Systemic Autoimmune Diseases

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Systemic Autoimmune Diseases

- Systemic Lupus Erythematosus (SLE)
- Systemic Sclerosis (Scleroderma)
- Sjögren’s Syndrome
- Inflammatory Myopathies
Case 1:

23 yo woman presents for evaluation of a facial and body rash, joint pain, and recurrent oral ulcers. She had two recent acute episodes of joint pain and was seen in the ER. Treated for pain. Since the second episode she continued to have daily joint pain. On exam she has a rash. No joint swelling. No oral or nasal lesions.
A 23-year-old woman presents for evaluation of a facial and body rash, joint pain, and recurrent oral ulcers. She had two recent acute episodes of joint pain and was seen in the ER. Treated for pain. Since the second episode she continued to have daily joint pain. On exam she has a rash. No joint swelling. No oral or nasal lesions.

The most important initial test in the diagnostic evaluation of this patient is:

A. Anti-dsDNA
B. CBC with platelets
C. Urine sediment and creatinine
D. ANA
E. Anti-phospholipid antibodies
Systemic Lupus Erythematosus (SLE)

- Inflammatory autoimmune disease / autoantibodies
- Unknown etiology
- Multiple abnormalities of both the innate and adaptive immune system
- More common in women in reproductive age: 6-10 fold
- US: 2-3 times more common in African-Americans
- Multisystem involvement
- Wide variety of manifestations
- Clinical course: exacerbations and remissions
SLE: pathogenesis

Genetic / hormonal / environmental factors

- Autoantibodies secretion
- Circulating immune-complexes
- Complement activation
- Deposits of immunoglobulin, IC and complement

B- and T-cell abnormalities

failure to clear apoptotic cell debris

Tissue injury

Early atherosclerosis

Complement deficiencies
Genetic factors

- Disease concordance: 2–5% in dizygotic compared with 24–57% in monozygotic twins
- HLA-DR2 and HLA-DR3 → more frequent in SLE

- Association with HLA genes and SLE
  *Not uniform*

  *Multiple genes may be responsible → different disease patterns*

- Few cases: associated with rare but highly penetrant mutations → homozygous deficiency of complement C1q, C2 or C4
- Majority of cases: genetic susceptibility is probably determined by relatively common variants
Dysregulated apoptosis

- Auto-antigen generation / Immune complex formation
- Auto-antigen recognition
- Auto-antigen presentation
- Auto-reactive T-cell maturation
- Auto-reactive B-cell maturation

Regulatory steps
- Auto-reactive B cells and autoantibody

Key genes
Diagnosis

- Clinical presentation: *detailed history and physical examination*
- Laboratory testing

Factors that increase diagnostic challenges:
- Patients with only few manifestations that evolve slowly over long period of time
- Intermittent signs and symptoms
- Periods of spontaneous exacerbations and remissions
- Other multisystem diseases may mimic SLE
Clinical presentation

• Heterogeneous disease → can affect every organ-system in the body
• Ranging from very mild to severe / life-threatening disease
• Immunological dysfunction may precede the onset of clinical disease by many years

• Most frequent manifestations:
  - constitutional symptoms: fatigue, malaise, fever weight loss
  - musculoskeletal
  - mucutaneous
• Antiphospholipid Syndrome
• Inflammatory myopathies
• Fibromyalgia
• Hepatitis C
• Infectious Mononucleosis
• Infective Endocarditis
• Lyme Disease
• B-Cell Lymphoma
• Mixed Connective Tissue Disease
• Preeclampsia
• Rheumatic Fever
• Rheumatoid Arthritis
• Scleroderma
• Serum Sickness
• Thrombotic Thrombocytopenic Purpura
• Undifferentiated Connective Tissue Disease
ACR Criteria for the Classification of SLE (1982 / 1997)

- Malar Rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
  - pleuritis, pericarditis
- Renal disorder
  - >0.5 g prot or cellular casts
- Neurological
  - Seizure or psychosis
- Hematological
  - Hemolytic anemia, or leukopenia, or lymphopenia, or thrombocytopenia
- Immunologic
  - Anti-dsDNA, anti-Smith, or APLA
- ANA

Any combination of 4 or more of 11 criteria, well-documented at any time during a patient's history, makes it likely that the patient has SLE (specificity 95% and sensitivity 75%)
ACR criteria for classification of SLE

- Developed to guarantee patient comparability in research trials.

- Patients with early SLE may have only a few symptoms, not fulfilling 4 criteria.

- Useful reminders of features associated with SLE.

- Spectrum of clinical manifestations in SLE is much greater than outlined by the criteria.

- Disease severity vary greatly among patients and is not measured by these criteria.
Lupus lesions

- Acute
  * Malar rash

- Subacute cutaneous Lupus
  * Annular-polycyclic papulosquamous

- Chronic Lupus
  * Discoid lesions

Non-specific lesions

- Urticaria
- Panniculitis
- Livedo reticularis
- Vasculitis
- Alopecia
- Oral or nasal lesions
- Vasculitis
- Raynaud’s phenomenon (> 50%)
Musculoskeletal features

- Arthalgias or arthritis → most common presenting symptom (> 50%)
- Typically not erosive or destructive
- Clinical (initially reversible) deformity: Jaccoud’s arthropathy (subluxations)
- Complications from disease or treatment: 
  - Avascular necrosis (not only in pts taking steroids)
  - Septic arthritis
- Myositis: pain and weakness
Jaccoud’s arthropathy
Serositis: pleurisy, pericarditis or peritonitis

- Common in autopsy studies
- may be painless / silent

- Pleural effusions → usually small and bilateral; exudate; when large – exclude other causes (infection)

- Pericarditis → tamponade is rare

- Peritonitis → may present with acute abdominal pain, anorexia, nausea, vomiting. EXCLUDE: bowel perforation, acute pancreatitis, infectious peritonitis.
Pulmonary

- Pleurisy w/wo pleural effusions
- Acute pneumonitis: clinically similar to infection
- Chronic interstitial disease
- Pulmonary hemorrhage → rare but high mortality
- Pulmonary hypertension
- Shrinking lung syndrome
Case 2

38 yo african-american female with a 20-y history of SLE: Serositis, rash, GN, seizures and Raynaud’s. She has positive ANA and anti-dsDNA. Low C3 and C4. She has been taking low dose prednisone continuously for the last 5 yrs because of recurrent episodes of rash, joint pain and oral ulcers.

She presents to the ER with chest pain and dyspnea.

BP 170/98  HR 104

Exam: lungs are clear, no pleural or pericardial rubs
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She presents to the ER with chest pain and dyspnea. BP 170/98 HR 104 Exam: lungs are clear, no pleural or pericardial rubs

**The most frequent cause of mortality in this patient is:**

A. Pulmonary hypertension  
B. Pleural effusion  
C. Myocardial infarction  
D. Libman-Sacks endocarditis  
E. Myocarditis
Cardiac

- Pericarditis
- Myocarditis
  Arrhythmias or conduction defects
  Unexplained CHF

- Endocarditis
  Libman-Sacks (non-bacterial verrucous) vegetations
  Mild valvular thickening → large lesions

- Early / accelerated atherosclerosis
Multiple studies emphasize the increased risk for premature atherosclerosis and cardiovascular disease in lupus patients

- Beyond the initial phase of the disease course, cardiovascular death is the main cause of mortality.

- Many patients with SLE have subclinical atherosclerosis early in the disease course.

- The risk of CAD at any level of traditional cardiovascular risk factors is higher than in the general population.
• Nurses' Health Study → association between SLE and CVD risk. Initial cohort of 119,329 CVD- and SLE-free women. During 28 years of follow-up, 8859 nurses developed CV events and 157 developed SLE. The RR for a CV event in women who developed SLE, compared with those without SLE, was 2.34 (95% CI 1.57-3.51, \( P < .001 \)), after adjusted for age, race, traditional CVD risk factors, family history, and medications – including HRT. When CAD and stroke were analyzed separately, the RRs were 2.31 (95% CI, 1.47-3.64, \( P < .001 \)) and 2.45 (95% CI, 1.01-5.92, \( P = .047 \)), respectively.

• Prospective follow-up of an international SLE cohort (1249 patients from 27 centers and 11 countries): Despite improvement in disease activity, organ damage and CVD risk factors (diabetes, smoking, obesity, low physical activity, hypertension, and hypercholesterolemia) risk of CVD continued to accumulate over 5 years.
Atherosclerosis in SLE

• Increased incidence of carotid plaques (more than five-times as high), intimal/media thickness and endothelial dysfunction (more than double).

• Risk of cardiovascular disease is higher with longer duration of disease.

• In patients with a vascular event, mortality is twice as high in SLE as in other patient groups.

• Risk factors associated with SLE: endothelial dysfunction, the inflammatory process, anticardiolipin antibodies and impaired renal function.

• How can the accelerated arteriosclerosis be influenced? Possible strategies:
  1. reduction of disease activity to improve endothelial function
  2. reduction of steroid use whenever possible.
Neuropsychiatric

- SEIZURES
- STROKE
- ASEPTIC MENINGITIS
- HEADACHE
- TRANSVERSE MYELITIS
- CRANIAL NEUROPATHY
- PERIPHERAL NEUROPATHY
- ORGANIC BRAIN SYNDROME
- PSYCHOSIS
- NEUROCOGNITIVE DYSFUNCTION
Hematologic abnormalities

- Anemia
  Different etiologies
  Coombs’ positive (or negative) hemolytic anemia

- Leukopenia
  2500 – 4000/mm³ (DDX: medications; infections)
  Lymphopenia

- Thrombocytopenia
  May be severe/refractory and associated with active SLE
  May be an isolated feature / independent of other SLE features
  APLA syndrome
  TTP
Case 3

45 yo female presents for follow-up of SLE. She has had some increasing fatigue, no other symptoms. Her urine sed shows 2+ protein, no blood, no casts. Cr 3.5. She has been on treatment with hydroxychloroquine and azathioprine 100 mg/day.

SLE was diagnosed 5 yrs ago: GN, malar rash, pleurisy and arthritis. ANA and anti-dsDNA positive. After treatment with prednisone and cyclophosphamide, her Cr remained stable 1.9 – 2.4.
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**You decide to:**

A. Start prednisone and increase azathioprine to 150 mg/day to treat her GN recurrence.
B. Start prednisone, stop azathioprine and start cyclophosphamide to treat her GN
C. Repeat renal biopsy
D. Get renal ultra-sound for evaluation of chronicity
E. Start prednisone, stop azathioprine and start mycophenolate mofetil to treat her GN
Renal disease

• Evidence of renal disease

  *Hematuria*
  *Cellular casts*
  *Proteinuria ( >0.5g/24h or 3+ )*

• WHO classification of lupus glomerulonephritis → light, IF and EM

  I  normal
  II mesangial
  Illa focal segmental / Illb focal proliferative
  IV diffuse proliferative
  V membranous
Role and timing of biopsy: controversial

INITIAL BIOPSY
- Prognosis / predicting outcome
- Treatment

<table>
<thead>
<tr>
<th>Activity / Chronicity index</th>
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<tbody>
<tr>
<td>Active lesions → more aggressive immunosuppressive therapy</td>
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<tr>
<td>Chronic lesions → lower survival; increased ESRD</td>
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REPEAT BIOPSIES
- Changes in treatment
- Different histologies may co-exist
- Histology may change over time
- Disease recurrence vs ESRD
SLE: Laboratory abnormalities

ANA

• positive in > 98%
• non-specific

Healthy controls – 3 to 30%
Sjögren's syndrome — 70%
Scleroderma — 40 to 75 percent
Juvenile rheumatoid arthritis — 15%
Rheumatoid arthritis — 25 to 50%

Anti-dsDNA

• > 90% specificity for SLE
• In some patients titer may correlate with disease activity

Hypocomplementemia

• Low C3 and C4 → may be associated with disease flares
<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>Frequency %</th>
<th>Clinical association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-dsDNA</td>
<td>70</td>
<td>nephritis</td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>30</td>
<td>nephritis, CNS</td>
</tr>
<tr>
<td>Anti-SSA</td>
<td>20-60</td>
<td>subacute cutaneous lupus</td>
</tr>
<tr>
<td>Anti-cardiolipin</td>
<td>30-50</td>
<td>art and venous thrombosis, recurrent fetal loss, thrombocytopenia</td>
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Drug-induced Lupus

- Similar to idiopathic lupus but usually milder disease

- Renal and CNS disease are rare
- Common: constitutional symptoms, arthralgias, rash, pleuropulmonary disease

- ANA – 99%
- Anti-dsDNA – rare
- Anti-histone – 95% (not specific)

- Usually resolves after discontinuation of the drug
Drug-induced Lupus

Most common:
• Procainamida
• Hydralazine

Others:
• Carbamazepine
• Chlorpromazine
• Isoniazid
• Methyldopa
• Minocycline
• Penicillamine
• Quinidine
Survival in SLE

• Improved survival:
  – 1955: 50% (5-year)
  – 1990s: 90% (10-year)

• Improved survival related to:
  – Earlier diagnosis
  – Dialysis and renal transplant
  – More potent Immunosuppressive agents

Mortality rate still 3 to 5 times greater than general population
Morbidity and Mortality in SLE

- **Early**: severe disease manifestations
  - Active SLE → renal and CNS disease
  - Infection

- **Later**: disease damage or treatment toxicity
  - Cardiovascular (MI / stroke)
  - Infection
Treatment in SLE is determined by….

- Patient’s individual factors
- Disease activity
- Disease severity
- Organ-system involvement
- Risk factors
- Prognosis
SLE: Treatment

- **Mild disease** → constitutional symptoms, musculoskeletal, skin, serositis

  - Non-steroidal anti-inflammatory drugs
  - Antimalarials (hydroxychloroquine)
  - Low dose oral corticosteroids
  - Calcium channel blockers (Raynaud’s)

- **Severe disease** → cardiac, renal, CNS

  - High dose corticosteroids
  - Cyclophosphamide
  - Azathioprine
  - Mycophenolate mofetil
SLE nephritis: treatment

- Determined by histology / severity / prognosis
- Patient’s factors: race, age, prior history of GN and exposure to past treatment ….

- Corticosteroid (CS) monotherapy
- CS + Cyclophosphamide or mycophenolate mofetil
- CS + Azathioprine (mainly used for maintenance)
Belimumab - fully human monoclonal antibody against B-lymphocyte stimulator (BLyS)

- Mild to moderate SLE
- SLE patients with stable disease receiving standard of care treatment
- Other biologics and cyclophosphamide were excluded
- Renal and CNS disease excluded from study
- Improvement in various clinical measurements of disease activity
- Patients were able to reduce steroid dosages
SLE : Preventive care

• Steroid-induced osteoporosis

• Prophylactic immunization

• Aggressive control of traditional risk factors for atherosclerosis
  • HTN
  • Hyperlipidemia
  • Diabetes
  • Smoking
Systemic sclerosis (scleroderma)

- Vascular disease with tissue ischemia caused by abnormal accumulation of extracellular matrix components (FIBROSIS)
- Affects mainly the skin and other organs
- Association with autoantibodies ANA + 95%
- Raynaud’s phenomenon >90% of pts
- No vasculitis

- Rare: 18-20 per million general population per yr
Scleroderma pathogenesis

Environmental factors ↔ Genetic factors

Activation of T- and B-cells and endothelial cells

Release of TGF-β, PDGF, IL-4 and other cytokines

Activation of fibroblasts and smooth muscle cells

Extracellular matrix production
Disease classification

- Diffuse scleroderma $\Rightarrow$ skin thickening affecting beyond face and distal extremities (trunk / proximal involvement)

- Limited scleroderma $\Rightarrow$ skin thickening restricted to distal extremities, face and neck
  - C alcinosis
  - R aynaud’s phenomenon
  - E sophageal dysmotility
  - S clerodactyly
  - T elangiectasia

- Sine scleroderma $\Rightarrow$ no skin thickening / characteristic internal organ involvement and serology
Case 4

- 45 yo african-american female with diffuse scleroderma presents for follow up. She has been taking prednisone 20 mg/day for myopathy. She has fatigue and a new constant severe headache. Her BP is 170/98. Her urine sed shows hematuria and proteinuria. Serum Cr is 2.3. The peripheral blood smear shows RBC fragments.

**You decide to start treatment with:**

A. Pulse corticosteroids + Cyclophosphamide
B. ACE-inhibitor
C. Increase dose of prednisone to 1mg/Kg
D. Furosemide
E. Penicillamine
Diffuse scleroderma

- Skin thickening
- Raynaud’s
- Internal organ involvement
- Rapid progression
- 10 – 20% pts → severe disease / life-threatening
- Anti-Scl-70 (Topoisomerase I) → 40% of pts
- Interstitial lung disease → rapid decline / high mortality

**Renal crisis:**

*Accelerated HTN and renal failure.*

*Microangiopathic hemolytic anemia and thrombocytopenia may be present.*

*Corticosteroid ( >15 mg/day) is a major risk factor*
Limited Scleroderma (CREST)

- Calcinosi
- Raynaud’s
- Esophageal Dysmotility
- Sclerodactaly
- Telangectasias
- Limited Cutaneous: Skin involvement distal to elbows/knees
- pulmonary fibrosis less likely
- pulmonary hypertension -- more frequent
- 60 -70% have Anti-Centromere antibody
- May be associated with primary biliary cirrhosis
Scleroderma: other manifestations

- Arthralgias / myalgias
- Myopathy
- Gastric antral vascular ectasia (GAVE): bleeding
- Small-bowel dysmotility: malnutrition and diarrhea
- Large-bowel – constipation is more common
- Cardiac: conduction defects / CHF (patchy myocardial fibrosis)

- Higher incidence of malignancy: lung, skin, liver
Treatment (scleroderma)

- No effective treatment for skin disease

- Organ-based Treatment → mainly directed to control of symptoms
  - Calcium-channel blockers
  - Proton pump inhibitors
  - ACE inhibitors

- Cyclophosphamide is used to treat inflammatory alveolitis.

- Steroids should be avoided
Sjögren’s syndrome

- Inflammatory disease affecting primarily the exocrine glands.
- Female: male 9:1
- More common: 4th – 5th decades
- Primary syndrome vs secondary: Rheumatoid arthritis, SLE, Scleroderma, polymyositis
Pathogenesis

- Lymphocytic infiltration → plasma cells, lymphocytes, macrophages
- Chronic lymphocytic sialadenitis.
Sjögren’s syndrome
Clinical Features

• Keratoconjunctivitis sicca (Dry eyes): burning, sandy or scratchy sensation, photosensitivity, redness

• Xerostomia (Dry mouth): difficulty swallowing or speaking, loss of taste, burning sensation, dental caries

• Parotid or major salivary enlargement – 60%. Often bilateral.
Extraglandular disease

- Arthralgias / arthritis → non-erosive
- Raynaud’s phenomenon
- Lymphadenopathy
- Pulmonary
- Renal (5%) → Distal tubular acidosis
- Hepatic
- Myositis
- Vasculitis (5%) → skin
- Peripheral neuropathy (vasculitic ?)
Sjögren’s syndrome
Differential diagnosis

• Medications
• Viral infections
• Psychogenic

• Sarcoidosis
• Salivary gland tumors
• Bacterial infections
• Viral infections
• TB

xerostomia
Parotid enlargement
Inflammatory myopathies

- Systemic muscle diseases
- Idiopathic
- Immune-mediated: myositis-specific autoantibodies
- Painless muscle weakness

- Rare: 5-10 cases per 1 million population
- More common in females 2:1
Inflammatory myopathies: clinical classification

- Polymyositis (PM)
- Dermatomyositis (DM)
- Childhood myositis
- Myositis associated with other CTD
- Myositis with malignancy
- Inclusion body myositis
Inflammatory myopathies

• Typical: Progressive painless symmetric proximal muscle weakness.

• Occasional (not typical): muscle pain

• Fatigue, fever, weight loss

• Skin rash in DM: may precede, develop simultaneously or after myopathy.
Skin lesions

- Gottron’s papules
- Heliotrope rash
- Malar rash
- V sign
- Shawl sign
- Photosensitivity
- Cuticular overgrowth
- Mechanic’s hands
- Calcinosis
Inflammatory myopathies: other organ involvement

- Arthralgias / inflammatory polyarthritis
- Lung
  - Interstitial lung disease
  - Respiratory muscle weakness
  - Aspiration pneumonia from pharyngeal muscle dysmotility
- Cardiac: usually asymptomatic
  - Myocarditis also a focal process
Inflammatory myopathies

Diagnosis

- Clinical presentation: symmetric proximal painless weakness + other features
- Increased CK
- EMG  **Myofiber destruction (non-specific)**
- Muscle biopsy  
  - Focal inflammation (mononuclear cells)
  - Degeneration and regeneration of muscle cells
  - Atrophy of muscle cells
  - Replacement of muscle by fibrosis and fat (late)
  - Vasculitis may be seen in dermatomyositis

- MRI may improve biopsy yield
- ANA  > 90% pts
Myositis-specific autoantibodies
disease features

• Anti-Jo-1 Anti-synthetase syndrome
  - Interstitial lung disease
  - Fever
  - Arthritis
  - Raynaud’s phenomenon
  - Mechanic’s hands

• Anti-Mi-2 Classic dermatomyositis
Myositis and malignancy

• Greater risk with dermatomyositis
• Ovarian, lung, pancreatic, stomach, colorectal, NH lymphoma
• Overall risk is greatest in the first 3 yrs after diagnosis of myositis
• Older patients $\rightarrow$ greater risk

Who should be screened?
What screening should be done?
Polymyositis / Dermatomyositis Treatment

- Exacerbations and remissions
- Persistent chronic active disease

• Main treatment → corticosteroids

• Simultaneous use of other immunosuppressive at disease onset should be considered
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
  - Tacrolimus

• Resistant disease
  - IvIg
  - Rituximab