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Case Report

Hantavirus Infection With Severe Proteinuria and Podocyte Foot-Process Effacement

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Nephropathia epidemica, a zoonosis caused by Hantavirus infection (most commonly subtype Puumala) is associated with flu-like symptoms and acute kidney failure. Kidney manifestations are characterized predominantly by tubulointerstitial nephritis, hemorrhage into medullary tissues, interstitial edema, and tubular cell necrosis. Kidney failure is accompanied by proteinuria, and in some cases, nephrotic-range proteinuria may occur. However, the cellular mechanisms of proteinuria remain to be elucidated. We describe a Hantavirus (Puumala) infection in a 27-year-old man with acute kidney failure and severe and rapidly reversible proteinuria. Light microscopy of a kidney biopsy specimen showed only minor changes of glomeruli. However, transmission electron microscopy revealed podocyte foot-process effacement. Immunofluorescence staining of the slit diaphragm protein podocin and the tight junction protein ZO-1 revealed a partial mislocalization of these proteins. Together, these findings highlight that Hantavirus infection may perturb podocyte integrity, resulting in glomerular proteinuria. These alterations of podocytes and consequently the glomerular filtration barrier may be transient and resolve within weeks.
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INDEX WORDS: Hantavirus infection; podocyte foot-process effacement; proteinuria; acute kidney failure.

Nephropathia epidemica, a subtype of hemorrhagic fever with renal syndrome (HFRS), is caused by infection with hantavirus, most commonly Puumala virus. Patients present with sudden onset of flu-like symptoms, abdominal pain, nausea, and headache. Typical laboratory findings are thrombocytopenia, elevated liver enzyme levels, elevated C-reactive protein level, and an increase in serum creatinine level indicative of acute kidney failure.[1-3] The differential diagnosis of Hantavirus infections includes other viral and bacterial diseases that cause acute kidney failure. For example, both leptospirosis and Hantavirus infections initially can present with flu-like symptoms followed by hemorrhagic events with hepatic and pulmonary involvement.[1]

Indivduals contract Hantavirus infection by inhaling aerosolized particles containing the virus or by contact with feces or urine of infected rodents. In Europe, more than 10,000 cases of HFRS are diagnosed each year, and this number has been increasing in recent years. The overall mortality is low (<0.5%),[4] but 5% of these patients require dialysis. Hantavirus infections were categorized in the group of communicable diseases with the highest priority for surveillance and epidemiology research.[5] Important risk factors for infection include contact with rodents (bank vole) and male sex.[6] The epidemiology is linked closely to climate conditions that favor proliferation of the infected host population.[7]

The diagnosis of Hantavirus infection can be confirmed by serologic testing with enzyme immunoassays.[1] Antibodies against Hantavirus can be detected 24 hours after the onset of symptoms. Infected patients have immunoglobulin M (IgM) and to a lesser degree, IgG antibodies that are directed mainly toward the nucleocapsid protein.[8]

The typical renal histologic finding in Puumala virus–HFRS is acute tubulointerstitial nephritis[9,10] with an inflammatory infiltrate composed of mononuclear cells, hemorrhage into the medullary tissues, interstitial edema, and tubular cell necrosis. Acute tubulointerstitial nephritis sometimes is accompanied by mild glomerular changes with hypercellularity and mesangial proliferation that do not correlate with the severity of proteinuria.[9] Only a few reports describe more severe glomerular involvement, such as mesangiocapillary glomerulonephritis type I[11] or rapidly progressive glomerulonephritis.[12] Electron microscopy has revealed occasional subendothelial electron-dense deposits; however, in most cases, only unspecific changes have been reported.[13,14]

CASE REPORT

A 27-year-old man was admitted to this hospital with flu-like symptoms, nausea, vomiting, and abdominal cramps. The patient said he had been in good health until 5 days previous, at which time he

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developed fever and felt exhausted. Dry cough occurred, but no sputum production was present. Urine output was normal and he did not take any medication.

On admission, the patient appeared ill. He reported flank pain. His temperature was 37.9°C, and blood pressure and pulse were normal. His abdomen was soft with normal bowel sounds, but with bilateral tenderness over the flanks. The rest of the physical examination had normal findings, and the patient did not have edema. Initial laboratory results included an elevated serum creatinine level at 2.5 mg/dL (reference range, 0.67-1.17 mg/dL; estimated glomerular filtration rate [eGFR], 31 mL/min/1.73 m^2 calculated with the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation) and serum urea nitrogen level, 28 (reference range, 5.9-20) mg/dL. A peripheral-blood count showed thrombocytopenia (platelets, $72 \times 10^3/\mu L$); leukocyte ($7.65 \times 10^3/\mu L$) and hemoglobin (14.1 g/dL) levels were normal. C-Reactive protein (35; reference range, <5 mg/L), lactate dehydrogenase (290 U/L), and liver enzyme levels (alanine aminotransferase, 83 U/L; aspartate aminotransferase, 55 U/L) were moderately elevated. A urine dipstick test showed protein (4+), blood (3+), and no leukocytes. The patient's urine protein-creatinine ratio was 22.5 g/g and urine output was 1.5 L per day. An abdominal ultrasound revealed slightly swollen kidneys with increased parenchymal echogenicity and small amounts of perirenal fluid collection. Urinary tract obstruction was excluded. The following day, serum creatinine level increased to 3.3 mg/dL (eGFR, 24 mL/min/1.73 m^2). Given the severe clinical course, we performed a percutaneous kidney biopsy. The patient received supportive care, intravenous fluids, and analgesics (metamizole).

Light micrographs showed glomeruli with normal mesangium and capillary tufts and several swollen podocytes. The lumina of some tubules were dilated, indicating acute tubular injury, and the interstitium displayed focal mononuclear cells in the cortex. No interstitial hemorrhage was found (Fig 1A). The biopsy specimen did not encompass parts of the medulla. Immunohistochemistry found no significant mesangial deposits of complement or immunoglobulin. Interestingly, electron micrographs revealed severe podocyte alterations with segmental foot-process effacement and loss of slit diaphragms (Fig 1B).

At this point, results of serologic tests for viral infections returned and showed antibodies against Hantavirus. The test did not distinguish between Puumala and Dobrava virus, but IgM antibodies indicated acute infection. Our patient convalesced well. At the 3-week follow-up, his kidney function had completely recovered (serum creatinine, 1.1 mg/dL; eGFR, ≥60 mL/min/1.73 m^2) and proteinuria reached physiologic levels (protein-creatinine ratio, 0.04 g/g).

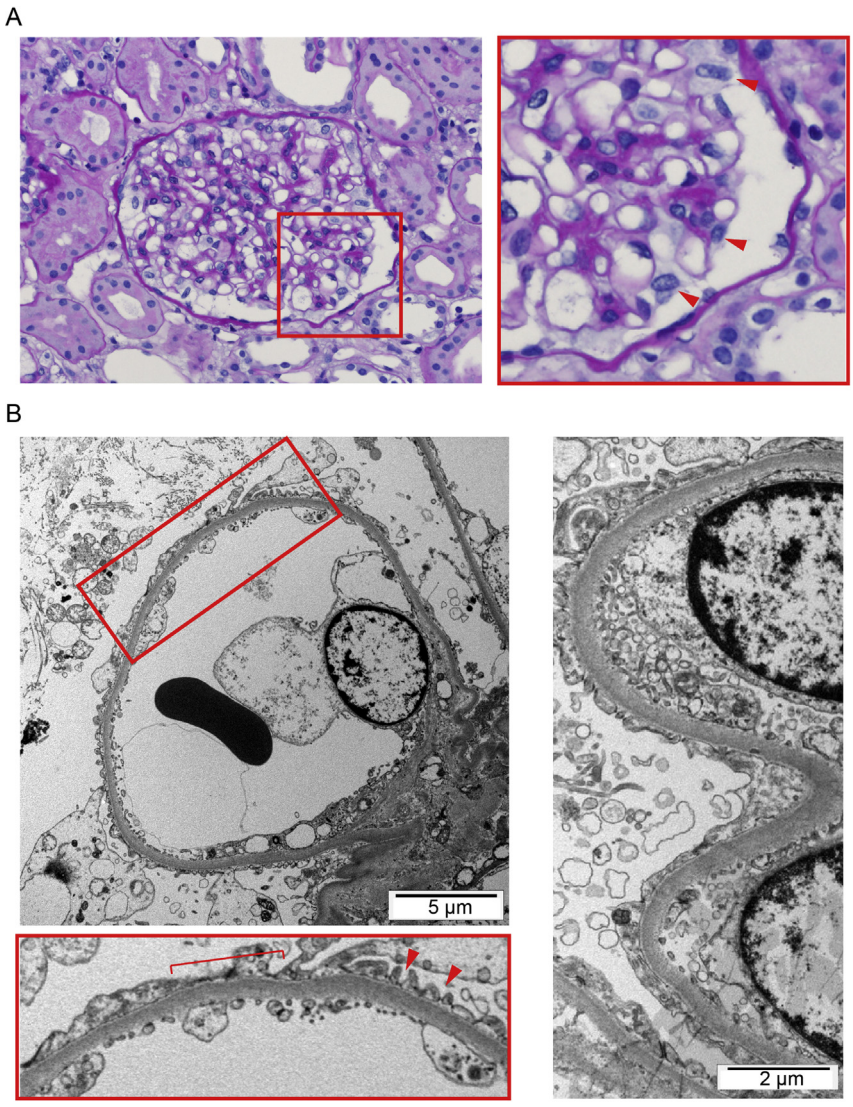

Figure 1. (A) Light microscopy of the Hantavirus-infected patient's kidney biopsy specimen shows a representative glomerulus. Mesangium and capillary tufts of the glomerulus are essentially normal. Swollen podocytes are indicated by arrows (periodic acid–Schiff staining; original magnification, ×400.) (B) Transmission electron microscopy shows podocyte foot-process effacement. (Lower panel) High magnification of segmental foot-process fusions with loss of slit diaphragms (bracket). Intact podocytes with slit diaphragms between adjacent foot processes are marked by arrows. (Right panel) High magnification of the cross sectional appearance of podocyte foot-process effacement.