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LETTER TO THE EDITOR

Oesophageal metastases of hepatocellular carcinoma after liver transplantation

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Hepatocellular carcinoma (HCC) that meets the Milan criteria is a common indication for orthotopic liver transplantation (OLT), with good results. Recurrence-free 1-year survival has been reported to exceed 84.7%, 5-year survival, 61.8% [1]. Recurrence of HCC after OLT within the Milan criteria is reported in approximately 20% [2]. HCC metastases to the oesophagus are very rare; reported rates in the literature are <0.4% [3].

We report a 55-year-old man who underwent OLT for HCC resulting from chronic hepatitis C virus infection. HCC was diagnosed 7 months before OLT. Preoperative computed tomography (CT) indicated that the HCC fulfilled the Milan criteria [4,5] with one lesion in the right lobe (1.5 cm, segment VI), and liver cirrhosis Child's C. Computed tomography was performed every 3 months; the last preoperative CT 2 months prior to transplantation showed one lesion in the right lobe (1.5 cm, segment VI), and two lesions in the left lobe (1.5 cm, segment II, and 1.5 cm, segment I). The preoperative Model for End-Stage Liver Disease (MELD) score was 18. The serum level of alpha-fetoprotein (AFP) was 1500.0 ng/ml (normal <10 ng/ml). To prevent progression, the HCC was downstaged preoperatively by transcatheter arterial chemoembolization with a combination of lipiodol and farmorubicin at 5.5 and 1.5 months prior to OLT. The two lesions in the left lobe were successfully embolized, but the lesion in the right lobe could not be, and partial thrombosis of the right portal vein precluded further embolization. Chemotherapy with medroxyprogesterone acetate (Farlutal®; Actavis Italy S.P.A., Saronno, Italy) was introduced because the hormone receptors were highly positive.

After 7 months on the waiting list, the patient underwent OLT in piggyback technique, without intraoperative complications. As embolectomy of the portal vein had been successful, the usual end-to-end anastomosis between the portal vein of the graft and the recipient could be created. Pathological examination of the explanted liver showed a tumour nodule 3.5 cm in diameter between the caudate and quadrate lobes with branches 8 cm long and 1 cm wide, and vascular invasion (G-2, pT3). With this post-OLT staging, the patient was not within the Milan criteria.

The patient received induction therapy with antithymocyte globulin (Lymphoglobulin®; Fresenius Medical Care AG, Bad Homburg, Germany), and methylprednisolone (Pred), which was started at 4 mg/kg/day and tapered to 0.2 mg/kg within 1 week, and totally withdrawn after 3 months. Maintenance immunosuppression consisted of Sirolimus (Sir) monotherapy.

Eight months after OLT, a gastroscopy was performed because of dysphagia. Biopsies were taken from several polypoid lesions in the distal oesophagus (Fig. 1); there were no oesophageal varices. The AFP level was 1426.0 ng/ml. Histology revealed tumour cell – conglomerations covered with squamous epithelium. The tumour cells showed a negative immunohistochemical reaction for cytokeratin 5 and 6, a positive immunohistochemical reaction for hepatocellular antigen, and a highly positive reaction for p53 and AFP; these findings were identical to those of the primary tumour. The polypoid lesions were diagnosed as submucosal oesophageal HCC metastases. Local therapy consisted of hyperthermia, photodynamic therapy and stent implantation in the distal oesophagus. Nine months after OLT, multiple recurrent

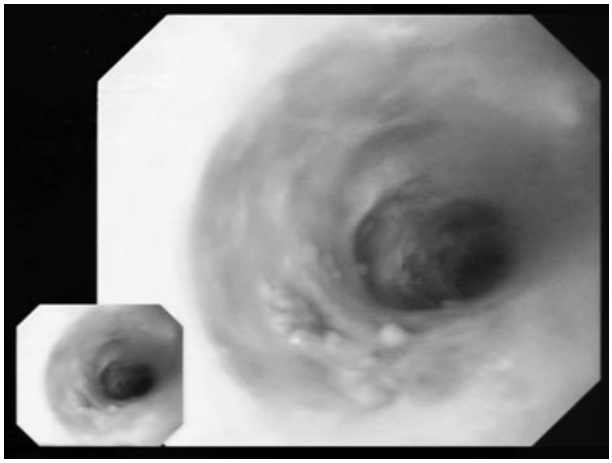

Figure 1 Polypoid lesions in the distal oesophagus: oesophageal metastases of hepatocellular carcinoma (HCC) after orthotopic liver transplantation (OLT).

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metastatic HCC lesions were seen in the liver upon computed tomography. The patient died 17 months after OLT of progressive hepatic failure subsequent to HCC recurrence.

Generally, extrahepatic metastasis of HCC is rare [3], even with advanced intrahepatic lesions, but the rate of multiple organ involvement with recurrent HCC after OLT is reported to be higher [6]. HCC usually metastasizes from the liver to the lung (18.1–49.2%), lymph nodes (26.5–41.7%), bone (4.2–16.3%), and adrenal glands (8.4–15.4%) [7–9] but very seldom to the GI tract; rates between 0.5% and 2% are reported in the literature [10,11]. HCC metastasis to the GI tract most commonly involves the duodenum, stomach, colon and jejunum. Only five cases of HCC metastasis to the oesophagus have been reported to date, and the literature shows only two cases in transplant recipients, both in China [12,13]. Two cases including the present case were symptomatic, with dysphagia and GI bleeding.

There are two different hypotheses concerning the way HCC metastasizes to the oesophagus: either by direct invasion of the GI tract via contiguation between the serosal side of a liver tumour and the oesophagus, or via haematogenous spread of tumour emboli that infiltrate the portal venous system. Hepatofugal blood flow in patients with portal hypertension may provoke dissemination to the GI tract. An association of HCC with distal oesophageal metastasis is possible because of portal-caval anastomosis via the left gastric vein to oesophageal varices. In the present case, there was a history of partial portal vein thrombosis prior to OLT (right portal vein), which was removed by thromboembolectomy during OLT. After OLT, there were no more signs of portal hypertension.

Orthotopic liver transplantation was performed in piggyback technique. The literature does not report tumour cell dissemination during OLT for HCC, regardless of technique. Further studies are necessary to evaluate tumour cell dissemination during OLT.

A recently published article in The Lancet Oncology evaluates OLT in HCC patients exceeding the Milan criteria, and recommends use of the up-to-seven criterion, meaning HCCs with seven as the sum of the size of the largest tumour in cm and the number of tumours [5]. In conclusion, therapy for HCC should be individual and tailored. As the current trend in liver transplantation is toward extended criteria for recipients with underlying malignant liver disease, and as two similar cases of recurrent HCC after OLT to the upper GI tract have recently been reported, transplant physicians should be aware of this rare complication.

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