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Case Report

A case of isolated metastatic hepatocellular carcinoma arising from the pelvic bone

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Reports of metastatic hepatocellular carcinoma (HCC) without a primary liver tumor are rare. Here we present a case of isolated HCC that had metastasized to the pelvic bone without a primary focus. A 73-year-old man presented with severe back and right-leg pain. Radiological examinations, including computed tomography (CT) and magnetic resonance imaging (MRI), revealed a huge mass on the pelvic bone (13×10 cm). He underwent an incisional biopsy, and the results of the subsequent histological examination were consistent with metastatic hepatocellular carcinoma. The tumor cells were positive for cytokeratin (AE1/AE3), hepatocyte paraffin 1, and glypican-3, and negative for CD56, chromogranin A, and synaptophysin on immunohistochemical staining. Examination of the liver by CT, MRI, positron-emission tomography scan, and angiography produced no evidence of a primary tumor. Radiotherapy and transarterial chemoembolization were performed on the pelvic bone, followed by systemic chemotherapy. These combination treatments resulted in tumor regression with necrotic changes. However, multiple lung metastases developed 1 year after the treatment, and the patient was treated with additional systemic chemotherapy. **(Korean J Hepatol 2012;18:89-93)**

Keywords: Hepatocellular carcinoma; Pelvic bone; Metastasis; Radiotherapy; Transarterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers and its incidence is increasing worldwide.[1] As the treatment of HCC has remarkably improved, the survival of patients with HCC has been prolonged. Consequently, extrahepatic metastasis of HCC is now diagnosed more frequently and the incidence of bone metastasis from HCC is also increasing.[2,3] However, cases of extrahepatic HCC without a detectable primary liver tumor have rarely been reported; in fact, bone metastasis from HCC, single or multiple, without the presence of a primary tumor has been reported in only six cases worldwide.[4-9] Because of insufficient experience with these cases, diagnostic and treatment approaches for these patients are challenging. Here, we present a case of metastatic HCC arising from the pelvic bone without a primary focus.

CASE REPORT

A 73-year-old man was admitted to our hospital for evaluation of severe back pain and right leg pain for 1 month. The medical history of patient revealed that he was diagnosed as a hepatitis B virus (HBV) carrier about 20 years earlier, but was lost to follow up. The patient was not a heavy drinker or smoker. There was no significant family

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Abbreviations: AFP, alpha-feto-protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; PET, positron emission tomography; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TACE, transarterial chemoembolization; 5-FU, 5-Fluorouracil

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history. On physical examination, a palpable and hard mass was noted in the right pelvic area. Hepatomegaly, liver masses, and ascites were absent. Initial laboratory findings were as follows: white blood cell count 4,830/μL, hemoglobin 15.2 g/dL, platelets 138,000/μL, total protein 7.8 g/dL, albumin 4.4 g/dL, aspartate aminotransferase (AST) 31 IU/L, alanine aminotransferase (ALT) 35 IU/L, total bilirubin 1.0 mg/dL, alkaline phosphate 98 IU/L, prothrombin time 14 second (INR 1.21), alpha-fetoprotein (AFP) 15.01 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) 864 mAU/mL. Hepatitis B virus surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) were positive. Hepatitis B e antibody (HBeAb), HBV-DNA with polymerase chain reaction, and serological markers of hepatitis C were negative. He belonged to Child-Turcotte-Pugh class A.

For evaluation of the pelvic mass, computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed. They demonstrated a 13×10 cm expansile mass that involved the right iliac bone (Fig. 1). The patient underwent an incisional biopsy with the impression of a malignant bone tumor. However, on pathological examination, the tumor was composed of polygonal cells with ample cytoplasm and trabecular pattern. In immunohistochemical stains, these tumor cells were positive for cytokeratin (AE1/AE3), hepatocyte paraffin 1 (HepPar1), and glypican-3,

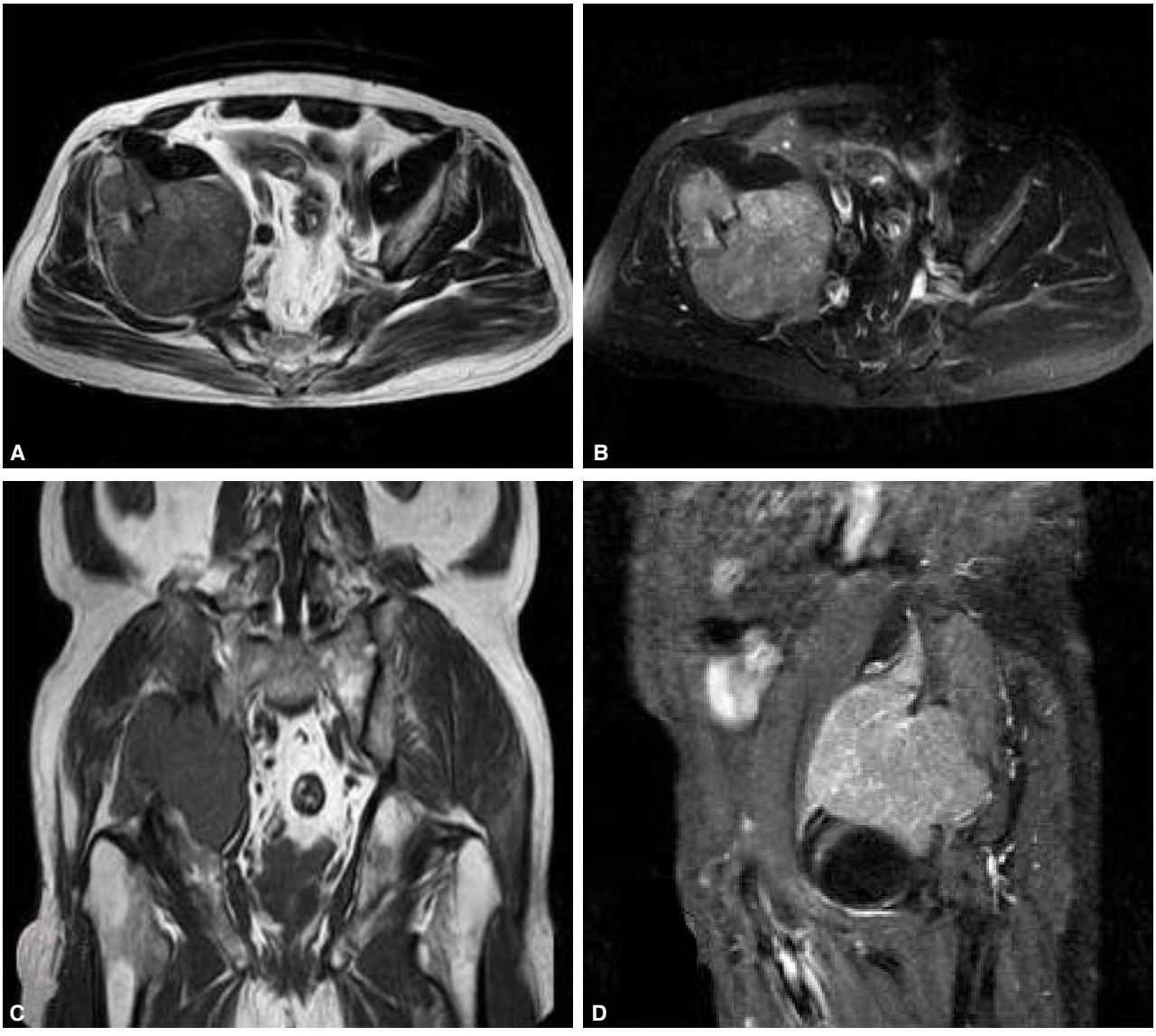

Figure 1. Pelvic magnetic resonance imaging (MRI). A 13×10-cm bone mass was found in the right iliac bone. (A, C, D: T1-weighted images, B: T2-weighted image).

which confirmed the diagnosis of HCC (Fig. 2). Tumor cells were negative for CD56, chromogranin A and synaptophysin, which are the markers of neuroendocrine differentiation. To find the primary focus, abdominal CT, MRI, positron emission tomography (PET) scans and angiography were performed. However, no tumor was found in the liver in these radiologic examinations.

We diagnosed this case as an isolated metastatic HCC of the pelvic bone without the presence of a primary cancer in the liver. Surgical resection of the tumor was recommended, but the patient refused an operation because of old age and the large size of the tumor. Instead, we decided to treat him with combined modalities. He started radiotherapy in the pelvic area with a total dose of 5,100 cGy in 17 fractions. One week after the end of radiotherapy, transarterial chemoembolization (TACE) was performed in the metastatic HCC of the pelvic bone via the right internal iliac artery (adriamycin 50 mg and 20 mL of lipiodol). Then, the patient was treated with five cycles of systemic chemotherapy based on 5-Fluorouracil (5-FU, 1,000 mg/m^2 on days 1, 2, and 3) and cisplatin (90 mg/m^2 on day 2 every 4 weeks). After the completion of chemotherapy, the tumor became almost necrotic. The AFP and PIVKA-II levels decreased to the normal ranges (2.85 ng/mL and 28 mAU/mL, respectively). As the treatment resulted in near complete regression of the tumor, the patient underwent close follow-up without chemotherapy. However, 12 months after chemotherapy, a CT scan revealed multiple lung metastases in both lungs with increasing AFP and PIVKA-II levels (182 ng/mL and 38 mAU/mL, respectively). He was treated with two cycles of systemic chemotherapy with the same regimen (5-FU 1000 mg/m^2 on days 1, 2 and 3 and cisplatin

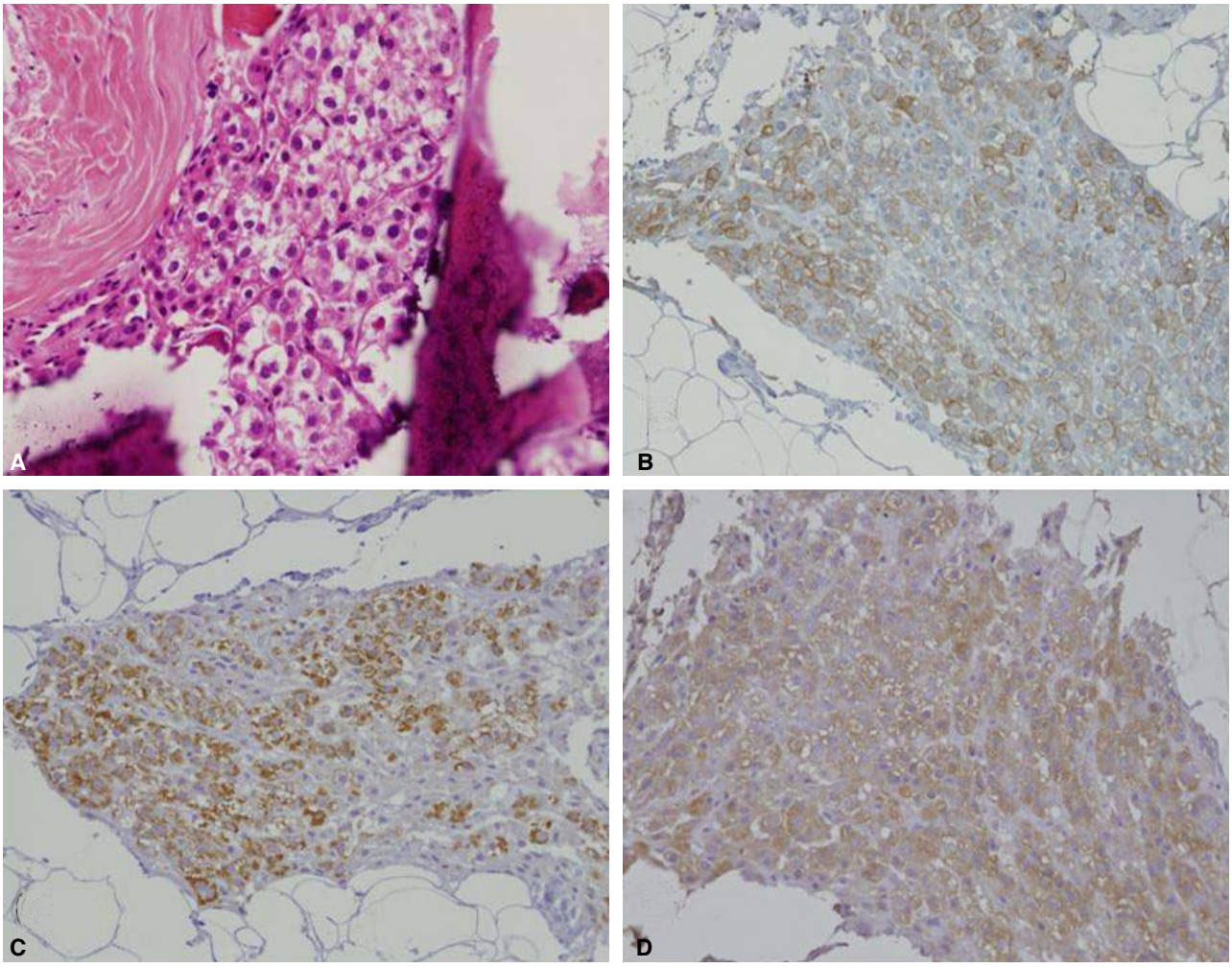

Figure 2. Microscopic findings of the pelvic bone mass. The tumor was a hepatocellular carcinoma with a trabecular pattern (A: hematoxylin and eosin, ×200). The tumor cells were immunopositive for cytokeratin (AE1/AE3) (B: ×200), hepatocyte paraffin 1 (C: ×200), and glypican-3 (D: ×200).

90 mg/m^2 on day 2). After two cycles of chemotherapy, the patient refused additional chemotherapy and we provided him with supportive care thereafter. Even though the lung metastases were newly developed, primary HCC had not been detected in the sequential radiological examinations, including abdominal CT and PET CT scans.

DISCUSSION

In this case, the final diagnosis was an isolated pelvic bone metastasis from HCC with unknown primary origin. Extrahepatic metastases from unknown primary HCC are exceptionally rare and only a few case reports of bone metastasis have been documented.[4-9] The hypothesis for explaining this unusual phenomenon is that the metastases are from a microhepatocellular carcinoma, which regressed spontaneously or was destroyed by the activated immune system.[6,7,10] However, the carcinogenesis mechanism as well as the natural history of this rare phenomenon is not well-known yet.[7] Thus, the diagnostic approach and treatment have been performed on an individual basis.

Although the nature of tumor cell could be confirmed by histological examination including immunohistochemical stains, we had to make a differential diagnosis with hepatoid adenocarcinoma and HCC development from ectopic liver.[11-13] Indeed, as there is no specific pathologic finding that could distinguish metastatic HCC from hepatoid adenocarcinoma or HCC arising from ectopic liver, information about involved organ, the presence of chronic liver disease and the degree of liver disease have been used as additional basis for differential diagnosis in previous studies.[4-9] For example, reporting on a case of HCC in chest wall without unknown origin, Asselah et al[4] made a final diagnosis of HCC arising in ectopic liver tissue, considering that the patient was not at high risk factors of HCC development and that the tumor developed in only parietal muscular tissue, which is an uncommon site for an HCC metastasis. In our case, we also had to make a diagnosis considering not only the pathological examination but also the clinical features of our case, even though we made a different diagnosis comparing from previous case. At first, in our case, neither hepatoid cells with large eosinophilic cytoplasm nor normal liver tissue was observed at microscopic histological examination, which could be shown in hepatoid adenocarcinoma or HCC arising from ectopic liver.[9,14] Second, 1 year after treatment, new metastases developed in lung, which is the most common metastatic site of HCC.[3,15] In previous studies, lung metastases from hepatoid adenocarcinoma or HCC arising from ectopic liver have rarely been reported.[16,17] Moreover, to our knowledge, there is no report that hepatoid adenocarcinoma or ectopic liver developed from pelvic bone, even though they can originate from various organs.[14,16,18] For these reasons, we made a final diagnosis of metastatic HCC with unknown primary HCC. However, we admit that our diagnosis may not be definitely confirmed in that histological was insufficient, as the specimen obtained from an incisional biopsy did not have non-cancerous tissue.

It can also be argued that a liver biopsy would be necessary for evaluating primary HCC in the liver. Coban et al[19] reported a patient who presented an isolated extrahepatic HCC of the chest wall without a primary focus. The patient had HBV-related liver cirrhosis, and a diffusely nodular and heterogeneous echogenic pattern was shown in ultrasonography, but there was no evidence of HCC in the liver. However, a liver biopsy was performed, and histological examination confirmed a diffuse type of HCC. But, we thought that the benefit of a biopsy was uncertain in our case because the patient had no clinical evidence of liver cirrhosis, and the liver parenchyma was smooth without a mass or infiltrating lesion. Moreover, we performed CT, MRI, PET scans, and angiography to find primary HCC, but no evidence of a primary liver tumor was found. Finally, we thought that liver biopsy was unnecessary in our patient. However, even though a primary tumor was not found in our case, an intensive search for primary HCC should be carried out when extrahepatic metastasis is observed as the initial presentation.

Although there is no standard treatment for extrahepatic metastasis without a primary focus, aggressive treatment including surgical resection results in good prognosis if a solitary lesion exists.[4,6,8,9] Iosca et al[6] reported a case that presented with an isolated left iliac bone metastasis from a primary unknown HCC. The patient was treated with TACE followed by the surgical resection. He was alive without recurrence over 45 months. However, we could not perform surgical resection because our patient refused operation. Instead, we treated him with combined modalities including radiotherapy, TACE and systemic chemotherapy. Although chemotherapy and radiotherapy have not been demonstrated

to increase the survival rate of HCC patients with bone metastasis, their ability to reduce pain and to increase quality of life has been reported in previous studies.[15,20] In our case, back and leg pain were relieved after treatment. Moreover, TACE was performed without complications to the pelvic bone metastasis in our case. Indeed, TACE was successfully performed for bone metastasis of HCC in previous studies,[6,21] and these results suggest that TACE could be considered as a treatment option for a bone metastasis from HCC. Even though multiple lung metastases developed, the tumor was well controlled for 12 months after the treatment. In conclusion, we think that individualized and multimodality treatment would be beneficial in such cases.

In summary, we reported a rare case of metastatic HCC of the pelvic bone without a known primary origin. In such cases, tissue biopsy and radiological examination should be performed and diagnosis should be made based on both pathological examination and clinical features. Individualized and combined modality treatment could be considered in such cases.

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