Approach to the Patient with Myopathy

June 25, 2026

Steve Lee, DO FACR
SCPMG Rheumatology
Associate Professor, Western Univ, CUSM, Touro Univ
Assistant Professor, LECOM, Loma Linda Univ

Disclosures

- Clinical Trial Support
  - Fate Therapeutics
  - GSK
  - Sanofi
  - Astra Zeneca

OUTLINE

- *Definition*
- *Epidemiology*
- *Pathophysiology*
- *Classification; diagnosis*
- *Clinical Features*
- *Special myopathic cases*
- *Treatment*

Idiopathic Inflammatory Myopathy

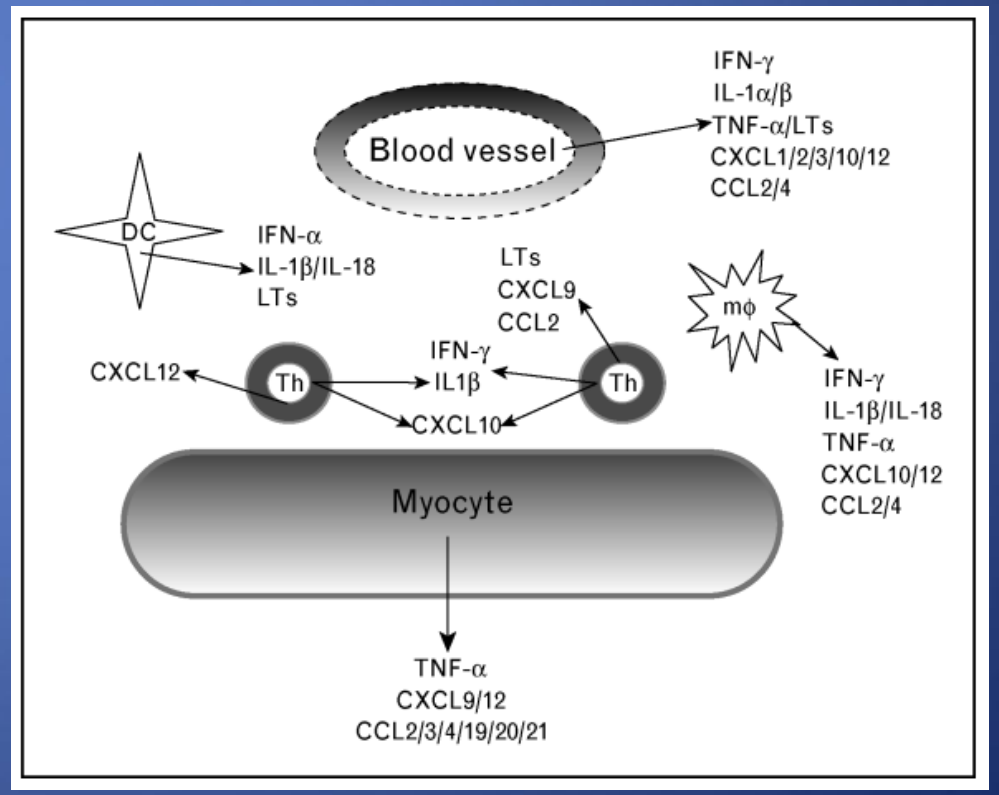
- Uncommon heterogeneous inflammatory muscle disorders featuring proximal muscle weakness
  - Adult Polymyositis
  - Adult Dermatomyositis
  - Special Cases:
    - Childhood DM
    - PM/DM associated with other CTD
    - Immune mediated necrotizing myopathy (anti-HMGCoA)

Epidemiology

- Rare: incidence from 2 - 10 new cases/ million persons (underestimate?)
- Bimodal: 10-15 yrs, 45-55 yrs
- 3-4:1 African-American to White
- F:M 2-3:1
- Overlap syndromes:
  - Scleroderma
  - lupus, MCTD

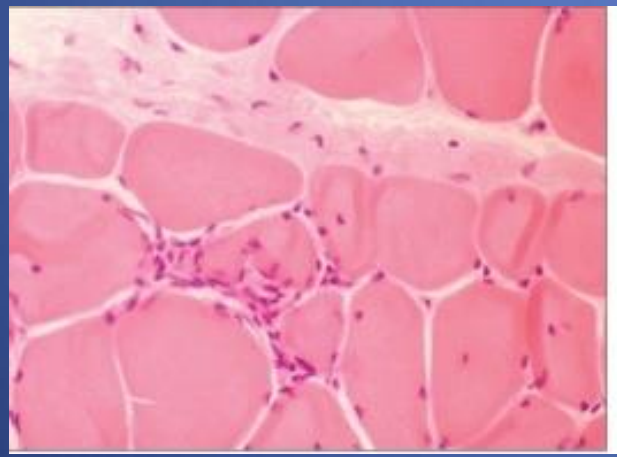
Common Pathophysiology

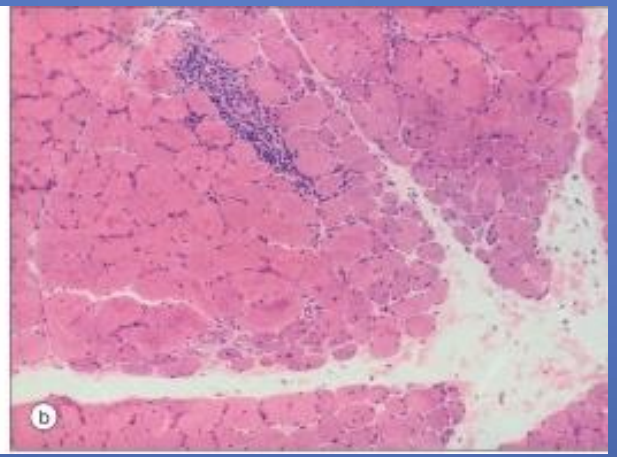
- B lymphocytes (myositis specific auto-Ab)
- Cytotoxic CD8+T cells for polymyositis
- CD4+T cells for dermatomyositis
- Pro-inflammatory cascade:
  - chemokines
  - complement activation
  - IL-1 and TNF
  - focal inflammation
  - death, repair

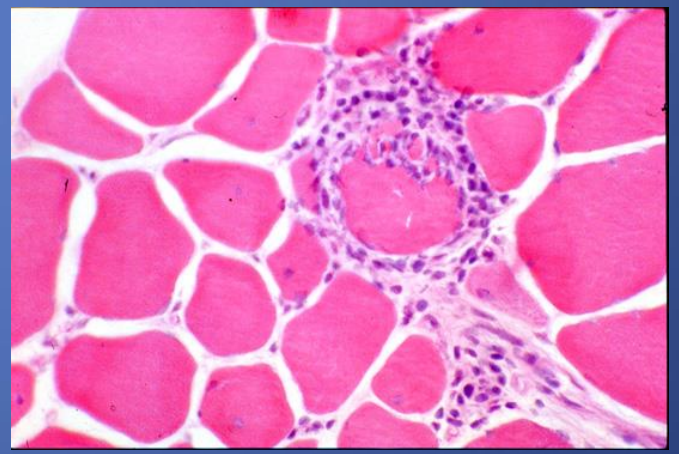


Difference between PM and DM

- **Polymyositis**
  - Inflammatory infiltrate within fascicle.
  - Scattered/isolated necrotic fibers.
  - Target= myofiber.
- **Dermatomyositis**
  - Perivascular infiltrate around fascicles.
  - Necrotic fibers in group.
  - Target= blood vessels.

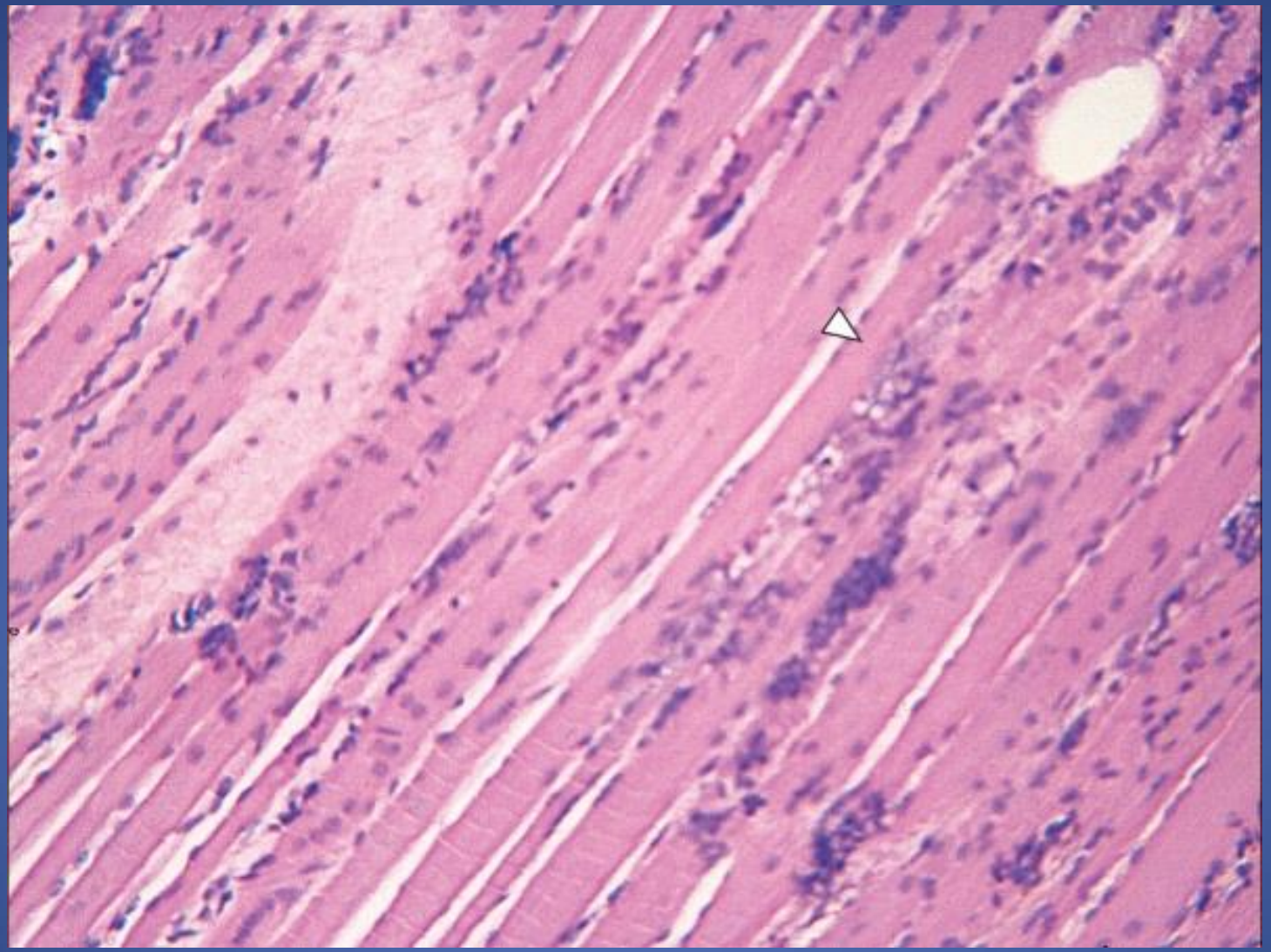






- Hematoxylin and Eosin cross-section of polymyositis:
- necrosis, regeneration and inflammation
- lymphocytic infiltration

Polymyositis: longitudinal



myofiber destruction; areas of degeneration and necrosis of myofibers in association with interstitial lymphocytic infiltration

Bohan and Peter Classification (1975)

1. Symmetrical proximal muscle weakness

   insidious and proximal muscles
2. Muscle biopsy evidence of myositis

   necrosis, phagocytosis, regeneration, atrophy, perivasc infiltrate
3. Increase in serum skeletal muscle enzymes

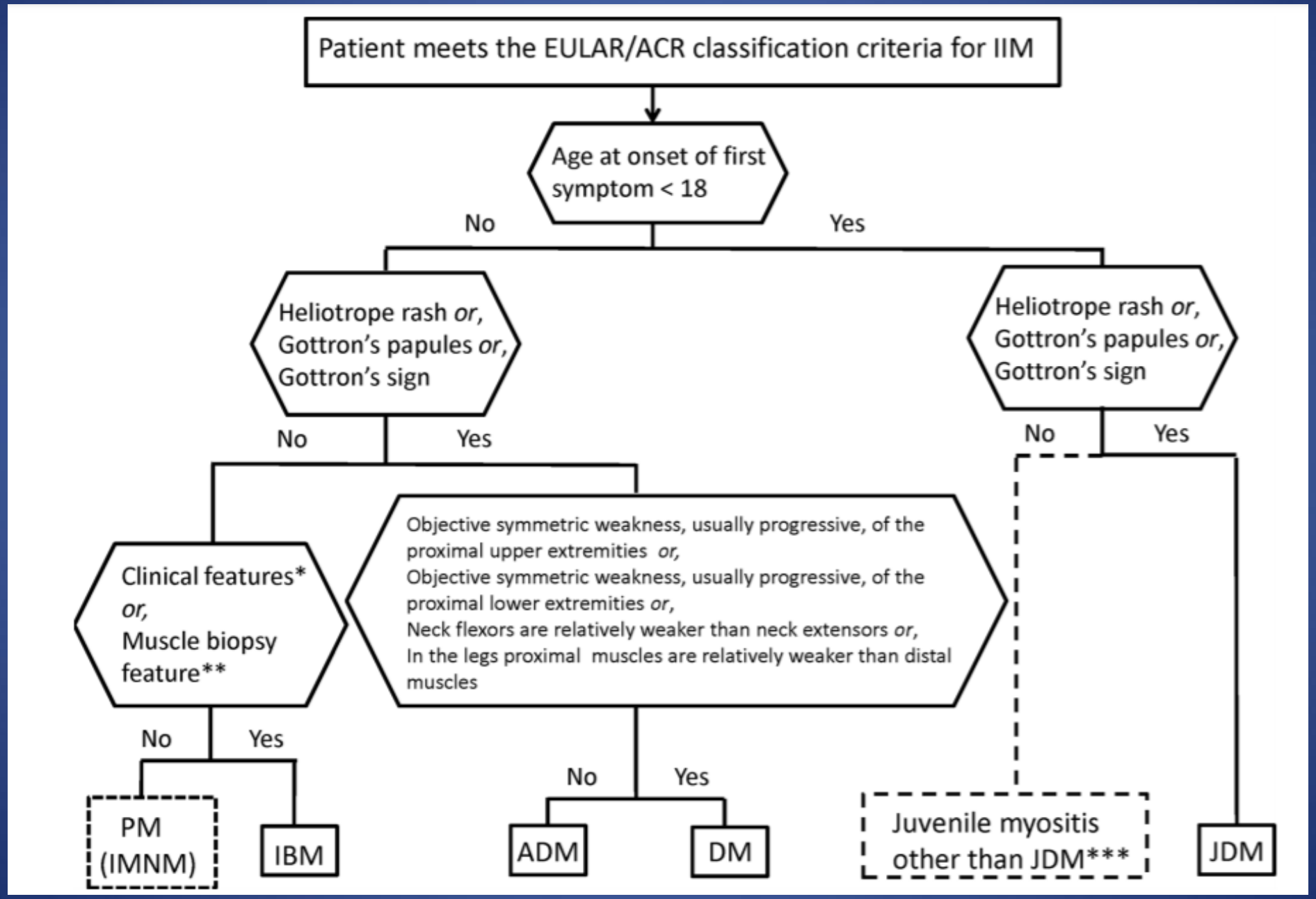
   CPK, aldolase, LDH, AST, ALT
4. Characteristic electromyographic pattern

   short polyphasic motor units, fibrillations, irritability and repetitive dc's
5. Typical rash of dermatomyositis
   heliotrope, gottrons, shawl, v neck

Polymyositis:
Definite: all of 1-4
Probable: any 3 of 1-4
Possible: any 2 of 1-4

Dermatomyositis:
Definite: 5 plus any 3 of 1-4
Probable: 5 plus any 2 of 1-4
Possible: 5 plus any 1 of 1-4

2017 ACR/EULAR Criteria for Immune Mediated Myopathy



Case 1

A 67 year-old female presents to her internal medicine physician with complaints of a rash on her face, in particular the eyelids. She states it is aggravated when she is in the sunlight. Additionally, she reports of muscle aches and weakness. She has the most difficulty when climbing the stairs or standing up from a seated position. Physical examination is remarkable for a rash that is purple in color and located on the eyelids. She also appears to have a papular rash affecting the knuckles. Lastly, she has weakness of the hip girdle muscles, with the motor strength of bilateral hip flexors and extensors being 3/5.

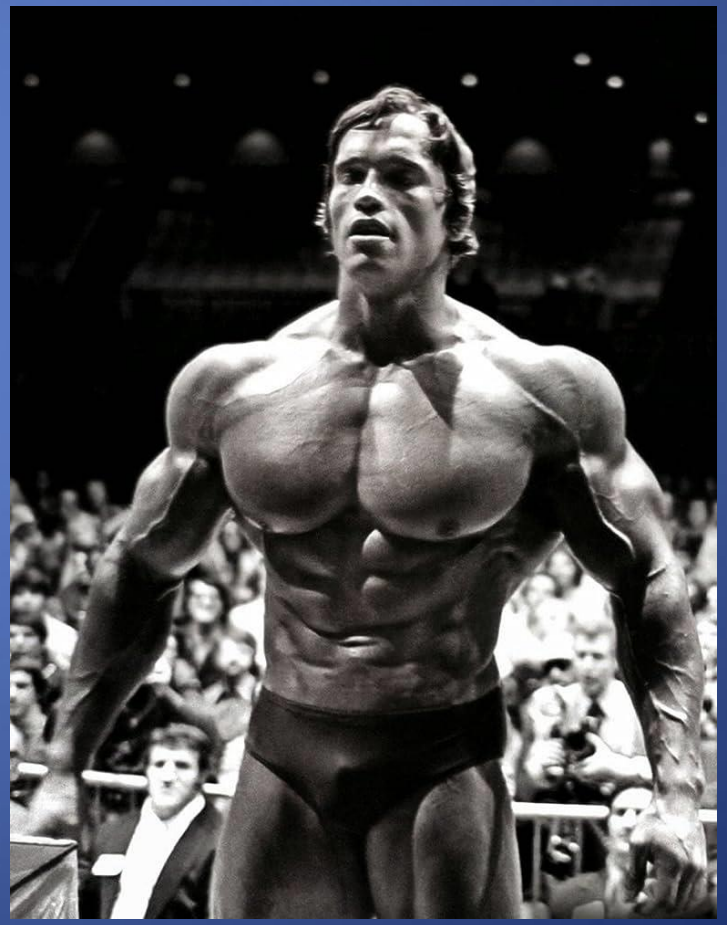
Which muscle enzyme is most sensitive for the detection of this condition?

A. Creatine phosphokinase (CPK)
B. Lactate dehydrogenase (LDH)
C. Aldolase
D. AST
E. ALT

Diagnosis: Muscle Enzymes

- Diagnosis; monitoring
  - Enzymes leak
- Sensitivity: CPK>aldolase>ALT/AST>LDH
- LDH may be most treatment specific

- Variations:
  - Muscle mass
  - Genetics
  - Kidney function



Diagnosis: Muscle Biopsy

- Gold standard for confirmation
- Pitfalls:
  - patchy disease and sampling error
  - Most myopathic muscle has highest yield
  - Biopsy the contralateral muscle to EMG
- Role of MRI mapping?

Clinical Features - Muscle

- Nonspecific fatigue, fevers, weight loss (constitutional, malignancy)
- Usually painless symmetrical muscle weakness
  - proximal>distal
  - stairs, toileting, abduction, neck flexion
  - gait abnormalities
- Dysphagia, nasal regurgitation of liquids
- Hoarseness or dysphonia (nasal voice)
- Ocular or facial weakness→ uncommon
  - consideration of another diagnosis

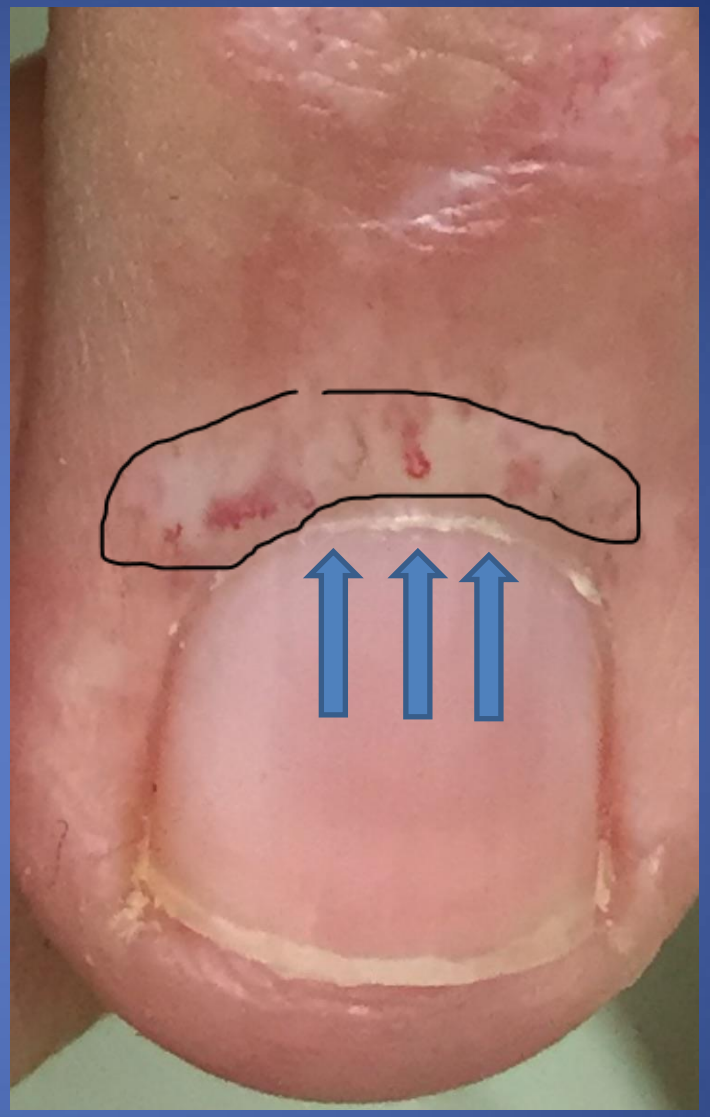
Clinical Features - Skin

- May precede, develop simultaneously or subsequently
  - Heliotrope rash
  - Shawl sign
  - V neck sign
  - Gottron's papules
    - scaly, erythematous or violaceous papules/plaques over hand IP joints
  - Holster sign
  - Samitz sign

Heliotrope rash

Erythematous/violaceous rash over the eyelids, face with/without perioribital edema

Clinical Features: Skin



Gottron’s papules

dilated capillary nailfold loops

Samitz sign

Special Myopathic Syndromes: Amyopathic Dermatomyositis

- Classical cutaneous DM
- No clinically apparent myopathy
- May herald future myopathy (50%)

Special Myopathic Syndromes: Autoantibodies

Autoantibodies	Clinical features
Anti-ARS (antisynthetase)	AS syndrome with moderate-to-serve muscle weakness with high muscle enzyme levels, RP, mechanic's hands, fever, arthritis, and ILD
Anti-Jo-1	Chronic continuous disease course, with clinical symptoms for >two years after diagnosis; mean five-year survival rate = 65%, usually due to ILD; AS syndrome features
Anti-PL-7	AS syndrome with higher frequency of ILD
Anti-PL-12	AS syndrome with higher frequency of ILD
Anti-EJ	Dermatomyositis and ILD
Anti-OJ	Myositis and ILD
Anti-KS	ILD with less myositis
Anti-Ha	NA
Anti-Zo	Myositis and ILD
Anti-SRP	Acute onset NM with severe weakness, high CK, cardiac involvement; refractory to treatment
Anti-Mi-2	Adult DM and JDM with hallmark cutaneous disease, milder myositis with good response to treatment
Anti-TIF1-γ (anti-p155/140)	CAM in adult DM; severe cutaneous disease in adult DM and JDM
Anti-SAE	Adult DM; may present with CADM first
Anti-MDAs (anti-CADM140)	CADM; rapidly progressive ILD
Anti-NXP-2	Predominantly JDM with subcutaneous edema, calcinosis, and servere muscle disease with contractures; increased risk of cancer in some adult DM studies
Anti-HMGCR	NM; associated with statin use in adults; severe proximal muscle weakness; partially responsive to immunosuppressive medications; better response to IVIg

Case 2:

cc: diffuse muscle soreness

HPI: 24 yo African American man with 10 lb wt gain. He usually lifts weights regularly but is just not lifting quite as many pounds as before but there is no definite weakness on exam.

CPK:

What do you do next?

- urgent muscle biopsy
- EMG
- TSH
- urine for myoglobin
- aldolase

Latest Ref Rng	15 - 190 IU/L
9/30/2011	2276 (H)
10/8/2011	2438 (H)
10/17/2011	1982 (H)

Component	CK	TSH	REPORT
Latest Ref Rng	15 - 190 IU/L	0.35 - 4.00 uIU/mL	< OR = 8.1 U/L
9/30/2011	2276 (H)		
10/8/2011	2438 (H)		
10/17/2011	1982 (H)		

Component	CK	TSH	REPORT
Latest Ref Rng	15 - 190 IU/L	0.35 - 4.00 uIU/mL	< OR = 8.1 U/L
9/30/2011	2276 (H)		
10/8/2011	2438 (H)		
10/17/2011	1982 (H)		
1/23/2012		>100 (H)	Aldolase: 10.7 (H)

Component	CK	TSH	REPORT
Latest Ref Rng	15 - 190 IU/L	0.35 - 4.00 uIU/mL	< OR = 8.1 U/L
9/30/2011	2276 (H)		
10/8/2011	2438 (H)		
10/17/2011	1982 (H)		
1/23/2012		>100 (H)	Aldolase: 10.7 (H)
9/8/2012	130	11.58 (H)	

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet.

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class.

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class. Is seen in the health center and labs are unremarkable except:

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class. Is seen in the health center and labs are unremarkable except:

Component	CK
Latest Ref R	<=398 U/L

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class. Is seen in the health center and labs are unremarkable except:

Component	CK
Latest Ref R	<=398 U/L
2/12/2013	**498651 (H)**

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class. Is seen in the health center and labs are unremarkable except:

- Treatment

Component	CK
Latest Ref R	<=398 U/L
2/12/2013	498651 (H)

Case 3

- 24 year old college student notes significant myalgias after track and field practice and feels like he is even dragging his feet. Skipped breakfast and lunch that day as he was running late for class. Is seen in the health center and labs are unremarkable except:

- Treatment

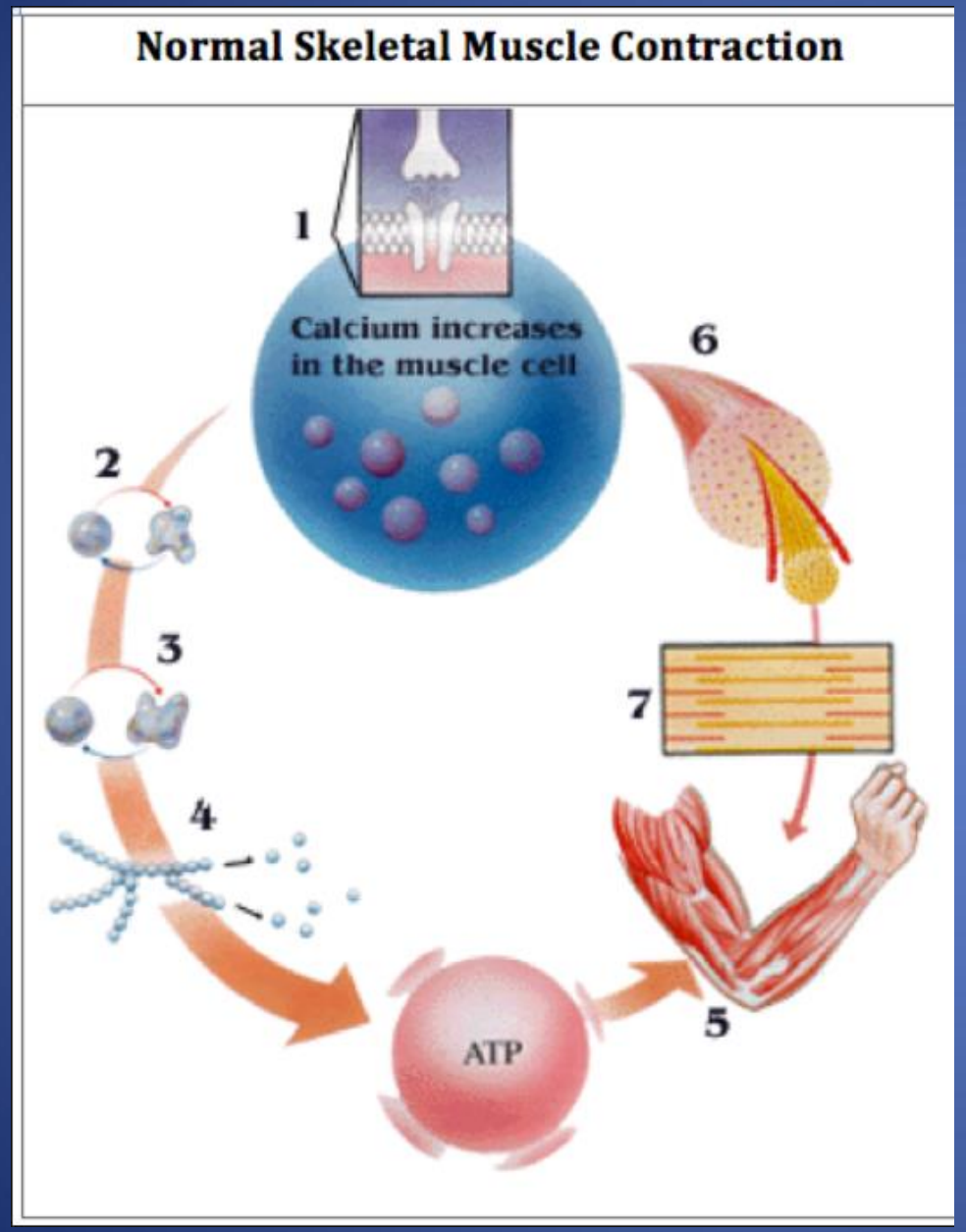
Component	CK
Latest Ref R	<=398 U/L
2/12/2013	**498651 (H)**
2/13/2013	**368800 (H)**
2/19/2015	**31,161 (H)**
4/22/2015	301

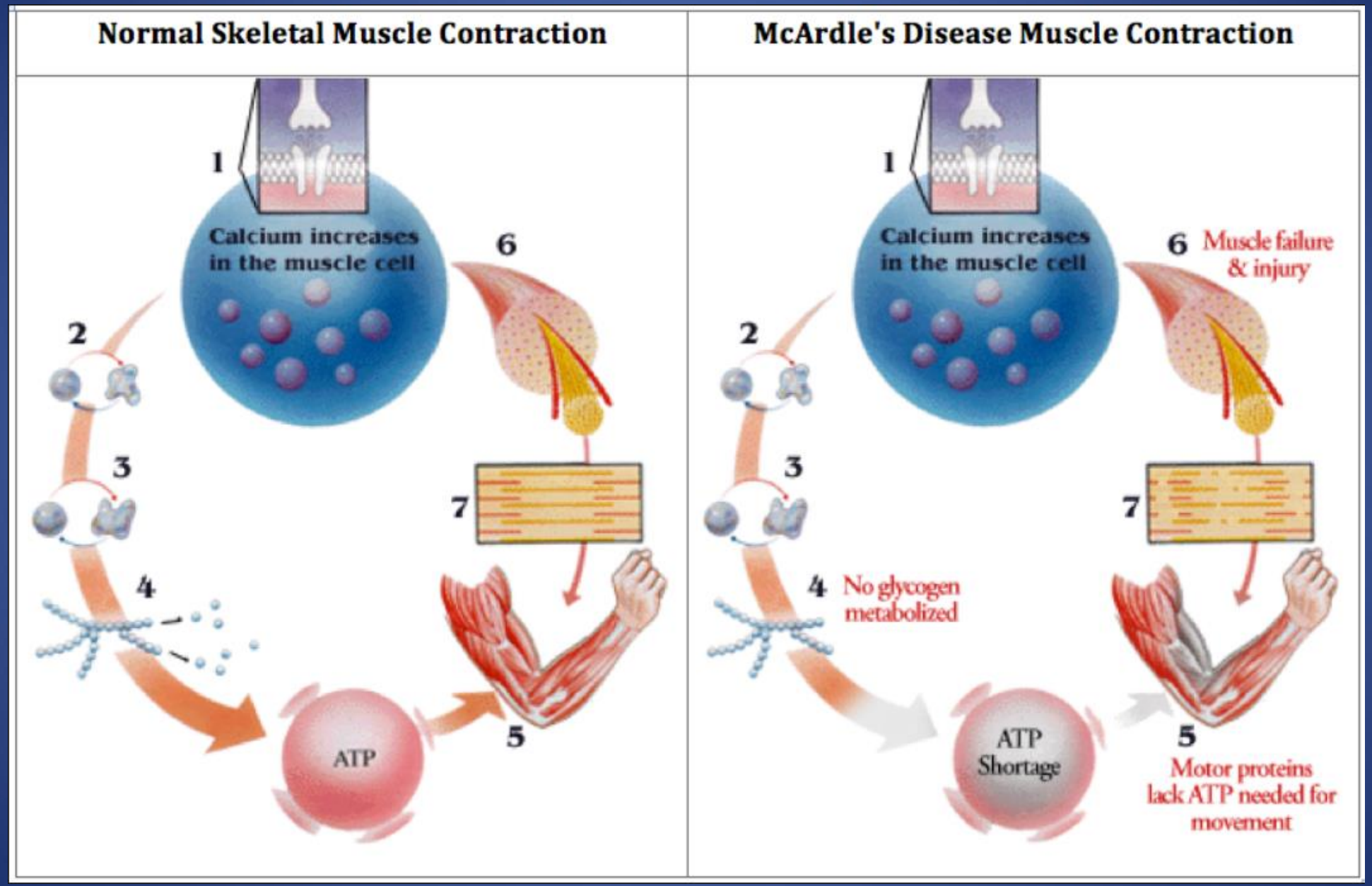
What is this condition?

- Muscle infarction
- ✓ Metabolic myopathy
- Polymyositis
- Muscular dystrophy

What was the treatment?

- glucocorticoids
- hemodialysis
- infliximab
- plasmapheresis
- ✓ cautious monitoring and diet and exercise counseling


Normal Skeletal Muscle Contraction
1
Calcium increases in the muscle cell
2
3
4
ATP
5
6
7


Normal Skeletal Muscle Contraction
1
Calcium increases in the muscle cell
2
3
4
ATP
5
6
7
McArdle's Disease Muscle Contraction
1
Calcium increases in the muscle cell
2
3
4
No glycogen metabolized
ATP Shortage
5
Motor proteins lack ATP needed for movement
6
Muscle failure & injury
7

Differential Diagnosis

- ‘tiredness’ vs ‘fatigue’ vs ‘low energy’
- clinical weakness
  - motor task (muscle weakness)
  - repetitive performance (fatigue)
- ROS (constitutional, ENT, skin, pulmonary)
- Neurological
  - Guillain barre
  - Myasthenia gravis
  - Amyotrophic lateral sclerosis
- Rheumatic
  - Lupus, vasculitis
- Other
  - Neoplastic, metastatic disease
  - Endocrine

General type	Subtypes/examples
Denervating conditions	Spinal muscular atrophies, amyotrophic lateral sclerosis
Sarcoidosis	
Neuromuscular disorders	Eaton–Lambert syndrome, myasthenia gravis
Genetic muscular dystrophies	Duchenne's facioscapulohumeral, limb girdle, Becker's, Emery–Dreifuss type, distal, ocular
Glycogen storage diseases	Adult-onset acid maltase deficiency, McArdle's disease
Lipid storage myopathies	Carnitine deficiency, carnitine palmityltransferase deficiency
Endocrine myopathies	Hypothyroidism, hyperthyroidism, acromegaly, Cushing's disease, Addison's disease, hyperparathyroidism, hypoparathyroidism, vitamin D deficiency myopathy, hypokalemia, hypocalcemia
Metabolic myopathies	Uremia, hepatic failure
Toxic myopathies	Acute and chronic alcoholism, drugs including penicillamine, clofibrate, chloroquine, emetine, statins, niacin, colchicine, checkpoint inhibitors
Nutritional myopathies	Vitamin E deficiency, malabsorption
Acute rhabdomyolysis	
Proximal neuropathies	Guillain–Barré syndrome, acute intermittent porphyria, diabetic lower-limb chronic plexopathies, chronic autoimmune polyneuropathy
Septic myositis	Including Staphylococcus, Streptococcus, *Clostridium perfringens (welchii)* and leprosy

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, M.D., Ph.D.

From the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, and the Johns Hopkins University School of Medicine, Baltimore — both in Maryland. Address reprint requests to Dr. Mammen at the Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 50 South Dr., Rm. 1146, Bldg. 50, MSC-8024, Bethesda, MD 20892, or at andrew.mammen@nih.gov.

N Engl J Med 2016;374:664-9.
DOI: 10.1056/NEJMra1515161

STATINS SIGNIFICANTLY REDUCE THE INCIDENCE OF CARDIOVASCULAR disease, are generally safe, and have an acceptable side-effect profile. Indeed, a recent meta-analysis confirmed that mild musculoskeletal problems, such as myalgia, occur in approximately equal numbers of persons treated with statins and those given placebo.[1] Only in rare cases, in approximately 1 of 10,000 treated persons per year,[2] do statins cause serious muscle damage, with weakness and elevated levels of creatine kinase. In the majority of such cases, the patients recover spontaneously after the statin treatment is discontinued.[3,4] It is now recognized, however, that in very rare cases, an autoimmune myopathy develops in patients treated with statins; this disorder is characterized by muscle weakness, evidence of muscle-cell necrosis on biopsy, and the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.[5-16] In contrast to most patients who have side effects from statin therapy, those with statin-associated autoimmune myopathy may have progressive weakness that must be controlled with immunosuppressive therapy. This review describes the clinical characteristics, diagnosis, proposed pathologic mechanisms, and treatment of statin-associated autoimmune myopathy.

REMARKS	REFERRING PHYSICIAN	REPORTED 10/26/2017 11:53
	LEE	STATUS FINAL

TEST	RESULT (* = OUT OF RANGE)	UNITS	REFERENCE RANGE
TEST NAME:	SEE BELOW		
ANTI-HMGCR AB, (EIA)			
RESULT:	SEE BELOW		
	>200*	Units	
NORMAL RANGE:	<20		

NEGATIVE. . . . . .<20
WEAK POSITIVE. 20-39
MODERATE POSITIVE. . .40-59
STRONG POSITIVE. . . .>=60

ANTI-HMGCR ANTIBODIES ARE USUALLY FOUND IN ASSOCIATION WITH NECROTIZING MYOPATHY RELATED TO STATIN THERAPY. HOWEVER, ABOUT 30% OF ANTI-HMGCR ANTIBODY POSITIVE PATIENTS WITH NECROTIZING MYOPATHY HAVE NEVER BEEN EXPOSED TO STATINS. THE LITERATURE SUGGESTS THAT FALSE POSITIVES ARE EXTREMELY RARE.

Treatment: Medications/non-drug

- Glucocorticoids:
  - high dose prednisone 1 mg/kg/day
  - taper gradually after 4 weeks

- Immunosuppressants:
  - Azathioprine
  - Methotrexate (unless ILD)
  - Mycophenolate mofetil
  - Tacrolimus

- IVIg – monthly x 6

- B cell depletion:
  - Rituximab

- Rehabilitation: muscle reserves
  - passive/active assisted ROM exercises
  - Strengthening/hypertrophy of reserves

Component	CK	REPORT	LDH
Latest Ref Rng	15 - 170 IU/L	< OR = 8.1	91 - 180 IU/L
10/15/2009	6902 (H)	Aldolase: 75.2 (H)	1340 (H)

Component	CK	REPORT	LDH
Latest Ref Rng	15 - 170 IU/L	< OR = 8.1	91 - 180 IU/L
10/15/2009	6902 (H)	Aldolase: 75.2 (H)	1340 (H)
10/23/2009			
10/30/2009	5370 (H)		1319 (H)
11/2/2009			
11/6/2009	7420 (H)	Aldolase: 101.1 (H)	1449 (H)
11/7/2009			
11/30/2009	4024 (H)	Aldolase: 82.6 (H)	1053 (H)
12/11/2009	3314 (H)	Aldolase: 67.8 (H)	772 (H)
1/5/2010	2418 (H)	Aldolase: 50.4 (H)	664 (H)
1/22/2010	251 (H)		459 (H)
2/17/2010	2459 (H)		519 (H)
3/18/2010	913 (H)	Aldolase: 17.8 (H)	345 (H)
4/27/2010	571 (H)	Aldolase: 10.0 (H)	249 (H)
6/3/2010	252 (H)	Aldolase: 4.5	183 (H)
8/11/2010	150	Aldolase: 4.0	175

Component	CK	REPORT	LDH
Latest Ref Rng	15 - 170 IU/L	< OR = 8.1	91 - 180 IU/L
10/15/2009	6902 (H)	Aldolase: 75.2 (H)	1340 (H)
10/23/2009			
10/30/2009	5370 (H)		1319 (H)
11/2/2009			
11/6/2009	7420 (H)	Aldolase: 101.1 (H)	1449 (H)
11/7/2009			
11/30/2009	4024 (H)	Aldolase: 82.6 (H)	1053 (H)
12/11/2009	3314 (H)	Aldolase: 67.8 (H)	772 (H)
1/5/2010	2418 (H)	Aldolase: 50.4 (H)	664 (H)
1/22/2010	251 (H)		459 (H)
2/17/2010	2459 (H)		519 (H)
3/18/2010	913 (H)	Aldolase: 17.8 (H)	345 (H)
4/27/2010	571 (H)	Aldolase: 10.0 (H)	249 (H)
6/3/2010	252 (H)	Aldolase: 4.5	183 (H)
8/11/2010	150	Aldolase: 4.0	175
12/27/2010	181 (H)	Aldolase: 4.7	190 (H)
1/19/2011	132	Aldolase: 5.9	182 (H)
3/30/2011	312 (H)	Aldolase: 6.0	202 (H)
5/5/2011	733 (H)		281 (H)

Prognosis

- Dermatomyositis and Polymyositis
  - 5 year survival is 95%
  - 10 year survival is 84%

- Mortality:
  - pulmonary or systemic complications
  - malignancy
  - medications, infections

- Poor markers:
  - older age at diagnosis
  - delayed treatment
  - cardiac and pulmonary involvement

Conclusions

- Recognize proximal muscle weakness
- Broad differential diagnoses: CPK, weakness
- 2017 myopathy guidelines
- Skin, vascular changes
- Auto antibody work up; medication effects
- Treatments and complications