Skin Manifestations of Dermatomyositis

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Overview

• Pathogenesis: Inflammatory cells in the skin, Interferon, medications (TNF inhibitors, statins), autoantibodies

• Clinical: Amyopathic vs Classical DM

• Lung Disease in DM

• Quality of Life in DM

• Evaluation and Treatment
Antibodies in Pathogenesis of DM

- 140-kDa [RNA helicase, melanoma differentiation-associated gene 5 (MDA-5); IFN induced with helicase C domain protein 1 (IFIH1)]
- 155/140-kDa (transcriptional intermediary factor 1-γ, TIF1-γ)
- May help increase understanding about antigens triggering immune reactions

Antibodies in Pathogenesis of DM

- p155/p140: present in sera of 23-29% Juvenile DM cases and associated with more severe skin involvement and generalized lipodystrophy

_Targoff IN et al, Arthr Rheum 54:3689, 2006; Bingham A et al, Medicine 87:70, 2008_
TNF inhibition and DM

- Nineteen different medications have been implicated,
  - Hydroxyurea (36 cases)
  - Penicillamine (10 cases)
  - HMG-CoA reductase inhibitors (6 cases)
- Association with tumor necrosis factor (TNF) inhibitors (Dastmalchi M, Ann Rheum Dis 67: 1760, 2008)
TNF inhibition and DM

Four additional cases

- One with severe flare within days of one injection of etanercept for a flare of arthralgias, mild rash
- Within days she developed very severe myalgias, arthralgias, exacerbation of her rash, shortness of breath, and fevers to 104.5 °F
- Aldolase was elevated (18 U/L; reference range 1.2-7.6 U/L)
- Pulmonary function tests (PFTs) showed mild restrictive lung disease with decreased carbon monoxide diffusing capacity (DLCO)

Klein R et al, Arch Dermatol, 146:780, 2010
TNF inhibition and DM

- The cytokine-shift hypothesis
  - Inhibition of TNF-α promotes the expression of type I interferon (IFN) by altering the balance between Th1 and Th2 cytokine production (Palucka AK et al, PNAS 102:3372, 2005)

- This increase in type I IFN may contribute to the exacerbation of symptoms
Overview

- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Treatment
Dermatomyositis
Dermatomyositis
Dermatomyositis: Inflammation related to increased glycoprotein + binding partner

Dermatomyositis
Dermatomyositis
Dermatomyositis
Dermatomyositis
Dermatomyositis
Nailfolds in Dermatomyositis

- Loss of nailfold capillary loops has strong association with cutaneous disease activity
  - Hemorrhages
  - Irregularly enlarged capillaries
  - Loss of capillaries

Before Treatment

After

Mugii, N Rheumatol 50:1091, 2011
Schmeling H et al, Rheumatology 50:885, 2011
Antip 155/140 Antibody

- Poikiloderma
- Flagellate erythema
- Bullae formation

Dermatomyositis
Mechanic’s Hands
Vasculopathy
Ulcers
Classification of DM

- I. Adult Polymyositis
- II. Adult Dermatomyositis
- III. DM/PM with malignancy
- IV. Childhood DM/PM
- V. DM/PM associated with other connective tissue disease (Overlap)
- VI. Amyopathic Dermatomyositis
- VII. Inclusion Body Myositis
Diagnostic Criteria for DM (Bohan and Peter’s)

- Symmetric proximal weakness with or without dysphagia or respiratory muscle involvement
- Abnormal muscle biopsy specimen
- Elevation of skeletal muscle-derived enzymes
- Abnormal electromyogram
- Typical skin rash
  - Definite DM: rash and 3 or 4 criteria
  - Probable DM: rash and 2 criteria
  - Possible DM: rash and 1 criterion
Diagnosis of DM

- Skin biopsy
- EMG or MRI
- Muscle biopsy
- Examples of myositis autoantibodies:
  - Anti-Jo-1
  - Anti-PM-1
  - Anti-Mi-2
  - CADM140
  - CADM140/155
Diagnosis of Amyopathic DM

- Typical skin changes of DM
- Lack of muscle weakness for 2 years or longer
- Normal serum muscle enzymes
- Normal electromyogram studies
- Normal MRI, P-31 magnetic resonance spectroscopy
Diagnosis of Amyopathic DM

- Problems in getting a diagnosis
- Often misdiagnosed with SLE
- SLE criteria often positive (malar rash, photosensitivity, +ANA, oral ulcers)
- Skin biopsy indistinguishable between DLE and DM
- Redoing criteria
Hypomyopathic DM

- Patients with DM-specific skin disease and no clinical evidence of muscle disease
- Subclinical evidence of myositis on laboratory, electrophysiologic, and/or radiologic evaluation
Clinically Amyopathic DM

- Amyopathic DM and hypomyopathic DM.
- This designation has been coined to emphasize the fact that their predominant clinical problem is skin disease.
Clinically Amyopathic DM

- A population-based retrospective study of dermatomyositis
- Rochester Epidemiology database
- 29 patients (1976-2007)
- Overall age-adjusted and sex-adjusted incidence of CADM was 2.08 per 1 million persons
- CADM 21% of dermatomyositis

Bendewald, MJ et al, Arch Dermatol 146:26, 2010
### Presentation of DM at University of Pennsylvania (3 years)

<table>
<thead>
<tr>
<th></th>
<th>Dermatology # patients</th>
<th>Rheumatology # patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Classic DM</strong></td>
<td>27 (32.5%)</td>
<td>24 (88.9%)</td>
</tr>
<tr>
<td><strong>Amyopathic DM</strong></td>
<td>33 (39.8%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td><strong>Hypomyopathic DM</strong></td>
<td>23 (27.7%)</td>
<td>2 (7.4%)</td>
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</tbody>
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*Quain and Werth, JAAD, 57:937, 2007*
Overview

- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Treatment
Interstitial Lung Disease with DM
Interstitial lung disease in DM

- Prevalence of pulmonary involvement as high as 46% in PM/DM
- Pulmonary disorders a common cause of morbidity in PM/DM
- ILD may lead to life-threatening complications, i.e., ventilatory failure, secondary pulmonary arterial hypertension, or cor pulmonale

Chen et al, Clin Rheumatol 28:639, 2009
Fathi et al, Ann Rhem Dis 63:297, 2004
Interstitial lung disease in DM

• ILD can occur prior to, at time of onset of initial PM/DM clinical manifestations, or after onset.

• Subset with rapidly progressive disease associated with high mortality

• Others with indolent or slowly progressive course

• Can regress with treatment (steroids, immunosuppressives)
Predictors of poor outcome of ILD in DM

- Worse PFTs initially and at follow-up
- Symptomatic: cough, dyspnea
- UIP pattern
- Steroid-refractory
ILD in CADM (11) vs Classic DM (13) in Japan

Mukae H et al, Chest 136:1341, 2009

FIGURE 3. Overall survival curves of patients with CADM-ILD and classic DM-ILD. Time indicates the number of months since the onset of respiratory or skin symptoms.
CADM-140 Antibodies DM

- 140-kDa [RNA helicase, melanoma differentiation-associated gene 5 (MDA-5); IFN induced with helicase C domain protein 1 (IFIH1)]
- Anti-CADM-140 autoantibodies significantly associated with CADM

Hamaguchi Y et al, Arch Dermatol 147:391, 2011*
CADM-140 Antibodies DM

- More rapidly progressive interstitial lung disease (ILD) when compared with patients without anti-CADM-140 autoantibodies (50% versus 6%; P = 0.008)

Hamaguchi Y et al, Arch Dermatol 147:391, 2011*
### ILD in DM at University of Pennsylvania (3 years)

<table>
<thead>
<tr>
<th>ILD</th>
<th>Classic DM</th>
<th>Amyopathic DM</th>
<th>Hypomyopathic DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>23 (40%)</td>
<td>9 (26%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Absent</td>
<td>35 (60%)</td>
<td>26 (74%)</td>
<td>14 (56%)</td>
</tr>
</tbody>
</table>

P=0.27

*Quain and Werth, JAAD, 57:937, 2007*
ILD in DM

- Patients with lower initial DLCO values have a higher prevalence of ILD
- Patients with normal initial DLCO may have a decrease in DLCO over time and may develop interstitial lung disease
- All patients should be screened with serial DLCO
- Other testing (HRCT, echocardiography) and need for pulmonary referral may be based on DLCO result

Morganroth et al, Arch Derm 146:729, 2010
Overview

- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Treatment
QoL DM (SF-36)

- QoL in DM worse than other diseases (Recent MI, HTN, type II diabetes)
- Particularly true in the emotional realm (vitality, social functioning, role-emotional, mental health)

Median Pain and Pruritus Scores in DM and CLE

Overview

- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Work-up and Treatment
Relationship of DM to malignancy

- Population-based retrospective study of 537 patients with biopsy-positive idiopathic inflammatory myopathy
- Childhood myositis (4%)
- Polymyositis [18%, SIR 2.0 (CI 1.4-2.7)]
- Dermatomyositis [(42%, SIR 6.2 (CI 3.9-10)]

*Buchbinder et al, Ann Int Med 134:1087,2001*
Relationship of DM to malignancy

- Adjusted relative risk for malignant disease was higher in the first 3 years after diagnosis of myositis than at any later time.
- Risk still increased 5 years after diagnosis [1.2 (0.5-2.5)]
- Relative risk for malignant disease in DM 2.4 (CI 1.3-4.2) relative to polymyositis

_Buchbinder et al, Ann Int Med 134:1087, 2001_
Relationship of DM to malignancy

- Lung (SIR 5.9, 3.7-9.2)
- Ovary (SIR 10.5, 6.1-18.1)
- Pancreatic (SIR 3.8, 1.6-9.0)
- Stomach (3.5, 1.7-7.3)
- Colorectal (2.5, 1.4-4.4)
- Non-Hodgkin lymphoma (3.7, 1.7-8.2)

*Hill et al, Lancet 357:96, 2001*
Work-up and Follow-up of DM

- Screen for malignancies where early detection and treatment improve patient outcome
- Occult blood in stool
- Tumor markers?
- Mammography
- Chest x-ray
- Pap smear
Work-up and Follow-up of DM

- High resolution Chest CT
- Abdominal ultrasound or CT
- Pelvic CT or ultrasound

- Maintain vigilance since risk remains high for years
- Re-evaluate for internal malignancy every 6-12 months after diagnosis for 2-5 years
Evidence for Systemic therapy

- Almost no prospective double-blinded randomized controlled trials
- Evidence poor for use of therapies
  - Expert opinion
  - Case series, usually retrospective
- Partially validated outcome measure should advance level of evidence
**CDASI**

**Dermatomyositis**

- Therapy determined by whether there is underlying muscle or pulmonary disease
- Interstitial lung disease in 25% of patients with amyopathic dermatomyositis (steroids ± Mycophenolate mofetil or Cyclophosphamide)
- Muscle disease must be treated differently (steroids, immunosuppressives, IVIG, ?Rituximab)
- “More research is needed to investigate the efficacy of immunosuppressant and immunomodulatory agents in DM” *(Choy et al, Cochrane Rev, 2007)*
Outcome of ILD

- 16 DM patients with ILD in 3 years
- 4 treated with Mycophenolate mofetil and had PFT data available
- 3 f/u for at least 1 year
- All 3 with normalization of PFTs and resolution of dyspnea
- Patient with pre- and post-treatment high resolution CTs had total resolution of interstitial opacities

*Morganroth et al, Arthritis Care & Res, in press*
ILD

Before CellCept

After CellCept
Treatment of amyopathic DM

- First Line Therapies
  - Sunscreens
  - Topical Steroids
  - Intralesional Steroids
  - Elidil or Protopic
  - Antimalarials (Hydroxychloroquine, Quinacrine, Chloroquine)
Sunscreens and Dermatomyositis

- Sunscreens
  - UVB #30 or greater
  - Mexoryl
  - Helioplex
  - Physical Blockers (Titanium, Zn Oxide)
Dermatomyositis: Skin

• Second-line therapies
  – Immunosuppressives (Methotrexate, Mycophenolate mofetil, Azathioprine, Cyclosporine, Tacrolimus)
  – Gluocorticoids
  – Thalidomide
  – IVIG
Side Effects of Plaquenil/Chloroquine

- Retinopathy
- Cardiomyopathy (CHF, heart block, restrictive cardiomyopathy)
- Myopathy-proximal muscle weakness
- Nausea, diarrhea
- Psychosis
- Hypo- and Hyperpigmentation
- Exanthem, hives
Experimental Therapies in Dermatomyositis

- **B cell directed therapy**
  - Anti-CD20 (Some evidence that may help muscle, not skin) *(Dinh et al, JAAD 56:148, 2007; Chung et al, Arch Dermatol 143:763, 2007)*

- **Cytokine inhibitors**
  - Anti-interferon-α
Raynaud’s Phenomenon

- Digital pain
- sequential pallor, cyanosis, rubor
- Acral ulceration less common

- Primary
- Secondary: underlying disease process, such as scleroderma, lupus, or dermatomyositis
Raynaud’s Phenomenon

- Endothelial dysfunction and vascular remodelling
  - Tissue ischemia
  - Digital ulcers
- Can occur in dermatomyositis, but more common in Systemic sclerosis
- Spasm of vessels intermittently
- Can cause ulcers, infection, ischemia or gangrene
• Nailfold capillaroscopy: dilated proximal nailfold in Raynaud’s associated with autoimmune disease
Treatment of Raynaud’s Phenomenon

- **Calcium Channel blockers**
  - Nifedipine 10-30 mg tid or 30-90 mg/day in SR
  - Amlodipine 5-10 mg a day
  - Diltiazem 30-120 mg tid

- **Angiotensin II Receptor Blockers**
  - Losartan 50 mg/day

- **ACE inhibitors**
  - Captopril 6.5-25 mg tid

- **Alpha-adrenergic blocker**
  - Prazosin 1-5 mg bid
Treatment of Raynaud’s Phenomenon

- Topical nitrates
- Prostacyclin and prostacyclin analogs (intravenously)
  - Variable effectiveness
  - Significant adverse effects
- Sildenafil and other phosphodiesterase type V inhibitors
- Endothelin Receptor antagonists
  - Bosentan 62.5-125 mg bid

1 Herrick AL et al, Arthritis.Rheum 63:775, 2011
Treatment of Raynaud’s Phenomenon

- Anti-platelet agents: aspirin, clopidrogel
- Low molecular weight heparin and tissue plasminogen activator
- Pentoxyfilline
- Local anaesthetic blocks and digital sympathectomy
Treatment of Raynaud’s Phenomenon with Botulinum Toxin

- Blocks vascular smooth muscle depolarization and vasoconstriction
- Blockade of central nervous stimuli for vasoconstriction
Treatment of Raynaud’s Phenomenon with Botulinum Toxin

• Blocks transmission of norepinephrine vesicle, prevention sympathetic vasconstriction of the vascular smooth muscle
• Blocks recruitment of specific alpha 2c-adrenoreceptor, which decreases the activity of chronically upregulated C-fiber nociceptors
• Subsequent reduction in cold-induced vascular smooth muscle constriction and pain

Treatment of Raynaud’s Phenomenon with Botulinum Toxin

- 10 units botulinum toxin A on each neurovascular bundle at the level of the MCP flexion crease
- 33 patients
- 28/33 with reduced pain
- Tissue perfusion changes 48% - 317%, using laser Doppler perfusion

Neumeister MW. J Hand Surg Am 35:2085, 2010