Hepatitis-B-virus-related fibrosing cholestatic hepatitis after renal transplantation with acute graft failure following interferon-α therapy

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Introduction

Fibrosing cholestatic hepatitis (FCH) is a rare and extremely severe pattern of hepatitis B virus (HBV) infection. This clinicopathological entity appears in immunosuppressed patients, either due to HIV infection [1] or transplantation [2–9], and is characterized by a cholestatic pattern of serum liver enzyme abnormalities, a course to liver failure in the short term, and a pathological picture defined by periporal and perisinusoidal fibrosis, mixed infiltrates, and signs of histological cholestasis [2]. Although its pathogenesis is not completely understood, it has been suggested that it may be induced by a direct viral cytopathic effect [3,5,7]. Furthermore it seems that mutant strains of HBV increase the risk of developing FCH [7]. There is scarce information regarding its response to therapy.

On the other hand, interferon-α (IFN-α) is currently widely used for the treatment of chronic active hepatitis (CAH) due to HBV and hepatitis C virus (HCV). This therapy has also been used in transplant recipients with irregular results. In fact, several reports have linked IFN-α administration to acute rejection and/or nephrotoxicity in this setting [10–13]. We report a renal transplant patient with FCH who developed acute graft failure after IFN-α therapy.

Case report

A 44-year-old male with chronic renal failure of unknown origin on haemodialysis for 10 months was admitted to our renal transplant unit for kidney transplantation. He was seropositive for hepatitis B virus surface antigen, as well as anti-HBc and anti-HBe antibodies. He was seronegative for HBeAg, anti-HCV antibody (ELISA 2) and cytomegalovirus (CMV). Serum hepatitis B virus DNA determined by PCR was negative. His pretransplant liver function was normal. Renal transplantation was successfully performed and immunosuppression based upon cyclosporin (10 mg/kg/day) and steroids (0.5 mg/kg/day) was initiated. He was included in an ongoing protocol to study the effects of fish-derived fatty acids on graft function and cyclosporin toxicity.

At discharge, 8 days after transplantation, the patient’s serum creatinine was 2.3 mg/dl, and the aminotransferase levels were in the normal range. In spite of receiving ganciclovir plus γ-globulin as prophylaxis for CMV infection, he was admitted at the hospital 2 months later because of CMV pneumonitis that responded well to a full therapeutic course of ganciclovir (5 mg/kg/12 h) and γ-globulin.

Three months later, he began to show slowly increasing liver serum enzyme values characterized by higher gammaglutamyl transpeptidase (GGT) than aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Liver echography was unrevealing. One month later, he referred slight dyspepsia and malaise. Cyclosporin was tapered and low-dose azathioprine (50 mg/day) was administered. Seven months after transplantation he presented with jaundice. Serum parameters were as follows: creatinine 2.1 mg/dl, AST 304 IU/ml (normal range 5–40), ALT 287 IU/ml (normal range 5–40), GGT 968 IU/ml (normal range 10–40), alkaline phosphatase 356 IU/ml (normal range 98–295), bilirubin 13.3 mg/dl (normal range 0.2–1.2). At this time, serum hepatitis B virus DNA determined by PCR was positive. However, the patient remained anti-HBe antibody positive and HBeAg negative, suggesting the presence of a viral precore mutant.

A liver biopsy was performed, revealing a disarray of hepatic architecture caused by fibrosis and necrosis. There was prominent periporal and moderate diffuse pericellular fibrosis (Figure 1). Portal tracts showed inflammatory lymphocytic and neutrophilic infiltrates spreading widely through the parenchyma. Ductular
proliferation was frequent at the periportal interfaces. Severe piecemeal necrosis and mild perivenous confluent necrosis were seen (Figure 2). Most hepatocytes exhibited a ground-glass and/or a 'feathery' cytoplasm and some others acidophilic degeneration. Immunohistochemically, diffuse cytoplasmic HBsAg was positive in almost 80% of liver cells (Figure 3). HBcAg was expressed in the cytoplasm and/or the nuclei of 60% of hepatocytes (Figure 4). A diagnosis of FCH was raised. Azathioprine was immediately withdrawn and IFN-α therapy (5 000 000 U s.c. thrice weekly) was initiated. Therapy was well tolerated in spite of some influenza-like syndrome, and resulted in clinical and analytical improvement (bilirubin 3.1 mg/dl, AST 186 IU/ml, ALT 129 IU/ml, GGT 768 IU/ml). Two weeks later he showed an acute deterioration of renal function (serum creatinine raised from 2.3 to 6.4 mg/dl). An ultrasound evaluation ruled out obstructive uropathy, and an empirical diagnosis of IFN-α-induced acute renal failure was suggested. The patient was unresponsive to high-dose steroids and 1 month later he re-initiated haemodialysis. Immunosuppressive therapy was stopped and IFN-α therapy was maintained, but subfulminant liver failure developed and the patient died 5 months after the onset of jaundice, only 1 year after transplantation.

Discussion

FCH was initially described in HBV-infected liver-allograft recipients as a new clinicopathological entity of ominous outcome [2]. Soon it was also reported in a patient with AIDS [1]. To our knowledge, only four cases after renal transplantation have been previously reported [6,8,9]. Therefore, it seems that immunosuppression is crucial in the development of this new entity that is clinically characterized by cholestasis, a mild to modest increase of serum aminotransferase levels, and a course to liver failure in the short term. The histological diagnosis is made by documenting severe periportal and perisinusoidal fibrosis, as well as cholestasis and ballooning, feathery, and ground-glass transformation of the hepatocytes. Inflammation is mild and mixed, lobular and portal. Precisely, the scarce inflammatory infiltrate and the increased viral burden that characterizes FCH may suggest that a direct viral cytopathic effect could induce this particular pattern of liver injury [2,3,5,7]. Moreover, significantly
enhanced HBV transcription has been demonstrated by DNA hybridization in biopsy specimens showing FCH, thus supporting this hypothesis [5]. Furthermore, great concern has recently been expressed on the role that several mutant forms of HBV could play in the development of FCH. Fang et al. were the first group to show that HBV precore mutants lacking HBeAg expression could induce FCH [4]. Also, the first reported case after kidney transplantation was caused by a precore mutant [6]. Indeed, Angus et al. have recently demonstrated that the risk of developing FCH after liver transplantation is significantly higher in HBV infected patients with a substantial population of precore mutant strains [7]. Our case, lacking HBeAg expression but showing anti-HBe antibodies and viral DNA by PCR after transplantation, seems likely to be another example of this condition. Along these lines, the special predisposition of precore mutant strains to cause this disease of massive viral replication with limited immune response could be explained by the lack of HBeAg that enables the virus to escape immune recognition.

The immunosuppressive protocol has also been studied as a risk factor for FCH. Besides their immunosuppressive effects, steroids seem to increase HBV transcription by binding the glucocorticoid-responsive element on HBV DNA, inducing an appreciable increase on intrahepatic HBV antigen expression in vitro [14]. Also, cyclosporin has been shown to increase serum HBV in experimental models [15]. Interestingly, azathioprine hepatotoxicity shares several pathological characteristics with FCH, suggesting a potential role of this drug in its pathogenesis [16]. Unfortunately, it seems that once the injury is established, immunosuppression withdrawal does not modify the clinical course of the disease [9].

The reported experience regarding therapy of FCH is scarce. One of the potentially useful drugs is IFN-α, as it has been successfully administered in the treatment of HBV and HCV-related CAH. However, its use in transplant recipients remains controversial. Our patient received a course of 5000000 U thrice weekly with initial response. Nevertheless, this therapy did not modify the course to liver failure and could account for the steroid-resistant acute allograft failure that followed therapy. Several reports link IFN-α to the induction of acute and/or chronic rejection [10,12,13]. Also, IFN-α administration has been related to the development of tubulointerstitial oedema, expansion of peritubular capillaries and diffuse tubular flattening in renal allografts. These lesions, although not fulfilling Banff criteria for acute rejection, also conditioned acute graft loss, and may represent some kind of nephrotoxicity [11]. Therefore the utility of this drug in this setting seems to be limited. New approaches to therapy include nucleoside analogues that inhibit viral replication. Among them, lamivudine administration has recently provided promising results in patients with FCH after liver transplantation [17].

In conclusion, FCH is an extremely severe potential complication of renal transplantation in HBV-infected patients. As the risk for this entity seems to be enhanced in those patients infected by precore mutant strains, the indication of transplantation in this particular group of patients should be carefully evaluated. IFN-α seems not to modify the course of this disease and may potentially induce acute graft dysfunction.

References
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