Hemorrhagic Fever with Renal Syndrome Caused by Hantavirus Infection: First Reported Case in Israel

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KEY WORDS: acute kidney injury, hantavirus, hemorrhagic fever with renal syndrome (HFRS), *Puumala orthohantavirus* (PUUV), Puumala, travel medicine

IMAJ 2022; 24: 621–622

We present the first reported case of hemorrhagic fever with renal syndrome (HFRS) caused by a Puumala type of hantavirus found in a visitor to Israel. As the initial presentation was non-specific and could fit any number of more common viral or tickborne infections, the diagnosis was difficult to make in a non-endemic area. As in many cases, the diagnosis was finally made due to repeated history taking and communication with the patient and his family. The clinical course was largely typical with prominent kidney injury. Less typically, pulmonary involvement also occurred.

PATIENT DESCRIPTION

A 77-year-old male tourist from southwest Germany presented to the emergency room 2 days after his arrival to Israel. Immediately after landing, he started vomiting and felt feverish. His past medical history was significant for Parkinson's disease treated with ropinirole, normal pressure hydrocephalus, and benign prostate hyperplasia.

On presentation, his temperature was 38.0°C with other vital signs within normal limits. He was obtunded and non-responsive to verbal stimuli. Physical examination revealed a mild resting tremor and facial flushing but was otherwise non-revealing. Laboratory results were significant for elevated creatinine (154 mmol/L, normal range 62–115 mmol/L), mild hyponatremia (126 mmol/L, normal range 136–145 mmol/L), mild thrombocytopenia (117 × 109 cells/L, normal range 166–389 × 109 cells/L), and elevated C-reactive protein (6.41 mg/dl, normal range < 0.5 mg/dl). Urine dipstick was positive for blood, and the fractional excretion of sodium was calculated to be 0.3%.

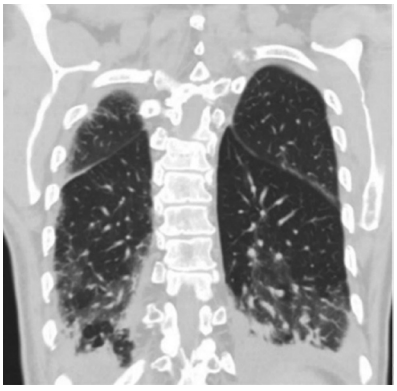
A computed tomography (CT) scan showed a few nodular and ground-glass opacities in the upper lobe of the right lung with signs of pulmonary congestion. There was marked bilateral perirenal fat stranding and thickening of the renal fascia with minimal fluid surrounding the right kidney [Figure 1]. The cranial images showed no structural abnormalities.

He was hospitalized with a working diagnosis of sepsis secondary to pneumonia or a urinary tract infection accompanied by acute kidney injury due to sepsis and dehydration. Treatment with intravenous ceftriaxone and isotonic fluids was initiated. Despite this treatment, the next day his condition continued to deteriorate. He required oxygen by nasal cannula and became severely agitated. Despite fluids, his urine output decreased and blood creatinine continued rising.

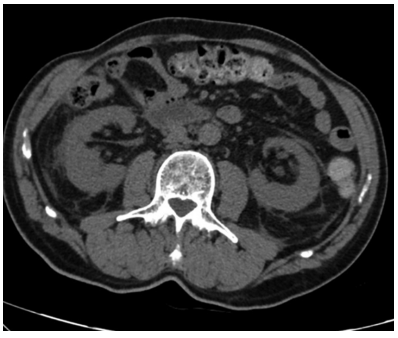
Laboratory tests further showed a worsening of his thrombocytopenia, reaching 71 × 109 platelets/L and his leukocytosis up to 17.9 × 109 cells/L (normal range 3.79–10.33 × 109 cells/L). A blood smear confirmed true thrombocytopenia with no signs of hemolysis. Urine microscopy showed a few scatted white blood cells and muddy-brown casts. Antibiotic coverage was broadened to include ampicillin aimed at *Enterococcus faecalis* growing from his urine cultures. Blood cultures were negative. Serologic studies for *Leptospira*, *Rickettsia*, *Coxiella burnetti*, *Treponema pallidum*, and human immunodeficiency virus were negative. A respiratory virus polymerase chain reaction (PCR) panel from a nasal swab was likewise negative. Echocardiography results were withing normal limits.

Figure 1. Whole-body computed tomography scan

[A] Signs of mild interstitial pulmonary congestion with small bilateral pleural effusions, along with ground-glass opacities in the right upper lobe



[B] Marked bilateral perirenal fat stranding, a minimal amount of fluid around the right kidney



As the patient continued to be intermittently obtunded and agitated, a second head CT was taken but showed no new findings. A lumbar puncture was contemplated but not performed at the insistence of the family, who instead offered an alternative diagnosis: Hantavirus infection because several cases recently diagnosed in their hometown. Hantavirus PCR and serologies were sent to the central virology laboratory at Sheba Medical Center, Tel Hashomer. IgM antibodies for hantavirus were reported as strongly positive, with serum PCR indicating infection with *Puumala orthohantavirus* (PUUV). After the diagnosis was made, antibiotic treatment was terminated.

During the next days, the patient continued to be oliguric, and creatinine continued to rise to a peak of 510 mm/L. The patient was followed closely, but no need for treatment with acute hemodialysis arose. After reaching a steady state, the patient entered a polyuric phase, reaching urine output of up to 6800 ml/day, requiring copious fluid infusion to mitigate fluid losses. Creatinine gradually normalized, reaching normal levels on the 12th day of hospitalization. By the day of his discharge, the patient had made a nearly full recovery and was well enough to travel under medical supervision back to Germany.

COMMENT

Hantaviruses are enveloped single-stranded RNA viruses forming a separate genus within the *Bunyaviridae* family. They are transmitted to humans by exposure to excreta from infected rodents. While other mammals may be infected, they do not infect humans. *Old-world hantaviruses* refer to the predominant group of hantaviruses in Europe and Asia. In Europe, the most common hantavirus is PUUV. This virus, identified as the causative agent in our case, is distributed throughout the continent. PUUV is the primary pathogen causing HFRS, classically manifesting with fever, visual disturbances, bleeding, hypotension, and severe kidney injury. The term *new-world hantaviruse* refers to the predominant species in the Americas. The northern Sin-Nombre virus and the southern Andes virus are known to cause the hantavirus cardiopulmonary syndrome (HCPS), which in its severe form can lead to respiratory failure and cardiogenic shock [1].

HCPS and HFRS are considered two distinct clinical phenotypes. Our case exhibited significant renal involvement. Considering this primary manifestation, it probably fits within the HFRS spectrum. However, mild pulmonary involvement manifesting as pulmonary congestion and the need for oxygen supplementation were also part of our patient's syndrome. This finding is notable as pulmonary involvement is not usually seen in the setting of HFRS. The common pathogenic mechanism to hantavirus syndromes has been suggested to be diffuse capillary leak, predominantly affecting the cardiopulmonary circulation in HCPS or the systemic-renal circulation in HFRS, although overlap is possible. The exact pathogenic mechanisms are still unclear, but impairment of endothelial cell defense against CD8 T-cell mediated cytotoxicity has been proposed as the main pathology [2].

There is still no proven therapy for hantavirus infections, and treatment is mainly supportive. Ribavirin has shown promise if administered early in the course of the disease [1]. The bradykinin receptor antagonist icatibant, which is usually used to treat acute episodes of hereditary angioedema, was described as a potent agent in the setting of severe HFRS [3]. While HCPS is often lethal despite best supportive care, HFRS caused by the PUUV harbors a favorable prognosis, with most patients returning to baseline kidney function.

In Israel, acute hantavirus infections are rarely reported. HCPS was previously described in Israel [4], but to the best of our knowledge, this is the first report of HFRS. The initial level of suspicion was low, and the diagnosis was finally made with the assistance of the patient's family. This low index of suspicion may lead to underdiagnosis of acute or subacute hantavirus infections. George et al. [5] found in an Israeli cohort IgG against PUUV in 12.3% (10/81) of hemodialysis patients, compared to 2% (1/50) of healthy controls. This previous infection may be a putative cause of renal damage, synergizing with other etiologies to ultimately cause end-stage renal disease. The source of these infections, however, remains unknown, especially as Israel is rich in people immigrating from Europe and Asia, where the initial infection may have occurred [5].

CONCLUSIONS

Hantavirus infection is a rare, difficult to diagnose, and possibly underdiagnosed infection in Israel and worldwide. A high index of suspicion should be required for patients arriving from abroad, and even developed countries have their own sets of unfamiliar endemic pathogens. In this case, the diagnosis could have been easily missed. Fortunately, communication and history taking have again proven to be the most potent tools a physician has. To the best of our knowledge, this episode is the first reported case of HFRS in Israel, although accumulating evidence we can speculate about the impact of undiagnosed infections.

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