Case Report

Veno-occlusive disease of the liver in renal transplant patients

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Introduction

Veno-occlusive disease (VOD) of the liver is characterized by histological findings which include fibrous obliteration of the small hepatic veins by connective tissue and centrilobular necrosis [1]. VOD is a classic complication of chemo-irradiation therapy prior to bone marrow transplantation [2] and is also thought to be related to azathioprine therapy after kidney transplantation [3]. VOD is characterized by jaundice, painful hepatomegaly and ascites. Elevated serum bilirubin and alkaline phosphatase levels are the most sensitive indicators of early VOD [3].

Tacrolimus (FK 506) is a potent immunosuppressive agent that has proved useful in improving the survival of transplanted organs. Among the numerous adverse effects of tacrolimus (neurotoxicity, insulin-dependent diabetes mellitus, nephrotoxicity, gastrointestinal toxicity, hepatotoxicity, cardiomyopathy, etc.), thrombotic microangiopathy (TMA) stands out as an infrequent but severe complication. The incidence of FK 506-associated TMA is between 1 and 4.7% [4]. Valaciclovir is an aciclovir prodrug used to treat infections caused by herpes simplex virus, varicella zoster virus and for prophylaxis against cytomegalovirus, especially in transplanted patients. The use of valaciclovir may be associated with gastrointestinal complaints and headache; TMA has also been reported in immunocompromised patients receiving high-dose prophylactic valaciclovir therapy [5]. Despite a 2–5% incidence of VOD previously reported in kidney recipients and related to azathioprine therapy [6], we only observed one case of biopsy-proven VOD under azathioprine up to 2000 among the 1000 liver biopsies we performed in kidney recipients at Hôpital Necker. Over the past 24 months, we have seen three cases of VOD, occurring as a complication of renal transplantation: this clear increase in the incidence of VOD in kidney recipients raises the question of its causality, and the recent introduction of tacrolimus in the renal transplantation setting may be a cause. These three new cases are important because they are the first cases of VOD seen after renal transplantation in patients receiving tacrolimus alone or in combination with valaciclovir or azathioprine.

Cases

We report on three cases of VOD of the liver occurring in renal transplant patients receiving tacrolimus as immunosuppressive therapy. In each case, VOD appeared a few weeks after renal transplantation and was histologically proven. One male (case 1) and two female (cases 2 and 3) patients were affected, with respective ages of 36, 44 and 64 years.

The course of these three cases was very similar, the renal disease being malformative uropathy. Only one patient (case 3) was positive for chronic viral infection [hepatitis C virus (HCV)] at the time of transplantation, with moderate activity and fibrosis on the liver biopsy (Knodell score 0.1.1.1). Patient 1 was undergoing renal transplantation for the first time, patient 2 for the second time and patient 3 for the third time.

In cases 1 and 3, immunosuppressive therapy consisted of induction with antithymocyte globulin, combined with steroids and azathioprine. Tacrolimus was introduced at day 10 post-transplantation in...
cases 1 and 3, but was started immediately in case 2, combined with corticosteroids and mycophenolate mofetil, but without azathioprine. Continuous, long-term anti-infectious therapy with valaciclovir and sulfamethoxazole-thrimethoprim was initiated at day 2 post-transplantation in all three patients.

All patients were discharged within a month of transplantation, with creatinine levels <150 μmol/l. In case 1, an episode of acute graft rejection on day 12 was controlled with three bolus injections of methylprednisolone and polyvalent immunoglobulins.

In all three cases, liver disease started during the first 3 months post-transplantation (at 90, 33 and 63 days, respectively) with the onset of cholestasis (alkaline phosphatase 350, 495 and 150 IU/l, respectively for an upper normal value (UNV) of 135 IU/l, and γ-glutamyl transferase 390, 450 and 300 IU/l, respectively, for a UNV of 45 IU/l for men and 30 IU/l for women), mild cytolysis (alanine aminotransferase 65 IU/L for a UNV of 45 IU/l and aspartate aminotransferase 90 IU/l for a UNV of 65 IU/l in all three cases) and hyperbilirubinaemia (34, 26 and 72 μmol/l, respectively, for a UNV of 17 μmol/l) (see case 3 in Figure 1). Only one patient (case 3) experienced clinical symptoms, which included abdominal pain, jaundice, fluid retention and ascites; the other two patients were clinically asymptomatic. HCV antibodies and HCV RNA detected using polymerase chain reaction remained negative in cases 1 and 2. Serum HBV DNA and HBs antigen were negative in all three cases. There were no other reasons for liver disease such as toxic exposure or viral infection, except in case 3, or autoimmune (anti-nuclear, anti-smooth muscle, anti-mitochondria and anti-liver kidney microsome 1 antibodies) and metabolic (iron, copper) disturbances. Signs of TMA were present in only one case (case 1): these included thrombocytopenia, haemolytic anaemia and elevated serum creatinine levels. The assay of tacrolimus levels revealed overdose (ranging from 15 to 25 ng/l, the UNV being 15 ng/l) prior to the occurrence of liver abnormalities in all three cases. Hepatobiliary ultrasonographic findings were normal. Given the persistence of biological abnormalities, including hyperbilirubinaemia, a liver biopsy was performed (8, 5 and 3.5 months post-transplantation, respectively) and revealed VOD with a loose proliferation of subintimal reticulin fibres, which often extended into the vessel lumen, causing total or near total vascular occlusion of the terminal hepatic venules and sublobular veins (Figure 2). Normal veins of this calibre were also seen, indicating only patchy involvement. Centrilobular sinusoidal congestion and dilatation were associated with multiple blood-filled spaces (peliosis hepatis) in cases 2 and 3. Warthin–Starry staining was negative, thus ruling out bacillary peliosis. No nodular regenerative hyperplasia or bile ductule proliferation was observed. In case 3, liver biopsy revealed mild additional lesions of viral hepatitis.

No specific treatment was initiated, except the withdrawal of azathioprine in cases 1 and 3 and of tacrolimus and valaciclovir in all three cases (Table 1). In cases 1 and 2, hyperbilirubinaemia disappeared within 2 months of the onset of VOD, and γ-glutamyl transferase and alkaline phosphatase levels declined 24 months after VOD onset. In case 3, ascites and abdominal pain disappeared 1 month after VOD, hyperbilirubinaemia 2 months after VOD, and alkaline phosphatase and γ-glutamyl transferase levels had returned to normal 19 months after VOD. In case 2, a liver biopsy was performed 14 months after

![Fig. 1. Serum levels of γ-glutamyl transferase, alkaline phosphatase and bilirubinaemia over time in case 3.](image-url)
the diagnosis of VOD to determine the presence of hepatic sarcoidosis (signs of cutaneous and pulmonary sarcoidosis); this diagnosis was confirmed, but VOD injuries had disappeared.

Discussion

These three new cases of VOD should be added to other reports of this disorder described in kidney recipients [3,6].

Clinically, VOD is a disease characterized by jaundice, painful hepatomegaly and ascites. Most transplant teams worldwide apply the clinical criteria which were proposed by two different groups, one in Seattle, WA and one in Baltimore, MD [7]. Liver biopsy revealed VOD defined by a concentric narrowing or fibrous obliteration of terminal hepatic venules and sublobular veins, dilatation and, ultimately, fibrosis of the centrilobular sinusoids and necrosis of the centrilobular hepatocytes [1]. The earliest change observed during VOD is subendothelial oedema, with red blood cells, fragments and haemosiderin-laden macrophages found in subendothelial zones of affected venules, along with congestion of sinusoids and hepatocyte necrosis.

The standard Baltimore and Seattle clinical criteria [7] for the diagnosis of VOD were not found in our three patients: two of them experienced no clinical symptoms of VOD and the other had symptoms but they did not appear within 30 days of transplantation but rather 63 days after the procedure, suggesting that VOD in renal recipients differs from that seen following bone marrow transplantation. Liver biopsies were performed because cholestasis was unexplained in all three cases, and the diagnosis of VOD was proved from the histological findings. Thus clinical criteria alone are insufficient in kidney recipients for recognizing or excluding VOD.

It is often difficult to ascertain the presence of drug-related hepatitis in kidney recipients: the chronological causal criteria are present, but semiological criteria are lacking because liver disease may occur for numerous reasons (a virus or drugs), and the reversibility of hepatic vascular injuries after drug discontinuation is

<table>
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<tr>
<th>Treatment withdrawal (days after renal transplantation)</th>
<th>Tacrolimus</th>
<th>Azathioprine</th>
<th>Valacyclovir</th>
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</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>193</td>
<td>139</td>
<td>93</td>
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<tr>
<td>Case 2</td>
<td>145</td>
<td>92</td>
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<tr>
<td>Case 3</td>
<td>210</td>
<td>84</td>
<td>53</td>
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unusual, progression towards nodular regenerative hyperplasia always being possible.

Although the pathogenesis of VOD remains incompletely understood, clinical and pathological findings support the idea that damage to the sinusoidal endothelium is at least a major contributor to its development. Such endothelial injury triggers the coagulation cascade by lowering levels of natural anticoagulants (proteins C and S, antithrombin III) and raising those of procoagulants (factor VIII, fibrinogen and von Willebrand factor) [8]. This results in thrombosis of the hepatic venules and ultimately in their fibrous obliteration. It seems likely that a range of factors contribute to initial endothelial lesions in a given patient. In a setting of bone marrow transplantation, the physical effects of radiation and the toxic effects of multiple chemotherapy may play a role [2]. In addition, some data have suggested a potential role for viral agents in the pathogenesis of VOD. Indeed, Mc Donald et al. [2] found an incidence of viral hepatitis prior to bone marrow transplantation that was three times higher in patients who subsequently developed VOD than in those who did not; the five patients described by Liano et al. [6] also displayed evidence of contact with HBV or HCV prior to the development of VOD. In the case of VOD occurring after kidney transplantation, the use of azathioprine has been put forward as one of the potential causes. This causal relationship was suggested in one case [3] by the improvement seen in VOD after the discontinuation of azathioprine and its recurrence after rechallenge.

In our patients, it was difficult to ascertain any causal relationship between VOD and tacrolimus because they also received other drugs (azathioprine in two cases and valaciclovir in all three cases), which subsequently were withdrawn. However, tacrolimus seems to be the principal candidate because: (i) the increased incidence of VOD in our unit over the past 2 years has been associated with the use of tacrolimus; indeed, when compared with the rate of <1 in 1000 cases prior to the tacrolimus era, the incidence of VOD now reaches ~1.9% amongst kidney recipients treated with tacrolimus (3/160); (ii) the three patients all exhibited signs of overdose; and (iii) after the withdrawal of tacrolimus, the liver abnormalities either disappeared (one case) or regressed (two cases).

The association of VOD with tacrolimus therapy raises the question of its vascular toxicity, which was strongly suggested by the onset of VOD at the time of the tacrolimus overdose. We cannot exclude a combined toxicity of tacrolimus and valaciclovir: all three patients were given the two drugs, which share the same mechanisms of toxicity, inducing thrombotic microangiopathy [4,5]. TMA was recognized in at least one patient who displayed its biological signs (elevated serum creatinine levels, haemolytic anaemia and thrombocytopenia). VOD and TMA display a similar pathogenesis, but different agents may be implicated [8]. We therefore hypothesize that tacrolimus, either alone or used in combination with valaciclovir, may be involved in endothelial toxicity in the liver, which results in VOD.

In two patients, the role of the combined administration of azathioprine and tacrolimus in the development of VOD could not be ruled out [3,6]. However, the histological features commonly attributed to azathioprine vascular (peliosis, nodular regenerative hyperplasia) and hepatocyte hepatotoxicity (hepatitis) [9,10] are frequent, whereas the diagnosis of VOD remains rare. In our experience, we have observed only one case of azathioprine-related VOD in >1500 kidney recipients (unpublished data) in the past 35 years. For this reason, the appearance of three VOD cases in a few months led us to seek another causal factor.

In one patient (case 3), hepatitis C infection was associated with a very mild hepatitis which may explain mild cytolysis, but not cholestasis and hyperbilirubinaemia.

In summary, tacrolimus (especially in the event of an overdose), alone or in combination with valaciclovir, azathioprine or viral hepatitis, may give rise to VOD. It is therefore necessary to monitor tacrolimus levels and liver parameters throughout treatment. In the event of clinical or biochemical abnormalities, a liver biopsy should be performed for the diagnosis of VOD, and tacrolimus should be withdrawn.

References


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