Classifying Myositis

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What is Myositis

• Inflammation of the muscle
  – Many causes for inflammation

Normal  Inflammation
Is Inflammation Harmful?

- Inflammation heals with scarring
- Scaring leads to muscle damage
- Damage causes weakness
How is Myositis Defined?

• Inflammation of the muscle that causes weakness
  – Associated with
    • Elevation in serum muscle enzyme levels
    • Abnormal electromyography (EMG) testing
    • Characteristic muscle biopsy findings
    • Rashes (dermatomyositis)

• Bohan and Peter 1975
Classification Schemes

Clinical groups (Adult or Juvenile)

- Polymyositis
- Dermatomyositis
- Inclusion body
- Myositis with other CTD
- Cancer-associated
- Eosinophilic
- Granulomatous
- Focal / Nodular
- Ocular / Orbital
New Advances in Science

- Genetics
- Imaging Studies
  - MRI
- Laboratory Studies
  - Autoantibodies
  - Markers present in muscle on biopsy
## Genetic Risk Factors

<table>
<thead>
<tr>
<th>IIM Group</th>
<th>HLA-DRB1</th>
<th>HLA-DQA1</th>
<th>Comments (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White IIM (PM, DM, IBM)</td>
<td>*0301</td>
<td>*0501</td>
<td>HVR1motif (~6)</td>
</tr>
<tr>
<td>JDM</td>
<td>*0301</td>
<td>*0501</td>
<td>IL1A1/A2 (~5)</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>*0301</td>
<td>*0501</td>
<td>In Whites (~30)</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>*05</td>
<td>*0301</td>
<td>In Blacks (~8)</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>*07(B9-trp)</td>
<td>*0201</td>
<td>In Hispanics (~18)</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>*04</td>
<td>?</td>
<td>In Whites (~7)</td>
</tr>
</tbody>
</table>

These markers may help define who is at risk for myositis.
Laboratory Studies

• Tests for autoantibodies
  – Autoimmune diseases test positive for autoantibodies
    • Thyroid disease – anti-thyroid antibodies
    • Lupus – anti-nuclear antibodies
    • Rheumatoid Arthritis – antibody to an antibody (RF)

• Myositis Specific Autoantibodies (MSA)
Myositis Specific Autoantibodies

• Anti-Mi-2 Dermatomyositis
• Anti-SRP Myositis
• Anti-p155 Cancer associated myositis
• Anti-HMGCR Statin induced myositis
• Anti-synthetase Syndrome
  – A collection of autoantibodies associated with a syndrome of symptoms and myositis
Anti-Synthetase Syndrome

• Characterized by
  – Fevers
  – Arthritis
  – Lung disease (interstitial pulmonary fibrosis)
    • severe
  – Hand rash (mechanic’s hands)
# Anti-Synthetase Syndrome

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Protein (kD)</th>
<th>RNA</th>
<th>Antigenic Element</th>
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<tbody>
<tr>
<td>Antisynthetases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>55</td>
<td>tRNA-His</td>
<td>HisRS</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>80</td>
<td>tRNA-Thr</td>
<td>ThrRS</td>
</tr>
<tr>
<td>Anti-PL-12 (1)</td>
<td>110</td>
<td>None</td>
<td>AlaRS</td>
</tr>
<tr>
<td>Anti-PL-12(2)</td>
<td>none</td>
<td>tRNA-Ala</td>
<td>tRNA-Ala</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>&gt; 130</td>
<td>tRNA-Ile</td>
<td>IleRS</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>75</td>
<td>tRNA-Gly</td>
<td>GlyRS</td>
</tr>
</tbody>
</table>
Antisynthetase Autoantibody
Immunoprecipitation Patterns

(a) Total RNA

(b) Molecular marker

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0S</td>
<td>5.8S</td>
<td>5.0S</td>
<td>tRNA</td>
<td>220</td>
<td>97.4</td>
</tr>
<tr>
<td>69</td>
<td>46</td>
<td>30</td>
<td></td>
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</table>
ELISA testing
Myositis Autoantibody Phenotypes Differ in Clinical Presentation, Genetics and Prognosis

- **Anti-α-aminoacyl-tRNA synthetases**
  - Interstitial lung disease, Arthritis, Fevers, Mechanic’s hands; DR3
  - 75% 5-year survival

- **Anti-Signal Recognition Particle**
  - Acute-onset PM, Severe weakness, Myalgias, Myocarditis; DQA1*0104
  - 25% 5-year survival

- **Anti-MI-2: chromodomain helicase DNA binding protein 4**
  - Classic Dermatomyositis, V-sign & shawl rashes, Cuticular overgrowth; DR7
  - 90% 5-year survival
Other new laboratory tests

• Presence of a protein on the muscle cells where inflammation is occurring
  • HLA-1

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Polymyositis</th>
<th>Myopathic dermatomyositis</th>
<th>Amyopathic dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathic muscle weakness</td>
<td>Yes* Myopathic</td>
<td>Yes* Myopathic</td>
<td>No† Myopathic or non-specific</td>
</tr>
<tr>
<td>Electromyographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle enzymes</td>
<td>High (up to 50 times normal)</td>
<td>High (up to 50 times normal) or normal</td>
<td>High (up to 10 times normal) or normal</td>
</tr>
<tr>
<td>Muscle-biopsy findings</td>
<td>Primary inflammation, with the CD8/MHC-1 complex and no vacuoles</td>
<td>Ubiquitous MHC-I expression, but no CD8-positive infiltrates or vacuoles; perifascicular, perimysial or perivascular infiltrates; perifascicular atrophy</td>
<td>Non-specific or diagnostic for dermatomyositis (subclinical myopathy)</td>
</tr>
<tr>
<td>Rash or calcinosis</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

† None of the criteria for amyopathic dermatomyositis is required for a diagnosis of amyopathic dermatomyositis.
Inclusion Body Myositis Criteria
(Griggs et al. 1995)

Clinical features

- Disease duration > 6 mos.
- Age of onset > 30 years
- Proximal and distal weakness involving quadriceps, finger flexors, and wrist flexor > wrist extensor weakness

Laboratory features

- Serum CK < 12 times normal
- Muscle biopsy showing inflammation with MNC infiltrates, vacuolated myofibers, and either: 1) intracellular amyloid deposits or 2) 16-18 nm tubulofilaments by EM
- EMG consistent with an inflammatory myopathy
Hyper-, hypo-, or agammaglobulinemia
Monoclonal gammopathy
Circulating immune complexes
Immunoglobulin and complement deposition in muscle vascular endothelium
Autoantibodies also seen in other diseases - ANAs, anti-Ro, anti-La, anti-thyroid, etc.
Myositis-associated autoantibodies - Anti-PM/Scl, -Ku, -U1RNP, -U2RNP
Myositis-specific autoantibodies - Anti-synthetases, -SRP, -Mi-2
Classifying Myositis is Difficult

- Spectrum of disease
- Different causes
- Some are genetic, some are inflammatory
- Usefulness of classifying is mostly for research
- Goal is to provide better therapy