Subclinical Myositis Is Common in Primary Sjögren's Syndrome and Is Not Related to Muscle Pain

BJÖRN LINDVALL, ANN BENGTSSON, JAN ERNERUDH, and PER ERIKSSON

ABSTRACT. ***Objective.*** Although muscle pain is common in primary Sjögren's syndrome (SS), the underlying mechanisms are mainly unknown. We studied all patients with SS at our rheumatology unit with respect to muscle pain in general and to fibromyalgia (FM), and correlated clinical data to muscle biopsy findings.

Methods. We investigated 48 patients with SS according to the modified European diagnostic criteria. The ACR criteria for FM were used to subgroup the patients. Muscle biopsy was performed in 36 patients. Light microscope morphology and immunohistochemical expression of MHC class I, MHC class II, and membrane attack complex (MAC) were studied.

Results. We found 44% of patients complained of muscle pain; 27% fulfilled the ACR criteria for FM, whereas 17% had other forms of myalgia. Muscle pain could not be related to histopathological findings. Signs of inflammation were found in 26 of 36 biopsies (72%), and inflammation combined with degeneration/regeneration (i.e., histological signs of polymyositis) in 17 biopsies (47%). However, only 5 patients (14%) had clinical as well as histological signs of polymyositis. Eight muscle biopsies (22%) showed histological features of inclusion body myositis (IBM). However, no patient had clinical symptoms suggestive of this disease. Abnormal expression of MHC class I, MHC class II, and MAC was found in 18 (50%), 16 (44%), and 27 (75%) patients, respectively.

Conclusion. Muscle pain, especially FM, is common in SS. Histopathological signs of myositis are very common in SS. However, muscle symptoms are not related to histological signs of muscle inflammation. IBM-like findings may represent vacuolar myopathic degeneration due to previous subclinical muscle inflammation rather than a specific clinical entity. (J Rheumatol 2002;29:717–25)

Key Indexing Terms:
SJÖGREN'S SYNDROME MUSCLE BIOPSY IMMUNOHISTOCHEMISTRY
MYOSITIS INCLUSION BODY MYOSITIS FIBROMYALGIA

Primary Sjögren's syndrome (SS) is an autoimmune disease characterized by ocular and oral dryness, i.e., sicca symptoms. However, other symptoms, such as fatigue and muscle pain, can be even more disabling than the sicca symptoms. Muscle pain has been reported in 33% of patients with SS[1], whereas fibromyalgia (FM) characterized by widespread chronic muscle pain, stiffness, and fatigue, has been reported in 47–55%[2,3].

Muscle biopsies from patients with SS often reveal perivascular inflammation or interstitial myositis without involvement of muscle fibers[4]. This picture, however, is common in several rheumatological diseases and the clinical significance is uncertain[5-7].

Muscle biopsy in FM has yielded unspecific findings, with the occurrence of ragged red fibers, moth eaten fibers, and type 2 fiber atrophy[8], as well as capillary changes with increased thickness of the endothelium[9].

In polymyositis (PM), proximal muscle weakness is a prominent clinical finding. Normal or elevated levels of muscle enzymes can be measured in serum, often in parallel with typical electromyographic findings. Ongoing PM is characterized by inflammatory infiltrates, muscle fiber degeneration and/or regeneration, as well as clinical signs of proximal muscle weakness[10]. Clinically significant signs of PM have been reported in 2.5–10% of patients with SS[11].

Patients with inclusion body myositis (IBM) usually have a typical clinical picture, including distal muscle weakness in the upper extremities and proximal weakness in the lower extremities. Morphological examination shows inflammation and muscle fiber degeneration associated with rimmed vacuoles and atrophic fibers[12]. Case reports of patients with SS and IBM-like features exist[13-15].

Major histocompatibility complex (MHC) class I and II have important pathogenic roles in the inflammatory

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myopathies[10,16]. Immunohistochemically IBM and PM are characterized by increased expression of MHC class I. The membrane attack complex (MAC) is characteristically found in muscle biopsies from patients with dermatomyositis[17,18]. Thus, immunohistochemical analysis may add information concerning the inflammatory process in muscle in SS.

Muscle histopathology in SS has been described in case reports of single patients and in smaller series[4,6,19,20]. We investigated all patients with SS registered at our rheumatology unit. The aim was to relate light microscope and immunomorphological muscle biopsy findings to clinical symptoms, especially regarding pain in relation to inflammatory myopathy. We also describe the features of myalgia in patients with SS.

MATERIALS AND METHODS

Patients. All 53 patients with primary SS registered at the rheumatology clinic were invited to participate. Patients with isolated sicca symptoms as well as patients with more complicated disease were included. The University Hospital of Linköping is a tertiary referral hospital as well as a secondary referral hospital serving Linköping and its surroundings. The study was approved by the local ethical committee.

The patients were contacted by telephone. After giving informed consent, 48 patients were interviewed and examined by one person (PE) in the outpatient clinic. The mean age was 62 years in the 45 participating women (range 35–82) and 66 years in the 3 men (range 54–78). All 48 patients were asked to undergo muscle biopsy (performed by BL); 36 patients did so. A third person (AB) examined patients with muscle pain with respect to FM. Of 21 patients with muscle pain, one died during the study and 4 were not willing to come for an additional visit.

SS was defined by the proposed European classification criteria[21], with the addition of anti-SSA or anti-SSB antibodies or focal sialoadenitis in labial minor salivary gland biopsy as an obligatory criterion among the 4 out of 6 mandatory criteria[22]. Patients with systemic lupus erythematosus, rheumatoid arthritis, and other diseases associated with secondary SS were excluded. Information regarding clinical conditions with possible relation to SS was collected from the medical records (Table 1). The medication of each patient was registered (Table 1).

Clinical evaluation. The patients were asked for the occurrence and characteristics of muscle pain during the last 3 months. The pain distribution was noted on a body sketch (Figure 1). The degree of muscle pain during the last week was recorded on a visual analog scale (VAS, length 100 mm, anchored at "no pain" and "worst imaginable pain"). FM was defined according to the American College of Rheumatology (ACR) criteria[23]. Subjective muscle weakness, stiffness, impression of joint swelling, and arthralgia were investigated. The joints were examined for tenderness and swelling.

All patients were examined using the Fibromyalgia Impact Questionnaire (FIQ)[24] and Health Assessment Questionnaire (HAQ)[25] and muscle strength in the hands was examined according to the Grippit method with reference values for different age and sex categories[26]. Sixteen patients with muscle pain were further examined with the Arthritis Self-Efficacy Scale (ASES)[27] and Quality of Life Scale (QOLS)[28]. Tender points (trapezius muscle, lateral epicondyle, trochanter, medial part of knees, and anterior tibial muscle) were examined for pain threshold and pain tolerance bilaterally using an electronic pressure algometer (Somedic AB, Stockholm, Sweden). An endurance test was done: patients were instructed to sit with arms abducted 90° as long as possible, and time was recorded. A balance test was also performed with the patient standing as long as possible with one foot in front of the other and time recorded. Tests were chosen according to the recommendation of Mannerkorpi and Ekdahl[29]. Blood samples were analyzed for creatine kinase (CK) (reference values < 3.3 μkat/l in men, < 2.5 μkat/l in women), erythrocyte sedimentation rate (ESR) (< 12 mm/h in men, < 20 mm/h in women), and C-reactive protein (CRP) (< 10 mg/l in men and women). Anti-SSA and anti-SSB antibodies were analyzed with the immunodiffusion method, and antinuclear antibodies (ANA) with immunofluorescence on HEp-2 cells.

Clinical evaluation with special reference to muscle and nerve function was performed in all patients who agreed to muscle biopsy. Manual muscle strength tests were performed, including test of neck flexors and extensors, arm abduction, arm flexors and extensors, wrist flexors and extensors, hip flexors and extensors, knee flexors and extensors, and foot plantar and dorsal flexors. Strength was graded according to the British Medical Research Council[30]. Myometer (Penny and Giles) tests on proximal and distal muscle groups (arm abductors, wrist extensors, hip flexors) were done as well. Further neurological examination included testing of cranial nerve functions, coordination, tendon reflexes, and sensibility. The findings were used for evaluation of proximal muscle weakness indicating PM, of forearm flexor muscle weakness and quadriceps muscle weakness indicating inclusion body myositis, and of signs indicating other neurological disorders. Myometer results were used for comparison with manual muscle test results.

Polyneuropathy was diagnosed in patients with 2 of the following 3 criteria: symmetrical distal sensory (I) or motor (II) disturbances, loss of distal tendon reflexes (III).

Biopsy technique and histological staining. Muscle specimens were obtained by semi-open technique with alligator forceps from the anterior tibial muscle[31]. Serial sections, including more than 100 sections, were routinely analyzed by histopathological examination. Formalin fixed (10% formaldehyde in phosphate buffer) and paraffin embedded specimens were stained with hematoxylin-eosin, Weigert-hematoxylin, van Gieson and Ladewigs stains. Histochemical examinations were also performed. Muscle specimens frozen in liquid nitrogen were stained for myofibrillar adenosine triphosphatase (ATPase preincubation at pH 9.4 and 4.6, respectively), NADH-tetrazolium reductase, phosphorylase, acid phosphatase, and myoadenylate deaminase. Modified Gomori-trichrome, hematoxylin-eosin, and van Gieson staining was also performed on the frozen material. Periodic acid Schiff (PAS) was used for staining glycogen and Oil red-O for lipids. All biopsies were examined by a trained examiner (BL) blinded to the diagnosis of the patient.

Immunohistochemical staining. Frozen specimens were cryosectioned in 6 μm consecutive sections for studies of MHC class I (Dako M 736, clone W6/32(1), dilution 1/100) and II (Dako M 704, clone DK22, dilution 1/50) and MAC (Dako M 777, clone AE11.(1), dilution 1/25). An enzyme immune complex method was used essentially as described by the manufacturer[32]. As negative controls, we used isotype matched IgG substituted for primary antibodies and omission of primary antibodies. These controls did not produce any significant staining. Cryosections on glass slides (PH 099, Novakemi, Stockholm, Sweden) were fixed with 100% acetone. After air drying, the sections were incubated with normal rabbit serum (Dakopatts, Dako X902, Glostrup, Denmark) diluted 1/10 in phosphate buffered saline (PBS), pH 7.2, for 10 min at room temperature to block nonspecific background staining. The primary monoclonal antibody, diluted in PBS with 1% bovine serum albumin (PBS-BSA), was then added for 30 min at room temperature. After washing, the sections were incubated 30 min with peroxidase conjugated rabbit anti-mouse immunoglobulins (Dakopatts, Dako P260) diluted 1/10 in PBS-BSA. The sections were washed and incubated 30 min with horseradish peroxidase-antiperoxidase (PAP) complex (Dakopatts, Dako P850) diluted 1/100 in PBS-BSA. A peroxidase substrate-chromogen solution (3,31-diaminobenzidine-tetrahydrochloride, DAB; Sigma, St. Louis, MO, USA) activated by H_2O_2 was added, resulting in a colored end product. After 5 min the procedure was stopped by rinsing with water.

Immunohistochemical grading. Grading of MHC class I was based on the

Table 1. Retrospective data from the patient records. Group 1: patients with FM; Group 2: patients with other muscle pain; Group 3: patients with no pain. No significant differences were found between groups.

Data	Group 1, 13 patients, %	Group 2, 8 patients, %	Group 3, 27 patients, %	All 48 patients, %
Anti-SSA antibodies	77	100	93	89
Anti-SSB antibodies	54	100	63	67
Antinuclear antibodies	69	75	81	77
Hypergammaglobulinemia	69	50	70	67
Hypothyroidism	23	25	15	19
Pulmonary involvement	23	25	4	12
Purpura	15	0	15	12
Other skin vasculitis	15	0	15	12
Polyneuropathy	15	12	7	10
Previously known myositis	0	12	4	4
Vitamin B12 deficiency	15	25	11	14
Pancreas enzyme substitution	8	12	4	6
Leukopenia	46	25	37	38
Raynaud's phenomenon	15	12	7	10
Babies with AV block	8	0	4	4
Distal renal tubular acidosis	31	12	22	23
Chloroquine treatment	23	0	7	10
NSAID treatment	15	12	26	21
Glucocorticosteroid treatment	15	25	11	14

AV: atrioventricular, NSAID: nonsteroidal antiinflammatory drug.

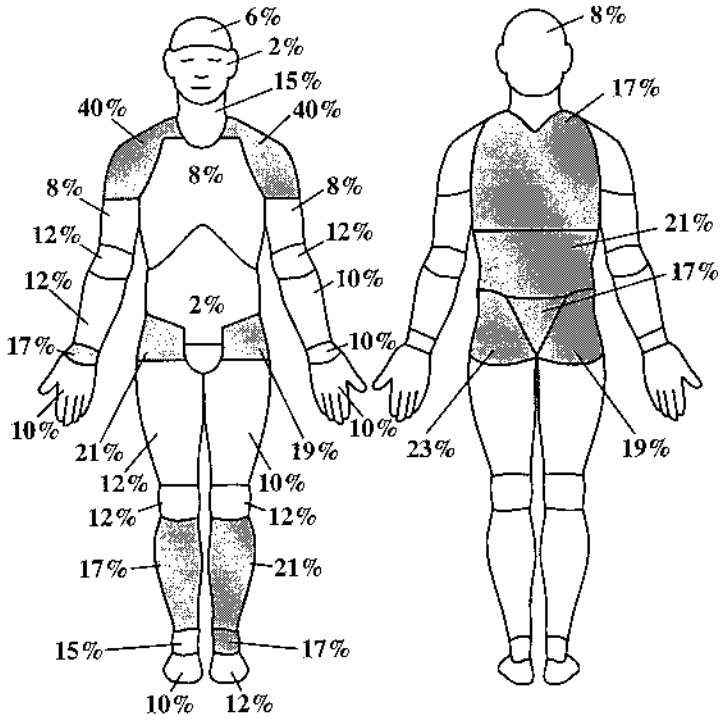

Figure 1. Distribution of pain in 48 patients with primary SS. Shaded areas: occurrence of pain in ≥ 17% of patients.

expression on muscle fiber membranes as well as the expression in the cytoplasm of the muscle fibers. The distribution of MHC class I expression was also considered. Normal appearance was graded 0, weak or partial sarcolemmal expression as 1 or 2, complete sarcolemmal expression with weak cytoplasmic expression as 3 and with more pronounced cytoplasmic expression as grades 4 or 5.

Grading of MHC class II was based on the expression in capillaries. No expression was graded 0. More extensive expression in capillaries was graded depending on distribution and intensity as 1–5. Normal expression, according to earlier studies, could be estimated to grades < 3 (B. Lindvall, et al, unpublished data).

Grading of MAC was based on the extension of capillary expression in the biopsy. Four grades were used, 0 to 3. Normally, MAC is expressed in arterioles and venules, but not in capillaries[17]. This expression was graded 0. Diffusely scattered expression in capillaries was graded 1, whereas more widespread expression was graded 2 or 3.

Morphological characteristics of PM, dermatomyositis (DM), and IBM. Morphological findings of PM include muscle fiber degeneration and regeneration in association with infiltrates of inflammatory cells. Fiber size variation and atrophic fibers are common, whereas perifascicular atrophy is a typical finding in DM[10].

The morphological characteristics of IBM are muscle fiber degeneration and regeneration together with infiltrates of inflammatory cells, atrophic fibers, and vacuoles containing eosinophilic granular inclusions with a rim of basophilic granular deposits, the so-called rimmed vacuoles[10,12].

Statistical methods. Mann-Whitney U test was used for comparisons of noncontinuous measures between groups and Spearman rank sum test for correlation analyses. Kruskal-Wallis test was used in cases of several nominal groups. Student t test was used for continuous variables and comparisons of means and Fisher's exact test for comparison of occurrences.

RESULTS

Clinical evaluation. Of the 48 patients with SS, 13 (27%) fulfilled the criteria for FM (Group 1), 8 (17%) had experienced muscle pain but did not fulfill criteria for FM (Group 2), and 27 (56%) were without muscle pain (Group 3).

Retrospective data from the patient records. The occurrences of autoantibodies, hypergammaglobulinemia, associated clinical conditions, and medication are shown in Table 1. No significant differences were detected between the groups.

In 2 patients, overt PM was diagnosed prior to this study. One of these had had sicca symptoms for 30 years. The first biopsy was normal, the second, taken during symptoms of active clinical PM, showed a pronounced inflammation together with muscle fiber degeneration and signs of vacuolar degeneration. The subsequent biopsies showed only mild inflammation and degeneration whereas the occurrence of rimmed vacuoles was increased.

Laboratory investigations. Mean values of CRP and CK did not differ significantly between the 3 groups. CK were within the normal range in all except 2 patients without pain (3.5 and 2.8 kat/l). ESR was higher in Group 2 (mean 62 mm/h) than in Group 1 (mean 34 mm/h; $p = 0.020$) and in Group 3 (mean 33 mm/h; $p = 0.003$).

Muscle and joint symptoms. Muscle pain was reported to occur "never" or "seldom" in 62.5%, "often" in 25%, and "always" in 12.5% of the 48 patients. The mean severity of pain on VAS during the last week was estimated to be 57 mm (SD 20) in patients with FM and 26 mm (SD 15) in patients with muscle pain but without FM. Muscle pain had a duration < 5 years before the study in 29%, and > 5 years before the study in 71% of the patients with muscle pain (Groups 1 and 2).

The muscle pain was aggravated by work, long periods of sitting, bad weather or extreme cold, whereas medication, massage, hot baths, or hot weather were factors reported to improve pain.

Figure 1 shows that the most common locations of muscle pain were around the shoulders, in the back, around the hips, and in the lower parts of the legs.

As shown in Table 2, subjective muscle weakness and muscle stiffness were more common in patients with FM (Group 1) than in patients without pain (Group 3). The occurrence of arthralgias and the sensation of joint swelling did not differ between groups.

According to the HAQ, Group 1 and Group 2 were more disabled than Group 3 ($p < 0.0001$ and 0.041, respectively). High FIQ values indicate more FM symptoms, and consequently FIQ values were highest in Group 1, lower in Group 2, and lowest in Group 3. In the FIQ instrument, VAS for depression, anxiety, and daytime fatigue are included. FM patients (Group 1) expressed more depression ($p = 0.012$) and anxiety ($p = 0.016$) than patients without pain (Group 3), and more fatigue than patients in Group 2 and 3 ($p = 0.013$ and < 0.001, respectively). Clinical examination revealed tender and swollen joints in total in 9% of the patients. No differences could be detected between the groups.

Clinical characteristics of patients with FM and non-FM muscle pain. Sixteen of the patients with muscle pain were investigated by a second investigator (AB). The results are shown in Table 3. Compared with patients in Group 2, patients with FM had impaired endurance, lower pain threshold and pain tolerance, and lower quality of life according to the QOLS as well as to the ASES for pain and other symptoms.

Clinical evaluation of neuromuscular function. In the neurological evaluation of 36 patients, only 7 patients were considered to be completely normal. Clinical signs indicating possible PM, i.e., proximal muscle weakness, were found in 12 patients (Table 4). Seven of these had mild proximal weakness restricted to upper extremities. No patient had clinical findings compatible with IBM.

The Grippit instrument used in all 48 patients revealed no significant differences in hand strength between patients with and without muscle pain. When the Grippit value in each patient was related to reference values for age and sex, the mean of normal Grippit values was 68% in Group 1, 75% in Group 2, 83% in Group 3.

Table 2. Results of interview investigation on occurrence of symptoms. Group 1: patients with FM; Group 2: patients with other muscle pain; Group 3: patients with no pain.

	Group 1, 13 patients	Group 2, 8 patients	Group 3, 27 patients	All 48 patients	Statistically Significant Differences
Subjective muscle weakness, occurrence, %	46	50	11	27	Subjective muscle weakness was more common in Group 1 than in Group 3 (p = 0.038), and more common in Group 2 than in Group 3 (p = 0.034)
Subjective muscle stiffness, occurrence, %	92	50	19	44	Muscle stiffness was more common in Group 1 than in Group 2 (p = 0.048), and more common in Group 1 than in Group 3 (p < 0.0001)
Arthralgias, occurrence, %	77	75	48	60	No difference
Feeling of swollen joints, occurrence, %	38	37	18	27	No difference
HAQ, mean (SD)	1.17 (0.81)	0.76 (0.79)	0.23 (0.35)	0.57 (0.71)	HAQ was higher in Group 1 than in Group 3 (p < 0.0001), and higher in Group 2 than in Group 3 (p = 0.041).
FIQ, mean (SD)	58 (17)	34 (20)	19 (16)	32 (24)	FIQ was higher in Group 1 than in Groups 2 and 3 (p = 0.008, and p < 0.0001), and higher in Group 2 than in Group 3 (p = 0.010).
Depression (from FIQ), mean mm VAS (SD)	41 (29)	18 (22)	17 (26)	23 (28)	Group 1 was more depressed than Group 3 (p = 0.012)
Anxious (from FIQ), mean mm VAS (SD)	42 (30)	22 (24)	18 (28)	25 (29)	Group 1 was more anxious than Group 3 (p = 0.016)
Daytime fatigue (from FIQ), mean mm VAS (SD)	80 (20)	48 (35)	40 (32)	52 (34)	Group 1 had more fatigue than Groups 2 and 3 (p = 0.013 and p < 0.001)

HAQ: Health Assessment Questionnaire[25]; FIQ: Fibromyalgia Impact Questionnaire[24].

Clinical signs of polyneuropathy were found in 18 patients. Other neurological diagnoses were cerebellar tremor (n = 1), previous cerebral stroke with remaining symptoms of hemisensory disturbances (n = 1), symptoms after earlier subarachnoid hemorrhage (n = 1), lumbar disc herniation (n = 2), and traumatic injuries resulting in chronic localized pain syndromes (n = 4).

Table 3. Results of tests used for evaluation of FM. Group 1: patients with FM; Group 2: patients with other muscle pain.

	Group 1, 12 Patients	Group 2, 4 Patients	p
Endurance test, s	37	116	< 0.001
Balance, s	82	115	0.335
Pain threshold, kPa/s	155	212	0.009
Pain tolerance, kPa/s	243	414	0.004
QOLS	94	80	0.051
ASES pain	33	52	0.005
ASES function	60	64	0.691
ASES other symptoms	54	71	0.023

QOLS: Quality of Life Scale[29]; ASES: Assessment of functional limitations and disability[30].

Muscular morphology. The muscle biopsy findings in each of the 36 patients are shown in Table 4. Seven biopsies were morphologically normal except for minimal changes of low diagnostic significance, i.e., the occurrence of a few atrophic fibers, a few fibers with centrally located nuclei. The most common abnormal finding was inflammation (Figure 2) (26/36 biopsies), which was mild in 19, moderate in 6, and severe in one of the biopsies. The inflammatory cells were unusually located perivascularly, but in 8 cases there were also endomysial and in 12 perimysial distribution. Muscle fiber degeneration and/or regeneration was seen in 20 biopsies. Rimmed vacuoles (Figure 3), which may be a component of IBM, were seen in 10 biopsies, and in 8 of these cases degeneration and inflammation, although mild, appeared as well. A combination of inflammation and muscle fiber degeneration/regeneration compatible with a morphological diagnosis of polymyositis was seen in 17 biopsies. Other unspecific morphological and histochemical

Table 4 Muscle biopsy and clinical findings in 36 patients with SS, grouped according to presence or absence of pain. Inflam: presence of inflammation (–, +, ++, +++); Endo: endomysial localization of inflammation (–/+); Peri: perimysial localization (–/+); Perivasc: perivascular localization (–/+); Degen/Regen: signs of degeneration and/or regeneration (–, +, ++, +++); MHC class I and II, grades 0–5; MAC grades 0–3 (see text); presence (+) or absence (–) of signs of morphological myositis, clinical signs of myositis, and polyneuropathy as defined in the text.

Sex	Age, yrs	Pain	Inflam	Endo	Peri	Perivasc	Degen/ Regen	Rimmed Vacuoles	Atrophy	MHC I	MHC II	MAC	Morphological Myositis	Clinical Myositis	Poly neuropathy
F	49	FM	+	+	+	+	+	–	+	2	3	0	+	–	–
F	64	FM	+	–	–	+	+++	+	+	0	1	1	+	–	+
F	59	FM	–	–	–	–	++	+	+	1	2	1	–	–	–
F	61	FM	+	+	+	+	–	–	+	3	3	2	–	–	–
F	58	FM	+	–	–	+	+	–	+	4	0	1	+	–	–
F	62	FM	–	–	–	–	–	–	+	2	1	1	–	–	–
F	40	FM	+	–	–	+	–	–	+	2	1	1	–	+	–
F	48	FM	++	+	+	+	+	–	+	4	3	1	+	+	–
F	61	FM	–	–	–	–	–	–	+	2	2	1	–	+	–
F	71	FM	+++	–	+	+	–	–	–	3	3	1	–	–	+
F	68	FM	–	–	–	–	–	–	+	1	2	0	–	–	+
F	83	Other	+	–	+	+	+++	+	+	0	3	2	+	+	+
F	64	Other	+	+	+	+	++	+	+	3	3	3	+	+	+
F	72	Other	+	–	–	+	–	–	+	1	0	1	–	–	+
F	70	Other	+	–	–	+	+	–	+	3	3	1	+	–	+
F	78	Other	++	–	+	+	+	–	+	1	1	0	+	–	–
M	55	Other	–	–	–	–	+++	+	+	3	0	2	–	+	+
F	73	Other	+	–	–	+	++	+	+	3	3	1	+	+	+
M	66	Other	+	–	–	+	–	–	+	2	1	0	–	+	+
F	73	No pain	–	–	–	–	+	–	+	3	3	1	–	+	–
F	57	No pain	++	+	+	+	++	–	–	4	2	1	+	–	–
F	40	No pain	–	–	–	–	–	–	+	1	0	1	–	–	–
F	53	No pain	–	–	–	–	–	–	+	1	0	0	–	–	–
F	74	No pain	+	–	–	+	+	+	+	3	3	1	+	–	+
F	66	No pain	+	–	–	+	++	+	+	4	0	3	+	–	+
F	61	No pain	+	–	–	+	+	+	+	3	4	1	+	–	–
F	61	No pain	++	+	+	+	+	–	+	3	2	0	+	–	–
F	56	No pain	++	–	+	+	–	–	+	2	1	1	–	–	+
F	62	No pain	–	–	–	–	–	–	+	0	0	1	–	+	+
F	77	No pain	+	–	–	+	++	+	+	3	5	1	+	+	+
M	79	No pain	+	–	–	+	–	–	+	1	1	1	–	–	+
F	44	No pain	+	–	–	+	–	–	+	0	4	0	–	–	–
F	36	No pain	++	+	+	+	++	–	+	4	5	0	+	–	–
F	66	No pain	+	–	–	+	+	–	+	1	3	1	+	–	–
F	64	No pain	–	–	–	–	–	–	+	3	3	0	–	+	+
F	73	No pain	+	+	+	+	–	–	+	3	2	1	–	–	–

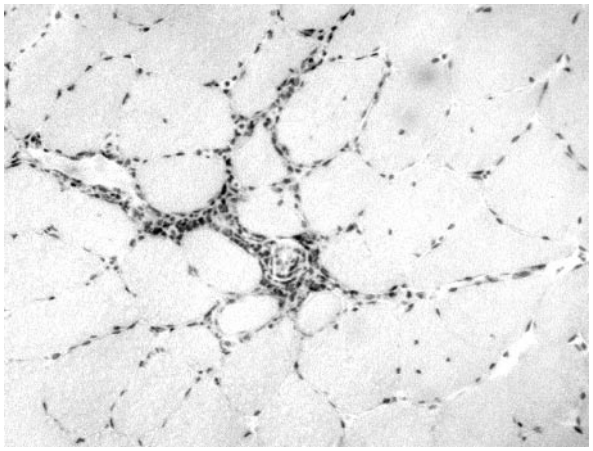

Figure 2. Muscle biopsy specimen showing perivascular inflammation (H&E stain).

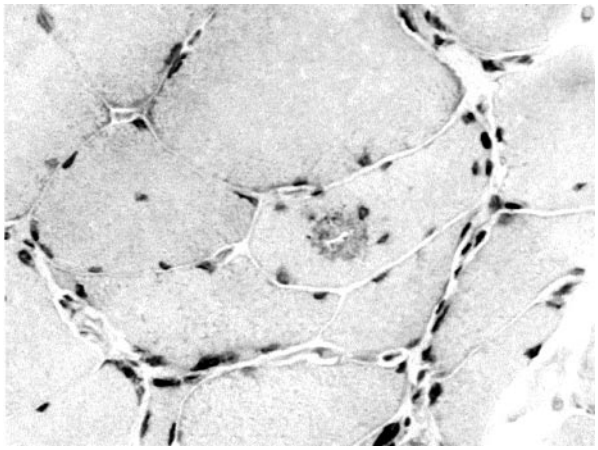

Figure 3. Rimmed vacuole in muscle fiber. Atrophic fibers are also visible (H&E stain).

changes of either myogenic or neurogenic origin were: internal nuclei (n = 26), variation of muscle fiber diameter (n = 24), split fibers (n = 13), atrophic fibers (n = 34), signs of small grouping (n = 13), ragged red fibers (n = 16), sarcoplasmic pads (n = 4), and secondary deficiency of myoadenylate deaminase (n = 2).

Immunohistochemical findings and relation to histological findings. An abnormal expression of MHC class I was found in 18 biopsies (50%) (grade ≥ 3), and signs of inflammation appeared in 15 of these. The grade of expression of MHC class I was related to grade of inflammation (p = 0.035) and to occurrence of muscle fiber degeneration (p = 0.024). Abnormal expression of MHC class I was not related to perivascular or perimysial inflammation or to IBM-like findings.

The capillary expression of MHC class II was abnormal in 16 biopsies (44%) (Table 4), but the extent of MHC class II expression was not correlated to any histopathological feature. Abnormal expression of both MHC class I and II was found in 10/26 biopsies with inflammation.

Pathological capillary expression of MAC was found in 27/36 (75%) biopsies, and signs of histological inflammation were found in 20 of these. The expression of MAC was significantly higher in muscle biopsies with IBM-like findings (p = 0.008). In patients with histological signs of PM (inflammation and degeneration/regeneration) the expression of MHC class I and MHC class II was significantly higher than in other patients (p = 0.031 and 0.034, respectively; Table 4). In contrast, the expression of MAC was similar in patients with and without signs of PM.

Clinical symptoms and other conditions related to muscle biopsy findings. Presence of pain was not related to any kind of muscle biopsy finding (Table 5). Morphological findings of myositis could not be correlated to muscle weakness. Five of 12 patients with clinical signs of possible myositis had histological inflammation and signs of degeneration/regeneration, i.e., morphological signs of PM. Four of 8 patients with rimmed vacuoles and morphological changes compatible with myositis had clinical signs of myositis. However, none of them had clinical symptoms compatible with IBM.

As shown in Table 5, pathological expression of MHC class I or II was not related to muscle pain or muscle weakness.

Patients treated with corticosteroids had greater occurrence of IBM-like findings (71 vs 17%; p = 0.011) and a greater extent of MAC expression (mean 1.6 vs 0.8; p = 0.031) in their muscle biopsies compared with untreated patients. Other signs of inflammation and degeneration, as well as the expression of MHC class I and MHC class II, did not differ.

Duration of sicca symptoms, the number of SS associated conditions (hypothyroidism, dRTA, etc; Table 1), hypergammaglobulinemia, and age did not influence the occurrence of muscular histopathology. However, MAC expression was positively correlated to duration of sicca symptoms (p = 0.011) and to the number of SS associated conditions (p = 0.006). No patient below 53 years of age had IBM-like findings in their biopsies.

DISCUSSION

The criteria for FM were fulfilled by 13 of 48 patients (27%), whereas 8 (17%) had experienced muscle pain with no FM. The remaining 27 (56%) had not experienced muscle pain. In investigations of SS, muscle pain was reported in 33% of patients[1], i.e., similar to our findings of 44% in total. FM, according to different criteria, was reported in 19, 47, and 55%, respectively[2,3,33]. In all studies the diagnostic criteria of SS and FM, as well as the selection mechanisms for recruitment of patients, must be considered. FM as defined by the ACR criteria occurs in about 2% of an adult population[34]. Vitali, *et al*[2] used other criteria for FM[35] as well as for SS, which may account for the different results they obtained. Tishler, *et al* used almost the same criteria as we did, but found a higher occurrence of FM[3]. However, in accord with other studies, we found a higher frequency of FM in SS than in the general population[34].

Table 5. Muscle histopathological and immunohistochemical findings in 36 patients with SS grouped according to presence or absence of muscle pain and proximal muscle weakness, respectively. No statistically significant differences were found. See text for grading.

	Muscle Pain		Proximal Muscle Weakness	
	Present, 19 patients (%)	Not Present, 17 patients (%)	Present, 12 patients (%)	Not Present, 24 patients (%)
Inflammation	14 (74)	12 (71)	7 (58)	19 (79)
Degeneration	11 (58)	9 (53)	7 (58)	13 (54)
Rimmed vacuoles	6 (32)	4 (24)	5 (42)	5 (21)
MHC class I ≥ 3	8 (42)	10 (59)	7 (58)	11 (46)
MHC class II ≥ 3	8 (42)	8 (47)	7 (58)	9 (38)
MAC ≥ 1	15 (79)	12 (71)	10 (83)	17 (71)

MHC: major histocompatibility complex class I and II; MAC: membrane attack complex.

ESR was higher in Group 2 than in Groups 1 and 3. In other respects no significant differences could be detected between the 3 groups in laboratory or clinical variables or muscle biopsy findings.

Clinical musculoskeletal symptoms (pain, muscle stiffness and weakness) were most prominent in the FM patients. The FM features in 27% of our patients with SS did not differ from the characteristics of other FM patients[36] as indicated by the FIQ, HAQ, pain, balance and endurance test, and algometer values. The mechanisms underlying muscle pain in FM are a matter of discussion, and the present study did not reveal any new clues. Our view is that the pain is probably due to a combination of peripheral and central mechanisms, the peripheral including changes in microcirculation and energy-rich phosphates, the central including central sensitization of nociceptive nerve cells in, for example, the dorsal horn[37]. There are possibilities for changes in muscle microcirculation in SS, possibly resulting in hyperalgesia and generalized muscle pain in individuals predisposed to a state of hyperexcitability.

Polymyositis, if defined as clinical symptoms of myositis combined with typical morphological myopathy changes, has been reported in 2.5–10% of patients with SS[6,11,20], which is in accord with our findings. In our retrospective analysis, 2 of 48 (4%) patients had a history of myositis demanding therapy. Of the 36 biopsied patients, 5 (14%) had proximal muscle weakness as well as morphological findings characteristic of PM, but not demanding therapy.

Histological muscle inflammation, with or without degeneration, was present in 26 of 36 muscle biopsies (72%), and the inflammation was always perivascularly localized, in accord with studies on muscle biopsies in SS[4]. Thus, subclinical muscular inflammation is common in SS but it cannot be related to muscle pain or to clinical inflammatory myopathy.

None of our patients had clinical symptoms of IBM. However, 10 of 36 biopsies (28%) showed rimmed vacuoles in association with muscle fiber degeneration, and inflammation as well in all but 2 biopsies. These morphological changes are similar to but not synonymous with the changes in IBM. Rimmed vacuoles occur in many neuromuscular disease states and are better interpreted as a general sign of degeneration than a sign of a specific disorder. Further, it is of interest that presence of vacuolar degeneration often is associated with treatment failure. The true pathogenetic mechanism behind sporadic IBM is a matter of debate[38]. Recently, several indications of a neurodegenerative pathogenesis have been described. Still, there are reports on association of sporadic IBM with different autoimmune disorders[39]. Earlier reports of occasional patients with SS and IBM may be explained by chance. The descriptions of these SS patients are not distinct, and they may be interpreted as cases with vacuolar myopathic degeneration and not true cases of IBM[13-15].

Although progress in understanding the pathogenesis of SS has emerged, many questions remain. Our immunohistochemical findings in muscle biopsies indicate certain phenomena that may be of importance. We found increased expression of MHC class I, MHC class II, and membrane attack complex, findings that are similar to those in dermatomyositis[17]. The pathogenesis of DM is believed to depend on complement activation resulting in a microvasculopathy[10,16-18], and the mechanisms of myositis in SS may be similar. Frequent expression of MAC in muscular capillaries (75%) and a significant relation between MAC expression and IBM-like changes support an additional hypothesis for explaining late muscular changes in SS. Patients treated with corticosteroids had a higher frequency of IBM-like findings and greater expression of MAC, whereas age was not related to any histopathological feature. Whether these histopathological findings are due to treatment with corticosteroids, or if these patients required corticosteroids because of a more serious inflammatory disease, is an unsolved question.

In conclusion, subclinical muscle inflammation is common in SS. A long standing subclinical myositis may develop into a degenerative vacuolar myopathy unresponsive to treatment. Evidence of this is that 10 of 36 (28%) patients showed signs of rimmed vacuoles in their biopsies. To determine whether treatment of subclinical myositis can prevent the development of manifest degenerative changes, prospective treatment trials are required. The presence of vacuolar changes is possibly related to the high frequency of MAC expression. MAC expression may suggest pathogenetic similarities to dermatomyositis. Muscle pain is not related to histological myositis and does not justify muscle biopsy. However, symptoms of FM do not rule out that muscle weakness could be due to clinically significant polymyositis. Thus, biopsy should be considered in patients with primary Sjögren's syndrome and muscle weakness.

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