

Advances in the Immunobiology and Treatment of Inflammatory Myopathies

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The clinical spectrum and immunopathogenesis of inflammatory myopathies are summarized with an update on possible triggering factors, cell degeneration, and emerging new therapies.

Introduction

Based on clinical, histologic, and immunopathologic criteria, the most clearly defined inflammatory myopathies include polymyositis (PM), dermatomyositis (DM), and sporadic inclusion body myositis (IBM) [1–5]. This distinction was recently confirmed with gene array studies that identified inflammatory and immunoregulatory genes characteristic for each subset. Although the exact mechanisms by which inflammation leads to myofiber cell loss are not completely understood, distinct patterns unique to PM, DM, or IBM offer insights into the complexities of the ongoing process. This review summarizes the most significant advances made the last year in the diagnosis, immunobiology, triggering factors, and therapies of PM, DM, and IBM.

Clinical Features and Progress in Diagnosis

DM affects children and adults and presents with subacute onset of proximal muscle weakness and typical skin changes accompanying (or more often preceding) muscle weakness. The weakness can be mild, moderate, or severe enough to lead to quadriparesis. PM is a subacute myopathy that presents with proximal muscle weakness and affects adults but rarely children. As a standalone entity, PM is rare and most often seen in association with systemic, autoimmune, or connective tissue diseases [1,4]. In contrast to DM, which is a distinctive entity, PM remains

a diagnosis of exclusion. Patients with PM should not have any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy [1,4].

IBM affects proximal and distal muscles and progresses slowly, leading to wheelchair confinement within several years of onset. It is the most common of the inflammatory myopathies in patients over 50 years old. IBM is often misdiagnosed as PM and is suspected only later when a patient with presumed PM does not respond to therapy. Weakness and atrophy of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue for early diagnosis. Dysphagia occurs in all the inflammatory myopathies but is more common in IBM, occurring in up to 60% of the patients, and may lead to episodes of choking.

The aforementioned clinical characteristics along with elevation of serum muscle enzymes and a myopathic electromyogram provide clues as to the type of the inflammatory myopathy. Diagnostic muscle biopsy may not be needed in DM, because the typical skin manifestations denote the disease (especially in children); however, in PM and IBM, the muscle biopsy is the definitive test for establishing diagnosis and for excluding other neuromuscular diseases.

In PM and IBM, the inflammation is primary, a term used to indicate that T-cell infiltrates, located primarily within the muscle fascicles (endomysially), surround individual, healthy muscle fibers and result in phagocytosis and necrosis. The major histocompatibility complex (MHC)-I molecule is ubiquitously expressed on the sarcolemma, even in fibers not invaded by CD8+ cells [6••,7••]. The CD8/MHC-I lesion is very helpful to confirm or establish the diagnosis and to exclude disorders with secondary, nonspecific inflammation [4,6••]. When the disease is chronic, the connective tissue is increased and may react positively with alkaline phosphatase. In IBM, in addition to the T cells invading MHC-I-expressing nonvacuolated muscle fibers, there are basophilic granular deposits distributed around the edge of slit-like vacuoles (rimmed vacuoles), amyloid deposits within or next to the vacuoles, hypertrophic fibers, angulated or

round fibers, increased connective tissue, eosinophilic cytoplasmic inclusions, and abnormal mitochondria characterized by ragged-red fibers or cytochrome oxidase-negative fibers [7••]. If all the aforementioned light microscopy features are fulfilled, electron microscopy to search for the tubulofilaments as emphasized is not needed [6••,7••,8]. The MHC/CD8 inflammatory pattern is specific for PM and IBM and distinct from the one seen in inflammatory dystrophies [7••]. This distinction was recently confirmed in a comparative analysis of specimens from patients with inflammatory myopathies and dysferlinopathies [9•].

Recent observations indicated that inflammation and MHC-I expression are present in both proximal and distal muscles of PM patients, even in muscles with seemingly normal strength [10•]. This confirms the longstanding view that the manifestation of muscle weakness is not determined by inflammation alone but also by the degree of necrosis and muscle fiber loss. Because of regional variability, it was recently suggested that the performance of two simultaneous biopsies may enhance the diagnostic yield in PM and IBM [11•]. However, in my view, one open biopsy performed from a symptomatic muscle and processed in an experienced laboratory is satisfactory in most patients. It is a matter of clinical judgment when to perform a second biopsy. As a good general rule, a second biopsy is considered when the histologic diagnosis is uncertain and the patient is worsening.

Progress in the Immunobiology of the Inflammatory Response

Dermatomyositis

In DM, the earliest immunopathologic changes preceding inflammation or structural alterations consist of complement activation and deposition of C3b, C4b, and C5b-9 membrane attack complex, the lytic component of the complement pathway, on the endomysial capillaries, which leads to destruction of capillaries, muscle ischemia, and compensatory dilatation of the lumen of the remaining capillaries [12–14]. The perifascicular atrophy is probably due to endofascicular hypoperfusion, which is prominent distally. The perifascicular fibers are regenerating/degenerating and express MHC-I, neural cell adhesion molecule, amyloid β precursor protein, cathepsin-L, calpain [14–16], the signal transducer and activator of transcription I [17], and the myxovirus resistance protein A [18], induced respectively by interferon (IFN)- γ and IFN- α/β , indicating a stressor effect and a prominent local inflammatory response [6••]. The lymphocytic infiltrates, prominent in the perimysial and perivascular regions, consist of B cells, CD4+ cells, and plasmacytoid/dendritic cells (DCs), which are positive for IFN- α and may be a major source of IFN- α secretion [18]. The messenger RNA (mRNA) for myxovirus resistance protein A is also elevated in the peripheral blood lymphocytes during the

active phase of the disease [19•]. Gene expression analysis has demonstrated the upregulation of genes participating in cell adhesion, angiogenesis, lymphocyte trafficking, and complement [20]. The gene for CAL protein has been shown to be disease relevant, because it is significantly overexpressed before therapy and selectively downregulated in the muscles of the patients who improved with immunotherapy [21]. Investigators have also observed an increased number of mature DCs along with the molecules CD142 and CD31, which play a role in cell transmigration [22•]. Collectively, in DM, an inflammatory cascade is mediated by complement deposition in the microvasculature and facilitated by IFN- α/β and IFN- γ ; upregulation of adhesion molecules, cytokines, chemokines, and molecules associated with endothelial cell activation and DC maturation; and an ischemic process resulting from the reduction of capillary network followed by active neovascularization [6••,22•].

Polymyositis and inclusion body myositis

In PM and IBM the primary effector cells mediating muscle fiber injury are CD8+ cells that surround and invade MHC-I antigen-expressing, non-necrotic muscle fibers [23–27]. The MHC-I/CD8 complex forms immunologic synapses, identical in PM and IBM, characterized by MHC-I antigen expression, probably induced by cytokines; and clonal expansion of autoinvasive, cytotoxic T cells, which contain perforin and granzyme granules that induce muscle fiber necrosis upon release [24,28,29,30]. Granulysin, another cytolytic molecule, is also expressed by these cells [31•]. Of interest, the number of granulysin-positive CD8 cells in the muscle was higher in the steroid-resistant cases.

In PM and IBM but not DM or dystrophies, only certain T cells of specific T-cell receptor families are recruited to the muscle from the circulation [32–36]. Further, the autoinvasive but not the perivascular T cells are clonally expanded, demonstrating restricted use of the J β genes and conserved amino acid sequence in the CDR3 region. These subpopulations of cells are also cytotoxic expressing perforin [36]. Based on sequential biopsy studies, even from different muscle, the clonally expanded autoinvasive T cells persist for more than 2 years, probably driven by the same antigen(s) [37–39]. Recent observations using spectratyping confirmed the clonal expansion of T cells in IBM [40•]. However, the suggestion that these clones recirculate in the blood was not substantiated, because the authors did not study simultaneously obtained muscle and blood specimens, and endomysial cells were examined only from three patients. In contrast, in simultaneously obtained muscle and peripheral blood specimens from a large number of patients with IBM, my laboratory has found that in IBM, the T cells expand in situ probably driven by local antigens [41].

Another feature that characterizes the MHC-I/CD8 complex formation of immunologic synapses is the

expression of costimulatory molecules B7-1, B7-2, BB1, inducible costimulatory ligand (ICOS-L), and CD40 on MHC-I–positive muscle fibers, and their respective counter-receptors CD28, CTLA-4, ICOS, and CD40L on autoinvasive CD8+ cells [30,42–45]. The BB1 and ICOS-L are functional molecules, because they are induced by IFN- γ or tumor necrosis factor (TNF)- α on human myoblasts and may confer antigen-presenting cell function on muscle fibers [24]. Hematopoietic DCs, the most potent antigen-presenting cells, could also participate in antigen presentation, because within the endomysial infiltrates there are abundant immature DCs expressing the CCL2-/CCR6 chemokine receptor complex [46]. Recently, myeloid DCs were also seen within the dense collections of lymphocytes in the vicinity of the muscle fibers or within the muscle fibers of PM and IBM patients, suggesting a possible role in local antigen presentation [47•].

A rather puzzling observation was the presence of CD138+ plasma cells in the muscles of these patients [47•]. With laser capture microdissection and single-cell polymerase chain reaction, it was observed that the immunoglobulin heavy chain transcripts had an oligoclonal pattern suggesting clonal expansion of some B-cell and plasma cell populations [48••]. Whether these data are sufficient to suggest an antigen-specific humoral-mediated process in the pathogenesis of PM and IBM remains unclear, especially because the same data were also obtained from the DM muscle. Further, no specific antibody recognizing muscle autoantigens has been found. Nevertheless, this carefully done study highlights the complexity of the immune response within the muscle microenvironment.

Cytokine Signaling, Chemokine Receptors, and Adhesion Molecules

Cytokines (interleukin [IL]-1, IL-1 receptors, IL-2, IL-5, IL-10, TNF- α , transforming growth factor [TGF]- β) and chemokines (monocyte chemoattractant protein-1a, macrophage inflammatory protein-1a, monokine induced by IFN- γ , IFN- γ -inducible protein 10) are variably overexpressed in PM, DM, and IBM and may contribute to costimulation, T cell activation, and transmigration [49–55]. Cytokines induce in human myotubes the synthesis of TGF- β , monocyte chemoattractant protein-1, macrophage inflammatory protein-1a, IL-1 β , and amyloid β precursor protein and may contribute to persistence of the inflammatory response [6••,7••,24,51]. Adhesion molecules and their ligands (eg, vascular cell adhesion molecule, intercellular adhesion molecule-1, lymphocyte function-associated antigen-I, very late appearing antigen-4, and metalloproteinases including metalloproteinase-disintegrins [56]) are also overexpressed on the endothelium or activated T cells and facilitate the transmigration of lymphocytes toward the muscle fibers.

Viruses as Possible Triggering Factors: A New Twist with HIV as a Paradigm

Although coxsackieviruses, influenza, paramyxoviruses, mumps, and cytomegaloviruses have been indirectly associated with myositis or implicated in breaking tolerance, molecular techniques have failed to confirm their presence in muscle [57,58]. The best evidence of a viral connection is with retroviruses, because humans infected with HIV and human T-cell leukemia virus (HTLV)-1 develop PM and IBM [59,60,61•]. At least seven HIV/HTLV-1–positive patients with IBM have been reported, and we have seen six more cases the last three years [61•], suggesting that the disease may be more common in HIV-positive patients who live longer and harbor the virus for several years. The most important observation in these patients was the presence of clonally-driven subpopulations of activated CD8+ cells that expand in situ and invade MHC-I–expressing muscle fibers, as seen in retroviral-negative PM and IBM [62••]. A number of these autoinvasive, clonally expanded T cells were retrovirally specific, as determined by tetramers that contain amino acid residues specific for the HLA-A viral peptide [62••]. Similar observations have been made in HTLV-1–positive patients with PM or IBM [63,64,65]. The virus was present only on the endomysial macrophages and not within the muscle fibers [62••], confirming previous observations [66,67]. This new study provides a paradigm that a chronic viral infection in genetically susceptible individuals can trigger viral-specific T-cell clones that persist in the muscle tissue and may lead to a chronic myopathy such as IBM if surface antigens are recognized on the muscle fibers.

MHC-I–associated Endoplasmic Reticulum Stress: Another Culprit in Myofiber Degeneration

In PM and IBM, MHC-I is expressed in all muscle fibers regardless of whether they are invaded by T cells or contain vacuoles [26,29,68]. In contrast, the vacuolated fibers always express MHC-I, but they are almost never surrounded by T cells [6••,7••]. These observations suggest that two processes may occur in parallel: a T cell-mediated cytotoxicity as described above and a nonimmune process involving the MHC-I upregulation. As discussed [6••,7••], the assembly and folding of MHC-I occurs in the endoplasmic reticulum (ER) and begins with the association of a heavy chain glycoprotein with β 2 microglobulin, which forms an unstable heterodimer complex that matures only when it binds to an antigenic peptide [69]. Antigenic peptides are synthesized in the cytosol by immunoproteasomes and transported to the ER where a system of chaperone proteins, including calnexin, calreticulin, GRP94, GRP78, and ERP72, ensure the proper maturation of MHC [6••,7••,69,70]. The ER maintains quality control by processing, folding, and exporting the MHC loaded with antigen. If glycoprotein/ β 2m/calnexin/calreticulum/GR57

complex, called “MHC class I loading complex,” does not bind to suitable antigens, the heavy chain glycoprotein is misfolded and removed from the ER to the cytosol for degradation [71,72].

In PM and IBM, the muscle fibers are overloaded by MHC molecules [6••,7••,68,73], and the antigenic peptides cannot undergo proper conformational change to bind to MHC-I complex. This leads to ER stress and further protein misfolding, as supported by the following: 1) enhanced immunoproteasome activity in conjunction with MHC-I [73,74]; 2) enhanced MHC-I assembly activity, evidenced by increased protein and mRNA expression of MHC-I, GRP78, GRP94, ERP72, calnexin, and calreticulin [73,74]; 3) misfolding of glycoproteins, evidenced by the accumulation of amyloid-related molecules and aggresomes in conjunction with ER-chaperone proteins and MHC [73,75,76]; and 4) cell stress response, evidenced by activation of nuclear factor- κ B, a means by which the cells protect themselves from ER stress [73,77], and upstream upregulation of α B crystalline in intact fibers [78,79] and its colocalization with MHC (Schmidt J, Dalakas MC, Unpublished data). Such stressor effects are also seen in MHC-I transgenic mice, suggesting that overexpression of MHC-I alone may be sufficient to induce ER stress [80].

Prognosis and Advances in Therapeutic Strategies

Patients with DM and PM (but not those with IBM) respond to steroids to some degree and for a period of time. Common immunotherapeutic agents such as azathioprine, methotrexate, cyclosporine, mycophenolate, and cyclophosphamide provide a steroid-sparing effect, but their efficacy as single agents is overall unimpressive [1,6••,7••,8,81]. Intravenous immunoglobulin has shown dramatic albeit unsustained benefits in difficult cases [81]. Tacrolimus may be beneficial in patients with interstitial lung disease.

The treatment of IBM remains challenging; it resembles primary progressive multiple sclerosis, in which immunoregulatory abnormalities coexist with axonal degeneration [7••]. As described earlier, new biologic agents targeting the main immunopathologic processes such as T-cell activation, transmigration, and antigen recognition may be rewarding [82,83•]. Such semispecific immunotherapies can be accomplished with monoclonal antibodies directed against T-cell regulatory pathways such as CD56 (alemtuzumab), costimulatory molecules (CD28/CTLA-4), adhesion molecules (integrins/lymphocyte function-associated antigen-1/intercellular adhesion molecule), cytokines (TNF- α), or B cells (CD20) [84•]. Results from the recently completed US National Institutes of Health study using alemtuzumab, which causes long-lasting T-cell depletion, are encouraging. Preliminary analysis suggests that alemtuzumab had induced T-cell depletion not only in peripheral blood but also in the muscle and had resulted in disease stability or improvement in the strength of some patients. Other promising agents being tested or considered include

the B cell-depleting monoclonal antibody rituximab for DM and PM [84•]; rapamycin, which acts via a calcineurin-independent pathway to prevent the translation of mRNA for key cytokines [82,83•]; and the anti-integrin natalizumab, which blocks the transmigration of T cells across the endothelium. In a recent study, six of eight patients treated with TNF- α inhibitors (six with etanercept, two with infliximab and etanercept) showed moderate increases in strength [85•]. In another small study, rituximab had modest benefits in three patients [86•].

A recent study by Bronner et al. [87•] suggesting that creatine supplementation can be beneficial in the treatment of PM and DM is of limited interest, because creatine has failed to improve neuromuscular disorders such as amyotrophic lateral sclerosis or dystrophies. Further, in this study, creatine was combined with exercise, which made it difficult to distinguish the benefit of creatine.

In spite of the progress in therapies and the emerging new drugs, some sobering news regarding the long-term outcome of PM and DM have been reported [87•]. These authors showed a 10% incidence of disease-related deaths due to cancer and pulmonary complications in PM and DM patients. Although after a 5-year follow-up, 65% of the patients had normal strength and up to 20% remained in remission without drugs, 80% had a chronic course. These numbers should be interpreted with caution because of the retrospective nature of the review, the heterogeneity of the patients, and the variability of the applied therapies. PM and DM are chronic diseases requiring maintenance therapy. The goal to induce remission without therapy is ideal but rather unrealistic for many chronic autoimmune neuromuscular diseases.

Conclusions

PM and IBM are T cell-mediated disorders; DM is a complement-mediated microangiopathy. In contrast to dystrophies, in PM and IBM the autoinvasive CD8+ T cells are cytotoxic and antigen driven, invading muscle fibers expressing MHC-I antigen and costimulatory molecules. In IBM, there are also degenerative features that include vacuolization, filamentous inclusions, and intracellular accumulations of amyloid- β -related molecules. Although viruses have not been amplified from the muscle fibers, several PM (and especially IBM) cases have been recently described in association with retroviral infections. Of interest, retroviral-specific and clonally expanded T cells were found to invade the muscle fibers, which suggests that a chronic persistent viral infection may be a potential triggering factor. Emerging data suggest that continuous upregulation of cytokines and MHC-I on the muscle fibers causes ER stress response, which may contribute to myofiber degeneration. New therapies using monoclonal antibodies against B-cells, lymphocyte signaling pathways, or T-cell transmigration molecules provide hope for more effective and long-lasting therapy.

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