CASE REPORT

Hepatoid adenocarcinoma: A wolf in hepatocellular carcinoma’s clothing

Paul Nguyen,* Samuel Hui*† and Marcus Robertson*†

*Department of Gastroenterology and Hepatology, Monash Health and †Department of Medicine, Monash University, Clayton, Victoria, Australia

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Correspondence
Paul Nguyen, Monash Health, 246 Clayton Road, Clayton, Vic. 3168, Australia.
Email: paul.m.nguyen5@gmail.com

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Introduction
Hepatocellular carcinoma (HCC) remains the most common malignant liver lesion in people with cirrhosis. Extrahepatic cancers rarely metastasize to the liver in the setting of cirrhosis. This is hypothesized to be due to advanced fibrosis and consequent hemodynamic changes that make the cirrhotic liver an “unfavorable soil” for metastases to deposit and develop.1 We present two cases of metastatic hepatoid adenocarcinoma (HAC) masquerading as HCC in a cirrhotic liver. This rare tumor may be misdiagnosed as HCC given its hepatoid differentiation and expression of alpha fetoprotein (AFP).

Case Report

Case 1. A 57-year-old woman with established Child–Pugh B liver cirrhosis secondary to prior alcohol excess was noted to have a newly elevated AFP of 5330 mcg/L (normal <9 mcg/L) during routine surveillance with no lesion appreciated on liver ultrasound. A multiphase CT liver revealed a 4 cm liver lesion in Segment 2, which appeared atypical for HCC (absence of arterial phase enhancement and peripheral enhancement in the portal venous phase); subsequent liver magnetic resonance imaging (MRI) demonstrated similar findings. Despite atypical imaging findings, the clinical context remained suspicious for HCC and she proceeded to a targeted biopsy of the lesion with concurrent locoregional treatment with microwave ablation (MWA). Histopathology revealed a highly pleomorphic epithelial malignancy with morphological features of HCC on hematoxylin and eosin (H&E) staining. On immunoperoxidase staining, the specimen was negative for cytokeratin (CK) 7 and hepatocyte specific antigen (HSA), and strongly positive for CK20, caudal-related homeobox transcription factor 2 (CDX2), and epithelial cell adhesion molecule/EPCAM (BerEp4; Fig. 1). This pattern is highly consistent with adenocarcinoma of gastrointestinal origin and the presence of positive CDX2 staining is suggestive of a lower gastrointestinal tract origin. Subsequent upper and lower gastrointestinal endoscopy and positron emission tomography (PET) scanning did not identify a primary lesion. There was a marked reduction of AFP to 3.2 mcg/L after initial MWA.

Case 2. A 56-year old man with a history of prior alcohol excess and treated hepatitis C, but no known cirrhosis, presented with chronic abdominal bloating. On examination, hepatomegaly and stigmata of chronic liver disease (spider naevi) were noted. CT multiphase liver revealed an 11 cm lesion of indeterminate nature in the right liver lobe as well as an additional focus of hyperintense with diffusion restriction, with absence of arterial enhancement, but enhancement in the portal venous phase (Fig. 2). Tumor thrombus was found in the right portal vein, right hepatic vein, and inferior vena cava. There were features of liver cirrhosis. Given the radiological findings were not consistent with hepatocellular carcinoma, the liver lesion was biopsied. This revealed a highly pleomorphic tumor on a background of cirrhosis, with immunoperoxidase staining negative for CK7 and HSA, and strongly positive for CK20 and CDX2. This was consistent with a poorly differentiated carcinoma with hepatoid differentiation of unknown primary. Upper and lower gastrointestinal endoscopy were unrevealing. PET scan did not

Abstract

Hepatoid adenocarcinoma (HAC) is a rare malignancy that may mimic hepatocellular carcinoma (HCC) given its hepatoid histologic appearance and production of alpha fetoprotein. Clinical management and prognosis of HAC varies considerably from HCC. We present two cases of metastatic HAC in a cirrhotic liver diagnosed after biopsy and histopathological evaluation. The cases underscore the importance of recognizing the limitations of diagnostic imaging and pursuing a biopsy where there is diagnostic uncertainty.
identify a definite site of primary tumor. The case was discussed at liver mass, upper GI oncology, and colorectal-oncology multidisciplinary meetings and the patient is currently planned for a combination of chemotherapy and immunotherapy.
Discussion

Hepatoid adenocarcinoma was first described in 1970 as an AFP-producing tumor of gastric origin with hepatocellular differentiation. It is an extremely rare malignancy, with published literature to date limited to case series and observational studies. HAC most frequently arises from the stomach, with primary lesions in the lung, pancreas, gallbladder, and urogenital system also reported. Metastatic disease, most frequently in the liver or lymph nodes, is common at diagnosis. Incidence is difficult to determine due to the rarity of the entity; one East Asian population study estimated an incidence of 0.014 per 100 000 people. The median age at diagnosis was 66 years and men were more commonly affected. The diagnosis is primarily based on histopathological assessment. Routine H&E staining reveals morphology similar to hepatocellular carcinoma and therefore immunoperoxidase staining is crucial. Staining patterns vary depending on the site of primary lesion and there is notable heterogeneity in the literature. The most common positive immunostains include AFP, CK 18, CK19, and CK AE1/AE3, carcinoembryonic antigen (CEA), and hepatocyte paraffin 1 (Hep Par1), while HAC usually stained negative for CK7 and CK20.

Evidence to inform clinical management is scarce. Curative surgery is rarely possible as the disease is usually advanced or metastatic at diagnosis, and palliative-intent locoregional or systemic therapy is usually the mainstay of treatment. Platinum-based combination chemotherapy regimens are commonly described. Organ-specific treatments such as anti-HER2 receptor monoclonal antibodies (e.g., trastuzumab) for HER2-positive HAC have shown positive results in combination with chemotherapy. There is currently no clear evidence for radiotherapy or immunotherapy. Prognosis is poor with a reported median survival of 5–11 months and a 5-year survival of 9%. One study concluded that older age at diagnosis, distant metastasis status, and surgery and chemotherapy candidacy were independent predictors of a poor prognosis.

In general, hepatic metastases are a rare finding in liver cirrhosis. One study found only 1.7% of 1454 biopsies of mass lesions in cirrhotic livers were metastases. The commonest primary malignancy was colorectal carcinoma (33%), followed by neuroendocrine tumors from any site (21%), pancreatic cancer (17%), upper gastrointestinal tract (8%), breast (8%), fallopian tube (4%), lung (4%), and a carcinoma of unknown primary. The finding of a rare malignancy such as HAC that has metastasized to a cirrhotic liver is therefore an exceptional circumstance. To our knowledge, no such cases have been previously reported.

These cases highlight the complexities of diagnosing HAC in patients with established liver cirrhosis who present with markedly elevated AFP levels and new liver lesions—a clinical scenario highly suggestive of HCC. Importantly, in both cases, the imaging findings did not meet the radiological criteria for HCC. This illustrates the importance of pursuing a biopsy in cases of diagnostic uncertainty and review by an experienced pathologist.

In conclusion, HAC is an extremely rare malignancy that remains a differential diagnosis in AFP-producing liver lesions without typical imaging characteristics of HCC. Given the hepatoid appearance, the histologic diagnosis relies on immunoperoxidase staining. The diagnosis is important to establish as management and outcomes for metastatic adenocarcinoma differ significantly from HCC.

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