INFLAMMATORY MUSCLE DISEASES

Nancy J. Olsen, M.D.
Rheumatic Diseases Division

INTERNAL MEDICINE GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

4 May 2006

Dr. Olsen acknowledges that she has not disclosed any financial interests or other relationships with commercial concerns related to this presentation. Dr. Olsen will be discussing off-label uses of medications in this presentation.

INFLAMMATORY MUSCLE DISEASES

Inflammatory muscle diseases include several syndromes which are of unclear cause and poorly understood pathogenesis. These are relatively rare disorders, with an estimated prevalence of 10 in 100,000 (0.01%). This is much lower than the prevalence of other autoimmune conditions such as rheumatoid arthritis (1%) or systemic lupus erythematosus (0.05%). However, there are several reasons for considering these unusual disorders in a medical grand rounds context. The first is that they enter into the differential diagnosis of the relatively common finding of elevated muscle enzymes. Second, there are many new approaches to diagnosis and treatment which have significant impact on the management of patients. Third, effects extend beyond muscle and involve other organ systems. Finally, the problem of statin-induced myopathy, while not an inflammatory disorder, has become a factor in the evaluation of muscle enzyme abnormalities. This presentation will consider three main types of inflammatory muscle disease: dermatomyositis, polymyositis and inclusion body myositis. Statin-induced muscle problems will be considered in the final section.

HISTORY AND DEFINITIONS

The criteria by which we define inflammatory myopathies is derived from a pair of 1975 articles by Bohan and Peter published in the New England Journal of Medicine (1;2). The authors, who were neurologists at UCLA, proposed a system for classification of muscle inflammation. While there are problems with this classification, and modifications have been proposed in recent years, the Bohan and Peter criteria remain the starting point for diagnosis and classification (Table 1).

Table 1   ***Criteria for Diagnosis of Polymyositis and Dermatomyositis***
1. Symmetrical weakness of the limb girdle muscles and anterior neck flexors, progressing over weeks or months with or without dysphagia or respiratory muscle involvement.
2. Muscle biopsy evidence of necrosis of Type 1 and 2 fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifasicial distribution, variation in fiber size and any inflammatory exudate, often perifascular.
3. Elevated muscle enzymes, especially CPK, aldolase and LDH.
4. EMG Triad: Small polyphasic action potentials, positive sharp waves and insertional irritability and bizarre high frequency repetitive discharges.
5. Dermatological component (Dermatomyositis only): Heliotrope rash with periorbital edema. A scaly dermatitis over dorsum of hands especially PIP joints (Gottron's sign) and involvement of knees, elbows, medial mealleoli, face and upper torso.

The authors proposed that definite dermatomyositis required 3 or 4 of these criteria in addition to the typical rash while definite polymoysitis required 4 criteria without the rash. A major problem with these criteria is that they have never been formally tested for sensitivity and specificity. In addition, newer developments such as imaging techniques and autoantibody profiling, which can offer quantitative data, are not included in this assessment. A recent increase in the numbers of multicenter clinical trials for myositis treatments has made more urgent the development of improved and validated criteria. To address this need, an international consortium, The International Myositis Classification Criteria Project, with the lead investigator at the Karolinska Institute, is in the process of being initiated.

Table 2: ***Classification of Inflammatory Muscle Diseases***
1. Primary Idiopathic Polymyositis
2. Primary Idiopathic Dermatomyositis
3. PM or DM associated with neoplasm
4. Childhood type associated with vasculitis
5. Association with collagen vascular disease

In addition to diagnostic criteria, Bohan and Peter proposed a classification scheme to help categorize these somewhat disparate disorders (Table 2). They astutely distinguished between DM and PM, which are now recognized as very distinct disorders. The separate category of inclusion body myositis subsequently has been added as a distinct category (3). The criteria and classification scheme were major breakthroughs, because they permitted compilation of information in a systematic fashion.

DERMATOMYOSITIS

Because of the characteristic and readily apparent rash, dermatomyositis (DM) is the most straightforward of the myositis syndromes. The rash is usually present at onset, is usually described as violacious or heliotrope in hue and has a predilection for areas of the face and extremities. Like lupus, the rash may flare on exposure to sun. In addition to the rash, the disease is characterized by weakness in proximal muscles of the upper and lower extremities. A more unusual variant, in which the skin is involved but the muscle is largely spared has been described as amyopathic dermatomyositis (4). Children can also develop DM, but the juvenile form has many differences with the adult disease, and therefore it is classified as a separate entity.

Demographic features of dermatomyositis patients include a predominance of females, who outnumber males with this disease by 1.5-2:1 (3). The age of onset is highly variable, but most cases appear in the third through seventh decades of life. In the US, DM is seen in all major racial and ethnic groups, but there are limited data to suggest that DM and PM are more common in African-Americans than in whites (5). Literature reports suggest that DM is present with similar features around the world. One recent study suggests a gradient in prevalence in Europe related to latitude, with higher rates in southern regions such as Greece (6).

Etiology and Pathogenesis

Very little is known about the causes of DM. The presence of autoantibodies and responses to immunosuppressive therapies suggest that immune system abnormalities are central to the process. Genetic predisposition has been postulated and links with HLA-region loci have been documented (7). As in lupus, it is almost certain that DM and the other inflammatory myositis syndromes are polygenic in origin. However, familial cases of dermatomyositis in adults are so rare that the finding of a patient and an adult daughter with the disorder merits publication (8). This is in contrast to the situation in lupus or rheumatoid arthritis, in which first degree adult relatives with the disorder are relatively common, and it suggests that the genetic component of DM is less important than in other autoimmune diseases. Environmental contributions have been postulated for many years, but no predominant candidate factors have emerged. Associations with seasonal onset, at least in some myositis patients, have been observed, and suggest triggers related to viral infections (9). However, the relative contribution of genetic and environmental factors to the development of DM remains largely unknown.

The pathogenesis of DM is dependent on complement fixation in muscle tissues, and this process especially targets vascular elements. Activation of endothelial cells and neovascularization have been recently described in DM muscles, pointing to the central role of blood vessels in the pathogenesis of muscle damage (10). In general, DM muscles show a loss of capillaries, and it has been postulated that neovascularization is a response to this decrease. Cellular infiltrates in DM muscle are predominantly composed of CD4+T lymphocytes and B lymphocytes. The T cells are not clonally expanded, as defined by the molecular characteristics of their receptors, and appear to have arrived more like bystanders at a fire than instigators of

the event. The central question in terms of etiology is what triggers the initial complement and endothelial activation; there are very few clues at present.

Diagnostic Tests

Serum muscle enzymes are usually elevated in patients with DM, but this is not a uniform finding. Some patients with persistently normal CK levels have active muscle inflammation and weakness; others may have amyopathic DM. It is therefore very important to remember that the presence of a normal CK level does not exclude the possibility of DM. Other muscle enzymes such as aldolase increase the sensitivity to detect abnormalities only slightly. Elevated muscle enzymes can appear on the liver profile, which may lead to misidentification of the problem, and on rare occasions, unnecessary liver biopsies (11).

Autoantibody profiles may be useful in confirming a diagnosis of DM, or other inflammatory myositis syndrome. Several of these are antibodies to tRNA synthetases; the most common one is Jo-1, which is anti-histidyl tRNA synthetase. Antibodies to Jo-1 may be a clue to the presence of underlying interstitial lung disease, one of the main extra-muscular complications of DM. Although these antibodies are highly specific (100% in most series), they have relatively low sensitivity. The highest is Jo-1, which has a sensitivity of about 25%; other anti-synthetases have sensitivities of less than 10% (12). It should be kept in mind that these sensitivities are generally determined in studies of populations that have been pre-screened for muscle problems. In a general medical clinic or ward, where the prevalence of such diseases is very low, the test is less useful. What these data mean, therefore, is that in cases in which a muscle disorder is likely, positivity on the MSA panel can be a very useful indicator of myositis. The trade-off is that the tests have relatively low sensitivity, so they are not useful screening tools.

Electromyography shows distinctive patterns in myositis patients and these results can be very useful in confirming a diagnosis. Furthermore, other causes of muscle weakness such as nerve injury are readily distinguished from primary muscle problems. Some patients find this test uncomfortable, however, and may question their physician's description of the procedure as "noninvasive." The EMG data are also highly dependent on the skill of the operator, and utility in some situations may be limited.

Imaging studies other than ultrasound and magnetic resonance are not useful. Plain X-rays and CT scans, for example, not sensitive to changes in soft tissues. An exception is in the evaluation of soft tissue calcification, which develops in some DM patients. Ultrasound can be useful to detect changes in muscles, and it has the advantage of being portable for use at the bedside or in clinics. However, the method remains dependent on the availability of an experienced operator, and it has not seen widespread use in this country. In contrast, MRI has major advantages in muscle evaluation. It is sensitive to changes in soft tissues and can produce images of relatively large areas of muscle. The process itself is noninvasive, and intravenous contrast is not required to visualize muscle changes (13).

Muscle inflammation is characteristically seen on MRI as areas of high signal intensity, or brightness, on the T2-weighted but not the T1-weighted images. Areas of fat infiltration, which may accompany muscle atrophy, can also appear bright on the T2 image (as well as on T1). The coexistence of fat and inflammation in a region of muscle may complicate interpretation. This problem is usually circumvented by fat-suppression or STIR sequences, which reduce the bright signal from fat, revealing areas of inflammation. Findings that have evolved from MRI studies have changed the evaluation of DM patients in many ways. First, since the skin rash and distribution of muscle weakness is so characteristic, the confirmation of an inflammatory pattern on MRI can, in some cases, obviate the need for muscle biopsy. This has become especially true in pediatrics, where the biopsy itself can be a traumatic procedure for the patient. Second, it has become obvious from the images that muscle involvement in DM can be patchy, explaining in part why some cases yield negative biopsy findings because lesions may be missed (14). A corollary is that the MRI can be useful for localization of the muscle biopsy site, thereby increasing the yield of information. Third, the pattern of involvement in DM shows a preference for involvement of muscles in certain compartments, typically the quadriceps muscles in the thigh (Figure 1) (15). Reasons for this preferential muscle localization are not known.

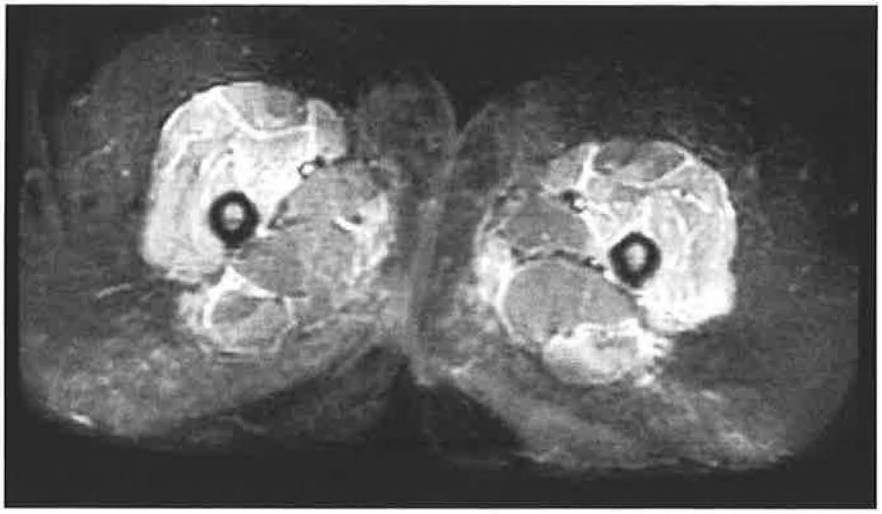


Figure 1 *STIR image of proximal thigh muscles in patient with DM. Areas of high signal intensity involve quadriceps muscles bilaterally, consistent with inflammation (J.C.Hunter, University of Washington).*

Even though MRI now provides excellent visualization of muscle tissue in vivo, the muscle biopsy remains the gold standard for establishing the diagnosis. In dermatomyositis, characteristic changes include atrophy of muscle fibers in perifascicular regions (Figure 2) and lymphocytic infiltrates, which may surround blood vessels (Figure 2). The infiltrating cell types, as noted above, are predominantly CD4+ T and B lymphocytes. In addition to these changes, complement fixation may be present on vessels and capillary numbers are generally decreased.

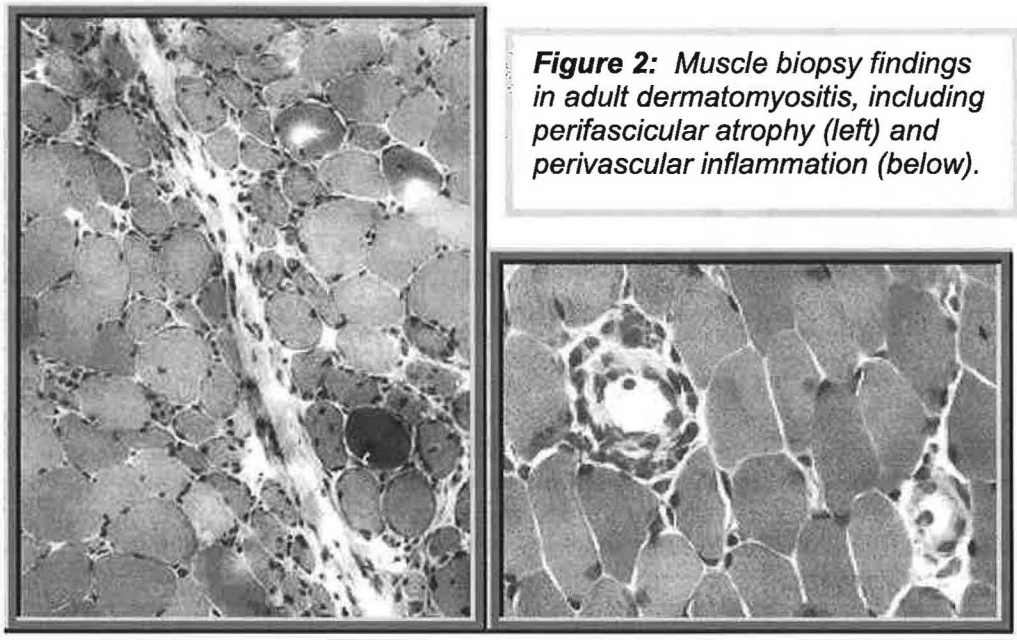


Figure 2: *Muscle biopsy findings in adult dermatomyositis, including perifascicular atrophy (left) and perivascular inflammation (below).*

Differential Diagnosis

The list of disorders that can cause elevated CK is long and includes such things as medications, infections and other connective tissue disorders. However, most of these conditions do not include the characteristic pattern of proximal muscle weakness with accompanying skin manifestations. The skin rash of DM is so characteristic, that there are very few imitators. The most difficult distinction is actually with lupus, which can have similar skin findings accompanied by photosensitivity. Even skin biopsies may be difficult to interpret as the changes of DM and SLE share pathologic features. Since DM can have amyopathic forms, the overall

appearance mimics lupus. Some treatments are common to both, including sun protection and immunosuppressive therapies. However, systemic manifestations are quite different in that the lupus patient carries a risk of nephritis while the DM patient requires screening for malignancy (see below). The presence of autoantibodies characteristic of one disease or the other (anti-Sm for lupus, anti-Jo-1 for DM) can be very useful. However, in the absence of these findings, continued followup should be carried out with both possibilities in mind.

Risk of malignancy

It has been clear for many years that dermatomyositis patients have an increased rate of malignancy. This means that in a subset of patients, DM is a paraneoplastic syndrome. The risk is at least 2-fold higher for patients with DM than PM, and increases after the age of 40 years; as a corollary, children with juvenile forms of DM probably do not have an enhanced risk of underlying malignancy. Patients with amyopathic DM are at equal risk to those with myopathic symptoms. The risk in DM patients is variable in different geographic locations, but may be estimated as about 6-fold increased over control cohorts. Increased risk correlates with older age of onset (> 45 years) and male gender (16). While most malignancies are identified around the time of the dermatomyositis diagnosis, some reports suggest that the malignancy can precede muscle symptoms by decades, although in this situation, relatedness of the two diseases may be more questionable (Figure 3) (17). Some studies suggest that while the malignancy risk is greatest for the first 3 years after diagnosis of DM, it remains elevated for 5 or more years.

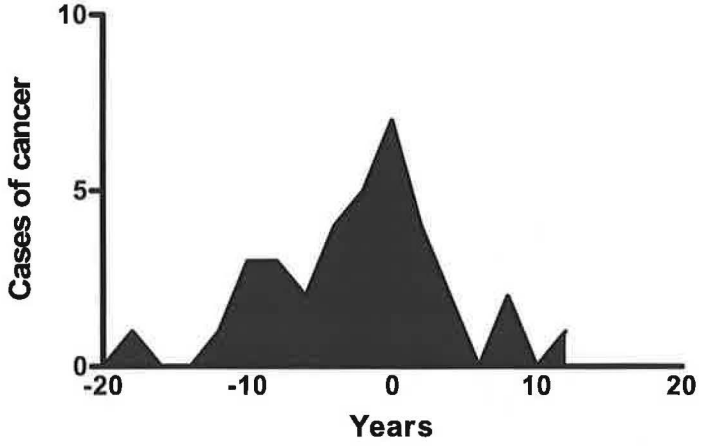


Figure 3: *Time between diagnosis of dermatomyositis and diagnosis of malignancy. The study population included 85 patients with biopsy-positive DM. A total of 36 of these patients (42%) had an underlying malignancy (from Buchbinder et al).*

The spectrum of malignancies reported to be associated with DM is very broad and reflects in part the prevalence for the local population. This means that in European and American studies, ovarian, breast, lung and prostate cancers are elevated while in Asian countries nasopharyngeal carcinoma has been the predominant cancer reported (16;18). Probably the most worrisome malignancy seen in our patients is ovarian cancer. One Swedish study calculated that the risk of ovarian cancer in a woman with DM is 17-fold higher than in her non-DM counterpart (19).

Given this risk, what should be done? The most important component of the management approach is to remember that this association exists. The next step is to carry out the usual screening tests for the most common malignancies. This means that adult patients with DM should have a thorough physical, including gynecologic and rectal exams. Imaging studies should include the chest, abdomen and pelvis; usually this is done with CT scanning. Men should have measurement of PSA and women should have mammography, regardless of their ages. In some cases, colonoscopy is advisable, based on personal or family history. Reassessment, and possibly repetition of these tests, is advisable for the first 1-2 years after the diagnosis of DM is made, keeping in mind that the risk is not lowered to baseline for at least three to five years.

Clues to an undetected underlying malignancy are few, so the suspicion has to remain high. In general the pattern of DM is no different than in patients who do not have an associated malignancy. However, nonresponsiveness to treatment including difficulty in controlling the skin rash might be an indicator that something else is going on and that further investigation is indicated. To complicate matters somewhat, a drop in levels of muscle enzymes to values in the normal range can occur in malignancy-associated DM, so this is not necessarily a good sign (Figure 4) (20).

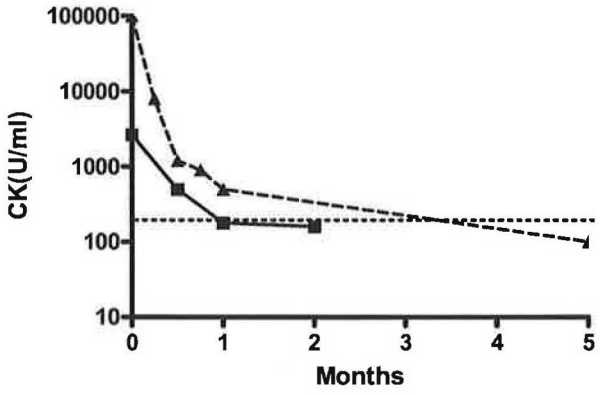


Figure 4 *Rapid decreases in serum CK levels seen in two women with DM and ovarian cancer. In each case, the malignancy was not detected at the time of DM diagnosis, but became apparent when other findings like ascites developed. Dotted horizontal line indicates normal CK level (from Klippel textbook, 1998).*

Treatment

Systemic glucocorticoids and immunosuppressives are required in most cases of dermatomyositis, even in amyopathic forms. This is not to belittle the importance of topical therapies, which can control skin manifestations. Most patients with dermatomyositis have sensitivity to the sun which is very similar to that seen in lupus. For this reason, sun protection with appropriate clothing, sunscreen and tinting of windows in the automobile are not to be overlooked. Topical glucocorticoids and immunosuppressives such as tacrolimus are also useful for affected areas of the skin. However, in most cases, systemic treatment is also required.

The first line of systemic treatment is glucocorticoids, used as oral prednisone in doses up to 60 mg daily. Of course, a side effect of steroid treatment is myopathy, so prolonged use of high doses is not advisable. A study conducted by Clarke and colleagues in Pittsburgh published in 1995 demonstrated that in fact poor functional outcome in myositis patients was associated with steroid-induced complications including avascular necrosis and fractures (21). To permit steroid doses to be tapered, immunosuppressive medications are usually initiated at the time of diagnosis. There are several controlled trials demonstrating that drugs including methotrexate and azathioprine are effective (22). Smaller series suggest that mycophenolate mofetil is useful. There is no convincing evidence to favor one of these agents over another on the basis of efficacy as long as there are no major extramuscular manifestations. For patients with lung involvement, cyclophosphamide may be needed, but this is rarely required for myositis alone. And the presence of vasculitic lesions that do not respond to drugs like methotrexate is a scenario where intravenous immunoglobulin (IVIG) is sometimes indicated. However in general, the choice of appropriate immunosuppressant is based on other issues such as tolerability and comorbid conditions. Once immunosuppressives are added at reasonable doses, the steroid dose is tapered, using muscle strength as the primary measure and muscle enzymes as a secondary measure of outcome. Although most DM patients have at least a partial response to these treatments, it is estimated that about 10% fail to improve. This indicates the need for additional effective treatments.

The observation that dermatomyositis muscle lesions contain B lymphocytes and that the disease and its subsets are associated with autoantibodies has led to an interest in the use of rituximab, which is a monoclonal antibody directed against the B cell antigen CD20 antigen. Treatment with rituximab leads to depletion of B lymphocytes. This drug has been recently approved for the treatment of another autoimmune disease, rheumatoid arthritis. Several reports of cases or small trials have suggested that rituximab may be useful in

patients with dermatomyositis. One open-label trial showed improvement in strength measurements for 6 patients treated over periods of 6-12 months (Figure 5)(23). In this study, patients who had either failed other immunosuppressants or who had severe weakness were treated with rituximab with weekly doses of 100 mg/m^2/infusion or 375 mg/m^2/infusion for four weeks. The patients were followed for 6 to 12 months, and muscle strength measurements were used as a measure of outcome. Improvements in strength and decreases in muscle enzymes were noted. Side effects were limited; one patient had a soft tissue infection that required antibiotic treatment.

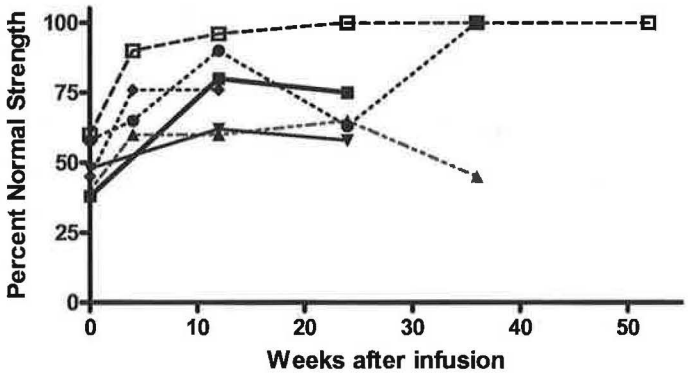


Figure 5 *Changes in muscle strength in 6 DM patients treated with rituximab. Patients 1-3 received 100 mg/m^2/infusion; patients 4-6 received 375 mg/m^2/infusion.*

Based on these and other findings, a multicenter trial of rituximab in adult and juvenile dermatomyositis or polymyositis, designated Rituximab in Myositis, or RIM (www.rimstudy.org), has been funded by NIAMS/NIH. Adult and juvenile patients at our medical center will be included in this trial, which is scheduled to begin by the summer of 2006.

Other biologics are being tested for efficacy in DM. These include the TNF inhibitors infliximab and etanercept, which are currently being evaluated in small trials (www.clinicaltrials.gov). Another novel agent which targets complement activation is eculizumab. This humanized monoclonal antibody prevents cleavage of C5 into its pro-inflammatory components, and has received orphan drug status by the FDA for treatment of DM. Small trials of this agent in DM have been conducted, but results have not yet been reported.

POLYMYOSITIS

A strict interpretation of the Bohan and Peter criteria would suggest that polymyositis (PM) is just DM without the rash. The current understanding is that this is not correct, and that in fact PM is a distinct immunopathologic entity. Furthermore, it is clear that application of the criteria alone leads to an over-diagnosis of PM which is thought to be a very rare disorder (24). PM should be viewed as a distinct disease with characteristic pathology and outcome and the diagnosis should be based largely on biopsy evidence.

Etiology and pathogenesis

Cellular analysis of biopsy tissues from affected muscles in PM patients is consistent with a predominantly cell-mediated damage of muscle tissue, rather than mediation by humoral factors, and complement is not involved. Furthermore, unlike DM where the infiltrate is composed of predominantly CD4+ and B lymphocytes, PM muscle biopsies show a predominance of CD8+ T cells which may be invading the muscle fibers themselves (Figure 6) (25). In addition, the CD8+ populations in the muscle show restricted clonality, consistent with an antigen-driven response, while the T cells in DM muscles are polyclonal. This difference between PM and DM is even apparent in analysis of peripheral blood T lymphyocytes (26).

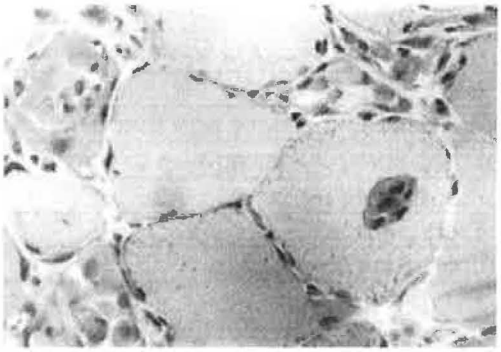


Figure 6 *Polymyositis muscle with direct lymphocytic invasion of muscle fiber.*

Diagnostic tests

In the absence of a rash, muscle weakness is the only clinical characteristic of PM. As in DM, this weakness can be accompanied by elevations in muscle enzymes and EMG abnormalities. Patients with PM may show positivity for some of the myositis-specific antibodies.

The appearance of the muscle biopsy, with direct invasion of muscle fibers, suggests that muscle damage may be greater in PM than in DM, where the infiltrate is largely perimysial. This impression is confirmed by MRI findings, which show extensive fat replacement of muscle tissues, apparent on the T1-weighted images (Figure 7) (27). The MRI findings are not however diagnostic. Similar changes may be observed in inclusion body myositis, for example. Therefore, unlike the situation in DM, where the characteristic rash and typical MRI findings can in some cases obviate the need for a tissue diagnosis, biopsy of involved muscles is required to establish a diagnosis of PM.

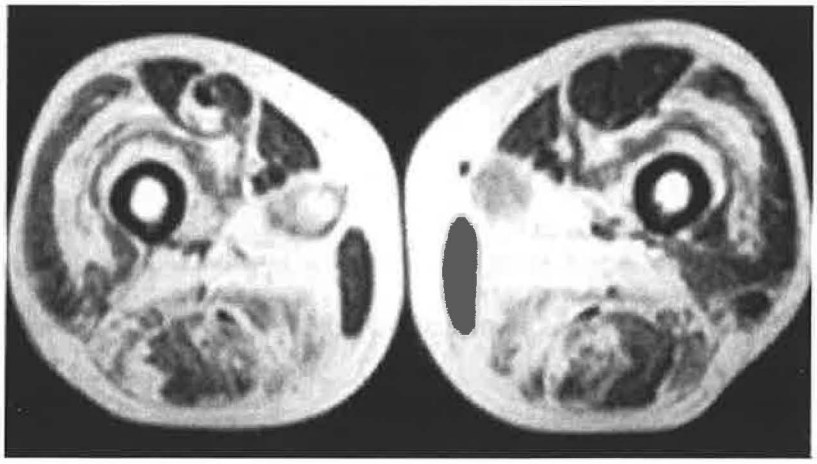


Figure 7 *T1-weighted image of proximal thigh muscles in PM. Extensive fat infiltration is especially notable in the posterior compartment.*

Although the muscle involvement as shown by biopsy and MRI scanning suggests a greater extent of irreversible muscle damage in PM than in DM, long term differences in outcome have not been reported.

Differential diagnosis

Many disorders can present with muscle weakness and elevated CK. Therefore, in the absence of the DM-defining rash, PM is definitely a major diagnostic challenge. Specialized referral centers such as the one at the NIH have noted a wide range of conditions that existed in patients who were referred for evaluation of a putative inflammatory muscle disease (Table 3)(28). Often these individuals have been referred for what is thought to be treatment-resistant myositis, when in fact the problem is an incorrect diagnosis.

Table 3 Conditions prompting referral for myositis evaluation

Condition	***Comments***
Muscular dystrophies	Several distinct types; usually younger age than PM patients
Mitochondrial disease	May have history of rhabdomyolysis; age up to third decade
Endocrine disorders	Stiff-person syndrome, thyroid disease
Drug toxicity	Statins, chloroquine, colchicines
Neurological disorders	Channelopathies, motor neuron disease

Clues to other diagnoses are largely derived from elements of the history and physical examination. Muscle dystrophies, for example, are often revealed by a family history. Neurologic abnormalities and muscle fasciculations are not generally part of PM; rhabdomyolysis might suggest a mitochondrial myopathy.

Table 4: Features leading away from a diagnosis of myositis

Family history of a similar illness
Weakness related to exercise, eating or fasting
Neurological signs, e.g. abnormal reflexes, sensory changes
Cranial nerve involvement
Muscle fasciculations or severe muscle cramping
Atrophy or hypertrophy of muscle
CK levels >100-fold elevated above normal levels.

Ultimately, the muscle biopsy should sort out these possibilities. However, even a previous report of PM on biopsy requires review by an experienced muscle pathologist, because misinterpretation of biopsy findings is not uncommon. It is often worth retrieving blocks and slides for re-review prior to embarking on another biopsy or other treatments.

Malignancy and PM

Most studies point to at least a 2-fold lower risk of malignancy in PM patients than in those with DM (18). There is the possibility, however, that these data are somewhat inaccurate due to the difficulty of establishing a diagnosis of PM, so there is a distinct possibility that other diseases were included with PM in some series. Nevertheless, once a diagnosis of PM is established, a survey for neoplasms should be carried out as in a patient with DM.

Treatment

Glucocorticoids and immunosuppressives are used for treatment of PM as for DM, with outcome measured as muscle strength, primarily, and decreases in elevated serum muscle enzyme levels, secondarily. Because of the likelihood that PM is associated with a greater decline in muscle mass and function, other non-immune or inflammatory therapies should be also considered here. These include physical measures in the form of physical therapy or supervised exercise. Once tapering of the initial high dose steroids has begun, patients should be encouraged to begin regular exercise to prevent further loss of muscle mass. Substantial evidence indicates that initiation of exercise does not aggravate or reactivate muscle inflammation in the majority of patients. Regimens that have been advocated include use of a stationary bicycle and step aerobics (29).

An adjunct to exercise for improving muscle strength and function is the nutritional supplement creatine. The rationale for the use of creatine can be found in the biochemistry of muscle energetics. The storehouse of high energy phosphate bonds in the muscle cell is phosphocreatine (PCr). Use of P-31 magnetic resonance spectroscopy to measure phosphate compounds in muscle in vivo, shows that levels of PCr and ATP are highly correlated (Figure 8; Park, JH, unpublished data). Since PCr production is dependent on levels of creatine, it is reasonable to postulate that increases in creatine could drive production of higher levels of PCr, and by association, ATP.

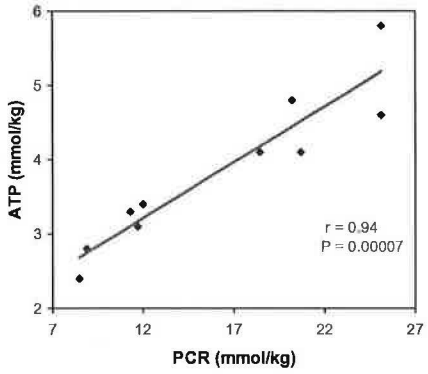


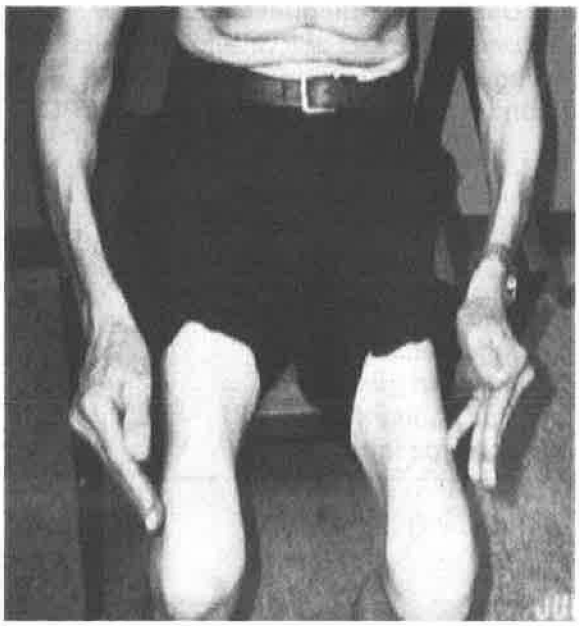
Figure 8: *Levels of ATP and phosphocreatine (PCr) measured in muscles of myositis patients using P31 MR spectroscopy.*

This hypothesis was investigated in a small pilot trial that included 5 inflammatory myositis patients,1 DM, 4 PM;(30) Treatment with creatine was initiated as a loading dose of 0.3 g/kg/day for one week followed by a maintenance dose of 0.075 g/kg/day. Creatine is a granulated powder; it was mixed with juice (grape juice was a favorite) for administration. Patients were also given supplemental magnesium (400-800 mg/day). Treatment was continued for 6 months. Evaluation was with standard strength assessments and P-31 MRspectroscopy to quantify muscle metabolites. At the end of the study period, a significant increase in the efficiency of muscle contraction, measured as a work/cost ratio, was observed (P=0.003) and the patient self-assessed functional status was also significantly improved (P=0.04). Tolerability was excellent and no side effects were observed. These results suggest that creatine might be a useful adjunct to therapy especially in patients who have had significant loss of muscle tissue.

INCLUSION BODY MYOSITIS

A PubMed search for the term "inclusion body myositis" returns with 721 citations, the first of which was published in 1971 (31); three-quarters of these reports have been published in the past 10 years. In contrast, the first clinical descriptions of PM and DM were published around 1890. Although inclusion body myositis (IBM) is a relatively newly described disorder, it has probably been around for a long time. Many cases labeled as treatment-resistant PM may in fact have been IBM. It is now recognized that the clinical and pathologic features of IBM distinguish it in many ways from PM and DM. Two major subtypes of IBM have been described. The hereditary form, which has a paucity of inflammatory features, will not be considered further here. Focus will instead be on the sporadic form (s-IBM), which has been labeled as the most common progressive debilitating muscle disease in persons over 50 years of age (32). Unlike PM and DM, s-IBM occurs predominantly in men, and the average age in most reported series is 60 years or older (33).

Clinical features



The onset of muscle weakness in s-IBM is insidious. Often, the patient is not aware of the changes until some major deficit in functioning occurs. Unlike PM and DM, distal muscle groups are affected and involvement of muscles of the hand, with loss of fine motor function, is especially debilitating. In addition, involvement of muscles may be asymmetric. Large muscle groups of the lower extremities may become profoundly weak so that the patient is at risk of losing the ability to get up following a fall. Most patients become unable to ambulate and eventually require a motoroized wheelchair due to the profound muscle atrophy (Figure 9).

Figure 9: *s-IBM patient with profound atrophy of quadriceps and finger flexors.*

Diagnostic tests

Serum muscle enzymes are usually elevated in IBM, but the increases are generally more modest than those seen with PM or DM. Autoantibodies are usually absent. The EMG may show a mixed myogenic/neurogenic picture. However, all of these findings are nonspecific and a muscle biopsy is required to establish the diagnosis. Although initial studies suggested a requirement for EM examination of tissues, the inclusion bodies are in fact visible by light microscopy. Three characteristic features are described: rimmed vauoles, intranuclear and cytoplasmic inclusion bodies and deposits of amyloid-like proteins (Figure 10). There has been some suggestion that the proteins found within the vacuoles share features with those found in Alzheimer's brain lesions (32;34). It appears as though the cellular machinery is unable to process these proteins, possibly due to defects in protein folding.

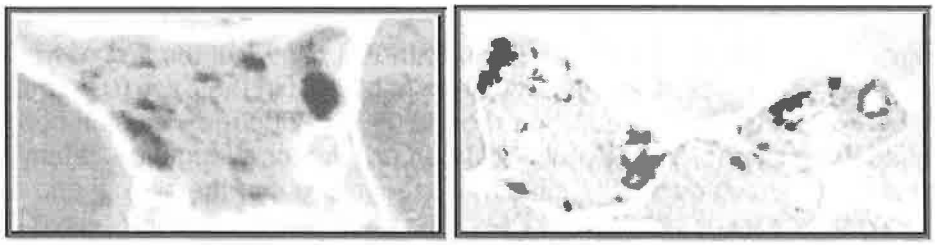


Figure 10: *Histologic appearance of IBM muscles, stained for amyloid-like components (left) and with an antibody directed at abnormally-accumulated proteins (right). The pattern of staining in the latter is described as "squiggly."*

Differential diagnosis

Patients with s-IBM may present initially as PM which is resistant to treatment. In these cases, review of the biopsy from the initial presentation sometimes reveals the characteristic inclusions. Other neurodegenerative processes, such as motor neuron disease, may enter into the differential diagnosis, and neurology consultation is often indicated.

Malignancy

The relationship between s-IBM and malignancy is unclear. If there is a relationship, it is definitely less than for DM and PM. It is reasonable to search for an underlying neoplasm when the diagnosis of s-IBM is made. These are generally older patients in whom neoplasms are more prevalent, so the usual screening procedures should be employed.

Treatment

The hallmark of s-IBM which distinguishes this disorder from DM and PM is the general unresponsiveness to glucocorticoids or immunosuppressive medications. Scattered reports of cases which are responsive to glucocorticoids do exist, but these are atypical. Improvement with IVIG also has been reported, but positive results are usually only very short-term in duration. The anabolic androgen oxandrolone was tested in a double-blind, placebo-controlled trial which enrolled 19 patients for a treatment period of 12 weeks. This small study showed a significant effect of oxandrolone to increase upper-body strength ($P=0.006$), and suggested that further trials, perhaps with a concomitant immunomodulating agent would be of interest (35). Overall, however, patients with s-IBM currently have no options for effective treatment.

STATIN-ASSOCIATED MYOPATHY

History and scope

Statins, which lower lipids through inhibition of HMG CoA reductase, are now the most prescribed class of drugs in the United States. With changes in guidelines for lipid control and aging of the population, the use of these drugs is likely to increase even more. It took several years after the first introduction of statins to see reports of muscle toxicity, starting in the early 1990's. Rare but dramatic cases of rhabdomyolysis and even death were reported to be associated with statin use. More commonly, treated patients reported milder symptoms such as myalgias, which nevertheless prompted repeated laboratory monitoring of CK levels and heightened concerns about serious complications. With greater use of these drugs, it has become clear that most patients have no significant muscle pathology and that severe muscle injury is rare. Current estimates are that muscle pain occurs in up to 11% of patients, but significant myopathy, with CK levels elevated to 10-fold over the normal range, is observed in only 0.5% of treated patients (36).

A recent retrospective study from the University of Wisconsin surveyed records from 437 patients seen over a period of 13 years using ICD-9 codes (including 13 different codes) indicating some type of muscle problem (36). After removal of patients with a defined myopathy or CK elevation that was clearly due to other causes, 45 subjects with potential statin-related problems remained. This group included individuals with normal CK levels in whom muscle symptoms were present, based on other reports suggesting that statin-induced myopathy can be associated with normal muscle enzyme levels. The majority of these patients had diffuse muscle pain; only 25% had weakness. Eight patients had findings consistent with rhabdomyolysis, and hospitalization was required in 6 of these individuals. The rhabdomyolysis patients were older ($P=0.02$) and had taken a statin drug for a shorter period of time ($P<0.05$), than patients without this complication. Followup data suggested that some of these patients were able to later tolerate another statin drug, but the group was too small to determine whether this was significant.

Etiology

Metabolic abnormalities contributing to statin-induced myopathy have concentrated on elements of the energy-generating pathways of muscle cells, especially those that relate to mitochondrial function. A mitochondrial etiology is suggested in part by biopsy changes observed in statin-treated myopathy patients. These include the presence of ragged red fibers and intracellular lipid accumulation (Figure 11). Similar changes are seen in mitochondrial myopathies, and some patients with idiopathic forms of mitochondrial myopathies develop rhabdomyolysis. So these findings suggest a contribution of mitochondrial abnormalities to the statin effects.

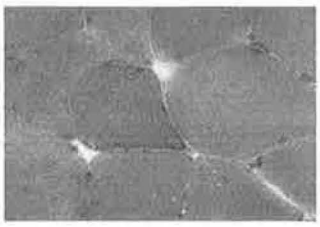


Figure 11: *Ragged red fiber in muscle biopsy from patient with statin-associated myopathy (left panel). Lipid accumulation in muscle cells of patient with statin myopathy (middle panel), which is largely resolved following 6 months off the drug (right panel).*

One clue to this connection is that the statin class of drugs inhibits synthesis of mevalonate, a pathway that is shared by coenzyme Q10, a component of the electron transport chain in mitochondria. As such, this molecule has an important role in intracellular energy transduction. Other properties of coenzyme Q10 include generation of antioxidants and inhibition of apoptosis. It follows that reduced levels of coenzyme Q10 could lead to mitochondrial dysfunction and functional impairment of the muscle cell. Taken together with the histologic data, the picture that emerges suggests that statins lead to decreased levels of coenzyme Q10, resulting in mitochondrial dysfunction and myopathy. The evidence for decreased serum levels of coenzyme Q10 is conflicting, and may be related to the dose of statin used (37). However, it is the level inside the muscle cell which is most important, since it is not known whether serum measurements reflect intracellular concentrations. One recent report included measurement of muscle coenzyme Q10 levels in muscle extracts (38). Although a few of the samples from statin-treated patients had very low coenzyme Q10 levels, the overall mean was not different than in untreated controls. So despite the attractiveness of the hypothesis, these data do not offer further support for it. Nevertheless, there has been some suggestion that patients who develop statin-myopathy changes might benefit from supplementation with coenzyme Q10. Mitochondrial myopathies are related to underlying genetic defects, and it is interesting to consider that patients with statin-induced changes might be genetically susceptible in some way. If so, identification of markers for this susceptibility would be useful in predicting which patients are at risk for this complication.

Practical advice

Many patients take statins and many of them will have myalgias, as noted above. What to do in clinical practice about this problem is less than clear. Obtaining a baseline CK might be useful for comparison with later levels if symptoms develop, but it is probably not needed. On the other hand, it is important to consider other causes of myopathy; hypothyroidism, for example has been found in patients referred for evaluation of a possible statin-related problem (39). Coenzyme Q10 might be a useful supplement, despite the data noted above, and is available over-the-counter; doses as high as 300 mg twice daily may be required. Muscle health should be emphasized. Generally this means an exercise program which starts at low levels and gradually increases in strenuousness. Switching to an alternative statin and/or use of a lower dose of the drug should be considered, if these possibilities are consistent with other aspects of the patient's care.

SUMMARY

Some things to remember about inflammatory muscle diseases:

1. Polymyositis and dermatomyositis are distinctly different disorders.
2. MR imaging is an excellent approach to evaluating muscle inflammation.
3. Do not use myositis-specific autoantibodies as screening tools.
4. When you consider DM andPM in a differential diagnosis, remember cancer risk.
5. Active muscle inflammation can occur with a persistently normal serum CK.
6. Consider IBM in patients labeled as treatment-resistant PM.

References

1. Bohan,A. and Peter,J.B. 1975. Polymyositis and dermatomyositis (first of two parts). *N.Engl.J.Med.* 292:344-347.

2. Bohan,A. and Peter,J.B. 1975. Polymyositis and dermatomyositis (second of two parts). *N.Engl.J.Med.* 292:403-407.

3. Dorph,C. and Lundberg,I.E. 2002. Idiopathic inflammatory myopathies - myositis. *Best.Pract.Res.Clin Rheumatol.* 16:817-832.

4. Euwer,R.L. and Sontheimer,R.D. 1993. Amyopathic dermatomyositis: a review. *J.Invest Dermatol.* 100:124S-127S.

5. Oddis,C.V., Conte,C.G., Steen,V.D., and Medsger,T.A., Jr. 1990. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. *J.Rheumatol.* 17:1329-1334.

6. Hengstman,G.J., van Venrooij,W.J., Vencovsky,J., Moutsopoulos,H.M., and van Engelen,B.G. 2000. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. *Ann.Rheum Dis.* 59:141-142.

7. O'Hanlon,T.P., Carrick,D.M., Arnett,F.C., Reveille,J.D., Carrington,M., Gao,X., Oddis,C.V., Morel,P.A., Malley,J.D., Malley,K. *et al.* 2005. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 allelic profiles and motifs define clinicopathologic groups in caucasians. *Medicine (Baltimore)* 84:338-349.

8. Davies,M.G. and Hickling,P. 2001. Familial adult dermatomyositis. *Br.J.Dermatol.* 144:415-416.

9. Sarkar,K., Weinberg,C.R., Oddis,C.V., Medsger,T.A., Jr., Plotz,P.H., Reveille,J.D., Arnett,F.C., Targoff,I.N., Genth,E., Love,L.A. *et al.* 2005. Seasonal influence on the onset of idiopathic inflammatory myopathies in serologically defined groups. *Arthritis Rheum* 52:2433-2438.

10. Nagaraju,K., Rider,L.G., Fan,C., Chen,Y.W., Mitsak,M., Rawat,R., Patterson,K., Grundtman,C., Miller,F.W., Plotz,P.H. *et al.* 2006. Endothelial cell activation and neovascularization are prominent in dermatomyositis. *J.Autoimmune.Dis.* 3:2.

11. Helfgott,S.M., Karlson,E., and Beckman,E. 1993. Misinterpretation of serum transaminase elevation in "occult" myositis. *Am.J.Med.* 95:447-449.

12. Lyons,R., Narain,S., Nichols,C., Satoh,M., and Reeves,W.H. 2005. Effective use of autoantibody tests in the diagnosis of systemic autoimmune disease. *Ann.N.Y.Acad.Sci.* 1050:217-228.

13. Scott,D.L. 2003. Imaging in Muscle Disease. In Imaging in Rheumatology. D.A.Isenberg and Renton,P., editors. Oxford University Press, Oxford. 188-209.

14. Wong,E.H., Hui,A.C., Griffith,J.F., Wong,S.M., and Szeto,C.C. 2005. MRI in biopsy-negative dermatomyositis. *Neurology* 64:750.

15. Park,J.H., Vital,T.L., Ryder,N.M., Hernanz-Schulman,M., Partain,C.L., Price,R.R., and Olsen,N.J. 1994. Magnetic resonance imaging and P-31 magnetic resonance spectroscopy provide unique quantitative data useful in the longitudinal management of patients with dermatomyositis. *Arthritis Rheum* 37:736-746.

16. Chen,Y.J., Wu,C.Y., and Shen,J.L. 2001. Predicting factors of malignancy in dermatomyositis and polymyositis: a case-control study. *Br.J.Dermatol.* 144:825-831.

17. Buchbinder,R., Forbes,A., Hall,S., Dennett,X., and Giles,G. 2001. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. *Ann.Intern.Med.* 134:1087-1095.

18. Hill,C.L., Zhang,Y., Sigurgeirsson,B., Pukkala,E., Mellemkjaer,L., Airio,A., Evans,S.R., and Felson,D.T. 2001. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 357:96-100.

19. Sigurgeirsson,B., Lindelof,B., Edhag,O., and Allander,E. 1992. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N.Engl.J.Med.* 326:363-367.

20. Olsen,N.J. 1998. Inflammatory Muscle Disease: Practical Problems. In Rheumatology. J.H.Klippel, Kieppe,P., and Arnett,F.C., editors. Mosby, London.

21. Clarke,A.E., Bloch,D.A., Medsger,T.A., Jr., and Oddis,C.V. 1995. A longitudinal study of functional disability in a national cohort of patients with polymyositis/dermatomyositis. *Arthritis Rheum* 38:1218-1224.

22. Villalba,L., Hicks,J.E., Adams,E.M., Sherman,J.B., Gourley,M.F., Leff,R.L., Thornton,B.C., Burgess,S.H., Plotz,P.H., and Miller,F.W. 1998. Treatment of refractory myositis: a randomized crossover study of two new cytotoxic regimens. *Arthritis Rheum* 41:392-399.

23. Levine,T.D. 2005. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 52:601-607.

24. Amato,A.A. and Griggs,R.C. 2003. Unicorns, dragons, polymyositis, and other mythological beasts. *Neurology* 61:288-289.

25. Lampa,J., Nennesmo,I., Einarsdottir,H., and Lundberg,I. 2001. MRI guided muscle biopsy confirmed polymyositis diagnosis in a patient with interstitial lung disease. *Ann.Rheum Dis.* 60:423-426.

26. Benveniste,O., Cherin,P., Maisonobe,T., Merat,R., Chosidow,O., Mouthon,L., Guillevin,L., Flahault,A., Burland,M.C., Klatzmann,D. *et al.* 2001. Severe perturbations of the blood T cell repertoire in polymyositis, but not dermatomyositis patients. *J.Immunol* 167:3521-3529.

27. Dion,E., Cherin,P., Payan,C., Fournet,J.C., Papo,T., Maisonobe,T., Auberton,E., Chosidow,O., Godeau,P., Piette,J.C. *et al.* 2002. Magnetic resonance imaging criteria for distinguishing between inclusion body myositis and polymyositis. *J.Rheumatol.* 29:1897-1906.

28. Christopher-Stine,L. and Plotz,P.H. 2004. Adult inflammatory myopathies. *Best.Pract.Res.Clin Rheumatol.* 18:331-344.

29. Wiesinger,G.F., Quittan,M., Aringer,M., Seeber,A., Volc-Platzer,B., Smolen,J., and Graninger,W. 1998. Improvement of physical fitness and muscle strength in polymyositis/dermatomyositis patients by a training programme. *Br.J.Rheumatol.* 37:196-200.

30. Park,J.H., Qi,J., Kroop,S.F., and Olsen,N.J. 2005. Preliminary trial of creatine and magnesium supplementation in myositis patients. *Arthritis Rheum* 52:S316 (Abstr.)

31. Yunis,E.J. and Samaha,F.J. 1971. Inclusion body myositis. *Lab Invest* 25:240-248.

32. Askanas,V. and Engel,W.K. 2006. Inclusion-body myositis: a myodegenerative conformational disorder associated with Abeta, protein misfolding, and proteasome inhibition. *Neurology* 66:S39-S48.

33. Oddis,C.V. and Medsger,T.A., Jr. 1995. Inflammatory myopathies. *Baillieres Clin Rheumatol.* 9:497-514.

34. Engel,W.K. and Askanas,V. 2006. Inclusion-body myositis: clinical, diagnostic, and pathologic aspects. *Neurology* 66:S20-S29.

35. Rutkove,S.B., Parker,R.A., Nardin,R.A., Connolly,C.E., Felice,K.J., and Raynor,E.M. 2002. A pilot randomized trial of oxandrolone in inclusion body myositis. *Neurology* 58:1081-1087.

36. Hansen,K.E., Hildebrand,J.P., Ferguson,E.E., and Stein,J.H. 2005. Outcomes in 45 patients with statin-associated myopathy. *Arch.Intern.Med.* 165:2671-2676.

37. Rundek,T., Naini,A., Sacco,R., Coates,K., and DiMauro,S. 2004. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch.Neurol.* 61:889-892.

38. Lamperti,C., Naini,A.B., Lucchini,V., Prelle,A., Bresolin,N., Moggio,M., Sciacco,M., Kaufmann,P., and DiMauro,S. 2005. Muscle coenzyme Q10 level in statin-related myopathy. *Arch.Neurol.* 62:1709-1712.

39. Wortmann,R.L. 2005. Dose-related statin myopathy: is it an issue? *Cleve.Clin J.Med.* 72:751-3, 756.