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CASE REPORT

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Necrotizing fasciitis caused by *Streptococcus pneumoniae* in mixed connective tissue disease

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Abstract A 42-year-old man was hospitalized because of chills, fever, and severe polyarthralgia. He had a 5-year history of mixed connective tissue disease (MCTD) with polyarthritis which had been treated with a nonsteroidal anti-inflammatory drug alone. On the second day of hospitalization, necrotizing fasciitis of the right leg developed. *Streptococcus pneumoniae* was later detected in a blood culture. Pneumococcal infections of the soft tissues are uncommon, and have been reported in immunosuppressed patients and patients with systemic lupus erythematosus. This is the first report of a case of necrotizing fasciitis caused by *S. pneumoniae* in a patient with MCTD.

Key words Necrotizing fasciitis · *Streptococcus pneumoniae* · Mixed connective tissue disease

Introduction

Necrotizing fasciitis is a severe infection involving the subcutaneous soft tissue, particularly the superficial fascia. This infection is usually preceded by particular clinical settings, including diabetes mellitus, alcoholism, and parenteral drug abuse.[1] The most common etiologic agent is group A β-hemolytic streptococcus, and necrotizing fasciitis due to *Streptococcus pneumoniae* is extremely rare. To our knowledge, only five cases of necrotizing fasciitis due to *S. pneumoniae* have been reported.[2–5] Interestingly, three of these five cases developed in patients with systemic lupus erythematosus (SLE). Connective tissue diseases, especially SLE, have been recognized as a risk factor for severe pneumococcal infections such as pneumonia, septicemia, and soft-tissue infections. We report a case of necrotizing fasciitis due to *S. pneumoniae* in a patient with mixed connective tissue disease (MCTD). This is the first report of a case of MCTD complicated by this infection.

Case report

The patient, a 42-year-old Japanese man, was admitted to the University of Tsukuba Hospital in May 1998 because of chills, fever, and severe polyarthralgia. He had a 5-year history of MCTD, which manifested predominantly as Raynaud's phenomenon, polyarthritis, elevated serum creatine kinase levels, and positive anti-U1 RNP antibodies. He had been treated with loxoprofen, a nonsteroidal anti-inflammatory drug (NSAID). Arthralgia abruptly developed 2 days before admission, and was so severe that the patient was treated with intravenous methylprednisolone, 1 g/day, in another hospital 1 day before admission. On physical examination, his blood pressure was 128/80 mmHg, his pulse rate was 96/min, and his temperature was 36.8°C. Fine crackles were heard at the bases of both lungs. Although chest X-ray at admission revealed no abnormal findings when the patient was in a supine position, thereafter a chest computed tomography scan showed a consolidation with an air bronchogram in the left lower lobe and pleural effusion in both lungs, suggesting coincident pneumonia. Swelling and intense tenderness were present in both shoulders, elbows, and wrists, in the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, and in the right knee and ankle. His fingers were swollen. Laboratory tests gave the following results: leukocyte count 1900/mm^3; neutrophil count 360/mm^3; lymphocyte count 490/mm^3; an increase in lactate

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dehydrogenase (842 U/l) and creatine kinase (788 U/l); C-reactive protein 21.8 mg/dl; hypocomplementemia (C3 23 mg/dl, C4 5 mg/dl, CH50 15.7 U/ml); hypergammaglobulinemia (IgG 3731 mg/dl, IgA 281 mg/dl, IgM 120 mg/dl); positive antinuclear antibody in a titer of 1:5120 with a speckled pattern; anti-U1 RNP antibody in a titer of 1:256; positive anti-dsDNA antibody 37 IU/ml (normal 0–7). Anti-Sm antibody was negative. Bone-marrow aspiration revealed hypercellularity with no malignant cells. Urinalyses showed proteinuria of 162 mg/dl with abnormal urinary sediments containing red cells and granular casts. Ultrasonography revealed mild splenomegaly. Prednisolone therapy was started at 60 mg/day for 4 days, followed by a weekly taper to a maintenance dose of 5 mg/day. Amikacin and ceftazidime were also begun after blood collection for culture. *S. pneumoniae* was detected later. On the second day of hospitalization, swelling of the right calf occurred, accompanied by a reddish discoloration, hemorrhagic changes, and bullae formation (Fig. 1). Since the swelling and erythema extended to the thigh, a surgical incision was performed on the 7th day of hospitalization, and the soft tissues of the right leg were debrided. No pus was recovered, and an exudate and necrotic tissues were observed spreading from subcutaneous fat to fascia. The underlying muscles were almost macroscopically intact. Cultures of necrotic tssues and exudate yielded no bacteria. The patient's condition gradually improved, and thereafter the polyarthritis and proteinuria disappeared. The clinical course is shown in Fig. 2. Leukopenia occurred twice during the course of treatment and improved after the use of granulocyte colony stimulating factor and a change of antibiotics; it was presumed to be induced by the antibiotics.

Discussion

The present case had hallmarks of MCTD such as anti-U1 RNP antibodies, Raynaud's phenomenon, swollen hands, and polyarthritis, and it fulfilled the criteria for MCTD defined by Kasukawa et al.[6] In the present case, given that the patient's lactate dehydrogenase, creatine kinase, and anti-dsDNA antibody levels were increased at admission, the elevation of activity of MCTD appears to have preceded the onset of infection, and to have caused polyarthritis, nephropathy, leukopenia, and hypocomplementemia. However, there is a possibility that such manifestations might have been partially caused or modified by pneumo-

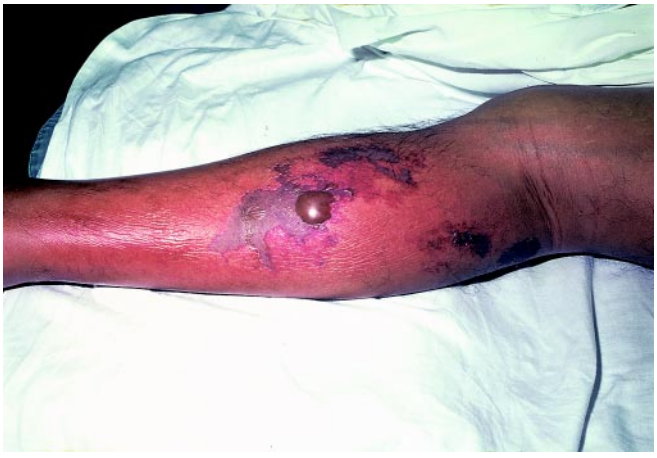

Fig. 1. Photograph of the patient's right leg

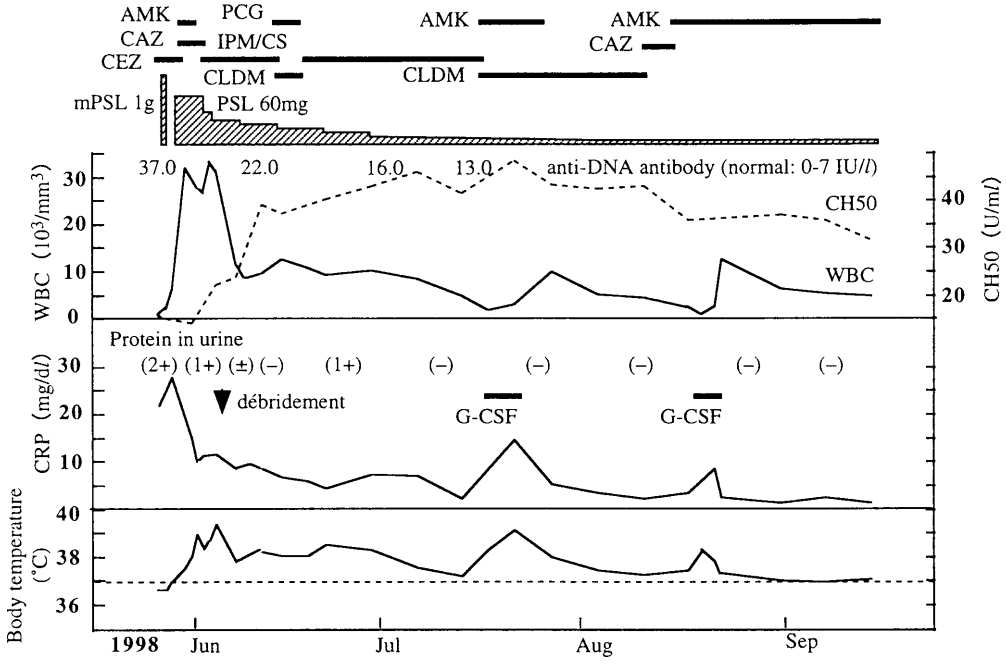

Fig. 2. Clinical course. *AMK*, amikacin sulfate; *CAZ*, ceftazidime; *CEZ*, cefazolin sodium; *CLDM*, clindamycin; *G-CSF*, granulocyte colony stimulating factor (lenograstim); *IPM/CS*, imipenem/cilastatin sodium; *mPSL*, methylprednisolone; *PCG*, benzylpenicillin benzathine; *PSL*, prednisolone

coccal infection. It is reported that, although rare, immune complex-mediated arthritis and immune complex-mediated glomerulonephritis can occur in patients with pneumococcal infection.[7,8] It is known that both exposure to and nasopharyngeal colonization by *S. pneumoniae* stimulate the emergence of antibody to pneumococcal capsular polysaccharides, even though the patient is asymptomatic.[9] This suggests that immune complex-mediated lesions may occur in the absence of recognized preceding infection. Leukopenia in pneumococcal infection is believed to result from the sequestration of neutrophils in the lung.[10]

Although the exact categorization of some bacterial infections of the soft tissues may be difficult, the infections have been classified into the more general categories of necrotizing fasciitis and cellulitis. Necrotizing fasciitis often requires an early surgical intervention. On the other hand, cellulitis, which involves only subcutaneous tissue, can be treated with antibiotics alone in most cases. In the present case, the clinical findings indicated necrotizing fasciitis due to *S. pneumoniae*. Although *S. pneumoniae* remains the most common cause of community-acquired bacterial pneumonia, its involvement in soft tissue infection is notably infrequent. Pneumococcal soft tissue infections often have predisposing factors, one of which is connective tissue disease, especially SLE.[3] Some mechanisms underlying the susceptibility of patients with SLE to such a fulminant infection have been reported, and include the use of certain immunosuppressants, splenic dysfunction, hypocomplementemia, and Fcγ receptor polymorphism.[11]

On the other hand, in patients with MCTD, only one case of serious pneumococcal infection has been reported.[12] In this reported case, pneumococcal septicemia occurred, and fibrosis and hypoplasia of the spleen were shown at autopsy, none of which was revealed in the present case. A case of cellulitis associated with MCTD has also been reported,[13] but the causative organism was *Neisseria meningitidis*. Interestingly, in that case, when migratory myalgias, arthralgias, and fever appeared, the patient was not receiving medication and hypocomplementemia was present, as in the present case. As these symptoms resembled previous flare-ups in the patient's condition, prednisone (40 mg/day) was started. However, after several days, cellulitis developed in the left calf. In the present case, since anti-dsDNA antibody was elevated, immunological alterations similar to those of SLE might have contributed to the development of pneumococcal infection. The onset of fever, chills, and polyarthralgia before the start of prednisolone decrease the likelihood that immunosuppression due to prednisolone predisposed the patient to pneumococcal infection, although prednisolone might aggravate the infection in spite of the concurrent administration of antibiotics. In addition, loxoprofen, which had been prescribed for a long period before admission, might also have been a factor involved in the aggravation of the infection. Cases of necrotizing fasciitis possibly induced by NSAID use have been reported.[14] One hypothesis is that a masking of the signs and symptoms of an existing infection leads to a delay in diagnosis and increases the severity of infection.[14]

In conclusion, we report, to our knowledge, the first case of necrotizing fasciitis caused by *S. pneumoniae* in a patient with MCTD. When a patient with MCTD has signs or symptoms suggestive of a flare-up of the disease, such as fever and polyarthralgia, the clinician should take into account the possibility of coincident infection, whether or not the patent is receiving immunosuppressive therapy.

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