Polymyositis and dermatomyositis: classification, risk factors and outcome

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Tubuloreticular structures in different types of myositis; implications for pathogenesis

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Abstract

In dermatomyositis (DM) there is strong histopathological evidence of a microvascular pathogenesis, including endothelial microtubular inclusions. In nonspecific myositis perimysial and perivascular infiltrates in the muscle biopsy similar to DM are found. Microtubular inclusions in endothelial cells were systematically searched for and found in 4 of the 20 muscle biopsies of nonspecific myositis patients (20%). Three had a CTD (SLE, scleroderma, and Sjögren syndrome). Ten patients with DM and 5 patients with sporadic inclusion body myositis served as positive and negative controls, respectively.
Introduction

Muscle biopsies of patients with dermatomyositis (DM) show mononuclear cell infiltrates around small blood vessels predominantly located in the perimysium. At the ultrastructural level abundant abnormalities are found in endothelial cells showing various stages of degeneration and regeneration. A characteristic finding early in the disease process is the presence of microtubular inclusions in endothelial cells, often preceding inflammatory cell infiltrates. These inclusions are related to the endoplasmatic reticulum (ER) or to the outer nuclear membrane and probably represent membranous specializations within the ER during a certain stage of cellular activity. Early capillary injury preceding muscle damage is the fundamental element of the vascular hypothesis in DM.

The pathogenesis of polymyositis (PM) is unclear and there are divergent opinions on the definition of PM. According to some investigators, the term PM can be used in all cases of auto-immune myositis manifesting with subacute limb-girdle muscle weakness without skin abnormalities, irrespective of the muscle biopsy findings. According to others the term PM should be restricted to non-DM myositis with endomysial infiltrates of T cells often infiltrating non-necrotic muscle fibres, suggesting a T-cell-mediated attack directed against muscle fibres. PM is the least frequent entity amongst the idiopathic inflammatory myopathies that comprise PM, sporadic inclusion body myositis (s-IBM), and DM. The vast majority of muscle biopsies of patients with myositis without skin abnormalities show mononuclear cell infiltrates predominantly at perimysial sites, often around small blood vessels similar to what is found in DM. This observation suggests that in this so-called nonspecific myositis (no DM, and no endomysial T cell infiltrates), a microvasculopathy plays a pathogenetic role, similar to DM. However, microtubular inclusions in muscle capillaries are described only as a histopathological feature present in a proportion of patients with DM or with myositis as a complication of SLE, and in the occasional patient with myositis and Sjögren syndrome. We did a systematic search for these abnormalities to investigate further the vascular hypothesis in nonspecific myositis.

Patients and methods

Patients

We investigated 20 muscle biopsies of patients with nonspecific myositis (13 women, 7 men, mean age 43 years, range 23-67). All patients had subacute onset of proximal weakness without skin changes, and were histopathologically characterized by inflammatory myopathy with predominantly perimysial/perivascular localization of mononuclear cells in the muscle biopsy specimen, without additional significant endomysially located cell infiltrate. Ten of them had an associated connective tissue disease (CTD), including
scleroderma (n = 3), mixed connective tissue disease (n = 2), systemic lupus erythematosus (n = 2), rheumatoid arthritis (n = 2), and Sjögren syndrome (n = 1). Three additional patients showed some features indicative of CTD (xerophthalmia and xerostomia, arthralgia, Raynaud phenomenon), and one patient had discoid lupus erythematosus. Muscle biopsies of 10 patients with DM (6 women, 4 men, mean age 50 years, range 27-78) served as positive controls and of 5 patients with s-IBM (2 women, 3 men, mean age 72 years, range 60-82) as negative controls. Diagnoses were based on criteria described previously.6,9

The duration of symptoms before biopsy ranged from 1 to 11 months in nonspecific myositis, from 2 to 12 months in DM, and from 1 to 10 years in s-IBM. None of the patients had received prednisone or other immunosuppressive drugs within 3 months preceding the biopsy.

Ultrastructural studies
Open biopsies of limb muscles had been performed for diagnostic purposes. Biopsy specimens were excluded if there was extensive necrosis of muscle fibres or if there were less than 10 fascicles available for examination. Muscle specimens were prepared for electronmicroscopy by standard methods.10 Blocks were chosen at random for each patient and were thin-sectioned. All capillaries to a maximum of 50 observed in the electron microscope were analysed for the presence of tubuloreticular structures without knowledge of the clinical diagnosis and the light microscopic findings. Tubuloreticular structures were identified as such if they were continuous with the outer nuclear membrane or the rough-surfaced endoplasmatic reticulum, and if the tubules measured 18-26 nm and formed an irregularly branching and anastomosing network.11 If tubuloreticular structures were seen in at least two capillaries these were photographed and reassessed by two investigators (MdV, JMR) without knowledge of the diagnosis.

Results
The results are presented in Table 1. Endothelial tubuloreticular structures were found in 4 patients with nonspecific myositis (20%) (figure 1). Perifascicular atrophy was absent. Three of the 4 patients had a concomitant CTD (SLE, scleroderma, and Sjögren syndrome). The fourth patient was diagnosed with cutaneous discoid lupus erythematosus, a chronic inflammatory condition of the skin which may evolve to systemic lupus erythematosus. Endothelial tubuloreticular structures were present in 4 of the DM patients (40%) (figure 1), of whom 1 had perifascicular atrophy, and in none of the s-IBM patients.
Table 1: Results of assessment of tubuloreticular structures in dermatomyositis, nonspecific myositis, and sporadic inclusion body myositis

<table>
<thead>
<tr>
<th></th>
<th>Age, years mean (SD)</th>
<th>Sex m/f</th>
<th>No. of biopsies showing tubuloreticular structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (n = 10)</td>
<td>50 (18)</td>
<td>4/6</td>
<td>4</td>
</tr>
<tr>
<td>Nonspec M (n = 20)</td>
<td>43 (12)</td>
<td>7/13</td>
<td>4</td>
</tr>
<tr>
<td>with CTD (n = 10)</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>CTD-like features (n = 4)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>only myositis (n = 6)</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>s-IBM (n = 5)</td>
<td>72 (9)</td>
<td>3/2</td>
<td>0</td>
</tr>
</tbody>
</table>

DM = dermatomyositis; Nonspec-M = nonspecific myositis; CTD = connective tissue disorder; s-IBM = sporadic inclusion body myositis

Discussion

Our results show that tubuloreticular structures in endothelial cells of muscle capillaries occur not only in DM, but also in nonspecific myositis, especially when there are also signs of CTD. This supports the hypothesis that patients with DM and nonspecific myositis share an immune-mediated injury of the muscle microvasculature. Investigations at the light...
microscopical level including determination of capillary density and microvascular deposition of membrane attack complex are needed to lend further support for this hypothesis. The occurrence of endothelial tubuloreticular inclusions in CTDs has been described previously, but has never been systematically looked for. Tubuloreticular structures in endothelial cells were first reported in SLE patients with chronic nephritis. In the ensuing years they were also observed in muscle and skin of patients with DM and very rarely in other connective tissue disorders, including scleroderma of the kidney, rheumatoid synovial tissue and Sjögren myositis.7,8,13,15 Besides their presence in CTDs, they have been described in HIV and other viral infections and in several tumors.16,17

Scrutinising the literature, we found earlier descriptions of endothelial inclusions in five cases of so-called polymyositis.13,15,18 Because of a lack of clinical data it is uncertain whether in these patients myositis occurred in isolation or associated with a CTD. Our findings showing microtubular inclusions in patients with nonspecific myositis, in particular those with concurrent presence of SLE, scleroderma or Sjögren myositis may implicate a difference in pathogenesis between myositis with and without CTD. However, in a previous study we did not find any differences between nonspecific myositis patients with and without CTD with respect to serum creatine kinase activity, erythrocyte sedimentation rate, the presence of autoantibodies, muscle biopsy abnormalities, clinical outcome and prognosis.4,18 It is of note, that in the same study about one-third of patients with an isolated nonspecific myositis at onset was shown to develop a CTD after a mean follow up of 6 years.18 Whether our results truly represent differences in pathogenesis between myositis with and without CTD remains to be elucidated.
References


