Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

<table>
<thead>
<tr>
<th>Name of the enterprise / Nature of the interest</th>
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<tbody>
<tr>
<td>Enterprise</td>
</tr>
<tr>
<td>Nothing to declare</td>
</tr>
</tbody>
</table>
A rare cause of myopathy in adults
Jorge Pinheiro MD, José Manuel Lopes MD, PhD

Joint Slide Seminar Electron Microscopy and Trainees:
Understanding diseases through the "big eye": an ultrastructural pathology seminar by pathologists in training
Clinical presentation

- 60 year-old woman

- Main complaints
  - Progressive muscle weakness during one year, affecting predominantly proximal limb muscles and the neck, disclosing "drop head"
  - Mild disphagia and horiness
  - Muscle pain
  - 10 kg weight loss

- Past & family history
  - No relevant medical history
  - Parents were consanguineous (cousins in 3rd degree)
  - No relevant family history of neurological disease
Physical examination

- Myopathic gait and “drop head”
- Proximal predominant tetraparesis
- Mild facial muscle paresia
- Muscle atrophy
- No ptosis nor diplopia
- No sensorial alterations

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>Superior limb</th>
<th>Inferior limb</th>
<th>Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proximal</td>
<td>proximal</td>
<td>flexion / extensio</td>
</tr>
<tr>
<td></td>
<td>distal</td>
<td>distal</td>
<td></td>
</tr>
</tbody>
</table>

| Grade       | G3            | G4+           | G4+           | G5           | G3           |
Ancilary studies

- **Electromyography (EMG):** Myopathic tracings (as shown in B) in the proximal muscles of the inferior limbs and in the proximal and distal muscles of the upper limbs, with more severe alterations in the proximal muscles.

- **ECG and cardiac ecography:** Normal

- **Spirometry:** Normal
Ancillary studies

- **Cell blood count:** mild bicytopenia with leucopenia (2920/mm³) and thrombocytopenia (133000/mm³)

- **Protein electrophoresis:** monoclonal gamopathy

- **Immunofixation:** Monoclonal gamopathy with lambda chains
Ancillary studies

- CK, aldolase and myoglobinlin: normal
- TSH normal
- Immunological study was unremarkable
  - ANA
  - anti-dsDNA
  - AMA
  - anti-neuronal
  - anti-ENA panel
- HIV, HCV, HBV: negative
Muscle biopsy (deltoid muscle)
ATPase pH 4.35

ATPase pH 9.4
Diagnosis

Adult-onset nemalinic myopathy (SLONM) associated with monoclonal gamopathy of unknown significance (MGUS)
Follow-up of the patient

- Muscle weakness
- Drop-head
- Muscle pain
- 10 kg weight loss

Worsening of the muscle weakness in the acute phase

- Jan. 2015
  - Melphalan

  - Autologous stem-cell transplantatio n

- Feb. 2016
  - Clinical stability of symptoms
  - Persistence of monoclonal gamopathy

- July 2017
  - Lenalidomide
Clinical classification of nemaline myopathy
(by disease onset and severity of motor and respiratory involvement)

- Severe congenital (neonatal) (16%)
- Amish NM
- Intermediate congenital (20%)
- Typical congenital (46%)
- Childhood-onset (13%)
- SLONM (4%)*

* The pathogenesis remains to be clarified

Ryan MM et al. 2001
### Frequency of genetic / phenotypic features and inheritance mode of nemaline myopathies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Inheritance</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEB</td>
<td>Up to 50%</td>
<td>AR</td>
<td>Typical congenital (majority), and other</td>
</tr>
<tr>
<td>ACTA1</td>
<td>15-25%</td>
<td>AD/AR</td>
<td>Range from severe congenital to childhood onset. Causes 50% of severe lethal NM</td>
</tr>
<tr>
<td>TPM3</td>
<td>2%-3%</td>
<td>AD/AR</td>
<td>Severe (AR), intermediate and childhood (AD)</td>
</tr>
<tr>
<td>TPM2</td>
<td>&lt;1%</td>
<td>AD</td>
<td>Typical congenital</td>
</tr>
<tr>
<td>TNNT1</td>
<td>Old Amish</td>
<td>AR</td>
<td>Amish NM</td>
</tr>
<tr>
<td>CFL2</td>
<td>Rare</td>
<td>AR</td>
<td>Typical congenital</td>
</tr>
<tr>
<td>KBTBD1</td>
<td>3</td>
<td>unknown</td>
<td>AD</td>
</tr>
<tr>
<td>KBTBD13</td>
<td></td>
<td></td>
<td>childhood onset, slowly progressive</td>
</tr>
<tr>
<td>KLHL40</td>
<td>unknown</td>
<td>AR</td>
<td>Severe, intermediate and typical congenital</td>
</tr>
<tr>
<td>KLHL41</td>
<td>unknown</td>
<td>AR</td>
<td>Severe, intermediate and typical congenital</td>
</tr>
<tr>
<td>LMOD3</td>
<td>unknown</td>
<td>AR</td>
<td>Severe and typical congenital</td>
</tr>
<tr>
<td>other</td>
<td>na</td>
<td>AR</td>
<td>na</td>
</tr>
</tbody>
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(adapted from North KM & Ryan MM, 2015)

Winter JM, Ottenheijm CAC (2017)
Definition: rare acquired, late-onset muscle disorder, with subacute progression, characterized by proximal muscle weakness and atrophy, and nemaline rods in myofibers.

Mean age at onset: 52 years (range 25 - 78)

Gender: 35 ♂/33 ♀
19.7% HIV related
- Early age at onset
- Disease progression similar to other nemaline myopathies
- No facial or respiratory muscle involvement
- Frequent myonecrosis and inflammatory infiltrates

35.5% MGUS related
- Worse prognosis, with rapid progression in 50% of cases (as in the present case)


