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 of AS.

Introduction

Primary sarcomas of the liver are rare tumors (approximately 1% of liver cancers) and an exceptional indication for liver transplantation (LT). The two main histological forms are epithelioid hemangioendothelioma (EHE) and angiosarcoma (AS). 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 indicat-
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 Tacrolimus and prednisone were decreased, then withdrawn in July 2006, and changed to everolimus (3 mg/day). Residual concentrations ranged from 10-14 µg/L. Mycophenolate mofetyl was withdrawn in October 2006.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 monotheraphy 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.

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.3 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 (<1/106 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.5 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.3 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.9 In this very particular situation, LT can be discussed, because post-transplant survival is similar to that in other liver disease.10 Our patient had several characteristics
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 transplantation in the European Union. Liver transplantation is a very rare indication for LT, although AS 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.

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                         | Unique                          |
|                        | Multinodular                   | Diffuse infiltration            |
| Anatomopathology        | No calcifications              | Disappearance of the architecture of the acini |
| Gold-standard therapy   | Symptomatic                    | Surgery (hepatectomy, liver transplantation) |
| Post-transplant outcome | Poor (<5%)                     | Good (70%)                      |
| (two-years’ survival, %)|                                |                                 |

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

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

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