Autoantibodies and prognosis

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Heterogeneity of IIMs

**Diagnosis**
- Polymyositis
- Dermatomyositis
- IBM
- Necrotising myopathy
- Paraneoplastic
- Amyopathic DM
- Myositis in overlap

**Autoantibody**
- Negative
- Jo-1
- Other ARS
- SRP
- Mi-2
- PM-Scl
- U1-RNP
- p155/140
- CADM-140

**Organ involvement**
- Lung
- Heart
- Oesophagus
- Calcinois
- Joints
- Other
Autoantibodies in myositis

Variable frequencies

30-90%
Autoantibodies in myositis

- Diagnostic tool
- Define clinically similar situations
- Correlation with disease activity
- Mediate disease pathogenesis?
Case 1

Diagnosis:
Immune mediated necrotizing myopathy with anti-SRP positivity.

Treated with Rituximab

11/2009 muscle strength markedly improved
walks with a cane
normal muscle enzymes
Case 2

Diagnosis:

Cancer associated dermatomyositis
with p155/140 positivity.
Conclusions

In daily clinical practice, myositis specific autoantibodies may help to:

Establish diagnosis and estimate prognosis

Justification for aggressive therapy in Case 1
Early cancer detection in Case 2
Autoantibodies in IIMs

• Myositis specific autoantibodies (MSA)
• Myositis associated autoantibodies (MAA)
• New autoantibodies
## Myositis specific antibodies (MSA)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reactivity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl-tRNA synthetase</td>
<td>15-30%</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>Threonyl-tRNA synthetase</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>Alanyl-tRNA synthetase</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Glycyl-tRNA synthetase</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Isoleucyl-tRNA synthetase</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Anti-KS (AsnRS)</td>
<td>Asparaginyl-tRNA synthetase</td>
<td>Rare</td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>Phenylalanyl-tRNA synthetase</td>
<td>Rare</td>
</tr>
<tr>
<td>Anti-YRS (Ha)</td>
<td>Tyrosyl-tRNA synthetase</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Antisynthetase syndrome

- Myositis
- Interstitial lung disease (89%)
- Arthritis (94%)
- Raynaud’s phenomenon (67%)
- Fevers (87%)
- Mechanic’s hands (71%)

- Anti-Jo-1 – similar pathology
  - Perimysial fragmentation
  - Macrophage predominance
  - Perifascicular changes (atrophy, regeneration, some necrosis)
  - Normal capillary density

Antisynthetase syndrome and ARS antibodies

Myositis

Interstitial lung disease

Jo-1, YRS, Zo, EJ, PL-7, KS, OJ, PL-12
### Myositis specific antibodies (MSA)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-SRP</td>
<td>Signal recognition particle</td>
<td>4-6%</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Nuclear helicase</td>
<td>4-18%</td>
</tr>
<tr>
<td>Anti-CADM-140</td>
<td>MDA5</td>
<td>19% of DM</td>
</tr>
<tr>
<td>Anti-p155/140</td>
<td>TIF-1</td>
<td>13-30%</td>
</tr>
<tr>
<td>Anti-NXP-2 (p140)</td>
<td>Nuclear matrix protein</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-SAE</td>
<td>SUMO-1 act. enz.</td>
<td>4% (8% DM)</td>
</tr>
<tr>
<td>Anti-200/100</td>
<td>HMGCR</td>
<td>6%</td>
</tr>
<tr>
<td>Anti-Mup44 (43kDa)</td>
<td>cN-IA</td>
<td>52-63% IBM</td>
</tr>
</tbody>
</table>
Immunoprecipitation in 308 patients with IIMs from a single centre

Lenka Pleštilová, in collaboration with Zoe Betteridge and Neil Mc Hugh, Bath, UK
Anti-SRP antibodies

• Older studies
  – severe disease
  – onset in the fall (anti-7SL RNA)
  – myalgia
  – bad response to treatment
  – short survival
A New Approach to the Classification of Idiopathic Inflammatory Myopathy: Myositis-Specific Autoantibodies Define Useful Homogeneous Patient Groups

Lori A. Love, M.D., Ph.D., Richard L. Leff, M.D., David D. Fraser, M.D., Ira N. Targoff, M.D., Marinos Dalakas, M.D., Paul H. Plotz, M.D., and Frederick W. Miller, M.D., Ph.D.
23 European anti-SRP patients

- disease onset in the fall and winter, 3 DM
- severe weakness, marked disability, dysphagia
- highly elevated CK
- ILD in 21%
- no association with cardiac involvement
- necrotizing myopathy with capillary abnormalities
- reasonably favorable prognosis
- (response to rituximab?)
Anti-Mi-2 antibodies

- Skin manifestations
- relatively mild disease
- treatment response - fair
- latitudinal gradient (UV intensity)
- tendency for antibodies to NT-fragment of the Mi-2β antigen to have a higher risk for malignancy

Anti-p155/140 antibody

- 155 kD, 140 kD (K562). Nuclear speckled.
- 13, 21, 30% of myositis patients
  - Heliotrope rash, Gottron’s papules, ulceration (in JDM), flagellate erythema
  - In 23, 29% JDM
  - In 75%, (71% vs. 11%), (50% vs. 4%) of cancer associated DM
- No ILD
- DQA1*0301 association
- Transcriptional intermediary factor 1γ

# Anti-p155/140 antibodies in IIM patients

<table>
<thead>
<tr>
<th>Author</th>
<th>All IIM</th>
<th>JDM</th>
<th>DM</th>
<th>PM</th>
<th>CAM</th>
<th>Anti-p155/140+ no CAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targoff</td>
<td>21%</td>
<td>29%</td>
<td>21%</td>
<td>0</td>
<td>75%</td>
<td>n=2</td>
</tr>
<tr>
<td>Kaji</td>
<td>13%</td>
<td></td>
<td></td>
<td></td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Gunawardena</td>
<td>23%</td>
<td>30%</td>
<td>0</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Chinoy</td>
<td>18.4%</td>
<td></td>
<td></td>
<td></td>
<td>50%</td>
<td>n=11</td>
</tr>
<tr>
<td>Trallero-Araguás</td>
<td>19%</td>
<td>23%</td>
<td>5%</td>
<td></td>
<td>62.5%</td>
<td>n=6</td>
</tr>
<tr>
<td>Vencovský (152 pts)</td>
<td>10.5%</td>
<td>19%</td>
<td>1.6%</td>
<td></td>
<td>41%</td>
<td>n=9 (6.6%)</td>
</tr>
</tbody>
</table>

Presence of anti-p155/140 in patients with disseminated and/or relapsed tumor (DR) or single episode and non-disseminated (NDNR) malignancy

Anti-TIF-1γ in European patients with IIMs.

Mann H et al. ACR 2011.
Anti-SAE autoantibody

4% myositis (8% of DM)  
Severe classical skin  
Mild myositis  
Dermatomyositis  
Periunguinal changes  
HLA-DRB1*04-DQA1*03-DQB1*03

Systemic features – dysphagia  
No or mild ILD  
Rare cancer

Anti-CADM-140 (MDA5) autoantibody

- First described in Japan (19 - 35% DM and 53 - 73% CADM), recently US 10 patients with DM (13%)
- Strongly associated with CADM and interstitial lung disease
- Poor prognosis (46% died within 6 months)
- Ulcerations, palmar papules, vasculopathy
- Drop in anti-MDA5 antibody <500 U/ml after treatment - improvement, whereas anti-MDA5 antibody >500 U/ml are resistant to treatment and die of respiratory failure in a short period.

Anti-p140 (anti-MJ), anti-NXP-2

- 140 kDa protein (nuclear matrix protein NXP-2)
- Weak or no immunofluorescence, sometimes dots in ANA test
- 23% JDM
- Association with calcinosis in JDM
- HLA–DRB1*08
- Recently - most frequent antibody in Italian cohort (17%)
- Younger age at onset, no ILD, no malignancy, good response

**Anti-200/100 kDa**

- Patients who take statins can develop immune mediated necrotising myopathy, which persists after statins discontinuation (some PM or DM)
- These patients only improve with immunosuppressive treatment
- 16 of 26 patients (62%) with necrotising myopathy had anti-200/100 kDa antibodies (63% exposed to statins)
- Worsened upon discontinuation of immunosuppression
- MAC deposition, capillary abnormalities, MHC-I expression (50-75%)

Anti-200/100 (anti-HMGCR)

- Autoantigen for anti-200/100 is 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)
- HMGCR is a target of statins
- Statins upregulate HMGCR protein levels
- Regenerating muscle fibres express high levels HMGCR

Dermatomyositis
- Skin
  - Anti-TIF1-β
  - Anti-SA
  - Anti-Mi-2
  - Anti-NXP2
- Malignancy
- ILD
  - Anti-MDA5
  - Anti-PL-12
  - Anti-KS
  - Anti-OJ
  - Anti-PL-7
  - Anti-EJ
  - Anti-Zo
  - Anti-YRS
  - Anti-Jo-1
  - Anti-Mup44
  - Anti-EIF3
  - Anti-HMGCR
  - Anti-43 kDa
  - Anti-SRP
  - Anti-TIF1-α
  - Anti-TIF1-γ
- Calciosis
- Juvenile DM

Polymyositis
- Muscle fiber necrosis
- Antisynthetase syndrome
- Inclusion body myositis
- Muscle weakness
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