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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.

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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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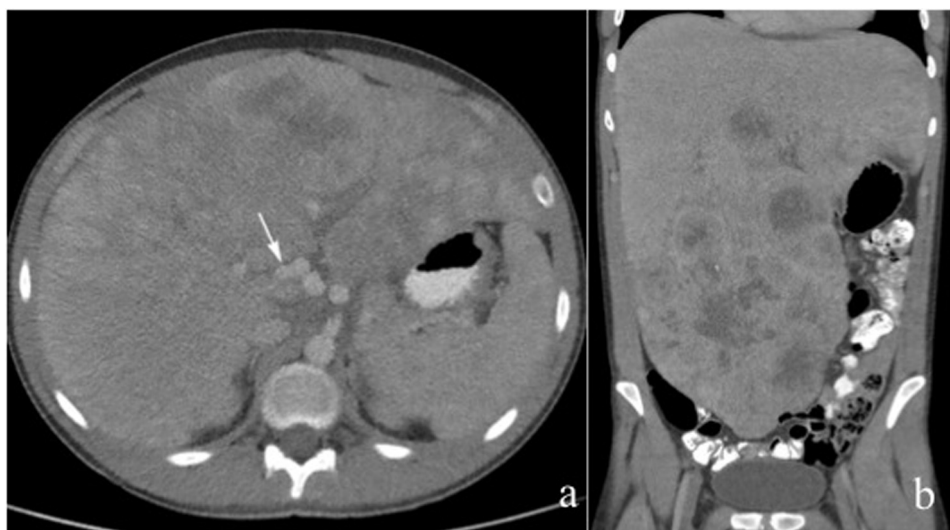


Fig. 1. Axial (a) and coronal (b) post-contrast CT, obtained during venous phase, show marked hepatomegaly with numerous hepatic lesions in left lobe and in segment 5. The lesions show peripheral enhancement and diminished central attenuation on venous phase. Note the enlarged hepatic arteries (arrow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

metabolism 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 × 19 × 11 cm with tumor measuring 25 × 12.5 × 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). Intra-departmental 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 neuroendocrine/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

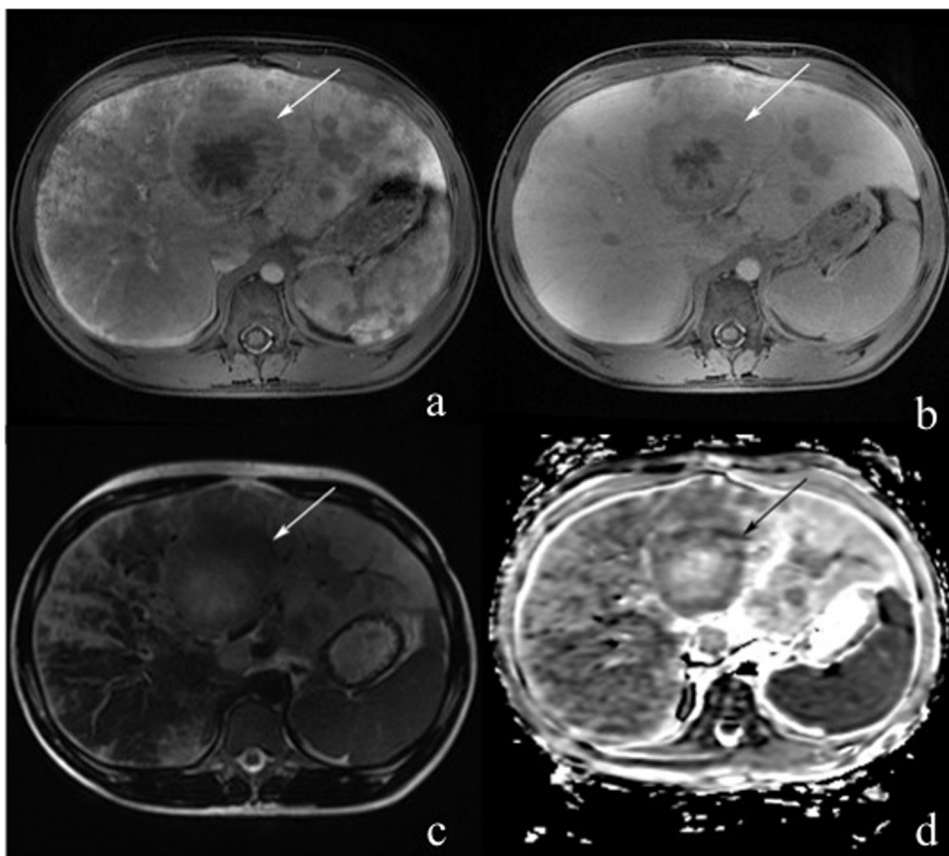


Fig. 2. Axial post-contrast T1-weighted images through the segment 4 dominant lesion (arrows), obtained during arterial phase (a) and with 3 min delay (b) show peripheral enhancement with progressive centripetal filling. There is no arterial hyperenhancement or washout. The lesions shows central hyperintensity on T2-weighted image (c) and peripheral diffusion restriction on ADC map (d). Note peripheral reticular areas of T2 hyperintensity and enhancement in the background liver suggestive of sinusoidal dilatation.

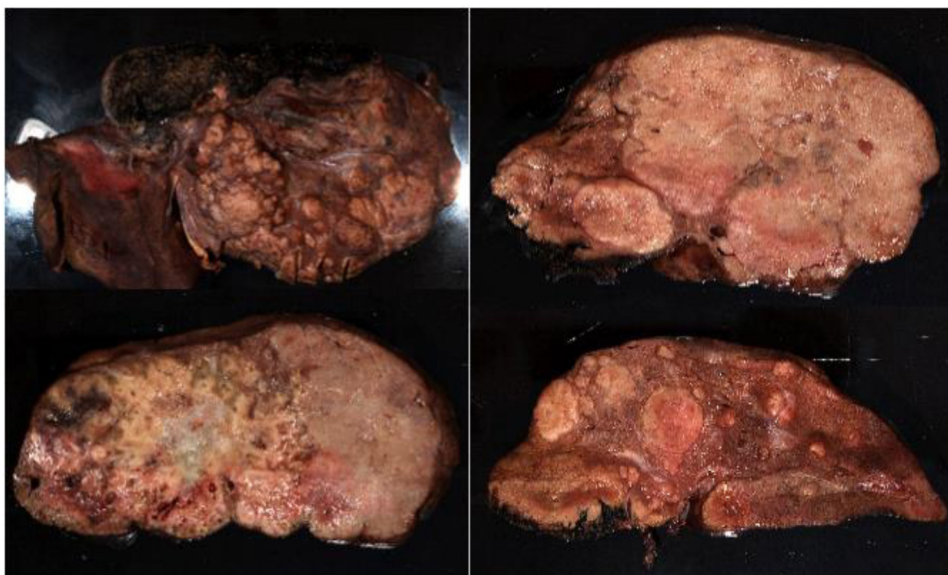


Fig. 3. Macroscopic image of resected liver (38 × 19 × 11 cm; weight: 3.3 kg) with multiple slices through tumor (25 cm in greatest dimension).

interrogated for loss of heterozygosity reflecting the second, gene deletion step responsible for loss of TSG function. A polymorphic microsatellite marker approach was used, capable of detection and quantifying TSG loss [6].

Detectable TSG mutational change was restricted to the neuroendocrine growth pattern, thereby affirming its increased biological aggressiveness and responsibility for metastatic spread (Table 1). A temporal sequence of multistep acquisition of TSG loss could be defined starting with 5q LOH followed closely in

time by 7p allelic imbalance (Table 1). Intratumoral molecular heterogeneity was prominently displayed in the neuroendocrine component with varying degrees of further mutation acquisition across individual targets including development of new alleles reflecting microsatellite instability (Table 1). Comparative molecular profiling between the different growth components of the tumor (neuroendocrine versus HCC-like) indicates that the derivation of these components was an early event in carcinogenesis. Lack of detectable neuroendocrine-associated mutations in the HCC-like component supports that the neuroendocrine component likely was not derived from the HCC-like cancer cells. More likely is that the early division of the growth components arose from a stem cell precursor capable of differentiation along separate cell lineage lines.

3. Discussion

This case represents a very unique tumor entity reported only one time previously in the literature in a Chinese report describing two cases. This study described two male patients with an average age of 57.5 years that were hepatitis B positive. Both tumors demonstrated three unequivocal mixed elements described as [1]: polygonal epithelial tumor cells growing in nests or trabeculae with positive staining for Hepatocyte and AFP, diagnostic of hepatocellular carcinoma (HCC). Cytoplasmic bile production was present in the tumor cells in one case [2]; elliptic or short spindle-shape small blue tumor cells growing in nests or organoid pattern with Syn/CgA/CD56 positivity confirming the presence of neuroen-

docrine carcinoma (NEC) component [3]; oval tumor cells growing in nests or glandular forms with positivity of CK19 and CK7 confirming differentiation of cholangiocarcinoma (CC). In both cases, the tumors contained at least 20% each of HCC, neuroendocrine and cholangiocarcinoma components [3].

Given the very limited report of cases such as ours with all three types of tumor differentiation, examining the known etiologies of MHCC and MANC tumors can perhaps best guide management and predict clinical outcomes. The clinical and pathologic features of MHCC tumors have been described in the literature for decades. In 1996 Nakamura et al. examined six patients with this diagnosis. Five of the six patients, ranging in age from 53 to 65, had underlying chronic liver disease, however the remaining patient was a 28-year-old female with a large 12 cm tumor and no other identifiable risk factors, similar to our patient. This patient remained alive and disease free at six years after surgery. The authors concluded that extensive surgery was an effective treatment and that, owing to the absence of metastases in dissected lymph nodes, hilar lymphadenectomy may not be necessary in selected patients [7]. In 1998 Ng et al. reported on 21 cases of this histology and noted a 6:1 male:female ratio, cirrhosis or chronic hepatitis in 77.8% of patients, elevated AFP levels above 300 ng/mL in 61.5% of patients, and overall short survival times, leading to their conclusion that MHCC was clinically and pathologically more similar to HCC than ICC [8]. Jarnagin et al. reported on 27 MHCC patients in 2002 over a 15-year study period. Whereas the majority of studies on this etiology report on Asian cohorts, only two of these patients were Asian. They found nearly equal male:female gender distribution and none

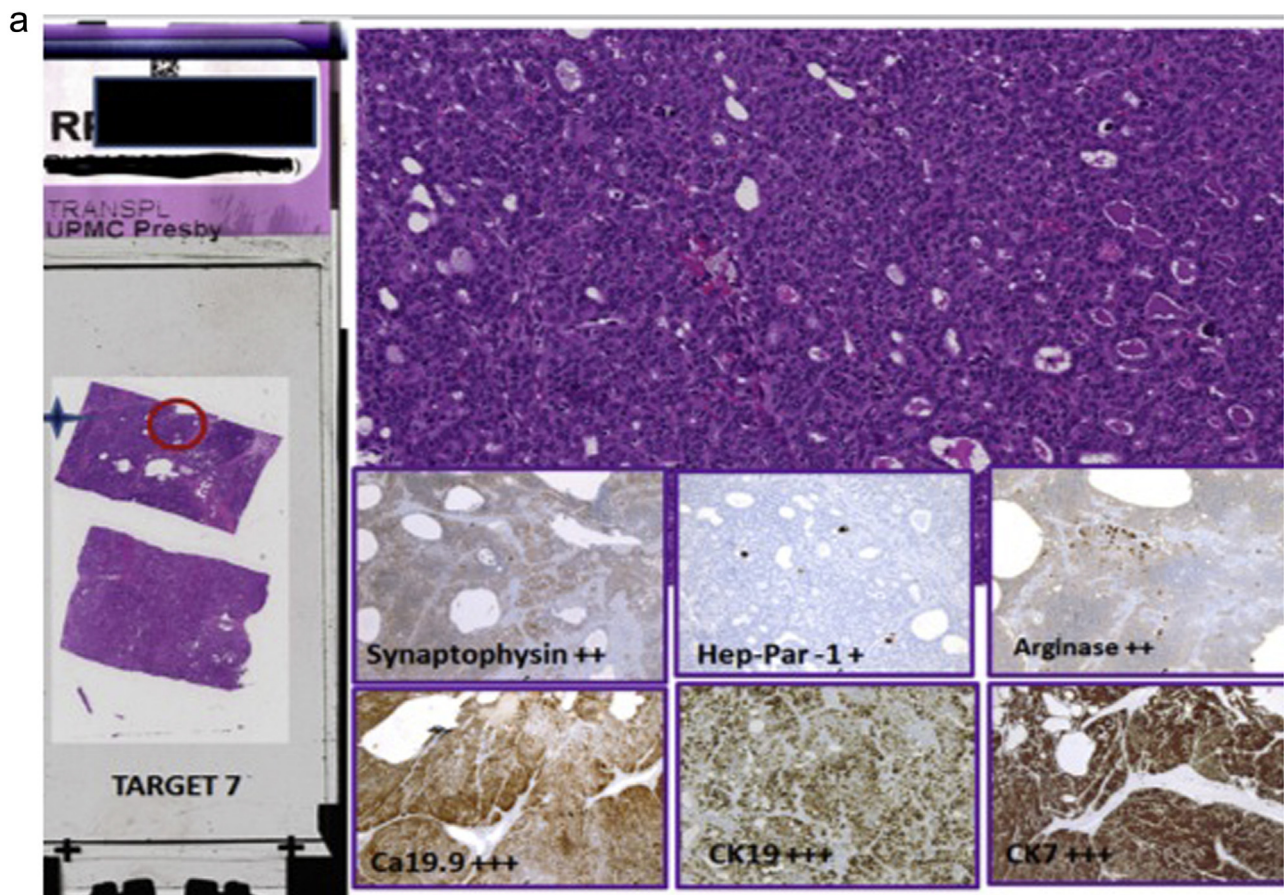


Fig. 4. a. Two representative sections of the tumor; tumor with trabecular and glandular patterns (blue star) shows focal hepatocellular phenotype (positive Arginase-1, rare positive cells with HepPar-1 and strongly positive cholangiocarcinoma phenotype CK7, CK19, Ca19.9). Adjacent section of tumor shows a solid pattern with neuroendocrine differentiation. b. Section of lymph node with metastatic carcinoma. Immunohistochemical stains show predominant neuroendocrine differentiation (positive synaptophysin and CD56 markers).

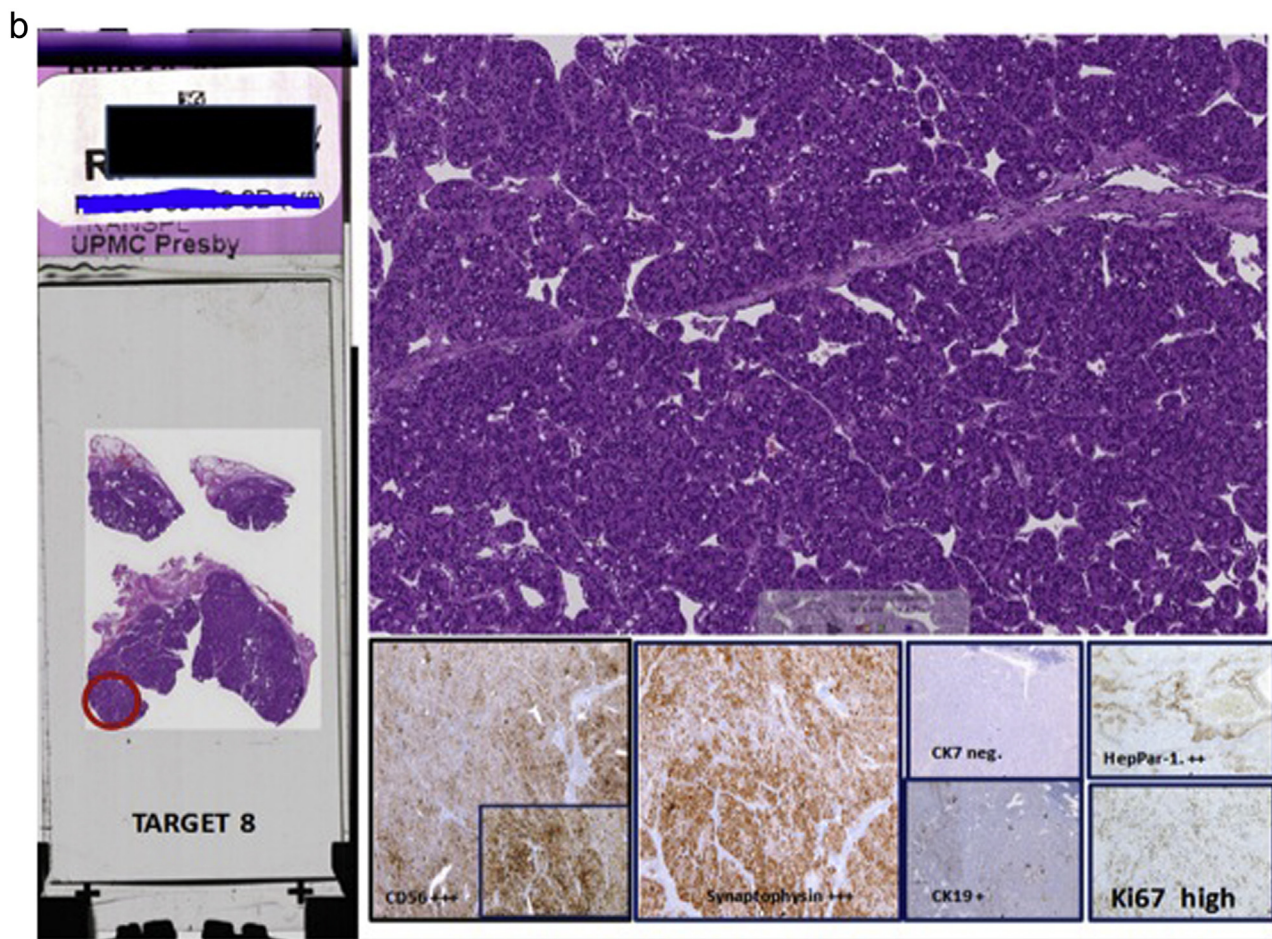


Fig. 4. (Continued)

of their MHCC patients were cirrhotic, though 15% were hepatitis B or C positive. 78% of patients were resected and five-year survival was 24% for the MHCC group, which was not significantly different from the HCC or ICC patients [9]. The differences in this study's patient cohort compared to the majority of other studies published may make it more applicable to the patient in our case.

Subsequent series continued to report on the management and prognosis of MHCC tumors, with varying and sometimes contrary results. In 2006 Tang et al. aimed to define the clinicopathologic features of MHCC with a retrospective analysis of 13 MHCC, 509 HCC and 41 ICC patients occurring over a 20-year period and did not find significant differences in survival between the groups [10]. Also in 2006, Lee et al. reported on 952 patients who underwent liver resection for primary hepatic neoplasm, and reported an incidence of 3.5% for MHCC. They found a significantly lower overall and disease-free survival for MHCC patients as compared to those with ICC or HCC, and advocated for a more aggressive treatment modality including lymphadenectomy [11]. In 2009 Kim et al. also pointed to poor postoperative survival in their series of 29 patients and echoed the recommendation for aggressive resection of tumor and lymph nodes [12]. In 2011 Park et al. described 43 patients with MHCC and also found that 84% of those who underwent resection recurred within 18 months, leading to a significantly worse overall outcome when compared to their counterparts with other primary liver tumors [13]. Most recently in 2016 Yoon et al. reported on 53 patients who underwent surgical resection for MHCC tumors over a 12-year period, comprising only 1.1% of their primary liver malignancies during that time period. Tumor recurrence rate was 80.7% at both 5 and 10 years and survival was 30.5 and 11.1% respec-

tively. When compared to contemporary patients with HCC and ICC, tumor recurrence rates did not differ ($p=0.43$) but survival for MHCC patients was significantly worse ($p=0.000$) [14].

Even more rare than MHCC tumors are reported hepatobiliary tumors that demonstrate pathologic features of MANC. Harada et al. reviewed 274 cases of biliary cancers including HCCs, ICCs and gallbladder cancers for neuroendocrine features using chromogranin A and synaptophysin markers. They found a significant neuroendocrine component in 4% of their reviewed hilar cholangiocarcinomas, all of whom had hepatolithiasis, in 10% of the gallbladder cancers and in 4% of extrahepatic cholangiocarcinomas. They did not find neuroendocrine differentiation in any of the reviewed ICCs, HCCs or in any of the intrahepatic cholangiocarcinomas that occurred in the absence of hepatolithiasis [2]. Other reported mixed liver tumors include rare cases of MHCC tumors with sarcomatous transformation, including one case reported in the Lee et al. series of a patient who underwent right hepatectomy but died within one month of multiple metastases [11]. Additional case reports of this variant exist in the Japanese literature [15,16].

Molecular analysis of our patient's complex liver tumor was noteworthy in a number of ways. Mutational profiling findings were striking between the different growth patterns with detectable mutational change confined to the neuroendocrine component in keeping with its greater apparent biological aggressiveness. The neuroendocrine tumor component shows prominent genomic instability with new mutation acquisition at each site sampled by microdissection (Table 1). Genomic instability in the neuroendocrine component was further evidenced by emergence of new microsatellite alleles consistent with a degree of microsatel-

Table 1
Copy number mutational profiling of different growth patterns.

		Neuroendocrine growth pattern							HCC growth pattern					LN metastasis	
		#1	#2	#3	#4	#5	#6	#7	#1	#2	#3	#4	#5	#1	#2
1p36	01p #1			50%	50%										
1p36	01p #2	50%													
1p34	01p #3														
1p22	01p #4														
3p24	03p #1														
3p24	03p #2														
3p24	03p #3														
3p24	03p #4														
5q25	05q #1														
5q25	05q #2	60%	60%	50%	60%	50%	50%	50%						60%	50%
7p11	07p #1			50%											
7p11	07p #2	50%				50%								50%	
9p22	09p #1														
9p22	09p #2														
10q25	10q #1	50%	60%					50%						50%	60%
10q25	10q #2														
17p13	17p#1														
17p13	17p #2														
17p13	17p #3		MSI												
17q25	17q #1														
17q25	17q #2														
18q23	18q #1														
18q23	18q #2	50%	60%												
19q12	19q #1														
19q12	19q #2														
21q25	21q #1														
22q13	21q #2														

14 discrete microdissection targets were taken of primary and metastatic tumor guided by microscopic growth pattern. Multiple targets of the each growth pattern were designed to inform molecular heterogeneity within each morphologic component. Copy number assessment was based on allelic imbalance using polymorphic microsatellite markers as previously described [4,5]. Blue indicates relative loss of the longer polymorphic microsatellite allele, Red indicates relative loss of the shorter polymorphic microsatellite allele. Grey indicates noninformative microsatellite marker status and blank indicates normal, balanced allele status. Detectable copy number imbalance was confined to the neuroendocrine growth pattern associated with genomic instability supportive of relative greater biological aggressiveness.

lite instability inherent within this growth component. Of potential clinical follow up value, the temporal sequence of serial mutation acquisition could be defined with early mutations involving allelic imbalance involving 5q and 7p. These are common sites for tumor suppressor gene loss and/or oncogene amplification, which in this patient were consistently present in all primary and metastatic

deposits of neuroendocrine tumor. Monitoring for evidence of tumor recurrence could thus take advantage of this observation by targeting molecular testing to detection of 5q and 7p copy number imbalance. This could be carried out in conjunction with imaging such as octreotide scintigraphy targeting the neuroendocrine component.

Preoperative diagnosis of mixed hepatic tumors by imaging alone is challenging and tissue sampling is usually required. Imaging findings of MHCC tumors overlap with those of HCC and cholangiocarcinoma and more commonly mimic cholangiocarcinoma rather than HCC. In minority of cases, however, features of both HCC (arterial hyperenhancement and washout) and cholangiocarcinoma (such as peripheral enhancement with progressive central filling, capsular retraction, upstream biliary ductal dilatation) can be seen at the same time. In a retrospective study by Folwer et al. sensitivity and specificity for correct diagnosis of MHCC was 30–35% and 80–100%, respectively [17]. In our presented case, the imaging findings were suggestive of fibrous stroma and were more compatible with cholangiocarcinoma. No features of HCC or neuroendocrine tumor were present. MRI also showed extensive sinusoidal dilatation in the background liver that was presumably secondary to outflow obstruction by the mass.

4. Conclusion

As with most mixed hepatic tumors, the preoperative diagnosis was uncertain and the postoperative pathologic diagnosis of this tumor as exhibiting HCC, ICC and neuroendocrine differentiation was challenging. The patient underwent aggressive surgical resection, as did other patients in the literature who presented with either MHCC or MANC tumors. The vast majority of studies reporting on these mixed hepatic tumors originate from Korea, Japan or China and describe patients with underlying liver disease, both of which differ from our reported patient who was North American and otherwise healthy, and whose clinical outcome remains to be seen.

Conflict of interest

None.

Funding sources

None.

Ethical approval

The patient in this case report is not involved in any research studies.

Consent

Written informed consent was obtained from the patient for publication of this case report and case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors contribution

Dr. Beard cared for the patient and wrote and edited the manuscript.

Dr. Finkelstein performed the molecular analysis and provided the interpretation and commentary.

Dr. Borhani was the radiologist for the case and provided the radiology images, interpretation and commentary.

Dr. Minervini was the pathologist for the case and provided the pathology images, interpretation and commentary.

Dr. Marsh was the patient's surgeon and contributed to the revisions and direction of the manuscript.

Guarantors

Dr. Beard and Dr. Marsh.

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