Atypical Presentation of Hepatocellular Carcinoma

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Hepatocellular carcinoma is one of the most common primary hepatic malignancies worldwide, although it is relatively uncommon in the United States. Persistent infection by hepatitis B or C virus is probably the most important cause of hepatocellular carcinoma worldwide. Cancers of the liver typically occur in the setting of cirrhosis and initially may escape clinical recognition because the symptoms and signs suggest progression of cirrhosis. Tumors may invade adjacent vascular structures, with metastasis typically occurring by the hematogenous route. The most frequent metastatic sites are the lung, bone, lymph nodes, and brain, respectively. We describe the case of a patient with previously unrecognized chronic hepatitis C who presented with back pain and neurologic symptoms as the initial manifestations of hepatocellular carcinoma that had metastasized to the sacrum. An approach to diagnosis and management of this unusual presentation is discussed.

CASE PRESENTATION

Patient Presentation and History

A 51-year-old male construction worker presented to the emergency department for evaluation of sudden onset of severe, sharp back pain radiating to the buttocks, which was associated with acute urinary retention and bowel incontinence. The patient reported that in the month prior to presentation he had experienced pain in his lower back and sacral region along with tingling and numbness in both buttocks extending into his scrotum and penis and radiating to both feet. His past medical history was significant for hypertension treated with hydrochlorothiazide, 25 mg/dL. The patient had smoked a pack of cigarettes a day for 30 years and reported a history of intravenous drug abuse and heavy alcohol use in the past.

Physical Examination

Physical examination revealed marked tenderness in the lumbosacral region on palpation. Motor strength was 5/5 throughout the upper and lower extremities. There was hyperalgesia in the S1 through S5 dermatomes bilaterally. Mild weakness of plantar flexion of the third, fourth, and fifth toes of both feet was observed, with greater weakness noted on the left than the right. Deep tendon reflexes were +2/+2 at the biceps, brachioradialis, triceps, and knees and 0/0 at the ankles. Plantar reflexes were flexor bilaterally. There was decreased perineal sensation and reduced rectal sphincter tone on digital rectal examination.

Diagnostic Evaluation

Initial laboratory evaluation revealed normal findings on complete blood count, electrolyte panel, and renal function tests. Results of liver function tests included: total bilirubin, 1.7 mg/dL; aspartate aminotransferase, 53 U/L; alanine aminotransferase, 47 U/L; alkaline phosphatase, 112 U/L; and albumin, 3.1 g/dL. Prothrombin time was 12.9 s.

The patient was admitted to the hospital for emergent magnetic resonance imaging (MRI) of the lumbosacral spine to assess for causes of cauda equina impingement involving the S1 to S5 roots. MRI demonstrated a lesion in the sacrum extending from S1 to S4, with significant narrowing of the caudal aspect of the spinal canal and involvement of the ala sacralis bilaterally (Figure 1). A subsequent computed tomography (CT) scan of the abdomen demonstrated 2 large liver nodules.

After an unsuccessful attempt to obtain cells from the sacral lesion using fine needle aspiration cytology, the patient underwent an open biopsy. Histopathology revealed hepatocellular cells in the sacral lesion, and immunohistochemical staining for α-fetoprotein (AFP) and hepatocyte-specific antigen (HSA) (Figure 2) were strongly positive, suggesting metastasis from a primary
hepatocellular carcinoma. CT-guided biopsy of the liver nodules confirmed the diagnosis of hepatocellular carcinoma. Serologic studies for hepatitis B and C viral exposure yielded positive antibody titers for hepatitis C virus.

**Clinical Course**

The patient received radiotherapy to the sacral area for symptomatic pain relief. Cisplatin-based chemotherapy was instituted for palliative management, and the patient was subsequently discharged. Six months later, the patient had improved symptomatically. His serum AFP level, which was 11926.1 ng/mL before treatment, had returned to within normal range with chemotherapy.

**DISCUSSION**

Hepatocellular carcinoma is relatively uncommon in North America and Western Europe (0.5%–2% of all cancers) but represents 20% to 40% of all cancers in countries where viral hepatitis is endemic.1 Globally, chronic hepatitis B and C infections are the major risk factors for hepatocellular carcinoma. Other well-documented risk factors are alcoholic and other types of cirrhosis,4 long-term use of oral contraceptive pills,2 hereditary hemochromatosis,5 and repeated aflatoxin ingestion.4

**Clinical Presentation**

The most common symptoms of hepatocellular carcinoma relate to its typically late diagnosis and reflect end-stage cirrhosis. Typical symptoms include weakness, malaise, anorexia, upper abdominal pain, and weight loss. Physical findings depend on the stage of the disease and may include hepatomegaly, jaundice, ascites, Dupuytren’s contracture, spider angiomata, asterixis, pedal edema, periumbilical collateral veins, and enlarged hemorrhoidal vein.

Hematogenous metastasis of hepatocellular carcinoma is frequent and typically involves the lungs and bones (in 0.5% of cases), usually at the terminal phase of the disease.6 Hepatocellular carcinoma presenting with signs and symptoms related to local spread or distant metastasis without abdominal discomfort or palpable mass is rare, comprising 1.5% to 5.3% of cases in different series.6,7 Low back pain with sudden onset of urinary retention and bowel incontinence as the initial presentation of metastatic hepatocellular carcinoma is extremely rare.7 There have been few studies and case reports of bone metastases from hepatocellular carcinoma.6–8 More frequently, bone lesions are observed after successful treatment of the primary liver tumor.9,10

**Diagnosis and Staging**

Tumor markers used in evaluating adenocarcinoma of potential hepatic origin include AFP, HSA, MOC-31 (a monoclonal antibody directed against cell surface glycoprotein), carinoembryonic antigen, and anticytokeratins. Serum AFP measurements are used both to screen high-risk patients for possible hepatocellular carcinoma and to monitor postsurgical patients for tumor recurrence.11 A negative immunohistochemical stain for AFP in a biopsy specimen does not, however, exclude hepatocellular carcinoma.12,13 HSA recognizes both benign and malignant liver-derived tumors.14 MOC-31 helps differentiate metastatic adenocarcinoma of the liver from hepatocellular carcinoma.15

Several radiologic modalities may be helpful in the diagnosis of hepatocellular carcinoma, including CT, MRI, digital subtraction angiography, ultrasonography, and lipiodol CT. CT may detect lesions as small as 1 cm
Treatment and Prognosis

The median survival for patients with untreated hepatocellular carcinoma is less than 4 months, with a 5-year survival of approximately 2%. The poor survival underscores the aggressive nature of this cancer, its propensity for hematogenous dissemination, and the extent of disease at the typical time of presentation. MRI is useful when CT results are inconclusive because it can differentiate dysplastic nodules from hepatocellular carcinoma and is more effective in distinguishing vascular lesions and focal fat from hepatocellular carcinoma. Lipiodol CT is highly sensitive at detecting hepatocellular carcinoma, even when the lesions are less than 1 cm.

In the event that imaging results are inconclusive, liver biopsy may be necessary to make the diagnosis of hepatocellular carcinoma. Typically, percutaneous liver biopsies are performed using CT or ultrasonographic guidance. Laparoscopic guidance greatly facilitates percutaneous biopsy and allows visualization of the liver and peritoneal cavity but requires expertise that may not be available in all clinical settings. Diagnostic accuracy of liver biopsy is diminished with smaller lesions (< 3 cm). Since these lesions probably are premalignant, biopsy is particularly important for distinguishing the lesions from hepatocellular carcinoma.

Several classification and staging schemes of hepatocellular carcinoma have emerged, including the tumor, node, and metastasis and the Okuda staging systems. No classification scheme has gained widespread acceptance, however.

CONCLUSION

When faced with the differential diagnosis for back pain and bone metastasis, physicians should consider the possibility of late-stage hepatocellular carcinoma. As described in our case, advanced hepatocellular carcinoma may present in a subtle manner, without its classic symptoms of jaundice, right upper quadrant pain, and recent weight loss. Immunohistochemical analysis is an effective tool in the evaluation of metastatic adenocarcinoma of unknown origin, as it can provide a tumor-specific diagnosis and direct subsequent therapy.

REFERENCES


