Urologic Pathology: A Potpourri of Challenging Cases

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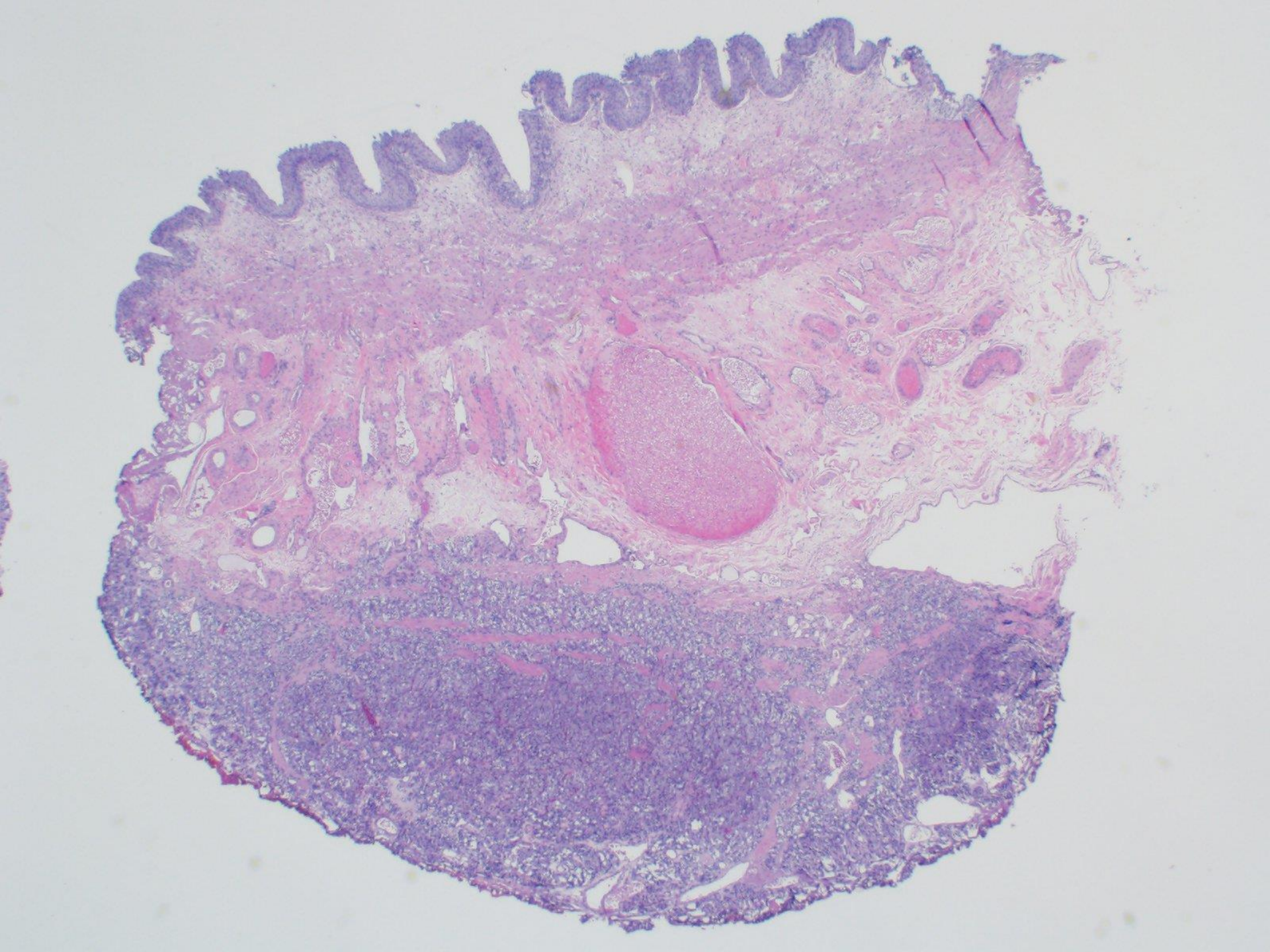
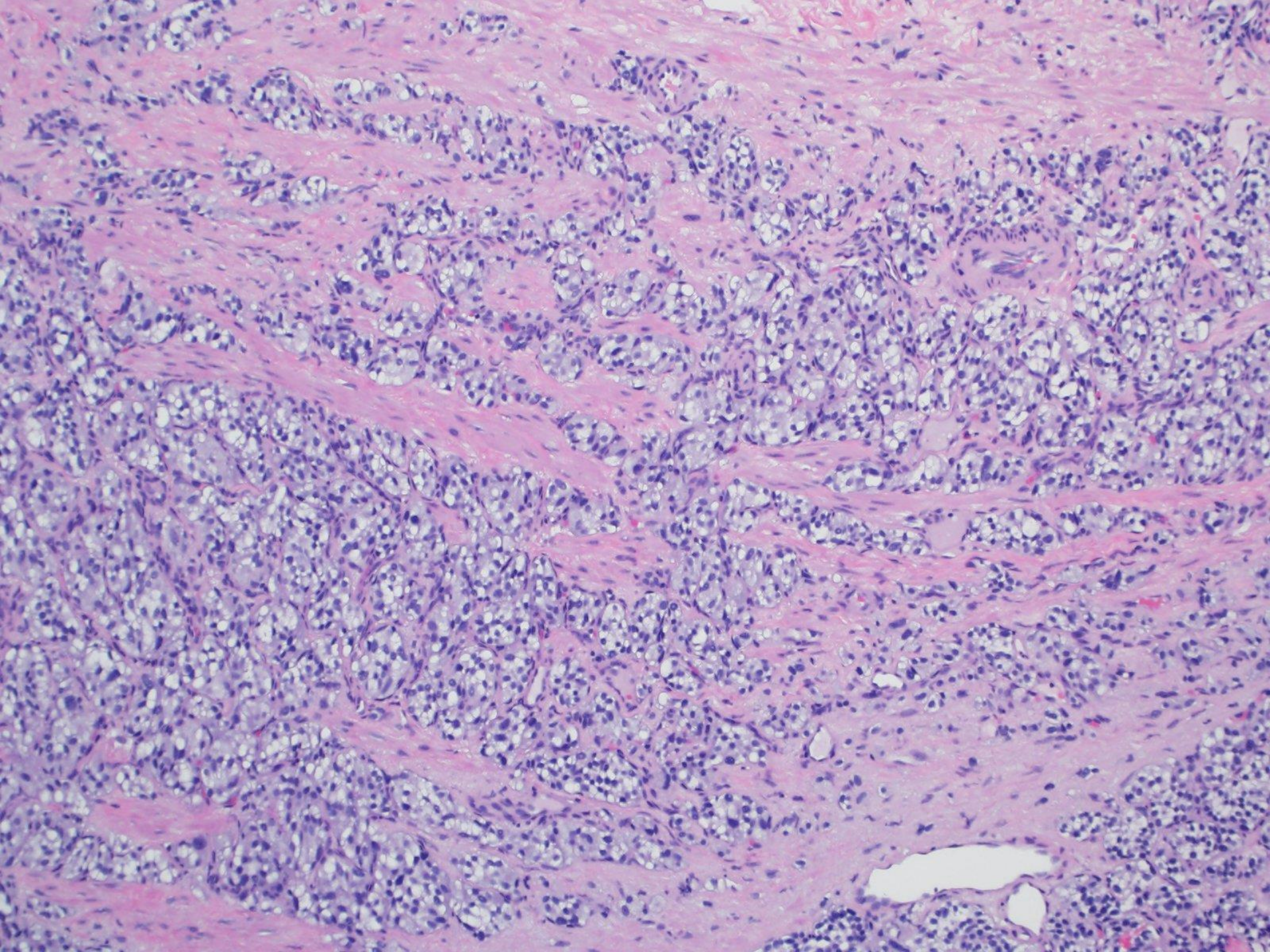
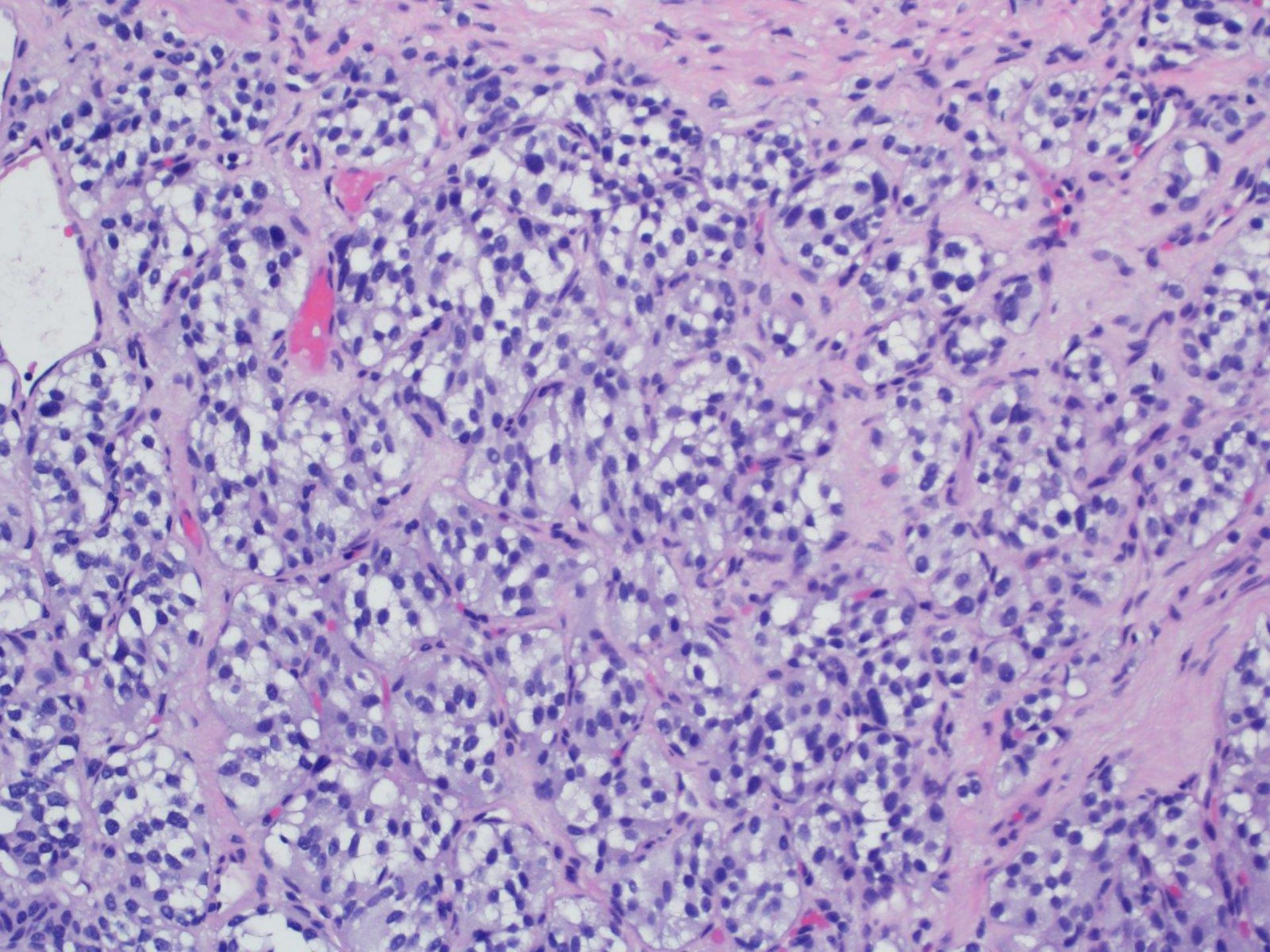
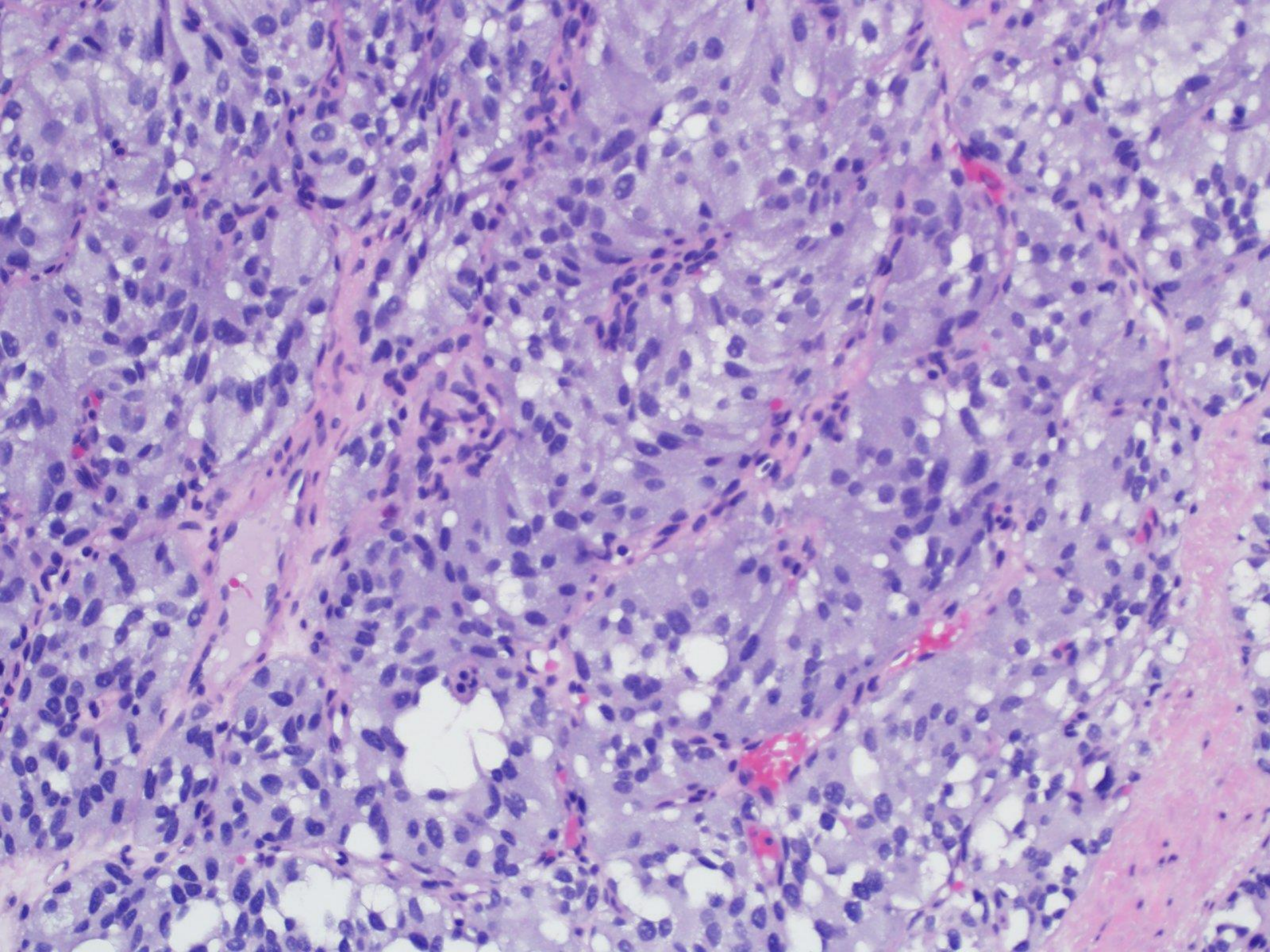
Case 1: Bladder Mass

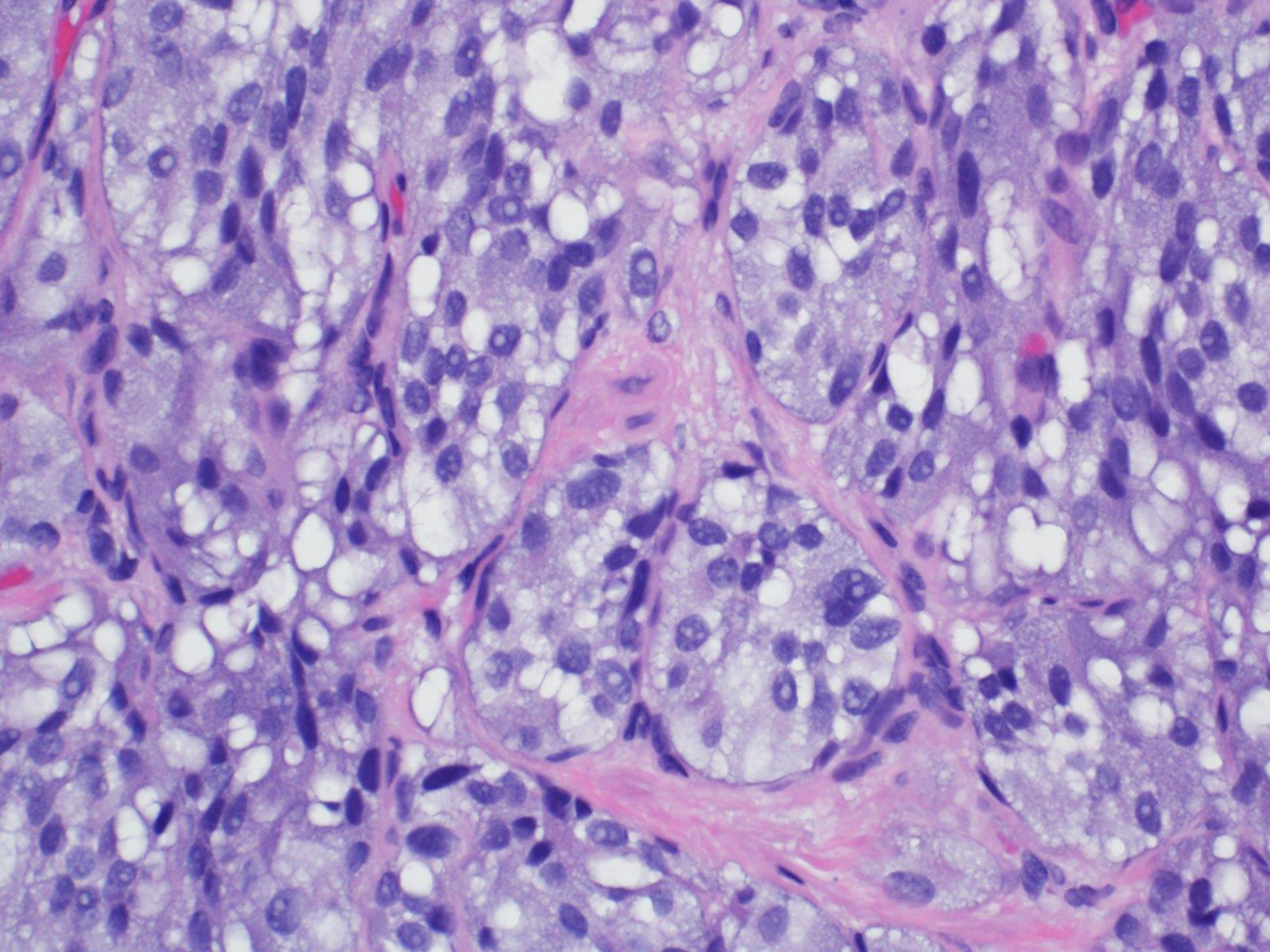
- 65 year old woman
- TURBT for hematuria
- Cystoscopy: bullous erythemamtous area that bled profusely on surgical excision
- Received: Transurethral resection specimen

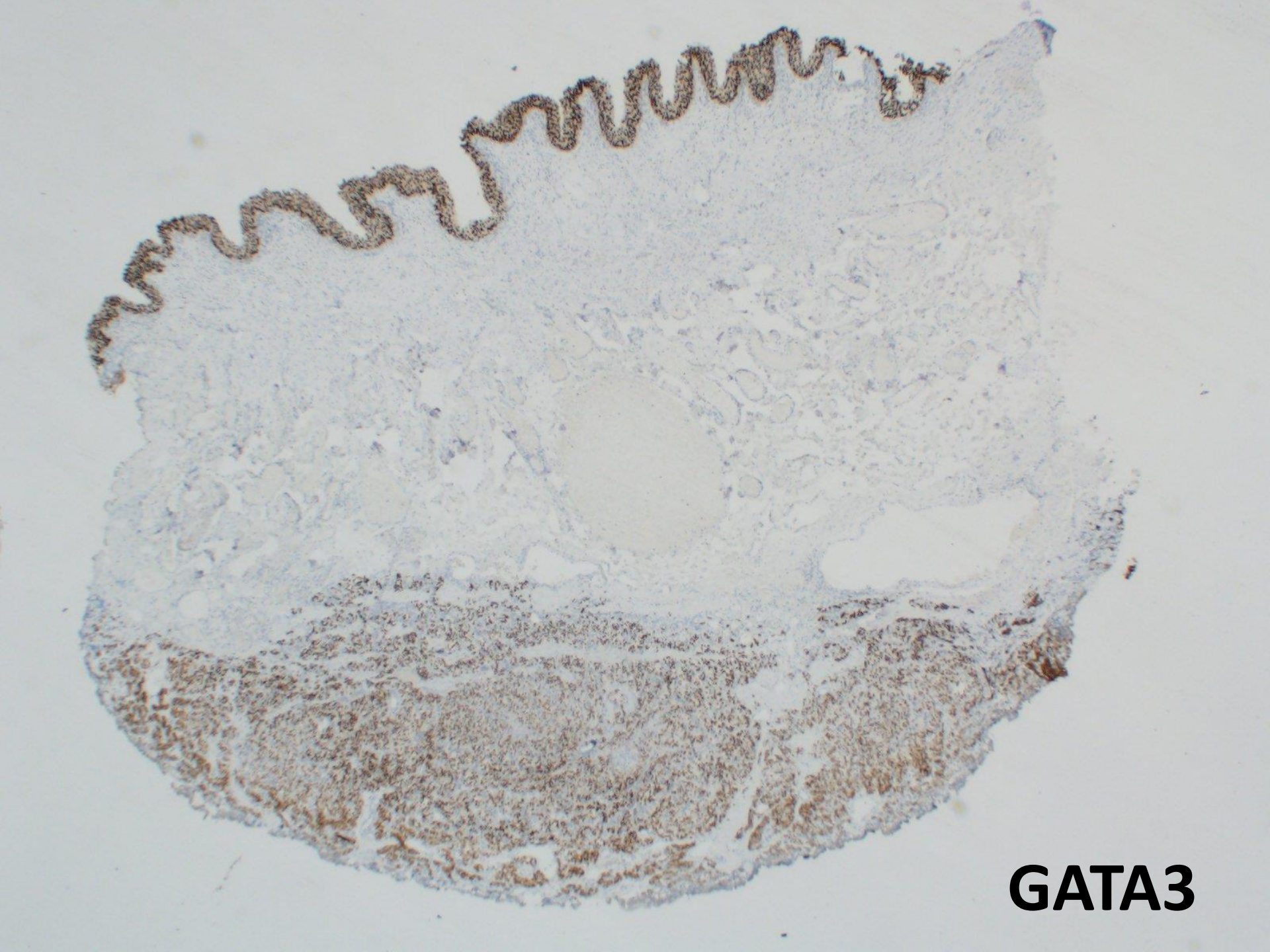








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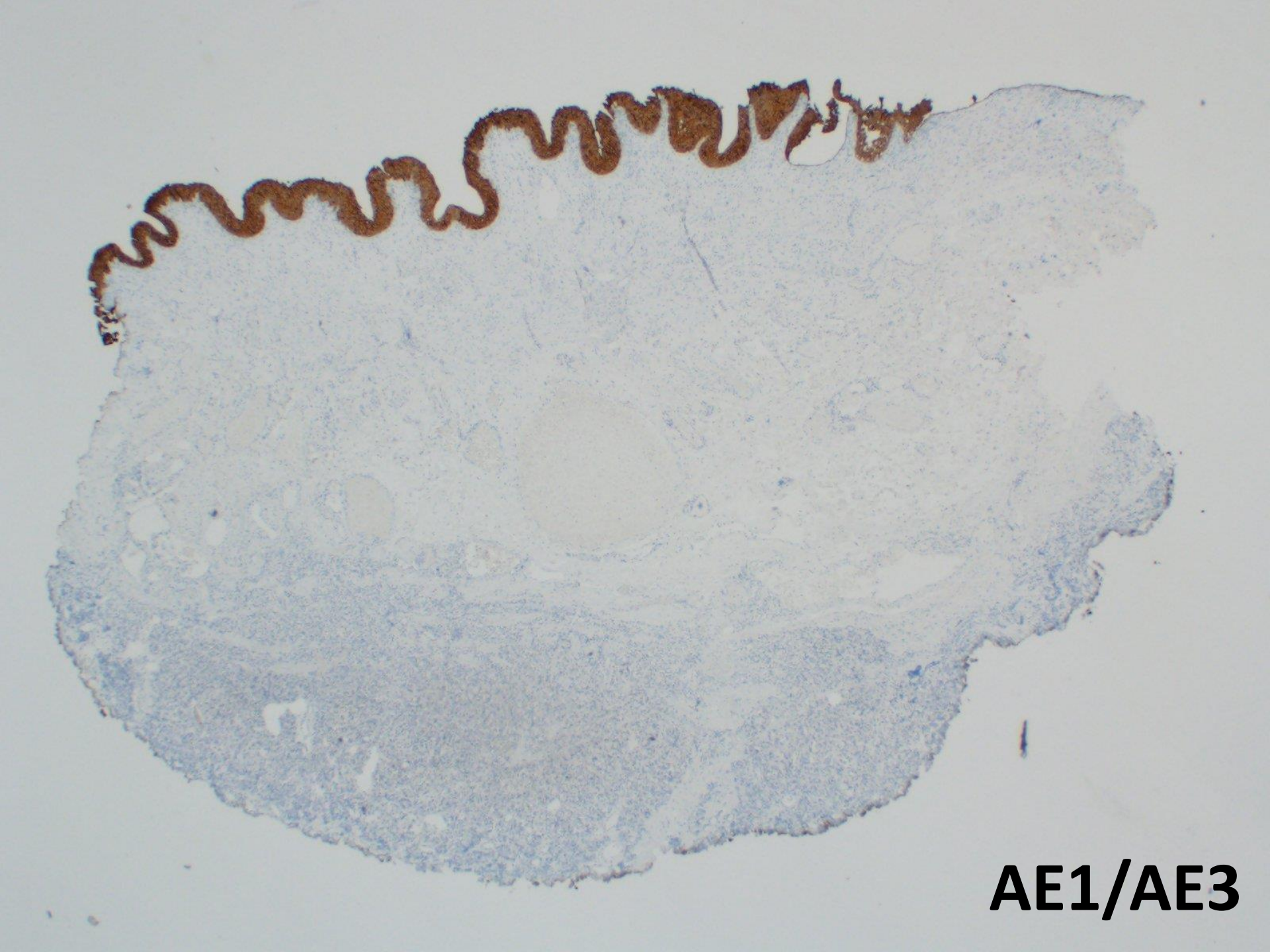
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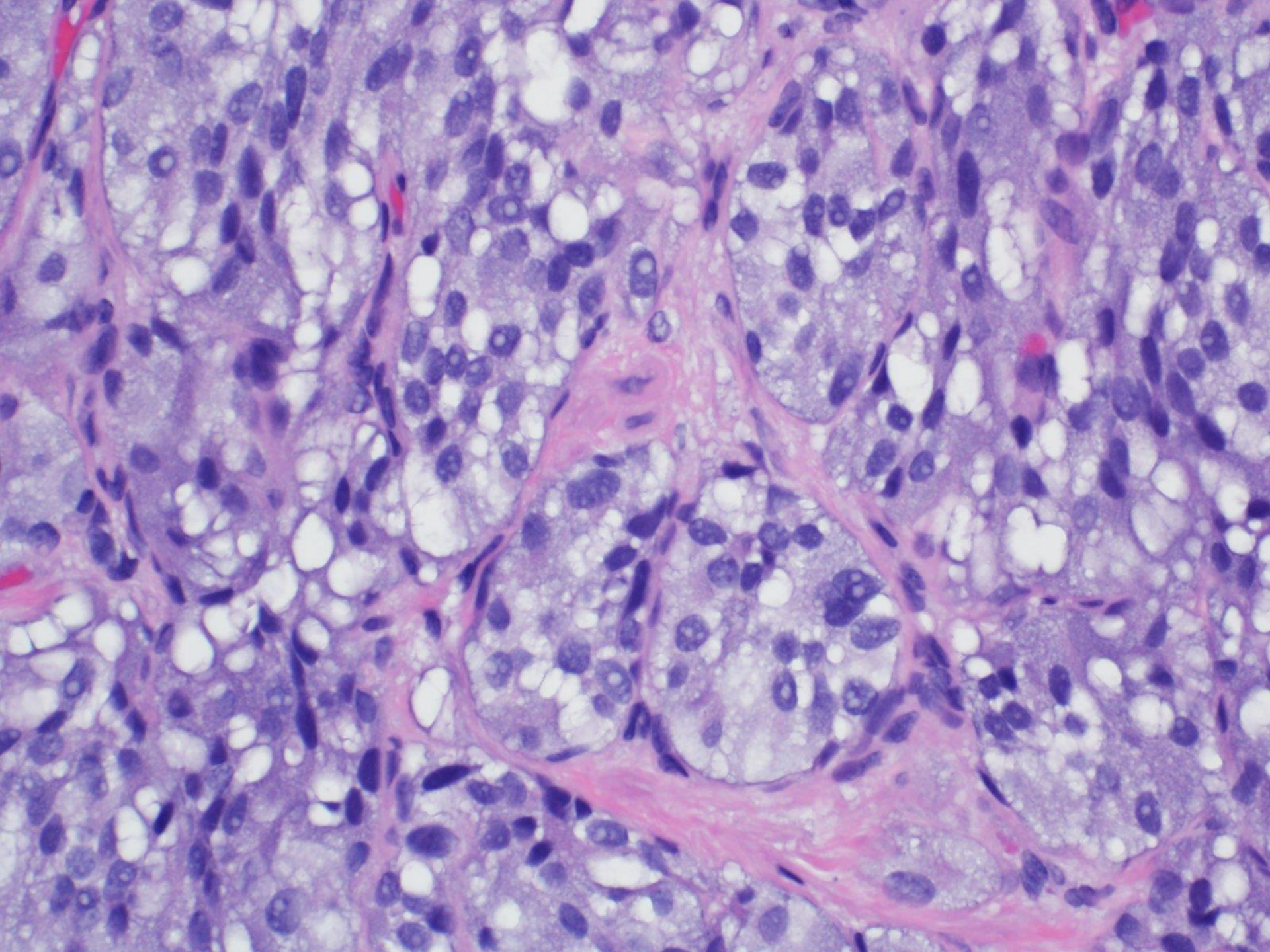

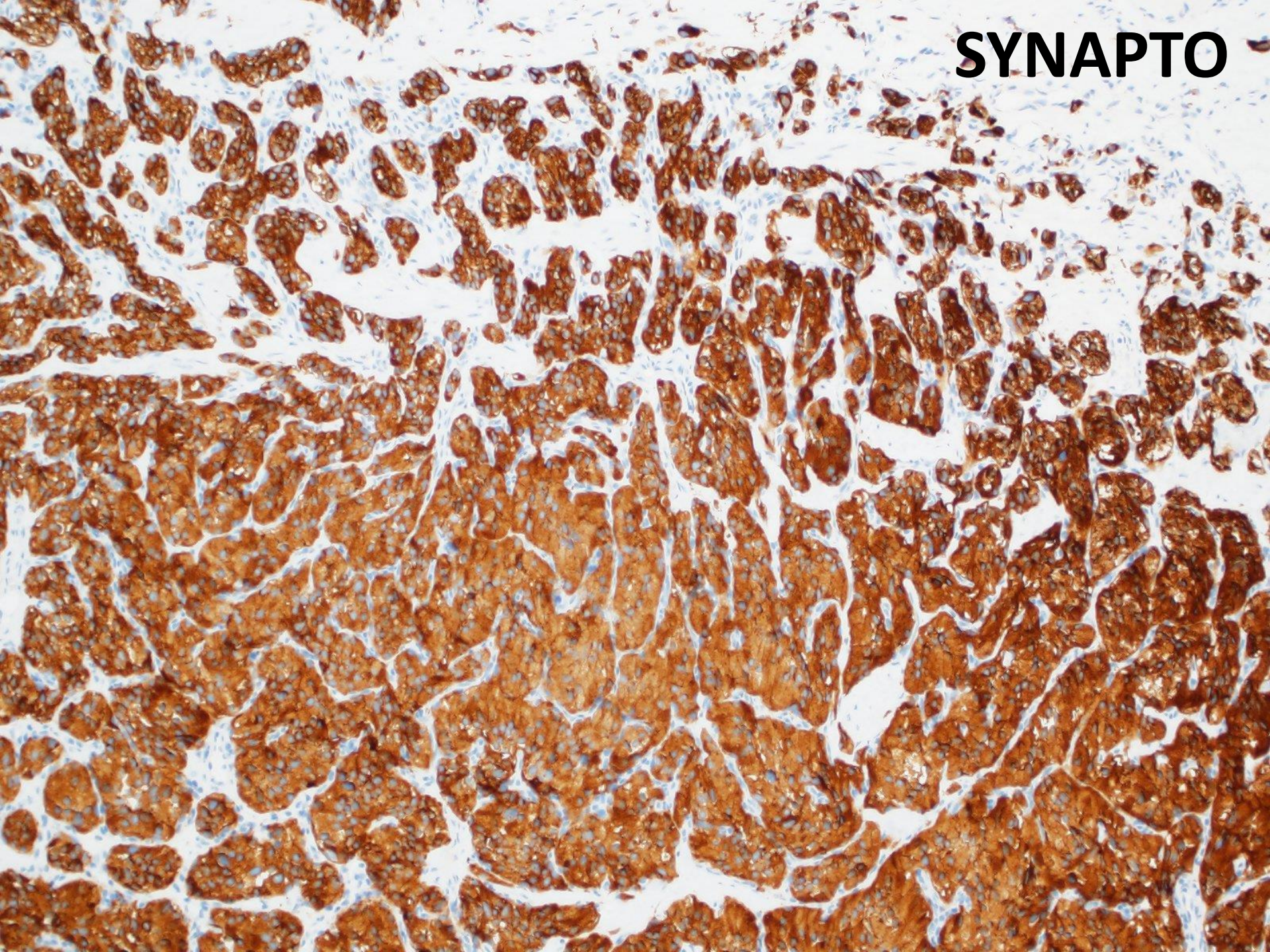
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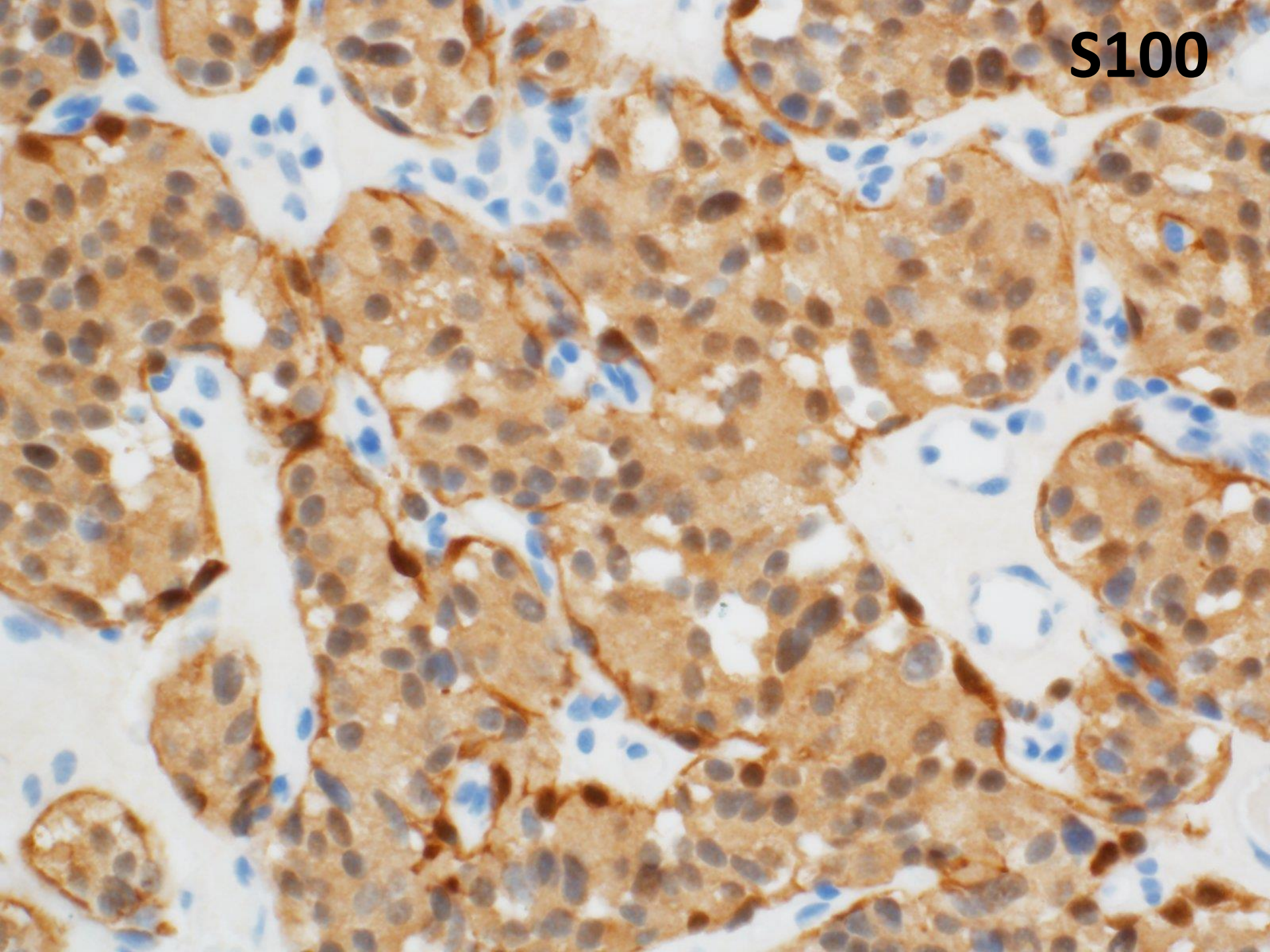
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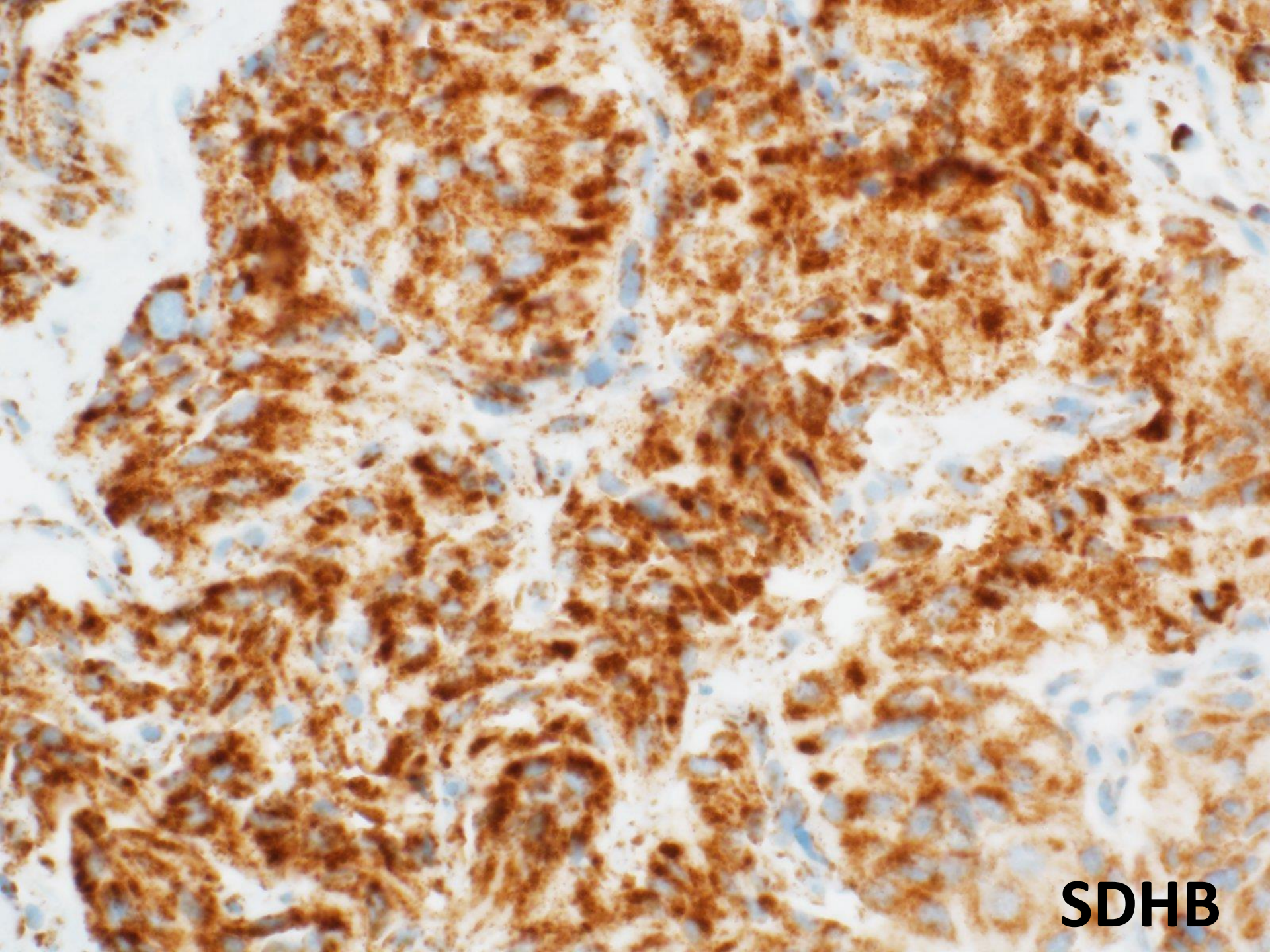

SDHB

Paraganglioma of the Bladder

- Paragangliomas: 10% extra-adrenal, 10% of these are in the bladder
- Less than 0.5% of all bladder tumors
- Female>male, average age: early 40s (wide)
- Clinical presentation
  - Hematuria (60%)
  - Micturition attacks (75%): symptoms of catecholamine excess on bladder filling or micturition (headache, blurred vision, HTN, sweating etc..)
- Cystoscopy: usually small (few cm) dome shaped nodules covered by normal (sometimes ulcerated) mucosa; dome, trigone

Pathology

- “Zellballen”: nests, plexiform thin network of capillaries or fibrous septa, sustentacular cells
- Polyhedral cells, acidophilic to amphophilic
- Central or eccentric nuclei, nucleoli
- Degenerative “endocrine atypia”, may be some mitoses
- Can invade deeply into muscularis propria
- IHC: CK-, NE markers+, S100 sustentacular cells, GATA3 + in 80% !! Pitfall !!

Differential diagnosis

- Urothelial carcinoma (esp nested)
  - Look for neoplastic surface urothelium
  - Atypia, mitoses, necrosis, lacks vascular pattern
  - PG features that can lead to misdiagnosis: diffuse growth, necrosis, clear cell areas, MP invasion, cautery artifact
- Metastatic renal cell carcinoma
- High grade prostatic adenocarcinoma
- Metastatic neuroendocrine tumors (e.g. carcinoid), melanoma, granular cell tumor,

Prognosis

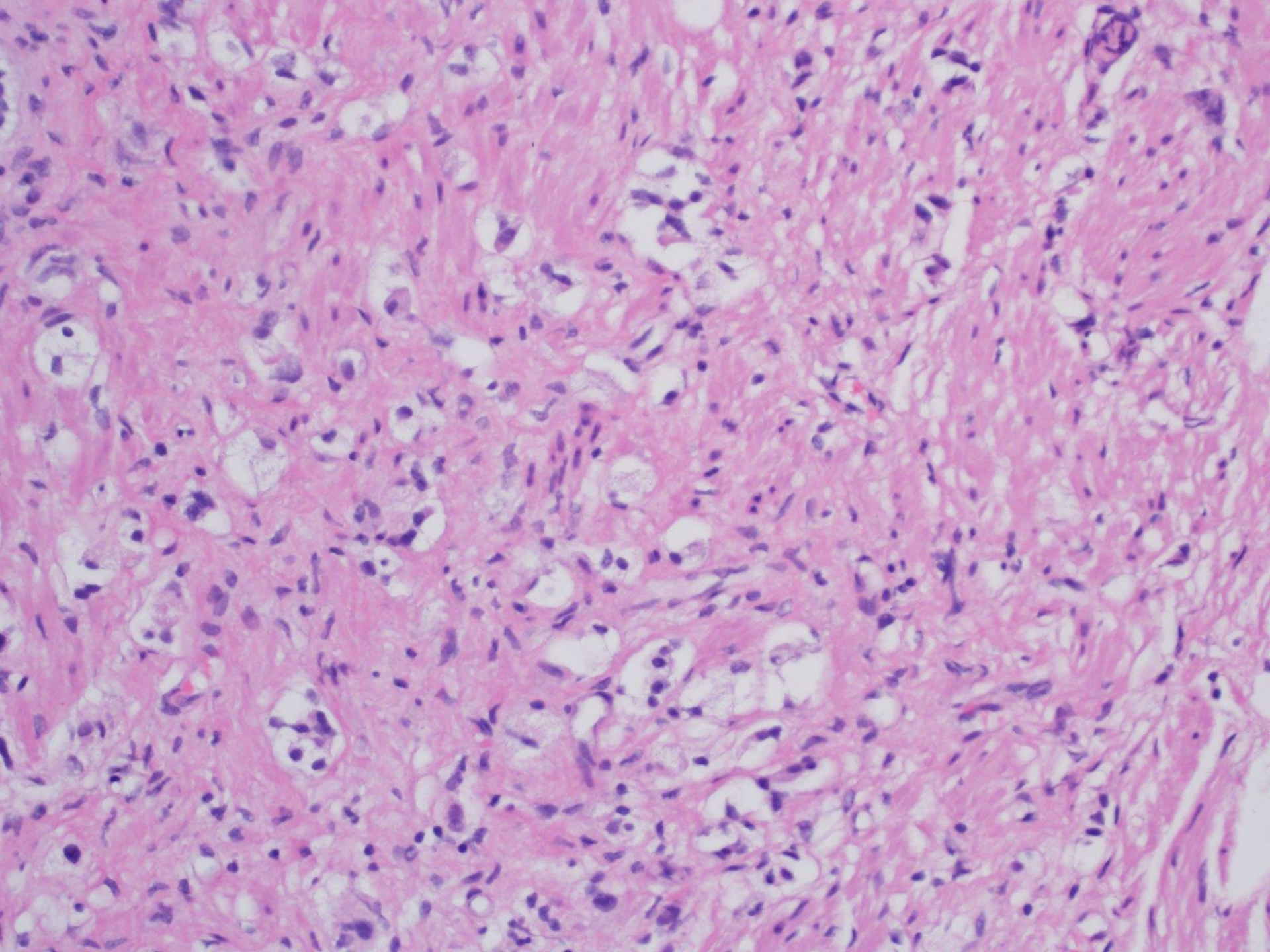
- 10-20% of bladder paragangliomas are malignant (more common than other sites)
- “Malignant” defined as metastatic
- No histologic features predict metastatic potential
- pT1/pT2 tumors have better prognosis
- Tumors with *SDH* mutations more likely to be malignant

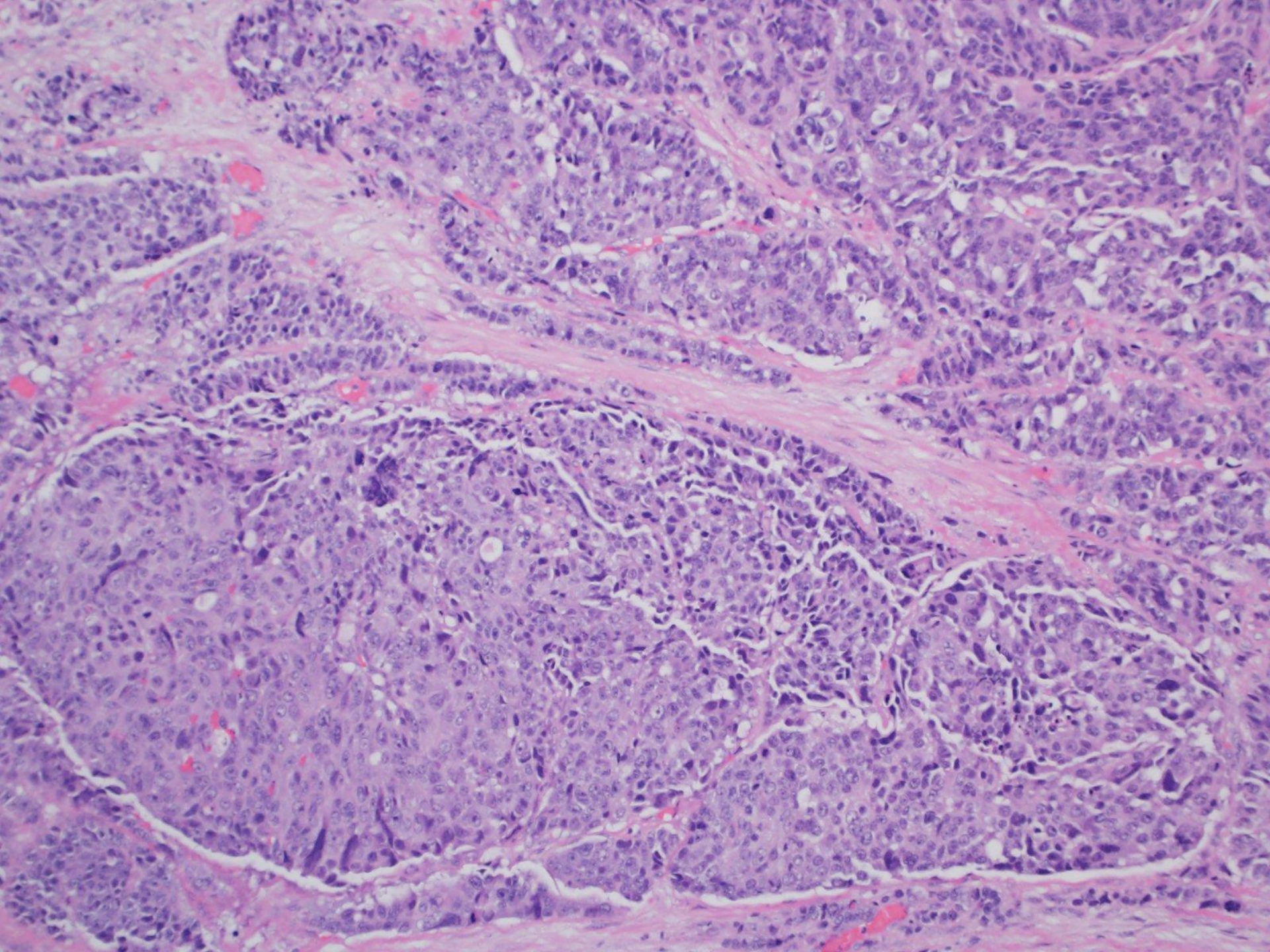
SDHB Immunohistochemistry

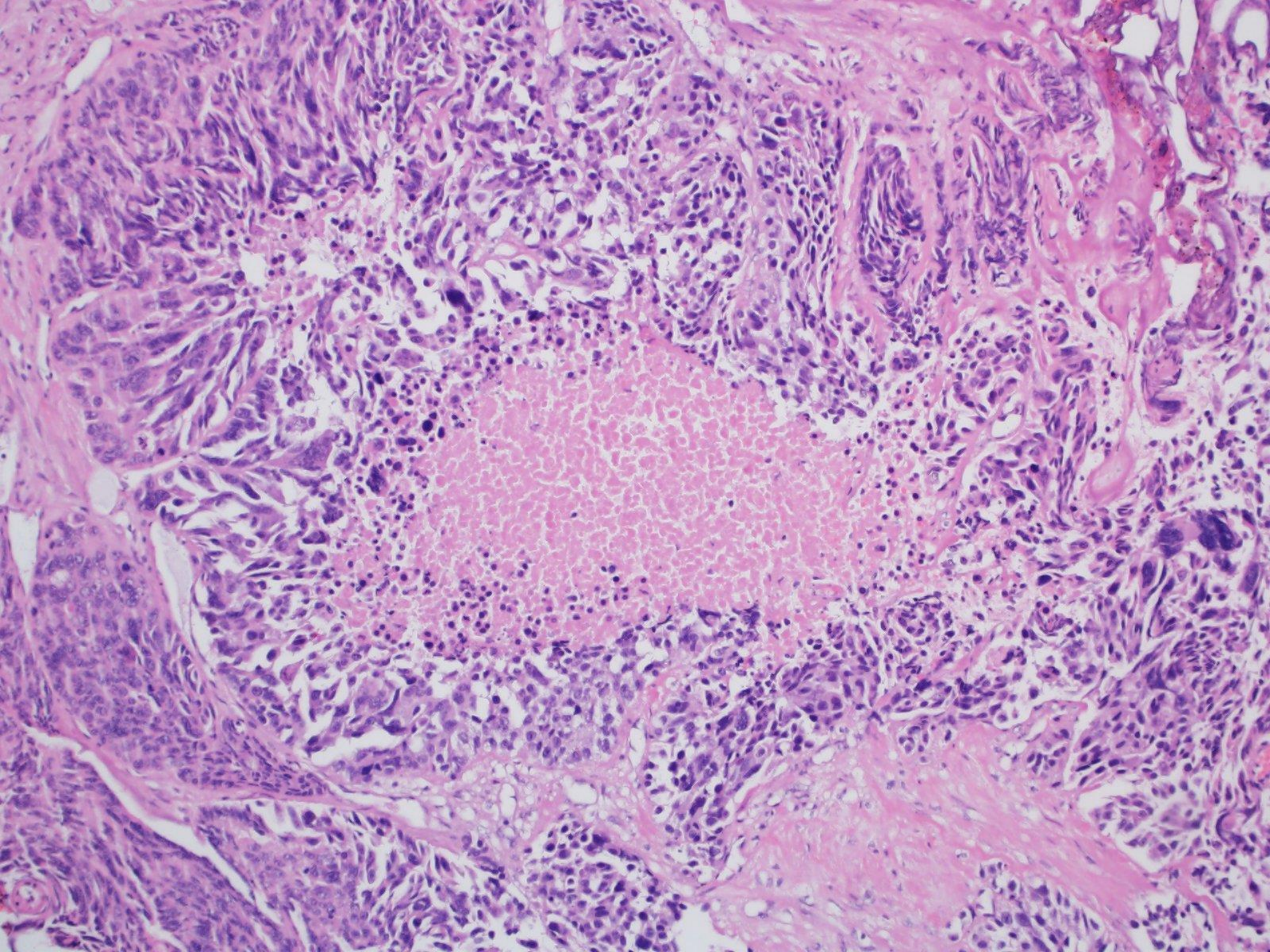
- 27-52% of bladder paragangliomas have *SDH* mutations, including germline and sporadic
- *SDH* mutations (subunits) → loss of SDHB protein expression
- Can be assessed immunohistochemically (abnormal – loss of SDHB expression by IHC)
- Implications
  - More likely malignant
  - Possible genetic counseling/screening for familial paraganglioma syndromes
- Other syndromic associations: VHL, MEN2, NF1

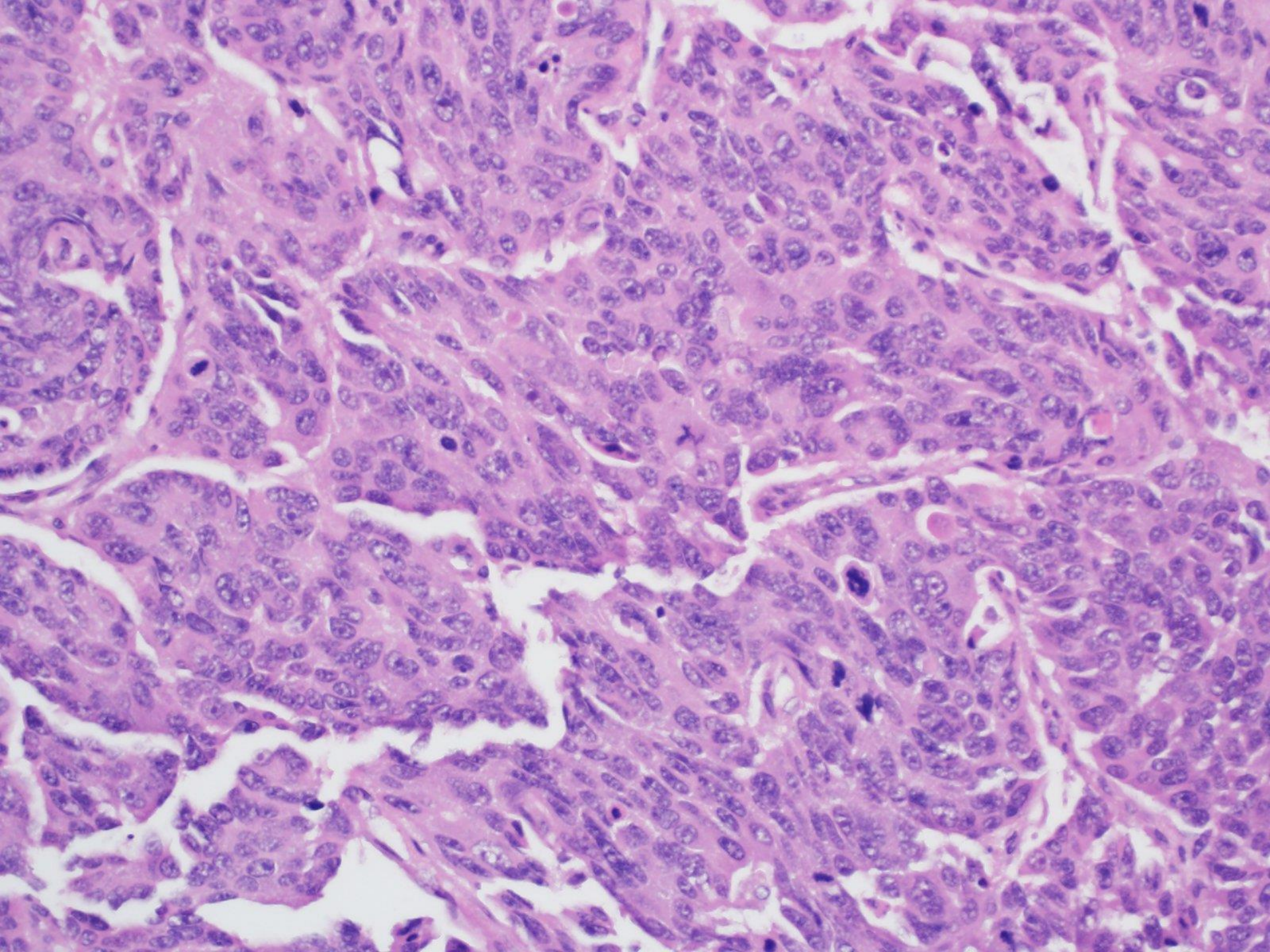
Case 2: TUR Prostate

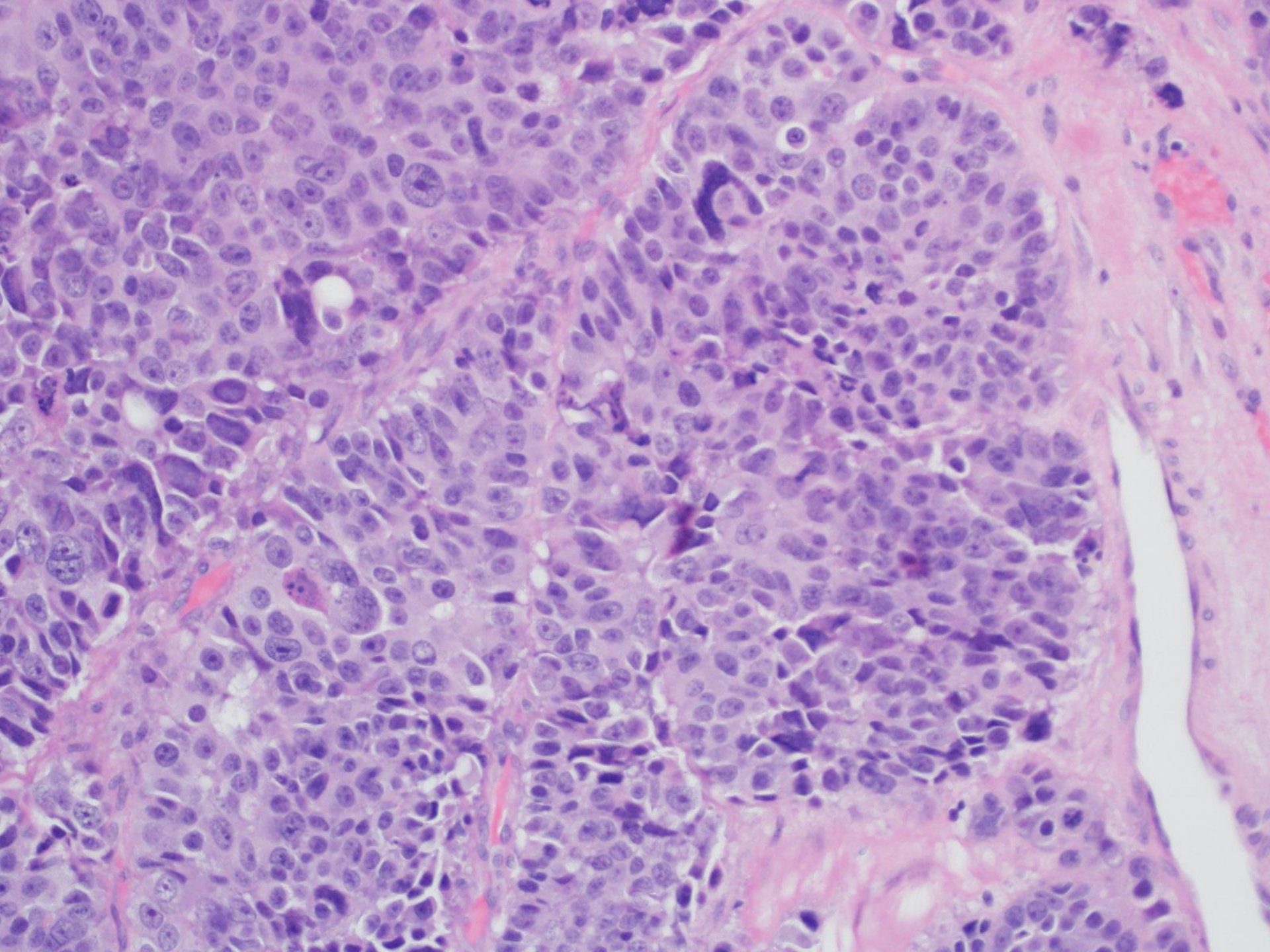
- 65 year old man with history of prostate cancer 5 years prior (cancer in all 6 biopsies, Grade group 3 (4+3=7))
- Did not have definitive therapy at that time
- Two years later, PSA of 140, started on androgen deprivation therapy but progressed
- Subsequently started on enzalutamide and PARP inhibitor for castration-resistant metastatic carcinoma (tumor positive for DNA damage repair mutations)
- Recent PSA <0.1
- Now voiding problems → TURP

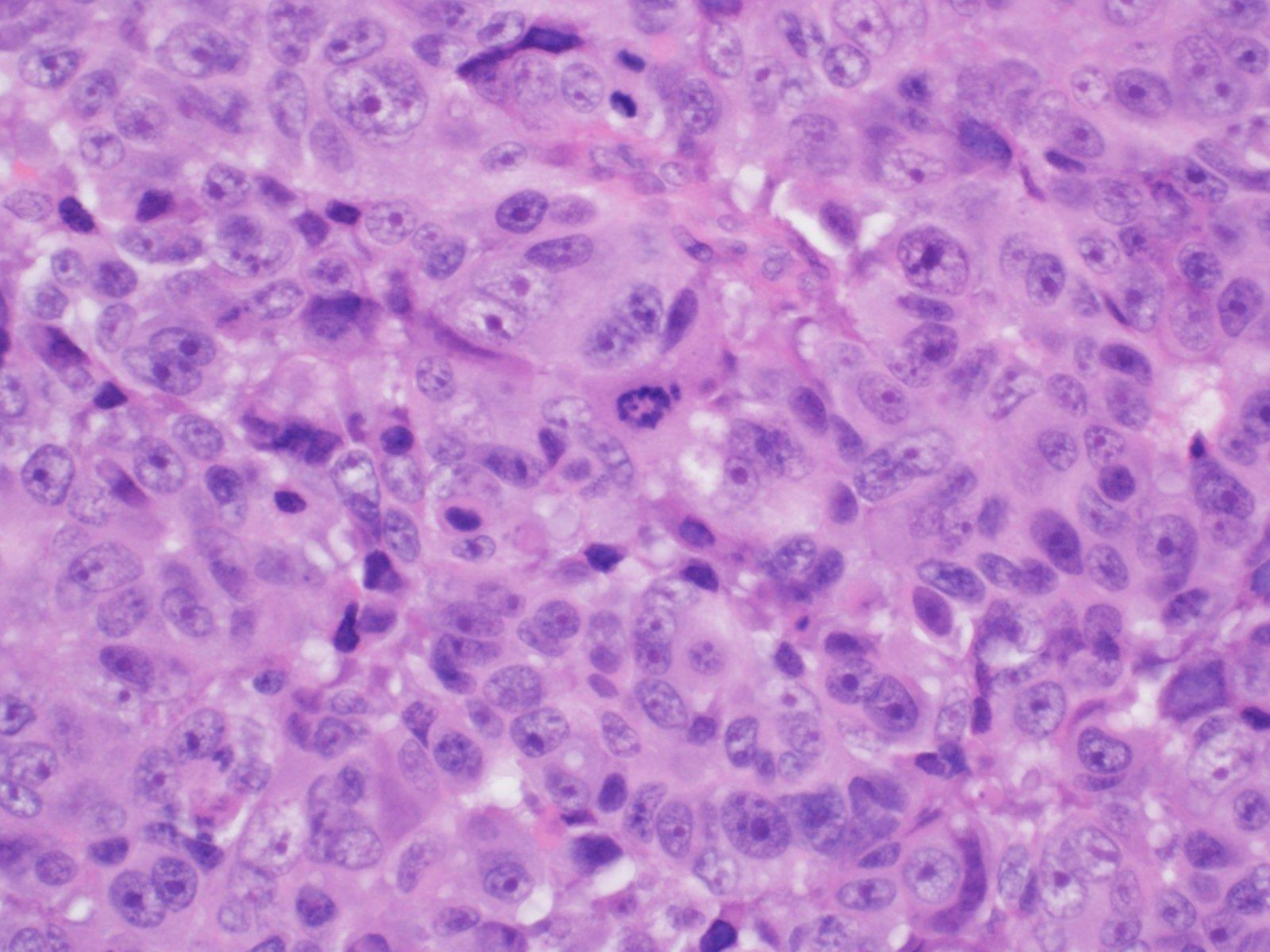


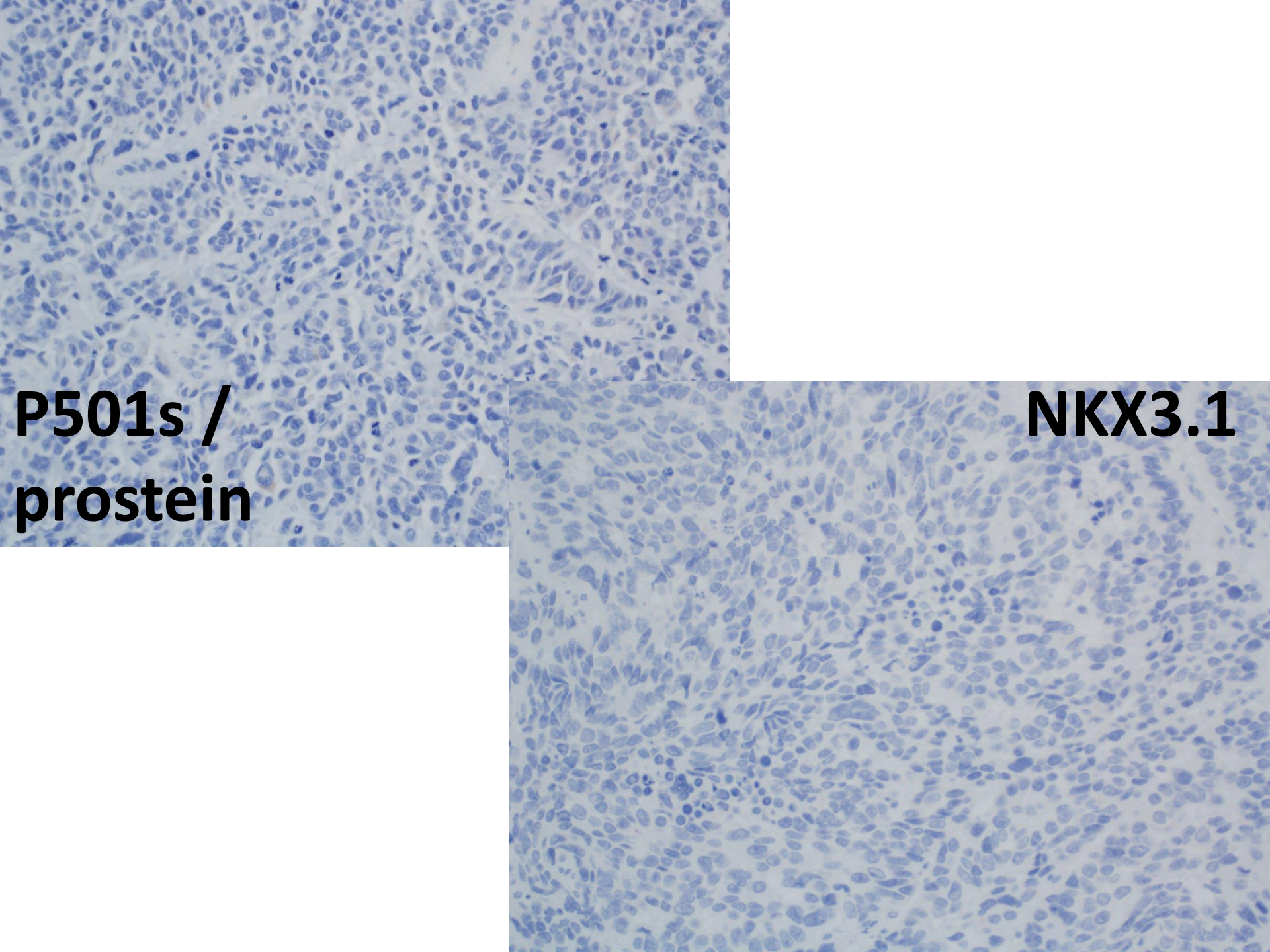


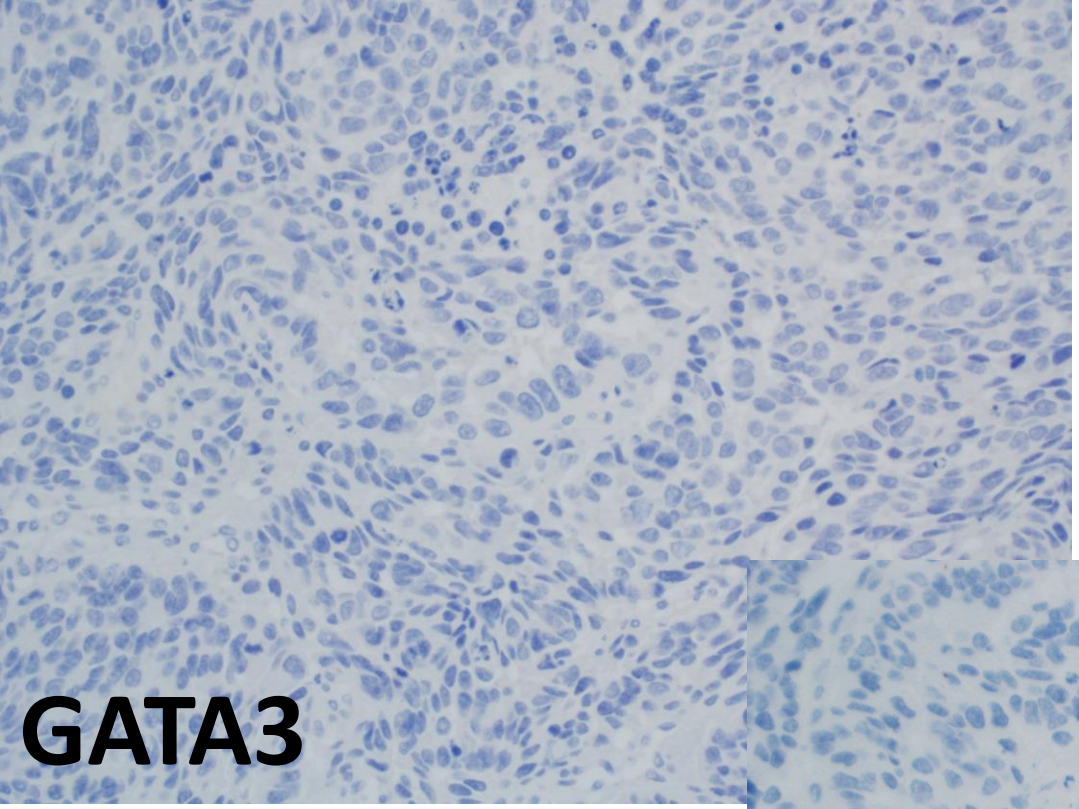









P501s /
prostein
NKX3.1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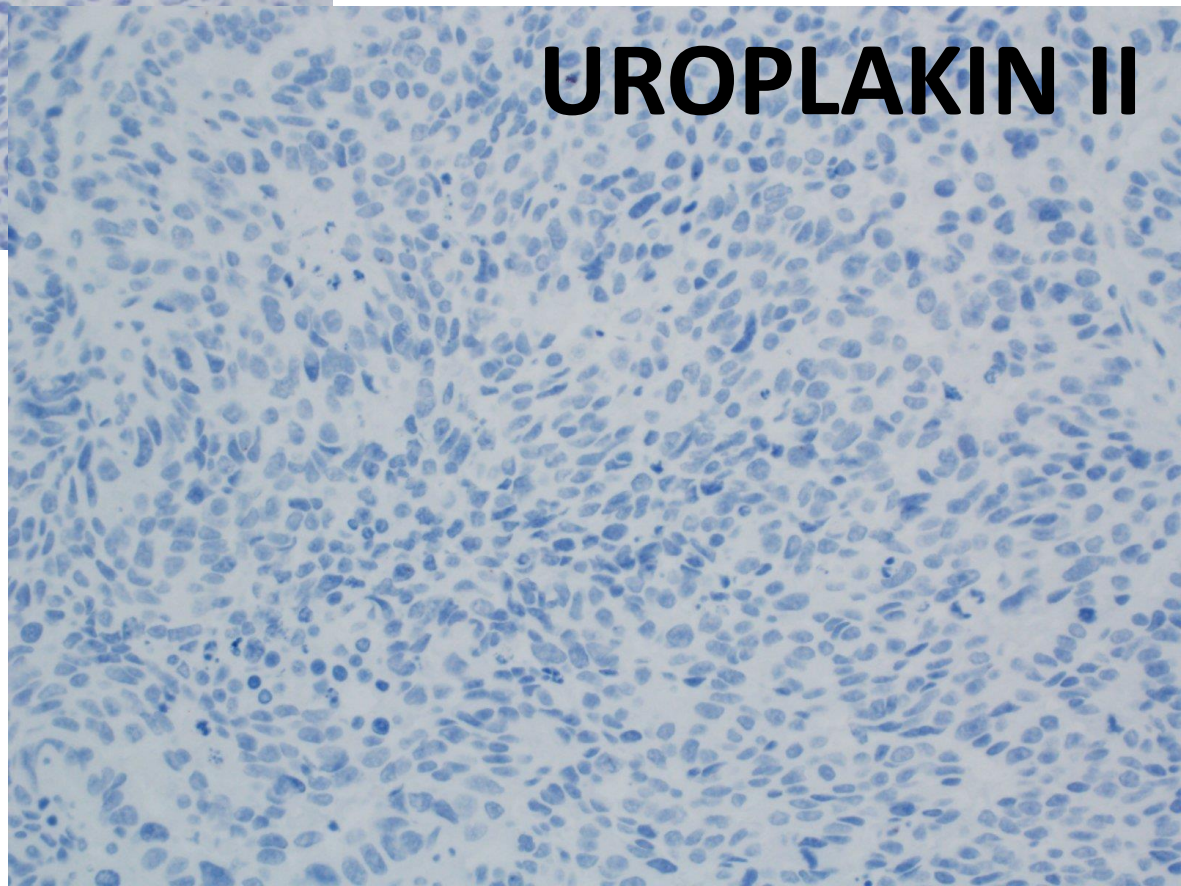
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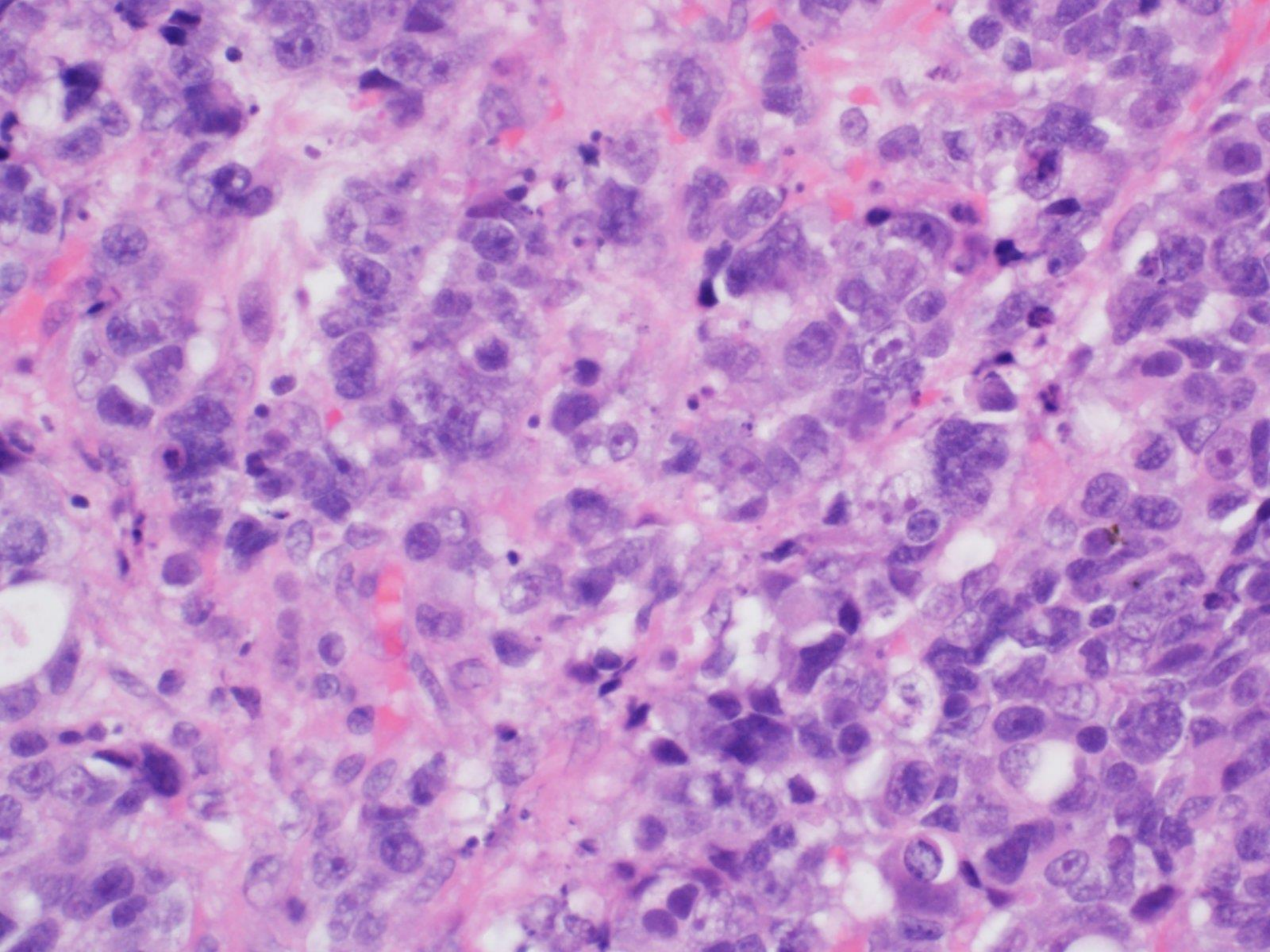

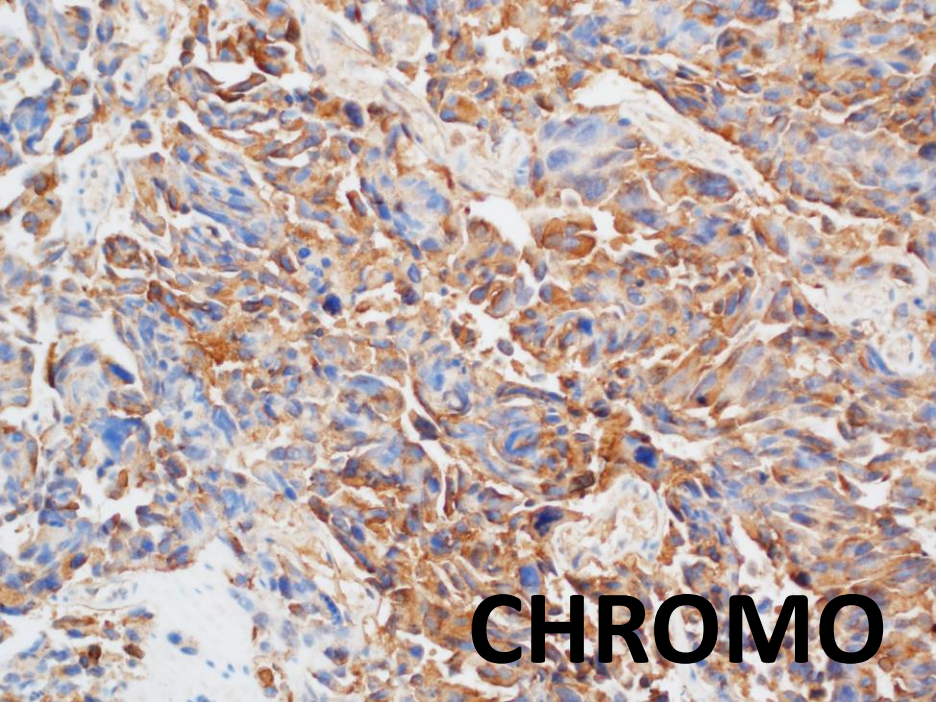
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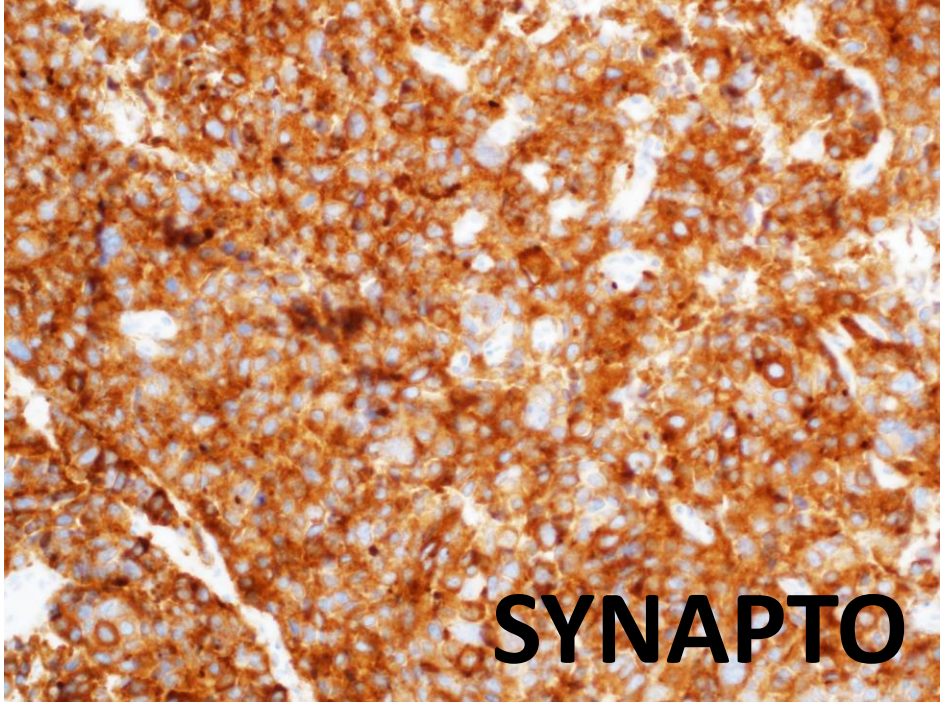
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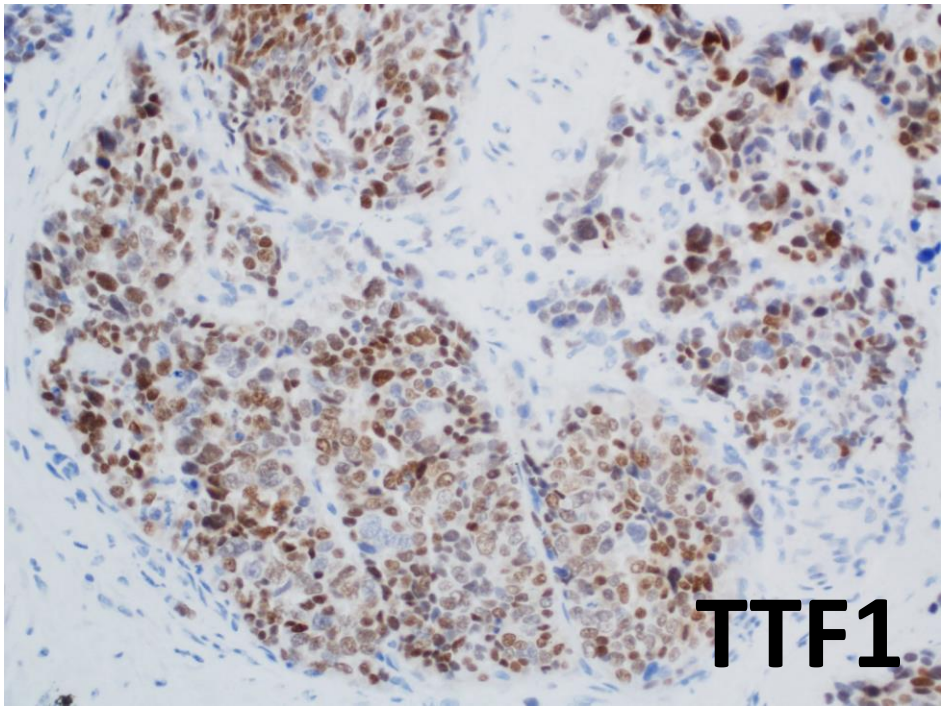

TTF1

Large Cell Neuroendocrine Carcinoma of Prostate

- Rare
- Many are progression of PCa after longstanding ADT
- Associated with rapid metastasis and death
- May treat with platinum-based chemo
- Pathology:
  - Sheets, ribbons, large nests with peripheral pallisading
  - Cells with amphophilic cytoplasm, large atypical nuclei with prominent nucleoli, coarse chromatin.
  - Necrosis, numerous mitoses
- Should express neuroendocrine markers

Neuroendocrine differentiation in Prostate

- Normal prostate contains neuroendocrine cells, difficult to see by H&E
- NE Differentiation recognized on IHC (chromo, synapto)
- Of particular interest – possible role in tumor progression and development of resistance to androgen deprivation (AD) therapy
  - NE cells lack androgen receptors
  - Tumor NE differentiation increases after AD and with development of castration-resistant PCa
  - Notion of NE “transdifferentiation” as a component of tumor progression
  - Different therapeutic implications for small cell/large cell ca

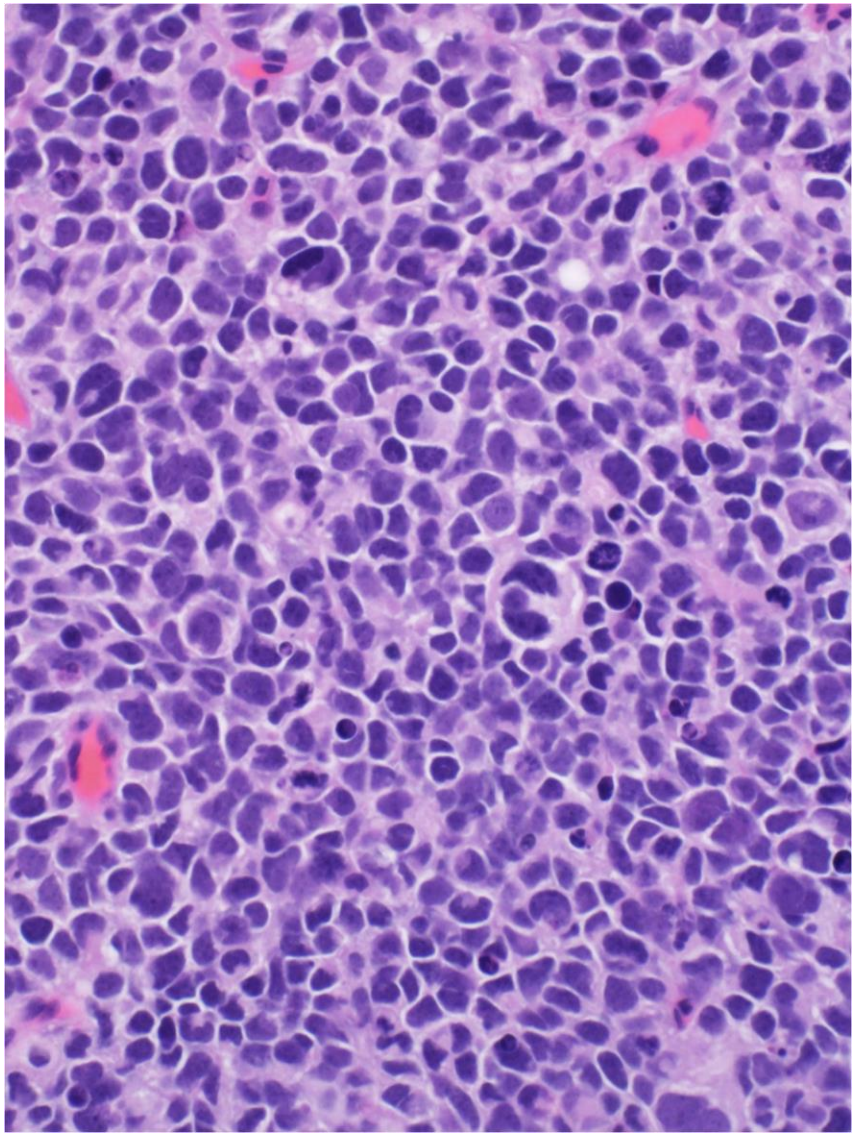
2016 WHO Classification of NE Tumors of Prostate

- **(Acinar) adenocarcinoma with neuroendocrine differentiation**
- **Well differentiated neuroendocrine tumor**
- **Small cell neuroendocrine carcinoma**
- **Large cell neuroendocrine carcinoma**

Some proposed additions:

- Adenocarcinoma with Paneth cell-like neuroendocrine differentiation
- Mixed neuroendocrine-acinar adenocarcinoma
- PCa with overlapping features of small cell and acinar adenocarcinoma
- Castration-resistant PCa with small cell carcinoma-like clinical presentation (aka “anaplastic PCa” by clinicians)

Small cell carcinoma of prostate



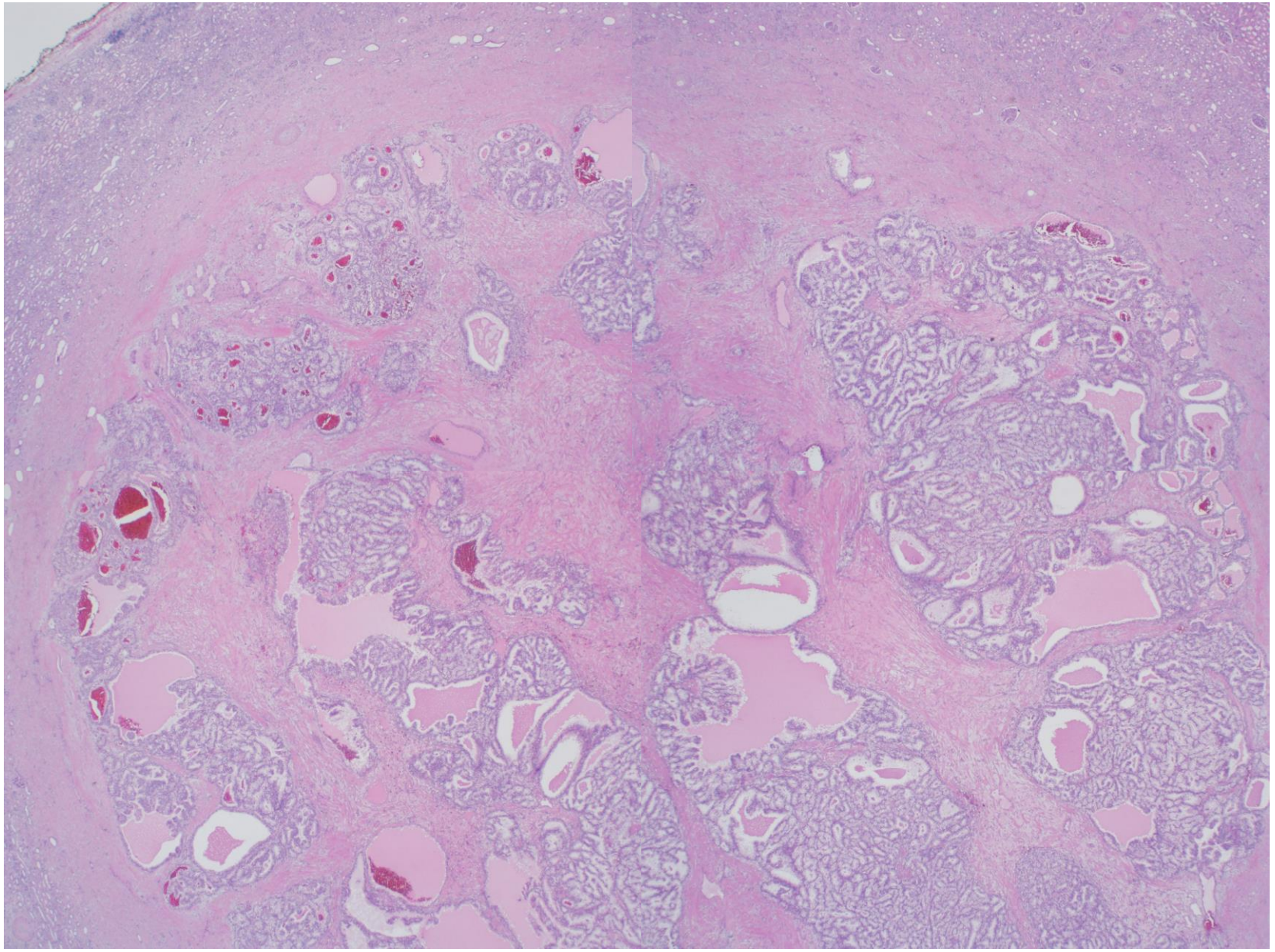
- Morphology as for lung small cell
- Half have a prior history of PCa
- Half admixed with acinar PCa at dx
- Most have NE markers, not all (not necessary)
- Do not tend to show diffuse prostate markers (PSA, Prostein, NKX3.1)
- May be positive for TTF1

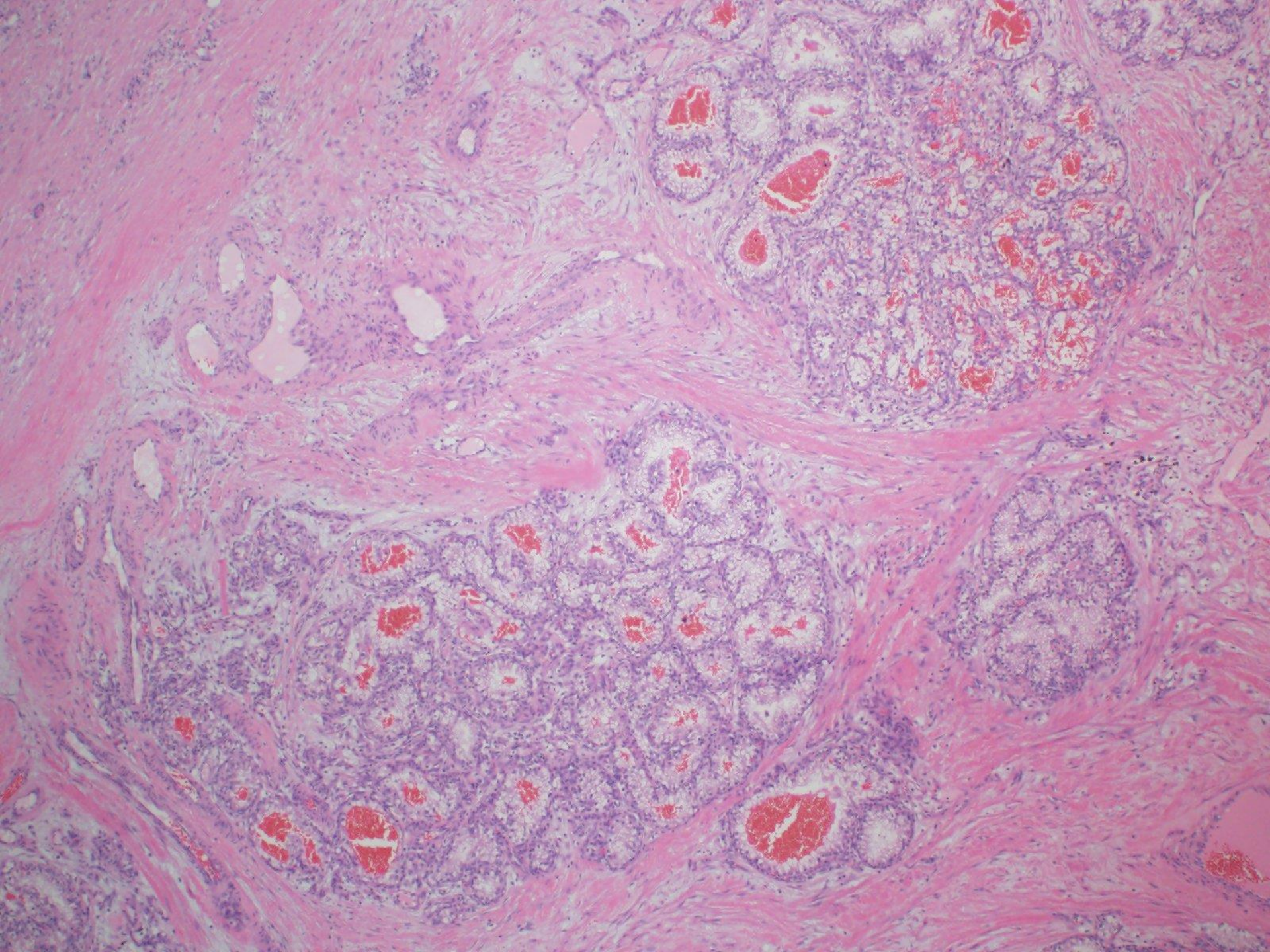
Key Issues

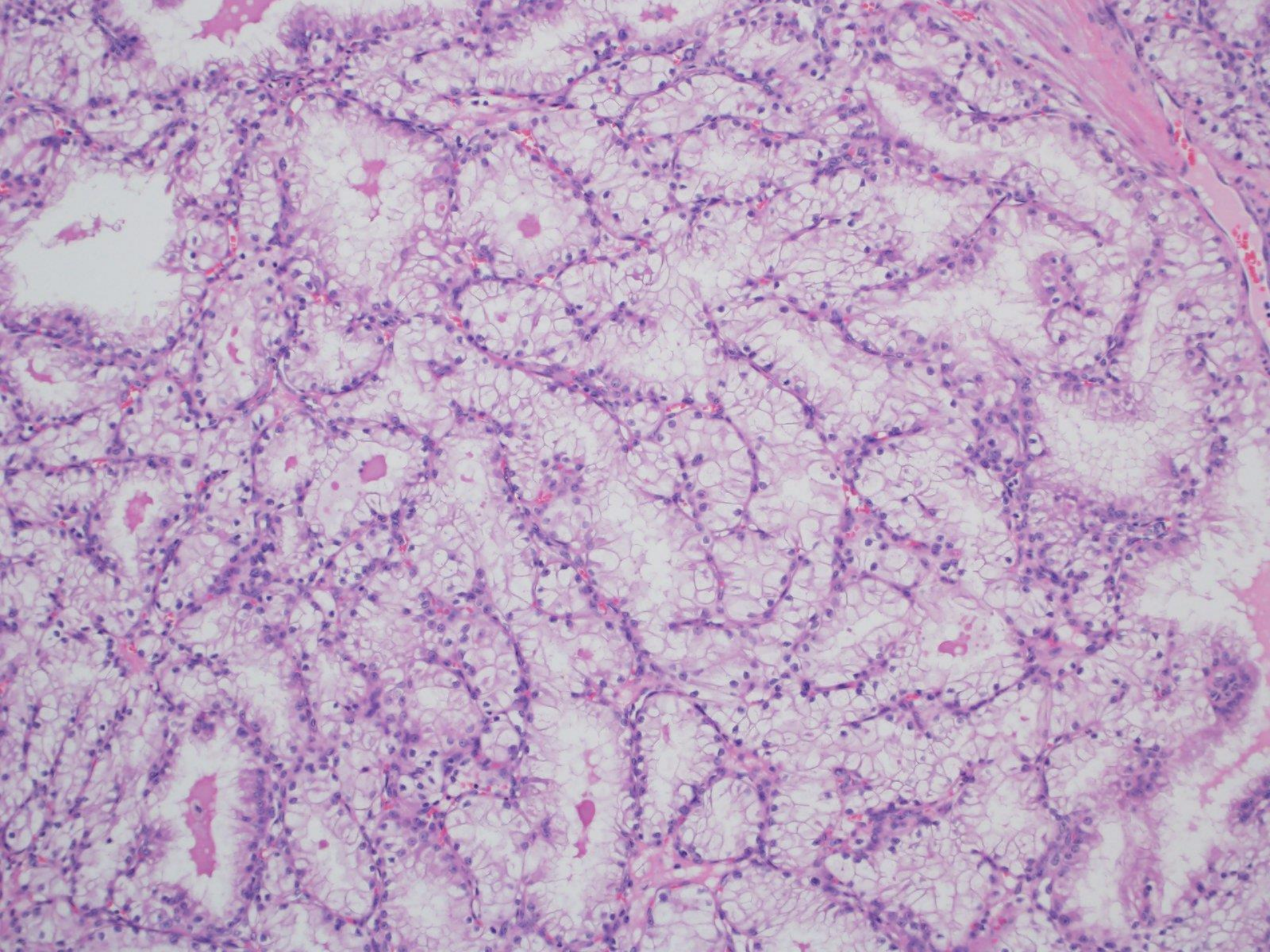
- Conventional 5+5=10 may show diffuse NE marker expression → need *bone fide* small cell (or large cell) carcinoma morphology on H&E for diagnosis (clinical significance – possible platinum-based chemo)
- It is not recommended to routinely do neuroendocrine markers on morphologically conventional acinar prostatic adenocarcinoma
- Role of NE markers
  - May be helpful to support small cell NEC
  - Should do to support large cell NEC
- Most do not grade high grade neuroendocrine carcinoma component

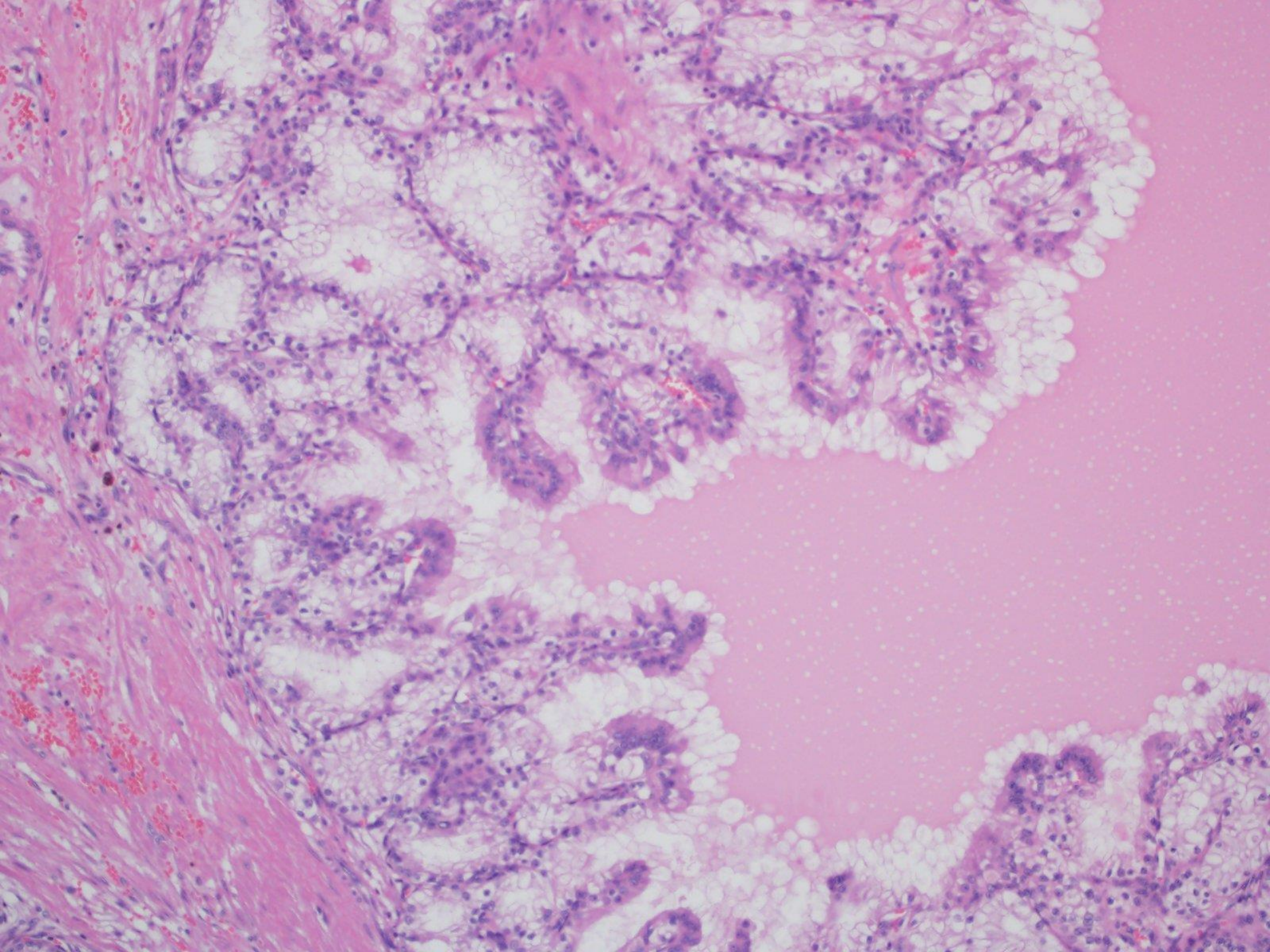
Case 3 Kidney Mass

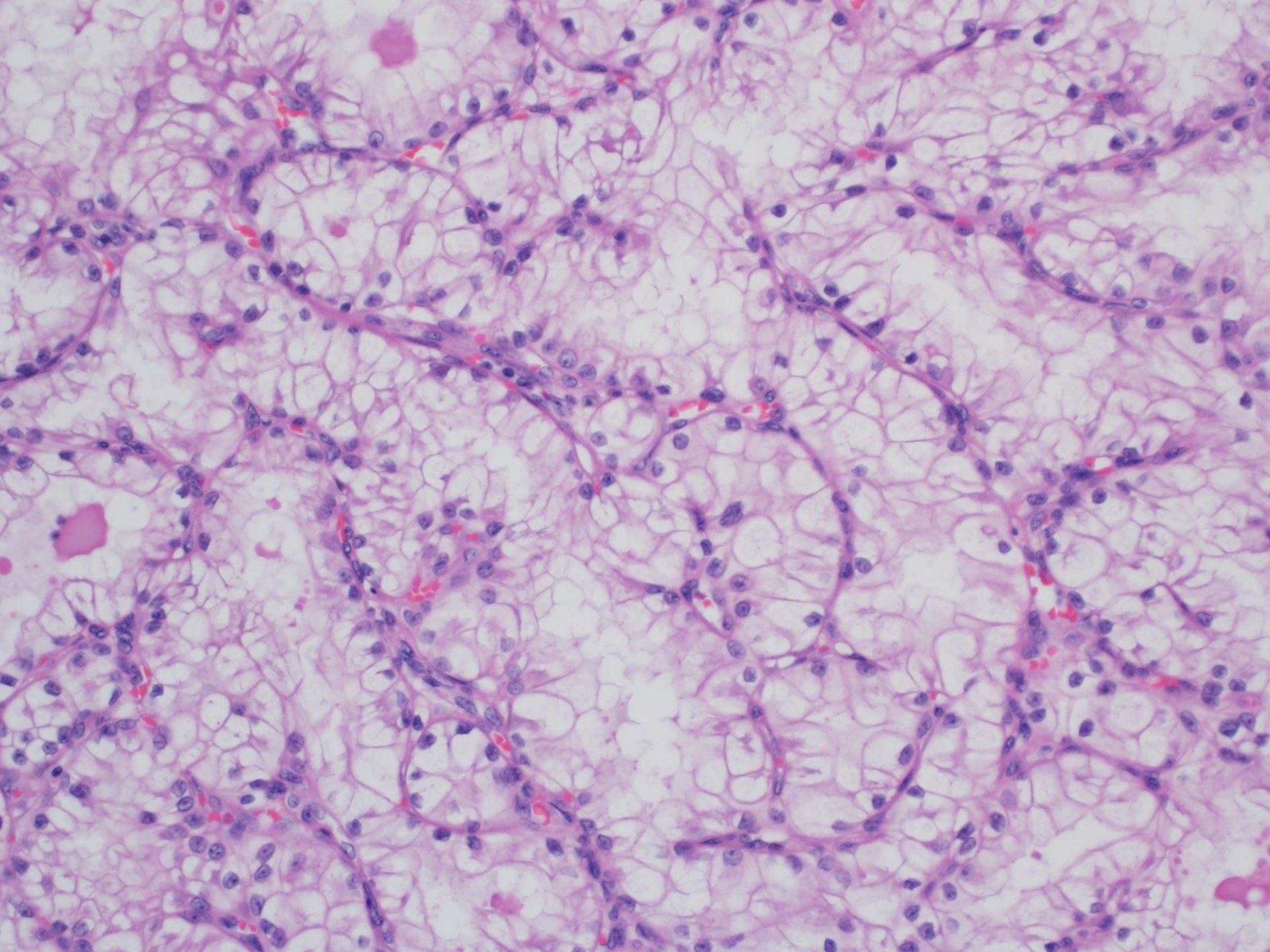
- 60 year old female presented with a renal mass
- Partial nephrectomy
- Gross: small well circumscribed/encapsulated 1.3 cm mass contained within kidney

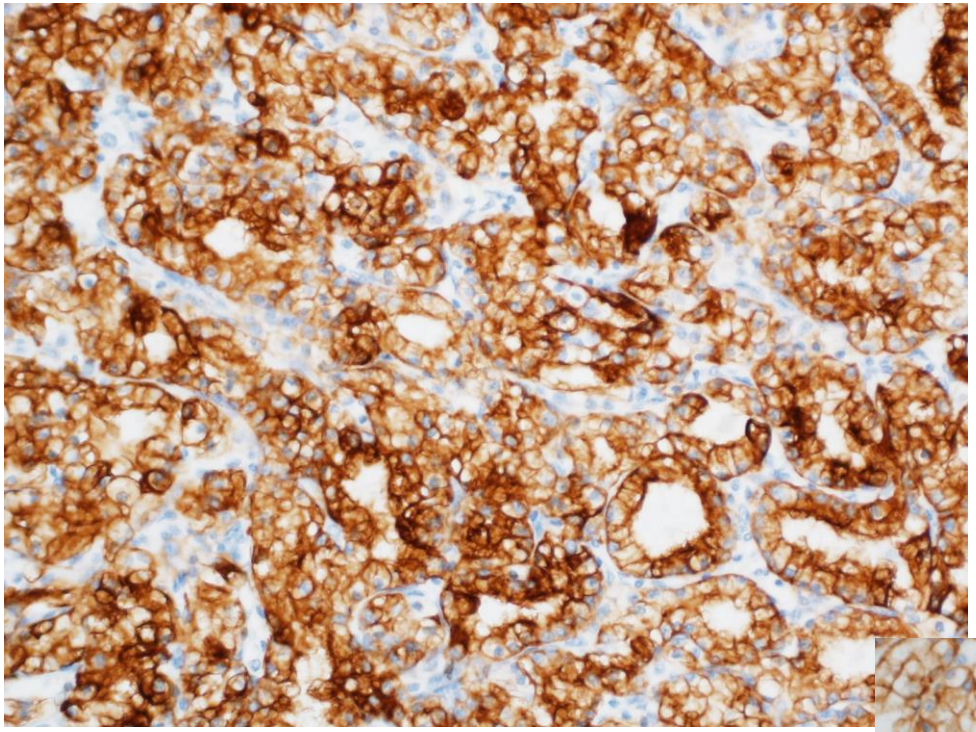






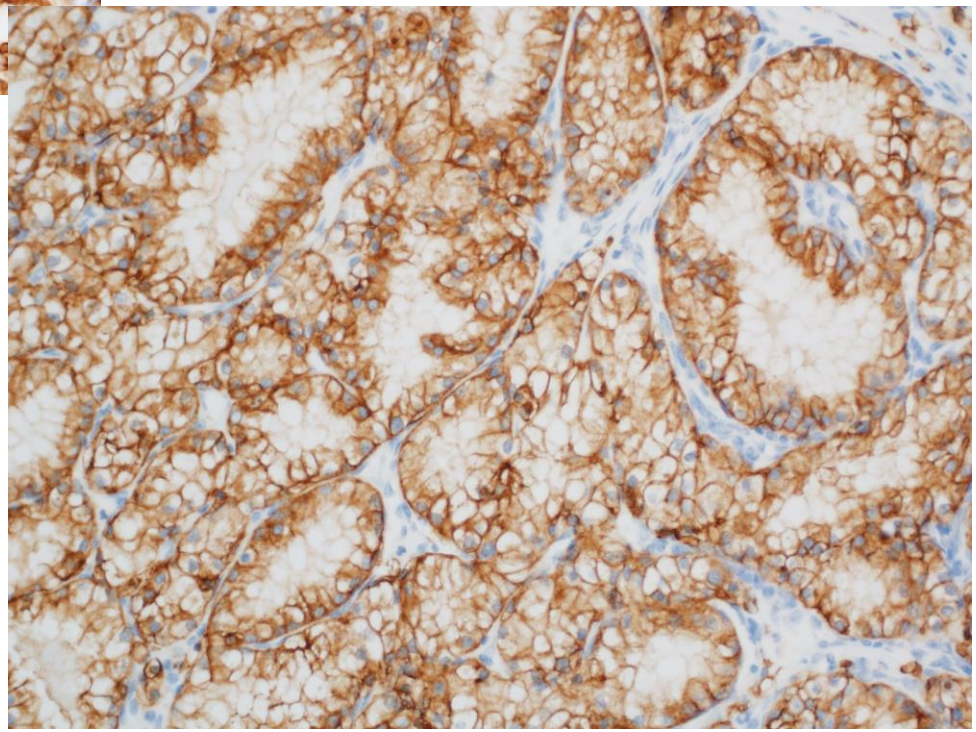






CK 7

Ca IX



Summarizing the findings

- Low power nodular appearance
- Epithelial component dissected by variable smooth muscle bundles
- Fibromuscular pseudocapsule
- Architecture: elongated tubules with frequent branching
- Cells with voluminous clear to mildly eosinophilic cytoplasm
- Diffuse CK7 positivity, CAIX positivity
- Differential:
  - Clear cell RCC: not typical vascular pattern, CK7 positivity
  - Clear cell papillary RCC: not reverse nuclear polarization
  - …..or something else

Renal Cell Carcinoma with leiomyomatous stroma (RCCLMS)

- Provisional/emerging entity in 2016 WHO as “RCC with (angio) leiomyomatous stroma”
- Renal tumors with clear cytology and admixed smooth muscle stroma
- Debate: single entity vs heterogeneous group?
- Literature on “RCC with fibromuscular stroma” likely contains a mixture of entities
  - Conventional Clear Cell RCC (CCRCC) can have fibromuscular stroma
  - Clear Cell Papillary RCC (CCPRCC) can have fibromuscular stroma
    - Tumor originally called ”Renal Angiomyoadenomatous Tumor/RAT” now believed to be on a spectrum with/same entity as CCPRCC
  - Tumors with fibromuscular stroma associated with TSC syndrome
    - “RAT-like” RCC
    - “TSC-associated papillary” RCC
  - Identical tumor with *TCEB1/ELOC* mutation
- The TSC and *TCEB1/ELOC* connection seems to hold a clue to a better delineation of a specific entity as it suggests a connection to the TSC gene pathway

"Renal Cell Carcinoma With Leiomyomatous Stroma" Harbor Somatic Mutations of *TSC1*, *TSC2*, *MTOR*, and/or *ELOC* (*TCEB1*): Clinicopathologic and Molecular Characterization of 18 Sporadic Tumors Supports a Distinct Entity

Rajal B. Shah, MD, Bradley A. Stohr, MD, PhD,† Zheng Jin Tu, PhD,* Yuan Gao, MD,‡ Christopher G. Przybycin, MD,* Jane Nguyen, MD, PhD,* Roni M. Cox, MD,* Fariborz Rashid-Kolvear, MD,‡ Michael D. Weindel, MD,* Daniel H. Farkas, PhD, HCLD,* Kiril Trpkov, MD,‡ and Jesse K. McKenney, MD**

- Classified sporadic "RCCs associated with fibromuscular stroma" into RCCLMS and CCRCC on morphologic grounds and CK7 staining
  - RCCLMS: Typical histology seen in TSC-associated tumors + diffuse CK7 positivity
  - CCRCC: Delicate branching "racemose" vasculature + negative/not diffuse CK7
  - (CCPRCC: Small tubules, scant cytoplasm, nuclear polarization)
- Genomic mutational analysis supported morphology/IHC:
  - RCCLMS: All have abnormalities in TSC gene pathway (*TSC1, TSC2, MTOR, ELOC/TCEB1*)
  - Control CCRCC: *VHL* gene abnormalities
- Proposed that RCCLMS is a specific entity and represents the sporadic counterpart to the TSC-associated RCC

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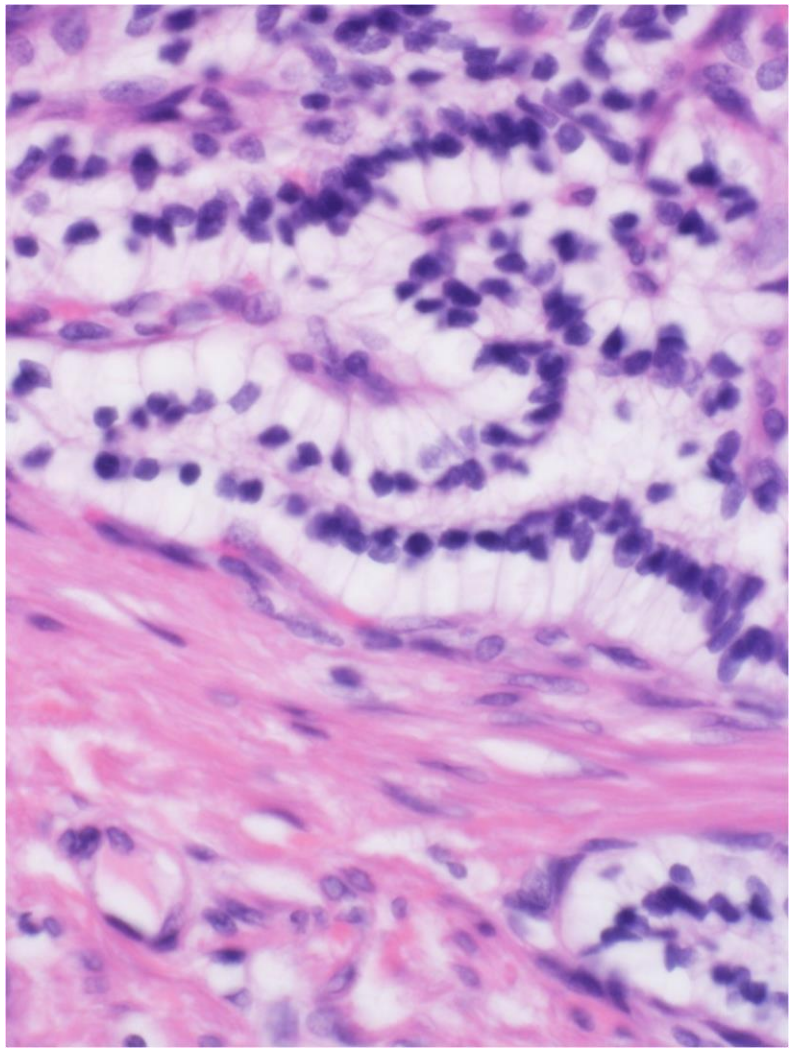
RCCLMS Differential diagnosis

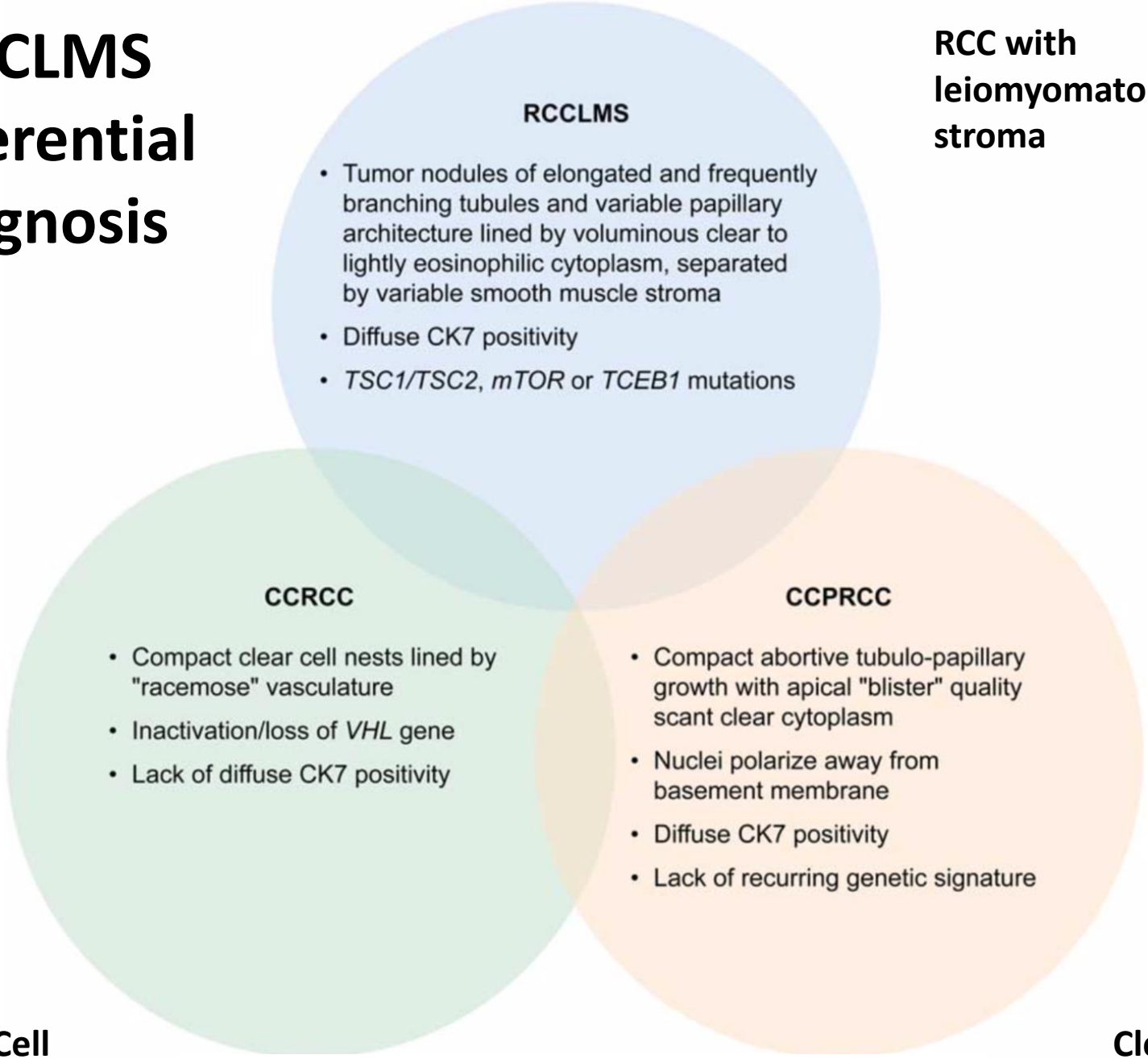


Nuclear polarization

- Conventional Clear cell RCC
  - Compact clear cell nests lined by delicate branching “racemose” vasculature
  - Lack of diffuse CK7 positivity
- Clear Cell Papillary RCC
  - Compact abortive tubulopapillary growth
  - Less voluminous clear cytoplasm
  - Nuclear polarization towards lumen/away from basement membrane

RCCLMS Differential diagnosis

RCC with leiomyomatous stroma



Clear Cell RCC

Clear Cell Papillary RCC

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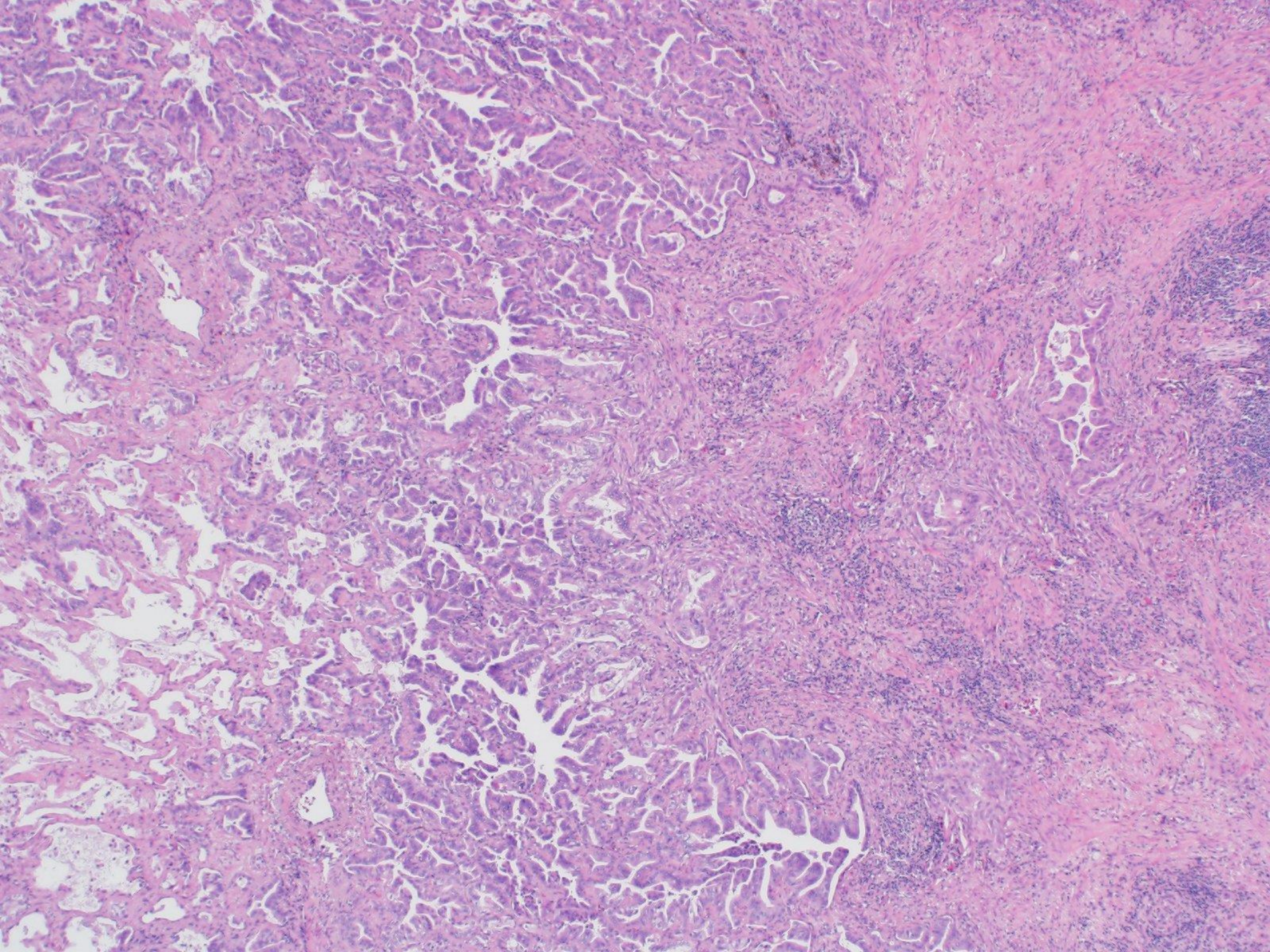
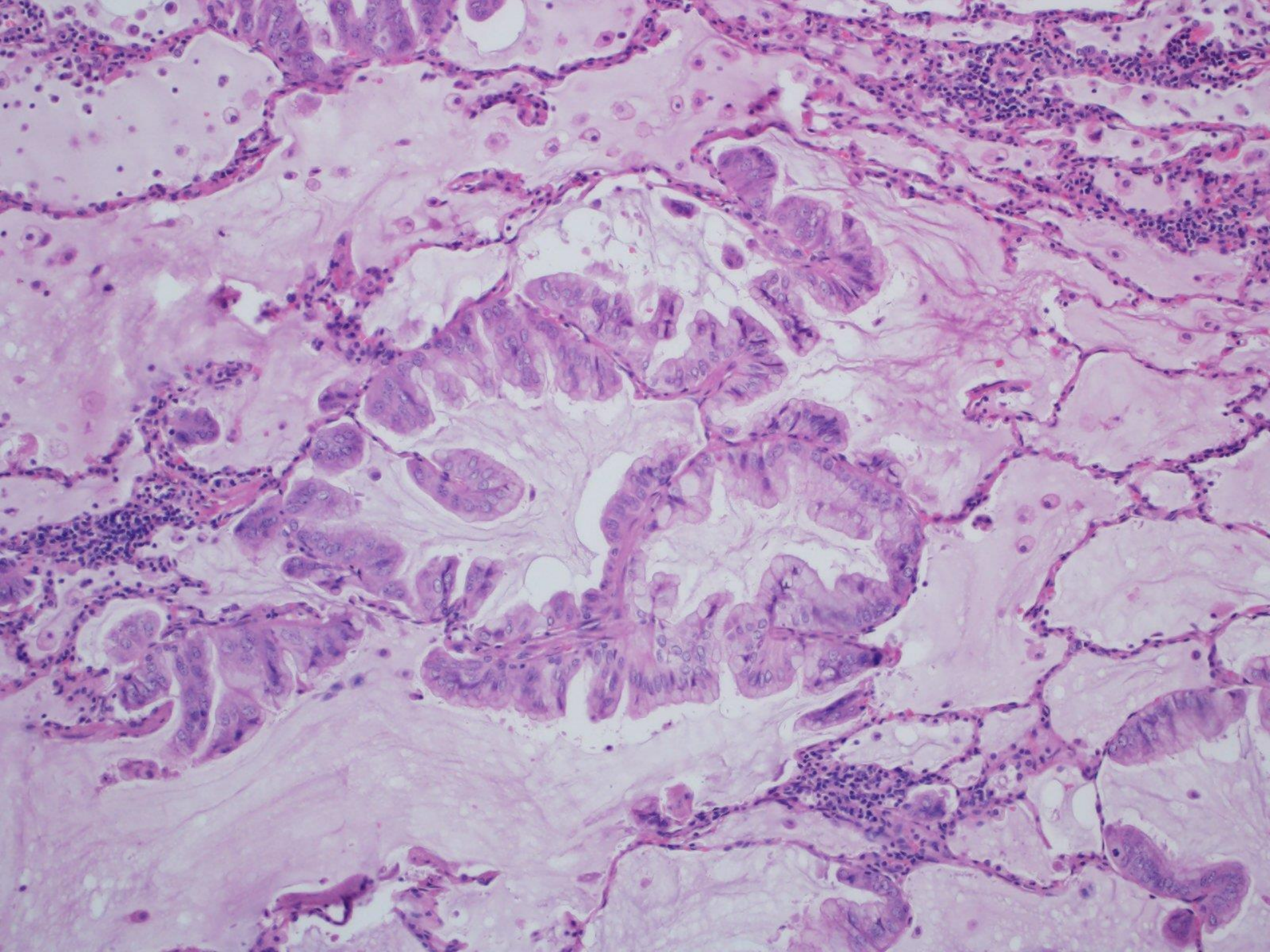
RCCLMS: Some Key Points

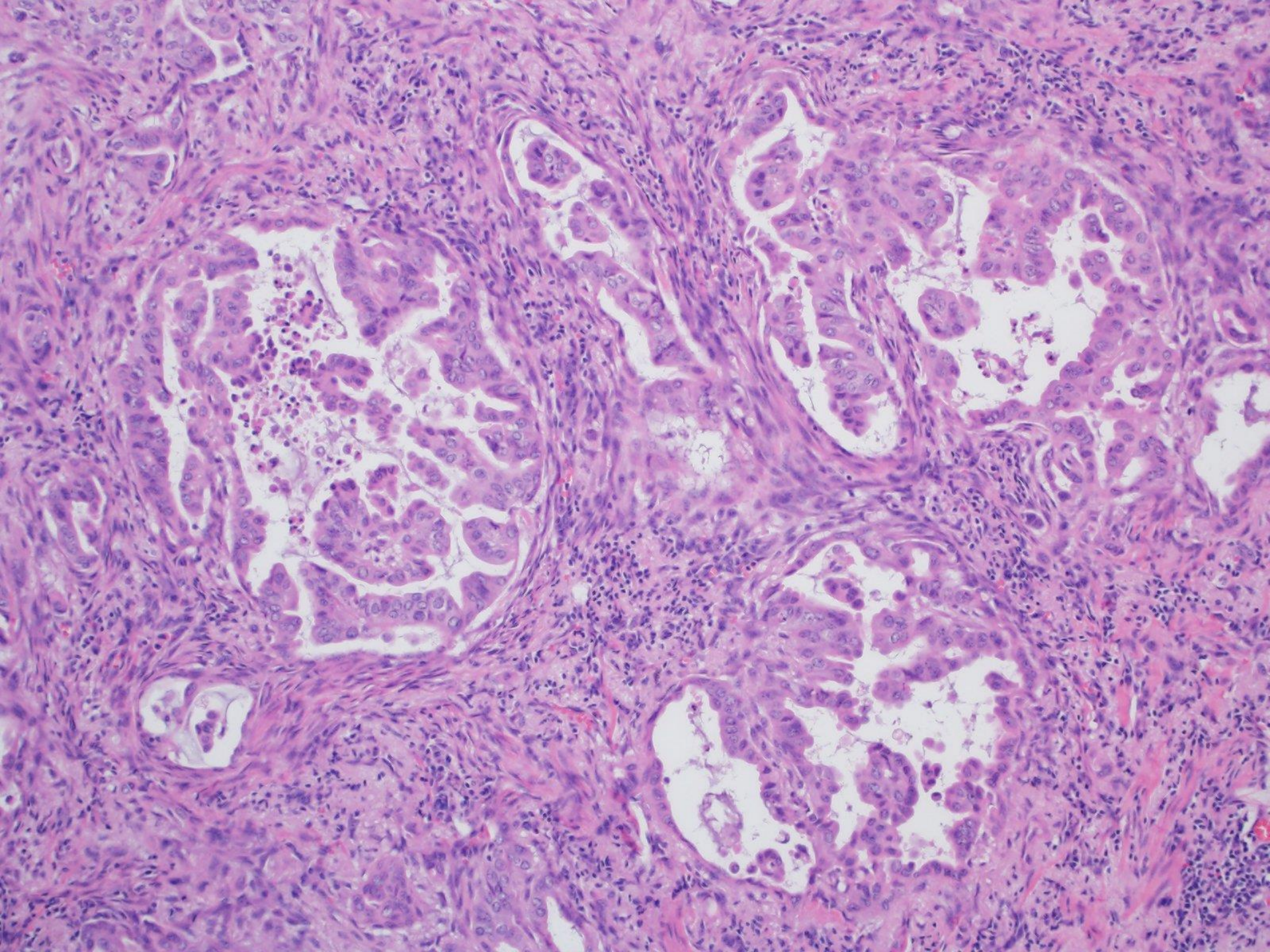
- Diagnosis: morphology and diffuse CK7
- Prognosis:
  - Appear indolent (so far)
- Same morphology can be seen in some RCCs in patients with Tuberous Sclerosis: might be a clue for TSC (look for AML tumorlets also)

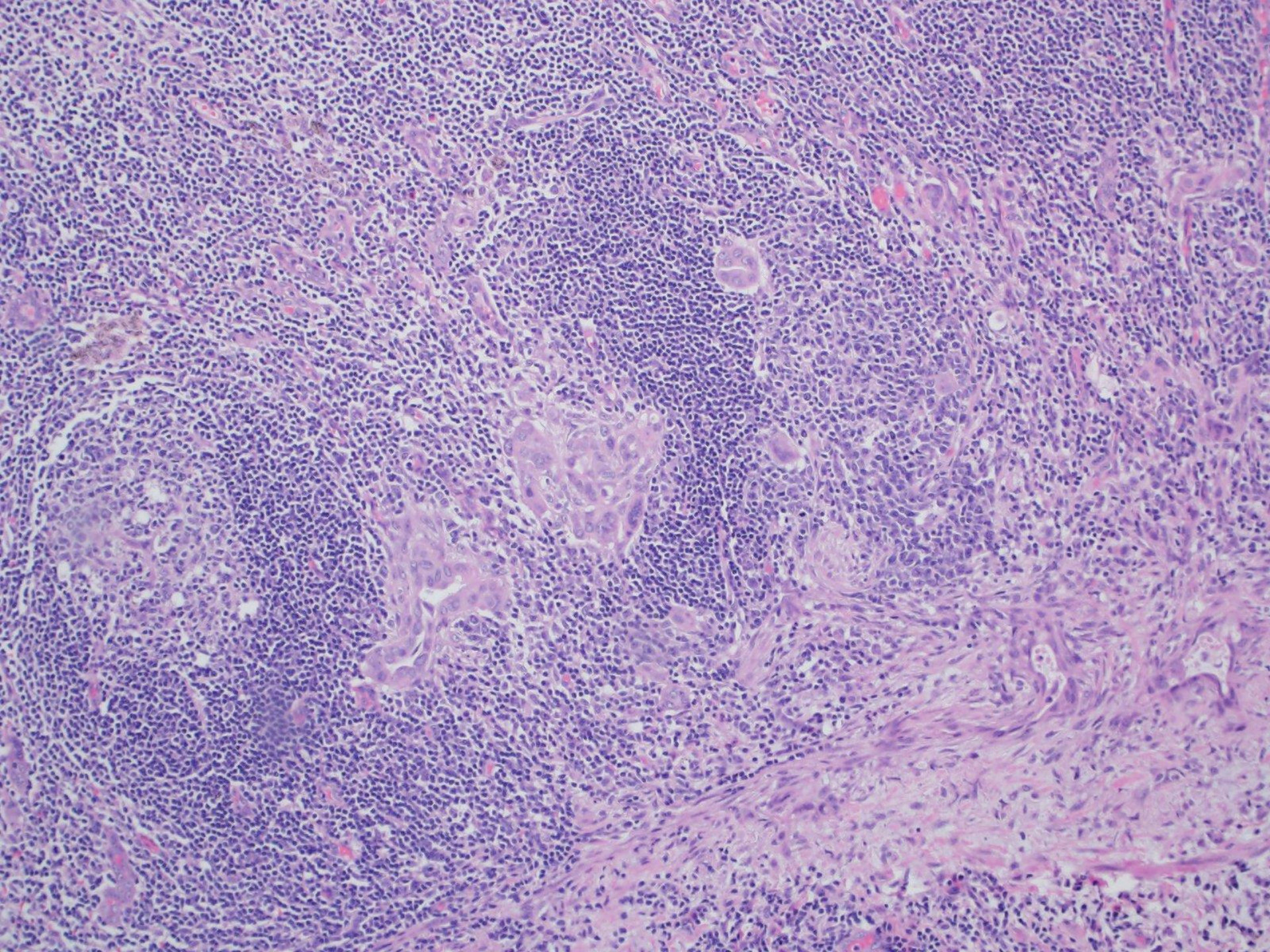
Case 4: Lung Tumor (and more)

- 50 year old male
- Lung mass biopsy:
  - "Invasive adenocarcinoma with areas showing mucinous differentiation"
- Segmental lobectomy for lung mass







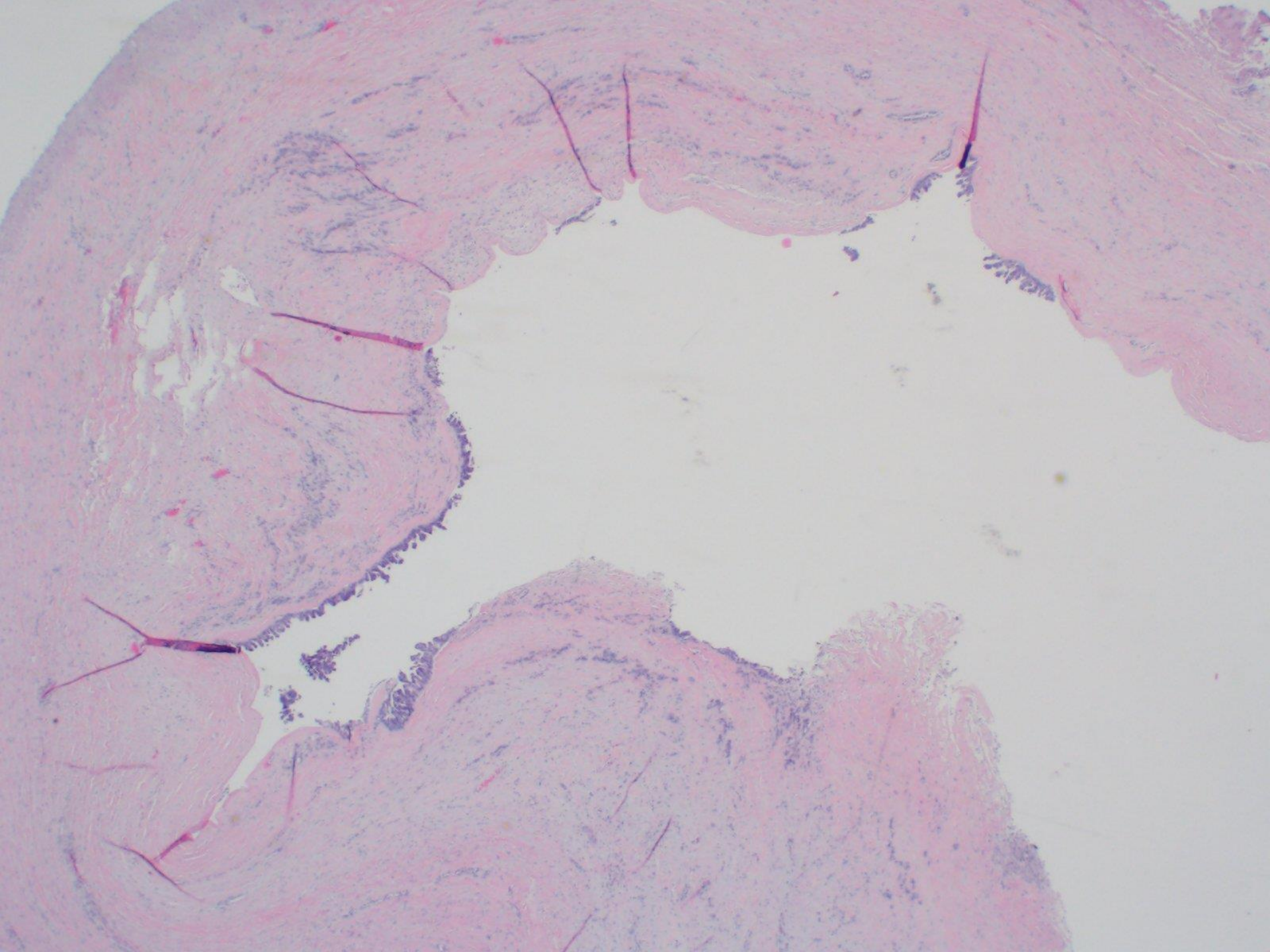


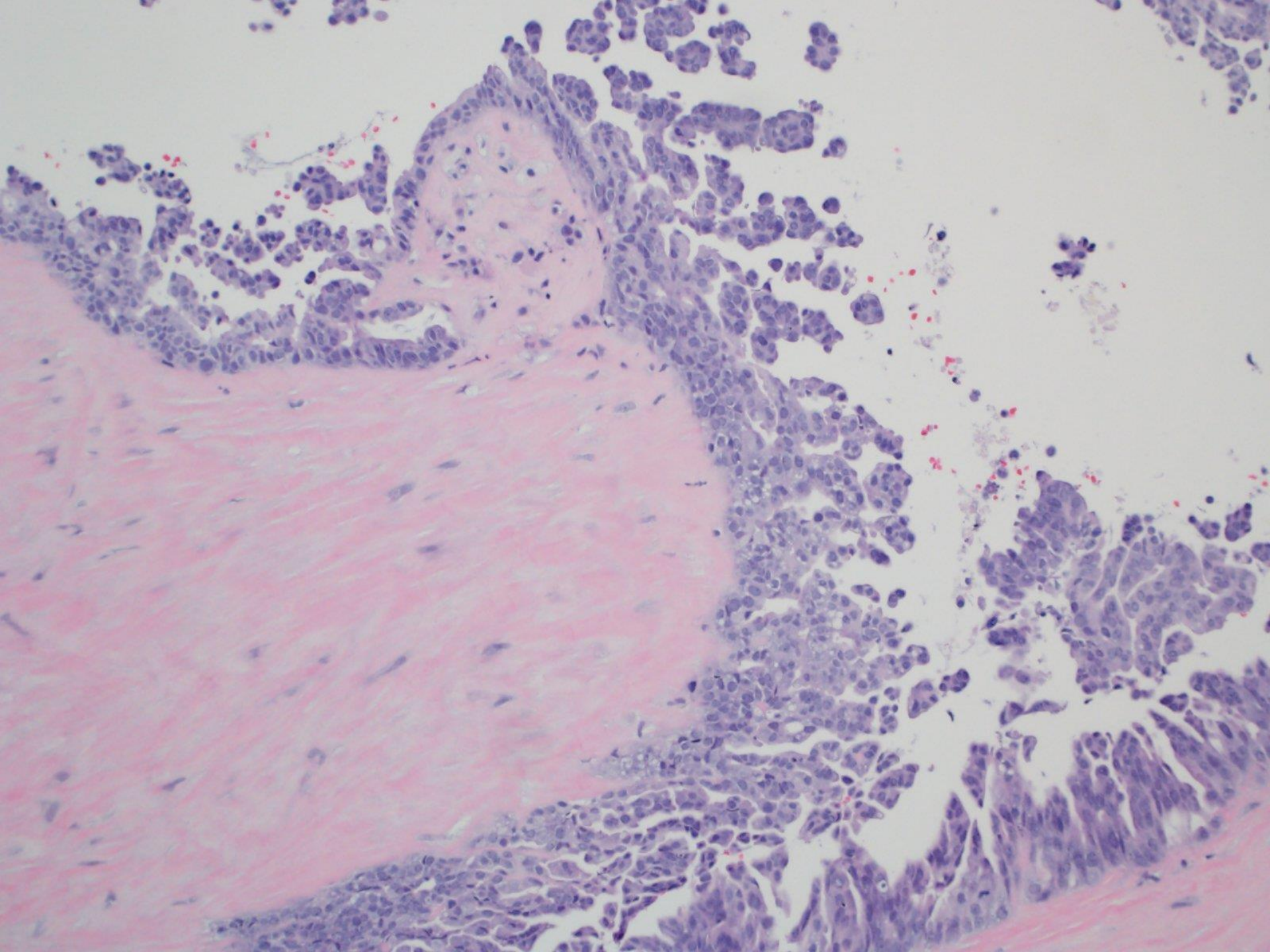
Tumor Board

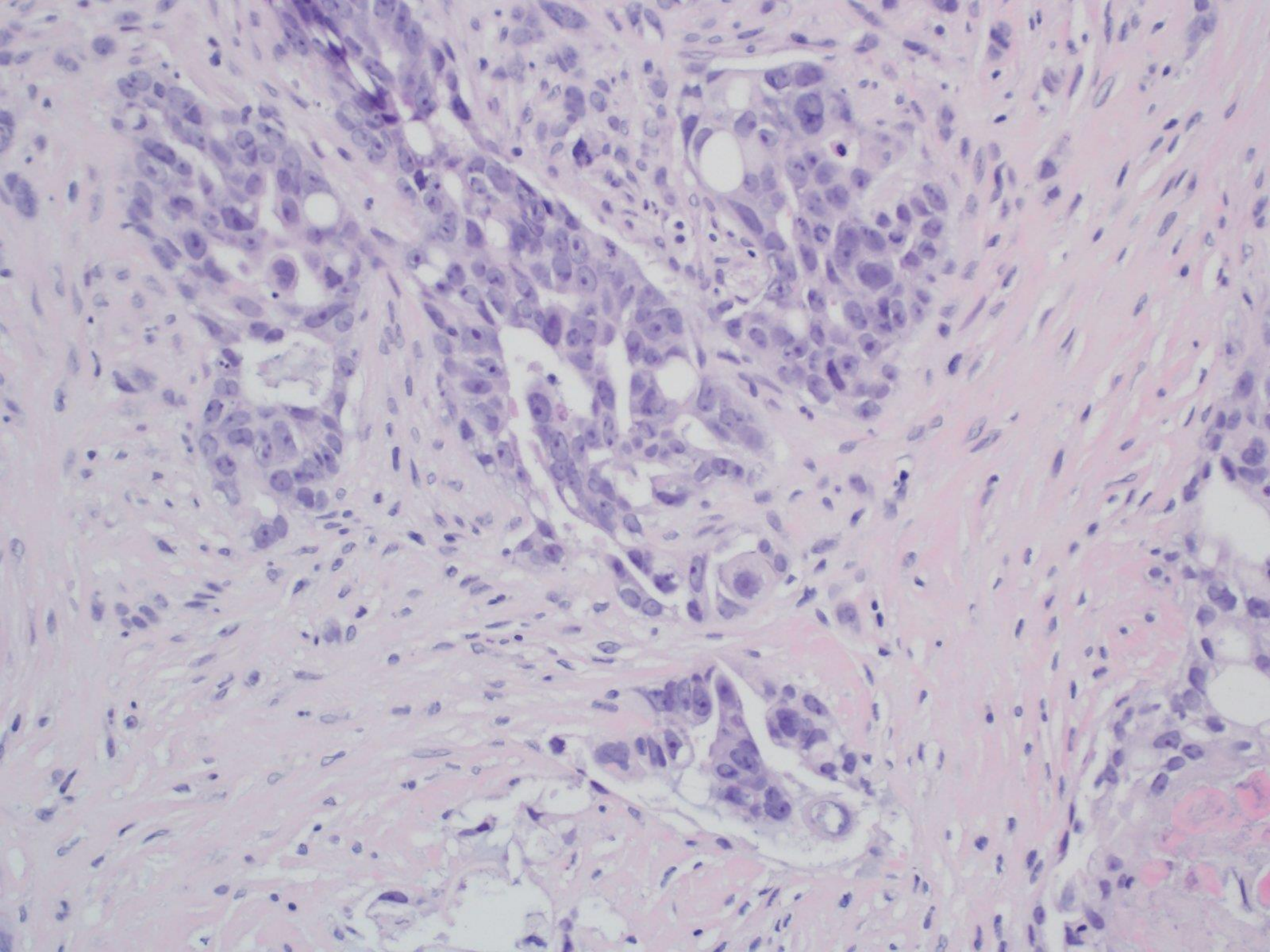
- “By the way, the patient had a testicular germ cell tumor in the past, at another institution…”

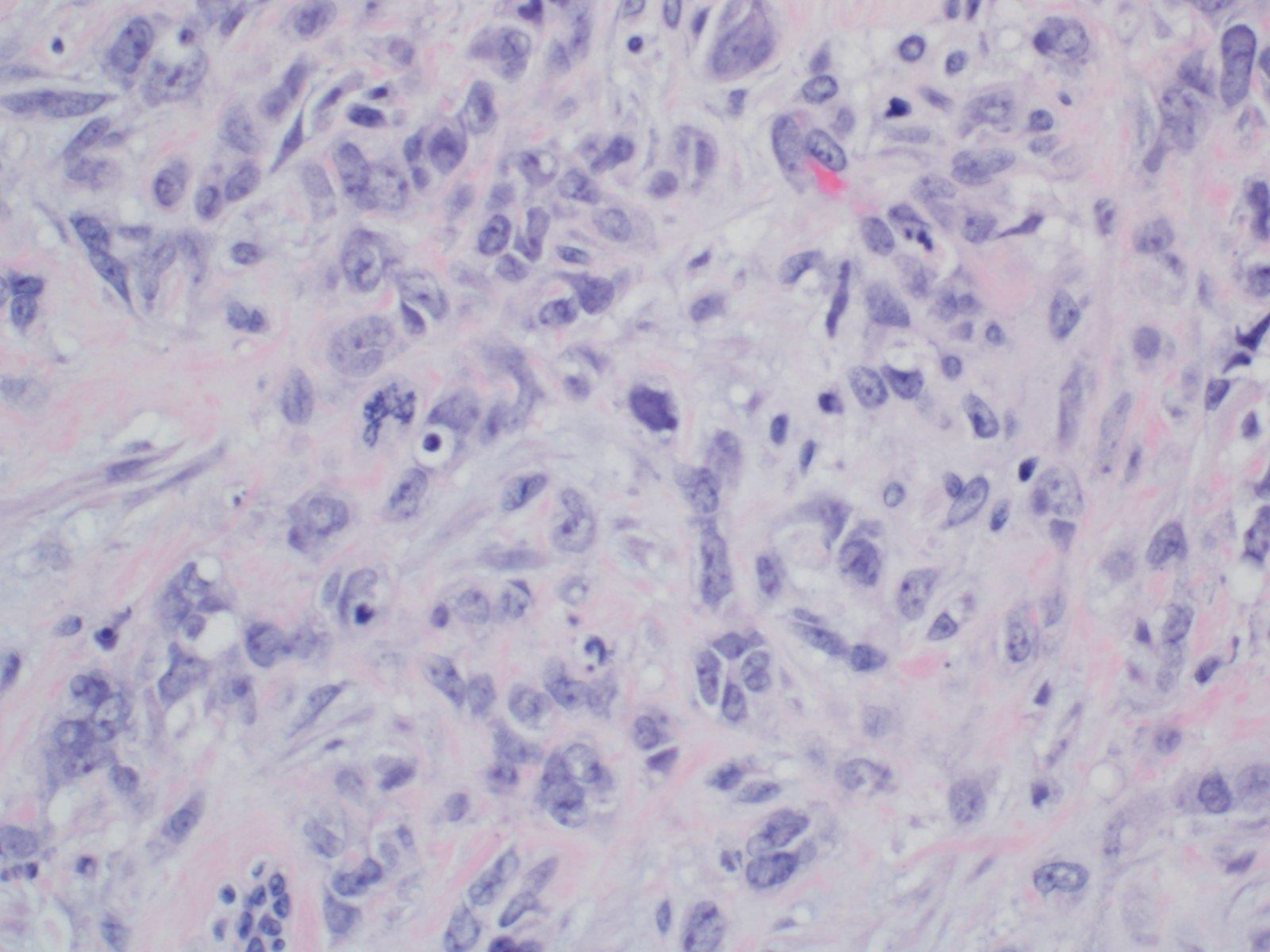
Testis mass (4 years previously)

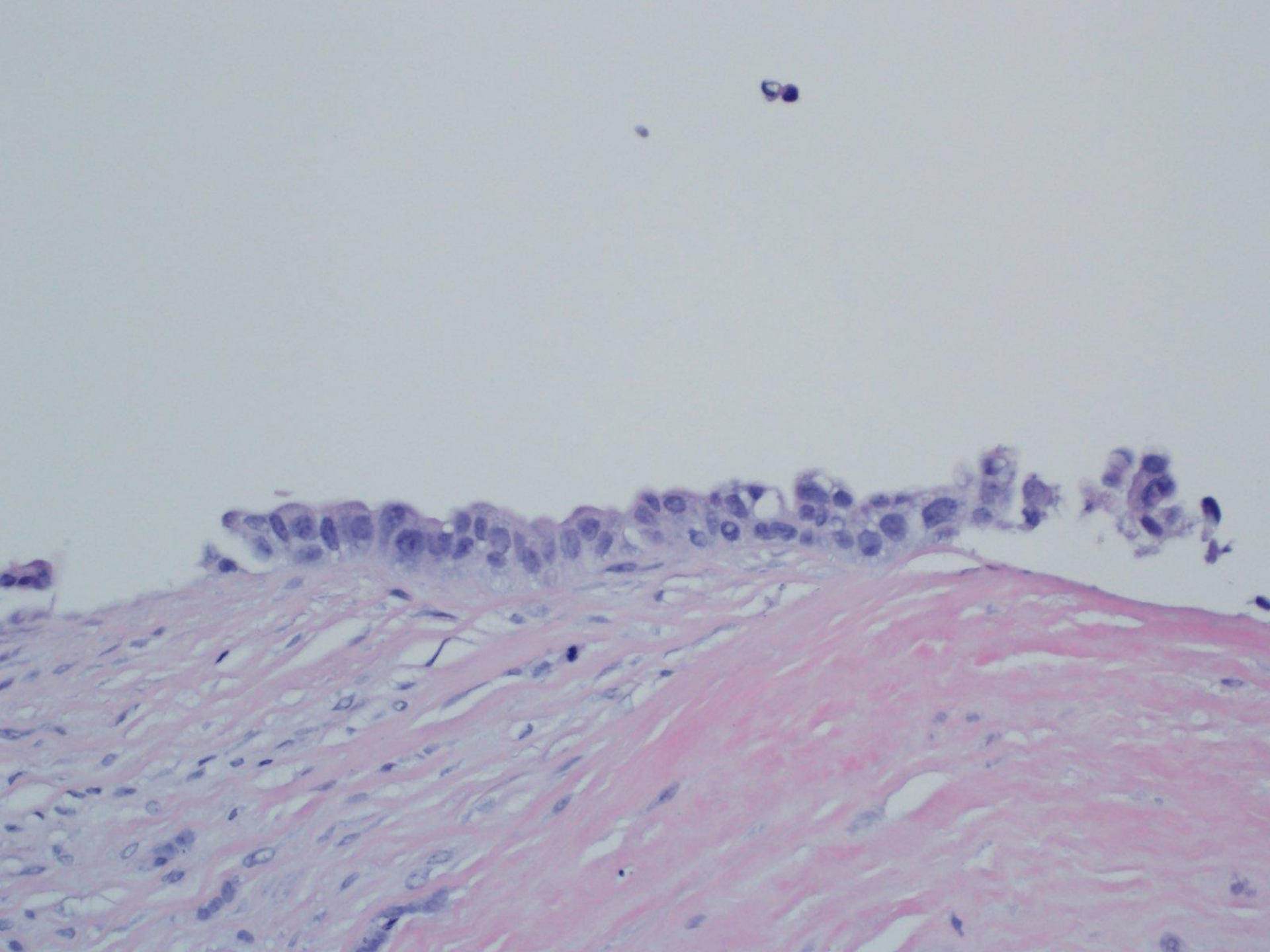
- 3.3 cm complex cystic mass
- Centered in testis
  - Involved rete testis, but not centered there
  - Epididymis appeared normal
- Radical orchiectomy performed

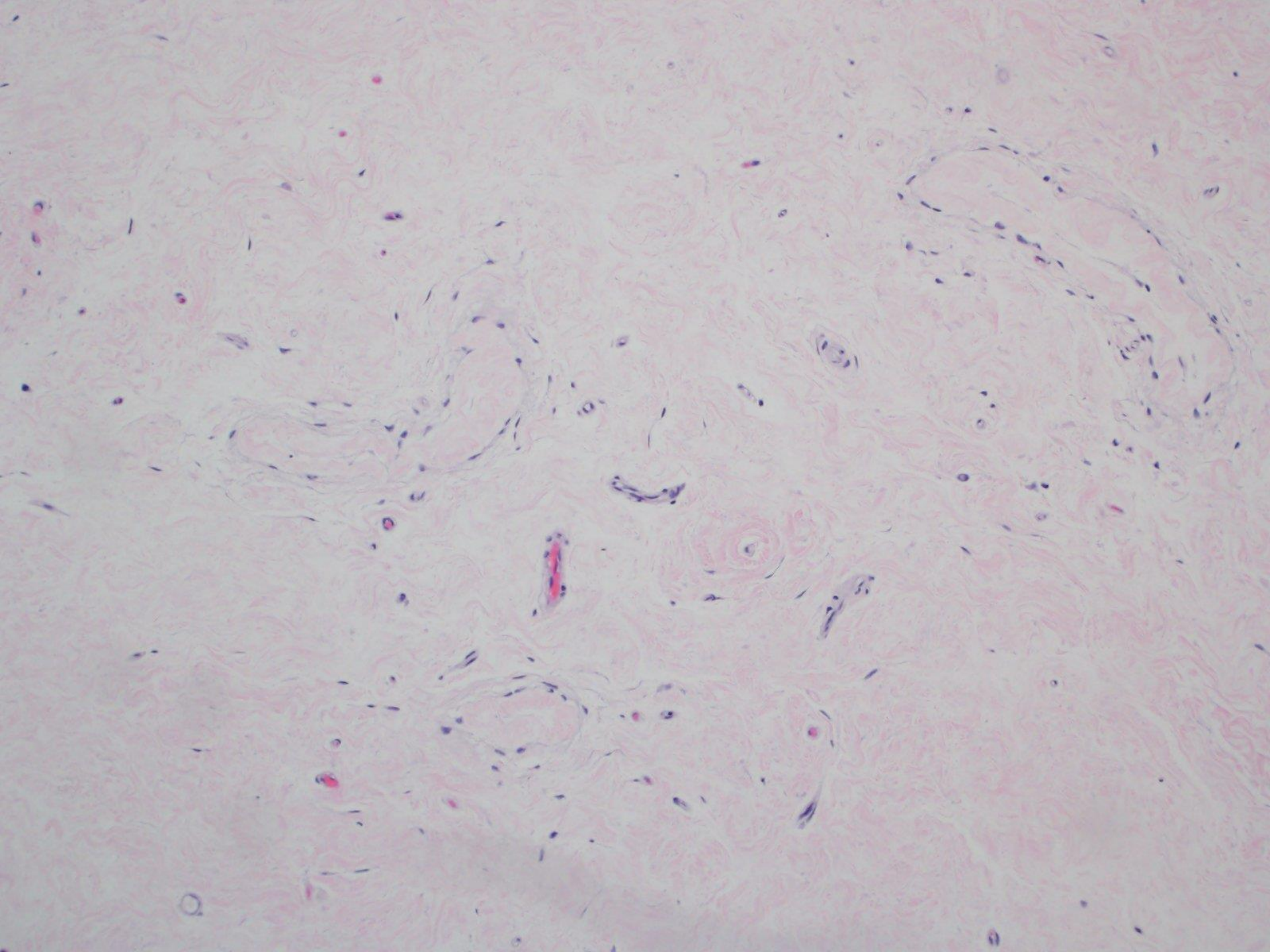












IHC

- Positive: CK7
- Negative: Germ cell markers, calretinin, WT1, multiple others

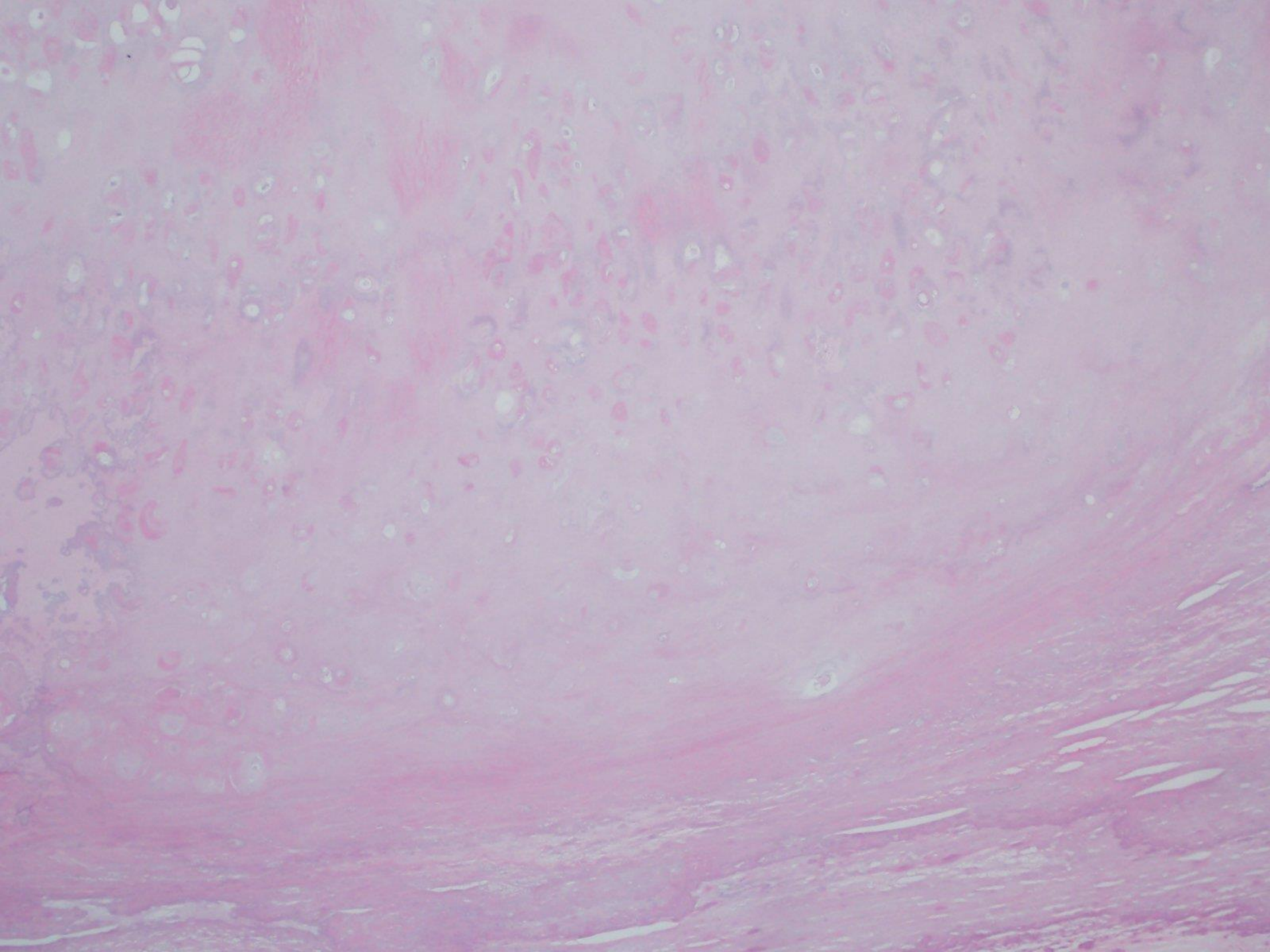
- Differential diagnosis
  - Metastasis
  - Ovarian type adenocarcinoma
  - Malignant Sertoli cell tumor
  - Adenocarcinoma of teratomatous origin

- Scarring of adjacent testis → Suggests regression of germ cell tumor
- Areas of cyst showing lower grade cells → Suggests origin in a pre-existing teratomatous cyst

Testis Tumor Diagnosis

- **High grade adenocarcinoma, most likely of teratomatous origin**

- Subsequent retroperitoneal mass excised



Lung Tumor

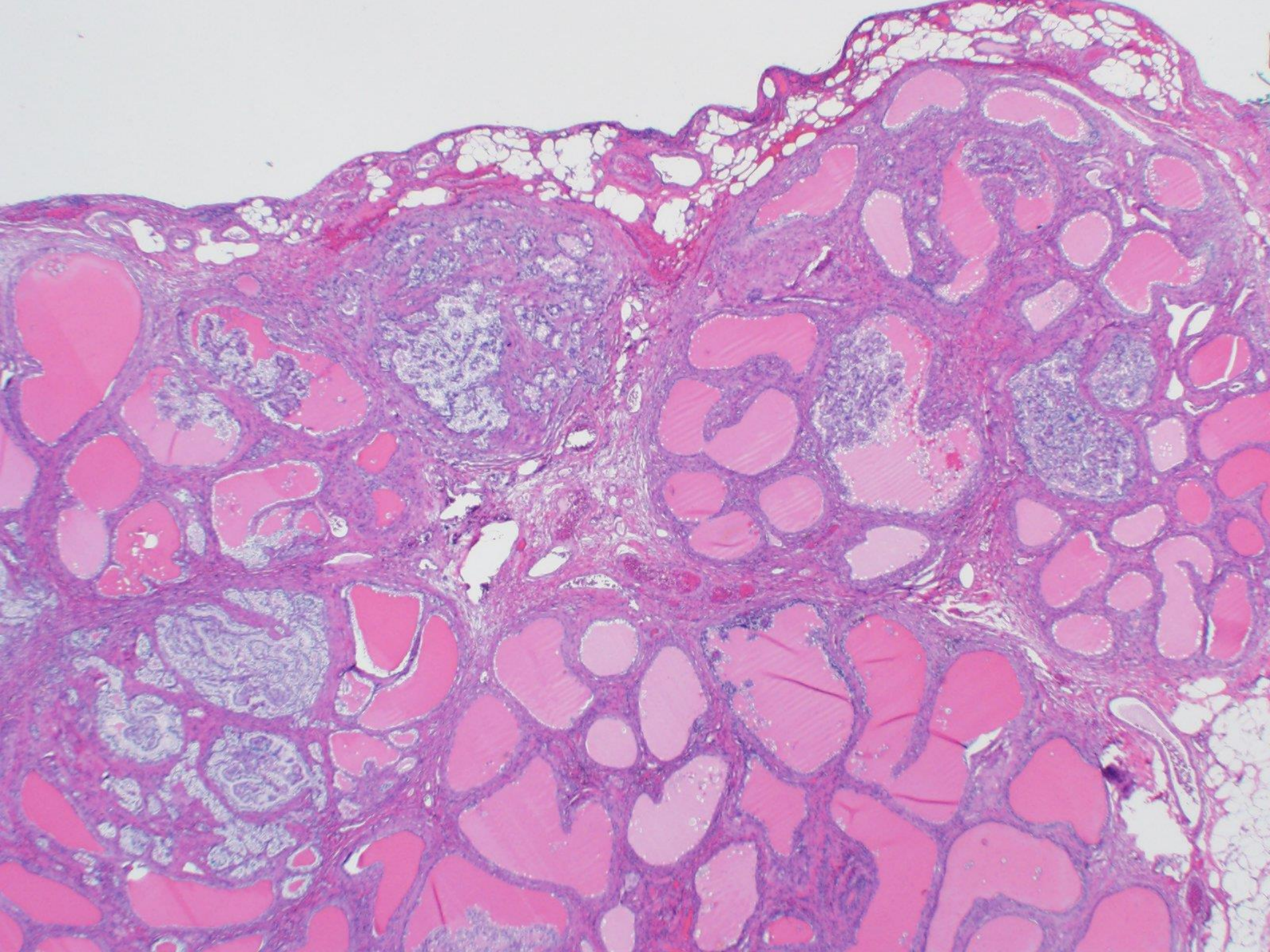
- With this history, and comparing morphology, we felt that metastasis from the testicular tumor was likely
- Immunohistochemistry not helpful
- Testing for isochromosome 12p [i(12p)] by FISH
  - Overrepresentation of 12p (usually as i(12p)) common (80%) in postpubertal germ cell tumors
- → **Positive** in the lung tumor

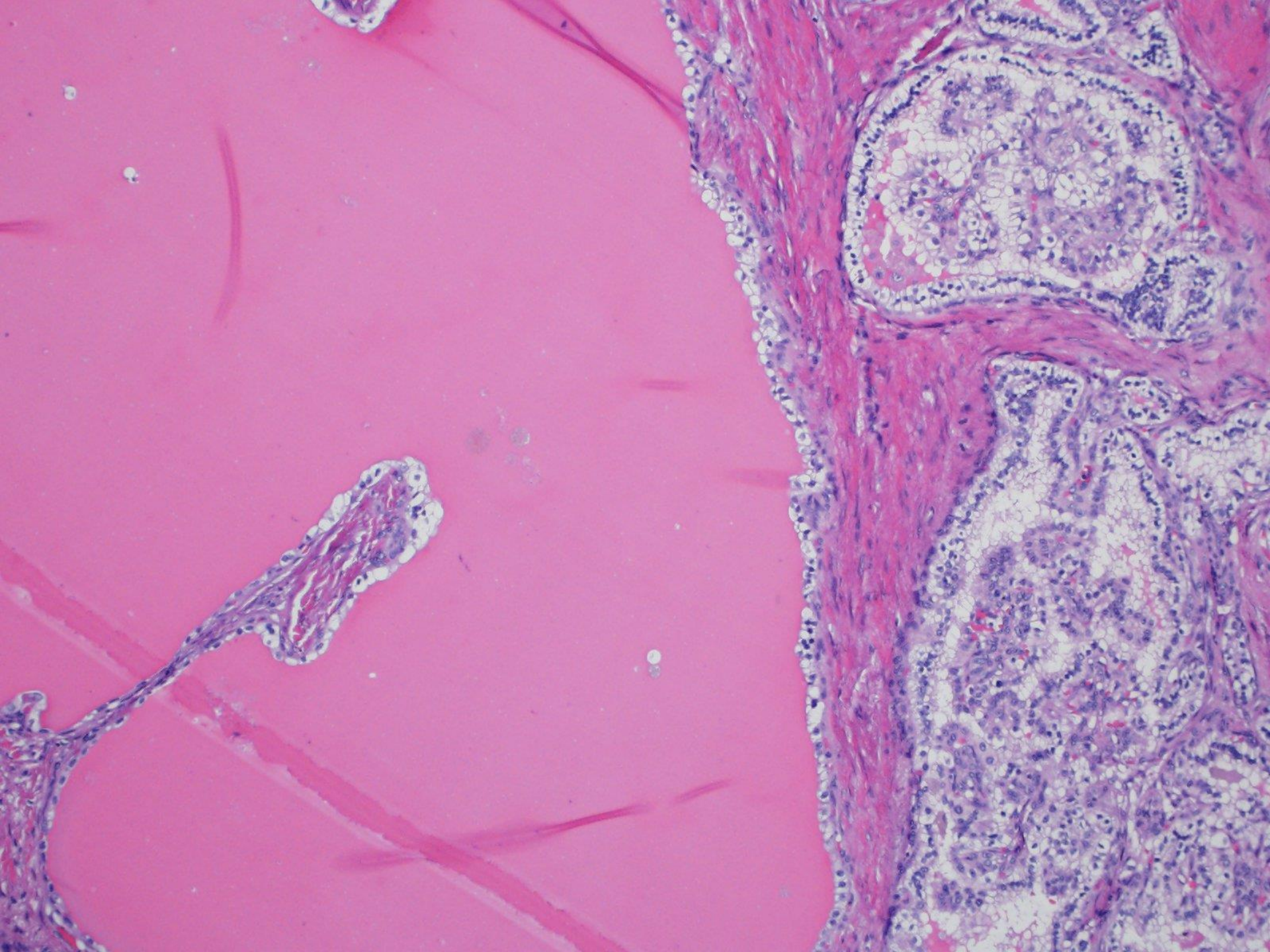
Teratoma with Secondary Somatic Malignancy

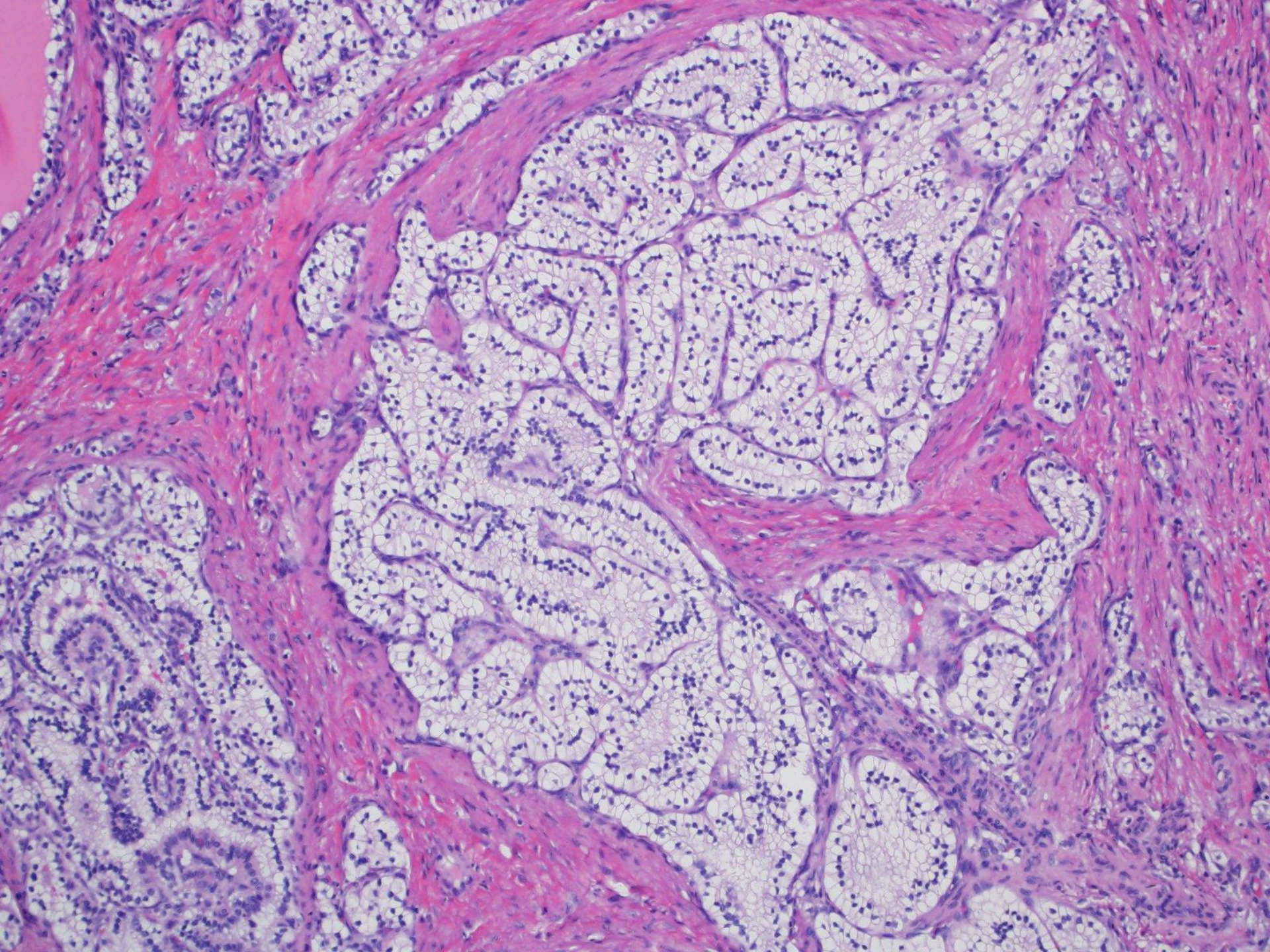
- Usually in post-treatment specimens
- Esp: lung, retroperitoneal lymph nodes
- May have mature or immature features
- Carcinomas: glandular, squamous, neuroendocrine, undifferentiated
  - Recognize by infiltrative growth
- Sarcomas: chondro, leio, lipo, rhabdo, undiff spindle…
  - Pure atypical population involving at least 4X field
- PNET, Wilms:
  - Pure atypical population involving at least 4X field
- Clinical significance of somatic type malignancy:
  - If metastatic: respond poorly to usual met GCT therapies
  - If confined to testis: unclear prognostic implication
- Takeaway: “Carcinoma of unknown origin” and history of prior GCT remember FISH test for i(12p)

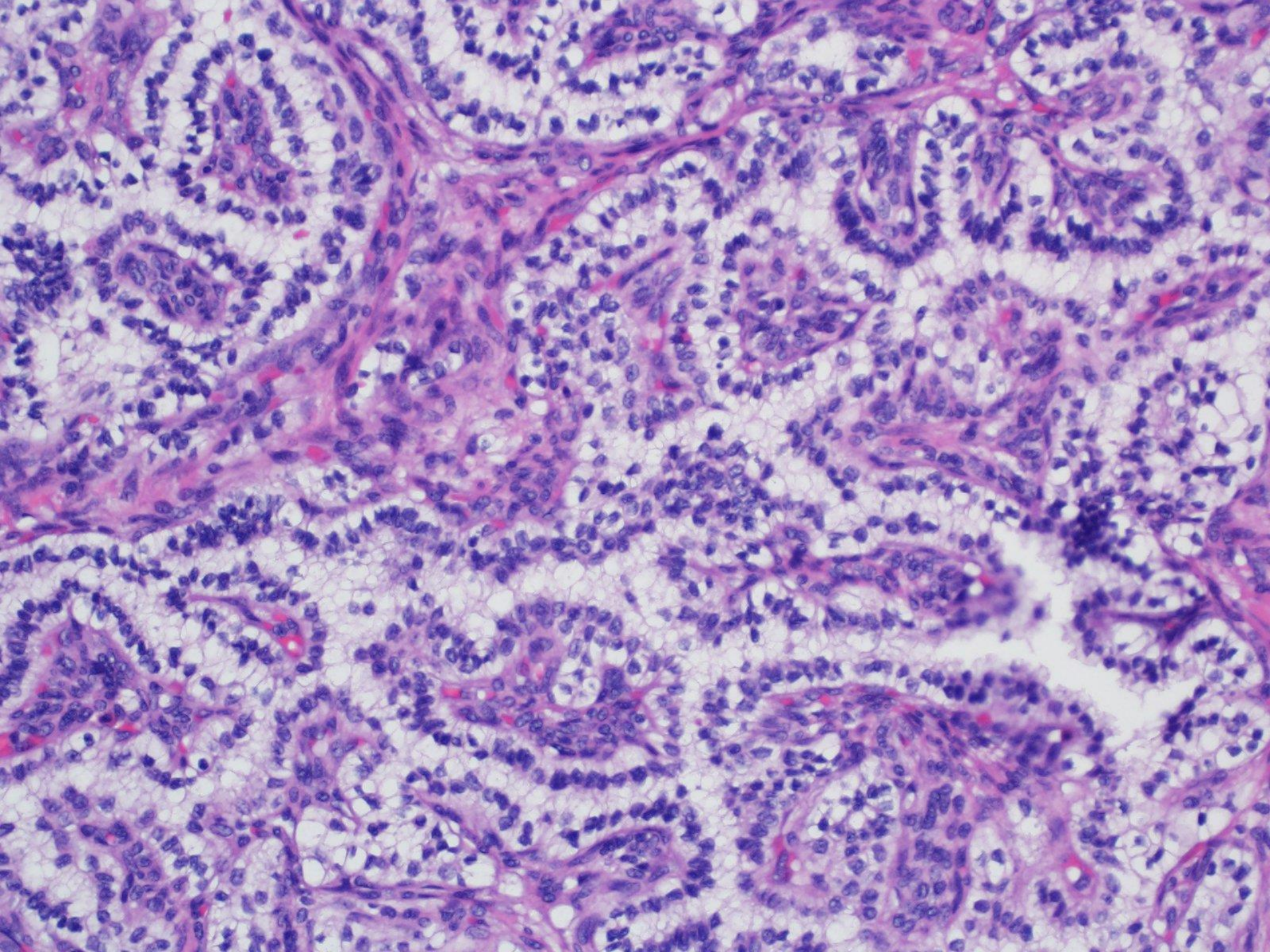
Case 5: Epididymal Masses

- Slowly growing bilateral epididymal “cysts” in 37 year old
- “Encysted hydroceles” “reactive/papillary hyperplasia”
- Received excisions from right and left epididymis
- Grossly: 2.3 cm and 3.5 cm tissue fragments showing a multicystic cut surface

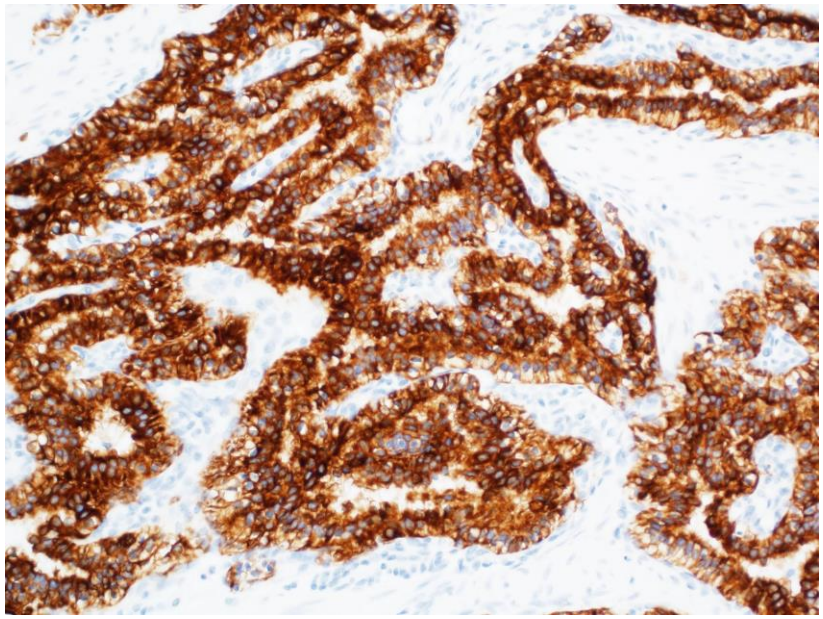




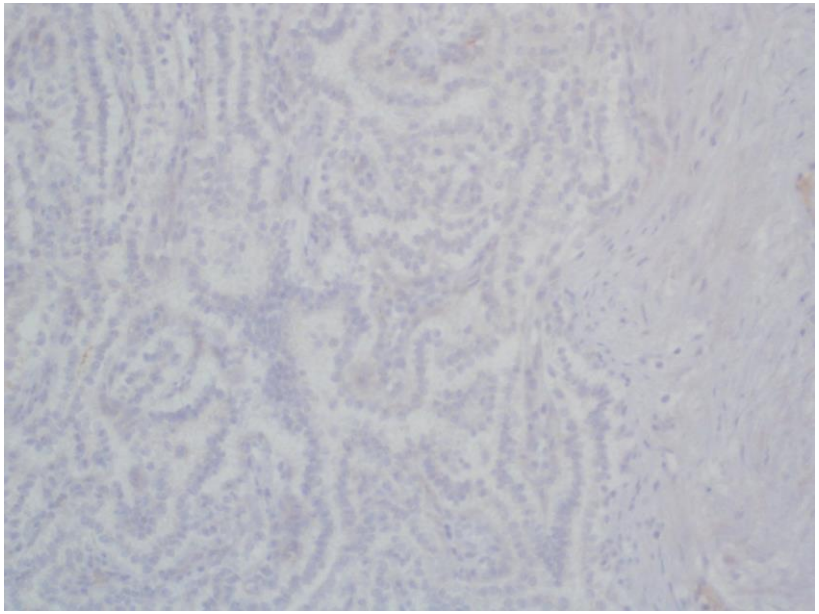




Cytokeratin 7



AMACR/p504s



Immunohistochemistry

Positive:

- PAX8, CK7, Carbonic anhydrase IX

Negative:

- AMACR/p504s, RCCma

(Like Clear cell papillary renal cell ca)

Papillary Cystadenoma of Epididymis

- Benign (very rarely malignant)
- Ages 16-81 years, average 36
- Sporadic or with von Hippel-Lindau (40%)
- May be bilateral (more likely a/w VHL)
- Histology
  - Tubules, cysts, often with eosinophilic colloid-like secretion
  - Papillary structures, single layer of bland typically clear cells
  - Reverse polarity (luminal orientation of nuclei, subnuclear vacuoles) is common
- Differential diagnosis
  - Few, given the distinctive appearance
  - Resembles clear cell papillary ca of kidney (but that entity does not metastasize)
  - Metastatic clear cell renal cell
    - More heterogeneous appearance
    - Greater atypia
    - Sinusoidal vascular pattern
- Key points: very distinctive, generally benign, association with VHL

Thank you!