

Series Editor: Bryan A. Liang, MD, PhD, JD

# Approach to Diagnosis and Management of an Idiopathic Inflammatory Myopathy

Case Study and Commentary: Carrie Edelman, MD

## DR. LIANG:

The inflammatory myopathies are a group of chronic disease states that show significant lymphocytic inflammation of striated muscle tissue. As noted in the case study presented by Dr. Edelman, the 3 main diseases within this category are polymyositis, dermatomyositis, and inclusion body myositis.<sup>1</sup> These inflammatory disorders are notably rare, with an incidence range of 0.5 to 8 cases per 1 million persons.<sup>2</sup> These myopathies are associated with significant morbidity and mortality rates, particularly related to cardiac, pulmonary, and life-threatening muscle complications and weakness.<sup>3-6</sup> Age-specific mortality rates are higher in older polymyositis and dermatomyositis patients.<sup>7</sup> A higher prevalence of inflammatory myopathy in patients older than 65 years has been reported, and these patients have significantly greater esophageal involvement, bacterial pneumonia, and malignancies than younger patients afflicted with the disease. In addition, older patients experience complete remission less frequently and have a higher overall mortality rate associated with each of these disorders.<sup>8-10</sup>

There is a significant need to explore the etiology or etiologies underlying the inflammatory myopathies, as no current satisfactory classification allows for simple differentiation. Some aspects of the various disease states are clear. It appears that a significant relationship exists between the inflammatory infiltrate and necrosis that is observed in these myopathies. In polymyositis and inclusion body myositis, cytotoxic CD8 lymphocytes invade the patient's muscle cells; through the actions of certain enzymes (eg, granzyme B, perforin), myofibers may be damaged.<sup>11</sup> Macrophages that are present in the necrotic areas phagocytize the necrotic materials, and then the area progresses to local development of fibrosis, replacing the formerly contractile myofibers.<sup>11</sup> This process may be affected by the presence of cytokines from the cells that compose the inflammatory infiltrate, along with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), a major constituent.<sup>11</sup>

In dermatomyositis, CD4 and B lymphocytes predominate. The vasculopathy associated with this inflammatory myopathy is potentially explained by the presence of perifascicular myofiber atrophy and, often, the terminal components of complement C5 though C9 that are deposited on the small vessels.<sup>11</sup> However, the similarities or differences between polymyositis and dermatomyositis continue to be debated.<sup>12,13</sup>

Other clues provide some insight into etiology. The autoimmune mechanisms postulated are based on similar presentations of other similar connective tissue disorders, and the human leukocyte antigen DR3 phenotype is overrepresented in both black and white persons affected by the disorder(s).<sup>14</sup> A potential viral etiology may also be involved, implicated by antibodies present against Jo-1 and PL-12; picornaviruses have surface antigens similar to aminoacyl-tRNA synthetase, to which Jo-1 and PL-12 autoantibodies are active.<sup>14</sup> Myocyte infection with picornavirus may lead to cell-surface expression of aminoacyl-tRNA synthetase-like molecules, which may then drive an immune response against these molecules.<sup>15</sup> Finally, other immunomodulated processes may be involved, including maternal microchimerism,<sup>16</sup> which is clinically important not only as a potential factor related to the induction of these disease entities, but also due to its potential to induce graft-versus-host disease—the latter being very similar in presentation to patients with juvenile idiopathic inflammatory myopathy.<sup>17</sup>

Generally, patients with an inflammatory myopathy present with a principal complaint of muscle weakness or fatigue, as in the case presented here. Muscle wasting is usually present only in longstanding, advanced

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cases.<sup>18</sup> A mainstay laboratory investigation remains the fractionated creatine kinase test, as was performed in this case study. However, it should be noted that patients with dermatomyositis or polymyositis may show normal levels of this enzyme fraction, particularly in cases in which there is severe muscle atrophy or there are circulating inhibitors of creatine kinase activity; normal levels in these settings are poor prognostic signs.<sup>19,20</sup>

Recent interesting developments in diagnostics may prove applicable to the idiopathic inflammatory myopathies. Recent work using DNA microarrays may allow providers to distinguish between the inflammatory myopathies, leading to greater specificity and appropriateness in treatment. DNA microarrays allow the identification of genes that are directing protein synthesis or that are inactive in a cell. This information is then utilized to obtain a “signature” of a particular disease state; each of the inflammatory myopathies has a characteristic signature, allowing for a greater accuracy of diagnosis and choice of treatment options.<sup>21</sup>

The idiopathic inflammatory myopathies are a rare group of disorders with debilitating and potentially lethal outcomes. Because of the rare nature of the disease, primary care providers must be cognizant of the constellations of vague signs and symptoms and their potential relation to these myopathies.

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#### **DR. EDELMAN:**

Idiopathic inflammatory myopathies are a group of autoimmune diseases characterized by proximal muscle weakness and inflammation of skeletal muscle. Specific forms of idiopathic inflammatory myopathy include polymyositis, dermatomyositis, and inclusion body myositis. Inflammatory myopathies have a bimodal distribution, occurring in patients between 10 and 15 years and 45 and 60 years of age, except for inclusion body myositis and malignancy-associated myositis, which occur in patients older than 50 years of age. The inflammatory myopathies are rare, with an annual incidence of 5 to 10 new cases per million population worldwide.<sup>22</sup> Like other autoimmune diseases, they occur predominantly in women (2:1), except for inclusion body myositis.<sup>22</sup> Persons of any race can be affected.

Patients with an idiopathic inflammatory myopathy usually present with symmetric proximal muscle weakness. The differential diagnosis of muscle weakness is extensive, and careful evaluation of patients is essential for proper diagnosis and treatment. Prognosis differs with each specific disease; however, untreated inflammatory myopathies have a 5-year mortality rate of 50%.<sup>23</sup>

Prompt diagnosis and treatment are important to limit morbidity and mortality associated with these diseases. This review discusses the diagnosis and treatment of polymyositis and dermatomyositis.

#### **CASE STUDY**

##### **Initial Presentation**

A 52-year-old woman presents to her primary care physician with increasing fatigue and a “lack of energy” in the past few months.

##### **History**

The patient works as a hairdresser and lives with her daughter and grandson. She reports that she has trouble mustering the energy to go to work, take care of her grandson, or do any housework. Review of systems is significant for myalgias, 5-lb weight loss over the past year, and gastroesophageal reflux. She denies fever, chills, cough, recent illness, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, constipation, rashes, weakness, and numbness.

The patient’s past history is significant only for hypercholesterolemia. She has no known drug allergies. Current medications include lovastatin and occasional ibuprofen use. She denies any alcohol or tobacco use and does not use over-the-counter dietary supplements. Her family history is significant for hypercholesterolemia and diabetes.

##### **Physical Examination**

On physical examination, the patient is afebrile with a heart rate of 70 bpm, blood pressure of 110/70 mm Hg, and respiratory rate of 12 breaths/min. Her pharynx is clear, and no oral or nasal ulcers are noted. Her lungs are clear to auscultation, and her heart rate and rhythm are regular with no murmurs. She has normal active bowel sounds with a soft abdomen; no organomegaly is noted. Skin is cool with no rashes. There is no synovitis on musculoskeletal examination. Neurologic examination is grossly nonfocal with 5/5 strength in all 4 extremities, proximally and distally. Sensation is intact.

- **What concerns are raised by this patient’s presentation?**
- **What laboratory tests should be ordered?**

This patient’s clinical picture consists of fatigue and myalgias of several months’ duration, gastroesophageal reflux, and 5-lb weight loss. There are no signs of acute infection. Fatigue and myalgias could be secondary to viral infection, but she does not describe the typical presentation. There is no history of anemia, but she has not had blood work done recently. Thyroid disease

or other endocrinopathies could initially present as fatigue and myalgias. Statin medications used in hypercholesterolemia may cause myalgias. Unintentional weight loss always raises clinical suspicion for malignancy or underlying chronic disease. Routine blood work with thyroid function tests and age-appropriate cancer screening would be appropriate in this patient.

### Laboratory Evaluation

The results of a complete blood count, basic metabolic panel, mammogram, and Pap smear are normal. Hemocult testing results are negative. The serum calcium level is normal. The thyroid-stimulating hormone (TSH) level is slightly elevated, but the rest of the thyroid function test results are within normal range. No treatment is initiated for the abnormal TSH level. The patient's cholesterol medication is held to determine whether it is the cause of the myalgias and fatigue. The physician asks the patient to return for follow-up in 2 months.

### 2 Months Later

Two months later the patient presents for follow-up and now reports having trouble holding up her scissors and blowdryer for extended periods of time at work. She states that her arms get "too heavy" when performing these tasks. She has trouble going up and down stairs, and several days ago she needed help getting up from a seated position on the floor after playing a game with her grandson. She needs to rock herself out of a chair in order to stand up. She continues to have fatigue. She denies dysphagia, shortness of breath, arthritis, or rashes. Physical examination now reveals 3/5 proximal muscle strength in the shoulder girdle of the upper extremities bilaterally and 4/5 proximal muscle strength in the pelvic girdle of the lower extremities bilaterally. The rest of the examination is nonfocal. The physician is concerned with the progression of her symptoms and refers her to a rheumatologist.

- What is the differential diagnosis of muscle weakness?
- What laboratory tests are used in the work-up of muscle weakness?

### Differential Diagnosis of Muscle Weakness

The differential diagnosis for muscle weakness is extensive and includes trauma, metabolic abnormalities, neurogenic causes, drugs and toxins, infections, connective tissue disease, and inflammation (Table 1).<sup>24</sup> The patient gives no history of trauma that could be causing her muscle pain and weakness. Based on her previous laboratory test results, she has no electrolyte

**Table 1.** Differential Diagnosis of Muscle Weakness

#### Metabolic disorders

Endocrinopathies: hypothyroidism, hyperthyroidism, hypoparathyroidism, acromegaly, Cushing's syndrome, Addison's disease, diabetic amyotrophy, vitamin D deficiency myopathy

Electrolyte disorders: sodium, potassium, calcium, magnesium, phosphorus abnormalities

Disorders of glycogen metabolism: McArdle's disease (acid maltase deficiency)

Disorders of lipid metabolism: carnitine deficiency

Mitochondrial myopathy

Myoadenylate deaminase deficiency

**Neurogenic disorders:** muscular dystrophies, myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, Guillain-Barré syndrome

#### Trauma

**Drugs and toxins:** corticosteroids, colchicine, hydroxychloroquine, chloroquine, penicillamine, cyclosporine, gold, nonsteroidal anti-inflammatory drugs, HMG-CoA reductase inhibitors, nicotinic acid, fibric acid derivatives, cocaine, heroin, marijuana, amphetamines, methadone, barbiturates, zidovudine, alcohol, cimetidine, propylthiouracil, over-the-counter dietary supplements

**Infections:** viral, bacterial, fungal, parasitic

#### Malignancy

**Connective tissue diseases:** idiopathic inflammatory myopathies, polymyalgia rheumatica, systemic lupus erythematosus, Sjögren's syndrome, vasculitis, sarcoidosis

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

abnormalities, thyroid function is normal, and she does not have hypoparathyroidism or hyperparathyroidism. She is not on any medications that would contribute to her muscle weakness. Because she has no family history of muscular dystrophies and the rest of her neurologic examination is normal, neurogenic causes of muscle weakness are less likely, although they cannot yet be excluded. Disorders of glycogen and lipid metabolism are usually only symptomatic with activity. The patient is 52 years old and has not presented with weakness until now, making disorders of metabolism less likely. She has no signs of acute infection, no travel history was given, and she has no risk factors for hepatitis or HIV infection. Inflammatory myopathies are consistent with the case patient's presentation. The fact that the patient has true weakness, not just muscle pain, excludes polymyalgia rheumatica, fibromyalgia, and chronic fatigue syndrome.

### Laboratory Work-up

Important laboratory work-up for the evaluation of muscle weakness includes measurement of creatine

kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. Thyroid function tests, a basic metabolic panel, measurement of hemoglobin, and measurement of calcium, magnesium, and phosphorus should be done to exclude endocrinopathies, anemia, and electrolyte abnormalities.

Creatine kinase is an enzyme involved in the formation of adenosine triphosphate and in the synthesis of creatine phosphate, which is a high-energy storage molecule in muscle tissue. Creatine kinase is found in myocardial tissue, skeletal muscle, brain, and various other tissues. Injury to skeletal or cardiac muscle causes the serum level of creatine kinase to rise. Serum creatine kinase levels are elevated in patients with cardiac ischemia, myopathies, myositis, rhabdomyolysis, hypothyroidism, hypoparathyroidism, and certain neurogenic disease and in patients who have undergone needle puncture, electromyography (EMG), and biopsy procedure. If serum creatine kinase levels are elevated and patients have cardiac complaints or risk factors, myocardial infarction must be ruled out. The serum creatine kinase level is used to identify and diagnose skeletal muscle myopathy because in muscle diseases it is elevated more frequently and significantly than other enzymes.<sup>25</sup> Serum creatine kinase levels along with physical examination are also used to monitor muscle disease activity.

Measurement of aldolase is also used in the diagnosis of myopathy. However, aldolase is not a muscle-specific enzyme; it can be elevated in myositis, myopathy, hemolysis, and hepatic disorders. Aldolase is a glycolytic enzyme that catalyzes the cleavage of fructose-1-6-diphosphate into 2 triose molecules. Measurement of this enzyme can be helpful in diagnosing myositis in the rare case of myositis that has a normal serum creatine kinase level.

The aminotransferases are enzymes that catalyze the transfer of an amino group from an amino acid to a keto acid. Aspartate aminotransferase and alanine aminotransferase are the most common types. Aspartate aminotransferase is found mostly in the liver, skeletal muscle, myocardium, and kidney, while alanine aminotransferase is found mostly in the liver. Plasma aspartate aminotransferase levels are elevated in myositis and inflammatory muscle disease.<sup>26</sup> Lactate dehydrogenase is a glycolytic enzyme that catalyzes the reversible conversion of lactate in the presence of NAD<sup>+</sup> to pyruvate and NADH and H<sup>+</sup>. Lactate dehydrogenase is found in virtually all tissues in the body and can be elevated in myositis.

### **Electromyography and Biopsy**

EMG is a good test to distinguish between myopathic

versus neuropathic causes of weakness. EMG is sensitive but not specific: myopathy due to inflammation could cause EMG changes similar to those seen in myopathy secondary to toxins, infection, or metabolic abnormalities. When evaluating muscle weakness, EMG is done unilaterally because idiopathic inflammatory myopathies are symmetric and a clean muscle biopsy can be done on the contralateral muscle if needed.

Muscle biopsy is used to confirm the diagnosis of myopathy. In idiopathic inflammatory myopathies, the muscle biopsy specimen shows necrotic tissue, regeneration of muscle fibers, an inflammatory infiltrate, atrophy, and fibrosis. Magnetic resonance imaging (MRI) is now being used to help identify involved muscle, which can better guide a biopsy. MRI of myositis demonstrates inflammation on T2-weighted images by the presence of edema. T1-weighted images demonstrate muscle atrophy and fatty infiltration consistent with muscle fibrosis. Edema and atrophy are nonspecific findings on MRI and cannot at this time replace muscle biopsy in diagnosing myositis.<sup>27</sup>

### **Case Patient—Further Laboratory Evaluation**

The patient is seen by a rheumatologist, who confirms her history and physical examination findings and orders additional work-up. Laboratory testing reveals the following serum levels: creatine kinase, 12,652 U/L; aspartate aminotransferase, 150 U/L; and alanine aminotransferase, 67 U/L. The erythrocyte sedimentation rate is 62 mm/h. Repeat TSH, complete blood count, and basic metabolic panel are normal. The EMG findings are consistent with a myopathic process; no neuropathic changes are noted. The biopsy specimen shows degeneration, regeneration, and inflammatory infiltrate with atrophy and fibrosis. The physician makes a diagnosis of polymyositis.

- **What is polymyositis?**
- **What are the criteria for diagnosis?**

### **Polymyositis**

Polymyositis is a type of idiopathic inflammatory myopathy. The muscle injury in polymyositis is secondary to inflammation of unknown etiology. Dermatomyositis, often characterized with polymyositis, is myositis with characteristic skin rashes. There is a juvenile dermatomyositis that occurs in children and adolescents in which patients present with proximal muscle weakness, characteristic rashes, and extramuscular manifestations. In amyopathic dermatomyositis, patients present with typical cutaneous disease without myositis.

Polymyositis and dermatomyositis are different

pathogenetically. Polymyositis is an antigen-directed cytotoxic T cell attack on myofibers within a fascicle. The predominate cell is a CD8+ T cell recognizing major histocompatibility complex class I antigens on myofibers; this antigen is not expressed on the surface of normal muscle fibers. Dermatomyositis is a humorally mediated disorder that targets primarily blood vessels. There are increased numbers of B cells and CD4+ helper cells. Perivascular inflammation and complement deposition can be seen in the vessel wall. Atrophy is mainly seen in the perifascicular muscle fibers secondary to ischemia from involved blood vessels.

Cytokines are being studied to determine their role in polymyositis and dermatomyositis and whether they are responsible for pathologic changes. It is known that TNF- $\alpha$  is produced and expressed by regenerating muscle fibers in inflammatory myopathies.<sup>28,29</sup> Interleukin 1- $\alpha$  expression in capillaries may have a pathologic function independent of the adjacent inflammatory infiltrates in both polymyositis and dermatomyositis.<sup>30–32</sup>

The diagnostic criteria that are used as the gold standard for diagnosing polymyositis and dermatomyositis were proposed in 1975 by Bohan and Peter<sup>33</sup>: symmetric proximal muscle weakness, elevation of serum skeletal muscle enzyme levels, a triad of findings on EMG, muscle biopsy abnormalities, and skin findings (Table 2). The laboratory tests used in the diagnosis of polymyositis are the tests discussed earlier regarding the evaluation of muscle weakness, specifically creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. On EMG, one sees polyphasic motor unit potentials that are of short duration and low amplitude. There are fibrillations, positive sharp waves, and insertional irritability with bizarre high-frequency repetitive discharges. The muscle biopsy demonstrates degeneration, regeneration, necrosis, atrophy, and an interstitial mononuclear infiltrate. MRI is not part of the diagnostic criteria from Bohan and Peter, but more recent criteria have been proposed that include the use of MRI as a tool similar to serum creatine kinase or EMG.<sup>34</sup>

Other laboratory tests may help with the diagnosis of polymyositis and dermatomyositis but are not part of the diagnostic criteria. Erythrocyte sedimentation rates can be elevated. Antinuclear antibodies are positive in up to 80% of myositis patients.<sup>35</sup> A group of myositis-specific autoantibodies are associated with specific clinical syndromes with different prognoses. The 3 main classes of myositis-specific autoantibodies include the anti-aminoacyl-tRNA synthetases, antisignal recognition particle, and anti-Mi-2. The most common

**Table 2.** Diagnostic Criteria for Polymyositis (PM) and Dermatomyositis (DM)

1. Symmetric muscle weakness on physical examination
2. Muscle biopsy evidence of an inflammatory myopathy
3. Elevation of serum levels of skeletal muscle enzymes
4. Electromyographic features of myopathy
5. Cutaneous eruption of typical dermatomyositis
Definite PM/DM: 4 criteria met (rash must be present for diagnosis of DM)
Probable PM/DM: 3 criteria met
Possible PM/DM: 2 criteria met

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antisynthetase antibody is Jo-1, and the syndrome associated with this antibody includes arthritis, myositis, fever, mechanic's hands, Raynaud's phenomenon, and interstitial lung disease. Polymyositis with the presence of this antibody has a poorer prognosis than polymyositis alone (Table 3).<sup>36</sup>

- What is the clinical presentation of polymyositis and dermatomyositis?
- What are the extramuscular manifestations?

### Clinical Presentation of Polymyositis and Dermatomyositis

Patients with polymyositis present with proximal muscle weakness that is insidious in onset and usually painless. Early on, patients can present with constitutional symptoms, such as fever, weight loss, and overwhelming fatigue. They have trouble getting out of a chair or up from a squatting position and cannot comb their hair or do overhead activity. Patients can have neck flexor weakness with trouble lifting their head off a pillow.

The gastrointestinal tract can be involved in polymyositis. Pharyngeal muscle weakness can present as dysphagia, hoarseness, and aspiration. Children with dermatomyositis can have vasculitis of the gastrointestinal tract. Ocular and facial muscle weakness is rare and usually suggests a neurologic disorder.<sup>37</sup> Musculoskeletal involvement includes myalgias, arthralgias, and a nonerosive polyarthritis. It occurs in 25% to 50% of patients with inflammatory myopathy. Cardiac involvement consists of asymptomatic nonspecific conduction abnormalities. Rarely, patients can have myocarditis with congestive heart failure, endomyocardial fibrosis, or pericardial effusion with tamponade. Kidney involvement is uncommon.

**Table 3.** Myositis-Specific Antibodies

Antibody	Associated Syndrome	Muscle Disease			
		Onset	Severity	Treatment Response	5-Year Survival (%)
Antisynthetase (most common Jo-1)	Arthritis, interstitial lung disease, fever, Raynaud's phenomenon, mechanic's hands	Spring	Acute/severe	Moderate	70
Anti-SRP	Cardiac involvement and myalgias	Fall	Acute/severe	Poor	25
Anti-Mi-2	Classic dermatomyositis	No seasonal predisposition	Acute/mild	Good	100

SRP = signal recognition particle.

Pulmonary involvement is common and can occur in up to 40% to 50% of the patients.<sup>38</sup> Dyspnea can occur due to respiratory muscle weakness. Aspiration pneumonia can occur secondary to pharyngeal involvement. Interstitial lung disease with fibrosis also can occur. Diffuse alveolitis is associated with a poor prognosis. Patients have abnormal findings on chest radiographs with bibasilar infiltrates. High-resolution computed tomography scans show ground-glass changes or fibrosis. Alveolitis may be responsive to therapy, but it has the potential to rapidly decompensate. Respiratory muscle weakness could lead to ventilatory failure.

The cutaneous manifestations of dermatomyositis include Gottron's papules, heliotrope rash, shawl sign, "V" sign, periungual telangiectasia, cuticular overgrowth, and poikiloderma. The rashes can precede, follow, or occur concurrently with the myopathy. Gottron's papules are pathognomonic for dermatomyositis. They are scaly, erythematous, or violaceous plaques over the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints. Gottron's sign is a macular erythema with scaling over the extensor surfaces, elbows, and knees. As the disease progresses, the lesions become atrophic, shiny, and hypopigmented. Heliotrope rash is a violaceous rash on the eyelids with periorbital edema. Photosensitivity rashes with macular erythema can occur in a "V" pattern over the anterior chest or in a pattern over the shoulders and upper back, known as shawl sign. Cuticular hypertrophy can occur with capillary change in the nailfold. Calcinosis is seen in juvenile dermatomyositis. Rashes on the scalp are also seen in dermatomyositis.<sup>39</sup>

• **How are polymyositis and dermatomyositis managed?**

**Approach to Management**

In assessing a patient with myositis, the extramuscular manifestations mentioned above must be investigat-

ed. A chest radiograph should be obtained, and if the results are abnormal, a computed tomography scan of the thorax should be done. Swallowing studies looking for aspiration and dysmotility are done to assess pharyngeal and esophageal involvement. Electrocardiography should be done to look for conduction abnormalities, and pulmonary function tests with diffusion studies also should be done.

Because there are not many well-controlled clinical trials of treatment of polymyositis, treatment is mostly based on empiric data. Corticosteroids are first-line therapy for treating patients with an idiopathic inflammatory myopathy. Oral corticosteroids are begun at a dose of 1 to 2 mg/kg (60 mg) of prednisone as a single daily dose or divided doses. When given in divided doses, prednisone is more potent. It has been shown that a delay in diagnosis and initiation of treatment is detrimental, with a negative impact on prognosis.<sup>40</sup> If patients present with severe myositis or have extramuscular manifestations such as pulmonary or cardiac involvement, intravenous pulse methylprednisolone (1 g/d for 3 days) is administered to control inflammation more rapidly.

The prednisone is continued at the initial high dose for several months until the patient demonstrates a response to the treatment regimen. Favorable response is a return of muscle strength and normalization of the serum creatine kinase level. The serum creatine kinase levels may normalize in 1 to 2 months, before the muscle strength returns to normal. In some patients strength can improve while the creatine kinase level remains elevated; therefore, the creatine kinase level should not be used as the only parameter for monitoring disease activity. Once the patient is definitely responding to therapy, the prednisone can be tapered. The dose of prednisone needs to be consolidated to a single morning dose. The prednisone taper is individualized to each patient's response to therapy. Usually the dose can be decreased by

10 mg/month, a decrease of approximately 20% of the dose. Patients' muscle strength and serum creatine kinase level are routinely measured to assure the patient continues to have a clinical response. Most continue prednisone at 5 to 10 mg/d until the disease has been in remission for 1 year.<sup>40</sup>

Another corticosteroid schedule is alternate-day dosing. Patients are started at higher oral doses of prednisone, 80 to 100 mg/d, and the alternate day is tapered quickly after 1 month of daily dosing. The alternate day is decreased by approximately 10 mg/wk over 3 months until the patient is on prednisone 80 to 100 mg every other day. It is thought that alternate dosing may limit side effects of the corticosteroids, but patients need to be carefully monitored for relapse. At the start of any corticosteroid regimen, osteoporosis prophylaxis should be given. These patients will be on prednisone for many months and will need calcium, vitamin D, and an antiresorptive agent to protect them.

If patients are not responding to the corticosteroids alone or the disease relapses on the current management, then another immunosuppressive agent is added. Patients with severe illness and extramuscular manifestations are sometimes started on prednisone with another immunosuppressive agent at the onset of disease. Retrospective analyses have shown good response to combined initial treatment versus corticosteroids alone.<sup>41</sup> Methotrexate is often used as a steroid-sparing agent or second immunosuppressive agent, although there are no controlled trials proving the efficacy of this treatment. One retrospective review suggested that weekly methotrexate may lower corticosteroid requirements.<sup>42</sup> Methotrexate is usually given orally or subcutaneously. Folic acid 1 mg/day or leucovorin weekly may limit some side effects of methotrexate.

Azathioprine has been studied in controlled, prospective, double-blind trials. At 3 months, no difference was found between a combination of prednisone and azathioprine and prednisone alone.<sup>43</sup> Overall, patients who received combination therapy functioned better and required lower doses of maintenance prednisone therapy. A randomized crossover study investigating oral azathioprine and oral methotrexate together versus intravenous methotrexate with leucovorin rescue suggested that the oral combination was more effective for treating refractory myositis.<sup>44</sup> A study of cyclophosphamide for refractory myositis found that the drug had no significant effect.<sup>45</sup> Case reports on cyclophosphamide and myositis associated with connective tissue disease have been favorable. Chlorambucil has been used for refractory dermatomyositis with good results. Cyclosporine has been studied in small series with some

effectiveness. Tacrolimus (FK506) has been found to be effective in patients with difficult-to-treat myositis and interstitial lung disease.<sup>46</sup>

Intravenous immune globulin (IVIg) was studied in a randomized, double-blind, placebo-controlled trial. It was found to be effective for treatment of refractory dermatomyositis.<sup>47</sup> No randomized controlled studies with IVIg exist for polymyositis. Plasmapheresis has not been proven to be effective, although anecdotally it has been used with some effectiveness. Total body irradiation for life-threatening disease has also been used.

Newer biologic agents used to block TNF- $\alpha$ , such as etanercept and infliximab (originally used in the treatment of rheumatoid arthritis), have anecdotally shown improvement in patients with refractory polymyositis and dermatomyositis.<sup>48,49</sup>

For cutaneous manifestations, patients should wear sunscreen to prevent formation of photosensitive lesions. Hydroxychloroquine 200 mg twice daily is effective for skin disease. If this is not effective, quinacrine 100 mg twice daily can be added.<sup>50</sup> Methotrexate has been shown to be effective for cutaneous manifestations.<sup>51</sup> IVIg monthly has been beneficial for skin lesions.<sup>47</sup> Colchicine, warfarin, aluminum hydroxide, probenecid, and diltiazem have all been used for calcinosis with limited success.

Patient education and physical therapy are important components of treatment. With active disease, exercise is limited to range of motion and stretching to prevent contractures and atrophy of muscle. When disease is controlled, more aggressive exercise is instituted for muscle strength, tone, and range of motion.

#### **Case Patient—Initiation of Corticosteroid Therapy**

The patient is started on prednisone 60 mg/d for 2 months, along with calcium 1500 mg/d and vitamin D 800 IU/d. Her serum creatine kinase levels improve and muscle strength returns to baseline. She is started on physical therapy and is placed on a slow prednisone taper with monthly evaluations of muscle strength and laboratory testing. Four months after diagnosis, the patient reports increasing weakness, although her serum creatine kinase levels have remained stable around 400 U/L. She is concerned that her disease has flared.

- **What are the potential causes of this patient's muscle weakness?**

This patient could be experiencing a flare of her disease, or she could have developed a corticosteroid myopathy. Corticosteroids are included among the drugs and toxins known to cause muscle weakness

(Table 1). They can cause atrophy of type II muscle fibers, which can also be seen in active myositis. Corticosteroids do not cause an inflammatory change, so many times the serum creatine kinase level does not rise. Determining whether the muscle weakness is from corticosteroid use or underlying disease activity is difficult. The prednisone dose can be rapidly decreased to see if muscle strength returns, or the dose can be increased if disease flare is suspected. An EMG may be of some help in distinguishing corticosteroid myopathy from active myositis. Corticosteroid myopathies cause EMG changes similar to changes that occur with myositis, but they usually lack abnormal spontaneous activity, such as fibrillation potentials. An EMG that shows fibrillations and positive waves is more suggestive of myositis. Such test results may or may not help guide treatment.

#### Case Patient—Reduction of Corticosteroid Dose and Follow-up

The steroid dose is reduced and oral methotrexate is added to the patient's regimen. Her strength improves to baseline and her creatine kinase normalizes. The physician is able to taper her prednisone to 5 mg/d, and she is maintained on methotrexate for 1 year after achieving remission.

During a routine physical examination 1 year after diagnosis, a breast mass is palpated. A mammogram confirms the presence of a lesion. Biopsy shows the lesion is benign.

#### • What is the association between malignancy and inflammatory myopathies?

There have been numerous studies investigating malignancy in association with inflammatory myopathies. It was thought that the incidence of malignancy was increased only in patients with dermatomyositis. A Swedish population-based study showed a significant increase in the risk of cancer in patients with dermatomyositis.<sup>52</sup> A Finland population-based study also observed a strong association between dermatomyositis and cancer, but such an association was not observed with polymyositis.<sup>53</sup> More recent studies have shown an increased incidence of malignancy in men and women with any idiopathic inflammatory myopathy. A study done in Israel followed patients over 11 years and found an increased incidence of malignancy in polymyositis and dermatomyositis patients, with a frequency 12.6 times that expected for the general population.<sup>54</sup> A recent population-based cohort study done in Australia showed an increased risk for malignant disease in biopsy-proven dermatomyositis, polymyositis,

and inclusion body myositis.<sup>55</sup> The risk was highest in the first 3 years after diagnosis of myositis but was still apparent 5 years after diagnosis.

The types of cancer associated with malignancy are typical for patients' age and sex. Ovarian cancer seems to be overrepresented in women with dermatomyositis.<sup>56</sup> It is recommended that any patient who is diagnosed with an idiopathic inflammatory myopathy should have an age-appropriate malignancy work-up, including a chest radiograph, mammogram, pelvic ultrasonogram, cancer antigen 125 test, prostate-specific antigen test, testicular and breast examinations, Pap smear, and rectal examination with Hemoccult testing and flexible sigmoidoscopy. **HP**

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