Necrotising myopathy, an unusual presentation of a steroid-responsive myopathy

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Abstract

Objective: To evaluate the clinical features, muscle pathology and response to treatment in patients with a necrotising myopathy, without mononuclear cell infiltrates.

Background: Mononuclear cell infiltrates in the muscle biopsy are the diagnostic hallmark of the immune-mediated idiopathic inflammatory myopathies (IIM). In patients with the typical clinical features of IIM, absence of these infiltrates in the muscle biopsy specimen casts doubt on the diagnosis and leads to uncertainty about therapeutical strategies.

Methods: A detailed description is given of the clinical, laboratory, and histopathological features of eight patients suspected to have an idiopathic inflammatory myopathy, in whom mononuclear cell infiltrates in their muscle biopsy were lacking.

Results: Eight patients (five men, three women, age range 40-69 years) had severe, symmetrical proximal weakness with a subacute onset. There were no skin abnormalities suggesting dermatomyositis. Serum creatine kinase activity was more than 10 times elevated. Repeated muscle biopsy specimens, taken from a symptomatic muscle prior to immunosuppressive treatment showed widespread necrosis, regeneration, and atrophy of muscle fibres, but no mononuclear cell infiltrates. Known causes of necrotising myopathy were excluded. Three patients had a malignancy. Adequately dosed and sustained immunosuppressive treatment eventually resulted in normal or near normal muscle strength in seven patients. One patient showed marked improvement.

Conclusion: Occasionally, patients who clinically present as an idiopathic inflammatory myopathy may lack mononuclear cell infiltrates in their muscle biopsy specimens. This subacute-onset, progressive necrotising myopathy should not deter the clinician from timely and appropriate treatment as we consider this myopathy to be steroid-responsive with a possible immune-mediated pathogenesis.
Introduction

Polymyositis (PM) and dermatomyositis (DM) are considered idiopathic inflammatory myopathies. In 1975 diagnostic criteria for PM and DM were established, including: (1) symmetric proximal muscle weakness; (2) elevation of muscle enzyme levels (especially serum creatine kinase (sCK) activity); (3) the electromyographic triad of a) small amplitude, short duration, polyphasic motor unit action potentials, b) fibrillations, positive sharp waves, increased insertional irritability, and c) spontaneous bizarre high frequency discharges; (4) muscle biopsy abnormalities, i.e., degeneration, regeneration, necrosis, phagocytosis, and an interstitial infiltrate of mononuclear cells; and (5) the typical skin rash in case of dermatomyositis. These criteria do not differentiate PM from DM except for the skin abnormalities. It was the merit of Engel and Arahata to stress histological differences between PM and DM, implicating different pathogenetic mechanisms. The histological hallmark of PM is the presence of mononuclear cell infiltrates surrounding and invading non-necrotic muscle fibres, associated with muscle fibre necrosis and signs of regeneration. Absence of these infiltrates should raise doubt about the diagnosis of PM. In those cases other diagnoses such as rhabdomyolysis, myopathy due to endocrine disorders or myotoxic drugs, acid maltase deficiency, sarcoglycanopathies, dystrophinopathy or other muscle dystrophies should be considered. Occasionally, patients with cancer may have the histopathological picture of a necrotising myopathy, but without signs of inflammatory cell infiltration. This was described as a variant of PM. In addition, in the older literature a few reports on PM were found wherein a small percentage of muscle biopsy specimens show necrotic and regenerating fibres without accompanying cell infiltrates. More recently, Emslie-Smith and Authier described a myopathy with necrotic and regenerating muscle fibres and only minimal cellular infiltration associated with so-called pipestem capillaries and membrane attack complex deposition in the capillaries. The authors suggested that this myopathy might be an unusual form of idiopathic inflammatory myopathy. In this study we describe eight patients with the clinical and laboratory features highly suggestive for an idiopathic inflammatory myopathy, but without the confirmation at a histopathological level, since the muscle specimens only showed necrotising myopathy without mononuclear cell infiltrates.

Methods

The case records of eight patients who had been diagnosed as an idiopathic inflammatory myopathy (IIM) were reviewed for clinical, laboratory and follow-up data. In these patients the diagnoses of IIM was not histopathologically confirmed as the muscle biopsy specimen showed only necrotising myopathy without mononuclear cell infiltrates. All presented with...
subacute (less than 6 months) progressive symmetrical proximal muscle weakness and more than 10 fold elevated sCK. None of the patients showed skin abnormalities. Family history was negative for neuromuscular disorders. Clinical evaluation of muscle strength was done by means of the MRC (Medical Research Council) grading scale. In all patients other causes of necrotising myopathy were ruled out including defects of dystrophin or sarcoglycan, hypo- and hyperthyroidism, and the use of myotoxic drugs or toxins. None of the patients mentioned a history of dark urine rendering rhabdomyolysis unlikely. Muscle specimens were obtained from weak muscles. In every patient at least one open muscle biopsy was taken before the initiation of prednisone or other immunosuppressive treatment. Four patients had two and one had three muscle biopsies. All muscle biopsy specimens were reviewed by two experienced observers (MdeV, JH). The haematoxylin and eosin (H & E) stained biopsies were meticulously screened for mononuclear cell infiltrates in a number of consecutive sections, and also screened for atrophic, necrotic or regenerating muscle fibres and for perifascicular atrophy. Necrotic muscle fibres were identified as those with diffuse pale staining and a hyaline appearance on H & E stains, and may or may not be invaded by macrophages. Additional cryostat sections were immunostained in seven patients for

Table 1: Clinical features of eight patients with necrotising myopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of onset (years)</th>
<th>Sex</th>
<th>Proximal weakness at onset</th>
<th>Pain</th>
<th>Dysphagia</th>
<th>CK (IU/L)</th>
<th>Cancer</th>
<th>Treatment</th>
<th>Follow-up (years)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Male</td>
<td>UL ++</td>
<td>-</td>
<td>-</td>
<td>9400</td>
<td>None</td>
<td>Prednisone</td>
<td>5</td>
<td>Still on prednisone &amp; IVIg</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Female</td>
<td>LL ++</td>
<td>++</td>
<td>+</td>
<td>14317</td>
<td>None</td>
<td>Prednisone</td>
<td>4</td>
<td>Low-doses prednisone</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Female</td>
<td>UL ++</td>
<td>-</td>
<td>-</td>
<td>4820</td>
<td>Rectum</td>
<td>Prednisone, MTX</td>
<td>3</td>
<td>Normal strength</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>Male</td>
<td>UL ++</td>
<td>-</td>
<td>-</td>
<td>1993</td>
<td>Oral cavity</td>
<td>Prednisone</td>
<td>8</td>
<td>Normal strength</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>Female</td>
<td>LL ++</td>
<td>++</td>
<td>+</td>
<td>6886</td>
<td>None</td>
<td>Prednisone</td>
<td>1</td>
<td>Low-doses prednisone</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Male</td>
<td>LL ++</td>
<td>++</td>
<td>++</td>
<td>11618</td>
<td>Rectum</td>
<td>Prednisone, AZA</td>
<td>2</td>
<td>Still on prednisone</td>
</tr>
</tbody>
</table>

weakness: ++ = severe (MRC grade strength ≤ 3 in some muscles); + = mild to moderate (MRC grade 4); - = no weakness (MRC grade 5 in all muscles); UL = upper limb, LL = lower limb; Dysphagia: + = present; - = absent; CK = creatine kinase; IVIg = intravenous immunoglobulin; AZA = azathioprine; MTX = methotrexate; Plasmaph. = plasmapheresis; Cyclo. = cyclosporin
T lymphocytes (CD3), B lymphocytes (CD20), macrophages (CD68), membrane attack complex (C5b-9), and major histocompatibility complex class I (HLA-ABC). Ultrastructural studies were done to search for microangiopathy and endothelial microtubular inclusions in seven patients and for pipestem capillaries in three patients.

Results

Clinical features

The clinical and laboratory features of the eight participating patients (five men, range 40 to 69 years) are shown in Table 1. All patients presented with subacute (less than six months), progressive symmetrical proximal muscle weakness. This proximal weakness was severe (MRC ≤ 3) in all except one (no. 4). Mild distal weakness was present in four patients (nos. 2, 3, 5, 8). Five patients (nos. 1, 2, 3, 7, 8) had dysphagia. Three patients (nos. 4, 6, 7) had cancer. Patient 6 had cancer three years prior to the onset of muscle weakness, in patient 4 and 7 muscle weakness antedated cancer by two and three years, respectively. No patients had cardiac involvement. The mean duration of follow-up was 4 years (range 1 to 8). Serum CK was elevated more than 10 fold in all patients. Sera tested for anti-Jo-1 antibodies in four patients (nos. 1, 2, 6, 7) were negative. In seven out of eight patients electromyography showed small amplitude, short duration, polyphasic motor unit potentials. Fibrillations and positive sharp waves were found in five patients. All patients were finally treated with high-dose prednisone (1-1.5mg/kg body weight). Treatment was needed over a long period of time as improvement of muscle strength took more than 3 months to become noticeable in five patients (nos. 1, 2, 6, 7, 8). In six patients (nos. 1, 2, 3, 6, 7, 8) muscle weakness relapsed during tapering off of prednisone. In three patients (nos. 2, 6, 7) the initial prednisone treatment trial was postponed because of the diagnostic study or tapered off quickly because of doubt about the diagnosis as inflammation was lacking in the muscle biopsy specimens. This resulted in further clinical deterioration and in patient 2 even temporary artificial ventilation was needed. A second trial with high-dose prednisone for at least four weeks and subsequently slowly tapered off, eventually resulted in a favourable response. Because of the severity of muscle
weakness and the absence of an immediate response on prednisone, five patients (nos.1, 2, 3, 6, 8) were also treated with other immunosuppressive or immunomodulating agents (Table 1). In three patients (nos. 2, 6, 8) addition of azathioprine was effective, in patient 3 methotrexate and in patients 1 and 8 monthly intravenous immunoglobulin (IVIg) therapy was beneficial. Finally all eight patients had clear improvement in muscle strength and normalization of sCK. Seven patients (nos. 1, 2, 3, 4, 5, 7, 8) had no or only slight proximal weakness not impairing their activities of daily living. Patient 4 and 7 died of cancer during follow-up. Patient 6 improved but had still moderate proximal weakness.

Case reports

Patient 1
A 40-year-old carpenter was referred with proximal weakness and difficulty with swallowing for the past month. Neurological examination showed moderate symmetrical proximal weakness of the upper limbs (MRC grade 4) and marked symmetrical proximal weakness of the lower limbs (MRC grade 3). There was no distal weakness. Sensation was normal and reflexes were present. Serum CK was 9400 IU/L (upper limit of normal 190 IU/L). Muscle biopsy revealed widespread necrotic fibres and regeneration, but no mononuclear inflammatory cell infiltrate. At the ultrastructural level neither pipestem capillaries nor endothelial microtubular inclusions were found. Prednisone 100mg daily was administered. As his condition deteriorated, a second muscle biopsy was performed showing the same abnormalities. Acid maltase deficiency, dystrophinopathy, and sarcoglycanopathies were excluded. Monthly intravenous immunoglobulin (IVIg) therapy, 2g/kg body weight, was initiated. In the ensuing months his strength improved and sCK decreased to 1300 IU/L. While tapering off the prednisone, weakness increased and sCK raised to 7230 IU/L. Because methotrexate and azathioprine were not tolerated, the dosage of prednisone was increased on which he improved. In the following three years the patient had two relapses with severe weakness and further elevation of sCK (6201 and 9964, respectively). Both relapses responded to high-dose prednisone, while continuing IVIg. After his last relapse (one and a half year ago) he improved considerably and is able to function normally with only slight proximal weakness while sCK decreased to 880 IU/l.

Patient 2
A 43-year-old woman noted progressive weakness over a few weeks. On examination she had severe symmetrical weakness (MRC grade 3) of her neck, shoulder girdle, and pelvic girdle muscles. There was slight distal weakness of her ankle flexors. Serum CK was 14.317 IU/L. A muscle biopsy from her left quadriceps femoris muscle showed necrotic, regenerating, and atrophic muscle fibres without mononuclear cell infiltrates. Despite treatment with prednisone 60 mg daily and methotrexate 15mg/wk the patient became progressively weak. Thereupon intravenous therapy with immunoglobulin and
methylprednisolone was added while oral prednisone medication was tapered off over a period of two months. Serum CK decreased to 3887 IU/L, without improvement of strength. Prednisone (60mg daily) was restarted, combined with cyclosporin. Her situation deteriorated until she became bedridden and had to be admitted to hospital. Since there was doubt about the diagnosis, a new biopsy was performed, once again showing no cellular infiltration. Acid-maltase deficiency and dystrophinopathy were excluded. Thereupon all medication was stopped considering the lack of response and the lack of histopathological proof of an inflammatory myopathy. However, the clinical picture progressively worsened. On examination, there was severe symmetric paresis (MRC grade 2-3) of all proximal muscles of arms and legs, and of the axial muscles. Serum CK was 14.866 IU/L. A muscle biopsy was repeated and again showed extensive necrosis but no mononuclear cell infiltrates. Because of respiratory insufficiency night-time artificial ventilation was required. High-dose prednisone (70 mg) was re-initiated and continued for 6 weeks, followed by a very slow dose reduction schedule. Azathioprine (150 mg) was added. In the following months her strength improved slowly, except for a slight paresis of both iliopsoas muscles and a slight waddling gait. At present prednisone dose is 10 mg on alternate days and there has been no relapse.

**Muscle pathology**

The results of muscle pathology are shown in Table 2. Because the clinical diagnosis of an idiopathic inflammatory myopathy could not be confirmed at the histopathological level, several biopsies have been taken: three patients (nos. 3,4,5) had one, four patients (nos. 1,6,7,8) had two and one patient (no 2) had even three open muscle biopsies taken from weak muscles. All specimens showed widespread necrotic, atrophic and regenerating muscle fibres. Although phagocytosis of necrotic fibres was evident, there were no perimysial, perivascular or endomysial mononuclear cell infiltrates, and no invasion of non-necrotic muscle fibres by inflammatory cells (Fig. 1). None of the specimens showed perifascicular atrophy. Immunostaining of the seven muscle biopsy specimens (nos. 1-7) showed T lymphocytes (CD3) or macrophages (CD68) or both, around and in the vicinity of necrotic and regenerating muscle fibres in all patients, but not around or invading non-necrotic muscle fibres. B cell lymphocytes were sparse or absent in all specimens. All muscle biopsies showed non-specific immunostaining of class I major histocompatibility (MHC-I) product on capillaries and on necrotic or regenerating fibres. There was variable MHC-I immunostaining of non-necrotic muscle fibres. In patient 6 no immunostaining was found. In five biopsies about 10% of non-necrotic muscle fibres stained positive for MHC-I whereas only in patient 7 more than 50% of non-necrotic fibres expressed MHC-I. None of the muscle biopsy specimens showed microvascular deposits of membrane attack complex (C5b-9).
Table 2: Muscle pathology of eight patients with necrotising myopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>x biopsies</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>light microscopic studies (haematoxylin-eosin stain)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>mononuclear cell infiltrates</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>necrosis</td>
<td>focal</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>scattered</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>diffuse</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>atrophy</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>regeneration</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>increase in endomysial connective tissue</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td><strong>immunocytochemical studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>T lymphocytes (CD 3)*</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B lymphocytes (CD 20)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrophages (CD 68)*</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>MHC-I on non-necrotic muscle fibres</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>-</td>
<td>&gt; 50%</td>
<td></td>
</tr>
<tr>
<td>microvascular deposits of MAC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ultrastructural studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.d.</td>
</tr>
<tr>
<td>microangiopathy/ microtubular inclusions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

- = absent; + = mild; ++ = moderate; +++ = severe; MHC-I = sarcolemmal immunostaining for major histocompatibility complex class I; MAC = membrane attack complex; n.d. = not done
* all around necrotic or regenerating muscle fibres

Figure 1: Patient 3. Biopsy specimen of the right quadriceps muscle shows marked variation in the size of muscle fibres, necrotic and regenerating fibres without mononuclear cell infiltrates. Haematoxylin-eosin, X500.
the ultrastructural level no microangiopathy or microtubular inclusions in endothelial cells indicative of DM were found in the seven muscle biopsy specimens that were examined (nos. 1-7). No pipestem capillaries as described by Emslie-Smith and Authier\textsuperscript{1,11} were seen in three muscle biopsy specimens (nos.1-3) we specially searched for.

Discussion

We describe eight patients with sub-acute, severe proximal muscle weakness and very high sCK activities suggesting an idiopathic inflammatory myopathy. As the muscle biopsy specimens, taken before initiation of prednisone therapy and from paretic muscles, reveal extensive muscle fibre necrosis but no mononuclear cell infiltrates, this may raise doubt about the diagnosis. Other diagnoses such as dystrophinopathy, sarcoglycanopathies, acid maltase deficiency and the use of myotoxic drugs were considered. This diagnostic work-up postponed therapy in some of the patients. In addition, in some, treatment trials were of inadequate duration and/or dose, which resulted in clinical deterioration and relapses. Given the sustained improvement on immunosuppressive therapy with eventually only minimal sequelae, it is very likely that an immune-mediated mechanism is involved. MHC-I expression on non-necrotic muscle fibres is a prerequisite for antigen-specific T cell-mediated cytotoxicity and may as such be helpful in diagnosing inflammatory myopathy.\textsuperscript{5,9,14} Supposedly, in PM almost every muscle fibre shows strong sarcolemmal immunostaining for MHC-I.\textsuperscript{5,9,14} However, MHC-I expression is not specific, since it may also be found on regenerating and non-necrotic muscle fibres in DM, and even in Duchenne muscular dystrophy.\textsuperscript{9,14} All muscle biopsy specimens of our eight patients expressed MHC-I on capillaries and necrotic or regenerating fibres, but only minimal MHC-I staining of non-necrotic muscle fibres was found in six patients and none in one patient. One can argue that the muscle pathology in our patients was not mediated by cytotoxic lymphocytes since inflammatory cells were lacking with minimal MHC-I staining on non-necrotic muscle fibres and that instead a humoral mechanism might be involved. Muscle fibre necrosis in these patients could well be caused by antibody-dependent complement-mediated lysis of the muscle fibre surface membrane. The minimally increased MHC-I expression may then be considered as a non-specific response to tissue injury.

In 1974, Munsat et al. also described sixteen cases with the clinical diagnosis of myositis without inflammatory cell infiltrates.\textsuperscript{16} Because five patients were on steroid treatment when biopsies were taken, this could cause the absence of lymphocytic inflammation. In nine of Munsat’s patients a rash was present and six muscle biopsy specimens showed perifascicular atrophy consistent with a diagnosis of DM. In two other reports\textsuperscript{7,18} a total of 16 patients were described with the clinical presentation of myositis, with muscle fibre destruction and regeneration, but without mononuclear cell infiltration on muscle biopsy. Because the
clinical features of these patients were not described in detail, we are not informed about the presence of skin abnormalities suggesting dermatomyositis or malignancies. In DM it is not unusual that mononuclear cell infiltrates in the muscle biopsy specimen are lacking, because of the patchy nature of this myositis. In these cases perifascicular atrophy, microvascular deposits of the C5b-9 complement membrane attack complex, foci of capillary depletion or endothelial microtubular inclusions at the ultrastructural level are considered diagnostic hallmarks. In our patients, however, no dermatological and no specific histopathological abnormalities were found that were consistent with a diagnosis of DM. In PM no such clear and specific abnormalities are known that can help to confirm the diagnosis in the absence of mononuclear cell infiltrates.

Emslie-Smith et al. and Authier et al. described pipestem capillaries and MAC deposits in capillaries in four patients with necrotising myopathy but minimal cellular infiltration. We cannot confirm these observations in the muscle biopsy specimens of three patients in whom we specifically searched for these morphological abnormalities.

Necrosis of skeletal muscle in association with carcinoma without significant inflammatory cell infiltration was described in 1969 by Smith and was confirmed by others. In most of these cases ‘myositis’ and cancer presented simultaneously. However, the risk for a malignant disease remains increased within three years following myositis diagnosis. As three of our eight patients had cancer, preceding or following the myopathy by less than three years, a causal relationship is very likely. The other five patients were not systematically screened for a malignancy, but during follow-up no neoplasm was diagnosed.

The absence of mononuclear cell infiltrates in the muscle biopsy specimens of our patients could be the result of a sampling error. Here, a MRI-guided biopsy might have been helpful as recent reports described the usefulness of MRI in detecting the precise location of inflammation. As this was a retrospective study a MRI-guided biopsy was not done. However, sampling error is not convincing as the biopsies were all taken from clinically weak muscles before administration of prednisone and even repeat biopsies lacked inflammatory cell infiltrates notwithstanding the same severe histopathological abnormalities.

In conclusion, patients who present with the clinical and laboratory characteristics of an idiopathic inflammatory myopathy but without mononuclear cell infiltrates in their muscle biopsies, may have immune-mediated, steroid-responsive necrotising myopathy and should be treated with sustained high-dose prednisone or other immunomodulating therapy.
References


