PHOTO QUIZ

Bilateral Conjunctivitis in a Returned Traveller

Sasha R. Fehily[1]*, Gail B. Cross[1], Andrew J. Fuller[1,2]

1 Infectious Disease Unit, Alfred Hospital, Melbourne, Australia, **2** Department of Microbiology, Alfred Hospital, Melbourne, Australia

* S.Fehily@alfred.org

Question

A 30-year-old female presented to a tertiary hospital with two weeks of fevers and left upper quadrant abdominal pain after returning from the Gili Islands, Indonesia. She was immunised against hepatitis B, hepatitis A, and typhoid. She did not take malaria prophylaxis and recalls being bitten by insects. Laboratory investigations revealed an elevated C-reactive protein level (158 mg/L), mild thrombocytopenia (148 10⁹/L), and deranged liver functions tests. Her malaria smear and blood and urine cultures were negative. Serology for dengue fever, chikungunya, human immunodeficiency virus, hepatitis B, hepatitis C, hepatitis A, leptospirosis, and rickettsia were sent. Two days into the admission, she subsequently developed significant bilateral conjunctivitis and was reviewed by the ophthalmology unit (Fig. 1). Ophthalmoscopy revealed a small, pale, inactive spot on the retina. The lens, macula, and retina otherwise appeared normal. Without antibiotic treatment, the patient's fevers and abdominal pain resolved, although the conjunctivitis worsened (Fig. 1). The patient in this manuscript has given written informed consent to publication of her case details.

Diagnosis

Murine typhus

An immunofluorescence test detecting IgG and IgM antibodies to Rickettsiae (murine typhus group), taken 14 days after the onset of clinical symptoms, was positive, with a titre of 1:8,192. All other serological tests were negative. Repeat Rickettsiae serology performed in convalescence, 14 days after the initial test, demonstrated a rise in the titre to 1:16,384. The patient's

Figure 1. Young woman with significant bilateral conjunctivitis.

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Table 1. Infectious causes of conjunctivitis—bacterial.

Diseases	Organism (Vector)	Vector (type)	Unilateral or bilateral conjunctivitis	Ocular manifestations and other common features
Bacterial Conjunctivitis [10]	*Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis*	Nil	Unilateral	Conjunctivitis with mucopurulent discharge, conjunctival hyperemia.
Hyperacute Bacterial Conjunctivitis [10]	*Neisseria Gonorrhoea*	Nil	Unilateral or bilateral	Conjunctivitis with severe copious purulent discharge, eyelid swelling, lymphadenopathy.
Adult Inclusion Conjunctivitis [10]	*Chlamydia trachomatis*	Nil	Unilateral or bilateral	Conjunctivitis with mucopurulent discharge, corneal scarring, blindness.
Rickettsioses [11]	Spotted fever group, Typhus group, Scrub typhus group	Ticks, fleas, mites, lice	Unilateral or bilateral	Systemic febrile illness, conjunctivitis, inner retinitis, headache, malaise, rash.
Leptospirosis [12]	*Leptospires*	Nil	Unilateral or bilateral	Systemic febrile illness, subconjunctival hemorrhage, conjunctivitis, uveitis, headache, arthralgia, rash, gastrointestinal symptoms.

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symptoms; a high, rising, positive murine typhus titre; and epidemiological risk factors support the diagnosis of a Rickettsial infection. A 2-fold rise rather than a 4-fold rise in Rickettsiae titre occurred in this case because the first serological sample was taken late in the illness. The patient was treated with oral doxycycline for two weeks and achieved a complete resolution of the conjunctivitis after three weeks.

Table 2. Infectious causes of conjunctivitis—viral.

Diseases	Organism (Vector)	Vector (type)	Unilateral or bilateral conjunctivitis	Ocular manifestations and other common features
Viral Conjunctivitis [10]	65% due to *Adenovirus* strains	Nil	Unilateral or bilateral	Pharyngoconjunctival fever: pharyngitis, conjunctivitis, high fever, bilateral lymphadenopathy. Epidemic keratoconjunctivitis: conjunctivitis with watery discharge, hyperemia, chemosis, ipsilateral lymphadenopathy.
Herpes Zoster virus [10]	*Herpesvirus*	Nil	Unilateral	Conjunctivitis with watery discharge, vesicular eyelid lesions, corneal ulceration.
Herpes Simplex virus [10]	*Herpesvirus*	Nil	Unilateral	Conjunctivitis with watery discharge, vesicular eyelid lesions.
West Nile virus [11, 13]	*Flavivirus*	Mosquitoes (*Culex*)	Bilateral	Systemic febrile illness, multifocal chorioretinitis, myalgia, arthralgia, rash, gastrointestinal symptoms.
Dengue fever [11]	*Flavivirus*	Mosquitoes (*Aedes aegypti*)	Bilateral	Systemic febrile illness, anterior uveitis, subconjunctival haemorrhage, scotoma, headache, myalgia, rash.
Chikungunya [11, 14]	*Alphavirus*	Mosquitoes (*Aedes aegypti*)	Unilateral or bilateral	Systemic febrile illness, anterior uveitis, retinitis, headache, rash, epistaxis, oedema.
Zika Virus [15]	*Flavivirus*	Nil	Bilateral	Systemic febrile illness, conjunctivitis, arthralgia, rash.
Rift Valley fever [11, 16]	*Bunyaviridae*	Ticks, Mosquitoes, Sand flies	Unilateral or bilateral	Systemic febrile illness, macular retinitis, headache, myalgia, arthralgia, gastrointestinal symptoms.
Measles [17]	*Measles virus*	Nil	Bilateral	Systemic febrile illness, conjunctivitis, cough, rhinitis, rash.
Rubella	*Rubella virus*	Nil	Bilateral	Mild fever, conjunctivitis, headache, myalgia, rash.
H1N1 [11, 18, 19]	*Influenza A H1N1*	Nil	Bilateral	Systemic febrile illness, cough, myalgia. Conjunctivitis, uveitis and retinitis are infrequently reported.

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Discussion

Murine typhus is endemic to Indonesia, with the prevalence of positive *Rickettsia typhi* antibody levels in humans being one of the highest in the world [1]. Outbreaks have been reported worldwide, but the endemic foci include the Southeast Asian, Mediterranean, and southern United States regions [2]. The environmental circumstances that potentiate the prevalence of this disease are port cities, coastal, and high altitude regions [3, 4]. Infections with this gram-negative intracellular bacterium remain under-diagnosed and underreported, despite being endemic worldwide [4]. Arthropod vectors, commonly the rat flea *Xenopsylla cheopis*, are responsible for the transmission of murine typhus to humans from an animal reservoir [5]. This is consistent with the increased prevalence in tropical port cities, where rats are abundant [3].

In Indonesia, murine typhus has been reported to cause 2.8% of acute undifferentiated fever [3]. The clinical features that manifest after an eight- to 16-day incubation period are usually non-specific, with patients exhibiting fever, headache, and a faint maculopapular rash [3]. However, the complete clinical triad is reported in fewer than 15% of patients [6]. Other clinical features that manifest are arthralgia, myalgia, gastrointestinal symptoms, and acute renal impairment [4]. Acute pulmonary failure and neurological complications are rare, with respective reported prevalence rates of 6%–12% and 15%–45% [2]. Bilateral conjunctivitis has been described in case reports, and a prospective observational study showed that conjunctivitis can occur in up to 21% of cases [2, 4, 7]. As was present in this case, Khairallah et al. observed white lesions on the retina in 50% of cases [8]. Abnormalities in the posterior segment of the eye, including fundal lesions and chorioretinal changes, were identified in 88.9% of the patients studied [8].

Elevated aminotransferases, hypoalbuminaemia, and hyponatremia are the biochemical abnormalities frequently reported [2]. Haematological findings that occur include leucocytosis, leukopenia, anaemia, and thrombocytopenia [2]. Although the infection is usually clinically mild, it can result in a severe illness and may even be fatal in up to 4% of hospitalised patients that are not treated with antibiotics [9].

The definitive diagnosis is based on epidemiological data, patient history, clinical signs, and positive convalescent serological testing [8]. This is notoriously difficult and frequently delayed given the non-specific clinical features. Additionally, there are no adequate diagnostic tests during the acute phase of illness. The gold standard for diagnosis is a 4-fold rise on the immunofluorescence assay detecting *R. typhi* IgM and IgG antibodies [7]. The preferred treatment of

Key Learning Points

- Murine typhus is an under-diagnosed infectious disease in returned travelers.
- Arthropod vectors are responsible for the transmission of this gram-negative intracellular bacterium to humans.
- Murine typhus should be considered in the differential diagnosis of returned travellers with bilateral conjunctivitis and fevers (Table 1, Table 2).
- There are no satisfactory diagnostic tests during the acute phase of illness.
- Doxycycline is considered to be the first-line antimicrobial therapy for the treatment of murine typhus.

murine typhus is early initiation of antimicrobial therapy, with the first-line agent being doxycycline [8].

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