Systemic Lupus Erythematosus (SLE)

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Outline

- Epidemiology/Natural History
- Diagnosis: ACR Criteria
- Clinical Manifestations
- Laboratory Manifestations
- Therapy
- Summary

Epidemiology

- Women: Men 5-10:1
- Peak incidence ages 15-40
- 1:2000
- Genetics
  - Identical twin concordance 25-50%
  - Non-identical twin concordance 4%
  - Sister/Mother with SLE
    - 4% chance of developing SLE
    - 30% chance of positive ANA

Natural History

- Varies according to which organ systems are affected and how severely.
- In 1950's: 50% 5 year survival
- Now (under optimal conditions) 90% survival at 10 years
- Premature atherosclerosis (early MI) is now a concern

Pathophysiology

- Genetics
  - HLA-DR, DQ, DP associated with SLE susceptibility
- Apoptosis – defective clearing of apoptotic cells
- Innate Immune System activation
  - TLRs
  - IFN-1
- Adaptive Immune System
  - T cells (TH1, TH17?)
  - B cells
  - Autoantibodies – Immune complexes

Diagnosis

Clinical

SLE Criteria (ACR)

Mnemonic: **SOAP BRAIN MD**

S erositis
O ral ulcers
A rthritis
P hotosensitvity

B lood
R enal
A NA
I mmunologic testing
N europsychiatric

M alar rash
D iscoid rash

- Blood
  - WBC < 4.0K
  - Hemolytic Anemia
  - Plts < 100,000
  - Lymphs < 1500
- Renal
  - Proteinuria
    - > 500 mg/24h
    - > 3+ dip
  - RBC casts
- Immunologic
  - DsDNA
  - Sm
  - Antiphospholipid Aby
- Neuropsychiatric
  - Seizure
  - Psychosis

Utility: give an organized way of thinking about a disease with many manifestations

SLE Criteria (Slicc - 2012)

Classify a patient as having SLE if The patient satisfies four of the criteria listed below, including at least one clinical criterion and one immunologic criterion … or - The patient has biopsy-proven nephritis compatible with SLE and ANA or anti-dsDNA antibodies.

- Clinical
  - Acute cutaneous lupus
  - Chronic cutaneous lupus
  - Oral ulcers
  - Nonscarring alopecia
  - Synovitis
  - Serositis
  - Renal
  - Neurologic
  - Hemolytic Anemia
  - Leukopenia
  - Thrombocytopenia
- Immunologic
  - ANA
  - DsDNA
  - Sm
  - APLs
  - Low complement
  - Direct Coombs

Arthritis Rheum. 2012 August ; 64(8): 2677–2686. doi:10.1002/art.34473.

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- Designed by clinical researchers to include patients with renal disease that most rheumatologists would agree is SLE *(they can be included in clinical studies)*
- Not (yet) widely adopted

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Clinical Manifestations

Oral/Nasal Ulcers

- Soft palate, buccal mucosa most common
- Classically painless
- Difficult to distinguish from common aphthous ulcers

Cutaneous

- Acute *(photosensitive)*
  A. Malar rash: spares the nasolabial fold
  B. Diffuse erythema
  C. Interarticular

Cutaneous (continued)

- Chronic – **Discoid**
  - Annular
  - Erythematous
  - Central Clearing
  - Scarring/Atrophy

Cutaneous (continued)

- Subacute: SCLE
  (subacute cutaneous lupus erythematosus)
  - Papulosquamous
  - Annular
    - Erythema and scale
    - Central clearing
    - No scarring/no atrophy
  - Associated with SSA and SSB antibodies

Photosensitivity

- Not *photophobia*
- Development of a rash from sunlight exposure
- Immunologic reaction that may cause other manifestations *(i.e. arthritis, serositis)*

Serositis

- Pleurisy
  - Chest pain that worsens with breathing
  - May (not) be associated with pleural effusion
- Pericarditis
  - Chest pain worsens with leaning forward
  - May (not) be associated with pericardial effusion

Pulmonary

- Pleurisy
- Pneumonitis
- Pulmonary Hemorrhage
- Pulmonary Embolism
- Pulmonary Hypertension
- “Shrinking Lung Syndrome”

Cardiac

- Pericarditis
- Myocarditis
- Endocarditis
- CAD

Musculoskeletal

- Arthralgias/myalgias common
- Distinguish *Arthritis* from *Arthralgia*

- Arthritis
  - Polyarticular
  - Inflammatory
  - Non erosive *(non-destructive)*
  - Reducible deformities

Neuropsychiatric

- Seizures
- Psychosis
- Organic Brain Syndrome *– most common*
- Depression
- Stroke
- Peripheral neuropathies

CNS Lupus

- Stroke
- Coma
- Cranial neuropathy
- others

- Multiple etiologies
  - Vasculopathy
  - Anti-neuronal antibodies
  - Vasculitis
  - Anti-phospholipid antibodies
  - Others

Renal

- Immune Complex Deposition on glomerular basement membrane
- DsDNA and complement likely pathogenic
- WHO

I Normal Glomeruli
II Mesangial *(Proliferative)*
III Focal Proliferative
IV Diffuse Proliferative
V Membranous
VI Advanced Sclerosing

Renal

- To biopsy or not to biopsy…
  - Pt w obvious SLE: Urine with protein, red cell casts, ↑ creatinine and ↑ BP: Probably Not
  - Exclude ATN, AIN, Drug effects: Probably Yes

- Therapy: later…

Others

- Lymphadenopathy
- Splenomegaly
- GI
  - Mesenteric vasculitis
  - Protein-losing enteropathy
  - Hepatomegaly
  - ?pancreatitis
- Vasculitis
- Ophthalmologic

Laboratory

Hematologic

- Leukopenia: WBC < 4.0 x 10^3
- Lymphopenia: Lymphs < 1500
- Thrombocytopenia: Platelets < 100,000
- Hemolytic Anemia
- Anemia chronic disease - most common

Immunologic

- Sm antibodies
  - (Smith not Smooth Muscle)
  - High specificity for SLE (>90%)
- DsDNA
  - (native or double-stranded) antibodies
  - High specificity for SLE (> 90%)
- SSA (Ro) Antibodies
- SSB (La) Antibodies
  - SLE, SCLE, Neonatal Lupus & 2° Sjogren's

Immunologic (continued)

- Antiphospholipid antibodies
  - ACLA
  - Elevated PTT (doesn't correct with plasma)
  - False positive VDRL (RPR)
  - DRVVT (dilute Russell Viper venom time)
  - ß-2 glycoprotein-1 antibodies
- Complement
  - Consumed in immune complex disease
  - Reflects disease activity
  - C3
  - C4
  - CH50

ANA

(**A**nti**N**uclear **A**ntibodies)

- Found in 93% of patients with SLE *(up to 30% general population)*
- Indirect Immunofluorescence
  - Most common method
  - Titers (< 1:80, … 1:640, > 1:640)
  - **Titers do not change with disease activity**
  - Patterns (homogeneous, speckled, centromere, nucleolar)
- Elisa
  - No titers or patterns
  - Results in Elisa units
  - Lower sensitivity *(higher false negatives)*

New!

- "ANA" is now outdated and even confusing
- Antibodies against cellular entities:
  - Nucleus
  - Cytoplasm
  - Cell Membrane
- "…one may suggest changing… to… anti-cellular antibodies" (ACA rather than ANA?)

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Therapy

Therapeutic decisions guided by clinical manifestations.

NSAIDS

- Useful: arthralgias/myalgias & mild arthritis
- May be treatment of choice for serositis
- Use with caution
- No therapeutic difference in agents

Hydroxychloroquine

- Useful in rash, arthritis, fatigue, serositis
- Prevents flares
- 300-400 mg/day *(keep dose < 6.5 mg/kg lean body weight – adjust by height)*
- Retinal toxicity *(rare at doses < 6.5 mg/kg)…still recommend annual ophthalmologic examinations*
- Nausea, diarrhea most common side effect
- Rare cytopenias

Corticosteroids

- Work quickly
- Can be life/organ saving therapy
- Many side effects
- Limit dose and length of therapy
- Arthritis: 5-15 mg
- Major Organ Involvement:
  - 1 mg/kg
  - 1000 mg IV pulses

Cyclophosphamide

- Indicated in proliferative lupus nephritis *(sometimes used for other manifestations)*
- Better outcome than prednisone alone or azathioprine
- Toxic
  - Cytopenias
  - Bladder
  - Ovary/Sperm
- 0.5 -1 g/m^2 IV monthly for 6 months

Mycophenolate

- Indicated in proliferative nephritis
- Non-inferior to cyclophosphamide
- 2000-3000 mg daily
- Side effects
  - Cytopenias
  - Gastrointestinal

Belimumab

- Newest
- Inhibits B cells
  - BAFF/BLYS
- Not tested for those with renal disease
- Adverse Effects
  - Infusion reactions
  - Depression
  - Infections

Rituximab

- Inhibits B cells
  - Antibody against CD20
- Clinical trials failed to show benefit (???)
- “Recue medication” in recalcitrant SLE
- Adverse Effects
  - Infusion reaction
  - Hypogammaglobulinema
  - Infections

Others

- Colchicine – useful in serositis
- Azathioprine – used as steroid-sparing agent
- Methotrexate
  - used as steroid-sparing agent
  - Useful in inflammatory arthritis

Avoid

- **Sulfa**
- **Estrogen (replacement doses)**
- **Tetracyclines**

- **Associated with flares of SLE**

Summary

- Remember **SOAP BRAIN MD**
- ANA found in 93% of patients with SLE
- Therapy guided by clinical manifestations
- Sm and DsDNA are very specific for SLE (in the right clinical setting)
- SLE can vary from a life-threatening illness to very mild disease that hardly affects lifestyle

- References

  - Petri M, et al. Arthritis Rheum. 2012 August ; 64(8): 2677–2686. doi:10.1002/art.34473
  - Ann Rheum Disease 2014;73:17-23
  - Squatrito D, et al. Autoimmun Highlights 2014; 5:33-45.
  - Hahn BH, et al. Arthritis Care & Res 2012; 64(6): 797-808.