Co-presentation of Adult-Onset Systemic Lupus Erythematosus and Nemaline Myopathy: A Case Report

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Rheumatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>RHE-16-1546.R1</td>
</tr>
<tr>
<td>Manuscript Type</td>
<td>Letter to the Editor (Case Report)</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Hindocha, Akshay; Northwick Park Hospital, Emergency Medicine Klimiuk, Peter; Pennine MSK Partnership Ltd, Pennine MSK Partnership Ltd Roberts, Mark; Neurology, Salford Royal Pal, Piyali; Salford Royal NHS Foundation Trust, Department of Neuropathology Evangelista, Teresinha; MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, John Walton Muscular Dystrophy Research Centre Lochmuller, Hanns; MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, John Walton Muscular Dystrophy Research Centre Chinoy, Hector; Salford Royal NHS Foundation Trust, The University of Manchester Rheumatic Diseases Centre</td>
</tr>
<tr>
<td>Keywords&lt;br&gt;Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:</td>
<td>Myositis and muscle disease &lt; RHEUMATIC DISEASES, Raynaud's syndrome &lt; RHEUMATIC DISEASES, Systematic lupus erythematosus and autoimmunity &lt; RHEUMATIC DISEASES, Muscle &lt; TISSUES, Genetics &lt; BASIC &amp; CLINICAL SCIENCES</td>
</tr>
</tbody>
</table>
Co-presentation of Adult-Onset Systemic Lupus Erythematosus and Nemalin Myopathy: A Case Report

Akshay Hindocha (MBChB, BSc), Peter Klimiuk (FRCP), Mark Roberts (MD FRCP), Piyali Pal (MBBS, MD Path), Teresinha Evangelista (MD), Hanns Lochmüller (MD), Hector Chinoy (PhD FRCP)

1Northwick Park Hospital, Northwest London Healthcare Trust UK; 2Pennine MSK Partnership Ltd, Oldham, UK, 3Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; 4Department of Neuropathology, Salford Royal, Manchester UK, 5John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle, UK, 6National Institute of Health Research Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust, The University of Manchester, Manchester, UK

Address for reprints and correspondence:
Dr Hector Chinoy
Centre for Musculoskeletal Research,
School of Biological Sciences
Manchester Academic Health Science Centre,
The University of Manchester
Tel: +44-(0)161-275-5993 Fax: +44-(0)161-206-1823
Email: hector.chinoy@manchester.ac.uk

Word count: 800

Keywords: Nemaline Myopathy, Systemic Lupus Erythematosus, neuromuscular disease.

Abbreviations: CNM: Congenital Nemaline Myopathy. CK: Creatinine Kinase, MRI: Magnetic resonance imaging, SLE: Systemic Lupus Erythematosus
Sir, Nemaline Myopathy is seldom encountered in a rheumatology setting. We present a 28-year-old Caucasian woman, gravida 1 para 1, who attended 6 weeks post-partum with a history of proximal weakness (especially evident in the arms), breathlessness on mild exertion, arthralgia, and symptoms suggestive of Raynaud’s phenomenon. Whilst not present clinically, she also complained of photosensitive rashes, and possessed clear photographic evidence to support this.

Since infancy, the patient was weaker than her peers. She required invasive support for nutrition during her first year of life, and as a child, she was particularly prone to falls. Due to fears that she could not handle natural labour, she underwent a caesarean section. There was no family history of consanguinity or muscle weakness.

On examination, there was a generalised loss of muscle bulk, especially in the upper limbs. She had myopathic facies, scapular winging, spinal scoliosis and pectus excavatum. Her strength on Kendall Manual Muscle Testing was 9/10 symmetrically for shoulder abduction, hip flexion, hip extension and knee extension. Reflexes were generally reduced, and Beighton score was 6/9. There was no clinical evidence of myotonia or fasciculations. Painless oral ulceration and patchy non-scarring alopecia were also noted.

Blood tests revealed: creatine kinase (CK) 18iu/l (29-168), creatinine 45µmol/l (53-97), ESR 12mm/hr, white cell count 4.3x10⁹/L (4-11), lymphocytes 0.8x10⁹/L (1-4), TSH 0.94miu/l (<10), abnormal titration of ANA by multiplex immunoassay, dsDNA titre 87iu/ml (0-13.9), C3 930mg/L (630-1600), C4 222mg/L (140-390), and negative extractable nuclear antibodies. A repeated white cell count was 2.6 x10⁹/L with lymphocytes of 0.8 x10⁹/L. Urinalysis was normal, and chest X-ray and pulmonary function tests were unremarkable.

Needle electromyography confirmed evidence of mild myopathic change in the proximal limb muscles, while magnetic resonance imaging (MRI) of both thighs revealed no oedema, fasciitis, atrophy or fatty replacement. A quadriceps muscle biopsy revealed a predominance of type 1 fibres, with many displaying rod-shaped eosinophilic accumulations on a modified
Gomori trichrome preparation (see figure 1). There was no lymphocytic inflammation, MHC class I upregulation, or other suggestive features of inflammatory myopathy. Analysis with electron microscopy revealed rod-like electron dense structures along the subsarcomere in parallel alignments.

Genetic analysis confirmed congenital nemaline myopathy (CNM), identifying two heterozygous recessive mutations in the Nebulin gene: NEB c.7550dupT (p.Met2517fs), which is pathognomonic of the disease, and NEB c.4337G>T (p.Gly1446Val). Nebulin is an important skeletal muscle protein that regulates the length and contractility of the thin filament. The former mutation results in premature termination of this protein, whilst the latter has been reported in genetic analysis of multiple families who suffer with nemaline myopathy. Both contribute to altering the cross-bridge cycling kinetics and calcium sensitivity of the thin filaments, resulting in the typical pattern of muscle weakness [1].

Based on our patient’s additional symptoms and serology, we also diagnosed Systemic Lupus Erythematosus (SLE) [2]. Hydroxychloroquine was commenced, though there was no discernible improvement in weakness, despite a modest improvement in arthralgia and mouth ulcers.

Nemaline myopathy is defined by presence of rod shaped nemaline bodies in muscle fibres, and may be classified into congenital (severe, intermediate and typical); juvenile onset; adult onset; or other forms. CNM has a reported incidence of 2 per 100,000 live births [3], and is predominantly caused by dominant and recessive mutations in muscle proteins including α-tropomyosin-3, β-tropomyosin, Nebulin, Actin α1, troponin-T type 1 and coflin-2 [1]. The resulting symmetrical muscle weakness principally affects neck flexor, facial, and bulbar muscles, though respiratory muscles may also be involved. The disease is familial, and usually manifests with gross motor developmental delay in childhood. This contrasts with sporadic late onset nemaline myopathy, which has an autoimmune aetiology and usually manifests after the third decade of life.
Serum muscle enzymes in nemaline myopathy tend to be in the normal range, though CK may be elevated. Electromyography usually shows myopathic changes, while MRI may show areas of hyperintensity [4]. Histopathology with the Gomori trichrome technique typically shows red stained, rod shaped, predominantly cytoplasmic nemaline bodies [3].

CNM presenting in adulthood is rare, and can mimic other more common rheumatological diseases. Polymyositis, which presents with a similar pattern of muscle weakness, can exhibit nemaline bodies in muscle biopsies [5]. Nemaline bodies may also be seen in HIV, Sjögren’s syndrome, monoclonal gammopathy and primary hypothyroidism [5, 6]. As in the described case, immune dysfunction may also worsen symptoms, unmasking hitherto undiagnosed CNM [6].

Treatment for nemaline myopathy is supportive, with breathing assistance, mobility aids and nasogastric feeding as required. Research into L-tyrosine and gene therapy may provide the potential to alter the disease course in the future [3]. To our knowledge, this is the first description of a patient co-presenting with CNM and SLE, and in such patients with a relevant childhood history, myalgia and weakness, further neuromuscular investigations may be appropriate, even in the face of a normal CK and imaging.

**Key Message**

Considering muscle investigations may be appropriate in patients with connective tissue disease with unusual weakness.

**Ethical Approval**

The subject’s written consent was obtained according to the declaration at Helsinki, and conforms with the standards currently applied in the United Kingdom.

**Declaration of Interest**

All authors formally declare that they have no conflicts of interest.
Acknowledgements

No Acknowledgements

Funding

No funding was received for this letter.

Disclosure Statement

All authors formally declare no financial interest, direct or indirect, that might affect the conduct of this work
References


Figure 1:

Figure 1 Gomori Trichome preparation of quadriceps muscle biopsy: *The red staining rod-like inclusions are characteristic of Nemaline Myopathy.*
Co-presentation of Adult-Onset Systemic Lupus Erythematosus and Nemaline Myopathy: A Case Report

Akshay Hindocha (MBChB, BSc), Peter Klimiuk (FRCP), Mark Roberts (MD FRCP), Priyali Pal (MBBS, MD Path), Teresinha Evangelista (MD), Hanns Lochmüller (MD), Hector Chinoy (PhD FRCP)

1Northwick Park Hospital, Northwest London Healthcare Trust UK; 2Pennine MSK Partnership Ltd, Oldham, UK, 3Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; 4Department of Neuropathology, Salford Royal, Manchester UK, 5John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle, UK, 6National Institute of Health Research Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust, The University of Manchester

Address for reprints and correspondence:
Dr Hector Chinoy
Centre for Musculoskeletal Research,
School of Biological Sciences
Manchester Academic Health Science Centre,
The University of Manchester
Tel: +44-(0)161-275-5993
Fax: +44-(0)161-206-1823
Email: hector.chinoy@manchester.ac.uk
Keywords:
Nemaline Myopathy, Systemic Lupus Erythematosus, neuromuscular disease.

Abbreviations: CNM: Congenital Nemaline Myopathy, CK: Creatinine Kinase, MRI: Magnetic resonance imaging, SLE: Systemic Lupus Erythematosus

Sir, Nemaline Myopathy is seldom encountered in a rheumatology setting. We present a 28-year-old Caucasian woman, gravida 1 para 1, who attended 6 weeks post-partum with a history of proximal weakness, especially evident in the arms. She also complained of breathlessness on mild exertion, as well as arthralgia, and symptoms suggestive of Raynaud’s phenomenon, oral ulceration, patchy alopecia, Whilst not present clinically, she also complained of photosensitive rashes, and possessed clear photographic evidence to support this, and symptoms suggestive of Raynaud’s phenomenon.

Since infancy, the patient was weaker than her peers. She had trouble feeding and required invasive support to ensure adequate nutrition during her first year of life, and, as a child, she struggled to ride a bicycle, and was particularly prone to falls. Due to fears that she could not handle natural labour, she underwent a caesarean section. There was no family history of consanguinity or muscle weakness.

On examination, there was a generalised loss of muscle bulk, especially in the upper limbs. She had myopathic facies, scapular winging, spinal scoliosis and pectus excavatum. Her strength on Kendall Manual Muscle Testing was 9/10 symmetrically for shoulder abduction, hip flexion, hip extension and knee extension. Reflexes were generally reduced, and Beighton score was 6/9. There was no clinical evidence of myotonia or fasciculations.

Painless oral ulceration and patchy non-scarring alopecia were also noted.

Blood tests revealed: creatine kinase (CK) 18iu/l (29-168), creatinine 45µmol/l (53-97), ESR 12mm/hr, white cell count 4.3x10⁹/L (4-11), lymphocytes 0.8x10⁹/L (1-4), TSH 0.94miu/l
(<10), abnormal titration of ANA by multiplex immunoassay, positive ANA, dsDNA titre 87iu/ml (0-13.9), C3 930mg/L (630-1600), C4 222mg/L (140-390), and negative extractable nuclear antibodies. A repeated white cell count was 2.6 x10⁹/L (4-11) with lymphocytes of 0.8 x10⁹/L (1-4). Urinalysis was normal, and chest X-ray and pulmonary function tests were unremarkable.

Needle electromyography confirmed evidence of mild myopathic change in the proximal limb muscles, while magnetic resonance imaging (MRI) of both thighs revealed no oedema, fascitis, atrophy or fatty replacement. A quadriceps muscle biopsy revealed a predominance of type 1 fibres, with many displaying rod-shaped eosinophilic accumulations on a modified Gomori trichrome preparation (See figure 1). There was no lymphocytic inflammation, MHC class I upregulation, or other suggestive features of inflammatory myopathy. Analysis with electron microscopy revealed rod-like electron dense structures along the subsarcomere in parallel alignments.

Genetic analysis confirmed congenital nemaline myopathy (CNM), identifying two heterozygous recessive mutations in the Nebulin gene: NEB c.7550dupT (p.Met2517fs), which is pathognomonic of the disease, and NEB c.4337G>T (p.Gly1446Val). Nebulin is an important protein in skeletal muscle that regulates the length and contractility of the thin filament. The former mutation results in premature termination of the Nebulin protein, whilst the latter mutation has been reported in genetic analysis of multiple families who suffer with nemaline myopathy. Both mutations contribute to altering the cross bridge cycling kinetics and calcium sensitivity of the thin filaments, resulting in the typical pattern of muscle weakness (1).

On the basis of our patient’s additional symptoms and serology, we also made an additional diagnosis of Systemic Lupus Erythematosus (SLE) (2).

Hydroxychloroquine was commenced, though there was no discernible improvement in muscle weakness, despite a modest improvement in arthralgia and mouth ulcers.
Nemaline myopathy is defined by presence of rod shaped nemaline bodies in muscle fibres, and may be classified into severe congenital; intermediate congenital; typical congenital (severe, intermediate and typical); juvenile onset; adult onset; or other forms. Congenital nemaline myopathies have CNM has a reported incidence of 2 per 100,000 live births (3), and are predominantly caused by dominant and recessive mutations in muscle proteins including α6-tropomyosin, β6-tropomyosin, Nebulin, Actin α-1, troponin-T type 1 and cofilin-2 (1). The resulting symmetrical muscle weakness principally affects neck flexor, facial, and bulbar muscles, though respiratory muscles may also be involved. The disease is familial, and usually manifests with gross motor developmental delay in childhood. This contrasts with sporadic late onset nemaline myopathy, which has an autoimmune aetiology and usually manifests after the third decade of life.

Serum muscle enzymes in nemaline myopathy tend to be in the normal range, though CK may be elevated. Electromyography usually shows myopathic changes, while MRI may show areas of hyperintensity (4). Histopathology with the Gomori trichrome technique typically shows red stained, rod shaped, predominantly cytoplasmic nemaline bodies (3).

Congenital nemaline myopathy CNM presenting in adulthood is rare, and can mimic other more common rheumatological diseases. Polymyositis, which presents with a similar pattern of muscle weakness, can exhibit nemaline bodies in muscle biopsies (5). Nemaline bodies may also be seen in HIV, Sjögren’s syndrome, monoclonal gammopathy and primary hypothyroidism (5, 6). As in the described case, immune dysfunction may also worsen or exacerbate the symptoms, unmasking hitherto undiagnosed congenital nemaline myopathy CNM (6).

Treatment for nemaline myopathy is supportive, with breathing assistance, mobility aids and nasogastric feeding as required. Research into L-tyrosine and gene therapy may provide the potential to alter the disease course in the future (3). To our knowledge, this is the first description of a patient co-presenting with congenital nemaline myopathy CNM and
SLE, and in such patients with a relevant childhood history, myalgia and weakness, further neuromuscular investigations may be appropriate, even in the face of a normal CK and imaging.

**Key Message**

Considering muscle investigations may be appropriate in patients with connective tissue disease with unusual weakness.

**Declaration of Interest**

All authors formally declare that they have no conflicts of interest.

**Ethical Approval**

The subject’s written consent was obtained according to the declaration at Helsinki, and conforms with the standards currently applied in the United Kingdom.

**Declaration of Interest**

All authors formally declare that they have no conflicts of interest.

**Acknowledgements**

No Acknowledgements

**Funding**

No funding was received for this letter.

**Disclosure Statement**

All authors formally declare no financial interest, direct or indirect, that might affect the conduct of this work.
References

Figure 1: Gomori Trichome preparation of quadriceps muscle biopsy: The red staining rod-like inclusions represent clusters of aggregated eosinophils, and are characteristic of Nemaline Myopathy.