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□ Case Report □

Multiple Gastric Ulcers as a Manifestation of Cytomegalovirus Infection in a Patient with Adult-onset Still's Disease

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Cytomegalovirus (CMV) is a relatively common viral pathogen, and CMV infection is generally assumed asymptomatic in general hosts. In immunologically compromised patients, CMV infection can cause further serious diseases such as pneumonitis, retinitis, encephalitis, and enterocolitis. A 40-year-old man is being presented with acute fever, myalgia, and sore throat. Laboratory findings have revealed elevated ESR, CRP, and ferritin levels. The patient was being treated for adult-onset Still's disease (AOSD). Three weeks later, although AOSD activity was under control, the patient began to complain about oral soreness, epigastric pain, and diarrhea. Endoscopy revealed multiple round ulcers with white patches in the esophagus and the stomach, sparing the colon. Anti-fungal agent is being administered but failed to bring improvements after 2 weeks of therapy. CMV infection is confirmed with pathology, antiviral agents were initiated after the ulcers subsided. Currently, clinical associations between CMV infection and AOSD are suggested. CMV infection may be considered as a differential diagnosis when multiple upper gastrointestinal ulcerative lesions develop within patients whom have been treated AOSD with immunosuppressive agents.

Key Words. **Cytomegalovirus, CMV, Gastric ulcer, Adult onset Still's disease, AOSD**

Introduction

Cytomegalovirus is a subgroup of herpes viruses, which shares the common characteristics of latency and reactivation. Since infection at an early age is common, antibodies against CMV are achieved by the adulthood in majority. Active infections are rare in healthy adults except for acute mononucleosis, and they generally develop in immunocompromised patients such as those with advanced human immunodeficiency viral infection, recipients of transplantations for bone marrow or other solid organs with intensive immunosuppressive therapy. Lungs, retinae, and meninges are common sites of infection, and also gastrointestinal tract is involved, the clinical course may be fatal in those patients.

Gastrointestinal CMV infections present with abdominal pain, diarrhea, gastrointestinal bleeding and perforation. Endoscopic findings could reveal ulcers at variable locations, most commonly the right colon and ileum, as well as enterocolitis and acute gastric mucosal lesion (1,2). Because both clinical manifestations and endoscopic findings are not specific for CMV infection, suspicion of disease and getting biopsy specimen are important for diagnosis.

AOSD is an auto-inflammatory disease with a constellation of symptoms and signs that include fever, skin rash, arthralgia/arthritis, sore throat, lymphadenopathy and elevated serum ferritin. Diagnosis is made by exclusion of several diseases which share similar clinical presentations including fever.

We experienced a case of multiple gastric ulcers as a manifestation of CMV infection diagnosed with biopsy and serology, which developed during immunosuppressive therapy in a patient newly diagnosed with AOSD, and we report this case with literature review.

Case Report

A 40-year-old man visited to emergency medicine with 10

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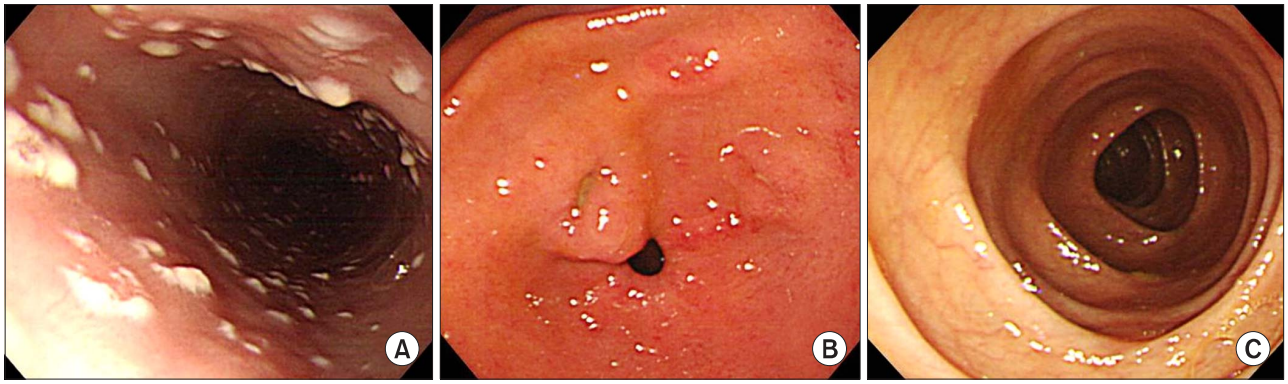

Figure 1. Gastrointestinal tract endoscopic findings. Multiple whitish plaques are observed in esophagus (A), variable-sized multiple superficial ulcers and erosions are shown in gastric antrum (B), and relatively normal-appearing colonic mucosa is shown (C).

days of fever, myalgia, sore throat, and atypical erythematous macules on anterior chest wall and both shins. He had been treated with antibiotics in a private clinic for 5 days without improvement and was transferred to our hospital after severe arthralgia on both wrists, elbows, knees, and ankles had developed. He had no specific medical history except for allergic rhinitis, and family history was unremarkable. He was a current smoker with a 30 pack-year history, and drinking habit was social. He was admitted to the department of infection. Initial vital signs were as follows: blood pressure 100/60 mmHg, pulse rate 88 rates/min, respiratory rate 18 rates/min, and body temperature 39.9°C. He looked acutely distressed, and throat was injected mildly without evidence of exudates or ulcers on physical examinations. Chest examination was unremarkable, and there were mild hepatomegaly and splenomegaly without tenderness. There were evanescent rashes on the chest and both lower extremities which only appeared with fever. There was no swelling, tenderness, or heat on wrists, elbows, knees and ankles. Laboratory findings revealed WBC 26,390/mm^3 (segmented neutrophil 87%, lymphocyte 8%, monocyte 5%, and atypical lymphocyte 0%), hemoglobin 14.8 g/dL, platelet 390,000/mm^3, ESR 39 mm/hr, and CRP over 19.0 mg/dL (normal range [NR]: 0～0.5 mg/dL). Liver panel was normal, and serum ferritin level was 16,320.34 ng/mL (NR: 4.6～204 ng/mL). The results of RF, anti-CCP antibody, ANA, anti-HIV antibody and HLA-B27 were negative. X-rays of affected joints did not reveal any abnormal findings. To identify the origin of the fever, cultures of blood, sputum and urine, transthoracic echocardiography, whole body bone scan, and bone marrow study were done. The results were all negative. Mild hepatomegaly and splenomegaly were observed on abdominopelvic computed tomography. The patient was diagnosed as AOSD and was transferred to the department of rheumatology. Fever and severe arthritis persisted despite the administration of naproxen

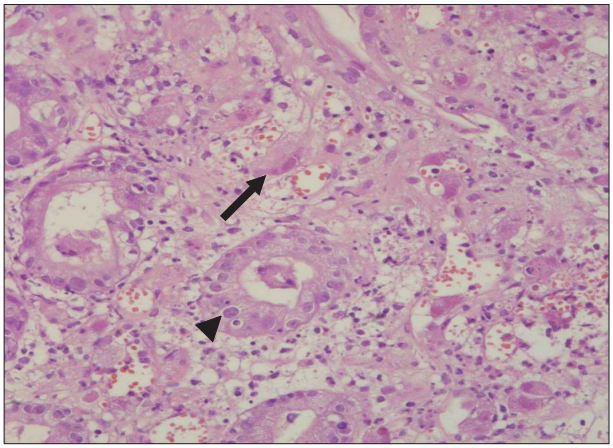

Figure 2. Microscopic findings of specimen obtained from gastrofibroscopic biopsy. The fibroblasts and endothelial cells show the intra-nuclear and cytoplasmic inclusions (arrow), and perinuclear halo (arrowhead), characteristic of cytomegalovirus infection (H&E stain, ×400).

and 30 mg of daily oral prednisolone. Two days of 1 g intravenous methylprednisolone was introduced and followed by high dose oral prednisolone (1 mg/kg). Methotrexate, cyclosporine and leflunomide were sequentially administered for not fully controlled symptoms. Fever, arthralgia and inflammatory markers such as CRP and ferritin gradually normalized in 3 weeks. Laboratory results at that time was as following; WBC 7,900/mm^3 (segmented neutrophil 57% and lymphocyte 36%), CRP ＜0.375 mg/dL, ferritin 238 ng/mL. But the patient began to complain of oral and epigastric soreness, with intermittent squeezing mid-abdominal pain and diarrhea. On physical examination, multiple white patches on oral cavity were observed, and gastrofibroscopy revealed multiple white patches from upper to lower esophagus, multiple ulcers in the antrum of stomach and erythematous duodenitis (Figure 1). On colonofibroscopy, terminal ileum and colon were relatively clean. The result of KOH

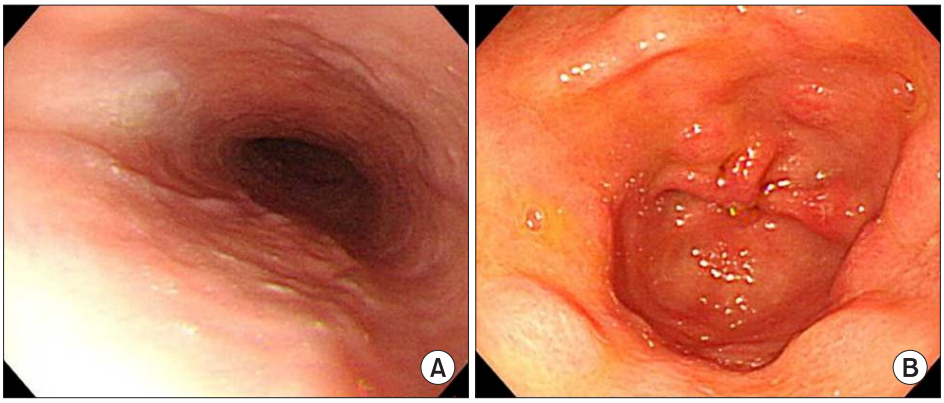

Figure 3. Follow-up of gastrofibroscopy in six months. Whitish patches (A) and ulcerative lesions disappeared. Mild gastric erosive lesions remained (B).

mount from esophageal lesion was consistent with monilial esophagitis. Although omeprazole (20 mg), sucralfate, and nystatin were administered, symptoms were not controlled for 2 weeks. Finally CMV infection was confirmed from the biopsy specimen obtained from the ulcer at the antrum of the stomach and positive result of serum CMV IgM antibody (Figure 2). After intravenous ganciclovir (5 mg/kg, twice daily) was introduced, the symptoms were improved and gastrofibroscopy followed up in 3 weeks showed resolution of the ulcerative lesions at gastric antrum (Figure 3). He was discharged uneventfully and symptom-free on low dose prednisolone and DMARDs.

Discussion

CMV is a member of herpesvius family, designated by Weller in 1957. A primary infection at an early period of life is asymptomatic in majority, and it becomes latent until it reactivates as a secondary infection, mostly in an immunocompromised host with rare exceptions of infection in healthy individuals. Antibody positivity was reported as 40～60% in United States and 60～100% in developing countries including Republic of Korea. Nowadays, the rate of CMV infections is increasing as the numbers of immunosuppressive therapies on recipients of transplants, patients with primary autoimmune diseases, and patients with HIV infection have increased (3-6). CMV infection could be mediated by vertical transmission to babies from infected mothers, intimate contact, and blood products.

Manifestations of CMV infections range from asymptomatic condition to life-threatening diseases such as pneumonitis, retinitis, cholecystitis, meningitis, encephalitis, pancreatitis, and gastrointestinal tract infection. CMV infection is a major cause of death in immunosuppressed patients, and co-infections with other bacteria, virus and fungi are frequently observed. CMV infection in transplantation recipients develops within 1～4 months of transplantation, primarily in the transplanted organs. Patients with advanced HIV infection who have decreased CD4+ T cell count are susceptible for CMV retinitis or disseminated CMV disease (7).

Gastrointestinal tract diseases by CMV had been frequently developed in patients with AIDS before the era of highly-active antiretroviral therapy (HAART). Currently, as the patients receiving immunosuppressive therapies in various situations are increased, reports of CMV infection are increased as well. Clinical manifestations of gastrointestinal CMV infection are generally non-specific but include abdominal pain, nausea, vomiting, diarrhea, and gastrointestinal bleeding (8,9). Although the most frequently involved site is right sided intestine, such as ascending colon and ileum, any part of gastrointestinal tract could be diseased (10), and cases of infection at multiple sites have also been reported. Endoscopic findings show multiple shallow ulcers or erosions, pseudomembranous plaques, and oblique ulcers. Both the symptoms and signs of CMV infection are not specific, as in the present case, high level of suspicion of the disease is important, and obtaining specimen from endoscopic biopsy at the site for identifying CMV infection is helpful for diagnosis. Diagnosis of CMV infection is based on the results of serology, pathology, viral culture of urine or blood, viral antigen, and DNA PCR, as well as relevant clinical presentations. Intranuclear or intracytoplasmic cytomegalic inclusion identified from the obtained tissue is diagnostic, as in the present case, but is not essential for diagnosis. Serum antibodies are measured by ELISA, in countries with high rates of positive IgG antibodies, elevated level of IgM or increasing levels of IgG could be diagnostic.

Treatment of CMV infections is conservative. Infections in healthy subjects do not require antiviral therapies but symptomatic care. Agents which inhibit viral replication such as ganciclovir, cidofovir, foscarnet are used for the immunocompromised. Leflunomide, a nonbiologic DMARD, is known to have anti-viral property for CMV by interfering with the virion assembly (11). In the present study, although the patient was co-treated with leflunomide, CMV infection developed. Authors

suggest that the CMV infection could have developed after starting immunosuppressive therapy including steroid pulse, and the anti-viral effect of leflunomide takes several months that improvement of epigastric soreness in three weeks might be effect of ganciclovir. Leflunomide could have helped preventing further reactivation in this patient.

Currently, clinical associations between CMV infection and AOSD are suggested. Treatment of AOSD with steroid with or without immunosuppressants could influence on reactivation of latent CMV (12,13). On the other hand, CMV infection is one of the probable triggering factors for development of AOSD (14). Similar features such as dysfunction of cytotoxic T cells or NK cells and increased serum level of IFN-γ are present, which could lead to an overwhelming systemic inflammatory response (10,15). More studies to confirm the observations are necessary.

Several domestic cases on CMV infections during immunosuppressive therapy in patients with rheumatologic disorders were reported (16). The majority of CMV infections had developed in patients with lupus or dermatomyositis, which is a consistent finding with that of data abroad (17). Lupus could raise intrinsic susceptibility to CMV infection due to defects in the immune system and dermatomyositis is known to carry 10～20% of opportunistic infections including fungus. This is the first case reported on the cytomegaloviral upper gastrointestinal tract infection sparing colon in a patient with AOSD in Korea.

The limitation of present case report is that the tests of state of CMV infection before immunosuppressive therapy were absent. So, whether the CMV infection was a trigger for AOSD or a sequela of immunosuppressive treatment is not known. Otherwise we assume that CMV infection was complicated by immunosuppressive treatments rather than a trigger event of AOSD. Because by the clinical presentations, CMV infection could not be suspected symptomatically before the diagnosis and treatment of AOSD.

Summary

CMV infection should be considered when multiple gastric ulcers develop in patients with rheumatic diseases such as AOSD treated with immunosuppressive agents. It is recommended that endoscopic biopsies should be undertaken in addition to the viral serology.

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