

Scrub Typhus in Chile

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PRACTICE POINTS

- Scrub typhus is clinically suspected in patients who present with a febrile macular or papular rash and a characteristic necrotic eschar known as tache noire while residing in or traveling to rural areas.
- Scrub typhus can lead to serious complications. Due to its changing epidemiology, dermatologists outside the usual area of distribution should be aware in the event that new cases emerge.

To the Editor:

Scrub typhus (ST) is an infection caused by *Orientia tsutsugamushi* (genus *Rickettsia*), which is transmitted by the larvae of trombiculid mites, commonly called chiggers. The disease mainly has been described in Asia in an area known as the Tsutsugamushi Triangle, delineated by Pakistan, eastern Russia, and northern Australia. Although this classic distribution remains, recent reports have documented 1 case in the Arabian Peninsula¹ and more than 16 cases in southern Chile.²⁻⁴ The first case in Chile was published in 2011 from Chiloé Island.² To date, no other cases have been reported in the Americas.¹⁻⁶

We describe a new case of ST from Chiloé Island and compare it to the first case reported in Chile in 2011.² Both patients showed the typical clinical manifestation, but because ST has become an increasingly suspected disease

in southern regions of Chile, new cases are now easily diagnosed. This infection is diagnosed mainly by skin lesions; therefore, dermatologists should be aware of this diagnosis when presented with a febrile rash.

A 67-year-old man from the city of Punta Arenas presented to the emergency department with a dark necrotic lesion on the right foot of 1 week's duration. The patient later developed a generalized pruritic rash and fever. He also reported muscle pain, headache, cough, night sweats, and odynophagia. He reported recent travel to a rural area in the northern part of Chiloé Island, where he came into contact with firewood and participated in outdoor activities. He had no other relevant medical history.

Physical examination revealed a temperature of 38 °C and a macular rash, with some papules distributed mainly on the face, trunk, and proximal extremities (Figure 1). He had a necrotic eschar on the dorsum of the right foot, with an erythematous halo (tache noire) (Figure 2).

A complete blood cell count, urinalysis, and tests of hepatic and renal function were normal. C-reactive protein was elevated 18 times the normal value. Because of high awareness of ST in the region, eschar samples were taken and submitted for serologic testing and polymerase chain reaction (PCR) targeting the 16S rRNA *Orientia* gene. Empirical treatment with oral doxycycline 100 mg twice daily was started. Polymerase chain reaction analysis showed the presence of *Orientia* species, confirming the diagnosis of ST. The rash and eschar diminished considerably after 7 days of antibiotic treatment.

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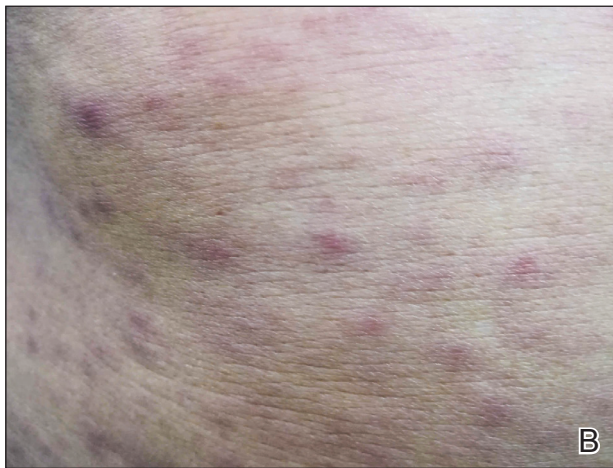


FIGURE 1. Scrub typhus. A and B, Mainly macular rash distributed centrifugally on the patient's trunk and extremities.



FIGURE 2. Tache noire—necrotic eschar on the dorsum of the right foot—with an erythematous halo characteristic of scrub typhus.

similar to a cigarette burn. This lesion is described in 20% to 90% of infected patients in different series.⁷ Two or 3 days later (1 to 3 weeks after exposure), high fever suddenly develops. Along with fever, a maculopapular rash distributed centrifugally develops, without compromise of the palms or soles. Patients frequently report headache and night sweating. Sometimes, ST is accompanied by muscle or joint pain, red eye, cough, and abdominal pain. Hearing loss and altered mental status less frequently have been reported.^{5,8}

Common laboratory tests can be of use in diagnosis. An elevated C-reactive protein level and a slight to moderate increase in hepatic transaminases should be expected. Thrombocytopenia, leukopenia, and elevation of the lactate dehydrogenase level less frequently are present.^{5,9}

Our case demonstrated a typical presentation. The patient developed a febrile syndrome with a generalized rash and a tache noire—type eschar associated with muscle pain, headache, cough, night sweats, and odynophagia. Because of epidemiologic changes in the area, the familiar clinical findings, and laboratory confirmation, histologic studies were unnecessary. In cases in which the diagnosis is not evident, skin biopsy could be useful, as in the first case reported in Chile.²

In that first case, the patient initially was hospitalized because of a febrile syndrome; eventually, a necrotic

Scrub typhus is a high-impact disease in Asia, described mainly in an area known as the Tsutsugamushi Triangle. Recent reports show important epidemiologic changes in the distribution of the disease, with new published reports of cases outside this endemic area—1 in the Arabian peninsula¹ and more than 16 in southern Chile.²⁻⁴

The disease begins with a painless, erythematous, and usually unnoticed papule at the site of the bite. After 48 to 72 hours, the papule changes to a necrotic form (tache noire), surrounded by a red halo that often is small,

eschar was noticed on his leg. He had been staying on Chiloé Island and reported being bitten by leeches on multiple occasions. Laboratory findings revealed only slightly raised levels of hepatic transaminases and alkaline phosphatase. After a more precise dermatologic evaluation, the eschar of a tache noire, combined with other clinical and laboratory findings, raised suspicion of ST. Because this entity had never been described in Chile, biopsy of the eschar was taken to consider other entities in the differential diagnosis. Biopsy showed necrotizing leukocytoclastic vasculitis in the dermis and subcutaneous tissue, perivascular inflammatory infiltrates comprising lymphocytes and macrophages, and rickettsial microorganisms inside endothelial cells under electron microscopic examination. The specimen was tested for the 16S ribosomal RNA *Orientia* gene; its presence confirmed the diagnosis.²

Classically, histology from the eschar shows signs of vasculitis and rickettsial microorganisms inside endothelial cells on electron microscopy.^{2,10} More recent publications describe important necrotic changes within keratinocytes as well as an inflammatory infiltrate comprising antigen-presenting cells, monocytes, macrophages, and dendritic cells. Using high-resolution thin sections with confocal laser scanning microscopy and staining of specific monoclonal antibodies against 56 kDa type-specific surface antigens, the bacteria were found inside antigen-presenting cells, many of them located perivascularly or passing through the endothelium.¹¹

The causal agent in Asia is *O tsutsugamushi*, an obligate intracellular bacterium (genus *Rickettsia*). *Orientia* species are transmitted by larvae of trombiculid mites, commonly called chiggers. The reservoir is believed to be the same as with chiggers, in which some vertebrates become infected and trombiculid mites feed on them.¹² Recent studies of Chilean cases have revealed the presence of a novel *Orientia* species, *Candidatus Orientia chiloensis* and its vector, trombiculid mites from the *Herpetacarus* species, *Quadrasetta* species, and *Paratrombicula* species genera.^{13,14}

A high seroprevalence of *Orientia* species in dogs was reported in the main cities of Chiloé Island. Rates were higher in rural settings and older dogs. Of 202 specimens, 21.3% were positive for IgG against *Orientia* species.¹⁵

In Chile, most cases of ST came from Chiloé Island; some reports of cases from continental Chilean regions have been published.⁶ Most cases have occurred in the context of activities that brought the patients in contact with plants and firewood in rural areas during the summer.³⁻⁶

The diagnosis of ST is eminently clinical, based on the triad of fever, macular or papular rash, and an inoculation necrotic eschar. The diagnosis is supported by epidemiologic facts and fast recovery after treatment is initiated.¹⁶ Although the diagnosis can be established based on a quick recovery in endemic countries, in areas such as Chile where incidence and distribution are not completely known, it is better to confirm the diagnosis with

laboratory tests without delaying treatment. Several testing options exist, including serologic techniques (immunofluorescence or enzyme-linked immunosorbent assay), culture, and detection of the genetic material of *Orientia* species by PCR. Usually, IgM titers initially are negative, and IgG testing requires paired samples (acute and convalescent) to demonstrate seroconversion and therefore acute infection.¹⁷ Because culture requires a highly specialized laboratory, it is not frequently used. Polymerase chain reaction is recognized as the best confirmation method due to its high sensitivity and because it remains positive for a few days after treatment has been initiated. The specimen of choice is the eschar because of its high bacterial load. The base of the scar and the buffy coat are useful specimens when the eschar is unavailable.^{5,17-19}

Due to potential complications of ST, empirical treatment with an antibiotic should be started based on clinical facts and never delayed because of diagnostic tests.¹⁸ Classically, ST is treated with a member of the tetracycline family, such as doxycycline, which provides a cure rate of 63% to 100% in ST.⁵

A 2017 systematic review of treatment options for this infection examined 11 studies from Southeast Asia, China, and South Korea (N=957).¹⁶ The review mainly compared doxycycline with azithromycin, chloramphenicol, and tetracycline. No significant difference in cure rate was noted in comparing doxycycline with any of the other 3 antibiotics; most of the studies examined were characterized by a moderate level of evidence. Regarding adverse effects, doxycycline showed a few more cases of gastrointestinal intolerance, and in 2 of 4 studies with chloramphenicol, patients presented with leukopenia.¹⁶ Several studies compared standard treatment (doxycycline) with rifampicin, telithromycin, erythromycin, and levofloxacin individually; similar cure rates were noted between doxycycline and each of those 4 agents.

Therapeutic failure in ST has been reported in several cases with the use of levofloxacin.²⁰ Evidence for this novel antibiotic is still insufficient. Further studies are needed before rifampicin, telithromycin, erythromycin, or levofloxacin can be considered as options.

Scrub typhus usually resolves within a few weeks. Left untreated, the disease can cause complications such as pneumonia, meningoencephalitis, renal failure, and even multiorgan failure and death. Without treatment, mortality is variable. A 2015 systematic review of mortality from untreated ST showed, on average, mortality of 6% (range, 0%–70%).²¹ When ST is treated, mortality falls to 0% to 30%.²² Cases reported in Chile have neither been lethal nor presented with severe complications.^{4,5}

Scrub typhus is an infectious disease common in Asia, caused by *O tsutsugamushi* and transmitted by chiggers. It should be suspected when a febrile macular or papular rash and a tache noire appear. The diagnosis can be supported by laboratory findings, such as an elevated C-reactive protein level or a slight increase in the levels of hepatic transaminases, and response to treatment. The

diagnosis is confirmed by serology or PCR of a specimen of the eschar. Empiric therapy with antibiotics is mandatory; doxycycline is the first option.

First described in Chile in 2011,² ST was seen in a patient in whom disease was suspected because of clinical characteristics, laboratory and histologic findings, absence of prior reporting in South America, and confirmation with PCR targeting the 16S ribosomal RNA *Orientia* gene from specimens of the eschar. By 2020, 60 cases have been confirmed in Chile, not all of them published; there are no other reported cases in South America.

When comparing the first case in Chile² with our case, we noted that both described classic clinical findings; however, the management approach and diagnostic challenges have evolved over time. Nowadays, ST is highly suspected, so it can be largely recognized and treated, which also provides better understanding of the nature of this disease in Chile. Because this infection is diagnosed mainly by characteristic cutaneous lesions, dermatologists should be aware of its epidemiology, clinical features, and transmission, and they should stay open to the possibility of this (until now) unusual diagnosis in South America.

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