Seeing the Signs: Visual Recognition of Autoimmune Connective Tissue Diseases

Utah Association of Family Practitioners CME Meeting at Snowbird, UT 1:00-1:30 pm, Saturday, February 13, 2016

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Potential Conflicts of Interest
2016

• Consultant
  – Centocor (Remicade-infliximab)
  – Genentech (Raptiva-effalizumab)
  – Alexion (eculizumab)
  – MediQuest Therapeutics
  – P&G (ChelaDerm)
  – Celgene*
  – Sanofi/Biogen*
  – Clearview Health*
  – Partners

• Paid speaker
  – Winthrop (Sanofi)
    • Plaquenil (hydroxychloroquine)
  – Amgen (etanercept-Enbrel)
  – Connetics/Stiefel

• Royalties
  – Lippincott, Williams & Wilkins*

• 3Gen – Research partner

*Active within past 5 years
Learning Objectives

• Compare and contrast the presenting and Hallmark cutaneous manifestations of lupus erythematosus and dermatomyositis
• Compare and contrast the presenting and Hallmark cutaneous manifestations of morphea and systemic sclerosis
Distinguishing the Cutaneous Manifestations of LE and DM
Skin involvement is 2nd most prevalent clinical manifestation of SLE and 2nd most common presenting clinical manifestation.
Comprehensive List of Skin Lesions Associated with LE

**LE-SPECIFIC**
- Acute Cutaneous LE
  - Localized ACLE
  - Generalized ACLE
  - Ten-like ACLE
- Subacute Cutaneous LE
  - Annular
  - Papulosquamous
  - Mixed patterns
- Chronic Cutaneous LE
  - "Classical" DLE
  - Localized
  - Generalized
  - Hypertrophic DLE
  - LE profundus
  - Mucosal DLE
  - LE tumidus
  - Chilblains LE
  - DLE-lichen planus overlap

**LE-NONSPECIFIC**
- Cutaneous vascular disease
  - Vasculitis
    - Leukocytoclastic
    - Palpable purpura
    - Urticarial vasculitis
  - Periarteritis nodosa-like
  - Vasculopathy
  - Dego's disease-like
  - Atrophy blanche-like
  - Periungual telangiectasia
  - Livedo reticularis
  - Thrombophlebitis
  - Raynaud’s phenomenon
  - Erythromelalgia (erythermalgia)
  - Alopecia (nonscarring)
    - "Lupus hair"
  - Telogen effluvium
  - Alopecia aerata
  - Sclerodactyly
  - Rheumatoid nodules
  - Calcinosi cutis
  - LE nonspecific bullous lesions
  - Epidermolysis bullosa acquisita-like bullous LE
  - Dermatitis herpetiformis-like bullous LE
  - Pemphigus erythematosus
  - Bullous pemphigoid
  - Porphyria cutanea tarda
  - Urticaria
    - Papulo-nodular mucinosis
  - Nail changes (red lunulae, dyschromasia)
  - Cutis laxa/anetoderma/mid-dermal elastolysis
  - Pigmentary changes
  - Acanthosis nigricans (Type B insulin resistance)
  - Erythema multiforme (Rowell’s syndrome)
  - Leg ulcers
  - Lichen planus
Primary Skin Change of Cutaneous LE

Photosensitive macular erythema and/or papulosquamous papules and plaques
LE-Specific Skin Disease
Interface Dermatitis
THE SPECTRUM
OF LUPUS ERYTHEMATOSUS

severe

ACLE

SCLE

CCLE

mild
Acute Cutaneous LE (ACLE)
Localized
Butterfly Pattern Red Face
Differential Dx

- ACLE/SCLE
- Acne rosacea
- Contact dermatitis (photo, airborne)
- Photosensitive drug eruptions
- Seborrheic dermatitis

When the diagnosis is in doubt, punch it out!
ACLE
Generalized
Acute Cutaneous LE

- Very photosensitive, non-scarring
- (+) ANA, a-dsDNA, a-Sm
- Strong association with active SLE
- Usually managed by rheumatologists, internists
THE SPECTRUM OF LUPUS ERYTHEMATOSUS

severe

ACLE

SCLE

CCLE

mild
Subacute Cutaneous LE (SCLE)

Papulosquamous

Annular
SCLE
Histopathology of SCLE
Direct immunofluorescence microscopy exam of SCLE

Dust-like pattern of IgG at dermal-epidermal junction
Drug-Induced SCLE

- **DIURETICS**
  - Thiazides
  - Spironolactone

- **CALCIUM CHANNEL BLOCKERS**
  - Diltiazem
  - Nifedipine
  - Nitrendipine
  - Verapamil

- **ACE inhibitors**
  - Captopril
  - Cilazapril

- **Acid Blockers**
  - Ranitidine
  - Omeprazole

- **NSAIDS**
  - Naproxen
  - Piroxicam

- **Beta Blocker**
  - Oxprenolol
  - Acebutolol

- **Lipid lowering**
  - Pravastatin
  - Simvastatin

- **ANTIMICROBIALS**
  - Griseofulvin
  - Terbinafine

- **ANTIHISTAMINES**
  - Cinnarazine/triethylperazine

- **Anti-seizure**
  - Phenytoin

- **Antimalarial**
  - Hydroxychloroquine

- **Sulfonylureas**
  - glyburide

- **Chemotherapy**
  - Taxotere/tamoxifen

- **Others**
  - Leufonamide
  - INF-a
  - Procainamide
  - Inhalants
    - Insecticides/fertilizer
    - Tiotropium
    - d-penicillamine
    - Etanercept/infliximab

- **Insecticides/fertilizer**

- **Tiotropium**

- **d-penicillamine**

- **Etanercept/infliximab**
Drug-induced SCLE Reports: 2011-Present

Percentage change in drug category incidence between new cases and 2011 report

- Chemotherapeutics: 19.9%
- PPIs: 16.2%
- Biologics: 10.2%
- Antibiotics: 7.5%
- Immunomodulators: 5.1%
- Statins: 1.1%
- Other: 1.1%
- Antiepileptics: 0.4%
- NSAIDs: -0.2%
- UV therapy: -1.7%
- Hormone-altering drugs: -1.7%
- Antihistamines: -7.7%
- Antifungals: -21.1%
- Antihypertensives: -26.7%
SCLE – A Snapshot

- Nonscarring, highly photosensitive
- ANA (+); anti-Ro/SS-A & anti-La/SS-B
- Genetic associations
  - 8.1 ancestral haplotype
    - A*01, B*08, DRB1*0301, DQB1*0201, TNFAB* a2b3 (TNF-α -308A), C2*C, C4 null
  - $C1QA$-Gly70$_{GGG/A}$
- Associations: SSj, neonatal LE
- Can be drug-induced
- Approximate 10% - severe SLE
- ~75% respond to antimalarials
THE SPECTRUM OF LUPUS ERYTHEMATOSUS

severe

ACLE

SCLE

CCLE

mild
Classical Discoid LE - Localized
Classical Discoid LE - Localized
DLE – Activity/Damage

**Active**
- Erythema, Adherent scale
- Induration, Follicular plugging

**Inactive (Damage)**
- Pigmentary change,
- Atrophy, Telangiectasia
Is It DLE or SCLE?

Active

Induration? Yes-DLE
DLE? When in Doubt
Check the Ears
Classical Discoid LE - Generalized
Classical Discoid LE - Generalized
Chronic Cutaneous LE
Variations on the Theme

- Hypertrophic/verrucous LE
  - Hyperkeratosis (SSCA-like)
- LE tumidus
  - Urticaria-like plaques
- LE panniculitis
  - Subcutaneous nodules
- Chilblains LE
  - Acral vasculopathic changes (fingers/toes)
  - Familial cases associated with TREX1 gene mutations
Chronic Cutaneous LE

“Classical DLE”

- Typically scarring, less photosensitive
- (-) ANA
- 20-30% of SLE patients get DLE lesions
- < 5% presenting with isolated localized DLE for 1-2 years develop SLE; somewhat higher with generalized DLE
Dermatomyositis

A member of the idiopathic inflammatory myopathies (IIM) that produces unique patterns of inflammatory injury to skin and/or proximal skeletal muscles.
Skin Disease in Dermatomyositis

• Disease-defining (Hallmark) inflammatory skin changes (with interface dermatitis)
  • Constant, defining

• Miscellaneous associated
  – Often rare
Miscellaneous, Less Commonly Encountered Skin Changes in DM

- Acquired ichthyosis
- Erythroderma
- Facial swelling without erythema
- Follicular hyperkeratosis
- Hypertrichosis
- Lichen planus
- Linear IgA bullous dermatosis
- Acquired lipoatrophy
- Malakoplakia
- Malignant erythema (suffusion)
- Mechanic’s hand
- Mucous membrane lesions
- Mucinous plaques of the palmar creases
- Mucinosis, cutaneous
- Nasal septal perforation
- Panniculitis
- Pityriasis rubra pilaris
- Steroid-induced acanthosis nigricans
- Urticaria, urticarial vasculitis
- Vasculopathic ulcers
- Vulvar and scrotal involvement
- Zebra-like stripes (centripetal flagellate erythema)
Hallmark skin disease seen in Classical DM or CADM
Primary Skin Change of DM

Heliotrope rash -- No

Confluent macular violaceous erythema

Can be more difficult to discern in darkly pigmented individuals
Heliotrope rash
DM Skin Biopsy Similar to LE-Specific Skin Disease Biopsy

Lupus band typically negative in DM
Pruritic Violaceous Scalp Erythema
V-Sign
Shawl Sign
Pruritic Macular Violaceous Erythema
Göttron’s Sign
Göttron’s Papules
Periungual telangiectasia
Holster Sign
Poikiloderma atrophicans vasculare (POIKILODERMA-hyperpigmentation, hypopigmentation, telangiectasis, atrophy)

Gottron’s papule-like lesion over medial malleolus of ankle
Spectrum of the Idiopathic Inflammatory Myopathies

- Amyopathic DM
- Hypomyopathic DM
- Classical DM
- Polymyositis/Inclusion Body Myositis

Muscle Involvement

Skin Involvement
Skin Disease Activity
Clinically-Evident Muscle Disease Activity
Classical DM (60%)

CDM

Disease onset
6 months
24 months
Skin Disease Activity
Classical DM (30%)

Clinically-Evident Muscle Disease Activity

Skin Disease Activity

- CDM
- Disease onset
- 6 months
- 24 months
Clinically-Amyopathic DM (C-ADM)
(~20% of all DM)

Clinically-Evident Muscle Disease Activity

Skin Disease Activity

C-ADM

Disease onset  6 months  24 months
Clinically-Amyopathic DM

- CADM is more common than previously thought
- Finite risk of interstitial lung disease, internal malignancy, late-onset weakness (predictors unknown)
- ANA (+), myositis-specific antibody (-), may have specific immunogenetic association (MDA-5/CADM140)
Management of DM

- Adult-onset DM
  - Screen for internal malignancy (greatest risk [25%] beyond 50 years of age)
    - Sex- and age-specific approach
  - Screen for interstitial lung disease
    - Baseline - pulmonary function tests with diffusion capacity (PFT) (25% abnormalities)
    - Persistent dry cough, dyspnea – repeat PFT, consider referral to pulmonary medicine/rheumatology
Management of DM

- Juvenile-onset DM
  - Monitor for vasculopathic tissue damage
    - Eye, Gl tract,
  - Monitor for calcinosis cutis
  - No significant risk for interstitial lung disease or internal malignancy
DM Autoantibodies

• ANA (50-70%)
• Myositis-specific autoantibody (10-20%)
  – Jo-1, PL-7, PI-12 (anti-synthetase antibody syndrome [myositis, arthritis, Raynaud’s phenomenon, mechanics hand lesion])
• New autoantibodies (10-30%)
  – Melanoma differention antigen 5 (MDA5) (interstitial lung disease association)
  – Transcription intermediary factor 1γ (TIF1γ) & Nuclear matrix protein (NXP-2) (internal malignancy association)
Mechanic’s Hand Lesion
Management of DM
“DM” Is No Longer Enough

Adult-Onset

Classic DM      Clinically-Amyopathic DM

Dermatomyositis Phenotypes

Classic DM      Clinically-Amyopathic DM

Juvenile-Onset
Distinguishing the Cutaneous Manifestations of Morphea form Systemic sclerosis
Scleroderma

Hardened, thickened, hide-bound skin associated with autoimmune microvascular injury and replacement of the dermis and subcutaneous tissue by dense fibrotic tissue
Scleroderma
Morphea (Localized Scleroderma)
Systemic Sclerosis

Localized Scleroderma/Morphea
SSc sine scleroderma

Systemic Sclerosis
Systemic Involvement
Skin Involvement
Scleroderma Skin Biopsy

Same in morphea and systemic sclerosis
Cutaneous Sclerosis

"Scleroderma"

Systemic Sclerosis (SSc)

Limited cutaneous sclerosis (CREST)
Diffuse cutaneous sclerosis

Scleroderma variants:
eosinophilic fasciitis,
eosinophilia myalgia
Pseudoscleroderma

Localized Scleroderma
(syn. Morphea)

Plaque  Linear  Generalized  Profunda/Deep
Presenting Manifestations of Morphea
Plaque Morphea
Linear Scleroderma/
Liner Morphea

En Coup de Sabre
Generalized Morphea/
Pansclerotic Morphea
Systemic Sclerosis vs. Morphea

- **Systemic Sclerosis**
  - Presents with Raynaud’s phenomenon
  - Nailfold telangiectasia
  - Sclerodactyly
  - SSc antibodies
    - Centromere
    - ScI-70 (Topoisomerase I)

- **Localized Scleroderma/Morphea**
  - Absence of the above
Presenting Manifestations of Systemic Sclerosis
Raynaud’s Phenomenon

Three colors in sequence:
1. White (vasoconstriction)
2. Blue (cyanosis)
3. Red (reactive hyperemia)
Raynaud’s Phenomenon

- **Primary** Raynaud’s phenomenon *(syn. Raynaud’s disease)*
- Absence of:
  - Periungual microvascular changes
  - Sclerodactyly
  - SSc autoantibodies
    - ANA, centromere, topoisomerase-1 (Scl-70)
- **Secondary** Raynaud’s phenomenon
  - SSc
Periungual Telangiectasia
Systemic Sclerosis & Dermatomyositis
Scleroderma in SSc
-Cutaneous Manifestations-

- Raynaud’s phenomenon
- Edema
- Microvasculopathy
- Cutaneous sclerosis (“scleroderma”)
- Matte-like telangiectasis
- Atrophy
- Pigmentary changes
- Calcinosis cutis
- Ulceration
Edema

Peau d’orange

Sausage Shaped Digits
Periungual Telangiectasia
(Microvasculopathy)
Ptyrigium Inversus Unguium
Sclerosis
Sclerosis & Atrophy
Atrophy → Autoamputation
Cutaneous Calcinosis
Telangiectasia
Ulceration
Systemic Sclerosis

- Two prognostic groups
  - SSc with **limited** cutaneous sclerosis (CREST syndrome)
    - Slower pace, milder course initially
    - Risk for pulmonary artery hypertension 15-20 years later
  - SSc with **generalized** cutaneous sclerosis
    - Rapid pace, severe systemic disease
SSc with limited cutaneous sclerosis

(CREST Syndrome)

C - Calcinosis
R - Raynaud’s
E - Esophageal dysmotility
S - Sclerodactyly
T - Telangiectasia
CREST Syndrome
Prognosis

• Low risk
  – Kidney, gastrointestinal tract

• High risk
  – Pulmonary and cardiovascular system
    • Pulmonary artery hypertension starting 15-20 years after disease onset
      – Presenting clinical symptoms-shortness of breath/dyspnea on exertion
SSc with Generalized Cutaneous Sclerosis
Guardsman’s Pass looking down toward Heber Valley
Distinguishing Cutaneous LE from Cutaneous DM

- Biopsy unhelpful
- Regional anatomy predilection
  - Pruritic scalp involvement
  - Face – Nasolabial folds
  - Fingers – Knuckles vs hair-bearing
- Finger nail fold microvascular changes
- Pruritus - Presence/absence
- Muscle inflammation
For Non-Dermatologists

Greenwald’s Law of Lupus


“…anything happening to a patient with SLE which is not immediately otherwise explicable will automatically be blamed on the lupus, regardless of pathophysiologic validity.”
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<td>LCV</td>
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**Greenwald’s Law of Lupus**
Recurrent tinea corporis in a man with terbinafine-induced SCLE was confused with reactivation of SCLE
For Questions & Comments

richard.sontheimer@hsc.utah.edu
7th Annual Course

• What – Intensive one-day course on Dx and Rx of skin problems commonly encountered in the primary care setting. Includes podium presentations and a hands-on skin biopsy workshop

• When - Friday, April 8, 2016
• Where - Alumni Hall, Medical Education Building
• For more information: Lisa.Estrada@hsc.utah.edu
Thank You

East Canyon, Fall 2013