Multiple myositis-specific autoantibodies in dermatomyositis: 2 cases and review of the literature

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Key words: antinuclear helicase protein; anti-SUMO—activating enzyme; anti-transcriptional intermediary factor 1-γ; dermatomyositis; Mi-2; SAE-1; TIF1-γ.

INTRODUCTION

Dermatomyositis (DM) is a multisystem idiopathic inflammatory myopathy often associated with 1 of 5 dermatomyositis-specific autoantibodies (DMSAs). DMSAs include anti-transcriptional intermediary factor 1-γ (anti-TIF1-γ), antinuclear matrix protein-2, anti-melanoma differentiation-associated gene 5, antinuclear helicase protein (anti-Mi-2), and anti-SUMO-activating enzyme (anti-SAE-1) antibodies. Anti-synthetase antibodies, such as anti-Jo-1, are also sometimes considered DM-specific. The coexistence of multiple DMSAs in a single patient is very rare. In this report, we present 2 cases that, to the best of our knowledge, are the first reported cases of adults with antibodies to TIF1-γ and either SAE-1 or Mi-2. We also review the few reported cases with both an anti-TIF1-γ antibody and a second DMSA (Table I).[1-3]

Abbreviations used:

DM:	dermatomyositis
DMSA:	dermatomyositis-specific antibody
SAE-1:	SUMO-activating enzyme subunit 1
TIF1-γ:	transcriptional intermediary factor 1-γ

CASE REPORT

Case 1

A 76-year-old woman presented with a 1-month history of burning pruritic rashes. Physical examination was notable for heliotrope rash, pink-violaceous patches on the face and extensor surfaces of the upper extremities, shawl sign, periungual erythema, and dilated nailfold capillaries, without evidence of myositis. Skin biopsies revealed epidermal atrophy and focal interface change suggestive of DM. Laboratory test results were significant for a positive antinuclear antibody titer of 1:640 with a speckled pattern, normal creatinine kinase, and normal aldolase. The Extended Myositis Panel (ARUP Laboratories) revealed the presence of anti-TIF1-γ and anti-SAE-1 antibodies. Chest computed tomography revealed small, stable, pulmonary nodules. Screening for malignancy or interstitial lung disease rendered a negative result. Prednisone was not tolerated because of muscle tightness and mania, while hydroxychloroquine and methotrexate were discontinued because of rash and diarrhea. Remission was achieved with cyclosporine and dexamethasone.

Case 2

An 80-year-old woman with a history of lung cancer 3 years previously presented with an 8-month history of fatigue and pruritus. Physical examination was notable for heliotrope rash, shawl sign, Gottron papules, nailfold capillary dropout, and proximal muscle weakness. Skin and muscle biopsies were consistent with DM. Laboratory test results revealed a positive antinuclear antibody titer of 1:1280 with a speckled pattern, an antinuclear ribonucleoprotein antibody index of 2.9 (normal range, 0.0-0.9), and a

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2022;25:72-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.05.018

Table I. Reported cases of adult dermatomyositis with anti-transcriptional intermediary factor 1-γ antibodies and additional dermatomyositis specific antibodies

Report	Age	Sex	DMSA	Cutaneous manifestations	Malignancy	Muscle weakness	Reported diagnosis
Kang et al[1]	36	M	TIF1-γ **MDA-5**	NR	Non-Hodgkin lymphoma	Yes	Dermatomyositis
Labrador-Horrillo et al[2]	38	F	TIF1-γ **MDA-5**	"Classical skin manifestations (ie, Gottron papules, heliotrope rash)"	Ovarian cancer	Yes	Dermatomyositis
Rams et al[3]*	NS	NS	TIF1-γ **MDA-5**	NS	Neoplastic disease	NS	Dermatomyositis
	NS	NS	TIF1-γ **MDA-5**	NS	Neoplastic disease	NS	Polymyositis
	NS	NS	TIF1-γ **MDA-5** **NXP-2** **Jo-1** **PL-7**	NS	None	Yes	SLE/myositis overlap
This report	76	F	TIF1-γ **SAE-1**	Heliotrope rash, malar rash, shawl sign, V-sign, periungual erythema, NFCC	None	No	Dermatomyositis
	80	F	TIF1-γ **Mi-2**	Gottron papules, heliotrope rash, shawl sign, NFCC	Lung cancer	Yes	Dermatomyositis

DMSA, Dermatomyositis-specific antibody; *MDA-5,* melanoma differentiation-associated gene 5; *NFCC,* nailfold capillary change; *NR,* not reported; *NS,* not specified; *NXP-2,* nuclear matrix protein 2; *SAE-1,* SUMO-activating enzyme subunit 1; *SLE,* systemic lupus erythematosus; *TIF1-γ,* transcriptional intermediary factor 1-γ.
*This paper reported specific skin manifestations and malignancies within the group of patients with anti-TIF1-γ antibodies but did not specify for individual patients.

creatinine kinase concentration of 331 U/L (normal range, 26-192 U/L). Her lung cancer was in remission, and no new malignancies were found during screening. The ARUP Extended Myositis Panel revealed positivity for both TIF1-γ and Mi-2 antibodies. Treatment included intravenous immunoglobulin, low-dose prednisone, and methotrexate.

DISCUSSION

Patients with dermatomyositis most often present with a single DMSA, each with a specific clinical phenotype. A few reports demonstrated the coexistence of anti-TIF1-γ with another DMSA, including 3 with anti-melanoma differentiation-associated gene 5 and one with antinuclear matrix protein-2 antibodies in adult DM (Table I),[1-4] as well as 2 with anti-Mi-2 antibodies in juvenile DM.[5,6] Given the older age of our cases as compared with most with DM, one might speculate that multiple autoantibodies may accumulate over time as described in lupus, but the presence of multiple DMSAs in juveniles and young adults argues against this. To the best of our knowledge, this is the first report of adult DM with coexistent antibodies to TIF1-γ and either SAE-1 or Mi-2.

We recognize that reports of multiple DMSAs in a single individual may be influenced by the specificity of the laboratory methodology utilized. The 5 DMSAs tested in the ARUP Extended Myositis Panel are tested using immunoprecipitation and immunoblot assays, the most specific methodology, as opposed to enzyme-linked immunosorbent assay-based tests. For Case 1, the results were "positive" for TIF1-γ and "low positive" for SAE-1 antibodies. The sensitivity and specificity of the ARUP Extended Myositis Panel for SAE-1 are 100% and 99.6%, respectively.[7] For Case 2, the results were "positive" for Mi-2 and "high positive" for TIF1-γ antibodies, which were confirmed by repeat testing. In addition, at the University of Rochester Medical Center, the ARUP Extended Myositis Panel has been ordered for 462 patients. These are the only 2 cases with multiple DMSAs (2/462, 0.4%), which is consistent with other reports of immunoprecipitation/immunoblot-based assays, supporting the specificity of these tests and rarity of this occurrence. In summary, the results for these 2 cases are not likely to be false positives.

Given the rarity of the condition, how double DMSA positivity differs from single DMSA positivity is unknown, including the effect on clinical phenotype. It is unknown, whether one antibody

phenotype may be dominant, which may be difficult to assess given the fact that: (1) most cutaneous features of DM are common to many antibody subtypes, and (2) subtype-specific features are not observed in all patients with that particular antibody. Case 1 presented with anti-TIF1-γ and anti-SAE-1 antibodies. Consistent with both antibody subtypes, this patient presented with widespread and severe skin involvement, but without distinguishing cutaneous features of some patients with anti-TIF1-γ antibodies.[8] This patient had stable pulmonary nodules that did not resemble interstitial lung disease or progress to malignancy, a feature recently described as a potential characteristic of patients with anti-SAE-1 antibodies.[9] In addition, this patient had to discontinue hydroxychloroquine because of a drug eruption, which is known to occur in many patients with DM, but which statistically has been associated specifically with positivity for anti-SAE-1 antibodies.[10] However, many with anti-SAE-1 antibodies develop progressive muscle disease with dysphagia, whereas this patient remained amyopathic, more like those with anti-TIF1-γ antibodies (who often have hypomyopathic disease). Case 2 had both anti-TIF1-γ and anti-Mi-2 antibodies. As in Case 1, this patient only had cutaneous features common to many DM subtypes and none particular to anti-TIF1-γ.[8] Moreover, the patient did not exhibit specific features of anti-Mi-2 antibody positivity, such as high creatinine kinase levels out of proportion to muscle involvement.[8] Increased rates of malignancy, though higher with anti-TIF1-γ antibodies, are associated with both types of antibodie. Overall, these cases exhibit mixed features that make it difficult to attribute their clinical presentation to one particular autoantibody.

In summary, there are few reports of patients with DM and multiple DMSAs. All previously reported cases with anti-TIF1-γ antibodies in adults also presented with anti-melanoma differentiation-associated gene 5 antibodies (Table I). Our report expands upon this literature to show that adults with anti-TIF1-γ can present with other DMSAs as well. The clinical presentation of these 2 rare cases suggests that one antibody phenotype is not dominant. In addition, this review of the reported cases of DM with multiple DMSAs indicates that the cancer risk associated with anti-TIF1-γ antibodies remains high despite the presence of a second type of DMSA. Additional studies will be necessary to better understand the pathogenesis of DM presenting with multiple DMSAs.

Conflicts of interest

None disclosed.

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