CASE REPORT

Metastasis of diffuse hepatocellular carcinoma to an extremely unusual site

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SUMMARY

Hepatocellular carcinoma is a common and aggressive malignancy the world over. Metastasis commonly occurs in lungs, bone, lymph node and adrenals. Skeletal muscle metastases from any primary is a rare occurrence, those occurring from hepatocellular carcinoma even more so. We present a case of a 61-year-old man presenting with hepatocellular carcinoma with synchronous symptomatic metastasis to the skeletal muscle. This article discusses approach to hepatocellular carcinoma with skeletal muscle metastases aetiopathogenesis, differential diagnosis and approach to treatment.

BACKGROUND

This is an unusual case as metastasis of hepatocellular carcinoma to the skeletal muscle is an extremely uncommon entity, with less than ten reported cases in literature. Furthermore, diffuse subtype of hepatocellular carcinoma with skeletal metastasis is even rarer. Despite this rarity, this possibility must be kept in mind because of the differential diagnoses that must be considered—hepatic metastasis from a sarcoma or synchronous malignancies—and the varied treatments required for each.

CASE PRESENTATION

A 61-year-old man presented with a history of weight loss of around 15 kg since 6 months, decreased appetite since 3 months and a painless, rapidly growing right hypochondrium mass and jaundice since 2 months.

He had a known case of alcohol dependence syndrome, having admitted to an alcohol intake of around 30 g/day for the last 30 years. He had no medical comorbidities, no history of tobacco usage or significant previous illnesses or hospitalisations. He also had no family history of any genetic illnesses or malignancy.

On examination, he was found to have mild pallor and icterus and the liver was palpable as a tender, hard mass in the right hypochondrium and epigastrium extending 5 cm below the right costal margin and 10 cm below the xiphoid process. A second discrete mass was palpable in left iliac fossa, measuring 5 × 4 cm, non-tender, variable (soft to hard) in consistency, just adjacent to but discrete from the medial aspect of the left iliac bone.

INVESTIGATIONS

Blood investigations showed total bilirubin was 3.2 mg%, direct bilirubin 2.6 mg% and alkaline phosphatase 558 IU/L (44–147 IU/L). Serum α

fetoprotein was 629 ng/mL (<10 ng/mL). Serology for hepatitis B and C was negative.

On radiological evaluation, abdominal ultrasonography showed diffuse hepatomegaly with multiple echogenic lesions in both lobes of liver, suggestive of metastases and a large poorly defined hypoechoic mass in the left iliac fossa.

Upper gastrointestinal endoscopy showed grade 2 oesophageal varices, portal hypertensive gastropathy and a duodenal ulcer.

Intravenous contrast-enhanced abdominal CT showed hepatomegaly with multiple hypodense lesions in both lobes of liver (figure 1) and a large poorly defined partially enhancing mass continuous with the left iliacus (figure 2).

Ultrasound-guided biopsy of the liver mass showed round to polygonal liver cells with clear to eosinophilic cytoplasm and dense nuclei, arranged in trabeculae and cords with evidence of reactive change and cholestasis and scanty fibrous stroma and mild mononuclear cell infiltrate, suggestive of clear cell variant of hepatocellular carcinoma.

Open biopsy of the left iliac fossa mass was performed under local anaesthesia which showed metastatic hepatocellular carcinoma, consistent with the liver biopsy (figure 3). Immunohistochemistry, though advised for differentiating primary and metastatic liver tumours, could not be performed in this case as the patient could not afford it.

DIFFERENTIAL DIAGNOSIS

Initially, a clinical differential diagnosis of hepatocellular carcinoma with metastases was considered. Another possibility considered was soft tissue sarcoma with hepatic metastasis. However, biopsy provided a confirmative histopathological diagnosis.

TREATMENT

As this patient presented with diffuse metastatic hepatocellular carcinoma, the treatment prescribed to him was palliative chemotherapy (doxorubicin). Other than the role of biopsy to confirm the diagnosis, there was no other indication for surgical intervention in this patient.

OUTCOME AND FOLLOW-UP

Currently the patient is on chemotherapy and traditional medicine.

DISCUSSION

Hepatocellular carcinoma is an aggressive tumour, with metastasis often occurring early and incidence being reported in some studies to be as high as 13%. Diffuse hepatocellular carcinoma, comprising

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Figure 1 Intravenous contrast-enhanced CT of the abdomen showing diffuse hepatocellular carcinoma.

5.4–17% of tumours, is a macroscopic variant with multicentric origin and intrahepatic spread, resembling cirrhosis, and often is associated with haematogenous and lymphatic spread.¹

The incidence of metastasis to the liver is higher than primary liver tumours, hence clinical evaluation of liver malignancy must include both. In this case, the differential diagnosis included hepatocellular carcinoma and hepatic metastasis from a soft tissue sarcoma. The distinction between the two may be difficult even on biopsy if the tumour is poorly differentiated.

Common sites of metastasis from hepatocellular carcinoma include lungs, lymph nodes, bone and adrenals.² Metastasis to the skeletal muscle is extremely rare, with fewer than 10 cases having been reported in literature,^{3–5} and is considered a poor prognostic factor. Skeletal muscle metastasis, already uncommon, is even rarer from hepatocellular carcinoma. This is the first reported case of diffuse variety of hepatocellular carcinoma metastasising to the skeletal muscle. More common sources of the primary include lung (30 cases in literature), colorectal (10 cases in literature) and kidney (8 cases in literature), bladder (4 cases in literature) and melanoma (5 cases in literature).⁶ Furthermore, skeletal muscle metastasis is often associated with metastasis to other sites at the time of diagnosis, explaining the poor prognosis.

Figure 2 Intravenous contrast-enhanced CT of the abdomen showing left iliac mass.

Figure 3 Histopathology of hepatocellular carcinoma metastasis to skeletal muscle.

Spread to the skeletal muscle is haematogenous and the several reasons have been proposed for the rare incidence. Continuous movement in the skeletal muscle may prevent implantation of tumour emboli.⁷ This may be why skeletal muscle metastases may be even rarer in muscles of the extremities than in postural muscles. Blood turbulence in skeletal muscle during active hyperaemia is also supposed to have a role in preventing metastasis. Release of lactate into the skeletal muscle during exercise is believed to inhibit implantation and proliferation of metastatic tumour emboli. Also, natural killer cells and/or lymphocytes, that play a major role in tumour immunity, are well-distributed in skeletal muscle circulation.⁸

Metastasis can be precocious, synchronous or metachronous, depending on the relation of detection of the metastasis with detection of the primary. In the other reported cases, presentation was metachronous, where the muscle metastasis was detected after a trisegmentectomy or radiofrequency ablation of the hepatocellular carcinoma. In one case, metastatic hepatocellular carcinoma of the intercostal muscle was confirmed by immunohistochemistry; however, the primary tumour could not be identified. In our case, the presentation was synchronous, with both the liver tumour and the metastasis to the iliac muscle being detected simultaneously. The most common presentation of skeletal muscle metastasis is pain,⁹ but in our patient, the left iliac mass was painless. Other sites of muscle metastases from hepatocellular carcinoma in literature include gluteus maximus, biceps femoris and intercostal muscles.

Current guidelines recommend imaging with or without biopsy for the diagnosis of hepatocellular carcinoma and although biopsy of metastatic lesions is not routinely indicated,¹⁰ in our case the biopsy was performed as metastatic lesion was at an uncommon site. Furthermore, synchronous primary malignancies are very rare but not unheard of.

In cases such as ours, where malignancy is suspected, open biopsy of deep seated lesions should be preferred in place of a direct or imaging guided core-needle biopsy because of the high-risk of postprocedure bleeding. In our case, in spite of opting for an open biopsy there was still postprocedure bleeding that had to be tackled surgically.

Histologically, hepatocellular carcinoma can be divided into clear cell and non-clear cell subtypes. In clear cell hepatocellular carcinoma, the subtype noted in this patient, the tumour is most commonly moderately differentiated; it is frequently associated with cirrhosis and has a slightly lower 3-year to 5-year survival rates than non-clear cell tumours. Immunohistochemistry has

proven to be a very useful tool to increase sensitivity and specificity of biopsied tumours.¹¹ It can determine origin of tumours and differentiate between primary and metastatic liver tumours, especially if poorly differentiated. However in developing countries, its use is restricted by its cost—it is not performed routinely.

In advanced cases such as ours, treatment is palliative. Ablative therapies, with percutaneous ethanol injection or radio-frequency ablation, help to increase disease-free survival as a stop-gap treatment or to prevent progression. However, chemotherapy is the mainstay for inoperable tumours. Drugs found to be most active individually are doxorubicin, cisplatin and 5-fluorouracil, with response rates at around 10% but no demonstrable impact on survival. Combination regimens have also been tried, and although response is slightly better, chances of toxicity are considerably higher. Chemoimmunotherapy, with a combination of interferon α and chemotherapeutics has a better response in young non-cirrhotic patients.¹² Antiangiogenesis agents such as bevacizumab, and sorafenib, an oral kinase inhibitor, have been shown to improve response rate compared to chemotherapy alone and to prolong survival.¹² Recent retrospective studies have shown that a combination of gemcitabine and oxaliplatin could be used as neo-adjuvant chemotherapy to reduce tumour size prior to surgery.¹³ External beam radiotherapy, previously not believed to be an acceptable treatment modality in hepatocellular carcinoma, recently has been shown to have moderate success in advanced inoperable hepatocellular carcinoma.¹⁴ Another available option is angiographically delivered yttrium microspheres, used as brachytherapy.¹⁵

Learning points

- ▶ Metastasis of hepatocellular carcinoma to the skeletal muscle is an extremely rare entity, but must be kept in mind because of the differential diagnosis—hepatic metastasis from a sarcoma or synchronous malignancies.
- ▶ Treatment of these metastatic lesions is only palliative, to relieve local symptoms. Surgery or radiotherapy may be employed.
- ▶ In tropical countries, similar lesions presenting in the liver and muscles should also raise suspicion of the possibility of parasitic cysts (eg, echinococcus).
- ▶ Treatment options for metastatic diffuse hepatocellular carcinoma are limited and prognosis is dismal. However, chemotherapy with newer drugs is showing better outcomes. External beam radiotherapy is also under study as a treatment modality for inoperable hepatocellular carcinoma.

Contributors BH was the primary consultant who worked up the case and planned the treatment. NS collected the data and case-related photographs and compiled the case report with AP.

Competing interests None.

Patient consent Obtained.

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