Massive alimentary tract bleeding due to cytomegalovirus infection in an elderly patient

Bora Koc,[1] Huseyin Yuce Bircan,[1] Semsi Altaner,[2] Ozlem Cinar,[3] Umit Ozcelik,[1] Alpaslan Yavuz,[4] Ozgur Kemik[5]

[1]Department of Surgery, [2]Department of Pathology, [3]Department of Anesthesia, Intensive Care Unit, Faculty of Medicine, Baskent University, Istanbul Research Hospital; [4]Department of Radiology, [5]Department of General Surgery, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey

Abstract

In recent years, cytomegalovirus (CMV) has been recognized as an important common pathogen in immunocompromized patients. This is due to the increasing number of immunosuppressive medications, intensive cancer chemotherapy use, recurrent transplantations, progressively aging population, and the higher number of human immunodeficiency virus infections. Cytomegalovirus infection especially interests the gastrointestinal tract, anywhere, from the mouth to the anus. Namely, the most commonly affected area is the colon, followed by duodenum, stomach, esophagus and small intestine. The most frequent manifestations of CMV colitis are: diarrhea, fever, gastrointestinal bleeding and abdominal pain. We report here the case of an 82-year-old woman, who was treated for non-Hodgkin lymphoma; she was admitted to the emergency department for abdominal pain and diffuse arthralgia, following massive upper- and lower- gastrointestinal bleeding, due to duodenal and colonic ulcers related to CMV infection.

Introduction

Cytomegalovirus (CMV) infections are commonly reported in severely immunocompromized patients, including those with acquired immunodeficiency syndrome and patients who have received immunosuppressive therapy after transplantation or chemotherapy for malignant disease.[1] CMV is a ubiquitous member of the herpes virus family and is a DNA virus. More than 90% of healthy adults are seropositive for CMV. Primary CMV infection in immunocompetent people is usually asymptomatic.[1-3]

The alimentary tract is the target organ of CMV infection, which may affect the gastrointestinal tract anywhere from the mouth to the anus. The most commonly affected site is the colon, followed by the duodenum, stomach, esophagus and small intestine.[1,3] Esophagitis, gastritis, duodenitis and enterocolitis are induced by CMV infection in the gastrointestinal tract.[4] Many reports show that CMV infection can cause colitis, ulcers, and, very rarely, pseudopolyps, pseudomembranes and even mass lesions.[5-7] The most common manifestations of CMV colitis are diarrhea, fever, gastrointestinal bleeding and abdominal pain.[7,8] We report a case of massive upper and lower gastrointestinal bleeding due to CMV-related duodenal and colonic ulcers in an elderly patient treated for non-Hodgkin lymphoma.

Case Report

An 82-year-old Turkish woman was admitted to the emergency department for widespread abdominal pain, diffuse arthralgia, dyspnea and weakness in the upper and lower limbs. She was treated with immunosuppressive drugs for non-Hodgkin lymphoma (diffuse B-cell lymphoma) six months beforehand.

According to the protocol for non-Hodgkin lymphoma, she was given a course of systemic chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin and vincristine. After the end of the chemotherapy, she underwent a remission period.

Additionally, she was chronically treated for

Parkinson disease, diabetes mellitus, hypertension and hypercholesterolemia. Her current medications were gliclazide, metformin, simvastatin, levodopa and losartan. She didn't receive antiplatelet or anticoagulant therapy prior to admission. Her pain was resistant to painkillers, including non-steroid anti-inflammatory drugs and morphine derivatives.

Initial physical examination revealed mild abdominal discomfort, anorexia, nausea and absence of fever. Bilateral crepitant rales were found at lung auscultation. An examination of the abdomen revealed mild direct tenderness of the epigastrium and the right periumbilical area, but no masses or organomegaly. Digital rectal exam was negative for melena and masses.

Routine laboratory investigations revealed: hemoglobin 9.24 g/dL, leukocyte count 18,800/mm^3, platelet count 128,000/mm^3, C-reactive protein level 38 mg/dL, international normalized ratio 1.4, protein level 6.1 g/dL, albumin level 2.8 g/dL. The serum electrolytes and blood chemistry were not remarkable. Stool specimens were positive for occult blood, but negative for parasites. Abdominal computerized tomography showed significant thickening of the wall of the first part of the duodenum, with infiltration of the locoregional fat. Since vital signs were stable, we decided not to perform any urgent endoscopic examinations. At Day 9 of hospitalization, the patient was transferred to the intensive care unit due to a high risk for major gastrointestinal bleeding.

Esophagogastroduodenoscopy was performed and revealed a deep 3 cm-diameter ulcer with blood clots, without fresh blood in the first portion of the duodenum. Three hours after the gastroscopy, the patient still had a low arterial blood pressure (70/45 mmHg), and her hemoglobin concentration decreased to 6.2 g/dL. We noticed fresh blood inside the nasogastric tube and active rectal bleeding. The patient continued to pass blood from the stomach and rectum. Up to 4 hours before surgical exploration, a total of 8 pints of packed red blood cells were transfused. On exploration, intraluminal blood was visualized throughout the entire gastrointestinal tract. The upper gastrointestinal endoscopy was then simultaneously repeated. Since the endoscopy showed fresh bleeding from the ulcer, localized in the first part of the duodenum, a distal gastrectomy was performed. The source-origin of the lower intestinal bleeding could not be precisely evaluated by simultaneous colonoscopy, and the patient underwent total colectomy with end

Correspondence: Ozgur Kemik, Yuzuncu Yil University Medical Faculty, Department of Surgery, Kampus, Ercis Yolu, Van, Turkey.
Tel.: +90.505.5566969 - Fax: +90.432.4251024.
E-mail: ozgurkemik@hotmail.com

Key words: cytomegalovirus, gastrointestinal bleeding, colitis.

Acknowledgements: the authors would thank Prof. Alp Demirag for discussion and suggestions about the diagnosis.

Contributions: BK, SA, OC, UO and HYB took care of patient and wrote the initial draft; AY, OK, BK and HYB edited manuscript with literature review.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 7 June 2014.
Revision received: 19 August 2014.
Accepted for publication: 19 August 2014.

Infectious Disease Reports 2014; 6:5512
doi:10.4081/idr.2014.5512

ileostomy. The lower and upper gastrointestinal bleeding definitively stopped after surgery.

Histological examination of the resected specimen showed focal areas of mucosal ulceration, with an underlying chronic inflammatory infiltrate (Figure 1). Scattered cytomegalic cells were present, with a characteristic *owl's eye* pattern of intranuclear inclusion, surrounded by a clear halo and a smaller granular cytoplasmic inclusions. The submucosa was edematous and congested. The muscularis and adventitia showed no significant changes. No evidence of malignancy was observed.

Immunostaining for CMV was positive for the cytomegalic cells both in the duodenum and in the colon (Figure 2). After the pathological diagnosis, CMV polymerase chain reaction on blood was performed and it resulted weakly positive (2000 copies/mL in whole blood; QIAGEN Symphony Quantitative Real-Time PCR, QIAGEN Sample & Assay Technologies, Germany).During the post-operative period,

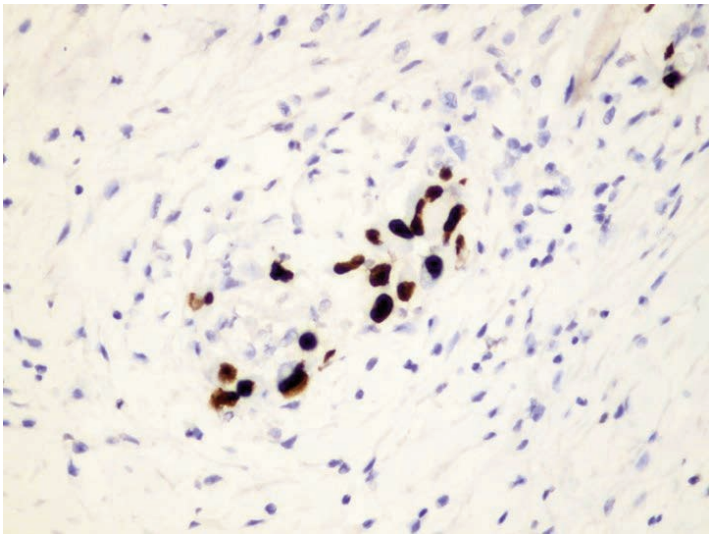

Figure 1. Cytomegalovirus enteritis. Multiple cytomegalovirus ulcers, some of which have hemorrhagic bases, are present.

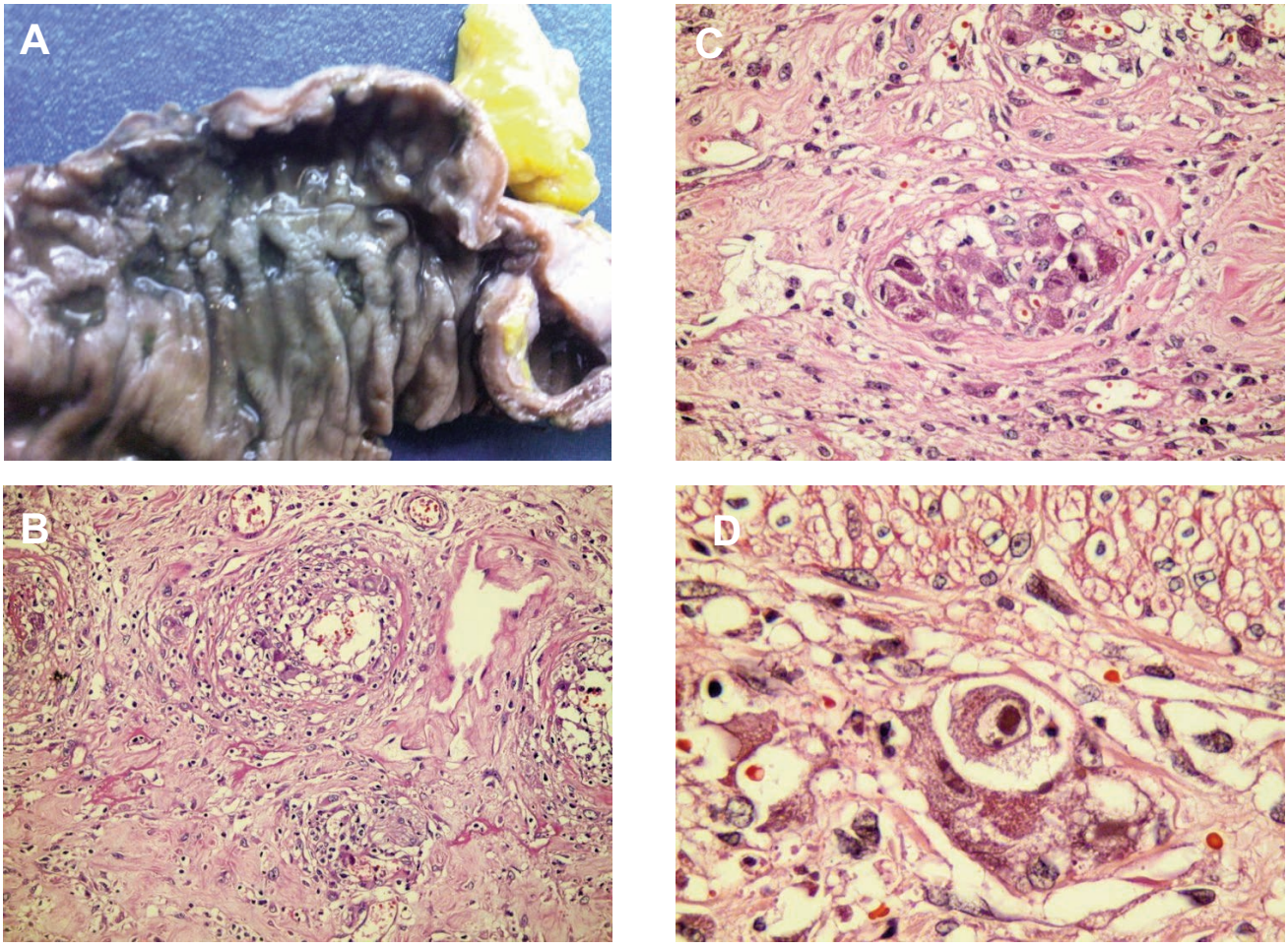

Figure 2. A) Colonic ulcer caused by cytomegalovirus with granulation tissue and necrosis at the base (Hematoxylin & Eosin, 50×). B) Typical nuclear inclusion within an endothelial cell and perineural stromal cells (Hematoxylin & Eosin, 200×). C) Characteristic *owl's-eye* inclusions are seen in endothelial cells in the ulcer base (Hematoxylin & Eosin, 400×). D) Immunohistochemistry highlights many inclusions in the stroma of a large bowel (Immunperoksidase, CMV, 400×).

the patient was stable and exhibited a hemoglobin level of 10.2 g/dL with no need of further blood transfusions. Because of the severe respiratory distress related to CMV pneumonia, the patient continued to stay in the intensive care unit. Ganciclovir (2×200 mg/day) was given intravenously to treat the CMV disease. The tough ache complaints (such as arthralgia or epigastric pain) that were resistant to traditional painkillers (non-steroid anti-inflammatory drugs and morphine derivatives), dissolved particularly after ganciclovir treatment.

On Day 16, the patient died from cardiorespiratory complications. A *post-mortem* examination was not performed.

Discussion

Recently, CMV has been recognized as an important common pathogen in immunocompromized patients. This is due to the increasing number of immunosuppressive medications, intensive cancer chemotherapy use, recurrent transplantations, progressively aging population, and the higher number of human immunodeficiency virus infections.[1] CMV infection often develops latently, after acute infection, with no evidence of signs or symptoms.[9] This disease is often diagnosed thanks to a pathologic and serologic examination, since the clinical symptoms are not specific.[10] The symptoms of CMV in the alimentary tract can range from mild anorexia to obvious hemorrhage and perforation. The pathogenesis of CMV enteritis is related to the infection of vascular endothelial cells.[11,12]

This virus can infect any part of the gastrointestinal tract, from the mouth to the anus, with the colon being the most commonly affected organ, and the stomach and small bowel being relatively affected. Additionally, the sigmoid colon and the rectum are the most affected portions of colon.[1,5,13,14] The antrum is the most common site affected by CMV in the upper gastrointestinal tract.

The clinical presentation of CMV disease in the gastrointestinal tract is multiple, with symptoms such as odynophagia, hematemesis, dyspepsia-like symptoms, diarrhea, rectal bleeding and even intestinal perforation.[15] However, CMV may also rarely involve the duodenum, causing duodenitis and presenting with upper gastrointestinal bleeding.[1] The present case describes the first CMV infection of both duodenum and colon, simultaneously presenting with bleeding. It is difficult to recognize the CMV infection of the gastrointestinal tract, however, it can be suspected in febrile immunocompromized patients with gastrointestinal signs and symptoms. The endoscopic features are relatively variable and may include macroscopically normal mucosa, diffuse erythema, nodules, pseudotumors, erosions and ulcers.[16] CMV infection cannot be initially demonstrated on gastrointestinal biopsies, but it can be exactly diagnosed using the specimens collected during surgery. Since the virus is located in deep tissue, biopsies should be performed deeply enough to obtain endothelial cells and fibroblasts within the lamina propria.[17] The *owl's eye* pattern is the hallmark of CMV infection in microscopic evaluation; however, classical intranuclear inclusions are not always found because CMV may infect the vascular endothelium or the stromal cells under ulcers as well as the mucosal epithelium.[18] Serology, on the other side, is not sufficient to diagnose the disease.[19] Of note, as a limitation of our case report, CMV molecular biology was not performed; however, histopathological changes suggestive for CMV infection were detected only in the surgical specimen and not in the specimen taken during endoscopy.

In the present case, the initial complaints of our patient were widespread abdominal pain, diffuse arthralgia and weakness in the upper and lower limbs. After microscopic evaluation of a specimen, hypertrophy was detected in nerve cells, justifying the intense pain complained by our patient. Meyer *et al.*[20] reported neural hyperplasia in CMV infection likely due to CMV inclusions and acute inflammatory changes.[21] Another important point in our report was the improvement in pain symptoms following ganciclovir treatment, likely related to recovery of neural hyperplasia.

The first-choice treatment for CMV infection is the antiviral therapy with ganciclovir. Systemic antiviral treatment has resulted in dramatically improved outcomes, and the treatment time usually ranges from 1 to 4 weeks.[22,23] The gastrointestinal complications of CMV infection, which include massive hemorrhage, toxic megacolon, perforation and stenosis, necessitate surgical resection.[5,24] Due to the high risk of complications and mortality from CMV infection in the elderly, all older patients must be offered antiviral treatment as soon as possible. In our case, delay in diagnosis and treatment onset were strongly associated with the fatal outcome.

Conclusions

Most gastrointestinal CMV infections respond well to ganciclovir treatment, independently from the cause of the underlying immunosuppression. Therefore, the patient should be offered an antiviral treatment as soon as possible. Early diagnosis of suspected CMC infection in immunosuppressed patients with gastrointestinal symptoms is of the utmost importance. It should not be forgotten that delayed diagnosis and treatment might increase the morbidity and mortality from CMV infection with major gastrointestinal bleeding.

References

1. Goodgame RW. Gastrointestinal cytomegalovirus disease. Ann Intern Med 1993;119:924-35.
2. Bang S, Park YB, Kang BS, et al. CMV enteritis causing ileal perforation in underlying lupus enteritis. Clin Rheumatol 2004;23:69-72.
3. Hinnant KL, Rotterdam HZ, Bell ET, Tapper ML. Cytomegalovirus infection of the alimentary tract: a clinicopathologicalcorrelation. Am J Gastroenterol 1986;81:944-50.
4. Kawate S, Ohwada S, Sano T, et al. Ileal perforation caused by cytomegalovirus infection in a patient with recurrent gastric cancer: report of a case. Surg Today 2002;32:1088-90.
5. Klauber E, Briski LE, Khatib R. Cytomegalovirus colitis in the immunocompetent host: an overview. Scand J Infect Dis 1998;30:559-64.
6. Swansiger B, Orchard JL. A colonic mass lesion due to cytomegalovirus in an immunocompromised patient. J Clin Gastroenterol 1996;22:41-4.
7. Crespo MG, Arnal FM, Gomez M, et al. Cytomegalovirus colitis mimicking a colonic neoplasm or ischemic colitis 4 years after heart transplantation. Transplantation 1998;66:1562-65.
8. Sakamato I, Shirai T, Kamide T, et al. Cytomegalovirus enterocolitis in an immunocompetent individual. J Clin Gastroenterol 2002;34:243-6.
9. Vancikova Z, Dvorak P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals: a review. Curr Drug Targets Immune Endocr Metabol Disord 2001;1:179-87.
10. de la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. J Clin Virol 2002;2:S1-12.
11. Cheung AN, Ng IO. Cytomegalovirus infection of the gastrointestinal tract in non-AIDS patients. Am J Gastroenterol 1993;88:1882-6.
12. Keates J, Lagahee S, Crilley P, et al. CMV enteritis causing segmental ischemia and massive intestinal hemorrhage. Gastrointest Endosc 2001;53:355-9.
13. Patel SM, Cohen P, Pickering MC, et al. Successful treatment of acute hemorrhagic cytomegalovirus colitis with ganciclovir in an individual without over immunocompromised. Eur J Gastroenterol Hepatol 2003;15:1055-60.

14. Lee J, Ng C, Deyali C. Cytomegalovirus colitis presenting as massive lower gastrointestinal bleeding in an immunocompetent patient. Indian J Surg 2008;70:28-31.
15. Wey-Ran L, Ming-Yau S, Chen-Ming H, et al. Clinical and endoscopic features for alimentary tract cytomegalovirus disease: report of 20 cases with gastrointestinal cytomegalovirus disease. Chang Gung Med J 2005;28:476-84.
16. Ko JH, Peck KR, Lee WJ, et al. Risk factors for cytomegalovirus gastrointestinal diseases in adult patients with cancer. Eur J Clin Microbiol Infect Dis 2014 May 23. [Epub ahead of print]
17. Akira H, Kiyohito T, Yu-ichi Y, et al. Cytomegalovirus gastritis. World J Gastrointest Endosc 2010;16:379-80.
18. Mihaiela M, Ivan T, Gilles B, et al. CMV enteritis causing massive intestinal hemorrhage in an elderly patient. Case Rep Med 2010;2010:385795.
19. Cetty R, Roskell DE. Cytomegalovirus infection in the gastrointestinal tract. J Clin Pathol 1994;47:968-72.
20. Meyer MF, Hellmich B, Kotterba S, et al. Cytomegalovirus infection in systemic necrotizing vasculitis: causative agent or opportunistic infection? Rheumatol Int 2000;20:35-8.
21. Lamps WL. Surgical pathology of the gastrointestinal system: bacterial, fungal, viral, and parasitic infections. New York: Springer US; 2010.
22. Biron KK. Antiviral drugs for cytomegalovirus disease. Antiviral Res 2006;71:154-63.
23. Ahmed A. Antiviral treatment of cytomegalovirus infection. Infect Disord Targets 2011;11:475-503.
24. Siciliano RF, Castelli JB, Randi BA, et al. Cytomegalovirus colitis in immunocompetent critically ill patients. Int J Infect Dis 2014;20:71-3.