Lupus Spectrum Disorders

The many different clinical manifestations of lupus

Many different antinuclear autoantibodies

UCTD
Discoid lupus
Rhupus
Scleroderma
Myositis
Sjogren’s
MCTD
Overlap Syndromes

Mild Lupus
Systemic Lupus Erythematosus
Severe Lupus

The many different clinical manifestations of lupus
Lupus Spectrum Disorders

• What do they have in common?
  – Systemic autoimmunity
  – Broad array of clinical manifestations
    • Fatigue
    • Joint pain
  – Symptoms often wax and wean
  – Symptoms evolve over time
  – Very hard to diagnose sometimes
  – We have no idea who gets these diseases or why
32 Million Americans are Positive for ANA
Spectrum of ANA

Antinuclear Antibody (ANA) Test Results in a Hypothetical Population.
Although the ANA may be present before the development of SLE, current estimates of disease incidence and test sensitivity and specificity suggest that most positive results are of uncertain (or no) clinical significance.
# Sensitivity of ANA in Rheumatology

## TABLE 1: Sensitivity of the ANA in Autoimmune and Nonrheumatic Disease

### Autoimmune Disease

- SLE: 95–100%
- Scleroderma: 60–80%
- Mixed connective tissue disease: 100%
- Polymyositis/dermatomyositis: 61%
- Rheumatoid arthritis: 52%
- Rheumatoid vasculitis: 30–50%
- Sjögren's syndrome: 40–70%
- Drug-induced lupus: 100%
- Discoid lupus: 15%
- Pauciarticular juvenile chronic arthritis: 71%

### Nonrheumatic Disease

- Hashimoto's thyroiditis: 46%
- Graves' disease: 50%
- Autoimmune hepatitis: 100%
- Primary autoimmune cholangitis: 100%
- Primary pulmonary hypertension: 40%

Systemic Lupus Erythematosus
The Many Faces of Lupus
The Many Faces of Lupus
History of Lupus

• Classical period
  – Disease first recognized in the Middle Ages and saw the description of the dermatological manifestation of the disorder
  – The term *lupus* is attributed to the 12th century physician Rogerius, who used it to describe the classic malar rash.
History of Lupus

Neoclassical period
Moric Kaposi’s recognition in 1872 of the systemic manifestations of the disease.

Modern period
1948 - discovery of the LE cell (the Lupus Erythematosus cell)
Characterized by advances in our knowledge of the pathophysiology and clinical-laboratory features of the disease, as well as advances in treatment.
History of Lupus

Lupus is Latin for wolf, and 'erythro' is derived from ἐρυθρό, Greek for "red." All explanations originate with the reddish, butterfly-shaped malar rash that the disease classically exhibits across the nose and cheeks.

- In various accounts, some doctors thought the rash resembled the pattern of fur on a wolf's face.
- In other accounts doctors thought that the rash, which was often more severe in earlier centuries, created lesions that resembled wolf bites or scratches.
- Stranger still is the account that the term "Lupus" didn't come from Latin at all, but from the term for a French style of mask which women reportedly wore to conceal the rash on their faces.
Demographics and Epidemiology

• Worldwide distribution
• Peak age onset 15-44 years
• Predominantly disease of women
  – Before puberty: 2:1 F:M
  – Ages 15-45: 15:1 F:M
  – After menopause: 3:1 F:M
• Monozygotic concordance: 24-69%
• Dizygotic concordance: 2-9%
Demographics and Epidemiology

- According to the LFA, 1.5 million Americans, and at least five million people worldwide, have a form of lupus (70% have SLE)
- Prevalence in Caucasian women is ~1 in 700
- Prevalence in Hispanic women is ~1 in 400
- Prevalence in African American women is ~1 in 245
Famous People with “Lupus”
Clinical Criteria for SLE

- Serositis
- Oral Ulcers
- Arthritis
- Photosensitivity
- Blood dyscrasia
- Renal Disease
- ANA positive
- Immunologic Changes
- Neurologic Disease
- Malar Rash
- Discoid Rash
# New Lupus Criteria

1) Must have 4 criteria with at least one clinical criterion AND one immunologic criterion OR

2) Lupus nephritis as the sole clinical criterion in the presence of ANA or dsDNA

## Clinical Criteria

1. Acute cutaneous lupus  
2. Chronic cutaneous lupus  
3. Oral ulcers  
4. Nonscarring alopecia  
5. Synovitis  
6. Serositis  
7. Renal  
8. Neurologic  
9. Hemolytic anemia  
10. Leukopenia or lymphopenia  
11. Thrombocytopenia

## Immunological Criteria

1. ANA  
2. Anti-dsDNA  
3. Anti-Sm  
4. Antiphospholipid antibody  
5. Low complement  
6. Direct Coombs test

Rashes of Lupus
Discoid Lupus

- Most common form of chronic cutaneous lupus
- Scalp involvement in 60%
- 5-10% of patients presenting with DLE will go onto extracutaneous disease
Mucosal Lesions

Serositis
Renal Disease in Lupus

Diffuse Proliferative GN

Membranous GN
Musculoskeletal

- 76-95% of case series
- Non-erosive
- Jaccoud’s (reducible deformities) in 3-43% of patients
- Synovial fluid in SLE
  - WBC 2K-15K, mostly lymphs
  - Low titer ANA may be present
CNS Lupus
Hematologic Manifestations

- Anemia
  - Hemolytic (8-12%)
  - Chronic disease
- Thrombocytopenia (<100K, 7-30%)
- Leukopenia (<4K, 35-66%)
- Lymphopenia (<1500)
- Splenomegaly (9-46%)
- TTP – rare, antibodies against ADAMTS 13
Antinuclear antibodies

- Rim (peripheral)
  - Associated with SLE
- Homogenous (Diffuse)
  - Associated with SLE, CTD
- Speckled
  - Associated with CTD
- Nucleolar
  - Associated with scleroderma
Presentation and Symptoms Vary and Evolve Over Time

Retrospective analysis of US military hospital databases was conducted to identify personnel with SLE, and symptoms associated with the ACR criteria for classification were recorded prior to diagnosis. Of 130 patients, 104 had ≥1 ACR criteria for classification prior to diagnosis. Data included at least annual examinations for female personnel and examinations every ≤5 years for male personnel.

The Puzzle that is Systemic Lupus Erythematosus

- Fatigue
- Rash
- Serositis
- CNS
- Oral ulcers
- Hair loss
- Heme-atologic
- Photo-sensitivity
- Kidney involvement
- Arthritis
- ANA
- anti-dsDNA
- anti-Sm
- CB-CAPS
- Fatigue
- CNS
- Rash
- Oral ulcers
Pattern Clustering in Lupus - Cluster 1

- Fatigue
- Rash
- Serositis
- CNS
- Oral ulcers
- Hair loss
- Heme-atologic
- Photo-sensitivity
- Kidney involvement
- Arthritis
- Serositis
- ANA
- anti-dsDNA
- anti-Sm
- CB-CAPS
- Rash
- Fatigue

Kidney involvement
Pattern Clustering in Lupus - Cluster 1

- **Arthritis**
- **ANA**
  - anti-dsDNA
  - anti-Sm
  - CB-CAPS
- **Rash**
- **Oral ulcers**
- **Hair loss**
- **Photo-sensitivity**

**Families**
- Rash (malar, discoid) – 96%
- Photosensitivity – 72%
- Oral ulcers – 15%
- Arthritis – 84%
- Anti-dsDNA+ ~ 50%
- Renal – <15%
- Serositis – <7%
- CNS – <2%
- Hematological – <20%
Pattern Clustering in Lupus - Cluster 2

Serositis – 23%
Hematologic – 35%

Slight increase in renal
Less skin involvement

Tend to be older onset SLE
Pattern Clustering in Lupus - Cluster 3

- Most heterogeneous features
  - Rash – 100%
  - Arthritis – 90%
  - Renal – 88%
  - Hematologic – 50%

- Serositis – 30%
- Photosensitivity – 24%
- Oral ulcers – 13%
- CNS – 5%
**Lupus Manifestations Vary Based on Age at Diagnosis**

**Early Onset SLE**  
More likely to have…

- Renal disease  
- Malar rash  
- Photosensitivity  
- Alopecia  
- Low complement  
- F:M 10:1

**Late Onset SLE**  
More likely to have…

- Pulmonary involvement  
- Serositis  
- Arthritis  
- F:M 4:1

**No difference in…**

- Autoantibody profile  
- Discoid rash  
- Oral ulcers
LUMINA

• LUpus in MInorities: NAture versus Nurture
  – University of Alabama at Birmingham†
  – University of Texas-Houston Health Sciences Center†
  – University of Puerto Rico Medical Sciences Campus*

• 617 African-American, Hispanic and Caucasian lupus patients aged 20 to 50 years
  – Assess genetic and socioeconomic factors on the course and outcome of lupus.

† Started recruitment in 1994
* Started recruitment in 2001
Lupus Manifestations Vary Based on Race and Ethnicity

- Hispanic and black patients tend to have more renal, hematological, and serosal manifestations following diagnosis\(^1\)

### Cumulative ACR Criteria Manifestations (%) in PROFILE Cohort per Ethnic Group\(^1\)

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Hispanic (n=78)</th>
<th>African American (n=216)</th>
<th>Caucasian (n=260)</th>
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</thead>
<tbody>
<tr>
<td>Malar Rash</td>
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<td>Discoid Rash</td>
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<td>Photosensitivity</td>
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<td>Oral/Naso Ucles</td>
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<td>Arthritis</td>
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<td>Serositis</td>
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<td>Cytopenias</td>
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Pooled cohort analysis (University of Birmingham, AL; Johns Hopkins University, MD; University of Texas Houston Health Sciences Center, TX) of 568 adults with SLE with a disease duration of <10 years from diagnosis to enrollment. Mean ages were 38-42 years, with 86%, 92%, and 96% female in the Caucasian, African American, and Hispanic patient groups, respectively.

What other diseases fall under the “Umbrella of Lupus”

- Sjogren’s
- UCTD
- Overlap Syndromes
- MCTD
- Scleroderma
Sjögren's Syndrome

- Female disease
  - ♂️/♂️: 9/1
- Common
  - 0.5-1% of adult females
- 4th -5th decade of life
- Slowly progressive
Sjögren's Syndrome

Glandular manifestations

Subjective:  
- Dry mouth  
  - difficulty with chewing, swallowing  
  - excessive fluid use
- Intermittent parotid gland enlargement

Objective:  
- Dry oral mucosa – mouth ulcers
- Tongue  
  - red
  - devoid of epithelium
  - cracked “crocodile skin”
- Teeth  
  - multiple caries
  - early loss
- Parotid gland enlargement
Sjögren's Syndrome
Sjögren's Syndrome
Sjögren's Syndrome

Parotid gland enlargement
Sjögren’s Syndrome
Extraglandular Manifestations

- **ENT**
  - Epistaxis
  - Otitis media
  - Parotid enlargement

- **GI**
  - Atrophic gastritis
  - Autoimmune pancreatitis

- **Neurologic**
  - Peripheral neuropathy
  - Cranial neuropathy

- **Renal**
  - Interstitial nephritis

- **Hematologic**
  - Anemia, leukopenia, lymphopenia
  - Lymphoma (44x risk!)

- **Pulmonary**
  - Pulmonary fibrosis

- **Rheumatologic**
  - Polyarthritis
  - Myalgia
  - Raynaud’s phenomenon

- **Skin**
  - Purpura, urticaria
  - Vasculitis
UCTD vs Overlap vs MCTD

Undifferentiated Connective Tissue Disease

Polymyositis-Scleroderma Overlap

Mixed Connective Tissue Disease
Terminology

• Undifferentiated Connective Tissue disease
  • Patient does not meet criteria for any given autoimmune disease but has features suggesting the early features of an autoimmune disease.

• Overlap Syndrome
  • One dominant autoimmune disease with overlap features of another.

• Mixed Connective Tissue disease
  • Patient meets criteria for MCTD generally with antibody positivity (RNP Ab)
Overlap Syndromes

<table>
<thead>
<tr>
<th>Rheumatoid arthritis-lupus</th>
<th>Rhupus</th>
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<tbody>
<tr>
<td>Scleroderma-polymyositis/dermatomyositis</td>
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<tr>
<td>Scleroderma-lupus</td>
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<td>Scleroderma-primary biliary cirrhosis-Sjögren's syndrome</td>
<td>Reynolds syndrome</td>
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<td>Scleroderma-rheumatoid arthritis</td>
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<td>Polymyositis overlaps</td>
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<td>Juvenile rheumatoid arthritis-lupus</td>
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<td>Psoriatic arthritis-lupus</td>
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<td>Raynaud's phenomenon overlaps</td>
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</table>
Mixed Connective Tissue Disease

• Autoimmune Disease

• Features of:
  • SLE
  • Scleroderma
  • Inflammatory Myositis (Polymyositis)
  • Rheumatoid Arthritis

• Serology: positive anti U1-RNP Ab

• Abbreviated as MCTD
MCTD - Epidemiology

- Female to male – 15:1
- Mean age at diagnosis – 37 (4-80)
- No racial or ethnic predispositions
- More common than PM/DM, less common than SLE, about as common as scleroderma
Clinical Features of MCTD

• Early Features
  • Arthritis – can be erosive or non-erosive
  • Raynaud’s
  • Puffy Hands/sausage digits

• Later features
  • Can develop skin thickening typical of Scleroderma
  • Can develop lupus manifestations
  • Can develop organ involvement: lungs, kidneys, muscle.
Systemic Sclerosis (Scleroderma)

- **Limited Scleroderma**
  - Skin thickening is distal to elbows and knees, not involving trunk
  - Can involve perioral skin thickening (pursing of lips)
  - Less organ involvement
  - Seen in CREST syndrome
  - Isolated pulmonary hypertension can occur

- **Diffuse Scleroderma**
  - Skin thickening proximal to elbows and knees, involving the trunk
  - More likely to have organ involvement
  - Pulmonary fibrosis and Renal Crisis are more common.
CREST Features

ACR and Mayo Foundation
Scleroderma Skin Manifestations

Sclero.org
International Scleroderma Network

Kahaleh B. Rheum Dis Clin N Amer 2008:57-71
Questions?