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The clinical features, diagnosis and classification of dermatomyositis



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ABSTRACT

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) characterized by an inflammatory infiltrate primarily affecting the skeletal muscle and skin. Most common and peculiar cutaneous lesions include Gottron's papules, Gottron's sign and heliotrope rash. Different DM subsets have been identified until now encompassing classic DM, amyopathic DM, hypomyopathic DM, post-myopathic DM, and DM sine dermatitis.

Patients with DM have a higher incidence rate of malignancy than the normal population. In these patients cancer occurs in about 30% of cases with higher occurrence in men and in elderly people.

Bohan and Peter's diagnostic criteria, proposed in 1975, have been widely accepted and used until now. In the last ten years muscle immunopathology, myositis specific autoantibodies testing, and the use of new techniques of muscle imaging such as contrast-enhanced ultrasound or Magnetic Resonance Imaging have been introduced in the diagnostic work-up of patients with DM leading to the development of new diagnostic criteria.

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1. Introduction

DM is an idiopathic inflammatory myopathy (IIM) characterized by an inflammatory infiltrate primarily affecting the skeletal muscle and skin with typical cutaneous lesions. Different DM subsets have been identified until now [1–3]. These includes classic DM, when muscular and skin involvement coexist, amyopathic DM (ADM), when the disease affects only the skin, hypomyopathic DM, when cutaneous manifestations of DM are associated with sub-clinical evidence of myositis, post-myopathic DM, when patients with previous classic DM present a recovery of myositis but skin rashes remain active, and DM sine dermatitis, when no rash is detected but histology feature of the muscular biopsy sample is indicative of DM.

DM affects both children and adults with an overall female/male ratio of about 2:1. Patients with IIMs have a higher risk of malignancy than the normal population which in DM occurs in approximately 30% of cases with a higher occurrence in men and in old age [1–4]. DM is a rare disease, although it seems to be the most common IIM in all age groups. The exact incidence and prevalence of the disease is unknown. The reported incidence of DM ranges from 1.2 to 17 new cases per 1,000,000 inhabitants with a

prevalence between 5 and 11 cases per 100,000 individuals [2,3,5,6]. An increasing incidence from the 1940's until now has been observed which is probably due not only to a real increase in disease incidence but also to the development of classification criteria (Bohan and Peter's criteria [7,8] were published in 1975), as well as to new diagnostic tools which contribute to improving diagnostic capability.

2. Clinical features

The onset in DM may be acute (days) or insidious (several months). The cardinal muscular symptom is muscle weakness, mainly affecting the proximal muscles; myalgias can be observed less frequently. The most common clinical sign is the decrease of strength in the proximal muscles associated with contractures. Muscular atrophy (40% of cases) tends to appear late in the course of the disease. In severe cases, respiratory and oropharyngeal muscle involvement can cause dysphagia, respiratory difficulties and *ab ingestis* pneumonia.

Skin manifestations sometimes concur, but more often precede by several months or years muscle involvement [1–3,7]. Euwer and Sontheimer [9] proposed a classification in which DM skin manifestations are subdivided into pathognomonic, highly characteristic and compatible skin lesions (Table 1). The most common and peculiar manifestations, including Gottron's papules, Gottron's sign and heliotrope rash, are shown in Fig. 1.

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Table 1
Cutaneous manifestations of dermatomyositis [9].

Pathognomonic skin lesions of DM

1. *Gottron's papules*

Papules having a violaceous hue overlying the dorsal-lateral aspect of interphalangeal and/or metacarpophalangeal joints. When fully formed, these papules become slightly depressed at the center which can assume a white, atrophic appearance. Associated telangiectasia can be present.

2. *Gottron's sign*

Symmetrical macular violaceous erythema with or without edema overlying the dorsal aspect of the interphalangeal/metacarpophalangeal joints, olecranon processes, patellae, and medial malleoli.

Highly-characteristic skin lesions of DM

1. Periorbital violaceous (heliotrope) erythema with or without associated edema of the eyelids and periorbital tissue.
2. Grossly-visible periungual telangiectasia with or without dystrophic cuticles.
3. Symmetrical macular violaceous erythema overlying the dorsal aspect of the hands and fingers (where it can track the extensor tendon sheaths), extensor aspects of the arms and forearms, deltoids, posterior shoulders and neck (the shawl sign), V-area of anterior neck and upper chest, central aspect of the face and forehead.

Compatible skin lesions of DM

1. *Poikiloderma vasculare atrophicans* (poikilodermatomyositis)

Circumscribed violaceous erythema with associated telangiectasia, hypopigmentation, hyperpigmentation, and superficial atrophy most commonly found over the posterior shoulders, back, buttocks, and V-area of the anterior neck and chest.

2. *Calcinosis cutis*

2.1. *Other clinical features*

General symptoms include fever, malaise, weight loss and arthralgias. Raynaud's phenomenon is more common in patients with idiopathic DM and in DM associated with other connective

tissue diseases. Cardiac involvement includes heart failure, left ventricular diastolic dysfunction, and hyperkinetic left ventricular contraction [10]. Interstitial lung disease (ILD) is commonly associated with anti-tRNA synthetase antibodies [11,12].

3. *Diagnosis*

Skin manifestations are easy to recognize by physical examination. Gottron and heliotrope rashes are DM specific manifestations and usually do not require histological confirmation. When muscle involvement is suspected, muscle biopsy is indicated before beginning treatment. Biopsy is usually performed in an area with active muscle involvement in the proximal muscles of legs or arms.

3.1. *Electromyography*

Needle electromyography provides a functional view of muscle damage. Although nonspecific, abnormalities may be observed in 70–90% of patients [2]. Increased spontaneous and insertional activity with fibrillation potential, complex repetitive discharges, positive sharp waves, small polyphasic motor units potentials, and early recruitment reflect ongoing muscle abnormalities. Late in the course of the disease, insertional activity may be decreased as a consequence of muscle fibrosis.

3.2. *Muscle imaging*

Muscle Magnetic Resonance Imaging (MRI) is the gold standard of the imaging study of muscle diseases, providing a detailed anatomic view of the extent of muscle involvement. In DM, T2-weighted images and short tau inversion recovery (STIR) show symmetric muscular edema, particularly in the musculature close



Fig. 1. Skin manifestation of DM A. Gottron's papules; B. Periungual telangiectasia with cuticular hemorrhage and dystrophy C. Mechanic's hand; D. Gottron's sign; E. Heliotrope rash; F. Poikilodermatomyositis. For definitions see Table 1.

to the limbs, which well correlate with the disease activity [13]. In T1-weighted images, fatty atrophy of the musculature is seen reflecting the chronic phase of DM. MRI is also very important in addressing the muscle biopsy site.

Muscular Ultrasound (US) was the first technique used for muscle evaluation. Acute muscular inflammation is characterized by normal or increased size, low echogenicity, and elevated perfusion of affected muscles, whereas in the chronic disease stage, muscle size and perfusion are reduced and echogenicity is increased.

Although MRI is very sensitive in detecting edematous muscular changes in active myositis, contrast-enhanced muscular US can measure perfusion abnormalities and can be considered a good alternative in exploring acute muscle inflammation, especially when MRI is not available. Moreover, being widely available and cheap, muscular US is a useful tool in the follow-up of muscle lesions and it can reveal complications such as fibrosis, cystic hematomas, or myositis ossificans [14].

3.3. Pathological findings

In DM muscle inflammation is perivascular or in the interfascicular septae and around fascicles; the inflammatory infiltrate consists primarily of B cells, macrophages and CD4+ cells [3,15]. Early in the inflammatory process, there is activation of the complement leading to the formation and deposition of the C5b-C9 complement membrane attack complex (MAC) on or around the endomysial blood vessels, with consequent capillary necrosis, microinfarcts, inflammation, endovascular hypoperfusion and eventually perifascicular atrophy, the characteristic histological feature of DM [3]. Skin lesions show perivascular inflammation with CD4-positive T-cells in the dermis; in chronic stages there is dilatation of superficial capillaries.

3.4. Laboratory abnormalities

High serum levels of muscular enzymes are the hallmark of muscle involvement [3]. Serum Creatine Kinase (CK), released in the serum during muscle damage, is the most sensitive muscle enzyme in the acute phase of the disease. Elevation in serum aldolase, myoglobin, lactate dehydrogenase (LDH), aspartate and alanine aminotransferase (AST and ALT) may also occur. During the active phase of the disease, serum inflammatory biomarkers (Erythrocyte Sedimentation Rate, C-reactive protein and others) may also be increased [16].

3.5. Autoantibodies

Autoantibodies associated with IIM are subdivided into myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA), the latter occurring also in autoimmune diseases without myositis [17–21]. Anti-Mi-2 antibody is associated with classical DM and is the most common MSA found in these patients. However, several novel autoantigens have been recently reported in DM, especially in association with ILD and cancer. MSA and MAA found in patients affected with DM are shown in Table 2. When MAA are detected an overlap syndrome is suggested [11,20].

4. Classification criteria

Several diagnostic criteria for IIMs have been proposed, but none of them have been properly validated. The first diagnostic criteria were elaborated in 1975 by Bohan and Peter [7,8], who subdivided DM into 4 subsets: idiopathic DM, juvenile DM, DM

Table 2
Autoantibodies in dermatomyositis [11,20,21].

Antibody	Frequency in DM	Clinical association
<i>Myositis-specific autoantibodies (MSA)</i>		
Anti-Mi-2	20–30%	Classical DM
Anti-CADM-140 (MDA5)	50%	ADM, severe ILD
Anti-SAE	5–8%	Adult DM
Anti-p155/140	40–75%	Cancer associated DM
	20–25%	Adult DM
Anti-MJ (NXP-2)	30%	Juvenile DM (no cancer)
	25%	Juvenile DM, severe cases with calcinosis
Anti-t-RNA synthetase	Anti-Jo1	5–10%
	Other	Rare
		Anti-synthetase syndrome. High frequency of arthritis and ILD
Anti-PMS1	Rare	Adult DM
<i>Myositis associated autoantibodies (MAA) [20]</i>		
Anti-Ro/SSA	19%	Anti-synthetase syndrome
Anti-U1RNP	8%	MCTD
Anti PM/Scl (75 and 100 Kda)	2%	Scleromyositis
Anti-Ku	1%	

DM: dermatomyositis; ILD: inflammatory lung disease; ADM: amyopathic DM, MCTD: mixed connective tissue disease.

associated with cancer, and DM associated with other connective tissue diseases.

Bohan and Peter [7,8] provided four muscular criteria and one cutaneous criterion (Table 3). It is worthy to note that in these criteria exclusion of other diagnosis was mandatory before classifying a patient as affected with IIM. One of the major criticisms addressed to Bohan and Peter's criteria was that they cannot clearly distinguish DM and polymyositis (PM) from inclusion body myositis (IBM) or other myopathies, particularly dystrophies [3], leading to misdiagnosis and inappropriate therapy. Bohan and Peter's criteria showed high sensitivity when tested in patients with IIMs and high specificity when tested in patients with other connective tissue diseases. However, in a retrospective study on 52 patients affected with IIMs, IBM and non inflammatory myopathies, these criteria showed a low specificity (Table 4) [22]. Therefore, in order to increase the specificity of Bohan and Peter criteria, it has been suggested to add MSA and muscle MRI findings [23,24].

New muscle-biopsy-based diagnostic criteria were proposed in 2003 by Dalakas & Hohfeld (Table 5) [3]. In this classification MHC-1/CD8 complex was used as a specific marker for differentiating PM and IBM from other muscular diseases, particularly dystrophies. According to these criteria, the diagnosis of DM is definite if myopathy is accompanied by characteristic rash and muscle histopathology. If rash is absent, but the biopsy sample is indicative of

Table 3
Bohan and Peter diagnostic criteria for dermatomyositis [7,8].

1) Symmetric proximal muscle weakness determined by physical examination
2) Elevation of serum skeletal muscle enzymes, including CK, aldolase, serum glutamate oxaloacetate and pyruvate transaminases, and lactate dehydrogenase
3) The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges
4) Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate
4) Typical skin rash of DM. Including a heliotrope rash and Gottron's sign/papules

The diagnosis of dermatomyositis (DM) is considered definite, probable and possible when skin rash is associated with 3, 2, or 1 muscular criteria, respectively.

Exclusion criteria: central or peripheral neurologic diseases, muscular dystrophies, granulomatous and infectious myositis, metabolic and endocrine myopathies, and myasthenia gravis.

Table 4
Comparison among three classification criteria.

Authors [Ref]	Point of strength	Concerns	Sensitivity ^a	Specificity ^a
Bohan & Peter 1975 [5,6]	Useful as screening tool. Used until now for enrolling patients in clinical trial.	Unable to differentiate PM from IBM or dystrophies. Imaging and autoantibodies are not considered.	0.943	0.294
Dalakas & Hohfeld 2003 [3]	Very high specificity. Patients with ADM are considered. Definition of histological features is precise. Imaging and autoantibodies are considered.	Low sensitivity of some items. Imaging and autoantibodies are not considered.	0.771	0.999
ENMC 2004 [30]	Definition of histological features is precise. Imaging and autoantibodies are considered. Definition of histological features is precise.	Overlap and paraneoplastic DM are not considered. Complex to use in clinical practice.	0.714	0.824

DM: dermatomyositis; PM: polymyositis; IBM: inclusion body myopathy; ADM: amyopathic dermatomyositis; ENMC: Amato/European Neuromuscular Centre Workshop.

^a Sensitivity and specificity are reported by Linklater et al. [22].

Table 5
Dalakas and Hohfeld's diagnostic criteria for dermatomyositis [3].

Criterion	Myopathic DM		Amyopathic DM
	Definite	Probable	Definite
Myopathic muscle weakness	Yes	Yes	No
Serum skeletal muscle enzymes	High or normal	High	High or normal
Electromyographic findings	Myopathic	Myopathic	Myopathic or non-specific
Muscle biopsy abnormalities	Perifascicular, perimysial or perivascular infiltrates;	perifascicular atrophy	Non-specific or non-diagnostic for DM
Rash or calcinosis	Present	Non detected	Present

DM: dermatomyositis.

DM, a diagnosis of “probable” DM can be made. Finally, in the case of patients with typical DM rashes, but without apparent muscle weakness, the diagnosis should be ADM. This classification was criticized because of the difficulty in correctly classifying patients when muscle biopsy is poorly informative and, thus, non-diagnostic [25–27]. However, muscle biopsy seems to be less useful for the diagnosis of DM than for PM or IBM. In fact, in patients

Table 6
Minimal set of cutaneous manifestations of DM for defining ADM [28].

Major cutaneous criteria:
<ul style="list-style-type: none"> • “Heliotrope rash” • Gottron's papules • Gottron's sign of DM
Minor cutaneous criteria
<ul style="list-style-type: none"> • Macular violaceous erythema (with or without associated scale/hyperkeratosis, pigmentary change, and/or telangiectasia) involving: <ul style="list-style-type: none"> • Scalp and/or anterior hairline • Malar eminences of face and/or forehead and/or chin • V-area of neck and/or upper chest (open collar area; V-sign) • Nape of the neck and/or posterior aspects of shoulders (shawl sign) • Extensor surfaces of the arms and/or forearms • Linear streaking overlying extensor tendons of the dorsal aspects of the hands • Periungual areas • Lateral surface of thighs and/or hips • Medial malleoli (Involvement of each of the above anatomical region qualifies as a single minor criterion) • Periungual nailfold telangiectasia and/or cuticular hemorrhage/infarct and/or dystrophic cuticles • Poikiloderma (concurrency of hyperpigmentation, hypopigmentation, telangiectasia, and superficial atrophy) • Mechanic's hand lesions • Cutaneous calcinosis • Cutaneous ulcers • Pruritus and/or cutaneous burning sensation

The hallmark cutaneous manifestations of DM will be presumed to be present if the following conditions are met: presence of two major criteria or one major criterion and two minor criteria (biopsy of at least one skin lesion should show changes consistent with cutaneous DM).

with DM, skin manifestations, including Gottron's papules and sign and heliotrope rash, are specific features, making histological diagnosis not always necessary. Dalakas & Hohfeld's criteria seem to be very specific (Table 4) [22], due, at least in part, to their precise definition of the histological findings associated with PM and DM.

Sontheimer et al. [28] proposed a minimal set of cutaneous manifestations of DM for defining ADM (Table 6). The diagnosis of ADM is allowed when specific cutaneous manifestations of classical DM persist for 6 months or longer with no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities, provided that they do not fulfill exclusion criteria, i.e. either the treatment with systemic immunosuppressive agents for at least two consecutive months within the first six months after the onset of skin manifestations, or the previous use of any drugs capable of triggering isolated DM-like skin changes.

In the classification proposed by the European Neuromuscular Centre (ENMC) different groups of IIMs, including immune-mediated necrotizing myopathy and nonspecific myositis were considered. This classification is based on clinical features, laboratory findings (including MSA), muscular MRI and muscle biopsy and consist of inclusion and exclusion criteria which have both to be satisfied in order to classify a patient as affected with IIM. In addition, DM is subdivided into four groups: 1) definite DM; 2) probable DM; 3) amyopathic DM and 4) possible DM sine dermatitis (Tables 7 and 8) [29].

Table 7
ENMC Classification criteria for dermatomyositis [29]. For criteria definitions see Table 8.

Dermatomyositis	
Definite dermatomyositis	1.All clinical criteria 2.Muscle biopsy criteria include c
Probable dermatomyositis	1.All clinical criteria 2.Muscle biopsy criteria include d or e, or elevated serum CK, or other laboratory criteria (1 of 3)
Amyopathic dermatomyositis	1.Rash typical of dermatomyositis 2.Skin biopsy demonstrates a reduced capillary density, deposition of MAC on small blood-vessels along the dermal-epidermal junction, and variable keratinocyte decoration for MAC 3.No objective weakness 4.Normal serum CK 5.Normal EMG 6.Muscle biopsy, if done, does not reveal features compatible with definite or probable DM
Possible dermatomyositis sine dermatitis	1.All clinical criteria with the exception of rash 2.Elevated serum CK 3.Other laboratory criteria (1 of 3) 4.Muscle biopsy criteria include c or d

DM: dermatomyositis; ENMC: European Neuromuscular Centre; MAC : membrane attack complex; CK: Creatine kinase; EMG: electromyography.

Table 8
Definitions of ENMC classification criteria for dermatomyositis [29].

1. Clinical criteria	<p>Inclusion criteria</p> <p>a) Onset usually over 18 years (post-puberty), onset may be in childhood in DM and non-specific myositis</p> <p>b) Subacute or insidious onset</p> <p>c) Pattern of weakness: symmetric proximal > distal, neck flexor > neck extensor</p> <p>d) Rash typical of DM: heliotrope (purple) periorbital edema; violaceous papules (Gottron's papules) or macules (Gatton's sign), scaly if chronic, at metacarpophalangeal and interphalangeal joints and other bony prominences; erythema of chest and neck (V-sign) and upper back (shawl sign)</p> <p>Exclusion criteria</p> <p>a) Clinical features of IBM: asymmetric weakness, wrist/finger flexors same or worse than deltoids; knee extensors and/or ankle dorsiflexors same or worse than hip flexors)</p> <p>b) Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness</p> <p>c) Toxic myopathy (e.g. recent exposure to myotoxic drugs), active endocrinopathy (hyper- or hypothyroid, hyperparathyroid), amyloidosis, family history of muscular dystrophy or proximal motor neuropathies</p>
2. Elevated serum creatine kinase level	
3. Other laboratory criteria	<p>a) Electromyography:</p> <p>Inclusion criteria</p> <p>I) Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges</p> <p>II) Morphometric analysis reveals the presence of short duration, small amplitude, polyphasic MUAPs</p> <p>Exclusion criteria</p> <p>I) Myotonic discharges that would suggest proximal myotonic dystrophy or other channelopathy</p> <p>II) Morphometric analysis reveals predominantly long duration, large amplitude MUAPs</p> <p>III) Decreased recruitment pattern of MUAPs</p> <p>b) MRI: diffuse or patchy increased signal (edema) within muscle tissue on STIR images</p> <p>c) Myositis-specific antibodies detected in serum</p>
4. Muscle biopsy inclusion and exclusion criteria	<p>a) Endomysial inflammatory cell infiltrate (T-Cells) surrounding and invading non necrotic muscle fibers</p> <p>b) Endomysial CD8 + T-cells surrounding, but not definitely invading non-necrotic muscle fibers, or ubiquitous MHC-1 expression</p> <p>c) Perifascicular atrophy</p> <p>d) MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on EM, or MHC-1 expression of perifascicular fibers</p> <p>e) Perivascular, perimysial inflammatory cell infiltrate</p> <p>f) Scattered endomysial CD8+ T-cells infiltrate that does not clearly surround or invade muscle fibers</p> <p>g) Many necrotic muscle fibers as the predominant abnormal histological feature. Inflammatory cells are sparse or only slight perivascular; perimysial infiltrate is not evident. MAC deposition on small blood vessels or perivascular capillaries on EM may be seen, but tubuloreticular inclusions in endothelial cells are uncommon or not evident</p> <p>h) Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM</p> <p>i) MAC deposition on the sarcolemma of non-necrotic fibers and other indications of muscular dystrophies with immunopathology</p>

DM: dermatomyositis; ENMC: European Neuromuscular Centre; MAC: membrane attack complex; IBM: inclusion body myositis; MUAPs: motor unit action potentials; MHC: major histocompatibility complex; MRI: magnetic resonance imaging; STIR: short tau inversion recovery.

Recently the performance of ENMC classification and Bohan and Peter's criteria [7,8] has been compared. Out of 99 patients with different forms of myopathies, 10 fulfilled the ENMC criteria for "DM" and "probable DM" and other 5 for "possible DM sine dermatitis". Out of them only 3 were classified as affected with DM according to Bohan and Peter's criteria whereas the other 12 cases were classified as PM (2 cases), IIM associated with cancer (3 cases), overlap syndromes (5 cases) and childhood IIM (2 cases) [30]. Notably, it has been shown that the sensitivity and specificity of the ENMC criteria were lower than those of Dalakas & Hohfeld's criteria (Table 4) [22].

Finally, the International Myositis Assessment and Clinical Study Group (IMACS) – a multidisciplinary group of more than 100 experts in adult and juvenile IIM – has tried to develop consensus guidelines for clinical therapeutic trials [31]. Experts agreed that "probable" or "definite" PM and DM, as defined by Bohan and Peter's criteria [7,8], are disease subsets which can appropriately be included in clinical trials. However, since other forms of myopathies have to be ruled out and in order to distinguish PM from IBM, characteristic biopsy findings were considered mandatory in order to classify a patient as affected with PM. Conversely, although experts concurred that Gottron's sign/papules or heliotrope rash alone would be sufficient to distinguish DM from PM or IBM, adult specialists were unable to reach a consensus as to whether muscle biopsy has to be considered mandatory and left this decision to the investigators of the individual clinical trials.

5. Therapy

Corticosteroids remain the mainstay drug in the treatment of DM [1–3]. Oral prednisone should be started at a dosage of 1–2 mg/Kg/day for 2–4 weeks, and then gradually tapered to the lowest effective dosage. Intravenous (IV) methylprednisolone should be used in severe cases [32].

Methotrexate (7.5–20 mg/week) is considered the first line immunosuppressive drug [1–3,33]. In refractory or intolerant patients, IV Ig (2 g/kg/month for 3 months) [34] or cyclosporine A (3–4 mg/kg/day) have been reported to be effective alone or in association with other immunosuppressants. Mycophenolate mofetil (2–3 g/day) and tacrolimus have also been effectively used [32]. Cyclophosphamide (1–2 mg/kg/day orally or 0.75–1 g/m² IV per month for 5–6 months) is usually reserved to more severe cases, due to the high frequency of side effects. Biological agents, especially Rituximab, have successfully been used in cases which do not respond to conventional therapy [35].

Patients must be awarded that skin manifestations of DM may be triggered or worsened by exposure to ultraviolet light and therefore the avoidance of sun exposure and the use of sunscreens are mandatory. Moreover, cutaneous manifestations may be controlled by the application of topical corticosteroids or the more recent class of calcineurin inhibitors, such as tacrolimus and pimecrolimus, and by the use of antimalarials, hydroxychloroquine sulfate or chloroquine phosphate, associated with quinacrine in resistant cases [1].

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