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BRIEF REPORT

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Successful outcome of liver transplantation in a patient with hepatitis C and common variable immune deficiency

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Abstract A 43-year-old man with common variable immune deficiency underwent liver transplantation for cirrhosis caused by hepatitis C virus (HCV). HCV had been acquired from a contaminated batch of immunoglobulin. He developed cirrhosis within 3 years of infection with the virus, then liver failure requiring liver transplantation. The immediate post-transplant course was uncomplicated. Five months after transplantation he developed liver failure, and the histological appearances were those of severe cholestatic hepatitis. Withdrawal of immunosuppression resulted in recovery from liver failure. Clearance of the HCV from serum was also observed and has been sustained during follow-up (despite the subsequent reintroduction of low-dose immunosuppression). The patient is alive and well more than 5 years after transplantation. His post-transplant course has been remarkable for the aggressive recurrence then clearance of the HCV.

Keywords Common variable immune deficiency · Liver transplant · Hepatitis C virus · Fibrosing cholestatic hepatitis · Viral clearance

Introduction

Common variable immune deficiency (CVID) is the second most common primary immunodeficiency disorder and is characterised by low serum IgG and IgA levels and variable levels of IgM. In addition, one third of patients are severely lymphopenic with reduced CD4 T cells and B cells and a relative increase in CD8 T cells, changes similar to those seen in AIDS. Patients usually present in childhood with recurrent respiratory infections, although later presentation is not unusual. Regular immunoglobulin infusion is standard treatment for many patients with CVID.

Worldwide, several batches of immunoglobulin have been contaminated with the hepatitis C virus (HCV) and many immunodeficient patients have become infected [1, 2, 4]. It is recognised that the clinical course of HCV in patients with CVID may be accelerated. In the UK, four of 25patients with primary hypogammaglobulinaemia, who acquired HCV from one contaminated batch of immunoglobulin, died of liver disease within 2 years of acquisition of the virus [4]. In another series, four of six patients with HCV had died of liver disease within 10 years [1].

In many countries, HCV is now the commonest indication for liver transplantation. The outcome of patients transplanted for this indication is generally good. Five-year post-transplant survival in our own centre is 71%. Only a few cases of transplantation for HCV-related cirrhosis on a background of CVID have been reported. Thus, the clinical course after transplantation of these patients has not yet been clearly defined [1, 12]. We report on one patient and discuss related management issues.

Case report

In October 1995 a 43-year-old man with CVID and with aggressive chronic HCV infection was referred to the liver unit at the Queen Elizabeth Hospital, Birmingham. CVID had been diagnosed in

1985 on the background of multiple lower respiratory tract infections and a typical immunological profile. At first measurement (April 1986) serum IgG was 0.76 (normal 8–18 g/l), IgA was 0.02 (0.9–4.5), and IgM was 0.2 (0.6–2.8). He had been treated with immunoglobulin infusions for many years. In December 1993 he acquired HCV, genotype 1a, from a contaminated batch of immunoglobulin (Gammagard, Baxter Healthcare, batch 93F21AB11B). The course of his liver disease had been extremely aggressive, with multiple flares of hepatitis associated with jaundice and aspartate aminotransferase (AST) levels above 1,000 U/l (normal 5–43 U/l).

Treatment with interferon was initiated in November 1994. A liver biopsy 3 months after this revealed minor lobular hepatitis and cholestasis with minimal fibrosis. Liver biochemistry was persistently abnormal and HCV PCR was persistently positive during interferon therapy. In May 1995 ribavirin 600 mg twice daily was added to the interferon therapy, but viral clearance was not achieved. Liver biopsy in August 1995 revealed advanced fibrosis and a moderate inflammatory infiltrate. Anti-viral therapy was discontinued because there was evidence of progressive liver disease despite treatment.

In late 1995 the patient developed decompensated liver disease with ascites formation. At the time of referral to the liver unit, and subsequently, the patient was HIV-negative. In June 1996 liver transplantation was performed (Fig. 1). A standard triple immunosuppressive regime of cyclosporin, prednisolone and azathioprine was used. The proposed standard immunosuppressive regimen required monitoring of blood cyclosporin levels (target range 200–250 ng/ml during the early post-transplant period, subsequently lower according to blood levels and renal function), azathioprine (up to 2 mg/kg/day indefinitely) and prednisolone (starting at 20 mg/day with complete withdrawal during the first 3 months post-transplantation). Antibiotic prophylaxis included ciprofloxacin 250 mg twice daily and fluconazole 100 mg daily, until the patient was discharged from hospital. IgG level was kept greater than 6 g/l with immunoglobulin infusion. In anticipation of an aggressive graft recurrence of HCV, he was also treated with ribavirin 600 mg twice daily and interferon 1.5 million units thrice weekly. If he was tolerant of treatment, it was planned to increase the dose of interferon to 3 million units thrice weekly for 6 months, and to continue ribavirin indefinitely. On the 8th day after transplantation, liver biopsy revealed mild acute cellular rejection. This was treated for 3 days with prednisolone 200 mg daily. The patient was discharged from hospital 11 days after transplantation. In mid-July, 5 weeks after transplantation, liver biopsy was performed for persistently abnormal liver function tests [AST 100 U/l, bilirubin 67 μmol/l (normal 1–22 μmol/l), alkaline phosphatase (ALP) 375 U/l (normal 70–330 U/l)]. Histology revealed mild hepatitis consistent with recurrent HCV infection, without evidence of acute cellular rejection.

Due to persistent leukopenia, interferon and azathioprine were withdrawn 2 months after transplantation. Because of possible gastrointestinal intolerance, ribavirin was reduced then stopped 3 months post-transplantation. Liver biochemistry gradually deteriorated during the subsequent months. Immunosuppression at this stage comprised cyclosporin 100 mg twice daily. In November, 5 months after transplantation, liver biopsy was again performed and revealed a picture of severe "fibrosing" cholestatic hepatitis (FCH). Endoscopic retrograde cholangiography, performed to exclude biliary obstruction, was normal. At this stage all immunosuppression was stopped.

During the next 6 weeks the patient's liver biochemistry worsened, to peak at: AST 1,543 U/l, bilirubin 268 μmol/l, ALP 722 U/l, before gradually improving. During this period the patient developed ascites. By May 1997 the patient had improved markedly; jaundice and ascites had been resolved (AST 140 U/l, bilirubin 21 μmol/l, ALP 1,226 U/l). Repeat liver biopsy, 12 months after transplant, showed considerable improvement. There was mild inflammatory activity and mild fibrosis, and the cholestatic features had notably improved. HCV PCR was performed several times in mid-1997 and was repeatedly negative. Over the subsequent 12 months the patient remained well, but had persisting cholestatic liver biochemistry AST 100–200 U/l, ALP 600–1,000 U/l, but normal serum bilirubin. Biopsy in July 1998 (20 months after immunosuppression had been stopped) revealed 70% bile duct loss, mild hepatitis and mild fibrosis. Mycophenolate mofetil 1.5 g daily was initiated.

Subsequently, the patient has remained well and is working full time. Repeated PCR on serum and liver tissue have failed to reveal any evidence of HCV infection. Despite histological evidence of chronic rejection, the most recent liver biochemistry (July 2001) is: AST 87 U/l, bilirubin 15 μmol/l, ALP 402 U/l (normal < 330).

Discussion

In most countries, HCV-associated liver disease has become the most common indication for liver transplantation. In patients who are HCV viraemic pre-transplantation, re-infection of the graft is inevitable. The subsequent course of the graft hepatitis is highly variable, but the majority of patients develop significant graft damage during follow-up. Graft and patient survival during the first 5 post-transplant years is not significantly different from that observed following transplantation for other liver diseases. However, it

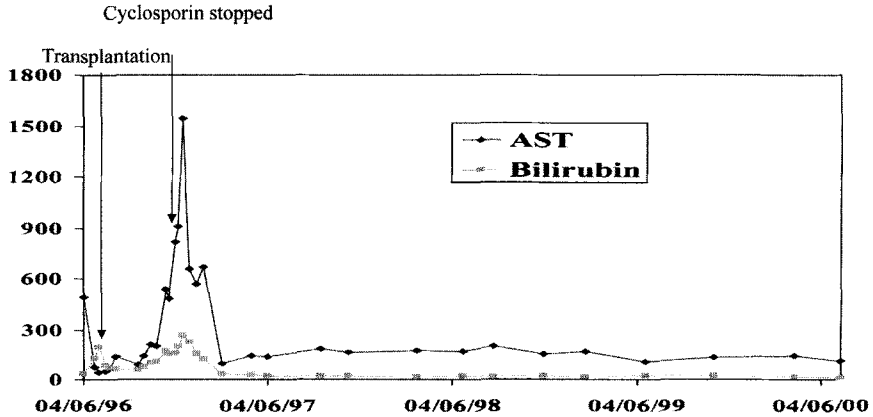

Fig. 1. Biochemical liver function observed from the time of liver transplantation until June 2000. Severe hepatitis was seen 6 months post-transplant. Subsequently, resolution was observed after withdrawal of immunosuppression

Table 1. Reported experience with liver transplantation for patients with CVID

Reference; year	Indication	Survival (months)	Cause of death
Gow and Mutimer; 2001 (this report)	HCV	60 (July 2001)	Alive
Bjoro et al. [1]; 1999	HCV	18	Recurrent HCV
Bjoro et al. [1]; 1999	HCV	1	*Aspergillus* brain abscess
Smith et al. [12]; 1995	HCV	23	Pneumonitis? cause
Smith et al. [12]; 1995	HCV	15	Complications of splenectomy

seems likely that more prolonged follow-up may reveal that graft loss due to HCV will be frequently observed towards the end of the first post-transplant decade. Spontaneous HCV clearance is believed to be rare, though published reports of clearance are lacking.

FCH is a syndrome that was originally described as a complication of hepatitis B recurrence in liver allografts. It is clinically characterised by hyperbilirubinaemia, mild to moderate elevations of transaminases, high levels of viral replication and progressive liver failure. Histologically, the lesion exhibits extensive peri-portal fibrosis, marked cholestasis, a mild inflammatory cell infiltrate and an absence of cirrhosis. Over recent years this syndrome has also been recognised to occur after transplantation in patients with chronic HCV infection [5]. FCH is felt to be a consequence of direct cytopathic injury to hepatocytes induced by enhanced viral replication fostered by immunosuppression.

In most instances FCH progresses rapidly to liver failure and death. Recently, FCH due to HCV has been reported to respond to anti-viral treatment with interferon, resulting in reduction in HCV RNA titres and resolution of the lesion [14]. In the case we describe, immunosuppression was withdrawn when the patient developed liver failure associated with the histological changes of FCH. This resulted in resolution of liver failure, improvement in liver histology and clearance of HCV.

Clearance of HCV after liver transplantation is unusual, and exactly why this occurred in our patient remains unclear. It is possible that complete withdrawal of immunosuppression may have been critical. Flares of hepatitis associated with reduction of serum viral titre may be observed following withdrawal of immunosuppression from patients with chronic HCV or HBV infection [13,15]. In hepatitis B infection, this response may be associated with hepatitis B virus e antigen seroconversion [13]. Direct measurement of immune response to HCV would permit a better examination of the mechanism involved [8].

Recurrence of HCV was particularly aggressive in our patient. Although it seems likely that his immunodeficiency was responsible for aggressive recurrence, viral factors may have been relevant. The patient we have described was infected with genotype 1a. The impact of HCV genotype on post-transplant graft injury is an unresolved issue. There are several reports of patients infected with genotype 1 suffering from more aggressive disease after transplantation, although none of these data have been collected prospectively [6,7]. The majority of well-documented cases of FCH related to HCV infection have also been associated with genotype 1 [7,9]. Evidence is mounting that genotype 1 is over-represented in patients who suffer from severe recurrence of HCV.

There are few published data that describe the outcome of liver allograft recipients with CVID. The patient we have described is alive with a good quality of life more than 5 years after transplantation. The clinical outcomes of four other patients with CVID, all transplanted for HCV cirrhosis, have also been reported. Overall, the results of liver transplantation in patients with CVID are disappointing. Of the five published cases, only one patient has survived more than 2 years (Table 1). Liver transplantation needs to be recognised as a high-risk procedure in this patient population.

In the patient we described, no significant sepsis complications developed, although the patient suffered from a primary immunodeficiency disorder and was on immunosuppressive medication after transplantation. Carefully targeted antibiotic prophylaxis is an essential component of the post-transplant care. Patients with CVID are particularly prone to infection with *H. Influenzae*. Ciprofloxacin provides good cover against *H. Influenzae*; we prescribed it until the patient was discharged from hospital. Patients are also prone to infection with pneumococcus and meningococcus. Pooled immunoglobulin should provide sufficient protection against both of these organisms. Defects in cell-mediated immunity in CVID predispose patients to invasive fungal infection. Our policy was to use fluconazole 100 mg daily until the patients were discharged from hospital.

Liver transplantation in patients with HCV and CVID can be successful, although it must be accepted that patients are at high risk of sepsis complications and severe recurrent HCV. Carefully targeted antibiotic prophylaxis is an essential part of the post-transplantation care. The impact of immunosuppressive treatment on the severity of HCV recurrence needs to be considered. Emerging data suggest that cellular rejection and corticosteroid treatment may be associated with more aggressive recurrence [3, 10]. Our

patient developed early, albeit mild, acute cellular rejection and was treated with bolus corticosteroids. This may have contributed to the subsequent development of severe HCV recurrence. A role for prophylactic anti-viral therapy is uncertain. Published data suggest that an anti-viral effect may be achieved, but safety and tolerance remain important issues [11]. Also, permanent clearance of HCV would be achieved for a minority of patients, and prophylaxis may need to be given indefinitely. Despite generally poor results of transplantation in patients with CVID, it should not be considered a contraindication. The use of immunosuppression and anti-viral treatment in this group needs further study.

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