

Is it really myositis? A consideration of the differential diagnosis

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Purpose of review

The idiopathic inflammatory myopathies are an important and treatable group of disorders. However, the potential toxicity associated with the immune therapeutic regimens used to treat these disorders may be significant; therefore, accurate diagnosis before such treatment is essential. The differential diagnosis is potentially large. Accurate diagnosis usually depends on a combination of careful clinical assessment in conjunction with detailed laboratory investigations. Muscle biopsy remains essential in achieving an accurate diagnosis that will then guide treatment. This review describes the diagnostic approach used.

Recent findings

There has been debate over the requirements for an accurate diagnosis of inflammatory myopathy (*i.e.*, polymyositis and dermatomyositis). It is increasingly recognized that there can be clinical and muscle histopathologic overlap between the features of inflammatory myopathies and those of other muscle disorders, in particular, the genetic muscular dystrophies. Pathologic findings of inflammation and major histocompatibility complex upregulation, although typical of inflammatory myopathies, have been shown to occur in some muscular dystrophies, complicating the diagnostic process. Inclusion body myositis is much less responsive to immunotherapy and is now recognized as the most common acquired muscle disease in those older than 50 years of age. It is likely that genetic muscular dystrophies and inclusion body myositis account for some cases of apparently "treatment-resistant" myositis.

Summary

A thorough clinical assessment, including a detailed family history, complemented by electromyography and creatine kinase measurements, should be undertaken in any patient with presumed idiopathic inflammatory myopathy. In addition, a muscle biopsy remains essential in all cases. A precise tissue diagnosis confirming features of an active inflammatory process should be achieved before immunosuppressive treatment is commenced. An increasing array of immunocytochemical and histoenzymatic stains now allows a full analysis and will help to confirm or exclude virtually all the differential diagnostic possibilities considered in this review. Electron microscopy may also be valuable in selected cases. Close collaboration between clinicians and muscle pathologists is essential in allowing the most accurate interpretation of myopathologic findings in the clinical context.

Keywords

myositis, inflammatory myopathies, muscular dystrophies, diagnosis

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Abbreviations

BMD	Becker muscular dystrophy
CK	creatine kinase
DM	dermatomyositis
DMD	Duchenne muscular dystrophy
IBM	inclusion body myositis
IIM	idiopathic inflammatory myopathy
LGMD	limb-girdle muscular dystrophy
MHC	major histocompatibility complex
PM	polymyositis

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Introduction

Myositis is strictly a term that is used to describe infection or inflammation of skeletal muscle. In clinical practice, the term is often used synonymously with the so-called idiopathic inflammatory myopathies (IIMs), a group of disorders characterized clinically by muscle weakness (principally proximal) and fatigue and pathologically by mononuclear inflammatory infiltrates in muscle [1]. The main clinical entities in the group are dermatomyositis (DM) and polymyositis (PM) [2]. They are, by definition, considered primary autoimmune diseases directed at as yet unidentified antigens within skeletal muscle. Inclusion body myositis (IBM) had previously been considered another member of the group of IIMs, but most investigators now consider this to be a primary degenerative disease of muscle in which there may be secondary inflammatory changes [3•].

Making a diagnosis of PM and DM is essential because of the treatability of these disorders, their association with malignancy and autoimmune rheumatic disorders, and the frequency of multisystem involvement. There are, however, a number of myopathic and neurogenic disorders that may cause diagnostic difficulty. It is essential that these disorders be differentiated from IIM, particularly in view of the potential toxicity of immunosuppressive therapy.

This review summarizes the clinical features of IIM, discusses common pitfalls in diagnosis, and briefly considers some of the conditions that may cause diagnostic confusion.

Clinical features of inflammatory myopathies

The clinical features of the inflammatory myopathies have been reviewed elsewhere [4,5,6••]. PM and DM are typically of subacute onset and are characterized by the development of progressive, symmetric, and usually painless, predominantly proximal muscle weakness. The weakness generally occurs earlier and is more severe in the pelvic girdle than the shoulder girdle. IBM is a more chronic disease, and diagnosis can be delayed by a number of years after symptom onset.

The diagnosis of DM is established by the presence of weakness associated with a rash on sun-exposed parts, elevation of creatine kinase (CK) activity, myopathic electromyographic findings, and a distinctive histopathologic picture. Although the onset is typically subacute, it can sometimes develop acutely over days. Presentation without a rash or with a typical rash but no apparent muscle pathology may occur rarely. The presence of the rash, however, is virtually pathognomonic of the condition. In children with the rash and muscle weakness, it may be reasonable not to consider a muscle biopsy in favor of an MRI scan, but we always perform muscle biopsies in our adult [older than 16 years] population.

Inclusion body myositis has a more chronic course, and a selective and asymmetric pattern of muscle involvement not usually seen in PM or DM may be helpful diagnostically. Patients typically develop wasting of the long finger flexors and the quadriceps, resulting in frequent falls. CK elevation is relatively modest and histology is distinctive. It is also resistant to therapy with conventional immunosuppressive treatments [6••].

Polymyositis is often the most diagnostically challenging because it lacks characteristic cutaneous manifestations (compared with DM), a unique distribution of weakness (compared with IBM) or a completely specific myopathologic appearance. There has recently been much debate regarding its diagnosis and differentiation from IBM [4,7••].

The most widely used criteria for the diagnosis of PM and DM are those of Bohan and Peter [8]. However, in the 1977 study of Bohan *et al.* [9], proximal muscle weakness was the presenting symptom in only 69% of patients, CK levels were normal in 5%, and more than 10% had a normal electromyogram, with many more lacking the typical triad of features described below. Furthermore, 12.5% of muscle biopsy samples revealed no abnormalities and were atypical in many other patients. Other more specific criteria have recently been proposed [4,10].

Depending on the individual case, the history should be directed to exclude specific alternative diagnoses, with

particular attention to the family history and medication history. The standard supportive laboratory investigations merit further consideration.

Serologic tests

Although aspartate and alanine aminotransferases, lactate dehydrogenase, and aldolase levels are elevated in IIM, the most widely used muscle enzyme assay is CK. This can be elevated as much as 50-fold in PM and DM but rarely much higher; serum CK that is elevated more than 100-fold should call the diagnosis into question. In IBM, the CK is more mildly elevated, as much as fivefold. CK levels may, however, rarely be normal in IIMs, even in the presence of inflammatory changes found on biopsy. The explanation for this is unclear but emphasizes the importance of undertaking muscle biopsy and not relying on CK for diagnostic purposes [11,12]. CK levels may also fluctuate from day to day (increasing significantly after major exercise), even in the absence of any intervention. Furthermore, CK elevation is nonspecific, merely indicating the presence of muscle damage, and should never be regarded as a diagnostic test. CK is elevated in muscular dystrophies and in some metabolic myopathies (particularly if there is any degree of rhabdomyolysis) and although the degree of elevation can be informative, there is considerable overlap.

A search for autoantibodies may be diagnostically useful in PM and DM and provide a clue to disease subtype. Indeed, the absence of a positive antinuclear antibody and an anti-Jo antibody should also raise doubts about the diagnosis. Although autoantibodies have been found in IBM [13,14], they are unusual. They are not associated with muscular dystrophies or metabolic myopathies, although their presence should not exclude these diagnoses [15]. The presence of acetylcholine receptor antibodies points to a diagnosis of myasthenia gravis.

Electromyography

Electromyographic findings in IIM are not specific and are useful only insofar as they confirm an active myopathic process. In PM and DM, there is evidence of increased membrane irritability such as positive sharp waves, fibrillation potentials, and complex repetitive discharges. Myopathic motor unit action potentials that are polyphasic and of short duration and low amplitude are seen. Finally, there is early or rapid recruitment of motor unit action potentials.

In IBM, there may be additional evidence of neurogenic changes with prolonged, large-amplitude motor unit action potentials. This can lead to diagnostic confusion with motor neuron disease [16].

Muscle biopsy

A definitive diagnosis of IIM relies on muscle biopsy, and erroneous interpretation of a muscle biopsy specimen is probably the most common cause of a clinical

misdiagnosis of IIM [17]. There are many pitfalls in both the analysis and interpretation of a muscle biopsy specimen, and these have been reviewed [17].

The key myopathologic feature of PM is considered to be endomysial lymphocytic infiltration. However, similar infiltration has been reported in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) [18], facioscapulohumeral dystrophy [19], limb-girdle muscular dystrophy (LGMD) type 2B [20], and congenital muscular dystrophy with primary merosin deficiency [21] as well as in IBM. It is therefore very important to also perform appropriate immunocytochemical staining in all cases to assess for deficiency of any of the known proteins that cause muscular dystrophies. In addition, genetic testing can be very helpful, such as the genetic test that is now widely available for facioscapulohumeral dystrophy. In IBM, there are additionally Congo red–positive amyloid deposits and rimmed vacuoles that represent an important diagnostic clue, and filamentous inclusions are usually present on electron microscopy.

The key myopathologic feature in DM is perivascular B cell–predominant inflammation associated with microinfarcts and perifascicular atrophy. Muscle inflammation

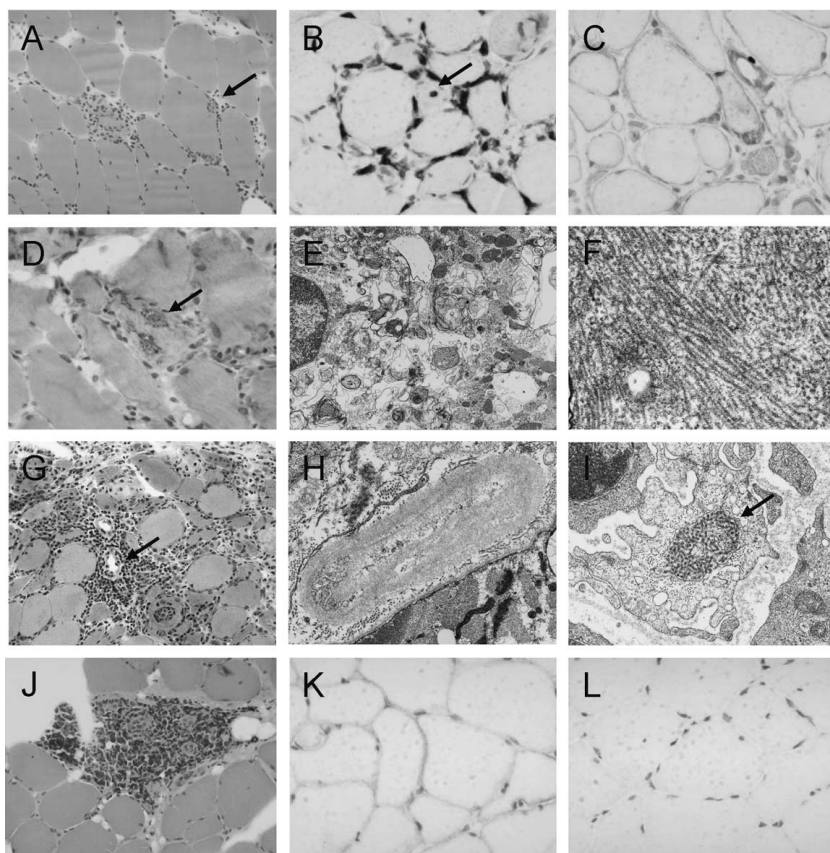
can, however, be patchy and is affected by the early use of steroids [22]. In cases in which typical changes are not found, particular care must be taken to exclude other possible diagnoses, and immunohistochemistry and enzyme studies should be undertaken on biopsy samples.

Major histocompatibility complex (MHC) class I proteins are not usually expressed on muscle fibers. However, in IIM, MHC class I is detectable by immunohistochemistry [23,24]. MHC class I is present not only on degenerating fibers but also in apparently normal fibers and in areas without overt inflammation. For this reason, it has been suggested that immunohistochemical evidence of MHC upregulation be included in the diagnostic criteria for IIM [4]. Although MHC upregulation is very helpful, it is not specific for IIMs. MHC class I upregulation, together with inflammatory infiltration, may also be found in muscle from patients with dysferlinopathies and DMD, and, as in IIM, MHC is present on normal as well as actively degenerating fibers [25•]. Interestingly, it has been observed that conditional upregulation of MHC class I in mouse skeletal muscle is sufficient to cause autoimmune myositis [26].

Examples of histopathologic findings in IIMs, IBM, and muscular dystrophy are shown in Figure 1.

Figure 1. Inflammatory changes can be found in muscle biopsy specimens from patients with a number of conditions including the idiopathic inflammatory myopathies and some types of muscular dystrophy

In polymyositis, the inflammatory cell infiltrate is predominantly endomysial (A) with infiltration of intact myofibers (arrow). CD8-positive T lymphocytes are the dominant cell type (B) and can be seen within nonnecrotic fibers (arrow). There is widespread expression of major histocompatibility complex (MHC) class I at the periphery of myofibers (C). Inclusion body myositis is characterized by the presence of rimmed vacuoles (D, arrow) that on ultrastructural examination are found to contain whorled membranous material (E) and randomly oriented 12- to 18-nm diameter fibrils (F). In dermatomyositis, the lymphocytic infiltrate is often perivascular in distribution (G, arrow), although it extends into the endomysium. Ultrastructural examination shows a variety of pathologic findings in the capillaries including empty loops of basal lamina indicating capillary loss (H) and the characteristic tubuloreticular inclusions in endothelial cells (I). Inflammation may be a feature of dysferlinopathy (J) in which the normal sarcolemmal distribution of dysferlin immunohistochemical staining (K) is absent (L). Hematoxylin and eosin (A, D, G, J); CD8 immunohistochemistry (B); MHC class I immunohistochemistry (C); electron microscopy (E, F, H, I); dysferlin immunohistochemistry (K, L). Original magnifications: $\times 40$ (A, G, J); $\times 80$ (B, C, D, K, L); $\times 5000$ (E, H); $\times 1600$ (F); $\times 12,000$ (I).



Consideration of the differential diagnosis

A broad differential diagnosis is presented in Table 1. In the presence of a typical rash in association with the other clinical features of DM, the diagnosis is often straightforward. Difficulties arise in patients with suspected PM or with DM without dermatitis. It is also important to review the diagnosis in patients who were considered to have an IIM but who have not responded to immunotherapy and are often labeled as having treatment-resistant PM or DM.

Alternative diagnoses should also be systematically excluded in patients with atypical investigation results, especially in patients with normal muscle biopsy specimens. A few specific disorders are briefly considered here.

Muscular Dystrophies

Limb-girdle muscular dystrophy

The LGMDs are a heterogeneous group of disorders presenting with a face-sparing, predominantly proximal, progressive muscular weakness associated with elevated muscle enzyme levels and dystrophic features on biopsy specimens (*i.e.*, degeneration and regeneration of muscle fibers) [27]. In recent years, there have been many gene discoveries [28•,29••]. There are at least 10 recessive forms, classed as type 2 LGMD, constituting 90% of cases [29••]. The proteins implicated are diverse and include sarcolemmal components responsible for membrane stabilization, proteases, nuclear membrane proteins, and others.

The distribution of weakness is often similar to that of IIM [30], and dysphagia may also occur [31]. Specific clinical features vary between subtypes [29••]; for example, the sarcoglycanopathies (LGMDs 2C to 2F) pre-

sent very much like the dystrophinopathies, with cardiomyopathy and calf hypertrophy.

Dysferlinopathy: limb-girdle muscular dystrophy 2B and Miyoshi myopathy

LGMD2B and Miyoshi myopathy are caused by mutations in the dysferlin gene. Dysferlin is an integral sarcolemmal protein believed to be involved in membrane fusion and repair [32••,33]. Dysferlinopathy is an autosomal recessive condition that is clinically heterogeneous [34], even in cases with identical genetic defects [35]. It usually presents in early adulthood with weakness in a proximal (LGMD2B), proximal-distal, or distal (Miyoshi myopathy) distribution.

Miyoshi myopathy starts distally in the legs, particularly in gastrocnemius and soleus muscles. Proximal progression to the pelvic girdle and the upper limbs then occurs, although the small muscles of the hand are spared. LGMD2B also usually affects the lower limbs years before the upper limbs and, as in IBM, the quadriceps muscle is often weaker than the hip muscles. Clinical clues include the fact that periscapular muscles are usually relatively spared.

Creatine kinase levels are always elevated, even in the preclinical stages, and can often be much higher than in IIM with levels in the tens of thousands. Electromyography is myopathic. Muscle histology can also be confusing. Patients with both LGMD2B and Miyoshi myopathy may have significant inflammation demonstrated on muscle biopsy samples [36,37] both endomysially and perivascularly [25•]. Muscle fibers also aberrantly express MHC class I, as in IIM [25•]. The key to diagnosis is immunohistochemistry findings that demonstrate an absence of sarcolemmal dysferlin. Genetic diagnosis is difficult due to the very large size of the gene (150 kb over 55 exons). Interestingly, the SJL/J mouse, which has been used as a model of autoimmune myositis [38], has been found to have a mutation in dysferlin, resulting in greatly reduced dysferlin expression [39].

Dystrophinopathy

Duchenne muscular dystrophy is the most common of the dystrophies and results from mutations in the plasma membrane-associated protein dystrophin [40••]. DMD rarely poses diagnostic problems, but other presentations of dystrophinopathy may be more difficult to differentiate from IIM.

Becker muscular dystrophy

Becker muscular dystrophy usually results from dystrophin mutations that result in abnormal but at least partly functional protein, whereas in DMD, there is loss of dystrophin expression. The age at onset in BMD is later than that in DMD, usually between the ages of 5 and 15 years, although it can present as late as the fourth de-

Table 1. Differential diagnosis of inflammatory myopathy

Muscular dystrophies, in particular:
Limb-girdle muscular dystrophy, especially type 2B (dysferlinopathy)
Miyoshi myopathy (dysferlinopathy)
Dystrophinopathy (Becker muscular dystrophy, isolated female manifesting carriers of dystrophinopathy)
Faciocapulohumeral dystrophy
Metabolic myopathies, in particular:
Myophosphorylase deficiency (McArdle disease)
Phosphofructokinase deficiency
Acid maltase deficiency
Mitochondrial myopathy
Endocrine myopathies
Drug-induced myopathy
D-penicillamine
Quinidine
Procainamide
β-hydroxy-β-methylglutaryl-coenzyme A reductase inhibitors (statins)
Interferon alpha
Interleukin-2
Motor neuron disease
Spinal muscular atrophy (late-onset forms)
Myasthenia gravis

cade. The pattern of wasting is very similar to that of DMD, but the severity is usually much less. Pelvic girdle and thigh muscles are involved first, with relatively early calf pseudohypertrophy. As with LGMD2B, confusion can arise with IBM due to frequent prominent involvement of the quadriceps muscle. Shoulder girdle weakness usually develops subsequently. Cardiac disease and mental retardation are rarer than in DMD, and this makes differentiation from IIM more difficult. Dystrophinopathies may be responsive to corticosteroids [41], and muscle biopsy sample can show mononuclear infiltrates, giving rise to further diagnostic difficulty.

The family history of X-linked inheritance can help clarify the diagnosis, but approximately one third of cases represent new mutations. Ninety-eight percent of mutations can be detected by a multiplex polymerase chain reaction screening 19 exons of the dystrophin gene, one of the largest in the genome [40••]. Diagnosis can also be confirmed by immunostaining muscle biopsy specimens for dystrophin. The protein is absent in DMD, but in BMD, although it is present, there is usually only partial sarcolemmal staining. The immunohistochemistry findings may, however, be normal. Western blot for dystrophin in muscle allows the determination of both the quantity and size of the molecule, reduced in 80% of patients with BMD and increased in approximately 5%. Fifteen percent of BMD patients have normal-size protein of reduced quantity.

Female carriers of dystrophinopathy

Because of lyonization (the random inactivation of one X chromosome during early development), most female carriers of a dystrophin mutation will switch off production of the mutant gene in 50% of chromosomes and express enough normal dystrophin from the remainder to prevent phenotypic expression. In some cases, however, nonrandom inactivation results in significantly reduced dystrophin levels and phenotypic expression [42]. Muscle weakness in female carriers occurs in approximately 19% of families with DMD and 14% of families with BMD [43].

Manifesting female carriers present from their late teens onward, with progressive proximal weakness of variable severity. The inflammation seen in DMD and BMD is, however, usually absent, and muscle biopsy samples reveal scattered muscle fibers with dystrophin levels reduced or absent on immunohistochemistry.

Facioscapulohumeral dystrophy

Facioscapulohumeral dystrophy is the third most common muscular dystrophy after DMD and myotonic dystrophy. Selective weakness is the main distinguishing feature. Patients commonly present with onset in the face, and subsequent periscapular and humeral weakness. Later progression to the lower limbs is seen, par-

ticularly distally, the reverse of the progression in the IIMs. A significant minority of muscle biopsy specimens from patients with facioscapulohumeral dystrophy show inflammatory change [19]. Almost all patients with facioscapulohumeral dystrophy harbor deletions of a tandem repeat, termed D4Z4, on chromosome 4q, and genetic diagnosis is available. Interestingly, there is no gene known at this locus, and it appears that the deletion modulates expression of more proximal genes on chromosome 4, an effect termed positional variegation [44].

Metabolic myopathies

Defects in many aspects of cellular metabolism can cause myopathy. Genetic metabolic myopathies present from anytime in childhood to adulthood and tend to be slowly progressive. It is unusual for the metabolic myopathies to show the classic electromyographic triad described for PM and DM. Furthermore, a biopsy specimen does not demonstrate inflammation, and with appropriate histochemical staining, a specific metabolic defect can often be identified. Sometimes there is diagnostic confusion if there has been rhabdomyolysis. In this setting, the biopsy specimen may appear to show an inflammatory infiltrate, but careful analysis usually reveals that it is only necrotic fibers that are surrounded by inflammatory cells and macrophages. In contrast, in IIMs, nonnecrotic fibers are the subject of inflammatory attack.

Several metabolic myopathies present with fixed or progressive proximal muscle weakness. The main classes are muscle glycogenoses, lipid storage disorders, and mitochondrial myopathies.

Muscle glycogenoses

The glycogenoses (glycogen storage diseases) are autosomal recessive enzyme deficiencies impairing glycogen metabolism. They may present with either a hepatic or muscle phenotype.

The most common of the muscle glycogenoses is McArdle disease (type 5 glycogenosis) caused by a deficiency of myophosphorylase. Onset is usually in early adulthood, typically with myalgia occurring soon after starting exercise. Extreme exertion may result in myoglobinuria. Some patients present late with a relatively fixed proximal myopathy, usually with a history of fatigue and exercise intolerance. Screening is by the forearm lactate test in which the normal increase in muscle lactate levels caused by repeated exercise is abolished. The nonischemic version of the test has been shown to be as effective as the ischemic lactate test and is less painful [45]. False positives are frequent, so the result must be confirmed by biochemical analysis of muscle enzyme activity or histochemical staining for myophosphorylase on muscle biopsy. A genetic test is also available.

Muscle phosphofructokinase deficiency (Tarui disease/type 7 glycogenosis) usually causes exercise-induced myalgia similar to McArdle disease, but a minority of patients present with a late-onset proximal myopathy [46,47], sometimes with no history of exercise intolerance.

The adult-onset form of acid maltase deficiency (type 2 glycogenosis) causes proximal muscle weakness that is greater in the pelvic than the shoulder girdle and can be mistaken clinically for PM or LGMD. CK levels are elevated in almost all cases. Electromyography shows non-specific myopathic changes but may be normal in as many as 25% of patients, and the muscle biopsy specimen usually shows lysosomal vacuolation but again may be normal in as many as 25% of patients [48]. Clinically, a major clue is relatively early diaphragmatic involvement [49]. The rarer brancher deficiency glycogenosis (type 4 glycogenosis) may also present as progressive proximal myopathy [50], although this is usually a rapidly progressive juvenile disease with marked hepatic involvement.

Lipid storage disorders

Carnitine palmitoyl transferase II deficiency is the most common of the lipid storage disorders. It usually manifests as muscle pain induced by prolonged exercise. Myoglobinuria is frequent. However, some patients present with a painless proximal myopathy. Muscle biopsy specimens show abnormal lipid accumulations, and muscle tissue can be used for specific enzyme assays. Other rarer lipid storage disorders can also present with proximal myopathy, including primary carnitine deficiency [51], which is easily treatable with carnitine supplementation.

Mitochondrial myopathies

Mitochondrial disease is very heterogeneous and can present in many ways including ophthalmoplegia, stroke, and epilepsy [52]. Mitochondrial myopathy usually presents as a symmetric proximal myopathy associated with fatigue, much like IIM.

Clinical clues prompting investigation of mitochondrial disease are few, and a detailed history and examination

are relied on to find associated features such as diabetes or evidence of a family history of features consistent with those of mitochondrial disease such as deafness, diabetes, and developmental delay. Pedigrees may demonstrate maternal inheritance in the case of mitochondrial DNA disorders, but nuclear mitochondrial diseases are inherited in a Mendelian fashion. The electromyogram is often normal. Diagnosis relies on a combination of clinical findings, muscle histology, biochemical studies, and molecular genetics [53•]. Muscle biopsy is the crucial part of the investigation, both for positive identification and for differentiation from other proximal myopathies. However, classic histologic features such as the presence of ragged red fibers are not entirely specific and may be seen in IBM or acid maltase deficiency, nor does their absence exclude mitochondrial myopathy.

Endocrine myopathies

A number of endocrinopathies are associated with proximal myopathy [54]. The features are summarized in Table 2. Thyroid and parathyroid dysfunction is easily screened by checking T4, thyroid-stimulating hormone, calcium, and phosphate levels. Cushing syndrome is usually clinically obvious from other stigmata by the time significant myopathy is evident, as is acromegaly. A history of exogenous steroid administration should always lead one to suspect steroid myopathy. In all these cases, myopathy resolves with treatment of the underlying endocrine disorder. Hypothyroidism is the most likely to mimic myositis clinically, with significantly elevated CK and inflammation in as many as 12.5% of biopsy samples [55].

Specific considerations in the differential diagnosis of inclusion body myositis

Although the most common condition that IBM is mistaken for is PM, there are a number of other differential diagnostic considerations [7••].

The early-adult onset distal myopathy with rimmed vacuoles (Nonaka myopathy) is an autosomal recessive disorder that is allelic with hereditary IBM, both of which are owing to mutations in the GNE gene [56]. Initial weakness occurs in the distal leg anterior compartment, and serum CK is moderately elevated, usually no

Table 2. Features of endocrinopathies associated with proximal myopathy

Endocrine disorder	Distribution	CK	Notes
Hypothyroidism	Proximal	↑/↑↑	Myoedema; type II atrophy on Bx, occasionally inflammatory
Hyperthyroidism	Proximal + distal ± bulbar	N/↓	Weakness > wasting; frequent myalgia; Bx sample normal
Cushing syndrome/steroid myopathy	Proximal	N	Fibrillation potentials absent on EMG
Hypoparathyroidism	Proximal	N/mild ↑	Very rarely causes myopathy; usually tetany; EMG/Bx sample normal
Hyperparathyroidism	Proximal	N	Hyperreflexia
Osteomalacia		N	Type II atrophy on Bx
Acromegaly	Proximal	N/↑	Late in disease course, when clinically obvious

Bx, biopsy; EMG, electromyogram; N, normal.

more than five times normal. The quadriceps muscle, often prominently affected in sporadic IBM, is typically spared. However, there is much overlap. Furthermore, in addition to the typical vacuolation of fibers found on muscle biopsy, endomysial inflammation can also be seen in distal myopathy with rimmed vacuoles [57•].

Vacuolar myopathy similar to sporadic IBM but without inflammation is also seen in distal myopathies, including Welander distal myopathy and tibial muscular dystrophy. Proximal involvement is, however, rare in Welander distal myopathy and occurs very late in tibial muscular dystrophy, and onset of both disorders typically begins in the long finger extensors (compare with finger flexor involvement in IBM). Miyoshi myopathy was discussed previously. A recent pathologic study of three cases of X-linked Emery-Dreifuss muscular dystrophy revealed an inflammatory process very similar to that of IBM [58]. However, in general X-linked Emery-Dreifuss muscular dystrophy poses little diagnostic challenge because early contractures, mainly of the elbows and ankles, are a prominent feature, and patients develop limitation of spinal flexion.

Conclusion

An accurate diagnosis of IIM is important because of the treatability of these conditions. Furthermore, misdiagnosis may lead to unnecessary exposure of patients to toxic immunotherapies.

Many neuromuscular disorders, in particular the genetic muscular dystrophies and metabolic myopathies, may potentially mimic the myositides. Usually a detailed clinical and myopathologic evaluation will allow the correct diagnosis to be made. Lack of response to immunotherapy should always lead to a review of the diagnosis before considering further and often increasingly toxic immunotherapies. Close collaboration between clinicians and muscle pathologists is essential to achieve the optimal management in patients with IIMs.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

- 1 Engel AG, Arahata K: Mononuclear cells in myopathies: quantitation of functionally distinct subsets, recognition of antigen-specific cell-mediated cytotoxicity in some diseases, and implications for the pathogenesis of the different inflammatory myopathies. *Hum Pathol* 1986, 17:704–721.
 - 2 Dalakas MC: Polymyositis, dermatomyositis and inclusion-body myositis. *N Engl J Med* 1991, 325:1487–1498.
 - 3 Askanas V, Engel WK: Proposed pathogenetic cascade of inclusion-body myositis: importance of amyloid-beta, misfolded proteins, predisposing genes, and aging. *Curr Opin Rheumatol* 2003, 15:737–744.
- This is a detailed review of what is currently known of the pathogenesis of IBM.
- 4 Dalakas MC, Hohlfeld R: Polymyositis and dermatomyositis. *Lancet* 2003, 362:971–982.
 - 5 Hilton-Jones D: Diagnosis and treatment of inflammatory muscle diseases. *J Neurol Neurosurg Psychiatry* 2003, 74(suppl 2):ii25–ii31.

- 6 Mastaglia FL, Garlepp MJ, Phillips BA, et al.: Inflammatory myopathies: clinical, diagnostic and therapeutic aspects. *Muscle Nerve* 2003, 27:407–425.
- A highly comprehensive recent review of the idiopathic inflammatory myopathies.
- 7 van der Meulen MF, Bronner IM, Hoogendijk JE, et al.: Polymyositis: an over-diagnosed entity. *Neurology* 2003, 61:316–321.
- A detailed clinicopathologic study of the subclassification of inflammatory myopathy by Bohan and Peter and more recent histopathologic criteria are reported.
- 8 Bohan A, Peter JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975, 292:344–347.
- 9 Bohan A, Peter JB, Bowman RL, et al.: Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine (Baltimore)* 1977, 56:255–286.
- 10 Mastaglia FL, Phillips BA: Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria. *Rheum Dis Clin North Am* 2002, 28:723–741.
- 11 Gran JT, Myklebust G, Johansen S: Adult idiopathic polymyositis without elevation of creatine kinase. Case report and review of the literature. *Scand J Rheumatol* 1993, 22:94–96.
- 12 Rider LG, Miller FW: Laboratory evaluation of the inflammatory myopathies. *Clin Diagn Lab Immunol* 1995, 2:1–9.
- 13 Hengstman GJ, Ter Laak HJ, van Engelen BG, et al.: Anti-Jo-1 positive inclusion body myositis with a marked and sustained clinical improvement after oral prednisone. *J Neurol Neurosurg Psychiatry* 2001, 70:706.
- 14 Selva-O'Callaghan A, Mijares-Boeckh-Behrens T, Labrador-Horrillos M, et al.: Anti-PM-Scl antibodies in a patient with inclusion body myositis. *Rheumatology (Oxford)* 2003, 42:1016–1018.
- 15 Funauchi M, Nozaki Y, Yoo BS, et al.: A case of limb-girdle muscular dystrophy with serum anti-nuclear antibody which led to a mistaken diagnosis of polymyositis. *Clin Exp Rheumatol* 2002, 20:707–708.
- 16 Dabby R, Lange DJ, Trojaborg W, et al.: Inclusion body myositis mimicking motor neuron disease. *Arch Neurol* 2001, 58:1253–1256.
- 17 Dalakas MC: Muscle biopsy findings in inflammatory myopathies. *Rheum Dis Clin North Am* 2002, 28:779–798.
- 18 Lundberg I, Brengman JM, Engel AG: Analysis of cytokine expression in muscle in inflammatory myopathies, Duchenne dystrophy, and non-weak controls. *J Neuroimmunol* 1995, 63:9–16.
- 19 Arahata K, Ishihara T, Fukunaga H, et al.: Inflammatory response in facioscapulohumeral muscular dystrophy (FSHD): immunocytochemical and genetic analyses. *Muscle Nerve* 1995, 2:S56–S66.
- 20 Fanin M, Angelini C: Muscle pathology in dysferlin deficiency. *Neuropathol Appl Neurobiol* 2002, 28:461–470.
- 21 Pegoraro E, Mancias P, Swerdlow SH, et al.: Congenital muscular dystrophy with primary laminin alpha2 (merosin) deficiency presenting as inflammatory myopathy. *Ann Neurol* 1996, 40:782–791.
- 22 Matsubara S, Hirai S, Sawa Y: Pulsed intravenous methylprednisolone therapy for inflammatory myopathies: evaluation of the effect by comparing two consecutive biopsies from the same muscle. *J Neuroimmunol* 1997, 76:75–80.
- 23 van der Pas J, Hengstman GJ, Ter Laak HJ, et al.: Diagnostic value of MHC class I staining in idiopathic inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 2004, 75:136–139.
- 24 Civatte M, Schleinitz N, Krammer P, et al.: Class I MHC detection as a diagnostic tool in noninformative muscle biopsies of patients suffering from dermatomyositis (DM). *Neuropathol Appl Neurobiol* 2003, 29:546–552.
- 25 Confalonieri P, Oliva L, Andreetta F, et al.: Muscle inflammation and MHC class I up-regulation in muscular dystrophy with lack of dysferlin: an immunopathological study. *J Neuroimmunol* 2003, 142:130–136.
- This is an interesting pathologic study comparing biopsy findings in dysferlinopathy with those seen in PM.
- 26 Nagaraju K, Raben N, Loeffler L, et al.: Conditional up-regulation of MHC class I in skeletal muscle leads to self-sustaining autoimmune myositis and myositis-specific autoantibodies. *Proc Natl Acad Sci U S A* 2000, 97:9209–9214.
- 27 Bushby KM: Diagnostic criteria for the limb-girdle muscular dystrophies: report of the ENMC Consortium on limb-girdle dystrophies. *Neuromuscul Disord* 1995, 5:71–74.
- 28 Kirschner J, Bonnemann CG: The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. *Arch Neurol* 2004, 61:189–199.
- This is a good general summary of the clinical and molecular aspects of congenital muscular dystrophies and LGMD.

- 29 Zatz M, de Paula F, Starling A, et al.: The 10 autosomal recessive limb-girdle muscular dystrophies. *Neuromuscul Disord* 2003, 13:532–544.
This is a detailed review of the clinical and molecular aspects of the recessive LGMDs.
- 30 Hoffman EP, Rao D, Pachman LM: Clarifying the boundaries between the inflammatory and dystrophic myopathies: insights from molecular diagnostics and microarrays. *Rheum Dis Clin North Am* 2002, 28:743–757.
- 31 Stubgen JP: Limb girdle muscular dystrophy: a radiologic and manometric study of the pharynx and esophagus. *Dysphagia* 1996, 11:25–29.
- 32 Bansal D, Miyake K, Vogel SS, et al.: Defective membrane repair in dysferlin-deficient muscular dystrophy. *Nature* 2003, 423:168–172.
This excellent study sheds light on the biologic role of dysferlin in calcium-dependent membrane fusion and repair.
- 33 Davis DB, Doherty KR, Delmonte AJ, et al.: Calcium-sensitive phospholipid binding properties of normal and mutant ferlin C2 domains. *J Biol Chem* 2002, 277:22883–22888.
- 34 Ueyama H, Kumamoto T, Horinouchi H, et al.: Clinical heterogeneity in dysferlinopathy. *Intern Med* 2002, 41:532–536.
- 35 Illarioshkin SN, Ivanova-Smolenskaya IA, Greenberg CR, et al.: Identical dysferlin mutation in limb-girdle muscular dystrophy type 2B and distal myopathy. *Neurology* 2000, 55:1931–1933.
- 36 McNally EM, Ly CT, Rosenmann H, et al.: Splicing mutation in dysferlin produces limb-girdle muscular dystrophy with inflammation. *Am J Med Genet* 2000, 91:305–312.
- 37 Rowin J, Meriggioli MN, Cochran EJ, et al.: Prominent inflammatory changes on muscle biopsy in patients with Miyoshi myopathy. *Neuromuscul Disord* 1999, 9:417–420.
- 38 Rosenberg NL, Ringel SP, Kotzin BL: Experimental autoimmune myositis in SJL/J mice. *Clin Exp Immunol* 1987, 68:117–129.
- 39 Bittner RE, Anderson LV, Burkhardt E, et al.: Dysferlin deletion in SJL mice (SJL-Dysf) defines a natural model for limb girdle muscular dystrophy 2B. *Nat Genet* 1999, 23:141–142.
- 40 Muntoni F, Torelli S, Ferlini A: Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol* 2003, 2:731–740.
This is an excellent review of the molecular genetics and associated phenotypes of the dystrophinopathies.
- 41 Escolar DM, Scacheri CG: Pharmacologic and genetic therapy for childhood muscular dystrophies. *Curr Neurol Neurosci Rep* 2001, 1:168–174.
- 42 Pegoraro E, Schimke RN, Garcia C, et al.: Genetic and biochemical normalization in female carriers of Duchenne muscular dystrophy: evidence for failure of dystrophin production in dystrophin-competent myonuclei. *Neurology* 1995, 45:677–690.
- 43 Hoogerwaard EM, Bakker E, Ippel PF, et al.: Signs and symptoms of Duchenne muscular dystrophy and Becker muscular dystrophy among carriers in The Netherlands: a cohort study. *Lancet* 1999, 353:2116–2119.
- 44 Tupler R, Gabellini D: Molecular basis of facioscapulohumeral muscular dystrophy. *Cell Mol Life Sci* 2004, 61:557–566.
- 45 Kazemi-Esfarjani P, Skomorowska E, Jensen TD, et al.: A nonischemic forearm exercise test for McArdle disease. *Ann Neurol* 2002, 52:153–159.
- 46 Argov Z, Barash V, Soffer D, et al.: Late-onset muscular weakness in phosphofructokinase deficiency due to exon 5/intron 5 junction point mutation: a unique disorder or the natural course of this glycolytic disorder? *Neurology* 1994, 44:1097–1100.
- 47 Sivakumar K, Vasconcelos O, Goldfarb L, et al.: Late-onset muscle weakness in partial phosphofructokinase deficiency: a unique myopathy with vacuoles, abnormal mitochondria, and absence of the common exon 5/intron 5 junction point mutation. *Neurology* 1996, 46:1337–1342.
- 48 Ausems MG, Lochman P, van Diggelen OP, et al.: A diagnostic protocol for adult-onset glycogen storage disease type II. *Neurology* 1999, 52:851–853.
- 49 Moufarrej NA, Bertorini TE: Respiratory insufficiency in adult-type acid maltase deficiency. *South Med J* 1993, 86:560–567.
- 50 Bornemann A, Besser R, Shin YS, et al.: A mild adult myopathic variant of type IV glycogenosis. *Neuromuscul Disord* 1996, 6:95–99.
- 51 Karmaniolas K, Ioannidis P, Liatis S, et al.: Primary carnitine deficiency in a male adult. *J Med* 2002, 33:105–110.
- 52 McFarland R, Taylor RW, Turnbull DM: The neurology of mitochondrial DNA disease. *Lancet Neurol* 2002, 1:343–351.
- 53 Taylor RW, Schaefer AM, Barron MJ, et al.: The diagnosis of mitochondrial muscle disease. *Neuromuscul Disord* 2004, 14:237–245.
This review provides a useful diagnostic approach to mitochondrial myopathy.
- 54 Alsheklee A, Kaminski HJ, Ruff RL: Neuromuscular manifestations of endocrine disorders. *Neurol Clin* 2002, 20:35–58, v–vi
- 55 Madariaga MG: Polymyositis-like syndrome in hypothyroidism: review of cases reported over the past twenty-five years. *Thyroid* 2002, 12:331–336.
- 56 Nishino I, Noguchi S, Murayama K, et al.: Distal myopathy with rimmed vacuoles is allelic to hereditary inclusion body myopathy. *Neurology* 2002, 59:1689–1693.
- 57 Yabe I, Higashi T, Kikuchi S, et al.: GNE mutations causing distal myopathy with rimmed vacuoles with inflammation. *Neurology* 2003, 61:384–386.
This case report demonstrates that patients with hereditary IBM may have inflammation on biopsy.
- 58 Fidzianska A, Rowinska-Marcinska K, Hausmanowa-Petrusewicz I: Coexistence of X-linked recessive Emery-Dreifuss muscular dystrophy with inclusion body myositis-like morphology. *Acta Neuropathol (Berl)* 2004, 107:197–203.