Myositis or dystrophy? Traps and pitfalls

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Inflammatory or necrotizing myopathies, myositis and other acquired myopathies, new insight in 2011.
Benveniste O et al. (Paris, France)
Observations on the classification of the inflammatory myopathies
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Summary

Some hereditary myopathies can mimic acquired myositis especially when they first present in adulthood with a limb-girdle distribution of weakness. Although inherited myopathies are generally painless and progress very slowly there are exceptions, which can further add to diagnostic confusion. The diagnosis is made even more difficult when inflammatory infiltrates are present on muscle biopsy. This is common in certain dystrophies in particular e.g. dysferlinopathies or facioscapulohumeral dystrophy. On the other hand, acquired (and treatable with immunosuppressants) necrotizing myopathies with anti-SRP antibodies can be very slowly progressive, with clinical and pathological features compatible with limb girdle dystrophies. These two situations can lead to either inappropriate immunosuppressant treatment in a patient with dystrophy, having mistaken it for an acquired inflammatory myopathy, or to therapeutic abstention in a patient with a treatable acquired myopathy thinking that it was a dystrophy. Pointers helping to distinguish between these two traps are here reviewed.

Many myopathies with non-inflammatory origin can mimic at their onset myositis. That is particularly likely if the onset is in adulthood, evolution is rapid, affecting predominantly limb girdle muscles, and even more if there is muscle pain. Such confounding diseases can be acquired, such as late onset nemaline myopathy (sometimes associated with monoclonal gammopathy) [1] or genetic disorders such as late-onset Pompe disease [2] or myotonic dystrophy type 2 (also known as proximal myotonic myopathy), which typically presents in middle-age and is often painful [3]. Generally, complementary investigations and especially muscle biopsy lead to the correct diagnosis. Furthermore, immunological and/or pathological methods to characterize myopathies (both acquired and inherited) have made dramatic progress during the last decade.
For instance, the presence of certain auto-antibodies in the blood, or the overexpression of MHC class I in muscle fibers on biopsies, can help in the diagnosis of inflammatory myopathies [4,5]. In the same vein, the classification of the dystrophies has been revolutionised by the discovery of the genes and proteins responsible for the disease [6]. Immunohistochemistry and/or Western blotting with antibody against the corresponding protein is routinely used for the diagnosis of the dystrophies. Nevertheless, despite all this recent progress in diagnostic techniques, all muscle specialists have experienced problems with diagnosis leading to over-treat of patients with dystrophy, thinking that it was an acquired inflammatory myopathy or, on the other hand, to therapeutic abstention in a patient with treatable acquired myopathy thinking that it was a dystrophy. We will consider both situations and see which laboratory findings may help to prevent falling into these two traps.

**False myositis**

**Representative case**

In 1991, a 27-year-old woman, with no family history of myopathy, presented with progressive proximal limb-girdle muscle weakness and myalgia over 6 months. She was able to walk without aid, but had difficulty standing up from a chair. Weakness was prominent in the proximal and axial muscles. She could swallow and breathe normally, eye and tongue movements were normal, and her speech was clear. No fasciculations were seen, and tendon reflexes and sensation were preserved.

Serum creatine kinase (CK) activity was 5000 U/L (normal < 170 U/L). Electromyography showed a myopathic pattern (short duration, small amplitude, polyphasic motor unit potentials). A first muscle biopsy showed signs of inflammatory myopathy with small perimysial and endomysial infiltrates and regenerating fibres (figure 1). The diagnosis of polymyositis was made. She was first treated with prednisone (1 mg/kg/day) and azathioprine. She progressively worsened leading to escalating immunosuppression. From 1991 to 2001, intravenous immunoglobulins (IVIg), methotrexate, cyclophosphamide, ciclosporin A, and plasma exchange were tried in different combination but always with prednisone. No clear improvement was observed. From 1998, she was wheelchair-bound, could neither stand nor walk unaided, and was totally dependent for many daily life activities. Distal weakness, with notable calf atrophy, was subsequently noticed. Her CK level remained stable overtime (from 4000 to 9000 U/L). Corticosteroids and IVIg induced respectively diabetes and a pulmonary embolism. Four further muscle biopsies were performed, with a more dystrophic pattern (fibrosis, necrosis…) emerging overtime and the possibility of a late-onset genetic myopathy was raised. In 2002, anti-dysferlin antibodies became available in our center, immunofixation and Western blot revealed dysferlin deficiency (figure 1). The diagnosis was confirmed by the genetic analysis showing compound heterozygous c.1834C>T and c.3967C>T mutations.

**Discussion**

Dysferlinopathies are autosomal recessive muscular dystrophies caused by mutations in the dysferlin gene. Dysferlin deficiency causes three main phenotypes: distal Miyoshi myopathy, limb-girdle muscular dystrophy (LGMD) type 2B and a mixed proximo-distal phenotype [7]. This heterogeneity can be observed even within the same family [8] indicating no general genotype/phenotype correlation. In one of the largest reported cohorts of dysferlinopathy (n = 40), 10 patients (25%) were initially misdiagnosed as having polymyositis because of histological inflammatory muscle infiltrates associated with rapid progression and/or pain [7]. Overall, inflammation on muscle biopsies in dysferlinopathy was observed in 34% (n = 40) [5], 62% (n = 26) [9] and 69% (n = 13) [10]. Concerning the pathological features of inflammation, some differences between dysferlinopathy and polymyositis were observed but not sufficient to be diagnostic. In a study on 10 dysferlinopathy patients [11], all had inflammation, typically arranged in small clusters surrounding blood vessels and muscle fibers. There were generally fewer inflammatory cells in dysferlinopath than polymyositis patients [11], and notably CD8+ T cells were rare. In dysferlinopathy, non-necrotic muscle fibers invaded by CD8+ T cells were absent [11]. Furthermore, seven of the 10 patients also showed positivity of MHC class I on apparently normal fibers [11], although expression was variable. Muscle fibers from patients with inflammatory myopathies also frequently express MHC class I on their surface which is not observed in normal muscle [5]. MHC class I staining is now regarded as an additional diagnostic test for myositis with a sensitivity of 78% and a specificity of 95% [12]. Clinical factors that can compound the difficult in distinguishing between dysferlinopathy and myositis include the age of onset (22–23 years) [7,8], that can vary from 12 to 59 years [8], the occasional rapidity of disease progression, and the lack of cardiac, respiratory and facial impairment in dysferlinopathy. In general, cases of dysferlinopathy misdiagnosed as polymyositis and treated with immunosuppressants have been reported [13–15] to show no clear evidence of improvement, as for our patient. Nevertheless, it has to be noted that Lerario et al. reported recently two

**Glossary**

| CK | creatine kinase |
| FSHD | facioscapulohumeral dystrophy |
| IVIg | intravenous immunoglobulins |
| LGMD | limb-girdle muscular dystrophy |
cases of dysferlinopathy in whom rituximab (anti-CD20 monoclonal antibody depleting B cells) seemed to ameliorate limb girdle and grip strength [16]. Although many dysferlinopathy patients have muscle inflammation, the molecular mechanisms that initiate and perpetuate this inflammation are not well understood. Nevertheless, a recent study showed that dysferlin-deficient primary muscle cells can express toll-like receptors and can produce IL-1β [17], which is pro-inflammatory.

Other genetic diseases can also be accompanied by inflammation on muscle biopsy, for example facioscapulohumeral dystrophy (FSHD, for review [18]). Generally inflammation within muscle is modest [18] but in 33% (n = 18), patients had numerous inflammatory cells exceeding 600 per 1000 muscle fibers [19]. In FSHD, as in LGMD2B, non-necrotic fibers invaded by mononuclear cells with CD8+ cells were not observed [19], by contrast to what is classically described in polymyositis or inclusion body myositis. Concerning the latter, facial involvement in some patients can also induce some confusion with FSHD [20].

LGMD type 2I, caused by mutations in the Fukutin-related protein gene is one of the most common form of LGMD and often presents in childhood. Muscle biopsy, here again, can show inflammatory infiltrates and MHC class I over-expression [21]. The existence of polymyositis in childhood is greatly debated (whereas dermatomyositis is well-recognised). The presence of inflammatory infiltrates within muscle of young people (without skin features of dermatomyositis) is more likely to be seen as a feature of paediatric LGMD or Duchenne/Becker muscular dystrophy than primary myositis [22]. Moreover, LMNA mutations were recently reported in patients showing substantial inflammatory infiltrates in the muscle biopsy, which could lead to diagnostic error [23].

Eosinophilic myositis is a rare inflammatory myopathy sometimes idiopathic but frequently associated with parasitic infections, systemic hyper eosinophilia, vasculitis or intoxication. Recently, eosinophilic myositis has been described in six young patients (< 10 years) with genetically confirmed calpainopathy (LGMD2A) [24], but also in one child of 10 years with a γ-sarcoglycanopathy (LGMD2C) [25].

In conclusion, the distinction between the two entities is certainly more difficult in adults than in children where the presence of inflammatory infiltrates is frequent in LGMD. The clinical presentation (presence of distal weakness is more compatible with dysferlinopathy and facial weakness with FSHD), and the evolution of disease under treatment (complete immunosuppressant resistance is unusual for a myositis, but slight improvement can occur during a dystrophy) have to be carefully noted. MRI is not of particular help since hyperintensities observed on STIR images are not specific to myositis and/ or inflammation, and may precede fatty degeneration in dys-
trophies [26]. In cases of persisting doubt, even after using all available diagnostic tools, it may be appropriate to perform a second (third . . .) muscle biopsy.

**False dystrophy**

**Representative case**

In 1999, a 29-year-old man, with no family history of myopathy, presented with very slowly progressive proximal limb-girdle muscle weakness, leading to reduced sport performance (weightlifting). In 2000 he was hospitalized in psychiatry for “severe depression” and his CK level was found to be 3000 U/L. Electromyography showed a myopathic pattern. Initial muscle biopsy showed an excessive variability in the fibre size without inflammation (figure 2). Immunostaining and Western blot were normal for the main proteins known to cause LGMD (dystrophin, sarcoglycans, beta-dystroglycan, dysferlin, calpain). The staining for alpha-dystroglycan was patchy but gene analyses of FKRP and Lamin A/C were normal. The diagnosis of LGMD of unknown genetic type was made. In 2008, the patient walked with a cane, but he was not able to climb stairs without help. The deficit was more pronounced in the pelvic girdle (psosas MRC 2/5, gluteus medius and maximus MRC 3/5) than in the shoulder girdle (deltoid, biceps brachii MRC 4/5). Echocardiogram showed a dilated cardiomyopathy with an ejection fraction of 50% (there was no history of alcoholism).

Treatment with ramipril and bisoprolol was then started. A second muscle biopsy showed many necrotic fibers (figure 2). A test for antinuclear antibodies was finally performed on Hep-2 cells; it was negative (no nuclear fluorescence) but the immunologist noticed a diffuse cytoplasmic fluorescence evocative of anti-SRP antibodies. Their presence was then confirmed on a specific dot blot and we concluded, after 10 years of observation, that he had an acquired necrotizing myopathy with anti-SRP antibodies. In October 2008, he was treated with prednisone (1 mg/kg/day), azathioprine (2 mg/kg/day) and IVIg (2 g/kg/month). Over three months, CK level normalized and muscle strength slowly improved. The dose of corticosteroids was tapered to a maintenance dose of 7 mg/day and the IVIg was stopped after 8 months. Eleven months after the beginning of immunosuppressants, he can walk outside without a cane and muscle testing of both girdles was MRC 4/5 for all muscles.

**Discussion**

Autoantibodies directed against signal recognition particles (SRP) are present in a minority (4–6%) of patients with inflammatory [27,28] and/or acquired necrotizing myopathies [29,30]. Anti-SRP antibodies are generally associated with severe proximal myopathy with heart (as for our patient) and lung involvement [31,32]. Typically, weakness becomes severe, disability develops rapidly over a period of months.
and high serum CK (3000 to 25 000 IU/l) are noticed [31]. Frequently, resistance to steroid therapy is also found [33,34]. Nevertheless, second or third lines of immunosuppressants generally achieved clinical remission. Sometimes for refractory forms we have used biotherapy such as rituximab and we are currently conducting a prospective, phase II open trial of rituximab on refractory anti-SRP patients (http://ClinicalTrials.gov Identifier: ClinicalTrials.gov Identifier: NCT00774462). More recently, slowly progressive myopathies associated with these antibodies and mimicking limb girdle muscular dystrophy, as in our patient, have also been described [35,36]. Growing pathological evidence further suggests that anti-SRP myopathy is a distinct form of myositis, characterized by major muscle fibre necrosis but with little or no inflammatory infiltrates or MHC class I expression (figure 2), and sometimes a particular pattern of complement C5b-9 deposition [35]. Given the pathological features that can mimic a dystrophy at its onset, the detection of anti-SRP antibodies is the key to the diagnosis. Until recently, a routine commercial assay was not available leading to diagnostic difficulty. Nevertheless, the search of antinuclear antibodies (ANA) always gives a characteristic cytoplasmic pattern of immunofluorescence on Hep-2 cell and bound SRP can be now easily confirmed on a validated commercial dot blot assay. The main message is that in a case of limb girdle necrotizing myopathy (of either rapid onset, or slowly progressive mimicking a LGMD) with high CK level and negative ANA but with cytoplasmic fluorescence on Hep-2 cells, then the presence of anti-SRP antibodies must be sought.

**Conclusion**

The classifications of idiopathic myositis and LGMD is changing [4,6] because of the development of new diagnosis

| **Table I** |
| Main differences between myositis, anti-SRP necrotizing myopathy and those limb girdle muscular dystrophies that are often associated with muscle inflammation (e.g. LGMD 2B or dysferlinopathy, FSHD) |
| Clinical presentation |
| Familial history | No | No | Sometimes |
| Age of onset | Adulthood | Adulthood | Young adult |
| Rapidity of progression | Rapid | Rapid but sometimes very slow | Typically slow |
| Heart involvement (e.g. dilated cardiomyopathy) | Rare | 30% | Common in some dystrophies (e.g. LGMD2I) |
| Response to immunosuppressants | Yes | Yes, sometimes need of escalating drugs | No or transient |
| Complementary investigations |
| IIF on Hep-2 cells | 50% ANA (nuclear fluorescence) | No ANA but 100% cytoplasmic fluorescence | No |
| Characterized auto-antibodies | 30% (anti-jo-1, PL7, PL12, PmSc, Ku, RNP...) | 100% anti-SRP | No |
| CT scan | Frequent ILD (with anti-jo-1), sometimes lethal | 30% ILD | No ILD |
| CK level | Variable | Median 8000 UI/L | Variable but frequently > 5000 UI/L |
| Pathological features |
| Inflammation | Constant, sometimes profuse, within endomysium | Rare | Not rare, but in small clusters surrounding blood vessels and muscle fibers |
| CD8+ cell infiltrate | Yes | No | No |
| MHC class I over-expression | Diffuse | No | Local |
| Necrotized fibers | Yes | Main feature | Yes |
| Interstitial fibrosis | No | No | Yes |

LGMD: limb girdle muscular dystrophy; IIF: indirect immunofluorescent; ANA: anti-nuclear antibody; ILD: interstitial lung disease.
tools. Nevertheless, traps persist in the clinical and pathological presentation, leading to the potential to confuse LGMD with inflammation for acquired myositis, and treatable necrotizing myopathy (with anti-SRP) for LGMD. The main differences are summarized in the table I. The distinction between these diseases is important since their therapeutic approaches and prognosis are completely different.

Conflict of interest: none.

References


