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Case Report

Cytomegalovirus as an Insidious Pathogen Causing Duodenitis

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A 60–year-old woman with rheumatoid arthritis treated with methotrexate for a decade complained of slight epigastric discomfort. A positive cytomegalovirus (CMV) antigenemia test indicated the probability of CMV-related gastrointestinal infection, for which esophagogastroduodenoscopy was performed. Endoscopic findings showed a non-specific duodenal mucosal lesion; however, pathological investigation revealed evidence of CMV duodenitis. There is scarce information on the clinical and pathological features of CMV-related duodenitis, likely due to its low prevalence. CMV infection in the upper gastrointestinal tract should be considered as a differential diagnosis in high-risk individuals, particularly those with symptoms relating to the digestive system. Biopsy examinations are preferable for the definitive diagnosis of CMV gastrointestinal infection, even without specific endoscopic features.

Key words: antigenemia, cytomegalovirus (CMV), gastrointestinal infection, methotrexate, opportunistic infection

Cytomegalovirus (CMV) is a herpesvirus that is usually latent in the human body, but has the potential to cause various clinical symptoms by reactivating in immunocompromised hosts. Gastrointestinal (GI) infections caused by CMV generally occur in the large intestine [1]. In the upper GI tract, the stomach and esophagus are common sites for CMV reactivation whereas duodenal involvement is rare [2]. Thus, clinical or pathologic features of CMV infections occurring in the duodenum have scarcely been determined.

Here, we present a case of CMV reactivation in the duodenal mucosa occurring in an immunocompromised patient with rheumatic arthritis, with particular attention given to endoscopic findings. We consider that the endoscopic imaging and clinical course presented in this case report would be of use for physicians treating patients with duodenal CMV infection.

Case Presentation

A 60–year-old woman with rheumatoid arthritis was admitted to our hospital owing to cellulitis on her upper extremities. Her rheumatic symptoms had been controlled with methotrexate for approximately 10 years. Ten mg per week of methotrexate and 400 mg per day of etodolac were prescribed at admission. There was no recent history of blood transfusion or *Helicobacter pylori* eradication. She had never been treated with glucocorticoid or biological agents.

CMV antigenemia (pp65. C7–HRP) was evaluated

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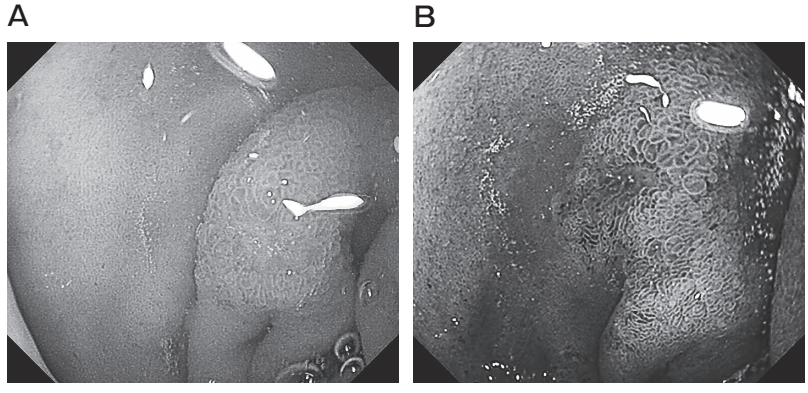

Fig. 1 Endoscopic appearance of cytomegalovirus (CMV)-related duodenal lesion. Esophagogastroduodenoscopy revealing partial redness with erosion in the duodenum (A). Narrow-band imaging emphasizing swollen villi around the erosion, suggesting mucosal inflammation (B).

Table 1 Results of laboratory examination on admission

White blood cell	4,290/mm^3	LDH	383IU/L
Nt	91.0%	AST	117IU/L
Lym	6.0%	ALT	76IU/L
Mono	1.0%	γ GTP	41IU/L
Eo	1.0%	T-bil	0.82mg/dL
Baso	1.0%	BUN	20.6mg/dL
Hemoglobin	8.3g/dL	Cre	0.61mg/dL
Platelet	28.1$\times$10^4/mm^3	Alb	2.9g/dL
ESR	104mm/h	CRP	9.88mg/dL
		Na	138mEq/L
D dimer	0.9μg/mL	K	4.3mEq/L
		Cl	105mEq/L
CMV-C7HR	Positive	CK	23IU/L
	20/50,000cells	HbA_{1c}	5.5%

on admission as part of our routine testing in immunocompromised patients, and the result was found to be positive (20 pp65-positive cells per 5×10^5 cells) (Table 1). CMV-specific IgM/IgG, CD4 cell counts and CMV DNA copies in blood were not examined at that time. Serum examination of the specific antibody for *H. pylori* was negative. Besides the cellulitis, the patient presented with epigastric discomfort, and esophagogastroduodenoscopy was performed, as we suspected GI involvement of CMV. Atrophic gastritis was apparent in the gastric antrum. Histology was positive for neutrophils and monocytes, but negative for *H. pylori*, atrophy and intestinal metaplasia. Thus, *H. pylori* gastric infection was unlikely. In the duodenum, on the other hand, a reddish, erosive edematous mucosa was observed in the duodenal bulb (Fig. 1). Partial mucosal redness was seen in the second portion. Biopsy samples were taken from the stomach, duodenal bulb, and the second portion of the duodenum. Histology of the gastric sample was negative for both *H. pylori* infection and CMV infection. However, micropathological examination of the biopsy specimen taken from the duodenal bulb revealed an acute inflammatory cell infiltration, accompanied with aggregation of lymphocytes (Fig. 2A). The presence of intranuclear inclusion bodies was also detected (Fig. 2B). Further, CMV-positive cells were immunohistochemically observed in intraepithelial cells (Fig. 2C-D). No evidence of CMV infection was detected in the other specimens. The complication of CMV retinitis was not apparent by fundus examination. Consequently, the diagnosis of CMV duodenitis was made, and valganciclovir was administered after treatment with methotrexate was ceased. Two weeks after the diagnosis of CMV duodenitis, serum levels of CMV-specific IgM and IgG were confirmed to be 0.51 TV and 172U/mL, respectively. After 3 weeks, although a follow-up endoscopic examination was not performed, the patient's symptoms had disappeared and CMV antigenemia was confirmed to be negative. She appeared to be free of GI symptom recurrence 14 months after valganciclovir treatment was discontinued.

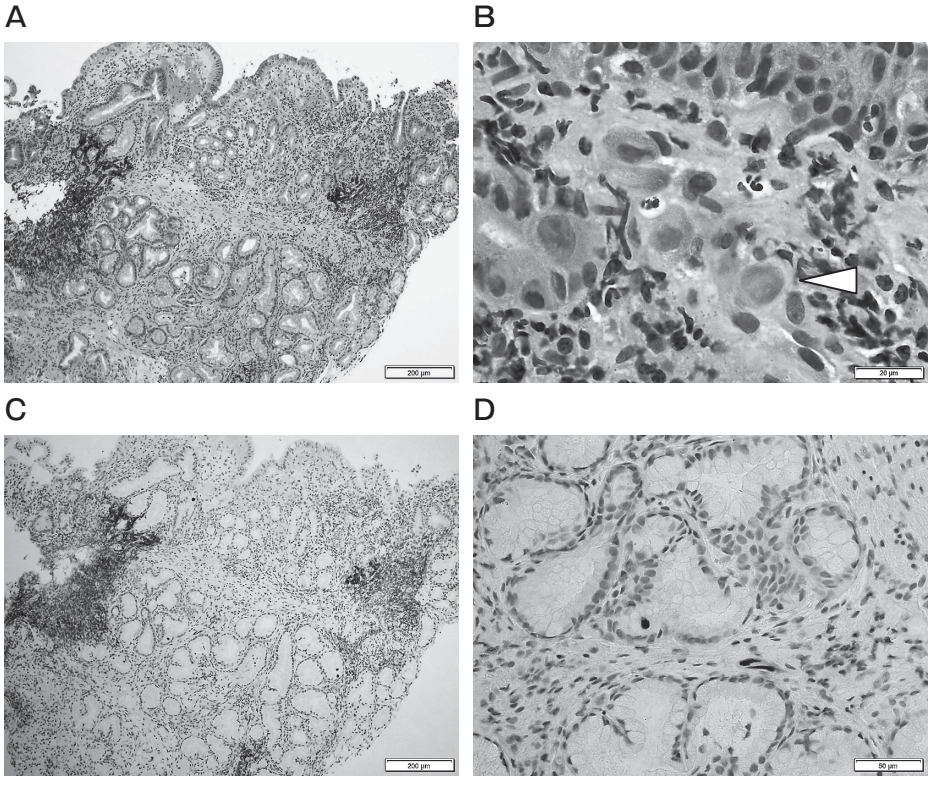

Fig. 2 Microscopic features of CMV-related duodenal lesion. Results of hematoxylin and eosin staining (A, B) and immunohistochemical staining (C, D) are shown. The immunohistochemistry was performed using a polyvalent horseradish peroxidase polymer detection system (Ventana Medical Systems, Tucson, AZ, USA). Primary antibodies against anti-CMV clones DDG9 & CCH2 (M085401, 1: 100 dilution; DAKO, Santa Clara, CA, USA) were used. Proper antigen retrieval was carried out with CC1 buffer for 60 min according to the manufacturer's instructions. Infiltration of inflammatory cells (A) and the emergence of intranuclear inclusion bodies (B, arrowhead) are seen in the biopsied duodenal specimen. CMV-positive cells are sporadically observed among the intraepithelial cells (C, D).

Discussion

CMV infection is a relatively common condition in immunocompromised patients, although duodenal involvement is extremely rare. Bonetti *et al.* investigated 30 patients with CMV infection occurring in the upper GI tract, and found that the stomach is the most common site of involvement (63.3%, 19 cases), followed by the esophagus (30%, 9 cases), and the cardia (20%, 6 cases). According to his review, duodenal involvement has been seen in only one patient (3.3%), with multiple ulcers in the duodenum [2]. In a report on 9 cases of rheumatic arthritis patients with upper GI-tract CMV infection [3], duodenal lesions were seen in only 1 case. Thus, clinical characteristics of CMV-related duodenal lesions have not been well elucidated. The reason for the low occurrence rate of CMV infection in the duodenum is unknown, and further investigation is required.

In general, CMV antigenemia shows high sensitivity and specificity for viremic cases: 93.5% and 94.3%, respectively [4]. The test often yields positive results before the infection is manifested in organs, thus aiding early diagnosis and pre-emptive therapy [5, 6]. In cases of localized CMV, however, the sensitivity of the CMV antigenemia assay dramatically decreases [7]. Jang *et al.* reported its sensitivity and specificity for diagnosing GI CMV diseases as 54% and 88%, respectively [1]. According to Ozaki *et al.*, who summarized 9 cases (10 events) of upper GI tract CMV infections in patients with rheumatic diseases, the sensitivity of CMV antigenemia was only 50% [3]. To our knowledge, there have

been no data focusing specifically on duodenal CMV infection. Thus, the utility of the CMV antigenemia assay for the diagnosis of duodenal CMV infection should be determined hereafter.

Endoscopic features of CMV infection in the upper GI tract are generally non-specific. Morphologies of CMV gastric involvement are reported to vary from patchy erythema to thickened mucosa, hypertrophy of the gastric folds, exudates, erosions, or ulcers [8, 2]. Similarly, endoscopic manifestations of CMV-related duodenal lesions have been reported to be various: mucosal depigmentation [9], ulcers with or without fresh bleeding [10, 11], and even pseudotumor formations [12]. It is noteworthy that the duodenal ulcers caused by CMV infection can lead to intestinal perforation, which requires surgical treatment [13]. Our case showed a reddish, erosive edematous mucosa in the duodenal bulb as a manifestation of CMV-related duodenitis. This fact implies that we need to recall the relevance of CMV infection for nonspecific mucosal lesions in the duodenum.

Microscopic analysis, rather than macroscopic features, would be more important as a diagnostic tool for CMV-related upper GI infection. The sensitivity and specificity of immunohistochemical methods for the diagnosis of CMV GI infection are reported to be higher: 89% and 100%, respectively [1]. Even if histopathological examinations including the immunohistochemical staining showed negative results, the intestinal CMV load may be elevated [14]. Thus, micropathological examinations should be taken into consideration for suspected GI mucosal lesions, especially when patients are at risk of CMV infection. In patients with rheumatic arthritis, the use of glucocorticoid therapy is considered a risk factor for developing the disease [3], although our patient had never received steroid treatment. We speculate that the methotrexate treatment was mainly responsible for immunosuppression in this case, leading to the reactivation of CMV. CMV-specific IgM/IgG, CD4 cell counts and CMV DNA copies in blood were not examined at her initial presentation. In the future, these data, in addition to the medication history, should be collected from individual cases with CMV-related upper GI infection, since doing so will promote a better understanding of the etiology and epidemiology of this disease entity.

Mucous membrane disorders of the duodenum have various etiologies. Representative conditions include use of non-steroidal anti-inflammatory agents (NSAIDs) and *H. pylori* infection. The patient had taken etodolac, a kind of NSAID, for the purpose of rheumatic pain control. The drug is a cyclooxygenase-2 selective inhibitor, which is less damaging to the mucous membrane of the gastrointestinal tract. Endoscopic findings showed atrophic gastritis; however, the result of micropathological examination denied evidence of *H. pylori* infection, and her serum specimen was negative for the specific antibody for *H. pylori*. Thus, the relevance of *H. pylori* infection was unlikely in our case.

In conclusion, we have reported a case of CMV duodenitis, in which the mucosal lesion presented a non-specific manifestation on endoscopy findings. Though rare, CMV infection in the upper GI tract should be included in the differential diagnoses of immunocompromised patients with GI manifestations. Even when the lesion appears non-specific, biopsy sampling and pathological investigations can lead to the diagnosis of CMV infection in the upper GI tract.

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