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A massive hepatic tumor demonstrating hepatocellular, cholangiocarcinoma and neuroendocrine lineages: A case report and review of the literature

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ABSTRACT

INTRODUCTION: Mixed hepatocellular and cholangiocarcinoma tumors (MHCC) are described in the literature, as are the more rare mixed adenoneuroendocrine carcinomas (MANC) of hepatobiliary origin. Only two cases of tumors with characteristics of all three histologies/phenotypes have been previously described in one Chinese study.
PRESENTATION OF CASE: Herein we report clinical, microscopic and molecular features of a 25 cm mixed hepatic tumor with hepatocellular, cholangiocarcinoma and neuroendocrine differentiation arising in an otherwise healthy 19-year-old North American Caucasian male without any identifiable risk factors.
DISCUSSION: The patient underwent multimodality imaging and the tumor was biopsied preoperatively, and it was initially interpreted to be hepatocellular carcinoma fibrolamellar type. A left trisegmentectomy with lymphadenectomy was performed and the tumor was definitively diagnosed based on the surgically resected specimen. Integrated microscopic and molecular features defined the differing biological aggressiveness of growth pattern components. Cases in the literature of MHCC and rare cases of MANC have largely undergone aggressive surgical resection as well, however the majority of studies on mixed hepatic tumors to date reflect Eastern patient cohorts and populations with underlying liver disease, thereby limiting extrapolation on management or outcomes in this case.
CONCLUSION: This is one of the only reports of a hepatic tumor arising from hepatocellular carcinoma, cholangiocarcinoma and neuroendocrine lineages. Increased awareness of this tumor type may optimize improve future management.

1. Introduction

Though rare in comparison to other primary liver tumors such as hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC), mixed hepatocellular carcinoma and cholangiocarcinoma (MHCC) tumors are well-described and can be noted in the literature as early as 1903 [1]. Rare mixed adenoneuroendocrine carcinomas (MANC) of hepatobiliary origin have also been reported [2]. To date only two previous cases of a single hepatic tumor demonstrating HCC, ICC and neuroendocrine differentiation have been reported, both from the same Chinese study [3]. Herein we describe a 25 cm mixed hepatic tumor with HCC, IOC and neuroendocrine differentiation, diagnosed in an otherwise healthy North American Caucasian male patient and managed at an academic tertiary care center. Our report is in accordance with the SCARE guidelines [4].

2. Presentation of case

In July 2016 an otherwise healthy 19-year-old male was seen for evaluation of a large liver mass. This was discovered when hepatomegaly was noted during a routine physical exam, and on assessment he did report some vague intermittent abdominal pain over the last several months. He had no other medical problems, including hepatitis or congenital liver abnormalities, or past surgeries. He took no medications and was allergic only to penicillin with a reaction of a rash. He did not smoke or drink alcohol and

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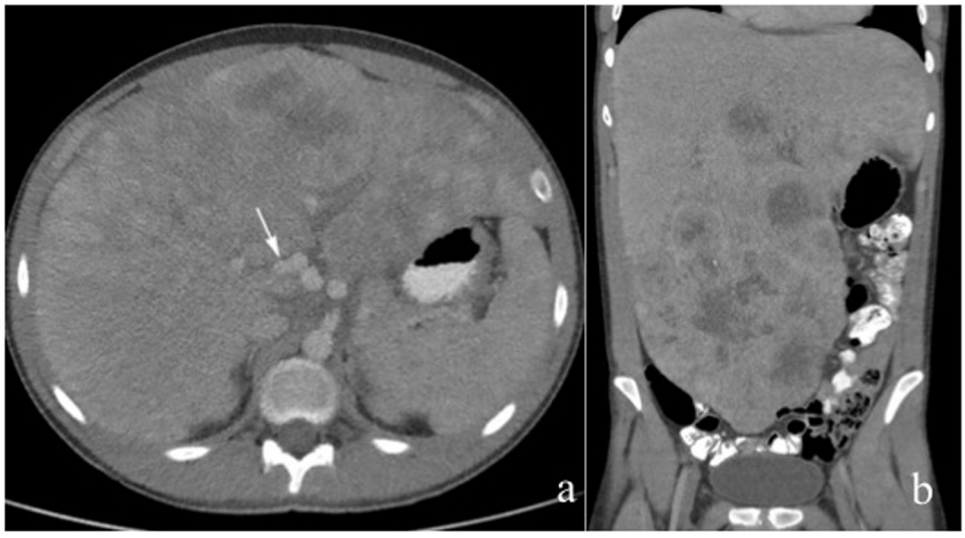

Fig. 1. Axial (a) and coronal (b) post-contrast CT, obtained during venous phase, show marked hepatomegaly with numerous hepatic lesions in left lobe and in segment 5. The lesions show peripheral enhancement and diminished central attenuation on venous phase. Note the enlarged hepatic arteries (arrow in b).

there were no medical problems in his immediate family aside from a grandmother who was a smoker and died of lung cancer.

His workup prior to presentation at our institution included an initial abdominal ultrasound that reported multifocal masses within the liver, and subsequent CT scan of the abdomen and pelvis with oral and venous phase IV contrast that showed marked hepatomegaly with liver extension into the pelvis and, numerous bilobar hepatic lesions predominantly in segments IV and V (Fig. 1). The dominant lesions were centrally hypodense and no frank cirrhotic features were appreciated. Full laboratory studies were performed with normal complete blood count, basic metabolic panel and coagulation studies. The only liver function abnormalities were an elevated AST of 187 U/L (normal range 15–37 U/L) and elevated alkaline phosphatase of 189 U/L (45–117 U/L). Tumor markers included an elevated LDH of 770 U/L (87–241 U/L), an elevated CA19-9 of 284 U/mL (0–40 U/mL), and normal beta-HCG, CEA, AFP and neuron-specific enolase. He underwent a CT-guided liver biopsy with a total of seven 18-gauge fine needle aspiration samples obtained. On pathology review this was initially felt to represent a HCC fibrolamellar type (FL-HCC), and he was referred to our institution for further management. MRI with gadoxetate disodium (Eovist®) was subsequently obtained. The dominant lesions showed central T2 hyperintensity and peripheral diffusion restriction with progressive centripetal enhancement suggestive of fibrolamellar HCC versus cholangiocarcioma, although the former was favored based on the patient's demographics (Fig. 2). No arterial hyperenhancement or washout was present. Note was also made of peripheral reticular areas of signal alteration involving the background liver, suggestive of sinusoidal dilatation.

The patient underwent a left hepatic trisegmentectomy with cholecystectomy and lymphadenectomy by an experienced hepatobiliary surgeon. Intraoperatively this mass was found to occupy most of the upper abdomen with extension into the pelvis. Two enlarged lymph nodes, one para-aortic and one at the portal vein, were resected. A very enlarged hepatic artery and many intrahepatic collaterals were noted, but otherwise vascular and biliary anatomy was normal. Intraoperative ultrasound demonstrated that the caudate lobe and segments 6 and 7 were free of tumor. The patient was discharged from the hospital on postoperative day 9. He was treated adjuvantly with six cycles of gemcitabine and cisplatin systemic chemotherapy. Follow-up CT scan four months after surgery showed multiple necrotic periportal, mesenteric, and retroperitoneal lymph nodes with mild-to-moderate hypermetabolism suspicious for metastatic disease. EUS-guided lymph node biopsy of the representative enlarged aortocaval node showed all three tumor types, with the neuroendocrine component being the most aggressive. An octreotide scan was performed and was negative for uptake. He was then treated with capecitabine and temozolomide and after two cycles underwent a gallium 68 dotate scan which did not demonstrate any uptake, indicating that the previously seen enlarged lymph nodes were not of well-differentiated neuroendocrine tumor origin. Most recent CT scan, performed after his third cycle of capecitabine and temozolomide and eight months after surgical resection, did not demonstrate any disease progression.

On pathologic examination, the specimen weighed 3.3 kg and measured $38 \times 19 \times 11$ cm with tumor measuring $25 \times 12.5 \times 11$ cm and occupying 75% of the capsular surface (Fig. 3). Representative sections of the tumor including sections of the paraaortic lymph node were submitted to extensive workup using mainly hepatocellular (HepPar-1, glutamine synthetase, Arginase-1, CAM5.2, AFP, Glypica-3, Beta catenin), adenocarcinoma (CK7, CK19, Ca19.9, MOC31,CK20), and neuroendocrine markers (synaptophysin, chromogranin, CD56 and Ki67) (Fig. 4). Intradepartmental review at Children's Hospital of Pittsburgh was also requested. Overall, based on the histopathological findings and immunohistochemical profile, this tumor was felt to represent a malignant epithelial neoplasm with multiple lineages including hepatocellular, cholangiocarcinoma and neuroendocrine carcinoma. Histologic features of hepatoblastoma or fibrolamellar type HCC were not observed. Metastatic carcinoma was found in the two lymph nodes demonstrating predominantly neouroendocrine/adenocarcinoma features. Testing was also performed for PD-L1 and was found to be positive in the neuroendocrine tumor lineage including the lymph node metastasis. The tumor was staged as T2a, N1.

To better understand the biological potential of individual growth pattern components, microdissection of unstained formalin-fixed, paraffin-embedded tissue sections guided by microscopic dissection, was employed to gather DNA from distinct areas of this complex, multicomponent neoplasm [5]. To further characterize molecular heterogeneity, multiple microdissection targets (5–7 individual targets) were taken from HCC/cholangiocarcinoma versus neuroendocrine neoplasia growth areas as well as from the metastatic lymph node (LN) tumor (Table 1). A broad panel of tumor suppressor genes (TSG) was