Inflammatory Myopathies

Clinicopathologic classfication can aid understanding and guide treatment.

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Idiopathic inflammatory myopathies (IIM) are heterogeneous inflammatory disorders causing immune-mediated muscle injury. IIMs are traditionally classified as polymositis and its subtypes (eg, antisynthetase syndrome [ASynS] and overlap myositis [OM]), immune-mediated necrotizing myopathy (IMNM) (also called necrotizing autoimmune myopathy [NAM]), sporadic inclusion body myositis (sIBM), and dermatomyositis (DM). In addition, other organs, including skin, joints, lungs, gastrointestinal tract, and heart, are frequently affected, indicating the systemic nature of these disorders. In this review, we highlight updates in the diagnosis and management of IIMs and propose a new classification.

Classification of IIM

The discovery of myositis autoantibodies and distinct histopathologic subgroups created a strong need for new classification criteria based on etiology rather than phenotype, leading to the development of the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria..[1] Although the EULAR/ACR classification criteria do not differentiate polymyositis (PM) from IMNM and ASynS, emerging data suggest these are distinct entities. The existence of PM is also now being questioned,[2] which is supported by a hypothesis-free, unsupervised hierarchic clustering analysis.[3] We propose a comprehensive model for IIM classification based on clinical features, serology, myopathology, imaging, and treatment response (Figure 1). In this model, the 4 main IIM subtypes are DM, IBM, IMNM/NAM and OM, which includes ASynS.

Clinical Characteristics

Dermatomyositis

DM is a heterogeneous, multifactorial, chronic autoimmune disorder with characteristic skin changes and involvement of muscles, blood vessels, joints, esophagus, and lungs. DM is thought to be due to an autoimmune attack on affected organs, likely triggered by environmental factors in genetically susceptible individuals.[2] Clinically, 7 groups of cutaneous manifestations have been reported in DM (Table e1).[4]

Cutaneous disease precedes myositis by 3 to 6 months in 30% to 50% of cases, and in 10%, muscle symptoms appear before skin findings develop.[5] The 5 known myositis-specific autoantibodies (MSAs) in DM are antiMI-2, antinuclear matrix protein (antiNXP-2), antitranscription intermediary factor 1-γ (antiTIF1γ), antimelanoma differentiation-association protein (antiMDA-5), and antismall ubiquitin-like modifier activating enzyme (antiSAE). Emerging evidence suggests clinical features, including interstitial lung disease (ILD), cancer association, prognosis, and myopathologic features vary depending on the antibodies involved (Table e2). Because the definition of DM has been inconsistent, reported prevalence of MSAs in DM varies widely between 20% and 80%.[5,6] Muscle and skin involve-

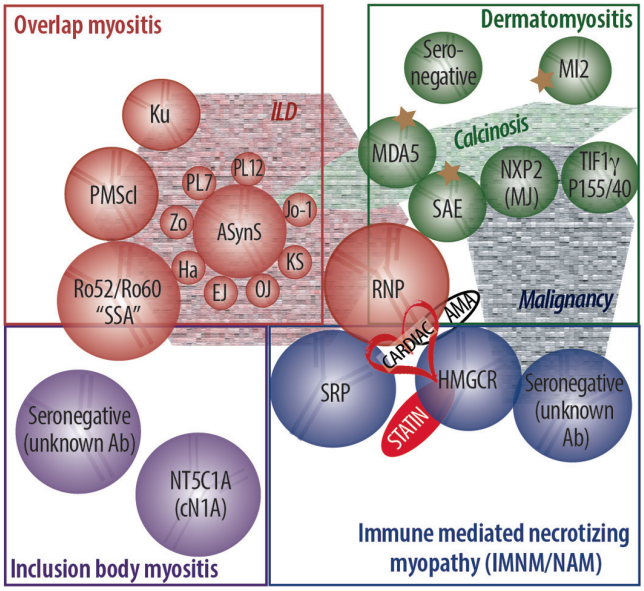

Figure 1. Classification of idiopathic inflammatory myopathies based on their clinicopathologic phenotypes (ie, dermatomyositis, inclusion body myositis, immune-mediated necrotizing myopathy, or overlap myositis) and presence of myositis-specific antibodies/myositis-associated antibodies (spheres). Abbreviations: Ab, antibody, ASynS, antisynthetase syndrome; HMGCR, hydroxymethylglutaryl-CoA reductase; ILD, interstitial lung disease; MDA5, melanoma differentiation-associated protein 5; NT5C1A, 5′-nucleotidase cytosolic IA; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; Tif1γ, transcription intermediary factor 1-γ.

ment ranges from clinically amyopathic or hypomyopathic DM (eg, MDA-5$^+$ DM[7]) to minimal or no skin involvement (eg, DM sine dermatitis typically seen in NXP2$^+$ DM).[8] Skin biopsy demonstrates a vacuolar interface dermatitis with dermal mucin deposition.[5] These findings are also seen in lupus erythematosus. Sarcoplasmic expression of myxovirus resistance A (MxA) has been reported to be among the most sensitive and specific myopathologic findings in DM.[9,10] Antimitochondrial antibodies (AMA) also identify a possibly distinct phenotype frequently associated with chronic skeletal muscle disease and severe cardiac involvement. In antiAMA$^+$ DM, muscle biopsy features are nonspecific; however, necrotizing myopathy is the most common finding. AntiAMA$^+$ IIM may be associated with coexisting primary biliary cirrhosis and autoimmune hepatitis.[11] DM-like skin findings occur in other IIMs (eg, ASynS, IMNM[12], OM), and a comprehensive evaluation including clinical features, MSA, muscle and skin biopsy, and muscle MRI may be warranted before diagnosing DM if there is myositis with a DM-like skin rash (Table e1).

Overlap Myositis and Antisynthetase Syndrome

OM may be the most heterogenous IIM, and ASynS the most common and largest distinct clinical entity within OM and adults with myositis. Traditionally, ASynS has been classified within PM and DM, but emerging evidence suggests ASynS is a distinct clinical entity.[5] Classically, ASynS consists of myositis, ILD, mechanic's hands (Table e1), pyrexia, Raynaud phenomenon, and arthritis; however, the syndrome is often incomplete. ASynS might initially be diagnosed as idiopathic ILD or inflammatory arthritis. Autoantibodies that recognize 8 of the 21 antiaminoacyl-tRNA-synthetase antibodies (ARS) have been described and are associated with ASynS (Figure 1). AntiJo1 is the most common among ARSs. Muscle biopsy in ASynS shows inflammatory myopathy with perimysial pathology and perifascicular necrosis;[13] which may be seen only in antiMi2$^+$ DM. The most distinctive myopathologic feature of ASynS is negative sarcoplasmic MxA expression.[9,10] Considering the increased risk of ILD in ASynS, medications that may increase risk of ILD (eg, methotrexate) should be avoided in people with OM. Close monitoring with high-resolution chest CT and pulmonary function tests for ILD and its complications, (eg, pulmonary hypertension) are needed in ASynS. AntiPM/SCL$^+$ OM is also likely a distinct with more extramuscular features than other IIMs and weaker arm abductors than hip flexors.[14]

Immune-Mediated Necrotizing Myopathy

IMNMs comprise a heterogenous IIM subtype, typically distinguished by profound proximal weakness, highly elevated creatinine kinase (CK), certain MSAs (Figure 1), specific myopathologic features, irritable myopathy on EMG, severe edema on muscle MRI, and resistance to conventional immunosuppressive medications.[15] Muscle biopsy typically shows predominant muscle fiber necrosis with the absence of clear inflammation. Anti HMG-CoA reductase (antiHMGCR)- and antisignal recognition particle SRP (antiSRP)-associated myopathies each may account for 5% to 6% of all IIM.[16]

HMGCR is the pharmacologic target of statins. Weakness in antiHMGCR$^+$ IMNM may not always be as dramatic as seen in antiSRP$^+$ IMNM. In a recent large cohort study, up to 40% of patients with elevated CK and antiHMGCR$^+$ status had no weakness at their initial visit, but a great majority later developed weakness.[17] Although antiHMGCR are associated with IMNM and statins, only 40% to 60% of individuals with these autoantibodies have a history of statin use. Overall, statin-naïve individuals with antiHMGCR$^+$ IMNM were less likely to be white, had age under 50 and higher CK levels at presentation, and were less responsive to treatment. AntiHMGCR$^+$ IMNM occurs at all ages. Dysphagia has also been noted in this IIM subtype. Although ILD appears uncommon in antiHMGCR$^+$ IMNM, malignancy may be more frequent.

In antiSRP$^+$ IMNM, severe limb and neck weakness, dysphagia, respiratory insufficiency, and cardiac involvement are more frequent.[16,18] AntiSRP$^+$ IMNM may have more rapidly progressive weakness at presentation that can result in marked muscle atrophy and disability. Severe weakness can progress over months. Relative to other IIMs, there is a reported predominance in people under approximately age 45, women, and Black persons.[19]

Seronegative (antiHMGCR$^-$ and antiSRP$^-$) IMNM has been reported in association with malignancy, viral infections (HIV or hepatitis C), and other connective tissue diseases (eg scleroderma). Typical clinical findings include severe weakness, highly elevated CK levels (although normal or mildly elevated CK does not exclude diagnosis), and resistance to conventional immunosuppressive therapy. A distinct subtype described recently is immune checkpoint inhibitor (ICI)-associated myopathy, with common ocular involvement, frequent lymphopenia, and necrotizing histopathology. In contrast to antiHMGCR$^+$ and antiSRP$^+$ IMNM, seronegative IMNM myopathology includes necrotic fiber clusters. Mortality of the ICI associated myopathy is among the highest of IIM subtypes (42%).[20]

Sporadic Inclusion Body Myositis

In sIBM, muscle-invading cytotoxic T cells are highly differentiated, and secondary degenerative changes of unknown cause occur. In contrast to other IIMs, sIBM is more prevalent in men, treatment refractory, and gradually progressive. The refractoriness of sIBM to therapy may be a result of the highly differentiated T-cell population, which is not effectively reduced by corticosteroids.[20] sIBM is the most common acquired muscle disease in people over age 50 and is characterized by a slow and gradually progressive disease course. There is often asymmetric involvement of distinct muscle groups (eg,

finger and wrist flexors or knee extensors) and a mildly elevated CK level. A serum antibody directed against 5′-nucleotidase (antiNT5C1A), also known as cytosolic 1A (cN1A), appears to be common in sIBM, with a sensitivity of 70% and specificity of approximately 90%. NT5c1A$^+$ sIBM is associated with more severe motor, bulbar, and respiratory involvement.[22] sIBM is associated with other autoimmune disorders such as Sjögren syndrome, and the myositis-associated antiRo52 and antiRo60 are commonly seen. Findings of muscle MRI in IBM can be highly specific.[23] Up to 30% of people with the typical clinical IBM phenotype, do not have the distinctive pathologic features of IBM (ie, rimmed vacuoles, mitochondrial pathology, amyloid deposits) on muscle biopsy, but rather inflammation alone, which can lead to misdiagnosis of polymyositis.

Diagnostic Testing

Muscle Enzymes

Serum CK level is among the most sensitive and commonly used biomarkers for IIM. A normal CK level, however, does not rule out IIM, and occurs in certain IIM subtypes (eg, amyopathic or hypomyopathic DM, antiMDA-5$^+$ DM) or end-stage "burned out" IIM. Isolated or concomitant elevation in aldolase level is suggestive of an immune myopathy with perimysial pathology.[24] In the absence of other risk factors, isolated elevated CK under 40,000 U/L was not considered a risk factor for acute kidney injury, especially in the setting of myositis.[25] In the authors' opinion, acute kidney injury caused by highly elevted CK in IIM is extremely rare.

Myositis Autoantibodies

It is becoming increasingly evident that MSAs are important for IIM classification,[3] and can predict clinical manifestations, extramuscular system involvement (especially ILD and cancer) (Table e3). Assays for over 20 myositis autoantibodies (Figure 1) are commercially available and have been divided into MSAs and myositis-associated autoantibodies (MAAs). Several single and multiplex commercial assays are available for detecting most, but not all MSAs. The most reliable test for MSAs is the immunoprecipitation assay, which is not widely available and lacks standardization, limiting the wide practical use of these antibodies. MSAs could offer unique opportunities not only for the early and more accurate diagnosis of myositis or a related condition, but also as a mechanism for personalizing management and monitoring the course of disease.

Detection of more than 1 MSA in the same individual is extremely rare, although MAAs can sometimes coexist. MSAs are relatively specific for IIM subtypes and should be checked early in the diagnostic work-up (Figure 2, Table). Among adults clinically diagnosed with DM at the Johns Hopkins Myositis Center, 84% have either a positive MSA or MAA.[6] Recent studies show there are 3 subgroups of antiMDA-5$^+$ DM: 1) rapidly progressive ILD and a high mortality rate (18.1%); 2) pure dermatorheumatologic symptoms and a good prognosis (55.4%); and 3) severe skin vasculopathy, frequent signs of myositis (proximal weakness: 68.2%; P<.0001), an intermediate prognosis, and male predominance (72.7%) seen in the remaining 26.5%.[7] Approximately 60% to 70% of children with IIM have an identifiable myositis autoantibody[26]; however, clinical correlations of MSAs in adult and juvenile IIM are different (eg, antiTIF1γ$^+$ or antiNXP-2$^+$ DM in children is not associated with increased cancer risk. Likewise, antiNXP2$^+$ DM is associated with more calcinosis in children.

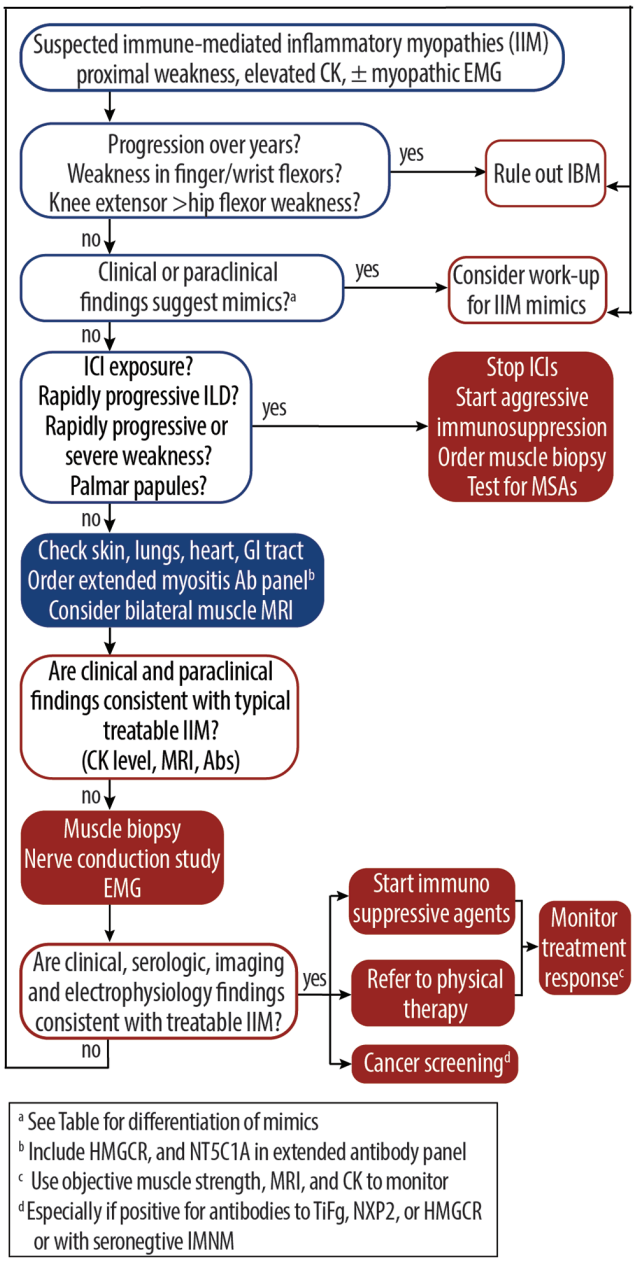

Figure 2: Diagnosing inflammatory immune-mediated myopathy.

TABLE. FEATURES SUGGESTING INCLUSION BODY MYOSITIS AND IIM MIMICS THAT DO NOT BENEFIT FROM IMMUNOSUPPRESSION

Pattern of the muscle weakness	Asymmetric weakness, distal weakness (with mild-moderate proximal weakness). selective weakness (eg, isolated finger flexors), ocular or facial weakness
Period: disease course	Gradually progressive weakness (years, not months), fluctuations
Phenomena: extramuscular symptoms	Early respiratory failure, significant weight loss, autonomic symptoms, severe edema, severe pain
Pills: myotoxic exposure	Statins, hydroxychloroquine, colchicine, corticosteroids
Plasma: blood tests	Normal or extremely elevated (creatine kinase [CK]>50K), constantly elevated CK for years (dystrophy), lack of myopathy-associated antibodies (MAA) or myopathy-specific antibodies (MSA), elevated thyroid stimulating hormone, cortisol, abnormal serum protein electrophoresis
Pathology: muscle	Significant type 1 fiber predominance, fiber type grouping, predominant mitochondrial pathology, vacuoles, no inflammation, muscle fiber hypertrophy, sarcoplasmic acid phosphatase stain positive
Picture: muscle MRI	Absence of edema on STIR sequence, selective involvement, OR selective sparing of certain muscles; severe fat replacement (T1 hyperintensity)
Physiology: EMG	Fasciculations, neurogenic changes, clear myotonia.
Pedigree: genetics	Positive family history, disease onset at young age
Pharmacology: treatment response	Absence of any objective improvement in motor strength with appropriate immunosuppressive treatment

Electrodiagnostic Studies

EMG is an essential tool for ruling out IIM mimics (eg, amyloid myopathy, vasculitis, toxic exposures, and inherited disorders like Kennedy disease). Typical EMG findings are proximal muscle involvement and sensory nerve sparing that can confirm myopathy and sometimes be used to identify a muscle to biopsy or assess for active (ie, presence of fibrillations) vs inactive disease (eg, steroid use or disuse myopathy). EMG may help identify a clinical pattern of muscle involvement, especially for affected muscles that can still seem strong on clinical examination (eg, sIBM).

Skeletal Muscle MRI

Skeletal muscle MRI is useful for assessing IIM disease activity and treatment response, disease chronicity, accurate lesion location, and identifying useful biopsy sites. Skeletal muscle MRI is highly sensitive but often very nonspecific for IIM. A common pitfall is conflating muscle edema with myositis. Muscle edema on MRI may be seen in autoimmune conditions like IIM but can also be seen in several nonautoimmune conditions including rhabdomyolysis, trauma, subacute denervation, radiation therapy, infectious myositis, compartment syndrome, diabetic muscle infarction, and can even be a physiologic finding during and briefly following muscle exercise.[27]

Muscle Biopsy

Although muscle biopsy is generally considered the standard diagnostic tool for IIM, findings can be nonspecific, or inconclusive, and muscle damage may appear similar across multiple diseases, especially if certain stains are not used. The diagnostic utility of muscle biopsy has been evolving with the development of IIM classifications and newer diagnostic tools (eg, MSAs and muscle MRI). As a result, muscle biopsy may not be required in antiHMGCR$^+$ or antiSRP$^+$ myopathy[15] or well-characterized amyopathic or hypomyopathic DM. Emerging findings suggest a seropathologic correlation among IIM subtypes.[2] (Table e2). Muscle biopsy remains an important tool to further characterize the IIM subtype, exclude rare disease mimics, and may also continue to contribute to understanding pathogenesis.

Cancer-Associated Myositis

Cancer associated myositis (CAM) is defined as any cancer diagnosed 3 to 5 years before or after IIM onset. Cancer risk in IIM is dependent on several factors (Table e3).[28] Cancer screening is recommended in those who are at high risk for cancer (eg, antiTIF1γ^+ (odds ratio [OR], 27) and antiNXP2$^+$ (OR, 3.7) DM. Over 50% of adults with antiTIF1γ^+ will have an associated cancer.[26] Adults under age 40 with antiTIF1γ^+, however, may not have increased malignancy risk, whereas up to 75% of adults over age 40 who are antiTIF1γ^+ have malignancy.[26] There is no evidence-based recommendation or expert consensus for cancer screening in people with IIM. Certain IIM subtypes such as sIBM or clinically amyopathic DM may not be associated with increased cancer risk. AntiJo-1$^+$ ASynS maybe associated with lower risk of cancer than in the general population (Table e3). A wide variety of cancers have been diagnosed in IIM, including breast cancer, squamous cell carcinoma, multiple myeloma, ovarian cancer, lymphoma, lung cancer, esophageal cancer, and others. ^{18}F-fluorodeoxyglucose positron emission (FDG-PET) may be comparable to a large number of conventional screening tests, including physical examination, laboratory tests (eg, complete blood count and serum chemistry panel), thoracoabdominal CT, tumor mark-

ers (eg, prostate-specific antigen [PSA]), gynecologic examination, ovarian ultrasonography, and mammography.[28] Use of ^{18}F-FDG PET is limited, however, by availability and concerns for increased rates of false-positives and subsequent overdiagnosis. Clinicians should discuss the risks and benefits of malignancy screening with patients, as part of a shared decision-making process in the context of the individual's IIM subtype risk factors summarized in Table e3.

IIM Mimics

IIM misdiagnosis can lead to inappropriate and potentially harmful therapy; therefore, accurate diagnosis of IIM is essential. With the exception of sIBM, truly treatment-resistant myositis is rare and often later proven to be misdiagnosed genetic myopathy. Multiple hereditary and acquired neuromuscular conditions can present with proximal muscle weakness and elevated muscle enzymes, and some disorders such as dysferlinopathy, facioscapulohumeral dystrophy and calpainopathy may even show inflammation on muscle biopsy, potentially leading to misdiagnosis as IIM. Common IIM mimics clues for differentiating these from treatable IIMs are listed in Table e4. The course of myopathy associated with antiHMHGCR$^+$ and antiSRP$^+$ status can occasionally resemble muscular dystrophy, especially in children. All children with suspicion for muscular dystrophy should be screened for these autoantibodies.[30]

Diagnostic Approach

We propose a diagnostic approach for IIMs (Figure 2) in which, sIBM is considered untreatable and ruled in or out early in the process to avoid unnecessary harmful exposure to immunosuppressive agents. Because results of autoantibody testing may take 2 weeks or more to, we suggest empiric treatment for clinically suspected potentially life-threatening IIMs (eg, antiMDA-5$^+$ DM with rapidly progressive ILD or ICI-associated inflammatory myopathy) or "limb-threatening" IIM with a very rapid disease course (eg, antiSRP$^+$ IMNM) if muscle biopsy is not readily available. It is also essential to differentiate between IIMs and untreatable mimics (Table).

Treatment

We propose a treatment algorithm for IIMs (Figure e1). Evidence-based IIM treatment is challenging because of heterogeneity, evolving classification, and a lack of randomized clinical trials. Glucocorticoids are considered the first line therapy for IIMs; however, they have significant long term side effects. Methotrexate and azathioprine are the first-line nonsteroidal immunosuppressive agents for myositis. Mycophenolate mofetil and calcineurin inhibitors are typically used for refractory ILD. Multiple immunosuppressive and immunomodulating agents and recently developed biologic agents have been tried. Accurate diagnosis is essential to avoid using medications with potential side effects for untreatable myositis (sIBM). Treatment of myositis should be individualized and requires a multidisciplinary approach.

Response to treatment must include objective improvement in muscle strength and function, not merely based on subjective reports or serum CK levels. Other medications can be added to steroids based on the clinical response to treatment, comorbidities, IIM subtype, and serological findings. In a retrospective study of 123 people with IIM (defined by Bohan and Peter criteria), the addition of 2 g/kg IVIG for 6 months improved muscle strength and dysphagia in 78%.[31] IVIG could be used as a monotherapy in antiHMGCR$^+$ IMNM and adjunct therapy in antiSRP$^+$ myositis.[32]

In a clinical trial of 195 participants with PM or DM refractory to steroid and at least 1 added immunosuppressive agent, 83% had clinical improvement at 44 weeks after treatment with rituximab (750 mg/m^2 to a maximum dose of 1 g, given weekly for 2 weeks.[33] In another study, median muscle strength increased 21.5% as measured by hand-held dynamometry 24 months after 2 infusions of rituximab (1000 mg) 2 weeks apart.[34]

Abatacept is a T-lymphocyte activation inhibitor that has decreased disease activity in nearly half of participants in a clinical trial with DM (n=9) or PM (n=11) refractory to treatment.[35] Another group of12 individuals with refractory IM (11 PM, 1 DM) who received infliximab 5 or 7.5 mg/ kg had dose-dependent clinical improvement defined as more than a 15% manual muscle strength (MMT) improvement at week 16.[36] Pharmacotherapy of the IIMs is summarized in Table e5.

Conclusion

To increase understanding of disease mechanisms and develop new therapies, new proposed classification criteria need to be validated for the IIM disease spectrum. Criteria should capture IIM with mild or no overt muscle weakness and predominantly extramuscular manifestations (eg DM or ASynS) while also distinguishing IIM from other myopathies. ■

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TABLE e1. DERMATOLOGIC FINDINGS IN DERMATOMYOSITIS

	Name	Description	Comments
Pathognomonic	Gottron papules	Flat-topped, lichenoid, often violaceous papules and plaques overlying the bony prominences of the knuckles of the hands, including the metacarpophalangeal and interphalangeal joints	Hallmark of dermatomyositis (DM)
	Gottron sign	Erythematous or violaceous macules and patches overlying the extensor tendons of extremities, including over the elbows and knees	
Characteristic	Shawl sign	Red-to-violet colored poikilodermatous patches or thin plaques on the central aspect of the posterior shoulders, neck, and upper back	
	V-sign, psoriasiform scaly plaques of the scalp	Confluent macular, often atrophic erythema on the lower anterior aspect of the neck and the upper anterior portion of the chest	
	Heliotrope rash	Symmetrical violaceous erythema of the upper (and less often the lower) eyelids and periorbital region with edema	
	Periungual telangiectasia	Periungual telangiectasia, small hemorrhagic infarcts, cuticular hypertrophy, and ragged cuticles	
Compatible	Poikiloderma	Circumscribed areas with hyper- and hypopigmentation, telangiectasia, and superficial atrophy	Typical localization photoexposed skin on upper portions of chest and extensor surfaces of the arms
	Holster sign	Macular, violaceous erythema, often with reticulated, livedoid, or linear configuration over the lateral aspects of the hips and upper thighs	
	Heliotropism	Periorbital edema without skin color changes, and facial swelling	Common finding, particularly in early stages of the disease
Less common	Calcinosis cutis vesiculobullous		70% of pediatric DM frequent in antiNXP2$^+$ DM
	Erosive, ulcerative, (necrotic lesions)		3%-19% of DM, particularly common in antiMDA5$^+$ DM
	Cutaneous small vessel vasculitis	Petechial macules, palpable purpura, urticaria-like lesions, livedo reticularis, and skin or oral ulceration	Most common in juvenile DM
Rare	Mechanic's hands,	Hyperkeratotic, scaly plaques that develop on the radial and ulnar aspects of the thumb, index, and third fingers	MDA-5$^+$ DM and antisynthetase syndrome (ASynS)
	Follicular hyperkeratosis (Wong-type)	Follicular and hyperkeratotic erythematous papules on the extensor side of the extremities associated with palmar keratoderma	
	Erythema flagellatum	Linear patches and plaques on edematous background, often on back	
	Panniculitis	Painful, indurated nodules on buttocks, arm, thighs, and abdomen	
	Mucinosis	Papules and plaques with a reticular pattern; lesions may resemble scleromyxedema or cellulitis-like dermatosis	
	Erythroderma	Affecting more than 90% of the body surface area is rare and has been patients presenting with this pattern may warrant more thorough malignancy screening	May be associated with cancer
	Oral mucosal changes		
Recently described	Inverse Gottron papules	On the palmar creases (as opposed to classic Gottron papules), and may appear white, atrophic, or have a triangular configuration with hyperkeratosis	Associated with antiMDA-5$^+$ interstitial lung disease (ILD)
	Sleeve sign	Violaceous macular erythema restricted to lateral aspects of upper arms; this location is compatible with the contour of the sleeves	
	Hiker's feet	Hyperkeratosis of the toes and plantar surface of feet	Mostly associated with antiJo1$^+$ ASynS and mechanic's hands
Nonspecific	Photosensitivity		
	Raynaud phenomenon		
	Pruritus		

TABLE e2. CLINICAL SEROPATHOLOGIC FEATURES OF INFLAMMATORY IMMUNE MYOPATHIES

Subtype	Antibody target	Clinical features	Disease association	Distinctive pathology features
Dermatomositis (DM)	NXP2	Dysphagia, proximal and distal weakness, DM sine dermatitis, calcinosis, pediatric DM	Cancer	Microinfarctions (regional ischemia), sarcoplasmic antimyxovirus protein A (antiMxA+) (in addition to classic muscle biopsy findings in DM[a])
	Tif1g	Oval palatal patch	Cancer	Punch out vacuoles, mitochondrial abnormality, antiMxA$^+$ (In addition to classic muscle biopsy findings in DM)
	MDA5	Clinically amyopathic (CA) DM, myositis, DM with rapidly progressing-ILD, palmar ulcers	Rapidly progressing interstitial lung disease (ILD) with high mortality	Maybe minimal abnormality in CADM cases, otherwise antiMxA$^+$ (In addition to classic muscle biopsy findings in DM[a])
	Mi2	Severe muscle weakness, highly elevated creatinine kinase (CK), good response to treatment	No association with cancer or ILD	Perifascicular necrosis, immune myopathies with perimysial pathology (IMPP), sarcoplasmic antiMxA$^+$ (In addition to classic muscle biopsy findings in DM[a])
	SAE		Dysphagia	Classic muscle biopsy findings in DM
Antisynthetase syndrome (ASynS)	Jo1	Myositis	ILD, arthritis and arthralgia, mechanic's hand, Raynaud phenomenon	IMPP, perifascicular necrosis, sarcoplasmic antiMxA$^-$
	PL7/ PL12		Higher risk for ILD	IMPP, perifascicular necrosis, sarcoplasmic antiMxA$^-$
Immune-mediated necrotizing myopathies (IMNM)	HMGCR	Age <40 maybe statin-naïve severe, treatment refractory; age >40 typically, statin-induced, response to intravenous immunoglobulin (IVIG)	Dysphagia, increased risk of cancer	Scattered inflammation with patchy necrotic fibers, IMPP
	SRP	Rapidly progressive weakness with severe muscle atrophy and severe disability	ILD, cardiac involvement	Scattered necrotic fibers, abundant regenerating fibers, little or no inflammation, reduced endomysial capillary, increased endomysial connective tissue
Inclusion body myositis (IBM)	NT5C1A	Gradually progressive, asymmetric weakness, selective involvement of knee extensors>hip flexors, finger, and wrist flexors; muscle MRI may show vasti involvement >rectus femoris	Dysphagia, Sjögren syndrome	Endomysial inflammation, nonnecrotic muscle fiber invasion by lymphocytes, rimmed vacuoles, mitochondrial pathology, aggregates

Antibody target abbreviations: HMGCR, hydroxymethylglutaryl-CoA reductase; MDA5, melanoma differentiation-associated protein 5; NT5C1A, 5'-nucleotidase cytosolic IA; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; Tif1γ, transcription intermediary factor 1-γ

[a] Classic DM findings in muscle biopsy: perivascular inflammation, perifascicular atrophy, perifascicular Cox-negative fibers

TABLE e3. INFLAMMATORY IMMUNE MYOPATHY FEATURES AND CANCER ASSOCIATION

	Risk factors	Possible protective factors
Demographic	Age >45 years at diagnosis, male sex	
Clinical features	Dysphagia, cutaneous ulcerations, structural derangement of microvasculature with disorganized capillary distribution)	Interstitial lung disease, Raynaud phenomenon
Subtype		Antisynthetase syndrome, overlap myositis, sIBM, juvenile DM
Blood test findings	Mildly elevated/normal creatine kinase (CK) level; low complement	Lymphocytopenia
Autoantibodies	Tif1γ, NXP2, SAE and HMGCR, seronegative IMNM or IIM	Positive myopathy-associated antibodies for Jo1 or any antisynthetase antibodies, antiRo
Muscle biopsy	Regional muscle fiber necrosis, vascular pathology with damaged walls and capillary loss in perimysium	
Treatment response	Myositis refractory to therapy	

Abbreviations: DM, dermatomyositis; HMGCR, hydroxymethylglutaryl-CoA reductase; IIM, inflammatory immune-mediated myopathy; IMNM, immune-mediated necrotizing neuropathy; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; sIBM, sporadic inclusion body myositis; Tif1γ, transcription intermediary factor 1-γ.

TABLE e4. DIFFERENTIATION OF INFLAMMATORY IMMUNE MYOPATHIES FROM COMMON MIMICS

Disease	Distinctive clinical and paraclinical features from treatable IIM
Inclusion body myositis	Age>50, gradually progressive, characteristic pattern of muscle weakness (asymmetric finger flexors and knee extensor weakness), anti5'-nucleotidase cytosolic IA (antiNt5c1A), characteristic thigh MRI finding of T1 hyperintensity vasti>rectus femoris
Facioscapulohumeral muscular dystrophy	Asymmetric limb weakness, facial and ocular weakness, scapular winging, weakness in abdominal muscles (Beever sign), autosomal dominant, D4Z4 contraction in *DUX4* gene (most common),
Dysferlinopathy	Distal weakness, asymmetry, autosomal recessive (AR), *dysferlin* (*DYSF*) gene mutation,
Calpainopathy	Scapular winging, predominantly eosinophilic infiltration in muscle biopsy, autosomal recessive *calpain 3* gene mutation
Pompe disease	Profound respiratory muscle weakness, myotonia in EMG, distinctive muscle biopsy features (vacuoles, abnormal acid phosphatase stain), AR, *acid alpha-glucosidase* (*GAA*) mutation,
McArdle disease	Exertional rhabdomyolysis and muscle stiffness, second wind phenomenon, distinct muscle biopsy features (sub-sarcolemmal blebs, abnormal myophophorylase deficiency), autosomal recessive, *muscle glycogen phosphorylase* (*PYGM*) mutation
Thyroid myopathies	Hypothyroidism (subjective muscle discomfort, mild-moderate proximal weakness, delayed contraction and relaxation of muscle stretch reflexes, and mild-to-severe creatine kinase elevation)
Mitochondrial myopathies	Exercise intolerance, muscle biopsy: ragged red fibers (in Gomori trichrome) and ragged blue fibers (in NADH), no muscle inflammation
Steroid toxicity myopathy	No prominent edema in muscle MRI (short tau inversion recovery [STIR] sequences), nonirritable myopathy in EMG, Improvement in muscle weakness after tapering steroids
Chloroquine toxicity myopathy	No prominent edema in muscle MRI (STIR sequences); muscle biopsy findings of vacuoles and abnormal acid phosphatase stain
Colchicine toxicity myopathy	Typically occurs in the setting of chronic kidney disease, muscle biopsy findings of vacuoles and abnormal acid phosphatase stain
Kennedy disease	Fasciculations (especially perioral) gynecomastia, neurogenic EMG, X-linked recessive, trinucleotide repeat expansion in androgen receptor gene,

TABLE e5. IMMUNOTHERAPY FOR IMMUNE-MEDIATED INFLAMMATORY MYOPATHIES

Therapy	Dose; administration	Side effects	Monitoring
Azathioprine	2-3 mg/kg; daily oral dose in morning	Flu-like illness, hepatotoxicity, infection, leukopenia, macrocytosis, neoplasia, pancreatitis, teratogenicity	Blood count, liver enzymes
Cyclophosphamide	1.5-2 mg/kg; daily oral dose in morning or 0.5-1.0 g/m^2; monthly intravenous (IV) infusion for 6-12 months	Alopecial, bone marrow suppression, hemorrhagic cystitis, infections, infertility, neoplasia, teratogenicity	Blood count, urinalysis
Cyclosporine	2-3 mg/kg; twice daily oral dose	Gum hyperplasia, hypertension, hepatotoxicity, hirsuitism, infection, teratogenicity, tremor	Blood pressure, blood urea nitrogen (BUN)/ creatinine, liver enzymes, cyclosporine level
Intravenous Immunoglobulin (IVIG)	2 g/kg; IV infusion over 2-5 days then 1 g/kg; IV infusion every 4-8 weeks as needed	Anaphylaxis, arrhythmia, diaphoresis, flushing, headache, hypotension, aseptic meningitis, nephrotoxicity, stroke	Blood pressure, BUN/ creatinine, heart rate
Methylpred-nisolone	1 g in 100 mL normal saline; IV infusion over 1-2 hours, daily or every other day for 3-6 doses	Anxiety, arrhythmia, dysgeusia, flushing, fluid retention, hyperglycemia, hypokalemia, infection, insomnia, weight gain	Blood pressure, serum glucose, heart rate, serum potassium
Mycophenolate mofetil	Adults 1-2 g, children 1,200 mg/m^2; oral in 2 divided doses daily maximum 1 g/day in kidney failure	Amblyopia, bone marrow suppression, confusion, cough, diarrhea, headache, hypertension, infection, nausea, neoplasia, sinusitis, teratogenicity, tremor, vomiting	Blood count
Prednisone	Initiate at 0.75 to 1.5 mg/kg; oral daily dose	Cataracts, fluid retention, gastric irritation, hyperglycemia, hypertension, hypokalemia, infection, aseptic femoral necrosis, osteoporosis, weight gain	Blood pressure, cataract formation, serum glucose/potassium, weight
Rituximab	750 mg/m^2 to a maximum of 1 g; IV infusion repeated in 2 wks typically repeated every 6-18 months	Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy	Some check B-cell count before repeating doses, but this may be unneeded
Tacrolimus	0.1-0.2 mg/kg; in 2 divided oral doses daily	Gum hyperplasia, hypertension, hepatotoxicity, hirsuitism, infection, nephrotoxicity, tremor, teratogenicity,	Blood pressure, BUN/ creatinine, liver enzymes, tacrolimus levels