

Clinical characteristics of cytomegalovirus gastritis

A retrospective study from a tertiary medical center

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Abstract

Cytomegalovirus (CMV) gastritis is a rare opportunistic infection with diverse clinical manifestations. Our study aimed to investigate the clinical features of Chinese patients with CMV gastritis.

Six inpatients diagnosed with CMV gastritis were retrospectively enrolled, based on the finding of inclusion bodies in routine hematoxylin and eosin staining or positive anti-CMV monoclonal antibodies under immunohistochemistry in the gastric biopsy. Data, including demographics, diagnostic measurements, and medications, were collected.

Abdominal pain was the most frequently reported symptom, occurring in 4 patients. Five patients were immunocompromised with associated underlying diseases, and 3 patients had decreased leukocyte differentiation antigen 4 positive (CD4⁺) T lymphocyte counts. Only 3 patients had either positive cytomegalovirus (CMV)-immunoglobulin (Ig) M or increased copies of CMV-DNA peripherally. All patients had gastric lesions in the antrum of the stomach, including ulcers or erosions observed by gastroscopy. All patients received ganciclovir by intravenous injection (IV) as the first line anti-CMV therapy, and attained complete (4) or partial remission (2) during the follow-up.

CMV gastritis should be taken into consideration in patients with immunocompromised status who have abdominal pain, nausea, or vomiting. Gastroscopy and necessary biopsy are the major diagnostic methods for CMV gastritis. Early diagnosis leads to a better prognosis for these patients.

Abbreviations: CA72-4 = cancer antigen 72-4, CMV = cytomegalovirus, CMV-pp65 = cytomegalovirus pp65 antigenemia, CRP = C-reactive protein, CTX = cyclophosphamide, CVID = combined variable immune deficiency, DM = dermatomyositis, EMR = endoscopic mucosal resection, ESR = erythrocyte sedimentation rate, Ig = immunoglobulin, IHC = immunohistochemistry, IV = intravenous injection, IVIG = intravenous immunoglobulin, LDH = lactate dehydrogenase, MPGN = membranous proliferative glomerulonephritis, NA = not available, NHL = non-Hodgkin lymphoma, PCR = polymerase chain reaction, PET/CT = positron emission tomography/computed tomography, PSC = primary sclerosing cholangitis, SD = standard deviation, WBC = white blood cell.

Keywords: clinical manifestation, cytomegalovirus, gastritis, infection

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1. Introduction

Cytomegalovirus (CMV) is a DNA virus belonging to the Herpesviridae family. The seroprevalence of CMV, indicating previous or current CMV infection, varies from 40% to 100% depending on the population studied or detection method used.^[1-3] One study from Wuhan in China revealed 76.1% of patients with inflammatory bowel disease were CMV-immunoglobulin (Ig) G positive, compared with 50.7% of healthy controls.^[4] Although acute or reactivated CMV infection can occur in immunocompetent patients, immunocompromised status still presents the most important risk factor for CMV infection, especially for disseminated CMV infection.^[2-5]

Gastrointestinal involvement in CMV infection is very common, with the colon being the most frequently affected site.^[5] However, upper gastrointestinal tract involvement, especially CMV gastritis, has rarely been recognized or reported, and there have been only a very few case reports or case series with small sample sizes.^[6] CMV gastritis can cause life-threatening complications, for example, perforation and hemorrhagic shock.^[7-9] Early diagnosis and timely medication could effectively improve the prognosis of patients. Therefore, we performed this retrospective study to describe the clinical, endoscopic, and histopathologic features of CMV gastritis, and provide more information for clinical practice. To the best of

our knowledge, this is the first recorded case series in Chinese patients with CMV gastritis.

2. Methods

2.1. Patients

By searching the inpatient database of Peking Union Medical College Hospital from January 2007 to December 2017, a tertiary teaching hospital in Beijing, China, patients with the diagnosis of “cytomegalovirus disease,” “cytomegalovirus pneumonitis,” “cytomegalovirus hepatitis,” “other cytomegalovirus diseases,” “cytomegalovirus disease,” or “cytomegalovirus retinitis” based on the the ninth revision of the international classification of diseases or the tenth revision of the international classification of diseases codes were screened. Finally, 6 patients with definite cytomegalovirus gastritis were retrospectively enrolled, who had either inclusion bodies in routine hematoxylin and eosin staining or stained positive with anti-CMV monoclonal antibody immunohistochemistry in gastric biopsy specimens. Disseminated CMV disease was defined as involvement of ≥ 1 organs besides gastrointestinal tract. All patients were followed for at least 6 months either by checking medical records or telephone connection. The study was approved by the Ethical Committee of Peking Union Medical College Hospital (S-k590).

2.2. Data collection

The following data of the participants were collected: demographics (sex and age), underlying systemic diseases, medication history of immunosuppressive agents, clinical manifestations (general and gastrointestinal symptoms), laboratory tests, radiologic features, endoscopic abnormalities, histopathologic features, treatment, and outcomes.

Laboratory tests included complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum lactate dehydrogenase (LDH), serum CMV-IgM, CMV-IgG and cytomegalovirus pp65 antigenemia (CMVpp65), CMV-DNA load, serum Ig (IgG, IgM, or IgA), and lymphocyte subsets (CD4⁺T cells, CD8⁺T cells, and activated CD8⁺T cells [CD38⁺CD8⁺T cells]).

Gastroscopy abnormalities were recorded, such as the type of lesions (ulcer, erosion, hyperemia, or edema), sites of ulcer involvement (the esophagus, cardia, fundus, corpus, antrum of stomach, or duodenum), solitary or multifocal ulcers, and the shape and size of ulcers. Multiple ulcers were defined as ≥ 2 in number, whereas a large ulcer was a solitary ulcer >2 cm in diameter.^[10]

Histopathologic features of the biopsy specimen from the ulcers or erosions of the stomach or duodenum specified focused on the detection of virus inclusion bodies by routine hematoxylin and eosin staining and immunohistochemistry staining using anti-CMV monoclonal antibodies.

The medication history, including antiviral therapy (ganciclovir or foscarnet) or intravenous immunoglobulin (IVIG), was also collected. Outcome was evaluated according to the clinical symptoms (partial or complete remission) and gastroscopic appearances (partial or complete healing). Partial healing was defined as a decrease in the number and size of ulcerations and erosions, whereas complete healing was defined as clearance of a white-coated ulcer with covering epithelium or complete resolution of the lesion.

2.3. Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp., Illinois, USA) was used for data analysis. Continuous variables with normal distribution and non-normal distribution are presented as mean \pm standard deviation (SD) and median (range), respectively.

3. Results

3.1. Demographics, clinical, and laboratory features of patients with CMV gastritis

Table 1 shows the demographic, clinical, and routine laboratory test data of 6 patients with CMV gastritis.

The average age at diagnosis was 54 ± 17 years. The ratio of male to female patients was 2:1. Abdominal pain was the most frequently reported symptom, occurring in 4 patients. Other symptoms included fatigue (4), nausea (3), vomiting (3), diarrhea (2), fever (2), and weight loss (2). Patient 4 only experienced

Table 1
Demographic, clinical, and laboratory features of 6 patients with cytomegalovirus gastritis.

No	Gender	Age, y	Clinical symptoms	WBC (4–10 $\times 10^9/L$)	Lymphocyte (0.80–4.00 $\times 10^9/L$)	CD4 ⁺ T cells (561–1137 / μ l)	CD38 ⁺ CD8 ⁺ T cells (32.4–57.4%)	IgG (7–17 g/L)	Other system involved	Underlying diseases	Previous usage of corticosteroid or immunosuppressants
Case 1	Female	62	Upper abdominal pain, nausea, vomiting, fever, weight loss, fatigue	2.44	0.68	175	97.80%	11.7	Hematology	NHL (diffuse large B cell type)	None
Case 2	Male	25	Upper abdominal pain, nausea, vomiting, fever, weight loss, fatigue, diarrhea, blurred vision	1.9	0.35	90	93.00%	1.82	Retina, hematology	CVID, PSC	None
Case 3	Male	55	Diarrhea, fatigue	4.32	0.11	NA	NA	7.25	Lung, hematology	DM	Prednisone, CTX
Case 4	Male	76	Fatigue	3.98	0.86	814	59.10%	7.39	None	MPGN	Prednisone, CTX
Case 5	Female	59	Upper abdominal pain	5.65	0.84	418	53.90%	14.29	None	DM	Prednisone, CTX, tacrolimus
Case 6	Male	44	Upper abdominal pain, nausea, vomiting	9.26	2.55	1424	37.90%	11.41	None	None	None

CTX=cyclophosphamide; CVID=common variable immunodeficiency disease; DM=dermatomyositis; IgG=immunoglobulin G; MPGN=membranous proliferative glomerulonephritis; NA=not available; NHL=non-Hodgkin lymphoma; PSC=primary sclerosing cholangitis; WBC=white blood cell.

Table 2
Diagnostic measurements and medications of the 6 cases of cytomegalovirus gastritis.

No.	Serum CMV-IgM	Serum CMV-pp65	Serum CMV-DNA (PCR, copies/ml)	Lesion site of upper gastrointestinal tract	Gastroscopy findings	Inclusion bodies	CMV IHC staining	Medication	Medication duration	Effect	Follow-up gastroscopy findings
Case 1	Positive	Negative	NA	Body, angle, antrum	Multiple irregular deep ulcers 0.5 to 1.5 cm in size	Negative	Positive	Ganciclovir	4 weeks	Partial remission	Improved but not healing
Case 2	NA	NA	30,000	Angle, antrum, duodenum	Multiple irregular superficial ulcers 0.5 cm in size	Negative	Positive	IVIg + Ganciclovir + Foscarnet sodium	6 weeks	Partial remission	Ulcer healing
Case 3	Negative	Negative	600,000	Antrum, esophagus	Multiple oval superficial ulcers 0.5 cm in size	Positive	Positive	IVIg + Ganciclovir	4 weeks	Remission	Ulcer healing
Case 4	Negative	Negative	Negative	Antrum	Multiple oval superficial ulcers 0.5 cm in size	Positive	NA	Ganciclovir	3 weeks	Remission	Ulcer healing
Case 5	Negative	Negative	Negative	Fundus, angle, antrum	Multiple erosions	Positive	Positive	Ganciclovir	4 weeks	Remission	NA
Case 6	Negative	Negative	Negative	Antrum	A large dirty deep ulcer 2 cm × 3 cm in size	Positive	Positive	Ganciclovir	16 weeks	Remission	Ulcer healing

CMV = cytomegalovirus; CMV-pp65 = cytomegalovirus pp65 antigenemia; Ig = immunoglobulin; IHC = immunohistochemistry; IVIG = intravenous immunoglobulin; NA = not available; PCR = polymerase chain reaction.

fatigue and consented to gastroscopy due to a high level of cancer antigen 72-4 (CA72-4). Three patients had disseminated CMV infection, including pneumonia, retinitis, or hypocytosis.

Five patients were immunocompromised with underlying associated diseases as follows: dermatomyositis (2), combined variable immune deficiency (CVID, 1), type I membranoproliferative glomerulonephritis (MPGN) (1), and primary gastric diffuse large B-cell lymphoma (1). Upon the onset of CMV gastritis, 3 patients were still receiving corticosteroid or immunosuppressants.

Four patients had moderate to severe anemia and 3 patients had lymphocytopenia. Four patients had elevated levels of ESR and LDH and 3 patients had increased CRP. The lymphocyte subsets of 5 patients were analyzed. Three patients had decreased CD4⁺ T lymphocyte counts, which were <200/ μ L in patients 1 and 2. Three out of 5 patients had an increased percentage of CD38⁺CD8⁺ T lymphocytes among the CD8⁺ T lymphocytes. Three patients had decreased B lymphocyte counts. For the serum

level of immunoglobulin, only patient 2 with CVID had very low levels of IgG, IgM, and IgA. All patients were negative for HIV, hepatitis B, and hepatitis C on screening.

3.2. Diagnostic measurements and medications of patients with CMV gastritis

The diagnostic measurements (serology CMV test and histopathologic findings), medications, and outcomes of patients are presented in Table 2.

For the serology tests of CMV, only 1 patient out of the 5 tested had positive CMV-IgM, and none had positive CMVpp65 antigen. Two patients had increased copy numbers of peripheral CMV-DNA. In all, 3 of the 6 patients had either positive CMV-IgM or increased copies of CMV-DNA.

Nonspecific abdominal adenopathy was the most common finding in enhanced computerized tomography (CT) scans of the abdomen. Gastric wall thickening was found in 2 patients. Patient 6 had a striking thickness of the gastric antrum wall of >2.0 cm, with hypermetabolic uptake and a standardized uptake value max of 30.45 under positron emission tomography/computed tomography (PET/CT), as shown in Fig. 1. Histopathological examination of >5 repeated biopsies taken by different methods, including endoscopic mucosal resection (EMR) and deep bites, did not find any dysplasia or malignant cells.

Under gastroscopy (Fig. 2), all patients had gastric lesions in the stomach, including ulcers and hyperemia in 5 patients and multiple erosions in 1 patient. Multiple ulcers with irregular or oval shape and variable size from 0.5 to 1.5 cm were observed in 4 patients. Involvement of the gastric antrum could be seen in all patients. Esophageal and duodenal ulcers occurred in patients 3 and 2, respectively. For the histopathologic features (Fig. 3), inclusion bodies were observed in the biopsy samples of 4 patients. All (5/5) patients had positive immunohistochemistry staining using anti-CMV monoclonal antibodies.

All patients received ganciclovir IV as the first line anti-CMV therapy. The dosage is 5 mg/kg every 12 hours for patients with normal renal function and 2.5 mg/kg every 12 hours for patients with renal insufficiency. The duration of anti CMV medication varied from 3 to 16 weeks. Patient 2 also received foscarnet as the combination medication. IVIG was administered to 2 patients.

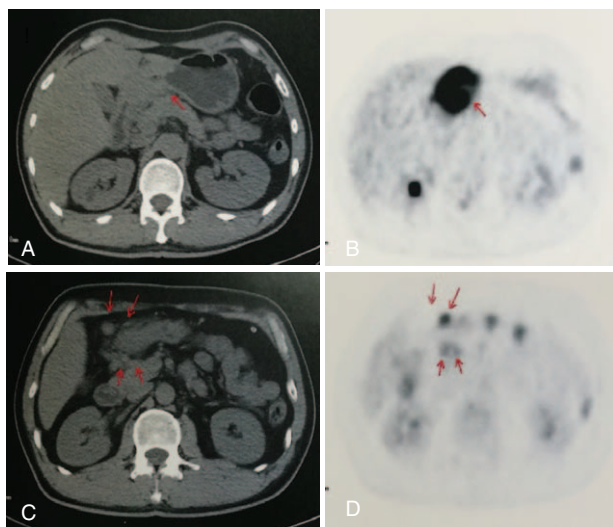


Figure 1. Positron Emission Tomography/Computed Tomography (PET/CT) of Patient 6. PET/CT revealed a thickened antrum wall (A, arrow) by CT scan and hypermetabolic involvement (B, arrow) by PET, respectively; hence, lymphadenopathy was diagnosed (C and D, red arrow).

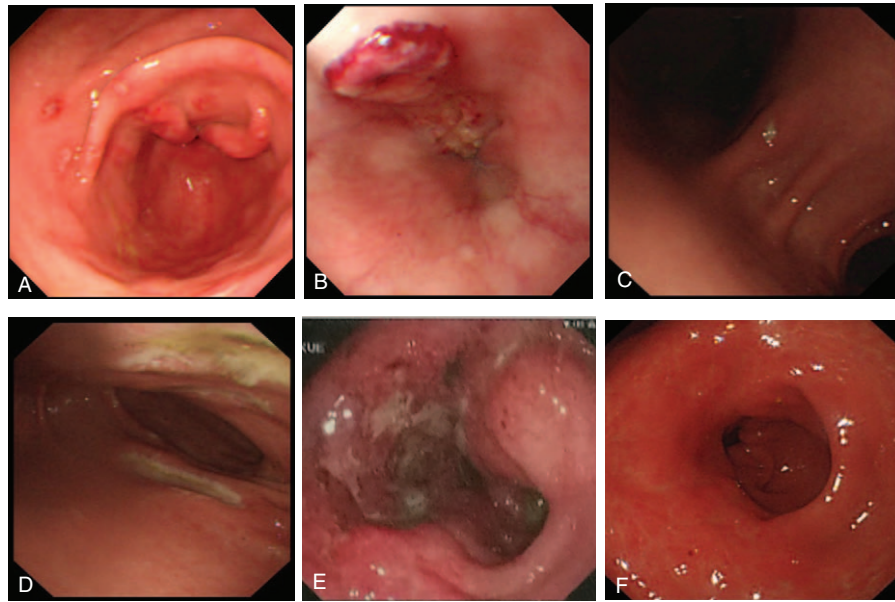


Figure 2. Illustrations of gastroscopic features. (A) Multiple superficial ulcers in the antrum 0.5 cm in size (Patient 3). (B) Irregular deep ulcer in the esophagus (Patient 3). (C) Oval superficial ulcer in the gastric angle (Patient 2). (D) Multiple large ulcers in the duodenum (Patient 2). (E) Large irregular deep ulcer in the gastric antrum (Patient 6). (F) Large ulcer in the gastric antrum and healing after antiviral therapy follow-up (Patient 6).

All patients achieved complete (4/6) or partial remission (2/6) and ulcer healing was observed in 4 out of 5 patients during the follow-up gastroscopies.

4. Discussion

Cytomegalovirus (CMV), a β herpes virus with double-stranded DNA, had a high seroprevalence of 40% to 100% in various populations.^[1] CMV gastritis is a rare and under-diagnosed disease, usually presenting as a co-morbidity of disseminated CMV infection. The prevalence of CMV infection of the upper

gastrointestinal tract has not been determined. To improve the recognition and early diagnosis of CMV gastritis in Chinese patients, this study retrospectively enrolled 6 patients with CMV gastritis. We found that CMV gastritis could be an aspect of disseminated CMV infection and our patients shared many features in common with those of previous studies, including middle-aged onset, male predominance, abdominal pain as the most common symptom, the antrum of stomach as the most frequently involved site, unspecific multiple ulcers in stomach, and resolution following at least 3 weeks of treatment with ganciclovir.^[1,6,10–12]

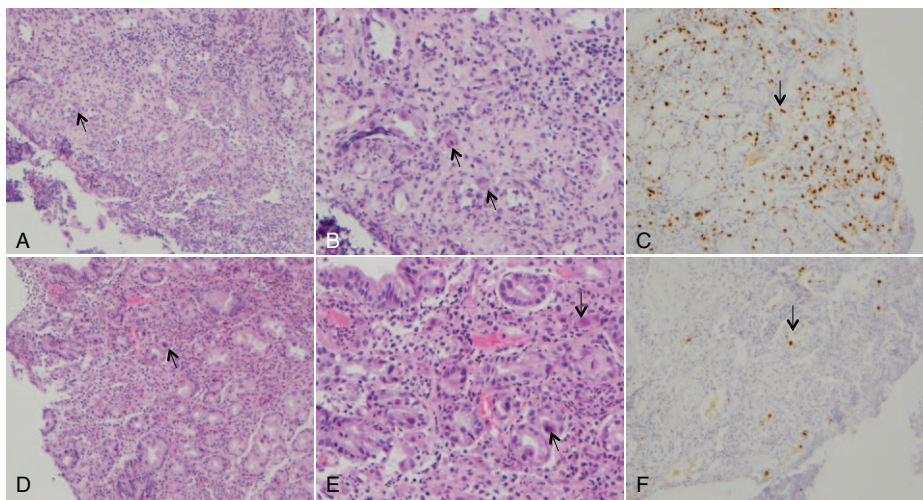


Figure 3. Histopathology of cytomegalovirus (CMV) gastritis in Patient 3. (A) Histological detection of CMV inclusion bodies (arrow), biopsy specimen of a gastric ulcer. Hematoxylin and eosin. $\times 100$. (B) Histological detection of CMV inclusion bodies (arrow), biopsy specimen of a gastric ulcer. Hematoxylin and eosin. $\times 200$. (C) Positive CMV immunohistochemistry (arrow). Biopsy specimen of a gastric ulcer. $\times 100$. (D) Histological detection of CMV inclusion bodies (arrow), biopsy specimen of an esophageal ulcer. Hematoxylin and eosin. $\times 100$. (E) Histological detection of CMV inclusion bodies (arrow), biopsy specimen of an esophageal ulcer. Hematoxylin and eosin. $\times 200$. (F) Positive CMV immunohistochemistry (arrow), biopsy specimen of an esophageal ulcer. $\times 100$.

It is well known that aberrant cell-mediated immunity contributes to the reactivation of CMV infection.^[13,14] Immunosuppressive diseases (acquired immune deficiency syndrome, lymphoma, organ transplantation, or rheumatoid arthritis) or exposure to immunosuppressive agents are the most important triggers for the CMV reactivation. The monitoring of lymphocyte subsets, specifically the number of CD4⁺ T lymphocytes, is crucial for the evaluation of cell-mediated immunity. The consensus on solid organ transplantation recommended that prophylaxis with oral valganciclovir be advocated in HIV-infected patients with a CD4⁺ T cell count <50/mm³ for immunocompromised patients.^[15,16] Beyond the number of CD4⁺ T cells, the increased percentage of activated CD38⁺CD8⁺ T lymphocytes in the total CD8⁺ T lymphocyte population also suggests virus infection. In this study, 3 patients had a decreased number of CD4⁺ T lymphocytes and B lymphocytes and also had an increased percentage of activated CD8⁺ T lymphocytes.

At the same time, CMV gastritis can occur in apparently immunocompetent patients and there is no consensus on the time-point for starting prophylaxis. In one case series study, 4 out of 30 patients with CMV infection with upper gastrointestinal tract involvement were diagnosed as harboring malignant lesions of various organs approximately 5 to 16 months after the histological detection of CMV infection,^[6] which might indicate a potential immune disturbance in these patients. However, the correlation between CMV infection and malignancy is still undetermined.^[17] CMV colitis is known to cause disease flares-ups, increasing the risk of steroid-refractory colitis, which suggests that CMV infection can exacerbate the symptoms or endoscopic appearances of underlying diseases.^[18,19] CMV gastritis could mimic and overlap with gastric malignancy in this study, as shown in patients 1 and 6. Patient 6 was an immunocompetent patient with a large ulcer in the antrum, obviously thickened wall observed under CT scan, and hypermetabolic involvement under PET/CT. EMR and repeated biopsies revealed no malignant cells. The complete remission of symptoms and ulcer healing in the antrum further supported the diagnosis of CMV gastritis without malignancy. Patient 1 experienced a partial improved of symptoms and gastroscopic findings after treatment with ganciclovir; however, repeated biopsies lead to a final diagnosis of non-Hodgkin lymphoma. Therefore, long term follow-ups of immunocompetent patients with CMV gastritis are required to determine whether there is underlying disease, regardless of apparent recovery.

The diagnosis of CMV gastritis should be taken into consideration when immunocompromised patients suffer from epigastric pain and nausea, with diagnosis dependent on gastroscopy and taking biopsies. The diagnostic potential of serum CMV-IgM antibody, antigen, and CMV viral load for CMV gastritis was relatively limited. One Japanese study reported that only 50% of patients with rheumatoid arthritis and CMV infection of the upper gastrointestinal tract had positive CMV antigenemia.^[20] Another cohort study also reported that the sensitivity of the CMV antigenemia assay for the diagnosis of CMV gastrointestinal disease was 54% with 95% confidence interval (41%–68%).^[21] Our study revealed no positive CMV antigenemia in 6 patients, only 1 out of 5 patients with positive CMV-IgM, and 2 out of 5 patients with positive CMV viral load. Thus, CMV gastritis must not be ignored or excluded where patients have no positive CMV antigenemia, IgM antibody, or increased CMV viral load.

There are some limitations of the current study. First, due to the rarity and underestimation, only 6 cases were collected and the small sample size greatly limited the strength of our study, for example, in evaluating the value of serum CMV tests, the epidemiology data, and the risk factors of CMV gastritis. Second, all patients being recruited from 1 center definitely caused a selection bias. Third, some studies involving solid organ transplantation recipients reported that monitoring of CMV specific CD4⁺ T and CD8⁺ T cells might help to identify patients at higher risk of developing CMV reactivation.^[22,23] Unfortunately, we were unable to conduct this test during the study period. Last, CMV gastritis could mimic or overlap with malignant gastric ulcers, but our study failed to reveal further indicators of use in differential diagnosis, limited by the small sample size. Therefore, multicenter prospective studies with larger numbers of CMV gastritis patients would be helpful for clinicians during the differential diagnosis and treatment process in the future.

In clinical practice, CMV gastritis might be an aspect of disseminated CMV infection, and also could be the sole involved site of CMV infection. It might be underestimated or misdiagnosed, especially in compromised patients with abdominal pain and other gastrointestinal symptoms. Although gastroscopy and taking necessary biopsies are invasive procedures, they are still the major diagnostic methods for CMV gastritis up to now. The establishment of novel markers for the monitoring of the immunity status in immunocompromised patients is key for its early diagnosis and prophylaxis.

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