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DIAGNOSTIC AND CLINICAL CHALLENGES OF HANTAVIRUS-ASSOCIATED ACUTE KIDNEY INJURY

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ABSTRACT

Introduction: Hantavirus infection is an uncommon zoonosis in Europe but remains an important cause of acute kidney injury, particularly in patients with environmental exposure to rodents. Renal involvement is the hallmark of the disease, although pulmonary manifestations may coexist and mimic immune-mediated pulmonary–renal syndromes, leading to diagnostic challenges in internal medicine.

Case description: A 46-year-old previously healthy man living in a rural area was admitted for acute febrile illness with asthenia and myalgia. Initial investigations revealed severe thrombocytopenia and acute kidney injury with proteinuria and microscopic haematuria. A computed tomography scan of the chest and abdomen showed bilateral pulmonary abnormalities, consistent with an acute pulmonary–renal syndrome. Extensive immunological and infectious investigations excluded autoimmune disease and alternative infectious causes. Hantavirus infection was confirmed by positive IgM and IgG serology, with molecular identification of Puumala virus. Renal biopsy demonstrated moderate acute tubular necrosis with minimal interstitial inflammation and preserved glomeruli. The patient was treated with supportive care only, resulting in rapid clinical improvement and complete recovery of renal function.

Conclusion: Hantavirus infection should be considered in patients presenting with acute pulmonary–renal syndrome, thrombocytopenia, and compatible epidemiological exposure. Early diagnosis allows appropriate supportive management, avoids unnecessary immunosuppressive therapy, and is associated with an excellent renal prognosis in Puumala virus infection.

KEYWORDS

Hantavirus, Puumala virus, acute kidney injury, pneumo-renal syndrome

LEARNING POINTS

- Hantavirus infection should be suspected in febrile patients with thrombocytopenia and acute pulmonary–renal involvement.
- Rural or rodent exposure is a critical epidemiological clue for diagnosing hantavirus-associated acute kidney injury.
- Puumala virus infection is usually self-limited and requires supportive care with an excellent renal prognosis.

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INTRODUCTION

Hantavirus infection is an uncommon but potentially severe zoonotic disease caused by enveloped ribonucleic acid (RNA) viruses of the Hantaviridae family[1]. In Europe, Old World hantaviruses predominantly cause haemorrhagic fever with renal syndrome (HFRS), a clinical entity characterized by systemic involvement with a marked tropism for the vascular endothelium, leading primarily to renal involvement but also to variable pulmonary manifestations[2]. Renal involvement is a major determinant of prognosis and is frequently reported, particularly in infections caused by Puumala, Dobrava-Belgrade, Hantaan, and Seoul viruses. Puumala virus infection, also referred to as nephropathia epidemica, generally leads to a milder form of HFRS but remains a frequent cause of acute kidney injury in endemic regions[3].

Despite the well-established endothelial tropism of hantaviruses, renal histopathological features remain insufficiently characterized, and management is largely based on supportive care, as no specific antiviral therapy is routinely recommended. Early recognition is therefore essential to avoid unnecessary invasive procedures and to ensure appropriate monitoring. We report the case of a middle-aged man presenting with an acute pulmonary-renal syndrome leading to the diagnosis of Puumala hantavirus infection, and we review the diagnostic and pathophysiological aspects relevant to clinical practice.

CASE DESCRIPTION

A 46-year-old man with no past medical history, presented to the emergency department with a 4-day history of high-grade fever (up to 40°C), asthenia, and diffuse myalgia. He lived in a rural area and reported regular exposure to farm environments, including recent cleaning of a chicken coop, as well as minor skin trauma from a thorn prick and an insect sting in the week preceding symptom onset. Three weeks prior to symptom onset, he had also acquired a rabbit. He reported no recent travel, no illicit drug use, and no known sick contacts. Physical examination showed fever of 38°C, blood pressure of 137/67 mmHg, heart rate of 95 beats per minute, and oxygen saturation of 96% on room air. Cardiopulmonary, abdominal, and neurological examinations were unremarkable. No rash or mucocutaneous bleeding was observed. Initial laboratory investigations revealed a white blood cell count of 6.93 g/l (normal range 4.5-10 g/l), haemoglobin of 14.2 g/dl (normal range 13.5-17.5 g/dl), and a platelet count of 42 g/l (normal range 150- 450 g/l). C-reactive protein was elevated at 89 mg/l (normal range <5 mg/l). Serum creatinine was 317 µmol/l (normal range 45-95 µmol/l), corresponding to an estimated glomerular filtration rate of 19 ml/min/1.73 m^2 (CKD-EPI equation) (normal range >100 ml/min/1.73m^2). Serum sodium was 128 mmol/l (normal range 135-145 mmol/l), potassium 4.2 mmol/l (normal range 3.5-5 mmol/l), and albumin 26.2 g/l (normal range 38-45 g/l). Urinalysis showed proteinuria at 4.12 g/l and microscopic haematuria without cellular casts. Lactate dehydrogenase levels were elevated at 380 U/l (normal range 80-200 U/l) and no schistocytes were identified on peripheral blood smear. Thoracoabdominal computed tomography revealed bilateral nonspecific pulmonary micronodules, perirenal fat stranding, and preserved kidney size. The clinical presentation was consistent with an acute pulmonary-renal syndrome. Renal biopsy revealed moderate acute tubular necrosis associated with mild interstitial oedema and minimal interstitial inflammation. Glomeruli were preserved, and no significant vascular lesions were identified *(Fig. 1)*. An extensive immunological workup, including antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, and cryoglobulinemia, was negative. Infectious investigations excluded leptospirosis and Legionella infection. Serological testing performed on serum samples using enzyme-linked immunosorbent assay (ELISA) showed positive hantavirus-specific IgM and IgG antibodies, which were confirmed by Western blot. Reverse transcription polymerase chain reaction detected Puumala hantavirus RNA, establishing the diagnosis of HFRS due to Puumala virus. Management consisted of supportive care, including intravenous fluid administration, antipyretics, and close monitoring of renal function and electrolyte balance. A short course of antibiotics was administered for a suspected secondary bronchial infection. The outcome was favourable. Patient general condition progressively improved and fever disappeared spontaneously on the third

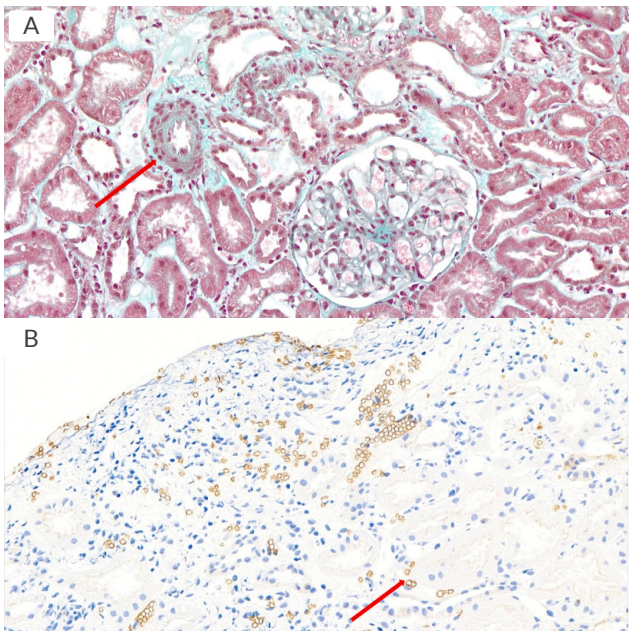


Figure 1. *Renal biopsy findings in Puumala virus associated nephropathy. A) Masson's trichrome stain, ×40. The interstitium shows moderate acute tubular necrosis with tubular epithelial cell swelling, luminal casts, and patchy interstitial edema (arrow). B) Immunohistochemistry for GLUT-1, ×40. Tubular epithelial cells show positive cytoplasmic staining for GLUT-1 (arrow), highlighting tubular integrity and confirming localization of viral injury to the tubular compartment.*

day. Laboratory monitoring showed platelet normalization at 1 week, C-reactive protein dropped to 10mg/l and glomerular filtration rate normalized at 69 ml/min/1.73 m^2. The patient was discharged after 10 days and was followed at our outpatient clinic. At 6 months he was asymptomatic with further improvement of laboratory values.

DISCUSSION

Hantavirus infection, although relatively uncommon, represents a significant cause of acute kidney injury (AKI), particularly in patients with environmental exposure to wild rodents in rural settings[2]. This case illustrates the diagnostic challenges associated with hantavirus-induced AKI and underscores the importance of considering this infection in patients presenting with unexplained fever, thrombocytopenia, and renal impairment, including in non-endemic areas or outside classical epidemic periods. The geographical distribution of hantaviruses closely reflects the ecology of their rodent reservoirs. Old World hantaviruses are endemic throughout Europe and Asia[4]. In 2023, approximately 1,885 cases of hantavirus infection were reported across 28 European countries, corresponding to an incidence of about 0.4 cases per 100,000 people, one of the lowest notification rates observed during the 2019–2023 period. The majority of cases were reported from Finland and Germany, which together accounted for more than half of all notifications. In France, hantavirus infections are mainly concentrated in the northeastern regions of metropolitan territory, with an average annual incidence of approximately 0.15 cases per 100,000 inhabitants. Surveillance data indicate around one hundred cases per year, predominantly affecting middle-aged adults, with a male predominance. Most infections are caused by Puumala virus, which is endemic in this region, although sporadic cases related to Seoul and Tula viruses have also been described[5]. The hallmark of hantavirus infection, particularly in cases caused by Old World hantaviruses such as Puumala and Dobrava-Belgrade viruses, is the development of HFRS. The pathogenesis of hantavirus disease is complex and involves a combination of endothelial dysfunction, immune activation, and host susceptibility. Viral replication occurs predominantly in endothelial cells, podocytes, and tubular epithelial cells without inducing a direct cytopathic effect[6]. This endothelial tropism leads to increased vascular permeability, which underlies many of the clinical manifestations of the disease. Endothelial dysfunction explains the frequent occurrence of proteinuria and haematuria. In addition, hantavirus-infected endothelial cells release adhesion molecules such as fibrinogen, fibronectin, and von Willebrand factor, which promote platelet activation and consumption, thereby contributing to thrombocytopenia and microvascular injury[7]. Clinically, HFRS typically evolves through successive phases, including febrile, hypotensive, oliguric, and convalescent stages. The oliguric phase is characterized by AKI with elevated serum creatinine, proteinuria, and haematuria. In nephropathia epidemica caused by Puumala virus, AKI is common but usually self-limited, with most patients achieving complete recovery of renal function, although long-term sequelae such as hypertension or subtle chronic kidney changes have been reported. Our case is consistent with this spectrum, presenting febrile illness, thrombocytopenia, and acute renal failure requiring supportive management. Renal involvement typically predominates in the renal cortex and manifests as an acute tubulointerstitial nephritis of variable severity, sometimes associated with mild glomerular involvement. Histopathological findings usually include vacuolization and necrosis of proximal tubular epithelial cells, interstitial oedema, mononuclear inflammatory infiltrates, and, in some cases, interstitial haemorrhage. Glomerular lesions are generally mild and nonspecific, although deposits of IgM and complement components have occasionally been reported[8]. In our patient, renal biopsy demonstrated moderate acute tubular necrosis with minimal interstitial inflammation and preserved glomeruli, findings consistent with previously described hantavirus-associated nephropathy and supporting a virus-related tubulointerstitial mechanism. Laboratory diagnosis of acute hantavirus infection relies on a combination of serological and molecular methods. Detection of nucleocapsid protein-specific IgM antibodies by ELISA is the cornerstone of diagnosis. Western blot improves diagnostic specificity and helps resolve cross-reactive serological results[9]. Molecular techniques, particularly reverse transcription polymerase chain reaction (PCR), are especially useful during the early phase of infection when viremia is present and allow species-level identification[9]. In our case, the diagnosis was confirmed by positive ELISA and Western blot serology, together with detection of Puumala hantavirus RNA by PCR. Management of hantavirus infection remains largely supportive and includes careful hemodynamic monitoring, fluid and electrolyte management, and renal replacement therapy when indicated. No antiviral therapy is currently routinely recommended. Ribavirin, a nucleoside analogue antiviral agent, has been shown to reduce mortality in severe forms of HFRS but its benefit in mild disease or in hantavirus cardiopulmonary syndrome remains controversial[9]. More recently, icatibant, a selective bradykinin B_2 receptor antagonist, has been used in a limited number of severe cases of nephropathia epidemica. By inhibiting bradykinin-mediated increases in vascular permeability, icatibant may reduce capillary leakage, hypotension, and renal oedema. Several case reports have described swift clinical and hemodynamic improvement following its administration, although evidence remains limited[10]. Prognosis largely depends on the viral species and the extent of organ involvement. Nephropathia epidemica caused by Puumala virus generally carries an excellent prognosis, whereas infections due to Hantaan or Dobrava viruses are associated with more severe disease and higher case fatality rates. Poor prognostic factors

include advanced age, significant comorbidities, marked thrombocytopenia, hypotension, and severe renal or pulmonary involvement. Although most patients recover fully, a minority may develop persistent hypertension, proteinuria, or mildly reduced glomerular filtration rate, highlighting the importance of long-term follow-up[6].

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