The Pathology of Systemic Therapy-Related Neuromuscular Disease

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AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS
Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

• Recognize common histopathologic patterns of systemic therapy-related neuromuscular disease
• Recall common neuromuscular diseases included in the differential diagnosis of toxic myopathies
• Plan an appropriate diagnostic approach for evaluation of toxic myopathies
• Summarize known and proposed mechanisms underlying systemic therapy-related neuromuscular disease
Patterns of systemic therapy-related myopathies

Vacuolar myopathy
Necrotizing myopathy with inflammation
Necrotizing myopathy without inflammation
Fiber size variation
Referral case: 55 year old man presenting with symmetric proximal lower extremity weakness. No medication list or examination findings provided.

Vastus lateralis muscle biopsy performed.
modified Gomori trichrome

❖ rimmed versus non-rimmed
❖ with sarcolemmal features versus without sarcolemmal features
AChE
dystrophin

MHC Class I was negative

Image courtesy of Steve Moore
Differential diagnosis – vacuoles with sarcolemmal features

• Inclusion body myositis
• Autophagic vacuolar myopathies
  – Danon disease
  – XMEA
  – Pompe disease (*join us 9 a.m. Friday in Platform 2!*)
• Other inherited myopathies with vacuoles
  – Myofibrillar myopathy
  – Hereditary inclusion body myopathies (e.g. *GNE*, *VCP*)
  – Oculopharyngeal muscular dystrophy
• Drug-induced myopathies
  – Chloroquine/hydroxychloroquine
  – Colchicine

Continue workup? Or long comment?
Myeloid bodies

Curvilinear bodies

Images courtesy of Steve Moore
Chloroquines – neuromuscular toxicity

• Low incidence estimated with a prevalence of 9.2% and annual incidence of 1.2% (Casado et al. Ann Rheum Dis. 2006)

• Onset of weakness months to years after starting therapy
  – No relation to dose

• Progressive, symmetrical proximal weakness +/- mild peripheral neuropathy and cardiac myotoxicity

• CK: normal or mildly - moderately elevated

• EMG/NCS: myopathic changes with fibrillation potentials and myotonic discharges +/- sensorimotor polyneuropathy

• Effects are slowly reversible following discontinuation of Rx
Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients

E Casado, J Gratacos, C Tolosa, J M Martinez, I Ojanguren, A Ariza, J Real, A Sanjuan, M Larrosa

119 patients under antimalarial treatment for rheumatic diseases

- Muscle enzyme rise (22/119 [18.5%])
- Normal muscle enzymes (96/119)

Follow up study 15 patients

- Electromyography + muscle biopsy (15 patients)
  - EMG
  - Muscle biopsy

- Myopathic pattern (8/15 patients [53%])
- Normal (7/15 patients [47%])

Lost from the study 7 patients

- Light microscopy
  - Normal or nonspecific (12/15 patients)
  - Antimalarial myopathy (15/15 patients)

- Electron microscopy
  - Vascular myopathy (3/15 patients)

=myeloid and/or curvilinear bodies
Degradation, recycling, and exocytosis

Inhibition of lysosomal enzymes

Myeloid bodies
Curvilinear bodies
Colchicine – neuromuscular toxicity

• Acute or long-term use
• Subacute proximal muscle weakness and peripheral neuropathy
• CK: Elevated 10-50X normal
• EMG/NCS: myopathic changes and axonal sensorimotor polyneuropathy
  +/- myotonic discharges
• Muscle weakness improves after discontinuation of Rx, but mild axonal neuropathy resolves more slowly
spheromembranous bodies
Microtubule

Inhibition of tubulin polymerization

Colchicine

Lysosome

Inhibition of exocytosis
Chloroquine/hydroxychloroquine or colchicine

- Vacuoles
  - acid phosphatase
  - +/- red rimmed
  - acetylcholinesterase
  - DGC proteins

- Immunostaining
  - complement C5b-9 deposition

- Ultrastructure
  - myeloid bodies (autophagic vacuoles)
  - curvilinear bodies (chloroquines only)
  - spheromembranous bodies (colchicine only? Or just autophagic pathology?)
Patterns of systemic therapy-related myopathies

- Vacuolar myopathy
- Necrotizing myopathy with inflammation
- Necrotizing myopathy without inflammation
- Fiber size variation
Referral case: 67 year old man presenting with symmetric proximal upper and lower extremity weakness. Currently taking aspirin and lisinopril. History of remote statin use; stopped 3 years prior to presentation. CK ~5400 and EMG/NCS showed a diffuse, active myopathy.

Biceps muscle biopsy performed.
MHC Class I

complement C5b-9

e-MHC
Differential diagnosis - necrotizing myopathy with inflammation

- Inflammatory myopathy
  - Inclusion body myositis
  - Dermatomyositis spectrum (perifascicular atrophy)
  - Anti-synthetase syndrome (perifascicular necrosis)
- Immune-mediated necrotizing myopathy - IMNM (a.k.a. necrotizing autoimmune myopathy – NAM)
  - Anti-HMGCR myopathy
  - Anti-SRP myopathy
- Muscular dystrophy with inflammation
- Drug-induced/toxic myopathies
  - Statins (+/- anti-HMGCR antibodies)
  - Immune checkpoint inhibitors
Clinical update while working up muscle biopsy

- Myositis panel testing
  - Negative for Anti-Jo-1, Mi-2, PL-7, PL-12, Sj, OJ, SRP, Ku, Anti-PM/Scl, U2 SN RNP

- Anti-HMGCR autoantibody testing
  - Strong positive at >200

Anti-HMGCR Ab EIA Interpretation:

- Negative..............<20
- Weak Positive........20-39
- Moderate Positive...40-59
- Strong Positive......>=60

STATIN-ASSOCIATED ANTI-HMGCR MYOPATHY
Statins – muscle toxicity and autoimmunity

- Occurs in ~ 2-3/100,000 patients treated with statins
  - ~15 million Americans
- Can occur anytime after starting the medication, or even after medication has been discontinued
- Direct myotoxicity self-limited and quickly resolves, if not, autoimmunity develops \( \rightarrow \) anti-HMGCR antibodies
- Symmetric proximal muscle weakness and pain
- CK: >10x normal
- EMG: active myopathic process
- Atorvastatin more strongly associated with myopathy compared to simvastatin or rosuvastatin
  (Basharat et al. J Am Coll Cardiol 2016)
## Anti-HMGCR antibodies without exposure to statins

<table>
<thead>
<tr>
<th>Location of study</th>
<th>Percent of patients with no prior statin exposure</th>
<th>Total number of anti-HMGCR+ patients</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>56%</td>
<td>45</td>
<td>Allenbach et al. Medicine 2014</td>
</tr>
<tr>
<td>China</td>
<td>86%</td>
<td>22</td>
<td>Ge et al. PLoS ONE 2015</td>
</tr>
<tr>
<td>Japan</td>
<td>82%</td>
<td>45</td>
<td>Watanabe et al. J Neurol Neurosurg Psychiatry 2016</td>
</tr>
</tbody>
</table>

Of note: these patients can have increased risk of cancer
Consensus histopathologic features of IMNM

• Universally present features:
  – Necrotic fibers with scattered distribution in different stages of necrosis/myophagocytosis/regeneration
  – Macrophage predominant, paucilymphocytic

• Additional features to consider:
  – MHC Class I sarcolemmal expression can be diffuse or limited to necrotic fibers (not perifascicular)
  – Complement C5b-9 deposition may be seen
  – Endomysial fibrosis is often prominent
  – Enlarged capillaries may be prominent
ALL 25 biopsies showed CD3+ lymphocytes
- MHC Class I expression only patchy
- Complement C5b-9 deposition on sarcolemma → direct pathogenic role of aAbs activating the complement pathway
- Regenerating muscle cells express high levels of HMG-CoA reductase protein (required for normal muscle cell differentiation)
Are anti-HMGCR antibodies pathogenic?

- Anti-HMGCR antibody titer directly correlated with CK level and disease activity
- Arouche-Delaperche et al. anti-HMGCR antibodies (and anti-SRP antibodies) induced myofiber atrophy and impaired muscle regeneration in primary human muscle cell cultures due to a defect in myoblast fusion (Ann Neurol 2017)
Statin-related necrotizing myopathy and IMNM – diagnostic clues

• Myonecrosis:
  – Necrotizing myopathy with various stages of necrosis distributed throughout the biopsy

• Inflammation:
  – Endomysial or perimysial T-cell inflammation often present, but may be sparse (IHC helpful to identify)

• Immunostaining:
  – MHC Class I most often limited to necrotic fibers (NOT perifascicular)
  – Complement C5b-9 deposition common
Patterns of systemic therapy-related myopathies

- Vacuolar myopathy
- Necrotizing myopathy with inflammation
- Necrotizing myopathy without inflammation
- Fiber size variation
Referral case: 15 year old boy admitted with new onset seizures and CNS vasculitis who was treated with high dose corticosteroids. During his prolonged hospital stay he developed sepsis, respiratory failure, and renal failure. After extubation he developed profound muscle weakness.

Sural nerve and quadriceps muscle biopsies performed.
Control muscle
Control muscle

CRITICAL ILLNESS MYOPATHY AND POLYNEUROPATHY
Critical illness myopathy (CIM) and polyneuropathy (CIP)

- a.k.a. myosin heavy chain loss or acute quadriplegic myopathy
- High dose corticosteroids and/or neuromuscular junction blockade agents, mechanical ventilation, and prolonged hospitalization
- Occurs in more than 25% of patients mechanically ventilated in the ICU for at least 7 days
- Significant clinical overlap between CIM and CIP
- CK: variably elevated
- Can resolve in weeks to months
  - CIM better outcome than CIP (severe CIP patients can remain quadriplegic)
- High mortality (up to 50%)
LOSS AND RENEWAL OF THICK MYOFILAMENTS IN GLUCOCORTICOID-TREATED RAT SOLEUS AFTER DENERVATION AND REINNERVATION

ROBERTO MASSA, MD, STIRLING CARPENTER, MD, PAUL HOLLAND, PhD, and GEORGE KARPATI, MD

MUSCLE & NERVE 15:1290–1298 1992

myosin heavy chain
Review of Critical Illness Myopathy and Neuropathy

Starane Shepherd, MD¹, Ayush Batra, MD¹, and David P. Lerner, MD¹
Critical illness myopathy and neuropathy – diagnostic clues

Classification of CIP & CIM according to pathological features

Critical illness polyneuropathy and myopathy:
a systematic review

Chunhui Zhou1,2, Limin Wu1,2, Fengming Ni1, Wei Ji1, Jiang Wu1, Hongliang Zhang1

NEURAL REGENERATION RESEARCH
January 2014, Volume 9, Issue 1
Patterns of systemic therapy-related myopathies

- Vacuolar myopathy
- Necrotizing myopathy with inflammation
- Necrotizing myopathy without inflammation
- Fiber size variation
Referral case: 72 year old woman with a history of inflammatory polyarthritis presenting with slowly progressive bilateral, symmetric proximal muscle weakness. Her medications include prednisone, atorvastatin, and lisinopril.

Quadriceps muscle biopsy performed.
Differential diagnosis - type II fiber atrophy

- Disuse
- Hypothyroidism
- Myasthenia gravis
- Chronic alcoholism
- Drug-induced/toxic myopathies
  – Corticosteroids
Corticosteroids – muscle toxicity

• Incidence from 2.4 – 21% of patients taking steroids long-term
• Highest risk is chronic exposure to high-dose oral steroids
• Slowly progressive proximal muscle weakness
• Fluorinated (e.g. dexamethasone, triamcinolone, etc) > non-fluorinated (e.g. prednisolone, hydrocortisone, etc)
• CK: normal
• EMG/NCS: normal or show subtle myopathic changes
• Reduction in dose, alternate-day dosing, or switching to a non-fluorinated steroid can alleviate weakness
Anti-anabolic

- Inhibition of amino acid transport into muscle
- Inhibit action of insulin and IGF-1
- Inhibit myogenesis by downregulating myogenin

Catabolic

- Activation of ubiquitin-proteosome system
- Activation of lysosomal system (cathepsins)
- Activation of calcium-dependent system (calpains)
Corticosteroid-induced myopathy – diagnostic clues

- Type II fiber atrophy
- Rule out other underlying causes
Take-home points

• **Chloroquines and colchicine**
  – Very few **defining** diagnostic features when comparing systemic-therapy related VM and other causes
  – If chloroquine-related, EM can help

• **Statins**
  – Anti-HMGCR antibodies (IMNM) can be present even without exposure to statins (even in pediatric patients)
    – Necrosis with endomysial/perimysial lymphocytic inflammation, patchy MHC Class I and complement C5b-9 deposition

• **Critical care myopathy/polyneuropathy**
  – Patients in ICU exposed to steroids +/- NMJ blockade with mechanical ventilation
  – EM can help - thick filament loss most diagnostic finding
  – High mortality

• **Corticosteroids**
  – Selective type II fiber atrophy due to decreased protein synthesis with concomitant increased proteolysis

• **FOR ALL**
  – Full recovery **possible** with removal of offending agent (variable responses)
  – Consider systemic therapy-related disease in workups and mention this in your report comment!
<table>
<thead>
<tr>
<th>Histopathologic Pattern</th>
<th>Drug</th>
<th>Mechanism</th>
<th>Diagnostic clues</th>
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</table>
| vacuolar myopathy               | chloroquine/hydroxychloroquine | lysosomal activity inhibition           | 1. myeloid bodies (EM)  
2. curvilinear bodies (EM)                                                       |
|                                 | colchicine                    | inhibition of microtubule polymerization| 1. spheromembranous bodies (a.k.a. myeloid bodies) (EM)                            |
| necrosis with inflammation      | statins                       | myotoxicity/immune-mediated            | 1. necrosis in various stages  
2. lymphocytic inflammation (possibly sparse)  
3. patchy MHC Class I  
4. complement C5b-9 deposition |
| necrosis without inflammation  | critical care myopathy/polyneuropathy | microvascular, metabolic, and/or electrical alterations? | 1. loss of thick filaments (EM)  
2. variable necrosis  
3. type II fiber atrophy |
| type II fiber atrophy           | corticosteroids                | increased proteolysis, decreased protein synthesis | 1. type II fiber atrophy |
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