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CASE REPORT

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A rare and challenging case of extrahepatic costal metastases from an unknown primary hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) typically presents with a primary hepatic mass. Nevertheless, on rare occasions, the initial presentation can be exclusively related to extrahepatic metastases and the most common sites of metastases are the lungs, lymph nodes, bones, and adrenal glands. While, bone metastases are generally accompanied by multiple metastatic spreads elsewhere in the body or previously diagnosed HCC, cases of solitary bone metastases with no liver lesion at imaging have been reported. Indeed, two rare entities of HCC have been reported in the literature which are the ectopic hepatocellular carcinoma and the infiltrative type of hepatocellular carcinoma with a very challenging radiologic diagnosis and poor prognosis. In this article, we present a case of extrahepatic costal metastases of hepatocellular carcinoma, which was diagnosed through a bone biopsy, with no focal lesion on liver imaging including ultrasound, multiphase MRI, and CT scan except for the presence of a portal vein thrombosis. It is important to consider the possibility of HCC metastases when evaluating rapidly growing extrahepatic lesions in patients with chronic liver disease and to consider the tumor characteristics and imaging findings as well as limitations to make accurate and timely diagnosis leading to improved patient management. Our patient had probably an infiltrating HCC because of two prominent factors: the presence of portal vein thrombosis and a markedly elevated alpha-fetoprotein (AFP). A liver biopsy was crucial in order to confirm the diagnosis but unfortunately it could not be performed because of the unexpected death of the patient due to hemorrhagic shock. It is also worth noting in this case, that the elevated level of AFP raised the suspicion on an underlying HCC and contributed to more elaborate diagnostic tests.

Keywords: Hepatocellular carcinoma, Extrahepatic costal metastases, Alpha-fetoprotein, Spontaneous regression, Ectopic hepatocellular carcinoma, Infiltrative hepatocellular carcinoma.

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Introduction

Hepatocellular Carcinoma (HCC) is a significant global health problem, ranking as the fifth most common cancer worldwide and the second leading cause of cancer-related deaths in men (1). The diagnosis of HCC is established by detecting a typical enhancement pattern; heterogeneous enhancement in the arterial phase and washout in the portal venous phase, using a multiphase MRI or CT Scanning in the context of chronic liver disease (2). And despite the availability of medical imaging, detecting HCC in its early stages is still a challenging task and most cases are diagnosed in advanced stages, which is associated with a poor prognosis, with extrahepatic metastases occurring in about 15 to 17% of cases, most notably in the lungs, lymph nodes, bones, and adrenal glands. However, extrahepatic metastases are rarely the primary presentation of HCC, and are accompanied in general by a concomitant liver mass (3, 4).

A unique and diagnostic challenge for clinicians and radiologists is the absence of a primary liver lesion due to its very low incidence and the lack of typical imaging features. Indeed, hepatocellular carcinoma must be considered in cases of a growing extrahepatic mass in patients with cirrhosis. An elevated AFP can be

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helpful in such cases and the threshold of 400 ng/mL has the best sensitivity and specificity (5).

The literature has reported cases of HCC without a liver mass. Such cases include ectopic HCC which can be metastases from an unknown primary HCC (6) or secondary to the presence of ectopic liver tissue of which the pathogenesis remains unclear with the occurrence of a rare developmental anomaly (7–11). Cancers of unknown primary (CUP) comprise approximately 3- 5% of all malignant epithelial tumors (12) and the ectopic HCC is very rare with an estimated incidence of only 0.24–0.47 % (8). The specific biological mechanisms responsible for this distinctive clinical behavior of CUP are not well understood. It could involve the spread of cancer cells while the primary site remains small, or it could be attributed to the spontaneous regression of primary HCC liver lesions without medical intervention due to hypoxia (13).

The second entity is the infiltrating HCC (7% to 13% of HCC lesions) (14–16), where in contrast to the ectopic HCC, the liver is involved and infiltrated by the spread of minute tumor nodules, difficult to detect at imaging because of its diffuse phenotype, and often ill-defined. This type has a poorer prognosis and can rarely benefit from curative treatment (17).

Case report

A 57-year-old man with chronic alcohol abuse, presented at the emergency department, for fatigue, abdominal distension, and lower extremity edema. He also reported diarrhea for the past two months. There was no weight loss or loss of appetite.

Physical examination revealed spider angiomas, prominent periumbilical vessels, abdominal distension, hepatosplenomegaly, and flank dullness on percussion.

Lab results were notable for liver function test abnormalities (alanine transaminase (ALT) 115 U/l, aspartate transaminase (AST) 488 U/l, total bilirubin 29 umol/L, gamma-glutamyl transferase (GGT) 496 U/l, alkaline phosphatase (ALP) 583 U/l); macrocytic anemia (hemoglobin 9.1 g/dL), no thrombocytopenia, inflammatory syndrome (C-reactive protein 22.4 mg/L), mildly elevated creatinine (108 umol/L), hypoalbuminemia (24 g/L), and normal coagulation parameters (prothrombin time (PT) 92%).

Abdominal ultrasonography revealed signs of cirrhosis with moderate ascites and portal vein thrombosis, without focal liver lesion. The hepatitis panel results indicate the presence of hepatitis C antibodies, as well as the absence of hepatitis B antigens and antibodies.

Autoimmunity tests yielded negative results and a diagnosis of alcoholic liver cirrhosis was made. (the presence of hepatitis C infection could not be confirmed because the HCV RNA test was not available).

The presence of portal vein thrombosis prompted concern for hepatocellular carcinoma. This suspicion was further supported by the highly elevated AFP level (1035 UI), despite the absence of any apparent liver

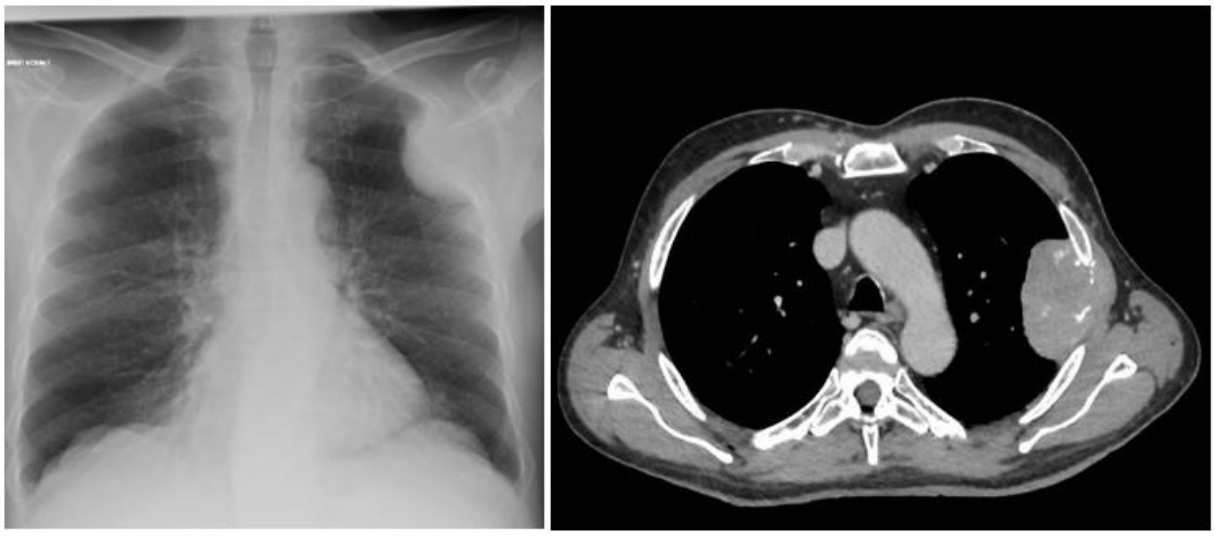

Figure 1. Left parietal mass at the thoracic level, located in the center of the 3rd rib, and accompanied by a lytic bone lesion.

lesion on ultrasound or CT scan of the chest, abdomen, and pelvis. However, a left parietal mass was identified at the thoracic level, located in the center of the 3rd rib, and accompanied by a lytic bone lesion, which could potentially indicate a primary sarcoma or a secondary lesion (Figure 1). To rule out an infiltrative pattern of HCC, an MRI was conducted, which did not reveal any hepatic lesion (Figure 2).

Following an upper gastrointestinal endoscopy, the patient was found to have hiatal hernia, erosive bulbitis, and hypertensive gastropathy. Additionally, the endoscopy revealed the presence of large esophageal varices with no red signs.

In response, the varices were treated with band ligation with the hypothesis of hepatocellular carcinoma in mind, as well as the potential use of antiangiogenic therapy.

The patient underwent an ultrasound-guided biopsy of the 3rd rib lesion, and the histological examination showed a carcinoma with hepatoid features, including trabecular pattern and large cells with round nuclei plus eosinophilic or clarified cytoplasm, expressing glypican 3 and HerPar1 at immunohistochemistry (Figure 3), all being consistent with histological and immunophenotypical characteristics of a moderately differentiated secondary lesion of HCC. The proliferation marker Ki67 is expressed in approximately 40% of the tumor cells.

Few days later following the discharge of the patient, his condition deteriorated rapidly and he passed away tragically due to hemorrhagic shock from uncontrolled variceal bleeding.

Unfortunately, the hepatic biopsy was not performed.

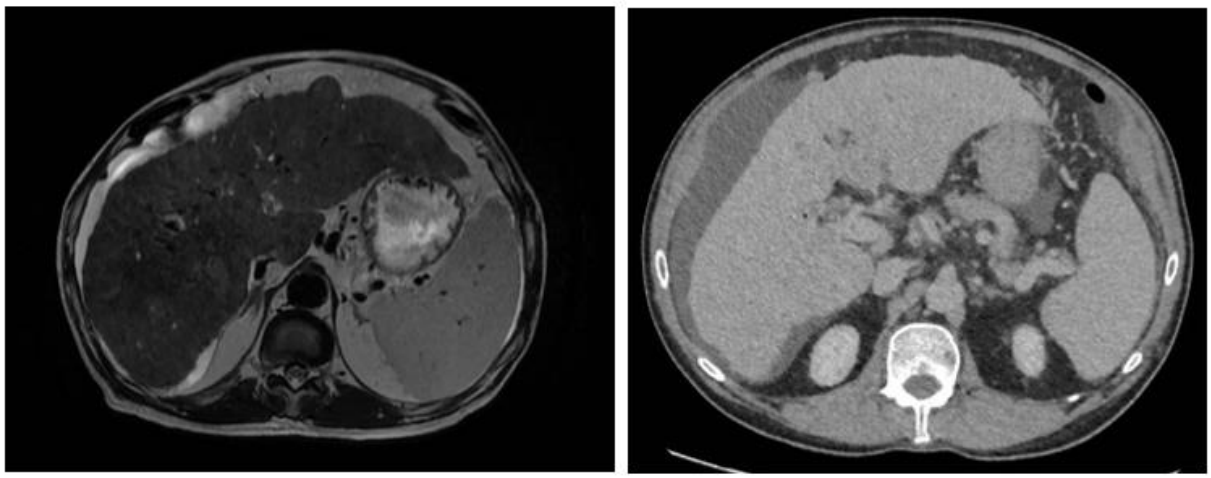

Figure 2. Multiphase MRI (left) and CT (right) scan showing signs of cirrhosis with moderate ascites and portal vein thrombosis, without focal liver lesion

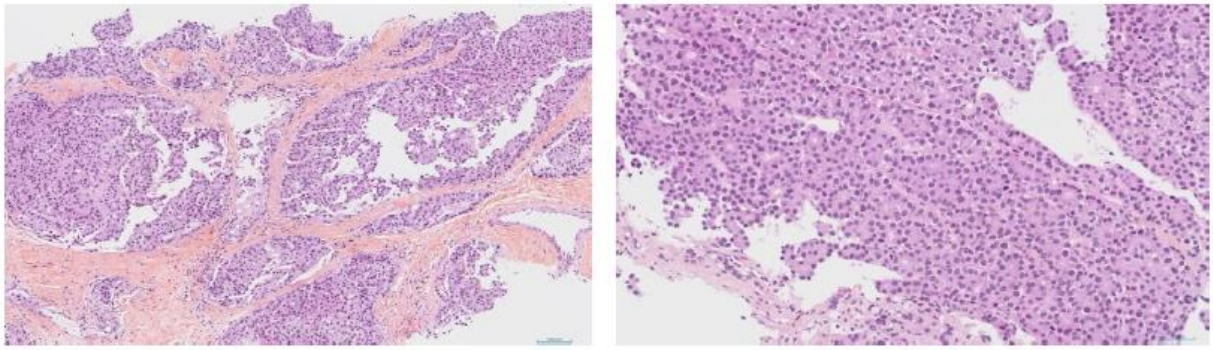

Figure 3. Histological examination of core needle biopsy showed a carcinoma with hepatoid features, including trabecular pattern and large cells with round nuclei and eosinophilic or clarified cytoplasm, expressing glypican 3 and HerPar1 at immunohistochemistry.

Discussion

Hepatocellular Carcinoma (HCC) is a significant global health concern, ranking fifth among the most common cancers worldwide and being the second leading cause of cancer-related deaths in men (1). Its incidence has been on the rise in developed countries in recent years, particularly due to the NAFLD/NASH pandemic (18). It is among the main risk factors for HCC along with chronic alcohol consumption, hepatitis B, and hepatitis C (19).

Screening high-risk patients is crucial for early detection of HCC to allow for curative treatment, and the abdominal ultrasound is the preferred screening modality, while MRI may be used if ultrasound is not optimal (20, 21). Ultrasound (US) screening has an overall accuracy of approximately 84% for all stages of HCC. However, its accuracy is lower for early-stage HCC in cirrhotic patients, ranging from 47% to 63%. In contrast, MRI-based surveillance in cirrhotic patients has shown higher sensitivity (86%) compared to US screening, but it comes with a higher cost and is more time-consuming. Another imaging modality is the dynamic contrast-enhanced CT, which has demonstrated a sensitivity for early detection ranging from 66.7% to 73%, slightly better than US screening. Nonetheless, CT has limitations, such as the cumulative radiation doses associated with repeated scans (22, 23).

The accuracy of hepatocellular carcinoma detection may be enhanced by combining imaging modalities with biomarkers, such as alpha-fetoprotein; however, its utility is limited due to the occurrence of normal AFP levels in a significant percentage of patients with HCC (40%). Also, it can rise in various chronic liver diseases without HCC as well as in other types of malignancies (24). Although AFP measurement is debated and not recommended as a solitary screening test for HCC, it can be valuable in atypical cases such as the present one, encouraging additional diagnostic examination (25, 26).

Despite advanced screening techniques, the majority of HCC cases are diagnosed at an advanced stage with the presence of extrahepatic metastases. Metastatic spread can occur through different routes, including lymphatic dissemination, hematogenous spread or by direct invasion, leading to the development of intrahepatic and extrahepatic metastases (4), and patients may rarely experience initial symptoms exclusively related to extrahepatic metastases.

Among extrahepatic metastases, bone metastases are rare, occurring in about 10% of cases, and are usually accompanied by multiple metastatic sites or known HCC (27, 28).

In the current case, the patient presented with portal vein thrombosis and a highly positive AFP without focal liver lesion. A mass on the left costal area was observed in a chest X-ray and thoracic CT scan, which was suspected to be HCC metastases, where the diagnosis was confirmed by a biopsy of the corresponding costal mass. In this case, the differential diagnosis consisted of an ectopic HCC or a secondary lesion of an infiltrating HCC with portal vein thrombosis as the only sign.

Cases of solitary bone metastasis with no focal liver lesion are extremely rare. This entity is known as ectopic hepatocellular carcinoma (EHCC) which can be a metastasis from an unknown primary HCC or a type of hepatocellular carcinoma developing from hepatic parenchyma in organs or tissues located outside the liver (7–11, 29–31). The pathogenesis of ectopic HCC remains unclear with a congenital theory, involving a variation in the hepatic diverticulum development during embryology (32). Thus, it can manifest in several areas close to the liver, such as the gallbladder, hepatic ligaments, omentum, retroperitoneum, and thorax (33) and is considered as having high propensity for hepatocellular carcinoma.

According to reports, the occurrence rate of an ectopic or accessory liver is around 0.24–0.47 %, with the gallbladder representing the most frequent site (8, 10).

The second possibility is the presence of an unknown primary HCC in the same context of carcinoma of unknown primary; in such instances, metastatic tumors can develop before the primary tumor reaches a size detectable by imaging studies (34), and the primary tumor can appear in some cases during or after treatment. It can also correspond to a spontaneous regression of the primary HCC, but it is a rare occurrence. Indeed, the term "spontaneous regression of HCC'' is used to describe the self-reversal of HCC without any medical interventions, and was initially documented in 1972. The underlying causes of spontaneous regression are believed to involve hypoxia and an immune response (13).

In cases of localized ectopic HCC without metastases, radical operation is necessary for curative treatment case. In the literature review of Qicen Liu et al., a total of 26 patients underwent operations, with 24 of them receiving radical resection. The majority of patients who underwent this procedure experienced a successful recovery. However, it is noteworthy that six out of the 24 patients experienced a recurrence following the radical resection (32).

Another category of HCC is the infiltrative type of HCC, which is characterized by the spread of multiple microscopic lesions throughout the liver (35) and is often challenging to diagnose due to its invasive nature; it does not consistently exhibit the expected imaging characteristics of HCC, and can mimic background changes in cirrhosis. It may be limited to one liver segment but also spread throughout the entire liver parenchyma.

Typically, the tumor appears poorly defined on ultrasonography and exhibits minimal as well as inconsistent arterial enhancement, together with heterogeneous washout, during contrast material-enhanced computed tomography and magnetic resonance (MR) imaging. It may become more discernible compared to the surrounding liver parenchyma in diffusion-weighted, T1-weighted, and T2-weighted MR imaging (36). In some cases, isolated portal vein thrombosis may be the initial and sole indicator of infiltrative HCC (15). As previously mentioned, relying solely on imaging may not be sufficient for detection of infiltrative HCC. Indeed, it has been observed that imaging failed to reveal a discrete lesion in 42.7 % of patients with infiltrating HCC (37). As a result it is typically detected at an advanced stage and has the poorest prognosis among other HCCs (38).

Therefore, radiologists and treating clinicians should be knowledgeable about the atypical appearances of infiltrative HCC to avoid missed or misdiagnosed cases during imaging evaluations.

Additionally, the infiltrative HCC is often associated with markedly elevated AFP levels, which highlights the role of the AFP in such cases.

The diagnosis is confirmed through pathologic analysis, which reveals the presence of minute tumor nodules within large regions of the liver (36).

These two categories underscore the importance of maintaining a high level of suspicion for the diagnosis of HCC in patients with cirrhosis even in the absence of liver mass.

In our case, it was important to differentiate between these two entities since the nature of the infiltrating HCC (the large size, the diffuse nature, and the propensity for the involvement of blood vessels) limits the available treatment options excluding surgical resection, liver transplantation, and thermal ablation (37, 39). Because of two prominent factors, i.e., the presence of portal vein thrombosis and a markedly elevated alpha-fetoprotein (AFP), the most probable diagnosis is the infiltrating HCC but unfortunately, due to the unexpected death of the patient, it was not possible to proceed with the hepatic biopsy for the purpose of obtaining a pathological diagnosis.

Finally, we would like to emphasis AFP importance in our case. Despite the high sensitivity and specificity of multiphase liver MRI and CT scan (23), the imaging results of our patient did not detect any liver lesion, and the diagnosis of HCC was only confirmed by pathologic analysis of the extrahepatic metastases. In this case, AFP raised the suspicion on an underlying HCC and was a helpful biological marker.

Conclusion

In summary, this case study emphasizes the uncommon occurrence of isolated bone metastases from hepatocellular carcinoma without any detectable primary lesion on imaging. It is crucial to maintain a high level of clinical suspicion for the diagnosis of HCC in individuals with chronic liver disease, even when typical clinical signs are absent and to consider the possibility of HCC metastases when evaluating rapidly growing lesions in unusual locations.

The positive result of the alpha-fetoprotein test confirms its usefulness as a valuable biomarker to increase suspicion of hepatocellular carcinoma and prompt additional diagnostic examinations to confirm the diagnosis. The detection of infiltrating HCC at imaging is challenging with a missed lesion in 50% of cases, leading to a delayed diagnosis and a poor prognosis in the absence of a curative treatment. In such situations, the presence of portal vein thrombosis can be a crucial sign for guiding the diagnosis, and determining the need for a liver biopsy for histological confirmation.

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Conflict of interests

The authors have no conflicts of interest to declare.

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