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Unsuspected primary malignancy in the setting of elevated serum alpha-fetoprotein

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ABSTRACT

Hepatocellular carcinoma is the most common solid liver cancer and is screened for with serum alpha-fetoprotein (AFP) in patients with chronic hepatitis or cirrhosis. However, other tumors can produce AFP, and one of these is the "hepatoid" adenocarcinoma, arising in extrahepatic sites. We present a patient with chronic hepatitis C, multiple liver tumors, and a marked elevation in AFP who was mistakenly thought to have hepatocellular carcinoma, but primary hepatoid adenocarcinoma arising at the gastroesophageal junction was discovered at autopsy.

KEYWORDS Alpha-fetoprotein; hepatocellular carcinoma; hepatoid

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide[1] and the fastest growing cause of cancer-related death among men in the USA.[2] Chronic hepatitis C infection results in a 17-fold increased risk of developing HCC by promoting the development of cirrhosis.[2] Alpha-fetoprotein (AFP) is a fetal serum protein, secreted by the fetal liver and yolk sac, that can be reactivated in malignancies. AFP reactivation often occurs in HCC, where up to 80% of patients have elevated AFP, most above 500 ng/mL.[3] However, other primary nonhepatic tumors can produce AFP, including yolk sac tumors and some primary gastrointestinal, renal, and lung cancers.[3] We report a nonhepatic malignancy with elevated AFP, mistakenly thought to represent primary HCC.

CASE DISCUSSION

A 53-year-old man with chronic hepatitis C was admitted for abdominal pain and abnormal liver enzymes. Computed tomography revealed innumerable hypodense lesions in all lobes of the liver, a nodular liver contour, and ascites. The largest liver lesion measured 10.3 cm in diameter, and his serum AFP was 3861 ng/mL (normal 10–15). A clinical diagnosis of HCC was made, and he was initiated on sorafenib with outpatient follow-up.

Two weeks later, he returned to the emergency department, hypoxemic with dyspnea, lower extremity edema, tender abdominal distension, and confusion. Computed tomography revealed worsening hepatomegaly, and the largest tumor had grown to 15 cm in diameter *(Figure 1)*. He was admitted with acute respiratory failure, small bowel obstruction due to compression by the enlarging liver, possible upper gastrointestinal bleeding, and decompensating liver function. Despite supportive measures, he experienced increasing pain and discomfort, as well as worsening liver function. Because he was no longer a candidate for sorafenib or for surgery to relieve the extrinsic small bowel compression, he requested comfort care and died within 24 hours.

Autopsy revealed a massively enlarged liver, weighing 7550 g (mean normal weight about 1500 g). The hepatic parenchyma was distorted by numerous centrally necrotic tumor masses; however, the intervening parenchyma was icteric but not cirrhotic. Microscopically, the tumor patterns favored metastatic, poorly differentiated adenocarcinoma with a clear cell component *(Figure 2)* rather than primary HCC, and immunohistochemical stains for hepatocyte paraffin 1 (HepPar-1) were negative in tumor cells. At the gastroesophageal junction, a large, 6.0-cm-diameter fungating tumor mass was present, highly consistent with a primary adenocarcinoma. Microscopically, this also was a poorly differentiated

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adenocarcinoma *(Figure 3)* that extended through the muscularis propria to the serosa with widespread lymphovascular invasion. Staining for AFP was strongly positive in this tumor, indicating its "hepatoid" nature, and a likely source for the elevated serum levels. The patterns at both sites were similar, and all findings indicated metastatic adenocarcinoma to the liver from the gastroesophageal junction.

DISCUSSION

The first case of an AFP-producing gastric cancer was reported in 1970,[4] but not until 1985 was this tumor called "hepatoid adenocarcinoma" by Ishikura et al.[5] These were primary gastric carcinomas with "hepatoid" differentiation, defined by AFP production.[6] This occurs because the stomach and liver are both derived from the primitive foregut.[5] Hepatoid gastric adenocarcinomas are rare but generally occur in elderly patients and are twice as likely to occur in men.[7] Sixty percent occur in the antrum,[7] though ours did not. These cancers commonly metastasize to the liver, where clinical confusion with HCC can occur, but the elevated AFP produced by these tumors is independent of liver metastasis.[6]

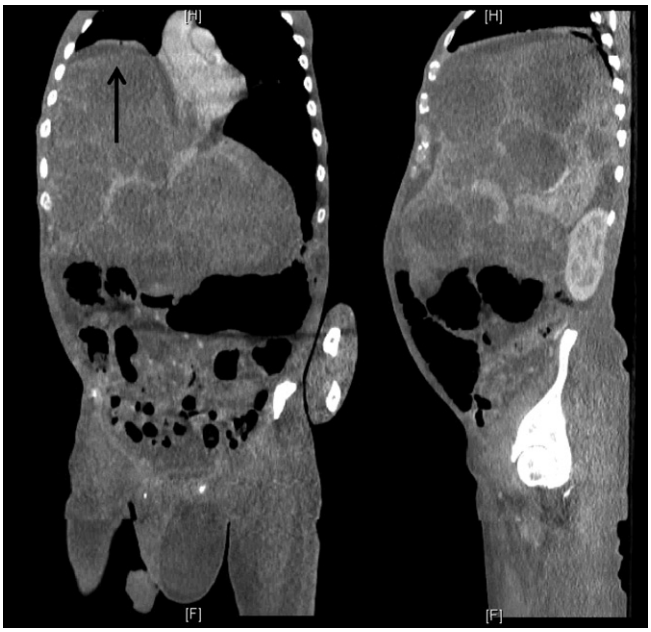

Figure 1. Coronal and sagittal views of computed tomography with contrast (single phase) of the abdomen reveal multiple hypoechoic hepatic lesions (arrow) causing elevation of the right hemidiaphragm and compression of the small bowel.

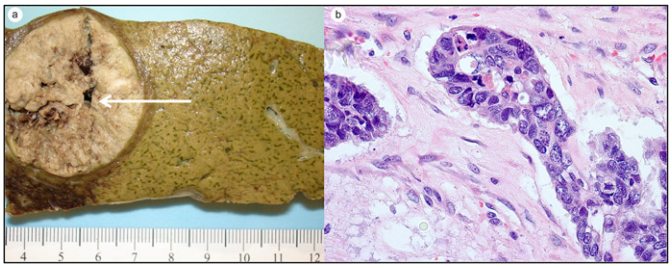

Figure 2. (a) Gross examination of the liver reveals a circular hepatic mass with central necrosis (white arrow) and a background of icteric but noncirrhotic liver parenchyma. **(b)** Hematoxylin and eosin staining reveals poorly differentiated adenocarcinoma within the liver mass (400×). Characteristics include atypical, hyperchromatic cells with poorly formed glands and solid portions, similar to the gastroesophageal tumor shown in *Figure 3*.

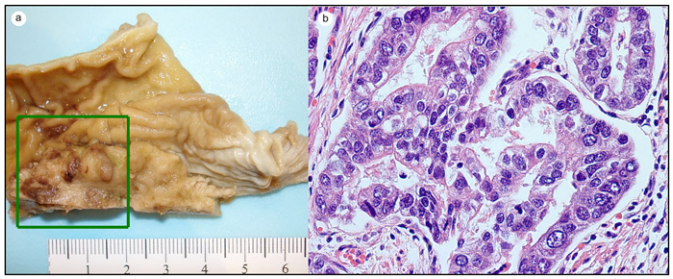

Figure 3. (a) Gross examination reveals a 6-cm tumor located at the gastroesophageal junction (green outline). **(b)** Hematoxylin and eosin staining reveals areas of poorly differentiated adenocarcinoma, similar to the liver tumors (400×).

One aid to distinguish hepatoid adenocarcinoma from HCC is that HCC is far more likely to arise within a cirrhotic liver (with the exception of hepatitis B infection); therefore, if the hepatic parenchyma is not cirrhotic by imaging studies, a biopsy may accurately classify the tumor. Immunohistochemical studies for the HepPar-1 antigen can be performed. HepPar-1 employs an antibody to the membrane of hepatocellular mitochondria in normal and neoplastic hepatocytes[8] and is the most sensitive and specific marker for hepatocyte differentiation.[9] (The negative staining of the liver tumor for HepPar-1 in our case strongly supports its metastatic nature.)

Overall, the prognosis for hepatoid adenocarcinoma of the stomach is extremely poor. In comparison to non–AFP-producing adenocarcinoma, the AFP group has a higher incidence of vascular invasion, lymph node metastasis, and liver metastasis, and the 5-year survival is only 28%.[10,11] Due to the rarity, treatment recommendations are limited, but most patients are treated with surgical resection and chemotherapy.[12,13] AFP measurements have utility for tumor surveillance following therapy.

Guidelines for management of HCC suggest diagnosis by radiologic imaging alone if venous-phase washout is available and present within typical hypoechoic lesions. When venous-phase washout is visualized in the appropriate clinical setting, the specificity for HCC reaches 95%, and biopsy is rarely performed due to the risk of bleeding and tumor seeding. However, imaging may not be reliable in the presence of a large tumor burden replacing most of the parenchyma, as in our case. Therefore, if findings suggest a noncirrhotic liver, or if this cannot be reliably determined, biopsy is recommended.

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