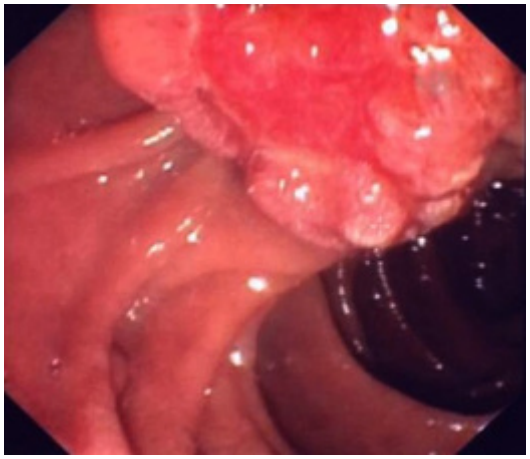
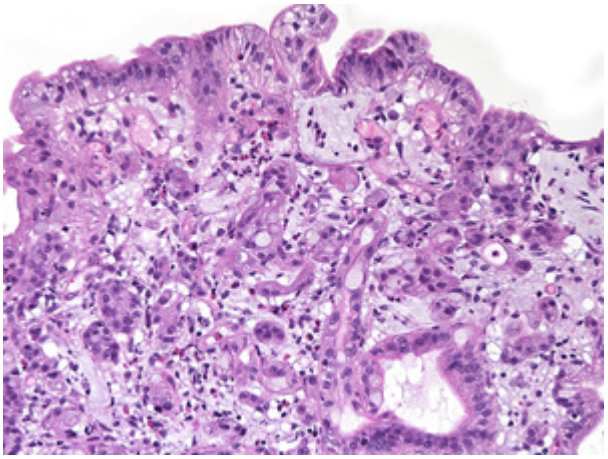
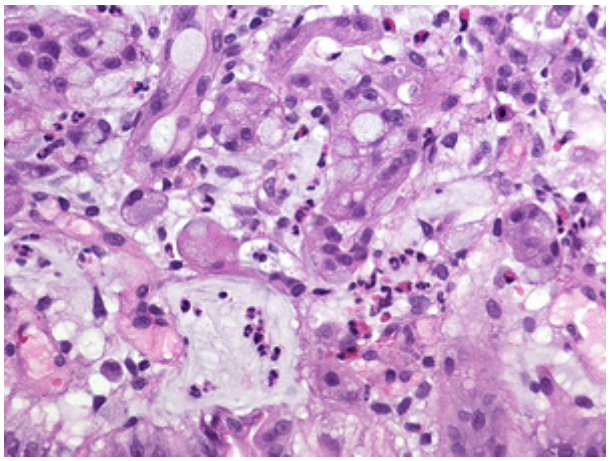
June 2015

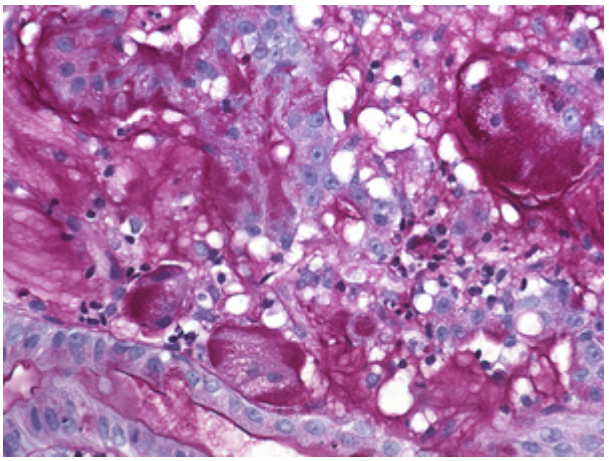
Ulcerated tumour of the ampulla of Vater in a 65-year-old male.

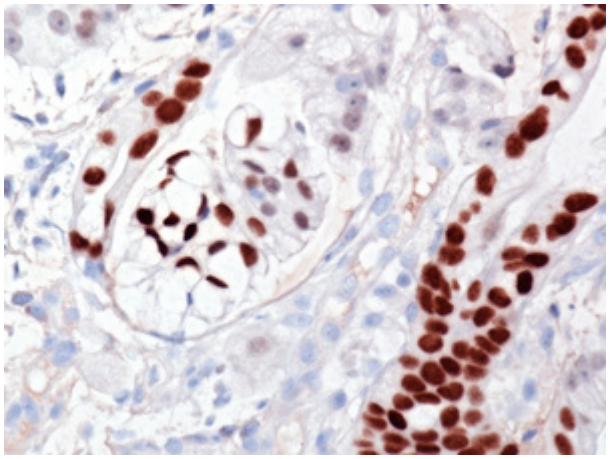
What is your diagnosis?

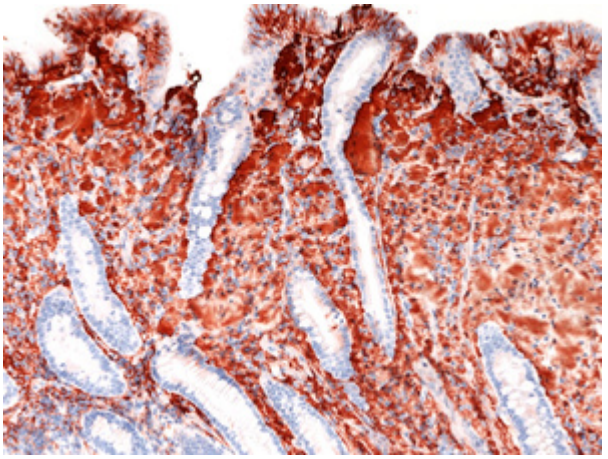


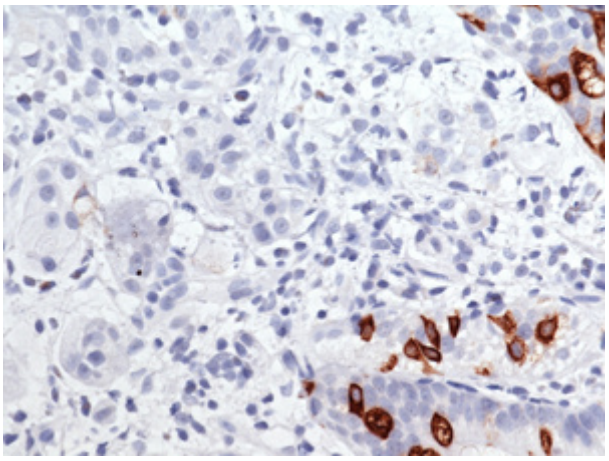
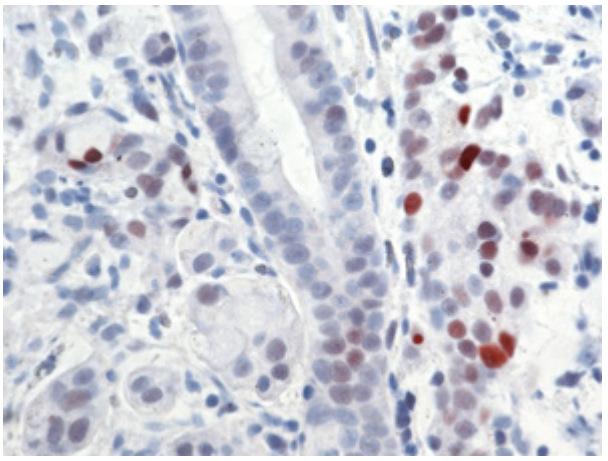










Diagnosis:

Invasive adenocarcinoma (intestinal-type) with mucinous and signet ring cell component.

Comment:

The patient is submitted with abnormal liver function tests with predominantly cholestatic pattern. Endoscopy shows an ulcerated tumour in the papilla (Panel A) and biopsies are taken. Upon histology, infiltrative neoplastic glands with tubular growth pattern as well as areas of extracellular mucin with isolated or small clusters of signet ring cells are seen (Panels B-C). The cells are positive on PAS stain (Panel D). Immunohistochemistry reveals expression of CK7, CK20, and CDX2 (Panel E) and MUC5AC (Panel F), while only faint positivity for MUC2 is seen in isolated tumour cells (Panel G). MUC1 and MUC6 are negative. Some cells are strongly marked with an antibody directed against TP53 (Panel H). There is retained (normal) expression of the mismatch repair proteins MLH1, MSH2, MSH6 and PMS2 (not shown).

Carcinoma of the ampulla (papilla) of Vater is an uncommon neoplasm and it represents 0.2-0.5% of all gastrointestinal malignancies. Ampullary carcinomas are more frequent in men and are usually diagnosed in patients between 60 and 80 years of age. Tumours are defined as primary ampullary if they are centred on, circumferentially surrounding or replacing the ampulla. They can be classified according to their primary site of growth as carcinomas associated with an intra-ampullary papillary-tubular neoplasm (IAPN), if they involve the distal ends of the common bile duct and pancreatic duct with a prominent intraluminal growth, as ampullary duct characterized by insidious carcinomas that cause plaque-like thickening of the ampullary portion of the duct walls, as ampullary duodenum when they are predominantly or exclusive present on the duodenal surface, and as ampullary not otherwise specified corresponding to tumours localized at the papilla of Vater that lack the specific characteristics described above. These site-specific subcategories have distinct biologic and prognostic properties, with ampullary duodenum and IAPN-associated carcinomas presenting better prognosis than ampullary duct tumours.

Most malignant neoplasms of the ampulla of Vater are adenocarcinomas. Intestinal-type adenocarcinomas express markers of intestinal differentiation, such as CDX2 and MUC2. CK7 can be positive and MUC1 is usually negative. Pancreatobiliary-type adenocarcinomas are positive for CK7, CK19 and MUC1, but lack MUC2 and CDX2 expression. MUC5AC may be positive in both types, and there is increased expression of TP53 in about 70% of cases. The immunohistochemical typing of ampullary adenocarcinomas is necessary and should always be done, as the distinct subtypes are generally believed to carry distinct prognostic properties, with intestinal-type adenocarcinomas showing better prognosis than pancreatobiliary-type cancers. However, the distinction may not be straightforward in all cases, and mixed types can occur.

On the molecular level, KRAS mutations are found in about 40% of cases. Notably, there is no correlation with histological type. The impact on prognosis is still largely unclear. However, according to a very recent publication the KRAS(G12D) mutation may be associated with a subset of patients with poor outcome and

may be used to identify patients at risk of early recurrence and poorer survival who may benefit from adjuvant therapy.

Up to 10% of ampullary carcinomas demonstrate high-level microsatellite instability (MSI-H), which is not due to germline mutations but due to epigenetic silencing of one of the mismatch repair genes (usually MLH1). This finding has been associated with improved patient survival. As in the colon, MSI-H ampullary adenocarcinomas often show mucinous differentiation and/or intratumoural inflammatory infiltration.

For further reading:

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