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**Omadacycline in the treatment of scrub typhus: Three case reports**

Lang XM *et al.* Omadacycline in treatment of scrub typhus

Xue-Mei Lang, Yun Qiu, Ya-Juan Jia, Hong Sun, Su-Min Gao, Hong-Mei Zhao

## Abstract

### BACKGROUND

Scrub typhus is a naturally occurring acute infectious disease that is primarily transmitted through the bites of chiggers or larval mites infected by *Orientia tsutsugamushi* (*O. tsutsugamushi*). Omadacycline, a novel tetracycline, exhibits potent antibacterial efficacy against both typical bacteria and atypical pathogens. However, omadacycline application in the treatment of scrub typhus remains limited.

### CASE SUMMARY

In the present work, we report several cases of scrub typhus, with the main clinical symptoms being fever, the formation of eschars or ulcers, local or systemic lymphadenopathy, headache, myalgia and rash. Blood samples were collected before omadacycline was administered, and *O. tsutsugamushi* infection was confirmed through targeted next-generation sequencing (tNGS). After two days of treatment, the patients' symptoms, including fever, were alleviated, with no adverse drug reactions.

### CONCLUSION

tNGS is an effective method for diagnosing scrub typhus. Omadacycline can be considered an alternative option for anti-infective therapy in patients with *O. tsutsugamushi* infections.

**Key Words:** Omadacycline; Scrub typhus; *Orientia tsutsugamushi*; Targeted next-generation sequencing; Eschar; Case report

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**Core Tip:** Scrub typhus is a naturally occurring acute infectious disease that is primarily transmitted through the bites of chiggers or larval mites infected by *Orientia*

*tsutsugamushi* (*O. tsutsugamushi*). In the present work, we report three cases of scrub typhus, with the main clinical symptoms being fever, the formation of eschar or ulcers, local or systemic lymphadenopathy, headache, myalgia and rash. Blood samples were collected before the administration of omadacycline. Omadacycline can be considered an alternative option for anti infective therapy in patients with *O. tsutsugamushi* infections.

## **INTRODUCTION**

Scrub typhus is a naturally occurring infectious disease that is transmitted primarily through the bites of chiggers or larval mites infected by *Orientia tsutsugamushi* (*O. tsutsugamushi*). The clinical manifestations of tsutsugamushi disease include fever, eschars or ulcers at the bite site, lymph node enlargement, and skin rash. Most cases generally resolve on their own, but in a few cases, severe complications or even death may occur[1,2]. The main endemic region for scrub typhus is the "tsutsugamushi triangle," which extends from the northernmost regions of South Korea, Japan, and Russia to northern Australia and westward to Pakistan and parts of Afghanistan[1]. Within this area, China is a significant endemic region[3]. The population most susceptible to tsutsugamushi disease consists primarily of farmers and workers[4].

<sup>1</sup> Omadacycline possesses broad-spectrum antibacterial activity against gram-positive and gram-negative aerobic, anaerobic, and atypical bacteria. In clinical practice, there is only one reported use of oral omadacycline[5], while intravenous omadacycline has not been reported for the treatment of scrub typhus. In this report, we present three cases of scrub typhus treated with intravenous omadacycline, which resulted in favorable outcomes.

## **CASE PRESENTATION**

### ***Chief complaints***

**Case 1:** A 59-year-old female presented with a week-long fever.

**Case 2:** A 68-year-old elderly woman presented with a fever that had persisted for more than 10 days.

**Case 3:** A 51-year-old female presented with a fever that had persisted for 13 days.

### *History of present illness*

**Case 1:** The patient developed a fever one week prior after continuous fieldwork exposure, with a maximum body temperature of 39 °C. The patient visited Huai'an Hospital three days prior. Routine blood work revealed a white blood cell (WBC) count of  $4.4 \times 10^9/L$  and a neutrophil percentage of 53.4%. Despite three days of treatment with moxifloxacin (400 mg by intravenous infusion once daily) for infection, the patient's fever persisted. The patient was transferred to our hospital for further treatment.

**Case 2:** The patient was admitted to Shuyang Mercy Hospital on November 3, 2023, due to fever that had persisted for five days. She developed a fever after agricultural work, with a maximum body temperature of 39.5 °C. Other symptoms included chills and pain in the right lower limb. The patient self-administered amoxicillin and ibuprofen but still experienced intermittent fever. Routine blood work revealed a WBC count of  $3.7 \times 10^9/L$  and a neutrophil percentage of 57.5%. Despite receiving a combination of azithromycin (500 mg by intravenous infusion once daily) and moxifloxacin (400 mg by intravenous infusion once daily) for antiinfective therapy for five days, the patient's fever persisted. The patient was transferred to our hospital for treatment on November 8, 2023.

**Case 3:** The patient had a fever after outdoor activity in a park, with a maximum body temperature of 39 °C occurring on November 24, 2023. Other symptoms included chills, headache and fatigue. Two days before admission, the patient went to the Huai'an Fifth

People's Hospital for treatment. Piperacillin/tazobactam and Reduning were administered to her in that hospital. However, the effect was not satisfactory.

### *History of past illness*

**Case 1:** The patient has a history of good health.

**Case 2:** The patient had a history of hypertension and cerebral infarction.

**Case 3:** The patient had a history of obsolete pulmonary tuberculosis, uterine leiomyomas and an allergy to quinolones.

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### *Personal and family history*

No significant family history.

### *Physical examination*

**Case 1:** The physical examination results were as follows: Body temperature, 36.4 °C; pulse, 106 bpm; respiration rate, 20 breaths/min; and blood pressure, 138/85 mmHg. An eschar with a diameter of approximately 2 cm × 2 cm was found in the right axilla of the patient; the area surrounding the eschar was red (Figure 1A). Enlarged lymph nodes were palpable in both the axillary and inguinal regions. No other significant abnormalities were observed.

**Case 2:** The physical examination results were as follows: Body temperature, 37 °C; pulse, 78 bpm; respiration rate, 21 breaths/min; and blood pressure, 98/49 mmHg. An eschar with a diameter of approximately 1.5 cm × 1.5 cm was found in the right popliteal fossa (Figure 1B). Enlarged inguinal lymph nodes were palpable.

**Case 3:** The physical examination results were as follows: Body temperature, 38.1 °C; pulse, 92 bpm; respiration rate, 20 breaths/min; and blood pressure, 115/75 mmHg. An

eschar with a diameter of approximately 2.0 cm × 1.5 cm was found on her left anterior chest, with part of the eschar already peeled off (Figure 1C).

### ***Laboratory examinations***

**Case 1:** The main laboratory test findings are shown in Table 1. *O. tsutsugamushi* was detected through targeted next-generation sequencing (tNGS) examination (Genoxor, Hangzhou).

**Case 2:** Other laboratory test findings are shown in Table 1. Scrub typhus was diagnosed by tNGS (Genoxor, Hangzhou).

**Case 3:** The main laboratory test findings are shown in Table 1. We strongly suspected that the patient had scrub typhus and collected a blood sample for tNGS analysis (Genoxor, Hangzhou), which confirmed our diagnosis.

### ***Imaging examinations***

**Case 1:** Chest and abdominal computed tomography (CT) scans revealed multiple enlarged lymph nodes in the axillary, clavicular, and abdominal regions, accompanied by splenomegaly.

**Case 2:** A chest CT scan revealed an old lesion in the upper right lung. No abnormalities were detected *via* cardiac or abdominal color Doppler ultrasound.

**Case 3:** Chest and abdominal CT scans revealed old lesions in both lungs, slightly enlarged lymph nodes in both axillae, and fatty liver.

### **FINAL DIAGNOSIS**

The final diagnosis for this patient was scrub typhus.

## **TREATMENT**

**Case 1:** After admission, the patient was promptly administered omadacycline (HaiZheng Pharmaceutical, China) *via* intravenous infusion. Initially, a dose of 200 mg was given, followed by a dose of 100 mg once daily for antiinfective treatment.

**Case 2:** After hospitalization, the patient received antiinfective treatment with omadacycline (HaiZheng Pharmaceutical, China), following the same administration method as Case 1.

**Case 3:** After the diagnosis of scrub typhus was confirmed, omadacycline (HaiZheng Pharmaceutical, China) was administered promptly.

## **OUTCOME AND FOLLOW-UP**

**Case 1:** The patient's body temperature normalized on the second day after initiation of omadacycline. Following a five-day course of treatment, the patient was discharged with no recurrence of symptoms.

**Case 2:** After two days of treatment, the patient's axillary temperature returned to normal. The patient recovered and was discharged after five days of hospitalization.

**Case 3:** After two <sup>6</sup>days of treatment, the patient's body temperature returned to normal, and the accompanying symptoms disappeared. Five days later, the patient was discharged with no complaints of discomfort.

## **DISCUSSION**

*O. tsutsugamushi*, the pathogen responsible for inducing scrub typhus in humans, is characterized as a gram-negative obligate intracellular bacterium. The main pathological manifestation of scrub typhus is focal or disseminated vasculitis involving small blood vessels and multiple organs[6]. The onset of scrub typhus typically occurs



between 6 and 21 days after exposure to *O. tsutsugamushi*, with clinical symptoms often presenting in an atypical manner. Patients may experience fever, fatigue, muscle aches, headache, and cough, among other symptoms. An eschar, a specific and crucial diagnostic indicator in scrub typhus cases, may manifest in different body regions but is commonly observed in areas with thinner and wetter skin, such as the armpits, groin, neck, and waist[7,8]. All three cases reported in this study presented clinical symptoms within one week after outdoor activities. In addition to some atypical clinical manifestations, the typical eschar appears in various parts of the body. Scrub typhus can lead to multiorgan dysfunction, resulting in damage to the respiratory, digestive, nervous, cardiovascular, and hematological systems, as well as abnormal liver and kidney function[9]. Liver involvement is frequent in scrub typhus, manifesting mainly as increased transaminase levels. A study by Hu *et al*[10] revealed alanine aminotransferase (ALT) and ALT elevation rates of 89.3% and 91.7%, respectively, suggesting a close association between scrub typhus and elevated liver enzyme levels. All three of our patients had higher than normal levels of aminophenase.

For patients with scrub typhus, early diagnosis and treatment are key factors in ensuring a favorable prognosis. In the past, the Weil-Felix test has been used as an auxiliary diagnostic method for scrub typhus, but its sensitivity and specificity are both low. Currently, indirect immunofluorescence assay (IIFA) is considered the gold standard for diagnosing scrub typhus. However, IIFA is not vigorous enough to detect infection at early stages, and enzyme-linked immunosorbent assay has the same shortcomings[11]. Next-generation sequencing (NGS) is the latest technique for detecting scrub typhus and has superior performance in the diagnosis of scrub typhus in early stages and eschar-negative cases[12,13]. Compared with metagenomic NGS (mNGS), tNGS has greater accuracy and sensitivity in pathogen detection, as well as lower testing costs[14]. Therefore, for patients suspected of having scrub typhus, tNGS may be a better choice than mNGS. The diagnoses of all three cases reported here were confirmed by tNGS. In clinical practice, we also encounter patients who are highly suspected of having scrub typhus but who test negative according to tNGS. We

consider that the main reason for this false-negative result may be related to the pathogen not entering the bloodstream or a low presence of the pathogen in the bloodstream.

Early and appropriate antibiotic treatment is crucial to prevent progression to severe scrub typhus. Doxycycline is the most widely used antibiotic, and tetracycline, chloramphenicol, azithromycin, and rifampicin are also effective choices for the treatment of scrub typhus[15]. Owing to its good efficacy and few side effects, azithromycin is the preferred drug for treating scrub typhus in pregnant women and children, and to avoid increasing the resistance of *Mycobacterium tuberculosis* (*M. tuberculosis*) to rifampicin, rifampicin is recommended only in areas where *M. tuberculosis* is resistant to other drugs[16,17]. There is little difference in treatment efficacy between tetracycline and doxycycline[15]. Omadacycline is a novel tetracycline-derived antibiotic. Omadacycline has broad-spectrum antibacterial activity against gram-positive and gram-negative aerobes, anaerobes, and atypical pathogens. Omadacycline overcomes common tetracycline resistance mechanisms, such as bacterial efflux pumps and ribosomal protection proteins; thus, it still has good antibacterial activity against minocycline-resistant, doxycycline-resistant, methicillin-resistant, *Staphylococcus aureus*, and drug-resistant, gram-negative bacteria[18]. Omadacycline is characterized by a low protein binding rate, large distribution volume, low systemic clearance rate, and long half-life; it is not metabolized by the liver and is excreted mainly through feces (81.1%) and the kidneys (14.4%). Accordingly, for elderly patients or those who have impaired liver or kidney function, the dosage of omadacycline does not need to be adjusted[19]. In our study, before being admitted to our hospital, all three patients received other antibiotic therapies, but all of the patients had unsatisfactory therapeutic outcomes. Furthermore, all of the patients were elderly and had impaired liver function, but after receiving standard intravenous omadacycline treatment, they were discharged from the hospital with no discomfort. The mean time to defervescence with doxycycline or azithromycin for the treatment of scrub typhus ranges from 25 to 224 hours[20]. In our reported cases, all three patients achieved

normal body temperature within 24 hours of starting omadacycline therapy, but larger studies are needed to confirm this finding. There are no case reports of the use of intravenous omadacycline to treat scrub typhus, and only one case report of the use of oral omadacycline[5]. Therefore, our study can provide an additional reference for the treatment of scrub typhus with omadacycline. However, our study has a limited number of patients, and further research with more patients is needed to investigate the mechanism of action, safety, and effectiveness of omadacycline in the treatment of scrub typhus.

### **CONCLUSION**

The presence of an eschar is a crucial diagnostic indicator for scrub typhus, making careful physical examination essential in clinical practice. tNGS represents a novel effective method for diagnosing scrub typhus. Omadacycline can be considered an alternative option for anti-infective therapy in patients with *O. tsutsugamushi* infections, particularly in patients with a poor response to macrolides or fluoroquinolone antibiotics.

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