Idiopathic Inflammatory myopathies

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No Disclosures
Learning Objective

- Able to recognize clinical and pathologic features of major subtypes of inflammatory myopathy (IM)
- Update on Myositis Specific Antibodies and identifying different clinical phenotypes
- Treatment of inflammatory myopathies
Idiopathic inflammatory myopathies (IIM) or Myositis

A family of rare autoimmune, systemic disorders that share chronic inflammation of muscle of unknown cause and often involve other organ systems.

The management of myositis is best done by a multidisciplinary team, including, but not limited to, an internist, rheumatologist, neurologist, pulmonologist, dermatologist, physical therapist, occupational therapist.
Classification

- Adult-onset dermatomyositis (DM)
- Adult-onset polymyositis (PM)
- Overlap myositis
  *Myositis associated with other connective tissue diseases*
- Anti-Synthetase Syndrome (ASS)
- Immune-mediated necrotizing myositis (IMNM)
- IBM
- Juvenile-onset Myositis
- Cancer-Associated Myositis

Managing Myositis. A practical guide. Rohit Aggarwal and Chester Oddis
Bohan and Peter 1975 PM/DM Criteria

First rule out all other forms of myopathy!

- Symmetrical weakness, usually progressive, of the limb-girdle muscles
- Muscle biopsy evidence of myositis
  - Necrosis of type I and IIb muscle fibers, phagocytosis, degeneration and regeneration of myofibers with variation in myofiber size, endomysial, perimysial or interstitial mononuclear cells
- Elevation of serum levels of muscle-associated enzymes
  - CK, Aldolase, LD, AST, ALT
- Electromyographic triad of myopathy
  - Short, small, low-amplitude polyphasic motor unit potentials
  - Fibrillation potential, even at rest
  - Bizarre high-frequency repetitive discharges
- Characteristic rashes of dermatomyositis

Definite PM=all first 4, probable PM=3 of first 4, possible PM=2/4
Definite DM=rash+3 other; probable DM=rash+2 other; possible DM=rash+1 other

Bohan&Peter 1975, NEJM 292:344 and 403
Shortcomings of Bohan and Peter Classification Criteria

Rohit Aggarwal – Myositis presentation
### Definite IIM
- probability $\geq 90\%$ ~ score $\geq 7.5(8.7)$

### Probable IIM
- probability $\geq 55\%/<90\%$ ~ score $= 5.5(6.7)$

### Possible IIM
- probability $\geq 50\%/<55\%$ ~ score $5.3-5.5/6.5-6.7$

### Non IIM
Probability $< 50\%$ ~ score $< 5.3/6.5$

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**Se 87%/93%**

**Sp 82%/88%**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score No muscle biopsy</th>
<th>Score With muscle biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age of onset of first symptom assumed to be related to the disease $\geq 18$ and $&lt; 40$ years</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Age of onset of first symptom assumed to be related to the disease $\geq 40$ years</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td></td>
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<tr>
<td>Objective symmetric weakness, usually progressive, of the proximal upper extremities</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Objective symmetric weakness, usually progressive, of the proximal lower extremities</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Neck flexors are relatively weaker than neck extensors</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>In the legs, proximal muscles are relatively weaker than distal muscles</td>
<td>0.9</td>
<td>1.2</td>
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<tr>
<td>Skin manifestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heliotrope rash</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Gottron’s papules</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Gottron’s sign</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Other clinical manifestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia or esophageal dysmotility</td>
<td>0.7</td>
<td>0.6</td>
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<tr>
<td>Laboratory measurements</td>
<td></td>
<td></td>
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<tr>
<td>Anti-Jo1 autoantibody present</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Elevated serum levels of CK or LDH$^<em>$ or ASAT/AST/SGOT$^</em>$ or ALAT/ALT/SGPT$^*$</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Muscle biopsy features—presence of:</td>
<td></td>
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<tr>
<td>Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Perimysial and/or perivascular infiltration of mononuclear cells</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Perifascicular atrophy</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Rimmed vacuoles</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2:** Components of the 2017 EULAR/ACR classification criteria for adult and juvenile IIM

When no better explanation for the symptoms and signs exists these classification criteria can be used.
Limitations of 2017 ACR/EULAR Classification Criteria

- Not enough patients from rare subgroups
- Only 1 MSA-Anti Jo1 was documented
- MRI excluded-available 38% cases
- EMG excluded

Valerie Leclair, Inglid Lundberg. New Myositis Classification Criteria-What we have learned since Bohan and Peter. Current Rheumatology Reports (2018) 20:18
Epidemiologic features of PM/DM

- Annual incidence 2-19 cases/million
- Peak age of onset
  - DM: bimodal->5-15 yo and 45-65 yo
  - PM : rarely< 15 y, mean age 50-60 yo
  - IBM >50 yo
- F:M ratio 2-3:1 overall
  - 1:1 JDM
  - Overlap myositis 8-10:1
  - IBM-more common in men
- Ethnicity-US: African American> Caucasians~3-4:1
Pathogenesis

- Remains poorly understood
- Recent in-vivo and in-vitro transcriptomic studies have evidenced the type I IFN-inducible genes are upregulated in DM muscle tissue, skin and blood
- IFN-signature (and IFN-score) ~ with severity of the disease
- IFN-signature (IFN-I and IFN-II) differs among IIM subgroups
- IFN-signature needs to be standardized for a general use in clinics and for investigation of IIM pathogenesis

Dana. P. Asherman. Pathogenesis of Myositis
Evaluation of Patients with suspected Myositis

• History
• Physical exam
• Laboratory test and radiographic studies
• Electromyography
• Muscle Biopsy
History: Patterns of muscle weakness

- Myositis always proximal > distal except IBM

**Proximal weakness**
- Difficulty rising from a chair (hip muscles) or combing hair (shoulder muscles)

**Distal weakness**
- Difficulty standing on toes (gastrocnemius/soleus muscles) or hands grip or activities (intrinsic hand muscles)
- Symmetric vs asymmetric
  - *PM and DM almost always symmetric*
  - *IBM is mostly asymmetric*
- Focal symptoms of weakness or sensory loss indicate a neurologic cause
Other manifestations of Myositis

- Cardiomyopathy
  Generally asymptomatic
  PAH possible
  ECHO in suspected cases

- Lung
  ILD-ac, subacute, chronic
  Respiratory muscle weakness
  PFTs and HRCT chest

- Other muscle groups 10-30%:
  Pharyngeal muscles -> dysphonia
  Upper esophageal muscles -> dysphagia (nasal regurgitation of fluids) - order esophagogram

- Arthritis similar to RA

- Raynaud’s phenomenon

- Systemic Features - fever, fatigue, myalgia

- Rash, Calcinosis - DM, JDM
Drugs associated with Myopathy

- Alcohol, illicit drugs (e.g cocaine)
- Statins
- Glucocorticoids
- Hydroxychloroquine
- Anti Thyroid agents
- Antibiotics
- Chemotherapeutic agents
- Cimetidine
- Fibric acid derivatives (gemfibrozil)
- Over the counter agents
Physical Examination

- Must have objective muscle weakness-MMT
- Severity and distribution of muscle weakness
  - *symmetric (except IBM)*
  - *proximal>*distal (except IBM)*
  - *non-focal*
- Early atrophy-IBM and other myopathies
- Neurologic survey
  - *sensory deficit-not myositis*
- Extramuscular signs
  - *Rash, cuticular thickening and hyperemia, capillary changes, CV, pulm, GI, MSK*
Manual Muscle Test (MMT)
Laboratory

- There are 5 muscle enzymes: Creatine kinase (CK), aldolase, AST, ALT, LDH
- Most cases CK >5-100x ULN
  
  *Very high or very low-rule out other myopathies*
  
- In JDM: AST, ALT>>CK
- Follow the most elevated serum muscle enzyme
- Unlike PM, 20% DM have normal muscle enzymes despite muscle weakness
- 90% of inflammatory myopathy will be positive for either a nuclear or a cytoplasmic Ab. >20% of myositis pt are ANA neg
- MSA and MAA identify clinical subsets among the major categories of IIM
- MSA are mutually exclusive
- A patient with a MSA can have an MAA, esp SSA/Ro (52kd)
## EMG Goal

1. Identify the presence and distribution of electrodiagnostic features of myopathy
2. Determine if there are features more suggestive of inflammation
3. Aid in selecting a muscle for biopsy
4. Determine if there is another cause of weakness such as neuropathy or radiculopathy

<table>
<thead>
<tr>
<th>Good sensitivity 85%, low specificity 33%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased insertional activity with spontaneous fibrillations</td>
</tr>
<tr>
<td>Myopathic low amplitude and short duration polyphasic motor unit action potentials</td>
</tr>
<tr>
<td>Complex repetitive discharges</td>
</tr>
<tr>
<td>NCS nl, except in IBM – Neuropathy can develop along with myopathy</td>
</tr>
</tbody>
</table>
MRI

- T1 weighted MRI: for anatomy
- T2 fat suppressed (STIR): for muscle edema
- Not specific - intramuscular edema can be found in several other disorders (e.g. trauma, myonecrosis, infection, rhabdomyolysis, and noninflammatory myopathies)
- Use to assess damage vs active disease, treatment response and target for biopsy
Figure 2 | Thigh MRI from a patient with dermatomyositis.

a | In T1-weighted images, fat is bright and muscle is dark.
b | In short tau inversion recovery sequences, normal muscle is dark and inflamed muscle is bright. Long arrows indicate the inflamed left vastus lateralis muscle. Short arrows highlight the left biceps femoris muscle; the bright rim around this muscle is consistent with fascial inflammation.

Biopsy

- **Muscle Biopsy**
  
  _Should be performed in most cases to confirm the suspected diagnosis_
  
  _The histologic pattern can be helpful both diagnostically and prognostically_

- Biopsy a muscle that is weak but not severely so

- Biopsy deltoïd, vastus lateralis over quadriceps

- **Skin biopsy**

  _Interface dermatitis usually with mucin similar to SLE_

Muscle Pathology

PM: Inflammatory exudate in muscle with or without invasion of non-necrotic fibers by mononuclear cells

DM: perimysial/perivascular inflammation with/without (50/50%) perifascicular atrophy
II: primarily B cells, CD4+ T cells, plasmacytoid dendritic cells->IFN-alfa-contributes to atrophy

C5b-9 MAC in endothelial cells – associated with reduction of endomysial capillaries and microinfarcts
Characteristic clinical features of adult-onset DM

- Rash maybe the fist clinical manifestation
- Muscle disease-follows or co existent with rash-Subacute or chronic proximal more than distal muscle weakness
- 70% elevated muscle enzymes, 20-30% nl CK-amyopathic DM, ASS but EMG/MRI maybe abn
- MSA 50-70% identify clinical subsets
- 5 year survival- 92% unless associated with cancer -62%
SKIN in DM

- Heliotrope rash <-50% DM: purple-erythematous rash affecting eyelids
- Facial erythema-malar region, forehead, NLF (spared in SLE)
- Gottron’s papules-60-80%DM, purple to erythematous flat or raised lesions over the dorsal MCP/PIP/DIPs, also over extensor surfaces of the wrists, elbows and knees
- V-sign rash: erythematous confluent rash-ant chest and neck
- Shawl sign: erythematous rash over shoulders, prox arms
- Holster sign: lat aspect prox thighs
- Nailfold abn: periungual erythema, cuticular overgrowth, dilated capillary loops
- Photosensitivity
- Subcutaneous calcifications
- DM mimics: trichinosis, allergic contact dermatitis, drug reactions-Hydroxyurea, penicillamine, diclofenac, anti TNF
Managing myositis. A Practical Guide. Rohit Aggarwal and Chest Oddis

Fig. 6.2 Facial erythema with “heliotrope rash” and eyelid edema

Fig. 6.3 Scaly, psoriasiform-like plaques on the scalp

Fig. 6.4 Photodistributed erythema and poikiloderma on the chest (“V sign”)

Fig. 6.5 Erythema and poikiloderma on the upper back (“Shawl sign”)

Fig. 6.6 Hyperkeratosis, lichenification, erythema, and scale on the sides of the finger (“mechanic’s hands”)

Fig. 6.7 Erythematous scaly plaque on the elbow (“Gottron sign”)

Fig. 6.8 Erythema and scale on the lateral thigh (“Hollander sign”)

Fig. 6.9 Erythema and scale on the lateral thigh (“Hollander sign”)

Fig. 6.9 Erythema and scale on the lateral thigh (“Hollander sign”)
Cuticular Thickening and Erythema

Nail fold capillary abnormality
Autoantibodies in myositis

- MAA (auto antibodies also found in other conditions in which myositis can occur): Ro, PMScl, U1RNP, Ku
- MSA are highly specific and useful to classify patients as having clinico-serologic syndromes with distinct clinical features and prognosis
- MSA are mutually exclusive with very rare exceptions-great biomarkers

Anti synthetase syndrome

- Aminoacyl-tRNA synthetase
  - All are located in the cytoplasm
  - Catalyze the attachment of a particular amino acid to its transfer RNA (tRNA)

- Anti synthetase antibodies-recognize 8 of the 21 aminoacyl tRNA synthetases
  - Highly specific
  - Most common MSA-35-40%IIM
  - Can precede disease onset
  - Critical in disease pathogenesis

<table>
<thead>
<tr>
<th>Histidyl-tRNA</th>
<th>Jo1</th>
</tr>
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<tbody>
<tr>
<td>Threonyl-tRNA</td>
<td>PL7</td>
</tr>
<tr>
<td>Alanyl-tRNA</td>
<td>PL12</td>
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<tr>
<td>Isoleucyl-tRNA</td>
<td>OJ</td>
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<tr>
<td>Glycyl-tRNA</td>
<td>EJ</td>
</tr>
<tr>
<td>Asparaginyl-tRNA</td>
<td>Ks</td>
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<tr>
<td>Tyrosyl-tRNA</td>
<td>Ha</td>
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<td>Phenylalanyl-tRNA</td>
<td>Zo</td>
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<tr>
<td>Lysyl-tRNA</td>
<td>CS</td>
</tr>
<tr>
<td>Glutaminyl-tRNA</td>
<td>JS</td>
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</table>
Anti-synthetase syndrome

- Clinical features: ILD, Myositis, inflammatory arthritis, Raynaud’s, Fever, Mechanics hands
- Syndrome can be incomplete-idiopathic ILD or inflammatory arthritis
  - Muscle disease-Jo1, PL7, EJ
  - Arthritis-Jo1
  - ILD-KS, EJ, OJ, PL12
Pulmonary manifestations in IIM

- >30% myositis patients have ILD
- Onset variable: most of the time occurs at the same time of myositis diagnosis
- Course: acute and fulminant ILD, chronic progressive, or asymptomatic (subclinical)
- ILD subtype classified as NSIP-most common, COP and UIP
- ILD leads to poor functional status in 30% of patients
- No correlation between extent and severity of muscle or skin disease and development of ILD
- Secondary PAH can occur due to chronic pulmonary vasoconstriction from hypoxemia
- Patients also may have respiratory muscle weakness

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Case presentation

- 45 Y/O male with 7 month history of rapidly progressive, proximal more than distal muscle weakness and a red, itchy, burning rash on dorsum of fingers

- Two months after onset noticed a lump at the angle of his left neck

- Used to smoke a 1 ½ pack for 15 years, quitted 20 years ago
Case Presentation

- CK 6295 U/L, AST 391 U/L, ALT 267 U/L, ANA speckled type, titer 1:640
- ENA, dsDNA, RF and paraneoplastic panel neg
- Negative CT chest, abdomen and pelvis with contrast
- Normal colonoscopy and serum PSA
- CT of the neck: nonspecific enhancing mass anterolateral to the left common carotid artery
- FNA consistent with squamous cell carcinoma
- Modified radical neck dissection
- Treated with prednisone and IVIG with complete muscle recovery
• Cancer is the leading cause of death for adults with myositis
• Early diagnosis is essential to improve outcomes
• Screening is essential to improve early detection

International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening: an International Myositis Assessment and Clinical Studies Group (IMACS) initiative

### IM diagnosis
(within 3 years of symptom onset)

- **Juvenile-onset IM**
  - Cancer screening not routinely required
- **Adult-onset IM**
  - Cancer risk stratification based on risk factors
- **IBM**
  - Cancer screening not routinely required

### IM subtype

<table>
<thead>
<tr>
<th>'High risk' factors</th>
<th>'Intermediate risk' factors</th>
<th>'Low risk' factors</th>
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</thead>
<tbody>
<tr>
<td>Dermatomyositis</td>
<td>CADM</td>
<td>ASSID</td>
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<tr>
<td>Polymyositis</td>
<td>Polyarthritis</td>
<td>CTD-associated IM</td>
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<td>IMM</td>
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### NSA and MAA

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<tr>
<th>Anti-TIF1I antibodies</th>
<th>Anti-SAEI antibodies</th>
<th>Anti-GRP antibodies</th>
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<tbody>
<tr>
<td>Anti-NXP2 antibodies</td>
<td>Anti-HMGCR antibodies</td>
<td>Anti-AT antibodies</td>
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<td>Anti-M2 antibodies</td>
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<tr>
<td></td>
<td>Anti-MDA5 antibodies</td>
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</table>

### Clinical features

- Age >40 years at IM onset
- Persistent high disease activity despite therapy
- Dysphagia (moderate to severe)
- Cutaneous necrosis
- MSAx sex
- Raynaud phenomenon
- Inflammatory arthropathy
- Interstitial lung disease

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**All patients with IM, irrespective of cancer risk, should continue to participate in country- or region-specific age- and sex-appropriate cancer screening programmes.**

### Screening criteria

- ≥2 'High risk' factors?
  - **Yes**
    - High risk of IM-related cancer
      - Screening at time of diagnosis: Basic and enhanced screening panels
      - Screening at follow-up: Basic screening panel at 1, 2 and 3 years after IM onset
      - Consider additional screening: 18F-FDG PET-CT, upper and lower GI endoscopy
  - **No**
    - Moderate risk of IM-related cancer
      - Screening at time of diagnosis: Basic and enhanced screening panels
      - Screening at follow-up: None

- ≥2 'Intermediate risk' factors or ≥1 'High risk' factor?
  - **Yes**
    - Standard risk of IM-related cancer
      - Screening at time of diagnosis: Basic screening panels
      - Screening at follow-up: None
  - **No**
    - Does not fulfil criteria for high or moderate risk

### Basic screening panel

- Comprehensive history
- Comprehensive physical examination
- Complete blood count
- Serum liver function tests
- Serum CRP
- Serum protein electrophoresis
- Urinalysis
- Plain chest X-ray radiograph

### Enhanced screening panel:

- CT scan of the neck, thorax, abdomen and pelvis
- Cervical screening
- Mammography
- Prostate-specific antigen
- CA 125
- Pelvic or transvaginal ultrasound for ovarian cancer
- Fetal occult blood

### Screening for nasopharyngeal carcinoma:

- Consider nasendoscopy at the time of diagnosis of adult-onset IM in geographical regions where the risk of nasopharyngeal carcinoma is increased
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Take Home Points

- Diagnosis of IIM relies on clinical features, muscle biopsy and autoantibodies.
- The clinico-serologic classification of IIM can assist in defining and predicting extra-muscular manifestations, clinical course, association with malignancy and response to therapy.
- Investigation of the pathogenic role of MSAs and their corresponding autoantigens will help us to understand the pathophysiology of IIM and identify new therapeutic targets.
- Multisystem condition-6 core set measures have been developed by IMACs to assess the overall disease activity.
- GCT are the mainstay of therapy. The addition of cDMARDs (MTX, AZA, tacro/cyclosporine) first line adjunct to CST. PT has additional beneficial effects on muscle performance.
- RTX, IVIG, PLEX have been used in patients with refractory IIM.
Thank you

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OHSU MYOSITIS CENTER

Multidisciplinary clinic rheum (me)-neuro(Dr Nizar Chahin)

Please send referral to neurology neuromuscular OHSU for myositis clinic