Correlation of Clinicoserologic and Pathologic Classifications of Inflammatory Myopathies

Study of 178 Cases and Guidelines for Diagnosis

Carla Fernandez, MD, PhD, Nathalie Bardin, MD, PhD, André Maues De Paula, MD, Emmanuelle Salort-Campana, MD, Audrey Benyamine, MD, Jérôme Franquais, MD, Nicolas Schleinitz, MD, PhD, Pierre-Jean Weiller, MD, Jean Pouget, MD, Jean-François Pellissier, MD, and Dominique Figarella-Branger, MD, PhD

Abstract: The idiopathic inflammatory myopathies (IIM) are acquired muscle diseases characterized by muscle weakness and inflammation on muscle biopsy. Clinicoserologic classifications do not take muscle histology into account to distinguish the subsets of IIM. Our objective was to determine the pathologic features of each serologic subset of IIM and to correlate muscle biopsy results with the clinicoserologic classification defined by Troyanov et al, and with the final diagnoses. We retrospectively studied a cohort of 178 patients with clinicopathologic features suggestive of IIM with the exclusion of inclusion body myositis. At the end of follow-up, 156 of 178 cases were still categorized as IIM: pure dermatomyositis, n = 44; pure polymyositis, n = 14; overlap myositis, n = 68; necrotizing autoimmune myopathy, n = 8; cancer-associated myositis, n = 18; and unclassified IIM, n = 4. The diagnosis of IIM was ruled out in the 22 remaining cases. Pathologic dermatomyositis was the most frequent histologic picture in all serologic subsets of IIM, with the exception of patients with anti-Ku or anti-SRP autoantibodies, suggesting that it supports the histologic diagnosis of pure dermatomyositis, but also myositis of connective tissue diseases and cancer-associated myositis. Unspecified myositis was the second most frequent histologic pattern. It frequently correlated with overlap myositis, especially with anti-Ku or anti-PM-Scl autoantibodies. Pathologic polymyositis was rare and more frequently correlated with myositis mimickers than true polymyositis. The current study shows that clinicoserologic and pathologic data are complementary and must be taken into account when classifying patients with IIM patients. We propose guidelines for diagnosis according to both clinicoserologic and pathologic classifications, to be used in clinical practice.

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Abbreviations: ANA = antinuclear antibodies, CAM = cancer-associated myositis, CK = creatine kinase, CTD = connective tissue disease, DM = dermatomyositis, IBM = inclusion body myositis, IIM = idiopathic inflammatory myopathies, MAA = myositis-associated autoantibody, MCTD = mixed connective tissue disease, MHC-1 = major histocompatibility complex, class 1, N = normal, NAM = necrotizing autoimmune myositis, OM = overlap myositis, pDM = pathologic dermatomyositis (diagnosed based on muscle biopsy), PM = polymyositis, pPM = pathologic polymyositis (diagnosed based on muscle biopsy), SLE = systemic lupus erythematosus, SRP = signal recognition particle, SS = systemic sclerosis.

INTRODUCTION

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of acquired muscle diseases characterized by muscle weakness and inflammatory infiltrates in skeletal muscle. Among them, polymyositis (PM) and dermatomyositis (DM) were defined in 1975 by Bohan and Peter2,3 with the following diagnostic criteria: 1) symmetric proximal muscle weakness, 2) elevation of serum skeletal muscle enzymes, 3) electromyographic changes, 4) muscle biopsy abnormalities (necrosis, regeneration, perifascicular atrophy, inflammatory exudates), 5) typical skin rash of dermatomyositis (heliotrope rash, Gottron sign, and Gottron papules). A diagnosis of definite/probable/possible DM is diagnosed if skin abnormalities (criteria 5) are present in addition to respectively 3, 2, or 1 of the other criteria. Additionally, Bohan and Peter2,3 pointed out the associated occurrence with connective tissue diseases (CTDs) and malignancies. This historical classification has become subject to increasing debate, because DM is differentiated from PM by skin changes only, and overlap myositis (OM) is loosely defined, leading to misclassification of patients, overdiagnosis of PM, and nonrecognition of OM.26,27

An important advance in understanding the pathogenesis of IIM over the past 20 years has been the identification of myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs) as markers of clinical subsets, disease prognosis, and treatment response.5,6,12,18,23,26 MAAs are not specific but may be found in patients with myositis in the context of overlap syndrome, especially those with features of systemic sclerosis (SS).16 They are directed to nuclear or nucleolar antigens, such as PM-Scl, Ku, U1-RNP, Ro60/SSA, and La/SSB.23 MSAs appear to be more clinically relevant and include antibodies directed against aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, JS, and KS), signal recognition particle (SRP), nuclear helicase Mi-2, and p155.5,13,17,23

As a result, even if the Bohan and Peter classification is still useful as an approach for diagnosing myositis, it is obsolete as a basis for distinguishing the different subsets of diseases. Troyanov et al26 developed an interesting clinicoserologic classification where overlap clinical features as well as MAA and MSA were positioned at the core of the classification system.
They found that myositis with overlap features (OM) was the most common IIM. Anti-Mi-2, which is not associated with overlap clinical features, was considered to be specific for pure DM. This new classification was proven to predict the response to prednisone and IIM course.‡ However, we note that neither the Bohan and Peter classification nor the new clinicoserologic classification considers histopathologic findings to distinguish the subsets of IIM.

In contrast, numerous pathologists have a different approach, and consider that muscle biopsy is the most sensitive tool to diagnose IIM.† Muscle histology allows 4 main subtypes of IIM to be distinguished on the basis on distinct immunopathologic features: DM, PM, sporadic inclusion body myositis (IBM), and necrotizing autoimmune myositis (NAM).§

DM is considered to be a complement-mediated microangiopathy leading to destruction of capillaries and hypoperfusion of the perifascicular regions. Muscle biopsy shows perivascular/perimyocellular inflammation often associated with perifascicular atrophy or microinfarcts. The major histocompatibility complex, class 1 (MHC-1) antigen is upregulated especially in perifascicular areas, and immune complex deposition in the vessels is common.¶

PM and IBM are characterized by the presence of cytotoxic T-lymphocytic endomyosial infiltrates that focally surround and invade non necrotic muscle fibers, with relative sparing of the vasculature.†† The MHC-1 antigen is ubiquitously upregulated on the surface of most fibers. In IBM, rimmed vacuoles plus or minus inclusions are present. Currently, the pathophysiological bases of IBM are still under debate, and degenerative processes have been incriminated in addition to possible immunopathological events. IBM was not included in the new clinicoserologic classification of IIM by Troyanov et al,∥ or in the last European Neuromuscular Centre (ENMC) international workshop on adult IIM.¶¶

NAM, also called immune-mediated necrotizing myopathy, is an increasingly recognized subacute myopathy characterized by very high creatine kinase (CK) levels, moderate to severe subacute muscle weakness, and numerous necrotic fibers invaded by macrophages on muscle biopsy, usually in the absence of both lymphocytic inflammation and diffuse MHC-1 overexpression.†††,‡‡‡,‡§§ NAM should be triggered by statins, viral infections, cancer, or autoimmunity. It is noteworthy that antibodies against SRP,††††,‡‡‡‡ have been identified in NAM, and, more recently, anti-HMG-CoA reductase has been identified in patients with statin-triggered autoimmune myopathy.†††∥ In view of these histologic considerations, we note that although OM is probably the most frequent subtype of IIM, pathologists have difficulty identifying it and usually do not propose this diagnosis on the basis of muscle biopsy.

This lack of consensus among physicians, immunologists, and pathologists leads to confusion regarding the real incidence of the different subtypes of IIM and their association with autoantibodies. To our knowledge, no study has been reported that describes clinical and immunologic data in comparison with pathologic features in a large series of patients with IIM.

We conducted the current study to determine the pathologic features of each serologic subset of IIM and to correlate muscle biopsy results with the clinicoserologic classification defined by Troyanov et al∥∥ and the final diagnoses.

### PATIENTS AND METHODS

#### Patient Cohort, Clinical Data, and CK Level

We retrospectively reviewed a cohort of adult patients (aged 16 yr or older at diagnosis) referred to our institution between 2001 and 2011 with a diagnosis of definite/probable/possible myositis according to the Bohan and Peter classification, and muscle biopsy abnormalities suggestive of myositis as defined by the last ENMC international workshop on IIM.†† Patients with muscle biopsy results suggestive of IBM or a diagnosis other than IIM were excluded. Finally, 178 patients were included in our cohort.

The following data were recorded: age, sex, typical skin rash of DM, clinical overlap features, association with cancer, and CK level before corticosteroid therapy. Clinical overlap features were defined as described by Troyanov et al∥∥ (Table 1). Because no patient in that study’s cohort had primary Sjögren syndrome, it was not included as an associated CTD in their clinicoserologic classification. However, because 5 patients in our series had clinically symptomatic and biopsy-proven Sjögren syndrome before the occurrence of myositis, always with both anti-SSA and anti-SSB autoantibodies, we have chosen to consider the Sjögren syndrome as a supplementary overlap feature and have classified these cases as OM.

#### Serologic Characterization

Antinuclear antibodies (ANA), anti-Sm, and anti-native DNA (commonly associated with systemic lupus erythematosus [SLE]) as well as the following MMAs and MSAs were screened in all patients’ serum: for MMAs, anti-PM-Scl and anti-Scl-70 (commonly associated with SS), anti-U1-RNP (commonly associated with SLE and Sharp syndrome), anti-SSA and anti-SSB (commonly associated with SLE and Sjögren), anti-Ku; and for MSAs, anti-synthetases (Jo-1, PL-7, PL-12, OJ, EJ, KS), SS-associated autoantibodies (SS-specific antibodies: centromeres, top I, RNA-polymerases I or III, Th; and antibodies associated with SS in overlap: U1-RNP, U2-RNP, U3-RNP, U5-RNP, Pm-Scl, Ku), and other autoantibodies (SRE nucleoporins).

| TABLE 1. Clinicoserologic Classification of Troyanov et al∥∥ |
|-----------------|-----------------|-----------------|
| **Clinicoserologic** | **IIM Subset** | **Features** |
| **PM** | Pure polymyositis (no DM rash, no overlap feature, and no overlap autoantibody) |
| **DM** | Pure dermatomyositis (no overlap features and no overlap autoantibody/anti-Mi-2 may be present) |
| **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 |

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide.

Clinical overlap features: polyarthrithis (symmetrical polysyovovinitis), Raynaud phenomenon, sclerodactyly, sclerodema proximal to metacarpal-phalangeal joints, typical SS-type calcinosis in the fingers, lower esophageal or small-bowel hypomotility, lung intestinal fibrosis proven by DLCO lower than 70% of the normal predicted value or chest imaging, disoid lupus, anti-native DNA antibodies plus hypercomplementemia, 4 or more of 11 American College of Rheumatology SLE criteria, anti-phospholipid syndrome.

‡Clinical overlap 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 anti-synthetases (Jo-1, PL-7, PL-12, OJ, EJ, KS), SS-associated autoantibodies (SS-specific antibodies: centromeres, top I, RNA-polymerases I or III, Th; and antibodies associated with SS in overlap: U1-RNP, U2-RNP, U3-RNP, U5-RNP, Pm-Scl, Ku), and other autoantibodies (SRE nucleoporins).

∥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.
Total ANA were detected by indirect immunofluorescence on HEp-2 cells (Bio-Rad, Hercules, CA) with a screening dilution of 1:100. Extractable nuclear antigens (ENA) were detected by ELISA using ENA ELISA test (Phadia, Freiburg, Germany). MMA/MSA (anti-Mi-2, Ku, PM-Scl, SRP, Jo-1, PL-7, PL-12) were researched by using a dot blot (OriGene, Mainz, Germany).

Troyanov et al.26 grouped antibodies directed against PM-Scl, ScI-70, U1-RNP, Ku, synthesates, and SRP under the term “overlap antibodies” (associated with OM). To obtain more detailed findings on the pathologic features of each clinico-serologic subgroup, we classified serologic profiles as follows: 1) lack of specific autoantibodies, 2) autoantibodies associated with SLE, Sharp and Sjögren syndromes, called SLE/MCTD/GS antibodies (native DNA, Sm, RNP, SSA plus SSB), 3) anti-PM-Scl, 4) anti-Ku, 5) anti-synthetase (Jo-1, PL-7, PL-12), 6) anti-SRP, 7) anti-Mi-2. Patients with anti-SSA alone were considered to have a nonspecific profile (group 1). Patients with both MSA (anti-synthetase, SRP, or Mi-2) and 1 or several MAAs were attached to their MSA subgroup.

**Muscle Biopsy**

Muscle specimens were frozen in liquid nitrogen cooled by isopentane, and serial 5 µ-thick sections were prepared using conventional histologic stains and histochemical reactions. Automated immunohistochemical detection of MHC-1 antigen (HLA-ABC, clone B 9.12.1, dilution 1/200, Immunotech, Marseille, France) and membrane attack complex C5b-9 (clone aE11, dilution 1/100, DAKO France, Trappes, France) were performed on frozen sections on Ventana BenchMarks.

For each muscle biopsy, the following parameters were recorded: perifascicular atrophy, microinfarcts, necrotic fibers (more than 3 per 1000 muscle fibers), perivascular/perimysial mononuclear cell infiltrates, endomysial inflammation, and invasion of nonnecrotic muscle fibers (Figure 1A-F). MHC-1 expression was defined as follows: absent (no expression), focal (only sparse fibers or groups of fibers expressed MHC-1), diffuse (MHC-1 was upregulated on the surface of most/all fibers), perifascicular or diffuse with reinforcement in the perifascicular region (MHC-1 expression was stronger in perifascicular fibers), both referred to as “dermatomyositis pattern” (DM pattern) of MHC-1 expression (Figure 1G-I). C5b-9 deposits (microthrombi of C5b-9) were searched for in intramuscular capillaries (Figure 1J).

**Definition of Clinico-serologic Subgroups, Pathologic Subgroups, and Final Diagnosis**

To classify the patients on the basis of clinical and immunologic data, we used the clinico-serologic classification proposed by Troyanov et al.26 (see Table 1). As suggested, cases where patients had both cancer and MMA or MSA were categorized as OM.

To classify the patients based on pathologic findings, we summarized consensual histologic features usually used for the diagnosis of myositis in a synthetic table inspired by the 119th ENMC international workshop on adult idiopathic inflammatory myopathies15 (Table 2). To distinguish DM/PM diagnosed pathologically based on muscle biopsy from DM/PM diagnosed based on clinico-serologic features, we named the categories “pathologic DM” (pDM) and “pathologic PM” (pPM) (by analogy with the TNM classification of malignant tumors system). The following pathologic categories were defined 1) pDM, definite, probable or possible, 2) pPM, 3) unspecified myositis, 4) necrotizing myopathy, 5) diffuse MHC-1 expression only (with normal muscle histology or minimal changes).

The final diagnosis was established at the end of follow-up on the basis of clinical, serologic, and pathologic features; additional investigations considered necessary by the clinicians (depending on clinical presentation); clinical course; and response to corticosteroid therapy.

**RESULTS**

**Clinical Data, Clinico-serologic Classification, and Final Diagnoses**

There were 117 females and 61 males (female to male ratio = 1.9) (Table 3). The mean age at diagnosis was 55.1 years (range, 17–85 yr). The overall frequency of DM rash and overlap features was respectively 51% and 34%. Mean CK level was 13.2 × normal (N < 170 U/L).

According to the clinico-serologic classification established by Troyanov et al.,26 OM was the most frequent entity encountered at diagnosis (74 cases, 42%), followed by pure PM (46 cases, 26%) and pure DM (40 cases, 22%). Eighteen cases (10%) were classified as cancer-associated myositis (CAM), with the following cancers: breast, n = 4; ovary, lung, n = 2 each; and n = 1 each for upper aerodigestive tract, stomach, colon, endometrium, lymphoma, prostate, malignant germinal tumor, mesothelioma plus colonic carcinoma, thymic carcinoma, and metastatic carcinoma of unknown origin. Fifteen other patients had a history of malignancy, but their clinical course did not support the diagnosis of CAM.

At the end of follow-up (final diagnosis), 156 of 178 cases were still categorized as IM: pure DM, n = 44; pure PM, n = 14; OM, n = 68; NAM, n = 8; CAM, n = 18; unclassified IM, n = 4. We note that 2 cases were associated with myasthenia gravis. Based on additional investigations and/or follow-up, we excluded the diagnosis of IM in the 22 remaining cases (12% of the initial cohort), called the “non-IM subgroup.” For these patients, the following diagnoses were retained: IBM, n = 14; unclassified (noninflammatory) myopathy, n = 2; viral myositis (1 case of myositis associated with human immunodeficiency virus (HIV) and 1 case of myositis associated with primary cytomegalovirus infection), n = 2; facioscapulohumeral dystrophy (proven by genetics), n = 1. For 3 patients, no diagnosis was convincing at the end of follow-up. An overview of baseline patient characteristics and final diagnoses is given in Table 3.

**Detailed Serologic Data**

ANA were positive in 102 patients (57% of cases). One or several specific autoantibodies were identified in 73 patients (41% of cases). The most common autoantibodies were anti-SSA and anti-Jo-1 (n = 24 each), followed by anti-RNP (n = 14), anti-PM-Scl and anti-SSB (n = 10 each), anti-Mi-2 (n = 9), and anti-Sm (n = 7). Anti-native DNA (n = 5), anti-SRP (n = 5), anti-Ku (n = 3), and anti-PL-7 (n = 1) were rare. Anti-Scl-70 and anti-PL-12 were not recorded. Only 1 specific autoantibody was detected in the majority of sera (50 of 73 cases); 2, 3, or 4 specific autoantibodies were detected in respectively, 12, 6, and 5 sera. Anti-SSA was the autoantibody most frequently associated with 1 or several other ones, predominantly anti-SSB (10 cases) and anti-synthetases (7 cases). Overall, anti-native DNA, anti-Sm, and MAAs were commonly associated with each other, except for anti-PM-Scl and anti-Ku, which were always found to be isolated. MSAs were found to be exclusive, except for 1 serum containing both anti-Jo-1 and anti-SRP antibodies.

According to the serologic profiles defined above, the 178 patients were classified as follows: 1) lack of specific autoantibodies, n = 110 (62%); 2) SLE/mixed connective tissue
disease/GS (SLE/MCTD/GS) autoantibodies, n = 17 (10%); 3) anti-PM-Scl, n = 10 (6%); 4) anti-Ku, n = 3 (2%); 5) anti-synthetase, n = 24 (13%); 6) anti-SRP, n = 4 (2%); association of anti-Jo-1 plus anti-SRP, n = 1; 7) anti-Mi-2, n = 9 (5%).

Clinical Features in Relation to Serologic Profile

The mean age at diagnosis was the lowest in the anti-SRP (mean age, 37 yr) and the SLE/MCTD/GS (mean age, 42.1 yr) subgroups. Mean age at diagnosis in the other categories was as

FIGURE 1. Pathologic features of idiopathic inflammatory myopathy. **A-C.** Pathologic dermatomyositis: perifascicular atrophy (**A**), perivascular lymphocytic infiltrates (**B**), and microinfarct (**C**). **D.** Necrotizing myopathy: numerous necrotic and regenerative fibers. **E-F.** Pathologic aspects suggestive of polymyositis: endomysial infiltrates (**E**), and invasion of a nonnecrotic muscle fiber by lymphocytes (**F**). **G-I.** Examples of MHC-1 overexpression: diffuse (**G**), diffuse with perifascicular reinforcement (**H**), focal (**I**). **J.** Microthrombi of C5b-9 in intramuscular capillaries. (A-F: Hematoxylin-eosin stain, G-J: immunohistochemistry. A-C original magnification × 100, D-E × 200, F × 630, G × 80, H-I × 40, J × 250.)
follows: for anti-PM-Scl, 56 years; anti-Ku, 59.3 years; anti-Mi-2, 53.4 years; no specific autoantibody, 56.5 years. CAM and the non-IIM subgroup represented the oldest categories (mean age, 63.2 yr and 62.2 yr, respectively). The female to male sex ratio was especially high in patients with anti-Mi-2 (SR = 8), anti-SRP (SR = 4), and anti-synthetase (SR = 3). DM rash was common in the case of anti-Mi-2 autoantibodies, CAM, anti-synthetase, and in the absence of specific autoantibodies (respectively 100%, 83%, 62%, and 56% of cases). It was less frequent in the SLE/MCTD/GS, anti-synthetase, and anti-PM-Scl subgroups (100%, 83%, and 80% of cases, respectively). They were rare in the case of anti-Ku or anti-Mi-2 autoantibodies, as well as in the absence of

TABLE 2. Pathologic Classification of IIM

| Pathologic IIM Subset | Features |
|-----------------------|----------|
| pDM                  | Definite | Perifascicular muscle atrophy plus DM pattern of diffuse MHC-1 expression*, with or without inflammatory changes |
|                       | Probable | Perivascular inflammatory exudates plus numerous necrotic-regenerative fibers or microinfarcts plus DM pattern of diffuse MHC-1 expression* |
|                       | Possible | DM pattern of diffuse MHC-1 expression* |
| pPM                   |          | Predominantly endomysial mononuclear cell infiltrates that focally surround and invade nonnecrotic muscle fibers, with relative sparing of the vasculature, plus diffuse MHC-1 expression |
| Unspecified myositis |          | Inflammatory changes with nonspecific localization nor additional features allowing a diagnosis or pDM or pPM |
| Necrotizing myopathy  |          | Inflammatory changes with absent or focal MHC-1 expression |
| Diffuse MHC-1 expression |        | Numerous necrotic-regenerative fibers with absent or minimal inflammatory changes, with absent or focal MHC-1 overexpression |

*DM pattern of MHC-1 expression: perifascicular or diffuse with reinforcement in the perifascicular region expression of MHC-1.

TABLE 3. Overview of Clinical, Serologic and Pathologic Features of 178 Patients

| Clinical Features, ANA, and CK Level | Sex  | DM Rash | Overlap Features | Paraneoplastic Features | Positive ANA |
|--------------------------------------|------|---------|------------------|-------------------------|--------------|
|                                      | 117 F, 61 M | 91 (51%) | 60 (34%) | 18 (10%) | 102 (57%) |

New clinicoserologic classification (from Troyanov et al26)

| Pure DM | Pure PM | OM | CAM |
|---------|---------|----|-----|
| 40 (22%) | 46 (26%) | 74 (42%) | 18 (10%) |

Serologic profile

| Nonspecific | SLE/MCTD/GS | PM-Scl | Ku | Synthetase | SRP | Jo-1 + SRP | Mi-2 |
|-------------|-------------|--------|----|------------|-----|------------|------|
| 110 (62%) | 17 (10%) | 10 (6%) | 3 (2%) | 24 (13%) | 4 (2%) | 1 (1%) | 9 (5%) |

Pathologic classification

| pDM (n = 101 [57%]) | pPM | Unspecified Myositis | Necrotizing Myositis | MHC-1 Only |
|----------------------|-----|----------------------|----------------------|------------|
| Definite | Probable | Possible |
| 71 | 13 | 17 | 27 (15%) | 29 (16%) | 14 (8%) | 7 (4%) |

Final diagnosis

| Pure DM | Pure PM | OM | NAM | CAM | UIMM | Doubt or Other Diagnosis |
|---------|---------|----|-----|-----|------|--------------------------|
| 44 (25%) | 14 (8%) | 68 (38%) | 8 (4%) | 18 (10%) | 4 (2%) | 22 (12%) |
| Among which 9 Mi-2+ | Among which 24 synthetase+, Jo-1 and SRP+, 10 scleromyositis PM-Scl+, 3 Ku+ | Among which 4 SRP+ |

Abbreviations: See Table 1. FSH = facioscapulohumeral dystrophy, UC myopathies = unclassified myopathies, UIMM = unclassified idiopathic inflammatory myopathy.
specific autoantibodies (respectively 33%, 11%, and 19% of cases). Overlap signs were never observed in association with anti-SRP or CAM. CK level was highest (>20N) in the anti-synthetase and anti-SRP subgroups, at an intermediate level (5–20N) in the remaining serologic subgroups of IIM, and lowest in the non-IIM subgroup (3.3N).

**Histopathologic Features in Relation to Serologic Profile**

According to the pathologic classification (see Table 2), patients were predominantly considered as having pDM (101 cases = 57%). The next most common pathologic aspects were unspecified myositis (29 cases = 16%) and pPM (27 cases = 15%). Necrotizing myopathy and isolated diffuse MHC-1 expression were rare (respectively 8% and 4% of cases) (see Table 3).

Muscle biopsy results were correlated with the serologic profile (Table 4). pDM was the most frequent pathologic picture in all serologic subsets of IIM, except for anti-Ku and anti-SRP; in contrast, it was not observed in the non-IIM subgroup. It was observed in 92%, 60%, and 70% of patients with anti-synthetase, anti-PM-Scl, and SLE/MCTD/GS serologic profiles, respectively. The most typical forms of pDM (definite pDM) were seen in association with anti-Mi-2, anti-synthetase, and cancer; in these cases, there was a high frequency of perifascicular atrophy, microinfarct, and DM pattern of MHC-1 expression.

**TABLE 4. Pathologic Features of IIM Related to Serologic Profiles**

| Serologic Profile       | Pathologic Classification | PDM (n=101) | Unspecified Myositis (n=29) | Necrotizing Myositis (n=14) | MHC-1 Only = (n=7) |
|------------------------|----------------------------|-------------|-----------------------------|-----------------------------|------------------|
|                        | Pathologic Classification | Definite (n = 71) | Probable (n = 13) | Possible (n = 17) | Total PDM (n = 27) |                      |                        |
| SLE/MCTD/GS (n = 15)  | 8 (53%)                   | 1 (7%)      | -                          | 9 (60%)                    | 2 (13%)          | 3 (20%)              | 1 (7%)                |
| PM-Scl (n = 10)       | 5 (50%)                   | 2 (20%)     | 7 (70%)                    | -                          | 3 (30%)          | -                      |
| Ku (n = 3)            | -                         | -           | -                          | 2 (67%)                    | -                | -                      |
| Synthetase (n = 24)   | 14 (58%)                  | 4 (17%)     | 4 (17%)                    | 22 (92%)                   | -                | 1 (4%)                | 1 (4%)                |
| SRP (n = 4)           | -                         | -           | -                          | -                          | 1 (25%)          | -                      |
| Jo-1+SRP (n = 1)      | 1                         | -           | -                          | 1                          | -                | -                      |
| Mi-2 (n = 9)          | 6 (67%)                   | 1 (11%)     | 2 (22%)                    | 9 (100%)                   | -                | -                      |
| CAM (n = 18)          | 11 (61%)                  | 2 (11%)     | 1 (6%)                     | 14 (78%)                   | 1 (6%)           | 1 (6%)                | 2 (11%)               |
| No cancer, no specific autoantibodies (n = 72) | 26 (36%)                   | 3 (4%)     | 9 (13%)                    | 38 (53%)                   | 12 (17%)         | 12 (17%)              | 6 (8%)                | 4 (6%)                |
| Non-IIM subgroup (n = 22) | -                       | -           | -                          | -                          | 13 (59%)         | 9 (41%)               | -                      | -                      |

**Histologic Features (No. of Cases)**

| Serologic Profile       | PFA | Microinfarct | PV/PM infiltrates | EM infiltrates | N & R Fibers | MHC-1 Expression | DM Pattern | Diffuse | Focal | Absent | CSb-9 | MT |
|------------------------|-----|-------------|-------------------|---------------|--------------|------------------|------------|--------|-------|-------|-------|-----|
| SLE/MCTD/GS            | 1/15| 1/15        | 10/15             | 4/15          | 14/15        | 6/15             | 5/15       | 4/15   | -     | -     | -     | -   |
| PM-Scl                 | 2/10| -           | 9/10              | 4/10          | 9/10         | 6/10             | 3/10       | 1/10   | -     | -     | -     | -   |
| Ku                     | -   | -           | 2/3               | 1/3           | 2/3          | 1/3              | -          | -      | -     | -     | -     | -   |
| Synthetase             | 8/24| 1/24        | 16/24             | 8/24          | 18/23        | 19/23            | 3/24       | 2/24   | -     | 5/24  |
| SRP                    | -   | -           | 2/4               | 1/4           | 4/4          | -                | 1/4        | 2/4    | 1/4   | -     | -     | -   |
| Jo-1+SRP               | 1/1 | -           | -                 | -             | -            | -                | -          | -      | -     | -     | 1/1  |
| Mi-2                   | 6/9 | -           | 7/9               | 2/9           | 7/9          | -                | 2/9        | -      | 2/9   | -     | 3/9  |
| CAM                    | 9/18| 3/18        | 10/18             | 4/18          | 14/18        | 16/18            | 4/18       | 4/18   | 1/18  | -     | 11/18 |
| No cancer, no specific autoantibodies        | 17/72| 15/72    | 42/72             | 21/72         | 14/72        | 56/72            | 34/72      | 22/72  | 15/72 | 1/23  | 23/72 |
| Non-IIM subgroup        | -   | -           | 11/22             | 20/22         | 15/22        | 17/22            | -          | 18/22  | 4/22  | -     | -     | -   |
| SPE                    | For IIM vs. non-IIM subgroup | 100% | 100% | 50% | 9% | 32% | 23% | 100% | 18% | 82% | - | 100% |
| PPV                    | 100% | 100% | 90% | 69% | 55% | 88% | 100% | 69% | 90% | - | 100% |

Abbreviations: EM = endomysial, MT = microthrombi, N & R Fibers= necrotic and regenerative fibers, NNF = invasion of nonnecrotic fibers, PFA = perifascicular atrophy, PPV = positive predictive value, PV/PM = perivascular/perimysial, SPE = specificity.
Almost all patients with pPM had a nonspecific serologic profile, as MAAs/MSAs were found in only 1 of 27 cases (1 patient with an anti-SRP). pPM corresponded to the most frequent pathologic pattern in the non-IIM subgroup (59% of cases).

Unspecified myositis was the most frequent pathologic expression of anti-Ku antibodies (2 of 3 cases) and was observed in 30% of patients with anti-PM-Scl autoantibodies. It represented the second most frequent pathologic pattern of the non-IIM subgroup (41% of cases).

Necrotizing myopathy was the pathologic hallmark of anti-SRP antibody (3 of 4 cases), but it also represented 20% of the SLE/MCTD/GS subgroup. Two patients belonging to the non-IIM subgroup showed a SLE/MCTD/GS serologic profile (1 anti-RNP and 1 SSA + SSB).

Perifascicular atrophy, microinfarcts, DM pattern of MHC-1 expression, and microthrombi of C5b-9 were the only pathologic findings that had a specificity and a positive predictive value of 100% for IIM (and more specifically DM) versus the non-IIM subgroup (see Table 3). In contrast, perimysial/perivasculare infiltrates, endomysial infiltrates, and necrosis were seen in all groups, whatever the serologic profile (except in the single case with anti-Jo-1 plus anti-SRP) or the final diagnosis, IIM or not. Specificity and positive predictive value of each pathologic feature for the diagnosis of IIM versus the non-IIM subgroup are given in Table 3.

### Correlation Between Pathologic Features, Clinicoserologic Classification, and Final Diagnosis

When muscle biopsy showed features of pDM (101 cases), cases were classified, in accordance with the clinicoserologic classification system, as OM (49% of cases), pure DM (34% of cases), CAM (14% of cases), and, rarely, pure PM (4% of cases) (Table 5). These latter cases corresponded to 4 patients with IIM without DM rash, overlap features, or specific autoantibodies. Findings suggestive of DM on muscle biopsy enabled us to correct the diagnosis, and at the end of follow-up cases were classified as follows: OM (n = 49), 49% of cases, including 22 patients with anti-synthetase, 1 patient with anti-Jo-1 plus anti-SRP, 7 with scleromyositis with anti-PM-Scl, and 1 patient with anti-Ku); pure DM (n = 38, 38% of cases, including 9 patients with anti-Mi-2); and CAM (n = 14, 14% of cases).

When muscle biopsy demonstrated pPM (27 cases), almost all cases were classified as pure PM using the clinicoserologic classification (89% of cases). But at the end of follow-up, only 52% (14 cases) were still considered as IIM; 11 of them were still considered PM (41% of cases), 1 patient with anti-SRP was considered as NAM, 1 patient with a history of cancer with paraneoplastic features was reclassified as CAM, and 1 patient was considered to have unclassified myositis. Among the 13 remaining patients for whom IIM was ruled out, IBM was the most frequent alternative diagnosis (10 cases). One patient was found to have viral myositis, and for the 2 remaining patients, no diagnosis was convincing at the end of follow-up.

When muscle biopsy demonstrated unspecified myositis (29 cases), cases were classified, in accordance with the clinicoserologic classification system, as pure PM (n = 13, 45% of cases), OM (n = 13, 45% of cases), and pure DM (n = 3, 10% of cases). At the end of follow-up, 41% of patients (n = 12) were considered to have OM (1 patient with overlap features was finally classified as IBM), among them 3 patients with anti-PM-Scl, 2 patients with anti-Ku, and 1 patient with anti-synthetase. Three patients (10%) were considered to have pure DM. The diagnosis of pure PM was maintained in 2 patients only (7% of cases); various diagnoses were made instead in the other

**Table 5. Correlation Between Pathologic Features, Clinicoserologic Classification, and Final Diagnoses**

| Pathologic Classification | Clinicoserologic Classification |
|---------------------------|---------------------------------|
|                           | Pure DM (n = 40) | Pure PM (n = 46) | OM (n = 74) | CAM (n = 18) |
| pDM (n = 101)             | 34 (34%)         | 4 (4%)           | 49 (49%)    | 14 (14%)     |
| pPM (n = 27)              | 0                | 24 (89%)         | 2 (7%)      | 1 (4%)       |
| Unspecified myositis (n = 29) | 3 (10%)        | 13 (45%)         | 13 (45%)    | 0            |
| Necrotizing myopathy (n = 14) | 0              | 4 (29%)          | 9 (64%)     | 1 (7%)       |
| MHC-1 (n = 7)             | 3 (57%)          | 1 (14%)          | 1 (14%)     | 2 (29%)      |

**Final Diagnosis**

| Clinicoserologic Classification | Pure DM (n = 44) | Pure PM (n = 14) | OM (n = 68) | NAM (n = 8) | CAM (n = 18) | UIM (n = 4) | Non-IIM Group (n = 22) |
|---------------------------------|------------------|------------------|-------------|-------------|-------------|-------------|------------------------|
| Pure DM (n = 40)               | 40 (91%)         | 0                | 0           | 0           | 0           | 0           | 0                      |
| Pure PM (n = 46)               | 4 (9%)           | 14 (100%)        | 0           | 4 (50%)     | 0           | 4 (100%)    | 20 (91%)               |
| OM (n = 74)                    | 0                | 0                | 68 (100%)   | 0           | 0           | 0           | 2 (9%)                 |
| CAM (n = 18)                   | 0                | 0                | 0           | 18 (100%)   | 0           | 0           | 0                      |

| Pathologic Classification | Clinical Classification |
|---------------------------|-------------------------|
|                           | Pure DM (n = 44) | Pure PM (n = 14) | OM (n = 68) | NAM (n = 8) | CAM (n = 18) | UIM (n = 4) | Non-IIM Group (n = 22) |
| pDM (n = 101)             | 38 (38%)         | 0                | 49 (49%)    | 0           | 14 (14%)    | 0           | 0                      |
| pPM (n = 27)              | 0                | 11 (41%)         | 0           | 1 (4%)      | 1 (4%)      | 1 (4%)      | 13 (48%)              |
| Unspecified myositis (n = 29) | 3 (10%)        | 2 (7%)           | 12 (41%)    | 0           | 0           | 3 (10%)     | 9 (31%)                |
| Necrotizing myopathy (n = 14) | 0              | 0                | 6 (43%)     | 7 (50%)     | 0           | 1 (7%)      | 0                      |
| MHC-1 (n = 7)             | 3 (43%)          | 1 (14%)          | 1 (14%)     | 0           | 2 (29%)     | 0           | 0                      |

**Abbreviations:** See previous tables.
patients (unclassified IIM, 3 cases; IBM, 3 cases; unclassified [noninflammatory] myopathy, 2 cases; viral myositis, 1 case; facioscapulohumeral dystrophy, 1 case; no diagnosis, 1 case).

Necrotizing myopathies on muscle biopsy were classified as NAM (50% of cases, n = 7, among them 3 patients with anti-SRP), OM (n = 6, among them 1 patient with anti-synthetase), and CAM (n = 1) at the end of follow-up. Isolated diffuse expression of MHC-1 (that is, with normal muscle biopsy, minimal changes, or mild rhabdomyolysis) was a rare occurrence; it supported the diagnosis of IIM but did not enable us to distinguish the different subtypes.

Based on the correlation between the clinicoserologic classification of Troyanov et al and the final diagnoses (see Table 5), we found that the classification system enabled us to correctly classify 79% of patients. This percentage reached 86% if the results of muscle biopsy were taken into account, as muscle histology facilitated the diagnosis of DM and NAM. The diagnosis was improved further if we considered that the finding of pPM and unspecified myositis at muscle biopsy instigated the search for rare MAA/MSA and IIM mimickers. All this shows that clinicoserologic and pathologic factors are complementary. Guidelines for diagnosis according to both classifications are given in Table 6.

**DISCUSSION**

To our knowledge we report here the largest recorded series of IIM (with the exception of IBM) that includes in the same study detailed clinical, immunologic, and histologic data. This work complements the findings of Troyanov et al26 and van der Meulen et al.27 studies that made significant headway in the field of IIM but did not account for, respectively, pathologic features and serologic profiles of patients.

**Clinical and Immunologic Features of the Current Series Are in Accordance With Recent Literature**

In 2005, Troyanov et al26 proposed a new clinicoserologic classification for IIM with overlap features and serologic profiles at the core of the system.2,3 Whereas PM was the most common IIM according to the classification of Bohan and Peter (45% of the cohort, versus 28% for DM and 24% for OM), using their new classification system the frequency of OM rose to 67%, the frequency of DM remained stable, and the frequency of PM fell to 10%.26 In the current series, the distribution pattern of IIM at the end of follow-up was similar (OM, 44%; pure DM, 28%; pure PM, 9%). The overall frequency of specific autoantibodies was 42% in our cohort of IIM and 78% in the subset of OM. Anti-Jo-1 were the most common overlap autoantibodies (24 cases). These results are similar to those of previous studies.5,12,23,26

**pDM Is the Most Frequent Histologic Pattern, but Is Common to Pure DM, OM, and CAM**

In the current series, pDM was the most frequent histologic pattern but was seen with various conditions: pure DM, OM, and CAM. So it is likely that pDM represents the histologic support for the diagnosis of pure DM, but also myositis of CTD, and almost all of CAM. Muscle biopsy by itself was not able to distinguish the different serologic subgroups reliably, even if typical pDM is suggestive of anti-Mi-2, anti-synthetase, or CAM.

In this context, the correlation between the pathologic classification and the clinicoserologic classification of Troyanov et al26 shows that the 2 classifications are complementary: on one hand, the muscle biopsy shows features of pDM, supporting the diagnosis of pure DM, OM, or CAM; on the other hand, the clinicoserologic data make it possible to distinguish these 3 clinicopathologic entities. Moreover, when a case is classified as pure PM using the clinicoserologic classification (no DM rash, no overlap features, no specific autoantibodies, no cancer), if muscle biopsy shows features of pDM, the case should be classified as pure DM.

**pPM Is Rare, and Other Diagnoses Must Be Ruled out Before Making This Diagnosis**

In the group of cases classified as PM with both the clinicoserologic classification and the pathologic classification (24 cases), less than half will be classified as PM at the end of

| TABLE 6. Guidelines for Diagnosis as a Function of Clinicoserologic and Pathologic Classifications* |
|---------------------------------|----------------|-----------------|-----------------|-----------------|
|                                | Pure DM        | Pure PM         | OM              | CAM             |
| pDM                             | Pure DM        | Highly demonstrative pDM instigates search for anti-Mi-2 | Pure DM | OM | Highly demonstrative pDM instigates search for anti-synthetase | CAM |
| pPM                             | Not recorded   | Search for IBM and IIM mimickers† | PM as a diagnosis of exclusion | If MSA or Ku+: OM | CAM |
| Unspecified myositis            | Pure DM        | Search for IBM and IIM mimickers† | PM as a diagnosis of exclusion | OM | Search for rare MAA (Ku, PM-Scl) | CAM |
| Necrotizing myopathy            | Not recorded   | Search for rhabdomyolysis etiologies | Seronegative NAM as a diagnosis of exclusion | NAM SRP+ or OM | CAM |
| MHC-1                           | Pure DM        | Pure PM         | OM              | CAM             |

*The background color indicates the frequency of the event in the current series: dark gray = frequent event (>10% of cases), light gray = event of intermediate frequency (2%–10% of cases), white = rare event (<2% of cases).

†IIM mimickers: viral myositis, inflammatory muscular dystrophy, and any other myopathy with secondary inflammatory changes.
follow-up. In this group, IBM was the most frequent diagnostic pitfall (14 cases). Our results are similar to those of van der Meulen et al, who concluded in a retrospective study of 165 Dutch myositis patients that pure PM was rare and over-diagnosed, accounting for only 2% of their patients. We conclude that neither of the 2 classification systems is stringent enough for the diagnosis of PM, this diagnosis can be retained only after the exclusion of IIM mimickers. In the same way, if a MAA is identified in association with pPM on muscle biopsy, the diagnosis of OM must not be systematically made, because the prevalence of MAA in the general population is high, and their main pathologic expression is pDM, not pPM. 

In the current series, 1 patient with anti-RNP and 1 patient with anti-SSA plus anti-SSB and Sjögren syndrome, both with pPM at muscle biopsy, were finally considered as having IBM and unclassified myopathy.

In Case of Unspecified Myositis and Necrotizing Myopathy, Unusual Autoantibodies Must Be Sought

Unspecified myositis was the second most frequently observed histologic pattern, after pDM. If the case is classified as pure PM according to Troyanov et al (no DM rash, no overlap features, no specific autoantibodies, no cancer), the diagnosis must be questioned as it will be finally retained in only 15% of cases (2 of 13 cases in the current series). In other cases, the clinico-serologic classification provides a basis for classifying a subgroup of cases as pure DM and OM, when cutaneous signs suggestive of DM or a specific autoantibody are present. Interestingly, in the setting of OM, a histologic aspect of unspecified myositis was suggestive of an unusual autoantibody such as anti-Ku or anti-PM-Scl. For these peculiar autoantibodies, only small series of patients with muscle biopsy have been reported, and the pathologic phenotype remains to be refined. Anti-Ku might be associated with rimmed vacuole formation.28

The current study confirms that necrotizing myositis gives grounds for searching for an anti-SRP autoantibody.11,14,22,24 As NAM was not recorded as an entity in the clinico-serologic classification, most cases were classified as OM or pure PM with this classification. It is important to remember that the diagnosis of NAM can be retained only when exposure to myotoxic drugs or toxins, endocrinopathy, or family history of a neuromuscular disease have been ruled out.6

Classification Schemes Should Be Updated Periodically Because of the Identification of Novel Autoantibodies

During the last years, a number of groups have reported the identification of clinically significant novel MSAs, such as anti-CADM-140 (identified in Japanese patients with cutaneous features of DM and rapidly progressive interstitial pneumonia but no clinically significant muscle disease), anti-SAE (in adult patients who present with clinically amyopathic dermatomyositis first and then progress to develop myositis with a high frequency of systemic features), anti-p155/140 (present in 10%–20% of myositis patients, especially adult patients with severe cutaneous involvement and increased risk of malignancy, and juvenile dermatomyositis), anti-p140 (juvenile myositis with calcinosis), and anti-HMG-CoA reductase (patients with statin-associated necrotizing myopathy).13,19,20 Detection of these novel autoantibodies is not yet widely available, and consequently, the classification schemes will need to be regularly updated according to the scientific advances in the field of myopathology and immunology.

In conclusion, the current study shows that the clinico-serologic and pathologic classification systems are complementary, and both should be used to better classify patients suffering from IIM. Guidelines for diagnosis according to both clinico-serologic and pathologic data are given in Table 6; we recommend applying these guidelines in clinical practice.

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