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A North American Cohort of Anti-SAE Dermatomyositis: Clinical Phenotype, Testing, and Review of Cases

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Objective. Antibodies against the small ubiquitin-like modifier (SUMO) activating enzyme (SAE) are one of the rarer specificities associated with dermatomyositis (DM). The purpose of this study is to describe the clinical characteristics of patients with anti-SAE autoantibodies in a North American cohort and to ascertain cancer prevalence. We also describe the performance characteristics of the line blotting (Euroimmun) method for antibody detection compared with an immunoprecipitation-based assay.

Methods. Sera from 2127 patients suspected of having myositis were assayed for myositis-specific autoantibodies using the Euroimmun platform. Those positive for SAE autoantibodies were assayed by a second method (immunoprecipitation) for confirmation. Only those cases positive by both methods were taken as definite cases of anti-SAE–positive DM. Chart reviews of these patients were completed to obtain information on clinical characteristics, cancer history, and treatment.

Results. Forty-three of 2127 sera were anti-SAE autoantibody positive by Euroimmun (≥15 units, +); of these, only 19 were confirmed positive by immunoprecipitation. All 19 cases had skin involvement and varying presentations of muscle, lung, and joint disease. Cancer occurred coincident with DM in two patients, and cancers were detected more than 5 years from symptom onset in three patients. In a population of suspected inflammatory myositis, a higher cutoff on line blot testing (≥36 units, ++) yielded better agreement with immunoprecipitation methods.

Conclusion. SAE autoantibodies associate with a clinical phenotype of DM, which most commonly presents with a rash first, followed by muscle involvement and varying extramuscular involvement. As coincident cancer was seen in anti-SAE–positive DM, judicious malignancy screening may be warranted.

INTRODUCTION

The discovery of myositis-specific and associated autoantibodies has been a great advance in the field of myositis, leading to improved diagnostics and better phenotyping of disease subgroups. Several dermatomyositis (DM)-specific autoantibodies have been described, and most have been associated with characteristic clinical phenotypes, treatment responses, and/or cancer (1,2). Included in this group are autoantibodies against the small ubiquitin-like modifier (SUMO) activating enzyme (SAE), which were first reported in 2007 by Betteridge et al. SAE is an autoantigen made up of two subunits, SAE1 (40 kDa) and SAE2 (90 kDa) (3). SAE controls the action of SUMO, which is linked to many processes involving chromatin. SUMO modification or sumoylation often works as a signal to facilitate protein–protein interactions on chromatin, influences enzyme activity and changes in protein

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SIGNIFICANCE & INNOVATIONS

- We describe the North American phenotype of anti-SAE dermatomyositis, one of the rarer dermatomyositis-specific antibodies, and show the prevalence of skin, muscle, lung, joint, and systemic features. Most patients initially present with a skin rash alone, but mild muscle disease can follow within several months.
- We elucidate the test performance of an increasingly used multiplex assay (Euroimmun), compare it with the gold standard of immunoprecipitation for the SAE antibody, and show that higher antibody cutoffs yield better agreement.

subcellular localization, and can enhance chromatin accessibility and gene activation (4).

Since the initial report of anti-SAE autoantibodies in two patients with DM, several other descriptions have been added from different cohorts with a prevalence ranging from less than 1% to 8% (5–11). Antibodies against SAE have been reported in DM cases exclusively, mostly in adult patients. The typical phenotype is usually that of widespread skin involvement with amyopathic or mild muscle involvement. The association with interstitial lung disease (ILD), dysphagia, other extramuscular involvement, and cancer has varied per cohort.

Although there has been increasing appreciation of the clinical manifestations of this autoantibody subgroup, the rarity of this antibody and differences seen in clinical presentations between cohorts render a need for further study. To date, there are little data from North America (10). This study was conducted to *1*) describe the clinical characteristics of patients with SAE autoantibodies in our single-center cohort, *2*) ascertain cancer prevalence, and *3*) compare anti-SAE autoantibody readouts obtained with a line immunoassay widely used for myositis antibody screening with the gold standard of immunoprecipitation. We also review the available literature on reported SAE cases.

PATIENTS AND METHODS

Patients and data collection. Patients seen at the Johns Hopkins Myositis Center in Baltimore, Maryland, were consented and enrolled into a longitudinal cohort study approved by the Johns Hopkins Institutional Review Board. Sera from 12 healthy individuals (used as control subjects in the immunoprecipitation assays) were obtained with informed consent. Banked sera from 2127 patients evaluated between May 2002 and January 2018 were tested for myositis-specific autoantibodies using line blotting per the manufacturer's protocol (Euroline Myositis Profile 4; Euroimmun). This cohort includes all patients suspected of having myositis at first visit, regardless of final diagnosis. Anti-SAE autoantibody status was assigned per the manufacturer's recommendations, as follows: negative = 0 to 7 units (U); borderline = 8 to 14 U; weak positive (+) = 15 to 35 U; moderate positive (++) = 36 to 70 U; and strong positive (+++) = 71 to 255 U. As per Euroimmun, both antigens (SAE1 and SAE2) were tested with a panel of 26 patients with myositis. All patients were positive for SAE1 antibodies, and eight were positive for SAE1 and SAE2 antibodies. There were no patients who had exclusively SAE2 antibodies. Therefore, only SAE1 is included on the Euroline, as it captured all cases of SAE. Those sera that tested positive for SAE autoantibodies by line blotting (≥15 U; n = 43) were then subjected to a confirmatory immunoprecipitation assay (described below). Only those patients who were positive for SAE autoantibodies by both assays were included for analysis (n = 19).

Immunoprecipitation assay to confirm SAE1 autoantibody status. Antibodies against SAE1 were detected by immunoprecipitation with ^{35}Smethionine-SAE1 generated by in vitro transcription/translation (IVTT) per the manufacturer's protocol (Promega) using full-length complementary DNA purchased from Origene. Immunoprecipitations were performed as follows: 1 µl of IVTT product was added to 1 ml of ice-cold lysis buffer (20 mM Tris pH 7.4/ 150 mM NaCl/1 mM EDTA pH 7.4/ 1% Nonidet P40 and a protease inhibitor cocktail). Serum (1 µl) was added to each, and the mixture was rotated (1 hour; 4°C) before adding 30 µl protein A agarose beads (Pierce) for 25 minutes at 4°C. The immunoprecipitates were subsequently washed, then electrophoresed on 10% sodium dodecyl sulfate–polyacrylamide gels and visualized by autoradiography. A strongly positive serum was included as a reference in each dataset; all immunoprecipitates were quantitated by densitometric scanning and were normalized to the reference included in each set. Sera from 12 healthy control subjects were also assayed by immunoprecipitation and quantitated as described above. These data were used to set the cutoff for antibody positivity (mean optical density value of the healthy controls + two SDs). Data from a representative set of immunoprecipitations are shown in Figure 1.

Chart review. A retrospective chart review was carried out for the 19 patients to ascertain demographics, clinical and physical examination features, ancillary testing, treatment, and cancer history. Physical examination findings were taken from the initial visit. In the case of ancillary tests, positive results closest to the time of the visit and maximal values (for muscle enzymes) were recorded. Clinical course was followed for all available visits to determine the development of additional symptoms. DM rashes were recorded as present or absent for each type of rash. Muscle involvement was defined as weakness on examination. Strength testing of the arm abductors and hip flexors was obtained on initial examination using manual muscle testing and was converted to the modified 10-point scale used by the International Myositis Assessment and Clinical Studies group (12). In the case of normal strength on examination, myopathy was defined by any of the following: the presence of positive findings (irritable myopathy) on

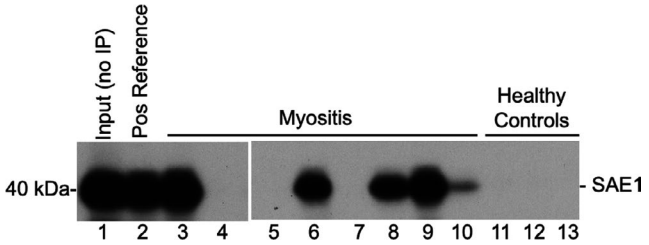

Figure 1. Immunoprecipitation (IP) assay to confirm small ubiquitin-like modifier activating enzyme 1 (SAE1) autoantibody status. Antibodies against SAE1 were detected by IP with ^{35}Smethionine-SAE1 generated by in vitro transcription/translation (IVTT IP) as described in the METHODS. Lane 1, input IVTT product (no IP); Lane 2, IP with a positive reference serum; Lanes 3-10, IPs performed with myositis sera; and Lanes 11-13, IPs performed with sera from healthy control subjects. The myositis sera in Lanes 3, 6, 8, 9, and 10 have antibodies against SAE1.

electromyography (EMG), edema on muscle magnetic resonance imaging (MRI) (defined as increased intramuscular signal on short tau inversion recovery or T2-weighted images), or an elevated creatine phosphokinase (CPK) level above the upper limit of normal. No muscle biopsies were available. ILD was defined as the presence of inflammatory or fibrotic opacities on chest computed tomography (CT). Available CT chest images were reviewed by a thoracic radiologist (CTL) and pulmonologist (SKD) with expertise in ILD, and interstitial findings were adjudicated. Arthritis was defined as objective joint swelling or tenderness to palpation noted on examination. Clinical outcome was determined by chart review, with designation as "improved/stable" if clinical parameters (muscle and skin/extramuscular disease) had improved on treatment as ascertained by the clinician, designation as "chronic" if the patient continued to have active disease by the last available follow-up visit despite escalation of therapy, designation as "remission" if the patient had no signs of active disease and was off immunosuppression, and designation as "death" if patient was expired on follow-up. The type and number of medications used by each patient were also recorded. History of cancer was ascertained from the chart, including cancer type, onset relative to myositis, and outcome.

Statistical analysis. Statistical analyses and descriptive statistics were performed using Stata version 14. The presence of clinical features was quantified and expressed as a percentage of the total group. For continuous variables such as CPK, mean and median values were obtained with SDs. Cohen's κ was used to assess the agreement between different antibody methodologies.

RESULTS

Banked sera from 2127 patients (1844 with myositis) consecutively evaluated at the Johns Hopkins Myositis Center (May 2002-January 2018) were tested for myositis antibodies using line blotting per the manufacturer's protocol (Euroline myositis panel, Euroimmun). Forty-three patients were found to have SAE autoantibodies by line blotting (≥15 U was used as the cutoff for assigning a positive antibody status, per the manufacturer's guidelines). Of these, anti-SAE positivity was confirmed in 21 patients using immunoprecipitation. Of these 21 patients, two were found to have low positive results by both line blot (+ units) and immunoprecipitation. A chart review revealed these two cases to be a patient with juvenile DM with anti-RNP and anti-Ro antibodies and a patient with DM associated with anti-TIF1γ antibodies (assayed through the Oklahoma Medical Research Foundation panel). Both were not on immunosuppression at the time of enrollment into the cohort. These borderline cases were therefore not included in the final analysis of confirmed anti-SAE cases for purposes of describing a clear phenotype.

Of the original 43 patients, 22 were positive by line blotting but negative by immunoprecipitation (Table 1). Of these 22 patients, only two were moderately/strongly positive by line blotting, whereas the remainder were all in the low positive (+) range. A chart review to confirm disease phenotype showed clinician-ascertained diagnoses of inclusion body myositis (n = 6); polymyositis (n = 3) necrotizing myopathy with HMG-coA reductase (HMGCR) antibodies (n = 3); antisynthetase syndrome (n = 3); other DM with antibodies to NXP2, TIF-1γ, and Ro (n = 3); and other muscle disease with possible metabolic or mitochondrial myopathy (n = 4). The two cases that were moderately/strongly positive by line blotting both had necrotizing myopathies with anti-HMGCR antibodies.

Table 1 shows the comparison of SAE testing using Euroimmun with the gold-standard method of immunoprecipitation, showing good agreement between the two tests at moderately to strongly positive levels on Euroimmun. Using higher antibody cutoffs (≥36) yields a sensitivity of 100% and a specificity of 88%. At a higher cutoff (≥71), improvement in specificity is gained at the cost of sensitivity. Both thresholds (≥36) and (≥71) yield a κ of more than 0.80.

Clinical characteristics of the 19 patients with DM with SAE autoantibodies are detailed in Table 2. These patients were mostly Caucasian and female. Median time from onset of symptoms to evaluation at the Myositis Center was 12 months (ranged from 3 to 96 months). All patients had skin involvement, with more than half initially presenting with a rash alone. The most common rashes seen were the typical Gottron papules, shawl sign, periungual

Table 1. Performance characteristics of Euroimmun versus IP

Autoantibody (Euroimmun Versus IP)	Cutoff ≥15 (+)	Cutoff ≥36 (++)	Cutoff ≥ 71 (+++)
Positives on Euroimmun, n	43	22	17
Sensitivity	NA	100	89
Specificity	NA	88	100
κ	NA	0.86	0.90

IP, immunoprecipitation; NA, not applicable; +, weak positive; ++, moderate positive; ++, strong positive.
Number of patients tested with both assays: 43.
Number of IP positive results: 19.

Table 2. Patient demographics and clinical characteristics

Patient Characteristics (N = 19)	Results
Sex, female, n (%)	14 (74)
Age, mean (SD), y	53.3 (11.32)
Race, Caucasian, n (%)	13 (68)
First presenting symptom, n (%)	
Rash only	11 (58)
Rash and muscle	7 (37)
Muscle only	1 (5)
Gottron papules, n (%)	18 (95)
Heliotrope rash, n (%)	16 (84)
V sign, n (%)	16 (84)
Shawl sign, n (%)	16 (84)
Periungual erythema, n (%)	16 (84)
Gottron sign, n (%)	14 (74)
Sleeve sign, n (%)	13 (68)
Diffuse erythema, n (%)	8 (42)
Mechanic's hands, n (%)	7 (37)
Scalp involvement, n (%)	5 (26)
Calcinosis, n (%)	2 (11)
Subjective weakness, n (%)	10 (53)
Weakness on examination, n (%)	8 (42)
Arm abductor strength, mean (SD)	9.2 (1.4)
Hip flexor strength, mean (SD)	8.7 (2.3)
Associated antibodies, n (%)	
ANA	9 (47)
Ro	2 (10)
RF	1 (5)
CCP	1 (5)
PL-12	1 (5)
NXP2	1 (5)
CPK, mean (SD)	255.4 (367.1)
CPK, median (range)	107 (29-1277)
Aldolase, mean (SD)	8.3 (3.29)
Aldolase, median (range)	7.9 (4.2-19.3)
MRI with edema, n (%)	9/15 (60)
Myopathic findings on EMG, n (%)	7/14 (50)
Arthritis, n (%)	8 (42)
ILD, n (%)	7/9 (77)
Dysphagia, n (%)	8 (42)
Raynaud, n (%)	5 (26)
Weight loss, n (%)	6 (32)
Fever, n (%)	1 (5)
Malignancy, n (%)	5 (26)
Cancer-associated DM*	2 (10)
Treatments used, n (%)	
Prednisone	15 (79)
IVIG	10 (53)
Methotrexate	10 (53)
Rituximab	6 (32)
Mycophenolate mofetil	5 (26)
Hydroxychloroquine	5 (26)
Azathioprine	2 (11)
Etanercept	2 (11)
Tofacitinib	1 (5)
Tacrolimus	1 (5)
Sulfasalazine	1 (5)
Outcome, n (%)	
Improvement	8 (42)
Chronic active	7 (37)
Death	1 (5)
Remission	3 (15)

CPK, creatine phosphokinase; DM, dermatomyositis; EMG, electromyography; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.
* Cancer-associated DM was defined as cancer detected within 3 years of DM onset.

erythema, V sign, and Gottron sign (in order of decreasing frequency). No skin ulcerations were seen. More than one-third of patients presented with diffuse erythema, and calcinosis was rare. In the two patients who had calcinosis, this was observed in more than one location for both (buttocks, thighs, and upper arm). Although no characteristic rash pattern was noted, the rashes could be quite severe (Figure 2A). The presence of muscle involvement was determined from symptom onset and throughout follow-up in our center. In our series, all cases of myopathy were captured at the initial visit given the length of time to evaluation at our center, and no further incident cases were seen on follow-up. In those in whom muscle disease occurred later than skin disease, this ranged from an interval of 2 to 17 months, with a mean of 7 months. Only half of the patients complained of subjective weakness, with less than half manifesting with a decrease in strength on examination. Despite this, two additional cases were found to have edema on MRI (Figure 2D), and three more were found to have both irritable myopathy on EMG and edema on MRI in the absence of weakness. Muscle enzymes were usually within normal limits, with only four patients presenting with elevated CPK and six presenting with elevated aldolase. None of our patients underwent a muscle biopsy. Inflammatory arthritis was present in less than half of the cases (Figure 2B). Of the nine patients who had an available CT scan for review, two had normal lungs, three had ILD findings that could be classified as an inflammatory pattern (two with organizing pneumonia pattern), and two patients had a fibrotic pattern. The other two patients had nonspecific interstitial changes that did not fulfill criteria for a classifiable ILD pattern, and findings are detailed in Table 3. Nodular pulmonary opacities (including solid and ground glass nodules) were seen in the majority of patients (Figure 2C). Pulmonary function tests were normal for all these patients except for two who had mild restriction. Of note, ancillary tests (MRI, CT, EMG, and pulmonary function tests [PFTs]) were completed based on need and availability and therefore were not uniformly obtained.

Only two patients were treatment naive at the time of enrollment into the cohort. Most patients were on prednisone and at least one more immunosuppressant, including rituximab in one patient (initiated 3 months before the visit). Most patients had a chronic course that required multiple medication changes (median 3.5; ranged from 1 to 5). Methotrexate and intravenous immunoglobulin (IVIG) were the most commonly used medications in our cohort together with steroids (highest prednisone dose of 80 mg). Patients were followed for an average of 3.8 years (up to 8 years), with two patients seen only once. These two patients were clinically stable and chose not to follow-up longitudinally given their distance from our center. Of the three patients in remission as of the time of the last visit, two were off all medications (9 months and 3 years, respectively), whereas the last remains on 200 mg hydroxychloroquine because of preference (>6 years).

There were five cases of cancer in our cohort of anti-SAE–positive patients. The first was a case of poorly differentiated

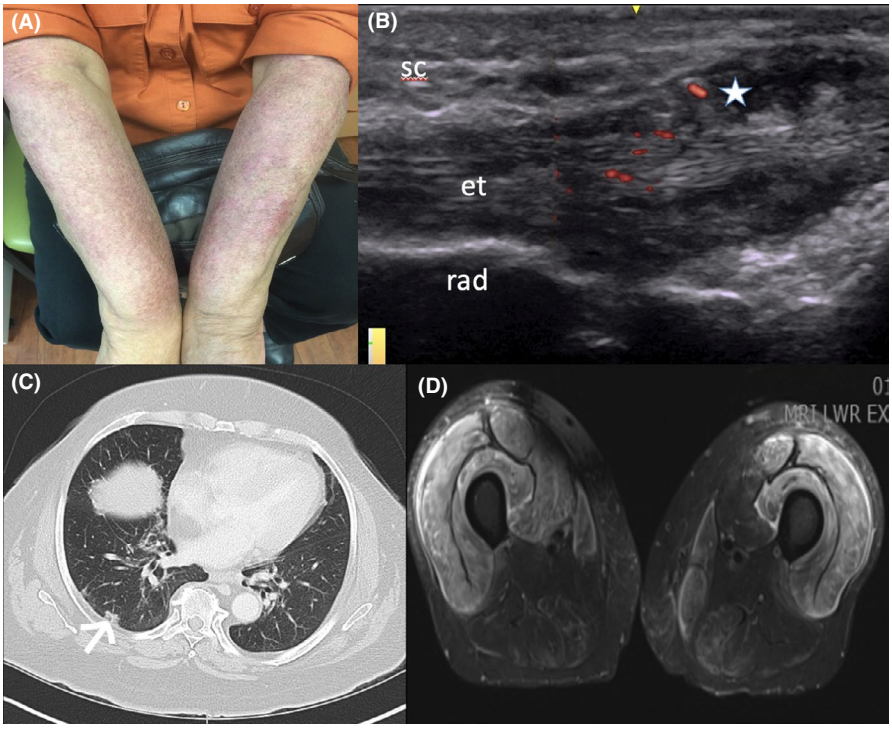

Figure 2. Clinical features of anti–small ubiquitin-like modifier activating enzyme dermatomyositis. **A**, Erythematous plaques over the forearms. **B**, Tenosynovitis of the wrist extensors with Doppler signal on ultrasound. Star indicates fluid within tendon sheath. **C**, Computed tomography chest image showing scattered ground glass opacities, increased peripheral interstitial lung markings, and pleural-based nodularities. Arrow indicates ground glass nodule. **D**, Short τ inversion recovery magnetic resonance image of the thighs showing marked muscle and fascial edema in the anterior thigh compartment; corresponding creatine phosphokinase on the same day was 80. et, extensor tendon; rad, radius; sc, subcutaneous tissue.

carcinoma (66-year-old woman) found within 3 months of a diagnosis of DM. The patient had presented with a rash and weakness initially, and a work-up for cancer was commenced as part of an overall evaluation. This was metastatic upon discovery, and the patient expired less than 1 year from diagnosis. The second case was of a moderately differentiated colon adenocarcinoma (60-year-old man) diagnosed contemporaneous with DM. The patient had been hospitalized for symptoms of weakness and joint pain, with a CT showing thickening of the colon. The patient underwent colon resection and has been cancer free with stable

Table 3. Pulmonary findings in nine patients with available chest CT

Subject	CT Findings	Craniocaudal/Axial Distribution	Nodular Pulmonary Opacities	PFTs
1	Fibrotic pattern: reticulation, traction bronchiectasis, and bronchiolectasis	Lung bases; peripheral	Multiple pleural-based nodules	Mild restrictive defect
2	Inflammatory pattern: multifocal consolidations (organizing pneumonia) and pneumomediastinum*	Diffuse, peripheral and peribrochovascular	Multiple pulmonary nodules	Mild restrictive
3	Normal lungs	NA	Multiple pulmonary nodules	Restrictive with decreased DLCO
4	Fibrotic pattern: reticulation, traction bronchiectasis, and bronchiolectasis	Lung bases; peripheral	Multiple ground glass nodules	Normal
5	Normal lungs	NA	None	Normal
6	Unclassified pattern: minimal foci of scarring	Lung bases; peripheral	None	Normal
7	Inflammatory pattern: irregular consolidation (organizing pneumonia)	Lung bases, dependent lower lobes; peripheral	Multiple pleural-based nodules	Normal
8	Unclassified pattern: minimal foci of fibrosis and moderate emphysema	Lung bases; peripheral	Multiple pulmonary nodules	None
9	Inflammatory pattern: multifocal subpleural ground glass opacities	Lung bases; peripheral	Multiple ground glass nodules	None

CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; NA, not applicable; PFT, pulmonary function test.
* Repeat CT scan 3 years later with minimal residual findings.

disease for more than 4 years. The other three cases were of papillary renal cell cancer (63-year-old woman) occurring 5 years after the onset of DM, breast cancer (59-year-old woman) occurring 7 years after diagnosis, and an Epstein-Barr virus-positive B cell lymphoproliferative disorder in the maxilla (61-year-old woman) found 5 years after the diagnosis of DM. For these three cases, cancer and DM outcomes are either stable or in remission at last follow-up.

DISCUSSION

In our well-characterized single-center longitudinal cohort, the SAE autoantibody was found to be exclusively present in patients with skin involvement, often presenting with subjectively mild muscle weakness, or muscle involvement that develops later in the course of the disease. This is similar to descriptions from other groups (2,3,5,7–10,13–16). We also found the typical DM rashes to be prevalent. Diffuse erythema has been proposed to be a typical skin finding in patients with SAE autoantibodies but has notably been described only in Asian cohorts (8,14,16). In our experience, anti-SAE–positive patients often presented with severe skin rashes that could be quite pruritic. Muscle involvement was detected even when patients denied weakness, suggesting that a rigorous screening for muscle involvement should be performed. As muscle disease could ensue after skin disease (up to 17 months after), more longitudinal follow-up is necessary to confirm the true prevalence of each manifestation.

A significant proportion of patients may initially present as a clinically amyopathic DM (11/19 in our cohort). However, in contrast to other clinically amyopathic DM subgroups such as DM with MDA-5 antibodies, the ILD in SAE disease is mild and, in fact, may be missed (Figure 2C). In our cohort, complaints of dyspnea or cough were rare, and PFTs showed normal findings or mild restrictive defects. Multiple reports have described preserved lung function despite findings of ILD (usually of nonspecific interstitial pneumonitis) on CT (8,15,17). Systematic review of the CT imaging in our cohort revealed that most of them do not fit a classical pattern of ILD and do not appear to have physiologic consequences of the observed changes. Of the nine patients reviewed, six had a pattern including peripheral nodules (Figure 2C). This is not a pattern previously described for this patient population. In light of the concern for malignancy, it is notable that none of these patients had or developed lung malignancies or lung metastases. Although these lesions were not biopsied, it might be hypothesized that these reflect an inflammatory process in the lung that does not conform to standard ILD radiographic patterns. Awareness of this imaging finding may help to inform decisions regarding biopsy in patients with lung nodules and anti-SAE antibodies.

One of the other notable findings in our cohort was the presence of inflammatory arthritis and tenosynovitis (Figure 2B), with the development of joint contractures in at least two patients. This required more therapies directed at the joint manifestations, such as sulfasalazine, etanercept, and tofacitinib. Dysphagia, as well as Raynaud and other systemic symptoms, occurred similarly as in other studies.

To date, there are approximately 80 cases reported in various small cohorts (summarized in Table 4), with a recent multicenter European study reporting an additional 42 cases with an overall prevalence of 2.6% (6). As has been noted in other antibody specificities, there may be a difference in presentation depending on the ethnic background (18,19). A comparison of Eastern and Western case descriptions suggests that there is a higher risk for diffuse erythema, dysphagia, ILD, and malignancy in Eastern groups (14). The Johns Hopkins cohort used in this study more closely resembles Western cohorts given our predominantly Caucasian population. It is noteworthy that the two patients in our study cohort who developed calcinosis with severe and refractory skin disease were both African American. Although the prevalence may vary, disease manifestations of skin, muscle, lung, joint, dysphagia, and infrequent systemic symptoms have been consistent across studies. Only one case report described a patient who had no skin rashes and had prominent weakness, rapidly progressive ILD, and myocarditis ensuing in death (20). Whether this represents an atypical case or a false positive based on the diagnostic testing used or whether it will be corroborated by additional case descriptions remains to be seen.

Although most cases of anti-SAE–associated DM are described as having a good prognosis, we note that many of our patients required multiple medication changes because of difficulty in initially controlling the skin disease. We cannot exclude a referral bias, as we are a tertiary specialty center, and patients tend to be seen for complex cases. Notably, there was a higher utilization for IVIG in our cohort, which we have found to be very useful for treating the skin disease. Methotrexate was also used more frequently owing to articular symptoms. Future studies to characterize response to treatment will be important and may also reveal pathophysiologic differences. For example, one recent study suggests that anti-SAE–positive patients with DM are at an increased risk for developing hydroxychloroquine-induced skin eruptions (odds ratio = 8.42) compared with other DM groups (21).

The overall prevalence of cancer-associated myositis (cancer within 3 years of DM symptom onset) among the anti-SAE1–positive patients with DM in our cohort was 10% (2/19). An additional three cases were included when followed-up for more than 5 years. Given the small numbers, no clear phenotypic differences were found between those with cancer and those without.

We show that there can be reasonable agreement between Euroimmun and the gold-standard method of immunoprecipitation depending on which antibody cutoffs were used. For example, at lower cutoffs (≥15/+), 24/43 patients were false positives. The use of multiplex Euroimmun assays for clinical serologic testing of myositis antibodies has become increasingly popular, and there is a need to define its performance for each antibody specificity (10,22,23).

Table 4. Reported cases of anti-SAE–associated myositis

Author, Year (Reference)	Number of cases	Ages or Mean Age, % F	Cohort Location	Clinical Presentation	SAE Detection Method	Cancer
Betteridge et al, 2007 (3)	2	52 F and 62 M	United Kingdom	DM first before muscle and mild ILD	IP; IP blotting	0
Betteridge et al, 2009 (5)	10	62 y, 64%	United Kingdom	DM mostly at onset followed by muscle, dysphagia (78%), mild ILD (18%), arthritis (18%), and systemic features (82%)	IP; immunodepletion	2 (NR)
Zampeli et al, 2010 (11)	6	NR	Greece	DM associated with Gottron sign and dysphagia	Euroimmun line immunoblot assay	0
Muro et al, 2012 (17)	2	57 F and 70 M	Japan	DM, mild muscle, mild ILD/ PAH, and no dysphagia or arthritis	IP Western blotting; ELISA	1 (rectal)
Tarricone et al, 2012 (9)	5	NR	Italy	DM with muscle and no arthritis/dysphagia/ ILD	IP; immunoblotting	0
Fujimoto et al, 2013 (25)	7	69 y, 57%	Japan	DM, myositis, dysphagia (29%), ILD (71%), and systemic features (57%)	IP; Western blotting	1 (colon)
Bodoki et al, 2014 (7)	4	47 y, 50%	Hungary	Severe classical DM with muscle, arthralgia (50%), dysphagia (75%), and ILD (25%)	IP	1 (colon)
Chen et al, 2015 (26)	2	NR	China and Japan	Classic DM	IP; immunoblotting	NR
Ge et al, 2017 (8)	12	59 y, 79%	China	DM, mild myositis (67%), ILD (64%), dysphagia (64%), and arthralgia (34%)	ELISA; IP	2
Zamora et al, 2018 (20)	1	78 M	Spain	Myositis, no skin rash, RP-ILD, and myocarditis	Monospecific dot blot assay	0
Peterson et al, 2018 (10)	19	55 y, 73%	United States	DM, muscle (58%), incomplete data on lung (4/7), and dysphagia (3/5)	LIA; IP	1 (renal cell)
Inoue et al, 2018 (16)	6	65 y, 83%	Japanese	DM diffuse erythema with "angel wings," muscle, ILD (66%), and dysphagia (50%)	IP; Western blotting	1 (renal cell, colon)
Matsuo et al, 2019 (13)	1	65 M	Japan	DM, mild muscle, asymptomatic ILD, and dysphagia	ELISA	Sigmoid cancer
Jia et al, 2019 (14)	1	48 F	China	DM and no muscle, ILD, or dysphagia	NR	0
Gono et al, 2019 (15)	2	47 F and 64 M	Japan	CADM with ILD (preserved function) and dysphagia	IP; immunoblotting	0
Betteridge et al, 2019 (6)	42	NR	Europe (United Kingdom, Sweden, Hungary, Czech Republic)	DM associated with any rash	IP	NR

CADM, clinically amyopathic dermatomyositis; DM, dermatomositis; ELISA, enzyme linked immunosorbent assay; F, female; ILD, interstitial lung disease; IP, protein immunoprecipitation; LIA, line immunoblot assay; M, male; NR, not reported; PAH, pulmonary hypertension; RP-ILD, rapidly progressive interstitial lung disease; SAE, small ubiquitin-like modifier activating enzyme.
* Systemic features were defined as fever, weight loss, and raised inflammatory markers.

Our study has limitations, which include the retrospective nature and lack of comparison with other DM subsets. Patient visits used for this study preceded our use of the Clinical Disease Activity Score Index (24) in routine clinical care; thus, the lack of a skin activity score also limits our ability to comment on the severity of the skin disease. We could not determine the true prevalence of SAE autoantibodies in our myositis cohort, as the samples tested were not all purely myositis or DM. Rather, they represented all those suspected to have an inflammatory muscle and/or skin disease. It should be noted that although we used an immunoprecipitation protocol based on an input of radiolabeled SAE protein, there are alternate immunoprecipitation approaches that use unlabeled cell lysates as input, followed by Western blot detection of SAE (17,25). How the latter assay compares with the IVTT immunoprecipitation and Euroline antibody readouts was not addressed here. These limitations notwithstanding, we present results from a well-characterized longitudinal cohort that sheds further light on the phenotype in a North American center, with SAE autoantibody status confirmed using two different methods.

In conclusion, SAE autoantibodies are one of the rarer DM-specific autoantibodies. Skin disease dominates the clinical picture, but attention to muscle, lung, and joint involvement is warranted, as this can be subtle in presentation. There may be slight

differences in phenotype among different cohorts, and further information is needed in underrepresented ethnicities. This study showed only a weak association with cancer. Future studies with larger numbers of anti-SAE–positive patients, adequately powered, may definitively answer the question of cancer association.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Albayda had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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