INFLAMMATORY MYOPATHIES

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OBJECTIVES

- Subtypes of Inflammatory Myopathies
- Cases
- Diagnostic advancements
- Current treatment algorithm and novel therapies on horizon

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Inflammatory Myopathies

- Myositis
- Heterogenous group of rare diseases that affects multiple organs and systems, including the muscles, skin, lungs and joints
- CK level, EMG and Muscle Biopsy
- MRI and Antibody testing
- Broad treatment options, but their choice and combination are still largely based on expert opinion

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TYPICAL PATTERN OF IMMUNE MEDIATED INFLAMMATORY MYOPATHIES

- Proximal upper/lower extremities weakness
- Truncal muscle weakness
- Pharyngeal muscle weakness
- Diaphragmatic or accessory muscle weakness

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Creatinine Kinase

Group	Constituents	Upper Limit of Normal (U/L)
High	Black men	1201
Intermediate	Nonblack men	504
	Black women	621
Low	Nonblack women	325

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CASE

- 73 year old woman
- 6 Months ago, started having pain over both arms and legs
- 4 months ago started having trouble with getting up from the chair
- 2 weeks later troubled with reaching out objects above the shoulder level
- Works as a hair dresser
- Referred by a cardiologist

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EXAM

- Cranial nerves: normal
- Deep tendon reflexes: knees: 1/1; ankle: 0/0
- Sensory: vibration: 0 seconds over both great toes

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MOTOR EXAM

	RIGHT	LEFT
DELTOID	4	4
BICEPS	4	4
TRICEPS	4+	4+
FINGER FLEXORS	5	5
FINGER EXTENSORS	5	5

	RIGHT	LEFT
ILIOPSOAS	4	4
HIP ADDUCTORS	4	4
QUADRICEPS	4+	4+
ANKLE DORSIFLEXORS	5	5
ANKLE PLANTARFLEXORS	5	5

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SUMMARY

- 73 year old woman with proximal upper and lower extremity weakness
- No ocular symptoms
- No bulbar symptoms
- No sensory symptoms
- Reduced reflexes

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ELECTRODIAGNOSTICS

- NCS : No large fiber neuropathy
- EMG: Irritative myopathy (florid abnormal discharges and short duration, small amplitude motor unit potentials with early recruitments)

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PAST MEDICAL HISTORY AND MEDICATIONS

DM-2

Very recent diagnosis of autoimmune hepatitis (due to elevation of AST and ALT)

Medications: Atorvastatin which was discontinued about 2 months prior to her weakness

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LABS

- CK : 9037

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MUSCLE BIOPSY

- Myopathy with necrotizing feature
- Myofiber necrosis

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IMNM Immune Mediated Necrotizing Myopathy

- Anti SRP
- Anti HMGCR
- Minimal extramuscular manifestation
- Autoantibody-negative immune-mediated necrotizing myopathy has been associated with a relatively high risk of malignancy
- Differential in patients with a genetically undiagnosed myopathy resembling a limb-girdle muscle dystrophy

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Pathogenesis

- Initiation and maintenance of autoimmunity is not well understood
- Anti- HMCCoA Reductase Myopathy suggest a potential model for those with statin triggered disease

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Histopathology

- Macrophages are predominant inflammatory cell invading muscle tissue
- Some CD4+, CD8+ and plasmacytoid dentric cells may also be be present in perivascular and endomysial region

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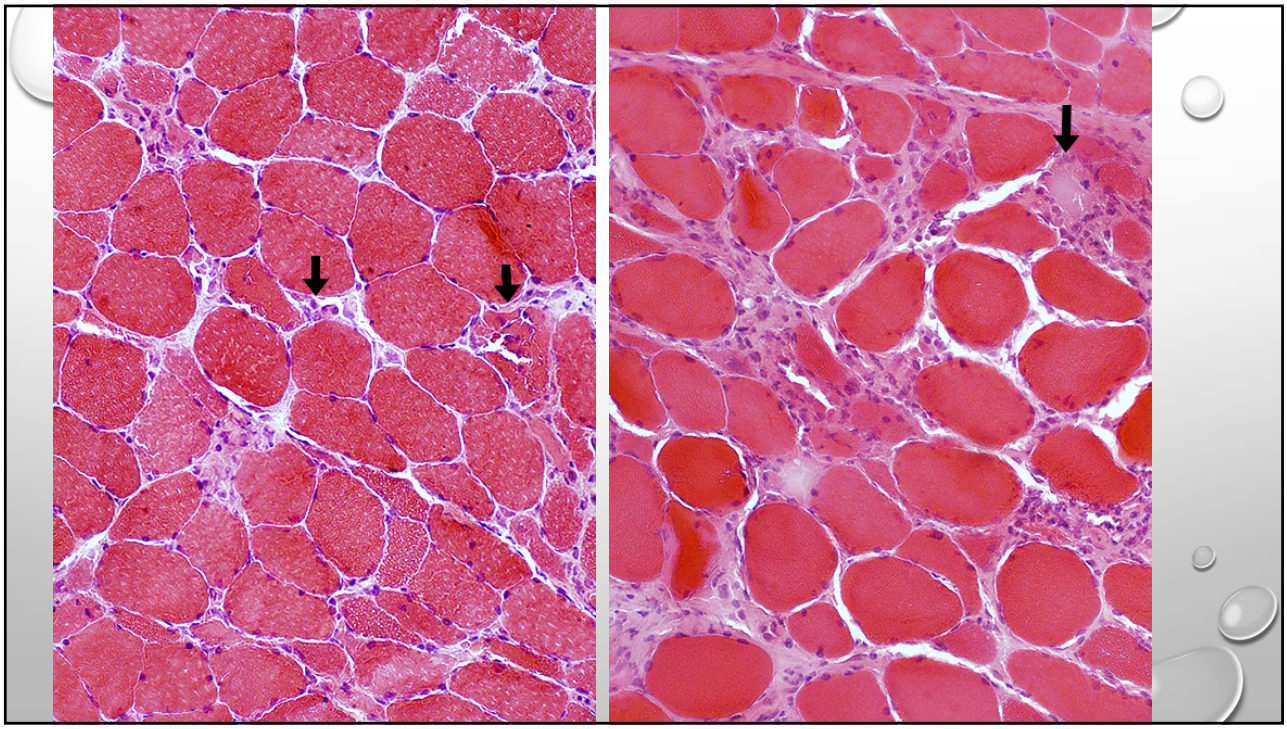

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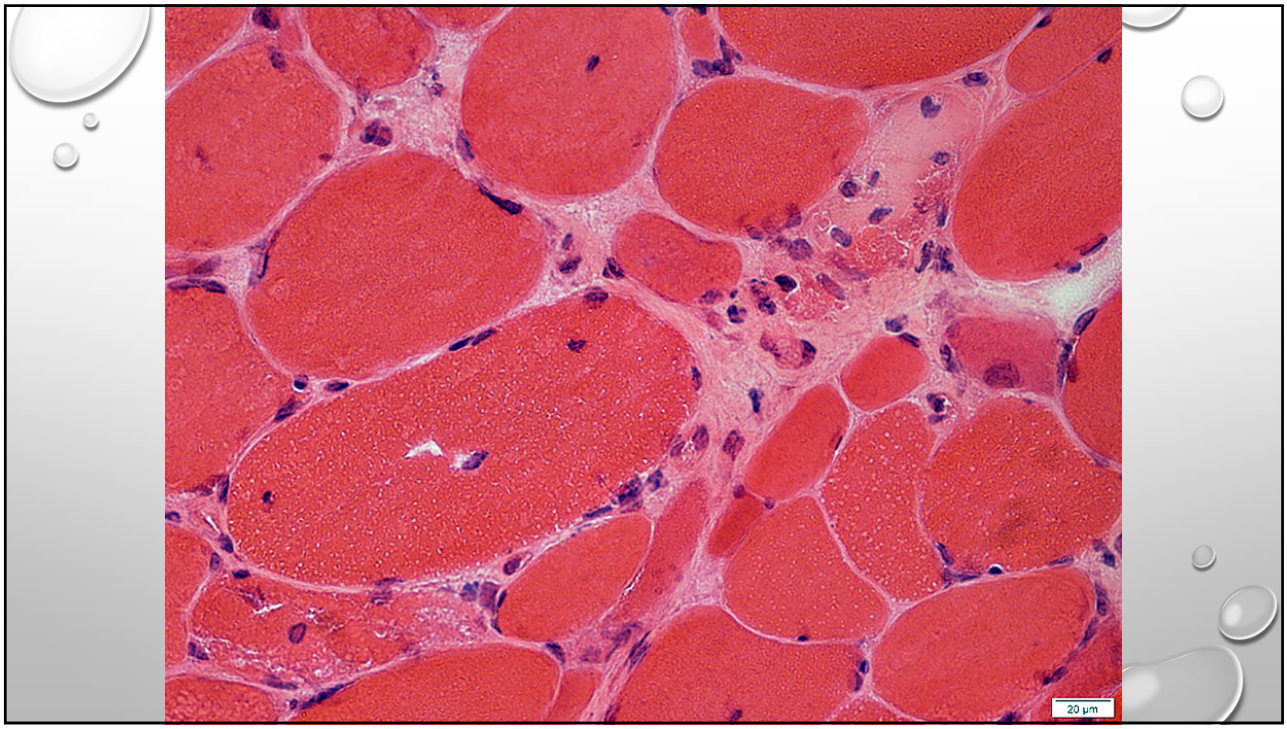

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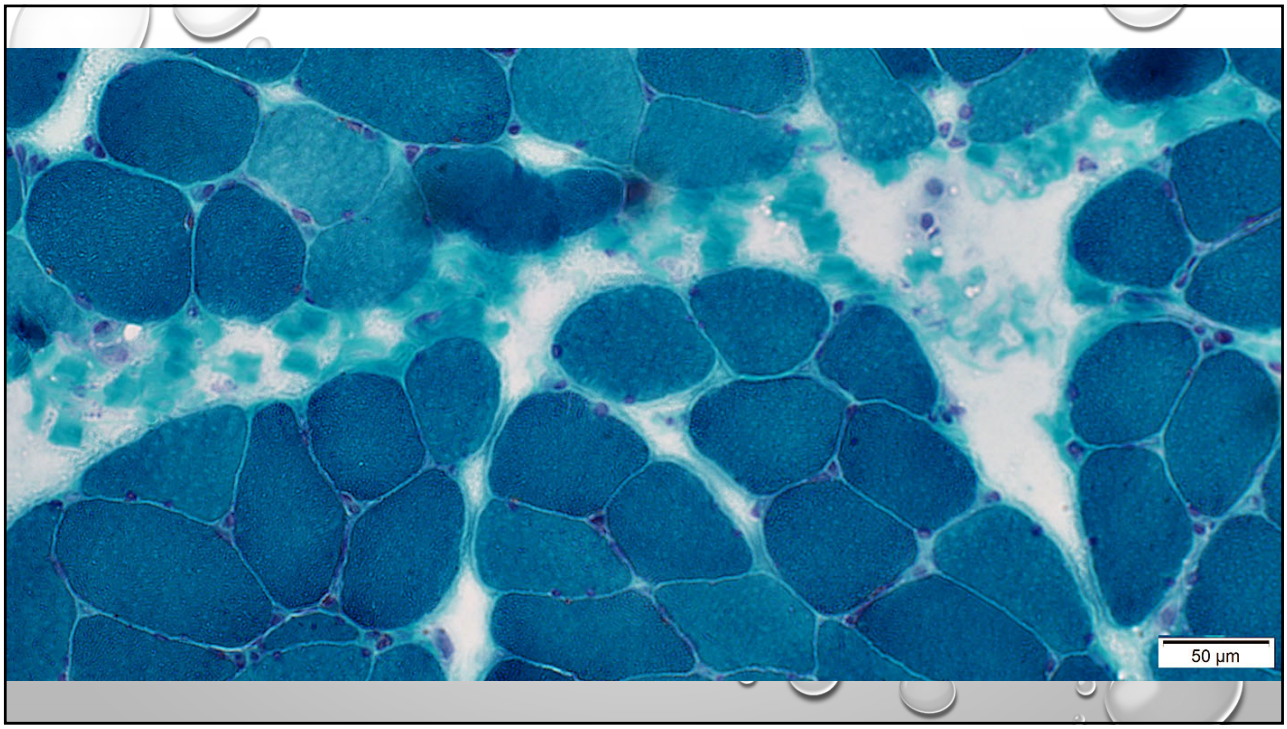

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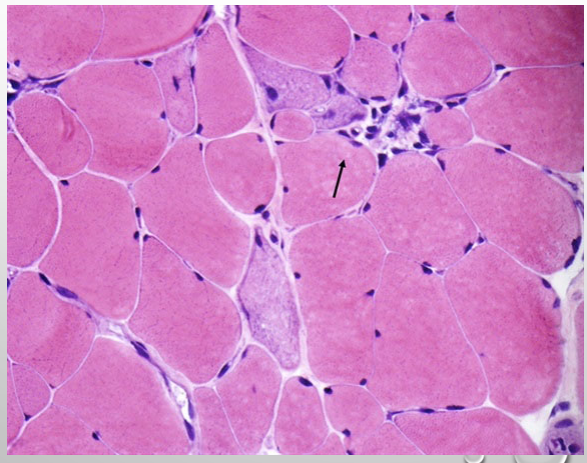

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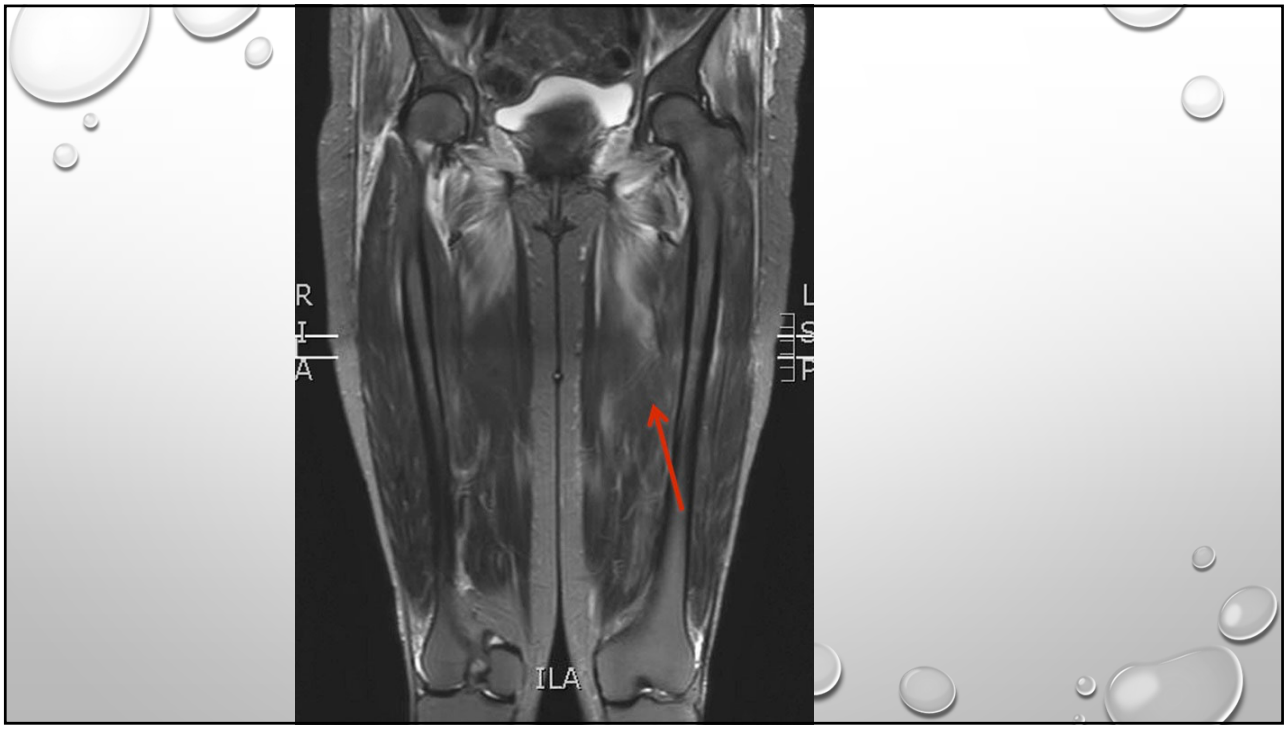

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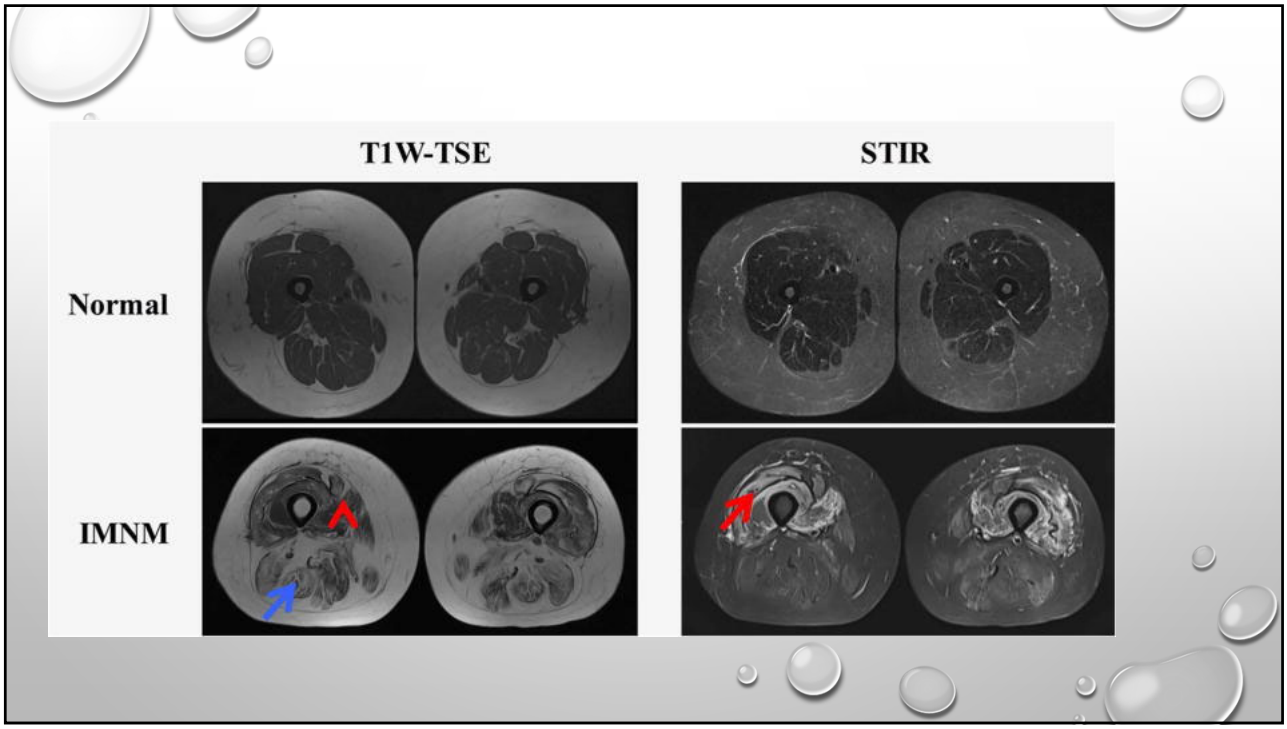

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OUR PATIENT

ANTI HMGCR > 200

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DISPOSITION

- IVIG 2gm/kg q 3 weeks
- Prednisone 40 mg daily
- 4 weeks later, abovementioned combination resulted in substantial improvement
- 8 weeks later, normal strength
- Prednisone has been tapered down to 0
- Has been on tapering IVIG regimen (40 gm once very four weeks)
- During April and May 2020, IVIG was skipped. Back on maintenance

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STATIN AND MYOPATHY

- Several case-control studies have implicated DRB111:01 as a risk factor for anti–HMG CR myopathy. DRB111:01 has been found in 70% of patients with anti–HMG CR antibodies, but only in 15%
- THE ANTI–3-HYDROXY-3- METHYLGLUTARYL COENZYME A REDUCTASE Antibody associated immune-mediated necrotizing myopathy was first described in patients with a history of statin exposure with weakness that continued to progress despite stopping use of the statin mediation; however, up to one-third may be statin naïve and may have a more resistant treatment response.
- Class-2 HLA-allele DRB108:03 with anti-SRP myopathy

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Idiopathic inflammatory myopathy

Bohan and Peter *N Engl J Med*. 1975 Feb 13;292(7):344-7
- DM
- PM

ENMC Workshop *Neuromuscul Disord*. 2004 May;14(5):337-45
- DM
- PM
- Immune-mediated necrotizing myopathy
- Nonspecific myositis
- (IBM)

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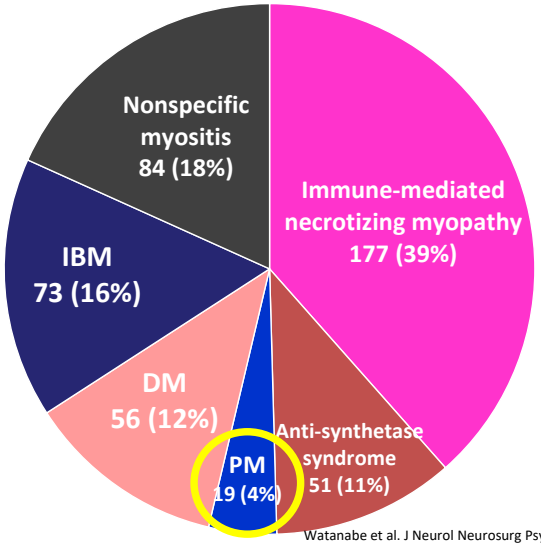
Myositis Project

460 IIM cases (Oct 2010 – Dec 2014)



Watanabe et al. J Neurol Neurosurg Psychiatry. 2016 Oct;87(10):1038-44
Suzuki et al. Autoimmun Rev. 2017 Jul;16(7):693-700

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Neurology®

August 12, 2003; 61 (3) EDITORIALS

Unicorns, dragons, polymyositis, and other mythological beasts

Anthony A. Amato, Robert C. Griggs

First published August 11, 2003, DOI: https://doi.org/10.1212/WNL.61.3.288

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POLYMYOSITIS

- Proximal upper and proximal lower extremities weakness (limb girdle pattern)
- CD 8+ T cells
- Invasion of non-necrotic endomysial muscle fibers by T cells is required to make definitive diagnosis

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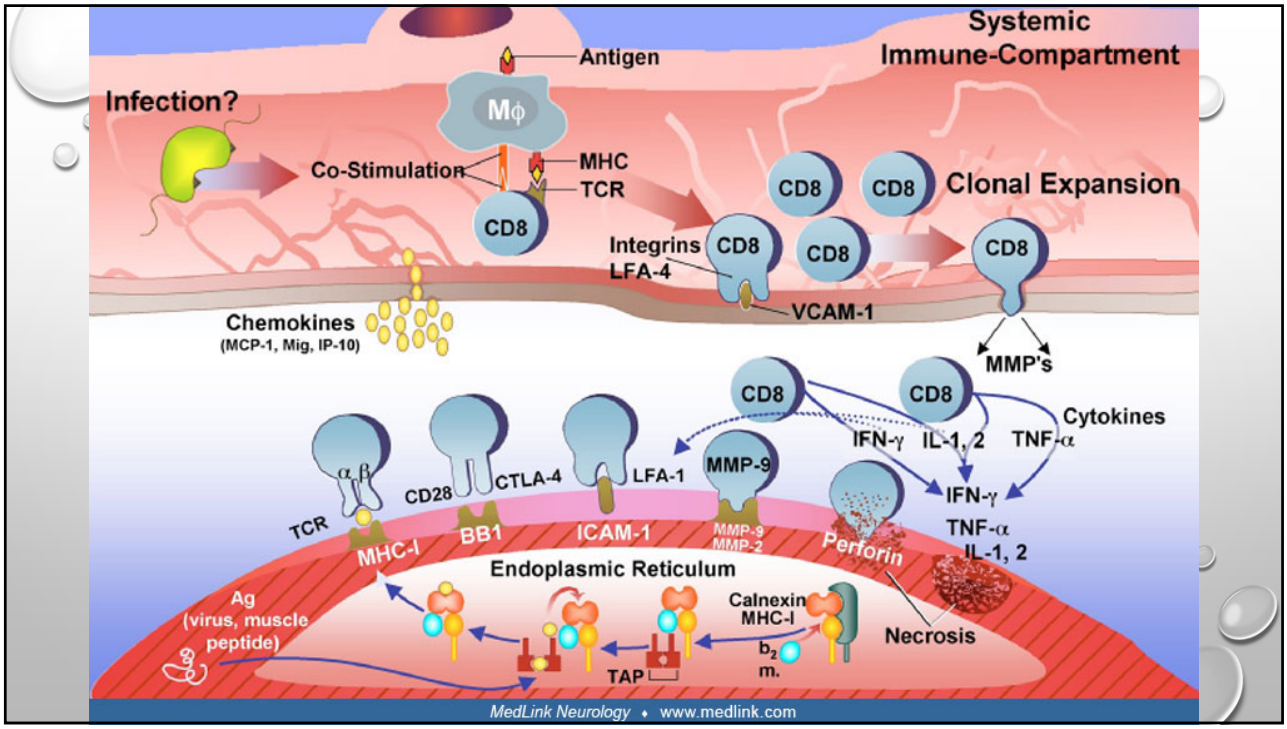

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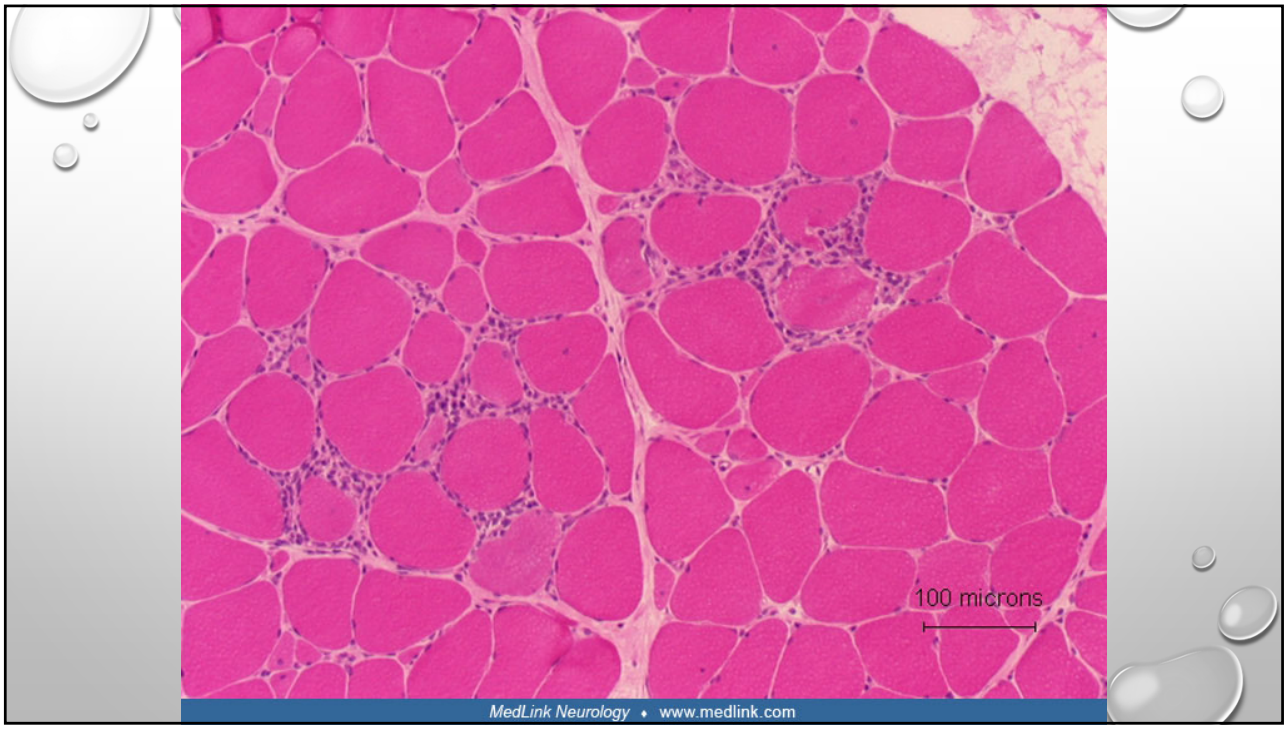

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CASE

- 55 Year old woman with progressive weakness over lower extremities
- Over the course of past 6-7 years she got worse to the point that she became wheelchair bound
- History of low back pain/spinal stenosis/two spine surgeries over the past five years

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CASE

- Motor exam: iliopsoas: 2/5 bilaterally; quadriceps: 4+/5; ADFs: 5/5; upper extremities: normal
- Reflexes: knees: 1/1; ankle: 0/0
- CK: **450-600**
- EMG/NCS: Axonal sensorimotor polyneuropathy with needle examination showing widespread neurogenic changes. No myopathic changes were seen

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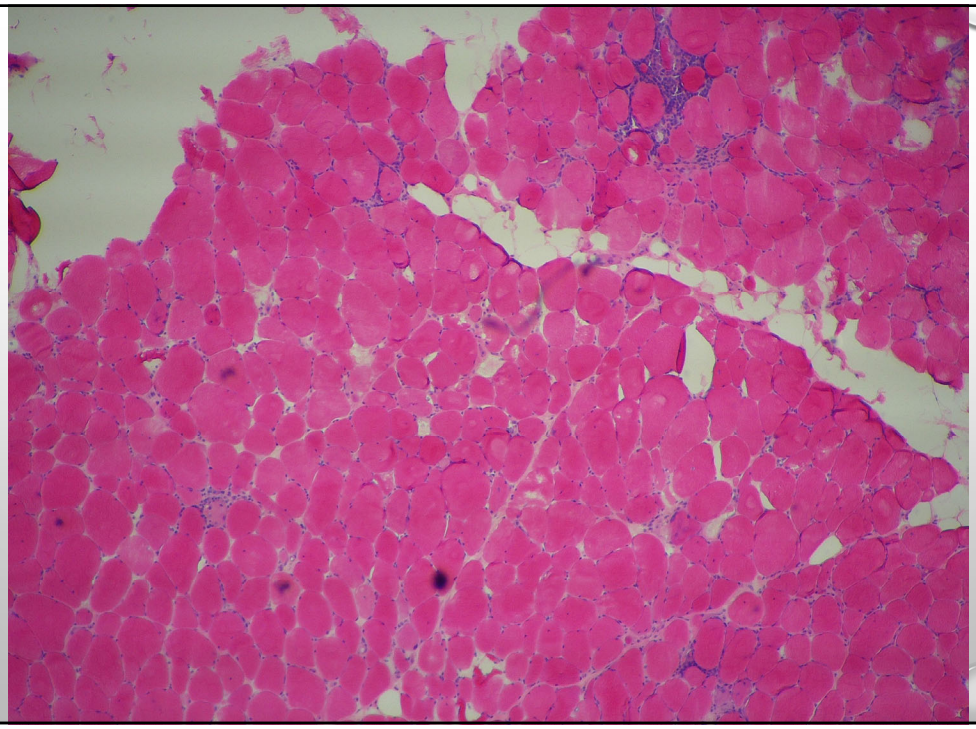

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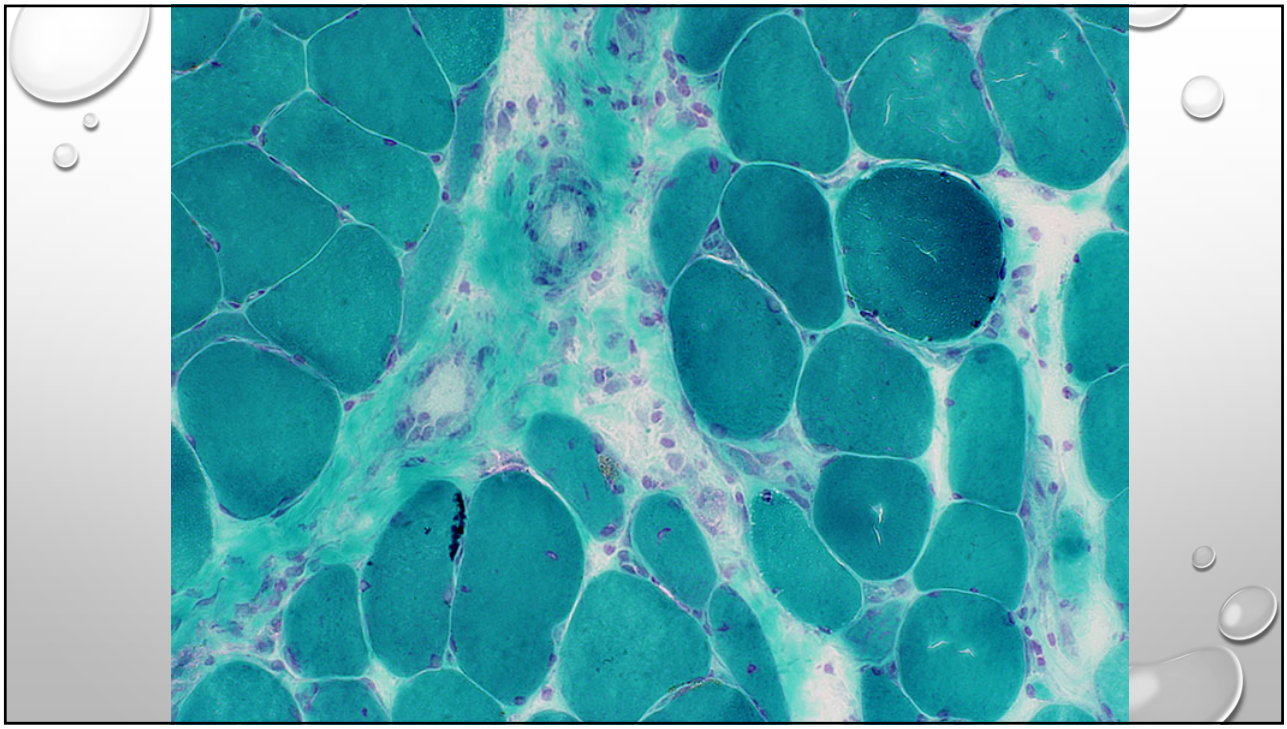

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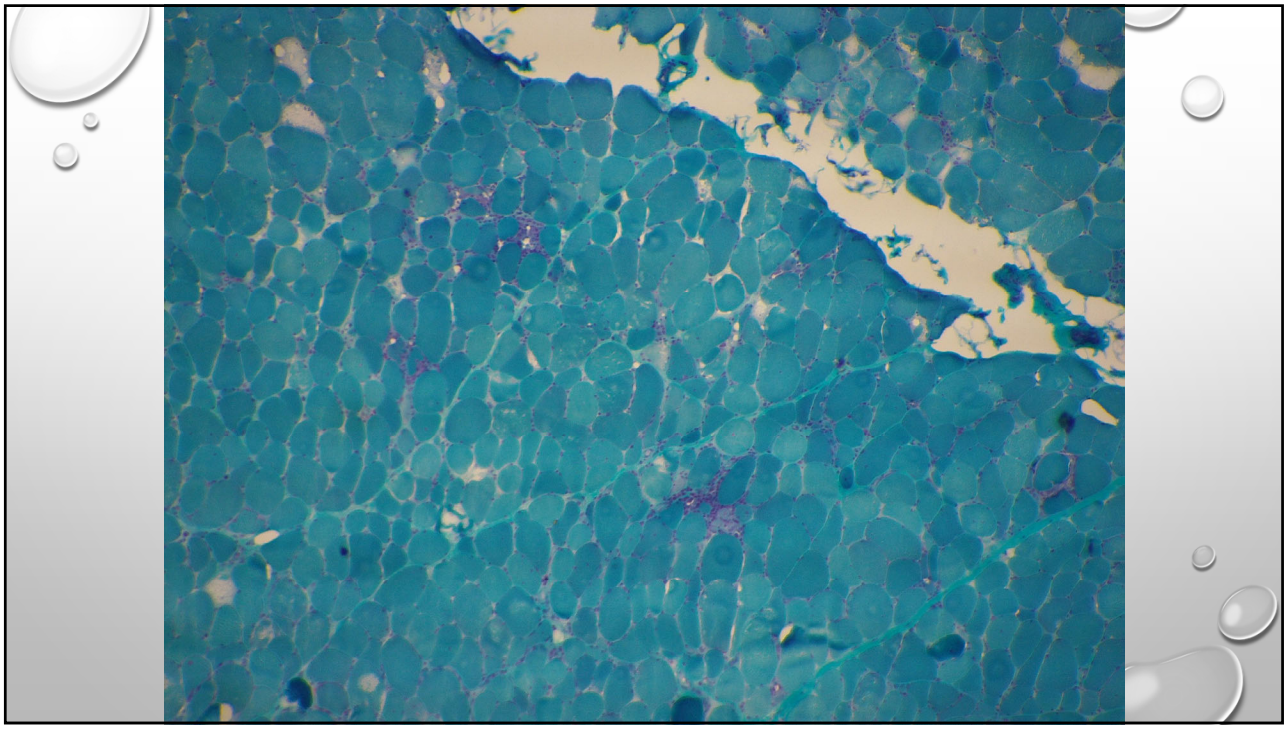

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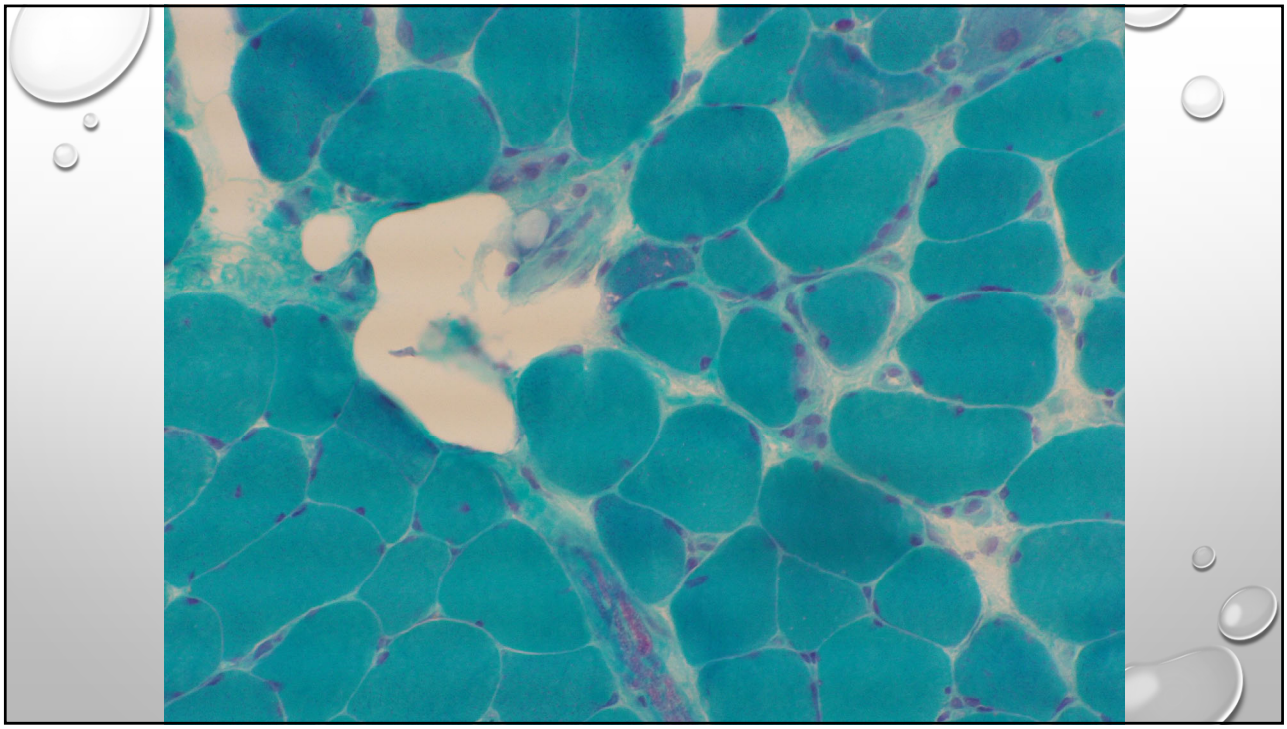

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COURSE

- IV Solumedrol followed by tapering steroids
- IVIG for 3 months

- No improvement
- Six months later, she developed left fourth and fifth digits weakness
- ANTI5C1A Antibody was sent out to Wash U: Positive
- IVIG/steroids were discontinued
- Diagnosed with sIBM

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INCLUSION BODY MYOSITIS

- Slowly progressive weakness
- Most common inflammatory myopathies in patients older 45
- Distinct pattern of weakness
- Not typical findings

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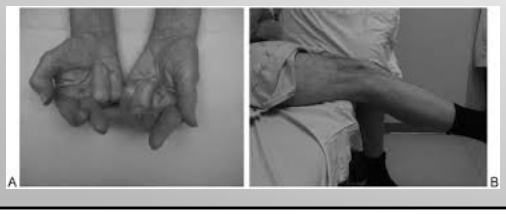
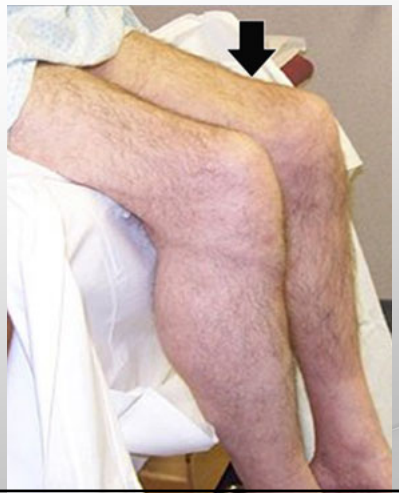
Clinical Features

- ➢ Preferential, but not exclusive weakness pattern
- ➢ Asymmetric
- ❑ Quadriceps
- ❑ Finger flexors
- ❑ Ankle dorsiflexors





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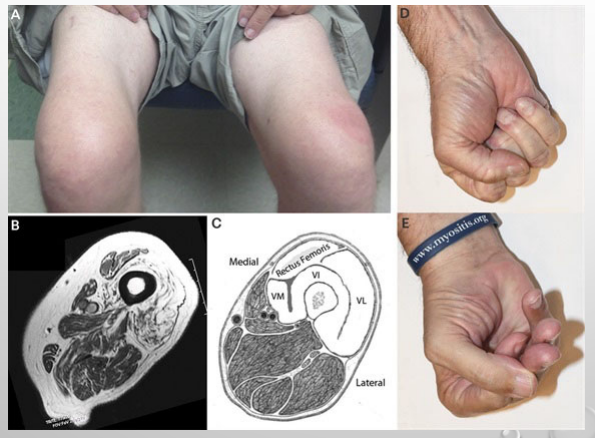

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Diagnosis

- CK is modestly elevated

- EMG may show fibrillation potentials and positive sharp waves
- Myopathic Motor Unit Potentials
- Motor Unit Potentials can be large, suggesting neurogenic process
- Muscle Biopsy
- Serum Antibody against NT5C1A

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Misdiagnosis

- ❑ Frequently delayed and misdiagnosis is common
- ❑ Mean time to correct diagnosis after the onset of symptoms has been estimated at 5.2 to 5.6 years
- ❑ ~ 6 % limb girdle pattern weakness (more common in women)
  - ➢ Polymyositis
  - ➢ Amyotrophic lateral sclerosis
  - ➢ CIDP

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Microscopic Pathology

- ❑ INFLAMMATORY INFILTRATES
  - Within the endomysium (within fascicles, around muscle fibers)
  - Invasion of T cells into non-necrotic myofibers
- ❑ DEGENERATIVE
  - Rimmed vacuoles
  - Sarcoplasmic aggregation and deposition of various proteins e.g. TDP-43 and p-62

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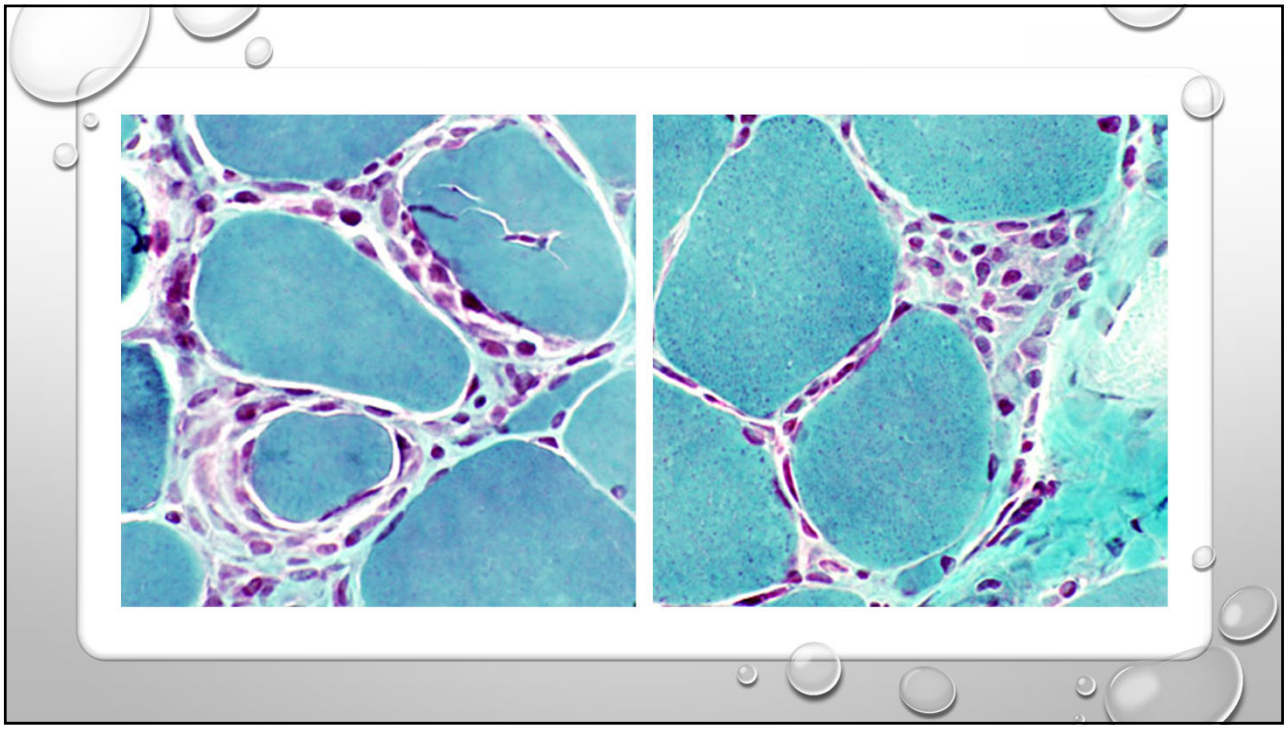

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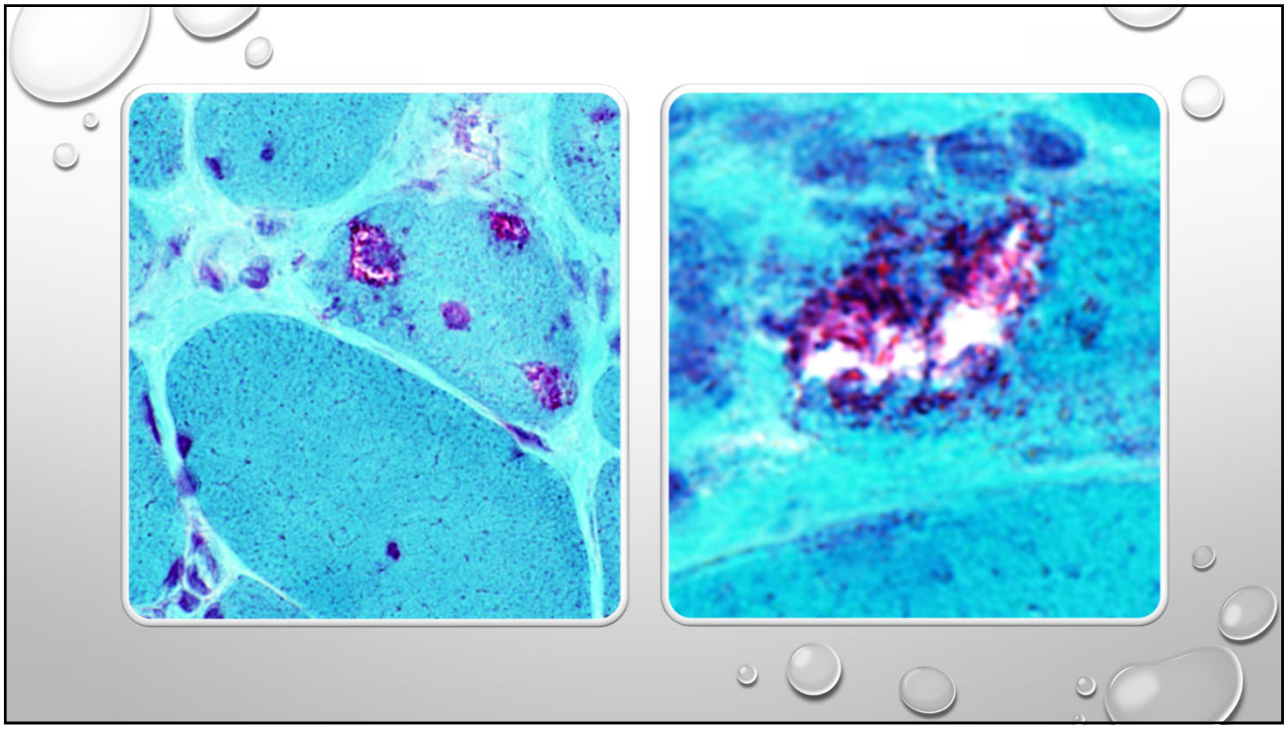

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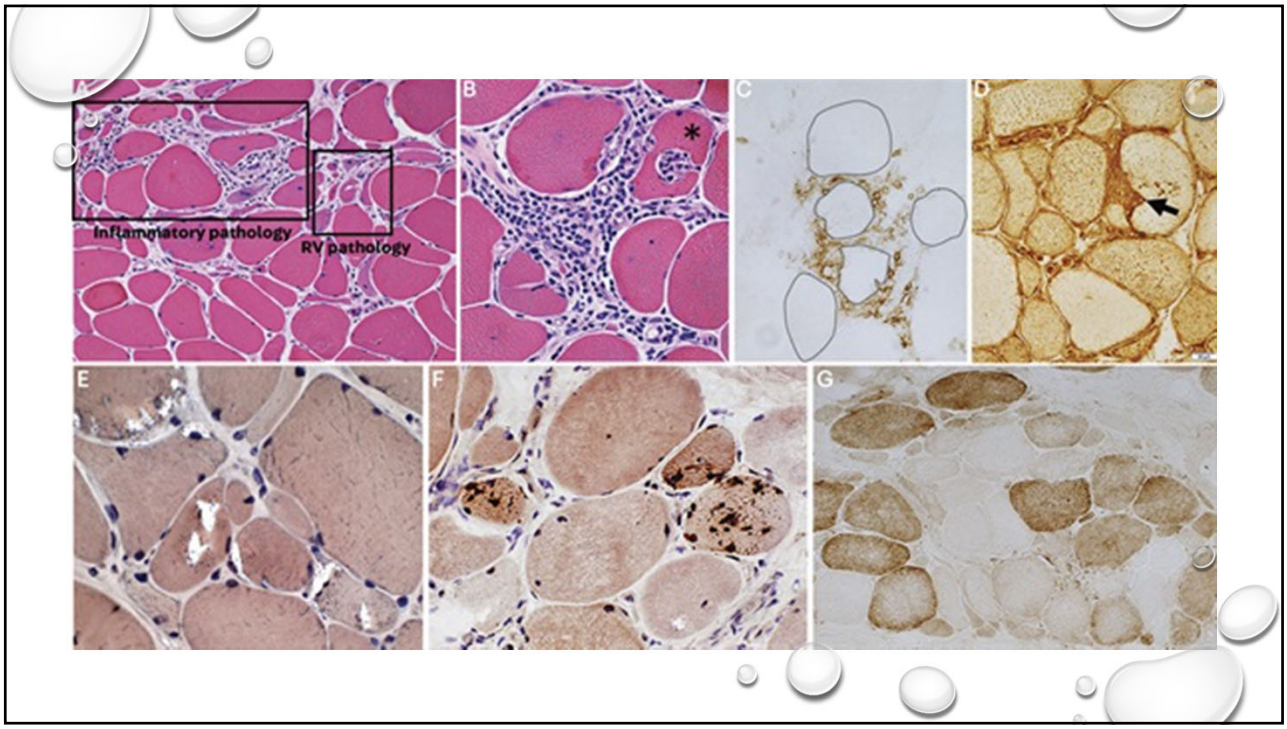

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Disease Mechanisms

- Non necrotic fibers by cytotoxic T cells
- Myonuclear degeneration
- B cells activation
- Mitochondrial pathology
- Viral infection
- Molecular toxicity

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Management and treatment trials

- No treatment has been demonstrated to be effective at slowing or reversing disease in IBM as of today

- IVIG + prednisone
- Immunotherapies such as Azathioprine; methotrexate
- Biologic such as Natalizumab, Alemtuzumab; Etanercept

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CASE

- 58 year old woman

- Muscle pain x 4 months

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HISTORY

- Weakness over both upper extremities
- Head drop
- Chronic widespread body ache
- Dysphagia

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EXAM

- AAO X 3; Speech normal
- CNs : orbicularis oculi: 5/5; orbicularis oris: 5/5
- Deep tendon reflexes: normal
- Sensory: normal

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MOTOR EXAM

	RIGHT	LEFT
DELTOID	3	3
BICEPS	3	3
TRICEPS	4+	4+
FINGER FLEXORS	5	5
FINGER EXTENSORS	5	5

	RIGHT	LEFT
ILIOPSOAS	3	3
HIP ADDUCTORS	4-	4-
QUADRICEPS	3	3
ANKLE DORSIFLEXORS	5	5
ANKLE PLANTARFLEXORS	5	5

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DIAGNOSTICS

- ❑ Repetitive nerve stimulation: normal
- ❑ Nerve conduction study: normal
- ❑ EMG:

  complex repetitive discharges

  Myopathic motor unit potentials

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LAB WORK UP

- CK: 11,000
- ANA and rheumatoid factor: normal
- Acetylcholine antibody titer: normal

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WORK UP

- High resolution CT scan of chest: normal
- MRI left shoulder:

  Heterogenous edema in left deltoids
- Pulmonary function tests: normal

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FURTHER WORK UP

- Muscle biopsy
- Malignancy work up negative
- Discharged on prednisone 40 mg a day
- Subsequently, prednisone was increased to 60 mg a day

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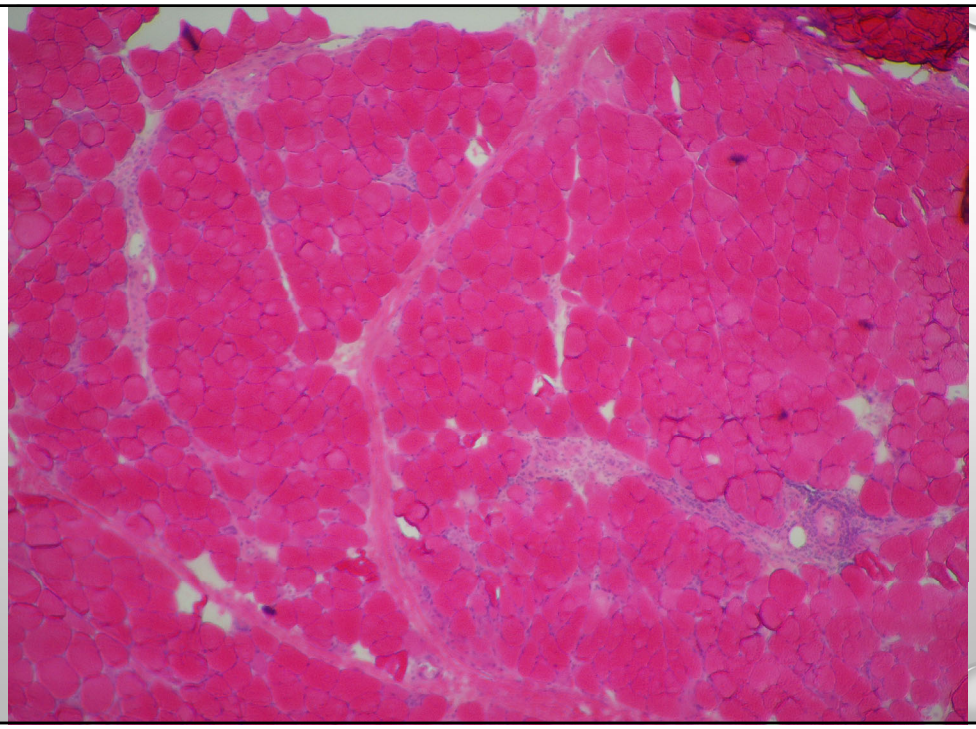

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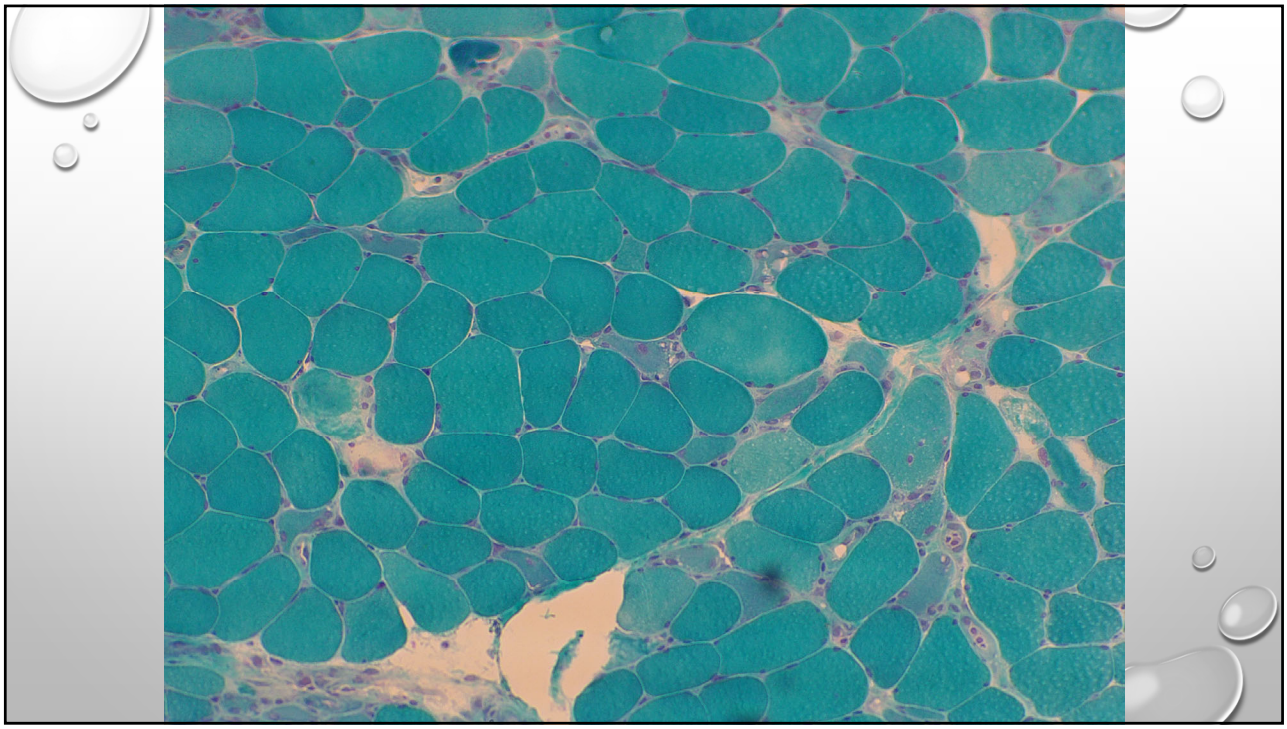

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DERMATOMYOSITIS

- Proximal muscle weakness (accompanied by or preceded by skin rash)
- CPK up to 30 times normal
- Irritative myopathy by EMG
- Associated myositis specific antibodies
- Skin changes (rash and or subcutaneous calcification)

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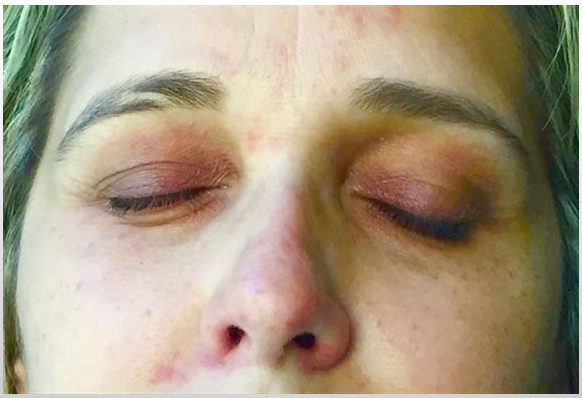
Heliotrope or violaceous discoloration



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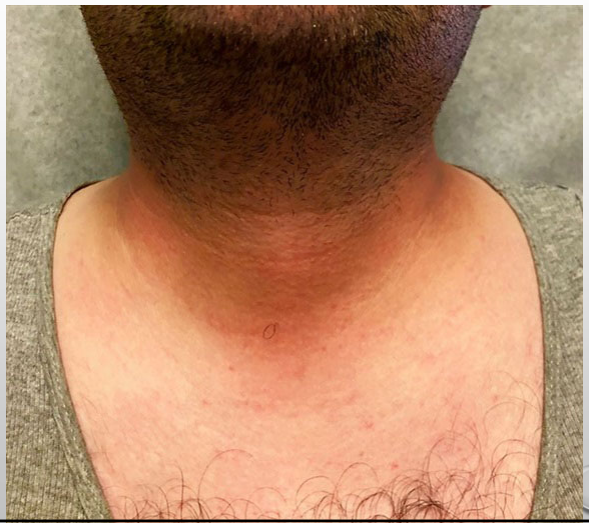
V Sign/anterior neck



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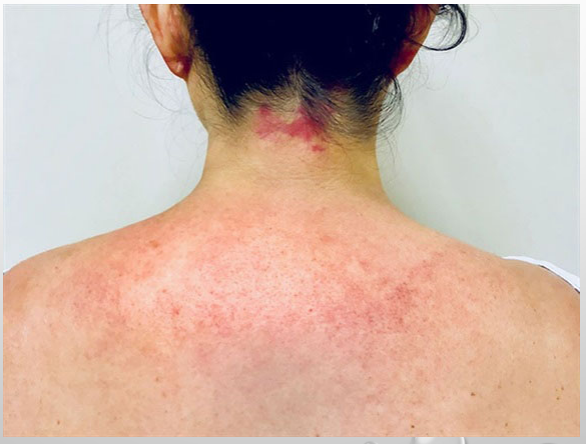
Shawl sign/posterior neck



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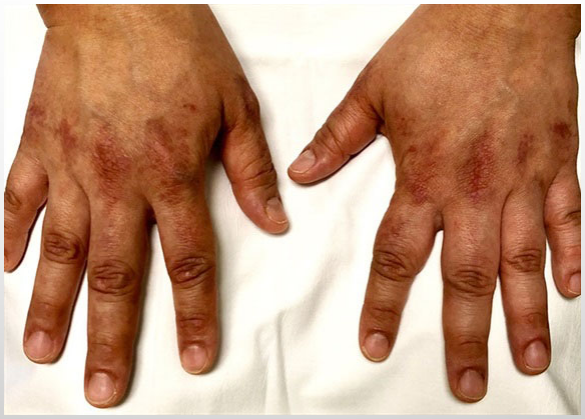
Gottron sign/MCP joints



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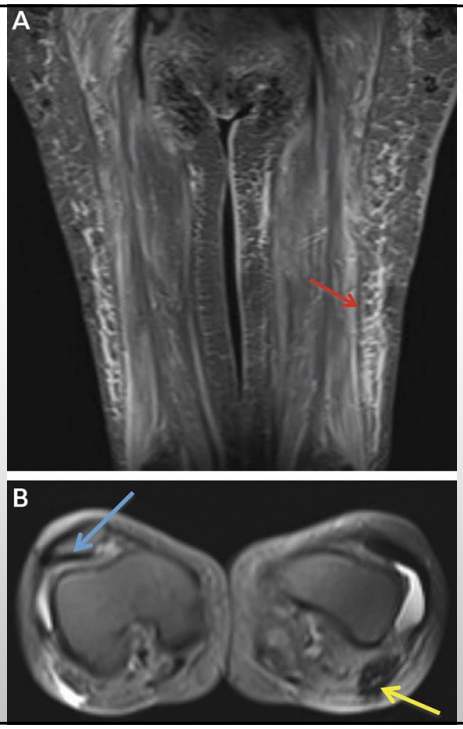

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DM

- Complement mediated autoimmune microangiopathy
- Affects both children and adults
- High CK in 90% and up to 50 x ULN
- CK does not correlate with severity of weakness

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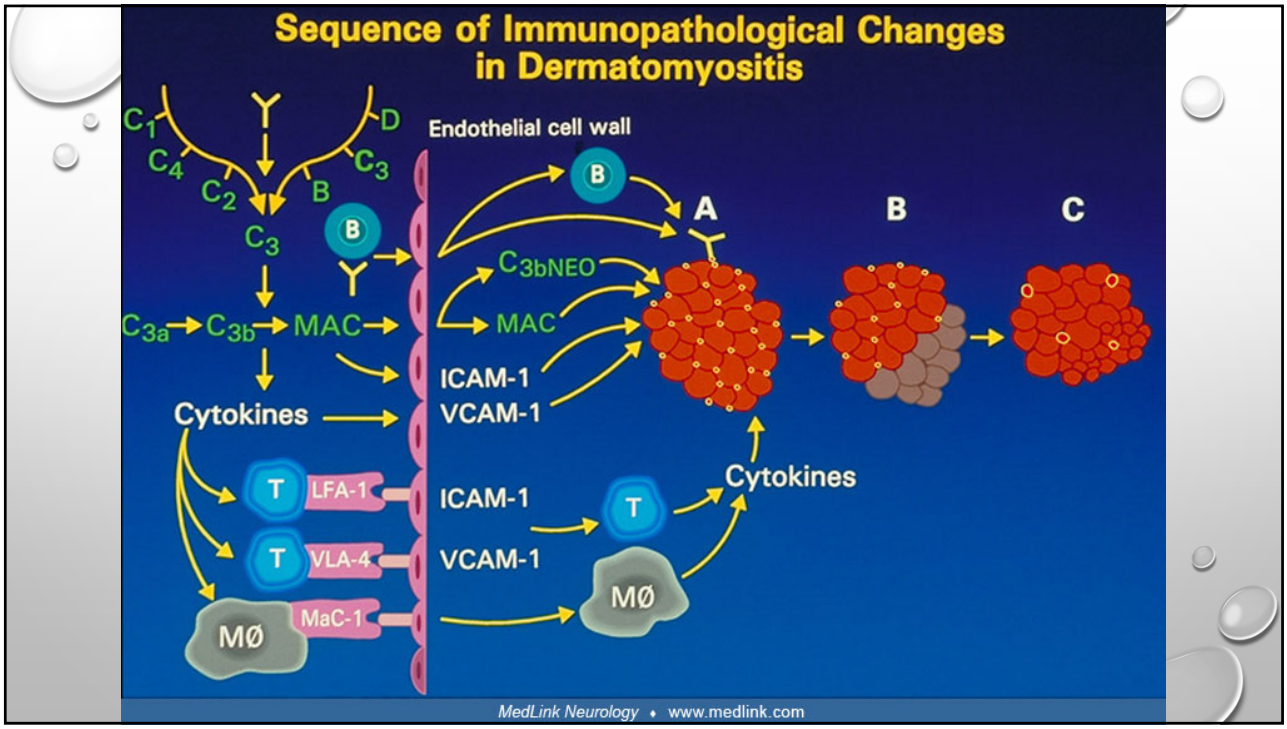

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PATHOGENESIS

- The combination of several immunogenetic risk factors, including class-2 human leukocyte antigen (HLA) alleles, and environmental
- Interferon overproduction has been a proposed mechanism of the pathology seen in dermatomyositis because dermatomyositis muscle has been shown to contain abundant interferon-secreting plasmacytoid dendritic cells. Additionally, interferon-inducible genes are highly upregulated in dermatomyositis, and the gene expression in the blood correlates with dermatomyositis disease activity; but the mechanism of interferon overproduction leading to the loss of capillaries and perifascicular atrophy still remains unclear.

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SPECTRUM OF DM

- Most with skin and muscle involvement
- Only muscle
- Only skin (Amyopathic Dermatomyositis or Dermatomyositis sine Myositis)

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ASSOCIATED CONDITION

- ILD 10-20%
- Incidence of cancer ranging 6 %-45% (most occurring first 2 years)

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AUTOANTIBODIES

- **Anti- MI-2;** Severe skin manifestation but good response to treatment
- Transcriptional intermediary factor 1Y**(TIF1Y);** Increased risk of malignancy
- Antinuclear matrix protein **(NXP2):** Increased risk of calcinosis and malignancy
- Anti- melanoma differentiation- associated protein 5 **(ANTI-MDA5);** Skin changes and severe cardiopulmonary involvement
- **Anti SAE** – minimal muscle involvement, classic skin rash and dysphagia

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BACK TO OUR PATIENT

- Was on prednisone for 3 weeks……
- Was getting worse in terms of weakness over proximal upper extremities.
- Now worsening of weakness over proximal lower extremities.
- Swallowing impairment was getting worse

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CASE

- Reduced prednisone to 50 mg with tapering regimen. ….
- IVIG….

  25 gm for four days…….

  Followed by……

  25 gm once a week…….

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DISPOSITION

- Within one and half week……

  Dramatic improvement……

  Significant improvement in muscle strength

  Dysphagia improved

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4 MONTHS LATER

- Muscle strength almost normal….
- Improvement in swallowing
- Off prednisone
- IVIG maintenance/ 40 gm every 4 weeks. Tried to reduce the dosage which led to worsening of strength at one point.

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TWO YEARS AGO

- Diagnosed with breast cancer
- Underwent mastectomy and was treated with tamoxifen
- In remission

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Antisynthetase Syndrome

- Myositis

  +

- Multisystem disease

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TWO OR MORE OF THE FOLLOWING

- Myositis
- Interstitial lung disease
- Arthritis
- Raynaud phenomenon
- Fevers
- Hyperkeratotic lesions along the radial and palmar surfaces of fingers, known as **MECHANIC'S HANDS;** sometimes erythematous skin rash

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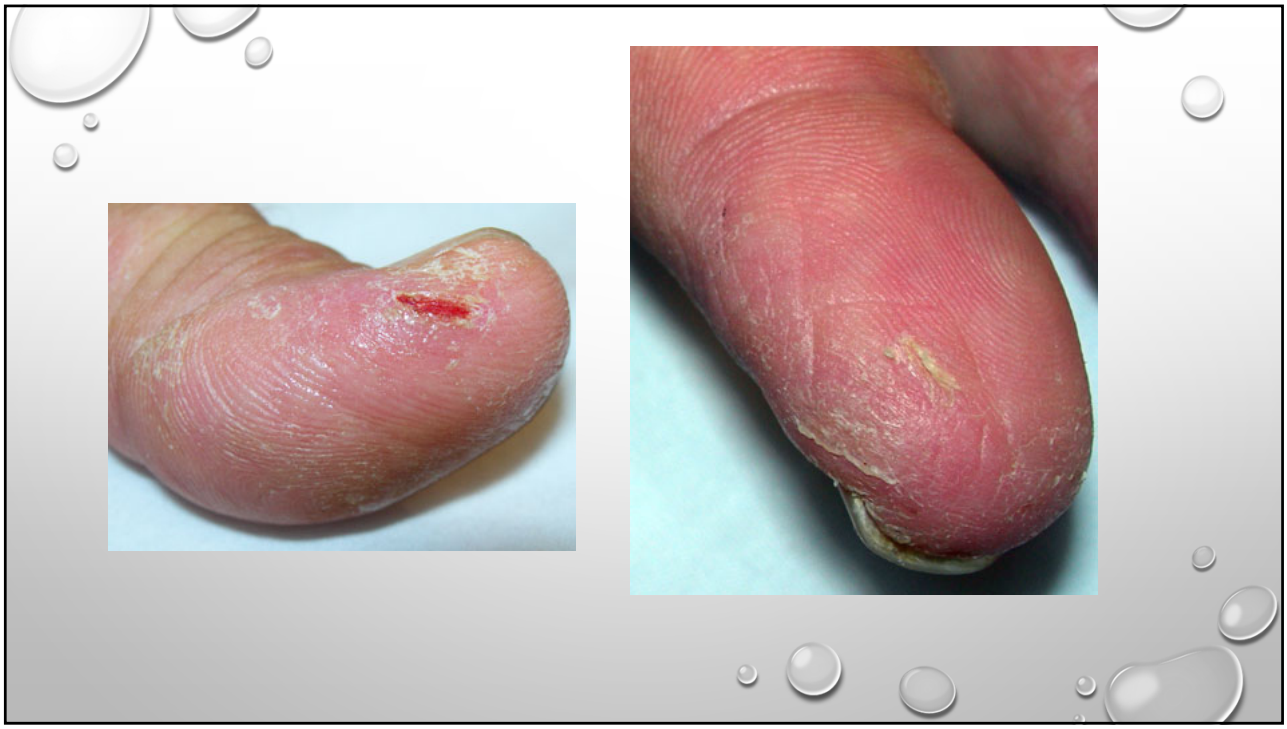

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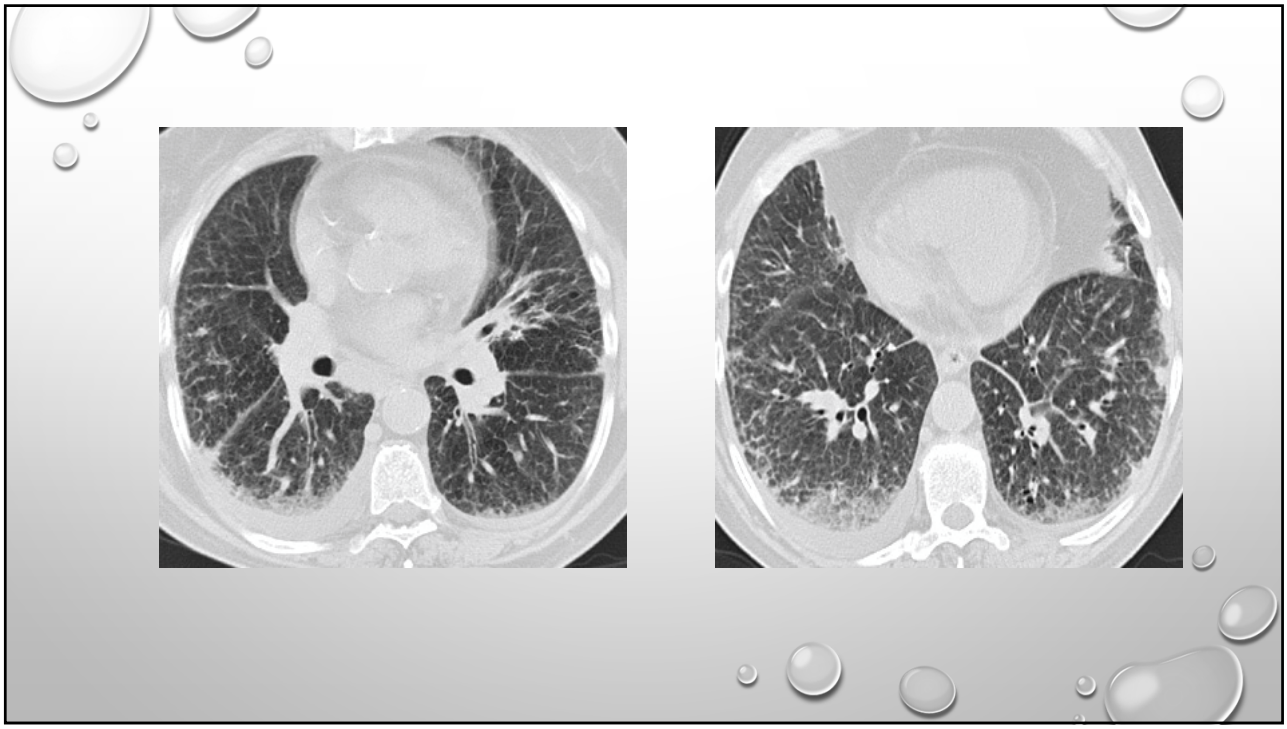

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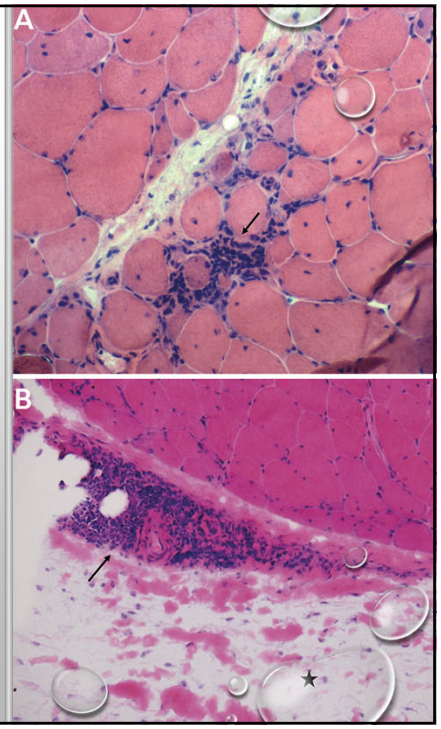
Histopathology

- Unique pattern of perifascicular necrosis
- Sacrcolemal deposition of complement
- Fragmentation of the perimysium, and increased perimysial alkaline phosphatase activity



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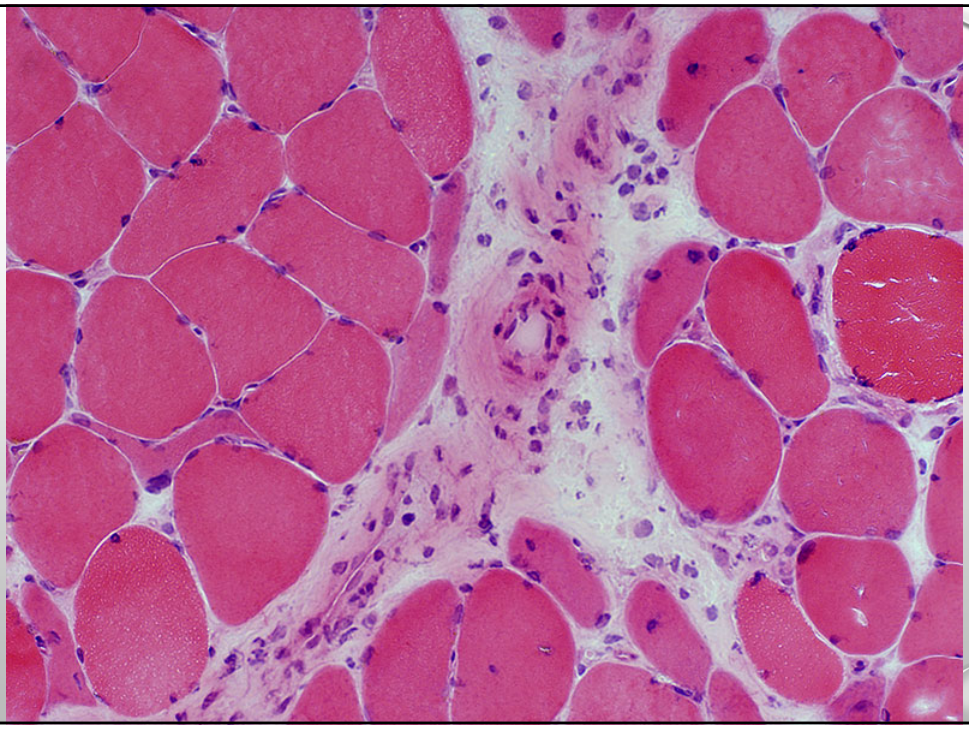

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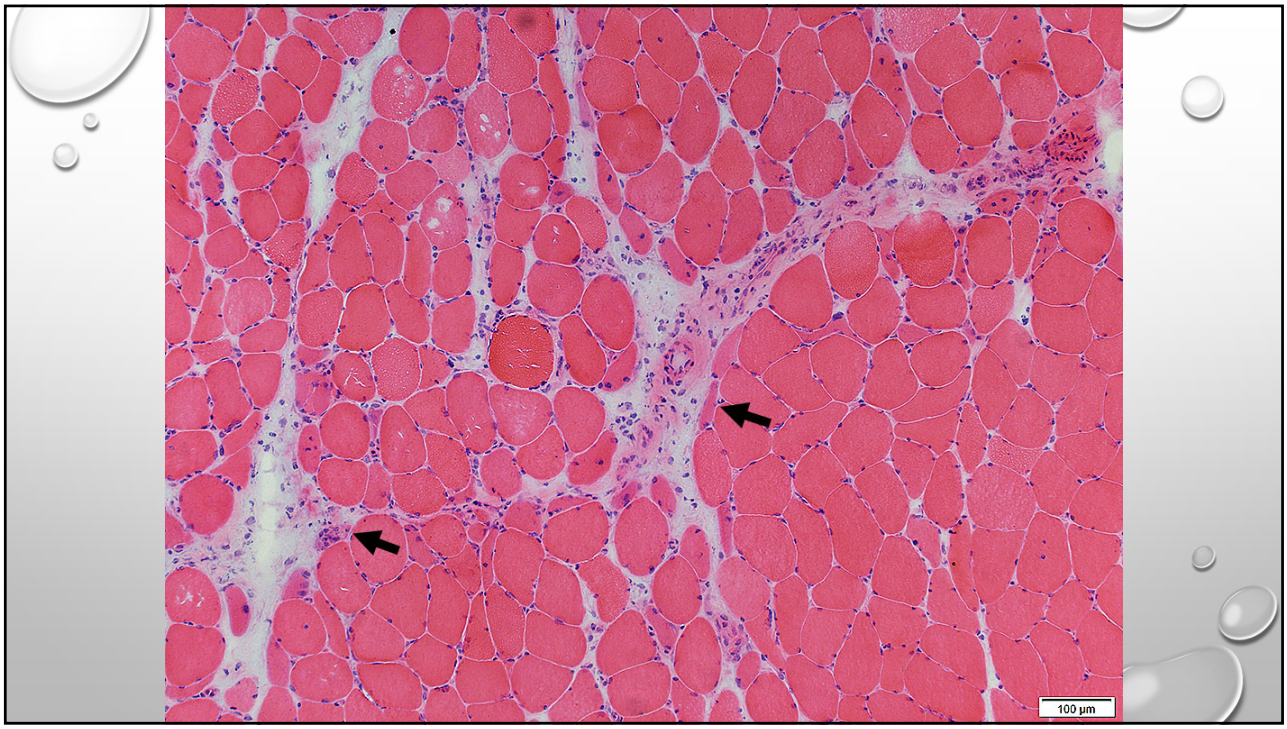

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ANTIBODY

- T RNA SYNTHETASE
- **ANTI JO-1 ➔ Muscles**
- **ANTI PL-12 ➔ Lungs**
- **ANTI PL 7 ➔ Lungs**

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MANAGEMENT

- Steroids
- Immunosuppresive agents
- IVIG
- Biologic agents
- Combination regimens

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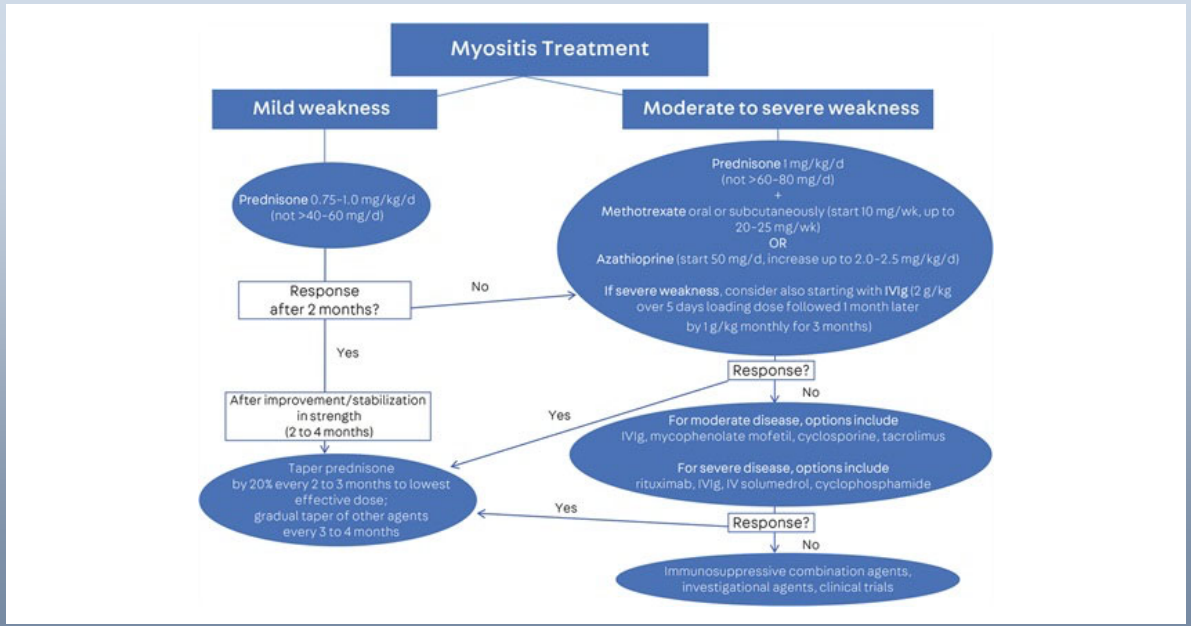

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RITUXIMAB IN MYOSITIS
RIM STUDY, 2013, ARTHRITIS RHEUMATOLOGY

- Did not meet the primary or secondary end points
- Rituximab has been shown to have beneficial effects in patients with Antisynthetase syndrome, primarily anti–Jo-1, and also in anti–Mi-2 autoantibody–positive subjects in a post hoc analysis of a randomized controlled trial of rituximab in refractory dermatomyositis and polymyositis Rituximab has also been shown to be effective in treating patients with anti-SRP antibody immune-mediated necrotizing myopathy who were refractory to conventional immunotherapies

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PRODERM STUDY
(BMJ, 2021)

- A total of 95 adult DM patients (mean age: 53 years; 75% females; 92% caucasian) were enrolled, with 47 and 48 randomized to IVIG and placebo, respectively. Baseline clinical characteristics (including medical history and prior DM medication) were balanced between the 2 arms.
- The study met the primary endpoint at week 16, with the proportion of responders being significantly higher in the IVIG group (37/47; 78.7%) as compared to the placebo group (21/48; 43.8%; p-value 0.0008

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HORIZON

- IVIG
- Complement inhibitors
- FcRn blocker
- anti–TNF agents
- Janus kinase inhibitors
- a monoclonal antibody that blocks interleukin 6
- an anti–interferon-alpha monoclonal antibody
- a monoclonal antibody blocking interleukin 2 receptor α-chain, CD25 antigen, present on the surface of activated T lymphocytes
- a novel synthetic phosphorothioate oligonucleotide antagonist to toll-like receptorsjanus kinase inhibitors

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CONCLUSION

- Approach to the patient …....

❑ Neuromuscular Exam

❑ CK level

❑ EMG/MR images/Muscle Biopsy

❑ Appropriate diagnosis

❑ Immunotherapy

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CONCLUSION

- Immune Mediated Myopathies are very treatable conditions
- Can be associated with malignancy
- Supportive care in Inclusion Body Myositis
- Polymyositis is becoming increasing rare

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