Systemic Lupus Erythematosus and the Antiphospholipid Syndrome
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Conflict of Interest
• Disclosures: None

Overview
• Diagnostic Classification Criteria of SLE
• The many faces of SLE
• A little bit about other forms of SLE—cutaneous and drug induced
• Treatment
• Antiphospholipid Syndrome

What is systemic lupus erythematosus?
• An autoimmune multi-system disease in which many different organ-systems are involved. Disease occurs in the presence of auto-antibodies most commonly an ANA
• The great imitator

SLE Epidemiology
• Prevalence ~ 50/100,000
• Second to fourth decade of life
• 9:1 female: male ratio
• More common in those of African, Latino, and Asian ethnicity

Diagnostic Criteria: Four necessary and one ought to be a positive ANA
• Malar Rash
• Discoid Rash
• Photosensitivity
• Aphthous ulcers
• Arthritis
• Serositis (pericarditis or pleuritis)
• Renal proteinuria or casts
• Neurologic: Seizures or Psychosis
• Hematologic: anemia, leuko or lymphopenia, thrombocytopenia
• Immunologic: Anti-DNA, Anti-Sm, Anti-phospholipid antibody
• ANA
Other commonly described symptoms

• Fatigue
• Headaches
• Malaise
• Cognitive impairment--- “Lupus fog”
• Myalgias

Case 1

A 33 year old woman comes to see you. Over the past year, she has had a rash over the bridge of her nose that looks like this:

Case 1: Continued

The rash really did not bother her but recently she was at the beach and after going out in the sun, she felt feverish, ill, had malaise and had a rash that looked like the following slide and mouth sores as well.
Case 1: Continued

Her younger sister is a medical student and sent off an ANA that was positive at a titer of 1:320 and she had dsDNA at 45 units (positive). Her sister thinks she has lupus but the patient thinks that she is just being a medical student who is being hypochondriacal by proxy... Who is correct?

The medical student- (Aren’t they always?)

- Malar rash
- Photosensitivity
- Aphthous Ulcers
- Positive ANA
- Positive anti-ds DNA

Cutaneous Lupus: Discoid Lupus

- Patients have defined plaques that become thickened over time. Can scar and leave hypopigmented lesions
- 10-15% of patients develop systemic lupus- in the subset that are ANA positive
- Lesions occur in 10-15% of patients with SLE
- Treatment: sun avoidance, antimalarials, dapsone, immunosuppressive agents, thalidomide

SKIN DISEASE
Cutaneous Systemic Lupus Erythematosus (SCLE)

- More common in Caucasians
- 75% of patients are women
- Lesions occur in sun-exposed areas
- Two types of lesions:
  - Papulosquamous
  - Polycyclic annular

Sub acute Cutaneous Lupus Erythematosus.
Other Skin Findings

• Alopecia
• Vasculitis
• Raynaud’s
• Bullous Lesions
• Urticarial Lesions
• Panniculitis
• Nail Lesions

Case 2

A 40 year old male whom you have been following for several years with SLE manifested by malar rash, positive serologies and renal disease complains of chest pain when he breathes in.
Pulmonary

- Pleuritis
- Lupus Pneumonitis
- Chronic Interstitial Lung Disease
- Pulmonary Hemorrhage – mortality approaches 50%
- Shrinking Lung Disease – secondary to diaphragmatic paralysis and lung disease

Case 3

A 35 year old woman whom you have followed for SLE for many years – she has joint symptoms, renal disease and positive serologies and she has required steroids, has read on the internet that she is at risk for having a heart attack… What should you do?

Cardiovascular

- *Accelerated atherosclerosis-disease +drugs.*
- Pericarditis
- Valvular heart disease – most often seen in conjunction with the anti-phospholipid syndrome – unusual
- Coronary Vasculitis – rare
- Myocarditis – rare

Case 4

A 32 year old woman is referred from her PCP with one month of joint swelling affecting her pips and mcps. She has a history of psoriasis and her pcp believes that she has psoriatic arthritis.

Case 4 continued

- Despite being placed on NSAIDs and low dose steroids. She calls your office and tells you that she has been having fevers of 102 degrees and feels terrible. Her initial labs revealed a wbc of 2.8. You decide to send off an ANA – returns at 1:1280 and ds DNA is 84.
Musculoskeletal

• 95% of patients will have musculoskeletal complaints
• Arthralgias and Arthritis
• Septic Arthritis
• Osteonecrosis-risk increases with steroid use greater than 20 mg a day
• Myositis – more commonly seen in patients with Mixed Connective Tissue Disease (MCTD)
• Myopathy- secondary to steroids – proximal muscle weakness

Case 5

A 25 year old woman is referred to you for a hematocrit of 25 and a platelet count of 90,000. She has a history of pleuritis and a positive ANA and a false positive VDRL.

Hematologic

• Anemia-usually Coomb’s positive
• Leukopenia- WBC less than 4000
• Lymphopenia- lymphocytes less than 1500
• Thrombocytopenia-Platelet count less than 100,000

Case 6

A 29 year old woman with a history of mild SLE- arthritis, malar rash, positive serologies presents with edema, proteinuria and rbc's in her urine. What would you like to do?

Renal Disease

• Proteinuria greater than 500mg protein/24 hour urine
• Presence of casts

WHO Classification

• Class I: Normal or Minimal Change
• Class II: Mesangial glomerulonephritis
• Class III: Focal proliferative glomerulonephritis
• Class IV: Diffuse proliferative glomerulonephritis
• Class V: Membranous glomerulonephritis
• Class VI: Global sclerosis >90% sclerosed lesions
**Activity vs. Chronicity**

Another way of assessing disease is to look for the degree of activity in the involved renal specimens. So most renal pathologists will also mention activity verses chronicity.

**Case 7**

A 45 year old woman with a history of SLE main manifestations hematologic and arthritis presents with altered mental status.

**Neuropsychiatric Manifestations of Systemic Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Psychiatric</th>
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<tbody>
<tr>
<td>- CVA*</td>
<td>- Psychosis</td>
</tr>
<tr>
<td>- Seizures*</td>
<td>- Cognitive disorder</td>
</tr>
<tr>
<td>- Transverse myelitis*</td>
<td>- Pseudo dementia</td>
</tr>
<tr>
<td>- Optic neuritis</td>
<td>- Functional</td>
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<tr>
<td>- Meningitis</td>
<td></td>
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<tr>
<td>- Headaches</td>
<td></td>
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<tr>
<td>- Organic brain syndromes</td>
<td></td>
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<tr>
<td>- Neuropathies</td>
<td></td>
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<tr>
<td>- * Associated w/Antiphospholipid Abs</td>
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**Other**

- Sjogren’s Syndrome
- Gastrointestinal abnormalities including abdominal pain, anorexia, peritonitis, pancreatitis, hepatitis
- Secondary fibromyalgia

**Case 8:**

You are asked to see a 38 year old woman with a history of maybe a rash over the bridge of her nose which she has been told is acne rosacea and some joint aching. She has an ANA sent that is positive at 1:40

**Autoantibodies**

- ANA- found in 95% of patients
- Anti-ds-DNA- 40%-80% of patients
- Anti-Sm- 25% of patients
- Anti-histone- seen in drug induced SLE
- Anti-Ro, Anti-La - Sjogren’s, SCLE
- Anti-RNP- Mixed Connective Tissue Disease
- False positive VDRL- an anti-phospholipid antibody
**Case 9**

A 63 year old man is started on procainamide by a world famous electrophysiologist. The gentleman develops joint pain, a skin rash. Work-up reveals a positive ANA and anti histone antibody.

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**Drug Induced SLE**

- Patients present with lupus like illness
- Usually arthritis, rash and serositis
- Positive ANA and anti-histone antibody
- Rare to have renal, neuropsychiatric, or vasculitic disease
- Often responds to drug withdrawal, NSAIDS or low dose prednisone

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**Drugs Involved**

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
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<tbody>
<tr>
<td>Procainamide</td>
<td>Beta blockers</td>
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<tr>
<td>Hydralazine</td>
<td>D-Penicillamine</td>
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<tr>
<td></td>
<td>INH</td>
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<tr>
<td></td>
<td>Quinidine</td>
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<tr>
<td></td>
<td>PTU</td>
</tr>
<tr>
<td></td>
<td>Hydantoins</td>
</tr>
<tr>
<td></td>
<td>Trimethadione</td>
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<td></td>
<td>Chlorpromazine</td>
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**Treatment SLE- general**

- Sun avoidance and protection
- Diet
- Exercise
- Smoking cessation

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**Treatment: Mild Disease**

- NSAIDs
- Antimalarials
- Low dose prednisone < 10mg a day

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**Treatment: Severe Disease**

- Steroids .5-1mg/kg/day-renal, CNS
- Cyclophosphamide-monthly pulses 500-1000mg/meter-squared or biweekly for 12 weeks–renal, CNS
- Azathioprine 1-2mg/kg/day- renal
- Mycophenolate Mofetil 0.5-3grams/day-renal
- Methotrexate 7.5-20mg/week-arthritis
Other Therapies

- Cyclosporine A
- Rituximab
- Belimumab
- Abatacept
- Bone marrow transplant

Summary SLE

- SLE is a multi-system autoimmune disorder
- SLE can look like many different disease entities
- To diagnose SLE the ANA should be positive
- A positive ANA does not make the diagnosis
- Direct the treatment towards the underlying symptoms
- All patients unless contraindicated should be on hydroxychloroquine
- Can use steroids and other immunosuppressive agents
- Watch out for new therapies (e.g., belimumab) as they become available—full use to be determined

The Antiphospholipid Antibody Syndrome

Antiphospholipid Antibody Syndrome: Major criteria

- The presence of an anticardiolipin antibody (IgG or IgM) and/or lupus anticoagulant on two separate occasions 12 weeks apart plus one of the following clinical events:
  - Arterial thrombotic events
  - Venous thrombotic events
  - Recurrent pregnancy losses:
    - 3 or more first trimester losses
    - A second trimester loss or severe intrauterine growth retardation

Other clinical features

- Thrombocytopenia
- Livedo reticularis
- Raynaud’s phenomenon
- Migraines
- Coomb’s positive hemolytic anemia

Associated medical conditions

- Sneddon’s syndrome: Strokes and livedo in young women
- Evan’s syndrome: Thrombocytopenia and Coomb’s positive hemolytic anemia
- CVAs and Myocardial Infarctions in individuals under 40
- Sudden multisystem occlusive disease
Antiphospholipid Antibody Tests

- False positive VDRL
- Lupus Anticoagulant
- Anticardiolipin Antibody- ELISA testing

False positive VDRL

- Substrate for the VDRL is embedded in cardiolipin
- Low sensitivity and specificity
- Of more historical interest than clinical

Lupus Anticoagulant

- In vitro prolongation of clotting test- in vivo pro-coagulant
- Activated PTT, Platelet neutralizing procedure, Kaolin clotting time, dilute Russell Viper Venom time all used
- The lupus anticoagulant test should be confirmed by adding phospholipid and normalizing the test result

Three possibilities:

<table>
<thead>
<tr>
<th>LAC</th>
<th>Confirmatory</th>
<th>What does it mean?</th>
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<tr>
<td>-</td>
<td>-</td>
<td>Negative</td>
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<tr>
<td>+</td>
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<td>Negative</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Positive</td>
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Anticardiolipin Antibodies

- Developed in the 1980s.
- ELISA test: Should be standardized using an international standard. Will be reported as GPL units. (>22 positive in our lab).
- All subsets: IgG, IgM, IgA, IgD seen although the IgG is the most clinically relevant.
- Anti- B-2 glycoprotein-1 is also used.

Antibodies in Various Patient Populations

- Healthy controls: 1-2%
- Recurrent miscarriage population: 5-10%
- SLE: 20-40%
- SLE with livedo or Raynaud’s: 80%
- Stroke, MI under age 40: 20%
- HIV infected: IgM 50-60%
Patients who should be evaluated for antiphospholipid antibodies

- SLE patients
- Patients under age 40 with CVA, MI no obvious risk factors
- Recurrent venous or arterial clots
- Women with recurrent first trimester pregnancy losses, or second trimester loss

Treatment: Patients with documented clot plus antibodies

- Lifelong anticoagulation- generally warfarin
- Target INR 2.5
- Recurrent episodes, severe arterial episodes target INR 3-3.5

Treatment: Antibodies in the absence of clinical events

- Some advocate the use of prophylactic aspirin therapy although it is not proven in studies.

Future

1) We may be able to predict which antibodies are pathologic.
2) Anti-complement therapy may be an option.

Summary

- The Antiphospholipid Syndrome is defined as:
  Arterial clots, venous clots or obstetrical complications in the presence of an antiphospholipid antibody. The antibody testing needs to be positive on two separate occasions at least 12 weeks apart.
- Treatment for the arterial or venous complications is life-long anti-coagulation

Question 1.

A 23 year old woman presents with a history of malaise, facial rash and achiness. Appropriate work-up includes:

a) ANA
b) CBC w/diff, LFTS, creatinine and u/a
c) dsDNA
d) All of the above
As a first pass for the evaluation of suspected SLE a complete history and physical should be performed. Appropriate laboratory testing includes a cbc with differential, liver function tests, creatinine and urinalysis. I avoid sending an ANA and/or dsDNA unless there is a strong suspicion of SLE is not appropriate.

A 43 year old woman presents with a DVT with no clear precipitant. PMH is notable for two first trimester miscarriages and one second trimester miscarriage. Appropriate testing includes:

- Lupus anti-coagulant
- Anticardiolipin antibody
- VDRL
- a, b, and c
- a and b only

Both a and b should be sent off – The history is suggestive of antiphospholipid syndrome
Send off both the lupus anticoagulant and anticardiolipin antibody when you have a high suspicion for the antiphospholipid antibody syndrome
A VDRL is not a good screening assay for this disorder

References
- Harrison’s textbook of medicine, Chapter on SLE
- Brigham and Women’s Experts approach to Rheumatology
- Rheumatology : Hochberg et. al, Fifth Edition