Covert clues: the non-hallmark cutaneous manifestations of dermatomyositis

Rochelle L. Castillo[1]^, Alisa N. Femia[2]

[1]Department of Medicine, Division of Rheumatology, NYU Grossman School of Medicine, New York, NY, USA; [2]Ronald O. Perelman Department of Dermatology, NYU Grossman School of Medicine, New York, NY, USA

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Correspondence to: Alisa N. Femia, MD. Ronald O. Perelman Department of Dermatology, New York University Langone Medical Center, 240 E 38th St, 11th Floor, New York, NY 10016, USA. Email: alisa.femia@nyulangone.org.

Abstract: Dermatomyositis (DM) is a strikingly heterogenous disease characterized by a broad and ever-evolving spectrum of cutaneous manifestations that transcend the classic "hallmarks" defined by Peter and Bohan in 1975. Despite the increasing preponderance and ubiquity of autoantibody, radiologic, and electrophysiologic testing, the diagnosis of DM still hinges largely on prompt detection of cutaneous manifestations of this condition. While pathognomonic cutaneous features of DM are more readily recognizable, many patients present with subtle and/or atypical skin manifestations, and diagnosis of DM may require clinician identification of these cutaneous clues. In this review, we highlight several of the lesser-known skin manifestations of DM, specifically, panniculitis, diffuse subcutaneous edema, erythroderma, calcinosis, ulceration, flagellate erythema, Wong-type DM, gingival telangiectasias, and the ovoid palatal patch. We describe the clinical and histopathologic presentation of these cutaneous findings. While manifesting less frequently than the heliotrope rash, Gottron's papules, and Gottron's sign, these cutaneous clues are equally important for clinicians to recognize in order to facilitate timely diagnosis and early intervention.

Keywords: Skin; cutaneous; myositis; dermatomyositis (DM)

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The presence of pathognomonic skin findings that are readily recognized by healthcare providers across the range of medical specialties has given dermatomyositis (DM) a unique diagnostic advantage over the other idiopathic inflammatory myopathies. From Peter and Bohan in 1975 to the EULAR/ACR classification criteria of 2016, the heliotrope rash, Gottron's papules, and Gottron's sign have endured as the indisputable cutaneous hallmarks of DM (1,2). However; over the years, a myriad of other skin manifestations with varying degrees of specificity have emerged as characteristic clues to diagnosing DM, leading to further expansion of the known DM phenotype. Further, in a subset of DM patients, sparing of the muscles has been observed, prompting Sontheimer to propose the term "clinically amyopathic DM" to refer to DM patients with neither clinical nor serologic, electrophysiologic, or radiologic evidence of muscle involvement (amyopathic DM) or those with findings of myopathy on work-up but no overt clinical disease (hypomyopathic DM) (3-5).

In recognition of this evolving heterogeneity, the Skin

^ ORCID: 0000-0002-1704-9420.

Table 1 List of 25 potential dermatomyositis classification criteria divided into categories of distribution, morphology, symptomatology, pathology and contextual factors proposed by the Skin Myositis Delphi Group (6)

Categories	Criteria
Distribution	• Scalp
	• Eyelid
	• Nasolabial fold
	• Upper chest 'V'
	• Upper back 'shawl'
	• Elbow, knee
	• Lateral upper thigh/hip
Morphology	• Erythema to violaceous erythema
	• Erythematous papules/plaques (often flat-topped) ± scale over the dorsal metacarpophalangeal/interphalangeal (MCP/IP) joints
	• Macular erythema over the dorsal MCP/IP joints
	• Nailfold capillary loops by eye/microscopy
	• Nailfold erythema
	• Cuticular dystrophy
	• Poikiloderma
	• Lateral digit fissuring/hyperkeratosis/papules
	• Linear extensor erythema of digits
	• Eyelid edema
	• Erythematous palmar macules and papules
Symptomatology	• Pruritus of scalp
	• Photosensitivity
Labs/pathology	• Interface dermatitis
	• Dermal mucin
	• Presence of DM-specific myositis antibodies
Contextual factors	• Interstitial lung disease on CT
	• Muscle weakness

Myositis Delphi Group consisting of 50 dermatologists and rheumatologists from North America, South America, Europe, and Asia identified and proposed 25 items that could be incorporated into a more encompassing and comprehensive classification criteria for skin-predominant disease (*Table 1*) (6). These items could potentially expand the definition for what constitutes a "hallmark" cutaneous manifestation and subsequently facilitate early diagnosis and treatment, which is particularly critical in the subgroup of patients with skin-limited disease. Validation studies are currently in progress.

For the purposes of this review, we present several less common cutaneous findings of DM that, while relatively rare, are equally important to recognize in order to facilitate timely diagnosis and management of DM.

Panniculitis

First described in 1924, clinically-apparent DM-associated panniculitis, defined as inflammation of the subcutaneous

fat, is considered a rare manifestation that has been reported in about 30 adult and juvenile DM patients (7-11). However, subclinical panniculitis has been described in up to 10% of cases and thus, may occur more frequently than initially thought (12-15). It appears as tender, indurated, erythematous nodules and plaques on the proximal extremities and/or abdomen typically with sparing of the face (10,14,16,17). Ulceration, lipoatrophy, and calcinosis may also be present (8,13,18,19). Temporally, it can develop prior to, simultaneously with, or after the diagnosis of DM (10,19). Histopathologically, it appears as a lobular panniculitis with lymphocytic and plasma cell infiltrates often accompanied by the characteristic epidermal and dermal changes found in DM, namely vacuolar interface dermatitis and mucin deposition (16,20). Of note, the histopathology of panniculitis in DM is virtually identical to that of lupus panniculitis in the absence of overlying epidermal changes of discoid lupus erythematous, and as such, correlation with other clinical attributes such as anatomic distribution of lesions and concurrent symptomatology are required to distinguish between the two entities (20,21). An association with various solid malignancies was reported in six cases of adult DM and with the anti-melanoma differentiation associated gene 5 protein (MDA5) antibody in a large Mediterranean cohort (OR: 3.85, 95% CI: 1.11–13.27, P<0.05) (18,22). In one case series, four out of 18 showed positivity for anti-Mi-2, two for anti-small ubiquitin-like modifier-activating enzyme (SAE), and one each for anti-transcription intermediary factor 1-gamma (TIF-1-gamma), anti-nuclear matrix protein-2 (NXP2), and anti-ribonucleoprotein (RNP) (20).

The approach to treatment is the same for classic DM with high-dose systemic corticosteroids constituting first line treatment and refractory cases managed with pulse-dose steroids, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, and/or intravenous immunoglobulin (IVIG) (2,5). In general; however, DM patients with panniculitis have been found to be responsive to treatment, which suggests that presence of panniculitis may portend a good prognosis based upon limited case reports (19,23).

Diffuse subcutaneous edema

While periorbital and focal/localized subcutaneous edema especially in poikilodermatous sites is a common feature of DM, more widespread edema, sometimes to the point of anasarca, is considerably rare (24-29). To date, only 20 or so cases involving juvenile and adult patients with DM presenting with diffuse limb, trunk, and/or generalized subcutaneous edema have been reported in the literature since it was first described by Nitsche in 1988 (24,30-38). Most cases are idiopathic but an associated malignancy has been reported in a few (28,32,36,38). Onset can precede, accompany, or follow the diagnosis of DM. The mechanism for this more intense form of edema that exceeds that seen in typical DM is unclear; a hypothesis is that it represents excessive vascular permeability and subsequent leakage as a consequence of immune complex deposition (25,31,39). This more severe form of subcutaneous edema is not clearly correlated with autoantibody status, although subcutaneous edema defined as pitting or non-pitting extremity edema accompanying the active phase of the disease has been found to occur more often in anti-NXP-2 positive than in anti-NXP-2 negative patients (36% *vs.* 19%, P=0.01) (40). Histopathology is non-specific and shows findings typical for DM. Fat-suppressed T2-weighted and/or short τ inversion-recovery (STIR) magnetic resonance imaging (MRI) has been found to be useful in identifying the extent of the subcutaneous and muscle edema and in monitoring treatment response (24-26,35). Presence of subcutaneous edema may indicate a more severe form of DM that requires more aggressive management and may carry a worse overall prognosis (24,26,31). In many cases, pulse dose steroids and/or IVIG was required to gain control of the disease (24-28,32).

Erythroderma

Erythroderma, also referred to as exfoliative dermatitis, is a rare, potentially life-threatening condition characterized by diffuse erythema and scaling involving more than 80–90% of the body surface area (41,42). A pre-existing dermatosis, most commonly psoriasis or atopic dermatitis, is the most common cause of erythroderma; however, about 20% of cases remain idiopathic (41-46). Autoimmune connective tissue diseases as a group are considered an uncommon cause of erythroderma, with DM even less so. To date, less than 10 cases of DM-associated erythroderma have been reported, mostly in adults, with some occurring as a paraneoplastic syndrome accompanying a gastric or hepatobiliary malignancy (47-55). Erythroderma can be the presenting feature that eventually leads to the diagnosis of DM or can occur concomitantly or after the diagnosis of DM. The histopathology is non-specific and includes the findings typical for DM, specifically vacuolar interface

change, papillary dermal edema, and a dermal perivascular lymphocytic infiltration (49). There is no clear relationship with autoantibody status; anti-Mi-2 was positive in one case and TIF-1-gamma in another case associated with gastric adenocarcinoma (48,51). Treatment is the same as for classic DM and, if occurring as a paraneoplastic syndrome, involves addressing the concomitant malignancy.

Calcinosis

Calcinosis, or the dystrophic deposition of calcium salts (specifically carbonate apatite) in the skin and soft tissues, is a well-recognized feature of juvenile DM, occurring in about 40% of JDM patients (56-58). However, it is only about half as common in adults, with a prevalence of about 20% and tends to occur later in the disease course (59,60). DM-associated calcinosis can be categorized into four overlapping types—calcinosis circumscripta, which appears as superficial, discrete papules or nodules on the skin and around joints; tumoral calcinosis, which occurs deeper in the dermis, subcutaneous tissue, muscle, and/or fascia; deposits along the myofascial planes known a calcinosis universalis; or an extensive, generalized form known as exoskeletal calcinosis (56,57,61-63). The lesions may be associated with significant pain and discomfort, particularly if concomitant ulceration, panniculitis, and secondary infection occur (56). The distribution of DM-associated calcinosis is somewhat distinct from that of systemic sclerosis in that lesions prominently occur not only on the extremities, but also on the trunk (59,64). More so, calcinosis can develop on virtually any site, including the face and jaw (59,65,66). An association between the presence of anti-NXP-2 antibody and presence and severity of calcinosis is well-established in both juvenile and adult DM patients (40,67-69). On biopsy, calcinosis cutis appear as largely acellular calcium deposits in the skin and subcutaneous tissue that stain with von Kossa silver stain or Alizarin red (70). Plain radiographs may also be useful to determine the pattern, depth, and spread of calcinosis (71). Treatment remains challenging and no guidelines exist for selecting the best initial regimen. Several classes of drugs have been used in various combinations. Anti-inflammatory medications such as IVIG, systemic and intralesional steroids, infliximab, abatacept, rituximab, colchicine, minocycline, and thalidomide have been employed with varying degrees of success. Another approach includes the use of medications that influence serum calcium and phosphate levels such as diltiazem, bisphosphonates, probenecid, aluminum hydroxide, warfarin, and intradermal, intralesional, or intravenous sodium thiosulfate. Surgical removal of calcinotic nodules is an option for those with more contained, limited forms of the disease (59,72).

Ulcers

One of the most widely substantiated clinical and autoantibody correlations in adult (but not juvenile) patients with DM is that between cutaneous ulcers and anti-MDA5 antibody positivity, with odds ratios ranging from 10 to 18 in some cohorts (73-75). The other features that characterize anti-MDA5 disease include clinically amyopathic DM, rapidly-progressive interstitial lung disease, and painful palmar papules (73,74,76,77). However, the relationship between skin ulcers and anti-MDA5 positivity is not exclusive as it has also been observed in DM patients harboring other myositis-specific and myositis-associated antibodies (73). Ulceration in DM patients can occur in various locations such as the elbows, knees, and trunk; however, several sites such as the digital pulp, periungual areas, and the skin overlying Gottron's papules are more specific for the anti-MDA5-associated phenotype (73,74,78,79). The ulcers develop as a consequence of multiple, varied pathologic processes such as mechanical trauma, calcinosis, and immune-mediated vascular damage; in patients with anti-MDA5 positivity, it is largely attributed to profound vasculopathy induced by a high type-1 interferon signature (74,80). Independent of whether or not it occurs in the context of anti-MDA5 positive disease, the presence of ulcers has been linked to a more severe disease course in both adult and juvenile DM patients that is punctuated by frequent flares and an increased incidence of complications such as serious infections (gangrene, osteomyelitis), extensive tissue necrosis, and/or systemic ulcerative disease and thus, is largely considered an adverse prognostic factor (73,74,81-83). A significant correlation between ulceration (typically with accompanying cutaneous necrosis) and malignancy has also been described in several European cohorts (84-86), although not in a United States-based cohort (73). There are no established ulcer-directed therapies but cyclophosphamide, cyclosporine, and azathioprine with or without steroids have been shown to be effective in several case reports (74,82,87-89). Most patients, however, will require multiple immunomodulatory drugs in the DM armamentarium such as pulse- or high-dose steroids, IVIG, and other disease-modifying anti-rheumatic drugs (DMARDs). Medications that aim to offset

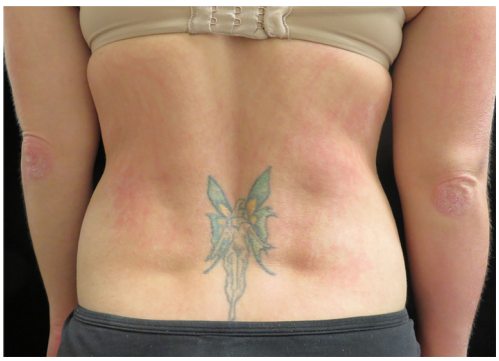

Figure 1 Flagellate erythema. Streak-like erythematous eruption on the arms and mid- to lower back of a patient with DM. DM, dermatomyositis.

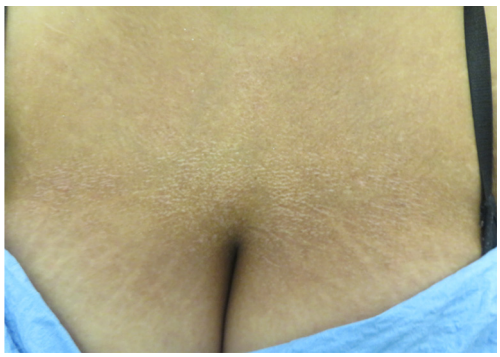

Figure 2 Wong-type dermatomyositis. Pinkish, hyperkeratotic, follicular papules with "islands of sparing" in the lumbosacral area.

the vasculopathy in MDA5-positive patients by improving blood flow (e.g., antiplatelets and calcium channel blockers) have been used with mixed results (74,78).

Flagellate erythema

As the name implies, flagellate erythema is a linear, lacy, streak-like erythematous eruption of macules, papules, and/or plaques on the skin accompanied by pruritus or pain (*Figure 1*) (90,91). Initially described as a distinct side effect of bleomycin exposure, it has since been reported to arise in conjunction with a host of other agents and conditions, including DM (90-101). It is considered a rare manifestation of DM, observed in only 5% of patients in one cohort, and has been noted to occur both prior to and in tandem with the other classic cutaneous signs (101). Only two cases have been reported in juvenile patients to date with the vast majority occurring in adults (97,102). Compared to its bleomycin-induced counterpart which is said to be more brownish in appearance, the flagellate erythema seen with DM is said to be more erythematous, a finding reflective of the higher degree of inflammation (96,98). Histopathologic information derived from 4 cases revealed the typical DM findings of interface dermatitis with a perivascular lymphocytic infiltrate (52,95,102,103). There are no clear phenotypic or antibody associations nor prognostic implications; a positive anti-MDA5 and a positive anti-TIF-1 were noted in 1 case each and concomitant malignancy in 3 cases (95,99,104,105). In contrast to the other cutaneous lesions of DM, flagellate erythema can resolve spontaneously; however, treatment of the other manifestations of DM is still required (90,99).

Wong-type DM

First described in the 1960s by a Hong Kong-based physician after whom it was eventually named, Wong-type DM is a rare variant in which DM clinically and histopathologically overlaps with pityriasis rubra pilaris (PRP), a chronic inflammatory papulosquamous disorder characterized by reddish-orange, variably-sized plaques and follicular papules with intervening areas of unaffected skin known as "islands of sparing" (*Figure 2*) (106,107). To date, there are fewer than 30 reported cases of Wong-type DM in both children and adults (108-114). An association with malignancy was seen in half of the original cohort reported by Wong; however, subsequent reports have not validated this association. Thus, it is unclear whether having the Wong-type phenotype of DM increases the risk of malignancy in excess of what would be expected with classic DM (115). Clinically, Wong-type DM presents with a combination of classic cutaneous DM features such as the heliotrope eruption, Gottron's papules, and poikiloderma alongside the typical reddish-orange confluent papules and plaques that characterize PRP. Hyperkeratosis of the palms and soles is often present. Histopathologically, an overlap between the two disease entities is likewise observed, with vacuolar interface alterations and abundant dermal mucin occurring with alternating mounds of para- and orthokeratosis and follicular plugging (115,116). Onset of PRP varies and can occur prior to, simultaneously with, or after the diagnosis of DM. There is no consistent correlation with autoantibody status; one case was positive for anti-MDA5 (111). Treatment is typically directed at DM rather than PRP and consists of corticosteroids and the

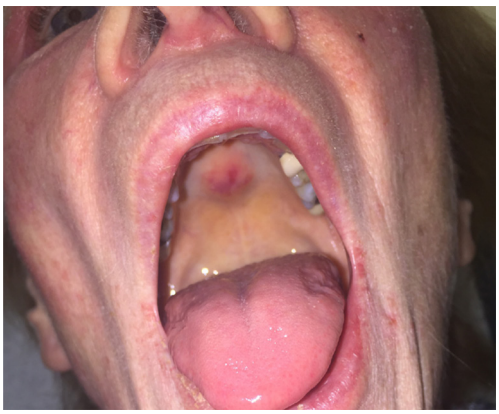

Figure 3 Ovoid palatal patch. Well-defined, ovoid, non-ulcerative erythematous patch on the posterior hard palate.

steroid-sparing DMARDs, with good musculocutaneous response in the majority of patients (115,116). Retinoids, which are used to treat PRP, have anecdotally been used in this context, but there is a lack of literature regarding this class of medications for this entity.

Gingival telangiectasias

Telangiectasias on the skin (in the setting of poikiloderma) and of the nail fold capillaries are well-known features of DM (6,117). However, telangiectasias can also present in the gingival and oral mucosa, a finding that mirrors antibody-mediated vasculopathy seen in DM and can serve an important diagnostic role in JDM (118-120). This finding has been described in both juvenile and adult patients, with one case series reporting a prevalence of 20% in adult DM patients (121). Recurrent, refractory gum bleeding is the usual presenting symptom. Gingival telangiectasias typically occur with other overt musculocutaneous signs of DM but in two cases, were found to develop a few weeks prior, highlighting their role in facilitating early diagnosis in these rare circumstances (118,122). Treatment is the same as for classic DM; additionally, a referral to a periodontist may also be warranted, especially for those with persistent bleeding and discomfort.

Ovoid palatal patch

Another intraoral lesion that has been observed in DM is the ovoid palatal patch. Appearing as a well-defined, arcuate, non-ulcerative erythematous patch on the posterior hard palate, it is strongly associated with the presence of TIF-1-gamma antibodies and with malignancy (*Figure 3*) (123-125). Biopsy of the patch is consistent with the typical DM findings. The approach to therapy is the same as for classic DM with emphasis on a thorough work-up for malignancy.

Conclusions

While the majority of patients with DM will present with hallmark or characteristic cutaneous, muscular, and systemic and systemic symptoms, for those in whom the clinical picture is less straight forward, recognition of non-hallmark cutaneous findings may be particularly crucial. In a disease such as DM that is strikingly heterogenous and that is associated with such dire conditions as malignancy and rapidly-progressive interstitial lung disease, timely diagnosis and early intervention is unquestionably of paramount importance. Dermatologists, rheumatologists, and healthcare providers should thus remain cognizant of these cutaneous clues, however covert, in order to facilitate the diagnostic process and subsequently improve overall patient outcomes.

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