Case report

Anti-EJ antibody positive interstitial lung disease with skin changes at the fingertips

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Summary

Antisynthetase syndrome is characterized by the presence of anti-aminoacyl-tRNA synthetase antibodies and characteristic clinical features. We report an anti-EJ antibody-positive case presenting an ILD with slight hyperkeratotic skin changes on the fingertips that appeared simultaneously with respiratory symptoms. We suspected those skin changes of a disease manifestation of antisynthetase syndrome, and thus investigated anti-synthetase antibodies. This case implies that broader spectrum of the patients should fall in antisynthetase syndrome even though the present diagnostic criteria call for mechanic’s hand as a skin manifestation. Careful examination of the finger skin and antibody testing should lead to a proper understanding of the pathological processes.

Key words— aminoacyl-tRNA synthetases; anti-EJ antibody; antisynthetase syndrome; interstitial lung disease

Introduction

Antisynthetase syndrome is characterized by the presence of at least one anti-aminoacyl-tRNA synthetase (anti-ARS) antibody and the following features; inflammatory myopathy, interstitial lung disease (ILD), arthritis, fever, Raynaud’s phenomenon and mechanic’s hands. This syndrome falls into the category of idiopathic inflammatory myopathy (IIM). However, some cases present skin manifestations together with minimal or no muscle manifestations. ILD associated with antisynthetase syndrome sometimes progresses rapidly and leads to premature death. Particularly, ILD with amyopathic antisynthetase syndrome has a poorer prognosis. Prompt treatment with corticosteroid and immunosuppressive drugs are reportedly useful to control progression of the ILD especially for patients with rapidly progressive ILD associated with antisynthetase syndrome. However, without mechanic’s hands or muscle involvement, it is difficult to make a diagnosis of antisynthetase syndrome. We herein report on an anti-EJ antibody-positive ILD case having slight skin changes of the fingertips.

Case report

A 49-year-old Japanese man, a current smoker with no significant past medical history, was admitted to our hospital with a 2-month history of progressive dyspnea on exertion, and a 1-month history of persistent non-productive cough. Physical examination revealed fine crackles and decreased breath sounds in the bilateral lower lung fields, and no muscle weakness or tenderness. Raynaud’s phenomenon was not present. He had a slight roughening of the skin of the fingertips especially in both of the thumbs and the right 3rd and 4th finger (Fig. 1). Initial blood test showed a normal complete blood count and elevated lactate dehydrogenase (431 U/L), KL-6 (7705 U/mL), and SP-D (1380 ng/mL). Other laboratory tests including liver and muscle enzymes were within normal limits. Anticytoplasmic antibodies were positive with titer 1:40 by fluorescent antinuclear antibody (ANA) testing. Anti Jo-1 antibodies, myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA), proteinase-3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA), anti SS-A/Ro, and SS-B/La antibodies were negative. Arterial blood gas disclosed the normal level of oxygen and decreased level of carbon dioxide, resulting in increased alveolar-arterial oxygen difference (A-a DO₂) (Room air, PaO₂ 77.7 mmHg, PaCO₂ 34.6 mmHg, A-aDO₂ 28.8 mmHg). Reduced vital capacity (%VC 51.3%) with normal forced expiratory volume in one second (FEV₁% 87.9%) were found with spirometry. Carbon monoxide diffusing capacity (DLco) was not evaluated because of forceful coughs. Chest X-ray disclosed interstitial opacity and volume reduction of the bilateral lower lung fields.
Chest and abdominal CT scan revealed bilateral ground glass opacities in the lung bases with reticular markings sparing the subpleural region, which were consistent with a nonspecific interstitial pneumonia (NSIP) pattern (Fig. 2). No other abnormalities including malignancy were found. No abnormal signals were found with magnetic resonance imaging of the thigh muscles. Skin biopsy of the lateral surface of the finger was performed to disclose histological changes including acanthotic dermatitis with spongiotic change, slight mucinosis of the dermis and slight inflammatory cell infiltration in the junction of the epidermis and dermis without liquefaction degeneration.

Although the pathological findings of the skin are consistent to hand eczema, they can be found in the skin lesions of dermatomyositis. Since the skin lesion appeared simultaneously with respiratory manifestation, we performed further evaluation of the autoantibodies. RNA immunoprecipitation of the patient’s sera revealed presence of anti-EJ antibodies and no other anti-ARS antibodies, including anti-OJ, anti-KS, anti-PL-7 or anti-PL-12 antibodies. Anti-signal recognition particle (anti-SRP) antibodies were negative.

We made diagnosis of antisynthetase syndrome, considering the simultaneous appearance of ILD and skin changes, and commenced treatment with a combination of prednisolone 50 mg/day (1 mg/kg/day) and tacrolimus. Within four weeks, dry coughs and dyspnea on exertion resolved. The skin changes of the fingers disappeared. Laboratory tests revealed serum KL-6 and SP-D decreased (3824 U/ml and 224 ng/ml, respectively at 35 days after treatment). Pulmonary function was improved (%VC 76% and %DLCO 74.9% at 36 days after treatment) as well as interstitial changes in the Chest CT (Fig. 3). Prednisolone was gradually tapered for 6 months. No recurrence of ILD or development of other manifestations has been observed.

**Discussion**

We present here an anti-EJ antibody-positive patient presenting an NSIP pattern of ILD. Although the skin changes were not necessarily characteristic to antisynthetase syndrome, the simultaneous appearance with ILD argue for their association.

Although diagnostic criteria for antisynthetase syndrome has been proposed by Solomon et al., which requires the presence of an anti-ARS antibody and two major conditions (ILD and the diagnosis of inflammatory myopathy), or one major and two minor conditions (arthritis, Raynaud’s phenomenon or mechanic’s hands) for diagnosis, no consensus has been established. Since the skin changes of the present case were not typical mechanic’s hands, this classification was not fulfilled. Nevertheless, this case suggests that broader spectrum of the patients with skin manifestations should fall in antisynthetase syndrome.

In approximately 40% of the ILD patients associated with antisynthetase syndrome, ILD preceded myositis.
According to a Japanese retrospective study using 6 anti-ARS antibodies screening, 7% of patients with idiopathic interstitial pneumonia were positive for anti-ARS antibodies. These facts suggest that a certain number of antisynthetase syndrome patients present ILD alone or with atypical skin changes at the beginning and might be treated as patients with idiopathic interstitial pneumonia. Marie et al. reported that ILD in anti Jo-1 positive patients deteriorated even with immunosuppressive therapy in 11 out of 66 patients, and led to premature death in 5 of them. Hervier et al. suggested that amyopathic patients with ILD and anti-ARS antibodies should have a poorer survival than myopathic patients. Considering that treatment responses of ILD depends greatly on the underlying etiology, amyopathic patients with antisynthetase syndrome associated ILD should be discriminated from idiopathic ILD patients for prompt treatment. In the present case, detection of anti-EJ antibodies was essential for discrimination.

The differentiation between mechanic’s hand and hand eczema is sometimes difficult. Mechanic’s hand is characterized with well demarcated roughening and cracking of the skin over the lateral and palmer aspects of the fingers, typically on the ulnar aspect of the thumbs and the radial aspect of the other fingers of both hands. In contrast, hand eczema is typically not demarcated and frequently observed in the dominant arm. Both can show pathological findings of hyperkeratosis, parakeratosis and acanthosis, but colloid bodies in the epidermis, mucin deposition in the dermis, and liquefaction degeneration of the basal layer are dominantly seen in mechanic’s hands and spongiosis of the epidermis is dominantly seen in hand eczema. In this case, lesions were not well demarcated and the pathological finding of spongiotic change without colloid body or liquefaction degeneration led to the pathological diagnosis of hand eczema. It is difficult to discriminate these two conditions pathologically, and the clinical course, that is, simultaneous appearance of skin lesions with systemic symptoms is the most important point for a proper diagnosis.

Recently, a new ELISA system for detecting anti-ARS antibodies, including anti-Jo-1, anti-EJ, anti-KS, anti-PL-7, and anti-PL-12 antibodies was developed and is now approved in Japan. It is of great use to detect a broader range of anti-synthetase antibodies although it does not detect anti-OJ antibody, which makes up 5% of anti-ARS antibodies in Japan, anti-Zo, or anti-Ha antibodies. ILD patients, especially with skin changes, have to be invested for presence of anti-ARS antibodies.

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Conflicts of interest

H.Kohsaka has served as a consultant to Chugai Pharmaceutical Co., LTD. and Teijin Pharma Limited and received honoraria for lecture fees from Chugai Pharmaceutical Co., LTD; Mitsubishi Tanabe Pharma Corporation; and Ono Pharma ceutical Co., Ltd; and received research grants from Bristol-Myers Squibb; Eisai Pharmaceutical; Mitsubishi Tanabe Pharma Corporation; and Takeda Pharmaceutical Co. All other authors have declared no conflicts of interest.

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