Travel-Acquired Scrub Typhus: Emphasis on the Differential Diagnosis, Treatment, and Prevention Strategies

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Scrub typhus should be considered in any febrile patient presenting with a macular rash, a polyadenopathy, an eschar, or a history of environmental exposure in endemic areas. The differential diagnosis includes malaria, typhoid fever, leptospirosis, and arboviroses. Doxycycline 100 mg twice daily for 7 days should be initiated as soon as the disease is suspected.

We report one case of scrub typhus in a Belgian patient following travel from southern India and discuss the differential diagnosis as well as the treatment and prevention strategies. Similar cases have been reported in the literature but with little or no discussion of the differential diagnosis, which is critical as some of the endemic diseases to be considered can have a rapidly fatal outcome.

Case Report

A 51-year-old Belgian traveler, with no medical history, was admitted in the University Hospital of Antwerp in November 2002 for a fever of 1 week's duration. He had returned the previous day from a month-long backpack excursion in southern India. During his stay abroad, high fever developed abruptly 7 days before consulting our department and was associated with severe myalgia, dry cough, and skin rash. On admission, the patient presented with a temperature of 39.6°C, a disseminated maculopapular rash with confluent vasculitic lesions on both legs, and sensitive enlarged lymph nodes in the cervical and axillary areas. He was prostrate and answered questions slowly, although adequately. A small, red-brown, exulcerated lesion compatible with an eschar was noted in the left axilla.

Laboratory findings revealed a normal white blood cell count, a lowered platelet count (110,000/μL), elevated liver enzymes [alanine transaminase (ALT): 136 IU/L and aspartate transaminase (AST): 165 IU/L], elevated lactate dehydrogenase (1,445 IU/L), and a normal bilirubin level. Repeated blood smears and blood cultures were negative. Chest X-rays and abdominal ultrasonography were normal.

The patient was immediately treated with intravenous ciprofloxacin for suspected typhoid fever. Twenty-four hours later, scrub typhus was considered and doxycycline (200 mg daily) was added for 7 days. Fever abated 48 hours later, and the patient was discharged after 5 days. One week later, he experienced a left-sided trigeminal neuralgia, which lasted 10 days under symptomatic treatment. Recovery was uneventful thereafter. Blood cultures remained negative for *Salmonella typhi*, and serologic tests remained negative for all relevant diseases such as dengue; leptospirosis; viral hepatitis A, B, C, and E; cytomegalovirus (CMV); Epstein–Barr virus (EBV); human immunodeficiency virus (HIV); *Rickettsia conori*; and *Rickettsia typhi*

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(formerly *Rickettsia mooseri*). Serology for *Orientia tsutsugamushi* was performed in the "Unité des Rickettsies," Marseilles (courtesy D. Raoult). The indirect immunofluorescence assay (IFA) showed immunoglobulin (Ig)M titer of 32 and IgG titer 32 in the first sample (day 9 of fever), and in the paired serum (3 wk later), titers of 64 for IgM and 128 for IgG were observed.

Discussion

Scrub typhus, a potential fatal rickettsiosis, is caused by *O tsutsugamushi*, an obligate, intracellular, arthropod-borne, gram-negative bacterium. The organism is transmitted to humans by the larval stage of trombiculid mites (chiggers). Chiggers are prevalent in scrub vegetation and tall grass of rural areas, where local residents, tourists, and military personnel in the field are particularly at risk for their bites. Rodents (about 20 species of rats) make up the major reservoir of *O tsutsugamushi*, but tree shrews, birds, and monkeys have also been reported as hosts.[1,2] The disease is endemic in northern Japan, Southeast Asia, the western Pacific islands, eastern Australia, China, eastern and western Russia, and in India, where outbreaks of scrub typhus have been reported during cooler months.[3–5] Most travel-acquired cases of scrub typhus occur in patients returning from Southeast Asia (Table 1).[9,10]

The presentation of scrub typhus may be nonspecific; therefore, many other region-specific and cosmopolitan diseases must be considered in the differential diagnosis, including mainly malaria, typhoid fever, leptospirosis, other rickettsioses, arbovirus infections, and mononucleosis-like syndromes (primarily EBV, CMV, *Toxoplasma gondii*, and HIV infections).

The presence of an eschar is a key clinical feature of scrub typhus. This develops on the place of the chigger bite during the incubation period (range: 6–21 d) in about 50% of travel-related cases. It is painless, measures usually 3 to 6 mm in diameter, and can occur on any part of the body, often on the scrotum or in the axillary regions. The chigger bite is usually not remembered by the patient, and the eschar must be actively looked for by the physician. Of note, the differential diagnosis of an eschar with fever in travelers should include viral infections (herpes simplex virus), bacterial conditions (anthrax, tularemia, ecthyma, other rickettsioses according to endemicity), and fungal diseases (aspergillosis, fusariosis, mucormycosis). The other rickettsial infections ever reported to date in India are Mediterranean spotted fever (*Rickettsia conorii* ssp. *conorii*) and Indian tick typhus *(R conorii* ssp. *indica)*.[11,12] Interestingly, there is a discrepancy in the frequency of reported eschar lesions in both local cases and in travelers' cases (Table 1). These differences are likely to reflect differences in host immunity, heterogeneity in the virulence of strains, geographical differences in disease epidemiology, or investigators' clinical diagnostic skills.[6–10]

A skin rash develops in about 50% of returning travelers diagnosed with scrub typhus. A macular rash appears at the end of the first week, mainly on the trunk and thighs, becomes maculopapular, and

Table 1 Reported clinical symptoms in scrub typhus patients

Authors	Tattersall[6]	Berman and Kundin[7]	Ogawa and colleagues[8]	Jensenius and colleagues[9,10]
Year of publication	1945	1973	1998	2004, 2006
Number of cases	500	87	462	23
Location	India/Burma	South Vietnam	Japan	Thailand, Burma, Vietnam, and Malaysia, Papua New Guinea, The Philippines, Korea, India
Population	Soldiers and local	Soldiers	Local	Travelers
Fever (%)		100	98	100
Rash (%)	64	34	93	50
Headache (%)	100	100	46	100
Eschar (%)	11	46	87	55
Adenopathy (%)	92	85	52	85
Splenomegaly (%)	47	43		43
Hepatomegaly (%)	64	34	36	NR
Elevated transaminases (%)	NR	NR	87	15

NR = not reported.

spreads peripherally. Like dengue, scrub typhus may present with thrombocytopenia and even bleeding signs; however, Watt and colleagues observed in northern Thailand that hemorrhagic complications, especially bleeding from the gums, occurred more frequently in dengue patients.[13] Secondary syphilis or disseminated gonococcal disease (DGD) may also manifest with a maculopapular rash; however, other features, such as the presence of tenosynovitis involving the wrist, ankles, and digits for DGD, condyloma lata, and mucous patches for syphilis, will help discriminate these potentially travel-related conditions from scrub typhus.

Polyadenopathy is often described in patients with scrub typhus (Table 1). Primary EBV, CMV, *T gondii*, and HIV infections are therefore part of the differential diagnosis. The presence of lymphocytosis will help discriminate these diseases from scrub typhus. Splenomegaly is another feature of scrub typhus (roughly 40% of the cases), but it is also frequent in enteric fever, which is another disease very endemic in southern Asia. In addition, both enteric fever and scrub typhus present most of the time with normal or low white blood cell count. Enteric fever, however, rarely causes generalized lymphadenopathy.

Jaundice sometimes occurs in scrub typhus, and this picture may mimic severe malaria, viral hepatitis, or leptospirosis (Weil's syndrome). Of note, scrub typhus patients can often manifest hepatic inflammation, as evidenced by elevated levels of AST and ALT. In such cases, many alternative diagnoses must be considered, such as dengue, leptospirosis, Q fever, enteric fever, viral hepatitis, and mononucleosis-like syndromes. In addition, scrub typhus and leptospirosis coinfection seems frequent in endemic rural areas; this should also be kept in mind when managing febrile exposed travelers.[14]

Severe neurological complications of scrub typhus have been reported in travelers, including meningoencephalitis, with delirium, focal signs, papilledema, and coma.[15,16] Central nervous system involvement with rapid disease progression should raise the possibility in the differential diagnosis of meningococcal disease, leptospirosis, West Nile infection, or Japanese encephalitis. Other reported complications of scrub typhus include hearing loss, myocarditis, renal failure, and interstitial pneumonia, leading sometimes to adult respiratory distress syndrome and septic shock.[17] The case fatality rate for untreated classical cases is about 6%.[9]

Historically, the first serologic assay used for the diagnosis of rickettsiosis was the Weil-Felix agglutination test. It is based on serological cross-reactions and involves antigens from three *Proteus* strains: *Proteus vulgaris* OX-2 and OX-19 and the OX-K strain of *Proteus mirabilis*. However, it is no longer recommended due to poor sensitivity and specificity.[18] Modern techniques such as the current gold standard, IFA, or the immunoperoxidase assay are the most reliable and preferred serodiagnostic methods for scrub typhus infection; however, they are only available in a limited number of medical academic, public health, or specialized centers due to special technical requirements. More recently, polymerase chain reaction–based assays of *O tsutsugamushi* from patient's blood, skin, or lymph node samples from patients have been developed.[18]

The treatment of choice for scrub typhus infection is doxycycline 100 mg/dose administered twice daily (orally or intravenously) for adults or 2.2 mg/kg for children <45.4 kg.[16] This treatment should be initiated empirically as soon as the diagnostic is suspected and likely. The optimal duration of treatment has not been established, but current recommendation suggests at least 3 to 7 days for nonlife-threatening cases to a maximum of 15 days for severe or complicated disease.

Alternatively, chloramphenicol (500 mg four times a day orally for 7 d in adults or 150 mg/kg/d for 5 d in children) in endemic areas has been proven effective in treating scrub typhus and preventing relapse. Of note, doxycycline- and chloramphenicol-resistant strains have been reported from northern Thailand;[19] alternative drugs to use in such cases include rifampin (600–900 mg/d) or azithromycin (500 mg the first day and 250 mg/d later) for 7 days.[20] The latter regimen is also safe to use during pregnancy and in children. Data on the clinical efficacy of fluoroquinolones for treatment of scrub typhus are scarce. Ciprofloxacin use, based on the experience with pregnant women in India, was shown to be ineffective and is not recommended.[21] Suspected dual infections of scrub typhus and leptospirosis could be treated preemptively with penicillin G 1.5 million units intravenously every 6 hours or ceftriaxone 1 g intravenously or intramuscularly every 24 hours for 7 days combined with doxycycline.[14] In addition, scrub typhus, enteric fever (with fluoroquinolones-resistant strains of *S typhi*), and leptospirosis are the most pressing diagnoses in a severely ill adventurous traveler. In such situations, a combination of doxycycline and ceftriaxone could be a safe empirical treatment pending the results of blood cultures.[22]

Chemoprophylaxis with a weekly dose of 200 mg of doxycycline is controversial owing to limited

studies,[23] but this medication has been suggested for travelers at high occupational risk, such as soldiers on field operations.[3] Travelers in endemic regions should be warned to avoid cleared jungle areas known to contain infected "mite islands" and to use repellants to the top of boots and socks as well as the hem of trousers. To date, there is no vaccine for scrub typhus.

In summary, it is of great importance to increase awareness among Western clinicians about the epidemiology, the diagnostic challenges, and the clinical management of scrub typhus to avoid any therapeutic delay.

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Declaration of Interests

The authors state that they have no conflicts of interest.

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