CASE REPORT

Metastatic hepatocellular carcinoma to the pelvis and vertebrae in a patient with chronic hepatitis 'C' with unknown primary

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SUMMARY

A 54-year-old man infected with hepatitis C virus presented to us with pain in the right iliac fossa radiating to the back and right thigh for the past 2 months. Imaging of the abdomen and pelvis was performed, which revealed a soft tissue mass adherent to right iliac blade and right ala of sacrum. Trucut biopsy of the mass was performed and immunohistochemical stains Glypican-3 and Hep-par 1 were used for histopathological analysis, which diagnosed the mass as hepatocellular carcinoma. This is a unique case of metastasis of hepatocellular carcinoma to the bone in which imaging of the liver did not show any primary lesion. Liver function tests showed that aspartate transaminase and alanine transaminase were twice the normal range with a high viral load and significantly raised serum α -fetoprotein. The patient was treated with intravenous 5-fluorouracil and radiotherapy as a palliative measure with only moderate clinical improvement.

BACKGROUND

Hepatocellular carcinoma is the fifth most common cancer in the world and with hepatitis C as one of its aetiological agents, its incidence is on the rise in Pakistan.¹ Ours is a unique case in which a patient with chronic hepatitis C had a soft tissue mass in the right iliac blade and right ala of sacrum, which was found to be hepatocellular carcinoma on histopathological analysis without any primary lesion in the liver.

CASE PRESENTATION

A 54-year-old man, a school teacher, who was diagnosed with hepatitis 'C' 6 years earlier, presented to us with pain in the right lower quadrant of the abdomen for the past 2 months. The pain was dull and continuous with radiation to the back and right thigh. On physical examination of the abdomen and pelvis, the site of right iliac fossa was tender. An ultrasound of the abdomen and pelvis along with CT scan and MRI of the abdomen and pelvis was performed, which depicted a large heterogeneously enhancing soft tissue mass involving the right iliac blade and right ala of sacrum (figures 1 and 2). Trucut biopsy of the mass was advised, which was then stained with two immunohistochemical stains having a very high sensitivity in detecting hepatocellular carcinoma, namely, Glypican-3 and Hep-par 1. The sample turned out to be positive. Before the diagnosis of

hepatocellular carcinoma, the patient, being from a poor background, had refused testing for the genotype of hepatitis 'C' virus and could not afford the newer costly drugs.² He was treated for hepatitis 'C' using pegylated interferon and ribavirin,³ but the viral load constantly remained in the high range. Currently his viral load is still high at 9.2×10^6 IU/mL.

INVESTIGATIONS

CT and MRI of the abdomen and pelvis depicted a large $13 \times 10 \times 20$ cm heterogeneously enhancing soft tissue mass eroding the right ilium along with right sacral ala. The mass extended medially into the pelvis and lower abdomen, pushing the iliopsoas muscle, common iliac and external iliac vessels medially with extension posterolaterally into the soft tissues of the gluteal region (figures 1 and 2). The liver revealed smooth margins and normally enhancing parenchyma with no focal lesions except hypertrophy of the left lobe (figure 3), which is a characteristic feature of chronic liver disease, given the history of hepatitis C in the patient since 2007. Biopsy and H&E staining of the tissue showed a trabecular and pseudoglandular pattern of tumour with polygonal cells showing moderate atypia, eosinophilic granular cytoplasm and endothelial wrapping (figure 4); immunohistochemical staining with Glypican-3 and Hep-par 1 confirmed the presence of hepatocellular carcinoma (figures 5 and 6). Viral count was found to be 9.2×10^6 IU/mL. Serum α -fetoprotein was significantly raised at 430 ng/mL, while liver function tests showed alanine transaminase (ALT) and aspartate transaminase (AST) to be twice the normal range, 80 and 86 IU/L, respectively. Platelet count was $253\,000/\text{mm}^3$. Bone scan and CT of the chest were performed to look for other possible metastases. CT of the chest showed a 1.8×1.7 cm mass in the left neural foramina in proximity to the spinal cord and eroding the body of T7 vertebra. Another 2.6×1.9 cm soft tissue mass was seen in the right paravertebral region of C7 vertebra causing erosion of lateral margin of body and right transverse process, although the bone scan did not pick up any abnormality in these areas (figure 8). Bone scan showed non-homogeneous and moderately increased tracer uptake in the right iliac bone with extension of the tracer uptake laterally beyond the normal bony outline and relatively decreased tracer uptake in the lateral part of iliac crest. It also

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Figure 1 CT of the abdomen and pelvis showing a 13×10×20 cm heterogeneously enhancing soft tissue mass involving the right iliac blade and ala of sacrum. The mass is displacing the adjacent iliopsoas muscle and iliac vessels medially with indistinct intervening fat planes.

showed a focal area of decreased tracer uptake in the left infero-lateral aspect of sacrum.

DIFFERENTIAL DIAGNOSIS

Pain in the right iliac fossa has many differentials on the basis of the knowledge of local anatomy, including appendicitis, cholecystitis, ureteric colic, Crohn's disease, diverticulitis, mesenteric adenitis and testicular torsion. However, radiological investigation revealed a soft tissue mass eroding the right iliac blade and adherent ala of sacrum suggesting a malignancy, most probably a metastasis. Biopsy provided the ultimate diagnosis of hepatocellular carcinoma but, the fact that the imaging did not detect any primary source in the liver makes it a unique case.

TREATMENT

According to the latest research, sorafenib has shown promising results in improving the survival of patients with advanced

hepatocellular carcinoma; it has also shown remarkable results in combination with 5-fluorouracil in some studies.⁴ But in our case, we had to resort to the less efficacious option of only using 5-fluorouracil, as the patient could not afford the high cost of Sorafenib.⁵ The patient also had pain of moderate severity in the right iliac fossa so we gave him 40 Gy of external beam radiation in 20 fractions to the iliac area as palliative treatment.⁶ For metastasis to the spine, the patient received 300 cGy of radiation in 10 fractions to prevent paraplegia.

OUTCOME AND FOLLOW-UP

After treatment with 5-fluorouracil and radiotherapy, the patient reported moderate symptomatic improvement, but returned after a few months with increased severity of pain in the right iliac fossa. On CT of the abdomen and pelvis, the size of the lesion invading the right ilium was found to have increased to

Figure 2 MRI of the abdomen and pelvis revealing a soft tissue intensity well-defined mass in the right iliac fossa with loss of fat planes and medially displaced psoas muscle.

Figure 3 Normally enhancing parenchyma of the liver with smooth margins and no focal lesion.

22×13.2 cm (figure 9); the lesion involved the right sacral ala and upper part of right sacroiliac joint causing the patient discomfort in right iliac fossa. Another soft tissue mass of 4.5×3.8 cm was seen involving and destroying the left ala of sacrum and extending anteriorly into the pelvis. α -fetoprotein of the patient was also found to have risen significantly to 108 795 ng/mL. The patient was given zoledronic acid as palliative treatment for his pain, to which he responded significantly.^{8 9}

DISCUSSION

Metastasis of hepatocellular carcinoma without a primary source is a very unique phenomenon and has been reported very rarely in the literature.^{10 11} The explanation for this might be a microhepatocellular carcinoma that has been destroyed by the immune system or one that regressed spontaneously.¹² Another explanation could be the presence of ectopic liver tissue that transformed into hepatocellular carcinoma.¹³ Our

patient has also been hepatitis C positive for the past 6 years; his viral load is high, 9.2×10^6 IU/mL; he has used pegylated interferon and ribavirin, but with no improvement. It is worthy to mention here that chronic hepatitis C infection is one of the major risk factors for causing hepatocellular carcinoma.¹⁴ The current standard protocol for the diagnosis of hepatocellular carcinoma is imaging and/or biopsy.¹⁵ In our case, CT of the

Figure 4 H&E-stained slide of the tissue taken after biopsy.

Figure 5 Glypican-3-stained slide of the tissue taken after biopsy.

Figure 6 Hep-par 1-stained slide of the tissue taken after biopsy.

Figure 7 Reticulin-stained slide of the tissue taken after biopsy.

abdomen and pelvis along with MRI was performed, which clearly depicted the mass eroding the right iliac bone and right ala of sacrum (figures 1 and 2). Trucut biopsy of the mass was carried out and special immunohistochemical stains were used. One of the stains is Glypican-3, it is a membrane-bound heparan sulfate that is expressed in the cells of patients with hepatocellular carcinoma; our patient's biopsy tested positive for it¹⁶ (figure 5). To further support the diagnosis another immunohistochemical stain known as Hep-par 1 was used. Hep-par 1 is a monoclonal antibody with a sensitivity higher than that of Glypican-3; our patient also tested positive for it¹⁷ (figure 6). The last stain that was used was reticulin; this stain outlines trabeculae greater than three cells in thickness in hepatocellular carcinoma; it was positive around thickened trabeculae in our patient supporting the diagnosis of hepatocellular carcinoma (figure 7).¹⁸ Hepatocellular carcinoma most commonly metastasises to lung, abdominal lymph nodes and bone.¹⁹ To rule out metastases, bone scan and CT of the chest were performed. CT of the chest detected a soft tissue mass eroding the body of T7 vertebra and another soft tissue mass in the right paravertebral region of C7 vertebra causing erosion of lateral margin of body and right transverse process (figure 8). Bone scan only showed disease process in the right ilium and sacrum, where hepatocellular carcinoma had already been confirmed through biopsy. Liver function tests including ALT and AST are not significant markers of liver histological status until they are markedly raised; ALT and AST were found to be 80 and 86 IU/L, respectively, in our case, that is, twice the normal range.²⁰ α -fetoprotein is a tumour marker that can be used for surveillance of hepatocellular carcinoma in high-risk individuals and can also help in supporting the diagnosis of hepatocellular carcinoma if it is significantly raised; it was found to be significantly elevated, at 430 ng/mL, in our patient.²¹ For the palliation of hepatocellular carcinoma, we treated our patient with intravenous 5-fluorouracil and gave him 40 Gy of radiation in

Figure 8 CT scan showing metastatic lesions in the C7 and T7 vertebrae.

Figure 9 CT scan showing a large 22×13.2 cm heterogeneously enhancing soft tissue mass centered on the right ilium causing its destruction and also involving the right sacral ala and upper part of right sacroiliac joint. Another 4.5×3.8 cm soft tissue mass involving and destroying the left ala of sacrum and extending anteriorly into the pelvis can also be seen.

20 fractions to the iliac area, which helped in relieving his severe agony.²²

Learning points

- ▶ Metastatic hepatocellular carcinoma without a primary source in the liver is a rare occurrence.
- ▶ Glypican-3 and Hep-par 1 have very high sensitivities, as immunohistochemical stains, in detecting hepatocellular carcinoma.
- ▶ Hepatitis C is one of the main aetiological factors responsible for causing hepatocellular carcinoma.
- ▶ A significantly high level of α -fetoprotein can help in supporting the diagnosis of hepatocellular carcinoma.
- ▶ External beam radiotherapy and bisphosphonates are useful in controlling painful bone metastasis.

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Contributors SHA performed the literature research and wrote the Discussion section of the report. MZIK was involved in the management of the case and wrote the Investigations and Case presentation sections. MI wrote the introduction and assisted in the literature review. SJAH identified the case and wrote the Summary.

Competing interests None.

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