LUPUS UPDATES 2019

Steve S Lee, DO, FACR
Steve.s1.lee@kp.org
Southern California Permanente Med Group, Fontana, CA
Associate Clinical Professor
Western University of Health Sciences
Assistant Clinical Professor
Loma Linda University School of Medicine
UCR School of Medicine

Disclosures

- Speaking fees:
  - Novartis
- Clinical Investigator:
  - EMD Serono, Inc
  - Amgen
  - Roche/Genentech

OUTLINE

- Definition and history
- Epidemiology
- Pathophysiology
- Cases:
  - Classification and diagnosis
  - Clinical Features
  - Treatment

"erythema centrifugum" and later "lupus érythèmateux" (1838, 1850):
Laurent-Théodore Biett
Pierre Louis Cazenave

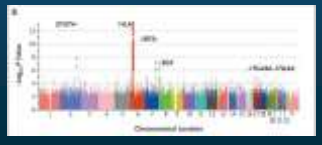
"seborrhoea congestiva"
"inflammatio folliculorum"

DEFINITION

- *"Inflammatory heterogeneous autoimmune disorder affecting multiple organ systems characterized by the production of auto-antibodies directed against cell nuclei"*

EPIDEMIOLOGY

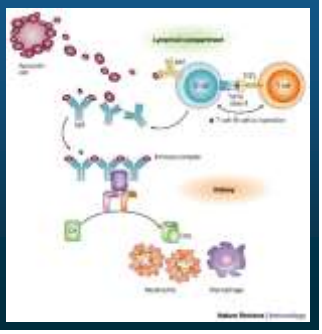
- Age, gender, race and genetics
  - Peak incidence 14-45 years
  - Female predominance 10:1 (severity is =)
  - Black, SE asian
  - Genetics:
    - HLA DRB1
    - protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*)
    - *ITGAM* or *ITGAX*



Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, Lee AT, Chung SA, Ferreira RC, Pant PK, Ballinger DG. Association of systemic lupus erythematosus with C8orf13–BLK and ITGAM–ITGAX. New England Journal of Medicine. 2008 Feb 28;358(9):900-9.

Etiology

- *Environmental*
  - *UV light*
  - *Viruses*
  - *Hormones (Estrogen)*
  - *TOBACCO*



Question 1

What lab is most specific for lupus?

anti-histone

CRP

thrombocytopenia

✔ *anti-dsDNA*

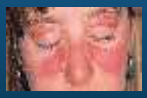
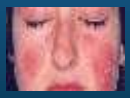
ANA

CLINICAL FEATURES: General Clinical

- *Fatigue*
- *Fevers*
- *Malaise*
- *Weight loss*
- *Anorexia*
- *Alopecia*
- *Raynaud's*
- *Lymphadenopathy*

Dermatologic domain

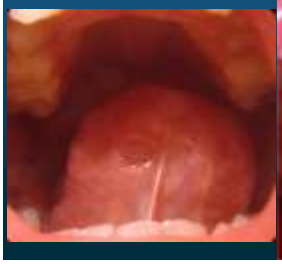
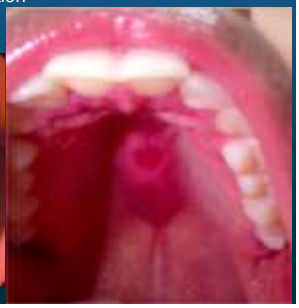
- Malar Rash
  - Fixed erythema; malar eminences
  - Spares the nasolabial folds


- Discoid Lupus Erythematosus (DLE)
  - Erythematous patches with central clearing
    - keratotic scaling
    - follicular plugging

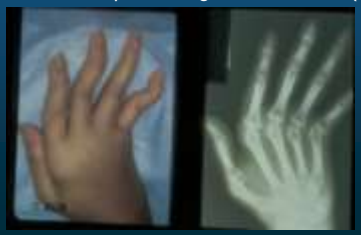

ORAL ULCERS

- Oral/nasopharyngeal ulceration
- Usually painless

CLINICAL FEATURES: Musculoskeletal

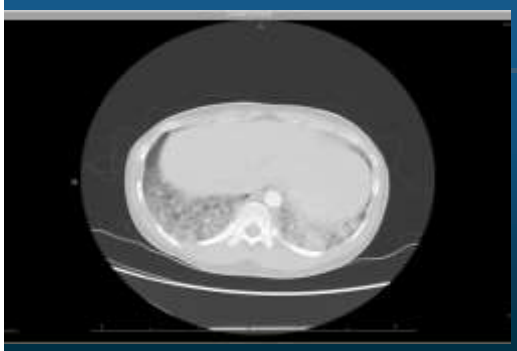
- transient, small joints, symmetrical
- “Jaccoud’s” arthritis
- Most common presenting feature of SLE (90%)

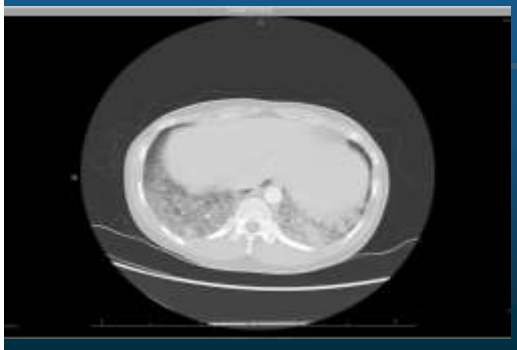


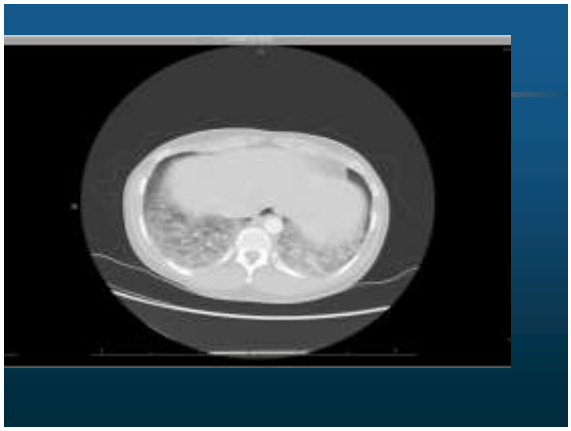
Case 2

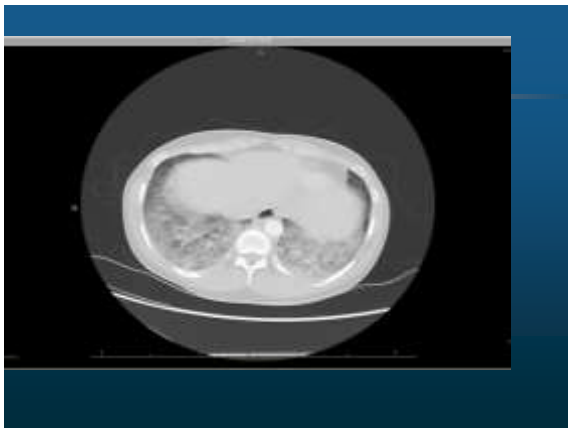
23 Cambodian female with several weeks of worsening white, painful fingers that can turn blue and red. She tried natural options including CBD, plant based diet and mindfulness as well as echinacea for “immune health”

She now presents to ED with dyspnea and hemoptysis. She is intubated. CT chest reveals….









Question

What is the best initial treatment for this severe presentation of lupus?

- *Stop echinacea*
- *Mycophenolate*
- ✓ *Methylprednisolone*
- *Cyclophosphamide*
- *Plasmapheresis*

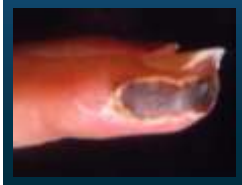
CLINICAL FEATURES: SEROSITIS

- Pleural
  - Pulmonary hemorrhage (EMERGENCY)
- Peritoneal
  - Mesenteric vasculitis
- Cardiac
  - Pericardial effusion

(Steroid and mycophenolate worked for my patient!)

SLE - VASCULOPATHY

- Dilated nailfold capillary loops
- Raynaud's phenomenon
- Digital ulcers



CLINICAL FEATURES: Cardiac

- Nonserosal:
  - Cardiac Arrythmias
  - Accelerated Atherosclerosis
- Immunologic:
  - Libman Sacks endocarditis
  - Valvular heart disease

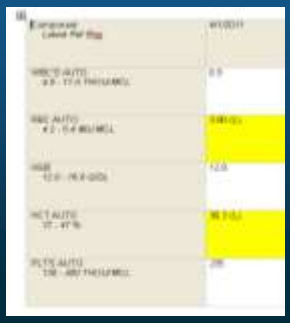
Lupus - Endocarditis

Noninfective thrombotic endocarditis involving mitral valve in SLE.
Nodular vegetations along line of closure and extending onto chordae tendineae.

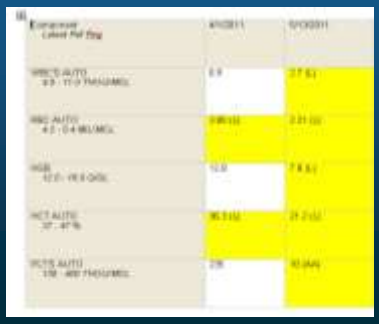
CLINICAL FEATURES: HEMATOLOGIC DISORDER

A) Hemolytic anemia – "AHA"
OR
B) Leukopenia - less than 4,000/mm^3
OR
C) Lymphopenia - less than 1,500/mm^3
OR
D) Thrombocytopenia - less than 100,000/mm^3

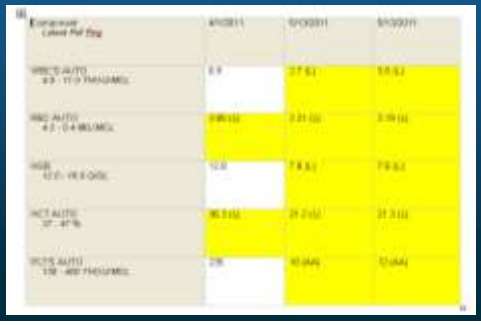
PANCYTOPENIA



PANCYTOPENIA



PANCYTOPENIA



CLINICAL FEATURES: Neurologic

Psychosis
Seizures

behavior/personality changes
migraines
depression
cognitive impairment
stroke
chorea
catatonia
pseudotumor cerebri
longitudinal myelitis – neuromyelitis optica (Devic's)
peripheral neuropathy
aseptic meningitis

*** steroid psychosis or primary psychiatric disease*

CLINICAL FEATURES: Renal (Lupus Nephritis)

- Hallmark: proteinuria (>0.5 gms daily) and casts
  - "Foamy" urine
  - Nephrotic syndrome
    - Hypoalbuminemia
    - Hyperlipidemia
    - Thrombophilia

WHO CLASSIFICATION OF LUPUS NEPHRITIS

Class I	Normal
Class II	Mesangial
IIA	Minimal alteration
IIB	Mesangial glomerulitis
Class III	Focal proliferative glomerulonephritis
Class IV	Diffuse proliferative glomerulonephritis
Class V	Membranous glomerulonephritis
Class VI	Glomerular sclerosis

Immunological findings

- **ANA** - 95-100%-sensitive but highly nonspecific for SLE
- **Anti-dsDNA**-specific(60%)-specific for SLE
- 4 RNA associated antibodies
  - **Anti-Sm (Smith)**
  - Anti Ro/SSA-antibody
  - Anti La/SSB-antibody
  - Anti-RNP
- **Antiphospholipid antibodies**
  - Lupus anticoagulant-antibodies to coagulation factors. Prolonged aPTT
  - Anti-cardiolipin
  - Anti-beta 2 glycoprotein
- **Depressed serum complement (c3, c4)**
- Anti histone antibodies
- **Coombs**

2012 SLICC Classification Criteria

SLICC[1] Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria	Immunologic Criteria
1. Acute Cutaneous Lupus*	1. ANA
2. Chronic Cutaneous Lupus*	2. Anti-DNA
3. Oral or nasal ulcers *	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab *
5. Arthritis *	5. Low complement (C3, C4, CH50)
6. Serositis *	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal *	
8. Neurologic *	
9. Hemolytic anemia	
10. Leukopenia *	
11. Thrombocytopenia (<100,000/mm³)	

[1]SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

2019 European League Against Rheumatism/ American College of Rheumatology Classification Criteria for Lupus

Arthritis & Rheumatology, First published: 06 August 2019, DOI: (10.1002/art.40930)

CLASSIFICATION CRITERIA

- Useful for trials, but diagnosis is ultimately **clinical**
- Not all "Lupus" is SLE
  - Drug induced lupus (anti-histone antibody)
    - Anti-hypertensives (hydralazine)
    - Anti-infectives (Isoniazid, terbinafine)
    - Procainamide
    - Anti-epiletics
  - Discoid Lupus
  - Subacute Cutaneous Lupus
  - Lupus pernio
- Non-rheumatic:
  - HIV, HBV, HCV, endocarditis, viral infections
  - hematologic malignancies, lymphoma
  - rosacea, OA and TPO antibodies

SLE – Treatment I

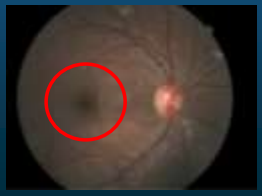
- **Mild severity** (mild skin or joint involvement)
  - NSAID
  - low dose glucocorticoids
  - hydroxychloroquine
- **Intermediate severity** (serositis, cytopenia, marked skin or joint involvement):
  - glucocorticoids (1 mg/kg/day)
  - azathioprine
  - methotrexate, leflunomide
  - mycophenolate mofetil

SLE – Treatment II

- **Severe life-threatening organ involvements** (pulmonary hemorrhage, pericarditis, nephritis, systemic vasculitis, hematologic, neuropsychiatric manifestations)
  - glucocorticoids (up to 1000 mg/day x 3 days)
  - IV cyclophosphamide
  - plasmapheresis
  - IV immunoglobulin
  - mycophenolate mofetil
  - belimumab
  - rituximab

SLE – TREATMENT PRINCIPLES

- Only 4 FDA approved treatments, many off label
- Recognize side effects, toxicity, infection risk and other complications
- Cholesterol, aspirin, sunscreen, ACE inhibitors, tobacco cessation, calcium, 25 OH vit D
- Teratogenicity
- Adherence
- Rare hydroxychloroquine AE:



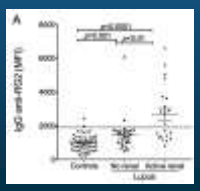
Lupus and Pregnancy

- No increase in infertility
- Pre-conception quiescence for >6 months
- High rates of flares:
  - Preeclampsia
  - Fetal Loss
  - Preterm Delivery
  - Low Birth Weight Infant
  - DVT/PE

- Neonatal lupus and complete heart block
  - SSA/SSB

Lupus and microbiome

- *Lachnospriaceae dysbiosis in lupus nephritis patients*



Silverman GJ, Azzouz DF, Alekseyenko AV. Systemic Lupus Erythematosus and dysbiosis in the microbiome: cause or effect or both?. Current opinion in immunology. 2019 Dec 1;61:80-5.
Azzouz D, Omarbekova A, Heguy A, Schwudke D, Gisch N, Rovin BH, Caricchio R, Buyon JP, Alekseyenko AV, Silverman GJ. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. Annals of the rheumatic diseases. 2019 Jul 1;78(7):947-56.

In Summary….

- Quintessential autoimmune condition
- Autoantibodies and risk factors and demographics
- Clinical domains
  - Skin and msk
  - Renal, pulmonary, hematologic
- CBC, urine protein/creatinine, complement and anti-dsDNA
- Hydroxychloroquine, steroids, immunomodulators, biologics