Polymyositis and dermatomyositis: classification, risk factors and outcome

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Polymyositis: an overdiagnosed entity

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Abstract

Background: According to widely used criteria (Bohan and Peter criteria, 1975), dermatomyositis (DM) is differentiated from polymyositis (PM) only by skin changes. More recent criteria also include histopathologic characteristics enabling the distinction between PM and DM, and the differentiation of sporadic inclusion body myositis (s-IBM) from PM. The authors investigated the applicability of diagnostic features for diagnosing PM and DM.

Methods: The authors performed a retrospective follow-up study of 165 patients with: 1) a previous diagnosis of myositis; 2) subacute onset of symmetrical, proximal weakness; and 3) presentation between 1977 and 1998 excluding other neuromuscular disorders.

Results: The diagnoses at initial evaluation based on clinical, laboratory and histopathologic criteria were: PM 9 (5%); DM 59 (36%; 54 isolated, three with associated connective tissue disease (CTD), two with associated malignancy); unspecified myositis (perimysial/perivascular infiltrates, no PM or DM), 65 (39%; 38 isolated myositis, 26 with associated CTD, 1 with malignancy); and possible myositis (necrotizing myopathy, no inflammatory infiltrates), 32 (19%; 29 isolated myositis, 3 with associated CTD). At follow-up, five of the nine patients with PM had typical s-IBM features. None of the remaining four patients complied with the assumed typical signs of PM. Ten of the 38 patients with isolated unspecified myositis had been diagnosed with a CTD.

Conclusions: Polymyositis is an overdiagnosed entity. At evaluation, more than half the patients with autoimmune myositis can not be specifically diagnosed with PM or DM. A quarter of patients with isolated unspecified myositis subsequently developed connective tissue disease.
Introduction

Polymyositis (PM) and dermatomyositis (DM) are inflammatory myopathies with a presumed autoimmune pathogenesis. In 1975, Bohan and Peter defined the following diagnostic criteria: 1) subacute, symmetric proximal weakness, 2) muscle biopsy abnormalities (necrosis, regeneration, perifascicular atrophy, inflammatory exudates), 3) elevated serum creatine kinase (sCK) activity, 4) EMG changes, and 5) typical skin abnormalities. Exclusion criteria were a slowly progressive course, a positive family history, and various neuromuscular disorders. A diagnosis of definite PM requires criteria 1 through 4, and a definite DM is diagnosed if skin abnormalities are present in addition to three of the other criteria. Thus, only skin features are used to differentiate DM from PM. Additionally, Bohan and Peter distinguished the associated occurrence with connective tissue diseases (CTDs) and malignancies. In 1984, an elegant histopathologic study showed that in PM and in sporadic inclusion body myositis (s-IBM), but not in DM, mononuclear cells in the endomysium focally surround and invade non-necrotic muscle fibers. A refinement of the diagnostic criteria followed, with inclusion of the histopathological differences between PM, DM, and s-IBM. By then, s-IBM had become recognized as a slowly progressive, proximal and distal, prednisone-resistant inflammatory myopathy with degenerative features. Further immunohistochemical studies have shown evidence for a major histocompatibility complex class I (MHC-I) restricted cytotoxic T-cell response against an (auto-) antigen expressed by muscle fibers in PM and s-IBM, whereas DM appears to be primarily a B-cell-mediated microangiopathy. Despite the growing evidence that PM, DM and s-IBM are histopathologically and also pathogenically different diseases, the Bohan and Peter criteria are still widely used. Valid definition of disease entities is of paramount importance for further investigations into the pathogenesis, and for future therapeutical interventions designed to act more specifically. The distinction between PM and s-IBM is vital because of the differing therapeutic prospects.

In a large unselected patient group we investigated the applicability of generally accepted clinical, laboratory, and histopathologic diagnostic features for diagnosing patients with PM and DM.
associated symptoms, signs and diseases; and laboratory features at initial evaluation. Two of us (J.E.H., M.dV.) reread the sections from open muscle biopsies taken from all patients at initial evaluation without knowledge of the clinical data at initial evaluation or findings at follow-up evaluation. The hematoxylin-eosin (HE)-stained cryostat sections were scored for localization (endomysial with or without invasion of nonnecrotic muscle fibers, perivascular, perimysial, see figure) and extent (absent, mild, moderate, extensive) of mononuclear cell infiltrates, extent of necrosis and regeneration, presence of rimmed vacuoles, and extent and localization (perifascicular, scattered) of muscle atrophy. Inclusion criteria for eligibility were: 1) subacute onset (<1 year) and 2) symmetric, proximal more than distal weakness or muscle soreness. Exclusion criteria were 1) features compatible with a diagnosis of s-IBM (facial weakness, weakness distal equally severe or more severe than proximal, marked asymmetric weakness, >3 per 1000 muscle fibers containing basophilic rimmed vacuoles; 2) features suggestive of rhabdomyolysis (rapid increasing or decreasing sCK, exposure to myotoxic drugs); 3) features suggestive of muscular dystrophies (positive family history; symptoms and signs evolving during >1 year); 4) insufficient clinical data of disease course, or no muscle biopsy specimen available for revision; and 5) completely normal findings in muscle biopsy.

Based on the clinical data at initial evaluation and reassessment of muscle biopsies, we then diagnosed the eligible patients for the purpose of this study as follows: 1) definite PM: sCK

**Figure 1:**

A: Mononuclear cells surrounding and invading non-necrotic fibers in the endomysium, B: Atrophied muscle fibers in the periphery of a muscle fascicle, C: Mononuclear cells located in the perimysium, D: Mononuclear cells located around blood vessels
more than two times elevated, inflammatory myopathy with mononuclear cells surrounding and preferably invading individual nonnecrotic muscle fibers in the endomysium; 2) definite DM: typical DM skin abnormalities or perifascicular muscle atrophy; 3) unspecified myositis: inflammatory myopathy, perimysial/perivascular localization of mononuclear cells in the muscle biopsy specimen without additional endomysially located cell infiltrate, allowing a diagnosis of PM, or without perifascicular atrophy or skin changes, allowing a diagnosis of DM; and 4) possible myositis: sCK more than two times elevated and necrotizing myopathy, but no or only minimal mononuclear cell infiltrates in the muscle biopsy specimen. Each of these categories were subdivided into isolated myositis, myositis associated with CTD (in the presence of well-defined CTD), or myositis associated with malignancy (in the presence of a malignancy diagnosed <2 years before presentation of myositis).

Two of us (M.vdM., I.M.B.) re-examined 111 patients after a follow-up period of at least 1 year. We checked these patients for CTDs diagnosed during the entire follow-up period and for malignancies that were diagnosed within 2 years after initial evaluation of myositis. Myositis-specific antibodies (MSAs; antibodies to Jo-1 and other tRNA synthetases, Mi-2 and SRP) were analyzed. Of the patients who died or declined to visit our outpatient clinic, the clinical charts were reviewed for any disease that developed after onset of myositis. Medical ethical committees approved the study protocol.

Differences between groups were analyzed with the Student’s *t*-test for continuous variables and the chi-square test for categorical variables (SPSS version 8, 1999).

## Results

Two hundred sixty-eight patients were identified and assessed for eligibility for the study. Of these, 103 were excluded because 1) features suggestive of s-IBM, rhabdomyolysis

<table>
<thead>
<tr>
<th>Table 1: Diagnosis at presentation</th>
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<tr>
<td>N (%)</td>
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<td>N (%)</td>
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<tr>
<td>Isolated</td>
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<tr>
<td>With CTD</td>
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<td>With malignancy</td>
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<tr>
<td>Sex: number of women (%)</td>
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<td>Mean duration of symptoms at presentation, mo (SD)</td>
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<tr>
<td>Mean disease duration at follow-up, y (SD)</td>
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<td>Number of patients re-examined (%)</td>
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*More women in the unspecified group compared to the rest (p = 0.03).
† Longer disease duration in PM than in the other patients (95 % CI of the difference: 2.8-8.3).
or muscular dystrophy were present (73 patients); 2) clinical data were insufficient to determine disease course after presentation (18 patients); 3) no biopsy specimen was available for review (4 patients); or 4) the biopsy findings were completely normal (8 patients), leaving 165 patients for the analysis. Fourteen biopsies were taken shortly after prednisone therapy was started (four isolated DM, six unspecified myositis [two isolated, four with CTD], and four possible myositis [two isolated, two with CTD]). We re-examined 111 of the 165 included patients (67%) after a mean follow-up of 6.5 years (range 1 – 23 years). Thirty-four patients had died (21%), 5 could not be traced (3%), and 15 patients declined to be re-examined (9%). The 54 patients who were not re-examined were no different from the others with respect to diagnosis, sex, or age. Information on the clinical course could be obtained from the charts of all patients. Table 1 and 2 show the diagnoses made based on the clinical data and biopsy results at initial presentation. Table 3 shows the diagnoses at initial and follow-up evaluations. At initial evaluation, definite PM was diagnosed in 9 out of the 165 patients (5%; 95% CI, 3 to 10%; see table E-1 on the Neurology Web site). In these nine patients with PM, mean duration of signs and symptoms before presentation was 5.6 months longer (95% CI of

<table>
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<th>Table 2: Diagnosis at presentation, laboratory characteristics</th>
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</tr>
<tr>
<td>PM (n = 9)</td>
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<tr>
<td>isolated (n = 9)</td>
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<tr>
<td>+ CTD (n = 0)</td>
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<td>+ mal (n = 0)</td>
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<tr>
<td>DM (n = 59)</td>
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<tr>
<td>isolated (n = 54)</td>
</tr>
<tr>
<td>+ CTD (n = 3)</td>
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<tr>
<td>+ mal (n = 2)</td>
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<tr>
<td>Unsp myositis (n = 65)</td>
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<tr>
<td>isolated (n = 38)</td>
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<tr>
<td>+ CTD (n = 26)</td>
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<tr>
<td>+ mal (n = 1)</td>
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<tr>
<td>Poss myositis? (n = 32)</td>
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<tr>
<td>isolated (n = 29)</td>
</tr>
<tr>
<td>+ CTD (n = 3)</td>
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<tr>
<td>+ mal (n = 0)</td>
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<tr>
<td>Total group</td>
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§ Two MSAs were found in one patient: SRP and anti-synthetase not Jo-1. † Mi-2 antibodies occurred significant more often in DM (p = 0.02). * Patients with unspecified myositis were significant younger (95 % CI of difference: 4-14). ‡ Jo-1 antibodies occurred significant more often in patients with unspecified myositis (p = 0.01). ** Patients with possible myositis had significant higher sCK (95 % CI of difference: 259-3112). ¶ Two MSAs were found in three patients: Mi-2 and anti-synthetase not Jo-1.
the difference, 0.3 to 10.8) than in the other groups. There was a nonsignificant difference with regard to sCK activity and age between patients with PM and the other categories. In patients with PM, sCK was lower and age at onset was higher. In four patients (Patients 6 through 9), the disease progressed slowly despite treatment with high-dose sustained prednisone. Follow-up re-examination revealed finger flexor weakness in one patient (Patient 6) and prominent distal leg weakness in three patients (Patients 7, 8 and 9). A repeat muscle biopsy in one of these patients (Patient 8) showed basophilic rimmed vacuoles. Another patient (Patient 5) had initially responded well to high dose prednisone, but he remained corticosteroid dependent and never regained normal muscle strength or sCK levels. His repeat muscle biopsy showed abundant rimmed vacuoles and nuclear 18- to 21-nm tubulofilaments using electron microscopy. One patient (Patient 1) differed from the other patients with PM because she never, at any time, had detectable muscle weakness. She complained of muscle soreness and arthralgia of the finger joints, and had a positive rheumatoid factor. Another patient (Patient 2) was remarkable because she had finger extensor weakness at initial evaluation that did not improve despite adequate treatment. The muscle biopsy of one patient (Patient 3) showed abundant reactive

<table>
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<tr>
<th></th>
<th>Jo-1</th>
<th>Mi-2</th>
<th>SRP</th>
<th>Synthetase</th>
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<tr>
<td>0/ 8</td>
<td>1/ 7</td>
<td>1/ 7</td>
<td>1/ 7</td>
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<tr>
<td>12/ 36 (33%)</td>
<td>9/ 42 (21%)</td>
<td>0/ 37</td>
<td>2/ 37 (5%)</td>
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<td>11/ 32 (34%)</td>
<td>9/ 38 (24%)</td>
<td>0/ 33</td>
<td>2/ 33 (6%)</td>
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<td>1/ 1 (100%)</td>
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<tr>
<td>9/ 35 (26%)‡†</td>
<td>4/ 30 (13%)‡</td>
<td>0/ 30</td>
<td>1/ 30 (3%)‡</td>
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<td>2/ 19 (11%)</td>
<td>0/ 19</td>
<td>0/ 19</td>
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<tr>
<td>2/ 11 (18%)‡†</td>
<td>0/ 11</td>
<td>1/ 11 (9%)‡</td>
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<tr>
<td>2/ 23 (9%)</td>
<td>3/ 22 (9%)‡</td>
<td>2/ 22 (9%)</td>
<td>2/ 22 (9%)</td>
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<tr>
<td>2/ 20 (5%)</td>
<td>3/ 20 (15%)‡</td>
<td>2/ 20 (10%)</td>
<td>2/ 20 (10%)</td>
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<tr>
<td>1/ 20 (5%)</td>
<td>0/ 2</td>
<td>0/ 2</td>
<td>0/ 2</td>
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<td>1/ 3 (33%)</td>
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<tr>
<td>20/ 108 (19%)</td>
<td>20/ 95 (21%)</td>
<td>3/ 96 (3%)</td>
<td>6/ 96 (6%)</td>
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sCK = creatine kinase activity in serum in U/l; non-specific auto-antibodies any of, ANA, ENA, RF, a-Sm, a-dsDNA, a-RNP, aSSA, aSSB; MSA = myositis specific auto-antibodies; SRP = signal recognizing protein; synthetase = anti-synthetase auto-antibody, other than Jo-1/ Unsp myositis = unspecified myositis; Poss myositis = possible myositis.
inflammation in the vicinity of many necrotic muscle fibers, which made it difficult to assess whether inflammatory cells surrounded nonnecrotic fibers. Another patient (Patient 4) had only minimal non-disabling bilateral iliopsoas weakness and muscle stiffness, which resolved quickly after administration of short-duration low-dose prednisone.

A diagnosis of definite DM was established in 59 out of the 165 patients (36%; 95% CI, 2 to 44%) based on the presence of typical skin abnormalities in 32 patients, perifascicular atrophy in 4 patients, and both features in 23 patients. The muscle biopsy of the 32 patients with DM who were diagnosed based on their skin abnormalities showed perivascular/perimysial infiltrates in 26 patients and no or minimal infiltrates in 6 patients. Eleven patients had proximal muscle complaints without objectified muscle weakness. Patients with DM more often had anti-Mi-2 antibodies than the other patients (12/36 vs 8/59; \( p = 0.02 \)). Three patients had an associated CTD at onset of DM (two scleroderma, one mixed connective tissue disease [MCTD]). Two patients had an associated malignancy diagnosed < 2 years before the onset of DM. One woman was subsequently diagnosed with systemic lupus erythematosus (SLE) 6 months after initial evaluation of the DM, and five patients developed a malignancy within 2 years after the diagnosis of DM.

A diagnosis of unspecified myositis was made in 65 patients (39%; 95% CI, 32 to 47%). Patients with unspecified myositis were younger (40 vs 49 years; 95% CI of the difference: 4 to 14), more often female (53/66 versus 67/99; \( p = 0.03 \)), and more often had anti-Jo-1 antibodies (9/35 vs 11/73; \( p = 0.02 \)) compared with the rest of the patients. They did not differ from the other patient groups with respect to sCK activity, erythrocyte sedimentation rate (ESR), the presence of other MSAs, or the presence of nonspecific autoantibodies. Thirteen patients had proximal muscle complaints without objectified muscle weakness. Twenty-six patients had an associated CTD (seven, SLE; seven, MCTD; five, scleroderma; four, rheumatoid arthritis [RA]; and three, Sjögren’s syndrome). Ten of the 38 patients with isolated unspecified myositis developed a CTD during the course of the disease (26%; 95% CI, 13 to 43%), and three patients were diagnosed with a malignancy within 2 years after the diagnosis of myositis (8%; 95% CI, 2 to 21%).

Thirty-two patients (19%; 95% CI, 14 to 26%) were assigned to the possible myositis category. The biopsy specimens of these patients showed a necrotizing myopathy containing no or only minimal inflammatory cells in the vicinity of necrotic fibers. Ten of these patients had severe weakness, high sCK, abundant necrosis in the muscle biopsy, and a favorable outcome of their myositis after sustained treatment with high-dose prednisone, as described elsewhere.26

Patients with possible myositis had higher sCK activity than the other patients (4,038 U/l vs 2,352 U/l; 95% CI of the difference, 259 to 3,112). There were no differences in age, sex, MSAs, nonspecific autoantibodies, or ESR compared to the other patients. Three patients had proximal muscle complaints without objectified muscle weakness. Three patients had an associated CTD at onset of the muscle complaints (two, MCTD; one, Sjögren’s syndrome). Two patients developed a malignancy within 2 years after onset of possible myositis.
In this study we used clinical (rate of onset, distribution of weakness), laboratory (elevated sCK) and histopathological criteria for the diagnosis of the adult idiopathic inflammatory myopathies (IIMs), excluding s-IBM, based on disease features that are generally accepted to be valuable for the diagnosis of PM and DM and for differentiation from s-IBM.\textsuperscript{4,15-18} We did not include EMG findings because these are not likely to be of added value for the diagnosis of, and the distinction between IIMs.\textsuperscript{4} Likewise, detection of MSAs seems not to be of high additional differential diagnostic value as noted by us and by others. Although MSAs are specific for the IIMs,\textsuperscript{27,28} they are not found to be useful in differentiating the IIM subtypes, including s-IBM.\textsuperscript{29} Our most important finding is the extremely rare occurrence of PM, which ultimately could only be diagnosed in 2% of patients with an inflammatory myopathy (and even less if patients with juvenile DM or s-IBM at initial evaluation are considered). At initial evaluation, this diagnosis was made in nine patients. These nine patients had longer disease duration before initial evaluation and tended to be older and have lower sCK activity than did the other patients, features suggestive of the diagnosis s-IBM. Five of the nine patients showed features at follow-up evaluation that we regard as highly suggestive of s-IBM. In one of these patients (PM Patient 5), a dystrophy or myopathy with rimmed vacuoles can not be ruled out. It is of note, that none of the remaining four patients complied with the assumed typical clinical picture of young adults with limb-girdle distribution of muscle weakness. In large series of patients, frequencies of PM were 30 to 60% of all patients.

\begin{table}
\centering
\caption{Frequencies of diagnoses at presentation and follow-up}
\begin{tabular}{l|c|c}
\hline
 & Presentation & Follow-up \\
\hline
PM isolated & 9 (5%) & 4 (2\%)* \\
+CTD & - & - \\
+mal & - & - \\
DM isolated & 54 (33\%) & 48 (29\%) \\
+CTD & 3 (2\%) & 4 (2\%) \\
+mal & 2 (1\%) & 7 (4\%) \\
Unspecified myositis isolated & 38 (23\%) & 25 (15\%) \\
+CTD & 28 (17\%) & 36 (23\%) \\
+mal & 1 (0.1\%) & 4 (2\%) \\
Possible myositis isolated & 29 (18\%) & 27 (17\%) \\
+CTD & 3 (2\%) & 3 (2\%) \\
+mal & - & 2 (2\%) \\
Total & 165 (100\%) & 160 (97\%)* \\
\hline
\end{tabular}
\end{table}

* Five patients (3\%) who were diagnosed with PM showed features that were highly suggestive of s-IBM at follow-up.
s-IBM and juvenile DM excluded. In these studies, diagnoses were based on the 1975 Bohan and Peter criteria, which do not consider the histopathological differences between PM and DM and the differentiation of s-IBM from PM. By now, it is generally recognized that PM and s-IBM show endomysial mononuclear cell infiltrates that focally surround and invade nonnecrotic muscle fibers. Many patients diagnosed with treatment-resistant PM in the past retrospectively have been rediagnosed with s-IBM. Moreover, in recent years it has become clear that the muscle biopsy can also show endomysial infiltrates for several muscular dystrophies. Our results show that PM is an overdiagnosed condition and is by far the least common of the inflammatory myopathies. This should be investigated further in a prospective study that includes immunohistochemical characterization of the endomysial infiltrates, MHC-I expression, and adequate exclusion of muscular dystrophies. Our study also revealed that a definite diagnosis of PM or DM was not possible for 59% of patients at initial evaluation. In 40%, this was because of the absence of distinctive features allowing a diagnosis of PM or DM. The muscle biopsies of these patients showed perimysial and perivascular localization of the inflammation, suggestive of a primary microangiopathy, as found in patients with DM. The muscle biopsies of a large majority of all patients with myositis and associated CTD showed a histopathology of unspecified myositis (28/32). Furthermore, in 26 of 32 patients with DM who were diagnosed based on their skin abnormalities, histopathologic features were similar to those found in patients with an unspecified myositis. It should also be noted that anti Jo-1 antibodies occurred in almost the same proportion of patients with DM (9/42) as with unspecified myositis (9/35). This finding further contradicts the notion that Jo-1-associated myositis is distinct from DM, and is in line with previous observations. Future studies, including phenotyping of inflammatory cells and histochemical and electron microscopic investigations of the skeletal muscle microvasculature, may clarify if DM, myositis associated with CTD, and our group of isolated unspecified myositis have pathogenetic mechanisms in common. It should be noted that, in view of the limitations of a retrospective study design, it is possible that subtle skin changes were overlooked in some of our patients with unspecified myositis. We would like to stress that our diagnosis of unspecified myositis corresponds with the diagnosis of definite PM according to the Bohan and Peter criteria based on the mere absence of DM skin changes. The implication of this notion goes beyond semantics: nowadays, a diagnosis of PM has become connected with a presumed immune mechanism (activated T-cells that are directed primarily against an as yet unknown muscle fiber antigen). This hypothesis originates from observations of mononuclear cells focally surrounding and invading nonnecrotic fibers, which, however, is no feature of the category of patients described here with unspecified myositis. Nineteen percent of our patients were diagnosed with possible myositis because the muscle biopsy specimen showed a necrotizing myopathy but contained no inflammatory exudate. This group corresponds with a diagnosis of probable PM according to Dalakas. However,
the designation ‘probable PM’ implies that there is a similar pathogenesis to ‘definite PM’, for which there is no evidence as yet. The absence of clear inflammation could be the result of a sampling error, although this is not plausible because the biopsies were taken from a severely affected muscle showing abundant myopathic abnormalities. Admittedly, we did not systematically perform (immuno)histochemistry and DNA analyses to exclude muscular dystrophies. This can be investigated further in a prospective study that should include current possibilities to diagnose specific muscular dystrophies, and immunohistochemical studies such as MHC-I expression. However, despite the lack of inflammatory infiltrates, the prednisone-induced complete resolution of muscle weakness and normalization of sCK in 60% of the re-examined patients (data to be described separately), the presence of MSAs in approximately the same proportion of patients as in the other IIM subtypes, and the absence of any differences with the other patients strongly indicate that this category should be regarded as an immune-mediated myopathy. Considering our methods used for patient identification, it is conceivable that the prevalence of this patient type is underrated in our study.

It is of note that one-fourth of the patients with isolated unspecified myositis developed a CTD during the follow-up period. Furthermore, 8% of patients with isolated unspecified myositis and 7% of patients with isolated possible myositis developed a malignancy after onset of the myositis. Therefore, a patient with isolated unspecified myositis should be carefully followed for the development of CTD. Also, a work-up for diagnosing malignancies should not be limited to patients with DM but also should include patients with isolated unspecified and isolated possible myositis.

Our study focused on showing that applying currently used diagnostic criteria might lead to erroneous subclassification of patients with IIM. Potentially, our findings can facilitate future studies of pathologic mechanisms, which should form the basis for improving the classification of the IIMs.
References