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Case Report

Two Rare Metachronous Metastases of Hepatocellular Carcinoma After Liver Transplantation

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A 59-year-old male with hepatocellular carcinoma (HCC) due to liver cirrhosis caused by the hepatitis C virus underwent cadaveric whole liver transplantation. Two years later, he had a metastatic HCC in the superior mediastinum. Over the following postoperative year, he underwent transcatheter arterial chemoembolization (TACE) for 4 tumors in the implanted liver. In the third post-TACE month, he was emergently hospitalized due to intracerebral hematoma with a tumor invading the bone in the medial frontal segment. He underwent emergency intracranial tumorectomy and hemorrhage removal. The histopathologic diagnosis was metastatic HCC. He regained consciousness as well as the ability to speak and to feed himself, resulting in an improved quality of life. The incidence of HCC recurrence after liver transplantation is observed in approximately 8% to 11% of selected cases, with frequent relapses observed in the implanted liver, bones, adrenal glands, and lungs. Mediastinal and intracranial metastases from HCC post-liver transplantation are very rare.

Key words: Hepatocellular carcinoma – Mediastinal metastasis – Intracranial metastasis – Liver transplantation

Hepatocellular carcinoma (HCC) is one of the most common primary cancers in the world. The prevalence of HCC is high in Japan, with approximately 30,000 deaths occurring annually.[1] The prognosis of HCC patients has improved as a result of progress in diagnostic modalities such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) and therapeutic procedures such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol

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injection (PEI), transcatheter arterial chemoembolization (TACE), and liver transplantation (LT). These improvements have contributed to improved survival rates and increased rates of detection of extrahepatic metastasis from primary HCC.[2–6] The incidence of extrahepatic recurrence of HCC has been reported to range from 14% to 25.8%. The most frequent metastatic sites are the lungs, lymph nodes, bones, and adrenal glands.[2,7–10] However, posttransplant tumor recurrence is observed in approximately 8% to 11% of selected patients, with frequent relapses observed in the implanted liver, bones, adrenal glands, and lungs.[6,11] Metastases in the mediastinum and central nervous system are very rare, especially post liver transplantation.[11] We herein describe the case of a patient who developed metachronous mediastinal and intracranial metastasis of HCC after undergoing liver transplantation.

Case Report

A 59-year-old male with cirrhosis of the liver caused by the hepatitis C virus presented with 4 focal hepatic lesions on dynamic CT and MRI. The HCC lesions measured 3 cm in diameter at segment eight, 1 cm in diameter at segments four and five, and 1.3 cm in diameter at segment one. The patient exceeded the Milan criteria; however, he and his family strongly desired liver transplantation. He underwent cadaveric whole liver transplantation under sufficient informed consent. His postoperative course was uneventful. In the fourth postoperative month, the serum alpha-fetoprotein (AFP) level was found to be slightly elevated. To determine the reason for the increased AFP level, the patient was referred to undergo positron emission tomography (PET) several times; however, PET did not demonstrate any abnormal uptake. Two years later, the serum AFP level was 900 ng/mL, and CT revealed the presence of an abnormal mass in the superior mediastinum (Fig. 1). No metastases in the brain or bone were identified on head MRI or bone scintigraphy at that time. The patient underwent tumor resection, and a pathologic examination demonstrated the presence of metastatic hepatocellular carcinoma without a lymph node component (Fig. 2). After undergoing resection for mediastinal metastasis of HCC, the patient's serum AFP level decreased to 6.3 ng/mL; however, over the following postoperative year, re-elevation of the serum AFP level up to 139.9 ng/mL was observed, and dynamic CT showed 4 tumors in liver segments four and eight. The patient underwent TACE, and no viable HCC lesions were identified on follow-up dynamic CT. In the third post-TACE month, the patient was emergently hospitalized after a sudden loss of consciousness with stertor. Head CT revealed a 6-cm intracerebral hematoma in the right temporal lobe and a 2-cm circular tumor invading the bone in the medial frontal segment (Fig. 3). The patient underwent emergency intracranial tumorectomy and hemorrhage excision. The histopathologic diagnosis was metastatic hepatocellular carcinoma (Fig. 4). The patient's postoperative course was uneventful. Follow-up CT showed no recurrence in the head, chest, or liver, and the patient's serum AFP level decreased to 57.5 ng/mL. He regained consciousness as well as the ability to speak and to feed himself, resulting in an improved quality of life. In the third post-emergency-surgery month, the AFP level was found to be re-elevated to 5493 ng/mL on a scheduled follow-up examination. Head MRI revealed a tumor located nearby the surgical site in the head (Fig. 5). We suspected a recurrence of HCC and planned to administer radiotherapy. In the fourth post-emergency-surgery month, the patient unfortunately died of a cerebral hemorrhage from an HCC recurrence that was clinically suspected during standby for radiotherapy (Fig. 6).

Fig. 1 CT showing the abnormal mass in the superior mediastinum.

Discussion

The most frequent metastatic sites of HCC are the lungs, lymph nodes, bones, and adrenal glands.[2,8–10] However, posttransplant tumor recurrence is observed in approximately 8% to 11% of cases, with frequent relapses observed in the implanted liver,

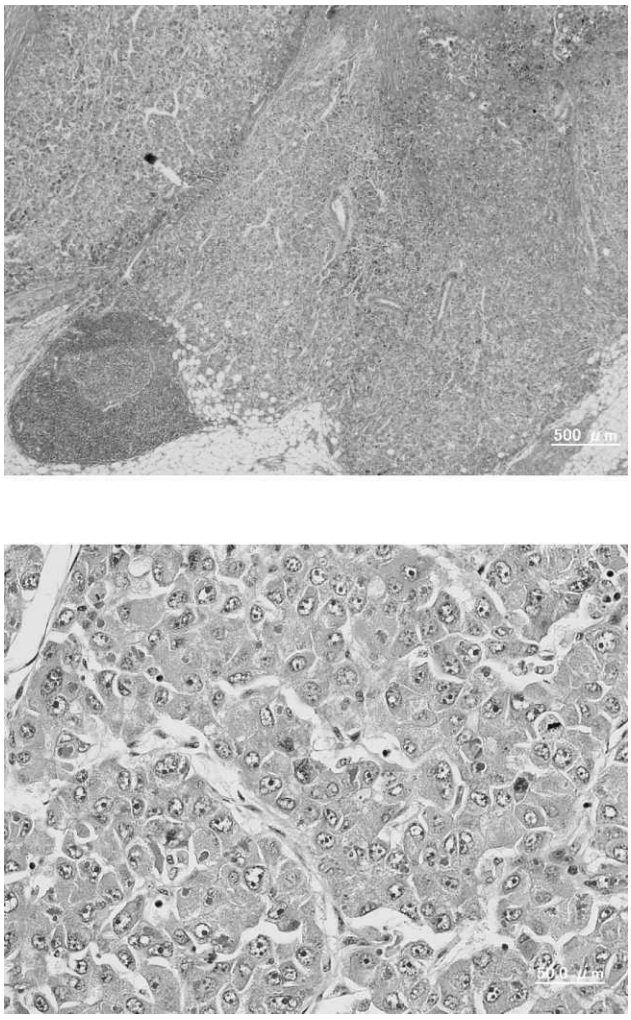

Fig. 2 A pathologic examination showed the tumor to be composed of diffuse proliferation of atypical polygonal cells. The cells had enlarged nuclei, prominent nucleoli, and eosinophilic cytoplasm.

bones, adrenal glands, and lungs.[6,11] In our patient, metastasis may have occurred before the liver transplant, which is consistent with the early elevation of the serum AFP level after surgery and the patient's status of HCC beyond the Milan criteria. Fanca *et al* have suggested that immunosuppression may increase the growth rate of tumors.[11] Some authors have reported mediastinal lymph node metastases from HCC; however, there are only a few reports showing metastasis of HCC to the mediastinal fibroadipose tissue.[12,13] In our case, a pathologic examination performed after mediastinal resection revealed metastatic HCC without a lymph node component. Central nervous system (CNS) metastasis of HCC is also reported to be rare,[5] especially in post-liver-transplant patients.[11] Intracranial metastasis of HCC is known to be associated with hemorrhage because metastatic lesions from HCC are hypervascular, and most patients have coagulopathy due to liver cirrhosis, leading these patients to manifest stroke-like events.[14] In general, the operative indications for metastatic brain tumors are as follows: (1) symptomatic disease, (2) a solitary tumor, (3) a feasible operative site, (4) the primary lesion can be cured, and (5) significantly long remission is expected.[15] The goal of therapy for metastatic intracranial tumors is at most symptomatic improvement. Our patient was also diagnosed with a stroke and exhibited operative indications. His consciousness completely recovered, and he regained his ability to speak and eat by himself with an improved quality of life. Unfortunately, most extrahepatic metastases of HCC are multiple and are not amenable to operative resection. The treatment options for extrahepatic metastases of HCC are limited. The prognosis of patients with extrahepatic metastases is very poor, and the 1-year survival rate and median survival period in patients with extrahepatic metastases have been reported to be 20.3% to 24.9% and 4.6 to 7 months, respectively.[2,4,16]

Fig. 3 Head CT showing the 6-cm intracerebral hematoma in the right temporal lobe and the 2-cm circular tumor invading the bone in the medial frontal segment.

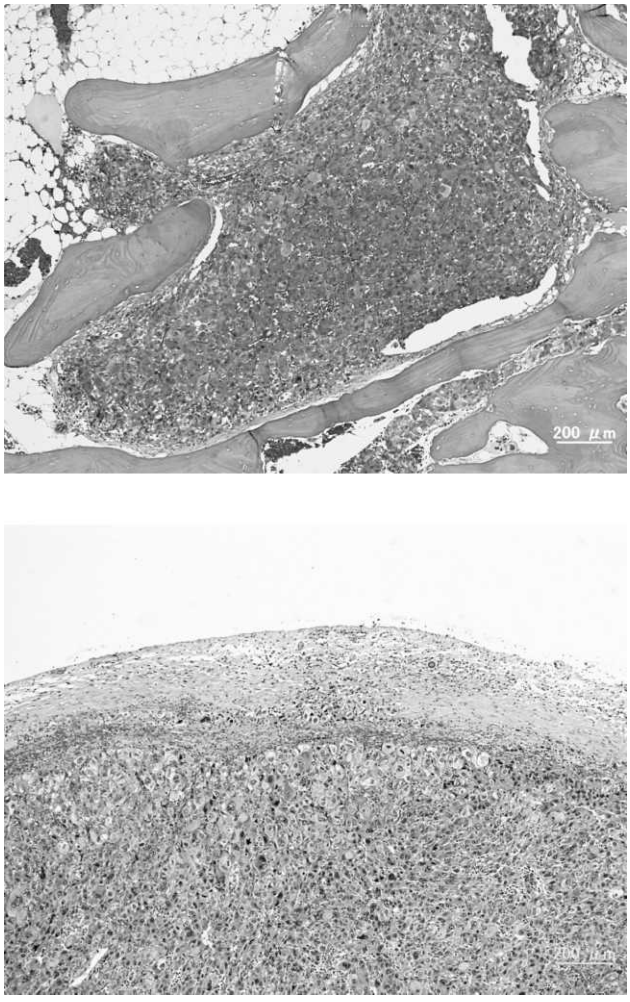

Fig. 4 The pathologic examination showed the bone marrow to be filled with atypical cells.

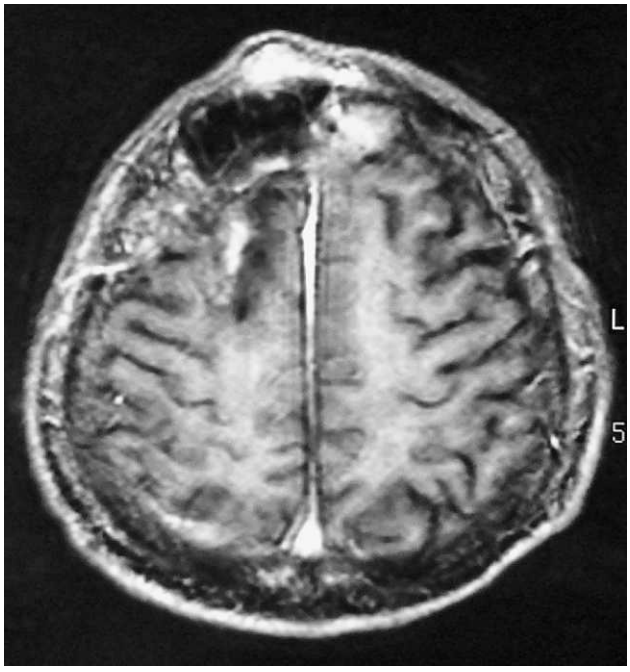

Fig. 5 Head MRI showing a tumor located near the surgical site in the head.

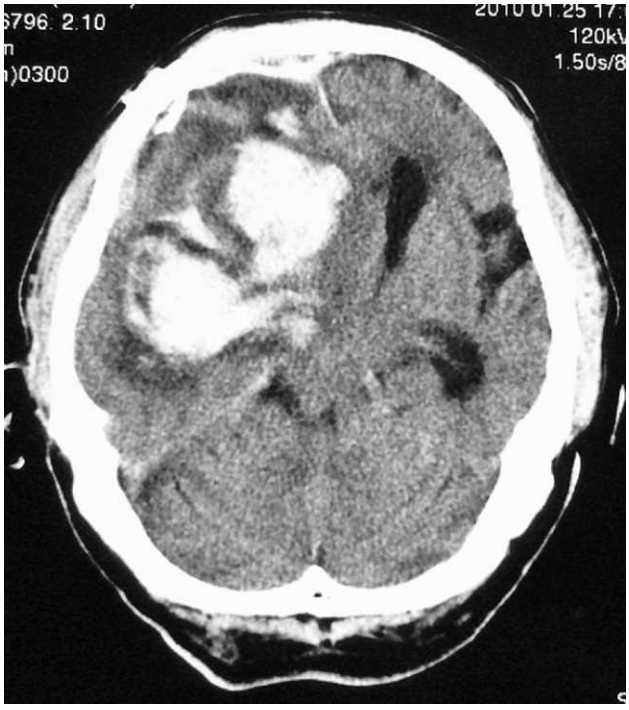

Fig. 6 Head CT showing a recurrence of a cerebral hematoma in the right temporal lobe.

In contrast, some reports suggest that aggressive treatment prolongs survival, as in our case.[7,15,17–19] Our patient survived 23 months from the first recurrence in the superior mediastinum and 4 months from the CNS metastasis with a good quality of life. At present, systemic adjuvant chemotherapy has not been found to offer any survival benefits; therefore, surgical resection can mean a chance for a better quality of life and long-term survival in selected patients, without poor prognostic factors, whose intrahepatic tumors are controlled.

In conclusion, providing careful follow-up and controlling extrahepatic recurrence following treatment are very important for improving the quality of life and prognosis. Unfortunately, the treatment options for extrahepatic metastasis of HCC are

limited. Further studies are needed to develop standard treatments, including systemic adjuvant chemotherapy, to improve the quality of life and prognoses of HCC patients with extrahepatic metastases.

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