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Review

Clinical, Immunopathologic, and Therapeutic Considerations of Inflammatory Myopathies

Marinos C. Dalakas

Neuromuscular Diseases Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, U.S.A.

Summary: The inflammatory myopathies encompass a group of heterogenous muscle diseases which have in common an acquired myopathy with histological signs of endomysial inflammation. We present evidence based on recently emerged clinical, histologic, immunopathologic, demographic and therapeutic observations that these myopathies comprise three major and distinct groups: polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis (IBM). Immune-mediated mechanisms characteristic for each group appear to play a primary role in the pathogenesis of these diseases. In DM there is an intramuscular microangiopathy mediated by the $C_5b\text{-}_9$ membranolytic attack complex, leading sequentially to loss of capillaries, muscle ischemia, muscle fiber necrosis and perifascicular atrophy. In contrast, in PM and IBM the muscle fiber injury is initiated by sensitized $CD8^+$ cytotoxic T cells that recognize MHC-I restricted muscle antigens, leading to phagocytosis and fiber necrosis. Among the viruses implicated in the cause of inflammatory myopathies, only the retroviruses, HIV, HTLV-1 and simian retroviruses, have been convincingly associated with PM. Retroviruses, therefore, appear to be the leading group of viruses capable of triggering these diseases. The treatment of inflammatory myopathies has been largely empirical. A detailed therapeutic plan based on our experience with a large number of patients is presented. Patients with bona fide PM or DM respond to steroids to some degree and for some period of time. In contrast, patients with IBM do not respond to any therapy and the disease should be suspected when a patient with presumed PM has failed treatment. Methotrexate and cyclophosphamide are disappointing. Cyclosporine and Azathioprine are commonly used but they are of uncertain benefit. Plasmapheresis is ineffective. High-dose intravenous immunoglobulin is a promising new therapeutic modality. **Key Words:** Polymyositis—Dermatomyositis—Inclusion-body myositis.

The inflammatory myopathies encompass a heterogeneous group of subacute or chronic acquired muscle diseases, characterized by proximal muscle weakness

Address correspondence and reprint requests to Dr. M. C. Dalakas at Neuromuscular Diseases Section, Building 10, Room 4N248, NINDS, National Institutes of Health, Bethesda, MD 20892, U.S.A.

and inflammation in the muscle biopsy (1–8). Although these myopathies have been viewed for years as being pathogenetically similar (9–11), the emergence over the last 10 years of rather distinct clinical, laboratory, prognostic, therapeutic, demographic, histologic, and immunopathologic criteria has defined three major and distinct subsets: polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis (IBM) (1–8,12). Each group retains its characteristic clinical, immunopathologic, and morphologic features regardless of whether it occurs separately or in connection with other systemic diseases.

The cause(s) of PM, DM, and IBM are unknown. Their association, however, with other putative or definite autoimmune diseases or viruses, the evidence for a T-cell-mediated myocytotoxicity or complement-mediated microangiopathy, the presence of a variety of autoantibodies, and their response to immunotherapies have all strengthened the hypothesis of an autoimmune role in their pathogenesis.

CLINICAL FEATURES

PM, DM, and IBM are different diseases (1–8). DM affects both children and adults, and females more often than males, whereas PM is seen after the second decade of life and very rarely in childhood. IBM is more frequent in males (male:female ratio of 3:1) over the age of 50 years, and it is more common in whites than in blacks. Patients commonly present with a myopathy characterized by proximal and often symmetrical muscle weakness that develops subacutely (weeks to months) and occasionally insidiously, as in IBM, but rarely acutely. Tasks requiring the use of proximal muscles are compromised first, whereas fine motor movements that depend on the strength of distal muscles are affected only late in DM and PM but fairly early in IBM. Falling is common in IBM owing to early involvement of the quadriceps muscle and buckling of the knees. Ocular muscles remain normal, even in advanced untreated cases, and if these muscles are affected, the diagnosis of inflammatory myopathy should be in doubt. Facial muscles also remain normal except, rarely, in advanced cases. The pharyngeal and neck flexor muscles are often involved, causing varying degrees of dysphagia. In advanced cases and rarely in acute cases, respiratory muscles also may be affected. Severe weakness is almost always associated with muscular wasting. Sensation remains normal. The tendon reflexes are preserved, but may be absent in severely weakened or atrophied muscles. Myalgia and muscle tenderness may occur in some patients, usually early in the disease, and more often in DM than in PM. Unlike the progression of the weakness accompanying dystrophic processes, which is observable from one year to the next, the weakness in PM and DM may progress noticeably, often almost month by month. The exception is IBM, in which painless weakness and atrophy develop and progress very slowly (over months or years), resulting in severe disease that resembles limb–girdle dystrophy. Other clinical characteristics specific for each of these three groups are the following.

Dermatomyositis (DM)

This is a distinct clinical entity identified by a characteristic rash accompanying, or more often preceding, the muscle weakness. The skin manifestations include a

heliotrope rash (blue–purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron rash). The initial erythematous lesions may result in scaling of the skin accompanied by pigmentation and depigmentation, giving at times a shiny appearance. The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck, and anterior chest (often in a V sign), or back and shoulders (shawl sign), and may be exacerbated after exposure to the sun. The rash may be difficult to appreciate in dark-skinned people, and sometimes it is so faint, transient, or indiscernible that DM is diagnosed only in retrospect with the later discovery of subcutaneous calcifications (1–4). Dilated capillary loops at the base of the fingernails are also characteristic of DM. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling mechanic's hands. Subcutaneous calcifications, although more often in childhood, occur in several adults with DM and can be extensive (Fig. 1A). Sometimes calcium deposits extrude on the skin and cause ulcerations and infections (Fig. 1B). DM in children resembles the adult disease, except for more frequent extramuscular manifestations, as discussed later.

DM usually occurs alone, but may be associated with systemic sclerosis, mixed

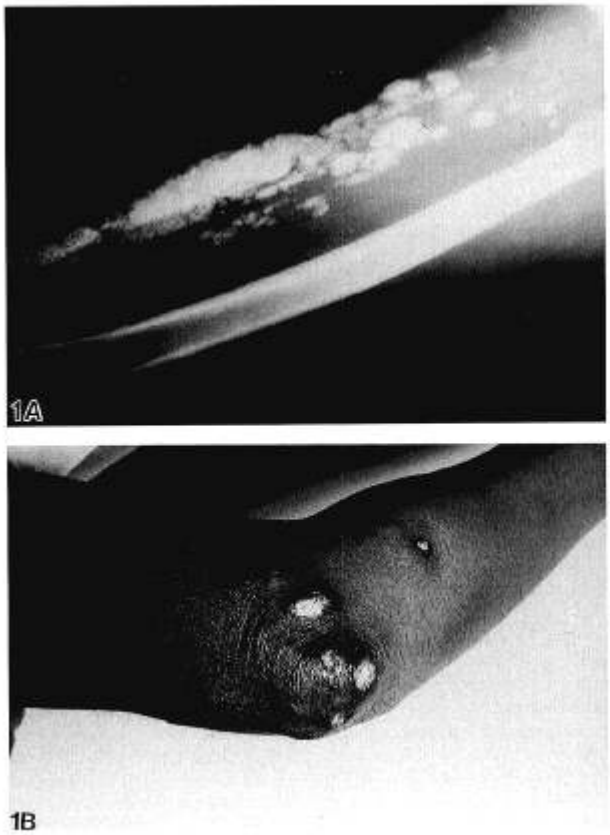

FIG. 1. A: Subcutaneous calcifications in the arm of a patient with dermatomyositis as seen by x-ray film. Note a floccular appearance of subcutaneous calcium deposits. B: Calcium deposits extruding onto the skin in a 28-year-old patient with dermatomyositis.

connective tissue disease, other autoimmune conditions, or malignancies (Table 1). Fasciitis and skin changes similar to those found in DM were noticed in patients with the eosinophilia–myalgia syndrome associated with the ingestion of contaminated L-tryptophan (13). The contaminant found in the implicated lots, and less likely the L-tryptophan itself or its metabolites, were responsible for the changes noted in the skin, the fascia, and the perimysium (13).

Polymyositis (PM)

In contrast with DM, which is a distinct entity because of the characteristic skin rash, PM has no unique clinical features, and its diagnosis is one of exclusion. It is best defined as an inflammatory myopathy of subacute onset (weeks to months) and steady progression occurring in adults who do *not* have (a) a rash, (b) involvement of eye and facial muscles, (c) a family history of a neuromuscular disease, (d) endocrinopathy, (e) a history of exposure to myotoxic drugs or toxins,

TABLE 1. *Inflammatory myopathies and associated conditions**

Associations	Dermatomyositis	Polymyositis	Inclusion body myositis
Age of onset	Adults and children	Adults >18 years	Adults >50 years
Associated with connective tissue diseases	Yes, with scleroderma and mixed connective tissue disease	Yes	Yes, in up to 15% of cases
Overlaps with connective tissue diseases	Yes, with scleroderma and mixed connective tissue disease	No	No
Associated with systemic autoimmune diseases[a]	Infrequently	Frequently	Infrequently
Associated with malignancies	Probably	No	No
Associated with viruses	Unproved	With HIV, HTLV-1; possibly with other viral or postviral conditions	Unproved
Associated with parasites and bacteria	No	Yes[b]	No
Associated with drug-induced myotoxicity[c]	Yes	Yes	No
Familial association	No	No	Yes, in some cases

* Adapted from (1).

[a] The most commonly associated systemic autoimmune diseases are Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-vs.-host disease, discoid lupus, ankylosing spondylitis, Behçet's disease, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hyperagammaglobulinemic purpura, hereditary complement deficiency, and IgA deficiency.

[b] Parasitic (protozoa, cestodes, nematodes), tropical, and bacterial myositis.

[c] D-Penicillamine (for DM and PM), ZDV (for PM), and contaminated L-tryptophan (for a DM-like illness). Other myotoxic drugs may cause myopathy but not *inflammatory* myopathy.

and (f) neurogenic disease, dystrophy, biochemical muscle disease, or IBM, as determined by muscle enzyme histochemistry and biochemistry. Unlike in DM, in which the rash secures early recognition, the actual onset of PM cannot be easily determined, and the disease may exist for several months before the patient seeks medical advice. The reported seasonal onset of PM, determined on the basis of record review or the patients' own recollection of onset of symptoms (14), may not be reliable because the disease can be lingering for months before it becomes noticeable by the patients. All claims of seasonal onset should therefore be viewed with skepticism or disregarded.

Polymyositis appears to be a syndrome of diverse causes that may occur separately or in association with systemic autoimmune or connective tissue diseases and certain known viral or bacterial infections (Table 1). It is very rare in childhood and if a diagnosis is made in patients below the age of 16 years, a careful review is needed to exclude another disease, especially certain dystrophies that may be associated with endomysial inflammation (1). Other than D-penicillamine and zidovudine (ZDV), which can cause a myopathy with endomysial inflammation like that seen in PM (15), myotoxic drugs such as emetine, chloroquine, steroids, cimetidine, ipecac, and lovostatin do not cause PM. Instead, they elicit a toxic *noninflammatory* myopathy that is histologically different from PM and does not require immunosuppressive therapy (1). Several animal parasites, such as protozoa (*Toxoplasma, Trypanosoma*), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as *parasitic* polymyositis. In the tropics, a suppurative myositis known as *tropical* polymyositis or *pyomyositis* may be produced by *Staphylococcus aureus, Yersinia, Streptococcus,* or other anaerobes (16). Pyomyositis, previously rare in the West, can now be seen in patients with acquired immune deficiency syndrome (AIDS) (17). Certain bacteria, such as *Borrelia burgdorferi* of Lyme disease and *Legionella pneumophila* of legionnaire's disease, may infrequently be the cause of PM (18,19). Other rare systemic conditions associated with PM are listed in Table 1.

Inclusion-Body Myositis (IBM)

Although IBM is commonly suspected when a patient with presumed PM does not respond to therapy, involvement of distal muscles, especially foot extensors and finger flexors, in more than 50% of the cases may be a clue to the early clinical diagnosis (1–8,12). The weakness and atrophy can be asymmetric with selective involvement of the quadriceps, iliopsoas, triceps, and biceps muscles. Weakness of the deep finger flexors of the fifth, fourth, and third digits associated with atrophy of the flexor digitorum muscle in the forearm, is almost pathognomonic for IBM (Dalakas, M. C.; unpublished observations). Because of the distal weakness, and the early loss of the patellar reflex owing to severe weakness of the quadriceps muscle, a neurogenic disease is often suspected. The weakness and atrophy can also be asymmetrical and mimic lower motor neuron syndromes especially when the serum creatine kinase (CK) is not elevated. The diagnosis is always made by the characteristic findings on the muscle biopsy, as discussed later. IBM can be associated with systemic autoimmune or connective tissue

diseases in up to 15% of the cases (Table 1). Familial cases, some with an associated leukoencephalopathy, may be found (1,20). Patients with IBM account for almost 50% of all cases of "polymyositis unresponsive to therapy" referred to our institution.

Extramuscular Manifestations

Aside from the primary disturbance of the skeletal muscles, extramuscular manifestations may be prominent. General symptoms, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, may occur when the inflammatory myopathy is associated with a connective tissue disorder. Contractures of the joints may occur, especially in childhood DM. At least 50% of the patients have dysphagia due to involvement of the oropharyngeal striated muscles and distal esophagus (1,6). Dysphagia may be prominent in IBM and rarely can be the presenting symptom. Cardiac abnormalities may be present in up to 40% of the patients and include atrioventricular conduction defects, tachyarrythmias, low ejection fraction, and dilated cardiomyopathy. Congestive heart failure and myocarditis, confirmed at autopsy, may be seen in up to 20% of the patients, either from the disease itself or from hypertension associated with long-term steroid use. Pulmonary involvement, causing dyspnea, nonproductive cough, aspiration pneumonia, and hypoxemia, may occur as the result of primary weakness of the thoracic muscles, drug-induced pneumonitis (e.g., from methotrexate), or interstitial lung disease. Interstitial lung disease may precede the myopathy or occur early in the disease and develops in up to 10% of patients with PM or DM, one-half of whom have anti-Jo-1 antibodies (1,6), as discussed later. Gastrointestinal ulcerations, seen more often in children with DM, especially before the conventional use of immunosuppressive drugs, may result in melena or hematemesis due to vasculitis and infection. Ulceration may be rarely preceded by *pneumatosis intestinalis,* as the vasculitis allows a submucosal dissection of intraluminal bowel gas. Subcutaneous calcifications are not infrequent, especially in childhood DM, as discussed above and shown in Fig. 1.

It is still uncertain whether malignancies are more frequent in patients with PM and DM (21–24). Methodologic deficiencies, such as the absence of diagnostic criteria for patient selection and the need for comparison of age-matched patients with other connective tissue diseases or autoimmune neuromuscular diseases, have been predominantly responsible for the conflicting reports (1,21–24). These problems, along with a long-term preconceived bias that alerts the clinician to a more vigorous search for malignancies in these patients, were the main reasons for the recently reported high incidence of malignancies in patients with PM and DM (25). Based on more convincing data, however, (1,22–24), we believe that the incidence of malignancies is increased only in patients with DM, but not PM or IBM. The extent of the search required for occult malignancy in adults with DM is still unsettled. Because oftentimes the tumors are either uncovered at autopsy (in spite of a thorough search in life) or on the basis of abnormal findings on the medical history and physical examination (1,4,22–24), a blind, extensive, and expensive radiologic search is not recommended. A complete *annual* physical examination, with pelvic and rectal examinations, urinalysis, complete blood cell

count, blood chemistry tests, chest radiograph, and a mammogram, should suffice.

Overlap Syndrome

This term is used loosely to define the up to 20% of patients with PM or DM who may have features of another connective tissue disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, or mixed connective tissue disease (1–4,6). However, "overlap syndrome" indicates that the characteristics of two different disorders are common to both. In that sense, it is only DM, and not PM, that truly overlaps, and only with scleroderma and mixed connective tissue disease (Table 1). Specific signs of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits, are present in DM but not PM, whereas signs of rheumatoid arthritis, SLE, or Sjögren's syndrome are very rare in DM. Patients with the overlap syndrome of DM/systemic sclerosis may have a specific antinuclear autoantibody, the anti-PM/Scl, directed against a nucleolar protein complex (1,26).

DIAGNOSIS

The clinically suspected diagnosis of PM, DM, or IBM is established or confirmed by examining the serum muscle enzymes, the electromyographic findings, and, above all, the muscle biopsy.

Muscle Enzymes

The most sensitive enzyme is CK, which in the presence of disease can be elevated as much as 50 times the normal level. Although CK usually parallels the disease activity, it can be normal in active DM and rarely even in active PM. In IBM, CK is not usually elevated more than tenfold, and in some cases may be normal even from the beginning of the illness. CK may also be normal in patients with untreated, even active, childhood DM and in some patients with PM or DM associated with a connective tissue disease, reflecting the concentration of the pathologic process in the intramuscular vessels and the perimysium. Along with the CK, the serum aldolase, serum glutamate–oxaloacetate transaminase (SGOT), serum glutamate–pynivate transaminase (SGPT), and lactate dehydrogenase (LDH) may be also elevated. The presence of high SGOT, SGPT, and LDH in a patient with early disease who has fatigue and minimal weakness often directs attention toward the diagnosis of liver disease and an unnecessary liver biopsy, if the CK level is not concurrently checked to exclude a myogenic origin of the "liver enzyme" elevation. If SGOT is higher than SGPT, a myogenic cause should be suspected; when SGPT is higher than SGOT, liver disease may be more likely.

Electromyography

Needle electromyography shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation, and increased

spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. This electromyographic pattern occurs in a variety of acute, toxic, and active myopathic processes and should not be considered diagnostic for the inflammatory myopathies. Mixed myopathic and neurogenic potentials (polyphasic units of short and long duration) are more often seen in IBM but they can be seen in both PM and DM as a consequence of muscle fiber regeneration and chronicity of the disease. Electromyographic studies are generally useful for excluding neurogenic disorders and confirming either active or inactive myopathy. Although in up to 30% of patients with IBM electromyographic signs of axonal neuropathy have been reported (27), we believe this figure is excessive when the nerve conduction data are compared with age-matched control patients (Dalakas, MC and Luciano, C; unpublished observations).

Muscle Biopsy

The muscle biopsy is the definitive test not only for establishing the diagnosis of DM, PM, or IBM, but also for excluding other neuromuscular diseases. Although the presence of inflammation is the histological hallmark for these diseases, there are additional unique histological features characteristic for each group. Specifically, in DM, the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around rather than within the fascicles. The intramusuclar blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, especially in children, and obliteration of capillaries (1–5). The muscle fibers undergo necrosis, degeneration, and phagocytosis often in groups involving a portion of a muscle fasciculus in a wedge-like shape, or at the periphery of the fascicle due to microinfarcts within the muscle. This results in perifascicular atrophy, characterized by two to ten layers of atrophic fibers at the periphery of the fascicles (Fig. 2). The presence of perifascicular atrophy is diagnostic of DM, *even in the absence of inflammation*. In contrast, in PM and IBM, the endomysial infiltrates are mostly within the fascicles (endomysially) surrounding individual, healthy, muscle fibers resulting in phagocytosis and necrosis. There is no perifascicular atrophy and the blood vessels are normal. When the disease is chronic, the connective tissue is increased. Although the inflammatory pattern of IBM is similar to that of PM, sometimes in the former the inflammation is sparse. The histological hallmark of IBM is the triad of (a) basophilic granular inclusions distributed around the edge of slit-like vacuoles (rimmed vacuoles), (b) angulated fibers often in small groups, and (c) eosinophilic cytoplasmic inclusions (Fig. 3). At high magnification, the vacuoles appear to contain granular material, which on electron microscopy represent membranous whorls (1–5,7,8,12). Filamentous inclusions in the cytoplasm or myonuclei, prominent in the vicinity of the rimmed vacuoles, are pathognomonic of IBM. The vacuolated muscle fibers contain strong ubiquitin immunoreactivity localized to the cytoplasmic tubulofilaments (28). These vacuoles also contain Congored- or crystal violet-positive amyloid deposits (29) that immunoreact with β-amyloid protein, the type of amyloid that has been sequenced from the amyloid fibrils of blood vessels of patients with Alzheimer disease (30). The significance of amyloid deposits in the degenerating of phagocytic vacuoles of IBM, is at the present, uncertain.

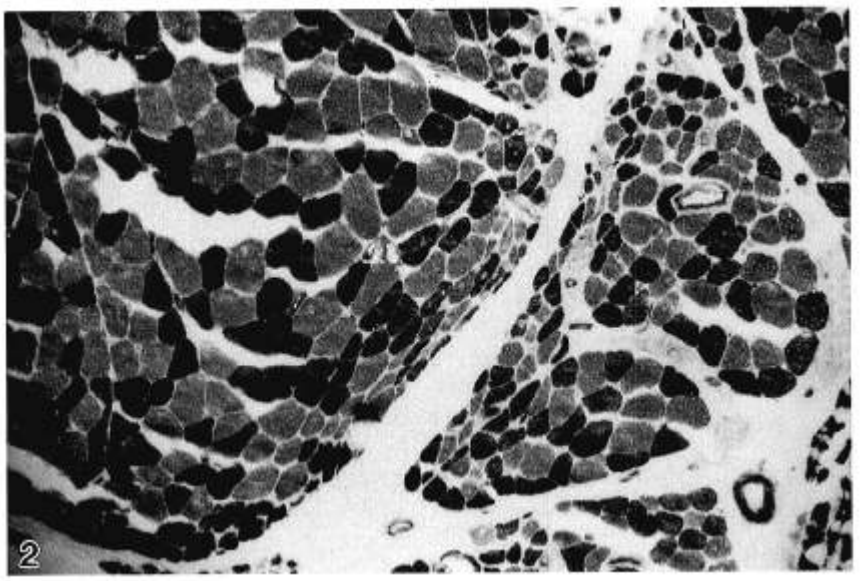

FIG. 2. Transverse frozen section of muscle biopsy specimen from a patient with adult dermatomyositis shows typical perifasicular atrophy (ATPase, ×160).

Although the characteristic clinicopathological features of DM and IBM allow their diagnosis even in the absence of endomysial inflammation, in PM the presence of a primary intramuscular inflammatory response is an invariable feature of the disease and the absence of inflammation should raise a critical concern about the diagnosis. For those patients who have an acquired myopathy that fulfills the clinical criteria for PM, as described earlier, but the muscle biopsy shows a noninflammatory myopathy, the term *probable* PM is preferable (1). A repeat muscle biopsy from another site may be more informative in these patients and we recommended it (1). Accordingly, as shown in Table 2, the diagnosis of PM is *definite* when a patient has an acquired, subacute myopathy fulfilling the exclusion criteria noted above, elevated CK, and a muscle biopsy with the histologic features of PM. The diagnosis is tentative (*probable* PM) if the myopathy and elevated CK are associated with a muscle biopsy showing nonspecific myopathic features without primary inflammation. The diagnosis of DM is *definite* because of the characteristic rash even if inflammation is not present in the muscle biopsy. Cases of DM may be *mild* or *early* when a patient has the typical rash but seemingly normal strength, easy fatigue, and occasionally elevated CK. The diagnosis of IBM is *definite* when the characteristic histologic features are present in the muscle biopsy of a patient who has the appropriate clinical picture (Table 3).

PATHOGENESIS

Immunopathologic Findings

In DM, the endomysial infiltrates have a higher percentage of B cells, a higher ratio of CD4 (helper cells) to CD8 (suppressor–cytotoxic T cells), close proximity

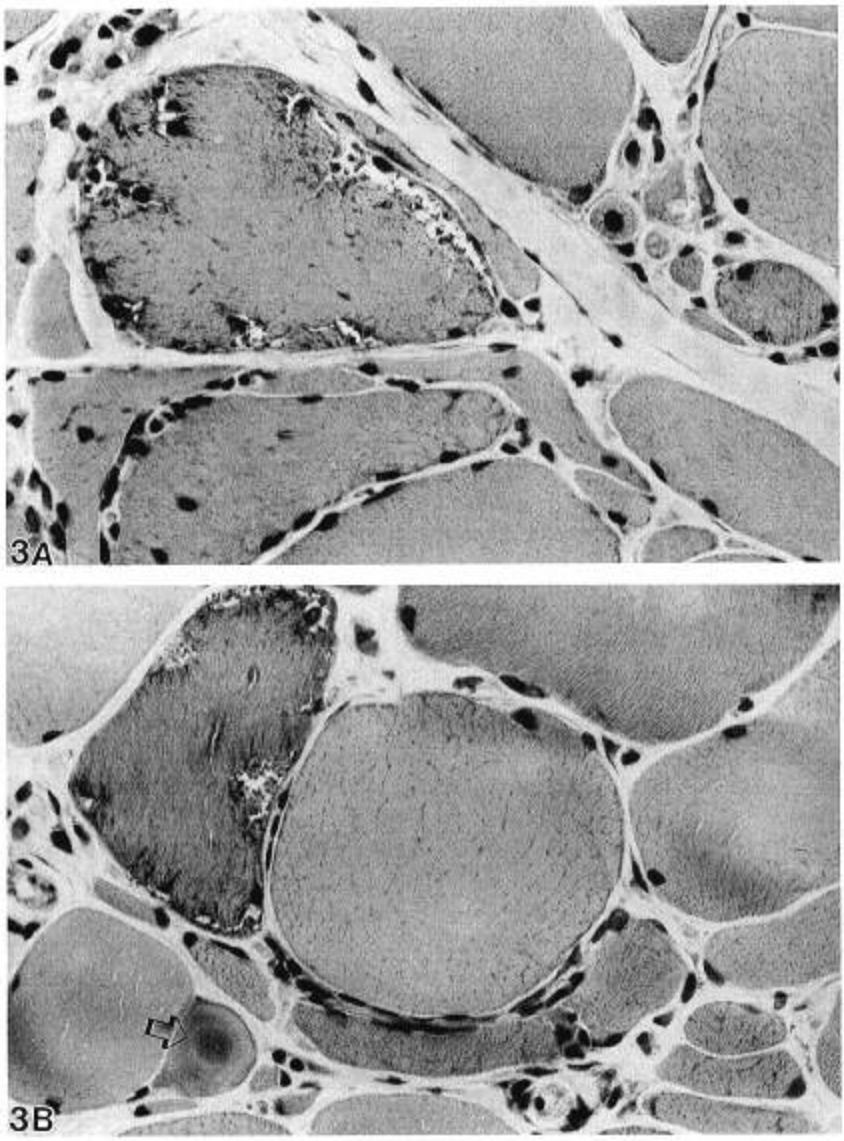

FIG. 3. Transverse frozen sections of a muscle biopsy from a patient with inclusion-body myositis shows the typical rimmed vacuoles. Small fibers in groups and one eosinophilic inclusion (arrow, **B**) are also noted.

of $CD4^+$ cells to B cells and macrophages, and a relative absence of lymphocytic invasion of nonnecrotic muscle fibers, all of which suggest a mechanism primarily mediated by humoral processes (1–3,5,8,31). This immune process is directed against the intramuscular microvasculature and is mediated by the complement C5b-9 membranolytic attack complex (MAC), implying activation of the complement pathway by antibodies bound to microvascular components (1,31–33). On the basis of double immunolocalization of the capillaries, using the lectin *Ulex*

TABLE 2. *Diagnostic criteria for inflammatory myopathies**

Criteria	Polymyositis		Dermatomyositis		Inclusion body myositis, definite
	Definite	Probable[a]	Definite	Mild or early	
Muscle strength	Myopathic muscle weakness[b]	Myopathic muscle weakness[b]	Myopathic muscle weakness[b]	Seemingly normal strength[c]	Myopathic muscle weakness with early involvement of distal muscles[b]
EMG[d]	Myopathic	Myopathic	Myopathic	Myopathic or nonspecific	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy[d]	Diagnostic for inflammatory myopathy of the PM type	Nonspecific myopathy without signs of primary inflammation	Diagnostic for DM	Nonspecific or diagnostic for DM	Diagnostic for IBM
Rash or calcinosis	Absent	Absent	Present	Present	Absent

* Adapted from (1).

[a] An adequate trial of prednisone or other immunosuppressive drugs is warranted in *probable* cases. If, in retrospect, the disease is unresponsive to therapy, repeat muscle biopsy should be considered to exclude other diseases or possible evolution to IBM.

[b] Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, or no biochemical muscle disease (excluded by muscle biopsy).

[c] Although strength is seemingly normal, patients often have new onset of easy fatigue, myalgia, and reduced endurance. Careful muscle testing may reveal mild muscle weakness.

[d] See the text for details.

europaeus as a specific endothelial marker and antibodies to complement C5b-9 MAC, the deposit of complement on the capillaries is the earliest and most specific lesion in DM and precedes inflammation or structural changes in the muscle fibers (1,31–33). This is followed by necrosis and marked reduction in the number of capillaries per each muscle fiber, as shown in Fig. 4, resulting in ischemia, muscle fiber destruction often resembling microinfarcts, and inflammation. Larger intramuscular blood vessels also may be affected in the same pattern, leading to actual infarcts. Residual perifascicular atrophy (Fig. 2) reflects the endofascicular hypoperfusion prominent distally.

In PM and IBM, there is evidence not of microangiopathy and muscle ischemia, as in DM, but of an antigen-directed cytotoxicity mediated by cytotoxic T cells (1,31,34–37). This conclusion is supported by the presence of $CD8^+$ cells, which along with macrophages initially surround healthy, nonnecrotic muscle fibers and eventually invade and destroy them. The muscle fibers, either next to or remote from the areas of inflammation, strongly express the class I major histocompatibility complex (MHC-I) antigen, which is absent from the sarcolemma of normal muscle fibers (35). Because cytotoxic T cells recognize antigenic targets in association with MHC-I antigen, these findings indicate that in PM and IBM the primary immunopathologic mechanism is mediated by cytotoxic T cells and is restricted to MHC-I antigen. The target antigen in the sarcolemma recognized by T cells, however, is still unknown. In vivo kinetics of indium-labeled autologous

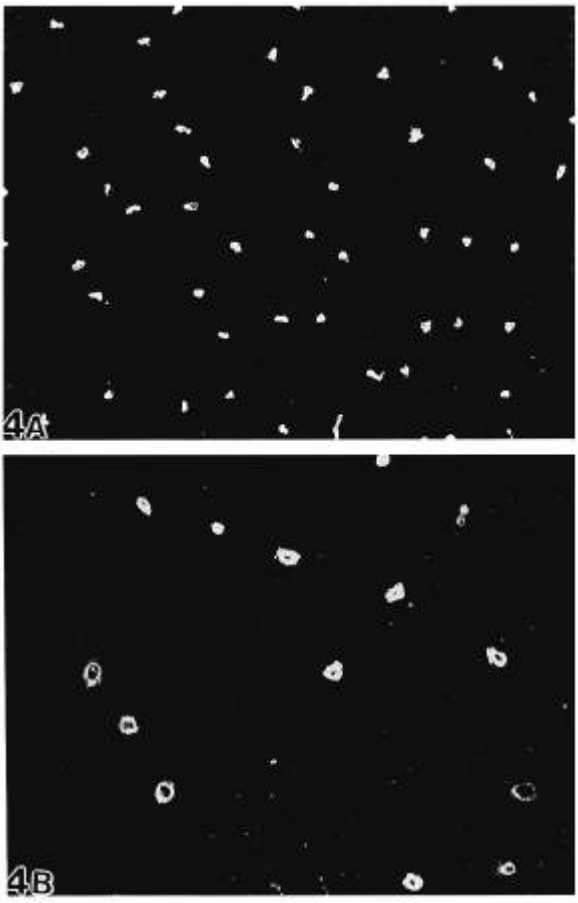

FIG. 4. Transverse frozen section of muscle biopsies from a patient with dystrophy (A) and dermatomyositis (B); note the marked reduction in the number of capillaries in the dermatomyositis patient. There is also an associated dilation of the remaining capillaries in an effort to compensate for the ischemia related to the loss or obstruction of the distal capillaries. (×220).

lymphocytes in PM patients shows increased uptake in the major muscle groups when compared with controls or with other nonmuscle tissues such as liver, lung, or spleen (6). The lymphocyte trafficking in the muscle is also proportional to the degree of inflammation in the concurrently done muscle biopsies (1,6). These in vivo data are consistent with previous in vitro studies and support the view that circulating sensitized lymphocytes are directed abnormally and specifically to muscle, in proportion to disease activity.

Role of Autoantibodies

Various autoantibodies against *nuclear* and *cytoplasmic* antigens are found in up to 20% of patients with inflammatory myopathies (26,38–41). The antibodies against nuclear antigens include those against ribonucleoproteins, anti-Ro/SS-A, anti-Sm, or anti-La/SS-B, which are not myositis specific as they are more closely associated with the group of mixed connective tissue syndromes.

The antibodies to cytoplasmic antigens are directed against cytoplasmic ribonucleoproteins that are involved in translation and protein synthesis. They include

antibodies against various *synthetases, translation factors,* and proteins of the *signal-recognition particles*. The most common are the antisynthetases, which are directed at the aminoacyl transfer RNA synthetase, a group of cytoplasmic enzymes that catalyze the attachment of a particular amino acid (histidine, alanine, threonine, isoleucine, or glycine) to its cognate transfer RNA (1,38–41). The antibody directed against the histidyl transfer RNA synthetase, called *anti-Jo-1,* accounts for 75% of all antisynthetases. At least 50% of PM or DM patients with *anti-Jo-1* antibodies also have interstitial lung disease and often Raynaud's phenomenon or arthritis. Because some of these antibodies can inhibit the translation of messenger RNA or the transport of polypeptides across the endoplasmic reticulum, it has been suggested that they might be directed at antigens involved in protein synthesis (6,38–40). Contrary to previous contentions, however (6,14), these antibodies are also non-muscle specific because they are directed against ubiquitous targets and most likely represent epiphenomena of no pathogenic significance. Because they are almost always associated with interstitial lung disease and occur even in the absence of myositis, they are as likely to be specific markers for the interstitial lung disease as for the myopathy. At present, their only value is their tendency to define serologically a small subset, up to 8%, of patients with PM or DM who also have interstitial lung disease.

Role of Viruses

Picornaviruses have been proposed as possible triggering agents for some patients with either PM or DM, because of their structural association with the Jo-1 antigen. Jo-1, a histidyl transfer RNA synthetase, is an enzyme that joins histidine to its cognate transfer RNA in the early stages of protein synthesis. This enzyme can interact with, and join, histidine not only with its native histidyl transfer RNA but also with the genomic RNA of an animal picornavirus, the encephalomyocarditis virus, whose tertiary structure has regions of homology with the histidyl transfer RNA synthetase of *Escherichia coli* and muscle proteins (1,39–41). A theoretical interaction between this virus and the synthetase may result in a stable complex (such as that formed between the synthetase and its native transfer RNA substrate) that may be presented to the immune system as foreign, generating an autoimmune response. Alternatively, antibodies generated against a related picornavirus that a patient may be infected with could theoretically cross-react with the histidyl transfer RNA synthetase (Jo-1) and also with muscle proteins in a phenomenon of molecular mimicry. Although there are no experimental data to support the theory that these reactions may result in myositis or that these autoantibodies are against muscle-specific antigens triggered by specific viruses, picornaviruses have been sought extensively in the muscles of both PM and DM patients. In spite of reports that Coxsackievirus or related enteroviral RNA have been found within the muscle fibers of PM and DM patients (42,43), our very sensitive technique using the polymerase chain reaction has not confirmed these reports (44,44a). The presence of mumps viral particles and antigens in the muscle biopsies of patients with IBM (45) also could not be confirmed by us and others (44a,46).

Retroviruses are the most promising viral candidates in the cause of PM because they can trigger an inflammatory myopathy in both humans and primates. The retroviruses known to have an association with polymyositis are given below.

The Human Immunodeficiency Virus Type 1 (HIV-1)

In HIV-positive patients, an inflammatory myopathy (HIV-PM) can occur either as an isolated clinical phenomenon, being the first clinical indication of HIV infection, or concurrently with other manifestations of AIDS (47,48). HIV seroconversion can also coincide with myoglobulinuria and acute myalgia, suggesting that myotropism for HIV may be symptomatic early in the infection. Studies using in situ hybridization, polymerase chain reaction, immunocytochemistry, and electron microscopy failed to demonstrate viral antigens within the muscle fibers but only within occasional interstitial mononuclear cells in proximity to the muscle fibers (49). Human myotubes in culture are also resistant to infection with intact HIV and to transfection with a naked HIV proviral DNA construct, indicating that in HIV-PM there is no evidence of persistent infection of the muscle fiber with the virus and that viral replication does not take place within the human muscle (50,51). In the muscle biopsy specimens of HIV-PM, the predominant cells are $CD8^+$ cells and macrophages that invade or surround MHC-I-antigen-expressing nonnecrotic muscle fibers (49) in a pattern analogous to that seen in polymyositis, as described above. This, along with a relative paucity of $CD4^+$ cells, suggests that the development of HIV-PM is independent of the $CD4^+$ cell, and that a T-cell-mediated and MHC-I-restricted cytotoxic process is a common pathogenetic mechanism in both PM and HIV-PM.

These observations indicate that a systemic viral infection such as HIV can trigger the immunopathologic mechanism that leads to the development of PM even in the absence of the virus from the muscle fiber. The various cytokines or toxic lymphokines released by the HIV-infected endomysial inflammatory cells may contribute to this process by exposing new muscle antigens against which there is no self-tolerance, generating a secondary autoimmune response. The resulting endomysial inflammation may subsequently become self-sustaining if it cannot be downregulated by the host. Alternatively, activated T cells resulting from the persistent systemic viral infection might have recognized putative sarcolemmal autoantigens within the muscle, leading to phagocytosis and muscle fiber necrosis.

The Human T-Cell Lymphotrophic Virus (HTLV-1)

HTLV-1 does not only cause a myeloneuropathy—referred to as tropical spastic paraparesis (TSP)—but also PM, which may coexist with TSP or may be the only clinical manifestation of HTLV-1 infection (52,53). A T-cell-mediated and MHC-I-restricted cytotoxic process triggered by the virus appears also to be the main mechanism of HTLV-PM (54).

Human Foamy Retrovirus (HFR)

Transgenic mice for HFR develop inflammatory myopathy with the HFR genome detectable in the muscle (55).

The Simian Retrovirus Type I (SRV-1) and the Simian Immunodeficiency Virus (SIV)

These viruses can cause immunodeficiency, Kaposi's sarcoma, and PM in infected monkeys (56,57).

The association of PM with five different retroviruses resulting in disease identical to seronegative PM, without the presence of viral antigens within the muscle fibers, suggests that viruses can trigger the development of an inflammatory myopathy without necessarily causing a lytic, transient or persistent, viral infection of the muscle.

TREATMENT

The evidence described above that immunopathologic mechanisms are primarily involved in PM, DM, and IBM justifies the need for treating these diseases with immunosuppressive therapies. All of the treatment trials, however, have been *empirical* and large-scale control therapeutic studies against the immunologically specific forms of childhood DM, adult PM, or adult DM have not been conducted (1,58–60). As the specific target antigens are also unknown, these therapies are not selectively targeting the autoreactive T cells or the complement-mediated process on the intramuscular blood vessels but instead they are inducing a nonselective immunosuppression or immunomodulation.

The goal of therapy in PM, DM, and IBM is to improve the function in activities of daily living as the result of improvement in muscle strength. Although when the strength improves the serum CK falls concurrently, the reverse is not always true because most of the immunosuppressive therapies can result in a decrease in serum muscle enzymes without necessarily improving muscle strength. Unfortunately, this has been misinterpreted as "chemical improvement," and has formed the basis for the common habit of "chasing" or "treating" the CK level instead of muscle weakness, a practice that has lead to a prolonged use of unnecessary immunosuppressive drugs and erroneous assessment of their efficacy. The prudence of discontinuing these drugs if, after an adequate trial, they have only led to a reduction in CK and not to objective improvement in muscle strength has been repeatedly stressed (1,58–60). The following therapies are commonly applied to treat PM, DM, or IBM.

Corticosteroids

Prednisone is the first-line drug of *empirical* treatment. Because the effectiveness and relative safety of prednisone therapy will determine the future need for stronger immunosuppressive drugs, I prefer an aggressive approach of high-dose prednisone from early in the disease (1,58–60). A high dose of 80–100 mg/day as a *single* daily morning dose for an initial period of 3–4 weeks is preferable. Pred-

nisone is then tapered over a 10 week period to 80–100 mg *daily on alternate days* by gradually reducing an alternate "off-day" dose by 10 mg/week, or faster if necessitated by side effects, though this carries a greater risk of breakthrough of disease. If there is evidence of efficacy, and no serious side effects, the dosage is reduced gradually by 5–10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. *In a patient responding to prednisone,* a "maintenance" dose of 10–25 mg every other day may be needed to secure continuous improvement or stability. On the other hand, if by the time the dosage has been reduced to 80–100 mg every other day (approximately 14 weeks after initiating therapy) there is no objective benefit (defined as increased muscle strength and not as lowering of the CK or a subjective feeling of increased energy), the patient may be considered unresponsive to prednisone and tapering is accelerated while the next–line immunosuppressive drug is started.

The single-dose, alternate-day program minimizes side effects (cushingoid appearance, diabetes, obesity, high blood pressure, osteoporosis, avascular necrosis of the hip, and retarded growth in children) while adequately controlling the underlying disease. I do not start therapy with a high single-dose, alternate-day program, as some recommend (61), without a preceding high daily dose schedule, because empirically the response may be inadequate. Furthermore, based on the mechanism of action of steroids on lymphocyte function and induction of immunosuppression, it is more difficult to induce a remission with a single-dose, alternate-day program, but it is easy to maintain it once it has been achieved with high single daily dosage (60). Moreover, dose spacing of the prednisone (alternate-day regimen) results in lower plasma concentrations of prednisolone (the active component of prednisone), resulting in less benefits, although less unwanted side effects, presumably by decreasing the total exposure of tissues to prednisolone. I also prefer to give the prednisone as a single dose in the morning because the higher morning natural cortisol concentration results in a competitive decrease in the metabolism of the administered prednisolone, resulting in a decreased clearance of the unbound (active) prednisolone and, theoretically, a greater beneficial effect.

Collateral Program

Every patient is requested from the beginning of steroid therapy to start a strict diet of low-carbohydrate, low-salt, high-protein intake. Self-discipline to avoid gaining weight is also emphasized, and the patient's compliance is monitored by checking body weight during each visit. This dietetic regimen decreases the chance for developing hypertension, especially in predisposed individuals. Bananas, often suggested to compensate for the possible loss of potassium induced by corticosteroids, are discouraged because their high caloric content can enhance weight gain. We instead prescribe 40–60 mEq/day of potassium in divided doses as either tablets or oral liquid form. To diminish or prevent possible gastrointestinal discomfort, the patients are given antacids between meals. Because antacids containing magnesium hydroxides, such as Maalox or milk of magnesia, can loosen stools, we often use a combination or alternation with another that can

constipate, such as Amphojel, which contains aluminum hydroxide (58–60,62). In patients with a tendency for high blood pressure, a product containing magaldrate (Riopan), which is very low in sodium, is suggested. Mylanta, which is low in sodium and contains a combination of aluminum hydroxide and magnesium hydroxide, is often preferable. Because prolonged use of aluminum hydroxide antacids can rarely cause muscle weakness, alternation with a calcium-containing antacid, such as Tums, may be employed. Coadministration of vitamin D may be considered, especially in female patients, when long-term therapy is required. Histamine H_2-receptor antagonists such as Cimetidine, 300 mg three times a day, or ranidine, 150 mg at bedtime, are other alternatives, especially for individuals with gastrointestinal discomfort. Although their superiority to antacids in preventing gastric complaints has not been established, they have been very well tolerated and the rate of compliance is superior to that for antacids. The patients are reassured that if "flushing" or redness in the face, insomnia, and mild action tremor of the hands develop, they will disappear with lowering the steroid dosage and that these symptoms should not be of concern. Routine use of isoniazid (INH) prophylaxis is not used except in immunosuppressed patients, those at high risk of exposure to tuberculosis, patients with a recently documented positive purified protein derivative (PPD) test, or those with a previous history of tuberculosis. If INH is used, pyridoxine, 100 mg/day, is administered concurrently to prevent INH neuropathy.

Steroid Myopathy vs. Disease Activity

The long-term use of prednisone may cause mild worsening of proximal muscle strength associated with a normal or unchanged CK level, which is referred to as "steroid myopathy." The term steroid myopathy, however, is a misnomer because steroids do not cause histological signs of myopathy but rather selective atrophy of type II muscle fibers. It may be difficult to distinguish between steroid-induced myopathic weakness and increased weakness related to disease activity because the two can coexist, or the increased weakness has become steroid resistant or it may be caused by other factors, such as decreased mobility, infection, or an associated systemic illness. The decision to adjust the prednisone dosage *in a patient who has previously responded* to treatment may be influenced by reviewing the past 1 to 2 months' history of the muscle strength, mobility, serum CK, medication changes, and associated medical conditions. For example, if in the past 2 months (a) the level of steroid dosage has been unchanged or increased; (b) the CK level during the same period has been more or less stable; (c) new or increasing signs of steroid intoxication such as increased body weight, hypertension, striae, and cushingoid features have developed; and (d) the patient's physical mobility is reduced, the most likely cause of increasing muscle weakness is *steroid myopathy* (atrophy of the type II muscle fibers). One the other hand, in a patient who for the past 1 to 2 months has increased CK levels, no new overt signs of steroid toxicity with reduced or unchanged dosage of steroids, and no evidence of a systemic illness or infection, an increasing muscle weakness is most likely due to exacerbation of the disease, that either will require more prednisone or it has

become resistant to steroids. When all of these signs are not clear, we arbitrarily lower or raise the prednisone dosage, waiting for the answer, which may be evident in about 2 to 8 weeks, according to the change in the patient's strength. This approach may be helpful to distinguish a steroid-myopathy from an active disease that is still responding to steroids, but it may not clarify if the new weakness has become steroid-resistant. A new muscle biopsy may not reveal the cause of increased weakness because active inflammatory disease can be present even when steroid intoxication was the cause of increasing weakness, as shown in Fig. 5A. Conversely, type II muscle fiber atrophy, the histological corellate of steroid myopathy, can coexist with active inflammation—even in a patient who has never received steroids—owing to disuse and immobilization of a limb from contractures, pain, or weakness (Fig. 5B). Electromyography is also of limited value because it is not informative in type II muscle fiber atrophy. However, it may occasionally be of some help if it shows fibrillations and positive sharp waves in many sites of proximal muscle groups, indicative of active myopathic disease. A clinical sign that I have found to be of some help in a few patients is the strength of neck flexor muscles, which usually worsens with exacerbation of the disease but remains unchanged with steroid-induced muscle intoxication.

Side Effects of Corticosteroids

The most common side effects seen in patients with PM or DM treated for long periods with corticosteroids are (a) abnormality of fat distribution with generalized obesity—hence, the need for strict caloric restriction; (b) lipolytic action resulting in hyperlipidemia, which can rarely cause fat emboli in the femoral head and aseptic necrosis of the hip; epidural lipomatosis resulting in spinal cord compression is rare but should be suspected if a patient on long-term steroid therapy is developing back pain and signs of myelopathy; (c) diabetes—hence, the reason for low-carbohydrate diet; (d) retarded growth in children with DM, which can be minimized with the alternate-day program; (e) menstrual irregularities; (f) edema and hypertension—hence, the need for a low-salt diet from the beginning of therapy; (g) osteoporosis especially in woman—hence, the suggestion of coadministering vitamin D or calcium supplements in women receiving long-term steroid therapy; (h) gastrointestinal complications, although not as common as believed, can be helped with antacids or histamine blockers, as described above; in children with DM, who may have early signs of intestinal perforation related to vasculitis, steroids may potentially trigger gastrointestinal bleeding; (i) skin changes, including acne, ecchymosis, facial hirsutism, and striae; (j) posterior subcapsular cataracts and, rarely, glaucoma, hence the need for frequent eye examinations; and (k) central nervous system complications such as insomnia, irritability, and exacerbation of the physiologic action tremor in the hands, which are commonly seen with the high daily dose and always subside when the dose is reduced. Behavioral changes, such as psychosis and depression, have not been frequent in our group of patients with PM or DM.

Among the interaction of prednisone with other drugs, it is worth remembering that anticonvulsants such as phenobarbital, carbamazepine, and phenytoin, which

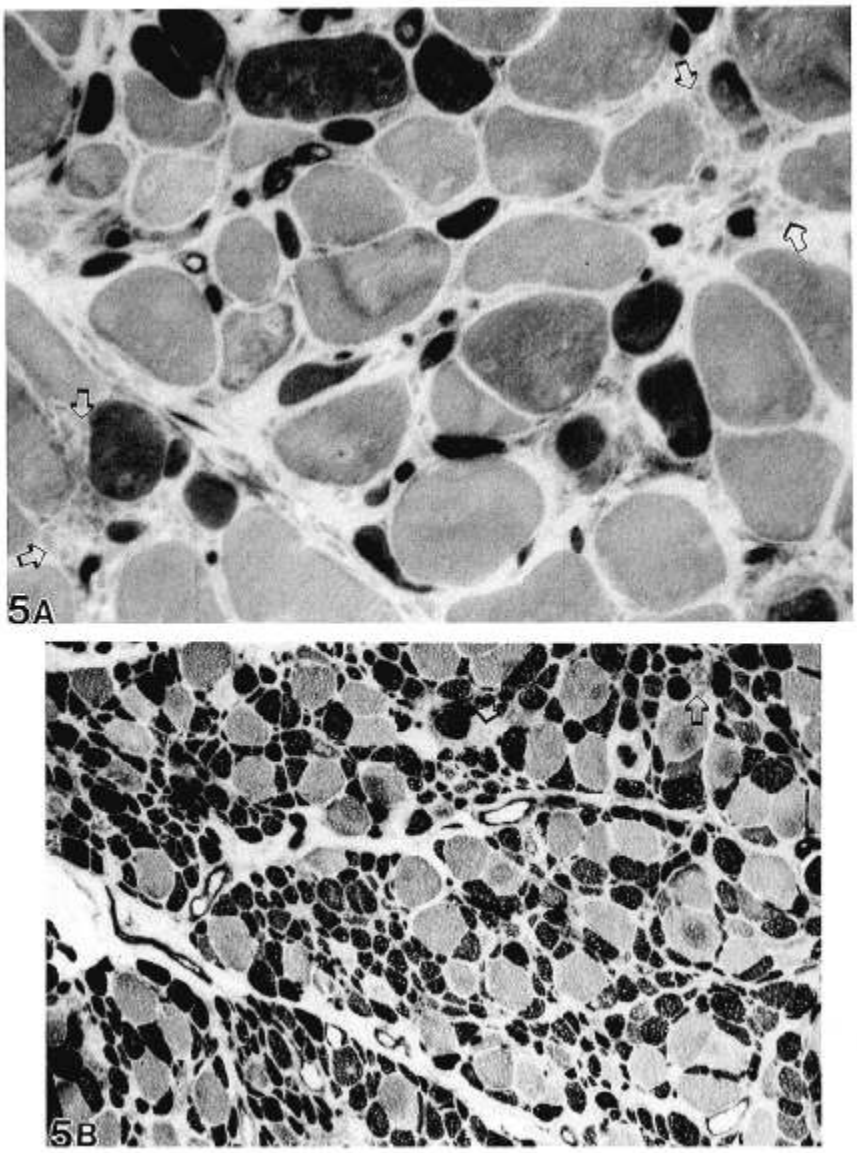

FIG. 5. Transverse frozen section of a muscle biopsy from a patient with polymyositis and steroid myopathy stained with ATPase, pH 9.4. **A:** Atrophy of type II (dark) muscle fibers coexists with inflammatory infiltrates (arrows) that are unstained with this stain (×300). **B:** Transverse frozen section of a muscle biopsy sample from a quadriplegic patient with severe, acute polymyositis of 6 weeks' duration stained with ATPase, pH 9.4 (×125). Marked, selective type II muscle fiber atrophy is noted. Although there are no visible signs of inflammation with this stain at this magnification, many areas of the muscle biopsy had marked inflammatory infiltrates, some of which are delineated by the arrows.

are inducers of the hepatic microsomal enzyme system, may alter the extent of prednisolone metabolism, accelerating the elimination of prednisone and methylprednisolone (60). Somewhat higher than anticipated steroid doses may therefore be required in such patients to achieve therapeutic response.

"Prednisone Failures" and Nonsteroidal Immunosuppressive Therapies

Although it is my view that almost all of the patients with *bonaefide* PM or DM respond to steroids to *some degree* and *for some period of time,* a number of them fail to respond or become steroid resistant. The decision to start an immunosuppressive drug in PM or DM patients is based on the folowing factors: (a) need for its "steroid-sparing" effect, when in spite of steroid responsiveness the patient has developed significant complications; (b) attempts to lower a high steroid dosage have repeatedly resulted in a new relapse; (c) an adequate dose of prednisone for at least a 2–3 month period has been ineffective; and (d) rapidly progressive disease with evolving severe weakness and respiratory failure (1,58–60). The preference for selecting the nextline immunosuppressive therapy, however, is empirical based on personal experience with each drug and its relative efficacy/safety ratio. Such therapies used in the treatment of patients with PM, DM, or IBM are as follows:

Azathioprine, a derivative of 6-mercaptopurine, is given orally. Although lower doses (1.5–2 mg/kg) are commonly used, for effective immunosuppression we prefer higher doses up to 3 mg/kg. This drug is my first preference because compared to the others it is well tolerated, has fewer side effects, and, empirically, it appears to be as effective as the other drugs whose value in PM and DM has also not been established. Because azathioprine is usually effective after 3–6 months of treatment, patience is required before its ineffectiveness is prematurely concluded. The major toxicity of the drug includes thrombocytopenia, anemia, leukopenia, pancytopenia, drug fever, nausea, and, rarely, liver toxicity. An elevation of liver enzymes, if slight, only needs observation. Most of the time, elevation of liver enzymes in these patients is related to a "fatty liver" from the long-term steroid use rather than from the use of azathioprine. Azathioprine, which is metabolized by xanthine oxidase, if given concurrently with allopurinol, can be severely toxic to the liver or bone marrow and their combined use in not recommended.

Methotrexate, an antagonist of folate metabolism, is a drug heavily favored by rheumatologists, in spite of its disappointing efficacy in PM or DM. In our experience, methotrexate has been either ineffective or has shown only marginal and mostly subjective benefit at a cost of considerable toxicity to the patients. It can be given intravenously over 20–60 min at weekly doses of 0.4 up to 0.8 mg/kg, or orally starting at 7.5 mg *weekly* for the first 3 weeks (given in a *total* of three doses, 2.5 mg every 12 h), increasing gradually by 2.5 mg/week up to a total of 25 mg weekly. A relevant side effect is *methotrexate pneumonitis,* which can be difficult to distinguish from the interstitial lung disease related to the primary disease and it is often associated with Jo-1 antibodies, as described above. Other side effects include stomatitis, gastrointestinal symptoms, leukopenia, and hepatotoxicity.

Cyclophosphamide, an alkylating agent, given intravenously or orally (2.0–2.5 mg/kg, usually 50 mg p.o. three times/day) has been ineffective in our hands (63) in spite of occasional promising results reported by others (64). The drug may be helpful in a subset of patients who also have interstitial lung disease (1). It is our belief that the risk/benefit ratio of this drug only rarely justifies its use. Side effects

include nausea, vomiting, alopecia, hemorrhagic cystitis, pulmonary fibrosis, bone marrow suppression, secondary malignancies, or sterility. Monitoring of the complete blood count with care to maintain the white blood cell count above 3,500/mm^3 with adequate neutrophil count (no less than 1,500–2,000/mm^3) and the lymphocyte count above 1,000/mm^3 are essential.

Cyclosporine has been used with limited success. Although the toxicity of the drug can now be monitored by measuring optimal trough serum levels (which vary between 100 and 250 ng/ml), its effectiveness is uncertain. A report that low doses of cyclosporine could be of benefit in children with DM needs confirmation (65). Based on the patients referred to us, the drug has been disappointing. The results from the double study of cyclosporine in this dosage are still being expected.

Plasmapheresis is not helpful. In the first double-blind, placebo-controlled study that has been conducted in PM and DM patients, plasmapheresis was ineffective (66).

Total lymphoid irradiation is an extreme remedy that can be considered for extreme situation. It has been helpful in two of our patients and had long-lasting benefit (67). The long-term side effects of this treatment, however, should be seriously considered before deciding on this experimental approach. Total lymphoid irradiation has been ineffective in IBM (1,68).

Intravenous immunoglobulin (IVIg) taken from human serum pools, is a new promising, but very expensive, therapy. In a small uncontrolled study, IVIg has been effective (69,70). A controlled double-blind study of IVIg at doses of 2 g/kg/month is underway at our institution (M. C. Dalakas, principal investigator).

Until further controlled drug trials are completed, I recommend based on our present experience and the relative risk/benefit ratio the following step-by-step empirical approach of the treatment of PM, DM, or IBM: *step 1:* high-dose prednisone; *step 2:* if the need for a "steroid-sparing" effect arises, try azathioprine; *step 3:* if step 2 fails, try high-dose intravenous immunoglobulin; and *step 4:* if step 3 fails, consider a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and the patient's general health: methotrexate, cyclosporin, cyclophosphamide (which could be considered earlier if the patient has interstitial lung disease), or total-body or lymph-node irradiation.

PRACTICAL THERAPEUTIC CONSIDERATIONS

Based on the information described above regarding the efficacy of these therapies and our experience with more than 300 patients referred to us, the following observations and practical tips may be useful:

(a) Patients with bonafide PM and DM should almost always respond to prednisone to a *certain degree* and for *some period of time*.

(b) Patients with DM, as a group, respond better than patients with PM.

(c) A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or another disease. In these cases, a repeat muscle biopsy and a more vigorous search for the *other* disease are recommended.

(d) *Calcinosis,* a manifestation of DM, does not resolve with immunotherapies,

but new calcium deposits may be prevented if the primary disease responds to the available therapies. Diphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, and surgical incision have all been tried without success.

(e) A patient who has not responded to an adequate dose and duration of prednisone will, most likely, respond only marginally to other conventional immunotherapies. Such therapies, however, should be tried for a reasonable period. On the other hand, a patient who has responded to steroids could benefit from the administration of further immunosuppresive therapy.

(f) If prednisone or other immunosuppressive therapies have not helped, or have become ineffective in improving the patient's strength, they should be discontinued to avoid severe irreversible side effects for, contrary to common belief, their continuation does not "maintain stability" or prevent further disease progression.

(g) High-dose IVIg is emerging as a new, promising, and safe drug for the treatment of patients with bonafide PM or DM that have become resistant to therapies.

(h) Patients with an acute, fulminant course associated with rhabdomyolysis especially after viral infections, may not respond to immunotherapies. Such therapies, however, should be aggressively tried before this conclusion is reached.

(i) IBM is generally resistant to all therapies. Some cases of probable PM, often referred to us as "definite" PM, may also be resistant to all therapies, as found retrospectively. Whether such patients have an unidentified dystrophic process is unknown.

(j) Patients with interstitial lung disease may have a high mortality, requiring aggressive treatment with cyclophosphamide.

(k) Physical therapy to preserve existing muscle function and avoid disuse atrophy of the weak muscles or joint contractures should start early in the disease.

(l) When the treatment of PM is unsuccessful, the patient should be re-evaluated and the muscle biopsy re-examined. A new biopsy might be considered to make sure that the diagnosis is correct or the disease has not evolved into IBM. Although it may be difficult to distinguish histologically an early case of IBM from classic PM, it is my belief that IBM develops de novo and is not the evolution of a classic PM. Only a high degree of clinical suspicion, however, may allow its early diagnosis. The disorders most commonly mistaken for PM are: IBM, sporadic limb–girdle dystrophy, metabolic myopathy (e.g., phosphorylase deficiency), endocrinopathy, and neurogenic muscular atrophies.

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