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CASE REPORT

**Seungmin Bang · Yong-Beom Park · Byung Seung Kang
Min Chan Park · Min Ho Hwang · Ho Keun Kim
Soo-Kon Lee**

CMV enteritis causing ileal perforation in underlying lupus enteritis

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Abstract We report a case of cytomegalovirus (CMV) enteritis in a 31 year-old -woman with lupus enteritis. In August 2002 the patient complained of severe abdominal pain. An abdominopelvic CT scan at the time showed free air in the peritoneal cavity and wall thickening of the ileal loop. She was diagnosed as having panperitonitis due to an ileal perforation, and underwent an emergency laparotomy. The surgical specimen revealed CMV inclusion bodies in the infarcted lesion. Her symptoms improved following the initiation of ganciclovir therapy. To the best of our knowledge, this is the first report in the English literature of an ileal perforation due to CMV infection in a patient with lupus enteritis.

Keywords Cytomegalovirus · Enteritis · Lupus enteritis · Systemic lupus erythematosus

Abbreviations *CMV* Cytomegalovirus · *SLE* Systemic lupus erythematosus

S. Bang · Y.-B. Park · B. S. Kang · M. C. Park · M. H. Hwang
S.-K. Lee (✉)
Division of Rheumatology,
Department of Internal Medicine,
Institute for Immunology and Immunological Disease,
BK 21 Project for Medical Science,
Yonsei University College of Medicine,
Shinchon-dong 134, Seodaemoon-gu,
120–752 Seoul, Korea
E-mail: sookonlee@yumc.yonsei.ac.kr
Tel.: +82-2-3615410
Fax: +82-2-3936884

H. K. Kim
Department of Pathology,
Institute for Immunology and Immunological Disease,
BK 21 Project for Medical Science,
Yonsei University College of Medicine,
Shinchon-dong 134, Seodaemoon-gu,
120–752 Seoul, Korea

Introduction

Severe complications of cytomegalovirus (CMV) can occur in a patient in an immunocompromised state, such as in cases of human immunodeficiency virus infection, in those undergoing cancer chemotherapy or receiving long-term treatments with corticosteroids, and in recipients of organ transplants [1]. Gastrointestinal (GI) symptoms of CMV infection, including abdominal pain, diarrhea, bleeding or perforation, are very similar to those of lupus enterocolitis. Therefore, given a situation of symptomatic aggravation, with previously diagnosed lupus enterocolitis, it is important to determine whether the cause is acute exacerbation of the underlying disease or something else, such as CMV infection. Recently, we experienced CMV enteritis resulting in an ileal perforation and panperitonitis in a patient who had been diagnosed with lupus enterocolitis. To our knowledge, this is the first report of such a case in the English literature.

Case report

In August 2002 a 31-year-old woman visited the emergency room with severe abdominal pain. The abdominal pain had developed 18 h prior to her visit, and had progressed. As for her medical history, she had been diagnosed with systemic lupus erythematosus (SLE) 2 years earlier, and at that time had fever, malar rash, photosensitivity, polyarthritis, abdominal pain and diarrhea. On laboratory examination her antinuclear antibody, anti-ds DNA antibody, anti-Ro antibody and anti-RNP antibody were positive. Leukopenia, lymphopenia, decreased C3 and C4 levels and proteinuria were also observed. She had no history of any episodes of arterial or venous thrombosis, or spontaneous abortion. Two months prior to this admission, she had been admitted with diffuse abdominal pain and intermittent blood-tinged, tarry stools. An abdominal CT scan at that time revealed no specific findings. However, mesenteric angiography showed arterial stenosis, partial obstruction, or focal aneurysmal dilatation, involving the inferior mesenteric, left colic and sigmoid arteries, which were compatible with mesenteric vasculitis due to SLE. The test for antineutrophilic cytoplasmic antibody was negative, and that for anticardiolipin IgG antibody was positive (46 GPU/ml), but those for anticardiolipin IgM antibody and lupus anticoagulant were negative. Steroid pulse therapy was initiated for the lupus enteritis, followed by maintained high-dose corticosteroid and azathioprine treatment. The abdominal pain was improved by the treatment, and a colonoscopic examination then revealed no specific lesions from the rectum to the cecum. Therefore, the patient was discharged, on prednisolone (60 mg/day) and azathioprine (100 mg/day), 1 week prior to the current admission.

On physical examination at this admission, her bowel sounds were silent in all four quadrants, and direct and rebound tenderness was observed on the whole abdomen. Her temperature was 37.1°C, pulse rate 90 bpm, blood pressure 90/60 mmHg and respiration rate 19/min. Her white blood cell count was $1750/mm^3$, hemoglobin 9.9 g/dl and platelet count 290 $000/mm^3$. Her serum amylase and lipase were 411 and 73 IU/ml, respectively. The erythrocyte sedimentation ratio (ESR) was 8 mm/h, C-reactive protein 8.34 mg/dl (normal < 0.8 mg/dl) and serum concentrations of C3/C4 were 34/6.12 mg/dl, respectively. The anti-ds DNA antibody titer was 265.8 IU/ml.

An abdominopelvic CT scan revealed free air in the peritoneal cavity and wall thickening of the long segment of the small bowel, mainly the ileum (Fig. 1).

With these physical examination and abdominopelvic CT scan findings, she was diagnosed as having panperitonitis due to a small bowel perforation. The patient underwent an emergency laparotomy. The small bowel and total colon were hyperemic, and a segment of the ileum above the ileocecal valve about 80 cm in size was cyanotic and strictured. At 60 cm above the ileocecal valve two sites of bowel perforation were found, both measuring about 2×2 cm. A segment of the ileum, estimated to be 60 cm, including the perforation sites, was resected and an end-to-end anastomosis performed.

A pathological examination showed a transmural infarction around the perforation site and the endothelial cells of the blood vessels in the granulation tissue to have many inclusion bodies, suggestive of certain viral infections. Immunostaining of the lesion with the CMV-specific antibody proved positive (Fig. 2). However, in the region of the relative healthy specimen the endothelial cells did not react positively to the CMV-specific antibody. Serological studies of the CMV infection showed negative for CMV IgM, but that the CMV IgG was more than 400 AU/ml (upper normal value < 6 AU/ml), and that the CMV early antigen was positive. Her diagnosis was confirmed as panperitonitis due to CMV infection, which was superimposed on the underlying lupus enteritis. Her prednisolone dose was reduced to 30 mg/day, and the azathioprine was stopped. Intravenous ganciclovir (5 mg/kg b.i.d.) was initiated to eradicate the CMV. With an operation and medical treatment, she recovered without any complications. On the 33rd day after the operation the patient was discharged. She is now doing well, and her abdominal pain has subsided.

Fig. 1 An abdominal CT scan revealed free air in the peritoneal cavity (*black arrow*), a prehepatic space, a reactive fluid collection and wall thickening of the long segment of the small bowel

Discussion

CMV is a DNA virus and member of the herpes virus group. In Korea and Japan more than 90% of the population is seropositive for CMV, compared to 40% in other developed countries [1, 2, 3]. When CMV infection is acquired beyond the neonatal period it generally results in CMV mononucleosis, or may produce subclinical symptoms [4]. However, CMV can be a life-threatening infection in immunocompromised patients. The GI tract may be affected anywhere from the mouth to the anus, with the esophagus and colon the most common sites, but in the small bowel it is relatively rare [5].

A high index of suspicion for CMV infection must be maintained in the immunocompromised host. Factors associated with an increased risk of CMV disease include CMV-negative recipients of CMV-positive organs, recipients of organs poorly matched for HLA antigens, transfusion of multiple blood products, and an age greater than 50 years [6, 7]. More importantly, the incidence and severity of a GI CMV disease parallels the degree of cellular immune dysfunction [8].

The clinical manifestations of a GI CMV infection include malaise, anorexia, fever, nausea, diarrhea,

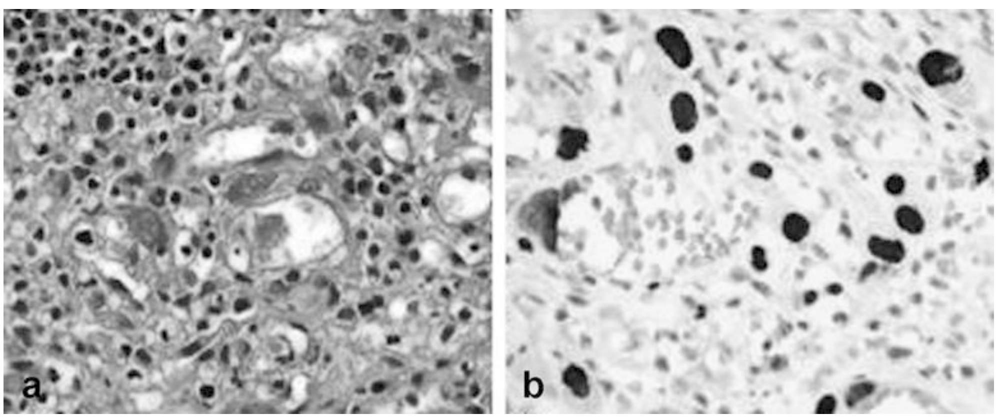

Fig. 2a, b Necroinflammatory exudate, transmural inflammation and granulation tissue formation were noted at the perforation site. Some of the endothelial cells in the granulation tissue had markedly enlarged nuclei, with intranuclear and cytoplasmic inclusions (**a**). These endothelial cells showed strong immunoreactivity to the CMV antibody (**b**) abdominal pain, ileus, GI bleeding and perforation [9]. However, in SLE patients it is sometimes difficult to determine whether the clinical manifestations are due to the exacerbation of the underlying SLE or to CMV infection [10, 11]. Furthermore, certain viral infections can induce clinical manifestations resembling SLE, and some may act as pathogenic factors for SLE [12]. GI symptoms, for example vague abdominal pain, are frequently encountered in patients with SLE. According to Drew [1], a diagnosis of CMV enteritis is substantiated by the presence of CMV inclusions, which is the most important evidence supporting a diagnosis of CMV enteritis. The absence of any other pathogen, the presence of CMV antigens in peripheral blood leukocytes and/or the isolation of CMV in cultured biopsy tissue, can help to substantiate a diagnosis of CMV infection, unless characteristic CMV inclusions are found.

The pathophysiology of CMV-induced ulceration is thought to be ischemic mucosal injury secondary to infection of the vascular endothelial cells [5, 13]. Although CMV may infect various GI cell types, the vascular endothelial cells are the most common site. CMV endothelial cell invasion leads to enlarged swollen cells, luminal compromise, fibrin thrombi, local vasculitis and damage to the tissues supplied by the affected vessels [13].

Without treatment, CMV infection of the GI tract in a host with sustained immunodeficiency is progressive and associated with a high mortality rate [14]. Fortunately, ganciclovir and foscarnet have excellent antiviral activity against CMV, and both uncontrolled and controlled trials have demonstrated the resolution of symptoms and lesions in patients with histologically confirmed GI CMV disease [15].

Our patient was unique in that she suffered ileal perforations due to the CMV infection during immunosuppressive therapy, namely, high-dose corticosteroid and azathioprine, for the underlying lupus enteritis. Without pathological confirmation of the CMV infection in this case, the patient might have been misdiagnosed as having an acute exacerbation of lupus enteritis, which would have indicated dangerously intensification of the immunosuppressive treatment. It might be logical to ask whether the CMV inclusion bodies or the incidental findings caused the bowel perforation. On this topic, the pathological findings raised an interesting point. Multiple submucosal granulation tissues, due to the underlying lupus vasculitis, were observed on pathological examination of the whole resected bowel. However, CMV inclusion bodies were found only in the endothelial cells in regions of the granulation tissue around the perforation sites. In contrast, no evidence of CMV infection was found in the other areas of the resected bowel. Thus, the pathophysiological mechanism of our patient's presentation was thought to be either primary infection or reactivation of CMV in the intestinal endothelial cells around the granulation tissues, with underlying lupus enteritis, leading to thrombosis, hypoxia, transmural infarction and perforation. The mechanism appears to be mainly related to an increased susceptibility to a superimposed CMV infection, as the intestinal endothelial cells had previously been exposed to chronic hypoxia due to the underlying lupus enteritis, and the long-term immunosuppression with steroids and azathioprine had caused deterioration of the host's immune system. It is also important to discriminate the underlying cause of the ileal hypoxia for the patient.

The patient had experienced no thrombotic episodes or spontaneous abortion. Although the anticardiolipin IgG antibody was positive, the underlying mesenteric vascular lesions, as shown by the angiography, were unlikely to be related to antiphospholipid syndrome. An ANCA test was negative, and she had no symptoms or signs satisfying the American College of Rheumatology 1990 criteria for the classification of vasculitides. Therefore, it was reasonable that the underlying mesenteric lesions were attributable to lupus vasculitis.

In summary, CMV enteritis should be considered as a part of the differential diagnosis of a GI illness in patients with lupus enteritis, especially while under immunosuppression for lupus enteritis, as this is a treatable condition which, when untreated, is associated with significant mortality and morbidity.

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