Liver transplant is now considered to be a successful treatment modality for early hepatocellular carcinoma. In addition, advances in immuno-suppressive therapy have greatly prolonged post-transplant survival of patients with hepatocellular carcinoma. However, both the posttransplant physiologic condition and immunosuppressive therapy affect the patient’s natural immunity, resulting in accumulating and more problematic complications. Three years after a male patient with hepatocellular carcinoma underwent living-donor liver transplant, he presented with esophageal metastasis from recurrence of hepatocellular carcinoma. This is an extremely rare complication, perhaps with an ominous prognosis, and, to the best of our knowledge, the first such case to be published in the English literature.

Key words: Esophageal metastasis, Living-donor liver transplant

Introduction

Liver transplant for patients with early hepatocellular carcinoma (HCC) is a successful treatment modality. The 5-year overall posttransplant survival of HCC patients is as high as 75%, and patients have a lower rate of disease recurrence than patients who underwent liver resection. However, both the posttransplant physiologic condition and immunosuppressive therapy affect the patient’s natural immunity, resulting in accumulating and more problematic posttransplant complications such as higher occurrence rate of de novo malignancy and unusual posttransplant HCC metastasis. According to the literature, HCC accounts for less than 0.4% of metastatic esophageal tumors. In this article, we present a case of esophageal metastasis from recurrent HCC after living-donor liver transplant. To the best of our knowledge, this is the first such case published in the English literature.

Case Report

A 44-year-old man underwent liver transplant in our hospital because of alcoholic liver disease complicated by refractory bleeding from esophageal varices. During the initial evaluation, the patient’s Model for End-Stage Liver Disease score was 27, Child-Pugh score resulted in C classification, laboratory results showed no hepatitis B virus or hepatitis C virus infection, and abdominal sonography and computer tomography showed no suspicious tumors or lesions. However, α-fetoprotein levels were abnormal at 279.78 ng/mL. In November 2010, because bleeding from esophageal varices had reoccurred and because the hepatic encephalopathy had worsened after admission to our hospital, the patient underwent living-donor liver transplant.

A right hepatic lobe graft with venoplasty of right and middle hepatic vein from the patient’s blood-type-identical brother was recovered. The graft weighed 1060 g, and the graft-to-recipient weight ratio was 1.4%. Histopathologic examination of the explanted liver revealed active cirrhosis characterized by chronic hepatitis with moderate piecemeal necrosis. Incidental findings of foci of moderately differentiated HCC up to 0.3 cm in diameter with venous permeation were noted. One day after liver transplant, the patient was given immunosup-
pressive therapy based on a standard rapid-taper regimen of corticosteroids and low-dose tacrolimus monotherapy (1 mg every 12 hours) to the currently recommended target level.

After discharge from our hospital, the patient continued regular follow-up visits at our post-transplant outpatient department, which included α-fetoprotein tests and abdominal sonography. Thirty-six months after liver transplant, 3 hypoechoic lesions were detected, suggestive of HCC recurrence. The tumors were treated with transarterial chemoembolization. Two months later, during his second course of transarterial chemoembolization, his α-fetoprotein level rose abnormally to 17.62 ng/mL. The patient was hospitalized about 1 month later because of progressive abdominal discomfort, frequent postprandial nausea, mild dysphagia, and tarry stools. An upper gastrointestinal endoscopy revealed 1 ulcerative mass with bleeding in the lower third of the esophagus (Figure 1). Histologic examination of the biopsy specimen revealed poorly differentiated carcinoma and polygonal tumor cells arranged in a microtrabecular pattern with patchy necrosis, suggestive of metastatic HCC when compared with the previous pathology results. Subsequent examinations showed no further distant metastasis of HCC (Figures 2 and 3). However, the patient's liver function rapidly deteriorated, and he developed hepatic encephalopathy. The patient died 1 month after esophageal metastasis was diagnosed.

**Discussion**

In 1964, a surgical team led by Dr. Thomas Starzl performed the first human liver transplant, which is now the best treatment modality for patients with end-stage liver disease and HCC. With improvements in surgical methods, posttransplant care, and immunosuppressive regimens, patients with HCC who receive liver transplants have a better prognosis than patients who receive liver resection. However, as a curative modality for HCC, concerns remain regarding the possible clinical outcomes of post-transplant patients. That is, some patients may have recurrence of HCC after liver transplant, resulting in significantly lower survival rates versus patients without recurrence.

Because of concerns of HCC recurrence and its effect on survival, liver transplant is recommended for selected HCC patients only. In 1996, Mazzaferro and

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**Figure 1.** Upper Gastrointestinal Endoscopy of an Ulcerative Mass With Bleeding in the Lower Third of the Esophagus

**Figure 2.** Chest Computed Tomography Scan

**Figure 3.** Chest Computed Tomography Scan

*Abbreviations:* CT, computed tomography; PET, positron emission tomography

Increased fluorodeoxyglucose uptake (early maximum standardized uptake value of 2.37; delayed maximum standardized uptake value of 2.80) is shown in the lower third of the esophagus.
associates\(^{8}\) proposed an effective method to select patients for liver transplant, known as the Milan criteria. Patients who met the criteria had a 4-year survival rate of 85\% and a recurrence-free survival rate of 92\%.\(^{9}\) A few years later, Yao and associates\(^{3}\) presented their excellent outcome results for HCC patients who received liver transplants, resulting in creation of an expanded set of criteria called the University of California, San Francisco criteria. The survival rates of patients meeting their expanded criteria could achieve 90\% at 1 year and 75\% at 5 years. Of note, although recurrence of HCC was shown in 8 patients (11.4\%) in their study, none survived more than 10 months after recurrence.\(^{3}\)

With the incidence of HCC steadily rising worldwide and with better surveillance strategies for patients at a higher risk for HCC, the number of HCC patients needing liver transplants is expected to increase. However, because of the limited availability of organs from deceased donors, living-donor liver grafts are presently more common. Recently, Park and associates proposed 6 risk factors related to higher HCC recurrence after liver transplant, comprising a preoperative \(\alpha\)-fetoprotein level of \(> 400 \text{ ng/mL, an Edmondson and Steiner grading system value of 3 or 4, presence of partial tumor necrosis with transarterial chemoembolization, presence of minimal tumor necrosis with transarterial chemoembolization, pre-sence of microvascular invasion, and receipt of liver from a living donor.}\(^{9}\) In contrast to time to transplant from deceased donors, living-donor liver transplants have shorter wait times for recipients. This effect, known as the “fast-track” effect, and may result in neglect of different tumor characteristics in the HCC patient leading to biologically aggressive tumors inextricably com-mingled in the transplant candidates. In addition, because a living-donor graft is smaller, there is a more vigorous need for regeneration after transplant. As a result, the microenvironment for hepatic cell regrowth also may contribute to the HCC relapse.

Although HCC recurrence after liver transplant has a significant effect on the patient’s prognosis, treatment outcome data are limited. In the few published studies,\(^{7,10,11}\) the median time to recurrence was 7.9 to 12.9 months and the median survival time after HCC recurrence was 8.7 to 12 months. One prognostic factor related to the survival is time from liver transplant to recurrence. Survival rates for patients with early recurrence was shorter than for patients with late recurrence,\(^{7,11,12}\) most possibly because tumors with a well-differentiated histology have a more benign disease behavior than poorly differentiated tumors. In other words, the earlier the tumor recurred, the more aggressive the tumor behaved, resulting in a worse prognosis for patients with early recurrence. Another prognostic factor was the site of recurrence. Patients who have recurrence presenting as bone metastases or with multiorgan involvement at initial diagnosis would have a significantly shorter survival rate than those who have recurrence in liver or lung.\(^{7,11,12}\) Treatment for HCC recurrence after liver transplant also depends on the site of recurrence. Although the possibility of curative resection after recurrence is low, patients with resectable disease would have a better outcome than those with unresectable.\(^{7}\) Also, because single-organ recurrence is often shown to progress to multiorgan involvement,\(^{12}\) systemic treatment should also be considered for all patients after locoregional treatment.

In conclusion, recurrence of HCC after liver transplant as esophageal metastasis, although rare, may indicate an extremely poor prognosis and therefore should be considered as a possible site of recurrence. Patients with high risk factors related to posttransplant recurrence should especially be followed up with endoscopic examination as a cautionary measure.

References


