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【 CASE REPORT 】

Dermatomyositis Complicated by Digital Ischemia and Lung Adenocarcinoma in a Patient with Positive Anti-signal Recognition Particle Antibodies

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Abstract:
A 58-year-old Japanese woman was diagnosed with anti-signal recognition particle (SRP)-positive dermatomyositis associated with Sjögren's syndrome, rheumatoid arthritis and lung adenocarcinoma. She presented with cutaneous lesions, including ulceration of her right middle finger. Tissue specimens obtained from her right deltoid muscle were positive for $CD4^+$ T-cell infiltration and the sarcolemma showed the upregulation of major histocompatibility complex (MHC) class I antigens. The present case suggests that overlapping autoimmune diseases or complications of malignancy may result in an atypical clinical presentations and histological findings in patients with anti-SRP antibody-positive dermatomyositis.

Key words: anti-signal recognition particle antibodies, dermatomyositis, lung carcinoma, digital ischemia, amputation

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Introduction

Inflammatory myopathies are a group of muscle diseases characterized by skeletal muscle inflammation. They are classified into four major diseases: polymyositis, dermatomyositis, sporadic inclusion body myositis, and necrotizing autoimmune myositis (1). Approximately 50% of patients with myositis have defined autoantibodies, which are called myositis-specific autoantibodies (MSAs) and myositis-associated antibodies (2). Anti-signal recognition particle (SRP) antibodies, one of the MSAs, are detected in 4-8% of patients with idiopathic inflammatory myopathies (1). Patients with anti-SRP antibodies often present with histological features of necrotic myopathy, characterized by an absence of inflammatory cell infiltration and the low sarcolemmal expression of major histocompatibility complex (MHC) class I antigens. The typical clinical features of anti-SRP myopathy include rapidly progressing muscle weakness, marked elevation of serum creatine kinase (CK) levels, and resistance to glucocorticoid treatment (2). Cutaneous lesions and malignant tumours are uncommon in patients who are positive for anti-SRP antibodies (2-6). We herein describe the case of a 58-year-old Japanese woman with anti-SRP dermatomyositis and prior diagnoses of Sjögren's syndrome and rheumatoid arthritis whose clinical presentation and histological findings were atypical. Over the clinical course, the patient was further diagnosed with lung adenocarcinoma.

Case Report

A-58-year-old Japanese woman was admitted to our hospital due to ulceration of her right middle finger. Ten years prior to her admission, the patient had been diagnosed with Sjögren's syndrome, based on the detection of anti-SS-A and anti-SS-B antibodies, in combination with pathological findings that were suggestive of chronic sialadenitis. The patient had also been diagnosed with rheumatoid arthritis (RA), based on stiffness and arthritic changes in her fingers, in combination with the mild elevation of her serum C-

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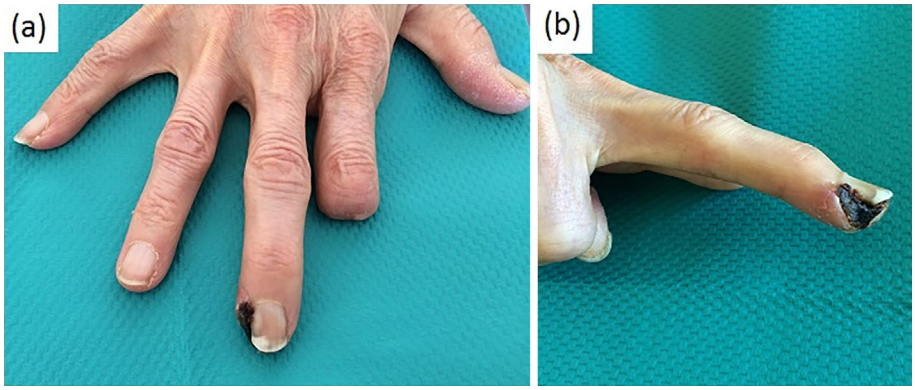

Figure 1. **(a, b) Ulceration of the right middle finger and the amputation of the right index at the level of the proximal interphalangeal joint.**

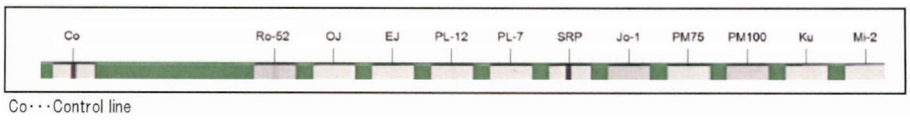

Figure 2. **Immunoblotting was strongly positive anti-SRP antibodies and slightly positive anti-SS-A antibodies (Ro-52).**

reactive protein (0.55 mg/dL) and rheumatoid factor (23.6 U/mL) levels. Since these diagnoses, the patient has received long-standing treatment with oral methylprednisolone (4 mg/day) and methotrexate (2 mg/week). Her antecedent history was otherwise unremarkable, with the exception of a 40-year smoking history. Her right index finger had been amputated at the level of the proximal interphalangeal joint, at another hospital, one year prior to the current admission.

A physical examination on admission revealed the following salient findings: Raynaud's phenomenon of her right index and middle fingers; rash on her face and anterior chest; and Gottron's papules on her elbows. There was no evidence of sclerosis of the skin (Fig. 1). Arthralgia and joint swelling were not present. A neurological examination revealed symmetrical proximal weakness of all four extremities (grade 3/5 weakness of the neck flexors, and grade 4/5 weakness of the pectoralis major, iliopsoas and hamstring muscles). Her distal extremity strength and all reflexes were normal. The patient's speech was normal, but she had dysphagia.

Laboratory investigations revealed elevated serum levels of CK, aldolase and myoglobin (500 U/L, 6.2 U/L, and 179.5 U/L, respectively). Her serum levels of C-reactive protein, rheumatoid factor, and IgG were within normal limits (0.17 mg/dL, 6.6 IU/mL and 1,510 mg/dL, respectively), as was her erythrocyte sedimentation rate (7 mm per hour). A serum tumour marker test indicated normal levels of carcinoembryonic antigen (CEA), CA19-9, and squamous cell carcinoma (SCC) (5.2 ng/mL, 3.2 U/mL, 0.3 ng/mL, respectively). Anti-SRP antibodies were detected in an immunoblotting assay (Fig. 2). Further testing detected anti-SS-A and anti-SS-B antibodies. The patient was negative for the following antibodies: aminoacyl-tRNA synthetase (ARS), Mi-2, Ku, MDA5, PM/Scl-100, PM/Scl-75, Scl-70, centromere, RNA polymerase 3, RNP, cyclic citrullinated peptide (CCP), myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), and proteinase (PR3)-ANCA. She was also negative for anti-Tif1-γ antibodies.

On contrast-enhanced computed tomography imaging, there was no evidence of the narrowing of blood vessels or interstitial lung disease. Pleural thickening was identified in the apex of the right lung and was considered to be associated with old pleural inflammation. Magnetic resonance imaging with T2-short-tau inversion recovery revealed a high intensity area in the right deltoid muscle. Electromyography of the left deltoid muscle revealed the early recruitment of motor units. A histological examination of specimens obtained from the right deltoid muscle, using hematoxylin and eosin staining, revealed a small amount of necrotic and regenerating fibres. The number of necrotic fibres that was observed in the specimens did not suggest necrotic myopathy. Evidence of $CD4^+$ T-cells infiltration and the sarcolemmal upregulation of MHC class I antigens was also present on immunostaining (Fig. 3).

Based on Bohan and Peter's criteria, the patient was diagnosed with dermatomyositis. The ulcer was treated with intravenous argatroban and oral beraprost. Although these drugs prevented the progression of the ulcer, the ulcer persisted. After the diagnosis of dermatomyositis, the patient was treated with regular oral prednisolone (1 mg/kg/day) and subsequent high-dose intravenous immunoglobulin therapy (0.4 g/kg/day, for 5 days). Following these treatments, her symptoms (ulceration, rash, and muscle weakness) improved and her serum levels of muscle enzymes normalized.

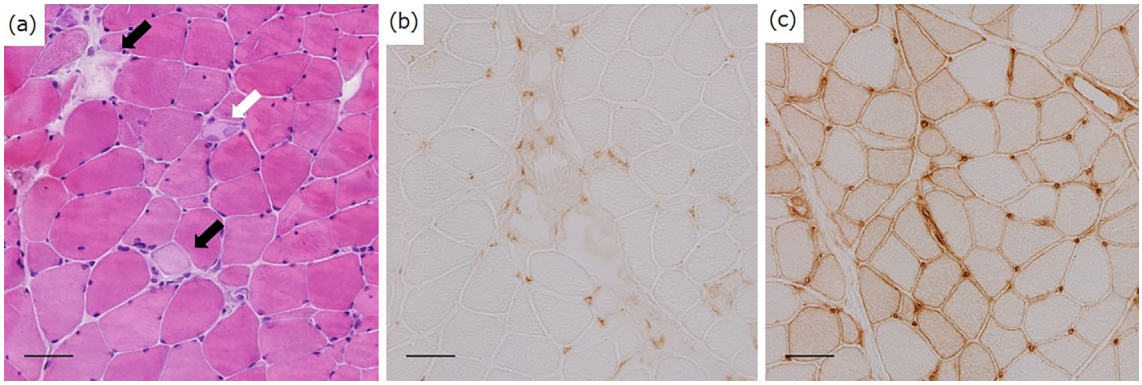

Figure 3. **(a) Hematoxylin and Eosin staining, showing a small amount of regenerating (white arrow) and necrotic fibres (black arrow). (b) Immunohistochemical staining showing $CD4^+$ T-cells. (c) Immunohistochemical staining for MHC class I antigen showing intense sarcolemmal labelling (brown) (Scale bars: 50 μm, original magnification ×200).**

Halfway through treatment, the patient underwent ^{18}F-fluorodeoxyglucose positron emission tomography imaging (^{18}F-FDG-PET CT), which revealed the uptake of FDG in the apical portion of her right upper lung. A transbronchial lung biopsy was performed and lung adenocarcinoma was confirmed. Following the gradual tapering of prednisolone therapy, the patient underwent right upper lobectomy and was subsequently discharged from the hospital. However, a postoperative pathological diagnosis revealed pleural dissemination and metastasis of the adenocarcinoma to the pulmonary lymph nodes (invasive adenocarcinoma, acinar predominant). The patient is currently undergoing chemotherapy.

Discussion

MSAs are useful for confirming the diagnosis of autoimmune myositis and for defining disease subsets (1). However, in our patient, abnormal muscle histopathological findings, including the infiltration of inflammatory cells and the sarcolemmal upregulation of MHC class I antigens, and the presence of cutaneous lesions, including ulceration of her right middle finger, were atypical findings for anti-SRP myopathy. Suzuki et al. reported that 2% of anti-SPR antibody-positive patients with myopathy had dermatomyositis (6). Based on Bohan and Peter's criteria, the patient was diagnosed with dermatomyositis. However, a histological study showed none of the typical findings of dermatomyositis, such as vasculitis and perifascicular atrophy; rather, scattered necrotizing fibers were observed, which might have been affected by some immune-mediated mechanisms. Previous studies have reported the possible coexistence of anti-SRP antibodies with other autoantibodies and that these cases may present with an atypical anti-SRP myopathy (1, 7-10). Kao et al. reported that among 909 cases of connective tissue disease (SSc, n=790; overlap syndrome, n=109) anti-SRP antibodies were detected in two patients with systemic sclerosis (SSc) and one patient with antisynthetase syndrome (7). Takada et al. reported that patients who test positive for anti-SRP antibodies and without myositis may present with arthritis, especially RA in the Japanese population (10). Thus, the coexistence of anti-SRP myopathy with other autoimmunity diseases can result in diverse symptoms among patients with anti-SRP antibodies. Conversely, myositis is often complicated with malignancy, including ovarian, lung and gastrointestinal adenocarcinoma, known as a paraneoplastic syndrome (11). It is also known that digital ischemia, which is uncommon among patients with dermatomyositis, sometimes appears as a paraneoplastic phenomenon (12, 13). In our case, although intravenous argatroban and oral beraprost prevented the progression of the ulcer, marked wound healing was observed after steroid therapy. This clinical course suggests that an overlapping inflammatory syndrome played an important role in her digital ischemia. In contrast, the fact that argatroban and beraprost were useful in preventing the progression of her digital ischemia also suggested involvements of thromboembolic mechanism due to fragments of the carcinoma and a vasoconstrictive substance produced by the tumor cells (13). As noted above, the atypical findings of anti-SRP myopathy that were observed in our patient might be a consequence of either an overlapping inflammatory syndrome or a paraneoplastic syndrome. With regard to the treatment of her comorbid diseases, we believe that the treatment of malignancy was a priority as any delay in this treatment would have the potential to lead to a fatal outcome. In addition, myositis itself is a component of paraneoplastic syndrome, which is dependent on the treatment of the malignancy. It is known that cutaneous necrosis and ulceration (which were evident in our case) are risk factors for malignancy among patients with myositis (11). Our case raises the importance of performing a detailed examination to detect malignancies in patients presenting with myositis, especially those with known risk factors for malignancy, even if they test positive for anti-SRP antibodies. In conclusion, we described a case of dermatomyositis complicated by digital ischemia and lung adenocarcinoma in a patient who tested positive for anti-SRP antibodies. Unfortunately, the limited number of patients

presenting with overlapping anti-SRP antibody positivity and another autoimmune disease or malignant tumour makes it difficult to clarify the relationship between anti-SRP antibodies and these conditions. Further clinical investigations are needed to reveal the importance of anti-SRP antibodies to the clinical course of autoimmune diseases and malignancy.

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

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