Ectopic Hepatocellular Carcinoma in the Mediastinum with Brain Metastasis: A Rare Case Report

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ABSTRACT

Ectopic hepatocellular carcinoma (EHCC) is an extremely rare neoplasm, especially in the mediastinum, which shares morphologic characteristics with intrahepatic hepatocellular carcinoma (HCC). Its clinical features remain unclear, posing significant diagnostic and therapeutic challenges. The prognosis is also unclear due to its rarity and potential variability. This study reports the first case of EHCC in the mediastinum with subsequent brain metastasis. A 50-year-old man presented with shoulder and chest discomfort persisting for 5 months, accompanied by progressive weight loss and fatigue over the preceding 2 years. Imaging showed a mediastinal mass initially suspected to be lymphoma due to its malignant characteristics. However, histopathological examination identified the lesion as HCC, supported by characteristic immunohistochemical markers, despite normal abdominal imaging. Two months later, the tumor progressed despite intensive radiotherapy, and the patient experienced recurrent seizures. Subsequent brain imaging confirmed multiple intracranial metastases. Unfortunately, the patient died 6 months after diagnosis. The ectopic liver is more susceptible to hepatocarcinogenesis than the main liver; this is attributed to its incomplete functional structure. EHCC can be considered as differential diagnosis of mediastinal masses, even when no intrahepatic HCC is found. The rarity of EHCC in the mediastinum poses difficulties in developing treatment protocols. This case emphasizes the diagnostic challenges and aggressive nature of ectopic HCC and the need for comprehensive management strategies. There are currently no definite guidelines regarding the diagnosis, treatment, and prognosis of EHCC.

Keywords*: ectopic hepatocellular carcinoma, mediastinum, metastasis.*

INTRODUCTION

Ectopic hepatocellular carcinoma (EHCC) is a hepatocellular carcinoma arising from hepatic parenchyma in extrahepatic tissue and is more prone to hepatocarcinogenesis. It is a rare malignancy for which the clinical features are not fully elucidated.[1] The reported incidence of ectopic livers ranges from 0.23% to 0.47%, with the gallbladder followed by hepatic ligaments and omentum being the most common locations.[2,3] However, most of the patients do not have the typical risk factors for HCC developing from the main liver, such as HBV/HCV infection, alcohol abuse, exposure to toxins, or metabolic diseases.[2]

EHCC of the mediastinum is extremely rare. In fact, there are currently no standard criteria for diagnosing EHCC in the mediastinum, but

the mediastinal lesions can be well examined through cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI).[4] Histological examination can be performed for establishing diagnosis and/or treatment planning.[5] The clinical features, management, and prognosis of EHCC of the mediastinum remain unclear due to its rarity and have never been reported in the literature. This study reports the first case of a 50-year-old man with EHCC arising in the mediastinum that subsequently metastasized to the brain. It provides additional insight into EHCC, particularly in the mediastinum.

CASE ILLUSTRATION

A 50-year-old man presented with worsening shortness of breath exacerbated by lying down, along with left shoulder discomfort that improved with rest and occasionally radiated to his chest over the past 5 months. He reported night sweats and a 10 kg weight loss during this period. Despite a history of coronary artery disease treated with angioplasty and medications (clopidogrel, bisoprolol, atorvastatin), he still felt easily fatigued. Physical examination showed tachycardia (110 bpm) and tachypnea (24 breaths/min) with oxygen saturation of 89–92% on room air. Thoracic exam showed dullness on percussion and decreased breath sounds over the medial basal right lung. Laboratory results indicated hypochromic microcytic anemia (hemoglobin, 9.3 g/dL) and normal cardiac enzymes (troponin I and CKMB). ECG showed no signs of acute coronary syndrome. Alpha-fetoprotein (AFP) and beta-HCG levels were within normal limits, but neuron-specific enolase was elevated to more than twice the normal value.

At our hospital, a thoracic CT scan was conducted following a previous chest X-ray (**Figure 1**), which showed an oblong, round mass forming an obtuse angle with the right thoracic paravertebrae, suspected to be a lung tumor or lymphoma. The initial thoracic CT scan (**Figure 2**) confirmed a large superior-anterior mediastinal mass with malignant characteristics, measuring approximately 9 cm, invading the superior vena cava, and is poorly demarcated, initially suspected to be lymphoma, with a nodule at the right pleura and lower right paratracheal lymphadenopathy. Subsequent biopsy of the mediastinal mass indicated well-differentiated hepatocellular carcinoma with features suggestive of high-grade dysplasia. Abdominal MRI showed no abnormalities in the liver or other intra-abdominal organs but confirmed an anterior mediastinal mass. Immunohistochemistry analysis (**Figure 3**) supported the diagnosis of low-grade hepatocellular carcinoma. The patient was scheduled for 30 sessions of radiotherapy targeting the mediastinal mass.

Two months later, the patient was readmitted to the hospital due to recurrent seizures. Collaborating with neurologists, we conducted a head MRI showing multiple rim-enhanced intra-axial lesions at the cortex-subcortical junction of the left frontoparietal lobe, right occipital lobe, and right cerebellar hemisphere. The largest lesion, approximately 2 cm in diameter, was observed in the left frontoparietal lobe, accompanied by surrounding vasogenic edema, causing cerebral edema with a 3 mm right subfalcine herniation, indicative of metastatic involvement. Concurrently, thoracic CT scan evaluation (**Figure 2**) demonstrated progressive disease, with a slight reduction in the size of the target lesion (to 7 cm), and increased lymphadenopathy, and there were new lesions

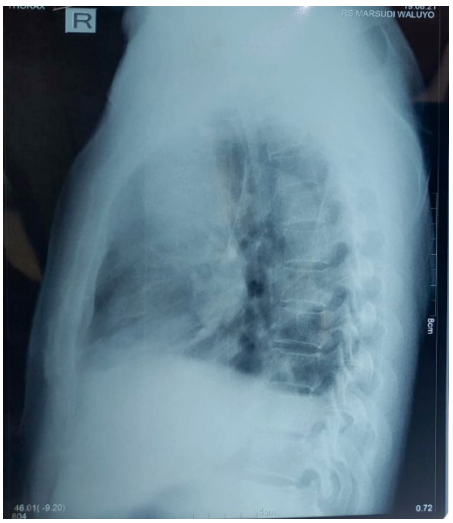

Figure 1. Chest X-ray lateral dextra. There is an oblong round mass forming an obtuse angle with the right thoracic paravertebrae suspected to be a lung tumor or lymphoma.

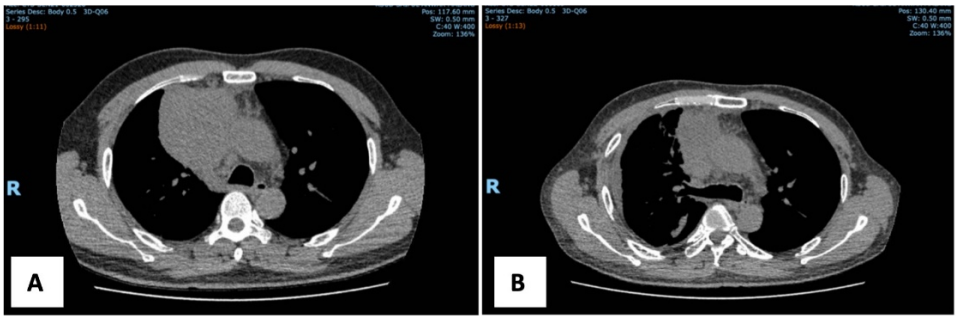

Figure 2. Thoracic CT scan. (A) First examination: there is superior-anterior mediastinal mass with malignant characteristics invading the superior vena cava, size 7.3 cm × 7.4 cm × 9.0 cm. **(B)** Four months of evaluation: the superior-anterior mediastinal mass is reduced in size, but other pathological lesions persist and even new lesions of pleural and pericardial effusion appear, size ± 5.9 × 6.7 × 7 cm.

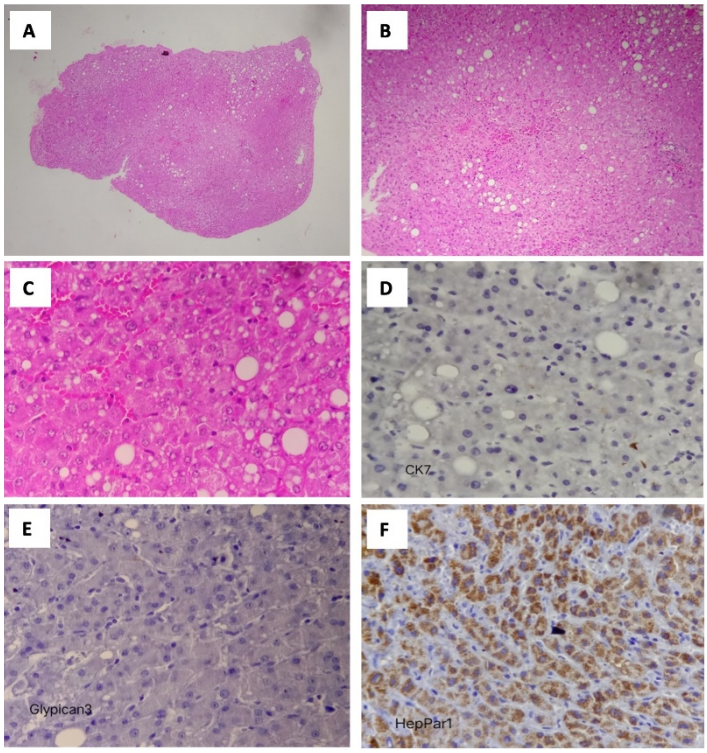

Figure 3. Tumor biopsy. **(A)** Tissue sections containing tumors with solid patterns (HE staining, original magnification 40×); **(B)** HE staining, original magnification 100×; **(C)** the tumor consists of a proliferation of oval to polygonal cells with round nuclei; some are large pleomorphic. Findings are consistent with well-differentiated hepatocellular carcinoma dd high-grade dysplasia nodule (HE staining, original magnification 400×); **(D)** negative CK7 immunohistochemistry (original magnification 400×); **(E)** negative Glypican3 immunohistochemistry (original magnification 400×); **(F)** positive HepPar1 immunohistochemistry in the cytoplasm of tumor cells. Immunophenotype supports a low-grade HCC (original magnification 400×).

with pericardial and right pleural effusions. The patient underwent thoracentesis, yielding 3 L of pleural fluid, and was scheduled for head radiotherapy. Pleural fluid cytology showed class II findings, including mesothelial cells with inflammatory changes. Despite intensive radiotherapy, the patient's condition deteriorated, and he passed away within the following 3 months.

DISCUSSION

This study discusses an exceedingly rare case of hepatocellular carcinoma originating from an ectopic liver nodule located in the mediastinum. The mediastinum is the central cavity between the lungs, housing vital structures such as the thymus, heart, major blood vessels, lymph nodes, nerves, and parts of the esophagus and trachea. Its three main regions are anterior, posterior, and middle, with the anterior mediastinum as the most common location of mediastinal mass, including various solid and cystic lesions, both benign and malignant.[4] Masses in the mediastinum can arise from intrinsic structures, developmental anomalies that extend into the mediastinum, or metastasis from malignancies outside the mediastinum.[6] In this case, a thoracic CT scan showed a mass in the superior-anterior mediastinum accompanied by lymphadenopathy around the right lung, initially raising suspicion of lymphoma. The lesion exhibited malignant characteristics, as it had invaded the superior vena cava and exhibited poor demarcation, resulting in impaired lung function.

EHCC, also known as hepatoid carcinoma, is an extremely rare neoplasm that has similar morphologic features to HCC but grows in various organs outside the liver.[2,7] Extrahepatic liver tissue can be categorized into two main types: ectopic liver, which consists of islands of normal liver tissue not connected to the main liver, and accessory liver lobes, which remain connected to the main liver.[3,8] Ectopic liver formation occurs due to early or late developmental anomalies or disruption of embryonic hepatogenesis, leading hepatic tissue to migrate aberrantly within the septum transversum.[9] Moreover, liver tissue could be produced de novo elsewhere by pluripotent endoderm. Ectopic liver tissue can occur in various locations such as the gallbladder, spleen, retroperitoneum, pancreas, adrenal gland, portal vein, diaphragm, thorax, gastric serosa, testes, and umbilical vein.[10] EHCC, which was first described in 1985 by Ishikura et al.,[11] typically originates from the stomach and can affect various parts of the gastrointestinal tract, lungs, and genitourinary tract.[7] Reported incidences of ectopic livers range from 0.23% to 0.47%, with the gallbladder being the common site, followed by hepatic ligaments and omentum.[2,3] However, cases originating from the mediastinum are exceedingly rare, with most reported instances occurring in Asian males.[7,10] We report a 50-year-old Indonesian man who had EHCC arising from the mediastinum confirmed by postoperative histopathological examinations.

An ectopic liver can lead to malignant or benign diseases, such as hemangiomas, adenomas, or focal nodular hyperplasia associated with an ectopic liver.[1] However, the ectopic liver is more prone to hepatocarcinogenesis than the main liver. This heightened carcinogenic tendency is attributed to its incomplete functional architecture, lacking adequate arterial supply, venous drainage, and biliary ducts, which results in metabolic deficiencies, increased exposure to carcinogens, and impaired reparative nuclear mechanisms. Furthermore, ectopic liver tissue may initially develop as asymptomatic benign tumors; thus, it remains undiagnosed until progressing to malignancy later and manifesting symptoms. Interestingly, this malignant transformation is unrelated to liver diseases such as viral hepatitis infection or cirrhosis in the main liver.[1,5] However, most of the patients do not have the typical risk factors for intrahepatic HCC development, such as HBV/HCV infection, alcohol abuse, exposure to toxins, or metabolic diseases, and the ectopic liver is not cirrhotic.[2] Notably, our patient did not exhibit traditional HCC risk factors, tested negative for HBsAg and anti-HCV antibodies, and had no cirrhosis in the main liver.

Currently, there are no standardized diagnostic criteria for EHCC in the mediastinum. Cross-sectional imaging techniques such as CT and MRI are crucial for evaluating mediastinal lesions. CT is generally recommended for assessing most anterior mediastinal masses, whereas MRI excels in distinguishing between cystic and solid masses.[4] When clinical diagnosis is uncertain, histological examination becomes essential for confirming diagnosis and guiding treatment decisions.[12] In the literature, ectopic livers vary in size, generally small in diameter with an average size of about 17 mm, and most of them are asymptomatic, so the diagnosis of EHCC is

made incidentally during surgery, laparoscopy, or autopsy.[13,14] Occasionally, they cause unexpected problems, like hepatocarcinogenesis, and cause clinical problems such as compression, pain, or bleeding.[5,10] Thus, EHCC is difficult to diagnose at an early stage before progression.

In our case, the patient arrived at our hospital with previous chest X-ray results showing a thoracic mass, prompting further evaluation. A thoracic CT scan confirmed the presence of a mediastinal mass, leading to a biopsy followed by immunohistopathological analysis. The histopathology indicated either a well-differentiated hepatocellular carcinoma or a high-grade dysplastic nodule. Immunostaining with cytokeratin (CK)7 was performed to differentiate between these possibilities by evaluating stromal invasion, as high-grade dysplasia nodules typically exhibit more significant CK7-positive ductular staining in the marginal area of the tumor than HCC, where CK8 or CK18 are more commonly detected.[15,16] Hepatocyte paraffin-1 (HepPar-1) staining confirmed the diagnosis of HCC, characterized by a diffuse cytoplasmic granular staining pattern with high sensitivity (over 70%) and specificity.[17] Pathological cell features and clinical symptoms of EHCC remain unclear because there were no previous reports in the medical literature to guide understanding.

Currently, there is no established treatment protocol for mediastinal EHCC. Surgical resection is generally recommended due to the localized nature and limited vascularity of ectopic liver nodules.[2,3] Several case reports have highlighted that outcomes following resection were more favorable when HCC involved an ectopic liver rather than the intrahepatic form, although this might vary based on the exact anatomical site, with limited long-term follow-up data available.[5,10] In cases like EHCC originating in the pancreas, survival rates are notably lower with chemotherapy alone than with surgery plus adjuvant chemotherapy.[7] The recent study showed that tyrosine kinase inhibitors such as sorafenib, regorafenib, and lenvatinib may be effective against advanced HCC in targeting tumor angiogenesis and growth, but their efficacy in EHCC requires further validation due to limited data.[3] Given that this is the first reported case of EHCC in the mediastinum, optimal treatment strategies remain unclear. Surgery was considered too risky due to the tumor's location, prompting treatment with radiotherapy, which unfortunately resulted in progressive disease. The patient developed brain metastasis, complicating the management further.

The prognosis of EHCC remains unclear due to its rarity and possible heterogeneity.[5] For example, EHCCs in the gastrointestinal tract often present with an unfavorable prognosis due to liver metastasis at diagnosis, indicating an advanced stage.[2] Little is known about EHCC in the mediastinum, including its metastatic potential to the liver or other nearby organs. In the intrahepatic HCC, progression is associated with transcription factor 12 (TCF12), which regulates cell development and differentiation and promotes the tumorigenesis and progression through pathways such as C-X-C chemokine receptor 4 (CXCR4), mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), enhancing cell proliferation and migration.[18] It remains unclear whether similar mechanisms contribute to EHCC metastasis. There are also no established guidelines for postoperative monitoring of recurrent EHCC. Aaras et al. recommend biannual follow-up of AFP measurement and CT imaging for patients with EHCC, with initial MRI of the liver to rule out primary intrahepatic HCC.[19] This patient had an abdominal MRI confirming no intrahepatic HCC, and his AFP levels remained low, contrasting with other EHCC cases where AFP is often elevated. Despite its rarity, awareness of ectopic/accessory liver and its potential complications is crucial.

CONCLUSION

EHCC's heterogeneity poses challenges in diagnosis, necessitating comprehensive systemic and combined diagnostic approaches to avoid misdiagnosis. Our case is the first reported instance of EHCC originating in the mediastinum, diagnosed histologically rather than through imaging, unlike classical HCC. Moreover, the patient lacked risk factors for

chronic liver disease or cirrhosis. Unfortunately, the patient experienced rapid disease progression with EHCC metastasizing to the brain, resulting in death 6 months after diagnosis. Due to limited data, further studies with long-term follow-up are needed to establish standardized treatment protocols and predict the natural history and prognosis of mediastinal EHCC compared to the more common hepatoid carcinoma.

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare related to this study.

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