Infiltrative non-mass-like hepatocellular carcinoma initially presenting with isolated malignant portal vein thrombosis: A case report and review of the literature

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Abstract

Hepatocellular carcinoma (HCC) shows a rising incidence and mortality rates worldwide. HCC is divided into several distinct subtypes, both morphologically and histopathologically. Among these subtypes, infiltrative HCC may be the most challenging subtype to diagnose, given its characteristic myriad of tumor nodules blended with normal hepatocytes without a distinct mass-like lesion. Herein, we report an unusual case of an infiltrative HCC initially presenting with isolated malignant portal vein thrombosis and provide a brief review of the literature regarding the infiltrative HCC subtype. Additionally, we demonstrate how sonoelastography could aid in detecting the appropriate biopsy area in the infiltrative HCC subtype. To our knowledge, there have not been previously reported cases describing the use of sonoelastography in the evaluation of the appropriate area for the targeted liver biopsy.

Introduction

Hepatocellular carcinoma (HCC) is predicted to be the sixth most common cancer and the fourth leading cause of cancer-related death worldwide, with over 800,000 new cases and 700,000 deaths annually(1). It is well known that HCC most commonly arises in the context of a cirrhotic background. The major causative factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin exposure, excessive alcohol intake, smoking, obesity, type 2 diabetes, and certain inherited metabolic diseases(2-5). Various histopathologic and morphologic subtypes of HCC, some of which are not included in the WHO classification of the digestive system tumors, are described throughout the literature(6-14). El Jabbour et al.(15) described these HCC subtypes as steatohepatitic, clear cell, scirrhous, infiltrative, fibromellar carcinoma, combined hepatocellular-cholangiocarcinoma, combined hepatocellular and neuroendocrine, granulocyte colony-stimulating factor producing, sarcomatoid, carcinosarcoma, carcinosarcoma with osteoclast-like giant cells and lymphocyte rich, in decreasing order of frequency(7).

Among these, infiltrative type HCC may be the most difficult one to recognize both clinically and radiographically, because this HCC subtype is characterized by multiple minute tumor nodules that spread throughout the liver parenchyma, without forming a mass-like lesion. Given this appearance of infiltrative HCC, some authors have named this entity as diffuse HCC, cirrhotomimetic HCC, or cirrhosis-like HCC(6-14).

Portal vein invasion is a known complicated feature of HCC, occurring by direct local venous extension or metastatic spread. However, the initial presentation of HCC as an isolated portal vein thrombosis is incredibly rare, with very few cases reported in the English literature to date(15).

We, herein, present an unusual case of HCC initially presenting as an isolated malignant portal vein thrombosis without any other findings suggesting HCC. Additionally,
we provide a brief review of the literature regarding the infiltrative type of HCC. To our knowledge, the use of sonoelastography for the targeted liver biopsy has not been reported so far.

**Case report**

A 46-year-old woman was referred to our ultrasonography (US) department with the initial presumed clinical diagnosis of acute cholecystitis. She initially presented to the emergency department with epigastric and right upper quadrant pain. Physical examination revealed abdominal tenderness in the epigastrium and right upper quadrant with palpation and liver inferior limit at 4–5 cm below the costal margin. The blood test results on admission were as follows: hemoglobin = 12.3 g/dl, leucocytes = 5550/mm$^3$, platelets = 303,000/mm$^3$, AST=29 IU/l, ALT = 23 IU/l, total bilirubin = 1.21 mg/dl, HBS antigen (-) and anti-HCV (-).

Gray-scale ultrasonography (US), Doppler US, and strain sonoelastography examinations were performed by an experienced radiologist with a Logiq S7 Expert machine (GE Healthcare, Milwaukee, WI) equipped with a C1-5-D convex probe. US examination revealed diffuse inhomogeneous left hepatic lobe without any localized formation and significant dilatation of the left portal vein (26 mm) with thrombus extending into the right portal vein (Fig. 1, Fig. 2). Triphasic computed tomography (CT) of the liver was subsequently performed to collaborate with the US findings further. The entire left hepatic lobe showed enhancement during the arterial phase, followed by washout during the late venous phase (Fig. 3 A and B). Additionally, a tumor thrombus with a similar enhancement pattern was demonstrated within the left and right portal veins (Fig. 3 A and B). In our case, neither US nor CT scans brought out any discrete mass-like lesion. Serum alpha-fetoprotein (AFP) level was within the normal range, as well. Given the lack of a discrete mass lesion, the sonoelastography-guided biopsy was performed from the left liver lobe parenchyma (Fig. 4). The biopsy revealed infiltrative hepatocellular carcinoma, which was later confirmed by immunohistochemistry.

**Discussion**

Infiltrative HCC accounts for approximately 10–20% of all HCC cases$^{16-20}$. It is characterized by multiple, widespread minute tumor nodules throughout the liver, which appears as a spreading, ill-defined mass with indistinct margins. Although risk factors associated explicitly with infiltrative HCC are not well-established, there is emerging data suggesting an association with hepatitis B virus (HBV) infection$^{21,22}$. Serum alpha-fetoprotein (AFP) levels are reported to have poor diagnostic accuracy in infiltrative HCC, with variable serum AFP levels$^{23,24}$, even within the normal range, as with our case. However, other possible HCC serum biomarkers, such as Lens culinaris agglutinin reactive AFP (AFP-L3) and Des-gamma-carboxyprothrombin (DCP), have recently been introduced, and AFP-L3 positivity is reported to be more commonly associated with infiltrative HCC subtype and to portend a poor prognosis$^{25-27}$.

Infiltrative HCC often poses a diagnostic challenge for radiologists to detect on cross-sectional imaging due to its infiltrating nature, especially in a heterogeneous cirrhotic background. Its histopathologic characteristics correspond to permeative ill-defined appearance on cross-sectional imaging. Ultrasonography (US), multiphasic contrast-enhanced computed tomography (CT) and magnetic resonance (MR) imaging are documented to be helpful for the diagnosis of infiltrative HCC. On US, the permeative ill-defined appearance of this entity is translated into heterogeneous echotexture. Although US plays a limited role in the diagnosis of infiltrative HCC$^{28}$, it can be used to detect appropriate area for targeted liver biopsy. In the setting of infiltrative HCC, sonoelastography could be
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Portal vein tumor thrombosis is a ubiquitous finding in infiltrative HCC\(^{10,17–20,23,29–32,34}\). It may even be the first sign of infiltrative HCC, as in our case\(^{29}\). Tumor extension into the hepatic veins is not as common as the portal vein\(^{30}\). On US, tumor thrombus may be seen as hypo/hyperechoic intraluminal filling defects that expand the portal vein. The significant distension of the vessel, the arterialization of the thrombus, and the presence of pulsatile flow in the thrombus are highly specific features of portal vein tumor thrombus\(^{18–20,35–37}\). Contrast-enhanced US has recently been proposed to differentiate benign and malignant PV thrombi in patients with HCC\(^{38,39}\). On contrast-enhanced CT and MR images, malignant thrombus exhibits a similar enhancement pattern to the originating tumor\(^{18,37,40,41}\). Malignant thrombus shows restricted washout appearance during the venous phase is reported to be less common in infiltrative HCC than in other HCC subtypes\(^{17,19,30,31}\), it is still accepted as a valid sign to detect infiltrative HCC\(^{32}\). More specifically, infiltrative HCC often seems hypointense to liver on T1-weighted sequences and hyperintense to liver on T2-weighted with high b-value diffusion-weighted sequences\(^{11,17–20,23,29–33}\).

**Fig. 3.** Axial contrast-enhanced CT images show streaky and heterogeneous enhancement of the PV thrombus during the late arterial phase (A) with washout during the portal venous phase (B), which is diagnostic of tumor thrombus.

**Fig. 4.** On sonoelastographic image, normal parenchyma is coded in red-green color (star mark), whereas portal vein tumor thrombosis and the affected left lobe parenchyma are coded in blue-green (black arrow) and pure blue color (white arrow), respectively. Based on the color bar on the left side, red color reflects less stiff tissue, while blue color reflects more stiff tissue than the rest. Besides, green color reflects medium-stiff tissue.
A number of diseases including focal confluent fibrosis, geographic fatty infiltration, arterioporal shunting, microabscesses, cholangiocarcinoma, hepatic infarction, and diffuse metastatic disease (pseudocirrhosis) can mimic infiltrative HCC. Unlike HCC, focal confluent fibrosis generally seems hypovascular in the arterial phase and exhibits delayed enhancement\(^\text{18,20,31,42-44}\). Geographic fatty infiltration can be distinguished from infiltrative HCC by performing in- and out-of-phase, and fat-saturated MR sequences\(^\text{18,20,45}\). Arterioporal shunting can be seen as a peripheral wedge-shaped area, only enhancing in the arterial phase without any abnormality on the delayed phase images\(^\text{20}\). Hepatic microabscesses typically manifest as peripheral and septal enhancing lesions on contrast-enhanced CT and MR imaging, which is atypical for infiltrative HCC\(^\text{46}\). The infiltrative nature of cholangiocarcinoma may cause diagnostic confusion. However, it should be kept in mind that cholangiocarcinoma is less likely to be associated with tumor thrombosis and generally causes capsular retraction\(^\text{11,47,48}\). Further, cholangiocarcinoma mostly shows peripheral centripetal enhancement pattern, which is uncharacteristic of infiltrative HCC\(^\text{18}\). In a single case report, Shim et al. described a patient with hepatic infarction secondary to PV thrombophlebitis, which had been misdiagnosed as infiltrative hepatic malignancy with neoplastic thrombus\(^\text{49}\). Diffuse metastatic disease, especially related to treated metastatic breast cancer, can mimic cirrhosis and thus infiltrative HCC\(^\text{50-52}\). In this regard, a clinical history of the primary cancer may lead to the correct diagnosis.

The prognosis of patients with infiltrative HCC is substantially worse when compared to those who have a focal/nodular subtype\(^\text{21}\). Because most people with infiltrative HCC present at an advanced stage and have major vascular invasion at presentation\(^\text{18,19,21,23}\), surgical resection and transplantation are usually considered unfeasible\(^\text{18,19,53}\). The role of intra-arterial therapy in patients with infiltrative HCC is controversial according to current conflicting research\(^\text{23,54-56}\). Sorafenib, a multi-target tyrosine kinase inhibitor, was the first drug approved for the first-line treatment of advanced HCC and has shown favorable results to date\(^\text{57-61}\). However, resistance or intolerance to sorafenib has given birth to new research concerning the second-line treatment options\(^\text{62-64}\). Hsiao et al. documented that sorafenib with concurrent multiple-line therapies had significantly improved overall survival in patients with advanced HCC\(^\text{65}\). Additionally, gene therapy, together with immunotherapy, is a promising treatment option on the horizon\(^\text{66}\).

**Conclusion**

Infiltrative HCC often poses a diagnostic challenge for radiologists. Due to its diffuse and permeative nature, this entity is generally diagnosed at an advanced stage, which portends a poor prognosis. Isolated portal vein thrombosis may be the first and the only sign of infiltrative HCC. Therefore, it is essential to follow up the patients with portal vein thrombosis in short intervals, even in the setting of normal laboratory findings or the lack of a discrete mass. Knowledge of the critical tumor characteristics and imaging findings is crucial for radiologists to make a timely diagnosis and thus provide appropriate patient management.

**Conflict of interest**

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.
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