Inflammatory Muscle Disease Workshop

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Disclosure

• Nothing to Disclose
Objectives

- Diagnose Inflammatory Muscle Disease
- Discuss Laboratory Findings
- Review Underlying Neoplastic Disease Associations
- Approach to treatment
Inflammatory Myopathies

- Polymyositis (PM) and Dermatomyositis (DM) are the most common
- Non-suppurative muscle inflammation
- Annual incidence 2-10 cases/million
- Peak age at onset bimodal: 10-15y.o; 45-55y.o.
- Female to Male 2-3:1
Classification

1. Adult Polymyositis
2. Adult Dermatomyositis
3. PM/DM Associated with Malignancy
4. Childhood DM (less often PM)
5. PM/DM assoc with other CTD’s

Proposed diagnostic criteria for polymyositis and dermatomyositis

- Symmetric proximal muscle weakness
- Elevated muscle enzymes (CPK, aldolase, transaminases, LDH)
- Myopathic EMG abnormalities
- Typical changes on muscle biopsy
- Typical rash of dermatomyositis

- PM diagnosed as definite with 4 out of 5 of the criteria or probable with 3 out of 5
- DM diagnosed as definite with rash plus 3 out of 4 of the criteria or probable with rash plus 2 out of 4 criteria

Symmetrical Proximal Muscle Weakness
Symmetrical Proximal Muscle Weakness:

- Weakness occurs earliest and insidiously over 3-6 months
- Most severely around the shoulder/pelvic girdles and neck flexors
- Pain is typically absent or minimal
Symmetrical Proximal Muscle Weakness:

Practical Questions to Patients
Laboratory findings
Laboratory findings

- Creatine kinase (CK) is elevated in most patients
- Other markers of muscle damage: aldolase, AST, ALT, and LDH
- Myoglobinuria can be seen in active disease
EMG

- Typical findings in PM/DM: Polyphasic motor unit action potentials (MUAP’s) with short duration and low amplitude
- Findings in neuropathic disorders are large amplitude and long duration MUAPs
EMG

Comparison between
(a) normal motor units
(b) brief polyphasic units as seen in myopathies
(c) high amplitude and long duration polyphasic units characteristic of reinnervation/neuropathic
Nerve Conduction Velocity

• NCV are abnormal in neuropathic diseases
• NCV are normal in inflammatory myopathies with the exclusion of:
Nerve Conduction Velocity

• NCV are abnormal in neuropathic diseases
• NCV are normal in inflammatory myopathies with the exclusion of: IBM in which neuropathic disease can occur along with the myopathy
Muscle Biopsy: Hints for Pathologists and Surgeons
Polymyositis

- The muscle biopsy shows endomysial mononuclear cells and myonecrosis.
- A cell-mediated autoimmune disorder in which cytotoxic T-cells and macrophages invade and destroy myofibers.

DIMITRI P. AGAMANOLIS, M. D.
Dermatomyositis: Is a **vasculitis** which involves endomysial and perimysial capillaries and arterioles. This vasculitis begins with endothelial swelling and is followed by endothelial necrosis and capillary loss.
Dermatomyositis:
Immune complex deposition in vessels a complement mediated
vasculopathy; perifascicular often around blood vessels.
Dermatomyositis: acute myositis: Lymphocytes and histiocytes have infiltrated the muscle fibers. Many of these skeletal muscle fibers appear normal. Two are necrotic, and another is fragmented and invaded by macrophages.
Dermatomyositis: chronic myositis: There are diffuse skeletal muscle changes with atrophy of some muscle fibers. Newly formed fibrous tissue has replaced some of the muscle bundles. A mild mononuclear-inflammatory reaction is present.
**Dermatomyositis:** A diffuse interstitial mononuclear infiltrate is present, along with active degeneration of a large muscle fiber.
Imaging
Localized nodular myositis: thigh (MRI)

Focal abnormal muscle signal is demonstrated of the thigh of a patient with nodular myositis. This uncommon condition presents as recurrent acute episodes of localized muscle pain and swelling and may progress to more typical, chronic polymyositis.
MRI

- MRI scanning can help direct muscle biopsy
- Demonstrate areas of edema/inflammation
Dermatomyositis: Nailfold Capillaroscopy

- Changes of nailfold capillary patterns have been described in certain patients with systemic sclerosis, dermatomyositis, mixed connective tissue disease, and Raynaud's syndrome.

- These changes are characterized by loss of (drop-out) nailfold capillary loops that surround the remaining, enlarged dilated capillaries.
Dermatomyositis: periungual involvement (nailfold capillaroscopy)

- Upper left, A normal nailfold capillary pattern shows the uniform morphology and homogeneous distribution of the small capillary loops just below the cuticle.

- Upper right, Capillaroscopy in a patient with systemic sclerosis illustrates dilation of isolated capillary loops, with loss of surrounding loop structures.

- Lower right, The abnormal pattern is from a patient with childhood dermatomyositis. Dilated capillary loops are present, as well as areas of arborized clusters of capillary loops.

- Lower left, Distortion of the normal capillary loop architecture is seen in a patient with adult dermatomyositis. Note the loss of normal homogeneous distribution of the capillaries and the alterations in the morphology of the vessels, including the dilated and enlarged "giant" capillary loops.
Dermatomyositis

• Can DM present with no muscle abnormalities?
• Amyotrophic Dermatomyositis
• Half or more will develop muscle disease over time, however a significant proportion have skin disease only
Extramuscular Manifestations

- Constitutional: fatigue, low-grade T°
- MSK: Arthralgias, arthritis
- Pulmonary: ILD (5-10%), Aspiration pneumonia, PAH, respiratory muscle weakness
- GI: esophageal dysmotility
- Cardiac: Myocarditis, dysrhythmias, conduction blocks
- Vascular: Livedo reticularis, Raynaud’s
APPROACH FOR EVALUATION OF MUSCLE DISORDERS

• Determine if this is a manifestation of systemic illness or a neuromuscular disorder.

• The clinical evaluation should focus on the pattern of weakness (proximal vs distal), fatigability, soreness, skin rash, muscle atrophy, and fasciculations.

• Family history is important.

• Useful laboratory studies include CK, erythrocyte sedimentation rate, serology for collagen vascular disease, acetylcholine receptor antibodies, and electromyography (EMG). Functional testing (Tensilon test) are diagnostic in some cases.
Approach

- Based on the clinical and laboratory evaluation, muscle disease can be divided into two broad categories, myopathy and denervation atrophy.
- **Myopathy** means a condition with proximal weakness, elevated CK, and myopathic EMG changes. This broad group includes the muscular dystrophies and inflammatory myopathies.
- **Denervation** most often causes distal weakness and atrophy, and neuropathic EMG changes. CK is normal. A more specific diagnosis can be obtained by a muscle biopsy.
- Consult Rheumatology/ Neurology
Diagnosis of Myositis

• Suspect the disease
• Rule out other conditions
• Confirm the diagnosis
Differential Diagnosis

• Hypothyroidism: “The great pretender”

• Drug-induced myopathies
  Corticosteroids, colchicine, statins, zidovudine, hydroxychloroquine, alcohol

• Infections
  – Viral, HIV, toxoplasmosis, trichinosis, bacterial pyomyositis

• Connective tissue disorders
  – Lupus, scleroderma, MCTD

• Systemic vasculitis
  – PAN, Wegener’s granulomatosis
Differential Cont’d

- Metabolic myopathies
  - Disorders of carbohydrate and lipid metabolism
- Electrolyte disturbances
  - Hyponatremia, hypernatremia, hypokalemia, hypophosphatemia,
  - Hypercalcemia/Hypocalcemia
- Inclusion body myositis
- Sarcoid myopathy
- Amyloid myopathy
- Neurologic disorders
  - Myasthenia gravis, motor neuron disease (ALS), muscular dystrophy
- Other CTD’s including Rheumatoid, PMR, FM, Vasculitis
History

- Triggers: Infection
- Medications
- Social History: Alcohol, recreational drugs
- Systemic symptoms: B symptoms
- Sensory symptoms: neuropathy or spinal cord disease
- Distribution
- Evolution of symptoms
- Symmetry
History

- Modifying factors: fatiguability in MG
- Diplopia
- Exercise: Metabolic myopathy
- Family history: MD
- Pain everywhere: What condition?
- Progressive or Episodic
- CTD symptoms
Helpful Neurologic Hints

- Muscle wasting: UMN or LMN: LMN
- Fasiculation: Ant horn Disease
- Muscle Tone Reduced: LMN
- Proximal Weakness: PM
- Reflexes Reduced: LMN
Inclusion Body Myositis

- Males affected more than females
- Age of onset usually greater than 50
- Slowly progressive
- Distal and asymmetric muscle weakness
- Myopathic and neuropathic changes on EMG
- Mononuclear cell infiltrates and vacuoles containing amyloid on muscle biopsy
- Responds poorly to corticosteroids
Inclusion body myositis

Sparse inflammation, mild fiber size variation, and a few angulated fibers are seen in this muscle biopsy specimen from a patient with muscle weakness. Red-rimmed or lined vacuoles representing abnormal filaments (inclusion bodies) are seen.
Figure 1. Characteristic histological features in cross-sections of muscle biopsies in patients with inclusion body myositis.

(A) Inflammation and vacuoles. Note endomysial inflammation, with lymphocytes invading non-necrotic, healthy-appearing muscle fibers, and 'red-rimmed' vacuoles in two muscle fibers (arrows) not invaded by inflammatory cells. If the course of the same vacuolated fibers is followed at considerable length in longitudinal sections, they remain devoid of autoinvasive inflammatory T cells. (B) Intracellular deposits of amyloid, easily identified with crystal violet stain on frozen sections. (C) Scattered cytochrome-oxidase-negative fibers, indicative of abnormal mitochondrial function. (D) Strong major histocompatibility complex class I expression (green) in all fibers, regardless of whether they are invaded by T cells.
Laboratories

- CBC
- CK
- LDH, AST, ALT
- Electrolytes; Ca
- Thyroid
- Urine
- ESR, cRP
Laboratories

• Myositis-Associated Autoantibodies:
  • ANA (50-80%)
  • Anti RNP antibody (ENA)
  • Anti PM-Scl Ab (PM-scleroderma overlap)
  • Anti-Ku Ab (PM-scleroderma overlap)
  • Anti-CADM-140 (amyotrophic DM)
## Myositis-specific antibodies

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>DISEASE ASSOCIATION</th>
<th>PREVALENCE</th>
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<tbody>
<tr>
<td>Anti-tRNA synthetases (Jo-1)</td>
<td>Dermatomyositis, Polymyositis; interstitial lung disease, “mechanic’s hands”</td>
<td>20-50%</td>
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<td>Anti-SRP (signal recognition protein)</td>
<td>African-American women, poor prognosis: Severe, resistant PM</td>
<td>Rare (&lt;5%)</td>
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<tr>
<td>Anti-Mi-2</td>
<td>Older women, “shawl sign,” good prognosis; Classic DM</td>
<td>5%</td>
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<tr>
<td>PM/SCL</td>
<td>Polymyositis/scleroderma overlap</td>
<td>Rare</td>
</tr>
<tr>
<td>Clinical Significance of Myositis Specific Autoantibodies</td>
<td>Anti- Synthetase (anti-Jo-1)</td>
<td>Anti SRP</td>
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<tr>
<td>Onset</td>
<td>Acute; spring</td>
<td>Very acute; winter</td>
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<tr>
<td>Clinical Manifestations</td>
<td>PM&gt;&gt;DM ILD (40-60%)</td>
<td>Severe PM Cardiac Involvement</td>
</tr>
<tr>
<td>Steroid Response</td>
<td>Moderate</td>
<td>Poor</td>
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Malignancy

• Is there an increased risk with DM or PM?
Malignancy

- Is there an increased risk with DM or PM?
- DM (3-6X); PM (1-2X)
- Cancers are present at Dx or in F/U in 10-15%
- Cancers associated: lung, stomach, ovary, breast, pancreas, lymphoma
Malignancy: Screen

- Age appropriate: history/ physical
- Breast, pelvis, prostate,
- Stool OB
- C-Xray
- Mammogram
- Routine Labs
- Consider Abd/pelvic CT
- Re-evaluate for future development over 3-5 years
Treatment

• Corticosteroids: Mainstay
  – Dose 1-1.5mg/kg
  – Continue until improved strength and normalization of CK

• Immunosuppressives: MTX, azathioprine most common
  – Rarely: CTX, cellcept, chlorambucil, cyclosporine

• Plaquenil for cutaneous manifestations of DM
Other Therapies

- IVIG: Severe refractory DM/PM
- Plasmapheresis
Prognosis

• Depends on clinical subgroup
• Similar 5 yr survival for idiopathic DM/PM and assoc CTD’s (>85%)
• Serologic subgroup:
  – Anti-MI 2 favorable: 5 yr >90%
  – Anti-synthetase (Jo-1): less favorable: 5 yr >65%
  – Anti SRP: 5 yr 30%
Conclusion

• Consider the disease
• Approach rationally
• Help when you need it
• Refer appropriately