Scrub Typhus-Induced Serious Gastric Ulcer Bleeding

Chisho Hoshino, Masashi Narita, Akane Yamabe, Yoshiyuki Sekikawa, Kana Ishihara, Hiroshi Ikeda, Noriyuki Satoh and Minoru Inoue

Abstract

A 67-year-old woman presented with melena and general weakness. Upper gastrointestinal (GI) endoscopy revealed multiple ulcers and projectile bleeding in the stomach. She also complained of a 10-day history of a fever and was diagnosed with scrub typhus based on a positive result of the eschar polymerase chain reaction (PCR) testing. She fully recovered with endoscopic hemostasis, and administration of minocycline and omeprazole. In a patient with GI manifestations, scrub typhus, a condition with pathologically systemic vasculitis, should be considered in the possible background in endemic areas. The eschar PCR testing is a rapid and useful diagnostic tool to identify a specific strain.

Key words: scrub typhus, Orienta tsutsugamushi, vasculitis, gastric ulcer, gastrointestinal bleeding, polymerase chain reaction

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Introduction

Scrub typhus is an acute febrile illness caused by Orienta tsutsugamushi, which is transmitted by the bite of trombiculid mite (1). The clinical symptoms are non-specific, including fever, skin rash, myalgia, general malaise, headache, and lymphadenopathy (1). It is characterized by focal or disseminated vasculitis and perivascularitis, which may involve the lungs, heart, liver, spleen, and central nervous system (1). Gastrointestinal (GI) involvement caused by scrub typhus had not been well described until Kim et al first reported that 22.7% of the patients had GI manifestations and all of the symptomatic patients had one or more endoscopic abnormalities (2). Here, we report a case with massive gastric ulcer bleeding associated with scrub typhus-induced systemic vasculitis. Factors associated with its clinical severity and appropriate diagnosis are also discussed.

Case Report

On a spring day in northern Japan, a 67-year-old woman presented to our hospital with melena. Five days prior to admission, she visited a general practitioner complaining of a 5-day history of a fever and headache, and a 2-day history of epigastric discomfort, but the cause was not determined, and the melena subsequently developed a day before admission. She had no past history of gastrointestinal (GI) diseases. She was taking an antihypertensive drug but no other medications including nonsteroidal anti-inflammatory drugs, steroids or aspirin. On admission, her consciousness was clear, blood pressure 66/40 mmHg, pulse rate 126 beats/min, and body temperature 36.2°C. An Eschar was seen in the right thigh without any other skin rash (Fig. 1). No superficial lymph node was palpable. Mild epigastric tenderness was noted with decreased bowel sound. Massive dark red stool passage was present from the anus. The remainder of physical examinations was uneventful. Laboratory examination revealed the following: a leucocyte count of 1.1×10⁴/μL, hemoglobin 6.3 g/dL, platelet count 4.6×10⁴/μL, blood urea nitrogen 88.4 mg/dL, serum creatinine 1.69 mg/dL, total protein 3.8 g/dL, albumin 2.0 g/dL, aspartate aminotransferase 209 IU/L, alanine aminotransferase 152 IU/L, lactate dehydrogenase 609 IU/L, C-reactive protein 1.8 mg/dL, fibrinogen 61 mg/dL, fibrinogen degradation products 17.8 μg/mL. A large volume of intravenous infusion and transfusion were initiated immediately. Upper GI endoscopy revealed 4 gastric ulcers in the corpus and one ulcer with projectile bleeding in the cardiac portion (Fig. 2). Given the bleeding tendency, histopathologic examination was not carried out.
The results of serologic titer for rickettsial diseases using immunoperoxidase reaction examined at Ohara Research Laboratory (Fukushima, Japan) are shown in Table 1. Nested polymerase chain reaction (PCR) and DNA sequence analysis targeting the \textit{O. tsutsugamushi}-specific 56-kDa protein gene was performed using a sample of eschar at Fukushima Prefectural Institute of Health, which identified Karp type \textit{O. tsutsugamushi}. Serum IgG antibody for \textit{Helicobacter pylori} was negative. Based on the results of these investigations, she was finally diagnosed with gastric ulcer bleeding associated with scrub typhus caused by Karp type \textit{O. tsutsugamushi} infection. She fully recovered with endoscopic hemostasis, and administration of 7 days of minocycline (200 mg/day) and 8 weeks of omeprazole (20 mg/day).

### Discussion

GI manifestations are common in systemic vasculitis such as leukocytoclastic vasculitis, polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis (3, 4). Scrub typhus is also focal or disseminated vasculitis characterized by the destruction of endothelial cells and perivascular inflammation (1). Thus, GI manifestation in scrub typhus is more likely to result from GI involvement in systemic vasculitis.

Kim et al (2) reported that endoscopic features seen in patients with scrub typhus are characterized by superficial hemorrhage, multiple erosions and ulcers without any prediction sites and biopsy specimens obtained showed the characteristic features of acute vasculitis with an infiltration of acute inflammatory cells and thrombus in blood vessels. According to this report, 2 gastric bleeding cases were reported in 58 patients with GI manifestations and the occurrence of endoscopic features was correlated with the clinical severity of illness. According to a database analysis from 104 institutions in Japan (5), a delay in appropriate treatment of more than 2 days has a significantly higher risk of complication. In this report, 13.8% of patients had at least one complications and 1.9% had digestive tract bleeding. In the present case, epigastric discomfort developed 3 days after the onset of disease and the interval between the onset of GI manifestations and initiation of minocycline treatment was 7 days.

A diagnosis can be made in the presence of a significant increase in the serum antibody. The indirect fluorescent antibody and indirect immunoperoxidase are both serology standard techniques (6). More than a 4-fold increase in antibody titer between two consecutive samples is diagnostic (7), but cannot guide the initial treatment. A single acute serum sample requires using a cut-off antibody titer ranging from 1:10 to 1:400 without hard evidence (7). The representative strains of \textit{O. tsutsugamushi} in Japan are classified serologically as the Karp, Gilliam, Kato, Irie/Kawasaki, and Hirano/Kuroki (8). However, commercially, a serologic test is available only for limited strains (9) and serologic cross-reaction renders identification of a specific strain difficult (10). In contrast, on the basis of nucleotide sequence analysis targeting a major outer membrane protein called the 56-kDa Orientia type-specific antigen, \textit{O. tsutsugamushi} strains have been divided into the following subtypes: Gilliam, JG (Japanese Gilliam), Karp, JP-1 (Japanese Karp type-1), JP-2 (Japanese Karp type-2), Kato, Kawasaki, Kuroki, Shimokoshi and others (Fig. 3) (11). The PCR method for identifica-

### Table 1. The Results of Serologic Titer for Rickettsial Diseases Using Immunoperoxidase Reaction

<table>
<thead>
<tr>
<th>Immunoperoxidase reaction</th>
<th>IgG titer</th>
<th>IgM titer</th>
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<tbody>
<tr>
<td>\textit{Orientia tsutsugamushi}</td>
<td>Gilliam</td>
<td>&lt;40</td>
</tr>
<tr>
<td></td>
<td>Karp</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Kato</td>
<td>&lt;40</td>
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<tr>
<td></td>
<td>Irie/Kawasaki</td>
<td>&lt;40</td>
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<td></td>
<td>Hirano/Kuroki</td>
<td>&lt;40</td>
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<td></td>
<td>Shimokoshi</td>
<td>&lt;40</td>
</tr>
<tr>
<td>\textit{Rickettsia japonica}</td>
<td>&lt;40</td>
<td>&lt;40</td>
</tr>
<tr>
<td>\textit{Rickettsia typhi}</td>
<td>&lt;40</td>
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</tr>
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tion of specific strain has been developed for confirmed diagnosis in the early acute stage (8). Recently, eschar has received attention as a diagnostic sample because it can be collected readily and can be the site where O. tsutsugamushi proliferates (12). In a prospective study, eschar PCR was useful as a rapid, sensitive and specific technique, despite negative serology or prior antibiotic treatment (12). In the present case, eschar PCR was of great help in the rapid diagnosis because the causative strain was identified within a day. However, this technique is only available in specialized laboratories and cannot be applied to a patient without the presence of eschar.

The occurrence of scrub typhus is known to be seasonal because periods of epidemics are influenced by the activities of the infected mite (9). In northern Japan, scrub typhus is known to occur in spring, fall and winter (9), where Leptotrombidium pallidum transmitting Karp or Gilliam type strain is dominant (13, 14), while in the other areas of Japan, the disease mainly occurs in late fall and winter (9), where Leptotrombidium scutellare transmitting Irie/Kawasaki or Hirano/Kuroki type strain is dominant (13, 14). Both L. pallidum and L. scutellare infest mammals including humans in the fall (13). But only L. pallidum, which may be involved in the transmission of the more virulent strain than L. scutellare, hibernate over the winter season, and can cause scrub typhus in the spring when the temperature increases (13). An in vivo study which determined the 50% mouse lethal doses for the representative strains of each subtype (15) showed that strains from subtypes Kato, JG, Gilliam and Karp exhibited a high level virulence to mice. Given these findings, in addition to the delay in appropriate treatment, a highly virulent strain might be implicated in the serious gastric complication in the present case. But fortunately, the worst outcome was avoided because other vasculitis-associated abnormalities such as liver or renal dysfunction, and coagulation disorders were also well controlled.

In conclusion, GI manifestations are common in a patient with scrub typhus and if treatment is delayed, it could cause serious GI complications resulting from GI involvement in systemic vasculitis. Thus, in a patient with GI manifestations, scrub typhus should be considered in the differential diagnosis in endemic areas. Identification of a specific strain is desirable because its clinical severity may be associated with the strain type. The eschar PCR testing is a rapid and useful diagnostic tool to identify a specific strain.

The authors state that they have no Conflict of Interest (COI).

References