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The polymorphous spectrum of dermatomyositis: classic features, newly described skin lesions, and rare variants

Dermatomyositis belongs to a group of rare autoimmune diseases characterized by a variable degree of skin symptoms and myopathy. The clinically diagnostic hallmarks of dermatomyositis are heliotrope rash, Gottron's papules and weakness of the proximal muscles. Along with pathognomonic, characteristic, and compatible cutaneous features, several uncommon and rare skin manifestations have been reported. In addition, new skin lesions have been described in dermatomyositis patients. Furthermore, rare clinical subtypes of dermatomyositis have been reported in the literature, including Wong-type dermatomyositis, characterised by the coexistence of dermatomyositis and pityriasis rubra pilaris with hyperkeratotic, erythematous, follicular confluent papules on the back of the hands along the bony prominences. In addition, plenty of autoantibody subsets have been recently described that are related to distinct clinical features and systemic involvement, such as anti-MDA5 autoantibodies. We reviewed the English- and German-language scientific literature using the key words "dermatomyositis", "autoantibodies", and "clinical features", alone or in combination, focusing on particular cutaneous symptoms and their association with defined autoantibody profiles. Furthermore, we focused on rare subtypes of dermatomyositis, unusual clinical features, and recently described skin lesions.

Key words: amyopathic dermatomyositis, clinical features, dermatomyositis, diagnostic criteria, paraneoplastic dermatomyositis, Wong-type dermatomyositis

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Dermatomyositis (DM) belongs to the group of autoimmune myositides, rare autoimmune diseases which are characterized by skin rashes and myopathy to variable degrees (*table 1*) [1-3]. DM is a rare disease with two peaks of incidence: one in childhood between 5 and 15 years of age and one in adulthood between 40 and 60 years, with a female preponderance [1-3]. DM can be associated with malignancy [4]. Therefore, a screening investigation is mandatory. However, evidence-based guidelines on this topic are lacking.

The aetiopathogenesis of DM is still unclear, but a range of factors, such as genetic predisposition, environment triggers, and immune- as well as non-immune-mediated mechanisms play a role in the development of the disorder [2, 3]. Several points support the autoimmune origin of DM. Indeed, DM may be associated with other autoimmune disorders and is characterized by several subsets of autoantibodies. Furthermore, a DM hallmark is the presence of T-cell-mediated myocytotoxicity or complement-mediated microangiopathy [2, 3]. Indeed, the primary target in DM is the endothelium of the endomysial capillaries which is attacked by the membranolytic attack complex (MAC), formed by C3b, C3bNEO, and C4b fragments and C5b-9 [2, 3]. However, specific target antigens and the trigger that initiates the pathogenesis of DM have not yet been identified.

Pathognomonic skin features are Gottron's sign and Gottron's papules; in addition, characteristic skin features, such as heliotrope rash, shawl-sign, V-sign, and nail-fold changes (Keining's sign) have been described [5-7]. Compatible skin signs are represented by poikiloderma (the combination of atrophy, dyspigmentation, and telangiectasia) on photo-exposed areas, holster sign, periorbital oedema, and facial swelling [5-7]. Along with pathognomonic, characteristic, and compatible cutaneous features, several uncommon and rare skin manifestations have been described [5-7].

Based on a recent meta-analysis, the prevalence of neoplasia was reported to be 14.8% in DM patients [8]. A slightly more elevated relative risk has been reported in the male population. Lung and gastrointestinal neoplasia have been mainly reported in DM patients [8-11]. However, nasopharynx carcinoma has been also described in association with DM [8-11]. Furthermore, different types of carcinoma are reported to be more frequently detected in different populations [8].

Autoantibodies specific to idiopathic inflammatory myopathy (myositis-specific autoantibodies [MSAs]) are clin-

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Table 1. Classification of dermatomyositis according to the European Neuromuscular Centre*.

Type of DM	Criteria
Definite DM	1) All clinical criteria 2) Perifascicular atrophy based on muscular biopsy
Probable DM	1) All clinical criteria 2) One of the following criteria: MAC deposition on small blood vessels/reduced capillary density/tubuloreticular inclusion in endothelial cells on EM/MHC-1 expression on perifascicular fibres Elevated serum CK Other laboratory criteria
Clinically amyopathic DM	1) Typical skin features of DM (table 4) 2) Reduced capillary density, deposition of MAC on small blood vessels along the dermo-epidermal junction, and variable keratinocyte surface expression of MAC on skin biopsy 3) No objective weakness 4) Normal serum CK 5) Normal EMG 6) No features of definite or probable DM based on muscle biopsy
Possible DM without skin features	1) All clinical criteria except for rash 2) Elevated serum CK 3) One of the following features based on muscular biopsy: MAC deposition on small blood vessels/reduced capillary density/tubuloreticular inclusion in endothelial cells on EM/MHC-1 expression on perifascicular fibres Perifascicular atrophy based on muscular biopsy 4) Other laboratory criteria
Criteria	**Details**
Clinical criteria	1) >18 years 2) Subacute onset 3) Symmetric proximal weakness/neck flexor weakness 4) Heliotrope periorbital oedema/Gottron's papules/Gottron's sign/V-sign/Shawl sign
Elevated serum CK	
Other diagnostics	1) Electromyography (one of the following features): • Fibrillation potentials/positive sharp waves/complex repetitive discharges • Short duration, small amplitude, polyphasic MUAPs 2) MRI: oedema within muscle tissue on STIR images 3) Myositis-specific serum antibodies
Muscle biopsy criteria	1) Endomysial inflammatory cell infiltrate (T-cells) surrounding and invading non-necrotic muscle fibres 2) Endomysial CD8+ T-cells surrounding non-necrotic muscle fibres/ubiquitous MHC-1 expression 3) Perifascicular atrophy 4) MAC deposits on small blood vessels/reduced capillary density/tubuloreticular inclusion in endothelial cells on EM/MHC-1 expression on perifascicular fibres 5) Perivascular, perimysial inflammatory cell infiltrate

*CK: creatine kinase; DM: dermatomyositis; EM: electron microscopy; IBM: inclusion body myositis; MAC: membrane attack complex; MUAPs: motor unit action potentials; MHC: major histocompatibility complex; MRI: magnetic resonance imaging; STIR: short tau inversion recovery*Adapted from Lundberg et al. [15].*

ically useful biomarkers to determine the prognosis of DM patients [12-14] (*table 2*). Many MSAs are also associated with peculiar clinical subsets of DM, making them useful in predicting and monitoring some clinical manifestations [12-14]. For example, anti-melanoma differentiation-associated protein 5 (MDA5) antibodies are often associated with rapidly progressive interstitial lung disease (ILD), as well as antibodies against aminoacyl tRNA synthetases, such as anti-precipitation line (PL) 7 and anti-PL12 [13, 14]. In addition, some subsets of antibodies are more frequently detected in specific populations. For example, anti-MDA5 antibodies are identified more frequently in Asiatic patients than in the Caucasian ones [13-15]. However, the importance of these antibodies and their role in the pathogenesis of DM is still unclear, because they are not specific to any particular tissue or disease subset and, moreover, may be detected in patients without DM. In addition, the detection of MSAs is not included in the diagnostic criteria for DM.

Given the numerous new findings associated with MSAs and their clinical correlation, *e.g.* the association between anti-synthetase syndrome (ASyS) and DM, we provide an update on our current knowledge of DM showing also some representative clinical pictures (written consent to publish clinical photographs was provided by patients).

Cutaneous spectrum of DM

In the diagnosis of DM, cutaneous features play a key role. According to the criteria proposed by Bohan and Peter (*table 3*), a typical skin manifestation is mandatory to diagnose DM [16, 17]. In more than 50% of DM patients, skin lesions precede muscle involvement by months or years [5]. Essentially, cutaneous involvement in DM can be classified into three categories, based on pathognomonic, characteristic, and compatible clinical features [14, 18]

Table 2. Autoantibody profile.

Antibody	Most common DM subtype	Common clinical features	Frequency
Myositis-specific autoantibodies			
Anti-aminoacyl tRNA synthetases (Anti-Jo-1)	DM JDM	High frequency of ILD Arthritis Mechanic's hands Polysynovitis Raynaud's phenomenon High mortality rate	9-24%
Other anti-aminoacyl tRNA synthetases (*e.g*. anti-PL7, anti-PL12)	DM JDM	High frequency of ILD Arthritis	<5%
Anti-CADM-140 (MDA5)	DM JDM	Rapidly progressive ILD Cardiac involvement Digital ulceration Hair loss Inverse Gottron's papules Mechanic's hands Oral ulceration Poor response to therapy	Asians: 10-48% Caucasians: up to 13%
Anti-Mi-2 (NuRD)	DM JDM	V-neck sign Shawl sign Mild myositis Photosensitivity Paediatric patients show a more severe increase in serum CK than adults Good response to therapy	20-30%
Anti-MJ (NXP-2)	JDM PDM	Calcinosis cutis (more often in JDM) Joint contractures Gastrointestinal ulceration Severe skin involvement	23% (JDM) 5% (PDM)
Anti-p155/140 TIF1-gamma	DM JDM PDM	Inverse Gottron's papules Photosensitivity Skin erosions and ulcerations Severe skin involvement V-neck sign Shawl sign	20-25% (DM) 30% (JDM) 40-75% (PDM)
Anti-SAE	DM	Usually diagnosed as amyopathic, but later systemic manifestation	Caucasians: 6-8%
Anti-SRP	DM JDM	Raynaud's phenomenon Severe muscle involvement High CK serum levels Poor response to therapy	Caucasians: 5% Afro-Americans: 8-13%
Myositis-associated autoantibodies			
Anti-Ku	Overlap myositis	Arthritis Altered oesophageal motility Raynaud's phenomenon	Up to 1%
Anti-PM-Scl	JDM Overlap myositis	ILD Arthritis Altered oesophageal motility Raynaud's phenomenon	2-4%
Anti-Ro/SSA	Overlap myositis Anti-synthetase syndrome	In cases of concomitant anti-Jo-1 antibodies, high risk of ILD development Photosensitivity	2-19%
Anti-U1RNP	JDM Overlap myositis		12-16%

CK: creatine kinase; DM: dermatomyositis; EMG: electromyography; ILD: interstitial lung disease; JDM: juvenile dermatomyositis; MDA5: melanoma differentiation-associated gene 5; NuRD: nucleosome remodelling deacetylase; NXP-2: nuclear matrix protein; PDM: paraneoplastic dermatomyositis; PL7: threonyl-tRNA-synthetase; PL12: alanyl-tRNA-synthetase; PMS: post-meiotic segregation increased 1; RNP: ribonucleoprotein; SAE: small ubiquitin-like modifier activating enzyme; SRP: signal recognition particle; TIF1-gamma: transcriptional intermediary factor 1 gamma tRNA: transfer ribonucleic acid.

Table 3. Bohan and Peter diagnostic criteria for dermatomyositis.

Criteria	Details
1. Symmetric proximal muscle weakness	Progresses over weeks to months with or without dysphagia and/or diaphragmatic weakness
2. Elevation of skeletal muscle enzyme levels	Elevated enzymes including creatine kinase, aspartate transaminase, alanine transaminase, and/or lactate dehydrogenase
3. Abnormal EMG results	Polyphasic, short, small motor unit potentials, fibrillation potentials, positive sharp waves, increased insertional irritability, and repetitive high-frequency discharges
4. Muscle biopsy abnormalities	Histopathological findings of degeneration, regeneration, necrosis, and interstitial mononuclear infiltrates
5. Typical skin rash of dermatomyositis	Heliotrope rash or Gottron's sign

Probable DM: requires criterion 5 and at least two criteria from 1-4; Possible DM: requires criterion 5 and at least one criterion from 1-4. Definite DM requires criterion 5 and at least three criteria from 1-4. EMG: electromyography

Table 4. Classification of cutaneous features of dermatomyositis.

Type of skin manifestation	Cutaneous lesion
Pathognomonic	Gottron's papules Gottron's signs: symmetric purplish erythema
Characteristic	Heliotrope oedematous erythema Nail-fold changes: periungual telangiectasia, hypertrophy of the cuticle, and small haemorrhagic infarcts (Keining's sign) Violaceous erythema on the shoulders and neck (Shawls sign) Violaceous erythema on the upper chest (V-sign) Scalp changes: atrophic, erythematous, and scaly plaques Violaceous erythema on dorsum of the hands, extensor forearms, and arms
Compatible	Poikiloderma: hypo-and hyperpigmentation, telangiectasia, and atrophy Violaceous erythema on the lateral thighs (Holster sign)
Less common	Subepidermal multiloculated vesiculobullous on the dorsal surfaces of the hands or forearms Necrotic lesions Cutaneous vasculitis Calcinosis cutis: calcium deposits in the skin and subcutaneous tissue, present as superficial or subcutaneous nodules, especially on the elbow and knee
Rare	Mechanic's hands: hyperkeratosis of the lateral fingers and palms Centripetal flagellate erythema Follicular hyperkeratosis Panniculitis Cutaneous mucinosis Erythroderma Oral mucosa changes: gingival telangiectasia and oral erosions/ulcerations
Recently described	Inverse Gottron's papules: papules or erythema on the palmar surfaces of the hand joints Gottron's papules/Gottron's sign with ulceration Digital pulp ulcerations "Hiker's feet": bilateral dryness, cracking, and hyperkeratosis on the soles and toes
Non-specific	Photosensitivity Raynaud's phenomenon Pruritus/burning

(*table 4*). In addition, several other skin manifestations have been reported, including non-specific and rare skin features [14, 18].

Pathognomonic skin features are Gottron's papules (*figure 1A*) and Gottron's sign (*figure 1B*). On the other hand, Gottron's papules present as slightly elevated, purplish lesions on an erythematous background over bony prominences, mainly on the metacarpophalangeal, interphalangeal, and distal interphalangeal joints. Gottron's papules are usually detected also on the nail borders. On the other hand, Gottron's sign is characterized by erythematous macules in a linear arrangement on the extremities, mainly accentuated on the dorsal and lateral side of the hands and fingers. Usually, it is associated with later desquamation. Gottron's sign can also be detected on other body areas, mainly the knees and elbows.

Characteristic skin features include heliotrope rash, shawl and V-sign, nail-fold changes (Keining's sign), and scaly dermatitis of the scalp. Heliotrope rash presents as symmetric purplish erythema with oedema involving mainly the upper eyelids (*figure 2A-C*). It is usually associated with pruritus. Heliotrope rash can also involve the cheeks, nose, and nasolabial folds. Occasionally, the heliotrope rash presents only as subtle mild discolouration of the eyelid

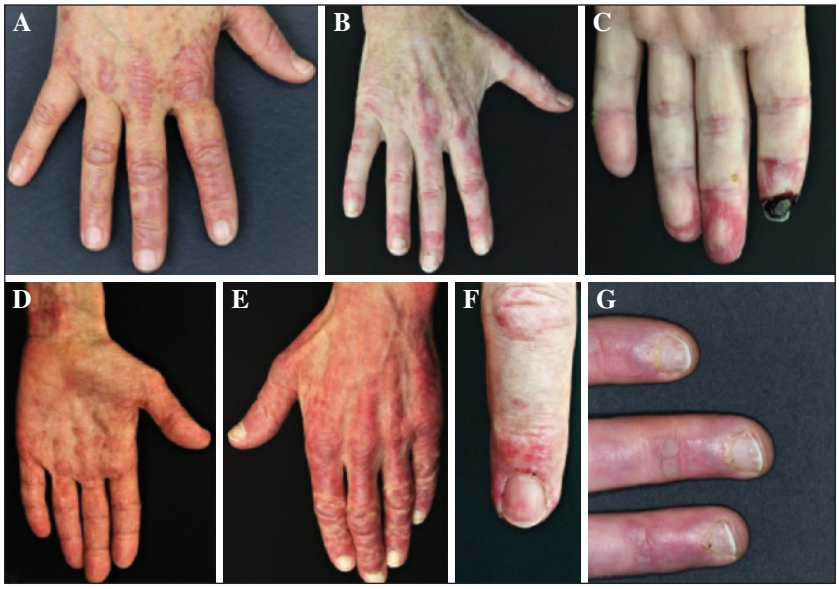

Figure 1. Characteristic clinical features of dermatomyositis (hands). **A)** Erythematous, infiltrated papules at the metacarpophalangeal and interphalangeal joints (Gottron's papules). **B)** Erythematous macules, aligned in a linear pattern along the extensor tendons of the hands (Gottron's sign). **C)** Erythematous macules and necrotic ulcerations of the fingertips, often associated with cutaneous vasculitis and anti-MDA5 antibodies. **D)** Inverse Gottron's papules located at the palmar surface are very rare and commonly associated with interstitial lung disease. **E)** Thickening of the fingers with palmar hyperkeratosis (mechanic's hands). **F)** Gottron's papules of the interphalangeal joint associated with haemorrhaging of the nail bed. **G)** Periungueal telangiectasia with associated cuticular overgrowth (Keining's sign) and small haemorrhagic infarctions of the nail-folds.

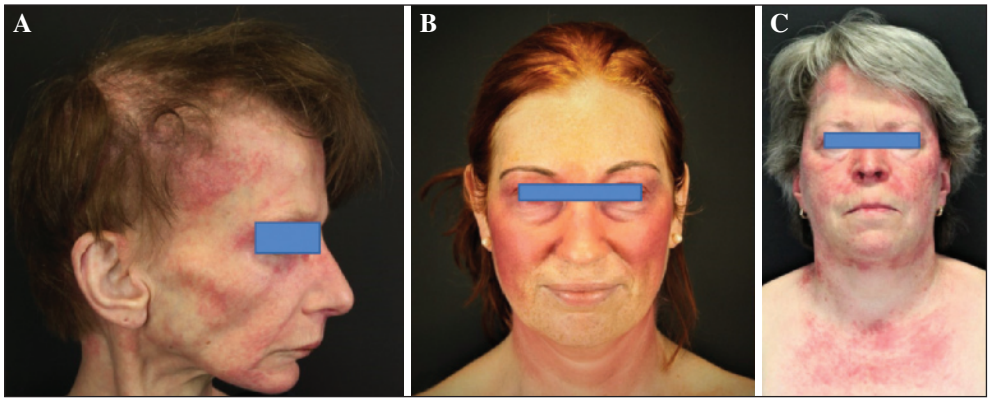

Figure 2. Characteristic clinical features of dermatomyositis (face). **A)** Periorbital erythema (heliotrope erythema), erythematous eczematous plaque on the temple, and alopecia. **B)** Periorbital violaceous erythema with oedema (heliotrope erythema) involving also the cheeks. **C)** Erythema of the cheeks and upper chest (V-sign) with characteristic sparing of the submental (*i.e.* UV-protected) area.

borders. Shawl and V-signs are represented namely by an erythematous maculopapular rash on the upper back and deltoids (shawl-sign) (*figure 3B*), as well as a V area on the upper chest (V-sign) (*figure 2C, 3A*). Characteristic nail-fold features are represented by periungual telangiectasia with dystrophic or overgrowth cuticles, and small haemorrhagic infarcts. This phenomenon is called "Keining's sign" (*figure 1F, G*). Scalp involvement manifests with a dusky erythematous scaly dermatitis (*figure 2A*), often misdiagnosed as seborrheic dermatitis or psoriasis. Usually, it is associated with intense pruritus. In some patients, non-scarring alopecia has been reported, usually in association with a flare of the systemic disease [3].

Compatible skin signs include poikiloderma (the combination of atrophy, dyspigmentation, and telangiectasia) on photo-exposed areas, holster sign, periorbital oedema, and facial swelling. Poikiloderma usually affects the upper chest and buttocks, but can also be detected on the thighs and hips (*figure 3C*). It is usually asymmetric and has a chronic course. This skin feature is also seen in cutaneous T-cell lymphoma (mycosis fungoides) and chronic radiodermatitis. Therefore, a punch biopsy of these lesions is always recommended. The holster sign is characterised by poikiloderma of the hips and lateral thighs, resembling a handgun holster (*figure 4C, D*). Bilateral periorbital purple oedema has also been described and may cause facial swelling [7].

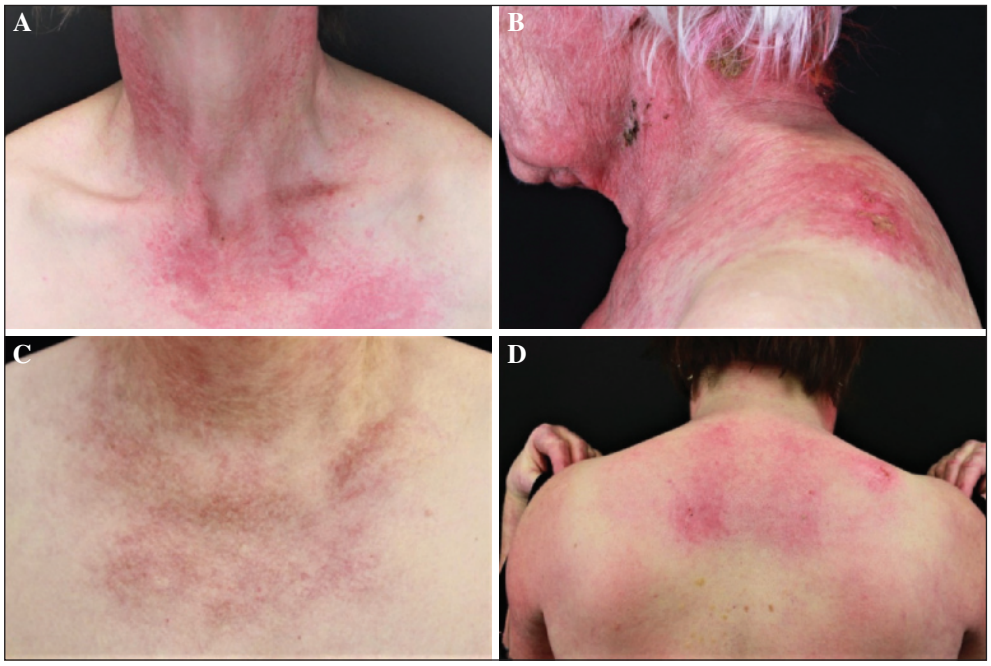

Figure 3. Characteristic clinical features of dermatomyositis (trunk, shoulders). **A)** Dusky red erythema on the upper chest (V-sign). **B)** Dusky red erythema on the shoulders (shawl-sign) associated with superficial ulcerations. **C)** Coexistence of atrophy, teleangiectasia, and cutaneous dyschromic pigmentation (poikiloderma). **D)** Dusky red erythema on the shoulders (shawl-sign).

Less commonly, cutaneous vasculitis manifestations and calcinosis cutis have been described in DM patients [6]. Cutaneous vasculitis can manifest as vesicles, necrosis, erosions or ulcerations. In the majority of cases, cutaneous vasculitis has been reported in juvenile DM (JDM). Palpable purpura, urticarial lesions, livedo reticularis, and digital (*figure 1C*) and oral ulcers have also been described in JDM patients with vasculitis. Furthermore, vasculitic skin manifestations have been mainly associated with underlying malignancy [6]. Calcinosis cutis is characterized by cutaneous and/or subcutaneous calcium deposits. Clinically, it manifests as bump nodules, mainly located on the elbows, knees, and buttocks. Calcinosis has been reported in up to 70% of JDM patients and in around 10% of DM cases in the adult population [19]. Elimination of subcutaneous calcium precipitations may lead to chronic, recalcitrant skin ulcerations. Calcinosis cutis has been frequently related to solid neoplasia or blood malignancy [19].

DM is also known for its polymorphous skin manifestations. Indeed, rare cutaneous features have been described, including mechanic's hands, flagellate erythema, panniculitis, mucinosis, inverse Gottron's papules (*figure 1D*), erythroderma, and oral manifestations. Mechanic's hands presents as hyperkeratosis, scaling, and fissuring of the lateral fingers, resembling a toxic irritant contact dermatitis (*figure 1E*), and less commonly involves the palm. In addition, mechanic's hands has been considered the most characteristic cutaneous marker of ASys [20], but it has also been reported in classic and clinically amyopathic DM (CADM) [18]. Flagellate erythema has been occasionally reported in DM patients. It can involve the back, lateral chest, and/or upper buttocks (*figure 4B, E*), and is characterized by multiple linear erythematous lesions, resembling whiplash marks on the skin [6, 18]. Flagellate erythema can also be present in adult-onset Still's disease, bleomycin-induced dermatitis, and shiitake dermatitis, which is provoked by ingestion of shiitake mushrooms [21].

Panniculitis has been rarely described in DM patients [18]. It may be characterized by erythema followed by subcutaneous calcification. Usually, panniculitis involves the upper thighs and buttocks. Longstanding panniculitis leads to lipodystrophy which is more common in jung than adult DM patients [22]. Pathologically, DM-related panniculitis is characterized by lobular panniculitis with a pronounced lymphocytic and plasmacellular infiltrate [22].

Mucinosis has been infrequently described in DM patients. It presents as erythematous papules and/or plaques, and scleromyxedema. Erythroderma has also been rarely reported in DM and can be related to neoplasia. It usually presents as an erythematous scaly rash. Oral mucosa involvement in DM includes gingival telangiectasia [23], erosions, ulcers, hyposalivation, and leukoplakia. Gingival telangiectasia is the most common oral finding and is considered as an important diagnostic marker in JDM, as reported by Ghali *et al*. [23].

Bullous lesions in DM have been rarely reported in the literature [24]. As reported by Kubo *et al*. [25], vesicle formation is occasionally found in Japanese DM patients. The incidence of internal malignancies is reported to be much higher in patients with vesiculo-bullous DM than other cutaneous manifestations of DM. In the paper by Kubo *et al*. [25], 19 cases of DM with vesiculo-bullous lesions were reviewed. All except for one case showed subepidermal blisters; intraepidermal blisters were recognized in only one case. In another paper by Nishigori *et al*. [25], three DM patients with subepidermal bullae and mucin deposition in the upper dermis were described. Marked subepidermal oedema, mucin deposition, and mechanical stress were cited as major causes of subepidermal bulla formation. Two

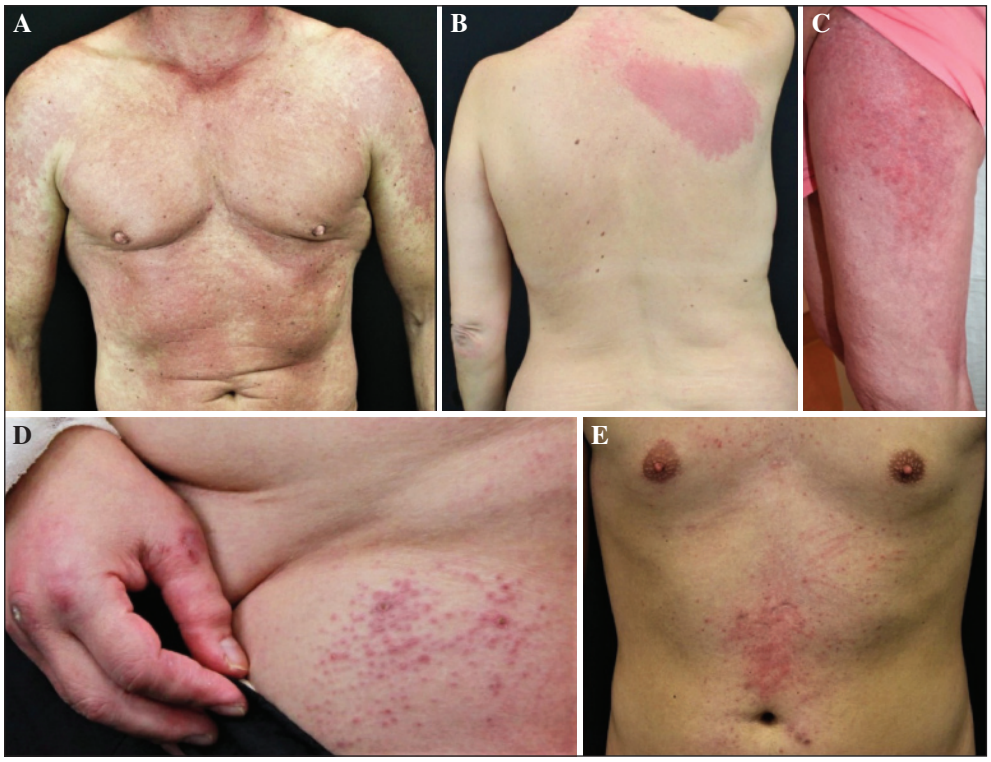

Figure 4. Cutaneous features of distinct clinical variants of dermatomyositis. **A)** Papulo-erythematous lesions on the chest and shoulders in a patient with clinically amyopathic dermatomyositis (CADM). **B)** Flagellate dermatitis in a female patient with CADM. **C)** Dusky red plaque on the lower part of the thigh (holster sign). **D)** Dusky red plaque on the lower part of the thigh (holster sign) associated with Gottron's papules and finger ulcerations in a patient with anti-MDA5 antibodies. **E)** Flagellate dermatitis in a patient with juvenile dermatomyositis.

of these cases were associated with malignancy. On the one hand, vesicles appeared at the time of diagnosis of the underlying; on the other hand, one of the patients developed a number of vesicles even although the underlying malignancy was cured.

Classic DM and systemic involvement

Classic DM is characterised by a variable degree of muscle weakness that gradually worsens. Usually, the muscle involvement is symmetric and proximal, but distal muscle weakness can develop later in the course of the disease [2, 3]. Myalgias and muscle tenderness have also been reported in up to 30% of patients [2, 3]. Furthermore, patients can be affected by dysphagia, dysphonia, and weakness of respiratory muscles [2, 3]. The characteristic rash of DM can occur before, after, or at the same time as muscle weakness [2, 3].

ILD affects the prognosis of DM patients, increasing both morbidity and mortality. Up to 40% of DM cases may be affected by ILD during the course of the disease [2, 3]. It has been reported that more than 75% of DM patients with antisynthetase antibody developed ILD [2, 3]. However, a better ILD prognosis in patients with anti-Jo antibody has been described [2, 3]. Clinically, ILD is characterized by subjective dyspnoea upon exertion, cough, and decreased tolerance to exercise. Three different clinical courses have been described: acute, severe involvement; chronic, slowly progressive symptoms asymptomatic disease with detection of lung involvement on imaging. Muscle disease usually arises before the onset of lung disease, but this is not always the case. Clinically amyopathic DM (CADM) can also be associated with ILD, and rapidly progressive ILD is observed more frequently in this subgroup of patients [2, 3]. Lung involvement in DM patients is characterized by a restrictive disease pattern, detected on pulmonary function tests (forced vital capacity [FVC] or total lung capacity [TLC] <80% predicted for age) or by a decrease in diffusing capacity of carbon monoxide. However, an imaging study is mandatory for a diagnosis of ILD [2, 3]. High-resolution CT (HRCT) scanning is a useful tool for the detection and follow-up of ILD. Several characteristic features on HRCT have been described, including nodules, linear opacities, fibrosis, and bronchiectasis.

Corticosteroids are the mainstay for the treatment of ILD. It has been reported that continuous treatment with corticosteroids over one year improves FVC [26]. However, other data supporting their use in these patients are controversial [27]. Azathioprine is commonly used as a corticosteroid-sparing adjuvant in the management of various forms of ILD [27]. Based on a retrospective analysis, azathioprine was reported to improve the survival of these patients [28]. In addition, several studies reported the efficacy of azathioprine as maintenance therapy after intravenous cyclophosphamide [27].

Cyclophosphamide is the only immunosuppressive agent studied for ILD in randomized clinical trials [29, 30]. Although the change in FVC in these studies is small and of

questionable importance, several observational studies have also shown improvement in FVC treated with cyclophosphamide [27]. However, the optimal duration and mode of treatment remain unclear [30]. Mycophenolate mofetil reduces T-cell and B-cell proliferation by inhibition of inosine monophosphate dehydrogenase, a crucial factor in purine synthesis. This has been tried in several ILD patients with generally positive results [27]. Indeed, a sustained improvement in FVC and a reduced corticosteroids intake in patients on mycophenolate mofetil have been reported [31]. Rituximab, a monoclonal antibody against the B-cell surface antigen CD20, has also been reported as therapeutic option [31]. Despite a predominantly negative outcome in a large randomized trial of rituximab in myositis patients, some case series have suggested a favourable effect of rituximab for ILD [31]. The efficacy of imatinib, a tyrosine kinase inhibitor of BCR-Abl, is doubtful. Indeed, in a study conducted on 20 patients with scleroderma-like ILD, imatinib was poorly tolerated and only 60% of the patients completed the study [27]. Other therapeutic options include methotrexate, tacrolimus, and cyclosporine [27].

In DM patients, oesophageal involvement is commonly represented by dysphagia to solids and liquids due to loss of pharyngo-oesophageal muscle tone [2, 3]. Aspiration pneumonia can also occur in cases of extreme affection of pharyngo-oesophageal muscles. Oesophageal involvement can be evaluated by manometry, which may show low-amplitude/absent pharyngeal contractions and reduction of upper oesophageal sphincter pressure.

Although cardiac involvement can occur in DM, the patients are asymptomatic [2, 3]. Myocarditis has been reported in about 30% of DM cases based on autopsy studies. Isolated, subclinical electrocardiographic changes are commonly noted, but they are not clinically significant. Valvular abnormalities, as well as congestive heart failure, have been rarely reported.

Two different main subtypes of muscular involvement have been histologically reported [15]. On the one hand, loss of capillaries, deposits of C5b-C9 on the capillary endothelium, and the presence of endothelial microtubular inclusions (vasculopathy) in the muscles, associated with perifascicular atrophy with intense HLA class I staining, necrotic myofibers, and foci of perivascular infiltrates of lymphocytes, as well as macrophages in the perimysium, are consistent with the myovasculopathy pattern of DM [15]. On the other hand, myofiber necrosis, regeneration in the perifascicular region, and minimal T-cell lymphocytic inflammatory infiltrates are consistent with the immune-mediated necrotizing myopathic pattern of DM [15].

Amyopathic DM

The classic Bohan and Peter criteria for DM include muscle involvement as a cardinal feature for diagnosis [16, 17] (*table 3*). However, it has been reported that up to 20% of DM patients lack muscle involvement or show subclinical muscle features [32]. These patients are classified under the umbrella CADM (*figure 4A*). To this group belong patients who have neither clinical nor laboratory evidence of muscle disease, as well as patients who lack clinically apparent muscular features but have muscle involvement evidenced by magnetic resonance imaging (MRI), electromyography (EMG) or muscle biopsy [32]. An *ante litteram* CADM subset was first described by Pearson *et al*. in the 1960s to distinguish DM patients with cutaneous involvement, but without evidence of muscle disease. The definition "pre-myopathic DM" has been later introduced to describe those patients who have skin involvement and no muscle disease for less than six months [33]. However, a subset of CADM patients who developed muscular disease more than six months after initial skin features has been reported [33].

Several other definitions for DM without clinical muscle involvement have been proposed, but most of them are not clinically useful, because they require extensive workup or can only be made retrospectively. In addition, no significant distinctions in pathophysiology or in clinical outcome have been reported between CADM patients and classic DM patients [32].

The first population of CADM patients was described in 1991 by Euwer and Sontheimer [34] (*table 5*). The authors presented six patients with pathognomonic cutaneous signs of DM (Gottron's papules and Gottron's signs), a consistent skin biopsy, and no evidence of muscle involvement or elevation of muscle enzymes within two years of diagnosis [34]. A larger population (37 patients) was described by El-Azhary *et al*., who reported that almost all patients had acral skin involvement [35]. Furthermore, Cao *et al*. described a series of 16 CADM patients, highlighting that all patients had Gottron's papules, periungual telangiectasias, and/or erythema; in addition, 15 out of 16 patients showed periorbital heliotrope rash [36]. The authors also highlighted that four patients had an internal malignancy; two were diagnosed at the time of DM presentation, and the other two were detected after a two-year follow-up period [36]. Finally, Bendewald *et al*. reported that CADM patients represented 20% of all DM cases among a cohort of 29 patients [1].

CADM patients show features of subclinical myositis based on histopathological or imaging evaluation. Pathologically, signs of early involvement have been reported in CADM muscle biopsies. More specifically, Gitiaux *et al*. observed patchy capillary loss of discrete microvascular units and C5b9 membranolytic attack complex deposits [37]. MRI and ultrasound studies evidenced muscle inflammation

Table 5. Euwer and Sontheimer criteria for the diagnosis of clinically amyopathic dermatomyositis (CADM).

Criteria	Clinical features
Major cutaneous criteria	Heliotrope rash Gottron's papules Gottron's sign
Minor cutaneous criteria	Macular violaceous erythema V-sign Shawl sign Holster sign Keining sign Poikiloderma Mechanic's hand Cutaneous calcinosis Cutaneous ulcers Pruritus

To diagnose CADM, two major criteria, or one major criterion and two minor criteria (a biopsy of at least one skin lesion should show changes consistent with cutaneous dermatomyositis).

in DM patients with normal muscle enzyme levels and normal EMG studies [38, 39]. In addition, a functional MRI study showed that CADM patients had inefficient muscle metabolism at exercise compared to controls, while classic DM patients showed abnormalities in metabolism at rest [40].
It is also important to continue to follow CADM patients in order to monitor myositis. Indeed, CADM patients may also develop clinically apparent muscle symptoms later in their disease course, as reported by El-Azhary *et al*. [35]. Indeed, the authors described two out of 25 CADM patients who developed clinical weakness within five years of follow-up. In addition, Cao *et al*. reported two CADM cases out of 16 who developed clinical muscle weakness with elevated CK levels more than two years after initial cutaneous presentation [36].
Although early systemic treatment may limit the development of clinical myositis [32], the CADM population may develop muscle involvement later, even while on systemic therapy, and therefore require continued clinical monitoring.
Serologically, the CADM subgroup is not a homogeneous disease entity. Although Hoshino *et al*. showed that 65% of CADM cases were positive for anti-melanoma differentiation associated-protein 5 (MDA5) antibody [13], Koga *et al*. demonstrated, in an another study, that anti-MDA5 antibodies were not 100% sensitive and specific for the diagnosis of CADM, as several patients with anti-MDA5 antibodies had clinical myositis [41]. In addition, in one study, 10% of CADM patients had antibodies against transcriptional intermediary factor 1-gamma (TIF1-gamma) [13]. Furthermore, Hamaguchi *et al*. found different anti-aminoacyl-tRNA synthetase antibodies in CADM patients, including anti-PL-12 (28% of cases), anti-glycyl-tRNA-synthetase (ani-EJ) (18%), anti-histidyl-t-RNA-synthetase (anti-Jo-1) (8%), anti-asparaginyl-tRNA synthetase (anti-KS) (8%), and anti-PL-7 (7%) [12].
Similar to classic DM, a subset of CADM patients has been reported to show early and rapid ILD which can lead to early mortality, highlighting the importance of early lung screening also in CADM patients [32]. Indeed, Mukae *et al*. found that ILD related to CADM was associated with a higher mortality rate in comparison to ILD in classic DM [42]. In addition, CADM patients had a shorter mean duration of symptoms prior to hospital admission and were more prone to develop acute pulmonary symptoms within two months of hospital admission [42]. Furthermore, Ye *et al*. showed that CAMD patients more often developed rapidly progressive ILD, with an associated poorer prognosis [43].
CADM patients are reported to be at possibly greater risk of systemic malignancy, although how this cancer risk compares to that for classic DM patients is currently unclear. Indeed, Chen *et al*. reported that none of 20 CADM patients enrolled in a Taiwanese study were found to have an associated malignancy [44]. However, Azuma *et al*., reported that in a cohort of 15 CADM patients 20% had an associated malignancy (two had lung cancers and one had thymic cancer) [4]. In addition, Fung *et al*. reported that five out of six CADM patients developed or presented with an associated malignancy, namely three nasopharyngeal carcinomas, one unknown primary, and one non-small cell lung carcinoma [45]. Finally, a systematic review of CADM patients performed in 2006 highlighted that 14% of 301 evaluated CADM patients had an associated malignancy, most commonly nasopharyngeal carcinoma and breast carcinoma [33]. Therefore, an adequate malignancy screening would appear to be useful in CADM patients as well.
In conclusion, CADM is not likely to be considered a distinct pathophysiological subset within the DM spectrum. Indeed, CADM patients have similar clinical skin findings to classic DM. In addition, CADM patients are not characterized by a specific autoantibodies, but instead may have several classic DM-specific autoantibodies. The clinical picture and prognosis of CADM patients appear to be more associated with autoantibody subset, rather than absence of myopathy.

Juvenile DM

JDM is a rare chronic autoimmune condition that affects children and adolescents. Its incidence is between 1.9 to 4.1/1,000,000 inhabitants [46], and a female predominance has been reported (F:M ratio = 2.3:1). JDM is most commonly diagnosed in the 4-10-year-old age group [46], and its aetiology is still not completely understood. The genetic predisposition to JDM is complex and polygenetic [47]. Of note, a positive family history for autoimmune diseases, mainly type 1 diabetes and systemic lupus erythematosus, has been reported [47].
Characteristic clinical features of JDM include proximal muscle weakness and specific skin manifestations, including a heliotrope rash and Gottron's papules over extensor surfaces and the small joints of the hands. Calcinosis cutis, ulceration, and nailfold changes are typically observed at the time of diagnosis [47]. Most of the affected children show also fever, malaise, weight loss, and additional non-specific symptoms [47]. Calcinosis cutis and ectopic calcification in muscles have been reported in about 25% of children with JDM [48]. Risk factors for calcinosis are young age at disease onset and a prolonged disease course. Calcinosis may lead to skin ulceration and nerve compression [48]. Indeed, it affects mostly pressure areas. Multiple treatments have been investigated for calcinosis cutis. Because of the rarity of this phenomenon studies on the different therapeutic options are limited [49, 50]. Diltiazem, a calcium channel blocker, has been successfully used for treating calcinosis cutis. It reduces the formation of calcium crystals by altering intracellular calcium levels [19, 51]. In addition, it may also improve activation of the vascular musculature in lesional tissues and reduce tissue damage and calcification. Because of its anti-inflammatory effects, colchicine has also been used for the treatment of calcinosis cutis, but the results are inconclusive [19]. Minocycline has also been reported as effective therapy by altering osteoclast function, chelating calcium, and inhibiting matrix metalloproteinases [19, 52]. Warfarin has been postulated to reduce the level of calcium in the lesional skin by inhibiting vitamin K-dependent gamma-carboxylation [53]. Indeed, high levels of gamma-carboxyglutamic acid have been reported in patients with calcinosis cutis [53]. However, the efficacy of this therapy remains uncertain [19, 54, 55]. Because of their role in inhibiting proinflammatory cytokine production, bisphosphonates have also been used for calcinosis cutis. However, their efficacy remains ambiguous [19, 56, 57]. Several case reports showed the efficacy of IVIG in treating calcinosis

cutis with variable results [58]. Rituximab has been increasingly used because of positive effects in DM skin lesions [50]. Although one study on JDM patients did not report improvement, most studies showed at least partial response [50]. TNF-alpha inhibitors, particularly infliximab, may have a beneficial effect on calcinosis cutis in JDM, but their use is limited due to possible severe exacerbation of associated pulmonary fibrosis [59]. Surgery and physical therapies can be also considered in cases of calcinosis cutis [50]. However, the surgical management of digital calcinosis cutis may lead to skin necrosis [60]. Less invasive procedures, including carbon dioxide laser or extracorporeal shock wave therapy, may be useful, but the level of evidence is weak [50]. Lipoatrophy or scarring due to ulceration have been reported in about 30% of patients [48].

The course of disease is variable. Early disease onset is reported to be predictive of a poorer outcome, although this observation has not been universally confirmed [61, 62]. Female gender, negative Gower's sign (a habit due to lack of hip and thigh muscle strength) at disease onset, and positive photosensitivity have been reported as predictors of possible complete clinical remission [61, 62]. Conversely, the presence of rash at three months and presence of nailfold abnormalities at six months after disease onset have been reported as signs of poor prognosis [61, 62]. Furthermore, it has been reported that circa 80% of patients with JDM show ongoing disease activity in adulthood [61, 62]. In contrast to DM in adulthood, JDM has not been clearly associated with malignancy and cases of malignancy in children with JDM are limited to case reports [63, 64]. To date, neoplasia has been detected in only 12 JDM patients [65]. Of those patients, nine showed unusual clinical features such as splenomegaly or atypical rash. JDM patients with cancer were mostly affected by blood malignancy, including acute leukaemia and Hodgkin's disease [65]. A more in-depth evaluation to rule out malignancy should be performed if the physical examination reveals unusual findings such splenomegaly or lymphadenopathy.

JDM autoantibodies have not been largely described, and their specificity does not seem to differ from autoantibodies seen in adult DM patients. However, MSAs and myositis-associated antibodies have been described in approximately 70% of JDM cases [66].

Anti-TIF1-gamma are the most commonly observed autoantibodies in JDM patients (18-35% of cases); the highest prevalence has been reported in Caucasian patients and in a younger age group (median age: seven years) [63, 64, 67]. Furthermore, anti-TIF1-gamma has been associated with cutaneous ulceration, severe cutaneous involvement, and extreme muscle weakness [63, 64, 67]. Anti-MDA5 antibodies were identified in 6-38% of JDM patients and has been linked to arthritis, cutaneous ulcerations, and milder disease activity [63, 64, 67]. However, a subset of JDM patients with anti-MDA5 antibodies was affected by ILD and the disease course was more pronounced in Asiatic patients [63, 64, 67]. Patients with anti-U1-ribonucleoprotein (RNP) antibodies are reported to be more prone to developing JDM at older age [63, 64, 67]. Furthermore, anti-U1-RNP antibodies have usually been reported in JDM patients with overlap syndrome, which is characterized by polymyositis and sclerodema-like features [63, 64, 67]. Antipolymyositis-systemic scleroderma antibodies are associated with an increased risk of developing ILD, arthritis, and Raynaud's syndrome [63, 64, 67]. Furthermore, PM-Scl antibodies are most commonly associated with scleroderma-like features [63, 64, 67]. Anti-Ro autoantibodies have been described in association with poor prognosis [63, 64, 67], and have been reported in 6% of JDM patients [63, 64, 67]. However, JDM patients with myositis overlap syndrome may show anti-Ro autoantibodies in up to 25% of cases [63, 64, 67].

Several differential diagnoses should be taken into account, especially lupus erythematosus, eczema and psoriasis. Indeed, an incorrect diagnosis could lead to a delay in therapy, contributing to long-term disability. A thorough physical examination is mandatory. In particularly, this should focus on skin rashes, Gottron's papules, myalgia, muscle fatigue, and reduced proximal muscle strength. To substantiate the diagnosis of myositis, MRI at the site of clinical myopathy (in most instances, the thigh or shoulder girdle muscles) should be performed. After MRI, a deep muscle biopsy is critical to distinguish DM from other myopathies. The serological detection of DM-specific autoantibodies may help to confirm the diagnosis of DM and may be indicative of specific clinical subsets of DM.

Paraneoplastic DM

The association between myositis and neoplasia was firstly described in 1916, when Stertz reported a case of myositis in a patient with gastric cancer [9]. Based on a recent meta-analysis the prevalence of neoplasia was reported at 14.8% in DM patients [9].

The relative risk of carcinoma in DM ranges between 3 and 8% [10, 68, 69]. Furthermore, a slightly more elevated relative risk has been reported in the male population (M:F ratio of 5.29:4.56) [9, 11]. As expected, the risk of malignancy increases with the age of the patients. Indeed, the relative risk of malignancy is reported to be 2.79 for patients <45 years and 3.13 for those >45 years [9, 11]. The risk of malignancy among DM patients is higher in the first year after diagnosis (especially in the first three months after diagnosis of DM) [10], and then steadily decreases over five years, but remains slightly elevated in comparison to the general population [9, 11].

Lung and gastrointestinal neoplasia have been mostly reported in DM patients [10, 68, 69] (*table 6*). In addition, plenty of cases of malignancy of the nasopharynx have been described [44, 70] (*table 6*). However, different malignancies have been reported in association with DM, including ovarian, breast, prostate, and kidney cancer, as well as different types of haematological malignancies [8, 10, 44, 68-70] (*table 6*). In addition, the significant variety of malignancies associated with DM may reflect differences in malignancy risk across different populations. Indeed, in a Taiwanese study, the most commonly associated malignancy was nasopharynx carcinoma [44], while in a Japanese study, gastric cancer was the most frequently detected neoplasia in patients with DM [4]. In addition, the incidence of ovarian cancer in DM patients has been recently revaluated [9, 11]; whereas previous papers reported a 10-fold increase in the risk of ovarian cancer in female DM patients [10, 68], a recent study described only a five-fold increased risk [11].

It has been hypothesized that the increased incidence of malignancy in DM patients may be partially due to a more

Table 6. Neoplasias commonly associated with dermatomyositis*.

Author	Year	Country	Most frequent neoplasias	Total number of cases
Rose *et al*. [91]	1994	France	CLL (2%) Colon (2%)	10
Buchbinder *et al*. [70]	2001	Australia	H&N (17.6%) Lung (17.6%)	17
Hill *et al*. [68]	2001	Denmark Finland Sweden	Lung, trachea (21.5%) Ovary (14.7%)	88
Stockton *et al*. [10]	2001	Scotland	Lung (39.5%) Colon (14.6%)	48
Chen *et al*. [44]	2014	Taiwan	Nasopharynx (33.7%) Lung (24.7%)	89
Requena *et al*. [73]	2013	Spain	Ovarian (NR) Urinary bladder (NR)	12
Sellami *et al*. [92]	2018	Tunisia	Breast (42.8%) Nasopharynx (14.2%) Urinary tract (14.2%)	14

**Series with ≥ 10 DM patients CLL: chronic lymphatic leukaemia; H&N: head and neck; NR: not reported.*

complete cancer screening in this population [11]. However, a higher risk of malignancy has been reported in DM patients also before the onset of cutaneous or muscular features [2, 3]. Indeed, cancers may be detected prior to, at the time of, or after onset of DM [2, 3]. In JDM, malignancies have been rarely reported, however, it is important to perform comprehensive cancer screening for atypical cases or patients with splenomegaly or lymphadenopathy [65, 71].
In DM patients, a broad cancer screening should be performed, although no guidelines have been published [72]. However, a recent Spanish study proposed CT screening of the chest, abdomen, and pelvic area for all newly diagnosed DM patients [73]. Recently, an association between anti-TIF1-gamma (p155/140) IgG and paraneoplastic DM has been described [74]. Moreover, the expression of a shared antigen between regenerating muscle cells and cancer cells has been postulated [74].

Wong-type DM

Wong-type DM (WTDM) is a rare clinical subset of DM, characterized by the coexistence of DM and pityriasis rubra pilaris (PRP) cutaneous features [75]. It was named after Wong, who in 1969 described a series of 11 patients with DM and particular skin lesions, consisting of hyperkeratotic, erythematous, follicular confluent papules on the back of the hands, arranged in a linear fashion over the bony prominences [75]. However, two other cases of DM with PRP features were described before Wong's series, by O'Leary and Christianson [76], respectively. To date, around 30 cases of WTDM have been described in the literature [76].
The exact sex ratio for WTDM is unknown because this information has been omitted in several reports. However, Umanoff *et al*. reported a sex ratio (M:F) of 1:2.5 [77]. WTDM can affect any age (the median age is 46 years), but usually affects individuals >20.5 years, although few paediatric WTDM patients have been described in the literature [78]. Ethnicity could be a possible risk factor, as several authors did not clearly report ethnicity of the patients [76, 79]. Asian ethnicity has been clearly reported in 14 cases; patients from other reports were either Caucasian or their ethnicity was not reported [76].
Clinically, WTDM patients show hyperkeratotic, erythematous, follicular confluent papules, usually arranged in a linear fashion over the bony prominences, on the neck and back [75, 76]. Heliotrope rash and Gottron's papules have been widely described in WTDM patients [77], while palmar-plantar keratoderma (PPK) has been rarely reported [76]. Indeed, PPK has been described in only 11 patients [76], and only two patients out of 11 in the original Wong's series showed this feature [75]. Clinical muscular involvement has been usually reported, although few WTDM patients without muscular symptoms have been described [76, 77]. The temporal relationship between the appearance of cutaneous and muscular involvement is variable, as reported for classic DM [76]. Indeed, cutaneous involvement may develop before, simultaneously with, or after myositis [14].
The relationship between WTDM and neoplasia is not completely defined. In Wong's series, 12 cases of paraneoplastic DM were reported, but whether the neoplasms were associated with classic DM or WTDM was not specified [75]. However, malignancy was shown not to be associated with WTDM [76, 77], although the small number of reported cases and median age at presentation may have influenced this conclusion.
Pathologically, WTDM shows follicular hyperkeratosis, with keratotic plugs filling dilated follicular infundibula [80, 81]. Rarely, erector pili myositis has been described [82]. Although the aetiopathogenesis of WTDM is not clearly understood, it was thought that erector pili myositis could affect the hair cycle, leading to follicular keratotic plugging [82]. However, this theory does not seem plausible regarding WTDM without erector pili myositis or the presence of PPK [80].
According to Haro *et al*., WTDM may represent the association between PRP and DM in the same patient, because a common pathogenic factor could be involved in the spread of both clinical lesions [80]. However, this point of view

does not clarify why most patients have no PPK, which is a main PRP feature. Therefore, the hypothesis of Haro *et al*. may be considered only when a WTDM patient presents also with PPK [80].
In conclusion, WTDM is an extremely rare subtype of DM. Because of the rarity of WTDM, several points need to be clarified, in particular, the possible role of ethnic factors and association with neoplasia.

Antisynthetase syndrome (ASyS)

ASyS is the most common overlapping myositis [83-85]. ASyS is characterized by the presence of MSAs directed against tRNA-synthetases (ARSs) [84]. To date, eight different anti-ARSs autoantibodies have been described [84]. Among them, anti-Jo-1, that specifically recognizes histidyl-tRNA-synthetase, is the most frequently reported [84].
Although validated classification criteria for ASyS have not yet been reported, the association between these autoantibodies, inflammatory myopathy, and ILD has been extensively described [84, 85]. In addition, ASyS muscular histology differs from that of other inflammatory myopathies [86, 87]. Therefore, some authors distinguish ASyS as an entity in its own right. However, several features of ASyS pathogenesis and classification need to be further clarified [84].
The pathogenicity of anti-ARSs antibodies in ASyS has been reported in several studies, demonstrating their capacity to inhibit ARSs activities *in vitro* [88, 89]. In addition, ARSs play several roles in immune system activation, leading to tolerance breakdown and immune-mediated tissue damage [84, 85]. Although ARSs are ubiquitously expressed, only few organs are affected during the disease course. The lung is the most commonly involved organ [84, 85]. Indeed, more than three quarters of the patients with ASyS show an involvement of the lungs [84, 85]. However, ASyS still remains a heterogeneous disease in terms of clinical features, severity and progression. Significant associations with single-nucleotide polymorphisms affecting ARSs could ultimately explain the polymorphous clinical features, and the different subtypes of anti-ARSs have been correlated with disease expression and severity [86, 90]. However, studies with larger patient cohorts are needed to better clarify the clinical significance of the different subtypes of anti-ARSs. ■

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