Mod Rheumatol (2001) 11:72–75

CASE REPORT

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Recurrent ischemic colitis in a patient with malignant rheumatoid arthritis (MRA)

Received: February 24, 2000 / Accepted: September 5, 2000

Abstract A 63-year-old male with a 5-year history of malignant rheumatoid arthritis (MRA) developed recurrent massive melena and abdominal pain. Methylprednisolone pulse therapy and high doses of oral prednisolone markedly improved the clinical symptoms and normalized immunological disorders. However, he died of disseminated intravascular coagulation secondary to pneumonia caused by methicillin-resistant *Staphylococcus aureus*. Although a high dose of glucocorticoid therapy is effective for ischemic colitis complicated with MRA, intensive care to avoid any opportunistic infection is required.

Key words Glucocorticosteroid therapy · Intestinal infarction · Malignant rheumatoid arthritis · Rheumatoid vasculitis

Introduction

Malignant rheumatoid arthritis (MRA) is designated as rheumatoid arthritis with vasculitis (also referred to as rheumatoid vasculitis), and shows a variety of symptoms based on vasculitis, including peripheral mononeuropathy, digital ulcers, and visceral infarction, as well as subcutaneous nodules, pericarditis, pleuritis, and pneumonitis.[1,2] Patients with MRA are also characterized by the presence of high levels of rheumatoid factor, cryoglobulins, immunocomplexes, and decreased circulating complement. Intestinal infarction in patients with MRA, usually due to systemic vasculitis, is uncommon and serious, with a high mortality rate.[3–5] Herein we report the clinical features and outcome of a case with complicated MRA and intestinal infarction treated by methylprednisolone pulse therapy and the administration of a high dose of oral prednisolone.

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Case report

The patient, a 63-year-old Japanese man, had a 5-year history of seropositive erosive arthritis, involving predominantly the hands, feet, elbows, and shoulders. Because he had not received any medication, pain and stiffness restricted him to a sedentary lifestyle. On February 16, 1997, the patient was admitted to Ooba Hospital, Kyoto, Japan, for management of his rheumatoid arthritis (RA). On examination, the patient was pale and cachexic. His physical examination revealed a body weight of 49 kg and a body temperature of 36.5°C; blood pressure at the brachial artery was 180/84 mmHg. He had inspiratory crackles because of pulmonary fibrosis defined by bilateral reticulonodular shadows on chest roentgenography and a moderate honeycomb appearance on computed tomography.

Pulmonary function tests revealed a vital capacity of 2620 ml and a forced expiratory volume ($FEV_{1.0}$) of 1640 ml (66.7% of the forced vital value). The abdomen was diffusely tender, and bowel sound was normal. The distal extremities were cold and pale bilaterally. Rheumatoid nodules were observed at the lateral sides of the right wrist and left elbow joints. Initial laboratory evaluation revealed normal urinalysis, a hemoglobin level of 9.1 g/dl (normal 13–15.5), and a leukocyte count of 4100/mm^3 (normal 4000–9000). Other laboratory findings were as follows: billirubin 0.8 mg/dl (normal 0.6–1.1); blood urea nitrogen 17 mg/dl (normal 6–19); glucose 112 mg/dl (normal 70–100); erythrocyte sedimentation rate (ESR) 34 mm/h (normal 2–10); alkaline phosphatase 59 IU/l (normal 36–92); lactate dehydrogenase 341 IU/l (normal 200–400); albumin 2.61 g/dl (normal 3.7–4.92); total protein 5.8 g/dl (normal 6.5–8.2). Immunological studies showed C-reactive protein (CRP)

1.5 (normal <0.3), CH_{50} <15 (normal 30–40), C_3 34 mg/dl (normal 47–84), C_4 10 mg/dl (normal 14–44), IgG 3343 mg/dl (normal 1002–2004), IgA 1105 mg/dl (normal 100–385), and IgM 646 mg/dl (normal 54–352). Antinuclear antibody, antidouble-strand DNA antibody, and LE-test were negative. The rheumatoid factor was highly positive to 2475 IU/ml (normal <15).

The patient was treated with weekly injections of gold sodium thiomalate (25 mg/week) and nonsteroidal anti-inflammatory drugs (diclofenac sodium, 75 mg/day). Although the clinical symptoms of RA were improved markedly, he developed pneumonia, with symptoms including productive cough, high fever, and exertional dyspnea. Since *Hemophilus influenzae* and *Pseudomonas aeruginosa* were isolated from his sputum, he was treated with ampicillin and cefotiam hexetil hydrochloride for a week with no improvement. Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from his sputum. He was treated intensively with a combination of vancomycin and minocycline, to which MRSA is sensitive, resulting in a marked improvement.

On April 26, the patient developed severe central abdominal pain and massive bright red rectal bleeding. Emergency colonoscopy revealed erythematous and edematous mucosa, submucosal hemorrhages at skipped parts of the sigmoid colon, and hepatic flexure of the ascending colon (Fig. 1). Although a diagnosis of ischemic colitis was made, and initial management consisting of general supportive measures including bowel rest, volume repletion, and transfusions was employed for 2 days, his symptoms intensified rather than regressed. Because of the patient's profile of pulmonary fibrosis and rheumatoid nodules, and immunological abnormalities including a strongly positive rheumatoid factor, elevated ESR and CRP, hypocomplementemia, and the existence of immune complexes, rheumatoid vasculitis was strongly suggested. Therefore, he received intravenous methylprednisolone pulse therapy (1 g/day, for 3 days) followed by oral administration of a high dose of prednisolone (40 mg/day), which markedly improved his clinical symptoms and normalized his immunological abnormalities. On June 1, a minor recurrence of ischemic colitis appeared, while prednisolone was then gradually reduced to 20 mg/day. A second application of methylpredonisolone pulse therapy and an increased dose of prednisolone to 40 mg/day markedly improved his symptoms again. Colonoscopy carried out on June 12 revealed that the mucosal damage was healing, but that the lesions observed at the first attack were extended from the sigmoid colon to the upper descending colon, and from the ascending colon to the middle of the transverse colon (Figs. 1 and 2). The third attack of ischemic colitis occurred on July 30, when prednisolone was reduced to 15 mg/day. Although another application of methylpredonisolone pulse therapy and an increase of prednisolone to 30 mg/day were repeated, the patient's course was complicated by respiratory failure secondary to pneumonia caused by MRSA. During treatment of the patient with a combination of antibiotics, his platelet count decreased below 10000/ml, and coagulation was severely impaired: PT 18.8 s (normal 10–14), APTT >200 s

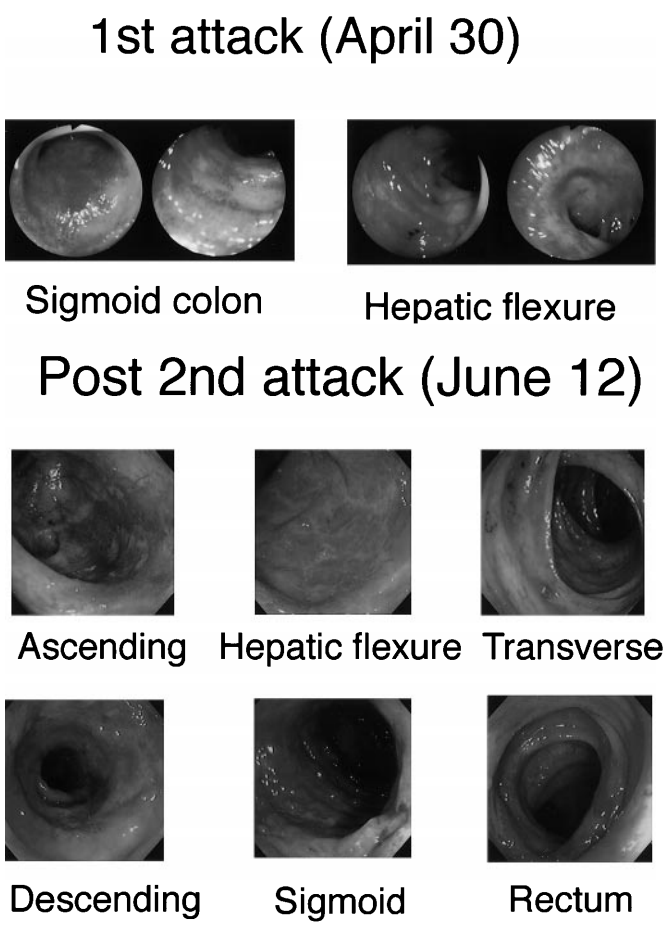


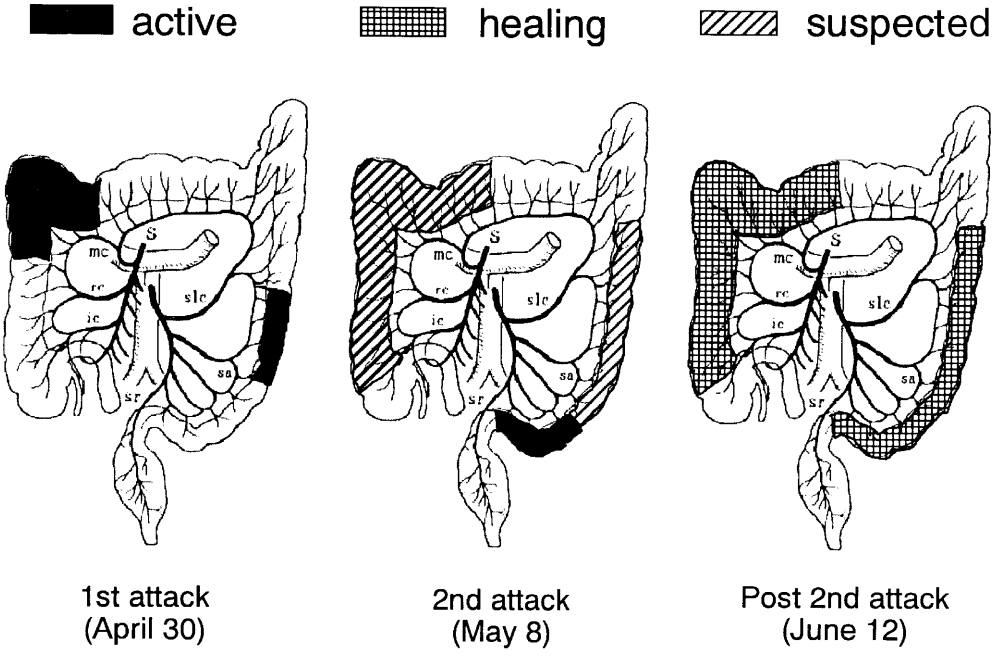
Fig. 1. Colonoscopy, performed on April 26 (the first episode of melena) and June 12 (after the 2nd episode)

(normal 20–40), fibrinogen 124 mg/ml (normal 200–400), and AT-III 53% (normal 79–121). A diagnosis of disseminated intravascular coagulation (DIC) was made, and anticoagulation therapy with gabexate mesilate (FOY) and heparin were started. The patient finally died from multiple organ failure due to DIC on August 2. The clinical course of this patient is summarized in Fig. 3.

Discussion

A range of vascular lesions can occur in rheumatoid arthritis, and these may be encountered singly or in combination. These changes include intimal proliferation, necrotising arteritis of both small and medium-size arteries, a subacute arteritis, and a leukoclastic vasculitis of the venules and capillaries in the skin.[6] As a result of these vascular changes a variety of clinical features have been described, which include skin rashes, cutaneous ulceration, peripheral gangrene, peripheral neuropathy, and, rarely, visceral lesions. In Japan, rheumatoid arthritis with vasculitis is designated as malignant rheumatoid arthritis (MRA), and a Japanese research committee of the Ministry of Health and Welfare

Fig. 2. Schema of lesions of ischemic colitis



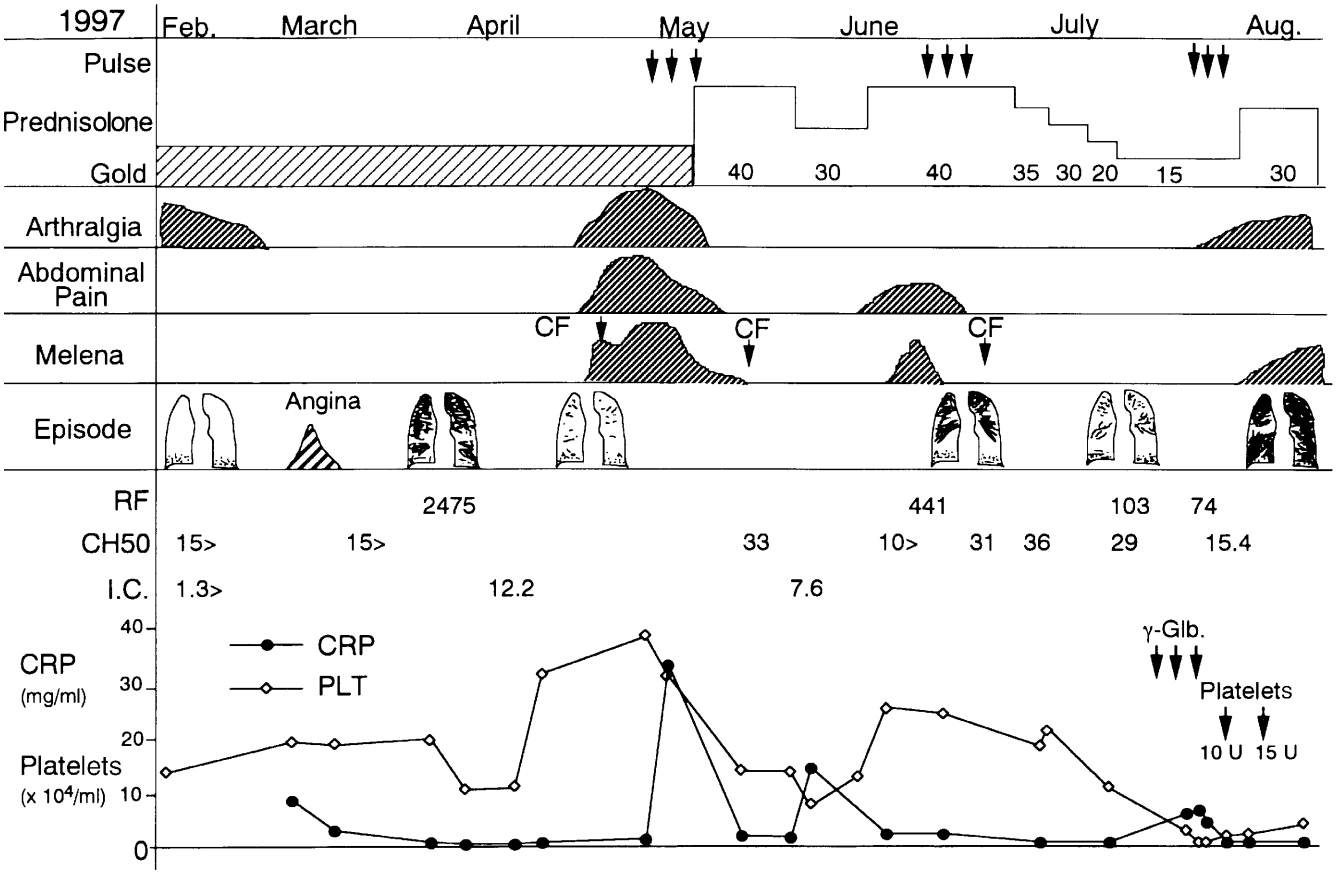


Fig. 3. Clinical course of the patient. *RF*, rheumatoid factor; CRP, C-reactive protein; *I.C.*, immune complex; *CF*, colono scopy

of Japan proposed criteria for a diagnosis of MRA.[7] Our patient met these criteria with evidence of peripheral neuropathy, rheumatoid nodules, and pulmonary fibrosis, and abnormalities in immunological examination, including a high titer of rheumatoid factor, hypocomplementemia, and the existence of immune complexes. A diagnosis of intestinal infarction complicated with MRA was made for the following reasons. His clinical symptoms intensified rather than regressed during the initial supportive care. A mucosal biopsy after colonoscopy showed intravascular thrombosis and mucosa damage without evidence of amyloidosis. Normal coagulation studies, and negative results for lupus anticoagulant and anticardiolipin antibodies, ruled out antiphospholipid syndrome.

Vasculitis in intestinal vessels is an infrequent complication of RA. In postmortem examinations, rheumatoid vasculitis has been demonstrated in approximately 25% of all patients with rheumatoid arthritis. Clinically apparent rheumatoid vasculitis, however, occurs in less than 1% of rheumatoid arthritis patients; of those, mesenteric vasculitis is noted in about 20%.[8] The involvement of small arteries can cause multiple ischemic ulcers of the intestine, resulting in hemorrhage or perforation,[9] and the involvement of lager arteries may cause segmental bowel gangrene.[10,11] Intestinal infarction in patients with MRA, usually due to systemic vasculitis, is a serious condition with a high mortality rate, even after surgical intervention.[3–5] To our knowledge, 32 cases from 28 reports of MRA complicated with intestinal infarction have been reported in Japan, and approximately a half of these cases died from hemorrhage or perforation. Therefore, an effective therapy for MRA needs to be established. We treated this patient with methylprednisolone pulse therapy and the administration of a high dose of oral prednisolone, which markedly improved his clinical symptoms and normalized immunological abnormalities such as hypocomplementemia and the existence of immunocomplexes. Since his symptoms recurred when glucocorticoid was gradually decreased, a more aggressive therapy using immunosuppressive drugs such as cyclophosphamide and cyclosporin-A may be necessary.[12,13] However, any immunosuppressive therapy may cause opportunistic infections in compromised hosts. Our patient also had a recurrence of MRSA pneumonia, in spite of our efforts to decrease the dose of oral prednisolone very rapidly. The patient finally died from multiple organ failure due to DIC caused by MRSA pneumonia just after the third methylpredonisolone pulse therapy. Therefore, intensive care to avoid any opportunistic infection is very important for MRA patients being treated with immunosuppressive drugs.

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