

AUTOIMMUNE-MYOSITIS

INTRODUCTION

Autoimmune myositis is an inflammatory process characterised by chronic inflammation of striated muscle (polymyositis) and sometimes skin (dermatomyositis). Autoantibody associations define homogeneous subsets (eg Jo-1, anti-Mi-2). The clinical features include *painless* proximal muscle weakness with or without a rash. Other organ involvement includes joints, lungs (fibrosis), heart and GIT tract. Investigations usually show an abnormal EMG, elevated CPK and abnormal muscle biopsy.

EPIDEMIOLOGY

In polymyositis/dermatomyositis, several different classification systems have been proposed. Although all classifications identify these disorders as part of a single disease spectrum, certain important features are used to separate subsets, including the distinctions between childhood and adult onset, polymyositis versus dermatomyositis and the presence or absence of malignancy and other connective tissue diseases. In polymyositis/dermatomyositis, approximately 50% of patients can be classified by myositis-specific autoantibody status, and for several of these autoantibodies, strong HLA associations have been described (see later).

Incidence by Age, Race and Sex

The annual incidence of polymyositis/dermatomyositis ranges from 2-10 new cases per million persons. Although inflammatory myopathy can occur at any age, the observed pattern of incidence includes childhood and adult peak and a paucity of patients with onset in the adolescent and young adult years. The incidence sex ratio is: 2.5:1 female to male. This ratio is lower (nearly 1:1) in childhood disease and with associated malignancy, but is very high 10:1 when there is an associated connective tissue disease. Polymyositis/dermatomyositis has a 3-4:1 Black to White incidence ratio, with a Black young adult onset peak.

Environmental Factors

No striking associations with environmental factors have been identified. Disease onset is more frequent in the winter and spring months, especially in childhood cases, consistent with precipitation by viral and bacterial infections. Serum antibodies to coxsackie B viruses are more frequent in childhood dermatomyositis compared with juvenile RA controls. In one study, polymyositis/dermatomyositis patients reported excessive physical exercise antedating illness significantly more frequently than controls, but this association has not been confirmed. D-penicillamine is a drug capable of inducing true myositis.

Genetic Factors

The occurrence of polymyositis/dermatomyositis in monozygotic twins and first degree relatives of cases supports a genetic predisposition, at least in some families. It is not uncommon to find that close relatives suffer from other autoimmune diseases. White children with dermatomyositis and adults with polymyositis have an increased frequency of HLA-B8/DR3, and HLA-B14 and

B40 have been observed more commonly in adults with dermatomyositis coexisting with another connective tissue disease. In polymyositis, Whites were noted to have HLA-B8/DR3, while Blacks more often had HLA-B7/Drw6. HLA is considerably more closely linked to several recently identified serum autoantibodies which have been found to define clinically homogeneous patient groups. Anti-Jo-I antibody patients have a significantly increased frequency of HLA-DRw52 compared with control person, and those with anti-PM-Scl, nearly all possess HLA-DR3 or DRw52.

PRESENTATIONS

The most frequent problem is insidious, progressive painless proximal muscle weakness over the course of 3-6 months prior to the first physician visit. Some patients, especially children and young adults with dermatomyositis, have a more acute onset with muscle pain and weakness developing rapidly over the course of several weeks. In the latter case, constitutional features such as fever and fatigue are more common. A few patients complain only about proximal myalgias. There is also a subset of patients with very slowly evolving weakness over the course of 5-10 years before diagnosis; they are typically men with pelvic girdle and distal extremity muscle weakness who have inclusion body myositis on muscle biopsy. Differentiation from muscular dystrophy may be difficult in this circumstance. The degree of muscle weakness at the time of first physician evaluation is highly variable.

Of particular note is the rarity of Raynauds phenomenon and arthralgias in pure polymyositis (except anti-Jo-1 disease) and the absence of distal extremity and neck extensor weakness in patients with malignancy.

In addition to the shoulder and pelvic girdle, other striated muscles may be weak. Examples of such findings, which each occur at presentation in approximately 5% of patients, are bulbar muscle weakness with dysphonia, pharyngeal dysphagia leading to aspiration pneumonia and respiratory muscle weakness, with or without interstitial lung disease causing dyspnea.

The rash of dermatomyositis can precede myositis. Anti-Jo-I antibody patients may first note Raynaud's phenomenon, polyarthralgias and/or polyarthritis, or dyspnea due to interstitial lung disease. When an overlap syndrome is present, one may encounter early scleroderma symptoms and signs such as puffy fingers, sclerodactyly, and distal esophageal dysphagia or lupus findings including photosensitive and/or malar skin rash, alopecia, pleurisy or oral ulceration.

CLINICAL FEATURES

1. Constitutional. Fatigue in the sense of loss of well-being is present in most patients with polymyositis/dermatomyositis. Fever occurs in a few individuals with dermatomyositis, especially children and young adults. Significant weight loss is uncommon.

2. Skeletal Muscle. Patients complain of difficulty in performing activities requiring normal upper and/or lower limb strength. Pelvic girdle weakness leads to reduced strength in running, climbing stairs, and arising from a chair or toilet seat. Walking may become clumsy with a waddling gait, and the patient may fall more frequently and if so, be unable to arise from the floor without assistance. Upper extremity weakness is manifested by difficulty raising an

object overhead, inability to keep one's arms up while combing hair, or loss of grip strength. Neck flexor weakness is appreciated by difficulty raising the head from a pillow. Bulbar weakness results in hoarseness or dysphonia, difficulty in initiating swallowing with regurgitation of liquids through the nose and episodic coughing immediately after swallowing. Muscle pain is present in up to a half of patients but is seldom volunteered during history taking. Physical examination is necessary to confirm weakness of individual muscles or groups of muscles. The severity of muscle weakness at each visit should be recorded. The distribution of the muscle weakness is usually symmetric, affecting all proximal muscles. The shoulder and hip girdles are involved equally. The severity of weakness is almost always less in the distal muscles of the extremities, except in the circumstance of inclusion body myositis. Overall, distal muscles are weak in only 10-20% of patients. Ocular and facial muscles are rarely involved. Muscle tenderness is present in half of patients but is not a prominent finding. Swelling of muscle is usual, and atrophy is a presenting feature only in long-standing previously undiagnosed myopathy, particularly inclusion body myositis. True muscle hypertrophy favors one or another of the forms of muscular dystrophy.

3. Skin. When typical, the skin lesions of dermatomyositis are often virtually pathognomonic of this disease. The sites of predilection are the upper eyelids, malar areas, bridge of the nose and nasolabial folds, V areas of the anterior chest and neck, upper back, extensor surfaces of the elbows, knees, metacarpophalangeal and proximal interphalangeal joints and the periungual areas. Characteristic early lesions are erythematous or violaceous (heliotrope, lilac) and *scaling* is a prominent feature. Edema may be present, especially where the subcutaneous tissue is loose, such as the upper eyelids. Slightly raised or flat plaques over the finger joints are known as Gottron's papules. Cracking or fissuring of the distal digital pad skin has been termed 'machinist' or 'mechanic' hands. Later in their evolution, the affected skin lesions become shiny, atrophic and often hypopigmented. Other cutaneous findings reported to be associated with polymyositis/dermatomyositis include panniculitis, cutaneous mucinosis, vitiligo, and multifocal lipoatrophy.

4. Other Features

Joints. Polyarthralgias and/or polyarthritis, if they occur, are rheumatoid-like in distribution. The wrists, knees and small joints of the hands are most frequently affected. Arthritis tends to occur early in the course of disease and to be mild and transient. Deforming arthritis is unusual.

Calcinosis. Calcification can be a disabling late problem in polymyositis/dermatomyositis. It occurs most commonly in chronic dermatomyositis, especially with onset in childhood and is rare in adult onset disease. Myositis may be well-controlled or inactive at the time when calcinosis appears. Intracutaneous, subcutaneous, and fascial sites are affected, as well as the connective tissue surrounding muscle bundles. There is a predilection for sites of repeated microtrauma (elbows, knees, flexor surfaces of fingers, buttocks).

Respiratory. Dyspnea on exertion is a nonspecific but serious symptom in patients with polymyositis/dermatomyositis. It may be due to non-pulmonary problems such as inspiratory and expiratory respiratory muscle (diaphragm, intercostal) weakness, or congestive heart failure or

cardiac arrhythmia from myocardial or conduction system involvement. Intrinsic causes of dyspnea include interstitial alveolitis or fibrosis, aspiration pneumonia from pharyngeal dysmotility, superimposed bacterial infection, and methotrexate pulmonary toxicity. Cough is frequent, especially with advanced interstitial disease. Pleurisy and pleural effusion are rarely noted. Physical examination findings include decreased chest expansion with weakness of the muscles of respiration and bibasilar fine, crepitation.

There are three common presentations of lung disease in polymyositis/dermatomyositis. The most severe is an aggressive form of diffuse alveolitis with a nonproductive cough and rapid progression of dyspnea; the opposite is the case in a more slowly progressive form of lung disease in which disability from myopathy may mask the severity of the pulmonary involvement; finally, many asymptomatic persons have radiographic and/or physiologic manifestations of interstitial lung disease.

Cardiac involvement. Cardiac involvement is common but seldom symptomatic until it is very advanced. The most frequent abnormality is a rhythm disturbance, and, thus, palpitations or symptomatic arrhythmias may occur. Less common is congestive heart failure due to myocarditis or fibrous replacement of the myocardium. Symptomatic pericarditis is rare.

Gastrointestinal tract. Cervical (pharyngeal) dysphagia in myositis is characterized by difficulty in initiating swallowing, nasal regurgitation of liquids and dysphonia. When severe, there may be aspiration into the tracheobronchial tree. The differential diagnosis includes cricopharyngeal muscle dysfunction. Involvement of the smooth muscle of all portions of the intestinal tract from the thoracic esophagus through the colon is uncommon, except when there is overlap with systemic sclerosis. Such patients virtually always have associated Raynaud's phenomenon.

Renal involvement. Renal disease is rare in polymyositis/dermatomyositis.

Association with malignancy. The relationship between myositis and malignancy is controversial. The most common relationship (50%) is myopathy preceding evidence of malignancy. The frequency of malignancy in myositis derived from large medical center case series is regarded to be 1-15%, but community studies would suggest a lower figure, closer to 5%. Cancer in myositis patients is most frequently obvious rather than occult. Thus, work-up for malignancy in myositis patients should consist of a careful history and physical examination and routine laboratory evaluation with directed individualized follow-up of any abnormalities found which cannot be explained by myositis e.g. iron-deficient anemia or microscopic hematuria. An increased index of suspicion of malignancy is warranted if the patient has digital vasculitis or a normal serum creatine kinase level.

DIFFERENTIAL DIAGNOSIS

MUSCLE WEAKNESS

*Denervating conditions: spinal muscular atrophies, amyotrophic lateral sclerosis

*Neuromuscular junction disorder: Eaton-Lambert syndrome, myasthenia gravis

- *The genetic muscular dystrophies: Duchenne's fascioscapulohumeral, limb girdle, Becker's, Emery-Dreifuss type, distal, ocular
- *Myotonic diseases: dystrophia myotonica, myotonia congenita
- *Congenital myopathies: nemaline, mitochondrial, centronuclear, central core
- *Glycogen storage diseases: adult onset acid maltase deficiency, McArdle's disease
- *Lipid storage myopathies: carnitine deficiency, carnitine palmitoyltransferase deficiency
- *The periodic paralyses
- *Myositis ossificans: generalized and local
- *Endocrine myopathies: hypothyroidism, hyperthyroidism, acromegaly, Cushing's disease, Addison's disease, hyperparathyroidism, hypoparathyroidism, vitamin D deficiency myopathy, hypokalemia, hypocalcemia
- *Metabolic myopathies: uremia, hepatic failure

Toxic myopathies: acute and chronic alcoholism, drugs including penicillamine, clofibrate, chloroquine, emetine

- *Nutritional myopathies: vitamin E deficiency, malabsorption
- *Carcinomatous neuromyopathy: carcinomatous cachexia
- *Acute rhabdomyolysis'
- *Proximal neuropathies: Guillain-Barre syndrome, acute intermittent porphyria, chronic autoimmune polyneuropathy
- *Microembolization by atheroma or carcinoma
- *Polymyalgia rheumatica
- *Other collagen vascular diseases: rheumatoid arthritis, scleroderma, systemic lupus erythematosus, polyarteritis nodosa
- *Infections: acute viral, including influenza, mononucleosis, rickettsia, coxsackie virus, rubella and rubella vaccination, acute bacterial including typhoid
- *Parasites: including toxoplasma, trichinella, schistosoma, cysticerci, sarcosporidia
- *Septic myositis: including staphylococcus, streptococcus, clostridium *welchii*, and leprosy

Myasthenia gravis is the prototypical disorder of the neuromuscular junction, in which weakness often affects the extraocular and bulbar muscles and becomes worse with repetitive contraction. A similar pattern of activity-increased weakness is found in Eaton-Lambert syndrome. Both of these diseases can cause proximal muscle weakness, but can be separated from polymyositis/dermatomyositis by their characteristic electromyographic patterns as well as absence of serum muscle enzyme elevation.

Glycogen storage diseases result from enzyme deficiencies involving the glycolytic pathway. McArdle's disease, or myophosphorylase deficiency, is caused by failure to degrade glycogen for energy under anaerobic conditions. Disorders of muscle lipid metabolism may mimic polymyositis. Carnitine deficiency results in inability to transport long-chain fatty acids into mitochondria for oxidation, leading to lipid accumulation in muscle fibers and a chronic proximal myopathy.

Other causes of proximal myopathy include vitamin D deficiency, adrenal insufficiency, hypophosphatemia, hyperthyroidism, carcinomatous neuromyopathy and exposures to various toxic substances. A variety of drugs are capable of producing inflammatory or noninflammatory myopathy include: chloroquine, cimetidine, clofibrate, colchicine, corticosteroids, cyclosporin. Ethanol, heroine, ipecac, levadopa, lovastatin, penicillamine, phenytoin, nicotinic acid, vincristine, zidovudine.

OTHER INFLAMMATORY MYOPATHIES

1. **Inclusion body myositis**, is characterized by painless proximal and distal muscle weakness of insidious onset, typically in older men. The serum creatine kinase level is normal or minimally elevated. Other connective tissue disease features are usually absent. Muscle biopsy shows vacuoles with basophilic granules and both intranuclear and intracytoplasmic tubulofilamentous inclusions. Although these inclusions resemble viral particles, the presence of large numbers of activated T cells in the endomysial infiltrate suggests immune-mediated muscle damage. The clinical features include:

- Insidious yet progressive proximal and distal muscle atrophy and weakness
- Affects predominantly elderly male population
- Rare or no association with malignancy or other connective tissue diseases
- Creatine kinase normal or only minimally elevated usually <5-6 times normal
- Mixed myopathic and neuropathic electromyographic features
- Resistance to corticosteroids and immune-suppressive drugs

2. **Infectious agents**, are capable of producing polymyositis. Viruses reported to cause widespread, generally mild and self-limited myositis include influenza A and B, hepatitis B, coxsackie, rubella (both natural infection and following immunization with live attenuated virus), echo, and human immunodeficiency virus. Echovirus has been associated with myositis in patients with X-linked hypogammaglobulinemia.

3. **Other.** Myositis with an eosinophilic inflammatory infiltrate has been reported; it may be part of the spectrum of the hypereosinophilic syndrome, may be focal or nodular, or be associated with eosinophilic fasciitis or the newly described eosinophilic myalgia syndrome due to the ingestion of contaminated L-tryptophan. In the latter two disorders, the infiltrates occur in perimysial locations and true myofiber necrosis with weakness and creatine kinase elevation are unusual.

INVESTIGATIONS

Musculoskeletal

Enzymes Elevated serum levels of enzymes which leak from injured skeletal muscle are valuable aids in detecting active muscle inflammation. In order of sensitivity, they are creatine kinase, aldolase, the transaminases (AST and ALT) and lactate dehydrogenase. Creatine kinase is accepted as the most reliable enzyme test. Three exceptions in which creatine kinase levels have been normal in biopsy-proven myositis are cases with a circulating inhibitor of creatine kinase activity, late-stage disease with severe atrophy and a few instances of early disease. The latter situation should raise the suspicion of malignancy.

Electromyogram. Electrical testing is a sensitive but nonspecific method of evaluating inflammatory myopathy. Typical findings include irritability of myofibrils (fibrillation potentials) on needle insertion and at rest, and short duration, low amplitude, complex (polyphasic) potentials on contraction.

There is little correlation between the amount of weakness or functional disability and the electromyographic findings. The electromyogram is helpful in the selection of a muscle for biopsy. An MRI is also useful in identifying oedematous muscle to biopsy.

Biopsy. Muscle biopsy should be performed in all cases to confirm the diagnosis of inflammatory myopathy. The presence of chronic inflammatory cells in the perivascular and interstitial areas surrounding myofibrils is pathognomonic. The infiltrate consists predominantly of lymphocytes, but other cells are often present, including histiocytes, plasma cells, eosinophils and polymorphonuclear leukocytes. Immunocytochemical studies have shown that a large number of activated T cells are present in the endomysial inflammation. More common than inflammation are degeneration and necrosis of myofibrils, phagocytosis of necrotic cells, and myofibril regeneration.

Even in apparently typical cases, another diagnosis may be revealed: inclusion bodies, dystrophic or neuropathic features, amyloidosis, toxic changes, unusual cellular infiltrates, granulomas, arteritis, or vacuoles suggesting a metabolic myopathy. It should be remembered that a muscle biopsy in myositis is not always diagnostic. A non-diagnostic biopsy can be found for several reasons. First, inflammation is not uniformly distributed and/or sometimes little or no inflammation is visible even if degenerating and regenerating myocytes are present in a section; Second, the inclusions of inclusion body myositis are sometimes not present in a biopsy so that an early clinical suspicion of the diagnosis may not be confirmed; Third, many of the changes found in typical cases of myositis are not pathognomonic but occur in other disorders. For example, inflammation is found in some dystrophies; Fourth, some features characteristic of other disorders can be found in biopsies from typical cases of myositis. For example, small angulated fibers of neuropathic degeneration are sometimes found scattered in myositic muscle.

Serum myoglobin. Myoglobinemia may be more sensitive than the serum creatine kinase level in some patients and can be used as an adjunct to serum muscle enzyme tests in diagnosis and follow-up.

Skin. Skin biopsy of early, active lesions reveals epidermal atrophy, liquefaction and degeneration of the basal cell layer, and perivascular infiltration of lymphocytes and histiocytes in the upper dermis. In dermatomyositis, a striking vasculopathy of small vessels is found. Immunofluorescence does not show immunoglobulin or complement at the dermal-epidermal junction as is found in systemic lupus.

Joints. In one form of polymyositis associated with serum anti-Jo-1 antibody, arthritis may become chronic and deforming with a characteristic radiographic feature of joint subluxation without erosions.

Lung. Reduced respiratory muscle strength is determined by measuring inspiratory pressures at the mouth. Affected individuals are unable to generate an adequate cough and thus are at increased risk of aspiration pneumonia. The chest radiograph in interstitial lung disease shows bilateral basilar thickening. In some patients with a normal chest film, thin section computerized axial tomography reveals evidence of interstitial fibrosis. Advanced disease may

result in the radiographic picture of 'honeycomb' lung. Ventilation-perfusion studies are abnormal, and pulmonary function tests show a restrictive physiologic pattern with reduced forced vital capacity and, often, reduced diffusing capacity for carbon monoxide.

In active alveolitis, the gallium scan is often abnormal, and bronchoalveolar lavage fluid contains increased numbers of macrophages, lymphocytes and neutrophils. Open lung biopsy typically shows excessive alveolar macrophages along with other chronic inflammatory cells, interstitial fibrosis and vascular thickening.

Heart. There is disagreement about the frequency of cardiac disease. The most common alterations encountered are conduction defects and atrial and ventricular dysrhythmias, including complete heart block, which are due to involvement of working myocardium and/or the conducting system. Left anterior hemiblock and right bundle branch block are the most frequently encountered conduction abnormalities.

Cardiomegaly and reduced left ventricular ejection fraction, along with congestive heart failure, are found in less than 5% of patients.

Intestine. Distal esophageal hypomotility can be demonstrated by cine-esophagram or manometry in a high proportion of patients.

OTHER DISORDERS

Miscellaneous conditions reported in association with polymyositis/dermatomyositis include autoimmune hypothyroidism, ophthalmologic abnormalities such as ophthalmoplegia, retinopathy (rare) and Evans syndrome or autoimmune hemolytic anemia with thrombocytopenia.

Serum Autoantibodies

In polymyositis/dermatomyositis, greater than 80% of patients have autoantibodies to nuclear and/or cytoplasmic antigens, and approximately half these patients have been shown to have myositis-specific antibodies. Autoantibodies typically associated with other connective tissue diseases may be found in myositis or overlap syndromes but are not myositis-specific. They include anti U1-RNP, antiPM/Scl, anti-(SS-A), anticentromere, antimitochondrial and others. Although a few patients have more than one autoantibody, multiple myositis-specific serum antibodies are rarely if ever detected in the same patient.

The most frequently identified antibody, anti-Jo-1, is found in only about 20% of all myositis patients tested. Anti-Jo-1 is the most common of a group of anticytoplasmic aminoacyl-tRNA synthetase enzymes and is itself directed against histidyl-tRNA synthetase. Due to the cytoplasmic location of the antigens to which they are directed, such autoantibodies are often found in patients who are antinuclear antibody (ANA) negative. Patients with these antisynthetase antibodies often have polymyositis, dermatomyositis or myositis in overlap rather than non-myositis diagnoses. The 'antisynthetase syndrome' is characterized by fever, inflammatory and sometimes deforming polyarthritis, Raynaud's phenomenon, and interstitial lung disease.

Antibodies to signal recognition particle (anti-SRP) mark a separate subgroup of myositis patients with anticytoplasmic antibodies. These patients have the acute onset of severe muscle disease (polymyositis without rash) and respond poorly to therapy. They have no increase in

interstitial lung disease, arthritis or Raynaud's phenomenon, but have greater than expected cardiac complications.

Anti-Mi-2 is an antinuclear antibody found in 5-10% of myositis patients overall and is strongly associated with the rash of dermatomyositis. It is also identified in juvenile dermatomyositis. Anti-Mi-2 patients have none of the clinical associations seen with the antisynthetase antibodies. Anti-PM-Scl is an antinucleolar antibody that identifies a subset of myositis patients with features of systemic sclerosis. This antibody may also be seen in persons with polymyositis, dermatomyositis or systemic sclerosis alone, i.e. without being called 'overlap'. Anti-U1-RNP antibodies are found in patients with so-called 'mixed connective tissue disease'.

Immunogenetic mechanisms appear to play a role, as the anti-Jo-1 antibody is associated with HLA-DR3 in Whites and the other antibodies to translation-related antigens are associated with HLA-DRw52. Anti-PM-cl has increased expression of HLA-DR3 compared with control populations. Anti-SRP antibody positive patients have HLA-DR5 in a higher than expected proportion.

NATURAL HISTORY

In some patients, dermatomyositis (but seldom polymyositis) is an illness of brief duration followed by remission which does not require continued therapy. The majority of patients, however, have multiple exacerbations and remissions or persistent disease activity necessitating chronic use of corticosteroids and/or immunosuppressive drugs. With each episode of myositis, there is the potential for absolute loss of muscle mass. The rate of progression and amount of muscle loss differ according to clinical classification and serum autoantibody. The best functional outcome occurs in dermatomyositis, while the worst is in inclusion body myositis and polymyositis with the anti-SRP antibody.

A high proportion (up to 50%) of untreated polymyositis/dermatomyositis patients seen at major medical centers die of its complications. Factors associated with poor survival in these reports include older age, malignancy, delayed initiation of corticosteroid therapy, pharyngeal dysphagia with aspiration pneumonia, myocardial involvement, and complications of corticosteroid and/or immunosuppressive drugs. Additional adverse risk factors for survival among childhood dermatomyositis patients are gastrointestinal vasculitis and sepsis. The best survival is among patients with anti-PM-Scl and anti-Mi-2.

MANAGEMENT

Summary. Therapy should halt the inflammatory process *and* preserve muscle function and strength. Corticosteroids are the mainstay of treatment.. Methotrexate and azathioprine may be important adjunctive agents. Therapeutic approaches to dermatomyositis, polymyositis and inclusion body myositis are similar.

Since myositis can have a number of causes diagnostic accuracy and exclusion of other illnesses is very important prior to treatment. After establishing the diagnosis the next important step is to assess the course of the disease. In this regard the clinician should consider both physical and laboratory features. In patients with dermatomyositis, remission of rash may be anticipated to be

a mark of disease remission. The clinician, however, should be aware that degree and severity of rash frequently may not vary with other aspects of the disease. Persistent rash can be a chronic and vexing problem even in patients otherwise doing well. For this reason it is not always possible to use rash as a guide to therapy, although in an individual patient it may be. Likewise, nail bed and periungual telangiectasia may not change in concert with other aspects of the disease.

In general, the reason for accepting the risks of therapy is to maintain or gain strength. Assays of strength and function represent the means of determining whether this goal is being achieved. In this connection, the clinician should keep certain factors in mind. Control and remission of inflammation as the result of medical therapy, therefore, should be expected to lead to an increase in strength and endurance. This does happen and can be documented in the clinical setting. The role of the treating physician, therefore, is to use medications to increase function to the degree possible. It may not be possible in some patients to anticipate a full return of strength.

Laboratory features are also assessed in an ongoing fashion. Remission to normal of elevated serum enzyme levels is a favorable sign, and elevations in the course of follow-up may indicate disease exacerbations.

PREVENTION

Contractures, particularly at the shoulders, knees, and ankles, should be prevented whenever possible. A program of physical therapy should begin with passive range of motion exercises at disease onset and progress to strengthening maneuvers when disease remission permits.

EDUCATION AND PSYCHOSOCIAL SUPPORT

The chronicity of illness with unanticipated periods of flare produces stress in both the patient and physician. Doubts and difficulties of assessment of progress lead to anxiety. In this context it is important to be able to measure progress and to keep the overall goals and course in mind. The patient should be educated to expect downturns and to remain aware of the progress already made. The physician must not allow temporary periods of frustration and anxiety to lessen a calm control of the selection of therapeutic agents. In addition to these factors, patients will experience difficulties in coping with their life situation, jobs, and family relations. This is a time when support is required, based upon a realistic appraisal of goals and needs. Corticosteroid therapy itself also may be a contributing factor to periods of psychological change.

PHYSICAL FACTORS

Passive range of motion exercises should begin at disease onset and continue throughout. In general, a gentle, graded and supervised program of muscle strengthening should begin when evidence of disease activity has subsided and drug therapy is minimal. In patients with long-standing, treated illness with moderately elevated serum enzyme values, the need to institute an active exercise program may be met before these guidelines are satisfied. In all instances, care must be taken not to place excessive demands upon muscle which has only limited fitness. The work environment should be evaluated, as well as the need for rest periods during the day.

PHARMACOLOGIC AGENTS

Corticosteroids Corticosteroids represent the mainstay of therapy for most patients. The usual practice is to begin treatment with daily oral medication in the range of 40-80 mg/day of prednisone or its equivalent for approximately 4-6 weeks or until maximum benefit or remission of disease is achieved. The dose may then be gradually reduced with careful monitoring of clinical state and laboratory findings. Be aware of steroid side-effects developing. Despite these difficulties, most patients with polymyositis and dermatomyositis can usually be treated with corticosteroid alone. Careful and frequent monitoring can be used to titer the dose of medication to the patient's need and minimize the chances of development of unwanted effects. Situations in which other agents may be considered include:

- life-threatening, progressive illness unresponsive to adequate corticosteroid therapy;
- partially responsive illness requiring doses of corticosteroids that have side effects difficult or impossible to tolerate;
- chronic illness with poor response and/or progressive deterioration;
- contraindication or inability to tolerate the use of corticosteroids.

In these circumstances, additional medications have been employed.

Methotrexate In most dosage protocols, methotrexate is used in conjunction with corticosteroid. With the acceptance of oral methotrexate for the treatment of RA, similar schedules have been employed for patients with myositis. Weekly oral methotrexate, in doses from 7.5-30mg, is now probably the most common approach.

Azathioprine has also been used successfully. Patients treated with azathioprine and corticosteroids show improvement in functional ability and require less prednisone for maintenance than patients treated with prednisone alone. Areas of potential toxicity include bone marrow suppression, gastrointestinal intolerance, hepatotoxicity and increased susceptibility to infection.

Cyclophosphamide Cyclophosphamide has probably been used in fewer patients than methotrexate or azathioprine. It has been used orally, and more recently intravenously. However, conflicting data have been reported with this agent, and poor results have also been noted.

Cyclosporin Cyclosporin has been used successfully in small numbers of patients. Doses have ranged from 2.5-3.5mg/kg/day. In one case, improvement was observed in a child who had been treated with cyclosporin alone. However, not all observers have reported success with cyclosporin. Nephrotoxicity and the development of hypertension are among possible untoward effects.

Hydroxychloroquine Hydroxychloroquine has also been used concomitantly with corticosteroids in patients with dermatomyositis with improvement in both rash and muscle strength and with a decrease in the amount of prednisone therapy needed. Beneficial effects have not always been sustained, and retinal toxicity represents a potential hazard.

Other Forms of Therapy Other forms of more specialized therapy have been used in difficult cases. These have included plasmapheresis, whole body radiation and intravenous immunoglobulin, No prospective controlled trials of these forms of therapy are available.

ETIOLOGY AND PATHOGENESIS

PATHOLOGY

The central pathologic findings of myositis are the injury and death of muscle cells (myocytes) and inflammation. The consequences of the primary process are often evident too: regeneration and hypertrophy of muscle cells, atrophy of muscle cells, and the replacement of muscle by fibrosis and fat. No one of these features alone is diagnostic for myositis, but a combination of characteristics helps separate it from other conditions, and also may distinguish different types of myositis .

PATHOGENESIS

Unquestionably, study of the pathogenesis of idiopathic inflammatory myopathy must center upon the immunologic abnormalities. There are two principal reasons for this focus. First, this family of diseases is among those properly designated as autoimmune because of the presence of autoantibodies in the serum of many patients. including some that are specific to myositis. Second, the pathologic processes seen by light microscopy and the alterations of other parameters of immune function implicate the cellular and humoral immune system.

Immunologic abnormalities in patients with inflammatory myopathies.

Cellular abnormalities

Activated T and B lymphocytes in skeletal muscle

Increased peripheral mononuclear cell trafficking to muscle

Increased proportions of peripheral T and B lymphocytes bearing activation markers

Elevated serum IL-1, IL-2, soluble IL-2 receptors, and soluble CD8 receptors

Decreased proliferative responses of peripheral mononuclear cells to T cell mitogens

Increased proliferative responses of peripheral mononuclear cells to autologous muscle

In both polymyositis and inclusion body myositis, individual muscle cells which appear otherwise normal may be invaded by T-cytotoxic (Tc) cells, of which a proportion are activated (DR+). The dominant T cells in the inflammatory infiltrate nearby are also CD8+. Ultrastructural examination shows that the muscle fibers are honeycombed by cavities filled with both invading macrophages and CD8+ cells sending spike-like extensions into the myocytes. In the perimysium and perivascular region, the proportion of T-helper (TH) cells rises, but in contrast to dermatomyositis, B cells are not abundant in the lesions. Natural killer (NK+) cells are very uncommon in all three diseases.

Humoral abnormalities

Immunoglobulin and complement deposition in muscle vascular endothelium Autoantibodies also present in other autoimmune diseases (antithyroid, anti-Sm, anti-Ro, anti-La, etc.)

Myositis-specific autoantibodies

Hyper-, hypo-, and agammaglobulinemia

Monoclonal gammopathy

Several outstanding features characterize the myositis-specific autoantibodies (MSA) recognized so far. First, they are directed at cell components proteins and ribonucleoproteins common to every cell. Second, they are directed at intracellular, usually intracytoplasmic, molecules, which are not thought to be expressed on the cell surface. Third, the target molecules (autoantigens) are usually parts of the protein synthetic machinery.

Most of the MSA are directed at intracytoplasmic components, and thus they are not 'antinuclear' antibodies; a diffuse cytoplasmic staining of target cells is apparent with sera from patients with some MSA. Because many of the target antigens are ribonucleoproteins (molecular complexes of one or more proteins with one or more molecules of RNA) immunoprecipitation of cytoplasmic extracts and analysis of the precipitated RNA offers the fastest route to a correct characterization of most MSA

The fact that the target autoantigens of these disease-specific autoantibodies are both intracellular and common to all cells implies that these autoantibodies are the footprints of another event such as a prior viral infection of muscle cells. In this scenario, the infection or other event causes the myositis and also causes the autoantibody synthesis, although the autoantibodies themselves do not participate in damage to the muscles.

For the clinician the MSA have another importance. Each of them appears connected to a particular clinical syndrome, with a group of common clinical features, a predominant HLA type, a characteristic onset, and probably a characteristic response to therapy. The first hint of this was the recognition that patients with the most commonly recognized MSA, anti-Jo-1, frequently have interstitial lung disease. A startling discovery was that there are a few patients (probably about 5-10% of all myositis patients), who have antibodies to another enzyme of this family (glycyl-, threonyl-, isoleucyl-, or alanyl-tRNA synthetase), and in addition they usually have interstitial lung disease. These same patients also often have fevers, arthritis, Raynaud's phenomenon, and a roughened surface of the lateral and palmar surfaces of their index fingers, termed 'machinist' or 'mechanic's' hands. Some of these patients have one of the rashes typical of dermatomyositis and almost all have the HLA-DRw52 alloantigen. They often have a rapid onset and aggressive course, and although they may respond to treatment with corticosteroids, they most often require cytotoxic therapy later as corticosteroids are tapered.

A second group of patients has antibodies to a less well-characterized antigen, Mi-2, and they almost all have a variant of dermatomyositis with a rash of the upper chest and back. Their HLA type is often DR7, and they respond relatively well to therapy. The rare patients with antibodies to the intracellular signal recognition particle (SRP) almost always have an extremely rapid and severe disease onset, and have little extramuscular disease. There are patients with autoantibodies to other cytoplasmic proteins, but the clinical illnesses and the target autoantigens have not yet been so well defined. Nevertheless, the observations on the patients with MSA strongly hint that each of them will form a coherent clinical and immunogenetic group, and that

each of these groups may come to be recognized as, in effect, a separate disease - either as a result of a different environmental agent (infection or toxin) for each, or as a result of the same agent having a different effect depending on the genetic make-up of the individual

ETIOLOGY

Infectious agents, drugs, and toxins all have claim for attention as etiologic agents in inflammatory muscle disease. These include:

Drugs and toxins: Chloroquine (Vacuolar myopathy), Colchicine (Vacuolar myopathy), Corticosteroids (Type II fiber atrophy), Emetine, Ethanol (Acute rhabdomyolysis and chronic myopathy), Heroin, Lovastatin, Penicillamine (Typical polymyositis), Zidovudine (AZT, Mitochondrial myopathy):

Infectious agents including Bacteria (Staphylococcus: Most common cause of pyomyositis), Clostridia, Rickettsia, Mycobacteria; Parasites (Toxoplasma, Trichinella, Schistosoma, Cysticercus, Sarcocystis, Borrelia; Viruses (Coxsackievirus-Serologic association with juvenile dermatomyositis), Echovirus (Associated with hypogammaglobulinemia), influenza, Adenovirus (Cultured from an inclusion body myositis muscle biopsy), Mumps, Hepatitis B, Rubella, HIV (AIDS patients can present with polymyositis), HTLV-1 (High anti-HTLV-1 antibodies in Jamaican myositis patients) and;

Genetic factors, HLA-DR3, -DRw52

SUMMARY

In summary, a wide range of insults from drugs and toxins to infectious agents can result in the clinical and pathologic syndrome of myositis. Although specific environmental agents can be identified in individual cases of myositis, in the vast majority of cases, the causes are still unclear. New ways of categorizing patients, such as through the use of myositis-specific autoantibodies, should improve our understanding of the complex interactions among the genetic factors, environmental stimuli, and immune responses in this heterogeneous group of patients who share chronic muscle inflammation.