OBJECTIVE: To analyze the prevalence of myositis-specific and myositis-associated autoantibodies and their clinical correlations in a large series of patients with dermatomyositis/polymyositis.

METHOD: This cross-sectional study enrolled 127 dermatomyositis cases and 95 polymyositis cases. The disease-related autoantibody profiles were determined using a commercially available blood testing kit.

RESULTS: The prevalence of myositis-specific autoantibodies in all 222 patients was 34.4%, whereas myositis-associated autoantibodies were found in 41.4% of the patients. The most frequently found autoantibody was anti-Ro-52 (36.9%), followed by anti-Jo-1 (18.9%), anti-Mi-2 (8.1%), anti-Ku (4.1%), anti-SRP (3.2%), anti-PL-7 (3.2%), anti-PL-12 (2.7%), anti-PM/Scl75 (2.7%), and anti-PM/Scl100 (2.7%). The distributions of these autoantibodies were comparable between polymyositis and dermatomyositis, except for a higher prevalence of anti-Jo-1 in polymyositis. Anti-Mi-2 was more prevalent in dermatomyositis. Notably, in the multivariate analysis, anti-Mi-2 and anti-Ro-52 were associated with photosensitivity and pulmonary disorders, respectively, in dermatomyositis. Anti-Jo-1 was significantly correlated with pulmonary disorders in polymyositis. Moreover, anti-Ro-52 was associated with anti-Jo-1 in both diseases. No significant correlation was observed between the remaining autoantibodies and the clinical and/or laboratory findings.

CONCLUSIONS: Our data are consistent with those from other published studies involving other populations, although certain findings warrant consideration. Anti-Ro-52 and anti-Jo-1 were strongly associated with one another. Anti-Ro-52 was correlated with pulmonary disorders in dermatomyositis, whereas anti-Jo-1 was correlated with pulmonary alterations in polymyositis.

KEYWORDS: Dermatomyositis; Idiopathic Inflammatory Myopathies; Myositis-Associated Autoantibodies; Myositis-Specific Autoantibodies; Polymyositis.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) constitute a heterogeneous group of chronic systemic autoimmune diseases with high morbidity and disability rates (1). Based on their clinical and histopathological features, IIMs can be classified as polymyositis (PM), dermatomyositis (DM), juvenile dermatomyositis, inclusion body myositis, malignancy-associated myositis, and other collagen disease-associated types of myositis.

The etiologies of PM and DM remain unknown, but they are believed to be multifactorial and might include genetic, immunological, and environmental causes. Moreover, there is strong evidence that cellular and humoral autoimmune mechanisms play important roles in these myopathies (2,3).

Previous studies have reported that more than 50% of IIM patients have high autoantibody titers, but recent studies using high-sensitivity techniques have shown that the frequency of autoantibody positivity could reach 80% (4,5). The description of a broad spectrum of myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) (5-12) has allowed for better clinical categorization of IIMs at diagnosis. Moreover, the characterization of different MSAs and MAAs has provided
evidence of their putative clinical prognostic value and associations (5).

However, the majority of past studies have generally analyzed MSA and/or MAA profiles in patient groups with autoimmune IIM, without discriminating between DM and PM in subgroups (13), in small groups of DM or PM patients (6,11,14), and in DM/PM overlap syndrome, malignancy-associated myositis, inclusion body myositis and/or other collagen disease-associated types of myositis (6,11-13). Moreover, no similar studies analyzing MSAs and MAAs have been performed in a Brazilian population with DM and PM.

Herein, we compared MSA and MAA autoantibody reactivity patterns and their possible clinical associations in a large series of Brazilian patients with autoimmune IIM, including PM and DM.

# MATERIALS AND METHODS

The present cross-sectional study involved 222 patients with DM/PM who met at least three (for PM) or four (for DM) of the criteria defined by Bohan and Peter (15). All patients were treated for inflammatory myopathies in the outpatient clinic of a tertiary hospital center. The patients (aged ≥18 years) were selected based on the availability of serum samples that had been obtained at the time of diagnosis (from 2000-2012) and stored at -20°C. The patients with systemic autoimmune comorbidities or malignancies were excluded.

Patient demographic features and clinical manifestations at disease onset were obtained through a systematic review of medical records. These features included bodily symptoms, cutaneous involvement (i.e., heliotrope, Gottron’s sign, “V” of the neck, Shawl’s sign, photosensitivity, Raynaud’s phenomenon, ulcers, or calcinosis), heart involvement (i.e., myocarditis or heart failure, as revealed by myocardial scintigraphy and echocardiogram exam), gastrointestinal tract involvement (upper dysphagia), articular involvement (arthralgia or arthritis), pulmonary disorders (incipient pneumopathy, ground-glass lesions and/or basal fibrosis, as revealed by computed tomography [CT]), and limb muscle strength graded according to the Medical Research Council classification: grade 0, absence of muscle contraction; grade I, slight signs of contractility; grade II, movements of normal amplitude but not against the force of gravity; grade III, normal range of motion against gravity; grade IV, full mobility against gravity and against a degree of resistance; and grade V, complete mobility against strong resistance and against the force of gravity (16).

Laboratory evaluations were performed at disease onset using automated kinetic methods. The evaluations included determining the serum levels of creatine kinase (normal range, 24-173 IU/L), lactate dehydrogenase (20-350 IU/L), alanine aminotransferase (10-36 IU/L), aspartate aminotransferase (10-36 IU/L), and aldolase (1.0-7.5 IU/L). The erythrocyte sedimentation rate (ESR) < 20 mm/1st hour) and C-reactive protein (CRP) < 5 mg/L levels were obtained using the Westergren and immunoturbidimetric methods, respectively, at the time of diagnosis.

The following autoantibodies were investigated in this study: anti-Jo-1 (histidyl-), anti-PL-7 (threonyl-), anti-PL-12 (alanyl-), anti-EJ (glycol-), anti-OJ (isoleucyl-RNA synthetase), anti-SRP (signal recognition particle), anti-Mi-2 — all included in the group of MSA autoantibody profiles; and anti-PM-Scl 75, anti-PM-Scl 100, anti-Ku, anti-Mi-2, and anti-SS-A/Ro-52 kDa — all belonging to the MAA autoantibody profile. For assessment, a commercially available line blot test kit (Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany) was used according to the manufacturer’s protocol. The results were arbitrarily defined as negative (0/+++/), weakly (++/++/+), moderately (+++/+++/), or strongly (+++/**++) reactive by two independent researchers (MGPC and SKS) who had no knowledge of the diagnostic data from each analyzed case. In the present study, only the moderate or strong reactivity results were considered.

Statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The demographic and clinical features are expressed as the mean and standard deviations (SD) for the continuous variables or as frequencies and percentages for the categorical variables. The medians (25th-75th percentiles) were calculated for the continuous variables that were not normally distributed. Comparisons between the patients with and without specific autoantibodies were performed using Student’s t-test or the Mann-Whitney u-test for continuous variables, and p<0.05 was considered significant. Moreover, for each disease (DM or PM), all statistically significant univariate parameters that were considered for adjustment were selected and analyzed by stepwise multiple logistic regression (multivariate analysis). Pearson’s chi-squared test or Fisher’s exact test was used to evaluate the categorical variables. Age at disease onset and gender were adjusted, and the measurements are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The STATA computer program, version 7 (STATA, College Station, TX USA), was used for the statistical analysis.

# RESULTS

Demographic and clinical features of patients

The median ages at disease onset (interquartile ranges) were 43 years (33-57) and 41 years (31-53) for the PM and DM patients, respectively, with a predominance of female gender and Caucasian race in both groups (Table 1).

Bodily symptoms occurred in half of the patients in both groups. Regarding extra-muscular manifestations, articular involvement affected approximately 40% of the PM and DM patients, followed by dysphagia and Raynaud’s phenomenon. Approximately one-fourth of the PM and DM patients were bedridden, and 10% of had dysphonia. No heart involvement was found in either group. As expected, cutaneous involvement was exclusively or more frequently observed in the DM patients and included heliotrope, Gottron’s sign, photosensitivity, and other symptoms (e.g., ulcers, calcinosis, “V” of the neck, and Shawl’s sign). At the time of diagnosis, muscle weakness was categorized as grade IV (upper and lower limbs) in the majority of PM and DM patients.

Pulmonary disorders, demonstrated by CT, were observed in one-third of the patients in both groups.

The median serum levels of muscle-related enzymes were increased in all PM patients and in approximately 90% of the DM patients (Table 1). Similarly, the median values for ESR and CRP were increased in both groups.
Autoantibody profile

The prevalence of reactivity to any autoantibody (MSA and/or MAA) was 54.1% in all patients included in this study. Patients from the PM and DM subgroups had similar prevalences of reactivity, 58.9% vs. 50.4%, respectively ($p = 0.223$). A higher prevalence of MSA was observed in the PM patients (45.3% vs. 13.5%, $p = 0.036$) because of higher positivity for anti-Jo-1 in this subgroup (31.6% vs. 9.5%, $p = 0.001$). Conversely, anti-Mi-2 was more frequently found in the DM patients (11.8% vs. 3.2%, $p = 0.019$). Reactivity to the remaining MSA-related autoantibodies was low (<5%) and was comparable between the DM and PM patients. Anti-OJ binding was not found in any of the patients studied. Concomitant positivity for any of the autoantibodies included in the MSA and MAA sets was more frequently observed in the PM patients than in the DM patients (31.6% vs. 19.7%, $p = 0.042$). MAA positivity was similar in both groups ($p = 0.317$). The percentages of patients with reactivity to these autoantibodies among the PM and DM patients are shown in Table 2.

No differences in age at disease onset, gender, or clinical or laboratory findings were observed among the DM and PM patients with distinct MSA and/or MAA profiles. However, the univariate analysis showed that anti-Mi-2-positive DM patients were significantly more likely to exhibit photosensitivity and Shawl’s sign (Table 3). Moreover, in the multivariate analysis, only the DM patients who were anti-Mi-2-positive were significantly more likely to be photosensitive. Furthermore, anti-Ro-52-positive DM patients were significantly more likely to exhibit pulmonary disorders and anti-Jo-1 positivity, as revealed by the univariate and multivariate analyses. Anti-Jo-1 reactivity was associated only with anti-Ro-52 positivity and not with a particular clinical manifestation in these patients (Table 3). Similarly, there was no significant association between the other MSAs and MAAs and any clinical or laboratory profiles for DM.

Similar to the MAA findings in DM patients, anti-Ro-52-positive PM patients were significantly more likely to exhibit pulmonary disorders and positivity to anti-Jo-1 than those patients who were anti-Ro-52-negative, as demonstrated by the univariate analysis. In the multivariate analysis, only pulmonary disorders were independently associated with anti-Ro-52 positivity in the PM patients. Contrasted with the findings in DM patients, anti-Jo-1-positive PM patients were
DISCUSSION

We observed positivity for MSA and/or MAA in half of the patients with DM/PM (2). In the present study, we found low prevalences in the serum of IIM patients, compared to other anti-aminoacyl-tRNA synthetase antibodies. In our series, anti-Jo-1 was more significantly present in the PM patients than in the DM patients. When analyzed by disease, anti-Jo-1 was significantly associated with pulmonary disorders or articular manifestations in DM patients. In contrast, in the group of PM patients, this autoantibody was correlated with pulmonary disorders and anti-Ro-52 reactivity.

Concerning the other anti-aminoacyl-tRNA synthetase antibodies, we found low prevalences in the present study. Moreover, we did not observe patients with positivity to anti-OJ.

Another subgroup of patients with IIMs is characterized by the presence of antibodies directed against SRP. This antibody has been detected in the serum of 4-6% of patients with IIMs (27-29), whereas in the present study, we found this positivity in 3.2% of the patients. Myopathies associated with anti-SRP antibodies are characterized by aggressive necrotizing myositis, which is evidenced by rapidly progressive proximal muscle weakness and marked increases in the creatine kinase level. Moreover, anti-SRP-positive patients are less responsive to conventional drug treatments.

Table 2 - Frequency of myositis-specific and myositis-associated autoantibodies in patients with DM and PM.

| Parameters                  | All (n = 222) | PM (n = 95) | DM (n = 127) | p-value |
|-----------------------------|--------------|-------------|--------------|---------|
| MSA positivity              | 83 (34.4)    | 43 (45.3)   | 40 (31.5)    | 0.036   |
| Anti-Jo-1                   | 42 (18.9)    | 30 (31.6)   | 12 (9.5)     | <0.001  |
| Anti-Mi-2                   | 18 (8.1)     | 3 (3.2)     | 15 (11.8)    | 0.019   |
| Anti-SRP                    | 7 (3.2)      | 4 (4.2)     | 3 (2.4)      | 0.436   |
| Anti-PL-7                   | 6 (2.7)      | 3 (3.2)     | 3 (2.4)      | 0.997   |
| Anti-PL-12                  | 7 (3.2)      | 3 (3.2)     | 4 (3.1)      | 0.718   |
| Anti-EJ                     | 6 (2.7)      | 2 (2.1)     | 4 (3.1)      | 0.635   |
| Anti-OJ                     | 0            | 0           | 1.000        |         |
| MAA positivity              | 92 (41.4)    | 43 (45.3)   | 49 (38.6)    | 0.317   |
| Anti-SSA/Ro-52              | 82 (36.9)    | 37 (38.9)   | 45 (35.4)    | 0.591   |
| Anti-Ku                     | 9 (4.1)      | 7 (7.4)     | 2 (1.6)      | 0.350   |
| Anti-PM/Scl75               | 6 (2.7)      | 1 (1.1)     | 5 (3.9)      | 0.297   |
| Anti-PM/Scl100              | 5 (2.3)      | 1 (1.1)     | 4 (3.1)      | 0.190   |
| MSA+MAA positivity          | 55 (24.8)    | 30 (31.6)   | 25 (19.7)    | 0.042   |
| MSA and/or MAA              | 120 (54.1)   | 56 (58.9)   | 64 (50.4)    | 0.223   |

Values are expressed as n (%). P-value, comparison between the PM and DM groups. DM, dermatomyositis; PM, polymyositis.

Table 3 - Independent associations of autoantibodies with specific sets of clinical, imaging, and laboratory features by stepwise multiple logistic regression in patients with DM and PM.

| Diseases          | MSA/MAA | Parameters          | OR     | 95% CI  | p-value |
|-------------------|---------|---------------------|--------|---------|---------|
| Dermatomyositis    | Anti-Mi-2| Photosensitive       | 8.6    | 1.9-40.1| 0.002   |
|                   | Anti-Ro-52| Pulmonary disorders | 5.2    | 1.1-24.9| 0.020   |
|                   | Anti-Jo-1| Anti-Jo-1           | 3.1    | 1.4-7.0 | 0.006   |
|                   | Anti-SRP | Anti-Ro-52          | 16.5   | 3.2-84.3| <0.001  |
|                   | Anti-Jo-1| Pulmonary disorders | 15.9   | 3.1-82.9| <0.001  |
| Polymyositis       | Anti-Ro-52| Anti-Jo-1           | 4.7    | 1.8-12.2| 0.001   |
|                   | Anti-Jo-1| Articular manifestations | 0.70   | 2.7-18.6| <0.001  |
|                   | Anti-Ro-52| Pulmonary disorders | 3.1    | 1.3-7.8 | 0.010   |
|                   | Anti-Ro-52| Anti-Ro-52          | 6.8    | 2.5-18.2| <0.001  |

OR, odds ratio; CI, confidence interval; MSA, myositis-specific autoantibodies; MAA, myositis-associated autoantibodies.
The main components of the Ro/SS-A system are two distinct major proteins with molecular weights of 52 kDa (Ro-52) and 60 kDa (Ro-60). Reactivity to the Ro-SS-A protein has been correlated with the clinical features of Sjögren’s syndrome and systemic lupus erythematosus (33). However, the presence of anti-Ro in IIMs has also been described (34-36), and the association of anti-Ro-52 with anti-Jo-1 has been described in IIM patients in 10% of cases (34-36). Particularly in patients with anti-synthetase syndrome, the presence of anti-SSA/Ro-52 antibodies causes more severe interstitial lung disease (37). Other authors have found that the presence of anti-Ro-52 is associated with a particular phenotype of anti-synthetase syndrome, resulting in more severe myositis and joint impairment. Moreover, the coexistence of anti-Ro-52 appears to be associated with an increased risk of cancer (38). In the present study, anti-Ro-52 was significantly associated with anti-Jo-1, independent of the type of disease. However, in DM patients, anti-Ro-52 was associated with pulmonary disorders, independent of anti-Jo-1 reactivity.

Regarding MAAs, anti-PM-Scl has been found in 8-10% of patients with myositis-scleroderma overlap, whereas anti-Ku has been observed in 20-30% of these patients (3,9,39,40). The prevalence described herein was lower and could be explained by the exclusion of systemic autoimmune disease comorbidities, such as systemic sclerosis. Furthermore, these autoantibodies were not correlated with any clinical or laboratory parameters of DM or PM.

Our study was limited by being a retrospective study, with the typical problems specific to this type of cohort. Second, in the present study we also included patients with probable diagnoses of PM (i.e., meeting three of the four Bohan and Peter’s criteria) (15). In these cases, it was not possible to distinguish inclusion body myositis from other types of myositis or from certain dystrophies. Third, the blood samples had been stored for approximately 10 years and, therefore, might not have functioned properly in the antibody assays. Additionally, we did not include a healthy control group with which to compare antibody reactivity among the groups.

In conclusion, our data are consistent with those from other published studies involving other populations, although certain particularities do warrant consideration: a) we observed high frequencies of anti-Jo-1 and anti-Ro-52, followed by anti-Mi-2, in the subjects of the present study; b) anti-Ro-52 and anti-Jo-1 were strongly associated with one another; c) anti-Ro-52 was correlated with pulmonary disorders in dermatomyositis, whereas anti-Jo-1 was correlated with pulmonary alterations in polymyositis; and d) these autoantibodies should be analyzed routinely in practice, in contrast to the other MSAs and MAAs that were present in low frequencies and that were not associated with the clinical or laboratory parameters of PM and DM.

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AUTHOR CONTRIBUTIONS

Cruellas MG participated in the data collection, autoantibody analysis, and manuscript preparation. Souza FH participated in the manuscript preparation. Viana VS and Levy-Neto M participated in the manuscript revision. Shinjo SK contributed to the study design and participated in the data collection and manuscript revision.

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