GU Hereditary Syndrome Associations: Real Case Based Review and “Next Steps”

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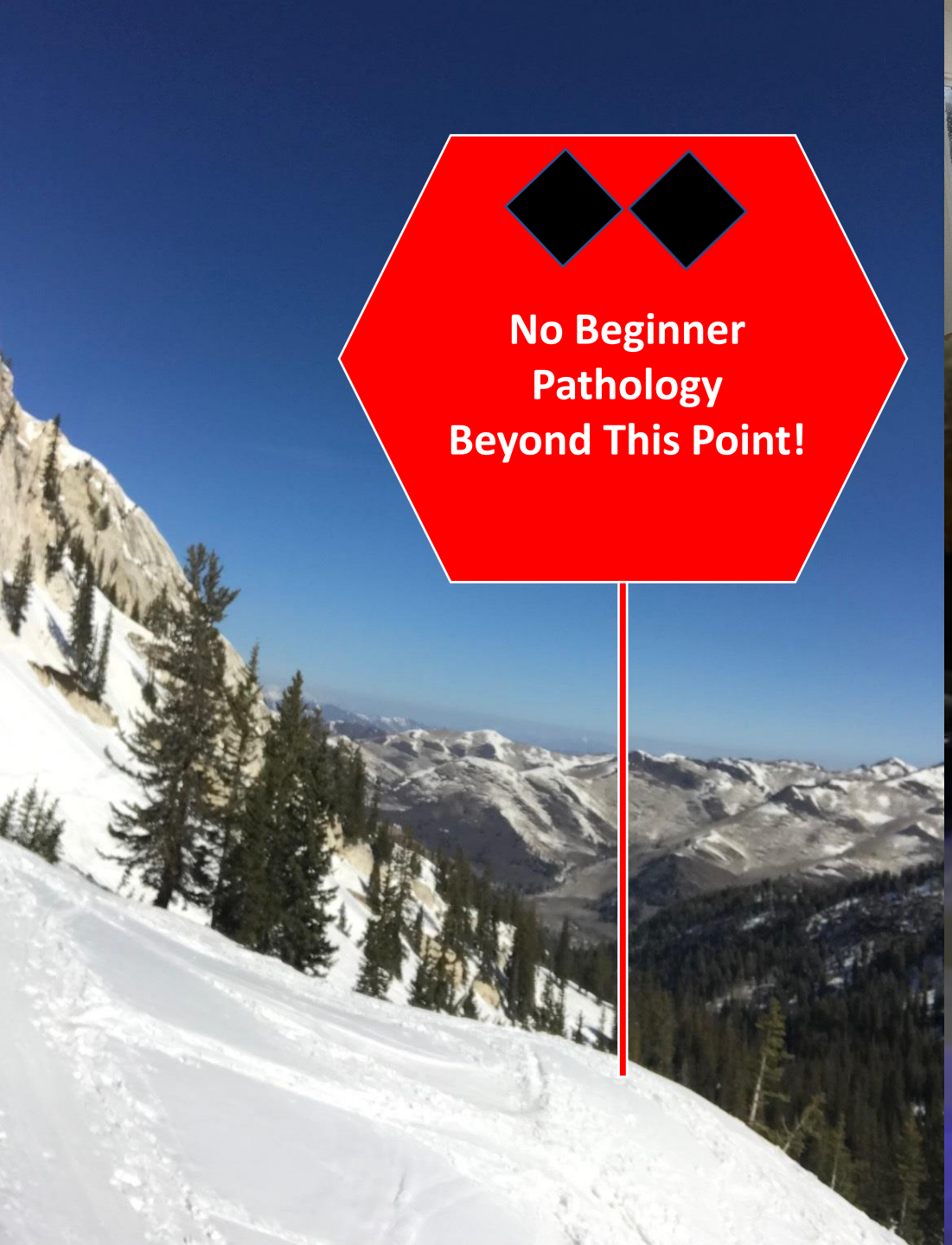
Learning Objectives:

- Review GU Cancer Syndromes
- Explore morphologic, immunohistochemical, FISH, and other ancillary methods related to syndromic diagnosis / detection.
- Review NCCN 2023 genetic testing guidelines
  - With particular attention to pathologic diagnosis
- Updates regarding IHC interpretation
- Review unusual presentations of rare syndromes

Outline

4 Real Cases

2 Additional Bonus Cases with Atypical Features



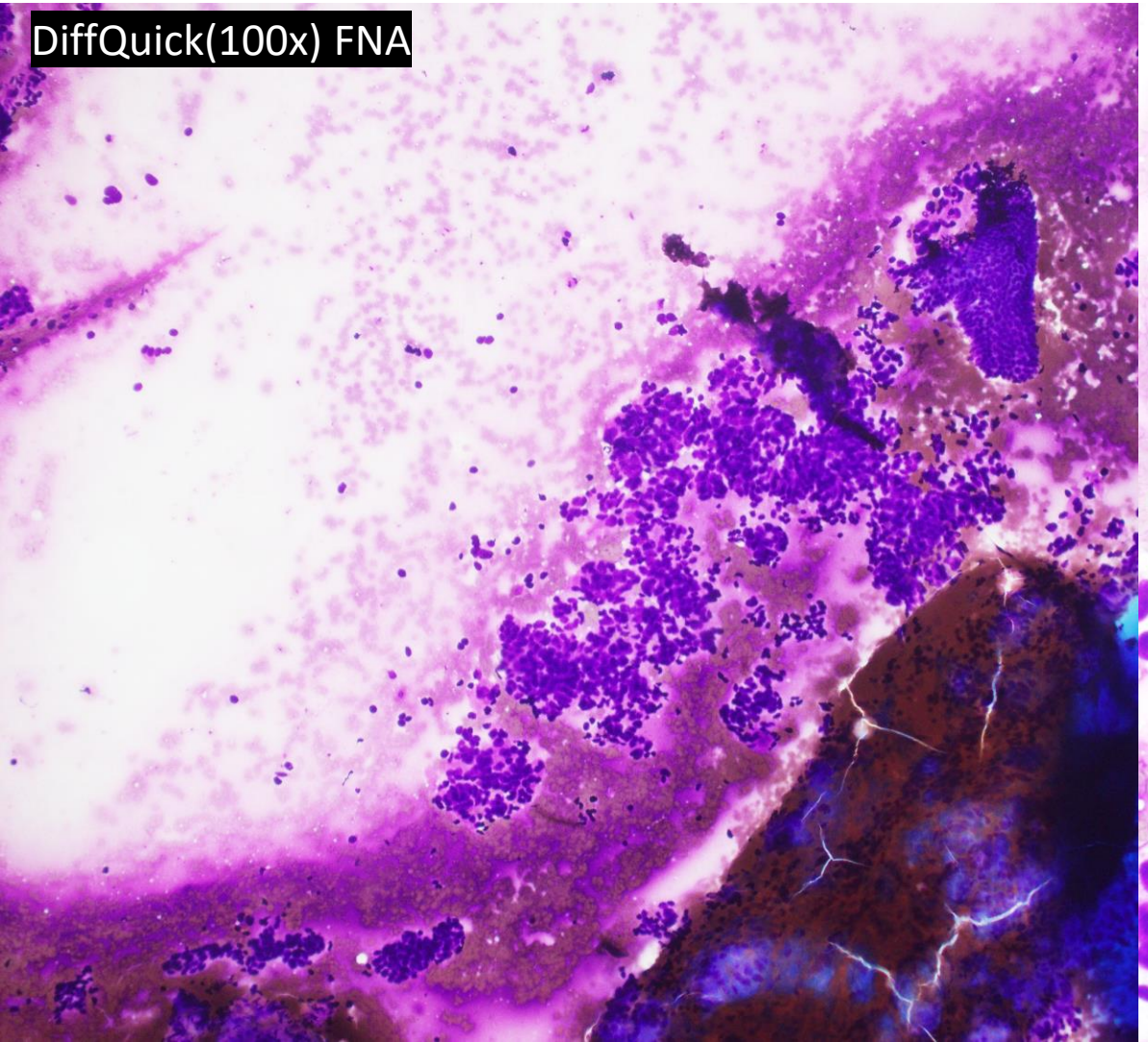
ARUP®
LABORATORIES

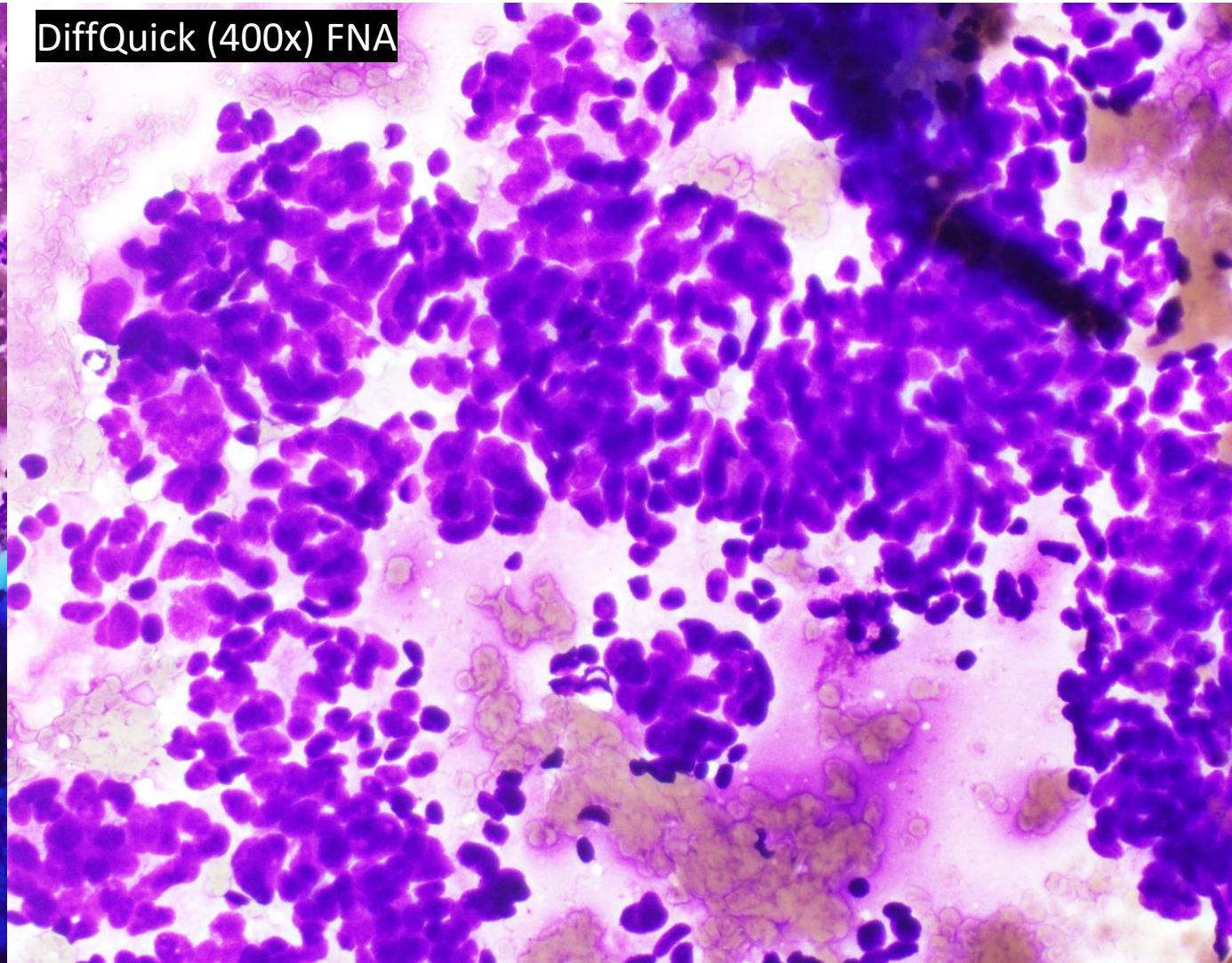
Case 1:

31M – Incidental Pancreatic Mass (2.5 cm) Discovered On Unrelated Imaging

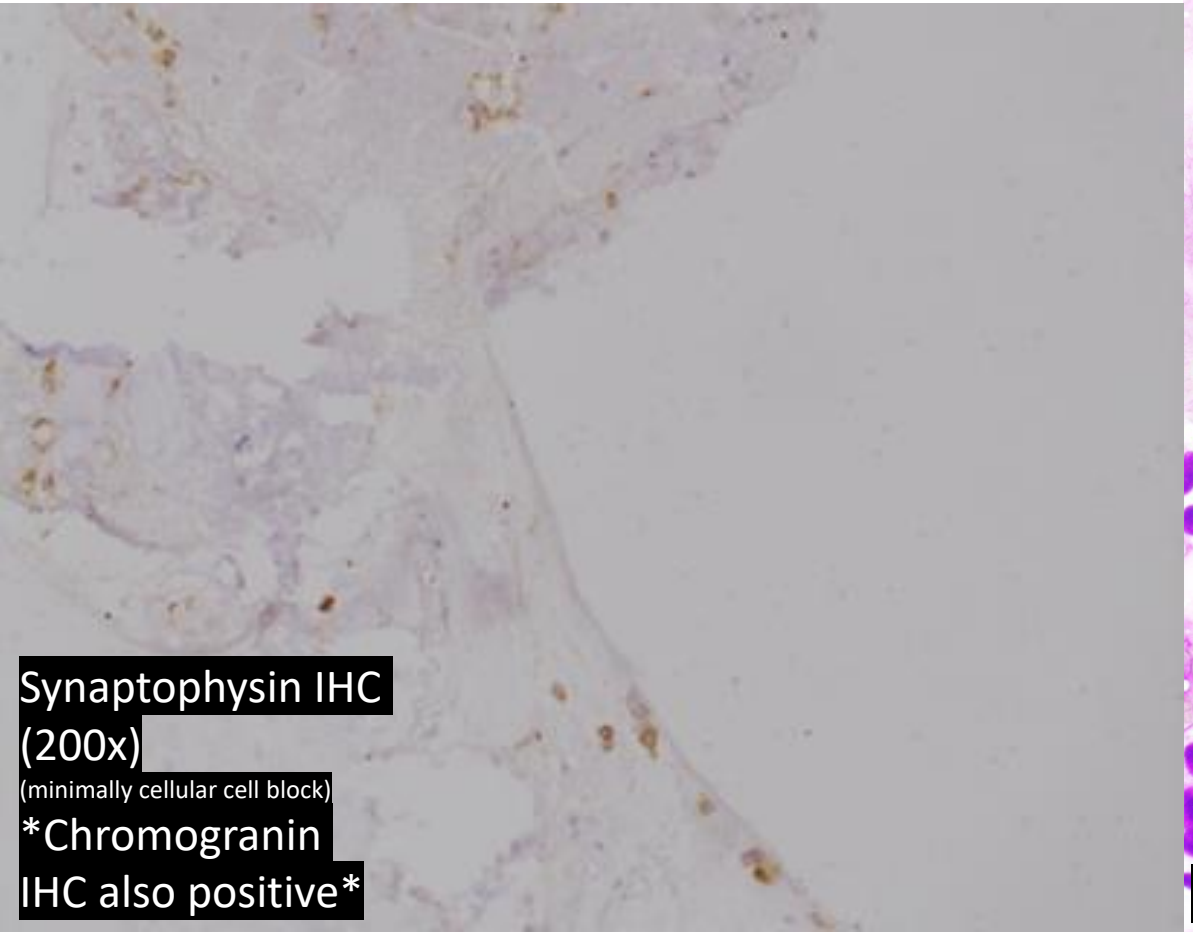
Fam Hx: Father died of metastatic renal cell carcinoma when patient was a child

Case 1:
31M – Incidental Pancreatic Mass (2.5 cm) Discovered On Unrelated Imaging

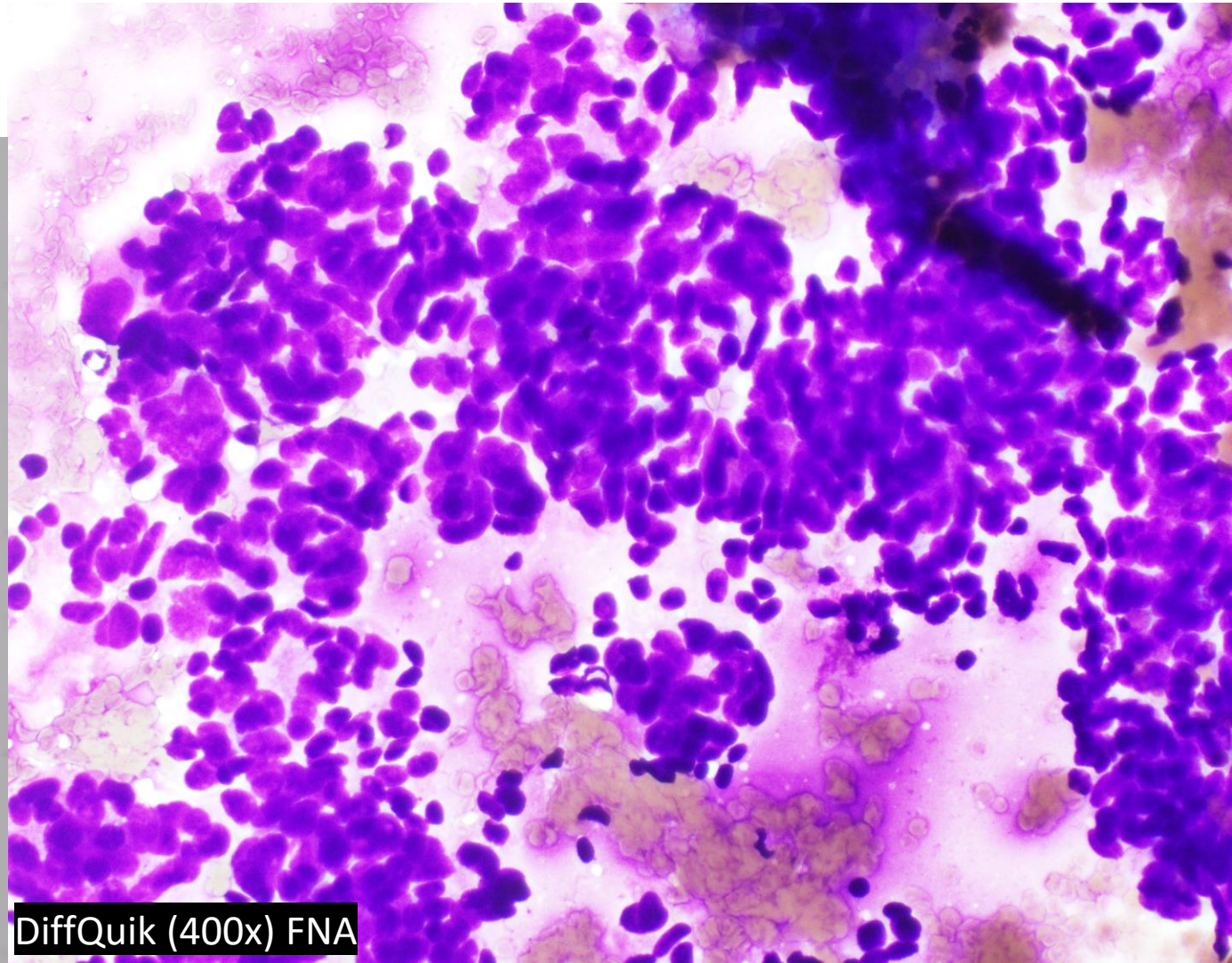




31M – Incidental Pancreatic Mass (2.5 cm) Discovered On Unrelated Imaging



Synaptophysin IHC (200x)
(minimally cellular cell block)
Chromogranin IHC also positive



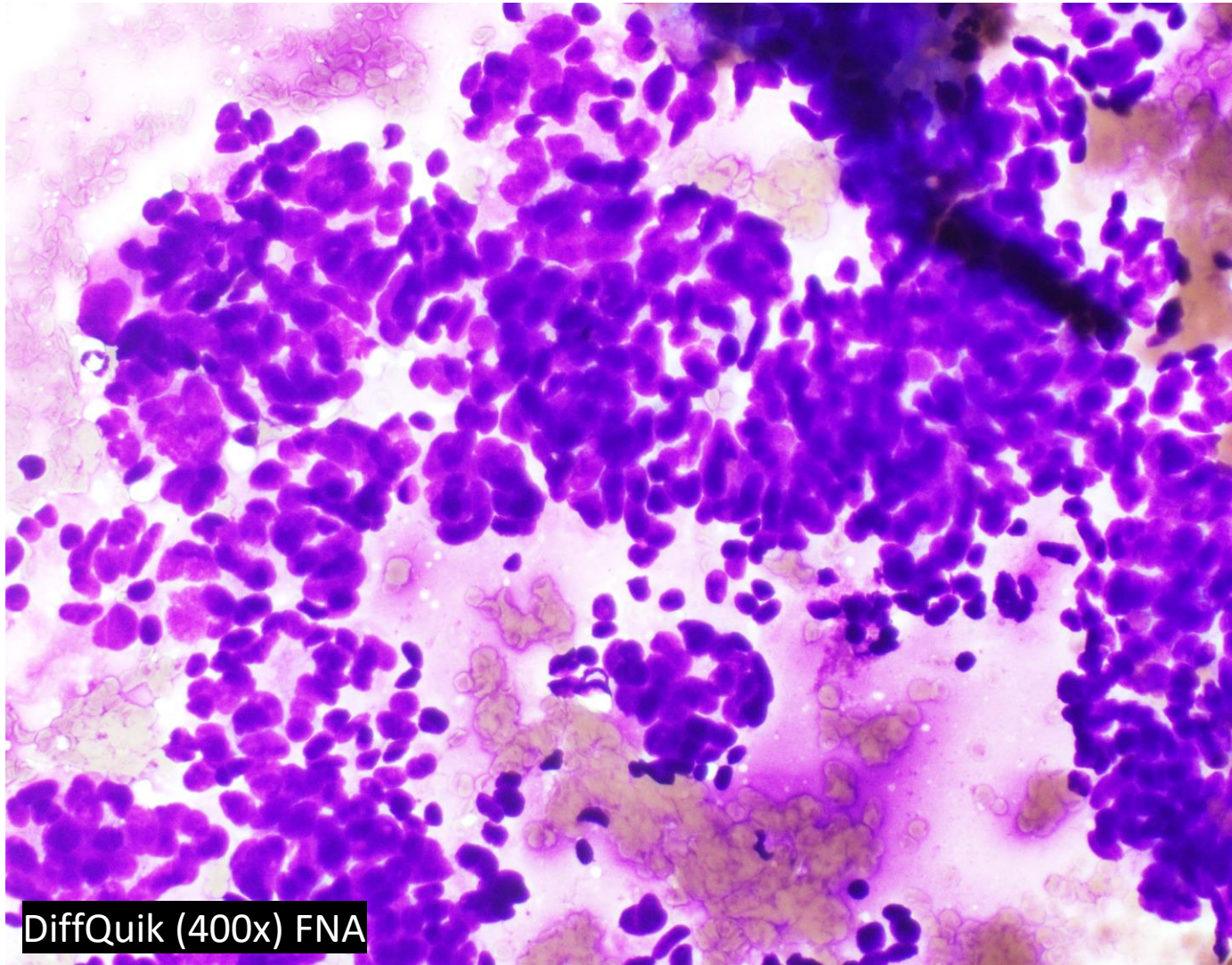
DiffQuik (400x) FNA

31M – Incidental Pancreatic Mass (2.5 cm) Discovered On Unrelated Imaging

PANCREAS, HEAD, ENDOSCOPIC ULTRASOUND GUIDED FINE NEEDLE ASPIRATION:

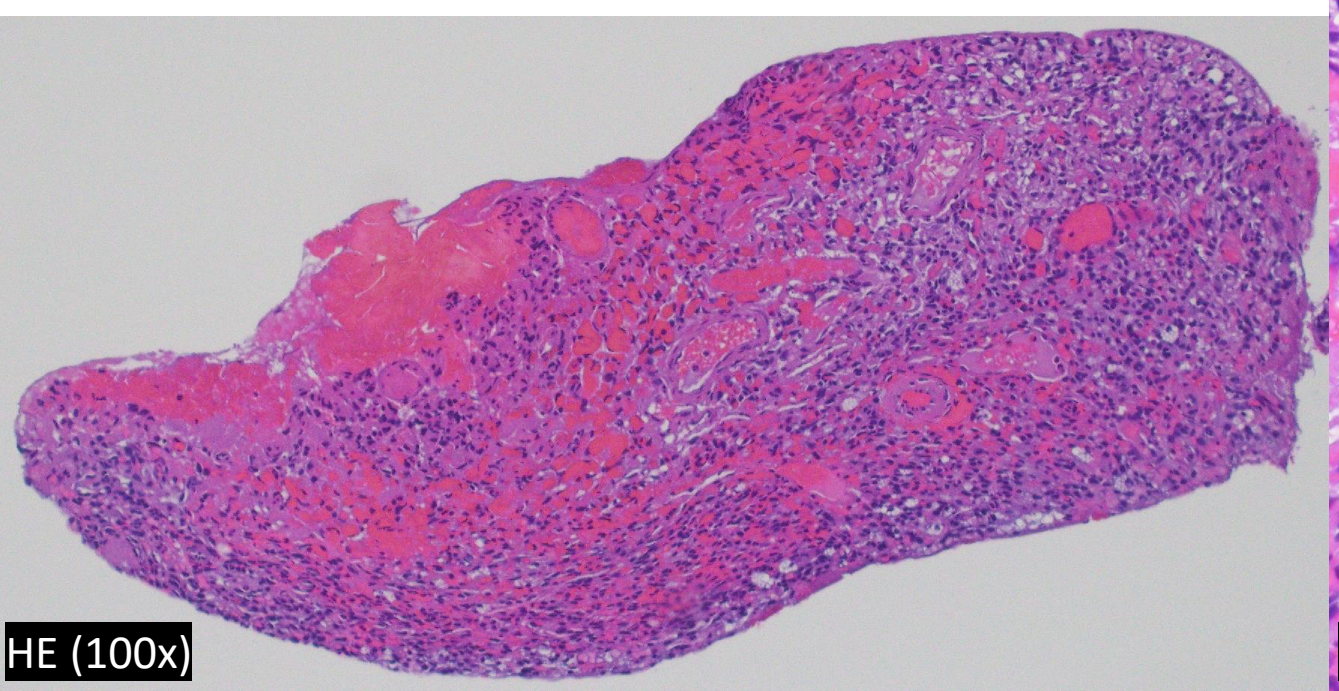
- Neoplastic cells present.
  - See comment.

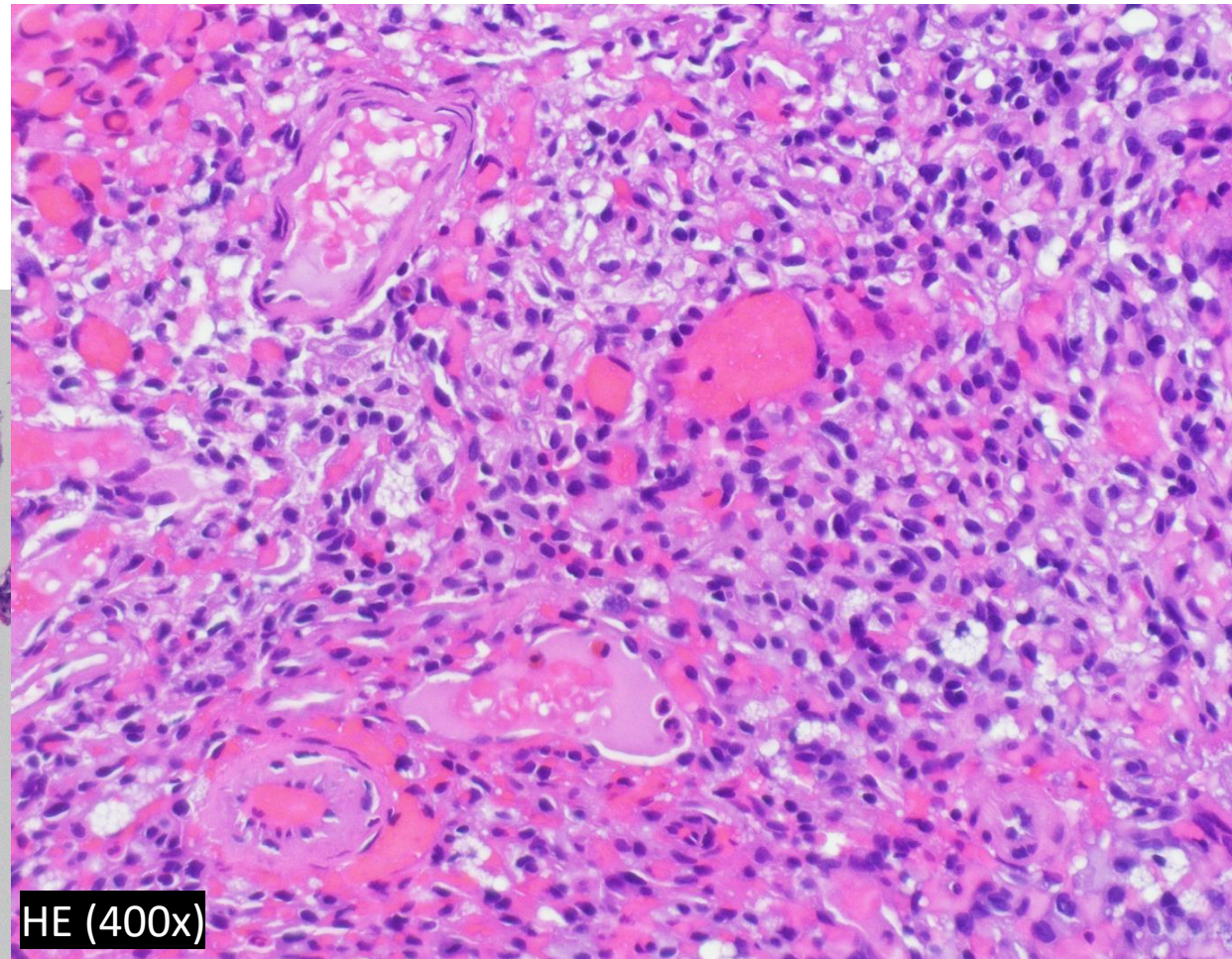
"…suggestive of neuroendocrine tumor…"



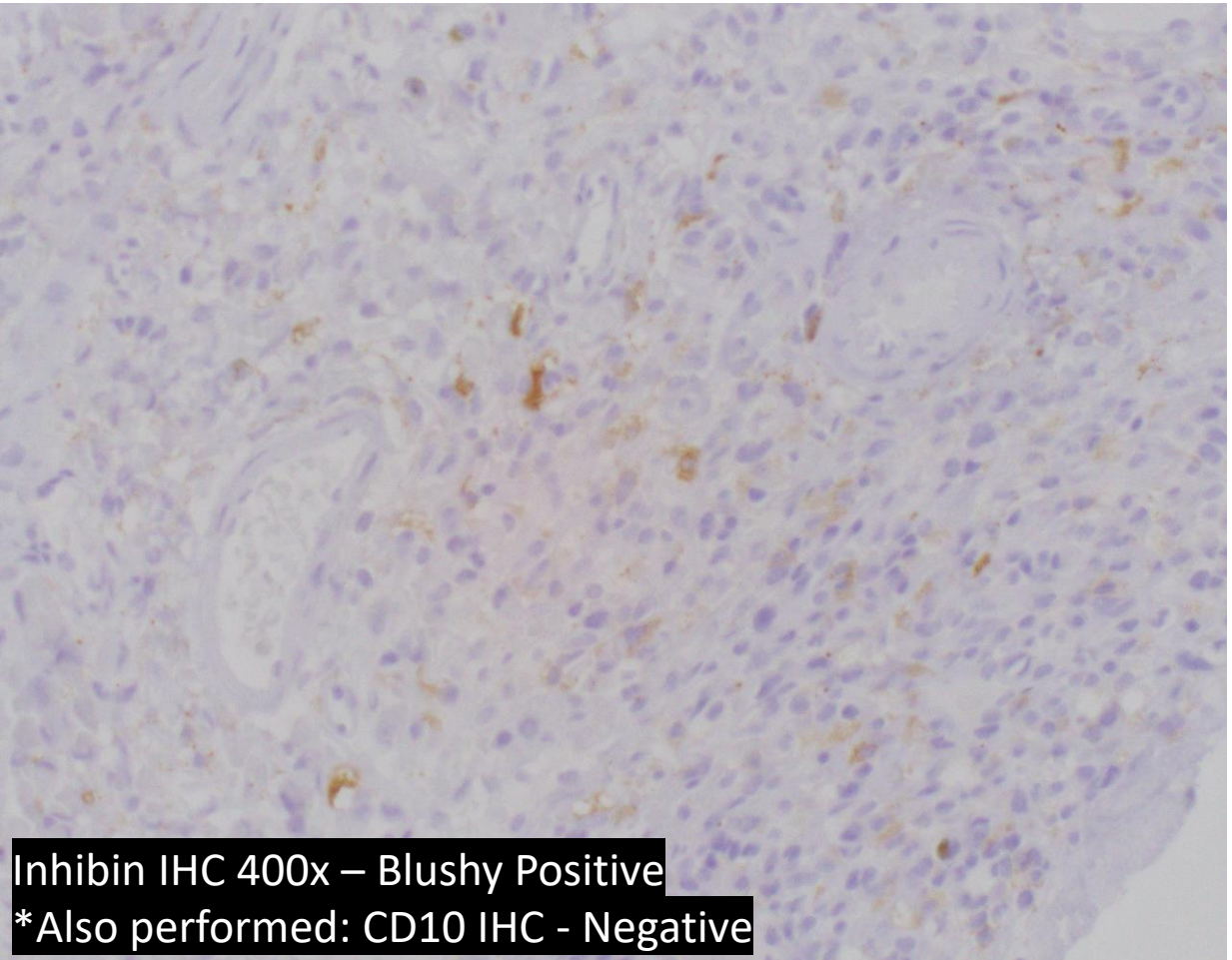
DiffQuik (400x) FNA

One year later…
T11-L1 Mass

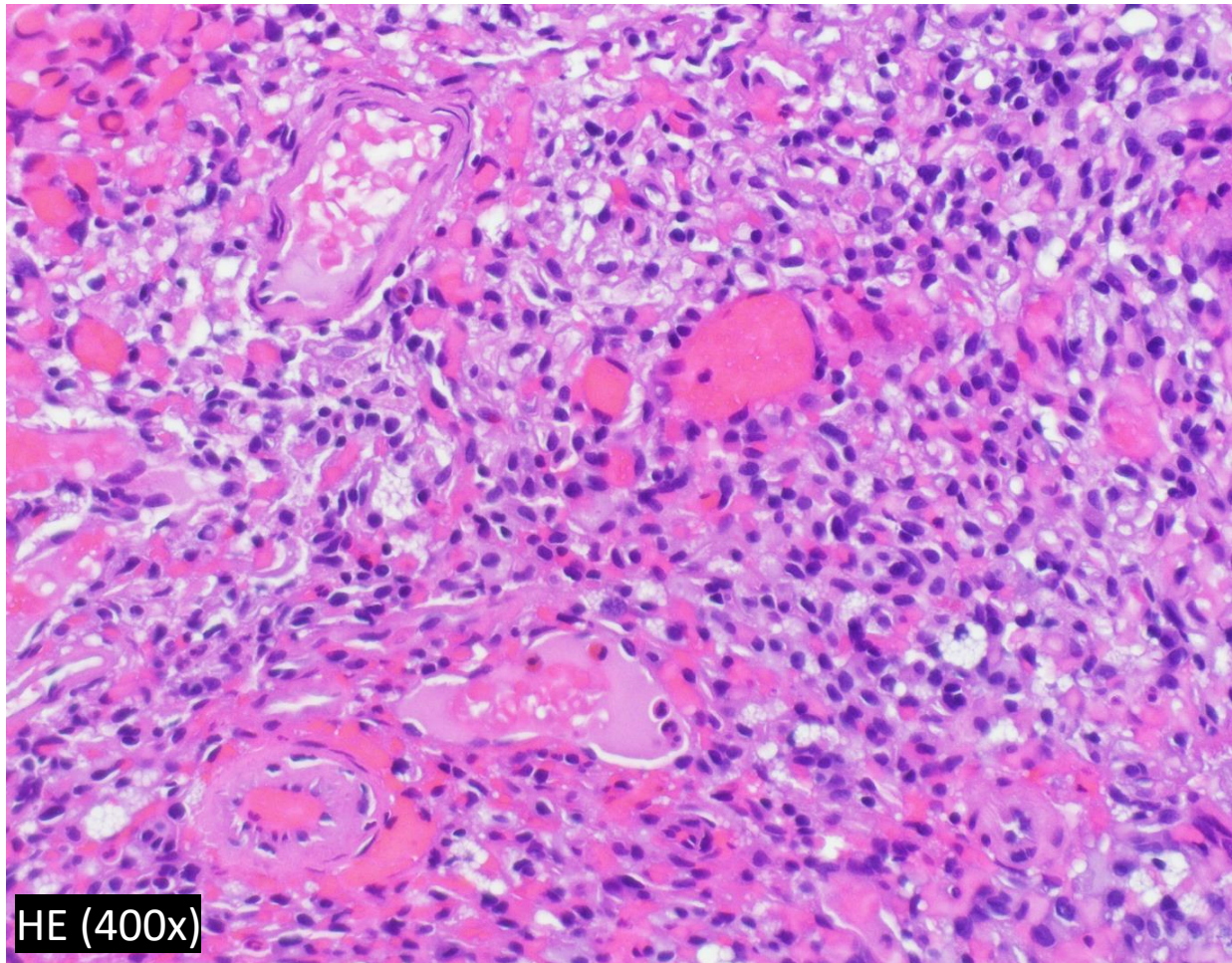

HE (100x)


HE (400x)

One year later…
T11-L1 Mass
Multiple other cerebellar masses.



Inhibin IHC 400x – Blushy Positive
*Also performed: CD10 IHC - Negative



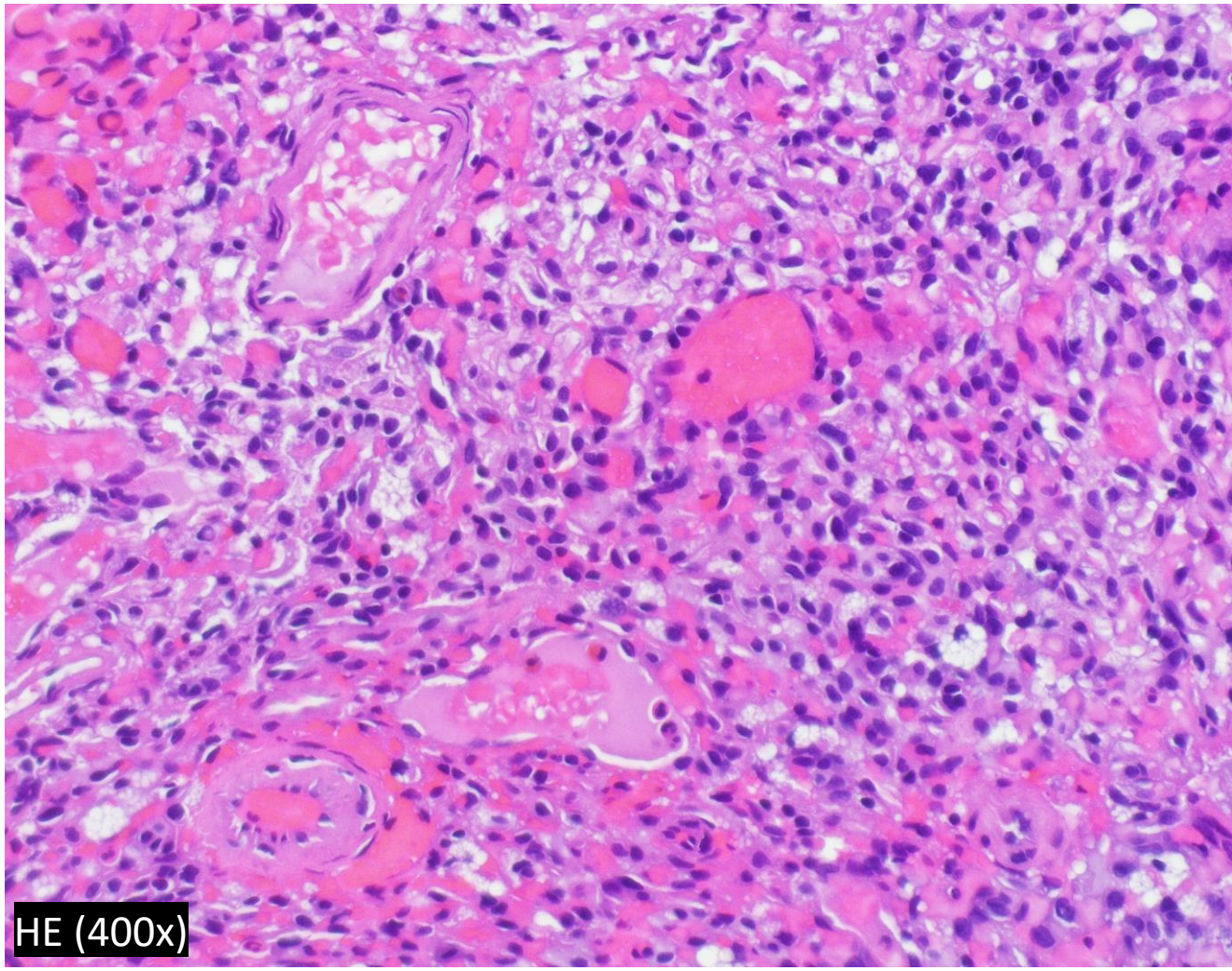
HE (400x)

SPINE, THORACIC TUMOR T11-L1, EXCISION:
HEMANGIOBLASTOMA, WHO GRADE I.

- Benign - WHO Grade 1 (By Definition)
- Most Common VHL Manifestation
- Extremely rare (Incidence: ≤0.1 / 100,000)
- Highly vascular neoplasm with surrounding clear/foamy cells
- Classically located in cerebellum > retina > spinal cord.

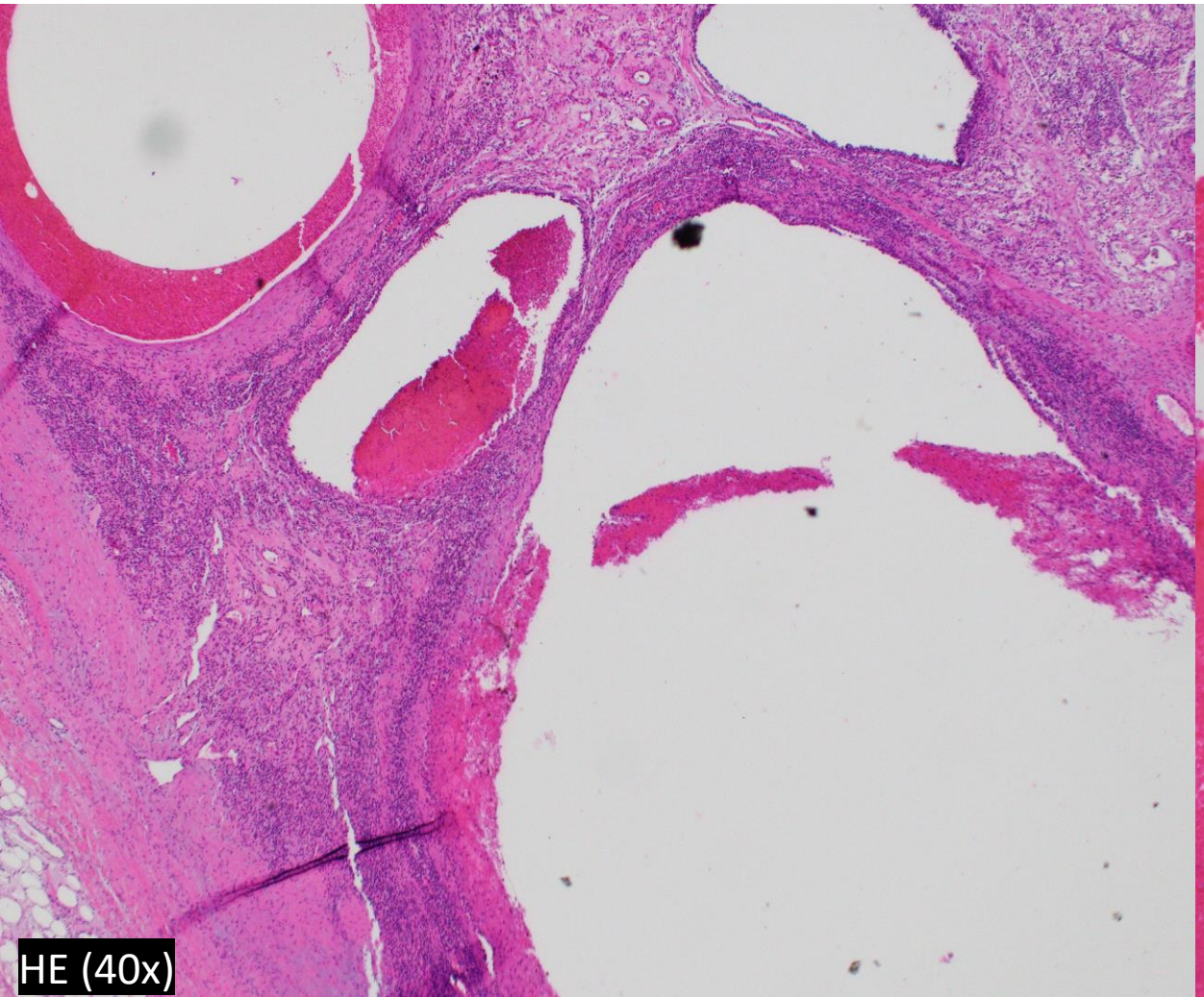
- Sporadic (60-78%)
  - Older (Mid 40's)
- VHL Associated (22-40%)
  - Younger (Mid 20's – 30's)

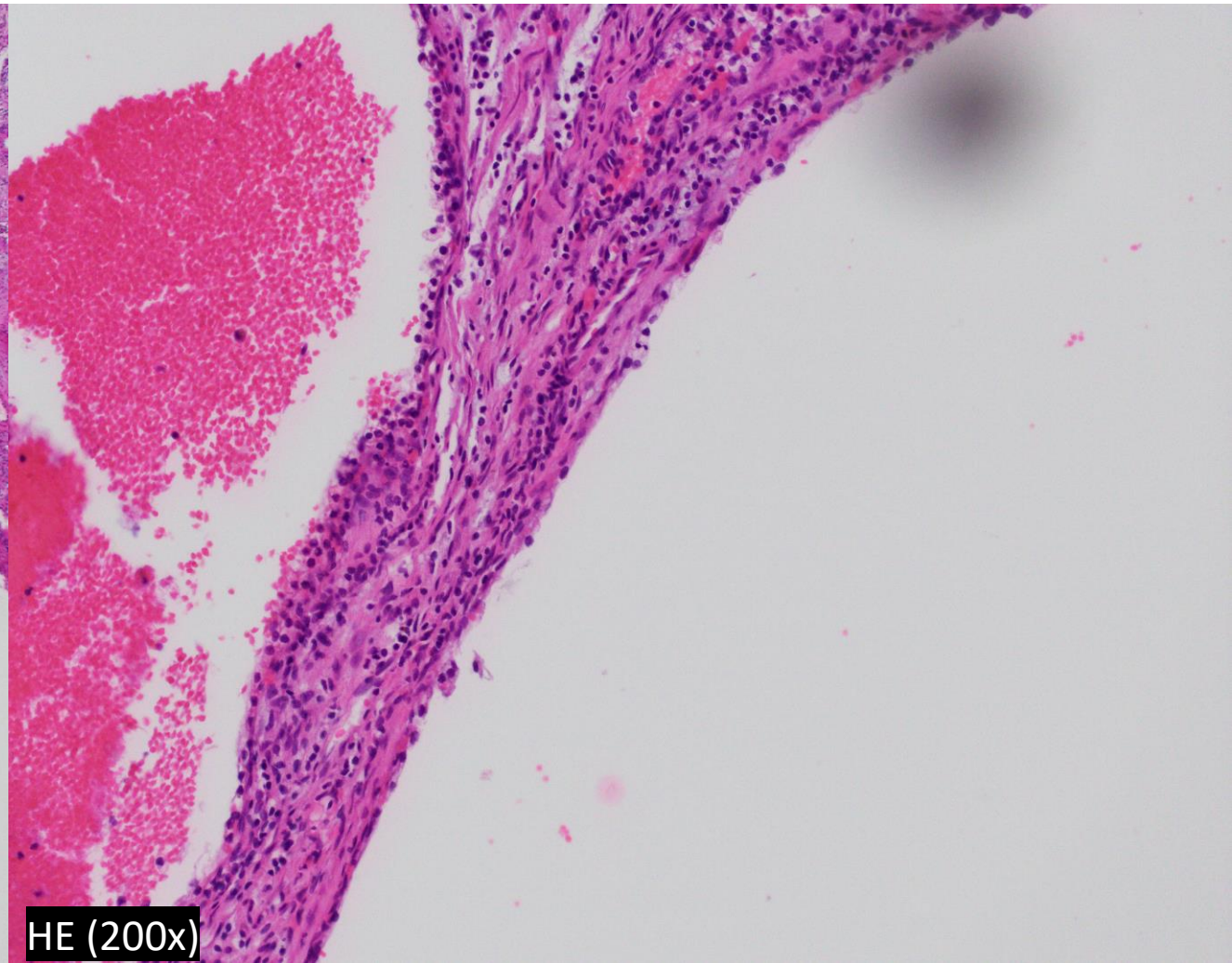
- ANY pediatric patient should be further tested
- Retinal (34%) and CNS (29%) hemangioblastoma are the earliest presenting signs of VHL in patients <18 years
- Among Cohort of Familial-VHL Patients:
  - 55-70% will develop hemangioblastoma in lifetime
  - Again – the most common manifestation of VHL



Klingler, JH., Gläsker, S., Bausch, B. *et al.* Hemangioblastoma and von Hippel-Lindau disease: genetic background, spectrum of disease, and neurosurgical treatment. *Childs Nerv Syst* **36**, 2537–2552 (2020).
Yin X, Duan H, Yi Z, Li C, Lu R, Li L. Incidence, Prognostic Factors and Survival for Hemangioblastoma of the Central Nervous System: Analysis Based on the Surveillance, Epidemiology, and End Results Database. Front Oncol. 2020 Sep 9
Conway JE, Chou D, Clatterbuck RE, Brem H, Long DM, Rigamonti D. Hemangioblastomas of the central nervous system in von Hippel-Lindau syndrome and sporadic disease. Neurosurgery. 2001 Jan;48

2 months later (Radical Nephrectomy)





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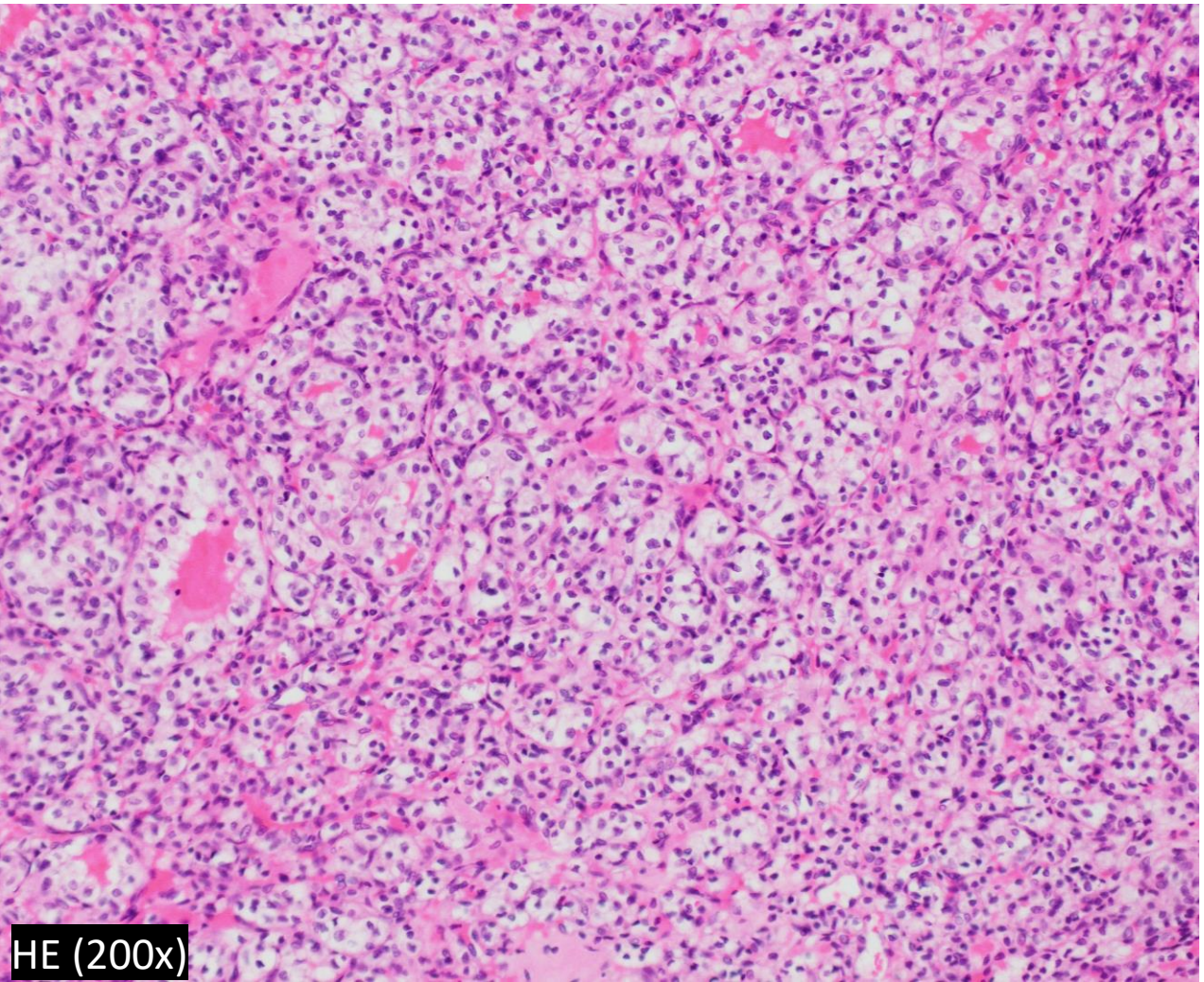
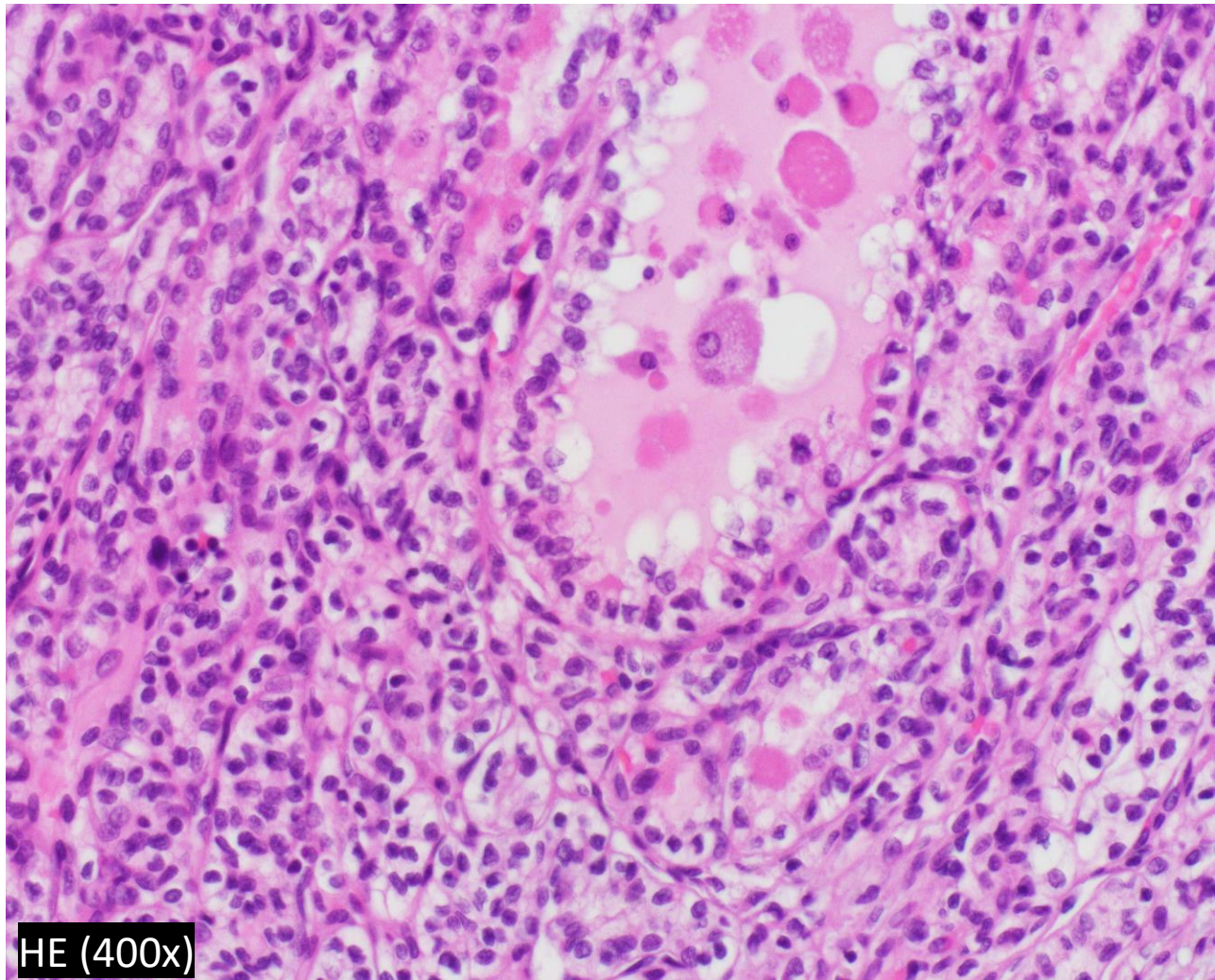

HE (200x)


HE (400x)

Radical Nephrectomy

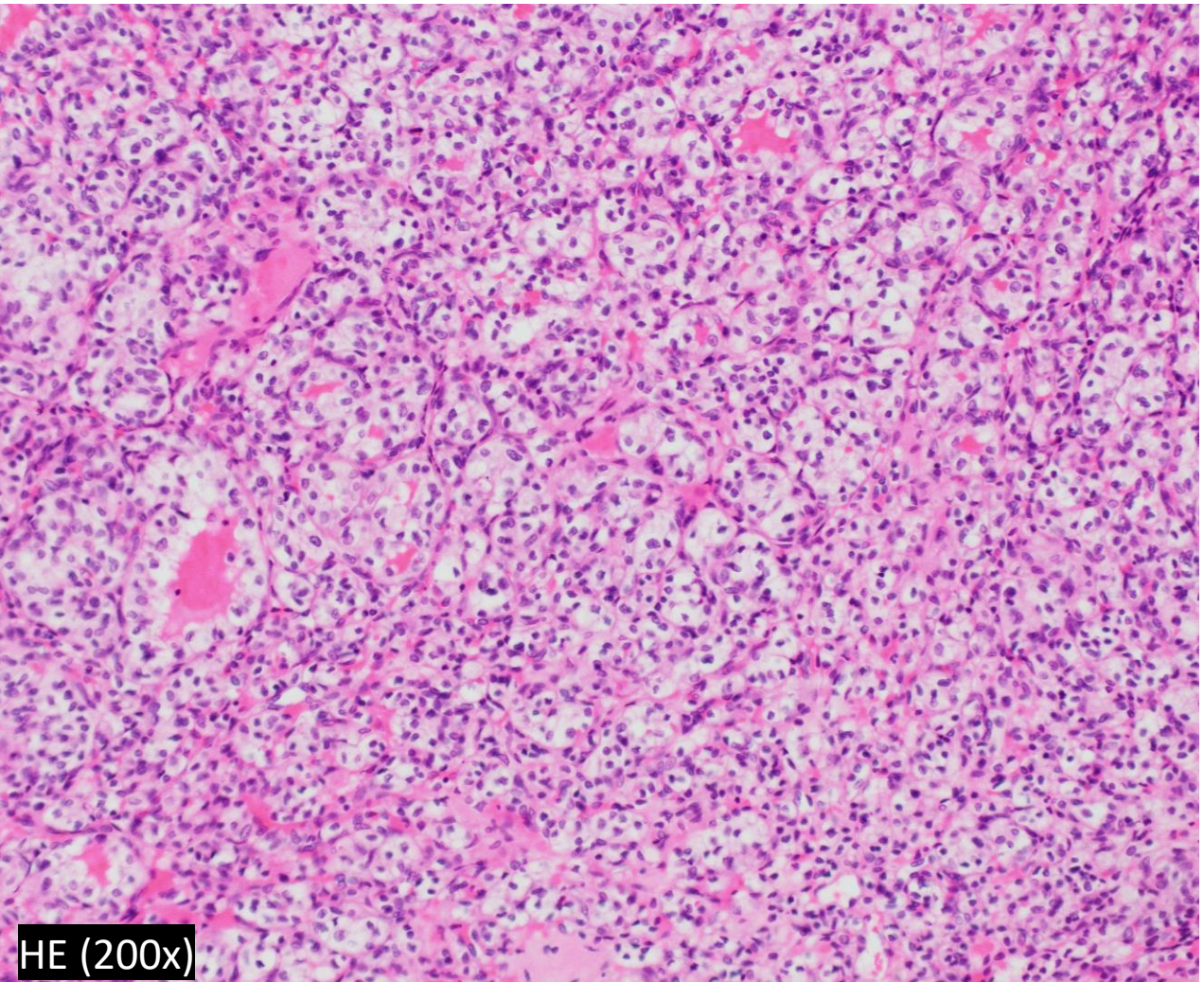
- LEFT KIDNEY, RADICAL NEPHRECTOMY:
- - CLEAR CELL RENAL CELL CARCINOMA, TWO TUMOR MASSES (6.0 X 5.5 X 3.0 CM; AND 2.2 x 1.5 x 1.5 CM).
- - CYSTIC DEGENERATION AND SCARRING NOTED.
- - SURGICAL MARGINS, NEGATIVE FOR CARCINOMA.
- - SEE SYNOPTIC REPORT.

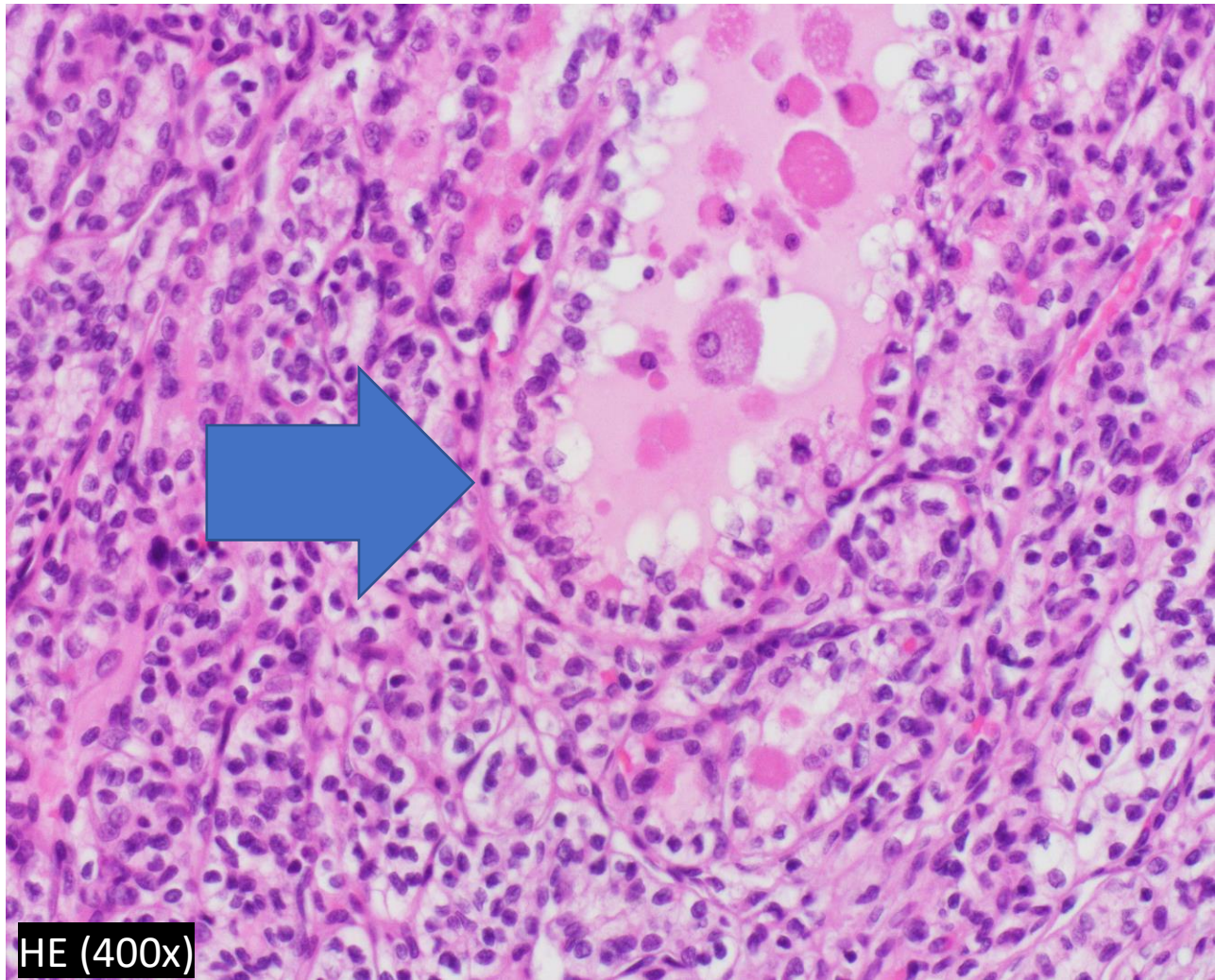
- Grade and stage are key determinants that will drive prognosis – BOTH in VHL and sporadic RCC's.

- **VHL associated CC-RCC more likely to be bilateral and younger age than sporadic tumors.**
- Multifocality and recurrence increased in VHL associated tumors.

- Low-grade CCPT-like areas are described at a greater rate in VHL-associated tumors.

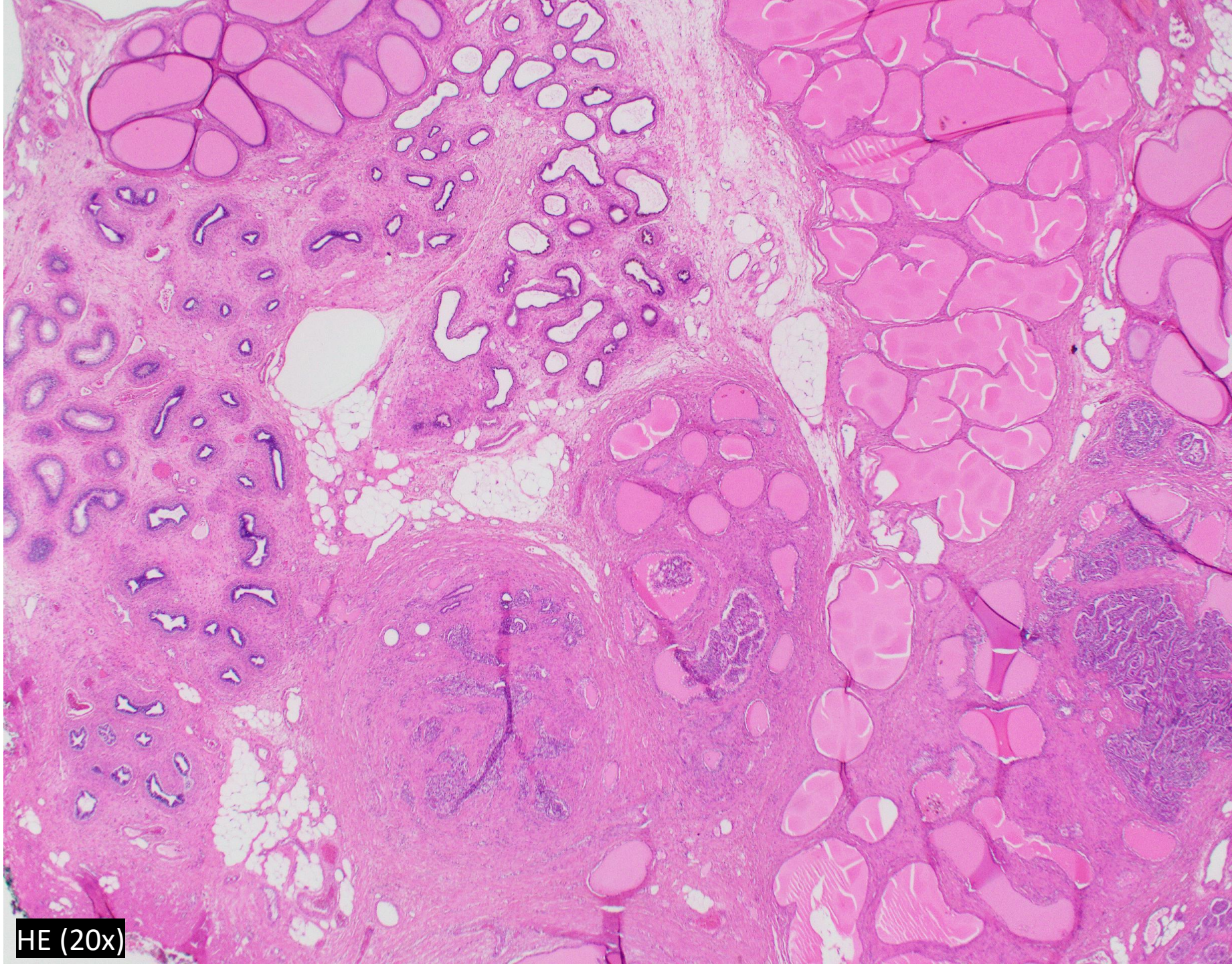
2 months later (Radical Nephrectomy)





3 years later…

Painful Testicular Lesion



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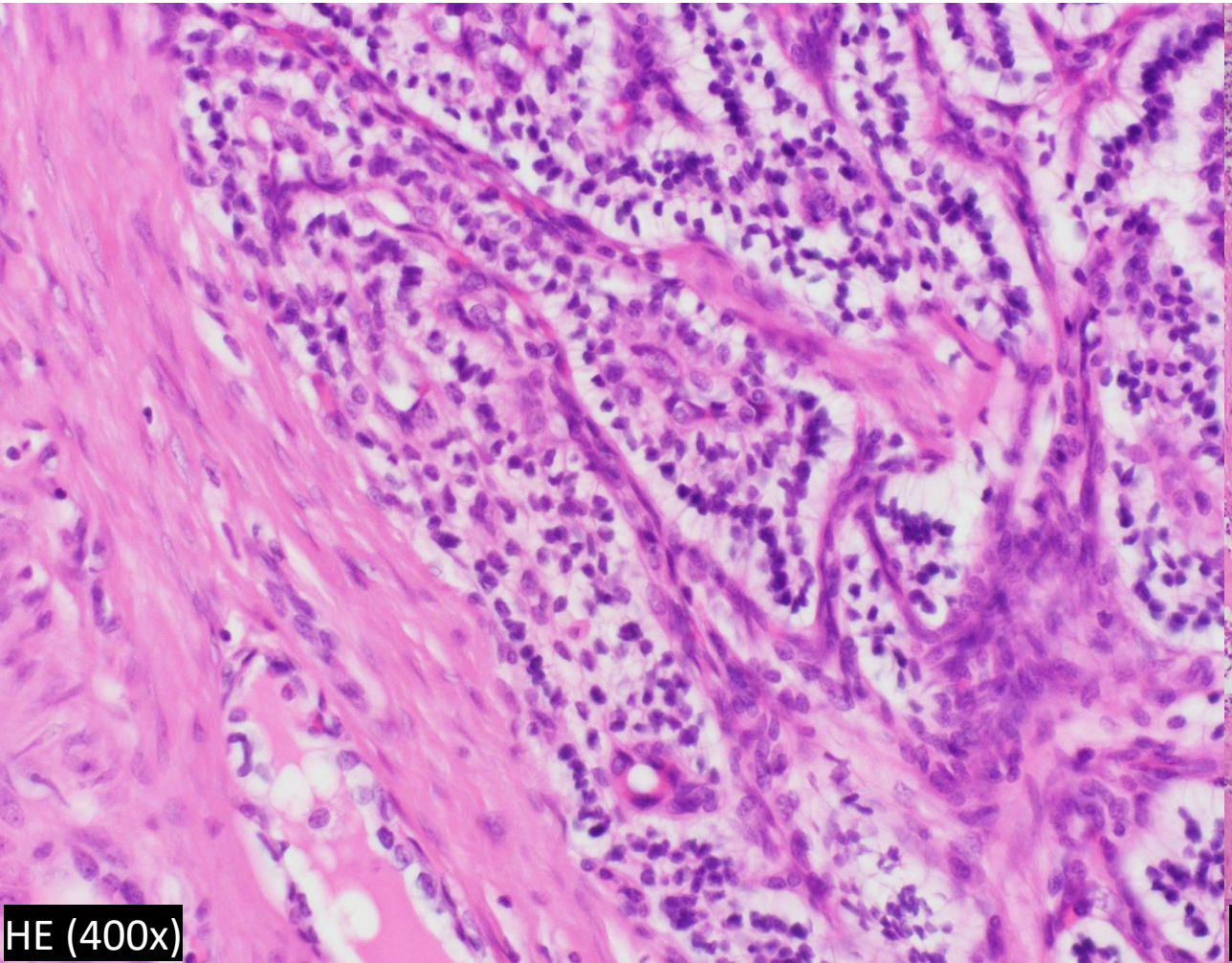
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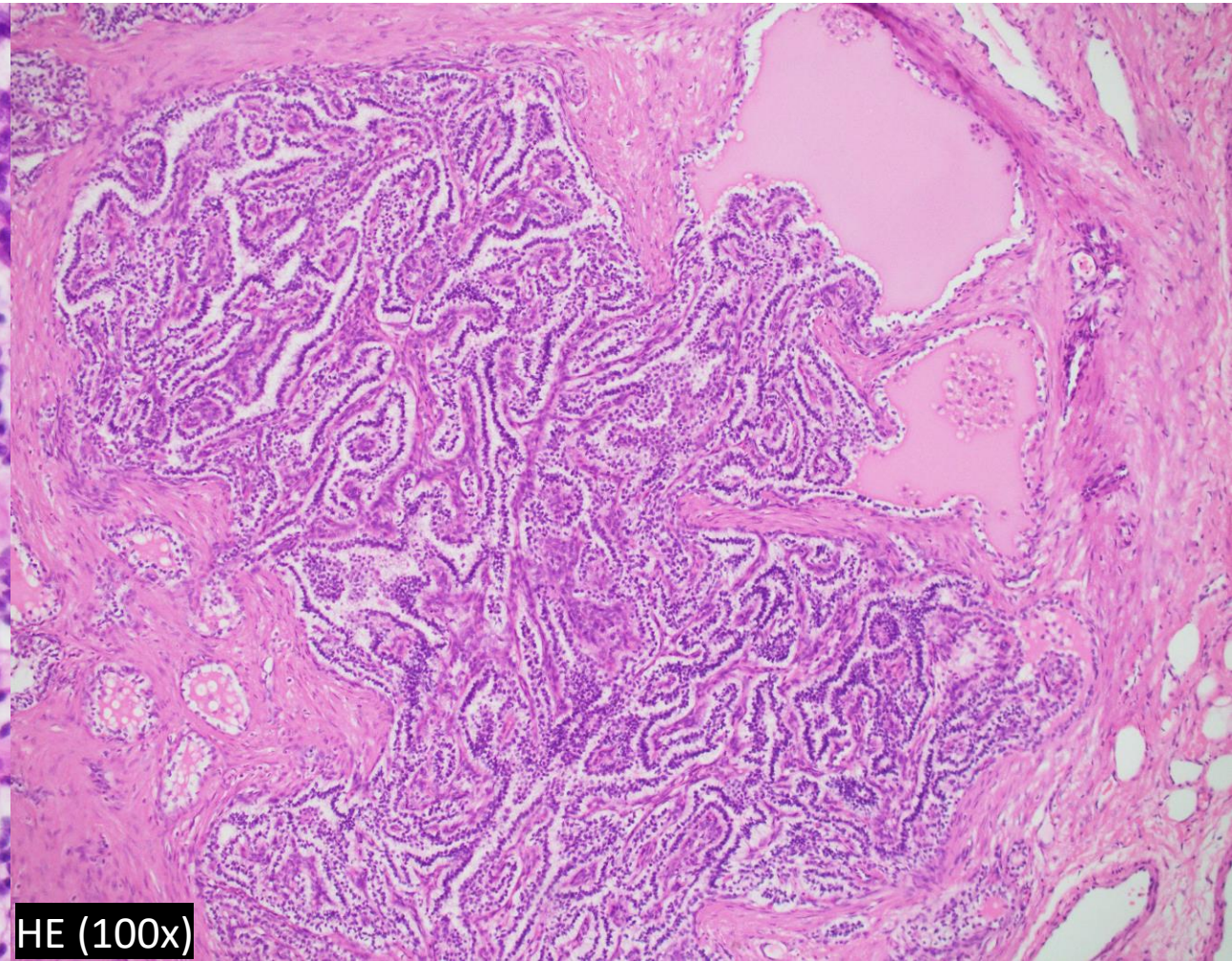
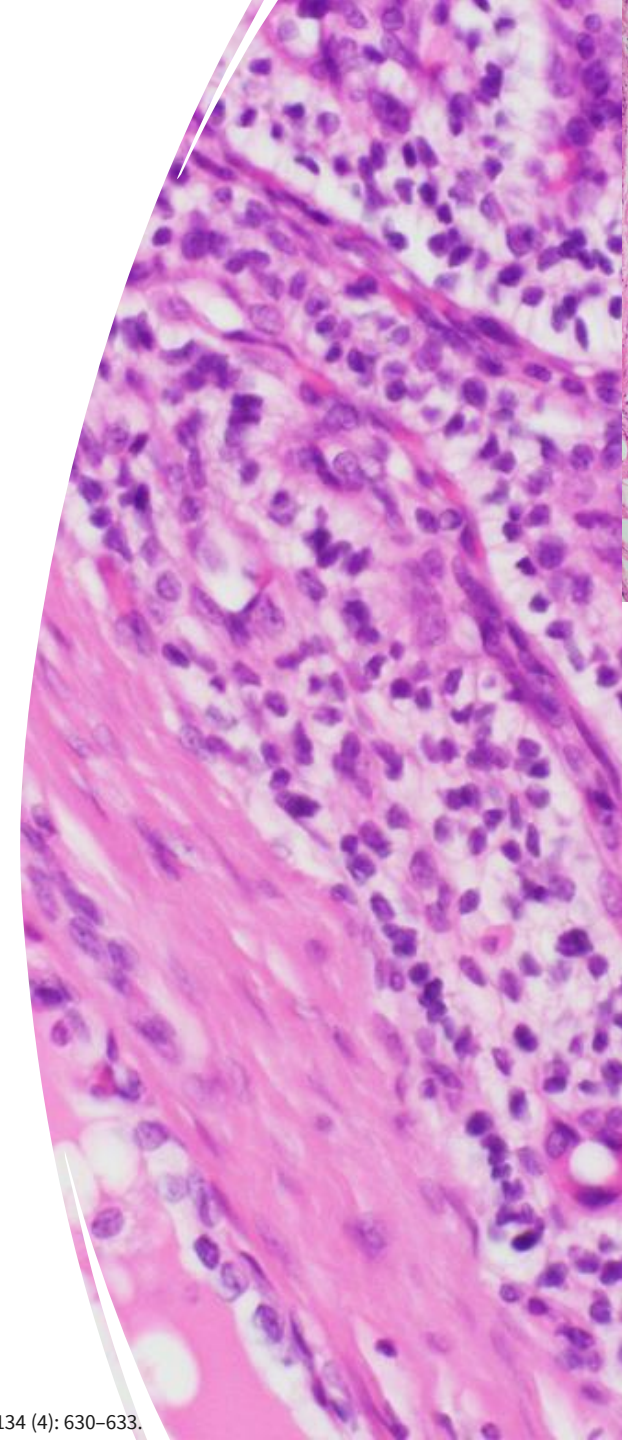

HE (100x)

Papillary Cystadenoma of Epididymis

- Benign (RARE) epididymal tumor with strong association with VHL
  - **Bilateral (40% of cases):**
    - **VHL Association: 16 VHL+/24 cases (66.7%)**
    - **WHO '22 says "pathognomonic"**
  - Unilateral (60% of cases):
    - VHL Association: 8 VHL+/35 cases (22.8%)
- Cysts with intracystic papillary projections, low grade cytology, clear cytoplasm.
- "Renal Clear Cell Papillary Tumor – like" nuclear arrangement and overall morphology.
- Minimal atypia

- Positive IHC: CA-IX, CK7, PAX8
- Negative IHC: CD10 (possibly weak/focal), RCC-Ag, p504s (AMACR)



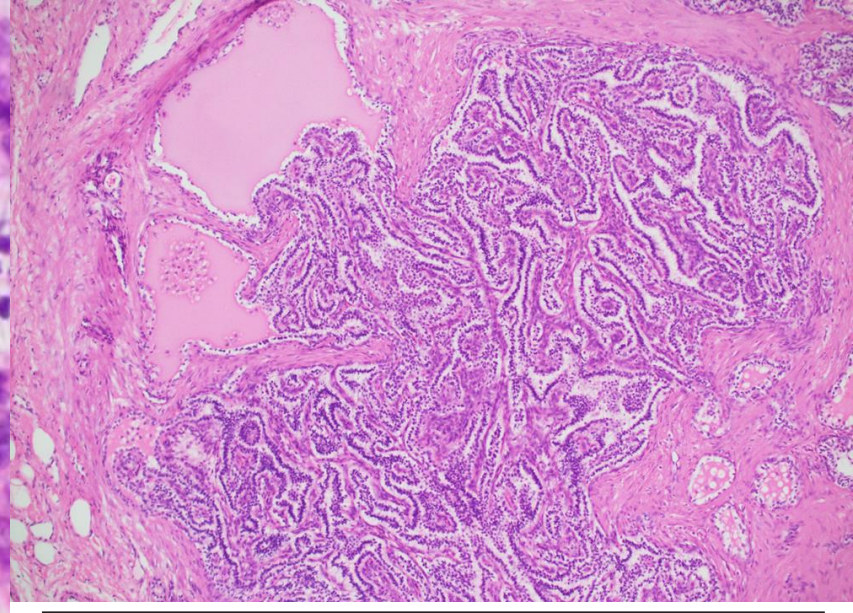


Table 1. Clinical Features of 59 Reported Cases of Papillary Cystadenoma of the Epididymis[a]

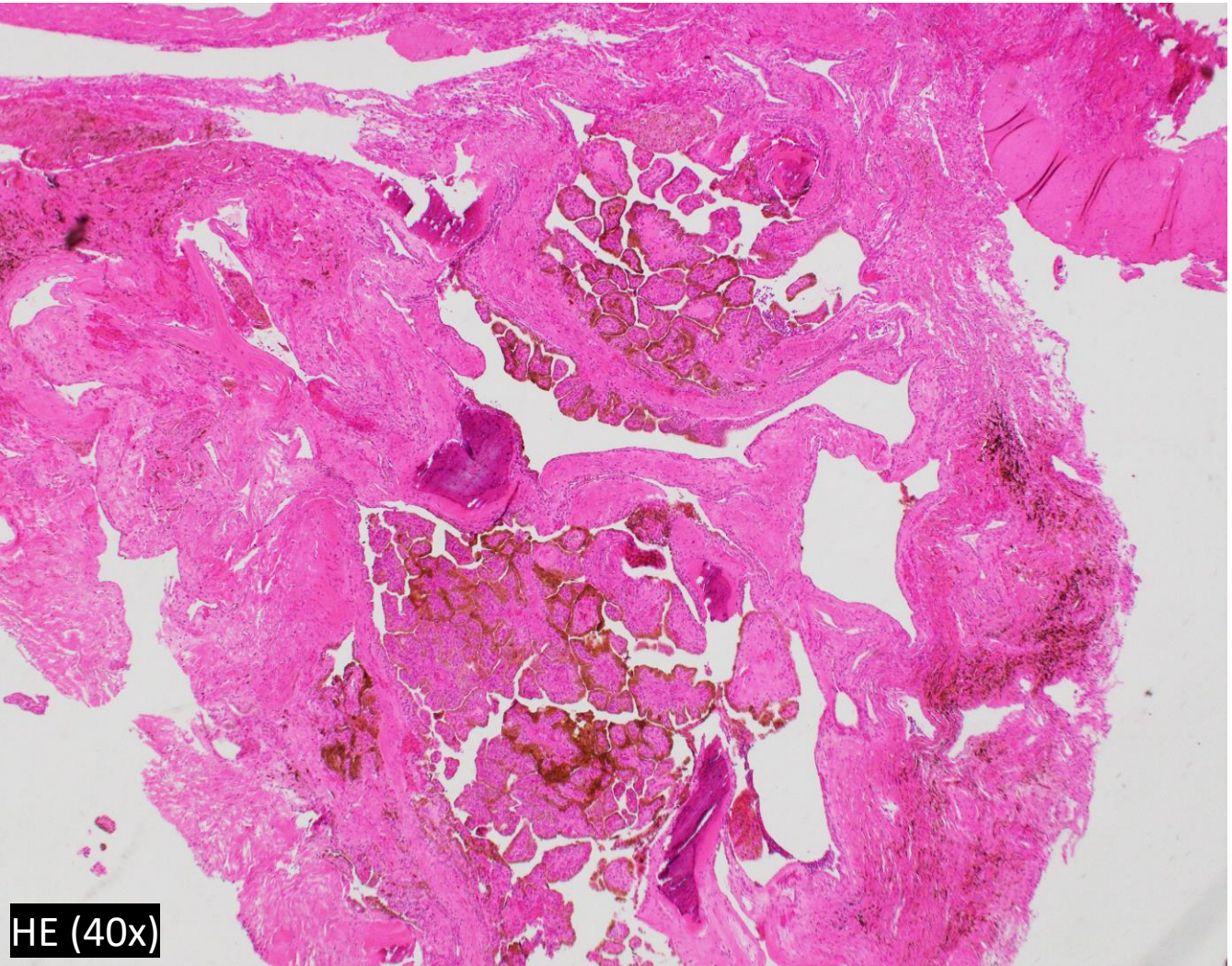
Age (information known for 59 cases), y	
Range	16–76
Mean	35
Median	30
Clinical presentation (information known for 54 cases), No. (%)	
Swelling or mass	21 (39)
Incidental finding	20 (37)
Infertility	8 (15)
Pain	5 (9)
Laterality (information known for 59 cases)	
Unilateral, No. (%)	35 (59)
VHLD	8
No evidence of VHLD	27
Bilateral, No. (%)	24 (41)
VHLD	16
No evidence of VHLD	8
Association with VHLD (information known for 59 cases), No. (%)	
VHLD	24 (40)
No evidence of VHLD	35 (60)

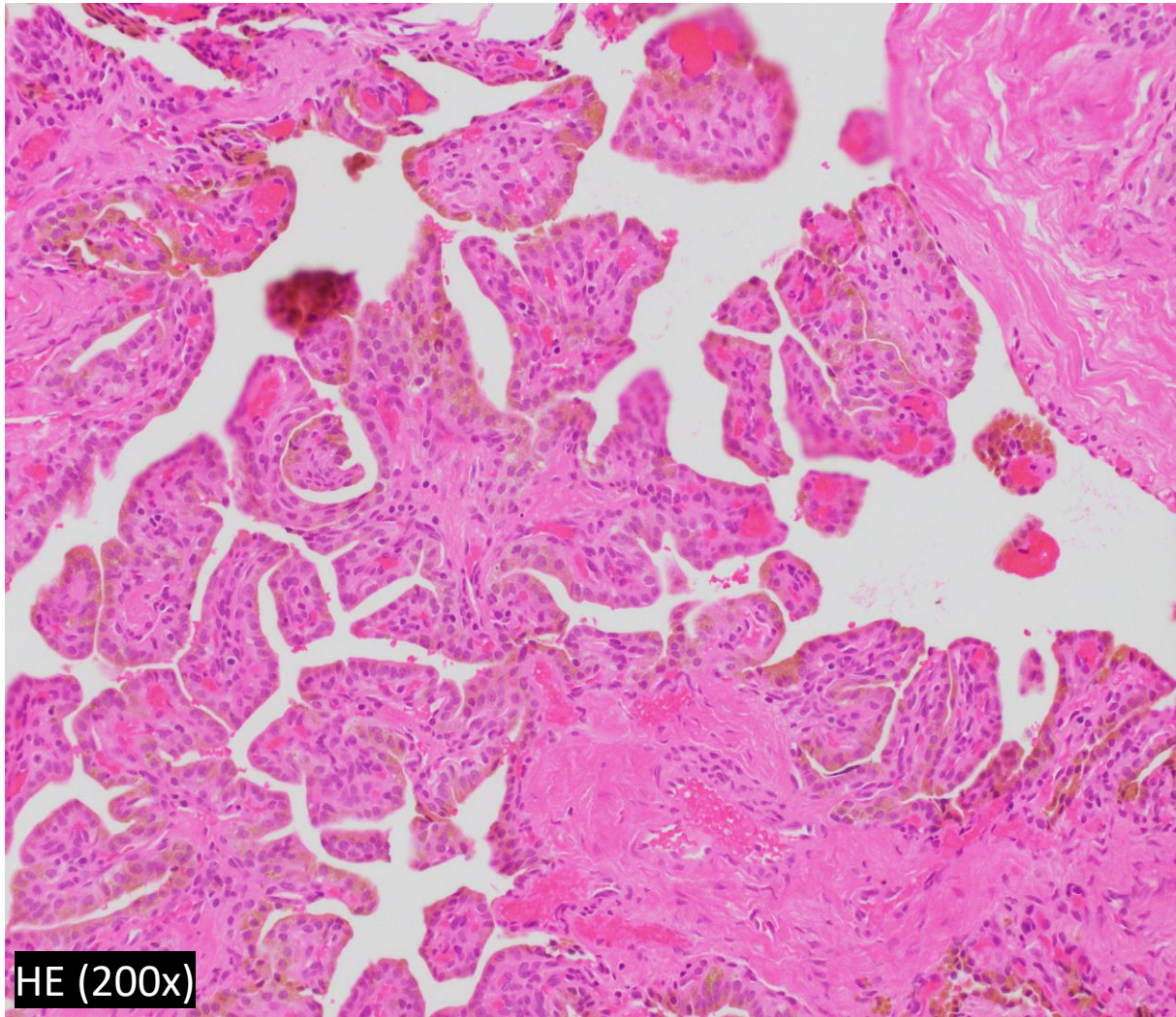
Abbreviation: VHLD, von Hippel-Lindau disease.

[a] Analysis includes all cases in the English-language literature in which the diagnosis was confirmed histologically.

Karen J. Odrzywolski, Sanjay Mukhopadhyay; Papillary Cystadenoma of the Epididymis. *Arch Pathol Lab Med* 1 April 2010; 134 (4): 630–633.

3 months later…
Unilateral hearing loss, tinnitus, and ataxia
New Inner Ear Mass





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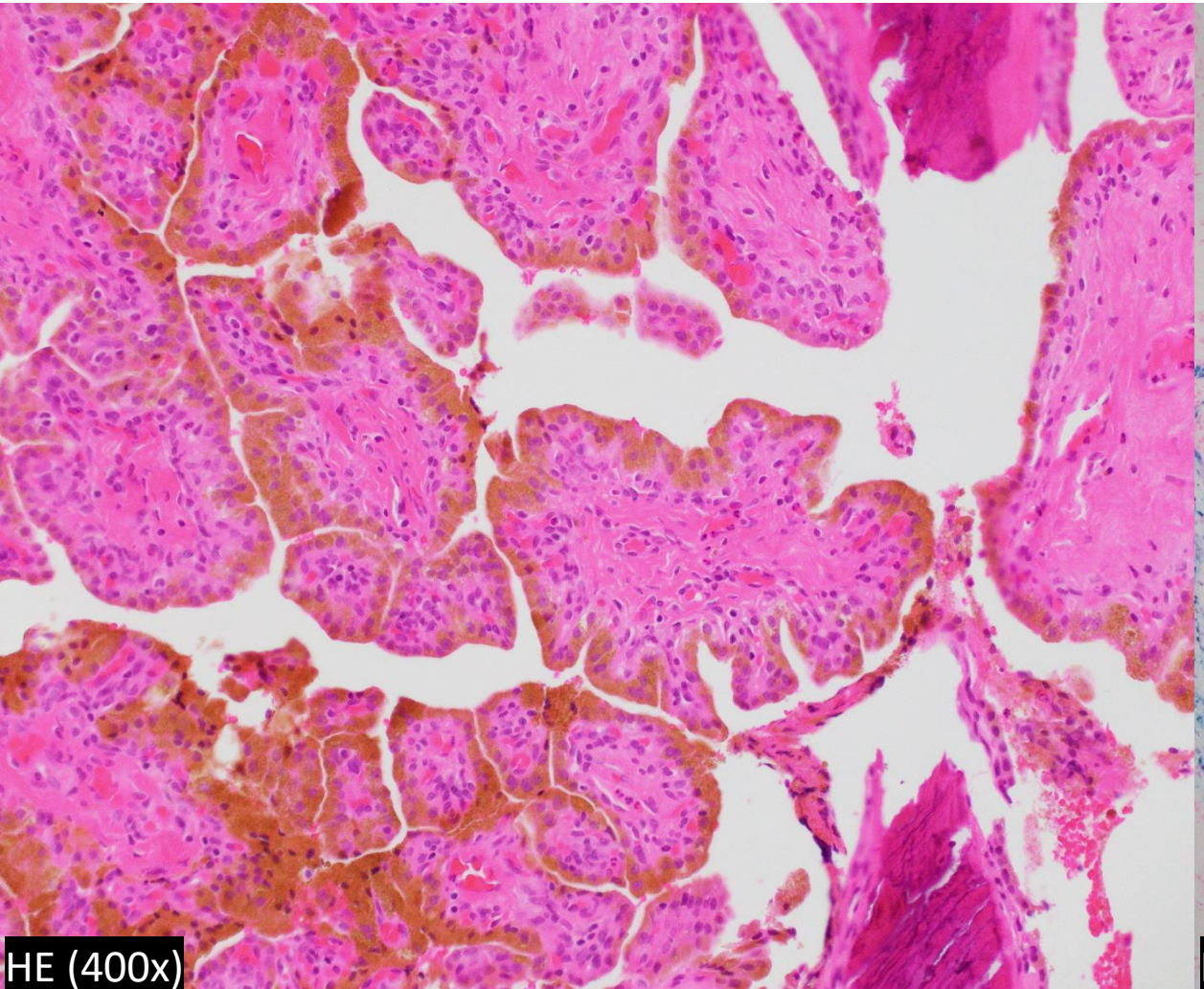
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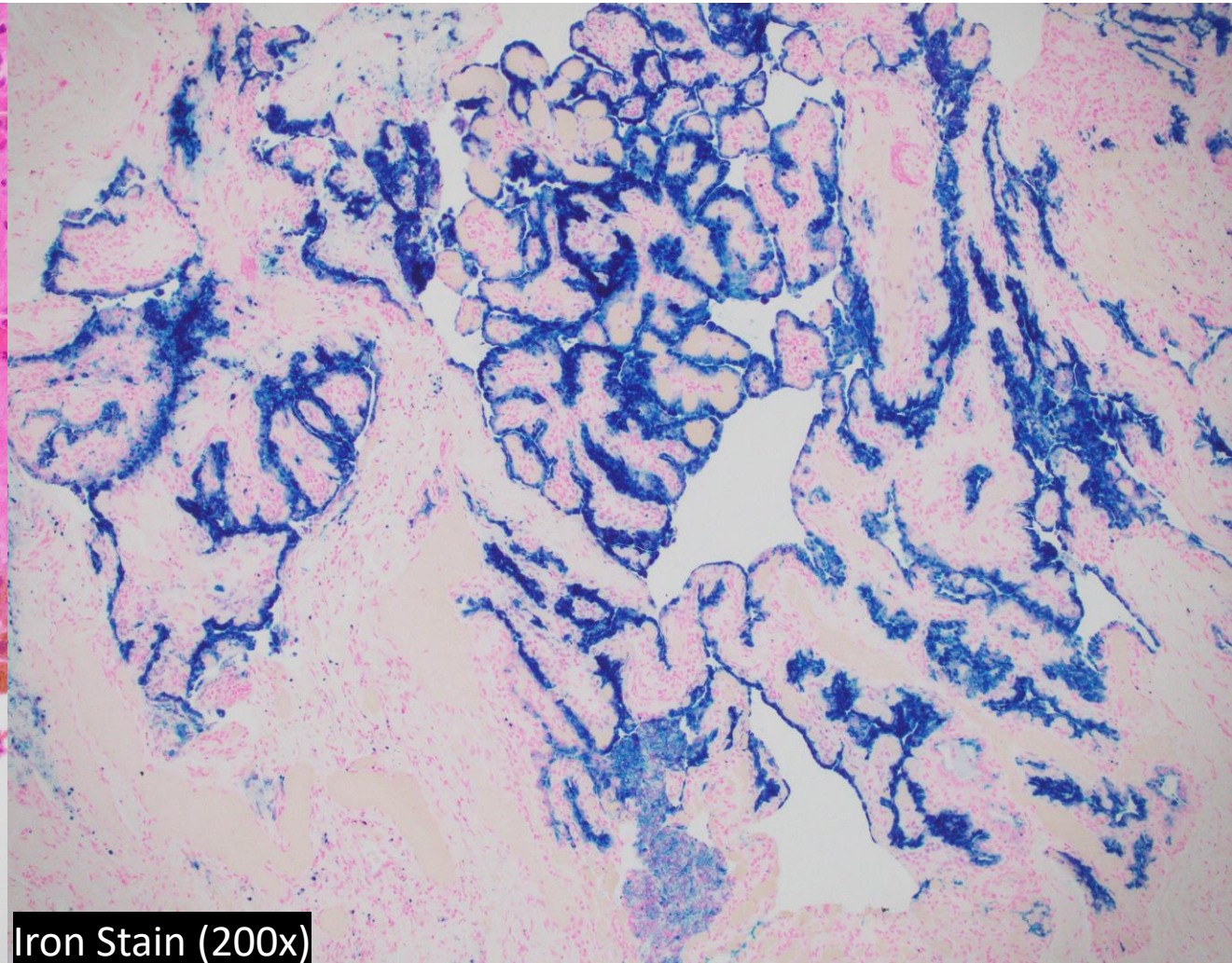
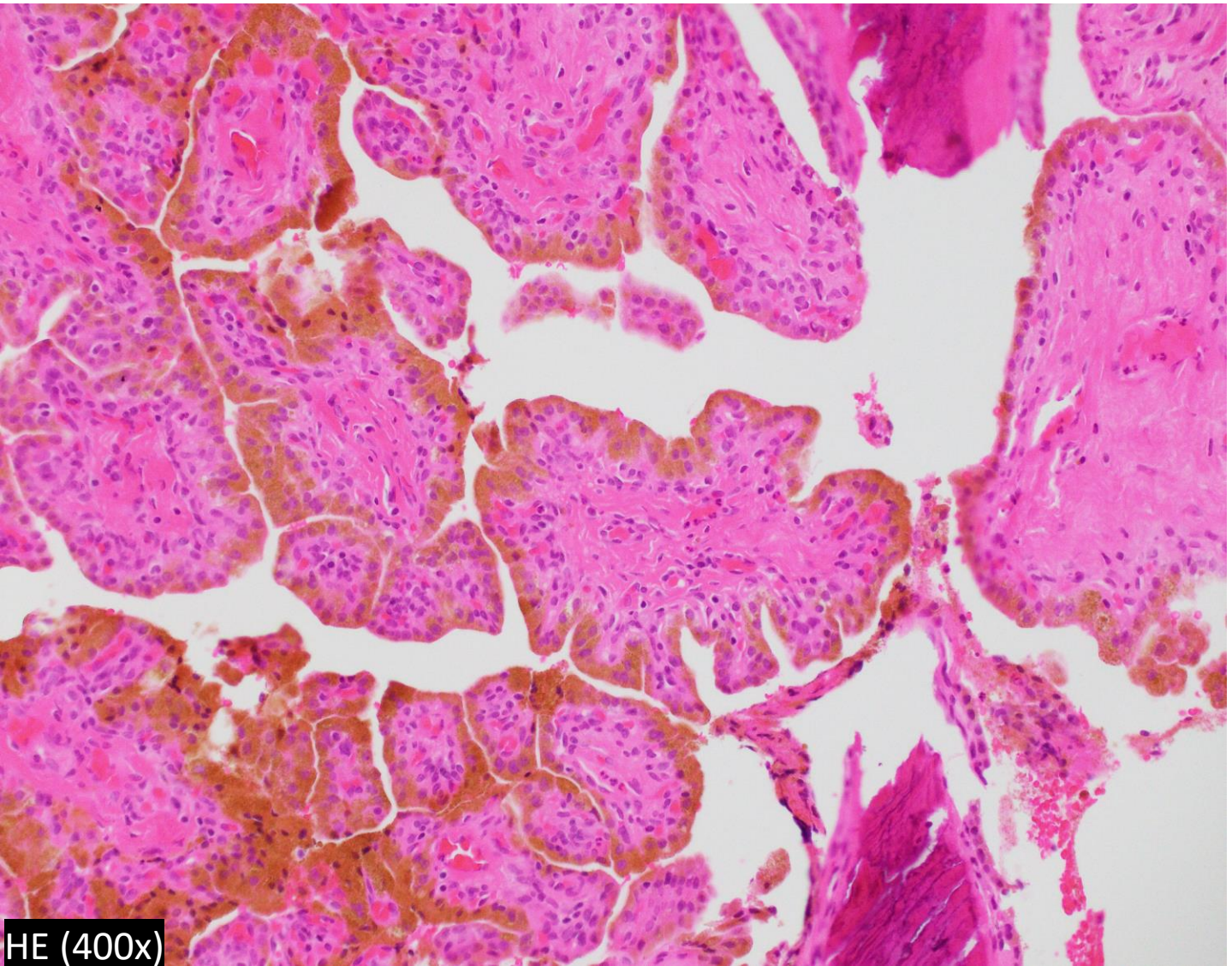

Iron Stain (200x)

Endolymphatic Sac Tumor



- Single layer of **BLAND** cuboidal cells on papillary stalks

- Markedly **locally destructive and locally aggressive** – may cause death given proximity to brain

- Positive IHC: **Keratins**, **PAX8** (>85%)
- Positive SS: **Iron** granules in apices of cytoplasm

- Complete resection required or risk of recurrence
  - Frequently limited by encasement of cranial nerves or intraoperative bleeding

von Hippel-Lindau (VHL)

- VHL - tumor suppressor gene: **3p25**
- Autosomal Dominant (AD)
- Highly penetrant (>97-98% by age 60 yrs)
- Heterogeneous presentation
  - Eyes typically first organ impacted in pediatric setting
  - A single presenting tumor (as opposed to this case) is NOT uncommon
- Hundreds (>500) of pathogenic mutations have been described with variable clinical impacts. Variations in degradation of hypoxia-inducible factor (HIF).
  - Four clinical sub-types described

VHL Subtype	Pheochromocytoma	CC-RCC
Type 1	↓	Y
Type 2a	Y	Y (LOW RISK)
Type 2b	Y	Y (HIGH RISK)
Type 2c	Y	↓

- **Referral for genetic testing/counseling**, screening / imaging implications, organ-preserving surgery is **CRITICAL to management of life-long disease**

Urinary and Male Genital Tumors. WHO 2022. 5th Edition.
Hoffman MA, Ohh M, Yang H, Klco JM, Ivan M, Kaelin WG Jr. von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. Hum Mol Genet. 2001 May 1;10(10):1019-27.

Summary of VHL Associated Tumors

- **Kidney**
  - Renal Cysts (Frequently multiple)
  - Clear Cell Renal Cell Carcinoma
    - Potentially with low-grade morphologic features that may initially suggest clear cell papillary renal tumor (IHC: CC-RCC phenotype)

- **Epididymis (Male) / Broad Ligament (Female)**
  - Papillary Cystadenoma

- **Pancreas**
  - Pancreatic serous cystadenoma (Tail cysts)
  - Pancreatic neuroendocrine tumors (NETs)

- **Adrenal (and other)**
  - Paraganglioma (Pheochromocytoma)

- **Neuro-axis and Eye**
  - Hemangioblastoma
  - Angiomatosis

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NCCN Guidelines Version 3.2023
Hereditary Renal Cell Carcinoma

CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES[a]

1. An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. An individual with RCC with any of the following criteria:
▸ Diagnosed at age ≤46 y ▸ Bilateral or multifocal tumors → at any age! ▸ ≥1 first- or second-degree relative[b] with RCC
3. An individual whose tumors have the following histologic characteristics:
▸ Multifocal papillary histology ▸ HLRCC-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC ▸ Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid) ▸ Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person (See Table 1) ▸ Succinate dehydrogenase (SDH)-deficient RCC histology[e]
4. An unaffected individual[c,d] with any of the following criteria:
▸ ≥2 first- or second-degree relatives[b] with RCC (on the same side of the family) ▸ Any first degree relative who meets the criteria in boxes 2 and 3 who is unable or unwilling to genetically test

"Close Blood Relative"
1st degree: parent, sibling, child

2nd degree: half sibling, aunt, uncle, grandparent, grandchild

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

VHL

Management of localized renal masses in VHL is typically guided by the **"3 cm rule"**

- Intervene at a time point of maximal benefit to the patient
- **Limit the risk of metastatic disease** but also **consider recurrent and multiple resections** these patients will have over the course of their lifetime with subsequent development of **chronic and progressive renal failure**.
- Patient should undergo **partial nephrectomy (if possible)** and consider referral to centers with surgical expertise in complex partial nephrectomies and management of VHL patients.
- Ablative treatment considered if significant medical or surgical risk to undergo an operation.

There is now a drug for that! Ask your doctor if…

August 2021: FDA approved (HIF-2α inhibitor) **- Belzutifan** (Merck & Co.)

Treatment of patients with **VHL disease-associated RCC** who require therapy for RCC but do not require immediate surgery.

Clinical trial (2021), enrolled 61 patients with VHL-associated RCC.

- 97% had previously undergone a tumor reduction procedure.
- **Overall response rate was 49%** (95% CI, 36–62) after a median follow-up of 21.8 months.
- **30 patients with partial response. An additional 30 patients (49%) had a best response of stable disease.**
- **Only 1/61 patients had tumor growth.**

Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, Oudard S, Else T, Maranchie JK, Welsh SJ, Thamake S, Park EK, Perini RF, Linehan WM, Srinivasan R; MK-6482-004 Investigators. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021 Nov 25;385(22):2036-2046. doi: 10.1056/NEJMoa2103425. PMID: 34818478; PMCID: PMC9275515.

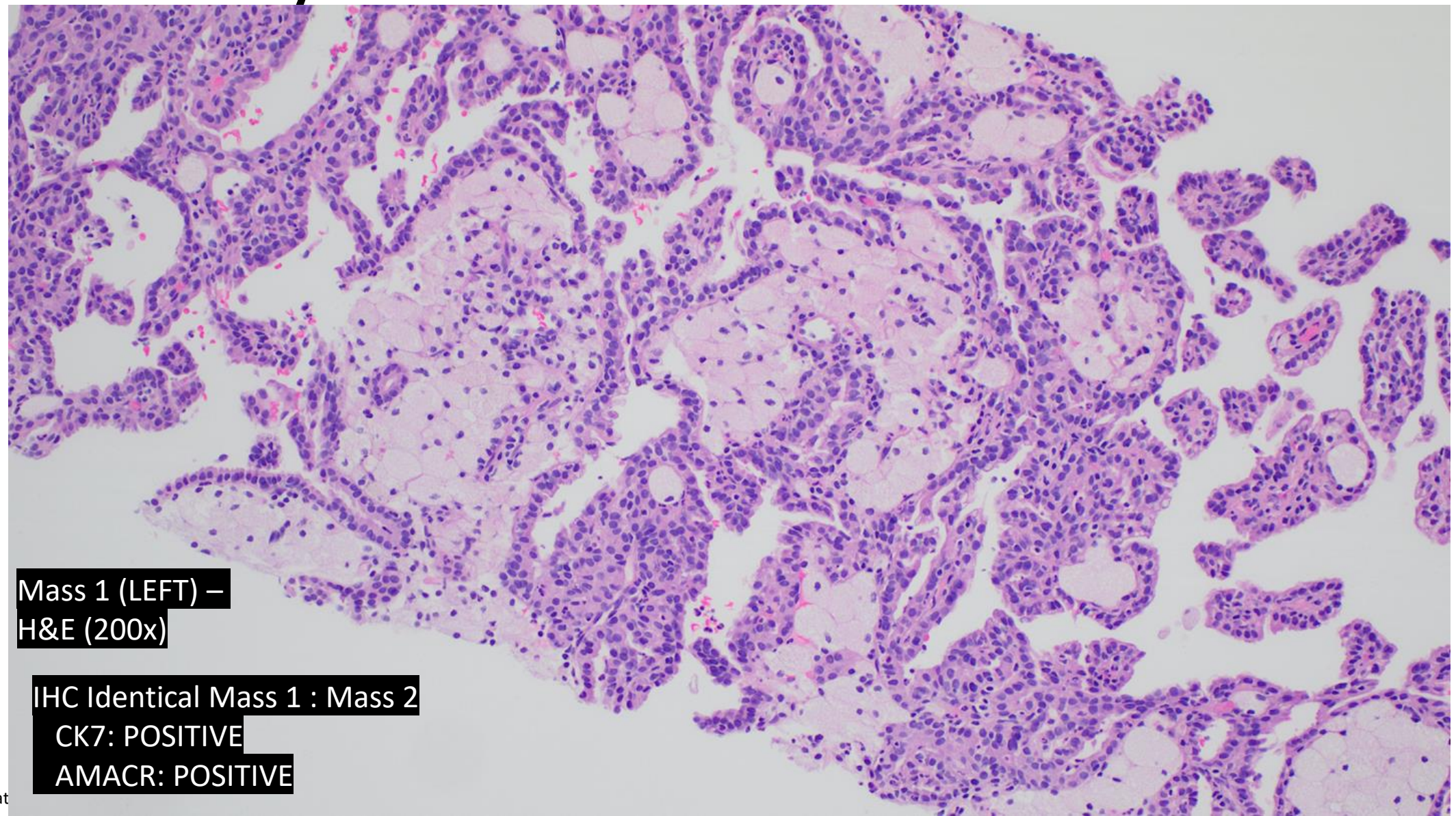
VHL Take-Home Points

1. VHL has a heterogeneous clinical presentation both within and outside of the GU tract.

2. Pathologist recommendation of genetic testing based on NCCN guidelines: young age, tumor combinations, bilaterality, or multifocality may have tremendous screening and familial benefits.

3. Clinical (or pathologist) recognition of VHL has become even more important with the recent development of effective pharmaceutical options (Belzutifan).

Case 2 - 46M Multiple Renal Masses, Bilaterally



Mass 1 (LEFT) –
H&E (200x)

IHC Identical Mass 1 : Mass 2
CK7: POSITIVE
AMACR: POSITIVE

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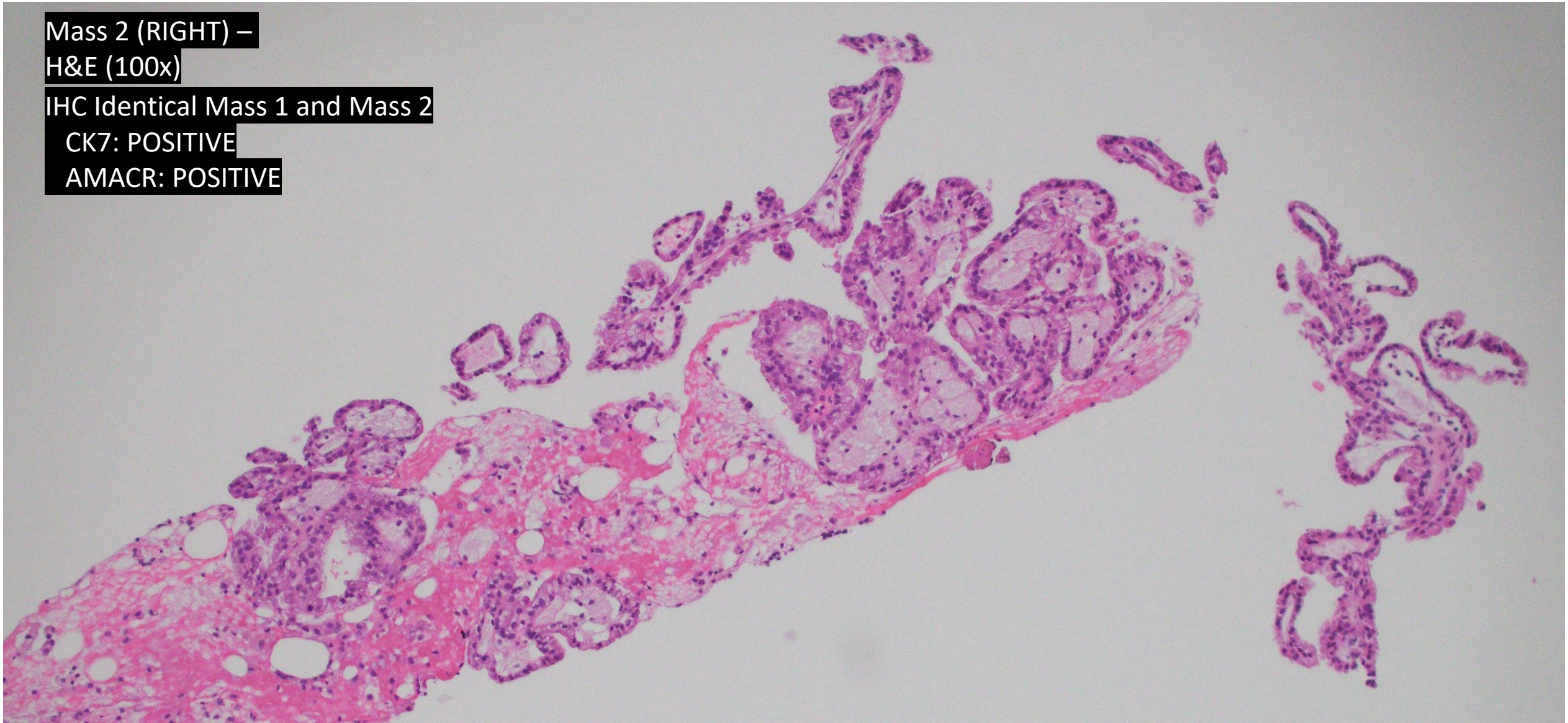

Case 2 - 46M Multiple Renal Masses, Bilaterally

Dx: "Multifocal (Bilateral) papillary renal neoplasms"

- Biopsy cores (<15 mm) prevent definitive diagnosis of papillary renal cell carcinoma (formally Type 1 papillary RCC)
- Imaging correlation: Both >15 mm

- Tumors ≤15mm would be better classified as **papillary adenoma**.
- Capsular features rarely helpful on biopsy
  - Adenomas typically lack pseudocapsule

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Hereditary Renal Cell Carcinoma

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Case 2 – Hereditary Papillary Renal Cell Carcinoma Syndrome (HPRCC)

- Multifocal or bilateral papillary renal cell carcinomas (Formerly Type 1)
- Autosomal Dominant (AD) with high (nearly 100%) penetrance.
- EXTREMELY RARE – much more so than VHL, and more so than fumarate hydratase deficient RCC.
  - True incidence too infrequent to quantify (WHO ’22)
- Associated with ***MET* (7q31) germline missense mutations.**
  - 10-15% of sporadic P-RCC also demonstrate *MET* mutations.
  - ***MET* amplifications** are seen in >80% of **sporadic P-RCC**
- Same **3.0 cm size recommendation** for partial nephrectomy
  - Lifetime disease with considerations for nephron-sparing kidney preservation

Hereditary P-RCC Take-Home Points

1. NCCN 2023 suggests that genetic counseling / testing be considered in multifocal or bilateral P-RCC or patients <46 yrs.

2. Pathologist recommendation of genetic testing based on bilaterality, or multifocality will have more minor impact as compared to VHL given both rarity and relative aggressiveness of PRCC.

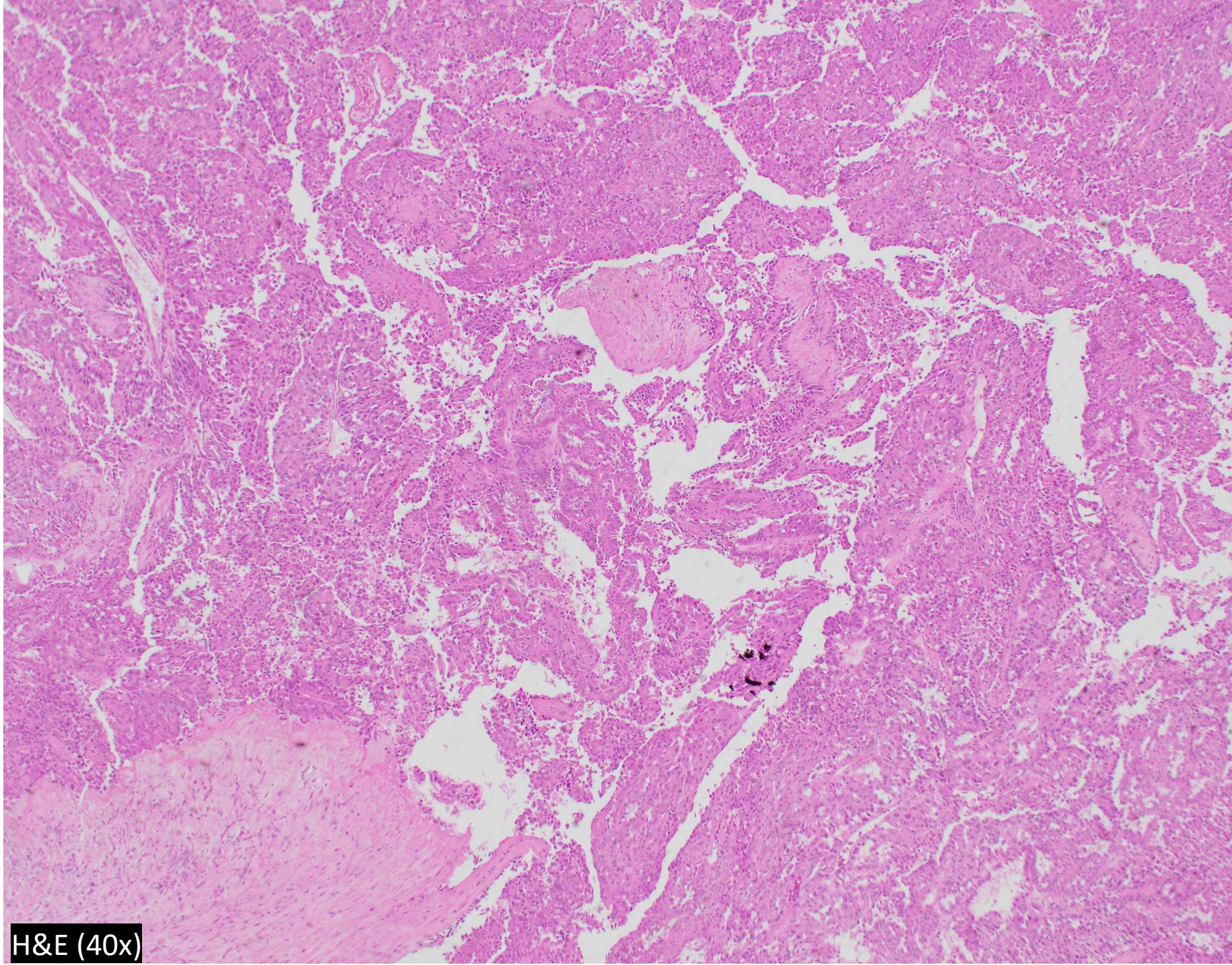
3. Partial nephrectomy (nephron sparing) surgery remains the treatment of choice. Same 3.0 cm criteria for excision as recommended with VHL.

Case 3

55F
Renal Mass

Radiologically involving renal vein and collecting system

Confirmed on gross exam



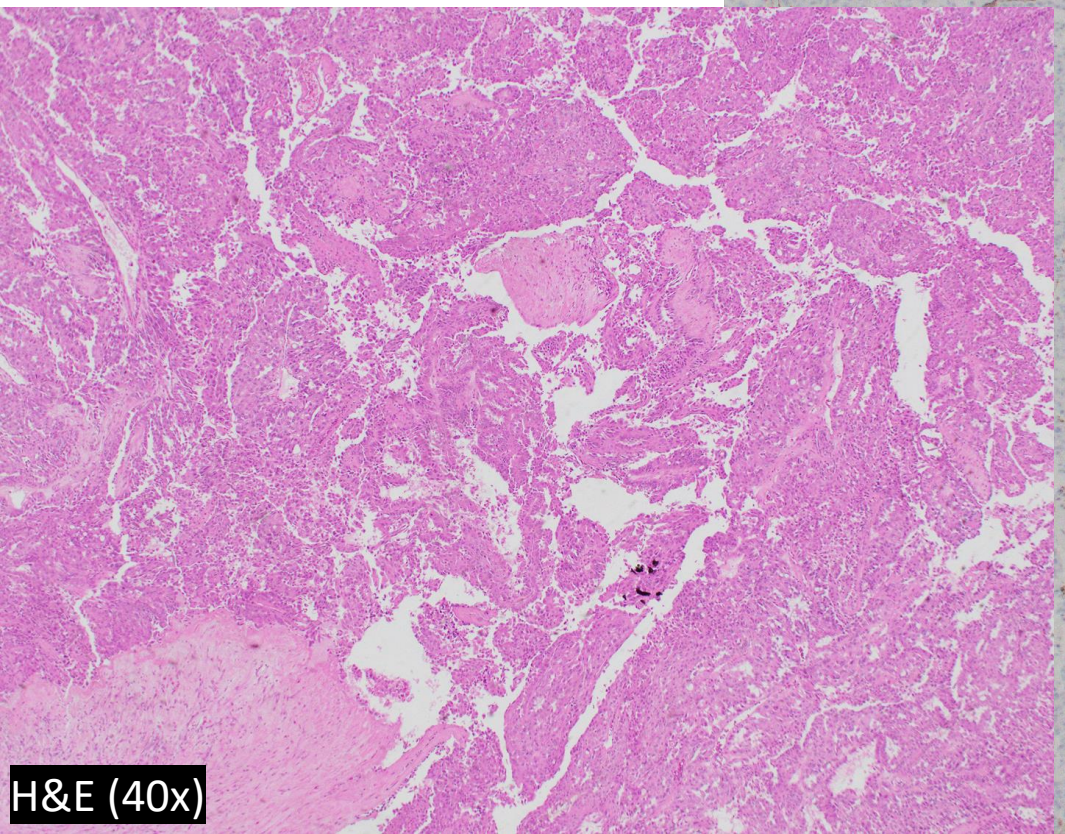
Case 3

H&E (400x)

Fumarate Hydratase (FH) IHC

Complete loss of staining in tumor cells.

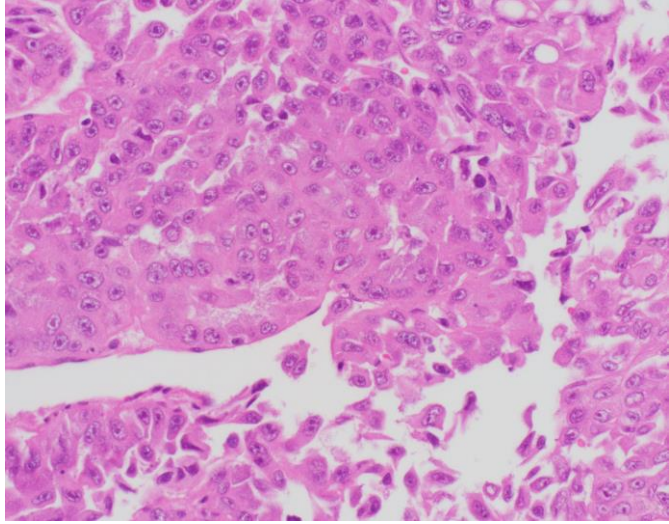
FH-Deficient RCC



H&E (40x)

FH-IHC (40x)

Case 3: Fumarate-Hydratase Deficient RCC / Hereditary Leiomyomatosis & RCC (HLRCC)



- Architecture classically described as:
  - Papillary, tubular, tubulo-papillary, cystic, intracystic papillary, solid, collecting duct-like, and sarcomatoid patterns.
  - **Large nuclei with viral inclusion-like eosinophilic nucleoli.**
- Advanced stage: ≥pT3 (57%) or metastasis (19%) at time of presentation is the norm.
- Typically **younger** patients (Teens – 40's)

- **FH-deficient RCC is preferred terminology in the absence of germline molecular confirmation**.
  - No consolidated study of germline vs somatic incidence rates – (*this admittedly needs more looking into)*
  - Germline initially appears significantly more common (>75-80%)
- FH-IHC (loss) and 2-succinocysteine (2SC-IHC positivity) are both effective surrogate markers to suggest FH mutation.

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Hereditary Renal Cell Carcinoma

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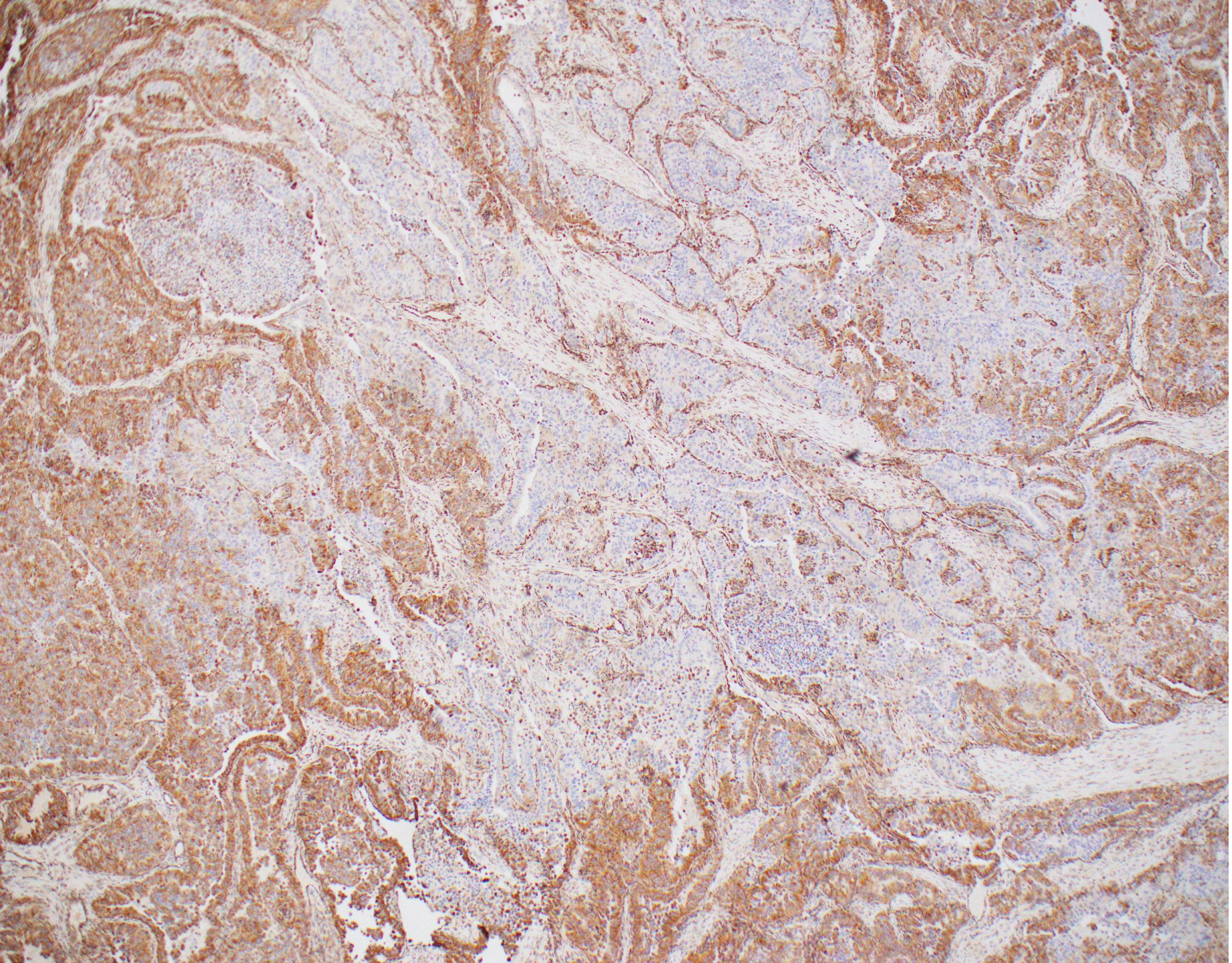
2. An individual with RCC with any of the following criteria:
▸ Diagnosed at age ≤46 y ▸ Bilateral or multifocal tumors ▸ ≥1 first- or second-degree relative[b] with RCC
3. An individual whose tumors have the following histologic characteristics:
▸ Multifocal papillary histology
▸ HLRCC-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC
▸ Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)
▸ Angiomyolipomas of the kidney and one additional tuberous sclerosis complex (TSC) criterion in the same person (See Table 1)
▸ Succinate dehydrogenase (SDH)-deficient RCC histology[e]
4. An unaffected individual[c,d] with any of the following criteria:
▸ ≥2 first- or second-degree relatives[b] with RCC (on the same side of the family) ▸ Any first degree relative who meets the criteria in boxes 2 and 3 who is unable or unwilling to genetically test

Trpkov, K et al. Fumarate Hydratase–deficient Renal Cell Carcinoma Is Strongly Correlated With Fumarate Hydratase Mutation and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome. The American Journal of Surgical Pathology 40(7):p 865-875, July 2016. | DOI: 10.1097/PAS.0000000000000617



FH-Deficient RCC with subset (40%) of tumor cells with complete loss of FH staining.

Highly suspicious IHC pattern.

Referred for genetic testing…

Positive for germline FH mutation

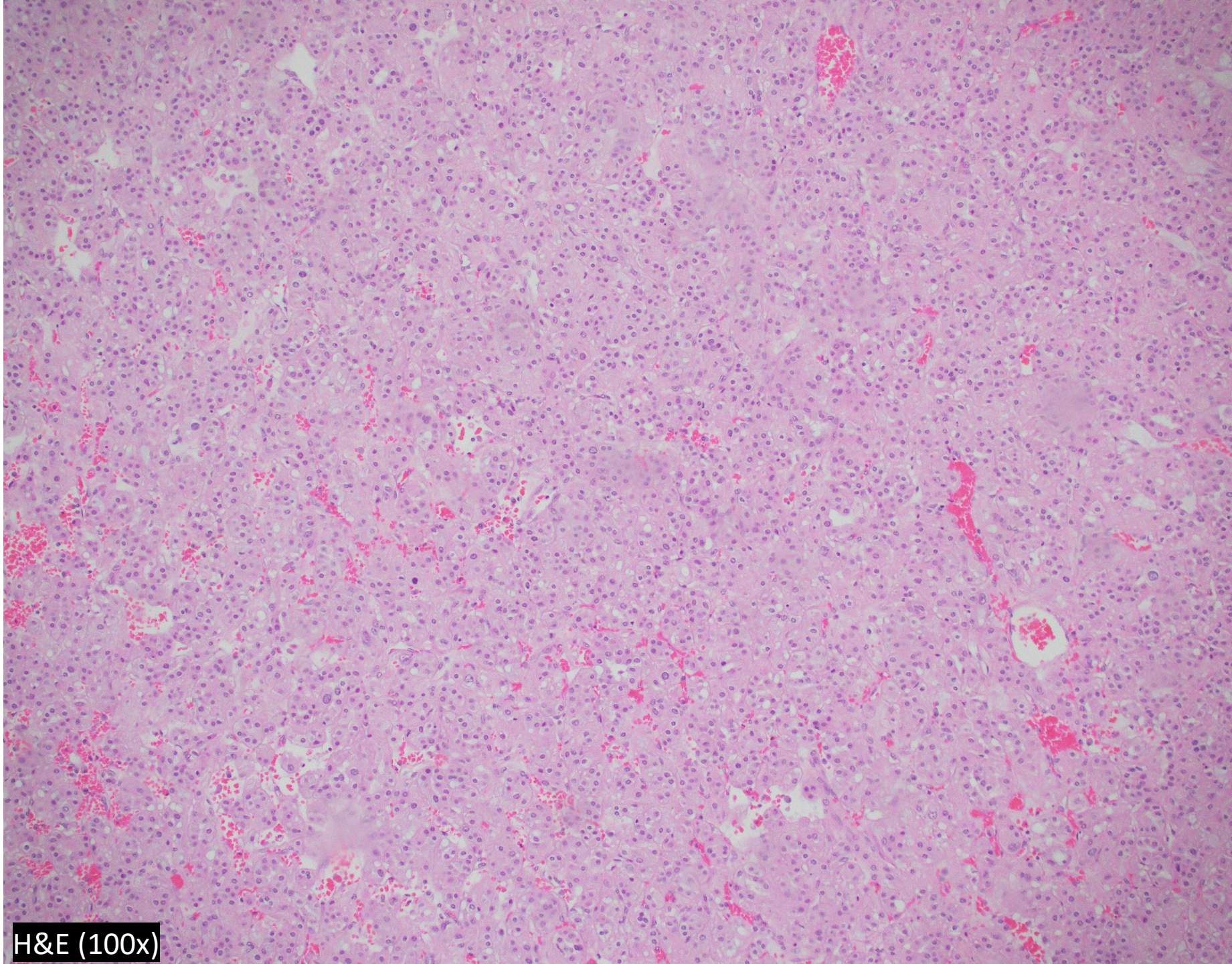
ANY abnormal loss of FH staining is considered reason to **pursue further genetic testing.**

Case 3.2:

16 F
Radiologically aggressive renal mass

FH-Deficient RCC

(Pathology is Hard)

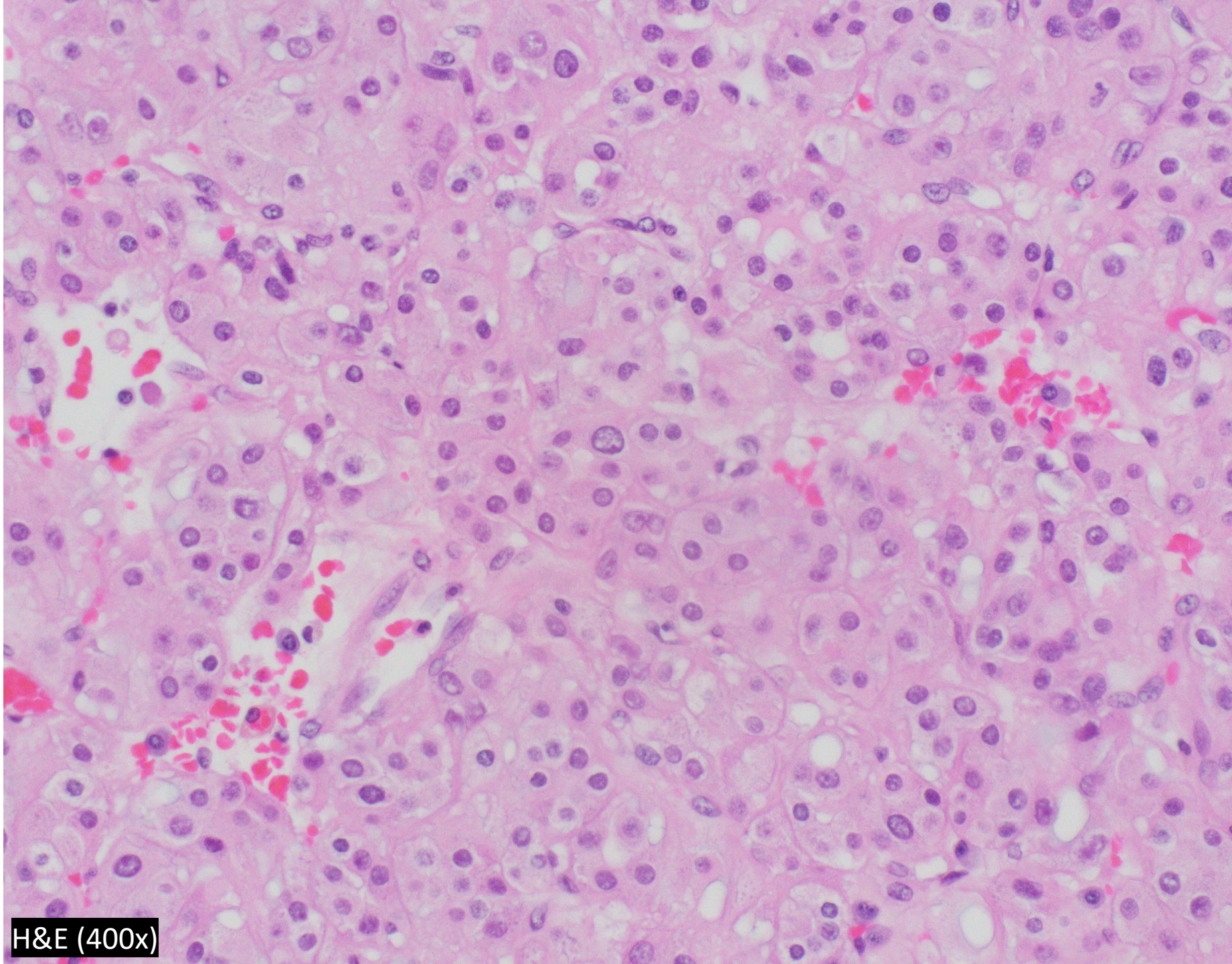


Case 3.2:

IHC:

CD117 – Negative
CK7 – Negative
SDHB – Retained

Fumarate Hydrase: Lost in all Tumor Cells



Low-grade Oncocytic Fumarate Hydratase-deficient Renal Cell Carcinoma: An Update on Biologic Potential, Morphologic Spectrum, and Differential Diagnosis With Other Low-grade Oncocytic Tumors

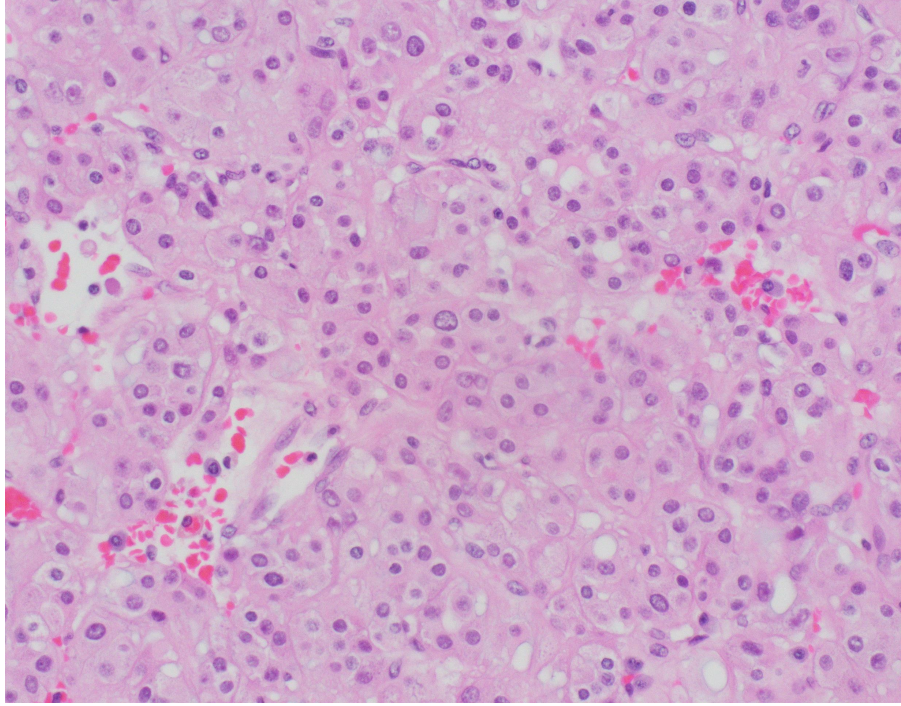
Ameer Hamza, MD, Deepika Sirohi, MD,† Steven C. Smith, MD, PhD,‡ and Mahul B. Amin, MD§‖*

- The morphologic differential diagnosis could include:
  - Oncocytoma
  - Chromophobe RCC
  - SDH-deficient RCC
  - "LOT" Low-grade oncocytic tumor
  - Eosinophilic solid and cystic RCC
  - Eosinophilic vacuolated tumor.

- IHC workup is becoming complicated in CD117 negative low grade oncocytic tumors.

- Low grade areas admixed with more typical high-grade areas in ~1/3 cases – these behaved classically (very aggressive).

- Purely low-grade tumors without other aggressive features (LVI, LN Mets) MAY have a better prognosis. (Limited cases, Limited follow-up)

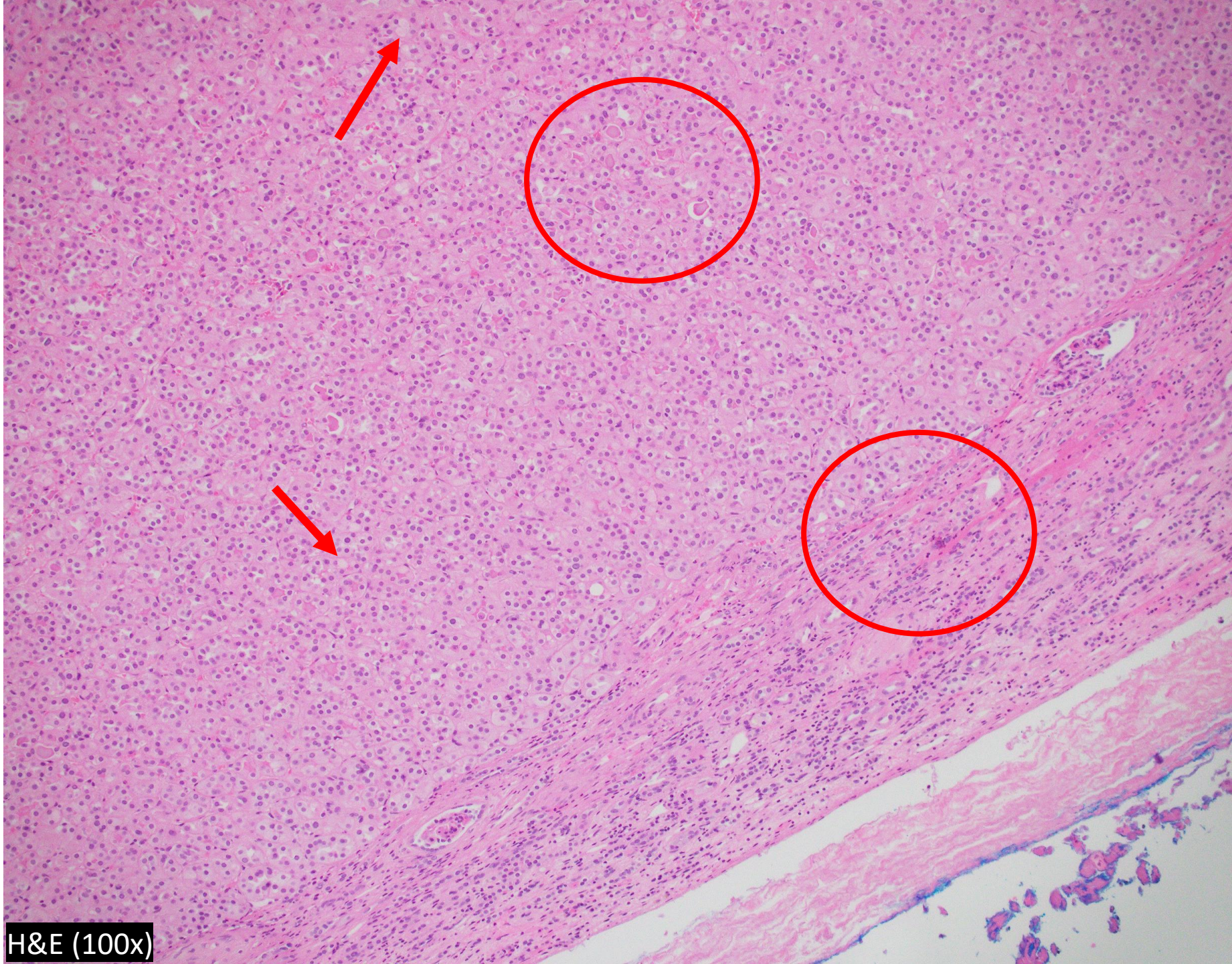


Proposed IHC workup based on our own experience:

- CD117 (c-KIT)
- CK7
- CA-IX
- FH
- SDH-B
- +/- CK20
- +/- GATA3

Case 4

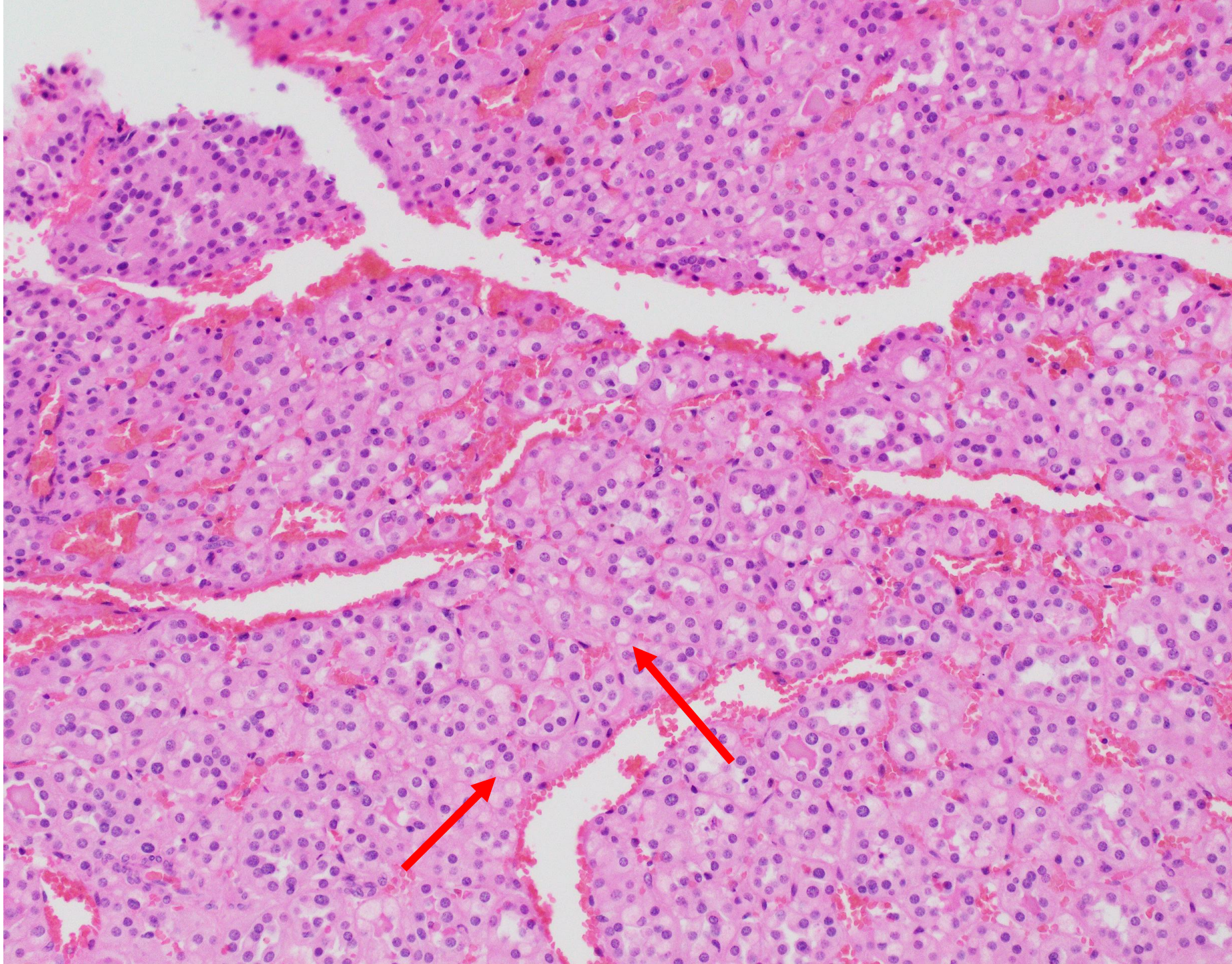
- Compact nests or sheets of bland eosinophilic tumor cells
- Microcysts with luminal eosinophilic secretions
- Peripheral entrapment of benign tubules may be seen
- Foamy cytoplasmic inclusions containing pale to eosinophilic material.



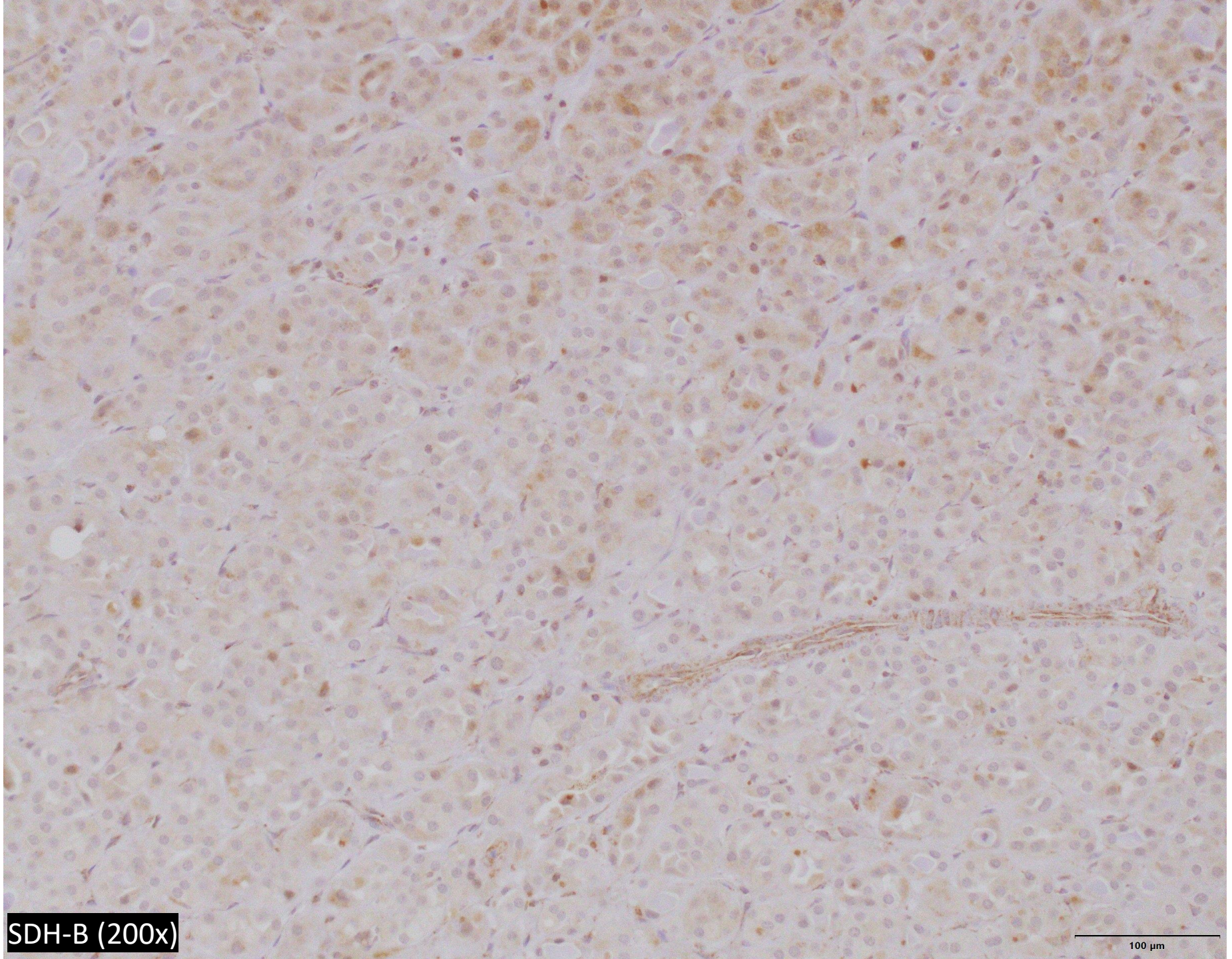
Case 4

- Compact nests or sheets of bland eosinophilic tumor cells
- Microcysts with luminal eosinophilic secretions
- Peripheral entrapment of benign tubules may be seen
- Foamy cytoplasmic inclusions containing pale to eosinophilic material.

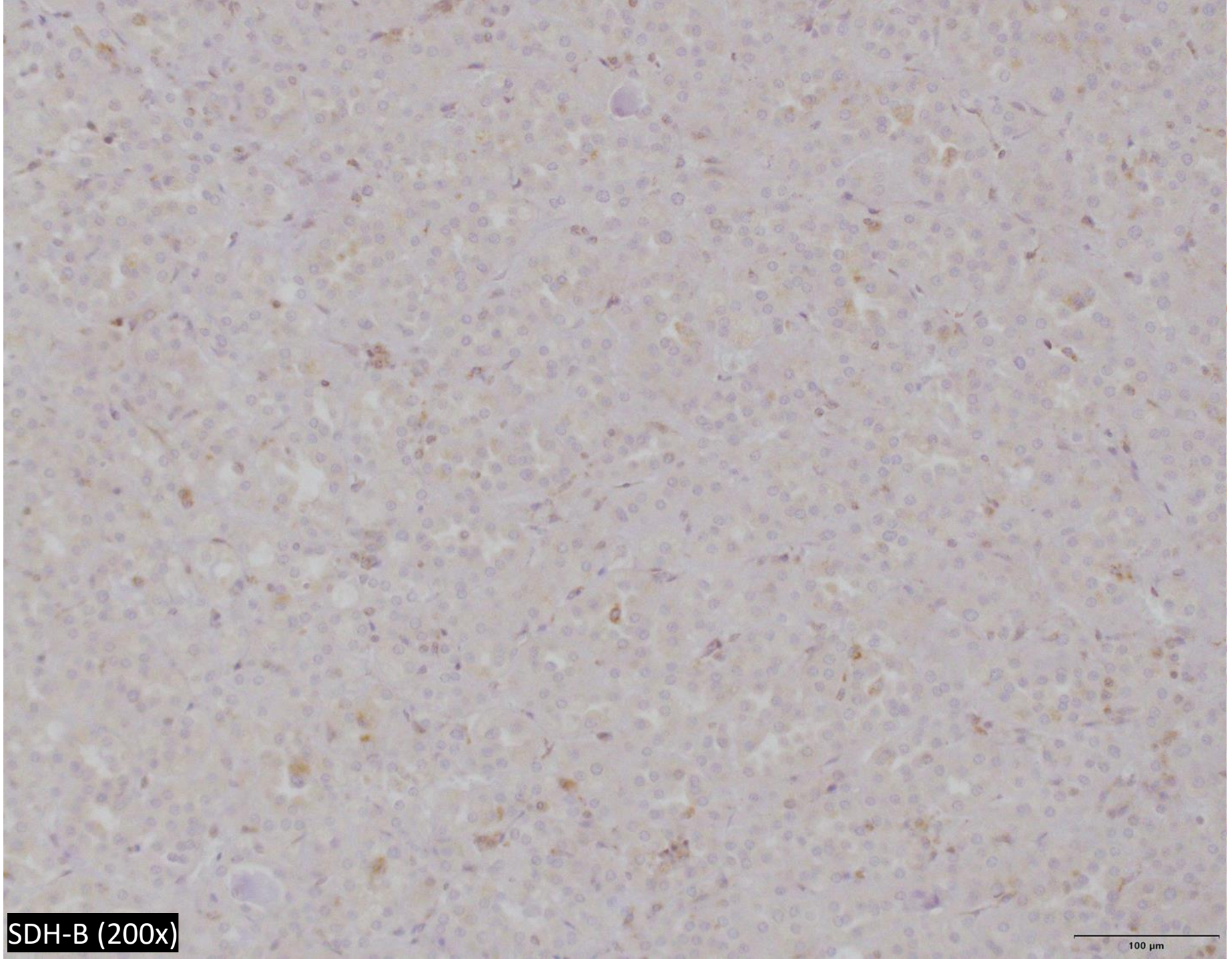
IHC:
CD117: NEGATIVE
CK7: NEGATIVE
FH: RETAINED
PAX8: POSITIVE



Case 4



Case 4



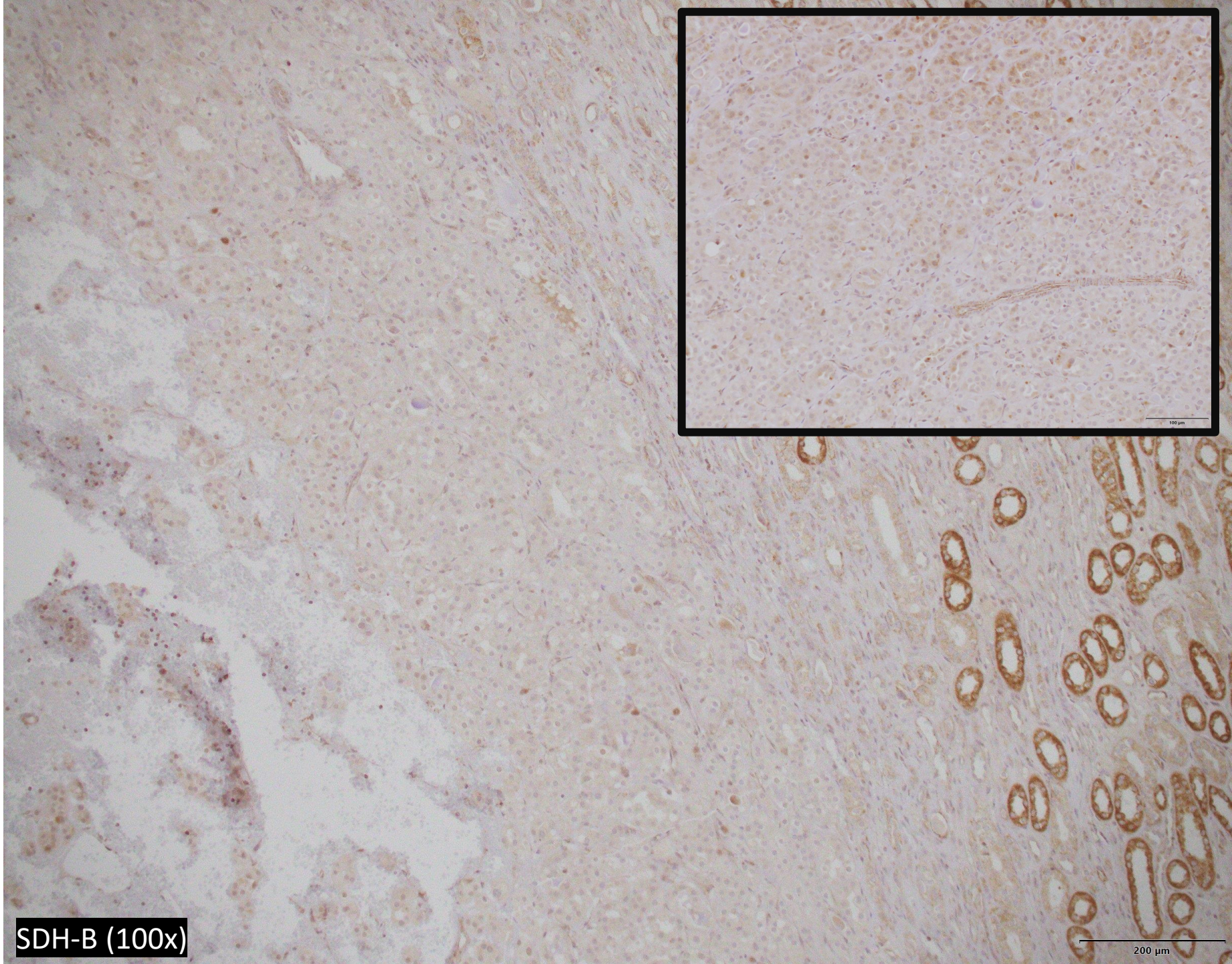
Case 4

SDH-B IHC

Excellent surrogate marker for SDH deficiency of ALL subunits.
(SDHA, SDHB, SDHC, SDHD, SDHAF)

SDH-B interpretation is in reality VERY challenging.

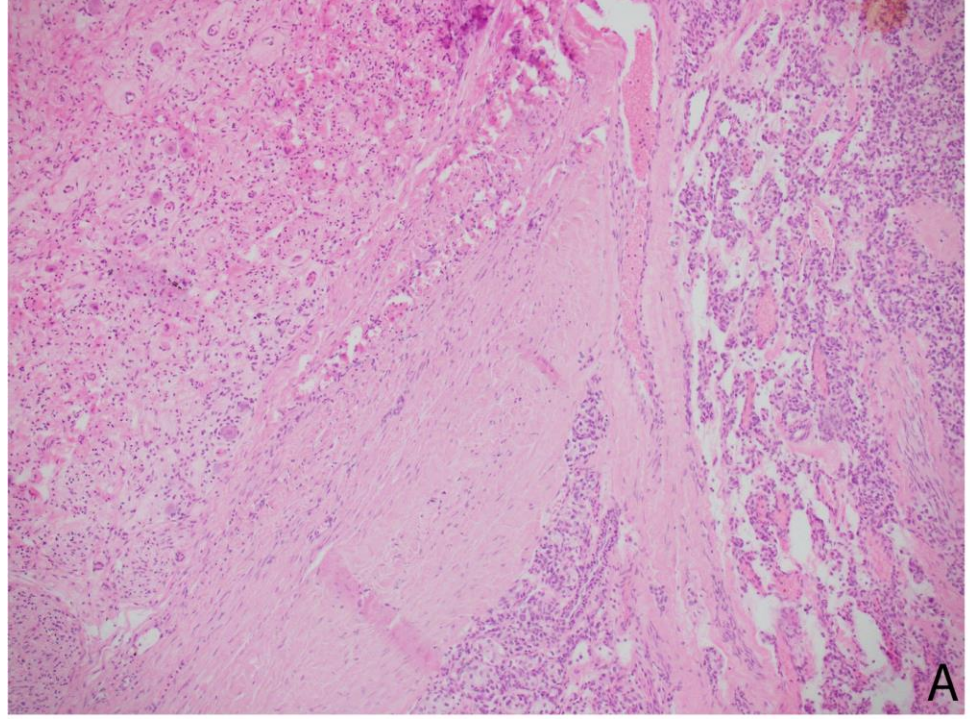
Patchy granular staining or heterogeneous staining should be reported as “suspicious” or “suggestive” with reflex **genetic testing.**

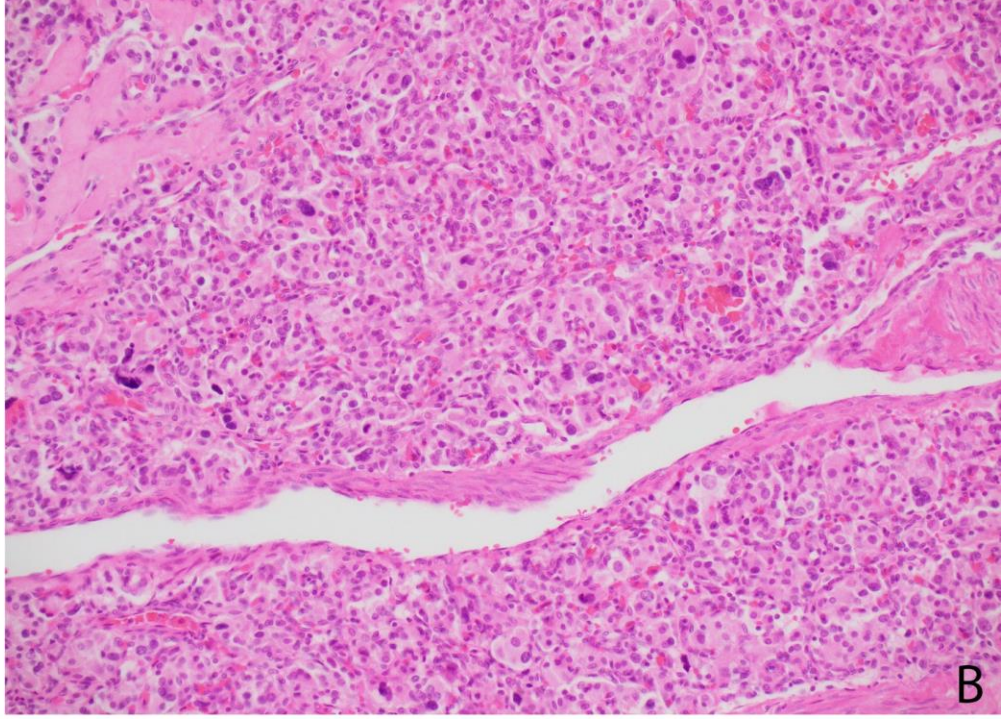


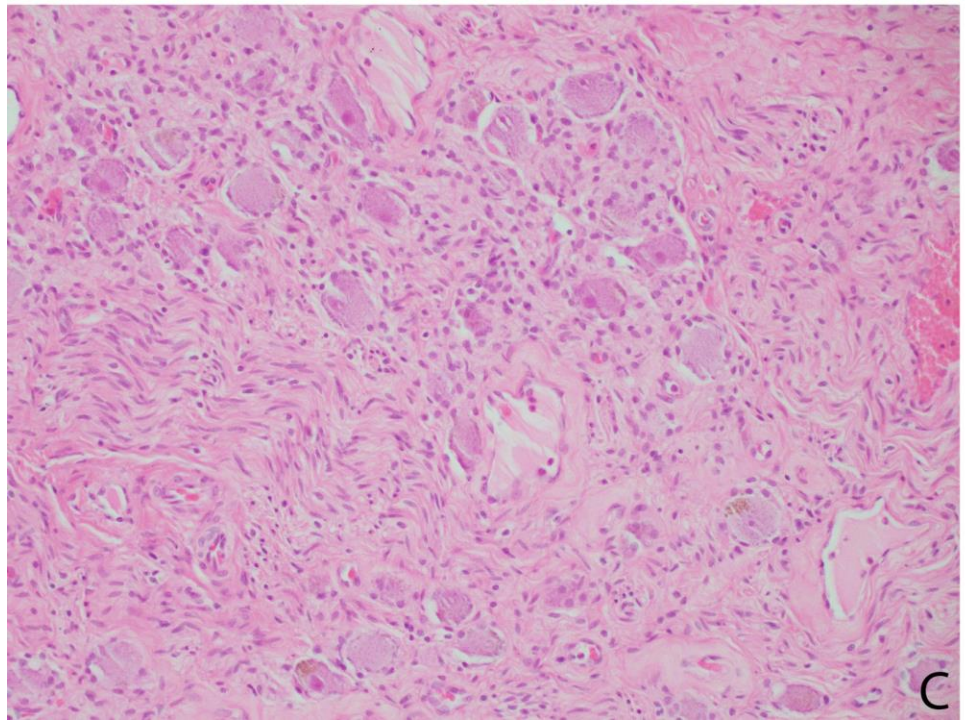
Case 4.2

40M Adrenal Mass

Family Members with known: SDH-B and SDH-C







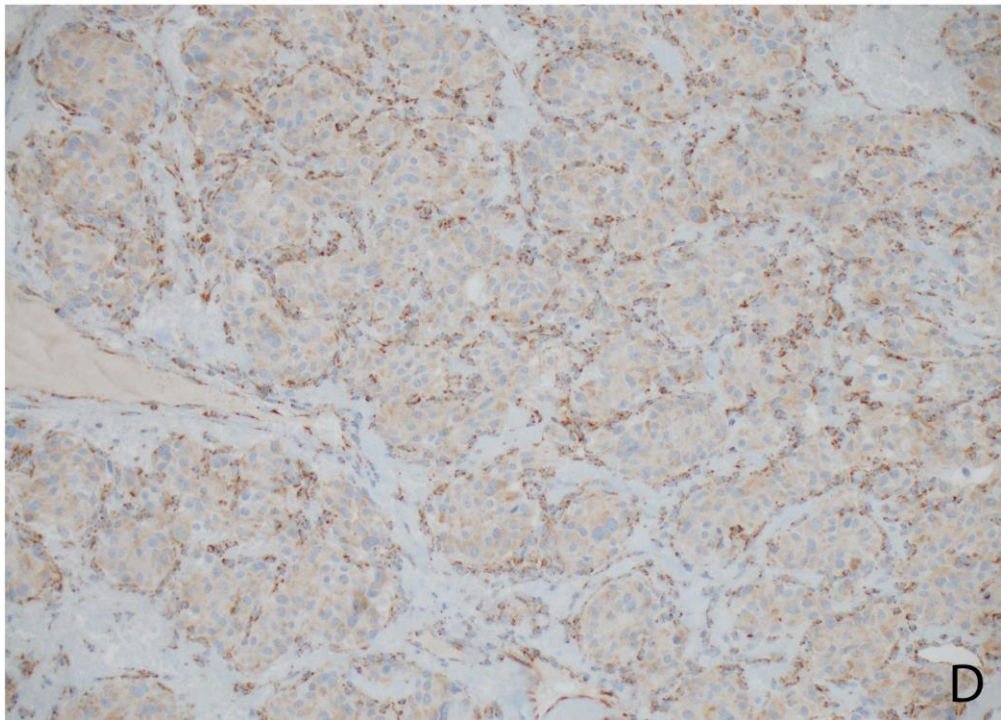


Fig. 1: A: Interface between ganglioneuroma (left) and pheochromocytoma/paraganglioma (right) (H&E 100x). B: Pheochromocytoma component (H&E 200x). C: Ganglioneuroma component (H&E 200x). D: Loss of SDHB staining, suggestive of *SDHx* mutation, note the retained staining in endothelial cells for internal control (SDHB IHC, 200x).

Case 4.2

40M Adrenal Mass

Family Members with known: SDH-B and SDH-C

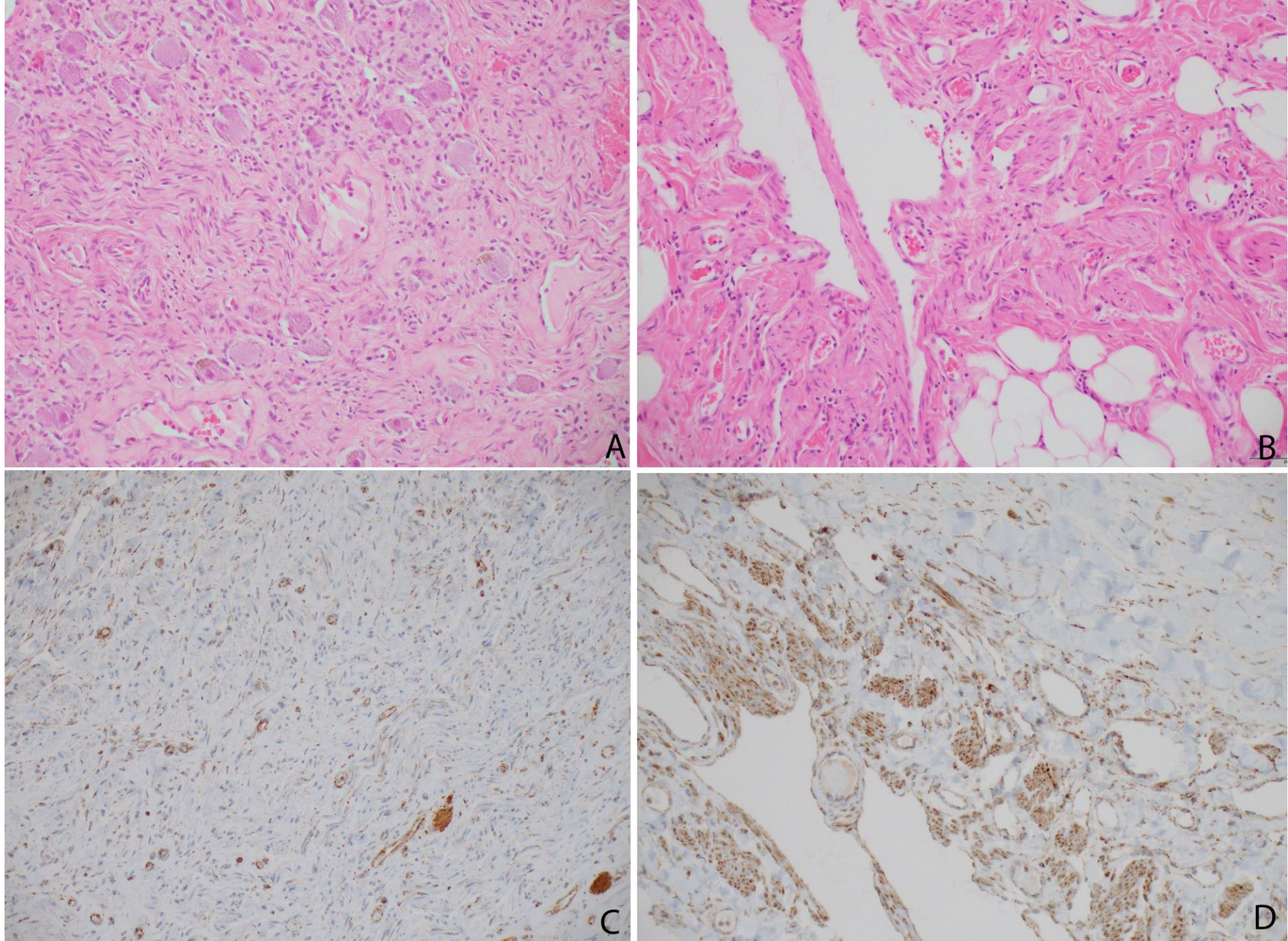


Fig. 2: A: Ganglioneuroma (H&E 100x). B. Neurovascular bundle distant from tumor. C. Ganglioneuroma component with loss of SDHB expression in neuronal cells, ganglion cells show weak staining (SDHB IHC 100x). D. Neurovascular bundle distant from tumor with retained SDHB expression in endothelial and neural tissue.

Case 4 – SDH Deficient Tumors

Table 14.03 Frequency of SDH germline mutations associated with each tumour type

WHO 2022

Tumour	*SDHA* mutation	*SDHB* mutation	*SDHC* mutation	*SDHD* mutation	*SDHAF2* mutation	*SDHC* epimutation (Carney triad)
Adrenal phaeochromocytoma	+	+	+/–	++	++	–
Abdominal paraganglioma	++	++++	+/–	++	+/–	+++
Head and neck paraganglioma	+	++	++	+++	+	++
Thoracic paraganglioma	+/–	+/–	+	+	+/–	+
SDH-deficient GIST	+++	+	+	+	+/–	++++
SDH-deficient renal cell carcinoma	+	+++	++	+/–	+/–	–
SDH-deficient pituitary adenoma / PitNET	++	+	+	+	+/–	–
Pulmonary chondroma	–	–	–	–	–	++++

Biallelic inactivation of SDH gene → SDH complex dysfunction → Accumulation of toxic Kreb's cycle metabolites → oncogenesis

The specific SDH subunit impacted will determine types of tumors and help predict aggressiveness.

(This determination should be made by molecular/genetic methods – NOT IHC)

SDH-B Deficiency: SIGNIFICANTLY higher risk of MALIGNANT pheochromocytomas/paragangliomas

SDH-B (Metastatic Rate (PG/PCA): 31-71%

Case 4 – SDH Deficient Tumors

- Familial SDH-deficient tumors appear morphologically IDENTICAL to sporadic mutations.
- Sporadic mutations are EXTREMELY rare, unlike other syndromes SDH deficiency *almost certainly predicts germline syndromic association.
- Metastatic PG/PCA suggests possible SDH (most likely SDHB) deficiency
- **<u>ALL</u> pheochromocytomas and paragangliomas (of ANY site) should be tested by SDHB IHC. (Endocrine Society 2014)**
  - Nearly 40% of PG/PCA are hereditary.
- **<u>ANY</u> abnormal SDH-B staining should be referred for additional genetic workup/testing.**

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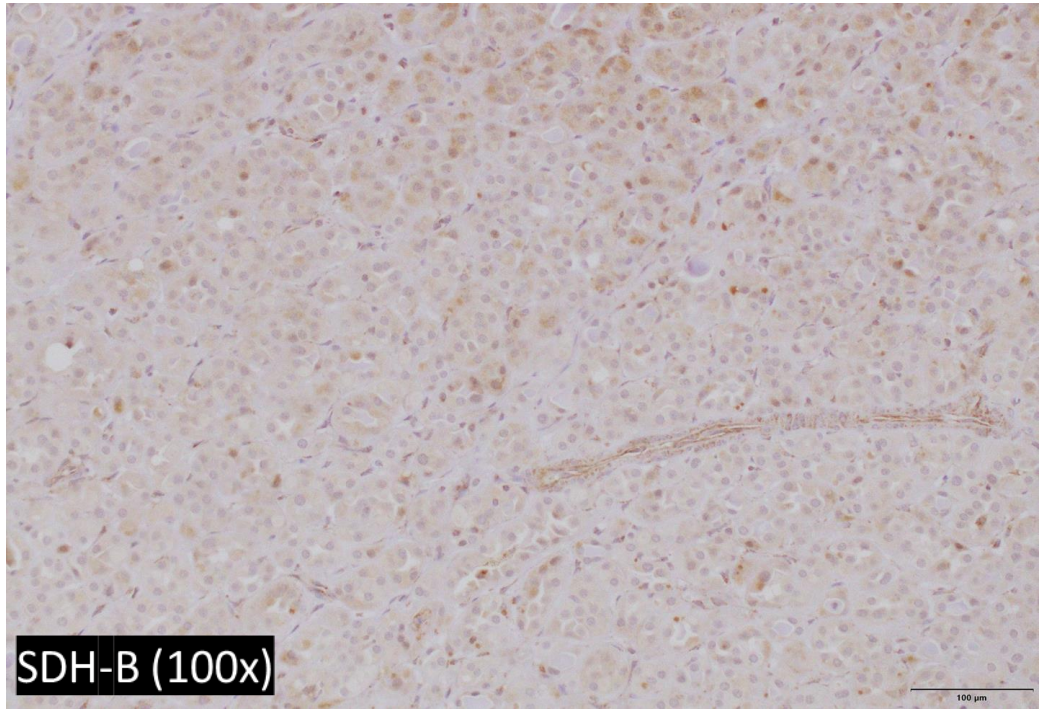

Gill AJ. Succinate dehydrogenase (SDH)-deficient neoplasia. Histopathology. 2018 Jan;72(1):106-116. doi: 10.1111/his.13277. PMID: 29239034.

Questions?