Myositis and Myopathy

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Myositis Differential

- Dermatomyositis
- Necrotising Myositis
- Inclusion Body Myositis
- Overlap disorders
- Polymyositis
- The trouble with hyperCKemia

Dermatomyositis

- Subacute presentation of proximal muscle pattern of weakness that is typically symmetric and accompanied or preceeded by skin manifestations.
- Can present in Adults and Children.
- Manifestations other than muscle and skin included: Gastrointestinal tract (typically dysphagia), Pulmonary and (rarely) cardiac.
- Associated in some cases with malignancy.

Dermatomyositis Skin Manifestations (Allegedly pathognomonic)

Gottron papules: dorsal metacarpophalangeal and interphalangeal joints may show the presence of overlying erythematous or violaceous papules with or without scaling or ulceration.
Heliotrope rash: This is a characteristic skin finding of dermatomyositis and presents with a violaceous, or an erythematous rash affecting the upper eyelids with or without periorbital edema. This finding may not be apparent in patients with dark skin patients.

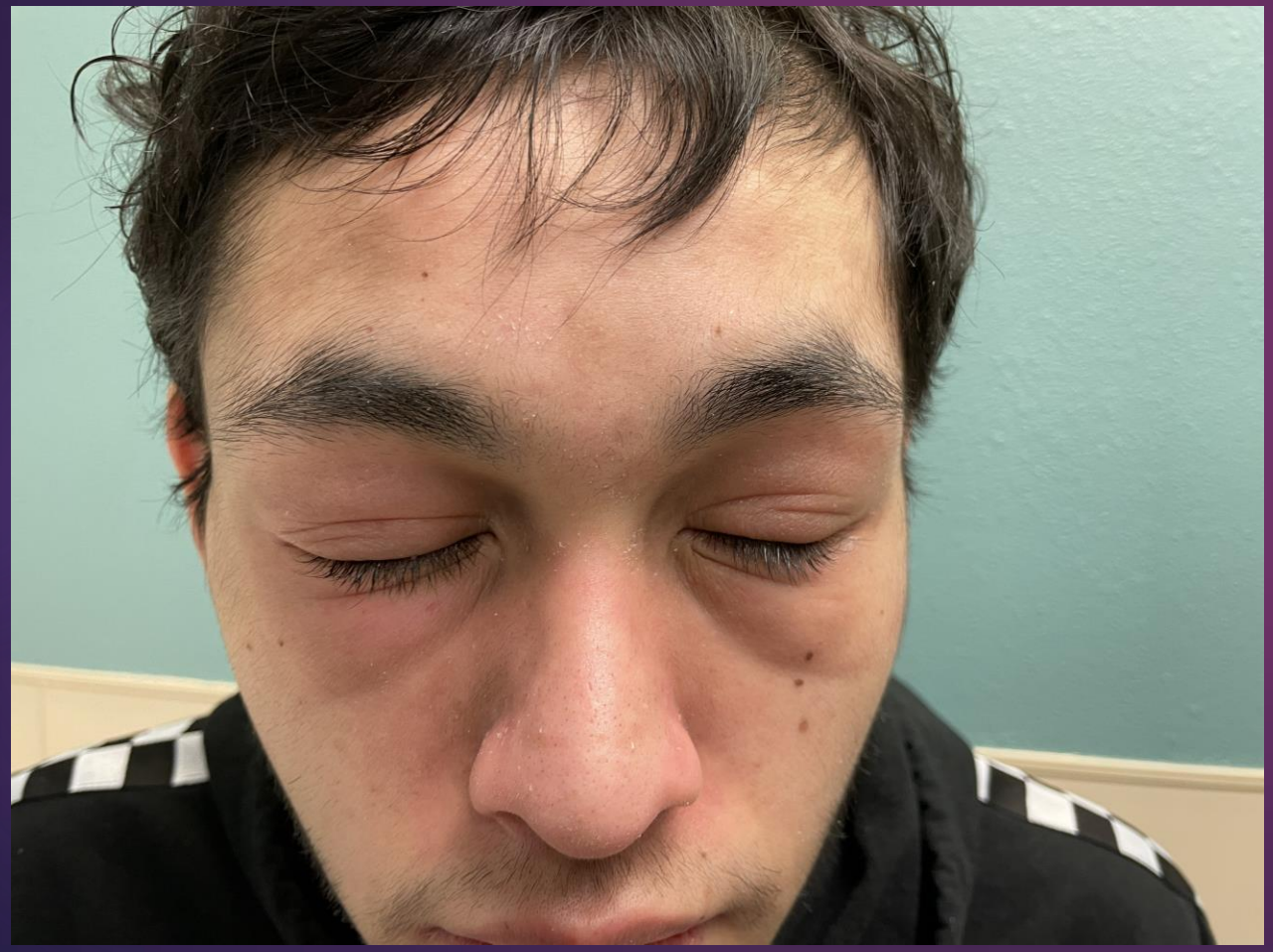
Qudsiya, Zainab., Waseem, Mohammad. (2023). Dermatomyositis Stat Pearls. NIH.

Dermatomyositis Skin Manifestations

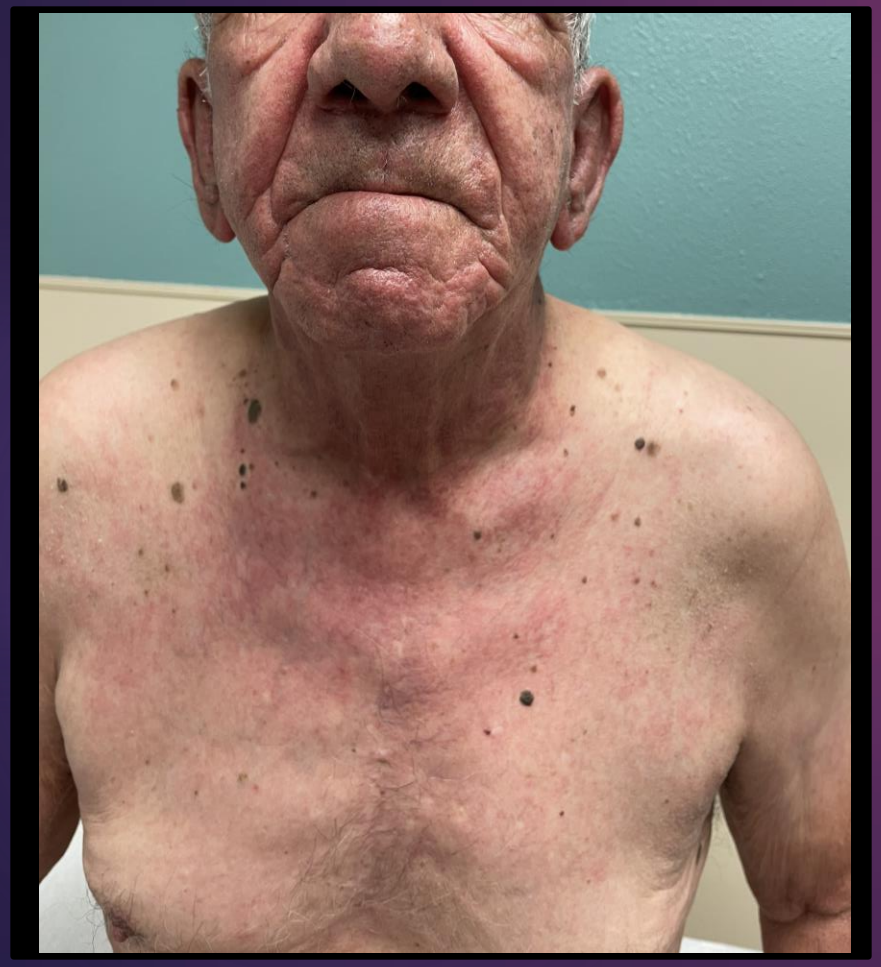
• ***Facial erythema***: erythema over the cheeks and nasal bridge involving the nasolabial folds. The rash may extend up to the forehead and laterally up to the ears.
Gottron sign: erythematous macules or patches over the elbows or knees
• ***Shawl sign***: erythema over the posterior aspect of the neck, upper back, and shoulders at times, extending to the upper arms.
• ***V sign***: ill-defined erythematous macules involving the anterior aspect of the neck and the upper chest.
• ***Poikiloderma***: atrophic skin with changes in pigmentation and telangiectasia in photo-exposed or non-exposed areas.
• ***Holster sign***: poikiloderma involving the lateral aspects of the thighs.
• ***Periungual involvement***: telangiectasias and cuticular overgrowth
• ***Mechanic's hands***: hyperkeratotic, cracked horizontal lines on the palmar and lateral aspects of the fingers.
• ***Scalp involvement***: diffuse poikiloderma, with scaling and pruritis.
• ***Calcinosis cutis***: calcium deposits in the skin

Qudsiya, Zainab., Waseem, Mohammad. (2023). Dermatomyositis Stat Pearls. NIH.

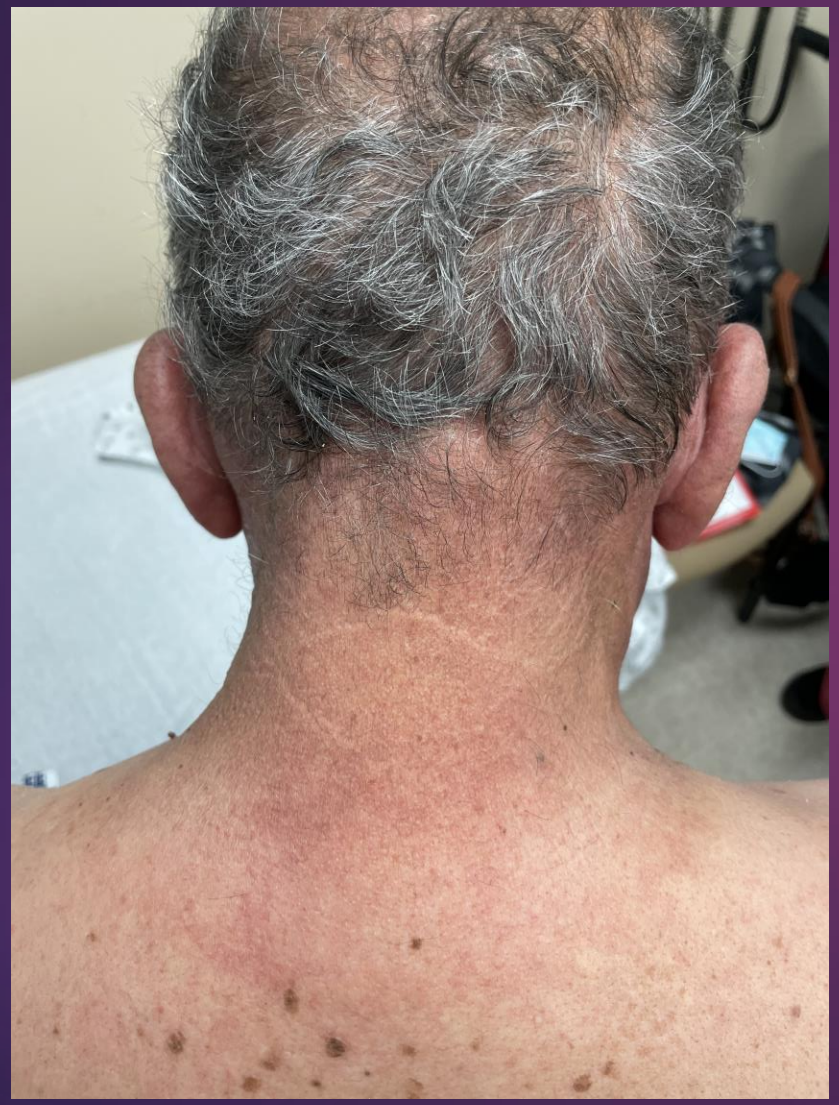
Heliotrope Rash

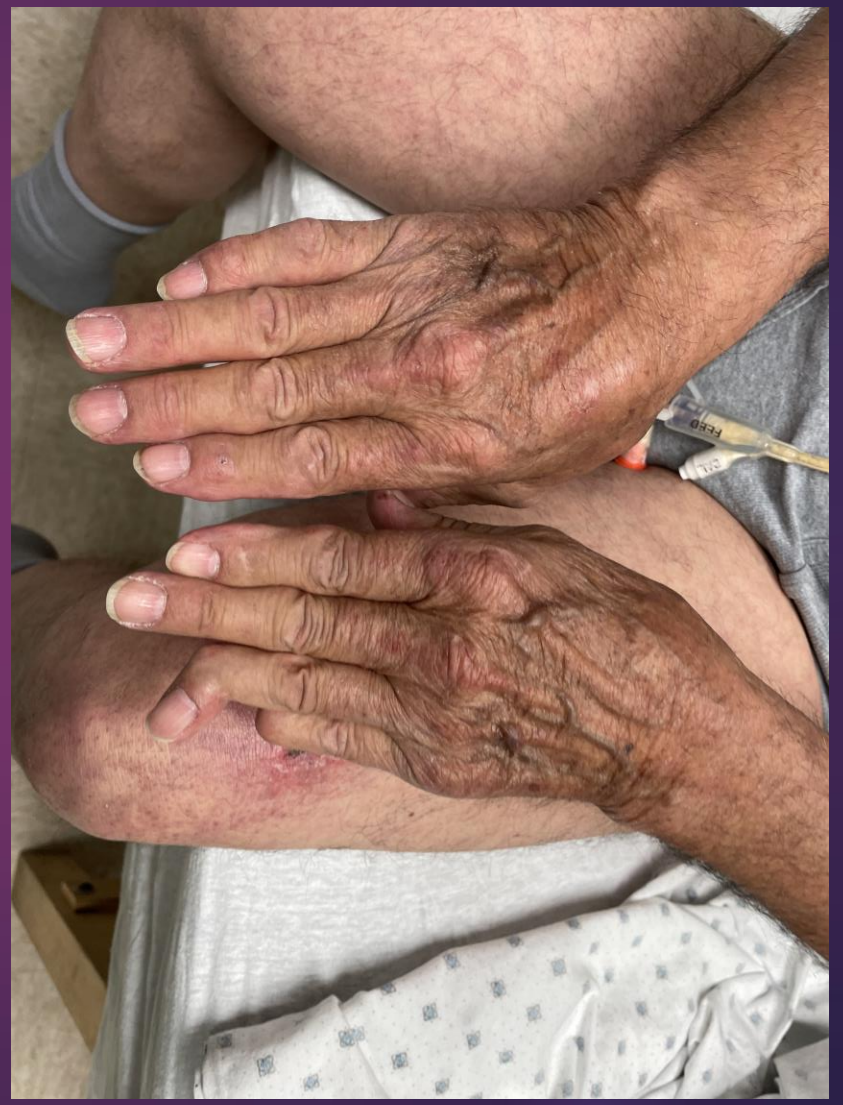


Dermatomyositis Skin Manifestations

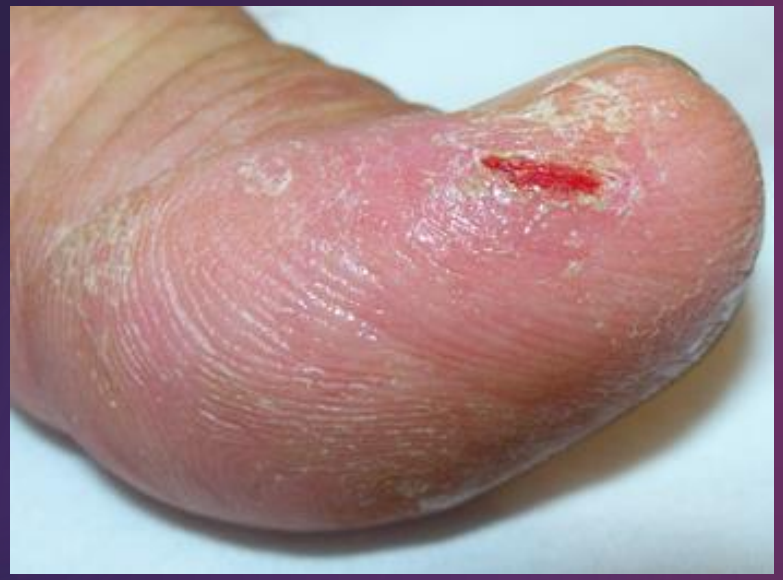


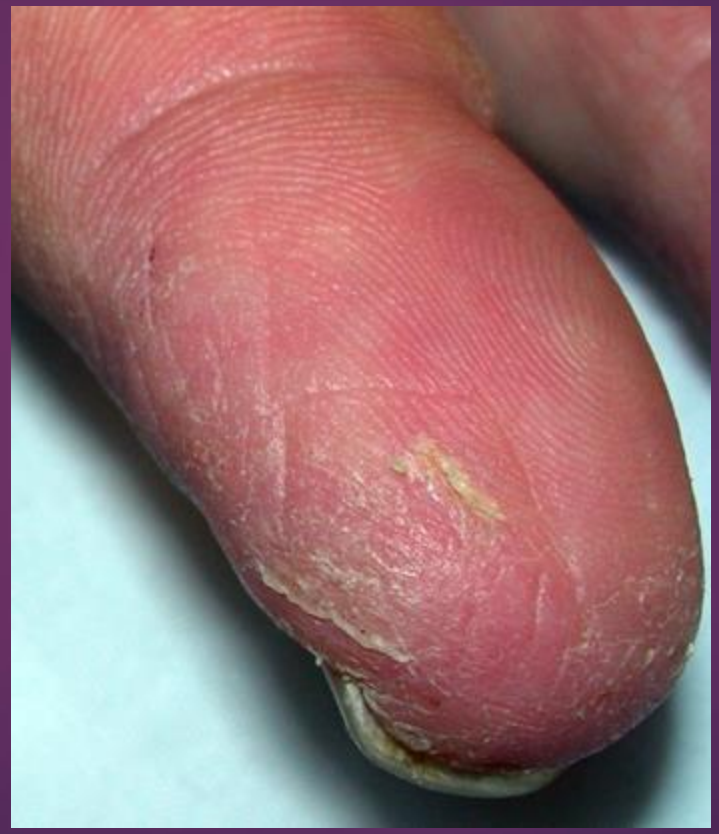
Dermatomyositis Skin Manifestations

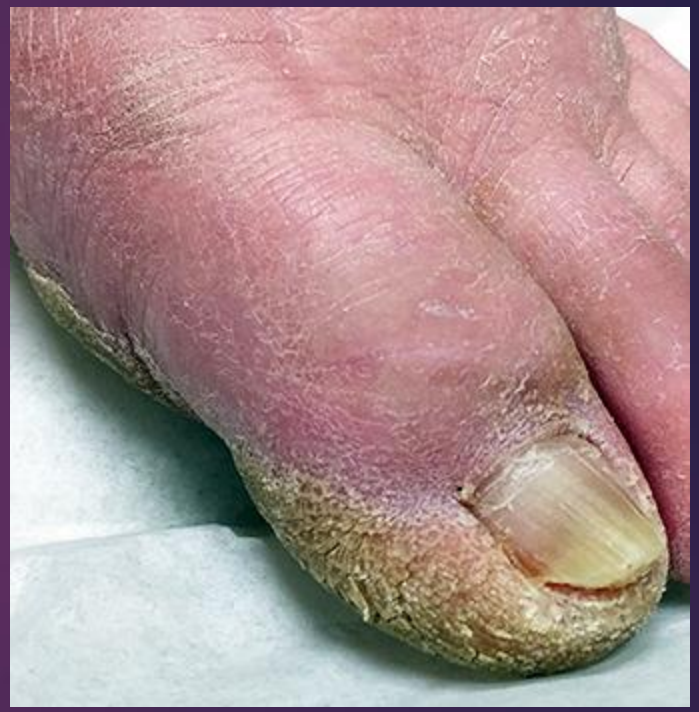




Mechanic's hands (and feet)

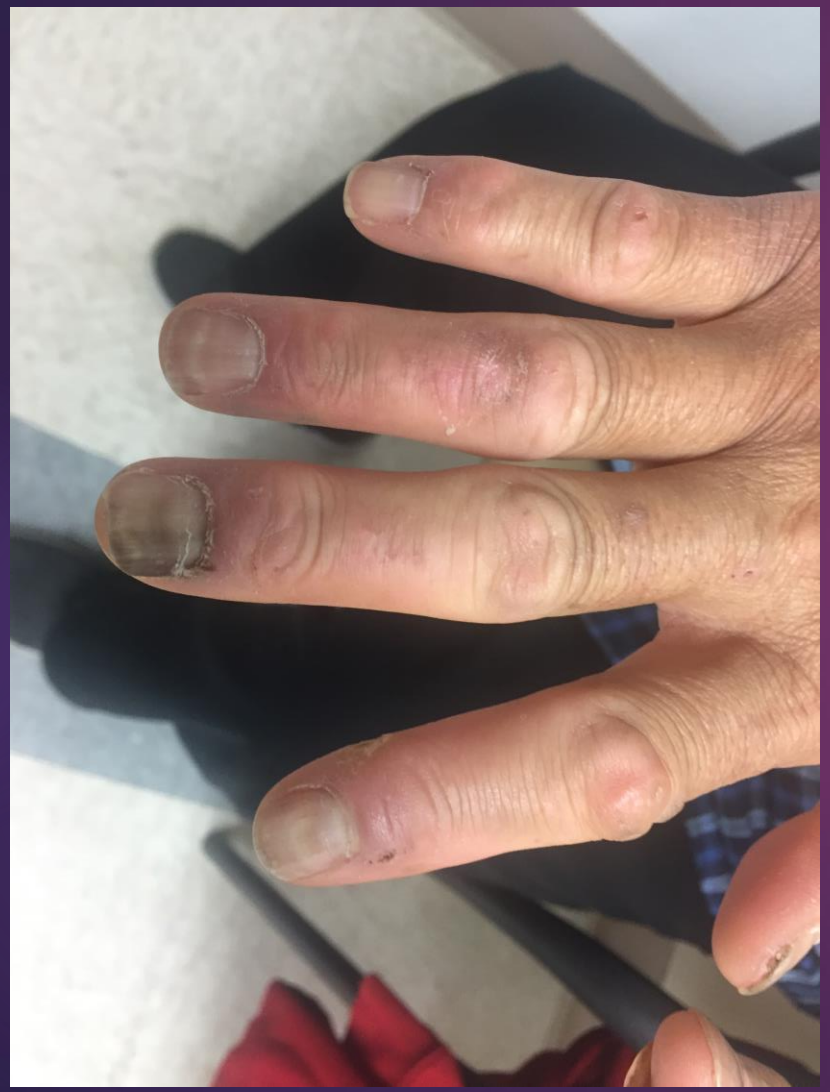






https://neuromuscular.wustl.edu/antibody/infmyop.htm#pm

Mechanic's hands (and feet)



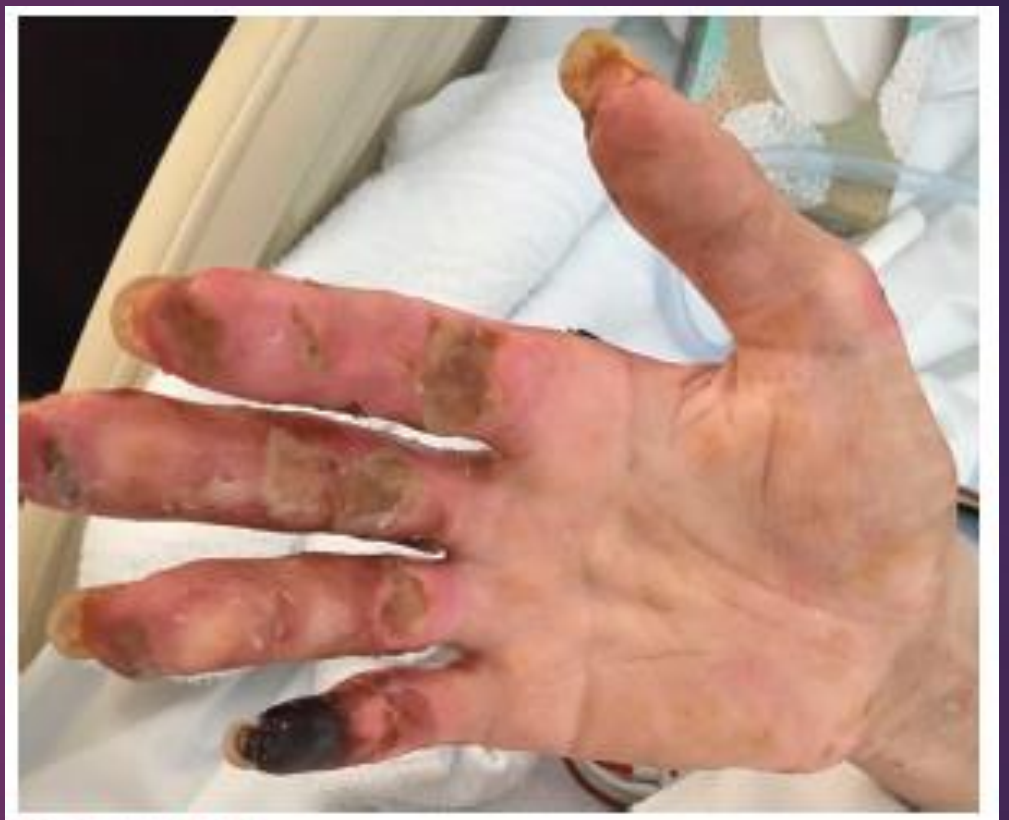
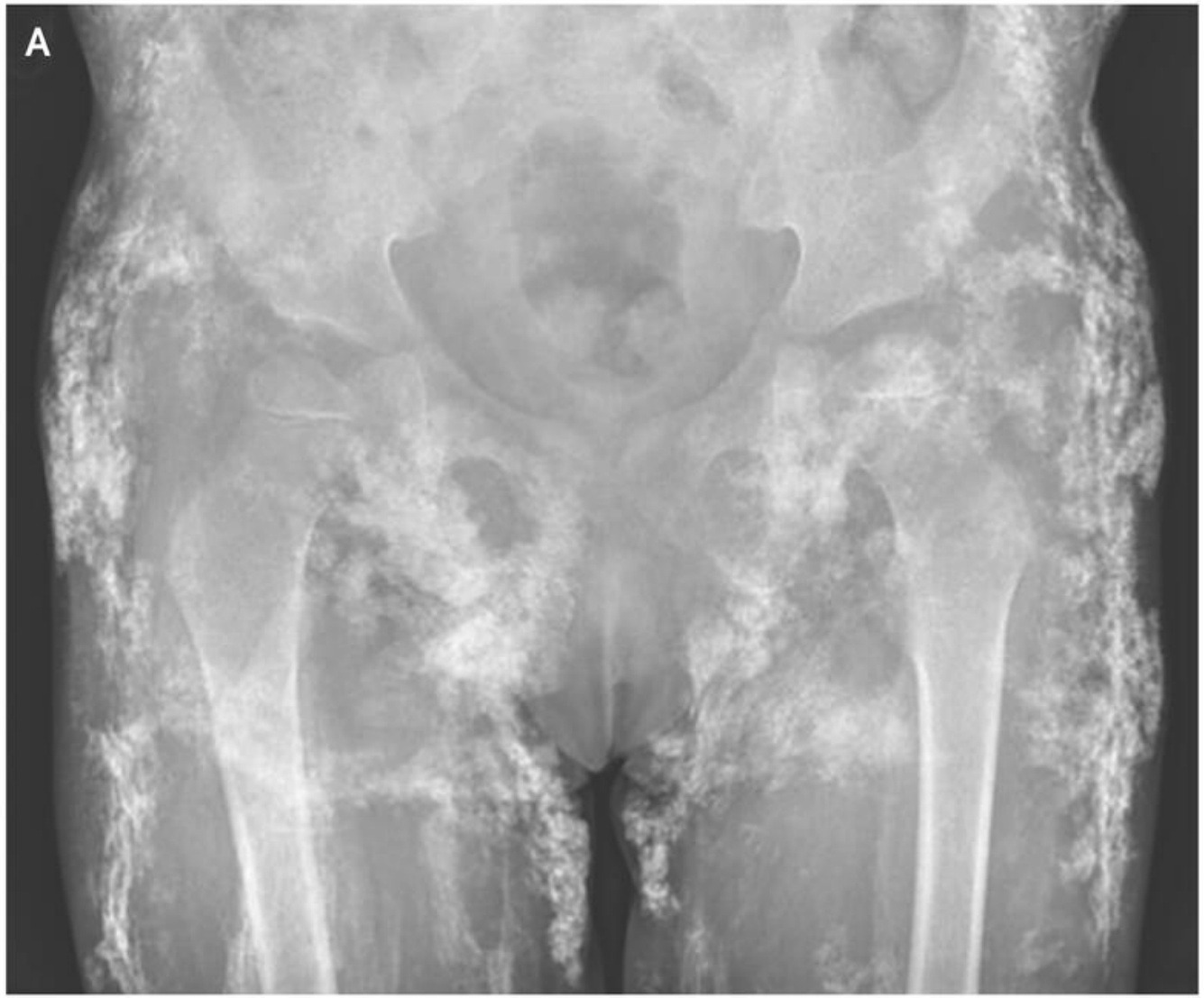
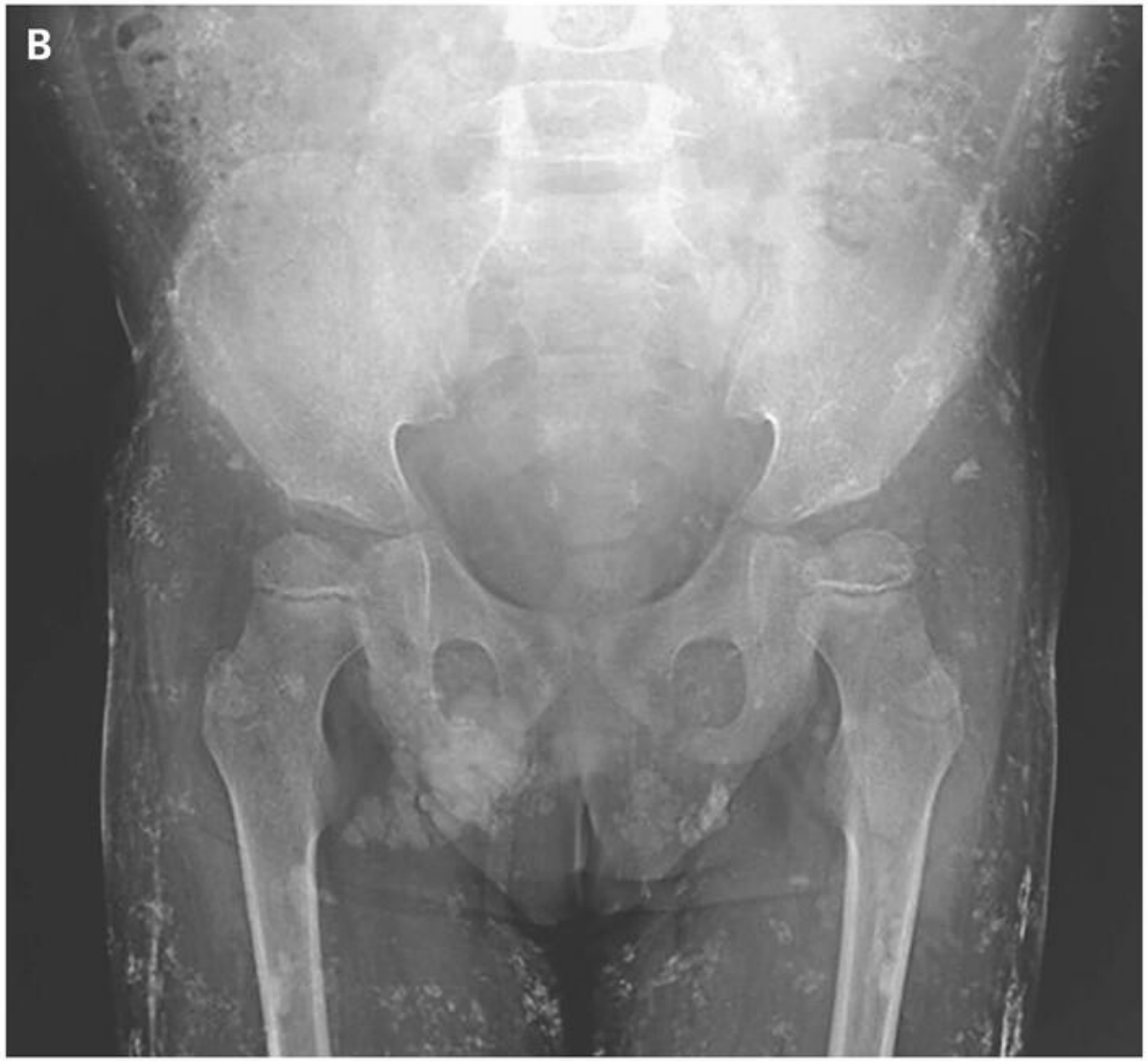


FIGURE 2-7
Severe skin ulceration affecting the interphalangeal joints in a patient with dermatomyositis associated with antibodies to melanoma differentiation-associated protein 5.

Goyal, NM. (2019). Immune-mediated Myopathies.

Calcinosis Cutae





Jianguo Li, M.D., and Zhixuan Zhou. (2019). Calcinosis in Juvenile Dermatomyosis. NEJM.

Dermatomyositis Workup

- CK – can be normal in some variants but is often > 1000.
- EMG/NCS – Can be helpful but usually doesn't change management. Irritable findings are common on needle study. Myopathic motor units can be seen but neurogenic is possible as well. Absence of EMG findings should not prompt abandoning workup.
- MRI thighs or upper arms – Can have T2 findings primarily in thighs > deltoids but can see in both. Similar to necrotizing myositis.
- Dermatomyositis autoantibody testing.
- Malignancy workup particularly with TIF-1-gamma and NXP-2 autoantibodies.
- Muscle Biopsy – Still gold standard for histopathologic diagnosis

Dermatomyositis Auto-antibodies

Myositis-Specific Antibodies (Based on Subtype of Myositis)	Characteristic Clinical Features
Dermatomyositis	
Anti-Mi-2	Classical skin rash, moderate muscle involvement, favorable response to immunotherapy
Anti-TIF-1γ	Strong association with cancer, severe skin rash, hypopigmented red on white patches, variable degree of muscle involvement
Anti-NXP-2	Increased risk of malignancy, classic skin rash, mild-to-moderate muscle involvement, subcutaneous calcifications, peripheral edema
Anti-MDA-5	Severe skin rash, no/minimal muscle involvement, skin ulcerations, rapidly progressive interstitial lung disease
Anti-SAE	Classic rash, mild muscle involvement, dysphagia

Goyal, NM. (2019). Immune-mediated Myopathies.

Dermatomyositis Auto-antibodies

Myositis-Specific Antibody	Muscle	Skin	Lung	Cancer
Dermatomyositis				
Mi-2	X	X		
TIF-1γ	X	X		X
NXP-2	X	X		X
MDA-5		X	X	
Antisynthetase				
Jo-1	X		X	
PL-7	X		X	
PL-12			X	
Immune-mediated necrotizing myopathy				
Signal recognition particle (SRP)	X			
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	X			
Antibody-negative immune-mediated necrotizing myopathy	X			X

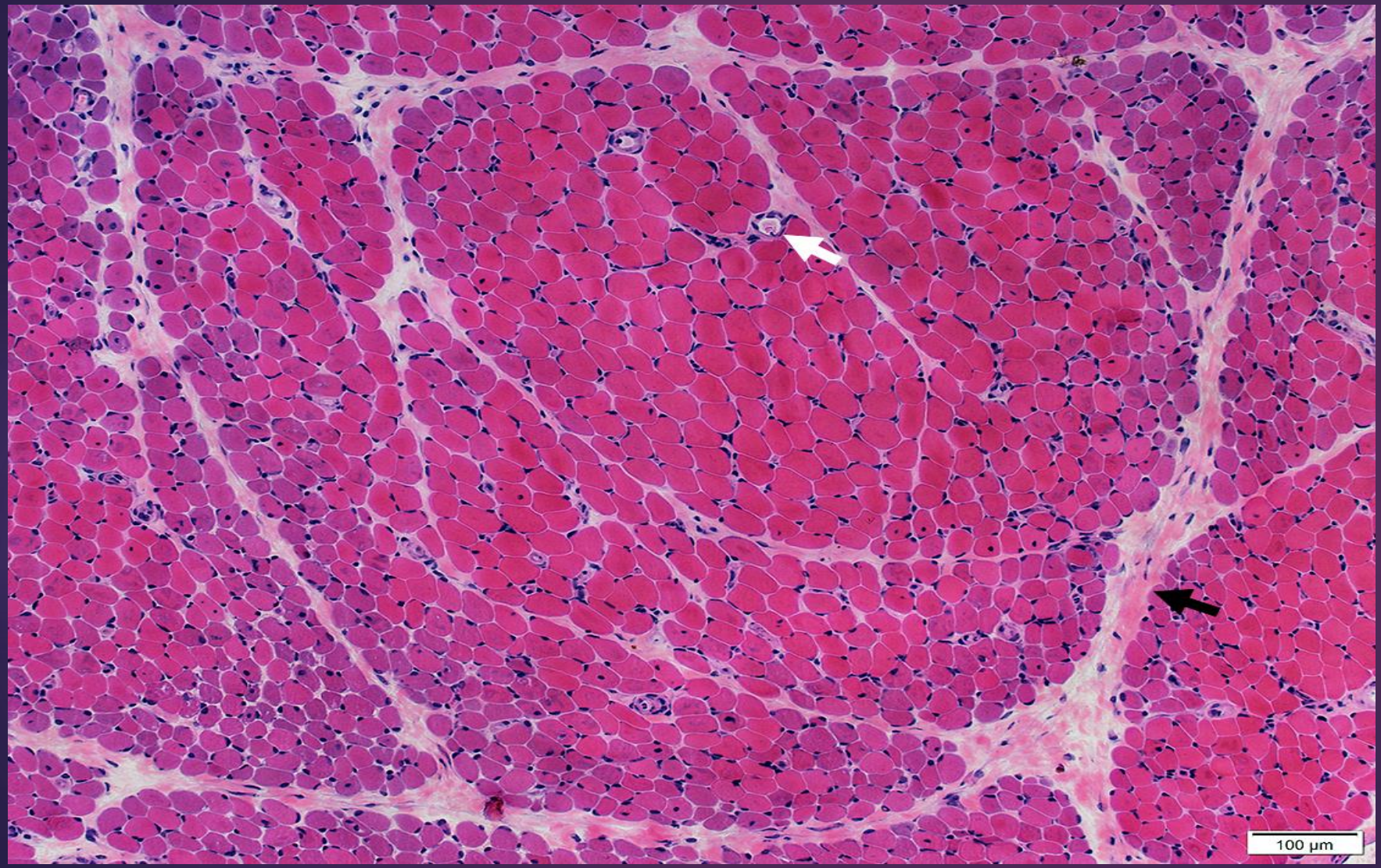
Goyal, NM. (2019). Immune-mediated Myopathies.

Dermatomyositis – Muscle Biopsy

- Muscle biopsy often shows the following findings, which can be diagnostic:
- *Perivascular and perimysial inflammatory infiltrate:* The infiltrate in dermatomyositis is concentrated around the perivascular and interfascicular regions and consists of B cells, CD4+ T helper cells, macrophages, and plasmacytoid dendritic cells. In contrast to polymyositis, CD8+ T cells and NK cells are rarely present.
- *Perifascicular atrophy*: Atrophy of muscle fibers, especially around the periphery of fascicles, is a hallmark histopathological feature of dermatomyositis. Degenerating and regenerating muscle fibers may be observed in the perifascicular region.
- *Microangiopathy*: Injury to intramuscular blood vessels takes the form of immunoglobulin and complement (C5b-C9 membrane attack complex) deposits on endomysial capillaries. A reduced capillary density and endothelial hyperplasia may be observed.

Qudsiya, Zainab., Waseem, Mohammad. (2023). Dermatomyositis Stat Pearls. NIH.

Dermatomyosis histopathology



Atrophic Muscle Fibers: Near Avascular Perimysial Connective tissue (Dark arrow) surrounding fascicle

Larger Muscle fibers: Within fascicle near intermediate sized perimysial vessels

Vessel in Vascular Perimysium: White Arrow

https://neuromuscular.wustl.edu

Antisynthetase Syndrome and Overlap Syndrome and Mixed Connective Tissue Disease

"Furthermore, clinical characteristics of patients with ASSD and IIM-SSc overlap patients might be similar. The presence of mechanic's hand, interstitial lung disease, Raynaud's phenomenon, and myositis is frequently found in both clinical syndromes. There is also recent literature data that supports the common pathogenic origin of PM/Scl OM and ASSD. However, the genetic features of IIM-SSc overlap patients are not known; thus, comparing clinical profile and genetic features of patients with ASSD and IIM-SSC OM might help us better understand the pathomechanism of this disease."

Szabo et al. (2022). Clinical, Serological, and Genetic Characteristics of a Hungarian Myositis-Scleroderma Overlap Cohort. Biomedical Research Institute.

Overlap Syndrome

- "Autoimmune myopathy may be associated with other well-defined autoimmune connective tissue disorders, known as overlap syndromes and include systemic lupus erythematous, Sjögren syndrome, rheumatoid arthritis, and systemic sclerosis. Although significant muscle weakness is not a typical feature in most of these isolated connective tissue conditions (and when present may be the result of disuse atrophy or arthritis), proximal muscle weakness is noted in patients with overlap myositis when a concurrent myositis exists with a known connective tissue disease."

Goyal, NM. (2019). Immune-mediated Myositis. Continuum Neurology.

Antisynthetase Syndrome Auto-antibodies

Antisynthetase syndrome	
Anti-Jo-1	Muscle involvement common, progressive interstitial lung disease, may have mild skin rash and mechanic's hands
Anti-PL-7	Severe interstitial lung disease, may have moderate muscle involvement
Anti-PL-12	Severe interstitial lung disease, may have mild or no muscle involvement
Anti-glycyl-transfer RNA synthetase (EJ), anti-OJ, anti-KS	High association with interstitial lung disease
Anti-Zo, anti-Ha	Rare, possible interstitial lung disease

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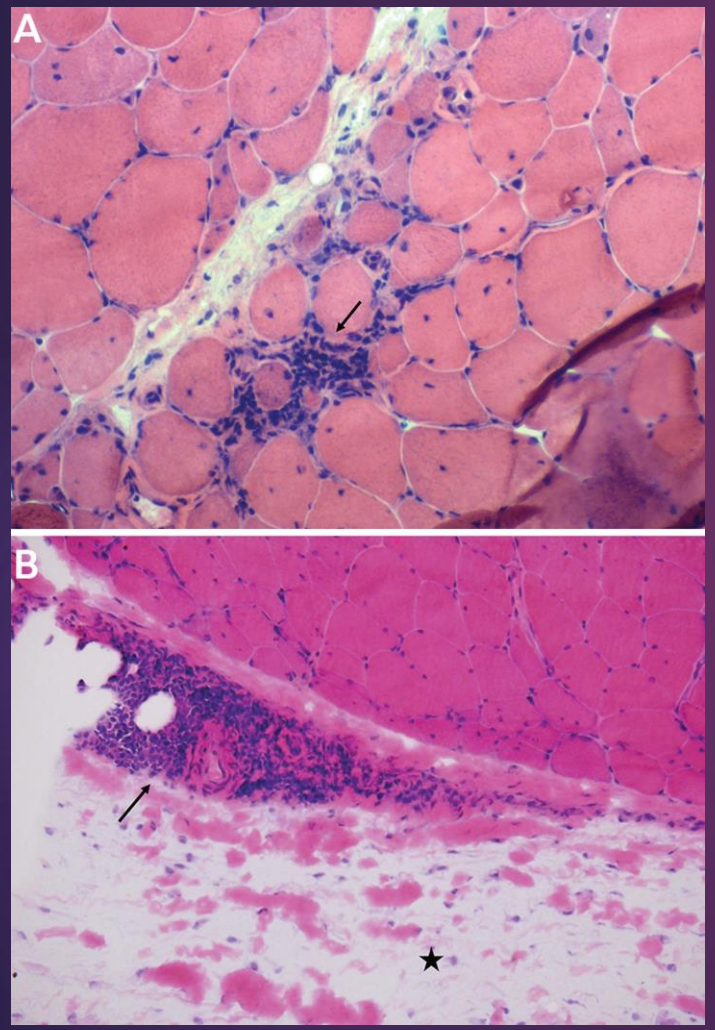
Antisynthetase histopathology



Muscle biopsy of a patient with anti–Jo-1 antisynthetase syndrome (hematoxylin and eosin stain). A, Muscle fiber undergoing necrosis in the perifascicular region of the biopsy (arrow). B, Perimysial fragmentation of the connective tissue (star) and inflammation surrounding vessels (arrow).

Goyal, NM. (2019). Immune-mediated Myopathies.

Dermatomyositis Auto-antibodies

Myositis-Specific Antibody	Muscle	Skin	Lung	Cancer
Dermatomyositis				
Mi-2	X	X		
TIF-1γ	X	X		X
NXP-2	X	X		X
MDA-5		X	X	
Antisynthetase				
Jo-1	X		X	
PL-7	X		X	
PL-12			X	
Immune-mediated necrotizing myopathy				
Signal recognition particle (SRP)	X			
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	X			
Antibody-negative immune-mediated necrotizing myopathy	X			X

Goyal, NM. (2019). Immune-mediated Myopathies.

Anti-synthetase/Overlap Myositis Workup

- CK – can be normal in some variants and usually < 1000 but can be higher in some autoantibodies.
- EMG/NCS – Can be helpful but usually doesn't change management. Irritable findings are common on needle study. Myopathic motor units can be seen but neurogenic is possible as well. Absence of EMG findings should not prompt abandoning workup.
- MRI thighs or upper arms – Can have T2 findings primarily in thighs > deltoids but can see in both. Similar to necrotizing/dermato myositis.
- Autoantibody testing.
- CT imaging for interstitial lung disease and other systemic evaluations.
- Muscle Biopsy – Still gold standard for histopathologic diagnosis and appears quite similar to biopsies of dermatomyositis.

Necrotizing Myositis

- Also known as Immune Mediated Necrotizing Myopathy (IMNM) or Necrotizing Autoimmune Myositis (NAM).
- Severe proximal muscle weakness with highly elevated CKs (median 4700) with minimal extramuscular involvement.
- Can see dysphagia and respiratory issues though this is likely still a skeletal muscle involvement.

Workup in Necrotizing Myositis

- CK (usually markedly elevated) typically ~ 2000 – 10000.
- EMG/NCS – Can be helpful but usually doesn't change management. Irritable findings are common on needle study. Myopathic motor units can be seen but neurogenic is possible as well. Absence of EMG findings should not prompt abandoning workup.
- MRI thighs or upper arms – Can have T2 findings primarily in thighs > deltoids but can see in both.
- Necrotizing myositis autoantibody testing – HMGCR, SRP.
- Muscle Biopsy – Still gold standard for histopathologic diagnosis.

Serum Testing in Necrotizing Myositis

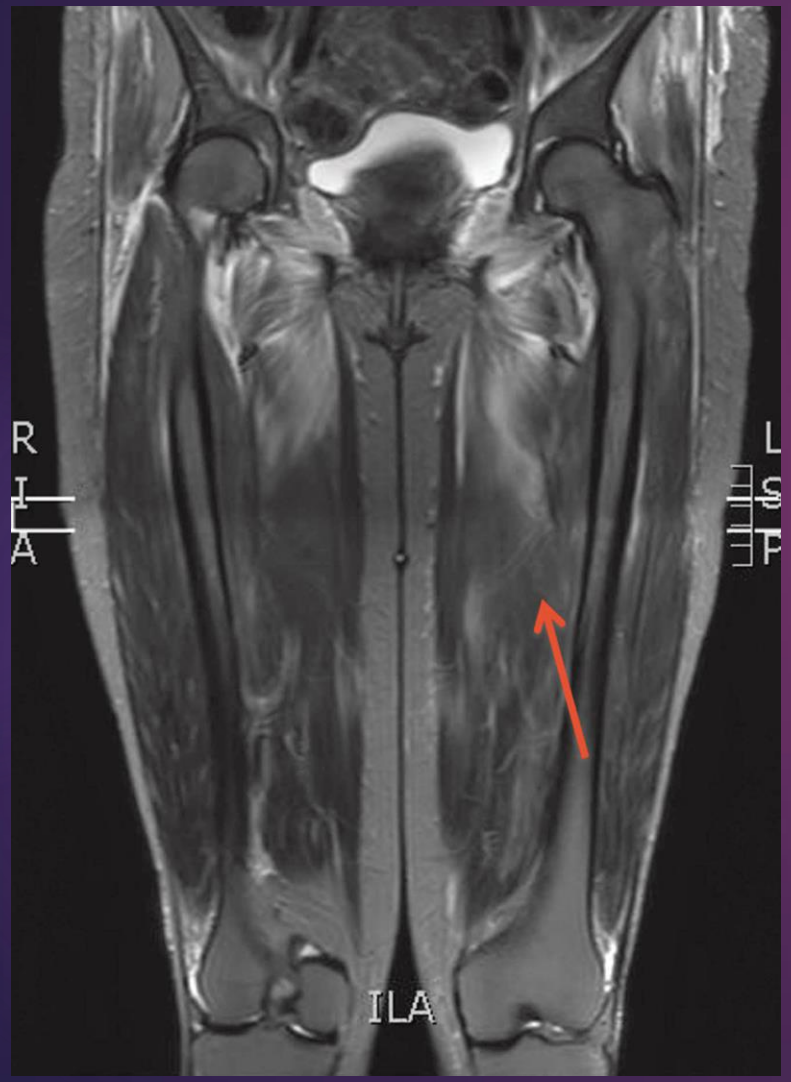
- HMGCR is so-called "statin myopathy". While it *is* associated with statins, the weakness and CK elevation persists despite stopping statins and can be seen in patients that have never taken statins. Rituximab has also been used to well demonstrable benefit.
- Anti-SRP is a more aggressive form of necrotizing myositis and typically needs triple therapy of steroids, non-steroidal oral anti-inflammatories like Azathioprine AND IVIg. Rituximab has also been used to well demonstrable benefit.
- Seronegative must be diagnosed by biopsy but response to this to immunomodulation is still well documented.

Necrotising Myositis Auto-antibodies

Immune-mediated necrotizing myopathy	
Anti–signal recognition particle (SRP)	Severe muscle involvement, rare but occasional lung involvement, no skin involvement
Anti–3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase	Severe muscle involvement, prior statin use (but 30% statin naïve), no skin or lung involvement
Antibody-negative immune-mediated necrotizing myopathy	Increased risk of malignancy

Goyal, NM. (2019). Immune-mediated Myopathies.

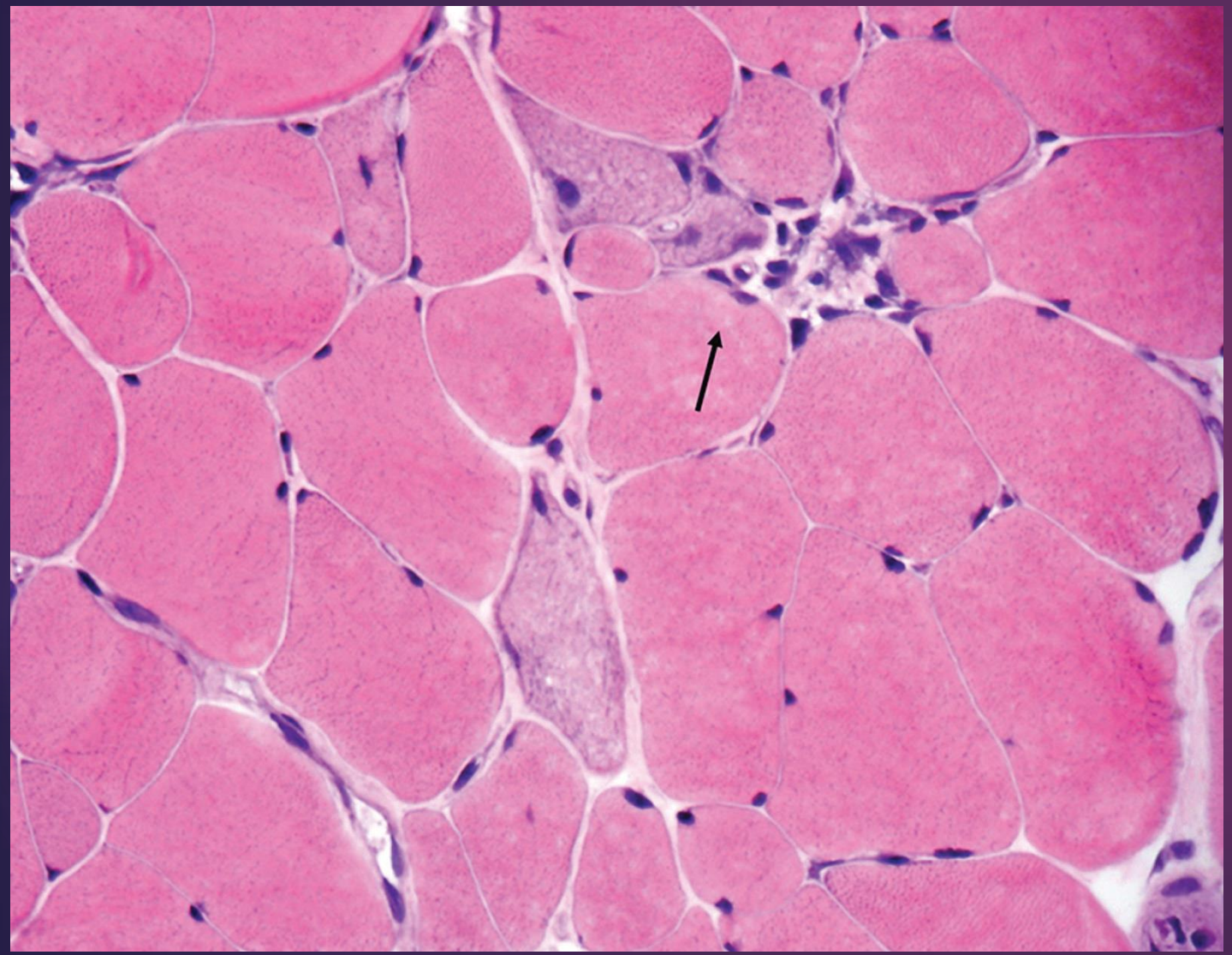
Necrotizing Myositis MRI



Thigh muscle MRI of a patient with immunemediated necrotizing myopathy. Patchy hyperintensity seen throughout the anterior compartment of the thigh (arrow, coronal section, short tau inversion recovery sequences) indicating edema in a patient with immune-mediated necrotizing myopathy and a creatine kinase elevation of 3000 U/L.

Goyal, NM. (2019). Immune-mediated Myopathies.

Necrotizing myositis histopathology



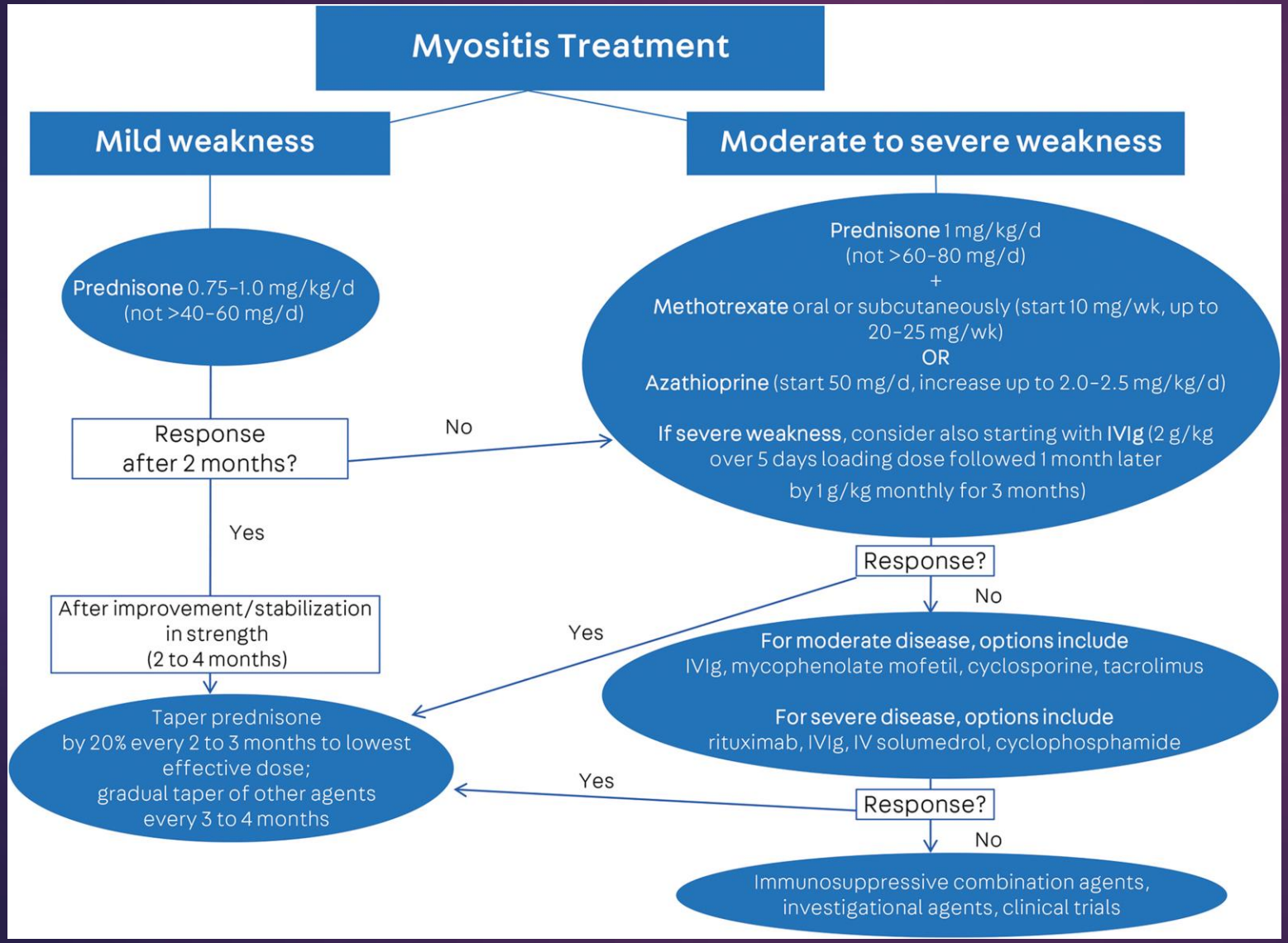
Muscle biopsy of a patient with anti–3-hydroxy-3-methylglutaryl coenzyme A reductase immune-mediated necrotizing myopathy (hematoxylin and eosin stain). Necrotic and degenerating muscle fibers (arrow) are seenwith a lack of lymphocytic endomysial inflammation.

Goyal, NM. (2019). Immune-mediated Myopathies.

Treatment

- Treatment of most Immune-mediated myositis will involve some combination of steroids, oral non-steroidal, IVIg and Rituximab are the mainstay.
- Mammen and Tiniakou (2015) found significant improvement in HMGCR patients on IVIg alone though there is suspicion that other immune-mediated myopathies may show similar findings.
- Treatment of overlap syndrome and anti-synthetase depending on the other systems involved may see benefit from more rheumatology specific treatments like Infliximab, Tociluzimab, Etanercept. This is by no means an exhaustive list.

Treatment Algorithm



Goyal, NM. (2019). Immune-mediated Myopathies.

Inclusion Body Myositis

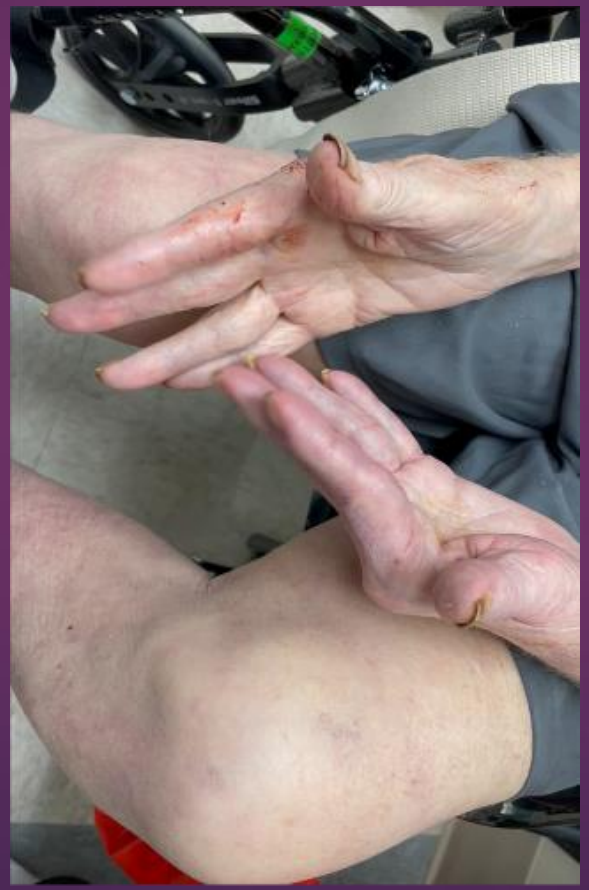
History and Epidemiological Features

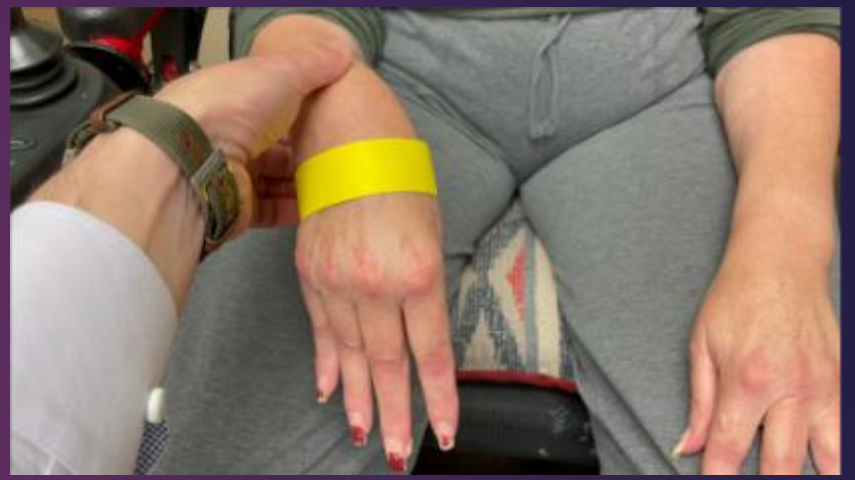
1. Age of onset later than 45 years (there are now exceptions to this)
2. Duration of symptoms more than 12 months
3. Serum creatine kinase level, not more than 15 times the upper limit of normal

Clinical Features:

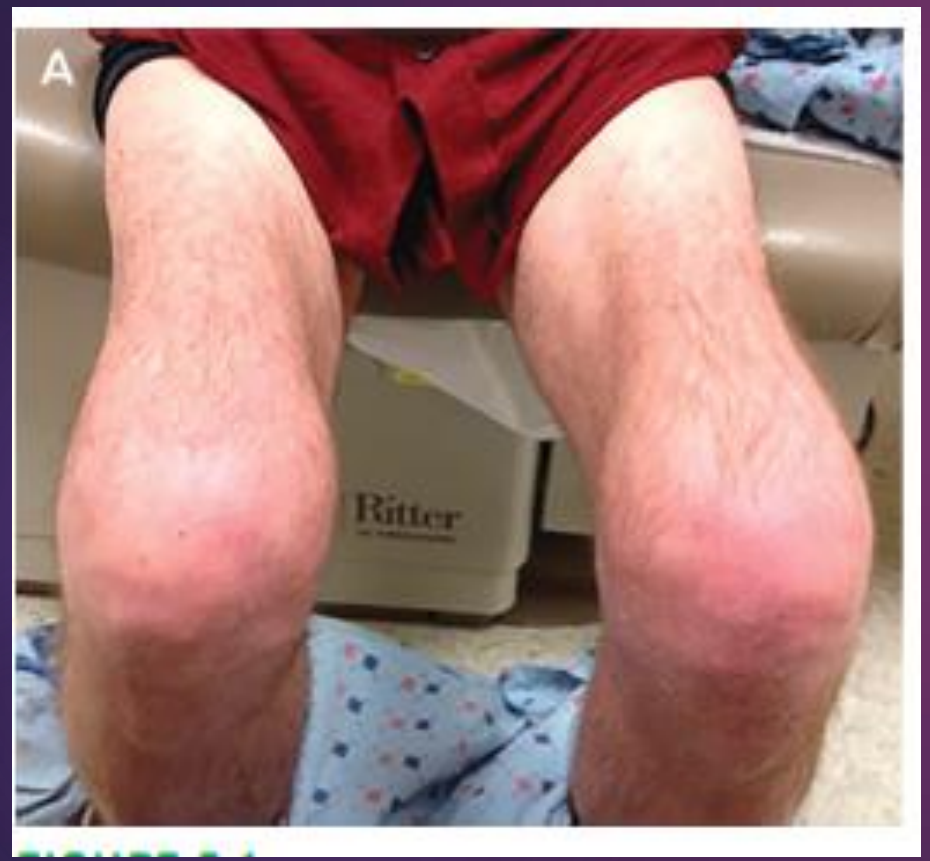
1. A weakness of quadriceps more than hip flexors with associated atrophy
2. A weakness of finger flexors more than shoulder abductors (deltoids)
3. Dysphagia

Flexor Digitorum Profundus Weakness in IBM





Quadriceps Weakness and Atrophy in IBM



Goyal, NA. (2022). Inclusion Body Myositis. Continuum Neurology.

Workup in IBM

- CK (usually modestly elevated or normal) If over 1200, would consider alternative diagnosis.
- EMG/NCS – Usually not helpful. Can find myopathic findings but rare. Chronic IBM usually looks neurogenic on EMG which can prompt incorrect evaluation if EMGer is not experienced with neuromuscular diseases.
- MRI thighs or forearms – Can show fatty replacement (T1 sequences) or edema/inflammation (T2 sequences).
- NT5C1A antibody testing – Positive in approximately 60% of IBM patients. It's fairly good specificity if the neuro examination is supportive but false positives have been reported in other inflammatory myopathies and ALS.
- Muscle Biopsy – Still gold standard for histopathologic diagnosis
- Barium Swallow and Speech/Swallow evaluation

MRI of thighs in IBM

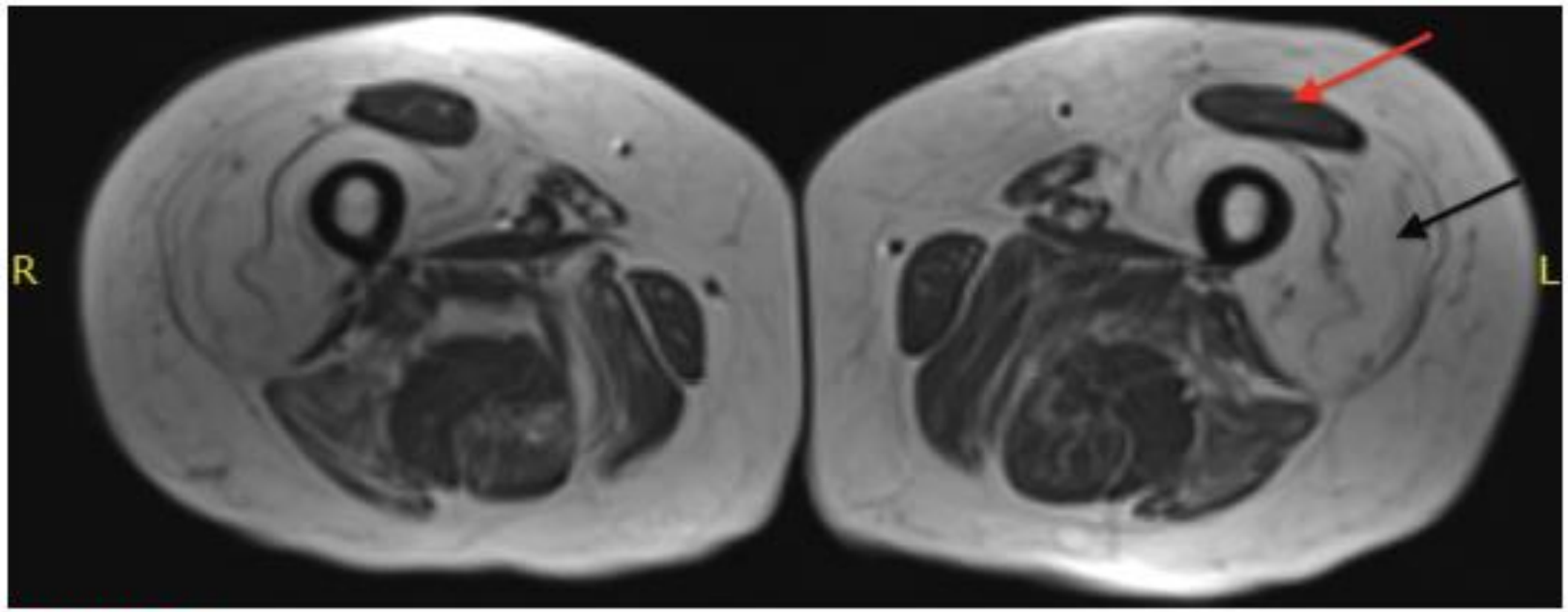


FIGURE 5-4
Axial T1-weighted MRI of the thigh muscles of a patient with inclusion body myositis. Significant hyperintensity indicative of fatty infiltration is seen in the anterior compartment muscles of the thigh, predominantly affecting the vastus lateralis (*black arrow*) and vastus medialis, yet with relative sparing of the rectus femoris (*red arrow*) and the posterior compartment muscles.

Goyal, NA. (2022). Inclusion Body Myositis. Continuum Neurology.

IBM pathological features and diagnosis

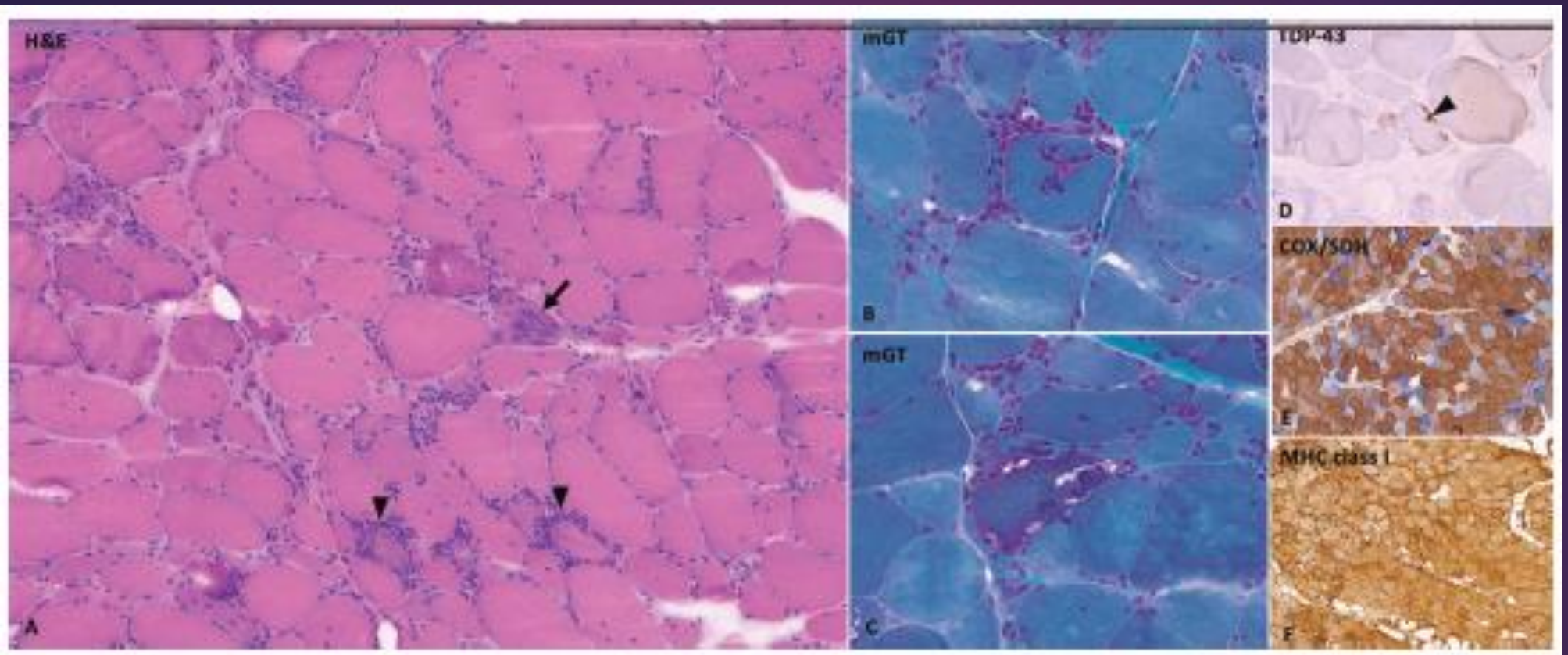
- ***Pathological Features:***

1. Endomysial inflammatory infiltrate
2. Rimmed vacuoles (this is not specific for IBM)
3. Protein accumulation or 15- to 18-nm filaments
4. Upregulation of MHC class I

- ***Classification Criteria:***

- *Clinicopathologically defined IBM:* Mandatory criteria + one or both of the clinical criteria plus 1, 2, and 3 of the pathological criteria
- *Clinically defined IBM:* Mandatory criteria plus all clinical criteria plus one or more, but not all the pathological criteria
- *Probable IBM:* Mandatory criteria plus one clinical criterion plus one or more, but not all the pathological criteria

IBM histopathology



Histopathology of inclusion body myositis. Hematoxylin and eosin (H&E) stain showing endomysial inflammatory infiltrate (*A, arrowheads*) and rimmed vacuoles (myofiber containing rimmed vacuoles, *A, arrow*) with severe myopathic features including significant fiber size variation, endomysial fibrosis, and necrosis and regeneration (*not shown*). Modified Gomori trichrome (mGT) stain showing lymphocytes invading a non-necrotic myofiber (*B, image center*) and rimmed vacuoles (*C, image center*). Presence of protein accumulation detected by TAR DNA-binding protein 43 (TDP-43) immunohistochemistry (*D, arrowhead*). Mitochondrial pathology demonstrated by many blue cytochrome c oxidase–negative/ succinate dehydrogenase–positive (COX/SDH) myofibers (*E*). Strong and diffuse sarcolemmal and sarcoplasmic upregulation of major histocompatibility complex (MHC) class I (*F*).

Goyal, NA. (2022). Inclusion Body Myositis. Continuum Neurology.

Polymyositis

POLYMYOSITIS

Historically, polymyositis has been characterized by a subacute onset of proximal muscle weakness, CK elevation, myopathic EMG, and endomysial inflammation with CD8+ T cell infiltrates seen on muscle biopsy. It has been increasingly recognized that polymyositis is a rare entity because many patients who were initially diagnosed with polymyositis are subsequently diagnosed with inclusion body myositis, antisynthetase syndrome without the rash, or an immune-mediated necrotizing myopathy based on further evaluation of characteristic clinical features, autoantibodies, and histopathology findings.[43,44] The diagnosis of polymyositis is seen now as a diagnosis of exclusion and patients should be followed closely to assess for the development of clinical findings that may indicate alternative diagnoses.

Goyal, NM. (2019). Immune-mediated Myopathies.

Polymyositis

- "Many historically diagnosed polymyositis have been mainly reclassified as IBM, IMNM, and ASS. Different types of myositis-specific antibodies (MSA) suggest distinct clinicopathological subsets of IIM. Excluding IBM, at least one-third of the IIMs have no known associated MSA."

Tanboon and Nishino. (2019). Classification of idiopathic inflammatory myopathies: pathology perspectives. *Current Opinion in Neurology*. 32(5):p 704-714.

The trouble with HyperCKemia

- "Elevated CK does not a myositis make…"
- ALS – frequently CKs < 1000
- Guillan-Barre Syndrome CKs < 1000
- Kennedy's disease/SMA CKs < 1000
- ~40 muscular dystrophies/congenital myopathies with CKs that can range into the tens of thousands.
- Metabolic myopathies
- Cardiac disease
- Liver disease

References

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References

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