Mod Rheumatol (2002) 12:259–262

CASE REPORT

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Cytomegalovirus-induced small intestinal bleeding complicated with cutaneous vasculitis: a case report

Received: September 6, 2001 / Accepted: December 25, 2001

Abstract A 17-year-old woman who was being treated with prednisolone for cutaneous vasculitis developed recurrent massive melena and abdominal pain. An emergency resection was performed because of uncontrollable melena, revealing many small intestinal ulcers with cytomegalic inclusion bodies, which were found by immunopathological staining. However, the cytomegalovirus (CMV) antigenemia (CMV-Ag) assay and the IgM antibody titer for CMV were negative on admission. This case indicates that a high state of alertness for CMV infection in immunocompromised patients with gastrointestinal bleeding is required even if the CMV-Ag assay and IgM antibody are both negative.

Key words Cytomegalovirus (CMV) · Cytomegalovirus antigenemia (CMV-Ag) assay · Immunocompromised host · Small intestinal bleeding

Introduction

Cytomegalovirus (CMV) infection usually occurs in compromised patients who have conditions such as malignancies, transplantation, autoimmune disease treated with immunosuppressive therapy, or acquired immune deficiency syndrome (AIDS).[1] Although many cases of gastrointestinal tract (GIT) involvement in CMV infection have been reported, small intestinal involvement is rare, probably owing to difficulties in diagnosis.[1–8] Recently, the CMV antigenemia (CMV-Ag) assay has become widely used as a diagnostic tool for CMV infection.[9–14] In particular, it is used to monitor transplant patients for CMV infection.[10,13,14] We report the case of a patient with cutaneous vasculitis treated by prednisolone who developed recurrent massive intestinal bleeding due to CMV infection. However, this patient did not test positive for CMV infection with the standard methods, i.e., CMV-Ag assay and IgM antibody titer for CMV.

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Case report

A 17-year-old woman developed multiple patchy erythemas with mild pain and ulcers on both lower legs in August 2000. A skin biopsy, performed by a dermatologist, revealed moderate vasculitis of small vessels, with fibrinoid necrosis in subcutaneous adipose tissue. Although many tests were performed to determine the etiology of this cutaneous vasculitis, the only test that was positive was antinuclear antibody titer. Therefore, she was tentatively diagnosed with "cutaneous vasculitis, probably due to collagen vascular disease," and treated with 30 mg prednisolone per day. After her prednisolone had been gradually tapered to 10 mg per day, she underwent a tonsillectomy on March 13, 2001, because of recurrent tonsillitis. No bacterial or viral pathogen was detected (including Epstein–Barr virus) by means of pharyngeal or blood culture and serological tests. After the tonsillectomy, she developed a high fever that did not improve after treatment with several types of antibiotic. It was then thought that she may have systemic vasculitis, and she was given methylprednisolone pulse therapy (1 g × 3 days) followed by 60 mg prednisolone. Although her high fever improved immediately, she developed severe abdominal pain and massive melena, and was given several blood transfusions. Gastroduodenal and colonic fiberscopies revealed only small erosions of the descending colon. Although Technetium-99m-labeled red blood cell scintigraphy suggested bleeding from the small intestine, angiography did not detect any aneurysms or bleeding points. She

was referred to our hospital, and admitted on April 20, 2001, because of uncontrollable, recurrent, massive melena.

The patient was 151 cm tall, and weighed 45.9 kg. Her pulse rate was 90 beats/min, blood pressure 128/72 mm Hg, and body temperature 36.5°C. Mild moon face and anemia were observed. No abnormal cardiopulmonary findings were noted, but limited mild abdominal tenderness around the umbilicus with decreased bowel sounds was observed. No sign of peritonitis could be detected. Although an abdominal X-ray and computed tomography (CT) showed dilatation of both the small intestine and the colon with the formation of an air–fluid level, intestinal edema and pancreatic swelling were not clearly evident. Initial laboratory examinations were as follows: urinalysis normal; white blood cell count 22 800/mm^3 (neutrophil 77.0%, eosinophil 0%, basophil 1.0%, lymphocyte 8.0%, monocyte 2%); red blood cell count 307 $\times$ 10^4/mm^3; hemoglobin 9.4 g/dl; hematocrit 28.1%; platelet count 39.7 $\times$ 10^4/mm^3; erythrocyte sedimentation rate 6 mm/h; total protein 4.3 g/dl; albumin 2.5 g/dl; billirubin 0.3 mg/dl; aspartate aminotransferase 20 U/l; alanine aminotransferase 21 U/l; lactate dehydrogenase 198 IU/l; alkaline phosphatase 178 U/l; amylase 501 U/l; pancreatic amylase 408 U/l; creatine phosphokinase 153 U/l; blood urea nitrogen 11.9 mg/dl; creatinine 0.49 mg/dl. Immunological studies showed C-reactive protein (CRP) 0.1 mg/dl, CH_{50} 42 U/ml, C_3 80 mg/dl, C_4 18 mg/dl, IgG 410 mg/dl, IgA 83 mg/dl, and IgM 100 mg/dl. Antinuclear antibody was $\times$80 (homogeneous and speckled), but other autoantibodies were all negative. Human immunodefficiency virus antibody and human T-cell leukemia virus antibody were negative. Epstein–Barr virus antibody and parvovirus B 19 antibody indicated a previous history of infection. CMV IgG antibody was $\times$160, IgM antibody was less than $\times$10, and the CMV antigenemia assay (C10, C11) was negative. Technetium-99m-labeled red blood cell scintigraphy, performed on April 25, 2001, in our hospital, also suggested bleeding from the small intestine.

An emergency operation was performed on April 27, 2001, because massive melena became more frequent and no further studies could be carried out. This operation revealed 11 small patchy ulcers (10–15 mm) within a 20–70-cm section of the ileum from the anal side of the small intestine (Fig. 1). Microscopic analysis showed a large number of cytomegalic inclusion bodies at the site of the small-vessel endothelium (Fig. 2). Since immunopathological staining for CMV antigen in the small intestine was positive (Fig. 3), CMV involvement in the ileum was believed to be the cause of the ulcers and the bleeding. No attempt was made to detect CMV-DNA in the blood by polymerase chain reaction. Other manifestations, including CMV retinitis, were not detected. After resection, the melena stopped and the patient recovered well. Ganciclovir was given intravenously at 400 mg/day (200 mg every 12 h) for 14 days, and prednisolone was gradually tapered off owing to the possibility of the involvement of other parts of the small intestine or colon. Indeed, small erosions in the descending colon had been detected by colonoscopy performed before transfer to our hospital. The patient was subsequently given oral

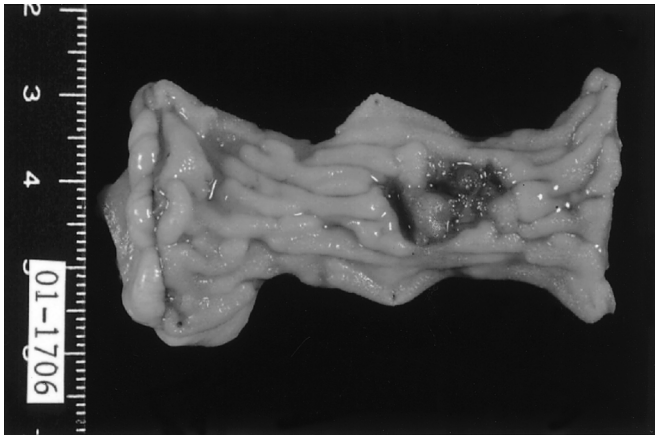

Fig. 1. Part of the ileum resected on April 27 showing one of the patchy ulcers

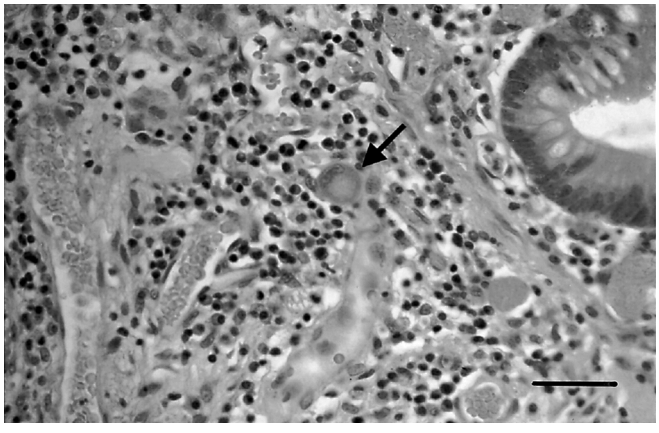

Fig. 2. Cytomegalic inclusion bodies in the small-vessel endothelium of the ileum (*arrow*, hematoxilin–eosin stain). *Bar* 50 μm

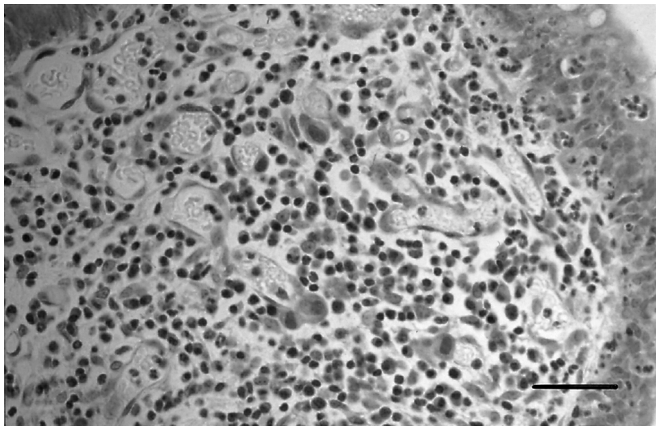

Fig. 3. Immunopathological staining of cytomegalovirus antigen showing positive-staining inclusion bodies in the small-vessel endothelium of the ileum. *Bar* 50 μm

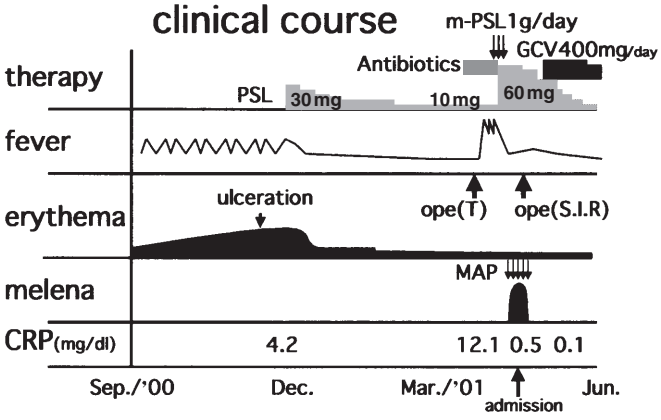

Fig. 4. Clinical course of the patient. *PSL*, prednisolone; *m-PSL*, methylprednisolone; *GCV*, ganciclovir; *ope (T)*, tonsillectomy; *ope (S.I.R.)*, small-intestinal resection; *CRP*, C-reactive protein; *MAP*, red blood cells in mannitol-adenine-phosphate

ganciclovir at 3 g/day, and her progress was followed in our outpatient clinic (Fig. 4).

Discussion

CMV is the fifth member of the Herpes virus family.[15] Almost all Japanese adults (about 90–95%) have antibodies to CMV because of subclinical infection from their mother at birth or from breast feeding.[16] Although the precise mechanism of CMV reactivation is unknown, clinical manifestations of CMV infection such as mononucleosis, pneumonia, hepatitis, and gastrointestinal ulcers are observed mainly in patients with malignancy, transplantation, autoimmune disease treated with immunosuppressive therapy, and AIDS.[1] The involvement of the GIT has been reported in more than 70 cases in Japan, and almost all of these also had an underlying immunosuppressive or debilitating disease.[2] Although the number of CD4 or the ratio of CD4/CD8 T cells was not clear in our case, the purified protein derivative (PPD) skin test was completely negative, suggesting defects in cellular immunity. Therefore, the patient was treated with prednisolone for cutaneous vasculitis for 4 months. The CMV infection of the ileum, and probably of the descending colon, were observed by colonoscopy as erosions. A review of the literature shows that the colon is the most common site of CMV infection in the GIT of immunocompromised patients, whereas infection in the upper GIT was more common in other patients.[1] Since small-intestinal involvement is rare and examinations such as small-intestinal scopy are difficult, only a few cases have been reported.[1,2,5,7] In this case, it is possible that intestinal involvement in cutaneous vasculitis led to systemic vasculitis such as polyarteritis nodosa, and that CMV infection occurred as a secondary infection. However, C-reactive protein was completely negative when the patient had massive melena, and abdominal angiography failed to detect any aneurysms. Moreover, other organs such as the kidney or lung were not involved, and a pathological analysis of the resected ileum showed mainly CMV infection rather than vasculitis. Therefore, CMV infection was considered to be the primary cause of the intestinal ulcers and melena.

Recently, the CMV-Ag assay has become a useful diagnostic tool for CMV infection.[9–14] Yoshihara et al.[17] reported that the CMV-Ag assay was extremely useful in the diagnosis of CMV involvement in autoimmune disease treated with immunosuppressive therapy. In addition, Hirata et al.[8] reported that three cases of CMV colitis, complicated by systemic lupus erythematosus, were diagnosed using the CMV-Ag assay and were effectively treated with ganciclovir. Misumi et al.[18] reported that an early diagnosis of CMV infection was made using the CMV-Ag assay in three cases of autoimmune disease. However, the sensitivity of the CMV-Ag assay is only 85%–90%,[19] and the number of positive leukocytes in GIT involvement after allogeneic marrow transplantation was reported to be lower than in pneumonia or viremia.[14] In this case, the CMV-Ag assay was negative on admission and after small-intestinal resection; therefore, the only way to detect CMV infection was by resection. The reason why the CMV-Ag assay was negative in this case is unclear, but there are two possible explanations. First, the affected lesion was limited to the GIT. Second, the assay may have been performed too late. The CMV-Ag assay might have been positive if it had been carried out immediately after the onset of infection. In contrast, some cases have been reported in which a CMV-Ag assay showed a mild positive result without any clinical signs of CMV infection.[16] Taken together, while the CMV-Ag assay can be useful for the diagnosis and monitoring of CMV infection, a high state of alertness for CMV infection in immunocompromised patients with gastrointestinal bleeding is necessary even if the CMV-Ag assay and the IgM antibody are both negative.

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