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Cutaneous Manifestations in Dermatomyositis: Key Clinical and Serological Features—a Comprehensive Review

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Abstract Dermatomyositis (DM) is a common idiopathic inflammatory myopathy. The pathogenesis is considered to be microangiopathy affecting skin and muscle. The cutaneous manifestations of DM are the most important aspect of this disease, and their correct evaluation is important for early diagnosis. The skin signs are various: Some are pathognomonic or highly characteristic, and others are compatible with DM. Recently, DM has been categorized into several disease subsets based on the various autoantibodies present in patients. Sometimes, characteristic cutaneous manifestations are strongly associated with the presence of specific autoantibodies. For example, anti-Mi-2 antibody is associated with the classic features of DM, including heliotrope rash, Gottron's papules, the V-neck sign, the shawl sign, cuticular overgrowth, and photosensitivity. Frequent cutaneous features in anti-transcriptional intermediary factor 1 gamma (TIF1γ)-positive patients are diffuse photoerythema, including "dusky red face," while skin ulcerations, palmar papules (inverse Gottron), diffuse hair loss, panniculitis, and oral pain and/or ulcers are sometimes associated with anti-melanoma differentiation-associated gene 5 product (MDA5) antibody. Here, we review important cutaneous manifestations seen in patients with DM, and we examine the relationship between the skin changes and myositis-associated autoantibodies. Correct evaluation of cutaneous manifestations and myositis-associated autoantibodies should help the clinician in the early diagnosis of DM, for a quick recognition of cutaneous signs that may be the symptom of onset before muscle inflammation.

Keywords Anti-MDA5 antibody · Anti-Mi-2 antibody · Anti-TIF1γ antibody · Cutaneous manifestation · Dermatomyositis · Myositis-associated autoantibody

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with characteristic cutaneous lesions. Some patients manifest the skin disease but without clinical muscle symptoms, a condition called amyopathic DM. Although the etiology remains unknown, autoantibodies to various cellular constituents are found in sera from patients with DM such as systemic lupus erythematosus (SLE) and systemic scleroderma (SSc) [1, 2]. Recent studies on myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) have clarified that they are useful tools for identifying clinical subsets of patients with DM [3, 4]. Since some MSAs are not always specific to myositis but are sometimes associated with respiratory and/or dermatological disease, the recent review recommends that we regard all recently established autoantibodies as MAAs instead of distinguishing between MSAs and MAAs [5].

Although myopathy is required as a finding for diagnosis of DM according to conventional criteria [6–9], DM can be diagnosed by accurate evaluation of the cutaneous manifestations. This review article discusses the cutaneous signs of DM and their relationship to MAAs.

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Cutaneous Manifestations of Dermatomyositis

The main cutaneous symptom of DM is erythema, although edema is also visible at lesion sites under slight skin tension and hyperkeratotic changes are discernable at skin sites that receive external irritation. We divide the cutaneous manifestations into those that are pathognomonic/highly suggestive and those that are characteristic/compatible with DM. Even for the former kind of presentation, only around 60~75 % of patients with DM had such eruptions in a Japanese multicenter study [8]. The important strategy for accurate evaluation is (1) to comprehensively recognize the simultaneous presence of multiple skin symptoms in a patient and (2) to confirm the pathological findings of skin biopsy specimens.

Highly Diagnostic, Frequently Observed Skin Lesions of Dermatomyositis

Heliotrope Rash

Heliotrope rash is periorbital erythema that is often accompanied with symmetrically distributed edema (Fig. 1a, b). The upper eyelid is mostly involved, possibly from the stimulus of blinking. In very rare cases, only edema with little color change is seen or the erythema is asymmetrical. Heliotrope rash and periorbital erythema can be seen in many other conditions, including systemic lupus erythematosus (Table 1).

Gottron Papules and Gottron Sign

Gottron papules and Gottron sign are papules and erythema, respectively, at the joint extensor. They are erythematous-to-violaceous plaques often overlying the dorsolateral aspect of metacarpophalangeal joints, proximal interphalangeal joints, and/or distal interphalangeal joints (Fig. 1c–e). Gottron sign can be seen also over bony prominences, such as the elbows, the knees, and, less commonly, the medial malleoli (Fig. 2g, h). According to Dr. R. D. Sontheimer, since "Gottron sign" was originally used to describe acral skin changes of familial acrogeria, "Gottron sign of DM" is a more accurate designation of the lesions addressed in the current review [10]. The points of differential diagnosis of Gottron papules/sign are listed in Table 2.

Occasional Observed Skin Lesions of Dermatomyositis

Facial Erythema

Facial erythema in DM is frequently seen at the malar area, the forehead, the temples, the medial angle areas of eye and around the nose, and the preauricular area (Fig. 1f, g). Basically, the nasolabial folds are spared. The distribution sometimes resembles that of seborrheic dermatitis. The auricle is sometimes targeted at the helix (Fig. 1h).

Periungual Changes

Periungual areas show erythema, dilated capillary loops, cuticular hemorrhages, and/or cuticular overgrowth (Fig. 1i, j), which can be also seen in patients with SSc and, rarely, in patients with SLE. As in SSc, the severity of telangiectasia and vessel dropout reflects the ongoing disease activity of DM, particularly in the skin [11].

Inverse Gottron Papules (Sign)

Papules or erythema overlying the palmar surfaces of the hand joints are less commonly seen (Fig. 1k, l) [12]. In a Japanese study, such eruptions were reported to be associated with acute/subacute interstitial lung disease (ILD) [13].

Mechanic's Hands

Mechanic's hands were reported to be the most characteristic cutaneous marker of anti-synthetase syndrome and consist of hyperkeratosis, scaling, and fissuring of the fingers [14, 15]. The lesions are distributed along the ulnar aspect of the thumb and radial aspect of the fingers and are most prominent on the index and middle fingers, with infrequent extension to the palm (Fig. 1m, n). Although mechanic's hands are found commonly in the setting of anti-synthetase syndrome, they are also seen in cases of polymyositis (PM), classic DM, and amyopathic DM not associated with anti-synthetase antibody [10], according to previous reports and our experience.

V-Neck Sign

Violaceous erythema is sometimes seen in the V area of the neck and the upper chest, probably caused by photosensitivity. Approximately 50 % of patients with DM experience photosensitivity [16], and severe photosensitivity may cause erythroderma. With long-standing inflammatory periods, poikilodermatous changes commonly develop in this area (Fig. 2a, b).

Shawl Sign

Shawl sign is symmetrical violaceous erythema that extends across the nape of the neck to the posterior aspects of the shoulders and upper back (Fig. 2d).

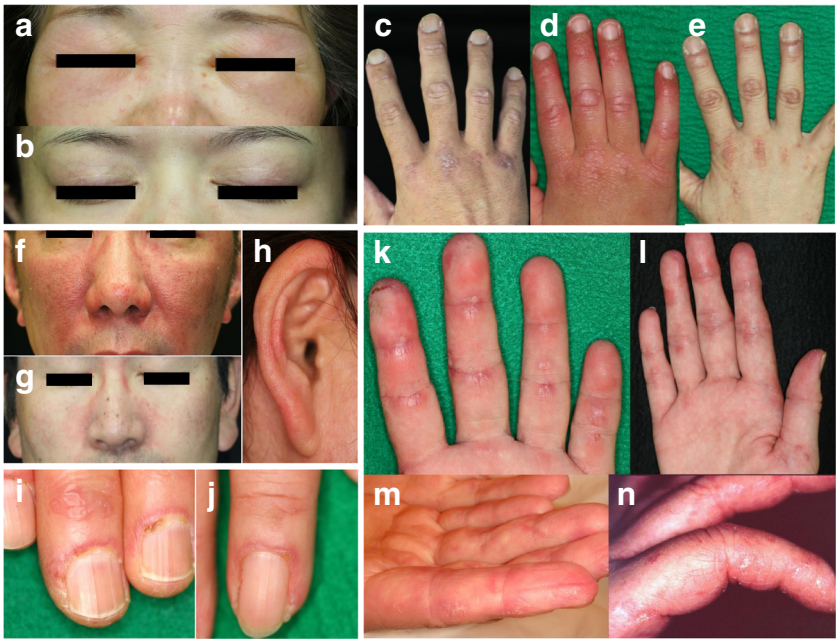

Fig. 1 Clinical images of dermatomyositis (part I): eruptions on face, hands, and fingers. **a**, **b** heliotrope rash. **c–e** Gottron papules and Gottron sign. **f–h** Erythema on the face and ear. **i**, **j** Periungual changes. **k**, **l** Inverse Gottron. **m**, **n** Mechanic's hands

Flagellate Erythema

The trunk should also be investigated when DM is suspected. Centripetal flagellate erythema, patchy violaceous erythema, and/or poikilodermatous changes appear less often on the back, lateral chest, and/or upper buttocks (Fig. 2c, d). Such manifestations can be seen in adult-onset Still's disease, bleomycin-induced eruptions, and dermatitis from ingestion of shiitake mushrooms.

Vesiculo-Bullous Eruptions

Multiloculated vesicles or bullous lesions can develop, rarely, on the dorsal surfaces of the hands or forearms and on other areas (Fig. 2e). Such eruptions may be caused by liquefaction degeneration of the epidermis, subepidermal edema with mucin deposition in the upper dermis or complications from autoimmune bullous diseases. Although a Japanese study showed the incidence of internal malignancy to be much higher in patients with vesiculo-bullous DM than in patients without bullous lesions [17], no such statistical analysis has been reported since then.

Table 1 Points of differential diagnosis for heliotrope rash versus dermatomyositis

Contact dermatitis
Angioedema
Erysipelas
Lupus erythematosus
Sweet's syndrome
Lymphoma
Thyroid dysfunction
Blepharitis granulomatosa
Superior vena cava syndrome

Purpura

Purpura is very rarely found in Gottron sign lying over bony prominences or other lesions (Fig. 2f).

Alopecia

Mild to moderate nonscarring diffuse alopecia of the scalp in DM is relatively common (Fig. 3a, b). Even after the disease activity diminishes, the alopecia may persist.

Panniculitis

Erythematous, firm, tender areas of panniculitis develop on some patients with DM. Some lesions are followed by calcification (Fig. 3c, d). They often occur on the buttocks and upper thighs. Lipodystrophy is also known to have a strong association with juvenile-onset DM (JDM). It can be regarded as a result of longstanding panniculitis [18].

Calcinosis Cutis

Calcification frequently occurs in areas of panniculitis or in poikilodermatous areas and increases over the course of months or years (Fig. 3c, d). Widespread or joint-site calcification sometimes causes functional problems and severe pain. Extrusion of calcium through the skin is associated with

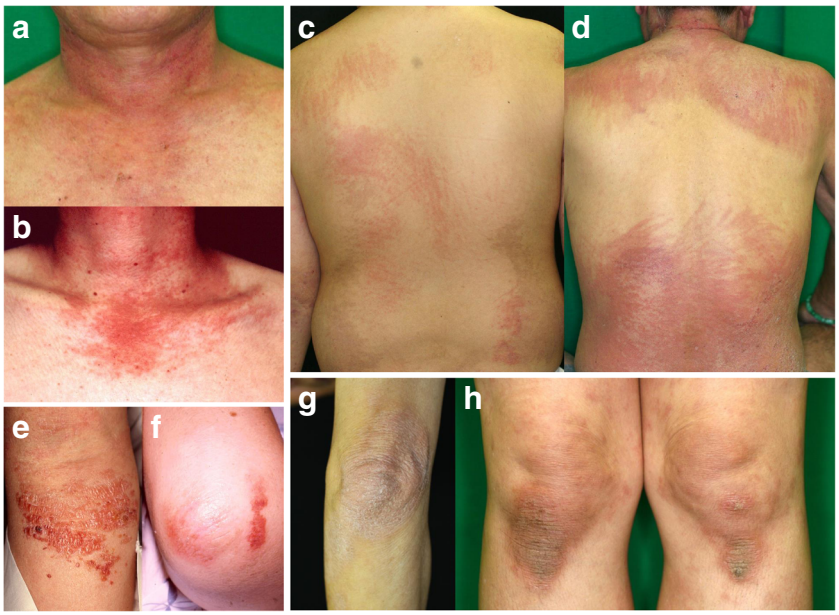

Fig. 2 Clinical images of dermatomyositis (part II): eruptions on neck, trunk, and extremities. **a**, **b** V-neck sign. **c**, **d** Flagellate erythema (**d** also shows shawl sign). **e** Vesiculo-bullous eruption. **f** Purpura. **g**, **h** Gottron sign

ulceration and infection. Calcinosis, a major cause of morbidity in patients with JDM, occurs in up to 30 % of cases [19].

Skin Ulcers

Skin ulcers are associated with cutaneous vasculitis or with vascular damage due to panniculitis/calcification. Some ulcers occur at the site of Gottron sign (Fig. 3e, f), and some occur on the buttocks and thighs. Figure 3g shows skin ulcers of holster sign: Violaceous erythema underlies the general area where a pistol holster is worn at a belt on the waist.

Poikiloderma

Poikiloderma is circumscribed violaceous erythema containing telangiectasia, hypopigmentation, hyperpigmentation, and superficial atrophy (Fig. 3h). This disease is commonly found on the posterior shoulder, upper arm, back, buttocks, and V-neck area.

Table 2 Points of differential diagnosis for Gottron papules/sign versus dermatomyositis

Knuckle pad
Verruca vulgaris
Lichen planus
Sarcoidosis
Acanthosis nigricans
Erythema elevatum diutinum
Multicentric reticulohistiocytosis

Pruritus

Severe pruritus is sometimes present, especially in the early course of the skin lesions from DM. It is often resistant to therapies of oral antihistamines and corticosteroid ointments.

Pathological Findings of Dermatomyositis Skin Biopsy

In the acute phase of dermatomyositis, the skin histological changes are indistinguishable from lupus erythematosus. The erythematous eruption shows slight hyperkeratosis and epidermal atrophy with effacement of the rate ridge (Fig. 4a). Basal cell liquefactive degeneration is typical, and cytoid bodies are sometimes found. There is upper dermal edema, and melanophages can be seen. Perivascular lymphocytic infiltration of activated T-lymphocytes and macrophages is present. Mucin deposits, which occur in the dermis, although not diagnostic, are suggestive of dermatomyositis.

Gottron papules are characterized by hyperkeratosis, acanthosis, and mild papillomatosis (Fig. 4b). The changes of interface dermatitis are seen as described above. Direct immunofluorescence of lesional skin may reveal granular deposits of immunoglobulin and complement at the dermal-epidermal junction. Magro and Crowson demonstrated C5b-9 deposition in blood vessel walls and at the dermal-epidermal junction in conjunction with a negative lupus band test with high specificity (94 %) and sensitivity (79 %) against lupus [20].

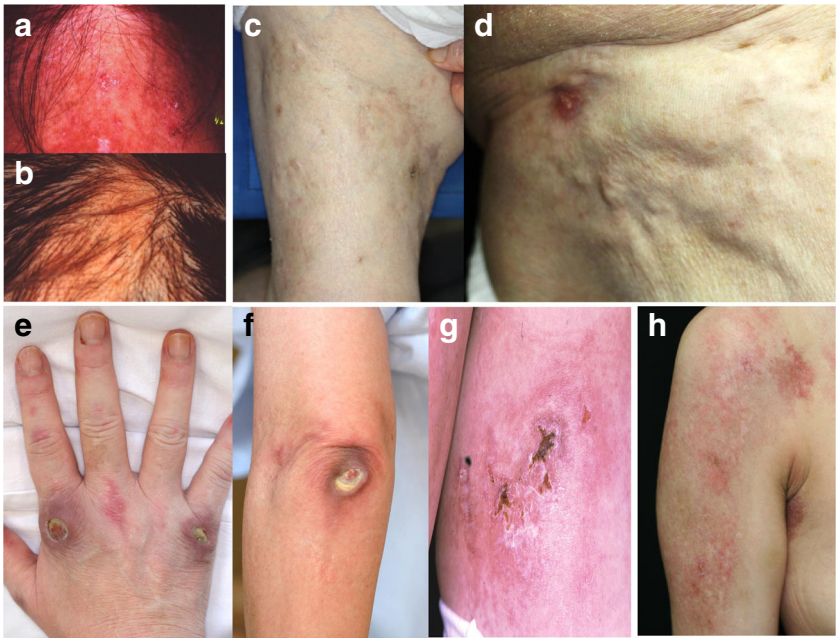

Fig. 3 Clinical images of dermatomyositis (part III): other cutaneous manifestations. **a**, **b** Alopecia. **c**, **d** Calcification (some parts accompanied with panniculitis). **e**–**g** Skin ulcer. **h** Poikiloderma

Cutaneous Manifestation of Dermatomyositis and Myositis-Associated Autoantibodies

Although elucidation of the association between MAAs and types of cutaneous manifestations would be useful for evaluating the etiology of MAAs, a strict association has rarely been established. There have not been many large cohort studies. The diverse results of the previous studies might also be due to racial differences or clinical backgrounds.

Anti-Mi-2 Antibody

The previous studies demonstrated that the anti-Mi-2 antibody is associated with the classic features of DM, including heliotrope rash, Gottron's papules, the V-neck sign, the shawl sign, cuticular overgrowth, and photosensitivity [21–23]. A recent Japanese study showed that nailfold punctate hemorrhages are more frequently seen in patients with anti-Mi-2 (89 %) than in patients with anti-melanoma differentiation-associated gene 5 product (MDA5) (37 %) or anti-transcriptional intermediary factor 1 gamma (TIF1γ)/α (44 %) [24]. A recent Brazilian study showed that anti-Mi-2-positive DM patients are significantly more likely to have photosensitivity and the shawl sign by univariate analysis but that, by multivariate analysis, the anti-Mi-2 antibody was associated only with photosensitivity [25]. According to a North American collaborative study, JDM patients with the anti-Mi-2 antibody showed the V-neck sign, the shawl sign, and cuticular overgrowth significantly less than adult DM patients did [26].

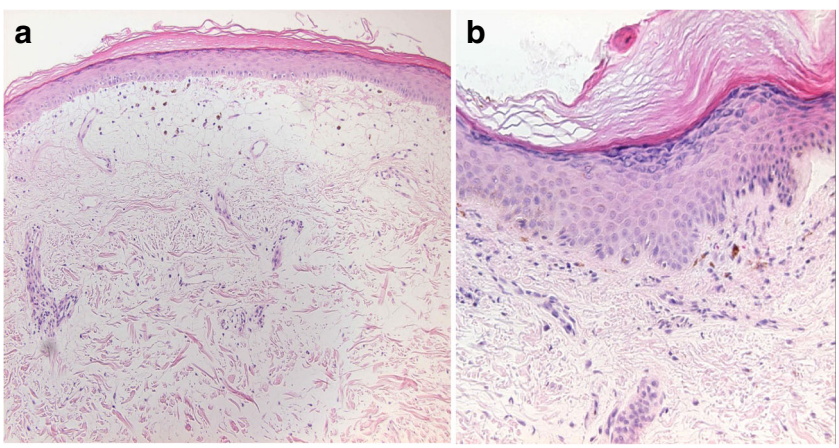

Fig. 4 Histopathology of dermatomyositis. **a** Histological image of a skin biopsy specimen from erythema on the chest. **b** Histological image of a skin biopsy specimen from Gottron sign (hand)

Anti-ARS Antibody

Although mechanic's hands are a well-known cutaneous sign associated with the anti-aminoacyl-tRNA synthetase (ARS) antibody [27], this sign can also be seen in various cases not associated with anti-ARS described above. Juvenile-onset patients with anti-ARS show mechanic's hands less frequently than adult-onset patients (32 vs 71 %) [26].

Hamaguchi et al. investigated the clinical features of adult Japanese patients with six different kinds of anti-ARS [28]. Mechanic's hands were shown in patients with anti-Jo-1 with the highest frequency (56 %), and the prevalence was significantly higher than in patients with anti-PL-12 (22 %), anti-KS (23 %), and anti-EJ (29 %). Heliotrope rash was found in 16 % patients with anti-ARS. Such manifestation was found predominantly in patients with anti-PL-7 (38 %) and anti-EJ (21 %). These frequencies were higher than those for patients with anti-Jo-1 (7 %). Gottron's sign (hand, elbow, and/or knee) was found in 27–45 % in patients with anti-EJ, anti-PL-7, anti-PL-12, and anti-Jo-1, whereas this manifestation and heliotrope rash were rarely found in patients with anti-KS or anti-OJ, possibly due to the very small number of DM patients with anti-KS or anti-OJ.

Anti-TIF1γ/α Antibody (Anti-155/140 Antibody)

Anti-155/140 antibodies, which were originally nabbed by Kaji et al., are identical to anti-p155 antibodies [29, 30]. Autoantibodies against a 155 kDa polypeptide and a 140 kDa polypeptide target TIF1γ and TIF1α, respectively [31]. Anti-155/140 antibodies always recognize TIF1γ and sometimes recognize TIF1α. Although it remains obscure as to whether all anti-p155 antibodies recognize only p155 (TIF1γ) in published reports, I would like to discuss both studies on anti-155/140 antibodies and on anti-p155 antibodies simultaneously here.

In a JDM study, patients with these antibodies had significantly more cutaneous involvement, including Gottron's papules ($P=0.003$), skin ulcers ($P=0.005$), and subcutaneous edema ($P=0.013$) in a UK cohort [32]. In a US cohort, generalized lipodystrophy was reported to be associated with these antibodies [33]. In a subsequent report of US cohort, anti-TIF1γ/α antibody-positive patients showed classic JDM features, including Gottron papules, heliotrope and malar rashes, periungual abnormalities, photosensitivity, linear extensor erythema, cuticular overgrowth, V-neck sign, shawl sign, lipodystrophy, and erythroderma [26].

Fiorentino et al. analyzed cutaneous manifestations in patients with anti-TIF1γ in detail [34]. Significantly, frequent cutaneous features in the antibody-positive patients were diffuse photoerythema, including scalp rash, facial rash, V-neck rash and back rash, holster sign, and palmar papules. These palmar papules were hyperkeratotic and verruca-like papules, which were different from anti-MDA5-associated palmar papules, which were erythematous and often tender. The skin disease severity scored using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) was significantly higher in the anti-TIF1γ-positive patients than in the anti-TIF1γ-negative patients.

We call the red face in DM patients with the anti-TIF1γ antibody "dusky red face" (Fig. 5). In such patients, a few cases develop erythroderma, which is not always associated with internal malignancy.

Anti-TIF1α Antibody

Since the anti-TIF1α antibody appears simultaneously with anti-TIF1γ antibodies, the specific clinical association of anti-TIF1α antibody should be considered by comparing patient groups with anti-TIF1α/γ antibody to those with anti-TIF1γ antibody alone. According to such a study performed by Fujimoto et al. [31], truncal erythema was the only skin manifestation found significantly more in patients with anti-TIF1α/γ antibody that in patients with anti-TIF1γ antibody alone (77 vs 33 %).

We showed that anti-Mi-2-positive patients simultaneously had the anti-TIF1α antibody [35]. Since anti-TIF1α-specific examination for a large number of anti-Mi-2-positive patients has not been performed, it has not been proven whether there are patients with monospecific anti-TIF1α antibody without anti-Mi-2 (and without anti-TIF1γ antibody).

Anti-MDA5 Antibody

Patients with the anti-MDA5 antibody have several distinguishable mucocutaneous features. Fiorentino et al. showed that skin ulcerations, palmar papules (inverse Gottron), mechanic's hands, Gottron sign (elbow/knee), hand swelling, diffuse hair loss, panniculitis, and oral pain and/or ulcers were associated with this antibody [36]. They also demonstrated a strong association between location of skin ulcer at the digital pulp/periungual region and this antibody in a subsequent study [37]. Anti-MDA5 antibodies were associated with ILD largely in patients with skin ulcers. Also in a Japanese study, although the presence of skin ulcers was not a prognostic marker in patients with anti-MDA5, skin ulcers were more frequently found in them than in patients with anti-Mi-2 or anti-TIF1 [24]. Also, in a JDM study, the anti-MDA5 antibody was associated with skin ulcers ($P=0.03$) and oral ulceration ($P=0.01$) in a UK cohort [38].

Anti-NXP2 Antibody

The anti-NXP2 antibody is common in JDM, in which it is identifiable in 13–23 % of patients [39, 40]. In a study by the JDM Research Group of the UK, the anti-NXP2 antibody was

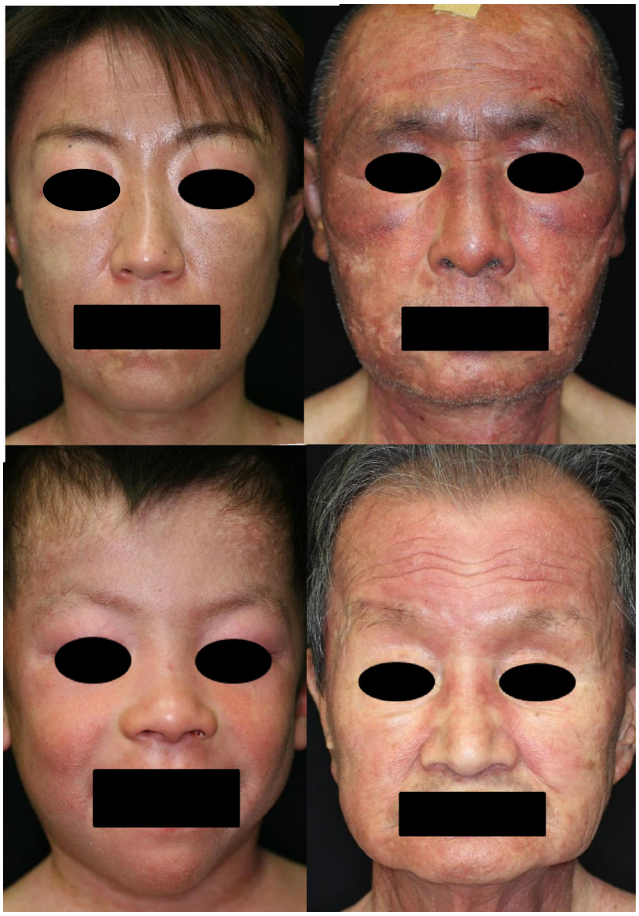

Fig. 5 Anti-TIF1-γ antibody-positive "dusky red face"

shown to have a significant association with calcinosis (OR 2.10, 95 % CI 1.10–4.01) [41]. Forty-three percent of anti-NXP2-positive patients developed calcinosis. In US patients with adult-onset DM, this antibody was strongly associated with calcinosis in multivariate analysis (OR 15.52, 95 % CI 2.01–119.90) [42]. In an Italian study of adult DM/PM, heliotrope rash (P=0.01) and calcinosis (P=0.09) were found to be more frequent in patients with anti-MJ antibodies, which were the most frequent specificity [43]. Japanese studies found no association between this antibody and calcinosis [44, 45].

Anti-SAE Antibody

Most patients with anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies present with skin lesions first and then develop myositis [46–48]. The initial studies showed that periungual eruptions appeared in all patients with the anti-SAE antibody and that mechanic's hands were found in none of them [46, 47]. However, subsequent studies showed the absence of periungual eruptions and the presence of mechanic's hands in some anti-SAE-positive patients [49, 50]. To date, fewer than 40 cases of anti-SAE antibody-positive patients have been reported, including our patients.

Anti-PM/Scl Antibody

Marie et al. noticed that anti-PM/Scl antibody-positive patients with PM/DM commonly had mechanic's hands, a finding similar to that for anti-ARS-positive patients [51]. They found that two of 20 patients with PM/DM presented hyperkeratotic rhagadiform hand symptoms. Interestingly, we also found three anti-PM/Scl antibody-positive patients with DM, and two of them had mechanic's hands in addition to distinctive sole hyperkeratotic rhagadiform symptoms [52].

Other MAAs

Cutaneous manifestations associated with the presence of the anti-TIF1β antibody, the anti-Ku antibody, anti-SRP, and anti-HMGCR have not been reported. We recently reported autoantibodies against DNA mismatch repair enzyme, including MLH1, MSH2, PMS1, and PMS2 in DM/PM; however, we were unable to find the characteristic DM cutaneous signs associated with these autoantibodies [53]. Table 3 summarizes the rough associations between cutaneous manifestations and MAA, except for heliotrope rash and Gottron papules/signs.

Concluding Remarks

Cutaneous involvement of DM is often found at areas that are stretched and/or rubbed. Mechanical stress associated with the

Table 3 Associations between skin lesions of dermatomyositis and myositis-associated autoantibodies

Cutaneous sign	Autoantibodies
Hair loss	Anti-MDA5
Oral ulcers	Anti-MDA5
Photosensitivity	Anti-Mi-2, anti-TIF1
V-neck sign, shawl sign	Anti-Mi-2 anti-TIF1 (scalp, face, neck, back; erythroderma)
Inverse Gottron	Anti-MDA5 (erythematous, tender), anti-TIF1 (not erythematous, not tender)
Cuticular overgrowth	Anti-Mi-2, anti-TIF1 (juvenile DM)
Nailfold punctate hemorrhage	Anti-Mi-2
Mechanic's hands	Anti-ARS, anti-MDA5, anti-PM/Scl
Skin ulcer	Anti-MDA5 (digital pulp/periungual) anti-TIF1 (juvenile DM)
Calcinosis	Anti-NXP2 (juvenile DM)

stretching of skin over joints could cause such skin disease. Microtrauma and/or ischemia from stretching at these sites could be a local factor. Around orbital areas, blinking is constantly performed during waking hours by the movement of the upper eyelids, which could also be a pathogenic factor.

The involvement of the face and extensor sides of the arms may be related to sun exposure in some patients with DM. These environmental stresses on the skin are known to be provoking factors of the Köbner phenomenon (isomorphic response).

The Köbner phenomenon, which was first described in psoriatic skin by Dr. Heinlich Köbner in 1876, is seen not only in autoimmune inflammatory dermatitis but also in the skin of patients with systemic autoimmune disease (lupus, dermatomyositis, etc.) and sarcoidosis [54]. Although the pathophysiology of the Köbner phenomenon has not been clarified, environmental stimuli are known to cause many inflammatory substances, including various cytokines, stress proteins, and adhesion molecules, to be released in local tissues, suggesting a cause of Köbner phenomenon. Also, some autoantigens are released from intracellular areas [55] and could be fragmented [56]. Future studies will be necessary to investigate whether UV light or other stimuli affect expression, structure, or subcellular localization of autoantigens targeted by MAA in the skin [57].

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