Significance of antibody testing in idiopathic inflammatory myopathies

Autoantibodies in myositis

- Frequency is variable 30-90%
- Usually only 1 autoantibody/1 patient
- Almost each year a new antibody discovered

Autoantibodies are associated with disease characteristics

- Disease manifestation
- Disease course
- Prognosis
- Response to treatment
- Extramuscular manifestations
- Complications
Myositis specific antibodies (MSA)

- Anti-ARS
  - Anti-Jo-1 Histidyl-tRNA synthetase 15-30%
  - Anti-PL-7 Threonyl-tRNA synthetase < 5%
  - Anti-PL-12 Alanyl-tRNA synthetase < 5%
  - Anti-EJ Glycyl-tRNA synthetase < 5%
  - Anti-QI Isoleucyl-tRNA synthetase < 5%
  - Anti-KS (AsnRS) Asparaginyl-tRNA synthetase Rare
  - Anti-Zo Phenylalanyl-tRNA synthetase Rare
  - Anti-YRS (Ha) Tyrosyl-tRNA synthetase Rare

Antisynthetase syndrome and ARS autoantibodies

- ILD

Myositis

- Jo-1
- YRS
- Zo
- EJ
- PL-7
- KS
- OJ
- PL-12

RIM study - subanalysis

Kaplan Meier: Myositis Autoantibody Subsets

Anti-SRP antibodies

- severe weakness, marked disability, dysphagia
- myalgia, highly elevated CK
- necrotizing myopathy with capillary abnormalities
- poor response to treatment
- shorter survival
- onset in the fall (anti-7SL RNA)
- cardiac involvement (?)

- ILD in 21%
- somewhat better 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
- NoILD
- DQA1*0301 association
- Transcriptional intermediary factor 1γ

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

- p155/140
  - negative 93% (n=751)
  - positive 7% (n=57)

Autoantibodies associated with calcinosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anti-NXP-2+ (n = 20)</th>
<th>Anti-NXP-2- (n = 130)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>14 (70)</td>
<td>6 (15)</td>
<td>0.0064</td>
<td>19.3 (7.99)</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>7 (47)</td>
<td>17 (11)</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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 (40% 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-Melanoma Differentiation-Associated Gene 5 Is Associated With Rapidly Progressive Lung Disease and Poor Survival in US Patients With Amyopathic and Myopathic Dermatomyositis

Anti-SAE autoantibody

4% myositis (8% of DM)  
Severe classical skin  
Mild myositis

Dermatomyositis  
Periunugual changes

HLA-DRB1*04-DQA1*03-DQB1*03

Systemic features – dysphagia  
No or mildILD  
Rare cancer


Anti-FHL1 autoantibodies are associated with severe muscle pathology

A

Phenotype based statin related myotoxicity (SRM) classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Phenotype</th>
<th>Incidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRM 0</td>
<td>CK &lt; 4xULN</td>
<td>1.5-26%</td>
<td>No muscle SxS</td>
</tr>
<tr>
<td>SRM 1</td>
<td>Myalgia, tolerable</td>
<td>0.3-33%</td>
<td>SxS with normal CK</td>
</tr>
<tr>
<td>SRM 2</td>
<td>Myalgia, intolerable</td>
<td>0.02-0.2%</td>
<td>CK&lt;4xULN, complete resolution on Dc</td>
</tr>
<tr>
<td>SRM 3</td>
<td>Myopathy</td>
<td>0.005%</td>
<td>CK &gt;4xULN &lt;10xULN, SxS, complete resolution on Dc</td>
</tr>
<tr>
<td>SRM 4</td>
<td>Severe myopathy</td>
<td>0.11%</td>
<td>CK &gt;10xULN &lt;50x, muscle SxS, complete resolution on Dc</td>
</tr>
<tr>
<td>SRM 5</td>
<td>Rhabdomyolysis</td>
<td>0.0001-0.008%</td>
<td>CK &gt;50x ULN, renal impairment + SxS or CK&gt;50x ULN</td>
</tr>
<tr>
<td>SRM 6</td>
<td>IMNM</td>
<td>0.0002%</td>
<td>anti-HMGCR, HMGCR expression in Bx, incomplete resolution on Dc</td>
</tr>
</tbody>
</table>

IMNM with anti-HMGCR antibodies

• First described as anti-200/100 kDa antibodies in 2010  
• High proportion of statin users among positive patients  
• Directed against 3-hydroxy-3-methylglutaryl-coenzyme A reductase  
• Increased HMGCR expression in muscles
IMNM associated with anti-HMGCR

- 25% of anti-HMGCR-positive patients require a wheelchair
- Disease improves by immunosuppressive treatment. It frequently relapses after treatment discontinuation.
- Some patients respond only to IVIGs.
- Disease is very rare
  - incidence 3 – 9/100000 statin users

Muscle biopsy results (+new cases of IIM)

- About 50% of IMNM are anti-HMGCR. All of them have statin exposure in the history.

The prevalence of statin exposure in anti-HMGCR-associated myopathy worldwide

- Johns Hopkins = 30/45 (67%)
- French cohort = 20/45 (44%)
- Czech cohort = 22/23 (96%)
- Australian cohort = 16/17 (94%)
- Chinese cohort = 3/20 (15%)

Anti-HMGCR+ IMNM „without statins”

- *Pleurotus ostreatus*, the oyster mushroom, naturally contains up to 2.8% lovastatin on a dry weight basis.

Fungus

Monascus purpureus

- produces a family of monacolin compounds, including monacolin K, which is identical to lovastatin

An example how autoimmune disease starts?

Enzyme (HMGCR) inhibited by statins

- Increased HMGCR expression in muscle

Loss of tolerance

*HLA (HLA-DM1*11:01 7% vs. 65%), binding of statin to enzyme?*

Autoantibody development

- Activity related to Ab levels – probably pathogenic effect?

Improvement after immunosuppressive treatment
Autoantibodies to Cytosolic 5'-Nucleotidase 1A in Inclusion Body Myositis

• Initially detected in 52%, 33% and 34% with very high specificity for IBM

Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases