Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

**Name of the enterprise / Nature of the interest**

<table>
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<tr>
<th>Enterprise</th>
<th>Interest</th>
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<td>Nothing to disclose</td>
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Pitfalls in the diagnostic pathology of myositis

Jan De Bleecker

Ghent University Hospital, Neurology Dept.

29th European Congress of Pathology
Amsterdam, 5/09/2017
• Current pathological classification of myositis
• Pitfalls
  – Techniques – standardization – ENMC workshops
  – Necrotizing myopathies
  – IIM mimics
  – MHC-I expression
THE IIM: ‘CLASSICAL’ CLASSIFICATION

1. Dermatomyositis (DM)
   Childhood (JDM) or adult form
2. Polymyositis (PM)
3. Inclusion body myositis (IBM)
4. Necrotizing autoimmune myopathy (NAM)
5. Anti-synthetase syndrome associated myositis
5. Unspecific myositis
   Granulomatous myopathy
   Inflammatory myopathy with abundant macrophages (IMAM)
   Macrophagic myofasciitis
   Eosinophilic fasciitis
DM case 1

[Image of tissue sample]
DM case 1
DERMATOMYOSITIS

[Image of muscle tissue with fibrotic changes]
DERMATOMYOSITIS	MAC
	UEA-1
DM case 3 CD31
DM case 2 COX/SDH
DM case 2 MHC-I
DM case 3
DM case 2 CD3
DM case 2 CD68
DM case 3 CD3
DM case 3 CD20
DM case 3 CD68
DERMATOMYOSITIS  CD3  CD22
THE IIM: CLASSIFICATION

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5. Unspecific myositis
POLYMYOSITIS
PM  Dystrophin  Laminin
Dystrophin
Dystrophin  ICAM-1
• Does ‘classical’ PM exist?

Van de Vlekkert et al. Neuromuscul Disord 2015;25:451-6
THE IIM: CLASSIFICATION

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   5. Unspecific myositis
IBM: MUSCLE BIOPSY FINDINGS

– myopathic changes
– endomysial infiltrate surrounding and invading nonnecrotic muscle fibers
– groups of atrophic muscle fibers
– rimmed vacuoles
– eosinophilic cytoplasmic inclusions
– mitochondrial changes: ragged red fibers, COX-negative fibers
Inflammatory Features Common in PM and sIBM

PM

MHC-I

MHC-I/CD8 lesion

Special features of sIBM

Vacuoles and Inflammation

COX-negative Fibers

CV-positive Amyloid
IBM case 1
IBM case 2 p62
IBM case 28 SDH/COX
THE IIM: ‘CLASSICAL’ CLASSIFICATION

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5. Anti-synthetase syndrome associated myositis
   5. Unspecific myositis
NAM case 1
NAM case 2
NAM case 3
NAM case 2 CD68
THE IIM: 'CLASSICAL' CLASSIFICATION

1. Dermatomyositis (DM)
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4. Necrotizing autoimmune myopathy (NAM)
5. Anti-synthetase syndrome associated myositis
5. Unspecific myositis
ASS case 2
ASS case 1
ASS case 1
ASS case 1 CD68
ASS case 1 MHC-I
ASS case 1 CD3
ASS case 1 MAC
ANTI-SYNTHETASE ANTIBODY MYOSITIS

MAC
ASS case 1 p62
ASS case 1 Alkaline Phosphatase
ASS case 2 Alk Phos
DM case 2 Alk Phos
NAM case 1 Alk Phos
THE IIM: ‘CLASSICAL’ CLASSIFICATION

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   Childhood (JDM) or adult form

2. Polymyositis (PM)

3. Inclusion body myositis (IBM)

4. Necrotizing autoimmune myopathy (NAM)

5. Anti-synthetase syndrome associated myositis
   5. Unspecific myositis
UM case 1
UM case 2
UM case 2
UM case 2 Alk Phos
UM case 2 MAC
PESTRONK CLASSIFICATION

1. Immune myopathy with perimysial pathology
2. Myovasculopathy
3. Immune polymyopathy
4. IIM with endomysial pathology
5. Histiocytic inflammatory myopathy
6. Inflammatory myopathy with vacuoles, aggregates and mitochondrial pathology
Pitfalls

- Uniformity across different labs
  - What stains?
  - Which structures should be assessed?
- Rigid classification system: pro’s and con’s
  - Comparable groups in research work
- Exclusion of significant proportion of biopsies/patients
- Delayed recognition of “new” IIM forms, e.g. NAM
- Publication bias
Participants of 2012 1st ENMC Workshop
Standardization of biopsy interpretation
Standardization of biopsy interpretation

Discussion

• Lessons learned with juvenile DM (L. Wedderburn, J. Holton): muscular – vascular – connective tissue – inflammatory changes

Group evaluation of biopsies

• Biopsy material requirements
• Selection histological and immunohistochemical stains
• Biopsy scoring methods

• Necessity to evaluate in a standardized way each morphologic structure in each biopsy to avoid bias of ‘predefined’ entities
Workshop report

193rd ENMC International workshop
Pathology diagnosis of idiopathic inflammatory myopathies
30 November – 2 December 2012, Naarden, The Netherlands

Jan L. De Bleecker\textsuperscript{a,*}, Ingrid E. Lundberg\textsuperscript{b}, Marianne de Visser\textsuperscript{c}, for the ENMC Myositis Muscle Biopsy Study Group\textsuperscript{1}

\textsuperscript{a} Department of Neurology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
\textsuperscript{b} Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, SE-171 76 Stockholm, Sweden
\textsuperscript{c} Department of Neurology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
### Scoring sheet

Based upon delphi first workshop

Domain scoring system

muscular – vascular

connective tissue – inflammatory

Qualitative and quantitative

0: absent

1: moderate

2: substantial

3: severe/abundant

Tentative diagnosis

### Participants (#12)

Frank Mastaglia, Anthony Amato, Jan De Bleecker, Elisabeth Rushing, Ichizo Nishino, Hans Goebel, Werner Stenzel, Henrik Daa Schroeder, David Hilton-Jones, Romain Gherardi, Marianne de Visser, Duygu Selcen, Janice Holton
Participants of 2014 2nd ENMC Workshop
Results of 2014 pre-workshop biopsy survey

- Full agreement on only one case!
  - case 21: Unspecific myositis
- Discussion PM vs. IBM
- Different scoring of severity and abundance
- Disagreement on presence/absence of non-necrotic muscle fibers
Conclusions of 2014 Workshop

- List of recommended diagnostic stains

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

- Define pathological changes
- Scoresheet: validation in new set of 30 biopsies
- Work in progress...
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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g Ghent University Hospital, Belgium
h Kansas University Medical Center, Kansas City, USA
i Université Paris Est, Creteil, France
j Mainz University Medical Centre, Mainz, Germany
k John Radcliffe Hospital, Headington Oxford, UK
l University College London, London, UK
m Karolinska Institutet, Stockholm, Sweden
n Johns Hopkins University, Baltimore, USA
o University of Western Australia, Perth, Australia
p National Center of Neurology and Psychiatry, Kodaira Tokyo, Japan
q Zurich University Hospital, Zurich, Switzerland
r Odense University Hospital, Odense, Denmark
s Mayo Clinic, Rochester, MN, USA
t Charité University, Berlin, Germany

Received 6 November 2014; accepted 2 December 2014
<table>
<thead>
<tr>
<th>ASS myositis</th>
<th>Anti-HMGCR NAM</th>
</tr>
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<tr>
<td>(Stenzel et al., Neurology 2015)</td>
<td>(Alshehri et al. (Pestronk group), Neurol Neuroimmunol Neuroinflammm, 2015)</td>
</tr>
<tr>
<td>fiber size variations</td>
<td>myonuclear pathology</td>
</tr>
<tr>
<td>myonuclear pathology</td>
<td>myonuclear enlargement, irregular shapes, empty central regions, clusters</td>
</tr>
<tr>
<td>perifascicular necrotic fibers</td>
<td>large clusters of contiguous damaged fibers</td>
</tr>
<tr>
<td>perimysial MAC deposition on the sarcolemma</td>
<td>immature fibers prominent in perifascicular areas</td>
</tr>
<tr>
<td>predominant sarcolemmal MHC-I in perifascicular areas</td>
<td>perimysial inflammatory aggregates</td>
</tr>
<tr>
<td>focal extension of inflammation into the endomysium</td>
<td>some inflammation surrounding perimysial vessels</td>
</tr>
<tr>
<td>alkaline phosphatase positive fragmented perimysial connective tissue</td>
<td>focal invasion of muscle fibers</td>
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Pathologic diagnosis, not a clinical one
NECROTIZING MYOPATHY
Pathologic diagnosis, not a clinical one

- Immune-mediated necrotizing myopathy: NAM – ASS myositis
- Metabolic myopathy
- Toxic myopathy
- Muscular dystrophy

Term ‘myositis’ means long-term steroids for the patient
Necrotizing myopathies: myositis vs. dystrophy

Pathologic diagnosis of necrotizing myopathy in Limb Girdle Muscular Dystrophy (FKRP – LGMD2I, ANO5 mutations- LGMD2L), even with (partial) clinical or CK improvement on immunotherapies - Exclusion of muscular dystrophy
Immune-responsive necrotizing myopathy masking a dystrophy

Case report

Significant response to immune therapies in a case of subacute necrotizing myopathy and FKRP mutations

J. Svahn a,*, N. Streichenberger b, O. Benveniste c,d, R. Menassa e, L. Michel e, H. Fayolle f, P. Petiot a
Necrotizing myopathies: myositis vs. dystrophy

- Pathologic diagnosis of necrotizing myopathy in Limb Girdle Muscular Dystrophy (FKRP – LGMD2I, ANO5 mutations- LGMD2L), even with (partial) clinical or CK improvement on immunotherapies

- Long-standing proximal weakness and very high CK in SRP-associated NAM – treatable

Major need for clinico-pathological interaction
Recognize muscular dystrophies with inflammation

- Dystrophinopathy (Duchenne>Becker)
- Dysferlinopathy (LGMD2B)
- Facio-scapulo-humeral dystrophy
- Caveolinopathy (LGMD1C)
- Calpainopathy (LGMD2A)
- Merosinopathy (congenital muscular dystrophy)
Unspecificity of findings: MHC-I on sarcolemma

- PM
- DM
- IBM
- NAM, statin-induced and other forms
- ASS myositis
- Dystrophinopathy (Duchenne)
- LGMDs, e.g. dysferlinopathy (LGMD2B)