# GI Case of the month

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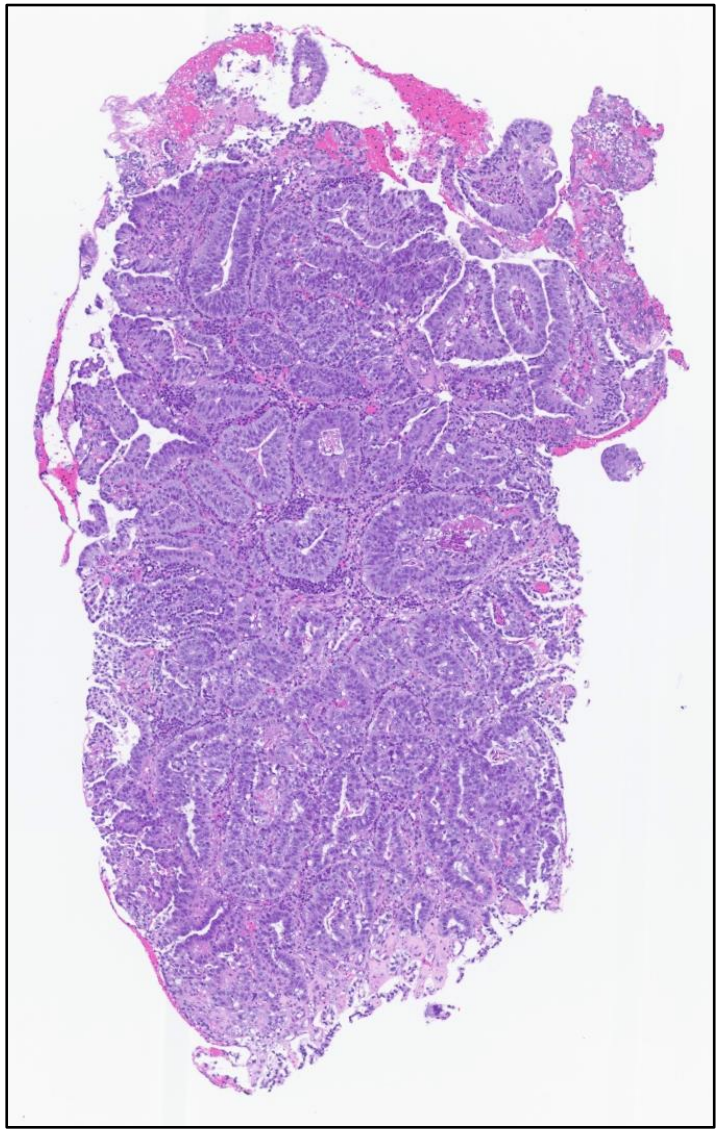
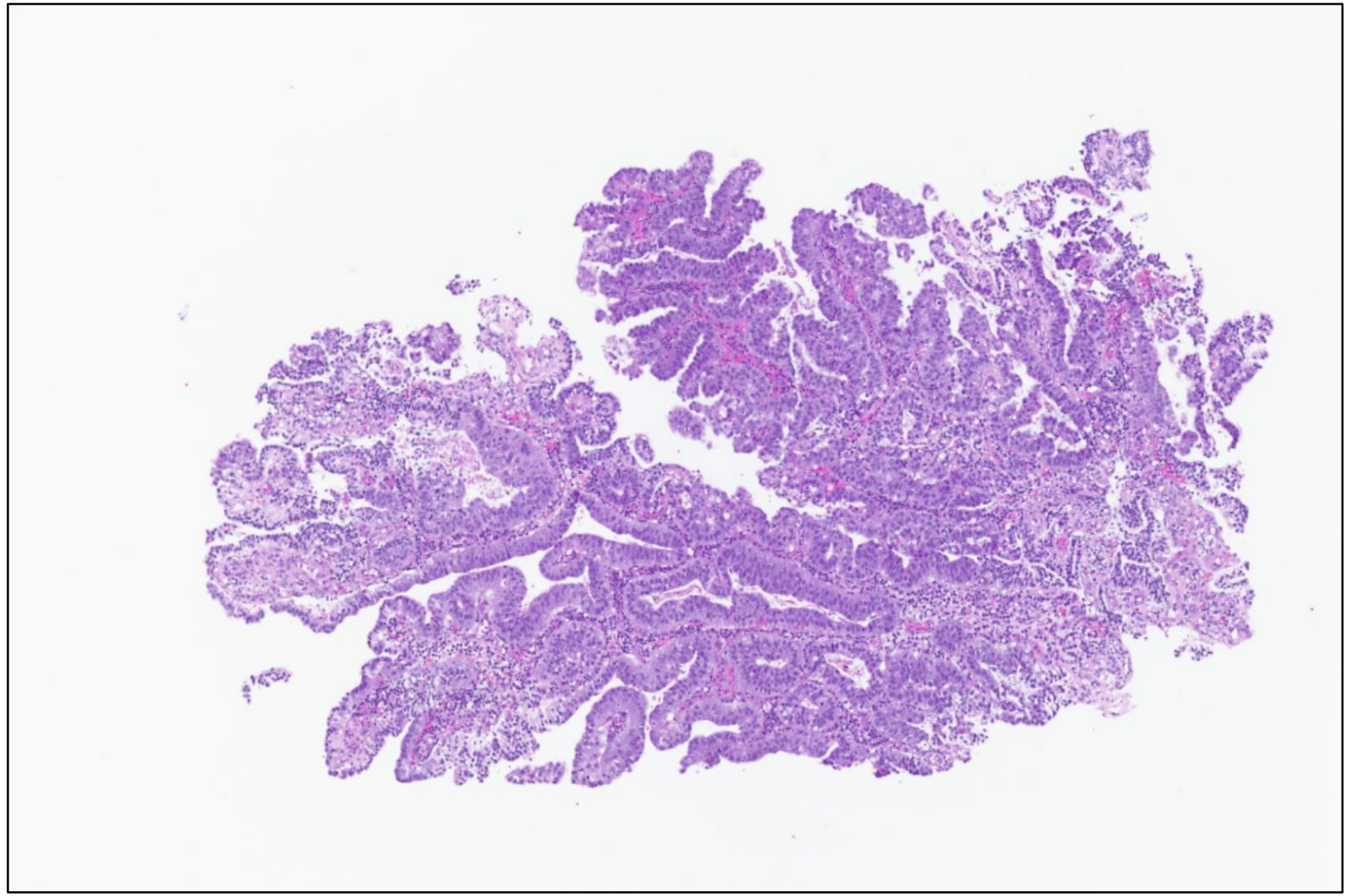
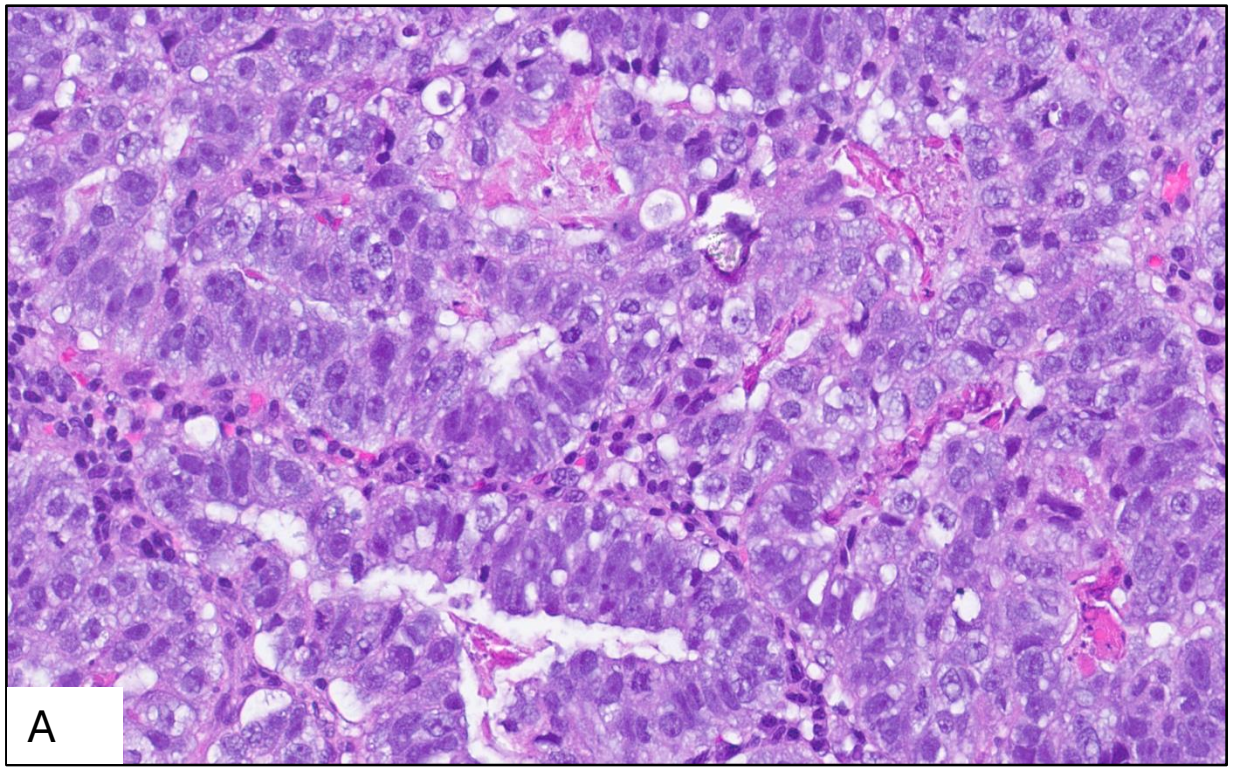
# Clinical History

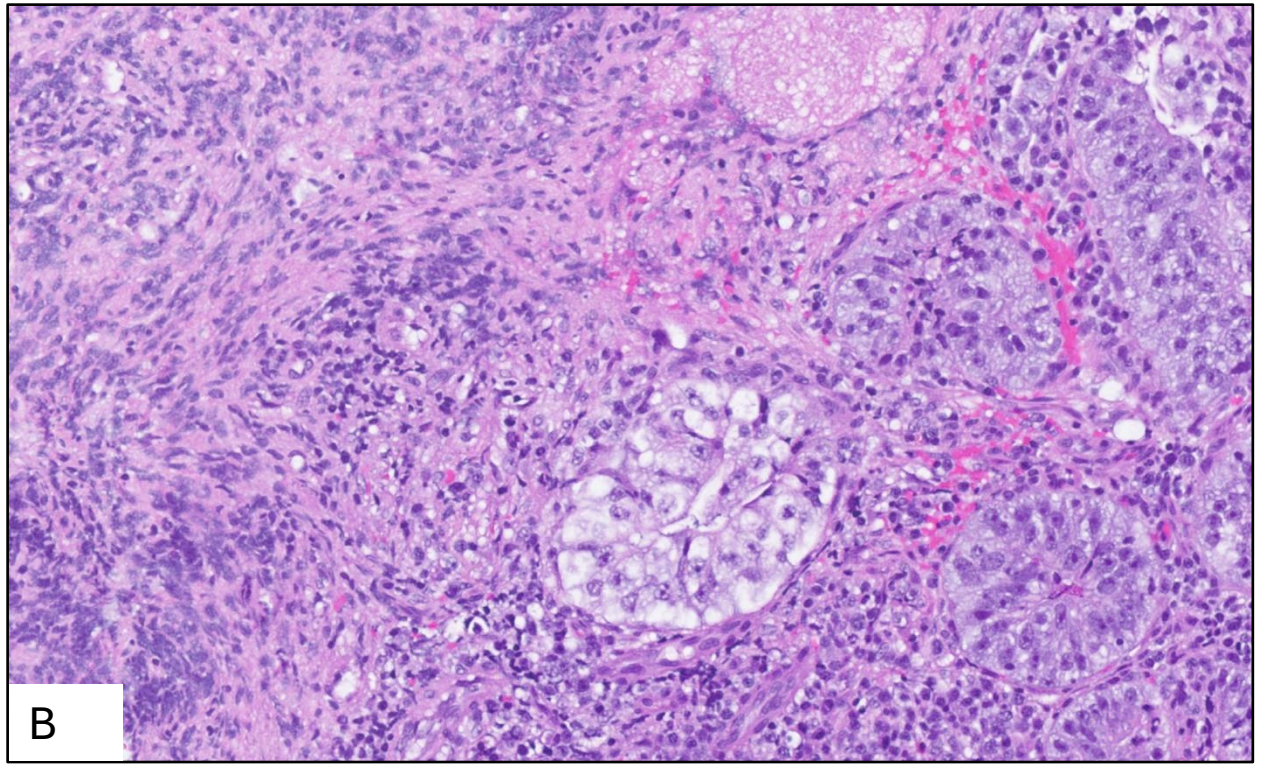
- **Patient:** A 69-year-old man presented with exertional dyspnea, cough, and dysphagia and was admitted to the intensive care unit for airway monitoring.
- **CT:** A circumferential mass involving the entire thoracic esophagus, measuring up to 5.0 × 5.2 cm immediately superior to the carina, with lower tracheal invasion and partial stenosis and lower esophageal occlusion. A 3.3-cm left adrenal mass was suspicious for metastatic disease.
- **Procedure:** Biopsy of the esophageal mass at 16 cm and tracheal biopsy.



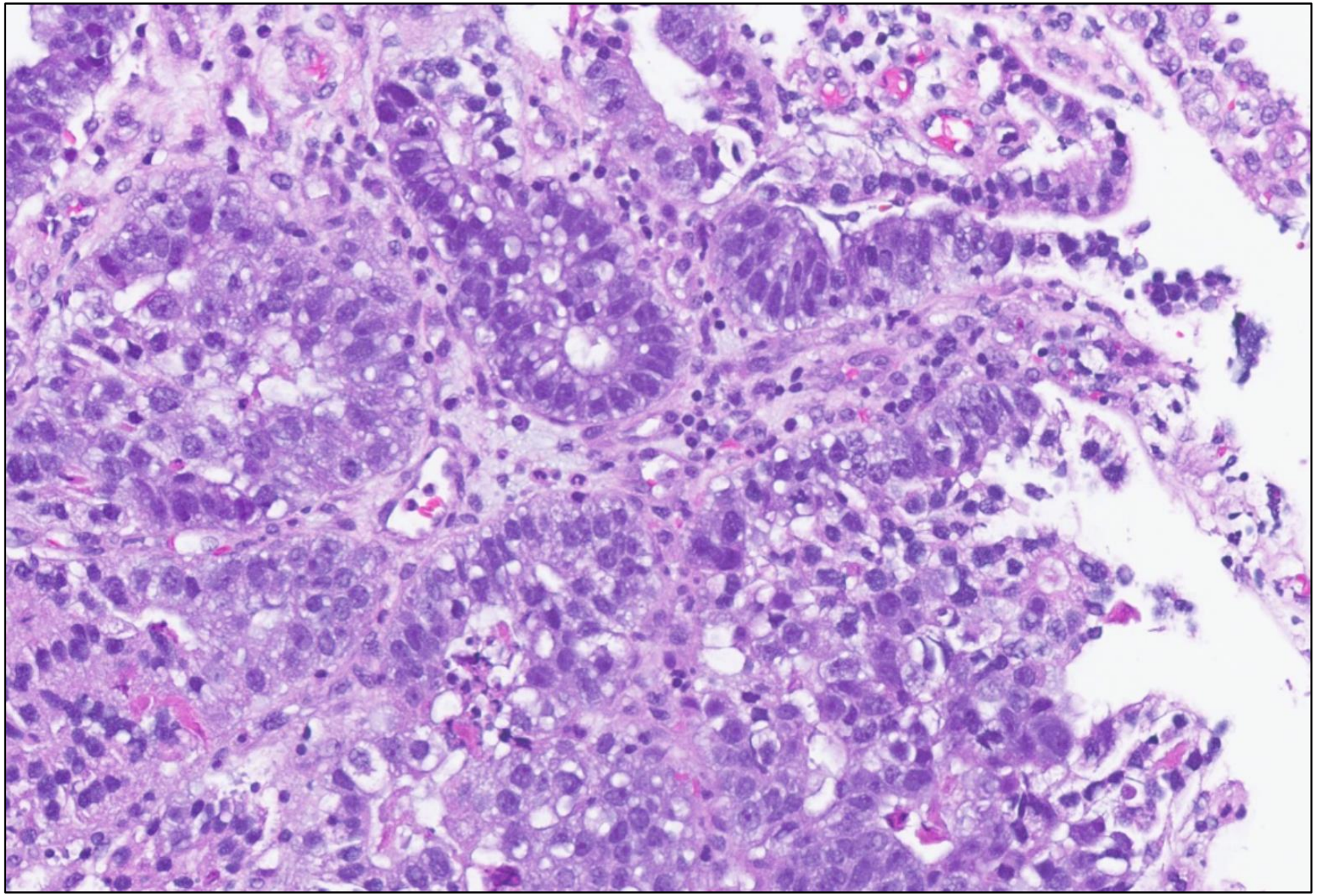


**The biopsy shows invasive adenocarcinoma with glandular and tubulopapillary architecture (H&E x40)**

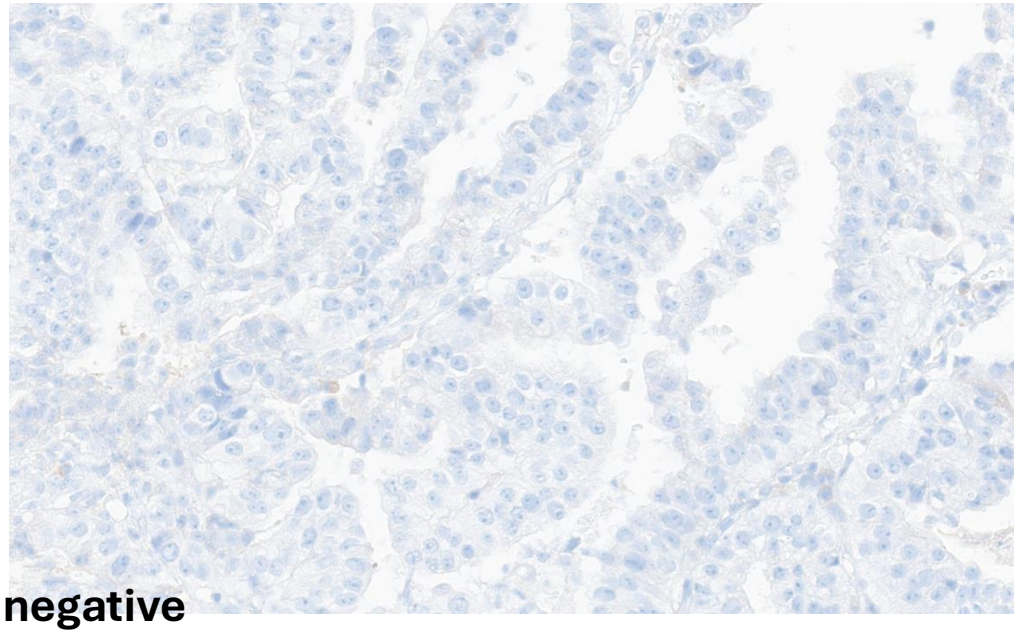


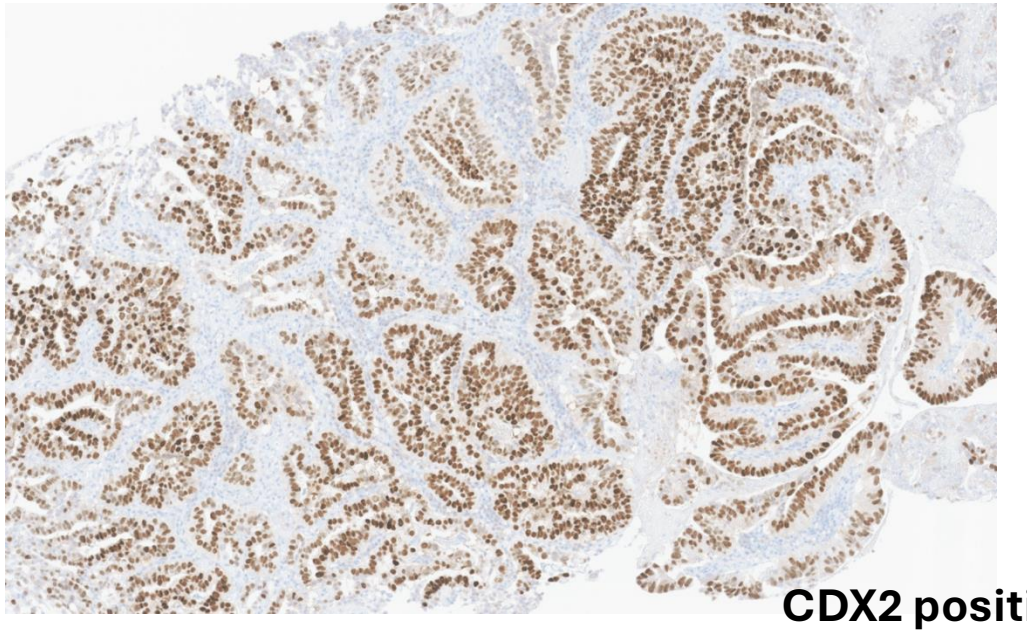

**The tumor cells shows subnuclear vacuolization (A) and focal areas shows clear cytoplasm (B)**
**The morphology was exactly the same from both the esophageal and the tracheal biopsies.**



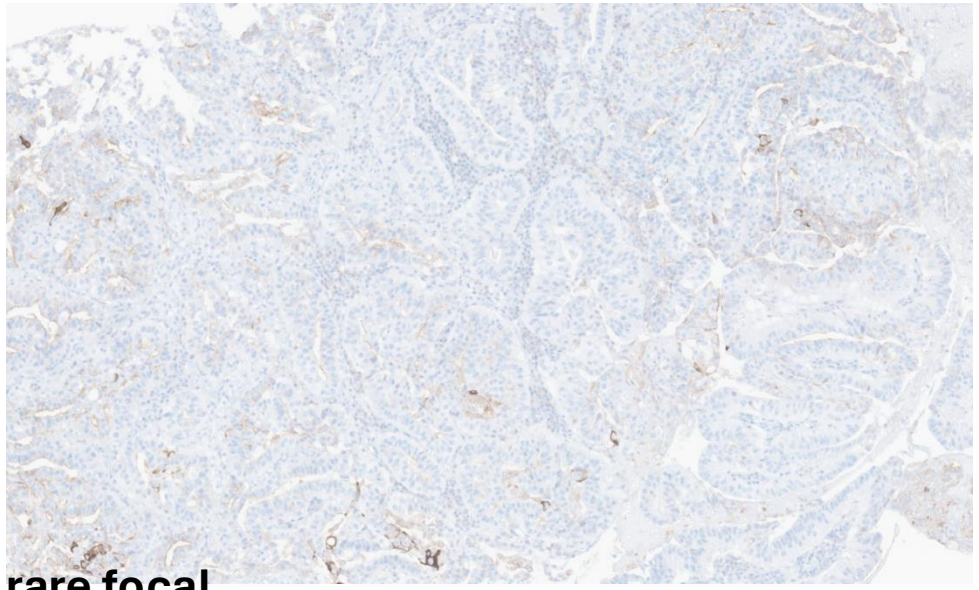
**Tumor cells with subnuclear vacuolization**



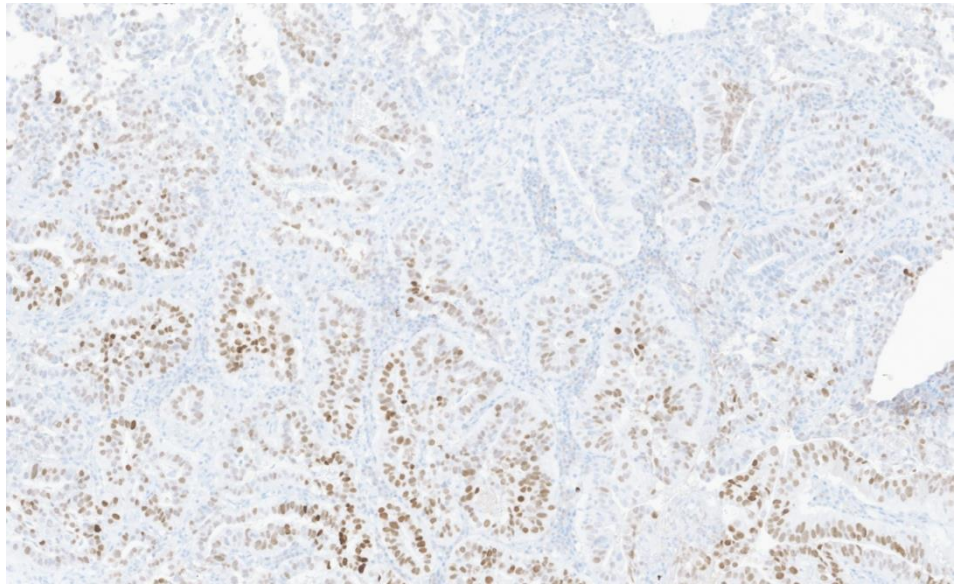
CK7 negative



CDX2 positive

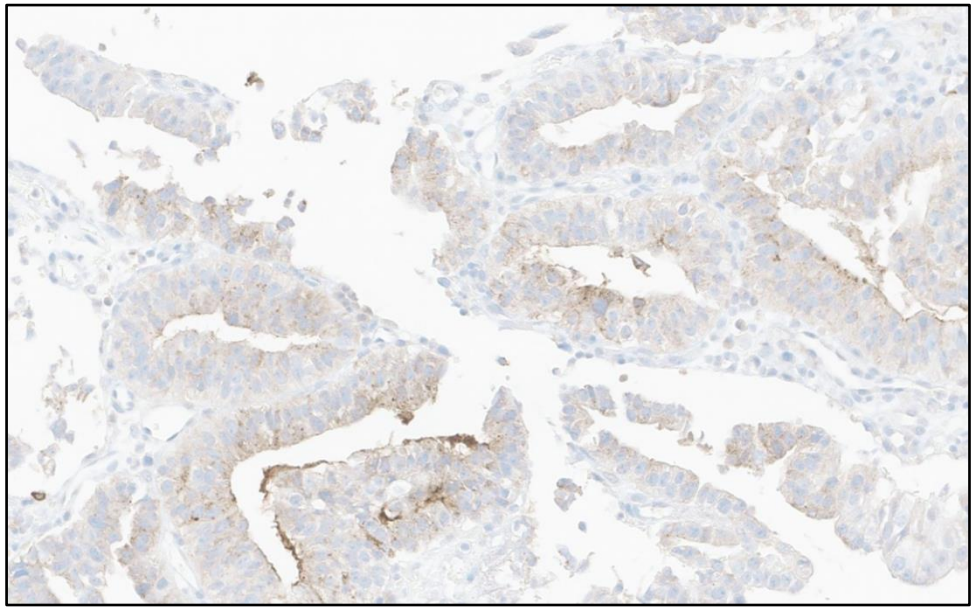


CK20 rare focal

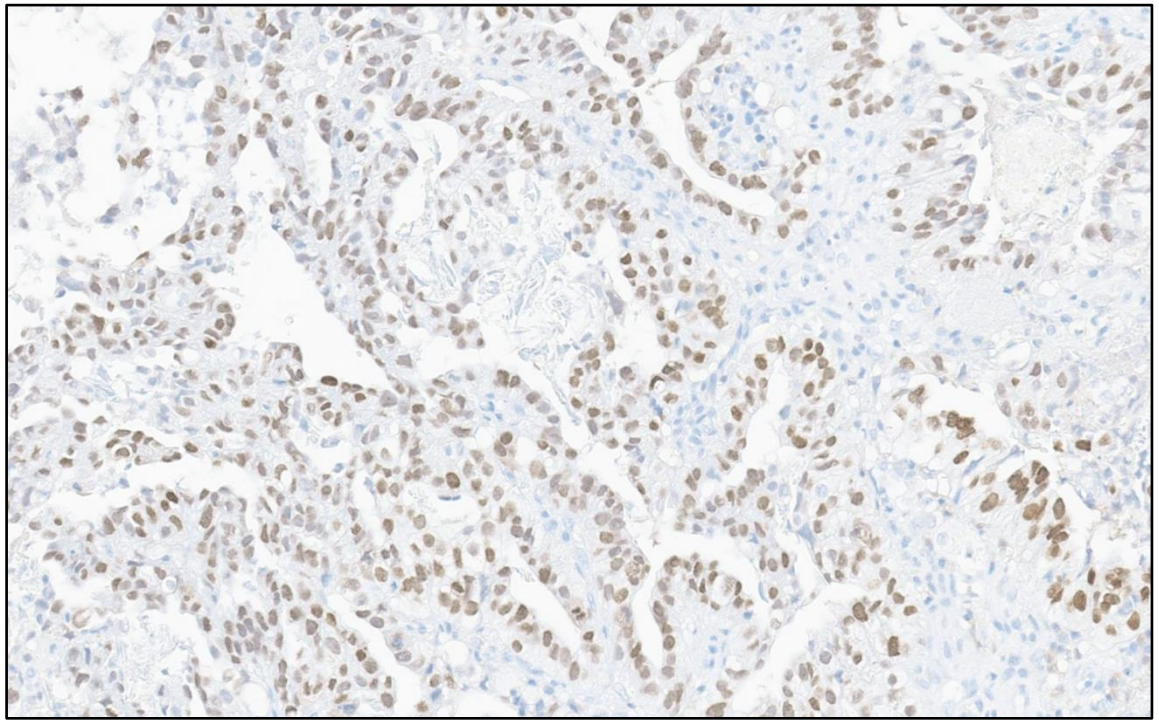


TTF1 patchy

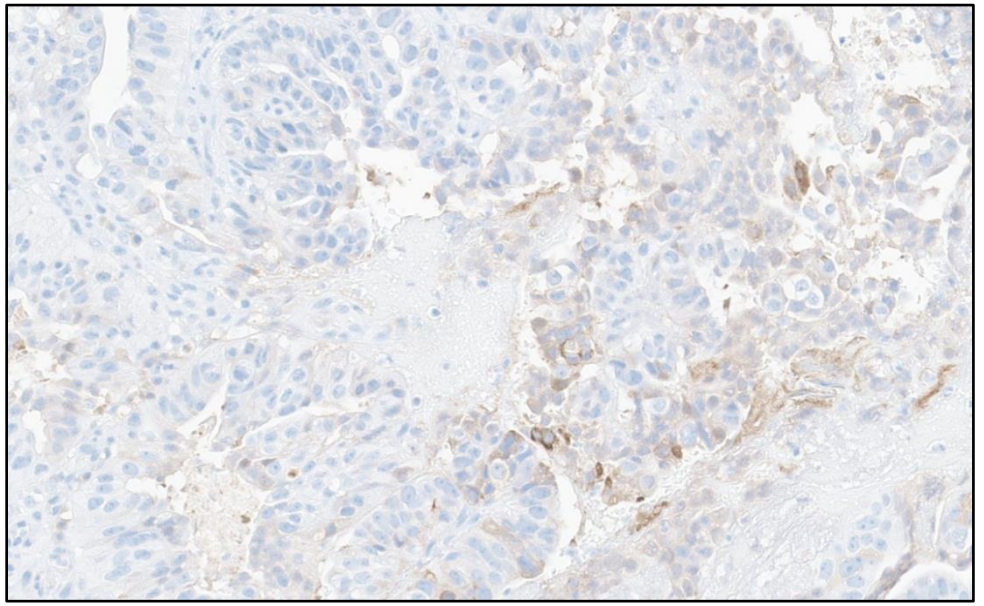
Due to the unique morphological features as well as the unusual immunohistochemical staining pattern, additional stains were performed to test for enteroblastic differentiation.



**Glypican 3**
**Focal**



**SALL4: positive**



**AFP: Focal**

**Tumor cells were positive for SALL4, focally for positive glypican-3, AFP, and patchy positive for TTF-1**
**Tumor cells were negative for Napsin A, PAX8, and p40. SMARCA4 (on tracheal biopsy) is retained**

# Biomarkers

Intact nuclear expression of MLH1, PMS2, MSH2, and MSH6 (MMR proficient)

HER2/neu negative.

PD-L1 (performed on the tracheal biopsy): PD-L1 TPS 0%

# Final Diagnosis

A. Esophagus, mass at 16 cm, biopsy

INVASIVE, MODERATELY DIFFERENTIATED ADENOCARCINOMA WITH ENTEROBLASTIC DIFFERENTIATION.

Fragment of esophageal squamous mucosa with mild reactive changes.

Tracheal biopsy shows same morphology and immunohistochemical profile.

# Question

- Which combination of morphologic and immunohistochemical findings most strongly supports a diagnosis of **adenocarcinoma with enteroblastic differentiation**?
- A. Solid growth pattern with p40 positivity
  B. Tubulopapillary architecture with clear cytoplasm and positivity for SALL4 and glypican-3
  C. Lepidic growth pattern with diffuse Napsin A and TTF-1 positivity
  D. Clear cell morphology with PAX8 and CAIX positivity

**Correct answer: B.** Tubulopapillary architecture, clear cytoplasm, subnuclear vacuolization, and expression of fetal gastrointestinal markers such as SALL4 and glypican-3 support enteroblastic differentiation.

A is incorrect because a solid growth pattern with p40 positivity supports squamous differentiation rather than adenocarcinoma with enteroblastic differentiation. C is incorrect because lepidic growth with diffuse Napsin A and TTF-1 expression favors a primary pulmonary adenocarcinoma. D is incorrect because clear cell morphology with PAX8 and CAIX expression favors clear cell renal cell carcinoma.

# Question

2- Which **emerging therapeutic target** may have particular relevance in adenocarcinomas with enteroblastic differentiation??

A. SALL4

B. Claudin-6

C. CDX2

D. AFP

**Correct answer: B.** Claudin-6. Claudin-6 expression has been reported in this subgroup and may represent a potential therapeutic target, including through emerging claudin-6–directed therapies such as CAR-T cell approaches.

A is incorrect: SALL4 is an oncofetal nuclear marker that supports enteroblastic differentiation, but it is not the principal emerging therapeutic target in this setting. C is incorrect: CDX2 is a nuclear transcription factor used as a marker of intestinal differentiation rather than as a therapeutic target. D is incorrect: AFP may support fetal gastrointestinal, hepatoid, or enteroblastic differentiation and can serve as a serum biomarker, but it is not the emerging therapeutic target highlighted in this tumor subgroup.

# Discussion

- Rare esophageal adenocarcinoma with enteroblastic differentiation, characterized by tubulopapillary architecture, focal clear cytoplasm, and subnuclear vacuolization, with expression of SALL4, AFP, and glypican-3 (1,2).
- This is now added to the WHO 6th edition of esophageal cancer chapter.
- This tumor is rare (0.7%) among esophageal adenocarcinomas and has been associated with aggressive behavior, including frequent lymphovascular invasion and increased nodal and hepatic metastases (1,2).
- Claudin-6 expression has been reported in this subgroup and represents a potential therapeutic target. Claudin-6–directed therapies, including CAR-T therapy (BNT-211-01), are currently under investigation (1,3).
- The main differential diagnosis in our case is fetal adenocarcinoma of the lung, which can share SALL4, AFP, glypican-3, and TTF-1 expression. In our case, the dominant esophageal mass, secondary tracheal invasion, and negative Napsin A favor an esophageal primary; patchy TTF-1 expression alone is insufficient to support a lung origin (4).
- Metastatic clear cell renal cell carcinoma is less likely given PAX8 negativity, strong CDX2 expression, enteroblastic morphology, and absence of a renal mass.
- Recognition of enteroblastic/fetal gut-like differentiation in esophageal adenocarcinoma is important for accurate diagnosis and may have prognostic and emerging therapeutic implications.

# References


1. Kraemer M, Zander T, Alakus H, Buettner R, Lyu SI, Simon AG, Schroeder W, Bruns CJ, Quaas A. Fetal gut cell-like differentiation in esophageal adenocarcinoma defines a rare tumor subtype with therapeutically relevant claudin-6 positivity and SWI/SNF gene alteration. Sci Rep. 2024 Jun 12;14(1):13474. doi: 10.1038/s41598-024-64116-2.
2. Murakami T, Yao T, Mitomi H, et al. Clinicopathologic and immunohistochemical characteristics of gastric adenocarcinoma with enteroblastic differentiation: a study of 29 cases. Gastric Cancer. 2016;19:498–507.
3. Mackensen A, Haanen JBAG, Koenecke C, et al. CLDN6-specific CAR-T cells plus amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial. Nat Med. 2023;29(11):2844–2853. doi:10.1038/s41591-023-02612-0.
4. Li Y, Xi SY, Yong JJ, et al. Morphologic, immunohistochemical, and genetic differences between high- and low-grade fetal adenocarcinomas of the lung. Am J Surg Pathol. 2021;45:1464–1475.