Dermatomyositis: Clinical features and pathogenesis

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Learning objectives
After completing this learning activity, participants should be able to define dermatomyositis and its variants in both adults and children; recognize the clinical features of DM (both cutaneous and systemic) and potential differences in presentation between adults and children; discuss DM pathogenesis, including genetic, environmental, and immune factors, with updated review on recently identified auto-antibodies; and recognize common features of DM on cutaneous and muscle biopsy as well as their significance in diagnosis of JDM.

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Dermatomyositis (DM) is an idiopathic inflammatory myopathy that is clinically heterogeneous and that can be difficult to diagnose. Cutaneous manifestations sometimes vary and may or may not parallel myositis and systemic involvement in time course or severity. Recent developments in our understanding of myositis-specific antibodies have the potential to change the diagnostic landscape of DM for dermatologists. Although phenotypic overlap exists, anti-Mi2, -MDA5, -NXP2, -TIF1, and -SAE antibodies may be correlated with distinct DM subtypes in terms of cutaneous manifestations, systemic involvement, and malignancy risk. This review highlights new findings on the DM-specific myositis-specific antibodies and their clinical associations in both adults and children. (J Am Acad Dermatol 2020;82:267-81.)

Key words: amyopathic dermatomyositis; dermatomyositis; juvenile dermatomyositis; idiopathic inflammatory myopathy; interstitial lung disease; malignancy-associated dermatomyositis; Mi2; MDA5; myositis-specific antibodies; NXP2; SAE; TIF1.

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) that is characterized by distinct skin lesions and a clinically heterogeneous constellation of systemic manifestations. In the absence of characteristic dermatologic findings or myopathy, DM can be difficult to diagnose. In addition, historical approaches to the diagnosis of DM have embraced the use of "overlap" syndromes to account for clinical heterogeneity, making diagnosis even more difficult. The first article in this continuing medical education series discusses the epidemiology, clinical

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Abbreviations used:

CADM:	clinically amyopathic dermatomyositis
CAJDM:	clinically amyopathic juvenile dermatomyositis
DM:	dermatomyositis
IFN:	interferon
IIM:	idiopathic inflammatory myopathy
ILD:	interstitial lung disease
JDM:	juvenile dermatomyositis
MDA5:	melanoma differentiation associated protein 5
MSA:	myositis-specific antibody
NXP2:	nuclear matrix protein 2
RP-ILD:	rapidly progressive interstitial lung disease

characteristics, histopathology, and pathogenesis of DM. Emphasis will be placed on the unique clinical manifestations associated with the presence of myositis-specific antibodies (MSAs).

EPIDEMIOLOGY

The epidemiology of DM is difficult to determine because a variety of classification systems (discussed in the second article in this continuing medical education series) have historically been used to diagnose the condition. Epidemiologic studies report incidence rates for the IIMs of 2.47-7.8 per 100,000 person-years and prevalence rates of 9.54 to 32.74 per 100,000 individuals.[1-3] DM-specific prevalence has been estimated at 1 to 6 per 100,000 adults in the United States.[3] DM is the most common of the IIMs with a recent analysis of 3067 patients in the Euromyositis registry identifying DM in 31% of patients.[4] DM affects both genders with a 2:1 female:male ratio. All ethnic groups are affected, but it is more common in African Americans.[5,6] Population-based data suggest that clinically amyopathic DM (CADM) occurs in ≥20% of adults with DM.[7]

The average age of diagnosis of DM is bimodal, with juvenile DM (JDM) most commonly diagnosed between 4 and 14 years of age and adult DM diagnosed between 40 and 60 years of age.[6] JDM is the most common inflammatory myopathy of childhood but remains rare, with an estimated incidence of 3.2 cases per million children per year.[8] Rates of clinically amyopathic JDM are not well established.[9] In a recent series of patients with clinically amyopathic JDM, 25% eventually developed muscle involvement.[10]

CUTANEOUS MANIFESTATIONS

Cutaneous manifestations of DM may be variable,[11] and precise skin criteria for DM diagnosis is an area of ongoing research. Traditionally, skin findings have been divided into pathognomonic (Gottron papules, Gottron sign, and heliotrope rash), characteristic, compatible, less common, rare, and nonspecific (Table I).[12,13] Patients may present with 1 or a combination of DM-related skin changes (Figs 1-8). The clinical course of DM skin lesions does not necessarily parallel that of muscle disease and may precede or follow myositis. Lesions are often pruritic or burning and are usually photosensitive.[14] Persistent severe pruritus can significantly impact patients' quality of life.[15,16] The cutaneous manifestations of DM associated with MSAs will be discussed in detail below.

MUSCLE MANIFESTATIONS

Approximately 80% of patients with DM have myopathy. The classic muscular manifestation is acute or subacute onset of symmetric, proximal muscle weakness. The myopathy is usually painless, and while elevations of creatine kinase, aspartate aminotransferase, and alanine aminotransferase are common, laboratory indicators of muscle activity may also be normal.[14,17] Dysphagia, dysphonia, and symptoms of aspiration indicate possible involvement of striated muscle of the pharynx and esophagus and are associated with a poor prognosis.[18] Notably, DM is not associated with sensory loss, ptosis, involvement of the extraocular muscles, or abnormal reflexes, which can help differentiate it from other neuromuscular disorders.[5]

Those with DM-consistent skin findings but without myopathy have what is termed CADM. CADM may by hypomyopathic (no objective weakness but evidence of subclinical muscle involvement on laboratory testing, biopsy, or imaging) or amyopathic (no evidence of muscle involvement on examination or workup).[19]

SYSTEMIC MANIFESTATIONS

Table II lists systemic manifestations of DM in adults and children. Specific manifestations and malignancy associations will be discussed in the context of MSAs to best reflect how these manifestations present in clinical practice. The clinical subsets associated with MSAs will be discussed separately for adult and juvenile DM because the significance of each antibody depends on the age of the affected individual.

HISTOPATHOLOGY

Skin

Skin biopsy specimens obtained from patients with DM are characterized by hyperkeratosis, epidermal atrophy, vacuolar interface dermatitis,

Table I. Cutaneous manifestations of adult dermatomyositis

Category	Finding	Clinical description[8,9,12,17,71]	Additional features
Pathognomonic	Gottron papules	Violaceous papules and plaques, sometimes with subtle scale, overlying the MCP and ICP joints of the hands	Dyspigmentation, atrophy, and scarring possible when lesions resolve[106]
	Gottron sign	Erythematous macules or patches over extensor surfaces of elbows, knuckles, knees, and ankles	Slight scale may be present[13]
	Heliotrope rash	Periorbital erythema with edema, most often of the upper eyelids	May also involve cheeks and nose[12]
Characteristic	Nailfold changes	Periungual erythema and telangiectasias, dystrophic cuticles, and hemorrhagic nailfold infarcts	Nailfold capillaroscopy may be useful adjunctive tool for monitoring disease activity[107-109]
	Shawl sign	Violaceous or erythematous macules and patches over posterior shoulders, neck, upper back, and possibly lateral upper arms	Poikiloderma may also be present in same distribution[13]
	V sign	Erythematous, confluent macules and patches over lower anterior neck and upper chest	Skin may also appear atrophic[13]
	Holster sign	Symmetric poikiloderma of hips and lateral thighs below the greater trochanter	May be reticulated, livedoid, or linear and is reported to be highly specific for DM[13]
	Scalp involvement	Atrophic, erythematous, sometimes pruritic scaly plaques	May be misdiagnosed as psoriasis or seborrheic dermatitis[110]
Compatible	Poikiloderma	Hypo- or hyperpigmentation, telangiectasia, and atrophy, usually found on upper chest and lateral upper arms	May be referred to as "poikiloderma atrophicans vasculare" or "poikilodermatomyositis"[13]
	Periorbital edema and facial swelling	Edema with or without erythema	
Less common	Vesiculobullous, necrotic, or ulcerative lesions	Variable	Often associated with cutaneous vasculitis,[13] ulceration associated with anti-MDA5 antibodies[93]
	Cutaneous vasculitis	Variable, but may include petechiae, palpable purpura, livedo reticularis, and ulceration	More common in JDM
	Calcinosis cutis	Superficial white papules or nodules, most commonly over bony surfaces or at sites of inflammation	Rare in adult DM (estimated 4% of adult DM patients[4])
Rare	Mechanic's hands	Hyperkeratotic, scaling, and fissuring of fingers and/or palms	More common in patients with anti-MDA5 antibodies[53] and antisynthetase syndrome[53,111]
	Flagellate erythema	Linear erythematous macules and patches on the back	Associated with absence of MSAs on serological testing[56] or presence of anti-Mi2 antibodies[70]
	Deck chair sign	Erythematous eruption sparing transverse skin folds	May be first cutaneous sign preceding classic DM skin findings*[112]
	Follicular hyperkeratosis ("wong-type DM")	Follicular, hyperkeratotic papules on extensor surfaces resembling pityriasis rubra pilaris	Hair follicle destruction and follicular hyperkeratosis on histopathology plus interface changes of DM[113]

Continued

Table I. Cont'd

Category	Finding	Clinical description[8,9,12,17,71]	Additional features
	Panniculitis	Painful, indurated nodules of buttocks, arms, thighs, and abdomen	Associated with anti-MDA5 antibodies[93]
	Mucinosis	Variable, frequently plaques appearing in a reticular pattern	
	Erythroderma	Widespread erythema	Associated with malignancy[12]
	Oral mucosal changes	Variable, but gingival telangiectasias, erosions, ulcers, and leukoplakia-like lesions reported	Ovoid palatal patch associated with anti-TIF1 antibodies[80]
Nonspecific	Raynaud phenomenon	Episodic vasospasm of fingers and toes in response to cold with triphasic color change[114]	More common in antisynthetase syndrome[5]

DM, Dermatomyositis; *ICP*, intercarpal phalangeal; *JDM*, juvenile dermatomyositis; *MCP*, metacarpal phalangeal; *MDA5*, anti—melanoma differentiation-associated protein 5; *MSA*, myositis-specific antibody; *TIF1*, transcription intermediary factor 1.
*S. Madsen et al, unpublished data, 2019.

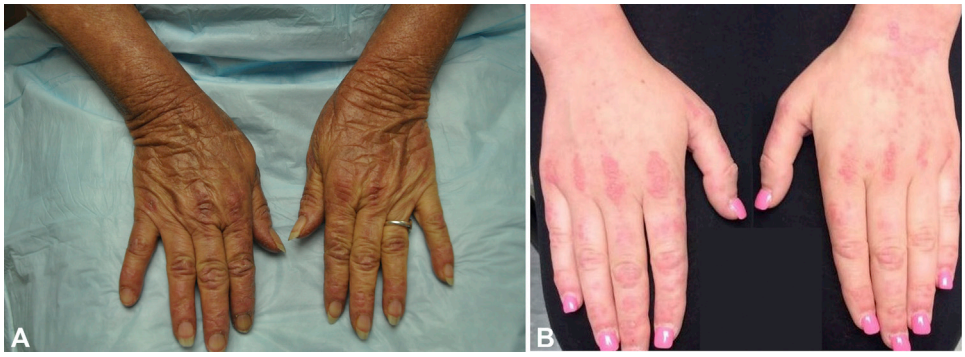

Fig 1. A and **B**, Gottron papules and the Gottron sign on the dorsal surfaces of the hands of two patients with dermatomyositis.

basement membrane thickening, dermal edema, pigmentary incontinence, mucin deposits, and a perivascular infiltrate composed of $CD4^+$ lymphocytes.[6] Endothelial cell damage, loss of capillaries, and vascular dilatation may also be seen.[20]

Muscle

Biopsy specimens of muscle from patients with DM are hallmarked by perifascicular atrophy.[14,21] However, atrophy may be patchy,[22] which can cause false negatives. A 2017 study estimated the sensitivity of perifascicular atrophy to be only 47% (though it is 98% specific).[23] Recent studies suggest that expression of myxovirus resistance protein A in myofiber cytoplasm may be a better indicator of muscle involvement,[23,24] with a sensitivity of 71% and specificity of 98%.[23] Other abnormalities observed in DM muscle include deposition of complement on endomysial capillaries[5] (35% sensitive and 93% specific[6]) and decreased capillary density. Inflammatory infiltrates are both perimysial and perivascular and consist of macrophages, $CD20^+$ B cells, $CD4^+$ T cells, $CD25^+$ plasma cells, and plasmacytoid dendritic cells.[5,25] Increased perifascicular expression of major histocompatibility complex class I has also been reported.[14,26]

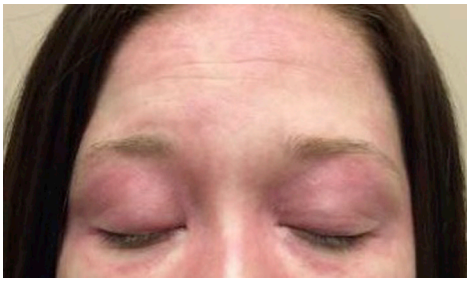

Fig 2. Heliotrope rash on the face of a patient with dermatomyositis.

Special considerations in JDM

There is considerable histologic overlap between DM in adults and children, but perifascicular atrophy seen on a biopsy specimen of muscle may be more reliably identified in JDM.[17] In addition, vascular

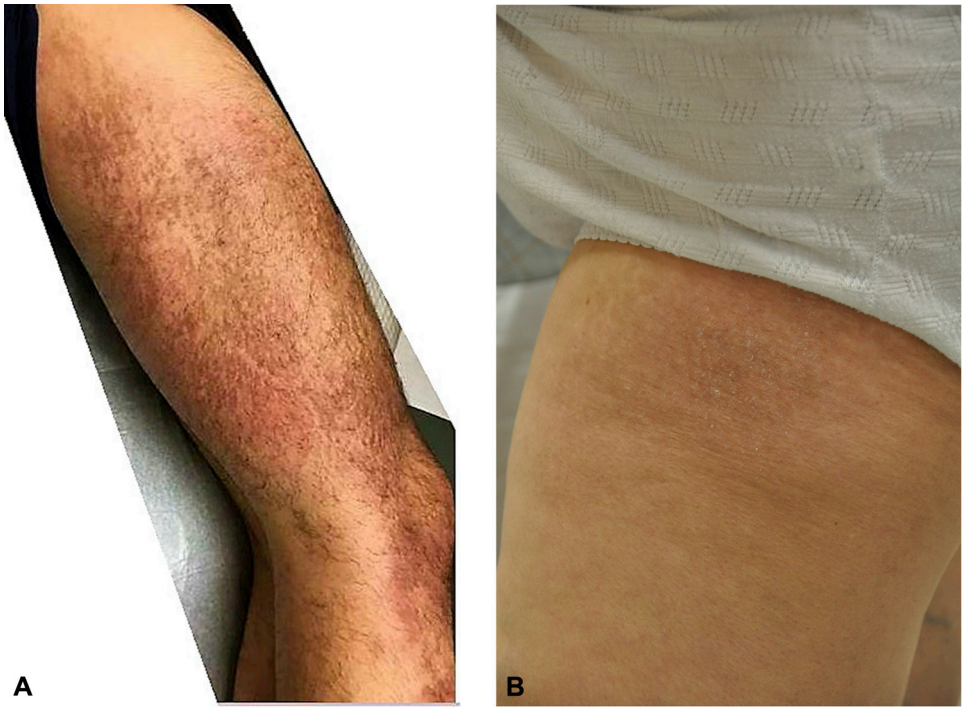

Fig 3. Holster sign on the (**A**) right lateral thigh and (**B**) right lateral hip of two patients with dermatomyositis.

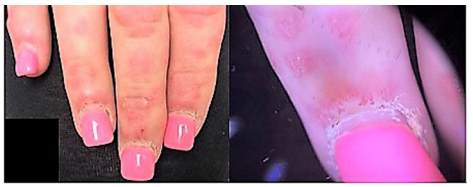

Fig 4. Characteristic nailfold changes of dermatomyositis. Dermoscopic image shows periungual erythema and telangiectasias and dystrophic cuticles.

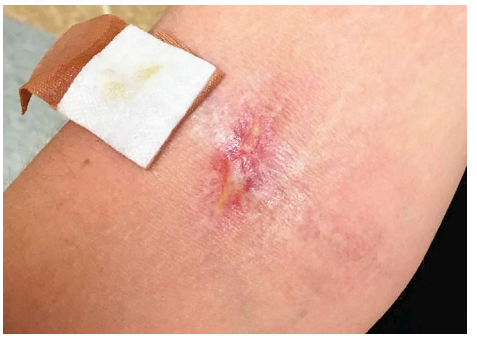

Fig 5. Ulcerative lesion on the antecubital fossa of a patient with dermatomyositis.

involvement in JDM is often more prominent.[27] Specific features of a muscle biopsy specimen and their associated JDM phenotypes are outlined in Table III.

PATHOGENESIS

The pathogenesis of DM is multifactorial, complex, and incompletely understood. Genetic, environmental, and immune mechanisms (including the recently discovered autoantibodies discussed below), are thought to play a role in both adult DM and JDM development.

Genetic risk factors

DM has a strong genetic component. Multiple genotyping studies have demonstrated associations between major histocompatibility complex polymorphisms and DM development,[28,29] and particular human leukocyte antigen (HLA) alleles have been correlated with autoantibody production in both adults[30,31] and children.[32,33] In addition, the International Genetics Consortium in Myositis has identified cytokine and lymphocyte signaling alleles associated with disease development, disease severity, calcinosis, and ulceration in genome-wide analyses of juvenile IIMs.[28] Epigenetic modification, including DNA methylation, histone modification, and microRNA activity, may also play a role in DM pathogenesis.[34,35]

Environmental risk factors

Multiple environmental factors may trigger chronic immune activation in genetically susceptible individuals.[30,36] Proposed triggers for DM include ultraviolet radiation, viral infections, medications,

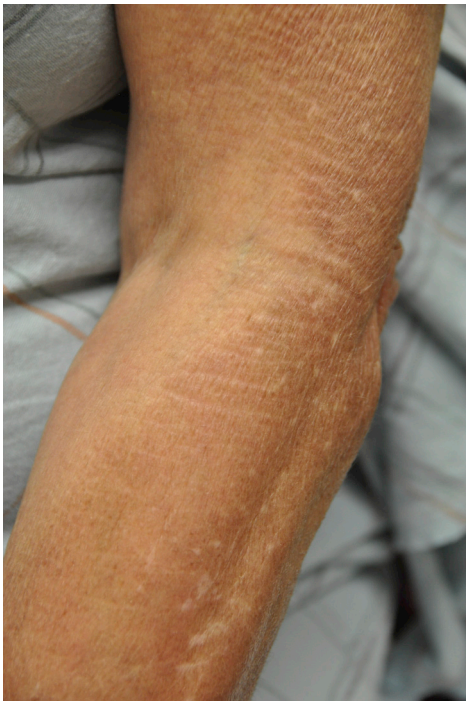

Fig 6. Characteristic poikiloderma on the lateral arm of a patient with dermatomyositis.

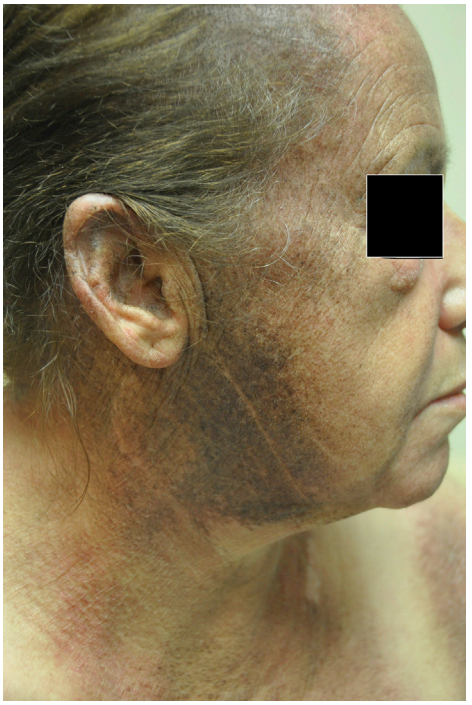

Fig 7. Scalp dark purpuric hyperpigmentation equivalent to erythema and subtle frontal diffuse alopecia in a patient with Fitzpatrick skin type V and dermatomyositis.

and smoking. Ultraviolet exposure has been linked with DM and anti-Mi2 antibodies in adult women[37] and with JDM and anti–transcription intermediary factor 1 (TIF1) antibodies in children.[38] Viral infections may play a role in triggering immune activation or disrupting immune tolerance,[39] but attempts to isolate viruses from DM muscle samples have been unsuccessful.[14] A 2017 study found that DM/JDM flares were associated with ultraviolet exposure, infections, and some medications, although only sun exposure (odds ratio, 2.2) and recent nonsteroidal antiinflammatory drug use (odds ratio, 1.9) remained significant predictors in multivariable analysis.[40] Smoking has been associated with DM and the development of interstitial lung disease (ILD), dysphagia, malignancy, and cardiac involvement.[4] Other potential environmental triggers are less well established, including a recent report of CADM developing after receiving a tattoo[41] and a case series of 3 patients who developed an acute onset or flare of DM after ingesting the herbal supplement IsaLean.[42]

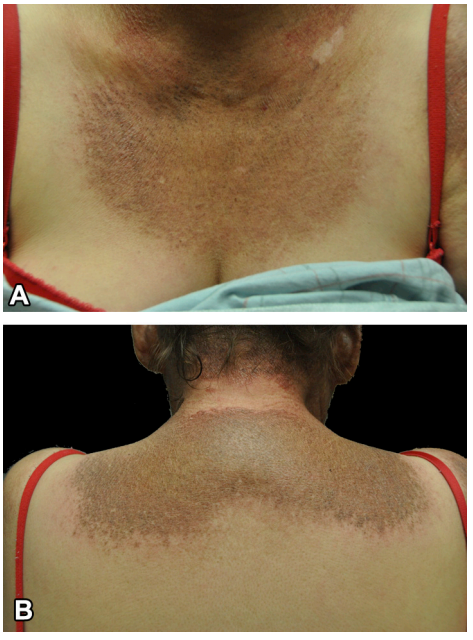

Fig 8. **A**, V sign with erythema and poikiloderma and (**B**) shawl sign in a patient with dermatomyositis.

Immune mechanisms

The sequence of immune activation in DM remains incompletely understood although it likely results from inappropriate complement activation.[43,44] It remains controversial whether this activation is antibody-dependent or whether it results from initiation of the classical complement cascade. Regardless, this activation results in capillary destruction that leads to ischemia and microinfarction, hypoperfusion, and perifascicular atrophy.[14] Altered expression of myogenic regulatory factors

Table II. Systemic manifestations of dermatomyositis in adults and children

Organ system	Adult DM	JDM
Pulmonary	Varying degrees of ILD most common,[17] ILD is associated with anti-MDA5 antibodies,[19] may be rapidly progressive, especially in Asian populations[89]; pulmonary hypertension or serositis also possible[17]	ILD rare (6% of cases), associated with anti-MDA5 antibodies[4,71]; respiratory muscle weakness affecting ventilation possible[71] and not correlated with other clinical measures of muscle weakness[115]
Cardiac	Cardiovascular risk factors are increased in patients with DM[116]; subclinical diastolic dysfunction is common[116]; myocarditis, myocardial fibrosis, arrhythmias, and congestive heart failure are all possible[116]; cardiac involvement does not correlate with disease severity and may develop at any time[117]	Clinically significant involvement uncommon, but systolic and diastolic dysfunction possible[118]; increased rates of hypertension, dyslipidemia,[116] and ECG abnormalities[116,119]; decreased heart rate variability[116,119]; pericarditis and myositis occur rarely[116]
Gastrointestinal	Dysphagia related to dysfunction of the pharynx or esophagus[120]; gastric and small intestinal motility may be affected[120]; rarely, vasculopathy may lead to GI tract infarction or perforation[121]	GI involvement in 5-37% of JDM cases[122]; dysphagia, dysmotility, vasculitis-related bowel pathology possible[122]; weakness affecting swallowing does not correlate with other clinical measures of muscle weakness[123]
Endocrine		Lipodystrophy in 10-30% of patients[124]; growth failure in 10% of cases[125]; bone mineral density may be reduced[71]
Vascular	Cutaneous vasculopathy may cause ulcerations, especially in patients with anti-MDA5 antibodies[92,93]	Vasculitis more common in JDM, especially involving the skin and small vessels[122]; GI involvement may lead to malabsorption, ulceration, or perforation[126]; central nervous system[122] and retinal involvement[127] also reported; nailfold capillaroscopy may be useful tool[107-109]

DM, Dermatomyositis; *ECG*, electrocardiographic; *GI*, gastrointestinal; *ILD*, interstitial lung disease; *JDM*, juvenile dermatomyositis; *MDA5*, anti−melanoma differentiation-associated protein 5.

(demonstrated in JDM muscle) may also contribute to atrophy because of impaired cell differentiation and maturation.[45]

In addition, there is considerable evidence that interferons (IFNs) play a role in DM and JDM. Marked upregulation of the type I IFN pathway has been demonstrated in the muscle, skin, and blood of patients with DM,[20,34,46-48] and cutaneous activity in adult DM has been shown to correlate with a type I IFN gene signature.[46] In patients with JDM, type I IFN score, type II IFN score, and tumor necrosis factor−alpha expression correlate with disease activity.[49] A persistent IFN response (perpetuated by chronic stimulation of antigen-presenting cells) has been implicated in multiple autoimmune diseases; the resulting T and B cell activation may be responsible for autoantibody production.[50] In DM and JDM, however, the pathogenic role of these autoantibodies remains unclear. The recent identification of antiendothelial cell antibodies in the plasma of children with JDM supports the conceptualization of JDM as an antibody-mediated vasculopathy.[51]

MYOSITIS-SPECIFIC ANTIBODIES

MSAs are antibodies that are exclusively associated with a diagnosis of an IIM.[52] DM-specific antibodies include anti-Mi2, anti−melanoma differentiation-associated protein 5 (MDA5), anti-NXP2, anti-TIF1, and anti−small ubiquitin-like modifier activating enzyme (SAE). Except for anti-Jo1, which is present in antisynthetase syndrome, MSAs have not yet been incorporated into the diagnostic criteria for IIMs. However, MSAs are potentially helpful to the dermatologist because: 1) they may facilitate diagnosis in the absence of a biopsy specimen of muscle and in clinically atypical DM cases[53,54]; 2) they impact prognosis and can help guide management[55-58]; and 3) they allow for clinical studies to select patients based on serologies, which may help further elucidate the significance of MSAs and improve the generalizability of these studies in clinical practice.[54]

The current limitations of MSAs are twofold: 1) there is still a "serologic gap," with a significant proportion of DM patients presenting without MSAs;

Table III. Biopsy features and associated phenotypes in juvenile dermatomyositis[71,128,129]

Phenotype	Muscle biopsy features
Severe disease course	Lymphoid follicles including networks of fDCs and high endothelial venules; high levels of CXCL13 and lymphotoxins; resident naïve CD45RA$^+$ T cells, and maternally derived B cells and pDCs
Chronic disease course with ulcerations	Severe arteriopathic changes, positive arterial direct immunofluorescence, severe capillary loss, endomysial fibrosis, and muscle infarcts
Chronic disease course	Extensive active myopathic changes and central nuclei without basophila

fDC, Follicular dendritic cell; *pDC*, plasmacytoid dendritic cell.

and 2) clinically available laboratory tests for MSAs can vary in their sensitivity and specificity. Results of laboratory testing for MSAs vary depending on the testing technique used, and estimated rates of MSA positivity in DM range from 20% to 50%.[59-61] Using commercial laboratories, it is not uncommon for MSA testing to be negative, even after a diagnosis of DM has been clinically confirmed[61]; this may be partially attributable to the variability in the accuracy of available commercial testing. Nonetheless, the clinical utility of MSA testing is increasing as commercial testing improves and is standardized, especially with recent studies suggesting that MSAs alone can accurately subdivide patients into their appropriate clinical diagnoses.[53] Although laboratory testing for MSAs and their use to classify IIMs remain somewhat exploratory, we believe this is a promising area of research. A summary of MSAs and their clinical associations in both adults and children is presented in Table IV.

Mi-2

Anti-Mi2 antibodies are directed against a nuclear DNA helicase involved in transcription.[34] The prevalence of anti-Mi2 antibodies among adult patients with DM varies based on ethnicity, geographic location, and method of testing,[62] but estimates in the literature range from 4% to 35%.[34,63-68] These patients present with "classic dermatomyositis" characterized by the development of pathognomonic cutaneous manifestations.[58,69] The cutaneous manifestations disproportionately associated with Mi-2 DM in adults include facial dermatosis, shawl sign, poikiloderma, and flagellate erythema.[70] Other more severe cutaneous features of DM, such as calcinosis and ulcerative vasculopathy, are not commonly seen in this clinical subset.

In addition, Mi-2 DM characteristically presents with proximal symmetric muscle weakness. Despite having clinically mild myopathy, these patients frequently have creatine kinase elevations that are out of proportion to their degree of muscle involvement. Fortunately, this form of DM is usually responsive to treatment. Mi-2 DM portends a benign prognosis and is not associated with an increased risk of development of malignancy or interstitial lung disease.[58]

Anti-Mi2 antibodies are identified in 4% to 10% of patients with JDM, and the clinical manifestations and prognostic implications are similar in adults and children. Anti-Mi2 antibodies are more common in Hispanic children who are older at disease onset (median age 11 years).[71,72] As in adults, clinical features include symmetric, proximal muscle weakness and pathognomonic cutaneous findings, and these patients tend to respond well to treatment.[71-73]

TIF1

TIF1 (previously p155/140) is a tumor suppressor protein that is responsible for serving as a transcriptional corepressor.[24,55] There are 3 subunits of the TIF1 protein (alpha, beta, and gamma), with each subunit having its own respective autoantibodies.[74,75] Antibodies to this family of proteins were first identified in 2006[76] and are found in 18% to 23% of adult patients with DM.[55] The primary clinical significance of anti-TIF1-gamma DM is its strong association with underlying malignancy. Identification of anti-TIF1 antibodies has a positive predictive value of 58% and a negative predictive value of 95% for cancer-associated DM (odds ratio, 27.26).[77] TIF1 antibodies are associated with the development of both solid and hematologic malignancies. Tumor rates reported in the literature are variable but range from 20% to 65%.[55,78] It has been hypothesized that anti-TIF1 antibodies are generated during an antitumor immune response.[24,55,79]

Anti-TIF1 DM has multiple other key clinical associations in adults: 1) severe, photosensitive cutaneous disease with heliotrope rash, v sign, and Gottron papules; 2) unique mucocutaneous findings, such as palmar hyperkeratosis, psoriasiform plaques, ovoid palatal patches, and atrophic hypopigmented patches with overlying telangiectasias; 3) hypomyopathic disease; 4) gastrointestinal involvement; and 5) a lack of other systemic

Table IV. Dermatomyositis-associated myositis-specific antibodies and their associated clinical features

Antibody	Target antigen	Incidence	Associated clinical features	Malignancy association
Anti-Mi2	Nuclear DNA helicase involved in transcription	Adult DM 4-35%	"Classic" cutaneous findings, facial dermatosis, shawl sign, poikiloderma, flagellate erythema; proximal, symmetric muscle weakness with highly elevated CK; treatment responsive	None
		JDM 4-10%	More common in Hispanic patients, older at disease onset; clinical features similar to adults	None
Anti-TIF1 (previously anti-p155/140)	Tumor suppressor protein that acts as transcriptional corepressor	Adult DM 18-23%	Severe, photosensitive cutaneous disease, palmar hyperkeratosis, psoriasiform plaques, ovoid palatal patches, atrophic hypopigmented patches with overlying telangiectasias; often hypomyopathic; GI involvement	Strongly associated with malignancy
		JDM 18-35%	More common in white patients, younger at disease onset; severe, treatment-refractory cutaneous disease, ulceration, muscle weakness, lipodystrophy, chronic disease course	None
Anti-MDA5 (previously CADM140)	RNA-specific helicase involved in antiviral immune response	Adult DM 10-30%	Clinically amyopathic disease; interstitial lung disease (may be rapidly progressive); cutaneous ulceration, painful palmar papules, panniculitis	None
		JDM 7-50%	Ulcerative skin and mucosal lesions; interstitial lung disease; milder muscle involvement; arthritis	None
Anti-NXP2	Nuclear protein involved in regulation of transcription and RNA metabolism	Adult DM 2-25% (varies by ethnicity)	Classic cutaneous findings; peripheral edema; calcinosis and ulceration rare	Increased risk of malignancy
		JDM 20-25%	Calcinosis cutis; disabling myopathy; GI bleeding related to vasculopathy	None
Anti-SAE	Nuclear enzyme involved in posttranslation modification of proteins	Adult DM 8% (varies by ethnicity)	Strong HLA associations; severe cutaneous disease; progressive muscle disease with dysphagia; fever and weight loss	Unknown
		JDM 2-8%	Severe cutaneous disease, minimal muscle disease	Unknown

CK, Creatine kinase; *DM*, dermatomyositis; *GI*, gastrointestinal; *HLA*, human leukocyte antigen; *ICP*, intercarpal phalangeal; *JDM*, juvenile dermatomyositis; *MCP*, metacarpal phalangeal; *MDA5*, anti—melanoma differentiation-associated protein 5; *MSA*, myositis-specific antibody; *NXP2*, nuclear matrix protein 2; *RNA*, ribonucleic acid; *SAE*, small ubiquitin-like modifier activating enzyme; *TIF1*, anti—transcription intermediary factor 1.

Table V. Non–dermatomyositis-associated myositis-specific antibodies

Antibody	Disease entity	Clinical association(s)
Anti-ARS (includes anti-Jo1 [histidyl], anti-PL7 [alanyl], anti-PL12 [glycyl], anti-EJ [isoleucyl], anti-OJ [isoleucyl], anti-KS [asparaginyl], anti-Zo [phenylalanyl], and anti-YRS/HA [tyrosyl])	Antisynthetase syndrome	Myositis with ILD, polyarthritis, Raynaud phenomenon, and cutaneous findings (Gottron papules, "mechanic's hands")[104]; more severe ILD and poorer prognosis with non-Jo1 antibodies[85]
Anti-SRP	Necrotizing myopathy (anti-SRP antibody syndrome)	Sudden, severe, and progressive muscle weakness, often with cardiac involvement and/or dysphagia[59,104]; treatment resistant[85]; no increased risk of malignancy[130]
Anti-HMGCR	Immune-mediated necrotizing myopathy	Increased risk of malignancy compared with the general population[130]; statin-induced myopathy[131]
CN1A	Inclusion body myositis	Progressive weakness and functional impairment in older patients (typically >50 years of age)[132]

ARS, Aminoacyl tRNA synthetase; *CN1A*, cytosolic 5'nucleotidase 1A; *HMGCR*, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; *ILD*, interstitial lung disease; *SRP*, signal recognition particle.

manifestations, such as interstitial lung disease, Raynaud phenomenon, and arthritis.[58,80-82]

In children with JDM, the frequency of anti-TIF1 antibodies is estimated to be 18% to 35%.[71] These antibodies are more common in white patients[71,72] with a younger age at disease onset (median 7 years).[71] Unlike in adult DM, anti-TIF1 antibodies in children are not associated with malignancy.[55] Clinical associations include severe, treatment-refractory, photodistributed cutaneous disease, cutaneous ulceration, greater muscle weakness, lipodystrophy, and a chronic disease course.[71,72]

MDA5

MDA5 (previously CADM140) is a RNA-specific helicase involved in antiviral immune response (including the production of type I IFN).[24,83] Autoantibodies against MDA5 are identified in the majority of adults and children with CADM[84,85] and in 10% to 30% of patients with DM overall.[57] This subset is identified most frequently in Asian patients, with the associated clinical significance demonstrating some degree of regional/ethnic variability.[86-88] Anti-MDA5 DM is associated with an increased risk of developing ILD, which in some cases may be rapidly progressive (RP-ILD).[24,83,89] RP-ILD is characterized by short-interval (<4 weeks) progression of ILD by subjective symptoms or objective metrics (eg, ground glass opacity on computed tomography, worsening PaO_2).[90] The presence of anti-MDA5 antibodies has an estimated sensitivity of 77% and specificity of 86% for the development of DM-associated RP-ILD.[91] The associated 6-month mortality is approximately 59%.[91]

Anti-MDA5 DM also presents with several unique cutaneous findings in both adults and children that are thought to be attributable to the development of cutaneous vasculopathy.[92,93] These include: 1) cutaneous ulceration frequently at the site of Gottron papules and the lateral nail folds; 2) painful palmar papules (termed inverse Gottron papules); and 3) panniculitis.[19,93-95]

Anti-MDA5 antibodies are the third most common MSA detected in children with JDM after anti-TIF1 and anti–nuclear matrix protein 2 (NXP-2).[71] The exact prevalence of anti-MDA5 antibodies in JDM is unknown, although estimates range from 7.4% per the United Kingdom Juvenile Dermatomyositis Registry[96] to near 50% in Japanese children with JDM.[96,97] Like their adult counterparts, children with anti-MDA5 DM have an elevated risk of developing ILD as well as ulcerative skin and mucosal lesions.[71,96] RP-ILD is less common in children, but rates of RP-ILM are higher in Asian JDM patients with anti-MDA5 antibodies.[71,96] Patients with JDM with these antibodies frequently demonstrate milder muscle involvement[96] (though less commonly amyopathic disease) and arthritis.[71]

NXP-2

NXP-2 is a protein involved in multiple nuclear functions, including regulation of transcription and RNA metabolism.[24] Anti NXP-2 antibodies (formerly anti-MJ) are detected in a relatively small percentage of adults with DM, although prevalence varies by ethnicity (14-25% in U.S. populations and 2-5% in

Japanese populations).[58,78,84,98-100] Like anti-TIF1-gamma DM, adults with anti-NXP-2 DM are at an elevated risk of underlying malignancy, although the tumor rate associated with NXP-2 antibodies (37.5%) is less than that conferred by anti-TIF1-gamma seropositivity.[57] This subset of DM patients typically presents with classic cutaneous findings. Peripheral edema may be seen in ≤35% of patients,[58,99] and calcinosis and distal ulcerations are observed in adults with anti-NXP-2 DM on occasion.[58] Calcinosis is a much less frequent finding in adults than it is in children with this antibody.

Anti-NXP2 antibodies are the second most common autoantibody in patients with JDM, with a frequency of 20% to 25%.[58,72] Like anti-TIF1 antibodies, anti-NXP2 antibodies are more common in younger, white patients (median age at disease onset 6 years).[71,72] NXP-2 JDM portends a poor prognosis and requires more aggressive management than other forms of JDM. The cutaneous hallmark of this subset is the development of calcinosis cutis, which occurs in >40% of NXP-2 antibody−positive individuals.[101,102] This form of JDM also presents with severe myopathy that frequently causes functional impairment and results in contracture development.[58] The severe myopathy associated with NXP-2 seropositivity develops secondary to vasculopathy-induced muscle ischemia.[71] This vasculopathy also predisposes individuals with NXP-2 antibodies to gastrointestinal bleeding.[72] Children with NXP-2 JDM do not have associated malignancies.

Anti-SAE

Anti-SAE DM is a more recently described subset of DM that occurs in ~8% of adults though frequency varies by ethnicity.[59] This subtype of DM is strongly associated with HLA-DQB1*03. HLA-DRB1*04 and 03-DQB1*03 are also risk factors.[103] Patients with this subset of DM present initially with severe cutaneous disease and minimal myopathy. These individuals typically develop progressive muscle involvement over time and frequently develop severe dysphagia.[104] Some case series have also suggested that patients with anti-SAE DM frequently have systemic symptoms, such as fever and weight loss.[103] The association of this subset of DM with malignancy and ILD is still unknown. Notably, the presence of anti-SAE antibodies has been reported to be predictive of hydroxychloroquine drug eruptions.[105] In children, anti-SAE JDM comprises only a small segment of JDM cases (6-8% in European cohorts and 2% in Asian cohorts) and is typically characterized by severe cutaneous involvement and minimal muscle disease in a manner analogous to adults.[71]

Other MSAs

Other MSAs occur in immune-mediated necrotizing myositis, inclusion body myositis, and antisynthetase syndrome. These antibodies may be identified during a work-up of a patient for DM. Table V lists these other MSAs and their associated clinical features.

In conclusion, the recent discovery of MSAs has revealed that DM is comprised of a heterogenous group of closely related clinical subtypes that can be distinguished from one another based on serology. Understanding the clinical implications of MSAs in DM will become increasingly important as more studies are done and autoantibody testing is standardized. The first article in this continuing medical education series provided readers with an understanding of the clinical significance of MSAs that will be essential for understanding the approaches to diagnosis, work-up, and management discussed in the second article in this series.

REFERENCES

1. Smoyer-Tomic KE, Amato AA, Fernandes AW. Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, Medicare supplemental insured, and Medicaid enrolled populations: an administrative claims analysis. *BMC Musculoskelet Disord*. 2012;13:103.
2. Bernatsky S, Joseph L, Pineau CA, et al. Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. *Ann Rheum Dis*. 2009;68:1192-1196.
3. Furst DE, Amato AA, Iorga ŞR, Gajria K, Fernandes AW. Epidemiology of adult idiopathic inflammatory myopathies in a U.S. managed care plan. *Muscle Nerve*. 2012;45:676-683.
4. Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann Rheum Dis*. 2018;77:30-39.
5. Findlay AR, Goyal NA, Mozaffar T. An overview of polymyositis and dermatomyositis. *Muscle Nerve*. 2015;51:638-656.
6. Aussy A, Boyer O, Cordel N. Dermatomyositis and immune-mediated necrotizing myopathies: a window on autoimmunity and cancer. *Front Immunol*. 2017;8:992.
7. Bendewald MJ, Wetter DA, Li X, Davis MDP. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. *Arch Dermatol*. 2010;146:26-30.
8. Mendez EP, Lipton R, Ramsey-Goldman R, et al. US incidence of juvenile dermatomyositis, 1995-1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. *Arthritis Rheum*. 2003;49:300-305.
9. Kim S, Kahn P, Robinson AB, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment plans for juvenile dermatomyositis with skin predominant disease. *Pediatr Rheumatol Online J*. 2017;15:1.
10. Gerami P, Walling HW, Lewis J, Doughty L, Sontheimer RD. A systematic review of juvenile-onset clinically amyopathic dermatomyositis. *Br J Dermatol*. 2007;157:637-644.

11. Patel B, Khan N, Werth VP. Applicability of EULAR/ACR classification criteria for dermatomyositis to amyopathic disease. *J Am Acad Dermatol*. 2018;79:77-83.e1.
12. Mainetti C, Terziroli Beretta-Piccoli B, Selmi C. Cutaneous manifestations of dermatomyositis: a comprehensive review. *Clin Rev Allergy Immunol*. 2017;53:337-356.
13. Bogdanov I, Kazandjieva J, Darlenski R, Tsankov N. Dermatomyositis: current concepts. *Clin Dermatol*. 2018;36:450-458.
14. Dalakas MC. Inflammatory muscle diseases. *N Engl J Med*. 2015;372:1734-1747.
15. Hundley JL, Carroll CL, Lang W, et al. Cutaneous symptoms of dermatomyositis significantly impact patients' quality of life. *J Am Acad Dermatol*. 2006;54:217-220.
16. Goreshi R, Chock M, Foering K, et al. Quality of life in dermatomyositis. *J Am Acad Dermatol*. 2011;65:1107-1116.
17. Schmidt J. Current classification and management of inflammatory myopathies. *J Neuromuscul Dis*. 2018;5:109-129.
18. Ogawa-Momohara M, Muro Y, Kono M, Akiyama M. Prognosis of dysphagia in dermatomyositis. *Clin Exp Rheumatol*. 2019;37:165.
19. Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Antimelanoma differentiation-associated gene 5 antibody: expanding the clinical spectrum in North American patients with dermatomyositis. *J Rheumatol*. 2017;44:319-325.
20. Wong D, Kea B, Pesich R, et al. Interferon and biologic signatures in dermatomyositis skin: specificity and heterogeneity across diseases. *PLoS One*. 2012;7:e29161.
21. De Bleecker JL, De Paepe B, Aronica E, et al. 205th ENMC International Workshop: pathology diagnosis of idiopathic inflammatory myopathies part II 28—30 March 2014, Naarden, The Netherlands. *Neuromuscul Disord*. 2015;25:268-272.
22. Iaccarino L, Ghirardello A, Bettio S, et al. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun*. 2014;48-49:122-127.
23. Uruha A, Nishikawa A, Tsuburaya RS, et al. Sarcoplasmic MxA expression: a valuable marker of dermatomyositis. *Neurology*. 2017;88:493-500.
24. Suzuki S, Uruha A, Suzuki N, Nishino I. Integrated Diagnosis Project for Inflammatory Myopathies: an association between autoantibodies and muscle pathology. *Autoimmun Rev*. 2017;16:693-700.
25. Lahoria R, Selcen D, Engel AG. Microvascular alterations and the role of complement in dermatomyositis. *Brain*. 2016;139(pt 7):1891-1903.
26. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10—12 October 2003, Naarden, The Netherlands. *Neuromuscul Disord*. 2004;14:337-345.
27. Pestronk A. Acquired immune and inflammatory myopathies: pathologic classification. *Curr Opin Rheumatol*. 2011;23:595-604.
28. Miller FW, Cooper RG, Vencovský J, et al. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. *Arthritis Rheum*. 2013;65:3239-3247.
29. Rothwell S, Cooper RG, Lundberg IE, et al. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. *Ann Rheum Dis*. 2016;75:1558-1566.
30. O'Hanlon TP, Carrick DM, Targoff IN, et al. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1, and -DQA1 allelic profiles distinguish European American patients with different myositis autoantibodies. *Medicine (Baltimore)*. 2006;85:111-127.
31. Chen Z, Wang Y, Kuwana M, et al. HLA-DRB1 Alleles as genetic risk factors for the development of anti-MDA5 antibodies in patients with dermatomyositis. *J Rheumatol*. 2017;44:1389-1393.
32. Wedderburn LR, Rider LG. Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment. *Best Pract Res Clin Rheumatol*. 2009;23:665-678.
33. Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. *J Intern Med*. 2016;280:24-38.
34. Gao S, Luo H, Zhang H, Zuo X, Wang L, Zhu H. Using multi-omics methods to understand dermatomyositis/polymyositis. *Autoimmun Rev*. 2017;16:1044-1048.
35. Gao S, Zhang H, Zuo X, et al. Integrated comparison of the miRNAome and mRNAome in muscles of dermatomyositis and polymyositis reveals common and specific miRNA-mRNAs. *Epigenomics*. 2019;11:23-33.
36. Miller FW. Environmental agents and autoimmune diseases. *Adv Exp Med Biol*. 2011;711:61-81.
37. Love LA, Weinberg CR, McConnaughey DR, et al. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti-Mi-2 autoantibodies in women. *Arthritis Rheum*. 2009;60:2499-2504.
38. Shah M, Targoff IN, Rice MM, Miller FW, Rider LG, Childhood Myositis Heterogeneity Collaborative Study Group. Brief report: ultraviolet radiation exposure is associated with clinical and autoantibody phenotypes in juvenile myositis. *Arthritis Rheum*. 2013;65:1934-1941.
39. Pignone A, Fiori G, Del Rosso A, Generini S, Matucci-Cerinic M. The pathogenesis of inflammatory muscle diseases: on the cutting edge among the environment, the genetic background, the immune response and the dysregulation of apoptosis. *Autoimmun Rev*. 2002;1:226-232.
40. Mamyrova G, Rider LG, Ehrlich A, et al. Environmental factors associated with disease flare in juvenile and adult dermatomyositis. *Rheumatology (Oxford)*. 2017;56:1342-1347.
41. Han B, Guo Q. Clinically amyopathic dermatomyositis caused by a tattoo. *Case Rep Rheumatol*. 2018;2018:7384681.
42. Zeidi M, Chansky PB, Werth VP. Acute onset/flares of dermatomyositis following ingestion of IsaLean herbal supplement: clinical and immunostimulatory findings. *J Am Acad Dermatol*. 2019;80:801-804.
43. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. *Ann Neurol*. 1990;27:343-356.
44. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol*. 2010;6:129-137.
45. Baumann M, Gumpold C, Mueller-Felber W, et al. Pattern of myogenesis and vascular repair in early and advanced lesions of juvenile dermatomyositis. *Neuromuscul Disord*. 2018;28:973-985.
46. Huard C, Gullà SV, Bennett DV, Coyle AJ, Vleugels RA, Greenberg SA. Correlation of cutaneous disease activity with type 1 interferon gene signature and interferon β in dermatomyositis. *Br J Dermatol*. 2017;176:1224-1230.
47. Greenberg SA, Higgs BW, Morehouse C, et al. Relationship between disease activity and type 1 interferon- and other cytokine-inducible gene expression in blood in dermatomyositis and polymyositis. *Genes Immun*. 2012;13:207-213.
48. Xie S, Luo H, Zhang H, Zhu H, Zuo X, Liu S. Discovery of key genes in dermatomyositis based on the gene expression

omnibus database. *DNA Cell Biol*. 2019. https://doi.org/10.1089/dna.2018.4256 [Epub ahead of print].
49. Moneta GM, Pires Marafon D, Marasco E, et al. Muscle expression of type I and type II interferons is increased in juvenile dermatomyositis and related to clinical and histologic features. *Arthritis Rheumatol*. 2019;71:1011-1021.
50. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol*. 2014;14:36-49.
51. Karasawa R, Tamaki M, Sato T, et al. Multiple target autoantigens on endothelial cells identified in juvenile dermatomyositis using proteomics. *Rheumatology (Oxford)*. 2018;57:671-676.
52. Gunawardena H. The clinical features of myositis-associated autoantibodies: a review. *Clin Rev Allergy Immunol*. 2017;52:45-57.
53. Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. *JAMA Neurol*. 2018;75:1528-1537.
54. Bottai M, Tjärnlund A, Santoni G, et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open*. 2017;3:e000507.
55. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis Rheum*. 2012;64:513-522.
56. Best M, Jachiet M, Molinari N, et al. Distinctive cutaneous and systemic features associated with specific antimyositis antibodies in adults with dermatomyositis: a prospective multicentric study of 117 patients. *J Eur Acad Dermatol Venereol*. 2018;32:1164-1172.
57. Fujimoto M, Watanabe R, Ishitsuka Y, Okiyama N. Recent advances in dermatomyositis-specific autoantibodies. *Curr Opin Rheumatol*. 2016;28:636-644.
58. Wolstencroft PW, Fiorentino DF. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep*. 2018;20:28.
59. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med*. 2016;280:8-23.
60. O'Connor A, Mulhall J, Harney SMJ, et al. investigating idiopathic inflammatory myopathy; initial cross specialty experience with use of the extended myositis antibody panel. *Clin Pract*. 2017;7:922.
61. Gandiga PC, Zhang J, Sangani S, Thomas P, Werth VP, George MD. Utilization patterns and performance of commercial myositis autoantibody panels in routine clinical practice. *Br J Dermatol*. 2019. https://doi.org/10.1111/bjd.18133 [Epub ahead of print].
62. Ghirardello A, Bassi N, Palma L, et al. Autoantibodies in polymyositis and dermatomyositis. *Curr Rheumatol Rep*. 2013;15:335.
63. Kang EH, Nakashima R, Mimori T, et al. Myositis autoantibodies in Korean patients with inflammatory myositis: anti-140-kDa polypeptide antibody is primarily associated with rapidly progressive interstitial lung disease independent of clinically amyopathic dermatomyositis. *BMC Musculoskelet Disord*. 2010;11:223.
64. Ikeda N, Takahashi K, Yamaguchi Y, Inasaka M, Kuwana M, Ikezawa Z. Analysis of dermatomyositis-specific autoantibodies and clinical characteristics in Japanese patients. *J Dermatol*. 2011;38:973-979.
65. Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. *Rheumatology (Oxford)*. 2010;49:2370-2374.
66. Petri MH, Satoh M, Martin-Marquez BT, et al. Implications in the difference of anti-Mi-2 and -p155/140 autoantibody prevalence in two dermatomyositis cohorts from Mexico City and Guadalajara. *Arthritis Res Ther*. 2013;15:R48.
67. Targoff IN, Reichlin M. The association between Mi-2 antibodies and dermatomyositis. *Arthritis Rheum*. 1985;28:796-803.
68. Shamim EA, Rider LG, Pandey JP, et al. Differences in idiopathic inflammatory myopathy phenotypes and genotypes between Mesoamerican Mestizos and North American Caucasians: ethnogeographic influences in the genetics and clinical expression of myositis. *Arthritis Rheum*. 2002;46:1885-1893.
69. Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: key clinical and serological features-a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51:293-302.
70. Daly ML, Gordon PA, Creamer D. Cutaneous features of dermatomyositis associated with myositis-specific antibodies. *Br J Dermatol*. 2017;176:1662-1665.
71. Wu Q, Wedderburn LR, McCann LJ. Juvenile dermatomyositis: latest advances. *Best Pract Res Clin Rheumatol*. 2017;31:535-557.
72. Rider LG, Shah M, Mamyrova G, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore)*. 2013;92:223-243.
73. Deakin CT, Yasin SA, Simou S, et al. Muscle biopsy findings in combination with myositis-specific autoantibodies aid prediction of outcomes in juvenile dermatomyositis. *Arthritis Rheumatol*. 2016;68:2806-2816.
74. Kim Y, Song KS, Sohn EH, et al. Anti-TIF1γ antibody and the expression of TIF1γ in idiopathic inflammatory myopathies. *Int J Rheum Dis*. 2019;22:314-320.
75. Fiorentino D, Casciola-Rosen L. TIF1 autoantibodies in dermatomyositis shed insight into the cancer-myositis connection. *Arthritis Rheum*. 2012;64:346-349.
76. Targoff IN, Mamyrova G, Trieu EP, et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. *Arthritis Rheum*. 2006;54:3682-3689.
77. Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. *Arthritis Rheum*. 2012;64:523-532.
78. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. *Arthritis Rheum*. 2013;65:2954-2962.
79. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med*. 2005;201:591-601.
80. Bernet LL, Lewis MA, Rieger KE, Casciola-Rosen L, Fiorentino DF. Ovoid palatal patch in dermatomyositis: a novel finding associated with anti-TIF1γ (p155) antibodies. *JAMA Dermatol*. 2016;152:1049-1051.
81. Fiorentino DF, Kuo K, Chung L, Zaba L, Li S, Casciola-Rosen L. Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis. *J Am Acad Dermatol*. 2015;72:449-455.
82. Casal-Dominguez M, Pinal-Fernandez I, Mego M, et al. High-resolution manometry in patients with idiopathic inflammatory myopathy: elevated prevalence of esophageal

involvement and differences according to autoantibody status and clinical subset. *Muscle Nerve*. 2017;56:386-392.
83. Sato S, Hoshino K, Satoh T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis Rheum*. 2009;60:2193-2200.
84. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum*. 2005;52:1571-1576.
85. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EKL. A comprehensive overview on myositis-specific antibodies: new and old biomarkers in idiopathic inflammatory myopathy. *Clin Rev Allergy Immunol*. 2017;52:1-19.
86. Chen Z, Hu W, Wang Y, Guo Z, Sun L, Kuwana M. Distinct profiles of myositis-specific autoantibodies in Chinese and Japanese patients with polymyositis/dermatomyositis. *Clin Rheumatol*. 2015;34:1627-1631.
87. Ceribelli A, Fredi M, Taraborelli M, et al. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. *Clin Exp Rheumatol*. 2014;32:891-897.
88. Lin JM, Zhang YB, Peng QL, et al. Genetic association of HLA-DRB1 multiple polymorphisms with dermatomyositis in Chinese population. *HLA*. 2017;90:354-359.
89. Ortiz-Santamaria V, Babot A, Ferrer C. Anti-MDA5-positive dermatomyositis: an emerging entity with a variable clinical presentation. *Scand J Rheumatol*. 2017;46:509-511.
90. Morisset J, Johnson C, Rich E, Collard HR, Lee JS. Management of myositis-related interstitial lung disease. *Chest*. 2016;150:1118-1128.
91. Chen Z, Cao M, Plana MN, et al. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care Res (Hoboken)*. 2013;65:1316-1324.
92. Ono N, Kai K, Maruyama A, et al. The relationship between type 1 IFN and vasculopathy in anti-MDA5 antibody-positive dermatomyositis patients. *Rheumatology (Oxford)*. 2019;58:786-791.
93. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation—associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *J Am Acad Dermatol*. 2018;78:776-785.
94. Fiorentino D, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. *J Am Acad Dermatol*. 2011;65:25-34.
95. Hall JC, Casciola-Rosen L, Samedy LA, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. *Arthritis Care Res (Hoboken)*. 2013;65:1307-1315.
96. Tansley SL, Betteridge ZE, Gunawardena H, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. *Arthritis Res Ther*. 2014;16(4):R138.
97. Kobayashi I, Okura Y, Yamada M, Kawamura N, Kuwana M, Ariga T. Anti-melanoma differentiation-associated gene 5 antibody is a diagnostic and predictive marker for interstitial lung diseases associated with juvenile dermatomyositis. *J Pediatr*. 2011;158:675-677.
98. Albayda J, Pinal-Fernandez I, Huang W, et al. Antinuclear matrix protein 2 autoantibodies and edema, muscle disease, and malignancy risk in dermatomyositis patients. *Arthritis Care Res*. 2017;69:1771-1776.
99. Rogers A, Chung L, Li S, Casciola-Rosen L, Fiorentino DF. Cutaneous and systemic findings associated with nuclear matrix protein 2 antibodies in adult dermatomyositis patients. *Arthritis Care Res (Hoboken)*. 2017;69:1909-1914.
100. Ishikawa A, Muro Y, Sugiura K, Akiyama M. Development of an ELISA for detection of autoantibodies to nuclear matrix protein 2. *Rheumatology (Oxford)*. 2012;51:1181-1187.
101. Tansley SL, Betteridge ZE, Shaddick G, et al. Calcinosis in juvenile dermatomyositis is influenced by both anti-NXP2 autoantibody status and age at disease onset. *Rheumatology (Oxford)*. 2014;53:2204-2208.
102. Gunawardena H, Wedderburn LR, Chinoy H, et al. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. *Arthritis Rheum*. 2009;60(6):1807-1814.
103. Betteridge ZE, Gunawardena H, Chinoy H, et al. Clinical and human leucocyte antigen class II haplotype associations of autoantibodies to small ubiquitin-like modifier enzyme, a dermatomyositis-specific autoantigen target, in UK Caucasian adult-onset myositis. *Ann Rheum Dis*. 2009;68:1621-1625.
104. Merlo G, Clapasson A, Cozzani E, et al. Specific autoantibodies in dermatomyositis: a helpful tool to classify different clinical subsets. *Arch Dermatol Res*. 2017;309:87-95.
105. Wolstencroft PW, Casciola-Rosen L, Fiorentino DF. Association between autoantibody phenotype and cutaneous adverse reactions to hydroxychloroquine in dermatomyositis. *JAMA Dermatol*. 2018;154:1199-1203.
106. Auriemma M, Capo A, Meogrossi G, Amerio P. Cutaneous signs of classical dermatomyositis. *G Ital Dermatol Venereol*. 2014;149:505-517.
107. Barth Z, Witczak BN, Flatø B, Koller A, Sjaastad I, Sanner H. Assessment of microvascular abnormalities by nailfold capillaroscopy in juvenile dermatomyositis after medium- to long-term followup. *Arthritis Care Res (Hoboken)*. 2018;70:768-776.
108. Bertolazzi C, Cutolo M, Smith V, Gutierrez M. State of the art on nailfold capillaroscopy in dermatomyositis and polymyositis. *Semin Arthritis Rheum*. 2017;47:432-444.
109. Manfredi A, Sebastiani M, Cassone G, et al. Nailfold capillaroscopic changes in dermatomyositis and polymyositis. *Clin Rheumatol*. 2015;34:279-284.
110. Kasteler JS, Callen JP. Scalp involvement in dermatomyositis. Often overlooked or misdiagnosed. *JAMA*. 1994;272:1939-1941.
111. Gusdorf L, Morruzzi C, Goetz J, Lipsker D, Sibilia J, Cribier B. Mechanics hands in patients with antisynthetase syndrome: 25 cases. *Ann Dermatol Venereol*. 2019;146:19-25.
112. Wernham AGH, Fremlin GA, Orpin SD, Salim A. Physician, beware! The deckchair sign can be seen in dermatomyositis. *Clin Exp Dermatol*. 2016;41:919-920.
113. Lupton JR, Figueroa P, Berberian BJ, Sulica VI. An unusual presentation of dermatomyositis: the type Wong variant revisited. *J Am Acad Dermatol*. 2000;43(5 pt 2):908-912.
114. Block JA, Sequeira W. Raynaud's phenomenon. *Lancet*. 2001;357:2042-2048.
115. Pouessel G, Deschildre A, Le Bourgeois M, et al. The lung is involved in juvenile dermatomyositis. *Pediatr Pulmonol*. 2013;48:1016-1025.
116. Schwartz T, Diederichsen LP, Lundberg IE, Sjaastad I, Sanner H. Cardiac involvement in adult and juvenile idiopathic inflammatory myopathies. *RMD Open*. 2016;2:e000291.

117. Jayakumar D, Zhang R, Wasserman A, Ash J. Cardiac manifestations in idiopathic inflammatory myopathies: an overview. *Cardiol Rev*. 2019;27:131-137.
118. Schwartz T, Sanner H, Gjesdal O, Flatø B, Sjaastad I. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. *Ann Rheum Dis*. 2014;73:1805-1810.
119. Barth Z, Nomeland Witczak B, Schwartz T, et al. In juvenile dermatomyositis, heart rate variability is reduced, and associated with both cardiac dysfunction and markers of inflammation: a cross-sectional study median 13.5 years after symptom onset. *Rheumatology (Oxford)*. 2016;55:535-543.
120. Gadiparthi C, Hans A, Potts K, Ismail MK. Gastrointestinal and hepatic disease in the inflammatory myopathies. *Rheum Dis Clin North Am*. 2018;44:113-129.
121. Kibbi N, Bekui A, Buckley LM. Colonic vasculopathy and perforation in the initial presentation of adult dermatomyositis in a patient with improving muscle weakness. *BMJ Case Rep*. 2016;2016. https://doi.org/10.1136/bcr-2015-213460.
122. Papadopoulou C, McCann LJ. The vasculopathy of juvenile dermatomyositis. *Front Pediatr*. 2018;6:284.
123. Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis*. 2017;76:329-340.
124. McCann LJ, Juggins AD, Maillard SM, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology (Oxford)*. 2006;45:1255-1260.
125. Sanner H, Gran JT, Sjaastad I, Flatø B. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. *Rheumatology (Oxford)*. 2009;48:1541-1547.
126. Mamyrova G, Kleiner DE, James-Newton L, Shaham B, Miller FW, Rider LG. Late-onset gastrointestinal pain in juvenile dermatomyositis as a manifestation of ischemic ulceration from chronic endarteropathy. *Arthritis Rheum*. 2007;57:881-884.
127. Starr MR, Softing Hataye AL, Bakri SJ. Asymptomatic multifocal paracentral acute middle maculopathy associated with juvenile dermatomyositis: optical coherence angiography findings. *Retin Cases Brief Rep*. 2019 [Epub ahead of print].
128. López De Padilla CM, Vallejo AN, Lacomis D, McNallan K, Reed AM. Extranodal lymphoid microstructures in inflamed muscle and disease severity of new-onset juvenile dermatomyositis. *Arthritis Rheum*. 2009;60:1160-1172.
129. Miles L, Bove KE, Lovell D, et al. Predictability of the clinical course of juvenile dermatomyositis based on initial muscle biopsy: a retrospective study of 72 patients. *Arthritis Rheum*. 2007;57:1183-1191.
130. Allenbach Y, Keraen J, Bouvier AM, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain*. 2016;139(pt 8):2131-2135.
131. Tiniakou E, Christopher-Stine L. Immune-mediated necrotizing myopathy associated with statins: history and recent developments. *Curr Opin Rheumatol*. 2017;29:604-611.
132. Tawara N, Yamashita S, Zhang X, et al. Pathomechanisms of anti-cytosolic 5′-nucleotidase 1A autoantibodies in sporadic inclusion body myositis. *Ann Neurol*. 2017;81:512-525.

Answers to CME examination

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