Journal of
*Clinical Medicine*

MDPI

*Review*

# Clinical Features and Cutaneous Manifestations of Juvenile and Adult Patients of Dermatomyositis Associated with Myositis-Specific Autoantibodies

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**Abstract:** Dermatomyositis is one of the idiopathic inflammatory myopathies, which is characterized with specific skin manifestations, and considered as an autoimmune disease. Dermatomyositis is a heterogeneous disorder with various presences, severities and characteristics of myositis, dermatitis, and interstitial lung disease. Our and others' data showed that myositis-specific autoantibodies have been associated with distinct clinical features. This article reviewed the epidemiology and characteristic clinical features of the different types of antibody-associated dermatomyositis in adult and juvenile patients, which include the severity of myopathy, the potential complication of interstitial lung disease, potential association with malignancies, and characteristic cutaneous manifestations.

**Keywords:** dermatomyositis; skin; autoantibody



**Citation:** Okiyama, N. Clinical Features and Cutaneous Manifestations of Juvenile and Adult Patients of Dermatomyositis Associated with Myositis-Specific Autoantibodies. *J. Clin. Med.* **2021**, *10*, 1725. https://doi.org/10.3390/jcm10081725

Academic Editor: Takako Miyamae

Received: 2 April 2021
Accepted: 14 April 2021
Published: 16 April 2021



## 1. Introduction

Dermatomyositis (DM) is one of idiopathic inflammatory myopathies (IIMs), which is characterized with specific skin manifestations, the pathologies of which are considered autoimmune diseases. DM is a heterogeneous disorder that can occur in adults and juveniles, and it has various phenotypes, including myositis, dermatitis, and interstitial lung disease (ILD) [1]. Recently, several myositis-specific autoantibodies not detected in patients with inherited muscle diseases have been identified [2], and they include anti-transcriptional intermediary factor 1 (TIF1) γ, anti-nuclear matrix protein 2 (NXP2), anti-melanoma differentiation-associated protein 5 (MDA5), anti-Mi-2, and anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies, in addition to already established anti-aminoacyl-transfer RNA synthetase (ARS) antibodies, including anti-Jo-1 antibody. These autoantibodies are not only highly disease-specific; our and others' data showed that they are associated with distinct clinical features [3,4]. In other words, these myositis-specific autoantibodies are useful to define DM better than before. This article reviewed the epidemiology and characteristic clinical features of the different types of antibody-associated DM in adult and juvenile patients, which include the severity of myopathy, the potential complication of ILD, and potential association with malignancies. The characteristic cutaneous manifestations are described in a separate chapter.

## 2. Epidemiology and Clinical Features of Subgroups Classified According to Myositis-Specific Autoantibodies

The characteristics of each subgroup are detailed in the following chapters, and summarized in Table 1.

### 2.1. Anti-TIF1 Antibody-Positive DM

The anti-TIF1 antibodies were originally reported as anti-155/140 and anti-p155 antibodies [5,6]. The antibodies target a 155-kDa nuclear protein, sometimes with a 140-kDa protein, which were subsequently identified as TIF1 family proteins belonging to the

tripartite motif (TRIM) superfamily: TIF1γ (TRIM33) and TIF1α (TRIM24), respectively. A number of reports from the USA, Europe and Japan revealed that the anti-TIF1γ antibody is associated with malignancies, especially in older adult patients [7–9]. In contrast, 35% of juvenile DM (JDM) patients have anti-TIF1γ antibodies by a review article depending on several large registries developed in the USA, Canada and the UK [10], while 17.4% and 22% of JDM patients do in a report of 58 cases from Turkey and another report of 64 cases from Argentina [11,12]. Moreover, the patients do not develop malignancies [6,10,11]. A chronic illness course and lipodystrophy have been associated with anti-TIF1 antibodies in JDM patients [10], and one-third of anti-TIF1 antibody-positive JDM patients have a relapse [11].

### 2.2. Anti-NXP2 Antibody-Positive DM

The anti-nuclear matrix protein 2 (NXP2) antibody was first identified in a cohort of JDM/juvenile polymyositis (JPM) patients, and was originally termed an anti-MJ antibody [12]. The cohort studies including a review of several large registries, and two cohorts with small case numbers, detected anti-NXP2 antibodies in 22%–25% of patients with JDM [10–12]. A cohort study reported that severe myopathy characterized by muscle contractures and atrophy was associated with anti-NXP2 antibody-positive JDM [12], and 43% of anti-NXP2 antibody-positive JDM patients have a relapse [11]. The risk of ILD was suggested in anti-NXP2 antibody-positive JDM, as well as anti-MDA5 antibody-positive patients [11]. Two cohort studies on adult, but not juvenile, PM/DM patients in Japan and the US suggested an association between the anti-NXP2 antibody and malignancy [8,13]. We also found that adult patients of anti-NXP2 antibody-positive IIMs in our Japanse cohort had a higher prevalence of malignancy than the general population with an increased age-standardized incidence ratio of malignancies (unpublished data).

### 2.3. Anti-MDA5 Antibody-Positive DM

The anti-MDA5 antibody, which was termed an anti-CADM-140 antibody that reacts with a 140-kDa cytoplasmic protein [14], has been reported to present a high specificity for clinically amyopathic DM (CADM) accompanied by rapidly progressive ILD (RP-ILD) [15]. The target antigen of anti-MDA5 antibody was subsequently identified as the retinoic acid-inducible gene I-like receptor MDA5/IFIH1 (interferon induced with helicase C domain protein 1). The anti-MDA5 antibody is frequently detected among DM patients in Asia (36.6% (53/145 cases) in China, and 15.8% (26/165 cases) in Japan) [16] and at a low frequency (2.8% (21/748 cases)) in a cohort of DM patients in a combined European cohort in which 87.4% of enrolled patients were Caucasian [17]. In JDM patients, anti-MDA5 antibodies were detected in 28%–33% of a Japanese cohort [18,19] and 7.4% of a UK-based cohort [20]. The disparity might be dependent on the ethic difference, environmental factors, or low sensitivity due to the absence of myopathies in the patients of anti-MDA5 antibody-positive DM.

Some case series have reported CADM frequencies of approximately 40% in anti-MDA5 antibody-positive DM adult patients; in the juvenile cohort, it was reported that anti-MDA5 antibody-positive patients had a lower prevalence of severe muscle weakness than anti-MDA5 antibody-negative JDM patients [20]. A meta-analysis of 16 studies estimated that the pooled sensitivity and specificity of anti-MDA5 antibodies for RP-ILD were 77% (95% confidence interval (CI), 64%–87%) and 86% (95% CI, 79%–90%), respectively, with a pooled diagnostic odds ratio of 20.41 (95% CI, 9.02–46.20) [16]. The anti-MDA5 antibody has been reported as a diagnostic and predictive marker for ILD, especially RP-ILD, even in JDM patients [19,21]. Nevertheless, only eight of the 44 Japanese juvenile patients (18%) and none of the UK juvenile patients developed RP-ILD [19,20].

### 2.4. Anti-Mi-2 Antibody-Positive DM

The anti-Mi-2 antibody mainly reacts to Mi-2β, a component of the nucleosome-remodeling deacetylase complex. The anti-Mi-2 antibody was detected less frequently in

JDM patients (3–8.7%) [10,11] compared to adult DM patients (12%) [17]. Patients with the anti-Mi-2 antibody tend to present with severe myositis [22,23]; however, they typically respond well to therapy [24,25] and show clinical remission [26].

### 2.5. Anti-SAE Antibody-Positive DM

The anti-SAE antibody, which targets a heterodimer of SAE1 (40 kDa) and SAE2 (90 kDa), was identified in DM patients in 2007 [27]. This antibody was observed in approximately 6% of patients with DM [17], and it was associated with inflammatory myopathy, characterized by extensive rash and dysphagia [27,28]. While anti-SAE antibody-positive juvenile patients have rarely been reported, we reported a case complicated with ILD [29].

### 2.6. Anti-ARS Antibody-Positive DM

Anti-ARS antibodies include anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Ha, and anti-Zo. Patients with a positivity of thease antibodies share characteristic clinical symptoms such as myositis, ILD, arthritis/arthralgia, Raynaud's phenomenon, and fever, moreover, are distinguished from DM and PM. Thus, the term "antisynthetase syndrome" is also used to describe this population [30]. A small population of anti-ARS antibody-positive patients has been reported in JDM/JPM [11,18].

**Table 1.** Subgroups of juvenile dermatomyositis characterized by myositis-specific autoantibodies.

| Antibody | TIF1 | NXP2 | MDA5 | Mi-2 | SAE | ARS |
|---|---|---|---|---|---|---|
| Population | 17–35% [10–12] | 22–25% [10–12] | 28–33% (Japan) [18,19]<br>7.4% (UK) [20] | 3–8.7% [10,11] | Rare | Rare [11,18] |
| Myopathy | Severe, persistent [10], relapse [11] | Severe, persistent [12], relapse [11] | None–mild [20] | Severe [22,23], responsive to therapy [24,25] | — | — |
| Interstitial lung disease | Improbable | Frequent [11] | Frequent, rapidly progress [19,21] | Probable | — | Frequent, chronic [30] |

## 3. Characteristic Cutaneous Manifestations

The characteristic cutaneous manifestations of each subgroup are detailed in the following chapters and summarized in Table 2.

### 3.1. Anti-TIF1 Antibody-Positive DM

Patients with anti-TIF1γ antibody-associated DM were reported to show severe cutaneous manifestations, including the V-neck sign, shawl sign, heliotrope rash, Gottron's papules/sign, and flagellate erythema [5,6]. These rashes are associated with exposure to ultraviolet light. Exposere to ultraviolet light increased the odds of the anti-TIF1 antibody being present in JDM patients [31]. Erythroderma, which is reported in 15% of JDM patients, is more common in those with the anti-TIF1 antibody [32], and these characteristic cutaneous manifestations were known as palmar hyperkeratotic papules, psoriasis-like lesions, and hypopigmented and "red on white" telangiectatic patches in a previous report [33]. Half of 10 patients with anti-TIF1 antibody-positive JDM in a cohort of Turkish JDM patients were reported to develop calcinosis [11].

### 3.2. Anti-NXP2 Antibody-Positive DM

This antibody was first detected in JDM patients; however, it can be detected in JPM patients [10]. We reported that DM sine dermatitis was associated with the anti-NXP2 antibody [34] and found that a part of juvenile patients and half of adult patients presented with the PM phenotype without DM-specific cutaneous manifestations in our anti-NXP2 antibody-positive case series (unpublished data). The anti-NXP2 antibody-positive DM may be characterized by the scantiness of DM-specific cutaneous manifestations.

In contrast, both juvenile and adult myopathy patients positive for anti-NXP2 antibodies have a high risk of calcinosis [35,36]. FDG-PET detected calcinosis [37]. However, in a study, the anti-MDA5 and anti-TIF1, as well as anti-NXP2 antibodies were associated with calcinosis in a cohort of JDM patients [11], and JDM onset within 6 years of age was a predictive factor for the development of calcinosis [11]. As calcinosis is not specific to anti-NXP2 antibody-positive DM, but for vascular damage, various risk factors, which include local pressure due to muscle weakness and increased blood viscosity accompanied by inflammation, for the development of calcinosis exist.

### 3.3. Anti-MDA5 Antibody-Positive DM

Cutaneous ulceration due to vascular injuries was reported to be related to rapidly progressive ILD in patients of anti-MDA5 antibody-associated DM [38,39]. Caracteristic palmar violaceous macules/papules [38,40] were often observed, in which vasculopathy in the medium and small dermal vessels was frequently observed [38].

We previously performed analyses on the histological findings of finger lesions from 74 DM patients characterized by myositis-specific autoantibodies (anti-MDA5, anti-TIF1γ, and anti-ARS) [41]. The analyses also showed that vascular injury in the upper dermis was frequently observed in anti-MDA5 antibody-positive DM [41]. Immunohistochemistry for myxovirus resistance A (MxA), one of type I interferon activity-associated molecules, revealed that epidermal keratinocytes express MxA in the skin samples of anti-MDA5 antibody-positive DM patients than in anti-TIF1γ antibody-positive DM patients, while few keratinocytes were expressed in anti-ARS antibody-positive DM patients [41]. Anti-MDA5 antibody-positive DM and JDM, but not anti-synthetase syndrome, are known as interferonopathies mediated by type I interferons based on our data and previous studies on muscle and blood samples [42–45].

### 3.4. Anti-Mi-2 Antibody-Positive DM

Few characteristic cutaneous manifestations have been reported for the anti-Mi-2 antibody DM. A previous retrospective study of 64 cases revealed that anti-Mi-2 antibody DM patients tended to present with a classic DM rash (Gottron papules/sign, heliotrope rash, periungual erythema, and/or violaceous rach including Holster sign) without additional skin changes, such as calcinosis, ulcers, panniculitis, and/or mechanic's hands [46]. Anti-Mi-2 antibody-positive DM is named "classic DM". Unlike in adults, V- and shawl-sign rashes and cuticular overgrowth are not associated with anti-Mi-2 antibody-positive JDM [32].

### 3.5. Anti-SAE Antibody-Positive DM

Patients with anti-SAE antibody-positive DM usually demonstrate extensive rashes [27], and we termed the cutaneous manifestations as erythroderma with the "angel wings" sign, which means diffuse erythema sparing the parts on the scapulas [28]. Although very few anti-SAE antibody-positive JDM patients were presented, we encountered a case of anti-SAE antibody-positive JDM who presented with extensive facial erythema without erythroderma [29].

### 3.6. Anti-ARS Antibody-Positive DM

Mechanic's hands are characterized by hyperkeratotic erythema on the sides of the thumbs and forefingers [47]. Patients with antisynthetase syndrome, including those with anti-ARS antibody-associated DM, generally present the mechanic's hands [30]. It is sometimes difficult for dermatologists to distinguish the mechanic's hands and Gottron's papules/sign of anti-ARS antibody-positive DM patients from eczema and/or psoriasis. Our previous analysis of the histological findings of finger lesions from 74 DM patients characterized according to myositis-specific autoantibodies (anti-MDA5, anti-TIF1γ, and anti-ARS) indicated that eczematous reactions (spongiosis) and psoriasiform dermatitis (psoriasiform acanthosis and parakeratosis) were significantly more frequently observed in

skin samples of anti-ARS antibody-positive patients than in anti-MDA5 or TIFγ antibody-positive patients [41]. In addition, MxA expression was rarely observed in skin samples [41], as well as muscle samples [42,43], of anti-ARS antibody-positive patients.

In JDM patients, anti-ARS antibody is also associated with mechanic's hands, Raynaud's phenomenon, and ILD [32].

**Table 2.** Cutaneous manifestations characterized by myositis-specific autoantibodies.

| Antibody | TIF1 | NXP2 | MDA5 | Mi-2 | SAE | ARS |
|---|---|---|---|---|---|---|
| Classic (Gottron papules/sign, heliotrope rash) | Frequent [5,6] | Sometimes absent [10] | Frequent, violaceous [38] | Frequent [46] | Frequent [27] | Sometimes absent [30], accompanied by eczematous/psoriasiform reactions [41] |
| Additional | Photosensitivity [31], erythroderma [32], calcinosis [11] | Calcinosis [35,36] | Palmar violaceous macules/papules and skin ulceration associated with vasculopathy [38,40,41] | Rare [46] | Erythroderma, Angel wings sign [28] | Mechanic's hands, Raynaud's phenomenon [30] |

## 4. Conclusions

DM and JDM include a broad spectrum, and may include cases of PM phenotypes without DM-specific cutaneous manifestations, Gottron papules/sign and heliotrope rash. Moreover, the severity of myopathy, the potential complication of ILD, and potential association with malignancies also present a broad spectrum, not only between juveniles and adults, but also among subgroups besed on these myositis-specific autoantibodies. Further studies, and an international and a wide range of investigators' consensus, are needed to classify adult and juvenile DM/PM cases to subgroups based on the myositis-specific autoantibodies. In addition, murine models for some of these subgrops, the anti-ARS antibody-associated group [48] and the anti-TIF1 antibody-associated group [49], have been established. These murine models might be useful to provide a basis for the development of subgroup-specific DM therapies.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable

**Conflicts of Interest:** The author declares no conflict of interest.

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