A Case of Disseminated Sporotrichosis Treated with Prednisolone, Immunosuppressants, and Tocilizumab under the Diagnosis of Rheumatoid Arthritis

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Abstract

We encountered a disseminated sporotrichosis patient with polyarthritis and progressive skin ulcers, who had been previously treated with prednisolone, tocilizumab, tacrolimus, and cyclophosphamide under the diagnosis of rheumatoid arthritis in another hospital. Making the diagnosis of leukocytoclastic vasculitis based on the clinical observation of skin ulcers, we intensified immunosuppressive therapy. Unfortunately, the patient developed septic shock. Blood culture revealed that the pathogenic organism was *sporothrixschenckii*. Any case of intractable arthritis or skin ulcers, which does not improve, despite adequate immunosuppressive therapy, is likely to be suspicious of sporotrichosis.

Key words: sporotrichosis, rheumatoid arthritis, immunosuppressive therapy, biological agent, leukocytoclastic vasculitis, skin ulcer

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Introduction

Sporothrixschenckii, a dimorphism fungus, is the causative agent of Sporotrichosis. Sporotrichosis is a subcutaneous infection which causes various systemic pathological symptoms in patients. Lymphocutaneous sporotrichosis is the most common form of sporotrichosis seen in clinical practice. After cutaneous infection by the fungus, a papule develops at the affected site. Several weeks later, nodules are formed in the lymph node near the site. In some cases, pus is discharged from the nodules and an ulcer is formed around the site. It is rare for the focus to expand to other limbs or the trunk of the body (1). However, another type of sporotrichosis may develop in patients who have smoking and/or drinking habits, or suffer from other diseases including diabetes mellitus, chronic obstructive pulmonary disease, and/or acquired immunodeficiency syndrome. Pulmonary,

osteoarticular, meningeal, and disseminated sporotrichosis infections are associated with infection of *sporothrixschenckii* (2-6). The symptoms of these infections are similar to those of rheumatoid arthritis, as well as those of other connective tissue diseases and angitis syndromes (7-9). Only a few studies have reported cases of sporotrichal arthritis patients, in whom disseminated sporotrichosis was induced by immunosuppressive therapy and biological agents (10, 11). We report a patient with sporotrichal arthritis, who based on the clinical observation of systemic skin ulcer, was previously diagnosed as rheumatoid arthritis with concomitant vasculitis in another hospital and died due to dissemination of sporotrichosis after immunosuppressive therapy in our hospital.

Case Report

In 2006, a 78-year-old man (a farmer) visited a clinic

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Figure 1. Photograph of ulcers: (A) hand, (B) scrotum, (C) foot.

with pain and swelling in his upper and lower joints. Under the diagnosis of rheumatoid arthritis, oral administration of prednisolone (5 mg/day) was started. As the joint pain worsened despite the medication, in June 2008 he was referred to another hospital. At that time, swelling developed in some joints of wrists, feet, knees, and shoulders, as well as metacarpophalangeal and proximal interphalangeal joints. Moreover, it was suspected that his synovial membranes of the left wrist joint, bilateral knee joints, and right ankle joint had become proliferated. The laboratory test conducted in the hospital showed the following data: C-reactive protein (CRP) level, 1.73 mg/dL; The matrix metalloproteinase-3 (MMP-3) level, 196 ng/mL (out of its normal range of 36.9-121). However, it is not clear whether rheumatoid factors (RF) and the titer of an anti-cyclic citrullinated peptide antibody (ACPA) were examined. The attending physician assumed based on the findings of X-ray examination that fibrinoid degeneration was induced by rheumatoid arthritis in his right Lisfranc's joint and right caput humeroulnare. Accordingly, his diagnosis remained as rheumatoid arthritis. Although salazosulfapyridine and bucillamine were administered, he had no response to the medication; his symptoms further worsened. No skin symptom, such as phlegmon, nodules, and erythemas, was observed. In September 2008, tocilizumab was additionally administered. After that, on the back of his right hand and right foot, phlegmon developed. He did not recover from phlegmon at all; in fact, an ulcer formed on the back of his right hand even after antibacterial therapy with meropenem trihydrate and itraconazole. Biopsy of the specimen collected from the ulcer showed infiltration of inflammatory cells into the tunica adventitia of veins and arterioles. Steatonecrosis and degeneration were also observed in the connective tissues. No periodic acid-Schiff (PAS) stain test was conducted. It was assumed that he had angitis. Prednisolone was continued and sodium aurothiomalate was additionally administered. The examination of the cultured ulcer cells revealed the existence of *Candida*; therefore, the antifungal drug was switched from itraconazole to fluconazole. Since arthritis and the ulcer seemed to be caused by angitis, the administration of tacrolimus, an immunosuppressive drug, was started in November; then, it was changed to cyclophosphamide at the

beginning of December. At the end of November 2008, his joint pain worsened and multiple systemic skin ulcers appeared on his arms, legs and scrotum. At the end of January 2009, he was referred and admitted to our hospital. At that point, however, his vital signs were stable with no fever. Lung and heart sounds were normal and no lymph nodes were palpable. He did not complain of tenderness and no swelling was detected in the liver or spleen when the abdomen was palpated. It was difficult to identify joints with the skin ulcer developed. The ulcers had smelly exudate. Erythemas developed around the ulcers, some of which had been necrotized (Fig. 1). The laboratory test provided the following data: white blood cell count, 7,800/ μ L; neutrophil count, 7,170/ μ L; CRP level, 3.51 mg/dL; total protein level, 6.2 g/dL; albumin level, 2.2 g/dL; and hemoglobin (Hb) A1c level, 6.4%; plasma marker of thrombus slightly higher than the previous data, fibrin degradation product level, 8.3 μ g/dL; D-dimer level, 2.9 μ g/dL; and thrombin-antithrombinIII level, 6.4 ng/mL. The gammaglobulin level and the complement activity stayed within their normal ranges with the exception that 48 mg/dL in complement C3 activity was relatively low. All the tests of RF, hemagglutination, and other autoantibodies (including ACPA, myeloperoxidase-antineutrophilcytoplasmic antibody, and proteinase-3-antineutrophilcytoplasmic antibody) showed negative reactions. MMP-3 level rose to 730 ng/mL (out of its normal range of 36.9-121), and the soluble interleukin-2 receptor level went up to 1,472 U/L (out of its normal range of 145-519). Histocompatibility locus antigen-B51 showed a negative reaction. β -D glucan and *Candida* antigen were not tested during the hospital stay. The examination of cultured cells collected from the ulcer showed the existence of methicillin-resistant staphylococcus aureus and fungus. X-ray examination of the limbs detected no osteo-erosion or atrophy. The pathology of skin ulcer was shown by infiltration of neutrophil in the walls of small arteries and arterioles in dermis. Partial fibrinoid degeneration with karyorrhexis suggested that leukocytoclastic vasculitis had developed. Furthermore, granulomas was observed (Fig. 3). From the diagnostic result, angitis, based on the findings of the skin biopsy which had previously conducted at the other hospital, it was suspected that he had rheumatoid arthritis

Figure 2. Pathology of skin ulcers. (A) Inflammation in dermis and tissues under dermis. (B) Fibrinoid degeneration in artery. (C) Karyorrhexis and granulomas.

Figure 3. Worsened skin ulcers of (A) hand, (B) foot and (C) new erythema.

with vasculitis (malignant rheumatoid arthritis), though he did not necessarily meet the standard diagnostic criteria of malignant rheumatoid arthritis in terms of three points described below.

1. Clinical symptoms: 1) polyneuropathy; 2) skin ulcer or

infarctions and gangrene in fingers and toes; 3) subcutaneous nodules; 4) episcleritis or iritis; 5) pleurisy or pericarditis; 6) myocarditis; 7) interstitial pneumonia or fibrosis of lung; 8) infarction of organs; 9) high value of RF in serum; and 10) low value of complement or positive of immune complex in serum.

2. Histological findings: Necrotizing angitis in small and middle arteries, granulomatous angitis and endarteritis obliterans in skin, muscles, nerves or another organ biopsy.

3. Standard diagnostic criterion: The criteria for diagnosing rheumatoid arthritis (1987, American College of Rheumatology) to be met, 1) three items of clinical symptoms, or 2) one item of clinical symptoms and histological findings in two organs.

Throwing the diagnosis of skin ulcer with vasculitis into doubt, alprostadil and prednisolone (orally, 30 mg/day) were continuously administered. While skin ulcers gradually worsened, fever went up to 39.0°C in mid-February 2009. Infection attributed to catheter deployment in the central vein was suspected; therefore, vancomycin hydrochloride and ceftazidime were administered. The following day, intravascular immunoglobulin therapy was started to control the infection. A week later, micafungin sodium was administered under the suspicion of infection due to a form of mycosis because β -D glucan was markedly elevated to 1,404 pg/mL (above the normal range of 0-20). Limb skins appeared melted with the tendons and muscles exposed, and

Figure 4. Fungus identified in blood culture.

Table 1. The Comparison between Sporotrichal Arthritis and Rheumatoid Arthritis

	Rheumatoid arthritis	Sporotrichal arthritis
Epidemiology	Prevalence rate : 0.8%	Prevalence rate : unknown
Risk factor	Male:Female = 1:3 Genetic element (Human leukocyte antigen-DR4)	Male:Female=6:1 gardeners, farmers, alcoholism, compromised host
distribution of - arthritis	Joints of fingers (proximal interpharangeal joint. metacarpophalangeal joint). hands, knees, foots	Joints of knees (64%), fingers and hands (50%), elbows (24%), foots (20%)
Laboratory data	Elevated C-reactive Protein (CRP), Erythrocyte sedimentation rate (ESR), platelet. Anemia. Rheumatoid factor positive (80-95%).	Elevated ESR (87.5%), elevated β -D glucan
X-ray of joints	Bone atrophy and erosion. Contracting of joints cleavage.	Bone atrophy and erosion.
Specific examination	Anti-cyclic citrullinated peptide antibody (ACPA) : positive	Culture or Periodic acid-Schiff stain (PAS)-based
Pathology	Inflammation and production of synovial. Granulomas.	Chronic and nonspecific inflammation of synovial. Granulomas.

ulcers were expanded. Then, new erythemas appeared and expanded toward the trunk of the body, forming additional ulcers (Fig. 3). Then steroid pulse therapy (methylprednisolone 1,000 mg/day for 3 days) was applied to treat the ulcers, which were resistant to vasodilators and oral prednisolone, under our decision that further intensified immunosuppressive therapy was needed. With the medication showing no response to the disease, as fever went up, his respiratory condition deteriorated. The X-ray examination showed bilateral consolidations and ground-glass opacities in the lung field. On the images acquired by computed tomography (CT) scan, consolidations were also observed with partial cavities. *Sporothrixshenckii* was identified by blood culture and ulcer cell culture (Fig. 4). Based on this finding, he was diagnosed as disseminated sporotrichosis with a concomitant lung disorder, receiving the medication of amphotericin-B. His respiratory conditions still showed no response to the

medication, and he died of respiratory insufficiency. Sputum culture examination also showed the existence of *sporothrixshenckii*. Autopsy was not performed.

Discussion

Sporotrichosis is one of diseases commonly observed in Japan, especially in the Kanto area, along Tonegawa River. Patients are infected with sporotrichosis after having a small injury and touching soil. For this reason, this disease often develops in farmers (12). Sporotrichosis, which shows various pathological conditions on the skin lesions (erythemas, nodules, ulcers, and abscesses), is difficult to diagnose in terms only by visual inspection of skin. The favorite sites of sporotrichosis include the skins of the face, upper limbs and dorsum of hands. Initially, indolence pustules or intradermal nodules appears. Then, they come to red granulomatous

nodules, and ulceration (15). Patients with disseminated-type sporotrichosis, who have smoking and/or alcohol drinking habits, suffer from diabetes mellitus, chronic obstructive pulmonary disease, and/or acquired immunodeficiency syndrome, or have immunosuppressive therapy are considered to fall into a high risk group (2-6, 10, 11). The comparison between sporotrichal arthritis and rheumatoid arthritis is shown in Table 1 (7, 8, 18). Good similarities are observed in distribution of arthritis, images, and pathology between these diseases. Some examinations, such as culture or detection of fungus by PAS staining, are not useful at the early stage of the disease (9). Referral to the patients' background and laboratory test data such as a RF, an ACPA, and β -D glucan, diagnosis should be meticulously undertaken. The present patient might have been exposed to sporotrichosis in progress of treatment for rheumatoid arthritis or he might have initially got sporotrichal arthritis. Against the background that monoarthritis is most commonly observed in the patients with sporotrichal arthritis, a case of polyarthritis without skin symptoms was reported (7). Another study showed that polyarthritis accounted for 50% of sporotrichal arthritis and additional articular symptoms were not observed in most of arthritis patients (14). In contrast, the present patient, who was RF and ACPA negative and had no response to the immunosuppressive therapy, might have initially gotten sporotrichal arthritis. No studies have reported angiitis to be caused by *sporothrixschenckii*; accordingly, it has not been revealed that angiitis determined initially by skin biopsy was induced by *sporothrixschenckii*. Another patient with disseminated sporotrichosis was reported, who under the diagnosis of rheumatoid arthritis, had been treated with immunosuppressants and etanercept, one of the tumor necrosis factor antagonists (10). The skin ulcers of that patient were closely similar to those in the present patient with the exception that skin biopsy was not done, making it unknown whether angiitis had developed or not. Differential diagnosis between sporotrichal arthritis and rheumatoid arthritis is difficult in some cases. Nodules are formed in the skin lesions of rheumatoid arthritis, which are subject to mechanical stimulus, such as the extensor of elbow joint, the back of the head and the sacral. In addition, small chloasmas, spot infarctions, and gangrene (in the fingers and toes), refractory ulcers (in lower legs), and livedo are observed (16-18). The skin lesions of sporotrichosis should be properly distinguished from those of rheumatoid arthritis; however, it was difficult to precisely diagnose the disease of the current patient because almost all skin lesions were ulcerated when he visited our hospital. We should always take sporotrichosis into account in treating patients by intensified immunosuppressive therapy and biological agents.

The authors state that they have no Conflict of Interest (COI).

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