

Cytomegalovirus esophagitis associated with gastroesophageal reflux disease in an immunocompetent patient: case report

Cesar Romaro Pozzobon ^{1, 2, *}, Fernanda Manhães Pozzobon ^{1, 3}, Geysa Bigi Maya Monteiro ⁴, Eduardo Madeira ^{1, 2}, Maria Chiara Chindamo ^{1, 5}

¹ Rede D'or São Luiz, Barra D'Or Hospital, Rio de Janeiro, Brazil.

² Federal University of Rio de Janeiro (UFRJ), Worker's Health Care Superintendence, Rio de Janeiro, Brazil.

³ Fluminense Federal University (UFF), Health Assistance Division, Niterói, RJ, Brazil.

⁴ Rede D'or São Luiz, Quinta D'Or Hospital, Anatomical Pathology Department, Rio de Janeiro, Brazil.

⁵ Federal University of Rio de Janeiro (UFRJ), Hepatology Department, Rio de Janeiro, Brazil.

* Correspondence: crpozzobon@me.com.

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Abstract: Cytomegalovirus infection has a wide variability of clinical presentations depending on the patient's immunity, ranging from asymptomatic infections in immunocompetent individuals to infections with significant morbidity and mortality in immunocompromised patients. We originally described a clinical case of severe cytomegalovirus esophagitis, confirmed by blood polymerase chain reaction (PCR) test and esophageal biopsy, in a young immunocompetent patient with a long-standing diagnosis of gastroesophageal reflux disease. Clinical improvement occurred only after the initiation of specific treatment with ganciclovir, providing a negative viral load. This report reinforces the importance of ruling out the etiology of cytomegalovirus infection in severe ulcerative esophagitis, even in immunocompetent individuals.

Keywords: Infectious esophagitis; Cytomegalovirus; Immunocompetent; Ganciclovir; Ulcerative esophagitis.



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1. Introduction

The spectrum of disease caused by cytomegalovirus (CMV) is diverse and mostly dependent on the host immunity. Immunocompromised individuals, such as those infected with the human immunodeficiency virus (HIV), patients with congenital or acquired immunodeficiency, active malignancy, immunosuppressive cytopenia, recent use of systemic steroids or chemotherapy, and organ transplant recipients, can present substantial morbidity and mortality associated with CMV infection ①②. Many organs including the eyes, esophagus, stomach, and colon can be affected. Esophagitis is the second most common gastrointestinal manifestation of CMV disease, after colitis ②③.

In immunocompetent patients, cytomegalovirus infection can present itself in four different ways. Asymptomatic infection is the most common, and the diagnosis is made retrospectively through serology. Congenital infection is the second form of presentation and can occur in 0.5 to 2 % of births, however with only 10% of cases being symptomatic. The third form occurs with contamination after blood transfusion or heart surgery with cardiopulmonary bypass, but only 4 % develop symptomatic disease. Finally, cytomegalovirus infection can have features of a mononucleosis syndrome with or without involvement of other organs, including the heart, lungs, bloodstream, skin, digestive tract, or central nervous system ①④.

Our interest was in the involvement of the digestive tract in immunocompetent patients. Although previously recognized as a rare condition, gastrointestinal involvement by CMV in immunocompetent patients has currently been reported. It may present as gastroenteritis, duodenitis, ileitis, colitis, proctitis or exacerbation of inflammatory bowel disease [3-6]. A few studies have described CMV infection in immunocompetent patients diagnosed with a critical illness [7, 8]. However, CMV esophagitis has rarely been documented in immunocompetent hosts [9, 10].

We report the case of a healthy woman with long-standing gastroesophageal reflux disease who presented with severe epigastric pain and fever diagnosed as CMV esophagitis.

2. Case Report

A 21-year-old Brazilian white woman, pharmacy student, previously healthy, with no relevant medical history, without previous use of medication, including anti-inflammatories or corticoids, with normal eating habits and who denied the use of alcohol or tobacco, diagnosed with gastroesophageal reflux disease (GERD), peptic esophagitis and slipping hiatal hernia for five years, was hospitalized due to severe epigastric pain. She reported the onset of symptoms three weeks earlier, complaining of epigastric pain radiating to the back and retrosternal region, nausea and lack of appetite. Two weeks before hospitalization she presented a low-grade fever and worsening of epigastric discomfort, with no relief using proton pump inhibitor (PPI). She denied weight loss, diarrhea, skin lesions, oral or genital aphthae, headache, and visual changes.

On physical examination at hospital admission, she had no evidence of anemia or jaundice, was hydrated, acyanotic, eupneic with stable vital signs. There was no evidence of oral lesions as well as lymphadenomegaly. Her abdomen was depressible, but with intense pain on superficial and deep palpation of the epigastric region. Intravenous morphine was needed for pain relief.

Admission tests showed normal levels of hemoglobin, hematocrit, leukocytes, platelets, aminotransferases, and C-reactive protein. D-dimer levels were elevated (6000 mcg/mL), which motivated the performance of computed tomography (CT) pulmonary and abdominal angiography, both exams with normal results. Lower limb doppler ultrasound was also negative for deep venous thrombosis. Abdominal ultrasound did not reveal cholelithiasis but identified an enlarged spleen (14 cm). During hospitalization she underwent upper digestive endoscopy which revealed circumferential, shallow, flat-edged, fibrinous ulceration located just above the esophagogastric junction associated with a large hiatal hernia (Figure 1).

Biopsies were not performed at this time due to the friability of the lesion and presumptive diagnosis of peptic esophagitis. Therapy with full dose of intravenous PPI, prokinetics and sucralfate was started. Despite the initial treatment, there was no clinical improvement. Empirical intravenous acyclovir was started due to the suspicion of esophagitis caused by herpes simplex virus. Serology for cytomegalovirus (Electrochemiluminescence immunoassay, COBAS 8000), herpes simplex virus 1 and 2 (HSV-1 and HSV-2, Chemiluminescence, MAGLUMI), Epstein Barr Virus (Chemiluminescence, Immulite 2000, SIEMENS), HIV (Chemiluminescence, ADVIA Centauro, SIEMENS), hepatitis B (Chemiluminescence immunoassay, ADVIA Centauro, SIEMENS) and hepatitis C (Indirect immunoassay, ADVIA Centauro, SIEMENS) were collected, in addition to quantitative CMV PCR (Abbott Real Time CMV) and anti-saccharomyces cerevisiae (Enzyme immunoassay, EUROIMMUN) and anti-cytoplasmic antibodies C and P (Indirect immunofluorescence, Sprinter XL, EUROIMMUN), for the investigation of inflammatory bowel disease.

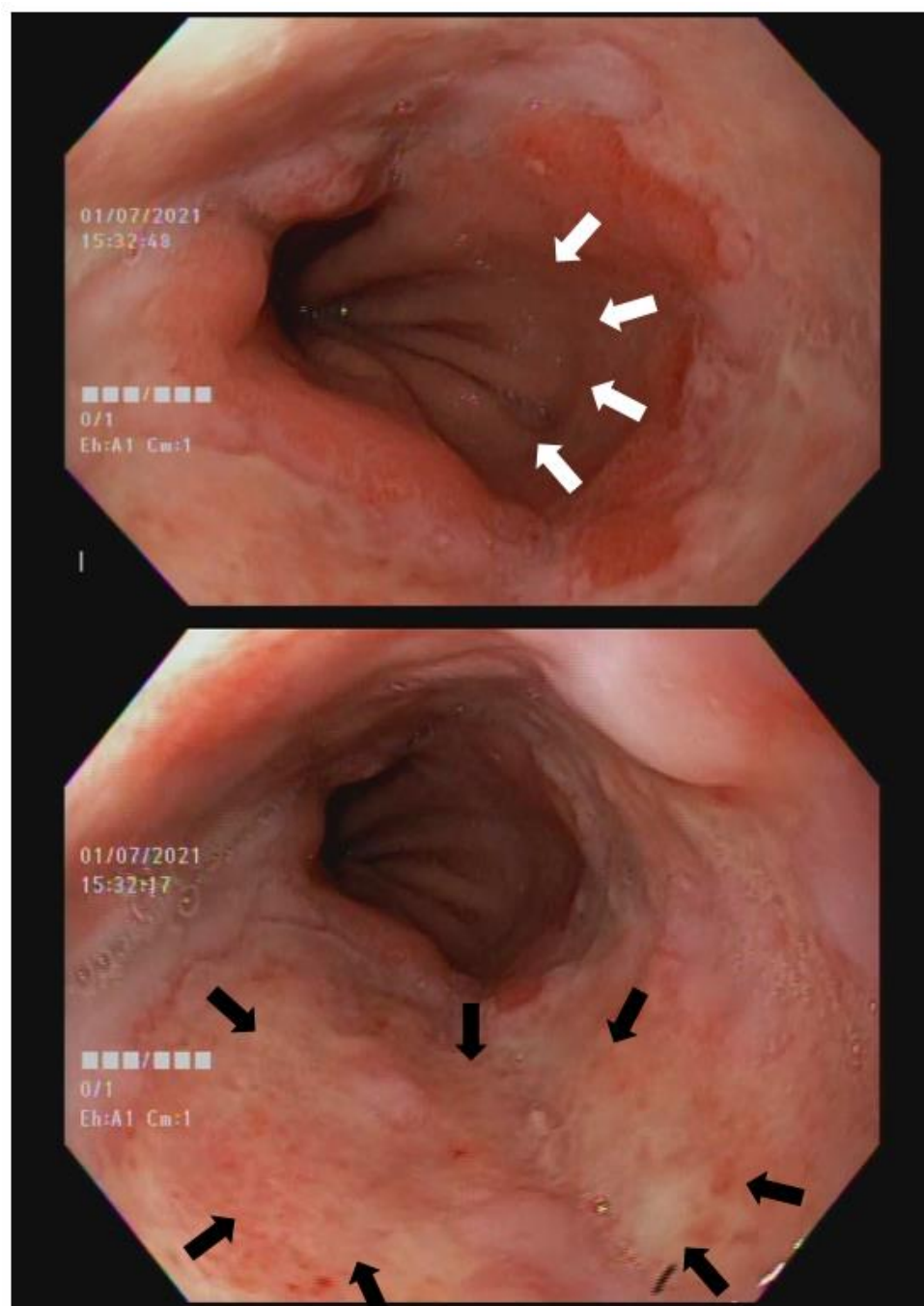


Figure 1: Circumferential ulcerated esophagitis (black arrow) associated with hiatal hernia (white arrow).

After 3 days of parenteral Acyclovir use, the quantitative CMV PCR result was 1188 copies/mL. IgG and IgM serology for CMV resulted positive, demonstrating low avidity for IgG. All other serologies resulted negative. The dosage of immunoglobulins A, M and G were normal as well as CD4 lymphocyte count. All tests performed for diagnostic investigation can be better visualized in Table 1 bellow. At this time, acyclovir was discontinued, and the patient underwent a new upper digestive endoscopy with biopsies. Because of a low food intake and a high nutritional risk, a peripherally inserted central catheter was punctured to start parenteral nutrition. Intravenous Ganciclovir was started at a dose of 5mg/kg bid.

Table 1: Diagnostic tests during investigation and results.

Diagnostic exams	Results
Complete blood count	Normal
Aminotransferases	Normal
C-reactive protein	Normal
D-dimer	6000 mcg / mL (high)
CT pulmonary and abdominal angiography	Normal
Lower limb doppler ultrasound	Normal
Abdominal ultrasound	Enlarged spleen (14 cm)
IgG and IgM serology for CMV	Positive
IgG and IgM serology for HSV-1 and HSV-2	Negative
IgG and IgM serology for Epstein Barr Virus	Negative
Quantitative CMV PCR	1188 copies / mL
Anti-saccharomyces cerevisiae antibodies	Negative
Anti-cytoplasmic antibodies C and P	Negative
Immunoglobulins A, M and G	Normal
CD4 lymphocyte count	Normal
Test for Helicobacter pylori on biopsy	Negative
Histopathological analysis	Cytomegalic inclusion
Immunohistochemistry	CCH2 positive

CT: computed tomography; CMV: cytomegalovirus; HSV-1 and HSV-2: herpes simplex virus 1 and 2; IgG and IgM: immunoglobulins G and M; PCR: polymerase chain reaction.

The histopathological analysis revealed extensive ulcerated esophagitis, with intense mixed and dense inflammatory infiltrate involving the mucosal and submucosal layers and granulation tissue, showing endothelial cell with cytomegalic inclusion. The test for *Helicobacter pylori* was negative. Immunohistochemistry demonstrated CCH2 positive and DDG9 negative antibody in the cells of interest (Dako-Agilent method) confirming CMV infection, with negative 10A3 and polyclonal (Ventana-Roche and Novus Biologicals methods respectively), ruling out the diagnosis of HSV-1 and HSV-2 infection (Figure 2).

After 2 weeks of treatment with Ganciclovir, she presented symptomatic improvement with progressively reintroduction of oral feeding. The sequential quantitative CMV PCR resulted negative. The patient was discharged using a PPI with a new upper digestive endoscopy scheduled within 3 months and was referred to further evaluation for surgical treatment of slipping hiatal hernia. The patient was followed up for 1 year and showed no clinical or endoscopic evidence of recurrence of CMV esophagitis.

3. Discussion

CMV infections in immunocompetent patients often present as asymptomatic infection, mononucleosis like syndrome or self-limited conditions. Severe cases of CMV infection in immunocompetent individuals were reported in 1.7%-5.2% of cases, with a mortality rate of 6% [5, 11].

In a systematic review of severe CMV infections in immunocompetent patients, the most affected site was the gastrointestinal tract (30% of the cases), classified as gastroenteritis, duodenitis, ileitis, colitis, proctitis, or exacerbation of inflammatory bowel disease [3, 5]. The second most frequent manifestation was related to central nervous system symptoms, followed by hematological disorders [5].

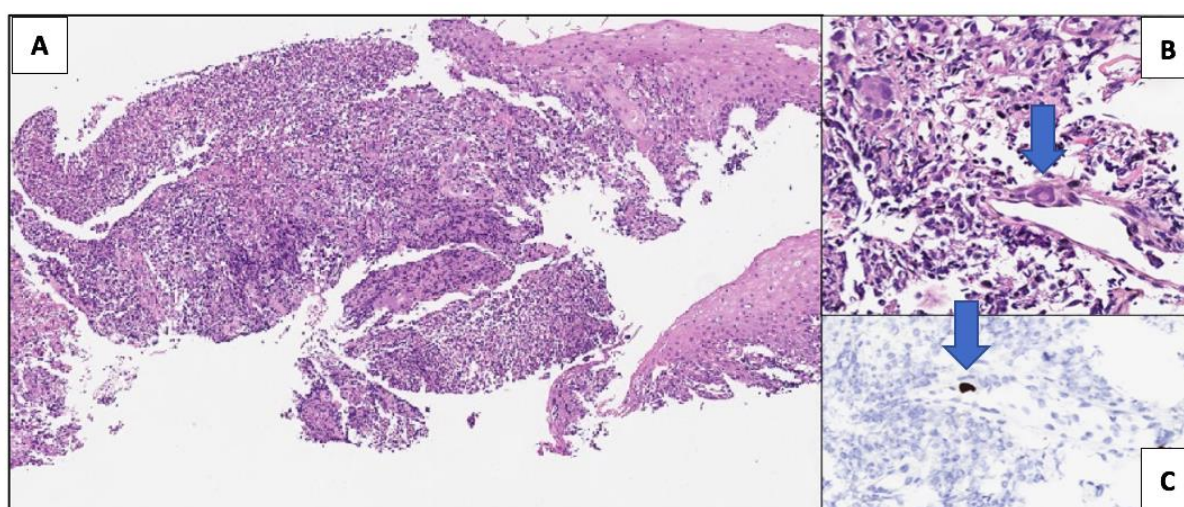


Figure 2. Histopathological analysis findings. Esophageal biopsy: A - Intense, ulcerated esophagitis associated with cytomegalovirus infection (40x H&E); B and C - Detail of the endothelial cell with cytomegalic inclusion (400x H&E), enhanced by immunohistochemistry (400x CMV).

Severe CMV esophagitis has rarely been reported in immunocompetent patients [9-10]. As a result, other conditions that could affect cellular and humoral immunity were also investigated. Immuno-electrophoresis was normal as well as the CD4 lymphocyte count. The preexisting history of gastroesophageal reflux disease with severe esophagitis could represent a predisposing factor in this case, which has not yet been reported.

Endoscopic findings can be variable in CMV esophagitis. The typical findings of CMV esophagitis in immunosuppressed patients are non-circumferential, deep ulcers with raised edges found in distal esophagus [12]. Additionally, ulcers tend to be linear or longitudinal in shape. In the presented case, the finding of circumferential, shallow, flat-edged, fibrinous ulceration located just above the esophagogastric junction and associated with a large hiatal hernia made the diagnosis of reflux esophagitis more likely. The refractoriness and intensity of pain, despite the use of a PPI, and the presence of fever at the beginning of the disease led to the suspicion of an infectious cause. For these reasons, biopsy of ulcers or erosions is essential for the proper diagnosis of the etiology of esophagitis [13].

The diagnosis of CMV infection was corroborated by the presence of CMV IgM and IgG antibodies. The low avidity of IgG suggests the presence of recent infection, confirmed by the detection of CMV DNA with a high viral load in the blood and typical findings in histopathological analysis.

The need for specific antiviral therapy in immunocompetent patients with severe infections is controversial since any presumed benefit of specific treatment should be weighed against its potential toxicity [5]. The decision to start treatment, in this patient, was based on the high viral load, the refractoriness of symptoms and the evidence of tissue invasion on biopsy. After the start of treatment, there was a total improvement of symptoms within 48 hours, with a negative viral load achieved within 14 days.

5. Conclusions

We report a case of severe CMV esophagitis in an immunocompetent patient who presented epigastralgia and low-grade fever, successfully treated with Ganciclovir. Our case corroborates the observations that CMV esophagitis can cause significant morbidity even in immunocompetent patients and reinforces the importance of ruling out this infectious etiology in the context of ulcerative esophagitis. A preexisting history of severe gastroesophageal reflux disease may represent a predisposing factor for CMV esophagitis.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki

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Conflicts of Interest: None.

Supplementary Materials: None.

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