Systemic Lupus Erythematosus
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Disclosures

- I have no financial or other commercial relationships relevant to this presentation

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Lupus: why it fascinates us

- The Clinician: a potentially fatal disease that is easily confused with many other disorders
- The Immunologist: intriguing because all the key components of the immune system are involved in the underlying mechanisms of the disease

Definition

- An Inflammatory Multisystem Disease of Unknown Etiology with Diverse Clinical and Laboratory Manifestations and a Variable Course and Prognosis
- Immunologic aberrations give rise to excessive autoantibody production some of which cause cytotoxic damage, while others participate in immune complex formation resulting in immune inflammation

Figure 1. The Immunological Disease Continuum, with Examples
Autoimmune Diseases

Diffuse
- Systemic Lupus Erythematosus
- Systemic Sclerosis
- Goodpasture’s Syndrome
- Primary Biliary Cirrhosis
- Multiple Sclerosis
- Idiopathic Thrombocytopenic Purpura
- Hashimoto’s Thyroiditis

Organ Specific

Epidemiology

- Recognized Worldwide
- Prevalence 15-50/100,000
- Incidence 1.8-7.6/100,000
- 90% are Women
- Racial Predispositions
  - African-American
  - African-Caribbean
  - Hispanic
  - Asian
- 22% of lupus is diagnosed in the first 2 decades of life
Should we screen for asymptomatic lupus in persons with risk factors?

- Not recommended - even if there is a family history of SLE
- Testing for ANA produces too many false positives
  - Up to 5% of healthy individuals have a positive ANA

The First Law of Lupus

- The rheumatologist is the last person to diagnose lupus
- Lupus Foundation of America survey (1997)
  - 2.4 million Americans self-reported SLE
  - Likely prevalence in 1997: 500,000
- “ANA-negative lupus” has decreased from 10% to <2% with advances in ANA testing

Genetic Susceptibility

Loss of Tolerance

Expansion Phase

Injury Phase
Central Mechanisms of the Induction of Tolerance

Peripheral Mechanisms of the Induction of Tolerance

The Waste-Disposal Hypothesis for Systemic Lupus Erythematosus
The Waste-Disposal Hypothesis for Systemic Lupus Erythematosus

1982 Revised Criteria
- Malar Rash
- Discoid Rash
- Photosensitivity
- Oral Ulcers
- Arthritis
- Serositis
- Renal Disorder
  - Proteinuria >0.5g
  - Cellular Casts
- Neurologic Disorder
  - Seizures
  - Psychosis
- Hematologic Disorder
  - Hemolytic Anemia
  - Leukopenia <4000
  - Lymphopenia <1500
  - Thrombocytopenia <100,000
- Immunologic Disorder
  - Positive LE Prep
  - Anti-DNA
  - Anti-Sm
  - False Positive Test for Syphilis
- Antinuclear Antibody

1997 Update in SLE Criteria
- ACR criteria for SLE were revised in 1997
  - LE prep was deleted
  - BFB for STS was expanded to include antiphospholipid antibodies and the lupus anticoagulant
Clinical Features: Overview

- Manifestations can be Constitutional or Organ Specific
- Organ Systems may be involved Singly or in any Combination
- Involvement of Kidney and CNS often Determines Morbidity and Mortality

The Evolving Spectrum of SLE

- Classic SLE
- Late Stage SLE
- APLS
- Latent SLE
- Drug Induced SLE

SLE Subsets

- Renal Lupus
  - Often dsDNA positive, low complements
- Ro+ lupus
  - Leukopenia, SCLE, neonatal LE
- APL dominated SLE
  - Strokes, thrombocytopenia, Libman Sachs lesions, thrombotic nephropathy
- RNP+ lupus
  - Esophageal dysfunction, myositis, Raynaud's
Cutaneous Features

- **LE-Specific**
  - Acute Cutaneous LE
  - Subacute Cutaneous LE
  - Chronic Cutaneous LE

- **LE-Nonspecific**
  - Alopecia
  - Oral Lesions
  - Raynaud’s/Vasculitis
  - Urticarial Lesions
  - Livedo Reticularis

**Acute Cutaneous LE**

**Subacute Cutaneous LE**
Musculoskeletal Features

- Arthralgia & Arthritis
  - The Most Common Presenting Feature of SLE
  - Usually Symmetrical
    - Hands, Wrists, Knees
  - Non-erosive, Non-destructive
  - Jaccoud’s Deformity
- Myositis
- Fibromyalgia

Jaccoud’s Deformity

Cardiovascular Features

- Pericarditis
- Myocarditis
- Left Ventricular Dysfunction
- Valvular Lesions (Libman-Sacks)
- Pulmonary Hypertension
- Coronary Arteritis
Lupus Nephritis

WHO Classification of Lupus Nephritis

- Class I
  - Normal or Minimal Change Disease (1-4%)
- Class II
  - Mesangial Glomerulonephritis (20%)
- Class III
  - Focal Proliferative Glomerulonephritis (25%)
- Class IV
  - Diffuse Proliferative Glomerulonephritis (37%)
- Class V
  - Membranous Glomerulonephritis (13%)

Diffuse Proliferative Lupus Nephropathy
WHO Class IV: Diffuse proliferative

- LM: Diffuse hypercellularity, mesangial and endocapillary proliferation, crescents, leukocytic infiltration
- EM: mesangial, subendothelial, subepithelial deposits
- IF: Mesangial and capillary Ig, C3. Extraglomerular deposits.
- Subclassed based on degree of necrosis and sclerosis

WHO Class IV (cont.)

- Most common form, around 40-50%
- Associated with worse prognosis: 5-year renal death rate 10-40%.
- Poor prognosis: African-American, Cr > 2.4 mg/dl, crescents, tubulointerstitial disease, vascular disease
- General indication for considering cytotoxic therapy

Membranous Lupus Nephropathy
WHO Class V: Membranous

- **LM:** diffuse membranous thickening, mesangial prominence
- **EM:** Epi/intramembranous deposits, mesangial deposits
- **IF:** Peripheral granular IgG, C3

WHO Class V (cont.)

- Prognosis variable. May have partial or complete remission with stable creatinines for 5 years or more.
- Overall 5-year renal death rate 10-30%.
- Therapy generally recommended for florid nephrosis or deterioration in renal function.

Lupus Nephritis

- 50% patients are symptomatic
  - Need for surveillance
    - Urinalysis (cells, protein)
    - dsDNA, C3
  - 30-40% nephritic presentation
  - 10% rapidly progressive GN
  - **Pearl**
    - Clinical presentation ≠ underlying histology
Indications for Renal Biopsy

- Initial Biopsy (prior to treatment)
  - Nephritic sediment
  - >0.5 g/24 hr. proteinuria + hematuria
  - <0.5 g/24 hr. proteinuria + hematuria + low C3 + positive anti-dsDNA
  - >1.0 g/24 hr. proteinuria (esp. if low C3 + positive anti-dsDNA)
- Repeat biopsy
  - Unexplained worsening proteinuria
  - Unexplained worsening of renal function
  - Persistent hematuria + proteinuria

Monitoring Lupus Nephritis

- Measuring GFR is ideal but impractical
  - Changes in serum creatinine more practical
  - >20-30% increase (even if within normal range)
- 24 hour urine for protein ideal
  - Spot urine protein/urine creatinine practical
  - 300 mg protein/30 mg creatinine = 3 g/24 hr proteinuria
- Serology
  - Anti-dsDNA antibodies, C3
  - Changes more valuable than absolute values
- Rule out non-SLE related causes of “renal flare”
  - Drugs, hypertension, dehydration, infection

Lupus Nephritis: Treatment

- To date, most experts agree - the treatment of lupus nephritis (LN) consists of
  - a period of intensive immunosuppressive therapy (induction therapy)
  - followed by a longer period of less intensive maintenance therapy
- Unfortunately, most studies – even those that are prospective and controlled – are plagued by “generic” problems
  - small number of patients,
  - diverse racial and socioeconomic backgrounds
  - heterogeneous inclusion criteria
  - short follow-up
Treating Lupus Nephritis

- The NIH protocol
  - Cytoxan 0.75g/m2 (0.5 g/m2 if CrCl<1/3 of expected)
  - WBC at 10 and 14 days
  - Adjust Cytoxan to max 1.0 g/m2 to keep WBC >1500
  - If WBC <1500, reduce next dose by 25%
  - Repeat monthly for 6 months, then every 3 months for 1 year after remission achieved

Alternatives

- Initial CellCept
- Initial Cytoxan followed by maintenance with azathioprine or CellCept

Neuropsychiatric Syndromes in SLE
Neuropsychiatric Syndromes in SLE

- **CNS**
  - Aseptic meningitis
  - Cerebrovascular disease
  - Demyelinating syndrome
  - Headache
  - Movement disorder
  - Myelopathy
  - Seizure disorders
  - Acute confusional state
  - Anxiety disorder
  - Cognitive dysfunction
  - Mood disorder
  - Psychosis

- **PNS**
  - Guillain-Barre syndrome
  - Autonomic neuropathy
  - Mononeuropathy
  - Myasthenia gravis
  - Cranial neuropathy
  - Plexopathy


Diagnosis of Neuropsychiatric SLE

- There are several clinical, laboratory/immunological, neuropsychological, and imaging tests available for SLE patients presenting with neuropsychiatric manifestations.
- However, their diagnostic ability to differentiate SLE from non-SLE-related neuropsychiatric involvement has not been adequately established.
- Current imaging techniques do not adequately discriminate between immune-mediated demyelination as a result of immune-mediated injury to myelin, and demyelination as a result of ischemic injury within the CNS.

When should patients with lupus be hospitalized?

- Life-threatening hematologic abnormalities
  - Thrombocytopenia
  - Hemolytic anemia
- Rapidly progressive renal disease
- Diffuse alveolar hemorrhage
- Central nervous system disease
- Unexplained fever
The Second Law of Lupus

- Anything that happens to a lupus patient is blamed on the lupus

45-year-old woman with lupus for 10 years

- LF is a 45 year old woman with SLE for 10 years with a history of serositis, arthritis, cutaneous lupus and nephritis
- Treated with prednisone 15 mg qd, hydroxychloroquine 400 mg qd and azathioprine 150 mg qd
- At diagnosis
  - ANA 1:2560, DNA 1:640, C3 24, C4<10

45-year-old woman with lupus for 10 years...

- Presents with acute chest pain for 3 hours
- EKG with non-specific ST-T wave changes
- CXR is normal
- CBC, Chem 7 and C3, C4 are normal
45-year-old woman with lupus for 10 years...

- CK 549, MB 58
- Troponin 4.4

Cardiovascular Disease and SLE

- Swedish Hospital Discharge Register (1964–1995)
  - SLE patients were at increased risk for death due to coronary heart disease or stroke
  - Standardized mortality ratio (SMR) 3.0, [95% CI 2.8–3.2]
  - The risk was substantially higher in the younger group of patients (20–39 years, SMR = 16, 95% CI 10–24)
- Atherosclerosis – defined as coronary-artery calcification or carotid plaque size – is also more common in SLE patients than healthy controls (31% vs. 9%)
  - Average age of 40, RR = 4.7, 95% CI: 1.7–12.6
  - Even after adjustment for possible confounding factors
  - It correlates with disease activity and damage scores

Drug induced LE

- At least two forms
  - Classic drug induced lupus
    - Characterized by arthritis, serositis, antihistone antibodies
    - No skin involvement
    - Procainamide, hydralazine, Minocin, INH, anti-TNF agents
  - Drug induced SCLE
    - Positive Ro
    - HCTZ, Calcium channel blockers, terbinafine
Impact of Co-morbidities

- SLE patients may be at increased risk for several co-morbidities including:
  - Infections
  - Cardiovascular disease
  - Osteonecrosis/osteoporosis and malignancies
- Treatment-related morbidity may not be easily separable from disease-related morbidity
  - An additive or synergistic effect?

Principles of Therapy for SLE

- Hydroxychloroquine for all patients
  - Prevents flares and safe in pregnancy
- NSAIDS
  - May be sufficient for arthritis and serositis
- Glucocorticoids are first-line for most lupus manifestations
  - Also responsible for weight gain, osteoporosis and diabetes
- Immunosuppressives:
  - Cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, belimumab

Preventive Care for patients with Lupus

- Low cholesterol diet
- Exercise
- Weight control
- Smoking cessation
- UV protection (to reduce flares from sun exposure)
- Calcium and vitamin D (to prevent osteoporosis)
- Routine dental evaluation
Summary

- Lupus is a rare but fascinating disease
- Heterogeneity in presentation
  - Can lead to diagnostic challenges
  - Lupus nephritis and CNS lupus are the most life-threatening manifestations
- Early complications in lupus arise from disease activity and infections
- Late complications arise from accelerated atherosclerotic disease