Necrotising myopathy associated with anti-signal recognition particle (anti-SRP) antibody

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Abstract

Objective

Prompted by the few studies available in the literature, we analysed patients with necrotising myopathy associated with anti-signal recognition particle (anti-SRP).

Methods

We conducted a retrospective, single-centre cohort study involving 14 patients with anti-SRP antibody followed between 2001 and 2016.

Results

Patients had a mean age at disease onset of 40.7 years and were predominantly female and of white ethnicity. At disease onset, all patients had limb muscle weakness with median serum of creatine phosphokinase level of 8080U/L, 64.3% had constitutional symptoms, 50% dysphagia, 42.9% myalgia, 21.4% and 14.3% pulmonary and articular involvement, respectively. There were no cases of cutaneous, neurological or cardiac involvements. Notably, 21.4% of patients had previous exposure to statins. Moreover, with the exception of one patient, all received methylprednisolone pulse therapy and/or human intravenous immunoglobulin (IVIg), as well as prednisone and different immunosuppressive drugs or rituximab. Relapse occurred in 64.3% of the cases. However, most patients had significant recovery of muscle strength, with half no longer using glucocorticoids and the remainder on a weaning regimen with low dose prednisone.

Conclusion

Unlike the cases described in the literature, there was a high frequency of extra-muscular symptoms in the patients studied. Moreover, one fifth of patients had previous exposure to statin use. There was a high relapse rates, but with good clinical and laboratory recovery, especially with pulse therapy regimen of methylprednisolone and/or IVIg.

Key words

dermatomyositis, statins, idiopathic inflammatory myopathies, necrotising myopathy, polymyositis

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Introduction

Idiopathic inflammatory myopathies are a heterogeneous group of autoimmune systemic muscular diseases that includes dermatomyositis, polymyositis, inclusion myositis, immune-mediated necrotising myopathy, among others. Each of these diseases presents distinct demographic, laboratory, clinical, histological and evolution features (1-4).

Immune-mediated necrotising myopathies comprise two large groups: (a) associated with the anti-hydroxy-methyl-glutaryl-coenzyme A reductase antibody (anti-HMG-CoAR) - frequently related to previous exposure to statins; (b) associated with the signal recognition particle antibody (SRP). These conditions affect patients around the sixth decade of life, predominantly females and white individuals (5, 6).

Patients with anti-SRP positive antibodies generally present with clinical signs of severe proximal muscle weakness, rapid onset, rare extra-muscular manifestations, very high levels of creatine phosphokinase (CPK) and muscle biopsy with necrotic and regenerating muscle fibres, in the presence of scarce or absent inflammatory infiltrates. This patient group has recurrent relapses and requires frequent reevaluation of drug treatment (5).

As the main differential diagnosis, necrotising myopathies associated with anti-HMG-CoAR antibody should be considered. These patients, although having similar clinical, laboratory and histological characteristics to individuals with anti-SRP antibody, have a strong association with the history of exposure to statins (5). It is therefore believed that this class of drug has a relevant role in the pathogenesis of the disease (5).

Initial treatment of myopathies associated with anti-SRP antibody is based on the use of glucocorticoids (oral or parenteral), followed by maintenance therapy with several immunosuppressants and, in some cases, rituximab (5-9).

Due to the rarity of the disease, the objective of the present study was: (a) to present the demographic, clinical, laboratory and evolution profiles of patients with necrotising myopathy associated with anti-SRP antibody followed at our tertiary service; (b) to evaluate the impact of the use of pulse therapy with methylprednisolone and / or IVIg in this sample.

Methods

A retrospective, single-centre cohort study was conducted in which 14 patients with necrotising myopathy associated with anti-SRP antibody were systematically reviewed between 2001 and 2016.

Patients were initially admitted to our tertiary service to investigate symmetrical, predominantly proximal weakness and significant elevation in serum CPK levels, without apparent cause (*e.g.* neoplasms and infections). The patients were submitted to the following complementary tests: anti-SRP positive and anti-HMG-CoAR negative antibodies; electroneuromyography revealing predominance of proximal myopathy without neurogenic pattern; and/or muscle biopsies (vastus lateralis or brachial biceps) disclosing the presence of necrotic muscle fibres and absence or scarcity of inflammatory cell infiltrates.

As part of the internal protocol of our service, serum samples were collected from patients at disease diagnosis and stored at - 80°C. Analyses of the anti-SRP and anti-HMG-CoAR antibodies, as well as anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ antibodies, were performed by using commercial solid-phase immunoblotting kit, a qualitative immunoassay line for detection of 11 human immunoglobulin G (IgG) autoantibodies against specific or associated myositis antigens in serum or plasma (Euroimmun, Lübeck, Germany).

Anti-SRP antibodies were determined using a commercial solid-phase immunoblotting kit, a qualitative immunoassay line for detection of 11 human immunoglobulin G (IgG) autoantibodies against specific or associated myositis antigens in serum or plasma. In order to increase the specificity of the method, the manufacturer's protocol was followed. Reaction positivity was defined according to a previously published study (10).

Anti-HMG-CoAR antibody was assayed by enzyme-linked immunonosorbent assay (ELISA), using re-

combinant HMG-CoAR protein and anti-HMG-CoAR polyclonal antibody (MyBioSource, CA, USA). For the purposes of this study, patients with anti-HMG-CoAR values of more than three standard deviations of the mean of 8 healthy individuals were considered positive.

The present study was approved by the local Research Ethics Committee.

Demographic, clinical, laboratory and therapeutic data were obtained by means of a review of the electronic medical records, containing previously standardised and parameterised data. The following parameters were analysed: age at disease diagnosis, sex, ethnicity, time between diagnosis and symptom onset, disease duration, constitutional, gastrointestinal (upper dysphagia), pulmonary (moderate dyspnea or computed tomography disclosing evidence of interstitial pneumopathy and/or "ground-glass" pneumopathy), joint (arthralgia and / or arthritis), cardiac (heart failure or valvular heart disease - transthoracic echocardiography, coronary syndrome), cutaneous, neurological, and muscular (myalgia) involvement, plus limb muscle strength, according to the *Medical Research Council* (11) (grade 0: absence of muscle contraction; grade I: signs of low contractility; grade II: normal amplitude movements but does not overcome the action of gravity; grade III: normal amplitude movements against the action of gravity; grade IV: integral mobility against the action of gravity and some degree of resistance; grade V: complete mobility against sharp resistance and against the action of gravity), previous and current drug treatment (including statins, corticosteroids and/or immunosuppressants), and serum CPK level (normal range: 24–173 IU/L), as determined by the automated kinetic method.

Disease relapse was defined as the return of clinical symptoms and/or increase in the serum of CPK level attributed to disease activity after exclusion of possible neoplastic or infectious processes.

Glucocorticoid was the initial therapy used (prednisone 1 mg/kg/day, oral) followed by dose tapering according to clinical and laboratory results. In cases of severe disease (progression of dyspnea, dysphagia, significant loss of muscle strength), pulse therapy with methylprednisolone (1 g/day for three consecutive days) and / or IVIg (2 g/kg, spread over 2 to 5 consecutive days).

With regard to glucocorticoid sparing agents, the following immunosuppressants were used: azathioprine (2–3 mg/kg/day), methotrexate (20–25 mg/week), cyclosporine (2–4 mg/kg/day), mycophenolate mofetil 3 g/day), leflunomide (20 mg/day), monthly intravenous cyclophosphamide (0.5–1.0 g/m^2 body surface area), rituximab (1 g, parenteral, at time zero and after 15 days). This cycle was repeated every six months for two consecutive years, according to the internal protocol of the service.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables, which were expressed as mean ± standard deviation (SD) or median (interquartile 25%–75%). Categorical variables were expressed as percentages (%). All statistical calculations were performed with the software SPSS v. 15.0 (Chicago, IL, USA).

Results

Fourteen patients with necrotising myopathy associated with anti-SRP antibody (Table I) were evaluated. Mean age of the patients at the time of diagnosis was 40.7±14.8 years, predominantly affecting white (71.4%) and female (85.7%) individuals. Median time between diagnosis and symptom onset was 3.5 (1.8–7.8) months, and the median duration of disease was 3.5 (1.8–5.3) years.

Constitutional symptoms were evident in two thirds of the cases. There was gastrointestinal (upper dysphagia), pulmonary and articular tract involvement in 50.0%, 21.4% and 14.3% of cases, respectively. No patients had cardiac, cutaneous or neurological involvement. Approximately half of the patients complained of generalised myalgia. All had objective muscle weakness of the limbs (upper and/or lower), most with grade III or IV. Median serum CPK level at initial disease diagnosis was 8080 (4355–14279) U/L.

Table I. General data for 14 patients with anti-SRP antibody associated inflammatory myopathies.

Age (years)	40.7±14.8
Female gender	12 (85.7)
White ethnicity	10 (71.4)
Time between diagnosis and symptoms (months)	3.5 (1.8-7.8)
Disease duration (years)	3.5 (1.8-5.3)
Constitutional symptoms	9 (64.3)
Involvement	
Gastrointestinal tract (upper dysphagia)	7 (50.0)
Pulmonary	3 (21.4)
Articular (arthralgia and/or arthritis)	2 (14.3)
Cardiac	0
Cutaneous	.0
Neurological	0
Muscular	
Myalgia	6 (42.9)
Muscle strength (upper limbs)	
Degree V	1 (7.1)
Degree IV	5 (35.7)
Degree III	8 (57.2)
Degree II	0
Degree I	0
Muscler strengh (lower limbs)	
Degree V	0
Degree IV	6 (42.9)
Degree III	7 (50.0)
Degree II	1 (7.1)
Degree I	0
Creatinophosphokinase (U/L)	8080 (4355-14279)

Data expressed as mean ± standard deviation, median (interquartile 25th–75th) or percentage (%).

Muscle biopsy was performed in all 14 patients and electromyography in 12.

None of the patients had antibodies against anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ or anti-EJ.

The drug treatments used are given in Table II. All patients received glucocorticoid (prednisone 1 mg/kg/day), while pulse therapy with methylprednisolone and IVIG was administrated in 12 (85.7%) and 8 (57, 1%) patients. Pulse therapy was performed more than once in 6 (42.9%) patients, with an interval of one month between applications, due to refractory clinical-laboratory status (patients: 1, 2, 5, 11, 12, 13). Regarding glucocorticoid sparing agents, several immunosuppressants were used, alone or in combination, depending on tolerance, side effects and refractoriness.

Three (21.4%) patients had a history of exposure to statins (sinvastatin or atorvastatin).

Table II. General data for 14 patients with anti-SRP autoantibody associated inflammatory myopathies.

Patient (n)	Age (years)	Gender	Ethnicity	Diagnosis – symptoms (months)	Disease duration (years)	Previous therapy			Relapses
						Pred	IS/IM	Statins	
1	35	F	Wh	6	1	S	MP*, AZA, IVIg*, RTX		Y
2	48	F	Wh	2	15	S	MP*, AZA, MTX, MMF, LFN, IVIg*, RTX		Y
3	27	F	Wh	2	3	S	MP, AZA, MTX		Y
4	62	M	Bl	4	7	S	MP, MTX, CP		
5	26	F	Wh	1	2	S	MP*, AZA, MTX, IVIg*		Y
6	28	F	Wh	9	6	S	MP, AZA, MTX, CP		Y
7	56	F	Wh	3	2	S	AZA, MTX, MMF		Y
8	49	F	Wh	4	10	S	AZA, MTX, IVIg		Y
9	45	F	Wh	1	2	S	MP, AZA, MTX, IVIg		
10	52	M	Ye	2	4	S	MP, AZA, MTX, CP, MMF, IVIg, RTX	Y	Y
11	49	F	Wh	1	1	S	MP*, MTX, IVIg*	Y	
12	18	F	Wh	4	7	S	MP*, AZA, MTX, IVIg*, RTX		Y
13	56	F	Bl	5	0	S	MP, IVIg	Y	
14	19	F	Wh	0	16	S	MP, MTX		
	40.7±14.8			3.5 (1.8-5.3)	3.5 (1.8-7.8)				

Data expressed as mean ± standard deviation; median (interquartile 25th–75 th) or percentage (%),
Ye: yellow; AZA: azathioprine; Wh: white; CP: cyclosporine; F: female; IVIg: human intravenous immunoglobulin; M: male: MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; Bl: black; RTX: rituximab; Y: yes; *: more than once.

Table III. General data for 14 patients with anti-SRP autoantibody associated inflammatory myopathies.

Patient (n)	Current therapy	Prednisone	Condition		
			Clinical	CPK (U/L) initial	CPK current (U/L)
1	Pred, AZA, RTX	Taper (5 mg/day)	MS V	26000	3342
2	-	-	Death	8500	-
3	AZA	-	MS V	14385	179
4	-	-	MS V	9500	94
5	Pred, MTX, IVIg	20 mg/day	MS IV	14243	3496
6	Pred, MTX	Taper (5 mg/day)	MS V	2076	90
7	MMF	-	MS V	7000	205
8	Pred, MTX	Taper (5 mg/day)	MS V	2500	855
9	Pred, AZA, MTX	Taper (5 mg/day)	MS V	11785	172
10	AZA, RTX	-	MS V	7600	158
11	Pred, MTX	Taper (5 mg/dia)	MS V	3707	150
12	Pred, MTX, RTX	-	MS V	4570	1465
13	Pred	Taper (20 mg/day)	MS IV	7659	283
14	-		MS V	17894	104

AZA: azathioprine; CPK: creatinophosphokinase; MS: muscle strength in four limbs (degree); IVIg: human intravenous immunoglobulin; MMF: mycophenolate mofetil; MTX: methotrexate; Pred: prednisone; RTX: rituximab.

Disease recurrence was observed in two thirds of the cases, during outpatient follow-up.

There was one death (patient 2), but this was unrelated to the disease. The individual presented mesenteric thrombosis without apparent cause, evolving with intestinal necrosis and septic shock. At the time of death, the disease was in remission and the patient had not used immunosuppressants for at least six months.

The current medications (immunosuppressive drugs and/or glucocorticoid) used are shown in Table III. At end of the present study, three (21.4%) patients were not using any immunosuppressants or glucocorticoids. One individual was using azathioprine alone, without glucocorticoid. The other patients were in use of several immunosuppressants, in addition to prednisone in a weaning regimen. All patients had muscle strength of between grade IV and V at the end of the study, even those with serum CPK levels above the normal range (patients: 1, 5, 8, 12, 13).

Discussion

Although a specific and defined group of necrotising myopathies, we observed significant phenotypic variety. More specifically, a high frequency of extramuscular symptoms was found in our patients compared to those described in the literature. In addition, some of our patients had previous exposure to statins. Finally, similar to the cases in the literature, we observed a high rate of recurrence, but with good disease remission, especially upon administration of pulse therapy with methylprednisolone and/or IVIg.

Although a rare entity, only those who fulfilled strict exclusion criteria were analysed in the present study analysing a sample of 14 patients with necrotising myopathy associated with anti-SRP antibody. Moreover, none of the patients had anti-HMG-CoAR antibody and/or anti-synthetase syndrome positivity, which might also explain the presence of pulmonary and joint involvement.

Despite constituting a retrospective study, the information was obtained from previously standardised and parameterised data, providing reliable data source. Finally, because we included

patients from a single centre, there was greater homogenisation of the therapeutic course established in the patients.

Regarding demographic data, there was a predominance of females and white individuals, akin to the literature (6, 12-14, 16). Age at disease diagnosis was relatively low (40.7 years), although within the previously described range: 38.4-51.3 years (6, 12-14, 16). A recent study (9) showed that the prognosis of necrotising myopathy associated with anti-SRP antibody is worse, the younger the patients at disease onset.

Time between symptom onset and diagnosis was 3.5 months, evidencing a relatively acute evolution of muscular weakness associated with elevated serum of CPK levels. By contrast, Suzuki *et al*. (6) described a period between symptom onset and diagnosis of up to 12 months in approximately 80% of patients.

Approximately two-thirds of our patients had constitutional symptoms at the time of diagnosis, data not previously reported in the literature. Neoplastic causes were excluded, which may be triggering factors of necrotising myopathy (17, 18).

Regarding disease severity, half of the patients had dysphagia at disease diagnosis, a relatively higher rate than that described in the literature (5, 8). The presence of dysphagia may lead to an increased risk of bronchoaspiration and, consequently, early mortality in this population (6, 19).

Interstitial lung disease has also been observed in patients with necrotising myopathy associated with anti-SRP antibody (6, 9, 14, 20, 21). In a larger retrospective multicentre study in a European cohort (16), interstitial lung disease was reported in 25% of the cases, which is comparable to the results of our study.

We identified a higher rate of articular involvement (arthralgia and/or arthritis) than that reported in the literature (15% *vs*. 4%) (6).

There were no cases of cardiac, cutaneous or neurological involvement in our study cohort. By contrast, in the literature, cardiac involvement has been associated with necrotising myopathies with anti-SRP antibody, characterised by conduction disorders, fibrosis and cardiac dysfunction, as well as coronary artery disease (2–18%) (6, 15, 16). With regard to neurological symptoms, these are typically related to muscular atrophy, peripheral sensory-motor neuropathies, alterations in deep tendon reflexes and winged scapula (10%) (6). In the case of skin alterations, the presence of rash (6%) and Raynaud's phenomenon (7%) have been described (6).

Myalgia has been observed as a clinical feature of necrotising myopathy associated with anti-SRP antibody, occurring in 66–80% of cases (6, 22, 23). In most previous studies (6, 14-16, 20-23), more than 50% had progressive and severe muscular involvement of ≤III/V by the Medical Research Council Scale (11). Approximately half of our patients complained of generalised myalgia and all patients had objective muscular weakness of the limbs (upper and/or lower limbs), predominantly grade III or IV.

Concerning drug treatment, given the greater possibility of refractoriness and high relapse rate, the use of glucocorticoid and immunosuppressants for a prolonged period is necessary in patients with necrotising myopathy associated with anti-SRP antibody (6, 9, 14-16, 20-24). Indeed, the relapse rate with glucocorticoid weaning, suspension or reduction of immunosuppressive dosage is around 70% (6, 14-16, 20-24). In addition, muscle weakness persists in majority of patients despite sequelae (6, 7, 14-16, 20-24).

In the study conducted by Suzuki *et al*. (6) half of the patients were refractory to various therapeutic regimens, and despite a decrease in serum CPK levels, recovery from muscle weakness was largely incomplete. In addition, most needed long-term immunosuppressive therapy (6).

Notably, the majority of patients analysed in the present study were using immunosuppressants in a weaning regimen of prednisone. In addition, at the end of the study, clinical stability was achieved in 11 of the 14 patients, most them weaned or without corticosteroids. This good clinical outcome may be the result of the internal protocol of our service, under which the majority of patients used IVIg associated with methylprednisolone pulse therapy at the time of disease diagnosis. Also, one third of the patients received this schedule more than once, with an interval of one month. The goal is to promote early induction of disease.

Refractory patients with necrotising myopathies associated with anti-SRP antibody treated with rituximab mostly showed improvement in muscle strength and a rapid decline in serum CPK level (8, 9, 20, 24, 25). After the initial rituximab cycle, glucocorticoid doses can be reduced while maintaining sustained response (8, 9, 20, 24). Four of our patients used rituximab as a complementary treatment, all of whom showed good response to immunobiological therapy.

Notably, three patients (21%) in the present study had a history of exposure to the use of statins before the onset of the disease. This rate is higher than that reported in the literature (5%) (6, 9). In addition, our patients did not exhibit the presence of anti-HMGCoAR antibody. Therefore, it is possible that previous exposure to statins may be a triggering factor not only of necrotising myopathy associated with anti-HMG-CoAR (25), but also of that related to the anti-SRP antibody, as observed in the present study.

There was one case of death, but this was not related to necrotising myopathy (in remission). The patient evolved with mesenteric thrombosis and intestinal necrosis without apparent cause, leading to septic shock. In the study by Suzuki *et al*. (5) the long-term side effects of glucocorticoid use may have been responsible for the death of 5% of the patients (two cerebral infarcts, two cases of coronary disease and bacterial pneumonia).

In summary, significant phenotypic variety was observed in our patients, with a high frequency of extra-muscular symptoms and some having a history of exposure to statins. There was also a high rate of relapse, but with remission of the disease in most of our series, mainly following administration of pulse therapy with methylprednisolone and/or IVIg. Further studies are needed to confirm the data found in the present study.

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