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CASE REPORT | LIVER

Imaging Negative Hepatic Lesions: A Rare Case of Infiltrative Hepatocellular Carcinoma Diagnosed With Endoscopic Ultrasound

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ABSTRACT

Hepatocellular carcinoma is a common malignancy with male predominance. It is further classified into different subtypes, among which the infiltrative subtype is the most difficult to diagnose with imaging because of its inherently ill-defined micro nodules involving a segment or entire hepatic parenchyma without a distinguishable mass. Owing to the aggressive nature and decreased survival expectations in most patients with infiltrative hepatocellular carcinoma, liver transplants and surgical resections are not recommended. Our case describes a middle-aged woman presenting with alpha-fetoprotein >20,000 and imagings negative for hepatic mass, thereby necessitating the use of endoscopic ultrasound with fine-needle aspiration.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide.[1] Infiltrative HCC accounts for approximately 7%–20% of all diagnosed HCC with most patients presenting with advanced disease at the time of diagnosis.[2] Hepatitis C virus (HCV) remains the primary risk factor of HCC cases in the United States. The incidence of HCC in patients with HCV cirrhotic disease is estimated to be approximately 0.5%–10% annually.[3] Prognosis is poor and estimated at a 5-year survival rate of <20% while those with fewer comorbidities and smaller lesions confined to the liver are estimated to have a favorable survival rate.[4] Diagnosis of HCC requires a sensitive imaging test. Imaging modalities commonly used include abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). In situations where imaging is not able to identify a mass, endoscopic ultrasound with fine-needle aspiration (EUS-FNA) has been shown to have a higher detection rate.[5]

CASE REPORT

A 61-year-old obese woman presented to the clinic with a complaint of generalized abdominal pain, exertional dyspnea, and worsening lower extremity edema. She had a medical history significant for HCV cirrhosis, treated with a sustained virologic response. She denied any history of cardiac disease, jaundice, or pruritus. She endorsed compliance with recommended daily sodium intake and medications. Examination findings were unremarkable, except for a distended abdomen, positive shifting dullness, and bilateral pitting lower extremity edema. Laboratory findings showed a white blood cell count of 3.33k/cmm (4.5–10), hemoglobin of 12.3 g/dL(12–16), platelet of 109k/cmm (150–440), international normalized ratio of 1.12 (0.9–1.3), Cr of 0.62 mg/dL (0.7–1.3), gamma-glutamyl transpeptidase of 359 unit/L (5–85), alkaline phosphatase of 159 unit/L (15–37), aspartate aminotransferase of 159 unit/L (15–37), alanine aminotransferase of 59 unit/L (12–78), total bilirubin of 1.2 mg/dL (0.2–1.0), alpha-fetoprotein (AFP) of >20,000 ng/mL (0.5–8.0), CA 125 of 505 unit/mL (1.5-35), CA 19-9 of 40U/mL (0–35), peritoneal fluid cytology was negative, model for end-stage liver disease of 16, and Child-Pugh B. A right upper quadrant ultrasound showed cirrhosis without evidence of a hepatic mass. A standard abdominal CT scan obtained in the venous phase showed splenomegaly and cirrhosis with no hepatic mass (Figure 1). Further studies with multiphasic MRI with contrast showed cirrhosis with portal vein thrombosis and cavernous transformation; no hypervascular hepatic mass was seen (Figure 2). The markedly elevated AFP left a high suspicion for HCC; hence, the patient was referred for EUS-FNA, which showed 12 × 16 mm nonocclusive portal vein thrombosis and heterogeneous

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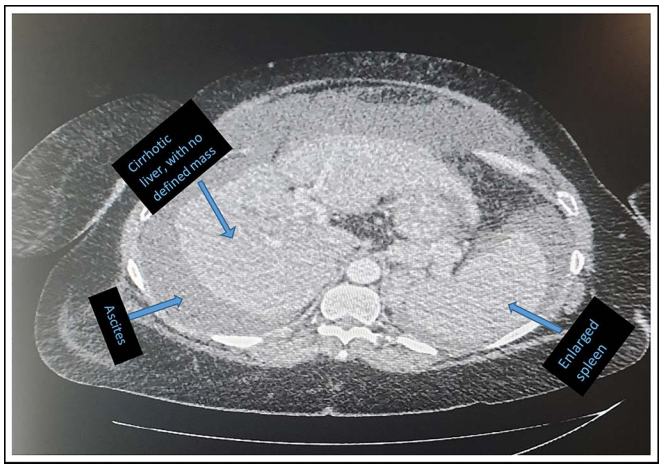

Figure 1. Standard abdominal computed tomography with contrast showing splenomegaly, ascites, and no defined hepatic mass.

and diffuse echogenicity worrisome for an infiltrative process (Figure 3). The biopsy report showed malignant cells positive for AFP while negative for trypsin, arginase, SF1, chromogranin, synaptophysin, and PAX 8. Immunostains marked tumor cells reactive for glypican-3 and negative for Hep Par1, supporting the diagnosis of HCC (Figure 4). On a follow-up visit, an oncology referral was discussed with the patient and she was agreeable. A month later, the patient died before she could follow up with oncology.

DISCUSSION

The morphologic growth pattern of HCC is subdivided into infiltrative, massive, and nodular. Infiltrative HCC is less likely to demonstrate washout on imaging and is usually associated with the presence of portal vein thrombosis as seen in our patient. Some hepatic lesions that mimic the infiltrative pattern of this malignancy include intrahepatic cholangiocarcinoma,

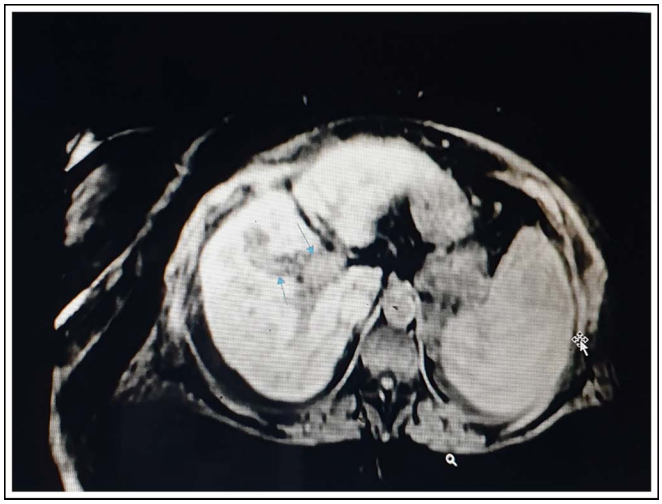

Figure 2. Multiphasic magnetic resonance imaging showing cirrhotic liver with portal vein thrombosis (blue arrows).

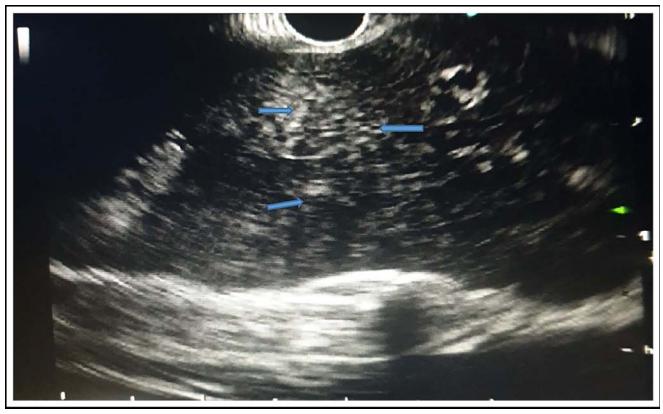

Figure 3. Endoscopic ultrasound with heterogeneous and diffuse echogenicity worrisome for an infiltrative process (blue arrows).

hepatic fat deposition, hepatic micro abscess, and focal confluent fibrosis. The pathogenesis has been linked to overexpressed signaling pathways, which include epidermal growth factor, vascular endothelial growth factor, beta-catenin pathway, Ras mitogen-activated protein kinase (MapK), and platelet-derived growth factor.[6,7] Sustained virologic response is associated with decreased risk of HCC; however, with a cirrhotic liver, patients still have an absolute risk of developing HCC. Initial diagnosis can be obtained noninvasively using abdominal ultrasound, CT, MRI, and EUS-FNA. Ultrasound is the best imaging modality recommended for HCC surveillance because it is readily available; however, its sensitivity for detecting early HCC is approximately 47% and varies depending on body habitus and severity of liver disease.[8] AFP, the most widely used serum marker for HCC, can be assessed in conjunction with ultrasound. This has been shown to increase the sensitivity of early HCC detection.[9] AFP cutoff level >20 ng/mL has a sensitivity of approximately 60% with low specificity.[10] However, a level of >400 is diagnostic for HCC with a specificity of almost 100% and a decrease in sensitivity to

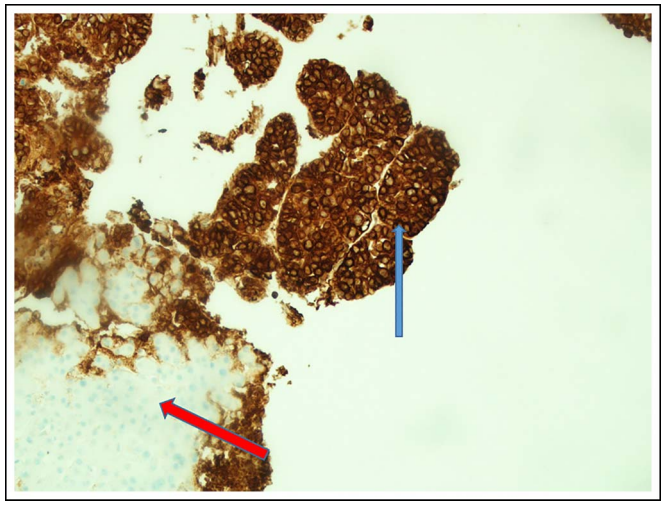

Figure 4. Hepatocellular carcinoma, 200×. Glypican-3 immunostain shows strong, diffuse staining in hepatocellular carcinoma (blue arrow). Background non-neoplastic liver is negative (red arrow).

approximately <45%.[11] Incremental changes in AFP are associated with an increased mortality rate.[12] The median survival rate of infiltrative HCC with AFP >400 is estimated to be approximately 5 months.[13] Our patient was diagnosed in 2022 with an AFP of >20,000 ng/mL, before which AFP had shown a progressive increase between 2018 and 2021 but remained <100 ng/mL (Figure 5). Abdominal ultrasound and abdominal CT at that time remained negative for any hepatic mass.

Owing to the low sensitivity and specificity of that level of AFP with negative imaging, further investigation with EUS was not considered. Having a spike in AFP of >20,000 with consistently negative imaging prompted us to probe further with EUS. EUS is superior to CT in detecting small hepatic lesions, with a sensitivity of 100% compared with 71% of CT.[14] Several studies have postulated the benefit of EUS with FNA in detecting HCC. A retrospective study by Awad et al[15] on preoperative evaluation of hepatic lesions using EUS showed that in all 14 patients who underwent EUS and CT, EUS detected additional hepatic lesions in 28% of the patients. Bogstad et al[16] reported a case of recurrent HCC diagnosed with EUS. Singh et al[17] reported a prospective study on EUS for the detection of HCC involving 17 patients, EUS detected a significantly higher number of nodular lesions compared with ultrasound ($P = 0.03$), CT ($P = 0.002$), and MRI ($P = 0.04$). The data on the treatment of infiltrative HCC are uncommon and are still being studied. Resection and transplantation are not considered options in its management because of tumor recurrence with approximately a 5-year survival rate of 18-32%.[18] Intra-arterial therapy (IAT) such as drug-eluting beads transcatheter arterial chemoembolization, conventional transcatheter arterial chemoembolization, or systemic chemotherapy like sorafenib is beneficial to these patients.[19] A retrospective study by Kneuertz et al[13] on the assessment of the presentation of diffuse HCC, treatment, and outcomes identified IAT to be a safer option for patients with infiltrative HCC with median survival at 1 and 3 years identified to be 49% and 34%, respectively. This is contrary to the study by Lopez et al, which reported 16% death within 30 days in IAT-treated infiltrative HCC patients.[20] Discrepancies in these studies have been attributed to poor patient selection, with the majority possessing risk factors that increase mortality such as high model for end-stage liver disease, Child-Pugh B or C, bilirubin >2, AFP >400, and portal vein thrombosis. Our patient had a poor prognosis with AFP >400 and portal vein thrombosis; IAT could not be considered because of a high chance of poor response; chemotherapy was an option but the patient deceased before following up with an oncologist. We recommend EUS be considered an integral modality while investigating the diagnosis of HCC, especially in patients with elevated AFP. Its utility includes both the visualization of an ill-defined area and the ability to complete diagnostic tissue acquisition.

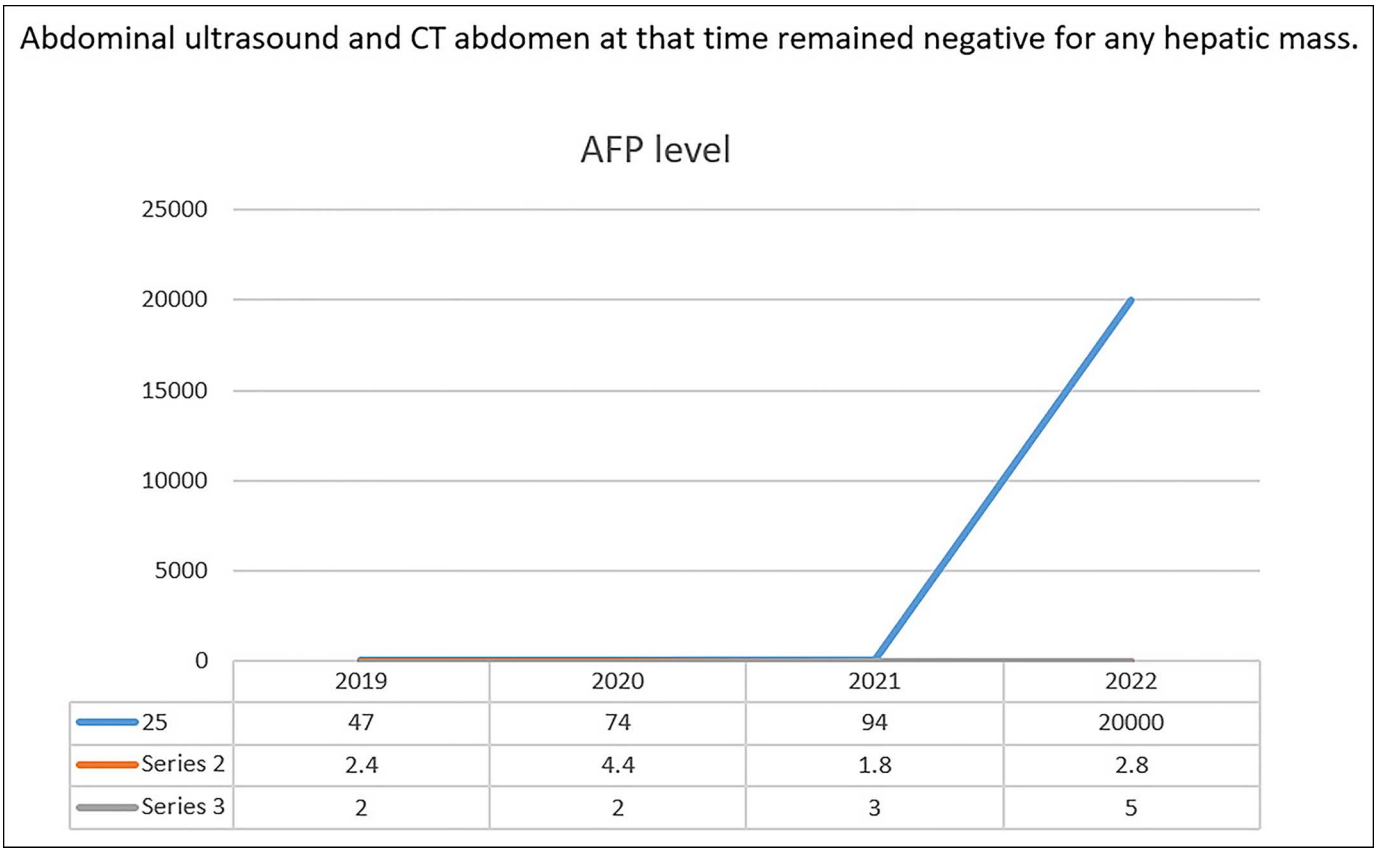

Figure 5. Progressive increase in patients' alpha-fetoprotein with a sudden spike to 20,000 within a year. AFP, alpha-fetoprotein; CT, computed tomography.

DISCLOSURES

Author contributions: T. Joshi evaluated this patient and presented the case to O. Ugonabo and M. Mohamed, who did a literature review on the case, wrote the full manuscript with relevant imaging and submitted it to T. Joshi and W. Frandah for final review. W. Frandah performed the procedures and biopsy that led to the diagnosis of infiltrative HCC while P. Jones provided pathology slides with explanatory captions. O. Ugonabo is the article guarantor.

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Informed consent was obtained for this case report.

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