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CASE REPORT

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A case of severe acute pancreatitis, in overlap syndrome of systemic sclerosis and systemic lupus erythematosus, successfully treated with plasmapheresis

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Abstract Here, we describe a case of severe pancreatitis in overlap syndrome of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) in an adult female patient. Treatment with plasmapheresis and high-dose prednisone successfully saved her life and led to remission of the pancreatitis. This is the first case report of severe acute pancreatitis in the setting of overlap syndrome of SLE and SSc. The advantages and disadvantages of the use of corticosteroids are discussed.

Key words Corticosteroid · Overlap syndrome · Plasmapheresis · Severe acute pancreatitis · Systemic lupus erythematosus (SLE) · Systemic sclerosis (SSc) · T helper type 1 cell

Introduction

Pancreatitis in the setting of systemic lupus erythematosus (SLE) has been reported to occur in about 0.2%–8.2% of patients with generalized flare of SLE.[1] Pathogenic mechanisms such as microthrombi, vasculitis, intimal thickening, and drugs have been reported, although the exact mechanism has not been revealed as yet. The contribution of corticosteroids to the pathogenesis of pancreatitis in SLE patients has been debated for decades. Some reports have shown that corticosteroids indeed cause or exacerbate the course of pancreatitis.[2] Other reports have shown that corticosteroids have no effect or ameliorate its course.[3,4] Therefore, the role of corticosteroids in SLE-related pancreatitis remains controversial.

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Pancreatitis in other rheumatic diseases has rarely been described. There are only a few reports showing acute pancreatitis as a complication of systemic sclerosis (SSc).

Here we report a case of severe pancreatitis in overlap syndrome of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Treatment with plasmapheresis and high-dose prednisone successfully saved the patient's life and led to remission of the pancreatitis.

Case report

A 36-year-old woman developed a fever of 38°C and polyarthralgia in April 2000. She was diagnosed as having overlapping syndrome of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) by the following evidence: Raynaud's phenomenon, scleroderma on her forearms and fingers, the findings of a skin biopsy which showed dermal compact collagen bundles and perivascular cuffing, positive anti-Sm, anti-RNP, anti-Scl-70 antibodies, and a low-grade complement in April 2001. Renal biopsy revealed lupus nephritis (WHO Ia), and the patient was treated with 20 mg/day prednisone for her facial erythema. On July 13, she was admitted to our hospital with high fever of 38°C and oral ulcers.

On admission, her body temperature was 36.2°C, heart rate 72 beats/min, and blood pressure 110/72 mmHg. Her consciousness was clear; she had a butterfly rash on her face and erythema on her chest and back. The laboratory data revealed that urinary protein was undetectable, erythrocyte sedimentation rate was 37.9 mm/h, white blood cell (WBC) count was 3700/μl (neutrophilic cells 76.6%, basophilic cells 0.3%, eosinophilic cells 0.1%, monocytes 6.8%, lymphocytes 16.2%), platelet count was 11.0×10^4/μl and hemoglobin was 12.8 mg/dl. Total protein and albumin were 6.6 g/dl and 3.6 g/dl, respectively. Liver enzymes were slightly elevated: serum alanine aminotransferase (ALT) at 50 (12–35) IU/l, aspartate aminotransferase (AST) at 45 (6–42) IU/l, total bilirubin (T-Bil) 0.5 (0.2–1.1) mg/dl, lactate dehydrogenase (LDH) at 604 (120–220) IU/l, alkaline phosphatase

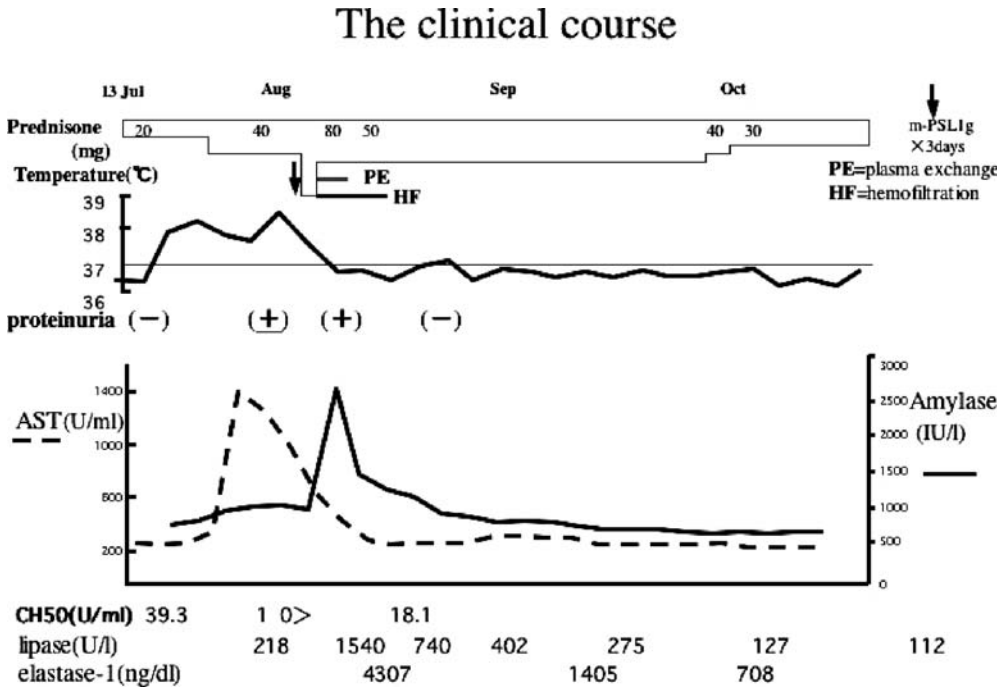

Fig. 1. Clinical course after admission. On admission, exacerbation of lupus was diagnosed and the prednisone dosage was increased from 20 to 40 mg/day. However, she still had high fever (over 38°C) with decreased complements, and elevated liver enzymes and serum amylase level. We conducted methylprednisolone (*mPSL*) pulse therapy (1 g/day for 3 days), followed by oral prednisone 80 mg/day. The next day she complained of upper abdominal pain, and physical examination revealed upper abdominal tenderness with muscle defense. Elevation of pancreatic enzyme was detected and severe pancreatitis was diagnosed. Treatment with plasmapheresis with hemofiltration and intra-arterial administration of nafamostat mesilate (240 mg/day) was initiated. Her symptoms and laboratory data relating to the pancreatitis gradually improved. *PE*, plasma exchange; *HF*, hemofiltration

(ALP) at 161 (70–210) IU/l. Serum amylase (pancreatic type) was slightly increased at 242 IU/l, renal function was normal and ferritin elevated to 1100 ng/ml. Coagulation function was abnormal with D-dimer 1.64 μg/ml, inhibitor–plasmin complex (PIC) 2.8 μg/ml, anti-thrombin-3 27.3 ng/ml, thrombin–antithrombin complex (TAT) 38.0 ng/ml, and thrombomodulin 29.8 U/ml. Immunological tests revealed a positive antinuclear antibody (1:1280) with speckled staining patterns, and anti-DNA antibody was 3 (normal <7) IU/ml. Complements were within normal range (C3 41, C4 6 mg/dl, CH_{50} 24 U/ml). Anti-Sm, anti-RNP, and anti-Scl70 antibodies were positive. Cryoglobulin and antigens and/or antibodies to hepatitis virus B or C were negative. Serum antibody test for Epstein–Barr virus, cytomegalovirus, and herpes simplex virus did not suggest present infection. The patient never complained of numbness or skin ulcers that could be associated with vasculitis. Her chest X-ray and electrocardiogram were normal. Her past history and family history were also unremarkable.

Exacerbation of lupus was diagnosed and prednisone dosage was increased from 20 to 40 mg/day. However, she still had high fever (over 38°C), with decreased complements and elevated liver function tests and serum amylase level. To suppress the disease activity, we conducted methylprednisolone (mPSL) pulse therapy (1 g/day for 3 days) followed by treatment with oral prednisone 80 mg/day. Soon after, her body temperature and liver function tests normalized. However, the next day she complained of upper abdominal pain. Physical examination revealed upper abdominal tenderness with muscle defense. Leukocytosis with a nuclear shift to the left (leukocyte count 7800/μl, neutrophilic cells 82.6% (Seg. 64.2%, Stab. 18.4%), basophilic cells 0.1%, eosinophilic cells 0.1%, monocytes 5.2%, lymphocytes 11.0%), mild hypoproteinemia (total protein 5.9 g/dl, albumin 2.7 g/dl), and hypocalcemia (7.8 mg/dl) were found. Neither biliary diseases nor hypertriglyceridemia was found. An elevation of pancreatic enzyme was detected: serum amylase (pancreatic type) 2677 IU/l (normal <175 IU/l), lipase1540 IU/l (normal 5–35 IU/l), and liver dysfunction was also detected: ALT 74 IU/l, AST 126 IU/l, LDH 646 IU/l, ALP 338 IU/l (Fig. 1).

A computed tomogram (CT) of the patient's abdomen (Fig. 2A) on the same day showed a swollen pancreas, fat necrosis, and the spread of inflammation into her pelvis. From the CT images, she was judged to have grade V pancreatitis. She was diagnosed as having acute pancreatitis of severity score 13 by the criteria of the Ministry of Health and Welfare of Japan.

Medication was started with intravenous antipancreatic enzyme (gabexate mesilate 2 g/day) and antibiotics. On August 3, because the severity of the pancreatitis was getting worse, she was transferred to the Gastroenterology Department and treated with plasmapheresis once a day for 3 days and with hemofiltration once a day for 1 week. She

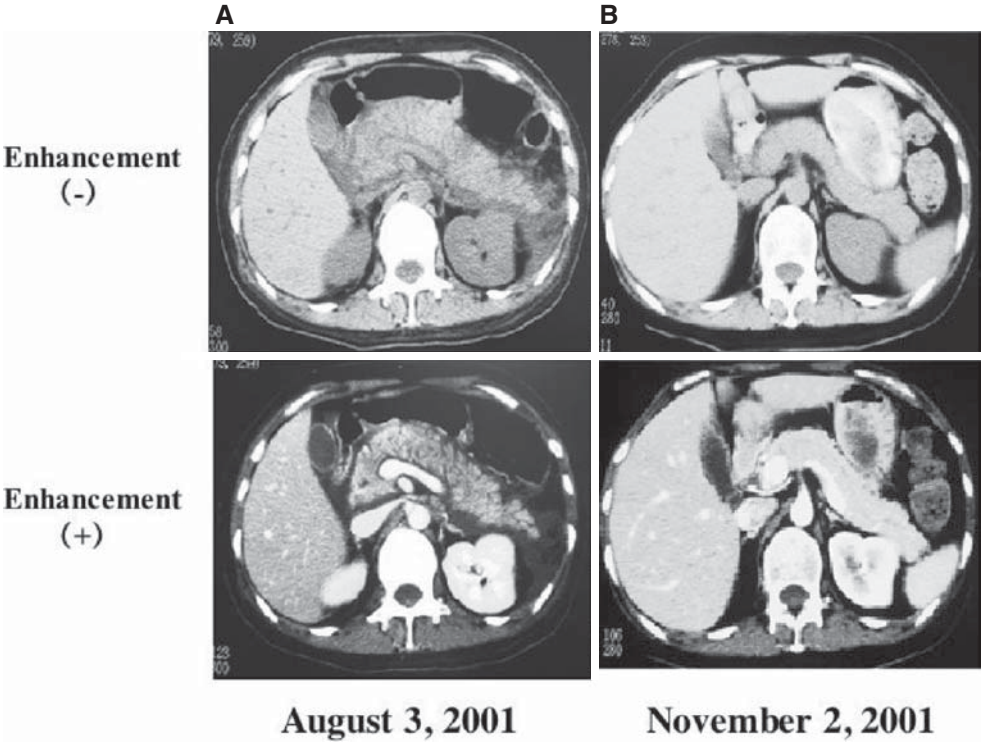

Fig. 2. Computed tomogram before (**A**: August 3, 2001) and after (**B**: November 2, 2001) the treatment

was then given nafamostat mesilate (240 mg/day) directly into a branch of the celiac artery by which blood is supplied to the pancreas. Her symptoms and laboratory data relating to the pancreatitis gradually improved (Fig. 2B).

The patient has been followed for 4 years and to date, prednisone has been gradually tapered to 9 mg/day with camostat mesilate (300 mg/day) being continued as maintenance therapy. No indications of pancreatitis have become apparent.

Discussion

It is reported that about 0.2%–8.2% of SLE patients develop pancreatitis, usually in the setting of a generalized SLE flare.[1] Pascual-Ramos et al. reported that 69% (22 out of 32 cases) had been severe regardless of its etiology and death was related to multiple organ failure and/or sepsis in five patients.[1]

The cause of acute pancreatitis has been discussed in many reports as well as pancreatic involvement by the disease, either though microthrombi, vasculitis, intimal thickening, or drug toxicity (including thiazide, furosemide, estrogen, tetracycline, and therapeutic agents of SLE [corticosteroids and immunosuppressive drugs]).[5,6] In the present case, acute pancreatitis occurred after the exacerbation of lupus and the patient had no history of medication that might induce pancreatitis except corticosteroids, suggesting that lupus itself was the likely cause of acute pancreatitis. However, as she complained of abdominal pain just after the treatment with mPSL pulse therapy, we were unable to rule out the possibility that mPSL pulse therapy might have worsened the pancreatitis. Therefore we decided to treat with plasmapheresis/hemofiltration and also intra-arterial administration of nafamostat mesilate (240 mg/day). With these treatments, we were able to save her life and to taper the dose of corticosteroid.

There is a major controversy concerning the role of corticosteroids in the pathogenesis of pancreatitis in SLE. In animal models, corticosteroids cause pancreatic lesions and peripancreatic fat necrosis. However, recent observations using a rat model of pancreatitis (Wbn/Kob rats) indicated that apoptosis of pancreatic acinar cells (an indicator of the pancreatitis in this model) related to decreased corticosteroids might be a trigger of chronic pancreatitis.[7] Also, clinical observation revealed that corticosteroids do not cause pancreatitis with SLE and suggested that corticosteroid should be administered during episodes of acute pancreatitis if clinically necessary.[8] Saab et al. reported eight pancreatitis patients with SLE. Only two out of eight patients manifested active concurrent systemic disease related to the SLE and other six patients had no evidence of SLE flare-up. Also, all their patients manifested both clinical and biochemical resolution of their pancreatitis with the administration of corticosteroids.[8] Although these findings indicated that corticosteroid is not an aggravating factor of pancreatitis with SLE, we chose alternative treatment such as plasmapheresis to reduce the risk of corticosteroid-induced severe pancreatitis in the case presented here.

Pathogenic mechanisms of acute pancreatitis in SLE, such as microthrombi, vasculitis, intimal thickening, and drugs have been reported thus far. However, the exact mechanism has not been revealed yet. The relative balance

of T-helper type 1 cells (Th1 cells) versus T-helper type 2 cells (Th2 cells) in SLE patients remains controversial. Some reports have suggested that SLE is a disease in which the actions of peripheral Th2 cells predominate over Th1 cells and other reports suggest a predominance of Th1 cells in SLE patients having class IV lupus nephritis as defined by the World Health Organization (WHO).[9–11] We recently reported that the levels of the Th1 chemokine interferon-inducible protein 10 (IP-10)/CXCL10 is increased in the cerebrospinal fluid of patients with central nervous system lupus, and demonstrated that CNS involvement in SLE is Th1 predominance.[12]

In respect of the Th1/Th2 dominance in pancreatitis in the setting of SLE, there are no reports thus far. However, the studies of immune function of autoimmune-related acute pancreatitis in humans and experimental immune-mediated pancreatitis model in mice revealed that Th1-type CD4+ cells were involved in the pathogenesis of pancreatitis.[13,14] In the present case, we measured the concentration of Th2 chemokine, thymus- and activation-regulated chemokine (TARC)/CCL17, and Th1 chemokine IP-10/CXCL10. As expected, the serum IP-10/CXCL10 level was elevated before the treatment (76.1 pg/ml) and its level decreased after the treatment (to less than 15 pg/ml). On the other hand, the serum TARC/CCL17 level was less than 15 pg/ml regardless of the treatment.

In conclusion, we experienced a severe case of acute pancreatitis in overlap syndrome of SLE and SSc patients and were able to save her life by plasmapheresis and intra-arterial administration of nafamostat mesilate. In addition, we found that the Th1 chemokine, IP-10/CXCL10, was elevated in our case, suggesting that pancreatitis in SLE is Th1 dominant. An accumulation of similar case reports might clarify the pathogenesis of pancreatitis in SLE.

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