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CASE REPORT | STOMACH

# The Unmasking of Cytomegalovirus as an Accomplice to *Helicobacter pylori*–Induced Severe Acute Gastroenteritis in a Healthy Host

Malek Kreidieh, MD[1], Dhineshreddy Gurala, MD[2], Shivantha Amarnath, MD[2], Jobin Philipose, MD[2], Robert Colef, MD[3], Ahmad Abou Yassine, MD[1], and Vivek Gumaste, MD[2]

[1]*Department of Internal Medicine, Staten Island University Hospital, Northwell Health, Staten Island, NY*
[2]*Division of Gastroenterology, Department of Internal Medicine, Staten Island University Hospital, Northwell Health, Staten Island, NY*
[3]*Department of Pathology, Staten Island University Hospital, Northwell Health, Staten Island, NY*

## ABSTRACT

Cytomegalovirus (CMV) belongs to the *Herpesviridae* family, and it is considered the largest virus to infect humans. Primary CMV infection frequently targets immunodeficient patients and is often symptomatic. However, it may remain latent or clinically unapparent for years in immunocompetent individuals. CMV infection rarely presents as an invasive disease in the latter group of individuals, in which case, the most common site of involvement in the gastrointestinal tract. When CMV affects the gastrointestinal tract, the colon and stomach are the 2 frequently involved sites. This case report describes a unique case of an immunocompetent patient who presented with acute excruciating periumbilical pain and was diagnosed with acute gastritis secondary to CMV infection and possible *Helicobacter pylori*–associated chronic active gastritis. Symptoms resolved entirely soon after treatment with antimicrobials that cover for both infections. The diagnosis was based on histopathologic findings from biopsies taken from the stomach during the endoscopic evaluation combined with positive CMV serology and positive CMV-deoxyribonucleic acid.

**KEYWORDS:** cytomegalovirus; helicobacter pylori; gastritis; primary infection; endoscopy; immunocompetent

## INTRODUCTION

Cytomegalovirus (CMV) belongs to the *Herpesviridae* family and the β-herpesvirinae subfamily. Owing to its 235-kilobase genome of double-stranded deoxyribonucleic acid (DNA), this enveloped herpes virus is considered the largest virus to infect humans.[1] In immunodeficient patients, such as those with a history of allograft transplants, cancer, or acquired immunodeficiency syndrome, and those receiving long-term immunosuppressive therapy, the manifestations of primary CMV infection might be severe, with the involvement of multiple organ systems, including the gastrointestinal and central nervous systems. By contrast, immunocompetent individuals have a less dramatic presentation due to CMV infection, where patients are often asymptomatic, and infection is often undiagnosed. However, it can also present as a viral infection or a mononucleosis-like syndrome.[2,3] Invasive disease with gastrointestinal involvement is rare in primary CMV infection, with only a few cases reported in the literature.[4,5]

After the resolution of the primary infection, CMV can persist in its human host for years. This is made possible by a myriad of immune evasion molecules that the virus encodes, enabling it to remain dormant in its host's myeloid cells and stem cells for life.[6,7] In immunocompromised hosts, the risk of CMV reactivation is high.[8,9] In immunocompetent individuals, a history of cirrhosis or exposure to severe trauma, burns, or shock can trigger reactivation resulting in severe morbidity. Organ damage is usually manifested by neurological, hematological, cardiac, ocular, or even gastrointestinal involvement.[2,5,10] Although invasive disease with gastric involvement can rarely occur with primary CMV infection in immunocompetent individuals, it has been more commonly reported in settings of reactivation in this group.[11]

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**Correspondence:** Malek Kreidieh, MD (mkreidieh@northwell.edu).

This case report describes a rare case of an immunocompetent patient who presented with acutely worsening periumbilical pain and was diagnosed with acute gastritis secondary to CMV infection and possible *Helicobacter pylori*–associated chronic active gastritis. The diagnosis was based on histologic findings from biopsies taken from the stomach during endoscopic evaluation.

## CASE REPORT

A 42-year-old previously healthy man not on any medications presented to the emergency department for severe, sharp periumbilical pain radiating to his right flank for 2 days associated with nausea, nonbilious nonbloody vomiting, reduced oral intake, and watery diarrhea. He denied the use of tobacco, alcohol, and any illicit drugs. His social history was unremarkable, and he had 1 sexual partner. He had no significant family history of autoimmune illness, malignancies, or human immunodeficiency virus. His vital signs were within normal limits at the time of presentation, except for a heart rate of 102 beats per minute. On examination, he had a soft abdomen with epigastric tenderness in the absence of guarding, rebound tenderness, or a palpable mass. Murphy, Psoas, and McBurney signs were all negative. He had no palpable cervical lymphadenopathy or pharyngeal erythema or exudates. The remainder of the physical examination was unremarkable. Laboratory tests at the time of presentation revealed a white blood cell count of 6.05 (normal = 4.5–11 $\times$ $10^9$/L), a hemoglobin of 15.2 g/dL (normal = 12.0–16.0 g/dL), and a platelet count of 236 K/uL (normal = 150–400 K/uL). Other laboratory parameters, including serum electrolytes, renal function, and liver function tests, were within normal limits.

A computed tomography scan of the abdomen and pelvis with intravenous contrast demonstrated increased gastric mucosal enhancement with mild mucosal edema suggestive of acute gastritis. The pancreas, spleen, liver, and gall bladder were otherwise unremarkable. The patient was started on a trial of intravenous pantoprazole with no improvement. Subsequently, an esophagogastroduodenoscopy was performed. It was notable for erosions along the stomach mucosa suggestive of severe erosive gastritis with prominent erythematous and edematous gastric folds (Figure 1). Multiple cold forceps biopsies were performed for histology. The remainder of the endoscopic evaluation was unremarkable. On histopathologic evaluation, the fragments of gastric mucosa from the antrum and body showed evidence of chronic active gastritis, with significant infiltration of neutrophils and lymphocytes into the lamina propria, as noted by Figure 2. No intestinal metaplasia or atrophy that would be indicative of severe or long-standing *H. pylori* infection was seen. Although chronic active gastritis is usually associated with *H. pylori*, the immunostains were negative for the bacteria in our case. Remarkably, the histological specimens demonstrated few epithelial nuclear viro-cytopathologic changes suggestive of CMV (Figure 3). Subsequently, CMV IgM, CMV IgG, and CMV polymerase chain reaction (PCR) were elevated at 97.8 AU/mL (n = 0–29.9 AU/mL), 3.10 AU/mL (n < 6 U/mL), and 11,200 IU/mL, respectively, favoring the diagnosis of acute primary CMV gastritis and ruled out CMV reactivation. Since the patient could not tolerate any oral intake with persistent nausea and vomiting, he was started on peripheral parenteral nutrition with lipid injectible emulsion 20% infusion for 7 days. By the time the CMV results were back and the infectious disease team was contacted, he was started on intravenous ganciclovir 420 mg twice daily. We noticed a marked improvement in symptoms a few days later. His peripheral parenteral nutrition was discontinued, and he was able to tolerate oral intake on day 8 of admission.

He was then discharged on day 9 of admission on oral valganciclovir 900 mg orally twice daily for 2 weeks, along with quadruple therapy to cover for *H. pylori*. He was asked to follow-up as an outpatient to evaluate his response to the prescribed treatments further. Unfortunately, however, the patient was lost to follow-up, and no repeat esophagogastroduodenoscopy was performed.

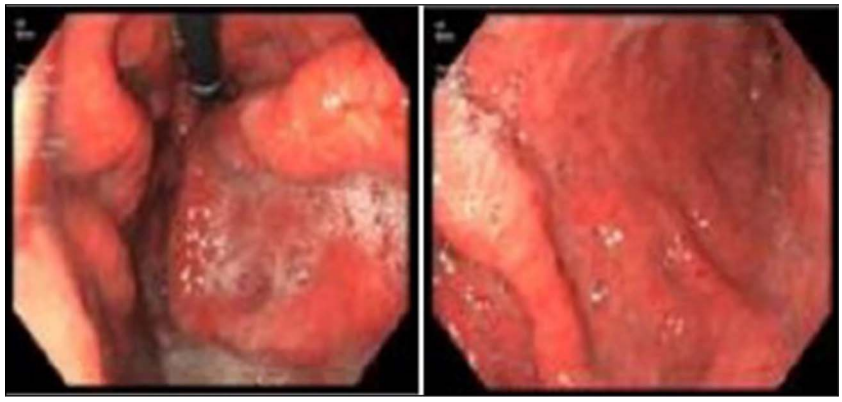

**Figure 1.** Endoscopic images of the gastric fundus (left), cardia (right), and gastric body (right) demonstrating severe erosive gastritis with prominent erythematous and edematous gastric folds.

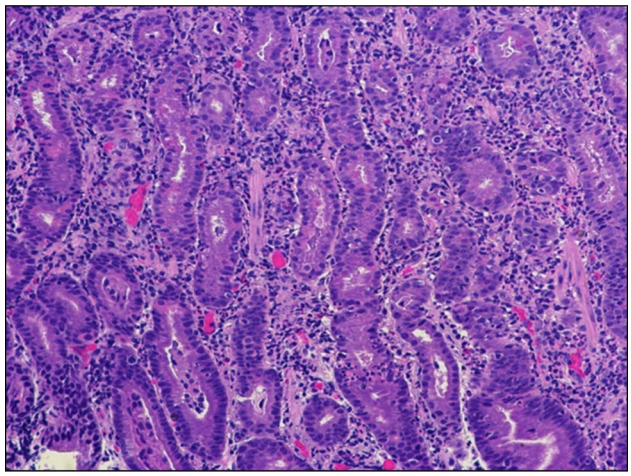

**Figure 2.** Histopathologic findings from gastric biopsies: Fragments of gastric mucosa from the antrum showing significant neutrophil and lymphocyte infiltration into the lamina propria.

## DISCUSSION

Primary CMV infection in immunodeficient patients is usually symptomatic. It may remain latent or clinically unapparent for years in immunocompetent individuals. When infection is clinically significant in immunocompetent patients, the typical presentation is that of a viral infection or mononucleosis-like syndrome.[2,3] Manifestations are nonspecific and include fever, epigastric discomfort, anorexia, nausea, vomiting, constipation, diarrhea, and a skin rash.[2,12,13] Although our patient was immunocompetent, his infection did not remain clinically insignificant. He presented with severe sharp epigastric pain radiating to the right upper and lower quadrants associated with nonbilious nonprojectile nonbloody vomitus, nonbloody nonmucoid watery diarrhea, and reduced oral intake.

It is rare for primary CMV infection to present as an invasive disease in healthy individuals as this is a consequence of reactivation in this group of people. When reactivation occurs, the most common site of involvement is the gastrointestinal tract, followed by the hematopoietic cells and central nervous system, and less commonly, the ocular, hepatologic, and pulmonary system.[10] The colon and stomach are the 2 most commonly involved sites.[14] The mechanism through which CMV infects the gastric mucosa remains unclear. However, it is postulated that the virus results in a transient elevation in transforming growth factor-alpha levels. This factor, in turn, binds and stimulates epidermal growth factor receptors located on gastric mucosal cell surfaces. This culminates in ameliorating gastric mucosal cell proliferation, mucus secretion, hypertrophic gastropathy, and vascular permeability secondary to cytomegalic vasculitis and leakage of proteins.[15–17]

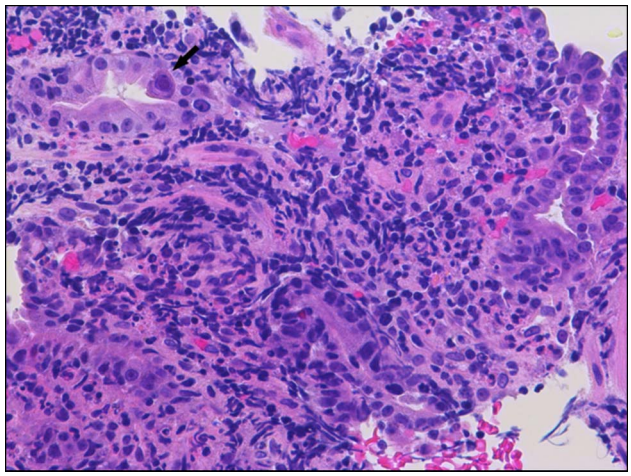

**Figure 3.** Histopathologic findings from gastric biopsies: Fragments of mucosa from the antrum showing evidence of cytomegalovirus inclusion body.

The stromal and epithelial cells are most commonly infected when the stomach is involved. Our patient was among the rare immunocompetent cases with a primary CMV infection with stomach involvement. The CMV detection by PCR, the positive CMV IgM serologic testing, and the negative CMV IgG serologic testing suggest the diagnosis of acute primary CMV infection rather than CMV reactivation. Combining the results of these serum tests with the epithelial nuclear viro-cytopathologic changes noted on histopathologic evaluation of gastric tissue biopsies favor the diagnosis of primary CMV gastritis.

Gastrointestinal involvement in CMV infection can result in a wide range of nonspecific and variable endoscopic abnormalities, ranging from patchy erythematous lesions, exudates, or microerosions to diffusely edematous mucosa, deep and round ulcerations, and pseudotumors.[18,19] CMV gastric ulcers are difficult to differentiate from *H. pylori* and nonsteroidal anti-inflammatory drug-related ulcers.[20] Although hyperemia, erythema, erosions, and ulcers are among the most common findings in CMV gastritis, inflammatory pseudopolyps, rugal hypertrophy, and diffuse edema with thickened gastric folds are less frequent findings.[21,22] Data from a recent case series describing the endoscopic and histological findings of the upper gastrointestinal tract in confirmed CMV infections among 30 immunodeficient and immunocompetent patients suggest that the lesions are usually restricted to one organ. The antropyloric portion of the stomach was noted to be the most frequently affected area, followed by the cardia, the lower esophagus, and the duodenum.[23] Interestingly, the stomach in our patient was diffusely involved. The endoscopic findings included both erosions and erythematous lesions throughout the whole mucosa and the less commonly reported edematous gastric folds. Our patient's detection of intranuclear inclusions was also a hallmark of CMV infection, which is not always present.

In the setting of the nonspecificity of endoscopic findings, the diagnosis of CMV gastritis is usually based on a combination of clinical findings, characteristic histopathological features, viral isolation by DNA amplification, or immunohistochemical analysis. When it comes to histopathology, evidence of foveolar hyperplasia, lymphoplasmacytic infiltrates, and eosinophilic owl-eye inclusions usually exist. It is important to note that

microscopic examination can miss the inclusion bodies on routine hematoxylin–eosin stains as CMV can infect vascular endothelium or stromal cells in the connective tissue under ulcers.[5,15] To improve the sensitivity of endoscopic findings in diagnosing CMV infection, the recommendation is to combine it with other techniques, including quantitative PCR or in situ DNA hybridization for CMV DNA or immunohistochemistry for CMV antigens in blood or gastric tissue.[24–26] CMV serology can also be checked, and this would help distinguish a primary infection in seronegative patients from CMV reactivation in seropositive ones. In our patient, the presence of hypertrophic gastric folds on esophagogastroduodenoscopy combined with the few epithelial nuclear viro-cytopathologic changes noted on histopathologic findings, the positive CMV IgM but not IgG serology, and the positive CMV-DNA by PCR helped in making the diagnosis of primary CMV gastritis. Of note, however, CMV-DNA by PCR was not checked in the biopsies taken from our patient's gastric tissue.

Although it is recommended to treat patients with CMV infections involving the central nervous system, the ocular system, or the pulmonary system with antiviral therapeutic agents,[10] there are no current guidelines that recommend the initiation of antivirals to treat CMV gastritis in healthy individuals. Owing to its self-limited clinical course, CMV gastritis should be treated conservatively in the immunocompetent host.[2] Owing to the severity of our patient's presenting symptoms leading to a marked reduction in oral intake and initiation of peripheral parenteral nutrition, we opted to start the patient on intravenous ganciclovir as in-patient and oral valganciclovir on an outpatient basis to treat his primary CMV gastritis. Nevertheless, future studies are needed to better evaluate the risks and benefits of treating primary CMV infection in immunocompetent patients.

Since CMV infection with gastrointestinal involvement is more common in immunocompromised patients than in immunocompetent ones, physicians must search for an underlying condition, such as malignancy, a lymphoma, an autoimmune disease, or another sort of an immunodeficiency, when dealing with a diagnosis of intestinal CMV infection in a previously healthy individual. For instance, in 1 study, 4 of 11 immunocompetent patients diagnosed with gastrointestinal CMV infection were found to have a malignant tumor.[19]

Whether coinfection of CMV with *H. pylori* occurred and whether it was purely coincidental remain unknown. As previously mentioned, although histopathologic findings revealed evidence of chronic active gastritis in the gastric antrum and body, the *H. pylori* bacteria were missing from the biopsies and immunostains were negative. In other words, our case may just represent an infection with a low bacterial load. Possible explanations for this include the use of proton pump inhibitors, which has been shown to lower the bacterial density and shift their populations from the stomach antrum to the corpus.[27] Alternatively, the recent use of antibiotics may suppress the infection but not reduce the inflammation.[28] In addition, sampling error is another possibility, and this refers to the biopsied region not capturing any organisms.[29] In our case, we prescribed quadruple therapy to cover for the *H. pylori* bacterium. There are several case reports on the coexistence of CMV and *H. pylori* infections in pediatric patients with Menetrier disease.[16,30]

Interestingly, some evidence sheds light on the possibility that the addition of chronic inflammation from CMV infection to *H. pylori*–induced gastritis can facilitate the development of gastric cancer.[31] For instance, in a study by Moral-Hernández et al, the prevalence of *H. pylori* infection in chronic gastritis was 48.1%, and that of CMV infection was 52.8%.[32] Since chronic inflammation is a risk factor for malignancy and since CMV infection has been implicated in 53.1% of gastric cancer cases, it can be assumed that CMV infection induces chronic gastritis and may be etiologically related to gastric carcinogenesis as a single infection or in synergy with *H. pylori*. This has been supported by evidence from a recent meta-analysis that demonstrated an association between human CMV infection and gastrointestinal cancer.[33] Therefore, it is essential to test for CMV and *H. pylori* infections and to treat them when suspected, as missing such infections might predispose patients to an increased risk of malignancy.

In conclusion, we described a rare case of an immunocompetent patient with remarkable epigastric pain and reduced oral intake diagnosed with acute gastritis secondary to CMV infection whose diagnosis was made based on histologic findings from biopsies taken from the stomach during endoscopic evaluation combined with positive CMV serology and positive CMV-DNA. Successful treatment of the CMV infection combined with the quadruple therapy to cover for the *H. pylori* bacterium led to a notable improvement in the patient's symptoms.

## DISCLOSURES

Author contributions: M. Kreidieh wrote manuscript. D. Gurala, S. Amarnath, J. Philipose, and V. Gumaste reviewed manuscript and suggested some edits. AA Yassine helped in editing the manuscript. R. Colef: provided pathology slides and description of pathology report. Article guarantor: Malek Kreidieh.

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