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ORIGINAL ARTICLE

Patients with inflammatory myopathies overlapping with systemic sclerosis: A Brazilian-Japanese bicentric study

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ABSTRACT

Objectives: This study aims to describe and compare the demographic, clinical, and laboratory characteristics and follow-up of representative samples of patients with myopathies and systemic sclerosis overlap syndromes (Myo-SSc) from two tertiary centers.

Patients and methods: This is a cross-sectional and retrospective study conducted between January 2000 and December 2020. Fourty-five patients were analyzed with Myo-SSc (6 males, 39 females; mean age: 50.2±15.4 years; range, 45 to 65 years) from two tertiary centers (n=30 from Brazil and n=15 from Japan).

Results: The median follow-up was 98 (range, 37 to 168) months. Muscle impairment started simultaneously with the diagnosis of systemic sclerosis in 57.8% (26/45) of cases. Muscle involvement occurred before the onset of systemic sclerosis in 35.5% (16/45) of cases, and after in 6.7% (3/45). Polymyositis was observed in 55.6% (25/45) of cases, followed by dermatomyositis in 24.4% (11/45) and antisynthetase syndrome in 20.0% (9/45). Concerning systemic sclerosis, the diffuse and limited forms occurred in 64.4% (29/45) and 35.6% (16/45) of the cases, respectively. Comparing the subgroups, Myo or SSc onset was earlier in Brazilian patients, and they had a higher frequency of dysphagia (20/45, [66.7%]) and digital ulcers (27/45, [90%]), whereas Japanese patients had higher modified Rodnan skin scores (15 [9 to 23]) and prevalence of positive anti-centromere antibodies (4/15 [23.7%]). The current disease status and mortality were similar in both groups.

Conclusion: In the present study, Myo-SSc affected middle-aged women, and its manifestation spectrum varied according to geographic distribution.

Keywords: Dermatomyositis, inflammatory myopathies, myositis, polymyositis, systemic sclerosis.

The idiopathic inflammatory myopathies (Myos) and systemic sclerosis (SSc) overlap syndromes (Myo-SSc) is defined, when the classification criteria for both conditions (Myo and SSc) are presents in a single patient.[1-5] This syndrome is a rare entity and scarcely described in the literature.[2-5]

Muscle involvement was first described in 1876 as a secondary component of SSc.[6] However, observational studies have demonstrated the existence of a heterogeneous impairment of muscle in SSc, from Myo-associated overlap syndromes to minimal myositis with capillary pathology.[7]

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According to the literature, Myo-SSc manifests through muscle impairment in patients with SSc who exhibit the following characteristics: clinical signs, including fatigue, myalgia or decreased muscle strength; laboratory results, such as increased serum concentrations of muscle enzymes; electromyographic data with a myopathic pattern; histological results, including the presence of inflammatory infiltrates in muscle tissues, fibrosis, and microangiopathy;[6] and serological results, including the presence of autoantibodies such as anti-U1RNP, Anti-PolyMyositis/Scleroderma (PM/Scl), and anti-Ku.[8]

Despite advances in imaging techniques and histopathology over the past five decades,[9] there is still a need for better and greater theoretical contributions to obtain a more complete characterization of Myo-SSc. To date, most studies consist of series or case reports and observational studies in which there are difficulties in establishing the clinical parameters,[10] laboratory data,[11] image/electroneuromyography,[12] and behavior of immunobiological markers.[5]

This situation is worrying, as the few data in the literature[1-10] show that patients with Myo-SSc have a worse prognosis. With more severe pulmonary, cardiovascular, muscular, and cutaneous involvements.[5,10-12] This denotes a worsening of the quality of life and possibly the need for earlier and more aggressive interventions. However, due to the rarity of this condition, the correct mapping of the natural history of the disease still lacks further theoretical contributions.

Therefore, the primary objective was to conduct a study analyzing the demographic, clinical, laboratory, and follow-up profiles of a sample of patients with Myo-SSc from two tertiary centers. Second, a comparison was made between the two populations (Brazilian and Japanese). Our hypothesis was that patients with Myo-SSc had a prognosis with their own clinical, epidemiological and serological characterization, reflecting on a worse prognosis and the need to map the natural history of the disease in a more longitudinal way.

PATIENTS AND METHODS

Study design and study population

This two-center, cross-sectional, retrospective study was conducted at Division of Rheumatology at Hospital das Clínicas-USP and Division of Rehabilitation Science at Kanasawa Hospital, between January 2000 and December 2020. Only patients with a diagnosis (clinical, imaging and autoantibody profile) of PM, dermatomyositis (DM) or antisynthetase syndrome (ASSD) were selected. Therefore, in the context of PM and DM, the patients fulfilled the Bohan and Peter criteria[13] and the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2017 classification criteria. Antisynthetase syndrome was defined according to Behrens Pinto et al.[14] In addition, SSc was defined according to the ACR/EULAR 2013 classification criteria.[15] Patients who did not meet criteria (muscle biopsy and magnetic resonance imaging of the shoulder/pelvic girdle) suggestive of SSc-induced Myo were excluded.

A total of 30 (2.6%) of 1,178 Brazilian patients seen at the Myopathies and Systemic Sclerosis outpatient clinic and 15 (2.1%) of 717 Japanese patients referred from the Myopathies and Systemic Sclerosis outpatient clinic to the rehabilitation service were considered to have Myo-SSc.

An analysis was performed using the patients' data and demographic and clinical features:

a. Epidemiology data: age at the first Myo or SSc, current age, sex, during of following up, and current follow up;
b. Clinical data: constitutional involvement (fever and arthritis); skin involvement (modified Rodnan skin score, "mechanics' hands," and type of SSc); muscular involvement: limb muscle strength, which was graded according to the Medical Research Council classification (Grade 0: absence of muscle contraction; Grade 1: slight signs of contractility; Grade 2: movements of normal amplitude but not against the action of gravity; Grade 3: normal range of motion against gravity; Grade 4: full mobility against gravity and against a degree of resistance; and Grade 5: complete mobility against strong resistance and against the action of gravity);[16] vascular involvement (Raynaud's phenomenon, cutaneous ulcers, digital ulcers and calcinosis); manifestations of visceral impairment: gastrointestinal

tract - upper dysphagia; pulmonary tract - pulmonary hypertension - estimated by transthoracic echocardiogram exam; interstitial lung disease found during the high-resolution chest computed tomography, and plethysmography with analysis of forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), and diffusing capacity for carbon monoxide (DLCO); cardiac and renal involvement.

In addition, charts were reviewed for scleroderma pattern (SD pattern) in nailfold capillaroscopy, which was defined as the presence of avascular areas or enlarged loops associated with at least one additional SD parameter (nailfold hemorrhages, reduced capillary density, enlarged loops and avascular areas),[17] disease relapse, and deaths. Disease relapse was defined as the presence or worsening of objective muscle weakness observed by the physician, accompanied by increased muscle enzyme serum levels, progression of lung disease, or cutaneous involvement (modified Rodnan skin score).

Laboratory analysis

The laboratory evaluation performed at DM, PM or ASSD ASSD onset included the determination of serum levels for creatine kinase (normal range: 24 to 173 U/L) using automated kinetic methods. The follow autoantibodies were assessed: anti-Scl-70, anti-Jo-1 (histidyl-), anti-PL-7 (threonyl-), anti-PL-12 (alanyl-), anti-EJ (glycil-), anti-OJ (isoleucyl-), anti-SRP, anti-Mi-2, anti-PM/Scl, anti-Ku, and anti-Ro-52. For assessment, a commercially available line blot test kit (Myositis or Systemic Sclerosis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany) was used following the manufacturer's protocol. The results were arbitrarily defined as negative (0/+++), weak (+/+++), moderate (++/+++), or strong (+++/+++) reactivity. In the present study, only results of moderate or strong reactivity were considered. Antinuclear antibodies (ANAs) and anti-centromere antibodies were detected by indirect immunofluorescence using HEp-2 cells as the substrate.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed in mean ± standard deviations (SD) or median (25^{th} to 75^{th}), while categorical data were expressed in number and frequency. The Kolmogorov-Smirnov test was used to evaluate the distribution of each variable. Comparisons between the patients' parameters were made using the Student t-test or the Mann-Whitney test for continuous variables. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 45 patients with Myo-SSc (6 males, 39 females; mean age: 50.2±15.4 years; range, 45 to 65 years) were included (Table 1). The first symptoms started between the third and fourth decades of life (41.2±16.2 years), but symptoms began earlier in the Brazilian group (36.7±13.1 years) compared to the Japanese group (50.2±18.1 years). The median outpatient follow-up time for all patients was 98 (range, 37 to 168) months. Twenty-nine patients (64.4%) are still under follow-up in the outpatient setting.

From a muscle point of view (Table 1), inflammatory Myo simultaneously initiated SSc in 26 (57.8%) of cases. In three (6.7%) and 16 (35.6%) of cases, Myo started, before and after SSc, respectively.

According Table 1, PM or myositis occurred in 25 (55.6%) of the cases, followed by DM in 11 (24.4%) cases, and ASSD in nine (20.0%) cases. Regarding SSc, the diffuse and limited forms represented 29 (64.4%) and 16 (35.6%) of the cases, respectively. The distribution of autoantibodies is also shown in Table 1.

As for the clinical profile, muscle weakness levels at the onset of the symptoms of inflammatory Myo, and serum creatine phosphokinase levels were comparable between the groups. The presence of fever, arthritis, pulmonary involvement, skin changes, heart disease, and gastrointestinal tract involvement were also similar between the groups. However, the frequency of dysphagia and digital ulcers was higher among Brazilian patients, whereas Rodnan skin score was higher among Japanese patients (Table 2).

Table 1. Demographic, clinical and laboratory profiles of patients with inflammatory myoapathies overlapping with systemic sclerosis from the two tertiary centers

	Total (n=45)					Brazil (n=30)					Japan (n=15)					
Parameters	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Sex																
Female	39	87.0				28	93.3				11	73.3				0.157
Current age (year)			50.2±15.4					47.7±13.3					55.1±17.7			0.179
Age at onset (year)			41.2±16.2					36.7±13.1					50.2±18.1			**0.021**
During of following up (month)				98	37-168				123	57-180				63	10-117	**0.010**
Current follow-up	29	64.4				23	76.7				6	40.0				**0.023**
Evaluation (disease onset)																
Simultaneously Myo and SSc	26	57.8				20	66.7				6	40.0				0.116
SSc before Myo onset	3	6.7				3	10.0				0	0				-
SSc after Myo onset	16	35.6				7	23.3				9	60.0				**0.023**
Type of myositis																
Dermatomyositis	11	24.4				9	30.0				2	13.3				0.288
Polymyositis/myositis	25	55.6				16	53.3				9	60.0				0.757
Antisynthetase syndrome	9	20.0				5	16.7				4	26.7				0.454
Type of SSc																
Diffuse	29	64.4				19	63.3				10	66.7				>0.999
Limited	16	35.5				11	36.7				5	33.3				>0.999
Autoantibodies																
Antinuclear antibody	42	93.3				28	93.3				14	93.3				>0.999
Anti-RNP	5	11.1				0	0				5	33.3				-
Anti-Sm	0	0				0	0				0	0				0
Anti-Scl70	6	13.3				3	10.0				3	20.0				0.384
Anti-centromere	5	11.1				1	3.3				4	26.7				**0.036**
Anti-Ro-52	13	28.9				11	36.7				2	13.3				0.165
Anti-OJ	0	0				0	0				0	0				-
Anti-EJ	0	0				0	0				0	0				-
Anti-PL-7	3	6.7				1	3.3				2	13.3				0.254
Anti-PL-12	1	2.2				1	3.3				0	0				-
Anti-PM/Scl	3	6.7				2	6.7				0	0				-
Anti-Ku	5	11.1				2	6.7				3	20.0				0.315
Anti-Mi-2	0	0				0	0				0	0				-

SD: Standard deviation; Myo: Inflammatory myopathies; SSc: Systemic sclerosis.

Table 2. Clinical and laboratory profiles of patients with inflammatory myoapathies overlapping with systemic sclerosis from the two tertiary centers

	Total (n=45)				Brazil (n=30)				Japan (n=15)				
Parameters	n	%	Median	Min-Max	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Muscle strength													
Upper limbs													0.813
Degree V	5	11.1			4	13.3			1	6.7			
Degree IV	31	68.9			19	63.3			12	80.0			
Degree III	9	20.0			7	23.3			2	13.3			
Degree II or I	0	0			0	0			0	0			
Lower limbs													0.413
Degree V	3	6.7			3	10.0			0	0			
Degree IV	34	75.6			22	73.3			12	80.0			
Degree III	8	17.8			5	16.7			3	20.0			
Degree II or I	0	0			0	0			0	0			
Maximum CK levels (U/L)			928	355-3943			1450	553-4340			848	355-2250	0.367
Fever	22	48.9			18	60.0			4	26.7			0.057
Dysphagia	23	51.1			20	66.7			3	20.0			**0.005**
Arthritis	16	35.6			12	40.0			4	26.7			0.514
Lung involvement													
Dyspnea	25	55.6			20	66.7			5	33.3			0.056
Ground-glass	39	86.7			25	83.3			14	93.3			0.647
Interstitial	34	75.6			20	66.7			14	93.3			0.070
Fibrosis	19	42.2			10	33.3			9	90.0			0.116
FVC (% predicted) (n=29)			71	58-84			65	55-78			73	53-97	0.272
FEV1 (% predicted) (n=29)			75	64-88			70	55-84			86	69-89	0.143
R (FEV1/FVC) (n=29)			1.05	0.95-1.11			1.05	0.98-1.08			1.04	0.78-1.46	>0.999
Diffusing capacity for CO (% predicted) (n=22)			48	36-70			58	38-76			47	30-54	>0.999
Pulmonary hypertension	12	26.7			8	26.7			4	26.7			>0.999
Raynaud phenomena	39	86.7			26	86.7			13	86.7			>0.999
Mechanics' hands	8	17.8			5	16.7			3	20.0			0.686
Cutaneous ulcers	21	46.7			13	43.3			8	53.3			0.546
Digital ulcers	35	77.8			27	90.0			8	53.3			**0.009**
Calcinosis	5	11.1			3	10.0			2	13.3			>0.999
Modified Rodnan skin score			10	4-17			6	4-12			15	9-23	**0.035**
Cardiopathy	7	15.6			6	20.0			1	6.7			0.395
Renal involvement	1	2.2			0	0			1	6.7			-
GIT involvement	10	22.2			7	23.3			3	20.0			>0.999

SD: Standard deviation; CK: Creatine phosphokinase; GIT: Gastrointestinal tract; FVC: Forced vital capacity; FEV1: Forced expiratory volume during the first second.

Table 3. Treatment and disease outcome of patients with inflammatory myoapathies overlapping with systemic sclerosis from the two tertiary centers

	Total (n=45)		Brazil (n=30)		Japan (n=15)		
Parameters	n	%	n	%	n	%	*p*
Current treatment							
Methotrexate	11	24.4	11	36.7	0	0	-
Mycophenolate mofetil	6	13.3	6	20.0	0	0	-
IVIG	10	22.2	4	13.3	6	40.0	0.062
Cyclophosphamide	5	11.1	3	10.0	2	13.3	>0.999
Cyclosporine	1	2.2	1	3.3	0	0	-
Azathioprine	3	6.7	2	7.6	1	6.7	>0.999
Tacrolimus	2	4.4	0	0	1	6.7	-
None	12	26.7	6	20.0	6	40.0	0.174
Glucocorticoid	45	100	30	100	15	100	>0.999
Rituximab	5	11.1	5	16.7	0	0	-
Current disease activity	10	22.2	8	26.7	2	13.3	0.456
Muscle activity	8	17.8	6	20.0	2	13.3	0.699
SSc activity	5	11.1	3	10.0	2	13.3	>0.999
Death	8	17.8	3	10.0	5	33.3	0.095

IVIG: Intravenous immunoglobulin; SSc: Systemic sclerosis.

Nailfold capillaroscopy was performed in all patients, except for one Japanese patient, and all had an SD pattern. The medications used in the last consultations are shown in Table 3.

Ten (22.2%) patients had disease activity (Myo or SSc), which was comparable between the Brazilian and Japanese groups (26.7% *vs.* 13.3%, respectively; p=0.456). The distribution of deaths was also similar between the groups.

Comparing the two groups, the mean age of the Japanese group was greater than that of the Brazilian group (55.1±17.7 *vs.* 47.7±13.3 years, respectively; p=0.021). However, the group of Brazilian patients had a follow-up in months that was twice as long (98 [37 to 168] *vs.* 123 [57 to 180] months, p=0.010), and a current follow-up that was four times longer compared to the Japanese group (23 *vs.* 6 months, respectively; p=0.023).

Clinically, the Japanese group presented the SSc phenotype after diagnosis of Myo in nine (60%) of their sample against seven (23.3%) of the Brazilian sample (p=0.023). Diffuse SSc (29 out of 45, [64.4%]) and DM (11 out of 45, [24.4%]) were the most common subtypes in both groups. In the analysis of symptoms, dysphagia (66.7% *vs.* 20.0%, p=0.005) and digital ulcers were more frequent in the Brazilian group (90.0% *vs.* 53.3%, p=0.009), while in the Japanese group there were higher Rodnan scores (6 [4 to 12] *vs.* 15 [9 to 23], p=0.035). All patients with digital ulcers (35 out of 45 [90%]) using vasodilator therapy (28 with sildenafil and 7 with bosentan).

Concerning autoantibody characteristics, the anti-Ro-52 was more prevalent in both groups (36.7% *vs.* 13.3%, p=0.165), whereas the anti-centromere was more common in the Japanese group (3.3% *vs.* 23.7%; p=0.036).

DISCUSSION

The present study showed demographic, clinical, laboratory and outcome profiles of a considerable series of patients with Myo-SSc at two tertiary centers (Japan and Brazil). Our patients with Myo-SSc had a current average age of 50 years, and were predominantly female (87%). In addition, while comparing the two groups, the Japanese group had a mean age with statistical significance. The data are consistent with previous studies in which patients with Myo-SSc varied between 40 and 60 years old and were mostly women.[1-3,6,11,12,18,19]

In the present study, it was possible to map cases of the natural history of Myo-SSc due to the long median follow up period of 98 (range, 37 to 168)

months. The Brazilian group had longer follow-up time and longer current follow-up. In previous studies the follow-up ranged from 48 to 93 months.[20,21] Moreover, in our sample, 26 (57.8%) of muscle impairment occurred concurrently with SSc, and the appearance of this impairment after SSc was statistically significant. This finding is in line with the literature, in which Myos tend to be secondary to SSc involvement, ranging from 32 to 78%.[10,19,20] This variation can be explained by the absence of well-established and consensual criteria for defining the complex and varied clinical spectrum of muscle involvement in Myo-SSc.[12] Another possibility is the presence of external factors. A recent cross-sectional retrospective study demonstrated that patients with SSc and exposure to products such as silica, pesticides, silicone and organic solvents had more muscle symptoms compared to controls.[22]

Twenty-nine (64.4%) of the analyzed patients with Myo-SSc had diffuse cutaneous SSc. According to data in the literature, muscle involvement in SSc is usually common in the diffuse form, with the most frequent symptoms being fatigue, weakness and generalized myalgia.[5] A cross-sectional and retrospective study, that evaluated patients with SSc and Myo, demonstrated that individuals with diffuse cutaneous SSc were more likely to develop more severe Myo,[20] with muscle weakness reported in up to 90% of these patients.[21] Reinforcing this data, the European Scleroderma Trials and Research (EScSG) showed a cohort that assessed weakness in patients with SSc, demonstrating that in diffuse SSc, there was an average incidence of weakness in 27 to 37% of patients, compared to 21 to 23% in limited SSc.[23]

Dysphagia and digital ulcers were more frequent in the Brazilian group. A review study noted that dysphagia was reported in up to 90% of patients with SSc, and 20 to 84% of inflammatory Myos, and it could occur at any stage during the course of the disease.[24] Anecdotal reports point to the presence of severe dysphagia in patients from Africa with SSc and muscle involvement.[4]

Digital ulcers also affected more of the Brazilian patients. It is noteworthy that the Brazilian subgroup had twice the prevalence of Raynaud's phenomenon compared to the Japanese subgroup.

The average modified Rodnan skin score was higher among the Japanese patients, which is in line with the higher rates of diffuse cutaneous SSc in patients with this group. A Brazilian study that evaluated the original and modified Rodnan skin scores and their correlation with the clinical picture of patients with SSc showed that both scores statistically significantly correlated to diffuse cutaneous SSc.[25]

Concerning autoantibody characteristics, the anti-Ro-52 was more prevalent in both groups, whereas the anti-centromere was more common in the Japanese group. This finding differs from previous studies in the United Kingdom, France[26-29] and Japan[6], in which the most prevalent autoantibodies were anti-Ku, and anti-PM/Scl75. In our study, only six (13.3%) patients had anti-Ku being that of these three (6.6%) were Japanese. Indeed, the Japanese population is known to have a higher prevalence of anti-Ku which, in turn, is intrinsically correlated with skeletal muscle symptoms.[6] The low incidence of positive anti-Ku in our global sample (Brazilian and Japanese individuals) might be one of the factors that explains the lower creatine phosphokinase levels in this subgroup.

Two other factors that deserve attention are the absence of anti-RNApol III and the timid prevalence of -Scl70 (6 cases [13.3%]) in the sample. We attribute the first event to two factors: Myo-SSc pictures present a predominance of diffuse cutaneous forms;[21-23] low incidence of that autoantibody in cases of SSc in limited cutaneous form with muscle involvement.[29] As for the low -Scl70 prevalence is common in patients with Myo-SSc seen in previous seroprevalence surveys.[28-30] Thus, it seems to be the serological behavior of this entity, although more robust studies are needed.

In the past five decades, epidemiological, histopathological, and laboratory studies have attempted to determine which phenotypes of patients with SSc would develop Myos and what impact this impairment has on these patients' prognosis.[9,19,27] Several case reports from the 19th century[2,3] referred to severe outcomes for these pathologies. In addition, patients with Myo-SSc are more severe, they tend to have

a worse prognosis,[20] greater morbidities, impaired quality of life[11] and incidence of cardiac involvement.[7,19] Besides that, corticosteroids, which are commonly used in inflammatory Myos, can be harmful in patients with Myo-SSc, as they increase the risk of SD renal crisis.[23] A German cohort demonstrated that patients with Myo-SSc developed musculoskeletal, lung fibrosis and heart involvement significantly earlier than patients with only SSc.[18] In our sample, 10 (22.2%) patients had clinical disease activity. Some factors that can explain this phenomenon are the age disparities (the Brazilian subgroup was younger) and clinical management (the Brazilian subgroup was more aggressive; e.g., in terms of immunobiological use).

While describing the therapies performed, it is observed that a large part of the sample did not need clinical drug control, followed by the use of intravenous immunoglobulin and methotrexate. In the analysis of subgroups, the Japanese sample showed greater use of intravenous immunoglobulin (40.0%) and cyclophosphamide (13.3%), but in the Brazilian group, the use of methotrexate (36.7%) and mycophenolate (20.0%) stood out.

The use of immunosuppressants in the Myo-SSc group was probably due to the disease's severity. A two-center, observational, retrospective study carried out in France comparing isolated and overlap SSc with other autoimmune diseases showed that overlap SSc was more likely to receive glucocorticoids, immunosuppressive drugs, and biologicals.[31] Another important consideration is that the disparities in therapy between the two countries can be explained by the lack of consensus in the literature concerning the management of Myo-SSc,[6,12,19,20,27,28] which provides conduct based on local experiences, and the availability of medicines in each country.

The main limitations of this study include its retrospective nature, the problems inherent in this type of research, and the fact that the data collection depended on medical records. Another limitation is the impossibility of estimating which pole of the disease (Myo or SSc) has muscle involvement, due to the lack of standardization of imaging/biopsy methods for this purpose. The small sample is highlighted, which is justified by its group of rare diseases. Finally, the data were from tertiary centers, in which patients have a more severe spectrum of diseases, with presentations and characteristics susceptible to overestimation or underestimation.

In conclusion, the followings can be drawn: *(i)* importance of more early and aggressive procedures with immunosuppressive drugs, particularly in pulmonary, cardiac, and cutaneous involvements; *(ii)* if available, in clinical suspicion - autoantibodies such as anti-Ro-52 and anti-centromere seem to be more prevalent; and *(iii)* active screening of digital ulcers with a closer look at Raynaud's phenomenon in these patients.

The variations and severity of SD with muscle impairment, although subtle, may indicate different subdivisions or clinical entities. However, we need further studies with larger samples and robust immunogenetic techniques to characterize patients' genotypes and phenotypes for the elaboration of effective treatments.

Ethics Committee Approval: The study protocol was approved by the Hospital das Clínicas, Faculty of Medicine, University of São Paulo Ethics Committee (date: 8.04.2011, no: 0114/11). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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