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Previous Pulmonary Fibrosis in Dermatomyositis/Polymyositis: A Predictive Factor for Pulmonary and Extra-Pulmonary Tuberculosis

Taysa Cristiane Moreira da Silva[1], Adriana Coracini Tonacio de Proença[2], Samuel Katsuyuki Shinjo[1*]

[1]Division of Rheumatology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
[2]Department of Infectious and Parasitic Diseases, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
Email: *samuel.shinjo@gmail.com

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Abstract

Objective: With scant studies in the literature, little is known about the risk factors for tuberculosis in patients with dermatomyositis/polymyositis. Therefore, the aim of the present study was to analyze the predictive factors for tuberculosis development in dermatomyositis/polymyositis. **Methods:** This single-center, retrospective, cohort study initially included 290 patients with dermatomyositis/polymyositis, from 2002 to 2016. Tuberculosis (pulmonary and/or extra-pulmonary) was confirmed after dermatomyositis/polymyositis diagnosis in 12 patients (4.1%) (Tuberculosis+ group). For the control group (Tuberculosis−), 24 patients without tuberculosis were arbitrarily selected in the same period and matched for age, ethnicity, gender, age at disease diagnosis, disease duration and type (dermatomyositis or polymyositis). **Results:** Tuberculosis occurred for a median of 16 months after dermatomyositis/polymyositis diagnosis. Clinical, laboratory and treatment features were similar in Tuberculosis+ and Tuberculosis− groups ($P > 0.05$). However, previous pulmonary fibrosis in dermatomyositis/polymyositis was more prevalent in the Tuberculosis+ group (41.7 vs. 8.3%; $P = 0.029$). Moreover, on a multivariate logistic regression model, pulmonary fibrosis was significantly associated with Tuberculosis (Odds ratio: 9.59, 95% confidence interval: 1.17 - 78.82). Tuberculosis affected 3 dermatomyositis cases for every 1 polymyositis case, with predominantly pulmonary followed by extra-pulmonary involvement (pleura, cutaneous, muscular, joint, soft tissue and hematologic).

Two or more sites were affected in 41.7% of cases. **Conclusions:** Previous pulmonary fibrosis in dermatomyositis/polymyositis was a predictive factor associated with tuberculosis development. Further studies are needed to confirm these results.

Keywords

Dermatomyositis, Infectious, Myositis, Polymyositis, Tuberculosis

1. Introduction

Dermatomyositis (DM) and polymyositis (PM) are rare systemic autoimmune myopathies characterized by progressive, symmetrical and predominantly proximal limb muscle weakness [1] [2] [3] [4] [5]. Moreover, cutaneous, pulmonary, joint, cardiac, and gastrointestinal tract involvement may also occur in these diseases, concerning cutaneous involvement in DM, heliotrope rash and Gottron's papulesare typical lesions [2] [3] [4] [5] [6]. However, other skin involvements may occur in DM, such as a "shawl" sign, "mechanic's hands", "V"-neck sign, periungual hyperemia, cuticular hypertrophy, facial rash, vasculitis, calcinosis, and ulcers, among others [2] [3] [4] [5] [6].

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* [7]. The World Health Organization reported an annual TB incidence of 5 - 91.8/100,000 patients [8]. Moreover, individuals with systemic autoimmune diseases or compromised immune systems are at higher risk of TB infection [7] [8] [9] [10].

Although there are few studies in the literature, a high prevalence of TB has been described in patients with DM/PM [11]-[38]. In addition, these studies have many limitations: 1) majority are case reports or series [20]-[37]; 2) DM/PM and/or TB diagnosis are based on registration data or the International Classification for Diseases (ICD) [14]-[19]; 3) studies analyzed DM/PM together with other systemic autoimmune diseases [16] [32] [38]; 4) studies evaluated DM/PM associated with other systemic autoimmune diseases (overlap syndromes) or neoplasms [19] [23]; 5) lack of a TB diagnosis definition [16] [17] [18] [19]; 6) control groups are matched for age and gender [17]; 7) studies analyzed TB together with other infectious diseases [11] [12] [15]. Therefore, these factors limit systematic analysis of possible parameters associated with TB in patients with DM/PM.

Thus, given these limitations and the scarcity of studies in the literature, the objective of the present study was to analyze possible factors associated with pulmonary and extra-pulmonary TB in patients with DM/PM.

2. Methods

The present single-center study included patients with DM or PM who fulfilled the Bohan and Peter criteria [4] [5].

Initially, patients with DM/PM and TB (TB+ group) were selected from an ongoing electronic database registry updated every 1 - 6 months for 290 DM/PM patients who attended in ourtertiary referral hospital (outpatient clinic) from 2002 to 2016. For every TB patient, two DM/PM patients without TB (TB− group) were arbitrarily selected from this electronic database registry during the same period and matched for age, ethnicity, gender, age at DM or PM diagnosis, disease duration and type (DM or PM).

Patients with probable or possible DM/PM, clinically amyopathic DM, inclusion body myositis, cancer associated myopathies, and myositis overlap syndromes were excluded. Moreover, cases presenting TB prior to DM/PM disease onset were also excluded.

The study was approved by the local Institutional Ethics Committee.

Demographic, drug therapy, clinical and laboratory data were obtained retrospectively through a systematic review of all patient medical records, which were previously parameterized and standardized.

The clinical manifestations considered were those presenting during the follow-up of these patients—initial and cumulative features: constitutional symptoms, skin (heliotrope rash, Gottron's papules), joint (arthralgia and/or arthritis), gastrointestinal (upper dysphagia) and pulmonary (subjective dyspnea associated with concomitant confirmed "ground-glass" on high-resolution chest computed tomography of the lungs) manifestations. Limb muscle strength was graded according to the Medical Research Council Scale as grade 0: absence of muscle contraction; grade I: slight signs of contractility; grade II: movements of normal amplitude but not against gravity; grade III: normal range of motion against gravity; grade IV: full mobility against gravity and some degree of resistance; grade V: complete mobility against gravity and strong resistance [39].

Laboratory data were based on time of DM/PM and of TB diagnosis: creatine phosphokinase (normal range 24 - 173 U/L) and aldolase (1.0 - 7.5 U/L), determined using an automated kinetic assay. Autoantibodies against cellular components were determined with indirect immunofluorescence using Hep-2 cells as the substrate. Autoantibody anti-Jo-1 was determined using the Western blotting method.

Data on prednisone were collected at TB onset, 6 months before TB diagnosis or from DM/PM symptom onset to TB diagnosis in TB patients. Moreover, these same parameters were collected in the same time period for those without TB. Data on immunosuppressive/immunomodulatory drugs were collected for the 6 months before TB onset in TB patients and in the same time period for those without TB, whereas data for intravenous methylprednisolone pulse therapy applications were collected from the onset of disease symptoms.

TB diagnosis was confirmed by the presence of *M. tuberculosis* in culture and/or by pathological anatomy and/or *M. tuberculosis* polymerase chain reaction (PCR Amplicor MTB—Roche Diagnostics).

Comorbidities analyzed included diabetes mellitus and systemic arterial

hypertension.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation, median [25th - 75th interquartile], or as percentages (%) for categorical variables. Student's t-test or the Mann-Whitney U-test for continuous variables was employed to evaluate the differences between the DM/PM groups. The 95% confidence intervals (95% CI) were calculated using binomial distribution. All variables that exhibited statistically difference on the univariate analysis (comparison of patients with and without TB episodes) were selected for adjustment. The age-, gender-, and ethnicity-adjusted odds ratios (ORs) and 95% confidence interval (CI) were calculated using an unconditional logistic model. These calculations were performed using the SPSS Statistics software program (version 15.0, USA). Values of $P < 0.05$ were considered statistically significant.

3. Results

Over 14-year period, 12 consecutive patients with DM/PM (9 DM and 3 PM) presented systemic TB infection. Demographic, clinical and laboratory features of these patients are given in Table 1.

Table 1. General features of dermatomyositis/polymyositis patients with and without systemic tuberculosis.

	TB(+) (n = 12)	TB(−) (n = 24)	P value
Demographic features			
Age at DM/PM diagnosis (years)	45.3 ± 14.1	44.7 ± 13.8	0.894
DM/PM diagnosis—symptom onset (mo)	3.0 [2.3 - 8.5]	4.0 [2.3 - 6.8]	0.665
TB diagnosis—symptom onset (mo)	23.0 [10.3 - 80.5]	54.0 [6.8 - 83.5]	0.728
Female gender	9 (75.0)	18 (75.0)	1.000
White ethnicity	10 (83.3)	20 (83.3)	1.000
Patients with DM	9 (75.0)	18 (75.0)	1.000
Patients with PM	3 (25.0)	6 (25.0)	1.000
Initial and cumulative features			
Constitutional symptoms	9 (75.0)	13 (54.2)	0.292
Heliotrope rash and/or Gottron's papules	9 (75.0)	18 (75.0)	1.000
Muscle strength			
Upper limbs	IV [IV - IV]	IV [IV - IV]	0.631
Lower limbs	IV [IV - IV]	IV [IV - IV]	0.882
Upper dysphagia	4 (33.3)	12 (50.0)	0.298
Joint involvement	9 (75.0)	9 (37.5)	0.075
Pulmonary involvement	9 (75.0)	10 (41.7)	0.083
Incipient pneumonia	5 (41.7)	7 (29.2)	0.479
Pulmonary ground-glass opacity	6 (50.0)	5 (20.8)	0.124

Continued

Basal pulmonary fibrosis	5 (41.7)	2 (8.3)	0.029
Creatine phosphokinase level			
At DM/PM onset	3599 [1597 - 4872]	1584 [635 - 5340]	0.728
At TB diagnosis	219 [25 - 714]	-	-
Autoantibodies			
Antinuclear factor	8 (66.7)	14 (58.3)	0.456
Anti-Jo-1	4 (33.3)	4 (16.7)	0.397
Systemic arterial hypertension	6 (50.0)	12 (50.0)	1.000
Diabetes mellitus	1 (8.3)	6 (25.0)	0.384

DM: dermatomyositis; PM: polymyositis; TB: tuberculosis. Results expressed as percentage (%), mean ± standard deviation or median [interquartile 25th - 75th].

Mean age of the patients at time of DM/PM diagnosis and TB diagnosis were 45.3 and 51.8 years, respectively, with a predominance of female gender and white ethnicity. Moreover, the time duration of symptoms prior to DM/PM diagnosis was 3.0 months.

The demographic, clinical and laboratory parameters in the TB+ and TB− groups ($P > 0.05$) were similar, except for a higher frequency of basal pulmonary fibrosis identified at time of DM/PM diagnosis in the TB+ group (41.7 vs. 8.3%, $P = 0.029$).

Concerning treatment regimen, glucocorticoid use (intravenous methylprednisolone pulse therapy and prednisone) was also similar in both groups. There was also no difference in the current and cumulative dose of prednisone in the two groups ($P > 0.05$) (Table 2).

The frequency of immunosuppressant/immunomodulator use (azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide) was also comparable in the two groups ($P > 0.05$) (Table 2). Moreover, leflunomide was used in one patient, only in the TB+ group, whereas cyclosporine (6 patients) and rituximab (2 patients) were used only in the TB− group.

On univariate and multivariate analysis, after matching for gender, ethnicity and age, previous pulmonary basal fibrosis was strongly associated with systemic TB development (OR 9.59, 95% CI 1.17 - 78.82).

The majority of TB cases were pulmonary (alone in 41.7% and associated with other sites in 16.7%), with extra-pulmonary involvement in 41.7% of the patients: pleura (16.7%), skin (16.7%) muscle (16.7%), joint (16.7%) and others (33.3%) (Table 3). Two or more sites were affected in 41.7% of cases. The diagnosis was established in 91.7% of the cases using culture, 25.0% with pathological anatomy and 50.0% with *M. tuberculosis* PCR.

Concerning TB treatment, 1/3 received the standard regimen for 6 months (rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, and rifampicin and isoniazid for another 4 months), 1/3 extended the treatment for 9

Table 2. Therapy regimens of dermatomyositis/polymyositis patients with and without systemic tuberculosis.

Therapy	TB(+) (n = 12)	TB(−) (n = 24)	P value
Glucocorticoids			
Prednisone (mg/day)[1]	20.0 [0.6 - 37.5]	16.3 [0.0 - 37.5]	0.655
Prednisone ≥ 20 mg/day[1]	7 (58.3)	11 (45.8)	0.362
Cumulative prednisone dose (g)[2]	3.0 [0 - 5.9]	0.9 [0 - 5.3]	0.482
Cumulative prednisone dose (g)[3]	12.2 [5.0 - 35.7]	12.1 [5.3 - 15.3]	0.638
Intravenous methylprednisolone pulse[4]	7 (58.3)	9 (37.5)	0.203
Immunosuppressive/immunomodulatory drugs			
Azathioprine[5]	8 (66.7)	13 (54.2)	0.721
Methotrexate[5]	4 (30.8)	6 (25.0)	0.700
Mycophenolate mofetil[5]	1 (7.7)	2 (7.7)	1.000
Cyclophosphamide[5]	1 (7.7)	1 (4.2)	0.562
Leflunomide[5]	1 (7.7)	0	-
Cyclosporine[5]	0	6 (25.0)	-
Rituximab[5]	0	2 (7.7)	-

TB: tuberculosis. [1]Data for prednisone at TB onset in patients with TB and during the same period for those without TB; [2]Cumulative prednisone dose: 6 months before TB diagnosis for TB(+) group, and during the same period for TB(−) group; [3]Cumulative prednisone dose: from disease symptom onset to TB diagnosis for TB(+) group, and during the same period for TB(−) group; [4]Intravenous methylprednisolone pulse applications from time of disease onset symptoms; [5]Data for immunosuppressive/immunomodulatory drugs were collected for the 6 months before TB onset in patients with TB and during the same period for those without TB.

Table 3. Tuberculosis features in dermatomyositis/polymyositis patients analyzed in the present study.

Patient	Gender	Age at TB diagnosis (years)	TB site	TB identification
1	F	70	Cutaneous	Culture, PA
2	F	21	Pleural effusion	Culture
3	F	35	Muscle, joint, blood	Culture, PA
4	M	78	Lung	Culture
5	M	57	Lung, pleural effusion	Culture, PCR
6	M	51	Lung, cutaneous, soft tissues	Culture, PA, PCR
7	F	59	Joint, soft tissues	Culture, PCR
8	F	48	Lung	Culture, PCR
9	F	49	Lung	Culture
10	F	56	Lung	Culture
11	F	53	Muscle, bone, soft tissues	Culture, PCR
12	F	44	Lung	Culture

PA: pathological anatomy; F: female; M: male; PCR: polymerase chain reaction to *M. tuberculosis*; TB: tuberculosis.

months (rifampicin and isoniazid to 7 months) and 1/3 had levofloxacin associated with the regimen (1/2 of them replacing isoniazid) with variable duration of treatment. Eleven out of 12 patients were cured, whereas one died during treatment (pulmonary thromboembolism complications). Moreover, during follow-up, there was no DM/PM disease relapsing.

4. Discussion

The results of the present study showed that the presence of previous basal pulmonary fibrosis in DM/PM was an isolated predictive factor for the development of TB in this population. In addition, the infection occurred in 3 DM cases for every 1 PM, predominantly affecting the lungs, followed by extra-pulmonary involvement (pleura, skin, muscle, joint, and hematologic).

Although DM/PM is a rare disease and with strict exclusion criteria in the present study, we performed an analysis of 12 consecutive patients with defined DM/PM who developed TB documented by culture and/or pathological anatomy. In addition, patients were matched for age, ethnicity, sex, age at diagnosis of DM or PM, duration and type of disease (DM or PM) with a group of patients without TB (control group). In this case, the pairing was fundamental for the analysis of the results, since the distribution of TB varies according to age [40], gender [41] [42] and with the inherent characteristics of TB [43]. Moreover, the similar DM/PM duration ensured similar exposure susceptibility to TB in both groups.

Although the present study was retrospective, patient information was extracted from previously standardized and parameterized data, providing reliable data for evaluation. In addition, the patients were from a single center, thereby reducing variability in diagnosis, exams and drug therapy.

In the present study, a higher prevalence of TB was found in DM than PM, corroborating the study by Marie *et al.* [11]. The relatively small sample size precluded evaluation of the parameters involved in the greater susceptibility of TB in DM; therefore, further studies in larger samples are necessary to investigate the higher prevalence of TB in DM in relation to PM.

The results of the present study also showed that the presence of previous pulmonary involvement was a predictive factor for the development of pulmonary and extra-pulmonary TB in patients with DM/PM. It is likely that the presence, for example, of changes in pulmonary architecture (pulmonary fibrosis) render the affected areas more susceptible to the action of the mycobacterium and, consequently, to the development of TB. Furthermore, damaged lung could also increase the susceptibility to dormant *M. tuberculosis* because of the decreased clearing effect in the damaged lung or the easy attachment of bacilli to the destroyed alveolar surface. Corroborating this hypothesis, Chen *et al.* [15] showed that patients with DM/PM and pulmonary interstitial disease were at greater risk of developing serious infections. However, the authors did not specify the etiology of these infections. Moreover, previous studies have demon-

strated that structurally-damaging lung diseases, such as chronic interstitial lung diseases [44], chronic obstructive pulmonary disease [45], bronchiectasis [46] or pneumoconiosis [47] can impair local host immunity and further increase susceptibility to TB infection and/or reactivation.

Treatment (glucocorticoid and/or immunosuppressant) can further compromise the immune system, leading to increased risk of serious infections. However, in the present study, there was no difference in drug therapy between the TB(+) and TB(−) groups.

Once the immunosuppression was similar between groups, another fact that could explain the tuberculosis manifestation would be the presence of latent tuberculosis that was not completely accessed in these patients.

Other factors, such as age, gender, degree of initial muscular weakness, dysphagia, cutaneous and joint involvement, presence of autoantibodies, and serum levels of muscle enzymes, were not predictive of TB development in the sample analyzed in the present study. By contrast, Marie *et al.* [11] observed that age, muscle weakness (including esophageal dysmotility and respiratory failure), dysphonia, lymphopenia, presence of neoplasia and immunosuppressive and/or glucocorticoid use were factors related to a higher incidence of opportunistic infections in DM/PM. However, these authors analyzed TB along with other opportunistic infections.

TB primarily attacks the lungs, however the infection can spread to other parts of the body, such as the pleura, lymph nodes, bones and joints, the central nervous system and the genitourinary system. In the present study, TB affected lungs in 75% of cases, but 50% of patients had extra-pulmonary impairment isolated or associated with the lungs. This is a high rate of extra pulmonary tuberculosis, comparing with immunocompetent patients, especially the skin and soft tissue impairment as well muscle and joint, which are rarely affected.

The higher prevalence of pulmonary involvement is consistent with previous reports by authors such as Chen *et al.* [15]. However, Marie *et al.* [12] also found a greater number of extra-pulmonary cases. This may be, in part, due to possible intrinsic immune dysregulation, allowing TB to develop in less commonly affected organs.

The present study has some limitations. The number of patients in the TB+ group may be considered small. However, the study was single-center with strict exclusion criteria, significantly reducing the sample size. In addition, parameters that can influence the development of TB, such as nutritional status, socioeconomic status, occupational history and exposure to TB contacts were not assessed. Finally, tuberculin sensitivity test was not performed systemically in the patients.

In conclusion, the results of this study show that the presence of previous basal pulmonary fibrosis was a predictive factor for the development of TB in patients with DM/PM. Thus, despite the need for subsequent studies to confirm our results, this finding contributes for further information on a largely unex-

plored subject, showing that physicians responsible for patients with DM/PM should be aware of the possibility of TB and that certain aspects of the patient's illness can increase this risk.

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Conflicts of Interest

All authors declare no conflict of interest.

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