Intestinal Perforation due to Concomitant Cytomegalovirus Infection during Treatment for Pneumocystis jirovecii Pneumonia in a Patient with Rheumatoid Arthritis

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Abstract

A 78-year-old woman with rheumatoid arthritis treated with methotrexate and corticosteroid was admitted to our hospital for dry cough and dyspnea. She was diagnosed as having Pneumocystis pneumonia based on elevated beta-D-glucan and positive PCR analysis of bronchoalveolar lavage fluid for Pneumocystis jirovecii. We started trimethoprim-sulfamethoxazole and high-dose corticosteroid therapy. Her pulmonary lesions gradually improved; however, she developed perforation of the ileum and subsequently died from sepsis. Histology of the perforated site was compatible with cytomegalovirus enterocolitis.

Key words: cytomegalovirus, enterocolitis, perforation, Pneumocystis pneumonia, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) causes significant morbidity and mortality. Gastrointestinal perforation (GIP) can occur during RA treatment (1) and it commands considerable attention in RA patients. Few reports have clarified the etiology of GIP by pathological evaluation in RA patients. We treated an RA patient who developed ileal perforation due to cytomegalovirus (CMV) infection during Pneumocystis pneumonia therapy.

Case Report

A 78-year-old Japanese woman with RA treated with methotrexate (MTX) 6 mg/week and daily doses of methylprednisolone 2 mg and celecoxib 300 mg was admitted to our hospital in April 2009 for dry cough and dyspnea that had developed 2 weeks before admission. We stopped the MTX and celecoxib, but she did not improve. Her height was 156 cm and body weight was 56 kg. Ambient air PaO₂ was 41.4 Torr, LDH was increased to 311 IU/L, and beta-D-glucan was elevated to 1,511 pg/mL. ELISA testing for human immunodeficiency virus type-1 antibody was negative. CMV antigenemia was not measured. Chest computed tomography showed bilateral patchy ground-glass opacities. Although bronchoalveolar lavage fluid showed no Pneumocystis jirovecii cysts, polymerase chain reaction (PCR) analysis was positive for P. jirovecii. We diagnosed her as having Pneumocystis pneumonia and started trimethoprim-sulfamethoxazole with adjunctive corticosteroid therapy (prednisolone 1 mg/kg) according to the protocol for treating Pneumocystis pneumonia in acquired immunodeficiency disease syndrome (2). Pulmonary lesions gradually improved, and oxygen therapy was stopped on hospital day 6; however, epigastralgia had developed on hospital day 4, and gastroscopy showed a gastric ulcer at the gastric angle. After we withdrew diet and initiated proton pump inhibitor therapy, epigastralgia improved with persistent appetite loss. The administered dose of prednisolone was reduced but was maintained at 20 mg daily for fear of increased RA activity after withdrawal of the MTX. On hospital day 31, she developed a fever of 39.4°C and lower abdominal pain with peritoneal irritation. Abdominal X-ray showed free air under the right diaphragm (Fig. 1). Emergency surgery revealed sites of perforations in the ileum at 15 cm and 20 cm from...
the ileocecal valve (Fig. 2). We began antibiotic therapy and performed partial ileal resection. Postoperatively, bloody diarrhea occurred repeatedly and hypotension developed. Histological examination of the resected ileum revealed CMV inclusion bodies (Fig. 3a), which were stained by antibodies against CMV, in the cytoplasm of the endothelial cells (Fig. 3b). We thus diagnosed her as having CMV enterocolitis and began ganciclovir therapy; however, she died from sepsis on hospital day 49. ELISA assay of paired sera obtained before death showed an increase in anti-CMV antibody titers from 0.77 to 1.99 U/mL for IgM and 81.3 to >128 U/mL for IgG antibodies. An autopsy was not performed.

**Discussion**

Immunosuppressive therapy dramatically impacts RA treatment, but opportunistic infections still occur. In this report, we present an RA patient who developed ileal perforation due to CMV infection during therapy for *Pneumocystis* pneumonia.

Concern is emerging regarding GIP and its relation to the safety of medications administered to RA patients. It has been reported that among 40,841 RA patients, 37 hospitalizations occurred for GIP (1). In these 37 patients, 31 perforations occurred in the lower gastrointestinal tract. Suggested risk factors for GIP include current corticosteroid use with or without nonsteroidal anti-inflammatory drugs and previously recognized diverticulitis. The etiology of GIP in
RA patients is reported to be diverticulitis, amyloidosis, or vasculitis (3), and there are no reports of CMV infection causing GIP.

CMV, a member of the Herpes-viridae family, commonly infects healthy individuals. Symptomatic disease in immunocompetent individuals is rare, and although CMV can remain latent for the life of the host, the potential for reactivation exists. In immunocompromised patients such as organ transplant recipients and AIDS patients, reactivation of CMV infection may result in severe diseases such as retinitis or pneumonia.

CMV is increasingly being recognized as a cause of unusual ulceration and enterocolitis throughout the alimentary tract in immunocompromised patients. Bowel involvement by CMV may cause vasculitis in the affected segment that results in ischemia and/or infarction and manifests as abdominal pain; intermittent, bloody diarrhea; and rarely, intestinal perforation or toxic megacolon accompanied by fever and weight loss. The right colon and ileum are reported to be predominant infection sites (4), and this was seen in the present case.

Connective tissue disease patients undergoing immunosuppressive therapy are susceptible to CMV infection (5, 6). CMV pneumonia can occur even with low-dose MTX therapy (7). A CMV patient with ileitis taking prednisolone 60 mg daily for 1 month for systemic lupus erythematosus (8) and a CMV patient with colitis treated with prednisolone 10 to 30 mg daily for 2 years for systemic lupus erythematosus (9) were reported, suggesting that single corticosteroid therapy for connective tissue diseases can precipitate CMV re-activation, although the critical dose or duration of corticosteroid therapy that triggers the development of CMV reactivation remains unknown. Yoda et al reported that CMV antigenemia assay was reported to be positive in 10 of 23 patients with connective tissue disorders, and 5 of these 10 patients developed CMV disease (5). Thus, treating our patient with MTX and corticosteroid resulted in risk factors for CMV infection.

Yoda et al also reported that 4 of their 10 CMV antigenemia-positive patients showed detection of P. jirovecii in induced sputum by PCR analysis, an increase in the serum beta-D-glucan level, and geographical ground-glass opacities on chest radiography (5), all suggesting that connective tissue disease patients with CMV infection are susceptible to combined opportunistic infection of P. jirovecii (5).

Thus, adjunctive corticosteroid therapy for Pneumocystis pneumonia is cause for considerable concern. Although MTX was withdrawn after the present patient was admitted, her steroid dose was adversely increased to treat the Pneumocystis pneumonia. The prednisolone dose was then reduced but was maintained at 20 mg daily, possibly worsening the concomitant opportunistic CMV infection. In such cases, the steroid dose might have to be reduced even if steroid therapy is continued as alternative therapy when MTX is withdrawn. This case emphasizes the importance of remaining alert to possible opportunistic CMV infection as a cause of GIP in RA patients treated for Pneumocystis pneumonia.

CMV may cause gastric inflammation or ulceration. In the present patient, gastroscopy showed gastric ulcer, but CMV infection was not confirmed by histology. Because gastric ulcer improvement occurred without antiviral therapy, we thought the ulcer was induced by a corticosteroid or nonsteroidal anti-inflammatory drug.

With increasing use of immunosuppressive therapy, CMV infection is expected to be more frequently encountered. Recent studies emphasize the usefulness of CMV antigenemia assay in diagnosing, monitoring, and treating immunocompromised patients (10). In the present case use of CMV antigenemia assay might have helped establish an earlier diagnosis of CMV infection.

The authors state that they have no Conflict of Interest (COI).

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