LETTER TO THE EDITOR

Hepatic veno-occlusive disease after liver transplantation: an unusual case report

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A 20-year-old female was submitted to liver transplantation because of type I autoimmune cirrhosis. She had triple immunosuppression (cyclosporine, prednisolone, azathioprine) for 10 days, when an episode of acute corticoresistant cellular rejection developed and was treated with tacrolimus. After 2 years of clinical stability, on tacrolimus and low dose prednisolone, the patient presented with adinamia, anorexia, painful hepatomegaly and ascitis with a serum-ascitis albumin gradient above 1.1 g/dl and high protein content (2.6 g/dl). Blood tests were normal except for normocytic and normochromic anemia (Hb 10.1 g/dl) and high bilirubinemia (1,9 mg/dl). A thoraco-abdominal-pelvic computed tomography showed pleural effusion, ascitis and homogenous hepatosplenomegaly and the coeliac arteriogram and hepatic eco doppler confirmed vascular permeability. Thrombophilia, infection and neoplasia were excluded. Hepatic veno-occlusive disease (VOD) was diagnosed by liver biopsy which revealed the typical signs of this entity: congestion, edema, perivenular hemorrhage at acinar zone 3 and fibrous obliteration of centrilobular veins by connective tissue (Fig. 1).

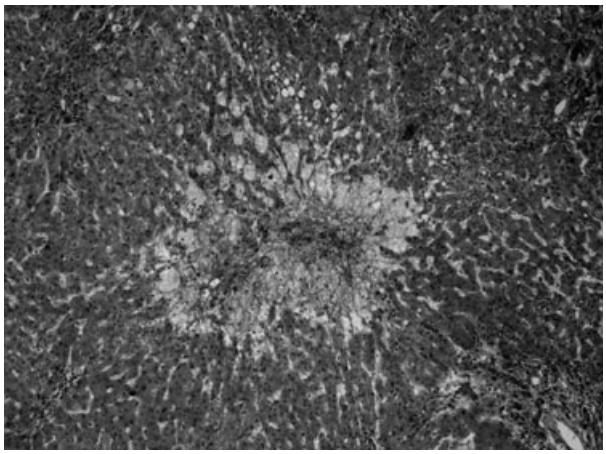

Figure 1 Fibrous obliteration of centrilobular veins by connective tissue (CAB, 100×).

The above deterioration, not responsive to medical therapy, required a liver re-transplantation, without major complications, except for a mild episode of acute cellular rejection. She remained asymptomatic for 3 years, when a recurrence of VOD, with a similar clinical picture, demanded a third liver transplantation (second re-transplant) which was successful.

Presently, at 30 years old (5 years after the third liver transplant), biliar stenosis was diagnosed and surgically corrected. A liver biopsy performed during surgery showed signs of auto-immune hepatitis and distortion of liver architecture by the presence of porto-portal septs.

The authors are reporting this case because of the rarity of VOD after liver transplantation and also discuss potential predisposing factors and therapeutic options. VOD is a very rare disorder, with a unique etiopathogenesis related to endothelial toxicity leading to fibrotic obliteration of the hepatic centrilobular veins with congestion and hemorrhage of the acinar zone 3 [1–3]. It was initially described in Jamaican consumers of herbal infusions of *Senecio* and *Crotalaria*, containing pyrrolizidine derived alkaloids [4,5]. Presently, VOD has been found most commonly after bone marrow transplantation with aggressive pretransplant chemotherapy and irradiation regimens [2,6], but additional causes have been described, such as treatment with azathioprine, mainly in renal transplants [7] but also in other diseases.

In liver transplant, VOD is a rare finding [8] and its occurrence has been related either with post-transplant azathioprine treatment or acute cellular rejection [9], both being present in this case. In the largest published series [10], the prevalence of VOD after liver transplantation was 1.9% (19 of 1023 patients). All had been on azathioprine and 89% had previous episodes of acute cellular rejection. Although the pathogenesis of the disease remains unknown, both the use of azathioprine and episodes of acute cellular rejection seem to act as co-factors.

The prognosis depends on the severity of the initial presentation, and the disease can either be reversible or severe with multiorgan failure and death, regardless of treatment. In marrow transplantation more than 50% of the cases have a benign evolution [3,6]. In severe cases, not responsive to medical therapy with drugs like recombinant tecidular plasminogen activator or defibrotide

[11], the transjugular intrahepatic portosystemic shunt has been used with clinical improvement, but with little effect on survival [12]. Liver transplantation is the last resource and may be the only alternative, although with contradictory results [13]. In a previous study [10], 58% of the patients (11/19) were re-transplanted but only three survived. None of these re-transplants was diagnosed with a recurrence of VOD, making our case an extremely rare situation, with only one previous report in the literature [14].

Authorship

A.M. and E.M. wrote the paper. A.C. was responsible for the histopathologic analysis. A.F., J.V., A.M., I.C., A.M. and E.B. contributed to the reviewing of the paper.

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