Polymyositis and dermatomyositis: classification, risk factors and outcome
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Polymyositis: an ongoing discussion about a disease entity

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Since its first description more than a century ago, there has been much debate about the diagnostic entity polymyositis. Because initial observations were of patients with dermatomyositis, it appeared that polymyositis was not possible without skin lesions. Distinctive clinical and histological features of polymyositis were not established until the late 20th century. The identification of inclusion body myositis as a distinct entity has further refined nosographic classification.
Early clinical observations

In 1887, Wagner¹ and Unverricht² independently described 3 patients who had a fatal outcome with acute muscle weakness in combination with skin lesions. They called this disease *polymyositis*. A few years later, Unverricht³ pointed to the almost simultaneously occurrence of cutaneous abnormalities and changed the name of the disease to *dermatomyositis*. At the end of his article, Unverricht³ emphasized, with particular eloquence:

> Ob daneben Fälle existieren, wo nur die Haut oder nur die Muskulatur von der Affection heimgesucht wird, ob es also eine reine Dermatitis und Polymyositis gregarinosa daneben giebt, darüber heute bereits Vermuthungen auszusprechen, dürfte als verfrüht erscheinen (It is too early to suspect that there are cases in which muscles or skin are affected independently, and that a pure dermatitis and polymyositis exist).³

After the observations of Unverricht, the terms *polymyositis* and *dermatomyositis* were used interchangeably and for some decades it was assumed that dermal lesions were always part of the disease. Only occasionally authors referred to those very rare cases of polymyositis in which skin abnormalities were absent.

In 1903, Steiner⁴ reviewed all previous cases (n=28) of poly- and dermatomyositis. He mentioned 3 patients in whom skin lesions were missing but supposed that these lesions could have been easily overlooked. In the absence of skin lesions, polymyositis was often alternatively described under different names such as *pseudotrichinosis*, *menopausal muscular dystrophy* and *late-onset progressive muscular dystrophy*. In 1954, Natrass⁵ suggested that some cases of menopausal muscular dystrophy and late-onset muscular dystrophy actually may have been polymyositis. He illustrated this point by describing 5 patients who recovered from their “muscular dystrophy” and stressed the clinical and pathological differences between these cases and more typical cases of muscular dystrophy. His patients were distinguished by the relatively acute onset of the disease, its clinical course with a tendency for spontaneous remission, and other clinical features such as presence of dysphagia in combination with specific pathological changes in muscle.

Nonetheless, the status of polymyositis as an autonomous clinicopathological entity remained ambiguous until the second half of the 20th century. In 1958, Walton and Adams⁶ summarized the situation:

> It may, therefore, be concluded from published work that although the classical clinical picture of dermatomyositis and of polymyositis has been recognized for many years, only recently has it been realized that polymyositis can occur in both subacute and chronic forms, without skin involvement....In many cases it may be difficult or impossible to distinguish the condition clinically from progressive muscular dystrophy.⁶
In addition, Walton and Adams gave a detailed description of the clinical key features of polymyositis, including proximal and symmetrical muscle weakness in the limbs that was sometimes accompanied by fatigue, pain, fever, and arthralgia. They stressed that cases of polymyositis may be missed because physicians typically do not consider the diagnosis when cutaneous lesions are absent. They also emphasized that polymyositis may occur in relationship to connective tissue diseases, such as scleroderma, systemic lupus erythematosus, and rheumatoid arthritis.

In 1975, these observations of Walton and Adams were confirmed by Bohan and Peter, who established separate diagnostic criteria for polymyositis and dermatomyositis. Their criteria for polymyositis included (1) symmetrical weakness of limb-girdle muscles worsening across weeks to months; (2) elevated activity of serum creatine kinase; (3) the electromyographic triad of small amplitude, short-duration polyphasic motor unit action potentials; fibrillations, positive sharp waves, and increased insertional irritability; and spontaneous, bizarre high frequency discharges; and (4) muscle biopsy abnormalities (ie, degeneration and regeneration of muscle fibers, necrosis, phagocytosis, perifascicular atrophy, and an interstitial infiltrate of mononuclear cells). According to these criteria, skin features were the only distinction between dermatomyositis and polymyositis. Bohan and Peter excluded patients with a slowly progressive course, a positive family history for muscular dystrophies, and some other well-defined neuromuscular disorders.

The criteria of Bohan and Peter have been of major importance for diagnosis, subsequent therapy, and scientific research for many years, and they are still used frequently. Bohan and Peter also suggested classifying all patients with myositis into 1 of 5 clinical subgroups: polymyositis, dermatomyositis, myositis associated with malignancy, childhood polymyositis or dermatomyositis and polymyositis with an associated connective tissue disorder.

Muscle biopsy

Pathological changes in skeletal muscles were shown by Wagner and Unverricht in their articles. In 1903, Steiner reported histologic abnormalities that were found in a small muscle specimen taken from a patient with polymyositis. However, it took until the 1950s for muscle biopsies to become a common diagnostic tool in differentiating myositis from other muscle disorders. This was emphasized by Christensen and Levison, who in 1950 stressed the importance of muscle biopsy findings in their report of 6 patients with polymyositis.

The only feature common to all six patients, and on which the diagnosis of polymyositis was made, was the outcome of the muscle biopsy, which in all six patients showed inflammatory infiltration in the interstitial connective tissue.
Walton and Adams\textsuperscript{6} confirmed that histologic findings were of paramount significance and related the most striking pathologic feature of polymyositis (ie, interstitial inflammation) to its etiology:

\begin{quote}
It is true that one may observe small collections of lymphocytes and histiocytes within any tissue which is the seat of a degenerative disease. However, the size and number of the inflammatory exudate and the large numbers of plasma cells ... were far in excess of what one would expect in a toxic, metabolic or degenerative process...The presence of the inflammatory infiltrates .. would suggest two possible pathogenetic processes, either an infective process or an allergic or hypersensitivity phenomenon.\textsuperscript{6}
\end{quote}

In the following years, the hypersensitivity hypothesis became popular, and researchers suggested that in polymyositis, sensitization of the lymphocytes to some component in the muscle occurred.\textsuperscript{10}

Although it was clear that a muscle biopsy plays a pivotal role in the diagnosis of myositis, specific histopathological features were not established until 1984 when Arahata and Engel showed a distinction between polymyositis and dermatomyositis on histopathological and immunohistochemical grounds.\textsuperscript{11} In polymyositis, mononuclear cells were mainly located in the endomysium and consisted of predominantly CD8+ cytotoxic T lymphocytes. These lymphocytes not only focally surrounded but also invaded nonnecrotic muscle fibers, which seemed to indicate antigen-specific, T cell-mediated cytotoxicity against the muscle fiber in polymyositis. In contrast, the predominant localization of B lymphocytes around blood vessels in the perimysium in dermatomyositis were consistent with a humoral pathomechanism directed against the intramuscular microvasculature. These observations led to a refinement of the criteria of Bohan and Peter by Dalakas in 1991, with inclusion of these specific histopathological abnormalities for polymyositis and dermatomyositis.\textsuperscript{12}

The distinction between polymyositis and inclusion body myositis

Meticulous descriptions of the histopathological characteristics of what was called polymyositis led to a remarkable observation when Adams et al\textsuperscript{13} and Chou\textsuperscript{14}, in 1965 and 1967, saw cellular inclusions in their muscle biopsy specimens of patients who otherwise fulfilled the clinical and histopathological features of polymyositis. The term \textit{inclusion body myositis} (IBM) was coined by Yunis and Samaha in 1971.\textsuperscript{15} At that time, IBM was mainly pathologically characterized by vacuoles rimmed by basophilic material and nuclear and cytoplasmatic filamentous inclusions. In later studies, IBM appeared to have specific clinical features as well. In 1978, Carpenter et al characterized the clinical features of IBM as follows:
Inclusion body myositis has a decided predominance in men. Weakness, the main feature in all patients, was generally slowly progressive and painless...The distribution of weakness was peculiar in that distal muscles were affected...There were no skin lesions...Serum creatine phosphokinase was normal or mildly elevated. Recognition of this disease is important because it demands a different therapeutic approach and implies a different prognosis than other types of idiopathic inflammatory myopathies.16

In 1991, Mendell et al17 observed small deposits of Congo red-positive staining material in the vacuolated muscle fibers of patients with IBM which turned out to be amyloid deposits. Because these deposits resembled the amyloid found in the plaques of patients with Alzheimer disease, a degenerative pathogenesis was suspected to play a role in IBM along with a cytotoxic process, identical to the immunopathologic mechanism supposed to underlie polymyositis. This idea became even more popular as Askanas et al,18 in 1994, described the presence of ubiquitin in muscle tissue, and in subsequent years, other proteins seen in Alzheimer disease were also found in patients with IBM. Diagnostic criteria for IBM proposed by Griggs et al in 1995 strongly emphasized its histopathological features.19

Some authors stress, however, that in patients with the clinical features of IBM, this diagnosis should not be rejected if the histopathological abnormalities are absent.20 In some patients, the clinical diagnosis of IBM can be confirmed only with repeated histologic examination, years after onset of the disease.21

Treatment

A clear differentiation of polymyositis from IBM is important because the prognosis and therapeutic options differ significantly. In the earliest reports of polymyositis, a gamut of remedies was advised, probably because no single treatment had been proven to be successful. Furthermore, results of therapy were difficult to interpret because of the occasional spontaneous recovery. Different results were described from treatment with wheat germ, quinidine, vitamin E, antibiotics, and even prostigmine.6 The advent of corticotropin and, thereafter, the various steroids in the late 1940s revolutionized the treatment of polymyositis. In 1951, Shy and McEachern described 5 patients with the clinical features of “menopausal muscular dystrophy” who dramatically improved after taking cortisone.22 In the ensuing years, this beneficial effect of steroid treatment was confirmed by many others, which brought Walton and Adams to conclude that every patient with polymyositis complex should be given a therapeutical trial of steroid therapy.6 Additionally, Hudgson and Walton stated,23

(T)he mode and duration of treatment is absolutely critical and, in our view, the all-too-common practice of administering oral corticosteroids in modest or even low doses for relatively short periods has given rise to the rather depressing results of treatment in the
experience of other observers. For some years now it has been our practice to administer prednisone via the oral route in high dosage (up to 80mg daily) until such time as there is clear-cut clinical and laboratory evidence of remission.\textsuperscript{23}

More recently, beneficial results were reported from additional immunomodulatory agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide. Indications for these drugs included recurrent relapses, unacceptable side effects of prednisone, or lack of response to prednisone. However, the evidence for these therapeutic regimes is based on expert opinion and not on the results of randomised clinical trials. Although patients with IBM may occasionally show a minimal and short-lasting response to steroid therapy, most authors agree that it is a treatment-resistant disorder thus far.

**Ongoing controversies**

During the past century, there has been much debate about the diagnosis of polymyositis as a clinical entity, and the discussion still goes on. In the beginning, only dermatomyositis was recognized; polymyositis could have been missed, particularly in patients without cutaneous lesions. The recognition and implementation of histologic criteria was a major step forward, although differentiation between polymyositis and muscular dystrophy remained difficult because the muscle biopsy specimens in the muscular dystrophies sometimes also revealed inflammatory cells.\textsuperscript{12} Many cases of polymyositis occur concomitantly with a connective tissue disease, rendering the term myositis with associated connective tissue disease more appropriate. More recently, recognition of IBM as a clinical entity has broadened the spectrum of the idiopathic inflammatory myopathies. In the past, many cases of IBM may have been misdiagnosed as polymyositis, especially in those patients who were resistant for steroids or in whom IBM could not be confirmed histopathologically in a first muscle biopsy specimen. The separate designations of IBM and myositis as part of a connective tissue disorder has currently left polymyositis as an uncommon diagnosis and some authors even wonder if polymyositis exists at all.\textsuperscript{24} Future studies are necessary to delineate the clinical and histopathological entity of polymyositis and determine its position in the spectrum of inflammatory myopathies.
References

Chapter 2

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