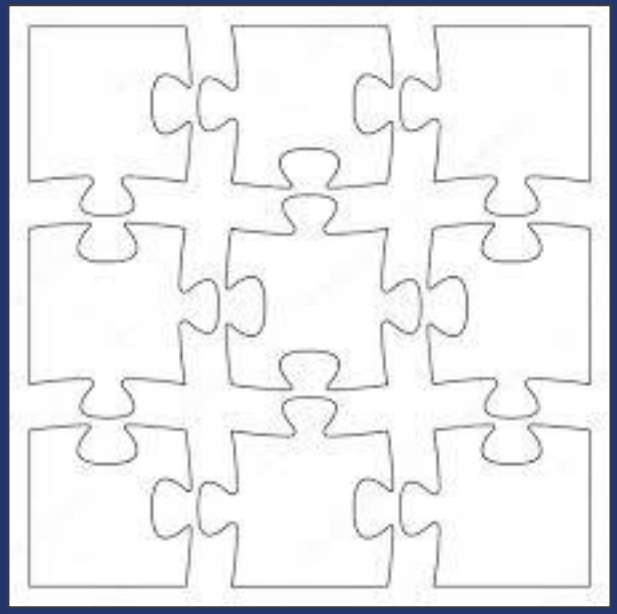
# How do you know you have the right diagnosis?

Ann M Reed MD
Duke University

The Myositis Association Annual Meeting
September 8th, 2017



# What Causes Autoimmune Disease Including Myositis

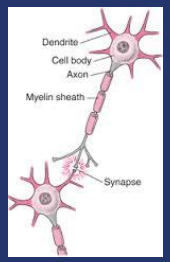

High cortisol levels

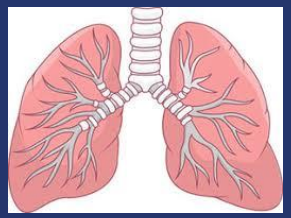
Inflammation

Immune System Confusion

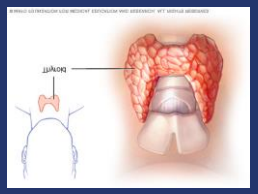
Autoimmune disease

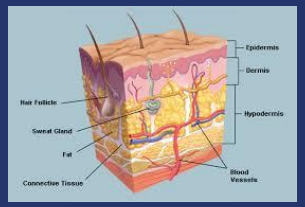
# Tissues affected by Autoimmune Attack

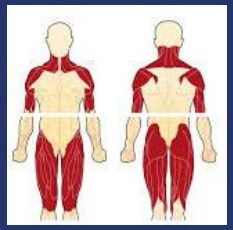


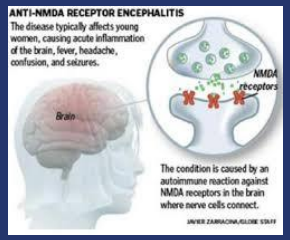



Autoimmunity






Triggers
Stress
Food allergies
Toxins
Environmental factors
Hormones
Metal

# Disorders

Addison's Disease
Autoimmune Inner Ear Diseaes
Bechet's Disease
Bullous Pemphigoid
Chronic Inflammatory Demyelinating Polyneuropathy
Cold Agglutinin Disease
CREST Syndrome
Crohns Disease
Dermatomyositis
Diabetes Mellitus
Goodpasture's Syndrome
Primary Biliary Cirrhosis
Sjogren's Syndrome
Graves' Disease
Guillain-Barre Syndrome
Hashimoto's Disease
Juvenile Arthritis
Lupus Erythematosus
Meniere's Disease
Myasthenia Gravis
PANDAS
Psoriatic Arthritis
Polymyositis
Rheumatoid Arthritis
Ulcerative Colitis

# What are inflammatory myopathies

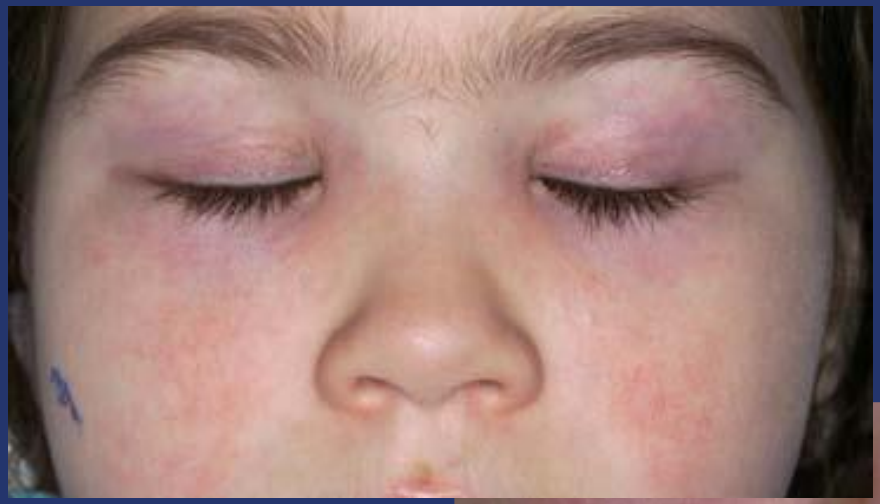
- Myopathy means muscle abnormality
- Inflammatory –immune reactive and mediated
- 4 major types
  - Dermatomyositis
  - Polymyositis
  - Necrotizing myositis
  - Inclusion Body Myositis

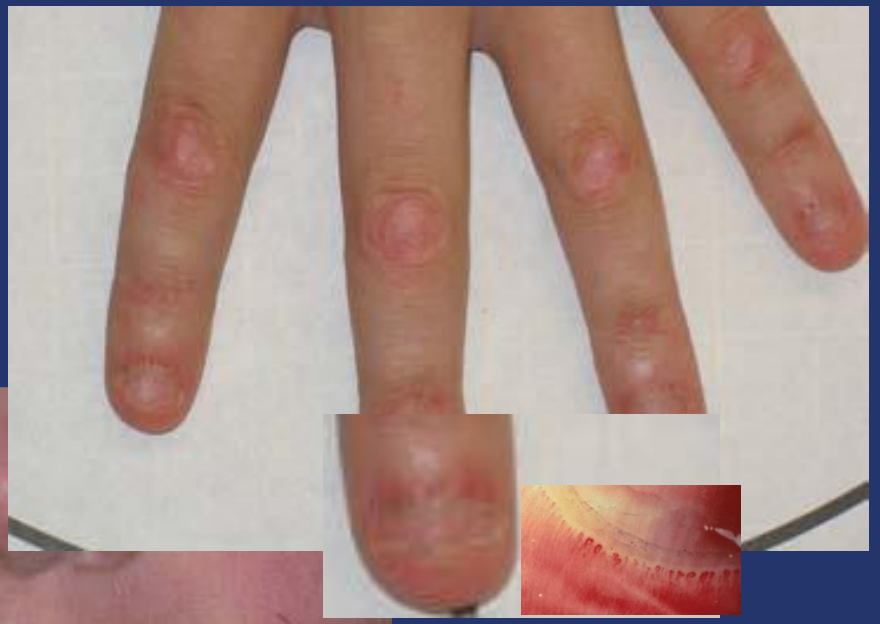
# Who is at risk?

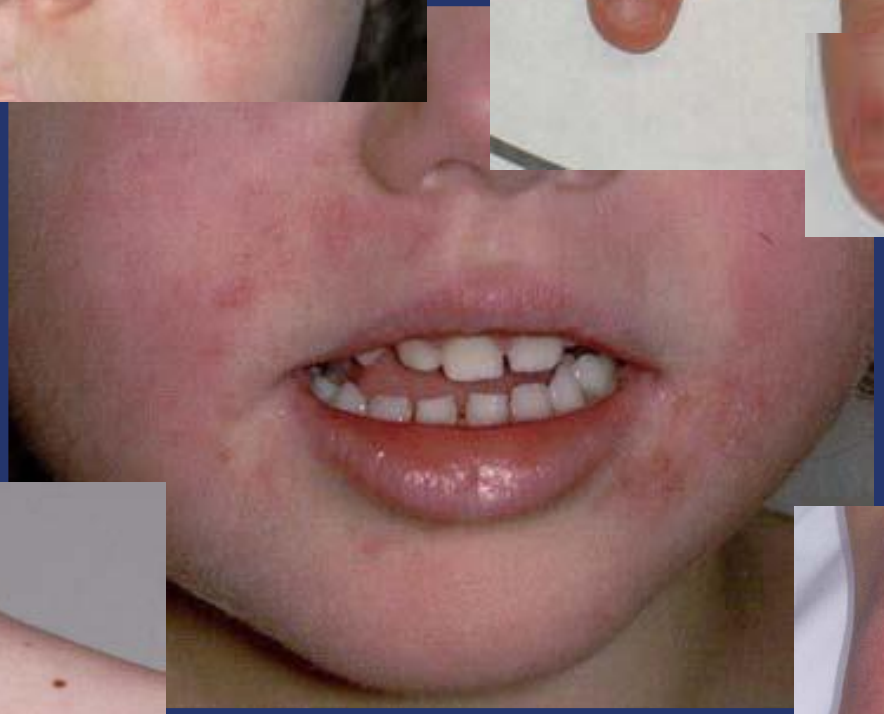
- Rare disorder in both children and adults
- Polymyositis and Dermatomyositis more common in women
- IBM more common in men
- Children predominantly juvenile dermatomyositis

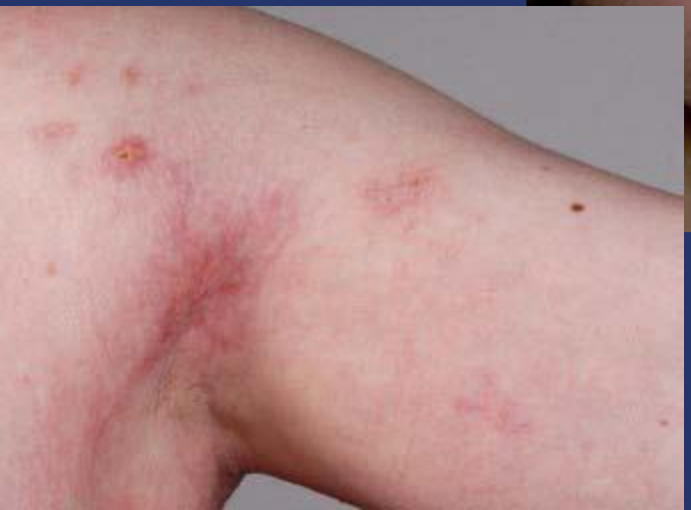
# Sign and Symptoms of IIM

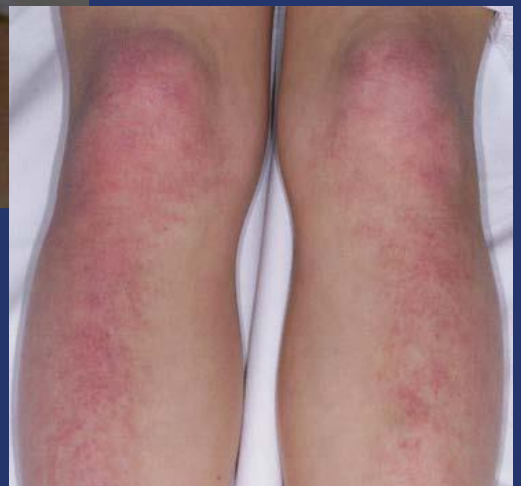
- Difficulty swallowing
- Muscle pain
- Muscle weakness -proximal muscles (shoulders, hips, etc.) tripping, falling and making it hard to raise the arms over the head, get up from a sitting position, or climb stairs
- Change in your voice
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle wasting (IBM)
- Skin rash
    - Red-purple rash on eye lids, over joints on hands, elbows, knees, face, shoulders

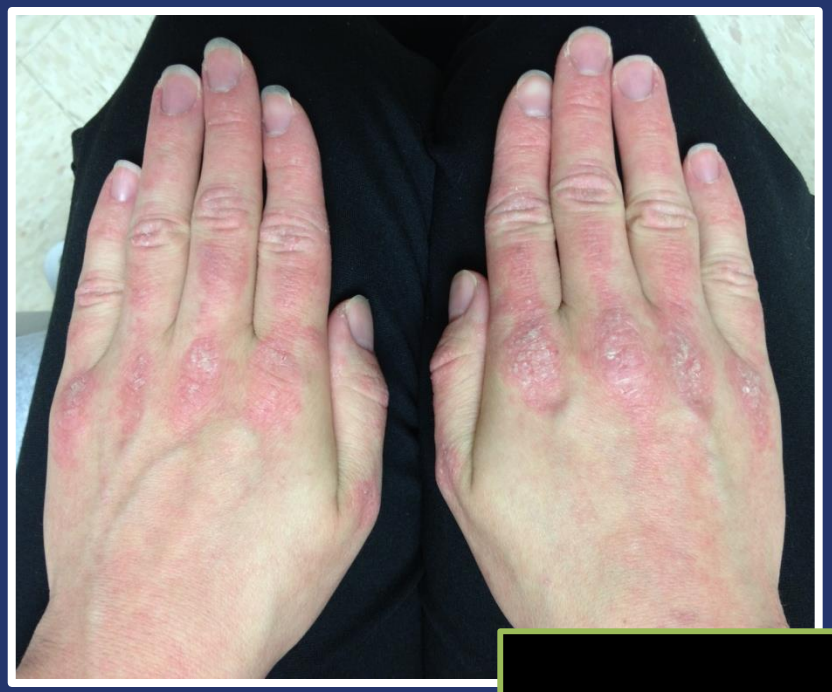


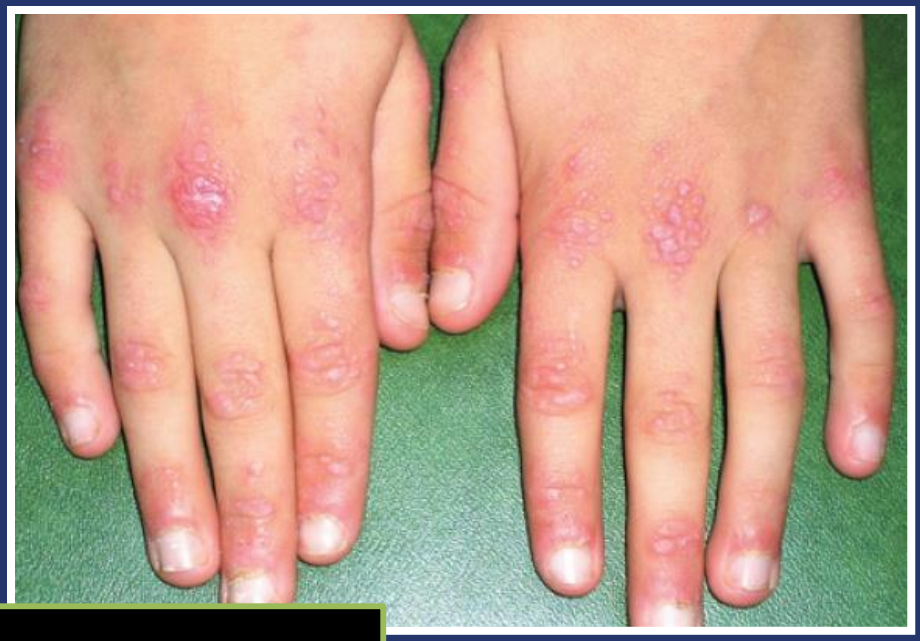




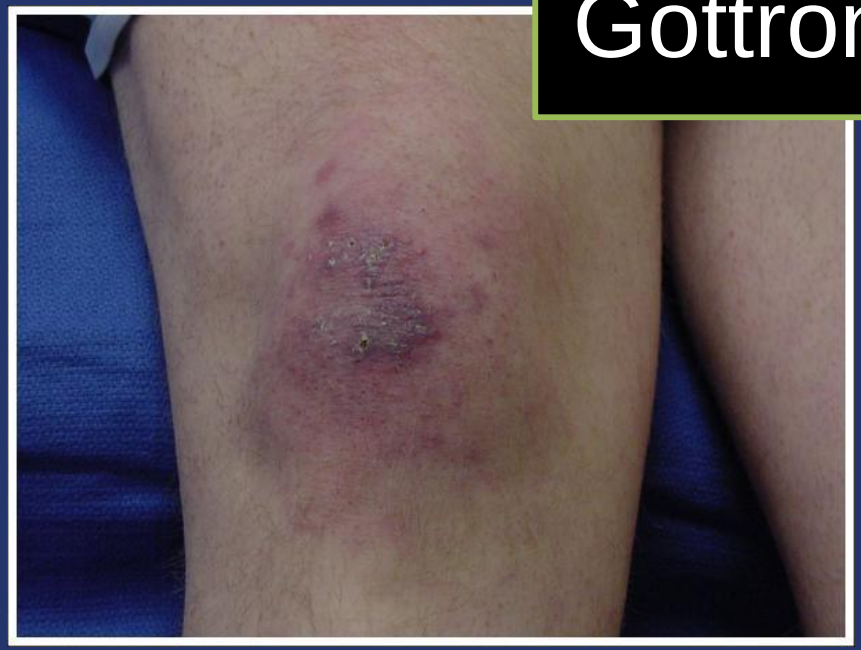


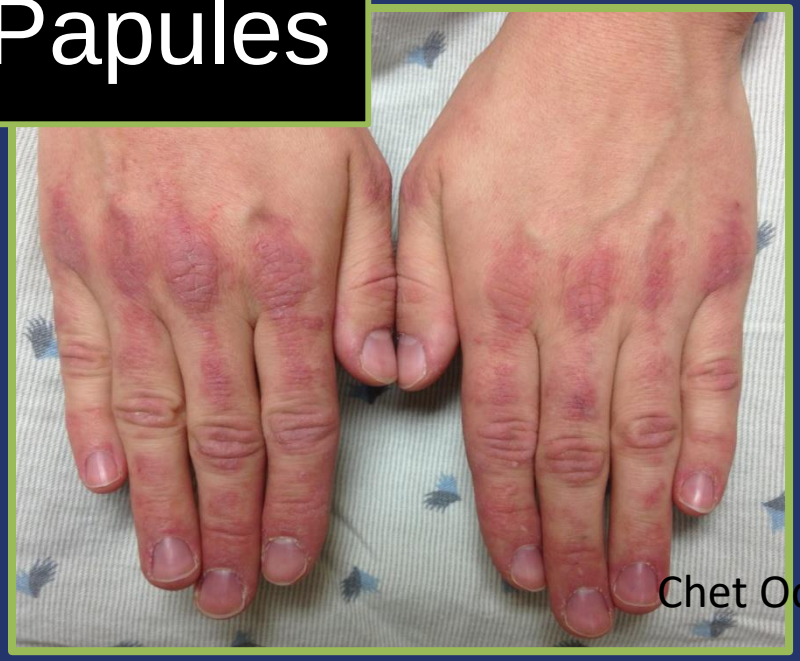




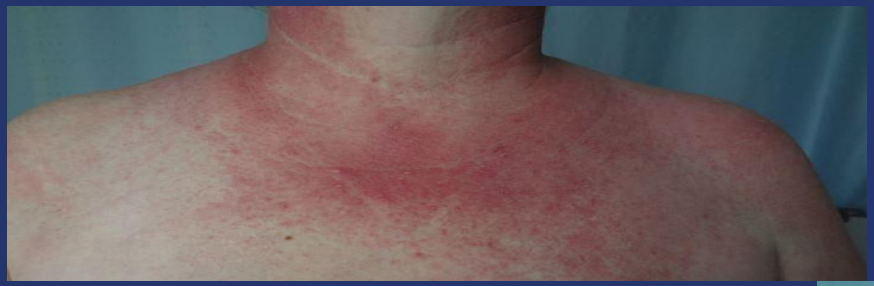


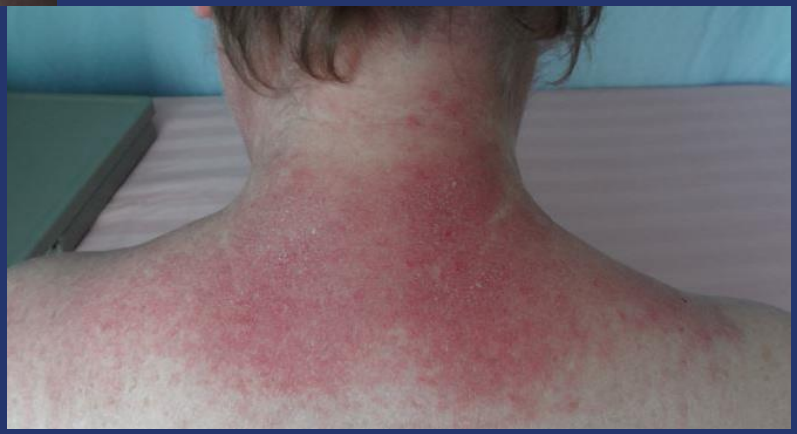
# Gottron Papules

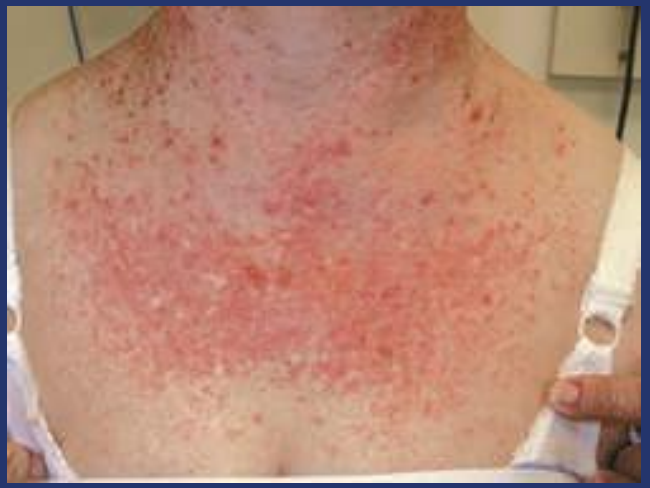




Chet Oddis



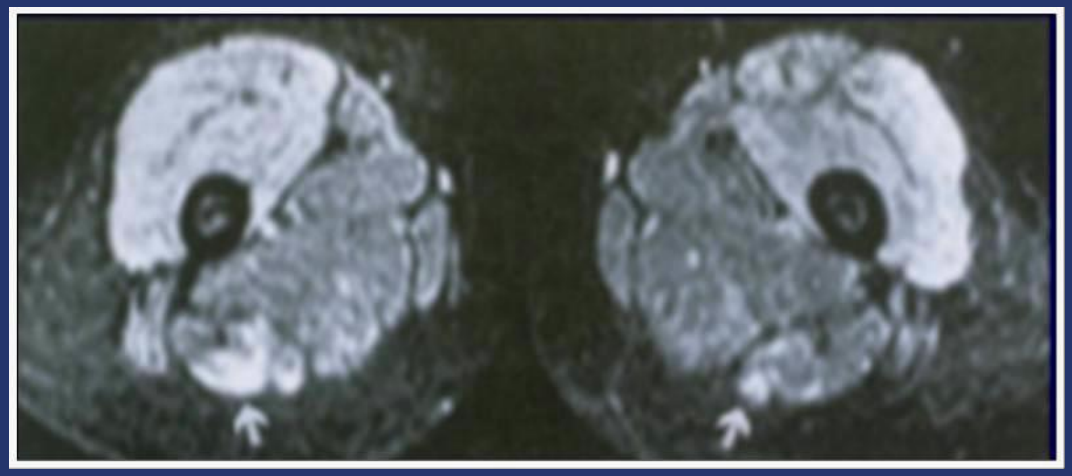


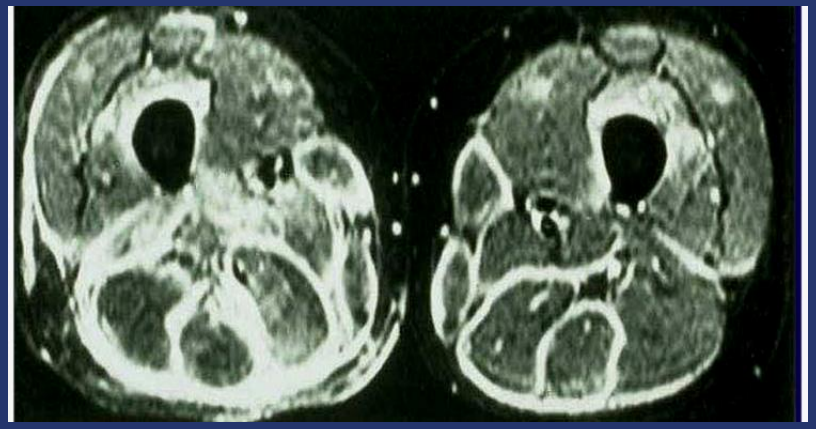


# Your evaluation

1. Muscle enzymes* **(CK, aldolase, AST, ALT, LDH)**
2. Muscle Biopsy*
3. EMG*
4. MRI*
5. PFTs **(high res CT)**
6. Swallow study
7. Blood tests* **(blood count, Cr)**
8. Myositis autoantibodies
9. Complete examination including muscle strength
10. Adults- malignancy evaluation

# Fat-Suppressed MRI of Muscle

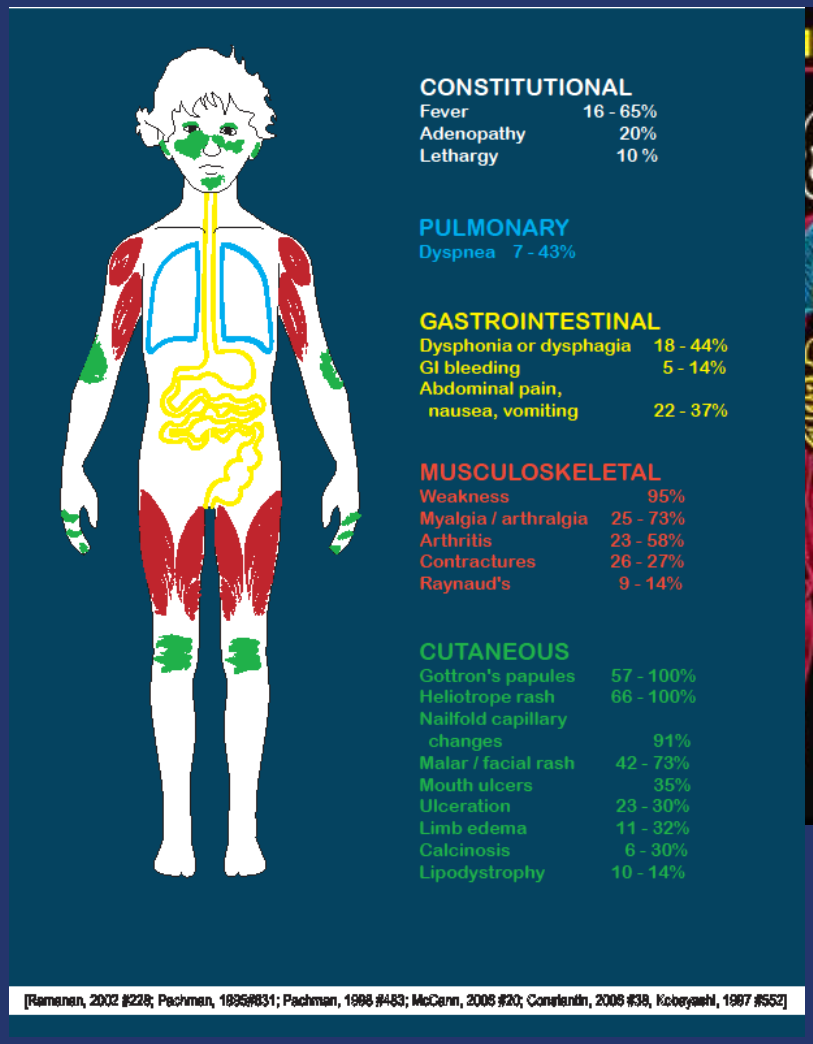


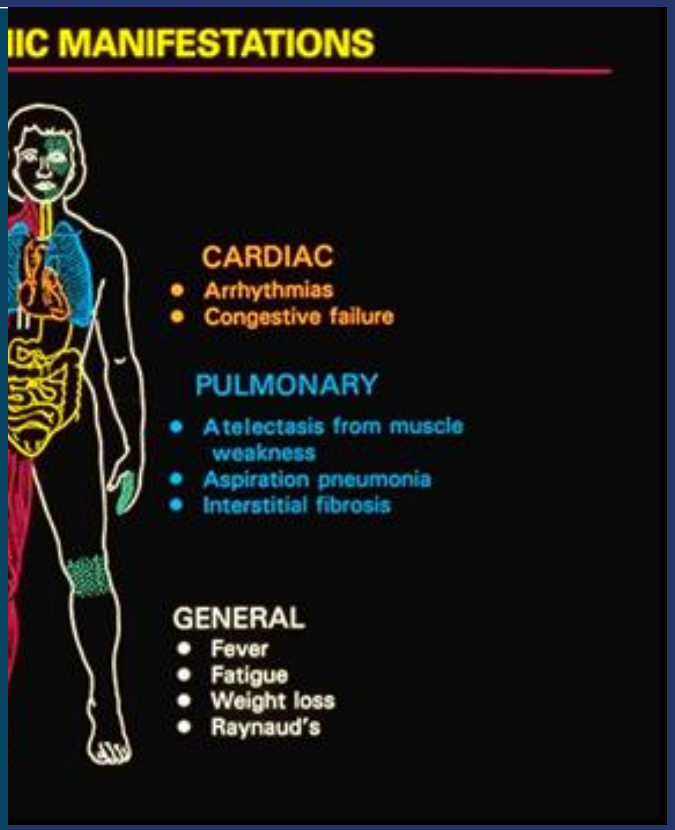


- $T_2$-weighted technique (or STIR image) suppresses fat signal
- Lose clarity of anatomic detail seen with $T_1$
- Increased signal = edema, inflammation
- Active myositis = increased STIR signal

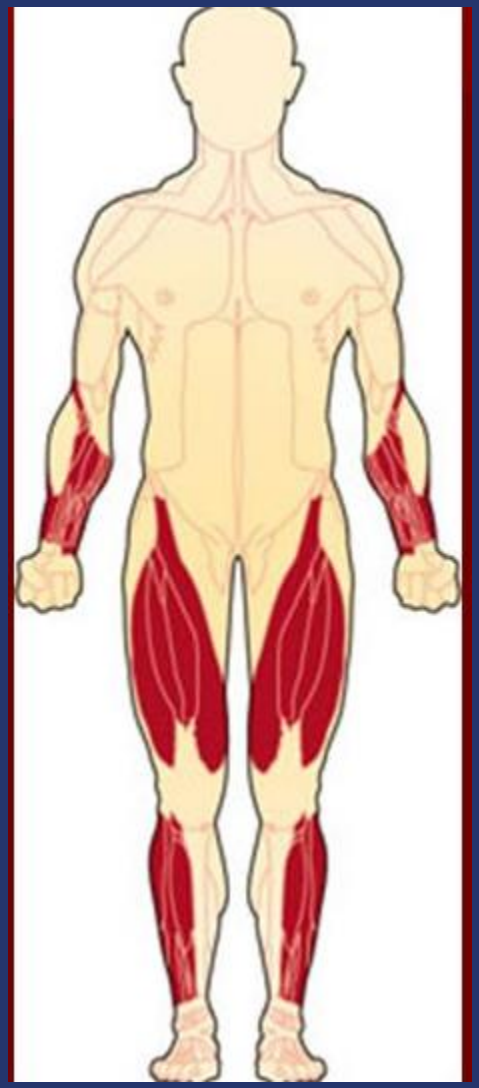
*STIR-MRI demonstrates disease activity*

# Clinical features



# Inclusion Body Myositis



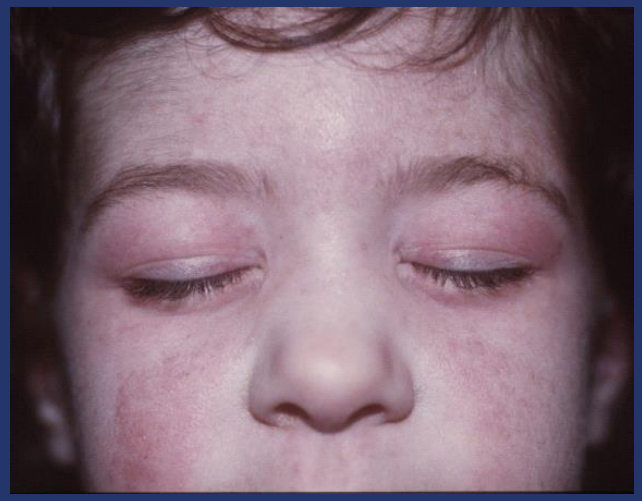
MDA.org

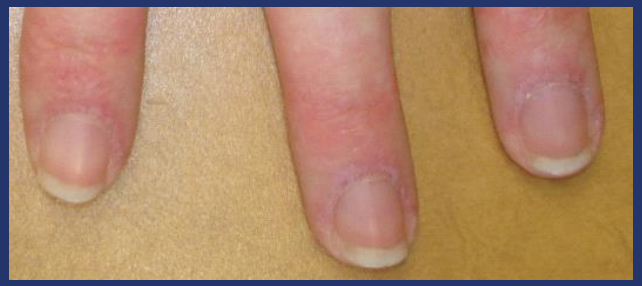
Sporadic inclusion body myositis (IBM) is an acquired inflammatory muscle disease

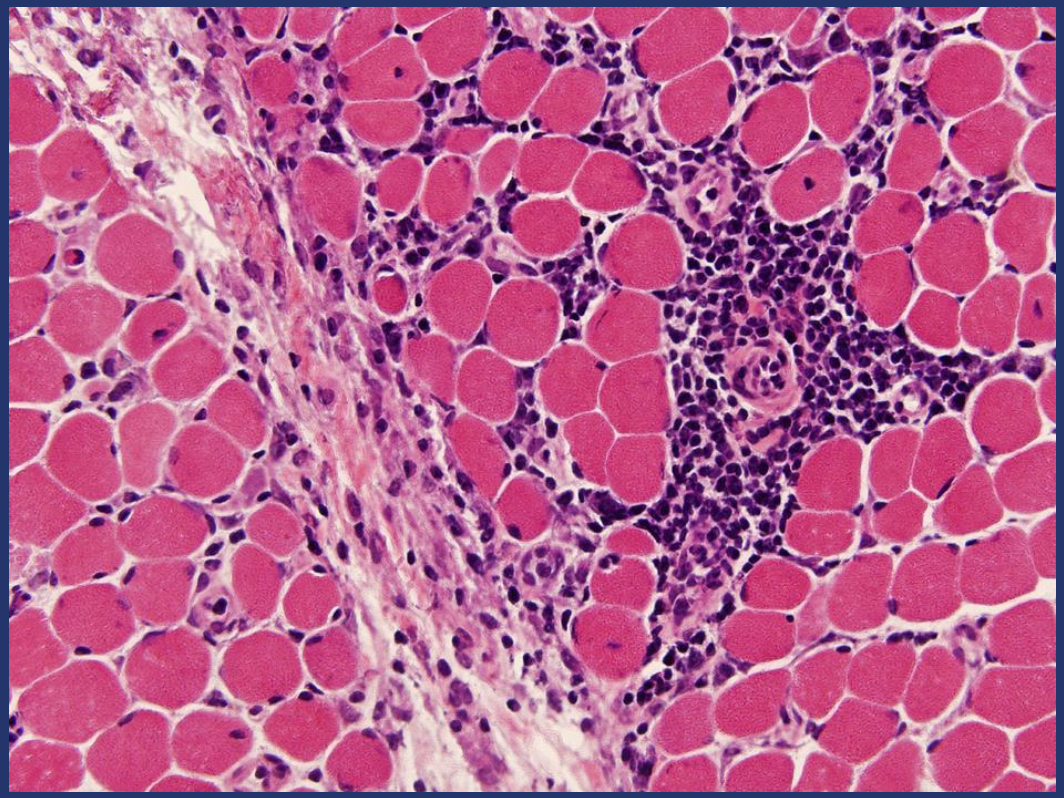
IBM is considered the most frequent muscle disease affecting individuals over 50

Clinical hallmark of IBM is early weakness and atrophy of the quads, wrists, finger flexors and distal forearms

# Juvenile Dermatomyositis clinical findings of disease activity







Clinical characteristics and mortality associated with juvenile and adult DM

**Table 1** | Clinical characteristics and mortality associated with juvenile and adult DM

| Disease features | Juvenile DM | Adult DM |
|---|---|---|
| Peak age of onset | 7 years[6,10–12] | 30–50 years[13] |
| Proportion of IMM cases | 80–95%[19,127,128] | 35–50%[129] |
| Proximal weakness | 85–95%[10,12] | 88%[130] |
| Characteristic rash | Gotton papule: 73–91%[7,131]<br>Heliotrope rash: 62–83%[7,131]<br>Malar rash: 42–57%[7,131]<br>Abnormal nailfold capillaries: 80%[131] | Gottron papule: 54%[130]<br>Heliotrope rash: 74%[130]<br>Malar rash: data not available<br>Abnormal nailfold capillaries: 43%[132] |
| Calcinosis or ulceration | 26–40%[19,131,133] | 2–16%[19,133] |
| Refractory or chronic disease | 59–63%[12,134] | 63%[133] |
| Malignancy | 1%[12,133] | 15–24%[41,133] |
| Myositis-specific antibodies | 2–40%[19,59] | 48–70%[38,59] |
| Interstitial lung disease | 7–19%[29] | 35–40%[30] |
| Gastrointestinal disease | 2–3%[4,19] | 1%[19] |
| Raynaud disease | 10%[135] | 11%[136] |
| Mortality | <5%[12,13,133] | 21%[133] |

Abbreviations: DM, dermatomyositis; IMM, inflammatory myopathic myositis.

Robinson, A. B. & Reed, A. M. (2011) Clinical features, pathogenesis and treatment of juvenile and adult dermatomyositis
*Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2011.139

nature REVIEWS RHEUMATOLOGY

# Criteria for inflammatory myositis DM, JDM and PM

- **Characteristic muscle findings**
  - Symmetrical proximal muscle weakness
  - Elevation of muscle derived enzymes
  - Typical EMG pattern
  - Vasculitis and/or inflammation on muscle biopsy
  - MRI

- **Characteristic skin rash**
  - Gottrons papules
  - Erythematous rash
  - Alopecia
  - Calcinosis
  - Periungual edema and telangiectasia

# Inclusion Body Myositis

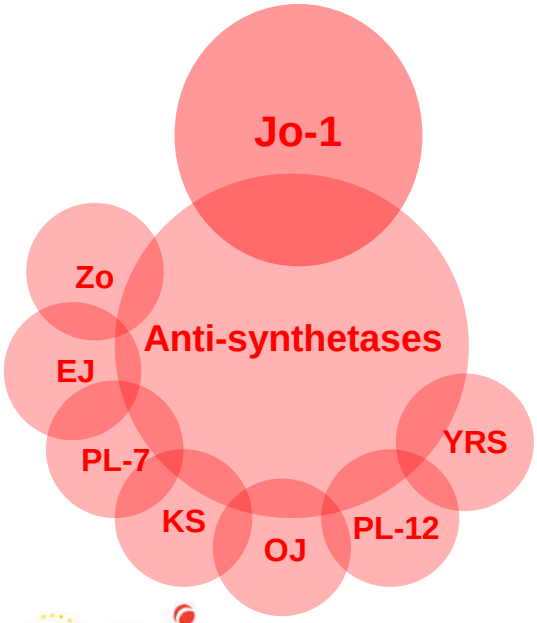
- Weakness Proximal and distal –arms and legs
- Finger weakness
- Wrist flexor weakness
- Quadriceps weakness

- Elevated muscle enzymes
- Biopsy
  - Inflammation
  - Rimmed vacuoles
  - Amyloid

# Myositis-specific autoantibodies

Myositis specific autoantibodies ⟶ Clinical phenotypes in adults and children

| Anti-synthetase syndrome | Necrotizing myopathy | Amyopathic dermatomyositis | Dermatomyositis |
|---|---|---|---|
| Fever<br>Raynauds<br>Lung fibrosis<br>Myositis<br>Arthropathy<br>Mechanics hands<br>+/- rash | High CK | Rash *sine* myositis<br>Hypomyopathic<br>Rash precedes myosit | Rash<br>Malignancy<br>Calcinosis/vasculitis (children) |




Anti-SRP

Anti-SAE

Anti-NXP-2

Anti-HMGCR

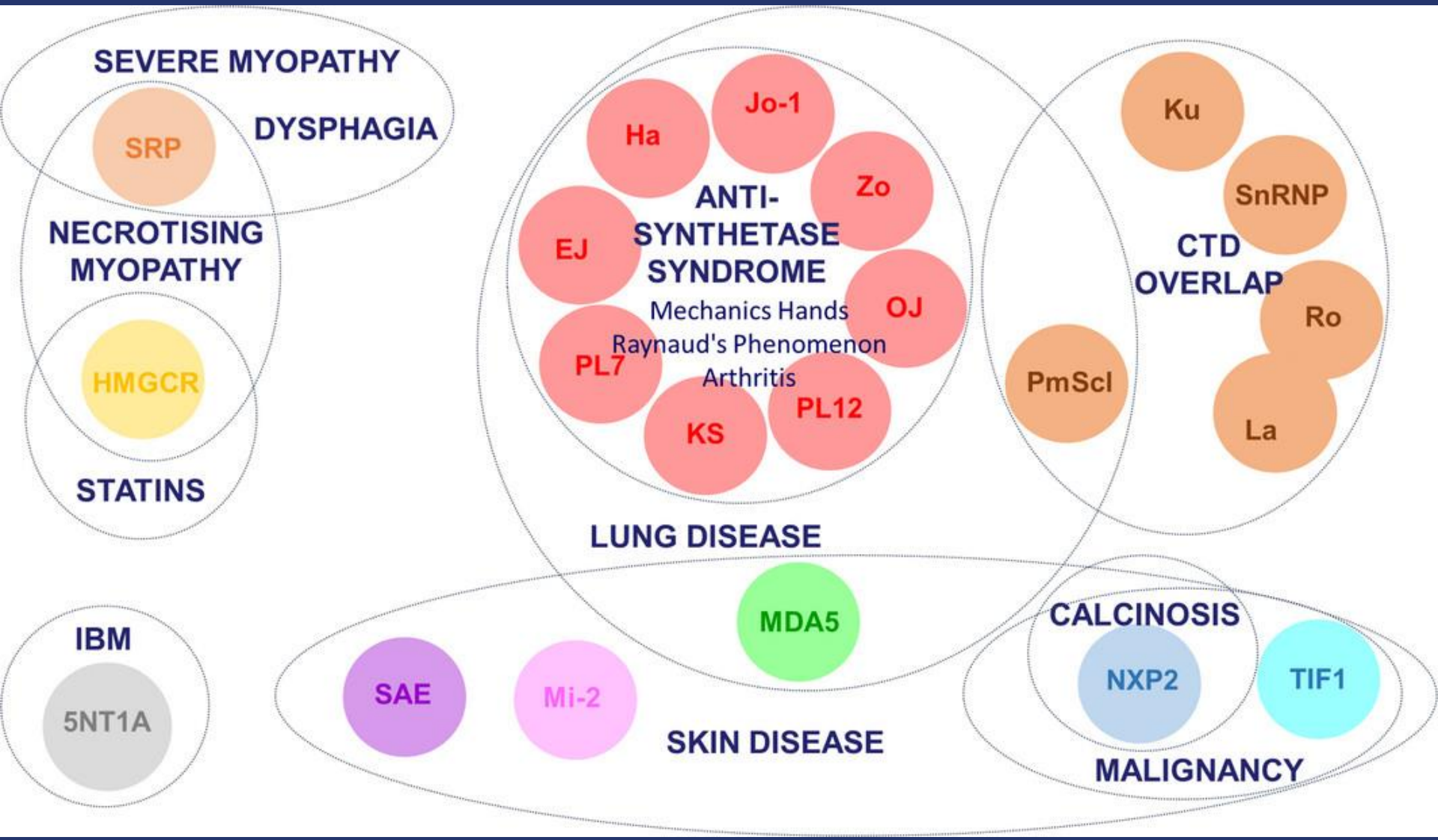
Anti-MDA-5

Anti-TIF1g

Anti-Mi-2

Duke Children's

*Slide courtesy of Dr. Hector Chinoy*



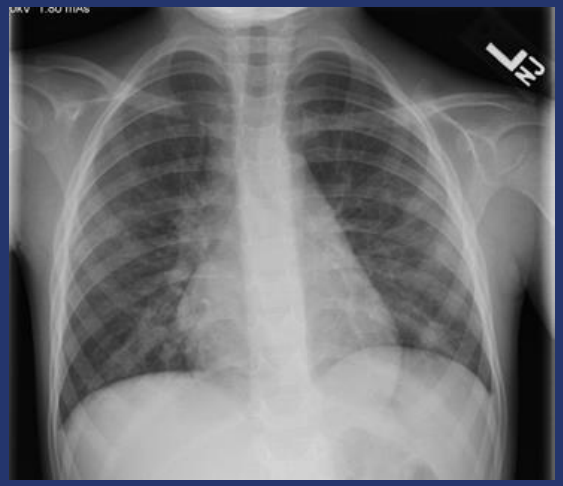

Betteridge, 2015

# Myositis specific autoantibodies (MSAs) –anti synthetases

**Anti-ARS:Aminoacyl-tRNA synthetases:**

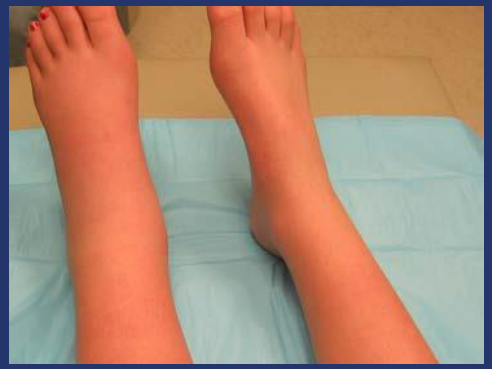
1–5% **JDM** **20-25% DM/PM**

**Typically associated with moderate to severe weakness**
**Arthritis**
**Mechanics hands**
**Raynaud's**
**Fevers,**
**Interstitial lung disease**



**Onset in spring**

Anti-Jo-1, Anti-PL-12, Anti-PL-7, Anti-EJ,
Anti-OJ, Anti-KS, Anti-Ha, Anti-Zo



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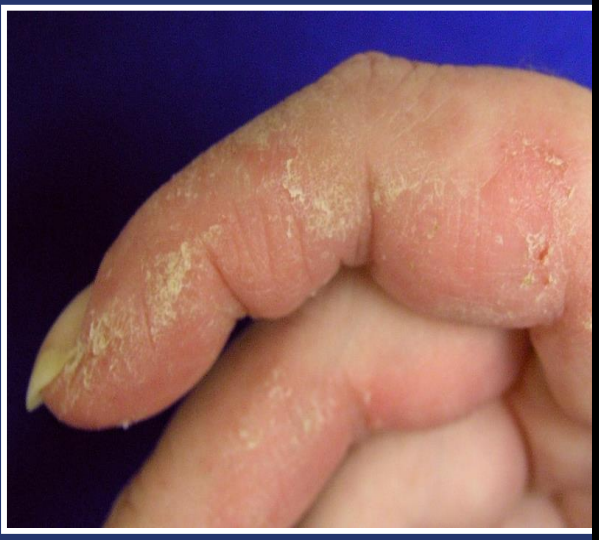
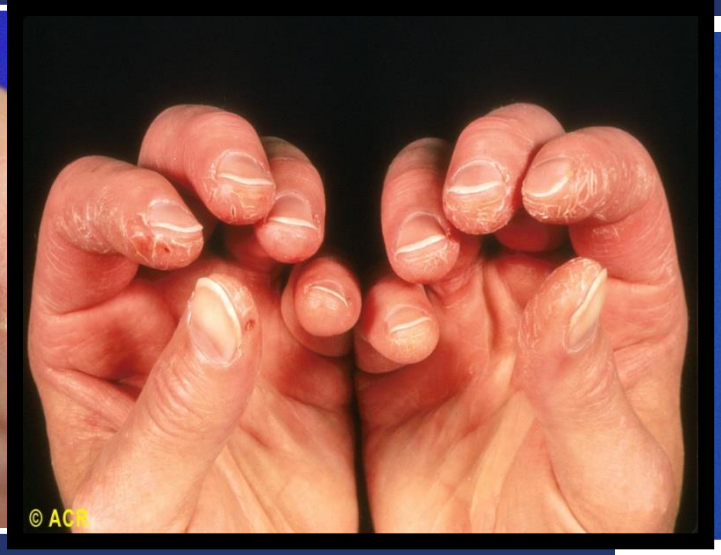
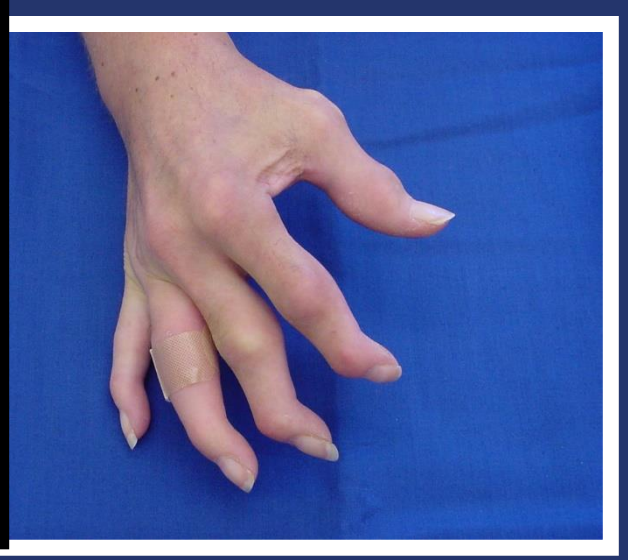
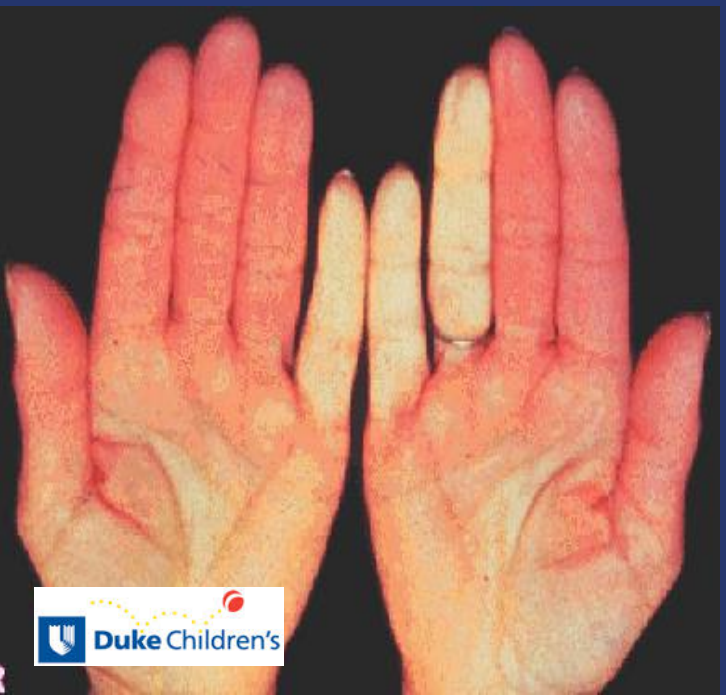
Gunawardena 2008, Wedderburn and Rider 2009, Tansley 2013

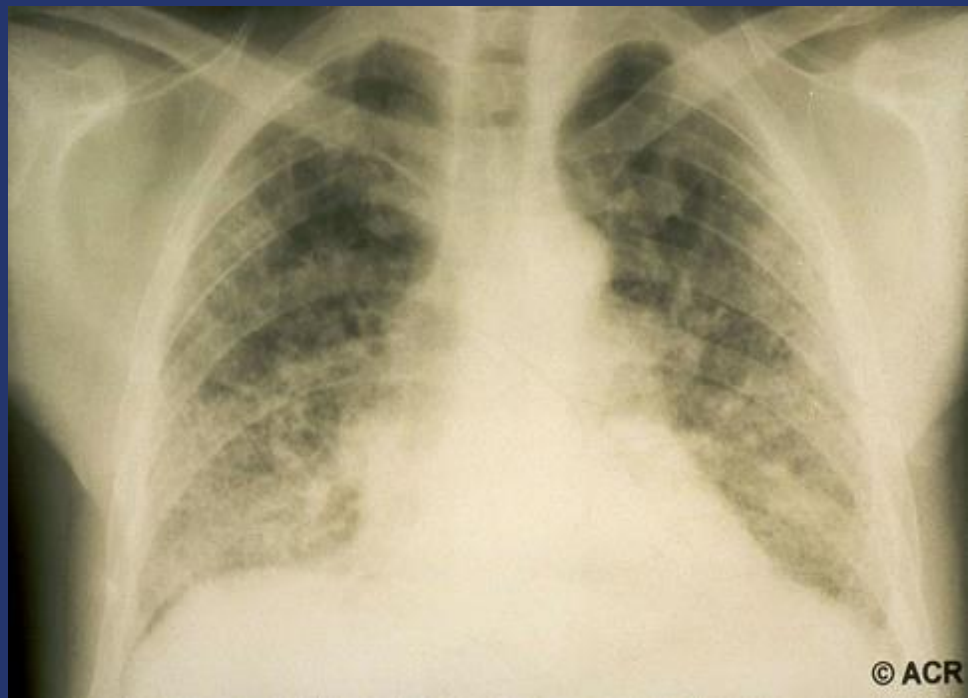




# Clinical Features: Anti-synthetase Syndrome



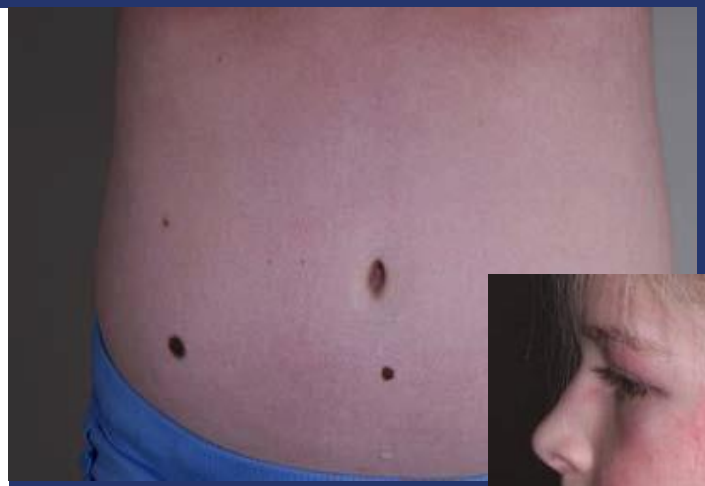
# TIF-1 gamma
## Transcriptional intermediary factor

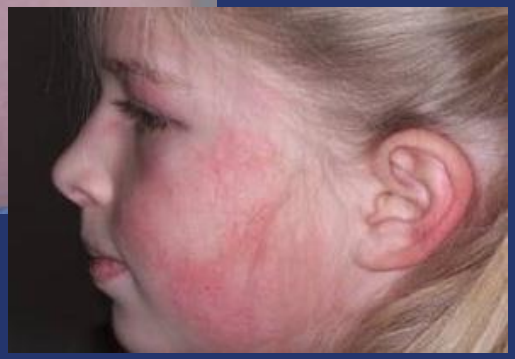
23–29%  JDM
13-31% Adult DM/PM

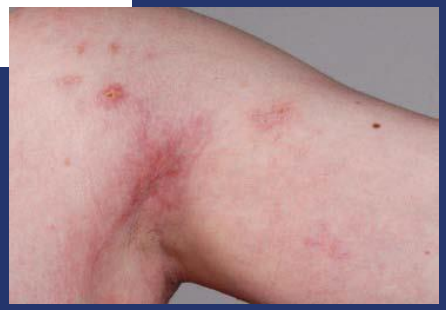
**Severe cutaneous involvement**
**Generalized lipodystrophy**
**Photoerythema**
**Psoriasiform**

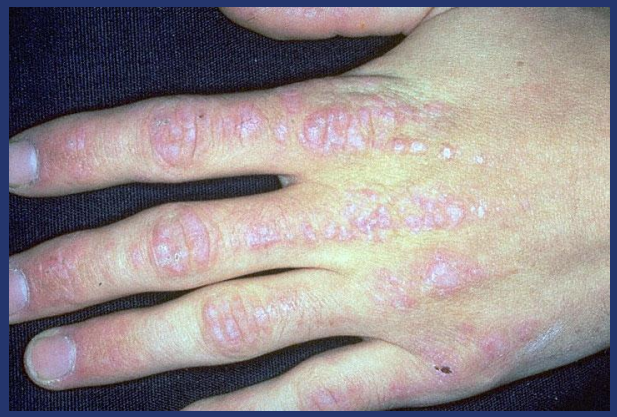
**Malignancy in adults**

TIF1 -cell proliferation, apoptosis and innate immunity and tissue regeneration
-inactivation (Smad)









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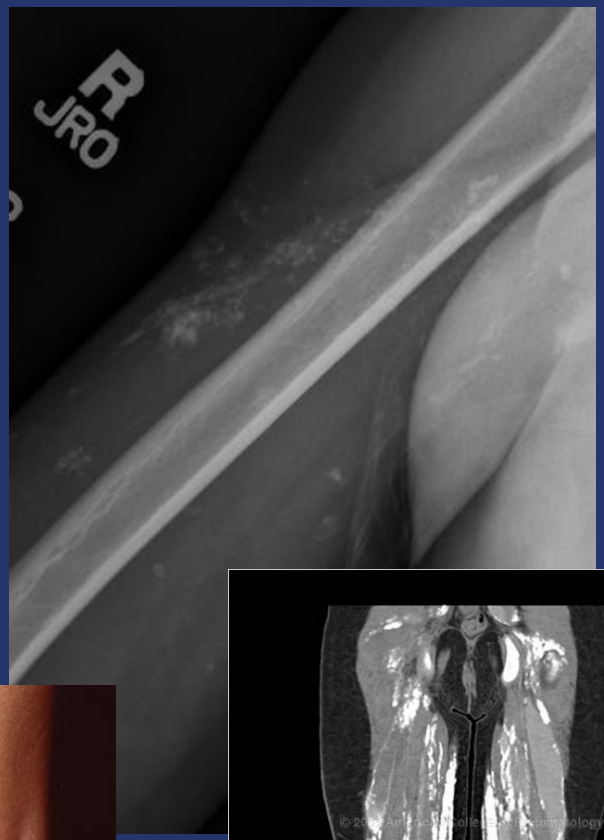
# Nuclear matrix protein NXP2

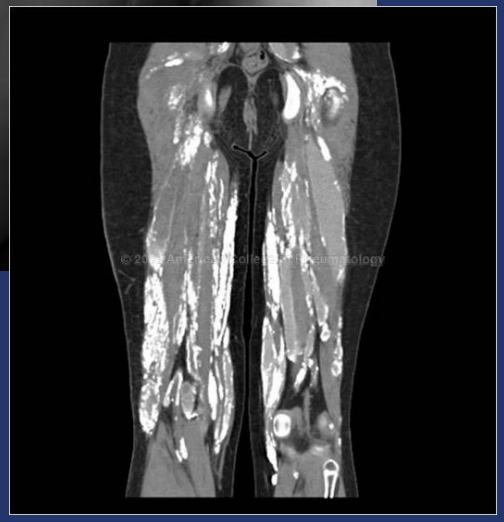
MJ

13-23%  JDM
1–17% adult PM/DM
Nuclear matrix protein NXP2

**Associated with calcinosis, contractures, skin disease**

Transcriptional regulation



Duke Children's

# Anti-Mi-2

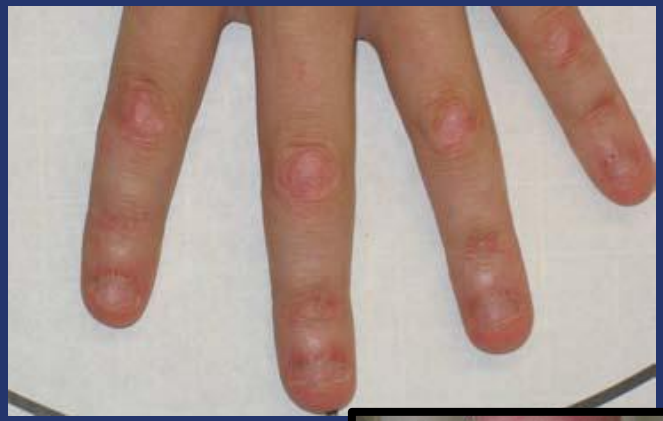
## Nucleosome remodelling deacetylase complex

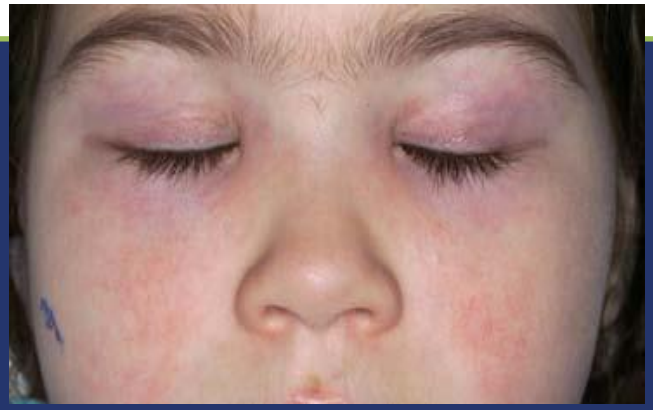
5-10% JDM
9-24% adult IIM

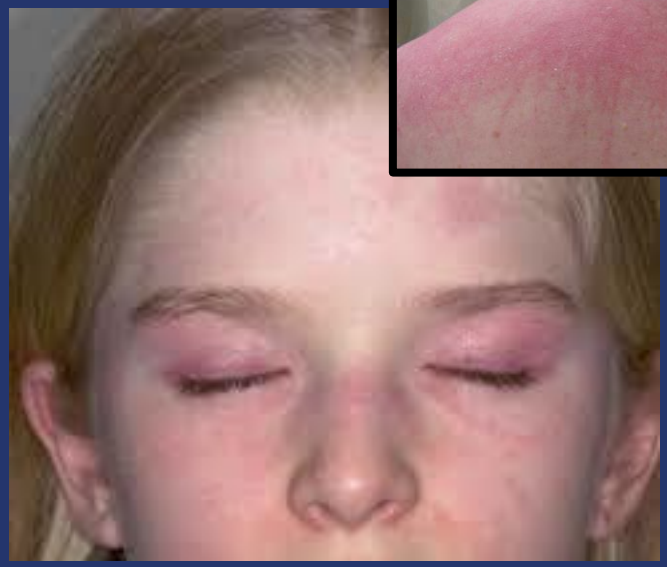
**Classical cutaneous disease- Gottron's papules, heliotrope rash, V-sign and shawl sign, cuticular overgrowth and UV exposure**

**Favorable prognosis –less severe muscle disease but worse biopsy scores**

Gene transcription and regeneration muscle and skin)







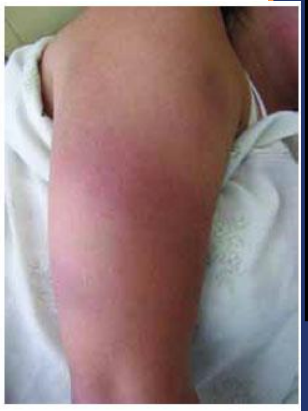
Duke Children's

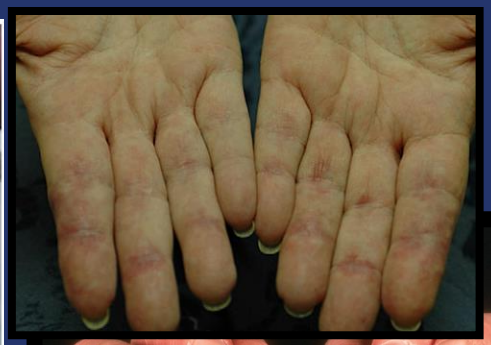
# MDA5

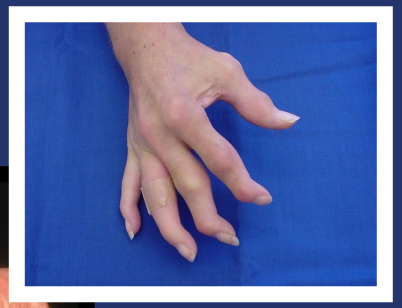
## Melanoma differentiation-associated gene 5

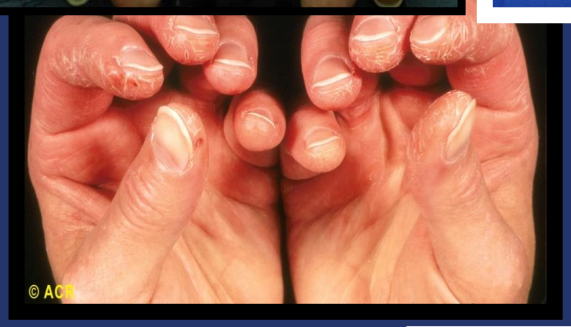
P140

20-30% JDM
10-48% Asian Adult DM
0-10% Caucasian Adult DM



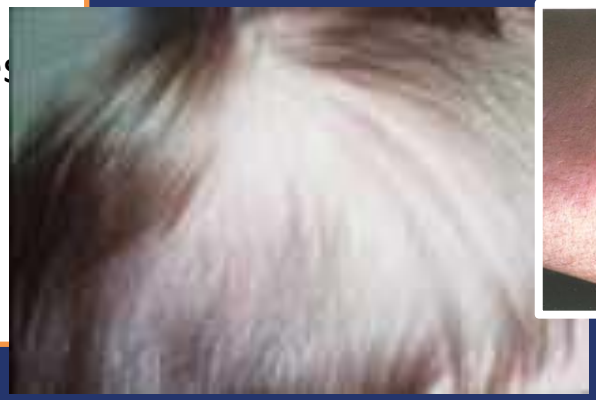


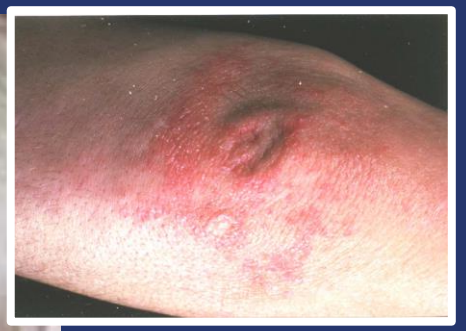




**Amyopathic**
**Malignancy-adults**
**Interstitial lung disease (20% JDM)**
**Ulceration**

Novel cutaneous phenotype -palmar papules
Severe cutaneous ulcerations
Vasculopathy
Rapidly progressive ILD





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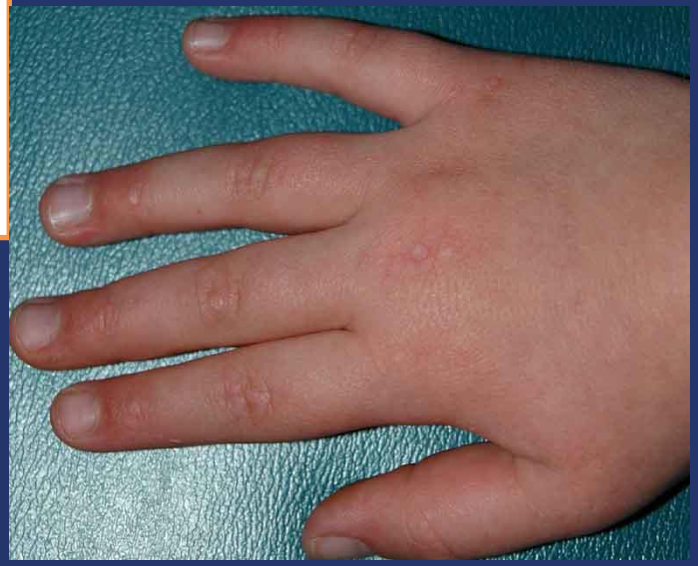
# SAE
## Small ubiquitin-like modifier activating enzyme

1% juvenile myositis
6% Adult Caucasian DM/PM
2% Asian Adult DM/PM

**Amyopathic at onset**
**Dysphagia**



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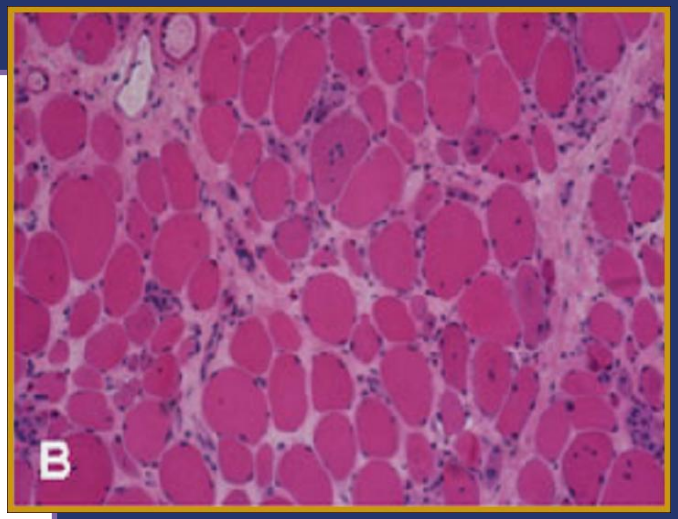
# Anti-SRP

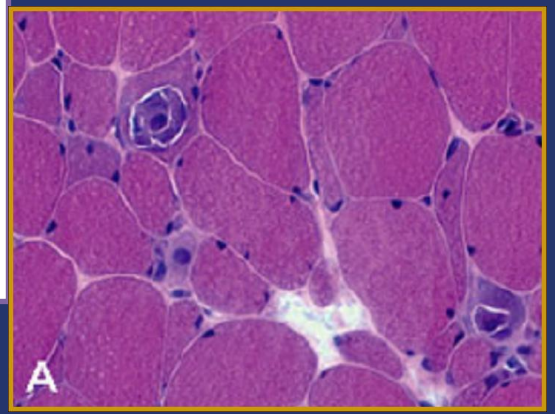
## Signal recognition particle

1–3% juvenile PM
5% Caucasian DM/PM
8-13% Asian/African DM/PM

**Severe refractory polymyositis-necrotizing myopathy**
**Rapidly progressive muscle disease**
**Dysphagia**
**? Heart disease and arthritis**

Necrotizing myopathy <u>without inflammation</u>
No MHC-1 immunostaining
MAC/C5b-9 staining (similar to DM)

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# HMGCR

## 3-hydroxy-3-methylglutaryl-coenzyme A reductase

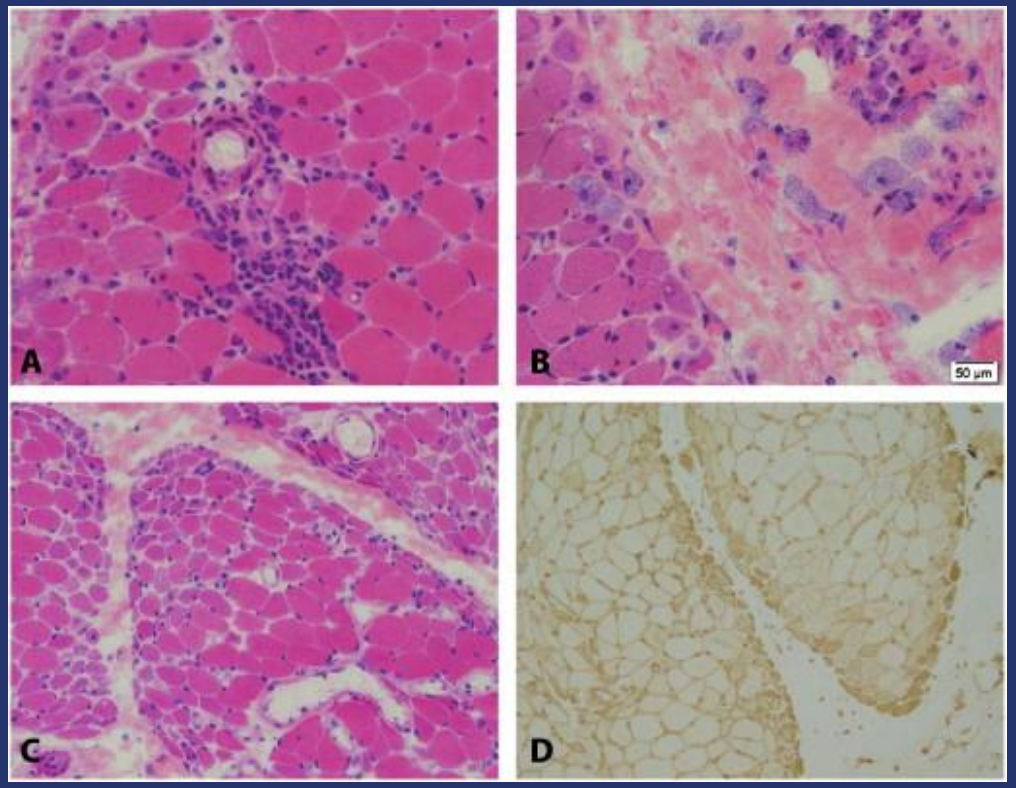
1% juvenile myositis

6% Adult DM/PM

**Highly elevated CKs**
**Necrotizing myopathy**
**Weakness**

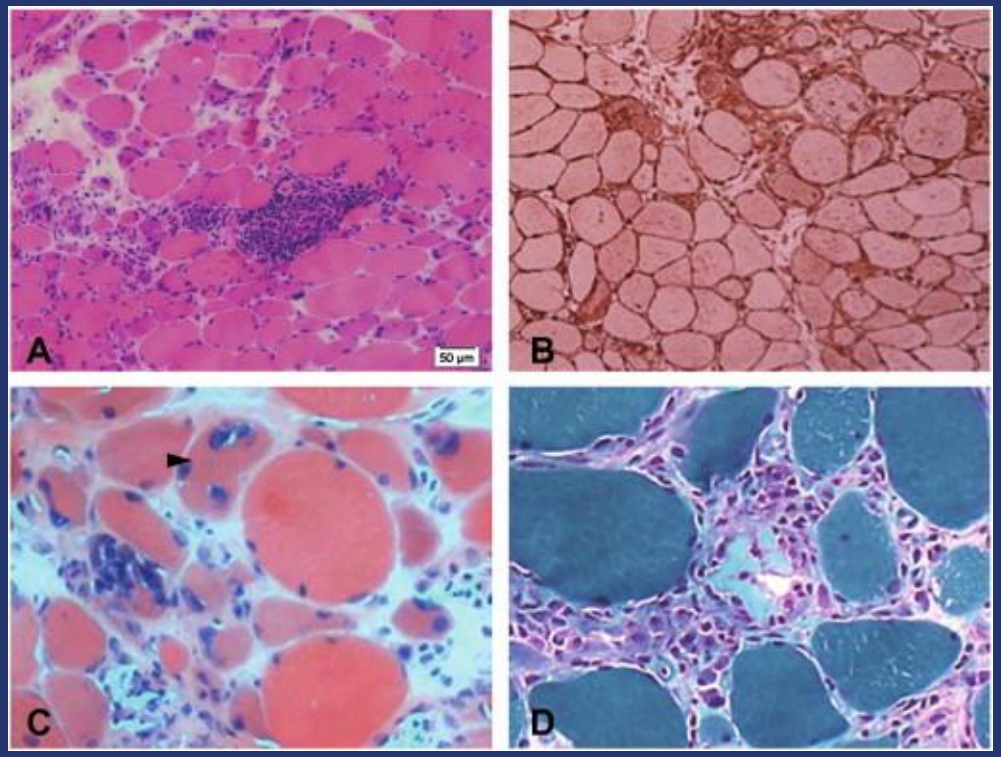
Respond well to treatment but relapse
Statin exposure in adults

# Dermatomyositis




A. endomysial and perivascular mononuclear inflammatory infiltrate;
B. fragmentation of perimysial connective tissue and infiltration with granular mononuclear cells and macrophages;
C. A &
D. perifascicular fibre regeneration

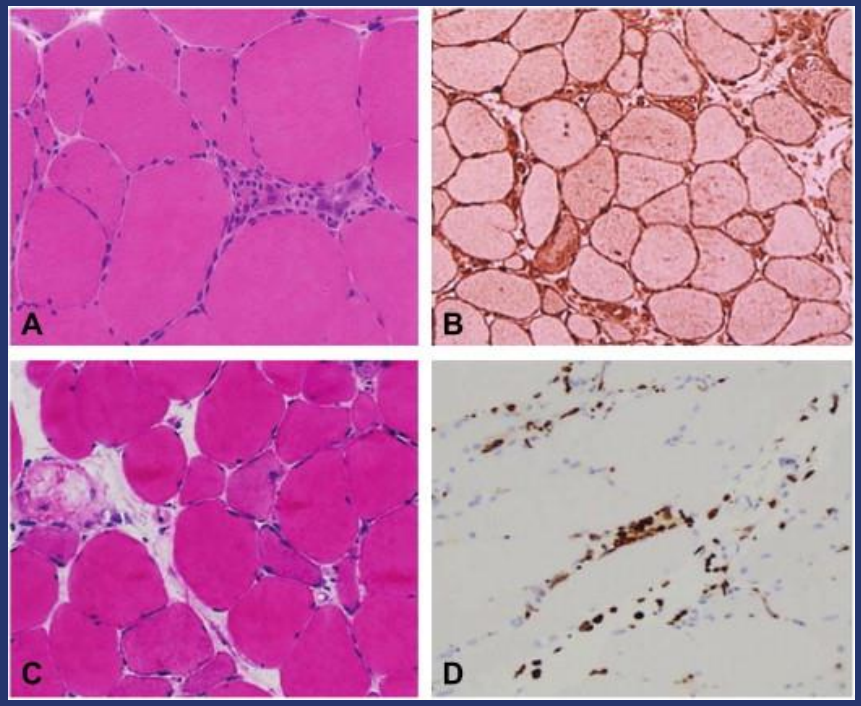
# Polymyositis



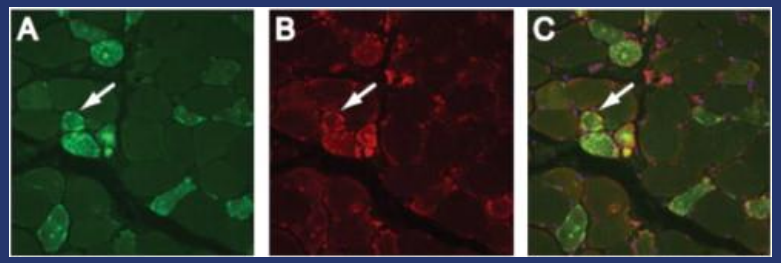

A. endomysial mononuclear inflammatory infiltrate (A–D); myofibre invasion by mononuclear cells (C, arrowhead); myofibre necrosis (C, D); and diffuse MHC-I antigen expression (B). A & C: haematoxylin and eosin; B: MHC-I immunohistochemis…

Yue-Bei Luo, Frank L. Mastaglia
http://dx.doi.org/10.1016/j.bbadis.2014.05.034

# Immune-mediated necrotising myopathy



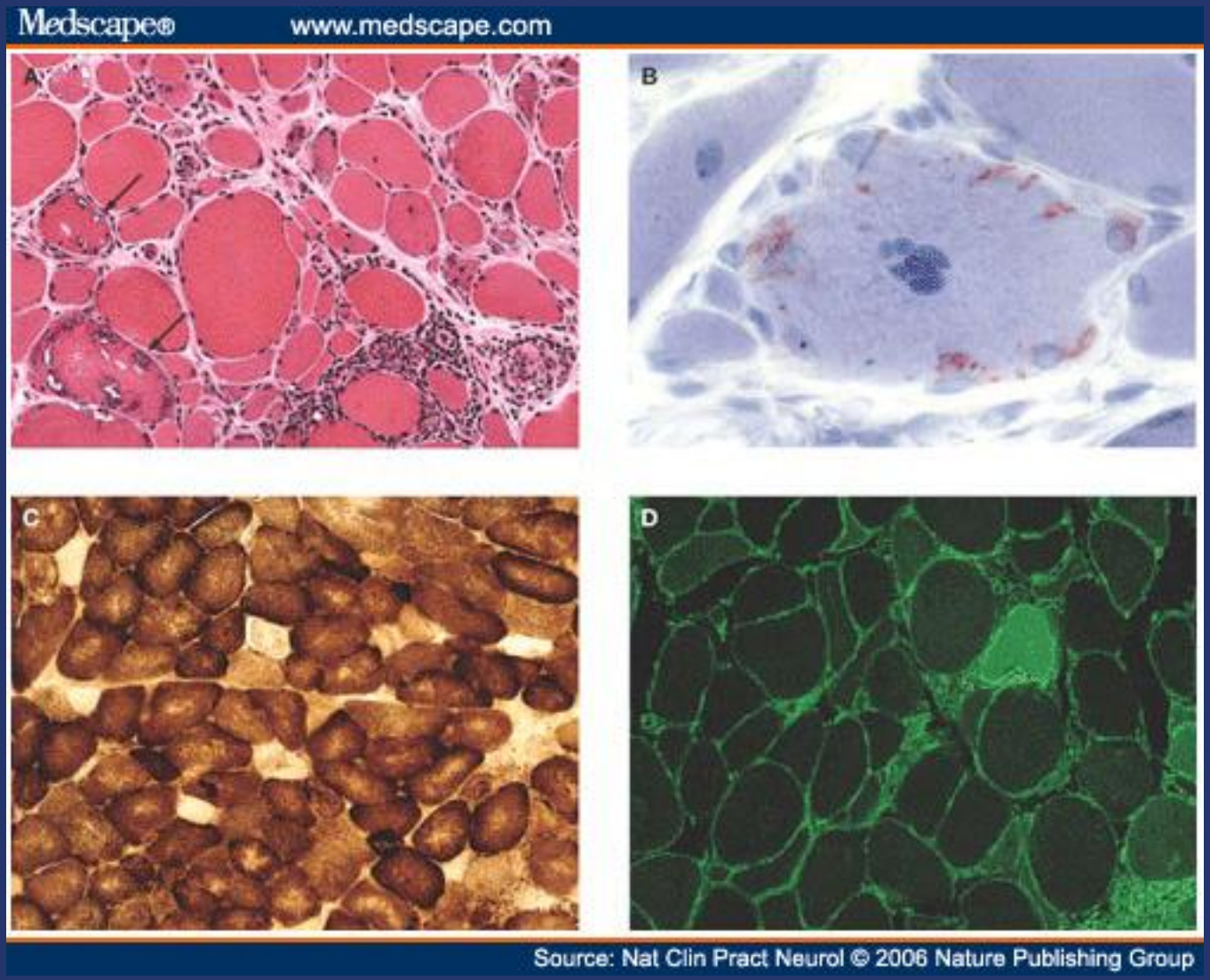

(A) muscle fibre necrosis with sparse inflammatory infiltrate; (B) diffuse sarcolemmal and sarcoplasmic MHC-I expression; (C) necrosis.




Up-regulation of HMGCR antigen in regenerating muscle fibres (arrows) in anti-HMGCR associated myopathy: A. anti-NCAM antibody; B. anti-HMGCR antibody; C. overlay image

Yue-Bei Luo, Frank L. Mastaglia

# Inclusion Body Myositis



# Decision making i.e. what else could it be?

- Other inflammatory myopathies
- Motor neuron disease
- Myasthenia gravis
- Muscular dystrophies
- Inherited myopathies
- Metabolic myopathies
- Drug–induced myopathies
- Endocrine myopathies
- Infectious myopathies

# Environmental factors

- Infections
- GI illness
- UV light
- Climate
- HLA genes

# How is it treated?

| Drug | Dose | Common side effects | Level of evidence for use in myositis | Special comments |
|---|---|---|---|---|
| Corticosteroids | Starting at 1 mg/kg or 60–80 mg/d in 2 or 3 divided doses | Osteoporosis, steroid myopathy, glaucoma, cataract, risk of infection | Case series | Usual initial therapy with or without additional immunosuppression |
| Methotrexate | Starting at 10–15 mg/wk (orally or subcutaneously) with an increase to 25 mg/wk | Hepatic toxicity, bone marrow suppression, risk of infection | Uncontrolled cohort studies | First-line immunosuppression unless contraindicated |
| Azathioprine | Starting at 50 mg/d and increased by 50 mg every 2 wk up to 2–3 mg/kg/d | Gastrointestinal symptoms, bone marrow suppression, hepatic toxicity, pancreatitis, risk of infection | Uncontrolled cohort studies | First-line immunosuppression unless contraindicated |
| Cyclosporine | Starting at 50 mg twice daily and increasing to final dose of 100–150 mg twice daily | Nephrotoxicity, neurotoxicity, abnormal glucose metabolism, hyperkalemia, headache, tremor, hypertension, risk of infection | Case series | Second-line immunosuppression; some evidence of efficacy in myositis-associated lung disease |
| Tacrolimus | Starting at 1 mg twice daily and slowly increasing for trough level of 8–12 | Similar to cyclosporine | Case series | Second-line immunosuppression; some evidence of efficacy in myositis-associated lung disease |
| Immunoglobulins | Starting at 2 g/kg/mo given over 2–5 d | Hypertension, volume overload, renal toxicity, headaches | One double-blind, placebo-controlled trial | Second-line immunosuppression for refractory myositis patients; some evidence of efficacy in dysphagia and refractory skin disease; can be used in patients with infection |
| Mycophenolate | Starting at 500 mg twice daily, slowly increasing to 2–3 g/d | Bone marrow suppression, gastrointestinal intolerance, risk of infection | Case series | For refractory cases; some efficacy in refractory skin disease and possibly in interstitial lung disease |
| Cyclophosphamide | Oral: 2-mg/kg/d dose | Malignancy, bone marrow suppression, hepatotoxicity | Case reports | Limited to very refractory cases with interstitial lung disease |
| Rituximab | 2 doses of 1,000-mg intravenous infusion 2 wk apart | Risk of infection | | For refractory cases; possible use in interstitial lung disease |

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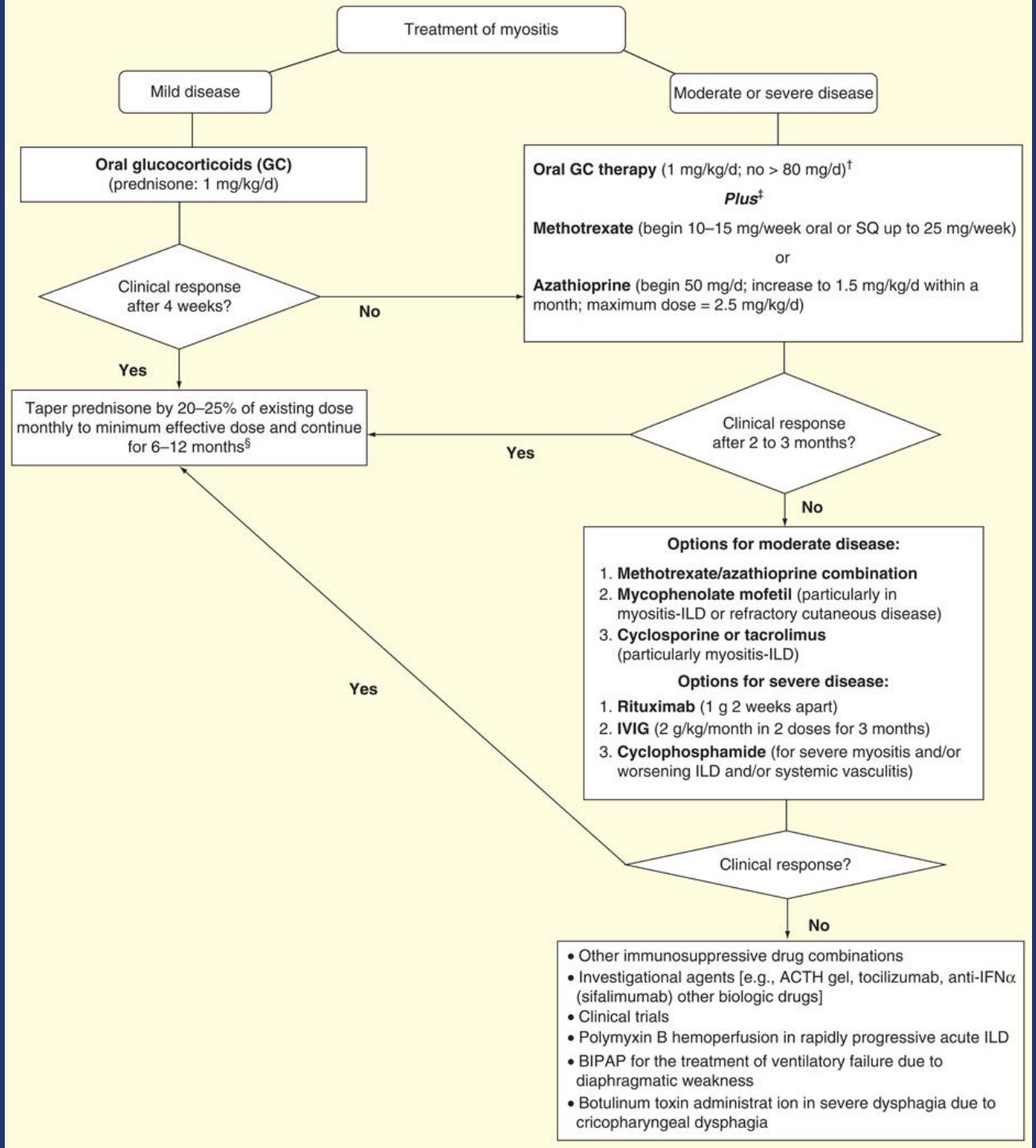


Moghadam-Kia et al
Expert Rev Clin Immunol.
2015;11(11):1265-75

# QUESTIONS?