Mod Rheumatol (2004) 14:250–253
DOI 10.1007/s10165-004-0301-x

CASE REPORT

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Panniculitis in a patient with mixed connective tissue disease

Received: July 24, 2003 / Accepted: February 9, 2004

Abstract A 51-year-old woman who had been suffering from mixed connective tissue disease (MCTD) for 8 years developed an erythematous rash with pain and tenderness on her left leg. A skin biopsy revealed septal panniculitis with multiple lymphangiectasis. No vasculitis was observed. An increase in her prednisolone dose from 5 mg to 20 mg/day led to an improvement in these lesions. Panniculitis is very rare in MCTD. The clinical significance of panniculitis in MCTD is also discussed.

Key words Lymphagiectasis · Mixed connective tissue disease (MCTD) · Panniculitis

Introduction

Sharp et al.[1] first described a syndrome, namely mixed connective tissue disease (MCTD), which shared the clinical features of two or more defined rheumatic diseases, such as systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM), or systemic sclerosis (SSc), in association with a high titer of antibody to U1 ribonuclear protein (U1 RNP).

Symptoms of sausage-like swollen fingers are a common cutaneous manifestation in MCTD. Other skin findings that are frequently present in SLE, DM/PM, or SSc may also be observed in this disease.

Panniculitis is occasionally associated with various infections, including β-hemolytic streptococcal infection and tuberculosis, drug administration (sulfonamides, oral contraceptives), sarcoidosis, inflammatory bowel diseases, and certain malignant neoplasms, pancreatitis, α_1-antitrypsin deficiency, trauma, injection of foreign or toxic substances, and rheumatic diseases such as SLE, DM, and SSc.[2,3] However, with respect to MCTD, few cases associated with panniculitis have so far been reported. We describe a patient with MCTD in whom panniculitis developed during the course of the disease, and we also discuss its clinical significance.

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Case report

A 51-year-old woman who had been suffering from mixed connective tissue disease (MCTD) for 8 years was referred to our hospital with an erythematous rash on her left leg in November 2001.

She had had general malaise since 1993. Thereafter, Raynaud's phenomenon, periungual erythema, swollen fingers, mild scleroderma in her hands and forearms, and polyarthritis in her extremities became manifest. Further studies revealed mild myositis, interstitial pneumonia, and seropositivity for antibody to U1 RNP. The diagnosis of MCTD was made according to the diagnostic criteria established by the Japan Ministry of Health and Welfare.[4] General malaise, polyarthritis, and myositis had been improved by steroid pulse therapy (intravenous infusion of methylprednisolone, 500 mg/day for 3 days) and following the administration of prednisolone since October 1995. Three years before this presentation, she developed renal stones. Her father died from renal cancer at 62 years of age, and her mother had a past history of thyroid carcinoma at 51 years of age. One sister died from a cerebral infarction at 52 years of age, and one brother died from pancreatic cancer at 49 years of age.

The skin lesion on the patient's left leg first appeared 5 months earlier as a small erythematous rash without pain or tenderness. This lesion had once been alleviated by increasing the prednisolone dose from 5 mg to 30 mg/day.

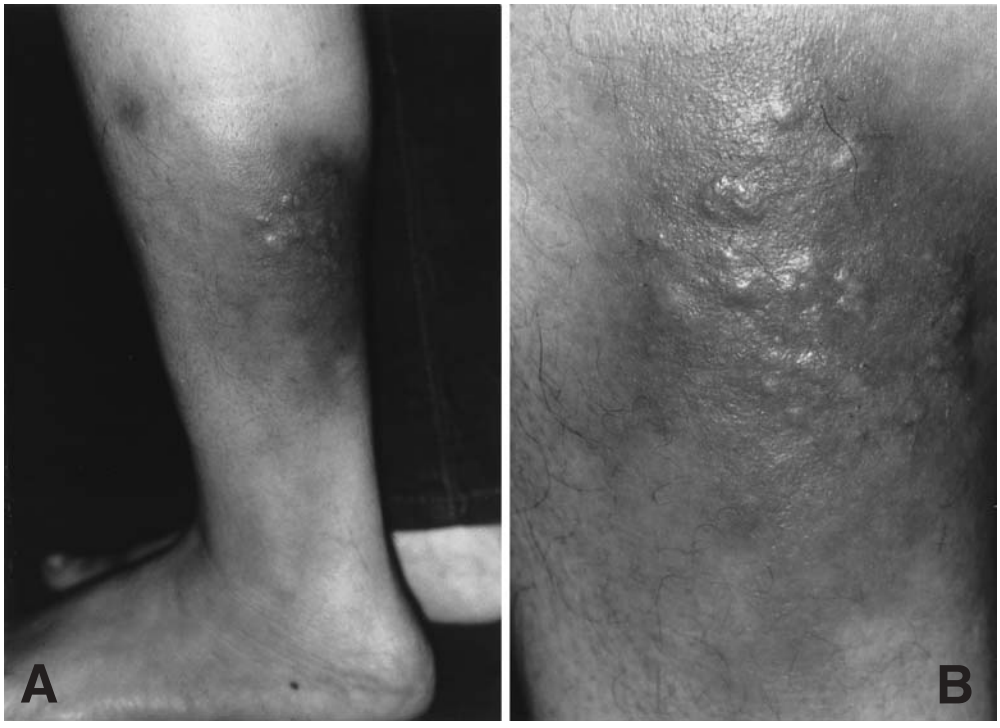

Fig. 1. **A** Appearance of an erythematous rash on the left leg. **B** Several vesicles in the rash were noted

However, after the subsequent tapering of the prednisolone dose to a level of 9 mg/day over the past 5 months, the rash reappeared and the number of the lesions also increased from one to three. These lesions were resistant to corticosteroid ointment therapy. However, her general condition had not worsened even after these skin lesions reappeared.

On admission, her height was 153 cm and her weight was 60 kg. Her consciousness was clear. Her blood pressure was 118/70 mmHg, heart rate 60/min, and body temperature 36.5°C. The conjunctivas were neither anemic nor icteric. Her cervical lymph nodes were not palpable, and the thyroid was not swollen. Her heart sounds were normal, and her breath sounds were not harsh, while late inspiratory fine crackles were present at the base of the right lung. The liver and spleen were not palpable. There was no tenderness in any joint. No weakness of the extremities was noted, and a neurological examination revealed no abnormality. The bilateral hands were slightly swollen. The erythematous rashes on the left leg were slightly swollen and the lesions measured 12 cm × 12 cm, 12 cm × 7 cm, and 2 cm × 2 cm. Superficial vesicles were noted in the rashes (Fig. 1). There were no other skin findings.

The laboratory data were as follows: hemoglobin, 14.0 g/dl; white blood cell count, 8300/μl (neutrophils, 73.3%; lymphocytes, 19.8%; others, 6.9%); platelet count, 27.1×10^4; total bilirubin, 0.4 mg/dl; aspartate aminotransferase, 34 IU/l; alanine aminotransferase, 44; lactate dehydrogenase, 259 (reference range 100–225); alkaline phosphatase, 159 (100–340); γ-glutamyltranspeptidase, 43; total protein, 7.4 g/dl; albumin, 4.1; blood urea nitrogen (BUN), 14 mg/dl; creatinine, 0.51 mg/dl; C-reactive protein, <0.3 mg/ml; Krebs der Lungen-6 (KL-6), 720 U/ml (<500); serum immunoglobulin(Ig)G, 1620 mg/dl; IgA, 231; IgM, 89; CH50, 42.9 U/ml (29–48); C3, 102 mg/dl (65–135); C4, 18 (13–35); circulating immune complex (CIC)–C1q, 1.6 μg/ml (<2.9); soluble thrombomodulin (TM), 22.2 U/ml (10.4–23.4). The antinuclear antibodies showed at a titer of 1:1280 with a speckled staining pattern. The antibody to U1 RNP was positive at a titer of 59.5 index (<22). Anti-Sm, anti-SS-A, anti-SS-B, anti-Scl-70, anticentromere, and anti-dsDNA were all negative. A roentgenogram of the chest showed ground glass opacity in the lower fields of the bilateral lungs. A spirogram showed a slight constriction disturbance: percentage vital capacity (%VC) decreased to 75.9% and percentage of one second forced expiratory volume ($FEV_{1.0\%}$) was 73.3%. An ultrasound study of the abdomen showed a layer of sand-like gallstones covering the bottom of the gallbladder and a small hepatic cyst (<1 cm) in the right lobe.

A specimen from the skin lesions on the left leg revealed (1) septal panniculitis with lymphocytic infiltrate and fat necrosis, (2) multiple lymphangiectasis in the dermis, and (3) dilation of venules between fat lobules. No vasculitis was observed (Fig. 2).

An increase in the prednisolone dose from 5 mg to 20 mg/day led to an improvement of these lesions. The subsequent tapering of prednisolone has not yet resulted in a recurrence of the skin lesions. In March 2003, the patient was symptom-free on prednisolone at 10 mg/day. It took 13 months to taper the prednisolone dose from 20 mg/day to 10 mg/day.

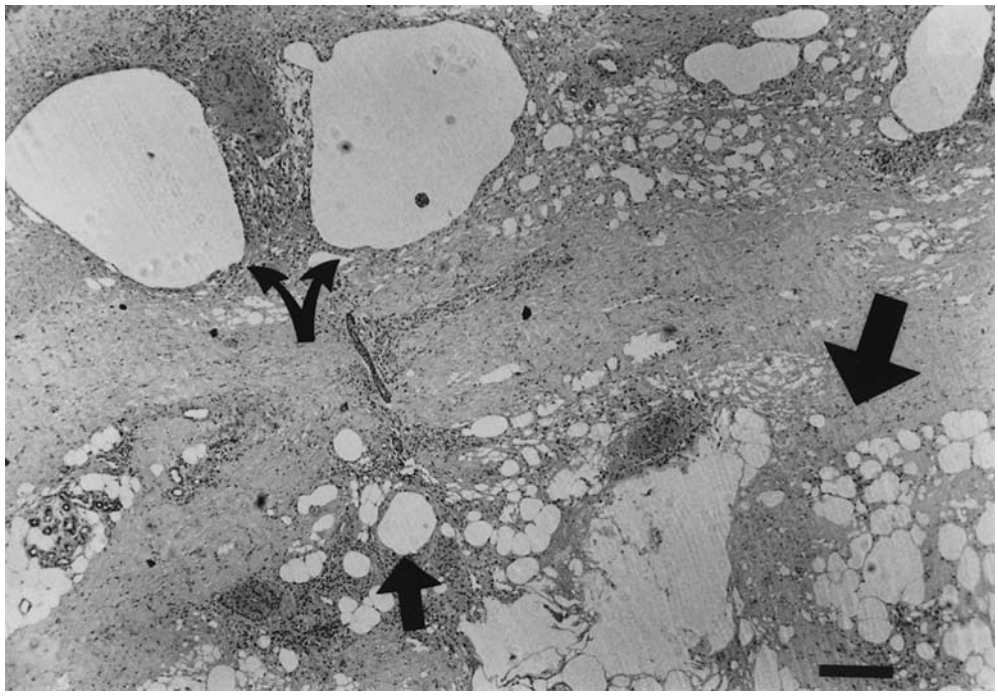

Fig. 2. A specimen from the skin lesions on the left leg revealed (1) septal panniculitis with lymphocytic infiltrate and fat necrosis (*large arrow*), (2) multiple lymphangiectasis in the dermis (*double arrow*), and (3) a dilation of venules between the fat lobules (*small arrow*). No arrow was observed. H&E stain. *Bar* = 100 μm

Discussion

Panniculitis is histologically classified into two types depending on the location of the inflammatory focus: septal panniculitis and lobular panniculitis. In the present case, a skin biopsy revealed septal panniculitis, which was not associated with vasculitis. Among the reported cases of septal panniculitis without vasculitis, erythema nodosum (EN), scleroderma panniculitis, eosinophilic fascitis, and necrobiosis lipoidica diabeticorum have all been observed. EN is located primarily over the extension surfaces of the lower extremities. The lesions may be associated with a variety of diseases, such as Behçet's disease, sarcoidosis, inflammatory bowel diseases, infections, drug administration, and certain malignant neoplasms. In the present case, tenderness at the lesion site of panniculitis has so far been mild compared with that noted in typical EN. Septal panniculitis, designated as scleroderma panniculitis, might be noted especially in the early stages of morphea and SSc. Mild scleroderma was noted in the hands and forearms in this patient. Proximal scleroderma has been reported in 21% of MCTD patients.[5] The skin on the left leg was not sclerosed. No sites of scleroderma panniculitis other than in the sclerosed skin area have yet been documented.[6] Eosinophilic fascitis and necrobiosis lipoidica diabeticorum were ruled out based on both the histopathological and the clinical features of this patient.

Lobular or septal panniculitis may occur in various connective tissue diseases.[6] In systemic lupus erythematosus and dermatomyositis, lobular panniculitis without vasculitis might sometimes be noted. With respect to MCTD, several cases accompanied by panniculitis have so far been reported. As far as we know, three patients with MCTD have been reported to have developed EN.[7–9] Itoh et al.[10] reported the case of a patient with MCTD who died from rapidly progressive pulmonary hypertension. Their patient has also suffered from painful subcutaneous calcification on the back of both her legs and buttocks, which might have been caused by repeated panniculitis. A histological classification of their patient's panniculitis has not yet been described. In the present case, there was no subcutaneous calcification, and the skin lesion was much smaller than the one in their case. Watabe et al.[11] reported the case of a patient with MCTD who developed mesenteric panniculitis. Taken together, panniculitis with several phenotypes (e.g., erythematous rash, EN, mesenteric type) might thus be associated with MCTD. Nezondet-Chetaille et al.[12] reported that the development of panniculitis was probably due to methotrexate for the treatment of MCTD. In our case, methotrexate had not yet been administered.

Regarding the characteristic features in our patient's pathological findings, multiple lymphangiectasis in the dermis and a dilation of the venules between the fat lobules was noted. Acquired lymphangiectasis is a condition in which dilated superficial lymphatics develop after damage to previously normal lymphatics. It occurs from the blockage of deep lymphatics causing dilated dermal lymphatic channels, which can lead to superficial vesicle formation. The reported extrinsic factors of acquired lymphangiectasis include a recurrent cutaneous infection, radiotherapy, surgery, scrofuluoderma, scleroderma, keloid, tumor, tuberculosis, repeated trauma,[13] and cirrhotic ascites.[14] However, none of these factors played a role in the present case. Septal panniculitis might be associated with the pathogenesis of this disease, but no similar cases have yet been reported.

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