New disease

An emerging infectious cause of renal impairment in the UK

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Hantaviruses are endemic in many central European countries, particularly the Balkans, infection causing non-specific 'flu-like symptoms and renal dysfunction which is self-limiting in the majority of cases. In this case, there was a diagnostic delay, resulting in numerous unnecessary investigations, prolonged hospital stay and almost an invasive renal biopsy. A travel history is therefore essential, to establish travel to an endemic region within the previous 2–6 weeks. With increasing travel and immigration, hantavirus is likely to be seen more frequently as an imported infection into the UK. However, further research is required to establish the potential for acquisition of infection here, as the animal host, the bank vole, is part of local wildlife. Therefore, the authors urge physicians to be alert to this possibility when faced with acute renal failure in association with an undiagnosed febrile illness, particularly when there is a history of an appropriate environmental or animal exposure.

BACKGROUND

This disease is likely to be seen increasingly in the UK as an imported infection due to patterns of travel and immigration, and in addition, as little is known about its endemicity in the UK, infection could be acquired here in people with occupational or recreational exposure, therefore, we wish to increase awareness of the syndrome in order to improve diagnosis and patient management.

CASE PRESENTATION

A 35-year-old Caucasian man presented to accident and emergency in January 2010 with a 4 day history of headache, backache, fever and myalgia. His symptoms were present on waking the morning after he had eaten at a Chinese restaurant. Initially headache predominated, which progressed to lumbar backache over 24 h. He had intermittent mild blurring of vision, but no orbital pain, and no other neurological symptoms, neck stiffness or photophobia. He developed fever and generalised myalgia, but no focal joint pain or swelling. He vomited once but had no other gastrointestinal upset. He also noticed dark urine, but denied frank haematuria, dysuria, frequency or oliguria. There were no respiratory symptoms, coryza or rash.

The patient had no previous medical history, was taking paracetamol and ibuprofen as required for his current illness, and had no allergies. He was married with one child, consumed 15–20 units of alcohol per week and did not smoke or take illicit drugs. He worked for London underground designing security systems but he had not been in a station for many months.

On examination, his temperature was 38.2°C, heart rate 110 beats per min and blood pressure 116/80. Oxygen saturations were 97% on room air with no respiratory distress. There were no signs of meningism, rash, lymphadenopathy or jaundice. He had dry mucous membranes, periorbital oedema, conjunctival suffusion and some right

upper quadrant tenderness, but no organomegaly. He was mildly tender over the lumbar spine. Cardiorespiratory, neurological and ear, nose and throat examinations were unremarkable.

INVESTIGATIONS

Results of initial investigations were as follows: haemoglobin 19.6 g/dl, packed cell volume 0.57, white cell count $17.2 \times 10^9/l$ (neutrophils 13.9, lymphocytes 2.9), platelets $80 \times 10^9/l$, urea 14.1 mmol/l, creatinine 150 $\mu\text{mol/l}$, albumin 32 g/l, sodium, potassium, bilirubin and transaminases levels were normal, C-reactive protein 90 mg/l and coagulation was normal. Urinalysis revealed protein ++ and blood ++. Chest radiograph was normal.

Further investigations (included in outcome and follow-up): ultrasound of renal tracts was normal. Blood, throat and urine cultures were negative, and nasopharyngeal swab for respiratory viruses was also negative. Blood film showed large reactive lymphocytes, low platelets, but no haemolysis. Serological testing was performed for leptospira, rickettsiae, Epstein Barr virus, cytomegalovirus, toxoplasmosis, HIV and hantavirus, as well as antistreptolysin O titre and meningococcal PCR. Antinuclear antibody, antineutrophil cytoplasmic antibody, immunoglobulins and complement testing were also requested. All were negative.

TREATMENT

The patient was admitted to a medical ward for intravenous fluids and monitoring of fluid balance and renal function. Blood, throat swab and urine were sent for culture and he was commenced on co-amoxiclav 1.2 g three times a day and doxycycline 100 mg twice daily.

OUTCOME AND FOLLOW-UP

On day 2, the patient's headache was resolving but lower back pain persisted. His fever also settled. His urine

Figure 1 Creatinine and platelet count through the course of the illness.

output was not accurately recorded, but appeared adequate. However, his creatinine increased to 332 $\mu\text{mol/L}$ and platelets dropped to $50 \times 10^9/\text{L}$ on day 3 (figure 1).

On more detailed questioning, he had travelled to Estonia, to spend Christmas and New Year with his wife's family, and returned to the UK 3 weeks before becoming unwell. He stayed in a rural, forested area, where he spent a lot of time outdoors sledging, and in a barn used for storage. He denied any animal contact or tick bites, ate local foods, and was well throughout his trip. He denied sexual contact other than his wife. Friends who had eaten with him in the restaurant were well.

On review by the infectious diseases team, a number of infections were considered. The neutrophilia was suggestive of bacterial infection, and the renal impairment and low platelets in keeping with bacterial sepsis, for example, streptococcal or meningococcal infection. Further possibilities included leptospirosis, typhus, or haemorrhagic fever with renal syndrome caused by hantavirus. Haemolytic uraemic syndrome due to *Escherichia coli* 0157 was felt to be unlikely. Non-infective possibilities included a vasculitis, primary glomerulonephritis, or drug-induced tubulointerstitial nephritis.

Ultrasound of renal tracts was normal. Blood, throat and urine cultures were negative, and nasopharyngeal swab for respiratory viruses was also negative. Blood film showed large reactive lymphocytes, low platelets, but no haemolysis. On haematological review, this was felt to be in keeping with acute viral infection, rather than a haematological disorder. Serological testing was performed for leptospirosis, rickettsiae, Epstein Barr virus, cytomegalovirus, toxoplasmosis, HIV and hantavirus, as well as antistreptolysin O titre and meningococcal PCR. Antinuclear antibody, antineutrophil cytoplasmic antibody, immunoglobulins and complement testing were also requested. A renal opinion was sought and he was transferred to the renal unit for monitoring and consideration of renal biopsy. His renal function normalised over days without need for dialysis, and he was discharged to complete a 2 week course of

doxycycline. Two weeks later, he still suffered from low-grade headaches but renal function remained normal. On review of outstanding results, hantavirus IgG (Puumala serotype) was positive at 1:4096.

DISCUSSION

Hantaviruses, of the *Bunyaviridae* family, have a natural reservoir in rodents with no detrimental effect on their survival. Transmission to humans occurs by inhalation of aerosolized excreta. Hantaan, whose host is the field mouse, is the most important worldwide, causing haemorrhagic fever with renal syndrome (HFRS) in Asia with lethality approaching 15%.¹ Puumala, present in bank voles (figure 2), is the main species in Europe, resulting in the milder illness nephropathia epidemica (NE) with 0.1% lethality.² North and South American species have various rodent hosts, and cause hantavirus pulmonary syndrome (HPS) in humans with a 50% lethality.³

There is some evidence for endemic hantavirus infection in the UK, with two cases reported in Scotland in the 1980s,^{4 5} and a series of five acute and 14 probable cases identified when serological screening of patients with symptoms was performed after three reports of confirmed hantavirus in Somerset between 1991 and 1992.⁶ Unfortunately, the exact serotype was not characterised. A seroprevalence study in Northern Ireland including 627 possible cases and 100 controls demonstrated 2.1% seropositivity in suspected cases, almost exclusively against a rat-derived hantaviral antigen of the Seoul serotype.⁷ Indeed, antibodies to Seoul and Hantaan were detected in 21.6% of brown rats, 3.2% of field mice and 28.8% of house mice in Northern Ireland.⁸

The bank vole host to Puumala virus is ubiquitous in the UK (excluding Northern Ireland), but surprisingly little is known about prevalence of Puumala infection. With increasing cases of nephropathia epidemica being reported in regions of north west Europe, due to effects of climate change, environment, rodent host ecology and human

Figure 2 Bank vole, *Clethrionomys glareolus*. Image courtesy of Offwell Woodland and Wildlife Trust; www.courtrysideinfo.co.uk.

behaviour on transmission dynamics, there is the potential for similar epidemics to take place in the UK.⁹

NE typically affects men aged 35–42 years, with farming, forestry, animal-trapping and military work as occupational risks.² Exposure may also occur during camping, or entering long abandoned buildings in endemic areas, however, the risk to tourists is low.¹⁰

After a 1–6 week incubation, sudden onset fever and headache occur, followed by gastrointestinal upset, back pain and petechial haemorrhages. Transient myopia occurs due to forward movement and thickening of the lens,¹¹ and is presumably what our patient was describing as blurred vision. 80%–90% of NE cases are relatively asymptomatic, though renal impairment with creatinine typically exceeds 150 mol/l, oliguria, haematuria and proteinuria may develop.^{2–3} Leucocytosis and thrombocytopenia occur in approximately 50% of NE cases.^{2–3} Five per cent of hospitalised NE patients will require renal replacement therapy (RRT), in contrast to 30%–50% with HFRS.¹² Serious haemorrhagic complications are uncommon.

Diagnosis is made by serological tests for hantavirus IgM and IgG, which are present by day 7 of infection.² Indirect immunofluorescence or enzyme immunoassays are most widely used to detect antibody against a range of hantavirus antigens: Puumala, Dobrava, Sin Nombre, Seoul and Hantaan, and can be performed on clotted blood sent to the Special Pathogens Reference Unit at the Health Protection Agency in Salisbury.¹⁰

Treatment is largely supportive correcting fluid balance, haemodynamic compromise and bleeding disorder. Admission to a high dependency unit and renal consultation is advised as short-term RRT may be required. Paracetamol is the preferred analgesic, avoiding non-

steroidal anti-inflammatories due to potential bleeding complications. Ribavirin causes increased mutations in replicating hantavirus,¹³ and reduces mortality in HFRS if commenced before the oliguric phase,¹⁴ but is not indicated in mild cases of NE where prognosis for renal recovery is favourable.

This case was most likely imported from Estonia, although the actual burden of hantavirus in the UK is unknown, and due to the non-specific nature of the presenting features, many cases could go unrecognised.⁹ Therefore, we urge physicians to be alert to this possibility when faced with acute renal failure in association with an undiagnosed febrile illness, particularly when there is a history of an appropriate environmental or animal exposure, as diagnosis may prevent unnecessary invasive investigations and interventions, and provide useful prognostic information.

Learning points

- ▶ Careful attention to travel, occupational and recreational history.
- ▶ Think of hantavirus infection in patients presenting with acute renal failure in association with a febrile illness and significant exposure, as a positive test may prevent unnecessary invasive diagnostic procedures such as renal biopsy.
- ▶ Further study is needed to investigate seroprevalence of hantavirus in UK rodents and humans.

Competing interests None.

Patient consent Obtained.

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