Patients with anti-small ubiquitin-like modifier activating enzyme-positive dermatomyositis resembling antisynthetase syndrome with poor prognosis: a bicentric international retrospective study and literature review

Camila Gusmão Vicente de Carvalho,[1] Barbara Bayeh,[1] Fernando Henrique Carlos de Souza,[1] Renata Miossi,[1] Pleiades Tiharu Inaoka,[2] Takashi Matsushita,[3] Naoki Mugii,[4] Samuel Katsuyuki Shinjo[1]

[1]Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de São Paulo, SP, Brazil; [2]Division of Rehabilitation Science, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Japan; [3]Department of Dermatology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Japan; [4]Department of Rehabilitation, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan

Correspondence: Samuel Katsuyuki Shinjo, Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de São Paulo, Av. Dr. Arnaldo, 455 – 3 andar, sala 3184, Cerqueira Cesar, CEP 01246-903, São Paulo, SP, Brazil.
Tel.: +55.11.3061.7176 - Fax: +55.11.3061.7490.
E-mail: samuel.shinjo@usp.br

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Summary

Objective. This study aimed to describe adult Brazilian and Japanese patients with anti-small ubiquitin-like modifier activating enzyme (SEA)-positive dermatomyositis (DM), as there are few studies in the literature. A literature review was also conducted.

Methods. This bicentric international retrospective study, conducted between 2012 and 2023, included patients with anti-SAE-positive DM (2017 European League Against Rheumatism/American College of Rheumatology classification criteria). All demographic features and clinical, laboratory, therapeutic, and follow-up data were collected from Brazilian and Japanese centers using pre-standardized and parameterized information.

Results. We included 17 adult patients with a median age of 65 years (56-76 years) and a predominance of females (82.4%). Constitutional symptoms at baseline were present in 58.8% of the patients. In addition to classical cutaneous DM lesions, one-third of the patients had myalgia and significant muscle weakness, whereas half presented with dysphagia, interstitial lung disease, and joint manifestations. The first-line treatment consisted of intravenous methylprednisolone and immunoglobulin pulse therapy in 41.2% and 28.6% of the patients, respectively. The median follow-up duration was 20 (13-74) months; at the last medical evaluation, half had active disease and were still using oral glucocorticoids (median dosage, 10.0 mg/day). Approximately one-fifth to one-third of the patients were diagnosed with different types of cancer, had severe infections, or died.

Conclusions. Patients with anti-SAE-positive DM not only resemble the phenotype of antisynthetase syndrome but are also associated with a poor prognosis.

Introduction

Dermatomyositis (DM) is part of the spectrum of idiopathic inflammatory myopathies, or systemic autoimmune myopathies. It is a rare chronic autoimmune disease that primarily affects the skin and striated skeletal muscle (1). Among the various myositis-specific autoantibodies found in DM, there is an anti-small ubiquitin-like modifier activating enzyme (SAE), the prevalence of which varies from 1% to 8% in patients with DM (2-7). This antibody was first described by Betteridge *et al.* in 2007 when 2 out of 20 patients with DM tested positive for anti-SAE autoantibodies (8). Initially, these patients had a clinically amyopathic condition with a predominance of skin changes and, after six months, developed myopathy associated with increased serum muscle enzyme levels and peripheral interstitial pneumonia; nonetheless, there was no sign of malignancy. Since the initial description of anti-SAE, few studies have been published (2-17), mainly limited to case reports (11-13) or case series with samples from a maximum of ten patients (4, 5, 8-10, 14, 15). Additionally, these studies were limited to evaluating patients from Asia (5, 7, 11, 13-15), Europe (3, 4, 8, 10, 12, 17) and North America (6, 16). Therefore, this bicentric international retrospective study aimed to analyze the demographic, clinical, laboratory, and therapeutic features of 17 Brazilian and Japanese anti-SAE-positive DM patients. We also reviewed the available literature on anti-SAE-positive cases.

Materials and Methods

Study design

This was a bicentric international retrospective study. Individuals with DM were assessed at the Inflammatory Myopathies Clinic of our tertiary services between May 2013 and May 2023. The study was approved by the Brazilian (CAAE 68523717.1.0000.0068) and Japanese research ethics committees, and all participants provided written informed consent.

Patients

We enrolled adult patients aged 18 years or older who met the 2017 European League Against Rheumatism/American College of

Rheumatology (EULAR/ACR) classification criteria for DM (1), and tested positive for anti-SAE autoantibodies. Patients with overlap syndrome, other inflammatory myopathies, or those positive for other autoantibodies myositis-associated or myositis-specific were excluded.

Data

Demographic characteristics, clinical data, and laboratory data were obtained at the first and last medical visits, and missing information was retrieved from patients' files. We collected demographic, clinical, laboratory, disease activity status, and therapeutic information using pre-standardized and parameterized information: i) demographics – age at disease diagnosis and sex; ii) clinical manifestations – symptoms onset, disease duration, outpatient follow-up time, cutaneous involvement (heliotrope rash, Gottron's papules/sign, facial rash, "mechanic's hand," skin and digital ulcers, calcinosis, vasculitis, "V-neck sign" and "shawl sign," Raynaud's phenomenon, systemic manifestations (cardiac, dysphagia, arthritis, arthralgia, and constitutional symptoms at baseline); limb muscle strength graded according to the Medical Research Council (MRC) classification (18); iii) laboratory data at baseline (and maximum) serum levels of muscle enzymes in blood samples – creatine phosphokinase (CPK), alanine aminotransferase, aspartate aminotransferase, and lactic dehydrogenase; iv) complementary examination – changes in high-resolution computed tomography images of the lung: interstitial lung disease (ILD); v) outcomes – diagnosis of neoplasms, severe infections (defined as an infection that required parenteral therapy or tuberculosis), and death; vi) disease status at the last medical appointment was defined according to the international consensus guidelines for trials of myositis therapies (proposed by the International Myositis Assessment and Clinical Studies Group) (19): clinical remission (no evidence of disease activity [clinical and/or laboratory data] for at least six months without DM treatment), complete clinical response (no evidence of disease activity for at least six months while still receiving myositis therapy), or disease relapse: recurrence of clinical (muscle or skin manifestations), and/or laboratory findings (elevated CPK or aldolase) with no explanation other than disease activity; vii) drug treatment – initial treatment (received in the first year after diagnosis) with intravenous methylprednisolone (IVMP) or intravenous immunoglobulin (IVIG), and current treatment with glucocorticoid and/or immunosuppressive, immunomodulatory, or immunobiological treatment. An analysis of the profile of myositis-specific and myositis-associated autoantibodies was performed in the serum samples of these patients, collected at disease onset or at the initial follow-up and stored at -20ºC. Anti-SAE autoantibodies were analyzed in Brazilian samples using a commercial immunoblotting kit (DL 1530-1601-4G, Euroimmun, Lübeck, Germany) according to the manufacturer's protocol, as previously described (20). Only patients with moderate or strong reactivity were included in this study. In Japanese samples, immunoprecipitation assays and/or proteome-wide autoantibody screening and quantification were performed with wet protein arrays [consisting of proteins synthesized from a proteome-wide human cDNA library (HuPEX) maintaining their three-dimensional structure] (FUSHIMI Pharmaceutical Co., Kagawa, Japan) (13).

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of the distribution of continuous variables. The results are presented as mean ± standard deviation or median (interquartile range, 25^{th}-75^{th}) for continuous parameters, and number (%) for categorical variables. Statistical analyses were performed using the IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA).

Literature review

We performed a qualitative systematic literature review of the PubMed database. The electronic searches used variants of the following research Medical Subject Headings (MeSH) terms with a syntax adjusted to each database: "anti-SAE"; "myositis-specific (auto)antibodies"; "myositis-associated (auto)antibodies"; with each of the following MeSH terms referring to autoimmune inflammatory myopathies: "myositis"; "systemic autoimmune myopathies"; "dermatomyositis"; "amyopathic dermatomyositis"; "clinically amyopathic dermatomyositis."

Data collection

Data were collected at two time points, April 2023 and June 2023. A literature search was conducted between April and July 2023. Manuscripts were selected primarily through analysis of their titles and abstracts. Two researchers collected data individually to ensure the trustworthiness of the findings, and divergences were addressed by a third senior researcher. Each sample article was read thoroughly, and the information was inserted into a spreadsheet (Table 1), including the author, publication year, study type, country, age (median in years), sex, type of idiopathic inflammatory myopathies, EULAR/ACR criteria, duration of follow-up, cutaneous lesions, arthritis, weakness, increased serum levels of muscle enzymes, dysphagia, lung involvement, constitutional symptoms, IVIG or IVMP pulse therapy, episodes of infection, neoplasia, death, and disease activity.

Eligibility criteria

Papers were analyzed based on the following eligibility criteria: at least one combination of the terms described in the search strategy appeared in the title, written in English, and addressed anti-SAE in DM. Reviews, monographs, dissertations, case reports, series reports (with up to a maximum of ten patients), and congress proceedings were excluded.

Results

Present study

A total of 17 patients with anti-SAE-positive DM were included in the study, of which 14 were from the Brazilian cohort and 3 from the Japanese cohort. Regarding ethnicity, all Brazilian patients were of South American origin, and none were of Japanese descent. The median age of the 17 patients was 65 (56-76) years, with a predominance of females (82.4%). DM and clinically amyopathic DM were reported in 53.0% and 47.0% of cases, respectively. None of the patients had other types of myositis-associated autoantibodies or myositis-specific autoantibodies.

Constitutional symptoms at baseline were present in 58.8% of patients (Table 2). All patients had Gottron's papules. Gottron's sign was observed in 94.1% of the patients, whereas heliotrope rash was reported in 64.7%. Mechanic's hands were described in three patients. Other cutaneous manifestations are presented in Table 2. One-third of patients had myalgia. Among patients with DM (n=9), muscle weakness was mild. MRC ≤3 in the upper and lower limbs was present in five and seven patients, respectively. The serum levels of muscle enzymes are listed in Table 2.

Dysphagia and joint manifestations were present in approximately half of the patients, whereas none of them had cardiac manifestations. Nearly half of the patients (47.1%) exhibited lung involvement, defined as diffuse ILD, on high-resolution computed tomography. Among these, half had an insidious onset within three months, while the other half were asymptomatic. Random ground-

glass opacities were observed on all computed tomography scans, and lower lobe reticulations were present in almost all cases (88%). The median follow-up duration was 20 (13-74) months. More than half of the patients achieved disease remission or complete clinical response, and only one-third had active disease (Table 3). First-line treatment consisted of IVMP and IVIG pulse therapy in 41% and 29.4% of patients, respectively (Table 3). At the final follow-up, two-thirds of the patients were still using glucocorticoids, with a median dosage of 10.0 (0-20.0) mg/day. Eight patients received immunosuppressive therapy; however, the choice of immunosuppressant was highly variable. Mycophenolate mofetil was a commonly used drug, and only one patient received immunobiologicals (abatacept) (Table 3). During follow-up, three patients were diagnosed with different types of cancer (Table 4). Severe infections occurred in four patients, and three patients died during the follow-up period (Table 4).

Literature review

A total of 15 studies on anti-SAE were available in the literature, including 5 case reports, 1 cross-sectional study, and 9 retrospective studies. Studies with fewer than 10 cases were excluded, resulting in 5 studies that were compared with the data from the present study (Table 1). Two studies were conducted in the United States (6, 19), one in China (7), one in the United Kingdom (17), and one in France (2). The study sample size ranged from 11 to 49 patients, and most of the patients were female. The mean age of disease onset ranged from 53 to 62 years. Three of these studies did not use the EULAR/ACR definition of DM (7, 16, 17).

The follow-up time ranged from 12 to 192 months, except for one study that did not mention this information (17). The presence of Gottron's papules/signal ranged from 75% to 100%, and heliotrope rash was present in 71.4% to 100% of patients. The "V-

Table 1. Data collected in each article included in the present review.

	Present study	Betteridge *et al.*[17]	Ge *et al.*[7]	Peterson *et al.*[16]	Albayda *et al.*[6]	Demortier *et al.*[2]
Publication year	2024	2009	2017	2018	2021	2023
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Country	Brazil / Japan	UK	China	USA	USA	France
Anti-SAE (n)	17	11	12	19	19	49
EULAR/ACR criteria	Yes	No	No	No	Yes	Yes
Female sex	12 (82.4)	7 (64)	9 (75)	14 (73.7)	14 (74)	41 (83.6)
Median age at onset (years)	65	62	59.1	55.4	53.3	53
Duration of follow-up (mo)	20	NA	21	12	192	39
Gottron' lesions	17 (100)	9 (82)	9 (75)	19 (100)	18 (95)	38 (77.5)
Heliotrope rash	11 (64.7)	9 (82)	9 (75)	19 (100)	16 (84)	35 (71.4)
"V"-neck sign	5 (29.4)	3/7 (43)	6 (50)	NA	16 (84)	38 (77.5)
"Shawl" rash	1 (5.9)	3/7 (43)	6 (50)	NA	16 (84)	28 (57.1)
Diffuse skin rash	10 (58.8)	NA	9 (75)	NA	8 (42)	NA
Skin ulceration	2 (11.8)	NA	7 (58)	NA	NA	9 (18,4)
Periungueal changes	1 (5.9)	8/8 (100)	NA	NA	16 (84)	38 (77.5)
Mechanic's hand	1 (5.9)	0	6 (50)	NA	7 (37)	NA
Joint involvement	9 (53.0)	2 (18)	4 (33)	2 (10.5)	8 (42)	12 (24.5)
Arthritis	2 (11.8)	2 (18)	?	2 (10.5)	8 (42)	?
Weakness	7 (41.2)	11/11 (100)	6 (50)	11 (58)	8 (42)	34 (69.4)
Raised CPK	Yes	9 (82)	Yes	2 (11.8)	Yes	Yes
CPK value (U/L)	186	NA	286	NA	256	200 (94-440)
Dysphagia	9 (52.9)	7/9 (78)	7 (64)	3 (60)	8 (42)	19 (38.8)
Lung involvement	8 (47.1)	2 (18)	7 (64)	4/7 (57.1)	7/9 (77)	8 (21)
ILD	8 (47.1)	2 (18)	7 (64)	1 (14.3)	7/9 (77)	8 (21)
Constitutional symptoms	10 (58.8)	9 (82)	NA	NA	6 (32)	NA
MP pulse therapy	7 (41.2)	NA	NA	NA	NA	10(20.4)
IVIg	5 (29.4)	NA	NA	NA	10 (53)	25 (51)
IVIg + MP pulse therapy	2 (11.8)	NA	NA	NA	NA	NA
Episodes of infections	4 (23.6)	NA	NA	NA	NA	NA
Neoplasia	3 (17.6)	2 (18)	2 (16)	1/16 (16)	5 (26)	8 (16.3)
Death	3 (17.6)	NA	1 (8)	0	1 (5.2)	5 (10.2)
Active disease	6 (35.3)	NA	1/9 (11)	3/15 (20)	7 (37)	9 (18)
Disease remission	2 (18.2)	NA	2/9 (22)	NA	3 (15)	NA
Complete clinical response	6 (35.3)	NA	5/9 (55)	12/15 (80)	8 (42)	28 (58.3)

SAE, small ubiquitin-like modifier activating enzyme; EULAR/ACR, European League Against Rheumatism/American College of Rheumatology; CPK, creatine phosphokinase; ILD, interstitial lung disease; IVIg, intravenous immunoglobulin; MP, methylprednisolone; NA, not applicable. Data in brackets are frequencies (%).

neck" sign and "shawl" rash ranged from 43% to 84%, and one study did not describe these signs (16). Mechanic's hands were evaluated in 3 studies; one did not find this feature (17), and 2 others described a prevalence of 37% and 50%, respectively (6, 7).

Arthritis ranged from 10.5% to 33% and was not cited in one of the studies (7), whereas weakness ranged from 42 to 100% and mean CPK elevation ranged from 200 U/L to 286 U/L. However, in two studies (16, 17), CPK values were not specified; only the number of patients with elevated CPK levels (82% and 11.8%) was demonstrated without specifying their values.

Dysphagia ranged from 38.8% to 78%, and pulmonary involvement ranged from 18% to 77%. A total of 4 studies considered ILD (2, 6, 7, 17), and one study considered ILD, ground-glass opacity potentially associated with smoking, and undefined lung involvement (16).

Constitutional symptoms have been reported in only two studies (6, 17), ranging from 32% to 82%. Betteridge *et al.* considered fever, weight loss, and raised inflammatory markers (17), and Albayda *et al.* considered only fever and weight loss (6). Both authors set these symptoms in a single group. Only two studies described the established treatment (2, 6), and approximately 50% of the patients were administered IVIG. Treatment with IVMP pulse therapy was administered to 20% of patients in one study (2); however, there is no information on whether it was performed concurrently with IVIG. No infectious episodes were reported in any of the studies evaluated. Neoplasia was present in 16-26% of

Table 2. General characteristics of 17 adult patients with anti-small ubiquitin-like modifier activating enzyme-positive dermatomyositis.

Characteristics	N=17
Age at disease onset (years)	65 (56-76)
Female sex	14 (82.4)
DM	9 (53.0)
Clinically amyopathic DM	8 (47.0)
Constitutional symptoms at baseline	10 (58.8)
Gottron's sign	16 (94.1)
Gottron's papules	17 (100)
Heliotrope rash	11 (64.7)
Facial rash	11 (64.7)
"V-neck" sign	5 (29.4)
"Holster" sign	3 (17.6)
Calcinosis	3 (17.6)
Skin ulcers	2 (11.8)
Digital ulcers	1 (5.9)
Raynaud's phenomenon	1 (5.9)
Vasculitis	1 (5.9)
"Mechanic's hands"	1 (5.9)
"Shawl" sign	1 (5.9)
Myalgia	7 (41.2)
Muscle strength (MRC) (only DM, n=9)	
Upper limbs	
IV degree	7 (41.2)
III degree	1 (5.9)
II degree	1 (5.9)
Lower limbs	
IV degree	6 (55.6)
III degree	3 (35.3)
II degree	1 (5.9)
Dysphagia	9 (52.9)
Arthralgia	6 (35.3)
Arthritis	2 (11.8)
Cardiac	0
Lung involvement (interstitial lung disease)	8 (47.1)
Maximum levels of muscle enzymes	
Creatine phosphokinase (U/L)	195 (52-409)
Aspartate aminotransferase (U/L)	38 (21-57)
Alanine aminotransferase (U/L)	28 (15-37)
Lactic dehydrogenase (U/L)	337 (281-672)

DM, dermatomyositis; MRC, Medical Research Council. Data are expressed as median with 25th-75th percentiles or percentage (%).

Table 3. Treatment characteristics and follow-up of 17 adult patients with anti-small ubiquitin-like modifier activating enzyme-positive dermatomyositis.

Characteristics	N=17
Current follow-up	
Duration of follow-up (months)	20 (13-74)
Disease status at the last medical evaluation (N=17)	
Active disease (clinical relapse)	6 (35.3)
Complete clinical response	6 (35.3)
Disease remission	5 (29.4)
Treatment	
Previous IVMP pulse therapy	7 (41.0)
Previous IVIG	5 (29.4)
Previous IVIG + IVMP pulse therapy	2 (11.7)
No IVMP or IVIG	7 (41.0)
Current treatment (N=17)	
Glucocorticoid	
Current use	11 (64.7)
Current dose (prednisone equivalent), mg/day	10.0 (0-20.0)
Immunosuppressive/immunomodulatory/immunobiological	
Methotrexate	2 (11.8)
Azathioprine	1 (5.9)
Mycophenolate mofetil	3 (17.6)
Leflunomide	2 (11.8)
Cyclosporine	1 (5.9)
Cyclophosphamide	1 (5.9)
Abatacept	1 (5.9)

IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone. Data are expressed as mean ± standard deviation, median (IQR 25th-75th), or percentage (%).

Table 4. Outcomes during follow-up.

Outcomes	N (%)
Cancer	
Laryngeal squamous cell carcinoma	1 (5.9)
Gastrointestinal tumor	1 (5.9)
Lung adenocarcinoma	1 (5.9)
Severe infections	
Sepsis (urinary, central venous catheter insertion)	2 (11.8)
Varicella zoster virus encephalitis	1 (5.9)
Retinal toxoplasmosis	1 (5.9)
Total episodes of infections	4 (23.6)
Death	
Infections	2 (11.8)
Neoplasia	1 (5.9)

Data expressed as a percentage (%).

patients. Two groups considered only associated cancers (3, 17). Cancer-associated myositis was defined as cancer occurring within 3 years of diagnosis of myositis, whereas one study described all cases of neoplasia during follow-up (6), with an average of 4.3 years since the onset of DM. Two studies did not describe the time elapsed between the myopathy and cancer diagnosis (7, 16). Death rates ranged from 0 to 10.2% and were not described in only one study (17).

Disease activity at the last medical visit was reported in four studies (2, 6, 7, 16), varying from 1% to 37%, and they also described a complete clinical response in 42% to 80% of patients. However, disease remission has only been reported in two studies (6, 7), ranging from 15% to 22%.

Discussion and Conclusions

This study evaluated the demographic, clinical, laboratory, therapeutic, and outcome aspects of anti-SAE-positive DM over a median 20-month follow-up. Few epidemiological studies have longitudinally examined this subgroup (Table 1). Our study is the first to include both Brazilian and Japanese cohorts simultaneously across multiple research centers, thus reducing methodological bias. We employed strict inclusion criteria based on the 2017 ACR/EULAR classification, at difference from previous research (7, 16, 17).

Patients with anti-SAE-positive DM typically exhibit skin involvement and muscle weakness (17). Heliotrope rash and Gottron's lesions, which are the primary dermatological indicators of DM, were prevalent in our study, consistent with previous findings (2-17). Additionally, "mechanic's hands," which are commonly associated with antisynthetase syndrome, were observed in three patients, a finding reported in only two previous studies (6, 7). Muscle weakness, typically mild, affected one-third of our patients with normal serum CPK levels, which is consistent with the existing literature. In DM, lung involvement, particularly ILD, is common and associated with higher morbidity and mortality (9). All the patients with pulmonary involvement in our study (47.1%) had ILD. Previous reports have shown varying prevalence of lung involvement, ranging from 18% to 77% (2, 6, 7, 16, 17), with some suggesting a higher ILD prevalence in Asians (7, 14), possibly due to ethnic factors. Gastrointestinal manifestations, notably dysphagia, are common in DM, including the anti-SAE-positive subtype, which symptom occurred in 52.9% of our patients, in line with the existing literature. However, joint involvement was more prominent than that previously reported, with symptoms in half of the patients, including arthritis (22%). Constitutional symptoms were initially present in most of our patients, a pattern noted in two previous studies (6, 17). Limited data are available on the established treatment for patients with anti-SAE-positive DM, and it should be tailored to each patient's circumstances, considering factors such as disease severity and duration, and previous treatments (3, 9). In our study, the initial therapy primarily consisted of IVMP or IVIG pulse therapy, followed by immunosuppressant therapy for the most severe cases. Two previous studies also outlined a standard approach involving IVIG and IVMP pulse therapy (2, 6).

During our follow-up, 35% of the patients maintained active disease, with the majority requiring glucocorticoids at an average dose of 10 mg/day. Prior long-term studies have reported active disease in 11% to 37% of cases at the final follow-up, with mortality rates ranging from 0 to 10% (2, 6, 7, 16). These findings suggest a more aggressive disease course and poorer prognosis associated with anti-SAEs. The incidence of cancer was 17.6%, which is consistent with previous reports (2, 4, 6, 7, 16), indicating an increased risk of malignancy. Although infections are a significant cause of mortality in DM, their occurrence in the anti-SAE-positive subgroup remains unclear. We identified four cases of severe infection, that resulted in two deaths. Overall, three patients died during the study. Although our study provides valuable insights into anti-SAE-positive DM, it is important to acknowledge its limitations. The retrospective, observational, and descriptive design may have introduced selection bias, potential confounding variables, incomplete medical records, and loss of follow-up. Nevertheless, our study lays a strong foundation for future research in this area, benefiting from the diverse patient populations and international collaboration between reference centers in Japan and Brazil.

Our study revealed a high incidence of pulmonary, muscular, and joint involvement in Brazilian and Japanese anti-SAE DM patients. Furthermore, we observed a greater prevalence of early dysphagia, severe infections, persistent disease, increased neoplastic risk, and increased mortality. Thus, our findings suggest that a phenotype resembling antisynthetase syndrome is linked to a worsened prognosis. Therefore, our study contributes to a more comprehensive characterization of patients with anti-SAE-positive DM, especially regarding the clinical symptoms, disease course, and overall prognosis.

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