

1. Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE)

- Prototypic autoimmune disease
- Loss of tolerance to self leads to immune system mediated damage to self
- Etiology of SLE unknown
- Each patient unique

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2. Epidemiology of SLE

Epidemiology of SLE

- Prevalence
- Ethnic/Racial differences
- Female predominance (5:1)
- Socioeconomic Factors

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3. Pathogenesis of SLE

Pathogenesis of SLE

- Genetic Factors
 - Increased frequency in close relatives
 - Ethnic susceptibilities support genetic influence
 - HLA-DR2 and –DR3 associations
 - Inherited complement deficiencies (C1q, C2, C4)

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4. Pathogenesis of SLE

Pathogenesis of SLE

Environmental factors

- Drug induced lupus
- Diet?
- Infectious triggers?

Hormonal factors

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5. Pathogenesis – Immunologic Abnormalities

Pathogenesis – Immunologic Abnormalities

Central Concept:

Tolerance to self violated → Autoantibodies produced

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6. B cells in SLE

B cells in SLE

- Auto antigen specific B cells are found in everyone
- Anergy and apoptosis prevent activation

In SLE: These B cells activate and produce autoantibodies

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7. T cells in SLE

T cells in SLE

- Probable central role in B cell activation
- Autoreactive T cell activation: failure of
 - Thymic delation
 - Peripheral T cell anergy
 - T-suppressor cells

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8. Pathogenesis – Immunologic factors

Pathogenesis – Immunologic factors

Tolerance violated; autoimmunity results

Hypotheses regarding pathogenesis:

- Infectious agent (virus?) impairs T cell
- Defective apoptosis

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9. Observed immune abnormalities in SLE

Observed immune abnormalities in SLE

- B cell hyperactivation – autoantibodies
- T cell
 - Futile hyperactivation (impaired cellular immunity)
 - Decreased suppressor cell function
- ANA (antinuclear antibodies)
- Other autoantibodies – cytoplasmic, cell surface
- Immune complex formation
 - Complement consumption (decreased serum levels a marker for disease activity)

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10. Principle of Indirect Immunofluorescence

Principle of Indirect Immunofluorescence

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11. Clinically relevant autoantibodies in SLE

Clinically relevant autoantibodies in SLE

- ANA - >95% of SLE cases
 - Caution! Positive in up to 10-15% of normals!
- Anti-dsDNA – specific for SLE
 - Marker for disease activity
- Anti-Sm – high specificity, low sensitivity
- Anti Ro (SSA), -La (SSB), -RNP - helpful but not disease specific
- Antiphospholipid – when pathogenic - thrombosis, fetal loss
 - Anticardiolipin, lupus anticoagulant, false + VDRL
all represent APLA

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12. Mechanism of tissue damage in SLE

Mechanism of tissue damage in SLE

- Immune complexes – deposition in vessels and tissues initiates inflammation leading to damage
- Autoantibodies – unclear role
- Cell mediate cytotoxicity?

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13. Clinical Features of SLE

Clinical Features of SLE

Constitutional symptoms – nonspecific but
can be profound

- Fatigue
- Weight loss
- Fever, sweats, chills
- Lymphadenopathy

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14. Systemic Lupus Erythematosus (SLE): Slide 15

Musculoskeletal - myalgias, arthralgias,
arthritis, periartthritis

- Migratory, nonerosive
- Hands, feet, knees
- Pain > physical findings
- Scant fluid
- Rare subcutaneous nodule

Myositis – Inflammation of muscles with release of
muscle enzymes.

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15. Cutaneous Manifestations

Cutaneous Manifestations

- **Malar rash in ½**
 - Photosensitive
 - Transient or chronic
 - Similar appearing rashes seen in pregnancy, rosacea, some normal individuals
- **Photosensitivity (50%) – usually to UV-B**
- **Discoid – annular, scaly plaques; scarring; head, neck & arms**
 - SLE – 25% have it
 - Discoid lupus – 10% with this alone will develop SLE

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16. Cutaneous manifestations

Cutaneous manifestations

- 4) **Subacute cutaneous lupus – small erythematous papules that coalesce into patterns; nonscarring**
 - Upper torso, neck, arms
 - Ro (SSA) association
 - 10% of SLE patients have it
 - May have this alone without systemic disease
- 5) **Lupus profundis/panniculitis**
 - nodules in dermis or subcutaneous tissue
 - Nodules may be under skin lesion or under normal skin (panniculitis)

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17. Cutaneous manifestations

Cutaneous manifestations

6) Alopecia – 70%

- Scarring – discoid lesion
- Nonscarring
 - Lupus hair – thin, fractured, frontal hairline
 - Diffuse stress reaction

7) Vascular

- Periungual erythema, livido reticularis, telangiectasias, Raynaud's
- Vasculitis
 - Urticarial/purpurral – post-cap, venules
 - Small arteries

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18. Pulmonary manifestations

Pulmonary manifestations

- Pleurisy
- Acute pneumonitis
- Acute reversible hypoxemia
- Chronic pneumonitis
- Pulmonary hypertension
- “Shrinking lung”
- Isolated diffusing capacity impairment

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Cardiac manifestations

Cardiac manifestations

- Pericardial involvement
 - Inflammation and effusions
- Myocardial involvement – acute or chronic
- Endocardial involvement
 - Libman-Sacks (verrucous endocarditis)
 - Diffuse valvular thickening
- Coronary artery disease - premature

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Hematologic manifestations

Hematologic manifestations

- Anemia
 - “Chronic disease”
 - Hemolytic
- Leukopenia
- Thrombocytopenia
- Hypercoagulable state
 - Associated with antiphospholipid antibodies

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21. Gastrointestinal manifestations

Gastrointestinal manifestations

Dyspepsia, dysphagia – common

Acute abdomen – serositis vs. vasculitis

Pancreatitis – usually mild, subclinical

Autoimmune (“lupoid”) hepatitis

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22. Neuropsychiatric (?25-50%) – Functional vs organic dif...

Neuropsychiatric (?25-50%) – Functional vs organic difficult

- Diffuse cerebral dysfunction –
Pathologically bland
 - Organic brain syndrome
 - Psychosis
 - Seizures – can be any kind, usually grand mal
 - Acute inflammation vs previous insult
- Focal cerebral dysfunction
 - Associated with antiphospholipid antibody
 - Stroke (5%) most ominous

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Neuropsychiatric

Neuropsychiatric

- 3) Peripheral neuropathy
- 4) Cranial neuropathy – usually affects eyes
- 5) Miscellaneous – movement disorder, transverse myelitis, meningitis
- 6) Eye – cytoid bodies (vasculitis of retinal capillaries)

Diagnostic tests: CSF analysis, EEG, MRI, SPECT, and other autoantibodies can be helpful but are nonspecific; clinical judgement most important

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24.

Lupus nephritis (50%)

Lupus nephritis (50%)

- Probably the most morbid manifestation of SLE is nephritis. This used to be a major cause of mortality in the pre-steroid era.
- Nearly all patients have EM and immunofluorescent renal abnormalities; 50% have clinically apparent disease.
- Occurs early in the course of the disease. If not present within 1 yr it probably won't occur.
- Histopathology – immune complexes and complement deposit in glomeruli in capillary wall, subepithelium, subendothelium, and mesangium

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25. Lupus Nephritis – clinical presentation

Lupus Nephritis – clinical presentation

- Hypertension – new onset
- Peripheral edema, weight gain
- Renal insufficiency or failure (Elevated creatinine)
- Asymptomatic urinary findings
 - Proteinuria
 - RBC, Less commonly WBC
 - Casts:
 - RBC casts ominous

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26. Classification of SLE with Reference to Glumerulonephritis...

Classification of SLE with Reference to Glumerulonephritis

Class	Renal Histology (type of lupus nephritis)	Prognosis for Renal Function
I	Minimal mesangial	Excellent
II	Mesangial proliferative	Good
III	Focal	Moderate
IV	Diffuse	Moderate-Poor
V	Membranous	Moderate
VI	Advanced sclerosing	Poor

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27. Treatment of Lupus Nephritis – NIH Data

Treatment of Lupus Nephritis – NIH Data

- Cyclophosphamide significantly reduced the risk of renal failure at 9+ years compared to oral corticosteroids alone
- Azathioprine had intermediate efficacy
- Pulse IV cyclophosphamide superior to pulse IV methylprednisolone in preventing 2x increase in creatinine in severe nephritis
- Chronicity index of prognostic importance

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28. 1982 revised criteria for classification of systemic lupus e...

1982 revised criteria for classification of systemic lupus erythematosus

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Tan E. The 1982 revised criteria for the classification of
Systemic lupus erythematosus. *Arthritis and Rheumatism*.
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29.

Management of SLE

Management of SLE

- Salicylates, nonsteroidal anti-inflammatory drugs
- Antimalarials (hydroxychloroquine, chloroquine, quinacrine)
- Corticosteroids
- Immunosuppressive/Cytotoxic drugs
 - cyclophosphamide, azathioprine, mycophenolate, methotrexate

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30.

Future Therapies

Future Therapies

- Targeted monoclonal antibodies
- Anti B cell therapy (eg Rituximab)
- Cytokine manipulation
- Bone marrow transplant

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