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A Case of Hepatocellular Carcinoma with Bone Metastasis Responding to Radiotherapy after Successful Hepatectomy of Primary Lesion

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ABSTRACT

Radical hepatectomy was carried out on a patient with hepatocellular carcinima (HCC) located in segment VIII of the liver. The patient was a 56-year-old man who showed positive for hepatitis C antibody and negative for hepatitis B surface antigen. Six months after hepatectomy, a lumbar plane X-ray and computed tomography examination revealed bone metastases in the lumbar vertebrae. The patient was subsequently treated by radiation to the lumbar vertebrae in response to lumbago. The metastatic lesion has been well controlled by radiotherapy on an oputpatient basis with no recurrence for 5 years and 3 months.

The prognosis of patients with HCC with distant metastases is poor. It is believed that the long survival of this patient can be attributed to successful radiotherapy of the bone metastasis after hepatectomy and the lack of recurrence in the liver.

Key words: *Hepatocellular carcinoma, Bone metastasis, Radiotherapy, Hepatectomy*

The prognosis of patients with hepatocellular carcinoma (HCC) with distant metastases is generally poor. The target organs of distant metastases from HCC are lung, bone, brain, adrenal glands and lumph nodes. We report a case with HCC and bone metastasis who markedly responded to radiotherapy.

CASE REPORT

A 56-year-old man complained of hematoemesis and was diagnosed with a duodenal ulcer on June 5, 1992. A subsequent abdominal echogram demonstrated a hepatic tumor in segment VIII. After transcatheter arterial infusion chemotherapy with 4 ml of Lipiodol and 40 mg of doxorubicin (L-TAI) on July 8, he was admitted to our department for hepatectomy. The hepatic arteriogram of this patient revealed corkscrew morphologies which coincided with liver cirrhosis; the tumor was detected in the anterior-superior segment of the liver with a diameter of 25 mm (Fig. 1). Fig. 2 is the computed tomography (CT) scan taken on admission, showing a 2 cm diameter high density area at segment VIII of the liver with a large accumulation of lipiodol and splenomegaly. According to the hematochemical examination, the platelet count was low with 5.8×10^4 / mm^3 and hepatic function was slightly deteriorated with an alanine aminotransferase (ALT) of 105 IU/liter, an aspartate aminotransferase (AST) of 157 IU/ liter, a bilirubin of 1.5 mg/ dl, a cholinesterase of 135 IU/ liter, a prothrombin activity of 43% and a indocyanin green ratension rate at 15 minutes (ICG R15) of 40% (Table 1). Tumor markers were ele-

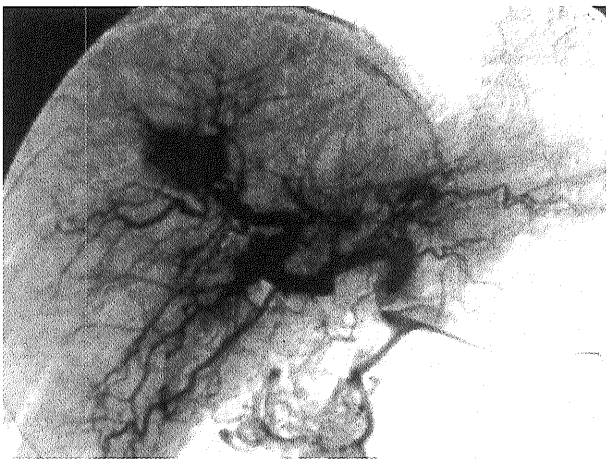

Fig. 1. The corkscrew shaped arteries of the liver indicate liver cirrhosis.
A tumor was detected with a large accumulation of Lipiodol.

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Table 1. Laboratory data on admission

WBC (/mm^3)	6600	Total bilirubin (mg/dl)	1.1
RBC (×10^4/mm^3)	314	AST (IU/liter)	63
Hgb (g/dl)	9.3	ALT (IU/liter)	91
Hct (%)	27.5	LDH (IU/liter)	332
Platelet (×10^3/mm^3)	90	ALPH (IU/liter)	258
PT (%)	23	γGTP (IU/liter)	30
APTT (sec)	45.5	T.P (g/dl)	8.7
HPT (%)	47.0	Albumin (g/dl)	3.8
ICG R15(%)	40	Total Cholest. (mg/dl)	182
		BUN (mg/dl)	16
AFP (ng/ml)	168.5	Creatinin (mg/dl)	0.79
PIVKA-II (AU/ml)	0.1		
HCV Ab	+		
HBsAg	–		

PT; Prothrombin time; ICG R15: Indocyanin green retension rate at 15 min; AFP: alphafetoprotein; PIVKA-II: protein induced Vitamin K deficiency and antagonist II; HCV Ab: anti hepatitis C antibody; HBs Ag: hepatitis B surface antigen

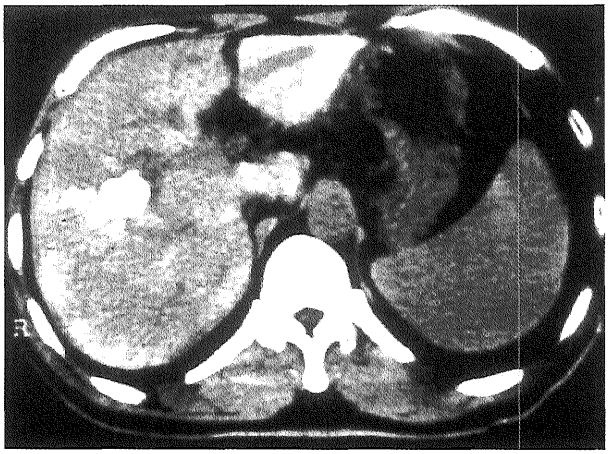


Fig. 2. CT on admission: A high density area, 20 mm in diameter, was found in segment VIII of the right liver with Lipiodol accumulation. Simultaneously, splenomegaly was also demonstrated.

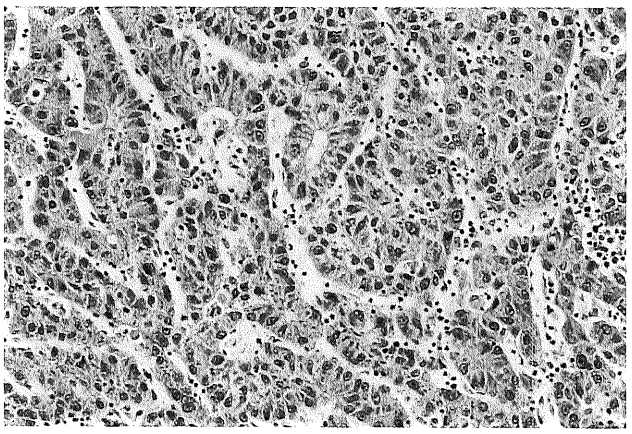


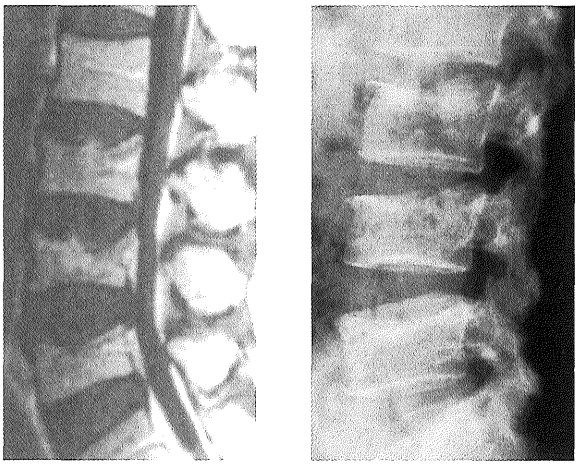
Fig. 3. Pathological findings of the hepatic tumor: The tumor showed a thick trabecular and pseudoglandular structure, and was diagnosed as a moderately defferentiated hepatocellular carcinoma (Edmondson type II).

vated with a protein induced by vitamin K deficiency and antagonist-II (PIVKA-II) of 0.1 AU/ml and an alpha-fetoprotein (AFP) of 168.5 ng/ml. The duodenal ulcer was found by gastrofiberscopy preoperatively.

On July 25, 1992, this patient received partial resection of the liver and trunchal vagotomy with pyroloplasty following diagnoses of HCC and duodenal ulcer. Pathological examination of the tumor showed a thick-trabecular and pseudoglandular structure surrounded by dilated sinusoidal space. The nuclei of the tumor cells with eosinophilic cytoplasm were round to ovoid and somewhat deformed with large nucleoli. Moderately differentiated hepatocelllular carcinoma (Edmondson II type) was diagnosed (HE × 100) (Fig. 3).

The patient's postoperative course was uneventful. As an outpatient basis, he complained of lumbago 6 months after hepatectomy. No abnormal findings were detected in the liver, lung, and adrenal gland by magnetic resonance imaging (MRI), CT scan and abdominal echogram. However, bone metastasis of the 2nd, 3rd, and 4th lumbar vertebrae was diagnosed by elevated AFP, CT scan, MRI (Fig. 4) and bone scintigram (Fig. 5). A lumbar plane X-ray revealed marked osteolytic findings of the 2nd, 3rd, and 4th lumbar vertebrae, which indicated lumbar metastases from the HCC. From March 4, 1993 to April 7, 1993, the patient received 5000 cGray of radiotherapy (Target dose; 200 cGy/day, TDF; 81.7, Field size; 8 × 12 cm, 10 MV Liniac X-ray) to alleviate his lumbago. The treatment gradually improved his lumbago and obviated the need for morphine sulfate administration which was used for the treatment of his lumbago 1 year later.

Fig. 6 shows MRI 10 months and 20 months after radiotherapy revealing no progression of lumbar lesions. Fig. 7 shows the postoperative course of the patient. The AFP level decreased after hepate-



(a) (b)

Fig. 4. MRI (a) and lumbar X-ray (b) showed osteplytic findings of the 2nd, 3rd, and 4th lumbar vertebrae 6 months after hepatectomy.

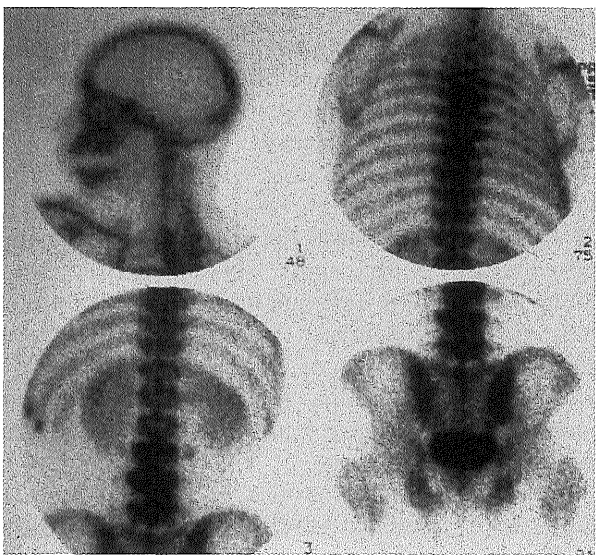
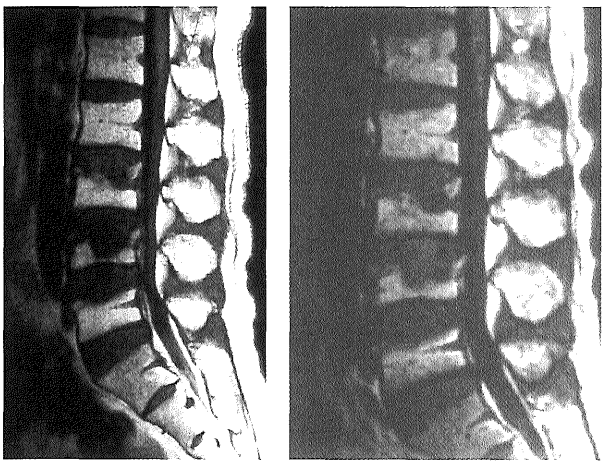


Fig. 5. The accumulation of ^{99m}Tc-MDP was recognized at the 2nd, 3rd, and 4th lumbar vertebrae 6 months after hepatectomy.



(a) (b)

Fig. 6. MRI 10 (a) and 20 (b) months after radiotherapy showed no progression of bone metastases.

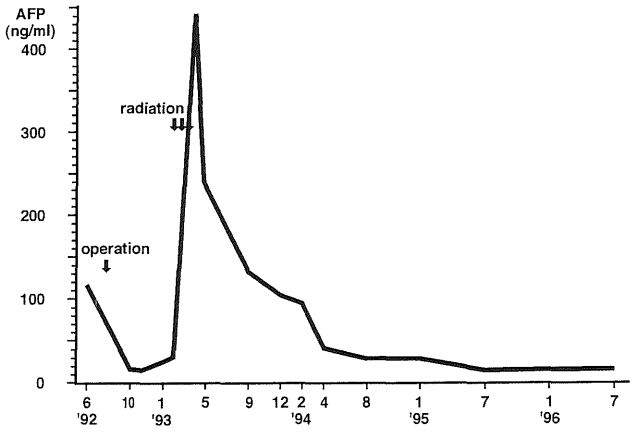


Fig. 7. Changes in serum AFP level before and after treatment.

ctomy, then rose to 448.1 ng/ml when the bone metastases were detected. However, following his response to radiotherapy, the AFP level returned to normal 17 months later.

Six years after hepatectomy (5 year and 3 months after the radiotherapy), examination on an outpatient basis by means of CT scan, MRI, lumbar plane X-ray, echogram and tumor markers, showed no recurrence in the patient and no progression of the bone lesions.

DISCUSSION

In generally, the prognosis of HCC patients is still poor compared to other gastrointestinal carcinoma patients. Cases which have distant metastases to the bone, lung, brain, adrenal gland, or lymph nodes are considered to be advenced stages of HCC. In such cases multiple metastases are found in the liver. Thus survival is short because there are no effective treatments. There are two routes of distant metastasis from a primary hepatic lesion. One is via the hepatic veins to the lung, brain, and bone, and the other is via the vertebral venous plexus from the portal veins and hepatic veins to bone[13]. The frequencies of bone metastases from HCC is rather high at 5.5–15.8%[6,15] following that to the lung and lymph nodes. Kawa et al reported 7.3% (16/221 cases) of bone metastases at hepatectomy[8]. The incidence of bone metastases at hepatectomy is low, but it is found at high frequensies at autopsy. According to the 12th National Japan Primary Liver Cancer Research group meeting, the rate of bone metastasis from hepatocellular carcinoma was 14.5% (77 / 530 cases) at autopsy[10].

Most of the cases with bone metastases are diagnosed after manifestation of pain and neurological disorders. Another case, that we observed, was a patient who was diagnosed with a metastatic tumor of the fenur from HCC after resection of right upper extremity. However, most of the cases with bone metastases occur following progression

Table 2. Hepatocellular carcinoma cases with bone metastases treated by radiotherapy after hepatectomy.

case	sex	age	tumor location of the liver	operation method	metastatic site	metastatic interval (post-hepatectomy) (months)	radiotherapy	prognosis (months)
1	M	67	S7	SVII subseg.	liver, femur	51	50Gy	7 died
2	M	58	S7 S8	partial reseciton × 2 ethanol injection	liver, thoracic vertebrae	10	33Gy	19 died
3	M	60	S5	partial resection	liver, thoraco-lumbar vertebrae	25	50Gy	8 died
4	M	56	S8	partial resection	lumbar vertebrae	6	50Gy	53 alive
5	M	68	S7	partial resection	liver, lumbar vertebrae	7	39Gy	5 died
6	M	53	S1	SI subseg.	liver, ribs, lumbar vertebrae	5	99Gy	13 died
7	M	51	S2	lateral segmentectomy	thoracic vertebrae	5	40Gy	8 alive

subseg., subsegmentectomy of the liver; Gy, gray

and reccurrence of the primary liver tumor. They are diagnosed as osteolytic lesions by plane X-ray examination, as the accumulation of radioisotope by bone scintigram, and as typical lesions by MRI. Fukuda et al[2] reported thet metastatic bone lesions were accurately detected with high sensitivity by PET using 18 FDGal. Moreover, they were able to differentiate HCC from other carcinomas by estimating the uptake (DAR). The diagnosis of bone metastases is not so difficult; we were able to diagnose it by CT, MRI, limbar plane X-ray and AFP level when the patient complained of lumbago.

Many treatment modalities are available for bone metastases, includings transcatheter arterial embolization (TAE), transarterial infusion chemotherapy[3], radiotherapy, resection[12] and combination therapy. Combination therapy of TAE with radiotherapy was also reported to be effective by Itoh[7] for cases with bone metastases. Systemic chemotherapy has been effective for treatment of primary liver tumors and bone metastases in some cases[3]. However, cases responding to treatment are not usually common; most cases with bone metastases do not respond to any kind of treatment.

Radiotherapy is not considered to be suitable for the treatment of HCC because of its low sensitivity. However, the pain associated with bone metastases can be alleviated by radiotherapy. Many authors have reported the effectiveness of radiotherapy for such pain[2,4,14]. However, the effectiveness of radiotherapy for pain is temporary, since the lesions reprogress in most cases. Nevertheless, palliation can be maintained in cases where the primary liver lesions are conrolled[1,2,14]. Nagano et al[11] reported that in cases with adrenal metastases, palliation could be maintained only if the primary tumors were controlled and there were no other distant metastases. According to these reports, we can conclude that it is necesary to control the primary tumors in order to treat distant metastases in HCC patients.

We have treated 7 patients with bone metastases with radiation (Table 2). Case 4 is reported here. All 7 patients were men. Five primary liver lesions were located in the right lobe of case 5, whose tumor was located in segment I. Two cases underwent subsegmentectomy, and 4 received partial hepatectomy because of their deteriorated liver function. The locations of the bone metastases were the femur in case 1 and the lumbar and thoracic vertebrae in case 5. The interval between hepatectomy and occurrence of bone metastases was 5 to 51 months. Radiotherapy was effective for the treatment of pain in all patients. However, its effectiveness was temporary: 5 of the 7 patients died from progression of the primary hepatic lesions within 1 year. All 5 patients had recurrent lesions in the liver. The surviving patient probably did so because he did not have a recurrent cancer in the liver. Unfortunately, we did not obtained a pathological specimen of the bone lesion in this patient, though the osteolytic findings with lumbar plane X-ray and the elevation of the AFP level strongly supported the diagnosis of bone metastasis from HCC. This patient has not shown a recurrence of the tumor in the liver nor a progression of the bone lesion 5 year and 3 months after radiotherapy.

Therefore our conclusion is that no treatment is effective for bone metastases if the hepatic lesions recur, but treatment of distant metastases and extended survival is possible if the cancer does not recur in the liver.

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