Hot Topics in Neuromuscular Literature

Cutting Edge Myopathy: Inherited and Acquired

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Financial Disclosure

• *I have no relevant financial disclosures*
Objectives

- To recognize some of the last year’s impactful literature in the topics of inherited and acquired myopathies
- The following will be discussed in each paper:
  - Background and gap of knowledge
  - Methods
  - Results
  - Conclusions and take home points
Muscular and extramuscular clinical features of patients with anti-PM/Scl autoantibodies

Rebecca De Lorenzo, MD, Iago Pinal-Fernandez, MD, PhD, Wilson Huang, BS, Jemima Albayda, MD, Eleni Tiniakou, MD, Chelonda Johnson, MD, MHS, Jose C. Millsenda, MD, Maria Casal-Dominguez, MD, Andrea M. Corse, MD, Sonye K. Danoff, MD, PhD, Lisa Christopher-Stine, MD, MPH, Julie J. Paik, MD, MHS, MD

Iota P. Mammo, MD, DPT

Neurol 2018;90:e2068-e2076. doi:10.1212/WNL.0000000000005638

Abstract

Objective

To describe sporadic myositis (MP).

Methods

Clinical study 2017 and 2018

Inflammm

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Abstract

Inflammm

Exon skip

Etepli Spondylo
dystro

Literture Discussed
A NEW TYPE OF HEREDITARY DISTAL MYOPATHY WITH CHARACTERISTIC SARCOPLASMIC BODIES AND INTERMEDIATE (SKELETIN) FILAMENTS

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(Received 2 January, 1980) (Revised, received 31 March, 1980) (Accepted 3 April, 1980)

Hereditary Distal Myopathy with Sarcoplastic Bodies

Difference from Welander’s distal myopathy:

- Faster progression
- Finger flexors > extensor involvement
- Sacroplasmic bodies

Gap of Knowledge:

- Unknown genetic cause
- Unknown pathophysiology
- Unknown nature of the sarcoplastic bodies
- More characterization of the phenotype

Myoglobinopathy is an adult-onset autosomal dominant myopathy with characteristic sarcoplasmic inclusions

Montse Olivé et al.
Myoglobin

- Myoglobin is a small cytoplasmic globular hemoprotein highly expressed in cardiac and skeletal muscle fibers.
- It is encoded by the myoglobin gene (MB) on chromosome 22q12.3.
- Functions:
  - It facilitates intracellular O2 transport.
  - It buffers intracellular O2 concentrations.
  - It serves as a reservoir of oxygen during hypoxic and anoxic conditions.
  - It acts as scavenger of reactive oxygen species (ROS) and nitric oxide.

Pedigrees of the Six Families

A Homogenous Phenotype

- Age of onset (33-49 years old)
- Onset: proximal lower limb and axial weakness
- Later: distal leg and hand muscle weakness
- Facial and extraocular muscles sparing
- Cardiac involvement: 6 patients
- More of a slow progression:
  - Respiratory failure requiring nocturnal non-invasive ventilatory in 10 years from onset
  - Wheelchair dependent in 15–20 years after disease onset
- Survival (6/14): death 18-30 years after onset, from respiratory and/or cardiac failure
- CK is mildly elevated (1.5-7 folds)
- Electromyography (EMG): Irritable myopathy

Muscle CT Scans

• **Sarcoplasmic bodies** in:
  • Both types 1 and 2 myofibers
  • All patients and pre-symptomatic individuals
  • Regardless of biopsied muscles

• Nonspecific myopathic changes

• Rimmed vacuoles filled with granular basophilic material, showing:
  • Strong acid phosphatase activity
  • Lysosome-associated membrane protein 1 (LAMP1) reactivity

• No major architectural changes, lack of oxidative activity at site of vacuoles

Abnormal Protein Aggregation

- Myoglobin, p62, and ubiquitin immunoreactivity are found in:
  - Abnormal myofiber regions containing vacuoles
  - Some, not all sarcoplasmic bodies

Electron Microscopy (EM)

- Very dense bodies surrounded by membrane
- Some were denser than others → different stages of the pathological process
- They were present in respiratory and cardiac muscles → cardiomyopathy was primary and not secondary to respiratory failure
- Two samples from individuals with no heart failure manifestations showed large number of sarcoplasmic bodies → long course

Identification of MB Mutation

- One group performed whole-exome sequencing of 3 affected individuals identified the same heterozygous missense variant (c.292C>T, p.His98Tyr) in MB (Spain)
- Other group identified 1 region on chromosome 22 through linkage analysis followed by targeted capture and sequencing of genes within the linkage region in 8 individuals (SWE)
- Sanger sequencing confirmed segregation of the same variant with the disease in all available family members and in three additional families
- The variant involves a highly conserved residue in the proximity of the oxygen-binding heme group and is absent in all unaffected relatives tested
- It was not present in the 1000genomes, ExAC, or gnomAD data sets
- All in silico predictors suggested the observed substitution in MB was deleterious

Biochemical Dysfunction

In His98Tyr variant, the following is affected:

- Affinity of MB protein scaffold to hemin
- Interaction of MB with molecular O2
- Ability to keep the heme in the reduced state (Fe2+)

→ more ROS

Take Home Points

- This is the first disorder caused by a mutation in MB
- The phenotype features autosomal dominant adult onset proximal lower limb and axial weakness progressing to involve proximal and distal muscles of all limbs
- Sarcoplasmic bodies are the pathological hallmark of the disease
- Respiratory insufficiency is a frequent complication and is the cause of death
- Cardiomyopathy was demonstrated in less than half of the patients cardiac involvement remains subclinical for a long time
- Deferential diagnosis includes late onset acid maltase deficiency, However, in Myoglobinopathy, in addition to the sarcoplasmic bodies:
  - Cardiac involvement is more common
  - Distal muscle involvement happens earlier
- All cases were caused by the same His98Tyr missense variant in MB mutational hotspot
Eteplirsen Treatment for Duchenne Muscular Dystrophy

Exon Skipping and Dystrophin Production

• Duchenne muscular dystrophy (DMD) is a rare X-linked recessive genetic neuromuscular disease

• Incidence: 1:3,500 to 5,000 newborn boys annually worldwide

• The majority of DMD cases are due to deletion mutations in the DMD gene → nonfunctional dystrophin protein

• Dystrophin is an essential part of the dystrophin-associated protein complex connecting actin to the extracellular matrix

• The use of ventilation support, steroids, and other supportive measures has increased the lifespan by several years

• Rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/
Eteplirsen

- Eteplirsen is useful in patients with DMD with mutations amenable to correction by skipping exon 51 of the DMD gene, FDA approved in 2016.
- It is a phosphorodiamidate morpholino oligomer, designed to target the pre-mRNA transcript of DMD → exon 51 is excluded (skipped) from the spliced mRNA.
- Patients with certain deletions (exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52–63) benefit from such therapeutic intervention.
- This enables the production of an internally truncated yet functional dystrophin protein.
- It stabilized ambulation in a randomized 24-week controlled study of 8 treated subjects versus 4 placebo controls, study 201 (NCT01396239).
- Study patients’ group included:
  - Patients who had deletions amenable to exon 51 skipping and
  - Could ambulate 200–400 m in 6 minutes (6MWT) at baseline
  - Were on a stable dose of corticosteroids for at least 24 weeks
- Open label extension phase up to 36 months of the 12 subjects (study 202, NCT01540409), showed that:
  - Eteplirsen-treated patients had a slower rate of decline and a 151-meter advantage in the 6MWT distance
  - Fewer treated patients lost ambulation compared with untreated, matched historical controls (16.6% vs. 46%)
  - Respiratory function was relatively more stable in treated patients → survival benefit
Gap of Knowledge: Dystrophin Threshold

• The absence of dystrophin protein in muscle fibers is the hallmark of DMD
• A defined threshold of dystrophin production has not been established
• Dystrophin is a large protein present in low abundance → detection by only Western blot analysis (WB) is difficult and does not show the localization of the protein
• In the 44 exon–amenable DMD patient population:
  o WB results varied from undetectable to 30% of normal
  o Dystrophin intensity measurements ranged from 13% to 25%
  o A slower rate of disease progression was reported
• DMD experts agree that even trace amounts of dystrophin provide meaningful benefit
• Evaluation of dystrophin levels in patients with DMD with standardized and validated methods is needed

Eteplirsen treatment for Duchenne muscular dystrophy

Exon skipping and dystrophin production

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Abstract

Objective
To describe the quantification of novel dystrophin production in patients with Duchenne muscular dystrophy (DMD) after long-term treatment with eteplirsen.

Methods
Clinical study 202 was an observational, open-label extension of the randomized, controlled
Patients and Methods

- Patients who underwent study 202 underwent muscle biopsies:
  - 4 weeks before the first administration of eteplirsen from the biceps muscle (3/12)
  - 24 weeks after the first dose of eteplirsen from the same side biceps
  - 48 weeks after the first dose of eteplirsen from the contralateral biceps
  - 180 weeks after the first dose of eteplirsen from deltoid (optional, 11/12)

- Biopsies were performed 24 to 96 hours after completion of an eteplirsen infusion

- Untreated control baseline tissue samples (n = 6) were obtained from patients with a mutation amenable to exon 51 skipping through a separate study (baseline control n=9)

- The following assays were performed:
  - Assessment of the dystrophin-related content by WB
  - Measurement of dystrophin-associated immunofluorescence intensity by (Bioquant Life Sciences imaging software)
  - Percent dystrophin-positive fibers (PDPF), fiber was counted if ≥30% of sarcolemma was positively stained
  - RT-PCR then Sanger sequencing of the slice junctions (final product) to confirm mechanism of action

Results: Quantitation of Dystrophin Expression

• 100% of treated patients displayed positive exon skipping by RT-PCR analysis

• Each PCR product had the predicted specific dystrophin mRNA PCR product sequence

• Nine of the 11 available biopsies demonstrated increase in dystrophin signal across the 3 quantitative assays. Two did not have a quantifiable dystrophin by WB

• Range of detectable dystrophin was 0.14-2.47% of normal. Range of dystrophin in untreated muscles was undetectable-0.37%, mean =0.08%

• The 3 quantitative assays showed significant difference between the amount of dystrophin in treated vs. untreated patients

Results: WB & Fluorescence Intensity

Labeling in Patients and Untreated Controls

Labeling at Baseline and Week 180

A. Patient L: Baseline  
B. Patient L: Eteplirsen-treated - Week 180

C. Patient L: Baseline  
D. Patient L: Eteplirsen-treated - Week 180

Take Home Points

• This study measured novel dystrophin production using 3 mechanistically distinct assays

• This consistency across the assays and the strong correlation between WB and fluorescence intensity measurements → confidence in the accuracy and precision of different methods

• The included analyses demonstrated that dystrophin can be measured in a robust, sensitive, accurate, and reproducible manner

• Assays capable of detecting novel dystrophin production can serve as pharmacodynamic/response biomarkers of efficacy for dystrophin restoring treatments

• This study provides Class II evidence that eteplirsen treatment is capable of:
  o Muscle cell penetration
  o Exon skipping
  o Induction of novel dystrophin production
Sporadic Late Onset Nemaline Myopathy (SLONM)

- SLONM is a rare adult muscle disease that is pathologically characterized by the accumulation of nemaline rods in muscle fibers with no/mild inflammation.
- It can be associated with a monoclonal protein (MP) or HIV infection.
- Predominantly proximal or axial muscle weakness.
- Respiratory involvement is the main cause of death.
- Patients with an associated MP (SLONM-MP) were thought to have a worse prognosis.
- IVIg and autologous stem cell transplant (ASCT) have had the highest reported clinical benefit.

SLONM Pathology

- By definition the muscle biopsy of every nemaline myopathy patient shows the presence of nemaline rods, on Gomori trichrome staining or electron microscopy.
- Sometimes a re-biopsy is required to establish the diagnosis.
- Unlike the inherited nemaline myopathy, rods tend to fill atrophic fibers in SLONM.
- EM: expansions and deposits of Z-disk and thin filament material.
- They increase with age and vary in number between muscles.
- They were also described in patients with:
  - Dermatomyositis and polymyositis.
  - Hypothyroid myopathy.
  - Acute alcoholic myopathy.
  - Spinal muscular atrophy.
Sporadic late onset nemaline myopathy

Nizar Chahin, MD; Duygu Selcen, MD; and Andrew G. Engel, MD

Abstract—Objective: To review the clinicopathologic features and outcome of sporadic late onset nemaline myopathy (SLONM). Background: Non-HIV-related SLONM is an uncommon disease of undefined etiology. Methods: This study is based on clinical, EMG, histochemical, immunocytochemical, and electron microscopy evaluation, and long-term follow-up of 14 patients observed at the Mayo Clinic between 1975 and 2003. Results: The disease presented between 43 and 81 years and evolved subacutely. The weakness was predominantly proximal in 13, equal proximally and distally in 3, and asymmetric in 4; dysphagia was a symptom in 6. The EMG showed myopathic features with fibrillations but the serum CK level at the time of initial examination or reevaluation was normal or below the Mayo Clinic's range of normal values for sex and age at the time of the assay. Seven patients had an associated monoclonal gammopathy. On light microscopy, the nemaline structures were best identified in 3-μm-thick frozen sections stained trichromatically or immunostained for α-actinin or myosin. Electron microscopy done in 12 cases identified the rods in all and revealed additional structural abnormalities. Seven patients with monoclonal gammopathy were followed for 1 to 5 years; five died of respiratory failure. Five patients without monoclonal gammopathy were followed for 4 to 23 years and none died of the disease. Immunotherapy in eight patients was of uncertain benefit. Conclusions: 1) Subacutely evolving weakness after age 40, normal to low CK level, myopathic EMG with fibrillations, and often a monoclonal gammopathy are clues for the diagnosis of sporadic late onset nemaline myopathy. 2) The diagnosis is confirmed by visualizing the rods in trichrome or immunostained cryosections. 3) An associated monoclonal gammopathy heralds an unfavorable prognosis.

NADADF, Elie MD, Margherita Milone, MD, PhD, Ankit Kansagra, MD, Francis Buadi, MD, and Tsoarchis Kourelis, MD

Neurology® 2019;93:e298-e305. doi:10.1212/WNL.0000000000007777

Abstract

Objective

To describe the clinical phenotype, long-term treatment outcome, and overall survival of sporadic late-onset nemaline myopathy (SLONM) with or without a monoclonal protein (MP).

Methods

We conducted a retrospective chart review of patients seen between September 2000 and June 2017 and collected clinical, laboratory, and survival data. Treatment response was classified as

Results: Demographic and Clinical Data

- Study included date from 28 patients with SLONM, 17 (61%) with an associated MP
- Median diagnostic delay was 35 months (4–120m)
- There was no difference in demographics or clinical features between patients with or without MP
- The most common symptom at onset was bilateral proximal limb weakness (43% of patients)
- The second most common symptom was axial weakness (39% of patients)

Results: Work Up

• No statistically significant difference in the baseline laboratory characteristics between patients with or without MP

• All patients (n=27) had early recruitment of short duration motor unit potentials
  o 13 (48%) long duration motor unit potentials in
  o 22 (82%) had fibrillation potentials

• Number of diagnostic muscle biopsies:
  o One in 19 (68%) patients
  o Two in six patients
  o Three in three patients
  o Two patients had two diagnostic muscle biopsies each

Results: Treatments

• Median follow-up from symptom onset for neurologic outcomes was 72 months (5–145 m)
• Patients received a median of two lines of therapy (range 0–6)
• A total of 48 distinct lines of therapy across all patients, including:
  o Plasma exchange: 19 (40%)
  o IVIg: 16 (33%)
  o ASCT: 7 (15%)
  o Chemotherapy (lenalidomide, thalidomide): 4 (8%)
  o Combination of chemotherapy and IVIg: 1 (2%)
  o One patient with SLONM without MP received no disease-specific treatment

• Median duration of therapy was:
  o IVIg: 12 months (range 4–116m)
  o Hematologic therapy: 15 months (range 6–24m)
  o Immunosuppressive treatment: 7 months (range 5–18m)

• Detailed clinical data enough to ascertain neurologic response was available for 15 patients

Results: Outcomes

- Marked response:
  - Mild residual weakness (MRC grade 4)
  - No functional limitation in ADL
  - No cardiac or respiratory dysfunction
- Moderate response:
  - Improvement on muscle examination in ≥4 muscle groups of any grade
  - Improvement on examination in <4 muscle groups but improvement in ADL
- Mild:
  - Improvement on examination in 1–3 muscle groups with no change in ADL
  - Mild improvement in ADL with no change in muscle strength
- No response:
  - No change or worsening of muscle strength on examination

- Median time to progression was longer for hematologic therapy and IVIg (median not reached) compared to immunosuppressive treatment (37 months), (p = 0.03)
- There was no difference in the overall survival of patients with or without MP
- The only unfavorable predictor of survival was age ≥58 years, risk ratio of 6.4
Take Home Points

• SLONM remains a clinically challenging disease
  o 18% of patients had other presentations than proximal or axial weaknesses
  o Median diagnostic delay was 35 months
  o More than one muscle biopsy was needed in 32% of cases

• Predilection for axial muscles makes respiratory involvement common

• The presence of MP in a patient with a myopathy should raise suspicion for SLONM (61%)

• There was no difference in the overall survival of patients with or without MP

• SLONM patients with or without MP may respond well to IVIg

• For patients with SLONM-MP who do not improve on IVIg, hematologic therapy including ASCT is a reasonable option
Inflammatory Myopathy Associated with PD-1 Inhibitors

• The programmed cell death 1 (PD-1) immunoglobulin was first identified in 1992
• It is highly expressed on T cells extracted from patients with tumors and causes immune suppression
• PD-1 inhibitors including nivolumab and pembrolizumab have shown significant benefit in the treatment of a range of cancer types
• With the increased use of PD-1 inhibitors, recognition of immune-related adverse events (irAEs) induced by these PD-1 inhibitors has become more important
• The reported neuromuscular irAEs are sometimes serious and require prompt attention
• PD-1 inhibitors caused irAEs were found to be associated with a survival benefit in melanoma and advanced or recurrent non small cell lung carcinoma

Epidemiology

• Estimated frequency of neurological autoimmune manifestations in PD-1 inhibitor-treated patients is 2.9%–4.2%
• Frequency of neuromuscular complications is generally low (1-2%)
• Neuromuscular complications usually have acute and sometimes dramatic onset
• Earlier reports have demonstrated that myositis as an irAE (irAE myositis) occur in:
  o Japanese cancer patients receiving nivolumab monotherapy: 0.25% (HLA-A*24:02-B*52:01-C*12:02 common in Japanese, 10%)
  o US cancer patients receiving nivolumab monotherapy: 0.15%
• Ocular dysmotility is common “myasthenia-like” or “pseudo-myasthenic” symptoms
• Diagnostic challenges:
  o An antibody medicated paraneoplastic syndrome is always in the differential diagnosis
  o Physicians may diagnose these patients with a preexisting myositis

Speculated Pathophysiology

Inflammatory Myopathy Associated with PD-1 Inhibitors

Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer

Mehdi Touat, MD, Thierry Maisonobe, MD, Samuel Knauss, MD, Omar Ben Hadj Salem, MD, Baptiste Hervier, MD, PhD, Karine Auré, MD, PhD, Tali-Anne Szweibel, MD, Nora Kramkinel, MD, Claire Lethroeume, MD, Jean-Frédéric Bruch, MD, Pauline Laly, MD, Jacques Cadranel, MD, PhD, Nicolas Weiss, MD, PhD, Anthony Béhin, MD, Yves Allenbach, MD, PhD, Olivier Benveniste, MD, PhD, Timothée Lenget, MD, Dimitri Psimaras, MD, Werner Stenzel, MD, PhD,* and Sarah Léonard-Louis, MD,*

Neurology® 2018;91:e985-e994. doi:10.1212/WNL.0000000000006124

Abstract

Objective

To report the clinicopathologic features and outcome of myositis in patients treated with immune checkpoint inhibitors (ICls) (rMyositis).

Patients

- **Nineteen** Japanese patients with PD-1 myopathy, recruited between July 2016 and June 2018
- They fulfilled the following inclusion criteria:
  - Received monotherapy with either nivolumab or pembrolizumab
  - Could provide blood samples, accompanied by full clinical information
  - Showed increase levels of serum creatine kinase (CK)
  - Exhibited objective muscle weakness supported by needle EMG, muscle MRI, or muscle biopsy
  - Signed an informed consent agreement
- **Positive control group (119),** recruited between October 2010 and December 2014:
  - 68 patients with anti-signal recognition particle-positive (SRP+) antibodies
  - 51 patients with anti-aminoacyl transfer RNA synthetase-positive (ARS+) antibodies
- **Disease severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5:**
  - Grade 1: asymptomatic CK elevation or myalgia alone → Withhold treatment
  - Grade 2: mild muscle weakness with minimal limiting of daily living abilities → Prednisolone 0.5–1 mg/kg
  - Grade 3: moderate muscle weakness and a requirement for hospitalization → Prednisolone (1–2 mg/kg) or IV equivalent
  - Grade 4: severe muscle weakness and a life-threatening condition →

- [https://ctep.cancer.gov/protocolDevelopment](https://ctep.cancer.gov/protocolDevelopment)
### Results: Demographic and Clinical Data

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<th>No/age / gender</th>
<th>CTCAE grade</th>
<th>Cancers</th>
<th>Drugs × cycles</th>
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<th>Initial muscle weakness</th>
<th>Creatine kinase (IU/L)</th>
<th>Anti-titin</th>
<th>Anti-Kv1.4</th>
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<td>Limb weakness</td>
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<td>19/80/M</td>
<td>4</td>
<td>Melanoma</td>
<td>P × 1</td>
<td>19</td>
<td>Dyspnea</td>
<td>9536</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
# Results: PD-1 Myopathy Compared to Positive Controls

<table>
<thead>
<tr>
<th></th>
<th>PD-1 myopathy (n = 19)</th>
<th>SRP + myopathy (n = 68)</th>
<th>ARS + myopathy (n = 51)</th>
<th>P-value PD-1 vs. SRP+</th>
<th>P-value PD-1 vs. ARS+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset (average)</td>
<td>70</td>
<td>55</td>
<td>60</td>
<td>0.0008</td>
<td>0.02</td>
</tr>
<tr>
<td>Male (%)</td>
<td>13 (68)</td>
<td>28 (41)</td>
<td>20 (39)</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Predisposing factors (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>4 (21)</td>
<td>3 (4)</td>
<td>1 (2)</td>
<td>0.02</td>
<td>0.006</td>
</tr>
<tr>
<td>Cancer</td>
<td>19 (100)</td>
<td>4 (6)</td>
<td>6 (12)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>1 (5)</td>
<td>8 (12)</td>
<td>8 (16)</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Muscle weakness (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>13 (68)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ptosis</td>
<td>15 (79)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Facial muscle involvement</td>
<td>8 (42)</td>
<td>3 (4)</td>
<td>2 (4)</td>
<td>&lt; 0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bulbar symptoms</td>
<td>10 (53)</td>
<td>46 (68)</td>
<td>15 (29)</td>
<td>0.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Limbs weakness</td>
<td>13 (68)</td>
<td>68 (100)</td>
<td>51 (100)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Severe limbs weakness</td>
<td>7 (37)</td>
<td>43 (63)</td>
<td>14 (27)</td>
<td>0.04</td>
<td>0.6</td>
</tr>
<tr>
<td>Neck weakness</td>
<td><strong>14 (74)</strong></td>
<td><strong>48 (71)</strong></td>
<td><strong>17 (33)</strong></td>
<td>0.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>4 (21)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0.007</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory muscle involvement</td>
<td>6 (32)</td>
<td>8 (12)</td>
<td>6 (12)</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>2 (11)</td>
<td>46 (68)</td>
<td>15 (29)</td>
<td>&lt; 0.0001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Decreased deep tendon reflex</td>
<td>5 (26)</td>
<td>31 (46)</td>
<td>8 (16)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Myalgia</td>
<td><strong>16 (84)</strong></td>
<td><strong>27 (40)</strong></td>
<td><strong>15 (29)</strong></td>
<td>0.002</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Blood examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (average, IU/L)</td>
<td><strong>5247</strong></td>
<td><strong>6589</strong></td>
<td><strong>4288</strong></td>
<td>0.17</td>
<td>0.37</td>
</tr>
<tr>
<td>Elevated C-reactive protein</td>
<td>3 (16)</td>
<td>13 (19)</td>
<td>31 (61)</td>
<td>0.7</td>
<td>0.0008</td>
</tr>
<tr>
<td>Antinuclear antibody positivity (%)</td>
<td>1 (5)</td>
<td>10 (15)</td>
<td>6 (12)</td>
<td>0.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Results: EMG and Imaging

• Needle electromyography was performed in 11 patients.
  o Short duration motor unit potentials with fibrillation potentials were recorded in eight patients.
• Nine patients underwent muscle MRI
Results: Serology and HLA Genotyping

- RNA immunoprecipitation showed negative
  - SRP
  - ARS
  - U1–U5 ribonucleoprotein
  - Ribosome
  - Sm
  - Ku
  - Th/To
  - SSA and SSB

- Enzyme-linked immunooassays showed negative
  - 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase)
  - Mi-2
  - Transcriptional intermediary factor 1γ
  - Melanoma differentiation-associated gene 5

**Positive** anti-striational antibodies
- Anti-titin antibodies in 10 patients
- Anti-Kv1.4 antibodies in nine patients
- 13 (68%) had at least one antibody

**Two patients** were positive for anti-acetylcholine receptor antibodies

<table>
<thead>
<tr>
<th>n (%)</th>
<th>PD-1 myopathy (n = 30)</th>
<th>Healthy controls (n = 920)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*02:06</td>
<td>3 (10)</td>
<td>82 (9)</td>
<td>0.7</td>
</tr>
<tr>
<td>A*24:02</td>
<td>16 (52)</td>
<td>358 (39)</td>
<td>0.1</td>
</tr>
<tr>
<td>A*26:01</td>
<td>4 (13)</td>
<td>72 (8)</td>
<td>0.3</td>
</tr>
<tr>
<td>B*15:01</td>
<td>3 (10)</td>
<td>70 (8)</td>
<td>0.7</td>
</tr>
<tr>
<td>B*27:01</td>
<td>5 (17)</td>
<td>60 (7)</td>
<td>0.05</td>
</tr>
<tr>
<td>B*40:02</td>
<td>8 (27)</td>
<td>56 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>C*01:02</td>
<td>5 (17)</td>
<td>141 (15)</td>
<td>0.8</td>
</tr>
<tr>
<td>C*03:03</td>
<td>7 (23)</td>
<td>109 (12)</td>
<td>0.08</td>
</tr>
<tr>
<td>C*07:02</td>
<td>5 (17)</td>
<td>137 (15)</td>
<td>0.8</td>
</tr>
<tr>
<td>C*12:02</td>
<td>9 (30)</td>
<td>117 (13)</td>
<td>0.01</td>
</tr>
<tr>
<td>DRB1*01:01</td>
<td>3 (10)</td>
<td>58 (6)</td>
<td>0.4</td>
</tr>
<tr>
<td>DRB1*04:05</td>
<td>4 (13)</td>
<td>103 (11)</td>
<td>0.8</td>
</tr>
<tr>
<td>DRB1*09:01</td>
<td>4 (13)</td>
<td>128 (14)</td>
<td>1</td>
</tr>
<tr>
<td>DRB1*15:01</td>
<td>3 (10)</td>
<td>62 (7)</td>
<td>0.5</td>
</tr>
<tr>
<td>DRB1*15:02</td>
<td>6 (20)</td>
<td>114 (12)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

HLA Genotyping, 15 patients
Results: Muscle Biopsy (7 Patients)

- Multifocal confluent areas comprising 10–15 muscle fibers undergoing necrosis and regeneration

- These are different from those in:
  - SRP + myopathy, scattered distribution
  - ARS + myopathy, perifascicular distribution

- Scattered endomysial inflammatory cell infiltrations, CD4+ and CD8+ T-cells were seen to roughly the same degree

- Expressions of major histocompatibility complex class I antigen mainly in the areas of necrotic muscle fibers
A 77 YOM with Metastatic Melanoma on Nivolumab Presenting with Acute Onset Weakness

H&E 20X
## Results: Treatment

<table>
<thead>
<tr>
<th>No.</th>
<th>Immunotherapy</th>
<th>PS</th>
<th>Tumor response</th>
<th>Other irAEs</th>
<th>Follow-up duration (m)</th>
<th>Neurological outcome¹, tumor status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IVMP, PSL (10mg)</td>
<td>2</td>
<td>PR</td>
<td>-</td>
<td>10</td>
<td>Remission at 20 wks; tumor growth; Remission at 2 wks, died of cancer</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>2</td>
<td>PD</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IVMP, PSL (50mg)</td>
<td>2</td>
<td>PD</td>
<td>+</td>
<td>6</td>
<td>Improvement over 7 wks</td>
</tr>
<tr>
<td>4</td>
<td>PSL (30mg)</td>
<td>2</td>
<td>PR</td>
<td>+</td>
<td>5</td>
<td>Remission at 8 wks</td>
</tr>
<tr>
<td>5</td>
<td>IVMP, PSL (20mg)</td>
<td>2</td>
<td>PR</td>
<td>+</td>
<td>12</td>
<td>Remission at 14 wks, died of cancer</td>
</tr>
<tr>
<td>6</td>
<td>PSL (70mg)</td>
<td>2</td>
<td>PR</td>
<td>+</td>
<td>10</td>
<td>Remission at 2 wks</td>
</tr>
<tr>
<td>7</td>
<td>PSL (50mg)</td>
<td>2</td>
<td>PR</td>
<td>+</td>
<td>6</td>
<td>Remission at 8 wks</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>2</td>
<td>SD</td>
<td>-</td>
<td>17</td>
<td>Remission at 4 wks</td>
</tr>
<tr>
<td>9</td>
<td>PSL (20mg)</td>
<td>2</td>
<td>PR</td>
<td>+</td>
<td>13</td>
<td>Remission at 6 wks, restart of pembrolizumab; tumor growth</td>
</tr>
<tr>
<td>10</td>
<td>PSL (10mg)</td>
<td>2</td>
<td>PD</td>
<td>-</td>
<td>5</td>
<td>Remission at 5 wks, died of cancer</td>
</tr>
<tr>
<td>11</td>
<td>PSL (40mg)</td>
<td>3</td>
<td>SD</td>
<td>+</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PSL (70mg), IVg</td>
<td>3</td>
<td>SD</td>
<td>-</td>
<td>6</td>
<td>Improvement over 8 wks; tumor growth</td>
</tr>
<tr>
<td>13</td>
<td>IVMP, PSL (50mg)</td>
<td>3</td>
<td>SD</td>
<td>-</td>
<td>11</td>
<td>Improvement over 10 wks</td>
</tr>
<tr>
<td>14</td>
<td>IVMP, PSL (80mg)</td>
<td>3</td>
<td>PD</td>
<td>+</td>
<td>3</td>
<td>Improvement over 12 wks, died of cancer</td>
</tr>
<tr>
<td>15</td>
<td>IVMP, PSL (30mg)</td>
<td>4</td>
<td>PR</td>
<td>-</td>
<td>6</td>
<td>Improvement over 12 wks, died of cancer</td>
</tr>
<tr>
<td>16</td>
<td>IVMP, PSL (60mg), PP, IVg, MG</td>
<td>5</td>
<td>SD</td>
<td>-</td>
<td>2</td>
<td>No improvement, died of myocarditis</td>
</tr>
<tr>
<td>17</td>
<td>IVMP, PSL (50mg), PP, IVg, MV, acromiolums</td>
<td>4</td>
<td>SD</td>
<td>+</td>
<td>8</td>
<td>Improvement over 12 wks; confined to a wheelchair, tumor growth, died of cancer</td>
</tr>
<tr>
<td>18</td>
<td>PSL (40mg), PP, MV</td>
<td>4</td>
<td>PR</td>
<td>+</td>
<td>14</td>
<td>Recovered over 25 wks, fracture of femoral hip</td>
</tr>
<tr>
<td>19</td>
<td>IVMP, PSL (1000 mg), PP, IVg, MV</td>
<td>4</td>
<td>SD</td>
<td>+</td>
<td>6</td>
<td>Worn off ventilation, bedridden, transferred to a nursing home</td>
</tr>
</tbody>
</table>

irAE = immune-related adverse events; IVg = intravenous immunoglobulin; IVMP = intravenous methylprednisolone pulse therapy; MV = mechanical ventilation; PD = progressive disease; PP = plasmapheresis; PR = partial response; PS = performance status; PSL = prednisolone (maximum daily dose); SD = stable disease.  
¹ Duration after the immunosuppressive therapy.
Take Home Points

• These clinical, histological, and immunological findings indicate that PD-1 myopathy is a discrete subset of inflammatory myopathy
• PD-1 myopathy did not arise from a paraneoplastic syndrome in these patients
• Disease severity was mild in 10 and severe in nine patients
• PD-1 myopathy occurred 29 days on average after the first treatment
• Ocular, facial, cardiac, and respiratory muscle involvement were frequently observed compared to the control groups
• Immunosuppressive therapy was effective \( \rightarrow \) prompt normalization of CK
• Making a decision to discontinue PD-1 inhibitors continues to be difficult
Anti-PM/Scl Associated Myositis

- The autoimmune myopathies are a heterogeneous group of disorders that affect skeletal muscle as well as other organ systems.
- Three common well defined autoimmune myopathies are dermatomyositis (DM), antisynthetase syndrome (AS), and immune-mediated necrotizing autoimmune myopathy (IMNM).
- Myositis frequently overlaps with other connective tissue diseases (40% of cases).
- Antibodies against 75-kDa and/or 100-kDa subunits of the human exosome complex (the PM/Scl complex) are commonly found in patients with myositis and systemic sclerosis (SSc).
- In addition to myositis, Anti-PM/Scl antibodies are often associated with a constellation of clinical manifestations including:
  - Interstitial lung disease (ILD)
  - Arthritis
  - Raynaud syndrome
  - Dysphagia
  - Mechanic’s hands

Anti-PM/Scl Associated Myositis

Muscular and extramuscular clinical features of patients with anti-PM/Scl autoantibodies

Rebecca De Lorenzo, MD,* Iago Pinal-Fernandez, MD, PhD,* Wilson Huang, BS, Jemima Albayda, MD, Eleni Tiniakou, MD, Cheilonda Johnson, MD, MHS, Jose C. Milisenda, MD, Maria Casal-Dominguez, MD, Andrea M. Corse, MD, Sonye K. Danoff, MD, PhD, Lisa Christopher-Stine, MD, MPH, Julie J. Paik, MD, MHS,† and Andrew L. Mamman, MD, PhD†

Neurology® 2018;90:e2068-e2076. doi:10.1212/WNL.0000000000005638

Abstract

Objective
To define the clinical features of myositis patients with anti-PM/Scl-75 and/or anti-PM/Scl-100 autoantibodies at disease onset and during the course of disease and compare them to patients with other forms of myositis.

Methods
In this longitudinal cohort study, the prevalence and severity of clinical features at disease onset and during follow-up were compared between anti-PM/Scl-positive patients and those with the

Patients and Methods

• Single center longitudinal cohort between 2002 and 2016
• Patients were classified as having:
  o AS if they had autoantibodies against Jo-1, PL-7, or PL-12
  o DM if they had autoantibodies against Mi2, NXP2, TIF1g, or MDA5
  o IMNM if they had autoantibodies against anti-SRP or anti- HMGCR
• Patients’ serum samples were tested for these antibodies by two different validated techniques
• Other factors, including the pattern of muscle weakness, muscle biopsy findings, or extramuscular features were NOT used for categorization
• Clinical data collected retro- and prospectively included:
  • MRC muscle strength grades (averaged between the two sides for each muscle and transformed into Kendall 0–10 scale)
  • Skin Manifestations.
  • Symptoms of esophageal involvement
  • Mechanic’s hand
  • Raynaud’s phenomenon
  • Arthritis
  • Pulmonary function tests

Patients and Methods (Cont.)

- Pulmonary hypertension was defined as:
  - Definite: mean pulmonary arterial pressure of ≥25mm Hg at rest by right heart catheterization
  - Probable: echocardiogram showed a right systolic ventricular pressure >40 mm Hg

- Muscle enzyme levels and pulmonary function tests were included for analysis if obtained within a period of 6 weeks before or after strength testing

- All available muscle biopsies from anti-PM/Scl-positive patients were evaluated for:
  - Perivascular inflammation
  - Perifascicular atrophy
  - Primary inflammation
  - Necrotizing features (muscle fiber necrosis without primary inflammation or perifascicular atrophy)

- Muscle MR imaging of 15 muscles bilaterally in each patient, recording the presence of:
  - Muscle edema
  - Fascial edema
  - Muscle atrophy
  - Fatty replacement

  Adjust for:
  - Sex and race
  - Duration of disease and age at onset
  - Immunosuppressive or immunomodulatory treatment

Patients (Cont.)

• 949 patients had known or suspected myositis and were tested for myositis autoantibodies

• **41 patients (4%)** were positive for anti-PM/Scl antibodies
  - 26 patients (63%) were positive for both anti-PM/Scl-75 and anti-PM/Scl-100
  - 8 patients (20%) were positive only for anti-PM/Scl-100
  - 7 patients (17%) were positive only for anti-PM/Scl-75

• **Positive control group:**
  - 178 patients with DM
  - 132 patients with AS
  - 135 patients with IMNM

• Among the anti-PM/Scl-75 positive patients, 30% met the diagnostic criteria for SSc

• No anti-PM/Scl-positive patient was positive for another myositis-specific autoantibody

• No anti-PM/Scl patient died during the period of this study or developed cancer within three years of the onset of the autoimmune disease

Results: Clinical Data

• At disease onset, weakness was present in 37% of anti-PM/Scl-positive patients

• It was present in a majority of patients with AS (55%, p < 0.05) and IMNM (81%, p < 0.001)

• During follow-up, patients groups developed weakness with no differences between groups

• In anti-PM/Scl-positive patients, the degree of arm abductor weakness was associated with younger age at onset (p < 0.001)

Results: Extramuscular Manifestations

Results: Muscle Biopsy

- **Perivascular inflammation** was the most common pathologic finding, found in 17 of 21 available biopsies (81%)
- Perifascicular atrophy was less frequent compared to DM (24% vs 56%, p = 0.02)
- Necrosis without primary inflammation was less frequent compared to IMNM (24% vs 80%, p < 0.001)
- Primary inflammation was more common than in DM (33% vs 9%, p = 0.03)

Take Home Points

• Patients with anti-PM/Scl autoantibodies have a distinctive pattern of muscle weakness in which arm abductors are weaker than hip flexors
• Compared to the other groups, anti-PM/Scl-positive patients are more likely to have extra-muscular manifestations
• Patients with anti-PM/Scl autoantibodies had higher rates of perivascular inflammation
• They were even more likely than patients with AS to have two of the classic features of AS: mechanic’s hands and Raynaud’s phenomenon
• Other points taken from individual comparisons:
  - Anti-PM/Scl-positive patients were more likely to develop lung and joint involvement than patients with DM or IMNM
  - Patients with AS have higher rates of ILD
  - Patients with IMNM had higher peak CK values and higher rates of irritable myopathy
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