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CASE REPORT

Imported scrub typhus in the Netherlands

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Summary Two cases of travel-acquired scrub typhus imported in the Netherlands are described. The characteristic eschar was absent in both cases. One case acquired scrub typhus in non-rural surroundings in India, highlighting that scrub typhus must also be considered a (sub) urban zoonosis.

Introduction

Scrub typhus is an acute, febrile illness caused by the obligate intracellular Gram-negative bacterium *Orientia* (formerly Rickettsia) *tsutsugamushi*. The pathogen is transmitted to humans by the larval stage of trombiculid mites called chiggers.[1,2] *O. tsutsugamushi* is distributed throughout the Asian Pacific rim, extending from northern Japan and far eastern Russia southward to northern Australia and westward to Pakistan and Afghanistan.[1–5] After an incubation period of 7–10 days, scrub typhus may begin insidiously with non-specific symptoms like headache and malaise or start abruptly with fever and chills. Eventually most patients suffer from fever, myalgia and headache, which may be accompanied by a rash and, typically, an inoculating eschar.[1,2,6–8] The severity of the infection can range from mild symptoms and signs to a complicated course involving respiratory distress syndrome, shock, acute kidney failure, disseminated intravascular coagulation and multi-organ failure, potentially culminating in death.[6,8,9] It causes an estimated 1 million cases among the indigenous population each year with a case-fatality rate up to 35%, depending on the virulence of the infecting strain, host factors and treatment.

Transmission of *O. tsutsugamushi* may occur in sharply delineated 'mite islands'. People entering these focal locations of scrub vegetation are at a high risk of acquiring the disease through the bites of infected mites. Of note,

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these 'mite islands' are not restricted to rural areas only, but may also be present in suburban surroundings. Hence, scrub typhus may manifest itself as an urban zoonosis.[1] Interestingly, travel-acquired cases of scrub typhus are reported infrequently in international travellers returning from endemic areas.[1,2] Only 16 of 99,355 patients reported to the GeoSentinel Surveillance Network in the period 1996–2008 were diagnosed with scrub typhus,[3] illustrating its rarity amongst travellers. Two imported cases of scrub typhus in the Netherlands are described, both lacking the characteristic eschar.

Case reports

Patient A, a 27-year-old woman without a medical history fell ill in Laos with high-grade fever, malaise, loss of appetite, dizziness and headache after 5 months of basic travelling through South East Asia. For a duration of two days she noticed a macular rash on her limbs. Two weeks after the start of symptoms, she was treated with amoxicillin for 6 days. The fever slowly resolved within three weeks. She sought subsequently medical advice in Vietnam, where Dengue was excluded. Laboratory tests revealed a raised C-reactive protein, raised liver enzymes and a lowered platelet count. A chest X-ray showed no abnormalities but abdominal ultrasound revealed an enlarged spleen. After return to the Netherlands, she had completely recovered. Routine laboratory analysis and a repeat abdominal ultrasound were normal. Serology against dengue, chikungunya, Japanese encephalitis, West-Nile virus, leptospirosis and *Rickettsia* (*R.*) *conorii* and *R. prowazekii*/*typhii* came back negative. The diagnosis of scrub typhus was confirmed by demonstration of specific antibodies to *O. tsutsugamushi* (IFA IgM $\geq$ 64; IgG $\geq$ 256) (Scimedx Corp., Denville, NJ, USA).

Patient B, a 54-year-old Dutch man travelled to Coimbatore in Southern India to work and stay in an orphanage. After 6 days he travelled back to the Netherlands as his wife required repatriation due to severe gastroenteritis. Three days after his return to the Netherlands, the patient developed fevers, myalgia, sweats and watery diarrhoea. A further three days later a rash appeared. Empirical treatment with ciprofloxacin for a presumed bacterial gastroenteritis was initiated by his general practitioner. Five days after his initial symptoms the patient was admitted. Physical examination revealed a low-grade fever of 38.1 °C, a heart rate of 96 bpm and a maculopapular rash on both arms. Laboratory examination revealed a normal platelet (platelets 159 $\times$ 10^9/L) and leukocyte (leukocytes 5.2 $\times$ 10^9/L) count. A slightly increased C-reactive protein level (14 mg/L) and mildly elevated liver function tests (ALT 82 U/L, AST 100 U/L and GGT 177 U/L) were noted. Chest radiography and abdominal ultrasonography were normal, and malaria smears were negative. Treatment with azithromycin 500 mg OD was initiated because typhoid fever and rickettsial disease could not be definitely ruled out on clinical grounds. Unfortunately, shortly hereafter the clinical condition of the patient deteriorated with progressive shortness of breath, an expanding petechial rash and high-grade fever. The patient was admitted to Intensive Care Unit (ICU) for non-invasive ventilation. Treatment was switched to ceftriaxone 2 g OD intravenously and oral doxycycline 100 mg twice daily as suggested for severely ill patients with compatible exposure to scrub typhus, enteric fever and leptospirosis.[9] Hereafter, the patient showed a remarkable recovery. He was discharged from ICU the next day and left the hospital six days later. Blood and stool cultures remained negative throughout his course of treatment. The diagnosis of scrub typhus was confirmed by demonstration of specific antibodies to *O. tsutsugamushi* (IFA IgM $\geq$ 64; IgG $\geq$ 256). Serology results for dengue virus, chikungunya virus, *R. prowazekii*/*typhii* and *R. conorii* were all negative.

Discussion

Scrub typhus often presents as a febrile illness with little to distinguish it clinically from co-endemic diseases such as typhoid fever, dengue and leptospirosis. Other rickettsial diseases such as Mediterranean spotted fever, Indian tick typhus (Indian subcontinent) and infections with *R. felis*, *R. helvetica* and *R. honei* may mimic scrub typhus in its clinical presentation including presence of an inoculating eschar.[2] The presence of an eschar is a characteristic feature of many rickettsial diseases and of scrub typhus but it is only present in 46–86% of scrub typhus patients in endemic regions.[7] Its absence, however, may lead to a significant delay in diagnosis and initiation of appropriate treatment.[10]

The eschar is not only an important sign for clinical diagnosis; a biopsy may also provide a vital sample for confirmation of the diagnosis through specific immunohistochemical staining or polymerase chain reaction. The presence of *O. tsutsugamushi* infection can be confirmed by serology, biopsy (culture) and polymerase chain reaction.[11,12] Polymerase chain reaction and sequencing on eschar biopsies could be a fast and more accurate confirmatory test than serology because it also allows for species differentiation and it has a high sensitivity early in the course of the disease. However, these techniques are only available in a limited number of specialized centres due to special technical requirements.[11,12] In routine clinical practice, diagnosis of scrub typhus therefore still relies on the demonstration of specific antibodies, even though they usually provide a retrospective diagnosis. The indirect fluorescent antibody (IFA) test remains the mainstay of serologic diagnosis of scrub typhus but lack consensus on diagnostic cutoffs for diagnosis.[12] To guarantee an optimal diagnostic yield, the IFA should ideally use antigens present in local strains of *O. tsutsugamushi* to detect convalescent antibodies because of the organism's antigenic heterogeneity. Therefore, a correct diagnosis of scrub typhus may be hampered by the characteristics and performance of the IFA test used to diagnose scrub typhus and potentially cross-reacting Rickettsial species.

Since *Orientia* and *Rickettsia* species are both sensitive to treatment with doxycycline, a misdiagnosis may have limited clinical consequences as long as patients receive presumptive treatment with doxycycline.[10,13-15] Most patients will improve within the first 48 h of treatment. This response to treatment may be useful diagnostically; failure of defervescence within 48 h is often considered evidence

that scrub typhus is not present and that an alternate diagnosis should be considered. Alternatively, an increased time to defervescence of fever may also be indicative of infection with a resistant *O. tsutsugamushi* strain as became clear from studies in northern Thailand, where the median time to defervescence for patients who were infected with doxycycline-resistant strains of *O. tsutsugamushi* was prolonged to 80 h.[16] Several antimicrobial agents that exhibit good intracellular penetration might substitute for doxycycline in the treatment of scrub typhus. In comparative studies in indigenous patients with mild scrub typhus in Thailand and South Korea, a 3-day course of 500 mg azithromycin and even a single dose of 500 mg azithromycin was shown to be comparable to a 7-day course of 200 mg doxycycline with comparable fever clearance times.[13–15]

In conclusion, scrub typhus is an infrequent but probably underdiagnosed cause of fever in returned, febrile travellers. It may present without the characteristic eschar as exemplified by both patients, which may delay the diagnosis and subsequent administration of an appropriate antibiotic treatment. The geographical history of *patient B* illustrates that the acquisition of scrub typhus is not limited to rural areas but can also be acquired during travel to suburban surroundings.

Conflict of interest

PJJvG received speaker's fee from GlaxoSmithKline and reimbursement from GlaxoSmithKline and SanofiPasteurMSD for attending symposia. However neither GlaxoSmithKline nor SanofiPasteurMSD had no influence regarding the preparation of this manuscript. The other authors have no conflicts of interest to declare.

KV acquired the literature data and drafted the manuscript. MMDM, LS and MB were involved in the acquisition of patient and follow-up data and made substantial revisions to the manuscript. PJJVG was involved in the conception and design of the study, in the analysis of the literature review, drafted and revised the manuscript. All authors approved the final version of the manuscript.

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