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Case study

Cytomegalovirus infective gastritis in an immunocompetent host misdiagnosed as malignancy on upper gastrointestinal endoscopy: a case report and review of literature☆,☆☆

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Summary Primary cytomegalovirus (CMV) infection is rare in immunocompetent hosts and generally asymptomatic. CMV infective gastritis in patients without immunosuppression is very unusual. A 44-year-old man presented with complaints of intermittent epigastric pain. He had no history of organ transplantation, human immunodeficiency virus infection, or immunosuppression of any type. Upper gastrointestinal endoscopy revealed ulcers in the gastric antrum and uplift of the gastric body. Computed tomography scan showed obvious thickening of the gastric wall and enlargement of retroperitoneal lymph nodes, suggesting malignancy. However, the first biopsy only showed ulcerative inflammation, necrosis, and mucosal erosions around the ulcer. Repeat biopsy and histopathological examination showed CMV inclusions in glandular endothelial cells. Immunohistochemistry findings supported the diagnosis of CMV infective gastritis. Symptoms subsided after treatment with intravenous ganciclovir, and the gastric ulceration and surrounding mucosal inflammation decreased. This case report and review of literature is presented to increase awareness regarding this rare disease.

1. Introduction

Cytomegalovirus (CMV) is best known as an opportunistic pathogen in immunocompromised patients. CMV infective gastritis is generally seen in patients with acquired immunodeficiency syndrome, organ and bone marrow transplantation, malignant lymphoma, or other immunosuppressed states [1]. It is very rare in healthy adults with a normal immune system; our literature search revealed only 4 previous reports over the period from January 2000 to December 2017. Upper

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gastrointestinal endoscopy is inconclusive in these cases; therefore, pathological diagnosis is particularly important. However, the histological picture in CMV infection is variable, and the diagnosis may be easily missed when only occasional inclusions are present in biopsy samples. Here, we report a case of CMV infective gastritis in an immunocompetent host in whom upper gastrointestinal endoscopy and enhanced computed tomography (CT) were suggestive of malignancy. The initial diagnosis was gastric cancer or lymphoma. CMV infective gastritis was diagnosed only after repeated biopsies and histopathological and immunohistochemical examination. We describe the clinical and pathological findings in our patient and review the literature related to CMV infective gastritis to improve awareness regarding this rare disease.

2. Materials and methods

2.1. Case presentation

In 2017, a 44-year-old man presented with complaints of intermittent epigastric pain and abdominal distention since 2 months. There was no associated nausea, vomiting, or diarrhea. Result of physical examination was negative. He denied history of homosexual behavior or drug abuse. He was not on any immunosuppressive treatment. The laboratory findings are listed in the Table.

Upper gastrointestinal endoscopic examination revealed multiple erosions in the mucosa of the gastric antrum and uplift of the gastric body (Fig. 1A). CT showed obvious thickening of the stomach wall in the antrum and enlarged retroperitoneal lymph nodes (Fig. 1B). Based on these findings, the provisional diagnosis was gastric cancer or lymphoma.

Repeat upper gastrointestinal endoscopy was performed, and biopsy specimens were sent for histopathological examination, immunohistochemistry, and in situ hybridization. The results were indicative of CMV infective gastritis. However, real-time polymerase chain reaction (PCR) was negative for CMV DNA, and enzyme-linked immunosorbent assay (ELISA) was negative for CMV immunoglobulin (Ig) M.

The patient was treated with intravenous ganciclovir (700 mg/d) for 21 days. The symptoms subsided. Repeat upper gastrointestinal endoscopy showed healing of the gastric ulcers and reduction in the surrounding mucosal edema (Fig. 1C). Because some thickening of the gastric wall was still present, intravenous ganciclovir treatment was continued for 3 more months. At the end of ganciclovir treatment, the gastric mucosa was normal (Fig. 1D).

2.2. Immunohistochemistry and in situ hybridization

Biopsy specimens were fixed in 10% neutral-buffered formalin and routinely processed. Paraffin-embedded blocks were sectioned (3 mm thick) and stained with hematoxylin and eosin. Immunohistochemistry was performed using the paraffin-embedded tissue samples. The primary antibodies used were CMV (ZSGB-BIO, 1:100), AE1/AE3 (ZSGB-BIO, 1:100), CD31 (ZSGB-BIO, 1:200), CD3 (ZSGB-BIO, 1:100), CD20 (ZSGB-BIO, 1:500), and Ki-67 (ZSGB-BIO, 1:600). EBV-encoded RNA in situ hybridization was performed using fluorescein-labeled oligonucleotide probes (ZSGB-BIO, ISH-6021).

3. Results

3.1. Pathological findings

The first endoscopic biopsy (June 2017) showed gastric mucosal ulceration and severe inflammation. The epithelium

Table Laboratory findings

CBC		Biochemistry		Viral examination	
WBC	11.2×10^9/L	TP	6.5 g/dL	HIV Ab (TRFIA)	(–)
Neu	65.7%	ALB	4.1 g/dL	HBs Ag (ELISA)	(–)
Lym	22.4%	AST	15 IU/L	HBs Ab (ELISA)	(+)
Mono	7.8%	ALT	12 IU/L	HCV Ab (ELISA)	(–)
Eos	3.7%	LDH	256 IU/L	CMV DNA (real-time PCR)	(–)
Baso	0.4%	T-Bil	7.1 μmol/L	EBV DNA (real-time PCR)	(–)
RBC	5.22×10^{12}/L	BUN	2.22 mmol/L	CMV IgM (ELISA)	(–)
Hb	14.7 g/dL	CRE	70.6 μmol/L		
MCV	85.7 fL	Na	142 mmol/L		
Plt	296×10^9/L	K	3.56 mmol/L		
		Cl	110 mmol/L		
		CRP	2.58 mg/dL		

Abbreviations: TRFIA, time-resolved fluoroimmunoassay; CBC, complete blood count; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mono, monocyte; Eos, eosinophil; Baso, basophil; RBC, red blood cell; MCV, mean corpuscular volume; Plt, platelet; TP, total protein;ALB, Albumin; AST, aspartate aminotransferase, ALT, alanine aminotransferase;LDH, lactate dehydrogenase; T-Bil, total bilirubin; BUN, blood urea nitrogen; CRE, creatinine; Na, natrium; K, potassium; Cl, chloride; CRP, c-reactive protein; HBs Ag, Hepatitis B surface antigen; HBs Ab, Hepatitis B surface antibody.

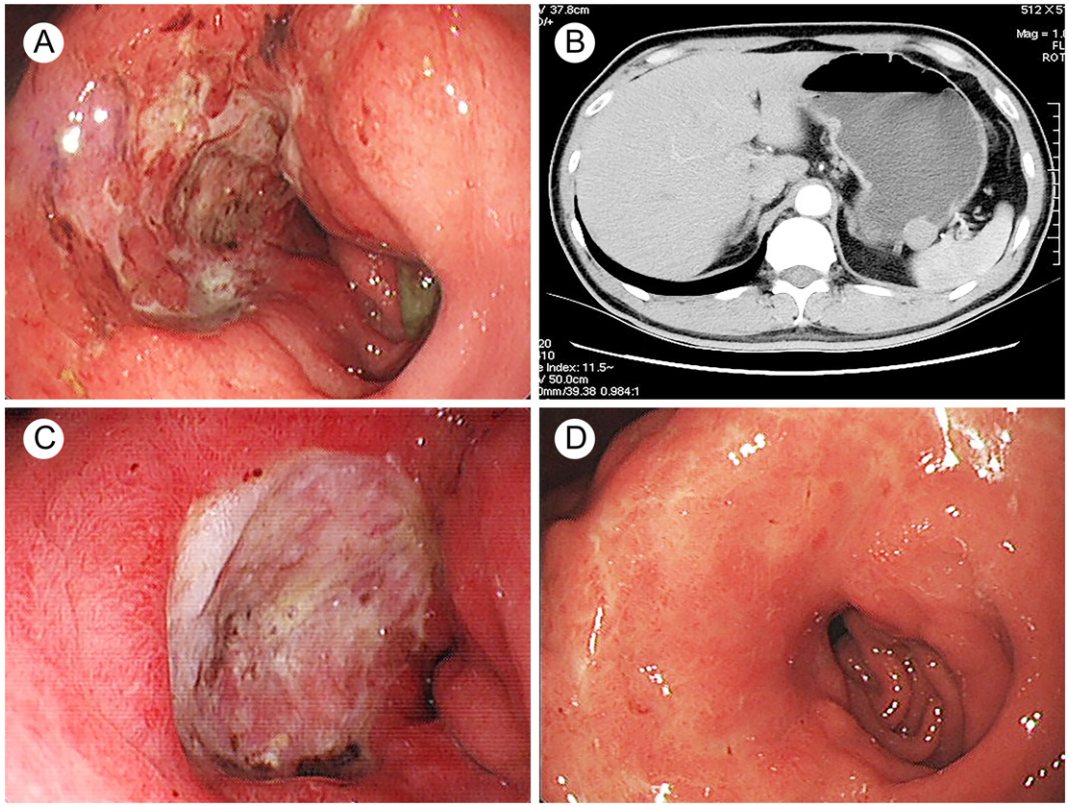

Fig. 1 Upper gastrointestinal endoscopy and CT findings. A, Upper gastrointestinal endoscopy shows multiple erosions in the gastric antrum and thickening of the stomach wall. B, CT shows obvious thickening of the antral wall and enlarged retroperitoneal lymph nodes. C, After 21 days of antiviral treatment, upper gastrointestinal endoscopy shows healing of the gastric ulcers and reduction in the surrounding mucosal edema. D, After 3 months of antiviral treatment, upper gastrointestinal endoscopy shows normal gastric mucosa.

was atypical at some places, with hyperplasia and heavy lymphocyte infiltration (Fig. 2A and B). Because the biopsy material contained only superficial mucosa and because of the severe infiltration, a lymphoproliferative disorder could not be ruled out. We therefore recommended review with repeat biopsy after a course of proton pump inhibitor treatment.

The second endoscopic biopsy (July 2017) showed ulceration with inflammation and necrosis; there was inflammatory exudation and granulation tissue proliferation (Fig. 2C), with atypical hyperplasia of lymphocytes in some granulation tissue (Fig. 2D). To distinguish hyperplastic lymphocytes from inflammatory reactive hyperplasia or clonal proliferation of tumors, we performed several immunohistochemical and in situ hybridization studies. The results did not support the diagnosis of gastric cancer or lymphoma.

A week later, the third endoscopic biopsy revealed large red eosinophilic bodies in glandular endothelial cells of the gastric mucosa (Fig. 2E and F); this was consistent with viral infective gastritis. Immunohistochemistry was positive for CMV antibody (Fig. 3A). We then reviewed the previous 2 biopsies; CMV antibody–positive cells were not found in the first biopsy. However, CMV immunohistochemical staining showed scattered positivity in the second biopsy (Fig. 3B), which further confirmed the existence of CMV infection. There could be 2 reasons for the negative result of the first biopsy: (1) CMV infection may require a certain process and period and (2) improper sampling under the gastroscope. Therefore, the final diagnosis was CMV infective gastritis.

The fourth endoscopy biopsy, obtained after 21 days of intravenous antiviral treatment, showed reduction of gastric mucosal erosions and inflammation (Fig. 2G and H), suggesting that antiviral treatment was effective.

The fifth endoscopy biopsy, obtained after completion of 3 months of antiviral treatment, showed normal gastric mucosa (Fig. 2I and J).

3.2. Immunohistochemistry and in situ hybridization

Positivity for CMV antibody was strong evidence in favor of CMV infective gastritis (Fig. 3A and B). Epithelium was positive for AE1/3. CD31 positivity indicated granulation tissue proliferation. CD3 and CD20 were positive, demonstrating mixed proliferation of T lymphocytes and B lymphocytes, which was polyclonal and not neoplastic. EBV-encoded

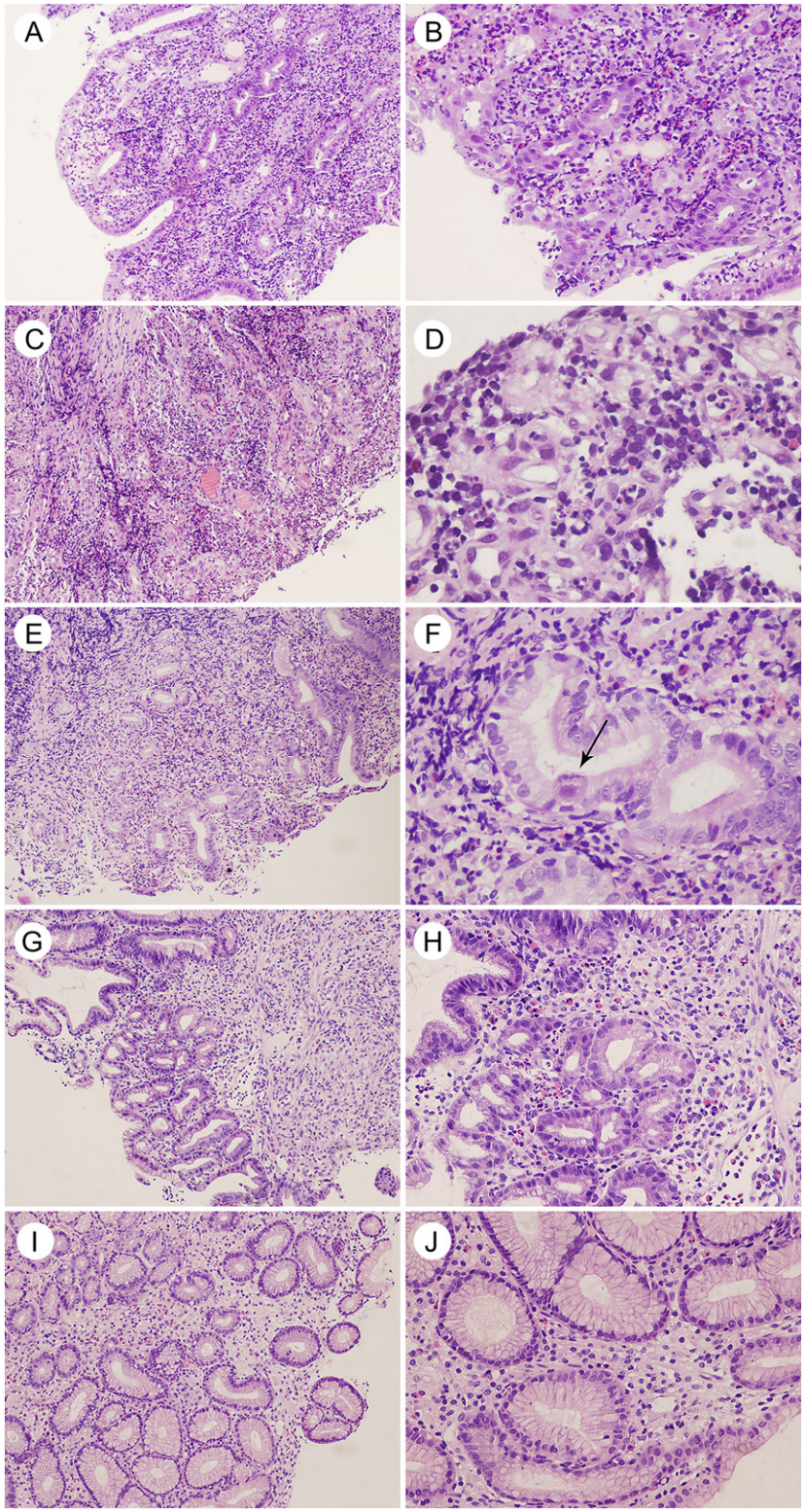

Fig. 2 Pathological features. A, The first endoscopic biopsy shows severe inflammation of the superficial gastric mucosa (H&E; original magnification ×100). B, Part of the epithelium is atypical, with lymphocytes infiltration and hyperplasia (H&E; ×200). C, The second endoscopic biopsy shows ulcerative inflammation and necrosis, inflammatory exudation, and granulation tissue proliferation (H&E; ×100). D, Typical hyperplasia of lymphocytes in granulation tissue (H&E; ×400). E, The third endoscopic biopsy shows mucosal erosion and ulceration (H&E; ×100). F, Large red eosinophilic bodies can be seen in the glandular endothelial cells (H&E; ×400). G, The fourth endoscopy biopsy (after 21 days of antiviral treatment) shows decrease in inflammation (H&E; ×100). H, Gradual healing of the gastric mucosa (H&E; ×200). I, The fifth biopsy (after 3 months of antiviral treatment) shows normal gastric mucosa (H&E; ×100). J, Regeneration of gastric glands (H&E; ×200).

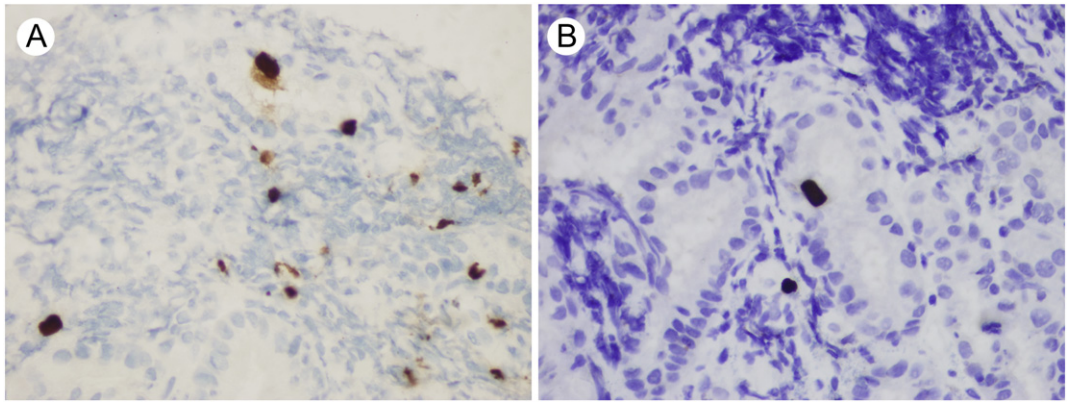

Fig. 3 Immunohistochemical findings. A, Positivity for CMV antibody is strong evidence of CMV infective gastritis (×400). B, CMV immunohistochemical staining shows scattered positivity in the second biopsy (×400).

RNA was negatively expressed, ruling out Epstein-Barr virus infection. The proliferative index based on Ki-67 staining was about 25%.

4. Discussion

The patient described in this report is the first case of CMV infective gastritis diagnosed at our hospital. Initial endoscopy and enhanced CT suggested gastric malignancy. The diagnosis was only established after repeated biopsy. Immunohistochemistry and in situ hybridization helped rule out gastric cancer and lymphoma. Subsequent endoscopic biopsy obtained from deep tissue revealed large red eosinophilic inclusion bodies, which were suggestive of viral infective gastritis. The patient recovered fully after a 3-month course of ganciclovir. The cause of CMV infective gastritis in this patient remains to be identified.

CMV infective gastritis mostly presents with epigastric discomfort or other nonspecific gastrointestinal symptoms. Patients with immunosuppression are more likely to suffer from severe symptoms. We conjecture that the strong immune defense response in immunocompetent patients leads to gastric mucosal erosions. In immunosuppressed patients, we suspect that the intensity of reaction and the severity of gastric mucosal involvement are inversely proportional to the residual immune function in patients.

Gastrointestinal symptoms, endoscopic manifestations, and histologic features tend to be diverse in CMV infective gastritis. Ulceration appears to be the most common manifestation. Ulcers may be single or multiple and either superficial or deep. CMV inclusions are more likely to be found in tissue at the ulcer bases than at the edges of ulcers or in superficial mucosa [1]. Therefore, the depth of endoscopic biopsy is an important consideration.

Similar to our patient, 3 of the 4 previously reported immunocompetent patients with CMV gastritis had abnormal proliferation of lymphocytes [2-5]. These 3 patients included a 58-year-old man with a small number of atypical lymphocytes in his peripheral blood [3], a 26-year-old man with a lymphoepithelial lesion in a part of the biopsied specimen [4], and a 31-year-old man with homogenous splenomegaly (14.6 × 13.4 cm) [5]. Thus, immunohistochemistry may be essential for differentiation of CMV gastritis from lymphoma. Monoclonal proliferation of lymphocytes is seen in malignant lymphoma, whereas inflammatory reactive hyperplasia is seen in CMV infective gastritis.

For diagnosis of CMV infective gastritis, pathological morphology and immunohistochemistry appear to be the most specific. Our literature review identified 26 articles describing a total of 27 cases of CMV infective gastritis over the 18-year period from January 2000 to December 2017. We found that CMV inclusions were detected in biopsy specimens and immunohistochemistry was positive for CMV antibodies in all patients. The results of serum CMV antigen assay and CMV DNA detection were not available for 8 patients. In the remaining patients, these results were not consistently positive. Serum CMV antigen assay was positive in 1 patient and negative in 1. PCR for CMV DNA was positive in 10 patients and negative in 5 patients. CMV IgM was positive in 5 patients and negative in 1. CMV IgG was positive in 2 patients and negative in 1. Thus, serological studies and PCR detection do not appear to be reliable for diagnosis of CMV infective gastritis, although they may be useful during follow-up of patients.

The experience with this patient and the literature review suggest that treatment with ganciclovir or valganciclovir is effective for CMV infective gastritis. In previous reports, immunocompetent patients treated with ganciclovir have shown good response [3,4]. Of the immunosuppressed CMV gastritis patients treated with ganciclovir or valganciclovir [6-15], 1 developed CMV retinitis [6], 1 worsened [14], and 1 died [7]. Therefore, it appears that although antiviral drug treatment may be sufficient for the immunocompetent host, other supportive treatments may be necessary in immunocompromised individuals.

To conclude, CMV infective gastritis is a very rare disease in immunocompetent patients. However, the possibility of viral infective gastritis must be kept in mind when a patient fails

to show any response to proton pump inhibitors and anti–*Helicobacter pylori* therapy. Biopsy specimens should be carefully observed for inclusion bodies. Immunohistochemistry should be performed to exclude CMV, Epstein-Barr virus, and other virus infections. Early diagnosis will help avoid unnecessary chemotherapy or operation. Further studies are necessary to improve our understanding of CMV infective gastritis.

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