Successful rituximab therapy for skin sclerosis and myositis in a patient with systemic sclerosis, myositis and Sjögren’s syndrome associated with autoimmune polyglandular syndrome

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Case Report

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Abstract

**Background:** Autoimmune polyendocrine syndromes (APSs) are relatively rare clinical conditions characterized by functional impairment of multiple endocrine glands due to loss of immune tolerance. These syndromes are broadly categorized as rare monogenic forms, such as APS-1, and a more common polygenic variety, APS-2. In APS-2, many autoimmune conditions can develop, including autoimmune rheumatic diseases. However, systemic sclerosis and myositis can occur as quite rare complications, for which no treatment strategy has yet been established.

**Case presentation:** A 25-year-old man who had been diagnosed as having type 1 diabetes developed finger stiffness. Although the subjective symptoms were relatively mild, extensive examinations including various autoantibodies, hormones and biopsy of the skin and minor salivary glands revealed that he had APS-2 (type 1 diabetes and autoimmune thyroid disease) accompanied by systemic sclerosis, myositis and Sjögren’s syndrome. Rituximab therapy was initiated for the progressive skin sclerosis, and this resulted in significant of both the sclerosis and the myositis.

**Conclusion:** Various autoimmune rheumatic diseases can develop in APS-2. Early diagnosis and immunomodulatory therapy may arrest the autoimmune process before irreversible organ damage has occurred, and rituximab appears to be a promising therapy for autoimmune rheumatic diseases associated with APS-2.

Background

Autoimmune polyendocrine syndromes (APSs) comprise a diverse group of clinical conditions characterized by functional impairment of multiple endocrine glands due to loss of immune tolerance [1]. These syndromes can be broadly categorized as rare monogenic forms, such as APS-1, and a more common polygenic variety, APS-2 [1]. APS-1 is a rare autosomal recessive disease caused by mutations in the autoimmune regulator gene, and is characterized by the development of at least two of three cardinal components during childhood: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (Addison’s disease). On the other hand, APS-2 can show courses characterized by at least two of three endocrinopathies: type 1 diabetes, autoimmune thyroid disease and Addison's disease. Although some authors have proposed splitting this syndrome into APS-2, APS-3 or APS – 4 [2], the broader term APS-2 is now considered appropriate for all affected patients because there is little evidence for distinct causes in such subcategories [1]. The prevalence of APS-1 and APS-2 is 1:100000 and 1: 1000, respectively, and APS-2 is a milder and later-onset disease. In APS-2, many autoimmune conditions can develop, including celiac disease, alopecia, vitiligo, primary ovarian insufficiency, pernicious anemia and various autoimmune rheumatic diseases.

Here we present a rare case of systemic sclerosis, myositis and Sjögren’s syndrome associated with APS-2 for which rituximab therapy was quite effective for control of progressive skin thickening and muscle lesions.
Case presentation

A 25-year-old Japanese male was referred to our hospital because of finger stiffness and body weight loss (-7 kg over 3 months). Three years previously, he had been diagnosed as having latent adult autoimmune (type 1) diabetes on the basis of a random plasma glucose level of 284 mg/dl, a hemoglobin A1c (HbA1c) level of 6.3%, and a markedly elevated serum anti-glutamic acid decarboxylase (GAD) antibody level (1143.3 U/ml, normal < 5.0). He had been treated with voglibose 0.6 mg daily and his HbA1c level was 5.7%. He had no family history of diabetes, thyroid disease or rheumatic disease. His height, body weight, blood pressure and pulse rate were 175 cm, 55 kg, 132/83 mmHg and 118/min, respectively. On clinical examination, the proximal interphalangeal (PIP) joints were slightly swollen and tender. Although Raynaud's phenomenon was absent, there was skin thickening on the fingers of both hands extending proximally to the metacarpophalangeal joints and anterior chest [modified Rodnan total skin thickness score (mRSS) 5 points at the first visit], and telangiectasia was evident on the anterior chest. Mild myalgia and muscle tenderness were evident on the bilateral thighs, without apparent muscle weakness. There were no other abnormal findings.

Laboratory data showed high serum levels of creatine kinase (CK) (1198 U/l) (normal: 59–248), aspartate aminotransferase (AST) 58 U/l (13–30), alanine aminotransferase (ALT) 58 U/l (10–42), and lactate dehydrogenase (LDH) 265 U/l (124–222). The serum C-reactive protein level was 0.05 mg/dl; IgG was 2111 mg/dl (861–1747), IgA was 327 mg/dl (93–393), and IgM was 64 mg/dl (33–183). Electrolytes, as well as urinalysis and renal function parameters, were all within the normal ranges. Rheumatoid factor and anti-CCP antibody were negative. Anti-nuclear antibody (ANA) was positive (x2560) with a nucleolar and speckled pattern, and only anti-Ro/SSA was positive (149 U/ml, normal < 9.9) among disease-specific autoantibodies including scleroderma or myositis-related autoantibodies. On the basis of the levels of thyroid-stimulating hormone (TSH) 0.01 µIU/ml (normal: 0.35–4.94), free triiodothyronine (FT3) 15.90 pg/ml (1.68–3.67), free thyroxine (FT4) 3.98 ng/dl (0.7–1.48) and TSH receptor antibody (TRAb) 21.6 IU/l (normal < 2.01), the patient was diagnosed as having Graves’ disease. Anti-thyroid peroxidase (TPO) antibody and anti-thyroglobulin antibody were also positive (576 IU/ml, normal < 5.61, and 118.0 IU/ml, normal < 27, respectively). Adrenocortical parameters were normal.

A forearm skin biopsy revealed atrophic eccrine glands entrapped within thickened dermal collagen, compatible with scleroderma (Fig. 1). Although subjective dry eyes and dry mouth were absent, Schirmer tests (right; 6 mm/5 min; left; 4 mm/5 min) were positive and biopsy of a minor salivary gland revealed periductal infiltration of lymphocytes (focus score 1) (Fig. 2). Axial T2-weighted magnetic resonance imaging (MRI) of both thighs revealed bilateral patchy hyperintense lesions, consistent with myositis (Fig. 3). On the basis of these results, the patient was diagnosed as having systemic sclerosis, Sjögren’s syndrome and myositis associated with APS-2 (type 1 diabetes and autoimmune thyroid disease). Further examinations revealed no evidence of any interstitial lung disease, or heart, renal and gastrointestinal lesions. Thiamazole was added to the voglibose, and the patient’s thyroid function gradually improved. However, the skin thickening rapidly worsened. Two months after the first visit, the mRSS had increased to 13 points (bilateral fingers 2 in each, bilateral forearms 3 in each, and anterior
chest 3). Although dyspnea was absent, pulmonary function tests revealed a decreased vital capacity (VC) (% VC 62.3%). Diffusing capacity (DLCO) was normal and high-resolution computed tomography demonstrated no interstitial lung lesions, suggesting that the decreased VC was due to sclerosis of the anterior chest skin.

Rituximab (RTX) was then administered at a dose of 375 mg/m² once a week for four weeks. During the initial 3 months after RTX therapy, there were no significant changes in the skin thickness (mRSS 12 points) or the level of serum CK (1605 U/l). However, at six months after completion of the RTX therapy, the mRSS had decreased to 7 points (bilateral fingers 1 in each, bilateral forearms 2 in each, and anterior chest 1). VC was slightly increased (% VC 66.5%) and the level of CK was decreased (725 U/l). At 6 months after the initial RTX therapy, we administered additional RTX at a dose of 375 mg/m² once a week for two weeks and methotrexate was administered as maintenance therapy. At one year after the first RTX therapy, the mRSS was 4 points (bilateral fingers 1 in each, bilateral forearms 1 in each, and anterior chest 0), % VC was 73.5%, and the level of CK was within the normal range (79 U/l).

**Discussion and conclusions**

This report describes a rare case of APS-2 accompanied by systemic sclerosis, myositis and Sjögren’s syndrome as non-endocrine autoimmune disorders. Sjögren’s syndrome has sometimes been reportedly associated with APS-2 [3], although the precise frequency has remained unclear. However, systemic sclerosis or myositis associated with APS-2 is quite rare.

In general, management of APSs includes hormone replacement therapy as needed and treatment of complications [1]. In the present case, symptoms associated with type 1 diabetes and Graves’ disease were mild and both conditions had been well controlled with non-immunosuppressive therapy. On the other hand, progressive skin sclerosis on the anterior chest was problematic because it had led to a decrease of VC.

RTX is a chimeric antibody against CD20, a cell membrane molecule specifically expressed in B cells. Although the pathogenesis of systemic sclerosis remains unclear, B cells are thought to play a central role, and B-cell depletion therapy with RTX has been attempted [4]. In Japan, the DESIRES study was conducted from 2017 to 2019 involving 56 Japanese patients with systemic sclerosis [5]. In this double-blind, placebo-controlled trial with a primary-endpoint measure of skin sclerosis, RTX demonstrated significant efficacy compared to placebo and RTX was approved for systemic sclerosis in Japan in 2021, although it has not been approved in the United States and Europe because the DESIRES trial involved only Japanese patients.

In the present case of APS-2, skin sclerosis and CK elevation were significantly improved with RTX, suggesting a significant role of B cells in APSs and associated non-endocrine autoimmune disorders. In fact, RTX has been reported to have beneficial effects on pneumonitis and malabsorption associated with APS-1 [1], although the number of cases has been limited so far.
APSs are insidious, being characterized by circulating autoantibodies and lymphocytic infiltration of affected tissues or organs, eventually leading to organ failure. The onset of APS-2 typically occurs in young adulthood, but diagnosis is difficult during the asymptomatic phase because there are no specific tests for detection of APS-2. However, testing for autoantibodies may be helpful for assessment of disease risk, as it has been reported that the relevant autoantibodies are frequently detectable years before disease onset [1]. Although APSs are rare, physicians should be aware of this condition and consider testing for various autoantibodies in young adult patients diagnosed as having autoimmune endocrine diseases. Physicians should also be aware that APS-2 carries an increased risk for development of other autoimmune diseases. In fact, in the present case, extensive examinations revealed various concurrent autoimmune diseases, even though subjective symptoms were mild. Early diagnosis and immunomodulatory therapy may be able to arrest the autoimmune process before irreversible organ damage has occurred, and RTX appears to be a promising therapy for autoimmune rheumatic diseases associated with APS-2.

In conclusion, we have presented a rare case of systemic sclerosis, myositis and Sjögren’s syndrome associated with APS-2. RTX was quite effective for treatment of skin sclerosis and muscle lesions.

**Abbreviations**

APSs  
Autoimmune polyendocrine syndromes  
CK  
creatinine kinase  
mRSS  
modified Rodnan total skin thickness score  
VC  
vital capacity  
RTX  
rituximab

**Declarations**

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report including clinical information and related images. The consent form has been stored by the corresponding author and may be obtained on request from the editor of this journal.
Availability of data and materials

Laboratory, imaging and pathology data are presented in this article. Additional data not presented in this article is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Author's contributions

TS, HN, SS, HK and KF were the attending physicians of the patient. TS wrote the manuscript. HK and HU performed histological examinations and obtained the diagnosis. TS, HN, SS, HK and KF contributed to discussion and reviewed/edited the manuscript. All authors have read and approved the final version.

Acknowledgement

Not applicable

References


Figures
Figure 1

Forearm skin biopsy reveals atrophic eccrine glands entrapped within thickened dermal collagen. (Hematoxylin and eosin stain, ×40).

Figure 2

Figure 2
A lip biopsy of the minor salivary gland reveals periductal infiltration of lymphocytes (Hematoxylin and eosin stain, ×100),

**Fig. 3**

![Magnetic resonance imaging of both thighs](image_url)

**Figure 3**

Magnetic resonance imaging of the both thighs. Axial T2-weighted image reveals bilateral patchy hyperintense lesions in the both muscles.