Immune aspects of myositis

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Myositis describes a heterogeneous group of disorders whose main pathologic feature is chronic inflammation of the affected muscles. The association of myositis with other autoimmune diseases, the response to corticosteroid and immunosuppressive therapy, the frequent occurrence of autoantibodies, and the presence of chronic inflammatory cells in the affected muscles of patients with myositis indicate that the myositis syndromes are autoimmune diseases. This review summarizes recent observations on the role of humoral and cellular mechanisms in myositis. During the past year, the most notable contributions included studies on the relationship among autoantibodies and various clinical and epidemiologic features of patients with myositis; further evidence for T-cell involvement in the pathogenesis of myositis; demonstration of amyloid proteins in muscle fibers of patients with inclusion body myositis; and a controlled trial of plasma exchange and leukapheresis in myositis.

Current Opinion in Rheumatology 1992, **4**:809–814

The term *myositis* encompasses a heterogeneous group of disorders characterized clinically by proximal muscle weakness and histologically by chronic inflammation of the affected muscles with a variable degree of muscle-fiber necrosis and regeneration. In addition to muscle weakness, patients with myositis manifest a wide variety of clinical features that include myalgia, arthritis, rash, Raynaud's phenomenon, and pulmonary fibrosis [1].

On the basis of clinicopathologic characteristics, myositis is divided into six categories: polymyositis, dermatomyositis, myositis associated with malignancy, inclusion body myositis, myositis with other connective tissue disease, and childhood dermatomyositis or polymyositis. Despite the clinical distinctions and certain laboratory differences among the clinical categories of myositis, the common pathologic feature of these disorders is the presence of chronic inflammatory infiltrates in the affected muscles. This review focuses on recent progress in the role of humoral and cellular immunity in the pathogenesis of myositis.

Abnormalities of humoral immunity

Suggestions that myositis may be the result of disordered immune function have arisen because of association of myositis with other autoimmune diseases (*ie*, systemic lupus erythematosus [SLE] and systemic sclerosis) and because of the presence of several autoantibodies in the sera of patients with myositis [2••–4••]. The autoantibodies in myositis can be separated into two classes (Table 1). The first class includes antibodies that are tissue specific, *ie*, those directed against muscle antigens. The second class includes antibodies that react with nuclear or cytoplasmic antigens of various tissues or organs.

With respect to the muscle-specific antibodies, early studies demonstrated the presence of antibodies directed against muscle proteins such as myosin and myoglobin. Subsequently, it was shown that these antibodies were not specific for myositis because they were also found in a wide variety of other diseases including muscular dystrophies, myasthenia gravis, and in noninflammatory neuromuscular diseases. The lack of disease specificity suggests that antibodies to muscle components could arise secondarily as a result of muscle injury, rather than as a cause.

The second class of autoantibodies that are directed against ubiquitous nuclear and cytoplasmic constituents have received greater attention because many of these antibodies are also found in other autoimmune diseases. In early studies, antinuclear antibodies (ANAs) were found in 25% to 30% of patients with myositis, particularly in patients with myositis in association with another connective tissue disease. With modern immunologic techniques such as immunoblotting and immunoprecipitation and the use of spe-

Abbreviations

ANA—antinuclear antibody; **RNP**—ribonucleoprotein; **SLE**—systemic lupus erythematosus.

Table 1. Autoantibodies in myositis

Specificity	Prevalence, %
Antimuscle (myosin, myoglobin) antibodies	80–90
Antinuclear antibodies	25–70
Anti-La/SS-B	5–20
Anti-Ro/SS-A	10–15
Antithyroglobulin	6–10
Rheumatoid factor	4–8
Myositis-associated antinuclear antibodies	
Anti-PM-Scl (nuclear protein complex)	8
Anti-Mi-2 (nuclear protein)	5
Myositis-associated anticytoplasmic antibodies	
Anti-Jo-1 (histidyl–transfer RNA synthetase)	5–25
Anti-PL-7 (threonyl–transfer RNA synthetase)	4
Anti-PL-12 (alanyl–transfer RNA synthetase)	3
Other antisynthetases	2
Anti–signal recognition particle	3

cial tissue culture cell substrates, almost 90% of patients with myositis will be found to have an autoantibody directed against some nuclear or cytoplasmic component. Recent investigations have demonstrated that about 20% to 30% of patients with myositis have autoantibodies seen mainly in patients with myositis. Many of these myositis-associated autoantibodies tend to be directed against cytoplasmic ribonucleoproteins involved in protein synthesis. One group, the antibodies to aminoacyl-transfer RNA synthetases, includes autoantibodies directed at five different cytoplasmic enzymes, *ie*, histidyl-, threonyl-, alanyl-, and isoleucyl-, glycyl-transfer RNA synthetase. The most common antisynthetase antibody is the anti-histidyl-transfer RNA synthetase (anti-Jo-1) seen in 5% to 20% of patients with myositis.

Recently, another group of anticytoplasmic antibodies has been identified and includes autoantibodies that are directed at the signal recognition particle (anti–signal recognition particle antibodies). Several additional myositis-associated antibodies have been reported, but they are found in a small fraction of patients with myositis.

From the early studies, it became apparent that the presence of autoantibodies in the sera of patients with myositis seemed to correlate with a certain category of myositis or certain clinical manifestations of the disease. For example, ANAs were more common in myositis associated with another connective tissue disease than in inclusion body myositis or myositis associated with malignancy. Interstitial lung disease was more common and severe in patients with myositis with anti-Jo-1 antibodies than in patients with myositis with anti–signal recognition particle antibodies.

The relationship among myositis-associated autoantibodies, immunogenetics, and a variety of clinical and epidemiologic features has been the subject of a study in 212 adult patients seen at the National Institutes of Health [5••]. Patients with antisynthetase autoantibodies had significantly more frequent arthritis, fever, interstitial lung disease, mechanic's hands rash, HLA-DRw52, and severe disease. Those with anti-Mi-2 antibodies had increased incidence of the V-sign rash (a rash in the V area of the neck), the shawl rash (a rash over the upper back and across the upper arms), cuticular overgrowth, DR7 and DRw53, and good response to therapy. The authors proposed that further subclassification of patients with myositis based on ANAs and anticytoplasmic autoantibodies may define more homogeneous groups of patients with myositis and lead to better understanding of the pathogenesis of this disease. Detection of some of these antibodies, however, requires specialized assays that are not available in most medical centers, posing a problem for large-scale studies.

In another study [6•], the same group of investigators examined the seasonal onset of myositis in 111 adult patients with polymyositis–dermatomyositis in relation to the presence of anti-Jo-1 and anti–signal recognition particle antibodies. The patients were classified into three groups according to myositis-associated autoantibodies. In patients with anti-Jo-1 antibodies ($n = 31$), the onset of muscle weakness began frequently between February and July, whereas in patients with anti–signal recognition particle antibodies, the onset of weakness began between September and February. Patients with polymyositis–dermatomyositis with neither autoantibodies demonstrated no seasonal pattern in the onset of weakness. When the patients were classified into the traditional clinical groups of polymyositis and dermatomyositis, regardless of the type of autoantibodies, they did not differ in seasonal pattern of onset of weakness. It was implied that there might be a seasonal environmental trigger for myositis, possibly a virus, and that patients with anti-Jo-1 and anti–signal recognition particle autoantibodies may differ from one another with respect to etiology.

Hirakata *et al.* [7•] compared the incidence and clinical correlations of myositis-associated antibodies found in Japanese patients with those in North American populations. Serum samples from 52 patients with polymyositis–dermatomyositis, 39 with myositis overlap with other connective-tissue disease, 126 with SLE, and 113 patients with systemic sclerosis were examined. As in North American patients, antibodies to aminoacyl-transfer RNA synthetases and to signal recognition particle were most common in patients with polymyositis–dermatomyositis, less frequent in patients with myositis-overlap syndromes, and absent in patients with SLE and systemic sclerosis. Also, the correlations of anti-aminoacyl-RNA synthetase antibodies to various clinical features of myositis in Japanese patients were similar to those in North Americans. For example, antibodies to various aminoacyl-transfer RNA synthetases correlated with both interstitial lung disease and polyarthritis. There was, however, a difference between Japanese and North American popula-

tions in the occurrence of anti-PM-Scl antibodies (seen in patients with scleroderma and myositis), which were not detected in Japanese patients, and in anti-ku (seen in patients with scleroderma and myositis) and anti-U2 (seen in myositis-overlap syndromes) ribonucleoprotein (RNP) antibodies, which were increased in Japanese patients. It was suggested that these differences could reflect variation in environmental or genetic factors.

An increased frequency of ANA has previously been reported in first-degree relatives of patients with autoimmune diseases such as SLE and systemic sclerosis. Using indirect immunofluorescence on HEp-2 cells (a human epithelial tissue culture cell line), Valentini *et al.* [8] examined the presence of ANA in five spouses and 41 first-degree relatives of nine probands with polymyositis–dermatomyositis and in 41 sex- and age-matched controls. ANAs were detected in 12 of the 41 first-degree relatives and in only two controls. ANA positivity was not correlated either to sex, age, or to household contact, suggesting a genetic rather than an environmental influence. The absence of disease in the seropositive relatives, on the other hand, suggests that although genetic factors may be responsible for the development of ANA in relatives of patients with polymyositis–dermatomyositis, apparently other factors, *ie*, environmental or developmental, are also required for the expression of myositis.

A multicenter prospective study [9•] examined the diagnostic and prognostic value of autoantibodies including ANA, anti–double-stranded DNA, anti-Sm, anti-RNP, anti-Ro/SS-A, anti-La/SS-B, anti-Jo-1, anti-Scl-70, and anti-PM-1 in 410 patients with early rheumatic diseases (less than a 1-year duration). Patients with polymyositis–dermatomyositis had a 54% incidence of ANA, with speckled pattern seen in 12 of the 20 ANA-positive patients ($n = 37$). Only 2% of patients were anti-Jo-1 positive, which is less than the 25% reported by other investigators. As in previous studies, ANA was present in the majority of patients with SLE (93%) and scleroderma (98%). The authors concluded that although ANA is very sensitive in patients with SLE and scleroderma even in early disease, it is not specific. In contrast, "specific" antibodies such as the anti-Jo-1 for polymyositis–dermatomyositis and the Scl-70 in systemic sclerosis with myositis were rare.

The association of myositis with other autoimmune diseases and the frequent occurrence of autoantibodies support the notion that myositis is an autoimmune process. The role of autoantibodies in the pathogenesis of myositis, however, is not yet understood. It appears unlikely that these autoantibodies themselves cause disease. No cytotoxicity to muscle cells has been demonstrated, and antibodies in general cannot enter healthy cells. Nevertheless, the presence of autoantibodies in patients with myositis may suggest an abnormal immune response against unknown provoking agents, perhaps viruses. They could also offer a means by which different subsets of patients would be defined and disease activity and outcome determined. Certainly, the presence of ANA or anticytoplasmic antibodies in the serum of a patient with muscle weakness provides diagnostic help by indicating the presence of autoimmune myositis rather than neuromuscular disease.

Table 2. Cellular immunity in myositis

Immunopathology
T cells and macrophages are the predominant cells in the inflammatory infiltrates of muscle
Most of the T cells in muscle are activated (DR+)
Muscle fibers in polymyositis–dermatomyositis express class I and class II antigens
T cells are cytotoxic to muscle fibers
Functional abnormalities
Proliferative responses of peripheral blood lymphocytes to autologous muscle
Release of lymphotoxin and chemotactic factors from peripheral blood mononuclear cells
Expression of T-cell activation markers (*ie*, interleukin-2 receptors) in peripheral blood
Inhibition of muscle Ca^{2+} transport by mediators of muscle-stimulated lymphocytes from polymyositis patients
Induction of class II major histocompatibility complex antigen expression on cultured muscle cells by interferon gamma

Cellular immunity in myositis

Several lines of evidence support a role for cell-mediated immunity in patients with myositis (Table 2) [10••]. The strongest indication that cellular immune mechanisms are involved in the pathogenesis of myositis has come from immunohistologic studies of the inflammatory infiltrates of affected muscles in patients with myositis. T cells and macrophages are the predominant cells of the inflammatory infiltrates in muscle, and their distribution is reminiscent of cell-mediated reactions. Moreover, T cells bearing activating markers, such as major histocompatibility complex class II antigens, are in close proximity to muscle cells, indicating a causal relationship between T cells and muscle injury. Previous studies have shown that cytokines, such as interferon gamma, induce strong expression of class I and class II antigens on cultured muscle cells. The findings of these *in vitro* studies in conjunction with the demonstration of aberrant major histocompatibility complex class I and class II molecules in biopsy specimens of patients with polymyositis–dermatomyositis suggest that cell-mediated immune mechanisms are actively involved in the pathogenesis of the disease. Furthermore, peripheral blood mononuclear cells of patients with polymyositis–dermatomyositis proliferate on ex-

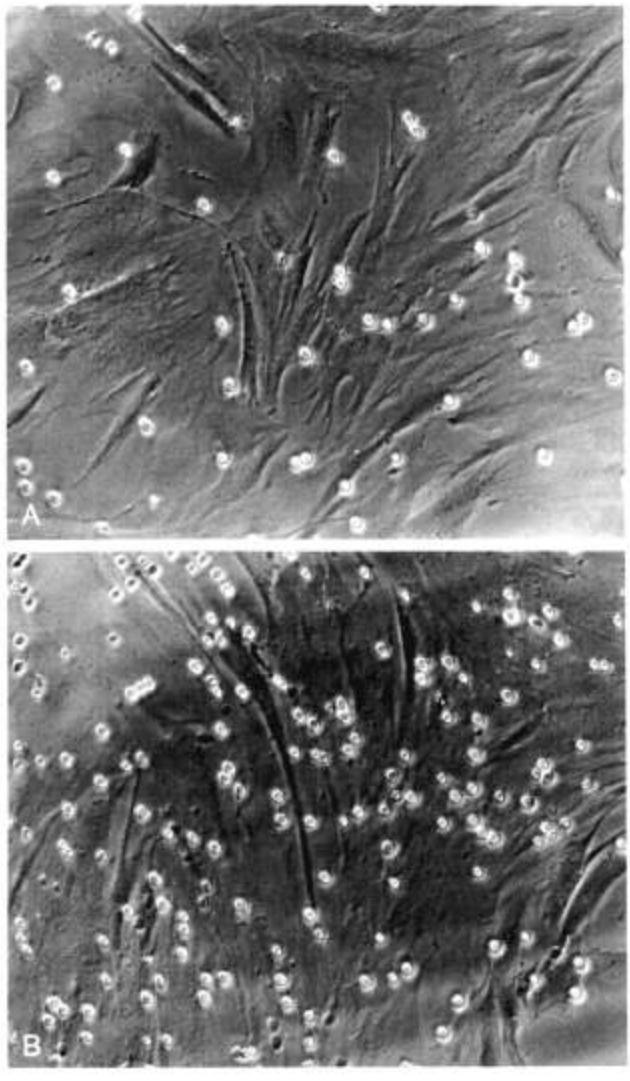

Fig. 1. Human interferon gamma increases the binding of T cells to cultured skeletal muscle cells. **A**, Four-day-old muscle cell culture containing only medium. **B**, Paired culture treated with interferon gamma (10 U/mL) showing four times as many T cells attached to muscle cell monolayers compared with the untreated culture (×200, phase microscopy).

posure to autologous or heterologous muscle extracts, and they are cytotoxic to cultured muscle cells.

Hohlfeld and Engel [11•] reevaluated the question of whether T cells from affected muscles of patients with myositis can kill autologous muscle cells. The authors found that some of the expanded T-cell lines from three of six patients with polymyositis, one of four patients with inclusion body myositis, and one of five patients with dermatomyositis showed low but statistically significant cytotoxicity against autologous myotubes (6% to 27% specific ^{51}Cr release; effector-target ratio, 20:1). These results support the hypothesis that T cells recognize autoantigen on muscle cells.

The questions regarding specific antigens against which the immune response is mounted and the mechanisms whereby mononuclear cells accumulate in affected muscles remain unanswered. On a theoretical level, chemoattractants and cytokines mediate lymphocyte migration and localization to inflammatory sites. Recent investigations have demonstrated that adhesion molecules also play a major role in the accumulation and homing of mononuclear cells in the inflammatory sites [12].

Based on these observations, Kalovidouris *et al.* [13••] examined the effect of human interferon gamma on T-cell adhesion to cultured muscle cells. Addition of recombinant interferon gamma to muscle cell cultures consistently enhanced (approximately four times) the adherence of T cells to muscle cells in a dose-dependent manner (Fig. 1). By blocking monoclonal antibodies, we found that the intercellular adhesion molecule 1 and its ligand, the lymphocyte function-associated antigen 1, were the major ligands for this adherence. These findings suggest that cytokines and adhesion molecules may play an important role in the accumulation of T cells in affected muscles. Understanding the molecular mechanisms mediating mononuclear cell accumulation in affected muscle of patients with myositis is likely to afford new insights into the pathogenesis of myositis.

Amyloid proteins and inclusion body myositis

Inclusion body myositis is a disorder resembling polymyositis, but distinctive because of certain clinicopathologic findings, which include insidious onset after 50 years of age, poor response to prednisone and immunosuppressive drugs, atrophic muscle fibers, and muscle fibers with characteristic rimmed vacuoles that contain cytoplasmic filamentous inclusions [14]. Clinically, its separation from other types of myositis, such as polymyositis, is difficult, and often a biopsy specimen from a patient with inclusion body myositis cannot be distinguished from that from a patient with polymyositis without electron microscopy. Moreover, the inclusions are present in a few fibers, and often, a first biopsy may not reveal any inclusions.

The uncertainties about the relationship of inclusion body myositis to the other groups of myositis have recently been brought to light by the finding of amyloid proteins in muscle cells of patients with inclusion body myositis. In one study [15••], fresh-frozen sections of muscle biopsy specimens from 24 patients with inclusion body myositis stained with Congo red dye demonstrated intracellular green–birefringent deposits, indicating amyloid proteins. The deposits were restricted to vacuolated fibers and showed no relation to the inflammatory infiltrate. Control biopsy specimens from 32 patients with polymyositis–dermatomyositis and from patients with a variety of vacuolar myopathies were negative for amyloid deposits except for those from two patients, one with hereditary vacuolar myopathy and

the other with distal myopathy. The amyloid-like deposits in that study were not characterized chemically.

Further information about the nature of the inclusions in inclusion body myositis came from another study [16•] of 10 patients with inclusion body myositis, in which strong immunoreactivity to ubiquitin in vacuolated muscle fibers and within the cytoplasmic tubulofilaments characteristic of inclusion body muscle was demonstrated. None of the 18 muscle biopsy control specimens, including those from normal muscle, those from five patients with polymyositis, and those from patients with other myopathies, contained the ubiquitin-immunoreactive inclusions. Ubiquitin is a 76–amino acid intracellular protein present in all cells whose synthesis increases in response to various metabolic disturbances and viral infection. The authors concluded that identification of ubiquitin can provide help in distinguishing inclusion body myositis from polymyositis and may facilitate understanding of the pathogenesis of inclusion body myositis. In another study [17•], the same authors demonstrated β-amyloid protein immunoreactivity in vacuolated muscle fibers of 10 patients with inclusion body myositis. The β-amyloid protein immunoreactivity was closely localized to ubiquitin immunoreactivity. None of the control muscle biopsy specimens had β-amyloid protein–positive inclusions. Notably, β-amyloid protein and ubiquitin have previously been found in brains affected by Alzheimer's disease. Further studies are needed to determine the significance of these new findings in inclusion body myositis and whether the presence of amyloid deposits in patients with inclusion body myositis and in those with Alzheimer's disease may indicate similar cellular mechanisms in both of these diseases.

Immunomodulatory treatments in myositis

Most patients with myositis can be treated with corticosteroids. The standard practice is to begin with 1 mg of prednisone per kilogram of body weight per day in divided dosages of 30 to 40 mg twice a day for approximately 6 to 8 weeks; the dose is then tapered over a period of 3 to 4 months to approximately 7 or 10 mg per day. Then, if there is no clinical improvement, *ie*, no increase in muscle strength, or if the patient is requiring higher doses of corticosteroids to suppress disease activity, an immunosuppressive agent—usually azathioprine or methotrexate—is added. When the patient has a poor response to corticosteroids or immunosuppressive agents, other alternatives that are either new or experimental could be considered [18•]. Indeed, the results of several uncontrolled trials have suggested that plasmapheresis and leukapheresis improve the clinical course of patients with myositis. The rationale for these treatments is that removal of plasma might remove from the blood the substance, possibly autoantibody, and removal of lymphocytes might remove the lymphocytes that cause the disease. The efficacy of plasmapheresis and leukapheresis was the subject of a recent randomized and blinded trial [19••]. In that study, 39 patients with polymyositis–dermatomyositis were randomly assigned to receive plasma exchange, leukapheresis, or sham apheresis in a double-blind manner given as 12 treatments over a 1-month period. The investigators found no benefit from plasmapheresis or leukapheresis compared with sham apheresis. In each of the three groups, only three of 13 patients had substantial improvement in muscle strength and functional capacity. An editorial on plasmapheresis in the treatment of myositis and SLE appears in the same issue as the published article [20•].

Intravenous immunoglobulin therapy is increasingly used in autoimmune diseases. Although the biologic effects of intravenous immunoglobulin in these diseases have not been elucidated, it is clear that the drug may influence the immune system in many ways [21•,22•]. Case reports and small series of patients in open trials [23,24] suggested that intravenous immunoglobulin therapy may have a beneficial effect on patients with myositis. A recent report [25] describes two patients with polymyositis resistant to corticosteroid and immunosuppressive therapy who were successfully treated with intravenous immunoglobulin (0.4 g/kg/d for 4 days). Further controlled trials are needed to substantiate the effectiveness of this therapy in patients with myositis. Investigation of the effect and mechanisms of action of intravenous immunoglobulin in patients with myositis could also provide additional insights into the pathogenesis of the myositis disorders.

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