

# Scrub typhus, the forgotten acute febrile illness: A case series from Negeri Sembilan, Malaysia

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### SUMMARY

Scrub typhus is a zoonotic bacterial infection caused by *Orientia tsutsugamushi*. Its clinical presentation is often mistaken for other acute febrile illnesses. This case series highlights the importance of obtaining a detailed history of outdoor exposure and considering scrub typhus as a possible diagnosis in patients presenting with fever, diarrhea, thrombocytopenia, and abnormal liver function tests. Thorough history taking, a high index of suspicion, and prompt initiation of treatment are crucial to reducing the mortality and morbidity associated with scrub typhus.

### INTRODUCTION

Scrub typhus is an infectious disease caused by a bacterium called *Orientia tsutsugamushi*.<sup>1</sup> Traditionally, it has been endemic to the 'tsutsugamushi triangle', posing a significant public health issue in the Asia-Pacific area. Globally, it threatens over one billion people and causes illness in approximately one million people annually.<sup>2</sup> Despite being a common cause of undifferentiated fever in Malaysia, it remains under-recognized in terms of healthcare policies, registries, and research.<sup>3</sup> Early recognition and treatment improve outcomes and help reduce mortality and morbidity. This paper presents four clinical cases of scrub typhus in Negeri Sembilan, Malaysia.

### CASE PRESENTATION

#### Case 1

A 42-year-old indigenous man presented with a 3-week history of fever, vomiting and diarrhoea. Physical examination revealed tenderness in the epigastric region, but no organomegaly. He works as a farmer and resides in the deep forest of Jelebu, a district in Negeri Sembilan. Initial blood results showed white blood cells (WBC) of  $9.3 \times 10^9/L$ , haemoglobin (Hb) of 85g/L, and platelet count of  $239 \times 10^9/L$ . His urea level was 10.9mmol/L, and creatinine was 93umol/L. Liver function tests showed a total bilirubin 93umol/L, alanine transaminase (ALT) of 318U/L, and alkaline phosphatase (ALP) of 629U/L.

Leptospira Ig M was positive, while C-reactive protein (CRP) was elevated at 119mg/L, and procalcitonin was 1.18ng/mL. Blood cultures showed no growth and hepatitis serology was non-reactive. A computed tomography (CT) scan of abdomen revealed hepatosplenomegaly with mild ascites. Based on these findings, the patient was initially treated for

leptospirosis with intravenous ceftriaxone 2g once daily. Despite 2 days of treatment, the patient remained febrile. Oral doxycycline was added to the treatment regimen, and his fever subsided 48 hours later.

Subsequent testing revealed a negative blood culture. Indirect immunoperoxidase (IIP) confirmed scrub typhus with an IgG titre of 1:800, strongly suggestive of active infection. Additionally, *Orientia tsutsugamushi* DNA was detected through serum Rickettsia polymerase chain reaction (PCR).

#### Case 2

A 48-year-old Indonesian man presented with a one-week history of fever, diarrhoea, and vomiting. He had multiple outpatient clinic visits prior to admission, where he was only given symptomatic treatment. He had been in Malaysia for 8 years, working as a rubber tapper, with no recent travel history before admission.

On presentation, he was tachypnoeic and confused. Abdominal examination revealed a soft abdomen without guarding. An ECG showed supraventricular tachycardia.

Laboratory investigations revealed a white blood cells of  $17.9 \times 10^9/L$ , platelet count of  $177 \times 10^9/L$ , and haemoglobin of 163g/L. He had severe acute kidney injury and metabolic acidosis, with deranged liver function test: ALT 111U/L, aspartate transaminase (AST) 113U/L, ALP 105U/L, and CRP 161.7mg/L. Plasma high-sensitivity troponin I was elevated at 806ng/L. He was intubated due to impending respiratory distress and severe metabolic acidosis. In view of thrombocytopenia with fever, he was initially treated as a case of severe dengue fever in the district hospital. However, dengue serology was negative, and no malarial parasites were seen on blood films. *Leptospira* IgM was also negative.

After consultation with infectious diseases specialists, he was empirically started on intravenous amoxicillin-clavulanate and oral doxycycline (100 mg twice daily), based on his occupational history. Unfortunately, the patient's condition deteriorated rapidly, and he passed away five hours after admission to the ICU.

Further testing revealed negative results for blood cultures, Dengue PCR, and *Leptospira* PCR. However, serum Rickettsia PCR detection of *O. tsutsugamushi* DNA, confirming a diagnosis of scrub typhus.

Table 1: Summary of Clinical Presentation, Investigations, and Outcomes in Four Cases of Scrub Typhus

Patient	Age, gender	Day of illness upon presentation	Clinical presentation	Eschar	White blood cell (x 10 <sup>9</sup> /L)	Platelet (x 10 <sup>9</sup> /L)	Creatinine (umol/L)	Total bilirubin (umol/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	ALP (U/L)	Primary diagnosis	Rickettsia PCR (Orientia tsutsugamushi DNA)	Rickettsia IIP test (serology)	ICU admission
1	42, M	20	Fever, abdominal pain, vomiting, diarrhoea	No	9.3	239	93	93	318	-	629	119	Leptospirosis	Detected	Scrub typhus Ig G 1:800	No
2	48, M	7	Fever, diarrhoea, vomiting	No	17.9	177	510	8	111	113	105	161.7	Severe dengue	Detected	Negative	Yes
3	44, M	7	Fever, diarrhoea, vomiting	Yes	20	109	88	105	165	-	419	238	Acute cholecystitis	Detected	Negative	Yes
4	33, F	7	Fever, diarrhoea, vomiting	Yes	21	75	70	23	74	201	260	234	Viral fever	Detected	Not available	Yes



Fig. 1: Case 3- Eschar over left arm

**Case 3**

A 44-year-old Bangladeshi man employed in an oil palm plantation presented with abdominal pain, fever and vomiting persisting for one week. Upon examination, he was found to be jaundiced and hypotension. He appeared septic, with abdominal pain localized to the right hypochondrium.

Laboratory tests revealed a white blood cell of  $20 \times 10^9/L$ , platelet count of  $109 \times 10^9/L$ , and hemoglobin level of  $134g/L$ . His total bilirubin was measured at  $105 \mu mol/L$ , with ALT at  $165U/L$  and ALP at  $419U/L$  and CRP was significantly elevated at  $238mg/L$ .

A CT scan indicated the presence of cholelithiasis with features consistent with cholecystitis. The patient was initially treated in surgical ward with intravenous amoxicillin-clavulanate for the suspected cholecystitis. Despite initial treatment, the patient's condition worsened. His fever persisted, and he developed fast atrial fibrillation (AF). He required inotropic support and mechanical ventilation due to respiratory failure and worsening sepsis. A chest X-ray (CXR) revealed cardiomegaly with bilateral lung infiltrates. Intravenous meropenem were initiated.

During antimicrobial stewardship (AMS) round, an eschar was noted on his left arm, raising suspicion for scrub typhus. The patient was subsequently treated with intravenous azithromycin and oral doxycycline for one week. Blood cultures and hepatitis screenings were negative. He was discharged in good condition following completion of the antibiotic course. The diagnosis of scrub typhus was

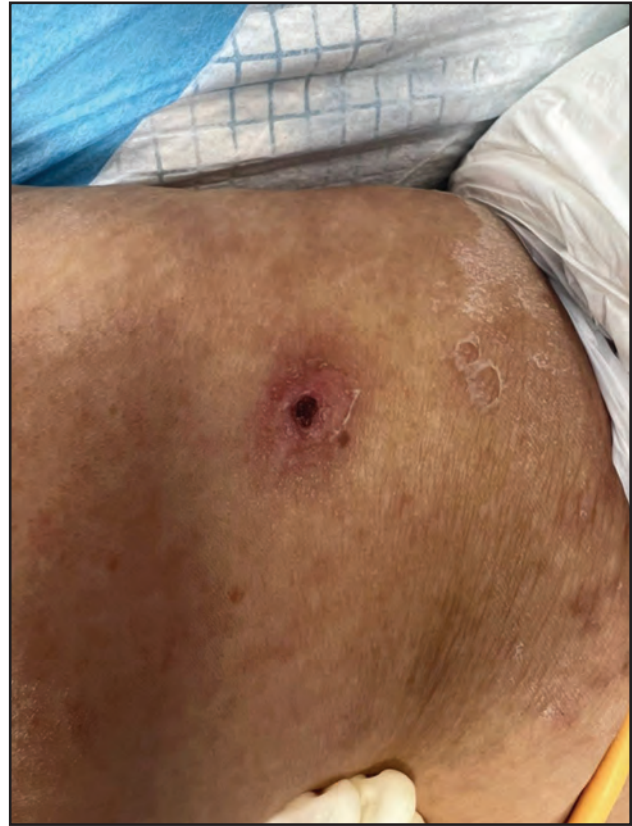


Fig. 2: Case 4 - Eschar over right inner thigh, with maculopapular rash over the surrounding skin

confirmed by a serum Rickettsia PCR, which detected *Orientia tsutsugamushi* DNA.

**Case 4**

A 33-year-old woman, working as a farmer in a lemongrass field, presented with a history of fever, vomiting, and loose stools for more than a week. She had initially visited a nearby clinic on day 3 of her illness, where she was treated for a suspected viral fever.

By day 7 of her illness, upon presentation to the hospital, she appeared critically ill, tachypneic, and required intubation due to severe metabolic acidosis, as well as inotropic support. On abdominal examination, there was tenderness in the right hypochondrium region. An eschar was noted on the inner aspect of her right thigh.

Laboratory investigations revealed a hemoglobin level of  $173g/L$ , a white blood cell count of  $21 \times 10^9/L$ , and a platelet count of  $75 \times 10^9/L$ . Her liver function tests showed a total bilirubin of  $23 \mu mol/L$ , ALT of  $74U/L$ , AST of  $210U/L$ , and ALP of  $260U/L$ . CRP was markedly elevated at  $234mg/L$ . The patient was diagnosed with scrub typhus and subsequently treated with intravenous azithromycin and oral doxycycline. Despite the treatment, her condition worsened, leading to severe renal injury and death on day 3 of admission. Blood cultures, leptospirosis PCR, and hepatitis serology were all negative. Serum Rickettsia PCR confirmed the presence of *Orientia tsutsugamushi* DNA, confirming the diagnosis of scrub typhus.

## DISCUSSION

*Orientia tsutsugamushi* is an arthropod-borne, gram negative, obligate intracellular bacillus.<sup>2</sup> Its prevalence ranges from 9.3% to 27.9% across Asia.<sup>4</sup> *O. tsutsugamushi* is transmitted to humans through the larval stage of chiggers. While the exact pathogenesis remains unclear, *O. tsutsugamushi* is thought to infect the vascular endothelial cells of small and medium vessels, leading to perivascular inflammation, vascular leakage, and end-organ damage.<sup>2</sup>

The incubation period of scrub typhus ranges from 6 to 21 days. Symptoms like as fever, nausea, and abdominal pain, are non-specific and can resemble other febrile illnesses. If left untreated, scrub typhus can lead to severe systemic complications including myocarditis, renal failure, and acute respiratory distress syndrome.<sup>2</sup> Outdoor activities such as farming or plantation work, increase the risk of contracting the disease.<sup>5</sup> In our cases, patients presented after about 10 days of illness with non-specific gastrointestinal symptoms. Despite clear outdoor exposure, they were initially misdiagnosed with leptospirosis or dengue. This emphasizes the need for a detailed exposure history, especially for those involved in outdoor work. Although eschar is a pathognomonic sign of scrub typhus, its prevalence varies across regions, with the highest occurrence in East Asia (78.7%) and the lowest in South Asia (32.8%).<sup>6</sup> In the cases reported here, eschars were identified in only two out of the four patients.

Laboratory findings in our patients include mild thrombocytopenia, elevated liver enzymes, and significantly elevated C-reactive protein (CRP) levels. These findings align with a study by Yazli et al., which indicates that white blood cell count and CRP levels tend to be higher in rickettsial infections and leptospirosis compared to dengue.<sup>3</sup>

The diagnosis of scrub typhus can be categorised into direct and indirect methods. Polymerase chain reaction (PCR) from serum, eschar tissue, or urine is a direct method of detecting *O. tsutsugamushi* DNA, and enables earlier diagnosis, especially during the bacteraemic phase. Indirect methods, such as immunofluorescent assays (IFA) and immunoperoxidase tests, detect antibodies to *O. tsutsugamushi*, but they required seroconversion or a fourfold rise in antibody titers between acute and convalescent phases, limiting their utility for early diagnosis.<sup>2</sup>

In our case series, both PCR and serology testing were outsourced to the Institute for Medical Research (IMR), with a turnaround time of 2 to 3 weeks. Notably, eschar samples were not sent for testing in the two cases where eschars were present, likely due to a lack of awareness among healthcare workers about the diagnostic importance of eschar tissue in scrub typhus. This highlights a knowledge gap that could impact the prompt and accurate diagnosis of scrub typhus. Given the turnaround time for diagnostic results, it is essential to initiate treatment promptly for patients presenting with suggestive symptoms and a history of outdoor exposure.

The median mortality for patients with scrub typhus was as high as 6% but was significantly reduced to 1.4% with appropriate treatment.<sup>4,7</sup> According to CDC guidelines,

doxycycline remains the first-line treatment and is safe for all age groups.<sup>1</sup> In critically ill patients, however, the absorption of oral doxycycline absorption may be impaired. In such cases, azithromycin is an alternative. Studies indicate that there is no significant difference in clinical outcomes between doxycycline and azithromycin monotherapy.<sup>8</sup> Varghese et al. found that combination therapy with doxycycline and azithromycin was more effective than monotherapy for severe scrub typhus.<sup>9</sup> In our case series, two patients received combination therapy; one recovered uneventfully, while the other succumbed to the disease on day three of treatment.

## CONCLUSION

Scrub typhus is a significant tropical disease, particularly prevalent in rural populations, and can lead to serious complications if not recognized promptly. When evaluating differential diagnoses in the context of acute febrile illness, scrub typhus should always be considered. A comprehensive exposure history and thorough clinical evaluation are essential for initiating prompt treatment, which can significantly improve patient outcomes and reduce morbidity and mortality associated with this disease.

## ACKNOWLEDGEMENT

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## DECLARATION

The authors have no conflict of interest to disclose.

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