CASE REPORT

Development of Ischemic Colitis and Scleroderma Renal Crisis Following Methylprednisolone Pulse Therapy for Progressive Systemic Sclerosis

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We describe a patient with progressive systemic sclerosis who developed ischemic colitis and scleroderma renal crisis following steroid pulse therapy. The possible pathogenic mechanisms of ischemic colitis and scleroderma renal crisis development are discussed. We conclude that the administration of steroids in high doses, especially via steroid pulse therapy, should be undertaken with caution for progressive systemic sclerosis patients.

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Key words: steroid pulse therapy, side effect, interstitial pneumonia, renal failure, pathogenesis

Introduction

Steroid pulse therapy is used to treat various conditions including nephrotic syndrome, some collagen vascular diseases, and idiopathic interstitial pneumonia, for which its effectiveness has been widely accepted. Nevertheless facial flushing, gastrointestinal intolerance, hypertension, psychological disturbance, glucose intolerance, and sleep disturbance have been reported as side effects of steroid pulse therapy (1). Moreover, more serious side effects of steroid pulse therapy such as sudden death (1), life-threatening sepsis (2, 3) and myocardial infarction (2, 4) have also been reported.

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In this report, we describe a patient with progressive systemic sclerosis (PSS) who developed ischemic colitis and scleroderma renal crisis (SRC), following steroid pulse therapy.

Case Report

A 60-year-old woman was admitted to hospital, in February 1992, complaining of dyspnea accompanied by non-productive cough, which had lasted for 6 months. She had experienced Raynaud's phenomenon since December 1990, as well as flexion contracture of the fingers of both hands and depigmentation of the skin from February 1991. On examination, she presented normal blood pressure, contraction of the lingual frenulum, and mild anemia. Fine crackles were audible throughout the entire lung field as well as systolic murmur of the heart. Stool examination for occult blood was negative, but urinalysis showed a 2+ reaction for protein. Laboratory blood tests revealed an erythrocyte sedimentation rate (ESR) of 90 mm/h, white blood cell count 9,500/mm³, red blood cell count 352 × 10⁶/mm³, hemoglobin 10.0 g/dl, and platelet count 31.0 × 10⁴/mm³. High values were observed for serum gamma globulin 2.49 g/dl, lactate dehydrogenase (LDH) 724 IU/l, blood urea nitrogen (BUN) 31.5 mg/dl, β₂-microglobulin 31.9 μg/ml, C-reactive protein (CRP) 3.52 mg/dl, and immunoglobulin G 2,408 mg/dl concentrations. In addition, the patient's urinary N-acetyl-β-D-glucosaminidase level of 23.4 U/g crea, and urinary β₂-microglobulin level of greater than 1 × 10⁴ μg/ml were also high. Tests for liver function, total cholesterol, blood glucose, creatinine, urinary acid, CH50, C3, C4, immune complex, prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III, and fibrin degeneration products showed normal values. Tests for antinuclear antibodies at a titer of 1:2,560 and Scl-70 antibodies were positive. Rheumatoid factor, anti-dsDNA antibody, anti-RNP antibody, anti-Ku antibody, anti-neutrophil cytoplasmic antibody, lupus anticoagulant, and anti-cardiolipin antibody were absent. Pulmonary function tests revealed restrictive impairment of function with a percentage forced vital capacity, %FVC, of 55.7% and a percentage forced expiratory volume in 1 second, %FEV₁, of
83.9%. Arterial blood gas analysis showed respiratory alkalosis with \( \text{PaO}_2 \) of 87.5 mmHg, \( \text{PaCO}_2 \) of 29.3 mmHg, and pH of 7.46. Echocardiography revealed mild aortic valve stenosis, mitral valve insufficiency, and enlargement of the left ventricular wall. Chest radiography demonstrated patchy ground glass opacity in addition to bibasilar reticulonodular shadow (Fig. 1).

A diagnosis of PSS was made due to sclerodermatous skin changes, bibasilar pulmonary fibrosis, and the presence of Scl-70 antibody, according to the criteria of a previous report (5). Additionally, since the patient experienced severe non-productive cough, tachypnea, and acute progressive dyspnea (Hugh-Jones V°) with interstitial changes in the lungs as well as persistent high levels of ESR, CRP, and LDH, the condition was considered to be an acute exacerbation of interstitial pneumonia associated with PSS. Therefore, the 1st course of steroid pulse therapy (methylprednisolone [MPSL]: 500 mg/day for 3 successive days) was started 4 days after admission, but the effectiveness of this treatment was only temporary. At this time, blood pressure increased to 150–180 systolic and 100–110 diastolic, and nilvadipine 8 mg/day was added. One week later, a 2nd course of steroid pulse therapy was administered: on the 1st 2 days, aggravation of dyspnea and general fatigue during and after drip infusion of MPSL were noted. On the 3rd day, the patient suffered from severe abdominal pain and diarrhea during drip infusion of MPSL, followed by recurrent bloody diarrhea. Emergency colonoscopy revealed rash, edema, erosion, ulcer, and bleeding in the sigmoid colon and to a lesser extent in the rectum. Furthermore, acute deterioration of renal function (the levels of BUN 31.5 mg/dl and creatinine 1.2 mg/dl increased to 86.5 mg/dl, 8.2 mg/dl, respectively) developed soon after, with gastrointestinal symptoms. Since blood pressure remained high, 140–190 systolic and 100–120 diastolic, and SRC was suspected, captopril 25 mg/day was immediately added which lowered the blood pressure to 130–170 systolic and 80–110 diastolic. Ophthalmoscopy revealed a cotton-wool patch and hemorrhage in addition to severe arterio-venous crossing phenomenon (grade III retinopathy according to the Keith-Wagener classification). Plasma renin activity level of 23 pg/ml was within normal limits. However, this value might be influenced by angiotensin-converting enzyme inhibitor. Hemodialysis therapy was introduced at 7 days after the 2nd course of steroid pulse therapy. The patient’s intestinal lesions healed during 2 weeks of rest, fasting, and intravenous hyperalimentation, but hemodialysis continued 3 times a week, due to chronic renal failure. The patient’s clinical course was satisfactory, but 9 months later she suddenly suffered cerebral infarction and died.

Biopsy findings: colon biopsy findings at emergency colonoscopy showed coagulation necrosis of the mucosa, severe inflammatory cell infiltration (Fig. 2), bleeding, and a decrease in ducts. Renal biopsy, which was carried out 5 months after the beginning of hemodialysis, revealed intimal hypertrophy of interlobular arteries and hyalinization in some glomeruli (Fig. 3), although there was an absence of fibrinoid necrosis and amyloid deposit in the kidney. Neither the thickness of basal membranes nor an increase in mesangial cells were observed in glomeruli.

Autopsy findings: Examination of the sigmoid colon revealed submucosal proliferation of vessels, although there were few abnormalities in the mucosa, which was considered repaired (Fig. 4). Examination of the kidneys revealed hyalinization in some glomeruli, numerous hyaline cylinders in the renal tubules, and interstitial inflammatory cell infiltration. Intimal hypertrophy of interlobular arteries was noted (Fig. 5). Examination of the mesenteric arteries revealed partial hypertrophy of the intima.
Figure 3. Renal biopsy, which was carried out 5 months after the beginning of hemodialysis, revealed intimal hypertrophy of interlobular arteries and hyalinization in some glomeruli. Neither the thickness of basal membranes nor an increase in mesangial cells were observed in glomeruli (HE stain, ×200).

Figure 4. Colon autopsy findings revealing submucosal proliferation of vessels, although there were few abnormalities in the mucosa, which was considered repaired (HE stain, ×200).

Figure 5. On renal autopsy, numerous hyaline cylinders were present in renal tubules, and interstitial inflammatory cell infiltration was observed. Intimal hypertrophy of the interlobular arteries was noted (HE stain, ×100).

Discussion

PSS is a systemic disease which involves not only skin, but also lungs, kidneys, skeletal muscle, the pericardium, and the gastrointestinal tract (6). Gastrointestinal lesions are frequently found in the esophagus, small intestine, large intestine, and stomach, in that order, and the pathological findings are usually sclerosis of the connective tissue and smooth muscle atrophy (6). The present case was diagnosed as ischemic colitis according to the criteria described by Williams and Wittenberg (7): 1) the symptoms are noted abruptly in the elderly patient, 2) the intestinal lesions present as acute segmental hemorrhagic colitis, 3) no antibiotics are used, 4) stool cultures are negative for pathogenic bacteria, and 5) colonoscopy and biopsy findings are compatible with ischemic colitis. Complication of PSS by ischemic colitis is very rare (8). Ischemic colitis develops as a result of impaired colonic blood supply, which can be caused by any of several factors including vascular, intestinal, hematological, and general factors (9). Vascular factors include atherosclerosis, vasculitis, and surgical vascular interruption. Vascular involvement in PSS is characterized by non-inflammatory fibrous intimal thickening and medial hypertrophy (6, 8), whereas minor cases resembling overlapping PSS-polyarteritis nodosa reveal necrotizing vasculitis with fibrinoid degeneration (10). In the case reported here, non-inflammatory fibrous intimal thickening was found in the interlobular arteries of the kidneys and in mesenteric arteries obtained at autopsy. On the other hand, some drugs that induce thrombosis, such as oral contraceptives, are thought to trigger ischemic colitis (9). Steroids also have thromboplastic activity and there are several reports of thrombosis and embolism induced by high-dose steroid administration. In this regard, in addition to the vascular and intestinal involvement associated with PSS, the thromboplastic activity of MPSL may have triggered the development of ischemic colitis. To the best of our knowledge, this is the first reported case of ischemic colitis induced by steroid pulse therapy.

The present case was diagnosed as SRC due to the rapid deterioration of renal function, hypertension, and retinopathy according to previously established criteria (11, 12). SRC is one of the most serious complications of PSS, and is characterized by rapid deterioration of renal function within a month (11). The detailed pathogenesis of SRC is still unknown. Reduced renal
blood flow induced by renal vascular involvement associated with PSS (11, 13, 14), hypertension (11, 14), administration of corticosteroids (15), dehydration (14), heart failure (14), anemia (12), or vasoconstriction due to cold or hormonal factors (11, 13, 14) are reported to be possible causes of SRC. In the present case, SRC was associated with ischemic colitis; decreased renal blood flow caused by diarrhea and intestinal bleeding may have induced SRC. Additionally, steroid pulse therapy itself might exert an influence on the onset of SRC via the steroid’s thromboplastic activity resulting in impaired renal blood flow.

In conclusion, steroid pulse therapy was strongly suspected of having induced ischemic colitis in a patient with PSS. Further, development of ischemic colitis was rapidly followed by SRC which may have been caused by reduced renal blood flow due to the ischemic colitis, the effect of the corticosteroid, or both. Therefore, we consider that the administration of steroids should be undertaken with caution in cases of PSS, and concomitant administration of anti-coagulants, such as warfarin, is recommended to prevent such serious side effects when administering steroids in high doses, especially via steroid pulse therapy.

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References