Case Report

Fatal hepatitis B virus infection with fibrosing cholestatic hepatitis following renal transplantation

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Key words: cholestatic; diagnosis; fibrosing; hepatitis B; immunosuppression; recurrence; renal transplantation; vaccination

Introduction

Renal transplant recipients with chronic HBV infection may have progression of HBV associated liver disease following transplantation.

This progressive hepatitis may take a number of forms. The most fulminant form appears to be that of fibrosing cholestatic hepatitis (FCH). FCH is a unique and often rapidly fatal form of progressive liver disease due to HBV that occurs only in the immunosuppressed patient. Initially described in liver transplant recipients with recurrence of HBV [1], FCH has now been described as a rare complication of renal transplantation [2–4].

This rare complication of HBV following transplantation highlights the risks of renal transplantation in patients with active HBV disease, which may well be a contraindication to transplantation. HBsAg-positive patients require careful assessment before transplantation, with close monitoring for the emergence of progressive HBV infection should transplantation be performed.

Case report

A 37-year-old woman with end-stage renal failure due to chronic glomerulonephritis underwent cadaveric renal transplantation in September 1995. She had been on haemodialysis for a period of 13 years. Prior to transplantation she had positive serology for HBsAg, hepatitis B ‘e’ antigen (HBeAg) and hepatitis B ‘e’ antibody (HBeAb). At the time of transplantation her serum bilirubin and liver transaminase levels were normal and she had undetectable levels of HBV DNA. Both the recipient and donor were seropositive for cytomegalovirus (CMV) antibody, suggesting past exposure.

After transplantation the patient received maintenance immunosuppression with prednisone 30 mg daily, azathioprine 100 mg daily, and cyclosporin 8 mg/kg/day. For the first 3 days post-transplantation she received tapered daily intravenous methylprednisone at a dose of 1000 mg, 500 mg and 100 mg sequentially.

Isoniazid prophylaxis (300 mg daily) was given because of a history of inguinal tuberculous lymphadenitis diagnosed and treated 6 years previously with 12 months of supervised combination therapy.

Eight weeks after transplantation the patient was admitted with deteriorating renal function. She was treated initially for rejection with two daily boluses of intravenous methylprednisone (1000 mg). Graft biopsy function tests at that time suggested mild cholestasis (Table 1). Liver function tests at that time suggested mild cholestasis (Table 1). Sixteen weeks after transplantation the patient was jaundiced with biochemical signs of progressive cholestasis (Table 1). Abdominal ultrasonography revealed normal architecture of the liver and biliary tree. Both isoniazid and azathioprine were stopped without benefit. Serological tests for hepatitis A (IgM, IgG), hepatitis C, and hepatitis D were negative, however a viral culture of plasma with immunofluorescence revealed CMV viraemia. She received a 3-week course of intravenous ganciclovir with documented clearance of CMV viraemia but without discernible effect on her progressive cholestatic hepatitis.

Over a 6-week period the patient deteriorated clinically, with progressive cholestasis and the development of hepatocellular failure. Her biliary anatomy was further defined with endoscopic retrograde cholangiopancreatography (ERCP), which revealed normal anatomy of both intrahepatic and extrahepatic ducts. At this stage repeat serology for HBV revealed a substantially elevated titre of HBV DNA (800 fmol/l).

The patient’s clinical condition continued to deteriorate and a percutaneous liver biopsy was performed.
The patient died three days after liver biopsy with advanced liver failure. Permission for postmortem examination was refused.

Histological examination of the liver biopsy revealed micronodular cirrhosis, ductular cholestasis and ballooning degeneration of hepatocytes with ground-glass intracytoplasmic inclusions. Minimal inflammation was present. Immunoperoxidase staining was strongly positive within hepatocytes for HBsAg and hepatitis B core antigen (HBcAg), but negative for CMV. The biopsy findings were consistent with previous reports of fibrosing cholestatic hepatitis.

### Discussion

FCH is a rapidly progressive form of hepatitis B infection that occurs only in the presence of significant immunosuppression. Its development imparts a poor prognosis, with death occurring in the first year following its development in the majority of patients [5,6]. The fact that it is a recently recognized condition may be a reflection of changes in the type and degree of immunosuppressive therapy now employed to prevent rejection. It has a different pathogenesis from chronic hepatitis in the immunocompetent patient, with hepatic injury probably mediated through the accumulation of large amounts of HBV particles [5]. This is in contrast to chronic hepatitis in normal individuals, in whom hepatic injury is the result of immune activity. This difference may account for the unusual clinical features of FCH, in particular the prominence of cholestasis.

The possibility of fatal HBV disease after renal transplantation necessitates a clear approach to the prevention and screening of HBV disease in the dialysis population. Vaccination of dialysis patients is routine in many centres, and in association with isolation of HBV carriers and reduced exposure to blood products has had a noticeable impact on the number of dialysis patients acquiring HBV [7]. Patients who are carriers of HBsAg should be evaluated with a liver biopsy if they are transplant candidates. A good case can be made to exclude patients with chronic active hepatitis or those with serum markers of active replication (HBVDNA, HBeAg) from transplantation, as these serum markers may predict a higher risk of fatal liver disease [8].

Patients with inactive HBV disease who receive a renal transplant require close monitoring for disease progression following transplantation. Liver biochemistry and HBVDNA levels should be closely followed in these patients, with a low threshold for performance of a liver biopsy should there be a significant change in either of these parameters.

Various treatment options for progressive HBV infection in the immunosuppressed patient have arisen from the experience of liver transplantation. Prophylactic infusions of HBV immunoglobulin as well as treatment with lamivudine appear to reduce disease activity [9]. Ganciclovir therapy has also been reported to reduce titres of HBVDNA [10] with one isolated case of prolonged survival in a case of FCH occurring in a liver-allograft recipient maintained on long-term ganciclovir [6].

Renal-transplant recipients with HBV reactivation differ from their liver-transplant counterparts. The life of liver-transplant recipients is critically dependent on function of the transplanted organ and thus the immunosuppression necessary to prevent rejection. In renal transplantation dialysis is an alternative method of replacing function of the transplant organ; therefore withdrawal of immunosuppression and loss of the graft is still compatible with life. Sudden cessation of immunosuppression in the setting of chronic viral hepatitis can result in acute liver decompensation consistent with a sudden increase in immune activity against large amounts of HBV. We are unaware of any reports of the effect of gradual reduction of immunosuppression, and it is possible that such reduction combined with antiviral therapy may allow the disease to regress to a less aggressive form.

In conclusion this case of rapidly fatal HBV infection following renal transplantation illustrates the need for a comprehensive approach toward HBsAg carriers both prior to and following transplantation, and strengthens the argument for routine HBV vaccination of all dialysis patients.

### References

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Received for publication: 1.12.97
Accepted in revised form: 18.2.98