CASE REPORT | LIVER

A Rare Case of Hepatocellular Carcinoma Presenting as Cervical Lymph Node Metastases and Review of the Literature

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ABSTRACT

Hepatocellular carcinoma (HCC) is a leading cause of cancer morbidity and mortality worldwide. Common sites of metastases include the lungs, regional lymph nodes, bone, and adrenal glands. Although rare, distant metastases to the cervical lymph nodes have been reported. With better therapies for viral hepatitis, there has been a shift in the landscape of chronic liver disease and the development of HCC with rising prevalence of HCC attributable to metabolic dysfunction-associated steatotic liver disease. In this study, we describe a case of metastatic HCC presenting as cervical lymphadenopathy in a patient with metabolic dysfunction-associated steatotic liver disease in the absence of cirrhosis.

KEYWORDS: metastases; hepatocellular; carcinoma; cervical; lymphadenopathy

INTRODUCTION

Primary liver cancer, of which 75%–86% are hepatocellular carcinoma (HCC), is now the sixth most common cancer globally and third leading cause of cancer-related death.[1] Traditional risk factors for the development of HCC include age, male sex, chronic viral hepatitis, tobacco use, alcohol use, aflatoxin exposure, and cirrhosis of any etiology.[2] Metabolic dysfunction-associated steatotic liver disease (MASLD) is also recognized as a risk factor of HCC independent of cirrhosis, accounting for up to 40% of MASLD-related HCC cases.[1,3,4] Extrahepatic metastatic spread of HCC commonly involves the lungs, lymph nodes (typically subdiaphragmatic regional lymph nodes), bone, and adrenal glands.[5] Distant lymph node metastases above the diaphragm are uncommon, and Uka et al found that in 151 patients with extrahepatic metastatic HCC, 9% of patients had metastatic lymph node involvement above the diaphragm.[5] Interestingly, within this study, no patients had supraclavicular or cervical lymph node metastases, which has been seldomly reported in the literature.[6–16] In this study, we discuss a case of a 65-year-old man with an atypical distribution of metastatic HCC presenting with cervical lymphadenopathy in the context of MASLD without cirrhosis.

CASE REPORT

A 65-year-old indigenous man was referred to our hepatology unit in August 2023 after a fine-needle aspiration of a left cervical lymph node revealed metastatic HCC (Figure 1). He reported a 36-pound unintentional weight loss over the preceding 2 years and the development of a palpable mass in his left cervical neck region. A computed tomography (CT) scan of his neck completed in July 2023 demonstrated a left cervical conglomerate nodal mass measuring 3.1 × 2.4 × 3.7 cm (Figure 2). A subsequent staging CT of his
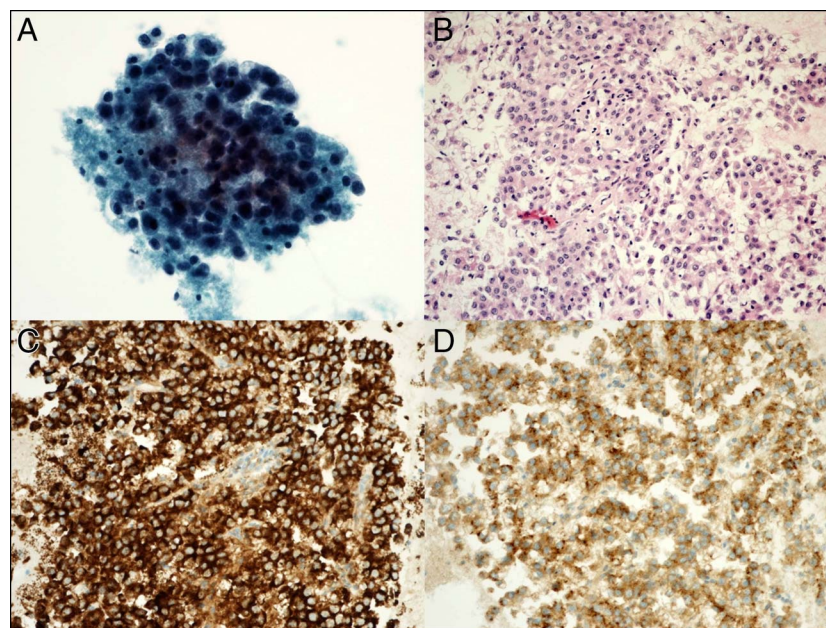
Figure 1. The fine-needle aspiration from the neck mass consists of single isolated and groups of atypical cells with high nuclear-to-cytoplasmic ratio, irregular enlarged nuclei, and occasional mitosis. Some tumor cells show granular cytoplasm while others contain vacuolated or clear cytoplasm (A and B). The immunocytochemical study reveals that the tumor cells are positive for HepPar-1 and glypican 3 (C and D, respectively), compatible with hepatocellular differentiation. The cytomorphology and immunoprofile are consistent with metastatic hepatocellular carcinoma. (A) ThinPrep preparation, Papanicolaou stain, original magnifications 400×. (B) Cell block, hematoxylin-eosin stain, original magnifications 200×. Tumor cells are immunoreactive to HepPar1 (C), and glypican 3 (D), original magnifications 200×.

chest, abdomen, and pelvis revealed a 6.6 × 5.6 cm segment II liver lesion suggestive of HCC, along with multiple mediastinal, bilateral hilar, and retroperitoneal lymph nodes suspicious for metastatic disease (Figure 2). No morphologic features of cirrhosis were noted, but hepatic steatosis was evident. Liver transient elastography demonstrated a fibrosis score of 4.2 kPa (F0 fibrosis) and a controlled attenuation parameter score of 267 dB/m (S2 steatosis).

His medical history included treated hypertension, dyslipidemia, type 2 diabetes, alcohol use of 10 standard drinks (140 g) weekly, and former tobacco use. He denied any family history of liver disease. He denied any signs or symptoms of

chronic liver disease including gastrointestinal bleeding, peripheral edema/ascites, or any symptoms consistent with hepatic encephalopathy. On physical examination, there were no features of muscle wasting, scleral icterus, telangiectasia, or peripheral edema. His initial laboratory investigations including a complete blood count (platelets: 258 × 10^9/L), aspartate aminotransferase (28 U/L), alanine aminotransferase (36 U/L), alkaline phosphatase (81 U/L), gamma-glutamyl transferase (75 U/L), total bilirubin (4 umol/L), and albumin (41 g/L) level were within normal limits. An alpha-fetoprotein level was normal at 2 μg/L. A chronic liver disease workup revealed no prior exposure to hepatitis B virus or hepatitis C virus.

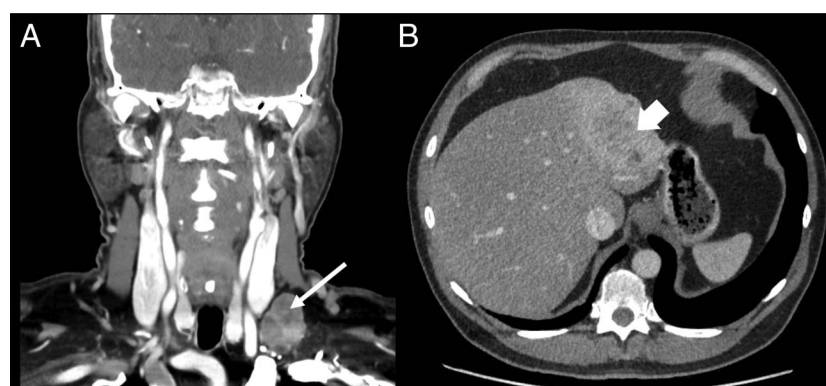**Figure 2.** (A) Left cervical level IV lymphadenopathy measuring 3.1 × 2.4 × 3.7 cm (narrow arrow). (B) Segment II liver lesion compatible with HCC measuring 6.6 × 5.6 cm (thick arrow).

Table 1. Patient demographics, metastatic spread of primary HCC of published reports collated from literature review

Study	Age (sex)	Known HCC before metastatic disease detection?	Sites of metastases	Diagnosis of metastatic HCC	Time to metastases identification (mo)	Primary HCC size (cm)	Primary HCC segment	Presence of cirrhosis	Risk factors of HCC	AFP (µg/L)	Treatment (outcome)	Survival (mo)
Tanoue et al, 2021[5]	63 (M)	Yes	Right cervical LN, superior mediastinal LN, subdiaphragmatic LN	Excisional biopsy of right cervical LN	36	5.0	VII & VIII	NR	NR	36.7	1. Initial hepatic resection of primary HCC 2. Sorafenib (disease progression) 3. Radiation & lenvatinib (progression and death)	43 (after metastases detected)
Madabhavi et al, 2014[6]	49 (M)	No	Right cervical LN, right and left suprarenal region	Excisional biopsy of right cervical LN	NA	8.4 × 8.5	NR	No	HBV	1.69	1. Sorafenib (NR)	NR
Liu et al, 2013[7]	56 (M)	No	Left supraclavicular LN, mediastinal LN, bilateral lungs	Excisional biopsy of left supraclavicular LN	NA	8.0	VI	NR	HBV	695.4	None (progression and death)	1
Kobayashi et al, 2012[8]	64 (M)	No	Left cervical LN	Fine-needle aspiration of left cervical LN	NA	NR	NR	Yes	HCV, cirrhosis	164,878	1. Hepatic arterial infusion chemotherapy with 5-fluorouracil and cisplatin (progression and death)	NR
Kim et al, 2011[9]	65 (M)	Yes	Left cervical LN, brain	NR	NR	NR	NR	NR	HBV	NR	1. PEI & TACE (NP)	NR
Karaman et al, 2007[10]	72 (M)	No	Left cervical LN, subdiaphragmatic LN	Excisional biopsy of left cervical LN	NA	NR	NR	NR	NR	300	NR	1
Taniai et al, 2005[11]	73 (M)	Yes	Left supraclavicular LN	Excisional biopsy of left supraclavicular LN	10	2.0 × 2.0	V	Yes	Cirrhosis	40.9	1. Microwave ablation	1.5 (after metastases detected)
Thorburn et al, 2003[12]	67 (M)	No	Right supraclavicular LN, porta hepatis LN	Fine-needle aspiration of right supraclavicular LN	NA	9.0 × 8.0 × 5.0	NR	Yes	Alcohol misuse, cirrhosis	198	NR	NR

Table 1. (*continued*)

Study	Age (sex)	Known HCC before metastatic disease detection?	Sites of metastases	Diagnosis of metastatic HCC	Time to metastases identification (mo)	Primary HCC size (cm)	Primary HCC segment	Presence of cirrhosis	Risk factors of HCC	AFP (μg/L)	Treatment (outcome)	Survival (mo)
Thorburn et al, 2003[12]	72 (F)	No	Right supraclavicular LN, porta hepatis LN, anterior pericardial LN, precarinal LN, anterior mediastinal LN	Fine-needle aspiration of right supraclavicular LN	NA	8.0	NR	Yes	PBC, AIH, cirrhosis	>3,000	1. Palliative chemotherapy (progression and death)	11
Köklü et al, 2003[13]	75 (M)	No	Right cervical LN, porta hepatis LN	Excisional biopsy of right cervical LN	NA	NR	NR	Yes	HBV, cirrhosis	158	NR	NR
Lau et al, 2000[14]	67 (M)	No	Right supraclavicular LN, mediastinal LN	Excisional biopsy of right supraclavicular LN	NA	NR	NR	NR	Tobacco use, diabetes	92,373	NR	NR
Toyoda et al, 1996[15]	48 (M)	Yes	Bilateral supraclavicular LN, bilateral cervical LN, mediastinal LN, paraaortic LN, peripancreatic LN	Fine-needle aspiration of supraclavicular LN	2	1.8	NR	Yes	HBV, cirrhosis	16.1	1. Initial hepatic resection of primary HCC 2. Systemic therapy with 5-flurouracial and cisplatin (progression and death)	16 (after recurrence detected)

AFP, alpha-fetoprotein; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LN, lymph nodes; NA, not applicable; NR, not reported; PBC, primary biliary cholangitis; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

He was diagnosed with Barcelona Clinic Liver Cancer Stage C disease in the context of MASLD without cirrhosis. Given his Eastern Cooperative Oncology Group score of 0, he was referred to medical oncology and has since completed 20 cycles of systemic therapy with the immune checkpoint inhibitor atezolizumab and vascular endothelial growth factor inhibitor bevacizumab as of September 2024.

DISCUSSION

This case of metastatic HCC represents a rare presentation of the disease manifested by the primary complaint of cervical lymphadenopathy. A review of the literature demonstrates that only 12 other cases of HCC metastasizing to cervical or supraclavicular lymph nodes have been reported (Table 1).[6–16] To our knowledge, we are the first to report a case of cervical lymph node metastases from a primary HCC in a patient with MASLD, without cirrhosis or chronic hepatitis B virus infection.

Patients with MASLD alone are currently not recommended to undergo HCC screening. Annual incidence rates of MASLD-related HCC in the absence of cirrhosis have previously been reported to be quite low (0.008%–0.03%) and as such have not met recent recommendations for an annual incidence cutoff approximately 1% to qualify HCC screening as cost-effective.[17,18] However, Mittal et al identified that in a US national cohort of patients with confirmed HCC, 37 of 107 patients (34.6%) with MASLD-related HCC did not have concurrent cirrhosis, a considerable proportion of patients.[4] Thus, further research to identify high-risk patients for developing HCC in the context of MASLD is desperately needed to guide primary HCC screening, especially considering the skyrocketing prevalence rates of MASLD.[19] It is further recommended that patients with HCC Barcelona Clinic Liver Cancer Stage A and greater have a noncontrast CT study of the chest completed to evaluate for metastatic disease.[1] Cases of extrahepatic metastases from HCC, such as our patient, may therefore be missed by current screening guidance. Given the rarity of such cases, however, it is difficult to identify which patients with HCC would benefit from further imaging to detect sites of distant metastases. Clinicians should be aware that such cases of distant metastatic spread of HCC can occur and use a thorough clinical history and physical examination to recognize these uncommon sites of metastases.

Primary hematogenous spread of HCC to distant organs is more common than lymphatic spread.[20] Complex lymphatic networks exit the liver and can be classified into both deep and superficial lymphatic systems. The superficial lymphatic system is found on the liver surface and develops along the bilateral coronary ligament, bilateral triangular ligament, and falciform ligament, which directly enter distant thoracic lymph nodes and, in turn, access the thoracic duct.[21] A primary HCC that is thus near the superficial lymphatic system, such as in our case,

may preferentially gain access to distant lymph nodes in the thoracic and cervical region through this pathway, which has been postulated in other cases as well.[6] Future studies on liver segment involvement, morphologic features, and immunocytological analysis of primary HCCs may be able to provide clinical guidance for patients who are high risk of rarer distant metastatic sites.

Based on the case reports outlined in Table 1 reporting survival outcomes, the median overall survival measured in months for those with cervical or supraclavicular nodal involvement from HCC is 6.25 months (range 1–43).[6,8,11–13,16] Although metastatic spread of HCC to cervical lymph nodes is rare, clinicians should bear in mind the potential for HCC when assessing patients with cervical lymphadenopathy, given poor survival outcomes associated with this degree of advanced metastases.

DISCLOSURES

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