Idiopathic Inflammatory Myopathies

Robert L. Wortmann, M.D., F.A.C.P., F.A.C.R.
University of Oklahoma College of Medicine-Tulsa

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by proximal muscle weakness and nonsuppurative inflammation of skeletal muscle. These are rare disorders with estimates of incidence ranging from 0.5 to 8.4 cases per million. Generally accepted criteria for the diagnosis of these diseases include 1) proximal muscle weakness, 2) elevated serum levels of enzymes derived from skeletal muscle, 3) electromyographic evidence of myopathy, and 4) inflammatory changes on muscle histology. The addition of a skin rash (criterion 5) allows the diagnosis of dermatomyositis. Specific diseases within the IIM are defined based on the patient's age, additional findings, or the coexistence of another disease. The presence of circulating myositis-specific autoantibodies (MSAs) allow for further classification.

Defined Diseases

Polymyositis

The clinical features of polymyositis in the adult are representative of all IIM. The disease typically begins insidiously over 3-6 months with no identifiable precipitating event. Shoulder and pelvic girdle muscles are most affected. Weakness of neck muscles, particularly the flexors, occurs in about half the patients, but ocular and facial muscles are virtually never involved. Dysphagia may develop secondary to esophageal dysfunction or cricopharyngeal obstruction. Pharyngeal muscle weakness may cause dysphonia and difficulty swallowing. Myalgias and arthralgias are not uncommon, but severe tenderness and frank synovitis are unusual. Raynaud's phenomenon is sometimes present, and periorbital edema may occur. Pulmonary and cardiac manifestations may develop at any time during the course of disease. Velcro-like crackles may be heard on chest auscultation with interstitial fibrosis or interstitial pneumonitis. Aspiration pneumonia may complicate the disease course in patients with swallowing difficulties. Cardiac involvement is usually restricted to asymptomatic electrocardiographic abnormalities, although supraventricular arrhythmia, cardiomyopathy, and congestive heart failure may develop.

The CK level is elevated at some time during the course of disease. Elevation of serum CK level is a reasonable indicator of disease severity. Other muscle enzymes are also elevated in most cases, including aldolase, AST, ALT and LDH.
Electromyography classically reveals the following triad: 1) increased insertional activity, fibrillations, and sharp positive waves; 2) spontaneous, bizarre high-frequency discharges; and 3) polyphasic motor unit potentials of low amplitude and short duration. This triad is characteristic but not diagnostic. The complete triad is seen in approximately 40% of patients. In contrast, 10%-15% of patients may have completely normal EMGs. On histology, muscle fibers are found to be in varying stages of necrosis and regeneration. The inflammatory cell infiltrate is predominantly focal and endomysial. T lymphocytes, especially CD8+ cytotoxic cells accompanied by a smaller number of macrophages, are found surrounding the invading initially non-necrotic fibers.

Dermatomyositis

The clinical features of dermatomyositis include all those described for polymyositis plus a variety of cutaneous manifestations. Skin involvement varies widely from patient to patient. Gottron's papules or sign — symmetric lacy pink or violaceous raised or macular areas typically found on the dorsal aspect of interphalangeal joints, elbows, patellae, and medial malleoli — are considered pathognomonic. Other characteristic changes include heliotrope discoloration of the

eyelids and macular erythema of the shoulders and neck (shawl sign), neck and upper chest (V-sign), face and forehead. Muscle histopathology of classic dermatomyositis shows perivascular infiltration of inflammatory cells, composed of B lymphocytes and CD4+ T helper lymphocytes, and capillary plugging with perifascicular atrophy.

Variants of dermatomyositis include amyotrophic dermatomyositis and juvenile dermatomyositis. The former describes patients with biopsy-confirmed, classic cutaneous findings of dermatomyositis have no clinical evidence of muscle disease. Some of these patients do progress over time and become weak. Juvenile dermatomyositis differs from the adult form because of the coexistence of vasculitis, ectopic calcification, and lipodystrophy. The accompanying may be devastating despite therapy.

Myositis and Other Collagen Vascular Diseases

Muscle weakness is a common finding in patients with collagen vascular diseases. The features of idiopathic inflammatory myopathy may dominate the clinical picture in some patients with scleroderma, systemic lupus erythematosus, mixed connective tissue disease, and Sjogren's syndrome.

Myositis and Malignancy

There is an association between IIM a malignancy, but the true incidence of this relationship is not clear. The association may be more common with dermatomyositis. The sites or types of malignancy are those expected for age and gender of the individual with the exception of ovarian cancer that is over-represented.

Inclusion Body Myositis

Inclusion body myositis (IBM) mainly affects older individuals. Symptoms begin quite insidiously and progress very slowly. The clinical picture may differ from that of typical polymyositis. There may be focal, distal, or asymmetric weakness and neurogenic or mixed neurogenic and myopathic changes can be observe with EMG. As the muscle weakness becomes severe, it is accompanied by atrophy and diminished deep-tendon reflexes. In some patients, the disease continues a slow, steady progression, while it seems to plateau in others, leaving the individual with fixed weakness and atrophy of the involved musculature.

On histology, IBM is characterized by the presence of intracellular lined vacuoles. Electron microscopy reveals either intracytoplasmic or intranuclear tubular or filamentous inclusions. These structures are straight and rigid-appearing with periodic transverse and longitudinal striations. Myelin figures (also called myeloid bodies) and membranous whorls are also common. Although the finding of lined vacuoles is not specific for IBM, the positive staining for amyloid proteins in the fibers that contain them is indicative.

Myositis-specific Autoantibodies

Several autoantibodies (MSAs) are found almost exclusively in patients with IIM. The presence of a particular MSA appears to identify relatively homogeneous groups of patients with regards to clinical manifestations and prognosis. With extremely rare exception an individual patient will have only one MSA. The most common MSAs are directed against amino acyl-tRNA synthetase activities. The most common of these is anti-histidyl-tRNA synthetase, termed anti-Jo-1. Patients with anti-synthetase autoantibodies typically manifest myositis (polymyositis more commonly than dermatomyositis) plus extramuscular features including interstitial lung disease, arthritis, Raynaud's phenomenon, and mechanic's hands. Typically these patients are difficult to treat because they tend develop or sustain complete remission. Anti-Mi-2 antibodies are directed against helicase activities. These are found almost exclusively in patients with dermatomyositis and who respond well to treatment. Anti -SRP (signal recognition particle) antibodies are found in sudden onset, treatment resistant polymyositis.

Treatment

Unfortunately the number of controlled trials is too small to provide significant evidence regarding therapy. Therefore the treatment of the IIM is largely empiric. Before initiating treatment, the patient's clinical status should be evaluated as objectively as possible. Pretreatment testing of the strength of individual muscle groups provides valuable information, and these baseline measures can be compared with those obtained after therapy is initiated. Chest radiography, pulmonary function studies, and fluoroscopic swallowing studies may be indicated. Muscle enzymes, including CK, aldolase, SGOT, SGPT and LDH, should be

measured in addition to other laboratory values that might be affected by therapy. Cancer screening tests indicated by the patient's age and gender should not be overlooked.

Physical therapy may play an important role in therapy. Bed rest may be required during intervals of severe inflammation. Passive range of motion exercise is encouraged during these intervals to maintain movement and prevent contractures. With improvement, therapy should include active-assisted, and then active exercises. Active exercises can be performed without adversely affecting diseased muscle and may prove beneficial in preventing atrophy of uninvolved tissue.

Glucocorticoids are the standard first-line medication for any IIM. Initially prednisone is usually given in a single dose of 1 mg/kg/day, but in severe cases the daily dose can be divided or intravenous methylprednisolone used. Clinical improvement is generally seen to occur gradually over 3-6 months. It is believed that the earlier in the disease course prednisone is started, the faster and more effectively it works. As many as 90%, of patients improve, at least partially, with glucocorticoid therapy, with 50%-75% of those achieving complete remission.

If a patient fails to respond to glucocorticoid therapy, another agent is added, usually either azathioprine or methotrexate. Methotrexate is administered on a weekly schedule at doses of 5-15 mg orally or 15-50 mg intravenously. The typical dose of azathioprine is 2-3 mg/kg/day (maximum of 150 mg/day). Other immunosuppressive agents have been used in steroid-resistant patients. Cyclophosphamide, 6-mercaptopurine, chlorambucil, cyclosporine, mycophenolate, etanercept, infliximab, plasmapheresis, lymphapheresis, total-body (or total-nodal) irradiation, and intravenous immunoglobulin have also been used. Hydroxychloroquine can be used to treat the cutaneous lesions of dermatomyositis, although it has no recognized effect on the myositis. Failure of treatment may result from in adequate dosages of the chosen medications, a treatment resistant IIM (IBM, anti-SRP positive myositis, or myositis with malignance), or an incorrect diagnosis. One should be particularly concerned about the latter, because the criteria used to define an IIM are nonspecific and the differential diagnosis of proximal muscle weakness and an elevated CK is extremely large.

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