Two cases of pulmonary metastasis after living donor liver transplantation for hepatocellular carcinoma

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Orthotopic liver transplantation (OLT) is the only chance of cure for many patients with unresectable but non-metastatic, hepatocellular carcinoma (HCC) and advanced liver cirrhosis. The main shortcoming of this strategy is the increased risk of tumor recurrence after liver transplantation because of either poor selection criteria or the fact that current staging methods cannot reliably detect micro-metastasis. The tumor cell dissemination must have occurred preoperatively or intra-operatively. Immunosuppression represents a risk factor for accelerated tumor growth, so the schedules of the immunosuppressant drugs have been modified through the years, aiming to reduce their dosage to the effective minimum. Many centers currently offer living-donor liver transplant (LDLT) only to patients fitting the Milan criteria1 (patients with single tumor <5 cm or fewer than 3 lesions, none of which are >3 cm). Based on these data, United Network for Organ Sharing (UNOS) also established and recommended the current listing criteria for HCC patients. We present two cases where strict inclusion based on the Milan criteria for selection for LTDT were made; however, both developed a fatal metastasis in the lung within 3 years of transplantation without an obvious involvement of the donor liver.

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Case 1

The first case was a 54-year-old woman diagnosed with chronic hepatitis C-induced liver cirrhosis in 1995, during a routine laparoscopic cholecystectomy. In 1997, she was found to have a highly vascular and suspicious mass lesions in a CT scan of liver with high alpha-fetoprotein (269 μg/L). The alpha-fetoprotein levels dropped to 161 μg/L within a few months of close observation. Ultrasound guided FNA and liver biopsy of those masses were negative for malignancy. In 1999, her follow-up ultrasound showed 2 definite mass lesions (3x2 cm and 2x1 cm). Her pre-transplant work up for LDLT included a CT scan of the abdomen and chest that showed no evidence of distant metastasis. A nuclear bone scan was also negative for bony metastasis. The patient underwent an LDLT in 1999 in Germany using the right lobe of the liver from her son, where the recipient liver was confirmed histopathologically to have only 2 mass lesions consistent with HCC. The tumor was moderately differentiated and localized to the liver. There was no evidence of vascular, lymphatic or surrounding structure invasion. In March 2000, she had reactivation of her hepatitis C virus (HCV) infection with impaired liver functions. Interferon and ribavirin were started in the standard doses. After 6 months, HCV (by PCR) became negative and liver functions returned to normal. She continued to have a sustained virological response for the following year. Her regular follow up was continued in the liver transplant clinic with liver function

tests every 3 months and ulltrasound at 6 months. A repeated CT of the liver in August 2002 showed no evidence of tumor recurrence, but her AFP remained high in the range of 70 to 139 μg/L. She received cyclosporine and prednisolone for her immunosuppression. In October 2002, she was admitted with right-sided lower chest pain, and a CT of the chest showed a lung mass (Figure 1), but the CT of the liver did not show any recurrence of the tumor in the transplanted liver. A CT-guided lung biopsy (Figure 2) confirmed the presence of metastatic carcinoma originating from the primary HCC. Later, the patient developed widespread brain and bony metastasis and expired in July 2003.

Case 2

A 60 year-old-man was discovered to have HCV infection in the year 2000 during a preoperative workup for elective eye surgery. In 2001, he was referred to his local hospital with increasing jaundice. The investigations confirmed the diagnosis of liver cirrhosis, secondary to HCV with two masses in the right lobe of liver and high alpha-fetoprotein. MRI and CT confirmed the two lesions of size 2.5 cm at the posterior segment of right lobe of the liver and 1.5 cm at the inferior segment of right lobe of the liver, their arterial phase enhancement was typical of HCC. His alpha-fetoprotein level was 4507 μg/L. There was no evidence of portal or hepatic vein invasion. In addition to the masses, there were several regenerating nodules throughout the liver parenchyma. A nuclear bone scan showed no evidence of bony metastasis. CT of the chest and abdomen did not identify a distant metastasis or any enlarged lymph nodes in the hilar, mediastinal or axillary region. There was no evidence of invasion or thrombosis of the portal or hepatic veins. The patient underwent LDLT using the right lobe of the liver from his son in March 2002 in the USA. The liver specimen surface was course and nodular, the regenerating nodules ranging in size from 2 to 5 mm. There was a bulging lesion measuring 3.5 cm in greatest dimension, along the superior medial aspect of the right lobe of the liver, consistent with moderately differentiated HCC (macro-trabecular type), and another low grade dysplastic regenerating nodular lesion along the inferior medial right lobe measuring 2.5 cm with a microscopic foci of trabecular HCC. There was no evidence of vascular, lymphatic or capsular invasion. His post-operative course was quite smooth. The patient had at 3-month intervals regular follow-up visits to the liver transplant clinic and had a normal alpha-fetoprotein (9.7 μg/L), chest X-ray and ultrasound (US) of the liver until May 2003.

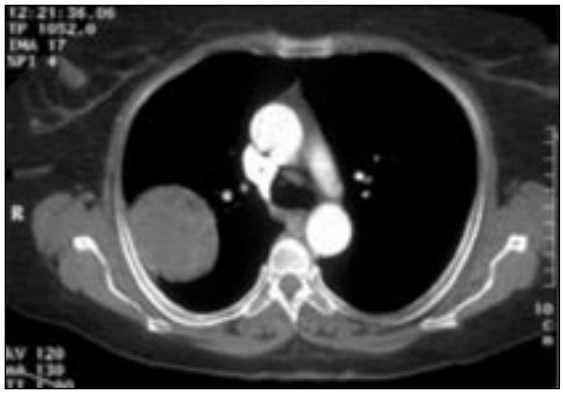

Figure 1. Metastatic HCC presenting as a large lung nodule in the right lung (contrast CT of the chest).

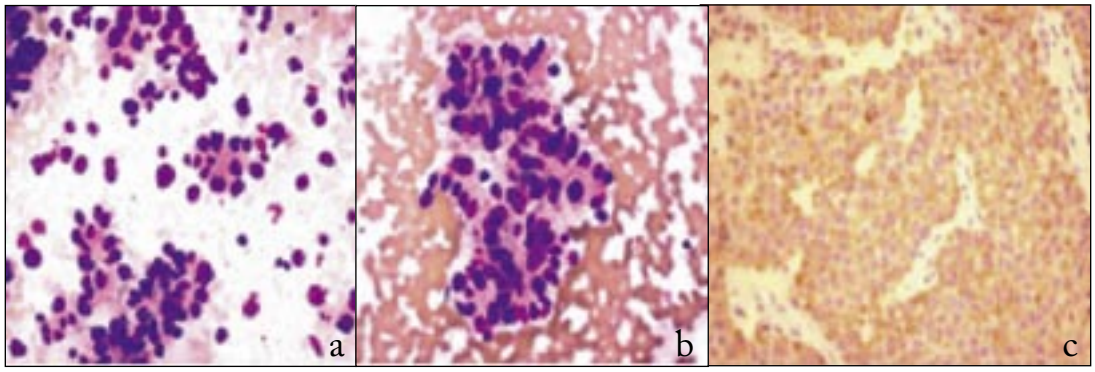

Figure 2 (CT guided lung biopsy). Fine needle aspiration (FNA) of lung mass (a and b) showing malignant cells with an acinar and trabecular arrangement. Many naked nuclei are noted in the background. These features are compatible with metastatic hepat
cells (immunoperoxidase 40X).

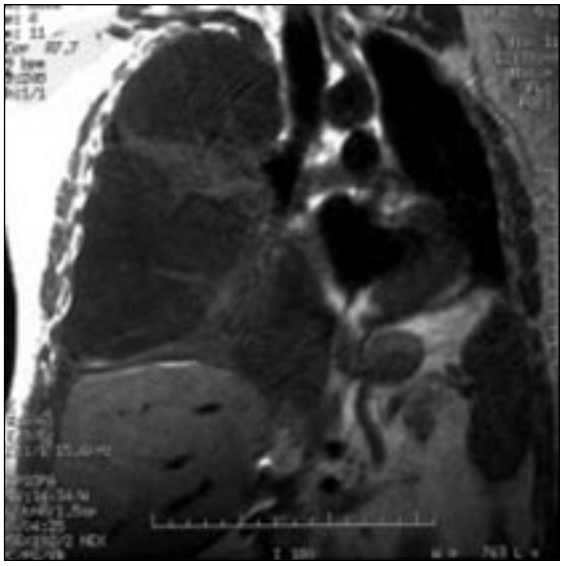

Figure 3. A large lobulated right pleural effusion with heterogeneous soft tissue density at the pleural base consistent with a soft tissue mass with areas of low signal intensity on T2-weighted images suggestive of areas of hemorrhage (contrast MRI of the chest).

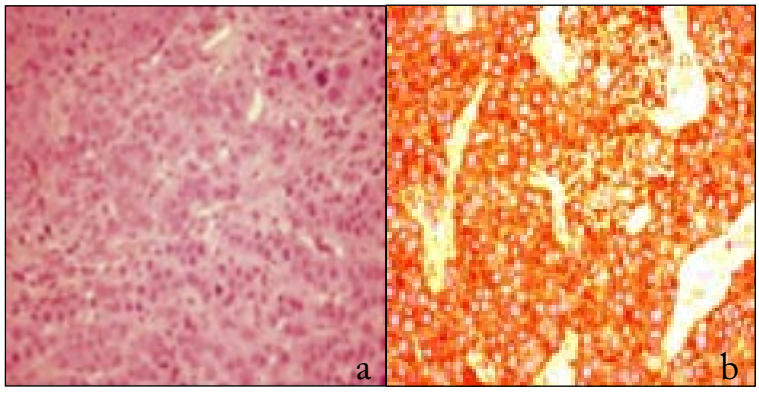

Figure 4. Pleural biopsy showing metastatic hepatocellular carcinoma a (H&E 40X); b (Immunohistochemical stain for alpha fetoprotein shows strong positivity in the tumor cells immunoperoxidase 40X).

He received FK-506 for his immunosuppression. His routine follow up in September 2003 showed very high alpha-fetoprotein (9970 µg/L). An MRI (Figure 3) and CT scan of the abdomen and chest demonstrated a large lobulated right pleural effusion with a heterogeneous soft tissue density at the pleural base. There was no evidence of abnormal high signal intensity or lesions in the liver. Mediastinoscopy was performed under general anesthesia and the biopsy was taken from the pleural base nodules. The pleural biopsy (Figure 4) showed metastatic HCC (the tumor cells were positive for hepatocyte specific antigen and alpha-fetoprotein). The patient expired in December 2003.

Discussion

Initial experience with OLT for HCC was disappointing because of the high recurrence rate of the tumor after transplantation. Attention was then focused on the pathological features of the tumor, the size and location of the tumor, the number of nodules, the involvement of the intrahepatic blood vessels, and the regional lymph nodes were all found to be related to the outcome. Selection of transplant candidates on the basis of favorable tumor features led to excellent results in the prospective trial carried out by Mazzaferro et al,[1] who reported 83% overall patient survival and 75% overall recurrence-free survival at 4 years. We describe two cases of cirrhosis of the liver with HCC in patients who underwent LDLT. We adopted the strict Milan inclusion criteria, regarding the size and number of the nodules before recommending them for LDLT. Their preoperative work up using US, CT and bone scan were negative for distant metastasis. There is no consensus among various transplant centers on the size and number of the enhancing nodules; the main emphasis described in the Milan criteria was on the size and numbers of tumor. To the contrary, some authors proposed that the size and number of tumors did not solely predict outcome and suggested that other parameters such as vascular invasion[2] or cell differentiation[3] (e.g., apoptosis-to-mitosis ratio) may be more important. The fact that vascular invasion commonly begins as tumor diameter approaches 5 cm likely explains the correlation of diameter with recurrence. Recently, Yao et al[4] compared University of California, San Francisco (UCSF) criteria (solitary tumor ≤6.4 cm, or three or fewer nodules with a largest lesion ≤4.5 cm and a total diameter ≤8 cm, without gross vascular invasion) with Milan and Pittsburgh modified tumor-node-metastasis (TNM) criteria. His analy-

sis suggested that UCSF criteria better predicted acceptable post-transplant outcome than Milan criteria. UCSF criteria conferred a different advantage over Pittsburgh criteria, which required information on microscopic vascular invasion that was difficult to ascertain preoperatively without the attendant risk of liver biopsy.

The factors that affect the prognosis of the liver transplantation in HCC are proper staging with the help of radiological studies and early detection of metastasis during the post-transplant follow up. Both of our patients developed a recurrence in the form of pulmonary metastasis within 3 years of transplantation without any significant metastatic lesion in the donor's liver. The question arises whether we can detect these hematogenous spreads early before the transplant. The present recommendation is a CT of the chest, abdomen and bone scan for distant metastasis, but these procedures may not detect the early hematogenous spread. Our two reported cases had regular follow up in the transplant clinic, where AFP and US were done at 3-6 month intervals, and a triple-phase contrast CT scan at the interval of 6-12 months, but still we were unable to detect early metastasis. We should not rely exclusively on tumor size and number of nodules, mainly due to the limits of imaging techniques. It was already described[5] that the pre-OLT stage was inconsistent with post-OLT stage in 48% preoperative known HCC patients according to TNM stages, and 14% according to the Milan criteria. These findings confirmed again the unpredictability of the post-transplant course in HCC patients. FDG-PET imaging had a clinically significant impact in patients with HCC.[6] This includes early detection of unsuspected metastatic disease in high-risk patients, including liver transplant candidates. Wudel et at recommended that FDG-PET should be considered as a part of the routine workup for the recurrence and management of HCC patients. Preoperative screening for micrometastasis in the bone marrow of HCC patients is sensitive and specific with AFP-RT-PCR (α-fetoprotein reverse transcription-polymerase chain reaction) and may have prognostic relevance.[7] Kienle et al believed that this assay should be considered in the preoperative workup before liver transplantation, to have an adequate selection of suitable patients.

One of our patients received cyclosporine and the other received FK-506, in the standard recommended dosage after LDLT. Vivarelli et al[8] suggested that limiting OLT to patients with the Mazzaferro criteria should be reassessed, because outcome is dependent mainly on the immunosuppressive regime. Patients with larger tumors may do well if immunosuppression is lowered. The main factor influencing outcome and tumor recurrence is the cumulative dosage of cyclosporine administered in the first postoperative year rather than the staging of the cancer. Vivarelli challenged the current widely accepted method of patient selection for OLT (i.e. tumor staging) because they failed to demonstrate that patients fulfilling the Milan criteria had less recurrence than those having more advanced HCC. This accelerated growth rate may include the use of immunosuppressive drugs and the consequent suppression of host immunity against the growth of micrometastasis.[9] This issue needs to be addressed with extreme caution, because opposite results and expanding criteria beyond those conventionally applied may negatively impact on organ shortage.[10]

Some of the authors suggested that if you cannot detect the hematogenous spread earlier, then at least treat the patient with various complementary therapies. A recurrence free 5-year survival of 55% in patients of HCC have been reported with a tumor size of 5 to 7 cm, by using a multimodal adjuvant therapy with preoperative chemoembolization or perioperative systemic chemotherapy or both.[11] However, recurrence-free 5-year survival was only 34% inpatients with larger tumors. Several other papers[12,13] have also shown that complementary therapies (resection, transarterial chemo-embolization, chemotherapy, percutaneous ethanol injection) may help control tumor growth while awaiting transplantation and thus reduce the risk of micrometastatic deposit in the early post-operative phase.

The other factors that predict an early metastasis are the nature of the HCC. Klintmalm et al[14] analyzed the impact of tumor features on survival and recurrence in 422 transplanted patients and showed that, in well-differentiated HCC, tumor size and vascular invasion did not affect survival or tumor recurrence, while grading was the only independent prognostic factor emerging from multivariate analysis. Patients with HCC >5 cm may have excellent survival prospects if the tumor is well differentiated.[15]

Are metastatic lesions more frequent in LDLT patients than cadaveric OLT patients? As happened with our patients, overall disease-free survival of patients undergoing LDLT for HCC is comparable to that of patients undergoing cadaveric transplants for similar tumors.[16]

In conclusion, the mortality in these two cases suggest that a new strategy is needed for selecting

HCC patients suitable for LDLT. This will require identifying patients whose risk of recurrence is as low as possible. The tumor differentiation (grade) may accurately reflect tumor aggressiveness and the consequent post-transplant risk of recurrence. To accomplish this goal we must require a liver biopsy before LDLT to determine the grade of the tumor. FDG-PET should be considered as a part of routine pre-transplant evaluation to detect early hematogenous spread. A CT of the abdomen and chest should also be a part of routine follow-up of at least 3-month intervals to detect the early lung metastasis, so the preoperative chemoembolization or perioperative systemic chemotherapy can be tried. Modification of the immunosuppression regime needs more trials before recommending a future strategy. The inclusion criteria for LDLT should be based on early detection of the tumor, and immunohistochemical or molecular biological techniques for identifying new biohumoral or pathologic factors

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