A case of scrub typhus with acalculous cholecystitis, aseptic meningitis and mononeuritis multiplex

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We present an unusual case of a patient with scrub typhus who developed acalculous cholecystitis, aseptic meningitis and mononeuritis multiplex. The patient was successfully treated with oral minocycline. To our knowledge, this is the first report of mononeuritis multiplex caused by scrub typhus.

Introduction
Scrub typhus (tsutsugamushi disease) is an acute febrile illness caused by Orientia tsutsugamushi and transmitted to humans by the bite of trombiculid mites. It is endemic in East and South-East Asia, the Western Pacific Islands, Australia, several parts of Russia, and India. In Japan, over 1000 cases per year were reported in the 1980s. Although this number has decreased over the years, its reported incidence has remained at around 400 cases per year since 2000 (Tachibana & Okayama, 2007). After an incubation period of 7–14 days, most patients develop high fever, headache and myalgia. Other symptoms such as rash, eschar and lymphadenopathy may also be evident. Here, we report a case of scrub typhus with acalculous cholecystitis, aseptic meningitis and mononeuritis multiplex.

Case report
A 72-year-old Japanese woman was admitted to hospital complaining of abdominal pain, nausea, vomiting, fever and rash. One week prior to the admission, she had developed fever (body temperature, 40°C) along with a headache. She was examined by a primary physician who prescribed cefcapene pivoxil. Following the prescribed antibiotics, a day later, she developed a generalized rash. She discontinued the antibiotics, but the rash did not resolve. She denied diarrhoea, and over the next few days, her headache gradually subsided. Two days prior to the admission, she developed right upper quadrant abdominal pain accompanied by nausea and vomiting. She had a history of an allergic reaction (skin rash) to pyrazolone and was a farmer who had never travelled abroad.

On admission to the hospital, her body temperature was 38.5°C, blood pressure was 139/71 mmHg and pulse rate was 113 beats min⁻¹. She was alert and oriented. Her neck was supple and the neurological findings were normal. She had right upper quadrant abdominal tenderness without guarding or rigidity, and a generalized blanching maculopapular rash over her body. Her white blood cell count was 9500 mm⁻³ (normal range, 3500–10 600 mm⁻³) and platelet count was 130 000 mm⁻³ (normal range, 130 000–350 000 mm⁻³). The serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin were 39 IU l⁻¹ (normal range, 10–40 IU l⁻¹), 20 IU l⁻¹ (normal range, 5–45 IU l⁻¹), 225 IU l⁻¹ (normal range, 80–260 IU l⁻¹) and 0.6 mg dl⁻¹ (normal range, 0.3–1.3 mg dl⁻¹), respectively. A contrast-enhanced computed tomography (CT) scan of the abdomen revealed mild splenomegaly, slightly enlarged para-aortic lymph nodes and thickening of the gall bladder wall. Ultrasound imaging also showed generalized oedematous thickening of the gall bladder wall of up to 8 mm without gallstones (Fig. 1a, b).

She was administered intravenous ciprofloxacin and clindamycin for the presumed diagnosis of acalculous cholecystitis. Since her skin rash was initially attributed to the allergic reaction to cefcapene pivoxil, β-lactam antibiotics were not administered. By hospital day 2, her fever, rash, abdominal pain and vomiting had only slightly improved.
On hospital day 3, she developed bilateral severe myalgia of the calves. Around the same time, the patient noticed a skin lesion behind her right knee; this was judged to be an eschar lesion, which is the characteristic skin lesion of scrub typhus (Fig. 1c). Thereafter, we re-examined her clinical records, and strongly suspected scrub typhus as the diagnosis. On specifically enquiring about any episode of tick bite, she recalled that she had been bitten by an insect behind her right knee at her farm 2 weeks prior to the hospital admission. Hence, we diagnosed her condition as scrub typhus, and replaced her antibiotics with minocycline, which was administered at a dose of 100 mg every 12 h. The myalgia and other symptoms improved considerably after minocycline treatment. Around hospital day 5, she developed hypesthesia of both the lower extremities and the right hand. She also complained of weakness in the fingers of her right hand. Neurological examination revealed weakness in the right interosseous muscles and hypesthesia in the right median, right ulnar, right sural and left saphenous nerve areas. Other neurological findings including those pertaining to autonomic function were normal. Cerebrospinal fluid showed an increased number of cells (23 mm$^{-3}$; 91% lymphocytes) (normal range, 0–5 mm$^{-3}$) and high protein level (79 mg dl$^{-1}$) (normal range, 15–45 mg dl$^{-1}$), while the glucose level was normal. Nerve conduction examination revealed decreased sensory nerve conduction velocity (NCV) in the right median nerve region distal to the wrist, and decreased motor nerve conduction in the right ulnar nerve in the region of the fourth interosseous muscle. Neurologists examined the patient and concluded demyelinating sensorimotor mononeuritis multiplex. After the 10 day course of oral minocycline, her neurological symptoms showed improvement, and finally she was discharged from the hospital on day 17. *O. tsutsugamushi* serotype Gilliam antibody levels determined by immunofluorescence assay on hospital day 7 were found to be high: the IgM titre was 1:320 (normal, <10) and the IgG titre was 1:40 (normal, <10). The patient refused invasive procedures, and thus biopsy and *O. tsutsugamushi* PCR of the eschar lesion were not performed.

Fig. 1. (a, b) Images showing the thickening of the gall bladder wall without gallstones. Computed tomography (a) and ultrasound (b) images. (c) Eschar lesion on the posterior region of the right knee.
Discussion

The patient’s predominant abdominal pain along with nausea, vomiting and the thickening of the gall bladder wall, as confirmed by the CT scan and ultrasonography, led to the initial diagnosis of acalculous cholecystitis. On MEDLINE, we identified only three case reports on acalculous cholecystitis caused by scrub typhus, including one written in Japanese (Inaba et al., 2004; Wang et al., 2003; Yang et al., 1995). In two of the three cases, patients underwent surgical procedures for the initial diagnosis of acute cholecystitis before the diagnosis of scrub typhus or even before treatment could begin (Inaba et al., 2004; Yang et al., 1995). One study reported the pathological and imaging findings of scrub typhus (Jeong et al., 2007). In this study, retrospective review of the CT scans and ultrasound images of 19 patients with scrub typhus revealed gall bladder wall thickening of ≥3 mm in 47% of patients. Gall bladder wall thickening without tense gall bladder distention, which is consistent with the intraoperative findings described in another report and observed in the CT scans and ultrasound images of our patient, was reported to be a feature of subserosal oedema caused by scrub typhus infection (Inaba et al., 2004; Jeong et al., 2007). Splenomegaly was found in 79% and lymphadenopathy in 47% of the patients; these conditions were also noted in our patient. Another study (Inaba et al., 2004) reported the pathological findings of a thickened gall bladder wall: it stated that various inflammatory cells including neutrophils, lymphocytes and plasma cells invaded under the mucosal epithelium.

Meningoencephalitis is the most common neurological manifestation of scrub typhus (Jeong et al., 2007). The involvement of the peripheral nervous system has been discussed in only four reports, and three of them were those of Guillain–Barré syndrome (Kim et al., 2008; Lee et al., 2007, 2009b). A case of brachial plexus neuropathy associated with scrub typhus was reported from Taiwan (Ting et al., 1992). In this report, the cause of brachial plexus neuropathy was attributed to axonal degeneration based on NCV study, which revealed low action potential amplitudes with a relatively normal conduction velocity (Ting et al., 1992). Our patient’s clinical and NCV study findings with decreased multiple sensory and motor NCVs were compatible with the diagnosis of demyelinating sensorimotor mononeuritis multiplex. We did not perform contrast-enhanced magnetic resonance imaging of the spine, and, therefore, the evaluation of axonal injury and radiculitis remains incomplete. Although biopsy of our patient was not performed, pathological changes such as lymphohistiocytic vasculitis due to the scrub typhus infection have been reported in multiple organs, and these could be a possible explanation of mononeuritis multiplex (Jeong et al., 2007; Lee et al., 2009a). Further studies are required to explain the mechanisms of the various neurological changes caused by scrub typhus. A prospective study (Pai et al., 1997) reported central nervous system involvement in cases of scrub typhus. Mild pleocytosis was present in 48% (n=25) cases, and nested PCR assay for O. tsutsugamushi was positive in 6 of the 25 cases. None of the patients presented nuchal rigidity, whereas only one patient had an altered mental status, which was described as drowsiness. Considering our patient’s cerebrospinal fluid findings and the presence of headaches at the early clinical stages, our diagnosis of aseptic meningitis seemed reasonable.

The serum antibody for scrub typhus was obtained on hospital day 7, i.e. 2 weeks after her symptoms developed. Unfortunately, since only one set of serum antibody tests was available, we could not prove the ≥-fourfold increase in titre, which is required to establish a definitive diagnosis (Blacksell et al., 2007). However, in our patient, the O. tsutsugamushi serotype Gilliam IgM titre was much higher than the most widely used cut-off value of 1:50 (Blacksell et al., 2007). The high titre along with her characteristic clinical findings, including the eschar lesion, and the response to minocycline treatment certainly indicates the diagnosis of scrub typhus. Because a commercially available O. tsutsugamushi antibody test that detects only Kato, Karp and Gilliam serotype was used, the possibility of infection by serotype Kuroki or Kawasaki, which are also endemic in Japan, cannot be ruled out.

In conclusion, scrub typhus can cause a variety of clinical symptoms with a wide range of severity. High clinical suspicion of scrub typhus is essential for its early diagnosis and treatment in the endemic area. We should keep in mind that scrub typhus may show diverse and atypical neurological changes involving not only the central nervous system but also the peripheral nervous system.

References


