CASE REPORT

Of mice and men

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SUMMARY

A case study of a patient returning from sub-Saharan Africa with a febrile illness and symptoms reminiscent of a previous malarial infection is discussed. The patient had a relative bradycardia with respect to febrile episodes, a transient macular rash and thrombocytopenia. The illness was conservatively managed for 1 month before positive *Rickettsia* serology and PCR results were reported. The patient was then treated with doxycycline with a complete resolution of symptoms.

BACKGROUND

This case demonstrates an underdiagnosed cause of febrile illness in the returning traveller.

Rickettsial diseases are varied and are broadly divided into typhus and spotted fever groups. A high index of suspicion is required for diagnosis, as well as appreciation of ecological factors involved in disease transmission and geographical knowledge of areas of endemic infection.

CASE PRESENTATION

In December 2012, a 53-year-old Caucasian man working for the British Embassy, presented with a 6-day history of fever, rigors, myalgia, headache and retro-orbital pain. He developed symptoms the same day he arrived in the UK from Nairobi, Kenya, where he has a family home.

Notably, no other members of his family were unwell. He had spent 3 days in Kenya, and prior to this, he had spent 2 weeks living and working in

Juba, the capital of South Sudan. He described feeling similar to when he contracted malaria, 20 years previously. He took atovaquone-proguanil (Malarone) chemoprophylaxis and slept under an insecticide-treated net. He had been immunised against yellow fever.

On examination, he was febrile at 39°C, with a respiratory rate of 20 breaths/min, heart rate 77 bpm (demonstrating a relative bradycardia, see figure 1), blood pressure 107/62 mm Hg and oxygen saturations 99% on room air. He developed an erythematous, macular rash on his back only at times of high fever. There was no lymphadenopathy and between episodes of fever, his skin was clear, with no rashes. No mucosal lesions were identified. Abdominal examination revealed mild right-upper quadrant tenderness, but there was no palpable hepatomegaly or splenomegaly. His case was discussed with a specialist at The London School of Hygiene and Tropical Medicine and advice was given not to initiate any treatment until a diagnosis was made. Following recommendations, blood was tested 2 weeks after the onset of symptoms for typhoid, dengue, malaria, typhus, *Toxoplasma*, brucella, cytomegalovirus (CMV), Epstein-Barr virus (EBV), sexually transmitted infections, yellow fever, tick-borne encephalitis and chikungunya (alphavirus).

INVESTIGATIONS

Initial blood test showed mild thrombocytopenia with platelets of $114 \times 10^9/L$, haemoglobin 14.8 g/dL,

Figure 1 The patient observation chart displaying relative bradycardia with temperature in °C and heart rate.

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white cell count $4.7 \times 10^9/L$, neutrophils $3.3 \times 10^9/L$, lymphocytes $0.8 \times 10^9/L$, monocytes $0.5 \times 10^9/L$ and eosinophils $0.1 \times 10^9/L$. Three blood films for malarial parasites and malarial antigen tests for *Plasmodium vivax* and *Plasmodium falciparum* were negative. Blood films showed a left shift of neutrophils and occasional atypical lymphocytes.

Urea and electrolytes showed: sodium 141 mmol/L, potassium 3.7 mmol/L, urea 5.8 mmol/L, creatinine 88 $\mu\text{mol/L}$ and magnesium 1.01 mg/dL. Liver function tests showed: bilirubin 11 $\mu\text{mol/L}$, alkaline phosphate 77 IU/L, alanine aminotransferase 49 IU/L, albumin 49 g/L and International Normalised Ratio 1.0. C reactive protein was elevated at 187 mg/mL. His chest radiograph was normal.

Serological investigations for dengue (IgM and IgG antibodies), brucella (ELISA IgG and IgM antibodies), HIV (1/2 antigen/antibody), *Toxoplasma* (IgM and IgG antibodies), *Syphilis* (IgM and IgG antibodies), alphavirus (chikungunya; IgG and IgM antibodies), CMV IgM antibody and EBV viral capsid antigen antibody were negative. Multiple stool and blood cultures did not grow any pathogens. IgG to yellow fever virus was positive at greater than 1 : 10 titre, consistent with his previous yellow fever immunisation.

A CT scan of the chest, abdomen and pelvis was unremarkable, without evidence of lymphadenopathy, malignancy or abscess.

DIFFERENTIAL DIAGNOSIS

Malaria, dengue, typhoid, brucella, acute HIV infection, leptospirosis, yellow fever and Rift Valley fever.

TREATMENT

The patient was managed with supportive treatment, comprising of fluids, antipyretics and analgesia. He continued to spike fevers for 4 days, most prominently at night, with persistent elevation in inflammatory markers and his platelet count fell to a nadir of $83 \times 10^9/L$. He also transiently developed a dry cough and some pleuritic chest pain, but serial chest radiographs were unremarkable.

The patient self-discharged before *Rickettsia* serology was available, as he wished to enjoy his holiday. A few days later, *Rickettsia* serology results were reported by the Rare and Imported Pathogens Laboratory, Porton Down, Salisbury and showed positive IgM antibodies to typhus fever group, *Rickettsia typhi*, with negative IgG antibodies. A semiquantitative titre of 1 : 256 was obtained by serial dilution. The assay used was an indirect immunofluorescent assay for the detection of human IgM and IgG antibodies to *Rickettsia* antigens: inactivated *Rickettsia rickettsii* and *R typhi* (FOCUS diagnostics kit, USA). IgM and IgG antibodies to *R rickettsii* (spotted fever group) were negative. PCR was positive to *Rickettsia* DNA (with low copy numbers) and given the clinical history, the Rare and Imported Pathogens Laboratory team felt that the diagnosis was most consistent with murine typhus (endemic typhus), caused by *R typhi* infection. Another possibility would be infection with *Rickettsia prowazekii*; however, the laboratory was unable to provide more specific speciation.

OUTCOME AND FOLLOW-UP

On advice of the local hospital microbiologists, the patient was then instructed to collect a 5-day prescription of doxycycline, which led to a complete recovery, 1 month after the onset of symptoms.

DISCUSSION

Murine (endemic) typhus is a flea-borne infectious disease caused by *R typhi*. The true incidence of this infection is difficult to establish because of the difficulty in distinguishing murine typhus from other causes of rash and fever. It is estimated that undiagnosed cases of murine typhus surpass reported cases by a factor of 4 to 1.¹ The organism, in common with other Rickettsiales, is an obligate intracellular, Gram-negative bacterium. It is primarily transmitted by the rat flea, *Xenopsylla cheopis*. Humans are infected by inoculation of infective flea faeces in usually painless bite wounds.

Murine typhus is prevalent in a wide variety of environments from hot and humid, to cold and semiarid. The disease is prevalent in every continent except Antarctica¹ and remains endemic to tropical and subtropical seaboard regions worldwide.² One study of travellers returning to France reported that the most common sites of murine typhus acquisition were Africa and Southeast Asia.³ In Juba, South Sudan serological studies indicate a high concentration of exposed individuals, with antibodies to *R typhi* seen in 33%.⁴ Reduction of human cases is brought about by the control of rat populations and their ectoparasites.^{1 4}

The primary pathological lesion is an inflammatory vasculitis characterised by perivascular infiltration of lymphocytes, macrophages, plasma and mast cells. Murine typhus is typically a mild illness with an incubation period of 8–16 days. The onset of the symptoms is usually relatively abrupt with fever, headache, chills and myalgia. Rash occurs in 20–50% of patients, typically near the end of the first week of illness. The rash appears as a maculopapular eruption on the trunk and spreads peripherally, sparing the palms and soles.⁵ This can aid in the differential diagnosis to distinguish the illness from malaria, as although rash has been reported with malaria, it is uncommon.

The mainstay of diagnosis is the indirect fluorescent antibody test. Timing of serological testing, relative to the onset of symptoms, is important in the interpretation of the result. Testing during the first 6 days of illness yields a positive serology in approximately half of those infected. By 13–15 days after onset of symptoms, all infected cases should yield a positive result, which persists for 3 weeks.⁶ Therefore, the appropriate timing of serological testing is as early as possible with an additional antigen testing by PCR, then at 1 week, then 3 weeks if there is a clinical suspicion. Convalescent testing should then follow this.

The treatment of choice is doxycycline or chloramphenicol, which hastens recovery. The clinical syndrome of murine typhus may be confused with many other acute infections, including malaria, typhoid, paratyphoid, leptospirosis, dengue and yellow fever. A relative bradycardia can be observed in all of these illnesses⁷ with one series reporting the finding of relative bradycardia in 49% of rickettsioses.⁸

The most commonly identified cause of systemic febrile illness in the traveller returned from sub-Saharan Africa is malaria.⁹ Various reports suggest Rickettsial infections, as a group which lie in the top three most frequent diagnoses,^{9–11} with one reporting 56 cases/1000 patients with a systemic febrile illness, returning from sub-Saharan Africa.⁹

Juba is a port on The Nile River in South Sudan. The patient had resided in an urban prefabricated camp and although he had not seen any rodents, he was aware of rat habitats by the riverside, which he occasionally visited. Unfortunately, due to the patient's professional travel commitments, we were unable to obtain convalescent *Rickettsia* serology results.

In conclusion, it is appropriate to have a high index of suspicion for Rickettsial infection in the returned traveller. Additional points in the history should include contact with large rat populations and other flea-carrying and louse-carrying animals.

Learning points

- ▶ Rickettsial infection in the traveller returning from sub-Saharan Africa is underdiagnosed and is more common than generally appreciated.
- ▶ The clinical presentation of Rickettsial infection is often non-specific and should be considered as a differential diagnosis when investigating suspected malaria.
- ▶ Knowledge of geographical areas where Rickettsial infections are endemic and a history including wildlife contact and insect bites are useful in making the diagnosis.

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