Anti-SAE dermatomyositis: clinical and histologic characteristics from a monocentric Italian cohort

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Abstract

Objective

Multiple myositis-specific antibodies have been identified, each associated with different clinical subsets of dermatomyositis (DM). Anti-SAE associated DM is considered the least studied subset. Our study aimed to evaluate the clinical and histological characteristics of DM patients with anti-SAE antibodies. As reference, patients with anti-Mi2 antibodies associated DM, representing a well-characterised subset, were analysed.

Methods

We recorded data from our DM cohort in the INflammatory MYositis REgistry (INMYRE). Patients were divided into two groups: those positive for anti-SAE and those positive for anti-Mi2 antibodies. Clinical characteristics, including skin, muscle, and extra-muscular involvements, were recorded. Available muscle biopsies were compared between the two groups.

Results

Of 92 DM patients, 10 (10.9%) were positive for anti-SAE and 17 (18.5%) for anti-Mi2. Anti-SAE positive DM patients showed classic DM findings but were characterised by a higher prevalence of skin itching (60% vs. 11.8%, $p<0.01$), shawl sign (40% vs. 5.9%, $p<0.05$) and lung involvement (30% vs. 0%, $p<0.05$) compared to anti-Mi2 positive patients. Furthermore, anti-SAE positive DM patients showed lower creatine kinase levels than those with anti-Mi2 (median [IQR]: 101 [58-647] vs. 1984 [974-3717], $p<0.05$) and a lower percentage of muscle fibre degeneration and necrosis (1.5%±1.7 vs. 5.9%±3.2, $p<0.05$) in muscle biopsies. No other differences were observed.

Conclusion

Anti-SAE DM represents a disease subset characterised by classic cutaneous involvement often associated with itching, less severe muscle involvement, but potential pulmonary involvement that should always be investigated in these patients.

Key words

dermatomyositis, myositis, autoantibodies

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Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with distinctive dermatologic manifestations. Classified as an autoimmune disorder, its exact aetiology remains elusive. Clinically, DM is identified by a pathognomonic skin rash, typically evidenced as Gottron's papules and heliotrope erythema, and proximal muscle weakness. The diagnosis is supported by elevated serum muscle enzymes, electromyographic findings, characteristic changes in muscle biopsy, and imaging studies (1-3).

The role of autoantibodies in DM, particularly myositis-specific autoantibodies (MSAs), has been increasingly recognised for their diagnostic and prognostic implications. Specific autoantibodies correlate with distinct clinical phenotypes (4). Among these autoantibodies, the anti-Mi-2 antibody is the oldest and best-known. It is typically linked to a classic DM phenotype and is associated with a favourable response to immunosuppressive treatment (5, 6). Recently, antibodies targeting the small ubiquitin-like modifier activating enzyme (anti-SAE) have been identified in DM patients (7). Patients with this antibody are the least described among those with DM. In certain patient cohorts, it appears associated with severe skin disease, mild muscle involvement, and a higher risk of malignancy (8-12). The identification of anti-SAE antibodies highlights the heterogeneity of DM and underscores the need for precise immunologic characterisation for optimal management.

The aim of our study is to describe the clinical, prognostic, and histological characteristics of an Italian cohort of adult patients with anti-SAE DM, and to compare these findings with the more well-established anti-Mi-2 subset.

Materials and methods

We conducted a monocentric observational study with prospectively collected data at the Rheumatology Unit of Policlinico of Bari, spanning from 2010 to 2024. We retrospectively analysed the medical charts of DM patients registered in INMYRE (study no. 6229, approval no. 84762, 2020/11/06; comitatoetico@policlinico.ba.it). All the patients included in this study were classified as DM according to the 2017 ACR/EULAR classification criteria for IIMs (13).

Myositis-specific antibodies (MSA) (Jo1, PL7, PL12, EJ, OJ, Mi2 a/b, TIF1-γ, MDA5, NXP2, SAE1/2, SRP) and myositis-associated antibodies (Ku, PM-Scl 100/75, Ro-52) were identified using the same line blot assay, performed according to the manufacturer's recommendations (Euroline Autoimmune Inflammatory Myopathies, Euroimmun, Germany). Patients with autoantibodies against Aminoacyl tRNA Synthetase (*e.g.* Jo1, PL-7, PL-12, OJ, or EJ) or against PM/Scl proteins or who fulfilled criteria for other connective tissue diseases were excluded from the analysis as they are considered distinct diseases (14).

Two groups of DM were analysed: patients with anti-SAE antibodies and patients with anti-Mi2 antibodies. We recorded the following data: demographics (age at disease onset and diagnosis, gender), outcome at the last follow-up visit (alive/death), and cause of death. Other clinical manifestations such as skin manifestations, itchy skin, Raynaud's phenomenon, arthritis, interstitial lung disease (ILD) and dysphagia were evaluated and recorded if presented during follow-up. ILD was defined by high-resolution computer tomography scan of the chest, while dysphagia was confirmed with fibre-optic endoscopic evaluation of swallowing (15). Cancer-associated myopathy (CAM) was defined as neoplasia detection before or within 3 years of DM onset (16). The presence of specific features of DM, including cutaneous or muscular involvement, was assessed at both onset and during follow-up. Muscle involvement was categorised as classic DM (*i.e.* muscle weakness at manual muscle test [MMT-8]), hypomyopathic DM (*i.e.* no muscle weakness but muscle abnormalities at laboratory and/or instrumental examinations), and amyopathic dermatomyositis (*i.e.* no muscle weakness and no muscle abnormalities at laboratory and/or instrumental examinations), according to the classification proposed by Euwer and Sontheimer (17). Maximum Creatine Kinase (CK)

levels and the lowest MMT8 values were recorded during the follow-up period. For histologic assessment, muscle samples were obtained via open surgery by a dedicated surgeon (D.D.) and immediately fresh-frozen in isopentane precooled in liquid nitrogen. All frozen samples were analysed in the Department of Neurophysiopathology (University of Bari, Italy), following standardised procedures (5). All patients had given informed consent for muscle biopsy as part of the diagnostic workup and for their medical records to be used for research purposes. Cryostat sections (7 µm thick) of muscle biopsy specimens were used. The following stains were studied for morphological characterisation: haematoxylin/eosin (H&E) and modified Gömöri trichrome (MGT). Immunohistochemical analysis was performed using the following antibodies: mouse anti-major histocompatibility complex type I (MHC-I) (1:50; Dako, Carpinteria, USA: M0736), anti-CD4 (1:40; Dako: M7310), anti-CD8 (1:40; Dako: M7103), anti-CD68 (1:50; Dako: M0876), anti-CD20 (1:100; Dako: M0755), anti-CD56 (1:50; Dako: M7304), anti-C5b-9 complex (1:25; Dako: M0777), and anti-CD31 (1:30; Dako: M0823). Perifascicular atrophy was defined as the presence of myofibres with a lesser diameter of under 40 µm for males and under 30 µm for females, affecting more than 6 fibres along one edge of the fasciculus (5). The presence or absence of each antigen, perifascicular atrophy, and myofibre degeneration/necrosis were assessed in all biopsies. Myofibres in necrotic or degenerative status were defined as the presence of focal pallor or hyalinisation, myofibrillar rarefaction, myophagocytosis, or myofibre vacuolation. For each patient, the total number of muscle fibres was manually counted, and the percentages of necrotic fibres were assessed (5). Whole slide images were processed using a virtual microscope based on ImageJ software version 6.1.1 (NIH, Bethesda, MD; http://imagej.nih.gov/ij).

Statistics

The Kolgomorov-Smirnov test was used to evaluate the distribution of continuous variables. Demographics and disease characteristics were evaluated using standard descriptive statistics. Categorical variables were expressed as number or percentage; continuous variables as mean (± standard deviation [SD]) or median and interquartile rage (IQR). Comparisons between groups were performed by Fisher's exact test and Student's t-test, when appropriate. A p-value <0.05 was considered statistically significant. Survival from disease onset was estimated using Kaplan-Meier (K-M) life-table method and differences between groups were compared using the log-rank test. Statistical analysis was conducted using IBM SPSS Software (v. 21.0, Armonk, NY, USA).

Table I. Characteristics of adult DM patients with anti-SAE and anti-Mi2 antibodies.

Variables	Anti-SAE1/2 patients (n=10)	Anti-Mi2 patients (n=17)
Age at diagnosis, year, mean (±SD)	60 (±19)	58 (±18)
Age at onset, year, mean (±SD)	59 (±19)	57 (±17)
Diagnostic delay, months, mean (±SD)	5 (±4)	14 (±28)
Gender, n. (%) (M/F)	1/9 (10/90)	1/16 (5.9/94.1)
Race, Caucasian, n. (%)	10 (100)	17 (100)
CK (UI/L), median (IQR)	101 (58-647)	1984 (974-3717)*
MMT-8 at onset (0-80), mean (±SD)	71 (±9)	68 (±8)
Subset DM, nr. (%)		
Classic DM	7 (70)	17 (100)
HDM	1 (10)	0 (0)
AMD	2 (20)	0 (0)
Ro52, n. (%)	3 (30)	1 (5.9)
Heliotrope rash, n. (%)	8 (80)	7 (41.2)
Gottron's papules/sign, n. (%)	8 (80)	14 (82.4)
Facial rash, n. (%)	6 (60)	13 (76.5)
V-sign, n. (%)	7 (70)	13 (76.5)
Shawl sign, n. (%)	4 (40)	1 (5.9)*
Mechanic's hands, n. (%)	0 (0)	1 (5.9)
Periungual telangiectasia, n. (%)	4 (40)	9 (52.9)
Digital ulcers, n. (%)	0 (0)	2 (11.8)
Calcinosis, n. (%)	1 (10)	2 (11.8)
Itchy skin, n. (%)	6 (60)	2 (11.8)**
ILD, n. (%)	3 (30)	0 (0)*
Arthritis, n. (%)	2 (20)	3 (17.6)
Cancer, n. (%)	2 (20)	2 (11.8)
Dysphagia, n. (%)	4 (40)	9 (52.9)
Raynaud phenomenon, n. (%)	0 (0)	3 (17.6)
Prednisone, n. (%)	10 (100)	17 (100)
Azathioprine, n. (%)	5 (50)	10 (58.8)
Methotrexate, n. (%)	6 (60)	13 (76.5)
Mycophenolate mofetil, n. (%)	2 (20)	3 (17.6)
Cyclophosphamide, n. (%)	0 (0)	0 (0)
Hydroxychloroquine, n. (%)	0 (0)	3 (17.6)
Cyclosporine, n. (%)	1 (10)	0 (0)
Rituximab, n. (%)	1 (10)	3 (17.6)
Intravenous immunoglobulin, n. (%)	1 (10)	1 (5.8)
Lines of DMARDs during f/u, median (IQR)	1 (1-3)	2 (1-3)

ADM: amyopathic DM; CK: creatine phosphokinase; DM: dermatomyositis; f/u: follow-up; HDM: hypomyopathic DM; ILD: interstitial lung disease; MMT-8: manual muscle test 8; SD: standard deviation. *p<0.05; **p<0.01; ***p<0.001 *vs*. anti-SAE.

Results

Our cohort included 92 DM patients, with 10 (10.9%) testing positive for anti-SAE antibodies and 17 (18.5%) for anti-Mi2 antibodies. Table I reports the main demographic and clinical features in ani-SAE and anti-Mi2 DM. Both groups were predominantly female (90% in anti-SAE and 94.1% in anti-Mi2). No significant differences were found in age of onset and diagnosis.

At onset, cutaneous involvement was the initial sign of disease in all patients with anti-SAE antibodies and in 15 (88.2%) of the patients with anti-Mi2 antibodies. Clinically, the main skin manifestations were similar between the two groups. However, a majority

of patients with anti-SAE experienced cutaneous itching (60% in anti-SAE *vs*. 11.8% in anti-Mi2, $p<0.01$) and shawl-sign was also more frequently observed in patients with anti-SAE DM (40% in anti-SAE *vs*. 5.9%, in anti-Mi2, $p<0.05$). Muscle involvement was present at onset in 3 (30%) of the anti-SAE patients and in 13 (76.5%) of the anti-Mi2 patients ($p<0.001$). During follow-up, both groups predominantly showed classic DM with muscle weakness (70% for anti-SAE *vs*. 100% for anti-Mi2) and no clinical difference in muscle impairment assessed by MMT-8 (mean ± SD: 71±9 for anti-SAE *vs*. 68±8 for anti-Mi2). However, anti-Mi2 patients demonstrated higher muscle myolysis, as indicated by maximum CK levels (median [IQR]: 1984 [974-3717] UI/L in anti-Mi2 *vs*. 101 [58-647] UI/L in anti-SAE; $p<0.05$). Regarding the muscle biopsies, 6 were analysed from patients with anti-SAE antibodies (Table II). These biopsies generally showed features compatible with a diagnosis of DM. In fact, 5 (83.3%) displayed perifascicular atrophy, and 4 (66.7%) showed increased MHC-I expression on myofibres. When comparing histological characteristics between the two cohorts (6 muscle biopsies from anti-SAE and 13 muscle biopsies from anti-Mi2), no statistically significant differences were observed. However, when assessing the percentage of fibres in necrosis or degeneration, these were more predominant in the anti-Mi2 positive patient cohort (mean% ± SD: 5.9±3.2 in anti-Mi2 *vs*. 1.5±1.7 in anti-SAE, $p<0.001$).

In terms of other organ involvements, 40% of anti-SAE patients showed ILD (2 organising pneumonia, 1 non-specific interstitial pneumonia with rapidly progressive course) compared to 0% in the anti-Mi2 group (Table I). No difference in treatment administered was observed in the two groups.

Median (IQR) follow-up was 21 (10-43) months in anti-SAE and 48 (23-88) in anti-Mi2 groups. The five-year survival rate was similar in both cohorts, being 66.7% in patients with anti-SAE antibodies and 82.4% in patients with anti-Mi2 antibodies (log-rank: 1.120, $p=0.29$) (Fig. 1). Three deaths were reported in each cohort. In the anti-SAE cohort, one death was due to the progression of ILD, one to a major cardiovascular event, and one from an unknown cause. In the anti-Mi2 cohort, one death was due to the progression of breast cancer, one due to a major cardiovascular event, and one due to an infectious event.

Table II. Histologic characteristics of antiSAE1/2 and anti-Mi2 muscle biopsies.

	Anti-SAE1/2 (6 pts)	Anti-Mi2 (13 pts)
Age at diagnosis, year, mean (±SD)	58 (±24)	56 (±27)
Gender, n. (%) (M/F)	1/5 (16.7/83.3)	1/12 (7.7/92.3)
Detection of myofibre in degeneration/necrosis, n. of patients (%)	3 (50)	11 (84.6)
Degeneration/necrosis, mean % of myofibres (±SD)	1.5 (±1.7)	5.9 (±3.2)*
Detection of perifascicular atrophy, n. of patients (%)	5 (83.3)	8 (61.5)
Detection of MAC on fibres, n. of patients (%)	1 (16.7)	8 (61.5)
Detection of MAC on capillaries, n. of patients (%)	2 (33.3)	9 (69.2)
Detection of MHC-I expression on sarcolemma, n. of patients (%)	4 (66.7)	10 (76.9)
Detection of CD4 infiltrates, n. of patients (%)	2 (33.3)	2 (15.4)
Detection of CD8 infiltrates, n. of patients (%)	1 (16.7)	2 (15.4)
Detection of CD20 infiltrates, n. of patients (%)	2 (33.3)	3 (23.1)
Detection of CD68 infiltrates, n. of patients (%)	4 (66.7)	10 (76.9)
Detection of regenerating fibres, n. of patients (%)	3 (50)	9 (69.2)

CK: creatine phosphokinase; MAC: membrane attack complex; MHC-I: major hhistocompatibility complex type I.
*$p<0.01$ *vs*. anti-SAE.

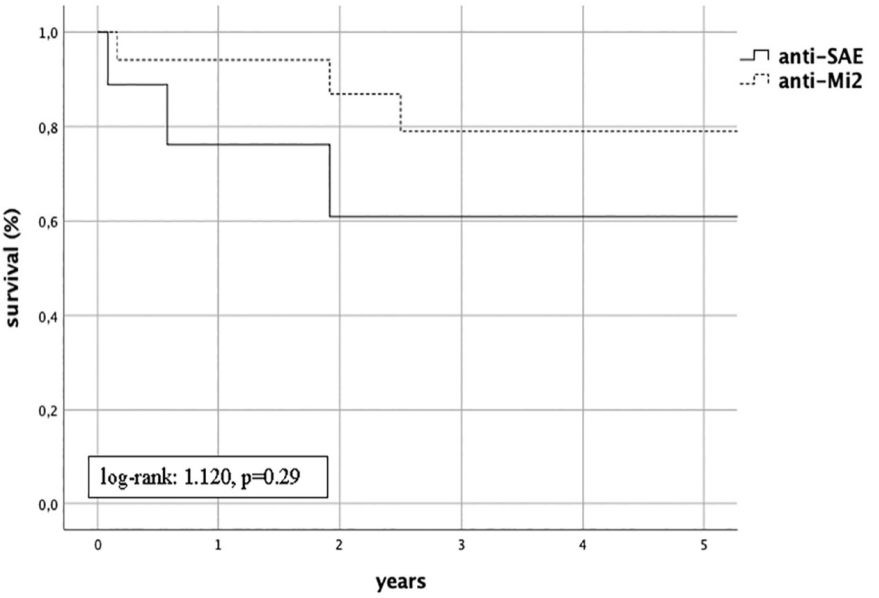

Fig. 1. Five-year survival of anti-SAE1/2 and anti-Mi2 population.

Discussion

In our cohort of 92 DM patients, those with anti-SAE antibodies predominantly exhibited the classic cutaneous manifestations typical of the disease. Compared to a parallel cohort of anti-Mi2 patients, the anti-SAE group notably showed a higher incidence of itching, shawl sing and pulmonary involvement. However, the severity of muscle involvement was less pronounced in the anti-SAE group compared to the anti-Mi2 group, despite a similar MMT-8 score was measured. This does not surprise us, as only a moderate correlation has been found between MMT values and CK (18). This finding aligns with our previous work, which showed that DM patients with anti-Mi2 antibodies experience greater myolysis, characterised by higher prevalence of muscle necrosis/degeneration (5). In

Table III. Reported cohorts of adult anti-SAE–Associated myositis.

Variables	Fornaro *et al.*	Albayda *et al.* (8)	Tarricone *et al.* (20)	Betteridge *et al.* (10)	Ge *et al.* (9)	Peterson *et al.* (19)	Demortier *et al.* (11)	Muro *et al.* (12)
Cohort number	10	19	5	11	12	19	49	65
Disease	DM 100%	DM 100%	DM 100%	DM 100%	DM 100%	DM 100%	DM 100%	DM 100%
Female, n (%)	90%	74%	NR	64%	75%	73.7%	83.7%	57.1%
Age, mean	60 y	53.3 y	NR	61.2 y	59.1 y	55.4 y	53 y	65 y
Race	Caucasian 100%	Caucasian 68%	NR	Caucasian 100%	Asian 100%	African/American: 21.1% Caucasian: 36.8% Hispanic/Latino: 36.8% Other 5.3%	NR	Asian 100%
Heliotrope rash, n. (%)	80%	95%	40%	82%	75%	100%	71.4%	43%
Gottron's papules/sign, n. (%)	80%	84%	100%	82%	75%	100%	77.5%	100%
V-sign, n. (%)	70%	84%	NR	43%	50%	NR	77.5%	71%
Shawl sign, n. (%)	40%	84%	NR	43%	50%	NR	57.1%	43%
Mechanic's hands, n. (%)	0%	37%	NR	NA	50%	NR	NR	43%
Periungual telangiectasia, n. (%)	40%	84%	20%	100%	NA	NR	77.5%	83%
Calcinosis, n. (%)	10%	11%	NR	NA	NA	NR	10.2%	0%
Muscle involvement, n. (%)	80%	79.9%	100%	100%	67%	57.9%	83.7%	86%
ILD, n. (%)	30%	77%	0%	18%	64%	57.1%	21%	57%
Arthralgia and/or arthritis, n. (%)	20%	42%	0%	18%	NR	NR	24.5%	0%
Cancer, n. (%)	20%	10%	20%	18%	18%	6.3%	16.3%	57%
Dysphagia, n. (%)	40%	42%	0%	78%	64%	60%	38.8%	43%

ILD: interstitial lung disease; NR: not reported.

our current study, although muscle biopsies in anti-SAE patients displayed classic inflammatory myopathy features like perifascicular atrophy and increased MHC-I expression, there was a lower frequency of degenerative necrotic fibres compared to anti-Mi2 patients. This is indirectly confirmed by the lower serum CK levels observed in the anti-SAE group. Our data on muscle biopsy corroborate the findings of Demortier *et al.* (11), who highlighted perifascicular atrophy (53.3%) and diffuse MHC-I immunostaining (60%) as the main findings in 15 biopsies from anti-SAE patients.

In the literature, anti-SAE antibodies are highly associated with DM (3). The frequency of anti-SAE in DM cohorts ranges from 2 to 10% (8-11, 19). In Table III, we present a summary of major cohorts of anti-SAE DM, providing an overview of the key characteristics and findings from these studied groups (8-12, 19, 20). Generally, this form of DM is characterised by a greater prevalence of pulmonary involvement, with incidences ranging from 20 to 70% of cases, as shown in Table III (8, 10, 12). Pulmonary involvement is variable in DM according to different MSA and is mainly associated with the anti-MDA5 subset, where it often presents as non-specific interstitial pneumonia and carries a high risk of developing into rapidly progressive ILD (21). It is important to emphasise that the primary type of ILD reported in anti-SAE DM is organising pneumonia (22), typically characterised by a chronic course and a favourable prognosis (23, 24). However, we observed a case of rapidly progressive ILD that led to death. In our study, the severity of skin involvement could not be assessed, although clinical cases suggest more severe cutaneous involvement in this DM subset (11, 25). Typical DM cutaneous manifestations, such as Gottron's sign and heliotrope rash, are highly prevalent in patients positive for anti-SAE antibodies, often reported in case series in more than 75% of cases (8-11). In our series, we found a higher incidence of the shawl sign compared to patients with anti-Mi2 antibodies, and a high incidence of this cutaneous sign was also observed in other cohorts, as indicated in Table III (8-12). Additionally, a small Japanese case series has identified a distinct rash in these patients, termed "angel wings," characterised by erythema over the shoulder and lumbar regions, sparing the inferior border of the scapular regions (26). We were unable to assess the presence of this feature in all patients as it was not recorded retrospectively. This sign should likely be distinguished from the shawl sign in future studies. As noted in other case reports, this subset often associates with intense cutaneous itching (25), which can be exacerbated by the use of hydroxychloroquine (27, 28). The data on cancer risk in patients with anti-SAE DM remains unclear, with an average incidence reported around 10-20% of cases. Only Muro *et al.* have reported an extremely high incidence of cancer, at 57% (12). Although this seems globally lower than in patients with TIF1gamma (29), it should not be overlooked. A recent rheumatology consensus on cancer risk in idiopathic inflammatory myopathies (IIMs) has classified DM, regardless of the autoantibody subset, as a high-risk factor that requires comprehensive neoplastic screening (30).

Lastly, dysphagia has been notably prevalent in all cohorts of anti-SAE DM, reported in the majority of studies as affecting over 40% of patients and sometimes necessitating gastrostomy placement (10, 26). Consequently, this symptom, with its profound impact on prognosis, must be carefully investigated in patients with anti-SAE antibodies. Our study has limitations, including a small sample size and the absence of standardised clinimetric evaluations, such as the Cutaneous Dermatomyositis Disease Area and Severity Index,

which are crucial for assessing therapy responses. Additionally, our findings are compared exclusively with anti-Mi2 DM, the most represented cohort in our population and characterised by the classic DM subset. Further investigation into the differences between various autoantibody subsets of DM will require additional characterisations for each antibody through multicentric studies. Finally, MSAs in our study were confirmed using a commercial line blot. Although this method has good sensitivity and specificity (31), it is not the gold standard for MSA research, which is immunoprecipitation.

In conclusion, this study provides additional data about this DM subset in an Italian cohort. It confirms that anti-SAE DM, though less common than other variants, represents a disease subset characterised by classic cutaneous involvement, often associated with itching, milder muscle involvement, but with potential pulmonary involvement that should always be investigated in these patients.

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