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LETTER TO THE EDITOR

Donor origin *de novo* HCC in a noncirrhotic liver allograft 3 years after liver transplantation

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Hepatocellular carcinoma (HCC) that originates *de novo* in liver allograft transplanted for benign disease has rarely been reported. By contrast, tumor recurrence after liver transplantation (LTx) for HCC in the setting of cirrhosis is frequently encountered. In this study, we report the first *de novo* HCC case of donor origin in a liver allograft after LTx for nutritive-toxic cirrhosis. There was no sign of pre-existing HCC in the explanted liver, or recurrence of hepatitis-associated or other cirrhosis type in the allograft. We employed microsatellite analysis to provide for the molecular proof. Our data show that *de novo* malignancies including HCC can occur even in the noncirrhotic liver allograft. Therefore, new lesions detected during follow-up require thorough and timely work-up to exclude malignancy.

A 59-year-old man with a history of alcoholic cirrhosis underwent an ABO-matched, orthotopic LTx from a deceased donor in May 2005. Based on pre-operative imaging studies and the histopathology examination of the explanted liver, we ruled out the presence of HCC within the cirrhotic liver. The liver allograft was procured from a 67-year-old man who died of intracerebral hemorrhage. The clinical charts of the donor revealed no history of relevant diseases, especially no history of cancer. The virology status of the donor was completely negative. We performed standard orthotopic LTx, with replacement of the vena cava and duct-to-duct biliary reconstruction. The intra-operative as well as postoperative course was uneventful. We employed an immunosuppressive regimen consisting of cyclosporine, mycophenolate mofetil (MMF), and prednisone, according to our protocol. The patient was discharged in a timely manner and received regular follow-up through our outpatient department. About 1 year after the transplantation, the patient developed ischemic type intra-biliary lesions (ITBL type I), with recurrent episodes of cholangitis. He was treated medically and repeated endoscopic interventions with intrahepatic stent placement were performed. Under these regimens, the transplant function remained stable and the patient was under surveillance by ultrasonography and MRI scan. In May 2008, about 3 years after the transplantation, ultrasonography revealed a heterogeneous echogenic mass within the right posterior sector of the liver allograft. Magnetic resonance imaging confirmed a suspicious tumor, with arterial enhancement about 4 cm in diameter. Alpha fetoprotein was within the normal levels (2 U/ml). In addition, a CT-guided percutaneous biopsy was performed and the histology was compatible with that of a HCC. To rule out pulmonary spread, we performed a CT thorax, which did not show any evidence of lung metastases. MMF was discontinued and the patient received a standard pre-operative work-up. We performed an uneventful atypical partial liver graft resection of segment 7. Macroscopically, there were no signs of cirrhosis or other tumor manifestations. The histo-pathological examination revealed a moderately differentiated (G2) HCC (pT1) with tumor-free resection margins. The adjacent nonmalignant liver tissue showed no signs of cirrhosis, but a 20% steatosis. The postoperative course was prolonged because of a biliary leakage from the resection area that required surgical revision. Despite prolonged recovery, the patient demonstrated a good condition, with almost normal liver function tests and no signs of HCC recurrence about 12 months after resection.

To prove the donor origin of the tumor, we analyzed DNA derived from the allograft donor as well as the patient's peripheral blood by comprehensive microsatellite analysis and determination of paternity. In addition, tissue DNA was extracted and analyzed from both the nonmalignant cadaveric liver allograft and the tumor tissue. In total, a set of 16 microsatellite markers with a high variability of sequence repetitions were used to establish the donor origin of the HCC tumor cells. As expected, blood-derived DNA displays distinct patterns of allelic variants. Exemplarily, the genetic profiles of two of these 16 markers are depicted in Fig. 1. For the HCC and nonmalignant liver tissue, we noted a slight admixture of the donor and recipient genetic signature. This is not surprising as the liver tissue will be contaminated with the recipient's blood. However, the predominant donor pattern and the close resemblance between the HCC and nonmalignant liver genetic profiles clearly establish the donor origin of the HCC.

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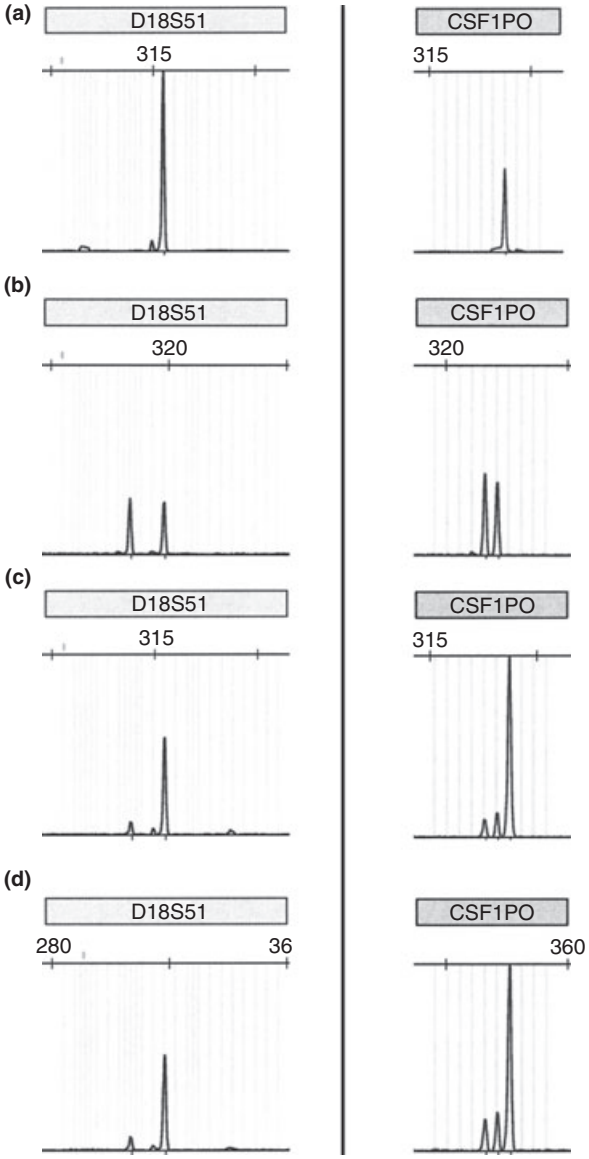

Figure 1 Chromatograms of two microsatellite markers (D18S51 and CFS1PO) exemplarily selected from a set of 16 markers used to establish the donor origin of HCC. Donor (a) and recipient (b) DNA are derived from peripheral blood, whereas HCC (c) and nonmalignant liver tissues (d) are derived from the allograft. We note the distinct genetic signature of the donor and recipient. For the two microsatellite loci (D18S51 and CFS1PO), the donor (a) is homozygous (one peak), whereas the recipient (b) is heterozygous (two peaks). Both the HCC and nonmalignant liver genetic signature (c and d) are almost identical, showing one dominant peak as noted for the donor. There is a slight notion of an admixture of recipient-derived DNA, resulting in the minor two peaks observed for the recipient.

Orthotopic LTx is well-established as a life-saving operation for patients with acute or chronic liver failure. However, the recipients are subjected to lifelong immunosuppressive therapy, with its many attendant risks. *De novo* malignancy after LTx is an undoubted risk after a successful operation and has been increasingly reported in the literature in recent years [1–4]. Recurrent and *de novo* malignancies are the second leading cause of death in liver recipients, following age-related cardiovascular complications [3–5]. Organ transplant recipients are considered to be at a greater risk of *de novo* malignancies related to immunosuppressive therapy. The reported incidence rates of *de novo* malignancy range from 3% to 26%, which is significantly higher compared to that of the general population [2,3]. The predominant *de novo* malignancies are post-transplantation lymphatic disease and cutaneous neoplasm [4–6]. Only a few reports can be found in the world literature on *de novo* HCC in patients with no previous history of malignancy in the explanted liver [7–10]. Importantly, all reported cases are associated with liver cirrhosis in the transplant allograft and most assume the donor origin of the HCC. The origin of the *de novo* HCC can be easily determined by molecular techniques established for forensic and paternity analysis [9–11].

This is the only case among over 1500 LTx s performed during the last decade at our center recognized as a rare noncutaneous *de novo* neoplasia. *De novo* HCC in a noncirrhotic liver allograft is important to acknowledge as donor transmitted malignancies are theoretically preventable by a careful long-term screening protocol, facilitating diagnosis at an earlier stage of the disease.

The rapid progression of *de novo* malignancies even in the noncirrhotic graft of immunocompromised transplant recipients warrants careful attention. Only lifelong close surveillance by specialized and dedicated teams familiar with the underlying risks allows the detection of such tumors at an early and potentially curable stage of disease.

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