Case Report: Neuritis and Gastrointestinal Hemorrhage in Scrub Typhus Patients

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Abstract. A 78-year-old woman with scrub typhus exhibited gastric hemorrhage with multiple gastric ulcers. This is the first report to confirm pathologically the presence of not only vasculitis but also, neuritis. The results suggest the necessity of studies confirming neuritis as the cause of gastric ulcer and bleeding in scrub typhus.

INTRODUCTION

Scrub typhus, an acute febrile zoonosis that occurs in rural Asia and on the Pacific and Indian Ocean islands, is transmitted by chigger bites or trombiculid mite larvae. *Orientia tsutsugamushi* is the microorganism responsible for the disease. The primary etiology of scrub typhus is the proliferation of *O. tsutsugamushi* within the endothelial cells that line small vessels, resulting in widespread vasculitis or perivasculitis.¹ Gastrointestinal (GI) bleeding is not an uncommon complication in scrub typhus patients, with reported cases of gastric ulcer bleeding and small bowel bleeding.^{2,3} However, to date, reports of histopathological findings of gastric ulcer bleeding in scrub typhus patients through stomach tissue examination have been nearly non-existent.

We encountered a patient who underwent surgery for gastric ulcer bleeding caused by scrub typhus and pathologically confirmed the findings of vasculitis and for the first time, neuritis.

CASE REPORT

A 78-year-old woman was admitted to the hospital for the chief complaint of worsening symptoms of general weakness that had begun 4 days before. The patient frequently worked in her garden, which was located near her residence. Her medical history indicated no previous use of prescription medications, such as non-steroidal anti-inflammatory drugs, and she reported no other past illness other than a diagnosis of hypertension. Her vital signs at the time of admission were as follows: blood pressure, 100/60 mmHg; pulse rate, 80 beats/minute; respiratory rate, 20 breaths/minute; and body temperature, 37.5°C. During her initial abdominal examination, no particular findings of interest were observed other than a suspected eschar at the epigastrium. The result of the peripheral blood test at the time of her initial admission revealed a white blood cell count of 16,530/mm³ (89.6% neutrophils). Moreover, the hemoglobin count was 10.9 g/dL, and the platelet count was 307,000/mm³. Other relevant data from the peripheral blood test included the following: prothrombin time, 10.8 seconds; international normalized ratio, 0.97; activated partial thromboplastin time, 25.7 seconds; fibrinogen level, 160 mg/dL (reference range = 200–400 mg/dL); fibrinogen degradation products, 30.4 µg/mL (reference range = 0–5.0 µg/mL); and D-dimer level, 2,228 ng/mL (reference range =

0–255 ng/mL). Because of the patient's outdoor activity history and the presence of an eschar, scrub typhus was suspected. As such, the patient was administered 200 mg doxycycline. On the second night after admission, melena was observed. The hemoglobin concentration at that time was 7.5 g/dL. The vital signs of the patient were as follows: blood pressure, 70/40 mmHg; pulse rate, 70 beats/minute; respiratory rate, 21 breaths/minute; and body temperature, 36.0°C. The finding of hypotension led to an endoscopic examination. Endoscopic findings confirmed the presence of a large pool of old blood and blood clots in the stomach. In particular, multiple large ulcers were observed in the lesser and greater curvatures of the stomach (Figure 1A). Furthermore, oozing was observed at the ulcer located near the cardia. In response, endoscopic hemostasis was performed by administering an epinephrine shot and argon-plasma coagulation. The patient was then transferred to the intensive care unit for additional treatment. On the fifth day of her admission, however, melena and hematemesis were observed. Her vital signs at that time were as blood pressure, 60/30 mmHg and pulse, 100–115 beats/minute, indicating a finding of hemorrhagic shock. Norepinephrine was used as a vasopressor drug. Despite the constant blood transfusion, administration of vasopressor drugs, and intravenous fluid injection, the blood pressure did not stabilize. Thus, a consultation with the Department of General Surgery was held to perform a total gastrectomy with intestinal interposition as an emergency surgery. After stomach resection, the gross pathological findings showed multiple mucosal ulcerations, and linear or oval mucosal erosions along the long axis of the stomach wall were observed after performing total gastrectomy (Figure 1B). A biopsy was performed to observe the full layer of the stomach wall containing the subserosa and the muscular layer near the ulcers. Hematoxylin-eosin (H&E) staining showed the common observation of acute inflammatory cell infiltration in the vascular walls (Figure 1C) and fibrin thrombi nearby. Acute and chronic inflammatory cell infiltrations at the myenteric nerve bundle (i.e., neuritis) were observed (Figure 1D). During the patient's hospitalization period, an immunofluorescent antibody assay for *O. tsutsugamushi* was performed. The antibody titer test result revealed a more than fourfold increase in immunoglobulin M (IgM) and IgG levels in 10 days from 1:16 to 1:160 and from 1:128 to 1:8,192, respectively.

Although the hemorrhage was no longer observed after the emergency surgery, disseminated intravascular coagulation (DIC) and shock occurred. Continuous leakage at the surgical anastomosis site led to a secondary peritonitis. On day 22 of the patient's admission, she was pronounced dead from septicemia.

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DISCUSSION

Because the central pathophysiological feature of scrub typhus is widespread vasculitis, various associated complications, including GI ulcers, encephalitis, renal failure, disseminated intravascular coagulopathy, and septic shock, can occur. However, the mechanism by which incidences of GI ulcer and hemorrhage occur in a scrub typhus patient is not well-known. However, GI bleeding may occur from microangiopathy that involves *O. tsutsugamushi* in the GI tract. Thrombocytopenia and DIC are also assumed to contribute to the bleeding tendency of scrub typhus patients. However, information regarding the relationship between scrub typhus and GI ulcer or hemorrhage is limited.

In a Thai study, 5 of 20 septic patients with scrub typhus reported hematemesis or melena.⁴ According to a study in South Korea, upper GI bleeding associated with scrub typhus occurred in 10.3% of scrub typhus patients. In addition, 3.4% of the patients required endoscopic clipping to stop the active bleeding.⁵ However, whether the cause of gastric mucosal lesions and GI bleeding is vasculitis from an *O. tsutsugamushi* infection, a stress lesion from an underlying disease or acute febrile illness, or some other cause has not yet been confirmed.

Although endoscopic hemostasis was performed in this patient because of GI bleeding on the second day of hospital admission, the hemorrhage persisted until the fifth day of admission. Consequently, emergency surgery was performed. According to the H&E staining results, acute inflammatory cell infiltrations were commonly observed in the vessel walls (Figure 1C). Such vasculitis was commonly observed not only directly beneath the ulcer but also, at the subserosa. Fibrin thrombi were also commonly observed near the lesions, with most of these findings occurring only in the smaller vessels.

The finding of particular interest was the presence of acute and chronic inflammatory cell infiltrations at the myenteric nerve bundle (Figure 1D). This endoneuritis was observed at the deep muscle layer irrelevant to ulcer bed. Although findings of neuritis may not seem peculiar in the abundance of inflammatory cells, the neuritis in the case of this patient was pathologically observed without the presence of any nearby inflammatory cells, confirming the inflammation of the nerves of the myenteric plexus. However, we were unable to confirm whether the observed neuritis was a phenomenon caused by vasculitis or some other factor not associated with vasculitis. After a comprehensive literature search, we concluded that this finding of neuritis is the first of its kind in a patient with

FIGURE 1. (A) Endoscopic findings subsequent to melena in a 78-year-old woman with scrub typhus revealing observations of multiple ulcerative craters in the lesser and greater curvatures of the stomach. (B) Gross pathology of the stomach after the emergency total gastrectomy was performed because of hemorrhage caused by melena on the fifth day of the patient's admission. There were multiple mucosal ulcerations (white arrows) and linear or oval mucosal erosions (black arrows). (C) Histopathological findings of gastric ulcer in the scrub typhus patient. Acute inflammatory cell infiltration in the vascular wall (arrows) was noted. Fibrin thrombi (Inset) were found frequently. H&E staining. (D) Histopathological findings of gastric ulcer in the scrub typhus patient. Acute and chronic inflammatory cell infiltration in the myenteric nerve bundle (arrows). H&E staining.

scrub typhus. Additional studies must be conducted to confirm whether ulcers associated with neuritis can form and whether ulcers can worsen as a result of neuritis.

There are some interesting study results associated with neuritis. The local application of low-dosage capsaicin has exhibited a protective effect against acute gastric lesions caused by stimulation of the nerve fibers by capsaicin.⁶ Capsaicin-sensitive afferent fibers play a pivotal protective role in acute gastric injury. The spinal afferent neurons monitor insults in the gastric mucosa and activate the local mechanisms of defense and repair through release of neurotransmitters such as calcitonin gene-related peptide at the stomach nerve ending which in turn exhibit potent vasodilatory activity. Consequently, the mucosal blood flow increases, and the acid disposal of the mucosa is catalyzed to facilitate local defense and repair.⁷ The stimulation of nociceptive neurons stimulates gastric mucosal defenses, and the ablation of nociceptive neurons weakens the gastric mucosal defense or inhibits the healing process of chronic ulcers.⁸

There are some reports of scrub typhus or *Rickettsia* spp. as a cause of neuritis^{9,10}; 8.3% of patients with facial palsy and 11.9% of patients with hearing loss had serological evidence of infection with *Rickettsia* spp.¹⁰ In this case of scrub typhus, we could not dismiss the possibility that neuritis influenced the incidence of gastric ulcer or hemorrhage. Additional systematic studies are necessary to investigate the possibility that neuritis in scrub typhus patients instigates motility disorders, vasoconstriction, disorders of intestinal mucin secretion, and increased stomach acid secretion.

In conclusion, this study is the first to report a neuritis finding in a scrub typhus patient, suggesting the necessity of additional studies to investigate the association between neuritis and gastric ulcer or bleeding.

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