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Short report

Hepatocellular carcinoma with neuroendocrine differentiation: a case report

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ABSTRACT

Hepatocellular carcinoma with neuroendocrine differentiation, where tumor cells stain for both hepatocellular and neuroendocrine markers, is extremely rare. We report a case of a 65-year-old man who presented with a 14-cm rapidly growing mass in the right lobe of his liver with local extension into the gallbladder and portal vein. Serum AFP was 4625 ng/mL. Liver biopsy showed a poorly differentiated neoplasm with cells showing nuclear pleomorphism, high nuclear/cytoplasmic ratio, and numerous mitoses. The tumor cells stain for AFP, glutamine synthase, arginase, and glypican-3. The same tumor regions also stain positively for synaptophysin, chromogranin, and CD56. Given this histological pattern, this tumor was ultimately diagnosed as hepatocellular carcinoma with neuroendocrine differentiation.

1. Introduction

Rare cases of concurrent hepatocellular carcinoma and neuroendocrine tumors (Tazi et al. 2011) and collision tumors with separate hepatocyte and neuroendocrine regions in the same liver lesion (Yamaguchi et al. 2004; Yang et al. 2009; Baker et al. 2016) have been reported in the literature. Even rarer are tumors comprised of cells that stain positively for both hepatocellular and neuroendocrine markers (Aboelenen et al. 2014; Barsky et al. 1984). We present a case of the rare hepatocellular carcinoma with neuroendocrine differentiation.

2. Case

A 65 year old man with no known past medical history was admitted for progressively worsening right upper quadrant pain over one month. The patient also endorsed occasional chills and weight loss. He denied any history of liver disease or other infections. Family history was negative for malignancies.

His laboratory studies were notable for slightly elevated alanine transaminase (57 U/L), normal aspartate transaminase (40 U/L), elevated alkaline phosphatase (178 U/L) and low serum albumin (2.6 g/L). Notably his serum α-fetoprotein (AFP) was elevated to 4625.0 ng/mL on initial presentation.

His computed tomography scan of abdomen and pelvis showed a 14 × 14 × 8 cm heterogeneous liver mass concerning for malignancy, with apparent invasion of the portal vein and gallbladder involvement (Fig. 1). The patient underwent a CT-guided biopsy for further evaluation and diagnosis.

3. Pathologic findings

Pathology received four core liver biopsies ranging from 0.7–1.6 cm in length, which were submitted entirely for processing. Hematoxylin and eosin staining demonstrated small, irregularly shaped neoplastic cells with pleomorphic and hyperchromatic nuclei, high nuclear to cytoplasmic ratios, and frequent mitoses (Fig. 2A). There was complete loss of hepatic architecture compared to the surrounding parenchyma. The Ki-67 index was high.

Immunohistochemical studies showed strong staining of the tumor for α-fetoprotein and glutamine synthase (Table 1, Fig. 2B-C). Stains for glypican-3 and arginase were focally positive, while staining for hep-Par1 was negative. In addition, the same tumor regions, and in some cases the same tumor cells, also stained positively for the neuroendocrine markers chromogranin, synaptophysin, and CD56 (Fig. 2F–H). Of note, the tumor showed patchy staining for CAM 5.2, pan-cytokeratin (AE1/AE3), CK7, and S100 but did not stain positively for HMB-45, neuron-specific enolase, CK20 or CD45. Given these findings, the tumor was diagnosed as hepatocellular carcinoma with neuroendocrine differentiation.

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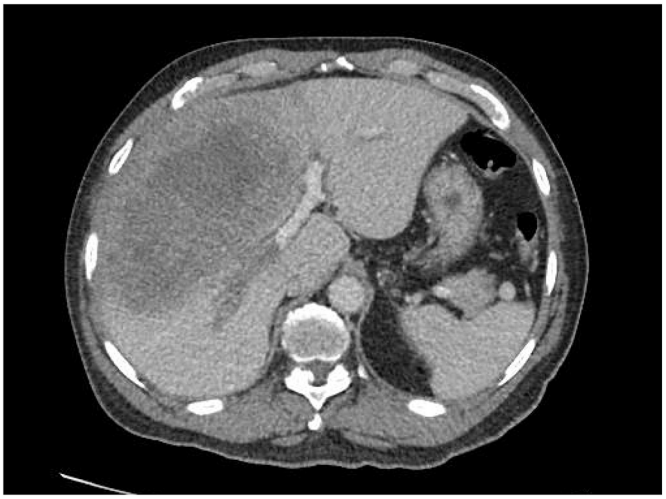

Fig. 1. CT abdomen and pelvis with contrast on presentation shows a heterogeneously enhancing mass in the right lobe of the liver. Portal vein thrombosis is also noted.

4. Discussion

4.1. Hepatocellular origin

The clinical presentation, serum AFP of 4625 ng/mL, and radiographic findings are highly suggestive of a hepatocellular origin for this poorly differentiated tumor. Elevated serum AFP over 20 ng/mL is 80–94% specific for hepatocellular carcinoma and levels of 400–500 ng/mL have specificity near 100% (Gupta et al. 2003). At a later visit the patient was found to have a serum AFP of over 17,000 ng/mL. AFP can be elevated in yolk sac tumors but imaging of his scrotum only showed a nonspecific fluid collection with a fat containing inguinal hernia without a mass. Strong immunohistochemical staining for α-fetoprotein and glutamine synthetase also support a hepatocellular origin. Of note, glutamine synthetase expression is associated with poor prognosis and tumor recurrence in advanced hepatocellular carcinoma (Osada et al. 2000).

Notably, hep-Par1 was negative in this tumor, even though case series have shown this stains positive in over 90% of hepatocellular carcinoma (Chu et al. 2002). However, this marker is less sensitive in tumors with high nuclear grade. For example, one case series showed 37 out of 44 grade 3 lesions positive for hep-Par1 and 1 out of 2 lesions positive in nuclear grade 4 (Yang et al. 2009). Another case series of 151 hepatocellular carcinomas showed only 46.4% sensitivity for hep-Par1 for poorly-differentiated tumors (Yan et al. 2010). A third series of 79 patients showed 64% sensitivity of hep-Par1 for poorly differentiated tumors (Nguyen et al. 2015).

Arginase, a stain with high specificity for hepatocellular carcinoma (Kandukuri et al. 2017), was focally positive in this tumor. Arginase has over 90% specificity for distinguishing between hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma (Radwan and Ahmed 2012). However, like hep-Par1, this stain is less sensitive in poorly differentiated hepatocellular carcinoma; in one series arginase-1 demonstrated 85.7% sensitivity for poorly differentiated hepatocellular carcinoma compared to over 96% for moderately and 100% for well differentiated tumors (Yan et al. 2010).

Glypican-3 staining was also focally positive. Glypican-3 helps distinguish hepatocellular carcinoma from benign hepatic lesions (Wang et al. 2008). Of note, it shows higher sensitivity for poorly differentiated tumors (85%) compared to moderately (80%) and well differentiated (60%) tumors (Nguyen et al. 2015). Thus, the immunohistochemical stains for AFP, glutamine synthetase, arginase, glypican-3, and hep-Par1 are consistent with a poorly differentiated hepatocellular carcinoma.

5. Neuroendocrine differentiation and clinical significance

The strong staining for synaptophysin, chromogranin, and CD56 indicate a neuroendocrine differentiation of this tumor. Notably, the same tumor regions stain for both hepatocellular and neuroendocrine markers. The case reports of such tumors generally describe large tumors with poor clinical prognosis. One case series of five patients described tumors ranging from 8 to 17 cm in maximum diameter. (Park et al. 2008). Of the four patients that were followed up in this series, one survived for 16 months after initial diagnosis while the other three died within 3 months after diagnosis. Another report describes a 20 cm tumor with a 99% neuroendocrine component and concurrent hep-Par1 and synaptophysin staining in 1% of tumor cells. Follow-up for six months after surgery detected no tumor recurrence. (Baker et al. 2016). A third report describes a 7.5 cm mass in the right liver with small-cell and moderately-well differentiated hepatocellular carcinoma components. This patient had recurrent tumor modules three months after surgery and died 1 year after operation. (Yang et al. 2009).

Occasional staining of hepatocellular carcinoma with neuroendocrine markers is not uncommon: immunohistochemical studies of 50 hepatocellular carcinomas in one case series demonstrated at least one neuroendocrine marker expression in 30 cases, most commonly S-100 and Leu-7 (CD57) (Zhao et al. 1993). However, few of these cases showed expression of more than one marker and none showed concurrent expression of synaptophysin and chromogranin. Also, 88% of tumors expressing neuroendocrine markers were of intermediate nuclear grade, in contrast to the high nuclear grade in this case.

There are two hypotheses about the origin of such tumors. One is that the neuroendocrine differentiation arises from a well to moderately-differentiated hepatocellular carcinoma (Yang et al. 2009). This would be compatible with tumors with separate neuroendocrine and hepatocellular components; in our case we did not find a separate hepatocellular carcinoma component. Another possibility is that it arises from a progenitor cell, as hepatocyte progenitor cells that express chromogranin A, neural cell adhesion molecule and S-100 protein (Roskam et al. 2004). Given the poorly differentiated histologic appearance of the tumor and its clinical history of rapid growth, this explanation seems to be a better fit.

Our review of the literature indicates that this patient has an extremely rare variant of hepatocellular carcinoma. One month after diagnosis he returned to the hospital with increased pain, ascites, and an AFP level of 17,363 ng/mL. Imaging showed increased size of his liver mass to 20 × 19 × 13 cm. Sorafenib treatment was considered for this patient, but has only been shown to be beneficial in patients with Child-Pugh-Class A liver disease. At the time of referral to oncology, this patient's liver disease was Child-Pugh-Class B. Due to the rapidly increasing size and suspected metastasis to the colon, patient was deemed not a surgical candidate, even for palliative debulking. Transarterial catheter arterio chemoembolization is often offered to patients with HCC to shrink tumor size. However, extension of the tumor into the hepatic portal vein precluded this patient for this procedure given that it would place the patient at greater risk for ischemic injury to liver given both blood supplies to the liver would be compromised by the procedure. Given extremely poor prognosis and limited therapeutic options, patient and elected to pursue hospice care to maximize his quality of life and spend the rest of his time at home with family.