The Myositis Alphabet soup: making sense of myositis antibodies

Jemima Albayda, MD
Assistant Professor
Johns Hopkins Myositis center

Disclosures

- None

Objectives

- To delineate the role of autoantibodies in inflammatory myositis evaluation
- To discuss the known myositis antibody associations and their clinical phenotypes
- To review statin-associated myositis
Use of Copyrighted Material

- Original or modified figures and tables from studies and articles are included in this talk with references provided.
- This information is intended solely for use in an educational lecture setting.
- Further distribution or use in other settings is strictly prohibited.

Idiopathic Inflammatory Myopathies

- Rare group of autoimmune muscle disorders.
- Characterized by primary inflammation in the muscle.
- Heterogenous in presentation.
- Extramuscular manifestations include skin, lung, joint, heart and GI tract involvement.
- Can have an increased risk of malignancy.

Bohan and Peter criteria for IIM

- Symmetrical weakness, usually progressive of the limb-girdle muscles.
- Elevation of serum levels of muscle-associated enzymes (CK, aldolase, LDH, AST, ALT).
- Muscle biopsy evidence of myositis.
  - Necrosis of type I and type II muscle fibers. Phagocytosis, Degeneration and regeneration of myofibers with variation in myofiber size. Endomysial, perimysial, perivascular or interstitial mononuclear cells.
- Electromyographic triad of myopathy.
  - Short, small, low-amplitude polyphasic motor units potentials.
  - Fibrillation potentials, even at rest; bizarre high frequency repetitive discharges.
- Characteristic rashes of dermatomyositis.
Advances
- Discovery of antibodies
- Understanding of histopathology
- Addition of imaging data
- Newer therapeutic agents

Myositis specific antibodies
- Autoantibodies targeting diverse intracellular antigens
- Seen only in myositis and not in other autoimmune diseases
- Tightly linked to phenotypic expression—clínico-serologic syndromes
- Creates more homogenous subsets
- Aids in diagnosis

Myositis antibody discovery

<table>
<thead>
<tr>
<th>Year</th>
<th>Jo-1</th>
<th>PL-7</th>
<th>C10</th>
<th>PL-12</th>
<th>MIA-2</th>
<th>SRP</th>
<th>SFP</th>
<th>TIF1-γ</th>
<th>HMGCR</th>
<th>SA</th>
<th>TEnA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Idiopathic inflammatory myopathies

- Dermatomyositis
- Polymyositis
- Inclusion Body Myositis
- Immune-mediated Necrotizing Myopathy

Dermatomyositis

- Dermatomyositis specific antibodies
  - Mi-2: classic DM rashes with favorable treatment response and prognosis
  - MDA5: clinically amyopathic DM and rapidly progressive ILD
    - Characteristic cutaneous ulcerations, palmar papules, panniculitis and oral ulcers
  - TIF1Y: strongly associated with malignancy (adult); diffuse photoerythema and "dusky red face", reduced risk of ILD

Dermatomyositis specific antibodies

- NXP2: in JDM associated with calcinosis, joint contractures and severe skin; in adults malignancy, subcutaneous edema and distal weakness
- SAE: associated with dysphagia and severe skin disease


Important Rashes

Immune-mediated necrotizing myopathy

- Many necrotic muscle fibers as the predominant abnormal histologic feature
- Inflammatory cells are sparse
- Usually very elevated muscle enzymes
- Severe weakness including dysphagia
IMNM specific antibodies

- SRP: rapidly progressive with marked CPK elevation and dysphagia
- HGMCR: related to statin use, but also seen in statin naïve patients

Statin-associated myositis

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Presentation of statin-associated autoimmune necrotizing myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of statin use</td>
<td>From 2 months to 10 years⁶⁴</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>Symmetric proximal arm and leg weakness, distal weakness possible, myalgia⁷⁵</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Dysphagia, arthralgia, Raynaud phenomenon¹⁷</td>
</tr>
<tr>
<td>Muscle enzymes</td>
<td>Mean creatine kinase value 19,333 IU/L⁵⁵</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Muscle edema, atrophy, fatty replacement, facial edema⁹⁴</td>
</tr>
<tr>
<td>Electromyography</td>
<td>Irreversible myopathy in most patients⁶⁵</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>Prominent necrotic and regenerating fibers without significant inflammatory infiltrate, diffuse or focal up-regulation of major histocompatibility complex class I expression⁷⁰</td>
</tr>
</tbody>
</table>

**Statin-associated myositis**

- May be statin naïve
- Can be seen in children and young adults → tend to be more severe
- In statin unexposed patients, other environmental sources possible: ex. mushrooms
- HLA-DRB1*11:01 and 07:01
- Anti-HMGCR not seen in self-limited statin myopathy cohorts


---

**Inclusion Body Myositis**

- Most common IIM in >50y/o
- Chronic course of slowly progressive weakness
- Both distal and proximal muscle weakness, asymmetric; dysphagia common
- Elevated muscles enzymes but not markedly so
- Myopathic and neurogenic changes on EMG
- Compatible muscle biopsy: endomysial infiltrates + rimmed vacuoles
- Course of disease appears to be unaffected by currently available treatment

---

**IBM**

![Image of IBM](https://www.muscular-dystrophy-association.org/about/ubehelp/38bodyisnotsymmetrical.html)
Asymmetric forearm scooping in IBM

IBM-related antibody

- Anti-cN1A (cytoplasmic 5'-nucleotidase 1A)
- Has a high specificity for IBM
- May also be found in patients with other autoimmune diseases like SLE or Sjogren’s syndrome


Polymyositis

- Proximal muscle weakness
- Elevated muscle enzymes
- Myopathic findings on EMG
- Compatible muscle biopsy: endomysial infiltrates, CD8+ T cells
- Diagnosis of exclusion
Polymyositis

From Muscular Dystrophy Association
http://neuropathology-web.org/chapter13/chapter13eInflammatory.html

Antisynthetase syndrome

- Myositis
- Interstitial lung disease
- Inflammatory arthritis
- Sterile Fevers
- Raynaud’s
- Mechanic’s hands

Myositis specific antibodies

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>ANTIGEN</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo-1</td>
<td>Histidyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>PM-1</td>
<td>Threonyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>PL-7</td>
<td>Alanyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>PL-12</td>
<td>Glycyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>EJ</td>
<td>Isoleucyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>OJ</td>
<td>Asparaginyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>KS</td>
<td>Phenylalanine tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
<tr>
<td>Zo</td>
<td>Tyrosyl tRNA synthetase</td>
<td>PM, DM, ILD</td>
</tr>
</tbody>
</table>

Dermatomyositis specific antibodies

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>ANTIGEN</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mi-2</td>
<td>DNA helicase</td>
<td>Treatment responsive</td>
</tr>
<tr>
<td>MDA5</td>
<td>Melanoma differentiation assoc gene 5</td>
<td></td>
</tr>
<tr>
<td>155/140</td>
<td>Transcription intermediary factor 1-gamma</td>
<td></td>
</tr>
<tr>
<td>140</td>
<td>Nuclear matrix protein (NXP-2)</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>Small ubiquitin-like modifier-activ. enzyme</td>
<td></td>
</tr>
</tbody>
</table>

IBM-specific antibodies

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>ANTIGEN</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1A</td>
<td>Cytoplasmic 5'-nucleotidase</td>
<td></td>
</tr>
</tbody>
</table>

Note: PM = polymyositis, DM = dermatomyositis, ILD = interstitial lung disease, IBM = inclusion body myositis.
Myositis antibodies

- Anti-SSA/Ro
- Anti-Ro52
- Anti-Ro60
- Anti-La
- Anti-PM-Scl 75
- Anti-PM-Scl 100
- Anti-Ku
- Anti-U1RNP
- Anti-mitochondrial

Myositis associated antibodies

Conclusions

- Heterogenous group of disorders presenting with weakness and evidence for immune-mediated organ damage
- Antibodies can confirm a diagnosis and contribute to definition of disease subsets
Questions?

• Thank you for your attention

References


References


