Case reports

A pilgrim's progress: severe *Rickettsia conorii* infection complicated by gangrene

This challenging case of acute febrile illness and rapidly evolving petechial rash and digital gangrene in a traveller who returned from North India and Nepal highlights the need for a high index of suspicion for rickettsial infection in returned travellers.

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Clinical record

A 47-year-old Australian man of Vietnamese origin presented to hospital 3 days after returning from a 2-week pilgrimage to Nepal and India in January 2012 with a 10-day history of fever and myalgia. He had developed high-grade fever with chills and rigors associated with myalgia 7 days after arriving in Nepal. Two days later, he developed nausea and vomiting. He had been vaccinated for hepatitis B and cholera before travel. He was not taking prophylactic antibiotics. He travelled with a group of 10 others who remained well. He recalled receiving a few mosquito bites, and noted rodent infestation and stray dogs in some of the temples he visited. A doctor in the group treated him empirically with oseltamivir after his initial symptoms began. A rash developed 2 days before his admission and 9 days after the onset of symptoms.

The main findings of an examination on admission were a high fever (40°C), a macular erythematous rash over his trunk and extremities sparing his palms and soles, and facial flushing. There were no eschars.

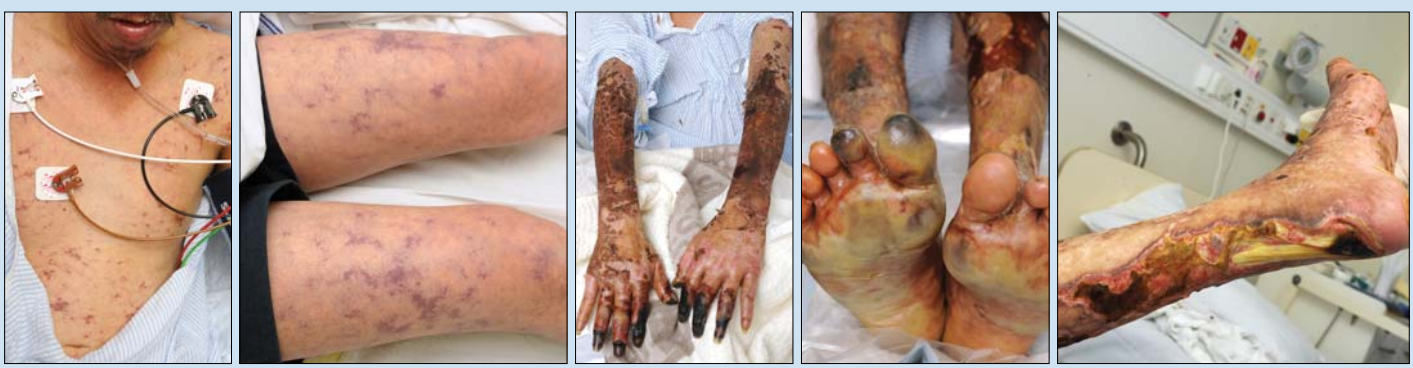
Laboratory investigations on admission showed a platelet count of 44×10^9/L (reference interval [RI], 150–450×10^9/L), white cell count of 14×10^9/L (RI, 4–11×10^9/L; 88% neutrophils), and haemoglobin concentration of 124 g/L (RI, 135–175 g/L). Biochemical tests and liver function tests showed the following levels (with RIs in parentheses): sodium, 124 mmol/L (137–145 mmol/L); urea, 6.1 mmol/L (2.7–8.0 mmol/L); creatinine, 74 µmol/L (50–120 µmol/L); albumin, 21 g/L (34–48 g/L); lactate dehydrogenase, 478 U/L (110–230 U/L); bilirubin, 31 µmol/L (2–24 µmol/L); γ-glutamyl transferase, 242 U/L (< 60 U/L); alkaline phosphatase, 243 U/L (30–110 U/L); alanine aminotransferase, 136 U/L (< 55 U/L); and aspartate aminotransferase, 159 U/L (< 45 U/L). The international normalised ratio was 1.2 (0.9–1.2). Laboratory features of disseminated intravascular coagulation such as elevated D-dimer and low fibrinogen concentrations were not present. There was no evidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Differential diagnoses included leptospirosis, enteric fever, dengue fever, chikungunya, malaria, rickettsiosis and influenza. Results of initial investigations were suggestive of dengue fever (IgM-positive, IgG-negative, although a test for dengue virus NS-1 antigen was negative). Blood cultures and serological tests for leptospirosis and rickettsia at admission were negative. Because of the broad differential diagnosis, and despite the initial positive serological test for dengue virus, the patient was treated empirically with ceftriaxone and doxycycline and nursed in a side room with infection control droplet precautions.

Over the next 48 hours, the patient developed increasing thigh pain, conjunctival injection, and his rash evolved into a petechial/haemorrhagic rash, particularly over the legs. He developed bilateral leg oedema. His fingertips and toes became dusky and swollen with poor capillary refill (Box 1). His oxygen requirement increased and he was transferred to the intensive care unit. Compartment syndrome was ruled out.

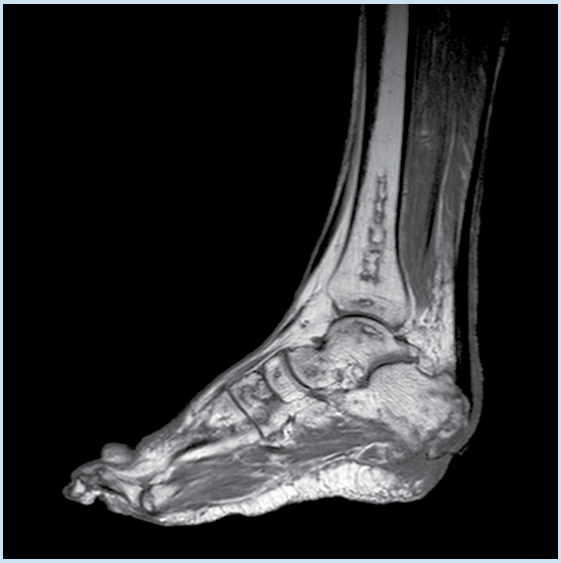
A skin biopsy showed epidermal necrosis, fibrin thrombi and associated vascular necrosis with variable inflammatory

1 Images of the patient's rash and developing symptoms at 12 days and 40 days after symptom onset



Day 12. *Day 40.*

2 Magnetic resonance image showing osteonecrosis of the marrow of the patient's tibia, fibula and bones of the foot



infiltrates including focal leukocytoclasis. A vasculitic component was reported, though not prominent. The result of a test for autoimmune vasculitis was negative. Therapy with doxycycline and ceftriaxone was continued. The patient's fever persisted and the digital ischaemia progressed. A ketamine infusion was initiated to control pain from the digital ischaemia. The white cell count increased to 34.3×10^9/L; the platelet count had recovered (539×10^9/L). Rheumatologist and vascular surgeon opinions were sought. Therapy with heparin (infused) and prostacyclin was commenced to improve microvascular perfusion. Methylprednisolone was given for 3 days, followed by prednisolone at a dose of 1 mg/kg, after which there was marginal improvement in the digital ischaemia.

The patient developed hypotension 48 hours later. This was associated with abdominal distension and a drop in the concentration of haemoglobin to 63 g/L. Computed tomography angiography of the abdomen showed a large retroperitoneal bleed with multiple sites of venous ooze. Prostacyclin and heparin infusions were ceased and the patient's haemodynamic status stabilised after transfusion of 9 units of blood. Repeat serological tests were performed 2 weeks after admission to hospital. The results for dengue IgM, IgG and NS-1 antigen were negative, suggesting an initial false-positive result. Repeat serological tests for rickettsia (indirect microimmunofluorescence assay detecting IgG and IgM antibody) were performed at the Australian Rickettsial Reference Laboratory using an inhouse assay for a range of rickettsia from the spotted fever group and typhus group. No antibody was detected in the patient's serum on presentation (titres all <128). However, the following titres were found in his convalescent serum:

- Spotted fever group — *R. australis* (Queensland tick typhus), 4096; *R. honei* (Flinders Island spotted fever), 1024; *R. conorii* (Mediterranean spotted fever), 8192; *R. sibirica* (North Asian tick typhus), 2048; *R. rickettsii* (Rocky Mountain spotted fever), 4096; *R. akari* (Rickettsial pox), 4096; and
- Typhus group — *R. prowazekii* (epidemic typhus), 256; *R. typhi* (Murine typhus), 1024.

These findings demonstrate seroconversion to rickettsia, and the high titre for *R. conorii* (8192) suggests that this may have been the infecting pathogen.

A real-time polymerase chain reaction targeting the citrate synthase gene was performed retrospectively on serum obtained on the day of admission. The result was positive, indicating rickettsia of the spotted fever group or typhus group, but further DNA amplification for species identification was unsuccessful. The patient completed 21 days of therapy with doxycycline. His fever resolved within 20 days of symptom onset and 10 days after the initiation of antibiotic therapy. Blurring of vision was noted 2 weeks into his hospital admission and fundoscopy showed retinal haemorrhages with focal thrombosis and mild papilloedema.

The patient underwent multiple surgical debridement procedures and amputations of gangrenous digits, and is currently undergoing rehabilitation. Twelve months later, he is still receiving ongoing treatment for chronic osteomyelitis of the calcaneum, but is otherwise well although unable to work. Osteomyelitis developed because of chronically exposed bone and ischaemic necrosis. Magnetic resonance imaging revealed multifocal osteonecrosis involving the marrow of the tibia, fibula and bones of the foot, most prominently the calcaneus (Box 2). The causative organism was *Escherichia coli* resistant to most β-lactam antibiotics (extended-spectrum β-lactamase-producing) and quinolones. As a result, the patient required a prolonged period of therapy with meropenem.

Discussion

Rickettsiae are small, obligate intracellular gram-negative bacteria. Rickettsial infections fall into three groups: the spotted fever group, the typhus group and the scrub typhus group. The vectors are invertebrates, whose habitats determine the geographical and temporal distribution of rickettsiae. Clinical manifestations vary between regions and hosts.[1]

The rickettsial species in this case — *R. conorii* — belongs to the spotted fever group, which is distributed worldwide.[1] Three known spotted fever group rickettsiae are recognised in Australia: *R. australis*, occurring down the east coast of Australia and transmitted by mammalian ticks; *R. honei*, occurring in South Australia, Victoria and Tasmania, and transmitted by reptile ticks; and *R. felis* in Victoria and Western Australia transmitted by cat fleas.[2] This is the first report of severe *R. conorii* infection in a traveller returning to Australia.

R. conorii infection occurs mostly in regions adjacent to the Mediterranean Sea as well as in sub-Saharan Africa, India and countries adjacent to the Black Sea, including Turkey, Bulgaria and Ukraine. Mediterranean spotted fever rickettsia (a subspecies of *R. conorii*, known as *Rickettsia conorii subsp. indica*) is known to occur in the Indian subcontinent, although there are no reported cases from Nepal in the literature.[3] A case of *R. honei* infection has been reported from Nepal.[3]

R. conorii is transmitted to humans by bites of the tick species *Rhipicephalus sanguineus*, typically carried by dogs.

R. conorii is able to adapt to different environments (ie, physiological conditions and nutrient changes) between hosts. Cases of *R. conorii* infection occur mainly in warmer months. On transmission to a human, *R. conorii* invades host cells, where it begins to replicate. The incubation period ranges from 3 to 15 days, depending on the route of pathogen entry and the pathogen load.

The common triad of clinical manifestations include fever, headache and maculopapular rash (seen in 97% of patients) with or without an eschar, which is pathognomonic and seen in over 70% of cases. The diagnostic feature of the eschar was first described by Boinet and Pieri in Marseille in 1925 and represents the site of inoculation, usually localised to the legs, arms or trunk. It has been identified on the scrotum in 2% of cases and found on scalp and retroauricular areas in children.[4,5] Petechial rash occurs in less than 10% of cases. Patients often have myalgia. Laboratory investigations often show neutropenia or lymphopenia, thrombocytopenia and elevation of liver transaminase levels. Hyponatraemia is commonly described.

Fulminant infection and death occur in 1.4%–5.6% of hospitalised patients, which is higher than the rate for most spotted fevers other than Rocky Mountain spotted fever, which has a mortality of 5%–7%. The severity of infection is related to the virulence of the pathogen, older age, male sex, G6PD deficiency, alcohol consumption, African American race, presence of pulmonary infiltrates and delayed administration of doxycycline, with a 20% increase in major organ dysfunction with each day of delay.[6,7] Doxycycline is the treatment of choice, although other antimicrobials such as macrolides have been reported to be effective.[8] The severity of disease in our patient was probably a result of his delayed presentation, as well as the virulence of the infecting rickettsial species.

Thrombotic complications are seen mostly in infections with *R. rickettsii* and *R. conorii*, and are due to disseminated endothelial injury, release of procoagulant factors, and activation of the coagulation cascade.[6] However, contrary to what is frequently described in case reports, disseminated intravascular coagulopathy is rare.[6] There is little in the literature on the treatment of this condition. Prednisolone has not been shown to confer additional benefit.[9] Multifocal osteonecrosis, as seen in our patient, has not been reported in the literature, but is probably caused by microvascular occlusion as seen in skin and other organs such as the eye.

Massive skin and tissue necrosis, and consequent gangrene requiring digit amputations of a magnitude similar to that seen in this case have been reported in a 54-year-old woman with *R. australis* infection complicated by type 1 diabetes in Queensland in 2009, and in an 8-year-old girl with Rocky Mountain spotted fever in 1978.[10] Both patients had an initial presentation of fever and rash which progressed rapidly to widespread dermal necrosis requiring significant debridement of eschar, skin grafting, amputation and challenging wound care, as for our patient.

Diagnosis of spotted fevers is based on molecular and, more commonly, serological techniques. The use of polymerase chain reaction to detect the citrate synthase (glt) gene from serum or tissue is useful in detecting early infection. Serological tests for rickettsia, preferably on paired sera, are a useful diagnostic tool in the later stages, especially in the third week of illness. Indirect fluorescent antibody assay is the best method of serological testing. Enzyme-linked immunosorbent assay, latex agglutination and western blot may also be used. There is significant cross-reactivity between rickettsia of the spotted fever and those of the typhus groups. The infecting rickettsiae usually produce the highest titre, but sometimes the end points for multiple species are the same. Laboratories should test both local and "overseas" rickettsial antigens to indicate the causative organism. Shell-vial cultures are not routinely performed and require a physical containment level 3 laboratory.

This case highlights that rickettsial infection should be considered and empirically treated in returned travellers with rash, even in the absence of classical features such as presence of eschar or headache, particularly when they have travelled to areas where rickettsial disease is endemic (including parts of Australia), as severe complications may occur in patients in whom treatment is delayed. It is important to note that serological tests for rickettsia may be negative until the third week of clinical illness, so a high level of clinical suspicion should be maintained, and molecular testing is required to obtain an early diagnosis. Thrombotic complications of infection, while rare, are related to infections with specific rickettsial species (*R. rickettsii* and *R. conorii*), delayed treatment and specific host factors. Early therapy with doxycycline and supportive care remains the most effective treatment for this condition.

Competing interests: No relevant disclosures.

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