Novel Classification of Idiopathic Inflammatory Myopathies Based on Overlap Syndrome Features and Autoantibodies

Analysis of 100 French Canadian Patients

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Abstract: Our objective was to improve the currently imperfect classifications of idiopathic inflammatory myopathies (IIM). In clinical practice, overlap features are common in IIM. This provided a rationale for positioning overlap clinical features at the core of a new classification system. We conducted a longitudinal study of 100 consecutive adult French Canadian patients with IIM. Clinical and laboratory data were obtained by retrospective chart review. Sera were analyzed for autoantibodies (aAbs) by protein A-assisted immunoprecipitation and double immunodiffusion. Overlap aAbs encompassed aAbs to synthetases, systemic sclerosis-associated aAbs, anti-signal recognition particle (SRP) and anti-nucleoporins. Patients were classified both at IIM diagnosis, based on data at presentation, and at the end of follow-up, based on cumulative findings. Three classifications were used: 1) the Bohan and Peter original classification, 2) a new version of that classification as modified by us, and 3) a novel clinicoserologic classification. As investigators were blinded to aAb results, the modified classification is strictly a clinical classification. Its core concept is the attribution of diagnostic significance to the presence of overlap features, that is, their presence resulted in a diagnosis of overlap myositis (OM). This approach allowed direct comparison with the original Bohan and Peter classification. By integrating aAb results to the modified classification, we also defined the clinicoserologic classification, which allowed to examine the added value of aAbs to diagnostic, therapeutic and prognostic stratification.

Whereas polymyositis (PM) was the most common IIM according to the original classification, accounting for 45% of the cohort at diagnosis, its frequency fell to 14% with the modified classification. Conversely, while the frequency of myositis associated with connective tissue disease was 24% according to the original classification, the frequency of OM was 60% when using the modified classification. At last follow-up, the frequency of PM fell further to only 9%, while the frequency of OM rose to 67%. Systemic sclerosis was the most common connective tissue disease associated with IIM, accounting for 42.6% of OM patients and 29% of the cohort.

The frequencies of overlap aAbs in the cohort and in OM patients were 48% and 70.5% (n = 48/68), respectively. The presence of overlap aAbs at IIM diagnosis identified additional OM patients unrecognized by the modified classification. The sensitivity of the modified classification for OM at diagnosis was 87%, suggesting that clinicians may rely on the modified classification for identification of most OM patients, while awaiting results of aAb assays.

The new classifications predicted the response to prednisone and IIM course. Using stringent definitions, IIM was classified as responsive or refractory after an adequate initial corticosteroid therapy, and the disease course as monophasic or chronic after a single adequate trial of prednisone. PM was always chronic and was associated with the highest rate (50%) of refractoriness to initial corticosteroid treatment. Dermatomyositis was almost always chronic (92% rate); however, its responsiveness to initial corticosteroid treatment was high (87%). OM was almost always responsive to corticosteroids (89%–100% rates). When OM patients were divided according to aAb subsets, anti-synthetase, SRP, or nucleoporin aAbs were markers for chronic myositis, whereas aAbs to U1RNP, Pm-Scl, or Ku were markers for monophasic myositis.

We conclude that the original Bohan and Peter classification should be abandoned as it leads to misclassification of patients. Much of IIM is composed of OM. The proposed modified and clinicoserologic classifications have diagnostic, prognostic, and therapeutic value.

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Abbreviations: aAbs = autoantibodies, ACR = American College of Rheumatology, ANA = antinuclear autoantibodies, antitopo I = anti-DNA topoisomerase I, CAM = cancer-associated myositis, CHUM = Centre Hospitalier de l'Université de Montréal, CK = creatine kinase, CTM = myositis with another connective tissue disease, DM = dermatomyositis, EMG = electromyogram, IIM = idiopathic inflammatory myopathies, MAA = myositis-associated autoantibodies, MSA = myositis-specific autoantibodies, OM = overlap myositis, OR = odds ratio, PM = polymyositis, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SRP = signal recognition particle.

INTRODUCTION

The major objective of the current study was to improve the classification of idiopathic inflammatory myopathies (IIM). In 1975, Bohan and Peter[4] proposed their original classification and diagnostic criteria for IIM. However, this topic has recently become the object of increasing debate[1,13,30,35,53]. The Bohan and Peter classification has been criticized for overdiagnosis of polymyositis (PM)[61]; for loosely defining myositis in overlap with another connective tissue disease (CTM)[33]; for clinical, genetic, and immunologic heterogeneity in all subsets[29]; and for being obsolete[26].

At the opposite end of the classification spectrum, the contrasting approach of Dalakas was histologic, emphasizing muscle biopsy as the definitive test for establishing the diagnosis of PM, dermatomyositis (DM), and inclusion-body myositis[12]. While distinct immunopathogenic mechanisms seemed to justify this classification, this pathologically defined PM[16,17,25] appears rare[1,26,61], and no study has described its clinical, autoantibody (aAb), and prognostic features. In contrast, a recent histologically defined cohort of 537 patients, using less stringent pathologic criteria, found that PM was the most frequent IIM, illustrating the pitfalls of defining IIM subsets by biopsy alone[7]. Furthermore, in a cohort of 165 patients with myositis other than inclusion-body myositis, the initial muscle biopsy could diagnose only 9 cases of PM and 27 of DM if clinicoserologic features were ignored, leaving the descriptive entities of unspecified myositis and possible myositis as the dominant subsets[61]. The lack of consensus in the classification of IIM is further highlighted by 2 reports using divergent IIM classifications although addressing a similar research question[7,20].

The discovery of myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) led to the proposal of a serologic approach complementary to the Bohan and Peter IIM classification, as striking associations of MSAs with clinical features, immunogenetics, and survival were observed[29]. However, this classification is limited by some constraints. First, the sophisticated methods required for identification of several aAbs are not always routinely available and are costly, therefore limiting their use by clinicians. Second, this serologic approach has led to the creation of a large and heterogeneous group of MSA- and MAA-negative patients, undefined with respect to diagnosis, prognosis, and survival. Third, although it has been suggested that MSAs may identify distinct disease entities[52,54], in practice these aAbs often segregate with overlap manifestations that may also be observed in the absence of MSAs[62].

These constraints and debate led us to search for a new approach to the classification of IIM that would bring together strong clinical evidence of myositis readily identifiable by clinicians with the diagnostic specificity of MSA and MAA tests. We and others have noted that, in clinical practice, overlap features are common in IIM[18,29]. However, this evidence is poorly reflected in the original Bohan and Peter classification, which emphasizes the presence of established connective tissue disease rather than the presence of overlap features to warrant a diagnosis of CTM[33,53]. In fact, many experienced clinicians now feel that most cases of IIM occur in the setting of overlap syndromes[1,18,26,62]. This provided the rationale for positioning overlap clinical features at the core of a new classification.

Hence, we developed 2 new classification systems of IIM that focus on overlap disease manifestations. We named the first new classification ''the modified Bohan and Peter classification.'' This approach allowed a direct comparison with the admittedly imperfect, yet extensively used, original Bohan and Peter classification. The second novel classification, referred to herein as ''the clinicoserologic classification,'' adds to the modified classification the results of MSA and MAA tests. This allowed us to examine the added value of these aAbs to diagnostic, therapeutic, and prognostic stratification. Finally, we studied these new classifications in a large cohort of French Canadian patients with IIM, in keeping with our previous studies of systemic autoimmune diseases in this population[15,28,48,49,60].

PATIENTS AND METHODS

Patients

We conducted a longitudinal study of 100 consecutive adult patients seen at the Centre Hospitalier de l'Université de Montréal (CHUM), a tertiary care center composed of 3 university hospitals (Notre-Dame, St-Luc, and Hôtel-Dieu hospitals), between March 1967 and April 2001. A list of IIM patients was obtained from Medical Records using discharge summary diagnostic codes corresponding to PM, DM, myositis, mixed connective tissue disease, and overlap syndrome. The number of IIM diagnoses during that period was, by decade: 2 patients in 1960–1969, 7 in 1970–1979, 29 in 1980–1989, 57 in 1990–1999, and 5 patients in 2000, with a single year high of 10 in 1996. The 5 inclusion criteria were as follows. First, only French Canadian patients were

eligible. Second, the illness fulfilled Bohan and Peter criteria for possible, probable, or definite PM or DM by the end of follow-up[4]. Patients with possible PM were included because this diagnosis is not uncommon in clinical practice and the prolonged follow-up provided an opportunity to examine its outcome. Third, patients had to be 18 years or older at myositis diagnosis (therefore juvenile DM as defined by Bohan and Peter was excluded). Fourth, inclusion-body myositis, rare forms of IIM, and non-IIM causes of myopathy (such as muscular dystrophies) were excluded. Also excluded were patients diagnosed as IIM in whom a non-IIM myopathy was ultimately diagnosed upon follow-up. Finally, a frozen serum sample had to be available for immunologic studies.

We previously reported on IIM in 30 French Canadians[60]. We took stock of extensive additional patient recruitment, longer follow-up, and the academic merger of Notre-Dame Hospital into the CHUM to expand our IIM cohort, which includes 28 of the original patients.

Data Collection

Data on history, physical findings, and laboratory investigations were obtained by retrospective medical record review using a standardized protocol. Treating physicians were contacted as needed to clarify key data, and written consent was obtained to communicate with and examine patients for further data collection. All living patients (n = 77) but 1 were examined or contacted by us between June 1999 and April 2001. Myositis diagnosis was made at CHUM in 87 patients, and 13 additional patients were referred with an established IIM diagnosis. A muscle biopsy and an electromyogram (EMG) were done in 87 and 88 patients, respectively.

Definitions for target organ involvement were as previously described[48]:

1) Raynaud phenomenon: at least 2 of 3 phases of color changes (white, blue, red), usually induced by cold exposure, and involving at least 1 finger of both upper extremities;
2) Arthritis: symmetrical polysynovitis;
3) Esophagus: systemic sclerosis-type changes in the distal esophagus (contractions of weak amplitude, slow or absent contractions, distension, hypotonia, or atonia of the lower esophageal sphincter);
4) Lungs: bibasilar interstitial fibrosis on chest radiogram or computed tomography scan, isolated DLCO reduction (<70% of predicted normal value) on pulmonary function tests;
5) Small bowel: clinical malabsorption and/or radiographic evidence of hypomotility;
6) Systemic sclerosis renal crisis: malignant hypertension and/or rapidly progressive renal failure.

Nailfold capillary microscopy was performed as previously described[48]. Deceased patients were identified by chart review and communication with treating physicians, and by telephone interview with family members.

Three Myositis Classifications

Patients were classified both at IIM diagnosis, based on available data at presentation, and at the end of follow-up, based on cumulative longitudinal findings. The length of follow-up was calculated from IIM diagnosis to the last visit or death. As shown in Table 1, 3 classifications were used: 1) the Bohan and Peter original classification[4], 2) a new version of that classification as modified by us, and 3) a novel clinicoserologic classification. The distribution of patients using the original and the modified Bohan and Peter classifications was done before results of IIM aAbs were determined by one of us (INT). Conversely, patients were classified according to the clinicoserologic classification only after results of IIM aAbs were available (see Table 1). In the latter classification, patients with both cancer and an overlap aAb were categorized by definition as overlap myositis (OM). This was based on a review of literature showing no association between cancer and overlap aAbs[8,9,10,24,29,31,32,37,38,40,43,52,58]. Because the presence of anti-Mi-2 is a highly specific marker for DM[54] and because cancer-associated anti-Mi-2 is rare (fewer than 5% of patients with DM and anti-Mi-2)[18,19,29,34,42,47], a single patient with anti-Mi-2, DM, and cancer was classified as DM. The American College of Rheumatology (ACR) classification criteria were used for the diagnosis of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)[2,23]. For IIM classification purposes, the 1980 ACR criteria for systemic sclerosis were used[50]; however, for descriptive purposes, more recent criteria were used, as proposed by us[28] and others[27,45]. Because no patient in the present study had primary Sjögren syndrome, this diagnosis was not included as an associated connective tissue disease for classification purposes.

Definitions

Remission of myositis was defined as the presence of 3 findings: normal serum muscle enzymes, disappearance of myalgia and normal or improved strength (that is, normalization of strength was not always achieved). In cases of myositis with persistently normal or near normal creatine kinase (CK) (defined as lower than twice the upper limit of the normal serum CK level), remission was defined by clinical improvement, with normalization of strength, without any evidence of active myositis on EMG or magnetic resonance imaging (MRI), when done. With the benefit of follow-up, no case of inactive disease with serum CK ''leakage'' was identified.

Recurrence of myositis was defined by serum CK elevation, with or without associated muscle weakness or myalgia, that led to a modification or a reintroduction of

TABLE 1. Three Classifications for Idiopathic Inflammatory Myopathies

Abbreviation	Description
Original Bohan and Peter Classification*	
PM	Primary polymyositis
DM	Primary dermatomyositis
CTM	Myositis with another connective tissue disease
CAM	Myositis associated with cancer
Modified Bohan and Peter Classification	
PM	Pure polymyositis
DM	Pure dermatomyositis
OM	Overlap myositis: with at least 1 clinical overlap feature[†]
CAM	Cancer-associated myositis: with clinical paraneoplastic features[‡]
Novel clinicoserologic Classification	
PM	Pure polymyositis
DM	Pure dermatomyositis
OM	Overlap myositis: myositis with at least 1 clinical overlap feature and/or an overlap autoantibody[§]
CAM	Cancer-associated myositis: with clinical paraneoplastic features and without an overlap autoantibody or anti-Mi-2

*Diagnostic criteria[5,53]:

1) Symmetric proximal muscle weakness.

2) Elevation of serum skeletal muscle enzymes.

3) Electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves and insertional irritability; and bizarre, high-frequency repetitive discharges.

4) Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate.

5) Typical skin rash of DM, including the heliotrope rash, Gottron sign, and Gottron papules.

Definite myositis: 4 criteria (without the rash) for PM, 3 or 4 criteria (plus the rash) for DM.

Probable myositis: 3 criteria (without the rash) for PM, 2 criteria (plus the rash) for DM.

Possible myositis: 2 criteria (without the rash) for PM, 1 criterion (plus the rash) for DM.

[†]Clinical overlap features: polyarthritis, Raynaud phenomenon, sclerodactyly, scleroderma proximal to MCP joints, typical SSc-type calcinosis in the fingers, lower esophageal or small-bowel hypomotility, DLCO lower than 70% of the normal predicted value, interstitial lung disease on chest radiogram or CT scan, discoid lupus, anti-native DNA antibodies plus hypocomplementemia, 4 or more of 11 ACR SLE criteria, antiphospholipid syndrome.

[‡]Clinical paraneoplastic features: cancer within 3 yr of myositis diagnosis, plus absence of multiple clinical overlap features; plus, if cancer was cured, myositis was cured as well.

[§]Overlap autoantibodies encompass antisynthethases (Jo-1, PL-7, PL-12, OJ, EJ, KS), SSc-associated autoantibodies (SSc-specific antibodies: centromeres, topo I, RNA-polymerases I or III, Th; and antibodies associated with SSc in overlap: U1RNP, U2RNP, U3RNP, U5RNP, Pm-Scl, Ku), and other autoantibodies (SRP, nucleoporins).

treatment. In cases of myositis with normal or near-normal serum CK, clinical deterioration was used, with the benefit of follow-up for final judgment. The onset of recurrence was defined by the onset of symptoms, or the first abnormal serum CK elevation, and not the time of modification of treatment. To describe the timing of myositis recurrence after a remission, descriptive terms were used: *early flare*, when recurrence of disease was noted while the patient was receiving a daily prednisone dose greater than 5 mg and/or was on another immunosuppressive therapy; *late flare*, when recurrence of disease was noted within a year of the definite lowering of daily prednisone to 5 mg or lower; *early relapse*, when recurrence of disease was noted more than a year after the definite lowering of daily prednisone to 5 mg or lower; and *late relapse*, when recurrence of disease was noted more than 5 years after the definite lowering of daily prednisone to 5 mg or lower.

Adequate initial corticosteroid therapy was defined by a daily prednisone dose of at least 40 mg for a month, followed by a steroid taper that was neither too rapid (based on clinical judgment) nor done in alternate-day fashion. *Refractory* myositis (as opposed to *responsive* myositis) defined a myositis where adequate initial corticosteroid therapy failed to induce remission. *Monophasic* myositis (as opposed to *chronic* myositis) defined myositis that responded to adequate initial corticosteroid therapy, but that also remained in remission for at least 1 year after the definite lowering of prednisone to 5 mg. If further follow-up was available and an early relapse occurred, the myositis was considered chronic. *Chronic* myositis defined myositis that was either refractory or that responded to adequate initial corticosteroid therapy only to recur on corticosteroid taper (early flare) or on definite lowering of prednisone to 5 mg a day (late flare or early relapse). This led to long-term corticosteroid treatment (daily prednisone >5 mg) or second-line therapy.

Immunologic Studies

Coded serum samples were frozen at −80 °C, and immunologic studies were done without knowledge of clinical data or diagnosis. The timing of serum samples to the diagnosis of myositis was as follows: 9 sera were obtained at least 6 months before IIM diagnosis, 45 sera were obtained at diagnosis, and 46 sera were obtained at least 6 months after diagnosis, with 23 of those more than 5 years after diagnosis. Antinuclear aAbs (ANA) and anticentromere aAbs were determined by indirect immunofluorescence on HEp-2 cells (Antibodies Inc., Davis, CA), and anti-DNA topoisomerase I (antitopo I) by ELISA, as described.[48] Anti-Ro and anti-La were determined by ELISA (Calbiotech, Spring Valley, CA).

MSAs and MAAs are collectively referred to herein as *overlap aAbs*, which were categorized into 3 groups. *aAbs to synthetases* encompassed anti-Jo-1, OJ, EJ, KS, PL7, and PL12 specificities[3,21,51,56]. *Systemic sclerosis-associated aAbs* encompassed systemic sclerosis-specific aAbs (aAbs to centromeres, topo I, Th, and RNA polymerases I/III)[8,37,48] as well as aAbs associated with systemic sclerosis in overlap (aAbs to Pm-Scl, U1RNP, U2RNP, U3RNP, U5RNP, and Ku autoantigens)[9,10,32,40,43,44,58]. *Other overlap aAbs*

included anti-signal recognition particle (SRP)[22,24,36,52] and anti-nucleoporins[11,58]. Neither anti-Mi-2 (which are DM-specific and are not associated with overlap manifestations, as measured by immunodiffusion or immunoprecipitation) nor anti-Ro and anti-La (which are commonly associated with MSAs and MAAs) were classified as overlap aAbs.

Sera were analyzed by one of us (INT) for aAbs by protein A-assisted immunoprecipitation, both for nucleic acid analysis and protein analysis, along with double immunodiffusion[3,51,56]. These tests together detect all of the described antisynthetases, the systemic sclerosis-associated aAbs (other than anticentromere and antitopo I), anti-SRP, anti-Mi-2, and anti-Ro and anti-La. The tests were performed as previously described[3,51,56]. Nucleic acid analysis used 3–5 mg of protein A-Sepharose, 20 μL of patient serum, and unlabeled HeLa cell extract (>10 power 6 cells). Immunoprecipitates were analyzed on 7–8M urea, 10% polyacrylamide gel electrophoresis developed with silver stain. Protein analysis used 1–2 mg of protein A-Sepharose, 10–15 μL of serum, and 35S-methionine-labeled HeLa cell extract (>10 power 5 HeLa cells). Immunoprecipitates were analyzed by SDS-polyacrylamide gel electrophoresis (between 8% and 10%). Immunodiffusion was performed using calf thymus extract.

Statistical Analysis

Chi-square analysis was performed for frequency comparisons among subsets (using the Fisher 2-tailed exact test, where applicable). Positive and negative predictive values, odds ratios (OR), and likelihood ratios were calculated using InStat and Prism 3.0 softwares (GraphPad Software, Inc., San Diego, CA). The Mann-Whitney U test was used for comparison of group means. Kaplan-Meier curves were constructed to estimate survival, and cumulative survival curves were compared using the log-rank statistic as described[48].

RESULTS

Demographics of the Cohort

All 100 patients were French Canadians, with a female:male ratio of 3 to 1. The mean age at diagnosis was 46.9 years (range, 18–79 yr), with age-specific frequency rates as follows: 9 patients were ≥70 years, 12 patients were 60–69 years, 20 patients were 50–59 years, 26 patients were 40–49 years, 19 patients were 30–39 years, 13 patients were 20–29 years, and 1 patient was 18 years old. The mean interval between clinical onset of muscle involvement and myositis diagnosis was 10.5 months (range, 0–155 mo). The mean duration of follow-up after myositis diagnosis was 8.7 years (range, 0.17–33.6 yr), corresponding to 5.5 years (range, 0.25–22.2 yr) and 9.7 years (range, 0.17–33.6 yr) for deceased and living patients, respectively.

At myositis diagnosis, according to Bohan and Peter diagnostic criteria[4], 36 definite, 45 probable, and 18 possible cases of myositis were seen, while a single patient had a DM rash and a myopathic EMG. At last follow-up, there were 47 definite, 41 probable, and 12 possible cases of myositis. Serum CK levels were normal in 7 patients. Muscle biopsy findings were consistent with the diagnosis of PM or DM in 78 patients. Before IIM diagnosis, 16 patients had a diagnosis of another connective tissue disease (6 RA, 3 SLE, and 7 systemic sclerosis patients), although in only 5 (31%) patients (4 RA and 1 SLE) was the diagnosis made at least 3 years earlier (range, 4–22 yr).

Sixteen malignancies were diagnosed (lymphomas and breast, n = 4 each; uterus, lung, and colon, n = 2 each; esophagus and skin, n = 1 each). Cancer was diagnosed either more than 3 years before IIM diagnosis (n = 2, 7 yr), concurrently (n = 3), within 3 years after diagnosis (n = 6) or more than 3 years after diagnosis (n = 5). Of the 6 patients diagnosed within 3 years after diagnosis, 3 were not classified as cancer-associated myositis (CAM) because the clinical course did not support it: 2 lymphomas appeared while on methotrexate therapy and were cured with methotrexate discontinuation, while myositis remained active; the third patient, who had multiple overlap features and anti-U1RNP aAb, developed esophageal cancer on follow-up.

Three Classifications of Idiopathic Inflammatory Myopathies

The distribution of the various IIM by Bohan and Peter original classification differed strikingly from those using the 2 newly defined classifications (Table 2). According to the original classification, PM was the most frequent entity, both at IIM diagnosis (n = 45, 45%) and at follow-up (n = 33,

TABLE 2. Distribution of 100 Patients at Myositis Diagnosis and Last Follow-Up According to 3 Classifications for Idiopathic Inflammatory Myopathies

Classification	PM (No.)	DM (No.)	CTM-OM (No.)	CAM (No.)	Total (No.)
Original Bohan and Peter classification at diagnosis	45	28	24	3	100
Original Bohan and Peter classification at last follow-up	33	30	31	6	100
Modified Bohan and Peter classification at diagnosis	14	23	60	3	100
Modified Bohan and Peter classification at last follow-up	9	18	67	6	100
Novel clinicoserologic classification at diagnosis	10	20	68	2	100
Novel clinicoserologic classification at last follow-up	9	19	68	4	100

33%). With follow-up, 12 (27%) of the 45 cases initially classified as PM were reclassified as DM (the patients had developed a DM rash, n = 4) CAM (n = 1), or CTM (n = 7).

However, using the modified Bohan and Peter classification, PM was a rare entity at IIM diagnosis, occurring in only 14 cases (14%) (see Table 2). Furthermore, with follow-up, 5 of these 14 (36%) cases were reclassified as OM. Thus, using the modified classification, only 9 of 45 (20%) cases diagnosed as PM by the original classification were still classified as PM at follow-up. CTM was present in only 24 (24%) cases according to the Bohan and Peter original classification at IIM diagnosis. In striking contrast, when the modified classification was used, OM was the most frequent entity encountered at diagnosis, accounting for 60% (n = 60 cases) of the cohort. Table 2 also shows that, using the modified classification, the overall frequency of OM in the cohort at last follow-up was 67% (n = 67). This demonstrated that the original Bohan and Peter definitions overlooked a major subset of IIM patients with overlap features. Conversely, at IIM diagnosis, the modified classification had correctly identified 88% (59/67) of OM cases (1 case classified as OM at diagnosis was reclassified as CAM at last follow-up).

At last follow-up, IIM patients were almost identically distributed using both the modified and the clinicoserologic classifications (see Table 2). Only 2 cases were classified differently: these cases classified as CAM by the modified classification had anti-Th and anti-Mi-2 aAbs, respectively, and were reclassified as OM and DM in agreement with the clinicoserologic classification criteria (see Table 1). Thus, at myositis diagnosis, the clinicoserologic classification identified almost all (66/67, 98.5%) cases ultimately categorized as OM by the modified classification at last follow-up. The exception was a patient who initially presented with fever and later developed overlap features of diffuse systemic sclerosis and renal crisis.

Almost all cases (n = 67/68, 98.5%) classified as OM at diagnosis according to the clinicoserologic classification retained that diagnosis at last follow-up (see Table 2). Of special interest is that, whereas the clinicoserologic classification identified at diagnosis 68 OM patients, the modified classification identified only 60 (88%) of these patients, indicating that 8 additional patients were identified because of the presence of overlap aAbs. It is noteworthy that 7 of 8 patients (87.5%) developed clinical features of overlap during follow-up, indicating that the presence of aAbs at diagnosis correctly predicted the onset of overlap manifestations.

Finally, we determined the sensitivities of the modified classification for OM patients at diagnosis and last follow-up, using as standard for the true frequency of OM the number of OM cases according to the clinicoserologic classification at last follow-up. Thus, the sensitivities of the modified classification for OM at diagnosis and last follow-up were 87% (59/68) and 98.5% (67/68), respectively.

Clinical Characteristics of Patients With Idiopathic Inflammatory Myopathies

In Table 3 we compare, at diagnosis and last follow-up, the frequency of various demographic and clinical features, using the original Bohan and Peter versus the modified classifications. A strong female predominance of IIM is noted, regardless of the IIM type. As expected, the frequency of various manifestations increased over time. For example, the frequency of proximal weakness at diagnosis in DM was 83%, but it reached 100% at follow-up. Similarly, in the OM group, the frequency of pulmonary involvement increased from 36% at diagnosis to 58% at last follow-up.

Also, when using Bohan and Peter original classification, overlap features are not restricted to the CTM group (see Table 3). For example, Raynaud phenomenon and arthritis, while present at diagnosis in 71% and 58% of CTM patients, respectively, were nevertheless both present in 33% of patients with primary PM according to Bohan and Peter criteria. Furthermore, when using the original classification, clinical overlap features were frequently found in all IIM subsets (except CAM). For example, PM patients were found to have fever at diagnosis in a frequency of 18%, and the cumulative frequencies of Raynaud phenomenon, arthritis, and interstitial lung disease were 36%, 36%, and 18%, respectively. Other overlap features noted in the primary PM group at last follow-up were esophageal dysmotility (27%), sclerodactyly (12%), trigeminal neuropathy (6%), and mechanic's hands (3%). The lack of discriminatory power of the original Bohan and Peter classification for overlap features in PM was also noted for primary DM patients: these DM patients were commonly found to have clinical overlap features at last follow-up, including interstitial lung disease (27%), Raynaud phenomenon (23%), and arthritis (17%) (see Table 3).

Although Table 3 emphasizes features at last follow-up, it is noteworthy that overlap features are frequently present already at IIM diagnosis among OM patients. For example, of the 38 patients with arthritis at last follow-up, this manifestation was present at diagnosis in 33 (87%) patients. Similarly, among 47 OM patients with Raynaud phenomenon at last follow-up, this feature was present at diagnosis in 37 (79%) patients.

Strong Association of Overlap aAbs With Overlap Clinical Features in Patients With Idiopathic Inflammatory Myopathies

Table 4 shows the distribution of aAbs in the various IIM: 48% (n = 48) of patients expressed at least 1 overlap aAb. Thus, aAbs to the various synthetases, systemic sclerosis-associated aAbs, and other aAbs were present in

TABLE 3. Clinical Features in 100 Patients With Idiopathic Inflammatory Myopathies Categorized at Myositis Diagnosis and Last Follow-Up According to Bohan and Peter Original Versus Modified Classifications

	Total No. (%)	PM Original No. (%)	PM Modified No. (%)	DM Original No. (%)	DM Modified No. (%)	CTM Original No. (%)	OM Modified No. (%)	CAM Original and Modified No. (%)
Total no. of patients	100	33 (33)	9 (9)	30 (30)	18 (18)	31 (31)	67 (67)	6 (6)
Mean age at diagnosis (yr)	46.9	51.0	60.1	42.4	44.4	45.1	44.9	56.9
Gender F:M	75:25	22:11	8:1	22:8	14:4	25:6	48:19	6:0
Mean interval from IIM onset to diagnosis (mo)	10.5	17.5	43.0	8.5	11.5	6.0	6.1	2.0
Mean follow-up after IIM diagnosis (yr)	8.75	7.5	6.1	10.5	12.3	8.0	8.1	10.4
Proximal weakness at diagnosis	92 (92)	30 (91)	8 (89)	25 (83)	15 (83)	31 (100)	63 (94)	6 (100)
Proximal weakness at last follow-up	100 (100)	33 (100)	9 (100)	30 (100)	18 (100)	31 (100)	67 (100)	6 (100)
Myalgia at diagnosis	47 (47)	12 (36)	2 (22)	20 (67)	13 (72)	12 (39)	29 (43)	3 (50)
DM rash at diagnosis	31 (31)	0	0	26 (87)	18 (100)	0	8 (12)	5 (83)
DM rash at last follow-up	38 (38)	0	0	30 (100)	18 (100)	3 (10)	15 (22)	5 (83)
DM calcinosis at last follow-up	7 (7)	0	0	4 (13)	4 (22)	2 (6)	2 (3)	1 (17)
Oropharyngeal dysphagia at diagnosis	12 (12)	8 (24)	3 (33)	2 (7)	2 (11)	1 (3)	6 (9)	1 (17)
Oropharyngeal dysphagia at last follow-up	19 (19)	10 (30)	4 (44)	5 (17)	5 (28)	3 (10)	9 (13)	1 (17)
Subjective dysphagia at diagnosis	44 (44)	17 (52)	7 (78)	12 (40)	8 (44)	11 (35)	25 (37)	4 (67)
Subjective dysphagia at last follow-up	55 (55)	19 (58)	7 (78)	18 (60)	11 (61)	14 (45)	33 (49)	4 (67)
Fever at diagnosis	14 (14)	6 (18)	0	3 (10)	0	4 (13)	13 (19)	1 (17)
Arthritis at diagnosis	34 (34)	11 (33)	0	4 (13)	0	18 (58)	33 (49)	1 (17)
Arthritis at last follow-up	40 (40)	12 (36)	0	5 (17)	0	21 (68)	38 (57)	2 (33)
Mechanic's hands at last follow-up	5 (5)	1 (3)	0	3 (10)	0	1 (3)	5 (7)	0
Pulmonary involvement at diagnosis	24 (24)	7 (21)	0	6 (20)	0	11 (35)	24 (36)	0
Pulmonary involvement at last follow-up	39 (39)	9 (27)	0	8 (27)	0	22 (71)	39 (58)	0
DLCO <70% at diagnosis	20 (20)	6 (18)	0	5 (17)	0	9 (29)	20 (30)	0
DLCO <70% at last follow-up	33 (33)	7 (21)	0	6 (20)	0	20 (65)	33 (49)	0
Interstitial lung disease at diagnosis	17 (17)	5 (15)	0	6 (20)	0	6 (19)	17 (25)	0
Interstitial lung disease at last follow-up	28 (28)	6 (18)	0	8 (27)	0	14 (45)	28 (42)	0
Raynaud phenomenon at diagnosis	37 (37)	11 (33)	0	4 (13)	0	22 (71)	37 (55)	0
Raynaud phenomenon at last follow-up	47 (47)	12 (36)	0	7 (23)	0	28 (90)	47 (70)	0
Sclerodactyly at diagnosis	18 (18)	2 (6)	0	0	0	16 (52)	18 (27)	0

continued

TABLE 3. *(Continued)*

	Total No. (%)	PM Original No. (%)	PM Modified No. (%)	DM Original No. (%)	DM Modified No. (%)	CTM Original No. (%)	OM Modified No. (%)	CAM Original and Modified No. (%)
Sclerodactyly at last follow-up	27 (27)	4 (12)	0	0	0	23 (74)	27 (40)	0
Scleroderma proximal to MCP joints at diagnosis	11 (11)	0	0	0	0	11 (35)	11 (16)	0
Scleroderma proximal to MCP joints at last follow-up	12 (12)	0	0	0	0	12 (39)	12 (18)	0
Trunk scleroderma at diagnosis	5 (5)	0	0	0	0	5 (16)	5 (7)	0
Trunk scleroderma at last follow-up	6 (6)	0	0	0	0	6 (19)	6 (9)	0
Lower esophageal dysphagia at diagnosis	19 (19)	2 (6)	0	2 (7)	0	15 (48)	19 (28)	0
Lower esophageal dysphagia at last follow-up	27 (27)	5 (15)	0	4 (13)	0	17 (55)	26 (39)	1.(17)
SSc-type small bowel involvement at diagnosis	4 (4)	1 (3)	0	0	0	3 (10)	4 (6)	0
SSc-type small bowel involvement at last follow-up	10 (10)	2 (6)	0	1 (3)	0	7 (23)	10 (15)	0
SSc-type calcinosis of the fingers at diagnosis	4 (4)	0	0	0	0	4 (13)	4 (6)	0
SSC-type calcinosis of the fingers at last follow-up	15 (15)	3 (9)	0	0	0	12 (39)	15 (22)	0
Trigeminal neuropathy at diagnosis	5 (5)	2 (6)	0	0	0	3 (10)	5 (7)	0

20%, 23%, and 5% of patients, respectively. Table 4 also shows that, when classified by Bohan and Peter original classification, overlap antibodies were seen in 56% and 55% of cases classified as PM at IIM diagnosis and last follow-up, respectively. Similarly, these aAbs were present in 21% and 30% of cases classified as primary DM at IIM diagnosis and follow-up, respectively. Again, this demonstrates the poor discriminatory power of the original Bohan and Peter classification.

Interestingly, while aAbs were found in 28% of PM and 17% of DM patients according to Bohan and Peter modified classification at diagnosis, no aAbs were found in these patients at follow-up (see Table 4). Furthermore, comparing the frequency of overlap aAbs at last follow-up between the original and modified classifications revealed a drastic drop from 55% to 0% for PM ($p < 0.01$) and from 30% to 0% ($p < 0.02$) for DM patients. In addition, of the 48 patients with aAbs, 47 (97.9%) patients were classified as having OM at follow-up by the modified classification. Thus, only 1 patient with an overlap aAb (anti-Th) did not develop overlap features at follow-up. Conversely, only a single patient without aAbs developed overlap features with follow-up (this PM patient initially presented with fever and later developed diffuse systemic sclerosis and renal crisis). Because the modified classification is based solely on the presence of clinical overlap features, and, furthermore, because patients were classified without knowledge of aAb assays, these results suggest that overlap clinical features were strongly correlated with overlap aAbs.

Indeed, the presence of overlap aAbs was strongly associated with overlap clinical features at IIM diagnosis (Table 5, panel A): of 48 patients with overlap aAbs, 40 (83.3%) had OM at diagnosis whereas of 52 patients without such antibodies, OM was present at diagnosis in only 20 (38%) patients ($p < 0.0001$; OR, 8; 95% confidence interval [CI], 3.1–20.5; specificity, 80%; positive predictive value, 83%; positive likelihood ratio, 3.33). The sensitivity of aAbs for overlap features was 66%, whereas the negative predictive value was 61%. aAbs were even more strikingly associated with overlap clinical features at last follow-up (see Table 5, panel B): of 48 patients with overlap aAbs, 47 (98%) had OM at last follow-up. In sharp contrast, of 52 patients without such aAbs, OM was present at last follow-up in only 20 (38%) ($p < 0.0001$; OR, 75; 95% CI, 9.6–589; specificity, 97%; positive predictive value, 97%; positive likelihood ratio, 23). These data indicate that, in the absence of overlap clinical features at diagnosis, the presence of overlap aAbs was strongly associated with the future onset

of such clinical features. However, as indicated by the sensitivity and negative predictive value, the absence of aAbs did not preclude the presence of overlap clinical features either at diagnosis or at follow-up.

Overlap Clinical Features and Overlap aAbs in 36 Cases Classified as PM or DM Using the Original Bohan and Peter IIM Subsets

As seen above, the original Bohan and Peter definitions resulted in classification as PM or DM of 36 patients with overlap features. This is further shown in Table 6, which highlights the overlap clinical features and aAbs of these patients. Overlap features such as Raynaud phenomenon (53%), arthritis (47%), interstitial lung disease (39%), and a decreased DLCO (36%) were the most common features. The frequency of aAbs (75%) was not significantly different in patients with a single clinical overlap feature at last follow-up versus those with more than 1 such feature (9/12 versus 18/24, respectively; p = NS). Furthermore, 27 (75%) cases classified as PM or DM expressed an overlap aAb, most commonly anti-Jo-1 (n = 12).

Seven patients who were not classified as having OM at diagnosis subsequently developed overlap clinical features, leading to their classification as having OM at last follow-up (see Table 6). Note that all these patients expressed an aAb at IIM diagnosis: anti-Jo-1 (n = 3), anti-KS, anti-Pm-Scl, anti-U5RNP, and antinucleoporins (n = 1 each). Finally, Table 6 also shows the clinical features of 9 OM patients without known overlap aAbs who were classified as having PM or DM. Except for SLE features and discoid lupus in 2 patients, their overlap clinical features were similar to OM patients with overlap aAbs. In 4 patients the serum sample was obtained 2–33 years after diagnosis, and it cannot be ruled out that the absence of aAb was secondary to immunosuppressive treatment. However, in 5 patients, the serum sample was obtained before (n = 1) or at the time (n = 4) of IIM diagnosis when patients were not treated, suggesting that there is an authentic subset of overlap aAb-negative OM patients.

Characteristics of IIM Groups as Defined by Clinicoserologic Classification

Because the clinicoserologic classification resulted in a striking redistribution of patients compared with the original Bohan and Peter classification, we studied the characteristics of patients within each IIM subset according to that classification and furthermore according to aAb status and specificity. In particular, we analyzed the newly defined subsets of ''pure PM'' and ''overlap aAb negative OM''.

Pure Polymyositis (n = 9)

From examination of Table 7 and comparison with Table 3, it can be seen that pure PM patients were older at

TABLE 4. Distribution of Overlap Autoantibodies* at Myositis Diagnosis and at Last Follow-Up According to Bohan and Peter Original and Modified Classifications

		Patients	Autoantibodies to Synthetases		SSc-Associated Autoantibodies		Other Autoantibodies		Total with ≥1 Autoantibody	
	Classification	n 100	n 20	% 20	n 23	% 23	n 5	% 5	n 48	% 48
PM	Original at diagnosis	45	12	27	10	22	3	7	25	56
PM	Modified at diagnosis	14	2	14	1	7	1	7	4	28 p = NS
PM	Original at last follow-up	33	10	30	5	15	3	9	18	55
PM	Modified at last follow-up	9	0	0	0	0	0	0	0	0 p < 0.01
DM	Original at diagnosis	28	4	14	2	7	0	0	6	21
DM	Modified at diagnosis	23	2	9	2	9	0	0	4	18 p = NS
DM	Original at last follow-up	30	5	17	4	13	0	0	9	30
DM	Modified at last follow-up	18	0	0	0	0	0	0	0	0 p < 0.02
CTM	Original at diagnosis	24	4	17	11	46	2	8	17	71
OM	Modified at diagnosis	60	16	27	20	33	4	7	40	67 p = NS
CTM	Original at last follow-up	31	5	16	14	45	2	6	21	68
OM	Modified at last follow-up	67	20	30	22	33	5	7	47	70 p = NS
CAM	Original or modified at diagnosis	3	0	0	0	0	0	0	0	0
CAM	Original or modified at last follow-up	6	0	0	1	17	0	0	1	17

*See Table 1 for the antigenic specificities included in each autoantibody group.

TABLE 5. Strong Association of Overlap Autoantibodies With Overlap Clinical Features at Diagnosis and Last Follow-Up in 100 Patients With Idiopathic Inflammatory Myopathies

A. Overlap myositis at diagnosis

	Yes	No		
Presence of autoantibodies	40	8	P < 0.0001* OR 8 95% CI 3.1–20.5	
Absence of autoantibodies	20	32	Sensitivity 0.66 PPV 0.83 Positive LR 3.33	Specificity 0.80 NPV 0.61

B. Overlap myositis at last followup

	Yes	No		
Presence of autoantibodies	47	1	P < 0.0001* OR 75 95% CI 9.6–589	
Absence of autoantibodies	20	32	Sensitivity 0.70 PPV 0.97 Positive LR 23	Specificity 0.97 NPV 0.61

*P, sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and positive likelihood ratio (LR) of overlap autoantibodies for overlap clinical features.

diagnosis and myositis onset was insidious. Indeed, the mean age at diagnosis was significantly greater in pure PM patients than in DM patients (60.1 SD 13.8 yr versus 44.4 SD 17 yr, respectively; $p < 0.03$, by 2-tailed Mann-Whitney U test) or OM (45 SD 13.7 yr; $p = 0.009$). Similarly, the mean interval from IIM onset to diagnosis was significantly longer in PM (43 SD 42 mo) than in DM (11.6 SD 36 mo; $p = 0.0001$), OM (6.2 SD 9.1 mo; $p < 0.0001$), or CAM (1.9 SD 1.5 mo; $p < 0.001$). Oropharyngeal dysphagia was present in 7 (78%) patients. None of the pure PM patients had anti-Ro or anti-La, and fluorescent ANA were absent except in 1 patient (see Table 7). None of the muscle biopsies disclosed DM-like features.

Despite these apparently homogeneous features, critical examination of global myositic features and course in individual patients with pure PM revealed that they could be consistent with other myopathies in several instances. For example, inclusion-body myositis could not be ruled out in 4 patients (Patients 16, 17, 21, 33), since myositis was characterized by late onset, slight increase in serum CK levels, and severe progressive weakness, and muscle electron microscopy was not performed. In Patient 22, a muscular dystrophy could have been present. The features in Patient 45 could be explained by a metabolic myopathy. Finally, although Patients 46 and 80 had no known overlap aAb, immunoprecipitation results suggested the presence of hitherto unidentified aAbs. This finding, in combination with the corticosteroid responsiveness and the absence of endomysial infiltrate on biopsy, raises the possibility of reclassification as OM on future follow-up.

Pure Dermatomyositis (n = 19)

Anti-Mi-2 was present in 3 (16%) patients, 1 of whom also had cancer. No other patient with anti-Mi-2 was found in our cohort. It is noteworthy that patients with anti-Mi-2 had a sudden onset of IIM, with high to very high serum CK levels (3299, 8060, and 23,325 U/L; N, 40–195 U/L). The patient with the highest CK had a refractory myositis.

Of the 16 anti-Mi-2 negative DM patients, none expressed other overlap aAbs. However 5 had a positive ANA, suggesting hitherto undefined aAbs. Anti-Mi-2 negative patients had extensive DM rashes, and 3 developed DM-type calcinosis. It is noteworthy that serum CK levels were normal or near normal (serum CK $\leq$ 550 U/L) in 11 (68.7%) patients. The DM course was monophasic in only 1 patient (n = 1/13), suggesting that anti-Mi-2 negative DM is a chronic IIM.

Overlap Myositis (n = 68)

The overall frequency of overlap aAbs in OM was 70.5% (n = 48/68). Anti-Jo-1 were the most common overlap aAb (n = 16, 23.5%). Antisynthetase syndrome features of arthritis, interstitial lung disease, fever, Raynaud phenomenon and mechanic's hands were frequent[59]. At IIM diagnosis, other noteworthy findings included high initial serum CK levels (>9000 U/L) in 8 (50%) patients, bilateral carpal tunnel syndrome in 6 (38%) patients, generalized edema suggestive of capillary leak syndrome in 5 (31%) patients (2 of whom also had unexplained tachycardia), and angiographically proven pulmonary emboli in 1 patient. Importantly, all anti-Jo-1-positive patients had a chronic myositis. One patient with hepatitis C proven serologically and by liver biopsy was cured of the concurrent myositis with α-interferon treatment without any corticosteroids.

Antibodies to other synthetases were identified in 4 additional patients. Anti-PL-7- (n = 2, 3%) and anti-PL-12- (n = 1) positive patients had severe interstitial lung disease. One patient with anti-PL-7 presented with adult respiratory distress-like syndrome, while the patient with anti-PL-12 had an established pulmonary fibrosis. These 2 patients died within 0.6 and 3.5 years of IIM diagnosis, respectively. Anti-KS aAbs were detected in a single patient, who presented with digital ischemia and deep venous thrombosis. Interstitial lung disease was diagnosed on follow-up and the course of myositis was monophasic.

Systemic sclerosis-associated aAbs were present in 23 (34%) of the OM patients. Anti-U1RNP were the most common, being present in 9 (13%) patients. All had systemic sclerosis, and all had a monophasic myositis. Survival was poor. Anti-Pm-Scl were present in 5 (7%) OM patients. One patient had arthritis as the only clinical overlap feature. A second patient presented with a DM rash and mechanic's hands, and developed Raynaud phenomenon within 1 year of diagnosis. The other patients had systemic sclerosis. No

chronic myositis was observed. Anti-RNA-polymerase I/III (n = 2) and antitopo I (n = 1) were associated with diffuse cutaneous systemic sclerosis. Anti-Th (n = 2) were present in a single patient with limited cutaneous systemic sclerosis, whereas the other patient had DM associated with skin cancer (spinocellular epithelioma). Anticentromere were present in 1 patient with limited systemic sclerosis and normal serum CK.

Anti-Ku- (n = 2, 3%) positive patients presented as RA and SLE, respectively. The SLE patient had high titers of anti-dsDNA, a DLCO of 50%, and a monophasic IIM course. Anti-U5RNP were detected in a single patient who presented

TABLE 6. Overlap Clinical and Autoantibody Features of 36 OM Cases Classified as PM or DM by Bohan and Peter Original Classification at Last Follow-Up

Patient	Overlap Autoantibody	Clinical Overlap Feature*	DM Rash	OM at IIM Diagnosis
3	Jo-1	Arthritis, ILD, DLCO	Yes	Yes
14	Jo-1	Arthritis, ILD, DLCO	No	Yes
29	Jo-1	ILD, DLCO	No	Yes
41	Jo-1	ILD	Yes	No†
43	Jo-1	Arthritis, ILD	No	Yes
52	Jo-1	Arthritis	No	No†
53	Jo-1	Arthritis, Raynaud, GI	No	Yes
57	Jo-1	Arthritis	No	Yes
66	Jo-1	Arthritis, ILD, DLCO	Yes	Yes
68	Jo-1	Arthritis, Raynaud	No	Yes
91	Jo-1	Arthritis, ILD, DLCO, calcinosis	No	Yes
99	Jo-1	GI	Yes	No†
56	PL-7	Raynaud, ILD, DLCO, GI	Yes	Yes
85	PL-7	Arthritis, ILD, DLCO	No	Yes
11	KS	ILD	No	No†
4	Pm-Scl	Arthritis, Raynaud, ILD, DLCO	Yes	Yes
10	Pm-Scl	Raynaud, ILD, DLCO, GI	Yes	Yes
30	Pm-Scl	Arthritis	No	Yes
82	Pm-Scl	Raynaud	Yes	No†
44	U1-RNP	Arthritis, Raynaud, sclerodactyly	No	Yes
77	U1-RNP	Raynaud, GI	No	Yes
51	U5-RNP	Raynaud, GI	Yes	No†
94	Th	Raynaud, GI, sclerodactyly	No	Yes
96	Centromere	Arthritis, Raynaud, sclerodactyly, calcinosis	No	Yes
25	Nucleoporins	GI	No	No†
15	SRP	DLCO	No	Yes
39	SRP	Raynaud, DLCO	No	Yes
	N = 27			
6	No	Raynaud, GI, sclerodactyly, calcinosis	No	Yes
9	No	Raynaud, anti-dsDNA, hypocomplementemia	Yes	Yes
28	No	Arthritis, ILD, DLCO	Yes	Yes
42	No	Arthritis, Raynaud	No	Yes
50	No	Arthritis, Raynaud, ILD	Yes	Yes
78	No	Raynaud	No	Yes
86	No	Raynaud, DLCO	No	Yes
87	No	Discoid lupus	No	Yes
97	No	Raynaud	No	Yes
	N = 9			

*ILD = interstitial lung disease; DLCO = carbon monoxide diffusion capacity <70% of predicted normal value; calcinosis = SSc-type calcinosis of the fingers; GI = lower esophageal and/or small bowel hypomotility.

†Patient not classified as having OM by modified criteria at diagnosis who subsequently developed overlap clinical features.

TABLE 7. Selected Cumulative Clinical and Laboratory Features of 9 Patients With Pure Polymyositis at Last Follow-Up

Patient	Age at Myositis Diagnosis (yr)	Diagnostic Delay (mo)	Positive ANA	High Serum CK at Diagnosis, U/L*	Lymphocytic Infiltrate on Muscle Biopsy	Oropharyngeal Dysphagia	Follow-Up (yr)	Noteworthy Finding
16	73	25	No	Yes, 243	Inadequate specimen	Objective	2.63	Severe neck flexor and quadricep weakness at diagnosis
17	54	20	No	Yes, 673	Endomysial, perimysial	Subjective	13.8	Responsive myositis; progressive weakness
21	74	10	No	Yes, 797	Perimysial, perivascular	Objective	7.83	
22	45	121	No	Yes, 2530	Discrete and focal	Objective	8.95	Initial symptom of dysphagia; severe progressive weakness
33	69	35	No	Yes, 841	Endomysial, invading	None	6.58	Severe quadriceps weakness
36	73	111	Yes	Yes, 4206	Perimysial, perivascular	Objective	0.33	Persistent CK elevation for years
45	39	18	No	Yes, 3075	Endomysial (discrete)	None	9.08	Myalgia as dominant feature; normal strength at diagnosis
46	47	8	No	Yes, 240	Perimysial, perivascular	Subjective	4.45	Responsive myositis
80	67	38	No	Yes, 1188	Perimysial, perivascular	Subjective	1.05	Responsive myositis

*Normal range, 40–195 U/L.

as having PM initially, followed by systemic sclerosis sine scleroderma (Raynaud phenomenon, lower esophageal and small bowel involvement) and a DM rash 9 years after IIM diagnosis.

Antinucleoporins (n = 3, 4%) and associated features will be reported elsewhere. Both patients with anti-SRP (n = 2, 3%) had sudden disease onset, 1 with fever and chest pain, and the other with severe muscle weakness causing an extrathoracic restrictive syndrome with paradoxal breathing. The former patient died of a stroke shortly after IIM diagnosis, whereas the latter had a chronic course over 7 years, responsive only to high-dose corticosteroids.

Overlap aAb negative OM accounted for 29% (n = 20/68 patients) of the OM cohort. Of these 20 patients, 18 (90%) had 2 or more overlap manifestations. Raynaud phenomenon, arthritis, interstitial lung disease and a decreased DLCO were most frequent. At last follow-up, a diagnosis of systemic sclerosis was common (n = 11/20, 55%)[27,28]. Among the 9 patients without systemic sclerosis, 1 patient had SLE, 1 patient had anti-dsDNA and hypocomplementemia, and 1 patient had discoid lupus. Although no overlap aAb was detected, this does not rule out that some patients expressed hitherto undefined aAbs, as discussed below. This is suggested by the fact that 8 (40%) of the 20 patients had a positive HEp-2 ANA. Interestingly, in these ANA-positive samples, the fluorescent nuclear patterns were large speckled (n = 4) and diffuse granular (n = 4), corresponding to undefined antigenic specificities. Anti-Ro (in association with anti-La) were present in only 1 patient with overlap aAb negative OM.

Cancer-Associated Myositis (n = 4)

Three patients had breast cancer, 1 of whom had disappearance of a DM rash the day after mastectomy, and 1 who was cured of both IIM and cancer with antineoplastic treatment. One patient had an aggressive T-cell lymphoma with mononeuritis multiplex.

Other Autoantibodies

Anti-Ro and Anti-La

Anti-Ro and anti-La aAbs were found by ELISA in 14% (n = 14) and 11% (n = 11) of IIM patients, respectively. Thus, anti-Ro and anti-La were present alone in 7 and 4 patients, respectively, and coexpressed in 7 patients. Anti-Ro were associated with aAbs to Jo-1 (n = 3), U1RNP (n = 2), PL-12, Pm-Scl, Ku, and nucleoporins (n = 1 each). A similar frequency was seen for anti-La. No association of anti-Ro and anti-La was noted with clinical manifestations, response to treatment, or survival. The fine specificity of anti-Ro was further analyzed by immunoblotting. Of the 14 anti-Ro-positive sera, 10 (71%) expressed anti-Ro52 (either alone, n = 6, or with anti-Ro60, n = 4), whereas 3 sera (21.5%) displayed anti-Ro60 activity only, and 1 serum was negative.

TABLE 8. Course of Myositis Following Initial Corticosteroid Treatment According to the Modified Bohan and Peter and Clinicoserologic Classifications

	Total	PM	DM	OM	OM With Autoantibodies to Synthetases, SRP, or Nucleoporins	OM With Autoantibodies to U1RNP, Pm-Scl, or Ku	OM With Other Overlap Autoantibodies or Without Autoantibodies	CAM
Responsive versus refractory myositis*								
Patients, n	100	9	18	67	25	16	26	6
Could not be evaluated†, n	25	3	3	13	6	2	5	6
Responsive myositis, n	66	3‡	13	50	17§	14	19	
Refractory myositis, n	9	3	2	4	2	0	2	
Rate of responsive myositis (%) (n responsive / n responsive + n refractory)	88	50	87	93	89	100	90	
Rate of refractory myositis (%) (n refractory / n responsive + n refractory)	12	50	13	7	11	0	10	
Monophasic versus chronic myositis*								
Patients, n	100	9	18	67	25	16	26	6
Could not be evaluated†, n	34	4	5	19	4	8	7	6
Monophasic myositis, n	21	0‡	1	20	1¶	8	11	
Chronic myositis, n	45	5	12	28	20	0	8	
Rate of monophasic myositis (%) (n monophasic / n chronic + n monophasic)	32	0	8	42	5	100	58	
Rate of chronic myositis (%) (n chronic / n chronic + monophasic)	68	100	92	58	95	0	42	

*See Patients and Methods for definitions.
†See Results for justification.
‡For PM, DM and OM with responsive versus refractory myositis, or with monophasic versus chronic myositis: $p < 0.01$ by chi-square test for trend.
§For OM autoantibody subsets with responsive versus refractory myositis: p = NS.
¶For OM autoantibody subsets with monophasic versus chronic myositis: $p = 0.0005$ by chi-square test for trend.

Coexistence of 2 Overlap Autoantibodies

It is noteworthy that only 2 (4%) of the 48 patients with overlap aAbs expressed simultaneously 2 such aAbs, namely anti-Jo-1 with anticentromere and anti-U1RNP with anti-U2RNP. In another patient, an initial anti-U1RNP response that was associated with clinical SLE features subsequently disappeared when anti-Jo-1-positive myositis was diagnosed.

Unidentified Autoantibodies

Finally, immunoprecipitation showed that several sera precipitated protein bands suggestive of unidentified aAbs. The clinical significance of these aAbs is unknown.

Outcome of Myositis According to the Novel Classifications

A major potential application of novel disease classifications is to provide more accurate outcome ascertainment. We therefore examined myositis outcome and survival in the cohort. Table 8 illustrates myositis outcome after adequate initial corticosteroid treatment (as defined above in the Patients and Methods section). The ability of corticosteroids alone to induce remission of myositis, that is, whether myositis was refractory or responsive, was assessed in 75 IIM patients. In 25 patients, this was not assessed for the following reasons: initial treatment consisted of both prednisone and a second-line agent (n = 11); presence of CAM, that is, cancer treatment may have influenced myositis outcome (n = 6); inadequate initial corticosteroid therapy (n = 3); death during initial corticosteroid treatment (n = 3); treatment refusal (n = 1); and α-interferon treatment (n = 1). We note that the rate of responsive myositis was 88% (n = 66), suggesting that corticosteroids alone as initial treatment of active myositis do induce remission (see Table 8). Responsiveness was highest in OM (93%) and DM (87%) and lowest in PM (50%) ($p < 0.01$). When OM patients were subdivided as having either anti-synthetase, SRP, or nucleoporin (n = 19); anti-U1RNP, Pm-Scl, or Ku (n = 14), or having other aAbs or none of these (n = 21), the rates were uniformly high and not significantly different, ranging from 89% to 100%.

We then examined in 66 patients the ability of a single trial of prednisone to produce a long-term remission of myositis, that is, whether myositis was monophasic or chronic.

This could not be assessed in 34 patients for reasons similar to those above. As shown in Table 8, the rate of monophasic myositis was only 32% and the rate of chronic myositis was 68% (including, by definition, 9 cases of refractory myositis), illustrating the chronicity of myositis in this population.

We note that when these rates were further analyzed in these 66 patients subdivided according to the modified classification at last follow-up, the long-term courses after an adequate initial prednisone treatment differed markedly: all PM (100%) and most DM (92%) patients had chronic myositis, while in OM patients this rate was only 58% ($p < 0.01$) (see Table 8). Furthermore, when OM patients were divided according to aAb subsets, the long-term course of myositis differed strikingly. Chronic myositis was present in 95% of patients with anti-synthetase, SRP, or nucleoporin aAbs; in none of patients with anti-U1RNP, Pm-Scl, or Ku; and in 42% of patients with none of these or with other aAbs ($p = 0.0005$) (see Table 8). Thus anti-synthetase, SRP, or nucleoporin aAbs are markers for chronic myositis, whereas anti-U1RNP, Pm-Scl, or Ku are markers for monophasic myositis.

We examined as well the timing of myositis recurrence from the moment prednisone was tapered to 5 mg or less (Table 9). Two conclusions can be drawn from the results. First, most recurrences (n = 16/21, 76%) occurred within 1 year of corticosteroid discontinuation, and despite the fact that patients had continuously received pharmacologic doses of prednisone for up to 7 years. Second, myositis relapses do occur, although uncommonly, even several years after prednisone has been stopped, particularly in patients without overlap aAbs (n = 4/5 patients) (see Table 9).

Survival According to Bohan and Peter Modified Classification at Follow-up

Death occurred in 23% of patients. The mean interval between IIM diagnosis and death was 5.1 years (range,

TABLE 9. Timing of Myositis Recurrence in 21 Patients From the Moment Prednisone Was Tapered to 5 mg or Less

Patient	Timing of Recurrence After Corticosteroid Discontinuation	Length of Initial Corticosteroid Treatment	First Recurrence	Clinical and/or Biochemical Recurrence*	IIM Subset	Associated Autoantibody
Late flares[†]						
53	Within 6 mo	6 mo	Yes	Biochemical	OM	Jo-1
3	Within 6 mo	7 mo	Yes	Both	OM	Jo-1
32	Within 6 mo	8 mo	Yes	Both	OM	Nucleoporins
41	Within 6 mo	8 mo	Yes	Both	OM	Jo-1
80	Within 6 mo	8 mo	Yes	Both	PM	None
6	Within 6 mo	11 mo	Yes	Both	OM	None
68	Within 6 mo	3 yr	No	Both	OM	Jo-1
25	Within 6 mo	7 yr	No	Both	OM	Nucleporins
70	6–12 mo later	9 mo	Yes	Clinical	DM	None
52	6–12 mo later	12 mo	Yes	Both	OM	Jo-1
94	6–12 mo later	14 mo	Yes	Biochemical	OM	Th
34	6–12 mo later	16 mo	Yes	Clinical	DM	None
58	6–12 mo later	2 yr	Yes	Both	DM	None
48	6–12 mo later	4 yr	Yes	Both	DM	None
65	6–12 mo later	5 yr	Yes	Both	DM	Mi-2
95	6–12 mo later	5 yr	No	Both	OM	None
Early relapses						
75	> 20 mo	20 mo	Yes	Biochemical	OM	None
90	> 4 yr	13 mo	Yes	Both	OM	None
31	> 4 yr	3 yr	Yes	Both	DM	None
Late relapses						
64	> 6 yr	13 yr	No	Both	DM	None
51	> 7 yr	12 mo	Yes	Both	OM	U5-RNP

*Biochemical recurrence: an increase in serum CK level that justified a change in treatment; clinical recurrence: same as biochemical plus presence of symptoms and signs of worsening myositis.

[†]As defined in Patients and Methods.

0.25–22 yr) and the median was 4 years. The frequencies of death in PM, DM, OM, and CAM were 33% (n = 3/9), 5% (n = 1/18), 24% (n = 16/67), and 50% (n = 3/6), respectively (p = NS by chi-square test for trend). Visceral involvement associated with IIM, notably systemic sclerosis-type complications, was the most common cause of death (48%, n = 11/23), followed by various cancers (26%, n = 6/23). Death due to IIM treatment occurred in a single patient due to azathioprine hepatoxicity. Of the 3 patients with anti-PL-7 and anti-PL-12, 2 died, as did 5 of the 9 (55%) patients with anti-U1RNP. These aAbs may be markers for poor survival in OM patients. The 10-year survival rate in the cohort overall was 73%, whereas in PM, DM, OM, and CAM it was 57%, 94%, 71%, and 62.5%, respectively (p = NS by log-rank test).

Outcome of Patients Classified as Having Possible Myositis

Of the 18 patients with possible myositis at IIM diagnosis according to Bohan and Peter diagnostic criteria, 6 (33.3%) patients developed during follow-up additional myositis criteria warranting their reclassification as probable or definite PM or DM. Of the 12 remaining patients (mean follow-up, 5.9 SD 4 yr), 11 (91.5%) were classified as having OM at last follow-up and 1 patient had PM. All patients had proximal muscle weakness and most (n = 10, 83%) had elevated serum CK levels at diagnosis. We note that, of the 9 patients who had an EMG, the results were myopathic, but not myositic, in 7 (77.7%) cases, hence the ''abnormal EMG'' criterion of Bohan and Peter was not fulfilled. Of the 7 patients with a muscle biopsy, it was positive in only 2 (28.5%) patients, a finding consistent with the spotty distribution of myositis[13]. An overlap aAb was present in 8 (66.6%) patients. One or more overlap feature was present in 11 (91.5%) patients at diagnosis, and 6 patients developed additional overlap features during follow-up. Importantly, of the 7 patients in whom the responsiveness of myositis to corticosteroids could be assessed, 6 (85.7%) had a responsive myositis.

DISCUSSION

Several conclusions can be drawn from analysis of our data, as outlined below.

1) *The original Bohan and Peter classification should be abandoned as it leads to misclassification of patients and masks that OM is the most common IIM.* Although PM was the most common IIM according to the original Bohan and Peter classification, accounting at diagnosis for 45% of the cohort, its frequency drastically fell to 14% with the modified classification. Conversely, while the frequency of CTM was 24% according to the original classification, the frequency of OM was 60% using the modified classification. At last follow-up, the frequency of PM further dropped to 9%, while OM rose to 67%. Thus, the use of the Bohan and Peter definitions clearly results in misclassification as PM of many patients with overlap features. Our results are similar to those of Van der Meulen et al[61] who concluded in a retrospective study of 165 Dutch myositis patients that pure PM was rare and overdiagnosed, accounting for only 2% of their patients. Furthermore, our data concur with the view that much of IIM is composed of OM[1,26,62].
2) *''Pure PM'' may be heterogeneous, encompassing true pure PM patients as well as myositis mimickers.* Recognizing that much of possible myositis is actually OM, as discussed below, allowed us to focus on features of pure PM since, by definition, none of these patients had overlap manifestations. Pure PM patients had in common an insidious onset at an older age, absence of known IIM aAbs, and absence of ANA. However, inclusion-body myositis and noninflammatory myopathies such as adult-onset muscular dystrophies could have been missed, as insidious proximal muscle weakness and endomysial inflammation at muscle biopsy may occur in these myopathies[1,14]. Further pathologic studies are needed to exclude other myopathies and to determine what proportion of pure PM patients would disclose the pathologically defined entity of PM at muscle biopsy[16,17,25].
3) *Systemic sclerosis is the most common connective tissue disease associated with IIM.* In the current study, systemic sclerosis was most common, accounting for 42.6% of OM patients and 29% of the cohort. Systemic sclerosis aAbs were present in 62% of these systemic sclerosis patients. Recent reports emphasized that the sensitivity of ACR criteria[50] for systemic sclerosis is low[27,28], and proposed the inclusion of systemic sclerosis sine scleroderma in the spectrum of systemic sclerosis, preferably in the presence of a systemic sclerosis-associated aAb[27,45] and/or typical nailfold capillaroscopy abnormalities[28,48]. Others have noted that ''scleromyositis,'' defined as an overlap syndrome with concurrent myopathy and features of systemic sclerosis and/or DM, was very common[18]. Dalakas expressed the view that only systemic sclerosis and mixed connective tissue disease may overlap with DM[12–14]. These data show that systemic sclerosis is increasingly recognized as the most common connective tissue disease associated with IIM. Interestingly, some of the salient features of the antisynthetase syndrome, such as Raynaud phenomenon and interstitial lung disease, are systemic sclerosis features as well. Furthermore, Marguerie has reported subtle systemic sclerosis-like findings in patients with antisynthetase aAbs[31]. Taken together, these data raise the question whether many extramuscular manifestations of patients with antisynthetase aAbs are actually systemic sclerosis-like manifestations. As a corollary, screening for systemic sclerosis-type visceral involvement, for example, interstitial lung disease,

pulmonary hypertension, and small-bowel hypomotility, may be of value in the diagnostic evaluation of IIM patients.

4) *Overlap aAbs should be specifically tested for at myositis diagnosis.* We have shown that patients with overlap aAbs are 23 times more likely to have overlap features than patients without these aAbs. Furthermore, these aAbs identify additional OM patients unrecognized by the modified classification and predict the onset of overlap manifestations.

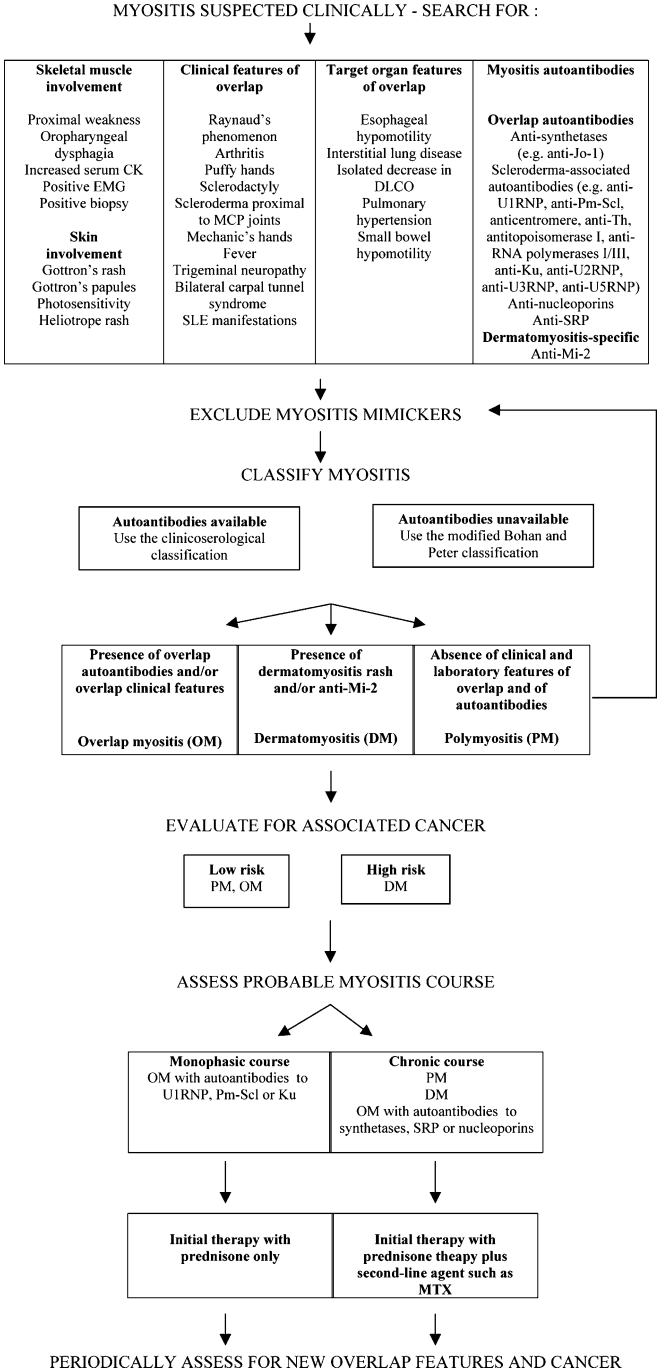

FIGURE 1. Approach to the diagnosis and management of autoimmune inflammatory myopathies using the modified Bohan and Peter and clinicoserologic classifications.

5) *The high diagnostic sensitivity of the modified classification for OM has practical clinical impact.* Given that assays for several overlap aAbs are costly and not always routinely available, clinicians may elect to rely on the high sensitivity (87%) of the modified classification for identification of most OM patients. Where such testing is available, clinicians may still use the modified classification to make a presumptive diagnosis, while awaiting results of aAb assays.

6) *Myositis course and response to prednisone are predicted by the new classifications.* Using stringent and uniform definitions, PM was associated with the highest rate (50%) of refractoriness to initial corticosteroid treatment and was always a chronic myositis. DM was almost always a chronic myositis (92% rate); however, contrary to PM, its responsiveness rate to initial corticosteroid treatment was high (87%). In sharp contrast, OM was almost always responsive to corticosteroids (89%–100% rate) and its course was predicted by associated aAbs. Thus, anti-synthetase, SRP, or nucleoporin aAbs are markers for chronic myositis (95% rate), whereas anti-U1RNP, Pm-Scl, or Ku are markers for monophasic myositis (100% rate).

7) *''Possible myositis'' is part of the spectrum of IIM.* We included patients with possible myositis because this entity is common in clinical practice. These patients had been diagnosed as having IIM by experienced academic rheumatologists and neurologists. Not surprisingly, 33.3% of the patients developed additional myositis criteria during follow-up, warranting their reclassification as probable or definite PM or DM. Interestingly, at follow-up, all remaining patients retained a diagnosis of IIM and 91.5% were classified as OM. In fact, at diagnosis, almost all these OM patients already had 1 or more overlap feature warranting a diagnosis of OM. Furthermore, an overlap aAb was present in 66.6% of patients. Importantly, the rate of responsiveness to corticosteroid therapy was high (85.7%). Taken altogether, these data suggest that the clinical spectrum of IIM encompasses possible myositis, accounting herein for 18% of patients, where myositis is likely present despite the absence of full diagnostic criteria. Identification of this subset is critical because it is corticosteroid responsive. Because overlap manifestations and aAbs are characteristically absent in inclusion-body myositis and in noninflammatory myopathies, the presence of overlap clinical manifestations and aAbs provides important diagnostic clues to the presence of IIM, even in the absence of definitive EMG and muscle biopsy results.

8) *The timing of recurrences after corticosteroid discontinuation has practical implications for future therapeutic trials.* Since 76% of recurrences occurred within 1 year of corticosteroid discontinuation, it follows that a minimum of 6 months, and preferably 12 months, should be used to define success or failure of a second-line agent in maintaining remission.

Taken altogether, these conclusions led us to formulate an algorithm outlining a novel clinical approach to the diagnosis and management of IIM (Figure 1). When myositis is suspected clinically, the first step is to confirm the diagnosis by searching for objective evidence of skeletal muscle involvement, and for clinical and laboratory evidence of overlap, as well as IIM aAbs. In the setting of skeletal muscle involvement, the presence of such overlap features and/or IIM aAbs argues strongly in favor of a diagnosis of IIM. As visceral involvement suggestive of overlap may be clinically inapparent, a visceral extension workup is necessary. If positive, these tests will also provide useful prognostic information. However, inclusion-body myositis and several noninflammatory myopathies are known to cause proximal weakness, elevated serum CK levels, and myopathic EMG findings[1,14,26]. Therefore, in particular in the pure PM subset, it is imperative to exclude inclusion-body myositis and IIM mimickers, and to confirm the diagnosis of myositis by open muscle biopsy, with appropriate preparation and examination of the tissue sample. MRI is not a substitute for muscle biopsy, except perhaps in isolated cases.

If IIM aAbs are available, myositis can then be classified as PM, DM, or OM according to the clinicoserologic classification (see Figure 1). If IIM aAbs are unavailable, the modified classification is employed. The specific IIM diagnosis defines the risk for an associated cancer, with the need for extensive and repeated cancer search in the DM subset in particular. Overlap aAbs and corresponding overlap clinical features are not reported to be associated with malignancies, except antitopo[63], an uncommon aAb in our report. Finally, by assessing the probable course of myositis after an initial adequate corticosteroid therapy, an individualized approach to treatment can be adopted (see Figure 1). The objectives are induction and maintenance of remission, while minimizing corticosteroid toxicity. Although initial corticosteroid monotherapy is favored by several authors[6,13,41], with slow tapering after serum CK normalization, this is most appropriate for OM patients with aAbs to U1RNP, Pm-Scl, and Ku. However, the initial use of a second-line agent such as methotrexate, concurrent with adequate initial corticosteroid therapy, should be strongly considered in PM, DM, and in OM patients with aAbs to synthetases, nucleoporins, or SRP, as suggested by our findings and others[46]. Finally, due to their effect on survival, periodical reassessment for overlap and cancer features is indicated.

There are some limitations to our study. Its design was retrospective and restricted to a single relatively homogeneous population. However, this design was necessary to develop these classifications. Could the high proportion of OM patients have resulted from referral bias, that is, could patients with muscle weakness without overlap features have been referred preferentially to neurologists rather than rheumatologists? If this was the case, it is likely that neurology patients were captured by the identification procedure. In addition, recent neurologic reviews emphasize that pure PM is the least common IIM and that the majority of cases of IIM occur in the setting of overlap syndromes[1,26,61]. A possible limitation is that some patients had unidentified aAbs. Some of these antibodies were suggestive of anti-MJ[39] or anti-155 kD[55,57], and further testing is being performed. Also, as several serum samples were obtained after diagnosis, it cannot be ruled out that immunosuppressive treatment led to a negative aAb test[29] and to underestimation of the frequency of overlap aAbs. If the latter limitation was valid, then the frequency of overlap aAbs would be even higher than reported herein. Finally, muscle biopsies in our study were not uniformly performed and independently reviewed. Therefore, conclusions as to potential findings on muscle biopsy in these newly defined IIM subsets would be speculative. It will be critical to study muscle biopsy findings with state-of-the-art methods, particularly in the pure PM subset, and to correlate them with current pathologic IIM subsets.

In conclusion, we propose a novel approach to the classification of IIM. This approach is logical, as it is primarily clinically based and in keeping with the clinical reasoning of physicians involved in the diagnosis and care of IIM patients. We provide data showing that this approach may be of diagnostic, therapeutic, and prognostic value. This approach will need to be validated prospectively and in multicentered international IIM cohorts.

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