Systemic Lupus Erythematosus Overview

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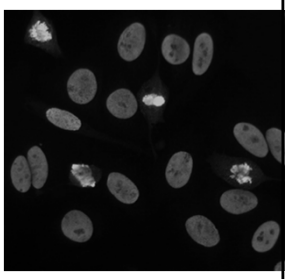
Definition

- An autoimmune disease characterized by:
  - Systemic inflammatory response in many organ systems
  - Dysregulated autoimmune response involving many arms of the immune system including T cells, B cells and macrophages

Autoantibodies in SLE: Anti-Nuclear Antibodies (ANA)

- Sensitive but not specific for SLE
  - Seen in many inflammatory, infectious, and neoplastic diseases
  - Seen in 5% to 15% of normal persons
  - It usefulness increases with high pretest probability



Incidence of Positive ANA

- Normal subjects 3-4%
- SLE 95-99%
- Drug-Induced Lupus 100%
- Discoid Lupus 30-40%
- Sub-acute cutaneous lupus 60-80%
- Incidence increases with age, chronic infections and other chronic conditions

Autoantibodies in SLE: Anti-ds DNA

- Seen in 60% of patients with SLE
- Highly specific for SLE but not diagnostic
- Strongest clinical association is with nephritis
- Titer tends to fluctuate with disease activity
- Methods vary
  - Crithidia IFA - relatively specific
  - ELISA - higher false positives

Anti Extractable Nuclear Antigen (Anti-ENA)

- Panel of antibodies that includes anti-RNP, anti-Sm, anti-SSA and anti-SSB
  - Anti ribonucleoprotein antibody (Anti RNP)
    - Found in mixed connective tissue disease and in low titers in a variety of other autoimmune diseases
  - Anti Smith antibody (Anti Sm)
    - Seen in 10% to 30% of SLE patients
    - Highly specific for SLE not diagnostic

Anti-ENA

- Anti-SSA
  - Incidence: SLE (25-57%) Also found in patients with Sjogren's
  - In SLE, anti-SSA are often associated with a photosensitive skin rash
  - Not uncommonly found in healthy subjects
- Anti-SSB
  - Incidence: SLE (15-30%). Also found in patients with Sjogren's

Epidemiology

- Etiology is unknown
- More common in Females (7:1-15:1)
- Both geography and race affect the prevalence of SLE
  - More common in urban areas
  - In the US prevalence ranges from:
    - 106 white women per 100,000 women
    - 406 African American women per 100,000 women
- Peak age of onset between 15-40

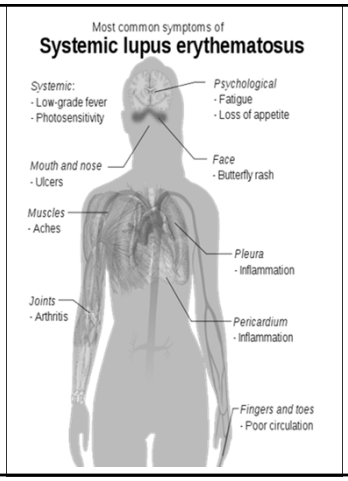
Genetics

- High concordance rate in monozygotic twins
  - 14-57%
- First degree relatives have a 17-fold increase risk of SLE compared to the general population
- 27% of children who have mothers with SLE will have ANA positivity
- Multiple polymorphisms have been identified
  - Deficiency of complement components (C1q, C2, C4 a/b)
  - Mutated TREX 1 gene

Diagnosis of SLE

Diagnosis

- A diagnosis of SLE should be based on the patient's symptoms and physical exam
  - A diagnosis of SLE is confirmed by laboratory tests
- Many versions of SLE criteria have been proposed:
  - 1997 ACR Criteria
  - 2012 SLICC Criteria: incorporates clinical features not included in the ACR criteria
  - 2015 Combined ACR/SLICC criteria to maximize positive predictive values
  - Most developed as clinical research tools for epidemiologic studies but not for diagnosis



1997 ACR Criteria for Identifying SLE

Skin Criteria

- Butterfly rash
  - Rash over cheeks
  - Sparing nasolabial folds
- Discoid Rash
  - Scaring rash
- Sun sensitivity
- Oral ulcerations

Systemic Criteria

- Arthritis (≥2 joints)
- Serositis
- Kidney involvement
  - Abnormal urine sediment +/- proteinuria
- Neurologic
  - Seizures, psychosis

Laboratory Data

- Hematologic disorders
- Immunologic tests
  - Anti-Sm
  - Anti-DSDNA
  - False positive for syphilis
- ANA positive

At least 4 out of 11 criteria needed for diagnosis

SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

Clinical Criteria

- Acute cutaneous lupus
  - i.e. Malar rash
- Chronic cutaneous lupus
  - i.e. Discoid rash
- Oral or nasal ulcers
- Non-scarring alopecia
- Arthritis
- Serositis
- Neurological involvement
- Renal involvement
- Hemolytic anemia
- Leukopenia (WBC < 4000)
- Thrombocytopenia (<100,000)

Immunologic Criteria

- Positive ANA
- Positive Anti-ds DNA
- Positive Anti-Sm
- Positive APS labs
  - Lupus anticoagulant
  - Anti-cardiolipin
  - Anti-beta2glycoprotein
- Low complements
- Positive direct coombs
  - Without presence of hemolytic anemia

SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

- ≥4 criteria needed for SLE diagnosis
  - At least 1 clinical and 1 laboratory criteria
  - Biopsy proven lupus nephritis with:
    - Positive ANA or positive anti-dsDNA

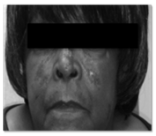
Revised 2015 Criteria for diagnosis of SLE

- Revised 2015 Criteria endorsed by the ACR
  - Combines 1997 criteria and SLICC criteria
  - 4 out of 16 points, definite SLE
  - 3 out of 16 points, probable SLE

Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

SKIN MANIFESTATIONS

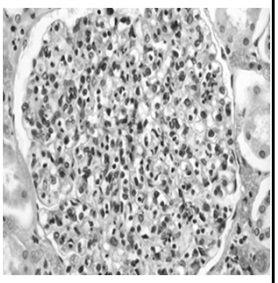
- Acute/sub-acute lupus rash: up to 2 points
  - Malar Rash: 2 points
  - Subacute SLE rash: 1 point
  - Palpable purpura/Urticaria: 1 point
  - Photosensitivity: 1 point
- Discoid lupus: 1 point
- Non scarring alopecia: 1 point
- Oral ulcers: 1 point



Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

ORGAN INVOLVEMENT

- Joint disease: 1 point
- Serositis: 1 point
  - Pleurisy
  - Pericarditis
- Neurological involvement: 1 point
  - Seizure
  - Acute psychosis
  - Acute confusion
- Kidney involvement: up to 2 points
  - Biopsy proven SLE: 2 points
  - Proteinuria >3+ grams or > 500mg/day: 1 point
  - Urinary casts: 1 point



Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

Hematologic Tests: up to 3 points

- Hemolytic anemia: 1 point
- Thrombocytopenia: 1 point
  - <100,000
- WBC count < 4000 mm3 with < 1500 lymphocyte count: 1 point

Serologic Tests: up to 3 points

- Low titer ANA: 1 point
- High tiger ANA: 2 points
- Positive Anti-dsDNA: 2 points
- Positive Anti-SM: 2 points
- Positive Antiphospholipid antibodies: 1 point
  - Lupus anticoagulant
  - Anti-Cardiolipin
  - Anti- Beta2glycoprotein APS labs
- Low complements: 1 point
  - C3, C4 or CH50

Drug-induced lupus: definite drug associations

- Hydralazine
- Procainamide
- Minocycline
- Chlorpromazine
- Isoniazid
- Penicillamine
- Methyldopa
- Interferon-alpha

Systemic Lupus Erythematosus Overview

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Treatment Principles

- Goals:
  - To control and reverse ongoing inflammation
  - To limit irreversible end-organ damage
- Tailor therapy based on extent of the disease and the specific organ(s) involved
- Potential toxicities of immunosuppressive drugs require vigilance
- Biologic therapies are very promising because of the possibility of targeting pathogenic mechanisms

Treatment Principles

- Induction therapy
  - The initial treatment that is administered to a patient with moderate-severe disease activity with the intention of rapidly suppressing the inflammatory process
  - Can be associated with significant toxicity
  - Short duration (months)
- Maintenances
  - Used to prolong the remission using drugs that have a lower toxicity profile

Current Approved Therapeutic Options

- Corticosteroids
  - Rapid action in most patients
  - Common adverse events
- Hydroxychloroquine
  - Useful for almost all lupus patients
  - Rare adverse events but requires periodic monitoring
- Belimumab
  - A biologic agent: the only one approved in lupus
  - Targets B cells
  - Modest effect in some patients

Current Unapproved Therapy: Induction Therapy

- Mycophenolate mofetil
  - Used for moderate/severe disease
  - Lower adverse event risk profile than cyclophosphamide
- Cyclophosphamide
  - Important drug used for life threating and severe disease
  - Significant short term and long term adverse events
  - Toxicity depends on multiple factors: route, accumulative dose
- Tacrolimus
  - Used for moderate/severe disease
  - Lower adverse event risk profile than cyclophosphamide

Current Unapproved Therapy

- Methotrexate
  - Used especially for the inflammatory arthritis and skin disease
  - Not in renal disease
- Azathioprine
  - Moderate disease
  - During pregnancy for moderate/severe disease
  - Maintenance of remission after induction therapy
- Mycophenolate mofetil
  - Used for moderate to life threating/severe disease
  - Contraindicated in pregnancy
  - Maintenance of remission after induction therapy

Current Therapy: Limitations

In addition to drug specific toxicity, immunosuppressive drugs share the following to varying degrees

- Increased risk of infection
- Increased risk of cancer
- Infertility
- Hematologic abnormalities
- Osteopenia

Current Therapy: Limitations

- Side effects of corticosteroids include
  - Diabetes
  - Cushingoid appearance
  - Osteoporosis
  - Osteonecrosis
  - Weight gain

Guiding Therapeutic Principles

- Use therapeutic combinations aimed at induction of remission, maintenance of remission, and supportive care
- Titrate to smallest possible dose to achieve the desired effect with least toxicity
- Strategic use of preventive therapies; antibiotics, vaccinations

Comorbidities of SLE

Atherosclerosis in patients with autoimmune disorders

- The risk of Cardiovascular disease (CVD) is very high in a prototypic autoimmune disease, systemic lupus erythematosus (SLE), and is also raised in other autoimmune diseases such as rheumatoid arthritis.
- A combination of traditional and nontraditional risk factors, including dyslipidemia (and to a varying degree, hypertension, diabetes, and smoking), inflammation, antiphospholipid antibodies (aPLs), and lipid oxidation, contribute to CVD in autoimmune diseases.

Arterioscler Thromb Vasc Biol. 2005 Sep;25(9):1776-85. Epub 2005 Jun 23.

Atherosclerosis in patients with autoimmune disorders

- Premature atherosclerosis is likely to be a major underlying mechanism, however other factors distinctive features may be playing a role (plaque rupture, thrombosis).
- Control of modifiable risk factors (blood pressure, glucose, tobacco exposure, cholesterol, sedentary life style).

Arterioscler Thromb Vasc Biol. 2005 Sep;25(9):1776-85. Epub 2005 Jun 23.

Reproductive issues

- Lupus does not significantly affect fertility
- Increased incidence of premature births
- Offspring of lupus patients have an increased prevalence of learning disability

Contraception:

Risks for lupus patients and benefits need to be considered

- IUD: increased risk of upper genital infections
- Oral contraceptive pill containing estrogen:
  - increased risk of thrombosis
  - increased risk for flare of disease
- Depo-provera injections and progestin-only pills are safer than traditional OCP in lupus

Bone Health

- Treatment and prevention of osteoporosis is problematic for lupus patients on chronic corticosteroids
  - Calcium and vitamin D
- Long term effects of bisphosphonates on future fetal growth are unknown
- Use of estrogen is associated with increased risk of flares in some studies

Diet and Exercise

- Heart healthy diet
- Avoid alfalfa sprouts (significant evidence) garlic, melatonin and rozerem, echinacea (very little evidence)
- Moderate exercise has significant beneficial effect

Infection prevention/monitoring

- Vigilance in evaluating suspected infectious processes
- Vaccination
  - Live virus vaccines: contraindicated
- Vigilance with screening studies
- Use prophylaxis while on aggressive immunosuppressive regimen

Sun exposure avoidance

- Sunlight exposure increases risk of lupus flare.
- Recommend use of SPF 45 or greater sunscreen throughout the year.

Autoimmune Diseases at a Glance

- Spectrum of diseases that vary from organ specific to systemic
- Almost every organ can be involved
- Autoimmune diseases' clinical manifestations can evolve over time
- A patient may have multiple autoimmune diagnoses

Autoimmune Diseases at a Glance

- Therapy is only partially driven by data and the guidelines are largely consensus based
- Comorbidities are multiple and require vigilance