LETTER TO THE EDITOR

Salvage live donor liver transplantation for a second recurrence of hepatocellular carcinoma

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Introduction

During the past years, live donor liver transplantation (LDLT) has become the most likely alternative for the expansion of the organ pool for adult patients with hepatocellular carcinoma (HCC) and end-stage liver disease [1–6]. However, indications for transplant for HCC patients in the era of LDLT are still subject to debate [7–9]. One of the arguable indications remains the performance of LDLT for recurrent HCC in the noncirrhotic liver, where the dramatic optimization of liver resection techniques on the one hand, and the question about the best 'oncologic' approach to these instances (second resection plus adjuvant chemotherapy versus transplantation plus immunotherapy) on the other hand, are still under deliberation [10–15].

Although the coexistence of multiple benign liver tumors, such as focal nodular hyperplasia (FNH), adenomas and hemangiomas, is already described [16,17], the combination of them and especially of FNH with HCC is very rare [18–21].

We report herein the case of a patient who underwent three surgical interventions. The initial surgery was aimed at resecting a combination of HCC, FNHs, and hemangiomas. The purpose of the second procedure was to remove an HCC recurrence. On the third occasion, our patient underwent salvage living donor liver transplantation for a second recurrence of HCC.

Case report

The patient is a noncirrhotic 33-year-old woman who was admitted to our hospital with upper abdominal complaints because of multifocal liver lesions. She has a positive history of oral contraception. Serial examinations for hepatitis A, B and C (HBs-Ag, anti-HBc, anti- HCV, anti-HAV) were negative. Preoperative evaluation showed normal levels for the tumor markers α-fetoprotein (AFP), carcinoembryonic antigen and carbohydrate antigen. According to the findings from imaging in computed tomography and magnetic resonance imaging, the lesions were assessed to be liver hemangiomas in combination with FNH (Fig. 1). In surgery, an HCC measuring15 cm in diameter involving segments V and VI, two FNHs lesions located in segments IVa and III (3 cm and 2 cm in diameter, respectively), and liver hemangiomas in segments IVa and VII were found. The patient underwent a right hepatectomy, wedge resection of segment IVb, and local resection of the focal lesions in segments IVa and III. Histopathologic examination showed a well differentiated, pT1 HCC with clear margins and no vascular invasion (Fig. 2a), two FNH lesions, and cavernous hemangiomas. There were no postoperative complications.

Three years later subsequent to the right hepatectomy and other resections, and 1 year after a successful pregnancy, the patient was re-admitted because of a HCC recurrence. She underwent a segment III resection. Pathology showed an rpT1, 11-cm diameter, moderately differentiated HCC with no vascular invasion and intact tumor capsule (Fig. 2b). Follow-up examinations during the subsequent 2 months demonstrated a new multifocal tumor recurrence in the remaining left liver lobe.

During the following 6 months, although the tumor increased in size, no metastases developed, as it could be shown in the computed tomography and magnetic resonance scans, as well as at the positron emission tomography and bone scintigraphy images. Because of the multifocal tumor growth, as well as of the previously performed liver resections, which were carried out with consecutive removal of the right and middle hepatic veins during the parenchyma transection, a third liver resection was not any more technically possible. Considering the young age of the patient, decision for exploring the transplant possibility was taken in the interdisciplinary transplant board. However, as there is hardly any information in the literature and also because of paucity of experience in the clinical praxis concerning transplantation for second recurrence of HCC, it was at that time not formally allowed to list the patient in 'Eurotransplant' for the waiting list of a deceased donor LT. Hence, we evaluated the opportunity to proceed with a live donor LT from the patient's sister. After completion of evaluation of both donor and recipient, right lobe LDLT was performed 9 months after the second liver resection. The post-transplant course was uneventful, and the patient was

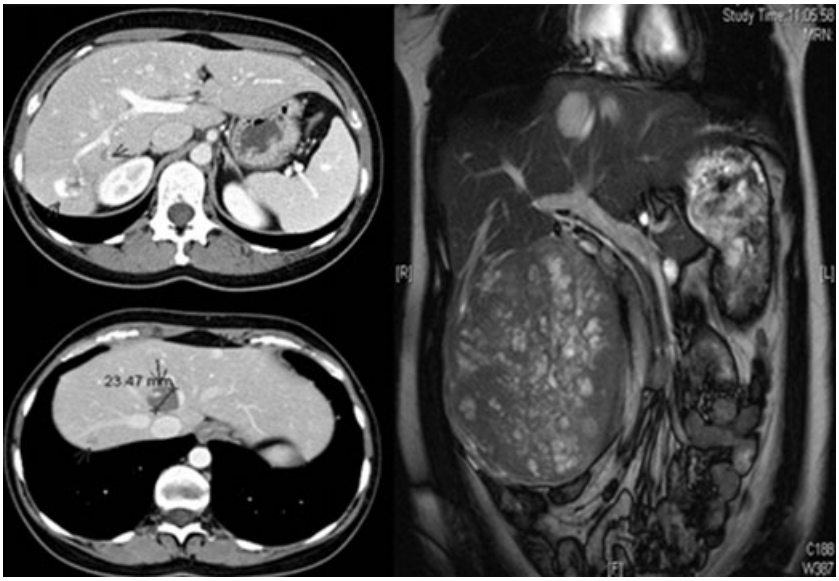

Figure 1 Computed tomographic and magnetic resonance imaging scans showing the 15 cm in diameter hepatocellular carcinoma involving segments V and VI [at the time considered as focal nodular hyperplasia (FNH)], two FNHs lesions in segments IVa and III, and liver hemangiomas in segments IVa and VII.

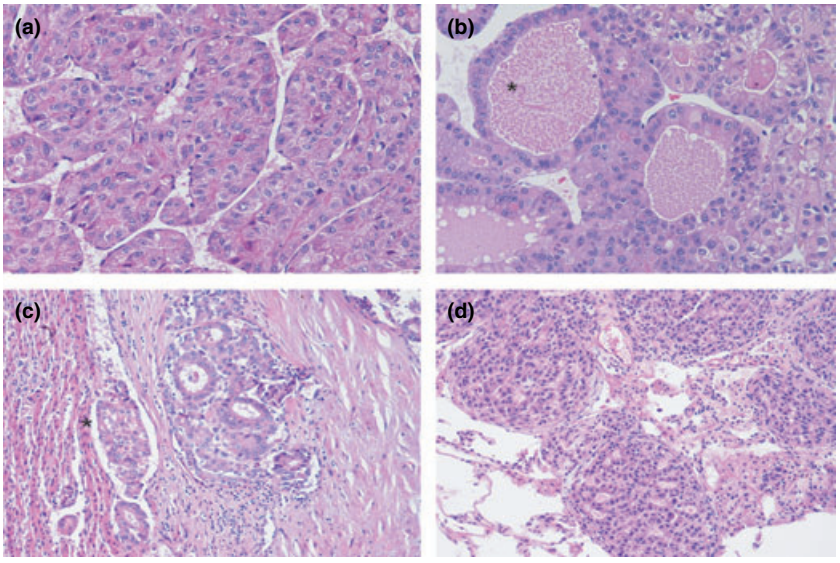

Figure 2 (a) Well-differentiated hepatocellular carcinoma (HCC) with only a discrete loss of cell plate architecture and minimal cytologic atypia (hematoxylin–eosin, original magnification ×200). (b) Moderately differentiated HCC with increased architectural distortion and presence of pseudoglandular structures (asterisk). In addition the nuclear atypia is slightly increased with hyperchromatic nuclei and increased nucleus to cytoplasm ration (hematoxylin–eosin, original magnification ×200). (c) Increased biologic aggressiveness reflected by multifocal growth and vascular invasion (asterisk). No definite changes in morphology (hematoxylin–eosin, original magnification ×100). (d) HCC metastasis in the lung. Morphology is similar to that of primary tumour (hematoxylin–eosin, original magnification ×100).

discharged on postoperative day 18. Histology of the explanted liver showed a multifocal, 3-cm diameter, pT2 moderately differentiated HCC with vascular invasion (Fig. 2c), as well as a 3-cm cavernous hemangioma. The rest liver parenchyma was normal, without any signs of fibrosis or cirrhosis. AFP levels were not detectable at any time. Follow-up studies showed a solitary metastasis in the right lung, which was successfully removed (Fig. 2d). Our patient is currently alive and in good physical condition, receiving oral chemotherapy with sorafenib. Immunosuppression was switched to rapamycin.

Discussion

Although the concept of LDLT as a 'salvage procedure' for recurrence of HCC after liver resection is not new [22–24], this case constitutes, to the best of our knowl-

edge, the first instance in which it is performed for a second recurrence of HCC. However, the results of this single case are not encouraging to merit performance of LDLT as extended indication in this rare clinical situation. Evaluating the tumor characteristics of this AFP-negative HCC during the course of this period of more than 4 years, an even more aggressive recurrence is to be observed (Fig. 2a–d). Indeed, the initial solitary, well differentiated HCC, is transformed consecutively to a moderately differentiated solitary one at the time of the first recurrence and to a multifocal growing, vessels-invading one at the time of the second recurrence. As a consequence of this tumor behavior and under the post-transplant immunosuppression, lung metastases occurred within the first post-transplant year.

This case also points out the unusual coexistence of three different multifocal liver tumors (HCC, FNH, hemangioma) and the subsequent recurrence of two of them (HCC and hemangioma). Also in the case of coexistence of multiple benign liver tumors, apart of the subjective patients' complaints, the risk for rupture, degeneration or liver insufficiency in very rare cases imposes sometimes an aggressive surgical approach. In the infrequent instances of coexisting HCC with multiple benign liver tumors, decision for surgical therapy is anyway inevitable.

The young age of the patient, the presence of initially favorable HCC characteristics, the encouraging results for 'salvage' LDLT, and the lack of experience for transplantation after multiple HCC recurrences, led us to make the decision to proceed with such an 'extended' indication for LDLT. Retrospective study of these fine changes of the HCC characteristics in pathology, as well as the post-transplant course did not reward the extension of the transplant indication in this case. It is our hope that the present report will provide unique information for the treatment of patients with such rare disease course and we would suggest a 'wait and see' policy rather than a transplant one.

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