Dermatologic Manifestations of Rheumatic Diseases

UCSF Advances in Internal Medicine Course

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Rheumatic Diseases

- Lupus erythematosus
- Dermatomyositis
- Scleroderma
- Miscellaneous

Lupus Erythematosus

Cutaneous classification/subsets:

**Acute:**
- SLE
- Bullous LE

**Subacute:**
- Subacute cutaneous LE
- Neonatal LE

**Chronic:**
- DLE
- Lupus panniculitis

Systemic Lupus Erythematosus

Skin manifestations of SLE

- **Specific**
  - malar rash
  - discoid rash
  - photosensitivity
  - oral lesions
- **Nonspecific**
It can be difficult to differentiate malar rash lupus from rosacea and a biopsy can be helpful.

The biopsy from a lupus patient shows a vacuolar interface dermatitis, epidermal atrophy and a perivascular/perifollicular lymphocytic infiltrate.

The biopsy from a rosacea patient shows a dilated capillaries and follicular infiltrate with neutrophils.

Discoid lupus erythematosus
Discoid Lupus Erythematosus

- “Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions”
- Differential dx:
  - face, neck: tinea barbae, tinea faciale, acne
  - scalp: tinea capitus, scarring alopecias
Photosensitivity

- “skin rash as a result of unusual reaction to sunlight, by patient history or physician observation”
- differential dx:
  - polymorphous light eruption (PMLE)
  - drug reaction

Photosensitivity

- SLE: Young women
  - Onset with sunburn
  - Resolves in weeks to months
  - Uncomfortable/painful biopsy
  - DIF: positive

- PMLE: Young-older women
  - Slight delay in onset (18-24 hr)
  - Resolves 7 to 10 days
  - Pruritic biopsy
  - DIF: negative

Oral ulcers
Oral Ulcers

- “Oral or nasopharyngeal ulceration, usually painless, observed by a physician”
- differential dx: aphthous ulcer

Specific skin manifestations of SLE

- The histology is also specific
- Therefore skin biopsies are very helpful in making a diagnosis of lupus erythematosus
- Not able to differentiate the different lupus subsets

Direct Immunofluorescence (DIF)

Skin manifestations of SLE

- specific
  - malar rash
  - discoid rash
  - photosensitivity
  - oral lesions

- nonspecific
  - vasculitis
  - vasculopathy (APS)
  - Raynaud’s phenomenon
  - chilblains
  - alopecia
  - calcinosis cutis
  - rheumatoid nodules
  - urticaria
Nonspecific skin manifestations of SLE

- Histology is very helpful in characterizing vasculitis or vasculopathies
- Nonspecific for SLE

Bullous lupus erythematosus

Criteria:
- ARA criteria for SLE
- Acquired, non-scarring bullous eruption
- Path: subepidermal blister with neutrophils
- DIF: granular IgG, IgA, IgM and C3 at DEJ
Rare: 3% of all lupus
Treatment:
  - Dapsone 50 to 150 mg qd

Subacute cutaneous lupus erythematosus

Lupus Erythematosus

Lupus subsets:

**Acute:** SLE
- Bullous LE

**Subacute:** Subacute cutaneous LE
- Neonatal LE

**Chronic:** DLE
- Lupus panniculitis
Subacute cutaneous lupus erythematosus

• ~10% of all SLE patients
• older patient with milder disease
• photosensitive skin eruption (non-scarring)
• 2 clinical variants:
  - papulosquamous (psoriasiform) and
  - annular polycyclic
• associated with SSA/Ro antibodies (70%)

Differential Diagnosis of SCLE

• Psoriasis
• Erythema multiforme
• Polymorphous light eruption

Drug-induced LE

<table>
<thead>
<tr>
<th>SCLE</th>
<th>SLE</th>
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<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Sulfonylurcines</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Pirimicaine</td>
<td></td>
</tr>
<tr>
<td>Diloxanem</td>
<td></td>
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<tr>
<td>Cilazapril</td>
<td></td>
</tr>
<tr>
<td>Terbinafine</td>
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<tr>
<td>PUVA</td>
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</table>

Neonatal Lupus Erythematosus
Neonatal lupus erythematosus

- congenital heart block (50%)
- cutaneous lesions (40%)
- both (10%)
- associated with maternal SSA/Ro antibodies

Cutaneous manifestations:
- appears a few weeks post-partum
- photosensitive (head and trunk)
- last for weeks to months, eventually clears
- annular lesions with central clearing
- No treatment is indicated

Lupus Erythematosus

Lupus subsets:
- Acute: SLE, Bullous LE
- Subacute: Subacute cutaneous LE, Neonatal LE
- Chronic: DLE, Lupus panniculitis

Chronic Cutaneous Lupus Erythematosus

- discoid lupus erythematosus
- hypertrophic (verrucous) DLE
- tumid lupus erythematosus
- lupus profundus
- chilblains LE
Lupus profundus/panniculitis

- 3 to 5% of LE cases
- ~1/2 occur c DLE
- lupus profundus = panniculitis c DLE
- characteristic: “saucer-shaped atrophy”
- pathology shows a lobular panniculitis with lymphocytes and plasma cells
- difficult to treat

Serologies

<table>
<thead>
<tr>
<th></th>
<th>DLE</th>
<th>SCLE/NLE</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>~ 30%</td>
<td>~ 80%</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>SSA/Ro</td>
<td>---</td>
<td>~ 70%</td>
<td>~ 40%</td>
</tr>
<tr>
<td>dsDNA</td>
<td>---</td>
<td>---</td>
<td>~ 30%</td>
</tr>
<tr>
<td>ENA (RNP, Sm)</td>
<td>---</td>
<td>---</td>
<td>~ 40%</td>
</tr>
<tr>
<td>SSB/La</td>
<td>---</td>
<td>---</td>
<td>~ 10%</td>
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</tbody>
</table>

Pathogenesis

Treatment
**Dermatomyositis**

**Definition:**
DM is a rare, idiopathic, inflammatory disorder of striated muscle and skin.

**History:**
- 1886: polymyositis (Wagner)
- 1891: 1st case report of dermatomyositis (Unverricht)
- 1930: Gottron’s papules (Gottron)
- 1935: association between DM and CA (Bezczeny)
- 1956: disease activity associated with SGOT (Siekert)
- 1975: Bohan and Peter establish criterid & classification
- 1979: amyopathic dermatomyositis (Pearson)
- 1987: Jo-1 antibodies associated with DM/PM (Targoff)

**Epidemiology:**
- any age, 2 peaks: childhood 10 to 15 years
- adults 45 to 65 years
- all ethnic groups (African Americans)
- female > male (2:1)
- incidence: 1-10/million/year U.S.
- prevalence: 10-60/million

**Specific:**
- Gottron’s papules
- Heliotrope rash

**Table 70-3. Classification of the Dermatomyositis-Polymyositis Complex Proposed by Bohan and Peter**

| Group 1: Primary idiopathic polymyositis |
| Group 2: Primary inflammatory dermatomyositis |
| Group 3: Dermatomyositis (or polymyositis) associated with infection |
| Group 4: Childhood dermatomyositis (or polymyositis) associated with vasculitis |
| Group 5: Polymyositis or dermatomyositis associated with collagen-vascular disease (overlap group) |

“Lacy, pink or violaceous areas (raised or macular) found symmetrically on the dorsal aspect of interphalangeal joints, elbows, patella and medial malleoli—are considered pathognomonic.”

Differential dx: lupus
Heliotrope rash

- "violaceous" discoloration of the eyelids
- periorbital edema
- macular erythema over extensor surfaces
- differential dx:
  - contact dermatitis of the eyelids

DM?

- Biopsy reveals eczema herpeticum.
- EMG is consistent with a steroid myopathy.

Dermatomyositis

- both Gottron’s papules and the heliotrope rash have specific histologic findings
- a skin biopsy can be very helpful in establishing a dx of dm
Dermatomyositis

Specific
- Gottron’s papules
- Heliotrope

Nonspecific
- Photosensitivity
- Poikiloderma
- Malignant erythema
- Hypertrophic cuticle
- “Mechanics hands”
- Nailfold capillary changes
- Calcinosis cutis

DM and malignancy
- There is an association
- Stronger for DM than PM
- All cancers represented
- Increased ovarian cancer

Amyopathic Dermatomyositis (ADM)
- ~10% of all DM cases
- Skin disease w/o muscle disease for > 6 months, but < 2 years = “provisional ADM”
- Skin disease w/o muscle disease for > 2 years
- ? Association with malignancy
- ? Association with pulmonary disease


Dermatomyositis

Serologies:

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>SSc</th>
<th>DM/PM</th>
</tr>
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<tbody>
<tr>
<td>ANA:</td>
<td>98%</td>
<td>85%</td>
<td>*60%</td>
</tr>
<tr>
<td>dsDNA</td>
<td></td>
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<tr>
<td>topo 1</td>
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<td></td>
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<tr>
<td>ENA</td>
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<td></td>
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<tr>
<td>(~Scl-70)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SSA/Ro</td>
<td></td>
<td></td>
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</tbody>
</table>


Myositis-specific autoantibodies (MSA)

<table>
<thead>
<tr>
<th>Antisynthetase antibodies</th>
<th>DM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Jo-1 = Histidyl-tRNA synthetase</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Signal recognition particle (SRP)</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Mi-2</td>
<td>8%</td>
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Scleroderma

Classification:

I. Localized scleroderma
   1. Morphea
   2. Linear scleroderma
   3. Eosinophilic fasciitis

II. Systemic sclerosis
   1. Limited scleroderma
   2. Diffuse scleroderma
   3. Sine scleroderma
   4. Overlap syndromes

Morphea

- asymmetric plaques
- 2 to 16 cm
- ivory center
- lilac border (active)
- hyperpigmented
- asymptomatic
- numerous variants:
  - bullous
  - guttate/LSA
  - nodular/keloidal
  - subcutaneous/profunda
  - segmental

Generalized Morphea

- ~30% of the morphea group
- >3 plaques
- confluent plaques
- indurated, hyperpigmented
- trunk, abdomen, legs
- asymptomatic
- ~chronic GVHD
- disabling pansclerotic morphea of children
- no internal organ involvement

Linear Scleroderma

- linear strip or band
- legs, arms, scalp
- attached to deep tissue
- joint contractures
- no internal organ involvement
- spina bifida occulta
Scleroderma Epidemiology


Scleroderma Classification:
I. Localized scleroderma
   1. Morphea
   2. Linear scleroderma
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II. Systemic sclerosis
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Natural history: diffuse vs. limited


Raynaud’s Phenomenon

Limited scleroderma: sclerodactyly

• 60% of SSC
• RP precedes
• squared-off telangiectasias
• subtle fibrotic changes
• indolent course
• internal organ involvement
• late, 5-10 years
• anticentromere antibodies
• better prognosis than diffuse
• increased mortality


Limited Scleroderma
The CREST Syndrome

- Calcinosis
- Raynaud’s phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasias

Is a specialized subset of limited scleroderma…

Natural history: diffuse vs. limited


Early: edematous phase

Middle: indurated phase

Diffuse Scleroderma

- 35% of SSc
- diffuse skin involvement
- characteristic facial features
- internal organ involvement
- early, w/in the first 5 years
- +anti-topoisomerase I (Scl-70)
- rapidly progressive
- worse prognosis
- increased mortality

Scleroderma: histology

Scleroderma Normal

Autoantibodies


Internal Organ Involvement in SSc

- Gastrointestinal ~ 80%
- Pulmonary ~ 50%
- Renal ~ 15%
- Cardiac ~ 10%


Survival in Scleroderma

N = 709

Systemic Sclerosis: Treatment

Treatment

- there is no cure
- manage by organ system
- supportive care
- DMARDs ?
- improved survival rates ?

Systemic Sclerosis: Treatment

Organ systems:

- Skin: same as localized, D-penicillamine
- RP: calcium-channel blockers
- GI: proton-pump inhibitors
- Renal: ACE inhibitors
- Lungs: ILD: Immunosuppression PAH: ERA (bosentan)
Systemic Sclerosis: Treatment

Organ systems:
- Skin: same as localized, D-penicillamine
- RP: calcium-channel blockers
- GI: proton-pump inhibitors
- Renal: ACE inhibitors
- Lungs: ILD: Immunosuppression, PAH: ERA (bosentan)

Pulmonary Involvement

I. Interstitial lung disease (~ 50%)
   - acute inflammatory phase (alveolitis)
   - late fibrotic phase

II. Pulmonary artery hypertension (~20%)

Scleroderma Lung Study (SLS)

Interstitial Lung Disease

Immunosuppressive therapy:
- cyclophosphamide PO 1 to 2 mg/kg/qd x 1 year


Adjusted mean difference between CYC and placebo (treatment effect) =

2.32 (95% C.I.: –0.04 to 4.70),
favoring CYC (p = 0.053)

* Covariance analysis using baseline
FVC % predicted as covariate (N = 142); Huber testing procedure

Interstitial Lung Disease

Other immunosuppressive drugs:
- Cyclophosphamide IV
- Mycophenylate mofetil
- Azathioprine
- Cyclosporin

Trials:
- Bosentan - did not work
- γ-IFN - did not work

Pulmonary Artery Hypertension
Pulmonary Artery Hypertension

FDA-approved therapies:
1. Epoprostenol (Flolan)-IV ($60-120K/yr)
2. Treprostinil (Remodulin)-SC ($550-90K/yr)
3. Bosentan (Tracleer)-PO ($30K/yr)
4. Sildenafil (PDE5, Viagra, Ravatio)
5. Iloprost inhaled (Ventavis)


Systemic Sclerosis: Treatment

- Biologics:
  TNF blockers have been disappointing
  Rituximab (anti-CD20)
- Clinical trials:
  Stem cell transplant:
  Scleroderma: Cyclophosphamide or Transplantation = “SCOT” trial/NIH

Scleroderma-like syndromes
- Toxic or drug-induced scleroderma
  - Vinyl chloride
  - Organic solvents and epoxy resins
  - Eosinophilic myalgia syndrome (L-tryptophan)
  - Toxic oil syndrome
  - Bleomycin

*Nephrogenic Fibrosing Dermopathy*
- Vibration injury
- Scleromyxedema
- Scleredema
- Eosinophilic fasciitis
- Graft-versus-host disease

Nephrogenic Fibrosing Dermopathy

- first cases in 1997 (reported in 2001)
- ~100 cases reported (registry @ Yale)
- indurated papules and plaques on the trunk and extremities, joint immobility and inability to walk
- association with renal disease:
  - renal failure, dialysis (hemo-, CAPD), transplant
- gadolinium-containing contrast agent exposure (MRI) is an independent risk factor
- unresponsive to steroids or immunosuppression
- can improve with improving renal fx

Cheng S et al MMWR 56(7), 2007