高雄榮民總醫院
Kaohsiung Veterans General Hospital

Surgicopathological Conference

高雄榮民總醫院 病理檢驗部
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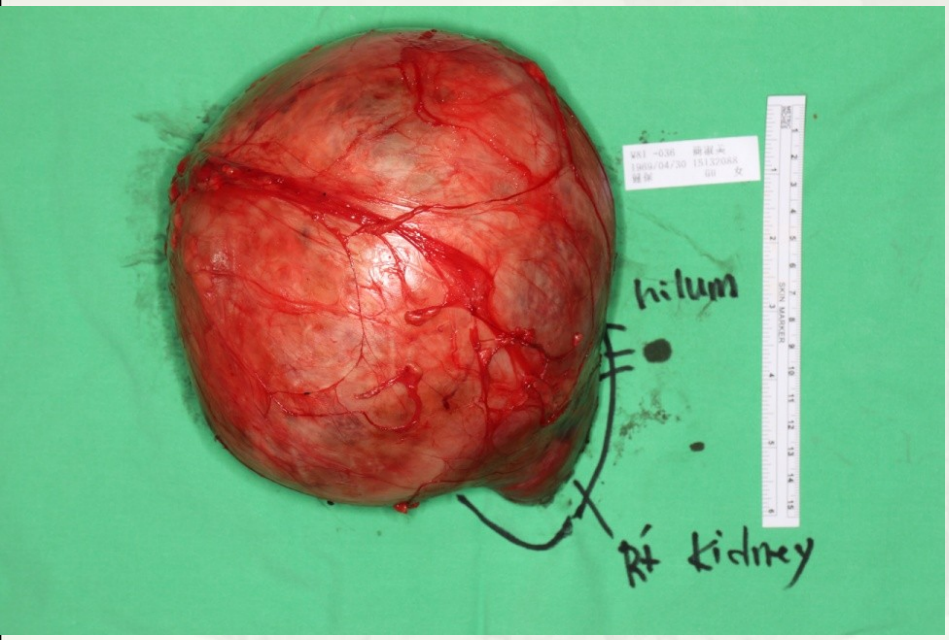
Clinical history

- 46 y/o female
- Past history : Denied any systemic disease

- Abdominal fullness off and on for 1 year
- Abdomen: RLQ palpable mass for 1 month

- CT: One huge cystic tumor of right kidney, 15 cm in size

Right nephrectomy



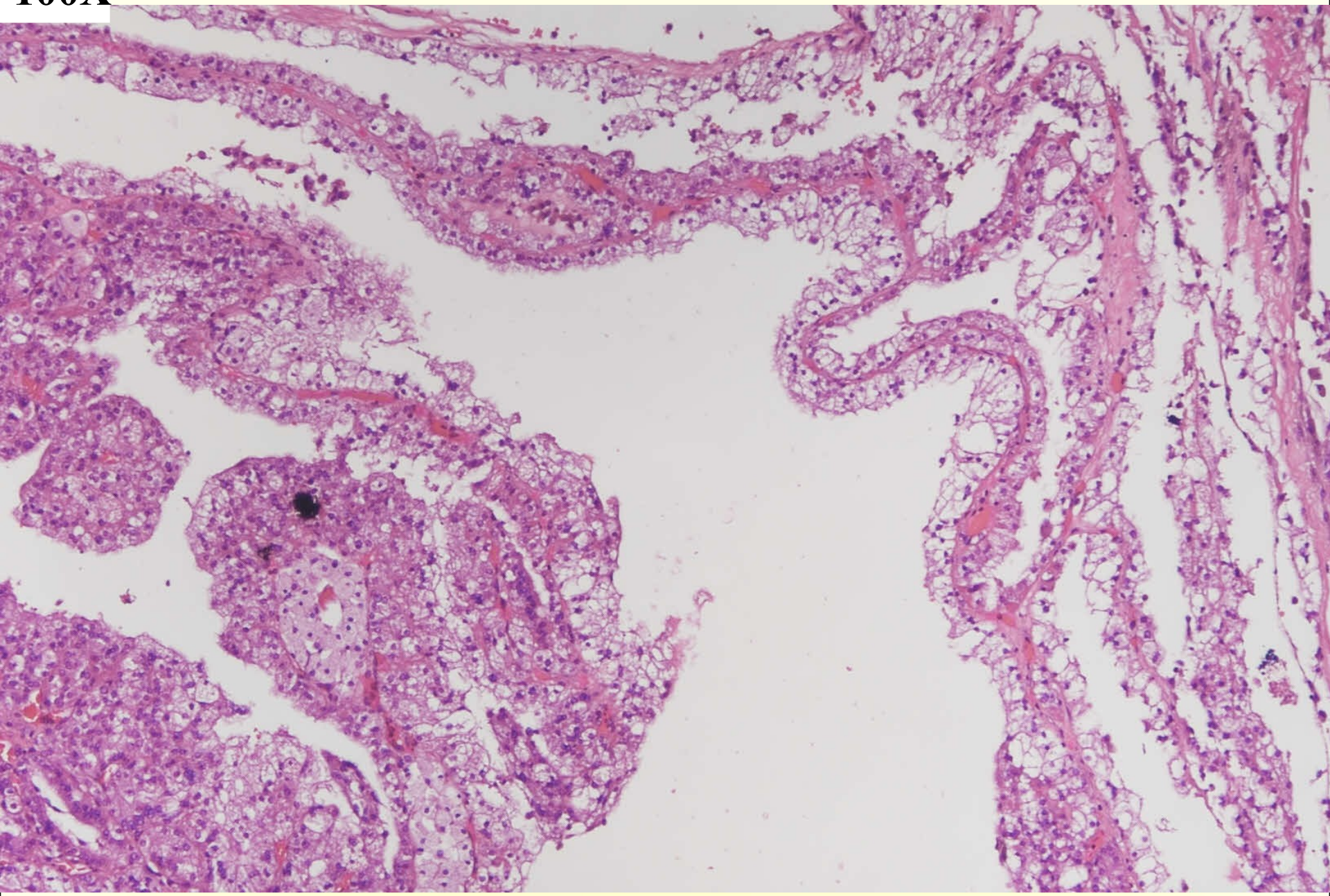
Gross finding

- Kidney: 6.5 x 5.3 x 3.6 cm, 300 gm
- Ureter: 5.4 cm
- No adrenal gland

- Huge cystic tumor over upper pole of right kidney, 13.5 x 10.8 x 10.3 cm
  - Necrosis and hemorrhage

Microscopic examination

100X



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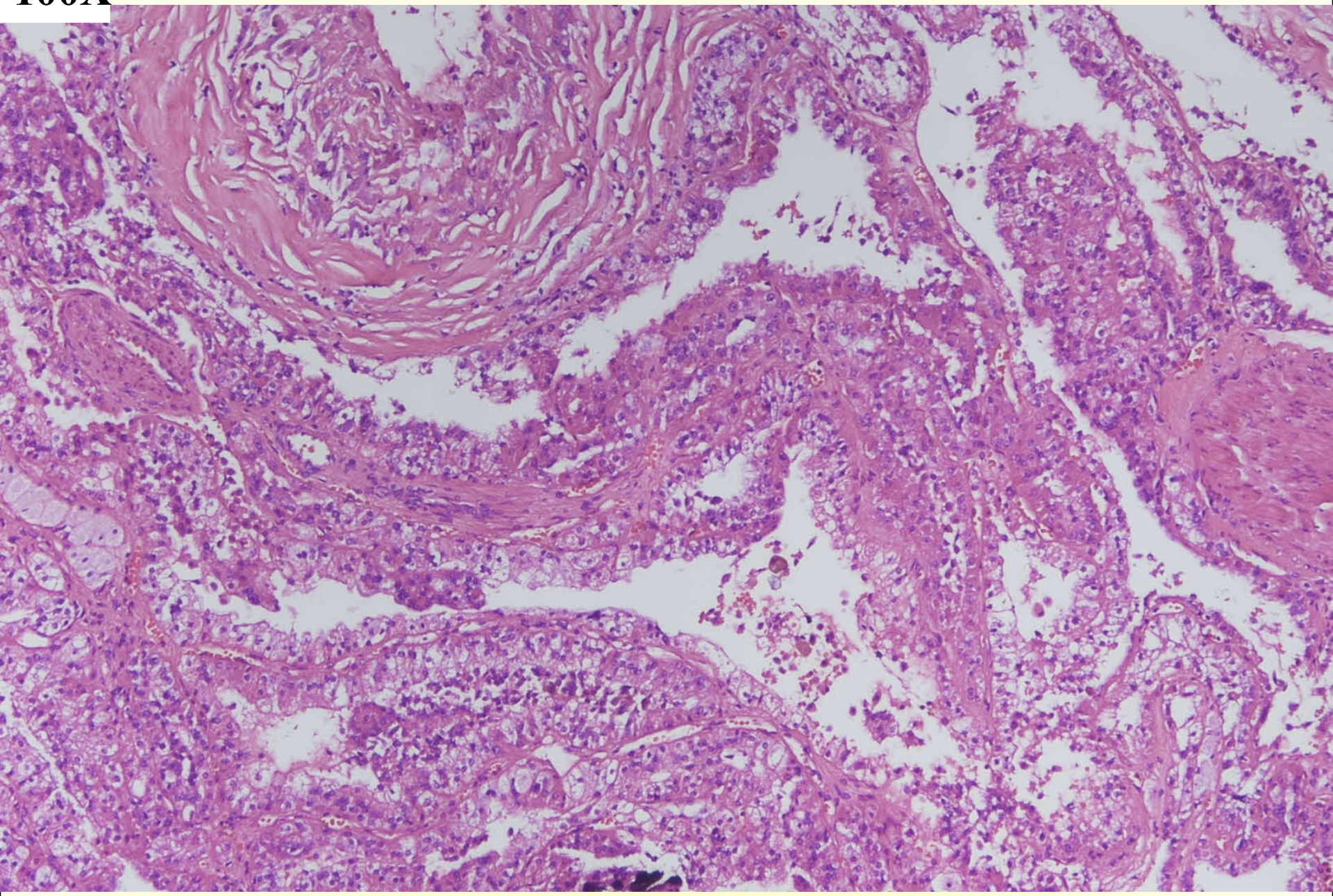

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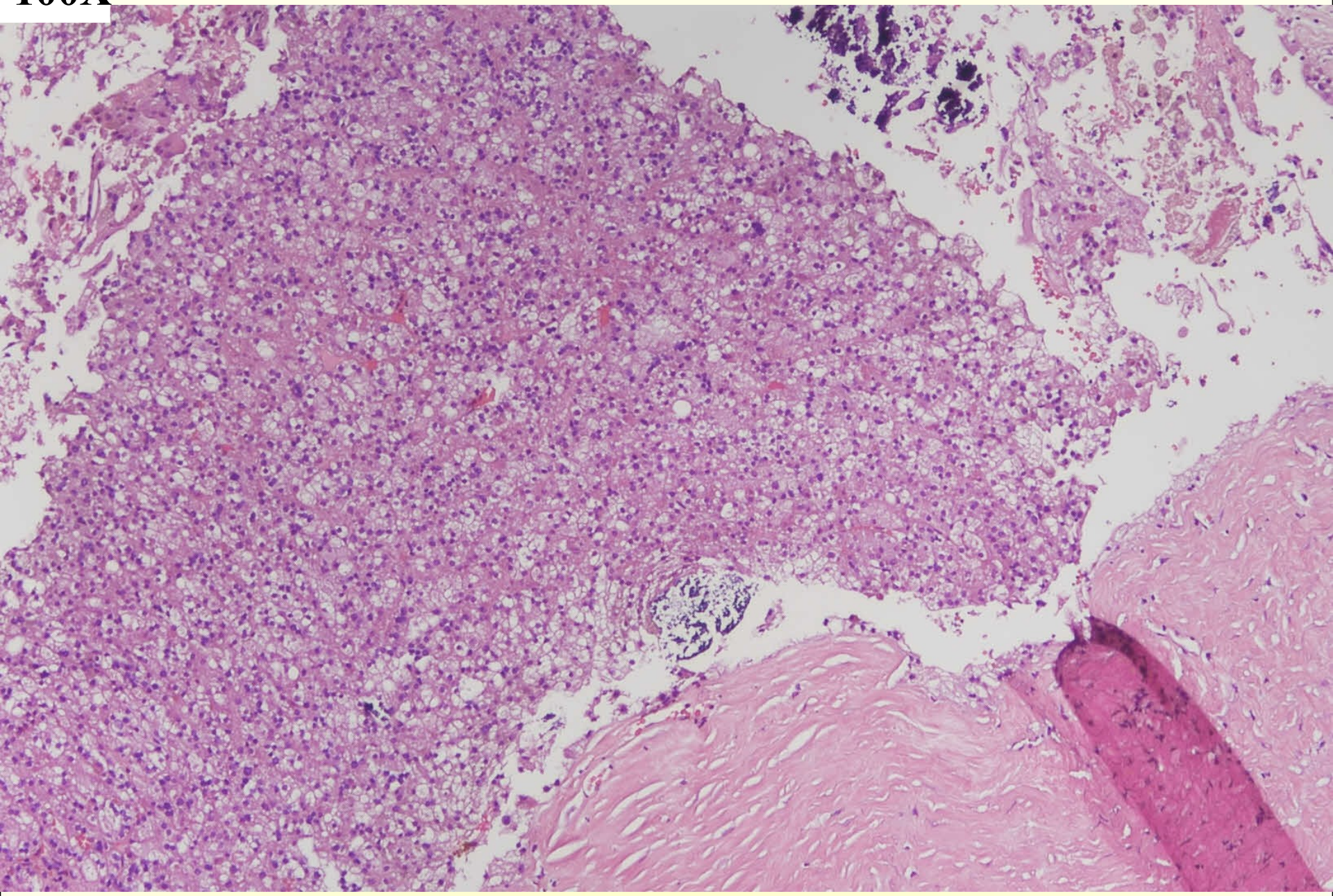

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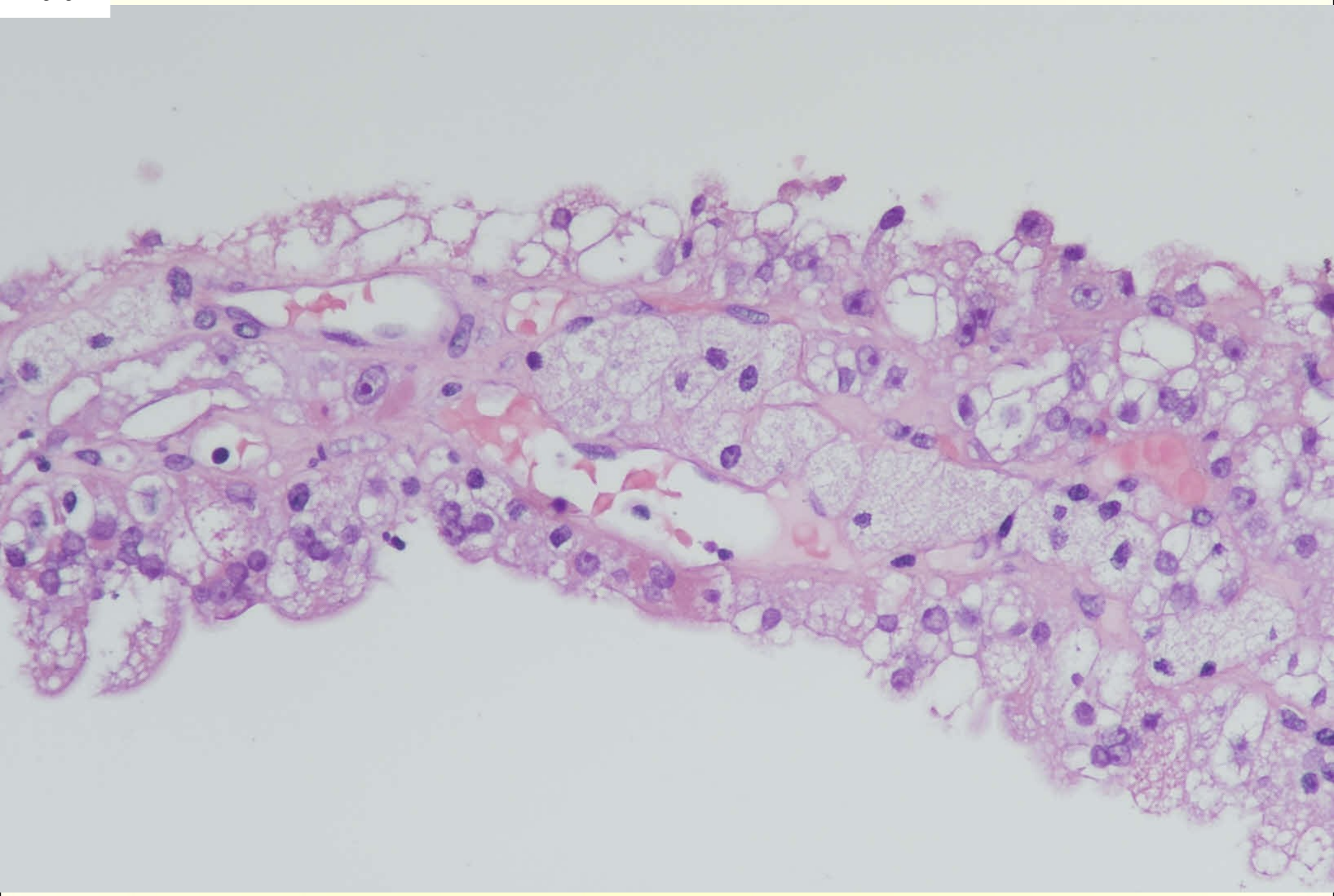

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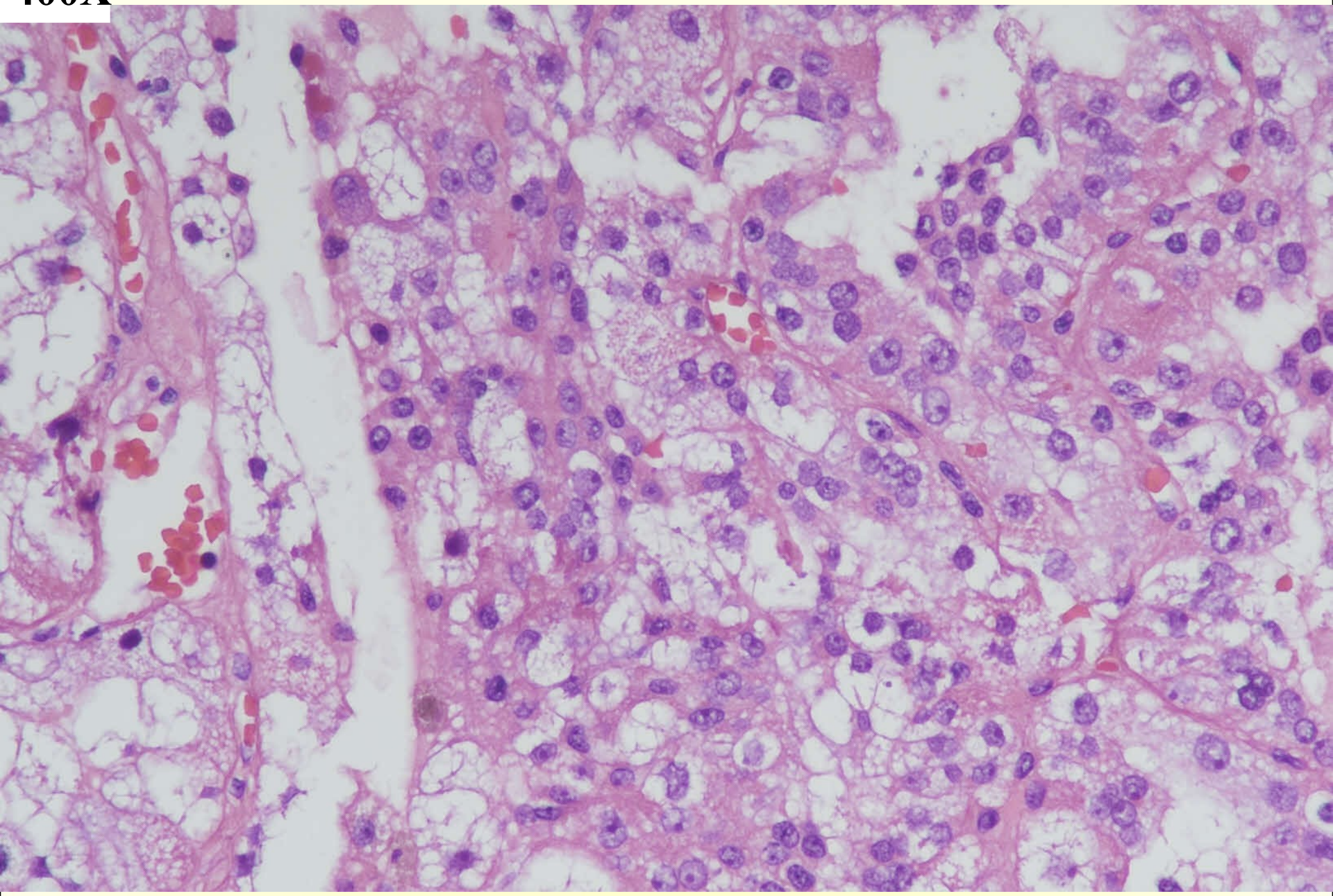

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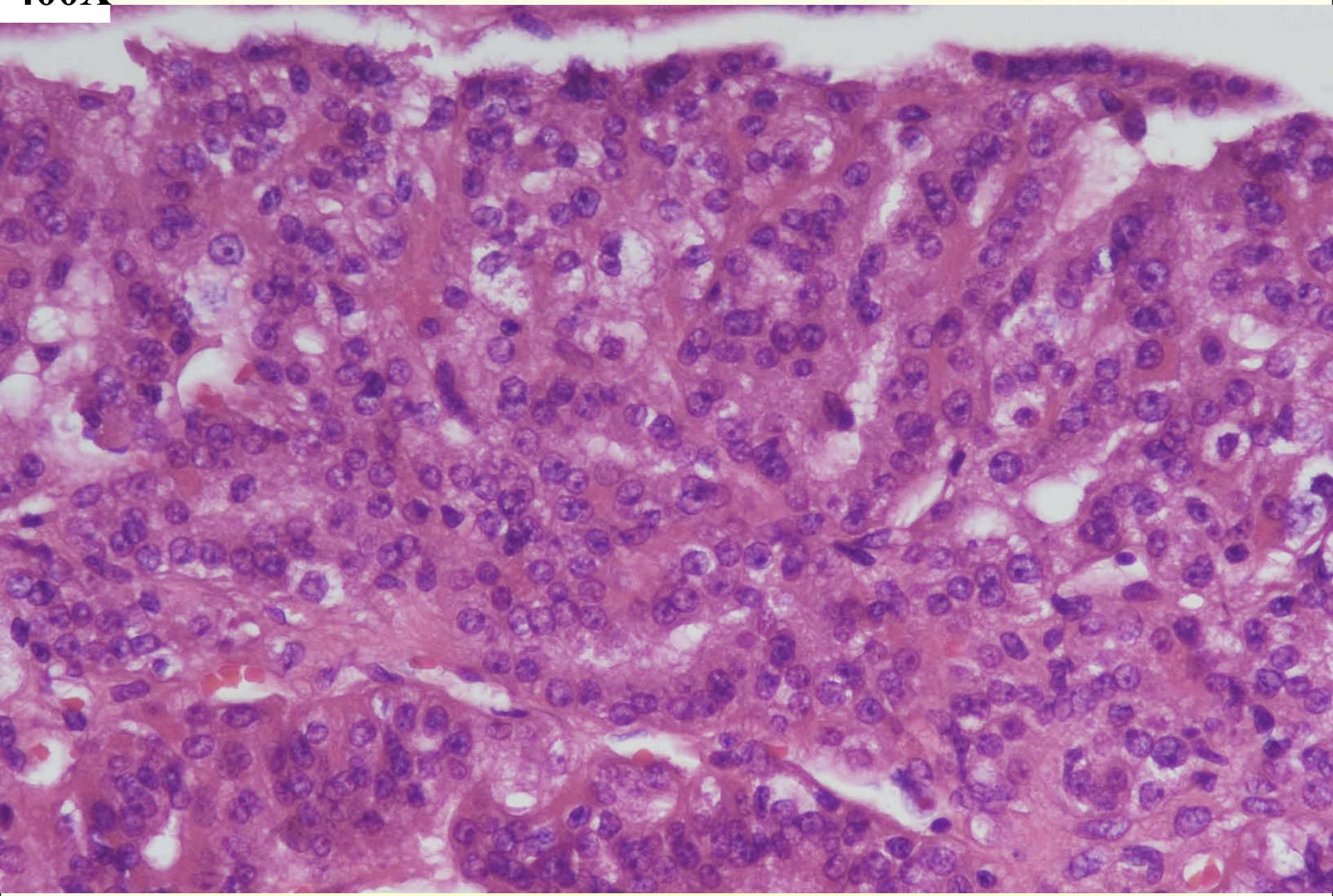

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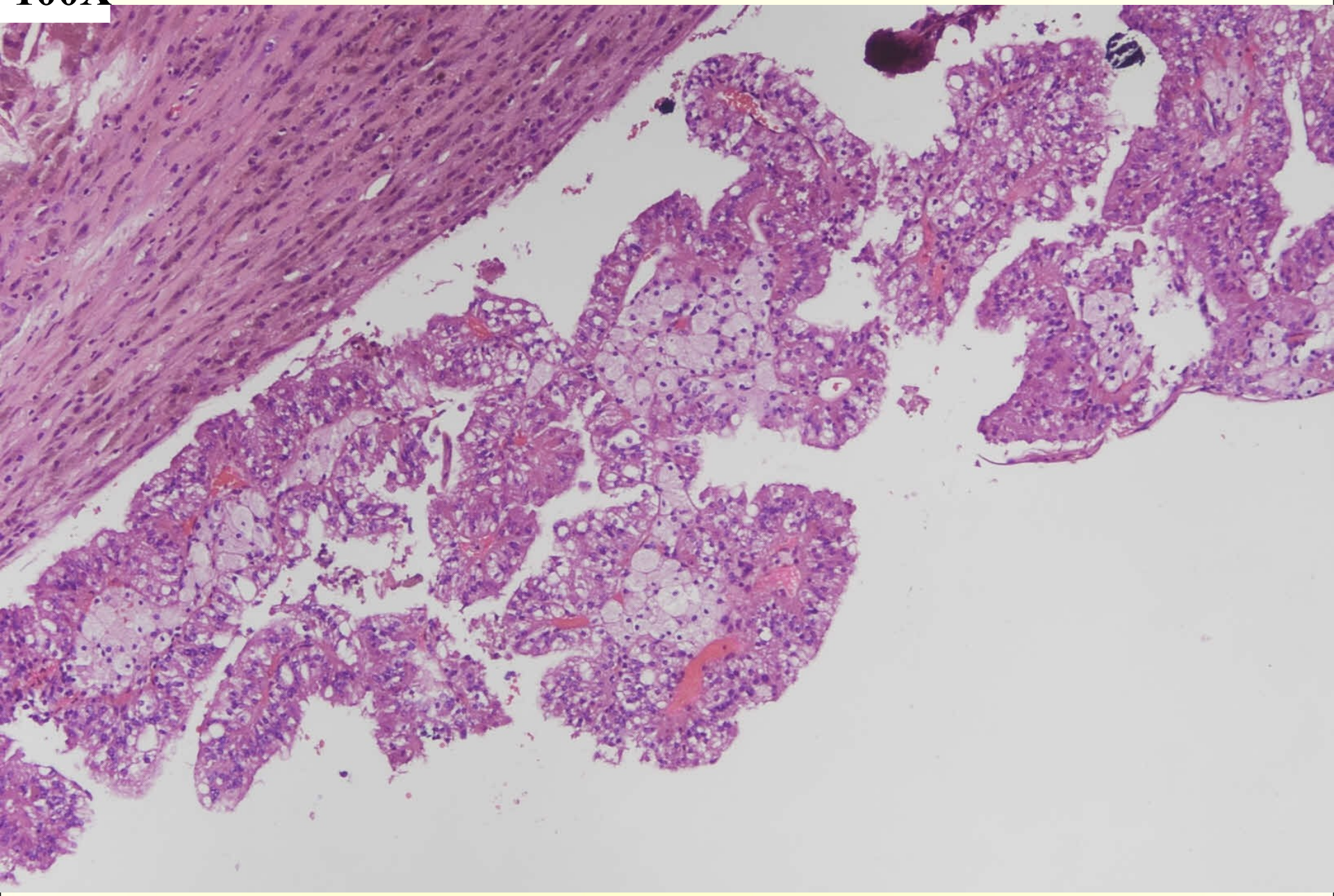

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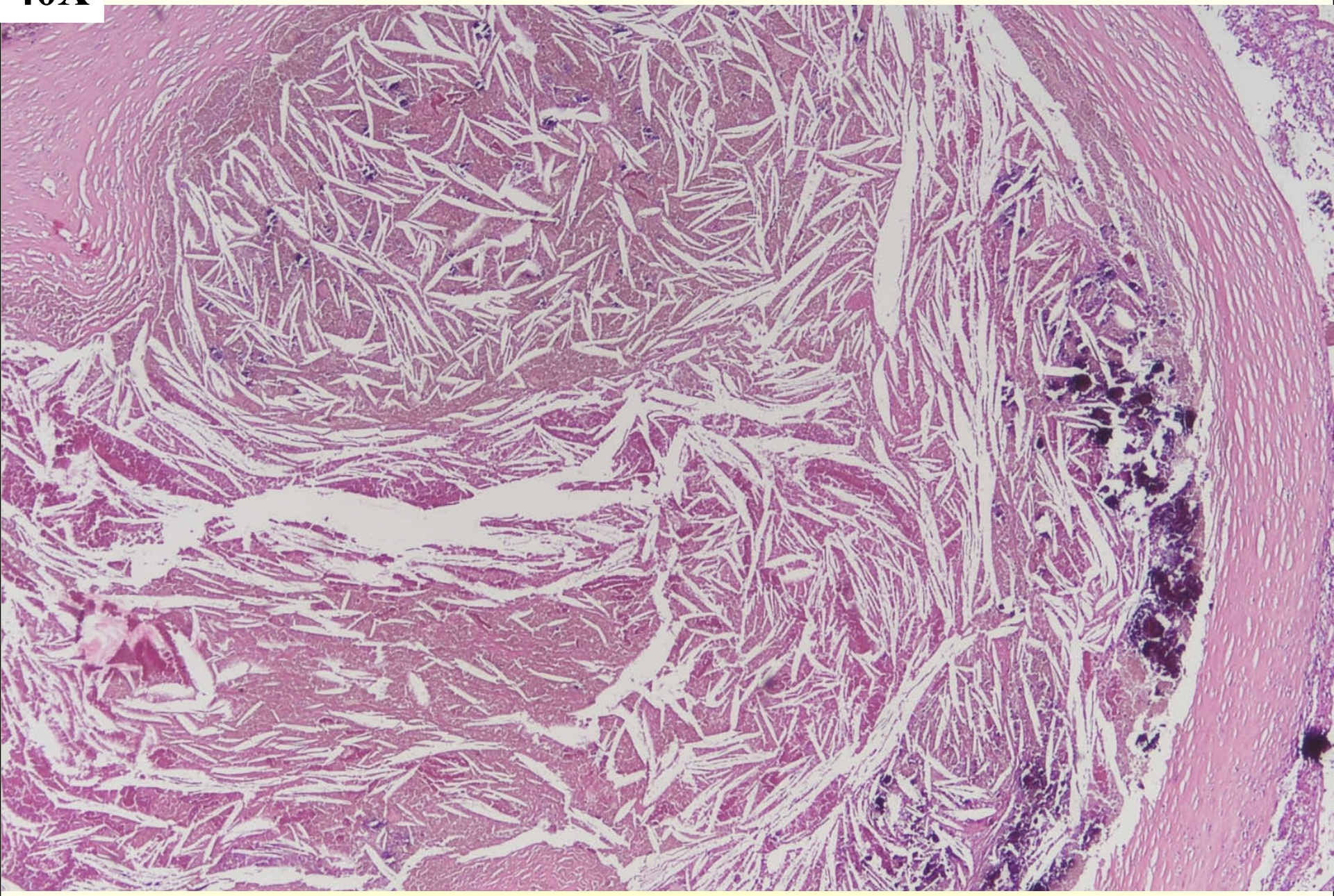

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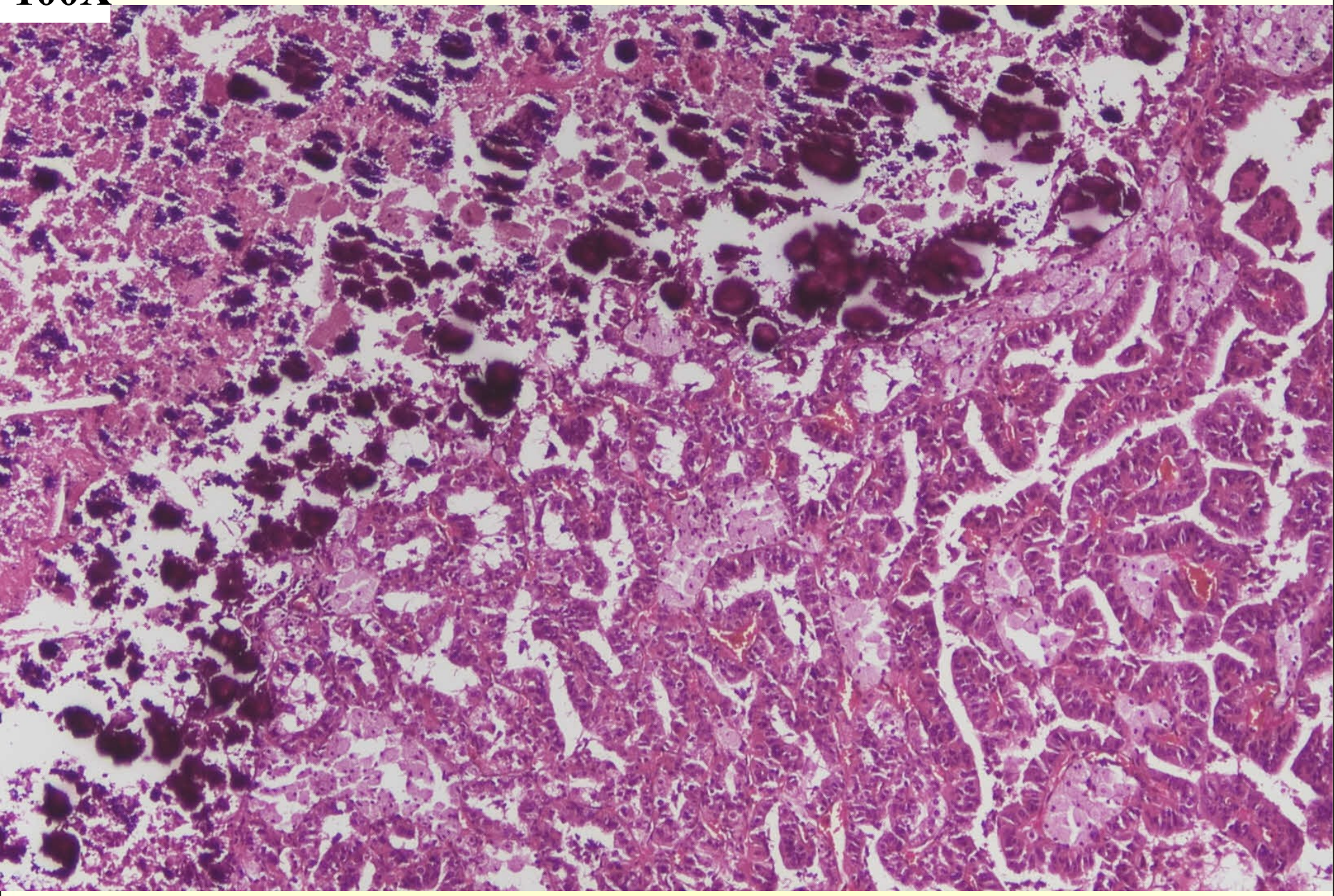


Summary of microscopic findings

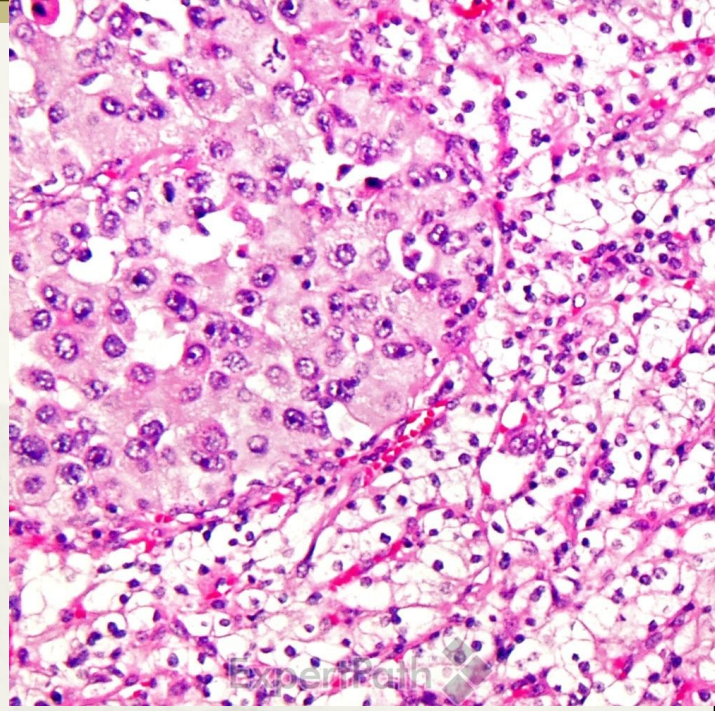
- Prominent papillary and/or solid nested growth patterns
- Epithelioid cells with abundant clear to granular eosinophilic cytoplasm, ISUP nuclear grade 3
- Psammomatous calcifications
- Tumor necrosis and hemorrhage

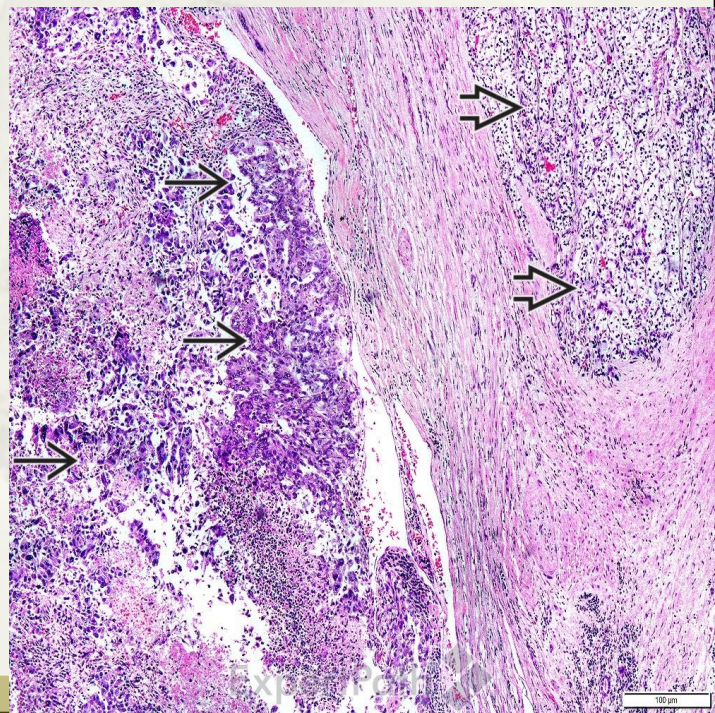
Differential diagnoses

- Clear cell renal cell carcinoma
- Papillary renal cell carcinoma
- MiT family translocation renal cell carcinoma
  - Xp11 translocation RCC
  - t(6; 11) RCC
- Clear cell papillary renal cell carcinoma
- Epithelioid angiomyolipoma

Clear cell RCC

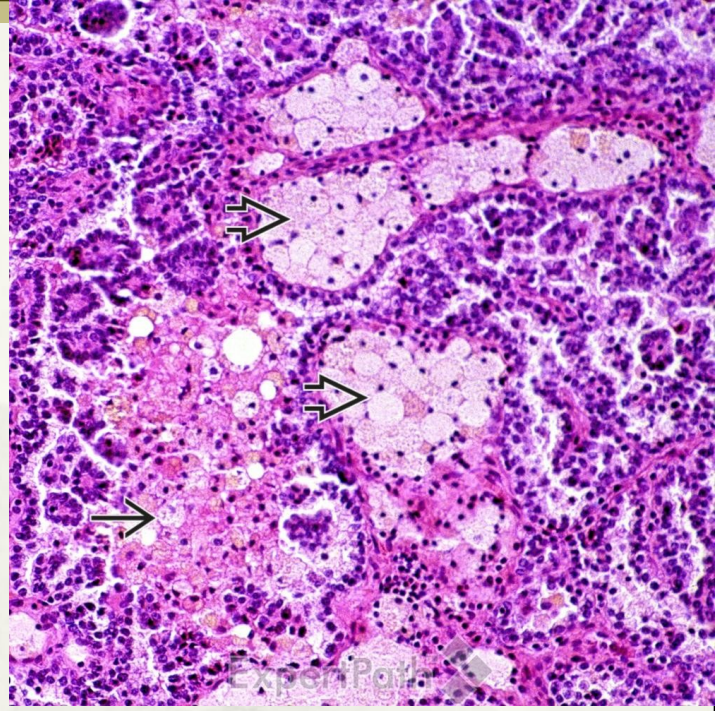
- Typically affect older adults
- Clear cells arranged in solid nests with delicate fibrovascular pattern
- High-grade cells with eosinophilic cytoplasm and papillae or pseudopapillae
- IHC: PanCK(+), CAIX(+)

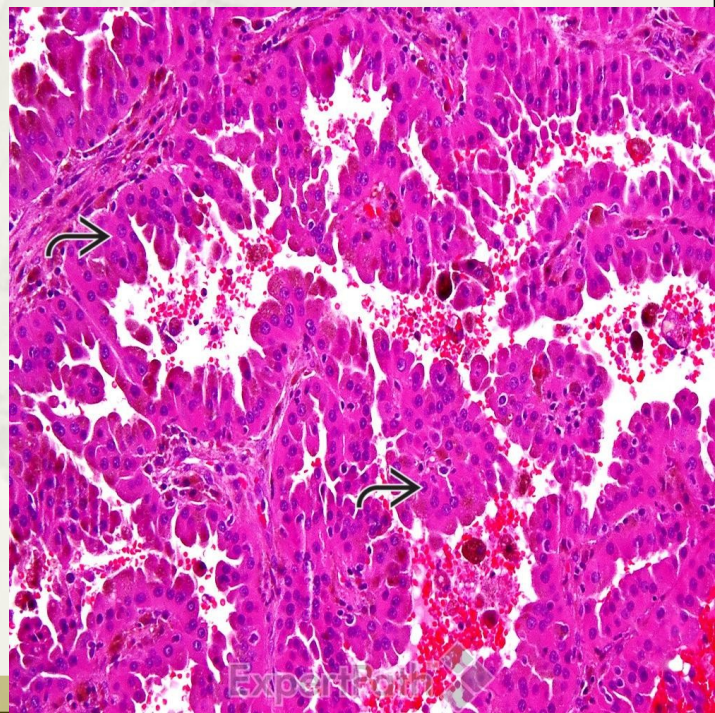




Papillary renal cell carcinoma

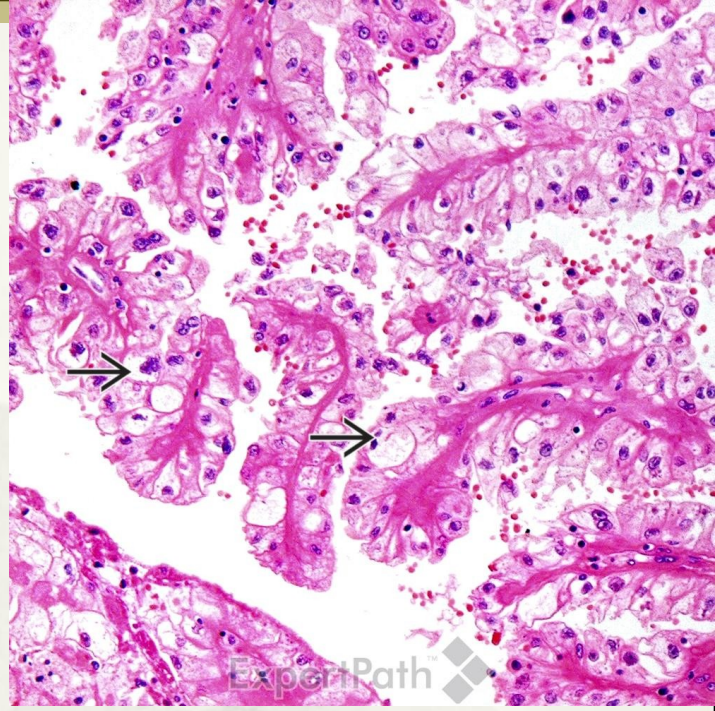
- **Predominant or exclusive papillary** architecture, with variable solid, tubular, and/or glomeruloid growth patterns
- Type 1: small, low cuboidal cells lining papillary structures which are stuffed by foamy macrophages
- Type 2: medium to large cells with eosinophilic cytoplasm and nuclear enlargement, pleomorphism, and pseudostratification
- **IHC** : PanCK(+), CK7(+), AMACR(+)

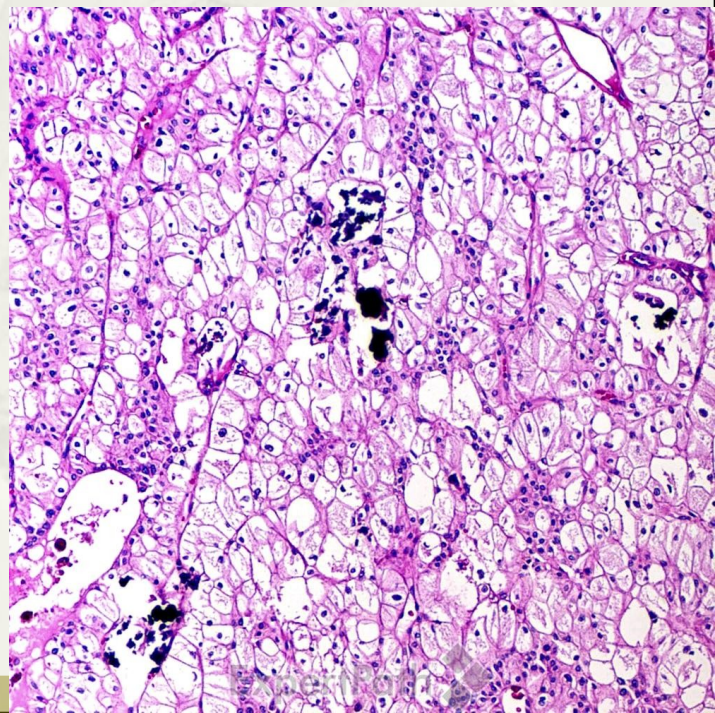




Xp11 translocation RCC

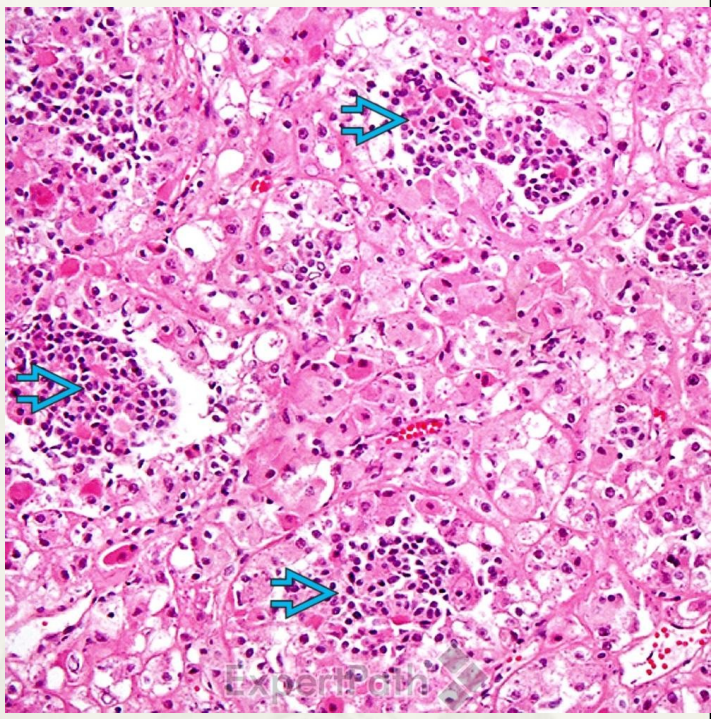
- Prominent papillary and/or solid nested growth patterns
- Epithelioid cells with abundant clear to eosinophilic/granular cytoplasm
- The nuclei are generally high grade
- Psammomatous calcifications
- IHC: PanCK(-/+), TFE3(+)
  - Highly sensitive and specific

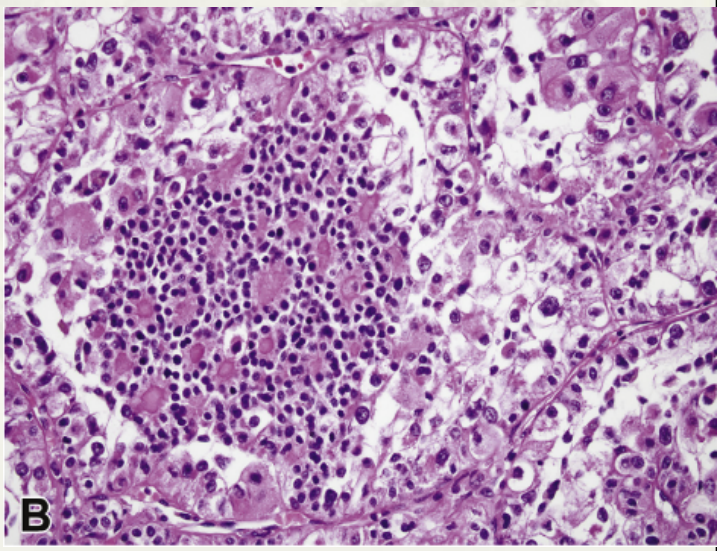




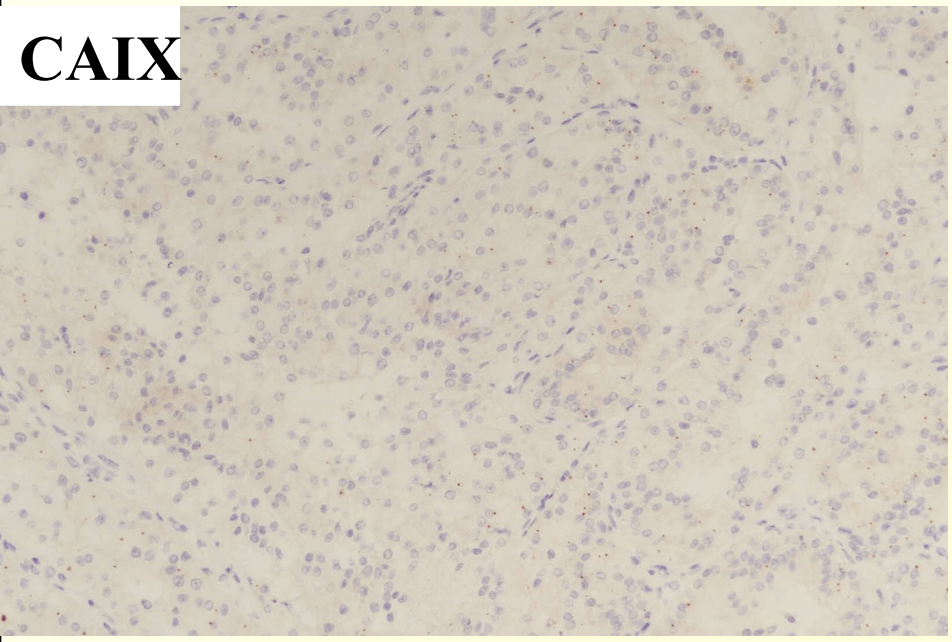
t(6; 11) RCC

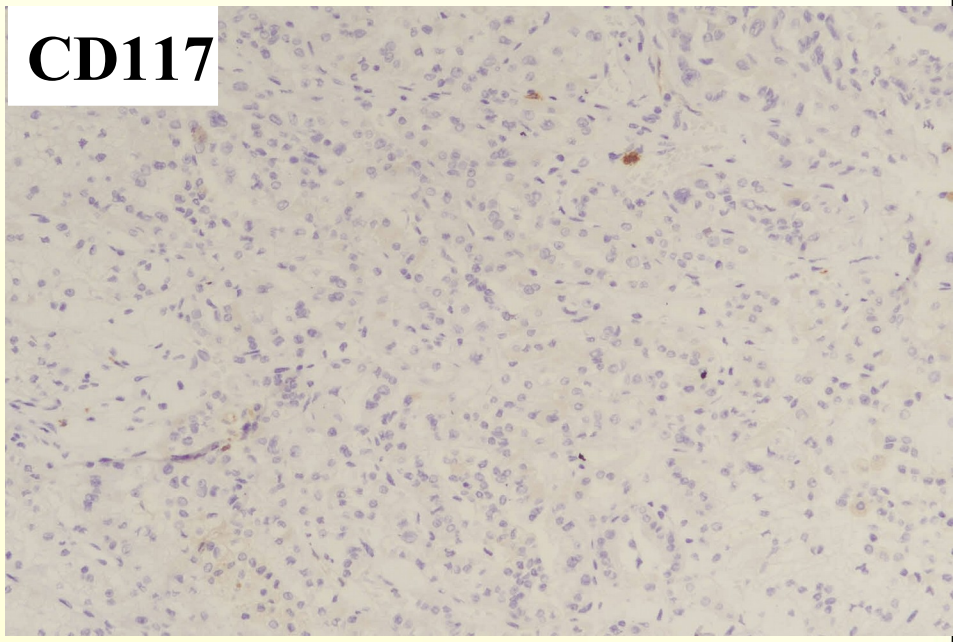
- Nests, sheets, and tubules
- Characteristic biphasic morphology
  - **Periphery**: Larger epithelioid cells
  - **Center**: Smaller cells clustered around hyaline basement membrane material
- IHC: TFEB(+), HMB-45(+), Melan-A(+)
- Break-apart FISH assays
  - Technical and fixation issues less common

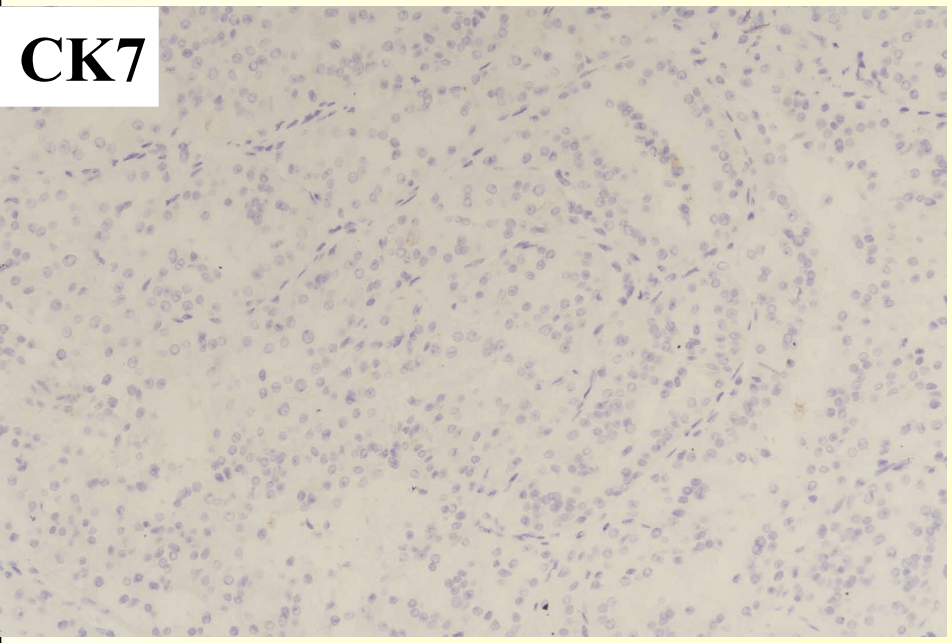


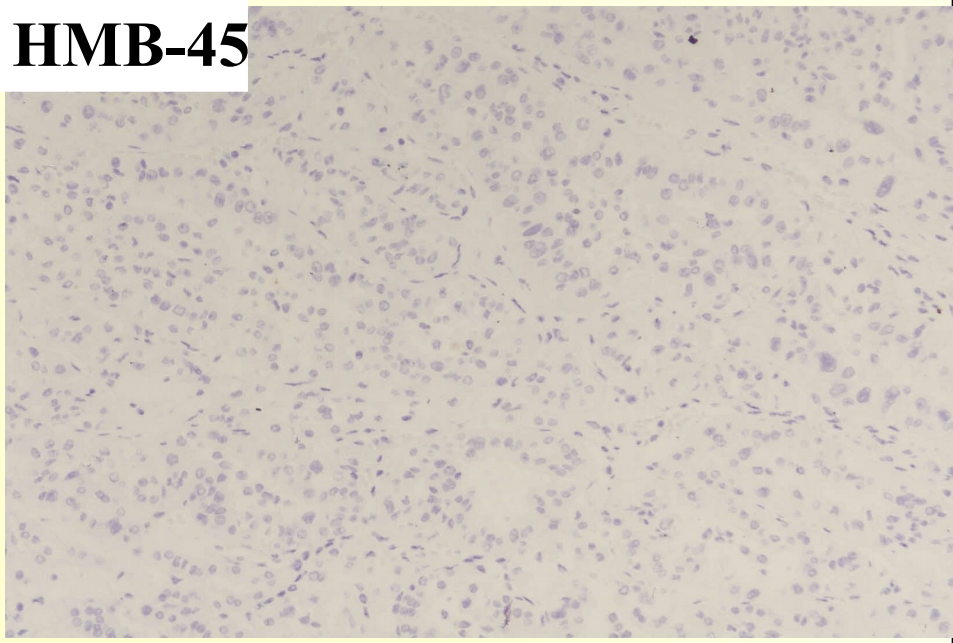


Immunohistochemistry

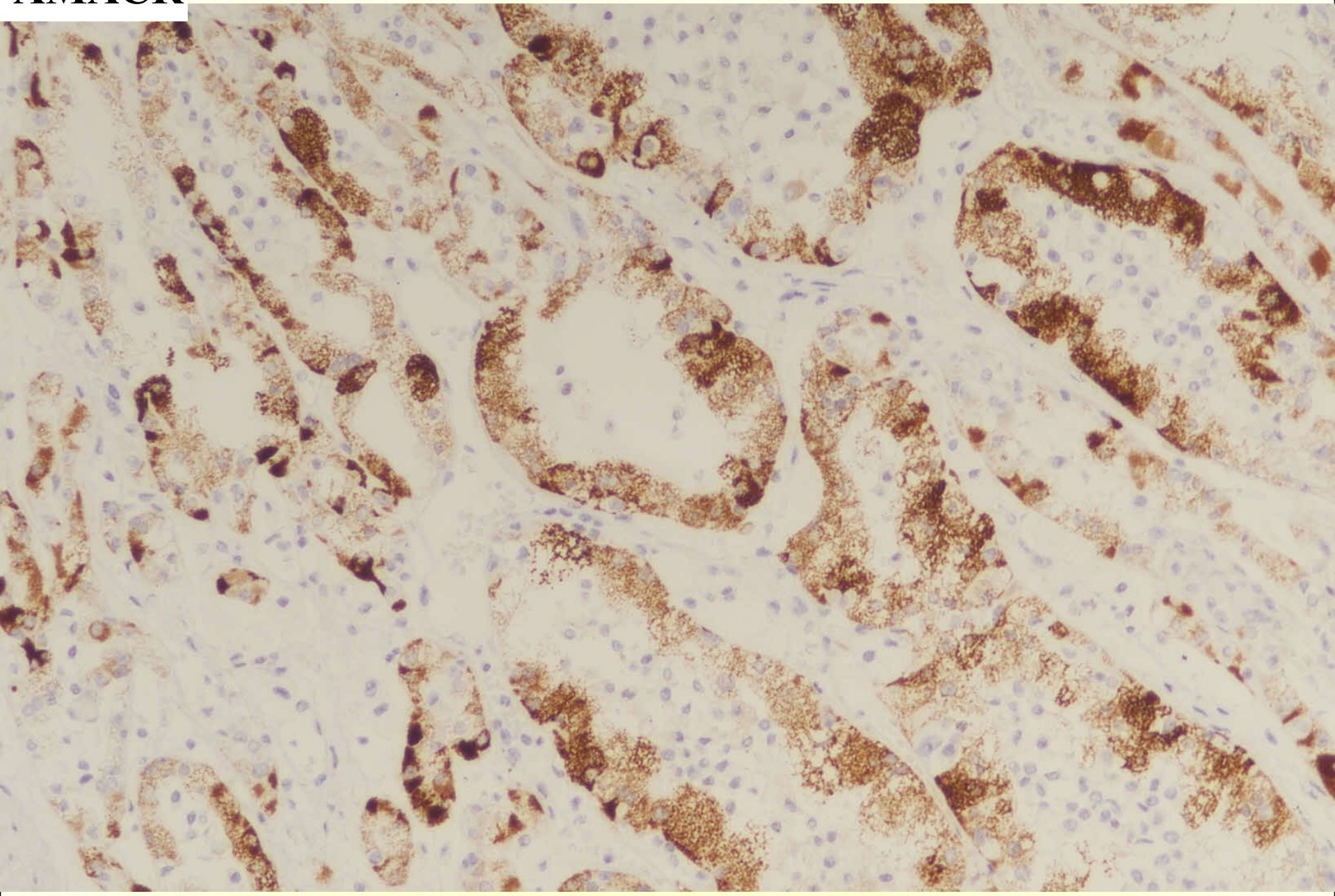

CAIX


CD117

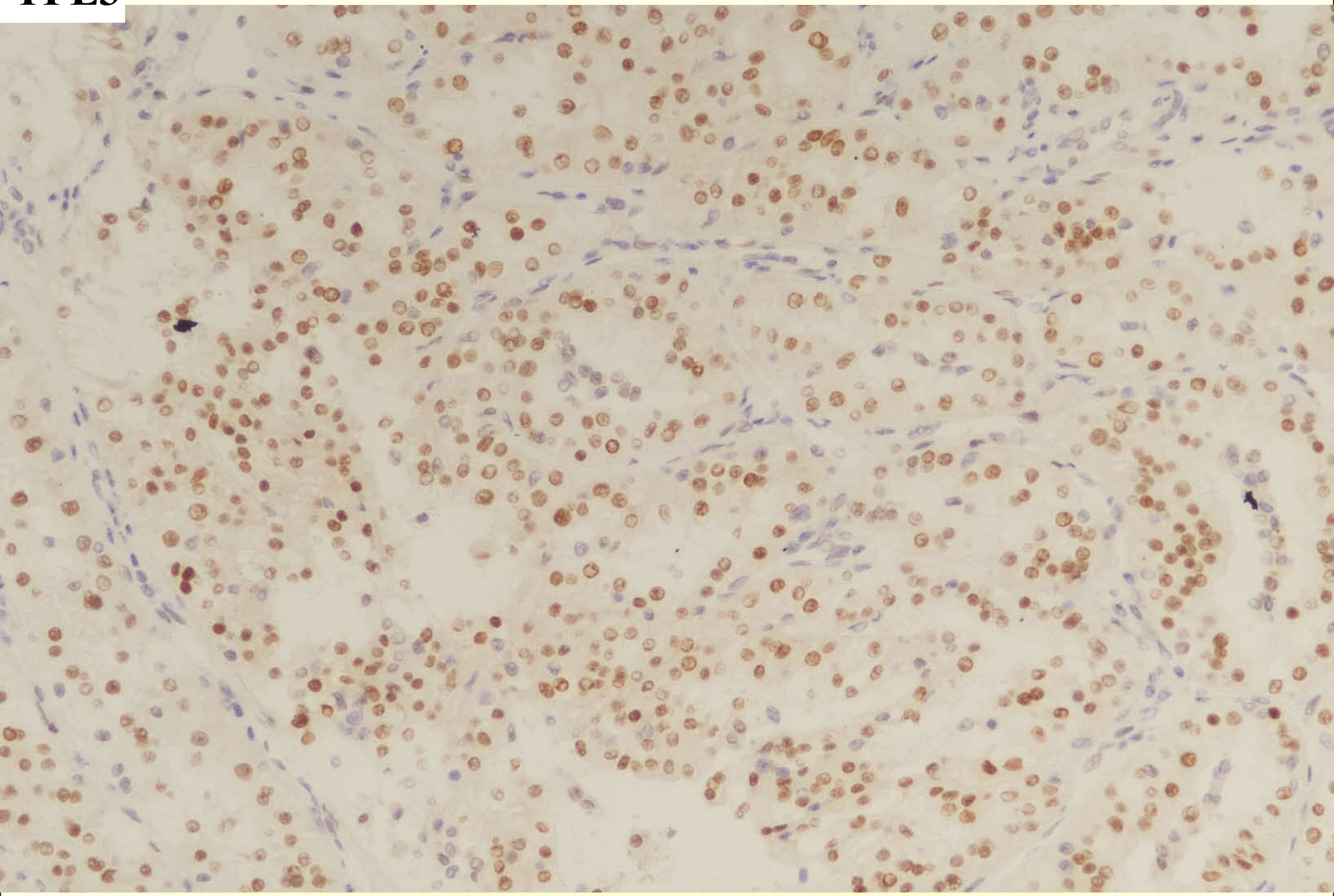

CK7


HMB-45

AMACR



TFE3



Final pathologic diagnosis

Compatible with MiT family translocation renal cell carcinoma (Xp11 translocation RCC), pT2bNX

Discussion

MiT family translocation renal cell carcinoma

Definition

- Microphthalmia transcription factor (MiT) family, including TFE3, TFEB, TFEC, and MiTF
  - Regulates differentiation in melanocytes and osteoclasts

- A relatively uncommon subtype of RCC
  - Characterized and defined by **gene fusions involving two members (*TFE3* and *TFEB*)** of the MiT family of transcription factors

MiT family translocation renal cell carcinoma

Xp11 translocation RCC

- ***TFE3* gene fusion**
- *TFE3* gene localized to chromosome Xp11.2
  - ***ASPSCR1*-*TFE3***; t(X; 17)(p11.2; q25)
  - ***PRCC*-*TFE3***; t(X; 1)(p11.2; q21)
  - **NONO, CLTC, SFPQ**

t(6; 11) RCC

- ***TFEB* gene fusion**
- *TFEB* gene localized to chromosome 6p21
  - ***MALAT1*-*TFEB*** fusion; t(6;11)(p21;q12)

The fusion genes result in overexpression of *TFE3* or *TFEB* protein which become detectable by IHC

Risk factor : Post-chemotherapy

- 15% of patients associated with prior **exposure to cytotoxic chemotherapy**
  - Either DNA topoisomerase II inhibitor (eg, etoposide) &/or alkylating agent (eg, cisplatin)
  - Disease occurs 2 to 14 years after exposure

Epidemiology

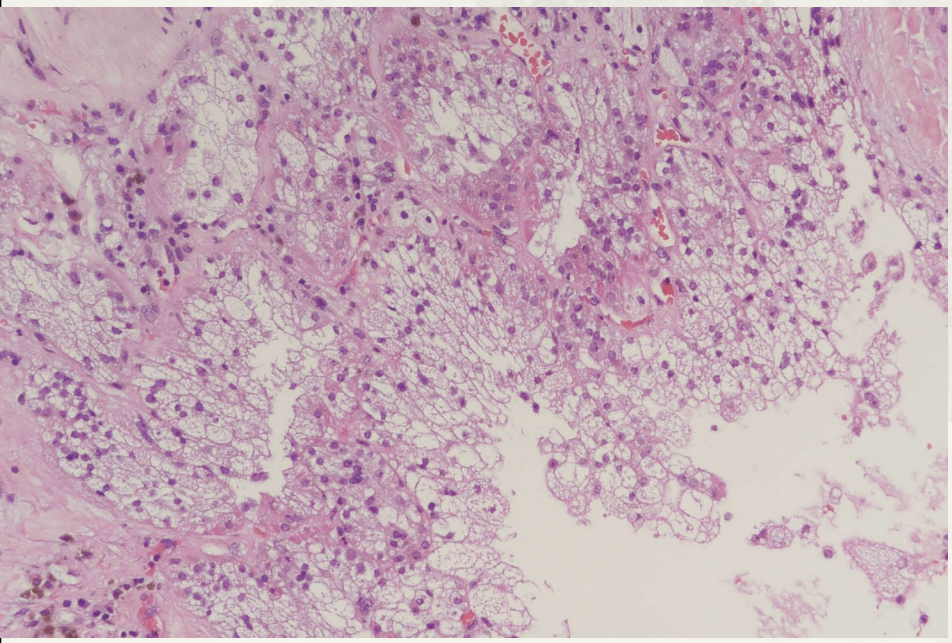
- **Xp11 translocation RCC**
  - Among children:
    - About 40% of RCC in children
  - In adults:
    - Reported 1.6 to 4% of all RCCs in adults
    - Absolute total number in adults still much > in children
      - Approximately 10 new pediatric and 1260 new adult cases each year in the United States

- **t(6;11) RCCs** less common than Xp11 translocation RCC
  - About 50 cases reported in literature
  - Age range: 3-68 yr (median: 31 yr)

In VGHKS

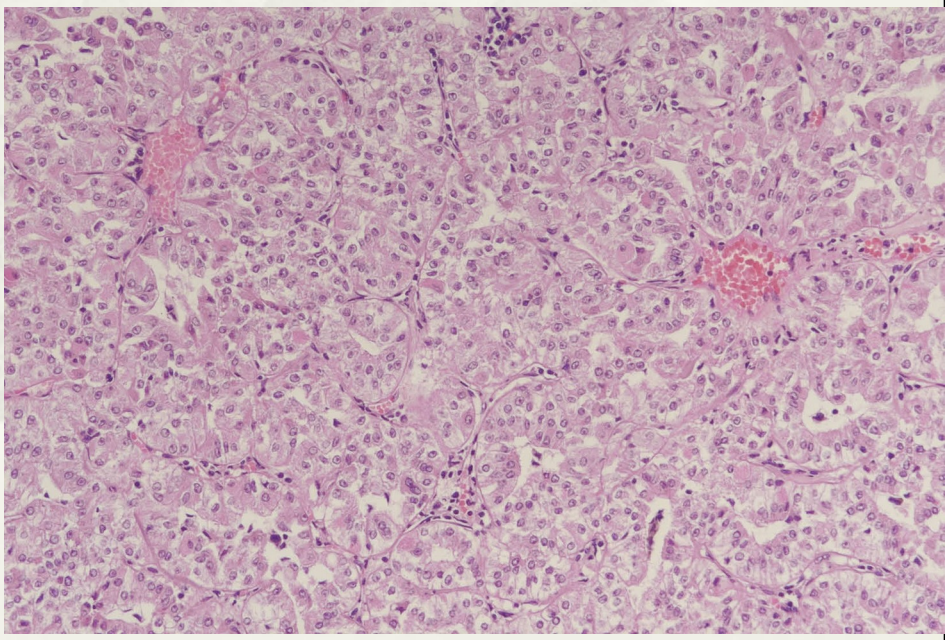
04-27190

46 y/o F, abdominal fullness and RLQ palpable mass



05-16235

46 y/o M, incidentally found renal tumor when colon cancer staging



Xp11 translocation RCC

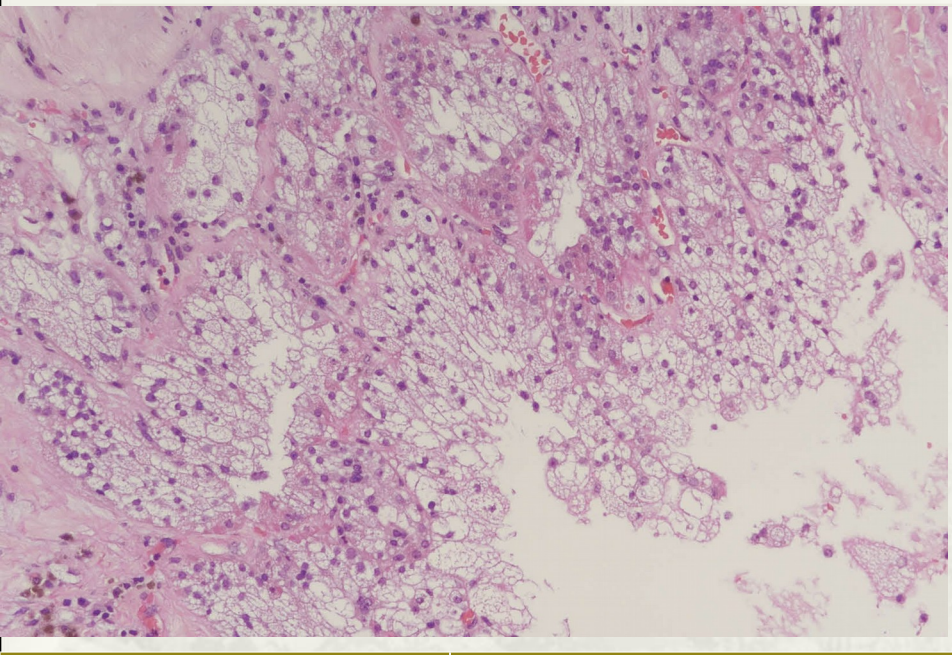
The fusion subtypes often have characteristic features and impact presentation

	ASPSCR1-TFE3	***PRCC-TFE3***
Architecture	Papillary, solid alveolar	Nested, acinar
Cytoplasm	Voluminous	Less abundant
Nuclear grade	Usually higher	Usually lower
Psammoma bodies	Abundant	Uncommon
Regional LN mets	More	Less

Most of the node-positive *ASPSCR1-TFE3* RCC remained disease-free without adjuvant therapy. Hence, **locally advanced stage may not predict adverse outcomes**.

Xp11 translocation RCC

04-27190



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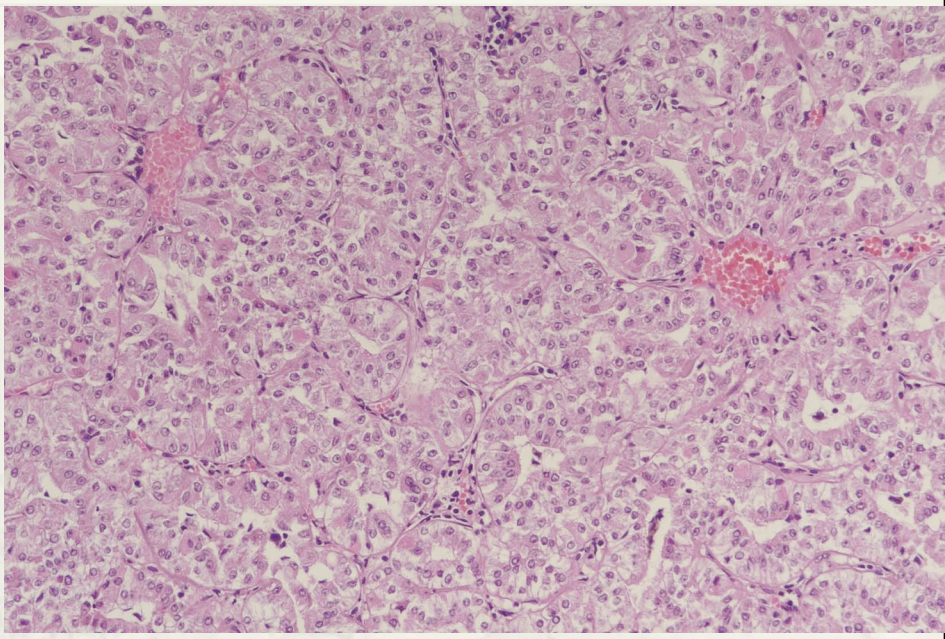

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Treatment

- Reported cases managed similar to conventional RCC
- The mainstay of treatment for **remains surgical**
- Most of the **node-positive** *ASPSCR1-TFE3* RCC **remained disease-free without adjuvant therapy**

- Associated with upregulation of MET, a tyrosine kinase receptor that drives oncogenesis
- MET inhibitors now in clinical trial for patients with advanced carcinoma
- Other targeted therapy: VEGF or mTOR inhibitors

Prognosis: Xp11 translocation RCC

- Among children
  - Usually present at advanced stage
  - **In spite of locally advanced presentation**, including lymph node metastasis, clinical behavior **usually less aggressive**

- In adults
  - Clinical course **more aggressive**, with multiple reported deaths due to disease

  - Overall, survival is similar to clear cell RCC
  - Potential to metastasize late (8-30 yr after diagnosis)
  - Only **distant metastasis** and **older age** at diagnosis independently predict death

Prognosis: t(6; 11) RCC

- **More indolent** neoplasms
  - Of the reported 50 cases, only 4 developed metastasis, and death in 3 cases
  - Most presented a t a low stage (pT1 or pT2)

Back to our patient

- According to the morphology, Xp11 translocation RCC with *ASPSCR1-TFE3* gene fusion should be considered
  - Still need molecular confirmation
- No adjuvant therapy after operation
- Follow-up CT: No evidence of recurrence

Summary: Pathology

- A rare subtype of RCC with gene fusions involving two members of the MiT family of transcription factors
  - Xp11 translocation RCC: *TFE3* gene fusion
  - t(6; 11) RCC: *TFEB* gene fusion
- Renal tumors with high-grade epithelioid cells with voluminous cytoplasm should always raise differential diagnostic consideration
  - The possibility is particularly high in younger patients

Summary: Clinical

- **Prognosis:**
  - Adults worse than children
  - Xp11 translocation worse than t(6; 11)
  - Only distant metastasis and older age at diagnosis independently predict death
- **Treatment:**
  - Mainstay is surgery
  - The agents in conventional RCC may be ineffective
  - Target therapy is on clinical trials
  - Follow-up is warranted due to potential to metastasize late

Thanks for your listening !!