



## Workshop report

## 205th ENMC International Workshop: Pathology diagnosis of idiopathic inflammatory myopathies Part II 28–30 March 2014, Naarden, The Netherlands

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### 1. Introduction

The idiopathic inflammatory myopathies (IM) are a heterogeneous group of diseases and diagnosis often necessitates a muscle biopsy. Five main entities are recognized: (1) dermatomyositis (DM); (2) polymyositis (PM); (3) necrotizing autoimmune myopathy (NAM); (4) sporadic inclusion body myositis (IBM); and (5) non-specific myositis. Other entities include granulomatous myopathy, macrophagic myofasciitis, and eosinophilic fasciitis (Shulman's syndrome). The pathological classification and subsequent identification of disease subgroups are extremely important for assessing

treatment options and prognosis in the individual patient, yet classification criteria have not been standardized and validated. The 193rd ENMC Workshop on the Pathologic Diagnosis of Idiopathic Inflammatory Myopathies was held in 2012, in order to establish guidelines for a standardized diagnostic work up. This 205th ENMC International Workshop brought together 20 experts with significant expertise in muscle biopsy reading from suspected IM patients from 11 countries from various parts of the world: Australia, Belgium, Denmark, France, Germany, Japan, The Netherlands, Sweden, Switzerland, the United Kingdom, and the United States of America.

**Jan De Bleeker** opened the workshop by presenting a round-up of the first workshop. In that workshop, international experts came together to discuss current practices in IM diagnosis and possible novel directions for the future. Emphasis was placed on the non-IBM sub-groups. Group evaluation and nominal group technique based consensus building were

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initiated to determine the requisite biopsy material, histological stains and biopsy scoring methods [1]. Recommendations were made for a minimum diagnostic panel of histological and histochemical stains and a working document was drafted on how to best define and score disease signs. The need persists to build international consensus on how to describe pathological features in muscle biopsies of patients suspected of an IM. Standardization of the pathologic criteria would lead to a comprehensive diagnostic routine that could be widely implemented. The goal of this 205th workshop was the further refinement of such a standard.

## 2. Pathology classification of the inflammatory myopathies: State of the art

Several participants analyzed past and current strategies to diagnose IM, and looked at possible future directions.

**David Hilton-Jones** discussed the origins of our understanding of IBM as a specific disorder and charted progress with respect to the evolution of diagnostic criteria based on pathological and clinical features. He pointed out that the earlier heavy reliance on the combination of pathological features had given way to clinical features dominating the diagnostic approach.

Arguably, IBM emerged in the 1970s when it was appreciated that many patients with “treatment-resistant PM”, on closer scrutiny, had a distinctive muscle biopsy and clinical features [2]. The suggested canonical pathological features, enshrined in the 1995 “Griggs” criteria [3], encompassed inflammatory infiltrates with the invasion of non-necrotic muscle fibers, the presence of vacuolated (rimmed) muscle fibers, and either intracellular amyloid deposits or 15–18 nm tubulofilaments visualized by electron microscopy. A biopsy showing all of these features allowed a diagnosis of definite IBM, irrespective of the clinical picture. Revised diagnostic criteria have been proposed [4–6] that have placed greater emphasis on specific clinical features, and its reproducibility has been borne out in several large clinical studies [7–9]. Extensive clinical experience has emphasized that biopsies from many patients at presentation do not show the canonical pathological features defined in the Griggs criteria, yet develop the clinical features of IBM in long-term follow-up [7,9,10]. There is evidence that some of the pathological changes, particularly rimmed vacuoles, may only appear later in the course of the disease [9]. Protein aggregation is a striking feature of IBM [11] and may be helpful in diagnosis, with the detection of p62, showing a characteristic subsarcolemmal and often perinuclear pattern of dense aggregates. In addition, deposits of transactive response DNA binding protein 43 kDa (TDP-43) has proven to represent a promising identifier [12,13]. The recent identification, by two separate groups, of an antibody against cytosolic 5′-nucleotidase 1A may add a new element to current diagnostic criteria [14,15].

Dr. Hilton-Jones concluded that IBM is associated with a very characteristic pattern of muscle involvement that in most cases allows a confident clinical diagnosis. Revised diagnostic criteria place more emphasis on the clinical features, but biopsy remains an important tool to exclude rare disease mimics, and

may also continue to contribute to our limited understanding of the pathogenesis of the condition.

**Anthony Amato** presented a literature summary of disease classification focusing on IM other than IBM. In 1975, Bohan and Peter formulated what has been the most commonly used diagnostic criteria for the classification of PM and DM [16,17], but these criteria are non-specific and do not take into account major advances in the field. The diagnostic criteria and classification do not recognize features on the muscle biopsy (e.g., perifascicular atrophy) that distinguish DM from PM, nor recognize the existence of IBM or NAM. Dalakas and Hohlfeld developed clinical criteria that incorporate histopathological features that further help to distinguish PM from DM [18]. A diagnosis of definite PM requires the demonstration of CD8+ lymphocytes surrounding and invading non-necrotic muscle fibers expressing MHC I antigen coupled with an important negative, the absence of rimmed vacuoles. In the absence of endomysial inflammation, a diagnosis of probable PM can be made if there is ubiquitous expression of MHC I, again in the absence of rimmed vacuoles and dystrophic changes. The diagnosis of myopathic DM requires the demonstration of perifascicular, perimysial or perivascular infiltrates and perifascicular atrophy (there was a provision in the criteria for amyopathic DM). Around the same time, it was reported that most of the biopsies from patients classified as PM by Bohan and Peter’s criteria would not be classified as such utilizing the requirement for inflammatory cells invading non-necrotic muscle fibers [19]. The categories of non-specific myositis and necrotizing myositis were added. A subsequent ENMC workshop in 2004 developed clinical, laboratory, and histopathological criteria for PM, DM, non-specific myositis, and NAM to ensure homogeneous groups in research studies [20]. Some have argued that insisting on specific histopathological features regarding the inflammatory infiltrates is inappropriate and reduces diagnostic sensitivity, thereby excluding certain patients from clinical trials [21]. Alternatively, separating patients according to histopathological criteria seems reasonable until their pathogenic basis can be elucidated [22]. More recently, Pestronk developed a purely histopathological classification system [23], which can be especially helpful when only minimal clinical information accompanies the biopsy specimen. However, like the ENMC 2004 criteria, these have not been assessed for reliability. The recognition of certain staining characteristics may be very helpful, for example, COX-negative perifascicular fibers in DM, more widespread COX negative fibers in IBM, and edematous/fragmented perimysium that stains with alkaline phosphatase in myositis as part of the antisynthetase syndrome.

**Werner Stenzel** discussed his personal views on classification. He demonstrated that patients with autoantibodies fall into specific clinical disease subtypes. Antisynthetase syndrome (ASS)-associated IM is characterized by sarcolemmal MAC staining on fibers adjacent to the perimysium, inflammatory perimysial fragmentation, and ultrastructural evidence of fine filaments in myonuclei. SRP- and HMGR-associated IM frequently display sarcolemmal MHC I staining, blood vessel MAC staining and/or

sarcolemmal MAC staining, and the important involvement of CD68+ cells in the pathology. In contrast to what is published in small series, inflammatory lymphocytic infiltrates can occur in anti-SRP and anti-HMGCR autoantibody positive necrotizing myopathies in about 1/4 of cases, although invasion of myofibers by CD8+ T cells is not a feature of these entities. He also discussed the problems of using rather non-specific descriptive items in myopathological routine and pointed out that this could be improved by including a broader spectrum of well-defined criteria.

**Romain Gherardi** discussed the rare diagnosis of definite PM, which represents less than 5% of biopsies. He pointed to the strong association of MHC II expression with ASS, compared to DM without anti-synthetase antibodies.

**Ichizo Nishino** discussed issues of clinical practice for IM biopsy diagnosis in Japan. He reported that his laboratory received 257 suspected cases of myositis from a total of 732 muscle biopsies from all over Japan submitted for pathological diagnosis in 2012. Among them, 35% were clinically suspected to have PM, 18% DM, and 17% IBM. However, pathological diagnosis revealed that only 4% had PM, which is most likely due to strict pathological criteria [19]. The most frequent diagnosis was NAM (21%), followed by DM (13%), IBM (11%), non-specific myositis (9%), and sarcoid myopathy (0.4%). Other non-myositis diagnoses included muscular dystrophy (9%) and neurogenic diseases (8%), other myopathies (7%), and non-diagnostic abnormalities (16%). Among 39 autoantibody-tested NAM cases, 41% had anti-SRP antibody, 10% anti-Mi2 antibody, and 10% anti-aminoacyl tRNA synthetase antibody. Interestingly, the recently reported IBM-related anti-cN1A antibody was also detected in serum of 21% of patients with NAM with anti-SRP antibody (paper submitted). Dr. Nishino also reported that endothelial cells in blood vessels in DM muscles are frequently highlighted on non-specific esterase staining with 92.5% sensitivity and 96.5% specificity against non-DM cases (paper in preparation).

**Henrik Daa Schroder** discussed the technical aspects of immunohistology of muscle and emphasized the need for standardization of procedures. Firstly, section thickness influences both the number of cells, in the case of inflammatory cells, and the density of enzyme or immunohistochemical staining. Secondly, the choice of primary antibodies also has a major influence on the results. Anti-CD68 antibodies have been standard for the detection of macrophages, but alternatives exist, for example, CD163 and CD14. Furthermore, immunostains differ with respect to the spectrum of monocytes/macrophages/dendritic cells that are labeled. But even between different clones, results for detecting the same antigen may differ. In most protocols, the CD68 clone PG-M1 proved superior to clone KP1 (Nordic immunohistochemical quality control, NordiQC, [www.nordiqc.org](http://www.nordiqc.org)). CD4 has been used for demonstrating T-helper cells, but the development of anti-CD4 antibodies with high affinity has resulted in antibodies that also detect macrophages and dendritic cells. As a consequence, one could consider the elimination of CD4 as a T lymphocyte marker and to employ only CD3 and CD8 for T lymphocyte characterization. Anti-NCAM/CD56 antibodies, being widely

used to detect fiber damage and regeneration, also call for attention as the region-specific nature of these antibodies can give rise to different staining patterns due to differences in isoform recognition.

To standardize immunohistochemistry, the use of controls is recommended in the form of small tissue arrays containing negative, minimal and densely staining elements. Most detection systems will function acceptably with the majority of primary antibodies, but in some difficult cases, 3-layer systems may prove superior to 2-layer systems, something Dr. Daa Schroder and his co-workers reportedly observed with anti-myosin antibodies and antibodies directed against muscle membrane proteins. Immunohistochemistry in some cases can substitute for enzymatic techniques, e.g. staining for myosin subtypes. To selectively visualize blood vessels antibodies directed against endothelium, e.g. CD 31, CD34 or von Willebrand factor can be used. Also, immunohistochemistry can be used to improve the detection of degeneration and regeneration by employing CD56, vimentin, nestin, or neonatal myosin antibodies. Importantly, such stains will enhance the detection of minimal changes and potentially the assessment of the degree of change compared to standard techniques, an aspect which will have to be considered in a standardized approach.

**Janice Holton** described the experience of the group at the UCL Institutes of Child Health and Neurology that led to the development of a score tool for assessing the severity of pathological features in muscle biopsies from patients with juvenile DM. The process began with the selection of an international group of clinicians and pathologists with experience in reporting juvenile DM biopsies. A Delphi survey was then carried out by email to ascertain a list of features that might be included in the score tool. This was followed by two consensus meetings and workshops in which nominal group consensus techniques were used to establish the components included in the score tool, the requisite stains and the definitions of individual items of the tool. The items of the tool were arranged in four domains (inflammatory, vascular, muscle fiber and connective tissue) with the use of a visual analog scale to illustrate the overall severity of pathology in the biopsy. The tool was tested by examining quadriceps biopsies to confirm the reliability and inter-scorer agreement of items in the tool [24]. In a third meeting, the inter-rater reliability of the tool was tested in both quadriceps and biceps and the intra-rater reliability was also assessed. A further aim was to determine whether items in the tool are associated with clinical measures of disease severity. At this meeting, it was found that the score tool performed equally well in quadriceps and biceps. Items with the highest reliability and scorer agreement in all scoring exercises were selected for the modified score tool. It could then be demonstrated that items in the modified score tool correlated with clinical measures of muscle strength [25]. In contrast to the juvenile DM biopsy study, the aim of the current workshop is to assess the diagnostic features of IM in muscle biopsies, however, the experience in juvenile DM may provide useful methodological information.

### 3. Analysis and discussion of previewed series of muscle biopsies

**Boel De Paepe** reported on the online scoring survey that preceded the workshop. In the survey, material was made available from 24 patients from the University Hospitals of Amsterdam, Berlin and Ghent (Supplementary [Table S1](#)). For all individual biopsies, H&E, NADH, SDH, and COX stains were provided. For most cases, Gomori trichrome, non-specific esterase and alkaline phosphatase were also available, and in a large selection, accompanied by immunostains for CD3, CD4, CD8, CD20, CD68, MHC I, MAC and p62. The material was available via an online digital platform (Slidepath, Leica), allowing the analysis of the entire biopsy. No clinical data were provided from the patients, not even age or gender. An expansive score sheet was drawn up based upon Delphi during the 193rd ENMC workshop and supplied to the scorers. An analysis was done on the score sheets from 12 respondents, all international experts in diagnostic reading of muscle biopsies.

There was strong disagreement on diagnostic criteria. In only one biopsy, the experts unanimously agreed on the pathological diagnosis, and scored it as representing a non-specific myositis. An animated discussion followed concerning the diagnostic criteria for PM and IBM. Variation in scoring the severity of myopathological changes pointed to the need for providing standards for quantitative scoring. There was also disagreement on the localization of inflammatory cell infiltrates and the invasion of non-necrotic muscle fibres. The quality of immunostaining was sometimes considered poor, which compromised interpretation. Requests for extra stains were frequent and consisted mainly of markers for blood vessels, fiber types, and inclusions.

### 4. Consensus building

#### 4.1. List of stains and score sheet

On the second day, consensus building included itemized discussions of myopathological methods and scoring, led by **Eleonora Aronica**, and the re-analysis of previewed cases, led by **Marianne de Visser**.

Based upon the achievements of the first workshop and further discussion, recommendations for IM diagnostic criteria were finalized. The group was unanimous on the necessity of H&E, COX/SDH, and MHC I staining. High scores were reached for trichrome, PAS, ATPases, NADH, MAC and CD8 and macrophage inflammatory cell markers. Many participants were concerned that performing a limited set of stains with a high yield in IM may not sufficiently exclude other neuromuscular diseases, and suggested that a basic panel of stains should be done in each biopsy ([Table 1](#)).

Participants agreed that there was a strong need to reduce the score sheet into a workable yet sufficiently informative document. The individual elements of the pre-workshop score sheet were reviewed one by one. After extensive group discussion, a decision was reached as to which items should be retained and how they should be quantified. This process ultimately led to a proposal of the score tool draft upon which all participants could agree (Supplementary [Table S2](#)).

Table 1  
Recommended list of IM diagnostic stains.

Required stains for muscle biopsies	Additional stains for suspected IM	Optional stains for suspected IM
HE	AK	CD20/CD79a
ATPases/Myosin F/S	CD3, CD8, CD68	CD4
NADH	HLA-ABC/MHC-I	CD138
SDH	MAC (c5b-9)	BDCA1/BDCA2
COX or COX/SDH	p62	HLA-DR/MHC-II
Gomori	CD31	TDP43
PAS		CD56/NCAM
Oro/Sudan B.		Myosin-fetal
AP		
NE		
Congo red		

Abbreviations: alkaline phosphatase (AK), fast/slow (F/S), acid phosphatase (AP), cytochrome c oxidase (COX), hematoxylin-eosin (HE), membrane attack complex (MAC), non-specific esterase (NE), succinate dehydrogenase (SDH).

#### 4.2. Definition of pathological changes

On the third day, the requirement for myopathological standards was tackled in a group discussion led by **Jan De Bleecker**. It was put forward that small task groups should be forged to document and describe selected pathological issues in detail. Also, the group agreed to evaluate a new set of 30 diagnostic biopsies and to subject the score sheet and other working documents to further discussion. The group will welcome all remarks from other experts in the field. The workshop participants agreed that a third workshop would be appropriate to further fine-tune the methodology.

### 5. Conclusions

After the exchange of state-of-the-art knowledge regarding classical and alternative classification criteria, new developments, and the re-analysis of previewed biopsies, participants arrived at a recommended list of stains for IM diagnosis, definitions of myopathological features, and a score sheet describing the latter. It was decided that the proposed diagnostic tools will be tested on new cases by the ENMC Myositis Muscle Biopsy Study Group members, to allow further fine-tuning.

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**Appendix: Supplementary material**

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2014.12.001.

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