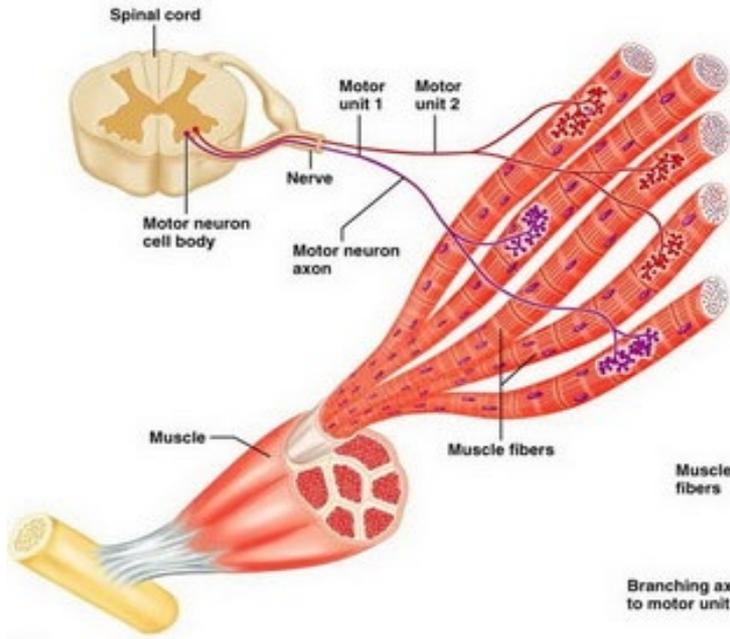


MYOPATHY

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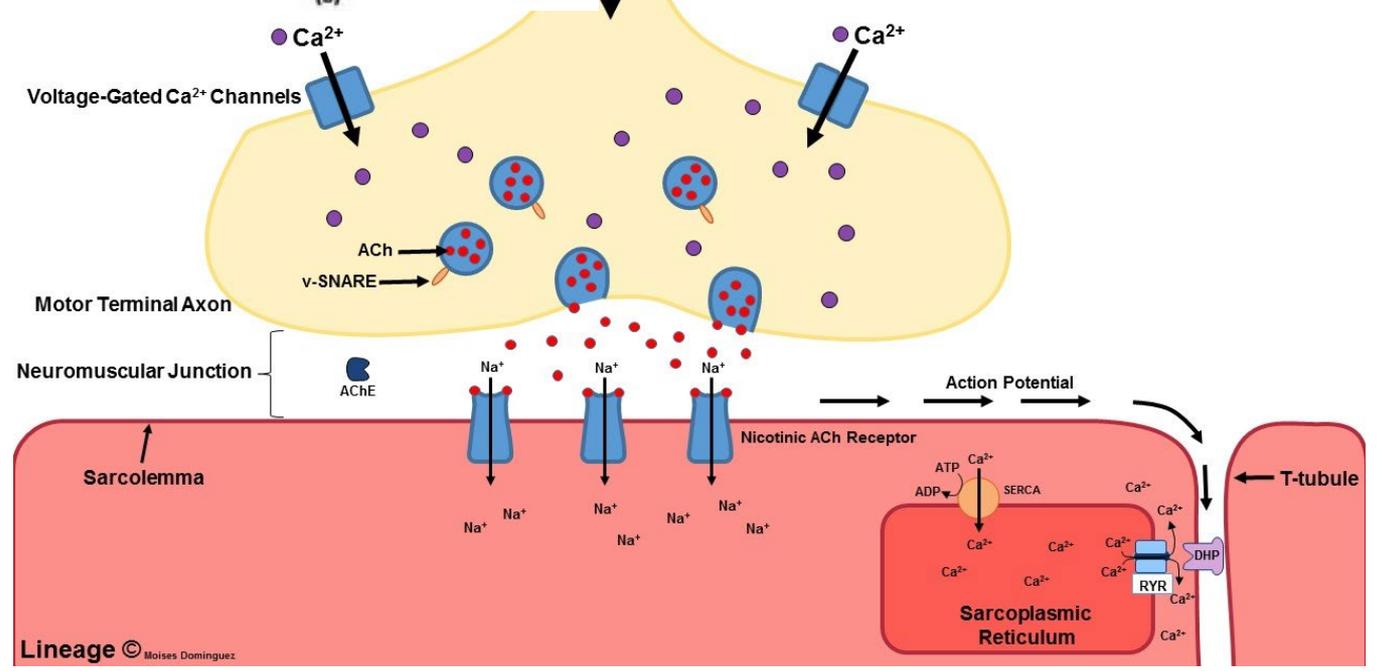


(a)

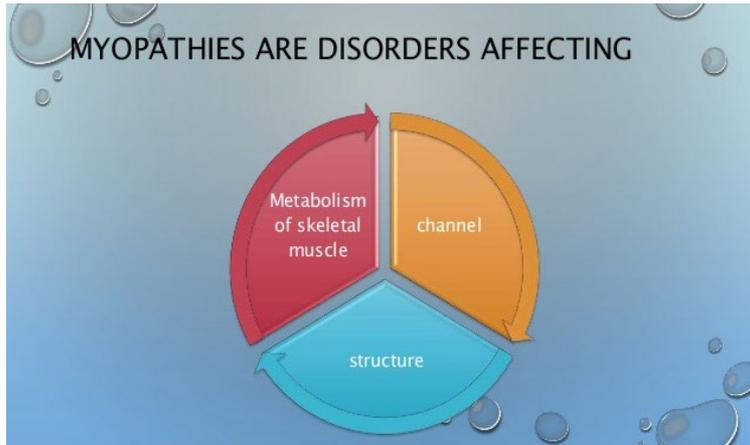
(b)

Nerve impulse

Neuromuscular Junction



- Myopathies are the heterogenous group of disorders involving structural changes or functional impairment, primarily of **skeletal muscle**.



-The **PURPOSE** of this review is to provide a clear picture of the diagnostic approach for various myopathies, based predominantly on the clinical history and examination.

-In approaching the **EVALUATION** of a patient with a suspected myopathy, one of the most important component is a **COMPREHENSIVE MEDICAL HISTORY**.

Myopathy Vs Neuropathy

Features suggestive of MYOPATHY:

- Sensations preserved.
- No fasciculations
- Atrophy of muscles occur LATE
- Preserved tendon reflexes
- Myoglobinuria may be present.
- Muscle pain or tenderness with palpation
- Elevated muscle enzymes, EMG +
- Weakness in the proximal muscle groups – difficulty rising from chair, climbing stairs, hair combing.

Features suggestive of NEUROPATHY:

- Sensory loss /Paraesthesias
- Fasciculations may be present
- Muscle atrophy and reduced reflexes
- Cranial nerve involvement may be present.
- Distal muscle weakness

MYOPATHY

Hereditary disorders

Acquired disorders

(Discussed later)

Congenital myopathies

Early onset of weakness & severe hypotonia. Other organs such as the brain, eyes, and skin may be involved.

Congenital Muscular Dystrophies

- Duchenne/Beckers muscular dystrophy (DMD/BMD)
- Myotonic dystrophy
- Distal myopathies
- Limb girdle muscular dystrophy (LGMD)
- facioscapulohumeral dystrophy (FSHD)

Primary metabolic myopathies

Glycogen storage diseases, lipid storage disease

Mitochondrial myopathies

-Defects in the mitochondrial respiratory chain impairs energy production & involves skeletal muscle, causing exercise intolerance, myoglobinuria, weakness, affects extraocular muscles causing ptosis & ophthalmoplegia.

Myotonia & Channelopathies

In skeletal muscle, disorders are associated with mutations in voltage-gated Na⁺, K⁺, Ca²⁺, and Cl⁻ channels leading to hypoexcitability, causing periodic paralysis and to hyperexcitability, resulting in myotonia or susceptibility to malignant hyperthermia.

Congenital muscular dystrophy vs Congenital myopathy

- Congenital muscular dystrophy (CMD) is characterized by a dystrophic pattern on muscle biopsy, whereas no necrotic or degenerative changes are present in congenital myopathies.
- Congenital muscular dystrophy is associated with **mental retardation and structural brain abnormalities** which are not seen in congenital myopathies.
- Patients with congenital muscular dystrophy and congenital myopathy are at high risk of complications including SEIZURES, restrictive lung disease, orthopedic deformities, cardiomyopathy, and malignant hyperthermia.



Figure 1: Patient with DMD use Gower s maneuver sign

Acquired Myopathies

Inflammatory myopathies

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Necrotizing Autoimmune Myopathy (NAM)
- Juvenile dermatomyositis

-Systemic vasculitis (RA, SLE, Wegener's granulomatosis, Scleroderma, Sjögren's syndrome, sarcoidosis)

-Myositis associated with malignancy.

Idiopathic Inflammatory Myopathies

Infectious myopathies

- Viral (Influenza, coxsackie, CMV, HIV)
- Bacterial (Staph, strep)
- Lyme myositis (spirochete)
- Fungal
- Parasitic (toxoplasmosis, trichinosis)

Endocrine myopathies

- Hypothyroidism
- Cushing syndrome (or exogenous steroid)
- Acromegaly

Electrolyte abnormalities

Severe hypokalemia, hyperkalemia, hypophosphatemia

Drug induced myopathies

- Statins
- Corticosteroids
- Colchicine
- Hydroxychloroquine
- Chloroquine
- Phenytoin
- Amiodarone
- Propofol Infusion
- Vincristine
- Cimetidine
- Zidovudine
- Alcohol
- Interferon alpha

Myopathy with neuropathy

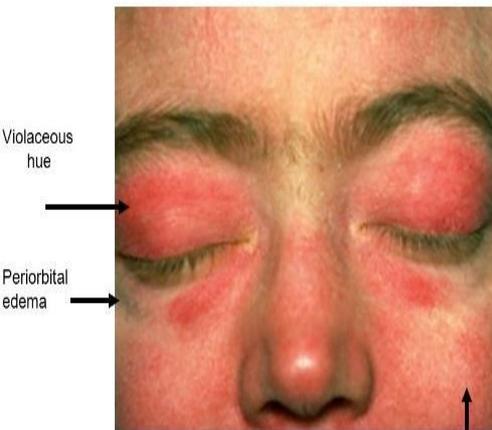
Idiopathic Inflammatory Myopathies (IIM)

- Idiopathic inflammatory myopathies include polymyositis versus dermatomyositis, Inclusion body myositis, necrotizing autoimmune myositis (NAM) and Juvenile dermatomyositis.
- **Myositis-specific antibodies** play a role in further categorization of IIMs (Discussed in detail).
- The idiopathic inflammatory myopathies present with **marked proximal and symmetric muscle weakness**, except for distal and asymmetric weakness in **INCLUSION BODY MYOSITIS**.
- On muscle biopsy, all the idiopathic inflammatory myopathies show **INFLAMMATORY EXUDATES EXCEPT** Necrotizing autoimmune myositis which shows **NECROSIS** of muscle fibres without inflammation.

DERMATOMYOSITIS

- Proximal symmetric muscle weakness (pelvic girdle > shoulder girdle muscles)
- SKIN FINDINGS: HELIOTROPE RASH & GOTTRON PAPULES, Mechanic's hands.
- Interstitial lung disease, Dysphagia, Myocarditis
- Peak Incidence – 40-50 years, predominantly seen in women.
- REGULAR AGE APPROPRIATE CANCER SCREENING must be done to look for internal malignancies of ovary, lung, stomach, colo-rectal cancer as dermatomyositis frequently occurs as PARANEOPLASTIC SYNDROME.
- DM-specific autoantibodies include anti-MDA5, anti-NXP2, anti-SAE, anti-Mi-2, anti-ARS, anti-TIF1-gamma.

Heliotrope Rash



Gottron Papules



Shawl sign in dermatomyositis



DM - Other Physical Findings

- Periarticular and subcutaneous calcifications.
- Raynaud phenomenon in almost 1/3rd of patients.
- Dilated or thrombosed nail-fold capillaries.



Mechanic's hands

Cracking of the finger pad skin, commonly involving the first, second, and third fingers

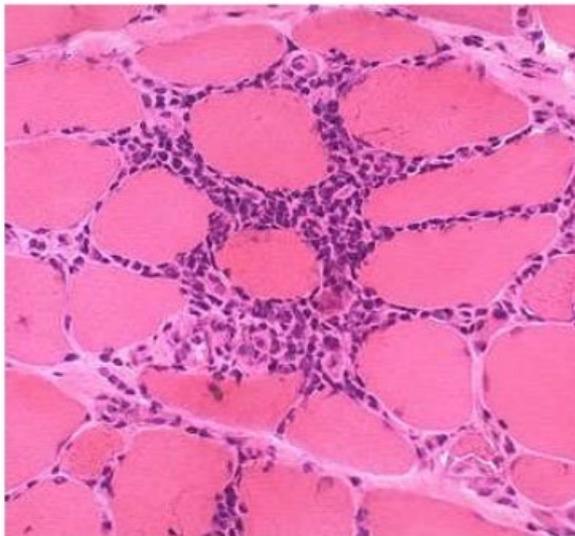


POLYMYOSITIS

→ Polymyositis has the similar symmetric proximal muscle weakness as seen in dermatomyositis (pelvic girdle > shoulder girdle) , **WITHOUT the skin findings.**

→ Polymyositis can also affect cardiac muscles causing inflammatory myopathy (myocarditis) and muscles involved in breathing.

→ There may be extra muscular involvement such as **ARTHRALGIA**, **Raynaud's phenomenon** and interstitial lung disease.



Muscle Biopsy in PM

Endomysial inflammatory infiltrate surrounding and invading non-necrotic muscle fibers with no vacuolization.

Inclusion Body Myositis

- In patients ≥ 50 years of age, IBM is the most common of the inflammatory myopathies.
- Weakness and atrophy of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis.
- ***Most common presentation*** - weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold objects such as golf clubs or perform tasks such as turning keys or tying knots.
- ***Recurrent Falls*** – Early Quadriceps weakness.

-IBM is associated with these antibody in about half of the patients.

Anti-cytosolic 5' -nucleotidase 1A (**anti-CN1A or anti-NT5C1A**).

-- Muscle histopathology shows endomysial inflammatory exudates accompanied by rimmed vacuoles and **inclusions or plaques of abnormal protein deposits**. Hence the name.

MYOSITIS SPECIFIC AUTOANTIBODIES

ROLE in idiopathic Inflammatory Myopathies

- Diagnosis
- Stratification
- Prognosis
- Organ Involvement
- Cancer risk
- Refractory disease

MYOSITIS SPECIFIC AUTOANTIBODIES

1- Polymyositis/Dermatomyositis:

- Anti-synthase antibodies (**Anti-Jo-1**)
- Anti-Mi-2 (specific for dermatomyositis)**

-**Anti-Jo-1**, anti-PL-7, anti-PL-12, anti-EJ, anti-KS, anti-OJ, anti-Ha, and anti-Zo antibodies target aminoacyl-tRNA synthetases and represent **ANTI-SYNTHASE SYNDROME** which is characterized by myositis, INTERSTITIAL LUNG DISEASE, arthritis, Raynaud's phenomenon, and mechanic's hands. .

-**Anti-TIF1- γ** and **Anti-NXP-2** antibodies are closely correlated with cancer-associated dermatomyositis

2- Inclusion body myositis (IBM):

- Anticytosolic 5'-nucleotidase 1A antibody

3- Necrotizing Autoimmune Myositis (NAM):

- Anti-signal recognition particle (Anti-SRP)

3-hydroxy-3-methylglutaryl-coenzyme A reductase (Anti-HMGCR)

-Although the pathogenic role of MSAs remains unknown, recent studies have shown that **myositis autoantigens are expressed at high levels in regenerating muscle fibers**, which may initiate or amplify autoimmune responses in Idiopathic Inflammatory Myopathies(IIM).

-In summary, **myositis specific autoantibodies define the phenotypes that exist within the clinical spectrums of various idiopathic inflammatory syndromes** by being actively involved in skin and muscle damages and subsequent disease management.

-CLINICAL SIGNIFICANCE : **Early detection** of these antibodies is **crucial** as it can aid in the prediction of a patient's clinical course and prognosis.

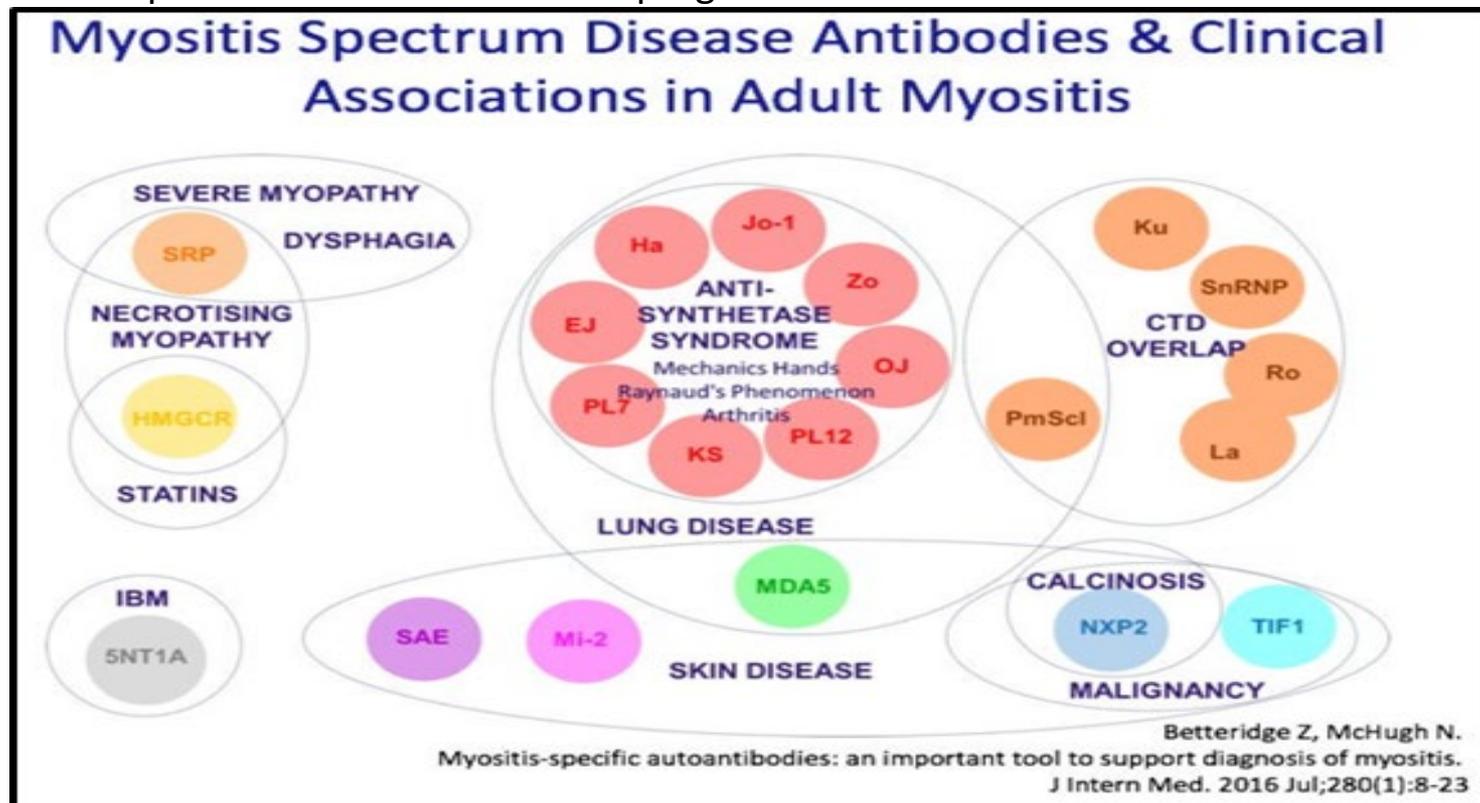


Table 2 Overview of myositis specific antibodies and contribution to clinical decisions.

MSA	Criticality/comment	Relevance/criticality
HMGCoA reductase	The presence of anti-HMGCR antibodies predicts poor response to corticosteroid and immunosuppressant therapy. This anticipation is relevant for the clinician.	Relevant, not critical; however, false negative might lead to omission of biopsy
TIF1y	Strong association with malignancy in elderly patients. Extensive screening for malignancy is necessary prior to treatment of IIM.	Critical, false negative result might lead to delayed diagnosis of cancer
SRP	Associated with severe treatment resistant myopathy, leading to long term immunosuppressive therapy The presence of SRP antibodies predicts poor response to corticosteroid and immunosuppressant therapy. This anticipation is relevant for the clinician.	Relevant, not critical; however, false negative might lead to omission of biopsy
MDA5	Positive result should trigger screening for ILD and if confirmed more aggressive treatment and clinical vigilance	Critical, False negative result may lead to less intensive (respiratory) monitoring with a delay
PM/Scl	In general, associated with a milder disease course	Not critical, low relevance
Ku	Often associated with SLE and/or SSc. Requires monitoring and treatment to coexisting SLE and/or SSc, especially when other antibodies are present (eg, anti-dsDNA). ¹²	Relevant, not critical
SAE	Severe cutaneous disease that classically precede DM with severe dysphagia and systemic symptoms.	Relevant, not critical
NXP2	Juvenile DM, diffused calcinosis. Cancer associated DM triggers consideration for screening for concurrent malignancy prior to treatment initiation.	Critical, similar to TIF1y, however, less pronounced
Mi-2	In general, associated with a milder disease course. If present without other MSA, reassures relatively mild disease phenotype.	Relevant, not critical; false positive can lead to a wrong perception of milder disease (no monitoring for ILD)
Jo-1, EJ, OJ, PL-7, PL-12	Positive result triggers the clinician to screen for ILD and to prospectively follow-up pulmonary function; often requires long-term immunosuppressive treatment <ul style="list-style-type: none">▶ Predicts better therapeutic response to rituximab¹³▶ Influences patient management when pulmonologists identify these antibodies in patients with unexplained ILD▶ Consider immunosuppressant strategies▶ Follow-up for appearance of extra-pulmonary manifestations of the antisynthetase syndrome¹⁴	Relevant, not critical; False negative results might have a negative effect on optimal therapy choice in severe myositis (more arguments for rituximab) and patients with unexplained ILD (as single manifestation) might experience delay in diagnosis.

DM, dermatomyositis; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; MSA, myositis specific antibodies; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

METABOLIC MYOPATHIES

→ Most cases present in childhood or in adulthood with **EXERCISE INTOLERANCE** (often with rhabdomyolysis), recurrent myoglobinuria and weakness.

→ Metabolic myopathies are caused by defects in cellular energy metabolism, including the breakdown of carbohydrates and fatty acids to generate adenosine triphosphate (ATP).

→ Accordingly, the three main categories of metabolic myopathies are glycogen storage diseases, fatty acid oxidation defects, and mitochondrial disorders due to respiratory chain impairment.

→ The **glycogen-storage diseases** present during brief bouts of **high-intensity exercise**, whereas **fatty acid oxidation defects and mitochondrial myopathies present during a long-duration/low-intensity endurance-type activity or during fasting** or another metabolically stressful event (eg, surgery, fever).

→ The clinical examination is often normal between acute events

DRUG INDUCED MYOPATHIES

→ Current and previous medication history should be obtained.

→ In general, they are **SPONTANEOUSLY & RAPIDLY REVERSIBLE** upon discontinuation of the drug as muscle cells have the capacity to regenerate, with the **exception of statin-induced autoimmune necrotizing myopathy**; however, the latter is reversible under immunosuppressants.

Extra:

→ In painful neuromyopathies, a rare eosinophilia-myalgia syndrome is a recently described disorder associated with the use of **L-tryptophan**.

Eosinophilia–myalgia syndrome (EMS) is characterized by subacute onset of **myalgias** and peripheral **eosinophilia**, followed by chronic neuropathy and skin induration.

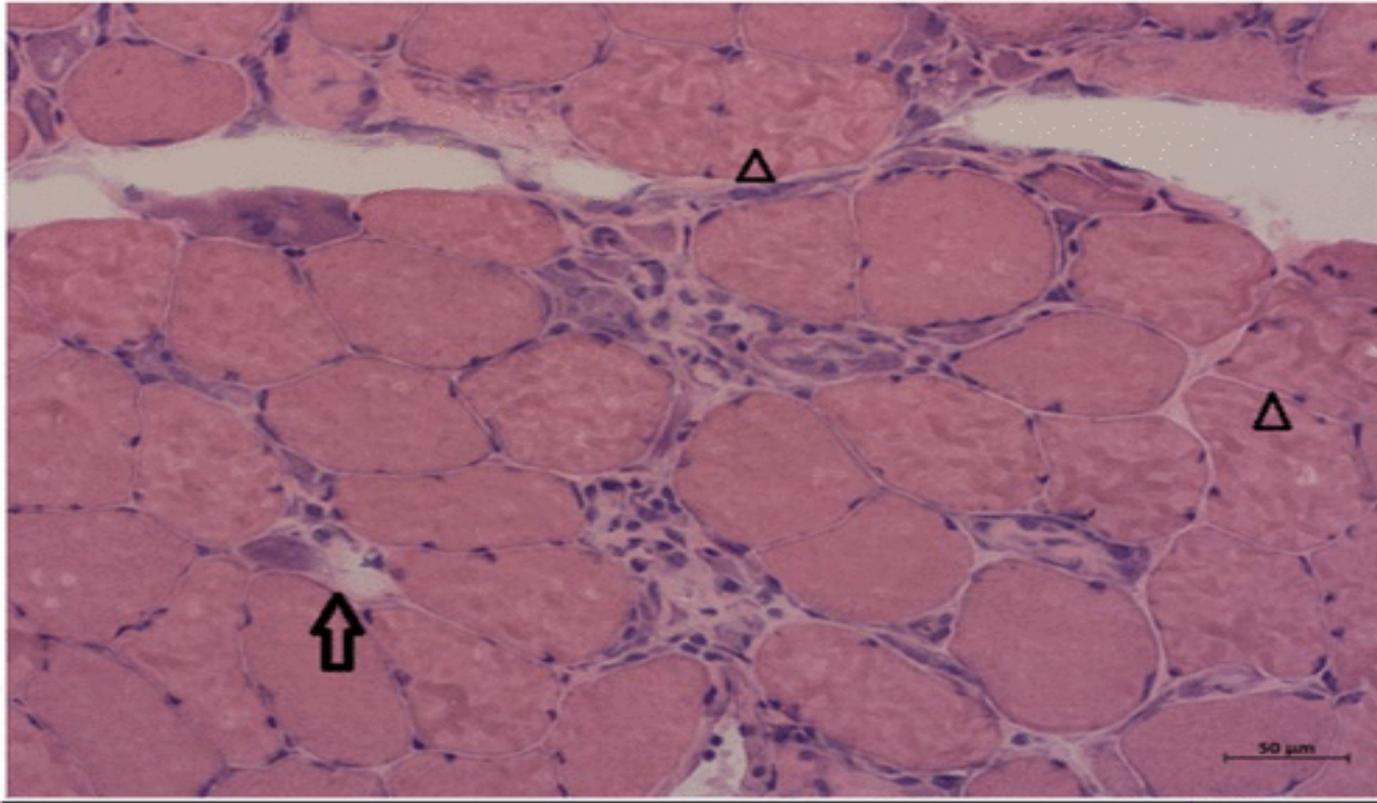
Statin Induced myopathy

- The most severe adverse effect of statins is myotoxicity.
- Clinical trials commonly define **statin toxicity as myalgia or muscle weakness with creatine kinase (CK) levels greater than 10 times the normal upper limit.** Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure and disseminated intravascular coagulation (DIC).
- The prevention of statin-related myopathy involves using the **lowest statin dose required to achieve therapeutic goals** and avoiding polytherapy with drugs known to increase systemic exposure and myopathy risk .
- Drug-drug interactions are one of the major risk factors associated with statin-induced myopathy. **Avoid co-prescription of statins with calcium channel blockers (amlodipine), fibrates (gemfibrozil), colchicine, azole antifungals, Niacin** which further aggravates the risk for rhabdomyolysis and severe myopathy.
- Statin myopathies are more likely to occur in the context of pre-existing neuromuscular disorders, hypothyroidism, vitamin D deficiency, and drug interactions.

Statin induced myopathy vs statin induced necrotizing autoimmune myopathy (NAM)

- In **statin induced myopathy, symptoms improve after discontinuation** of the drug.
- Statin-exposed patients with myopathy who **do not improve after discontinuation** of the drug, the possibility of **statin-associated immune mediated necrotizing myopathy** needs to be considered.
- In such patients, testing for the presence of **antibodies to signal-recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)** is support the diagnosis and distinguish patients with **statin-associated autoimmune necrotizing myopathy** from patients with self-limiting statin-associated myopathy.
- Rest of the patients who do not have these autoantibodies, benefit from **muscle biopsy for diagnosis showing necrotic muscle fibres with no inflammation**.
- Highly elevated CK levels. Often resistant to available off-label medications. Require aggressive immunosuppressive treatment to control the disease.

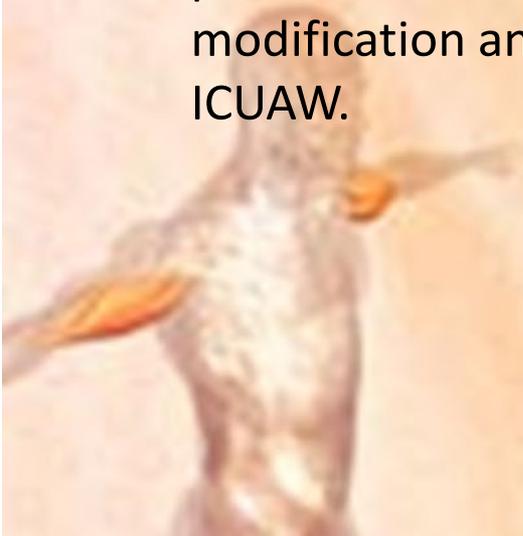
Necrotizing Autoimmune Myopathy triggered by statin



Hematoxylin-eosin–stained sections of quadriceps femoris showing various necrotic (arrow) and regenerating muscle fibers (arrowheads). Significant invasion of macrophages is also seen.

Critical Illness Myopathy

- Patients in the intensive care unit are at risk for developing critical illness myopathy, also known as myosin-loss myopathy, which should be **considered if ICU-acquired weakness (ICUAW) develops**.
- Weakness, critical illness neuropathy and/or myopathy, and muscle atrophy are common in patients who are critically ill, with up to 80% of patients admitted to the ICU developing some form of neuromuscular dysfunction.
- At present, no pharmacological intervention can be recommended to prevent or treat ICU-acquired weakness. Risk factor avoidance or modification and early activity may reduce the risk and severity of ICUAW.



CASE REPORT

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→ A 58-year-old woman presented with a 4-month history of progressive weakness of the shoulders and thighs. She reported inability to walk up stairs or lift heavy objects. She had to pick up her legs to get out of the car. The patient could still open jars and use utensils.

- She denied any fever, chills, weight loss, anorexia, joint pain, dysphagia, Raynaud's phenomenon, skin rash, and heat or cold intolerance.
- The patient's medical history was significant for hyperlipidemia which was initially treated with atorvastatin 40 mg daily for over a year. It was replaced with simvastatin 20 mg daily due to muscle pain.
- She was on simvastatin for 8 months when it was discontinued secondary to recurrence of muscle pain and weakness.
- Her past medical history also included diabetes mellitus type 2, hypertension, and hyperthyroidism.
- Her home medications at presentation were alprazolam, aspirin, glipizide, metformin, hydrochlorothiazide, lisinopril, and levothyroxine.

- On physical examination, she had **symmetric muscle weakness** scoring 2 out of 5 on hips and 4 out of 5 on shoulders.
- She was **unable to sit or stand without support**. The muscle strength of neck, elbows, wrists, hands, knees, and ankles were normal.
- **Deep tendon reflexes were intact with no sensory loss**. There was **no muscle atrophy or fasciculation**. She had no skin rash or active arthritis.
- Laboratory studies showed **significantly elevated creatine kinase (CK) of 7,562 units/L (normal range 26-192 units/L)** with normal thyroid-stimulating hormone of 1.9 mIU/mL and ESR of 19.
- Electromyography was performed on right upper and lower extremities and showed myopathic changes in the deltoid, hip flexors, and extensors.
- The patient subsequently underwent **biopsy of the left quadriceps**. Pathology showed abnormal **variation in myofiber size with pattern of degenerating and regenerating fibers**. There were **no inflammatory infiltrates** which strongly favored **necrotizing autoimmune myopathy**.
- **Tests for autoantibodies were negative**, including antinuclear antibody, rheumatoid factor, anti-Ro/SSA, anti-La/SSB, and anti-Jo-1. The myositis panel was negative for PL-7 Ab, PL-12Ab, EJ Ab, OJ Ab, SRP Ab, Mi-2 Ab, and Ku Ab.
- A computerized CT scan of the chest, abdomen, and pelvis was unremarkable for malignancy.

- The clinical diagnosis of **statin-associated necrotizing myopathy** was made given her history of statin exposure and the lack of evidence of connective tissue disease, active viral infection, or malignancy.
- The patient **was started on prednisone 60 mg daily** which tapered down to 10 mg in 4 months. She was also given **methotrexate up to 25 mg weekly**.
- However, the patient's weakness was refractory to treatment with CK level of **3,553 U/L at 4 months**. Immunosuppressive therapy was escalated to **azathioprine 100 mg daily then mycophenolate mofetil up to 3,000 mg**, also **without significant improvement at 8 months**.
- Finally, the patient received **rituximab 1,000 mg for two doses** which resulted in **dramatic improvement in her muscle strength, functional status, and CK levels**.
- **CK came down to a level of 751 units/L within 2 months after rituximab** and **upper limb strength was back to baseline by 1 month** and she was able to walk up stairs by 3 months' time.
- She maintained her remission with prednisone 10 mg and mycophenolate mofetil 3,000 mg.

-----END OF CASE REPORT-----

