How do you know you have the right diagnosis?

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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 Diseases
Bechet’s Disease
Bullous Pemphigoid
Chronic Inflammatory Demyelinating Polyneuropathy
Cold Agglutinin Disease
CREST Syndrome
Crohn’s 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
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

**CONSTITUTIONAL**
- Fever: 16 - 65%
- Adenopathy: 20%
- Lethargy: 10%

**PULMONARY**
- Dyspnea: 7 - 43%

**GASTROINTESTINAL**
- Dysphonia or dysphagia: 18 - 44%
- GI bleeding: 5 - 14%
- Abdominal pain, nausea, vomiting: 22 - 37%

**MUSCULOSKELETAL**
- Weakness: 95%
- Myalgia / arthralgia: 25 - 73%
- Arthritis: 20 - 58%
- Contractures: 20 - 27%
- Raynaud’s: 9 - 14%

**CUTANEOUS**
- Gottron’s papules: 57 - 100%
- Heliotrope rash: 86 - 100%
- Nailfold capillary changes: 91%
- Malar / facial rash: 42 - 73%
- Mouth ulcers: 35%
- Ulceration: 23 - 50%
- Limb edema: 11 - 32%
- Calcinosis: 8 - 30%
- Lipodystrophy: 10 - 14%

[References: 2022 [228]; Pashman, 1995#431; Pashman, 1996#4-53; McCarron, 2008 #20; Contini/Sn, 2008 #38; Keiperahl, 1997 #562]
Inclusion Body Myositis

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

<table>
<thead>
<tr>
<th>Disease features</th>
<th>Juvenile DM</th>
<th>Adult DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age of onset</td>
<td>7 years(^{6,10-12})</td>
<td>30–50 years(^{13})</td>
</tr>
<tr>
<td>Proportion of IMM cases</td>
<td>80–95(^{19,127,128})</td>
<td>35–50(^{129})</td>
</tr>
<tr>
<td>Proximal weakness</td>
<td>85–95(^{10,12})</td>
<td>88(^{130})</td>
</tr>
<tr>
<td>Characteristic rash</td>
<td>Gottron papule: 73–91(^{7,131}) Heliotrope rash: 62–83(^{7,131}) Malar rash: 42–57(^{7,131}) Abnormal nailfold capillaries: 80(^{131})</td>
<td>Gottron papule: 54(^{130}) Heliotrope rash: 74(^{130}) Malar rash: data not available Abnormal nailfold capillaries: 43(^{132})</td>
</tr>
<tr>
<td>Calcinosis or ulceration</td>
<td>26–40(^{19,131,133})</td>
<td>2–16(^{19,133})</td>
</tr>
<tr>
<td>Refractory or chronic disease</td>
<td>59–63(^{12,134})</td>
<td>63(^{133})</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1(^{12,133})</td>
<td>15–24(^{41,133})</td>
</tr>
<tr>
<td>Myositis-specific antibodies</td>
<td>2–40(^{19,59})</td>
<td>48–70(^{58,59})</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>7–19(^{29})</td>
<td>35–40(^{30})</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>2–3(^{4,19})</td>
<td>1(^{19})</td>
</tr>
<tr>
<td>Raynaud disease</td>
<td>10(^{135})</td>
<td>11(^{136})</td>
</tr>
<tr>
<td>Mortality</td>
<td>&lt;5(^{12,13,133})</td>
<td>21(^{133})</td>
</tr>
</tbody>
</table>

Abbreviations: DM, dermatomyositis; IMM, inflammatory myopathic myositis.
### Criteria for inflammatory myositis DM, JDM and PM

<table>
<thead>
<tr>
<th>Characteristic muscle findings</th>
<th>Characteristic skin rash</th>
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</thead>
<tbody>
<tr>
<td>• Symmetrical proximal muscle weakness</td>
<td></td>
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<tr>
<td>• Elevation of muscle derived enzymes</td>
<td></td>
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<tr>
<td>• Typical EMG pattern</td>
<td></td>
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<tr>
<td>• Vasculitis and/or inflammation on muscle biopsy</td>
<td></td>
</tr>
<tr>
<td>• MRI</td>
<td></td>
</tr>
<tr>
<td>• Gottrons papules</td>
<td></td>
</tr>
<tr>
<td>• Erythematous rash</td>
<td></td>
</tr>
<tr>
<td>• Alopecia</td>
<td></td>
</tr>
<tr>
<td>• Calcinosis</td>
<td></td>
</tr>
<tr>
<td>• Periungual edema and telangiectasia</td>
<td></td>
</tr>
</tbody>
</table>
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**
- Fever
- Raynauds
- Lung fibrosis
- +/- rash

**Necrotizing myopathy**
- Myositis
- Arthropyathy
- High CK

**Amyopathic dermatomyositis**
- Rash *sine* myositis
- Hypomyopathic
- Rash precedes myositis

**Dermatomyositis**
- Rash
- Malignancy
- Calcinosis/vasculitis (children)

Slide courtesy of Dr. Hector Chinoy
SEVERE MYOPATHY

DYSPHAGIA

NECROTISING MYOPATHY

SRP

HMGCER

STATINS

IBM

5NT1A

ANTI-SYNTHESE SYNTHETASE SYNDROME

Mechanics Hands Raynaud's Phenomenon Arthritis

Ha

Jo-1

Zo

EJ

PL7

PL12

KS

LUNG DISEASE

MDA5

SKIN DISEASE

SAE

Mi-2

CALCINOSIS

NXP2

TIF1

MALIGNANCY

CTD OVERLAP

Ku

SnRNP

Ro

PmScl

La

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

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)
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
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)
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
SAE
Small ubiquitin-like modifier activating enzyme

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

Amyopathic at onset
Dysphagia
Immune-mediated necrotizing myopathy autoantibodies

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 without inflammation
No MHC-1 immunostaining
MAC/C5b-9 staining (similar to DM)
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;
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

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

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

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

Oddis, et al
Treatment of myositis

Mild disease

Oral glucocorticoids (GC) (prednisone: 1 mg/kg/d)

Clinical response after 4 weeks?

No

Taper prednisone by 20–25% of existing dose monthly to minimum effective dose and continue for 6–12 months

Yes

Moderate or severe disease

Oral GC therapy (1 mg/kg/d; no > 80 mg/d)†

Plus‡

Methotrexate (begin 10–15 mg/week oral or SQ up to 25 mg/week)
or
Azathioprine (begin 50 mg/d; increase to 1.5 mg/kg/d within a month; maximum dose = 2.5 mg/kg/d)

Clinical response after 2 to 3 months?

No

Options for moderate disease:
1. Methotrexate/azathioprine combination
2. Mycophenolate mofetil (particularly in myositis-ILD or refractory cutaneous disease)
3. Cyclosporine or tacrolimus (particularly myositis-ILD)

Yes

Options for severe disease:
1. Rituximab (1 g 2 weeks apart)
2. IVIG (2 g/kg/month in 2 doses for 3 months)
3. Cyclophosphamide (for severe myositis and/or worsening ILD and/or systemic vasculitis)

Clinical response?

No

- Other immunosuppressive drug combinations
- Investigational agents [e.g., ACTH gel, tocilizumab, anti-IFNα (cilomilumab) other biologic drugs]
- Clinical trials
- Polymyxin B hemoperfusion in rapidly progressive acute ILD
- BIPAP for the treatment of ventilatory failure due to diaphragmatic weakness
- Botulinum toxin administration in severe dysphagia due to cricopharyngeal dysphagia
QUESTIONS?