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Case Report

Hepatitis E Virus–Induced Cryoglobulinemic Glomerulonephritis in a Nonimmunocompromised Person

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Hepatitis E virus (HEV)-related kidney disease and symptomatic cryoglobulinemia have been observed in solid-organ transplant recipients. However, HEV RNA in the cryoprecipitate has not yet been assessed. We report what to our knowledge is the first documented case of autochthonous HEV-induced cryoglobulinemic crescentic and membranoproliferative glomerulonephritis in an immunocompetent man with no notable medical history. He presented with edema, hypertension, increased serum creatinine level, and nephrotic syndrome. Type II cryoglobulinemia with monoclonal immunoglobulin G (IgG) κ light chain was detected. Anti-HEV IgG and IgM, as well as HEV RNA, were detected in serum and cryoprecipitate. Histologic analysis of a kidney biopsy specimen revealed features of crescentic and membranoproliferative glomerulonephritis. After HEV clearance, kidney and liver parameters improved and HEV RNA and cryoglobulinemia were undetectable. Hence, we conclude that HEV can cause severe kidney disease and should be considered in cases of unexplained glomerular disease.
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INDEX WORDS: Hepatitis E virus (HEV); viral RNA; membrano-proliferative glomerulopathy; membranoproliferative glomerulonephritis (MPGN); cryoglobulinemia; cryoprecipitate; immunocompetent; nephrotic syndrome; kidney biopsy; renal disease.

Hepatitis E virus (HEV) has a worldwide distribution. In developing countries in areas of poor sanitation, genotypes 1 and 2 HEV are transmitted between humans mainly by the fecal-oral route, usually by contaminated water. In developed countries, genotypes 3 and 4 are transmitted from animal reservoirs.[1] In the latter case, domestic pigs, in which infection is asymptomatic, constitute the main animal reservoir, with high prevalence in many countries. The virus transmits to humans primarily by consumption of uncooked or undercooked meat from infected swine or game (wild boar, deer, and rabbit), although a few cases of blood transmission have been reported.[2]

HEV-related kidney disease and symptomatic cryoglobulinemia have been observed in solid-organ transplant recipients[3-5]; however, HEV RNA in cryoprecipitate has not yet been assessed.[6] We report what to our knowledge is the first documented case of HEV-induced cryoglobulinemic crescentic and membranoproliferative glomerulonephritis (MPGN) in an immunocompetent adult.

CASE REPORT

A 48-year-old native French man with no notable medical history presented with fatigue, moderate edema of the lower limbs, and hypertension (blood pressure, 160/90 mm Hg), with no other clinical manifestations. One month before admission, he reported having had fever (temperature of 38°C), abdominal pain, and jaundice. The patient had not traveled abroad, but had eaten pork products. Serum creatinine level was 3.63 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 19 mL/min/1.73 m^2 as calculated by the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation[7]), and serum albumin level was 2.6 g/dL. Urinalysis showed microscopic hematuria (46 red blood cells/high-power field). Urinary albumin-creatinine ratio was 3 g/g. Alanine aminotransferase levels were 3-fold higher than the upper limit of normal (Fig 1A). Ultrasound images of the kidney and liver were unremarkable. Rheumatoid factor was 49 (reference range, 0-25) U/mL. C3 and C4 levels were within reference ranges. Antinuclear and antineutrophil cytoplasmic antibodies and antibodies to extractable nuclear antigens, double-stranded DNA, liver-kidney microsomes, smooth muscle cells, mitochondria, and glomerular basement membrane were not detected. Hepatitis A, B, and C (HCV) virus, HIV (human immunodeficiency virus), cytomegalovirus, and Epstein–Barr virus infections were ruled out by serologic and nuclear assay tests. No organisms grew from urine and blood cultures, and C-reactive protein level was within the reference range.

Anti-HEV immunoglobulin G (IgG) and IgM were detected by immunoassay (Wantai Biologic Pharmacy Enterprise),[8] and serum HEV RNA was quantified at 960 copies/mL.[9] Genotyping was not possible due to failure to amplify sufficient HEV RNA. Type II cryoglobulinemia with monoclonal IgG κ light chain was detected

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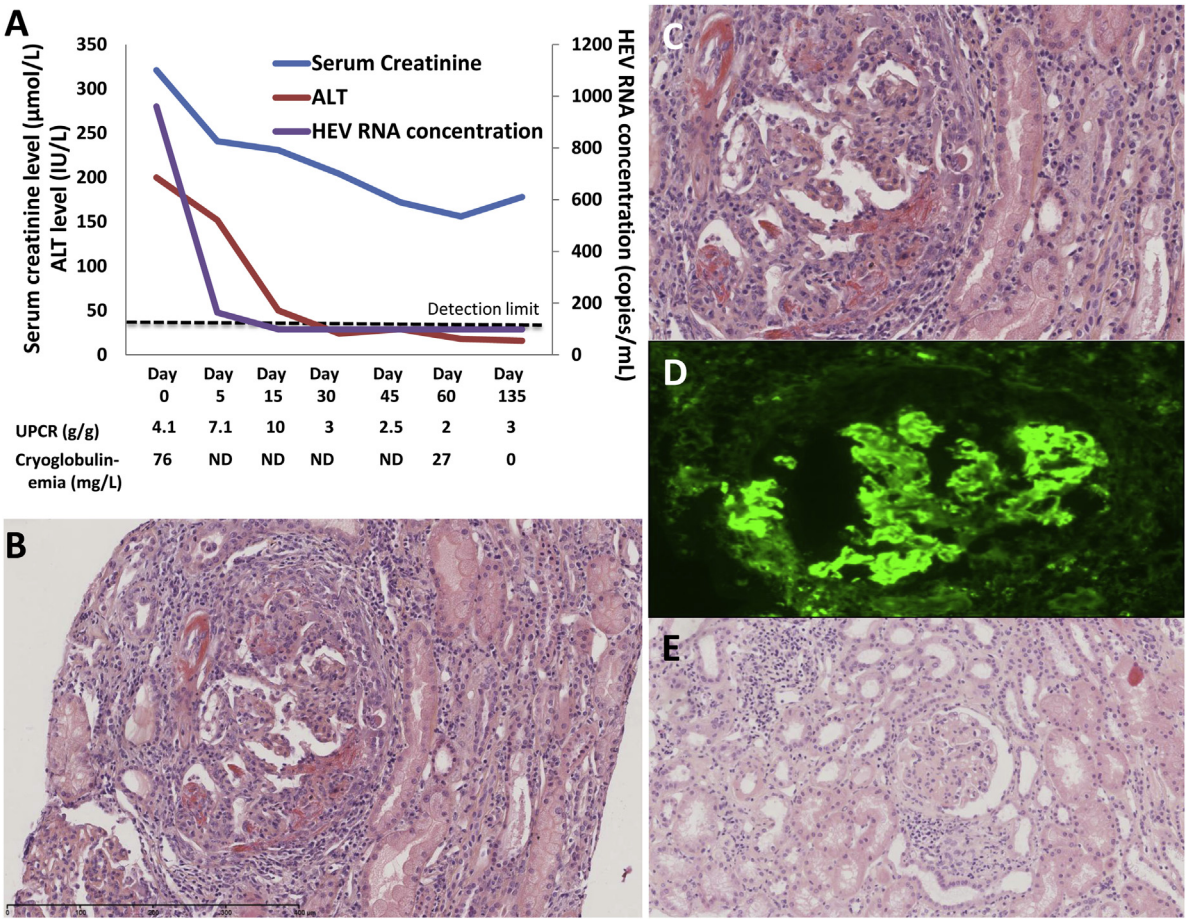

Figure 1. Disease course and kidney biopsy of the patient. (A) Laboratory results. Workup of the classical complement pathway detected no anomalies. Kidney biopsy specimen (hematoxylin and eosin; original magnification, [B] ×200, [C] ×400) shows lobular membranoproliferative exudative glomerulonephritis with fibrinoid necrosis, a cellular crescent with ruptured Bowman capsule, and fibrinoid necrosis of the glomerular vascular pole. (D) By immunofluorescence microscopy, deposits of immunoglobulin G (IgG) were visible (staining for IgM, C3, and C1q was positive [not pictured]). (E) A kidney biopsy specimen obtained 135 days after diagnosis (hematoxylin and eosin; original magnification, ×200) shows reduced exudative proliferation and vasculitis lesions. Abbreviations: ALT, alanine aminotransferase; HEV, hepatitis E virus; ND, not done; UPCR, urine protein-creatinine ratio.

(76 mg/L). To evaluate whether HEV was in cryoglobulins, cryoproteins were precipitated from serum and tested for anti-HEV IgG and IgM using the Wantai immunoassay. In addition, a polymerase chain reaction–based assay was used to detect HEV RNA, as previously described.[9] Anti-HEV IgG and IgM and HEV RNA were detected in cryoprecipitate. Hematologic diseases were ruled out by analyzing a bone marrow biopsy specimen. Histologic analysis of a kidney biopsy specimen revealed lobular membranoproliferative exudative glomerulonephritis with fibrinoid necrosis and cellular crescents with a ruptured Bowman capsule (Fig 1B and C). Immunofluorescence microscopy revealed subendothelial deposits of IgM, IgG, fibrinogen, κ and λ light chains, and complement components (Fig 1D).

The patient was treated with 7 sessions of plasmapheresis and steroid pulses (1 mg/kg/d for 18 days). Because serum HEV RNA level had decreased to 164 copies/mL 1 week after admission, ribavirin treatment was not initiated. Ramipril (1.25 mg/d) was given. In the days that followed, kidney and liver parameters improved and HEV RNA and cryoglobulinemia became undetectable. A kidney biopsy performed 135 days after diagnosis showed reduced exudative proliferation and persistence of the double-contour pattern (Fig 1E).

DISCUSSION

HEV can cause hepatic and extrahepatic manifestations, such as neurologic symptoms, kidney disease, severe thrombocytopenia, and aplastic anemia.[1] In a study comprising solid-organ recipients, eGFR was observed to decrease from 55.8 ± 18 mL/min/1.73 m^2 before infection to 50.8 ± 18 mL/min/1.73 m^2 during the acute HEV phase.[3] In 15 of 51 of these patients, MDRD Study equation–determined eGFR decreased by >20%; however, it recovered after HEV clearance. A few cases of HEV-induced glomerular disease have been reported in transplant recipients: for example, MPGN, membranous glomerulonephritis, and relapsing IgA nephropathy after kidney transplantation[3] (Table 1[3-5,10,11]). However, to our knowledge, no case of HEV-induced glomerular disease has been reported to date in a nonimmunocompromised patient. Therefore, the present case is the first to describe