

CASE REPORT

원발병소불명암 형태로 내원한 경추 및 골반뼈에 전이된 간세포암종

황세원, 이지은, 이정민, 홍숙희, 이명아, 전후근, 천호중¹, 이성학², 정은선²

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Hepatocellular Carcinoma with Cervical Spine and Pelvic Bone Metastases Presenting as Unknown Primary Neoplasm

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The occurrence of hepatocellular carcinoma (HCC) is closely associated with viral hepatitis or alcoholic hepatitis. Although active surveillance is ongoing in Korea, advanced or metastatic HCC is found at initial presentation in many patients. Metastatic HCC presents with a hypervascular intrahepatic tumor and extrahepatic lesions such as lung or lymph node metastases. Cases of HCC presenting as carcinoma of unknown primary have been rarely reported. The authors experienced a case of metastatic HCC in a patient who presented with a metastatic bone lesion but no primary intrahepatic tumor. This case suggests that HCC should be considered as a differential diagnosis when evaluating the primary origin of metastatic carcinoma. (**Korean J Gastroenterol 2015;66:50-54**)

Key Words: Hepatocellular carcinoma; Neoplasms, unknown primary; Neoplasm metastasis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer diagnosed in Korea.¹ Chronic hepatitis B, chronic hepatitis C, and alcoholic hepatitis are closely associated with the occurrence of HCC,² and active surveillance is ongoing in Asia including Korea. In cases diagnosed at early stage, surgical resection or liver transplantation is recommended for curative intent. However, intrahepatic local recurrence or extrahepatic distant metastasis is relatively common after curative treatment. Metastatic HCC usually presents with a primary hepatic mass or history of surgical treatment of primary

HCC, but rarely primary lesions could not be found by radiologic methods. We report on a case of stage IV metastatic HCC with multiple bone metastases but without primary intrahepatic HCC.

CASE REPORT

A 61-year-old male, with no underlying disease, was admitted to Seoul St. Mary's Hospital for evaluation of an incidentally found 3 cm-sized mass located at C5 spine (Fig. 1). He had experienced left upper extremity weakness and a tingling sensation for 2 months before visiting the hospital. On

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Fig. 1. Cervical MRI shows a 3 cm sized mass located at C5 spine (arrow).

Table 1. Motor Test of Upper Extremities

	Right	Left
Shoulder		
Flexor	5	2
Extensor	5	4
Elbow		
Flexor	5	3
Extensor	5	4

5, normal strength; 4, muscle holds the joint against a combination of gravity and moderate resistance; 3, muscle cannot hold the joint against resistance but moves the joint against gravity; 2, muscles moves the joint when gravity is eliminated; 1, flicker of movement; 0, no movement.

physical examination, motor deficits were detected in the left upper extremity (Table 1). Deep tendon reflexes were normal in the left upper extremity. On blood chemistry, AST and ALT were elevated to 418 U/L and 594 U/L. Total bilirubin was in normal range (1.58 mg/dL), but serum GGT and LDH were elevated to 459 U/L and 871 U/L. Serum HBsAg was positive, and anti-HCV was negative. HBV DNA level was elevated to 1,890,769 copies/mL and HBc Ab IgG, HBeAg was positive on blood chemistry. Serum AFP was elevated to 5,013.1 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) was elevated to 13,891 mAU/mL (Table 2). Cervical spine MRI showed a 3.2 cm sized mass involving C4 vertebral body and C5 vertebral pedicle with low signal intensity in a T1-weighted image and slight high signal intensity in a T2-weighted image. Mild cord compression and a moder-

Table 2. Laboratory Findings

Variable	Reference	Initial	After radiotherapy and TACE
HBsAg (index)	—	+	+
HBsAb (IU/L)	—	—	—
HBeAg/Ab (index)	—/—	+/-	+/+
HBV DNA PCR (copies/mL)	< 34	1,890,769	373
AFP (ng/mL)	< 10	5,013.1	47.3
PIVKA-II (mAU/mL)	< 40	13,891	6,344

TACE, transarterial chemoembolization; HBsAb, hepatitis B surface antibody; HBeAg/Ab, HBeAg/antibody; PIVKA-II, protein induced by vitamin K absence or antagonist-II.



Fig. 2. Abdomen CT scan shows a 7.6 cm sized hypervascular mass at the right iliac bone (arrow).

ate to severe compression fracture of the C5 vertebral body was detected. Vertebral metastases from unknown cancer primary were suspected. Abdomen and chest CT scans were performed for determination of the primary origin of cancer metastasis. On abdomen CT scan, a 7.6 cm sized metastatic hypervascular mass was detected at the right iliac bone (Fig. 2), but no suspected primary malignancy was detected. Based on the positive results of hepatitis B and elevated serum AFP and PIVKA-II, liver MRI was performed to rule out HCC. Liver showed a cirrhotic configuration with capsular retraction at segment 5 and segment 8, but no definite viable HCC was detected (Fig. 2).

From hospital day 1, spinal cord compression was suspected on C-spine MRI and high dose steroid (dexamethasone 10 mg loading, followed by 4 mg four times a day via intravenous) was administered. Despite administration of high dose steroid, left upper extremity weakness was not relieved. For symptom relief and for pathologic confirmation of the pri-

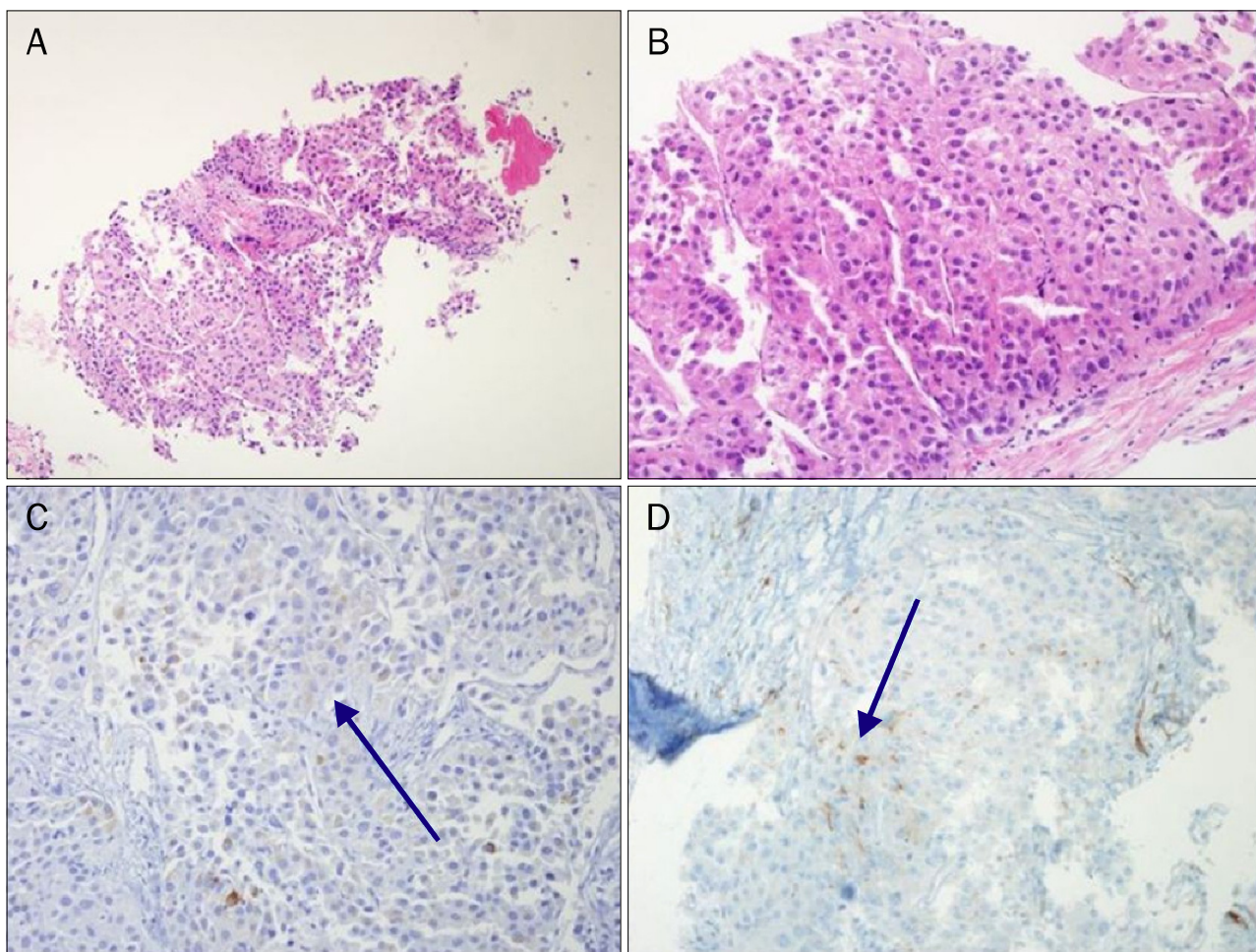


Fig. 3. Biopsy specimen of the iliac bone. H&E stain shows round, eosinophilic cytoplasm-rich cells with a trabecular arrangement, suggestive of hepatocellular carcinoma (A, $\times 100$; B, $\times 400$). The tumor cells showed focally positive immunoreactivity for hepatocyte surface antigen (C) and CD10 (D) with a canalicular staining pattern (arrows).

mary origin of the metastatic tumor mass, C5 corpectomy with sub-total tumor removal was performed. Percutaneous bone biopsy targeting the hypervascular iliac mass was also performed. Histopathological examination of both specimens showed round eosinophilic cytoplasm-rich cells, positive immunoreactivity for hepatocyte surface antigen and CD10 (Fig. 3), consistent with HCC.

After C5 corpectomy, 3 Gy/fraction of irradiation to the cervical spine was administered once daily (total accumulation dose, 30 Gy). Considering the iliac mass was confirmed as metastatic HCC, angiography and embolization was considered as a treatment option. Pelvic and right iliac angiography showed a hypervascular tumor located at the right iliac bone, and transarterial chemoembolization (TACE) of the iliac mass was performed for local treatment (Fig. 4). After TACE, irradiation (total accumulation dose, 40 Gy) was administered by 2.5



Fig. 4. A hypervascular tumor mass on the iliac bone (transarterial chemoembolization).

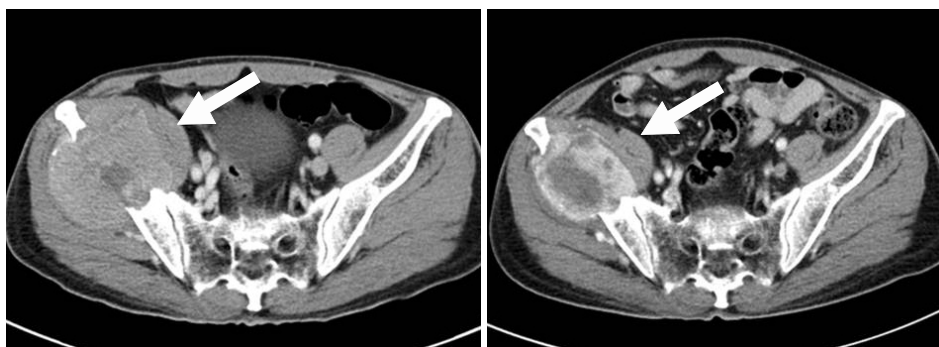


Fig. 5. Abdomen CT scan after 2 months of sorafenib shows partial regression of the tumor mass (arrows).

Gy/fraction once daily for local control of the iliac mass.

Although no definite primary HCC was detected based on liver MRI, the patient was diagnosed as metastatic HCC with C-spine and iliac bone metastasis. After local radiation therapy, sorafenib (400 mg twice a day, per oral) was administered for systemic treatment. After two months of medication, response evaluation was performed. On imaging findings, the iliac mass showed partial regression (Fig. 5). Blood chemistry showed decreased serum AFP and PIVKA-II (AFP 47.3 ng/mL and PIVKA-II 6344 mAU/mL, respectively). After 6 months of medication, the patient developed multiple lung metastases with no viable intrahepatic tumor. The authors recommended systemic chemotherapy after sorafenib failure, but the patient refused cytotoxic chemotherapy. Currently, he is under best supportive care.

DISCUSSION

Hematogeneous extrahepatic metastases of HCC are common, with lung, regional lymph node, kidney, and adrenal gland being the most frequent metastatic sites.³ Although bone metastasis from primary HCC is not common, the incidence rate is increasing due to prolonged median survival of stage IV HCC.⁴ The most common site of bone metastases is vertebra, followed by the pelvis and rib.⁴ HCC patients with extrahepatic metastases tend to show more aggressive clinical behavior compared to patients with advanced intrahepatic HCC.⁵ However, HCC cases presenting with extrahepatic metastases with no definite primary intrahepatic cancer are rarely reported.⁶⁻¹⁰

In our case, the patient was diagnosed as HCC with bone metastases but without primary HCC. The primary HCC could not be found by abdomen CT scan or liver MRI. Considering our patient had active hepatitis B, we supposed that bone metastases may have been aroused from primary HCC.

However, spontaneous regression of the primary mass may have occurred thereafter so that the primary mass could not be detected by radiologic imaging. Although the metastatic sites were various, cases with metastatic HCC with no primary sites are occasionally reported.⁷⁻¹¹ Spontaneous tumor regression is rare, but with higher incidence of HCC compared to other cancers.¹² Two meta-analyses on spontaneous regression of primary HCC have been reported, however the mechanism of this phenomenon has not yet been identified.^{12,13} Tumor hypoxia due to spontaneous hepatic artery thrombosis or rapid tumor growth, or inflammatory responses was suggested as possible mechanisms.^{12,13} Approximately 85 spontaneous tumor regression cases have been reported, but only 8 cases had pathologic confirmation of microscopic viable cancer cells in suspicious hepatic lesions.¹⁴

In patients presenting with metastatic HCC without a primary intrahepatic lesion, HCC arising from hepatoid adenocarcinoma or ectopic liver must be considered as differential diagnoses. In our case, the patient was newly diagnosed with HBV infection, which is a strong risk factor for HCC. Although endoscopy or colonoscopy was not performed in our institute, abdominal CT scan and PET-CT scan of the gastrointestinal tract showed no abnormal findings. Based on the patient's history, he had undergone endoscopy and colonoscopy at a local clinic before visiting our institution, and no abnormality was found at that time. No normal hepatocytes were detected during histologic examination of the biopsy specimen and the whole pathology specimen was replaced by malignant liver cells.

Hepatoid adenocarcinoma tends to arise from the gastrointestinal tract such as the stomach with no risk factors for HCC.¹⁵ Considering our patient had HBV infection with no abnormality of the gastrointestinal tract, the possibility of hepatoid adenocarcinoma was low, and based on malignant hep-

atocytes with no normal hepatocyte detected from the biopsy specimen, the possibility of HCC arisen from ectopic liver malignant hepatocytes was low.

In this study, although the patient showed disease progression with multiple lung metastases, no viable tumor was detected on PET-CT scan of the liver. Considering our patient did not receive systemic treatment after sorafenib failure, the authors presumed that the patient might develop intrahepatic HCC. However, as disease progressed, the patient developed multiple lung metastases in size and number, but no sequential bone metastases or intrahepatic HCC was detected. Other reported cases also showed progressive extrahepatic HCC with no viable intrahepatic HCC.⁸

Although prior cases showed isolated metastatic HCC of bone with favorable disease free survival up to 10 years,^{7,9,10} 2 cases, including our case, showed multiple lung metastases with rapid disease progression.⁸ Considering both patients showed extrahepatic HCC with no viable intrahepatic HCC, aggressive cytotoxic systemic chemotherapy might have been a treatment option. However in a case reported by Jung et al.,⁸ the patient received 2 cycles of cytotoxic chemotherapy, but appropriate response evaluation was not performed. And, in our case, the patient refused cytotoxic chemotherapy. Although cytotoxic chemotherapy is not a standard treatment, certain response outcomes of 5-fluorouracil based systemic chemotherapy were reported in a previous study.¹⁶ Even though the patient refused further treatment after sorafenib failure, cytotoxic chemotherapy should have been considered as a treatment option.

The limitation of our study is the lack of pathologic or angiographic confirmation of a hepatic lesion. Although there was no concrete confirmation of the primary site, the pathologic confirmation and successful treatment of extrahepatic lesions were available. Considering HCC shows a hypervascular nature, TACE at the extrahepatic metastatic sites was considered, and showed favorable outcome.

In conclusion, we report a rare case of extrahepatic HCC manifested as spinal cord compression by vertebral metastasis. The authors concluded this case as metastatic HCC with a spontaneously regressed primary HCC mass. Despite of low incidence, metastatic HCC should also be considered during evaluation of malignancy of unknown primary.

REFERENCES

1. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Prediction of cancer incidence and mortality in Korea, 2013. *Cancer Res Treat* 2013;45:15-21.
2. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. *J Hepatol* 2012;56(Suppl 1):S75-S87.
3. Kummar S, Shafi NQ. Metastatic hepatocellular carcinoma. *Clin Oncol (R Coll Radiol)* 2003;15:288-294.
4. Fukutomi M, Yokota M, Chuman H, et al. Increased incidence of bone metastases in hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2001;13:1083-1088.
5. Natsuiyaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005;20:1781-1787.
6. Ahmad Z, Nisa AU, Uddin Z, Azad NS. Unusual metastases of hepatocellular carcinoma (hcc) to bone and soft tissues of lower limb. *J Coll Physicians Surg Pak* 2007;17:222-223.
7. Takahama J, Taoka T, Marugami N, et al. Hepatocellular carcinoma of the iliac bone with unknown primary. *Skeletal Radiol* 2010;39:721-724.
8. Jung KS, Park KH, Chon YE, et al. A case of isolated metastatic hepatocellular carcinoma arising from the pelvic bone. *Korean J Hepatol* 2012;18:89-93.
9. Hofmann HS, Spillner J, Hammer A, Diez C. A solitary chest wall metastasis from unknown primary hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2003;15:557-559.
10. Hyun YS, Choi HS, Bae JH, et al. Chest wall metastasis from unknown primary site of hepatocellular carcinoma. *World J Gastroenterol* 2006;12:2139-2142.
11. Ahmad K, Sah P, Dhungel K, et al. An unusual case report of hepatocellular carcinoma metastasis to the chest wall presenting as breast lump. *Nepal J Medi Sci* 2012;1:138-140.
12. Oquiénena S, Guillen-Grima F, Iñarrairaegui M, Zozaya JM, Sangro B. Spontaneous regression of hepatocellular carcinoma: a systematic review. *Eur J Gastroenterol Hepatol* 2009;21:254-257.
13. Huz JI, Melis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. *HPB (Oxford)* 2012;14:500-505.
14. Sasaki T, Fukumori D, Yamamoto K, Yamamoto F, Igimi H, Yamashita Y. Management considerations for purported spontaneous regression of hepatocellular carcinoma: a case report. *Case Rep Gastroenterol* 2013;7:147-152.
15. Terracciano LM, Glatz K, Mhawech P, et al. Hepatoid adenocarcinoma with liver metastasis mimicking hepatocellular carcinoma: an immunohistochemical and molecular study of eight cases. *Am J Surg Pathol* 2003;27:1302-1312.
16. Lee JE, Bae SH, Choi JY, Yoon SK, You YK, Lee MA. Epirubicin, cisplatin, 5-FU combination chemotherapy in sorafenib-refractory metastatic hepatocellular carcinoma. *World J Gastroenterol* 2014;20:235-241.