Clin Kidney J (2012) 5: 170–172
doi: 10.1093/ckj/sfs012
Advance Access publication 15 March 2012

CKJ

Teaching Point
(Section Editor: A. Meyrier)

Hepatitis in a renal transplant patient—beyond the usual

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Keywords: hepatitis; immunosuppression; kidney transplant; viral infection

Introduction

Hepatitis E virus (HEV) is a non-enveloped single-stranded RNA virus that usually causes a self-limiting hepatitis. It is often transmitted via the faecal-oral route but can also be spread through vertical transmission, blood transfusions and zoonotic transmission in endemic areas. The numbers of non-travel-associated HEV infections have increased in industrialized countries in recent years, and these infections are now considered an emerging infectious disease in Western countries. HEV belongs to the family Hepeviridae. At least four major genotypes of HEV have been recognized. Genotypes 1 and 2 are restricted to humans and associated with epidemics in developing countries. Genotypes 3 and 4 are zoonotic and infect humans as well as several other animals in developing and industrialized countries.

HEV is a frequent cause of acute hepatitis and can cause fulminant hepatitis in pregnant women. It is traditionally considered an agent responsible for acute hepatitis but it does not become chronic. There have been reports of sporadic cases in the haemodialysis population [1] and in immunocompromised patients. Here, we report on a case of chronic active hepatitis E in a kidney transplant recipient.

Case report

A 50-year-old man with a history of previous chemotherapy for testicular seminoma developed end-stage renal disease in 2001. After seven years on home haemodialysis, he received a kidney transplant from his sister, which was a 2-2-2 mismatch. He received basiliximab as induction therapy and subsequent triple immunosuppression with tacrolimus (aiming for levels 8–12 ng/L), azathioprine and prednisolone. He had an uncomplicated early course and initially good graft function. Two months post transplant, he was found to have a raised alanine aminotransferase (ALT) level. Bilirubin, alkaline phosphatase and gamma-glutamyl transferase levels remained normal.

A liver ultrasound showed a homogenous liver with no evidence of duct dilatation and normal Doppler flows. Hepatitis B and C serology was negative, as was cytomegalovirus (CMV) polymerase chain reaction and liver autoimmune screen.

Changes were made to his medications: co-trimoxazole was stopped and azathioprine was switched to mycophenolate mofetil (MMF). This had little effect on the overall ALT rise (Figure 1). Subsequent testing for HEV RNA was positive, with Genotype 3 virus found. A liver biopsy showed a mild-to-moderate chronic inflammatory cell infiltrate with small lymphoid aggregates, minimal steatosis and moderate fibrosis.

A diagnosis of chronic active hepatitis E was made. His immunosuppression was reduced as a result; MMF was stopped, and his tacrolimus dose gradually reduced. Despite the fibrosis found on the liver biopsy, the patient's ALT gradually returned to normal with resolution of his HEV viraemia (two subsequent negative HEV RNA tests). Renal allograft function was stable throughout. The mode of hepatitis E infection remains unclear.

Discussion

There are many causes of raised liver enzymes in kidney transplant recipients, including sepsis, biliary tract dysfunction, drugs and common hepatotropic virus-related infectious diseases such as hepatitis B and C. HEV is a relatively rare but important aetiological agent to consider in this group, especially in endemic areas. Although occult infection of HEV may be transferred to the recipient via liver graft, other allograft organs appear to be clear for transmission of the virus. As a result, screening for HEV at the time of transplantation is currently only recommended in liver transplant donors and recipients in endemic areas, but not for renal or other solid organ transplantations [2].

The incidence of *de novo* HEV infections after transplantation and risk for reactivation in patients with antibodies against HEV before transplantation are unknown. In a study of 700 solid-organ transplant recipients in southwest France, there were 34 locally acquired HEV infections among patients with no antibodies against HEV, 47% of whom subsequently developed a chronic infection, with an incidence of 3.2/100 person-years [3]. Factors that increase the risk of chronic hepatitis in solid organ transplant recipients include shorter

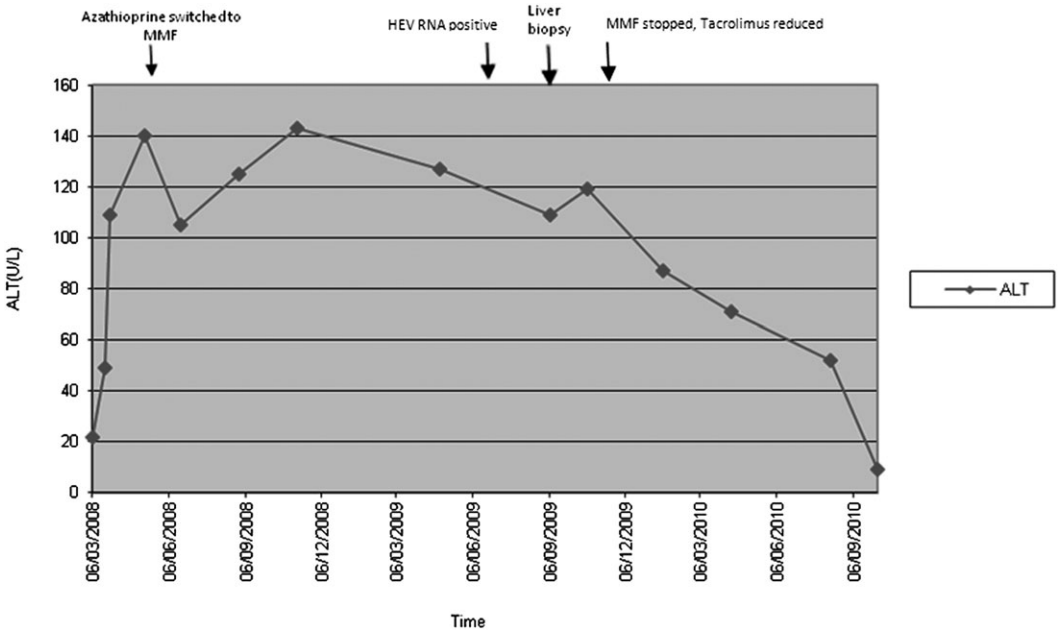

Fig. 1. Change in ALT over time.

interval since transplant, lower levels of liver enzymes and serum creatinine, lower platelet counts and tacrolimus-based immunosuppression (compared with cyclosporin A) [4].

In contrast to its acute and often self-limiting form in immunocompetent subjects, HEV can persist in immunocompromised patients in hepatocytes or macrophages [5], leading to chronic active hepatitis and even cirrhosis [6]. Rarely, HEV infection may result in non-hepatic complications in kidney transplant recipients. Neurological diseases that affect the peripheral or central nervous system have been demonstrated in this group with chronic HEV infection, with HEV RNA sometimes isolated from the cerebrospinal fluid.

Kamar *et al.*[7] published a case series of 14 transplant organ recipients with HEV infection. Eight of the 14 patients developed chronic hepatitis as indicated by persistently elevated liver enzyme levels and detectable serum HEV RNA at a median of 15 months. The histological findings typically suggested portal fibrosis with dense lymphocytic infiltrate and mild piecemeal necrosis, which were virtually indistinguishable from those observed in patients with chronic hepatitis C infection and certain types of autoimmune hepatitis. Interestingly, none of the patients in the series had their immunosuppression regime modified after diagnosis, or received any specific therapy, in particular anti-viral therapy.

The majority of patients with chronic HEV infection are asymptomatic, so a high index of suspicion is needed for prompt diagnosis. Diagnosis is confirmed by serological and molecular testing for HEV RNA. Testing for anti-HEV immunoglobulin M (IgM) and immunoglobulin G (IgG) differentiates acute infection from chronic infection. The IgM titre falls rapidly after infection, becoming virtually undetectable within 6 months. Anti-HEV IgG persists for longer than 6 months, although its actual duration of positivity is unknown. Anti-HEV IgG appears to afford protection against re-infection. Interestingly, the development of HEV IgG in renal transplant patients does not appear to be universal. The presentation of chronic hepatitis in renal transplant patients may be associated with normal liver enzymes and a negative serological assay. This phenomenon underscores the need for molecular studies in suspected subjects.

HEV seroconversion in transplant recipients occurs later in patients with chronic infection than in those with resolving infection. Humoral immunity is necessary to clear HEV and to prevent hepatitis E reactivation. Immunosuppressive agents such as mycophenolate and inhibitors of mTOR cause significant reduction in the humoral immune response by inhibiting the synthesis of antibodies, and the cell-cycle progression and differentiation of human B lymphocytes. Bryan *et al.* [8] have shown that antibodies to the HEV capsid can be protective against hepatitis E. Furthermore, cell-mediated immunity also appears to have a role in HEV clearance. In patients in whom the infections become chronic, the total lymphocyte counts and the CD2, CD3 and CD4 lymphocyte counts in particular are significantly lower than in patients in whom HEV infection resolved.

Exact treatment options are unclear, but decreasing the total burden of immunosuppression remains the first approach towards controlling hepatitis E in renal transplant recipients. Pegylated interferon alpha-2b has been shown to be useful in the management of chronic HEV infections in solid organ recipients in whom reduction of the immunosuppressive regimen alone is insufficient. The efficacy of ribavirin 12 mg/kg of body weight daily for 12 weeks was reported in kidney transplant patients with chronic HEV infection in 2010 [9]. However, eradication of the virus could not be claimed due to the short-term follow-up of 3 months.

Needless to say, it remains essential to identify routes of transmission so that preventive measures can be taken. A case-control study showed that factors associated with HEV infection in immunocompromised patients in the study area were the consumption of game meat, food products made with pork and mussels [10]. Thorough cooking of game meat and pork products and better information on HEV transmission would help minimize the risk for HEV infection.

No effective immunoprophylaxis against HEV is currently available. Immunoglobulin from infected patients is not effective in preventing outbreaks or sporadic cases. Vaccination

against HEV could be proposed to patients before or after organ transplantation. However, the efficacy of vaccination in these populations should be addressed. A recent randomized, double-blind, placebo-controlled Phase 3 trial conducted in China found the HEV 239 vaccine to be well tolerated and effective in the prevention of hepatitis E in the general population among both men and women aged 16–65 years [11].

We propose that long-term monitoring of liver function tests and HEV RNA is important to ensure complete resolution of the HEV infection. Further studies are needed to establish the exact incidence and prevalence of HEV infection amongst transplant recipients, as well as the longer-term outcomes of immunosuppression modification and pegylated interferon therapy on disease progression. HEV recombinant protein vaccines may become effective in preventing HEV infection in the near future.

Teaching points

(1)Serological testing for hepatitis E should be undertaken early in immunosuppressed transplant recipients with raised liver enzymes.

(2) First-line treatment should be to reduce immunosuppression.

(3) Potential local risk factors should be identified to prevent transmission and primary infection of other transplant recipients.

Acknowledgements. With thanks to Dr Bill Griffiths, for reviewing the case and providing advice.

Conflict of interest statement. None declared.

References

1 Mohammadmehdi Hosseini-Moghaddam S, Zarei A, Moayed Alavian S *et al.* Hepatitis E viral infection: a general review with a focus on haemodialysis and kidney transplant patients. *Am J Nephrol* 2010; 31: 398–407
2 Pischke S, Wedemeyer H. Chronic hepatitis E in liver transplant recipients: a significant clinical problem? *Minerva Gastroenterol Dietol* 2010; 56: 121–128
3 Mansuy JM, Peron JM, Abravanel F *et al.* Hepatitis E in the south west of France in individuals who have never visited an endemic area. *J Med Virol* 2004; 74: 419–424
4 Kamar N, Garrouste C, Haagsma EB *et al.* Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 2011; 140: 1481–1489
5 Labadie K, Larcher T, Joubert C *et al.* Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Invest* 2010; 120: 894–906
6 Gerolami R, Moal V, Colson P. Chronic hepatitis E with cirrhosis in a kidney transplant recipient. *NEJM* 2008; 358: 859–860
7 Kamar N, Selves J, Mansuy JM *et al.* Hepatitis E virus and chronic hepatitis in organ transplant recipients. *NEJM* 2008; 358: 811–817
8 Bryan JP, Tsarev SA, Iqbal M *et al.* Epidemic hepatitis E in Pakistan: patterns of serologic response and evidence that the antibody to hepatitis E virus protects against disease. *J Infect Dis* 1994; 170: 517–521
9 Mallet V, Nicand E, Sultanik P *et al.* Brief communication: case reports of ribavirin treatment for chronic hepatitis E. *Ann Intern Med* 2010; 153: 85–89
10 Legrand-Abravanel F, Kamar N, Sandres-Saune K *et al.* Characteristics of autochthonous hepatitis E virus infection in solid-organ transplant recipients in France. *J Infect Dis* 2010; 202: 835–844
11 Zhu FC, Zhang J, Zhang XF *et al.* Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; 376: 895–902

Received for publication: 11.9.11; Accepted in revised form: 25.1.12