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Recurrent hepatocellular carcinoma presenting as thoracic lymphadenopathy

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Abstract

Metastatic hepatocellular carcinoma (HCC) can involve the lung parenchyma. However, predominant thoracic lymphadenopathy involvement is less described and there are multiple alternative malignant and non-malignant causes of a similar appearance. Accurate tissue diagnosis is important to determine appropriate management and prognostication. Here, we report two cases of metastatic HCC recurrence causing large thoracic lymphadenopathy, diagnosed adequately and safely by linear endobronchial ultrasound (EBUS) transbronchial needle aspiration.

Introduction

Hepatocellular carcinoma (HCC) is the number one worldwide liver neoplasm, and also ranks within the worldwide top 10 malignancy-related deaths. It is most commonly associated with chronic viral hepatitis and cirrhosis. Males are more affected with a ratio of 2:1, and age-adjusted incidence has continued to increase. Extrahepatic metastases can be common at the time of diagnosis and commonly include lung, abdominal lymph nodes, bones, and adrenal glands. Endobronchial ultrasound (EBUS) has become an established technique to obtain tissue diagnosis for causes of thoracic lymphadenopathy.

Case Report

Case 1

A 64-year-old male was referred to our respiratory clinic for evaluation of pulmonary nodules and massive symmetrical bilateral hilar lymphadenopathy. He was a reformed intravenous drug user with hepatitis C-related cirrhosis. Other relevant history included 30 pack-years of tobacco smoking and marijuana use, plus a family history of pancreatic cancer. Two years prior, he was found to have an elevated alpha-fetoprotein (AFP) on surveillance and magnetic resonance imaging (MRI) of the abdomen identifying three nodular masses having features consistent with multifocal HCC. These were successfully treated with trans-arterial chemoembolization (TACE). Localized recurrence 12 months later was successfully managed with selective internal radiation therapy (SIRT). Continued surveillance 12 months later detected another solitary liver lesion, and an indeterminate lung nodule on abdominal MRI. Chest computed tomography (CT) confirmed additional bilateral lung nodules with the largest measuring 9 mm and very large bilateral hilar lymphadenopathy with a short axis of 27 mm (Fig. 1A). Positron emission tomography (PET) showed moderate fluorodeoxyglucose (FDG) uptake (SUV max 4.6) within the left and right hilar stations (Fig. 1B). The largest pulmonary nodule and liver nodule both showed mild tracer uptake. Linear EBUS (Olympus BF-UC180F, Japan) transbronchial needle aspiration (TBNA) of the hilar lymphadenopathy using a 22-G needle (Olympus Vizishot 2, Japan) showed yellow (bile-containing) malignant cells on rapid on-site examination (ROSE) (Fig. 2). Despite mild coagulopathy and thrombocytopenia, there were no procedural complications. Detailed cytological examination confirmed metastatic HCC, with negative microbiological cultures and flow cytometry. The patient proceeded onto treatment with sorafenib.

Case 2

A 61-year-old male with previous HCC was diagnosed with unprovoked left lower limb deep venous thrombosis (DVT) and concurrent pulmonary emboli. The CT pulmonary angiogram also detected large right paratracheal lymphadenopathy with a short axis of 25 mm (Fig. 1C). HCC was secondary to alcoholic and hepatitis C-related cirrhosis and had been treated with orthoptic liver transplantation six years ago. Other past medical history included type 2 diabetes, hypertriglyceridaemia, and hypertension. FDG-PET demonstrated moderate tracer uptake (SUV max 3.9) within the lymphadenopathy and no extrathoracic involvement (Fig. 1D). He proceeded on to linear EBUS-TBNA of the lymph node with ROSE showing bile pigment containing cells consistent with metastatic HCC, and confirmed with immunohistochemistry (Fig. 2). The procedure was followed by extension of the DVT, but the patient remained haemodynamically stable. Multidisciplinary team discussion recommended CyberKnife stereotactic body radiotherapy treatment after an EBUS-guided insertion of a fiducial marker. Adequate local disease control was achieved, with continued surveillance.

Discussion

HCC metastasis to predominantly thoracic lymph nodes is uncommon. To our knowledge, this is the first report of metastatic recurrent HCC that presented as predominantly bilateral thoracic hilar lymphadenopathy as in our first case. We found one other report of metastatic HCC presenting as paratracheal lymphadenopathy [1], similar to our second case. Our cases would join it as the only other metastatic HCCs described to have been diagnosed via EBUS bronchoscopy.

EBUS is an established minimally invasive technique in diagnosing causes of mediastinal lymphadenopathy and nodal staging of lung cancer. It has replaced surgery with its similar yield, lesser morbidity, and lower cost. In addition, it provides high specificities for diagnosis and high negative predictive values for determining non-small cell

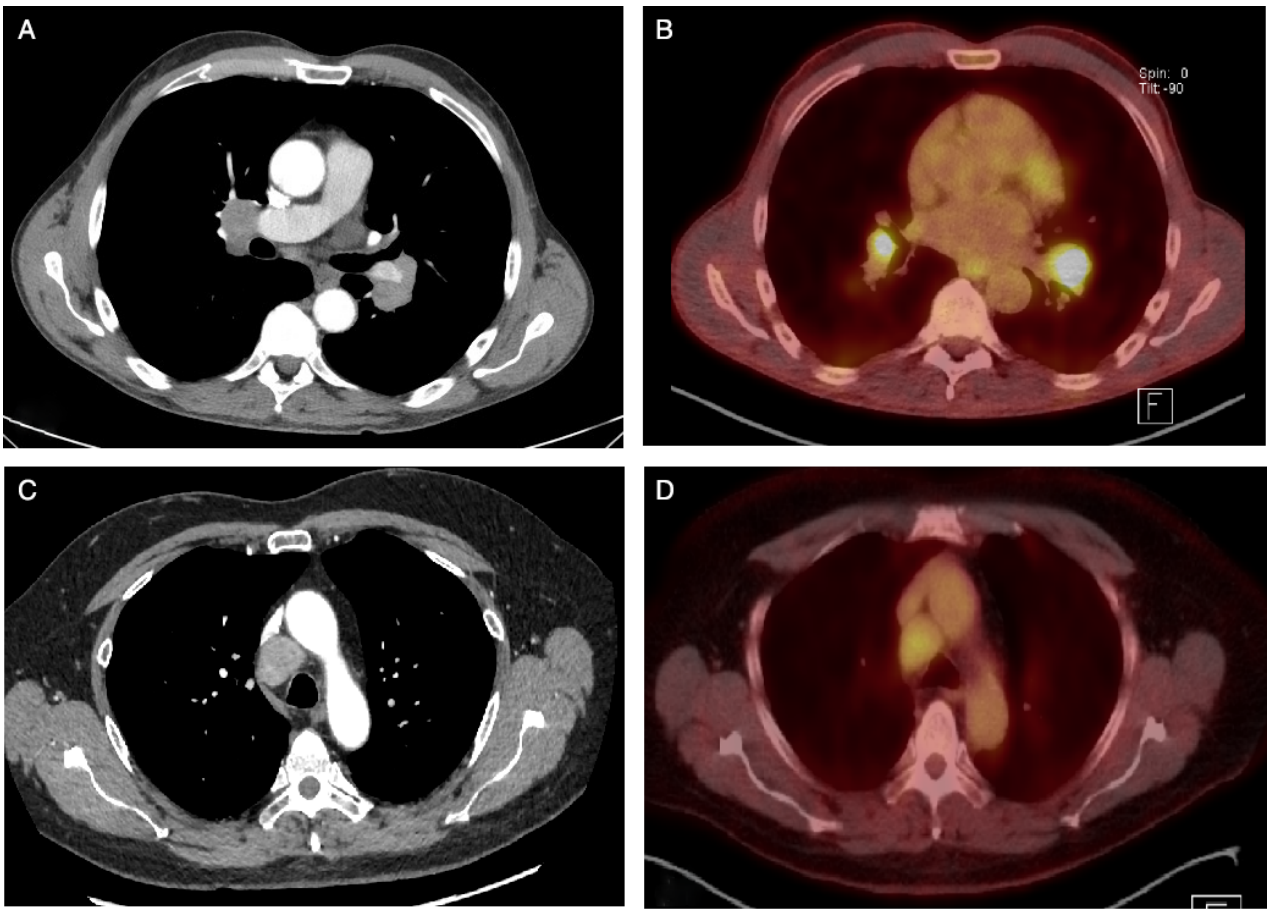

Figure 1. (A, B) Computed tomography (CT) and positron emission tomography (PET) showing enlarged and fluorodeoxygenase tracer uptake within bilateral hilar lymph nodes. (C, D) CT showing enlarged paratracheal lymph node with tracer uptake on PET imaging.

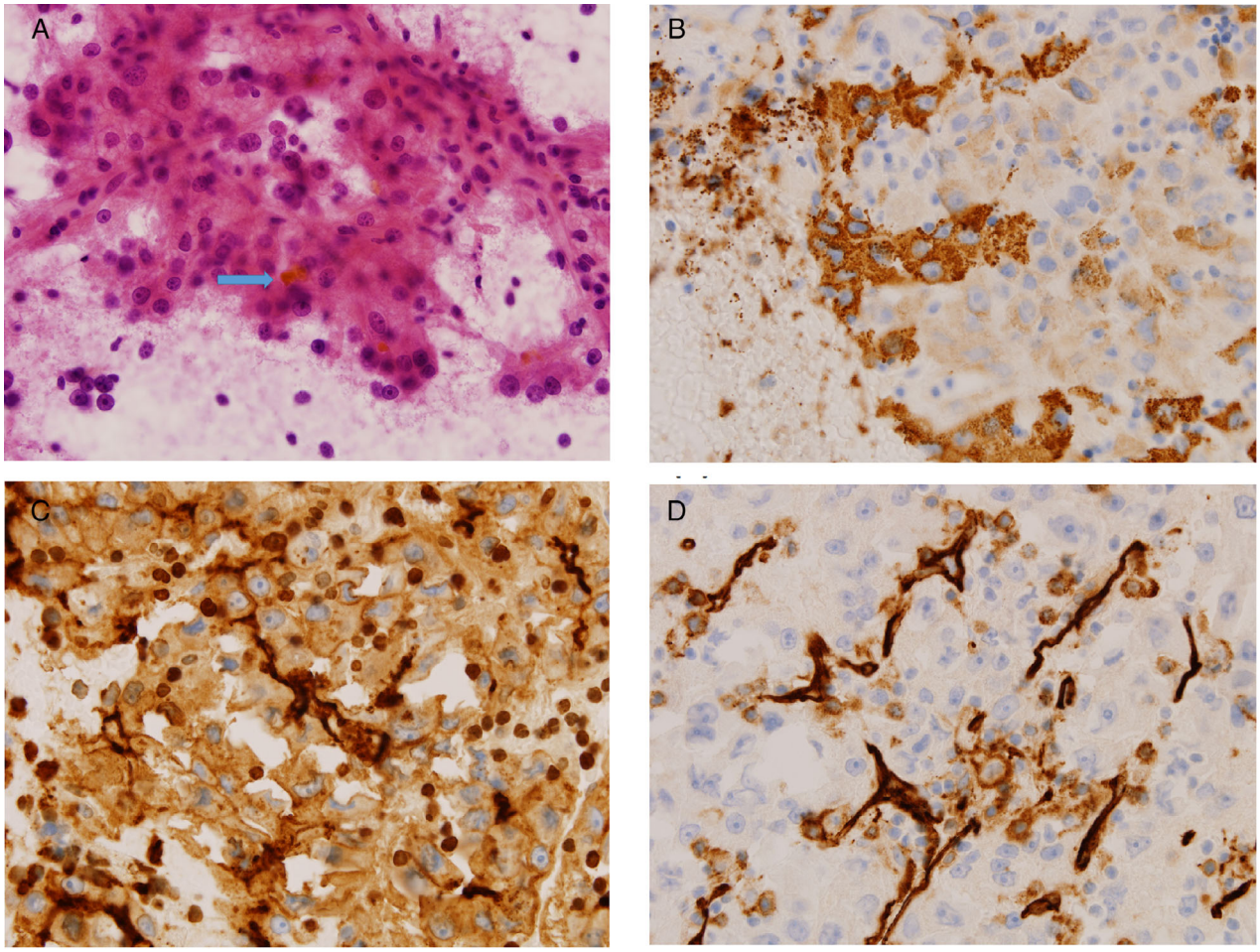

Figure 2. Thoracic lymph node cell blocks with (A) haematoxylin and eosin staining showing pleomorphic epithelial cells with hepatoid features containing irregular round nuclei and prominent nucleoli, eosinophilic cytoplasm, and characteristic bile pigment (arrow). Immunohistochemistry using (B) Hep par-1 staining to confirm hepatic cells, (C) Carcinoembryonic antigen (CEA) staining to delineate canaliculi and membranes plus (D) CD31 staining of transversing blood vessels.

lung cancer mediastinal involvement. Differentials considered for thoracic lymphadenopathy include metastatic thoracic or extra-thoracic malignancies, haematological malignancies, granulomatous disease, or atypical infections (particularly mycobacterial). Tissue confirmation is therefore important to determine optimal management. Safety profile of EBUS is excellent, including in patients with liver dysfunction as shown in our cases. Specimens obtained are adequate to confirm HCC and also sufficiently unique to be identified on ROSE. Various cytological staining is performed to confirm hepatic cells and bile (Fig. 2), with absence of additional stains such as thyroid transcription factor 1, MOC31, epithelial membrane antigen, and cytokeratin 19 to exclude alternative diagnoses.

The absence of enlarged or significantly FDG-avid locoregional abdominal lymphadenopathy or hepatic tumour is an uncommon presentation of HCC recurrence, but previous literature has associated this with the primary tumour having greater lymphovascular invasion [2]. This was not retrospectively established in our cases.

Both our cases, and the previous report by Alraiyes et al. [1], detected very large (>25 mm) asymptomatic thoracic lymphadenopathy. The size of the lymph nodes was seemingly disproportionate to the level of tumour burden, with only low-to-moderate FDG uptake on PET scan. Causes for this include delayed diagnosis, low tumour burden, or slower-growing neoplasms. It is also hypothesized to be intrinsic to HCC because of lower GLUT 1 or 2 transporter expression, increased efflux via P-glycoprotein, or increased enzymatic hydrolysis affecting tracer distribution [3].

Screening for HCC is usually performed using AFP levels to diagnose new or recurrent disease. This is then confirmed via ultrasound, CT, or MRI with typical imaging characteristics not requiring formal tissue confirmation. Routine

imaging of the thorax is usually not performed at initial HCC diagnosis. Previous work has questioned the role of regular thoracic screening, but 15% of HCC cases are diagnosed with metastatic diseases and a 40–47% incidence of thoracic involvement [4]. Similarly, in our cases, we are unable to determine if there was earlier evidence of thoracic disease and a prolonged interval could explain the large lymphadenopathy. Thus, this could argue for the broadening of initial imaging at HCC diagnosis or recurrence to include the thorax.

HCC treatment options include resection, transplantation, TACE, or percutaneous local ablation for intrahepatic disease; unresectable or extrahepatic disease can be managed with the tyrosine kinase inhibitor sorafenib. Our second case's oligometastasis was successfully treated with stereotactic radiotherapy.

In conclusion, metastatic HCC may present as hilar or mediastinal lymphadenopathy, which can be safely diagnosed using linear EBUS-guided sampling. In our experience, HCC metastasis to thoracic lymph nodes caused significant enlargement and further studies are required to evaluate the role of routine thoracic imaging in the initial assessment of HCC. Radiotherapy can be considered for the treatment of solitary metastasis, but efficacy requires further study.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Acknowledgment

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