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CASE STUDY

Panniculitis in dermatomyositis: Two cases with antitranscriptional intermediary factor-1 antibody as myositis-specific antibody and review of the literature

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Abstract

Dermatomyositis (DM) is a systemic disease characterized by chronic inflammation in the skin and muscle. A variety of myositis-specific autoantibodies (MSAs) are detected in patients with DM. These antibodies are associated with unique clinical subsets in DM. Panniculitis is a rare cutaneous manifestation of DM that most commonly presents as tender, erythematous subcutaneous nodules on the thighs, arms, and buttocks. We herein describe the clinical features of two DM-associated panniculitis patients with anti-TIF1 antibodies. Both are female patients and showed characteristic cutaneous features, including heliotrope rashes and Gottron's signs with muscle involvement. While one patient had a posterior mediastinum tumor, another had no cancer. Furthermore, to elucidate the clinical significance of anti-TIF1 antibodies in DM patients with panniculitis, we analyzed all cases with detailed information on the clinical features, including MSAs. A PubMed search of keywords "panniculitis" and "DM" was conducted. We found 23 cases with the detection of MSAs. A review of these cases and our two cases revealed a predominance of female gender (80%) with a median age of 48 years. Anti-MDA5 antibodies were detected in 11 patients (11/23, 48%), and anti-TIF1 antibodies were observed in four patients, including the current cases (4/23, 17%). Anti-Mi-2 antibodies were observed in four patients (4/23, 17%). Each patient had anti-NXP-2 antibodies or anti-SAE antibodies (2/23; 9%). Although the pathogenesis of panniculitis in DM remains unknown, differences in pathogenesis of DM-associated panniculitis according to MSAs may exist. Accumulation of additional cases is required to clarify the relationship between panniculitis and MSAs.

KEYWORDS
antitranscriptional intermediary factor-1 antibody, clinical feature, dermatomyositis, myositis-specific autoantibody, panniculitis

1 | INTRODUCTION

Dermatomyositis (DM) describes a group of idiopathic inflammatory disorders that primarily affects muscles and skin. Clinical manifestations of DM are heterogeneous, with varying degrees of myositis, skin rash, and accompanying symptoms such as interstitial lung disease and internal malignancy. Although the cause of this disorder remains unclear, autoimmunity is considered to play a critical role because of the presence of diagnostic autoantibodies—known as myositis-specific autoantibodies (MSAs)—as a prominent feature. A number of MSAs have been identified in patients with DM, including anti-aminoacyl-transfer RNA synthetase (anti-ARS), anti-Mi-2, antimelanoma differentiation-associated gene-5 (anti-MDA5), and antitranscriptional intermediary factor 1 (anti-TIF1) antibodies, as well as the more recently identified antinuclear matrix protein 2 (NXP-2) and antismall ubiquitin-like modifier activating enzyme (anti-SAE) antibodies. Each of the latter is, respectively, associated with characteristic cutaneous manifestations.[1]

Although DM is often characterized by classic skin findings (e.g., heliotrope rashes, Gottron's papules), cutaneous features in DM have remarkable phenotypic heterogeneity regarding both clinical and histologic presentations.[2,3] Panniculitis is a rare cutaneous manifestation of DM that is characterized by generally tender subcutaneous nodules on the arms, buttocks, thighs, and abdomen, as well as histologically nodular panniculitis with lymphoplasmacytic infiltration.[4] Thus far, little is known about the association between DM-associated panniculitis and MSAs. We herein describe the clinical features of two Japanese DM patients with panniculitis and anti-TIF1 antibodies. To elucidate the clinical significance of anti-TIF1 antibodies in DM patients with panniculitis, we analyzed all cases with detailed information on the clinical features including the information of MSAs retrieved through a PubMed search with the keywords “panniculitis” and “DM.”

2 | CASE REPORTS

2.1 | Case 1

A 48-year-old woman with a two month history of erythema on the thighs, which gradually became painful. Despite the application of topical steroids, skin eruptions gradually spread to the face and hands. Physical examination revealed muscle weakness, erythematous papule, and purplish erythema around the nose and on the upper eyelid, chest, upper back, the extensor of the upper limbs and both thighs (Figure 1A,B), periungual erythema, punctate hemorrhage on the perionychium, Gottron's sign on the proximal interphalangeal (PIP) joints of both hands, and palmar papules. Laboratory examinations revealed the following: CK = 133 U/L, Aldolase = 5.4 mg/mL, ANA titer of 1:40 with a homogeneous and speckled pattern, and anti-TIF1 antibody-positive at the titer of 195 AU/mL. Her electromyographic study showed a myogenic pattern. Computerized tomography revealed a postmediastinum tumor. There were no interstitial lung changes. A diagnosis of anti-TIF1 antibody-positive DM was made based on the above clinical features. She was treated with oral prednisolone at 1 mg/kg/day, and the dosage was gradually decreased. One and half years after the diagnosis of DM, the skin lesions of the thighs showed atrophic red and brownish patches with some bony to hard induration underneath (Figure 1C,D). Histological examination of the subcutaneous nodules on the left thigh revealed lobular lymphoplasmacytic panniculitis with fat necrosis and membranocystic changes in the subcutaneous fat, but no nuclear atypia (Figure 2). Abundant mucin interstitially deposited between collagen bundles of the dermis. Consequently, a diagnosis of DM-associated panniculitis was made.

2.2 | Case 2

A 48-year-old woman with a history of a skin rash on the face and hands, as well as general malaise for seven months. Physical

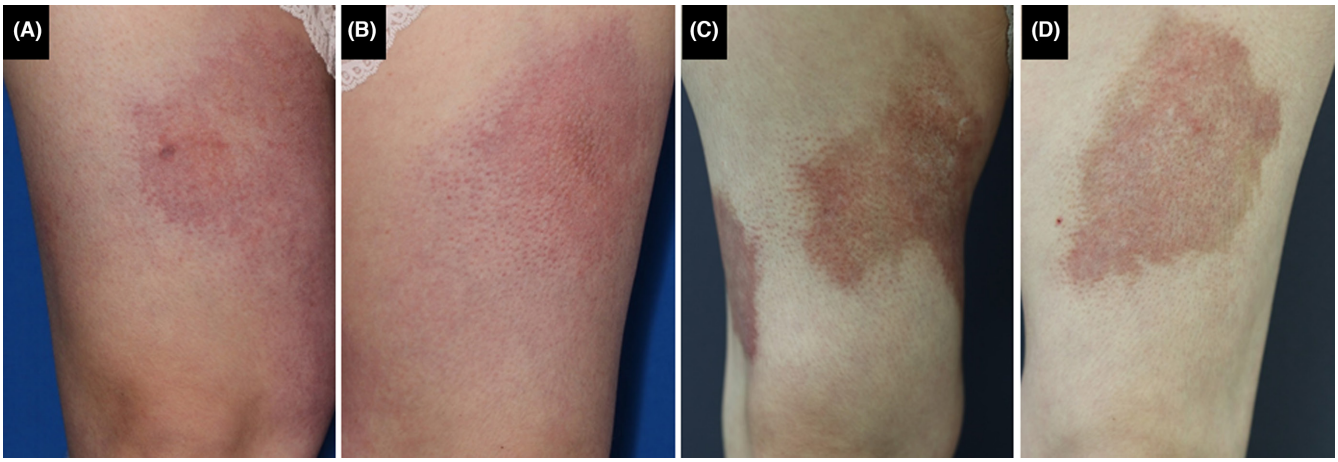

FIGURE 1 Clinical features of patient with anti-TIF1 antibody-positive DM with panniculitis. Case 1 (A-D). The purplish erythema on both thighs (A, B) were observed before treatment. One and half years later, atrophic red and brownish patches with some bony to hard induration underneath (C, D) were observed on both thighs

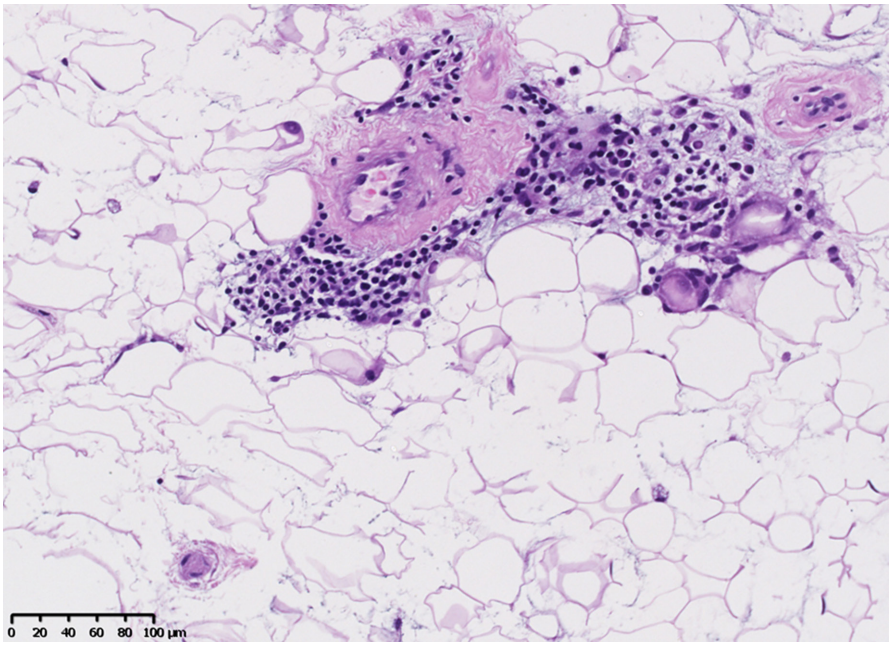

FIGURE 2 Histological examination of the subcutaneous nodules on the left thigh (Case 1). Lobular lymphoplasmacytic panniculitis with fat necrosis and membranocystic changes in the subcutaneous fat, but no nuclear atypia

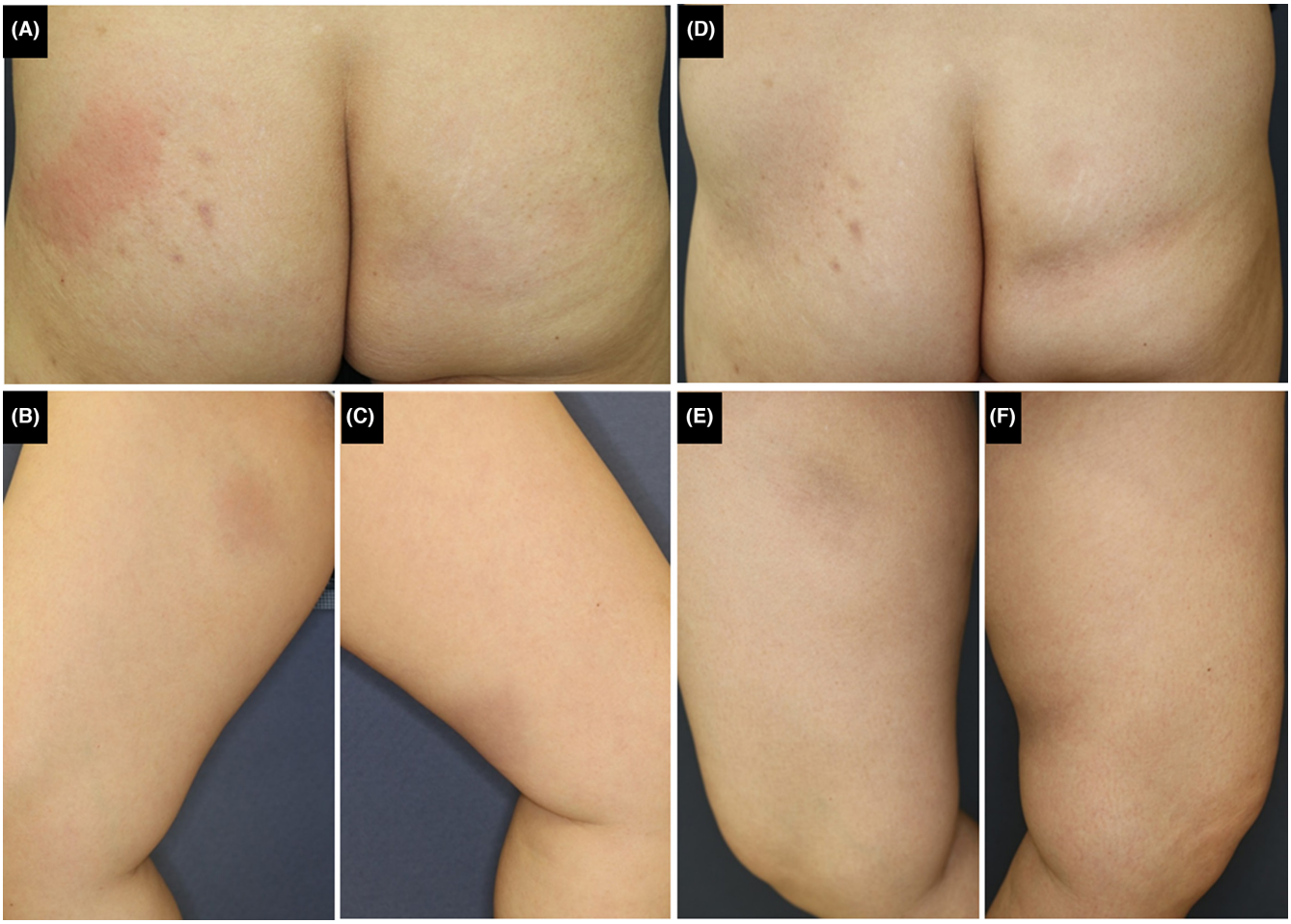

FIGURE 3 Clinical features of patient with anti-TIF1 antibody-positive DM with panniculitis. Case 2 (A-F). Tender erythema on the buttocks (A) and both thighs (B, C) was observed before treatment. One month later, subcutaneous dimpling with pigmentation was seen on the buttocks (D) and both thighs (E, F)

examination revealed muscle weakness, mild edematous erythema on both eyelids, and erythema on the forehead and around the nose wing. There was also periungual erythema, punctate hemorrhage on the perionychium, and erythematous papules on the PIP joints of the fingers. Tender erythema was also observed on the right upper arm, buttocks (Figure 3A), and both thighs (Figure 3B,C). Laboratory examinations revealed the following: ANA was positive with a titer of 1: >1280 and a speckled pattern, anti-TIF1 antibody-positive at a titer of 77 AU/mL, CK of 63 IU/L, and LDH of 277 IU/L. Electromyography demonstrated diffuse polyphasic units consistent with a myositic process. We, therefore, diagnosed the patient with anti-TIF1 antibody-positive DM. She was treated with oral prednisolone at 1 mg/kg/day and intravenous gammaglobulin. One month later, subcutaneous dimpling with pigmentation was noted in the buttocks (Figure 3D) and both thighs (Figure 3E,F). Histological examination of the subcutaneous nodules on the right thigh revealed a lobular lymphoplasmacytic panniculitis with fat necrosis and membranocystic changes in the subcutaneous fat but no nuclear atypia (Figure 4). No calcification was observed. We, therefore, diagnosed her as having DM-associated panniculitis with anti-TIF1 antibody.

3 | DISCUSSION

Panniculitis is an inflammation of the subcutaneous adipose tissue and is characterized by indurated, painful, and erythematous subcutaneous nodules commonly located on the thighs, arms, and buttocks. These nodules can progress to calcifications and lipoatrophy.[5] The panniculitis may precede, occur simultaneously with the symptom of DM, or appear late in the course of the disease.[4] Histologic examination of DM-associated panniculitis is nonspecific, showing a lobular panniculitis with lymphoplasmacytic infiltration. A histopathologic study demonstrated that 9% of skin biopsy specimens of patients with DM showed subclinical panniculitis,[6] suggesting that microscopic panniculitis might be more common than clinically recognized.

We herein describe two cases of lobular panniculitis in DM patients with anti-TIF1 antibodies. While rare, DM with panniculitis has been reported in the literature. We found 23 cases with the detection of MSA (Table 1).[7–15] Together with our two cases (cases 1 and 2), a review of these cases revealed a predominance of female gender (80%) with a median age of 48 years. Anti-MDA5 antibodies were detected in 11 patients (11/23, 48%), and anti-TIF1 antibodies were observed in four patients, including current cases (4/23, 17%). Anti-Mi-2 antibodies were observed in four patients (4/23, 17%). Each patient had anti-NXP-2 antibodies or anti-SAE antibodies (2/23, 9%). Malignancy was found in two cases: One had breast cancer with anti-MDA5 antibodies and another (our case 1) had a posterior mediastinum tumor with anti-TIF1 antibodies.

Anti-TIF1 antibody has a strong association with malignancy. A previous study[16] reported that the clinical features in anti-TIF1-positive adult DM patients with malignancy had more extensive skin involvement, such as Gottron's papules. Panniculitis may be a part of the active inflammatory phase of DM, which involves multiple immunologic effector mechanisms.[4,17] Meanwhile, a previous report revealed that panniculitis is significantly associated with anti-MDA5 antibody-positive DM cases (35.7%) compared with anti-MDA5 antibody-negative DM cases (12.6%).[8] Furthermore, some authors have suggested an association between anti-MDA5 antibodies and a specific, severe skin vasculopathy in adult DM patients, characterized by vascular fibrin deposition with variable perivascular inflammation.[18,19] The finding of perivascular inflammatory cell infiltration, endothelial swelling, and vasculitis in some cases of DM panniculitis suggests that angiopathy may also be a common pathogenetic factor

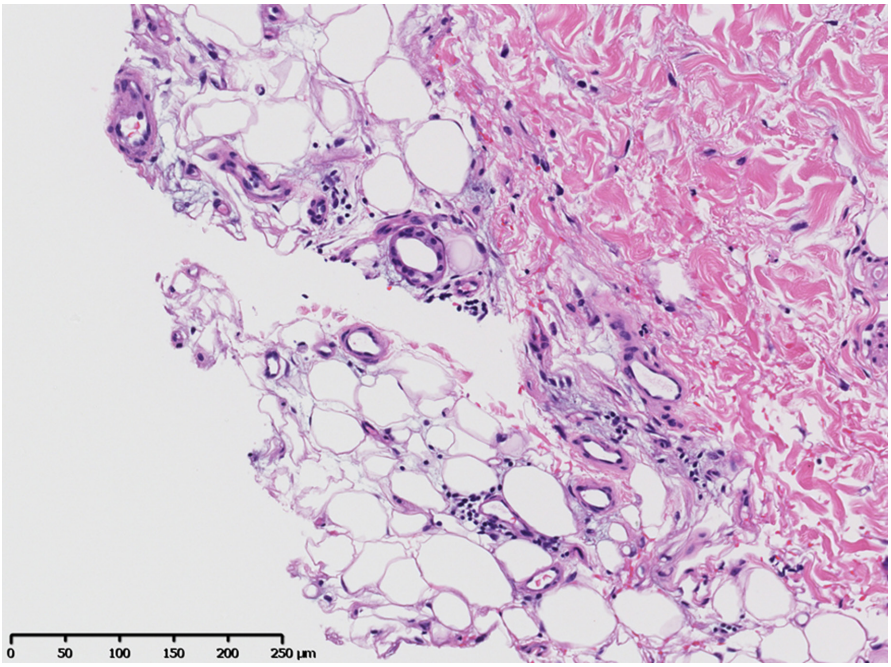

FIGURE 4 Histological examination of the subcutaneous nodules on the right thigh (Case 2). Histological characteristics were similar to Case 1

TABLE 1 Characteristics of documented cases of DM-associated panniculitis with MSA

No.	Reported year	Authors	Age	Sex	DM/PM	MSA	Malignancy	Myositis	ILD
1	2011[7]	Fiorentino D et al.	ND	ND	ND	MDA5	No	ND	ND
2			ND	ND	ND	MDA5	No	ND	ND
3	2014[8]	Labrador-Horrillo M et al.	57	F	DM	MDA5	Yes (Breast cancer)	Yes	No
4			41	F	DM	MDA5	No	Yes	Yes
5			53	F	CADM	MDA5	No	No	Yes
6			30	F	CADM	MDA5	No	No	No
7			52	F	DM	MDA5	No	Yes	No
8	2017[9]	Yanaba K et al.	40	F	DM	TIF1	No	Yes	No
9	2017[10]	Hasegawa A et al.	66	F	CADM	MDA5	No	No	Yes
10	2018[11]	Santos-Britz A et al.	ND	ND	ND	Mi-2	No	ND	ND
11			ND	ND	ND	Mi-2	No	ND	ND
12			ND	ND	ND	Mi-2	No	ND	ND
13			ND	ND	ND	Mi-2	No	ND	ND
14			ND	ND	ND	SAE	No	ND	ND
15			ND	ND	ND	SAE	No	ND	ND
16			ND	ND	ND	NXP-2	No	ND	ND
17			ND	ND	ND	TIF1	No	ND	ND
18	2018[12]	Hattori Y et al.	51	F	DM	MDA5	No	Yes	Yes
19	2020[13]	Galli S et al.	40	M	DM	MDA5	No	Yes	Yes
20	2020[14]	van Dongen HM et al.	20	M	DM	NXP-2	No	Yes	No
21	2021[15]	Kishida D et al.	32	F	CADM	MDA5	No	No	Yes
22	Our case 1	Takezawa K et al.	48	F	DM	TIF1	Yes (Posterior mediastinum tumor)	Yes	No
23	Our case 2	Takezawa K et al.	48	F	DM	TIF1	No	Yes	No
	Total		Median = 48 years	M:F = 2:10	DM:CADM = 9:4	MDA5 11 TIF1 4 Mi-2 4 NXP-2 2 SAE 2	Yes 2 (Breast cancer 1; Posterior mediastinum tumor 1); No 21	Yes 9; No 4	Yes 6; No 7

Abbreviations: CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; F, female; ILD, interstitial lung disease; M, male; MDA5, anti-MDA5 antibody; Mi-2, anti-Mi-2 antibody; ND, not determined; NXP-2, anti-NXP-2 antibody; SAE, anti-SAE antibody; TIF1, anti-TIF1 antibody.

for DM and panniculitis. Okiyama et al. recently reported a histologic analysis of cutaneous manifestation and classified same into MSAs-associated groups.[3] Vascular injury was observed more often in the MDA5 group than in the ARS and TIF1 groups.[3] Thus, there may be a distinct pathogenesis of DM-associated panniculitis among anti-MDA5 antibodies, anti-TIF1 antibodies, or other MSAs. More cases are required to clarify the relationship between panniculitis and MSAs.

To our knowledge, including our case, there are six cases of panniculitis in the setting of DM and malignancy.[8,17,20] Each case with rhabdomyosarcoma, rectal carcinoma, ovarian carcinoma, breast cancer, nasopharyngeal carcinoma, and posterior mediastinum tumor was reported. Given the limited number of cases of panniculitis in patients with DM and malignancy, the significance of this association remains undetermined. Although rare, DM and its potentially associated malignancies may need to be considered in patients with idiopathic lobular panniculitis.

DECLARATION SECTION

Approval of the research protocol: Not applicable.
Informed Consent: Yes.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Dr. Manabu Fujimoto is the Editor in Chief for the Journal of Cutaneous Immunology and Allergy. Management of the peer review process, and all editorial decision-making, for this article was undertaken by an Associate Editor.

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