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Myositis in primary Sjögren's syndrome: clinical and pathological report

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Abstract To clarify the clinical features of myositis complicated with primary Sjögren's syndrome (SS), we studied 89 patients with Sjögren's syndrome (one male and 88 females; mean age 56.0 ± 15.31 years). Myositis was diagnosed from clinical findings, muscle enzymes, electromyographic findings, and muscle biopsy findings. Myositis was diagnosed in 5 of 89 SS patients (5.6%). One patient developed myositis 7 months after the onset of SS. The other four patients were diagnosed with myositis and SS simultaneously. Muscular weakness was mild and slowly progressive over 4–14 months (mean 8.4 months). All patients were able to walk without any assistance at the start of prednisolone therapy. Muscular enzymes were slightly elevated (from 1.5- to 12-fold). All patients tested negative for anti-Jo1 antibody and tested positive for antinuclear antibody. Anti-Ro(SSA) antibody was positive in 4/5 (90%); anti-La(SSB) was positive in 2/5 (40%). Although the clinical features of all patients met the criteria for polymyositis of Bohan, they responded well to small or moderate doses of prednisolone, which could be decreased without a recurrence of muscular weakness in all patients. Myositis with Sjögren's syndrome showed relatively moderate symptoms and responded well to prednisolone. A prospective follow-up of patients may provide further information.

Key words Myositis · Polymyositis · Prednisolone · Primary Sjögren's syndrome (SS)

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of salivary and lacrimal glands, resulting in xerostomia and xerophthalmia. It is well known that extraglandular manifestations, involving the renal, lung, dermatological, musculoskeletal, and nervous systems, may complicate SS. Although myalgia is one of the common symptoms of SS, myositis has rarely been reported. The purpose of our study was to determine the prevalence and the clinical/laboratory characteristics of myositis in primary SS.

Patients and methods

Patients

We identified 89 patients (1 male, 88 females) who were followed by Internal Medicine, Yokohama City University School of Medicine, Yokohama, Japan, between June 2000 and March 2001. SS was defined by the presence of four of six European Community diagnostic criteria,[1] with one modification: the Saxon test was performed instead of the gum test. Other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, were excluded after clinical studies.

Myositis was diagnosed when the patients met more than three of the following criteria:

1. muscle weakness;
2. elevation of serum muscle enzymes;
3. electromyography (EMG) studies, myogenic change;
4. muscle biopsy abnormalities.

Points 3 and 4 were assessed only when there were clinical symptoms.

Methods

The following data were recorded for each patient.

1. Clinical findings. Age at entry, sex, sicca symptoms and findings (Schirmer test, Saxon test), extraglandular manifestations, associated autoimmune disease, onset of muscular symptoms, grading of muscular weakness on a scale from 1 to 6, as described previously.[2]
2. Laboratory findings. Blood cell count, serum IgG, IgA, and IgM, antinuclear antibodies (ANA) using Hep-2 cells as substrate (>80 × positive), rheumatoid factor (RF), latex fixation test (>20 IU/ml positive), antibodies to Ro(SSA), La(SSB), and U1-RNP, enzyme-linked immunosorbent assay (ELISA) (>10 U/ml positive), serum creatine kinase (CK) (normal range 46–188 IU/l), serum aldorase (normal range 1.7–5.6 IU/l), EMG findings.

All muscle biopsy specimens were obtained through open biopsy from the vartus lateralis or the deltoid muscle. Sections of muscle specimens were stained by the following methods: hematoxylin and eosin (H–E), modified Gomori trichrome, and NADH-tetrazolium reductase. A semiquantitative 3-point scale (−, ±, +) was used to grade morphological changes.

Statistical methods

Mann–Whitney's nonparametric test for comparison of groups was used.

Results

The clinical, laboratory, and pathological studies are summarized in Table 1. The average age of all primary SS patients was 56.0 ± 15.31 years (±SE). Eighty-eight patients were female and one was male. Eight patients (8.9%) complained of myalgia, but myositis was identified in only five patients (5.6%) (Table 1). All these were women, with a mean age of 61.2 years (50–74) (Table 2), and all had more than one extraglandular manifestation. The prevalence of Raynaud's phenomenon and neurological symptoms were 2/5 (40%) and 4/5 (80%), respectively. No patient had interstitial pneumonia. Patient 4 had a permanent pacemaker for sick sinus syndrome. All patients tested positive for ANA, and 80% tested positive for anti-Ro(SSA) antibody. Anti-U1RNP antibody was positive in 2/5 (40%) patients, but none had anti-Jo-1 antibody.

Myositis occurred concomitantly with SS in four patients, and followed the sicca symptoms in one patient (Table 3). Determination of CK revealed rather low to moderate increases of less than 2000 IU/l (195–1546 IU/l).

The average interval from the onset of muscle weakness until the time of muscle biopsy varied (range 6–24 months). Two patients had received small doses of prednisone (PSL) before muscle biopsy. The biopsy findings are summarized in Table 3. Variations in fiber diameter and regeneration were present in all patients. Mild degeneration of muscle fibers was detected in three patients. In patient 1, both lymphocytes and macrophages infiltrated the endomysium (Fig. 1). In other patients, interstitial lymphocyte infiltrates were very scarce. Vasculitis was not seen in any of five patients. No significant association was noted between serum CK level and the severity of muscle weakness in any patient. Furthermore, the severity of weakness was not related to either the intensity of inflammatory cells or degeneration.

All patients were treated with small to modest doses of prednisolone (PSL; initial dose 10–40 mg), and responded well to corticosteroid therapy. PSL was reduced slowly to maintenance levels of 2–5 mg per day. During the follow-up (25–79 months; average 46.6 months), three patients had a

Table 1. Profile of total primary Sjögren's syndrome patients (88 females and 1 male; mean age 56.0 ± 15.31 years)

	All patients	Patients with myositis	
Extraglandular manifestations	54 (60.6%)	5 (100%)	
Arthralgia/arthritis	18 (20.2%)	2 (40%)	
Skin eruption	12 (13.5%)	2 (40%)	
Interstitial pneumonia	7 (7.8%)	0	
Myalgia	8 (8.9%)	3 (60%)	
Myositis	5 (5.6%)	5 (100%)	
Autoimmune thyroid disease	13 (14.6%)	0	
Neurological symptoms	15 (16.8%)	4 (80%)	$P < 0.05$
Raynaud's phenomenon	9 (10.1%)	2 (40%)	
Serological findings			
ANA-positive	82 (93%)	5 (100%)	
Anti-Ro(SSA)-positive	73 (82%)	4 (80%)	
Anti-La(SSB)-positive	36 (41%)	2 (40%)	
RF-positive	44 (50%)	1 (20%)	
Anti-U1-RNP-positive	8 (8.9%)	2 (40%)	
IgG > 2100 mg/dl	43 (51%)	5 (100%)	$P < 0.05$
IgA > 300 mg/dl	33 (37%)	4 (80%)	
IgM > 200 mg/dl	15 (17%)	3 (60%)	

ANA, antinuclear antibody; RF, rheumatoid factor

Table 2. Clinical and laboratory findings for five patients with myositis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	74/F	63/F	62/F	57/F	50/F
Xerostomia	+	+	+	+	+
Xerophthalmia	+	+	+	+	+
Saxon test	+	+	+	+	+
Schirmer test	+	+	+	+	+
Extraglandular manifestations					
LN swelling	−	−	+	+	−
Arthralgia	−	+	+	−	−
Skin	−		+	+	
Raynaud's phenomenon	−	+	+	−	−
Nervous system	Trigeminal neuralgia	Carpal tunnel syndrome	Numbness	−	Carpal tunnel syndrome
Other	−	−	−	Arrythmia	−
Serological findings					
ANA	+	+	+	+	+
RF	−	−	+	−	−
Anti-Ro(SSA)	+	+	+	+	−
Anti-La(SSB)	+	−	−	+	−
Anti-RNP	−	+	+	−	−
IgG > 2100 mg/dl	+	+	+	+	+
IgA > 300 mg/dl	+	+	+	+	−
IgM > 200 mg/dl	+	−	+	+	−

LN, lymph node

Table 3. Muscular findings for patients with myositis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Onset	S	S	SS → myositis	S	S
Myalgia	−	−	+	+	+
Grade of muscle weakness	4	5	4	4	3
Duration	7	11	4	14	8
EMG findings	+	+	+	+	+
Serum CK, max	282	1204	195	583	1546
Serum aldorase, max	9.8	27.5	5.8	7.4	23.8
Histopathological findings					
Fiber diameter variation	+	+	+	+	+
Degeneration	+	−	−	+	±
Regeneration	+	+	+	+	+
Increased intersitial tissue	±	−	−	−	−
Inflammatory cell infiltration	+	−	−	±	−
Macrophage infiltration	+	−	±	−	−

SS, Sjögren's syndrome; S, myositis and SS were diagnosed simultaneously; grade, grading of muscle weakness, i.e., 1, no abnormality on examination, 2, easily fatigued and decreased exercise tolerance, 3, minimal degree of atrophy of muscle groups without functional impairment, 4, waddling gait, unable to run, 5, marked waddling gait, 6, unable to walk without assistance; duration, periods (months) between onset of weakness and start of treatment; EMG (electromyography) findings, myopathic change (low amplitude, short duration, etc.); Histopathological findings (a semiquantitative 3-point scale (−, ±, +) was used to grade morphological change); CK, creative kinase

reelevation of serum CK without muscle weakness. PSL was increased for two patients (patients 1 and 4) with CK elevation. No patients received an additional immunosuppressive agent (Table 4).

Discussion

Myalgia is frequently encountered in SS. Martinez-Lavin et al.[3] reported that 33% of SS patients complained of myalgia. Vrethem et al. reported a high prevalence (11/15; 73%) of inflammatory exudates in muscle biopsies from unselected asymptomatic primary SS patients. It must be stressed that none of these patients required treatment.

Symptomatic myositis was identified in 3% of primary SS patients in a report by Kraus et al.,[5] 6.6% in a report by Alexander et al.,[6] and 5.6% in this study.

It is worth mentioning that four of the five cases of patients with myositis were complicated with peripheral neuropathy. The prevalence was significantly higher than that in all patients in our study group (80% vs 16.8%, $P < 0.05$). In

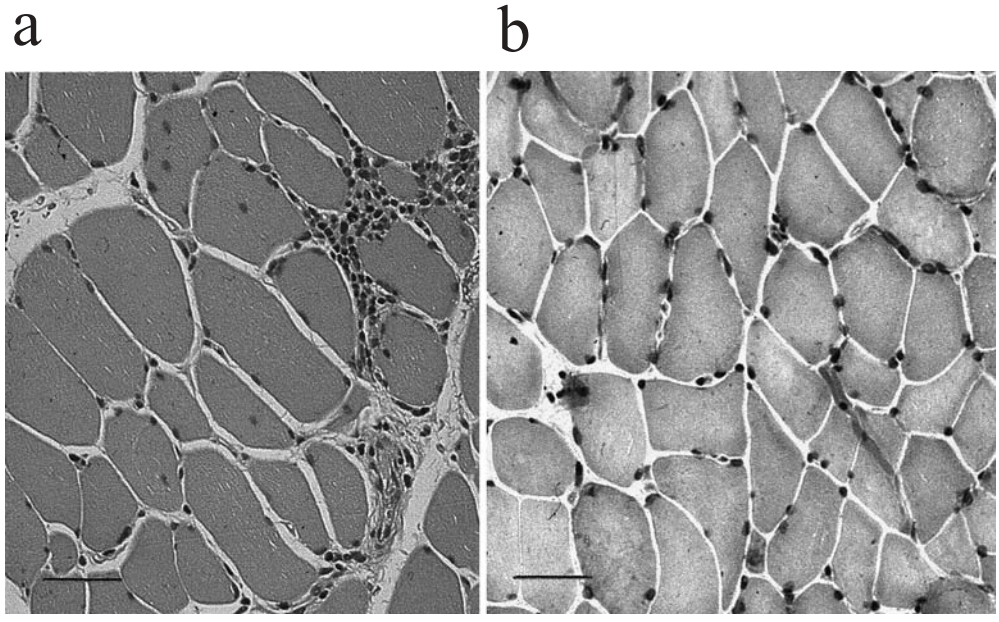

Fig. 1. Muscle biopsy findings (hematoxylin and eosin stain). **a** From patient 1: lymphocyte infiltrates are seen in the endomysial area around muscle fibers, in addition to the regeneration and degeneration of muscle fibers. **b** From patient 3: variations in muscle diameter and regeneration are seen. Lymphocyte infiltrates are absent. *Bar* 50 μm

Table 4. Treatment and clinical course

Patient	Follow-up (months)	PSL dose (mg/day)		Clinical course response[a]	
		At start	Present		
1	39	40	2	R	No relapse of muscle weakness in spite of mild elevation of serum CK
2	60	30	5	R	
3	25	10	5	R	Myalgia occurred occasionally without elevation of serum CK
4	79	10	2.5	R	No relapse of muscle weakness in spite of mild elevation of serum CK
5	30	20	2	R	No relapse of muscle weakness in spite of persistant elevation of serum CK (200–300)

[a] Response was defined as a clinical improvement and a decrease in muscular enzymes. Failure was defined as a lack of clinical response and/or the need to start another therapy
PSL, prednisolone

addition, serum IgG elevation was more common in myositis patients than in all patients (100% vs 51%, $P < 0.05$).

Vrethen et al.[4] analyzed neuropathy and myopathy in 17 patients with primary SS. They concluded that inflammatory myopathy was often involved in primary SS, and might be one of the autoimmune manifestations. Leroy et al.[7] described a 65-year-old woman who developed myositis 3 years after the onset of sicca symptoms. Her muscular symptoms fulfilled the diagnostic criteria for polymyositis of Bohan et al.;[8] these include muscle weakness, elevated serum muscle enzyme levels, myogenic changes in EMG, and positive muscle biopsy results. However, they reported this patient as a case of primary SS who developed myositis. Meanwhile, Gran and Myklbust[9] reported a 57-year-old woman who was diagnosed with SS and polymyositis simultaneously. They could not conclude that the diagnosis of two separate diseases was more correct than a diagnosis of a one-disease-model, such as primary SS, with muscle involvement. In our study, five patients also satisfied the diagnostic criteria for polymyositis. In all reported cases and in our five patients, the muscle symptoms were mild. In polymyositis, muscle weakness usually develops insidiously over a period of weeks to months, and patients have impaired performance in daily activities. However, the patients in our study showed mild to minor impairment, and all of them could walk without assistance, in spite of long intervals from the onset of muscle weakness to the start of treatment. In addition, CK elevations were mild to moderate. This finding was in contrast to the finding of polymyositis, in which CK elevation of several thousands of IU/l is frequently encountered. Furthermore, these five patients responded well to corticosteroid therapy, and to date the outcome appears to be favorable. In the report by Kraus et al.,[5] two primary SS patients who developed myositis were treated with moderate doses of PSL (15–20 mg/day), and the response was also excellent for our patients. We think that myositis associated with SS tends to be characterized by a less severe myositis with a better response to therapy compared with polymyo-

sitis. The distinction between SS developing with polymyositis versus SS with myositis as a manifestation is not well defined. The relative severity of the clinical features and the serological findings may be helpful. In addition, a prospective follow-up of patients may provide information about the prognosis of myositis, adequate dosages of PSL, immune mechanisms, and the influence of PSL therapy on the course of SS.

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