



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Systemic Lupus Erythematosus and the Antiphospholipid Syndrome

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- Harvard Medical School
- Medicine Residency @UCSF
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- Assistant Professor of Medicine@ HMS
 - Clinical focus: Systemic Lupus Erythematosus

Disclosures

- None

Key Learning Objectives

- Develop an approach to diagnosis and understanding of principles of treatment of systemic lupus erythematosus
- Learn to recognize and treat antiphospholipid syndrome

Overview

- What is SLE?
- Classification criteria
- Cases: Clinical manifestations
- Principles of treatment
- Antiphospholipid Syndrome

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SLE is the Prototypical Autoimmune Disease

1. Genes



C1q,C2,C4
HLA-D2,3,8
MBL
FcR 2A,3A,2B
IL-10
MCP1
PTPN22

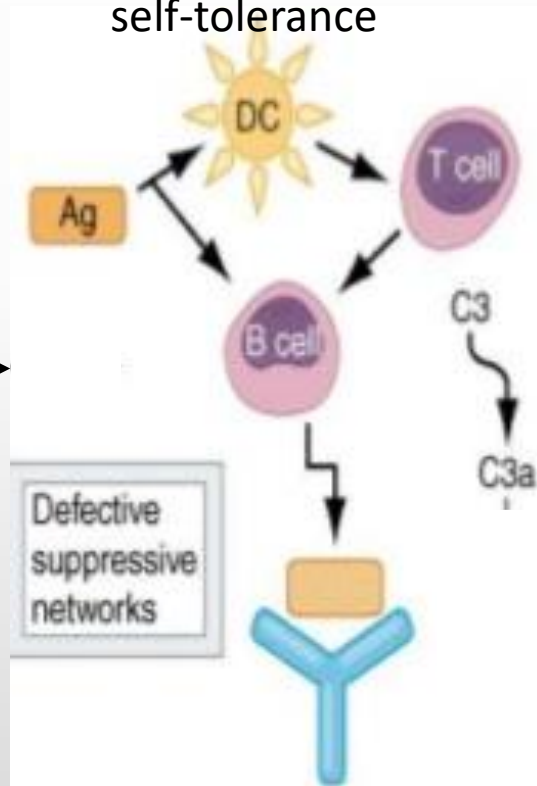
Environment



UV light
Gender
?Infection
Others

2. Abnormal Immune Response

- Failure of regulatory mechanisms that sustain self-tolerance



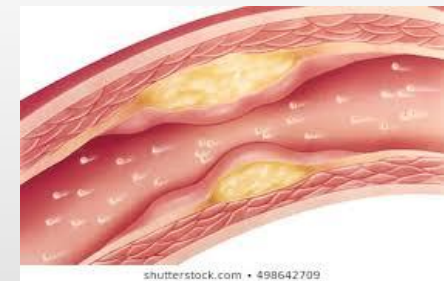
3. Autoantibodies Immune Complexes

4. Inflammation



Rash
Nephritis
Arthritis
NPSLE
Hematologic
Carditis

5. Damage

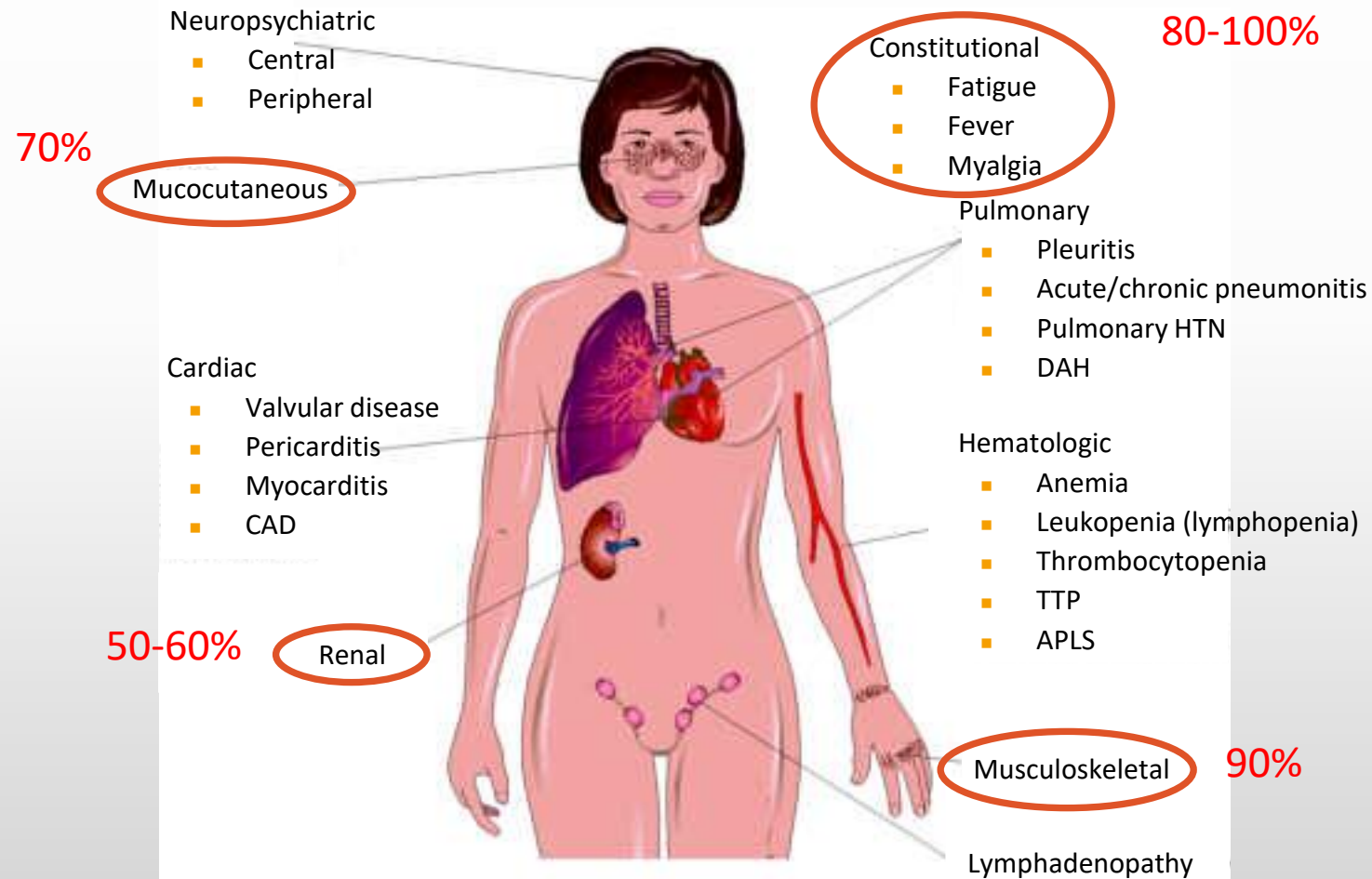


Renal Failure
Atherosclerosis
Pulmonary fibrosis
Stroke

SLE Epidemiology

- Prevalence ~ 1/1,000 in the US
- Diagnosed 9 times more often in women than men
- In the US, more common and severe in women of African, Hispanic, or Asian descent
- Genetic predisposition
 - HLA genes and complement components
 - >30 gene polymorphisms linked to lupus
- Possible contributors to those genetically predisposed
 - Sex chromosome genes, sex hormones
 - Environmental influences, including UV light exposure, smoking

Lupus = “The Great Imitator”



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2019 EULAR/ACR Classification Criteria for SLE

Requirements: +ANA, at least one clinical criterion, ≥ 10 points

Clinical Criteria	Weight	Immunologic Criteria	Weight
<i>Constitutional</i> (fever)	2	<i>Antiphospholipid antibodies</i>	
<i>Hematologic</i>		Anti-cardiolipin antibodies OR	
Leukopenia	3	Anti-B2GP1 antibodies OR	
Thrombocytopenia	4	Lupus anticoagulant	2
Autoimmune hemolysis	4	<i>Complement proteins</i>	
<i>Neuropsychiatric</i>		Low C3 OR low C4	3
Delirium	2	Low C3 AND low C4	4
Psychosis	3	<i>SLE-specific antibodies</i>	
Seizure	5	Anti-dsDNA antibody OR	
<i>Mucocutaneous</i>		Anti-Smith antibody	6
Non-scarring alopecia	2		
Oral ulcers	2		
SCLE OR DLE	4		
Acute cutaneous lupus	6		
<i>Serosal</i>			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
<i>Musculoskeletal</i> (joint)	6		
<i>Renal</i>			
Proteinuria $>0.5\text{g}/24\text{h}$	4		
Class II or V LN	8		
Class III or IV LN	10		

Few Notes About ANA Test

- ANA test was not designed as a screening test
- Up to 20% of healthy adults, particularly women, have a low titer ANA and do not go on to develop rheumatic diseases
- Causes of false positive tests:
 - Chronic infections (HIV, HBV, HCV, SBE)
 - Family history of rheumatic disease
 - Other autoimmune disease like GI or thyroid disease
 - Normal healthy people!
- Once a patient has a positive ANA, it does not need to be retested, unless symptoms change and there is an increased suspicion for a rheumatic disease

ANA-Negative Lupus

- Extremely rare
 - Sensitivity of ANA is > 98% in recent years
- EliA Rib-P Test
 - Recently FDA approved (June 2022)
 - Subset of SLE patients present with Ribosomal P antibodies (10-45%)
 - Highly specific for SLE
 - Associated with neuropsychiatric, kidney, and liver involvement
 - Some of these patients may be ANA negative
 - Not part of classification criteria for SLE at this time

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Case 1

- 33 yo woman comes to see you
- She has mouth sores and a rash over the bridge of her nose that looks like this:



Source: Usatine RP, Smith MA, Mayeaux EJ, Chumley HS: *The Color Atlas of Family Medicine*, Second Edition: www.accessmedicine.com
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Malar Rash

- Erythema over malar eminences
 - Flat or raised
 - Slight scale
 - Spares nasolabial folds
- Differential diagnoses:
 - Rosacea
 - Flushing
 - Mitral stenosis

Case 1

- You send an ANA that returns positive at a titer of 1:320 and subserologies notable for a dsDNA at 45 units
- Does she have SLE?

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Skin Manifestations of SLE



Acute cutaneous lupus



Subacute cutaneous lupus



Chronic cutaneous lupus



Lupus non-specific lesions

Case 2

- 32 yo woman develops ~ 1 month of joint swelling affecting the small joints of her hands
- Labs notable for WBC 2.8, ANA 1:1280, dsDNA 84 units

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Jaccoud's-like Arthropathy



Musculoskeletal Manifestations of SLE

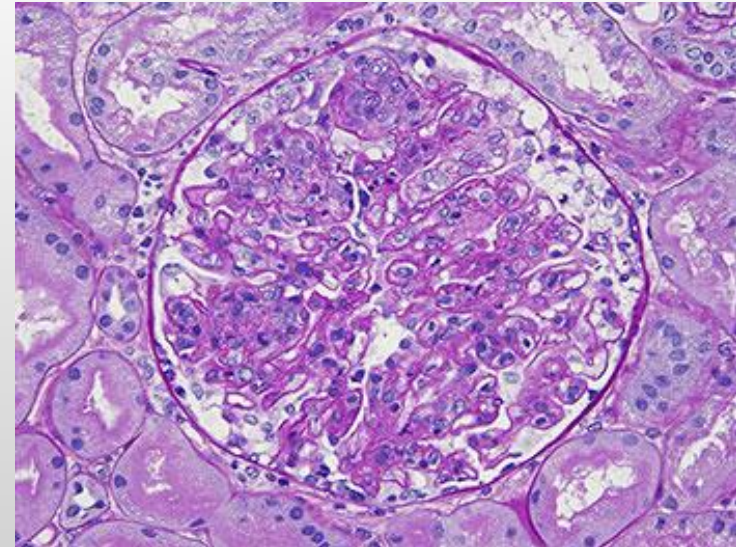
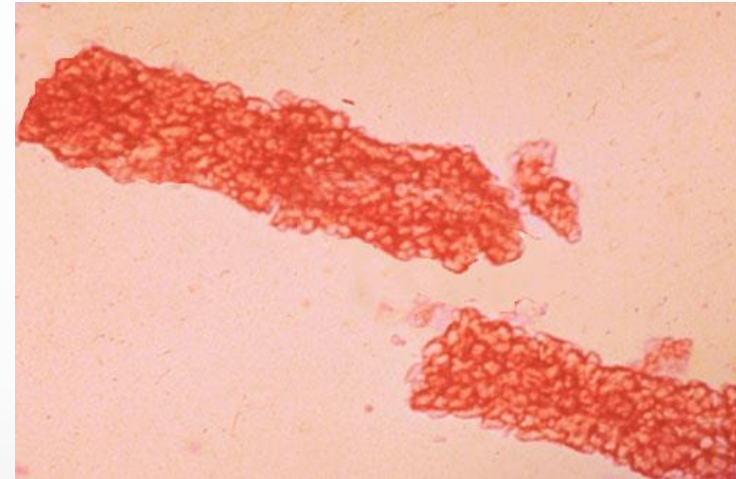
- Common: >90%
- Arthralgias and arthritis
- Septic arthritis
- Osteonecrosis—risk increases with steroid use > 20 mg per day
- Myositis—more commonly seen in patients with Mixed Connective Tissue Disease (MCTD)
- Myopathy—secondary to steroids—proximal muscle weakness

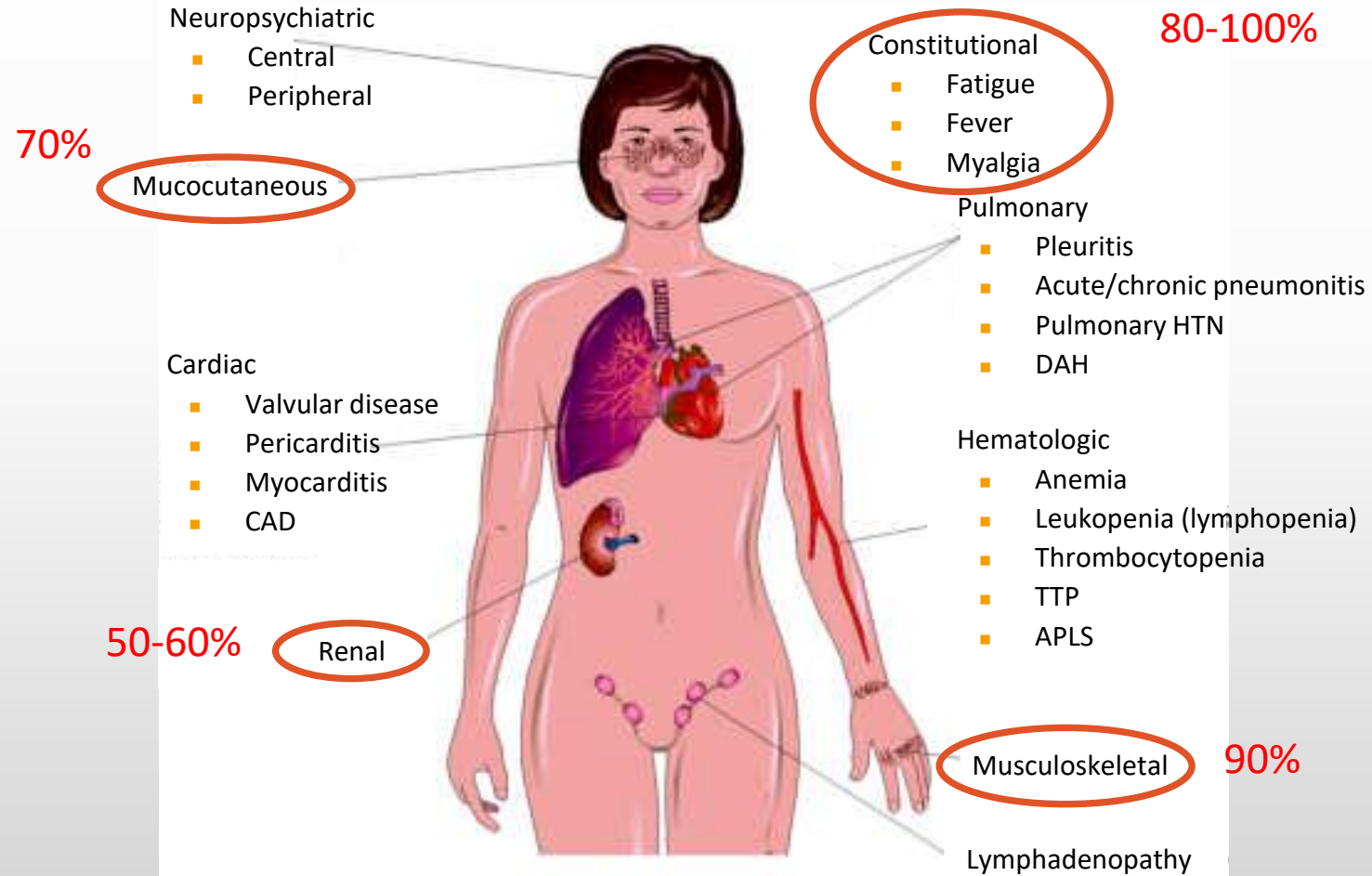
Case 3

- 29 yo woman with history of mild SLE (arthritis, malar rash, positive serologies) presents with edema, proteinuria, and RBC in her urine
- What do you do?

Lupus Nephritis

- Suspect if:
 - Microscopic hematuria
 - Red blood cell casts/dysmorphic red cells
 - Proteinuria > 0.5gm/day



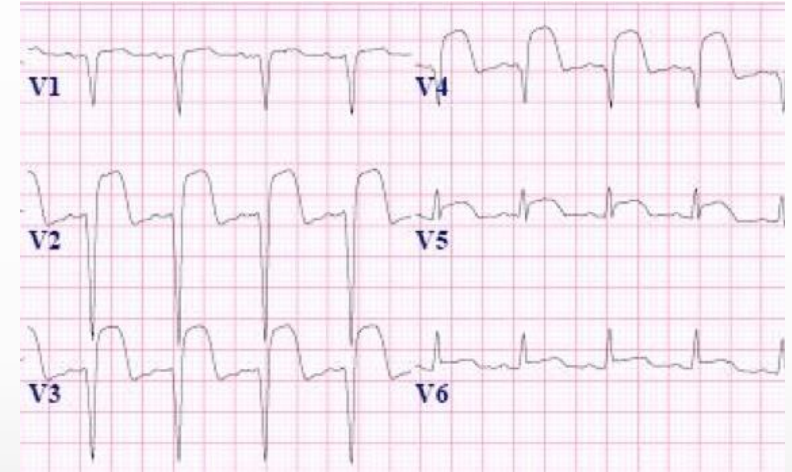


Hematologic Manifestations of SLE

- AIHA—Coomb's positive
- Leukopenia—WBC < 4000
- Lymphopenia—Lymphocytes < 1500
- Thrombocytopenia—Platelets < 100,000

Cardiovascular Manifestations of SLE

- Accelerated atherosclerosis
 - Disease + drugs
 - RR CVD in SLE at least 2x general population
 - Dramatically higher RR in younger pts (55x)
- Pericarditis
- Valvular heart disease
 - Usually with +aPL
- Coronary vasculitis—rare
- Myocarditis—rare



Pulmonary Manifestations of SLE

- Pleuritis
- Lupus pneumonitis
- Chronic interstitial lung disease
- Pulmonary hemorrhage (high mortality)
- Shrinking lung syndrome (secondary to diaphragmatic paralysis and lung disease)

Neuropsychiatric Manifestations of SLE

- **Neurologic**

- CVA
- Seizures
- Transverse myelitis
- Optic neuritis
- Meningitis
- Headaches
- Organic brain syndrome
- Neuropathies
- Associated with antiphospholipid antibodies

- **Psychiatric**

- Psychosis
- Cognitive disorder
- Pseudo-dementia
- Functional

GI Manifestations of SLE

- Abdominal pain
- Anorexia
- Peritonitis
- Pancreatitis
- Hepatitis

Other Common Symptoms

- Fatigue
- Headaches
- Malaise
- Cognitive impairment “lupus fog”
- Myalgias



Case 5

- 63yo man started on procainamide for an abnormal heart rhythm
- He develops joint pain and a skin rash
- Work-up reveals a high-titer positive ANA and anti-histone antibody

Drug-Induced SLE

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

Culprit Agents in Drug-Induced SLE

- Common

- Procainamide
- Hydralazine

- Rare

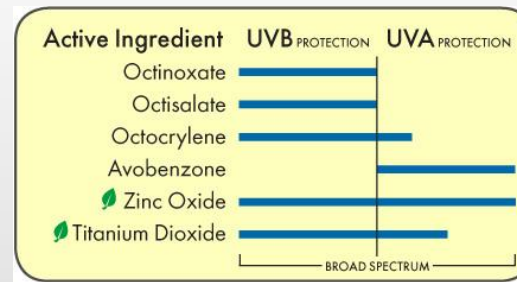
- Beta-blockers
- D-Penicillamine
- INH
- Quinidine
- PTU
- Hydrantoin anticonvulsants
- Chlorpromazine

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General Treatment Advice in SLE

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



Treatment: Mild Disease

- Symptoms: low grade fever, rash, arthralgia, fatigue
 - **Antimalarials**—hydroxychloroquine most common
 - All SLE patients should be on antimalarials unless contraindicated
 - Decreased frequency and severity of flares
 - Mortality benefit
 - Symptomatic benefit (constitutional, MSK, cutaneous)
 - Low dose prednisone < 10 mg/day
 - NSAIDs
- ~ 80% pts with mild disease achieve good control with these measures

Treatment: Moderate-Severe Disease

- Steroids: 0.5-1 mg/kg/day—renal, CNS
- Mycophenolate mofetil—renal, skin
- Azathioprine—renal, hematologic
- Tacrolimus —renal, skin
- Voclosporin—renal
- Methotrexate – arthritis, skin
- Belimumab– serositis, arthritis, skin
- Anifrolumab—skin
- Cyclophosphamide—renal, CNS
- Rituximab, Abatacept (off label)

Summary of 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 a diagnosis of SLE
- Direct treatment towards the underlying system involved
- All patients, unless contraindicated, should be offered hydroxychloroquine
- Steroids and other immunosuppressives are also commonly used
- Biologics other than belimumab are under investigation

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When to Think About Antiphospholipid Antibodies?

- Multiple early miscarriages
- Thrombocytopenia
- Stroke/TIA in younger patients
- DVT/PE
- Patients with lupus

Antiphospholipid Syndrome (APS): Major Criteria

- Clinical criteria:
 - Arterial thrombotic event
 - Venous thrombotic event
 - Recurrent pregnancy losses
 - 3 or more consecutive losses at < 10 weeks
 - 1 or more unexplained deaths of a morphologically normal fetus \geq 10 weeks
 - 1 or more premature births before 34 weeks because of placental insufficiency/pre-eclampsia

PLUS

- Laboratory criteria:
 - Anticardiolipin IgG or IgM moderate-high titer (>40 GPL units)
 - Beta2-glycoprotein 1 IgG or IgM moderate-high titer (>40 GPL units)
 - Lupus anticoagulant positive
 - On 2 separate occasions 12 weeks apart

Additional Autoantibodies

- Antiphosphatidylserine antibodies (aPS)
 - Recent studies suggest aPS antibodies may also be useful markers for antiphospholipid syndrome
 - Population-based studies show an independent association of aPS antibodies with ischemic stroke
 - Not part of APS Criteria at this time, but increasingly used in clinical practice (particularly aPS IgG and IgM)

“Non-Criteria” Manifestations

- Thrombocytopenia
- Coomb’s positive hemolytic anemia
- Livedo reticularis
- Raynaud’s phenomenon
- Migraines and cognitive dysfunction
- Valvular vegetations or thickening
- Renal disease—thrombotic microangiopathy



Associated Medical Conditions

- Sneddon's syndrome: strokes and livedo reticularis in young women
- Evan's syndrome: immune-mediated thrombocytopenia and Coomb's positive hemolytic anemia
- CVAs and MIs in individuals under age 40
- SLE
- Catastrophic APS (CAPS): sudden multisystem occlusive disease

Treatment: Vascular APS

- Lifelong anticoagulation—generally warfarin

Thrombosis	Optimal INR
Venous	~2.5
Arterial	~3
Recurrent	~3.5

- **AVOID direct acting oral anticoagulants**
 - Rivaroxaban for APS trial stopped early due to higher rate of arterial thrombosis in rivaroxaban arm

Treatment: Antibodies in the Absence of Clinical Events

- Thrombosis risk up to 4% annual risk
- Some advocate the use of prophylactic low dose aspirin (LDA)
 - Effectiveness of LDA not supported by RCT data
 - Data do suggest that may be protective in patients with SLE

Catastrophic Antiphospholipid Syndrome (CAPS)

- Consider when multiple clots over 7 days
 - Renal failure, diffuse alveolar hemorrhage, adrenal hemorrhage, encephalopathy can be seen
 - Can look similar to other thrombotic microangiopathies
- Treatment
 - Anticoagulants
 - High dose corticosteroids
 - IVIG
 - Plasma exchange
 - Eculizumab (off label)
 - Rituximab (off label)

Summary of APS

- 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 2 separate occasions at least 12 weeks apart
- Treatment for vascular thrombosis is life-long anticoagulation

Question 1

- 23 yo woman presents with malaise, achiness, and intermittent facial rash (that does NOT spare the naso-labial folds). Appropriate work-up includes:
 - A. ANA
 - B. CBC with differential, LFTs, creatinine and urinalysis
 - C. dsDNA
 - D. All of the above

Answer

- B: CBC with differential, LFTs, creatinine and urinalysis
- As a first pass for the evaluation of suspected SLE, a complete history and physical exam should be performed. Appropriate laboratory testing includes a CBC with differential, liver function tests, creatinine and urinalysis. Avoid sending an ANA and/or dsDNA unless there is a strong suspicion for SLE.

Question 2

- 43 yo woman presents with a DVT with no clear precipitant. PMH notable for 2 first trimester miscarriages and 1 second trimester miscarriage. Appropriate testing includes:
 - A. Lupus anti-coagulant
 - B. Anticardiolipin IgG and IgM
 - C. Anti-beta2glycoprotein1 IgG and IgM
 - D. Rapid plasma regain (RPR)
 - E. A, B, C and D
 - F. A, B, and C only

Answer

- F: A, B and C only
- History is suggestive of antiphospholipid syndrome
- All three types of antiphospholipid antibodies should be sent when you have a high suspicion for APS (and should be sent again as confirmation after 12 weeks)
- RPR is not a good screening assay for this disorder

References

- Classification criteria for systemic lupus erythematosus: a review. Petri M, Magder L. *Lupus*. 2004;13(11):829
- Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum*. 1999 Sep; 42(9): 1785-96
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