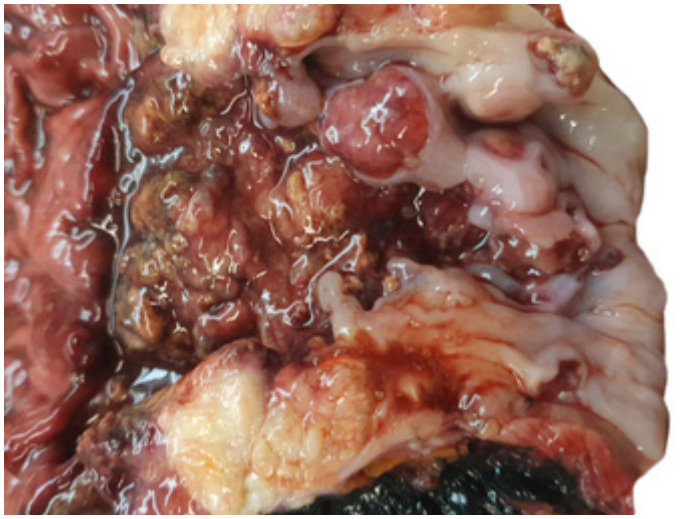
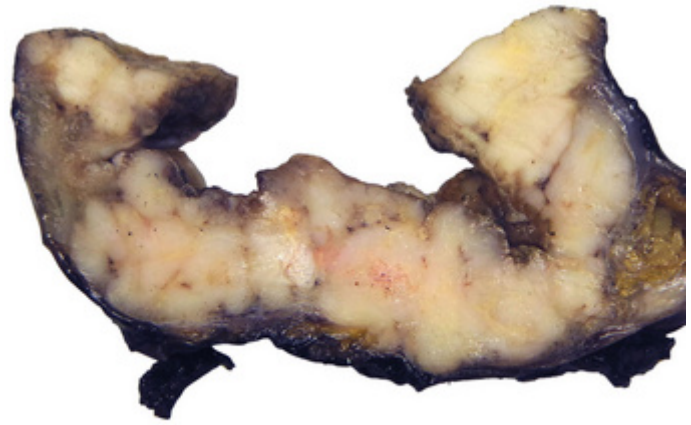
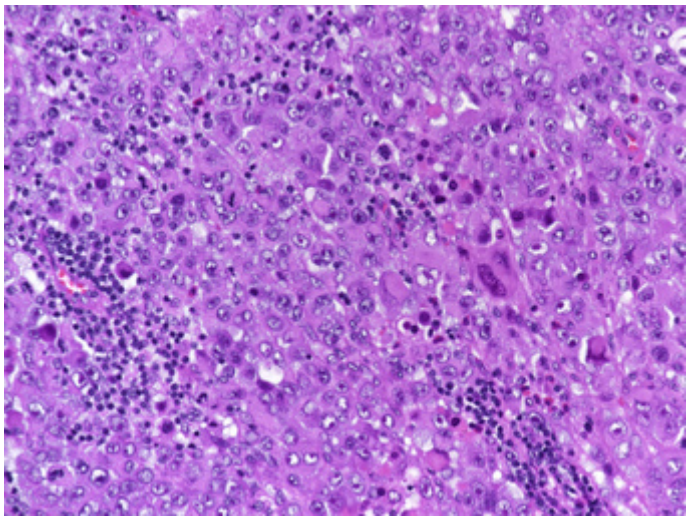
February 2021

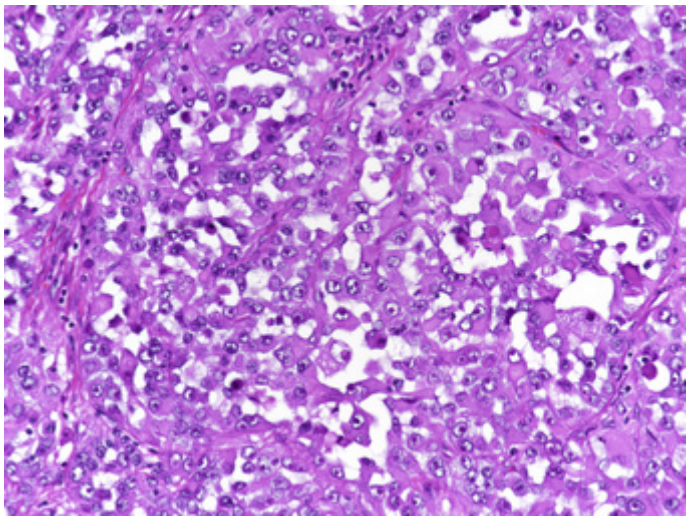
Oesophageal resection specimen of a 73-year-old male.

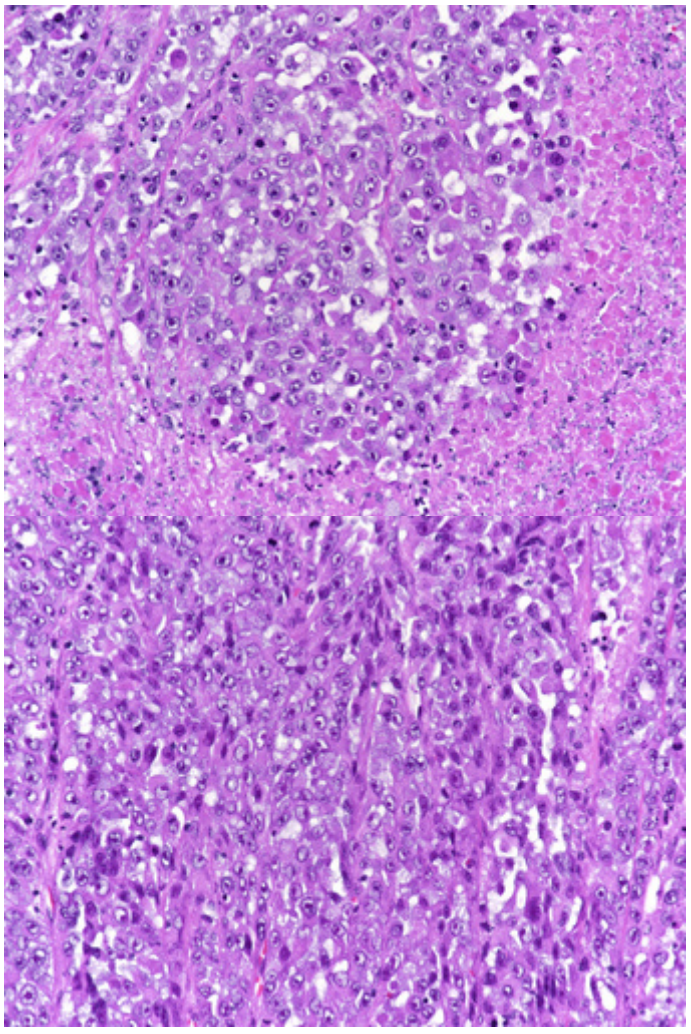
What is your diagnosis?

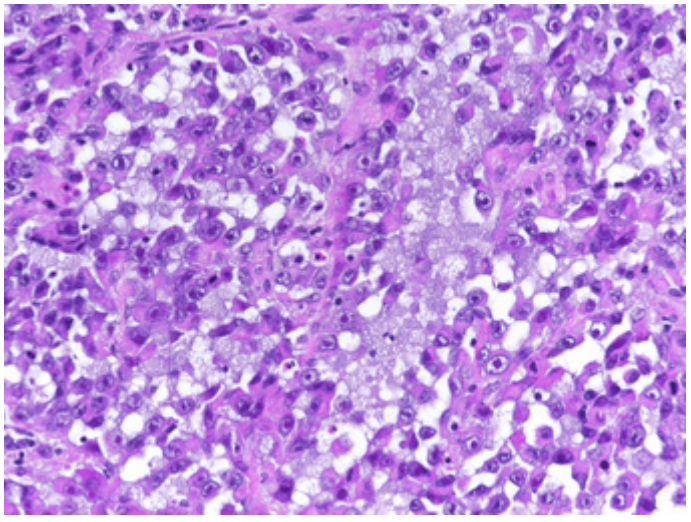


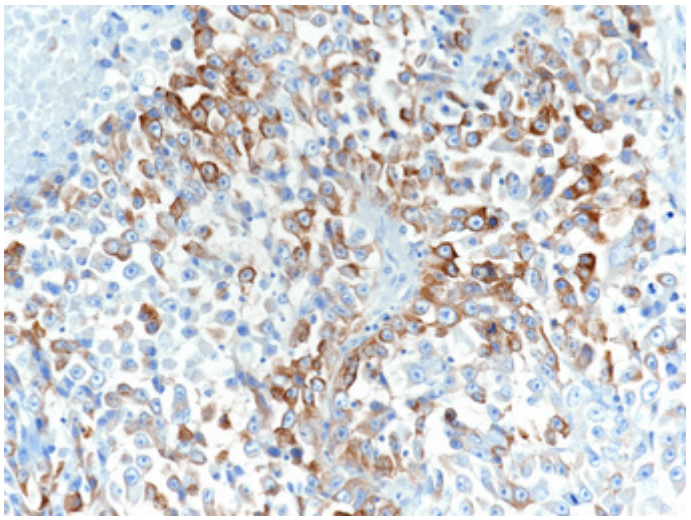


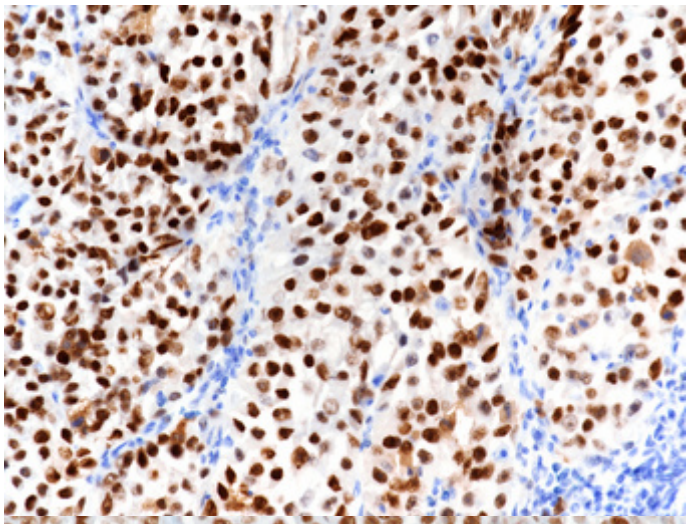


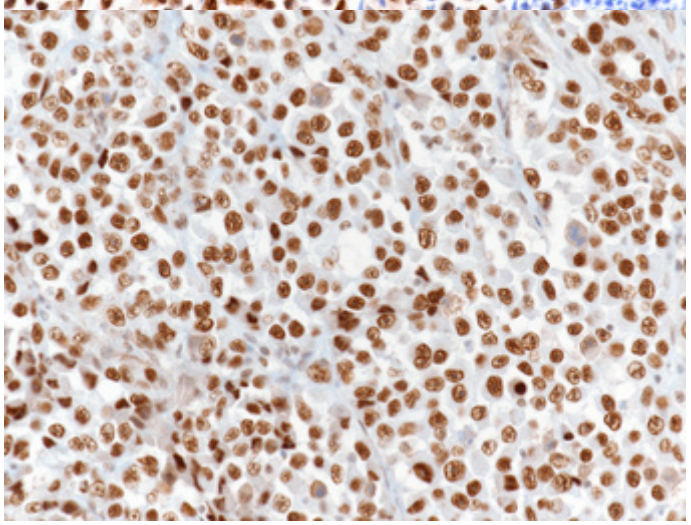


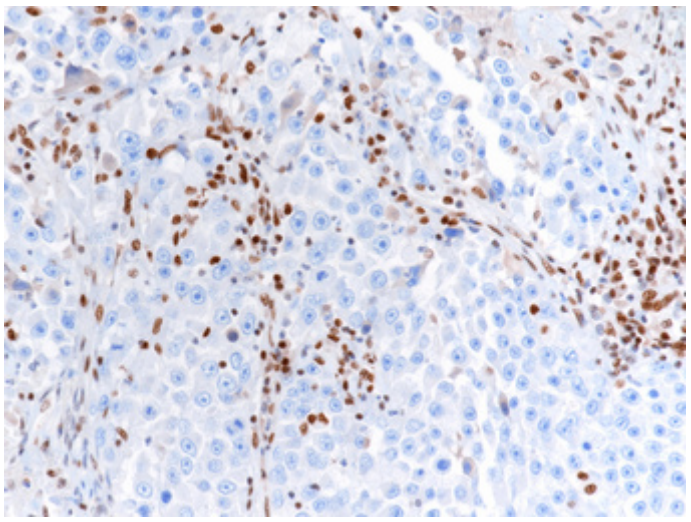


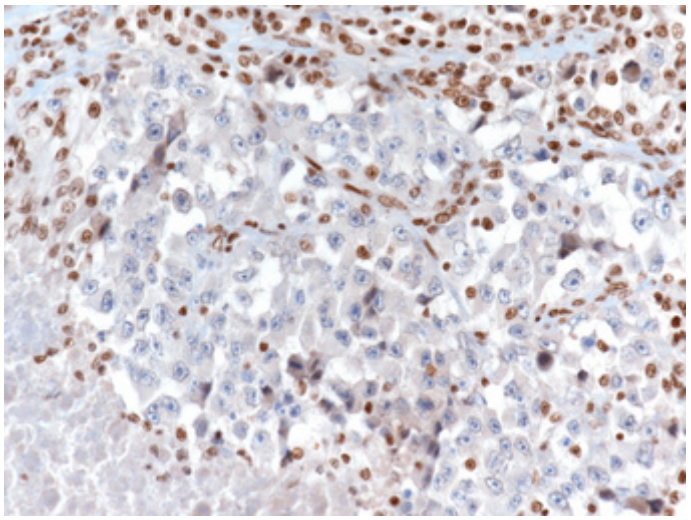


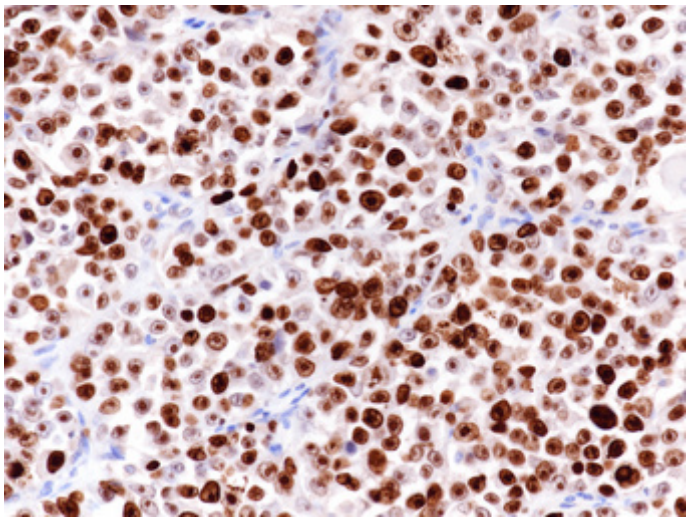












Diagnosis:

SMARCA4/SMARCA2-deficient carcinoma of the oesophagus/gastro-oesophageal junction.

Comment:

The resection specimen shows an ulcerated tumour within the distal oesophagus and/or at the gastro-oesophageal junction (with infiltration into the proximal stomach), measuring 7 cm in largest diameter (Panel A). The tumour thickens the wall of the oesophagus (cut-surface after fixation; Panel B), causing lumen stenosis. Several enlarged lymph nodes, measuring 4.5 cm in largest diameter, are included in the resection specimen.

Histology shows a sheet-like proliferation of discohesive undifferentiated tumour cells with large vesicular nuclei, prominent macronuclei and moderate amounts of eosinophilic cytoplasm with variable rhabdoid appearance (Panel C-D). Mitotic activity is high, and areas of necrosis are extensive (Panel E). There are few pleomorphic giant cells and small foci of spindle cells (Panel F). Intercellular mucin is present in small amounts (Panel G), while clear-cut foci of neoplastic gland formation or non-invasive precursors, such as Barrett's mucosa are not seen.

Upon immunohistochemistry, the tumour cells variably express pan-keratin (Panel H) and showed mutant p53 pattern (protein stabilization / overexpression; Panel I). The expression of INI1 is well preserved (Panel J), while the expression of SMARCA4 (Panel K) and SMARCA2 (Panel L) is lost in the tumour cell nuclei. The ki67 proliferation rate is exceedingly high (Panel M). The tumour is negative for S-100, Sox-10, neuroendocrine and GIST markers.

Undifferentiated carcinoma of the oesophagus and gastro-oesophageal junction has recently been included as distinct entity in the fifth edition of WHO Classification of Digestive Tumours. Very recently, an international collaboration of authors identified a subset of undifferentiated cancers in this location, which lack nuclear expression of SMARCA4/SMARCA2 (Horton et al.), thereby expanding the concept of SWI/SNF complex-deficient undifferentiated/rhabdoid tumours of the gastrointestinal tract (Agaimy et al.).

These tumours are believed to result from progressive dedifferentiation of a lower grade neoplasm and typically show aggressive clinical course. Areas of better differentiation may be identified after extensive sampling. On the molecular level, these tumours are characterized by high tumour mutation burden, which is associated with an increased likelihood of response to immune checkpoint inhibition.

Differential diagnosis mainly includes haematolymphoid malignancies, sarcomas, and malignant melanoma, but also the recently described primary malignant gastrointestinal neuroectodermal tumour (GNET), which is characteristically positive for S-100, but negative for typical melanoma markers, such as HMB-45 and Melan A. At least one neuroendocrine marker (preferably synaptophysin) is positive in the majority of cases, and SOX-10 protein was identified as an additional valuable marker.

SMARCA4/SMARCA2-deficient carcinomas may occur in many different sites, but have most commonly been described in the lungs. Since they are rare within the gastrointestinal tract, secondary tumour, that is, metastasis to the gastrointestinal tract should be excluded clinically.

For further reading:

- Agaimy A, Daum O, Märkl B, Lichtmannegger I, Michal M, Hartmann A. SWI/SNF Complex-deficient Undifferentiated/Rhabdoid Carcinomas of the Gastrointestinal Tract: A Series of 13 Cases Highlighting Mutually Exclusive Loss of SMARCA4 and SMARCA2 and Frequent Co-inactivation of SMARCB1 and SMARCA2. Am J Surg Pathol. 2016; 40: 544-53.
- Chetty R, Serra S. SMARCA family of genes. J Clin Pathol. 2020; 73: 257-260.
- Horton RK, Ahadi M, Gill AJ, Said S, Chen ZE, Bakhshwin A, Nichols M, Goldblum JR, Graham RP. SMARCA4/SMARCA2-deficient Carcinoma of the Esophagus and Gastroesophageal Junction. Am J Surg Pathol. 2020 Oct 6. Online ahead of print.
- Nambirajan A, Singh V, Bhardwaj N, Mittal S, Kumar S, Jain D. SMARCA4/BRG1-Deficient Non-Small Cell Lung Carcinomas: A Case Series and Review of the Literature. Arch Pathol Lab Med. 2021; 145: 90-98.

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