Fever, rash and hepatitis; what's the differential

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Introduction

A 55 year old male presented to the emergency department with a 7 day history of fever, myalgia and headache. On the day of presentation he had developed diarrhoea and vomiting, and had had an episode transient confusion. He was previously fit and well with no significant past medical history. The patient lived with his wife and had returned from a family holiday to a resort in Cyprus 3 weeks prior to presentation. On further questioning he worked as an electrical contractor and had been recently working in a local zoo, where he had been changing light bulbs in a warthog enclosure.

On examination he had a fine maculopapular rash over his abdomen and back. Chest was clear, heart sounds were normal and abdomen was soft. Small reactive cervical, axillary, and inguinal lymph nodes were palpable.
Observations on presentation showed a temperature of 38.7^{o}C and a heart rate of 110, he was normotensive.

Results

Blood tests revealed a normal full blood count, CRP of 84, sodium of 119, normal renal function and an acute hepatitis. ALT was 640, bilirubin 26 and ALP was 320.
A CT head was normal and a lumber puncture had a normal WCC, protein and glucose. CSF viral PCR was negative.
Liver USS showed increased echogenicity in the liver consistent with hepatitis but no focal lesions.

Initially he was started on Ceftriaxone to cover CNS infection pending the lumber puncture results. While an inpatient his liver function deteriorated before improving. A full infective screen was sent including specialist tests to the Rare and Imported Pathogens Lab (RIPL).

A full set of tests were sent including specialist tests to the rare and imported pathogens lab (RIPL). Initial positive test results showed hepatitis E IgM, and at this point ceftriaxone was stopped. Subsequently the results from RIPL showed and epidemic typhus group IgM was positive with a low titre of 1 in 64. He was treated in empirically with doxycycline and further samples were sent. The patient clinically improved and was discharged with infectious diseases follow up.

Hepatitis E confirmatory testing was negative for IgM and IgG and PCR –ve so it is likely that this initial result was cross reactivity.

Repeat epidemic typhus group serology, 6 weeks later showed an IgM with positive titre of 1 in 1,024 and epidemic group IgG positive 1 in 2,048 which is maximum titre.

Figure 1 Xenopsylla Cheopis the oriental rat flea (1)

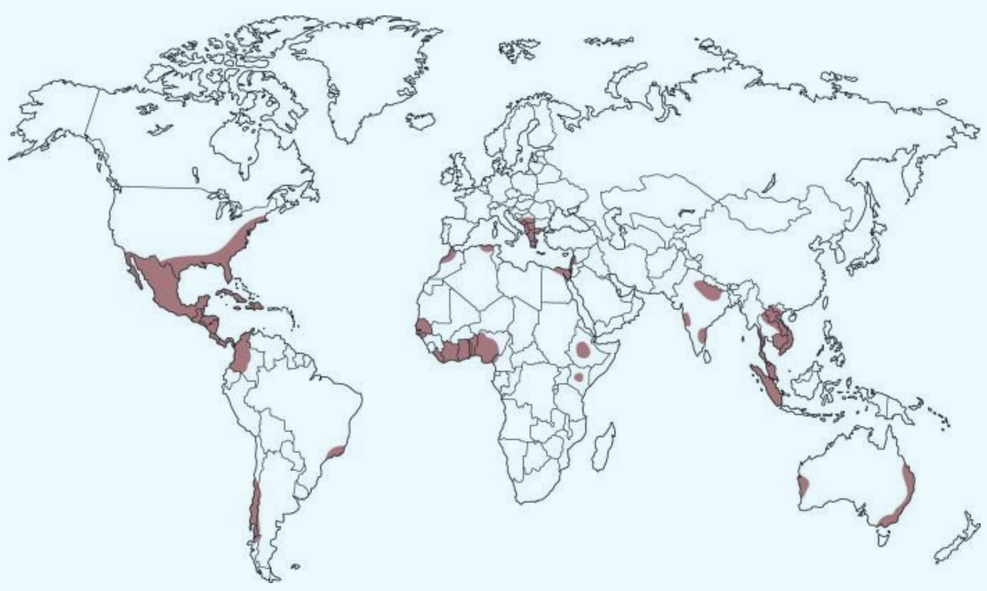
Discussion

The typhus group of the *Rickettsia* genus contains *R. prowazekii*, which causes classic epidemic or louse-borne typhus, and *R. typhi*, which causes murine or flea-borne typhus. The serological tests are unable to distinguish epidemic and endemic typhus, and given the clinical history endemic or murine typhus is clinically the most likely diagnosis.

Endemic typhus is a rickettsial infection caused by *R. typhi.* This is transmitted by flea bites, usually rat fleas (*xenopsylla cheopis*). These fleas are found worldwide, with the reservoir of rats, cats, dogs and opposums. The flea faeces contain the *R. typhi* and patients are infected when they scratch bites allowing the bacteria to inoculate the skin.

Endemic typhus has a worldwide distribution however it tends to cause outbreaks where there is a large rat population and poor sanitation. Clinically it presents with fever, rash and headache. The incubation period is 7-14 days. The rash is usually non-pruritic and maculopapular, but interestingly is often transient so can be missed. Hyponatraemia, transaminitis, and thrombocytopenia are common. Mycocarditis, seizures and renal failure have also been reported. Treatment is with doxycycline and patients usually make a full recovery even without treatment (3).

Figure 2. Geographical distribution of murine (flea-borne) typhus (2)



Outcome

Our patient made a full recovery, although it did take 3 weeks for liver function tests to return to normal. On further questioning his wife recalls he did have a bite from an "insect" while away but interestingly he spent his whole holiday in a holiday resort. He said that the accommodation was of a good standard and that he did not see any rodents while away or any stray cats. The case was discussed at the National RIPL teleconference in August at that point this had been the second imported case to the UK from Cyprus this year.

While this is a rare cause of transaminitis and rash in a returning traveller, given its worldwide distribution this condition should be considered in patients presenting with the above symptoms.

References
(1) CDC Murine typhus available online at https://www.cdc.gov/typhus/murine/index.html
(2) Courtesy of the Department of Entomology, London School of Hygiene and Tropical Medicine
(3) Manson's Tropical Infectious Disease (23rd edition) 2014 Chapter 22 Tropical Rickettsial Infections Daniel H. Paris, Nicholas P. J. Day