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>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
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</thead>
<tbody>
<tr>
<td>None</td>
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</tbody>
</table>
Why is pathology necessary in the work-up of myositis? - A clinician's view

Jonathan Baets MD, PhD
Neuromuscular Reference Centre, Antwerp University Hospital, Belgium
Laboratory of Neuromuscular Pathology, Institute Born-Bunge, Antwerpen, Belgium
Overview

❖ Terminology: **Idiopathic Inflammatory Myopathies** or **IIM**
❖ Do we need pathology? – disclaimer
❖ Myopathology: technicalities – another disclaimer
❖ Diagnosing patients: classifications and other nightmares
❖ What about treatment?
❖ Case vignettes
❖ Conclusions
Do we need pathology (for myositis)?

**PATHOLOGY IS ONLY AS GOOD AS:**

- Quality of the clinical indication
- Quality of muscle selection and biopsy
- Quality of sample processing
- Experience of the myopathologist
- Availability of key clinical features
- Clinical interaction to correlate findings

*Allenbach (2017) Neuropathol Appl Neurobiol*
Technical requirements

- Bergström needle vs. open surgical
- Motivated surgeon, fast transport
- Dry, unfixed, cooled but not frozen (glutaraldehyde for EM)
- Cryo-sections, 8-10 µm (no parafine!)
- Mounted material frozen in nitrogen-cooled isopentane
- Experienced myopathologist
How do we diagnose patients?

- Clinical presentation: weakness pattern, speed of progression, other features
- General laboratory findings including CK levels
- Auto-serology: myositis-associated (MAAs) and myositis specific (MSAs) Ab
- EMG and MRI
- **Muscle pathology**
- Pulmonary evaluation: X-ray/CT, lung function (ILD)
- Cancer screening
Early classification: the one, the other and the odd one out

- Bohan and Peter diagnostic criteria (1975): **polymyositis** (PM) vs. **dermatomyositis** (DM)
- Special category (1978): sporadic **Inclusion Body Myositis** (sIBM)
- Pathology was merely required to show evidence of myositis

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symmetrical weakness of limb-girdle muscles and anterior neck flexors</td>
</tr>
<tr>
<td>2</td>
<td>Muscle biopsy evidence typical of myositis</td>
</tr>
<tr>
<td>3</td>
<td>Elevation of serum skeletal muscle enzymes, particularly creatine kinase</td>
</tr>
<tr>
<td>4</td>
<td>Typical electromyography features of myositis</td>
</tr>
<tr>
<td>5</td>
<td>Typical DM rash, including heliotrope and Gottron’s papules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For the diagnosis of PM</th>
<th>For the diagnosis of DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>Item 5 plus 3 of items 1–4</td>
</tr>
<tr>
<td>Probable</td>
<td>Item 5 plus 2 of items 1–4</td>
</tr>
<tr>
<td>Possible</td>
<td>Item 5 plus 1 of items 1–4</td>
</tr>
</tbody>
</table>

Bohan (1975) NEJM; Carpenter Neurology (1978); Allenbach (2017) Neuropathol Appl Neurobiol; Clark and Isenberg (2017) EJN
Classification in more recent times

Polymyositis
An overdiagnosed entity

Unicorns, dragons, polymyositis, and other mythological beasts

What do we get for a precise tissue-diagnosis?

- **Classification** (now and in the future)
- Associated disorders and **prognosis**: ILD, neoplasms, …
- Confrontation with **auto-antibody testing** (MAAs and MSAs) - D. Pehl
- Tailored **treatment**, or not - B. Küsters
- Differentiation from **non-IIM disease**: toxic, inherited - J. De Bleecker
General clinical findings in IMM

- **Weakness:**
  - Typically proximal (stairs, getting up from chair, lifting objects)
  - Distal: rare unless advanced stages, exception sIBM (finger flexors)
  - Axial muscles may be involved: head drop, swallowing and breathing
  - Atrophy: in advanced (untreated) patients, early in sIBM
  - Myalgia: can be present but if severe consider fasciitis or rhabdomyolysis
- **Presentation:** subacute>acute>chronic

Dalakas (2015) NEJM
More specific clinical findings in IMM

- **Extra-muscular involvement:**
  - Systemic: fever, arthralgia and Raynaud’s (mainly in ASS)
  - Cardiac: rare
  - Pulmonary: interstitial lung disease (ILD) 10-40% (anti-Jo-1, anti-MDA5)

- **Skin changes:** periorbital heliotrope rash; erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (V-sign), and back and shoulders (shawl sign); Gottron’s rash

*Dalakas (2015) NEJM*
More specific clinical findings in IMM

- **NAM**: often (sub-) acute onset, very high CK levels, statin exposure in some, weakness can be pronounced
- **ASS/overlap myositis**: various associated features e.g. ILD, mechanics hands, Raynaud’s, arthritis, fever, weight loss
- **IBM**: slowly progressive weakness and atrophy of proximal muscles in legs and finger flexors in adults of >50y
Auxillary findings in IMM

- Serum CK levels:
  - sIBM x10 - ASS/NM/DM x50 - NAM>x50
  - If extremely high consider rhabdomyolysis
- Muscle MRI
  - Edema → inflammation
- Atrophy and fatty infiltration: sIBM, other
- EMG: acute vs. chronic myogenic changes

Salient findings on muscle biopsy

- Perifascicular atrophy
- Perivascular infiltrates
- Necrosis, myophagia and regeneration with limited inflammation
- Perifascicular infiltrates
- MHC-I upregulation
- Rimmed vacuoles
- Focal invasion of myocytes
Other reasons precise pathology is important

- Evaluation of Ab negative patients (around 50%)
- Useful if clinical presentation or serology inconclusive
- Correlation auto-Ab vs. morphology still incompletely understood
- Description of morphology vs. novel antibodies in the future
- Better pathomechanistic insights towards novel therapies
## Treatment?

### Table 2. Treatment of Inflammatory Myopathies: A Step-by-Step Approach.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment for Dermatomyositis, Polymyositis, and Necrotizing Autoimmune Myositis</th>
<th>Treatment for Inclusion-Body Myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset disease</td>
<td>Prednisone (1 mg per kilogram, up to 100 mg per day) for 4–6 weeks; taper to alternate days</td>
<td>Physical therapy; participation in research trial</td>
</tr>
<tr>
<td>When weakness at onset is severe or rapidly worsening</td>
<td>Intravenous glucocorticoids (1000 mg per day) for 3 to 5 days, then switch to oral regimen</td>
<td>Not applicable</td>
</tr>
<tr>
<td>For glucocorticoid sparing, if the patient’s condition responds to glucocorticoids</td>
<td>Azathioprine, methotrexate, mycophenolate, cyclosporine*</td>
<td>Not applicable†</td>
</tr>
<tr>
<td>If response to glucocorticoids is insufficient</td>
<td>Intravenous immune globulin (2 g per kilogram in divided doses over a period of 2 to 5 consecutive days)</td>
<td>Not applicable†</td>
</tr>
<tr>
<td>If response to glucocorticoids and intravenous immune globulin is insufficient</td>
<td>Reevaluate and reconsider diagnosis; initiate treatment with rituximab§ if diagnosis is reconfirmed, recommend participation in a research trial¶ if disease does not respond to rituximab</td>
<td>Participation in research trial</td>
</tr>
</tbody>
</table>

*Dalakas (2015) NEJM, Watanabe (2016) JNNP*
List of drugs currently used for idiopathic inflammatory myositis ad relative areas of effectiveness.

<table>
<thead>
<tr>
<th>Drug dosages</th>
<th>Myositis</th>
<th>Interstitial lung disease</th>
<th>Arthritis</th>
<th>Cutaneous involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>1 mg/kg/day or (IV)elim.v. bolus (0.5–1 g/day for 3 days) then tapering</td>
<td>2 g/kg divided over 2–5 days, every 4–8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose(s)elim Intravenous Immunoglobulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O (not)elim no supporting data.
● currently used but without supporting data.
●● small case series (~15 patients).
●●● large case series (~15 patients), guidelines, others.
! Warning.
* Topical formulation of calcineurin inhibitors effective.
# Treatment: the case of NAM

<table>
<thead>
<tr>
<th>Regimens, number (%)</th>
<th>Anti-SRP</th>
<th>Anti-HMGCR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=51)</td>
<td>(n=39)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>50 (98)</td>
<td>38 (97)</td>
<td>0.85</td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>4 (8)</td>
<td>12 (31)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>8 (16)</td>
<td>3 (8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>4 (8)</td>
<td>5 (13)</td>
<td>0.44</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>23 (45)</td>
<td>5 (13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>7 (14)</td>
<td>3 (8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>28 (55)</td>
<td>19 (49)</td>
<td>0.56</td>
</tr>
<tr>
<td>Intravenous methyl-prednisolone pulse therapy</td>
<td>22 (43)</td>
<td>14 (36)</td>
<td>0.49</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SRP, signal recognition particle.
NAM, HMGCR+: male, 43y

- 3 month symmetric proximal weakness, LL>UL, MRC 3/5
- CK 13 401 U/L (46-171 U/L)
- No rash, no statin exposure
- anti-HMGCR: positive (+++)
- Refractory to prednisone, azathioprine and methotrexate
- Marked biochemical and clinical response upon IVIg therapy
NAM, SRP+: female, 65y

- Progressive proximal weakness since 3m
- No skin changes
- CK 3276 U/L (46-171 U/L)
- anti-SRP ++
- PET-scan: ovarian mass
- Serous ovarian carcinoma stage IIIC
- Very limited response to steroid therapy
- Died 3m after diagnosis due to rapid progression of carcinoma
DM, anti-TIF1γ+: male, 68y

- Subacute (3-4m) symmetric proximal weakness
- CK 2298 U/L (46-171 U/L)
- Erythematous rash, Gottron’s papules, Shawl sign
- Smoker
- Anti-TIF1Y: positive
- PET-CT: normal, control planned
- Favourable response to corticosteroids/MTX
Overlap myositis, anti-PM-Scl+, female 40y

- 6w history of severe proximal weakness
- Respiratory weakness
- CK 3983 U/L (46-171 U/L)
- Anti-PM-Scl100+
- Mechanical ventilation on tracheostomy
- Slow but favourable response to corticosteroids and azathioprine
- Ambulatory with normal CK after 9m
IBM: male, 72y

- >>6m progressive proximal weakness LL and distal UL with marked atrophy
- CK 334 U/L (46-171 U/L)
- MRI: fatty infiltration and atrophy
- Supportive therapy
- Slow progression, after 2y walking and hand function worsen but remains ambulatory
Conclusions

- IIM form a heterogeneous group of presumed auto-immune disorders
- Muscle pathology remains integral part of clinical workup
- Specific expertise required for myopathology
- Evolving classification upon confrontation with auto-antibody status
- Various associated disorders, variable clinical course and therapy response
- Integration of clinical, serological and histological findings crucial
Questions?