An Unusual Cause of Hepatitis With Nephrotic Syndrome in a Kidney Transplant Recipient

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INTRODUCTION

Hepatitis E virus (HEV) infection is an emerging cause of viral hepatitis worldwide. HEV belongs to the family Hepeviridae, which includes 2 genera, namely, Orthohepevirus and Piscihepevirus. The Orthohepevirus genus has 4 species: A, B, C, and D. In humans, a majority of HEV infection is because of variants related to Orthohepevirus species A (HEV-A). On the other hand, Orthohepevirus species C genotype 1 (HEV-C1), normally found in rats and commonly known as rat HEV, rarely causes human hepatitis. Although most HEV infections are self-limiting and asymptomatic, part of the patients can develop fulminant hepatitis and extrahepatic manifestations. In addition, they can become persistent in immunosuppressed individuals. Although a wide spectrum of extrahepatic manifestations including glomerular injury has been reported during HEV-A infection, there have been little data regarding extrahepatic manifestations related to HEV-C1 infection in immunosuppressed patients. Early diagnosis of glomerulonephritis is important in kidney transplant recipients because it can affect the long-term graft outcome. Herein, we report the first case of biopsy-proven HEV-C1–related immune complex glomerulonephritis in a kidney transplant recipient.

CASE STUDY

A 78-y-old lady with end-stage kidney disease caused by diabetic nephropathy received deceased kidney transplant 10 y ago. Her immunosuppressive regimen included tacrolimus 2 mg/d (0.05 mg/kg/d), mycophenolate mofetil (MMF) 500 mg/d, and prednisolone 5 mg/d. Her serum creatinine was around 50 μmol/L (Ref 45–84), and there was no proteinuria. One year ago, she developed persistent watery diarrhea. There was no fever. Laboratory investigations revealed normal blood count but deranged liver function with alkaline phosphatase 190 IU/L (Ref 53–141), alanine aminotransferase 1066 IU/L (Ref 6–42), aspartate aminotransferase 89 IU/L (Ref <35), globulin 46 g/L (Ref 26–39), albumin 16 g/L (Ref 33–48), bilirubin 13 μmol/L (Ref 5–27), and prothrombin time 10.9 s (Ref 10.7–13.1). Her serum creatinine was 40 μmol/L, and the amount of urinary protein was 7.3 g/d. Infective causes of hepatitis, including hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, and HIV, could not be identified. The anti-HEV IgM and HEV-A RNA were negative. The serum cryoglobulin and autoimmune markers were also negative. The serum complement levels were normal. The donor-specific antibodies before and after the onset of proteinuria were both negative. There was no recent history of any type of vaccination. She did not take any over-the-counter medication. The whole blood tacrolimus trough level was 5.8 μg/L. Stool examination did not detect any pathogens. Colonoscopy showed diverticulosis only. Magnetic resonance cholangiopancreatography did not reveal any liver lesions or dilated biliary system.

In view of the unexplained hepatitis, further testing of the original blood samples revealed presence of HEV-C1 RNA (by quantitative reverse transcriptase-polymerase chain reaction) with a viral load of 5.47 × 10⁵ copies/mL. Fecal HEV-C1 viral load was 6.60 × 10⁸ copies/mL. Oral ribavirin 400 mg BID was commenced, and the dosage of MMF was gradually tailed down. Renal graft biopsy was performed, which showed diffuse moderate to marked mesangial matrix expansion and mesangial hypercellularity, together with segmental endocapillary proliferation (Figure 1). In addition, some silver-negative eosinophilic mesangial deposits were identified. The C4d staining was negative. Direct immunofluorescence study showed granular mesangial and capillary loop deposits for IgG (trace), IgA (1–2+), IgM (2–3+), C3 (trace), and C1q (1–2+) (Figure 2). Electron microscopy showed some medium-sized electron dense deposits in the mesangium and several ones in the subendothelial area and subepithelial area (Figure 3A and B).
The effacement of foot processes was very mild, affecting <15% of the capillary loop area. The pathological diagnosis was immune complex-mediated glomerulonephritis.

After ribavirin treatment, her clinical condition gradually improved with diarrhea subsided and liver enzymes completely normalized within 3 mo; however, there was persistent HEV-C1 viremia (5.50 × 10^4 copies/mL). MMF was finally stopped, and the HEV-C1 viral load dropped to <400 copies/ml in the following 3 mo. The amount of proteinuria also significantly improved (2 g/d). Her current immunosuppressive drugs were prednisolone 5 mg daily and tacrolimus 1.5 mg daily, and the renal function remained stable without evidence of rejection.

**DISCUSSION**

At the time of writing, only 18 patients with HEV-C1 infection have been documented in literature, with 17 of them (including our patient) reported in Hong Kong.3,6-8 Although HEV-C1 can be found in rats in many parts of the world, most molecular tests targeting HEV-A variants cannot detect HEV-C1 RNA. As a result, it is possible that HEV-C1 infection has been underdiagnosed in different areas. The exact route of viral transmission from rat to human is still unknown. Contact with environmental surfaces contaminated by rat droppings remains a possibility. Among all the reported HEV-C1 cases, 4 were kidney transplant recipients, and all of them had persistent infection. The demographic and clinical characteristics of these 4 patients are summarized in Table 1. In our patient, the pattern of liver injury was primarily cholestatic with markedly elevated gamma-glutamyl transferase. Although this might not be the most typical picture in patients with hepatitis, the exclusion of other possible causes of liver injury together with the normalization of liver enzymes after ribavirin therapy still makes HEV-C1 as the most likely cause.
of liver function derangement in our patient. In fact, similar cholestatic pattern of liver injury has also been encountered in some patients with HEV infection.1 With the rapid resolution of symptoms after treatment, liver biopsy was not performed in our patient.

The exact pathophysiologic mechanisms causing extrahepatic manifestations of HEV infection still remain largely unclear. Renal manifestations with proteinuria and impaired renal function have been observed in solid organ transplant recipients associated with genotype 3 HEV-A infection. Membranoproliferative glomerulonephritis, membranous nephropathy, and relapse of IgA nephropathy appear to be the most common glomerular diseases identified by renal biopsy. In addition, cryoglobulinemia is also frequent in these patients.9,10 Ribavirin is the treatment of choice for persistent HEV infection. After HEV clearance, cryoglobulinemia subsided with renal function and proteinuria improved.9 Although genotype 4 HEV-A infection was also shown to cause chronic hepatitis in kidney transplant recipients in our region, none of them developed renal complications.11

Our patient was the first and only one who was diagnosed to have renal manifestation of HEV-C1 infection. The source of infection remains uncertain. She developed sudden onset of nephrotic syndrome at the time of liver enzyme derangement, and renal graft biopsy confirmed the diagnosis of immune complex-mediated glomerulonephritis. The main differential

![Figure 3](image_url)

**FIGURE 3.** Ultrastructural study showed mesangial deposits (arrow) in (A) and subendothelial deposits (arrow) in (B). Magnification, × 2000.

| Gender | Age | Year of transplant | Onset of hepatitis | Infection type | Hepatitis B carrier | Immunosuppressive regimen | Clinical presentation | HEV IgM/IgG | Peak bilirubin (umol/L) | Peak ALT (U/L) | Peak prothrombin time (s) | Imaging findings | Ribavirin therapy | Death |
|--------|-----|-------------------|-------------------|----------------|---------------------|--------------------------|---------------------|------------|----------------------|----------------|------------------------|----------------|----------------|-------|
| Female | 78  | 2010              | September 2020    | Persistent     | No                  | Tacrolimus Mycophenolate mofetil | Diarrhea Abnormal LFT | ±          | 16                   | 101            | 11.5                   | Normal         | Yes             | No    |
| Male   | 67  | 1999              | May 2018          | Persistent     | No                  | Prednisolone Cyclosporine Sirolimus | Abnormal LFT         | ±          | 12                   | 141            | 10.9                   | Fatty liver    | Yes             | Yes   |
| Male   | 74  | 2003              | May 2018          | Persistent     | Yes (on tenofovir) | Prednisolone Sirolimus Mofetil Everolimus | Abnormal LFT         | +/+        | 11                   | 133            | 20.4                   | Fatty liver    | No              | Yes   |
| Female | 79  | NA                | Between August 2019 and December 2020 | Persistent | No                  | Prednisolone Tacrolimus | Nil                | ±          | 23                   | 101            | 11.5                   | NA             | No              | No    |

**TABLE 1.** Demographic and clinical characteristics of HEV-C1 infected kidney transplant recipients

HEV, hepatitis E virus; HEV-C1, Orthohepevirus species C genotype 1; LFT, liver function test; NA, not available.
diagnosis included autoimmune disease-associated glomerulonephritis, IgA nephropathy, C1q nephropathy, and infection-related glomerulonephritis. Although light microscopy showed proliferative glomerulonephritis, the immunofluorescence pattern was not typical of either IgA nephropathy or C1q nephropathy. In addition, our patient did not have any clinical evidence of autoimmune diseases or factors (like drugs) triggering lupus-like conditions. Thus, infection-related GN was suspected. With the absence of HEV-specific findings in the renal histology, it might be difficult to prove whether the glomerular injury was caused by HEV infection or not; however, the temporal relationship between the onset of HEV-C1 infection and the occurrence of nephrotic syndrome, the exclusion of other possible etiologies together with the significant improvement of proteinuria after ribavirin therapy and reduction of immunosuppression, suggests that the glomerulonephritis is likely caused by the HEV-C1 infection in our patient. The mechanism could be immune-driven similar to the glomerulonephritis associated with hepatitis C infection. In our patient, there was resolution of symptoms and normalization of liver enzymes shortly after ribavirin treatment. With the reduction of immunosuppressive regimen, there was also clearance of HEV-C1 viremia.

In conclusion, kidney transplant recipients are susceptible to persistent HEV-C1 infection, and kidney injury can occur in these patients. Screening for this virus in patients with glomerulonephritis, especially if it is also associated with unexplained hepatitis, is important. Since spontaneous clearance of HEV is highly unlikely in transplant patients, ribavirin should be started early. Reduction of immunosuppression, with consideration of the elevated risk of rejection, should also be considered. We believe that this case report can expand the current knowledge of potential glomerulopathy pattern as seen in this rare infection.

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