【 CASE REPORT 】

Severe Bleeding due to Cytomegalovirus Esophagitis in a Patient with Diabetes after Interbody Fusion Surgery

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Abstract:

A 49-year-old man with diabetes taking clopidogrel and celecoxib underwent interbody fusion surgery for spinal spondylolysis. Ten days after the surgery, he vomited a large amount of fresh blood. A blood examination revealed hemodynamic failure. Esophagogastroduodenoscopy showed an adherent blood clot and multiple superficial ulcers in the esophagus. Endoscopic hemostasis was successfully achieved. Biopsy specimens from the esophageal ulcer showed positive immunohistochemical staining results for anti-CMV antibodies. The esophageal ulcer improved after the oral administration of ganciclovir. This case emphasizes that CMV esophagitis with bleeding can occur in a diabetic patient with a poor nutritional status due to relative immune dysfunction.

Key words: cytomegalovirus esophagitis, diabetes, esophagogastroduodenoscopy, hypoalbuminemia

(Intern Med 58: 2949-2955, 2019)
(DOI: 10.2169/internalmedicine.2908-19)

Introduction

Cytomegalovirus (CMV) can sometimes affect the gastrointestinal (GI) tract, and the majority of such CMV infections have been reported in immunosuppressed patients (1, 2). The colorectum is the most frequently affected site in the GI tract. In contrast, CMV esophagitis is relatively infrequent (2, 3). The symptoms of CMV esophagitis include dysphagia, odynophagia, and epigastric pain, while massive bleeding followed by hypovolemic shock is rarely observed.

We herein report a patient with CMV esophagitis who presented with hematemesis after orthopedic surgery. In addition, the patient presented with hematemesis and hemodynamic failure due to CMV esophagitis. It is noteworthy that the patient did not show apparent immunosuppression, although diabetes and hypoalbuminemia might lead to relative immune dysfunction. This case underscores the fact that CMV esophagitis can occur in a diabetic patient with a poor nutritional status and cause massive bleeding.

Case Report

A 49-year-old-man was referred to Kurashiki Central Hospital owing to chronic back pain and paresthesia caused by spondylolysis, lasting for several years. He had a history of diabetes and cerebral infarction. He had been taking clopidogrel, cyclooxygenase-2 inhibitor celecoxib, and oral hypoglycemic agents (i.e., metformin, empagliflozin, and sitagliptin). Preoperative testing was negative for human immunodeficiency virus.

He underwent interbody fusion surgery for the treatment of S4 spondylolysis. Since his diabetic condition was uncontrolled, his HbA1c value was 9.0%. He had undergone intensive insulin therapy for four weeks prior to the surgery that had gradually improved his blood sugar level; however, the value had remained at 8.4%. There was no diabetic nephropathy or retinopathy. After the surgery, his white blood cell (WBC) count and C-reactive protein (CRP) level temporarily increased, and the serum albumin level decreased rapidly (Table 1). We hypothesized that the systemic response to surgical injury to the spine had led to the in-

Table 1.   **Progress of Laboratory Data.**

		Pre 7	POD2	POD5	POD7	POD10	POD13	POD15	POD35
Hb	g/dL	15.9	17.4	14.1	13.5	11.9	8.1	8.6	12
Alb	g/dL	4.1	3.8	2.5	2.5	2.7	2.6	2.8	4.1
BUN	mg/dL	13	26	17	10	20	6	4	14
Cr	mg/dL	0.57	0.73	0.44	0.46	0.62	0.55	0.61	0.63
WBC	/µL	7,000	27,800	13,100	11,800	9,100	7,700	6,800	7,600
CRP	mg/dL	0.09	22.51	5.76	3.73	2.3	0.57	0.39	0.06
FBS	mg/dL	-	306	148	212	166	163	145	-

Pre: preoperative day, POD: postoperative day, Hb: hemoglobin, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, WBC: white blood cell count, CRP: C-reactive protein, FBS: fasting blood sugar
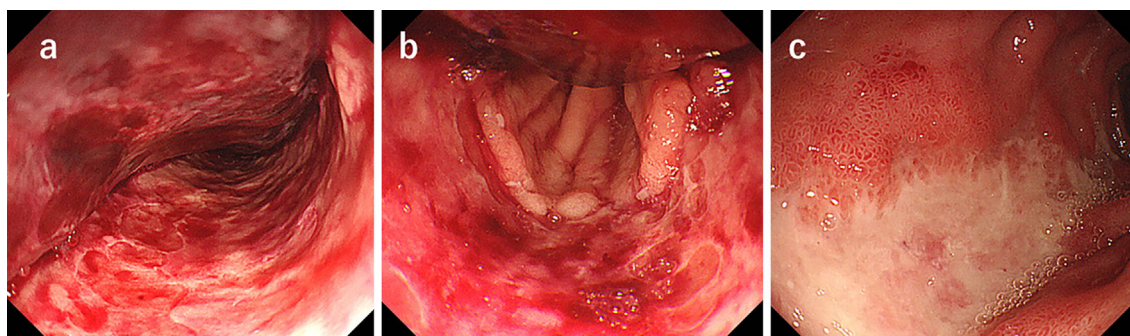

Figure 1. (a, b) An adherent blood clot occupying the esophagus and multiple superficial ulcers affecting the entire circumference of the upper to distal esophagus; (c) multiple superficial ulcers in the duodenum.

flammation and hypoalbuminemia because the WBC and CRP level normalized rapidly upon the administration of antibiotics until the day after the surgery, and only a low-grade fever remained. However, the patient complained of nausea after the surgery, and his food intake amount significantly decreased, necessitating peripheral intravenous nutrition. He started to consume a small amount of food on postoperative day (POD) 5. However, he experienced chest pain following the meal. Electrocardiogram and echocardiography examinations showed no abnormalities. Although a potassium-competitive acid blocker was administered on POD 7, this symptom did not resolve.

On POD 10, the patient suddenly vomited a large amount of fresh blood. His blood pressure and pulse rate were 77/43 mmHg and 120/min, respectively. Although computed tomography showed no bleeding site in the upper GI tract, blood clots were detected in the esophagus. Urgent esophagogastroduodenoscopy (EGD) also revealed an adherent blood clot occupying the esophagus (Fig. 1a). After removal of the blood clots, multiple superficial ulcers affecting the entire circumference of the upper to distal esophagus were observed (Fig. 1b). A red exposed vessel with oozing hemorrhaging was identified in the mid esophagus (Fig. 2a). Although multiple punched-out ulcers existed in the duodenum, no site of bleeding was observed (Fig. 1c). There was no mucosal damage in the stomach. Hemostasis for an exposed vessel was successfully achieved using hemoclips (Fig. 2b). He restarted taking clopidogrel along with a liquid

meal 2 days after the hemostasis, and no symptoms nor bleeding were observed thereafter.

EGD performed 15 days after surgery revealed incomplete healing of the multiple ulcers in the esophageal and duodenal mucosa (Fig. 3). Biopsy specimens from the esophageal ulcer showed an ulcerated mucosa with inflammation and intranuclear inclusion bodies (Fig. 4a). An immunohistochemical analysis revealed positivity for anti-CMV antibodies (Fig. 4b), while the patient showed negative results for CMV antigenemia. Intranuclear inclusion bodies and positive staining results for anti-CMV antibodies were not observed in the biopsy specimens of the duodenum ulcer. Repeated EGD after the two-week administration of oral ganciclovir revealed that the mucosa of the esophagus and duodenum was healed (Fig. 5). He had no symptoms of recurrence after a total of three weeks of ganciclovir administration.

Discussion

CMV is a species of the herpes virus and a common viral pathogen in humans. Serious infectious complications are induced either by reactivation of a latent CMV infection or by the acquisition of a primary CMV infection (4). Reactivation of CMV mainly occurs in immunosuppressed patients with various underlying diseases, such as concomitant immunodeficiency virus infection, transplant recipients who are taking immunosuppressive agents, those with malignant diseases
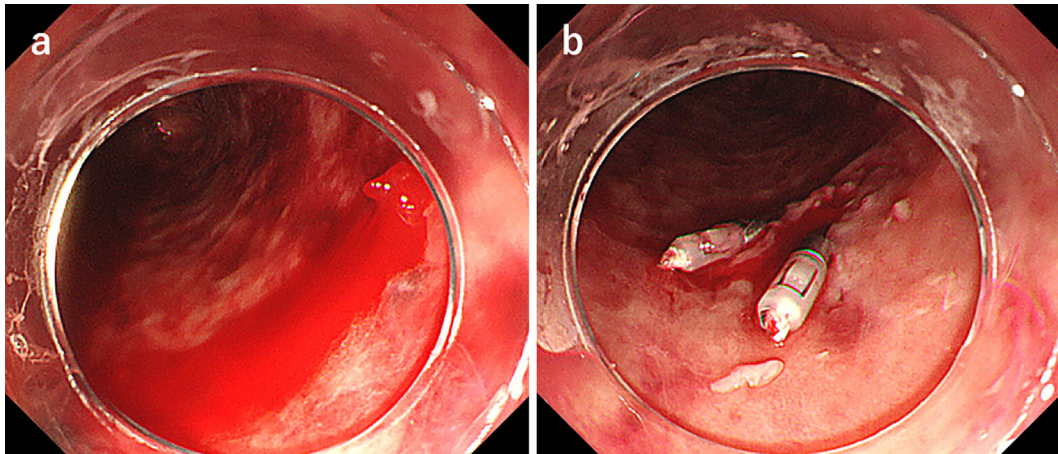
Figure 2. (a) A red exposed vessel with oozing hemorrhaging; (b) hemostasis of the exposed vessel was successfully achieved using hemoclips.
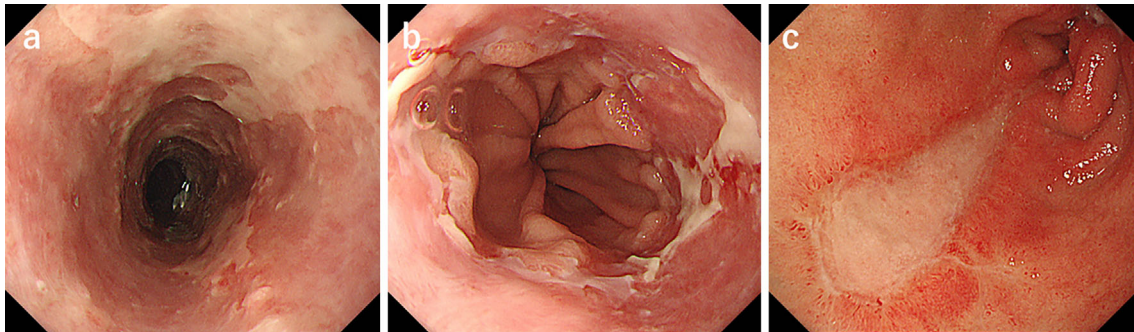

Figure 3. (a, b) Incompletely healed multiple ulcers in the esophagus; (c) incompletely healed ulcer in the duodenum.
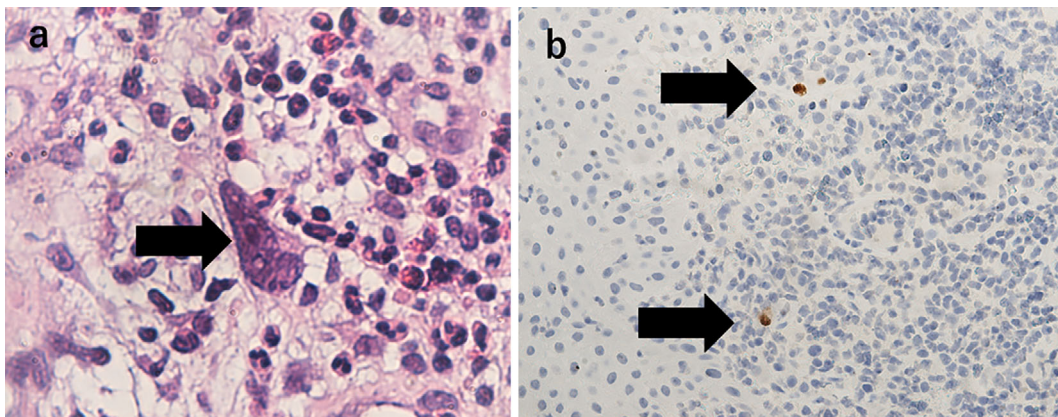

Figure 4. Histological findings of biopsy specimens. (a) Intranuclear inclusion bodies in Hematoxylin and Eosin staining (arrow); (b) immunohistochemical staining showing cells positive for anti-CMV antibodies (arrows).

and inflammatory bowel diseases, and patients undergoing chemotherapy or steroid treatment. Serious manifestations owing to CMV infection sometimes result in severe morbidity and mortality in affected patients (1, 4).

CMV infection is generally infrequent in immunocompetent patients. However, the numbers of case reports and case series describing CMV infection in immunocompetent pa-

tients have been increasing. Susana et al. reported that 25% (3/12) of patients with CMV infection in the GI tract were not immunodeficient or under immunosuppression treatment (5). Bonetti et al. reported that 50% (15/30) of the patients were apparently healthy individuals (6). We presumed that the patient in the present case was not severely immunosuppressed; however, we could not confirm this be-
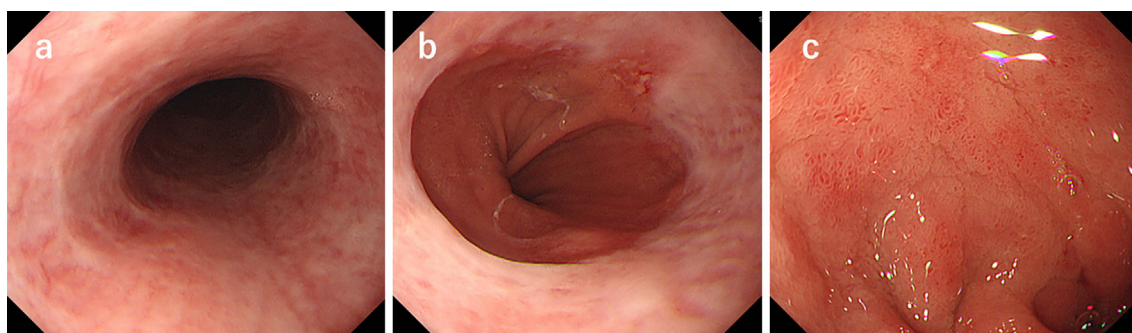
Figure 5. (a, b) The mucosa was healed from the upper to distal esophagus; (c) the duodenal mucosa was also healed.

cause we did not measure the CD4 and CD8 expression. Furthermore, uncontrolled diabetes and hypoalbuminemia might have caused immune dysfunction to some degree, leading to CMV infection in the esophagus. Some reports have indicated an association between CMV infection and diabetes mellitus (7-9). Lantini et al. noted that severe manifestations with CMV infection in an immunocompetent patient were partly associated with immune dysfunction, such as that observed in kidney disease or diabetes mellitus (7). Lee et al. reviewed reactivated CMV proctitis in an immunocompetent patient and reported that 54.5% (6/11) of patients with CMV proctitis had diabetes mellitus (9). The possible mechanisms underlying susceptibility to CMV in diabetes patients include hyperglycemia that causes damage to the neutrophil function, reduction of response to T cells, and dysfunction of humoral immunity (10). Previous studies regarding cell-mediated immunity reported that the T cell function was defective in poorly controlled type 1 diabetes patients (11). The complement system is associated with humoral immunity, and some studies have revealed a deficiency in the C4 component in diabetes (12). These deficiencies cause polymorphonuclear dysfunction and reduce the cytokine response. The B cell humoral immune response function is also affected by complement activation products. In addition, previous reports mentioned the association between hypoalbuminemia and CMV infection. Hypoalbuminemia revealed itself to be a significant risk factor for CMV infection in rheumatic disease and chronic lymphoproliferative diseases, such as in liver transplant recipients (13-15). Furthermore, Van et al. observed a decrease of CMV-specific immunoglobulin G and albumin levels in patients with CMV reactivation after renal transplantation (16). These findings indicate that CMV infection should be considered in the differential diagnosis, not only in apparently immunosuppressed patients but also in patients with relative immune dysfunction, such as those with diabetes and/or hypoalbuminemia.

Although the colorectum is the most common site of CMV infection in the GI tract, involvement of the upper GI tract, which leads to esophagitis, gastritis, duodenitis, gastric ulcer, or duodenal ulcer, has also been reported (3). The most common symptoms associated with CMV esophagitis are dysphagia, odynophagia, and epigastric pain (17). Hematemesis is a rare manifestation of CMV esophagitis, compared with CMV gastritis/duodenitis (18, 19). Hence, there have been few reports describing patients with CMV esophagitis who presented with hematemesis and/or hemodynamic failure.

To our knowledge, seven patients with CMV esophagitis showing hematemesis have been reported in the literature (Table 2) (5, 19-24). Five of the seven patients were under immunosuppression treatment and had been taking immunosuppressive agents such as steroids or cyclophosphamide. None of the patients had diabetes mellitus or hypoalbuminemia as far as we have searched. Among the seven patients, only three showed hemodynamic failure; all of them were immunosuppressed and had been taking immunosuppressive agents. Two patients required insertion of a Sengstaken-Blakemore tube, because the bleeding source could not be identified and the bleeding was uncontrollable. In the patient in the present case, although hemostasis was successfully achieved, it was difficult to detect the site of bleeding. In one patient in a previous study, a red exposed vessel was endoscopically treated using hemoclips (24), as in our case.

Representative endoscopic features of CMV infection in the upper GI tract include deep, punched-out ulcers. However, endoscopic features of previously reported CMV esophagitis are often nonspecific, including solitary or multiple deep ulcers and superficial ulcers, as shown in Table 2. The present patient also showed multiple superficial ulcers affecting the entire circumference of the upper to distal esophagus, which necessitated a differential diagnosis from other diseases, such as acute esophageal mucosal lesion, acute esophageal necrosis (AEN), and non-steroidal anti-inflammatory drug-induced ulcer (25, 26). In fact, this patient had been taking clopidogrel and celecoxib, which can also cause mucosal disorders and severe bleeding (27, 28). There has been only one case report describing AEN with CMV infection after renal transplantation (29). Although the pathogenesis of AEN remains unclear, it is considered that the temporary reduction of esophageal blood perfusion and acid reflux cause AEN. In the present case, we considered CMV infection to be the principal cause of esophagitis, as the esophageal ulcers were improved after the administration

Table 2. Summary of Published Cases of Cytomegalovirus Esophagitis with Hematemesis.

Reference	Endoscopic features/disease location	Clinical presentation	Treatment	Hemodynamic failure	DIC	Immune-compromised state	Comorbidity	Immuno-suppressive agents	Antithrombotic drug/NSAIDs	Diagnosis	Treatment	Outcome
(5)	deep ulcer/unknown	hematemesis/melena	unknown	no	no	AIDs, DLBCL		Immuno-suppressive agents	unknown	intranuclear inclusions or immunostaining	GCV+VGCV	alive
(19)	multiple ulcer/middle esophagus	hematemesis	S-B tube →operation	yes	yes	GPA	achalasia	PSL	no	surgical specimens: intranuclear inclusions/immunostaining	GCV	alive
(20)	superficial ulcer/unknown	hematemesis	epinephrine/thrombin	yes	no	SLE		PSL, cyclophosphamide	unknown	biopsy: immunostaining	GCV	alive
(21)	blackish discoloration/unknown	hematemesis/melena	none	no	no	no	alcoholism	none	no	biopsy: intranuclear inclusions	none	alive
(22)	superficial ulcer/lower esophagus	hematemesis	unknown	no	no	no	acute pancreatitis following ERCP	none	no	biopsy: immunostaining	GCV	death (pancreatitis)
(23)	severe ulcer/lower esophagus	hematemesis	S-B tube	no	yes	endstage renal failure	liver cirrhosis	PSL	no	autopsy: intranuclear inclusions	none	death (DIC)
(24)	superficial ulcer/middle esophagus	hematemesis	clipping	yes	no	MPA		PSL, cyclophosphamide	no	biopsy: intranuclear inclusions/immunostaining	GCV	death (pneumonia)

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, SLE: systemic lupus erythematosus, AIDs: acquired immunodeficiency syndrome, DLBCL: diffuse large B-cell lymphoma, PSL: prednisolone, GCV: ganciclovir, VGCV: valganciclovir, S-B tube: Sengstaken–Blakemore tube, DIC: disseminated intravascular coagulation, NSAIDs: non-steroidal anti-inflammatory drug

of the anti-CMV drug. However, it is quite possible that other factors contributed to the pathogenesis of the esophageal ulcer, such as hyperglycemia, hypovolemia, hypoalbuminemia, acid reflux, antiplatelet drugs, and NSAIDs.

The gold standard for the diagnosis of CMV infection in the GI tract is a histopathology analysis with immunohistochemical staining (30). The current patient and all previously reported patients, except for one, were diagnosed based on the results of histopathological examinations. However, histology has a low sensitivity, so CMV infection may be missed (31). In the present patient, although CMV was not detected in the duodenum, the duodenal ulcer might have been caused by a CMV infection as well, as it presented with a punched-out ulcer (Fig. 4C).

Anti-CMV drugs, such as ganciclovir and valganciclovir, were used in all cases. Lim et al. suggested that these drugs were important for preventing rebleeding from CMV-related lesions in the GI tract (32). Three of the seven patients died after bleeding due to disseminated intravascular coagulation, pneumonia, and/or progressive complications of pancreatitis. Although this lethal outcome was more likely to be associated with their immunosuppressed condition than with CMV esophagitis, the bleeding event obviously worsened their condition.

In conclusion, CMV esophagitis can occur not only in immunosuppressed patients but also in those with relative immune dysfunction caused by diabetes and hypoalbuminemia. Furthermore, although rare, CMV may cause massive bleeding, leading to hemodynamic failure. Physicians should therefore consider CMV esophagitis in the differential diagnosis of esophageal bleeding of unknown cause, even in patients without apparent immunodeficiency. A prompt histopathological diagnosis and administration of anti-CMV drugs are essential for management of CMV esophagitis.

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

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