Cryofibrinogenemia Associated with Sjögren's Syndrome: A case of Successful Treatment with High-dose Corticosteroid

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Abstract

Cryofibrinogenemia (CF) has not been often reported as a complication of various rheumatic diseases. We describe a 44-year-old woman with CF associated with Sjögren's syndrome (SS), who developed digital necrotic ulcerations and purpura of the lower legs. Cryoprecipitate was detected in her plasma, and immunoelectrophoresis showed that the cryoprecipitate was cryofibrinogen. Alprostadil was intravenously administered, but the ulceration was aggravated. Subsequently, administration of high-dose prednisolone (PSL) at 60 mg/day was started, and the ulceration remarkably improved. Cryofibrinogen, detected before the administration of high-dose PSL, was negative after PSL. This is the first case presentation of CF associated with SS successfully treated with high-dose corticosteroid.

Key words: cryofibrinogenemia, Sjögren's syndrome, corticosteroid, prednisolone, ulceration, purpura

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Introduction

Cryofibrinogen, described by Korst and Kratochvil in 1955, is an abnormal protein that reversibly precipitates in plasma by cold temperatures (4°C), and redissolves upon warming to 37°C (1). Cryofibrinogen is a cold insoluble complex of fibrin, fibrinogen, and fibrin split products with albumin, cold insoluble globulin, factor VIII, and other plasma proteins (2). Cryofibrinogenemia (CF) is a disorder characterized by cryoprecipitation with a variable clinical presentation. CF itself is often asymptomatic (3); however patients with clinically relevant skin lesions, such as purpura, livedo reticularis, ulceration, or gangrene, have been reported, as well as those with arthritis, and glomerulonephritis (4). CF may be primary or secondary to an underlying disorder including: carcinoma, infection, inflammation, collagen disease, thromboembolic disease, acute myocardial infarction, diabetes mellitus, and hypothyroidism (3-5). It has been reported that various organ disorders are associated with Sjögren's syndrome (SS), but CF associated with SS is rarely reported. Here, we describe the first report

of a case of CF associated with SS whereby treatment with high-dose corticosteroid was successful.

Case Report

In February 2004, a 44-year-old Japanese woman presented with a digital necrotic ulceration. Since 1980, she has suffered from Raynaud's phenomenon and dry mouth. From 2003, numbness of the bilateral lower legs developed. Two months before admission to our hospital, she started to experience palpable purpura of the lower legs, often induced by exposure to cold, and digital necrotic ulceration of the left fourth finger developed. She was pointed out as having positive antinuclear antibodies at a local hospital. She was suspected of having collagen disease, and PSL at 20 mg/day was started. In spite of PSL administration, the digital necrotic ulceration was aggravated, and she was admitted to our hospital in February 2004.

Examination on admission revealed a weight of 62 kg, blood pressure 136/88 mmHg, pulse 68/min, and temperature 36.7°C. No abnormal thoracic or abdominal findings were observed. The digital necrotic ulceration was observed

Figure 1. The digital necrotic ulceration: A, pretreatment of high-dose PSL; B, post-treatment of high-dose PSL.

on the left fourth finger (Fig. 1A) and multiple palpable purpura on the lower legs. Neurological examinations revealed hypalgesia and thermohypoesthesia on the sural nerve area of her bilateral lower legs. Laboratory studies were notable for the following values: white blood cell count of 6,200/ μ l with normal differentiation, hemoglobin 12.8 g/dl, platelet count 198×10^3 / μ l, ESR 35 mm/h (normal: 3-19), PT 100% (normal: 70-100), APTT 36.4 seconds (normal: 29.0-41.0), fibrinogen 297 mg/dl (normal: 150-400), α 1 antitrypsin 176 mg/dl (normal: 94-150), α 2 macroglobulin 252 mg/dl (normal: 130-250), and C-reactive protein (CRP) 0.07 mg/dl (normal: <0.3). There was no abnormality in serum transaminase, lactate dehydrogenase, creatinine, urea nitrogen, and on urinalysis. Immunological studies showed the following: a positive rheumatoid factor of 126.9 IU/ml, positive anti-nuclear antibodies with a titer of 1 : 640, positive anti-SS-A/Ro of >500 U/ml, anti-SS-B/La of 21.3 U/ml antibodies, and anticentromere antibody of 229.2 U/ml, negative or within normal limit C_3 and C_4 complement levels, immunoglobulin, anti-ds-DNA, anti-RNP, anti-Sm, anti-scl-70, anti-cardiolipin β 2 glycoprotein I, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), and proteinase-3 (PR3)-ANCA. HBs antigen and HCV antibody were negative. The chewing gum test identified reduced salivation (8 ml/10 min) from the salivary glands. $^{99m}\text{Tc-O}_4$ scintigraphy of the salivary glands showed a lower uptake of radioisotope in the parotid and submandibular glands. Lip biopsy demonstrated significant lymphoid cell infiltration in the minor salivary gland. She was diagnosed as having primary SS. A skin biopsy from a purpura lesion of the right lower leg was performed. In a small vessel of the upper dermis, an inflammation infiltrate consisting of neutrophils, lymphocytes, and macrophages was observed as well as nuclear dust and extravasation of erythrocytes. Immunofluorescent studies revealed C_3 located in the vascular walls, but no immunoglobulin deposits were found. The findings were compatible with the diagnosis of leukocytoclastic vasculitis (6, 11). The combination of her clinical symptoms and the finding on skin biopsy indicated a possibility of cryoglobulinemia (CG) or CF. Investigation for cryofibrinogen and cryoglobulin was performed using 14 ml of normal healthy donor ethylenediaminetetraacetic acid (EDTA) blood and the patient's EDTA blood centrifuged for 15 minutes at 37°C immediately fol-

Figure 2. Immunoelectrophoresis of cryoprecipitate solution: A, normal healthy donor; B, patient before treatment of high-dose PSL; C, patient after treatment of high-dose PSL; arrow, a dense band with fibrinogen.

lowing sampling. To each plasma sample an antiseptic (0.01% sodium azide) was added and incubated for 7 days at 4°C. Centrifugation (15 minutes at 2,000 g, 4°C) resulted in a visible precipitate in the patient's sample. The cryoprecipitate was washed three times with cold 0.9% sodium chloride solution. It was then dissolved in the solution at 37°C after 15 minutes (4, 6, 7). To analyze the precipitated protein, immunoelectrophoresis was performed and showed only a fibrinogen arc in the patient's sample (Fig. 2B), and not in the normal healthy donor sample (Fig. 2A). An immunoglobulin arc was not clearly detected by immunoelectrophoresis in the patient's sample. Based on these results, the diagnosis of CF was made.

PSL (15 mg/day), which was administered in a local hospital, was tapered and discontinued after the admission. She was treated with intravenous alprostadil (10 μ g/day) and oral aspirin (100 mg/day). The digital necrotic ulceration of the left fourth finger became aggravated despite these treatments, and a digital necrotic ulceration of the right first finger also developed. Therefore, treatment with high-dose PSL (60 mg/day) was started. After starting high-dose PSL treatment, the ulcerations gradually improved, and thus the PSL dose was tapered to 40 mg daily. At that time, plasma cryofibrinogen was undetectable (Fig. 2C). α 1 antitrypsin and α 2 macroglobulin, which increase in CF (5, 6), also normalized after treatment with high-dose PSL. Because there was marked improvement of the ulcerations at 6 weeks after starting high-dose PSL (Fig. 1B), alprostadil was discontinued. The patient was discharged in May 2004, in good general condition on PSL 40 mg daily. Although the PSL dose was gradually tapered to 8 mg daily, the patient was well without recurrence of the ulcerations in October 2006.

Table 1. The Present Case and Previously Reported Cases of Cryofibrinogenemia Secondary to Rheumatic Disease

No	References	Age	Sex	Diagnosis	Symptoms	Treatment	Outcome
1	4	37	M	Behçet's disease	Heamoptysis	Prednisone, Azathioprine	Remission
2	4	67	M	Periarteritis nodosa	Neuromyositis	Prednisone	Remission
3	4	50	F	Periarteritis nodosa	Purpura, livedo	Colchicine, Aspirin, IFN- α	Recurrence of skin lesions
4	8	21	M	Polyarteritis nodosa	Melaena	Operation	Remission
5	9	77	F	Polyarteritis nodosa	Livedo reticularis, digital gangrene	Methylprednisolone pulse	Remission
6	4	39	F	Polymyositis	Muscle weakness and pain	PSL 40mg	Improvement
7	4	76	F	Polymyositis	Fever, muscle weakness	Prednisone	Died (Septic shock)
8	4	57	F	Polymyositis	Muscle weakness	Prednisone	Remission
9	4	34	M	SLE	Kidney involvement	Cyclophosphamide, Prednisone, Aspirin	Remission
10	4	62	F	Scleroderma	Raynaud's phenomenon, skin necrotic ulcerations	Prostacyclin, Calcium blocker	Recurrence of skin lesions
11	10	49	M	Systemic sclerosis	Digital gangrene	Heparin, Dextran 40, Prostaglandin E1	Died
12	11	19	M	Henoch-Schönlein purpura	Petechiae, purpuric papules, abdominal pain	Methylprednisolone 60mg	Remission
13	12	29	M	Henoch-Schönlein purpura	Necrotizing skin, purpura, arthralgia	Stanazol 5mg, PSL 7.5mg	Amputation of fingers
14	13	64	F	Henoch-Schönlein purpura	Muscle weakness and pain, necrotic lesions, arthralgia	Cyclophosphamide (1mg/kg), PSL 75mg, Plasmapheresis	Remission
15	4	69	F	Sjögren's disease	Necrotic lesions, purpuric lesions	Prednisone	Died (Septic shock)
16	our case	44	F	Sjögren's disease	Necrotic ulcerations, purpura lesions	Alprostadi, Aspirin, PSL 60mg	Remission

Discussion

CF may be primary or secondary to an underlying disorder including: carcinoma, infection, inflammation, collagen disease, thromboembolic disease, acute myocardial infarction, diabetes mellitus, and hypothyroidism (3-5). Fifteen cases of CF secondary to rheumatic diseases, other than the present case, have been previously described (4, 8-13) (Table 1). Among these cases, CF associated with SS was rare. The age of patients varied from young to aged (range: 21-77 years), and the male/female ratio of patients was 7 : 9. Clinical symptoms that occurred due to CF tended to differ according to the underlying disease. Skin necrotic ulcerations, which also developed in the present case, were frequently observed in CF secondary to SS, scleroderma, Henoch-Schönlein purpura, and polyarteritis nodosa. The most commonly used pharmaceutical treatments include stanozolol, streptokinase, and steroids in CF (4, 6, 14-17). Prednisone or PSL was frequently administered to CF secondary to rheumatic disease. CF secondary to rheumatic disease did not recur as much as primary CF, and improved easily via treatment with corticosteroid compared with primary CF (Table 1). But three patients died. Among these three patients, two patients died of infection, and one patient of ischemia. CF secondary to SS except for the present case comprised only one case with both CG and CF and a death case. Because in the present case, CF was secondary to SS, rheumatic disease and the digital necrotic ulcerations aggravated after discontinuing PSL, we chose treatment with high-dose PSL. The ulcerations which did not improve by administration of alprostadi were ameliorated by treatment with high-dose PSL. Therefore, we thought that high-dose PSL was effective for the ulcerations. Amdo and Welker of-

fered that steroids should be used as needed for the treatment of an underlying inflammatory condition (e.g., collagen vascular disease), which can help in the control of CF (6). In CF secondary to SS, the present case constitutes the first case of successful treatment, and is the only clinical course reported in detail.

In the present case, since the findings of positive anti-SS-A/Ro, anti-SS-B/La antibodies, hyposalivation, and sialadenitis fulfilled the European diagnostic criteria of primary SS (18), diagnosis of CF secondary to SS was established after the detection of cryofibrinogen. Although CF may cause skin ulcerations generally (4, 6), Burger's disease, arterio-sclerosis obliterans, systemic sclerosis, anti-phospholipid syndrome, and vasculitis syndrome were considered possibilities as differential diagnoses of causes of the digital necrotic ulcerations. But sclerodactylia, lung fibrosis, and impaired mobility of the esophagus were not observed, and a contrast-enhanced CT scan of the lower extremities and doppler ultrasonography of the upper extremities revealed no stricture of the arteries and deep venous thrombosis. Moreover, CRP was negative throughout the course from the preadministration of PSL, and MPO-ANCA and anticardiolipin β_2 glycoprotein I antibody were also negative. Therefore, those diseases were thought to be unlikely in the absence of positive findings for these parameters. But we were not able to exclude local vasculitis without CRP elevation, because we did not perform a skin biopsy of the ulceration site in fear of delaying the recovery of the ulceration. CF may cause skin ulcerations, Raynaud's phenomenon, peripheral neuropathy, purpura, and leukocytoclastic vasculitis (4), and cutaneous vasculitis in primary SS also these clinical symptoms (19). Therefore, in the present case, the ulcerations were considered to be caused by CF and/or cutaneous vasculitis. CF itself is often asymptomatic, but in about 11%

CF is symptomatic (3). There is no correlation between the levels of CF and either disease intensity or cold sensitivity (4). Most symptomatic patients present either essential or collagen disease-related CF (3). Patients with symptomatic CF present with temporal association between exposure to cold and the onset of symptoms (6). Patients with isolated CF suffered more frequently from recurrent and necrotic skin lesion (mainly triggered by cold exposure) than patients with both CF and CG (4). CF may cause thrombotic occlusion of the small vessels, especially in the skin, via either reflex vasospasm, vascular stasis, and/or hyperviscosity (6). Typical skin biopsy findings in CF are cryofibrinogen plugging vessels, leukocytoclastic vasculitis, or dermal necrosis (6). In the present case, purpura lesion histopathological findings were leukocytoclastic vasculitis often induced by exposure to cold, and that the digital necrotic ulceration appeared at the same time. Although vascular occlusion and subsequent ischemic tissue damage are not rare in vasculitis (e.g., polyarteritis), cold-induced symptoms are not generally perceived in vasculitis (9). Thus, we thought that CF was associated with one of the causes of the ulcerations.

We detected the cryoprecipitate in the patient's EDTA

plasma and cryofibrinogen from the cryoprecipitate by immunoelectrophoresis. We thought that not only the detection of cryoprecipitate but also cryofibrinogen by immunoelectrophoresis should be performed to diagnose CF correctly, because cryoprotein is likely to consist of some kinds of protein (2). By using this method, cryofibrinogen was detected before treatment with high-dose PSL, and not after. But the plasma level of fibrinogen hardly changed before and after treatment with high-dose PSL. These results suggest that any factors leading to the formation of cryofibrinogen can be suppressed by high-dose PSL administration. It is true that cryofibrinogen was not detected after the administration of high-dose PSL, which may be related to the improvement of the ulcerations.

When rheumatic diseases are accompanied by cold-induced skin ulceration, it is necessary to consider the possibility that the ulceration is caused by CF. In such a case, high-dose corticosteroid therapy should be considered.

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