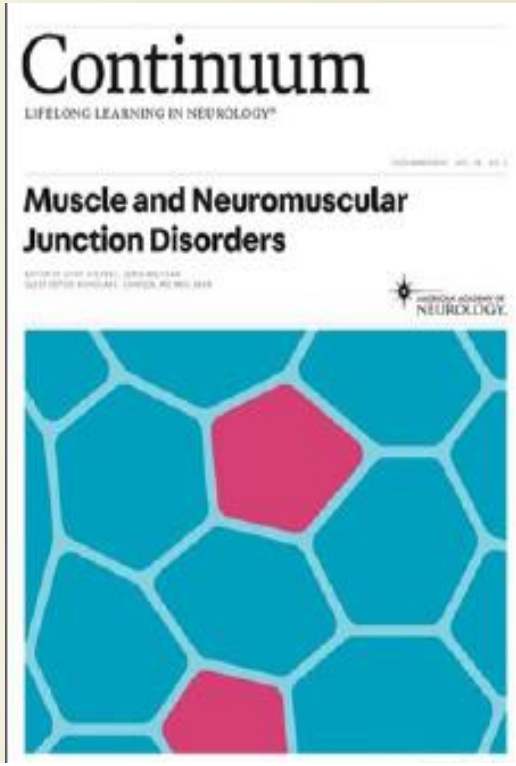
# Toxic myopathies

**Dr. Mohammad Yazdchi**

Professor of neurology

Electrodiagnostic fellowship

TBZMED




**Issue Overview**

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*Continuum: Lifelong Learning in Neurology®* is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

# Disclosure

- None

# Pathogenic Mechanisms of Toxic Myopathies

- **Necrotizing Myopathy**
- **Inflammatory Myopathy**
- **Amphiphilic**
- **Antimicrotubular**

## Necrotizing Myopathy

- Statins
- Other cholesterol-lowering agents
- Cyclosporine
- Propofol
- Labetalol
- Alcohol

## Inflammatory Myopathy

- Immune checkpoint inhibitors
- D-Penicillamine
- Cimetidine
- Phenytoin
- Interferon alfa
- Tumor necrosis factor inhibitors
- Imatinib
- Hydroxyurea

## Amphiphilic

- Amiodarone
- Chloroquine
- Hydroxychloroquine

## Antimicrotubular

- Colchicine
- Vincristine

**Mitochondrial Myopathy**

- Zidovudine
- Telbivudine and other antiretrovirals[a]

**Hypokalemic Myopathy**

- Diuretics
- Corticosteroids
- Laxatives
- Amphotericin
- Lithium
- Alcohol
- Toluene abuse
- Ingestion of excessive licorice

**Unknown**

- Emetine
- Febuxostat
- Finasteride
- Isotretinoin
- Levetiracetam
- Omeprazole

# Features That Raise Suspicion for a Toxic Myopathy

**Clinical Features**

- **Concomitant polyneuropathy (ie, a neuromyopathy)**
  - Amiodarone
  - Chloroquine/hydroxychloroquine
  - Colchicine
  - Telbivudine
- **Concomitant myasthenia gravis**
  - Immune checkpoint inhibitors
- **Acute, painful myopathy**
  - Statins
  - Other lipid-lowering agents
  - Cyclosporine
  - Labetalol
  - Alcohol (with binge drinking)

**EMG Features**

- **Myotonic discharges**
  - Chloroquine/hydroxychloroquine
  - Colchicine
  - Cyclosporine
  - Fibrates
  - Statins

- **Normal EMG in a patient with clinically suspected myopathy**
  - Corticosteroids
  - Chronic alcoholic myopathy

## Muscle Biopsy Features

- **Vacuoles**
  - Amiodarone
  - Chloroquine/hydroxychloroquine
  - Colchicine
- **Mitochondrial abnormalities (eg, many ragged red and cytochrome oxidase–negative fibers)**
  - Nucleoside-analogue reverse transcriptase inhibitors (eg, zidovudine)
- **Type 2 fiber atrophy**
  - Corticosteroids
  - Chronic alcoholic myopathy
- **Sarcolemmal major histocompatibility complex 1 and membrane attack complex expression on non-necrotic fibers**
  - Anti–3-hydroxy-3-methylglutaryl coenzyme A reductase myopathy associated with statins
  - Immune checkpoint inhibitors
  - D-Penicillamine

# NECROTIZING MYOPATHIES

- **cholesterol-lowering agents** the most common.
- mild symptoms, such as myalgia or cramps,
- asymptomatic creatine kinase (CK) elevation.
- Rarely, patients experience proximal muscle weakness
- in severe cases, myoglobinuria and renal failure.

- An elevated serum CK level
- **EMG :** irritable myopathy with fibrillation potentials, positive
- sharp waves, or complex repetitive discharges.
- Symptoms resolve upon stopping the offending agent,
- except in the rare cases of **statin-associated immune-**
- **Mediated necrotizing myopathy**.

**Necrotizing Myopathy**

- Statins
- Other cholesterol-lowering agents
- Cyclosporine
- Propofol
- Labetalol
- Alcohol

# Statins

- Statins lower cholesterol through inhibition of 3-hydroxy-3-methylglutaryl
- coenzyme A (HMG-CoA) reductase.
- The pathogenic mechanism by which statins cause myopathy :
- **Hypotheses include :**
- destabilization of the muscle membrane due to reduced cholesterol within
- the membrane and
- impaired energy production from reduced coenzyme Q10 production .

# Statin myopathy

- Muscle-associated adverse effects occur with all approved statins.
- Asymptomatic CK elevation occurs in up to 5% of treated patients,
- Myalgia and cramps affect as many as 20%of statin users.
- Symptoms may develop at any time but tend to begin a median of 1 to 6
- months after initiation.
- For as many as 30% to 50% of patients with myalgia while taking
- a statin, it has another possible cause.
- Statin-related myalgia generally affects large proximal muscle groups
- symmetrically,
- cramps affect small muscles in the hands and feet asymmetrically.

# Statin myopathy

- Rarely, severe pain and proximal weakness.
- The American College of Cardiology estimates:
- the incidence of severe myopathy to be 0.08% for lovastatin, simvastatin,
- and pravastatin.
- Concurrent use of medications that affect statin metabolism, including
- those that inhibit the cytochrome P450 3A pathway, increases the risk of
- toxic myopathy

## Drugs Associated With an Increased Risk of Statin Muscle Toxicity

- Amiodarone
- Azole antifungals
- Calcium channel blockers
- Colchicine
- Cyclosporine
- Ezetimibe
- Fibrates (eg, gemfibrozil)
- Niacin
- Protease inhibitors
- Rapamycin
- Sirolimus
- Excessive intake of grapefruit juice

# statin myopathy

- The combination of statins with either gemfibrozil or cyclosporine confers
- Especially high risk:
- the risk of symptomatic rhabdomyolysis among patients
- with statins is approximately 2 to 3 per 100,000 patient-years
- The risk of a toxic myopathy is dose dependent.

# statin myopathy

- **Additional risk factors include :**
- male sex,
- age older than 65 years,
- renal or hepatic failure, and
- hypothyroidism.
- Finally, a genome-wide association study found that 60% of
- patients with statin myopathy have a single nucleotide polymorphism
- located within the SLCO1B1 gene, which encodes a protein that regulates
- hepatic processing of statins.

# Statin myopathy, Management :

- In cases with objective weakness or rhabdomyolysis,
- the statin should be stopped immediately.
- Ck values may normalize in as quickly as 1week and rarely
- remain elevated longer than 2 months.
- Resolution of muscle pain and weakness occurs, on average, 2-3 months
- after cessation of a statin

# Immune-mediated necrotizing myopathy

- Rarely, immune-mediated necrotizing myopathy complicates statin
- therapy.
- This is characterized by proximal muscle weakness with or without myalgia,
- typically clinically indistinguishable from the toxic necrotizing form.
- When the statin is withdrawn, however, the myopathy does not improve;
- Immunomodulatory therapy is required and leads to symptomatic
- improvement.

# Immune-mediated necrotizing myopathy

- CK : CK values are typically 5000 to 10,000 U/L in patients with immune-
- mediated necrotizing myopathy.
- EMG : EMG will demonstrate an irritable myopathy in proximal
- muscles in both forms. Myotonic discharges have been reported with statin
- Induced toxic necrotizing myopathy, but this is not specific.
- Anti - HMG-CoA reductase antibody : most patients with statin-associated
- immune-mediated necrotizing myopathy develop antibodies against HMG-
- CoA reductase that are detectable in serum.

- **Muscle biopsy :** Muscle biopsy can also help distinguish between the
- Toxic necrotizing and immune-mediated forms of statin myopathy.

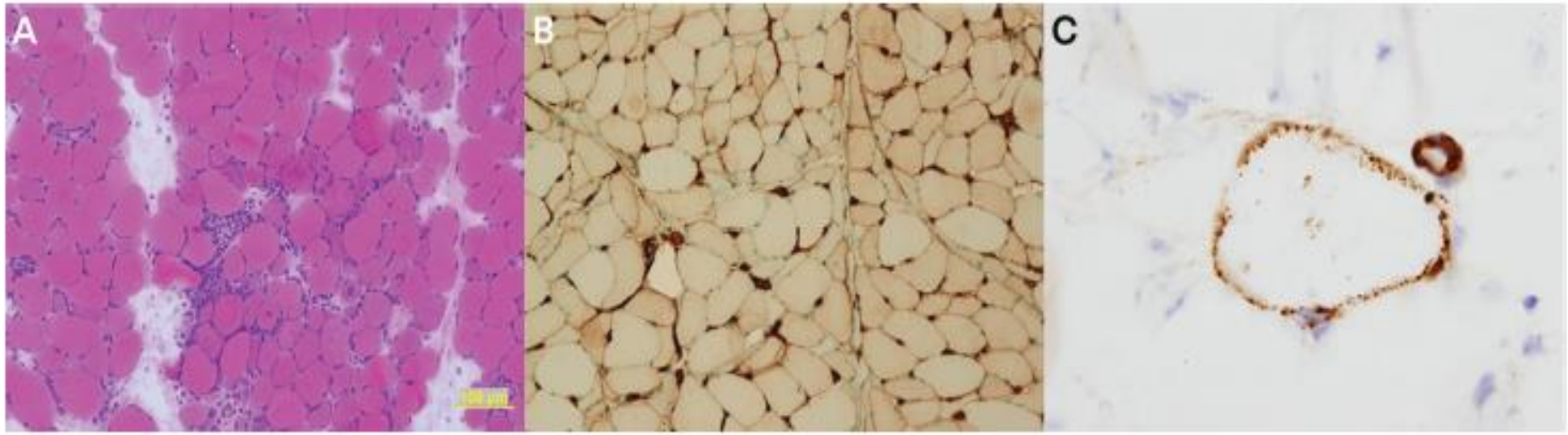



FIGURE 10-1

This muscle biopsy performed in a patient with proximal muscle weakness on a statin revealed necrotic myofibers, regenerating myofibers, and sparse inflammatory cells with myophagocytosis only of necrotic myofibers (*A*). This can be seen in both toxic necrotizing myopathy and statin-associated immune-mediated necrotizing myopathy. However, major histocompatibility complex 1 expression on the sarcolemma of non-necrotic myofibers (*B*) and deposition of complement membrane attack complex on both non-necrotic myofibers and capillaries suggest an immune-mediated pathogenesis (*C*).

- **When patients present with symptomatic hyperCKemia or weakness,**

- stop the statin,
- test for anti–HMG-CoA reductase antibodies, and
- closely follow the patient.
- With toxic necrotizing myopathy,
- the CK level usually begins to improve within a couple of weeks.
- If the anti–HMG-CoA reductase antibody results are negative and the CK
- level does not normalize, the authors perform a muscle biopsy.
- A muscle biopsy can be considered early in severe cases,
- but histology may reveal only widespread myofiber necrosis.

# Treatment of immune-mediated necrotizing myopathy

- In cases in which weakness is leading to disability and immune-mediated
- necrotizing myopathy is suspected
- IV immunoglobulin (IVIg) and/or
- prednisone
- while awaiting results of the anti–HMG-CoA reductase
- antibody testing.

# Other Lipid-Lowering Agents

- A higher reported risk is associated with :
- gemfibrozil compared with fenofibrate,
- high frequency of rhabdomyolysis in patients treated concurrently with a
- statin.
- Up to 5% of patients treated with gemfibrozil and lovastatin developed a
- severe myopathy.
- Niacin ( vitamin B3 ) and ezetimibe, most cases have occurred in
- patients also on a statin.

- Red yeast rice (Monascus purpureus), One of the compounds is monacolin
- K, the same ingredient that is in the prescription cholesterol-lowering drug
- lovastatin (Altoprev)
- alirocumab and evolocumab : inhibit proprotein convertase
- subtilisin/kexin type 9 (PCKS9) .
- PCSK9 is a protein that targets LDL receptors for degradation and its
- inhibition thereby enhances the liver's ability to remove LDL-C, or "bad"
- cholesterol, from the blood.

# INFLAMMATORY MYOPATHIES

- case reports have implicated several other
- medications as triggering
- autoimmune inflammatory myopathies :
- **D-Penicillamine,**
- **Cimetidine**
- **Phenytoin**
- **Interferon alfa**
- **Tumor necrosis factor inhibitors**
- **hydroxyurea**

# INFLAMMATORY MYOPATHIES

- **Immune Checkpoint Inhibitors:**
- Immune checkpoint inhibitors target mechanisms used by cancer to evade
- destruction by the immune system.
- **Ipilimumab**
- **nivolumab**
- **Pembrolizumab**
- **durvalumab and atezolizumab**

# Immune Checkpoint Inhibitors

- MG can also occur as a consequence of immune checkpoint
- inhibitors.
- overlap of myositis and MG appears to be common.
- When overlap is suspected, an elevated CK level can help establish
- myositis,
- decremental response to slow repetitive nerve stimulation and
- acetylcholine receptor antibodies suggest MG.
- Myocarditis can also be seen with or
- without clinically evident skeletal muscle involvement.

# AMPHIPHILIC MYOPATHIES neuromyopathy

- Chloroquine,
- hydroxychloroquine,
- amiodarone
- Amphiphilic molecules containing both hydrophobic and hydrophilic
- components, allowing them to interact with the lipid bilayer of cells and
- organelles. disruption of lysosomes, they form pathologic autophagic
- vacuoles filled with myeloid debris in muscle fiber and nerves; the
- neuropathy can be more severe than the myopathy.

# ANTIMICROTUBULAR MYOPATHIES

Antimicrotubular

- Colchicine
- Vincristine

- Colchicine is used to treat gout.
- Like with amphiphilic medications,
- patients taking colchicine can develop
- neuromyopathy.
- The toxicity results from the
- drug's interaction with tubulin dimers,
- preventing the formation of
- microtubules.
- This likely interferes with the movement
- and positioning of lysosomes, leading to
- the accumulation of vacuoles.

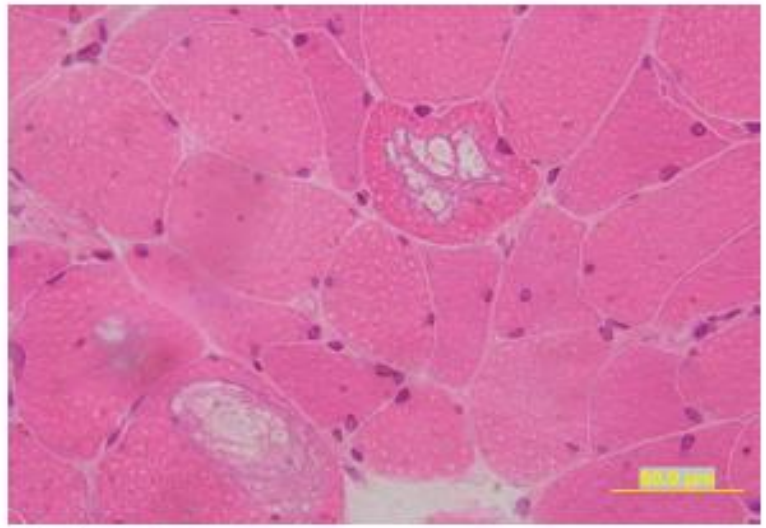
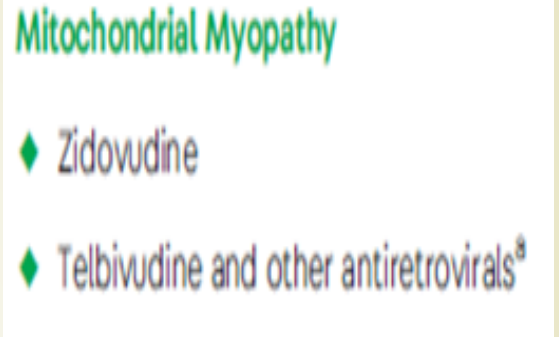


FIGURE 10-4
Muscle biopsy reveals autophagic vacuoles on hematoxylin and eosin (H&E) staining in a patient with myopathy due to colchicine.

# MITOCHONDRIAL MYOPATHY FROM ANTIRETROVIRALS




- **Zidovudine**
- The risk of mitochondrial toxicity of nucleoside analogue reverse
- Transcriptase inhibitors was exemplified with zidovudine treatment for HIV.
- Myopathy affected 17% of patients treated for HIV with
- zidovudine monotherapy for longer than 9months.
- HIV itself can also cause a proximal myopathy, but **myalgia** is a
- distinguishing feature common with zidovudine myopathy.
- Muscle biopsy is key for distinguishing between other HIV-associated
- myopathies.

# Steroid Myopathy

- Proximal muscle weakness can develop in patients with an
- endogenous (ie, Cushing syndrome) or iatrogenic excess of corticosteroids.
- skeletal muscle toxicity may be due to :
- decreased protein synthesis,
- altered carbohydrate metabolism,
- mitochondrial alterations, or
- reduced sarcolemmal excitability.
- Proximal weakness and atrophy affecting the legs more than the arms
- develop insidiously.

# Steroid Myopathy

- CK values are normal in steroid myopathy;
- gradual steroid taper can be
- informative because the symptoms of patients with steroid myopathy
- improve with dose reduction or cessation of therapy.

- If their symptoms instead worsen, an exacerbation of the
- underlying disorder is likely.

- A muscle biopsy is often not
- required but demonstrates
- preferential atrophy of type 2
- fibers, particularly glycolytic 2B
- fibers, with steroid myopathy

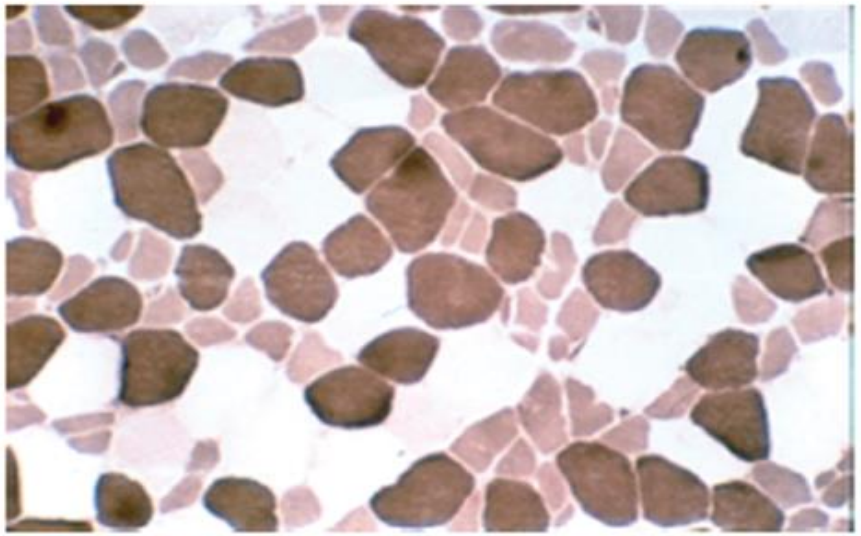


FIGURE 10-5
ATPase stain at pH 4.5 reveals selective atrophy of type 2b muscle fibers (intermediate staining) in a patient with corticosteroid myopathy.

# Critical Illness Myopathy

- Critically ill patients are at risk of developing
- critical illness myopathy (CIM),
- critical illness polyneuropathy (CIP),
- or both.
- CIM is more common than CIP;
- when CIP does occur, it usually coexists with CIM.
- The first sign of weakness : inability to wean the patient from
- mechanical ventilation.
- pathogenesis :
- sarcolemmal inexcitability
- myosin loss .

# Critical Illness Myopathy

- CIM also causes proximally predominant weakness and atrophy but spares
- bulbar muscles.
- CIP causes distally predominant weakness and sensory loss.
- Reflexes can be reduced or absent in either form as weakness progresses.

# MYOPATHY SECONDARY TO DRUGS OF ABUSE

- **Alcoholism :** A chronic proximal myopathy affects up to one-third of
- patients with chronic alcoholism.
- An estimated cumulative minimum of 10 kg of ethanol per
- kilogram of body weight is required to result in myopathy.
- Myopathy likely results from a combination of the
- toxic effects of alcohol
- nutritional deficiency,
- perhaps electrolyte imbalance,

- **Repeated IM heroin injection :** can lead to focal fibrotic myopathy with
- years of use.
- Opiate use is now estimated to be the second most common cause of
- compartment syndrome (after trauma) due to immobility in the setting of
- overdose.
- **cocaine, amphetamines, and phencyclidine :** Rhabdomyolysis