Myositis

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Overview

- **Myositis** = inflammation of the muscle
  - As evidenced by the presence of T/B cells on muscle biopsy
  - **Primary**—Immune-mediated
    - Dermatomyositis
    - Anti-synthetase syndrome
    - Immune-mediated necrotizing myopathy
      - HMG-CoA reductase
    - Overlap myositis—associated with SLE, Sjögren, RA, scleroderma
  - **Secondary**—Neurodegenerative; inflammation is a secondary feature
    - Inclusion-body myositis
Autoimmune myositis
Clinical-Common features

• Proximal muscle weakness
  • Shoulder and hip girdle muscles—deltoids, biceps, triceps, gluteus max/medius, quadriceps, hamstrings, iliopsoas
  • *How do they present?*
    • Difficulties walking, running, climbing stairs, rising from floor or chair
    • Difficulties washing/styling hair, doing overhead work
    • Neck flexor weakness
    • Advanced disease → diaphragmatic and bulbar (swallowing) weakness
  • Myalgia (not prominent symptom)

• All have normal to high CK
• Diagnostic workup similar – Clinical exam, CK, autoantibody, EMG, muscle biopsy, ±MRI of muscle, ±CT chest
• Muscle biopsy – shows necrosis, variable amount of inflammation (T helper cells, B cells), vascular abnormalities
Immune Mediated - Dermatomyositis

• Pathophysiology
  • Immune – **Interferon** overproduction; abundant **plasmacytoid** dendritic cells that induce T & B cells in pathological sections
    • Secretes autoantibodies → Complement activation/MAC → capillary damage → infarction
  • Genetic – genes induced by interferon are upregulated
    • Class 2 HLA alleles associated with DM
      • HLA-B08, HLA-DRB1*0301 associated with more severe disease
  • Environmental
    • Events that disrupt immune system; e.g. antecedent viral illness (preceding 6 months)

• Cascade reaction

Evidence for mechanisms contributing to juvenile dermatomyositis pathogenesis. pDC: plasmacytoid dendritic cell; c0: complement; Treg: regulatory T cell; IL: interleukin; MCP: monocyte chemoattractant protein; IFN: interferon; MHC: major histocompatibility complex; CXCL: Chemokine (C-X-C motif) ligand; MRP: myeloid-related protein; TLR: toll-like receptor; MAC: membrane attack complex; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule.

Dermatomyositis – Clinical

• Children & adults
• Subacute onset—manifest over weeks to months
• Muscle weakness + rash ± other organ involvement
• CK elevated – normal to high (few 100 to several 1000’s IU/L)
  • Why?
  • Due to muscle membrane damage and necrosis; via MHC-I mediated damage and MAC deposition
  • Does not always correlate with disease severity/response to medication
  • Caveat: AST/ALT also elevated. Surprised?
    • Practically: if CK elevated → can trend to monitor response to treatment
• Rash – may precede weakness by weeks to months
  • Photosensitive areas – extensor surfaces of joints (MCP, elbows, knees), anterior chest, posterior neck, face
  • Erythematous
  • Edematous
  • Occasionally pruritic
Dermatomyositis – Clinical

**Heliotrope rash.** Purple/violet discoloration over upper eyelids.

**Malar rash.**
May be associated with periorbital edema.

**V sign.** Erythematous skin changes in anterior neck.
Dermatomyositis – Clinical

**Shawl sign.** Erythema noted over posterior neck and upper back in the distribution of a shawl

**Gottron sign.** Scaling, erythematous changes over bony prominences—metacarpophalangeal joints but also proximal and distal interphalangeal joints. **Gottron papules** if raised and plaque-like

Dermatomyositis – Clinical

**Mechanic’s hands.** Rough, cracking appearance of the skin of the fingertips (especially in index and thumb, lateral aspects)

**Telangiectasia hemorrhages (arrow).** Present at the nailbeds (periungual abnormalities) with irregular thickened cuticles.

Dermatomyositis – Clinical

**Alopecia.** Focal patches and diffuse hair loss seen with erythematous eruptions over scalp. May be itching and scaling.

**Calciosynthesis.** Thick, linear, hyperpigmented, deep-seated nodules on medial thigh in juvenile DM. Calcium deposits within skin. More common in juvenile>adult DM.

Dermatomyositis – Clinical

Calcinosis. Calcium deposits eroding skin over the distal IPJ.

Severe skin ulceration. Pt with MDA-5 Autoantibodies

Dermatomyositis - Clinical

Other extramuscular manifestations:

• Cardiac – arrhythmias, cardiomyopathy, pericarditis, myocarditis, CHF

• Pulmonary – interstitial lung disease-DOE, nonproductive cough
  • Reticulonodular pattern or diffuse alveolar pattern with ground-glass appearance
  • Restrictive lung defect on PFTs; reduced diffusion capacity (DLCO)
  • Leading cause of death in DM

• GI—dysphagia, impaired gastric motility, aspiration pneumonia
  • Intestinal vasculopathy—ulceration, perforation, GI hemorrhage
    • Serious complication; juvenile>adult DM

• Rheum—large and small joint arthralgia
  • With or w/o underlying arthritis

• Malignancy – often adenocarcinomas; 2 years before or after muscle weakness/rash; reduced survival rate
Dermatomyositis - Clinical

C&D: ILD in anti MDA-5 positive DM patients

Dermatomyositis – Diagnosis

- CK – normal to several 1000’s
- EMG—confirm a myopathic process
  - Excludes nerve conditions with proximal muscle weakness—ALS, SMA, CIDP
  - NCS are normal; needle EMG shows myopathy with active muscle damage; *please indicate to EMGer that you are worried about a myopathy*
- Auto-antibodies

<table>
<thead>
<tr>
<th>Myositis-specific Ab</th>
<th>Characteristic Clinical Features</th>
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<tbody>
<tr>
<td>Anti Mi-2 (classic)</td>
<td>Classic skin rash; moderate weakness; favorable response to tx; low malignancy risk</td>
</tr>
<tr>
<td>Anti TIF-1γ</td>
<td>Increased risk of malignancy (adult); severe skin rash; hypopigmented red on white patches; variable weakness</td>
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<tr>
<td>Anti NXP-2</td>
<td>Increased risk of malignancy (adult); classic skin rash; mild to moderate weakness; subcutaneous calcifications; edema</td>
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<tr>
<td>Anti MDA-5</td>
<td>Severe skin rash; no/minimal muscle involvement; skin ulceration; rapidly progressive ILD; poor prognosis</td>
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<tr>
<td>Anti SAE</td>
<td>Classic rash; mild muscle involvement; dysphagia</td>
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Dermatomyositis – Diagnosis

- Tissue is usually necessary for definitive diagnosis.
- Usually done on muscle or skin.
- Muscle biopsy with perifascicular atrophy (we don’t know why)
  - Pathognomonic
- Mild inflammation cells (CD4 T cells, plasmacytoid dendritic cells) are located around the muscle cells and around vessels
- Reduced capillary density
- Ischemia

Muscle biopsy showing small, atrophic muscle fibers in a perifascicular (edge of fascicle) distribution (arrows).

Dermatomyositis – Diagnosis

- The newest diagnosis tool
- Do MRI with STIR without contrast
  - MRI of both thighs (high yield)
  - Hyperintensity on T1 & STIR
- Visualizes muscle edema (active disease), muscle atrophy (chronic), fatty replacement (chronic)
- Done if biopsy contraindicated (on anticoagulation) or not diagnostic
- Presence of subcutaneous edema, fasciitis
  - Specific for DM compared to other immune myositis
- Can help in selection of biopsy site
- Can be positive in presumed amyopathic DM

MRI of thighs. A: STIR-Subcutaneous hyperintensity throughout (red)
B: Axial image of thigh; marked atrophy of thigh (blue)
C: Subcutaneous calcification in posterior thigh (hypointensity; yellow)

Immune-Mediated: Antisynthetase Syndrome

- Autoimmune condition with myositis + ILD
- Associated with autoantibodies to aminoacyl transfer RNA (tRNA) synthetases
  - Enzyme that catalyzes binding of amino acid to their cognate tRNA
Antisynthetase Syndrome

Pathology

- Similar to DM—perifascicular atrophy, microvascular abnormalities

Autoantibodies

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<td>Anti Jo-1</td>
<td>Muscle involvement common (90% of pts); progressive ILD; may have mild skin rash or mechanic’s hand</td>
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<tr>
<td>Anti PL-7</td>
<td>Severe ILD; may have moderate muscle involvement</td>
</tr>
<tr>
<td>Anti PL-12</td>
<td>Severe ILD (50% of pts), may have mild or no muscle involvement</td>
</tr>
<tr>
<td>Anti glycyl-transfer RNA synthetase (EJ), anti OJ, anti KS</td>
<td>High association with ILD</td>
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<tr>
<td>Anti Zo, Anti Ha</td>
<td>Rare; possible ILD</td>
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Antisynthetase Syndrome - Clinical

• May have all or some of the following:
  • Inflammatory myopathy
    • Not in all patients
    • Most common in anti Jo-1
  • ILD
  • Arthritis
  • Raynaud syndrome
  • Fever
  • Mechanic’s hands
  • Rash similar to DM
• CK typically in 1000’s
  (average 4500 IU/L)

B: ILD in a anti Jo-1 positive DM pt.
Immune-Mediated Necrotizing Myopathy

- Severe proximal muscle weakness
- Rare extra-muscular involvement
- CKs are very high; several 1000’s (b/c of necrosis)

Autoantibodies

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<td>Anti 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (2/3rd of cases)</td>
<td>Severe muscle involvement; prior statin use (30% are statin naïve); no skin or lung involvement</td>
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<tr>
<td>Anti signal recognition particle (SRP) (5% of cases)</td>
<td>Severe muscle involvement; rare ILD; no skin involvement</td>
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<tr>
<td>Antibody-negative immune mediated necrotizing myopathy</td>
<td>Increased risk of malignancy (screen annually with CT chest, abdomen, pelvis, whole body PET, routine screens x 3 y)</td>
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Pathology

- Muscle biopsy shows necrosis and very minimal inflammatory cells
Diagnostics

- Thorough clinical exam, check CK, assess for other organ involvement (CBC, CMP), EMG, autoantibodies
  - 2nd tier diagnostics: CT chest, MRI of muscles
  - Muscle MRI – T1 hyperintensity and hyperintensity on STIR indicative of intramuscular edema; no fascial edema (unlike DM)
  - Anti SRP and anti HMG-CoA Ab levels, CK, and necrosis on muscle biopsy are highly correlated with disease activity (likely pathogenic antibodies)
    - Can trend CK (most practical) to measure response to treatment
HMG-CoA Reductase Necrotizing Myopathy

- Comprises ~2/3rd of immune mediated necrotizing myopathy cases
- 2/3rd of cases associated with statin use
  - 1/3rd are statin naïve (autoimmune) – more common in younger pts; can occur in a pediatric patient (teen)
- No clear correlation with type of statin or dose
- Length of statin exposure prior to developing symptoms range from weeks to years
- Slowly progressive myopathy
HMG-CoA Reductase Necrotizing myopathy

Pathogenesis

• Not completely understood
• HMG-CoA reductase expression is upregulated by statin exposure
• Immunogenetic risk factor:
  • HLA DRB1*11:01 is found in 70% of pts (10% of general pop)
  • May play a role in presenting HMG-CoA reductase peptides with exposure to statins that trigger immune response
• Regenerating muscle have ↑ HMG-CoA reductase protein
• Aberrant HMG-CoA reductase protein processing occurs
• Tolerance to HMG-CoA reductase is broken, the regenerating myofibers will serve as a source of autoantigen even after d/c of statin
• Ab are not on surface of myofiber; could be cross-reacting to surface Ag

HMG-CoA Reductase Necrotizing myopathy

- Incidence: 2 per million/yr
- Weakness, myalgias
  - No improvement after discontinuation of statin
- Very high CKs; mean 10,000 IU/L
- Send HMG-CoA reductase antibody assay
  - sensitivity of 94.4%, specificity 99.3%
  - Highly correlates with disease activity
- No association with cancer
- EMG
- Muscle biopsy
- Treatment:
  - Immediately stop statin (high risk for MI/stroke)
  - Prednisone
  - Methotrexate, azathioprine
  - IVIG
Anti SRP Necrotizing Myopathy

- Rare, 5% of myositis cases
- Severe muscle weakness, dysphagia
  - No ILD, no rash
- Very high CKs; several 1000’s
- No association with cancer
- High incidence of HLA DRB1*08:03
Overlap Myositis

- Autoimmune myopathy associated with a well-defined connective tissue disorders
  - SLE, Sjögren syndrome, RA, systemic sclerosis
- Proximal muscle weakness

**Nonspecific Autoantibodies**

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<td>Anti R052/TRIM21</td>
<td>R052 is most common (25% of overlap myositis cases)</td>
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<td>Anti PMScI</td>
<td>Associated with scleroderma; lung and esophageal involvement</td>
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<td>Anti Ku</td>
<td>Associated w/joint involvement, Raynaud syndrome, ILD</td>
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<tr>
<td>Ribonucleoprotein (U1 through U5 RNP)</td>
<td>Found in SLE, scleroderma</td>
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Polymyositis

- Very rare entity
- CD8 T cells on muscle biopsy
- Now a diagnosis of exclusion
# Immune Mediated Myositis Overview

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<thead>
<tr>
<th>Antibody</th>
<th>Muscle</th>
<th>Skin</th>
<th>Lung</th>
<th>Cancer</th>
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<tbody>
<tr>
<td><strong>Dermatomyositis</strong></td>
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<td>Mi-2</td>
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<td>TIF-1γ</td>
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<td>NXP-2</td>
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<td>MDA-5</td>
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<td><strong>Anti-synthetase</strong></td>
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<td>Jo-1</td>
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<td><strong>Necrotizing</strong></td>
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<tr>
<td>SRP</td>
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<tr>
<td>HMG-CoA R</td>
<td>X</td>
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<tr>
<td>Antibody negative</td>
<td>X</td>
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Treatment for all Immune mediated myositis

• Start prednisone (after biopsy)
  • Try not to exceed 40mg/d (absolute value)
  • May need to maintain this dose for 6 months; until normal strength
    • Can do 60mg/d for 2 weeks, but rapidly wean down to 40mg/d
  • Why?
    • To avoid steroid-induced myopathy

• Almost always need a steroid sparing agent
  • Methotrexate
  • Azathioprine
  • Mycophenolate mofetil

• May need a second immune agent
  • IVIG

• Stop statin for HMG-CoA reductase necrotizing myopathy
Try not to exceed 40mg/d

**Mild weakness**

- Prednisone 0.75–1.0 mg/kg/d (not >40–60 mg/d)
- Response after 2 months?
  - Yes
    - After improvement/stabilization in strength (2 to 4 months)
    - Taper prednisone by 20% every 2 to 3 months to lowest effective dose; gradual taper of other agents every 3 to 4 months
  - No

**Moderate to severe weakness**

- Prednisone 1 mg/kg/d (not >60–80 mg/d) +
  - Methotrexate oral or subcutaneously (start 10 mg/wk, up to 20–25 mg/wk)
  - Azathioprine (start 50 mg/d, increase up to 2.0–2.5 mg/kg/d)
  - If severe weakness, consider also starting with IV Ig (2 g/kg over 5 days loading dose followed 1 month later by 1 g/kg monthly for 3 months)
- Response?
  - Yes
    - For moderate disease, options include IV Ig, mycophenolate mofetil, cyclosporine, tacrolimus
    - For severe disease, options include rituximab, IV Ig, IV solumedrol, cyclophosphamide
  - No
    - Immunosuppressive combination agents, investigational agents, clinical trials

Do 60mg/d x 2 weeks max, then decrease to 40mg/d

Usually takes 6 months

Treatment for all Immune mediated myositis

- **Cancer screening**
  - Most malignancy occurs within first 3 years of myositis onset
  - CT chest, abdomen, pelvis
  - Age-appropriate cancer screen (mammo, colonoscopy, gynecological)
  - Consider PET
  - High risk subtypes should be screened ~annually
Neurodegenerative Inclusion Body Myositis (IBM)

- Neurodegenerative disease of muscle
- Most common adult onset myopathy; underdiagnosed
- Clinical:
  - Falls due to quad weakness
  - Finger flexion weakness (grip)
  - Dysphagia (late finding)
- Onset at ~ age 50
- M>F
- Risk of: Aspiration pneumonia, falls, restrictive lung disease
- High association with coexisting rheum disease like Sjögren
- Associated with HLA DRB1*03:01

IBM – Clinical Pathology

- Autoantibody: anti-5’ nucleotidase cytosolic IA (NT5C1A)
  - Used in diagnosis
  - Positive in 40-60% of sporadic IBM; not specific (positive in Sjögren, SLE)
  - More common in ♀; more severe phenotype (poorer prognosis) with reduced FVC, ↑mortality and dysphagia

- Muscle biopsy – needed for diagnosis
- Not responsive to immune drugs
- No treatment