Acute Gastric Mucosal Lesions Associated with Cytomegalovirus Infection in a Non-Immunocompromised Host

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A 75-year-old woman with epigastric pain and tarry stool was admitted to our hospital, where upper gastrointestinal endoscopic study revealed multiple gastric ulcers. The endoscopic biopsy specimens obtained on the seventh hospital day disclosed a few typical intranuclear cytomegalovirus inclusions. Cytomegalovirus-DNA was detected using polymerase chain reaction in a biopsy specimen. No immunologic abnormalities were demonstrated by any laboratory tests. While only a few cases of cytomegalovirus-associated gastric ulcer in non-immunocompromised hosts have been reported, this entity may be more frequently detected when careful histological examination is performed in the active stage rather than postponed until after healing of the ulcer.

Key words: gastric ulcer, polymerase chain reaction

Introduction

Cytomegalovirus (CMV) is an important pathogen in the immunocompromised host. However, CMV infection shows various clinical manifestations in not only immunocompromised but also non-immunocompromised hosts, such as infectious mononucleosis-like syndrome, hepatitis, encephalitis, meningitis, myocarditis, pericarditis, pneumonia, hemolytic anemia, and thrombocytopenia (1). Gastrointestinal (GI) CMV infection has been reported exclusively in immunocompromised hosts (2, 3).

We present a rare case in which acute gastric mucosal lesions associated with CMV infection were encountered with no signs of immunological abnormalities.

Case Report

A 75-year-old woman with epigastric pain and tarry stool was admitted to our hospital. She had been under treatment for lumbago with a non-steroidal anti-inflammatory drug (NSAID), loxoprofen, for 20 days. She had no history of any disease which would have resulted in an immunosuppressed state, nor had she received any blood transfusion or any immunosuppressants.

Emergency upper gastrointestinal endoscopic examination disclosed multiple gastric ulcers and hemorrhagic erosions at the antrum, the angle, and the lower and middle portions of the body of the stomach (Fig. 1). Laboratory data on admission revealed a white blood cell count of 4.6x10^9/l with 30% lymphocytes, hemoglobin 8.3 g/dl, and platelet count 316x10^9/l. The blood chemistry findings were all within normal limits. The immunoglobulin (Ig) levels were IgG 1,180 mg/dl, IgA 278 mg/dl and IgM 104 mg/dl. The percentages of lymphocyte subsets in peripheral blood mononuclear cells were as follows: T cells, 90% (normal range, 66–89); B cells, 3% (4–13); CD4+ cells, 41.4% (25–56); and CD8+ cells, 16.7% (17–44); the CD4/CD8 ratio was 2.47 (0.6–2.9). The lymphocyte blastoid transformation by phytohemagglutinin or concanavalin A was within normal limits (data not shown).

Administration of loxoprofen was promptly discontinued and she was treated with intravenous famotidine (40 mg/day) and oral sucralfate (4.0 g/day) under the diagnosis of NSAID-induced acute gastric mucosal lesions (AGML). On the 7th hospital day, two endoscopic biopsy specimens were obtained from the edge of the gastric ulcer, in the early healing stage, at the greater curvature of the angulus. The specimens presented focal marked inflammation and focal fibrosis accompanied by a few typical intranuclear CMV inclusions in the epithelial cells (Fig. 2). We decided not to take any biopsies from other lesions because of the risk of bleeding. CMV-DNA was detected in the biopsy specimen obtained from the same lesion on the 28th
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Figure 1. A large, round ulcer is observed at the middle portion of the body of the stomach together with multiple erosions at the lower portion.

Figure 2. Three typical CMV inclusions are seen in gastric epithelial cells (HE stain, ×400).

Figure 3. Polymerase chain reaction amplification of CMV-DNA in a biopsy specimen from the margin of a gastric ulcer. M, molecular weight marker; 1) human DNA as an negative control; 2) CMV-DNA for positive control; 3) patient's sample.

hospital day, using polymerase chain reaction technique (Fig. 3). Although IgG antibody to CMV was detected, IgM antibody was negative on the 28th hospital day.

The AGML showed a self-limited course during conventional therapy for only the peptic ulcer. Intracellular CMV inclusions were not detected in multiple endoscopic biopsy specimens obtained from gastric ulcers in the late healing stage on the 42nd hospital day.

Discussion

GI CMV infection most often afflicts immunocompromised hosts (2, 3). However, a few cases in non-immunocompromised hosts were recently reported (1). The colon and the stomach are the most frequent sites of CMV infection in the immunocompromised host, whereas the stomach is the most frequently reported site of GI CMV infection in the non-immunocompromised host.

In our literature search of the English and Japanese language reports (1966–1994), we found nine cases of CMV-associated gastric ulcers in non-immunocompromised hosts (4–11). Only four of the patients showed associated infectious mononucleosis-like syndrome or clinical signs suggestive of acute viral infection. Most patients had multiple ulcers and/or multiple erosions. In all of the patients except two who underwent gastrectomy (6, 10), the course was self-limited and the treatment consisted of only conventional therapy for peptic ulcer.

The pathogenesis of the AGML due to CMV infection is controversial. Some investigators consider CMV to be the primary pathogen (12, 13) and have suggested cytomegalic vasculitis to be the major pathogenetic mechanism of mucosal damage (12, 14), while others have described possible acceleration of injury by CMV superinfection in patients with preexisting lesions induced by other causes (15, 16). We speculate that most cases of CMV-associated AGML in non-immunocompromised hosts might be caused by the latter mechanism, because the course is self-limited with conventional therapy for the peptic ulcer and without specific therapy for CMV infection.

In the present patient, although cytomegalic vasculitis was not observed histologically and we cannot exclude the possibility that the CMV was innocuous but incidentally detected, we believe that CMV infection had an important role in the pathogenesis of AGML. The intracellular CMV inclusions which were demonstrated in the early stage of the disease could
Endoscopic biopsy has not always been performed in the evaluation of CMV infection with careful histological examination. Therefore, we emphasize that care should be taken to undergo gastrectomy under the diagnosis of advanced cancer. Meanwhile, it is noteworthy that the upper gastrointestinal endoscopic findings were consistent with typical NSAID-induced AGML. Moreover, it is noteworthy from AGML induced by other causes (5, 8), the present gastric ulcers or erosions cannot be differentiated morphologically. The diagnosis of GI CMV infection is based on the histological identification of intranuclear CMV inclusions in biopsy specimens (10). It was reported that CMV inclusions were found in the ulcer base and/or in the ulcer margin, and occasionally in nonulcerated gastric mucosa (17). The difference may be due to the difficulty in detecting CMV inclusions when their number is few, or it may reflect differences due to the timing of biopsy sampling. Although some investigators have emphasized the usefulness of the polymerase chain reaction and in situ hybridization techniques for rapid detection of CMV-DNA in gastric mucosal lesions (5, 7), these techniques may not be practical in a normal healthy patient such as ours who does not show clinical manifestations of acute viral infection suggestive of CMV infection. Although it is reported that CMV-associated gastric ulcers or erosions cannot be differentiated morphologically from AGML induced by other causes (5, 8), the present patient seemed to have a deeper ulcer than the ulcers associated with typical NSAID-induced AGML. Moreover, it is noteworthy that the upper gastrointestinal endoscopic findings were suggestive of early or advanced gastric cancer in four of nine patients in the literature (6, 9–11), and one of these patients underwent gastrectomy under the diagnosis of advanced cancer (6). Therefore, we emphasize that care should be taken to evaluate CMV infection with careful histological examination either when the biopsy specimens obtained from gastric mucosal lesions do not disclose malignancy in patients with cancer suspected endoscopically, or in patients with AGML having large and incurable ulcers.

Endoscopic biopsy has not always been performed in the acute stage of the ulcers and may be performed in the late healing stage; there may be some clinical cases in which histological study was not performed at all. In the present patient, intranuclear CMV inclusions were not detected in endoscopic biopsy specimens obtained from the gastric ulcer in the late healing stage, consistent with other reported cases. Moreover, in all reported cases, except for two in which operation was performed (6, 10), the course was self-limited without specific therapy for CMV. Therefore, many cases of CMV associated AGML may remain undiagnosed. We consider that this entity may be more frequently detected if careful histological examination or endoscopic biopsy of the gastric lesions is performed in the active stage rather than after healing of the ulcer.

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References