

Sporadic Late Onset Nemaline Myopathy vs. Atypical  
Polymyositis

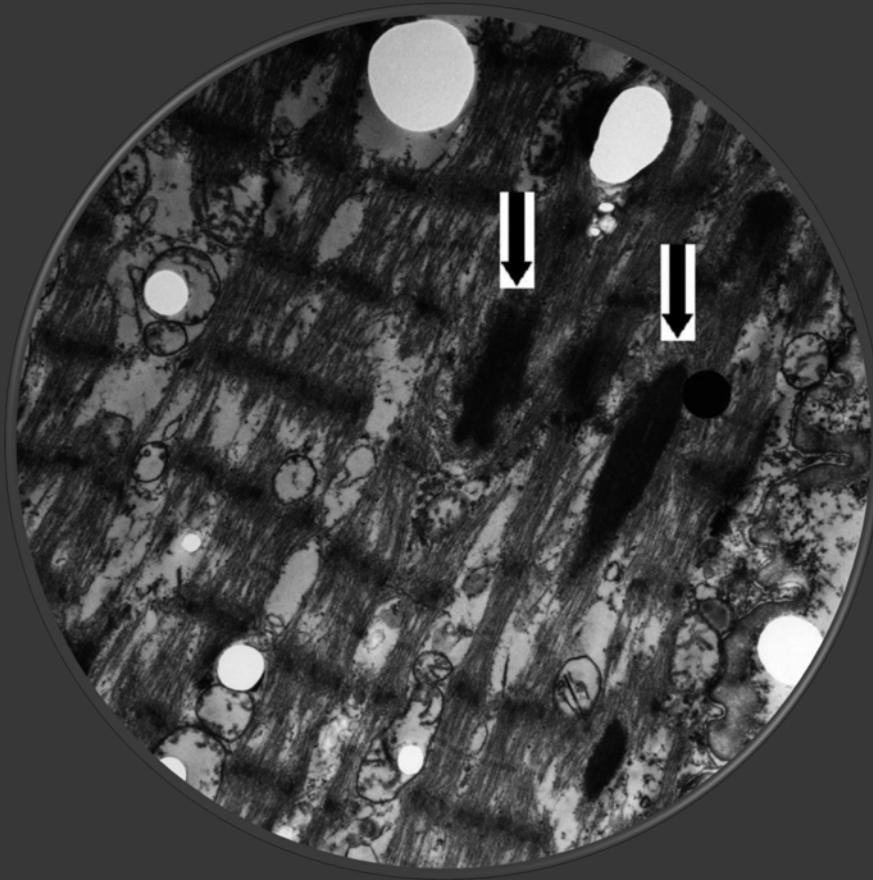
# DIAGNOSTIC THREADS

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# Introduction

From Greek word meaning Thread

**NEMA**



## Structure of Nemaline Bodies/Rods

Extensions of Z-disks

Comprised primarily of Z-disk protein  $\alpha$ -actin

Contain myotilin and sarcomeric  $\alpha$ -actin

# Nemaline myopathy

- One of the most common inherited congenital myopathies
- Genetic disease of skeletal muscle with weakness and rod-like bodies (nemaline rods) within myofibers
- Present at birth or early infancy with hypotonia and often respiratory insufficiency
- Death usually within first year of life

Sporadic Late Onset  
Nemaline Myopathy

## SLONM

- First described in 1966 by A.G. Engel in 2 patients
- Rare, acquired myopathy of unknown pathogenesis
  - Autoimmune dysregulation has been suspected
  - Associated with HIV with young adult onset (age 23-49)
  - HIV-negative onset middle to late adult (age 31-78)
- Characterized by progressive muscle weakness and atrophy
- Non- HIV SLONM has high association with monoclonal gammopathy
- As of 2014, only 51 reported cases of Non-HIV SLONM
  - 21 of these with monoclonal gammopathy

# Case Presentation

- 70 year old white female presents with proximal lower extremity muscle weakness. Slowly progressing over 10 years, faster last 4 years, now worsening over past year. Increased falls over past 4-5 years due to weakness.
- Initial referral to rheumatology was in 2008 for evaluation of weakness.

# Case Presentation

- Additional symptoms on initial presentation included Raynaud's, muscle and joint pain for 20 plus years, fatigue.
- PMH included lumbar spinal stenosis, Grade 1 spondylolisthesis L5-S1, OA, FMS, Morbid obesity.



# Case Presentation

- ⦿ Physical exam findings
  - 4/5 b/l thigh strength, UE and distal strength intact
  - No rash, no visible joint swelling
  - BMI 50.38
- ⦿ Labs
  - + ANA, weakly + RF, negative myositis panel, Aldolase nl, CK in mid 200 range
- ⦿ MRI of b/l thigh muscles showed no inflammation
- ⦿ Unfortunately, patient lost to follow up

# Case Presentation

- ⑥ 6 years later, patient returns to rheumatology clinic with worsening hip weakness and falls. Has been following with neurosurgery who feels spinal stenosis is stable and not the cause of weakness.
- ⑥ Further questioning reveals patient having some shoulder pain and possible upper extremity weakness, elbow contracture.

# Case Presentation

- Records reveal patient has consistently elevated CK's over past 5 years ranging from mid 200's to mid 600's.
- SPEP one year prior showed polyclonal hypergammaglobulinemia.
- Recent EMG performed locally was read as negative

# Current work-up

- AVISE CTD panel
  - Elevated ANA 1:1280 speckled pattern, all other nl
- CK, Aldolase, TSH, Hepatitis panel, HIV, myositis panel
  - CK 295, all other nl or negative
- CT chest, abdomen and pelvis negative for occult malignancy
- When patient returns for follow up, reports worsening hip/thigh weakness, using walker to ambulate, rotator cuff pain, questionable weakness, difficulty swallowing dry foods
- Dyspnea on exertion but extremely obese

# Current work-up

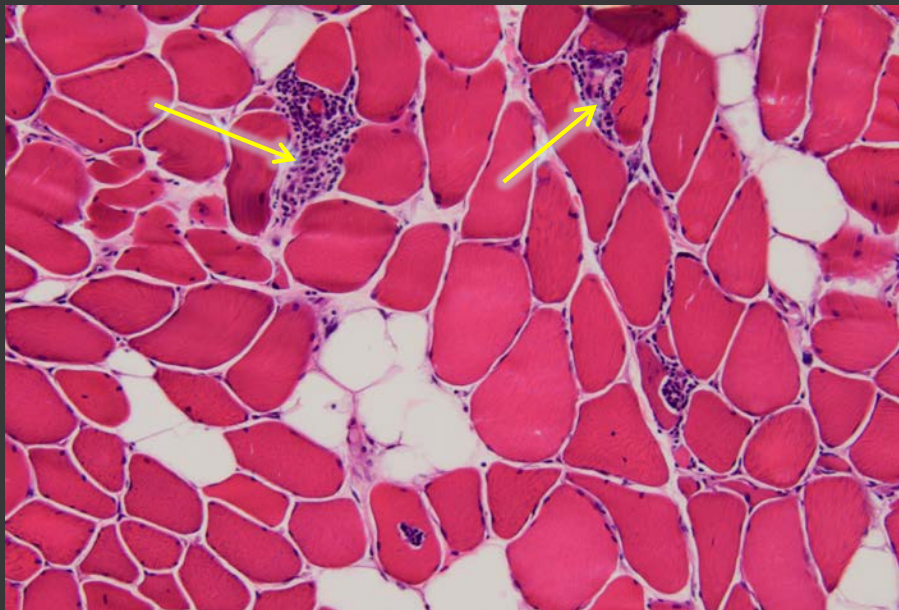
- Muscle biopsy of quadriceps, sent to muscle pathologist at academic institution for review.

# Differential Diagnosis

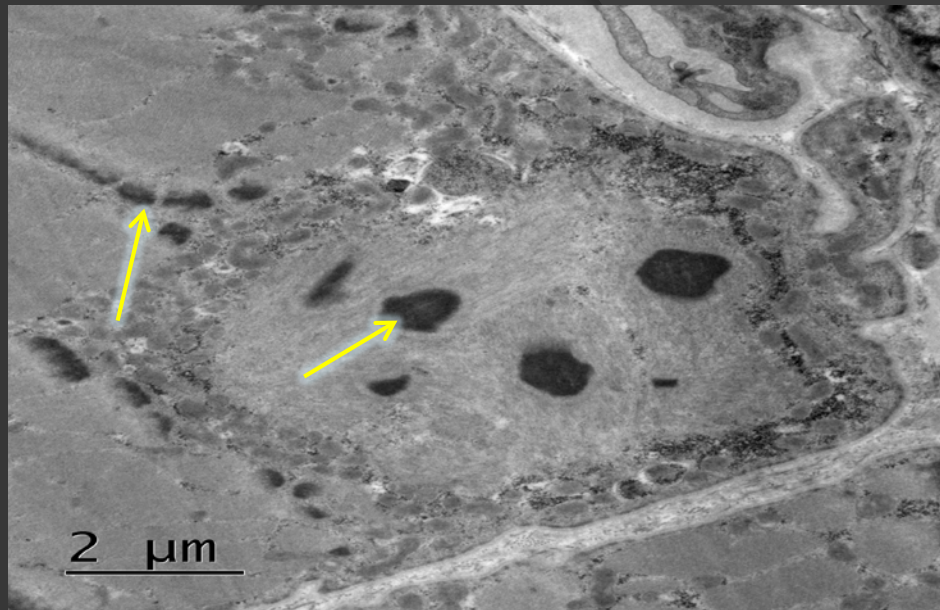
- Polymyositis
- Inclusion body myositis
- Malignancy associated myositis,  
however, CT's all negative

# Muscle pathology report

- ◎ 11/30/2015
  - Myopathy with inflammation and nemaline rods
- ◎ Comment
  - Myopathic changes and multifocal inflammatory cell infiltrates consistent with inflammatory myopathy
  - No rimmed vacuoles for classification of IBM seen, no perifascicular atrophy
  - Consider polymyositis or systemic CTD associated myositis



A. H and E staining



B. Electron microscopy

- A. Arrows showing inflammatory infiltrates
- B. Arrows showing nemaline rods
- C. Arrows showing increased granular sarcolemmal staining consistent with nemaline rods



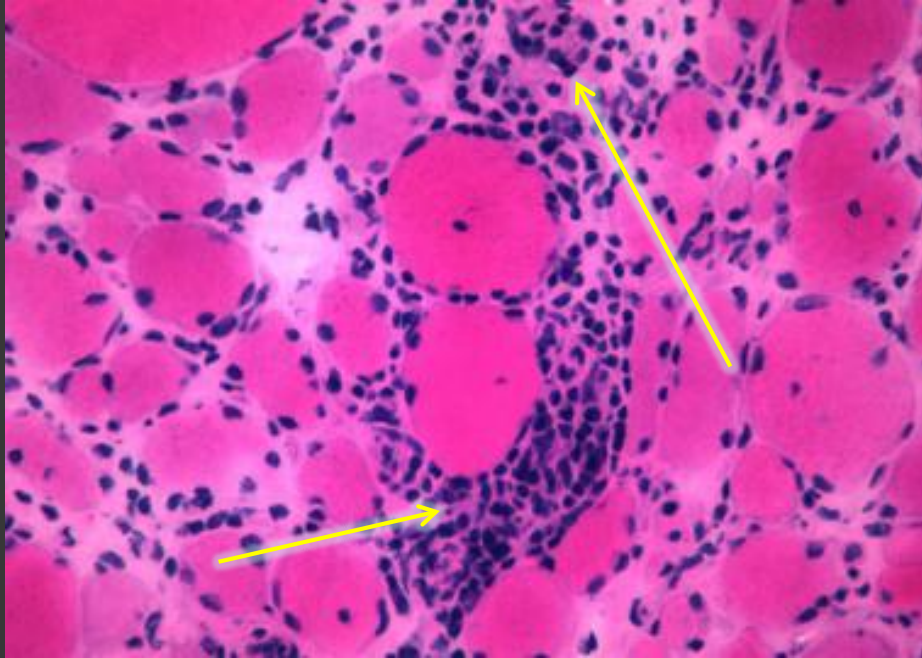
C. Modified Gomori trichrome staining



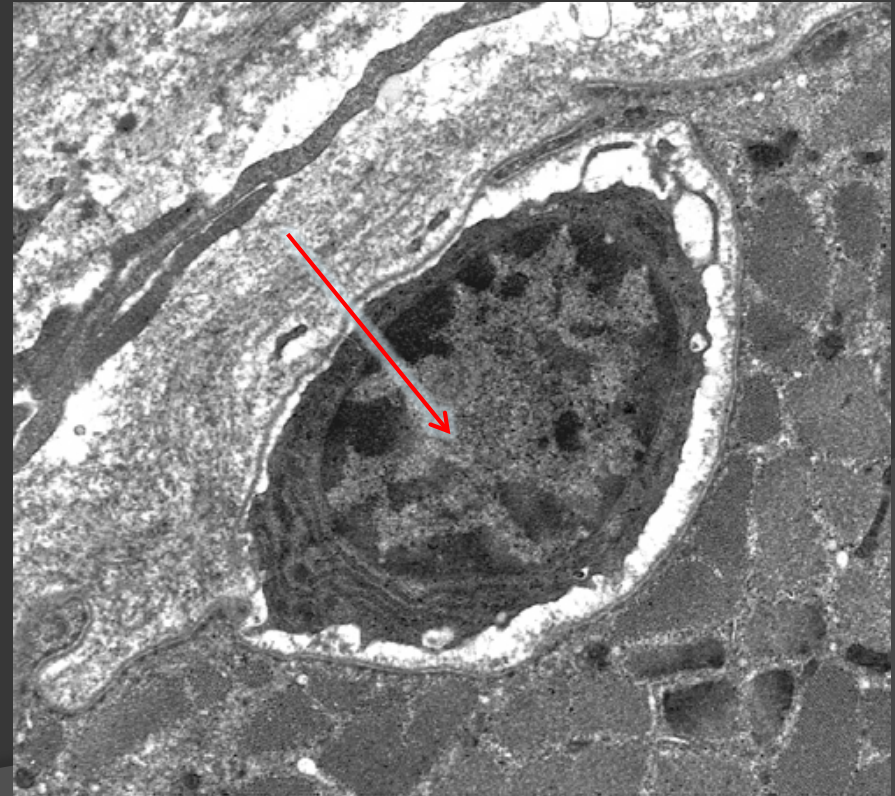
# Additional staining and studies

- ⦿ Trichrome staining
  - Nemaline rod-type inclusions
- ⦿ Ultrastructural studies
  - Confirm presence of nemaline rods
- ⦿ Most cases of SLONM do NOT show inflammatory infiltrates

## Muscle biopsy of patient with Polymyositis



Yellow arrows = inflammatory exudate  
In H and E staining of muscle biopsy  
Consistent with polymyositis



Red arrow = lymphocyte in myofiber  
Electron microscopy in polymyositis

# Threads of confusion

- Patient's clinical presentation, pathology and labs continue to present a combination of SLONM and polymyositis.
- Given patient's progressive weakness, patient sent to Mayo clinic for additional opinion and treatment recommendations.
- Mayo Clinic has most documented case reports and neurologist and pathologist familiar with SLONM.

# Further evaluation

- ⊙ EMG
  - Abnormal myopathic changes with fibrillation potentials
- ⊙ PFT's normal
- ⊙ Video swallow study
  - Mild oropharyngeal dysphagia
- ⊙ Labs
  - CK 409
  - Elevated kappa and lambda free light chains with normal ratio
  - SPEP/immunofixation showed no monoclonal gammopathy
  - Genetic studies ordered
  - All other labs including HMGCR, LFT's, ENA, ESR normal

# Further evaluation

- ⦿ Quadricep muscle biopsy reviewed
  - Agreed with previous findings
- ⦿ New biopsy of weak pectoralis muscle
  - Inflammatory myopathy with moderate autoaggressive inflammatory exudate
  - Inflammatory cells at perivascular sites in endomysium and perimysium
  - Multiple small nemaline rods, although fewer than previous biopsy
  - No congophilic staining indicating amyloidosis

# Impression/Plan

- Myopathy, chronic, inflammatory
  - Autoaggressive inflammatory exudate and nemaline rods on muscle biopsy, genetic tests pending
- \* Per neurology, clinical picture does not fully correlate with SLONM. Nemaline rods have occasionally been seen in inflammatory myopathy and may be secondary phenomenon.

# Impression/Plan

- Consider rare possibility of overlapping myopathies, one inherited and one acquired.
- Because of degree of clinical weakness and amount of inflammation on biopsy, treatment with immunotherapy indicated.
- With presence of nemaline rods, IVIG also justified.

# Treatment recommendations

- Solu-medrol 1gram IV weekly x 1 month, then 500 mg IV weekly x 1 month, then 250 mg IV weekly x 1 month
- Methotrexate starting 15 mg once weekly titrate up to 20 mg once weekly and maintain at this dose
- IVIG 0.4 grams/kg daily for 5 consecutive days each monthly x 3 months



# Discussion

- ◎ In the largest published study to date based on observations from Mayo clinic in 14 patients, SLONM typically presents as follows
  - After age 40
  - Sub-acutely evolving muscle weakness\*
  - Usually limb-girdle distribution but may have distal involvement
  - Dysphagia is common
  - CK is usually normal or below normal\*
  - EMG shows myopathic features with fibrillation potentials\*
  - Highly associated with monoclonal gammopathy\*\*

\*These are considered major clues to clinical diagnosis

\*\*When present, also points to diagnosis

# Discussion

- ⦿ The diagnosis of SLONM is confirmed by biopsy of clinically affected muscle but can be overlooked as they are small in length.
  - Trichromatic staining is required
- ⦿ Degree of rods present can also vary in individual muscle and fibers from same patient

# Discussion

- A HIV-associated SLONM presents earlier and has a slightly different pathological appearance
- Because of the viral presence and the high association with monoclonal gammopathy in non-HIV SLONM, a theory of autoimmune dysregulation in the presence SLONM exists, although the pathophysiology is still unclear

# Discussion

- ⦿ There are rare case reports of nemaline rods present in muscle biopsies of other autoimmune conditions.
  - Individual case reports include SLE, Sjögren's syndrome, dermatomyositis
  - Two cases of polymyositis include one juvenile onset and one adult onset

# Discussion

- Autoimmune dysregulation is further supported in the clinical improvement of SLONM in the presence of monoclonal gammopathy when treated with IVIG

# Polymyositis vs. SLONM

- ⦿ Although there has been some reported mild inflammatory exudate in SLONM, the degree is small
- ⦿ Inflammatory exudate is one of the hallmarks of polymyositis and is part of the diagnostic criteria by Bohan and Peter.

# Polymyositis vs. SLO NM

- Other differentiations include a higher expected CK in PM, usually 10x normal or greater
- Insidious onset and slower progression
- Better response to steroids

# Polymyositis vs. SLO NM

- Our patient presents a diagnostic dilemma in that neither her clinical course nor her muscle pathology present a clear differentiation of the two
- She has CK's only mildly elevated, with weakness progressing over 10 years.
- Her muscle biopsy demonstrates Both nemaline rods and a high degree of inflammatory exudate
- She has myopathic changes and fasciculations on EMG
- Finally, She has had a questionable hypergammopathy in the past



# Polymyositis vs. SLONM

- ⦿ The question still remains with this case, is it a true presentation of SLONM or a rare overlap of polymyositis with SLONM features.
- ⦿ Given her degree of weakness and further progression as well as her findings on biopsy and EMG, the decision to treat her as both an inflammatory and nemaline myopathy is recommended.

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# Acknowledgements

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Thank you

Questions?

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