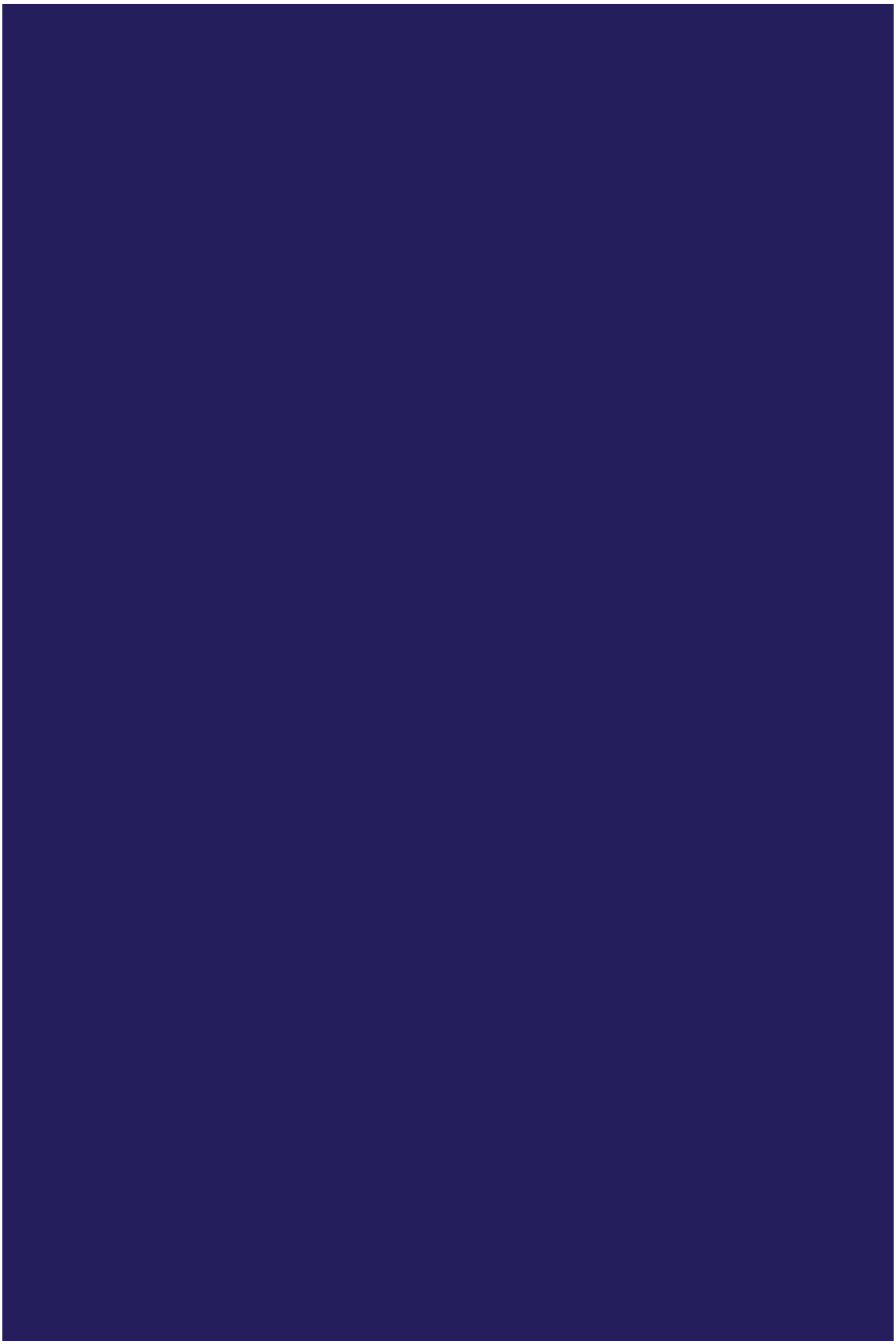
MYOSITIS

A physician's guide to the inflammatory myopathies



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PHYSICIAN'S GUIDE TO MYOSITIS

Myositis is a term used to represent the idiopathic inflammatory myopathies, rare diseases that are predominantly immune-mediated and cause skeletal muscle weakness. If left untreated, myositis can cause significant morbidity and even death.

WHAT IS MYOSITIS?

The word myositis literally means inflammation of muscle. In a clinical context, however, the term is used to identify the idiopathic inflammatory myopathies, rare diseases of skeletal muscle (1,2). These diseases are polymyositis, dermatomyositis, juvenile dermatomyositis, and inclusion body myositis. Polymyositis, dermatomyositis, and juvenile dermatomyositis are autoimmune disorders, whereas inclusion body myositis

has features of both autoimmunity and muscle fiber degeneration (3). These heterogeneous myopathies are characterized by muscle weakness that is usually proximal and symmetric, and nonsuppurative inflammation in skeletal muscle.

SIGNS AND SYMPTOMS

Polymyositis

The cardinal feature of polymyositis, symmetric weakness of proximal muscles (pelvic and shoulder girdle musculature) develops over weeks to months. Patients have difficulty in rising from a chair, climbing stairs, or performing activities that require their hands to be raised over their heads. In patients with more extensive disease, distal weakness can occur, neck flexor weakness can lead to head drop, pharyngeal muscle weakness can result in dysphagia and/or dysphonia, and diaphragm involvement can cause respiratory compromise. Myalgia may or may not be reported. On physical examination, fixed weakness is found in deltoids, biceps, triceps, hip flexors, quadriceps, and hamstrings.

Other features that may be present include fever, dyspnea (due to interstitial lung disease, aspiration, diaphragm weakness, or cardiomyopathy), arthralgia, arthritis, and Raynaud's

phenomenon. Patients may also have signs and symptoms of another connective tissue disease, such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease.

Dermatomyositis

Every sign and symptom listed for polymyositis can occur in patients with dermatomyositis, although myalgia and Raynaud's phenomenon are more common. The feature differentiating the two is the presence of cutaneous involvement. Skin changes can precede, coincide with, or develop after the onset of muscle weakness.

The most characteristic cutaneous manifestations of dermatomyositis include the heliotrope eruption (pink to violaceous erythema of the eyelids, occasionally with associated edema); Gottron's papules (raised erythematous to violaceous papules or plaques on the extensor surfaces of the metacarpophalangeal and interphalangeal joints); and Gottron's sign (erythematous to violaceous macules on the elbows, knees, and lateral malleoli) (4). In addition to these classic clinical findings, additional skin manifestations include erythema and/or poikiloderma in a photosensitive distribution. Typical sites include the midface (which can mimic the malar rash of systemic lupus erythematosus, but involves the nasolabial folds instead of sparing these sites), the anterior neck and chest

(V sign), and the posterior neck and shoulders (shawl sign). In addition to photosensitivity, cutaneous disease in dermatomyositis is often associated with intense pruritus. Scalp involvement can lead to both pruritus and hair loss. Some cutaneous lesions of dermatomyositis can ulcerate and become necrotic. Additional changes that may occur on the hands include periungual erythema, cuticular overgrowth, nail fold capillary changes (dilated capillary loops and drop out of nailfold capillaries), and hyperkeratosis and fissuring of skin on the lateral and palmar aspects of the fingers and hands (mechanic's hands). These rashes can occur alone or in combination. In addition, some patients with the skin disease of dermatomyositis present without muscle disease, referred to as amyopathic dermatomyositis. Notably, cutaneous involvement in dermatomyositis has been found to significantly impact patients' quality of life.

Juvenile Dermatomyositis

Every sign and symptom listed for dermatomyositis above can occur in children with the disease. Children may also experience problems that are rarely observed in adults. Subcutaneous calcification (dystrophic calcinosis) occurs more frequently in children, particularly among those in whom initiation of therapy is delayed or those in whom the disease is poorly controlled with medication. Gastrointestinal problems may include abdominal pain, hematemesis, or melena. These

are the result of bowel infarction or perforation caused by a vasculopathy. Finally, they may develop lipodystrophy, with generalized or focal loss of subcutaneous or visceral fat.

Inclusion Body Myositis

Although some patients with inclusion body myositis present with proximal symmetric muscle weakness, others present with a distal or asymmetric distribution. A common pattern of weakness involves the triceps, wrist flexors, distal finger flexors, quadriceps, and ankle dorsiflexors. Regardless of the muscles affected, weakness generally develops very slowly over months to years. The longer the weakness persists, the more atrophy will be apparent. Dysphagia is common in patients with inclusion body myositis, but the other extramuscular findings that can occur in polymyositis and dermatomyositis are not seen.

CAUSES

The causes of the various forms of myositis are unknown. Polymyositis and dermatomyositis (adult and juvenile) are believed to be caused by environmental triggers that lead to autoimmune dysfunction in genetically susceptible individuals. Autoimmunity is implicated because many of these patients have circulating autoantibodies and they respond to immunosuppressive therapies.

Although inflammatory cells are found in muscle tissue from patients with inclusion body myositis, especially earlier in the disease process, their role in causing muscle weakness is unclear. Although autoantibodies have been found in patients with inclusion body myositis, the weakness appears to be the result of a myodegenerative process, because inclusion body myositis does not respond to immunosuppressive therapy, unlike polymyositis and dermatomyositis.

Polymyositis and Dermatomyositis

The most likely environmental triggers implicated in polymyositis and dermatomyositis are infections. The onset of these diseases often coincides with an infection. Viruses are strong candidates. Enteroviruses can cause a self-limited myositis in children. Retroviruses, human immunodeficiency virus (HIV), and human T-cell lymphoma virus-1 (HTLV-1) can cause myositis. Several viruses can induce various forms of myositis in laboratory animals. High titers of anti-viral antibodies have been found in patients' serum. Nevertheless, attempts to identify virus in patients' tissue have failed (5). It is possible that a virus could be cleared from the body after triggering immune dysfunction. Other infectious agents implicated include certain bacteria and the parasite, toxoplasm in gondii.

Medications may also serve as a trigger. D-penicillamine can cause dermatomyositis. Statins can cause an immune-mediated necrotizing myopathy that has the clinical phenotype of polymyositis (1,2). Many patients with this myopathy have circulating antibodies to HMG CoA reductase and respond to intensive immunosuppressive therapy. Other medications implicated include zidovudine (AZT), hydroxyurea, interferons, L-tryptophan, and growth hormone. In addition, anti-tumor necrosis factor agents have also been implicated in inducing or exacerbating dermatomyositis and polymyositis.

At least 60 percent of patients with polymyositis and dermatomyositis have circulating autoantibodies. The antigen that these autoantibodies are directed against may play a role in the pathogenesis of these diseases. The most common circulating autoantibody is directed against Jo-1 (histidyl-tRNA synthetase). Jo-1 is known to be released from regenerating muscle fibers. When injected into certain mice, Jo-1 causes myositis. In-vitro, Jo-1 induces migration of CD4+ and CD8+ T cells, IL-2 activated monocytes, and immature dendritic cells. All of these cells are present in muscle samples from some patients with polymyositis and dermatomyositis. Thus, Jo-1 could provide a link between the innate immune system by recruiting immune cells into muscle, and acquired immunity by inducing autoantibody formation (6).

There is an increased risk of malignancy in patients with dermatomyositis (7). When the two coincide, treatment or removal of the malignancy may lead to improvement or remission of the myositis. The pathophysiologic link between the two conditions is unclear. The association of the onset of the two, usually within one year of each other, suggests that dermatomyositis may be the consequence of the malignancy or that the two share a common mechanism of disease. The antigens to which myositis-specific autoantibodies are directed are not only expressed in regenerating muscle fibers, but also

in malignant tissues. Thus, an autoimmune response directed against a malignancy may cross-react with regenerating muscle leading to myositis, or vice versa (8).

Ultraviolet light also appears to be a factor in the development of dermatomyositis. The ratio of dermatomyositis to polymyositis is directly correlated with exposure to ultraviolet light, the ratio being highest near the equator and becoming lower the farther away from the equator. Thus, ultraviolet light might trigger dermatomyositis or serve as an exogenous factor that could modify the clinical phenotype of dermatomyositis versus polymyositis (9).

Inclusion Body Myositis

The cause of inclusion body myositis is unknown. Whatever the cause, it leads to muscle fiber degeneration. Previously it was believed not to be an autoimmune disorder, because patients fail to respond to immunosuppressive therapy. More recently a circulating autoantibody directed at cytosolic 5′ nucleotidase 1A, an enzyme involved in purine nucleotide breakdown, has been found in up to half of patients (3). It has been postulated that binding of this autoantibody to its antigen could lead to abnormal nucleic acid metabolism, resulting in muscle fiber degeneration.

PROGNOSIS

Polymyositis and Dermatomyositis

About 40 percent of adults with polymyositis or dermatomyositis will have a monophasic illness and do very well. The vast majority of individuals in this group will be left with no functional disability. About 20 percent of patients will have a remitting and relapsing course, while the remainder will have a chronic progressive disease (10).

The cutaneous manifestations of dermatomyositis may or may not improve with therapy in parallel with the improvement of the myositis. In some patients the weakness and rash resolve together. In others, the two are not linked, with one or the other being more challenging to control. Often, cutaneous disease persists after adequate control of the muscle disease.

The overall five-year survival rate is 95 percent. In general, the autoantibody status helps to predict survival. Most patients with anti-Mi-2 autoantibodies have an excellent response to therapy. The presence of an anti-synthetase autoantibody reduces the mean five-year survival rate to 65 percent, typically due to associated pulmonary involvement. Patients with anti-signal recognition particle (SRP) antibody have a five-year survival rate of 30 percent, which is worse than the rate for patients who have dermatomyositis and an associated malignancy. Other factors that contribute to a poor survival include older age of onset, delayed initiation of therapy, concomitant malignancy, pharyngeal dysphagia with aspiration, interstitial lung disease, and cardiomyopathy.

Juvenile Dermatomyositis

About 60 percent of children have a monophasic illness, with the remainder having a remitting and relapsing course or progressive disease. However, between 65 and 80 percent have a normal to good functional outcome. Approximately 5 percent become wheelchair dependent (11).

The mortality rate is 1 to 2 percent. Risk factors for poor prognosis include unremitting severe disease, dysphagia, dysphonia, vasculopathy, and circulating anti-SRP antibodies. Delay in initiation of therapy is also associated with poor prognosis,

and with the development of subcutaneous calcifications. Of note, children with juvenile dermatomyositis do not have an increased risk of malignancy.

Inclusion Body Myositis

Whereas patients with inclusion body myositis have the worst functional outcomes, they have the best survival rate. The mean decline in muscle strength is slow but persistent at 3.5 to 5.4 percent per year. This results in the majority of individuals becoming completely wheelchair dependent. Life expectancy is normal at 81 years (12).

AFFECTED POPULATIONS

Polymyositis

The age of onset of polymyositis ranges from the late teens and peaks between 50 and 60 years. Females outnumber males in a 2 to 1 ratio. Polymyositis is slightly more common in African Americans than in Caucasians.

Dermatomyositis

The peak age of onset for adults with dermatomyositis is between 45 and 65 years, and the female to male ratio is 2 to 1. The incidence of dermatomyositis in African American women is 10 times that in Caucasian women between the ages of 55 and 64 years.

Juvenile Dermatomyositis

The mean age of onset is 7 years, with peaks for girls between 6 and 11 years. The most common age of onset in

boys is 6 years. Juvenile dermatomyositis is extremely rare in boys over 9 years of age. The overall female to male ratio is 1.7 to 1. The incidence in African American children is similar to that in Caucasian children.

Inclusion Body Myositis

Inclusion body myositis is a disease of the elderly, with onset of disease prior to age 60 years being very rare. This disease is more common in males, with a female to male ratio of 1 to 2.

DIAGNOSIS

Unfortunately, there is no specific test for the diagnosis of any type of myositis. The diagnosis is, therefore, made by finding a pattern of abnormalities on physical examination, laboratory studies, and analysis of muscle tissue. These abnormalities include muscle weakness, elevated serum levels of enzymes derived from skeletal muscle, myopathic changes on needle electromyography (EMG) of muscles, and inflammatory changes in muscle tissue using magnetic resonance imaging or muscle biopsy (13). None of these abnormalities is specific or unique to myositis. Furthermore, not all patients will manifest all of these findings. Therefore, other causes for these abnormalities must be excluded before rendering the diagnosis of one of the forms of myositis.

Physical Examination

Please refer to "signs and symptoms" beginning on page 3.

Muscle Enzymes

Elevated levels of enzymes derived from skeletal muscle are usually an indication of active muscle disease or injury. These enzymes include creatine kinase (CK), aldolase, alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). All or any combination of these can be elevated in an individual patient. The CK is the enzyme most commonly tested and followed, and is elevated in the vast majority of patients at presentation. Normal values are more likely to be encountered in dermatomyositis than in polymyositis. The increase in level ranges from 1.5 to 20 times the upper limit of normal.

Needle Electromyography (EMG)

The changes reported on needle EMG in patients with active polymyositis or dermatomyositis include polyphasic motor units of low amplitude and short duration (myopathic motor units); fibrillations and positive sharp waves; and bizarre, repetitive discharges. These myopathic changes are

characteristic of inflamed muscle but are not specific. Only 40 percent of patients will have all of these changes. In 10 percent, EMGs are entirely normal. This may be due to sampling error because not all muscles are affected in these diseases; muscles showing EMG abnormalities are those that are inflamed, whereas those lacking EMG abnormalities usually show no inflammation.

EMG changes in patients with inclusion body myositis can be identical to those described above. However, they may also have some changes that are considered neuropathic.

Magnetic Resonance Imaging (MRI)

MRI is a means of sampling large volumes of muscle in a non-invasive manner. The presence of edema in skeletal muscle by this technique is a strong indicator of inflammation and is suggested by increased signal on T2 and STIR sequences or by gadolinium enhancement. MRI is also an excellent method for determining the site for muscle biopsy, to make certain the specimen is taken from an abnormal area. In children, the presence of edema in muscle in a patient with proximal muscle weakness, elevated muscle enzymes, and myopathic changes on EMG may obviate the need for muscle biopsy.

Muscle Biopsy

Histology of skeletal muscle in classic polymyositis reveals degenerating and regenerating muscle fibers with CD8+ T cells invading and surrounding muscle fibers. In contrast, in dermatomyositis, perifasicular atrophy is observed and the invading inflammatory cells are CD4+ lymphocytes, plasmacytoid dendritic cells, and B lymphocytes localized to perivascular areas. In inclusion body myositis, the changes are similar to those seen in polymyositis, although milder; the finding of rimmed or lined vacuoles or inclusions in muscle fibers containing basophilic granular material can be helpful. In addition, histochemistry can reveal angular atrophic muscle fibers and fiber type grouping, signs of denervation and renervation, respectively.

In some patients the findings are far from classic, showing nonspecific myopathic changes. In others the biopsy can be normal. This is, again, believed to be the result of sampling error due to the heterogeneous or patchy distribution of changes within various muscles.

Autoantibodies

Greater than 60 percent of patients with polymyositis and dermatomyositis have circulating autoantibodies. Some of these

are termed myositis-specific autoantibodies (MSAs) because they are found only in patients with myositis. Others are termed myositis associated autoantibodies (MAAs) because they lack specificity and occur in overlap syndromes. Finally, certain autoantibodies would indicate an association with another connective tissue disease. For example, the presence of anti-double stranded-DNA antibodies would point to systemic lupus erythematosus, whereas the presence of anti-Scl-70 antibodies would indicate scleroderma as an associated disorder.

MSAs are of three types. Those directed against nuclear helicase are termed anti-Mi-2. Others are directed against antigens in the pathway for protein synthesis. These include antibodies directed against anti-signal recognition particle (anti-SRP) or against amino acyl-transfer-RNA synthetases. There are six anti-synthetases that can be measured in commercial laboratories: anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, and anti-KS.

The finding of an MSA helps predict the clinical pattern of disease as well as prognosis. Patients with anti-Mi-2 autoantibodies almost all have dermatomyositis and respond very well to therapy. Patients with anti-SRP autoantibodies have polymyositis, can have cardiomyopathy, and have the worst prognosis. Those with anti-synthetase autoantibodies can

have either polymyositis or dermatomyositis and are likely to also have interstitial lung disease, fever, arthritis, Raynaud's phenomenon, and mechanic's hands. These patients tend to have disease that is challenging to manage, often having a remitting-relapsing course.

Skin Biopsy

Histopathology of skin biopsies from patients with dermatomyositis shows perivascular inflammation, hyperkeratosis in the stratum corneum, epidermal atrophy, follicular plugging, and interface dermatitis (inflammatory cells at or obscuring the dermal-epidermal junction). These changes are not specific for dermatomyositis because they can also be seen in systemic lupus erythematosus.

Screening for Malignancy

The diagnostic evaluation in a patient with dermatomyositis should include screening for malignancy because of the high association between the two conditions. The best data indicates that approximately one in four patients with dermatomyositis will have an associated malignancy. In addition to a thorough history and physical examination, patients should be screened for malignancy appropriate for their age and gen-

der. CT scans of chest, abdomen, and pelvis are indicated. Women should also be screened for ovarian cancer with transvaginal pelvic ultrasound and measurement for CA-125.

Diseases to Exclude

Because the criteria used to establish the diagnosis of a particular form of myositis are nonspecific, patients with other diseases may fulfill them. The list of diseases that can cause muscle weakness, elevated muscle enzymes, myopathic EMG findings, and/or myopathic changes on muscle biopsy is extensive.

Primary neuropathic disorders that can mimic inflammatory myopathies include amyotrophic lateral sclerosis, chronic spinal muscular atrophy, and myasthenia gravis. The limb-girdle and facioscapulohumeral muscular dystrophies not only cause proximal muscle weakness, elevated enzymes, and myopathic EMG changes, but also can have inflammatory infiltrates in muscle biopsies early in their course. Myophosphorylase deficiency (McArdle's disease), acid maltase deficiency, and mitochondrial myopathies are metabolic disorders that should be considered. Endocrinopathies such as Cushing's syndrome, hypothyroidism, hyperthyroidism, hyperparathyroidism, and acromegaly must be ruled out. HIV or

HTLV-1 infections may be very difficult to differentiate from myositis. Statins, alpha-interferons, and some medications used to treat HIV infections can lead to muscle involvement and clinical confusion. Muscle biopsies from patients with myopathies caused by colchicine, hydroxychloroquine, or alcohol may show vacuoles in fibers and can thus be confused with inclusion body myositis.

The hereditary inclusion body myopathies should not be mistaken for sporadic inclusion body myositis. Although the hereditary inclusion body myopathies share some of the pathologic changes observed in sporadic inclusion body myositis — lined or rimmed vacuoles on histology and tubular inclusions on electron microscopy — these conditions are otherwise quite different. The average age of onset in hereditary inclusion body myopathy is between the teenage years and mid-twenties. The muscle weakness is usually distal and may be accompanied by ophthalmoplegia, brain white matter disease, or bulbar weakness. Creatine kinase levels range from normal to slightly elevated. EMG results are normal. Finally, there is no inflammation in muscle tissues. Inheritance can be autosomal dominant or recessive. Other than a suggestion that sialic acid may be useful, there is no specific therapy for these conditions.

TREATMENT

Patients with polymyositis and dermatomyositis (adult and juvenile) are treated with physical exercise and immunosuppressive agents (15, 16). The choice of which immunosuppressive agent(s) to use is empiric because evidence favoring any one is lacking. There have only been seven controlled clinical trials. All of these but one involved fewer than 40 subjects, and each trial involved different agents. Today, there is no evidence that patients with inclusion body myositis benefit from immunosuppressive therapy, but they do benefit from exercise.

Recent studies have shown that regular exercise not only improves strength and function for patients with all forms of myositis, but also has anti-inflammatory effects (15). Exercise programs should be tailored for each individual, begin at low intensity, and progress slowly. One approach is to have

the patient do aerobic exercise every other day three times a week alternating with anaerobic exercise for the alternate three days, then one day of rest.

Glucocorticoids form the foundation for the treatment of polymyositis and dermatomyositis (adult and juvenile). Depending on the severity of disease at the time of diagnosis, they may be initiated as a single agent or in combination with others. Most initial doses are the equivalent of 1 to 2 mg/kg per day of prednisone, although some advocate pulsing initially with high dose intravenous methylprednisolone. Regardless, high doses are usually maintained for 6 to 12 weeks or more, because these diseases tend to respond slowly. If a patient responds dramatically (for example, in one to two weeks) it is likely that the patient has an associated connective tissue disease such as systemic lupus erythmatosus.

Many other immunosuppressive agents have been employed to treat polymyositis and dermatomyositis. All of them have been effective in some cases, but ineffective in others. The agents shown to be effective in clinical trials include azathioprine, methotrexate, and intravenous immune globulin (IVIg). In very severe disease (patients with severe weakness and head drop, dysphagia, or aspiration pneumonia), any of these might be started along with high dose glucocorticoids. Whereas glucocorticoids might be used as a single agent in

a case diagnosed early with mild weakness and no other issues, in others, azathioprine or methotrexate might be added as a steroid-sparing agent. The choice of using a single agent or combination therapy from the outset comes down to clinical judgment.

Clinical trials with infliximab, etanercept, and rituximab have provided mixed results, although clearly some patients did benefit from these therapies. Rituximab was studied in 200 patients with refractory polymyositis, dermatomyositis, or juvenile dermatomyositis. The trial was deemed negative because the primary endpoint was not met. Nevertheless greater than 80 percent of subjects met the definition for improvement. It appears that patients who have anti-synthetase or anti-Mi-2 autoantibodies were the best responders. Other immunosuppressive agents that have proven to be beneficial for some patients in uncontrolled trials include chlorambucil, cyclophosphamide, cyclosporine, mycophenolate mofetil, and tachrolimus.

ACTH gel is the only medication, other than glucocorticoids, that has an FDA-approved indication for the treatment of polymyositis or dermatomyositis. Clinical trial data with this agent are, however, lacking (17). It is now recognized that ACTH has anti-inflammatory and immunomodulatory activities in addition to stimulating cortisol production by the adrenal cortex.

These are mediated by a group of compounds that bind to melanocortin receptors.

The sooner in the course of the myositis that safe and effective treatment is initiated, the better the chance for a successful outcome. Unfortunately, there are patients that do not achieve remission. When that happens, several questions should be addressed. Was the immunosuppressive dosing high enough or long enough? Could the concomitant development of steroid myopathy complicate the picture? In adults with dermatomyositis, could they have an associated malignancy? If these potentials can be eliminated, then it is possible that the patient either has a refractory form of disease (anti-SRP antibody-positive polymyositis, or inclusion body myositis) or the diagnosis of myositis is inaccurate.

Treatment of skin disease in dermatomyositis can be particularly challenging. All patients with adult or juvenile dermatomyositis need to be counseled regarding strict photoprotection because sun exposure is known to exacerbate their skin disease. In addition, topical corticosteroids, topical calcineurin inhibitors, and antimalarial agents are often given to improve skin disease and alleviate the associated pruritus. Many patients with refractory skin disease require additional therapies, such as methotrexate, mycophenolate mofetil, or intravenous immunoglobulin, among others.

INVESTIGATIVE THERAPIES

A study giving an antibody to interferon-alpha patients with polymyositis and dermatomyositis has been conducted. Interferon-alpha is produced by plasmacytoid dendritic cells. These cells are present in the inflammatory infiltrate in muscle from some patients. Products of genes that are unregulated by interferon-alpha are increased in muscle from most adults and children with dermatomyositis and in the blood from some patients with polymyositis.

Two trials are under way in patients with inclusion body myositis. Each seeks to block the action of myostatin, a cytokine that inhibits muscle growth. Myostatin levels are increased in inclusion body myositis. One strategy involves injection of virus containing the gene for follistatin into quadriceps muscles. Follistatin is a potent antagonist of myostatin. The other involves administration of bimagrumab, a human monoclonal antibody that binds with high affinity type II actin receptors. These are the receptors myostatin must bind to in order to inhibit muscle growth.

Information on current clinical trials is posted online at www.clinicaltrials.gov.

REFERENCES

1. Mammen AL. *Dermatomyositis and polymyositis: clinical presentations, autoantibodies and pathogenesis*. Ann NY Acad Sci 2010;1184:134-142.

2. Amato AA, Greenberg SA. *Inflammatory myopathies*. Continuum 2013;19:1615-1633.

3. Greenberg SA. *Biomarkers of inclusion body myositis*. Curr Opin Rheumatol 2013;25:753-762.

4. Callen J, Wortmann RL. *Dermatomyositis*. Dermatol Clin 2006;24:363-373.

5. Left RL, Love LA, Miller FW, et al. *Viruses in idiopathic inflammatory myopathies: absence of candidate viral genomes in muscle*. Lancet 1992;339:1192-1195.

6. Miller FW,Twitty SA, Biswas T, Plotz PH. *Origin and regulation of the disease-specific autoantibody response: antigenic epitopes, spectrotype stability, and isotype restriction of anti-Jo-1 autoantibodies*. J Clin Invest 1990;85:468-475.

7. Antiochos B, Brown LA, Wortmann RL, et al. *Malignancy is associated with dermatomyositis but not polymyositis in northern New England*. J Rheumatol 2009;36:2704-2710.

8. Rosen A, Casciola-Rosen L. *Stem cells in inflammatory disease*. Curr Opin Rheumatol 2005;17:699-700.

9. Okada S. *Global surface ultraviolet radiation intensity may modulate the clinical expression of autoimmune muscle disease*. Arthritis Rheum 2003;48:2285-2293.

10. Sultan SM, Iannou V, Moss K, Isenberg DA. *Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality*. Rheumatol 2002;41:22-26.

11. Ravelli A, Trail L, Ferrari A, et al. *Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multi-center study of 490 patients*. Arthritis Care Res 2010;62:63-72.

12. Cox FM, Titulaer MJ, Soni JK, et al. *A 12-year follow-up in sporadic inclusion body myositis: and end stage with major disabilities*. Brain 2011;134:3167-3175.

13. Bohan A, Peter J. *Polymyositis and dermatomyositis (first of two parts)*. N Engl J Med 1975;292:344-347.

14. Alexanderson K, Lundberg IE. *Exercise as a therapeutic modality in patients with idiopathic inflammatory myopathies*. Curr Opin Rheumatol 2012;24:1-7.

15. Marie I, Mouthon L. *Therapy of polymyositis and dermatomyositis*. Autoimmun Rev 2011;11:6-13.

16. Rider LG, Katz JD, Jones OV. *Developments in the classification and treatment of the juvenile idiopathic inflammatory myopathies*. Rhem Dis Clin N A. 2013;39:877-904.

17. Levine T. *Treating refractory dermatomyositis or polymyositis with adrenocorticotropic hormone gel: a retrospective case series*. Drug Design Devel Ther 2012;6:133-139.

The Myositis Association has support groups around the United States to allow myositis patients to share information about treatments and coping with the disease. Additionally, TMA's website (www.myositis.org) offers a Community Forum, which is a place where patients can post comments online regarding treatments and other information related to myositis. Discussions of treatments and therapies in the Forum are not the opinions of TMA or its Medical Advisory Board.

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