Sociedade Brasileira de Patologia

# Caso do mês

# Junho/2016

# Caso 2

**Camila Lucas Bandeira**

A.C.Camargo Cancer Center

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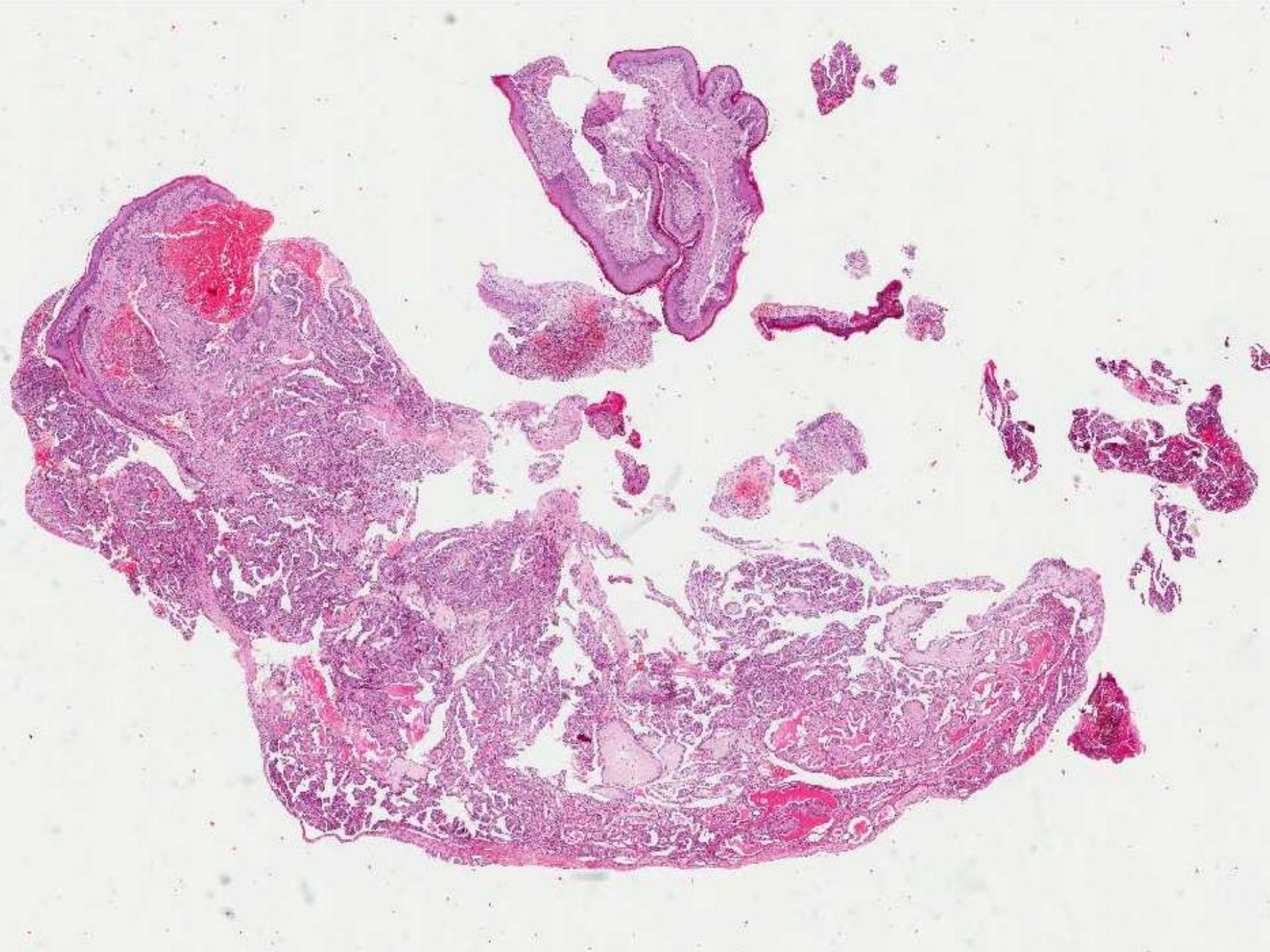
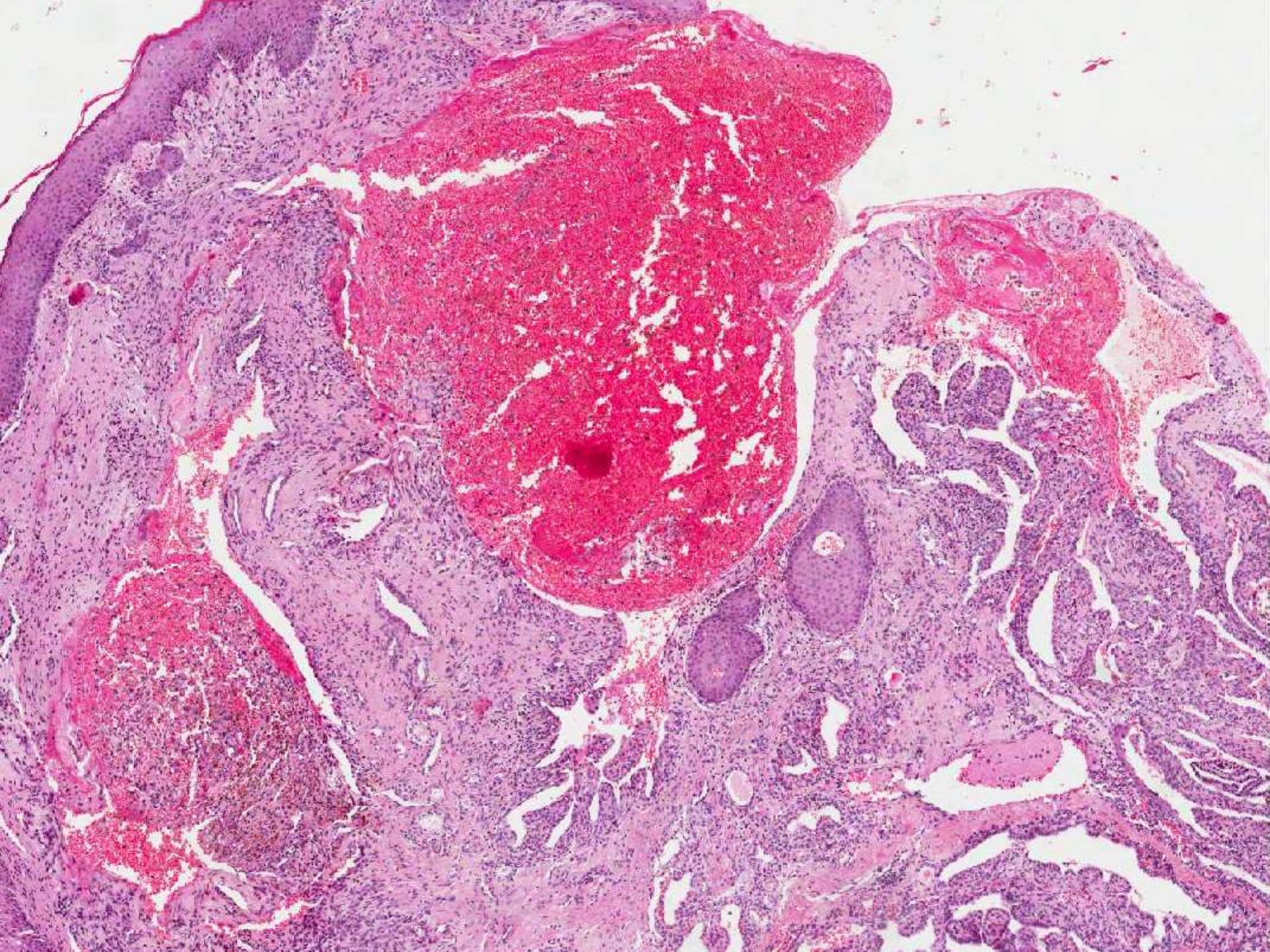
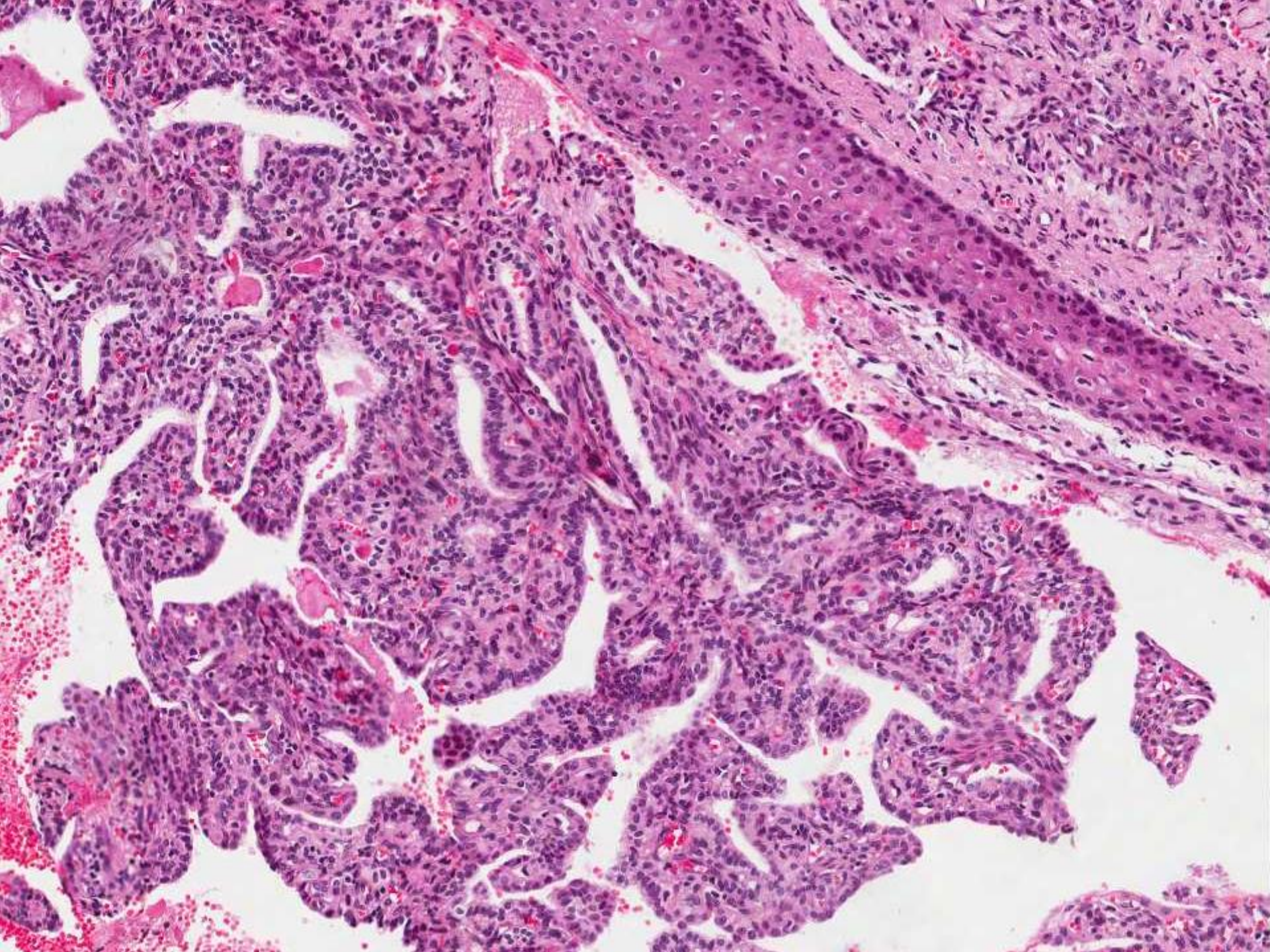
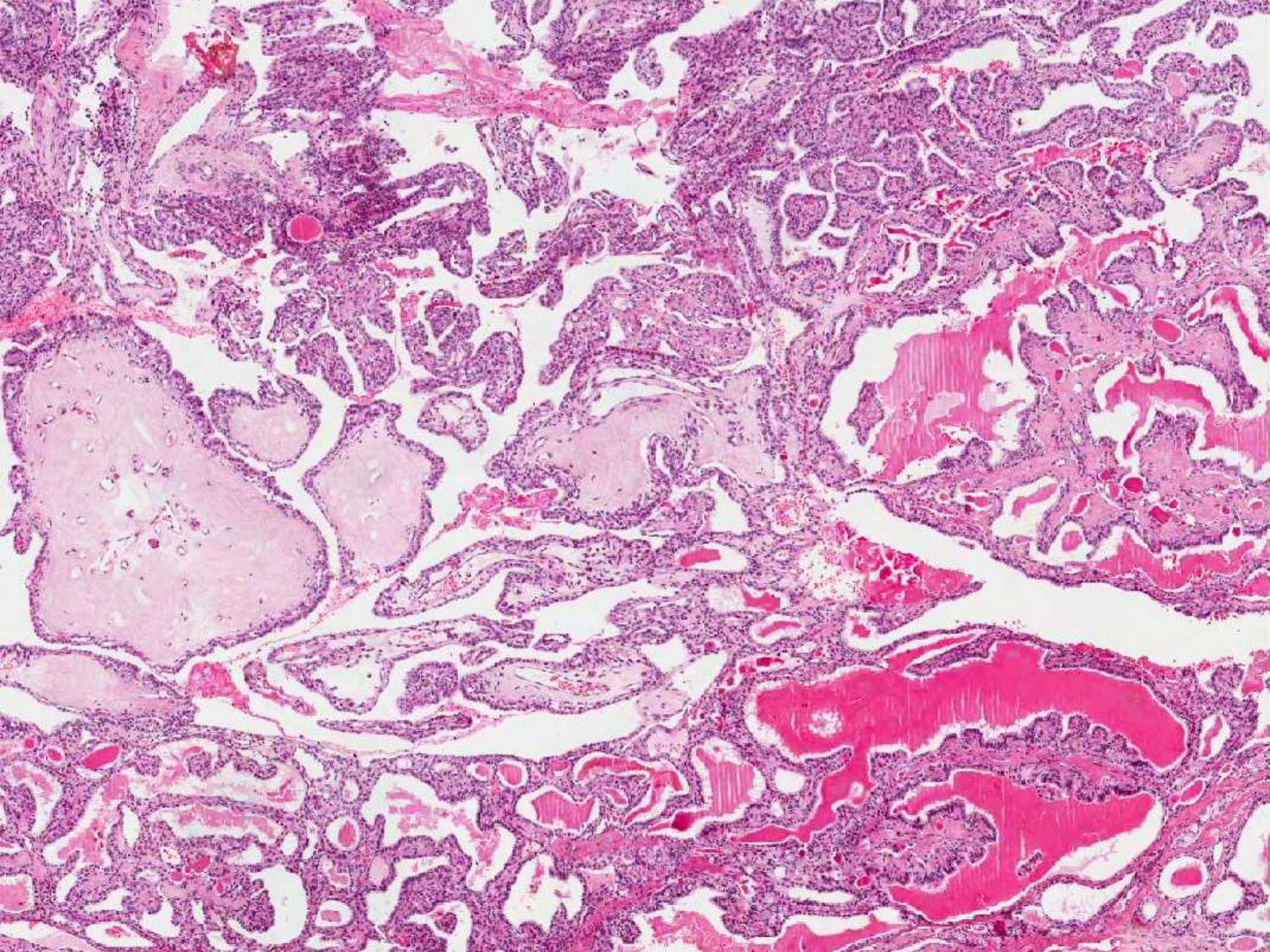
## DADOS CLÍNICOS

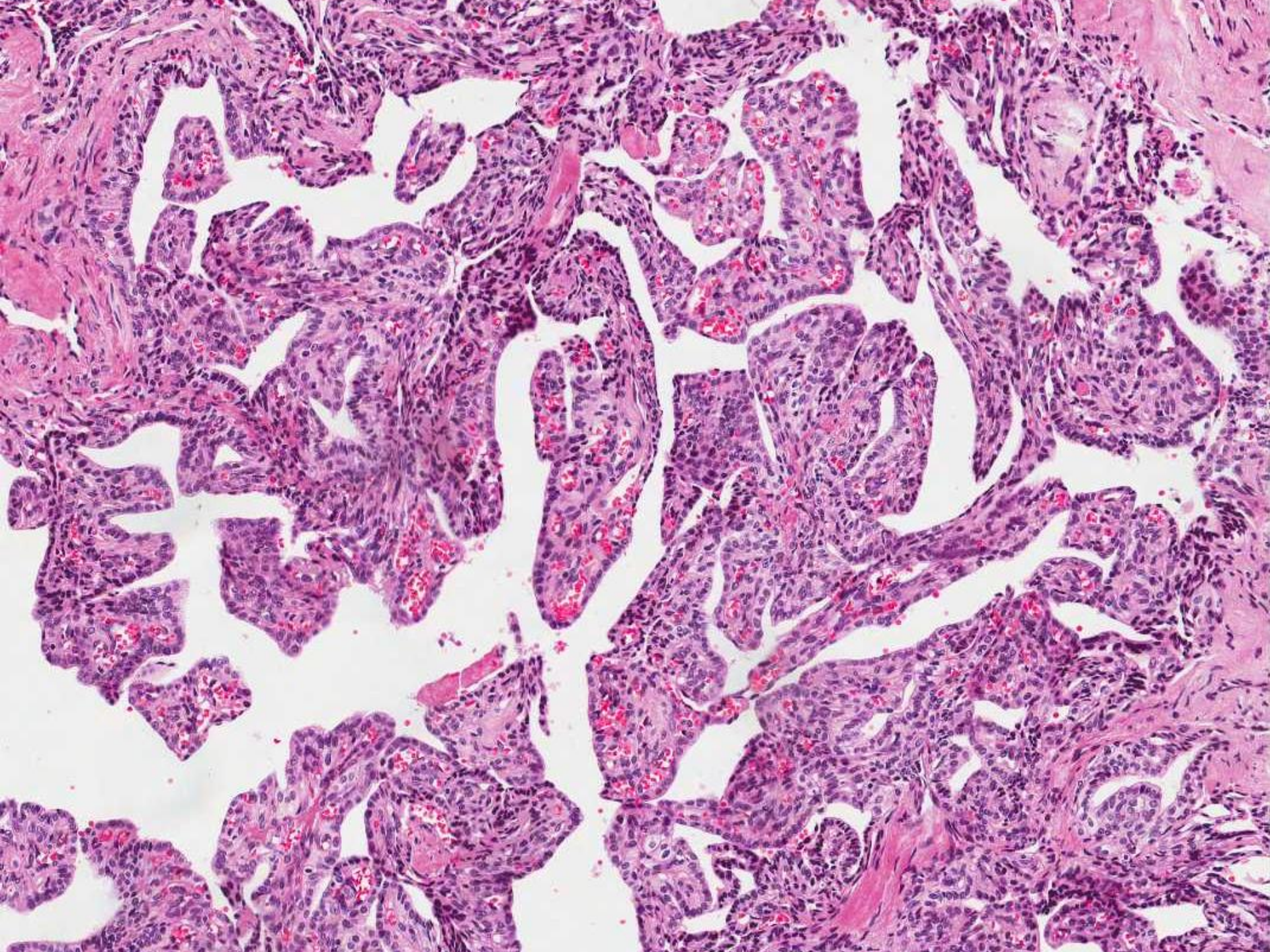
- Feminino, 25 anos, tumor em ângulo ponto-cerebelar
- História de ressecção de tumor em fossa posterior aos 13 anos
- Material proveniente da ressecção atual (recidiva).

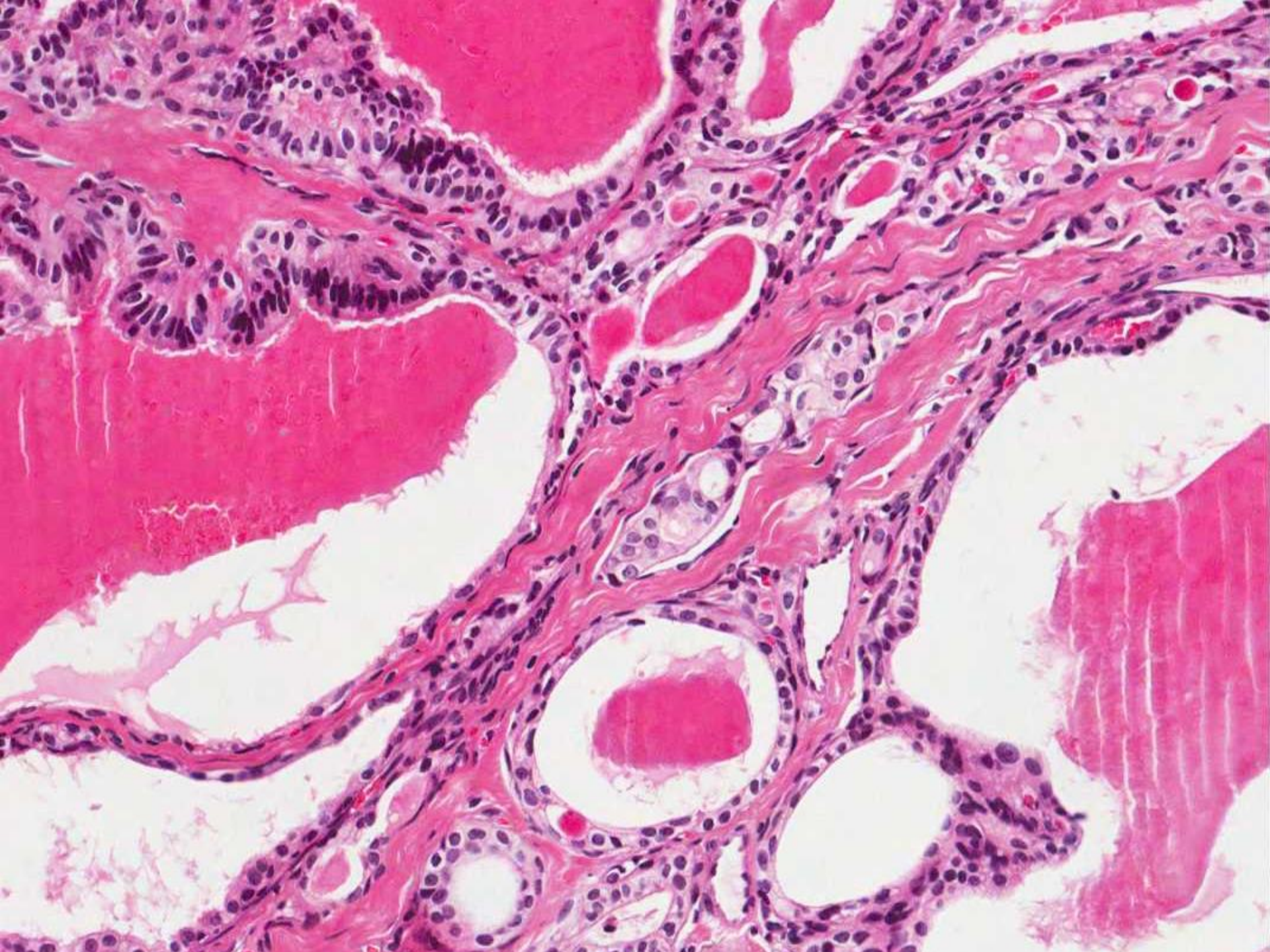


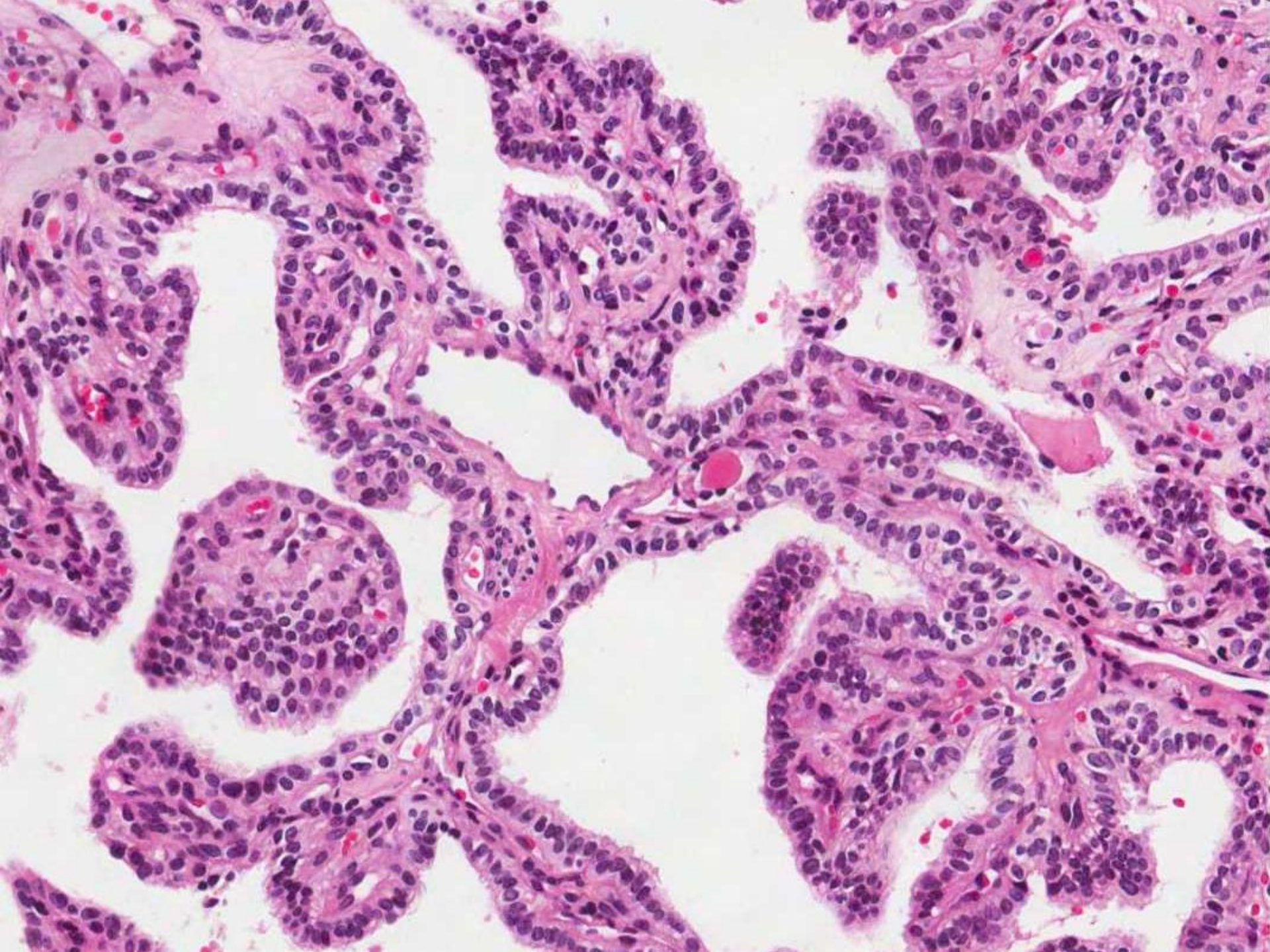


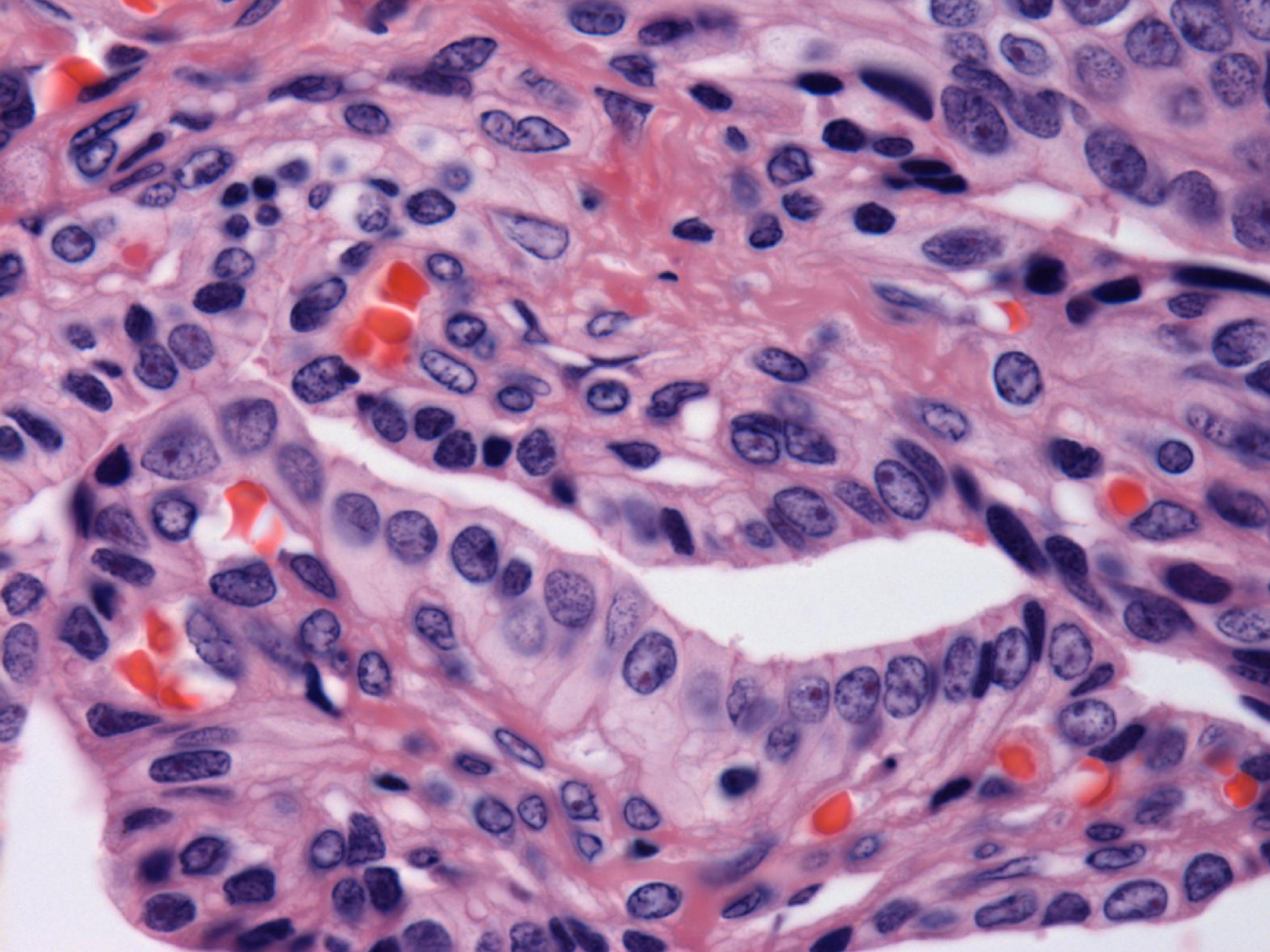


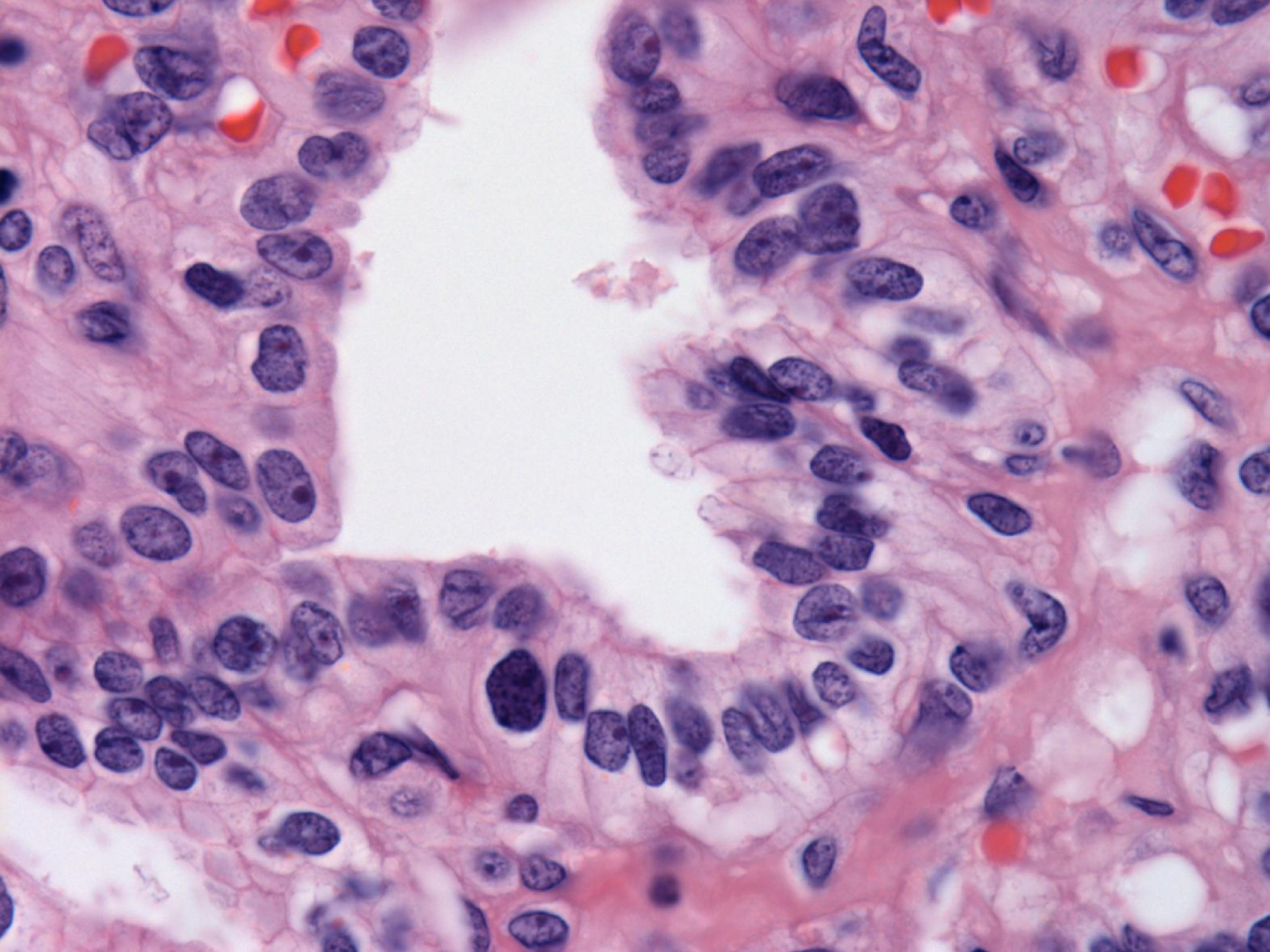


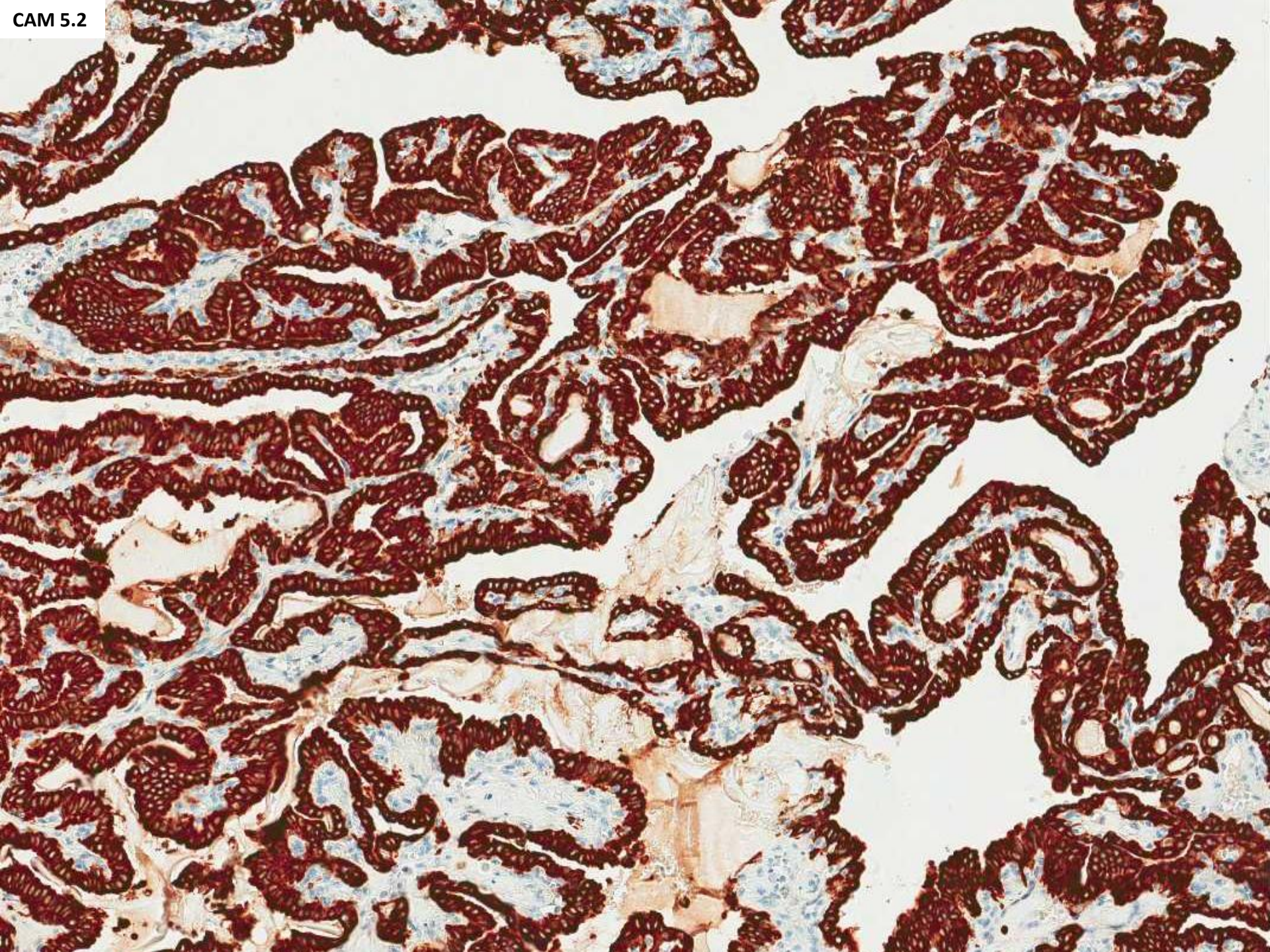








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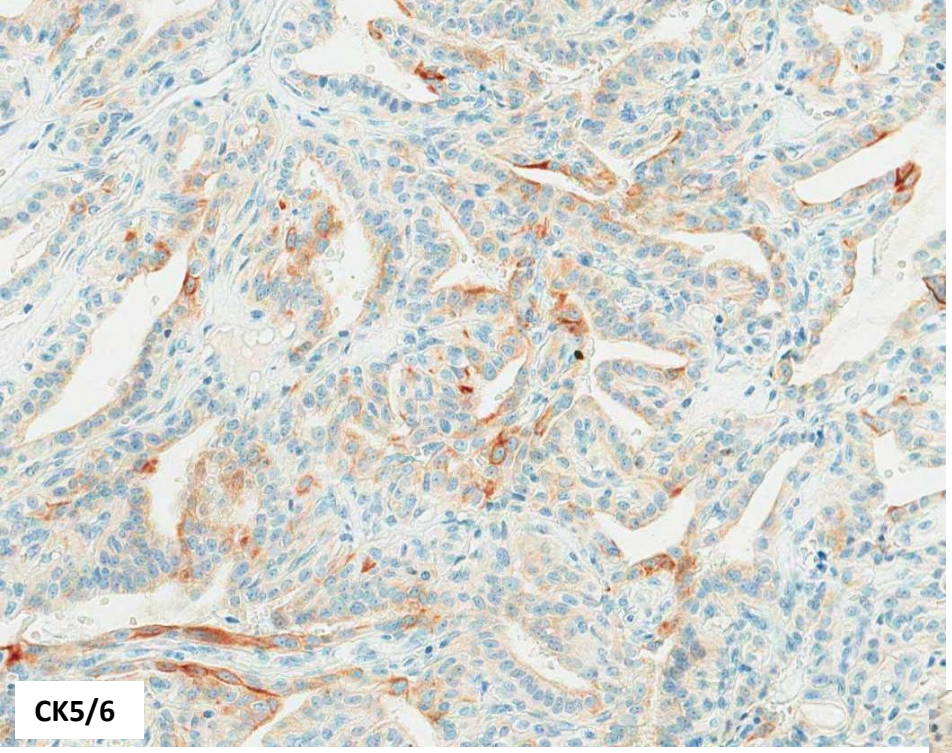
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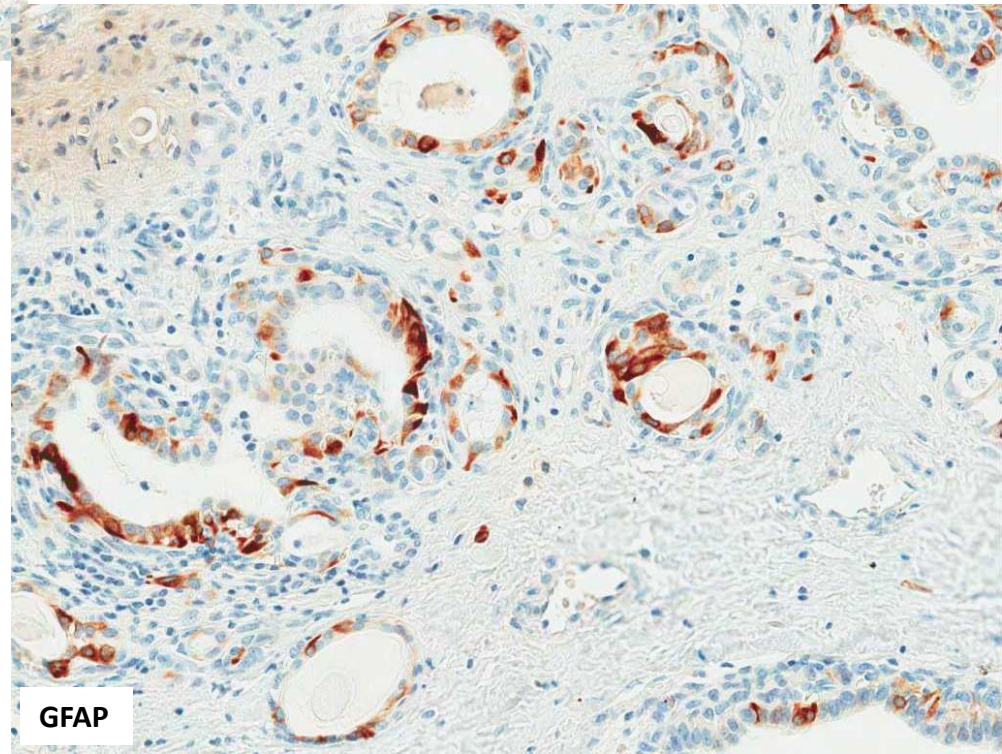
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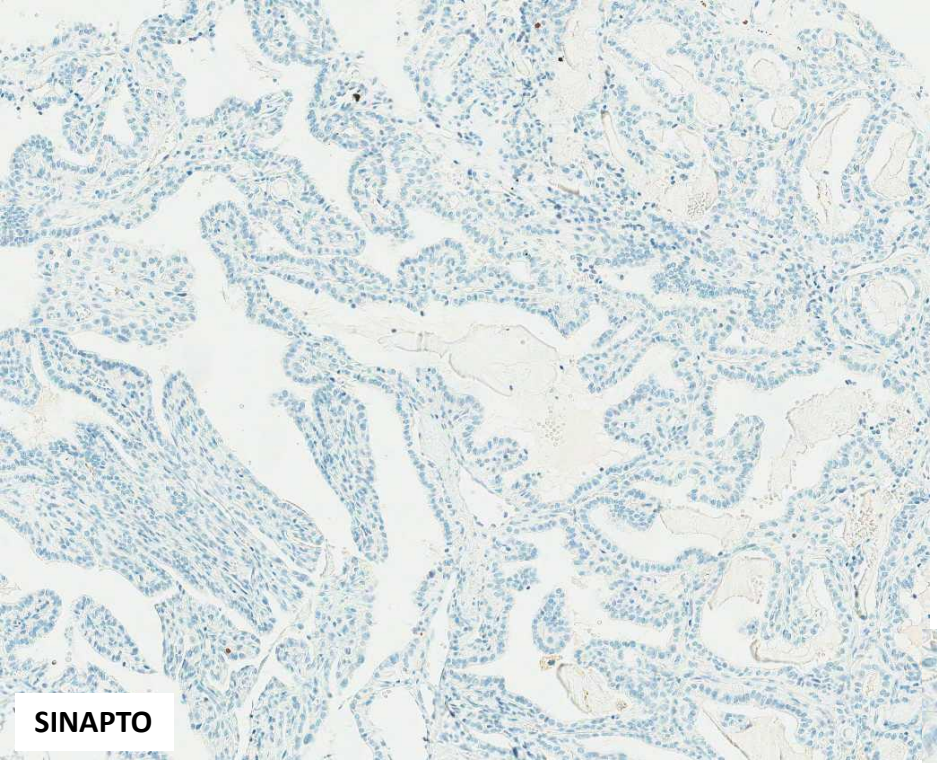
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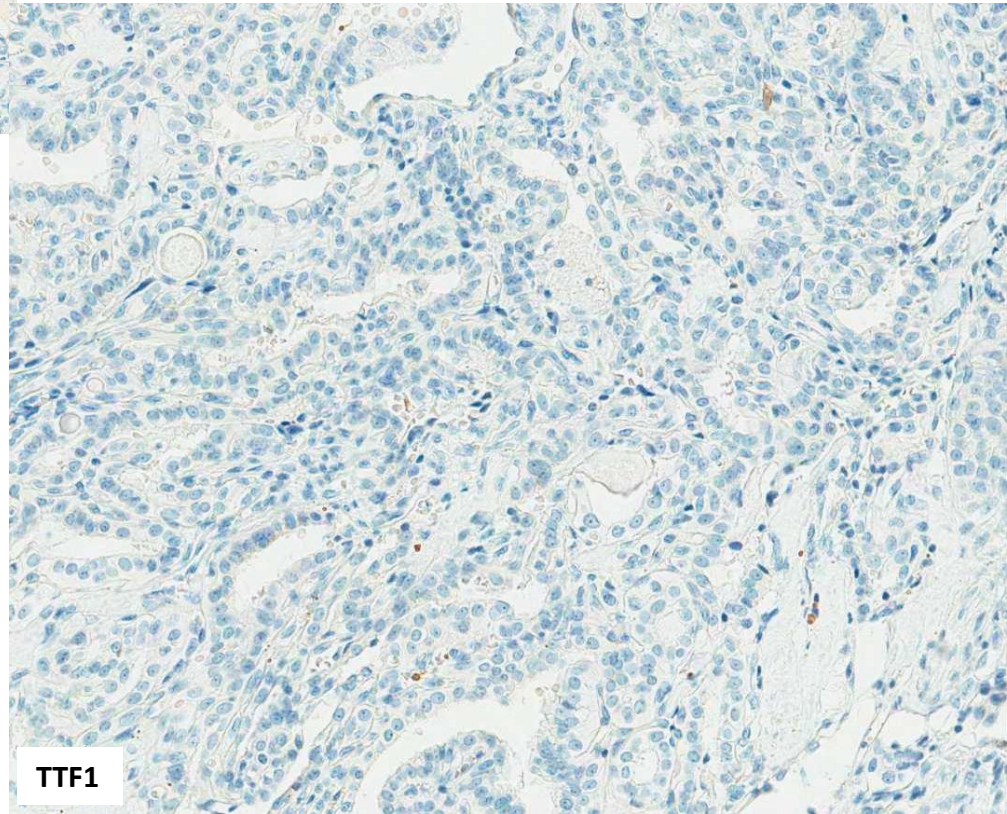
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DIAGNÓSTICO FINAL:

**TUMOR DO SACO ENDOLINFÁTICO**

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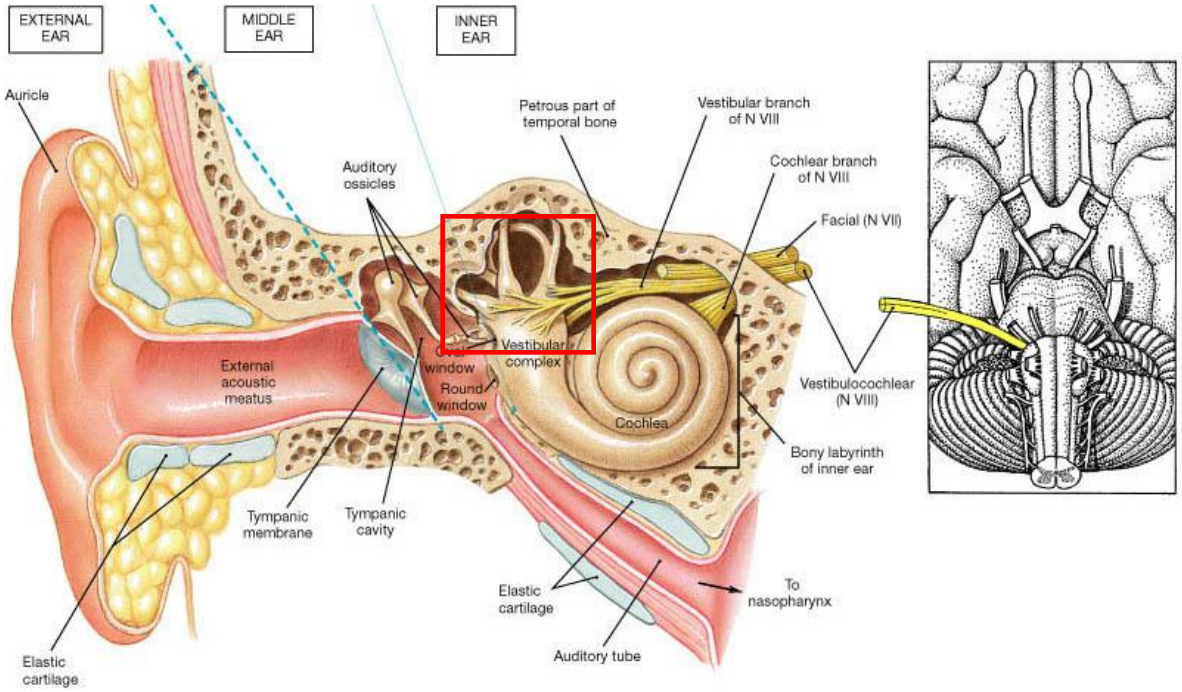
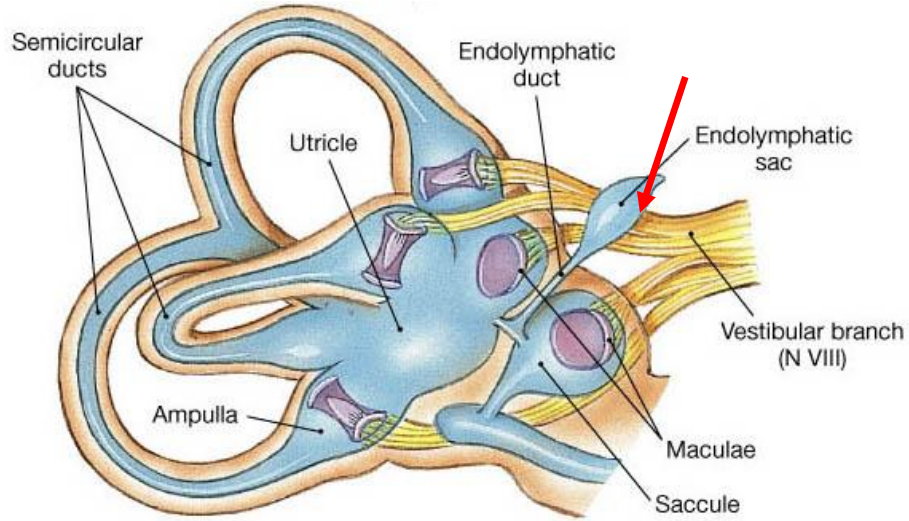
# TUMOR DO SACO ENDOLINFÁTICO

- Hassard et al, 1984
- Heffner, 1989 (20 casos):
  - Adenocarcinoma de baixo grau
  - Saco do osso temporal (= saco endolinfático)
- Adenocarcinoma de baixo grau de origem em saco endolinfático; Tumor de Heffner
- Raro; crescimento lento
- Localização: ângulo ponto-cerebelar/orelha interna




**(a) Vestibular complex (anterior view)**

Fonte: www.studyinukraine.eu/

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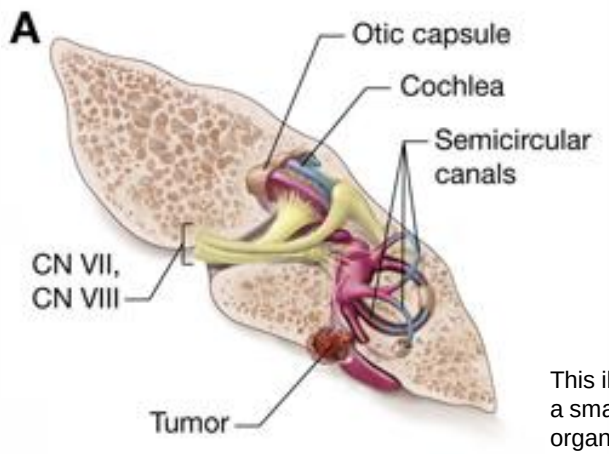
# TUMOR DO SACO ENDOLINFÁTICO

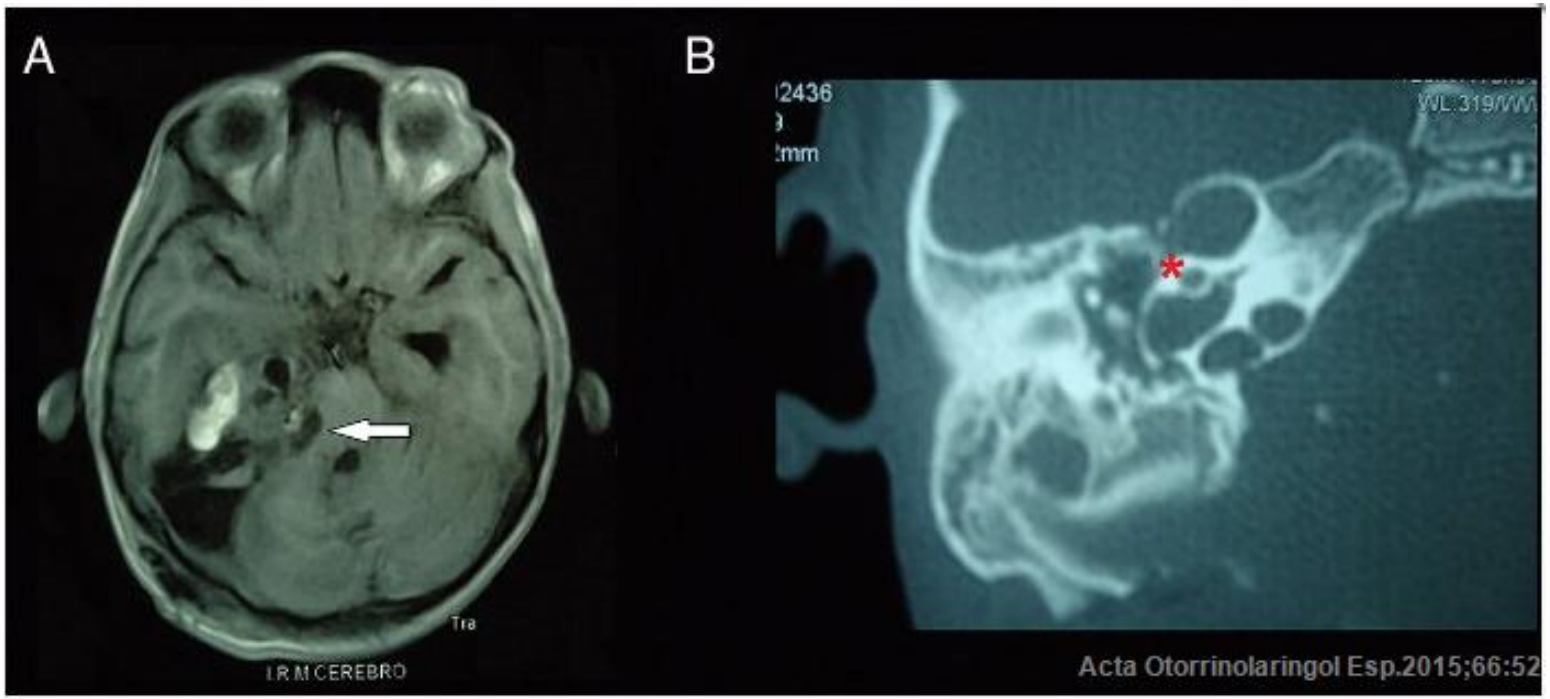
- Características clínicas:
  - Crescimento lento
  - Invasão do osso temporal
  - Metástases raras
  - História longa, sintomas otológicos
  - Tinnitus (92%), perda auditiva (95%), vertigem (62%), otalgia, otorragia, paralisia facial
  - Hemorragia ou hidropisia → perda auditiva súbita x gradual
- Destruição do osso petroso e da orelha interna



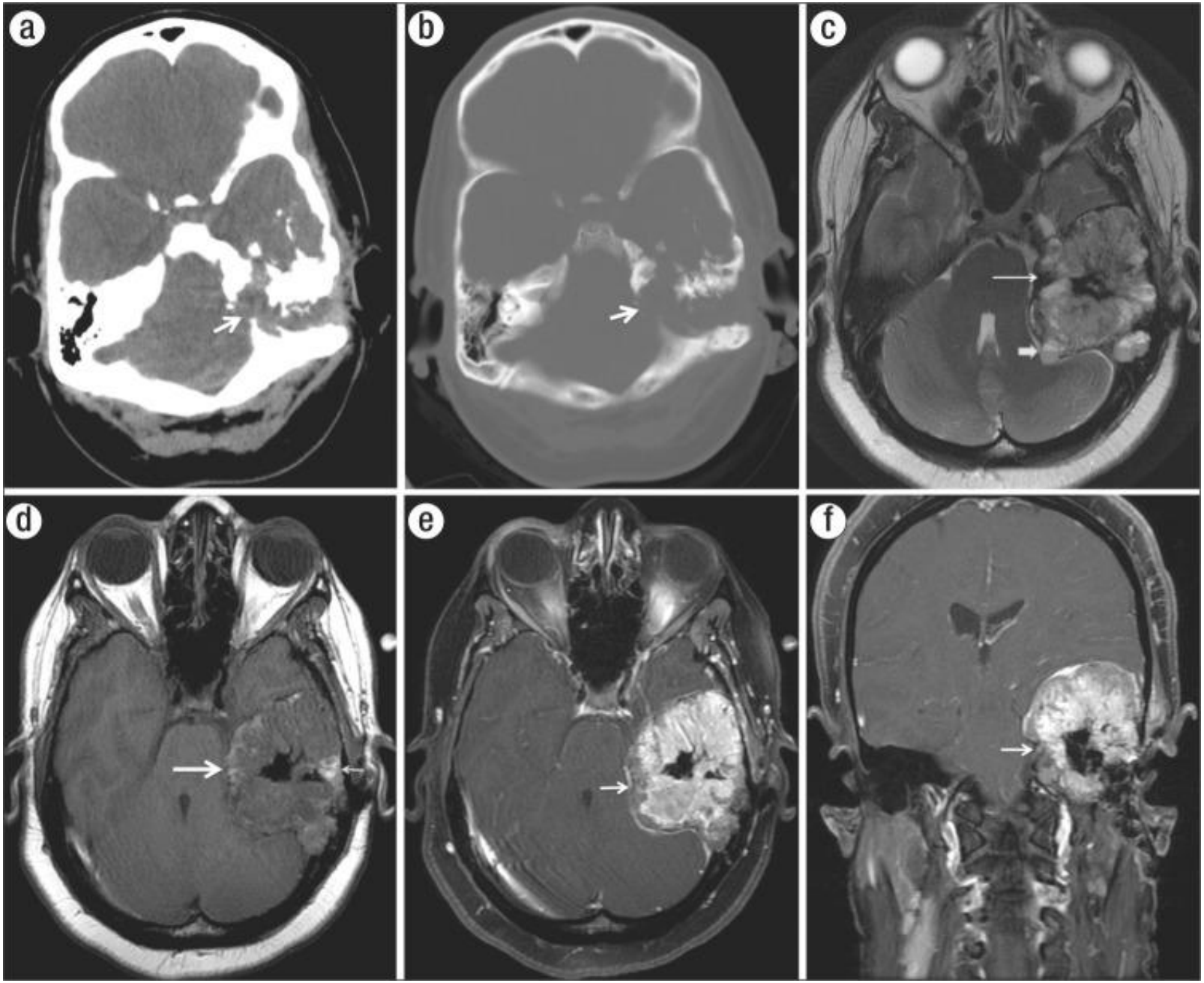

This illustration, courtesy of Alan Hoofring, shows the temporal bone in a VHL patient with a small ELST involving the endolymphatic sac. Bleeding from the tumor extends into the organs of balance and hearing. Fonte: NIH Clinical Center

# TUMOR DO SACO ENDOLINFÁTICO

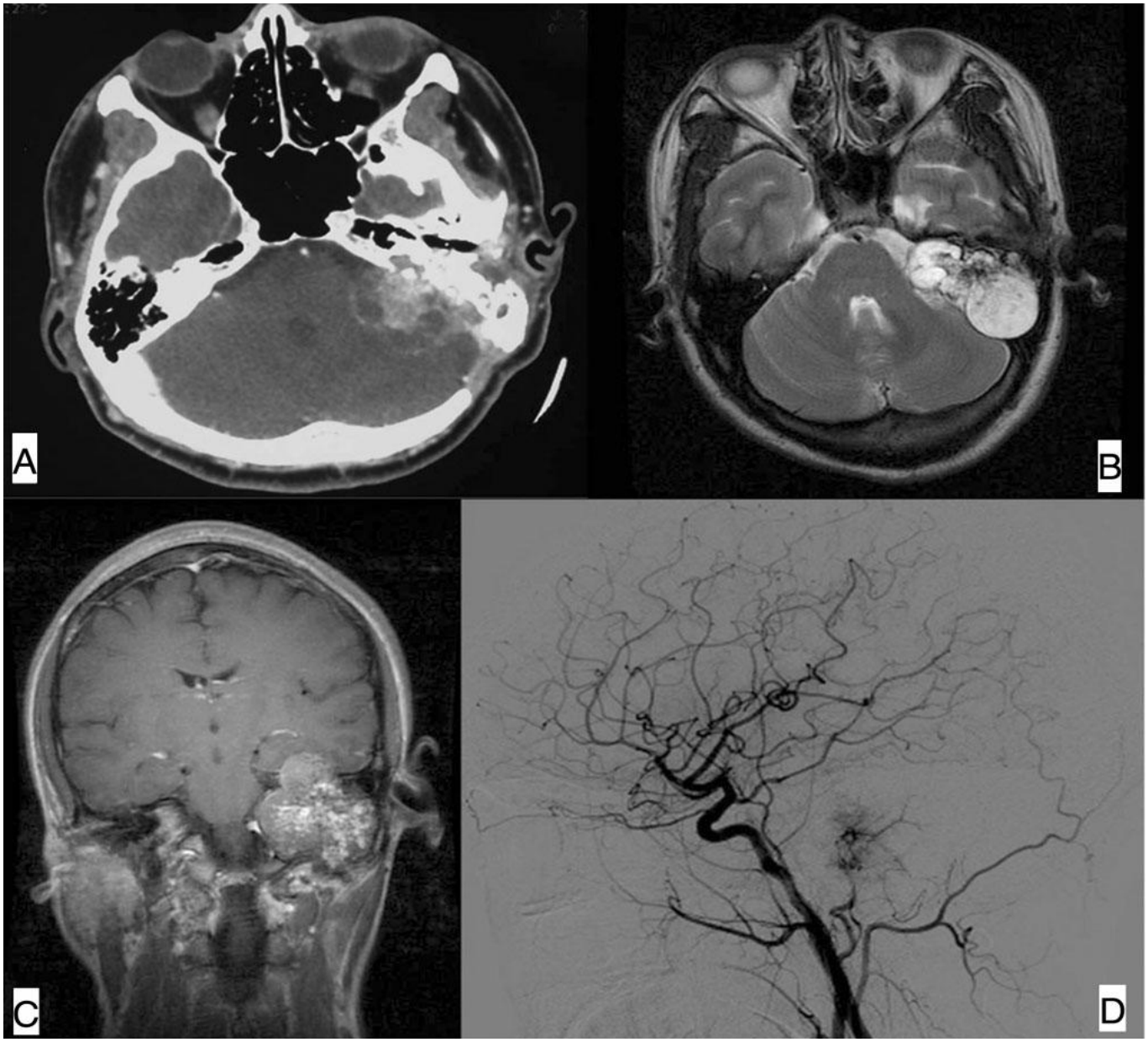
- Exames de imagem: equívocos diagnósticos
- Bem vascularizado
  - Paraganglioma
  - Hemangiopericitoma
  - Ramos da a. carótida externa/a. faríngea ascendente – a. auricular posterior
  - Ramos da a. vertebral – a. cerebelar anterior inferior (≠ CPP)




Fonte: Proc (Bayl Univ Med Cent). 2013 Apr; 26(2): 159-160.




Fonte: Zarghouni et al, 2013.




Radiographic views of endolymphatic sac tumor (ELST). A: CT scan shows the tumor was located at the left cerebellopontine angel (CPA) region with extensive petrous bone destruction. B and C: MRI shows the clear boundary mass at CPA with the destruction of the left petrous bone. D: The lateral Digital subtraction angiography view of the left external carotid artery shows irregular mass with abnormal vascular staining in the left CPA and the petrous bone region; the blood supply is mainly through branch vessels of arteriae auricularis posterior of the external carotid artery. Fonte: Du et al, 2015

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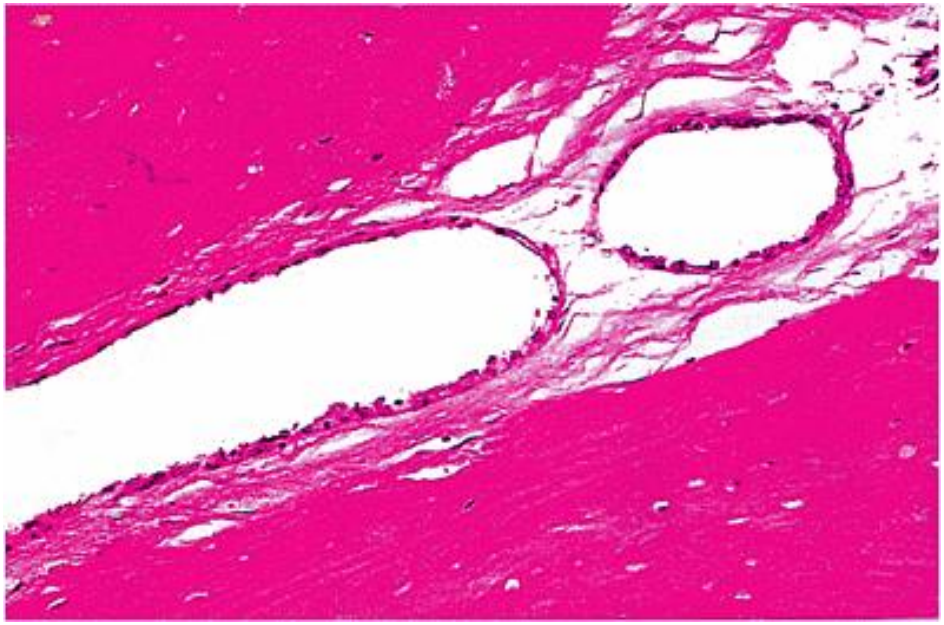
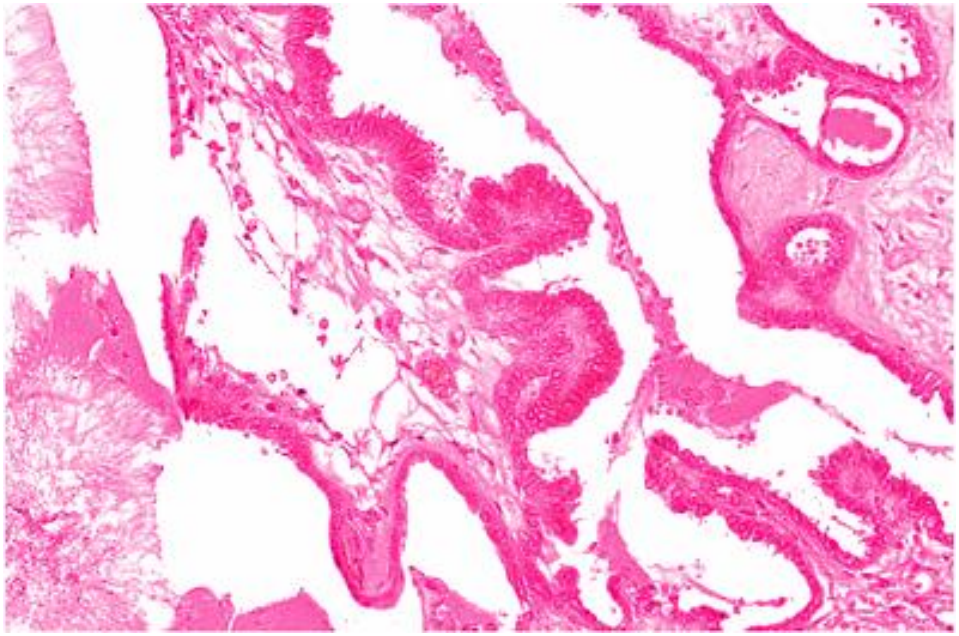
# TUMOR DO SACO ENDOLINFÁTICO

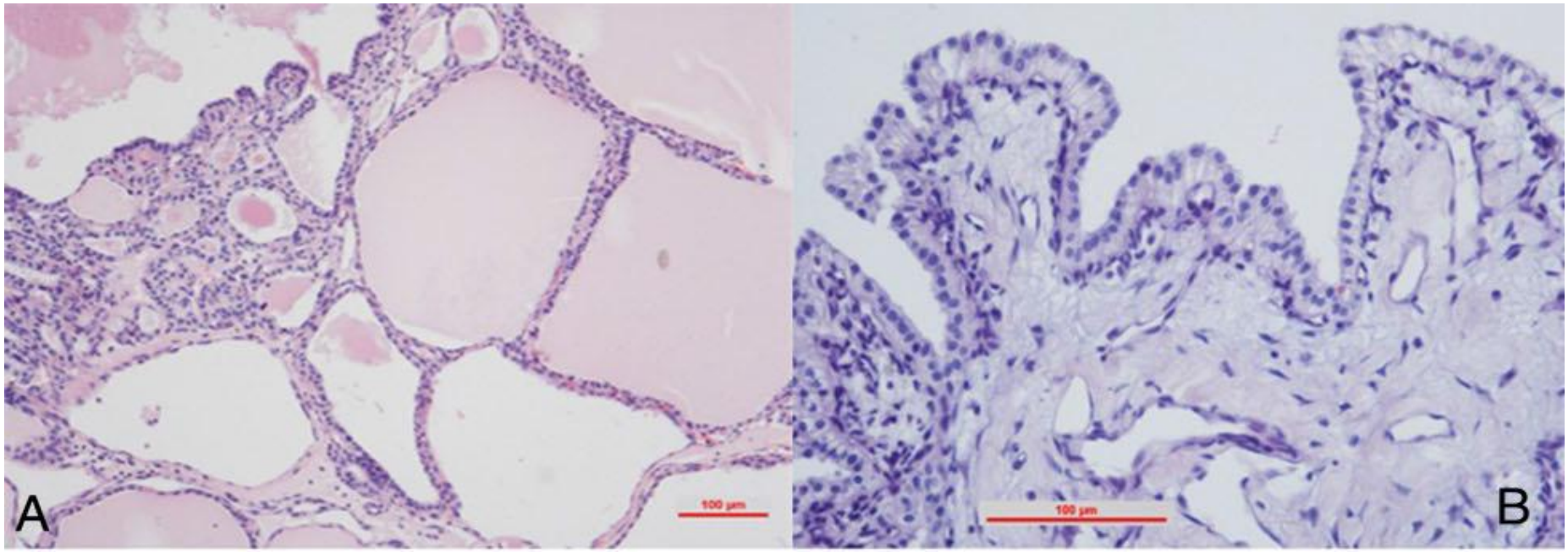
- Arquitetura papilar/glandular → papilar/tireoide-like
  - Vesículas do saco endolinfático normal
- Vasos e capilares abundantes em estroma fibroso
- Células endoteliais aglomeradas no estroma da papila
- Células claras e eosinofílicas
- Núcleo apical
- Diagnósticos diferenciais:
  - Papiloma do plexo coroide
  - Ependimoma papilar
  - Meningeoma papilar
  - Carcinoma metastático



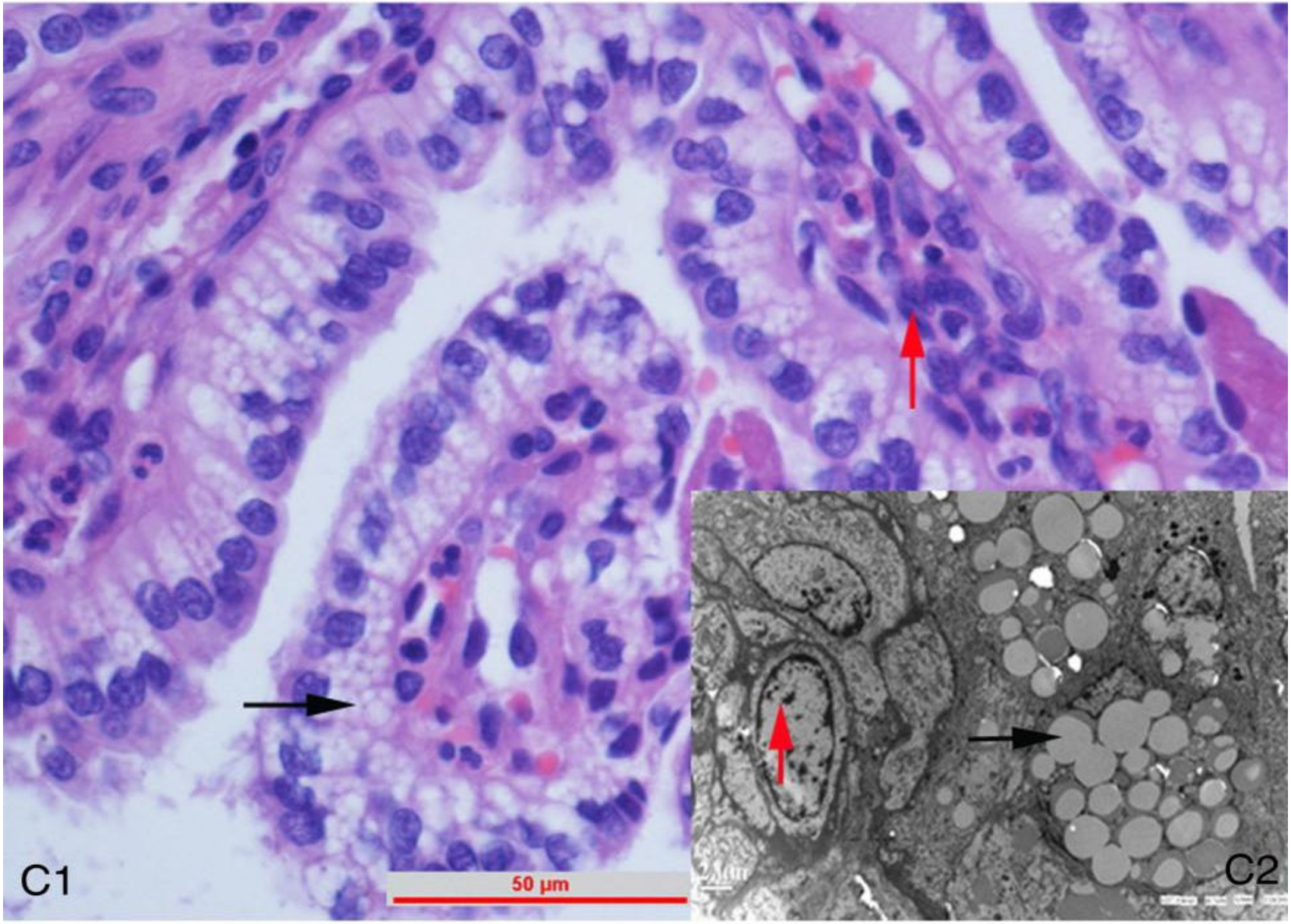
Ducto endolinfático dentro do aqueduto vestibular. O ducto é revestido por epitélio cuboidal baixo. Fonte: Histology for Pathologists, 3rd Edition.



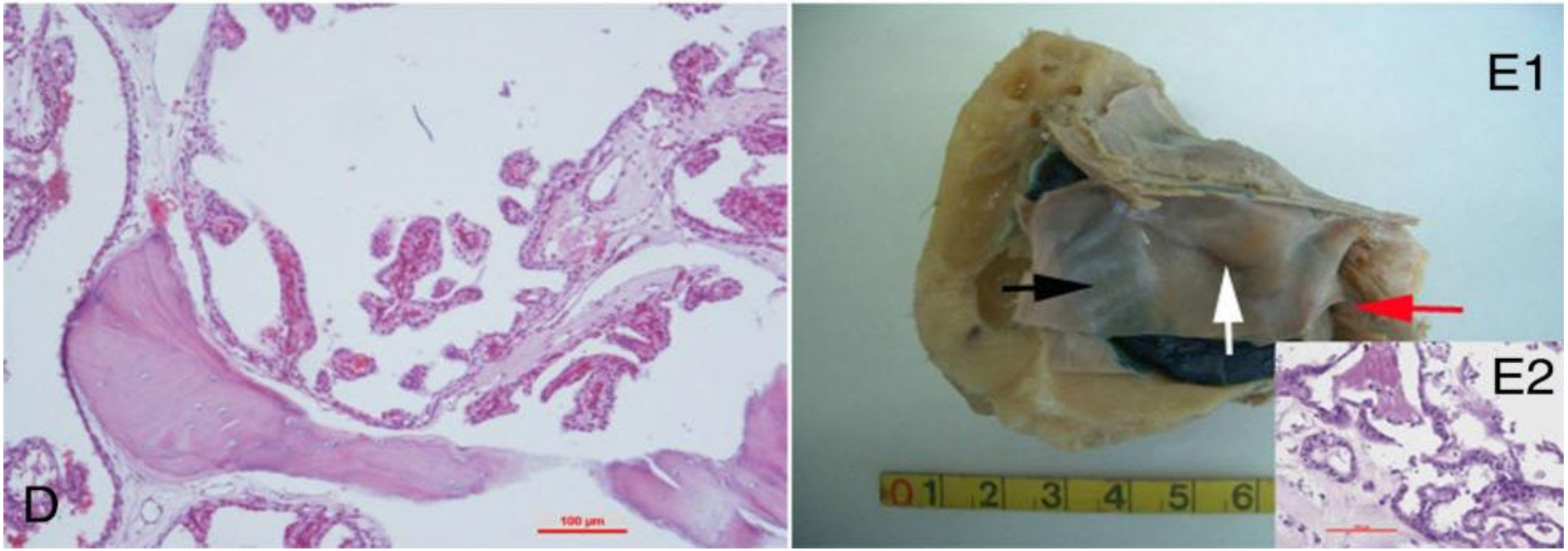
Saco endolinfático, revestido por epitélio colunar alto com arranjo papilar. Fonte: Histology for Pathologists, 3rd Edition.



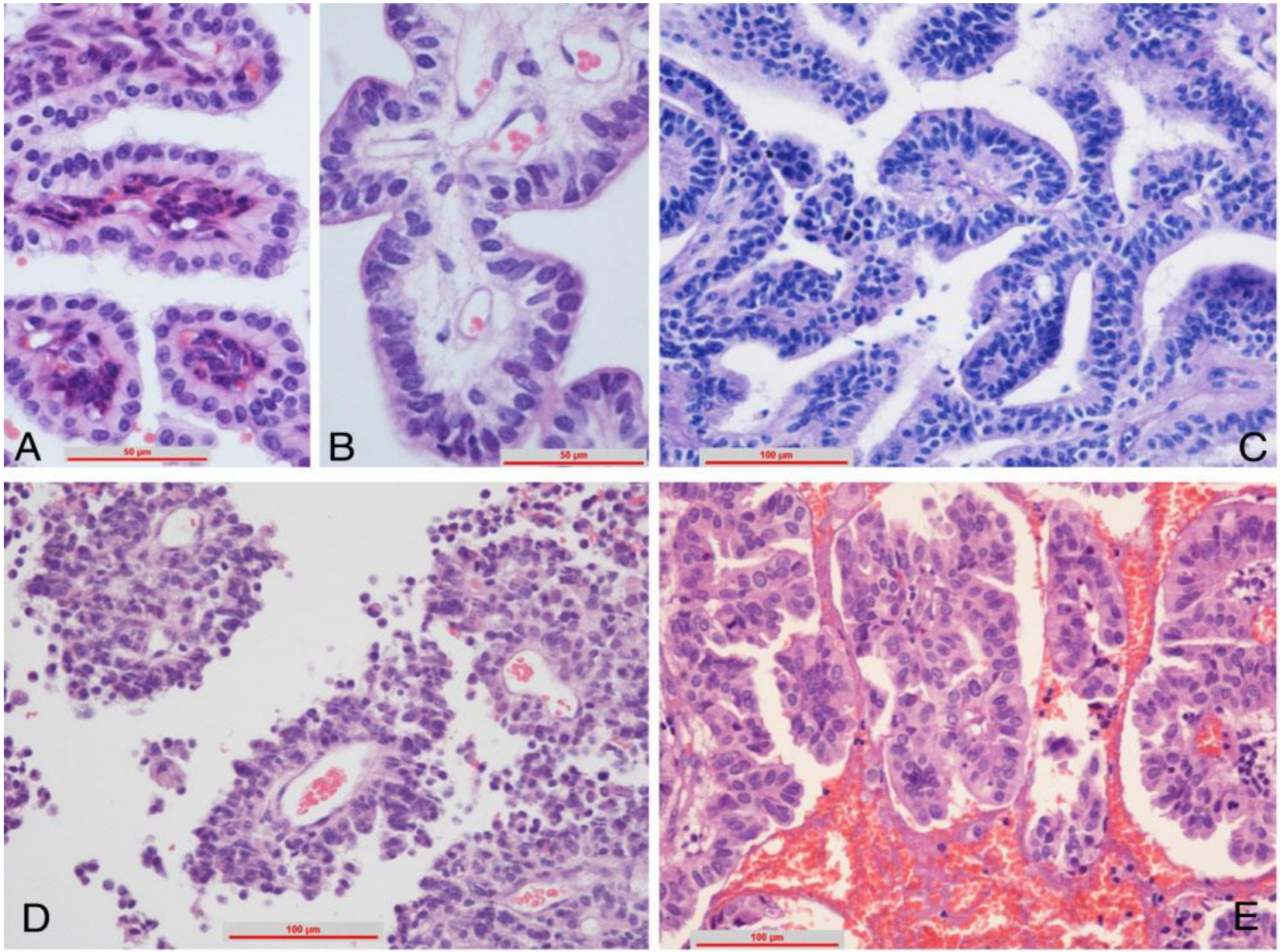

(A):The papillary-cystic glandular structure of endolymphatic sac tumor (ELST). Case 5 showed expanded glandular cavities and the secretion is similar to the thyroid structure. These areas may dominate the histological pattern, but are still accompanied by the papillary areas. HE ×100. (B) The papillary type area of ELST. Case 3 shows that the tumor cells are monolayer, the nuclei of the tumor cells are at the same level, often near the apical surface of the papillary.The fibrous stroma are rich in vasculatures with small vessels close to the epithelium lining the surface, which look like a double row of epithelial cells.HE ×200. Fonte: Du et al, 2015.



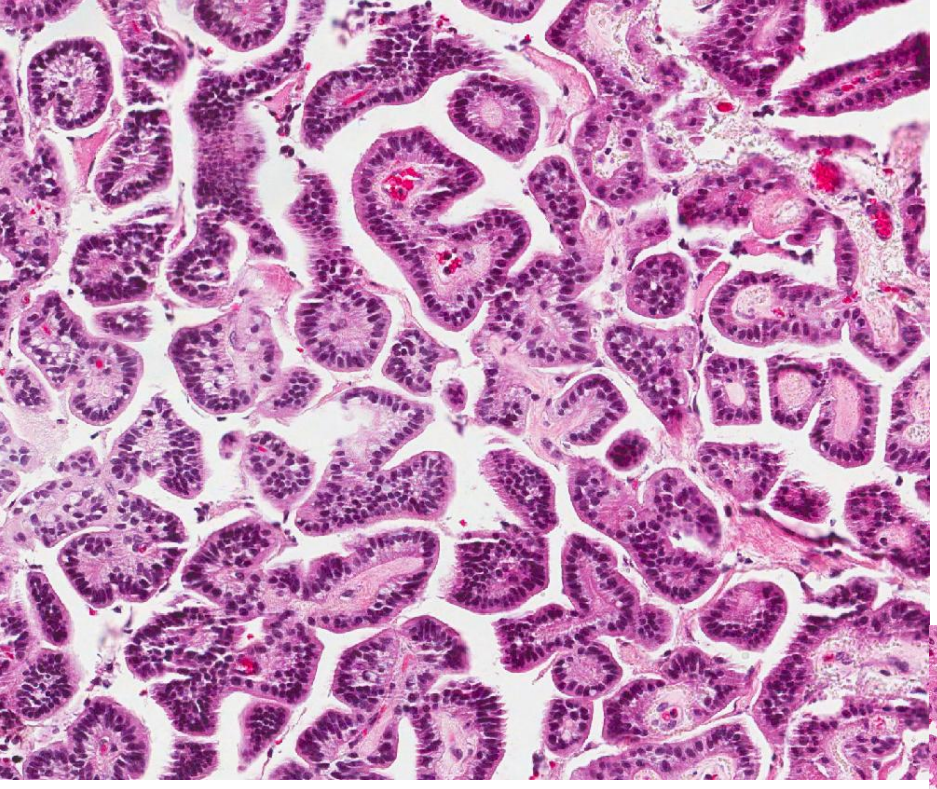

(C1) Clear cytoplasm, visible vacuoles (black arrow) and abundant endothelial cells (red arrow) in ELST in case 10. Note the round shaped, uniform sized vacuoles with a clear boundary in the cytoplasm. HE ×400. (C2) Electron micrograph showing that the nuclei are atypical, and that the cytoplasm is filled with 2 m visible vacuoles (black arrow).The endothelial cells of blood vessels always huddle together (red arrow). Fonte: Du et al, 2015.

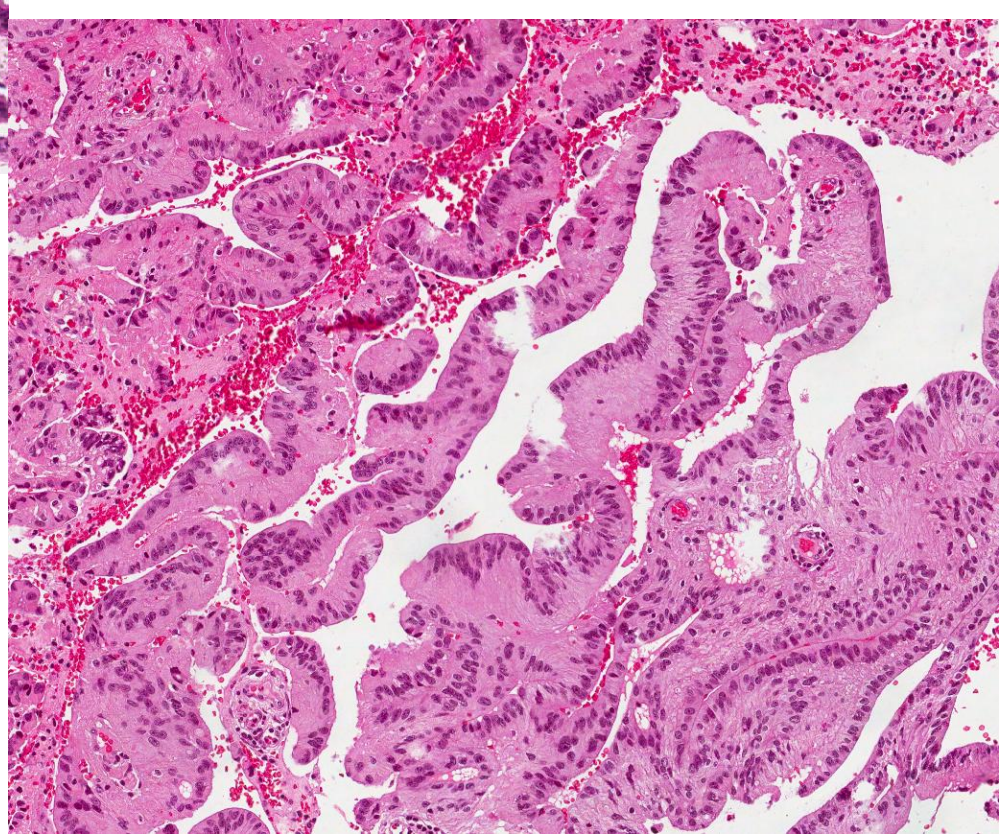



(D) Bone invasion of ELST in Case 4. HE ×100. (E1) The petrous bone showing the normal endolymphatic sac (white arrow), sinuses sigmoideus (black arrow) and internal auditory canal (red arrow). (E2) Normal endolymphatic sac shows glandular structure with cubic or columnar epithelial cells and visible eosinophilic colloid material in the glandular cavity. HE ×200. Fonte: Du et al, 2015.




(A)The papillae in endolymphatic sac tumor (ELST). HE ×400. (B) The papillae in choroid plexus papilloma (CPP). HE, ×400. (C) Papillary ependymoma (PE). HE ×200. (D) Papillary meningioma (PM). HE ×200. (E) Metastatic carcinoma (MC). HE ×200. Fonte: Du et al, 2015.





# TUMOR DO SACO ENDOLINFÁTICO

- Imuno-histoquímica:
  - AE1/AE3
  - CK de alto peso molecular
  - EMA
  - VEGF
  - CK de baixo peso molecular
  - Sinaptofisina
  - GFAP
  - S100

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# TUMOR DO SACO ENDOLINFÁTICO E VHL

- Doença de von Hippel-Lindau (VHL)
  - Treacher Collins (1894): tumores vasculares na retina
  - von Hippel (1904): *angiomatosis retinae*
  - Arvid Lindau: lesões císticas do cerebelo e hemangioblastomas
  - Charles Davison (1936): Doença de von Hippel Lindau
  - Mutações germinativas no gene VHL (50% proteína truncada)
  - Cistos viscerais (rim e pâncreas), carcinoma renal, paraganglioma, hemangioblastoma (SNC e retina), cistadenoma do epidídimo, tumores de ilhotas pancreáticas, tumor do saco endolinfático

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# TUMOR DO SACO ENDOLINFÁTICO E VHL

- Bausch et al (2015): 47% mutações missense, 22% grandes deleções, 18% mutações nonsense, 8% pequenas deleções intra-exônicas, 5% mutações em local de splice
- Esporádicos x associados a VHL
  - 16% dos pacientes portadores de VHL (Bausch et al: 3,6%)
  - 1ª apresentação
  - Bilateralidade
  - Óbito (outras causas)
  - Mutações germinativas de VHL em casos esporádicos: 39%

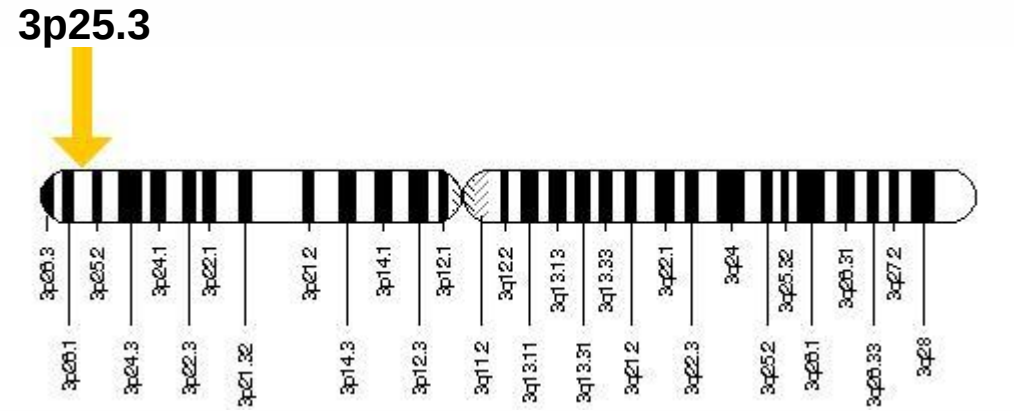
| Classification | *VHL* Mutation | Molecular Defect | Clinical Manifestations |
|---|---|---|---|
| Type 1 | Total or partial *VHL* loss<br>Improper folding | Upregulation of HIF | Hemangioblastoma<br>Renal cell carcinoma<br>Low risk of pheochromocytoma |
| Type 2A | *VHL* missense mutation | Upregulation of HIF<br>Inability to stabilize microtubules | Hemangioblastoma<br>Pheochromocytoma<br>Low risk of renal cell carcinoma |
| Type 2B | *VHL* missense mutation | Upregulation of HIF | Hemangioblastoma<br>Pheochromocytoma<br>High risk of renal cell carcinoma |
| Type 2C | *VHL* missense mutation | pVHL maintains ability to downregulate HIF<br>Decreased binding to fibronectin<br>Defective fibronectin matrix assembly | Pheochromocytoma only |

Abbreviations: VHL, von Hippel-Lindau; HIF, hypoxia inducible factor; pVHL, VHL tumor suppressor protein.

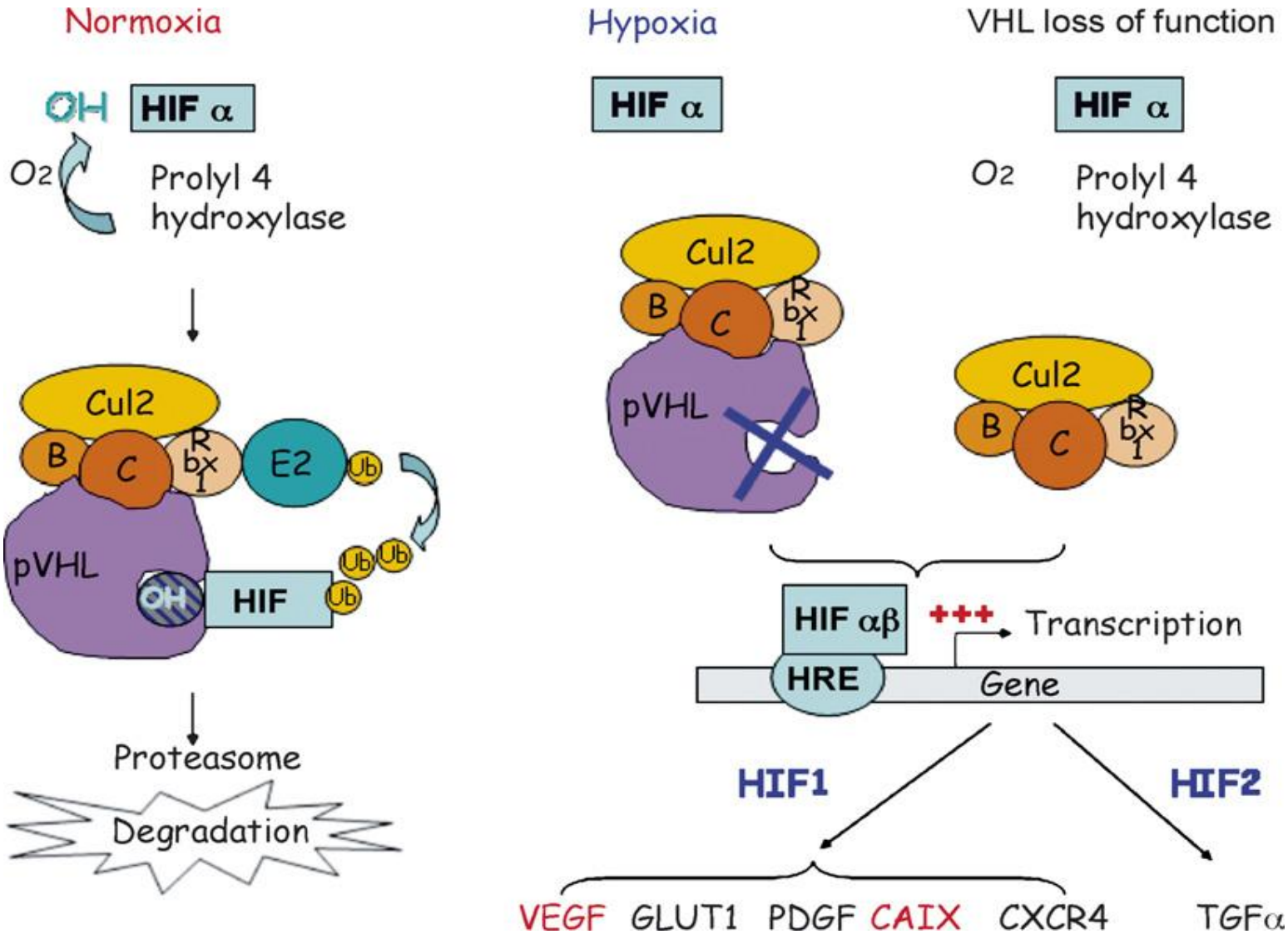
Fonte: jco.ascopubs.org

# TUMOR DO SACO ENDOLINFÁTICO E VHL

- O gene *VHL*
  - *von Hippel-Lindau tumor suppressor*, *E3 ubiquitin protein ligase*
  - Proteína VHL: complexo VCB-CUL2 (VHL - elongin BC – CUL2)
  - Degradação proteica, regulação gênica, controle da divisão celular, formação de matriz extracelular
  - Interação com HIF1α e HIF2α (divisão celular, angiogênese, eritropoese)




Fonte: ghr.nlm.nih.gov




Fonte: Patard et al, 2007.

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# REFERÊNCIAS


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