Dermatomyositis
...a narrative and clinical update

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Outline

- Case
- Criteria, clinical features, diagnostic evaluation
- Therapy
- Association with malignancy and screening recommendations
- Pathophysiology and spectrum of autoimmune myositis
Case

“…can anecdotes between colleagues help us decide the right thing to do?”

~Tess Jones, Ph.D.
V-sign rash
Gottron’s papules, purple to erythematous scaly rash over the knuckles and dorsum of the hand
Dermatomyositis ~ criteria, epi, clinical features, diagnostic evaluation
## Diagnostic criteria (Bohan and Peter, 1975)

1. Symmetric proximal muscle weakness
2. Biopsy evidence of myositis (MRI can subst)
3. Increased serum skeletal muscle enzymes
4. Characteristic EMG pattern
5. Typical DM rash
   - DM possible (#5 + any two of 1-4), probable (#5 + any 3), definite (all 1-5)
   - PM as above (minus #5)
### Clinical manifestations

- Hallmark is muscle weakness
  - Skin involvement
  - Interstitial lung disease
  - Raynaud’s
  - Inflammatory arthritis
  - Serum autoantibodies

### Epidemiology

- Annual incidence of 2-10 cases/million
- 2 peaks of onset: ages 10-15, 45-55
- Adult F:M is 2:1
- CAM (cancer-assoc myositis) = 10-15% all comers
Diagnostic criteria

- Proximal muscle weakness
  - Earliest symptom, insidious onset over three to six months
  - Most severe around the shoulder and pelvic girdles and neck flexors (facial/ocular weakness is unusual)
  - Pain is typically minimal (<weakness) or absent
- Elevated serum muscle enzymes
  - CK, aldolase, myoglobin, AST and ALT, and LDH. Myoglobinuria may be seen with active dz
- EMG sensitive (90%) but nonspecific.
  - Polyphasic motor unit action potentials with short duration and low amplitude
DDx of DM/PM

- IBM – more insidious, more distal wkns
- Hypothyroid
- Drug-induced – steroids, statins, antimalarials, antipsychotics, colchicine, etoh, cocaine, penicillamine, ART
- HIV – can be early or late
- ALS – more distal, asymmetric, w/ long-tract signs
**Muscle biopsy ~ gold std**

- **DM**: perivascular and perifascicular regions infiltrated by CD4+ PDC’s and T cells, B cells. Late component of complement (c5-9/MAC) appears before inflam cell infiltrate
  - perifascicular myofibril atrophy, endothelial cell hyperplasia of vessels, deposition of immune complexes.
- **PM**: fascicular infiltrate of inflam cells invading muscle fibers, primarily CD8+ T cells recognizing an antigen with increased MHC I expression
DM: Dermatologic Findings

- Rash is often the presenting complaint and may antedate myopathic sx by >1 yr
  - Heliotrope
    - Purple to erythematous rash affecting eyelids, malar region, forehead, and nasolabial folds (contrast SLE)
  - V-sign
    - Confluent erythematous rash over the anterior chest and neck
  - Shawl-sign
    - Erythematous rash over shoulders and proximal arms
  - Mechanic’s hands
    - Cracking and fissuring of the skin of the fingerpads
- Biopsy: interface dermatitis (complement and Ig at derm-epi jct)
hyperkeratotic changes and cracking of the skin on the lateral aspects of the fingers, anti-PM-Scl autoantibody.
DM: dermatologic findings

- Nailfold abnormalities
  - Periungual erythema
  - Cuticular overgrowth
  - Dilated capillary loops

- Subcutaneous calcification
  - Nearly exclusively in the juvenile form of DM, can be extensive

- DM mimics: include cutaneous manifestations of trichonosis, allergic contact dermatitis, drug rxns (diclofenac, penicillamine, hydroxyurea)
DM and SSc: periungual involvement

- **dcSSc**
- **adult DM**
- **childhood DM**
Treatment

- Corticosteroids are the mainstay.
  - Prednisone 1-1.5 mg/kg/d divided, until remission achieved (improved strength and enzyme normalization). Then taper and monitor for recurrence.
  - Response to steroids and long-term outcome is variable
  - If cancer is found underlying the myositis, may not need DMARD beyond prednisone and treatment of underlying disease.
Treatment II

- Immunosuppressants are used in steroid-resistant and life-threatening disease
  - MTX and AZA used most often
  - Small case studies support use of MTX in combo with CsA for steroid-resistant PM/DM.
- IVIG is effective in severe/refractory cases, in addition to steroids.
- Plasmapheresis is of questionable benefit
As in other refractory rheumatic disease, cyclophosphamide can be used if disease is severe esp with ILD, refractory, and risk of concurrent infection is minimal.

MMF and chlorambucil also reported to be useful in refractory disease.

HCQ helpful in cutaneous manifestations of DM

Rehab: passive/active assisted ROM during active phase, strengthening as inflammation subsides

Exercise is anti-inflammatory, lowers CRP and IL6
Treatment IV

- Rituximab
  - Anti-CD20 antibody results in B cell depletion in peripheral blood and tissues
  - 2 studies have shown improvement in muscle strength and decreased CK in IIM
  - Small studies report good efficacy, even in SRP+ cases

- aTNF – no benefit
- aIL6 (Tocil) - 2 pts did well
- IL1Ra (Anakinra) – some benefit (7/15) in an open-label study
- Alemtuzumab – one case study in IBM (4/13) improved
- Allo MSCT – one small study, equivocal
Association with malignancy
Association with Malignancy

- Association between malignancy and polymyositis was first proposed in 1916
- Several studies have indicated increased incidence of malignancy in DM
  - Callen et al (1980) first demonstrated stronger association between cancer and DM than with PM
- Common autoantigens between cancer and muscle tissue in some pts with DM.
- CAM in 10% of PM pts and close to 15% of DM adult pts
  - ovary, lung, cervix, pancreas, bladder, stomach
- DM: ovary, lung, colorectal, lymphoma, stomach, breast
- Most common histology is adenocarcinoma
- SE asian: increased risk of nasopharyngeal carcinoma
Association with malignancy

- Swedish study investigated the incidence of cancer & the rate of mortality in 788 pts with DM/PM between 1963-83
  - Increased risk of malignancy in DM pts, especially females

<table>
<thead>
<tr>
<th>RELATIVE RISK</th>
<th>MALE</th>
<th>FEMALE</th>
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<tbody>
<tr>
<td>DM</td>
<td>2.4</td>
<td>3.4</td>
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<tr>
<td>PM</td>
<td>1.8</td>
<td>1.7</td>
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- DM but not PM was associated with an increased risk of cancer mortality c/w the general pop. (mortality ratio =3.8)


Courtesy of Parul Sharma
Use of tumor markers

- 1979 Gianni et al.
  - 102 pts with new PM or DM
  - All got CT C/A/P, upper/lower endosc, CA125, 19-9, CEA
  - 10 pts with solid malig
    - Odds Ratio for developing was 30 with elev CA125
    - Odds Ratio 4.5 with elev CA19-9
    - No signal for abn CEA (4 pts with abn CEA without malig)

Inflamm Myopathy phenotype and use of antibodies

- Phenotype is not a clue to underlying CA:
  - Tumor presence neither affects severity, distrib of weakness, nor duration prior to dx, CK peak, nor presence of ILD
  - Pts with a tumor are not more or less likely to have a myositis-specific autoantibody (more later)
Screening (for cancer) recommendations

- Thorough history, physical, labs
  - Cbc, esr/crp, chem, UA/micro, CXR
    - CA125, CA19-9, +/-PSA
- Age-appropriate CA screen
  - colo/mammo/PAP/bimanual/hemocc
- Limited additional testing
  - Non-age-appropriate CA screen
    - early colo/mammo/hemocc
  - CT Chest/Abd/Pelvis
  - Transvaginal US if bimanual unrevealing
MSAs are also extant on tumors

Model of cancer-assoc myositis

- Tumors and regenerating muscle fibers express myositis autoantigens at high levels relative to healthy tissues.
- Early cancer $\rightarrow$ adaptive cytolytic antitumor immune response, directed at antigens shared with regenerating muscle cells.
- In the setting of nonspecific muscle injury (or subclinical tumor-induced myopathy), the antitumor response cross-reacts with regenerating muscle cells via molecular mimicry.
- Cancer may be fully contained and eradicated, or not.
- Thus pts with DM and no extant cancer may be authentic cancer survivors. This also explains why cancer may be missed early in DM.
Pathophysiology and spectrum of autoimmune myositis
A vast number of pro-inflammatory cytokines and chemokines are released within the muscle microenvironment. Intramuscular blood vessels upregulate several inflammatory mediators, indicating an active role in leukocyte recruitment in idiopathic inflammatory myopathy (IIM). Through further intercellular stimulation between endothelial cells, immune cells and muscle cells, immune responses are amplified, causing sustained inflammation. CCL, β-chemokine; CXCL, α-chemokine; DC, dendritic cell; IFN, interferon; IL, interleukin; LTs, lymphotoxins; mφ, macrophage; Tc, cytotoxic T-cell; Th, helper T-cell; TNF, tumor necrosis factor.

Figure 1. The muscle pro-inflammatory microenvironment of idiopathic inflammatory myopathies.

Role of cytokines and chemokines in idiopathic inflammatory myopathies.
De Paepe, Boel; Creus, Kim; De Bleecker, Jan

DOI: 10.1097/BOR.0b013e3283317b31

Also new evidence for CD28 null T cells and T-reg

Figure 1
Autoimmune myositis

Myositis associated Abs
- ANA (50-80%)
- U1-RNP
  - MCTD (Edema, synovitis, raynaud’s, myositis)
- PM-Scl
  - Phenotype similar to anti-synthetase
- Ro/SSA

Myositis specific Abs
- Anti-Jo-1 +6 others
  - Anti-synthetase syndrome: myositis, interstitial lung disease, arthritis, raynaud’s, mechanic’s hands
- Anti-SRP ~ Severe, refractory, necrotizing
- Anti-Mi-2
  - Classic DM phenotype
Serum Autoantibodies: anti p155/140

- Anti-p155 (Targoff, 2006)
  - Human transcriptional intermediary factor TIF1
  - Involved in TGFβ signaling (inactivated in some CA)
  - 6/8 of adult pts with CAM had DM and +anti-p55

- Anti-p155/140 association with CAM has been confirmed by other investigators
  - **High NPV (can rule-out occult malignancy in DM but not PM)**

Concluding remarks

- DM is associated with malignancies.
- Cancer can be diagnosed before, simultaneously with, or after the diagnosis of inflammatory myopathy.
- It is possible that DM patients without extant cancer may be authentic cancer survivors.
  - It is also possible that the cancer will become clinically evident within 3-5 years
- Assertive cancer screen for suspected DM/PM cases can begin upon presumptive diagnosis
Questions? …..References:

- Miller M., Clinical manifestations and diagnosis of adult dermatomyositis and polymyositis. UpToDate, March 2012.
- Mann H. et al., Clinical trials roundup in idiopathic inflammatory myopathies. Current Opinion in Rheumatology 23(6), 11/2011, p605-611
- Miller M., Malignancy in dermatomyositis and polymyositis. UpToDate, March 2012.
Prognostication

- Assoc w/worse outcomes:
  - Delay > 6mo after onset
  - Degree of initial weakness
  - Resp muscle weakness
  - dysphagia
  - ILD
  - Cardiac involvement
  - Assoc malignancy

Age, sex, rash or no rash, CK peak are nonpredictive

Miller M., Malignancy in dermatomyositis and polymyositis. UpToDate, March 2012.
IIM phenotypes

- Dermatomyositis DM
- Polymyositis PM
- Inclusion Body… IBM
- Juvenile… JDM
- Clinically Amyopathic DM… CADM
- Cancer Associated… CAM
- Myositis in overlap syndromes
  - Most trials have evaluated all IIM pts as a group
Screening is recommended

- Cancer screen
  - Thorough history/physical and lab evaluation
    - CBC, Chem, ESR, CRP, UA, stool
  - Age-appropriate cancer screening tests (PSA/colo), plus breast, rectal, pelvic exams
  - Tumor markers initially and at non-evidence based intervals
    - CA-125, CA 19-9
    - CEA, AFP, S100

- Negative autoantibody panel has a high NPV for CAM
  - Our patient had not read the journal article (she had a neg profile incl Jo-1/Mi-2)
  - +MSA/MAA should intensify search for CA and send p155 when available
    - If 155 neg, pay attention for 3-5 years
Imaging

- Radiological evaluation
  - Chest x-ray
  - Computed tomography (CT) scans of the chest, abdomen, and pelvis
  - Pelvic ultrasonography and transvaginal ultrasound for women with DM

PET/CT is felt comparable to broad CA screening (CT C/A/P + tumor markers, mammo, Gyn with US).

- If p155 negative, do single PET/CT to confirm.
- If p155 positive, do yearly PET/CT for 3-5 years.

Model of CAM by Casciola-Rosen, 2005

- Showed by immunohistochemistry that muscle biopsies from pts with PM and DM stain for 3 different autoantigens relative to normal muscle.
- Showed that autoantigen expression is high in cultured myoblasts and low in differentiated myotubules.
- Showed that myositis autoantigens are frequently expressed at increased levels in tumors.
Screening recommendations