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Case Report

Hepatic perihilar amphicrine cholangiocarcinoma: A case report

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ABSTRACT

Mixed neuroendocrine nonneuroendocrine neoplasms (MiNEN) are tumors composed of adenocarcinoma and neuroendocrine neoplasm and include collision, combined, and amphicrine. Within the hepatobiliary tree, tumors of this histologic type are extremely rare, particularly the amphicrine type. In this case study, we describe a 63-year-old man with a hepatic hilar amphicrine tumor. An initial diagnosis of neuroendocrine tumor was made based on biopsy (chromogranin and synaptophysin positivity). On resection, the tumor contained histologic features of both adenocarcinoma and neuroendocrine carcinoma. Immunohistochemically, all tumor cells expressed both chromogranin and synaptophysin, keratin 7, and Cam5.2. Mucin production was evident in both components demonstrated by mucicarmine stain. Albumin RNA in situ hybridization (ISH) was positive, supporting hepatic source. The tumor is classified as an amphicrine carcinoma given the dual expression of both adenocarcinoma and neuroendocrine markers in both components. This is the first amphicrine carcinoma of the hepatic hilum reported in the literature.

1. Introduction

Mixed neuroendocrine-nonneuroendocrine carcinoma (MiNEN) consists of nonneuroendocrine and neuroendocrine neoplasm components, each comprising at least 30% of the tumor [1,2]. Most frequently, the nonneuroendocrine component is an adenocarcinoma. Whereas most collision tumors consist of two morphologically and phenotypically populations that are sharply distinct, combined tumors show intermingling of the two components but with distinct immunophenotypes [3]. Rarely, MiNENs are of the amphicrine type [4,5]. In these tumors, both exocrine and neuroendocrine features are exhibited morphologically by the same neoplastic cell, which also shows a divergent immunophenotype. Primary MiNEN of the biliary tree is exceptionally rare [5–9]. We hereby present a case of perihilar hepatic amphicrine carcinoma and review of the literature.

2. Case report

A 63-year-old man with a history of cholecystectomy for cholelithiasis presented to his local provider with a chief complaint of recent onset of diffuse pruritus, intermittent nausea, and dark urine. The study was approved by the Institutional Review Board at Mayo Clinic. Laboratory workup revealed total bilirubin 2.6 mg/dL, alkaline phosphatase 233 U/L, GGT 590 U/L, ALT 152 U/L, and AST 70 U/L. CA19–9 was 76 U/mL (normal < 55 U/mL). Alpha-fetoprotein was normal at 2.8 ng/dL. Computed tomography (CT) scan revealed an ill-defined 5.9-cm mass involving both the liver hilum and the left hepatic lobe. The radiologic features, including thickening of the left hepatic duct and common hepatic duct, were most consistent with cholangiocarcinoma.

Both biliary brushings and a liver biopsy showed scant fragments of a neoplasm, consistent with a neuroendocrine tumor (NET), WHO grade 2 (of 3) [1]. Tumor cells were diffusely positive for keratin AE1/AE3, keratin 7, chromogranin, and synaptophysin. CDX2, ERG, FLI-1, HepPar, arginase-1, glypican-3, keratin 20 were negative. Ki-67 proliferative index was 7%.

No primary source of the NET, other than the liver lesion, was identified. The patient was referred for surgical resection of the tumor, and intraoperative ultrasound revealed that the tumor involved the left hepatic duct and hepatic confluence. An extended left hepatectomy with a caudate lobectomy, which included segments I, II, III, IVA and IVB and the middle hepatic vein, was performed. The right hepatic duct margin required additional resection to achieve a negative margin.

Grossly, a 5.8-cm firm, white-tan tumor was identified involving the hepatic hilum (centered around the left hepatic duct) and also significantly occupied the left hepatic lobe (Fig. 1). Two small satellite

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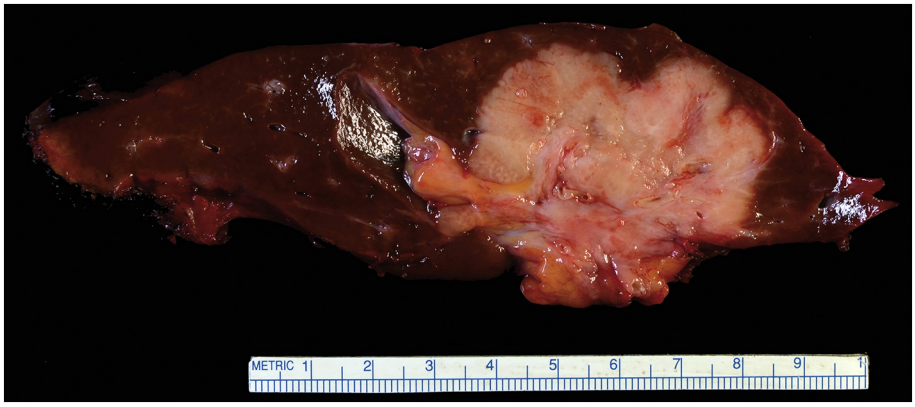

Fig. 1. Cross-section of hilar mass infiltrating hepatic parenchyma.

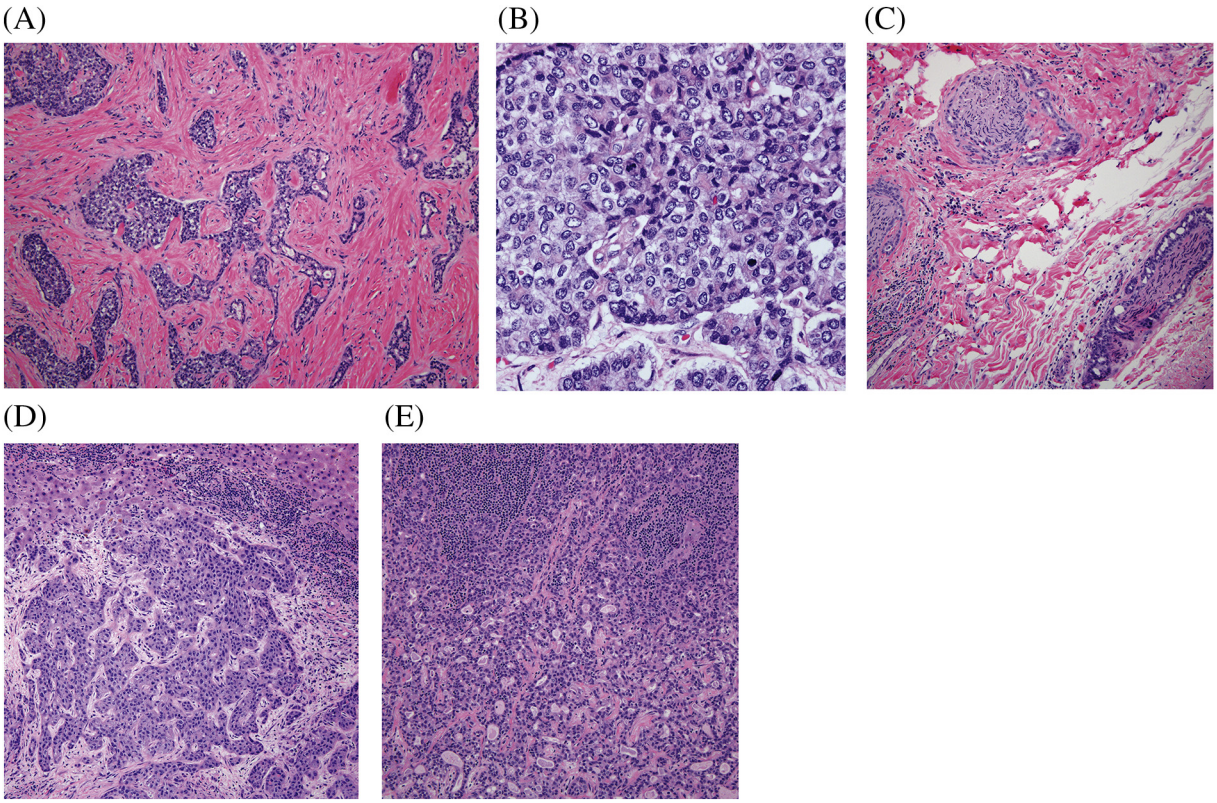

Fig. 2. H&E of hilar mass and metastasis. A nested neuroendocrine morphology (left) transitions to a tubular morphology (right) (A). The neuroendocrine-appearing area shows characteristic, finely dispersed chromatin and contains mitotic figures (B). Extensive perineural invasion is exclusively seen in the tubular component (C). Metastatic disease at presentation included hepatic satellite nodules with predominant solid features (D) and a lymph node with predominant tubular features (E).

nodules were also identified within the hepatic parenchyma. Histologically, two morphologic patterns were noted (Fig. 2). The first pattern showed small irregular and infiltrative ducts/tubules with cytologic atypia and a prominent paucicellular stroma, consistent with invasive adenocarcinoma, were evident. This component showed perineural invasion. The second pattern was composed of neoplastic cells arranged in nests and displayed uniform nuclei with evenly dispersed chromatin and inconspicuous nucleoli, consistent with NET. This pattern was identical to the histology seen in the preoperative biopsy and biliary brushings. The majority of the tumor, however, showed neoplastic cells exhibiting features of both components in the same cell, mostly characterized by nested tumor cells with neuroendocrine cytologic features but also containing intracytoplasmic mucin. By immunohistochemistry, tumor cells diffusely expressed keratin 7, CAM5.2, chromogranin, and synaptophysin. Mucicarmine stain revealed mucin production in all components (Fig. 3). Keratin 20 and CDX2 were negative. Ki-67 proliferative index was approximately 40%. Albumin RNA in situ hybridization (ISH) was positive (Fig. 3). Two satellite nodules were present: one displayed predominantly NET morphology, and the other had mixed features (Fig. 2). A single lymph node was positive for metastatic carcinoma and displayed predominant adenocarcinoma type morphology (Fig. 2), with a Ki-67 proliferation index of approximately 40% (Fig. 3). A diagnosis of amphicrine carcinoma was provided based on the morphologic and immunohistochemical evidence of divergent exocrine and neuroendocrine phenotype expressed by the majority of the tumor cells and in the absence of other tumors in the patient's body (including the gastrointestinal tract and pancreas). Pathologic stage was pT4, N1 [10] and the margins of resection were free of tumor.

Postoperatively, there were complications with biliary leak, and the patient is yet to receive his scheduled adjuvant chemotherapy. Four