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Inflammatory muscle diseases.

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REVIEW ARTICLE

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Inflammatory Muscle Diseases

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Inflammatory myopathies are the largest group of potentially treatable myopathies in children and adults. They constitute a heterogeneous group of disorders that are best classified, on the basis of distinct clinicopathologic features, in four subtypes: dermatomyositis, polymyositis, necrotizing autoimmune myositis, and inclusion-body myositis (throughout this review, I use this term to refer specifically to sporadic inclusion-body myositis).[1-6] A fifth subtype, termed overlap myositis, is also beginning to be recognized. The identification of the correct subtype and the distinction of these conditions from other diseases that have characteristics that mimic these conditions is fundamental, because each subtype has a different prognosis and response to therapies. This review reflects the current knowledge of these conditions, highlights how best to avoid erroneous diagnoses, describes the main clinicopathologic and immunologic features, and provides practical guidelines regarding therapies.

General Clinical Features

Patients with inflammatory myopathies have increasing difficulty with tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, or lifting objects.[1-6] Tasks requiring distal muscles, such as buttoning or holding objects, are affected early in inclusion-body myositis but only in advanced cases of polymyositis, dermatomyositis, and necrotizing autoimmune myositis. The ocular muscles are spared in all subtypes, but facial muscles are commonly affected in inclusion-body myositis.[3] In all disease subtypes, neck-extensor and pharyngeal muscles can be involved, which results in difficulty holding up the head (head drop) or in dysphagia. In advanced and rare acute cases, the respiratory muscles can be affected. Muscle atrophy is detected early in inclusion-body myositis, with selective atrophy of the quadriceps and forearm muscles, but it develops in all subtypes if the weakness is severe and chronic. Myalgia and muscle tenderness may occur, especially in patients with the antisynthetase syndrome (see the Glossary),[6,7] but if pain is severe and the weakness follows a "breakaway" pattern, in which the patient has difficulty sustaining effort, fasciitis or fibromyalgia should be ruled out.

Extramuscular manifestations may occur in all inflammatory myopathies, although they occur in inclusion-body myositis only in rare cases; these manifestations include systemic symptoms, such as fever, arthralgia, and Raynaud's phenomenon, as seen in the antisynthetase syndrome[4,6,7]; cardiac arrhythmias or ventricular dysfunction, in relatively uncommon cases in which the affected cardiac muscle is clinically symptomatic; and pulmonary complications, due primarily to interstitial lung disease, which are reported in 10 to 40% of patients.[8] The prevalence of interstitial lung disease, a condition that is best detected with high-resolution computed tomography, is as high as 70% among patients with anti–histidyl–transfer RNA (tRNA) synthetase (anti-Jo-1) or anti–melanoma differentiation–

Glossary

Anti–cytosolic 5′-nucleotidase 1A (anti-cN1A, or anti-NT5C1A): Autoantibody directed against the cN1A nuclear protein involved in RNA processing; associated with inclusion-body myositis.

Anti–histidyl–transfer RNA synthetase (anti-Jo-1): The most common autoantibody associated with the antisynthetase syndrome, which consists of myopathy, fever, interstitial lung disease, Raynaud's phenomenon, arthritis, and "mechanic's hands."

Anti–3-hydroxy-3-methylglutaryl–coenzyme A reductase (anti-HMGCR): Autoantibody directed against HMGCR, the pharmacologic target of statins; specific for necrotizing autoimmune myositis.

Anti–melanoma differentiation–associated protein-5 (anti-MDA-5): Autoantibody directed against a cytoplasmic RNA-specific helicase; associated with amyopathic dermatomyositis or rapidly progressive interstitial lung disease.

Anti-Mi-2: Autoantibody directed against a nuclear DNA helicase involved in transcriptional activation; associated with typical skin lesions of dermatomyositis.

Anti–signal recognition particle (anti-SRP): Autoantibody directed against a polypeptide complex involved in protein transport to endoplasmic reticulum; specific for necrotizing autoimmune myositis.

Anti–transcriptional intermediary factor 1 γ (anti-TIF-1γ): Autoantibody involved in cell growth and differentiation; seen in cancer-associated dermatomyositis, along with anti–nuclear matrix protein 2 (anti-NXP-2).

associated protein (MDA)–5 antibodies (see the Glossary).[6-8]

SPECIFIC CLINICAL FEATURES

DERMATOMYOSITIS

The specific clinical features of inflammatory myopathies are described in Table 1 and in the Supplementary Appendix, available with the full text of this article at NEJM.org. Dermatomyositis is seen in both children and adults, and the early symptoms include distinct skin manifestations accompanying or preceding muscle weakness; the skin manifestations include periorbital heliotrope (blue–purple) rash with edema; erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (in a V-sign), and back and shoulders (in a shawl sign); and a violaceous eruption (Gottron's rash) on the knuckles, which may evolve into a scaling discoloration.[1-7,9] The lesions are photosensitive and may be aggravated by ultraviolet radiation.[6,7,9] Dilated capillary loops at the base of the fingernails, irregular and thickened cuticles, and cracked palmar fingertips ("mechanic's hands") are characteristic of dermatomyositis.[1-3] Subcutaneous calcifications, sometimes extruding to the surface of the skin and causing ulcerations and infections, may occur and are especially common among children. If the patient's strength appears to be normal, the dermatomyositis may be limited to the skin (amyopathic dermatomyositis),[9] although subclinical muscle involvement is frequent.[1-3] In children, an early symptom is "misery," defined as irritability combined with a red flush on the face, fatigue, and a reluctance to socialize.[2,3]

The symptoms of dermatomyositis may overlap with those of systemic sclerosis and mixed connective-tissue disease[1-7]; in such cases, the typical skin rash is transient or faint. Overlap myositis is now starting to be recognized as a distinct entity; it manifests without the rash that is typical of dermatomyositis, with prominent pathologic changes in the perifascicular, interfascicular, and perimysial regions, and is frequently associated with antisynthetase antibodies.[10] In adults, the risk of cancer is increased during the first 3 to 5 years after the onset of dermatomyositis, with reported a frequency of 9 to 32%.[11,12] The most common cancers are ovarian cancer, breast cancer, colon cancer, melanoma, nasopharyngeal cancer (in Asians), and non-Hodgkin's lymphoma; the risk of these cancers necessitates a thorough annual workup in the first 3 years after disease onset.[11,12]

POLYMYOSITIS

Polymyositis is rare as a stand-alone entity and is often misdiagnosed; most patients whose condition has been diagnosed as polymyositis have inclusion-body myositis, necrotizing autoimmune myositis, or inflammatory dystrophy.[3,13] Polymyositis remains a diagnosis of exclusion and is best defined as a subacute proximal myopathy in adults who do not have rash, a family history of neuromuscular disease, exposure to myotoxic drugs (e.g., statins, penicillamine, and zidovudine), involvement of facial and extraocular muscles, en-

Table 1. Criteria Supporting the Diagnosis of Inflammatory Myopathies.

Criterion	Dermatomyositis	Polymyositis	Necrotizing Autoimmune Myositis	Inclusion-Body Myositis
Pattern of muscle weakness	Subacute onset of proximal symmetric weakness with characteristic skin rash in patients of any age	Subacute onset of proximal symmetric weakness in adults (diagnosis is made when other causes have been ruled out)*	Acute or subacute onset of proximal, often severe weakness in adults	Slow onset of proximal and distal weakness; atrophy of quadriceps and forearms; frequent falls; mild facial muscle weakness in people older than 50 years of age
Creatine kinase level	High, up to 50 times the upper limit of normal; can at times be normal	High, up to 50 times the upper limit of normal in early active disease; may linger at up to 10 times the upper limit of normal	Very high; more than 50 times the upper limit of normal in early active disease	Up to 10 times the upper limit of normal; can be normal or slightly elevated
Electromyography	Myopathic units (active and chronic)	Myopathic units (active and chronic)	Active myopathic units	Myopathic units (active and chronic) with some mixed large-size potentials
Muscle biopsy	Perivascular, perimysial, and perifascicular inflammation; necrotic fibers in "wedge-like" infarcts; perifascicular atrophy; reduced capillaries†	CD8+ cells invading healthy fibers; widespread expression of MHC class I antigen; no vacuoles; ruling out of inflammatory dystrophies	Scattered necrotic fibers with macrophages; no CD8+ cells or vacuoles; deposits of complement on capillaries‡	CD8+ cells invading healthy fibers; widespread expression of MHC class I antigen; autophagic vacuoles,§ ragged-red or ragged-blue fibers; congophilic amyloid deposits¶
Autoantibodies	Anti-MDA-5, anti-Mi-2; anti-TIF-1 and anti-NXP-2 (implicated in cancer-associated dermatomyositis)	Antisynthetase antibodies (often seen in overlap myositis) associated with interstitial lung disease, arthritis, fever, and "mechanic's hands"	Anti-SRP and anti-HMGCR, specific for necrotizing autoimmune myositis	Anti-cN1A (of uncertain pathologic significance)
Magnetic resonance imaging	May show active inflammation	May show active inflammation; could guide biopsy site	May show active inflammation; could guide biopsy site	Shows selective muscle involvement, but might be difficult to distinguish atrophy from chronic inflammation

* Drug-induced myopathies (e.g., penicillamine, statins, or antiretrovirals), inflammatory dystrophies (such as those due to mutations in the genes encoding dysferlin, calpain, or anoctamin; Becker's muscular dystrophy; facioscapulohumeral muscular dystrophy; or myofibrillar myopathies), inclusion-body myositis, necrotizing autoimmune myositis, metabolic myopathies, and fasciitis or fibromyalgia need to be ruled out.

† Similar pathologic changes in the perifascicular, perimysial, and interfascicular areas (to a lesser degree of severity) can be seen in overlap myositis (without skin lesions) or the antisynthetase syndrome.

‡ Metabolic muscle diseases presenting as myoglobinuria and toxic or drug-induced myopathies need to be ruled out.

§ In clinical inclusion-body myositis, when patients have the typical inclusion-body myositis phenotype, vacuoles are absent; such patients are erroneously thought to have polymyositis because of polymyositis-like inflammation; ragged-red fibers or cytochrome oxidase–negative fibers are frequently present and are helpful in diagnosis.

¶ TDP43 and p62 deposits, detected with the use of immunostaining, have been proposed as tissue biomarkers.

docrinopathy, or the clinical phenotype of inclusion-body myositis.[1-3]

NECROTIZING AUTOIMMUNE MYOSITIS

Necrotizing autoimmune myositis is a distinct clinicopathologic entity that occurs more frequently than polymyositis, accounting for up to 19% of all inflammatory myopathies.[13] It can occur at any age but is seen primarily in adults; it starts either acutely, reaching its peak over a period of days or weeks, or subacutely, progressing steadily and causing severe weakness and very high creatine kinase levels.[14,15] Necrotizing autoimmune myositis occurs alone or after viral infections, in association with cancer, in patients with connective-tissue disorders such as scleroderma, or in patients taking statins, in whom the myopathy continues to worsen after statin withdrawal (if the myopathy improves within 4 to 6 weeks after discontinuation of statins, it was probably caused by toxic effects of the drug rather than by immune myopathy).[3,4,6,14-16] Most patients with necrotizing autoimmune myositis have antibodies against signal recognition particle (SRP) or against 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR) (see the Glossary).[14-16]

INCLUSION-BODY MYOSITIS

Inclusion-body myositis is the most common and disabling inflammatory myopathy among persons 50 years of age or older.[1-5,17-23] Its prevalence, which was initially estimated in the Netherlands as 4.9 cases per million population,[18] is much higher when adjusted for age; in two later studies in Australia and the United States, the age-adjusted prevalence ranged from 51.3 to 70 cases per million.[19,22] In a small chart-review study conducted in one U.S. county, the estimated incidence of inclusion-body myositis was 7.9 cases per million in the 1980s and 1990s.[19] The disease starts insidiously and develops over a period of years, at times asymmetrically (i.e., it may start or be more severe in one extremity or on one side of the body), and progresses steadily, simulating a late-life muscular dystrophy or slowly progressive motor-neuron disease.[1-5] Although inclusion-body myositis is commonly suspected when a patient's presumed polymyositis does not respond to therapy,[3] features that can lead to an early clinical diagnosis include the early involvement of distal muscles, especially foot extensors and finger flexors; atrophy of the forearms and quadriceps muscles; frequent falls due to quadriceps muscle weakness causing buckling of the knees; and mild facial-muscle weakness.[1-5,20-23] The axial muscles may be affected, which results in camptocormia (bending forward of the spine) or head drop. Dysphagia occurs in more than 50% of the patients.[23]

DIAGNOSIS

The diagnosis of the exact subtype of inflammatory myopathy is based on the combination of clinical history, tempo of disease progression, pattern of muscle involvement, muscle enzyme levels, electromyographic findings, muscle-biopsy analysis, and for some conditions, the presence of certain autoantibodies (Table 1). Typical skin changes, with or without muscle weakness, indicate dermatomyositis; a subacute onset of proximal myopathic weakness points to polymyositis or necrotizing autoimmune myositis; and slowly progressive proximal and distal weakness with selective atrophy points to inclusion-body myositis. Electromyography is diagnostically useful in all disease subtypes to rule out neurogenic conditions and assess disease activity. Serum creatine kinase is elevated in all subtypes, but very high levels from the outset point to necrotizing autoimmune myositis. Magnetic resonance imaging (MRI) is helpful for diagnosis when muscle edema is present or myofasciitis is suspected, as well as for identification of the particular muscles affected by atrophy in inclusion-body myositis. Muscle biopsy is essential for the diagnosis of polymyositis, overlap myositis, necrotizing autoimmune myositis, and inclusion-body myositis, as well as for ruling out disease mimics such as dystrophies or metabolic or vacuolar myopathies. Assessment of autoantibodies is helpful for the diagnosis of necrotizing autoimmune myositis and for the classification of distinct subtypes and their associations with systemic organ involvement, such as interstitial lung disease.

Among muscle-derived enzymes in serum, the most sensitive indicator of inflammatory myopathy is creatine kinase, which is elevated in patients with active disease. The highest levels, up to more than 50 times the upper limit of normal, are seen in patients with necrotizing autoimmune myositis, and the lowest (less than 10 times the upper limit of normal) are seen in patients with inclusion-body myositis. Although serum levels of creatine kinase usually parallel disease activity, they can be normal or only slightly elevated in patients with active dermatomyositis, overlap myositis, or active inclusion-body myositis. Along with creatine kinase, aspartate aminotransferase and alanine aminotransferase levels are also elevated, a sign that is sometimes erroneously interpreted as indicating liver disease and that leads to an investigation with a liver biopsy instead of a muscle biopsy. Serum aldolase levels may be also elevated, especially if the fascia is involved.

Electromyography can show myopathic motor-unit potentials (short-duration, low-amplitude polyphasic units on voluntary activation) and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. These findings are useful in determining whether the myopathy is active or chronic and in ruling out neurogenic disorders, but they cannot be used for differentiating inflammatory myopathies from toxic or dystrophic myopathies.[1-5]

MRI can be used to identify edema, inflammation in muscle or fascia, fatty infiltration, fibrosis, or atrophy. It is useful for assessing the extent and selectivity of muscle involvement, especially in cases of inclusion-body myositis; for identifying disease activity; and for guiding the selection of the muscle with the greatest degree of inflammation to biopsy.[3,4,6,7]

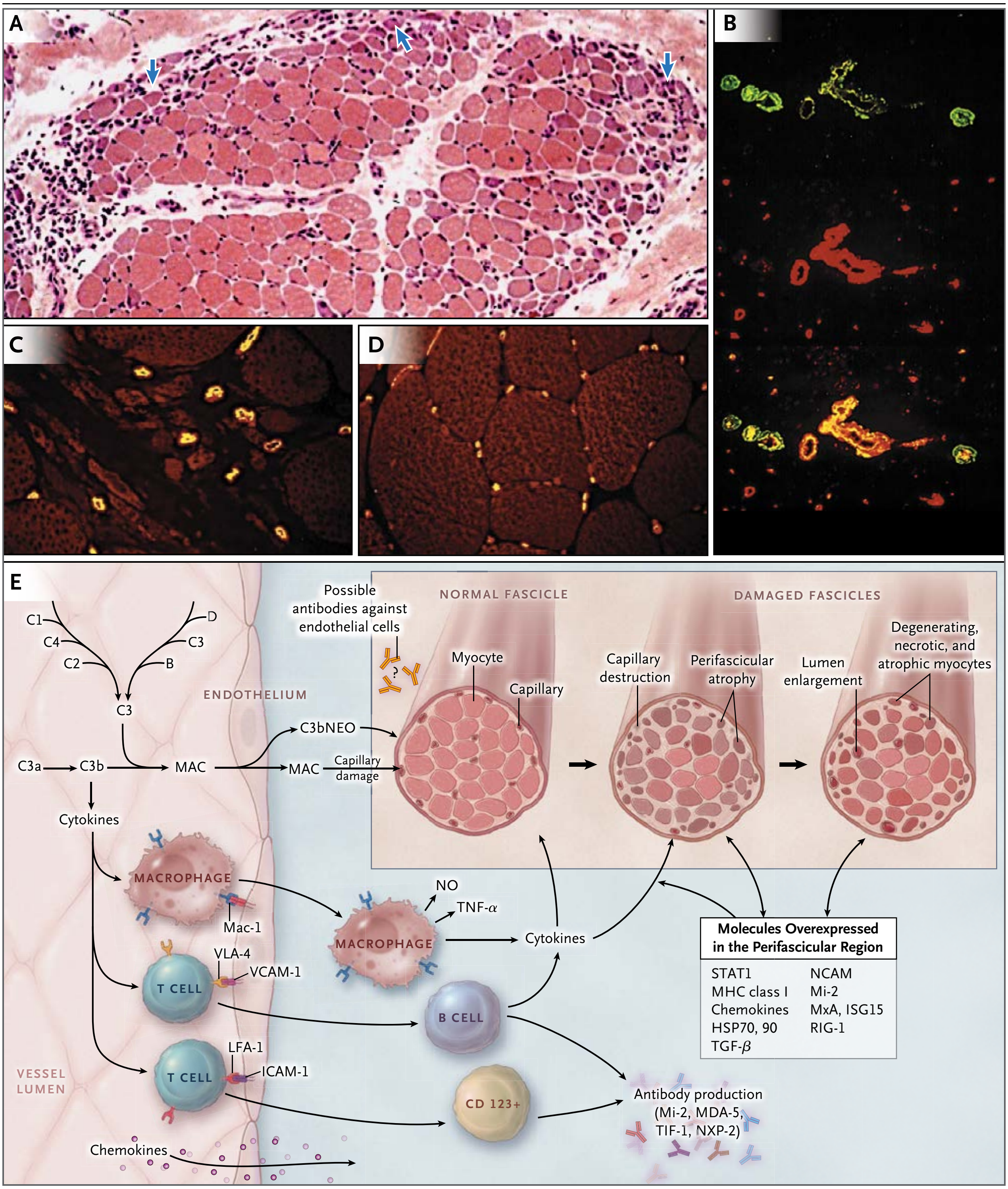
Examination of muscle-biopsy samples reveals features distinct to each disease subtype, and although the results are not always typical or specific, it remains the most important diagnostic tool. Muscle biopsy is most useful when the biopsy site is properly chosen (i.e., in a muscle that does not have clinical signs of advanced or end-stage disease but is also not minimally affected), the specimen is processed at an experienced laboratory, and the findings are interpreted in the context of the clinical picture.[1-3,24,25]

In dermatomyositis, the inflammation is perivascular and is most prominently located in the interfascicular septae or the periphery of the fascicles. The muscle fibers undergo necrosis and phagocytosis — often in a portion of a muscle fasciculus or the periphery of the fascicle — owing to microinfarcts that lead to hypoperfusion and perifascicular atrophy.[1-5] Perifascicular atrophy, which is characterized by layers of atrophic fibers at the periphery of the fascicles, often with perivascular and interfascicular infiltrates, is diagnostic of dermatomyositis (or of overlap myositis, when the skin changes are absent or transient)[1-5,10,24,25] (Fig. 1A).

In polymyositis and inclusion-body myositis, the inflammation is perivascular and is most typically concentrated in multiple foci within the endomysium; it consists predominantly of CD8+ T cells invading healthy-appearing, nonnecrotic muscle fibers expressing major histocompatibility complex (MHC) class I antigen (normal muscle fibers do not express this antigen) (Fig. 2A, 2C, and 2D). The finding of MHC expression and

Figure 1 (facing page). Dermatomyositis: A Complement-Mediated Microangiopathy.

Panel A shows a cross-section of a hematoxylin and eosin–stained muscle-biopsy sample with classic dermatomyositis perifascicular atrophy (layers of atrophic fibers at the periphery of the fascicle [arrows]) and some inflammatory infiltrates. Panel B shows the deposition of complement (membranolytic attack complex, in green) on the endothelial cell wall of endomysial vessels (stained in red with *Ulex europaeus* lectin), which leads to destruction of endothelial cells (shown in orange, indicating the superimposition of red and green). Consequently, in the muscles of patients with dermatomyositis (shown in Panel C), as compared with a myopathic control (Panel D), the density of the endomysial capillaries (in yellow–red) is reduced, especially at the periphery of the fascicle, with the lumen of the remaining capillaries dilated in an effort to compensate for the ischemic process.[1,2] Panel E shows a schematic diagram of a proposed immunopathogenesis of dermatomyositis. Activation of complement component 3 (C3) (probably triggered by antibodies against endothelial cells) is an early event leading to the formation of C3b, C3bNEO, and membrane attack complexes (MACs), which are deposited on the endothelial cell wall of the endomysial capillaries; this results in the destruction of capillaries, ischemia, or microinfarcts, which are most prominent in the periphery of the fascicles, as well as in perifascicular atrophy. Cytokines released by activated complement lead to the activation of CD4+ T cells, macrophages, B cells, and CD123+ plasmacytoid dendritic cells; enhance the expression of vascular-cell adhesion molecules (VCAMs) and intercellular adhesion molecule (ICAM) on the endothelial cell wall; and facilitate lymphoid cell transmigration to endomysial tissue through the action of their integrins, late activation antigen (VLA)–4, and lymphocyte function–associated antigen (LFA)–1, which bind VCAM-1 and ICAM-1. The perifascicular regions contain fibers that are in a state of remodeling and regeneration (expressing TGF-β, NCAM, and Mi-2), cell stress (expressing heat shock protein 70 [HSP70] and HSP90), and immune activation (expressing major histocompatibility complex [MHC] class I antigen, chemokines, and STAT1), as well as molecules associated with innate immunity (such as MxA, ISG15, and retinoic acid–inducible gene 1 [RIG-1]).



CD8+ T cells (termed the MHC–CD8 complex) is useful for confirming the diagnosis and for ruling out disorders with nonimmune inflammation, as seen in some muscular dystrophies.[2,3,5,17,25]

In necrotizing autoimmune myositis, there are abundant necrotic fibers invaded or surrounded by macrophages (Fig. 2E and 2F). Lymphocytic infiltrates are sparse, and MHC class I up-regulation is often prominent beyond the necrotic fibers.[3,4,6,14,25] Necrotizing autoimmune myositis is most often mediated by specific antibodies against SRP or HMGCR (see the Glossary), often with complement deposits on capillaries.[15,16]

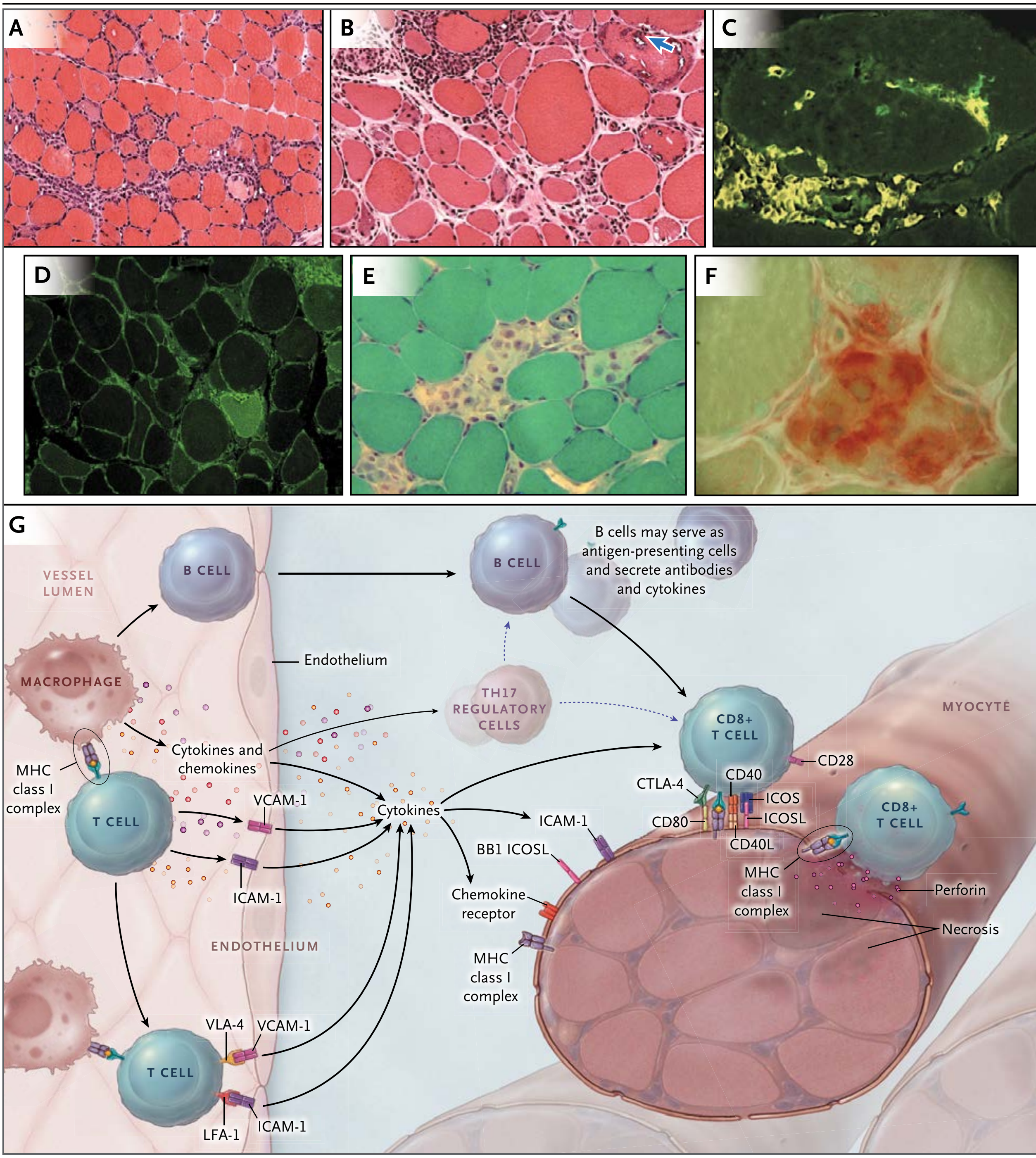
Inclusion-body myositis has all the inflammatory features of polymyositis, including the CD8–MHC complex, but in addition has chronic myopathic changes with increases in connective tissue and in the variability in fiber size, autophagic vacuoles that have walls lined internally with material that stains bluish-red with hematoxylin and eosin or modified Gomori trichrome (Fig. 2B), "ragged-red" or cytochrome oxidase–negative fibers representing abnormal mitochondria, and congophilic amyloid deposits next to the vacuoles, which are best visualized with crystal violet or fluorescent optics.[3-5,20-23] Electron microscopy shows tubulofilaments 12 to 16 nm in diameter next to the vacuoles.[20] In up to 30% of patients with the typical clinical inclusion-body myositis phenotype, vacuoles or amyloid deposits are not found in the muscle-biopsy sample and only inflammation is seen, which leads to an erroneous diagnosis of polymyositis.[26] Such patients have "clinical inclusion-body myositis" diagnosed on the basis of clinicopathologic correlation.[27,28] Data-driven criteria confirm that finger-flexor or quadriceps weakness, inflammation around nonnecrotic fibers with MHC class I expression, and cytochrome oxidase–negative fibers, even without vacuoles, are specific for the diagnosis of clinical inclusion-body myositis.[27,28]

Autoantibodies directed against nuclear RNAs or cytoplasmic antigens are detected in up to 60% of patients with inflammatory myopathies,[6,7,16,29] depending on the case series and the method of detection used. Although the pathogenic role of the antibodies is unclear, some appear to be specific for distinct clinical phenotypes and HLA-DR genotypes. These antibodies include those against aminoacyl tRNA synthetases (ARSs), which are detected in 20 to 30% of patients.[7,16] Among the eight different ARSs that have been identified, anti-Jo-1, the most widely commercially available antibody, accounts for 75% of all antisynthetases associated with the antisynthetase syndrome. This syndrome is characterized by myositis with prominent pathologic changes at the periphery of the fascicles and the perimysial connective tissue,[10] interstitial lung disease, arthritis, Raynaud's phenomenon, fever, and mechanic's hands.[7] In one rare case, $\gamma\delta$ T cells were found to recognize ARS, which provided the first pathogenic link between ARS and T-cell–mediated immunity.[30]

Necrotizing autoimmune myositis–specific antibodies are directed against the translational transport protein SRP or against HMGCR, the pharmacologic target of statins.[15,16] Anti-HMGCR, seen in 22% of persons with necrotizing autoimmune myositis, regardless of statin use, correlates

Figure 2 (facing page). Main Inflammatory Features of Polymyositis, Inclusion-Body Myositis, and Necrotizing Autoimmune Myositis and a Proposed Immunopathogenic Scheme for Polymyositis and Inclusion-Body Myositis.

Panels A and B show cross-sections of hematoxylin and eosin–stained muscle-biopsy samples from a patient with polymyositis (Panel A) and a patient with inclusion-body myositis (Panel B), in which scattered inflammatory foci with lymphocytes invading or surrounding healthy-appearing muscle fibers are visible. In inclusion-body myositis, there are also chronic myopathic features (increases in connective tissue and atrophic and hypertrophic fibers) and autophagic vacuoles with bluish-red material, most prominent in fibers not invaded by T cells (arrow). In both polymyositis and inclusion-body myositis, the cells surrounding or invading healthy fibers are CD8+ T cells, stained in green with an anti-CD8+ monoclonal antibody (Panel C); also visible is widespread expression of MHC class I, shown in green in Panel D, even in fibers not invaded by T cells. In contrast, in necrotizing autoimmune myositis (a cross-section stained with trichrome is shown in Panel E), there are scattered necrotic fibers invaded by macrophages (Panel F), which are best visualized with an acid phosphatase reaction (in red). Panel G shows a proposed mechanism of T-cell–mediated muscle damage in polymyositis and inclusion-body myositis. Antigen-specific CD8+ cells, expanded in the periphery and subsequently in the endomysium, cross the endothelial cell wall and bind directly to aberrantly expressed MHC class I on the surface of muscle fibers through their T-cell receptors, forming the MHC–CD8 complex. Up-regulation of costimulatory molecules (BB1 and ICOSL) and their ligands (CD28, CTLA-4, and ICOS), as well as ICAM-1 or LFA-1, stabilizes the synaptic interaction between CD8+ cells and MHC class I on muscle fibers. Regulatory Th17 cells play a fundamental role in T-cell activation. Perforin granules released by the autoaggressive T cells mediate muscle-fiber necrosis. Cytokines, such as interferon-γ, interleukin-1, and tumor necrosis factor (TNF) released by the activated T cells, may enhance MHC class I up-regulation and T-cell cytotoxicity. Activated B cells or plasmacytoid dendritic cells are clonally expanded in the endomysium and may participate in the process in a still-undefined role, either as antigen-presenting cells or through the release of cytokines and antibody production.



with creatine kinase levels and strength.[31] Dermatomyositis-associated antibodies include anti-Mi-2, which is associated with the typical skin lesions; anti-MDA-5, which is associated primarily with amyopathic dermatomyositis or interstitial lung disease[4,6,16]; and anti–transcriptional intermediary factor 1γ (anti-TIF-1γ) and anti–nuclear matrix protein 2 (anti-NXP-2), which are usually present in patients with cancer-associated adult dermatomyositis,[29] although their presence is influenced by geographic, racial, and genetic factors. Anti–cytosolic 5′-nucleotidase 1A (anti-cN1A) is detected in 60 to 70% of patients with inclusion-body myositis,[32,33] although the degree of sensitivity and specificity varies according to the method of detection used, and indicates B-cell activation.

PATHOLOGIC MECHANISMS

IMMUNOPATHOLOGY

The causes of inflammatory myopathies are unknown, but an autoimmune pathogenesis is strongly implicated. In dermatomyositis, complement C5b-9 membranolytic attack complex is activated early (before the destruction of muscle fibers is evident) and deposited on the endothelial cells, leading to necrosis, reduction of the density of endomysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts[1-6,24,25,34]; the remaining capillaries have dilated lumens to compensate for the ischemia[2,3,25] (Fig. 1A through 1D). The residual perifascicular atrophy reflects the endofascicular hypoperfusion, which is most prominent at the periphery of the fascicles.[2,3,24,25] The activation of membrane attack complex, presumably by antibodies, triggers the release of proinflammatory cytokines, up-regulates adhesion molecules on endothelial cells, and facilitates migration of activated lymphocytes, including B cells, CD4+ T cells, and plasmacytoid dendritic cells, to the perimysial and endomysial spaces (Fig. 1E). Innate immunity also plays a role that is based on increased expression of type I interferon–inducible proteins in the perifascicular region,[35] an area where other inflammatory, degenerative, or regenerative molecules are also overexpressed (Fig. 1E); it remains to be determined whether the effect of innate immunity is caused by retinoic acid–inducible gene 1 signaling in response to local signals from the damaged fibers, which leads to autoamplification of perifascicular inflammation by activating interferon-β and MHC class I[36] (Fig. 1E). In juvenile dermatomyositis, maternal chimeric cells may contribute to the pathogenesis of the disease.[37]

In polymyositis and inclusion-body myositis, CD8+ cytotoxic T cells surround and invade healthy-appearing, nonnecrotic muscle fibers that aberrantly express MHC class I (Fig. 2A through 2D).[38,39] MHC class I expression, which is absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells.[40,41] The CD8–MHC class I complex is characteristic of polymyositis and inclusion-body myositis, and its detection aids in confirming the histologic diagnosis.[2-5,25] The CD8+ T cells contain perforin granules directed toward the surface of the muscle fibers, which cause myonecrosis on release.[42] Analysis of T-cell–receptor molecules expressed by the infiltrating CD8+ T cells reveals clonal expansion of T-cell–receptor chains and conserved sequences in the antigen-binding region, which suggests an antigen-driven T-cell response.[43,44] This is further supported by the expression of costimulatory molecules and up-regulation of adhesion molecules, chemokines, and cytokines[45-47] (Fig. 2G). Th17 and regulatory T cells participate in the immune process.[48] The up-regulation and overload of MHC class I may also cause glycoprotein misfolding, which stresses the endoplasmic reticulum of the myofibers.[49] B-cell activation also occurs, most prominently in inclusion-body myositis[50] (although it is unclear whether the muscle can sustain germinal center formations), in which anti-cN1A autoantibodies are also detected (see the Glossary).

The factors that trigger inflammatory muscle diseases remain unknown. Genetic risk factors regulating immune responses against undefined environmental agents have been proposed.[7] Genetic interactions are supported by the associations between HLA-DRB1*03 and anti-Jo-1, between HLA-DRB1*11:01 and anti-HMGCR–positive necrotizing autoimmune myositis, and between HLA-DRB1*03:01 and HLA-DRB1*01:01 and inclusion-body myositis.[51] Viruses may be responsible for disrupting immune tolerance, but attempts to amplify viruses — including coxsackieviruses, influenza virus, paramyxoviruses (including mumps virus), cytomegalovirus, and Epstein-Barr virus — from the muscles have failed.[1-5] The best evidence for a viral connection involves retroviruses, because polymyositis or inclusion-body myositis develops in people infected with human immunodeficiency virus (HIV) or human T-cell lymphotropic virus I.[52,53] However, retroviral antigens are detected only in endomysial macrophages and not within the muscle fibers. The autoinvasive T cells are clonally driven, and some are retroviral-specific.[52] HIV-associated polymyositis and HIV-associated inclusion-body myositis should be distinguished from a toxic mitochondrial myopathy induced by antiretroviral drugs, which improves when the drugs are discontinued.[54]

DEGENERATIVE COMPONENT OF INCLUSION-BODY MYOSITIS

Inclusion-body myositis is a complex disorder because, in addition to the autoimmunity compo-

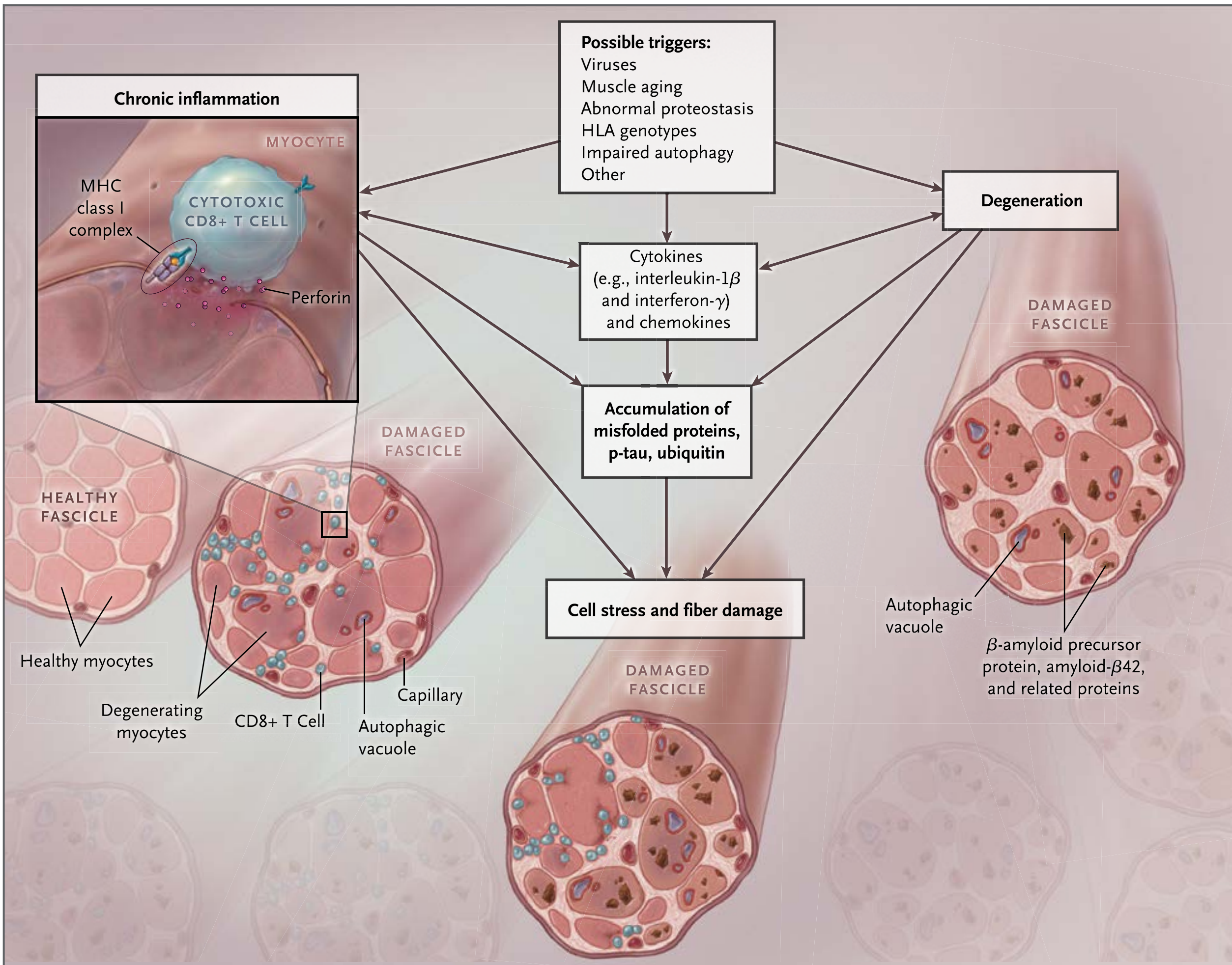


Figure 3. Proposed Mechanisms in Inclusion-Body Myositis.

Shown is a hypothetical schematic diagram of the pathogenesis of inclusion-body myositis, highlighting the interaction between the long-standing chronic inflammatory process and degeneration, which leads to cell stress and deposits of β-amyloid precursor protein, amyloid-β42, and misfolded proteins similar to the ones seen in neuroinflammatory disorders such as Alzheimer's disease. Therefore, inclusion-body myositis can be considered to be a peripheral model of neuroinflammation. The factors that trigger the disease are unclear, but viruses, muscle aging, protein misregulation (such as abnormal proteostasis), impaired autophagy, and HLA genotypes may play a role, either alone or in combination. Whether the primary event is inflammatory or degenerative is highly debated and remains unclear.

nent, there is an important degenerative component, highlighted by the presence of congophilic amyloid deposits within some fibers.[20-22] Similar to what is seen in Alzheimer's disease, these deposits immunoreact against amyloid precursor protein, amyloid-β42, apolipoprotein E, α-synuclein, presenilin, ubiquitin, and phosphorylated tau, which indicates the presence of protein aggregation.[20] Deposits of TDP43, a DNA-binding protein aberrantly translocated from the nuclei to the cytoplasm, and p62, a shuttle protein that transports polyubiquitinated proteins, detected within the muscle fibers with the use of immunostaining, have been advocated as diagnostic markers.[20,55] In vitro evidence suggests that amyloid-β42 and its oligomers are involved in the pathway of intracellular toxicity,[20] but it remains unclear how these proteinaceous aggregates, which are also seen in other vacuolar myopathies, induce an inflammatory and degenerative myopathy and what triggers disease, inflammation, or protein aggregation.[21] Laser microdissection of T-cell–invaded fibers in comparison with noninvaded or vacuolated fibers has revealed differential up-regulation

Table 2. Treatment of Inflammatory Myopathies: A Step-by-Step Approach.

Scenario	Treatment for Dermatomyositis, Polymyositis, and Necrotizing Autoimmune Myositis	Treatment for Inclusion-Body Myositis
Initiation of therapy		
New-onset disease	Prednisone (1 mg per kilogram, up to 100 mg per day) for 4–6 weeks; taper to alternate days	Physical therapy; participation in research trial
When weakness at onset is severe or rapidly worsening	Intravenous glucocorticoids (1000 mg per day) for 3 to 5 days, then switch to oral regimen	Not applicable
For glucocorticoid sparing, if the patient's condition responds to glucocorticoids	Azathioprine, methotrexate, mycophenolate, cyclosporine*	Not applicable†
If response to glucocorticoids is insufficient	Intravenous immune globulin (2 g per kilogram in divided doses over a period of 2 to 5 consecutive days)	Not applicable‡
If response to glucocorticoids and intravenous immune globulin is insufficient	Reevaluate and reconsider diagnosis; initiate treatment with rituximab§ if diagnosis is reconfirmed, recommend participation in a research trial¶ if disease does not respond to rituximab	Participation in research trial

* The use of these agents is based on experience but not on controlled studies. Azathioprine can be given at a dose of up to 3 mg per kilogram, methotrexate at a dose of up to 20 mg per week, mycophenolate at a dose of 2000 to 3000 mg per day, and cyclosporine at a dose of up to 300 mg daily. Intravenous cyclophosphamide (0.8 to 1 g per square meter of body surface area) and oral tacrolimus (4–8 mg per day) may help patients with interstitial lung disease.
† All glucocorticoid-sparing agents are ineffective, either alone or in combination.
‡ In some patients, the dysphagia responds to intravenous immune globulin.
§ Efficacy has not been established with a controlled study, but the evidence of efficacy is compelling.
¶ Candidate agents include eculizumab, alemtuzumab, tocilizumab (anti–interleukin-6), anti–interleukin-17, and anti–interleukin-1β.

of inflammatory signaling, such as interferon-γ–receptor signaling.[56] Compelling evidence suggests that aging, abnormal proteostasis (the network controlling proteins),[20] impaired autophagy, cell stress induced by MHC class I or nitric oxide,[21,57] long-standing inflammation, and proinflammatory cytokines such as interferon-γ and interleukin-1β[57,58] may cumulatively trigger or enhance degeneration, leading to further accumulation of stressor molecules and misfolded proteins[59] (Fig. 3).

TREATMENT OF DERMATOMYOSITIS, POLYMYOSITIS, AND NECROTIZING AUTOIMMUNE MYOSITIS

Strategies for the treatment of the inflammatory myopathies are described in Table 2. Oral prednisone administered once daily after breakfast at a dose of 1 mg per kilogram of body weight, up to 100 mg per day, is the first-line drug for the treatment of dermatomyositis, polymyositis, and necrotizing autoimmune myositis; this choice of drug is based on experience but not on controlled trials.[1-6,60,61] Some clinicians prefer to add an immunosuppressant agent from the outset.[6,61] In patients with rapidly worsening disease, it is preferable to administer intravenous methylprednisolone at a dose of 1000 mg per day for 3 to 5 days before starting treatment with oral glucocorticoids. After 3 to 4 weeks, prednisone is tapered, as dictated by the response of the disease to therapy, preferably by a switch from a daily dose to doses on alternate days[60]; however, if the objective signs of increased strength and ability to perform activities in daily living are absent at that time, tapering is accelerated so that treatment with a next agent can be started. A tactical error is the practice of "chasing" the creatine kinase level as a sign of response, especially in patients who report a sense of feeling better but not necessarily of feeling stronger. When the strength improves, the serum creatine kinase level drops, but a decrease in creatine kinase alone is not a sign of improvement.[60]

For patients in whom glucocorticoids produce a response, azathioprine, mycophenolate mofetil, methotrexate, or cyclosporine can be used empirically for glucocorticoid sparing.[2-4,6,60,61] When interstitial lung disease is a coexisting condition, cyclophosphamide or tacrolimus may be helpful.[6,60,62] In patients with dermatomyositis, topical glucocorticoids or calcineurin inhibitors and sunlight avoidance are recommended. When glucocorticoids fail to induce remission or in severe and rapidly progressive cases, intravenous immune globulin therapy (2 g per kilogram in divided doses over a period of 2 to 5 consecutive days) is appropriate.[2-4,6,60,61] In a double-blind study, intravenous immune globulin was found to be effective in the treatment of refractory dermatomyositis[63]; monthly infusions may be required to maintain remission.[60,63] In open-label trials, intravenous immune globulin has also appeared to be effective in the treatment of polymyositis and necrotizing autoimmune myositis.[6,60] Subcutaneous immune globulin has appeared to sustain remission in small-scale, uncontrolled studies.[64]

If the disease has not responded to glucocorticoids and intravenous immune globulin, the patient should be reevaluated, and if there are diagnostic uncertainties, a repeat muscle biopsy should be considered. If the diagnosis is reconfirmed, biologic agents that have been approved for the treatment of other immune diseases may be considered as experimental treatment options.[60] These include rituximab (an anti-CD20 antibody), which at a dose of 2 g (divided into two infusions 2 weeks apart) seems effective in some patients with dermatomyositis, polymyositis, or necrotizing autoimmune myositis. In a placebo-controlled study involving 200 patients, at week 8 there was no difference between the placebo group and the rituximab group, and on the basis of the study design, the results were not significant; however, at week 44, when all the patients had received rituximab, 83% met the definition of improvement.[65] Patients with anti-Jo-1, anti-Mi-2, or anti-SRP antibodies seem more likely to have a response.[66,67] Tumor necrosis factor inhibitors (infliximab, adalimumab, and etanercept) are ineffective and may worsen or trigger disease.[68] Other biologics that may be considered as experimental treatment include alemtuzumab, which is reportedly effective in polymyositis[69]; anti-complement C3 (eculizumab), which is effective in complement-mediated diseases and may be effective for the treatment of dermatomyositis and necrotizing autoimmune myositis; anti–interleukin-6 (tocilizumab)[70] and anti–interleukin-1 receptor (anakinra),[71] which have been effective in anecdotal cases; anti–interleukin-17; and anti–interleukin-1β (gevokizumab), which is being evaluated in an ongoing trial (EudraCT number, 2012-005772-34). Overall, the long-term outcome of inflammatory myopathies has substantially improved, with a 10-year survival rate of more than 90%.[72]

Treatment of Inclusion-Body Myositis

Because of T-cell–mediated cytotoxic effects and the enhancement of amyloid-related protein aggregates by proinflammatory cytokines in patients with inclusion-body myositis,[21,57,58] immunosuppressive agents have been tried as treatment for this disease subtype, but all have failed, probably because the disease starts long before patients seek medical advice, when the degenerative cascade is already advanced.[60] Glucocorticoids, methotrexate, cyclosporine, azathioprine, and mycophenolate are ineffective, and although some patients may initially have mild subjective improvements when treated with one of these agents,[60,61] no long-term benefit is achieved.[73] Intravenous immune globulin has been found to be ineffective in controlled trials but may transiently help some patients, especially those with dysphagia.[74,75] Alemtuzumab may provide short-term stabilization,[76] but a controlled study is needed. Treatment with anakinra has also not been successful.[77] Trials targeting muscle-inhibiting TGF-β molecules or muscle growth factors are in progress. Bimagrumab, an antibody that inhibits the signaling of a TGF-β superfamily receptor, was shown in a small-scale study to increase muscle volume after 8 weeks,[78] which has prompted an ongoing controlled study (ClinicalTrials.gov number, NCT01925209). A small, controlled, proof-of-concept study of arimoclomol (ClinicalTrials.gov number, NCT00769860), an agent that up-regulates heat shock protein response and attenuates cell stress, has been completed; the drug had an acceptable adverse-event profile, but whether there were clinically meaningful benefits is still unclear.[79]

At present, symptomatic therapies are the best option. For life-threatening dysphagia that is not responding to intravenous immune globulin, cricopharyngeal dilation or myotomy may be considered. As with all inflammatory myopathies, nonfatiguing resistance exercises and occupational and rehabilitation therapies are useful to improve ambulation, prevent falling, avoid disuse atrophy, and prevent joint contractures.[80]

Although the life expectancy of patients with inclusion-body myositis is normal, most patients with end-stage disease require assistive devices such as a cane, walker, or wheelchair.[23]

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