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ORIGINAL RESEARCH

Patients with pure dermatomyositis/polymyositis and anti-PM/Scl autoantibody resembling anti-synthetase syndrome

Samara Pereira Alves[I], Marilda Guimarães Silva[I], Isabela Bruna Pires Borges[I], Samuel Katsuyuki Shinjo[I]

[I] Universidade de São Paulo, Faculdade de Medicina FMUSP, Division of Rheumatology, São Paulo, Brazil.

OBJECTIVE: The anti-PM/Scl autoantibody has been described in patients with scleromyositis. However, there are scant studies evaluating its prevalence and reactivity in dermatomyositis and polymyositis.
METHOD: A cross-sectional, single center study evaluating the anti-PM/Scl autoantibody in 85 dermatomyositis and 32 polymyositis patients, without overlapping syndrome, was conducted between 2000 and 2016. Clinical data and complementary examinations were reviewed from electronic medical records with pre-parameterized information.
RESULTS: The mean age of dermatomyositis and polymyositis patients was 41.1 and 42.8 years, respectively. The presence of anti-PM/Scl was observed in 5 (5.9%) dermatomyositis and 2 (6.3%) polymyositis patients. Two of these patients also had the anti-Ku antibody. The relevant clinical manifestations of these 7 patients were constitutional symptoms (100% of cases), muscular (100%), pulmonary (85.7%) and joint (71.4%) involvement, "mechanic hands" (85.7%), Raynaud phenomenon (85.7%) and plantar hyperkeratosis (85.7%). The 7 patients had relapses of disease activity, but at conclusion of the present study, 5 had complete clinical response and 2 complete remission of the disease.
CONCLUSION: There is a low frequency of the anti-PM/Scl autoantibody in dermatomyositis and polymyositis patients. In addition, patients with this autoantibody exhibit a similar pattern of manifestations to that of antisynthetase syndrome.

KEYWORDS: Autoantibodies; dermatomyositis; myositis; polymyositis.

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E-mail: samara.bety@hotmail.com

INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are autoimmune systemic myopathies that primarily affect skeletal muscle. In the case of DM, there is also a cutaneous involvement, including the classic lesions known as heliotrope and Gottron's papules.[1,2] Extramuscular manifestations may also occur, with joint, cardiac, pulmonary and/or gastrointestinal tract involvements.[2]

The anti-PM/Scl antibody is considered to be associated with myositis and is typically described in patients with overlap syndrome, such as systemic sclerosis and autoimmune myositis.[3-12]

This autoantibody has also been described in few cases of DM or PM without overlapping syndrome.[4,5,7,8,11-19] However, in this context, the autoantibody was correlated with the presence of interstitial lung disease,[11,13,17-19] neoplasia[7,13,16,18,19] or palmar and/or plantar hyperkeratosis.[11,13,17-19]

However, the few study available have many limitations and it is therefore difficult to determine

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the true prevalence and reactivity of the anti-PM/Scl autoantibody in this population. For instance, previous studies failed to evaluate and/or exclude patients with (a) anti-MDA-5[5,7,8,11-16,18,19] and/or antisynthetase autoantibodies (anti-Jo-1, EJ, JO, PL-7 and/or PL-12),[7,11-14,16,18,19] (b) clinically amyopathic DM,[5,7,8,11-19] (c) patients with lung diseases,[5,7,8,11-19] (d) smokers (5,7,8,11-19), (e) neoplasias,[7,13,16,18,19] among others.

Therefore, the primary objective of the present study was to evaluate the prevalence of the anti-PM/Scl autoantibody in a large number of patients with pure DM or PM, addressing previous study limitations. A secondary aim was to evaluate a possible association between this autoantibody and the clinical and laboratory evaluations as well as the complementary exam parameters of patients with DM and PM.

PATIENTS AND METHODS

A cross-sectional, single-center study evaluating the presence of the anti-PM/Scl autoantibody in adult patients with definite DM or PM (defined or probable) according to the criteria of Bohan and Peter[1] was conducted. All patients evaluated were seen at our tertiary service between 2000 and 2016.

This study was approved by the institutional Ethics Committee.

Exclusion criteria were the presence of associated systemic autoimmune diseases (overlap syndrome) - including systemic sclerosis (skin hardening (fibrosis), sclerodactilia, telangiectasias), neoplasia, pulmonary infections (turberculosis, aspergilloma) and chronic obstructive pulmonary disease, history of smoking, suspected cases of other myopathies (muscular dystrophies, metabolic myopathies and necrotizing immune-mediated myopathies), clinically amyopathic DM, and positivity for anti-Scl70, anti-centromere, rheumatoid factor, antisynthetase (anti-Jo-1, PL-7, PL-12, OJ or EJ), anti-MDA-5, anti-SRP or anti-HMGCR autoantibodies.

Of the initial 340 patients, 223 were excluded after applying the exclusion criteria. Thus, 117 consecutive patients were analyzed: 85 (72.7%) DM and 32 (27.3%) PM patients.

The following data on eligible patients were evaluated from electronic medical records, with pre-standardized and parameterized information. The following information on the initial diagnostic investigation in patients with clinical-laboratory activity was assessed:

1. Demographics: age at disease diagnosis, time between diagnosis and symptoms onset, gender and ethnicity.

2. Clinical manifestations: constitutional symptoms (fever and weight loss), heliotrope, Gottron's sign/papule, facial rash, "V-neck" sign, "shawl" sign, periungual hyperemia, vasculitis, calcinosis, ulcers, Raynaud's phenomenon, palmar/digital hyperkeratosis ("mechanic hands") and plantar hyperkeratosis, muscle weakness of upper and lower limbs, dysphagia and pulmonary (dyspnea: moderate to low effort, rapid evolving dyspnea: less than 3 months after onset of general symptoms);

3. Changes on high-resolution computer tomography images of the lung: incipient pneumopathy, "ground glass" (opacity) and pulmonary fibrosis in both lung bases.

4. Serum levels of muscle enzymes in blood samples taken routinely for medical consultation: creatine phosphokinase (reference value: 32-294 U/L), and aldolase (1.0-7.5 U/L).

Recurrences of PM/DM were diagnosed on the basis of the following criteria: clinical relapse (i.e. muscle and/or dermatological manifestations); biochemical relapses (i.e. increase of serum muscle enzymes for which there was no other explanation).

A complete clinical response was considered after a 6-month continuous period of no evidence of disease activity while still receiving myositis therapy. Clinical remission was defined as the 6-month continuous period with no evidence of disease activity while not receiving any myositis therapy. Relapsing was defined as any renewed clinical and/or laboratory disease activity.[21]

Serum samples stored at -20ºC were collected for the analysis of the autoantibodies at the time of the initial investigation of the active disease (laboratory and clinical). Identification of the anti-PM/Scl autoantibody, as well as of anti-syntheses (anti-Jo-1, PL-7, PL-12, OJ and EJ), anti-SRP, anti-Ku and anti-Mi-2 were performed using a commercial kit (Myositis Profile 3, Euroimmun, Germany) according to the manufacturer's protocol. The evaluation of the results was based on the methods established in a previous study.[22] In the case of the anti-MDA-5 autoantibody, identification was performed using the Enzyme-linked immunosorbent assay (ELISA) method, through recombinant MDA-5 and the anti-MDA-5 monoclonal antibody (MyBioSource, CA, USA). Results were evaluated according to methods established in a previous study.[23] Anti-HMGCR antibody was assayed by enzyme-linked immunosorbent assay (ELISA), using recombinant HMGCR protein and anti-HMGCR polyclonal antibody (MyBioSource, CA, USA). For the purposes of this study, patients with anti-HMGCR values greater than three standard deviations from the mean of 8 healthy individuals were considered positive. The rheumatoid factor was assayed by the nephelometry method.

Statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of each of the continuous variables. The results were expressed as mean ± standard deviation for continuous variables, and number (%) for categorical variables. Median values (interquartile 25^{th} - 75^{th}) were calculated for continuous variables that did not have a normal distribution.

RESULTS

A total of 85 (72.7%) DM and 32 (27.3%) PM patients were included. Demographic, clinical, laboratory and complementary data are given in Table 1.

Mean age of patients with DM and PM was 41.1 and 42.8 years, respectively, and both groups were predominantly Caucasian females (Table 1). More than half of the patients had constitutional symptoms at disease onset. In addition, the majority of patients had Grade III or IV muscular strength in upper and lower limbs. Approximately one-third of the patients also had joint, gastrointestinal and pulmonary tract involvement.

Changes on computed tomography images of the chest were observed in both groups, with predominance of incipient pneumopathy, followed by "ground glass" lesions and pulmonary fibrosis.

The anti-PM/Scl autoantibody was observed in 5 out of 85 (5.9%) patients with DM, and 2 out of 32 (6.3%) with PM. In addition, 2 of these PM patients also had positivity for the anti-Ku autoantibody.

The overall characteristics of the 7 patients with anti-PM/Scl autoantibody are shown in Table 2. Age ranged from 28 to 84 years, and individuals were predominantly female gender and caucasian. Follow-up time ranged from 3 to 17 years.

All 7 patients presented constitutional symptoms. Other relevant clinical manifestations were muscular (100%), pulmonary (85.7%) and joint involvement (71.4%), "mechanic hands" (85.7%), Raynaud's phenomenon (85.7%) and plantar hyperkeratosis (85.7%).

Laboratory creatine phosphokinase and aldolase levels ranged from 210 to 8065 U/L, and 10 to 163 U/L, respectively.

Regarding the evolution of these 7 patients, all had disease relapse during the follow-up period and used glucocorticoids and different immunosuppressant drugs. At the end of the present study, 5 patients showed complete clinical response and 2 complete remission of the disease.

DISCUSSION

Our study revealed a low frequency of the anti-PM/Scl autoantibody in patients with DM and PM without overlap with other autoimmune diseases. In addition, these patients had a similar picture to that of antisynthetase syndrome, with relapses of disease activity.

The anti-PM/Scl antibodies were identified in 1977 by Wolfe et al.[24] These autoantibodies are directed against a nucleolar macromolecular complex of peptides of 75 kDa (PM/Scl-75 protein) and 100 kDa (PM/Scl-100 protein), with PM/Scl-75 considered the main autoantigen.[7]

In the present study, care was taken to exclude patients with a diagnosis of possible PM and probable or possible DM, according to the criteria of Bohan and Peter,[1] as well as patients with other autoimmune systemic diseases, thus avoiding any possible selection bias.

Available studies[4,5,7,8,11-19] have evaluated the presence of the anti-PM/Scl autoantibody in patients with DM and PM, but failed to report possible confounders of pulmonary involvement, such as current or previous pulmonary infections, chronic obstructive pulmonary disease, or a history of smoking and/or the presence of an antisynthetase syndrome. However, in the present study, patients with any of these parameters were excluded.

Unlike previous studies[13,19] our analysis included no patients with neoplasia, since this parameter was an exclusion criterion. The objective was to exclude any paraneoplastic conditions.

Reactivity to the anti-PM/Scl autoantibody as a function of disease activity (DM or PM) is unclear; therefore our analysis was based on blood samples collected at the time of the initial investigation of clinical and laboratory disease activity.

In contrast to the study by Muro et al, our 12 patients with clinically amyopathic DM presented, among various phenotypic features, a high prevalence of pulmonary involvement, especially in the presence of anti-MDA-5 autoantibody.[25-28]

After the application of strict inclusion and exclusion criteria, the prevalence of anti-PM/SCl in the present study was 5.9% and 6.3% in DM and PM patients, respectively.

We would also like to note that although previous studies had significant sampling limitations, the prevalence of the anti-PM/Scl autoantibody was observed in 7 - 8% and 7.5 - 7.9%, of DM and PM patients, respectively.[10,14,16] The lower prevalence of the anti-PM/Scl autoantibody in our series might have been due to the rigorous application of the inclusion and exclusion criteria.

A number of studies investigating several systemic autoimmune diseases or overlap syndromes have shown that the presence of the anti-PM/Scl autoantibody is associated with pulmonary conditions,[11,15,17-19,25,28-30] joint conditions,[5,11,15,18,30] Raynaud's phenomenon,[11,15,18,30,31] "mechanic hands"[17,18,25,28-30] and/or plantar hyperkeratosis.[5,7,11,13,17-19] In this respect, the phenotypic manifestation of this autoantibody resembles that of antisynthetase syndrome.[15,17,18,29,30]

In the present study, after application of the inclusion and exclusion criteria, the 5 DM and 2 PM patients with the anti-PM/Scl autoantibody also exhibited clinical symptoms similar to those of antisynthetase syndrome. All patients presented myositis, constitutional symptoms, including fever, at disease onset. Two of these 7 patients also had arthritis, Raynaud's phenomenon, "mechanic hands" and incipient pneumopathies.

It is important to note that previous studies have shown correlation of the anti-PM/Scl autoantibody with the presence of interstitial lung disease and plantar

Table 1. General features of patients with dermatomyositis and polymyositis.

	DM (N = 85)	PM (N = 32)	TOTAL (N = 117)
Age at disease diagnosis (years)	41.1±13.7	42.8±17.1	41.5±14.8
Symptoms to diagnosis (months)	4 (2-7)	4 (2-6)	4 (2-6)
Female gender	65 (76.5)	26 (81.2)	91 (77.8)
White ethnicity	72 (84.7)	27 (84.4)	99 (84.6)
Constitutional symptoms	49 (57.6)	17 (53.1)	66 (55.4)
Cutaneous			
Gottron's sign/papules	82 (96.5)	0	82 (70.1)
Heliotrope rash	74 (87.1)	0	74 (63.2)
Facial rash	56 (65.9)	0	56 (47.9)
Periungual hyperemia	52 (61.2)	0	52 (44.5)
"V"-neck sign	40 (47.1)	0	40 (34.2)
Vasculitis	22 (25.9)	0	22 (18.8)
"Shawl" sign	24 (28.2)	0	24 (20.3)
Ulcers	14 (16.5)	0	14 (11.9)
Raynaud's phenomenon	42 (49.4)	8 (25.0)	50 (42.7)
Calcinosis	4 (4.7)	0	4 (3.4)
Mechanic hands	16 (18.8)	6 (18.8)	22 (65.6)
Muscle strength (Grade)			
Upper limbs			
V	5 (5.9)	5 (15.6)	10 (8.5)
IV	64 (75.2)	19 (59.4)	83 (70.9)
III	14 (16.5)	7 (21.9)	21 (18.0)
II	1 (1.2)	0	1 (0.9)
I	1 (1.2)	1 (3.1)	2 (1.7)
Lower limbs			
V	3 (3.5)	0	3 (2.6)
IV	65 (76.4)	24 (75.0)	89 (76.1)
III	14 (16.5)	7 (21.9)	21 (17.9)
II	2 (2.4)	0	2 (1.7)
I	1 (1.2)	1 (3.1)	2 (1.7)
Joint	32 (37.6)	12 (37.5)	44 (37.6)
Gastrointestinal tract (dysphagia)	44 (51.8)	11 (34.4)	55 (47.0)
Pulmonary			
Dyspnea	31 (36.5)	8 (25.0)	39 (33.3)
Chest computed tomography			
"Ground glass" lesions	12 (14.1)	9 (28.1)	21 (17.9)
Incipient pneumopathy	25 (29.4)	10 (31.3)	36 (30.8)
Pulmonary fibrosis	7 (8.2)	2 (6.3)	9 (7.7)
Muscle enzymes			
Creatine phosphokinase (U/L)	989 (171-8000)	2314 (1134-8496)	1517 (268-7996)
Aldolase (U/L)	13 (7-55)	26 (19-75)	21 (9-58)
Autoantibodies			
Anti-PM/Scl	5 (5.9)	2 (6.3)	7 (6.0)
Anti-PM/Scl and/or anti-Ku	0	2 (6.3)	2 (1.7)
Anti-Mi-2	13 (15.3)	0	13 (11.1)

DM: dermatomyositis; PM: polymyositis.

Table 2. Demographic, clinical and laboratory features of the dermatomyositis or polymyositis patients with anti-PM/Scl.

	Dermatomyositis					Polymyositis	
Patients	1	2	3	4	5	6	7
Anti-PM/Scl	+	+	+	+	+	+	+
Anti-Ku						+	+
Age at diagnosis (years)	31	84	38	31	48	46	28
Gender (female)	F	F	M	F	F	F	F
White ethnicity	+	+	+	+	+		
Follow up time (years)	10	11	3	5	11	7	17
Constitutional symptoms	+	+	+	+	+	+	+
Cutaneous							
Heliotrope rash	+	+	+	+	+		
Gottron's papules/sign	+	+	+	+			
Facial rash			+	+			
"Shawl" sign			+	+			
"V"-neck sign			+	+			
Vasculitis			+				
Periungual hyperemia	+	+	+	+	+		
Raynaud's phenomenon	+	+	+	+	+	+	
Mechanic hands	+	+	+	+	+		+
Plantar hyperkeratosis	+	+	+	+	+		+
Muscle strength (Grade)							
Upper limbs	IV	V	IV	III	IV	IV	IV
Lower limbs	IV	IV	IV	IV	IV	IV	IV
Dysphagia	+		+	+		+	
Joint	+	+		+	+	+	
Pulmonary (dyspnea)		+	+	+	+	+	+
Incipient pneumopathy			+	+	+		+
"Grass ground" lesions		+			+		
Pulmonary fibrosis					+	+	
Initial creatine phosphokinase (U/L)	8065	640	390	4300	210	3136	1200
Initial aldolase (U/L)	163	12		50	10	55	21
Evolution							
Relapsing	+	+	+	+	+	+	+
GC/IS*	+	+	+	+	+	+	+
Current status	R	R	C	C	C	C	C

C: complete clinical response; GC: glucocorticoids; IS: immunosuppressant; R: disease remission. * Azathioprine, methotrexate, cyclosporin, mofetil mycophenolate, rituximab, intravenous human imumnoglobulin, pulse therapy with methylprednisolone.

hyperkeratosis.[5,7,11,13,17-19] Cox et al.[31] showed that, out of 9 patients with plantar hyperkeratosis, 8 had "mechanic hands" and 7 anti-synthetase syndrome. Therefore, it is possible that this plantar manifestation has the same underlying basis as "mechanic hand". In fact, we observed the presence of both plantar hyperkeratosis and "mechanic hands" in 5 anti-PM/Scl positive patients with DM and one with PM.

Limitations of the study included the fact that no pulmonary function tests and no objective esophagus studies, both important exams, were performed.

CONCLUSIONS

There was a low frequency of the anti-PM/Scl autoantibody among DM and PM patients without overlap

syndrome. In addition, patients with the presence of this autoantibody demonstrated a similar pattern of manifestations to that of antisynthetase disease.

AUTHOR CONTRIBUTION

S P Alves: planning, reviewing literature, executing and writing the present article.

M G Silva: reviewing literature, executing and writing the present article.

I B P Borges: planning, reviewing literature and writing the present article.

S K N Marie: planning, reviewing literature and writing the present article.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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PACIENTES COM DERMATOMIOSITE/POLIMIOSITE PURA E AUTOANTICORPO ANTI-PM/SCL SEMEMLHANTE À SÍNDROME ANTI-SINTETASE

OBJETIVO: O autoanticorpo anti-PM/Scl foi descrito em pacientes com escleromiosite. No entanto, há escassos estudos avaliando sua prevalência e reatividade em dermatomiosite (DM) e polimiosite (PM).

MÉTODOS: Estudo transversal, num único centro, que avaliou o autoanticorpo anti-PM/Scl em 85 DM e 32 PM, sem síndrome de sobreposição, no período entre 2000 e 2016. Os dados clínicos e os exames complementares foram revisados a partir de registros médicos eletrônicos com informações pré-parametrizadas.

RESULTADOS: A média de idade dos pacientes com DM e PM foi, respectivamente, de 41,1 e 42,8 anos. A presença de anti-PM/Scl foi observada em 5 (5,9%) DM e 2 (6,3%) pacientes com PM. Dois desses pacientes também possuíam o anticorpo anti-Ku. As manifestações clínicas relevantes desses 7 pacientes foram sintomas constitucionais (100% dos casos), envolvimento muscular (100%), pulmonar (85,7%) e articular (71,4%), "mãos mecânicas" (85,7%), fenômeno de Raynaud (85,7 %) e hiperqueratose plantar (85,7%). Os 7 pacientes apresentaram recidivas da atividade da doença, mas, no final do presente estudo, 5 apresentaram resposta clínica completa e 2 remissões completas da doença.

CONCLUSÃO: Há uma baixa freqüência do autoanticorpo anti-PM/Scl em pacientes com DM e PM. Além disso, os pacientes com este autoanticorpo apresentam um padrão semelhante de manifestações para a síndrome da antisintetase.

PALAVRAS CHAVE: Autoanticorpos; dermatomiosite; miosite; polimiosite.

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