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## An Overview of Polymyositis and Dermatomyositis

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## An Overview of Polymyositis and Dermatomyositis

### ABSTRACT

Polymyositis and dermatomyositis are inflammatory myopathies that differ in their clinical features, histopathology, response to treatment, and prognosis. While their clinical pictures differ, they both present with symmetrical, proximal muscle weakness. Treatment relies mainly upon empirical use of corticosteroids and immunosuppressive agents. A deeper understanding of the molecular pathways that drive pathogenesis, careful phenotyping, and accurate disease classification will aid clinical research and the development of more efficacious treatments. This review discusses current knowledge of the epidemiology, clinical characteristics, diagnostic evaluation, classification, pathogenesis, treatment, and prognosis of polymyositis and dermatomyositis.

Key words: inflammatory myopathy, dermatomyositis, polymyositis, inclusion body myositis, myositis specific autoantibodies

## INTRODUCTION

The idiopathic inflammatory myopathies (IIMs), collectively termed myositis, are characterized by weakness and chronic inflammation of skeletal muscle. Other organs are often involved, including skin, heart, gastrointestinal tract, and lungs. Separate IIM subtypes have been identified based on differences in clinical and histopathological findings and are classified traditionally into polymyositis (PM), dermatomyositis (DM), and sporadic inclusion body myositis (sIBM).<sup>1,2</sup> Much progress has been made in revising the Bohan and Peter original diagnostic criteria from 1975<sup>3,4</sup> in order to more accurately align clinical, laboratory, and histopathological data with prognosis and response to treatment. Two additional forms have been described recently, nonspecific myositis, and immune mediated necrotizing myopathy (IMNM).<sup>5</sup>

Additionally a number of autoantibodies have now been associated with these syndromes, and some are associated with specific phenotypes and prognostic connotations. Accurate definition of disease entities is crucial for future therapeutic interventions.

It should be noted that controversy regarding the diagnosis of IIMs exists, as there is no consensus on their classification. For example, some consider PM to be inclusive of IMNM,<sup>6</sup> while others feel it is a separate entity.<sup>5</sup> Some propose abandoning traditional terms such as PM, DM, and sIBM, and instead would classify them on the basis of myopathology in an attempt to more accurately categorize disease entities with similar clinical outcomes.<sup>7</sup> Many of the studies discussed in this review have utilized various classification schemes, some of which diagnose patients with IMNM or sIBM as having PM. This review describes current knowledge of the epidemiology, clinical characteristics, diagnostic evaluation, classification, pathogenesis, treatment, and prognosis of DM and PM. IMNM and sIBM have been reviewed recently.<sup>8-10</sup>

## EPIDEMIOLOGY

Epidemiological studies on IIMs have until recently involved small population-based studies and utilized medical records and muscle biopsy to identify patients.<sup>11</sup> The Bohan and Peter criteria, which were introduced before sIBM and IMNM were identified as separate diseases, have been used in most epidemiologic studies after 1975. For this reason many of the incidence and prevalence statistics for individual forms of IIM are inaccurate, thus it has been more appropriate to analyze data for IIMs as a collective group. Recent studies report incidence rates for IIMs between 4.27 and 7.89 per 100,000 person years and prevalence rates ranging from 9.54 to 32.74 cases per 100,000 individuals.<sup>12-14</sup> In an attempt to accurately characterize the relative prevalence of individual IIMs with respect to each other, a retrospective follow-up study of 165 IIM patients found 76 to have probable or definite PM using Bohan and Peter criteria; however only 4 of 165 patients were believed to have PM during a follow-up period using more up-to-date histopathologic criteria.<sup>15</sup> This suggests that PM is an exceedingly rare entity and is often misdiagnosed. DM and PM occur more frequently in women and in African-Americans, but IBM affects men more commonly.<sup>16</sup> DM affects both children and adults, whereas PM rarely occurs in the pediatric population.<sup>17</sup> A recent study utilized a national health-care claims database to determine that the mean annual medical cost of patients with IIM was \$15,539, significantly higher than the \$5210 of matched controls.<sup>18</sup> IIM patients were also admitted to the hospital more frequently and for longer periods of time compared to matched controls.<sup>18</sup>

### CLINICAL FEATURES

DM or PM should be suspected in any patient who presents with progressive weakness, particularly when the weakness is relatively symmetric, predominantly proximal, unassociated with sensory loss or ptosis with sparing of extraocular muscles. PM and DM typically present with varying degrees of symmetric proximal limb and truncal muscle weakness that develops

over weeks to months.<sup>1,9</sup> Distal muscle weakness can occur late in the disease process of PM and DM, but it is an early and prominent finding in sIBM, where wrist and finger flexor weakness cause difficulty with fine motor movements.<sup>1,19</sup> Myalgias are uncommon in DM and PM.<sup>1,20</sup> Deep tendon reflexes are normal except in severely weakened muscles, and sensation remains normal. Neck flexor weakness is a common component of inflammatory myopathies, however there are many reports of myositis causing neck extensor weakness that did not cause a dropped head syndrome (Figure 1 A).<sup>21,22</sup> Primary weakness of the diaphragm and accessory muscles may contribute to respiratory insufficiency in myositis patients and require assisted ventilation.<sup>23</sup> Weakness of the pharyngeal muscles may occur in advanced cases of IIM resulting in dysphagia, nasal speech, hoarseness, nasal regurgitation, and aspiration pneumonia.<sup>24,25</sup>

A diagnosis of myositis requires exclusion of a number of mimic conditions, including limb-girdle and facioscapulohumeral dystrophies, and metabolic, mitochondrial, endocrine, and drug-induced myopathies. Certain physical examination findings, such as pronounced lumbar lordosis, waddling gait, extraocular muscle weakness, scapular winging, calf hypertrophy, paramyotonia, and action or percussion myotonia, should raise concern for an etiology other than IIM.<sup>1,20</sup>

## DERMATOMYOSITIS

Dermatomyositis typically presents with subacute progressive proximal muscle weakness, a skin rash, or both.<sup>1</sup> In children, DM may also present as a febrile illness.<sup>20,26</sup> PM may be diagnosed erroneously in patients with DM who present with isolated proximal muscle weakness and develop the rash months later.<sup>26</sup> Approximately 6% of DM patients have no skin involvement.<sup>15</sup> Twenty percent of DM patients with typical histopathologic features on muscle biopsy may develop a rash but never develop muscle weakness, and are categorized as

amyopathic dermatomyositis (ADM).<sup>27</sup> It has been suggested that the skin manifestations of DM can be divided into 5 categories: pathognomonic, highly characteristic, characteristic, more common in juvenile DM, and rare in DM.<sup>28,29</sup> The pathognomonic lesion of DM is a violaceous papular rash on the metacarpophalangeal and interphalangeal joints, called Gottron papules (Figure 1 B). Highly characteristic lesions include purple discoloration of the eyelids (heliotrope rash) accompanied by periorbital edema. Other typical findings include an erythematous rash over the extensor surfaces of the elbows, knuckles, knees, and ankles (Gottron sign) (Figure 2 A), an erythematous macular rash on the face, neck, and chest, called the V sign (Figure 2 B) or on the back of the neck and shoulders (shawl sign), hyperkeratosis, scaling, and horizontal fissuring of the palms (Figure 3 A), periungual telangiectasias (Figure 3 B), malar rash (Figure 3 C), and thick distorted cuticles.<sup>28,30</sup> These lesions are photosensitive and are commonly pruritic.<sup>28</sup>

Lesions occurring more commonly in juvenile DM (JDM) include cutaneous calcinosis, which develops over pressure points.<sup>2,28</sup> Rare dermatologic findings include non-scarring alopecia, erythroderma, vesiculobullous lesions, leukocytoclastic vasculitis, and livedo reticularis<sup>28,29</sup>

Other common extramuscular manifestations include various cardiac abnormalities, interstitial lung disease (ILD), and malignancy.<sup>28,31</sup> Cardiac manifestations include arrhythmia, congestive heart failure, myocarditis, pericarditis, angina, and fibrosis.<sup>28,32</sup> Symptomatic cardiac involvement is uncommon in acute disease, however up to 50% of DM patients will have asymptomatic cardiac involvement on noninvasive testing.<sup>28</sup> In chronic DM, heart failure has been attributed to the effects of long-standing hypertension secondary to steroid use.<sup>28</sup> ILD is a disorder of unknown etiology; it is characterized by inflammatory infiltrates and interstitial fibrosis. DM-ILD is clinically more severe and carries a poorer prognosis than PM-ILD.<sup>23</sup> This is likely attributable to the presence of anti-melanoma differentiation associated gene 5 (*MDA5*)

antibodies which are associated with a rapidly progressive ILD and are detected exclusively in DM and ADM.<sup>31</sup>

DM has a strong association with specific malignancies, including ovarian, lung, pancreatic, stomach, and colorectal cancer.<sup>33</sup> Approximately 15% of adult DM patients, especially those older than age 40, have either a pre-existing malignancy or will develop a malignancy in the future.<sup>33</sup> Juvenile DM patients have a sixteen-fold increased risk of leukemia and lymphoma.<sup>33</sup> An underlying malignancy is particularly common in IIM patients who are elderly, male, have a shawl sign, demonstrate recurrent disease, or have autoantibodies to transcriptional intermediary factor (TIF).<sup>33</sup> Interestingly, IIM patients with ILD have a lower risk of developing malignancy.<sup>33</sup>

## POLYMYOSITIS

PM is a term that was used traditionally to denote all IIMs that were not DM or sIBM, but it is now a controversial entity with questionable specificity.<sup>28,34-37</sup> PM is frequently misdiagnosed, as it lacks a unique clinical phenotype.<sup>2,15</sup> The most common disease misdiagnosed as PM is sIBM, which is suspected retrospectively in many cases of presumed PM that have not responded to therapy.<sup>1,15,38</sup> PM may also be diagnosed incorrectly in cases of DM, IMNM, overlap syndrome associated with a connective tissue disease, muscular dystrophies, myalgia syndromes, or toxic and endocrine myopathies.<sup>15,37</sup> For these reasons, old case series utilizing Bohan and Peter criteria to identify PM patients are unreliable and provide an inaccurate and contaminated clinical picture of PM. Traditionally, PM is described as presenting with weakness of the proximal muscles that evolves over weeks to months and affects adults, but rarely children.<sup>1</sup>

## ANTI-SYNTHEASE SYNDROME



Patients with anti-synthetase autoantibodies may carry a diagnosis of DM or PM.

However a well-characterized series of patients with anti-Jo-1 autoantibodies, the most common anti-synthetase autoantibody, clearly demonstrated distinct pathological and clinical differences from DM and PM.<sup>39</sup> These patients suffer from a constellation of symptoms collectively termed antisynthetase syndrome, which includes myalgias, muscle weakness, and a combination of 'core' symptoms including ILD, Raynaud phenomenon, seronegative arthritis of the distal joints, fever, mechanic's hands, and a skin rash different from the heliotrope erythema seen in DM,<sup>9,40,41</sup> ILD is found in 79% to 95% of cases and may precede the development of myositis in up to one-half of patients.<sup>31</sup>

#### OVERLAP SYNDROME

Overlap syndrome occurs when a patient clearly meets the classification criteria for 2 or more autoimmune diseases.<sup>42</sup> When patients with IIM have another autoimmune or connective tissue disease, they are classified as having an overlap syndrome. PM and DM are most frequently associated with systemic sclerosis and mixed connective tissue disease.<sup>43,44</sup>

#### DIAGNOSTIC EVALUATION

In 1975 Bohan and Peter established diagnostic criteria for DM and PM which are summarized in table 1.<sup>3,4</sup> Although these criteria are imperfect, they are still used widely in both clinical and research settings and provide a starting point to discuss the diagnostic tools utilized to investigate IIMs. Many improved classification schemes have been proposed and will be discussed.

#### ELEVATED MUSCLE ENZYMES

Serum creatine kinase (CK) levels in patients with active DM may be normal, but most will be increased up to 50 times the upper limit of normal.<sup>2</sup> CK will be elevated 5-50 times in patients

with active PM, 10 times or more in IMNM,<sup>26</sup> and normal or only mildly elevated in sIBM (less than 10-fold normal).<sup>19</sup> Serum CK levels do not correlate well with disease activity when comparing different patients, however they can reflect changes in disease activity within an individual patient. Other muscle enzymes including aldolase, myoglobin, lactate dehydrogenase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also be elevated. IIM patients taking potentially hepatotoxic medications such as azathioprine (AZA) and methotrexate will also develop elevated transaminases. The liver enzyme  $\gamma$ -glutamyl transpeptidase (GGT) should be used to evaluate for liver damage in such patients, as it is not released by damaged muscle fibers.<sup>45</sup> Patients with a clinical manifestation similar to that seen in antisynthetase syndrome with myopathology in perimysial connective tissue may have an isolated aldolase elevation without a concomitant rise in CK.<sup>46</sup>

#### ELECTROMYOGRAPHY

The characteristic EMG features of myositis patients are: (1) increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic or complex repetitive discharges, (2) polyphasic motor unit action potentials (MUAPs) of short duration and low amplitude, and (3) early recruiting MUAPs.<sup>1</sup> Paraspinal muscles show the most prominent features on EMG examination and should be included routinely. Since other inherited or metabolic conditions may mimic IIMs, discovery of high frequency discharges or myotonic discharges in the paraspinal muscles should prompt the search for other disorders such as myotonic dystrophy type 2 or Pompe disease. EMG also plays a critical role in diagnostic evaluation by aiding in the identification of muscles recently or slightly involved that may be most suitable for biopsy.<sup>47</sup>

#### HISTOPATHOLOGY

Muscle biopsy can provide valuable diagnostic information in patients with suspected IIM. The pathological findings associated with IIM recognized by Bohan and Peter are summarized in table 1. It is important to emphasize that inflammatory cell infiltrates are not specific and can be seen in muscular dystrophies such as dysferlinopathy, metabolic myopathies following rhabdomyolysis, and sIBM.<sup>48</sup> Muscle biopsies should therefore be assessed for additional features that might suggest a muscular dystrophy, myotonic dystrophy, congenital myopathy or a metabolic disorder like late onset Pompe disease. In the years since the 1975 Bohan and Peter classification scheme, biopsies from patients with DM, PM, IMNM, and sIBM have been shown to have unique pathological features (Figure 4, Figure 5), suggesting that a different pathophysiological mechanism may exist for each. In a study of patients with suspected myopathy, open muscle biopsy failed to detect any pathological abnormality in 14% of patients.<sup>49</sup> In a retrospective analysis of the efficacy of multiple simultaneous percutaneous muscle biopsies in patients who presented with either weakness or myalgias, a definitive diagnosis of inflammatory myopathy required 2 biopsies 70% (19 of 27) of the time, and a single biopsy only 30% (8 of 27) of the time.<sup>50</sup>

#### Dermatomyositis

The earliest abnormality observed is deposition of the membrane attack complex (MAC) around small blood vessels.<sup>51,52</sup> Muscle atrophy and decreased capillary density are seen at the periphery of the fascicle (Figure 4 A, B). Inflammatory infiltrates in DM consist of perimysial and perivascular macrophages, B cells, and cluster of differentiation (CD) 4+ T-cells, primarily plasmacytoid dendritic cells.<sup>53</sup> Tubuloreticular inclusions can be found within intramuscular arterioles and capillaries on electron microscopy.<sup>54</sup> Muscle biopsies of patients with anti-Jo-1 antibodies, who are often diagnosed with DM, have similar findings on muscle biopsy (Figure 4

C) with the exception of a macrophage-predominant inflammatory response, fragmentation of perimysial connective tissue, a lack of MAC deposition on microvasculature, and a paucity of vascular pathology.<sup>9,55</sup> Although DM may appear to be clinically homogenous, 2 distinct clinical-pathologic types have been described.<sup>7</sup> One form, termed immune myopathy with perimysial pathology, is seen primarily in adults, is associated with ILD, and on muscle biopsy has myofiber necrosis and regeneration in perifascicular regions near areas of connective tissue pathology, illustrated by perimysial fragmentation and heavy staining with alkaline phosphatase.<sup>7</sup> The other distinct clinical-pathological pattern has been termed myovasculopathy; it is seen primarily in children and is not associated with ILD. On muscle biopsy there is evidence of damage to endomysial capillaries and intermediate-sized vessels illustrated by dark staining with alkaline phosphatase. Mitochondrial pathology is present, characterized by reduced cytochrome oxidase (COX) staining but preserved succinate dehydrogenase (SDH) staining in areas of perifascicular muscle fiber atrophy and vacuolation.<sup>7</sup>

### Polymyositis

The primary histological features in PM are fiber size variability, scattered necrotic and regenerating fibers, and perivascular and endomysial cellular infiltrates (Figure 5).<sup>1</sup> This infiltrate consists of macrophages and activated CD8+ cytotoxic T cells that can occasionally be seen invading non-necrotic muscle fibers which express MHC-I.<sup>2</sup> Including myofiber invasion by mononuclear cells as a diagnostic criterion for PM is controversial, as some believe it lowers sensitivity,<sup>56,57</sup> however given the paucity of specific findings on clinical exam and muscle histopathology in PM, such a criterion should be upheld to diagnose the questionable entity of “definite” PM.<sup>2,5</sup> The lack of specificity for PM on histopathology is further confounded by the fact that surface expression of MHC-I is not specific for IIMs and can be seen rarely in various

muscular dystrophies.<sup>58,59</sup> Staining for MHC-II or applying a cut-off of 50% or greater for the fraction of fibers that stain internally with MHC-I, however, appears to be 100% specific for IIMs.<sup>60,61</sup>

The above-described histologic pattern is not distinctive, since it also occurs in sIBM patients (Figure 5 C). The common misdiagnosis of PM in sIBM patients despite the performance of a muscle biopsy was illustrated by a study that found 16 of 43 patients (37%) with characteristics of PM on biopsy but had clinical evidence of sIBM.<sup>38</sup> Myopathologic changes, especially inflammatory changes, in PM and sIBM are identical, and rimmed vacuoles or inclusions (Figure 6 A, B) may not always be seen. The presence of ragged red fibers and an excess of COX-deficient fibers predicts steroid non-responsiveness and a clinical presentation more consistent with sIBM (Figure 6 C, D).<sup>62</sup> Not all sIBM biopsies contain characteristic features such as rimmed vacuoles or inclusions, and therefore attention must be paid to clinical features such as distal weakness to avoid making an erroneous diagnosis of PM.<sup>19,38</sup> IMNM may also be mistakenly misdiagnosed as PM on muscle biopsy. IMNM is characterized by scattered necrotic muscle fibers with myophagocytosis and minimal T-cell lymphocytic inflammatory infiltrates.<sup>9</sup> Some may classify this as PM,<sup>63</sup> however there is a clear histopathological difference between the 2, as IMNM biopsies have minimal inflammatory cell infiltrates that are confined to necrotic myofibers.

#### AUTOANTIBODIES

Antibody measurements are utilized frequently to evaluate patients with IIM and have been included in several revised classification schemes.<sup>35,64,65</sup> The role of antibodies in inflammatory myopathies is unclear; they may be directly involved in IIM pathophysiology or they may simply be an epiphenomenon. Antibodies can be categorized as myositis-associated

autoantibodies (MAAs) or myositis-specific autoantibodies (MSAs). The term MSA is applied to autoantibodies found predominantly in the serum of patients with myositis, however they may not be 100% specific.<sup>66</sup> MAAs on the other hand, are encountered primarily in other connective tissue diseases but are occasionally found in patients with myositis.<sup>64,66</sup> Several MAAs include anti-Ro, anti-La, anti-PM-Scl, anti-small nuclear ribonucleoproteins (snRNPs) U1, U2, U4/6, U5, and U3, anti-Ku, anti-KJ, anti-Fer, anti-Mas, and anti-hPMS1.<sup>28</sup> The MAA PM-Scl is typically associated with an overlap syndrome causing systemic sclerosis with minimal cutaneous involvement and PM or DM.<sup>40</sup> It has been reported that 60-80% of adult patients with PM, DM, or IMNM have at least 1 identifiable MSA.<sup>40,67</sup> With the exception of anti-155/140 (now referred to as TIF- $\gamma$  and TIF- $\alpha$ ) and anti-nuclear matrix protein 2 (NXP2), MSAs are associated with a decreased risk of malignancy.<sup>68</sup> Anti-Jo-1 antibodies were the first antibodies described in myositis and are more commonly detected compared to other anti-synthetase antibodies found in myositis.<sup>69</sup> Considering that some patients with anti-synthetase autoantibodies may not have muscle involvement, some object to their categorization as an MSA.<sup>70</sup> Several other antibodies observed in various forms of myositis include anti-SRP and anti-3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in IMNM<sup>8</sup> and anti-cytosolic 5-nucleotidase 1A (NT5C1A) in sIBM.<sup>71</sup> A summary of MSAs and their associated clinical presentation can be found in supplemental table 1.

## IMAGING

Magnetic resonance imaging (MRI) is becoming used increasingly to evaluate PM and DM. MRI can detect muscle necrosis, degeneration, and inflammation, and is characterized by increased signal intensity on short tau inversion recovery (STIR).<sup>72</sup> T1-weighted images are useful for detecting atrophy and chronic muscle damage,<sup>73</sup> whereas T2-weighted images are

useful for detecting active muscle inflammation, and their relaxation times have been correlated with disease activity.<sup>74-76</sup> New diagnostic criteria suggest MRI can be used to evaluate JDM in order to avoid EMG or muscle biopsy.<sup>77</sup> MRI is also being used to identify muscle sites for biopsy and to monitor treatment response.<sup>72-76,78</sup> Ultrasound, specifically doppler sonography, contrast-enhanced ultrasound, and sonoelastography may be also be used to differentiate between normal and pathologic muscle.<sup>79</sup> This provides a less expensive alternative for patients with contraindications to MRI.

#### APPROACH TO DIAGNOSTIC EVALUATION

The authors believe strongly that serum CK, nerve conduction study, and needle EMG should be done in all subjects suspected to have an inflammatory myopathy. Elevation in serum CK is seen in all cases of untreated PM, most cases of DM, and not infrequently in sIBM, but a normal CK does not rule out an inflammatory myopathy. Nerve conduction studies can evaluate for other causes of muscle weakness, such as myasthenia gravis or Lambert-Eaton myasthenic syndrome. Needle EMG examination is important to rule out a neurogenic disorder, such as spinal muscular atrophy that can present with symmetric proximal weakness and elevated serum CK levels. Furthermore needle EMG can assess whether the muscle is end-stage or has enough motor units to be a viable muscle for biopsy purposes.

The authors recommend routine use of myositis antibody panels to stratify risks associated with the myositis. We believe strongly that there are specific myopathologic changes associated with these antibodies, and disease behavior and treatment response may vary depending on the presence of specific antibodies.

Use of MRI is not as widespread in the United States as it is in Europe for identifying muscle involvement, following treatment response, and perhaps for selecting muscles to biopsy.

Insurance approval (and reimbursements) can be difficult for extremity MRIs used to identify patterns of muscle involvement and if approved, are often times restricted to limited studies of one limb. It is a powerful tool and should be used more frequently in the diagnostic and follow up process. Muscle ultrasound is becoming very popular for this purpose and is relatively inexpensive, portable, and may supplant the use of MRI in some cases.

For muscle biopsies, we recommend a standard battery of stains. In addition to routine staining with hematoxylin and eosin (H&E), Gomori-Trichrome, reduced nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), and adenine triphosphatase (ATPase) at different pHs, additional stains are recommended. Oxidative stains such as cytochrome oxidase and SDH should be done, especially to help identify ragged red fibers along with Gomori-Trichrome and to find fibers deficient in or lacking cytochrome staining, as is often seen in sIBM and in selected cases of DM. Metabolic stains, including periodic acid-Schiff (PAS) and lipid stains should be done. PAS stains can pick up glycogen deposits, especially in cases of Pompe disease, which can be mistaken clinically for PM. We find staining with alkaline phosphatase very useful; abnormalities on alkaline phosphatase in the perimysium are seen frequently in DM and in myopathies associated with collagen vascular diseases, such as scleroderma and systemic sclerosis.<sup>80</sup> Acid phosphatase and non-specific esterase are good for highlighting histiocytic infiltration in the muscle and also for detecting lysosomal abnormalities as can be seen in Pompe disease. Finally a battery of immunostains should be applied; we recommend staining for B-cells (CD20), T-cells (CD4 and CD8), and macrophages (CD68). Additionally MHC class I staining should be done in all cases of inflammatory myopathy. In additional cases, staining for the complement cascade (terminal complex C5-9b) may be helpful.

## CLASSIFICATION



There have been many attempts to establish classification and diagnostic criteria for IIMs. In 1975 Bohan and Peter proposed a system that attempted to establish clear guidelines for diagnosis and classification of PM and DM.<sup>4</sup> They stated these criteria were derived empirically, however no data were provided for sensitivity or specificity.<sup>4</sup> They also noted a diagnosis of IIM required exclusion of other conditions.<sup>4</sup> The Bohan and Peter criteria are considered to be too inclusive, allowing patients with various muscular dystrophies to be diagnosed with PM,<sup>48</sup> and they are unable to distinguish sIBM and IMNM from PM. Several other classification schemes have been proposed, all attempting to improve the homogeneity of diagnostic categories, such that treatment and prognosis may be evaluated accurately. No official classification system currently exists, as disagreement still continues. Many clinical patterns of inflammatory myopathy other than PM, DM, sIBM, and IMNM have been described and include brachio-cervical inflammatory myopathy,<sup>81</sup> paraspinal and scapular inflammatory myopathy,<sup>82</sup> and focal myositis.<sup>83</sup> The existence of such entities lends further support to the need for a new classification scheme.

Many believe clinical-serologic associations would more accurately categorize patients, and in 1991, a group suggested classifying IIMs based on MSAs.<sup>64</sup> Classification based on MSAs has been limited previously by lack of commercial availability, inability to differentiate sIBM (which may no longer be a problem),<sup>71</sup> and lack of specificity of MSA syndromes.<sup>41</sup>

Other classification schemes have placed more emphasis on muscle pathology. In 1978, sIBM was recognized as a clinicopathological entity distinct from PM based on unique features such as distal weakness and the presence of rimmed vacuoles on muscle biopsy.<sup>84</sup> In 1991, clinical and histopathological differences were used to refine classification criteria, allowing identification of sIBM as a distinct entity from PM,<sup>1</sup> and in 1995 a working definition of sIBM

was proposed.<sup>19</sup> The importance of these new histopathological criteria was demonstrated in 2003, when a retrospective follow-up study of 165 IIM patients suggested the diagnosis of PM is rare, and actually includes a heterogeneous group of disorders. Cases of so-called PM were likely to be sIBM, myositis associated with a connective tissue disorder, muscular dystrophies with inflammation, or even DM. The over-diagnosis of PM when using the Bohan and Peter criteria was illustrated in a case series of 68 IIM patients in which 50% of patients were diagnosed with PM.<sup>19</sup>

Another issue of classification is the distinction between PM and IMNM. In 2003, neurologists proposed 2 new distinct pathologic entities at a consensus conference of the European Neuromuscular Center (ENMC): IMNM and nonspecific myositis, which included patients with nonspecific perimysial/perivascular infiltrates, but without biopsy features diagnostic of DM or PM.<sup>5</sup> This created an inconsistency in nomenclature for IMNM and PM, as patients who meet ENMC criteria for IMNM also meet the still widely-used Bohan and Peter criteria for PM.

In 2011, another classification system was proposed, based solely on myopathology. This strategy avoids the inconsistencies of current classification systems,<sup>7</sup> such as 1) many IIM patients have little inflammation and don't fit any of the traditional subdivisions;<sup>9</sup> 2) IIM syndromes based on MSAs are nonspecific and include patients with both DM and PM;<sup>41</sup> 3) PM is a nonspecific term often used to denote all IIMs that are not DM or sIBM;<sup>35</sup> and 4) not all sIBM patients have inclusions on muscle biopsy, even after serial biopsies.<sup>15</sup> The myopathologic classification system utilizes pathologic characteristics, types of muscle fiber damage, and tissues involved to sub-classify IIMs, thereby abandoning categories such as DM, PM, sIBM, and IMNM. Instead it defines 6 new classes: 1) immune myopathies with perimysial pathology,

2) myovasculopathies, 3) immune polymyopathies, 4) immune myopathies with endomysial pathology, 5) histiocytic inflammatory myopathy, and 6) inflammatory myopathies with vacuoles, aggregates, and mitochondrial pathology. Whether or not this new classification will help distinguish treatable and untreatable IIMs is uncertain and requires further validation.

Consistent classification is imperative for drawing accurate conclusions in therapeutic trials. The accumulating alternative classification schemes used by various subspecialists are creating contradictory nomenclatures, which impair the ability to compare clinical studies and assess outcomes of clinical trials. For these reasons, members of the International Myositis Assessment and Clinical Studies (IMACS), the ENMC, and the pediatric rheumatology networks all have international multidisciplinary projects to develop classification criteria for adult and juvenile myositis. Rheumatologists direct IMACS, and neurologists direct the ENMC. There is a need for improved communication and collaboration between the two groups. IMACS has begun to devise new classification criteria utilizing an expert-driven systematic consensus process and there is some neurologic input in the process.

### PATHOGENESIS

The histopathological features of muscle from different IIM subtypes suggests that various disease mechanisms may exist, including immune and non-immune processes.<sup>36</sup>

### DERMATOMYOSITIS

Dermatomyositis is believed to be caused by a humorally mediated autoimmune attack where endomysial capillaries serve as the antigenic target, leading to activation of the complement system and MAC deposition on endomysial endothelial cells.<sup>1,51,52,85</sup> It has been hypothesized MAC deposition leads to damage of the intermediate-sized perimysial vessels, decreasing capillary density at the periphery of the fascicle, leading to watershed ischemia and

myofiber atrophy in a perifascicular pattern.<sup>86</sup> Several inconsistencies exist in this sequential pathophysiology. First, it is presumed that the endothelium of endomysial capillaries serves as the antigenic target of a humoral autoimmune attack. Evidence that suggests otherwise includes the observation of MAC deposition surrounding vessels rather than coinciding with lectin-binding of endothelial cell surfaces.<sup>52</sup> Second, the significance of MAC deposition is not clear, as variability in the frequency of MAC deposition in cases of DM has been observed, ranging from 26%<sup>85</sup> to 94%.<sup>52</sup> Third, the concept of perifascicular atrophy being caused by watershed ischemia is controversial; 1 study found no correlation between perifascicular atrophy and the degree of capillary depletion,<sup>52</sup> and another found that perifascicular atrophy and endomysial capillary MAC deposition were actually correlated inversely.<sup>85</sup> The link between ischemia and perifascicular atrophy is also not supported by animal models of skeletal muscle ischemia induced by embolism.<sup>87,88</sup> Such models reveal that the central portions of fascicles, not the periphery, are the first to be affected by ischemia.<sup>88</sup>

Although the link between ischemia and perifascicular atrophy is unclear, hypoxia has been suggested as a component of DM pathogenesis. Hypoxia-inducible factor 1- $\alpha$  (HIF-1- $\alpha$ ), and its downstream gene products are over-expressed in DM muscle.<sup>89</sup> Hypoxia may cause weakness in DM by reducing phosphocreatine and adenosine triphosphate (ATP) levels in muscle,<sup>90</sup> inducing production of interleukin (IL)-1 and tumor growth factor- $\beta$  (TGF- $\beta$ ), and possibly by producing high mobility group protein B1 (HMGB1), a DNA binding protein released into cytoplasmic and extracellular spaces when a cell is subjected to stress such as hypoxia.<sup>91</sup> HMGB1 reversibly upregulates MHC-I molecules in muscle fibers and induces muscle fatigue by irreversibly decreasing Ca<sup>2+</sup> release from the sarcoplasmic reticulum in

studies on single muscle fibers.<sup>92</sup> It is seen in endothelial cells and muscle fibers of patients with DM before inflammatory infiltrates can be detected.<sup>91</sup>

The inflammatory cells seen in DM are perimysial and perivascular and are composed of CD4+ T cells, B cells, dendritic cells (DCs), and macrophages.<sup>93</sup> The role of CD4+ T cells in DM pathogenesis is supported by the increased risk of developing DM in patients with specific human leukocyte antigen (HLA)-DR molecules, which function to present antigens to CD4+ T cells.<sup>94</sup> CD4+ T cells from IIM patients lack an activation molecule, CD28,<sup>95</sup> indicating an antigen has stimulated these T cells chronically to produce effector cells similar to the pro-inflammatory and apoptosis resistant natural killer cells. Type 17 T-helper cells have been found in muscle tissue of DM patients;<sup>96,97</sup> they are a major source of IL-17, a pro-inflammatory cytokine found to induce expression of IL-6 and MHC-I, which is commonly found on the sarcolemma of DM myofibers.<sup>98</sup> FOXP3+ regulatory T<sub>REG</sub> cells have been detected in DM muscle.<sup>99</sup> The number of T<sub>REG</sub> cells in peripheral blood of DM patients has been correlated inversely with disease activity.<sup>100</sup> The role for B cells in the pathogenesis of DM is supported by the presence of autoantibodies and by positive clinical responses to rituximab, a monoclonal antibody directed against B cells.<sup>101,102</sup> Plasmacytoid DCs (PDCs), a major source of type 1 interferon (IFN), are present in muscle and skin of patients with DM.<sup>103,104</sup> Macrophages are found in DM and contribute by presenting antigens to T cells, clearing necrotic muscle fibers, and generating a variety of cytokines and chemokines.<sup>105</sup>

A recently discovered adhesion molecule, KAL-1, may play a pivotal role in the pathogenesis of DM. It was found to be significantly down-regulated in DM patients who improved after intravenous immunoglobulin (IVIg) therapy.<sup>106</sup> Adhesion molecules allow for transmigration and recruitment of inflammatory cells and are up-regulated on capillary

endothelium after the activated complement system triggers release of pro-inflammatory cytokines.

Cytokines such as IL-1,<sup>107,108</sup> IL-15,<sup>109</sup> IL-6,<sup>108</sup> IFNs, and the previously discussed HMGB1 have been suggested to play a role in the pathogenesis of DM. IL-15 activates T cells to down-regulate expression of CD28, producing CD28null T cells, the predominant population of T cells seen in IIM muscle.<sup>95,110</sup> Reducing levels of IL-6 improved clinical outcome in a mouse model of myositis.<sup>111</sup> Many studies have implicated a role for type I IFN in DM pathogenesis. Complexes of ribonucleic acid (RNA) and anti-Jo-1 autoantibodies have been shown to activate IFN production in PDCs,<sup>112</sup> a cell population found in inflammatory infiltrates in skin and muscle of DM patients.<sup>103,104</sup> Muscle expression of IFN- $\alpha/\beta$  inducible transcript and protein is orders of magnitude higher in DM compared to PM and sIBM.<sup>113</sup> This correlates with the increased number of IFN- $\alpha/\beta$  secreting PDCs seen in DM muscle.<sup>113</sup> The tubuloreticular inclusions found in endothelial cells of DM muscle,<sup>114</sup> also develop in patients treated with IFN- $\alpha$ <sup>115</sup> and are recognized as a downstream marker of type 1 IFN signaling.<sup>116</sup> Type 1 IFN signaling in the blood has also been shown to correlate highly with disease activity in DM and PM.<sup>117</sup> Human myxovirus resistance protein A (MxA), an interferon- $\alpha/\beta$ -inducible protein that provides innate defense against several RNA viruses,<sup>118</sup> has been demonstrated consistently in myofibers of DM patients in regions of perifascicular atrophy and in the endothelium of endomysial capillaries.<sup>103</sup> Interestingly, MxA is absent in the perifascicular fibers and endomysial capillaries of sIBM and PM patients, however it is unclear if MxA simply serves as a marker of diseased myofibers or if it mediates myofiber and endothelial cell injury. IFN-stimulated gene 15 (*ISG15*), a type 1 IFN-inducible protein, is an ubiquitin-like modifier with poorly understood function. *ISG15* is the single most over-expressed gene in DM muscle

compared with both normal muscle and muscle from patients with other inflammatory myopathies.<sup>103</sup> A large-scale microarray study revealed transcripts which encode *ISG15*-conjugation pathway proteins were markedly upregulated in DM with perifascicular atrophy compared with non-DM samples.<sup>119</sup> These transcripts included *ISG15* and the *ISG15* conjugation pathway members *HERC5* and *USP18*.<sup>119</sup> Elevation of these transcripts and presence of *ISG15* protein and *ISG15* protein conjugates were 100% specific to samples of DM with perifascicular atrophy.<sup>119</sup> Cultured human skeletal muscle exposed to type 1 interferons produced similar transcripts and *ISG15* protein and conjugates.<sup>119</sup> Interestingly atrophic perifascicular myofibers in DM were deficient in a number of skeletal muscle proteins including titin, which is a major skeletal muscle protein that provides the scaffold for the sarcomere.<sup>119,120</sup> This finding is consistent with previous electron microscopic studies that found a loss of visible sarcomeric structure within DM perifascicular atrophic myofibers.<sup>121</sup>

## POLYMYOSITIS

The inflammatory infiltrates seen in PM are located in the endomysium and are composed of CD4+ T cells, CD8+ T cells, DCs, and macrophages.<sup>93</sup> It is thought that endomysial CD8+ T cells play a central role in the immune process by recognizing an unknown endogenous peptide presented by MHC-I molecules on non-necrotic muscle fibers<sup>1,34</sup> and then inducing myofiber necrosis by releasing perforin-1 and granzyme B.<sup>122</sup>

Many of the cytokines suggested to have a role in the pathogenesis of DM are also found in PM patients, including IL-1, 6, and 15.<sup>107,108</sup> Many of the inflammatory cell types found in DM patients are also found in PM, including Type-17 T-helper cells,<sup>96,97</sup> IL-6+ cells,<sup>108</sup> and FOXP3+ T<sub>REG</sub> cells.<sup>99</sup> Also similar to DM, B cells and clonally-expanded plasma cells are present in the inflammatory infiltrate, providing support for a chronic antigen-driven humoral immune

response.<sup>123</sup> The presence of clonally-derived immunoglobulin transcripts along with marked upregulation of B-cell activating factor (BAFF) in these biopsies suggests that maturation of B-cells to plasma cells occurs locally in the muscle and that myositis muscle provides a permissive environment for this to occur.<sup>124</sup>

Hypoxia has also been implicated in the pathogenesis of PM, as HIF-1- $\alpha$  and its downstream gene products have been found to be overexpressed.<sup>89</sup> Certain retroviruses have been associated with cases of PM and sIBM.<sup>125</sup> Cytotoxic CD8+ T-cells with receptors specific for viral peptides in HIV-positive PM and sIBM patients have been found to invade the MHC-I expressing muscle fibers, however virus has not been found within muscle.<sup>125</sup>

## GENETICS

An interaction between environmental and genetic factors is thought to be the initiating mechanism underlying various IIMs. For example, the *DRB1\*0301* allele is associated with a 15.5-fold increased risk of developing anti-Jo-1 autoantibodies.<sup>126</sup> The *DRB1\*11:01* allele is associated with an 11.7-fold increased risk of anti-HMGCR myopathy in whites and 26.4-fold increased risk in African American patients.<sup>127</sup> Other *MHC* alleles are associated with development of anti-PL-7, anti-signal recognition peptide (SRP), anti-MI-2, anti-small ubiquitin-like modifier activating enzyme 1 (SUMO-1) and several other MSAs.<sup>126,128-130</sup> Genetic susceptibility also plays a role in Caucasians with sIBM, as *HLA-DRB1\*03:01* and the 8.1 ancestral haplotype have been strongly associated with the disease.<sup>131</sup> Interestingly the carriage of *HLA-DRB4* appears to be protective and nullify the risk effect of *HLADR1\*03:01*.<sup>131</sup> Polymorphisms in other genes have also been shown to affect the risk of developing a form of IIM, for example the immunoglobulin  $\gamma$  heavy chain 13 allotype correlates directly with DM.<sup>132</sup> The tumor necrosis factor (*TNF*) promoter 308A polymorphism is associated with an increased



risk of developing juvenile DM, whereas the *TNF* promoter 238A polymorphism is associated with a decreased risk of developing juvenile DM.<sup>133</sup> The *IL-1α*+4845G allele decreases the risk of developing juvenile DM, whereas the *IL-1β*+3953T allele confers an increased risk of developing the same disease.<sup>133</sup>

### THERAPY

The mainstay of therapy for DM and PM is immunosuppression, physical therapy, monitoring for adverse events from medication, and prevention of complications.<sup>134</sup> Determining an optimal drug therapy for IIMs is also impaired by the lack of consensus on classification, clinical trial conduct, reporting, and standardized outcome measures that correlate with changes in patient disability and quality of life.<sup>134</sup> Another issue is the small number of randomized controlled trials of immunosuppression for the IIMs.

In compiling a treatment plan, several factors should be taken into consideration. If the patient has early active disease, rapid aggressive treatment is indicated. Delayed initiation of immunosuppressive treatment will result in further worsening of the patient's condition and a worse outcome. Early detection of symptoms of internal organ manifestations such as interstitial lung disease, myocarditis, or malignancy is also important in the treatment plan, because these lesions significantly affect survival. Treatment planning should also consider the long-term side effects of medication, for example, corticosteroid treatment itself is associated with myopathy.

### CORTICOSTEROIDS

Evidence from uncontrolled studies suggests that most patients with DM and PM respond to corticosteroid treatment, and as a result, corticosteroids are considered first-line therapy.<sup>134-136</sup>

The current standard of care is high-dose corticosteroids, starting with prednisone at 1 mg/kg/day with eventual taper to a minimal dose, anywhere from 4 weeks to several months after

initiation.<sup>135,136</sup> Patients with severe disease, such as ILD, dysphagia, or profound weakness, are typically started on 1g intravenous methylprednisolone per day for 3-5 days before switching to 1 mg/kg/day of prednisone for several months.<sup>135,136</sup> Many patients feel better immediately after starting corticosteroids, however strength improves over 2-3 months. In the case of 'steroid-responsive patients, the goal is to reduce the dose to the smallest, most effective amount. If there is no improvement after 3-6 months of prednisone or if the patient relapses while tapering, a second-line immunosuppressive agent should be added. Patients with other co-morbidities that will be exacerbated by corticosteroid use, such as hypertension, diabetes, osteoporosis, and obesity, should be started on a second-line agent early in their disease course and subsequently have their prednisone tapered to a minimal effective dose. It is important to monitor for adverse events from chronic high dose corticosteroids. Treatment with calcium combined with vitamin D for bone protection and proton pump inhibitors for gastric mucosa protection should be considered to help minimize the adverse side effects of steroids.

#### SECOND-LINE TREATMENTS

Common second line choices include AZA, methotrexate, and IVIg. Other agents used in the treatment of IIM are mycophenolate mofetil, tacrolimus, rituximab, cyclosporine, and cyclophosphamide. Second-line treatments can be added several months after initiating corticosteroids for 'non-responders' or as a steroid-sparing agent. Second-line agents may also be started immediately in patients with rapidly progressive disease, patients with respiratory muscle failure or dysphagia, and in patients with extra-muscular involvement such as ILD.<sup>31</sup> Several agents that are effective for myositis with ILD refractory to corticosteroids include mycophenolate mofetil,<sup>137</sup> cyclosporine,<sup>138</sup> and tacrolimus.<sup>139</sup> Use of second line agents for their steroid-sparing effect is based on empirical data, and their use as a sole treatment seems to

provide little benefit.<sup>135</sup> According to current practice parameters, empiric use of immunosuppressive therapy for patients with “refractory” IIM is appropriate,<sup>36</sup> however, there is no universal agreement on the definition of ‘refractory’ disease. Proposed definitions and management strategies of refractory IIM have been reviewed recently.<sup>140</sup> “Definite refractory” disease was defined as failure to induce remission after an adequate 3-month trial of steroid therapy. To be considered “chronic refractory disease” IIM patients must have also failed to improve after at least 1 second-line immunosuppressive or IVIg therapy. Common immunosuppressive and immunomodulating therapies are summarized in table 2.<sup>135</sup> AZA is usually effective after 4 to 8 months and peaks at 1-2 years, so patience is required before concluding the drug is not effective. The efficacy of methotrexate is typically seen at the 15mg/week dose, and prophylactic supplementation with folic acid is required. Methotrexate may cause pneumonitis and is therefore not recommended in patients with ILD or anti-Jo-1 antibodies. Co-administration of AZA and methotrexate is helpful for severe disease.<sup>141</sup> Cyclosporine is useful in newly diagnosed PM and DM. While benefits can be seen in under 6 months and it acts faster than both AZA and mycophenolate mofetil, cyclosporine is potentially more toxic. IVIg has been studied best in DM with a randomized placebo controlled trial with optional crossover that showed IVIg given at 2 g/kg monthly for 3 months was effective in 9 of 12 treatment-resistant DM patients.<sup>142</sup> Although prospective controlled trials are lacking, IVIg is generally believed to be effective in PM.<sup>143</sup>

#### NEW BIOLOGICAL THERAPIES

Rituximab is a monoclonal antibody directed against CD20, a surface marker of B cells. It has been used as a third line agent for treating patients with IIM but there is increasing evidence for the use of rituximab in inflammatory myopathies, specifically those associated with

MSAs. In 2007, rituximab was used successfully in 2 cases of treatment refractory anti Jo-1 myositis (unpublished observation, Mozaffar 2007). Patients were followed for approximately 2 years after treatment with rituximab and were noted to have an improvement in strength with a concomitant reduction in Jo-1 antibody titers and serum CK levels. Subsequently, 2 published reports demonstrated efficacy of rituximab therapy in anti Jo-1 myositis.<sup>102,144</sup> One described a case of life threatening anti-synthetase syndrome in a patient with concurrent anti-Jo-1 and anti-Ro/SSA antibodies with severe interstitial lung disease.<sup>102</sup> The patient's condition was refractory to glucocorticoids and cyclophosphamide but rapidly improved after treatment with 2 infusions of rituximab. The other study followed 11 patients with anti Jo-1 antibodies associated with antisynthetase syndrome with ILD and demonstrated that ILD improved or stabilized with rituximab infusion in 7 of 11 patients.<sup>144</sup> Rituximab has also been shown to have efficacy in patients with severe, treatment refractory myositis with anti-SRP antibodies.<sup>145</sup> Rituximab was recently studied in a large multicenter clinical trial involving 200 DM, JDM, and PM patients with refractory disease.<sup>101</sup> After receiving rituximab, 83% of patients (78% PM, 82% DM, 83% JDM) met the definition of improvement according to IMACS criteria during the course of the trial.<sup>101</sup> The correlation of clinical response with antibody titers illustrated by these studies suggests antibody titers may provide an excellent tool for prognostication, diagnosis, monitoring treatment efficacy, and making therapeutic decisions.

Abatacept is a soluble fusion protein that inhibits binding of co-stimulatory protein CD28 on T-cells, thereby reducing dendritic cell-mediated T-cell activation. Currently, there is a phase II, randomized, single blind study of abatacept in adults with treatment refractive DM and PM.

Anakinra is a recombinant, non-glycosylated form of human IL-1 $\alpha$  receptor that competitively inhibits binding of IL-1 to the IL-1 receptor. It has been approved for treatment of

moderate-to-severe, active, refractory rheumatoid arthritis. A pilot study of 15 patients with refractory myositis treated with anakinra showed improvement in IMACS disease activity score and muscle performance in 7/15 patients (3 DM, 3 PM, 1 sIBM), while 5 patients remained unchanged, and 3 patients worsened.<sup>146</sup>

TNF blockers, infliximab, etanercept, and adalimumab have not been consistently effective in the treatment of IIMs and have produced conflicting results.<sup>147,148</sup>

Sifalimumab is a human anti-IFN $\alpha$  monoclonal antibody that was studied recently in DM and PM.<sup>149</sup> Type I IFN-inducible transcripts and proteins were suppressed in blood and muscle of those treated, and a positive correlation was noted between type 1 IFN gene signature suppression and the degree of improvement from baseline on manual muscle testing scores.<sup>149</sup> A phase II open-label study is currently evaluating the long-term safety of a 600mg infusion of sifalimumab in adults with active systemic lupus erythematosus, DM, or PM who were previously treated in a clinical trial with sifalimumab.

## PHYSICAL THERAPY

Exercise and physical and occupational therapy are important components of treatment for patients with IIM.<sup>150</sup> Exercise has been shown to be safe and improve aerobic capacity and muscle strength in IIM patients.<sup>151</sup> In a randomized controlled trial of aerobic exercise in DM and PM, patient isometric peak force, exercise tolerance, and anaerobic threshold intensity improved, while muscle enzymes remained unchanged.<sup>151</sup> Resistance exercises have also been reported to be safe in patients with active PM or DM 1 to 3 months into their treatment.<sup>150</sup> Significant improvements in muscle strength and function without adverse events have also been demonstrated in patients with chronic DM and PM following a 9-week intensive strength-

training program.<sup>152</sup> In severe cases of IIM, passive range of motion exercises may be prescribed until strength and CK start to improve, at which point a strengthening program can be started.

#### RECOMMENDED APPROACH TO TREATMENT

The choice of treatment and the sequence in which various drugs are used is not evidence based, and it is often influenced by personal experience. The general experience of our clinic is to start with corticosteroids. We do not always start with a steroid sparing agent, but instead add 1 only if patients show dependence on a prednisone dose greater than 15 mg a day. If corticosteroids are inadequate, we add another immunosuppressant, often methotrexate or AZA. Methotrexate has become our steroid sparing agent of choice, as it is better tolerated and beneficial effects can be seen in 2-3 months. If these treatments are not working, especially in DM, we start rituximab. IVIg is an important therapeutic modality; we have used it successfully for monotherapy of DM and PM in a number of young individuals (to avoid long term side effects of steroids), individuals who are either pregnant or have contraindications to steroids (such as uncontrolled diabetes), or as a short-term measure to rapidly decrease the dose of steroids (if excessive steroid related side effects are occurring). We also give a trial of IVIg in patients who are developing dysphagia with DM. Figure 7 summarizes our personal recommendations for treatment of PM and DM.

#### PROGNOSIS

Early case series revealed a very poor prognosis for PM/DM, with 5-year survival rates lower than 50%.<sup>153</sup> PM and DM are still considered to have a poor prognosis; a 2012 United States series of 160 PM/DM patients demonstrated a 10 year survival rate of 62%.<sup>154</sup> In a Finnish study, the standardized mortality ratio among PM/DM patients compared to the general population was 2.92.<sup>155</sup> Deaths are mainly due to cardiac (22%) and pulmonary (22%)

complications, infections (15%), and cancer (11%).<sup>154</sup> The lung and digestive tract were the most common sites for fatal infections.<sup>156</sup> DM patients have a greater risk of dying from cancer than PM patients.<sup>155</sup> The cause of death in PM/DM changes with disease duration. Pulmonary complications are a frequent cause of death within the first 12 months of disease, while cardiac complications are a more common cause of death 5 years after PM/DM is diagnosed.<sup>32</sup> Approximately 20% of corticosteroid treated PM/DM patients will achieve remission and be off all treatment within a 5 year follow-up period, whereas 80% will experience a chronic continuous disease course requiring ongoing immunosuppressive treatment.<sup>157</sup>

It is important to be aware of the many prognostic factors for PM/DM to help guide care. Age is the most important predictor of mortality in PM/DM, as patients over 64 years old had a mortality rate of 47.8% compared to the 9.1% seen in younger patients.<sup>158</sup> Male gender, non-Caucasian race, cancer, esophageal involvement, respiratory involvement, and cardiac dysfunction, are predictors of poor prognosis in PM/DM.<sup>32,33,154,155</sup> Many of the MSAs are also predictive of prognosis and have been discussed.

## CONCLUSION

PM and DM are IIMs, each with unique clinical features, histopathology, response to treatment and prognosis. Although clinical evaluation, EMG, and muscle biopsy permit an accurate diagnosis of inflammatory myopathy, controversy exists regarding the classification of IIMs that will likely be resolved only by a deeper understanding of the pathogenesis of these disorders. Improved alignment of clinical, laboratory, and histopathological data will facilitate the development of more efficacious treatments.

## FIGURE LEGENDS

Figure 1. Systemic and dermatologic findings of myositis. (A) Head drop seen in a patient with anti-SRP-associated myositis. (B) Gottron papules are symmetric macular violaceous erythematous lesions overlying the dorsal aspect of the interphalangeal or metacarpophalangeal joints in DM. Photograph used for panel A is courtesy of Dr. George Lawry

Figure 2. Systemic and dermatologic findings of myositis. (A) Gottron sign, an erythematous rash over the extensor surfaces of the elbows, knuckles, knees, and ankles in DM. (B) The V sign, an erythematous V-shaped discoloration that occurs on the neck and upper chest in DM.

Figure 3. Systemic and dermatologic findings of myositis. (A) Mechanic Hands are hyperkeratotic lesions associated with DM. (B) Nail fold telangiectasias and periungual erythema in patient with DM. (C) The erythematous malar rash, also known as a butterfly rash, is a characteristic finding in DM. Photograph used for Panel A is courtesy of Dr. George Lawry.

Figure 4. Key myopathological features of DM. (A) ATPase stain and (B) Gomori trichrome stain show perifascicular atrophy. (C) Alkaline phosphatase staining (blue) shows primary involvement of perimysial connective tissue.

Figure 5. Key myopathological features of PM. (A) Muscle from a patient with PM, demonstrating fiber size variation with rounded atrophic fibers, increased internal nuclei, widespread fiber necrosis with phagocytosis, basophilic fibers undergoing regeneration, and perivascular and endomysial inflammatory infiltrates with mononuclear cell invasion of non-



necrotic myofibers (H&E). (B) Immunohistochemical stain of CD3 identifying T-cells invading the endomysium from a patient with PM. (C) Myopathological features common to both PM and sIBM, including fiber size variability, myofiber necrosis with phagocytosis, regenerating fibers, and perivascular and endomysial inflammatory cell infiltrates (H&E).

Figure 6. Histological features differentiating sIBM from PM. (A) H&E and (B) Gomori trichrome stains show rimmed vacuoles in sIBM. (C) Succinate dehydrogenase stain demonstrating increased irregular uptake of blue dye in fibers that would be considered ragged red fibers on Gomori-Trichrome, and (D) cytochrome oxidase (COX) stain demonstrating several COX-negative fibers. These findings are predictive of steroid non-responsiveness and a clinical picture of sIBM. In addition a number of COX-positive fibers are seen, consistent with ragged red fibers.

Figure 7. Proposed algorithm for treatment of PM, DM, and IMNM. CK, creatine kinase; IVIg, intravenous immunoglobulin.

Table 1. Definite PM: all 1-4. Probable PM: 3 of 1-4. Possible PM: 2 of 1-4. Definite DM: 5 + 3 of 1-4. Probable DM: 5+2 of 1-4. Possible DM: 5 + 1 of 1-4.

Table 2. Dosing and monitoring based on our clinic practice and Dalakas M. Immunotherapy of inflammatory myopathies: practical approach and future prospects. Current treatment options in neurology 2011;13:311-323. BUN, blood urea nitrogen; CBC, complete blood count; Cr, Creatinine; IM, intramuscular; IV, intravenous; LFT, Liver function test; PO, oral;

Supplemental Table 1. Clinical-serologic associations drawn from: Mammen A. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. Nature reviews Neurology 2011;7:343-354, Mohassel P, Mammen A. Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies: A review. Muscle & nerve 2013, and Larman H, Salajegheh M, Nazareno R, Lam T, Sauld J, Steen H, Kong S, Pinkus J, Amato A, Elledge S, Greenberg S. Cytosolic 5'-nucleotidase 1A autoimmunity in sporadic inclusion body myositis. Annals of neurology 2013;73:408-418. HMGCR, 3-Hydroxy-3-methylglutaryl coenzyme A reductase; MDA, Melanoma differentiation-associated gene; SUMO, small ubiquitin-like modifier; TIF, transcriptional intermediary factor;

**ABBREVIATIONS**

|         |   |
|---------|---|
| ADM     | Amyopathic dermatomyositis                      |
| ALT     | Alanine aminotransferase                        |
| AST     | Aspartate aminotransferase                      |
| ATP     | Adenosine triphosphate                          |
| ATPase  | Adenosine triphosphatase                        |
| AZA     | Azathioprine                                    |
| CD      | Cluster of differentiation                      |
| CK      | Creatine kinase                                 |
| COX     | Cytochrome oxidase                              |
| DC      | Dendritic cell                                  |
| DM      | Dermatomyositis                                 |
| EMG     | Electromyography                                |
| ENMC    | European Neuromuscular Center                   |
| GGT     | $\gamma$ -glutamyl transpeptidase               |
| H&E     | Hematoxylin and Eosin                           |
| HIF-1-a | hypoxia-inducible factor 1-a                    |
| HLA     | Human leukocyte antigen                         |
| HMGB1   | High mobility group protein 1                   |
| HMGR    | 3-Hydroxy-3-methylglutaryl-coenzyme A reductase |
| IFN     | Interferon                                      |
| IM      | Idiopathic inflammatory myopathy                |
| IL      | Interleukin                                     |

|               |   |
|---------------|---|
| ILD           | Interstitial lung disease                                       |
| IMACS         | International myositis assessment and clinical studies          |
| IMNM          | Immune mediated necrotizing myopathy                            |
| IVIg          | Intravenous immunoglobulin                                      |
| JDM           | Juvenile Dermatomyositis  |
| MAA           | Myositis-associated autoantibody                                |
| MAC           | Membrane attack complex   |
| MDA5          | Melanoma differentiation-associated gene 5                      |
| MHC           | Major histocompatibility complex                                |
| MSA           | Myositis specific autoantibody                                  |
| MUAP          | Motor unit action potentials                                    |
| MxA           | Myxovirus resistance protein A                                  |
| NADH-TR       | Reduced nicotinamide adenine dinucleotide tetrazolium reductase |
| NF $\kappa$ B | Nuclear Factor- $\kappa$ B                                      |
| NT5C1A        | Cytosolic 5-nucleotidase 1A                                     |
| NXP2          | Nuclear matrix protein 2  |
| PAS           | Periodic acid-Schiff  |
| PDC           | Plasmacytoid dendritic cell                                     |
| PM            | Polymyositis  |
| RNA           | Ribonucleic acid  |
| SDH           | Succinate dehydrogenase   |
| sIBM          | Sporadic inclusion body myositis                                |
| snRNP         | Small nuclear ribonucleoprotein                                 |

|              |   |
|--------------|---|
| SRP          | Signal recognition particle                       |
| STIR         | Short tau inversion recovery                      |
| SUMO-1       | Small ubiquitin-like modifier activating enzyme 1 |
| TGF- $\beta$ | Tumor growth factor – Beta                        |
| TIF          | Transcriptional intermediary factor               |
| TNF          | Tumor necrosis factor                             |

Accepted Article

Table 1. Bohan and Peter Diagnostic Criteria for Dermatomyositis and Polymyositis.<sup>3,4</sup>

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

**Table 2. Common Immunosuppressive and Immunomodulating Therapies.**<sup>135</sup>

| Drug                    | Route | Dose   | Side Effects   | Monitoring   |
|-------------------------|-------|--|--|--|
| Azathioprine            | PO    | 1.5-3 mg/kg/day  | myelosuppression, hepatotoxicity, malignancy, teratogenicity, alopecia, flu like hypersensitivity reaction         | Thiopurine methyltransferase enzyme activity prior to initiation. Weekly CBC and LFTs until stable dose reached. |
| Cyclosporine            | PO    | 3-6 mg/kg/day  | hypertension, nephrotoxicity, hepatotoxicity, myelosuppression   | Blood pressure, BUN, Cr, and LFTs  |
| Cyclophosphamide        | PO    | 0.7-1g/m <sup>2</sup> for 1 day/month for 5-6 months.                      | vomiting, alopecia, hemorrhagic cystitis, myelosuppression, malignancy, sterility                                  | Urinalysis, monthly CBC  |
| IVIg                    | IV    | 2g/kg over 2-5 days.<br>Then 0.4-2 mg/kg/month                             | Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke. | Heart rate, blood pressure, kidney function  |
| Methotrexate            | PO    | 7.5mg/week for 2 weeks.<br>Titrate to max<br>25mg/week in 2.5mg increments | Hepatotoxicity, myelosuppression, alopecia, pneumonitis, teratogenicity, malignancy, renal insufficiency.          | Weekly CBC and LFT x 1 month, monthly for 6 months, every 3 months remaining duration of treatment.              |
| Methotrexate            | IM/IV | 0.4- 0.8 mg/kg/week.<br>Increase 5mg/week to max 25 mg/week.               | Same as PO   | Same as PO   |
| Methylprednisolone      | IV    | 1g/day for 3-5 days<br>followed by prednisone                              | arrythmia, flushing, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection               | Heart rate, blood pressure, serum glucose, potassium   |
| Mycopenolate<br>Mofetil | PO    | 2-3g/day   | Hepatotoxicity, myelosuppression, nausea, diarrhea.  | Weekly CBC x 1 month, twice monthly for 2nd & 3rd month, and monthly thereafter.                                 |

**Table 2. Common Immunosuppressive and Immunomodulating Therapies**

| Drug       | Route | Dose   | Side Effects  | Monitoring  |
|------------|-------|--|---|---|
| Prednisone | PO    | 1 mg/kg/day and taper<br>after minimum 4 weeks   | hypertension, weight gain,<br>hyperglycemia, hypokalemia,<br>cataracts, gastric irritation,<br>osteoporosis, infection, aseptic<br>femoral necrosis | Weight, blood pressure, serum<br>glucose, serum potassium,<br>cataracts |
| Rituximab  | IV    | 750-1000 mg/m <sup>2</sup> and<br>repeated in 2 weeks.<br>Course may be repeated<br>at 7-9 months. | Infusion reaction, infection,<br>progressive multifocal<br>leukoencephalopathy  | B cell count prior to<br>subsequent courses                             |
| Tacrolimus | PO    | 0.1-0.2 mg/kg/day in two<br>divided doses.   | hypertension, hepatotoxicity,<br>nephrotoxicity, hirsutism, tremor,<br>gum hyperplasia, teratogenicity.   | Blood pressure, BUN, Cr,<br>LFTs  |



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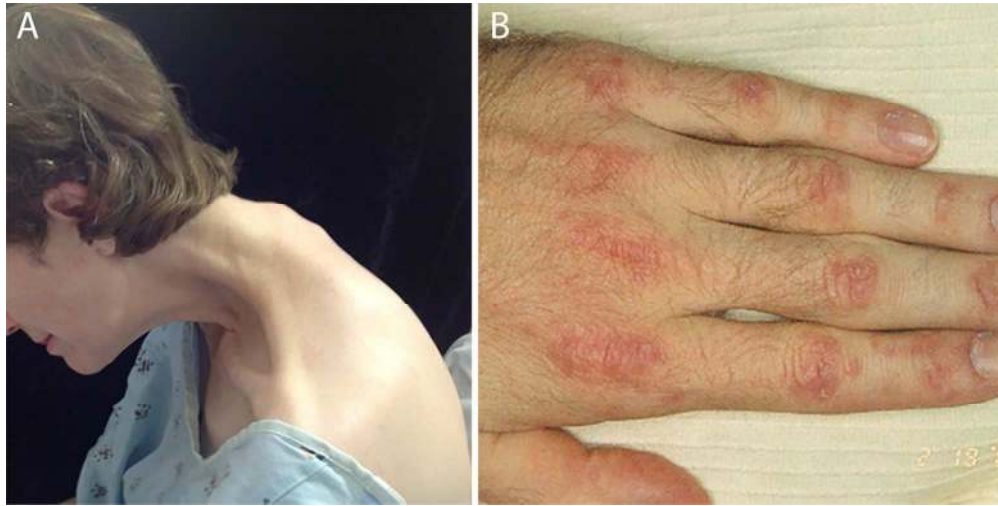


Figure 1. Systemic and dermatologic findings of myositis. (A) Neck drop seen in a patient with anti-SRP associated myositis. (B) Gottron papules are symmetric macular violaceous erythema overlying the dorsal aspect of the interphalangeal or metacarpophalangeal joints in DM. Photograph used for panel A is courtesy of Dr. George Lawry  
129x65mm (300 x 300 DPI)

Accepted



Figure 2. Systemic and dermatologic findings of myositis. (A) Gottron sign, an erythematous rash over the extensor surfaces of the elbows, knuckles, knees, and ankles in DM. (B) The V sign, an erythematous V shaped discoloration that occurs on the neck and upper chest in DM.  
129x75mm (300 x 300 DPI)

Accepted



Figure 3. Systemic and dermatologic findings of myositis. (A) Mechanic's Hands are hyperkeratotic lesions associated with DM. (B) Nail fold telangiectasias and periungual erythema in patient with DM. (C) The erythematous malar rash, also known as a butterfly rash, is a characteristic finding in DM. Photograph used for Panel A is courtesy of Dr. George Lawry.  
129x124mm (300 x 300 DPI)

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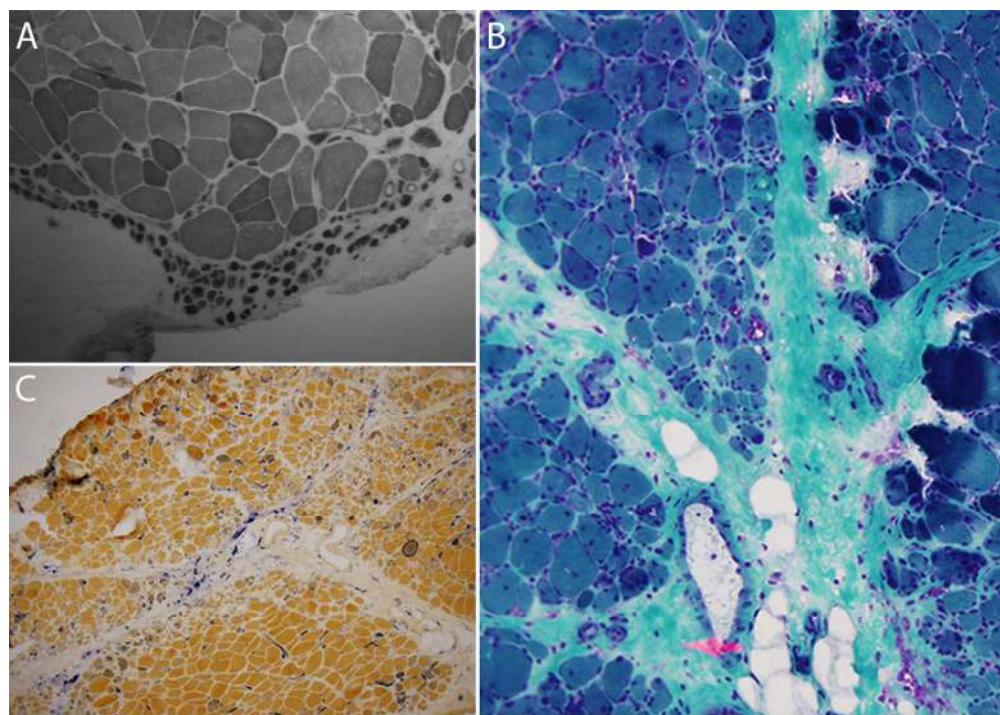


Figure 4. Key myopathological features of DM. (A) ATPase stain and (B) Gomori trichrome stain illustrating perifascicular atrophy in DM. (C) Alkaline phosphatase staining (blue) of DM muscle illustrating primary involvement of perimysial connective tissue.  
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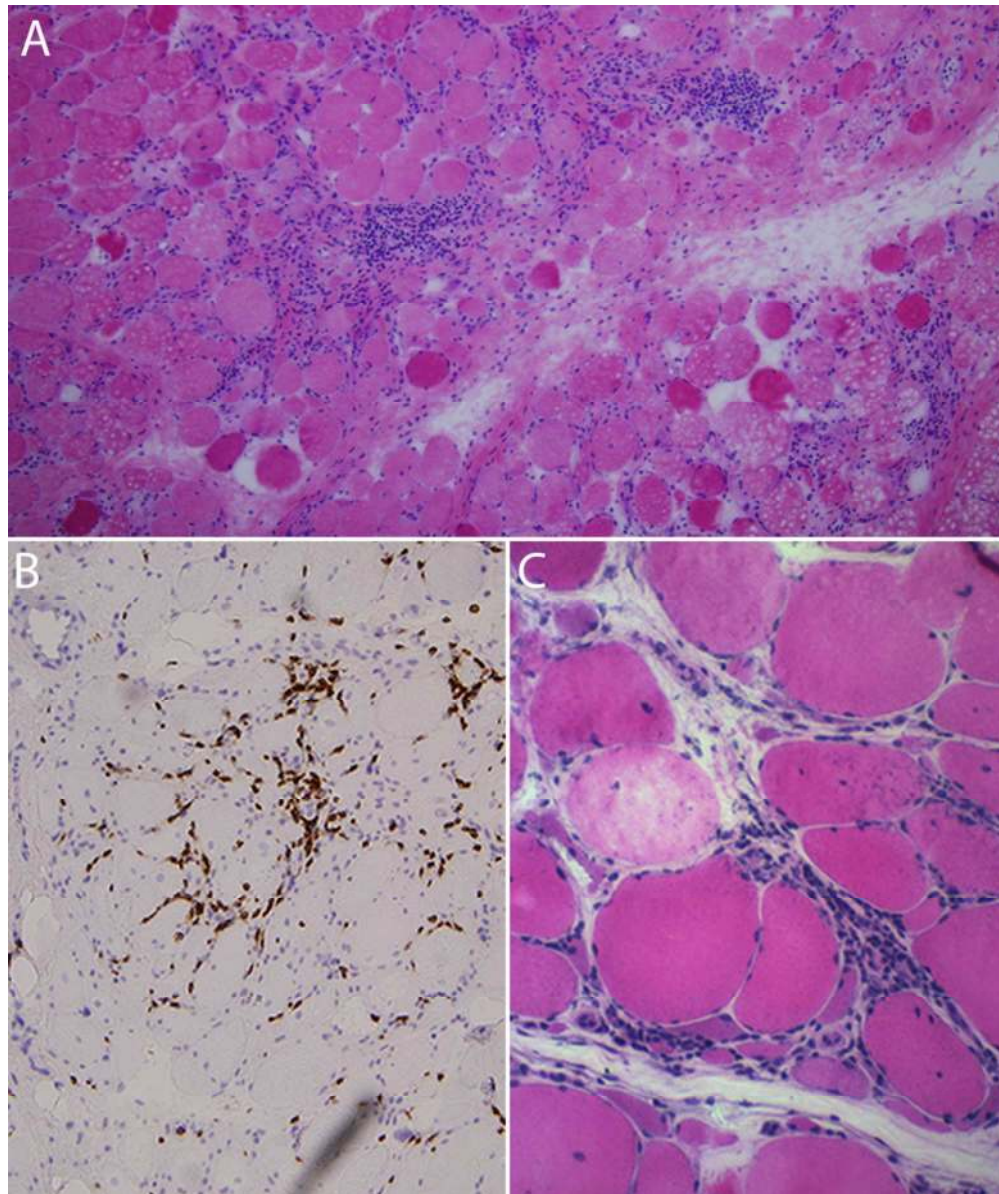


Figure 5. Key myopathological features of PM. (A) H&E staining of skeletal muscle from patient with PM, demonstrating fiber size variation with rounded atrophic fibers, increased internal nuclei, widespread fiber necrosis with phagocytosis, basophilic fibers undergoing regeneration, perivascular and endomysial inflammatory infiltrates with mononuclear cell invasion of non-necrotic myofibers. (B) Immunohistochemical stain of CD3 identifying T-cells invading the endomysium of muscle from a patient with PM. (C) H&E staining showing myopathological features common to both PM and sIBM, including fiber size variability, myofiber necrosis with phagocytosis, regenerating fibers, and perivascular and endomysial inflammatory cell infiltrates.

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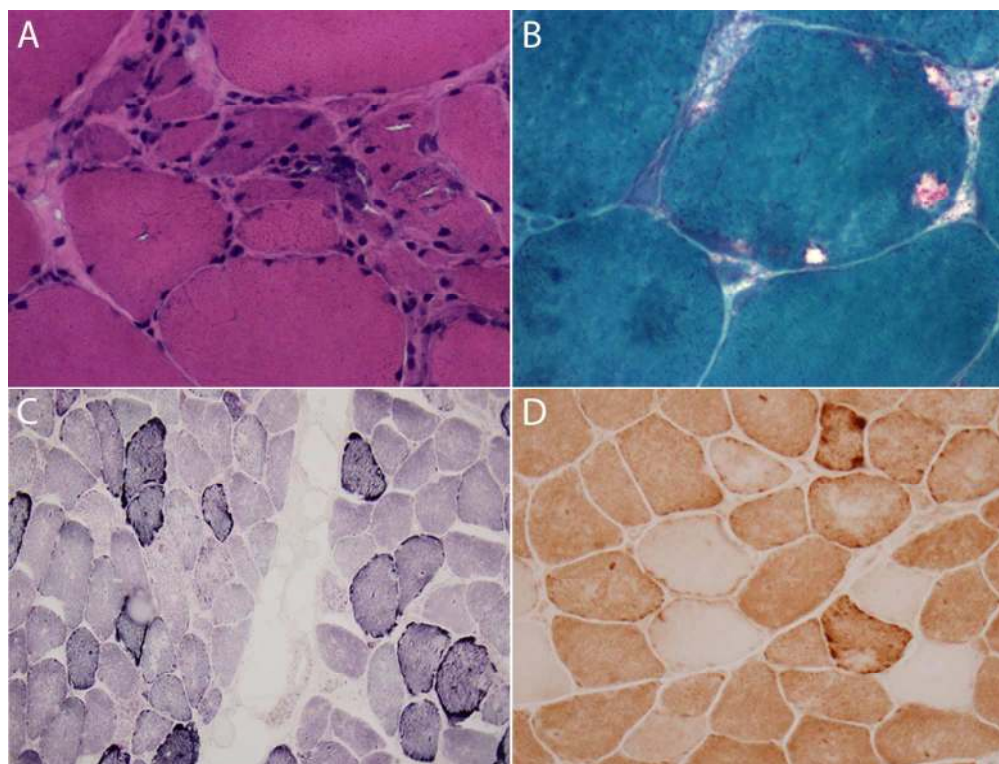
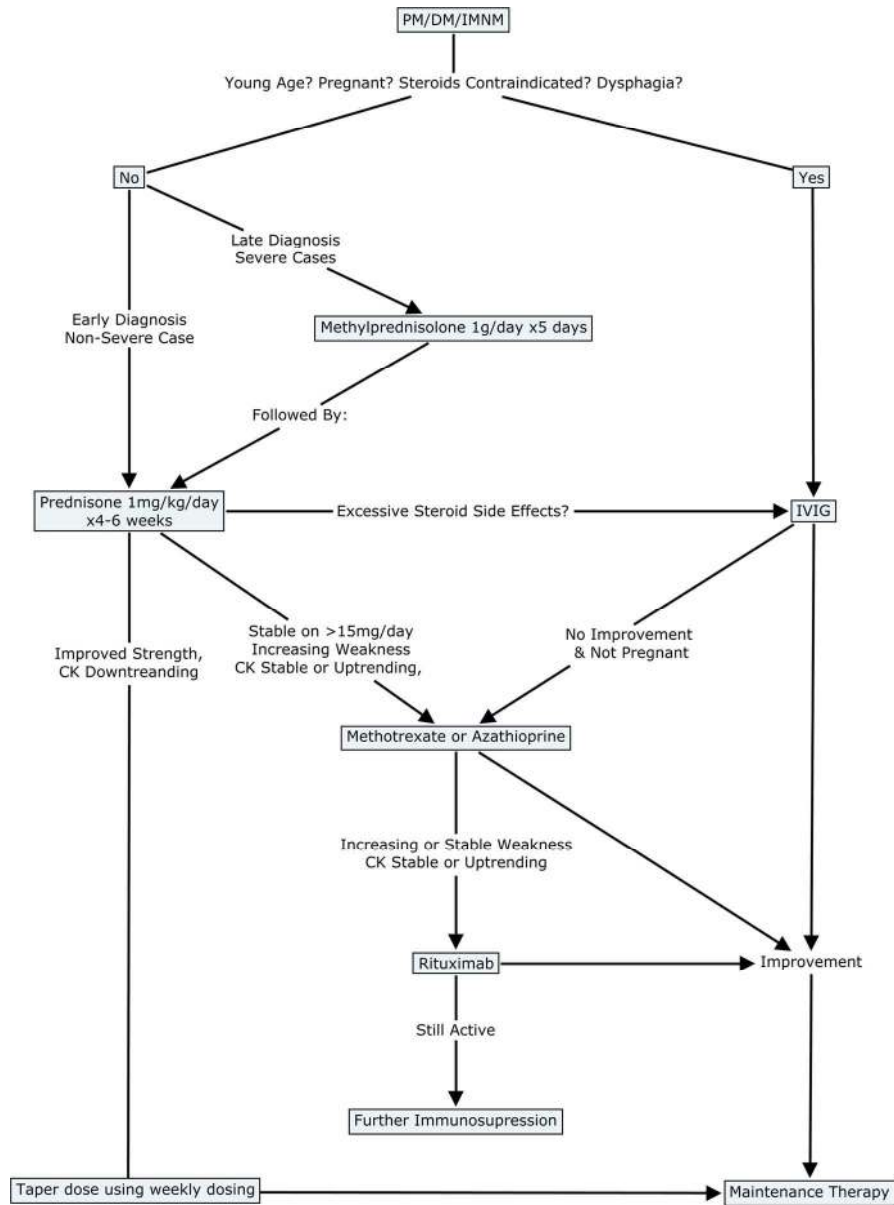


Figure 6. Histological features differentiating sIBM from PM. (A) H&E and (B) Gomori trichrome stains demonstrating rimmed vacuoles seen in sIBM. (C) Succinate dehydrogenase stain demonstrating increased irregular uptake of blue dye in ragged red fibers and (D) cytochrome oxidase (COX) stain demonstrating several COX negative fibers are predictive of steroid non-responsiveness and a clinical picture of sIBM. In addition a number of COX positive fibers are seen consistent with ragged red fibers.  
129x98mm (300 x 300 DPI)

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Proposed algorithm for treatment of PM, DM, and IMNM. CK, creatine kinase; IVIg, intravenous immunoglobulin.

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