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Primary sarcoma of the liver and transplantation: a case study and literature review

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Abstract

Primary sarcomas of the liver are rare tumors and their diagnosis is difficult to assess, particularly on percutaneous liver biopsy. Epithelioid hemangioendothelioma (EHE) is an infrequent indication for liver transplantation, and angiosarcoma (AS) is a widely recognized contraindication because of its poor prognosis. We report the case of a young woman who underwent liver transplantation (LT) for an infiltrative hepatic tumor with several features suggestive of EHE, although the analysis of the native liver revealed AS. Everolimus was used as the main immunosuppressive drug. More than two years after LT, her physical condition remained stable despite a local recurrence at 10 months. In this setting, the ranking of new immunosuppressive agents belonging to the family of the proliferation signal inhibitors will need to be precise, but their intrinsic properties suggest a potential use in treatments after LT for atypical malignancies.

Introduction

Primary sarcomas of the liver are rare tumors (approximately 1% of liver cancers) and an exceptional indication for liver transplantation (LT).[1] The two main histological forms are epithelioid hemangioendothelioma (EHE) and angiosarcoma (AS).[2] Those tumors, which share the same mesenchymal origin (endothelial cells edging the sinusoid), have very different natural history and prognosis, and require different treatments (Table 1). Although LT can be indicated in some cases of EHE because of a favorable long term outcome,[1,3] it is absolutely not advised for AS owing to a high risk of early local or general recurrence after LT.4 We report the case of a young woman who underwent LT for a infiltrative hepatic tumor, of which some characteristics and the clinical presentation were suggestive of EHE. However, the histological analysis of the explanted liver revealed AS. The preventive use of an immunosuppressive drug with antiproliferative properties belonging to the mammalian target of rapamycine (mTOR) inhibitors led to the usual two years' survival after LT, despite a local recurrence of AS.

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Case Report

A 41-year-old woman was admitted in April 2002 for acute hepatitis of unknown etiology. Previous liver function tests, performed in March 2002, were normal. The only remarkable medical history was obesity with a body mass index of 31.5. There was no history of excessive alcohol consumption (30 g/wk), medication, or toxic exposure. Biological testing excluded viral, bacterial, and autoimmune hepatitis. The computerized tomography (CT) scan revealed a homogeneous hepatomegaly and excluded a thrombosis of the sus-hepatic veins. A liver biopsy showed a granulomatous infiltration of the liver, with histiocytes but no centrolobular necrosis, as well as a steatosis (30% of the parenchyma). The diagnosis of acute hepatitis related to a vascularitis was made. Between 2002 and 2005 she was hospitalized for several episodes of acute disease, associated fever, maculopapulous eruption, elevation of liver enzymes (AST = 5 x ULN, ALT = 11 x ULN), and cholestasis (alkaline phosphatases = 20 x ULN, γGT = 10 x ULN). Because of the lack of success of the previous therapy, a systemic corticotherapy (dexamethasone = 250 mg IV) was begun in 2005, followed by oral prednisone (1 mg/kg/day). In May 2005 a low platelet count (99000/mm^3) was observed. The patient underwent a second liver biopsy. A vascular disease predominant in the pericentrolobular zone was observed, with congestive sinusoids, centrolobular vein thickening, and necrosis. The abdominal magnetic resonance imaging (MRI) showed a diffuse nodular infiltration of the liver (Figure 1). Because of the ineffectiveness of corticotherapy, methotrexate (15 mg/wk) was introduced.

In October 2005 she was referred for jaundice, ascitis, and edema. Prothrombin time was 50%, bilirubin was 90 mg/L, and α-fetoprotein was normal. A third liver biopsy was performed, showing a proliferation of CD31$^-$ and CD34$^+$ cells, compatible with the diagnosis of EHE or AS. A second MRI (November, 2005) revealed a hepatomegaly with diffuse, hypervascular and nodular infiltration of the liver (Figure 2). The measurement of the portal pressure revealed portal hypertension with a portosystemic gradient of 16 mmHg. The upper endoscopy found a portal hypertensive gastropathy and esophageal varices (grade 1). Clinical presentation orients the diagnosis toward a diffuse EHE with portal hypertension and hepatocellular insufficiency. Thus, LT was considered.

The patient underwent LT in December 2005.

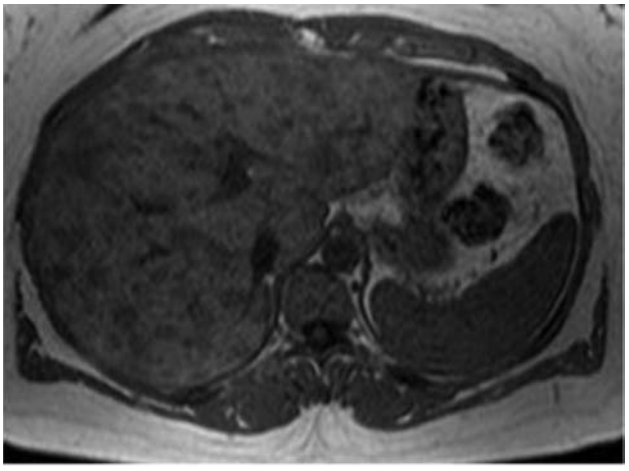

Figure 1. Abdominal magnetic resonance imaging in June 2005 (T1 without gadolinium injection) showing diffuse nodular infiltration of the liver.

Despite the preoperative suspected diagnosis, AS was confirmed finally at the pathological analysis of the explant, consisting of a diffuse AS with necrosis and invasion of the centrolobular veins (Figure 3). The initial immunosuppressive regimen included prednisone (20 mg/day), mycophenolate mofetyl (1 g x 2/day), and tacrolimus (6 mg x 2/day). Tacrolimus and prednisone were decreased, then withdrawn in July 2006, and changed to everolimus (3 mg/day). Residual concentrations ranged from 10-14 µg/L. Mycophenolate mofetyl was withdrawn in October 2006. A postoperative CT scan performed at month 10 revealed a local recurrence with a multimicronodular infiltration of the transplant (Figure 4). Systemic chemotherapy with paclitaxel was begun but had to be discontinued in February 2007 owing to neurological and mucous toxicity. Nevertheless, the CT scan at month 16 showed a partial response, while the patient was under everolimus and taxane therapy. At month 24, the patient was under monotherapy with everolimus (3 g/day). She had no biological toxicity to everolimus and was managing quite well, despite a progression of the disease with asymptomatic vertebral metastasis. At month 30 her general health status quickly decreased with terminal liver failure leading to death.

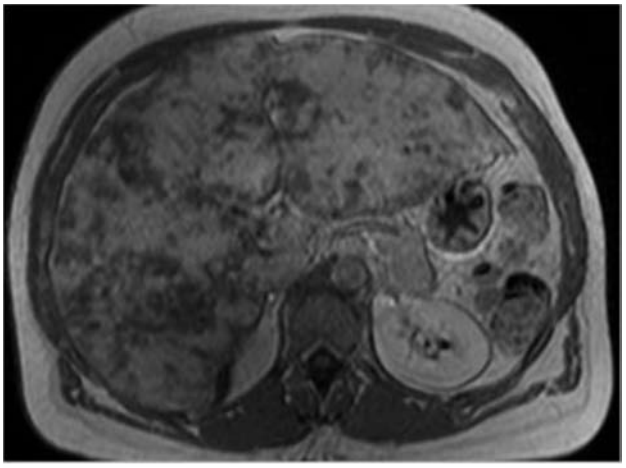

Figure 2. Abdominal magnetic resonance imaging in November 2005 (T1 with gadolinium injection) showing hepatomegaly related to hypervascular tumoral infiltration of the liver.

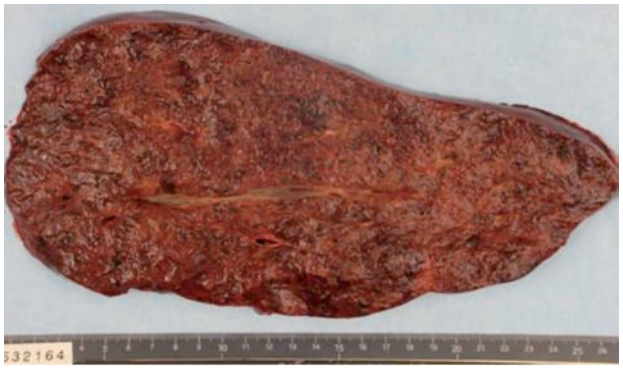

Figure 3. Transversal section of the native liver showing diffuse tumoral infiltration.

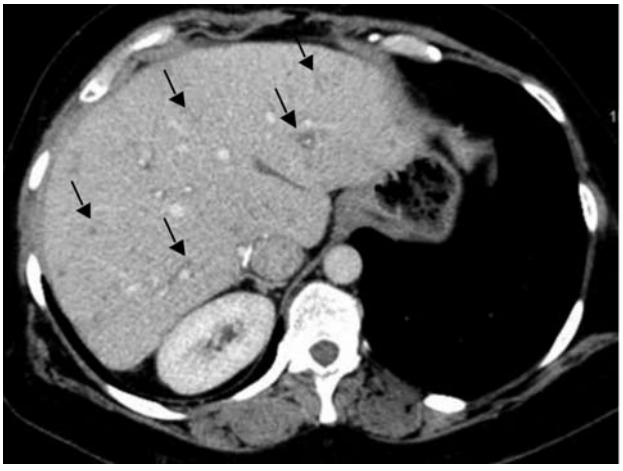

Figure 4. Injected computerized tomography scan (postoperative month 10) showing local recurrence of liver sarcoma.

Discussion

We report an atypical clinical observation, which is especially interesting in that it illustrates the difficulty in distinguishing the two forms of primary sarcoma of the liver. It also underlines the potential interest in the use of an immunosuppressive regimen with the new antiproliferative agents (mTOR inhibitors) in this very particular setting. Our report is not to promote LT for AS, based on this unusual case study, but rather to provide some ways to optimize the management of such patients. The diagnosis of primary sarcoma of the liver is made often at an advanced stage, because of its rarity and the fact that it is asymptomatic for a long time in patients with a normal nontumoral liver.[2] The diagnosis is confirmed by the pathological analysis of the tumoral tissue. Although its mesenchymal origin is assessed easily by panendothelial markers, the distinction between EHE and AS remains a delicate issue, particularly on a percutaneous liver biopsy. The main histological criteria to assess the diagnosis of EHE are nodes formed by a hyaline stroma, and particular epithelioid cells with intracytoplasmic red blood cell inclusions, and sometimes calcifications (which are not present in AS). At the edge of the nodes, sinusoids and hepatic veins are invaded by tumoral cells, but the architecture of the liver is preserved.[5] The histological characteristic of AS is the presence of atypical tumoral cells at the edge of the sinusoids, often causing vascular dilatations (cavernous type), or more rarely nodular solid tumors. In both histological forms, tumoral cells are $CD31^-$ and $CD34^+$. Hepatic AS is a rare vascular tumor ($<1/10^6$ persons) predominant in men (sex ratio, 4:1). The mean age is around 60 years.[4] The known risk factor for AS is exposure to a carcinogen such as arsenic and vinyl chloride. Metastases are found frequently at the time of the diagnosis, mainly located in the lung, spleen, and bones. The radiological characteristics of AS are not unequivocal. MRI or CT scans may show a multinodular tumor, a mass syndrome, or more rarely a diffuse infiltration of the liver.[6] The outcome of AS is very poor, regardless of the kind of therapy, with an overall mortality rate of 90% in the year of the diagnosis.[2] Some authors consider EHE as a low-grade sarcoma, more frequent among women aged 30 to 40 years. It is a particular form of sarcoma in that it has an intermediate malignant potential and a slow rate of progression.[7] The radiological examinations reveal a unique tumor, sometimes difficult to distinguish from other liver cancers.[8] In AS the panendothelial markers are positive. The gold-standard treatment is partial hepatectomy but, in a large number of the patients, a complete resection is impossible owing to the infiltrative pattern of the lesion.[7] In this very particular situation, LT can be discussed, because post-transplant survival is similar to that in other liver disease.[1,3] Our patient had several characteristics

Table 1. Comparison of the characteristics of HA and epithelioid hemangioendothelioma.

Characteristics	HA	Epithelioid hemangioendothelioma
Sex	Male	Female
Mean age	60	40
Risk factors	Carcinogenes	-
Clinical presentation	Aspecific	Aspecific
Radiological findings	Unique Multinodular Diffuse infiltration	Unique Calcifications
Anatomopathology	No calcifications Disappearance of the architecture of the acini	Preservation of the architecture of the acini
Gold-standard therapy	Symptomatic	Surgery (hepatectomy, liver transplantation)
Post-transplant outcome (two-years' survival, %)	Poor (<5%)	Good (70%)

Table 2. Review of the cases of primary sarcomas of the liver reported in the literature.

Type	Number of cases	References
Angiosarcoma	13 7	ELTR register (1) UNOS register (4)
Leiomyosarcoma	1	(18)
Epithelioid hemangioendothelioma	66 7	ELTR register (1) (7)

suggestive of EHE: gender, age, absence of toxic exposure, and a slow progression of the tumor. Nevertheless, the fact that the tumor presented as a hypervascular and multinodular lesion was less indicative of EHE, and the findings of the liver biopsy performed before LT were compatible with the diagnosis of AS. Only 16 patients who had LT for AS and 66 for EHE were recorded by the ELTR European Register between 1988 and 2001, representing 0.2% of the indications for LT.1 Some isolated case reports have been published about LT for other forms of sarcoma of the liver (Table 2). Taking into account the high risk of early locoregional recurrence of the disease after LT, we introduced everolimus at six months after LT. Everolimus is an immunosuppressive and antiproliferative agent belonging to the family of the mTOR inhibitors. This molecule has a specific cytostatic effect on tumoral cell proliferation in vivo and in vitro, and has been evaluated as an antioncogenic therapy.[9-15] Everolimus also has an antiangiogenic action, and is able to increase the antitumoral effect of chemotherapy.[16] Moreover, the use of mTOR inhibitors has been associated with a significant decrease in the risk of developing de novo cancers after renal transplantation.[17] These findings promoted an interest in using everolimus after LT in our patient in order to delay or decrease the recurrence of AS. A local recurrence occurred at month 10 but, after more than two years of follow-up, the outcome for our patient is better than that previously described in the literature. This unusual survival after LT for AS may be explained, at least in part, by the antitumoral properties of everolimus. Finally, primary sarcomas of the liver are very rare tumors. EHE is an exceptional indication for LT, although AS is a widely recognized contraindication. The belief of mTOR inhibitors having antiproliferative and antiangiogenic properties needs to be determined in those cases of misdiagnosed AS in order to delay or slow down the recurrence of the sarcoma.

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