World Lupus Day™

Systemic Lupus Erythematosus (SLE)

SLE – What is it?

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies resulting from the dysfunction of T cells, B cells, and dendritic cells. These antibodies are principally anti-nuclear and induce an inflammatory response throughout the body.

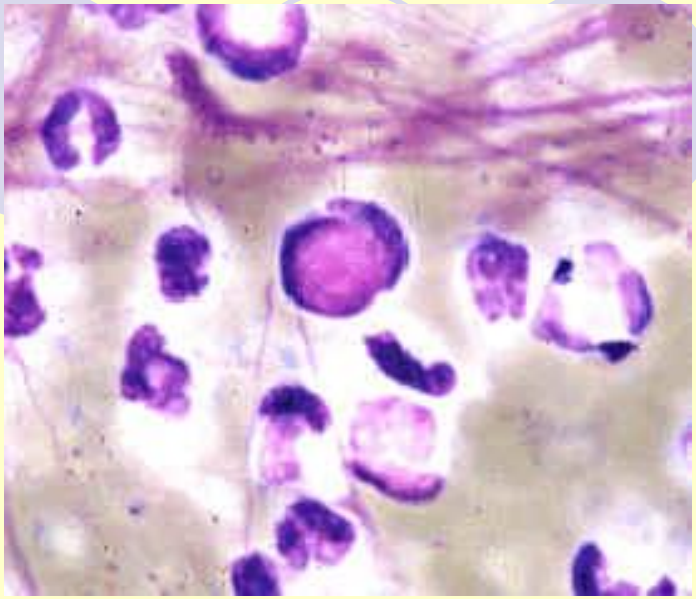
- *Sang et al. 2013; Perl A. 2009; Dorner et al. 2011*

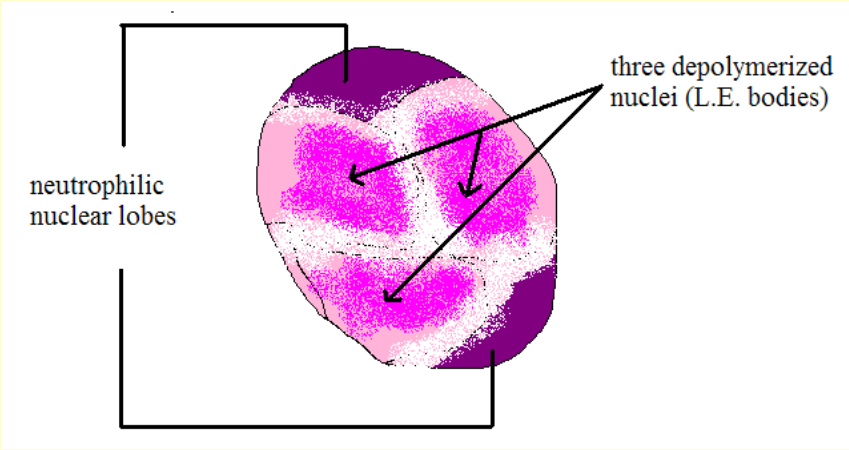
History

- 1948 – Malcolm Hargraves discovers the lupus erythematosus (LE) cell.
- 1957 – The first anti-DNA antibody is identified.

LE Cell

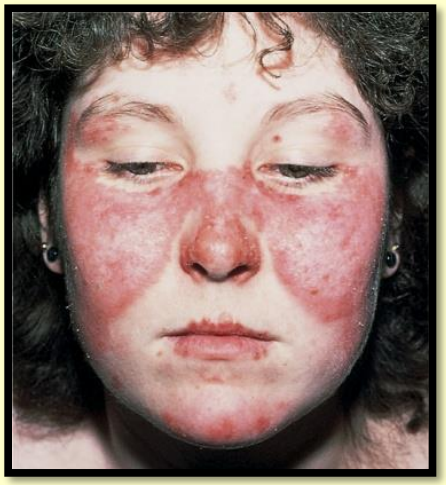
- The LE cell is a neutrophil that has engulfed the antibody-coated nucleus of another neutrophil.
- LE cells may appear in rosettes where there are several neutrophils vying for an individual complement covered protein.





General Symptoms

- Wide range of symptoms
  - Affects many systems
  - Symptoms wax and wane
- Most common symptoms
  - Mouth Sores
  - Hair Loss
  - Chest Pain
  - Extreme Fatigue
  - General Discomfort
  - Fever
  - Sunlight Sensitivity
  - Difficulty Breathing
  - Swollen Lymph Nodes
  - Skin Rashes (Butterfly Rash)



(Bartels et al. 2014; “What is Lupus?”; Shiel et al. 2014)

(http://www.lupusimages.com/browser/detail/129/mucocutaneous-sle-malar-rash)

Genetic Predispositions

- HLA genes most studied
  - HLA Class II gene polymorphisms
  - HLA DR2 and DR3
- Associated with autoantibodies:
  - Anti-Sm, anti-Ro, anti-La, anti-nRNP, anti-dsDNA, anti-PL
- Other Associated Genes
  - *BANK1*, *BLK*, IL-21-R, CD40, Lyn, *PTPN22*, TNFAIP3, FcγRs, *Blimp-1*
- Klinefelter Syndrome
  - Contributes to female susceptibility
  - Hypogonadotrophic hypogonadism

(Dorner et al. 2011; Mok and Lau. 2003; Hu and Deng 2014)

Etiology/ Pathogenesis

- Etiologic factors include:
- Immune dysregulation:
  - hypergammaglobulinemia
  - complement deficiency (C2, C4, C5)
  - autoantibody production
  - cytokine activitation
  - inability to clear immune complexes
    - organ and tissue deposition
  - T cell lymphocytopenia
    - defect in switch from T helper 0 to T helper 2 cells
      - thus promoting B cell activation.

Immunological Mechanisms

- Two Stage Disease
  - Loss of self-tolerance/Auto-Abs generation
  - Immune complex formation, causes inflammation/disease

- Stage One: Loss of Self-tolerance
  - Involves self-antigen presentation by DCs

- Role of Apoptosis
  - Impaired clearance of apoptotic cells
  - Results from defective complement system
    - C2, C4, C1q defects
    - Reduced CR1 receptors
  - Cells serve as immunogens
  - Induce auto-reactive T/B cells

(Ahmadpoor et al. 2014; Dorner et al. 2011; Mok and Lau. 2003)

Immunological Mechanisms

- Stage Two: Immune Complex Formation
  - Auto-Abs bind to:
    - Pieces of DNA
    - Nucleosomes
    - Proteoglycans
  - Immune complex formation
    - Accumulate in organ basement membranes
- Results of Immune Complexes
  - Local inflammation
  - Local complement activation
  - Local apoptosis
  - Positive feedback loop

(Ahmadpoor et al. 2014; Dorner et al. 2011; Mok and Lau. 2003)

1997 ACR Criteria

- Malar rash
- Discoid rash
- Photosensitivity
- Oral/nasal ulcers
- Serositis
- Nephritis
- Non-erosive arthritis
- Cytopenias
- Neuropsychiatric

- + ANA
- + Immunoserology
  - dsDNA Antibodies
  - Anti-Smith Antibodies
  - Antiphospholipid Ab's

Aim: more homogeneous population in research

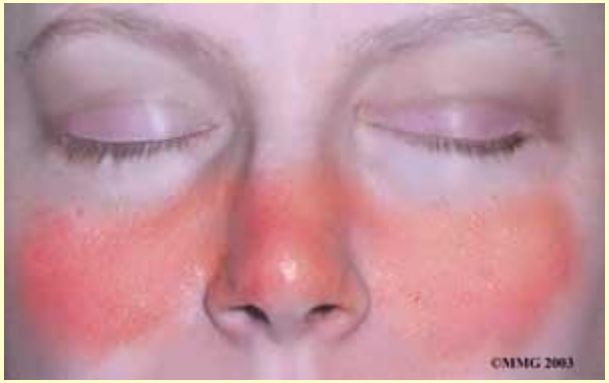
4/11 criteria: 88% Sensitivity/Specificity

System Specific Symptoms

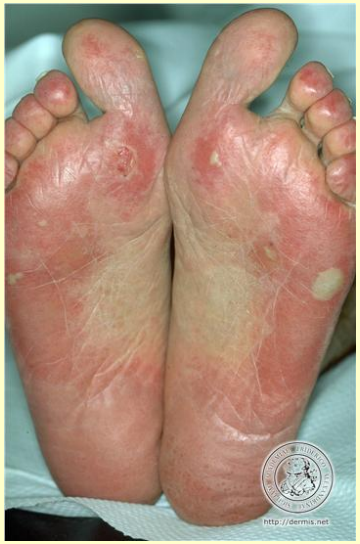
- Nervous System
  - Headaches, numbness, tingling, seizures, psychosis
- Digestive System
  - Nausea, vomiting, dyspepsia
- Cardiovascular System
  - Arrhythmias, pericarditis, myocarditis
- Respiratory System
  - Pleurisy, pleural effusion, pneumonitis, pulmonary hypertension
- Integumentary system
  - Raynaud's phenomenon, malar rash
- Excretory system
  - Edema, weight gain, acute renal failure

(Bartels et al. 2014)

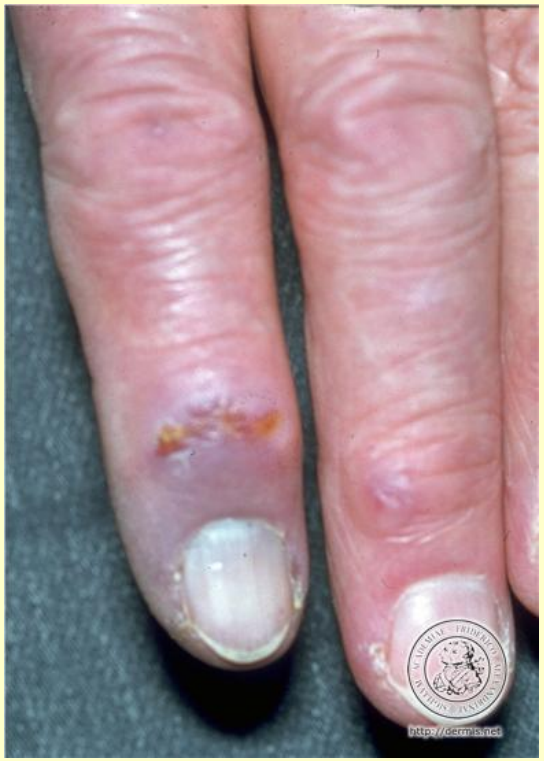
Systemic Lupus Erythematosus



butterfly rash



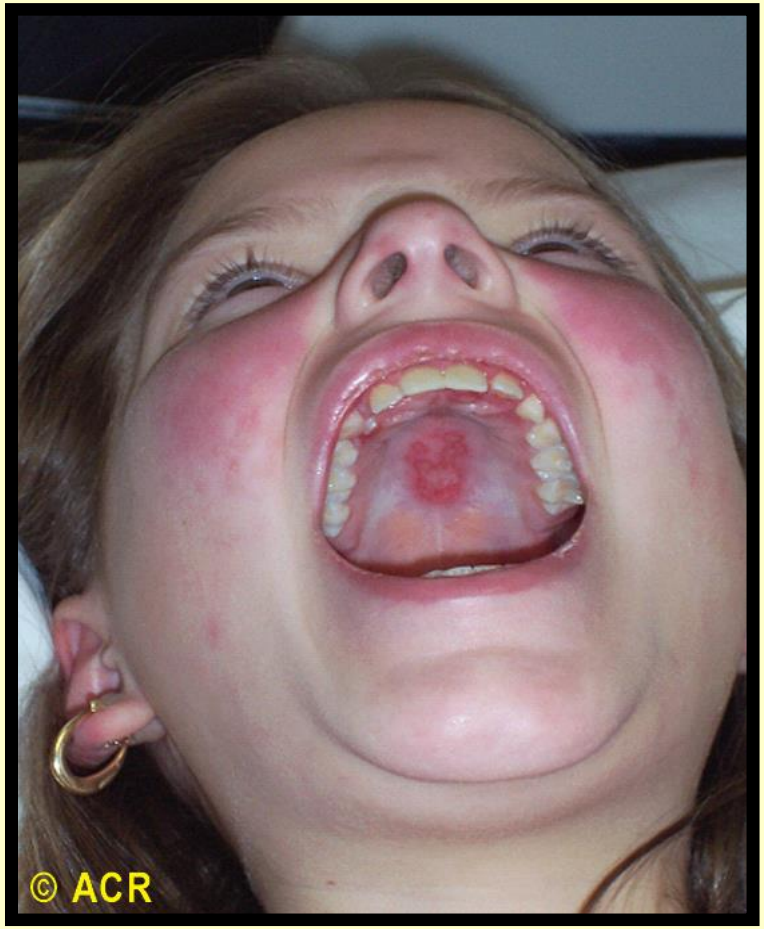
Skin rashes



Finger turns blue

Oral and Nasal Ulcerations

- Classically, PAINLESS ulcerations
- occur on the HARD palate
  - buccal = non-specific
- In the nose they occur on the septum
  - asx septal perforation can occur



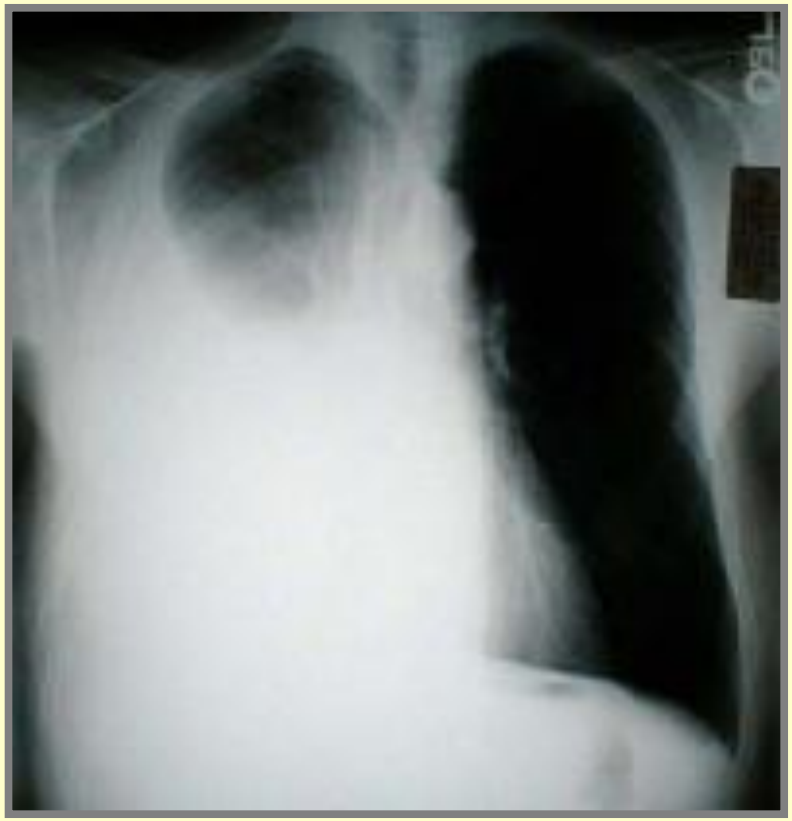
Treatment for Skin

- Sun block
  - 70% are photosensitive
  - at least 45 SPF
- antimalarial agents
  - NON immune suppressing
  - hydroxychloroquine >> chloroquine >>> quinacrine
  - ~70% response rate
    - monitor annual eye exams
- occasionally:
  - dapsone, steroids, azathioprine, rituximab

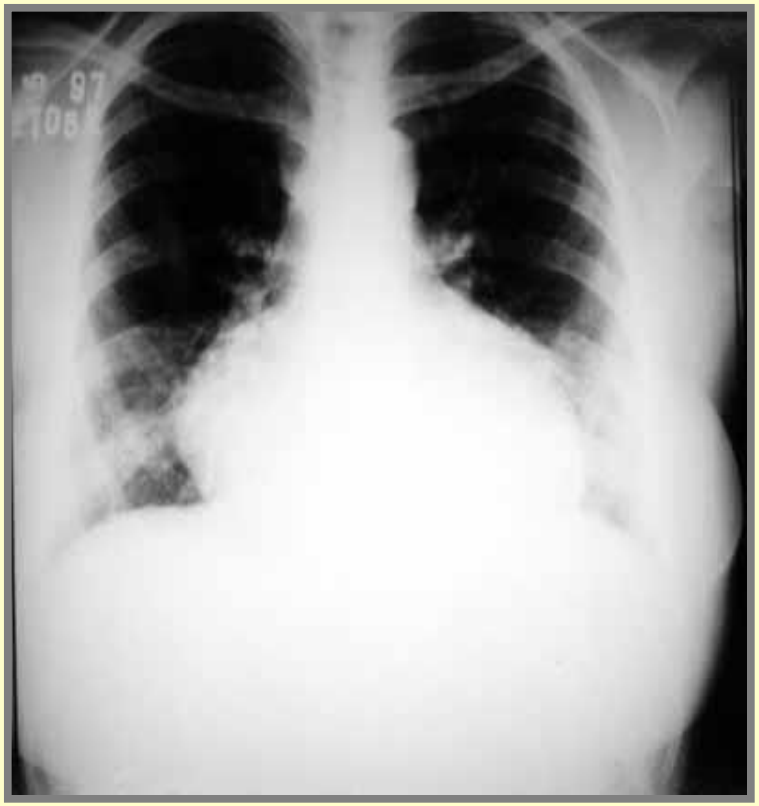
Serositis/ Cardio-pulmonary

- Pericarditis is most common cardiac complication (30%)
  - May be subclinical
  - Sx: precordial chest pain, ↑ by laying down, ↓ by sitting up and forward
  - Constriction, tamponade rare
- Pleural effusions (~30%) in children
  - 2º pleural inflammation or pneumonitis
  - or to nephrotic syndrome
  - Usually bilateral and small w/o respiratory compromise
- Pulmonary hemorrhage - rare
  - life threatening complication

SEROSITIS IN SLE



PLEURITIS



PERICARDITIS

Serositis Treatment

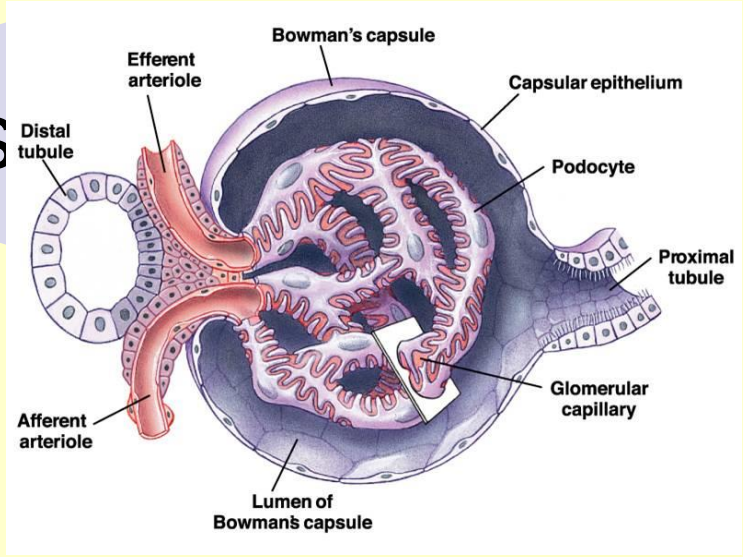
- Rule out infection
  - serosal fluid analysis for infection, ANA
    - + ANA *MAY* suggest lupus etiology
- Rule out other causes of chest pain or effusions: MI, PE, coaguloapthy, GI cause
- NSAID can help pain
- steroids low to moderate dose
  - 1-2 mg/k/d
  - max ~ 40-60mg a day
  - usually do not need very hi doses

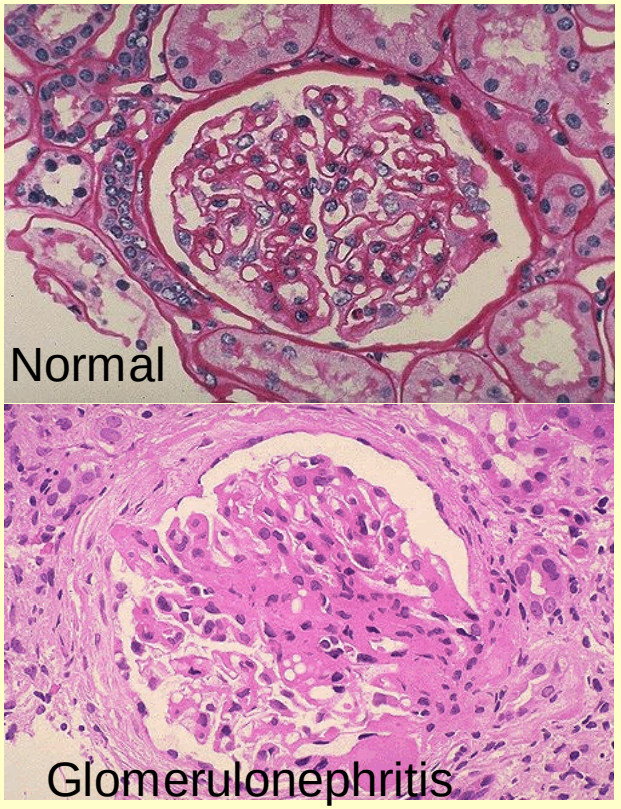
Nephritis

- Clinically active in 50-75% of pts
  - Likely to some degree in ALL with SLE
    - Bx, EM shows some change on all
- Presentation (in order of frequency):
  - Microscopic hematuria
  - Proteinuria
  - Lowered GFR
- Worst prognosis:
  - poorly controlled HTN ↑ creatinine
  - Class IV, nephrotic syndrome
  - males
- Renal disease usually w/in 2 yrs of onset

Renal (Kidney) Manifes

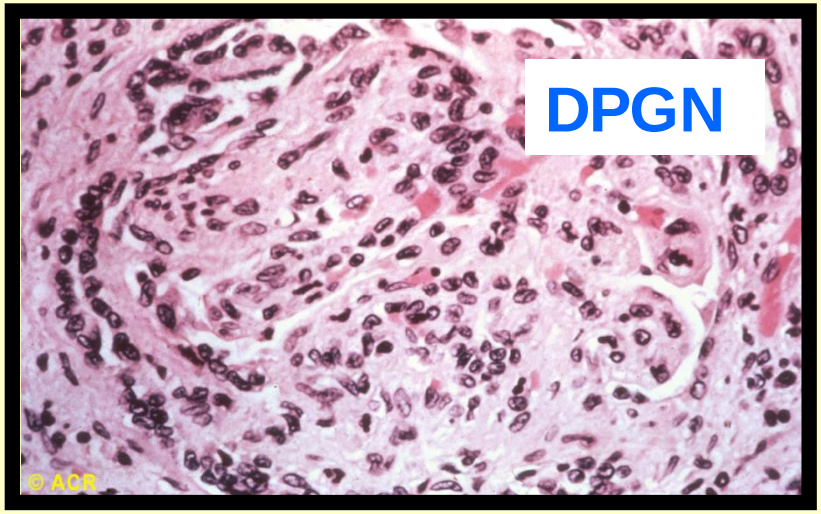
- 50-70% of all lupus patients experience renal developments.
- Most Dangerous:
  - Glomerulonephritis → where at least 50% of the glomeruli have cellular proliferation
    - Glomeruli – capillary beds in the kidney that filter the blood.
- Renal Failure because of Glomerulonephritis is the leading cause of death among lupus patients.

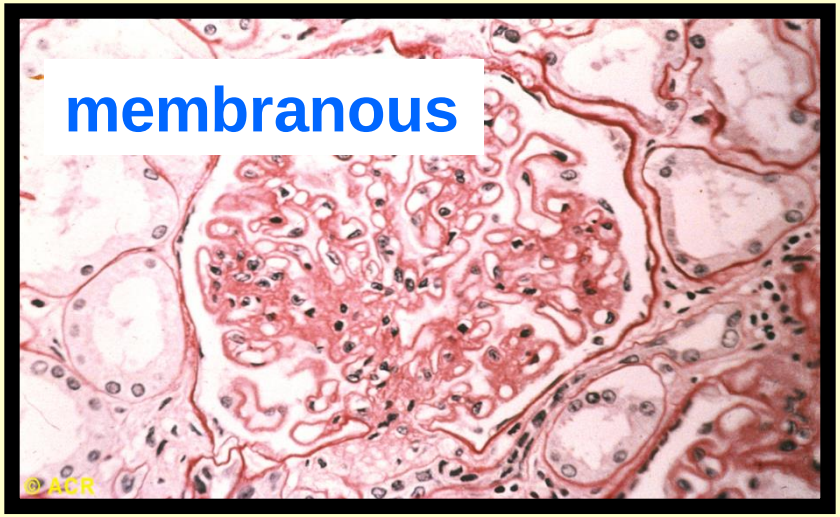




WHO Classification

- Class I — Normal
- Class IIA — Minimal change
- Class IIB — Mesangial proliferation
- Class III — Focal/segmental proliferation
- Class IV — Diffuse proliferative
- Class V — Membranous
- Class VI — Glomerulosclerosis



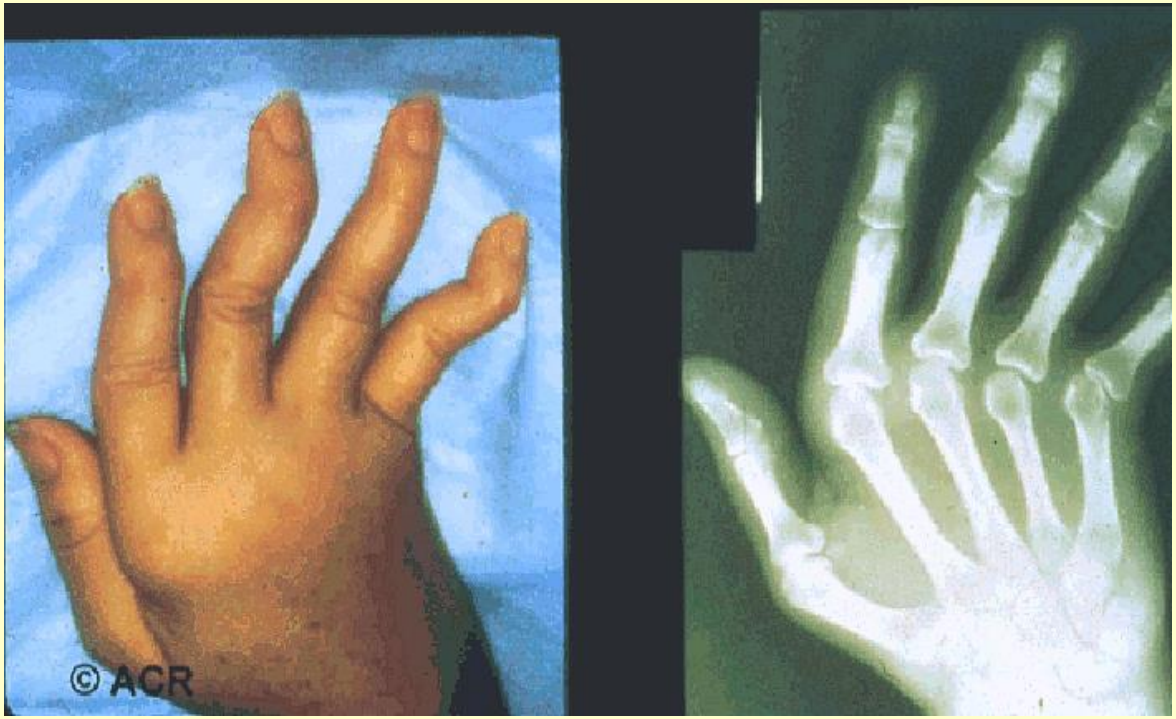


Treatment Renal Disease

- Crucial to control BP
  - poor control predicts ESRD
- mild class II to III
  - azathioprine, mycophenolate and possibly cyclophosphamide
- class IV
  - pulse cyclophosphamide
  - mycophenolate
  - 2-3 years maintenance
- Future roles for anti-B cell therapies (rituximab), other biologics

Arthritis

- Non-erosive, Painful or painless
- Jacoud arthropathy
  - reversible subluxation due to tenosynovitis
- Symmetric small and large joint involvement



Treatment of Arthritis

- Most pts respond to common regimen:
  - NSAIDs
  - anti-malarials
  - low dose prednisone $\leq$ 10 mg a day
    - beneficial in > 75% of pts
    - uncommon need for higher doses
- For those who fail:
  - methotrexate, leflunomide
  - consider anti-TNF agents (??drug induced LE)
  - consider rituximab

Cytopenias

- Rule out other causes:
  - medication induced, sepsis, TTP
- All cell lines can be affected
  - Hemolytic Anemia - Coomb's positive
  - Thrombocytopenia < 100,000
  - Leukopenia
    - Lymphopenia (<1500 cells/mm3)
- Treatment:
  - steroids: 1-2 mg/kg/d prednisone; ? pulse
  - IVIG
  - rituximab
  - consider TTP, urgent plasmapheresis

Neuropsychiatric Lupus

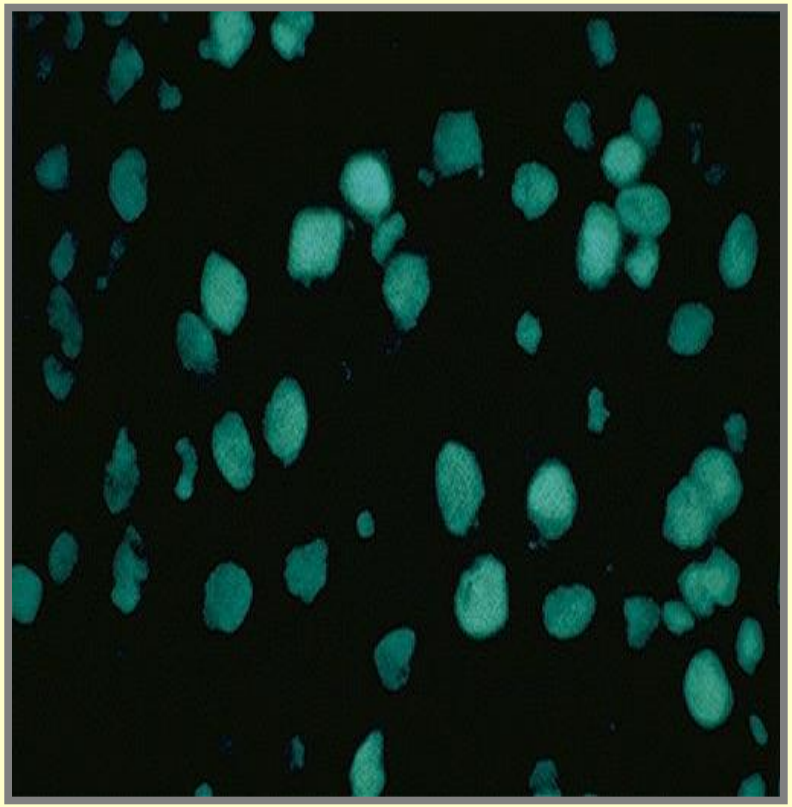
- Part of Criteria:
  - Seizures, psychosis
- More varied manifestations:
  - **Central nervous system**
    - Psychiatric: Psychosis - paranoia, hallucinations
    - Seizures - general or focal
    - Aseptic meningitis
    - Thrombotic: CVA/TIA
    - Other: Chorea, headache, Pseudotumor cerebri, myelopathy, cognitive
  - **Peripheral nervous system**
    - autonomic neuropathy
    - mononeuritis multiplex, polyneuropathy

- ACR Criteria A & R 1999 42:599

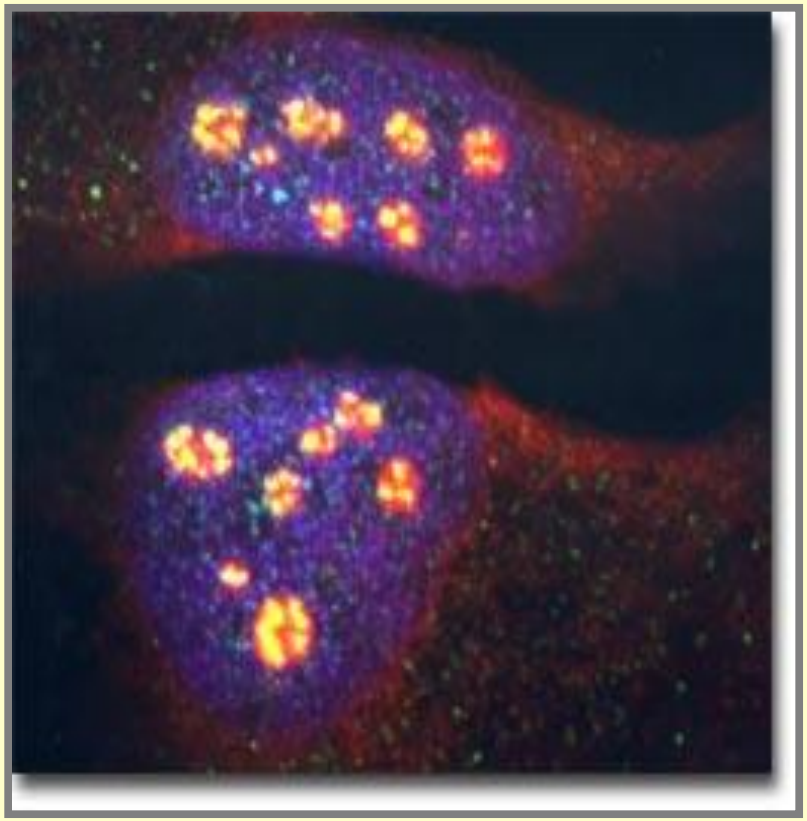
Positive ANA

- IFA
  - Usually peripheral or homogenous pattern
  - patterns have **poor** specificity for SLE
- > 98% of pts with SLE
- NOT sufficient for diagnosis
  - NOT predictive of severity
  - NO correlation with disease activity for most
- MORE common in healthy people
  - due to meds, viral infections, normal variation
    - 5% of general peds population
    - 20% adult population

ANTINUCLEAR ANIBODIES



HOMOGENOUS PATTERN



SPECKLED PATTERN

Immunoserologies

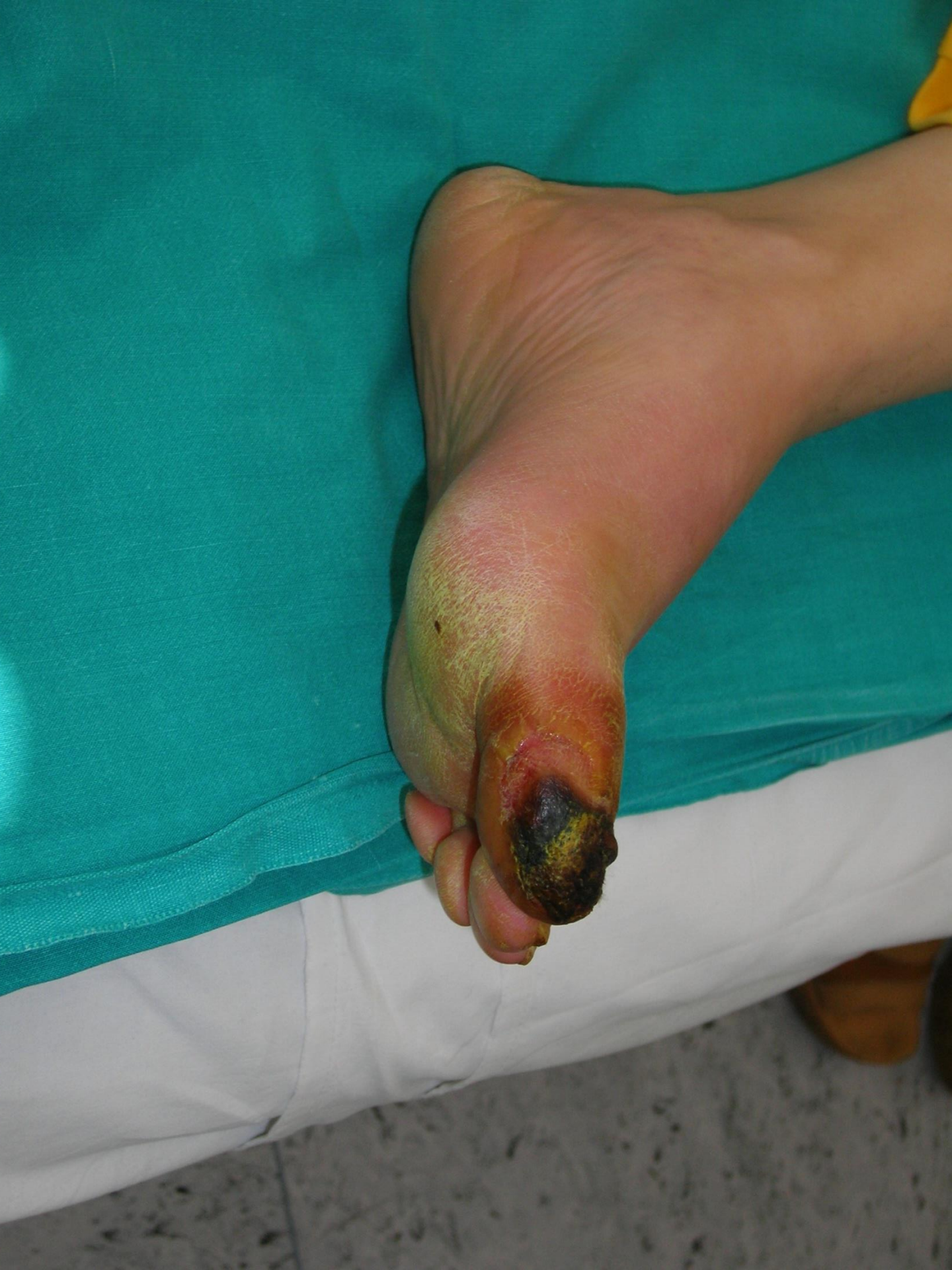
- Anti-Double-Stranded DNA Antibodies
  - Present in ~ 60% patients with active SLE
  - Very specific
  - Fluctuates with disease activity
  - may be predictive of nephritis
- Anti-Smith Antibodies
  - Present in 25-30% of SLE
  - Very specific
  - does not fluctuate with disease activity
  - Higher frequency in black females

Other antibodies

- Anti-SS-A (Ro) } neonatal LE,
- Anti-SS-B (La) } photosensitivity, rash
- Neuropsychiatric Lupus related ab:
  - features may be due to combos of these ab
    - anti-NR2 ab to glutamate receptor $\Rightarrow$ neuronal injury
    - anti-ribosomal- P
      - psychosis, depression
    - anti-neuronal
      - non-specific for SLE or certain NP features
    - anti-Neuro Myelitis Optica Ab
      - Devic's disease = optic neuropathy, myelitis
      - anti-aquaporin-4 ab: astrocyte foot processes, water channels, immune complex formation
  - NP Lupus Rheum Dise Clin N Am 31:273

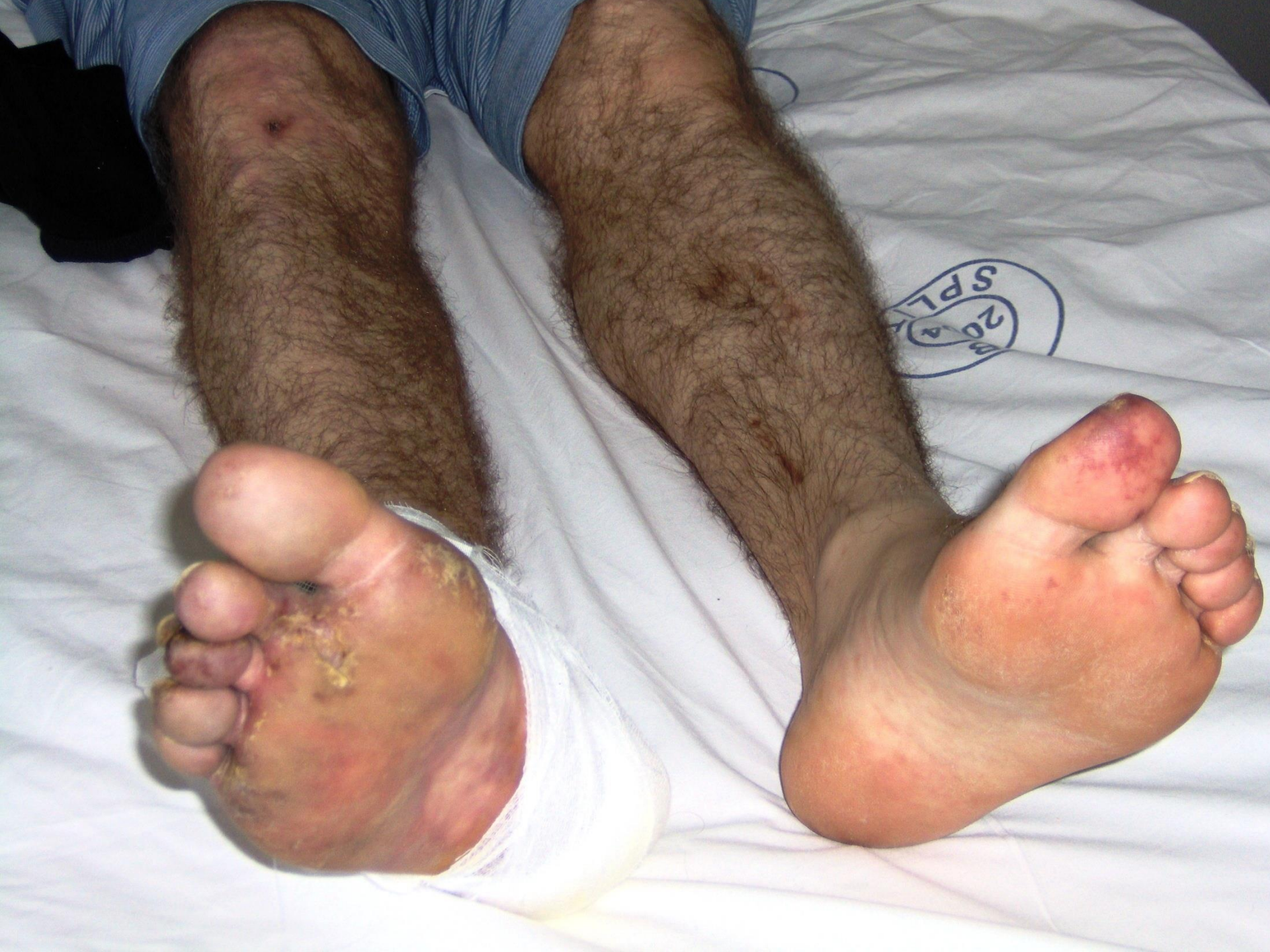
Antiphospholipid Antibodies

- Antibodies which bind to negatively charged phospholipids
  - **Anticardiolipin IgG, IgM**
  - **Anti β-2 Glycoprotein-1 IgG, IgM**
  - **Lupus anticoagulant,** Prolonged PTT
    - DRVVT, Platelet neutralization procedure
  - *Historical interest:*
    - *False positive RPR test*
      - *uses a cardiolipin-cholesterol-phosphatidylcholine antigen which can give false results*



Antiphospholipid Syndrome

- Presentations:
  - Recurrent fetal loss; 2nd, 3rd >1st trimester
  - Arterial thrombosis
  - Venous thrombosis
  - Thrombocytopenia
  - Livedo reticularis
  - Catastrophic APS
    - acute multifocal manifestations



PREGNANCY AND LUPUS

- Increased risk of disease activity during or immediately after (3 to 4 weeks) pregnancy
- Antiphospholipid antibodies pose a particular risk of miscarriages
- Congenital SLE (positive aRo/aLa mothers):
  - Congenital heart block
  - Rash/photosensitivity
  - Thrombocytopenia

PROGNOSIS

- Mortality:
  - 10-year survival rates ranging from 75-85%
  - > 90% of patients surviving more than 5 years
- Early deaths:
  - Infection
  - Active disease
  - Thrombosis
  - Renal failure
- Late complications:
  - Atherosclerosis
  - Osteoporosis
  - Avascular bone necrosis
  - Dementia

Current Options

- MILD to MODERATE Disease
- NSAIDs
- ANTIMALARIALS
- CORTICOSTEROIDS

- MAJOR ORGAN INVOLVEMENT
- Add IMMUNOSUPPRESSIVE agent
  - CYCLOPHOSPHAMIDE
  - MYCOPHENYLATE
  - AZATHIOPRINE


Thru Andy's Lens