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Two Cases of Scrub Typhus Presenting with Guillain-Barré Syndrome with Respiratory Failure

To the Editor,

Scrub typhus is an acute febrile disease caused by *Rickettsia*, and traditionally occurs in autumn. *Orientia tsutsugamushi* is an obligate intracellular Gram-negative bacterium that proliferates in vascular endothelial cells; this characteristic enables the involvement of multiple organs. The most common clinical features are conjunctival injection, high fever, and lymphadenopathy. Neurological complications, such as meningitis and hearing impairment with suspected cranial nerve (VIII) invasion, were reported in 12.5% cases [1,2]. However, involvement of brain parenchyma or peripheral nerves is rare. Only three cases of Guillain-Barré syndrome (GBS) related to scrub typhus have been reported [3-5]. We experienced two cases of scrub typhus-related GBS that presented with severe respiratory failure and were managed with mechanical ventilation, doxycycline, and immunoglobulin.

A 60 year-old male visited the emergency department after suffering weakness of the lower extremities for two days. Ten days before the visit, he had visited a local private clinic for headache and chills. After being diagnosed with scrub typhus, he was treated with doxycycline. His symptoms marginally improved, but weakness in both lower extremities developed. He had no other medical history except pulmonary tuberculosis 10 years previously. Vital signs were stable (blood pressure 120/70 mmHg, pulse rate 68/min, body temperature 36.6°C). A physical examination revealed lymphadenopathy in the right inguinal area, a maculopapular rash on the chest wall, and eschar on the right knee. He showed an alert mental status, and a manual muscle test (MMT) revealed lower extremity weakness (upper extremity, grade V; lower extremity, grade IV). Laboratory results showed a WBC count of 9,020/mm^3 (neutrophils 51.9%, lymphocytes 35.7%); hemoglobin (Hb), 12.2 g/dL; platelets, 269,000/mm^3; alanine aminotransferase (AST), 100 IU/L; alanine aminotransferase (ALT), 110 IU/L; blood urea nitrogen (BUN), 10 mg/dL; creatinine, 0.52 mg/dL; total protein, 6.5 mg/dL; albumin, 3.3 mg/dL; and C-reactive protein, 2.10 mg/dL. Lumbar puncture revealed a glucose level of 74 mg/dL, a total protein level 210 mg/dL, and white blood cell (WBC) count of 20/mm^3 (lymphocytes 90%). Serum *O. tsutsugamushi* antibody titer was positive (1:320). There was no serologic evidence of Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection or reactivation (VCA-IgG/IgM +/-, EADR-IgG -/±, EBNA IgG +/-, CMV IgG/IgM +/-). A human immunodeficiency virus (HIV) test was negative. Two days after admission, weakness in both extremities progressed (upper, grade II; lower, grade II), and he developed a mild disturbance of consciousness. Serum anti-ganglioside antibodies, GD1b IgG and GM1 IgG, and anti-myelin-associated glycoprotein antibody were negative, but GM1 IgM and GD1b IgM antibodies were positive (Table 1). An electromyography showed diffuse demyelinated neuropathy, which was prominent in the lower extremities. The brain magnetic resonance diffusion image was normal. Intravenous immunoglobulins were administered for five days (22 g, 400 mg/kg/day), and doxycycline was maintained at 100 mg/12 hr (PO). On day 4 after admission, the patient complained of dysphagia and dyspnea. The patient required mechanical ventilation due to respiratory muscle weakness. Eleven days after admission, he recovered spontaneous breathing, and the ventilator was removed. At 48 days after admission, his MMT grade recovered to normal, and he was discharged without complications.

In the second case, a 46 year-old female without any prior medical history, presented at an emergency department having suffered decreased mental status for 12 hours. Before admission, she had visited the local clinic complain-

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ing of fever and myalgia for the previous seven days. After diagnosis with type II diabetes mellitus and ketoacidosis, intravenous fluid replacement and glycemic control were initiated. During management of ketoacidosis, an unexplained decrease in mental status and hypoxemia were noticed. After intubation, she was transferred to our hospital. Initial vital signs were unstable (blood pressure 70/50 mmHg, pulse rate 127/min, respiration 12 times/min, and body temperature 38.6°C). Chest examination revealed rale sounds in the lower right lung field. A maculopapular rash on the entire body and eschar on the posterior site of the left knee were also noticed. MMT revealed weakness in both extremities (upper, grade III; lower, grade III).

Laboratory results showed a WBC count of 12,560/mm^3 (neutrophils, 77%; lymphocytes, 17%); Hb, 14 g/dL; platelets, 144,000/mm^3; AST, 40 IU/L; ALT, 29 IU/L; BUN, 45.1 mg/dL; creatinine, 1.06 mg/dL; total protein, 5.5 mg/dL; albumin, 2.3 mg/dL; and C-reactive protein, 3.17 mg/dL. Sodium, potassium, chloride, and glucose levels of 150 mEq/L, 3.8 mEq/L, 116 mEq/L, and 196 mg/dL, respectively, were also detected. HbA1C was 12.3%, and D-dimer, fibrin degradation product, and fibrinogen were 14 mg/mL, 52 mg/mL, and 137 g/L, respectively. An arterial blood gas test before intubation showed metabolic acidosis and hypoxemia (pH 7.122; PCO_2, 58.0 mmHg; PaO_2, 53.1 mmHg; HCO_3-, 15.3 mmol/L; SpO_2, 75.6%). Chest X-ray revealed ground glass opacity on both the lower lung fields. Serum *O. tsutsugamushi* antibody titer was positive at 1:320. There was no serologic evidence of EBV and CMV infection or reactivation, and an HIV test was negative. Bacterial growth was not detected on blood, urine, and sputum cultures. Serum *Mycoplasma pneumoniae* IgM and IgG, and *Streptococcus pneumoniae* and *Legionella* urinary antigens were also negative. Due to the diagnosis of diabetic ketoacidosis, nosocomial pneumonia, and septic shock with pulmonary edema, empirical antibiotics were administered (meropenem 1 g/8 hr, teicoplanin 400 mg/24 hr). Intravenous insulin injection and doxycycline 100 mg/12 hr (PO) were maintained for seven days. Five days after admission, her vital signs were stable, and her mental status was alert. Although her chest X-ray markedly improved after 13 days, muscle weakness in the extremities (upper, grade IV; lower, grade III) remained, and a low respiration rate (7-8/min) was detected. A brain computed tomography scan was normal, and electromyography showed acute sensoriomotor polyneuropathy, which may have been due to GBS. Spinal tapping revealed a WBC count of 1/m^3; RBC, 0/mm^3; protein, 118 mg/dL; and glucose, 64 mg/dL. Serum anti-ganglioside antibodies GD1b IgG/IgM and GM1 IgG/IgM and anti-myelin-associated glycoprotein antibody were all negative (Table 1). After recovery from intubation, rehabilitation maintenance was required. Two months after admission, MMT revealed normal muscle power, and she was discharged without complications.

Table 1. Comparison of clinical characteristics

	Case 1	Case 2
Sex/age, yr	Male/60	Female/46
Previous infection	+	+
Eschar	+	+
O.tsutsugamushi Ab	1:320	1:320
Manual muscle test (upper/lower)	V/V, IV/IV -> II/II, II/II	IV/IV, III/III -> III/III, III/III
Deep tendon reflex	Hyporeflexia	Hyporeflexia
Oropharyngeal palsy	+	-
Sensory disturbance	+	-
Respiratory failure	+	+
Antiganglioside antibody	GD1b (+), GM1 (+)	-

GBS is known to be associated with several infections, such as *Campylobacter jejuni*, CMV, EBV, and *M. pneumoniae*. Our first case was diagnosed as scrub typhus based on maculopapular rash, eschar, and an *O. tsutsugamushi* antibody test. Additionally, we could diagnose GBS based on neurological examination, electromyography, and the presence of anti-ganglioside antibodies. We excluded EBV, CMV, *Mycoplasma*, and other bacteria. Involvement of the respiratory system is observed in 10-30% GBS patients [3]; however, there is no evidence of respiratory failure requiring mechanical ventilation among the reported cases of scrub typhus-related GBS [3-5]. Typical electromyography findings of demyelinated neuropathy and lower extremity weakness were detected, and GD1b and GM1 IgM antibody results were also positive. A positive result for the anti-ganglioside antibody had not been observed in the reported cases [3-5]. GBS mortality rates are usually 3-7%, but mortality in patients requiring respiratory support can be as high as 20% [2]. Our cases required mechanical ventilation, but both recovered completely. The second case was combined with pneumonia, diabetic ketoacidosis, and scrub typhus, and was treated

with a broad spectrum of empirical antibiotics and fluid replacement. After laboratory and radiologic findings improved, ongoing dyspnea, progressive respiratory failure, and extremity weakness were observed. We diagnosed GBS based on neurological examination and electromyography, and excluded other GBS-related infections, such as CMV, EBV, and other bacteria.

Mimicry involves the sharing of antigens between the host and an infecting microorganism, and is a type of cross-reactivity similar to an autoimmune disease. It is enabled by the activation of receptors on B- or T-lymphocytes by both the host and microorganism [5]. Scrub typhus-related GBS is suspected to undergo a similar phenomenon. Gangliosides are important glycolipids associated with cell growth and signal transduction, and more than 100 subtypes exist [1]. *O. tsutsugamushi* antibody or antigens presented on infected cells are suspected to activate mimicry on myelin cells or peripheral nerve axons, which elicits immune reactions similar to autoimmune diseases. A positive result for the anti-ganglioside antibodies GD1b and GM1 IgM supports the conclusion that mimicry between pathogenic antigens and the myelin of peripheral nerves caused the immune reaction and GBS.

Keywords: Guillain-Barre syndrome; Scrub typhus; Respiratory insufficiency

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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