Systemic Lupus Erythematosus

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DEFINITION AND PREVALENCE

- Systemic lupus erythematosus(SLE) is an autoimmune disease
- Mediated by tissue-binding autoantibodies & immune complexes
- 90% of patients are women of child-bearing years
- The prevalence of SLE in the United States is 81–144 per 100,000
- lowest in white men

- A 22 years old female presented to you because of Rt. Knee arthritis which was started 5 days ago. She had oral ulcer and positive ANA test (1/320, Speckled). WBC: 4200, Hb: 11 (normochrome & normocytic), Plt: 155000, ESR: 45 Other autoantibodies were negative.
- What is your diagnosis?

Diagnosis

- Any combination of four or more criteria, with at least one clinical and one immunologic criteria (exception: Renal biopsy)

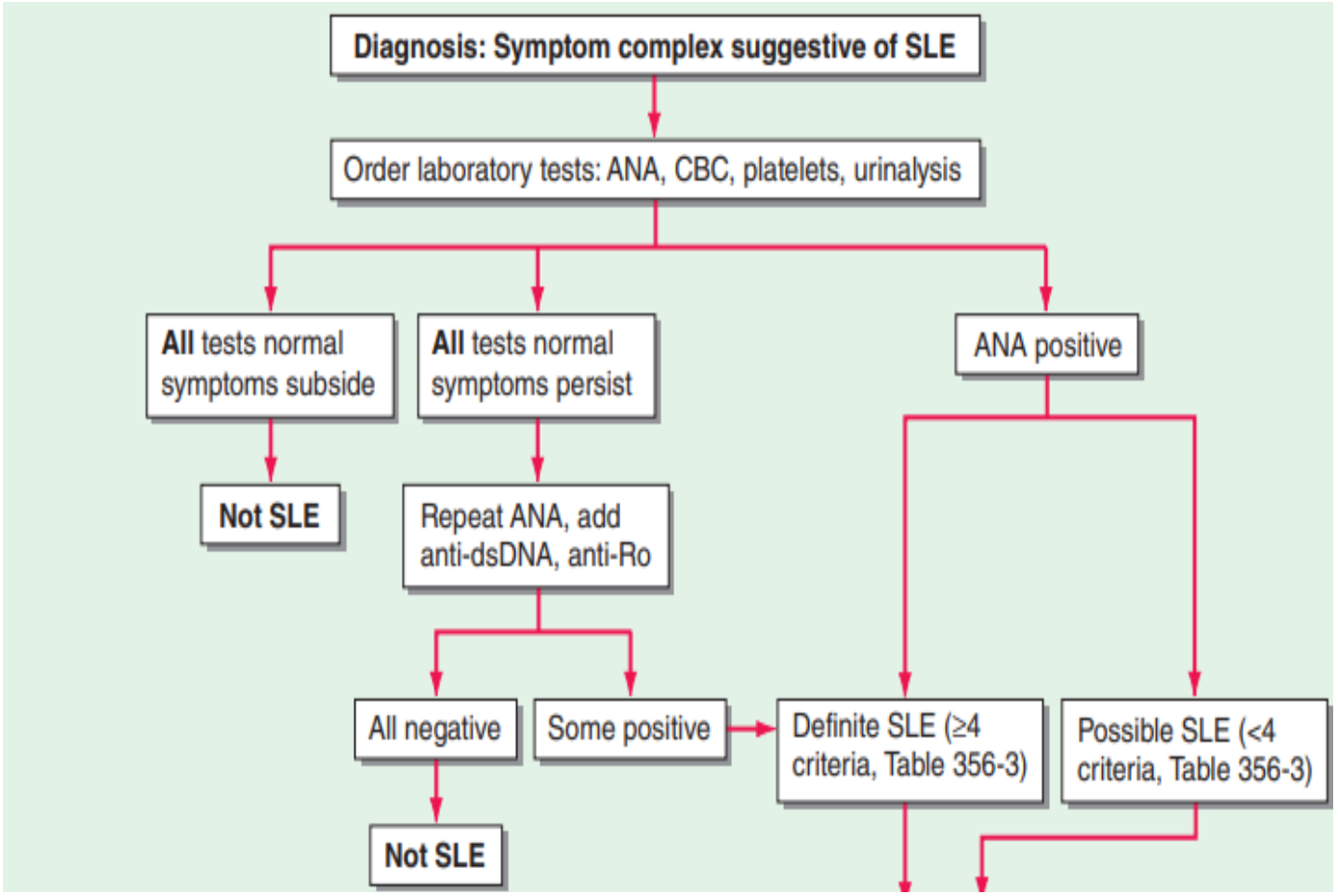
- ANA is positive in >98% of patients **during** the course of disease

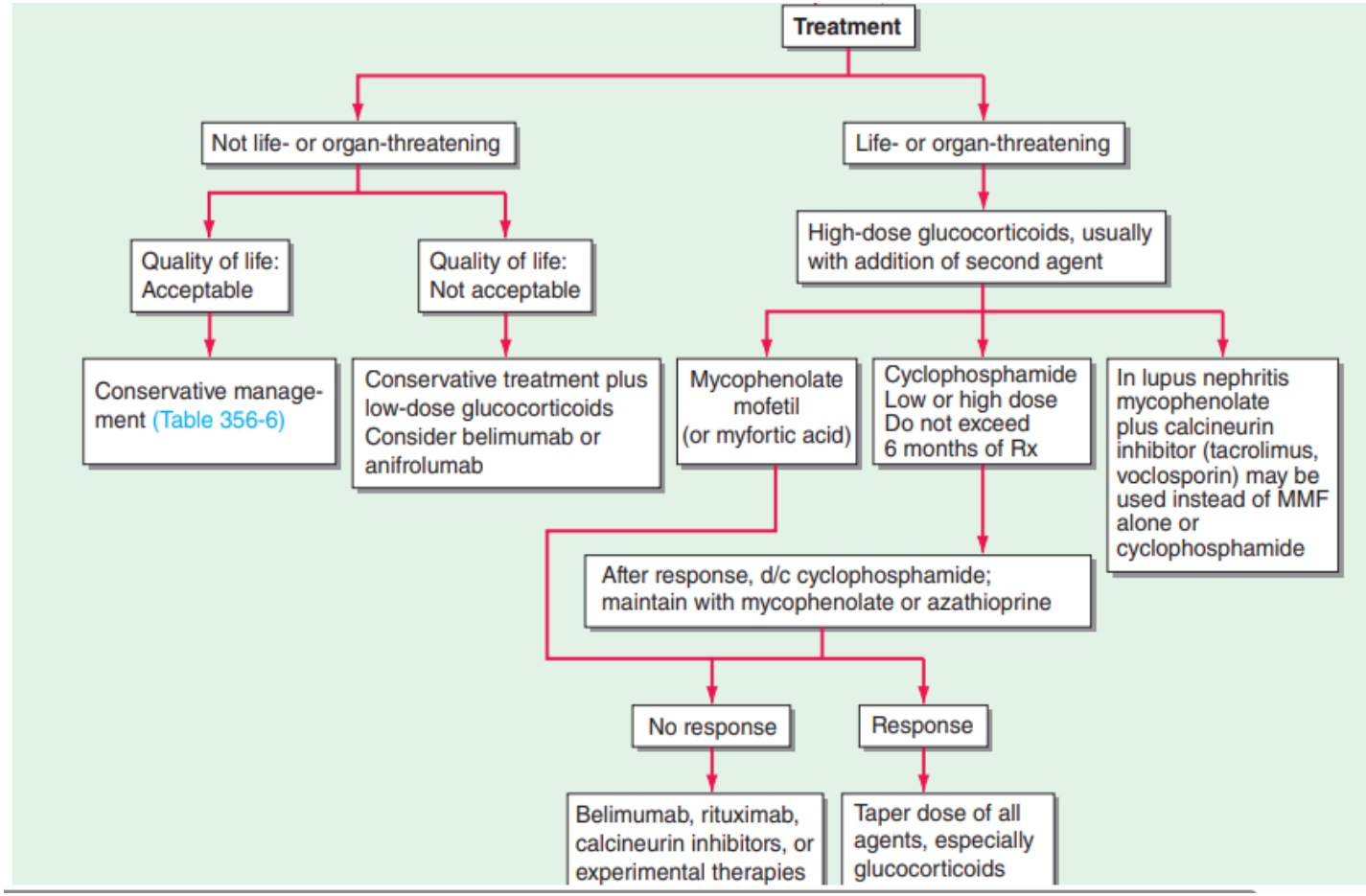
TABLE 356-3 Systemic Lupus International Collaborating Clinic Criteria for Classification of Systemic Lupus Erythematosus

CLINICAL MANIFESTATIONS	IMMUNOLOGIC MANIFESTATIONS
Skin	ANA > reference negative value
Acute, subacute cutaneous LE (photosensitive, malar, maculopapular, bullous)	Anti-dsDNA > reference, if by ELISA 2× reference
Chronic cutaneous LE (discoid lupus, panniculitis, lichen planus–like, hypertrophic verrucous, chillblains)	Anti-Sm
Oral or nasal ulcers	Antiphospholipid (any of lupus anticoagulant, false-positive RPR, anticardiolipin, anti–β_2-glycoprotein 1)
Nonscarring alopecia	Low serum complement (C3, C4, or CH50)
Synovitis involving ≥2 joints	Positive direct Coombs test
Serositis (pleurisy, pericarditis)	
Renal	
Prot/Cr ≥0.5	
RBC casts	
Biopsy[a]	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000/μL) or lymphopenia (<1000/μL)	
Thrombocytopenia (<100,000/μL)	

TABLE 356-4 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus (SLE)

	Positive ANA (titer at least 1:80) is obligatory entry criterion, followed by additive weighted criteria in 7 clinical and 3 immunologic domains. Accumulating ≥10 points classifies as SLE. *All manifestations must be attributable to SLE.*		
	CLINICAL CRITERIA		
DOMAIN	**CRITERIA**	**% OF PATIENTS WITH FEATURE[a]**	**WEIGHT**
Constitutional, 80%	Fever	50	2
Hematologic, 50%	Leukopenia	30	3
	Thrombocytopenia	20	4
	Autoimmune hemolytic anemia	10	4
Neuropsychiatric, 75%	Delirium	5	2
	Psychosis	7	3
	Seizure	11	5
Mucocutaneous, 80%	Nonscarring alopecia	15	2
	Oral ulcers	45	2
	Subcutaneous or discoid lupus	30	4
	Acute cutaneous lupus	70	6
Serosal, 50%	Pleural or pericardial effusion	50	5
	Acute pericarditis	35	6
Musculoskeletal, 95%	Joint involvement	90	6
Renal, 50%	Proteinuria >0.5 g/24 h	50	4
	Renal biopsy class II or V LN	25% of LN	8
	Renal biopsy class III or IV LN	60% of LN	10
	IMMUNOLOGIC CRITERIA		
DOMAIN	**CRITERIA**	**% OF PATIENTS WITH FEATURE[a]**	**WEIGHT**
Antiphospholipids	+ Anticardiolipin, anti–β_2-glycoprotein, or lupus anticoagulant (LAC)	40	2
Complements	Low C3 *or* C4	35	3
	Low C3 *and* C4	30	4


Diagnosis: Symptom complex suggestive of SLE
Order laboratory tests: ANA, CBC, platelets, urinalysis
All tests normal symptoms subside
All tests normal symptoms persist
ANA positive
Not SLE
Repeat ANA, add anti-dsDNA, anti-Ro
All negative
Some positive
Definite SLE (≥4 criteria, Table 356-3)
Possible SLE (<4 criteria, Table 356-3)
Not SLE


Treatment
Not life- or organ-threatening
Life- or organ-threatening
Quality of life: Acceptable
Quality of life: Not acceptable
High-dose glucocorticoids, usually with addition of second agent
Conservative management (Table 356-6)
Conservative treatment plus low-dose glucocorticoids Consider belimumab or anifrolumab
Mycophenolate mofetil (or myfortic acid)
Cyclophosphamide Low or high dose Do not exceed 6 months of Rx
In lupus nephritis mycophenolate plus calcineurin inhibitor (tacrolimus, voclosporin) may be used instead of MMF alone or cyclophosphamide
After response, d/c cyclophosphamide; maintain with mycophenolate or azathioprine
No response
Response
Belimumab, rituximab, calcineurin inhibitors, or experimental therapies
Taper dose of all agents, especially glucocorticoids

Healthy (‘normal’)Individuals

ANA	%
>= 1:40	20-30
>= 1:80	10-12
>= 1:160	5
>= 1:320	3

TABLE 356-1 Autoantibodies in Serum or Plasma in Systemic Lupus Erythematosus (SLE)

ANTIBODY	PREVALENCE, %	ANTIGEN RECOGNIZED	CLINICAL UTILITY
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests by immunofluorescence make SLE unlikely. Immunofluorescence is best standard test: titers of 1:80 or higher may separate clinically significant tests from false positives. Has good sensitivity but poor specificity for SLE.
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis. *Crithidia* immunofluorescence is more specific for SLE than ELISA methods.
Anti-C1q	33	Collagen-like determinants on complement component C1q	Present in 63% of lupus nephritis, associated with active lupus nephritis especially when anti-dsDNA is also present. Correlates with activity of nephritis. Not specific for SLE.
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNA	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites; correlates with high IFN-induced gene signature
Anti-Ro (SS-A)	30	Protein complexed to hY RNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus and neonatal lupus with congenital heart block.
Anti-La (SS-B)	10	47-kDa protein complexed to hY RNA	Usually associated with anti-Ro.
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE.
Antiphospholipid	50	Phospholipids, β_2-glycoprotein 1 (β_2G1) cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β_2G1, sensitive prothrombin time (DRVVT) for lupus anticoagulant; predisposes to clotting, fetal loss, thrombocytopenia.
Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs test; a small proportion develops overt hemolysis.
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia, but sensitivity and specificity are not good; this is not a useful clinical test.
Antineuronal (includes antiglutamate receptor 2)	60	Neuronal and lymphocyte surface antigens	In some series, a positive test in CSF correlates with active CNS lupus.
Antiribosomal P	20	Protein in ribosomes	In some series, a positive test in serum correlates with depression or psychosis due to CNS lupus.

SYSTEMIC LUPUS ERYTHEMATOSUS

2012 SLICC Classification Criteria

CLINICAL

- Acute cutaneous
- Chronic cutaneous
- Oral ulcers
- Non-scarring alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leucopenia / Lymphopenia
- Thrombocytopenia

IMMUNOLOGIC

- ANA
- Anti-dsDNA
- Anti-Sm
- Anti-Phospholipid
- Low complement
- Direct Coomb's test

Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the SLICC Classification Criteria for SLE. Arth & Rheum 2012; 64 (8): 2677-86.

- Why I got **LUPUS**?

PATHOGENESIS

SLE occurs in a framework of interactions between multiple susceptibility genes and environmental stimuli.

PREDISPOSING FACTORS

GENES

High hazard ratios (≥6);

Deficiencies of C1q,C2,C4 (rare)
TREX1 mutations affecting DNA degradation (rare)

Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes

*HLA-DRB1 (*1501,*0301), DR3, DQA2*
CR2, FCGR2A/B

Enhance innate immunity, including production of IFNs

TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs

Alter adaptive immunity B and/or T cell signaling

BANK1, STAT4, MSHS, IZKF3, TCF7

GENES FOR LUPUS NEPHRITIS

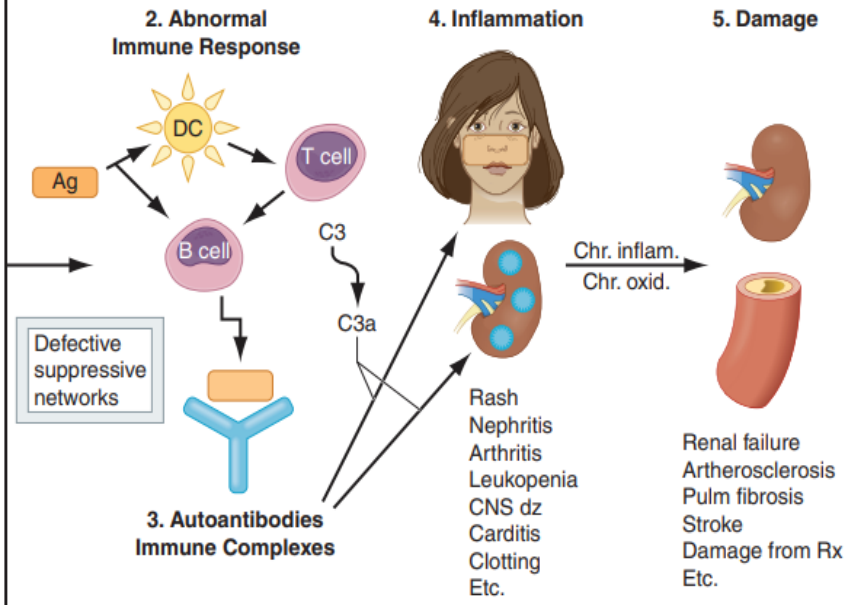
HLA-DR3, STAT4, APOL1 (African Americans),
FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNAse1

ENVIRONMENT/MICROENVIRONMENT

Ultraviolet light, smoking, crystalline silica, ?EBV infection, femaleness

EPIGENETICS

Hypomethylation of DNA: In CD4+T, B and monocytes
Some affect IFN production
Histone modifications: Some increase expression of predisposing genes and/or IFN production
MicroRNA affecting gene expression



- Which organ is preserved in lupus?

Clinical features of SLE

1.Contitutional
2.Skin
3.Musculoskeletal
4.Renal
5.Neuropsychiatric
6.Serous
7.Gastrointestinal
8.Lung
9.Cardiac
10.Hematopoetic

CUTANEOUS MANIFESTATIONS

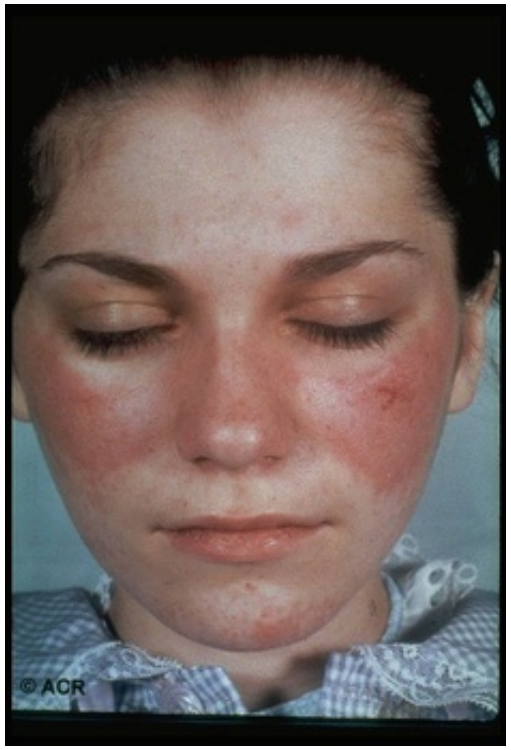
- Lupus dermatitis

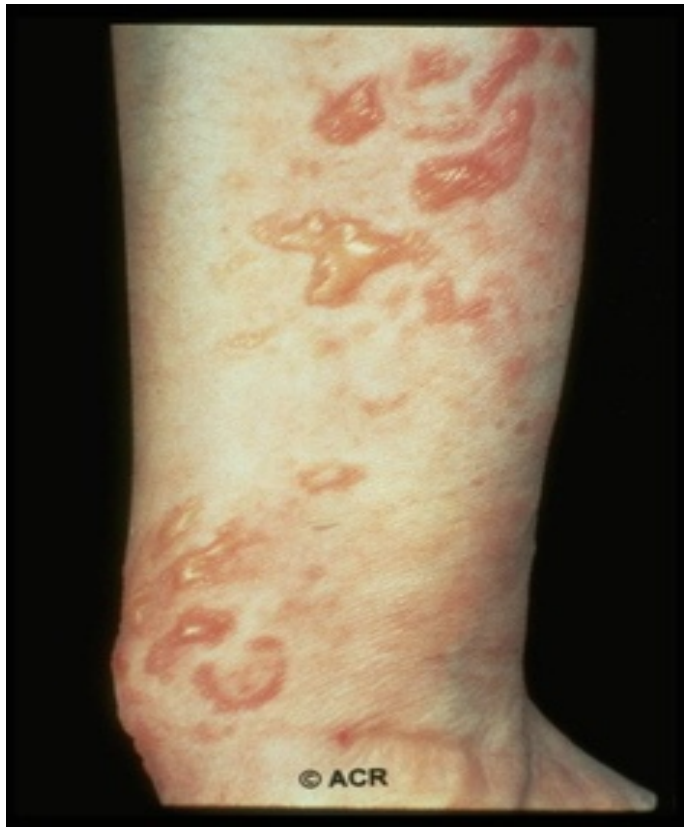
a) Acute: photosensitivity, Malar rash, Oral ulcer

b) Subacute: Subacute cutaneous lupus erythematosus (SCLE)

c) Chronic: Discoid lupus erythematosus (DLE)

MALAR RASH

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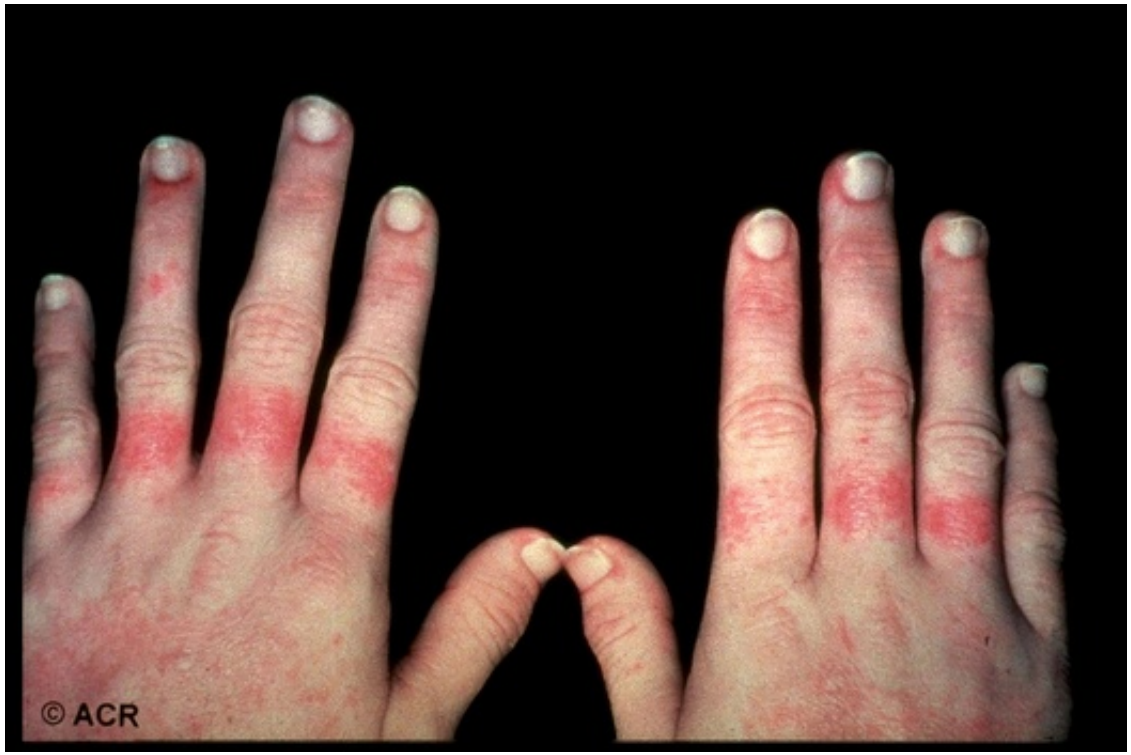
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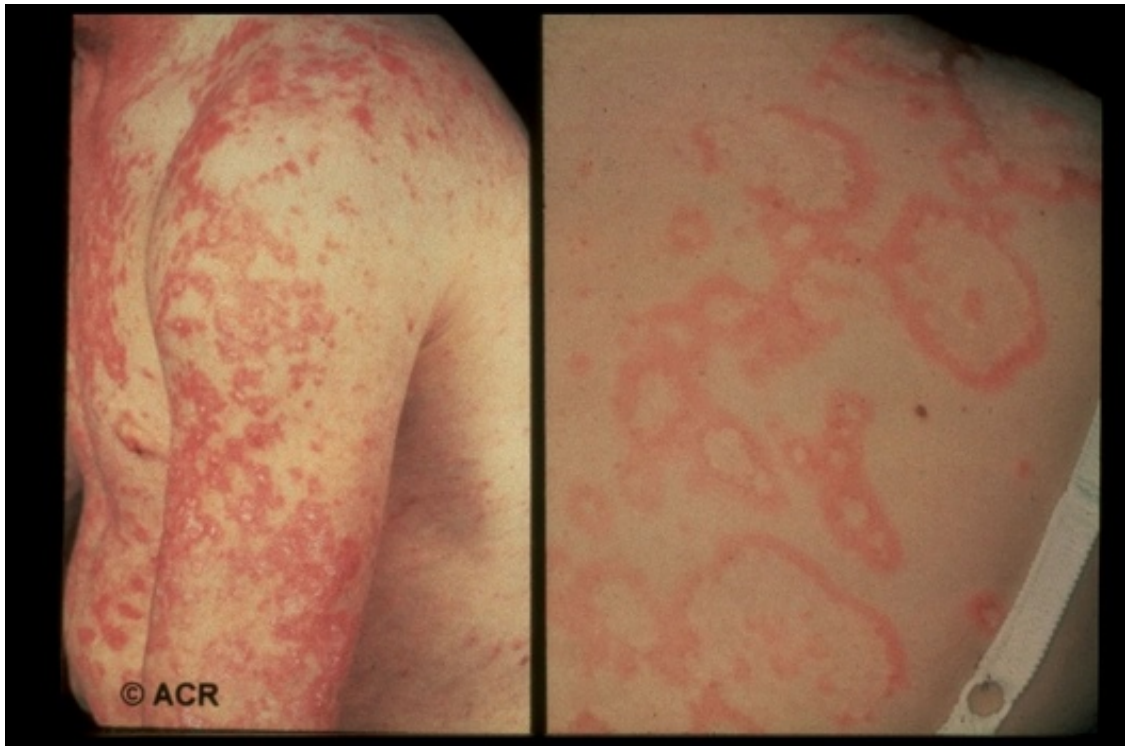
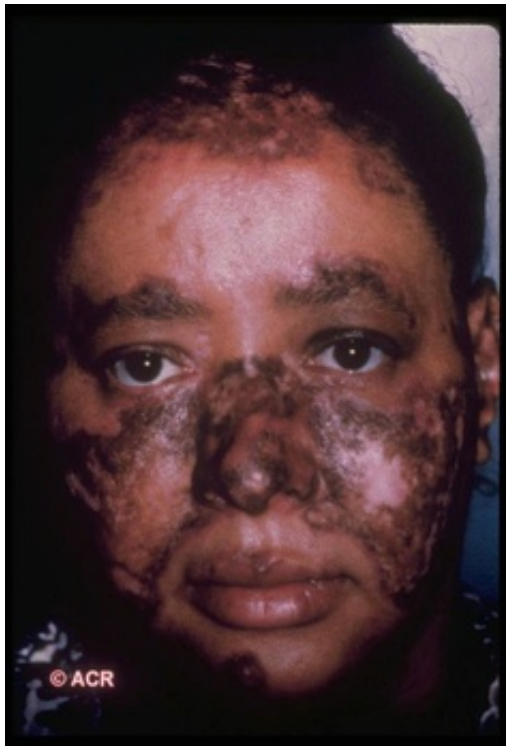
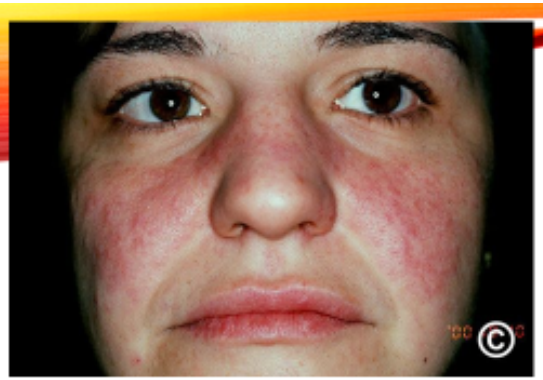
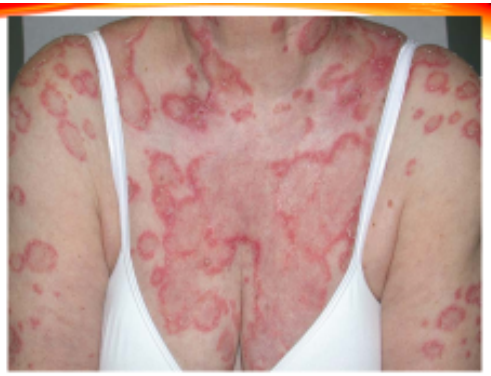
SCLE

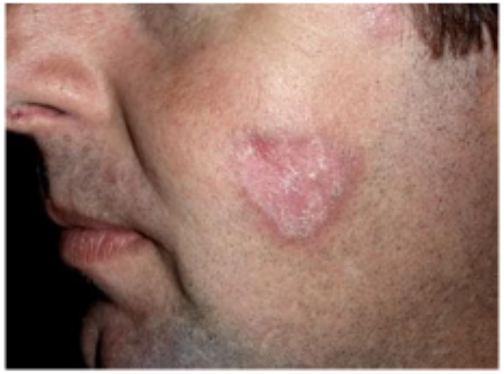


DLE

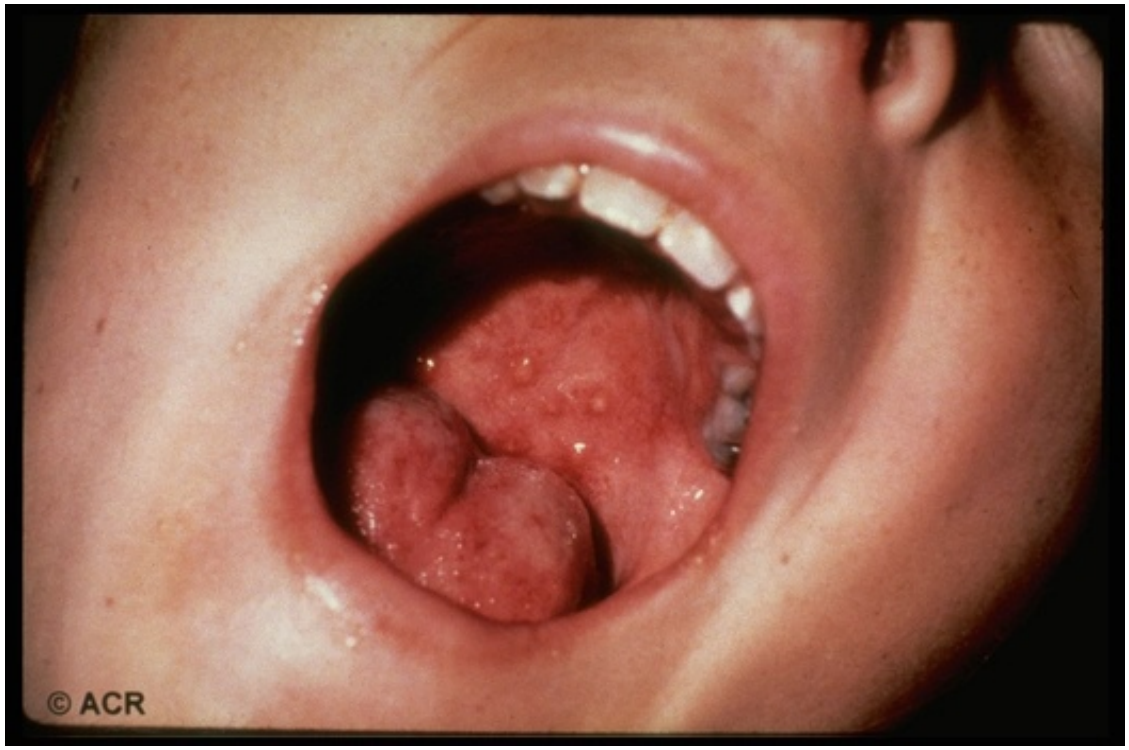




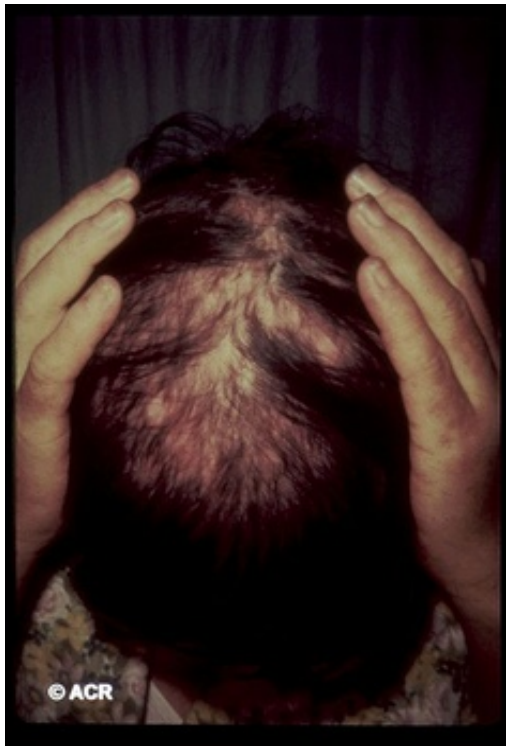


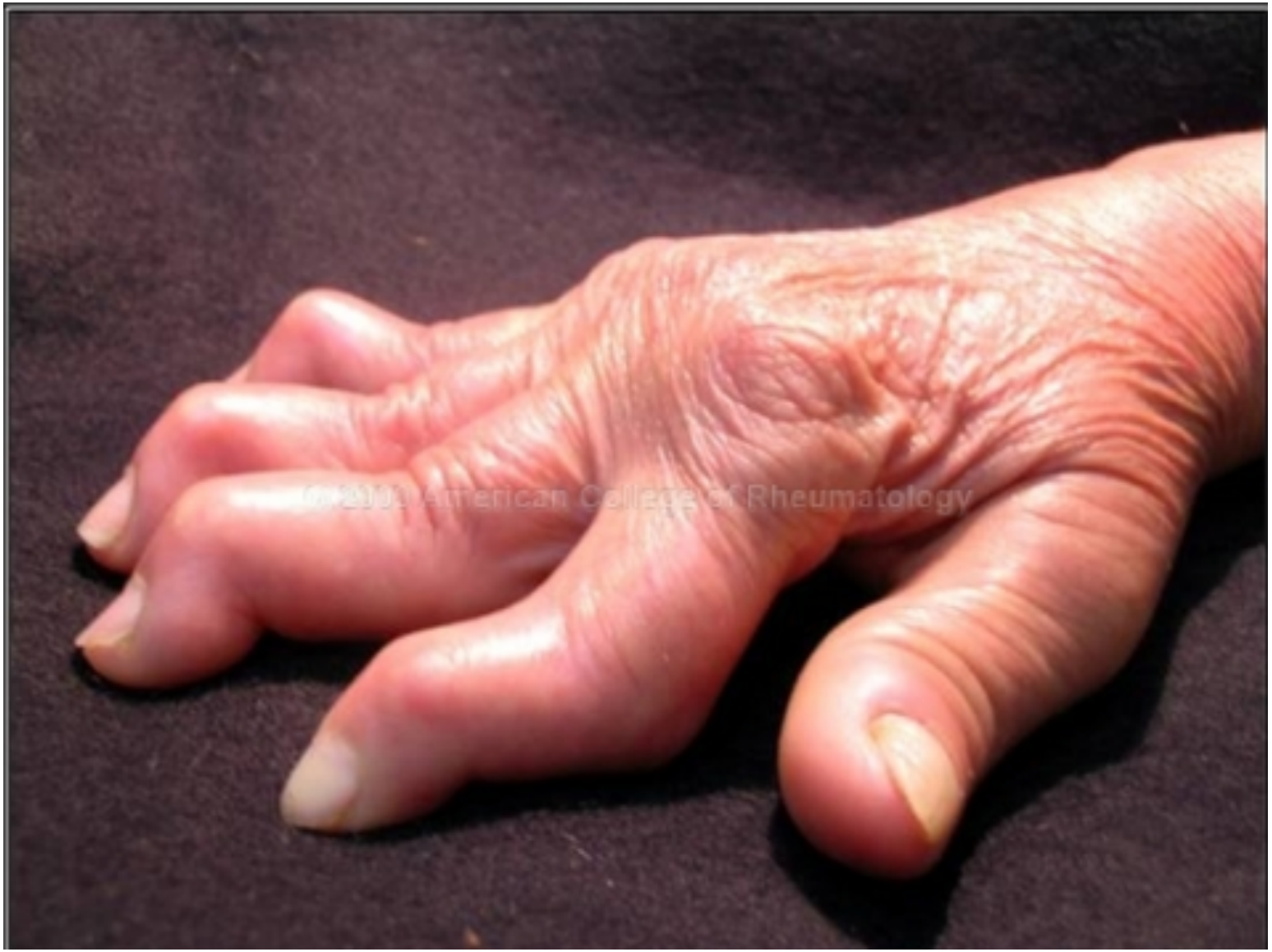


ORAL ULCER



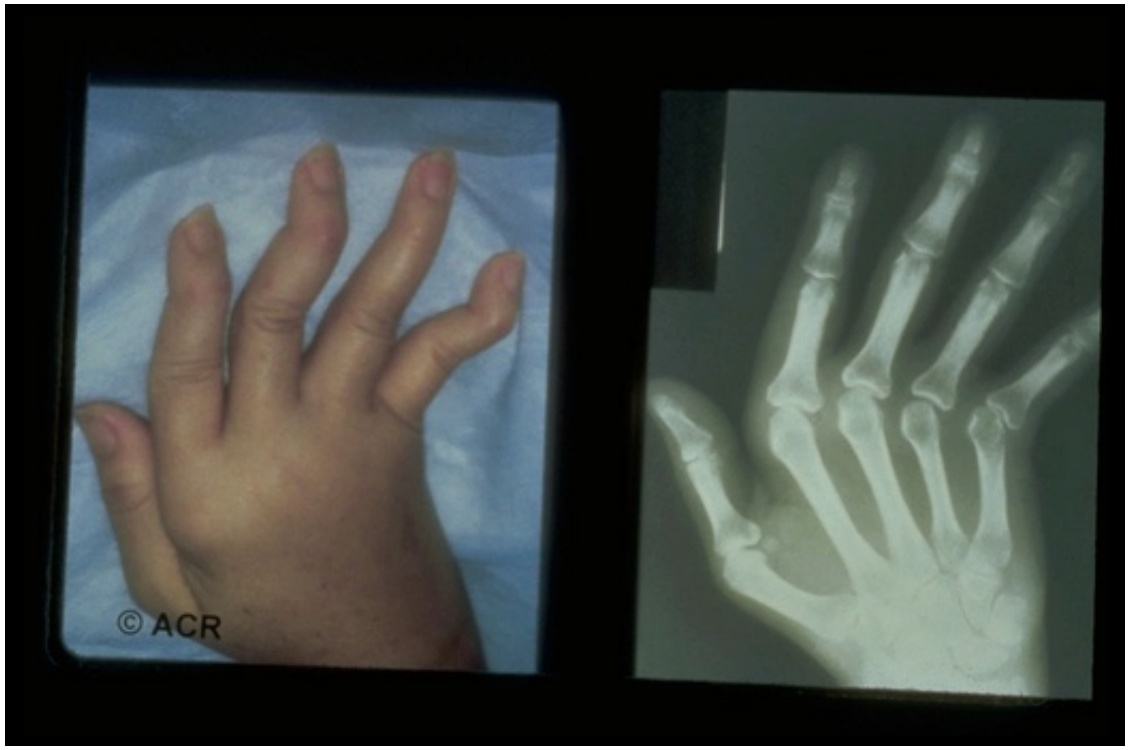
ALOPECIA





- What are the differences between hand deformity in RA & SLE?

MUSCULOSKELETAL MANIFESTATIONS



- Most people with SLE have intermittent polyarthritis
- Soft tissue swelling and tenderness in joints and/or tendons, most commonly in hands, wrists, and knees
- Ischemic necrosis of bone (INB)
- Myositis

- A 34 years old female with a 4 years history of lupus presented to you with 1800 mg proteinuria.

- What will you do next?

Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)

Class I Minimal mesangial lupus nephritis
Class II Mesangial proliferative lupus nephritis
Class III Focal lupus nephritis
Class IV Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V Membranous lupus nephritis
Class VI Advanced sclerosing lupus nephritis

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.
aIndicate the proportion of glomeruli with active and with sclerotic lesions.
bIndicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.
cClass V may occur in combination with class III or IV, in which case both will be diagnosed.

BUT

- Glomerulonephritis is not the whole story……

- Tubolointerstitial nephritis
- Antiphospholipid syndrome
- Renal vein thrombosis
- Infection
- Drug-induced nephritis

NEUROPSYCHIATRIC MANIFESTATIONS

1. Headache
2. Seizure
3. Stroke
4. Chorea
5. Neuropathy
6. Vertigo
7. Tinnitus
8. Transverse Myelitis
9. Aseptic Meningitis
10. MS-like Disorder
11. Guillan-Barre Syn.
12. SAH
13. Ataxia
14. Dementia
15. Psychiatric Disorders

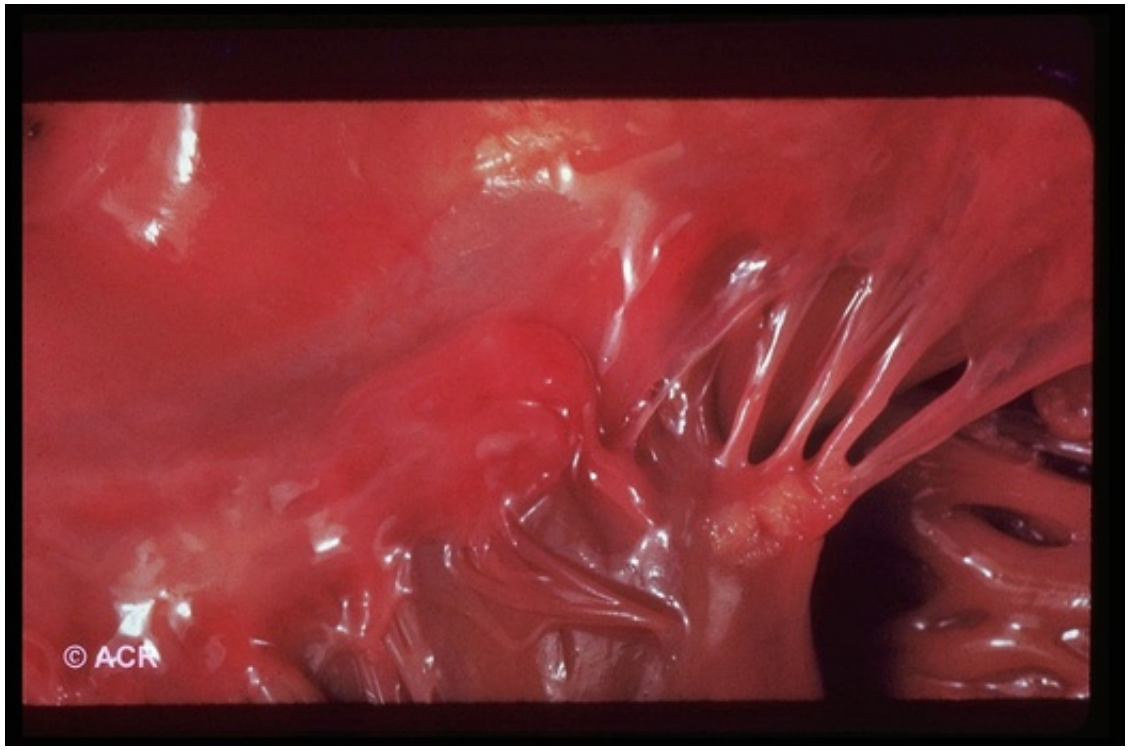
SEROSITIS

Pleurisy

Pericarditis

Peritonitis

CARDIAC INVOLVEMENT



Cardiac manifestations

- Pericarditis
- Myocaditis
- Libman-Sacks endocarditis
- CAD
- Conduction abnormalities

Myocarditis or endocarditis does not respond to immunosuppression

LUNG INVOLVEMENT

Pleurisy
Pneumonitis
Interstitial Fibrosis
Pulmonary Hemorrhage
Shirinking Lung Syndrome
Bronchiolitis Obliterans
Pulmonary Emboli

GASTROINTESTINAL MANIFESTATIONS

- Nausea, sometimes with vomiting, and diarrhea can be manifestations of an SLE flare
- Diffuse abdominal pain:

a) autoimmune peritonitis

b) intestinal vasculitis

Increases in serum AST and ALT are common when SLE is active

HEMATOLOGIC MANIFESTATIONS

- Anemia: most frequent
- Hemolysis
- Leukopenia: almost always consists of lymphopenia, not granulocytopenia
- Thrombocytopenia

OCULAR MANIFESTATIONS

- Sicca syndrome
- nonspecific conjunctivitis
- Retinal vasculitis
- Optic neuritis

Management of lupus

- A 32 years old female presented to you with left knee arthritis and skin rash started from 2 weeks ago. She is a know case of lupus which discontinued medication from 2 years ago.

- WBC: 4200, Hb: 10.2, Plt: 165000
- Cr: 0.8
- U/A: Normal
- Ast: 56, Alt: 68, Alp:152
- ANA: 1/320 AntidsDNA: Nl Anticardiolipin

- What will you prescribe for her?

➢ Hydroxychloroquine and other antimalarials

- Used to treat inflammatory arthritis, fatigue, skin involvement
- Prevents relapses
- Reduces risk for congenital heart block in neonatal SLE
- Antithrombotic effects are important in antiphospholipid antibody-related prothrombotic diathesis
- Well-tolerated with rare side effects (retinopathy; skin hyperpigmentation; neuromuscular or cardiac toxicity)

- She treated with prednisolon 5 mg/day, HCQ 400mg/day, ASA 80mg/day succesfully.
- 6 months later she presented with periorbital edema. On evaluation high blood pressure (170/110) and proteinuria (3500mg/day) revealed.
- Cr:0.9
- CBC: Nl
- AntidsDNA: Nl, C3, C4, CH 50: Nl

- What will you do now?

- Renal biopsy revealed class 5 lupus nephritis.
- What will you prescribe for her?

- A 28 years old lupus patient presented with arthritis, fatigue, urticaria and oral ulcer. CBC, Cr, U/A & ESR are normal. What will you prescribe?

1- Prednisolone 5 mg/d, HCQ 400mg/d

2- Prednisolone 30 mg/d, MTX 10mg/week

3- Prednisolone 60 mg/d, HCQ 400mg/d

4- Methylprednisolone & Cyclophosphamide

DETERMINATION OF DISEASE ACTIVITY AND SEVERITY

- An effective therapeutic regimen first requires the accurate determination of both disease activity and severity. Disease activity usually refers to the degree of inflammation, while severity implies that organ function and perhaps its underlying structure is quantitatively impaired.

GENERAL TREATMENT CONSIDERATIONS

- Sun protection
- Diet and nutrition
- Exercise
- Smoking cessation
- Immunizations
- Treating comorbid conditions (Accelerated atherosclerosis, pulmonary hypertension, antiphospholipid antibodies, and osteopenia or osteoporosis)

SLE & Pregnancy

- Higher flare rate in pregnancy + immediate post-partum
- Higher rate of pregnancy complications
  - Initial presentation during pregnancy is not uncommon
  - Consider pregnancy-related abnormalities that mimic SLE (eclampsia, HELLP syndrome)

- **Treat active lupus manifestations**
  - **Use hydroxychloroquine and prednisolone**
  - **If severe, consider IV glucocorticoids + azathioprine**
  - **Contraindicated: mycophenolate mofetil, methotrexate, cyclophosphamide (discontinue at least 3 months before attempting to conceive)**