Inflammatory Myopathies: Evaluation and Management

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ABSTRACT

The inflammatory myopathies, including dermatomyositis, inclusion body myositis, and polymyositis, are poorly understood autoimmune diseases affecting skeletal muscle. Dermatomyositis is a disease mainly of skin and muscle, but may affect lung and other tissues. Proximal or generalized weakness or skin rash are the typical presenting features. Inclusion body myositis has a specific clinical pattern of weakness that generally distinguishes it from other inflammatory myopathies, with prominent involvement of wrist and finger flexors, and quadriceps. Polymyositis generally presents with proximal or generalized weakness. Typical dermatomyositis muscle pathology is quite distinct, with perivascular inflammatory cells that include plasmacytoid dendritic cells, and abnormal capillaries and perimysial perifascicular myofibers. Both inclusion body myositis and polymyositis usually have infiltration into muscle of large numbers of inflammatory cells, typically surrounding and displacing, and sometimes invading, myofibers. Inclusion body myositis is refractory to corticosteroids and to several immunomodulating therapies that have been used. Dermatomyositis and polymyositis are treated with corticosteroids and a variety of agents. Osteoporosis and opportunistic infections pose a significant risk during treatment of patients. This review discusses the clinical manifestations, pathology, and treatment approaches for the inflammatory myopathies.

KEYWORDS: Dermatomyositis, inclusion body myositis, inflammatory myopathy, necrotizing myopathy, polymyositis

The inflammatory myopathies are diseases in which muscle appears to be injured by the immune system. The principal subtypes are dermatomyositis (DM), inclusion body myositis (IBM), and polymyositis (PM), although many patients have syndromes that are not easily classified and may best be labeled as nonspecific (or unspecified) myositis. Other subtypes include necrotizing myopathy, overlap syndromes (inflammatory myopathy occurring in a patient with a connective tissue disorder such as mixed connective tissue disease), granulomatous myositis, and eosinophilic myositis. The mechanisms initiating and maintaining these diseases are not well understood.[1] This review focuses on current and evolving approaches to evaluation and management of these diseases.

CLINICAL PRESENTATION, LABORATORY EVALUATION, AND PATHOLOGICAL FINDINGS

General Principles

The diagnosis of inflammatory myopathy and the specific subtype is based on a combination of clinical

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presentation, laboratory studies, and pathological findings in muscle biopsy samples. In general, symptoms of muscle weakness (difficulty arising from a low chair, climbing up or down stairs, getting into a car, washing hair, brushing teeth, or, in IBM, gripping objects) or skin rash (in DM) are the presenting features. Patients presenting with prominent diffuse pain, often attributed to muscles, usually do not have an inflammatory myopathy. Certain physical examination findings, such as pronounced lumbar lordosis and waddling gait, facial weakness, and scapular winging should in general lead to considerations other than inflammatory myopathy.

Laboratory studies other than serum creatine kinase (CK) are of limited value to support or refute the diagnosis of inflammatory myopathy. The CK may be normal in active untreated DM. Serum liver function tests, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), may be elevated in inflammatory or other myopathies; these enzymes are present in muscle. Some patients with PM- or IBM-like clinical patterns of weakness may have associated human T-cell lymphotrophic virus type 1 or HIV infection, so laboratory testing for these may be considered. Laboratory demonstration of autoantibodies, including antinuclear antibodies, anti-histidyl transfer RNA (anti-Jo-1) antibodies, and anti-Mi-2 antibodies may be helpful. The presence of antinuclear antibodies should prompt consideration of an additional diagnosis of connective tissue disease, such as systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD). The presence of anti-Jo-1 antibodies, which are associated with DM and PM, should raise suspicion for interstitial lung disease and prompt evaluation with pulmonary function tests and chest computed tomography (CT), and avoidance of methotrexate therapy (discussed later). Chest CT is additionally useful for consideration of sarcoidosis, which may have a DM-like presentation, and as part of a malignancy evaluation for adults with DM (see below).

Electrodiagnostic studies are also of limited value, mainly in excluding nerve disease or in detecting neuromuscular junction disease that may have a myopathy-like presentation, such as Lambert-Eaton myasthenic syndrome, and some patients with myasthenia gravis or specific congenital myasthenic syndromes. Needle electromyography (EMG) studies in inflammatory myopathies may show fibrillation potentials, positive sharp waves, short-duration and small amplitude motor unit action potentials, and full interference patterns in weak muscles. They may support a diagnosis of myopathy and suggest that the myopathy may be associated with muscle membrane irritability, but they do not distinguish inflammatory myopathies from many other muscle diseases, such as some inherited or toxic myopathies. When performed, needle EMG studies should be confined to one side to allow biopsy of an untraumatized contralateral muscle.

Muscle biopsy and the pathological examination of the specimen obtained is an important diagnostic procedure for patients with suspected inflammatory myopathies. In general, a mild to moderately weak muscle, but not a severely weak muscle, should be chosen. Severely weak muscles may show only nonspecific pathological features of end-stage destruction that may be seen in a wide variety of muscle and nerve diseases. Good choices often are the biceps and vastus lateralis, but specific cases need to be considered individually.

Dermatomyositis

Dermatomyositis affects children and adults. Adult DM generally presents as subacute progressive painless proximal weakness, a skin rash, or both. Juvenile DM may present similarly or as an acute or subacute febrile illness followed by skin, muscle, or sometimes multisystem involvement.

The skin involvement in DM may have diverse manifestations, including a heliotrope rash (purplish discoloration) on the eyelids; an erythematosus rash on the face, neck, and anterior chest ("V-sign"), upper back ("shawl sign"), elbows, or knees; a purplish scaly papular rash on the extensor surface of the hands (Gottron's papules); thickened and cracked skin on the dorsal and ventral surfaces of the hands ("mechanic's hands"); and other changes. Subcutaneous calcinosis is a significant problem in juvenile DM and uncommon in adult DM. Cutaneous symptoms in DM have a high impact on lowering quality of life in patients and include prominent pruritus.[2,3]

The pattern of proximal limb weakness in DM is not distinctive and does not distinguish DM from many other myopathies. Significant muscle asymmetries or prominent distal (forearm or lower leg) weakness together with skin rash should prompt consideration for sarcoidosis, for which clinical involvement similar to DM has been recognized.[4] Normal serum CK may be present in patients with progressing disease and does not exclude the diagnosis. When elevated serum CK is present in DM, reductions generally occur with treatment and elevation with relapse.

Additional evaluation of adult patients with DM should be performed because of its association with two other important clinical syndromes: interstitial lung disease and malignancy. Pulmonary function tests, chest CT, and laboratory testing for the presence of anti-histidyl tRNA antibodies (anti-Jo-1 antibodies) should be considered in all patients with DM. Malignancy has been estimated to be associated with 6 to 45% of adult patients with DM, with age-associated increased risk particularly in women older than 40 years. A malignancy evaluation, including physical examination (skin examination, breast and pelvic examinations in women, and

testicular and prostate examinations in men), blood studies (complete blood count, liver function tests, lactate dehydrogenase, prostate-specific antigen), stool for occult blood, CT (chest, abdomen, and pelvis), and colonoscopy should be considered in every adult patient with a new diagnosis of DM.

Muscle biopsy is an important diagnostic procedure in DM. The clinical syndrome in patients with typical skin and muscle features is quite specific for DM, although some patients with sarcoidosis have been reported with similar clinical but distinct pathological features.[5–7] The most supportive diagnostic features of muscle biopsies for DM evident in routine clinical studies are the presence of perifascicular atrophy (Fig. 1) and the absence of multiple myofibers surrounded by inflammatory cells. Perifascicular atrophy refers to the presence of small myofibers that are slightly darker and bluish in color in hematoxylin and eosin sections, typically located at the edges of fascicles. A more accurate term for this is perimysial perifascicular atrophy, as the small fibers are generally only present at the boundaries of fascicles with perimysial regions, not boundaries that border on other fascicles (Fig. 1B). Perifascicular atrophy is only variably present, and the diagnosis is not always clear pathologically, even in patients with typical clinical syndromes. Perivascular accumulations of inflammatory cells may be present in DM (Fig. 1C) but may also be present in IBM and PM. Many of these cells are plasmacytoid dendritic cells, the immune system's professional producer of interferon-α.[8] Capillary abnormalities, when demonstrated by electron microscopy showing the presence of tubuloreticular inclusions in endothelial cells, or by histochemical methods not widely used, are also supportive of the diagnosis. Immunohistochemical studies show that perifascicular fibers and capillaries express interferon-α-inducible proteins.[1,8]

Inclusion Body Myositis

Inclusion body myositis affects adults in middle and later life. The name was first applied to a patient with

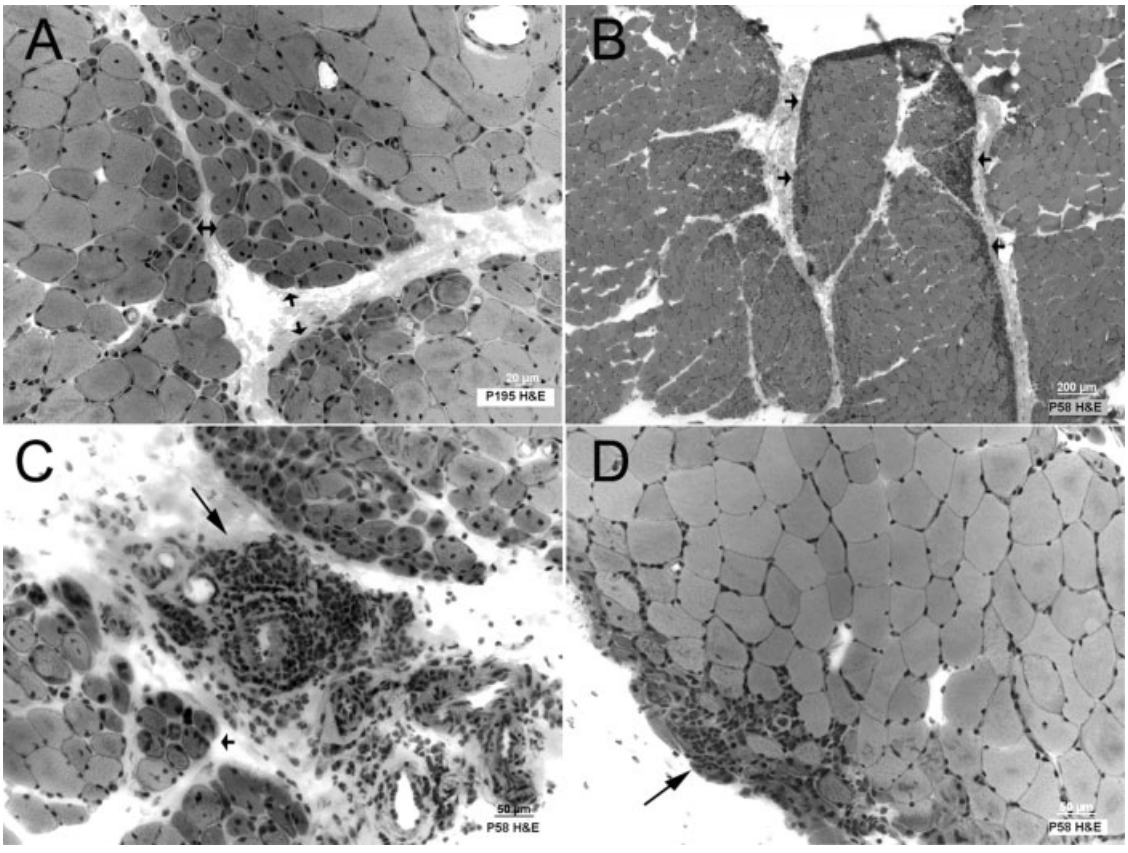

Figure 1 Perifascicular atrophy and perivascular inflammation in dermatomyositis (DM). (A) Perifascicular atrophy refers to small and darker (bluish color not visible on grayscale images) fibers in the portions of fascicles bordering perimysial boundaries (arrows). Smaller fascicles that are entirely surrounded by perimysial tissue may have small fibers throughout the entire fascicle, as is present in the fascicle in the center. (B) Perifascicular atrophy is more aptly called perimysial perifascicular atrophy, as portions of fascicles bordering perimysial regions (arrows) are much more affected than fibers that border other fascicles. (C) Perivascular inflammatory cells (large arrow) and nearby perifascicular atrophy (small arrow) are shown. (D) Inflammatory cells visible on hematoxylin and eosin (H&E) stains may extend into fascicles and surround myofibers (arrow) but only in the perimysial perifascicular regions.

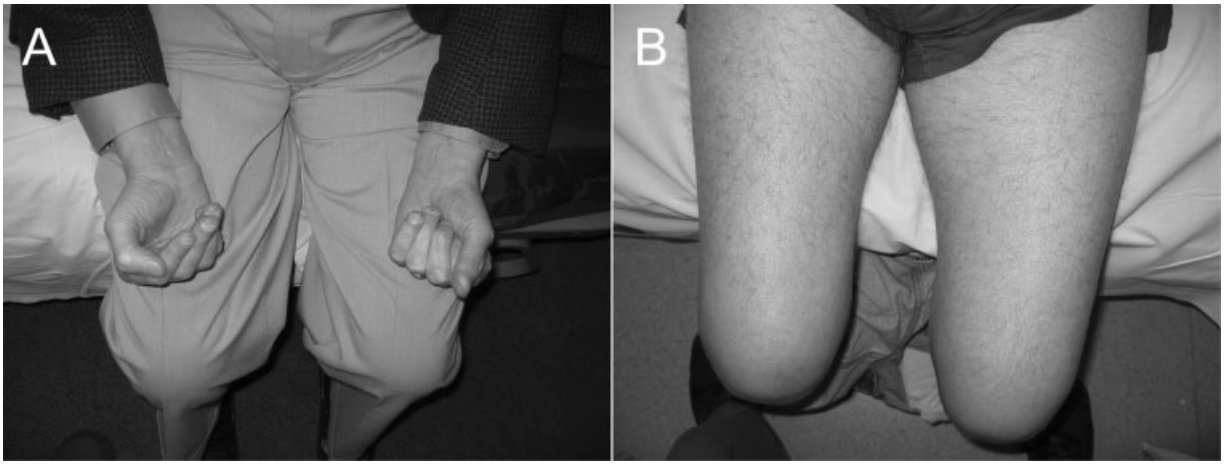

Figure 2 Finger flexor weakness and quadriceps atrophy in inclusion body myositis (IBM). (A) Patient is attempting to make a fist with both hands. Note asymmetric weakness—right is weaker than left—of finger flexors, particularly the deep finger flexors responsible for flexion at the distal interphalangeal joints. (B) Patient exhibits atrophy of left more than right medial thigh muscles.

symptom onset at age 18 years and findings at age 26 consisting of lordotic posture, leg limb-girdle weakness, and no atrophy or weakness of the quadriceps. This patient would not meet current criteria for the diagnosis of IBM.[9] Although onset over age 50 has been emphasized, symptom onset before age 50 is common (18 to 20% of patients).[10,11] Diagnosis has historically been frequently delayed by a mean of 5 to 8 years from symptom onset.[10,12–15]

The clinical presentation of IBM is quite distinct from that of other inflammatory myopathies. Atrophy and weakness of wrist and finger flexors and quadriceps are distinctive, and physical examination should focus on careful testing of these muscle groups. Comparison of wrist and finger extensors with corresponding flexors may demonstrate the greater involvement of the flexors and asymmetries (Fig. 2). Relative preservation of deltoids, compared with the forearm flexors, can be impressive and in marked contrast to the pattern of weakness seen in DM and PM. Contrasts between severe biceps weakness, but better preserved brachioradialis, and severe deep finger flexor weakness, but uncommonly involved adductor pollicis, have been emphasized as well.[11] Involvement of tibialis anterior may also be distinctive in IBM. Dysphagia can be a significant problem with a prevalence estimated as high as 66%.[11]

Serum CK is only modestly elevated; research criteria have proposed diagnostic criteria of an upper limit of 12 times the upper limit of normal,[16] although patients with higher values, up to 16 times the upper limit of normal, have been reported.[11] Serum electrophoresis and the more sensitive immunofixation should be considered because some patients have a detectable serum monoclonal immunoglobulin population.

The presence of multiple myofibers surrounded by inflammatory cells and many myofibers with rimmed vacuoles is highly supportive of a pathological diagnosis of IBM. Both IBM and PM (see the following section) may have similar patterns with respect to the location of inflammatory cells as seen in routine studies. The pattern of inflammatory cells deep within fascicles surrounding and sometimes invading myofibers (Fig. 3) is distinct from that of DM. What distinguishes IBM from PM in light microscopic examination is a sufficient number of rimmed vacuoles, although diagnostic and research criteria for what constitutes sufficient numbers of rimmed vacuoles have not been established. The presence of cytomembranous whorls and filamentous inclusions with electron microscopy (Fig. 4) is also highly supportive of a diagnosis of IBM. Difficulties with diagnosis occur in patients with typical clinical features but few inflammatory cells or with few rimmed vacuoles. Small numbers of rimmed vacuoles may be seen in patients with steroid-responsive PM syndromes.[17]

Polymyositis

Patients with acquired myopathies whose weakness improves with immunosuppressive therapies and relapses with taper of such therapy, but who lack the rash and pathological features of DM, are challenging to classify. Depending on various criteria, such patients may be categorized as having PM, nonspecific myositis, necrotizing myopathy, overlap syndromes, or other diagnoses. Patients with subacute progressive symmetrical proximal arm and leg weakness, without skin rash, and with muscle biopsy features of prominent inflammatory cells surrounding many muscle fibers, without perifascicular atrophy, are the patients that are most appropriately

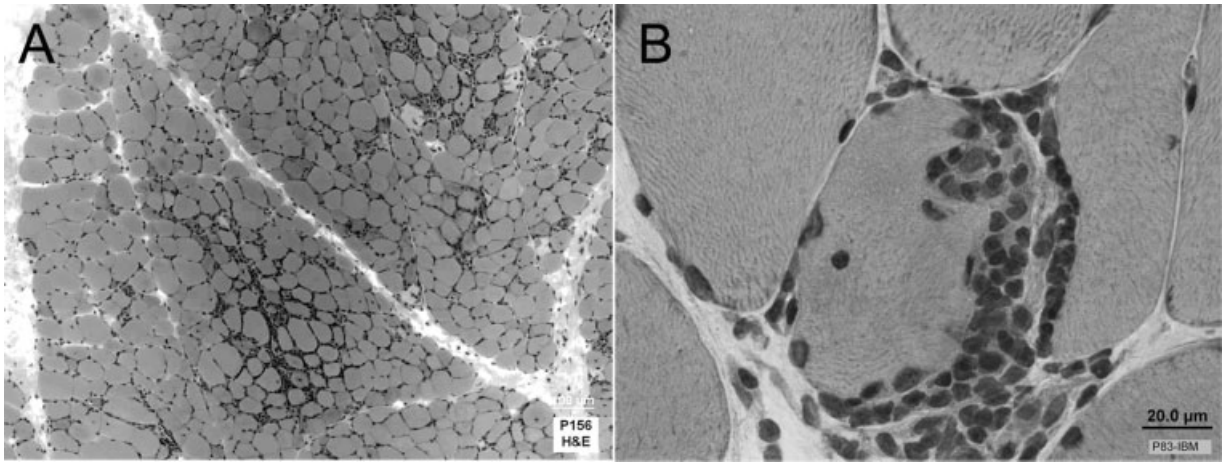

Figure 3 Location of inflammatory cells on hematoxylin and eosin stains in polymyositis and inclusion body myositis. (A) Polymyositis: Inflammatory cells are deep within fascicles surrounding multiple myofibers. (B) Inclusion body myositis: Invasion of an otherwise intact myofiber is seen.

classified as having PM or nonspecific myositis. Various research diagnostic criteria have been considered with regard to the challenges of PM diagnosis.[18–20] The practical issues are avoiding misclassification of certain muscular dystrophies, particularly limb-girdle muscular dystrophy (LGMD), and classifying IBM as PM. Most patients with LGMD and IBM meet widely used criteria for the diagnosis of PM.[21]

As with DM, there is an association with interstitial lung disease, but not a well-established association with malignancy. Serum CK is almost always elevated in patients with progressing PM. Connective tissue diseases should be considered through clinical evaluation and antinuclear antibody testing.

The pathological diagnosis of PM is reasonable when there are abundant inflammatory cells surrounding multiple myofibers and an absence of rimmed vacuoles. There are considerable differences in opinion, which range from support for diagnostic criteria that allow a diagnosis of definite PM with biopsy features that include some unspecified combination of muscle degeneration, regeneration, necrosis, and inflammatory cells,[22] to positions that the diagnosis should require invasion by CD8+ T cells (including cytotoxic and suppressor T cells) of non-necrotic muscle fibers with visible expression of major histocompatibility class 1 by immunohistochemistry on these fibers' sarcolemma.[23] The former criteria may lead to misdiagnosis of genetically determined myopathies, which may have variable degrees of inflammation present (the recent demonstration of an association of calpain mutations with eosinophilic myositis is one excellent example of this problem[24]), and may lead to IBM being diagnosed as PM. The latter is restrictive enough that many patients with immune-mediated myopathies need an alternative diagnosis, such as nonspecific or unspecified myositis.[20]

Necrotizing Myopathy

Necrotizing myopathy is a steroid-responsive subacute myopathy with muscle histopathology consisting of multiple necrotic and regenerating myofibers, and variable thickened blood vessels, but without prominent immune system cells within muscle present on hematoxylin and eosin and other routine histochemical procedures.[20,25–27] Immunohistochemical methods, however, may demonstrate T cells and CD68+ cells[28] (the latter have been characterized as macrophages but could also be plasmacytoid dendritic cells). This syndrome has frequently been associated with a malignancy or connective tissue disease. Some patients have anti–signal recognition particle antibodies.[29–31] Patients have had proximal or generalized weakness, often severe, developing more rapidly than typical in PM, and often with very high CK $>$ 10 times the upper limit of normal.

TREATMENT: INCLUSION BODY MYOSITIS

Several treatment approaches for IBM have been ineffective. IBM does not respond to prednisone. No benefit has been seen in controlled trials with β-interferon,[32,33] after 3 months of intravenous immunoglobulin (IVIg) without[34] and with prednisone,[35] and after 48 weeks of methotrexate.[36] A trial of 6 months of IVIg did not result in definitive improvement, although some effects may have been present.[37] Anti–thymocyte globulin[38] in a pilot trial had some benefit. The lack of response of IBM to these treatments to date do not diminish the role of the immune system in causing tissue damage in this disease; other accepted autoimmune diseases may also be highly refractory to various immunosuppressive therapies, such as anti–myelin associated glycoprotein (anti-MAG) associated neuropathies, or chronic progressive sensory neuronopathy associated with Sjögren's syndrome.

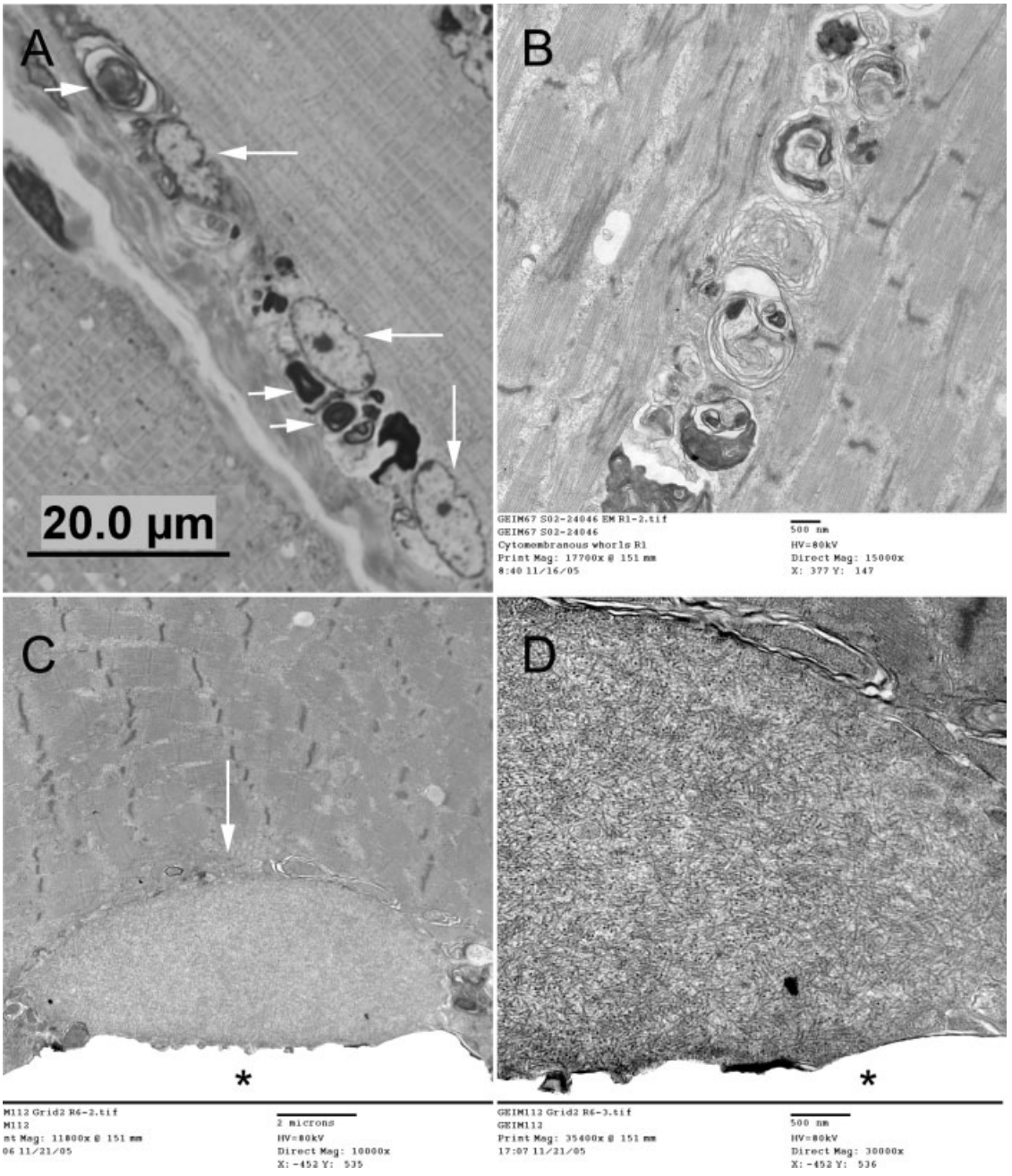

Figure 4 Cytomembranous whorls and tubulofilaments in inclusion body myositis (IBM). (A) A region of cytomembranous whorls (short arrows) and nuclei (long arrows) is seen on toluidine blue stained 0.1-µm thick sections. (B) Electron microscopy of cytomembranous whorls is shown. (C) A mass of tubulofilaments (arrow) is shown with some surrounding membranous material, at the edge of a vacuole (*); it is seen under higher magnification in (D).

TREATMENT: DERMATOMYOSITIS, POLYMYOSITIS, AND NECROTIZING MYOPATHY

Overall Approach

Patients with DM with muscle weakness and patients with PM are usually treated with systemic immunosuppressive therapies. For juvenile DM, unlike adult DM, aggressive treatment aimed at subsequent medication-free cure of disease has been advocated as a goal.[39] Patients with cutaneous manifestations of DM but without symptomatic weakness may be treated with systemic immunosuppressive therapies or topical glucocorticoids, topical tacrolimus, antipruritics, chloroquine, or other agents. Patients who present with a picture compatible with necrotizing myopathy and without a likely alternative diagnosis, such as a toxic myopathy, should be considered for

immunosuppressive therapy with the same approach as that used for PM.

Specific immunotherapies and their complications are discussed in the sections that follow. In general, high doses of corticosteroids are used initially to control disease and then tapered gradually. If disease cannot be controlled on low doses (the equivalent of ~20 mg of prednisone or less), the dose is increased and second agents, typically either methotrexate or azathioprine, are introduced for long-term control and repeat of the corticosteroid taper, again hoping to achieve disease control with low-dose corticosteroids. Alternative approaches include use of therapies initially or early on to avoid prolonged use of corticosteroids. Some patients may be controlled with IVIg monthly infusions alone, or IVIg or methotrexate may be introduced early in the treatment course together with corticosteroids.

Prevention of Osteoporosis

Corticosteroids are first-line agents for treatment of DM and PM. Osteoporosis has been considered the single most debilitating effect of chronic steroid use, and the greatest bone loss occurs in the first 3 to 6 months of their use.[40] Calcium (> 1 g/d) and vitamin D (400 IU/d) have long been recommended. Increasingly being used are aggressive preventive measures with bisphosphonates started the same day as initiation of glucocorticoid therapy. Bisphosphonate therapy should be avoided or used cautiously in premenopausal women given their potential teratogenicity. Alendronate (70 mg orally per week) and risedronate (35 mg orally per week) have both been shown in trials to prevent glucocorticoid-induced osteoporosis.[41,42] Patients need to take these medications with water fasting in the morning and remain sitting upright or standing for 30 minutes to prevent esophageal irritation. Future experience with newer bisphosphonates (ibandronate 150 mg orally once per month; pamidronate 90 mg intravenously [IV], then 30 mg IV every 30 months; clondronate 100 mg intramuscularly [IM] weekly; zoledronate 4 mg IV over at least 15 minutes given every 3 weeks) could lead to more routine use of these agents in selected populations in the future.

Risk of Infection

The risk of infection needs to be considered in advance when embarking on the typically chronic immunosuppression that is required for control of disease in patients with DM and PM. Although most patients do well, experienced clinicians have had patients develop serious opportunistic infections leading to death. Although there is no clearly defined increased risk of common viral infections in patients with inflammatory myopathies who are receiving chronic immunosuppressive treatment, opportunistic infections with *Pneumocystis carinii*, Legionella, Candida, Aspergillus, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, cytomegalovirus, and others do occur.[43] In the largest reported series, 12% of 156 patients with DM or PM developed opportunistic infections, with a 28% mortality rate. Depressed lymphocyte counts may increase the risk.[44] Prophylactic treatment with trimethoprim/sulfamethoxazole (Bactrim) given as one double strength tablet three times per week is effective prevention for *Pneumocystis carinii* pneumonia and should be considered in all patients receiving two or more immunomodulating therapies.

Before treatment, the history should be reviewed for tuberculosis (TB), a chest X-ray obtained, and, if suggestive of prior TB, TB skin testing performed. Patients with a history of TB or a positive PPD (purified protein derivative) test should be treated with isoniazid concurrently with immunosuppressive therapy.

Glucocorticoids

Glucocorticoids can be used in a wide range of regimens, but one typical regimen for adults is prednisone 1 mg/kg/d until definite and satisfactory improvement in strength occurs, usually with 1 to 3 months of treatment. Slow tapering by ~10 mg/mo will then bring patients down typically to a dose of 20 mg/d after ~6 months from the initiation of therapy. Treatment needs to be tailored to specific patients, given a wide range of responses. Alternative approaches include initial high-dose IV treatment (methylprednisolone 1 g/d × 3 to 5 days) for patients with severe disease, weekly bolus IV therapies used particularly in aggressive approaches to juvenile DM, and alternate-day dosing of prednisone rather than daily dosing.

Uncertainty exists regarding alternate-day versus daily dosing of corticosteroids. One single uncontrolled study describing comparisons of these approaches in PM showed less side effects with alternate-day therapies, but this study did not compare patients with equivalent doses or control for potential greater severity of disease for patients for which daily therapy might have been selected and maintained.[45] In a controlled trial comparing alternate-day with daily therapy in a muscle disease (Duchenne's muscular dystrophy), no difference in side effects was seen with equivalent dosing of these regimens.[46] Studies in other diseases have shown no difference for bone loss with daily versus alternate-day therapy.[47]

Methotrexate

Methotrexate is typically used for patients whose disease cannot be controlled on sufficiently low doses of corticosteroids to achieve acceptable side effects. Because methotrexate has pulmonary toxicity, it is important to

exclude interstitial lung disease in patients with DM or PM by chest CT scan, pulmonary function tests, and testing for anti-Jo-1 antibodies, and to avoid its use if present. Methotrexate is given once per week in divided doses, with one common approach starting with 7.5 mg/wk (administered as 2.5 mg every 12 hours × 3). The dose may be increased by 2.5 mg/wk, to as much as 20 mg/wk orally. Higher doses are given parenterally by IM injection, with doses higher than 40 mg/wk uncommon. The major side effects are alopecia, stomatitis, risk of infection, anemia, and renal or liver toxicity.

Azathioprine

Azathioprine, like methotrexate, has a better long-term side-effect profile than corticosteroids. It has a very delayed onset and peak effect so that interpretation of benefit requires patience and may be difficult. Because of the long delay in interpreting efficacy, the highest tolerated dose should be considered initially, often 2.5 to 3 mg/kg/d, with attention to bone marrow suppression and hepatotoxicity. Mild lymphopenia should not lead to discontinuation of the drug, as this may be in part the mechanism of its efficacy. Monthly blood counts, liver function tests, and amylase levels are recommended. Dosing can start at 50 mg/d and increase weekly by 50 mg. Abdominal pain and nausea, sometimes with frank pancreatitis, develops in a significant minority of patients, and generally requires discontinuation and subsequent avoidance of this drug.

Intravenous Immunoglobulin

Intravenous immunoglobulin is useful for some patients with DM and PM. It can be used (1) as initial treatment in severely affected patients with a goal of more rapid improvement, (2) occasionally as maintenance therapy in otherwise refractory patients, or (3) to reduce long-term corticosteroid use. Dosing is 2 g/kg total initially, given divided over 2 to 5 days, and then infusions are repeated every 2 to 4 weeks, with a total dosage of 1 to 2 g/kg/mo.

Other Immunomodulating Therapies

As with other immune-mediated neurological diseases, many other immunomodulating therapies may be used for DM and PM. These include cyclophosphamide, cyclosporine, tacrolimus, chlorambucil, and mycophenolate. Plasma exchange has not shown to be of benefit in a controlled trial.[48]

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