

## Short Communication

# Ulcerative Lesions with Hemorrhage in a Patient with Severe Fever with Thrombocytopenia Syndrome Observed via Upper Gastrointestinal Endoscopy

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**SUMMARY:** Severe fever with thrombocytopenia syndrome (SFTS) is a novel bunyavirus infection caused by the SFTS virus (SFTSV, family *Bunyaviridae*, genus *Phlebovirus*) with a high case fatality rate. A previously healthy 72-year-old man showed symptoms of fever, general fatigue, and altered consciousness. He was hospitalized for treatment. On day 3, considering the day on which fever appeared first during the disease course as day 0, he had bloody emesis. An emergency upper gastrointestinal endoscopic examination revealed multiple ulcerative lesions with continuously oozing hemorrhage in the stomach. He died on day 7. He was retrospectively diagnosed as having SFTS. Although it was less likely that the gastric ulcerative lesions were directly induced by SFTSV replication, it was evident that hemorrhagic emesis might occur in the patient in association with the pathophysiology of SFTS. The real-time imaging of gastric ulcerative lesions in a patient with SFTS is reported.

Severe fever with thrombocytopenia syndrome (SFTS) is a bunyavirus infection caused by the SFTS virus (SFTSV, family *Bunyaviridae*, genus *Phlebovirus*). This disease was first reported to be endemic to China in 2011 (1,2), and later reported to be endemic to Japan and South Korea (3,4). Hemorrhagic symptoms such as gingival oozing, bloody diarrhea, and hematuria are commonly observed in patients with severe and fatal SFTS (3,5,6).

The case fatality rate of SFTS is high. Cases of human-to-human transmission of SFTSV, including cases of transmission from patients to medical practitioners, have been reported (7–10). In these cases, transmission occurred through close contact with patient body fluids. This evidence indicates that strict contact precautions should be implemented to protect against nosocomial transmission in the treatment of SFTS-suspected patients in the SFTS-endemic areas.

A previously healthy 72-year-old man with a past history of cerebral infarction showed symptoms of fever, general fatigue, and altered consciousness with anarthria in Hiroshima Prefecture, western Japan, in June 2012. He was hospitalized for treatment.

Peripheral total blood cell counts on day 1, considering the day on which the symptoms appeared first as day 0, revealed severe leukopenia (1,020/mm<sup>3</sup>; normal range 3,900–9,800/mm<sup>3</sup>), thrombocytopenia (38,000/mm<sup>3</sup>; 131,000–362,000/mm<sup>3</sup>), anemia with a red blood cell count of 3,420,000/mm<sup>3</sup> (4,270,000–5,700,000/mm<sup>3</sup>), and hematocrit value of 30.8%

(40–50%). Aspartate transaminase, alanine transaminase, lactate dehydrogenase, and creatine phosphokinase levels were 331 IU (8–40 IU/L), 215 IU (4–45 IU/L), 718 IU (120–240 IU/L), and 502 IU/L (45–280 IU/L), respectively, suggesting liver and possible muscle damage.

A bone marrow aspiration examination performed on day 2 for the purpose of diagnosis (including differential diagnosis) revealed hemophagocytosis with hypocellularity and atypical lymphocytosis. The patient's ferritin level was 1,610.3 ng/mL (12.9–301.3 ng/mL). The antibody status for cytomegalovirus and Epstein-Barr virus showed pattern indicative past infections. We presumed that hemophagocytosis might be one of the factors responsible of the pancytopenia in this patient.

Steroid pulse therapy with 500 mg of methylprednisolone per day and 5 g of gamma globulin per day was administered from day 3 for the treatment of hemophagocytosis. The proton pump inhibitor lansoprazole was also administered for 5 days starting on day 2. A histamine H<sub>2</sub>-receptor antagonist was not administered. Furosemide was administered to treat renal insufficiency. He was transfused with whole blood to treat anemia.

Hemorrhagic emesis appeared on day 3. No nuchal rigidity or involuntary movement was observed. An emergency upper gastrointestinal (GI) endoscopic examination was performed. Ulcerative lesions with clear demarcations were observed at the fornix (Fig. 1B) and on both the anterior and posterior walls of the body of stomach (Fig. 1D, E, G, and H). Continuous oozing hemorrhage was observed from these ulcerative lesions (Fig. 1E and H). Fresh blood accumulated in the fornix and the gastric folds of the stomach (Fig. 1C, E, F, and H).

Despite these treatments, the patient's symptoms persisted, and his consciousness level gradually deteriorated. Obvious bloody diarrhea appeared on day 5. Labo-

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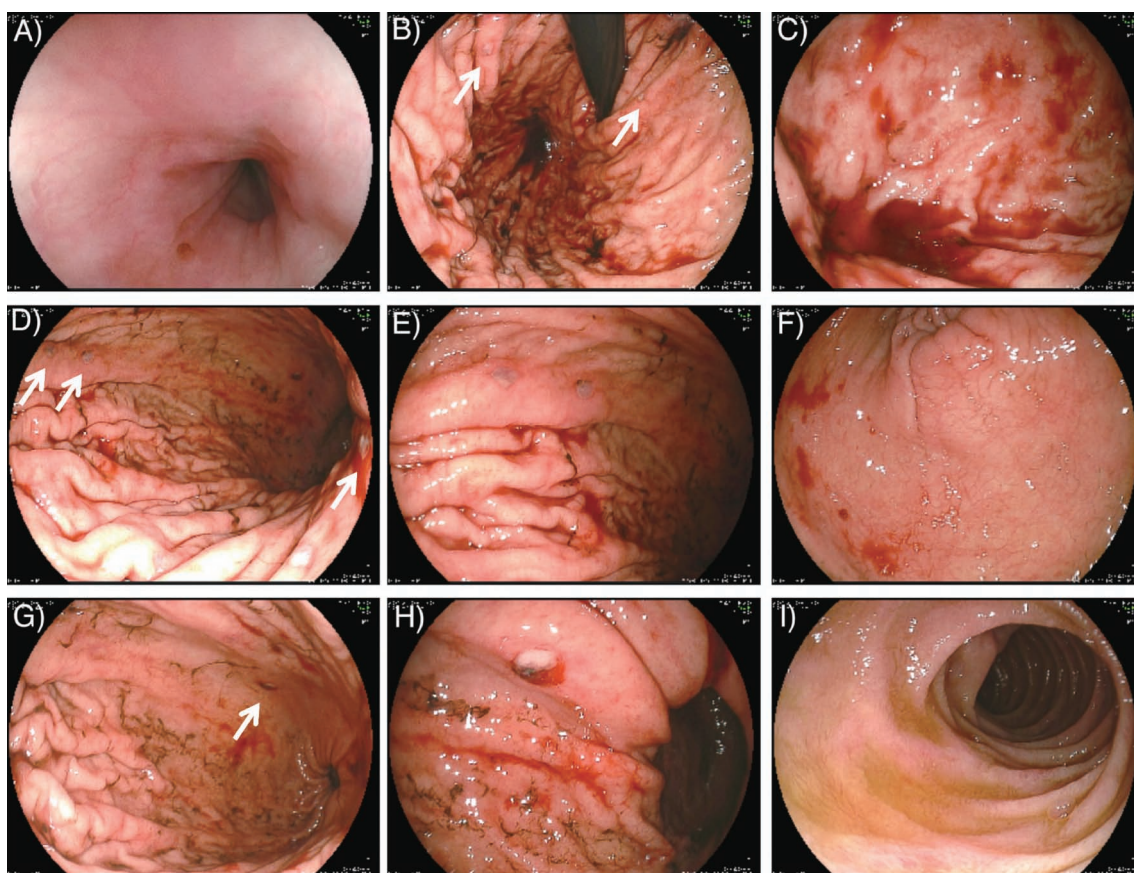


Fig. 1. Inside of patient's upper gastrointestinal tract observed through endoscopic examination. (A) No abnormal lesions were observed in the lower part of esophagus. (B) Two obvious ulcerative lesions were observed at the fornix (arrows). When the ulcerative lesions were positioned closely, the demarcations of the ulcers were clear. Furthermore, oozing hemorrhage from the ulcerative lesions were observed. The fundus was filled with fresh blood. No blood vessels were exposed. (C) The fornix was filled with fresh blood. This is an enlarged image of the site of blood filling in the fornix. (D) Ulcerative lesions were detected in the middle part of the body of the stomach (arrows). (E) An enlarged view of the ulcerative lesions observed at the upper-right part of the previous image (D, at the frontal part of greater curvature). Oozing hemorrhage was observed during the examination process. (F) Hemorrhage observed at the pyloric-ring at the side of greater curvature. (G) Frontal side of the lower part of the body of the stomach. Ulcerative lesion was present (arrow). (H) Image of oozing hemorrhage at the enlarged frontal view of the ulcerative lesion at the lower part of the body of the stomach (G). (I) No obvious lesions were observed at the descending part of the duodenum.

ratory tests for the evaluation of coagulopathy revealed the following results (normal ranges in parentheses): fibrinogen level, 75 mg/dL (200–400 mg/dL); prothrombin time, 21.8 s (10.0–13.5 s); activated partial thromboplastin time, 82.4 s (25.0–38.0 s). These results indicated that the coagulation capacity had worsened, suggesting the occurrence of disseminated intravascular coagulation (DIC). Furthermore, blood urea nitrogen and serum creatinine levels were 35.4 mg/mL (8.0–20.0 mg/mL) and 1.10 mg/mL (0.60–1.20 mg/mL), respectively. The creatinine level increased in the later phase of the disease course, suggesting a worsening of renal function. The patient's respiratory status deteriorated on day 5, and he was intratracheally intubated for assisted and mechanical ventilation. Death occurred on day 7 owing to multi-organ failure.

The Ministry of Health, Labour and Welfare of Japan made public the information that SFTS was endemic to Japan on January 30, 2013 (3). It was speculated that the patient might have SFTS. Serum samples that had been collected from this patient in the early phase of the disease and stored in a deep freezer were

sent to the Department of Virology 1, National Institute of Infectious Diseases (NIID), Tokyo, Japan, for virological examination. The serum sample was positive for the SFTSV on the basis of the virus isolation, conventional reverse transcription (RT)-PCR, and quantitative real-time RT-PCR results (11). A quantitative real-time PCR test performed in February–March 2013 revealed the SFTSV genome concentration as  $10^{6.7}$  copies/mL in the early phase of the disease. The patient was thus retrospectively diagnosed with SFTS.

The patient of the present case is 1 of 11 described in the literature (3). This is the first report describing real-time imaging conducted during an upper GI endoscopic examination of the inside of the stomach of a patient with SFTS who vomited fresh blood. The evidence that hemorrhagic manifestations have been observed more frequently in fatal cases of SFTS than in patients who survive suggests that the hemorrhagic manifestations might indicate a poor prognosis (5,6). In 2014, Takahashi et al. noted that hemorrhagic manifestations, including hematemesis, have been commonly observed in patients with severe or fatal SFTS (3). A gastric ulcer

was found during the postmortem pathological examination of their patient (the primary Japanese SFTS patient). However, the SFTSV antigen was not pathologically detected at the ulcerative lesions (3). The primary patient and the patient of the present study represent the only 2 Japanese SFTS cases in which gastric ulcers were observed.

The patient did not have a gastric ulcer or had taken any non-steroidal anti-inflammatory drugs such as aspirin before the onset of SFTS. The ulcerative lesions were observed at the fornix and middle part of the gastric body as a form or multiple gastric ulcers. The lesions were accompanied by continuously oozing hemorrhage.

Two of the patients with SFTS who died underwent autopsies and the pathological findings were reported (12). Although the novel findings in the report were fungal infections in the respiratory tract organs, there was no mention of whether the ulcerative lesions were present or not in the patients with SFTS, suggesting that ulcerative lesions were not observed in these patients.

It is likely that the ulcerative lesions are associated with the pathogenesis of SFTS, although it is possible that the lesions in this patient existed independently from SFTS. Furthermore, the ulcerative lesions found in patients with SFTS might not have been caused by the direct effect of SFTSV replication at the lesions. A previous study reported the presence of ulcerative lesions found through postmortem pathological examinations (3). SFTSV antigens were not observed at the ulcerative lesions, suggesting the lesions were not induced directly by SFTSV replication. It was evident that the pathophysiology of SFTS in the patient included hemophagocytosis and DIC. The hemophagocytosis, DIC, and multi-organ failure were factors contributing to the gastric ulcer formation. Therefore, it is quite likely that the gastric ulcers in the patient were induced indirectly in association with the pathophysiology of SFTS. Further study is needed to elucidate the cause of the lesions.

GI tract endoscopic examination might put patient at a high risk for occupational and nosocomial infections. When GI endoscopic examination is performed on febrile patients with hematemesis in SFTS endemic areas, medical practitioners (including the endoscopic examiner) should consider adopting strict contact protection procedures to protect against nosocomial transmission.

To the authors' knowledge, there are only 2 reports in the literature of ulcerative lesions found in a patient with SFTS, including the previous study describing imaging findings of ulcerative lesions via postmortem pathological examination (3), with the present study being the first report to describe real-time imaging of ulcerative lesions with continuously oozing hemorrhage

detected through GI endoscopic examination.

In summary, images of ulcerative lesions were captured during an upper GI tract endoscopic examination in a patient with SFTS. The gastric ulcer with oozing hemorrhage might have been the cause of the hematemesis observed in this patient with SFTS.

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The Institutional Research and Ethical Committees of NIID, Tokyo, Japan, approve this case report (No. 535). This case report was compiled after obtaining the written informed consent of the closest relatives of the patient.

**Conflict of interest** None to declare.

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