Case Report: Abducens Nerve Palsy and Meningitis by *Rickettsia typhi*

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Abstract. Patients with rickettsial infection may present with encephalitis or meningitis but neurologic involvement is rare in murine typhus. Here, we report two patients with *Rickettsia typhi* meningitis who presented with cranial neuropathy, presumably caused by two distinct disease processes. Recognition of the disease manifestations is important because rickettsial infections are potentially associated with significant morbidity. Simple effective treatments are available.

INTRODUCTION

Rickettsial infections are an important but often underrecognized cause of undifferentiated febrile illness. They are widely distributed throughout the world and can generally be divided into four groups based on contemporary phylogenetic analyses, namely ancestral (*Rickettsia bellii*, *Rickettsia canadensis*), typhus (*Rickettsia prowazekii*, *Rickettsia typhi*), transitional (*Rickettsia akari*, *Rickettsia felis*), and spotted fever groups (*Rickettsia rickettsii*, *Rickettsia conorii*, *Rickettsia sibirica*).¹ Murine typhus, caused by infection with *Rickettsia typhi*, is one of the most prevalent of the human rickettsioses. The major route of transmission typically involves the host – roof rats (*Rattus rattus*) and Norway rats (*Rattus norvegicus*) and the vector – rat flea (*Xenopsylla cheopis*).² In some parts of the world, domestic cats, opossums, and their fleas, *Ctenocephalides felis* also play a role in the transmission of murine typhus.² Murine typhus remains an important cause of acute febrile illness in Singapore and the disease incidence is the highest among the foreign immigrant workers who live in poor and unhygienic living conditions.^{3–5}

Rickettsial infections are difficult to diagnose because they share symptoms with many other common febrile illnesses. Their clinical presentations vary in severity from self-limiting mild illnesses to fulminant life-threatening infections. Patients with murine typhus generally present with sudden onset of non-specific symptoms including acute sustained hyperpyrexia, severe headache, myalgia, arthralgia, and malaise. Characteristic skin rashes and flea bites are occasionally found on physical examination.^{6,7} In its severe form, rickettsioses may present as culture-negative endocarditis,^{8,9} splenic rupture,^{10,11} and infection of the central nervous system as part of a multiple organ dysfunction syndrome.¹² Central nervous system involvement in murine typhus is considered a rare occurrence, especially when compared with other rickettsial infections.^{13–15} Patients with murine typhus involving the central nervous system typically present with headache, fever, and neck stiffness 10 days to 3 weeks after the initial onset of febrile illness.^{16,17} More serious neurological signs, such as diplopia, papilledema, and facial paralysis have also been reported.^{17–19} Here, we report two patients with murine typhus who developed aseptic meningitis with sixth nerve palsy.

Case 1. A 39-year-old Indian male foreign worker was admitted with a 9-day history of fever, night sweats, neck

pain, and diplopia followed by five episodes of vomiting on the day of admission. There was no photophobia, recent insect bites, or skin rashes. He had no significant past medical history and was not on regular medication. Physical examination revealed a temperature of 37.9°C, terminal neck stiffness, and right lateral gaze palsy. Fundoscopy showed bilateral papilledema. Laboratory investigations showed normal hemoglobin, white blood cell count of $5.21 \times 10^9/L$ with neutrophil of 81.3%, thrombocytopenia of $125 \times 10^9/L$, and raised C-reactive protein (CRP) of 165.2 mg/L. Liver enzymes were mildly elevated with alanine aminotransferase (ALT) of 48 IU/L, aspartate aminotransferase (AST) of 52 IU/L, and gamma glutamyl transpeptidase of 80 IU/L. Bilirubin, alkaline phosphatase (ALP), creatinine, and electrolytes were within normal limit. Other tests including urine analysis, blood and urine cultures, dengue panel, blood films for malarial parasites, hepatitis B and C screen, human immunodeficiency virus (HIV) serology, and chest radiograph were normal. The patient was started on intravenous ceftriaxone and acyclovir on admission to cover for bacterial and viral meningitis. Oral doxycycline 100 mg twice daily was added to cover for probable rickettsial infection in view of clinical presentation. Magnetic resonance (MR) imaging of the brain was performed on Day 2 of admission and revealed no abnormal brain parenchymal or meningeal enhancement. However, signs of raised intracranial pressure such as distension of the perioptic subarachnoid space, vertical tortuosity of the orbital optic nerve, and empty sella were present on the MR images (Figure 1A and B). A lumbar puncture was performed subsequently, which showed an opening pressure of 39 cmH₂O, white cell count of 26/ μ L with 37% lymphocytes, 36% monocytes, and 27% neutrophils, glucose level of 4 mmol/L (blood glucose 7 mmol/L), and protein 0.3g/L. Cerebrospinal fluid (CSF) gram stain, culture, herpes simplex virus (HSV) polymerase chain reaction (PCR), acid fast bacilli (AFB) smear, mycobacterial culture, fungal smear, fungal culture, and cryptococcal antigen were all negative. Patient's symptoms and fever gradually improved after 5 days of doxycycline. On the day of discharge, the serum *Rickettsia typhi* IgG titer collected on Day 2 of admission came back as 256. The convalescent specimen collected on Day 11 of admission revealed a titer of 8,192, consistent with a recent murine typhus infection. During follow-up after a month, the patient was well and had returned to work. His right lateral gaze palsy was present although not as prominent as when he was hospitalized.

Case 2. A 27-year-old Filipino male was hospitalized for a 3-day history of fever and generalized headache followed by a 1-day history of vomiting and progressive drowsiness. He had recently traveled to Indonesia for a 5-day trip and returned to

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FIGURE 1. (A) Vertical tortuosity of the orbital optic nerve and distension of the perioptic subarachnoid space indicative of raised intracranial pressure. (B) Empty sella (red arrow).

Singapore 1 day before the onset of symptoms. No animal contact, insect bite or contact with sick persons were noted during the trip. Other than a hepatitis B carrier, he had no other significant past medical history. On admission, his auricular temperature was 37.6°C, blood pressure was 117/68 mm of Hg, and pulse was 106/min. Examination of the heart, lungs, and abdomen was unremarkable. Neurological examination was limited as a result of drowsiness. His conscious level progressively deteriorated and required endotracheal intubation for mechanical ventilation. Initial laboratory results showed raised white blood cell count of $18 \times 10^9/L$ with 90% neutrophils, creatine kinase 1683 IU/L, CRP 41.2 mg/L, and procalcitonin 7.6 $\mu g/L$. Other blood tests including hemoglobin, platelet count, creatinine, electrolytes, ALT, AST, ALP, bilirubin, thyroid stimulating hormone, free thyroxine (T4), calcium, and ammonia levels were within normal range. A diagnosis of meningoencephalitis was entertained and the patient was

FIGURE 2. (A) Restricted diffusion in the midline of splenium of corpus callosum (red arrow). (B) Normal perioptic subarachnoid space and straight orbital optic nerve. (C) Pituitary gland is visible (red arrow).

started empirically on meningitic dose of intravenous ceftriaxone and acyclovir on the day of admission. Anti-tuberculosis drugs in the form of rifampin, isoniazid, ethambutol, and pyrazinamide were added in view of travel history. A pre- and post-contrast MR imaging of the brain revealed non-specific restricted diffusion in the midline of the splenium of corpus callosum suggesting encephalitis and diffuse leptomeningeal enhancement with sulcal fluid-attenuated inversion recovery (FLAIR) hyperintensities in keeping with meningitis (Figure 2A). No signs of raised intracranial pressure were detected on the MR images (Figure 2B and C). Lumbar puncture was performed and showed an opening pressure of 28 cmH₂O, white cell count of 100/μL with 89% lymphocytes, 8% neutrophils and 3% monocytes, protein 0.4 g/L, and glucose 5.8 mmol/L (blood glucose 7.4 mmol/L). The CSF gram stain, culture, HSV PCR, AFB smear, mycobacterial culture, *Mycobacterium tuberculosis* PCR, fungal smear, cryptococcal antigen, and VDRL (syphilis) were negative. The CSF adenosine deaminase (ADA) level was 1 IU/L. Other tests including initial chest radiograph, blood cultures, dengue panel, T-spot TB, HIV screen, leptospiral IgM, urine analysis, urine culture, endotracheal aspirate for AFB smear and mycobacterial culture, antinuclear antibody, thyroglobulin antibody, thyroid peroxidase antibody, anti-N-methyl-D-aspartate receptor antibody, and anti-voltage-gated potassium channel antibody were negative. *Rickettsia typhi* IgG titer performed on Day 4 of admission was < 64. Electroencephalography was performed and showed no evidence of epileptiform activity. His stay in the intensive care unit was complicated by the development of ventilator-associated pneumonia, which impeded his recovery. Anti-tuberculosis medications were discontinued after 12 days of therapy. He eventually underwent extubation after 2 weeks of stay in the intensive care unit. Formal neurological examination revealed bilateral lateral gaze palsy and dysmetria. He was discharged to a rehabilitation hospital after 1 month of hospitalization. During follow-up 2 months later, the repeated *Rickettsia typhi* IgG titer was 256, which confirmed his recent illness of murine typhus.

DISCUSSION

The diagnosis of rickettsial infections is often challenging. Signs and symptoms of these illnesses are nonspecific and resemble viral illnesses, making early diagnosis and treatment difficult. No rapid laboratory tests are available commercially to diagnose rickettsial infections early in the course of illness. Indirect fluorescent-antibody is currently the diagnostic method of choice and is preferable to the non-specific and insensitive Weil-Felix and other serologic tests.² A paired sample during the acute and convalescent phase is usually required to diagnose rickettsial infection by serological means.⁶ Real-time PCR assays are available with variable sensitivity and may be used for the diagnosis of rickettsial infection, particularly during the acute stage of illness.^{12,20}

In case 1, the presence of abducens nerve palsy and bilateral papilledema could be attributed to raised intracranial pressure as evidenced by raised CSF opening pressure and positive brain MR findings.²¹ Abducens nerve palsy is the classic example of a false localizing sign.²² It can occur in the context of raised intracranial pressure caused by stretching of the nerve in its long intracranial course or compression against the petrous ligament or the ridge of the petrous temporal bone. Elevated

intracranial pressure is often a feature of severe tuberculous meningitis,²³ cryptococcal meningitis²⁴ and severe bacterial meningitis.²⁵ Although not as well known as other types of meningitis, raised intracranial pressure is found in rickettsial meningitis as well. In 1986, Wenzel and others²⁶ reported five cases of acute febrile cerebrovasculitis with increased intracranial pressure presumably caused by rickettsial infection. In the case series, one patient had unilateral abducens nerve palsy and another patient had bilateral abducens nerve pareses. Similar findings of abducens nerve palsy, papilledema, and raised intracranial pressure were also found in two case reports of murine typhus with meningoencephalitis.^{27,28}

The patient in case 2 had a more severe clinical course than case 1. However, the presence of altered mental status and bilateral sixth nerve palsy could not be explained by raised intracranial pressure alone in view of mildly raised CSF opening pressure and absence of MR findings of raised intracranial pressure. In a case series of five patients with *R. typhi* meningoencephalitis published in 1998, elevated intracranial pressure was found in only one of the three patients with papilledema.¹⁶ Sixth nerve palsy and bilateral papilledema were present in one patient, but her CSF opening pressure was within normal limit (5 cmH₂O). In the year 1977, Manor and colleagues¹⁸ reported a case of severe bilateral papilledema in the absence of intracranial hypertension in murine typhus. The papilledema gradually resolved after the patient recovered from her illness. The presence of papilledema and/or sixth nerve palsy in these cases cannot be explained by raised intracranial pressure and brain imaging, suggesting that the cranial nerves may be directly involved by a separate process, which could be vasculitic in nature.^{16,29–31}

Signal alteration in the splenium of corpus callosum on brain MR imaging has been reported in a variety of conditions including infections, demyelination, ischemia, and metabolic abnormalities.³² Infectious etiology associated with splenium injury include viruses (e.g., HIV, HHV6, rotavirus, measles), bacterial (e.g., *Salmonella*, *Escherichia coli* O157:H7, tuberculosis, Lyme disease) and parasites (e.g., malaria, toxoplasmosis, cysticercosis).^{32,33} Though not common, transient splenic hyperintensity or the “Boomerang sign” has been reported in rickettsial encephalitis.^{34,35} The mechanism of how rickettsial infection affects the central nervous system leading to signal changes in the brain imaging is poorly understood. It is known that scrub typhus and epidemic typhus involve the brain in the following forms: 1) mononuclear cell meningitis without parenchymal involvement; 2) “typhus nodules” composed of predominantly oligodendroglial cells and few inflammatory cells; 3) perivascular cuffing of arteries; 4) focal hemorrhages in parenchyma and meninges; and 5) degeneration of ganglion cells.³⁶ On the other hand, the parenchymal lesion of the brain of Rocky Mountain spotted fever is basically a microinfarct seen in a variety of stages.³⁶ Murine typhus affects small blood vessels, creating “glial nodules” consisting of glial cells and mononuclear cells around grey matter capillaries. Unlike other forms of rickettsial infections, these changes rarely progress to thrombotic occlusion, microinfarctions, and microhemorrhages, thus explaining the rapid reversibility of most neurological signs.¹⁶

Not all patients with rickettsial meningitis have meningeal signs.³⁷ In rickettsial meningitis, the cerebrospinal fluid findings are consistent with aseptic meningitis. Pleocytosis of the CSF is usually present with a white cell count of

10–640 cells/mm³ and a predominance of mononuclear cells, a normal glucose level, and normal-to-elevated total protein levels.¹⁶ These CSF profiles are similar to those of leptospirosis, viral and tuberculous meningitis.³⁸ This may result in the use of inappropriate antimicrobial and antiviral therapies and in some cases long-term therapy for presumed tuberculous meningitis. There are several ways in which it can be used to distinguish tuberculous meningitis from other forms of meningitis. The ADA level in the CSF could be useful to differentiate tuberculous from non-tuberculous meningitis with high sensitivity and specificity.^{39,40} In case 1, the low CSF-ADA level of 1 IU/L made the diagnosis of tuberculous meningitis less likely. The rapid return of CSF cell counts to normal may help to differentiate rickettsial from tuberculous meningitis. The presence of rickettsial DNA in CSF samples can also be detected using nested PCR, but the sensitivity and specificity of this technique is yet to be determined.^{41,42}

Antimicrobial therapy is highly effective in rickettsioses if initiated early in the first week of illness.⁴³ Treatment should be started early in suspected rickettsial infections and should not await confirmatory testing. Doxycycline is the drug of choice and may be used for 7 to 10 days.⁴⁴ Chloramphenicol, fluoroquinolones, azithromycin, and rifampin may be used as alternatives.⁴³ However, the evidence to support their use clinically is limited and they should be used with caution. Fever usually subsides within 24–72 hours after starting antibiotic. The prognosis is generally good, however 10% of patients may require intensive care with up to 4% that will succumb to the disease.⁶ Occasionally despite with treatment, murine typhus may cause complications such as neuropsychiatric abnormalities (e.g., confusion, stupor, coma, and hallucinations) and other central nervous system abnormalities such as seizures, ataxia, and mild hemiparesis.^{6,16} The neurologic complaints may be prolonged but still respond to antibiotic treatment.¹⁵

Murine typhus infection should be included in the list of differential diagnosis in the case of pyrexia of unknown origin accompanied by cranial nerve palsy, especially in endemic areas. A trial of therapy with doxycycline can be considered in patients who are at high risk of rickettsial infection before a serological diagnosis is confirmed, as it is an easily treatable disease.

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