

Myositis in primary Sjögren's syndrome: data from a multicentre cohort

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Abstract Objective

In primary Sjögren's syndrome (pSS), muscle pain and/or muscular weakness is relatively frequent while myositis has been reported in 3% of patients. The aim of this study was to describe the prevalence of myositis in a multicentre Italian pSS cohort and to address the clinical manifestations, histological findings and therapeutic strategies.

Methods

Clinical, serological and therapeutic data from a pSS cohort of patients were retrospectively collected. According to Bohan and Peter's criteria, inflammatory myopathy (IM) was suspected in case of muscular weakness associated with increased creatine-phosphokinase (CPK) or abnormal electromyography (EMG). When performed, muscle biopsies were analysed.

Results

In a cohort of 1320 patients, 17 (1.28%) presented muscular weakness [in some cases myalgias (7/17, 41.1%)], accompanied by increased CPK [13/17, (76.4%)] and/or abnormal EMG [13/14, (92.8%)]. Ten out of 17 (58.8%) fulfilled at least three diagnostic criteria for IM. Muscular biopsy was performed in 13/17 (76.4%) cases with histologically confirmed myositis in 6/13 (46.1%) (1 "IBM-like"-5 "PM-like"). In two "PM-like" cases, several fibres showed a decreased histochemical cytochrome C oxidase (COX) stain. Two biopsies tested "negative", four showed "non-specific" findings. All patients were treated with corticosteroids followed by different DMARDs.

Conclusion

Our retrospective analysis shows a prevalence of myositis in pSS lower than previously reported, mainly appearing as an overlapping syndrome. Histological findings confirm the possible presence of an IBM or of a myopathy more similar to PM with a decreased COX activity. Classical immunosuppressants are effective although in most difficult cases IVIg or RTX may be used with benefit.

Key words

polymyositis, dermatomyositis, inclusion body myositis, Sjögren's syndrome, histology

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Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease mainly characterised by the presence of ocular and oral dryness; however a wide range of manifestations involving the skin, neurologic, haematologic, respiratory, gastrointestinal, genitourinary, and musculoskeletal systems can complicate the clinical course. Muscle involvement is relatively frequent in the form of diffuse pain and/or muscular weakness. Myalgia has been reported in 33% of patients although in about 47–55% of cases a possible overlap with fibromyalgia (FM) has been described (1-3). Inflammatory muscle diseases in terms of myositis have been reported in 3% of patients (4). Nonetheless, 5% to 73% of patients present with subclinical histopathological evidences of myositis (5, 6). In patients with muscular weakness and, less frequently, pain, an increase in muscular necrosis enzymes, such as creatine-phosphokinase (CPK), may be a useful tool to confirm the presence of myositis. Even if muscle biopsy is still considered the gold standard for the diagnosis of inflammatory myopathies, in cases where they overlap with another connective tissue disease muscle histology may not provide sufficient diagnostic specificity (7). According to Dalakas's myositis classification criteria (8), inflammatory myopathies can be divided into three different entities: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). Each entity is distinguished by typical histological findings and clinical manifestations. Recently, a new entity namely "immune-mediated necrotising myopathy" has been described (9, 10). Typical clinical and laboratory findings in PM or DM are the presence of a proximal muscular weakness associated with increased serum levels of CPK. IBM is more typically observed in older patients (about 50 years old) with predominant involvement of distal muscles in the upper extremities and proximal muscles in the lower extremities. Treatment of inflammatory myopathies is generally based on the usage of high doses of corticosteroids followed by immunosuppressive or biological agents.

So far, pSS muscle histopathology has been described only in a few case reports or small case series (11, 12) and the main finding seems to be a perivascular inflammation or an interstitial myositis without involvement of muscle fibres (5). Signs and symptoms typically associated with PM have been reported in 2.5–10% of patients (13). The overlap of IBM during pSS has also been described (14, 15).

The aim of this retrospective study was to describe the prevalence of inflammatory myopathies in a large multicentre Italian cohort of patients with pSS and to address the clinical manifestations, histological findings and therapeutic strategies.

Materials and methods

The case records of 1,320 patients with a diagnosis of pSS [according to the European (16) or the American European Criteria (17)] were reviewed in this observational, retrospective, cross-sectional multicentre study. Patients were recruited from 5 Italian referral Rheumatology Centres. Cumulative demographic, clinical, serological and therapeutic data were recollected according to a standard protocol. The clinical charts of patients with symptoms and/or signs of inflammatory myositis were carefully reviewed and the patients were contacted to obtain additional information, if necessary. Clinical charts of patients were selected if, according to Bohan and Peter's diagnostic criteria (18) for inflammatory myopathy (IM), they reported the presence of persistent invalidating muscular weakness (of proximal and/or distal mass muscles from upper and lower limbs), associated or not to severe muscle pain on grasping or spontaneous muscle pain supported by: increased serum levels of CPK (CPK normal value 60 - 190 UI/l) and/or abnormal electromyographic (EMG) findings. The possibility of an on-going myocardial ischemia as a possible reason for the increase in muscle enzyme was excluded. Drug use was properly investigated to evaluate any possible iatrogenic effects on muscle. In these patients, data regarding serological status were collected (ANA antibody-

Competing interests: none declared.

ies tested in immunofluorescence with a cut-off value 1:160; anti-SSA/SSB/RNP/Sm/Jo1 tested by commercially available ELISA).

When the EMG was performed, it was considered positive in the presence of electrical irritability, decrease in the mean duration of motor unit potentials or increase in the percentage of polyphasic motor unit potentials (short duration), and rapid firing of the motor unit potentials in relation to the level of activity. When performed (generally on deltoid or quadriceps femoris according to the most symptomatic site), muscle biopsies were reviewed by a dedicated pathologist. All biopsies underwent standard histological and histochemical analyses including Haematoxylin and Eosin (H&E), Gomori trichrome, sequential cytochrome c oxidase (COX)/succinate dehydrogenase (SDH) and ATPase. Immunohisto-

chemical analyses with the following antibodies were also performed: fast, slow and neonatal myosin, dystrophin (N-terminus, rod domain, C-terminus), sarcoglycans (α , β , δ , γ), dysferlin, major histocompatibility complex (MHC) class I, CD68, CD20, CD4 and CD8. Primary antibodies were visualised using horseradish peroxidase-conjugated secondary antibodies.

Results

Clinical findings

One thousand, three hundred and twenty patients with pSS (1075 diagnosed according to American European criteria, 245 diagnosed according to European criteria, 56 M, 1264 F, mean age 52 years; range 17–89 years) were considered. Mean age at diagnosis was 51.6 \pm 13.8 years and the mean follow up was 5 years (range 0–42 years). Seventeen patients (2.24%) with pSS [mean

age 55.5 years (range 27–75 years), 15 diagnosed according to American European criteria, 2 diagnosed according to European criteria] presented invalidating muscular weakness, and in some cases severe myalgias [7/17 (41.1%)], accompanied by increased serum level of CPK and/or abnormal EMG (Table I). A progressive muscular weakness arose in the proximal and in one case distal upper and lower limbs. None of the patients showed dysphagia, dropped head or symptoms related to a possible muscular involvement of respiratory system. In eight out of seventeen (47.05%) patients, muscular and sicca symptoms had occurred together at onset while in two patients (11.7%) muscle involvement preceded pSS diagnosis (approximately 17 and 33 years before pSS diagnosis respectively). Mean age at pSS diagnosis was 47 (range 14–69 years) years while mean age at muscle

Table I. Clinical, serological, histological and electromyographical findings in seventeen patients with pSS and muscular symptoms.

Patients	Sex	Age at SS Diagnosis	Muscular Symptoms onset	Muscular weakness	Mialgia	Interstitial Pneumonia	Auto Antibodies	CPK (folds above normal)	Muscle Biopsy	EMG/ENG
PT 1	F	46 years	61 years	Yes	No	No	ANA, aSSA, aSSB, RF	> x5	PM like	Pos
PT 2	F	57 years	58 years	Yes	Yes	No	Neg	> x2	PM like	Pos
PT 3	F	44 years	44 years	Yes	No	No	ANA, aSSA, aJo1	> x3	Non-specific*	Not done
PT 4	F	68 years	69 years	Yes	No	No	RF	Normal	IBM like	Pos
PT 5	F	62 years	52 years	Yes	No	No	ANA, aSSA, RF	> x3	PM like	Pos
PT 6	F	25 years	25 years	Yes	No	No	ANA, aSSA, aSSB, RF	Normal	Non-specific*	Pos
PT 7	F	37 years	42 years	Yes	Yes	No	ANA, aSSA, aSSB, aJo1 aRNP	> x18	PM like	Pos
PT 8	F	21 years	22 years	Yes	No	No	ANA, aSSA	Normal	Neg	Pos
PT 9	F	54 years	54 years	Yes	No	No	aSSA	> x3	Neg	Neg
PT 10	F	45 years	74 years	Yes	Yes	No	ANA	Normal	Non-specific*	Pos
PT 11	F	54 years	55 years	Yes	Yes	No	ANA	> x2	Neg	Not done
PT 12	F	63 years	63 years	Yes	Yes	Yes	Neg	> x5	Non-specific*	Pos
PT 13	F	65 years	65 years	Yes	Yes	No	ANA, aSSA,	> Normal	Not done	Pos
PT 14	F	14 years	23 years	Yes	Yes	No	ANA, aSSA, RF	> x15	Not done	Pos
PT 15	F	47 years	47 years	Yes	No	No	ANA, aSSA, aSSB, RF	> x10	Not done	Pos
PT 16	F	54 years	21 years	Yes	No	No	ANA, aSSA	> Normal	Not done	Not done
PT 17	M	53 years	53 years	Yes	No	Yes	ANA, aSSA, aJo1	> x40	PM like	Pos

*Scattered hypotrophic fibres in absence of muscle fibre degeneration/necrosis and/or inflammatory infiltrates. No sarcolemmal expression of major histocompatibility complex class I.

symptoms onset was 48.7 (range 23–74 years) years. Thirteen out of seventeen (76.4%) cases had increased serum levels of muscle enzymes [CPK mean value 1984.3 UI/l (range 226–12475 UI/l)]. In all cases except one, the possible iatrogenic origin of CPK serum level increase was excluded. In one patient (patient 12 in Table I), muscle enzymes increased following statin therapy but remained unchanged despite drug withdrawal. The presence of co-morbidities, such as metabolic/endocrine diseases or neuropathies possibly responsible for their symptoms, and abnormal serological findings were excluded in all cases. As well, a family history of neuromuscular disorders was recorded. EMG of upper or lower limbs (performed in 14 patients) showed signs of muscular damage in thirteen out of fourteen patients (92.8%). In 13/17 (76.4%) cases and 12/17 (70.5%) respectively anti-nuclear (ANA) and anti-SSA antibodies tested positive. Three patients (17.6%) were positive for anti-Jo-1 antibodies and one of these patients was also positive for anti-RNP antibodies.

The presence of FM in patients with muscle pain was found in 2 out of 7 patients (28%) (patients 2 and 11). No patient showed DM dermatologic manifestations. In two cases (patients 12 and 17) a diagnosis of interstitial pneumonia was performed according to chest computerised tomography findings. Ten out of 17 selected patients (58.8%) fulfilled at least 3 of the diagnostic criteria for IM. Five of these patients fulfilled all 4 criteria required for a “definite diagnosis” (patients 1, 2, 5, 7, and 17) and five fulfilled the 3 criteria for a “probable diagnosis” (patients 4, 12, 13, 14 and 15). Four patients did not satisfy Peter and Bohan’s criteria (6, 8, 9, 10). The remaining 3 patients were not completely characterised (patient 16 was lost at follow-up, while patients 3 and 11 did not undergo EMG).

Histological findings

Muscular biopsy was performed in 13/17 patients (76.4%). In 3/13 (23.07%) patients, muscle biopsy was unremarkable (reported as “negative” in Table I). In 4/13 (30.7%) patients histological analysis revealed only scattered

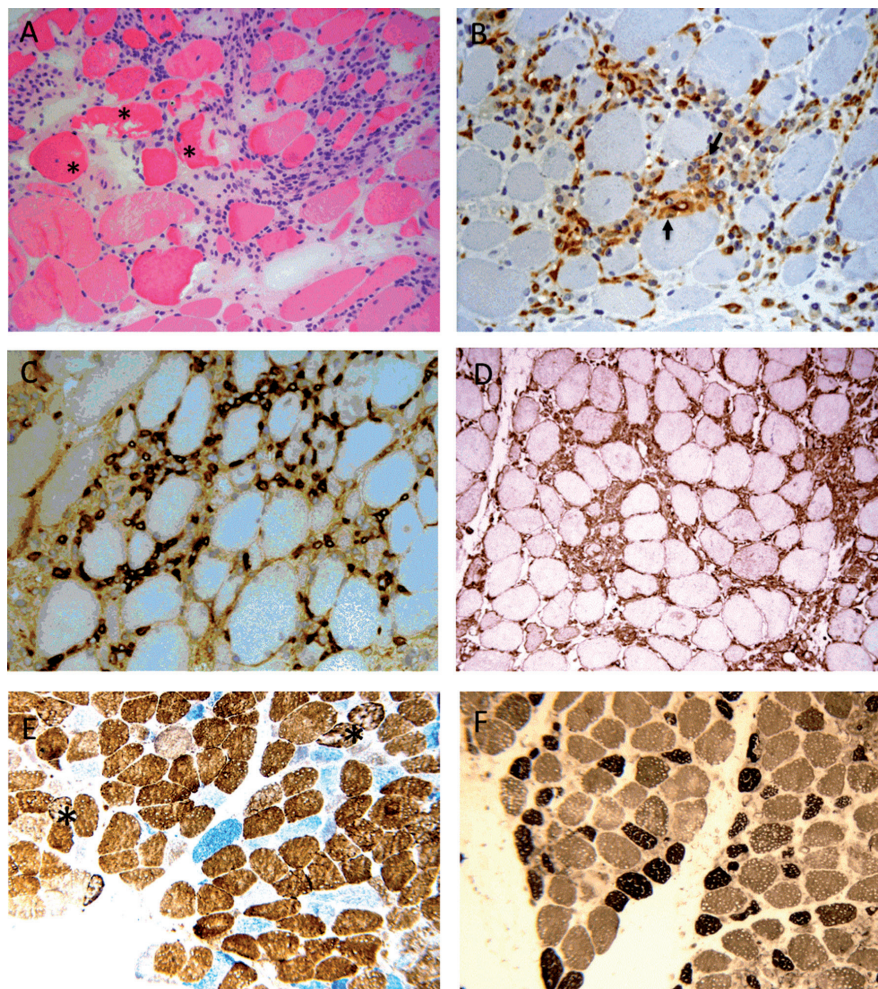


Fig. 1. Histologic features of muscle biopsy from a patient with pSS.

A. Endomysial inflammatory cell infiltrate. Several muscle fibres are atrophic and some fibres show hyper-eosinophilic cytoplasm, suggestive of necrosis (asterisks) (Haematoxylin and eosin stain; original magnification 40X). **B.** Macrophages are present in the endomysium with figures of myophagocytosis (arrows) (CD68 immunohistochemistry; original magnification 40X). **C.** CD8⁺T cells are diffusely distributed in the endomysium around muscle fibres (CD8 immunohistochemistry; original magnification 40X). **D.** Strong sarcolemmal upregulation of major histocompatibility complex (MHC) class I molecules (MHC class I immunohistochemistry, original magnification 10X). **E.** The image shows a mosaic pattern of COX-negative fibres. These cells appear blue since they are devoid of the COX activity (brown) but retain the succinate dehydrogenase (SDH) activity (blue). There are some lobulated fibres (asterisks) (Combined COX-SDH histochemistry; original magnification 10X). **F.** Type 2 fibres are hypotrophic (ATPase stain, PH9.4; original magnification 10X).

hypotrophic fibres (reported as “non-specific” findings in Table I) without inflammatory infiltrates. In 6/13 (46.1%) patients (patients 1, 2, 4, 6, 7 and 17 in Table I) an inflammatory myopathy was histologically confirmed. Specifically one case (patient 4 in Table I) showed muscle fibre necrosis, myophagocytosis and rimmed vacuoles staining positive with SMI310 and SM31, suggesting an IBM. Five cases showed muscle fibre necrosis and endomysial lymphocytic infiltrate (CD3⁺/CD8⁺) surrounding and invading non-necrotic fibres, suggesting a PM. Interestingly in two of these

four cases, several fibres showed a decreased histochemical cytochrome C oxidase (COX) stain (Fig. 1).

Treatment

All patients were treated with corticosteroids (from 1 mg/kg/day of prednisone equivalents up to 1 g daily for three consecutive days) followed by different DMARDs [hydroxychloroquine (HCQ), methotrexate (MTX), azathioprine (AZA), or cyclosporine (CyA)]. If necessary *i.v.* pulses of cyclophosphamide (CYC), cycles of intravenous immunoglobulin (IVIg)

Table II. Treatment strategies in sixteen patients with pSS and muscular symptoms.

Therapy	Patients Number	First line ¹	Second line ²	≥ Third line ³	Mean duration (months)	Primary inefficacy ⁴	Secondary inefficacy ⁵	Adverse events ⁶	Discontinuation due to remission	Ongoing treatment
Hydroxychloroquine	10/17 (58.8%)	7/10 (70%)	2/10 (20%)	1/10 (10%)	24	3/10 (30%)	2/10 (20%)	0	0	5/10 (50%)
Methotrexate	8/17 (47.05%)	3/8 (37.5%)	3/8 (37.5%)	2/8 (25%)	24	3/8 (37.5%)	2/8 (25%)	1/8* (12.5%)	1/8 (12.5%)	1/8 (12.5%)
Azathioprine	6/17 (35.2%)	0	5/6 (83.3%)	1/6 (16.6%)	27	0	3/6 (50%)	1/6 [†] (16.6%)	0	2/6 (33.3%)
Cyclosporine	6/17 (35.2%)	3/6 (50%)	1/6 (16.6%)	3/6 (50%)	33	1/6 (16.6%)	4/6 (66.6%)	0	1/6 (16.6%)	0
Cyclophosphamide	3/17 (17.6%)	1/3 (33.3%)	0	2/3 (66.6%)	7	0	1/3 (33.3%)	1/3 [‡] (33.3%)	1/3 (33.3%)	0
Mycophenolate	6/17 (35.2%)	1/6 (16.6%)	0	5/6 (83.3%)	11	0	1/6 (16.6%)	0	0	5/6 (83.3%)
Rituximab	2/17 (11.7%)	0	1/2 (50%)	1/2 (50%)	18	1/2 (50%)	0	0	1/2 (50%)	0
IVIg	3/17 (17.6%)	1/3 (33.3%)	0	2/3 (66.6%)	4.6	0	1/3 (33.3%)	0	2/3 (66.6%)	0

¹ The drug was used as first line therapy; ² the drug was used if first line therapy failed; ³ the drug was used if first and second line therapy failed; ⁴ primary inefficacy was defined as absence of clinical and serological response after three months of follow-up; ⁵ secondary inefficacy was defined as loss of efficacy; ⁶ adverse event is any undesirable experience associated with the use of the drug. *Elevated liver enzymes. [†]Leucopenia.

and also rituximab (RTX) were used (Table II).

Concerning patients with histologic evidence of IM, they were treated as follows. Patients 1 and 4 were both treated with cycles of intravenous immunoglobulin (IVIg) (0.4 g/kg/daily for 5 days). Patient 4 achieved a complete remission of clinical symptoms and laboratory findings. Patient 1, after 5 cycles of IVIg did not obtain complete remission and thus was treated with *i.v.* pulses of cyclophosphamide (CYC) (500 mg every two weeks for three months). Such therapy was successful, and the patient is still in remission in therapy with azathioprine 50 mg per day. *I.v.* pulses of CYC were also successful for patient number 2 who is still in remission in therapy with hydroxychloroquine. Patients 5 and 7 were both treated with rituximab (RTX) after failure of first line immunosuppressive therapy [mycophenolate mofetil 2g daily (MMF) and CyA]. One patient (patient 7) went into complete remission after 5 cycles, (1g two weeks apart every 6 months of RTX). The other patient (patient 5) experienced a clinical relapse after some months from first RTX administration. Patient 17 was initially treated with pulses of steroids with partial benefit. Recently micophenolate mophetil (2 g daily) was introduced; his evaluation is still ongoing.

Concerning the other four patients who fulfilled the criteria for IM (patients 12, 13, 14 and 15) but without evidence of histologic myositis (biopsy not performed in three of them and resulted “non-specific” in one) they were all treated with *i.v.* pulses of CYC fol-

lowed by MMF 2 g daily with complete remission of symptoms and normalisation of CPK serum levels.

The remaining 7 patients included in our cohort are still in treatment with hydroxychloroquine with partial benefit on muscle symptoms.

Discussion

Our retrospective analysis shows a prevalence of symptomatic myositis in pSS lower than previously reported (4). After selecting 17 patients suspected for IM on clinical grounds, only 6 cases had histological confirmed myositis and, according to Bohan and Peter's diagnostic criteria, only 10/1320 (0.75%) patients fulfilled at least the 3 required criteria for a probable diagnosis of myositis. According to such findings, these ten patients could be classified as having an overlapping syndrome. There are not many studies in the literature that determine the exact prevalence of muscle involvement in pSS patients; only a few case reports and small case series, mostly dated, have been describe so far. One of the largest studies performed by Kraus *et al.* in 1994 (4), reported a prevalence of myositis of 3%. However, this study was performed on a cohort of patients quite small when compared to ours (104 pSS patients vs 1320 pSS patients). We also need to consider other variables that make it difficult to compare significantly different cohorts including: age, sex, drugs and also geographic latitude (19). Indeed, the prevalence of DM is influenced by latitude, being more frequent in areas closer to the equator (19). Moreover, most of the patients in

our cohort were treated with hydroxychloroquine or low doses of steroids which might have influenced the low prevalence of IM. Our study has some limitations including the lack of muscular histology in some of the recruited patients and the sole consideration of symptomatic patients with serological or instrumental abnormalities, which prevents us from unveiling a possible subclinical myositis as Lindvall and colleagues have done.

Although muscular involvement is usually detected over the course of pSS (5), in some cases it may also appear at disease onset. In eight out of seventeen cases, signs or symptoms of a possible IM occurred at the same time or directly after overt sicca symptoms. In the other cases, muscular abnormalities occurred later (in one case almost 20 years after pSS diagnosis). Nonetheless, even if rarely, pSS may be also diagnosed after myopathy onset. Due to the low prevalence of IM, definite conclusions concerning the time relationship between the two conditions cannot be drawn. We have described seventeen patients who reported severe muscular weakness, and in some cases myalgias, and among them 76.4% showed increased levels of muscle enzymes. Nonetheless, in agreement with what has been previously reported by Lindvall *et al.* (5), abnormal EMG and histological signs of inflammation were found in patients with normal CPK. As expected, most of the patients tested positive for ANA or anti-SSA antibodies. The typical auto-antibody associated to myositis, anti-Jo1 antibody, was found in three cases. In two of them (patients 7

and 17), muscular histology confirmed the presence of a PM-like pattern and the patient presented all the typical symptoms and instrumental abnormalities. This lead us to consider these two cases as true overlap syndrome cases. The other patient (patient 3), although positive for anti-Jo1 antibodies, did not show evidence of inflammatory infiltrates (“non-specific” findings) by muscular histological analysis and did not fulfill the diagnostic criteria for primary PM. It is possible that overtime this patient will develop the full-blown picture of PM considering that it is well known that autoantibodies may precede the clinical onset of autoimmunity by many years (20). The presence in one patient of positive anti-RNP antibodies at high titers could be suggestive of mixed connective tissue disease (MCTD) but the criteria used to define this condition (21) were not satisfied. Interestingly enough, ten out of seventeen patients fulfilled at least three criteria for IM (probable IM). The five patients with all four criteria fulfilled were the same who had a PM or IBM like histological pattern. The other patient with an IBM-like pattern fulfilled 3 criteria. The remaining patients who also fulfilled 3 criteria presented increased serum levels of CPK and abnormal EMG but only in one case muscle biopsy was performed showing “non-specific” findings (patient 12). In the other patients, muscle biopsies were not performed and this lacking information is one of the main limitations of this retrospective study. According to our findings and to the above mentioned considerations, the six cases in which muscle histology confirmed the presence of a true inflammatory process were then classified as overlap syndromes. This can also be supposed for the other 4 patients who fulfilled 3 diagnostic criteria for a “probable diagnosis” despite the lack of histologic proof. One of the six patients with histological evidence of IM showed myopathological findings suggestive of IBM. In this patient the age of onset was 69 years old and distal muscle involvement supports a possible overlap between pSS and IBM, which has been previously described in several other case reports or

case series (22-25). Also, the presence of histological aspects of IBM in pSS, not associated to its typical clinical features, has been described (5). Even if such a relationship may be coincidental, those conditions seem to share different features including the slow, late and insidious onset and the genetic background (*i.e.* haplotype HLADR3 and genotype DQB*10201) (25). The cause of IBM is still unclear although there are some histological (CD8⁺ T cells infiltration, MHC I muscle fibre expression), serological (frequent detection of positive auto-antibodies such as ANA, anti-SSA, and rheumatoid factor) and clinical (association with autoimmune diseases) factors suggesting a possible immune-mediated origin (26, 27). In the remaining five cases of this cohort, the histological aspects were those of a PM. Interestingly, two out of five showed several COX negative fibres, consistent with mitochondrial dysfunction. While mitochondrial dysfunction is commonly observed in muscle biopsy from patients with IBM it has been more rarely described in association with PM. Siepman *et al.* (28) recently reported histological features of PM with COX-negative fibres (*i.e.* PM-Mito) in two patients with symptoms of IBM, one with positive aSSA and aSSB antibodies (28). Concerning the remaining 7 patients who did not fulfil the diagnostic criteria for IM, three with histological evidence of “non-specific” findings (patients 3,6, and 10), three with “negative” histology (patients 8-9-11) and one who did not perform the muscle biopsy (patient 16) (lost at follow up), we can only hypothesise a “myositis-like condition” because of the severe clinical muscular involvement. According to the biopsy (when performed) none of these patients presented an immune-mediated necrotising myopathy, mitochondrial or steroids myopathy, neuropathies or an endocrine myopathy. Three patients with increased CPK serum levels had “negative” or “non-specific findings” on the biopsy (1 patient with negative EMG and two patients where EMG was not performed). However, in some cases a muscle biopsy is negative and this might be due to a focal distribution

of the inflammatory infiltrates. Normal muscle biopsies have been reported in 10–20% of patients with IM. Sampling error due to skip lesions has been suggested as one possible explanation. Another reason for a negative biopsy, at least in some cases, may be treatment with corticosteroids before the biopsy sampling (29). Due to the loss at follow up and the lack of both histology and EMG for patient 16, it is not possible to draw any conclusion.

We believe it is important to underline case number 12. Indeed, according to the clinical symptoms accompanied by increased CPK serum levels, positive EMG and “non-specific” muscular histology, we can hypothesise a different origin for muscular involvement in this case. In this patient, CPK serum levels increased following statin therapy and no recovery occurred despite drug discontinuation. A persistent CPK elevation following statin therapy has been already described (30). Usually statin toxicity becomes evident with diffused myalgia associated in some cases with muscle weakness. As we could observe in our patient, CPK serum levels were usually mild elevated, not exceeding 10 times normal values. According to the biopsy, which did not show any kind of inflammatory infiltrates but only mild non-specific findings (scattered hypotrophic fibres in absence of muscle fibre degeneration/necrosis and no sarcolemmal expression of major histocompatibility complex class I), we were able to exclude the possible onset of a necrotising autoimmune myositis, which has been recently described following statin treatment (31). However we underline that this patient, despite the lack of anti Jo1 antibodies positivity and diagnostic muscle biopsy, presented a documented interstitial lung disease. Such a finding, which is one of the main extra muscular manifestations of IM, further supports our suspicion of an overlapping syndrome. Thus, confirmation by another muscle biopsy and/or searching for other associated IM autoantibodies (32), could be a useful tool to determine the diagnosis.

Not only statins, but also other drugs such as steroids, chloroquine, and colchicine, are potentially toxic to muscle

tissue (33). Another possible iatrogenic effect can be hypothesised for one patient who developed myositis during RTX administration (patient 1). Even if, as far as we know, there are not reports concerning RTX-induced muscle toxicity, a possible toxic effect cannot be completely excluded. Notably, in this patient, the presence of lymphocyte T only and not lymphocyte B, characterised the muscle inflammatory infiltrate, and the patient reported clinical and laboratory efficacy from azathioprine after failure of IVIg and cyclophosphamide. Actually, RTX has been used with benefit in small series of patients with refractory myositis (34, 35). In our experience, two patients not responding effectively to the traditional approach were started with RTX. In one of these, 5 cycles of RTX were effective for a progressive clinical and serological induction of stable remission. On the contrary, in the other case, two cycles of therapy did not lead to any relevant change in clinical symptoms.

The lack of high quality randomised controlled trials that assess the efficacy and toxicity of immunosuppressants in inflammatory myositis prevents us from drawing strong conclusions concerning therapy. Thus treatment of inflammatory myopathies is still empiric and based on insufficient evidence. Most of patients with PM and DM seem to respond to corticosteroids at least to some degree and for a period of time (36). High doses of corticosteroids are usually the most widely used first line approach but primary or secondary resistance, intolerance or cortico-dependence are observed in 30-50% of cases (37). Thus a second line of treatment with immunosuppressants such as MTX, AZA, leflunomide, CYC, CyA, tacrolimus or MMF, may be required (36).

In conclusion, we confirm that myositis is a rare complication of pSS, characterised by histological features sometimes common to PM or, less frequently, sharing features with IBM. Evidence of a frank IBM was demonstrated in this as well as in other case series. In our opinion, IM can occur over the course of pSS as an overlapping syndrome. The positivity of anti-Jo1 antibodies in three cases further supports such evidence.

The lack of histological evaluation in all of our included patients represents one of the main limits of our study and may be responsible for the low prevalence of IM detected. The processes driving the appearance of muscle inflammation in the form of an overlap syndrome over the course of pSS are still unknown. In agreement with other reports, muscle involvement seems to have a good outcome with only a small percentage of patients resistant to therapy. Based on our experience, classical immunosuppressants alone or in association, appear to be effective in inducing myositis remission. In most difficult cases the use of IVIg or RTX may be used as well, in some with clear benefit.

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