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 features, and pathogenesis of DM, focusing on recent developments in our understanding of myositis-specific antibodies and their clinical associations.

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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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,

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
### Table I. Cutaneous manifestations of adult dermatomyositis

<table>
<thead>
<tr>
<th>Category</th>
<th>Finding</th>
<th>Clinical description</th>
<th>Additional features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathognomonic</strong></td>
<td>Gottron papules</td>
<td>Violaceous papules and plaques, sometimes with subtle scale, overlying the MCP and ICP joints of the hands</td>
<td>Dyspigmentation, atrophy, and scarring possible when lesions resolve&lt;sup&gt;106&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Gottron sign</td>
<td>Erythematos macules or patches over extensor surfaces of elbows, knuckles, knees, and ankles</td>
<td>Slight scale may be present&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Heliotrope rash</td>
<td>Periorbital erythema with edema, most often of the upper eyelids</td>
<td>May also involve cheeks and nose&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Characteristic</strong></td>
<td>Nailfold changes</td>
<td>Periungual erythema and telangiectasias, dystrophic cuticles, and hemorrhagic nailfold infarcts</td>
<td>Nailfold capillaroscopy may be useful adjunctive tool for monitoring disease activity&lt;sup&gt;107-109&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Shawl sign</td>
<td>Violaceous or erythematos macules and patches over posterior shoulders, neck, upper back, and possibly lateral upper arms</td>
<td>Poikiloderma may also be present in same distribution&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>V sign</td>
<td>Erythematous, confluent macules and patches over lower anterior neck and upper chest</td>
<td>Skin may also appear atrophic&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Holster sign</td>
<td>Symmetric poikiloderma of hips and lateral thighs below the greater trochanter</td>
<td>May be reticulated, livedoid, or linear and is reported to be highly specific for DM&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Scalp involvement</td>
<td>Atrophic, erythematous, sometimes pruritic scaly plaques</td>
<td>May be misdiagnosed as psoriasis or seborrheic dermatitis&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Compatible</strong></td>
<td>Poikiloderma</td>
<td>Hypo- or hyperpigmentation, telangiectasia, and atrophy, usually found on upper chest and lateral upper arms</td>
<td>May be referred to as “poikiloderma atrophicans vasculare” or “poikilodermatomyositis”&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Periorbital edema and facial swelling</td>
<td>Edema with or without erythema</td>
<td></td>
</tr>
<tr>
<td><strong>Less common</strong></td>
<td>Vesciculobullous, necrotic, or ulcerative lesions</td>
<td>Variable</td>
<td>Often associated with cutaneous vasculitis&lt;sup&gt;13&lt;/sup&gt;, ulceration associated with anti-MDA5 antibodies&lt;sup&gt;93&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cutaneous vasculitis</td>
<td>Variable, but may include petechiae, palpable purpura, livedo reticularis, and ulceration</td>
<td>More common in JDM</td>
</tr>
<tr>
<td></td>
<td>Calcinosis cutis</td>
<td>Superficial white papules or nodules, most commonly over bony surfaces or at sites of inflammation</td>
<td>Rare in adult DM (estimated 4% of adult DM patients&lt;sup&gt;4&lt;/sup&gt;)</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Mechanic’s hands</td>
<td>Hyperkeratotic, scaling, and fissuring of fingers and/or palms</td>
<td>More common in patients with anti-MDA5 antibodies&lt;sup&gt;53&lt;/sup&gt; and antisynthetase syndrome&lt;sup&gt;53,111&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Flagellate erythema</td>
<td>Linear erythematos macules and patches on the back</td>
<td>Associated with absence of MSAs on serological testing&lt;sup&gt;10&lt;/sup&gt; or presence of anti-MI2 antibodies&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Deck chair sign</td>
<td>Erythematous eruption sparing transverse skin folds</td>
<td>May be first cutaneous sign preceding classic DM skin findings&lt;sup&gt;8-11,12&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Follicular hyperkeratosis (“wong-type DM”)</td>
<td>Follicular, hyperkeratotic papules on extensor surfaces resembling pityriasis rubra pilaris</td>
<td>Hair follicle destruction and follicular hyperkeratosis on histopathology plus interface changes of DM&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Continued
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, with a sensitivity of 71% and specificity of 98%.25 Other abnormalities observed in DM muscle include deposition of complement on endomysial capillaries5 (35% sensitive and 93% specific6) 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

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
involvement in JDM is often more prominent.\textsuperscript{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,\textsuperscript{28,29} and particular human leukocyte antigen (HLA) alleles have been correlated with autoantibody production in both adults\textsuperscript{30,31} and children.\textsuperscript{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.\textsuperscript{28} Epigenetic modification, including DNA methylation, histone modification, and microRNA activity, may also play a role in DM pathogenesis.\textsuperscript{34,35}

**Environmental risk factors**

Multiple environmental factors may trigger chronic immune activation in genetically susceptible individuals.\textsuperscript{30,36} Proposed triggers for DM include ultraviolet radiation, viral infections, medications,
and smoking. Ultraviolet exposure has been linked with DM and anti-Mi2 antibodies in adult women and with JDM and anti—transcription intermediary factor 1 (TIF1) antibodies in children. Viral infections may play a role in triggering immune activation or disrupting immune tolerance, but attempts to isolate viruses from DM muscle samples have been unsuccessful. 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. Smoking has been associated with DM and the development of interstitial lung disease (ILD), dysphagia, malignancy, and cardiac involvement. Other potential environmental triggers are less well established, including a recent report of CADM developing after receiving a tattoo and a case series of 3 patients who developed an acute onset or flare of DM after ingesting the herbal supplement IsaLean.

**Immune mechanisms**

The sequence of immune activation in DM remains incompletely understood although it likely results from inappropriate complement activation. 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.
Myositis-Specific Antibodies

MSAs are antibodies that are exclusively associated with a diagnosis of an IIM. 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; 2) they impact prognosis and can help guide management; 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.

The current limitations of MSAs are twofold: 1) there is still a “serologic gap,” with a significant proportion of DM patients presenting without MSAs;
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 confirmed61; 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 sub-units 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 200676 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 features of DM. The presence of anti-TIF1 antibodies in children with JDM is rare, and the clinical features of anti-TIF1 JDM are similar to adult cases.74,75

### Table III. Biopsy features and associated phenotypes in juvenile dermatomyositis71,128,129

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Muscle biopsy features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease course</td>
<td>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</td>
</tr>
<tr>
<td>Chronic disease course</td>
<td>Severe arteriopathic changes, positive arterial direct immunofluorescence, severe capillary loss, endomysial fibrosis, and muscle infarcts</td>
</tr>
<tr>
<td>with ulcerations</td>
<td></td>
</tr>
<tr>
<td>Chronic disease course</td>
<td>Extensive active myopathic changes and central nuclei without basophilia</td>
</tr>
</tbody>
</table>

fDC, Follicular dendritic cell; pDC, plasmacytoid dendritic cell.
### Table IV. Dermatomyositis-associated myositis-specific antibodies and their associated clinical features

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

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.
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 patients71,72 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 CADM84,85 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 PaO2).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-e 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 Registry96 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 Patients with JDM with these antibodies frequently demonstrate milder muscle involvement (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

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**Table V. Non—dermatomyositis-associated myositis-specific antibodies**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Disease entity</th>
<th>Clinical association(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS (includes anti-Jo1 [histidyl], anti-PL7 [alanyl], anti-PL12 [glycyl], anti-EJ [isoleucyl], anti-OJ [isoleucyl], anti-KS [asparginyl], anti-Zo [phenylalanyl], and anti-YRS/HA [tyrosyl])</td>
<td>Antisynthetase syndrome</td>
<td>Myositis with ILD, polyarthritis, Raynaud phenomenon, and cutaneous findings (Gottron papules, “mechanic’s hands”)104; more severe ILD and poorer prognosis with non-Jo1 antibodies85</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Necrotizing myopathy (anti-SRP antibody syndrome)</td>
<td>Sudden, severe, and progressive muscle weakness, often with cardiac involvement and/or dysphagia59,104; treatment resistant85; no increased risk of malignancy130</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>Immune-mediated necrotizing myopathy</td>
<td>Increased risk of malignancy compared with the general population130; statin-induced myopathy131</td>
</tr>
<tr>
<td>CN1A</td>
<td>Inclusion body myositis</td>
<td>Progressive weakness and functional impairment in older patients (typically &gt;50 years of age)132</td>
</tr>
</tbody>
</table>

ARS, Aminoacyl tRNA synthetase; CN1A, cytosolic S’nucleotidase 1A; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; ILD, interstitial lung disease; SRP, signal recognition particle.
Japanese populations. 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. This subset of DM patients typically presents with classic cutaneous findings. Peripheral edema may be seen in ≤5% of patients and calcinosis and distal ulcers are observed in adults with anti-NXP-2 DM on occasion. 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%. Like anti-TIF1 antibodies, anti-NXP2 antibodies are more common in younger, white patients (median age at disease onset 6 years). 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. This form of JDM also presents with severe myopathy that frequently causes functional impairment and results in contracture development. The severe myopathy associated with NXP-2 seropositivity develops secondary to vasculopathy-induced muscle ischemia. This vasculopathy also predisposes individuals with NXP-2 antibodies to gastrointestinal bleeding. 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. This subtype of DM is strongly associated with HLA-DQB1*03. HLA-DRB1*04 and 03-DQB1*03 are also risk factors. 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. Some case series have also suggested that patients with anti-SAE DM frequently have systemic symptoms, such as fever and weight loss. 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. 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.

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 heterogeneous 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


