Case Report

Rapid progression of hepatitis C-induced liver failure in renal allograft recipients

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Early mortality due to hepatitis C virus (HCV)-related liver failure in renal allograft recipients in the absence of fibrosing cholestatic hepatitis is reported infrequently. We report six renal allograft recipients with HCV infection who died of rapid progression to liver failure. Of these, 2 were detected anti-HCV positive at screening prior to kidney transplantation and 4 were diagnosed after transplantation following derangement of liver function (HCV RNA positive in all 4, anti-HCV positive in 2). Median interval between kidney transplantation and derangement of liver function was 11.8 months (range 2 to 25) and median interval between transplant and death was 27 months (range 11 to 53). Liver biopsy performed during the terminal illness in 3 patients and post-mortem liver histology in 2 patients showed chronic hepatitis with mean grade of 10.2 (range 9 to 12) and stage 2.4 (range 2 to 3). None had features of fibrosing cholestatic hepatitis. [*Indian J Gastroenterol* 2006;25:155-156]

Hepatitis C virus (HCV) infection in immunocompetent hosts has an indolent course. However, data on natural history of HCV infection in renal allograft recipients (RAR) are conflicting. Early mortality due to HCV-related liver failure in these patients, in the absence of fibrosing cholestatic hepatitis (FCH), is uncommon.[1] Many believe that HCV infection does not influence patient or graft survival, and it has been suggested that fewer than 10% develop advanced fibrosis even 10 years after infection.[2]

We describe the clinical presentation of six RAR who developed rapid progression to fatal liver failure due to HCV infection.

Case Reports

From January 2001 to December 2003, all RAR on follow-up at our hospital were evaluated for HCV, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infection by testing for anti-HCV (third-generation ELISA), HCV RNA (RT-PCR), HBsAg (ELISA), HBV DNA (PCR) and anti-HIV antibody (ELISA) at 6 monthly intervals. Tests were performed earlier in case of development of jaundice or deranged liver function tests. Patients who tested positive for HCV infection were tested for serum bilirubin, ALT, alkaline phosphatase and INR. Infection by other hepatotropic viruses was excluded by testing for IgM antibodies against hepatitis A virus, hepatitis E virus and cytomegalovirus. Abdominal ultrasonography was done in all cases. Percutaneous liver biopsy was done in patients with deranged liver function tests and HCV infection in whom INR was correctable with infusion of fresh frozen plasma. In those patients who died, post-mortem liver histology was studied if the family gave consent.

Of 330 RAR, 160 had undergone renal transplantation at our hospital and 170 elsewhere. HCV infection was detected in 44 (13.3%), HBV in 52 (15.7%) and dual infection in 22 (6.6%). Six RAR (median age 38 [range 25-57] years; 3 men) with HCV infection died of liver failure (Table). Of these, two were positive for anti-HCV before kidney transplantation and their liver biopsy showed chronic hepatitis grade 7 and grade 2 with no fibrosis.[3] No pre-transplant anti-viral therapy was given. Four patients were detected to have HCV infection after transplantation – in two on routine testing and in two on testing when jaundice developed. All six were HCV RNA positive while anti-HCV was positive in only four.

Median serum bilirubin used was 18.4 (range 6.9-33) mg/dL, ALT 361 (210-600) U/L and alkaline phosphatase 757 (195-1260) U/L. No patient had ultrasonographic evidence of extra-hepatic biliary obstruction. Liver histol-

Table 1: Clinical profile, biochemistry, viral markers and liver histology

Patient ID	1	2	3	4	5	6
Age / gender	29/M	32/M	57/M	25/F	40/F	46/F
Peak bilirubin (mg/dL)	8.8	6.9	20.5	33	11.4	30
Peak ALT (IU/L)	210	270	350	600	277	460
Peak alkaline phosphatase (IU/L)	796	760	1020	195	510	1260
Peak INR	1.8	2.9	4.1	3.1	3	4.5
Anti-HCV	Pos	Neg	Pos	Pos	Pos	Neg
HCV RNA	Pos	Pos	Pos	Pos	Pos	Pos
Liver histology	Post-mortem	Post-mortem	Ante-mortem	Ante-mortem	Ante-mortem	Not available
Grade	9	7	12	12	11	-
Stage	2	2	3	3	2	-

ogy (ante-mortem 3, post-mortem 2) showed chronic hepatitis with median grade of 10.2 (range 7-12) and stage 2.3 (range 2-3). No patient had features of FCH. In both patients with anti-HCV positive prior to kidney transplantation there was marked progression in the grade (7 to 12 and 2 to 7) and stage (0 to 3 and 0 to 2) of chronic hepatitis following transplantation at 8 and 26 months, respectively. Low-dose interferon-alpha and ribavirin treatment was administered to two patients but it had to be withdrawn due to worsening liver function.

Median interval between transplantation and derangement of liver function was 11.8 mo (range 2 to 25). Median interval between appearance of liver function abnormality and death was 15.2 (4-42) mo, and between transplantation and death was 27 (11-53) mo. Terminal illness was characterized by hepatic encephalopathy and ascites; sepsis could be demonstrated in 3 patients.

Discussion

Several reports suggested that the course of HCV-related chronic liver disease is indolent. In a recently published multivariate analysis, 7-year patient and graft survival rates were similar in anti-HCV-positive and anti-HCV-negative RAR.[4] In another study, anti-HCV-positive RAR had a better 5-year survival than anti-HCV-negative patients.[5] However, both these studies were based on detection of HCV infection using anti-HCV, which is relatively insensitive in RAR, rather than the more sensitive HCV RNA. In a study with 20-year follow-up, only 20% of RAR with HCV infection developed cirrhosis of liver and none developed hepatocellular carcinoma.[6] However, in another study,[7] a more rapid progression of liver disease was observed – HCV-positive RAR showed greater progression of necro-inflammatory activity (71% vs 16%) and fibrosis (50% vs 16%) after mean 7.1 years when compared with matched immunocompetent controls with HCV infection.

More recently, there are concerns regarding adverse short-term outcome in RAR with HCV infection. Immunosuppressive therapy has been shown to produce significant increase in hepatitis C viremia.[8] Early hepatic dysfunction was reported in four patients 1 to 4 months after kidney transplant.[9] All of them were anti-HCV negative at transplant. HCV RNA was positive at the time of appearance of hepatic dysfunction. Liver biopsy confirmed the presence of FCH in two patients. HCV RNA load was high (14 to 58 x 10^5 Eq/mL) and three patients had genotype 1 virus. The dose of immunosuppressive drugs was reduced after liver biopsy but two patients died of liver failure 16 and 18 months post-transplantation. Hepatic dysfunction 3 months after kidney transplantation in the absence of FCH leading to rapid progression to cirrhosis, poor response to interferon and death has also been reported.[10] Elderly patients with early onset of biochemical abnormalities after transplantation and persistently deranged liver biochemistry are particularly at risk of developing severe liver disease. No satisfactory treatment is available for chronic hepatitis C in RAR since interferon carries a risk of graft rejection.

We have presented six patients who developed rapidly progressive and fatal liver disease due to chronic hepatitis C after kidney transplantation. None had FCH on histology. Therapy with low-dose interferon and ribavirin was tried in two patients despite the risk of graft rejection but had to be withdrawn due to progressive hepatocellular dysfunction and development of hepatic encephalopathy.

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