Deciphering the Clinical Presentations, Pathogenesis, and Treatment of the Idiopathic Inflammatory Myopathies

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CASE PRESENTATION

An 11-year-old white girl developed scalp flaking and a red, pruritic facial rash, followed by scaling, palpable erythema over the knuckles, and erythema over her shoulders, arms, and legs. A reaction to poison ivy was initially diagnosed, but her rashes progressed despite treatment with topical ointments and antibiotics. At illness onset, the patient was experiencing stress due to the birth of a sister, and her rashes were noted to be exacerbated by sun exposure. By the time she was referred to a pediatric rheumatologist, she had developed progressive fatigue and experienced difficulty climbing stairs and carrying her school book bag. She was found to have mild proximal muscle weakness, a mildly elevated creatine kinase level of 270 U/L (to convert to µkat/L, multiply by 0.0167) and a positive antinuclear antibody at a dilution of 1 to 1280. Magnetic resonance imaging of the thigh muscle revealed diffuse increased muscle edema bilaterally on short tau inversion recovery images. Juvenile dermatomyositis was diagnosed.

Despite therapy with multiple immunosuppressive medications, including tacrolimus, cyclophosphamide, anti–tumor necrosis factor therapies, and rituximab, disease activity increased with attempted tapering of therapy in the girl. She continues to have persistent skin and muscle disease, which she has now had for more than a decade and includes photosensitive facial rashes (FIGURE 1), rashes in the V of the neck, rashes around the shoulders in the distribution of a shawl, widespread erythema, subcutaneous edema, and severe nailfold and gingival capillary changes. She was recently found to have the anti-p155 autoantibody that is directed against transcriptional intermediary factor 1 γ.

Diagnosis and Epidemiology of Idiopathic Inflammatory Myopathies

Myositis, a systemic autoimmune disease, is currently diagnosed by a combination of clinical and laboratory features, which include (1) the presence of symmetric, progressive muscle weakness of the shoulder and hip muscles; (2) elevated serum levels of muscle enzymes (including creatine kinase, aldolase, lactate dehydrogenase, and transaminases); (3) altered electrical activity on electromyography (consisting of polyphasic, short, and small motor-unit potentials, fibrillations, positive sharp waves, increased irritability, and high-frequency repetitive discharges); (4) myofiber degeneration and regeneration, chronic mononuclear cell infiltration, or perifascicular atrophy on muscle biopsy; and, (5) for dermatomyositis, scalp flaking and a red, pruritic facial rash, followed by scaling, palpable erythema over the knuckles, and erythema over her shoulders, arms, and legs. A reaction to poison ivy was initially diagnosed, but her rashes progressed despite treatment with topical ointments and antibiotics. At illness onset, the patient was experiencing stress due to the birth of a sister, and her rashes were noted to be exacerbated by sun exposure. By the time she was referred to a pediatric rheumatologist, she had developed progressive fatigue and experienced difficulty climbing stairs and carrying her school book bag. She was found to have mild proximal muscle weakness, a mildly elevated creatine kinase level of 270 U/L (to convert to µkat/L, multiply by 0.0167) and a positive antinuclear antibody at a dilution of 1 to 1280. Magnetic resonance imaging of the thigh muscle revealed diffuse increased muscle edema bilaterally on short tau inversion recovery images. Juvenile dermatomyositis was diagnosed.

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myositis, the presence of characteristic skin rashes, including the heliotrope rash (a red or purplish discoloration of the eyelids) or Gottron papules (raised erythematous plaques over the joint extensor surfaces). The presence of at least 3 of these clinical and laboratory features suggests that the patient has probable dermatomyositis or polymyositis; the presence of at least 4 clinical and laboratory features suggests that the patient has definite dermatomyositis or polymyositis. Characteristic skin rashes are required for a diagnosis of dermatomyositis. A collaborative myositis group clarified the requirement for a muscle biopsy in the absence of the characteristic skin rashes.

A diagnosis of myositis requires exclusion of a number of mimicking conditions. For patients presenting with weakness, the differential diagnosis includes muscular dystrophies, particularly limb-girdle and facioscapulohumeral dystrophies, metabolic and mitochondrial myopathies, endocrine myopathies (including thyroid disease), and drug-induced myopathies (http://www.neuro.wustl.edu/neuromuscular/index.html). For patients presenting with rash and weakness, a number of infectious myopathies and systemic autoimmune diseases must be considered. Many skin conditions, including psoriasis, eczema, and verrucae vulgaris can mimic the characteristic Gottron papules of dermatomyositis, and allergies can mimic the heliotrope rash.

Myositis syndromes are the most common causes of acquired muscle disease in adults, but are still rare disorders. The annual incidence of myositis is estimated to be 5 to 10 cases per million in adults and 1 to 5 cases per million in children; the estimated overall prevalence is 50 to 100 cases per million. Polymyositis and dermatomyositis peak in prevalence throughout childhood (mean age, 7 years) and in midlife (peak age, 30-50 years). Inclusion body myositis peaks after age 50 years. Epidemiological studies of US populations suggest that these disorders are increasing in frequency, perhaps due to environmental influences.

**Phenotypes and Their Importance**

Dermatomyositis is the predominant form of myositis seen in children (80%-85% of cases). In adults, about 35% to 50% of myositis cases are dermatomyositis. In children, polymyositis is seen in 2% to 8% of myositis cases, and myositis overlapping with another connective tissue disease constitutes 3% to 10% of childhood idiopathic inflammatory myopathy cases. In adults, these subgroups are more frequent, with polymyositis representing about 30% to 45% of adult idiopathic inflammatory myopathy cases and overlap myositis constituting approximately 20% of adult cases. Inclusion body myositis and cancer-associated myositis are unusual in children (<1%), and are more common among adult patients with inflammatory myopathy (10%-20%). Other phenotypes (based on pathological or clinical features, including macrophagic, eosinophilic, granulomatous, focal, and orbital myositis) are rare in both children and adults.

The clinical phenotypes differ in their key clinical features and prognoses. For example, polymyositis is characterized by moderate to severe weakness and a high frequency of interstitial lung (Figure 2A) and cardiac disease (including heart failure, arrhythmias, and ventricular dysfunction in ≤50% of patients), which negatively affect survival. Patients with adult or juvenile dermatomyositis have mild to moderate weakness and dystrophic calcification in approximately 25% of children, but less frequently in adults (Figure 2B). Other characteristic features of dermatomyositis include cutaneous and gastrointestinal tract ulcerations, which develop from underlying vasculopathy and tissue ischemia, and lipodystrophy (Figure 2C); both of which are more common in children. Survival ranges from 75% to 90% in patients with adult dermatomyositis and is greater than 95% in those with juvenile dermatomyositis. The risk of cancer in association with myositis is increased 2- to 4-fold, particularly in patients with adult dermatomyositis, and in males older than 50 years. Patients with myositis and cancer tend to have more severe weakness and rashes, lower levels of serum creatine kinase, and higher erythrocyte sedimentation rates. The associated malignancies are most commonly adenocarcinomas of the lungs, gastrointestinal tract, breast, and ovaries, as well as lymphoma, with a 5-year
survival rate of 60%. Patients with inclusion body myositis tend to be older men with slowly progressive proximal and distal weakness, which can be asymmetric and primarily involves the quadriceps and finger flexors, in addition to rapid development of muscle atrophy and frequent dysphagia. Although the 5-year survival rate is close

Table 1. Clinical and Autoantibody Phenotypes in Myositis

<table>
<thead>
<tr>
<th>Clinical or Autoantibody Phenotype</th>
<th>Demographics</th>
<th>Clinical Phenotype</th>
<th>Associated Clinical Features</th>
<th>Response to Therapy</th>
<th>Prognosis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyositis</td>
<td>Seen mainly in adults, peak onset at age 30-50 y</td>
<td>Absence of Gottron papules and heliotrope rashes</td>
<td>Moderate to severe weakness, interstitial lung disease, cardiac dysfunction, arrhythmias</td>
<td>Moderate</td>
<td>5-y survival in adults of 75%-94%</td>
<td>Miller, 2005; Love et al, 1991</td>
</tr>
<tr>
<td>Adult and juvenile dermatomyositis</td>
<td>Peak age at onset 7 y in children, 30-50 y in adults</td>
<td>Dermatomyositis is relatively more frequent in children than adults</td>
<td>Mild to moderate weakness, calcinosis; ulcerations, lipodystrophy in juvenile dermatomyositis</td>
<td>Good</td>
<td>5-y survival in adult dermatomyositis of 75%-90%; &gt;95% in juvenile dermatomyositis</td>
<td>Love et al, 1991; Feldman et al, 2008; Wedderburn and Rider, 2009</td>
</tr>
<tr>
<td>Cancer-associated myositis</td>
<td>Greater risk in males than females, age &gt;60 y, adenocarcinomas and lymphomas most common</td>
<td>Dermatomyositis more frequent than polymyositis</td>
<td>Severe weakness and rashes, high erythrocyte sedimentation rate, low creatine kinase</td>
<td>Variable</td>
<td>5-y survival in adults of 60%-66%</td>
<td>Hill et al, 2001; Madan et al, 2009</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Seen mainly in older white men</td>
<td>NA</td>
<td>Asymmetric proximal and distal weakness, early thigh atrophy, finger flexor weakness, dysphagia</td>
<td>Poor</td>
<td>5-y survival of 100%, but much functional disability</td>
<td>Needham and Mastaglia, 2007</td>
</tr>
<tr>
<td>Antisynthetase autoantibodies</td>
<td>Seen mainly in adults; in 25% of patients with myositis</td>
<td>Polymyositis, adult and juvenile dermatomyositis, overlap myositis</td>
<td>Interstitial lung disease, arthritis, fevers, Raynaud phenomenon, mechanic’s hands</td>
<td>Moderate</td>
<td>5-y survival in adults of 75%</td>
<td>Love et al, 1991</td>
</tr>
<tr>
<td>Anti–signal recognition particle autoantibodies</td>
<td>Seen in 3%-5% of patients with myositis</td>
<td>Polymyositis</td>
<td>Acute, severe proximal, and distal weakness, myalgias, cardiac involvement</td>
<td>Poor</td>
<td>5-y survival in adults of 20%</td>
<td>Love et al, 1991; Kao et al, 2004; Wedderburn and Rider, 2009</td>
</tr>
<tr>
<td>Anti-Mi-2 autoantibodies</td>
<td>Seen in 6% of patients with myositis</td>
<td>Adult and juvenile dermatomyositis</td>
<td>Mild to moderate weakness, dermatomyositis rashes, V and shawl rashes, cuticular overgrowth</td>
<td>Good</td>
<td>5-y survival in adults of 90%</td>
<td>Love et al, 1991</td>
</tr>
<tr>
<td>Anti-p155 (TIF-1γ) autoantibodies</td>
<td>Seen in 23%-29% of patients with dermatomyositis</td>
<td>Adult and juvenile dermatomyositis, overlap myositis with dermatomyositis, cancer-associated dermatomyositis</td>
<td>Moderate to severe weakness, V and shawl rashes, erythrodema, ulcers, edema, generalized lipodystrophy</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Gunawardena et al, 2009; Wedderburn and Rider, 2009</td>
</tr>
<tr>
<td>Anti-MJ (NXP-2) autoantibodies</td>
<td>Seen in 13%-23% of patients with dermatomyositis</td>
<td>Adult and juvenile dermatomyositis</td>
<td>Calcinosis, joint contractures, no trunk rash</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Gunawardena et al, 2009; Wedderburn and Rider, 2009</td>
</tr>
<tr>
<td>Anti-CADM-140 (MDA-5) autoantibodies</td>
<td>Reported in Japanese patients</td>
<td>Amyopathic dermatomyositis and other dermatomyositis</td>
<td>Rapidly progressive interstitial lung disease</td>
<td>Unknown</td>
<td>Unknown, but &gt;50% mortality in reported series</td>
<td>Sato et al, 2009</td>
</tr>
</tbody>
</table>

Abbreviations: MDA-5, melanoma differentiation–associated gene 5; NA, data not applicable; NXP-2, nuclear matrix protein 2; TIF-1γ, transcriptional intermediary factor 1 γ. 

Each clinical and autoantibody group is mutually exclusive. 

Mechanics’ hands are defined as hyperkeratosis on the palmar or lateral surfaces of the fingers, which can include cracking, fissuring, and scaling.
to 100%, many of these patients develop severe functional impairment and become dependent on a wheelchair. The heterogeneity of these disorders can be decreased by clustering patients using clinical and pathological features, and by the presence of certain autoantibodies. The myositis autoantibodies have been defined by their capacity to immunoprecipitate characteristic proteins or RNAs. New solid, phase-based methods have not been validated. Immunoprecipitation-Western blotting or immunoprecipitation-immunodepletion can detect autoantigens of lower abundance, such as the proteins targeted by the recently recognized p155 and MJ autoantibodies. Only a few commercial laboratories perform validated immunoprecipitation and immunoprecipitation-blotting assays for these autoantibodies.

Patients with anti–aminoacyl-transfer RNA (tRNA) synthetase autoantibodies (25% of adults and 5% of juvenile-onset cases) have a high frequency of moderate to severe myositis that is associated with characteristic extramuscular manifestations, which include interstitial lung disease, low-grade fevers, arthritis, Raynaud phenomenon, and mechanic’s hands (hyperkeratosis on the palmar or lateral surfaces of the fingers, which can include cracking, fissuring, and scaling). The most common of these autoantibodies is called the anti-Jo-1 autoantibody, which is directed against histidyl-tRNA synthetase. However, 5 other anti–aminoacyl-tRNA synthetases are targeted in myositis, and other autoantibodies, such as those to alanyl- and threonyl-tRNA synthetase, have been seen in association with idiopathic interstitial lung disease in the absence of myositis. Patients with anti–signal recognition particle autoantibodies tend to have an acute onset of severe polymyositis involving both proximal and distal muscle groups, and a high frequency of myocarditis and arrhythmias that negatively impact morbidity and mortality; many of these patients become dependent on a wheelchair and require extensive rehabilitation. Anti–Mi-2 autoantibodies (in approximately 6% of patients) occur exclusively in patients with dermatomyositis and are associated with mild muscle involvement, rashes in the V region of the neck and over the shoulders in a shawl distribution, and cuticular overgrowth.

Children with dermatomyositis have been found frequently to have anti-p155 or anti-MJ autoantibodies, which account for a large proportion of the autoantibody phenotypes associated with juvenile dermatomyositis. Anti-p155 autoantibodies, which target transcriptional intermediary factor 1, have been identified in up to 30% of patients with dermatomyositis and juvenile dermatomyositis, and in up to 75% of patients with dermatomyositis and malignancy. Data remain limited on the clinical phenotype associated with this autoantibody, but moderate to severe muscle weakness with classic dermatomyositis skin rashes, as well as more severe cutaneous involvement with a high frequency of ulcerations, erythoderma, subcutaneous edema, and generalized lipodystrophy (Figure 2C).

Figure 2. Characteristic Findings Associated With Clinical and Autoantibody Phenotypes in Myositis

A, Interstitial lung disease, defined by high-resolution computed tomographic (CT) scanning, is seen frequently in patients with polymyositis, as well as with the antisynthetase autoantibody phenotype. More recently, rapidly progressive interstitial lung disease has been associated with the anti–CADM-140 autoantibody. The chest CT scan depicted is from a 55-year-old female patient with anti–Jo-1 autoantibodies and interstitial lung disease. B, Dystrophic calcification around the elbow and forearm of a 10.5-year-old girl with juvenile dermatomyositis and anti-MJ autoantibodies. Anti-MJ autoantibodies are seen in up to 25% of patients with juvenile-onset dermatomyositis and less frequently in patients with adult-onset disease. Calcinosis is present in more than 60% of patients with the anti-MJ autoantibody phenotype. C, Lipodystrophy (loss of subcutaneous fat with frequent insulin resistance, diabetes, and hypertriglyceridemia) is associated with juvenile-onset dermatomyositis. Generalized lipodystrophy (a widespread loss of fat from the trunk and extremities), has been associated with anti-p155 autoantibodies. A loss of fat from the arm is seen in this 20-year-old woman with juvenile-onset dermatomyositis since age 8 years, who has anti-p155 autoantibodies and lipodystrophy.
have been seen frequently. Anti-MJ autoantibodies, which have been found to target the nuclear matrix protein 2 (NXP2), have been seen in up to 25% of patients with adult or juvenile dermatomyositis and are associated with a high frequency of calcinosis (Figure 2B), joint contractures, arthritis, and an absence of truncal rashes. A third emerging phenotype is associated with anti-CADM-140 autoantibodies, which are directed against an RNA helicase known as melanoma differentiation-associated gene 5 (MDA-5); this phenotype has been identified mainly in Japanese patients with amyopathic dermatomyositis and is associated with rapidly progressive interstitial lung disease (Figure 2A).

Pathogenesis
By definition, the causes of the idiopathic inflammatory myopathies remain unknown; however, data from similar autoimmune diseases support the hypothesis that these conditions result from chronic immune activation after exposure to environmental risk factors in individuals with a predisposing genetic background.

Genetic risk factors include polymorphisms of many genes that regulate responses to environmental agents, particularly human leukocyte antigen (HLA), and cytokine and immunoglobulin genes (Table 2). Specific genes at polymorphic loci, such as HLA DRB1*0301, TNF-α-308A, and Gm 3 23 5,13, are risk factors for all of the major clinical groups. Other alleles are specific to particular autoantibody phenotypes, and the genetic associations often are stronger with particular autoantibodies (Table 2).

### Table 2. Possible Factors Involved in the Pathogenesis of Myositis Phenotypes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Phenotype</th>
<th>OR Range</th>
<th>Comments</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphic genes</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HLA DRB1*0301</td>
<td>Polymyositis, dermatomyositis, juvenile dermatomyositis, inclusion body myositis, anti-synthetase autoantibodies</td>
<td>1.9-18.5</td>
<td>Stronger association with autoantibodies than clinical phenotypes; other HLA alleles are associated with other autoantibodies and other ethnic groups</td>
<td>O’Hanlon et al,11 2006; O’Hanlon and Miller,22 2009; Chinoy et al,23 2009</td>
</tr>
<tr>
<td>HLA DRB1*0701</td>
<td>Anti-MJ-2 autoantibodies</td>
<td>4.9-11.1</td>
<td>Stronger association with autoantibody than clinical phenotypes</td>
<td>O’Hanlon et al,11 2006; O’Hanlon and Miller,22 2009; O’Hanlon et al,24 2008</td>
</tr>
<tr>
<td>HLA DQA1*0301</td>
<td>Anti-p155 autoantibodies</td>
<td>5.4</td>
<td></td>
<td>O’Hanlon and Miller,22 2009</td>
</tr>
<tr>
<td>TNF-α-308A</td>
<td>Polymyositis, dermatomyositis, juvenile dermatomyositis, inclusion body myositis, anti-synthetase autoantibodies</td>
<td>2.5-5.0</td>
<td></td>
<td>O’Hanlon et al,24 2008</td>
</tr>
<tr>
<td>Gm 3 23 5, 13</td>
<td>Polymyositis, dermatomyositis, juvenile dermatomyositis, inclusion body myositis, anti-synthetase autoantibodies</td>
<td>2.2-3.4</td>
<td></td>
<td>O’Hanlon et al,24 2008</td>
</tr>
<tr>
<td>Gm13</td>
<td>Juvenile dermatomyositis</td>
<td>3.9</td>
<td></td>
<td>O’Hanlon et al,24 2008</td>
</tr>
<tr>
<td>Environmental agents</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infectious agents</td>
<td></td>
<td></td>
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<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Juvenile polymyositis, juvenile dermatomyositis</td>
<td>2.8</td>
<td>Evidence based on a case-control study</td>
<td>Gourley and Miller,25 2007</td>
</tr>
<tr>
<td>Echovirus</td>
<td>Juvenile dermatomyositis</td>
<td>NA</td>
<td>Many case series, particularly in patients with agammaglobulinemia</td>
<td>Reed and Ytterberg,26 2002</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>Polymyositis</td>
<td>NA</td>
<td>Multiple cases with dechallenge, several cases with dechallenge-rechallenge</td>
<td>Miller,7 2005</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>Juvenile dermatomyositis</td>
<td>NA</td>
<td>Multiple cases with dechallenge, several cases with dechallenge-rechallenge</td>
<td>Reed and Ytterberg,26 2002</td>
</tr>
<tr>
<td>Therapeutic cytokines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon α</td>
<td>Polymyositis, dermatomyositis</td>
<td>NA</td>
<td>Multiple cases with dechallenge</td>
<td>Miller,7 2005</td>
</tr>
<tr>
<td>Interferon γ</td>
<td>Polymyositis, dermatomyositis</td>
<td>NA</td>
<td>Multiple cases with dechallenge</td>
<td>Miller,7 2005</td>
</tr>
<tr>
<td>Medical devices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine collagen implants</td>
<td>Polymyositis, dermatomyositis</td>
<td>5.1-18.8</td>
<td>Associated with a delayed-type hypersensitivity response to collagen</td>
<td>Miller,7 2005</td>
</tr>
<tr>
<td>Other exposures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exertion</td>
<td>Polymyositis, dermatomyositis</td>
<td>3.9</td>
<td>Evidence based on a case-sibling study</td>
<td>Lyon et al,27 1989</td>
</tr>
<tr>
<td>UV radiation</td>
<td>Dermatomyositis, anti-MJ-2 autoantibodies in women</td>
<td>3.8-17.3</td>
<td>Global and US epidemiological studies support this association</td>
<td>Okada et al,22 2005; Love et al,29 2009</td>
</tr>
</tbody>
</table>

Abbreviations: HLA, human leukocyte antigen; OR, odds ratio; NA, information not available.

*Data are from white patients. Some genes are both risk factors for one phenotype and protective for another phenotype. Genes other than those listed are likely important.

Dechallenge refers to clinical improvement of the myositis after removing the agent, and rechallenge refers to reoccurrence of the myositis after reinstituting the agent.
other. Interactions of environmental and genetic risk factors (in the relative absence of protective factors) are considered an initial step in the process leading to immune activation and autoantibody formation in autoimmune diseases. One example is the interaction of cigarette smoking with HLA DRB1–shared epitope alleles, PTPN22, and anti–citrullinated-peptide autoantibodies in patients with rheumatoid arthritis.

Although the evidence is limited, different environmental exposures (e.g., infections, therapeutic agents, physical exertion, and collagen implants) have been reported to be involved in the development of certain myositis phenotypes (Table 2). Additional, albeit indirect, evidence supporting a role for the environment in myositis includes clinical improvement after removing the agent (dechallenge) and reoccurrence of the myositis after reinstituting the agent (rechallenge). A spring season of myositis onset has been described for adults with antisynthetase autoantibodies, and a summer season for myositis onset has been described for adults without defined myositis autoantibodies, which suggests that different environmental factors may be associated with each phenotype. Further evidence for the role of the environment comes from findings that UV radiation intensity at the location of disease onset is associated with dermomyositis and anti–Mi-2 autoantibodies, particularly in women. Of interest, children without a defined myositis autoantibody had a higher frequency of documented infections within 6 months of illness onset compared with those with defined myositis autoantibodies. The evidence supporting a role for the immune system in the pathogenesis of idiopathic inflammatory myopathy includes the findings that some patients with myositis have multiple autoimmune disorders; autoantibodies are characteristic of certain phenotypes; T-cell-mediated myotoxicity or complement-mediated microangiopathy are seen in particular clinical phenotypes; polymorphic immune response genes are primary genetic risk factors; and immunotherapies often result in clinical responses.

Research suggests that different immune processes are likely at play in different myositis phenotypes. In dermatomyositis, initial processes include activation of the complement cascade through C3 and deposition of the complement C5b-9 membrane-attack complex on the endomyial vasculature, with resultant capillary destruction, muscle ischemia, and dilatation of the remaining capillaries. These processes lead to infiltration of B lymphocytes, CD4 helper T cells, and plasmacytoid dendritic cells in perimysial areas of muscle fascicles and in small blood vessels. The major histocompatibility complex class I antigen and intracellular adhesion molecules are upregulated on the cell surfaces of damaged fibers and in perivascular areas, respectively. In contrast, polymyositis and inclusion body myositis are characterized by a predominant cytotoxic T-lymphocyte-mediated process involving perforin, with CD8 T cells accompanied by smaller numbers of macrophages surrounding and invading otherwise normal-appearing myocytes in endomyial areas. The major histocompatibility complex class I antigen is upregulated on the surface of the majority of muscle fibers, even those not affected by inflammation.

Other pathogenic processes include the likely role of type I interferons in dermatomyositis, and the possible role of autoantigens, whose fragments have chemokine activity. Additional factors include the endoplasmic reticulum stress response. These mechanisms appear to converge in the upregulation of NF-κB and activation of positive feed-
back loops to maintain the proinflammatory cascades that maintain chronic tissue inflammation.

**Therapy**

Although the pathophysiology of polymyositis and dermatomyositis are distinct, current therapies for these disorders (derived primarily from anecdote and uncontrolled studies) are similar and based on broad immunosuppression. The core therapeutic approach remains daily high-dose oral corticosteroid therapy, along with adjunctive steroid-sparing immunosuppressive therapies, which are used to treat disease activity, prevent mortality, and attempt to reduce long-term disability (Box). The treatment for inclusion body myositis with evidence of active disease is controversial, but some experts believe the primary goal of therapy is to slow the rate of disease progression by immunosuppression and physical therapy. The use of second-line therapies, such as high-dose intravenous pulse corticosteroids, methotrexate, intravenous gammaglobulin, azathioprine, or cyclosporine, as part of initial therapy in juvenile patients with moderate to severe disease or adult patients with poor prognostic factors is supported by consensus among specialists. Open-label studies suggest a shorter course of illness, reduced frequency of calcinosis, and fewer corticosteroid adverse effects result from early introduction of additional therapies. For patients with severe, refractory, or corticosteroid-dependent disease, combinations of second-line therapies or newer third-line therapies are frequently used (Box). Among these three-line agents, uncontrolled trials support the use of mycophenolate mofetil for patients with adult or juvenile myositis with severe disease and the use of intravenous monthly pulse cyclophosphamide for patients with severe or refractory juvenile dermatomyositis. Use of oral tacrolimus is supported by studies in patients with treatment-refractory disease, including those with difficult-to-treat disease associated with antisynthetase and anti–signal recognition particle autoantibodies.

Case series and small open-label trials suggest that rituximab, a monoclonal antibody directed against B lymphocytes, is often effective in patients with adult or juvenile dermatomyositis and severe refractory disease; however, improvement in skin disease activity is not clear. After receiving rituximab therapy, adults with antisynthetase and anti–signal recognition particle autoantibodies experienced a dramatic improvement in muscle strength and associated interstitial lung disease and a decline in autoantibody titers. Responses to anti–tumor necrosis factor therapies have been mixed, with a more consistent response in juvenile patients with dermatomyositis. All 5 patients with severe juvenile dermatomyositis improved 8 to 30 months after open-label treatment with infliximab; and in some cases, calcinosis also improved. Responses to infliximab and etanercept have varied in adult patients with dermatomyositis or polymyositis, with disease progression in some patients. Case reports of the development of myositis after anti–tumor necrosis factor therapy also suggest caution in the use of these agents for therapy. In an open-label trial of alemtuzumab for inclusion body myositis, a majority of patients improved in strength and function, paralleling the decline in peripheral blood and muscle T cells targeted by the monoclonal antibody. Stem cell transplantation is suggested as an option for severe, unremitting disease, with case reports of success.

The response to treatment differs among the clinical and autoantibody phenotypes. For example, patients with dermatomyositis tend to maintain on a lower dose of prednisone, and less than 50% require other therapies; although their disease activity often increases during prednisone taper, 13% do not require continued therapy. In contrast, patients with polymyositis more frequently require cytotoxic agents. In 40% of these patients, their disease activity increases during reduction of therapy. Patients with inclusion body myositis are often treated with lower doses of prednisone and fewer cytotoxic agents, but generally require ongoing therapy. Among the autoantibody subgroups, patients with antisynthetase autoantibodies require a moderate dose of prednisone. Sixty percent of these patients experience increased disease activity during tapering of therapy, and most patients require treatment most of the time. Patients with anti–signal recognition particle autoantibodies require a higher dose of prednisone, generally require concomitant therapy with other agents, and usually cannot be taken off therapy for years. Patients with anti–Mi-2 autoantibodies use the lowest dose of prednisone and spend approximately 20% of their time off therapy; fewer patients require treatment with other agents and only 25% experience increased disease activity during reduction of therapy.

**CONCLUSION**

Understanding the many mutually exclusive and stable myositis phenotypes aids in deciphering the mechanisms by which these conditions arise in patients, and aids in interpreting and anticipating their diverse clinical presentations and care. Given the differences in genetic and environmental risk factors, pathology, and prognosis among myositis phenotypes, future studies should incorporate phenotype status into their investigations of pathogenesis and therapy.

**Author Contributions:** Dr Rider had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rider, Miller. Acquisition of data: Rider, Miller. Drafting of the manuscript: Rider, Miller. Critical revision of the manuscript for important intellectual content: Rider, Miller. Obtained funding: Miller. Administrative, technical, or material support: Rider, Miller. Study supervision: Miller. Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported. Funding/Support: This research was supported by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

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### Role of the Sponsor:
The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

### Additional Contributions:
We thank Mark Gourley, MD, and Fred Ognibene, MD (both with the National Institutes of Health, Bethesda, Maryland), and Kathleen Coyle, MD (Food and Drug Administration), for their critical review of the manuscript. None of these persons was compensated for his or her contribution.

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