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Fibrosing cholestatic hepatitis in renal transplant recipient with CMV infection: A case report

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Abstract. Fibrosing cholestatic hepatitis (FCH) is an uncommon complication of renal transplantation. It is usually associated with hepatitis B and C viral infection. It is further rare in renal transplantation in absence of HBV and HCV infection. To the best of our knowledge, only three cases of FCH in renal transplantation, which were both HBV and HCV negative, have been reported to date. Out of these, two cases were diagnosed to have CMV infection and the third was attributed to azathioprin. We are presenting another case of FCH in a renal transplant recipient with CMV infection.

Key words: CMV infection, Fibrosing cholestatic hepatitis, Renal transplant

Introduction

Fibrosing cholestatic hepatitis (FCH) is a well-known entity in immunocompromised patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Patients characteristically presents with cholestasis and only mild to moderate elevation of aminotransferases. Histologically it is characterized by periportal and perisinusoidal fibrosis, minimal inflammation, ballooning of hepatocyte and histological cholestasis. Initially described in a liver transplant recipient with recurrence of HBV [1] and HCV [2], FCH is now also described as an uncommon complication of renal transplantation (RT) [3–7]. It is further rare in RT patient in absence of HBV and HCV infection. To the best of our knowledge, only three cases of FCH in RT recipients who were both HBV and HCV negative have been reported to date [8, 9]. Out of these, two cases were diagnosed to have CMV infection and the third was attributed to azathioprin. Shan et al. [10] attributed a case of FCH to parvovirus B19 infection but the patient was also having HBV infection. We report another case of HBV and HCV negative FCH in a renal transplant recipient.

Case report

A 26-year-old nonalcoholic man with end stage renal disease underwent live related renal transplant with the brother being the donor in June 2001. His basic disease was presumed chronic glomerulonephritis for which he received haemodialysis through AV fistula for 6 months prior to RT and did not receive any blood transfusion during maintenance haemodialysis. During pretransplant period and at the time of transplant his liver functions were normal and he was negative for both HBsAg and anti-HCV antibody, which as a policy we screen every month while patient is on dialysis. Both donor and the recipient were positive for IgG CMV and negative for IgM CMV. He received standard triple drug immunosuppression comprising cyclosporine, azathioprin and steroids at the time of transplant and had an uneventful immediate postrenal transplant period. In July 2002, he had an asymptomatic increase in serum creatinine to 2.2 mg% from the baseline serum creatinine of 1.2 mg% and graft biopsy done revealed acute rejection (Banff grade 1). He was treated with methyl prednisolone pulses to which he responded and his serum creatinine settled to 1.2 mg%.

In May 2003, he presented with yellowish discoloration of eyes and urine with decreased appetite for 1 week prior to admission. On examination he was afebrile, icteric, and had 2 cm nontender hepatomegaly with smooth surface and regular margins. There was no ascites clinically. His investigations revealed haemoglobin 12.5 gm%; total leucocyte count (TLC) 7600/mm^3 with normal differential count; serum creatinine 1.2 mg%; total bilirubin 10.1 mg% (N – 0.8–1.0) with direct bilirubin of 7.6 mg%; AST 120 IU (N: upto 50 IU); ALT 104 IU (N: upto 50 IU); alkaline phosphatase (ALP) 176 IU (N: 80–280 IU); HBsAg negative; anti-HCV negative; IgM HAV negative; IgM HEV negative; IgM HBcAg negative; HBeAg negative; PCR HCV negative. USG abdomen showed hepatomegaly, cholelithiasis without obstruction of the biliary tract and mild ascites. There was no evidence of portal vein hypertension. Azathioprin was stopped at admission and he was continued on 3 mg/kg of cyclosporine and 7.5 mg of prednisolone. During the next seven days he developed clinical ascites with associated pain in abdomen and his total bilirubin increased to 22.1 mg% with direct bilirubin of 17.6 mg%. His other investigations revealed AST 117 IU; ALT 108 IU; ALP 166 IU and mild increase in serum creatinine to 1.9 mg%. Ascitic fluid examination revealed WBC of 240/ml with predominant polymorphs; glucose nil and proteins 2.4 gm%; SAAG < 1.1. His cyclosporine C2 level was 694 ng/ml. His both IgM and PCR for CMV came positive. He was started on injection gancyclovir and IV antibiotics for bacterial peritonitis. Over the next 3 weeks his total bilirubin dropped to 5.5 mg%; AST 68 IU; ALT 46 IU; ALP 145 IU; and his serum creatinine decreased to 1.3 mg%. However, patient could not continue therapy further because of financial constraints. After the incomplete treatment his bilirubin increased to 26.5 mg% with AST of 172 IU; ALT 128 IU over next 2 weeks. At this stage he underwent liver biopsy (Figure 1), which showed marked bile ductular proliferation, chronic inflammation and fibrosis, with focal areas of spotty necrosis. Hepatocytes showed focal ballooning along with intracellular cholestasis. Immunohistochemistry for HBsAg and HBcAg were negative. These features were compatible with the diagnosis of FCH. The patient's general condition deteriorated and he died after 10 days.

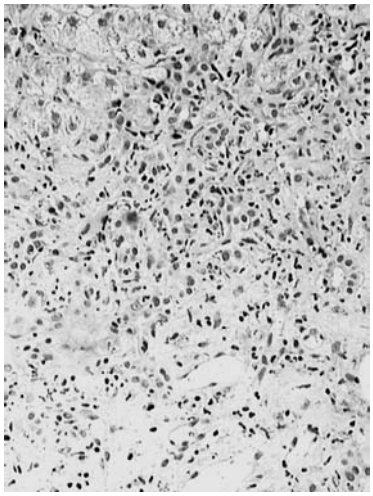

Figure 1. The photomicrograph shows portal tract with marked bile ductular proliferation, chronic inflammation and spotty necrosis with ballooning degeneration (H & E ×800).

Discussion

FCH is a rapidly progressive form of hepatitis that occurs in the presence of significant immunosuppression. HBV and HCV have been attributed to FCH in renal transplant recipients. The clinical course is characterized by rapid progression to liver failure and death. The microscopic appearance is characterized by periportal fibrosis, cell ballooning, cholestasis and a relatively scant inflammatory infiltrate [1, 11]. This type of liver injury in patients with hepatotropic viral infection (HBV or HCV) is directly related to the degree of immunosuppression as the entity is not seen in immunocompetent patients with chronic hepatitis B or C. FCH has been postulated to result from a direct cytopathic effect of HBV or HCV on hepatocytes associated with immunosuppression [1, 12–14].

Bustillo et al. [8] reported two patients with pathological picture suggestive of FCH syndrome, who were negative for both HBV and HCV, suggesting the involvement of other hepatotropic viral agents in the development of this form of liver disease. They isolated CMV in one patient and in the other patient azathioprin were implicated as the culprit. In another report by Duseja et al. [9], the patient presented with obstructive jaundice due to stricture at the lower end of the common bile duct. Jaundice persisted inspite of effective biliary drainage and later CMV was isolated from the

wall of the gall bladder following surgery for empyema. Our patient died and at autopsy liver biopsy showed features suggestive of FCH. A causal relationship between CMV infection and FCH like syndrome may be possible in patients negative for both HBV and HCV infection. CMV has also been proposed to enhance the azathioprin related hepatotoxicity [15]. Most of the patients reported with FCH were on azathioprin and the potential role of azathioprin in the development of FCH has been suggested in the past [16]. However, progression of azathioprin related liver disease after discontinuation of the drug has been reported earlier [17, 18].

The poor outcome of FCH is well known and the two previously reported cases and the present one with CMV related FCH had fatal outcome. Though our patient showed response to gancyclovir therapy, he could not continue therapy because of his poor financial status. How effective can gancyclovir be in treating patients with CMV related FCH is unclear as of now as the number of reported cases are very few. To date, the only possible therapy of these patients is decreasing the immunosuppression. Thus, an early biopsy is indicated for the diagnosis and further management of these patients.

In conclusion, FCH-like syndrome is one of the fatal complications of renal transplant recipients, even in the absence of both HBV and HCV infection, suggesting other causative agents of which CMV infection may be one of the possible aetiology.

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