

Fulminant gastrointestinal graft-versus-host disease concomitant with cytomegalovirus infection: Case report and literature review

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Author contributions: Okubo H and Nagata N contributed equally to this work; Okubo H, Nagata N and Uemura N designed the research; Okubo H, Nagata N provided the discussion of the pathology and clinical features and wrote the paper.

Supported by Grant from the National Center for Global Health and Medicine

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Received: October 25, 2012 Revised: December 2, 2012

Accepted: December 15, 2012

Published online: January 28, 2013

Abstract

Here, we report a case of fulminant gastrointestinal graft-versus-host disease (GI-GVHD) with cytomegalovirus (CMV) infection in 44-year-old woman. Despite the difficulties associated with the treatment of GI-GVHD and GI-CMV disease, the mucosal findings and the clinical course showed marked improvements during long-term clinical observation. The endoscopic findings were remarkable, with diffuse sloughing mucosa in the stomach and highly active inflammation and deep discrete ulcers throughout the colon. Changes in the CMV quantitative polymerase chain reaction results were correlated with the endoscopic mucosal findings and were useful for assessing the efficacy of the treatment. Although a definite diagnosis of GI-GVHD is generally made by endoscopy with biopsy, the gross appearance of this disease can vary depending on the endoscopy. In this paper, we also conduct a literature review of patients with GI-GVHD.

Key words: Acute gastrointestinal graft-versus-host disease; Allogeneic stem-cell transplantation; Cytomegalovirus gastrointestinal disease; Cytomegalovirus-polymerase chain reaction; Endoscopy

Okubo H, Nagata N, Uemura N. Fulminant gastrointestinal graft-versus-host disease concomitant with cytomegalovirus infection: Case report and literature review. *World J Gastroenterol* 2013; 19(4): 597-603 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i4/597.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i4.597>

INTRODUCTION

Graft-versus-host disease (GVHD) is a serious complication of allogeneic hematopoietic stem cell transplantation (HSCT) and mainly attacks the skin, gastrointestinal (GI) tract and liver^[1-5]. GI-GVHD, in particular, can cause life-threatening complications, such as massive diarrhea, hemorrhage, paralytic ileus, and perforation^[6,7]; therefore, the accurate diagnosis of GI-GVHD is essential. Although endoscopic observation is an indispensable diagnostic tool, various mucosal patterns are observed on endoscopy^[8]. In addition, testing for cytomegalovirus (CMV) infection is necessary because the complication of GI-GVHD with CMV infection will reduce the quality of life (QoL) of the patients^[9]. This reduction in the QoL occurs because CMV-related GI disease is exacerbated by the administration of steroids for the treatment of GI-GVHD when antiviral drugs are not administered^[10]. Here, we report a rare case of fulminant GI-GVHD detected by endoscopy and its clinical course, and we review related literature on the endoscopic findings of GI-GVHD.

CASE REPORT

The patient, a 44-year-old woman with acute myeloid leukemia who was diagnosed 18 mo earlier, underwent

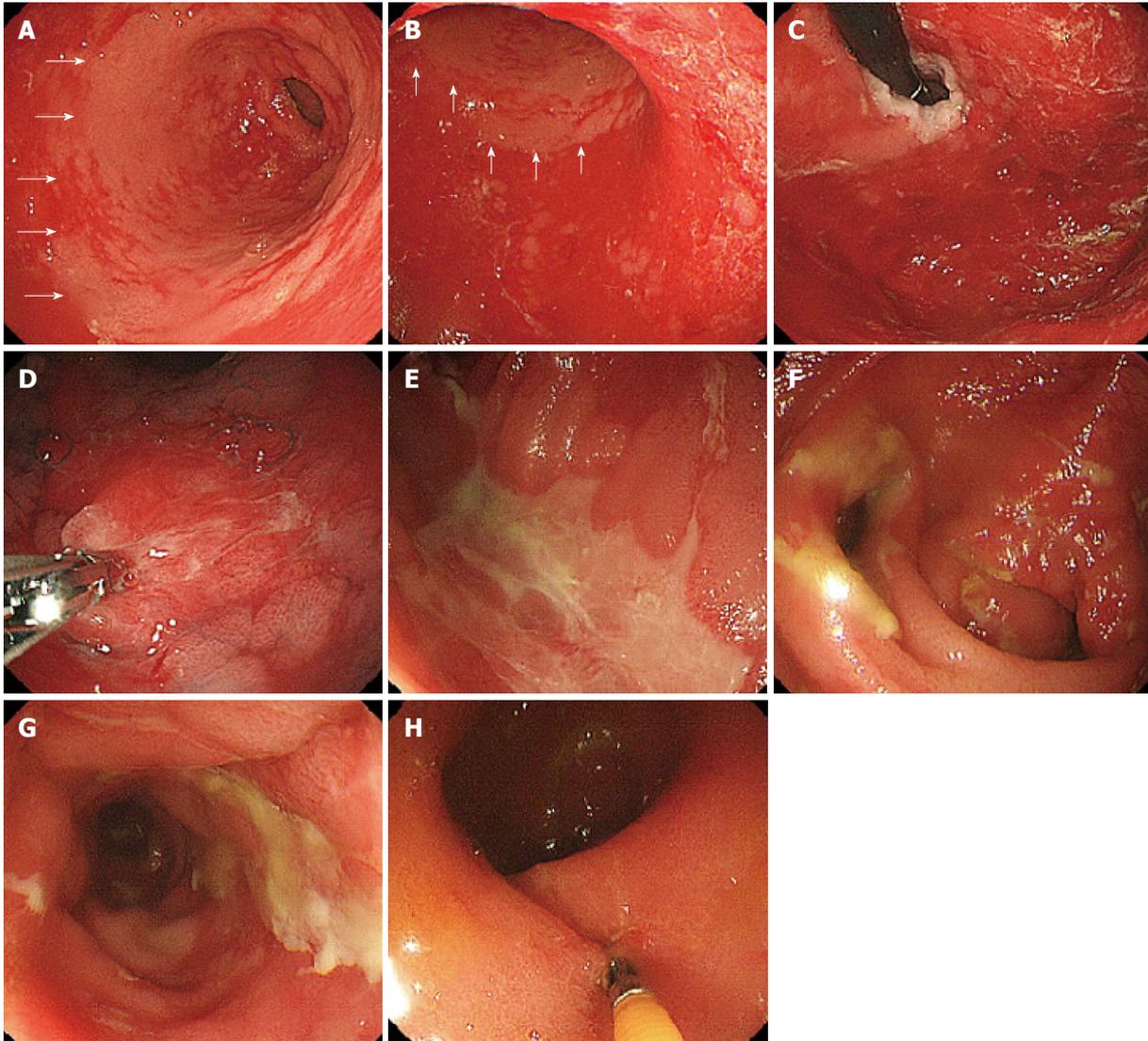


Figure 1 Upper and lower gastrointestinal endoscopic findings. A: The gastric mucosa in the antrum of the stomach. The antrum is the only segment exhibiting normal mucosa (arrows); B: The gastric mucosa in the lower segments of the corpus of the stomach. This mucosa demonstrates diffuse sloughing, whereas the antrum is the only segment exhibiting normal mucosa (arrows); C: The gastric mucosa in the upper segments of the corpus of the stomach; D: The greater curvature of the stomach near the center. A biopsy was taken from the edematous and sloughing mucosa of the greater curvature of the upper corpus; E: Shallow ulcer with fur at the cecal valve and cecum; F: Discrete longitudinal ulcer in the terminal ileum; G: Longitudinal ulcer with fur surrounded by the inflamed edematous mucosa of the sigmoid colon; H: Edematous mucosa of the rectum.

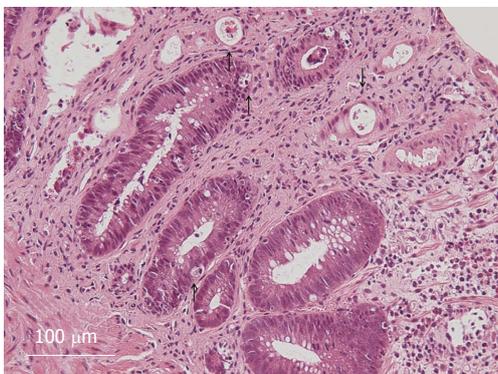


Figure 2 Histological findings. Biopsy specimen from the sigmoid colon revealing a crypt with multiple apoptotic cells (arrows) with severe lymphocytes corresponding to acute gastrointestinal graft-versus-host disease (GVHD). The presence of gland apoptosis is histological evidence of acute GVHD (hematoxylin and eosin stain, $\times 40$).

allogeneic bone marrow transplantation 3 mo prior to the examination. A full-body skin rash appeared on day 26 after the transplantation. On day 85 after the transplantation, she experienced watery diarrhea more than 10 times per day and developed abdominal pain. Upper GI endoscopy showed diffuse sloughing of the mucosa with diffuse erythema and hemorrhage in the antrum and corpus of the stomach (Figure 1A-D). Lower GI endoscopy revealed multiple deep discrete ulcers with exudative and mucosal oozing in the terminal ileum end and throughout the entire colon (Figure 1E and F). Biopsy specimens from the upper and lower GI tract revealed diffuse erythema, erosions, and sloughing mucosa with active bleeding in the stomach, as well as multiple erosions and a small discrete ulcer with active bleeding in the lower GI tract. Gland apoptosis showed histological evidence of acute GVHD (Figure 2). Moreover, the

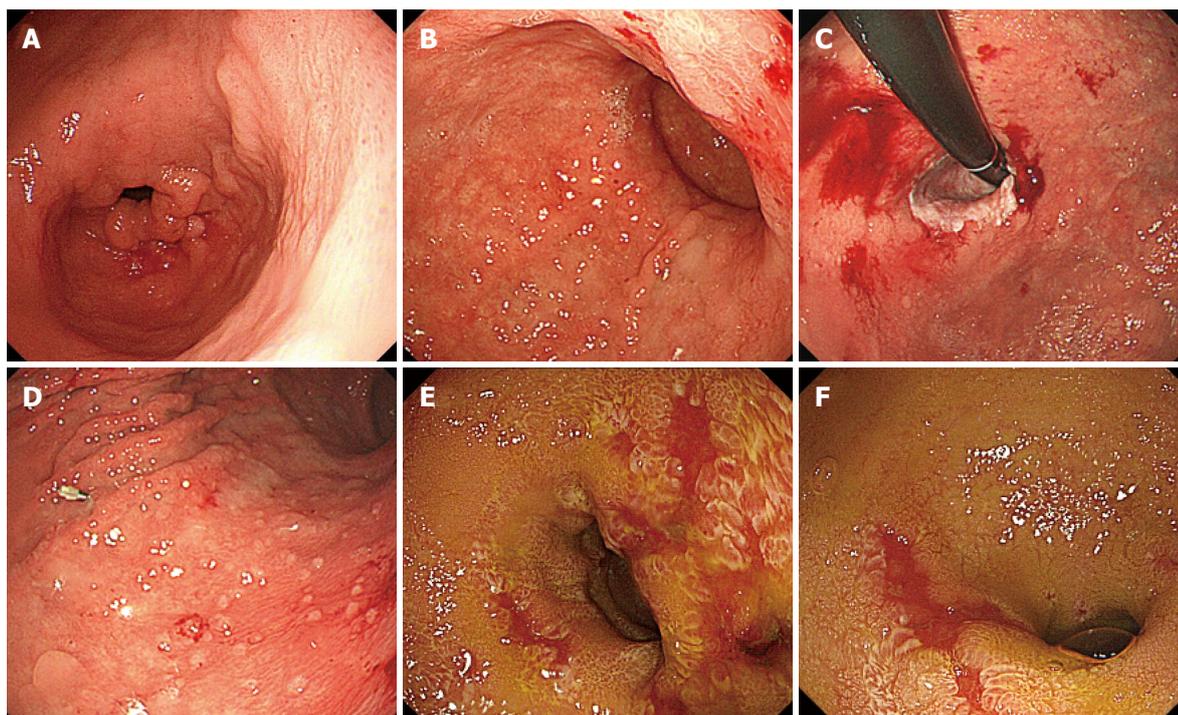


Figure 3 Upper and lower gastrointestinal endoscopic findings 70 d after the steroid therapy. A: The gastric mucosa in the antrum of the stomach. The mucosa is normal but somewhat edematous; B: The gastric mucosa in the lower segments of the corpus of the stomach, which has improved even though the rough gastric mucosal patterns and edematous changes remained; C: The gastric mucosa in the upper segments of the corpus of the stomach, which has also improved; D: The greater curvature of the stomach near the center. The endoscopic clipping has remained; E: Sigmoidoscopy revealing multiple discrete ulcers in the sigmoid colon; F: Disappearance of the visible vascular pattern in the sigmoid colon.

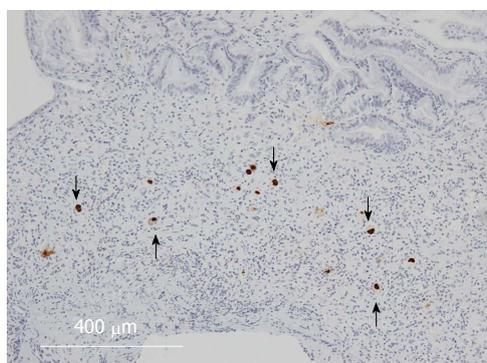


Figure 4 Immunostaining of the biopsy specimen. Immunohistochemically stained biopsy specimen from an ulcer of the sigmoid colon showing multiple cytomegalovirus-positive cells (arrows) (immunohistochemical stain, $\times 40$).

biopsy specimens showed CMV infection detected by polymerase chain reaction (PCR) at remarkably elevated concentrations of 4.0×10^4 copies/ μg DNA, but immunochemical staining for the CMV antibody was negative. Finally, the patient was diagnosed with severe GI-GVHD concomitant with a CMV infection. Other organ involvement included a whole-body skin rash and slight liver dysfunction.

The treatment for acute GVHD was started with an initial dose of prednisolone 1 mg/kg per day (50 mg/d) and for CMV infection with an initial dose of ganciclovir (GCV) 10 mg/kg per day. After 40 d of treatment, the patient improved clinically. Then, GCV was discontinued because of thrombocytopenia that appeared 60 d after

the treatment. After 64 d, however, CMV was detected in the blood by a CMV-antigenemia assay, and the maintenance dose of GCV (5 mg/kg per day) was resumed. After 70 d, upper and lower endoscopy showed that the endoscopic findings of mucosal sloughing had improved (Figure 3A-D) but that the colonic mucosa remained ulcerative and inflamed (Figure 3E and F). Both upper and lower GI tract biopsies revealed CMV-infected cells in immunohistochemically stained tissue specimens (Figure 4), and the CMV-PCR from the GI tract biopsy was 2.0×10^5 copies/ μg DNA. Intravenous GCV at 5 mg/kg every 12 h as the induction therapy was re-started and then changed to the maintenance therapy, and the prednisolone dose was tapered. Although the treatment continued for an additional 102 d, the CMV-PCR from the GI tract biopsy was 1.0×10^3 copies/ μg DNA. Oral valganciclovir at 900 mg/d was started, with oral prednisolone 10 mg administered every other day. After 162 d, the upper and lower endoscopy showed notable improvements in the mucosal findings (Figure 5), and the CMV-PCR count from a GI tract biopsy was within the normal range of $< 4.0 \times 10^3$ copies/ μg DNA.

DISCUSSION

Nausea and vomiting, appetite loss, abdominal pain, and watery diarrhea are common symptoms of GI-GVHD. Watery diarrhea appears in almost all cases of GI-GVHD and occasionally becomes chronic or causes bleeding. Therefore, this symptom is a major factor that reduces

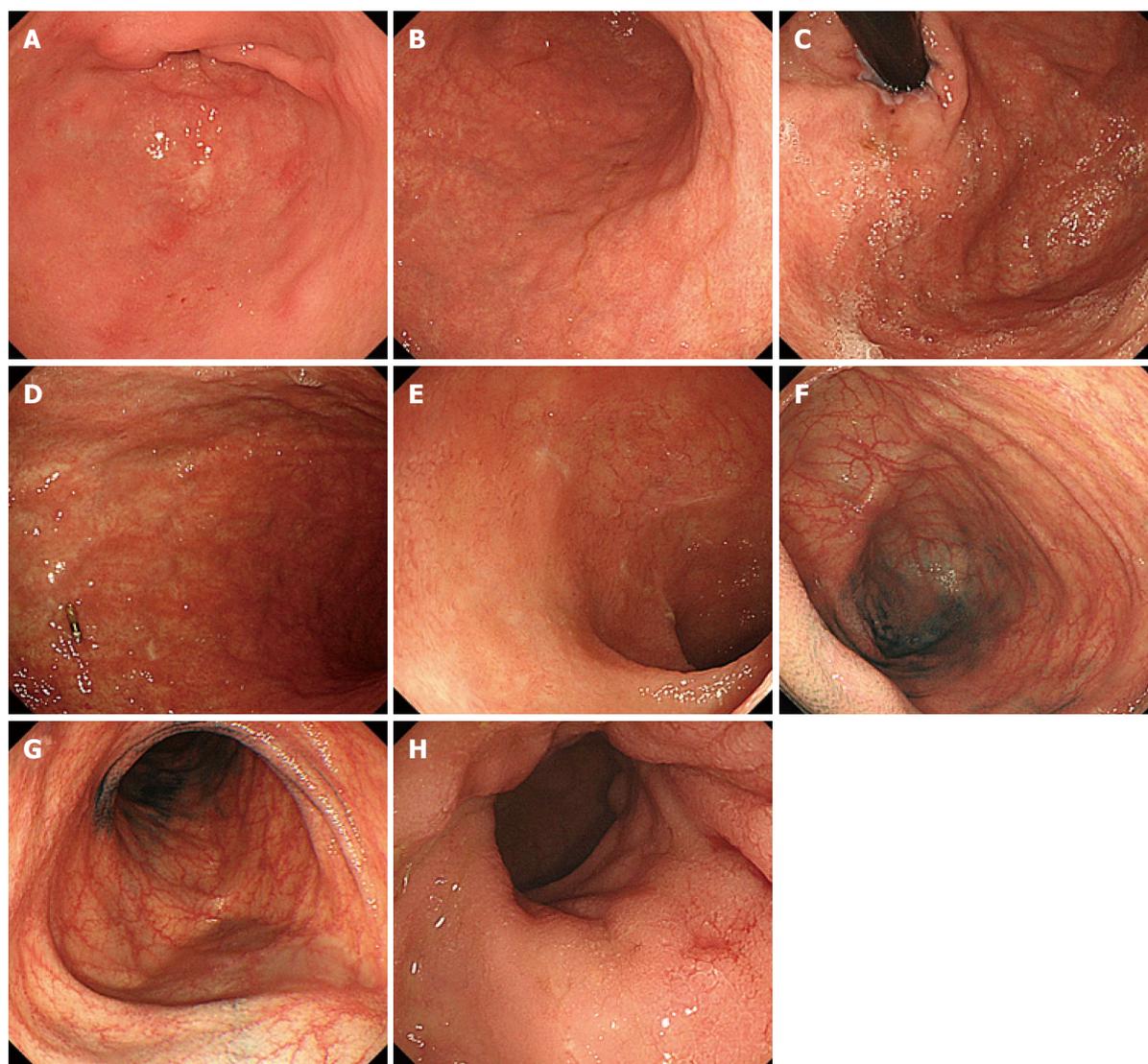


Figure 5 Upper and lower gastrointestinal endoscopic findings 162 d after the steroid and anti-cytomegalovirus therapies. A: The gastric mucosa in the antrum of the stomach; B: The gastric mucosa in the lower segments of the corpus of the stomach; C: The gastric mucosa in the upper segments of the corpus of the stomach; D: The greater curvature of the stomach near the center. The endoscopic clipping has remained, and nearly the entire mucosa of the stomach has improved to a normal state; E: Normal mucosa in the cecal valve and cecum; F: Normal mucosa in the terminal ileum; G: Marked improvement of the inflammation of the colonic mucosa, and healed ulcers in the sigmoid colon; H: The vascular patterns are now visible, indicating that the normal mucosa has returned in the rectum.

patient QoL^[11]. Moreover, after HSCT, CMV infection of the GI mucosa and GI-GVHD can both cause diarrhea^[12,13].

Diseases characterized by the development of GI symptoms after HSCT include not only CMV and GI-GVHD infection but also virus infections caused by enterovirus, adenovirus, rotavirus, and Epstein-Barr virus, complications with bacterial and fungus infections, and colitis associated with thrombotic microangiopathy and regimen-related toxicity. In routine clinical examination, differentiating among these diseases is difficult^[14], particularly because GI-GVHD is frequently associated with CMV infection^[15,16]. In this case, because of the severe GI-GVHD accompanied by CMV infection, the patient developed frequent and long-term bloody diarrhea and abdominal pain, which appeared to have led to serious symptoms such as anemia, malnutrition, and dehydration.

The endoscopic findings reflected the severity of the

clinical symptoms. The lower GI tract exhibited severe signs of multiple deep ulcers, edema, and erythema, with no normal mucosa observed. The upper GI endoscopy revealed diffuse sloughing of the mucosa in the stomach, except for the antrum. Although the endoscopic findings of chronic GI-GVHD may include the characteristic esophageal web and strictures^[2], various endoscopic findings are associated with acute GI-GVHD depending on the severity of the inflammation. We reviewed the English literature in the MEDLINE database by searching with “gastrointestinal”, “GVHD”, and “endoscopy” as key words (Table 1). Although there are some reports of normal mucosal findings, a large number of studies reported findings of erythema, erosions, and edema. Because the symptoms were generally mild in the upper GI tract, the lower GI tract often had relatively severe inflammatory symptoms, with occasional actively bleeding ulcers. In addition, although tortoise shell-like mu-

Table 1 Literature review of the endoscopic findings in gastrointestinal graft-versus-host disease

No.	Ref.	Patients	Involved GI tract	Endoscopic findings
1	Sultan <i>et al</i> ^[23]	Acute GVHD patients less than 18 yr old (<i>n</i> = 40)	Stomach, duodenum, sigmoid and rectum	Normal, erosions, ulcer
2	Kreisel <i>et al</i> ^[24]	GI-GVHD patients (<i>n</i> = 175)	Stomach, duodenum, colon and rectum	Normal, edema, erosions, aptha, ulcer, nonspecific
3	Aslanian <i>et al</i> ^[25]	Acute GVHD patients (<i>n</i> = 18)	Stomach, duodenum, total colon and rectum	Normal, erythema, edema, erosions, ulcer
4	Martínez <i>et al</i> ^[26]	GI-GVHD patients (<i>n</i> = 20)	Stomach, duodenum, colon and rectum	Normal, erythema, edema, erosions, ulcer, bleeding
5	Krishna <i>et al</i> ^[27]	A 49-yr-old man	Stomach, duodenum, colon and rectum	Normal, erosions
6	Al Ashgar <i>et al</i> ^[28]	A 23-yr-old male who had undergone allogeneic HSCT	Sigmoid colon and rectum	Erythema, edema
7	Varadarajan <i>et al</i> ^[29]	Acute GVHD patients (<i>n</i> = 11)	Stomach, duodenum, small bowel, colon and rectum	Normal, erythema, edema, erosions, ulcer, bleeding
8	He <i>et al</i> ^[17]	GI-GVHD patients (<i>n</i> = 32)	Colon and rectum	Erythema, edema, erosions, ulcer, bleeding, tortoise shell-like mucosa, pseudomembrane mucosa
9	Xu <i>et al</i> ^[8]	GI-GVHD patients (<i>n</i> = 8)	Stomach, duodenum, colon and rectum	Normal, erythema, edema, erosions, ulcer, bleeding
10	Cheung <i>et al</i> ^[30]	GI-GVHD patients (<i>n</i> = 44)	Stomach, duodenum, colon and rectum	Normal, erythema, edema, erosions, ulcer, nonspecific, bleeding
11	Ross <i>et al</i> ^[31]	GI-GVHD patients (<i>n</i> = 92)	Stomach, duodenum and rectum	Normal, erythema, edema, erosion, ulcer, nonspecific
12	Harada <i>et al</i> ^[32]	GI-GVHD patients (<i>n</i> = 15)	Colon and rectum	Erythema, edema, erosion, nonspecific
13	Khan <i>et al</i> ^[33]	Acute GVHD patients (<i>n</i> = 38)	Stomach, duodenum, colon and rectum	Edema, erosion, ulcer, bleeding, nonspecific, pseudomembrane mucosa
14	Silbermintz <i>et al</i> ^[34]	An 8-yr-old child	Small bowel	Erosion, bleeding
15	Holmberg <i>et al</i> ^[35]	GI-GVHD patients (<i>n</i> = 90)	Stomach, duodenum, colon and rectum	Normal, erythema, edema, ulcer
16	Onozawa <i>et al</i> ^[36]	An 18-yr-old male	Stomach, duodenum, colon and rectum	Normal, nonspecific
17	Yeh <i>et al</i> ^[37]	GI-GVHD patients (<i>n</i> = 4)	Stomach, duodenum, small bowel, colon and rectum	Erythema, edema, erosions, ulcer, bleeding, nonspecific
18	Schulenburg <i>et al</i> ^[38]	GI-GVHD patients (<i>n</i> = 29)	Stomach, duodenum, colon and rectum	Ulcer, erythema, erosion, normal
19	Cruz-Correa <i>et al</i> ^[39]	GI-GVHD patients (<i>n</i> = 44)	Stomach, duodenum, colon and rectum	Normal, erythema, edema, erosions, ulcer, bleeding, nonspecific
20	Wakui <i>et al</i> ^[40]	GI-GVHD patients (<i>n</i> = 44)	Stomach, duodenum, colon and rectum	Erythema, erosion, ulcer
21	Terdiman <i>et al</i> ^[41]	Acute GI-GVHD patients (<i>n</i> = 12)	Stomach, duodenum, colon and rectum	Normal, nonspecific

GI-GVHD: Gastrointestinal graft-versus-host disease; HSCT: Hematopoietic stem cell transplantation.

cosa and pseudomembrane formation are occasionally observed, no particular findings are reportedly associated with the colorectal mucosa. Moreover, even though some papers report mucosal sloughing and ulceration^[8], a wide area of sloughing mucosa along with ulcers and inflamed mucosa, as observed in the present case, has never been reported. We believe that a combination of severe GVHD and CMV infection is the pathogenesis responsible for these symptoms^[13]. According to He *et al*^[17], GI-GVHD accompanied by CMV infection causes deep, discrete ulcers. The ischemic consequences of occluded blood vessels caused by enlarged vascular endothelial cells due to CMV infection are thought to be the mechanism underlying the GI mucosal damage^[18]. Similarly, ischemic alteration, in addition to the cytotoxicity caused by GVHD^[19], is a likely cause of the severe symptoms in our patient.

The early and accurate diagnosis of CMV infection in the GI tract is the key to preventing severe symptoms, such as perforation and bleeding^[20]. In this case, even though immunostaining with an anti-CMV antibody was negative, the quantitative PCR results of the biopsy specimens were positive, with a high value of 1.0×10^4 cop-

ies/ μ g DNA, which enabled the diagnosis of CMV-GID. The diagnostic accuracy of the quantitative PCR method using biopsy samples is reportedly superior to that of immunostaining to determine the involvement of CMV in the GI symptoms^[21]. This case showed that the results of the CMV quantitative PCR were closely correlated with the post-treatment improvement of the mucosa, suggesting the usefulness of the technique for evaluating the effects of CMV treatment.

In conclusion, when endoscopic observation is performed on HSCT patients with postoperative GI symptoms, it is necessary to look for signs of mucosal sloughing and ulcers. In addition to a detailed endoscopic observation, biopsy samples should be examined for the characteristic pathological features of GVHD^[22] and for signs of CMV infection. The course of this case suggests that the quantitative PCR of biopsy samples is useful for revealing CMV infection in the GI tract.

ACKNOWLEDGMENTS

We thank Hisae Kawashiro, the clinical research coordinator, for helping with the data collection.

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