A PARALYZING BITE: AN UNORTHODOX CASE OF SCRUB TYPHUS IN A NON-ABORIGINAL MALAYSIAN PATIENT

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Abstract

Scrub typhus is an acute febrile illness caused by the bacteria *Orientia tsutsugamushi*, which can be transmitted to humans through the bite of infected trombiculid chigger mites. Besides the typical clinical features of fever and eschar formation, the central nervous system has been reported to be involved as evidenced of reported cases ranging from meningitis to meningoencephalitis. Here, we describe an atypical presentation of scrub typhus case that occurred in a 34-year-old Malay male who presented with quadriplegia following an insect bite at the back of his neck. Our case displayed unusual findings of this rare condition in a non-aboriginal Malaysian population. Based on previous literature, we emphasized the importance of prompt diagnosis of scrub typhus in order to reduce the mortality and morbidity and to improve the quality of life for patients with complications of this disease.

Keywords: *Scrub Typhus, Encephalomyelitis, Quadriplegia, Malaysia*

Introduction

Scrub typhus, also regarded as tsutsugamushi disease, is a zoonotic disease caused by the bacteria *Orientia tsutsugamushi*. It is a mite-borne disease characterized by fever with headaches, lymphadenopathy and multi-organ involvement. This disease usually responds rapidly to doxycycline (1). An eschar is pathognomonic for scrub typhus if present in a patient with acute febrile illness from an endemic area, and when present, it is a valuable clue to the diagnosis (2). Complications involving the central nervous system due to scrub typhus such as meningitis and meningoencephalitis have been reported in previous studies (3, 4). Other neurological complications include seizure, cranial nerve deficit, cerebral infarct, brain hemorrhage, polyneuropathy and sensorineural hearing loss (3, 5, 6). In addition, atypical complications such as cerebral infarct, transverse myelitis, polyneuropathy, and acute disseminated encephalomyelitis (ADEM) have been reported in other studies (6, 7).

Scrub typhus is a public health concern in the remote areas of Southeast Asian nations, including Malaysia. The aboriginal population, one of the most socio-economically deprived groups in the Malaysia, is commonly exposed to the bite of trombiculid chigger mites (vector for scrub typhus) due to their daily activities and living areas such as those of farmers and fishermen; and residing in jungles (8). However, cases of scrub typhus among the non-aboriginal population of Malaysia are rarely reported hence leading to a poor index of suspicion and late diagnosis (8, 9).

We will be describing an atypical case of scrub typhus with central nervous system (CNS) involvement in a 34-year-old Malay male who presented with neurological deficits following a two-week history of an insect bite during fishing. Our case presents typical findings and unusual complications of this rare incidence among a non-aboriginal Malaysian population. Our report emphasizes the importance of having a high index of suspicion in diagnosing scrub typhus among non-typical populations to reduce the mortality of this disease. To the best of our knowledge, this is the first described case of scrub typhus with CNS involvement in Malaysia.

Case Report

A 34-year-old dark skinned Malay man who works as a labourer with no history of relevant medical illness

presented to a general practitioner clinic in Kelantan (a northeast state of peninsular Malaysia) with fever, headache, neck swelling with whitish discharge and an eschar-like skin lesion. He had a history of insect bite over the posterior side of his neck during fishing in a secluded fishing area in the woods of Tumpat district two weeks prior to the clinic visit. He was prescribed a painkiller and discharged home. Three days later, he developed a left side body weakness associated with slurred speech, lethargy and became cyanotic. He was brought to the emergency department of the district hospital by family members. There were no history of fitting, nausea, vomiting or symptoms of upper respiratory tract infection. The Glasgow Coma Scale (GCS) upon examination was 13 over 15 (4 for best eye response, 4 for best verbal response and 5 for best motor response), and pupils were sluggishly reactive to light with right lateralization. Patient was then immediately transferred to the general hospital for further management.

On admission to the general hospital, patient was intubated, sedated and ventilated in view of poor and deteriorating GCS (10 over 15), with arterial blood gas test results indicating carbon dioxide retention. On neurological examination prior to intubation, muscle power grading was zero on the left side, with normal muscle tone and presence of brisk plantar reflexes bilaterally. Plantar response was down going and sensation was intact bilaterally. Physical examination revealed a white crusted skin lesion measuring 2x2 cm, with a black painless papule and central necrosis suggestive of eschar on the posterior side of neck. No conjunctival suffusion was noted.

Initial laboratory tests revealed a white cell count of 21.7 x 10^9/L (normal range: 4 – 11 x 10^9/L), hemoglobin levels of 15.0 g/dL (normal range: 12.0 – 17.0 g/dL), and platelet count of 285 x 10^9/L (normal range: 150 – 400 x 10^9/L). His renal profile revealed potassium level of 3.9 mmol/L (normal range: 3.50 - 5.10 mmol/L), sodium level of 137 mmol/L (normal range: 136 – 145 mmol/L), urea level of 5.7 mmol/L (normal range: 1.70 – 8.30 mmol/L) and creatinine level of 67 µmol/L (normal range: 62 – 106 µmol/L). As for the liver function test, the albumin level was 41 g/L (normal range: 35 – 52 g/L), alkaline phosphatase was 58 units/L (normal range: 40 – 129 units/L, alanine aminotransferase was 53 units/L (normal range: 10 – 40 units/L) and aspartate aminotransferase was 19 units/L (normal range: 15 – 40 units/L).

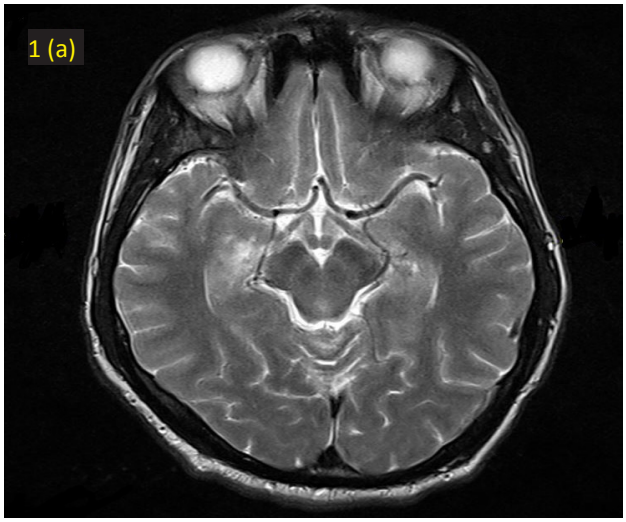
Electrocardiogram and echocardiography were conducted to assess any cardiac pathology and was found to be normal. The initial chest radiograph showed clear lung fields with no cardiomegaly. Computed tomography (CT) scanning of brain on the day of admission showed bilateral hypodensity in the parieto-occipital region which could be due to ischemia or posterior reversible encephalopathy. Contrast-enhanced CT scanning of the brain showed focal increased vascularity at left fronto-parietal region with prominent vessel peripherally which may represent early focal cerebritis. Lumbar puncture was performed and revealed clear and colourless cerebrospinal fluid. Microscopic examinations showed absence of pus cells; no organism detected upon Gram staining; India ink staining was negative; and the rapid agglutination antigen detection tests were negative for *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, Group B *Streptococcus* and *Streptococcus pneumoniae*.

In view of the history of insect bite, presence of eschar, leukocytosis, high level of alanine aminotransferase and abnormal imaging findings, a diagnosis of meningoencephalitis secondary to possible scrub typhus with secondary transaminitis was made. He was treated on intravenous antibiotic (ceftriaxone 2 g twice daily) and oral antibiotic (doxycycline 100 mg twice daily). After five days in intensive care unit (ICU), patient underwent a tracheostomy due to failed extubation. He was then transferred to the high-dependency unit on day 10 of admission for continuation of treatment and nursing care. However, on day 11 of admission, his body weakness worsened as he progressed to develop right-sided body weakness.

Urgent magnetic resonance imaging (MRI) was performed for further evaluation of the central nervous system. It showed an ill-defined lesion at right temporal which is hypointense on T1, hyperintense on T2 (Figure 1); and abnormal signal intensity of the spinal cord seen from level C2 until C6 which is hyperintense on T2 (Figure 2), suggestive of temporal encephalitis or cerebritis and myelitis, respectively. Figure 3 showed better delineation of the right temporal lesion with disruption of normal blood vessel at this region. In view of these imaging findings, the patient was started on intravenous methylprednisolone 500 mg daily for 3 days with continuation of the previous antibiotic regime.

Serological test for scrub typhus using indirect immunoperoxidase (IIP) test was conducted only at day 14 of admission. The results showed a titre of 1:50 for scrub typhus immunoglobulin M (IgM) and 1:400 for immunoglobulin G (IgG) (reference range: ≥1:50 - ≤1:400). IIP test results for endemic typhus IgM, IgG and tick typhus IgM, IgG were negative. Blood and cerebrospinal fluid cultures showed no growth.

Following 2-week course of doxycycline and completion of methylprednisolone, the patient showed clinical improvement as he was no longer ventilator-dependent. He showed slight improvement of the neurological deficits but needed assistance for routine daily living activities. He was on nasogastric tube feeding and required physiotherapy for therapeutic exercises. The patient was discharged from hospital 3 weeks after admission. His GCS upon discharge was 10 over 15 (4 for best eye response, verbal response was not testable as patient was on tracheostomy and 6 for best motor response). His total white cell count improved from 21.7 x 10^9/L to 14.0 x 10^9/L. He was followed up



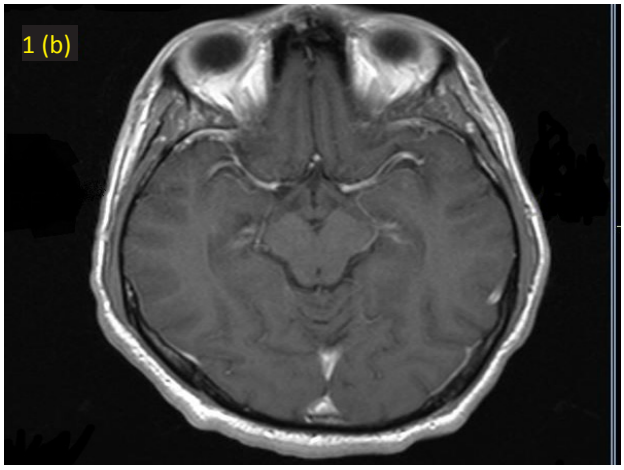
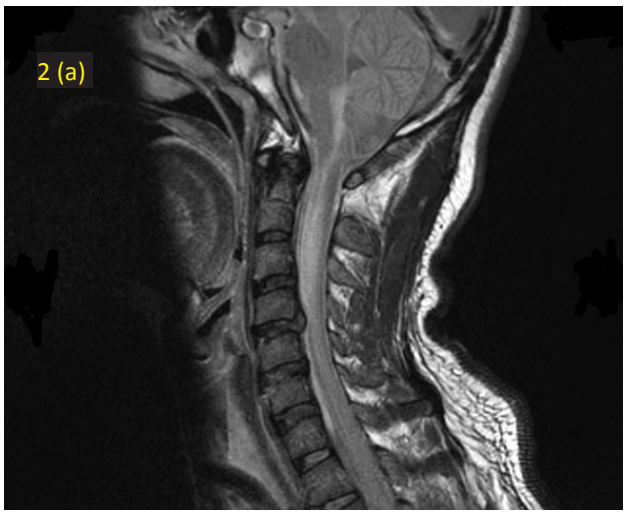


Figure 1: (a) Axial T2 and **(b)** T1 post contrast showed an ill-defined lesion at right temporal which is hypointense on T1, hyperintense on T2, not suppressed on fluid attenuated inversion recovery (FLAIR) suggestive of temporal encephalitis or cerebritis



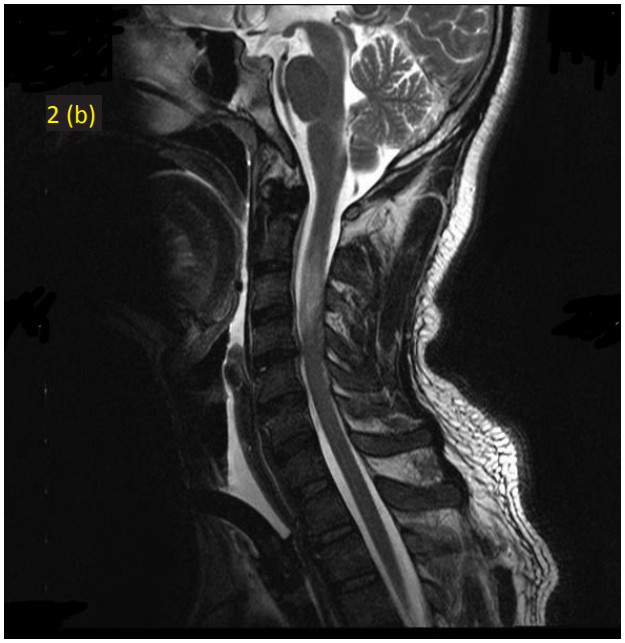


Figure 2: (a) Sagittal fluid attenuated inversion recovery (FLAIR) image and **(b)** T2 image of cervical spine MRI showed abnormal signal intensity of the spinal cord seen from level C2 until C6. The spinal cord is hyperintense on T2, not suppressed by FLAIR, showed no enhancement post-contrast and extension of abnormal signal intensity to the medulla oblongata posteriorly. These features most likely represent myelitis

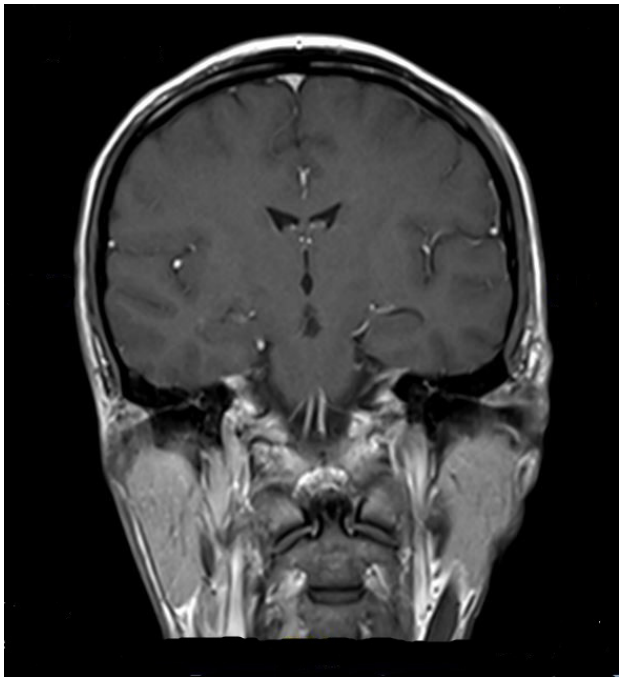


Figure 3: Post-contrast coronal T1 image showed better delineation of the right temporal lesion with disruption of normal blood vessel at this region due to encephalitis

regularly by the rehabilitation unit to improve his quality of life.

Discussion

Scrub typhus is among the most underdiagnosed and under-notified febrile illnesses in Southeast Asian region as reported by the World Health Organization (WHO) (10). Scrub typhus has an array of clinical manifestations ranging from simple fever to multi-organ involvement including CNS, resulting in substantial morbidity and mortality (11).

In Malaysia, scrub typhus among the Malay population is uncommon and is more rampant among aborigines due to their nature of works, lifestyles and living areas. Scrub typhus is commonly found in areas with a suitable climate, plenty of moisture and scrub vegetation. Areas inhabited by aborigines like forest clearings, riverbanks, and grassy regions provide optimal conditions for the infected mites to thrive (12). It is well-documented that the incidence of scrub typhus ranged from 3.2% to 3.9% monthly in two settlements of aborigines in West Malaysia (13). The prevalence of *O. tsutsugamushi* antibody was up to 36.4% in seven subgroups of Malaysian aborigines particularly among aborigines who worked in agricultural activity and as fishermen (8). Moreover, the presentation of eschar which is pathognomonic for scrub typhus is more easily noticed on patients with fair skin tone such as East Asian and Caucasian people than those with dark skin (2). Due to these epidemiologic and clinical attributes, it is possible that scrub typhus among the Malay population is under-diagnosed.

Similarly with our patient, approximately 1 to 2 weeks after being bitten, patient begin to have flu-like and febrile illnesses, myalgia, body discomfort and eschar formation at the bite site (14). Fever and headache are the most common presentations among scrub typhus patients (1). Serious complications such as systemic organ failure occur in some patients. The lung is one of the primary target organs for *Orientia*, leading to pulmonary complications such as interstitial pneumonia in severe cases (15). Complications involving CNS such as meningitis and encephalitis can arise in untreated or late stage of undiagnosed scrub typhus, causing patients to become delirious or even develop seizures. Focal neurological signs with atypical complications like cerebral infarction, ADEM, polyneuropathy and transverse myelitis have been reported (7, 15). These manifestations may be due to direct invasion of CNS by the organism or may be due to the unique propensity of the organism to infect vascular endothelial cells, thereby causing microinfarct (16, 17). Similar with our case findings, ADEM associated with scrub typhus had been reported in Taiwan in which the patient also developed quadriplegia (18). In this complicated and rare case, radiologists play a crucial role in the diagnosis. Serial cranial magnetic resonance images demonstrated similar findings with our case which were progressively extensive areas of signal hyperintensity on conventional T2-weighted and fluid attenuated inversion recovery (FLAIR) sequence images (18).

The IIP technique can be used for the serologic diagnosis of scrub typhus. According to previous study, the *Rickettsia tsutsugamushi* antibodies (IgM and IgG) titers determined by the IIP technique had good correlation with those determined by the indirect immunofluorescence technique. Thus, the IIP technique was suitable and practical for quantifying both IgG and IgM antibodies to the *Orientia* (19). As for the treatment of scrub typhus, doxycycline is an effective choice of antibiotic as reported in several trials and a meta-analysis, although resistance has been documented (20). In fulminant ADEM, early high-dose intravenous methylprednisolone can be beneficial. Recent study showed that a patient with ADEM recovered substantially without requiring maintenance steroid therapy after being treated with high-dose intravenous methylprednisolone 2 days after onset of neurologic symptoms (21).

Review of the previous studies found that fever and headache are the most typical features and eschar is pathognomonic for scrub typhus. Atypical complications such as cerebral infarction, polyneuropathy, ADEM and transverse myelitis have been reported and can be detected with MRI. Early suspicion and recognition of the disease among the non-endemic population by physicians and radiologists is crucial for early management and prevention of serious neurological complications.

Conclusion

Scrub typhus should be suspected in all subgroup of population especially amongst those that are involved in activities or works that predispose them to the disease. Such patients could develop serious neurological complication following scrub typhus if they are not given early treatment. The diagnosis is often confirmed by the identification of both IgG and IgM antibodies to the *Orientia*. For uncomplicated scrub typhus cases, patients usually respond rapidly to doxycycline while patients with neurological complications might require high-dose intravenous methylprednisolone.

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Competing Interests

The authors declare that they have no competing interests.

Financial Support

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Informed Consent

Verbal informed consent was obtained from the patient's next of kin for inclusion in this report. Research and ethics committee approval for case reports is not a requirement according to Medical Research and Ethics Committee and Institute for Clinical Research Malaysia.

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