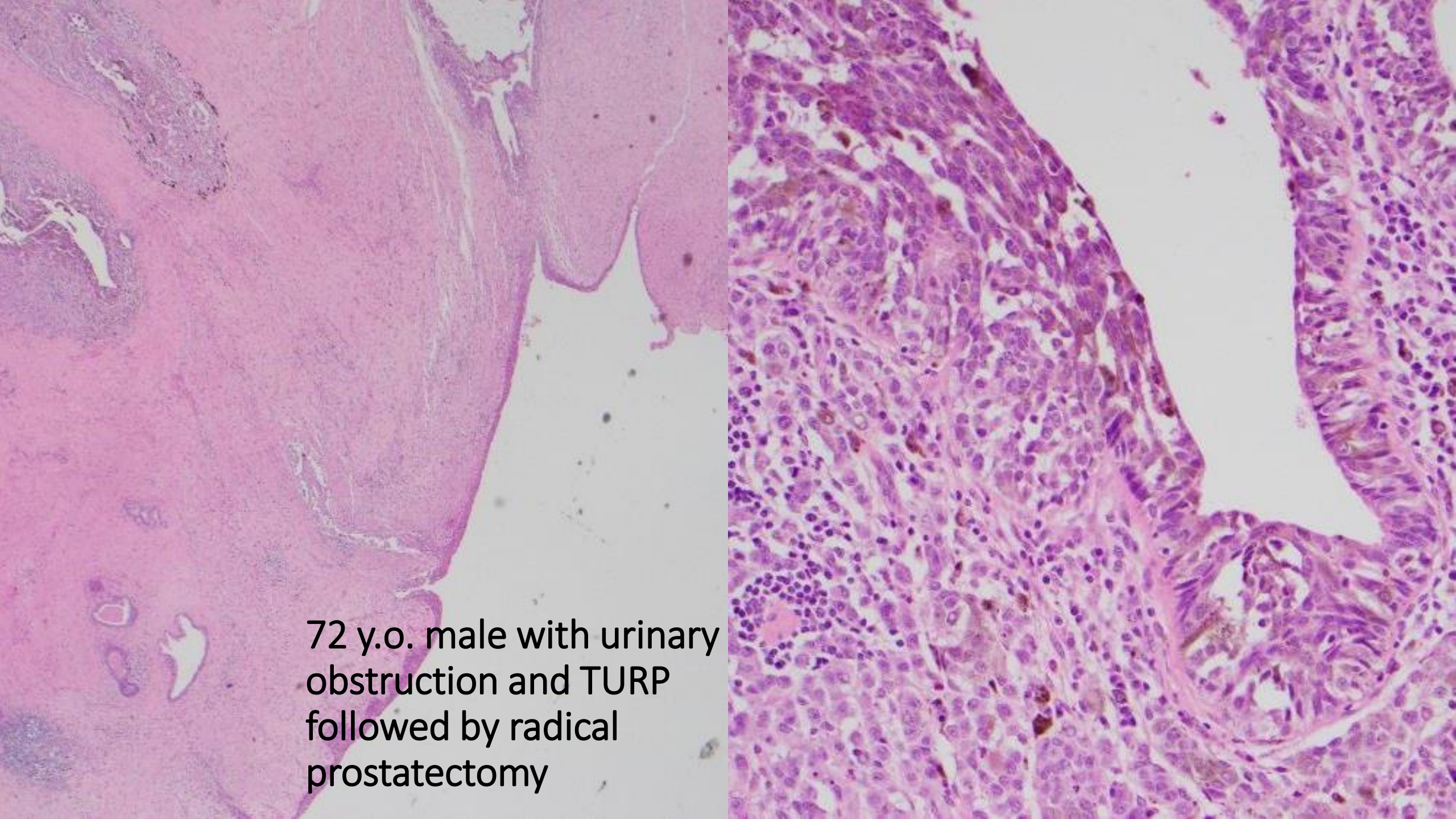




HMB 45 and MITF

Epithelial and muscle markers negative

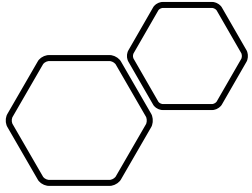
Diagnosis: Malignant Melanoma



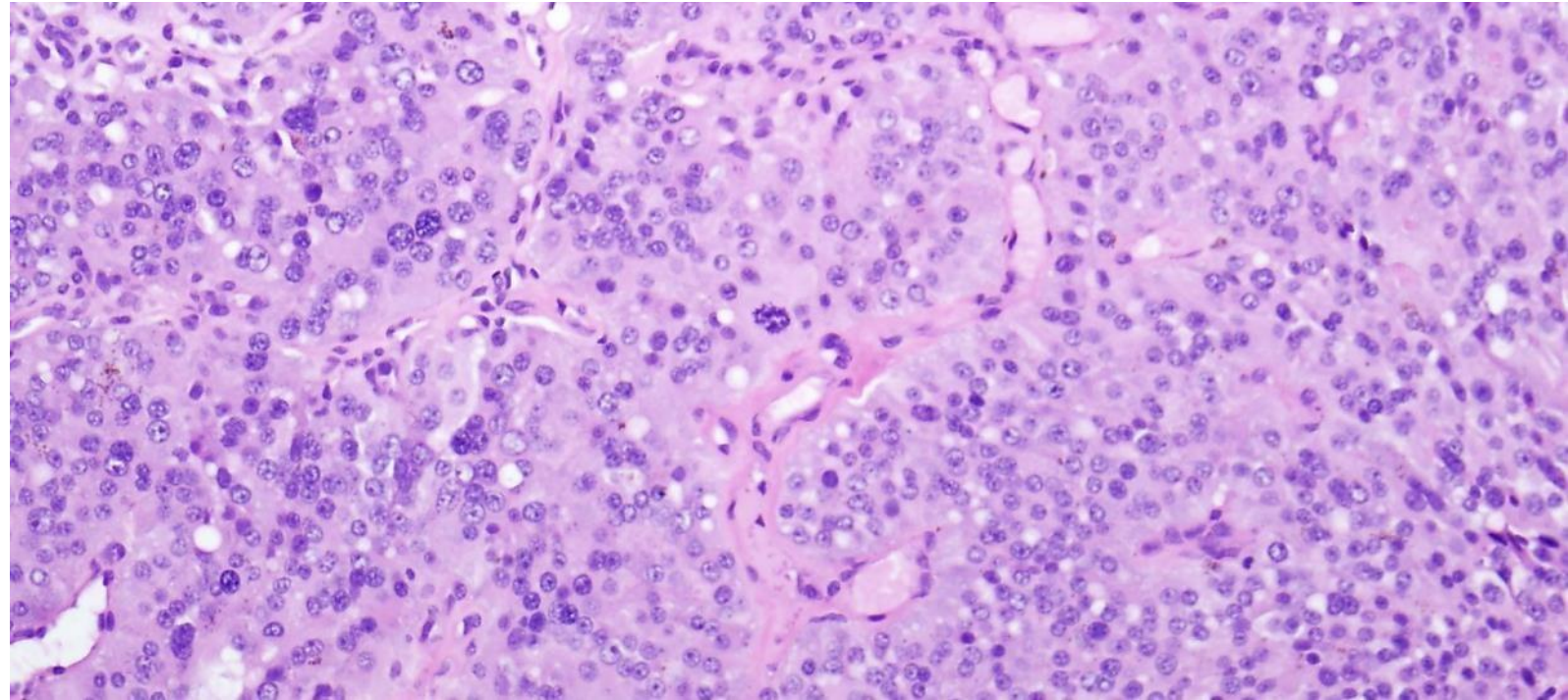
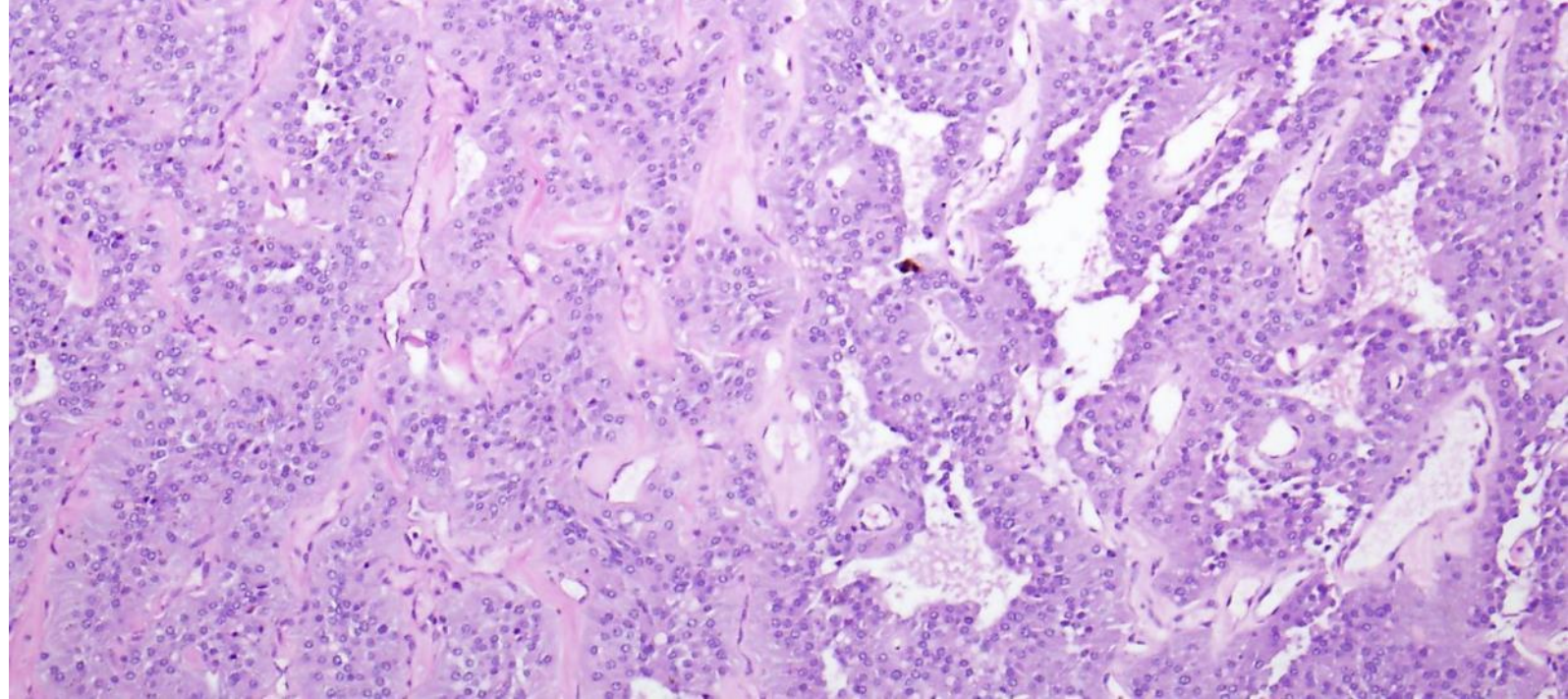
72 y.o. male with urinary obstruction and TURP followed by radical prostatectomy

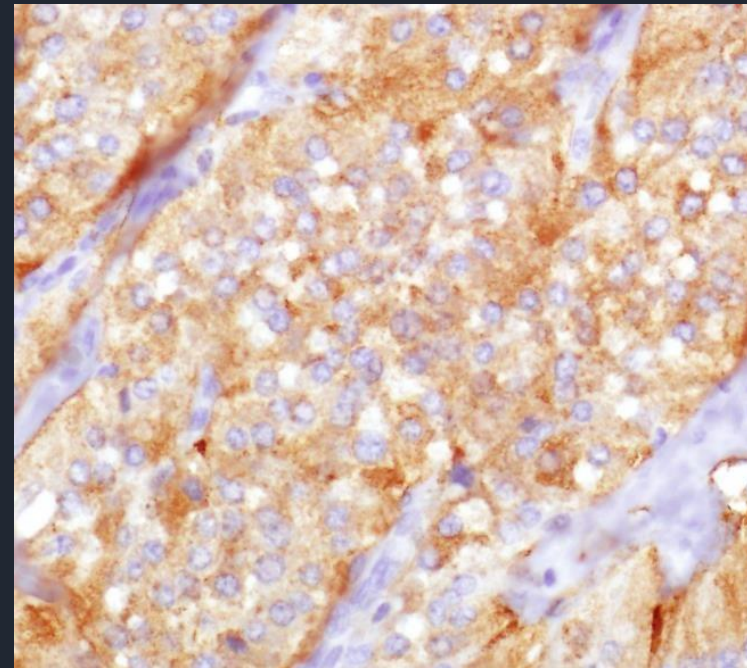
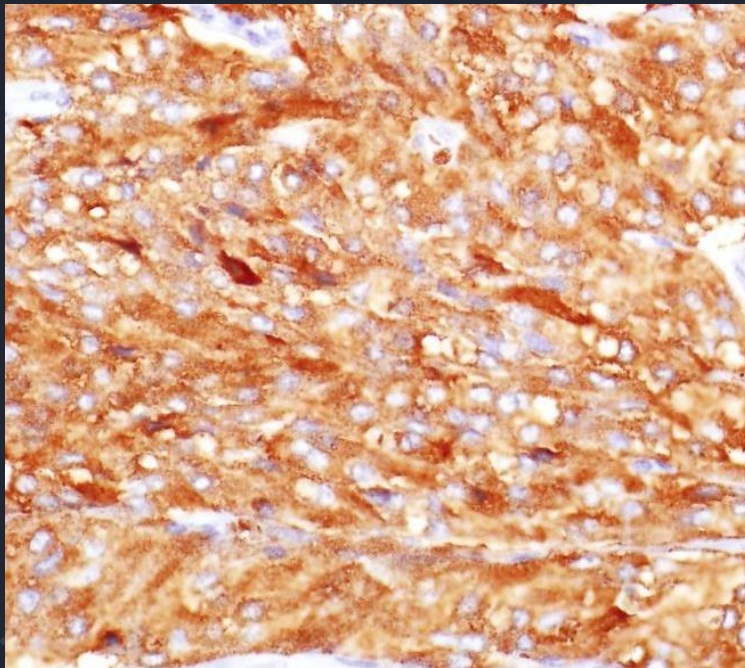
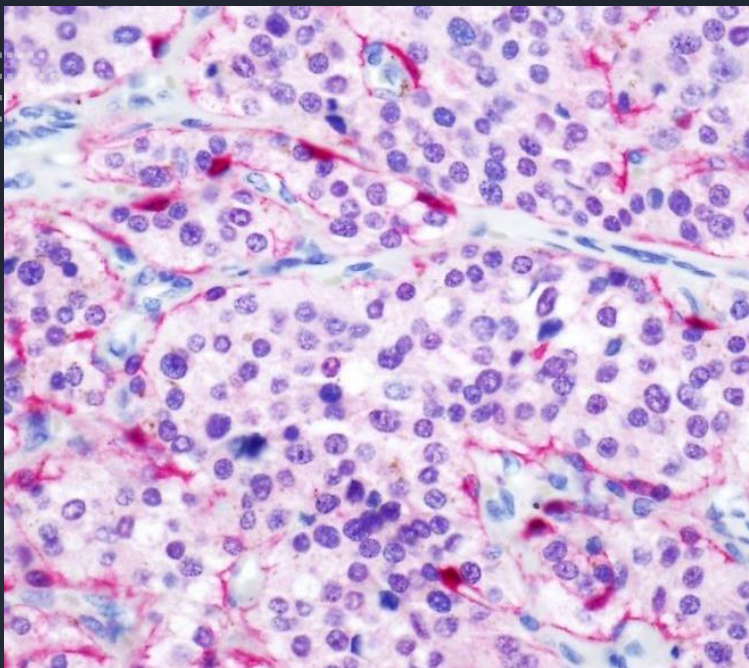
Mucosal Melanoma

- Current Case: suspected primary mucosal melanoma of the prostatic urethra
 - No evidence of other primary site currently or past
 - Evidence of intramucosal/epithelial component
 - Additional testing recommended: at a minimum KIT and BRAF
 - Low TMB more common in primary mucosal melanomas

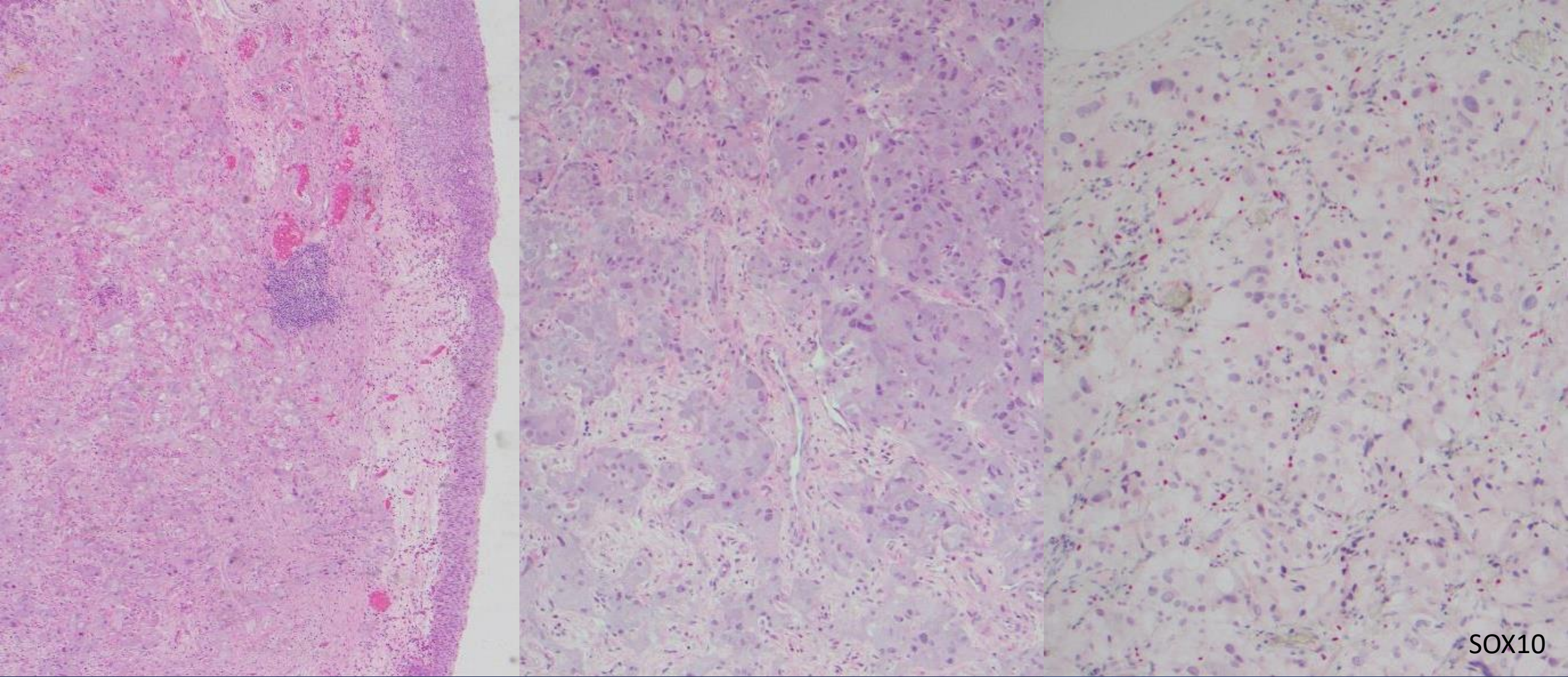


- 60 year old TURBT – outside diagnosis of urothelial carcinoma
 - Presented to our institution for treatment planning.
 - Outside IHC GATA3+



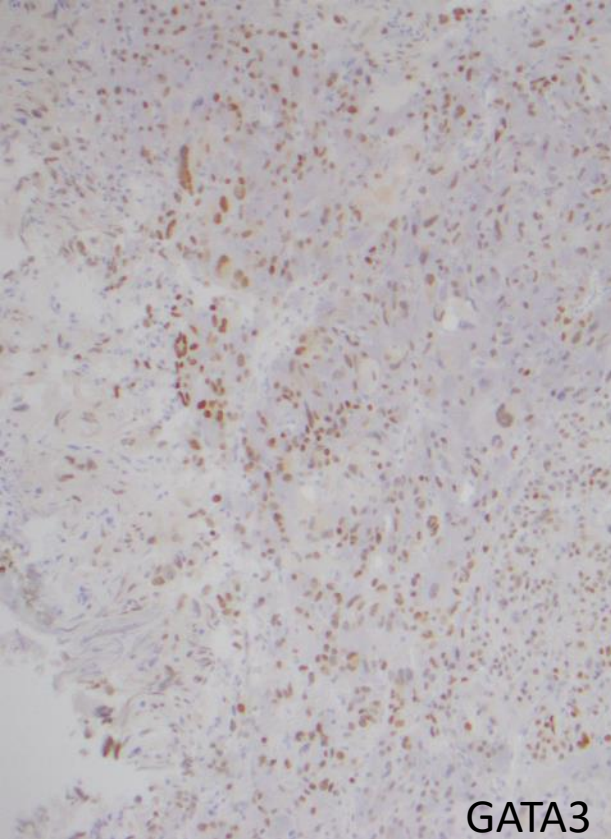


(+) S100, Chromogranin, Synaptophysin
(-) CK7

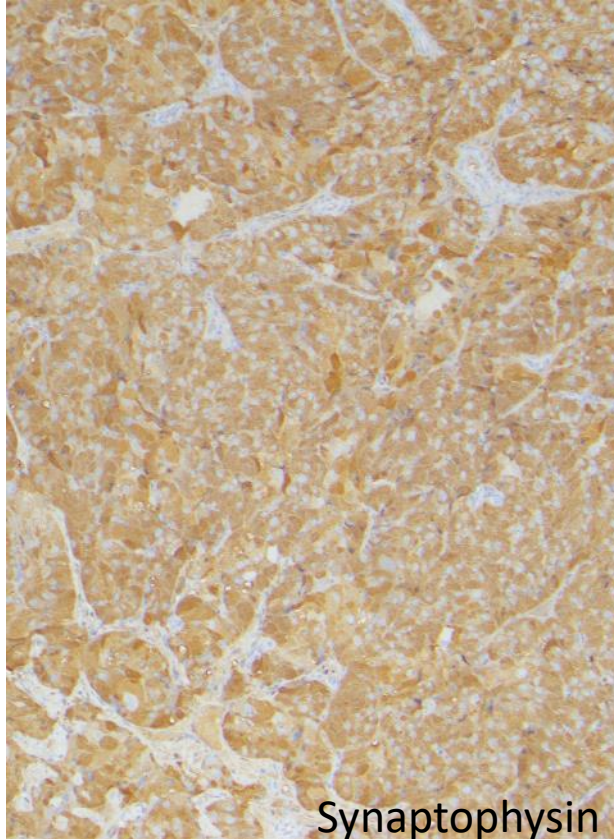


SOX10

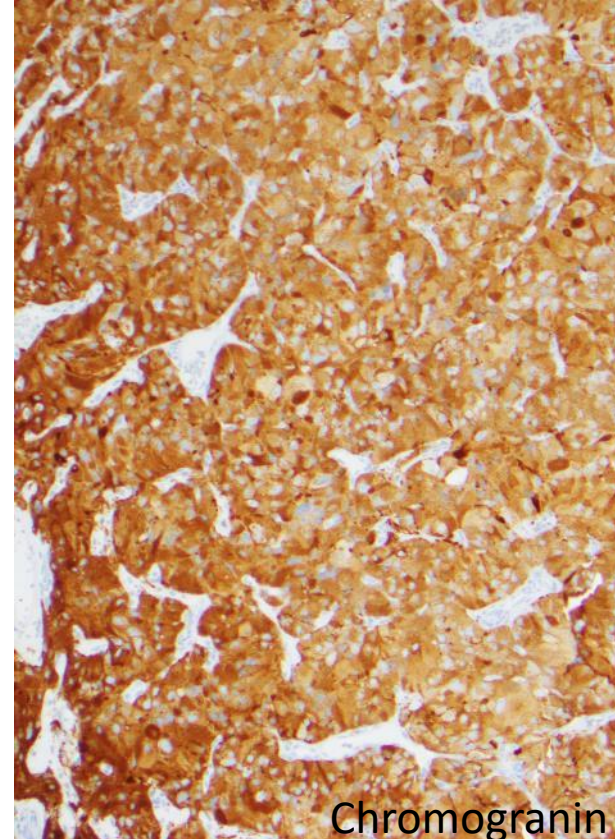
63 year old female outside consultation
original dx of "melanoma"



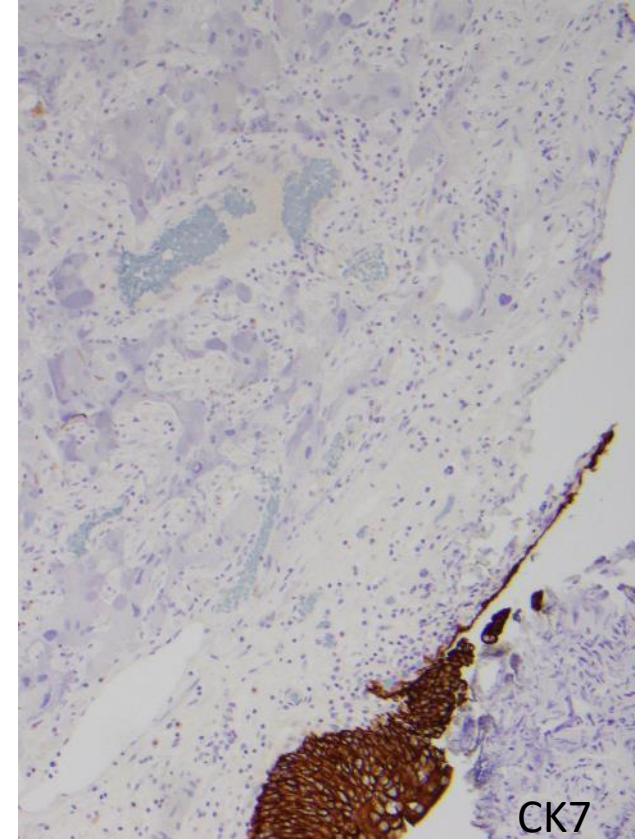
GATA3



Synaptophysin



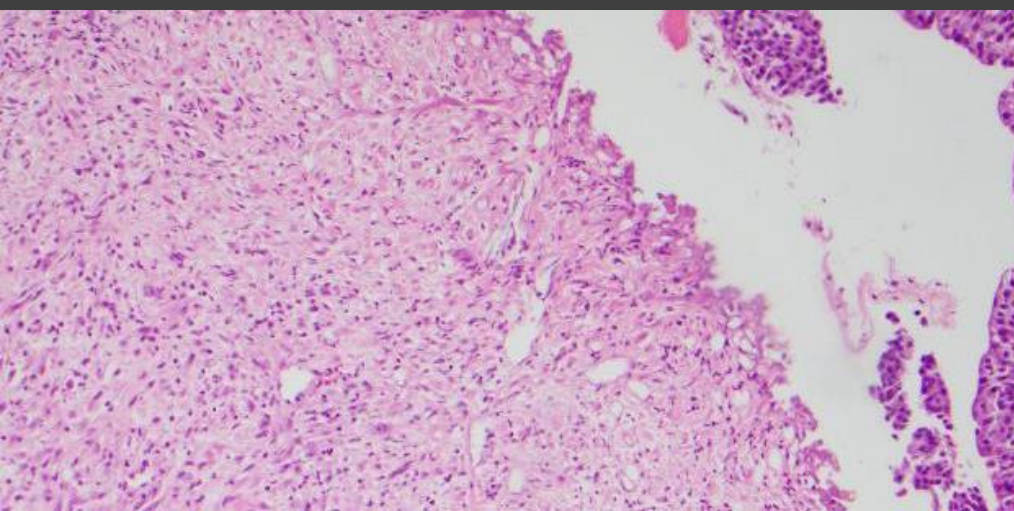
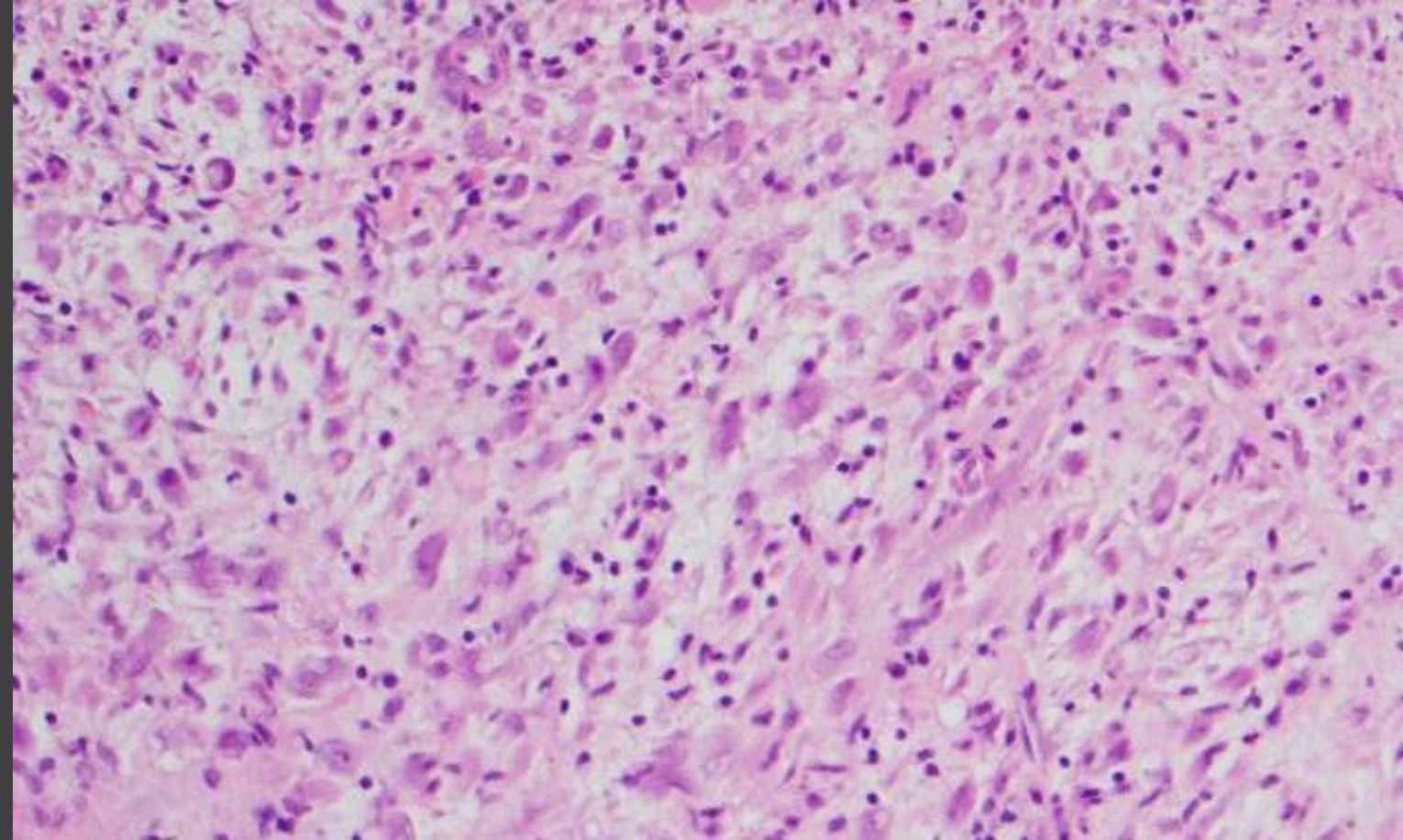
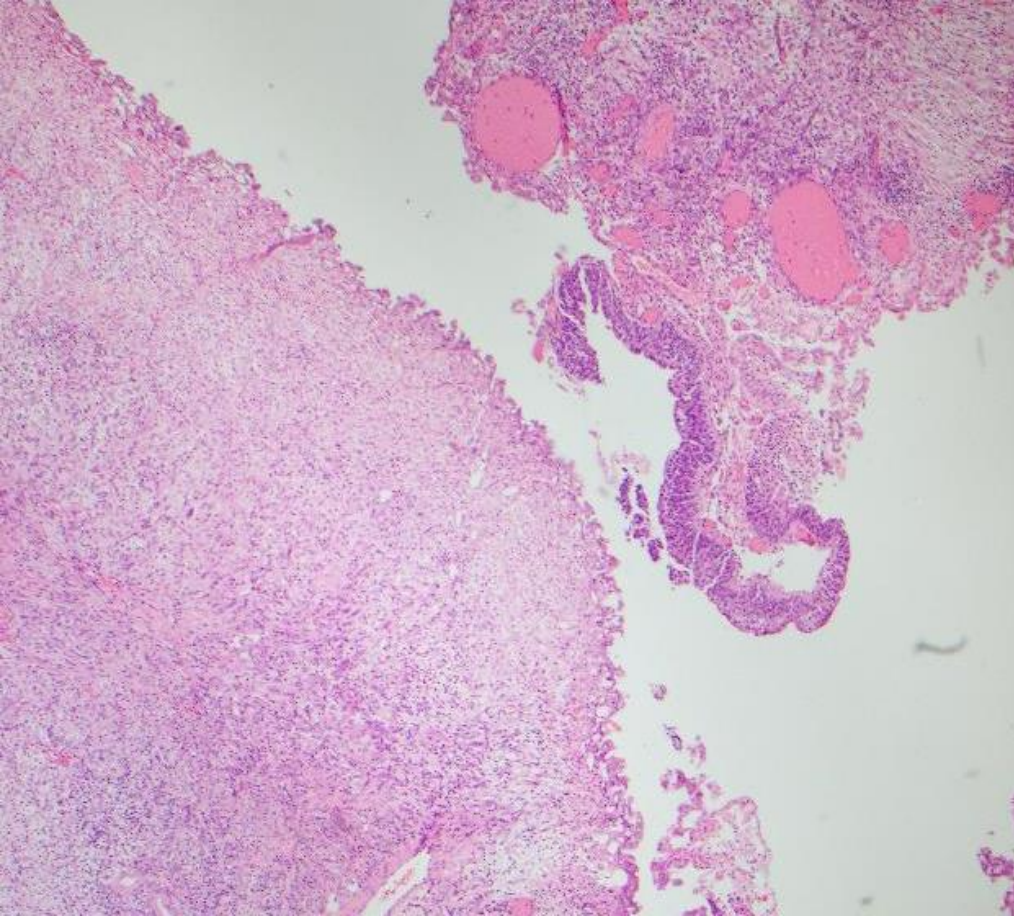
Chromogranin



CK7

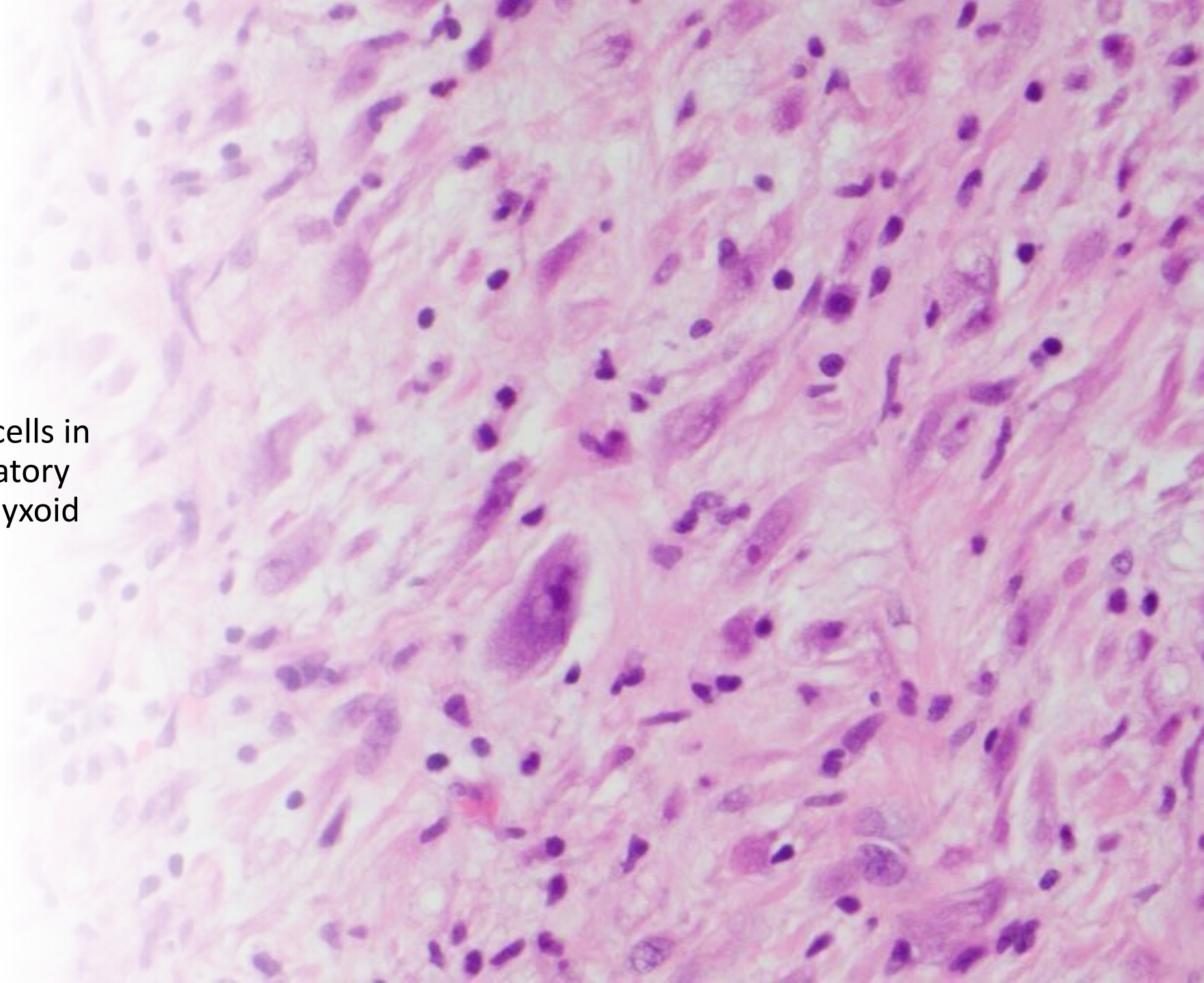
PARAGANGLIOMA

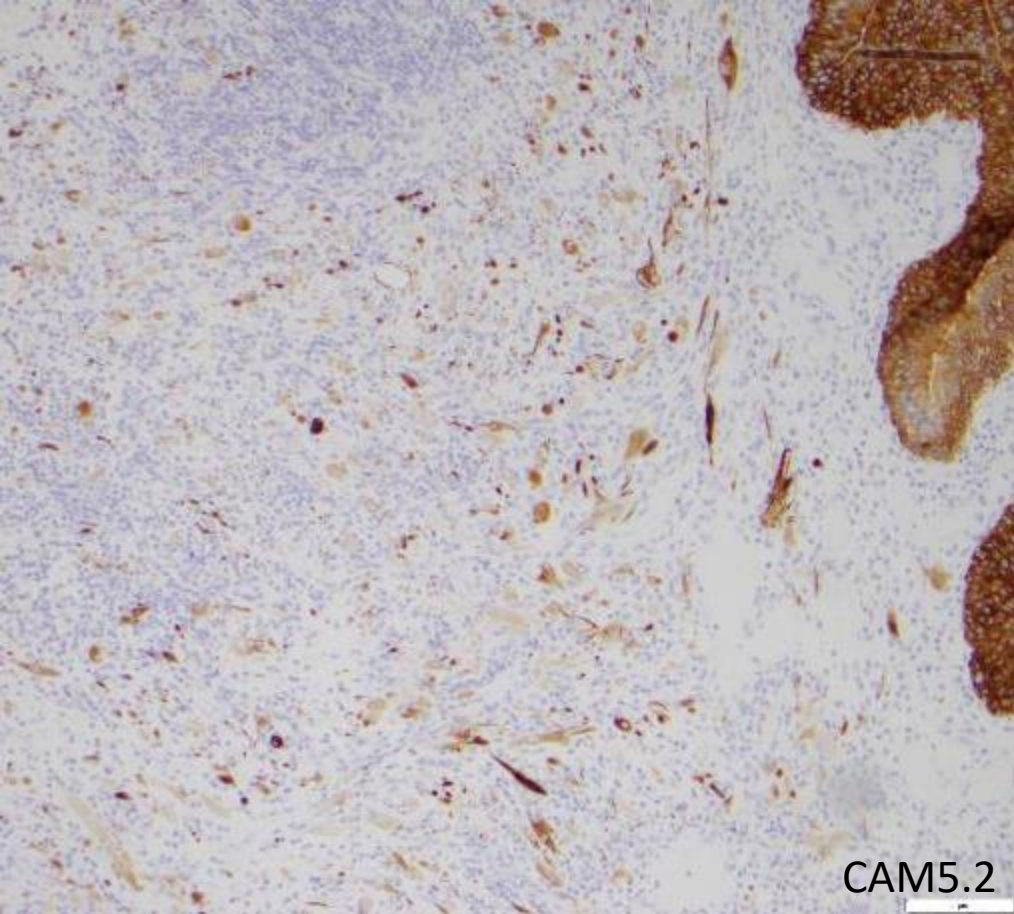
- Reported in bladder, urethra, prostate, seminal vesicles, kidneys
- 30-40% associated with hereditary disease (even higher in children) – strong consideration for genetic counseling/testing
- SDH related genes (A-D and SDHAF2), Carney-Stratakis syndrome, VHL, MEN2



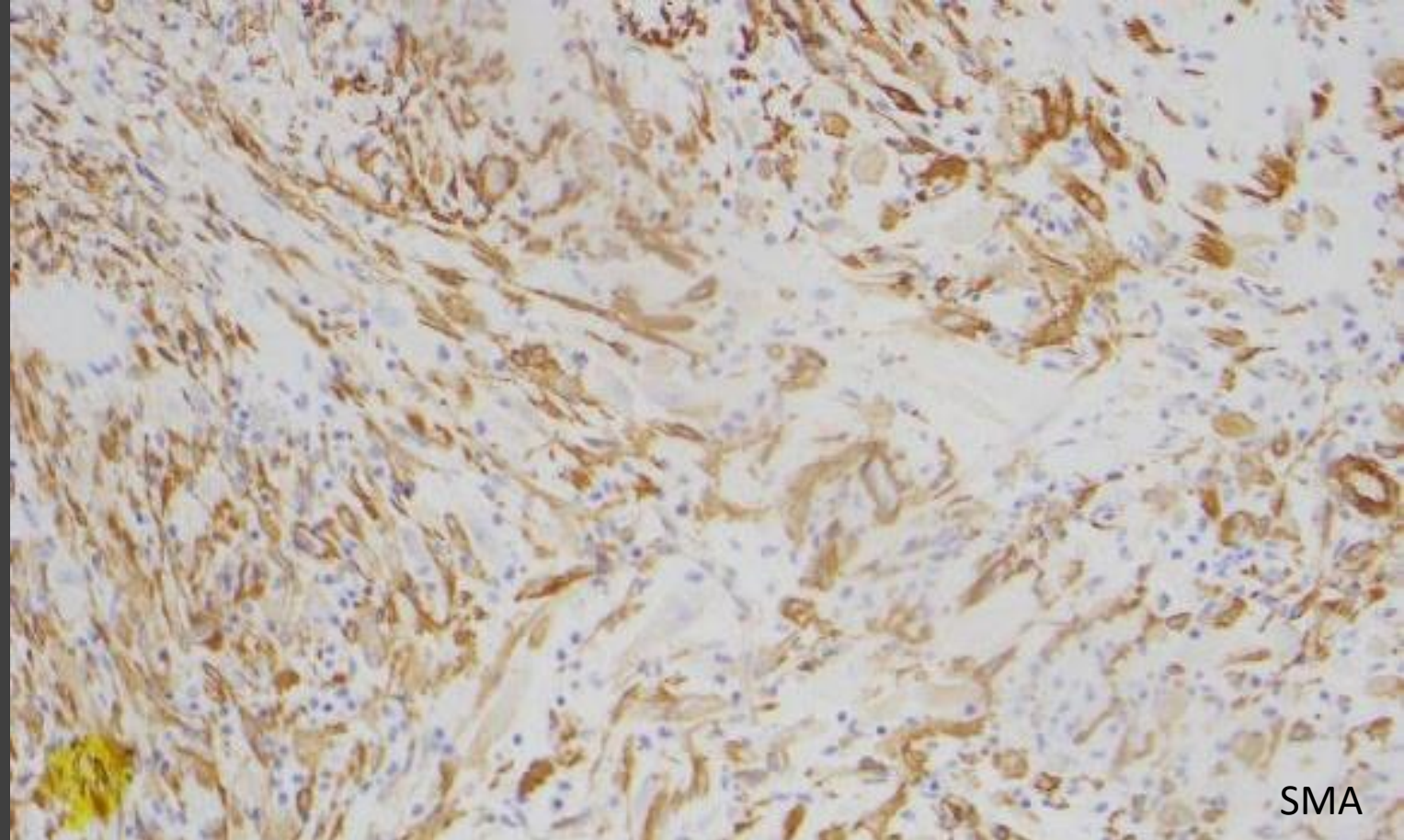
79 year old bladder mass

- Occasional mitoses
- Spindled and epithelioid cells in association with inflammatory cells and edematous to myxoid stroma

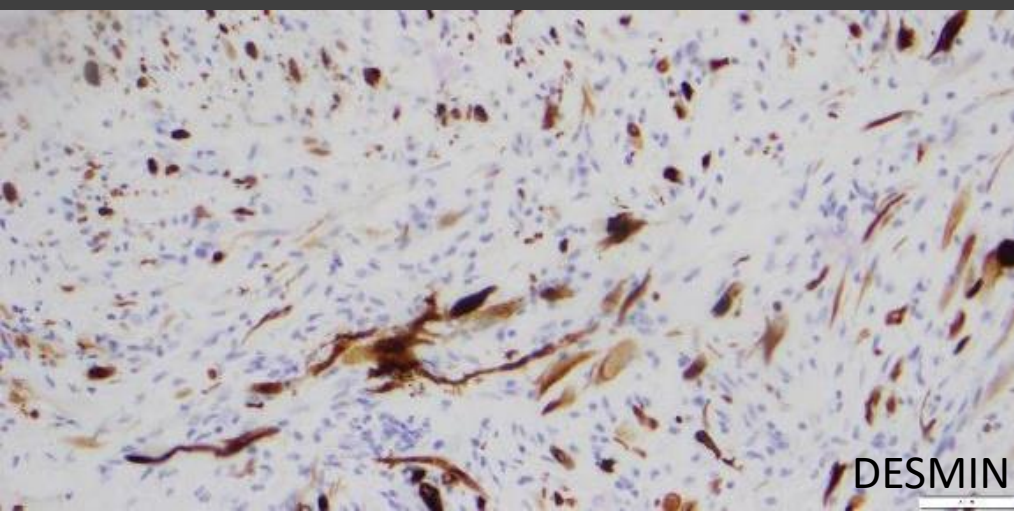




CAM5.2



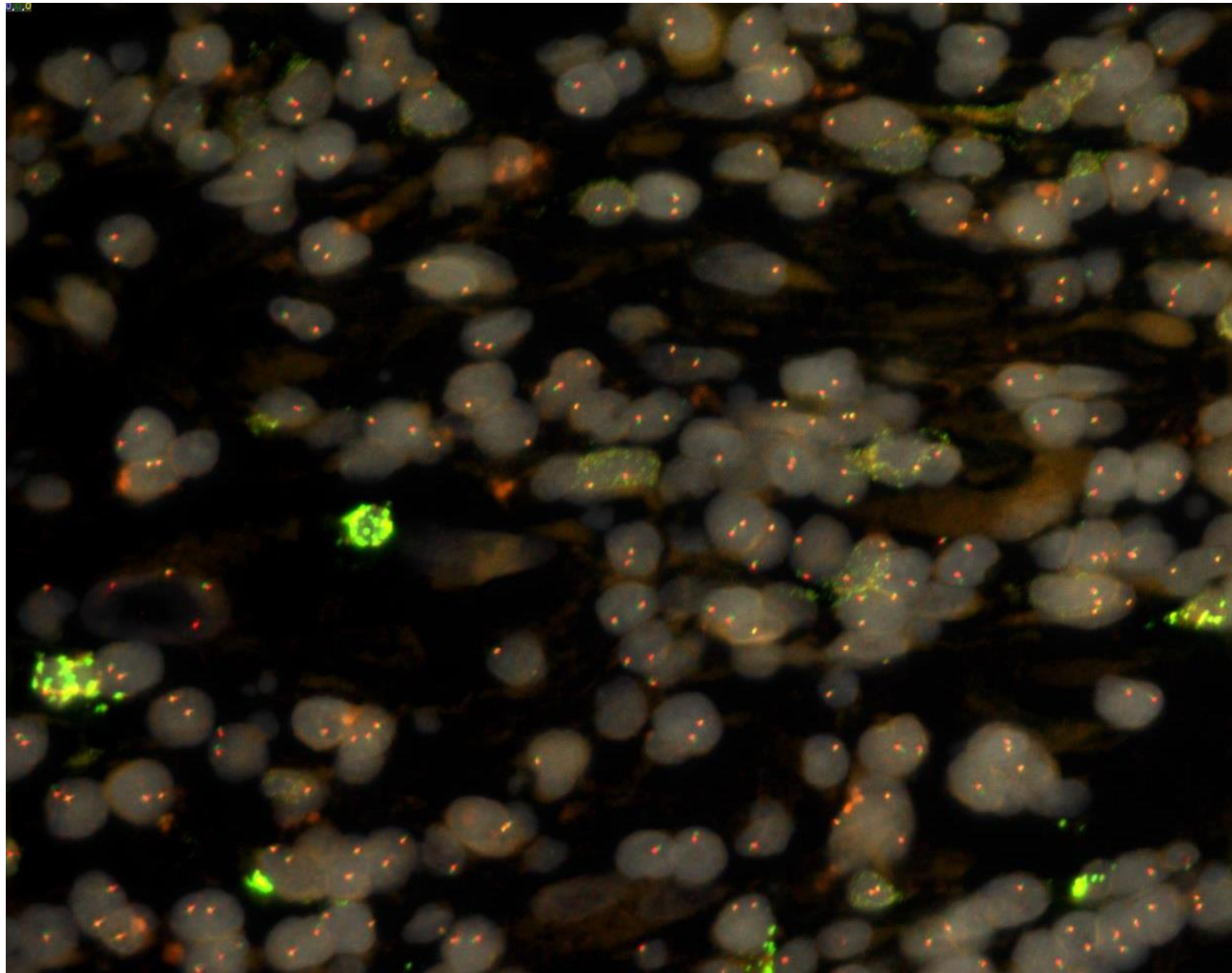
SMA

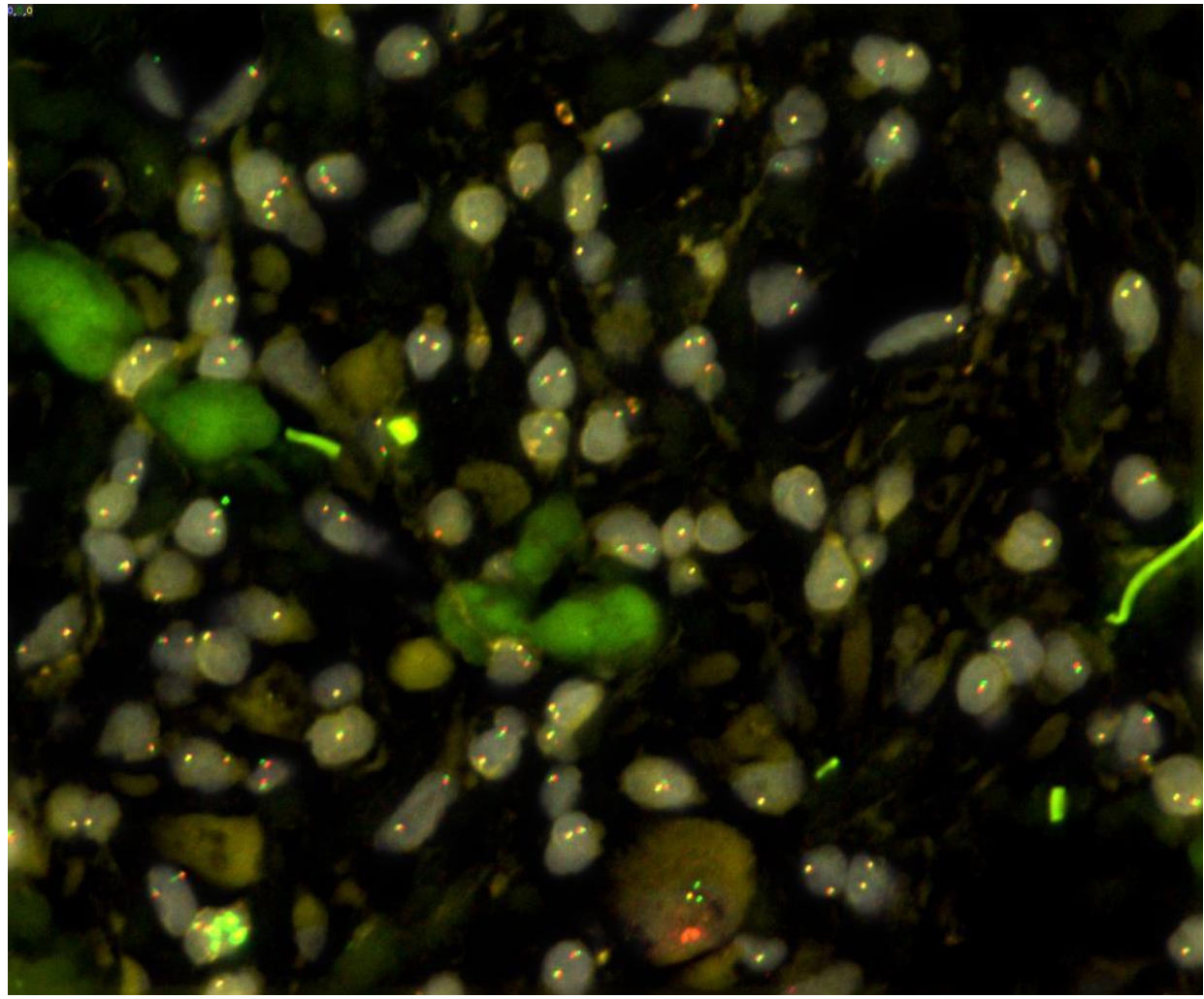
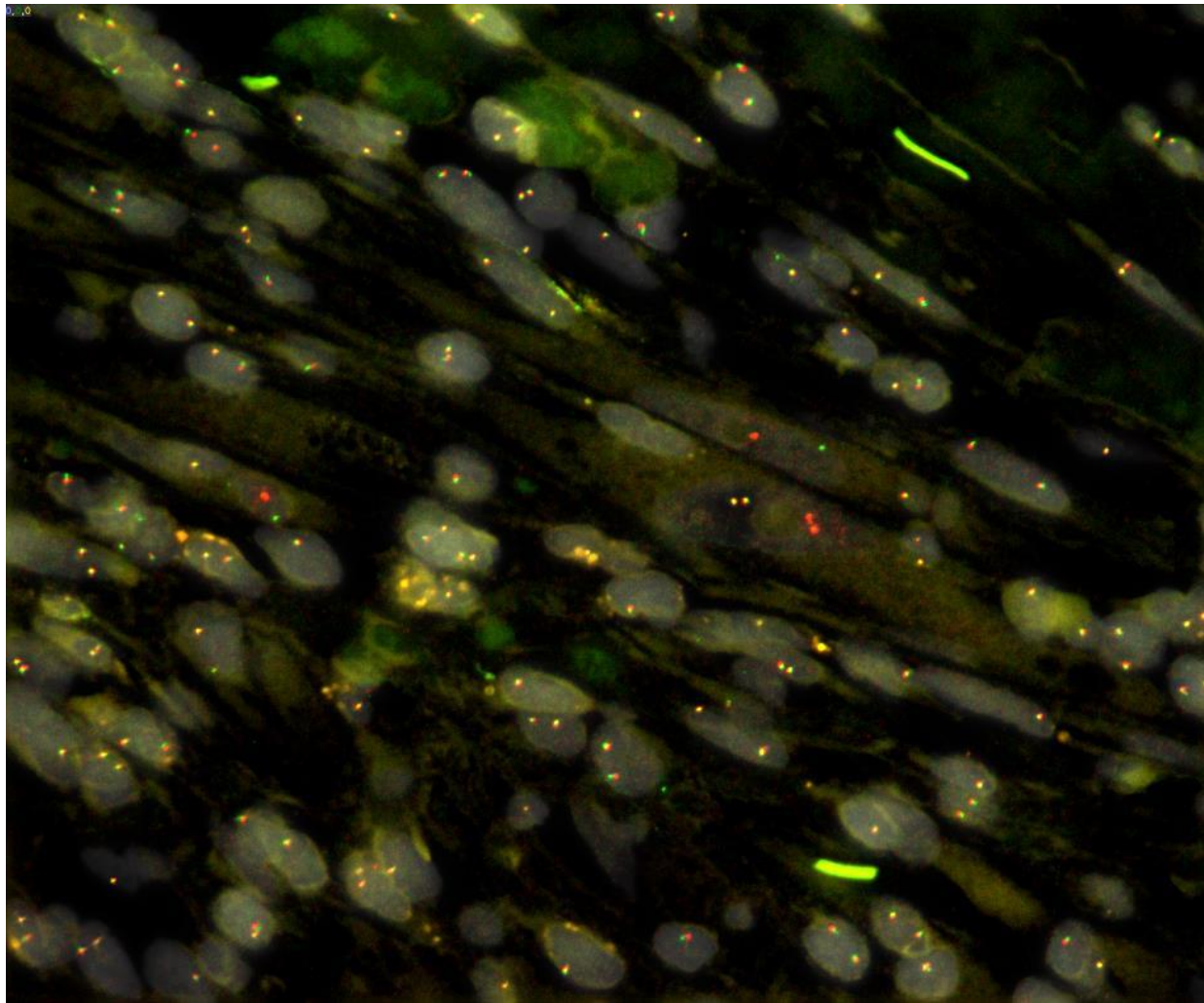


DESMIN

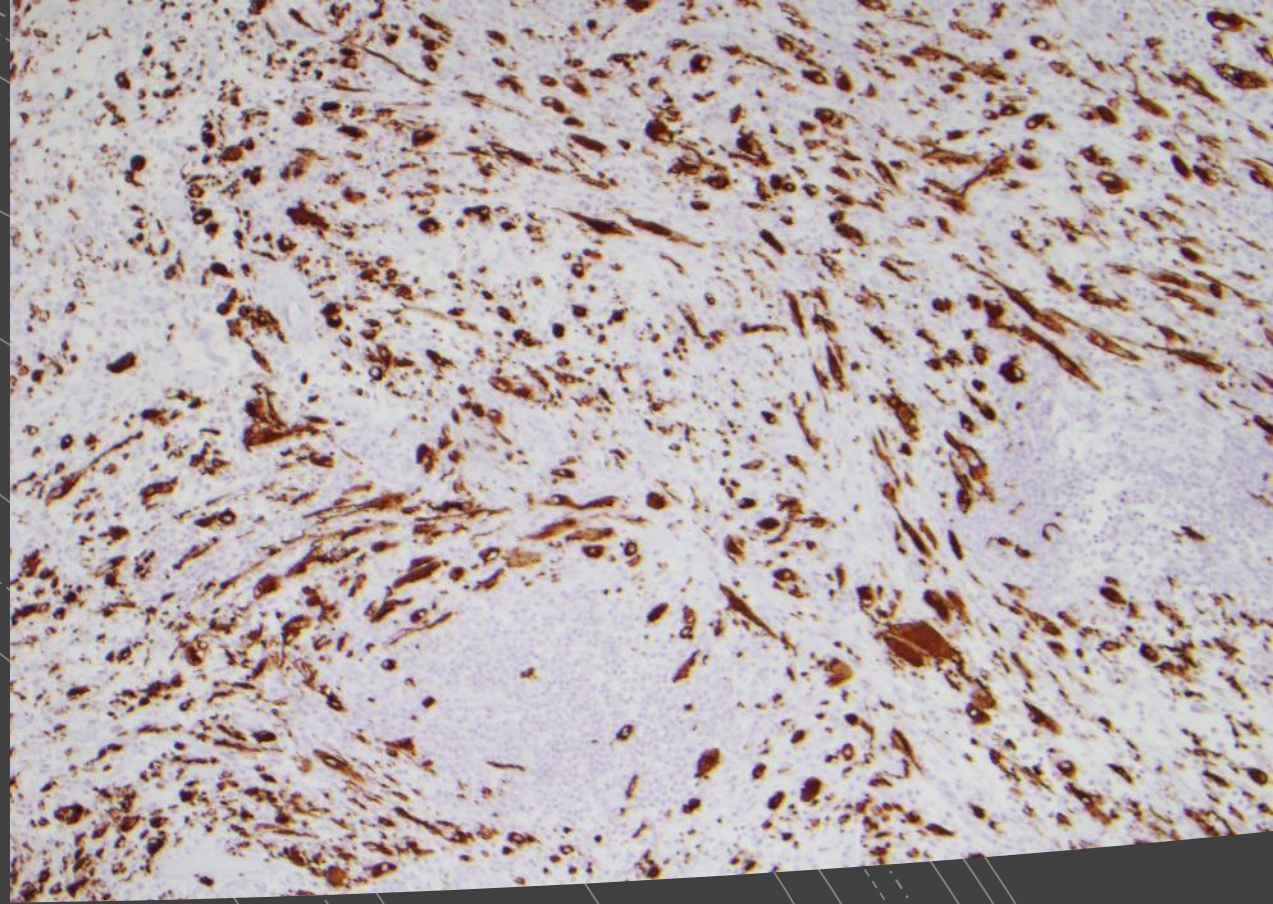
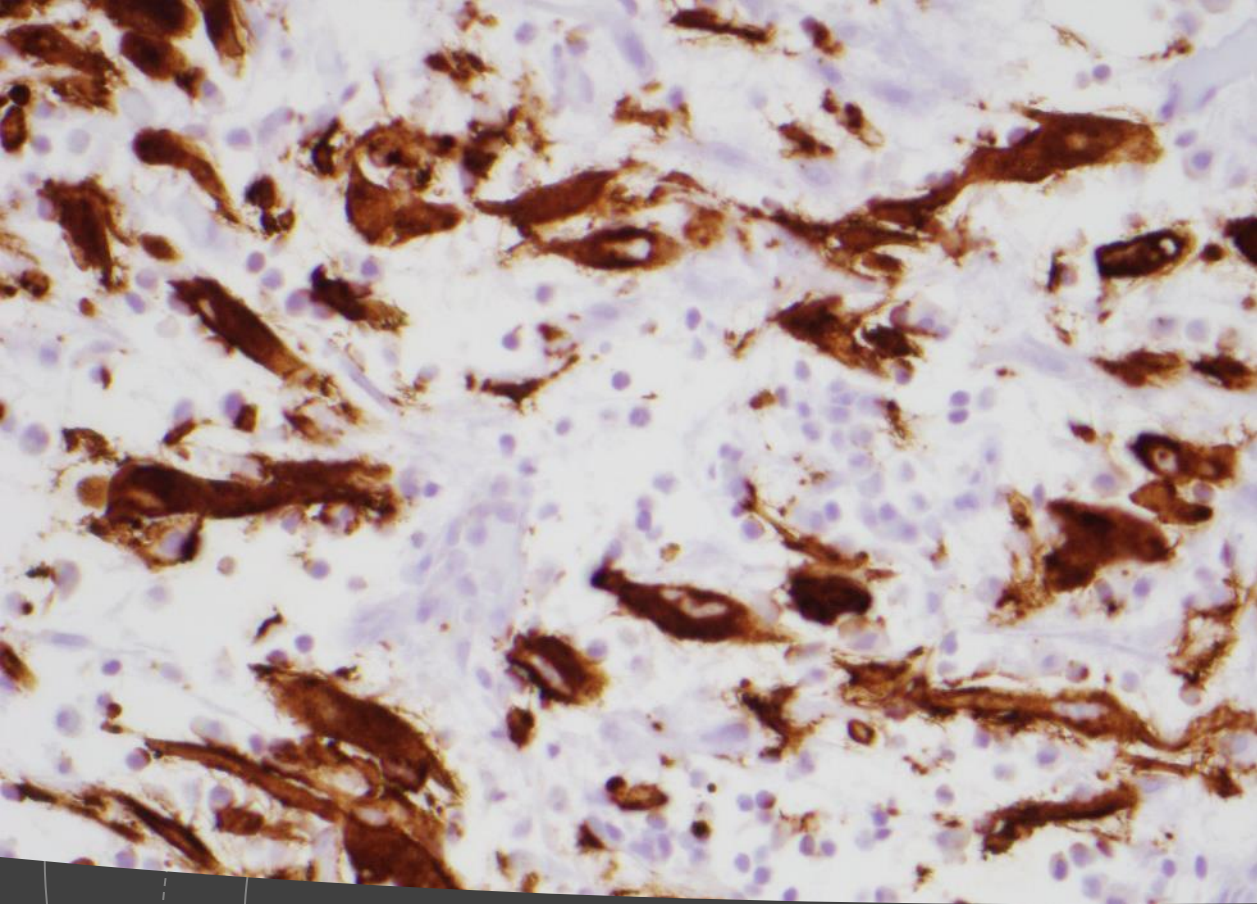
+Muscle and Keratin IHC

-
- Initial FISH diagnosis of “ALK not rearranged”

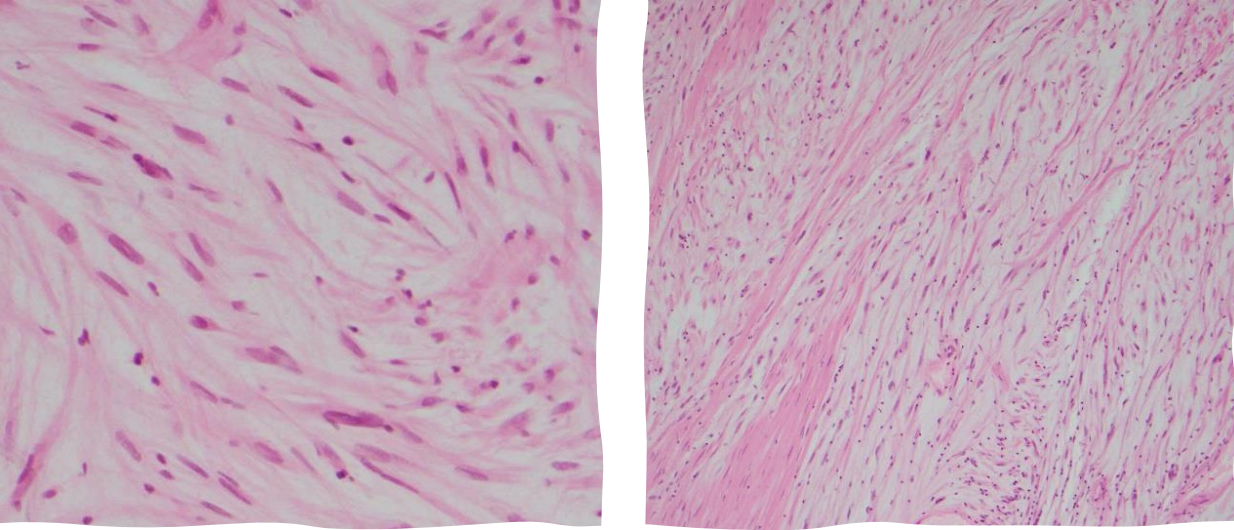




ALK FISH

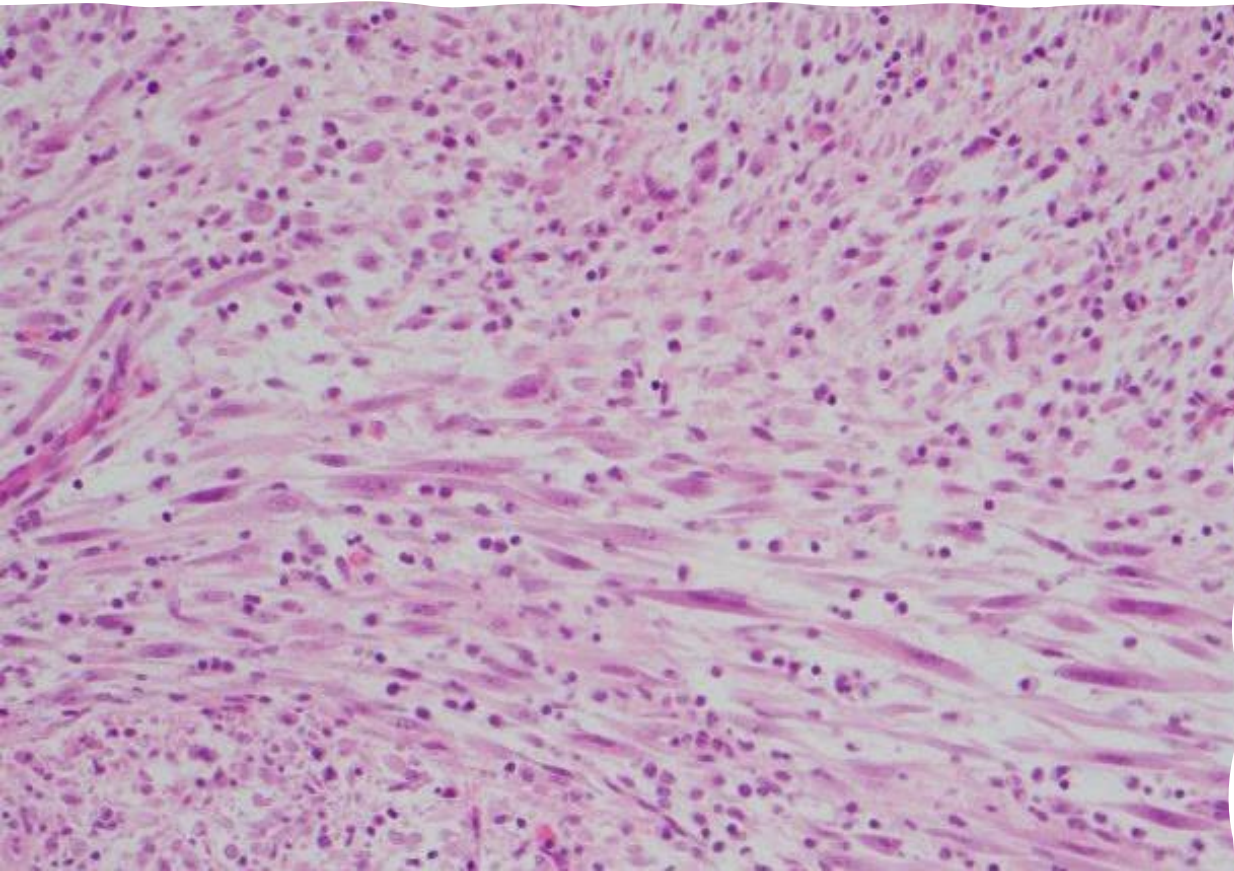


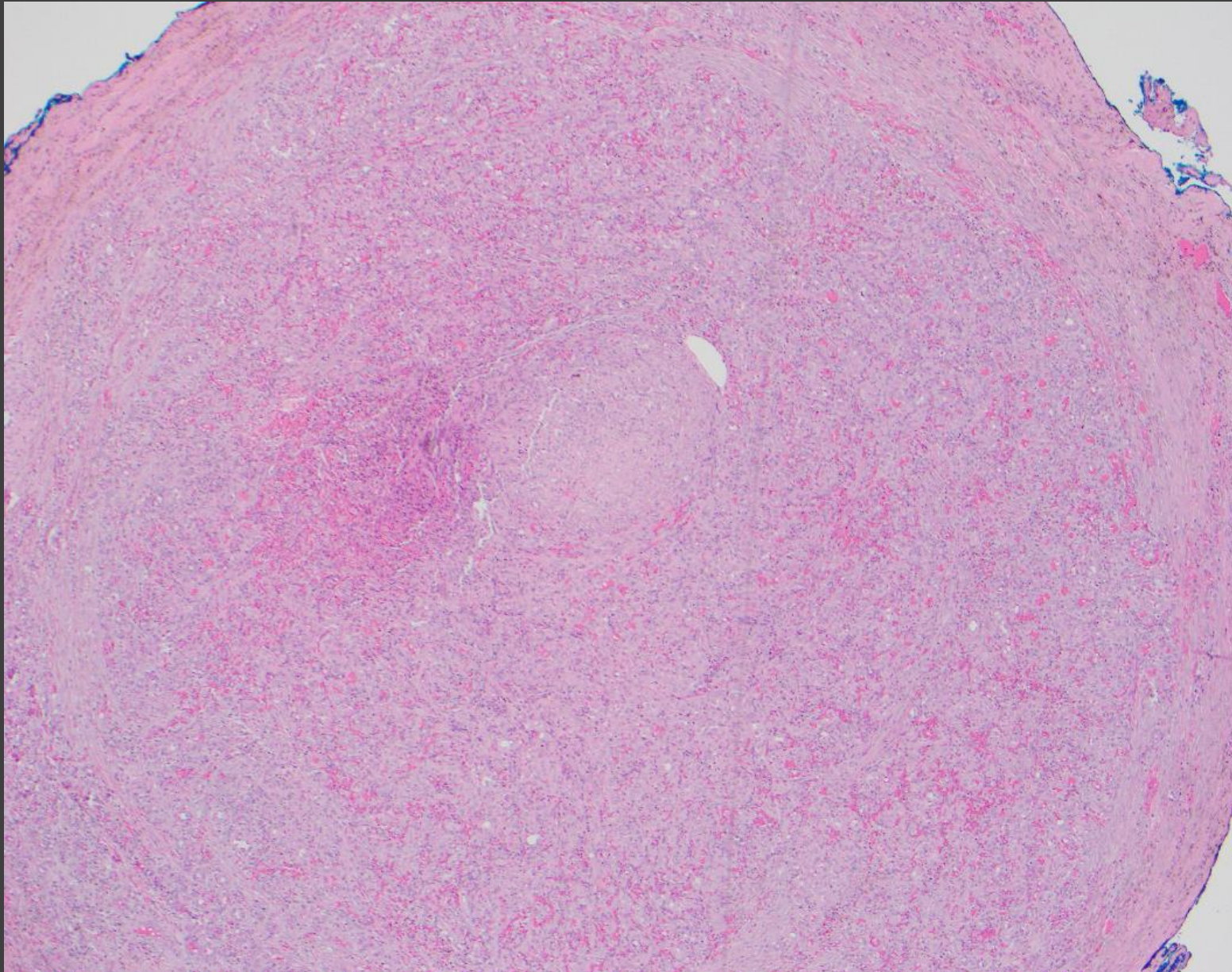
ALK IHC



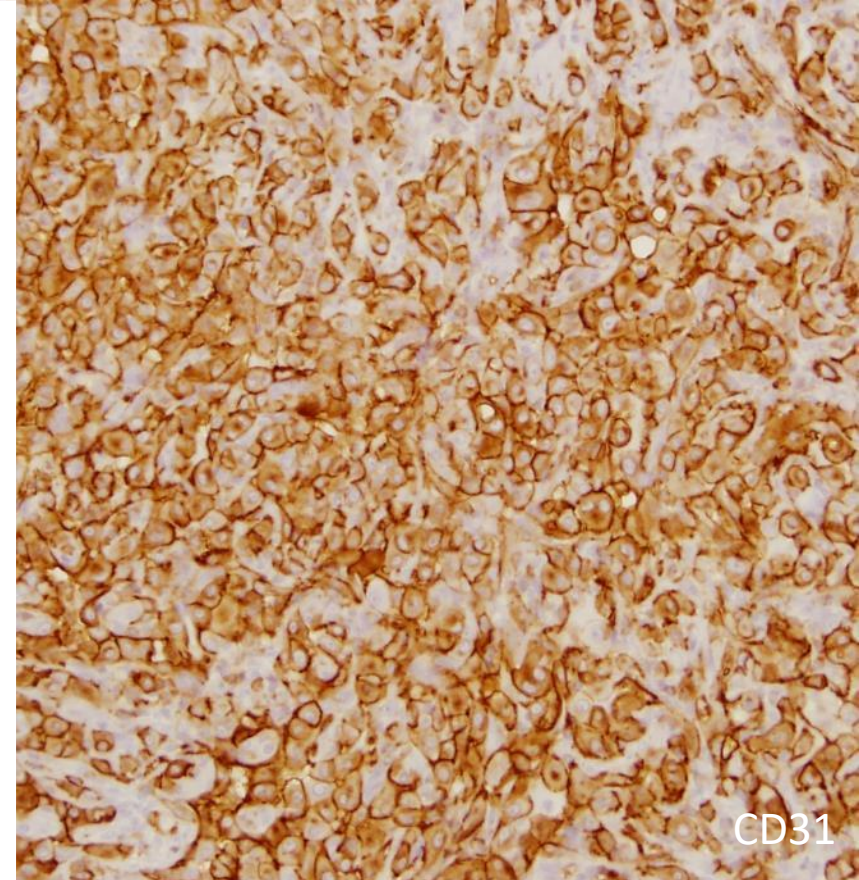
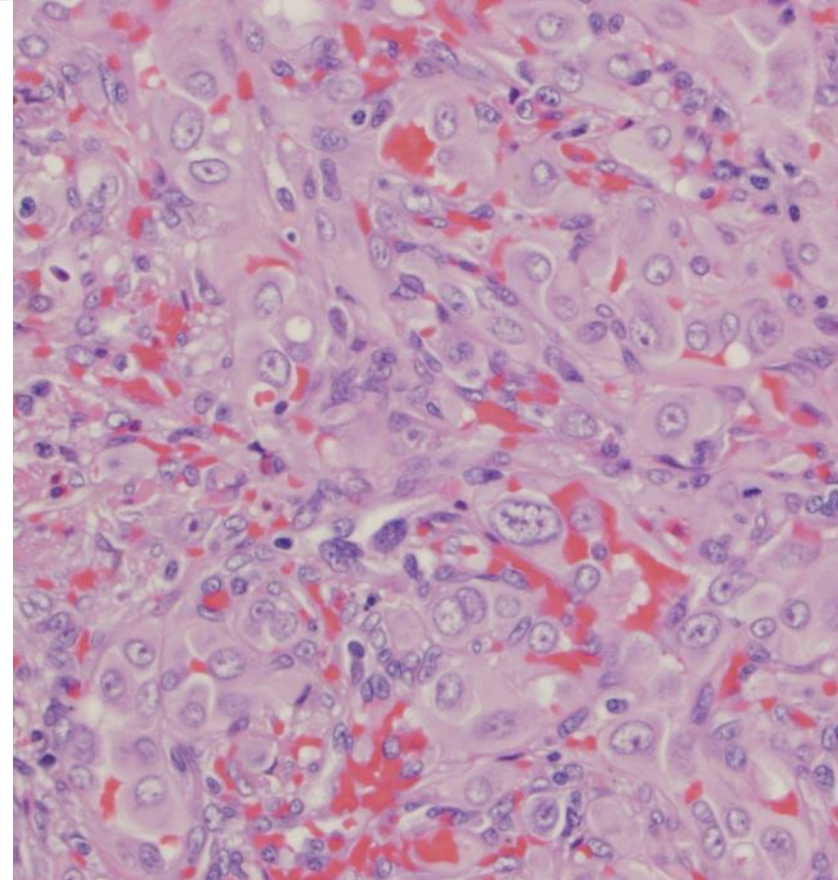
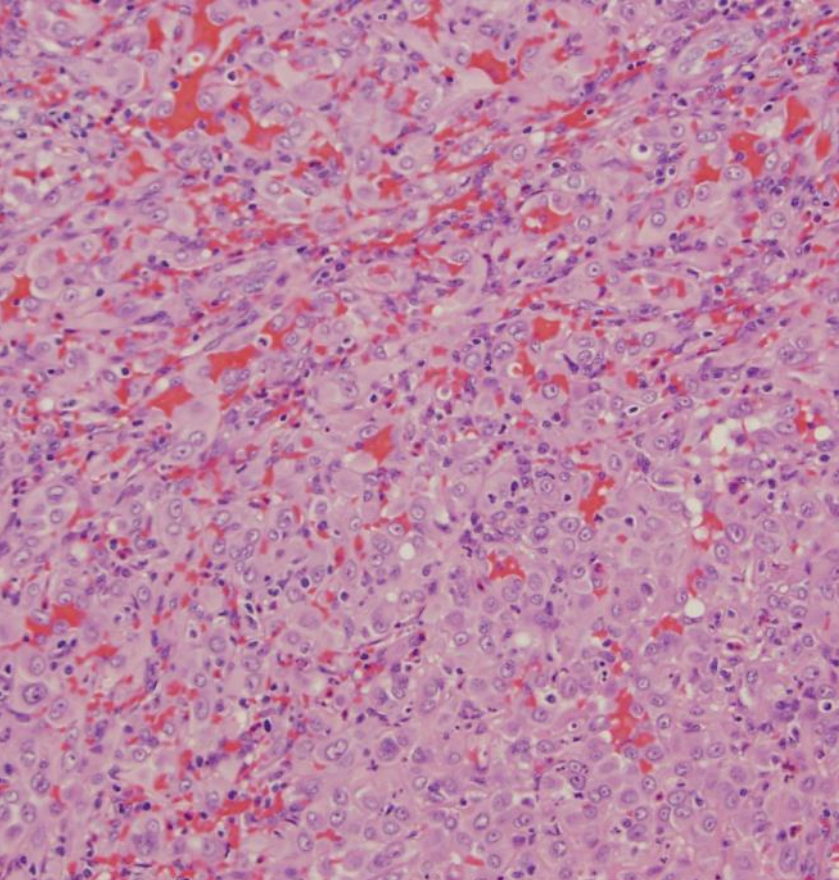
Variable Morphology

- ALK rearranged in >50% of cases
- 1/3 may recur and rarely metastasize
- DDX Includes:
 - Fibromatosis
 - Leiomyosarcoma
 - IgG4 sclerosing disease
 - Hematopoietic malignancy
 - GIST
 - Carcinosarcoma





30 year old
male with
distal penile
urethral mass



CD31

- Somewhat circumscribed epithelioid and highly vascular lesion
- Negative for epithelial markers in this case
- (+) CD31 and ERG



Epithelioid Hemangioendothelioma

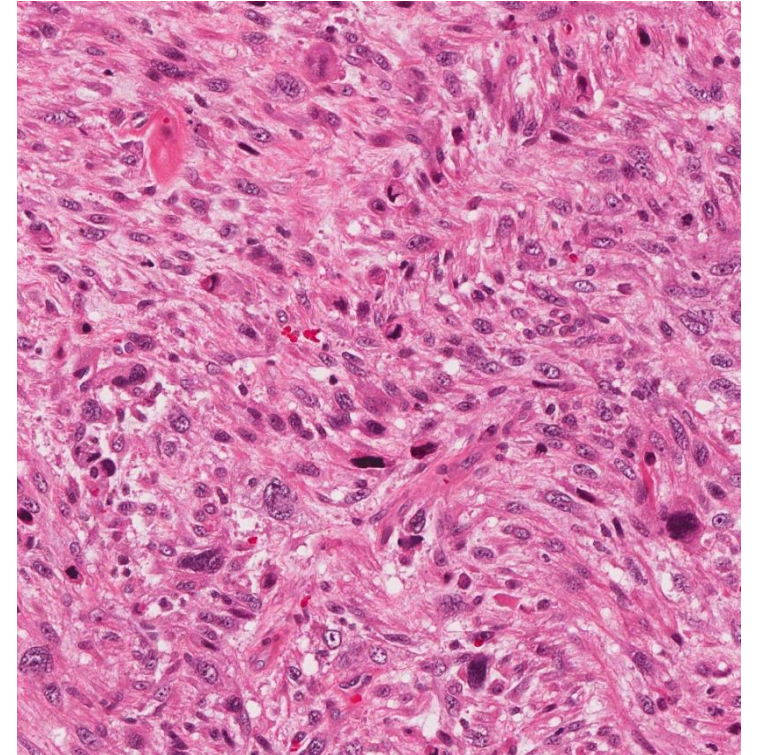
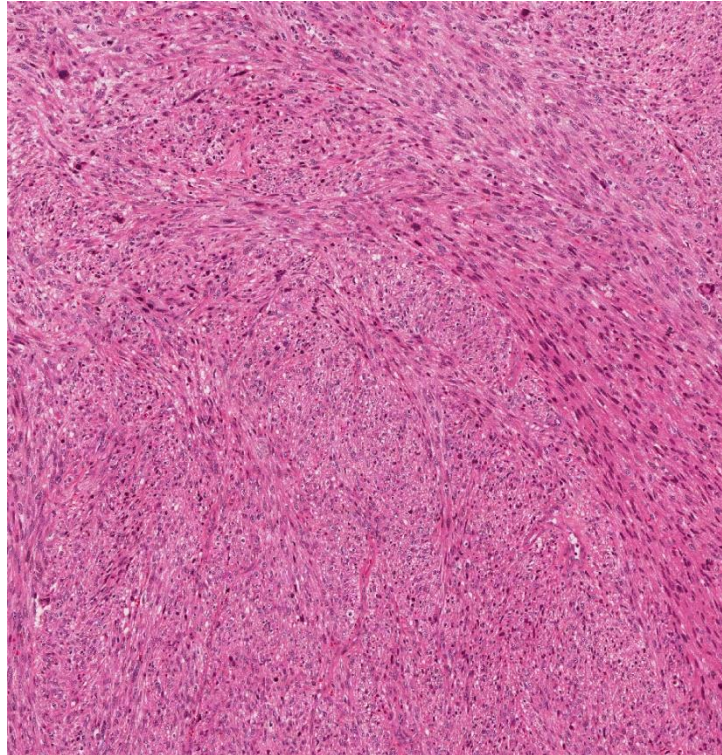
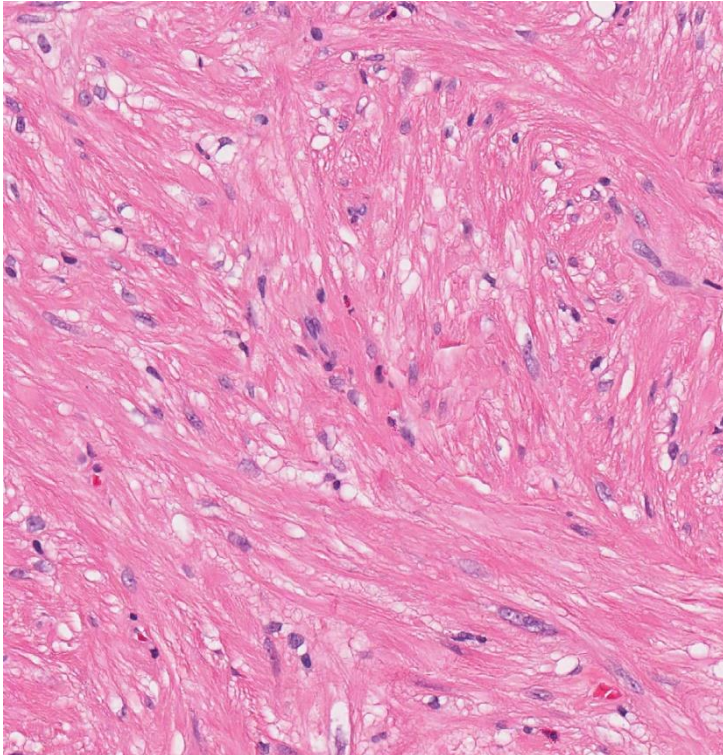
- Vascular neoplasm with unpredictable behavior
- Positive for vascular markers with variable expression of keratin
- Locally recur (10-20%) and may metastasize to lungs and lymph nodes (20-30%)
- Recurrent molecular abnormalities
 - *WWTR1-CAMTA1*
 - *YAP-TFE3*

The background of the slide consists of two histological images of bladder tissue stained with hematoxylin and eosin (H&E). The top image shows a low-power view of the bladder wall, with a large, irregular, and densely cellular area on the left side, likely representing the tumor. The bottom image is a high-power view showing a dense population of atypical, spindle-shaped cells with hyperchromatic nuclei and scant cytoplasm, characteristic of angiosarcoma. The cells are arranged in a disorganized, infiltrative pattern.

Primary Angiosarcoma of the
Bladder

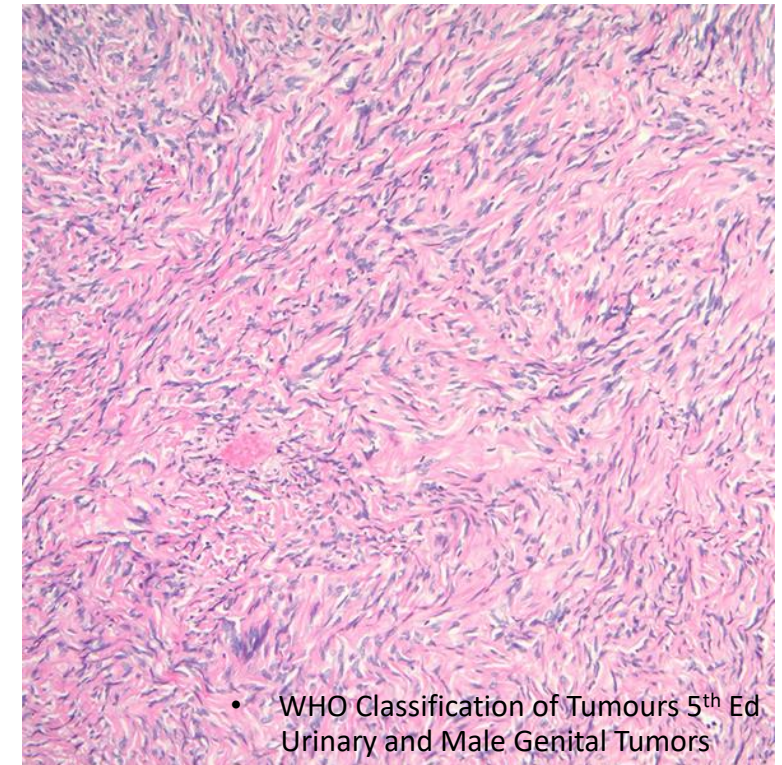
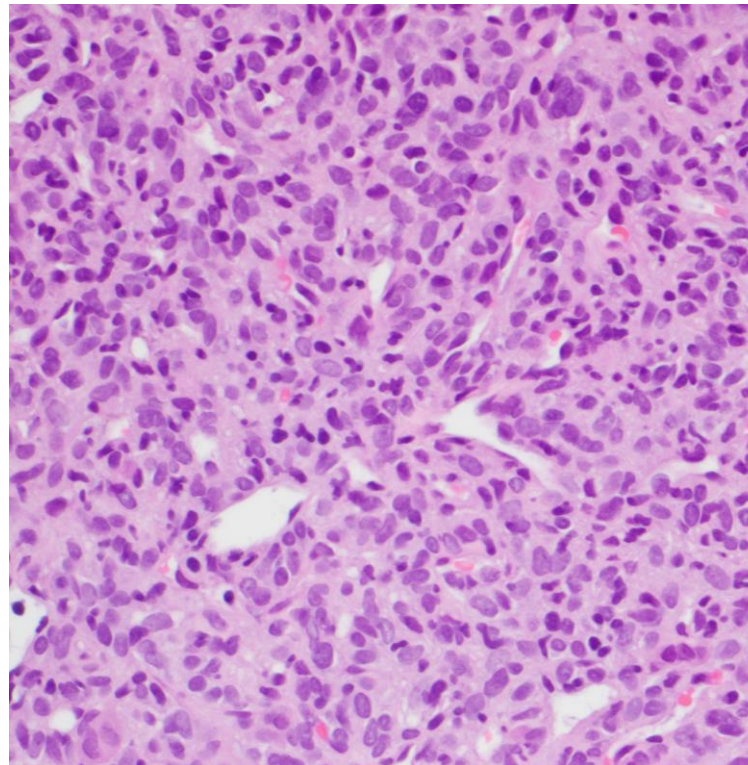
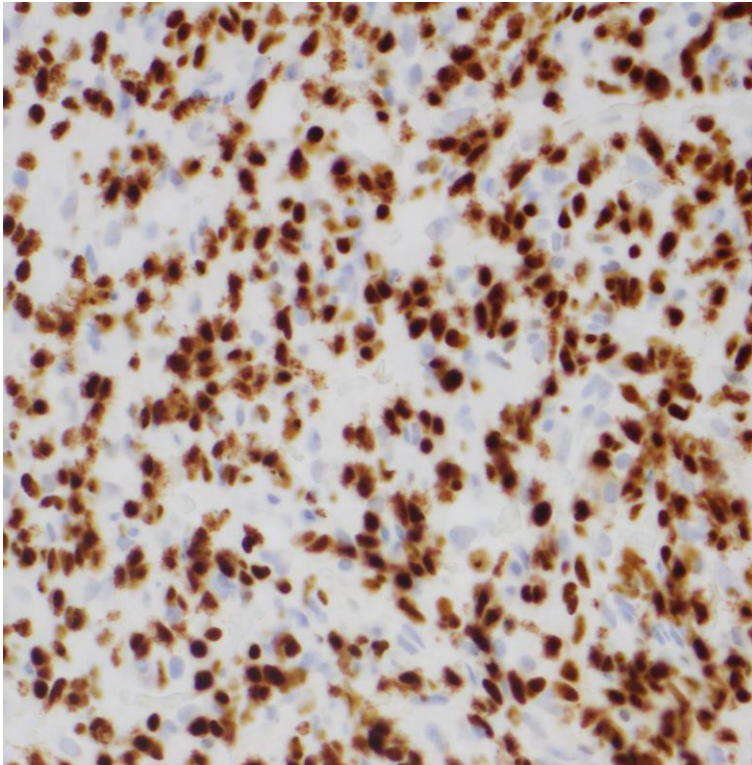
Exceedingly Rare <40 cases in
literature
Association with radiation

Leiomyosarcoma



Solitary Fibrous Tumor

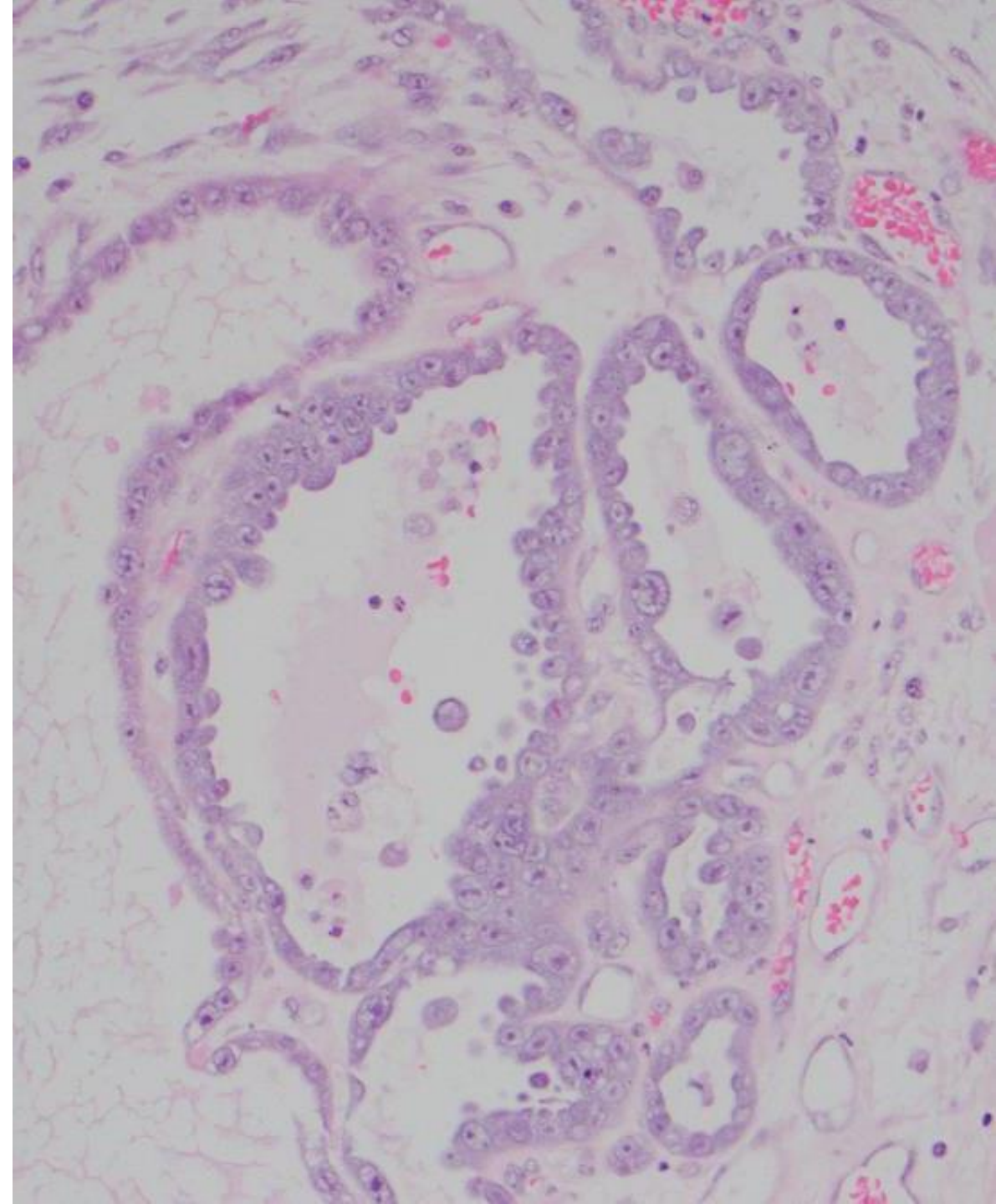
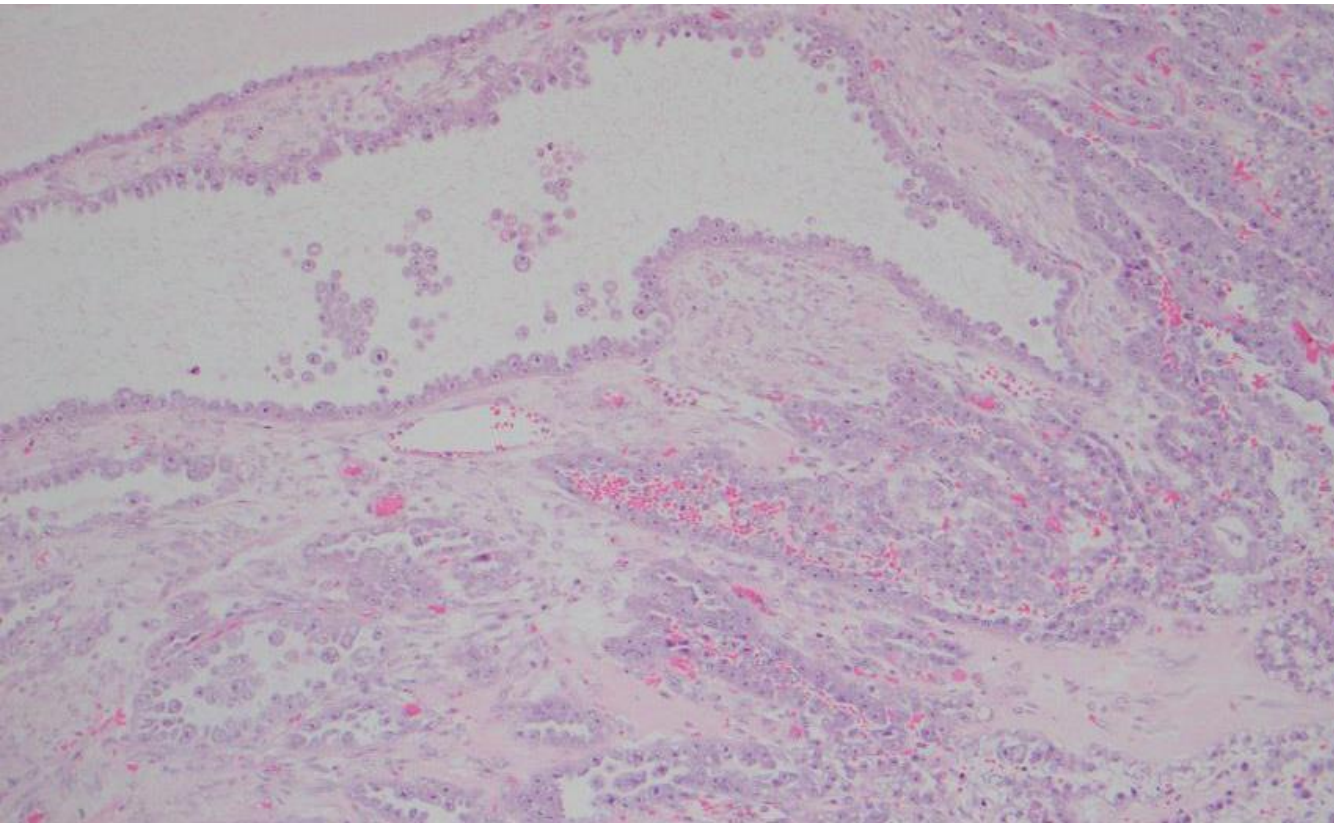
- *NAB2::STAT6* fusion (+ nuclear STAT6 IHC)
- spindled cells arranged haphazardly with collagenous stroma and staghorn (hemangiopericytoma like) vessels
- Reported along entire urinary tract
- 10-20% recur/metastasize
 - patient age (≥ 55 years), large size (≥ 15 cm), increased mitotic activity, and necrosis associated with increased risk

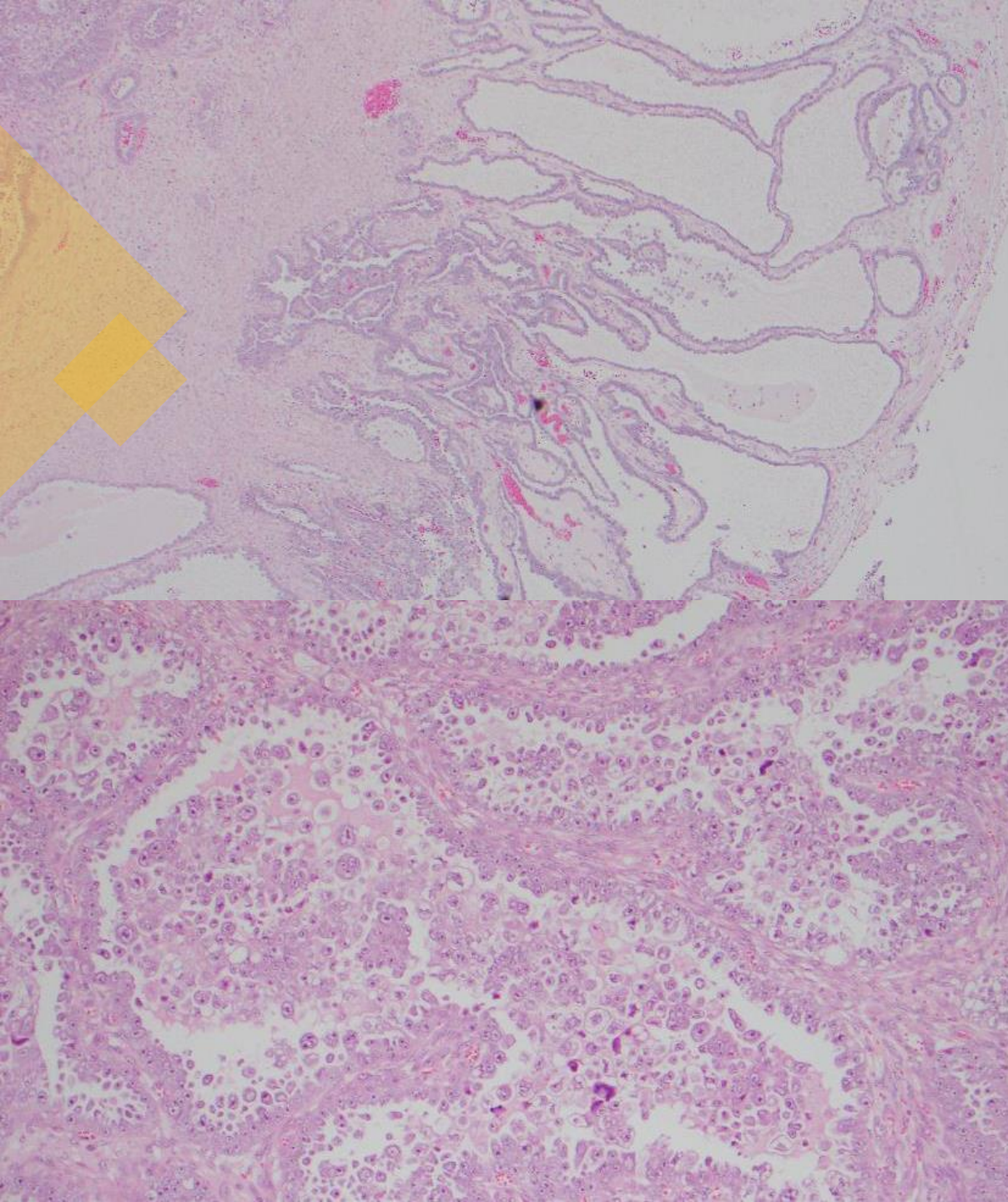


• WHO Classification of Tumours 5th Ed
Urinary and Male Genital Tumors

Bonus Case 😊

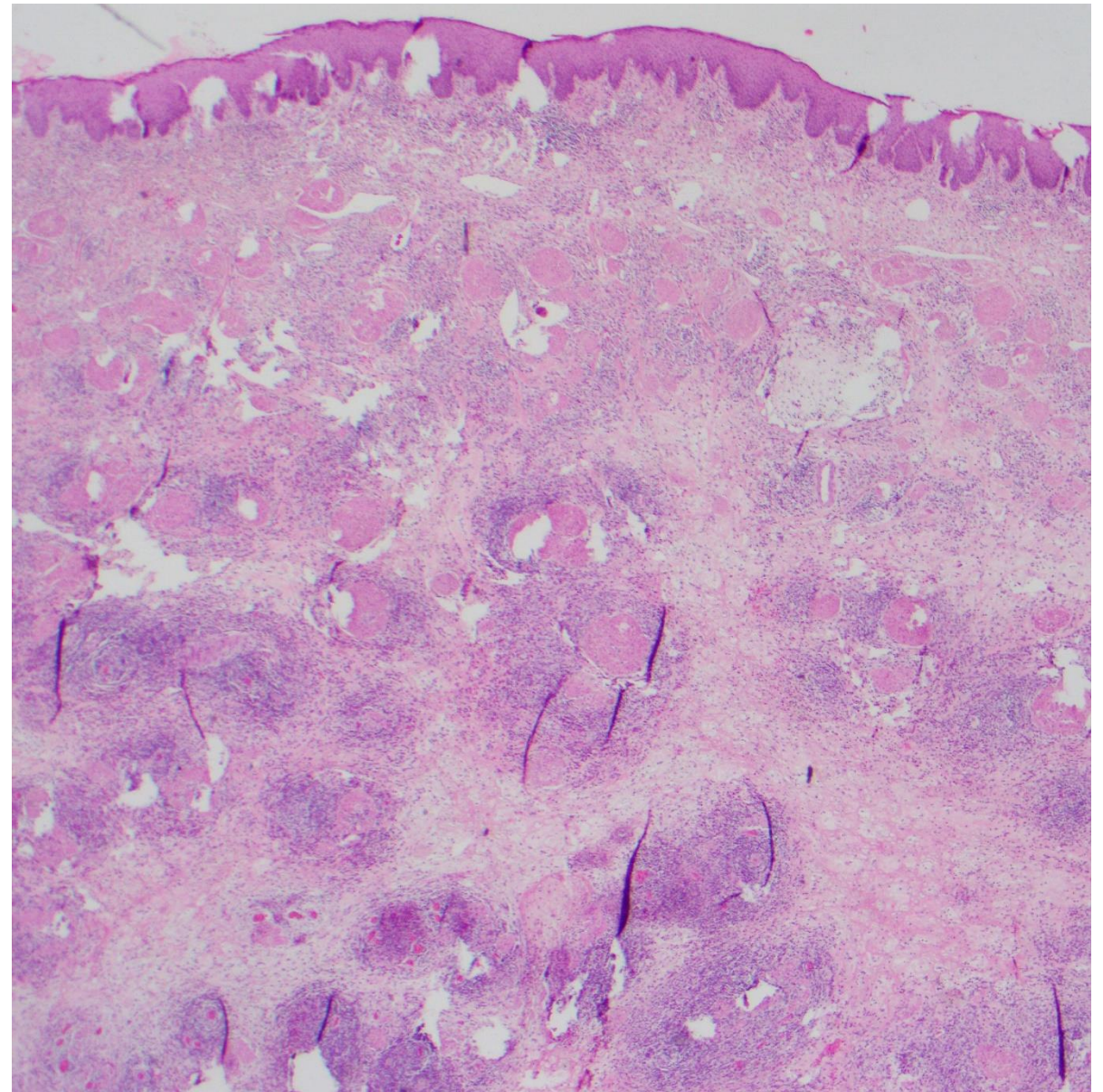
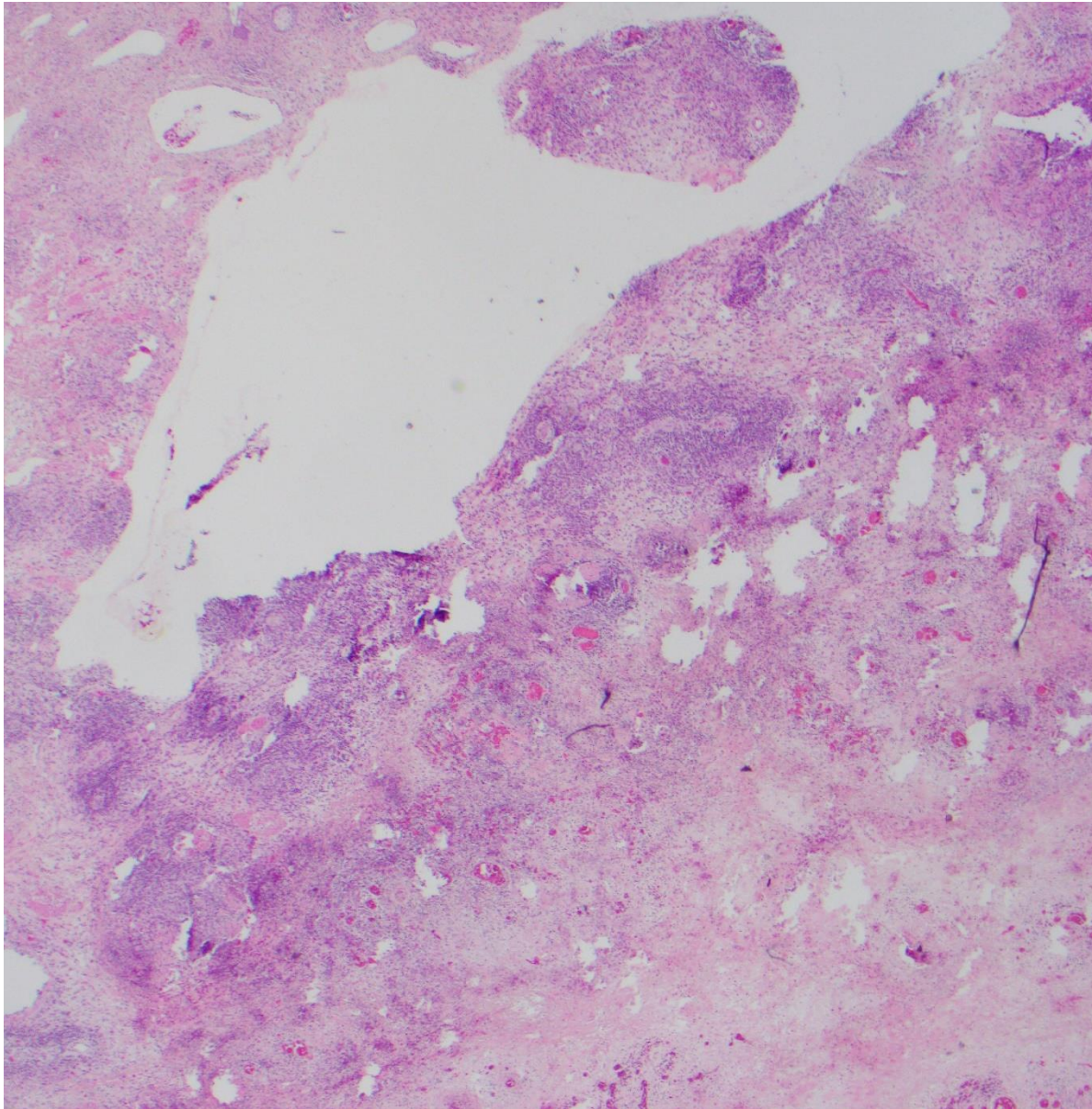
- 73 year old male with pelvic mass



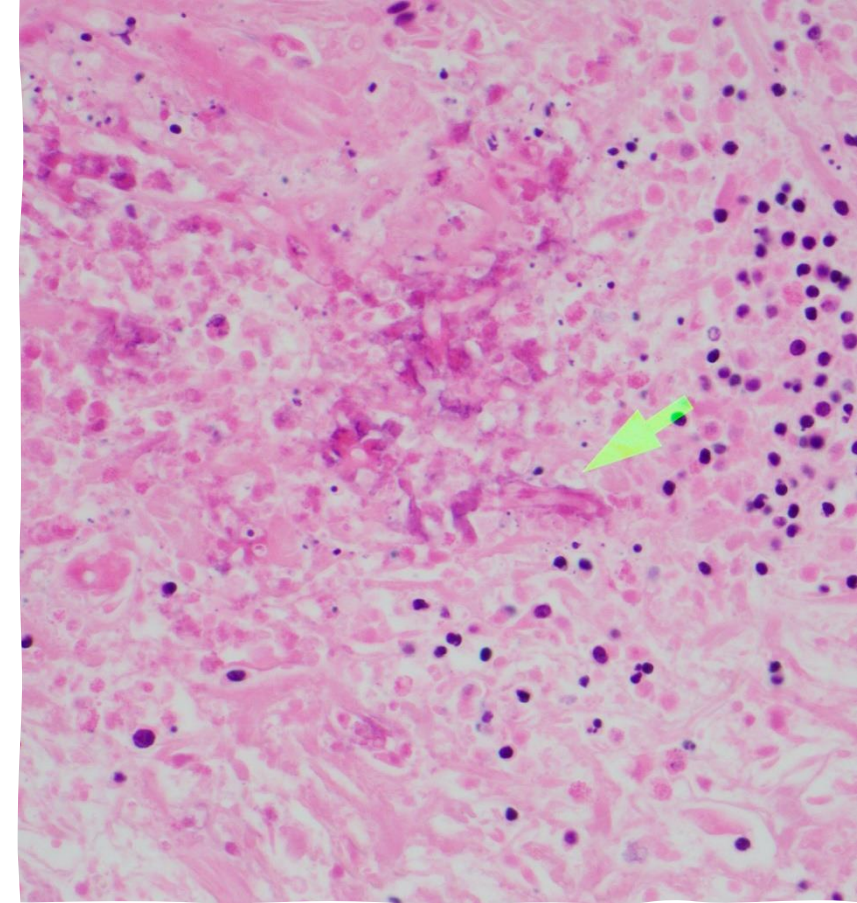
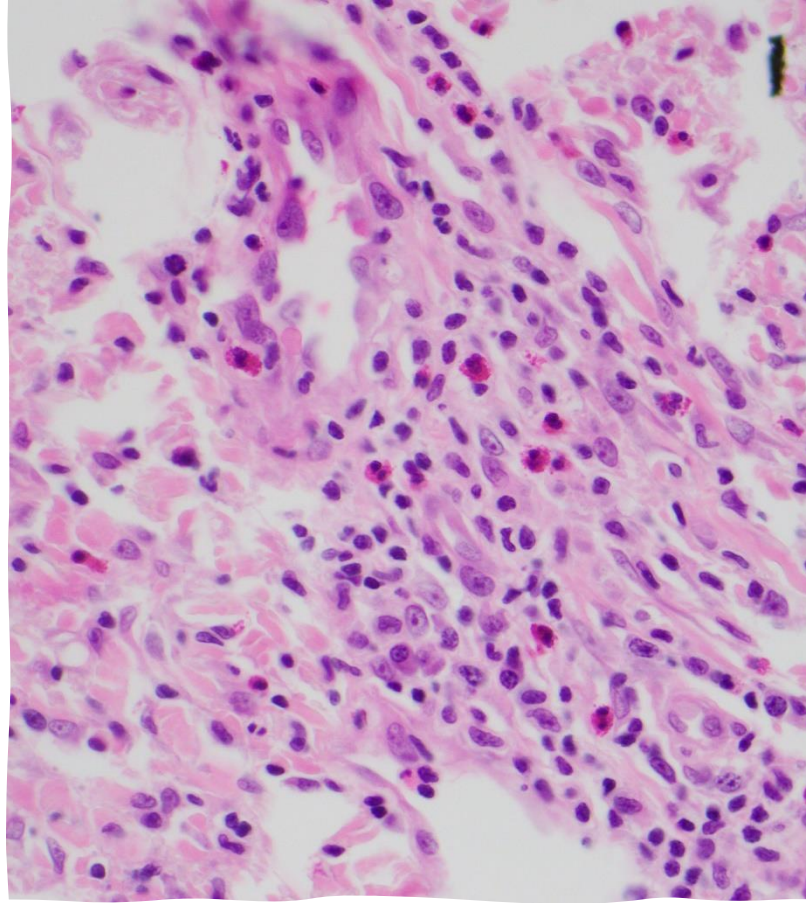
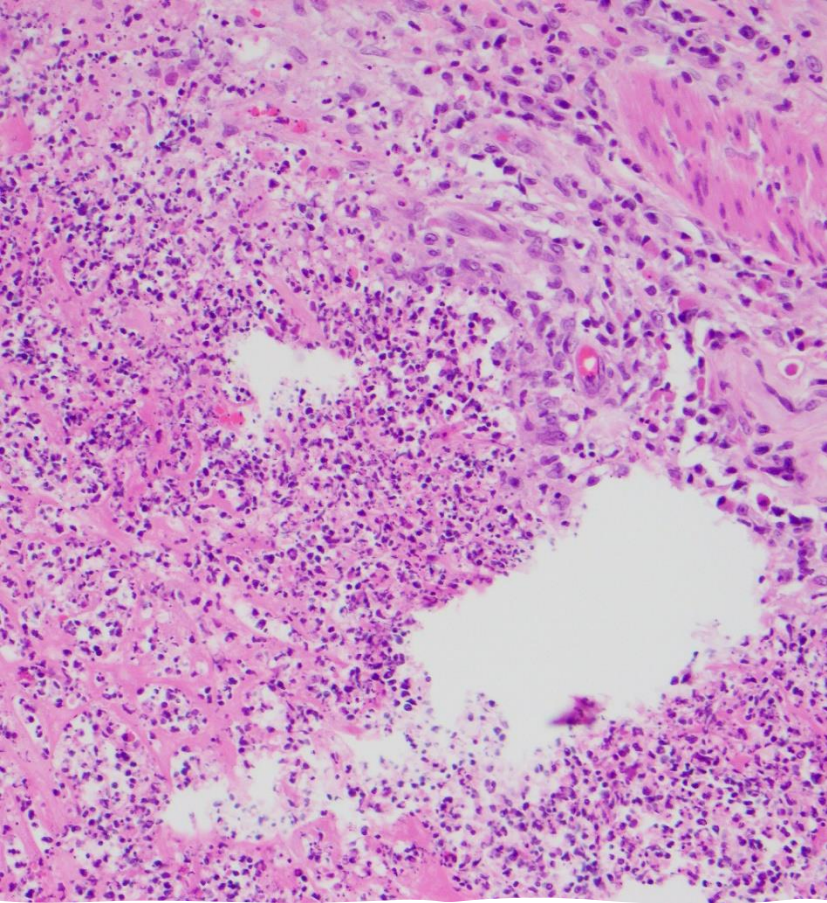


- CK7, CK5/6, PAX8, Ber-EP4, Napsin-A (+)
- CK20, GATA3, Uroplakin II, PSA, NKX3.1, MART-1, WT1 (-)
- Mullerian duct cyst with malignant transformation (clear cell adenocarcinoma)
 - Exceedingly rare

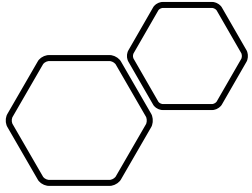
BONUS CASE #2



70 year old with progressing penile lesion with no response to antibiotic therapy

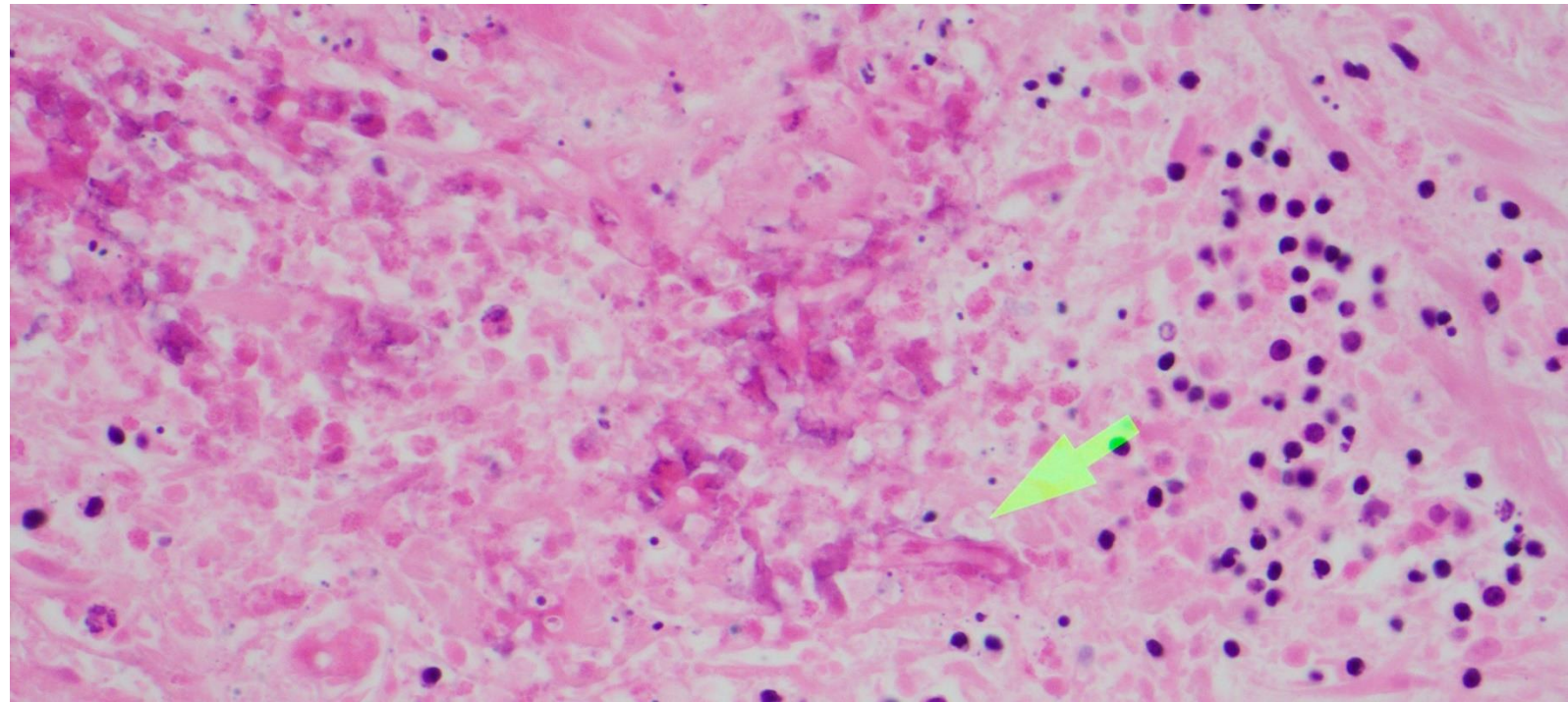
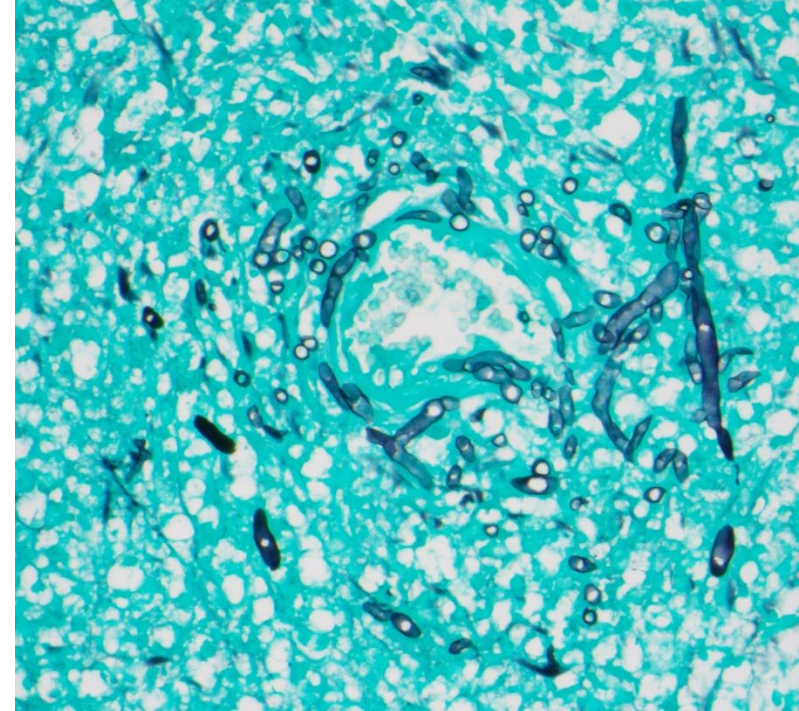
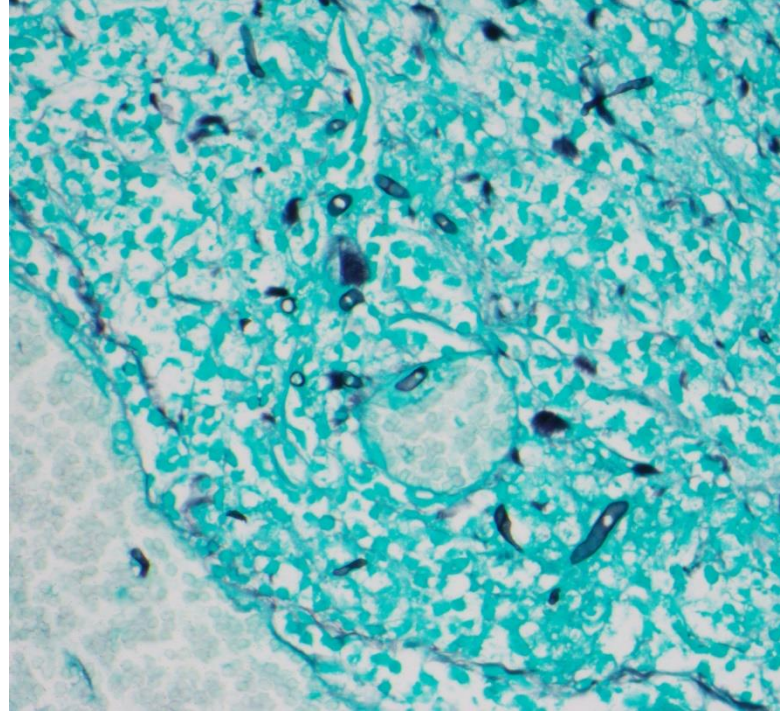


- Mixed granulomatous, eosinophilic, and neutrophilic infiltrate with degree of vasculitis, necrosis of deep soft tissue, and mostly spared viable epithelium
- Initial stains including PAS-F, T. pallidum IHC, and Gram Stain negative
- Consultation of colleague revealed possible fungal elements



Angioinvasive Fungal Infection

- Subcutaneous Zygomycosis
- Clinical picture of relatively painless and subacute clinical picture is unusual
- Leading candidate *Basidiobolus ranarum* (Basidiobolomycosis)



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- THANK YOU!

