Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Systemic Lupus Erythematosus

Objectives :

This lecture will introduce you to the answers of the following questions:

1. What is SLE?
2. What are the Clinical features of SLE?
3. How to diagnose SLE?
4. How to treat SLE?
5. Prognosis of SLE

Done by :

Team leader: Al Hanouf Al Jaloud

Team Members:

Abdullelah Al Saeed — Al Anoud Al Mansour

Majd Al Barrak — Meaad Al Nofaie

Revised by: Yazeed Al-Dossare

Resources :

Doctors slides + notes: prof. Abdulrahman Al Arfaj
Books: Kumar, Step up, MKSAP
Online sources: Osmosis, MedEd
436 team

Definition:

- Chronic, multisystem inflammatory disease characterized by **autoantibodies directed against self**-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.

  SLE is a syndrome consisting of collection of signs, symptoms, and lab data.

Background:

- First written description in13th century (Rogerius) named it lupus (Latin for wolf) as cutaneous similar to a wolf bite.
- Osler recognized systemic features without skin .
- Diagnosis with (LE) cells in 1948.
- Anti-DNA was described in 1959

Epidemiology:

- **Locally:**
  - 2 cases of SLE among 10,372 studied (prevalence of 19.28 per 100,000).
- **Internationally:** variable prevalence :.
  - Denmark (21.7/100,000).
  - Britain, 12 cases per 100,000.
  - India prevalence (3.2/100,000) .
  - 39 cases per 100,000 population in Sweden.

Pathophysiology:

- Disturbances in the immune system:
  - Normally our immune cells communicate with each others to help in recognizing whether this specific cell is foreign or not. However when this mechanism breakdown your body start attacking itself (joints, blood, cns, kidney, etc) and this when the disease start manifesting
  - High ratio of CD4+ to CD8+ T cells. Serum C3/C4 are low in active disease.
  - Defects in immune cell tolerance leading to
    - Production of **autoantibodies targeting antigens located in nuclei**, **cytoplasm**, on **cell surfaces**, and in **plasma proteins**
  - Autoantibodies
    - Mostly **immune complex formation** (e.g kidney)
    - Direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).
  - Cell-mediated autoimmunity also play part.
  - Tissue damage follows

Aetiology:

Specific cause(s) of SLE is unknown.

- Multiple factors are associated include :
  - Genetic
  - Hormonal (disease of women)
  - Racial
  - Environmental factors

Environmental:

- worldwide variability of prevalence the disease(black in africa and US)
- influence of environmental factors on the course of the disease, eg:
  - **Ultraviolet light**, viruses EBV, drugs.cause or exacerbate, silica dust, cigarette smoking, alfalfa sprouts.

Genetic predisposition:

- Multitude of genetic associations suggests a complex genetic predisposition.
- Concordance rate in **monozygotic twins is 25-70%.**
- If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250.
- Relatives have a high prevalence of other autoimmune diseases.
- **HLA-DR2 and HLA-DR3** and other HLA genes occur more often in SLE than in the general population.
- null complement alleles and congenital **deficiencies of complement (C4**, **C2**, and other early components) are associated with an increased risk of SLE.

Hormonal factors: Important factor

- F:M ratio of prevalence in different age groups:
  - In children, f:m ratio is 3:1
  - In adults, f:m ratio is 10-15:1
  - In older, the ratio is approximately 8:1 .
- Age at onset :
  - 65% have onset between 16 and 55.
  - 20% before age 16 , and
  - 15%t after age 55 .
- Higher prevalence in men with **Klinefelter disease**. (bc of the extra X chromosome)
- Exogenous estrogen and exacerbations of SLE.
- Men at all ages have the same risk of disease as women who are **prepubertal or postmenopausal** because low estrogen
- Males do not have an age-related peak in incidence.
- Estrogen plays a major factor

Sex	Number	Percent
Male	58	9.3
Female	566	90.7
Total	624	100

Slei n saudi arabia kkuh. asarfaj

Aetiology cont.

Racial and geography:

- Higher prevalence (2.5- to 6-fold) in USA **African** American women than in white women.
  - But, cf occurs infrequently in Blacks in Africa .
- Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians.
- More common in urban than rural areas .
- Also In New Zealand, 50 per 100,000 Polynesians, but only 14.6 cases per 100,000 in the whites.
- In France, more common among immigrants from Spain, Portugal, North Africa, and Italy

Types:

- A) Spontaneous SLE. Typical lupus
- B) Cutaneous lupus erythematosus **(skin lesions without systemic disease)**
- C) Drug-induced lupus discussed more later
- D) ANA-negative lupus
  - Arthritis, Raynaud phenomenon, **subacute cutaneous lupus**
  - Serology:
    - ANA negative
    - Ro **(anti-SS-A)** or, antiphospholipid antibody-positive
    - Risk of **neonatal lupus** in infants of affected women
      - Clinical Findings Associated With Neonatal Lupus
        - Skin lesions
        - Cardiac abnormalities (AV heart block)

Organ involvement in SLE:

Joints Most common presentation In SLE	90%	Pleuropericardial	60%
Skin:		Kidney	50%
Rashes	70%	Raynaud's	20%
Discoid lesions	30%	Mucous membrane	15%
Alopecia	40%	CNS (Psychosis/convulsions)	15%

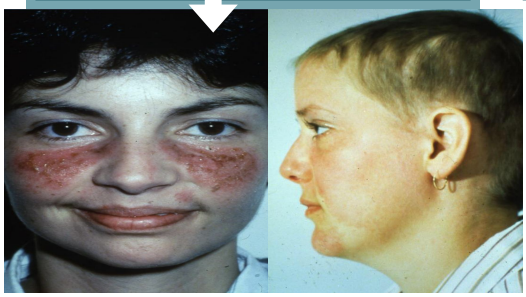
Clinical presentation, and Diagnostic Criterion.

You need to at least have 4 of the 11 clinical presentation mentioned to diagnose SLE.
And ANA must be one of them!

3 Rashes

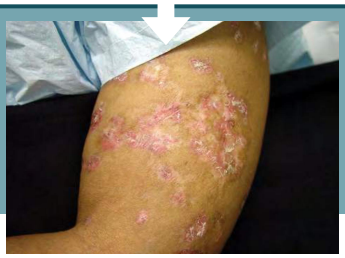
1- Malar rash

Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. This is due to the photosensitivity sun hits the checks but shadows the fold "وادي بين هضبتين ;p", which is in contrast to the rash of dermatomyositis.



2- Discoid rash

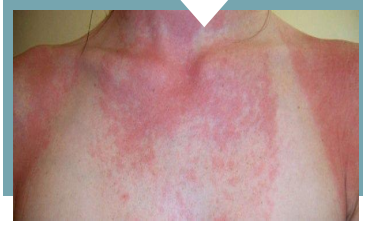
Erythematous raised patches with adherent **keratotic scaling** and **follicular plugging**; **atrophic scarring** may occur in older lesions



Extra

3- Photosensitivity

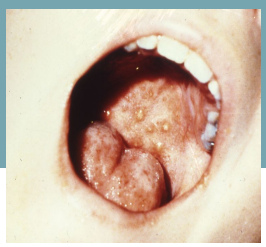
Skin rash as a result of **unusual reaction to sunlight**, by patient history or physician observation



Extra

4- Oral ulcers

Oral or nasopharyngeal ulceration, usually painless, observed by physician



5- Arthritis

Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion.

6- Serositis (inflammation of the serous layer of the pleura, pericardium & peritoneum)

Pleuritis
convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion

Or Pericarditis
documented by ECG or rub or evidence

Or pericardial effusion

Diagnostic Criterion cont.

7. Renal disorder
(glomerulonephritis)

a) Persistent proteinuria
greater than 0.5 grams per day or greater than 3+ if quantitation not performed
Or
b) Cellular casts
may be red cell, hemoglobin, granular, tubular, or mixed

8. Neurologic disorder

a) Seizures
in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance
Or
b) Psychosis
in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance

9. Hematologic disorder

Either:
a) Hemolytic anemia
with reticulocytosis
b) Leukopenia
less than 4,000/mm3 total on 2 or more occasions
c) Lymphopenia
less than 1,500/mm3 on 2 or more occasions
d) Thrombocytopenia
less than 100,000/mm3 in the absence of offending drugs

10. Immunologic disorder either:

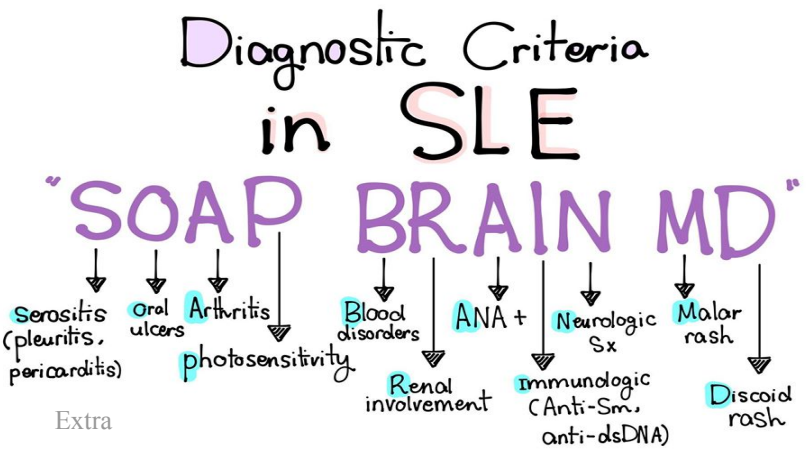
a) **+ve antiphospholipid antibodies** by either:
1) an abnormal serum level of IgG or IgM anticardiolipin antibodies,
2) +ve test result for lupus anticoagulant using a standard method,
3) **False positive serologic test for syphilis known to be positive for at least 6** months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test

b) **Anti-DNA: antibody** to native DNA in abnormal titer Highly associated with lupus nephritis,+ it correlates with disease activity so it's used for monitoring.

c) **Anti-Sm:** presence of antibody to Smith nuclear antigen

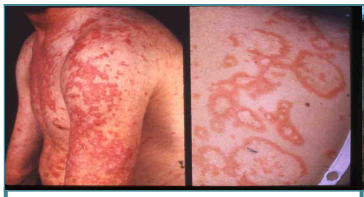
11. Antinuclear antibody

An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome
ANA has to be +ve if the features above are presents to diagnose SLE (it's present in 99% of the patients) thus if it's -ve think about other disease causing the symptoms like lymphoma or infection

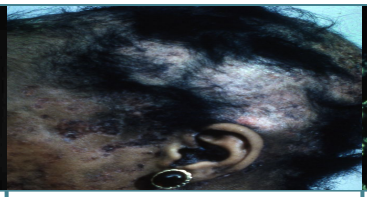


Extra

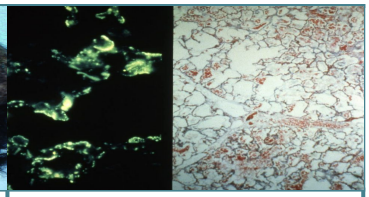
Clinical features cont.



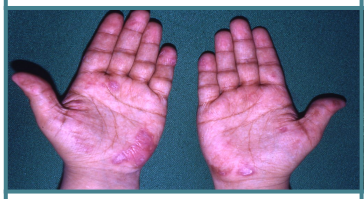
(SCLE) Subacute Cutaneous Lupus Erythematosus associated with Anti-SSA & **neonatal lupus.**
- If this lady got pregnant the chances of her baby having a complete heart block is 2%



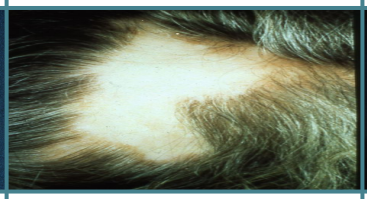
Chronic discoid rash;
Hits deeper & destroys the hair follicles and pigment cells causing post inflammatory hypopigmentation or hyperpigmentation.



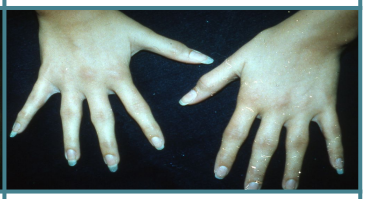
Lupus in the lung capillaries → inflammation of the vessels → break in the walls of the vessels → blood comes out → **Pulmonary alveolar hemorrhage** (mortality is 50%)



bullous rash



Non scarring alopecia



Externally not distinguishable from RA, but X-ray shows non erosive correctable deformity
436

Antibodies Associated with Rheumatic Diseases:

Antibodies to:	*Percentages of patients*	*Antibodies to:*	*Percentages of patients*
Native DNA Mainly with lupus nephritis.	SLE: 50% - 60%	**Nucleolar antigens**	Scleroderma: 40% - 50%
Sm antigen	SLE: 30%	**Scl-70**	Scleroderma: 10% - 20%
Histones When positive think drug induced lupus!.	Drug-induced SLE: 95% SLE: ≤ 60% Rheumatoid arthritis: 20%	**PM-1**	Polymyositis: 50% Dermatomyositis: 10%
SS-A Ro Newborns of +ve mothers who are at risk of developing **neonatal lupus** which can manifest as a heart block	Sjogren's syndrome: 70% SLE: 30% - 40% Scleroderma and mixed connective tissue disease: frequency and titers low	**RNP**	Mixed connective tissue disease: 95% - 100% SLE: 30% at low titers Scleroderma: 10% - 20%
SS-B La	Sjogren's syndrome: 60% SLE: 15%	**Centromere antigens**	CREST: 80% - 90%

SLE – Presenting and Prevalent Symptoms:

ARA Criteria [n = 624] SAUDI ARABIA

ARA Criteria	+ve at presentation n (%)	+ve on * follow up n (%)	Total prevalent (%) n
Malar rash	265 (42.5)	34(5.4)	299(47.9)
Discoid rash	99 (15.9)	11(1.8)	110(17.6)
Photosensitivity	165 (26.4)	26(4.2)	191(30.6)
Oral ulcer	223 (35.7)	21(3.4)	244(39.1)
Arthritis	454 (72.8)	7(1.1)	461(73.9)
Serositis	82 (13.1)	89(14.3)	171(27.4)
Renal disorder	281(45)	18(2.9)	299(47.9)
Neurological disorder	98(15.8)	20 (3.2)	172(27.6)
Hematological disorder	505 (80.9)	31(4.9)	536(85.9)
Immunological disorder	470 (75.3)	30 (4.8)	500(80.9)
ANA	622(99.7) Almost in all patients	0	622(99.7)

Other presenting symptoms (n = 624).

Just read it

Fever	(30.6)	Splenomegaly	(2.6)
Weight loss	(23.1)	Hepatosplenomegaly	(6.1)
Fatigue	(42.5)	Genital ulcers	(1.4)
Arthralgia	(86.9)	HTN	(28.4)
Raynaud's phenomenon	(8.7)	Myalgia	(6.6)
Alopecia	(47.6)	Pancytopenia	(12.2)
Lymphadenopathy	(20.0)	Pleuritis	(1.58)
DVT	(7.4)	Pericarditis	(20.7)
Ascites	(8.9)	Pulmonary symptoms	(28.0)
Hepatomegaly	(3.2)	Gastrointestinal symptoms	(38.6)

Classification Criteria for SLE: Just read it

- SLICC PI: DR. MICHELLE PETRI
- SLICC classification criteria for Systemic Lupus Erythematosus
- New Investigator: Dr. Ana-Maria Orbai Funding Source: National Institutes of Health
- Seventeen criteria were identified in a very time-consuming and laborious process which involved the consensus diagnosis of over 700 patient scenarios, the reduction in the number of potential variables by extensive logistic regression analyses, the use of recursive partitioning to derive classification rules and the refinement of the rules when agreement was not achieved. In a second step, another set of over 600 patient scenarios was used to validate the criteria. This process took well over a decade from its conception to publication.
- The SLICC criteria for SLE classification requires: 1) Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion OR 2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Just read it

Clinical Criteria	Immunological Criteria
1. Acute cutaneous lupus	1. ANA above laboratory reference range
2. Chronic cutaneous lupus	2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory
3. Oral ulcers: palate	3. Anti-Sm
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)	4. Antiphospholipid antibody: any of the following
5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in two or more joints and thirty minutes or more of morning stiffness.	5. Low complement
6. Serositis	6. Direct Coombs test in the absence of hemolytic anemia
7. Renal	
8. Neurologic	
9. Hemolytic anemia	
10. Leukopenia (< 4000/mm3 at least once)	
11. Thrombocytopenia (<100,000/mm3) at least once	

New ACR and EULAR criteria for classification of SLE

All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2–positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

Primary Central Nervous System Lupus:

Neurologic Signs or Symptoms

- *Meninges:*
  - Headache, meningismus
- *Cerebrum:*
  - Dementia, strokes, subarachnoid hemorrhages
- *Cerebellum:*
  - Ataxia
- *Spine:*
  - Paraparesis, MS-like disorder
- *Cranial and peripheral nerves:*
  - Neuropathies, mononeuritis multiplex
- *Other:* migraine, seizures, tremor, rigidity, chorea, SIADH, myasthenia gravis & Guillain-Barre syndrome

Drug Induced Lupus

➔ (consider before diagnosing native lupus) Rare

- Sex ratios are nearly equal.
- **Nephritis and CNS *not* common.**
- No anti- native DNA or hypocomplementemia.
- Resolution on discontinuation of drug. Up to 6 months if not you have to treat it
- Associated with **Anti-Histone**

Drugs associated with lupus erythematosus: which induces lupus

◄ ***Definite association***: doctor said you only need to know these

Chlorpromazine (antipsychotic) Methyldopa (antihypertensive)
Hydralazine (antihypertensive) Procainamide (antiarrhythmic)
Isoniazid (antibiotic) Quinidine (antiarrhythmic).

◄ *Possible association:*

Beta blockers, Methimazole, Captopril, Nitrofurantoin, Carbamazepine, Penicillamine, Cimetidine, Phenytoin, Ethosuximide, Propylthiouracil, Hydrazines, Sulfasalazine, Levodopa, Sulfonamides, Lithium, Trimethadione

◄ *Unlikely Association:*

Allopurinol, Penicillin, Chlorthalidone, Phenylbutazone, Gold salts, Reserpine, Griseofulvin, Streptomycin, Methysergide, Tetracyclines, Oral contraceptives

Investigations: Extra

- **Blood count:**
  - Normochromic, normocytic anaemia
  - Neutropenia
  - Lymphopenia
  - thrombocytopenia.
- **ESR:** raised **CRP:** usually normal unless the patient has a coexistent infection.
- **Urea and creatinine:** only rise when renal disease is advanced.
- **Low serum albumin/high urine protein/creatinine ratio:** early indicators of lupus nephritis.
- **Serum:**
  - Complement C3 and C4 levels: reduced in active disease.
  - **Autoantibodies:**
    - ANA: Sensitive but not specific
    - Anti-ds DNA (in 70%): very specific (but not sensitive)
    - Anti-Smith (in 30%): very specific (but not sensitive)
    - Antiphospholipid
    - Antihistone (in 70%) are present in >95% of cases of **drug-induced lupus** If negative, drug-induced lupus can be excluded.
    - Ro (SS-A) and La (SS-B) are found in 15% to 35%.
      - Associated with:
        - Sjögren syndrome
        - **Subacute cutaneous SLE**
        - Complement deficiency (C2 and C4)
        - ANA-negative lupus
        - Neonatal lupus (with congenital heart block)
- **Histology:** Characteristic deposition of IgG and complement in kidney or skin. biopsies

treatment

General considerations: Prevention

- Avoid uv light and sun (sunscreening).
- Antimalarial to prevent relapses. (hydroxychloroquine. Must do annual eye examination because it can cause retinal toxicity!!)
- Treat hypertension and dyslipidemias .

Treat depending on the organ system(s) involved:

- Skin, musculoskeletal, and serositis
- NSAIDs, HCC (hydroxychloroquine) , local cs.

- More serious organ involvement (CNS,**renal**)
- **Immunosuppression** with high-dose steroids,AZA and/or cyclophosphamide,mycophenolate , Tacrolimus
- Targeted therapy(biological), rituximab, belimumab

Other treatments:

- plasma exchange for TTP or diffuse alveolar hemorrhage
- intravenous immunoglobulin for severe steroid-unresponsive thrombocytopenia.

Treatment cont:

- **Skin:**
  - mild: local steroids + hydroxychloroquine
  - severe: systemic steroids + hydroxychloroquine
- **Joints:**
  - NSAIDs + hydroxychloroquine
    - if NSAIDs fails use steroids instead
- **Kidney, heart, lungs & CNS:**
  - steroids (methylprednisolone) + cyclophosphamide or mycophenolate

Explanation:

- When you make the diagnoses treat with:
  - Strong drugs+high doses to put them into remission then,
- Every patient should get for **maintenance**:
  - **Hydroxychloroquine** "antimalarial drug which is effective in maintaining lupus and preventing flares"
- During **flares (Acute** exacerbations):
  - **Steroids** given only in flares/Acute state
- Lupus nephritis:
  - Cyclophosphamide > mycophenolate

Prognosis:

- Poor prognostic factors for survival in SLE include :
  - **Renal disease** (especially diffuse proliferative glomerulonephritis).
  - **Hypertension**
  - **renal and central nervous system (CNS) disease**
  - less education (?poor compliance)
  - Poor socioeconomic status (?inadequate access to medical care).
  - Black race (? low socioeconomic status)
  - Presence of antiphospholipid antibodies
  - High overall disease activity
  - Male sex
    - Men similar freq of renal, skin, arthritis, and CNS as women,
    - But less photosensitivity,
    - more serositis,
    - an older age at diagnosis,
    - and a higher one year mortality.
  - Young age
    - SLE in **children more severe**,higher malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities

Remission:

- After appropriate therapy, many patients go into a clinical remission requiring no treatment.
  - a long-term follow-up of 667 patients noted:
    - ≈25 % had at least one treatment-free clinical remission lasting for at least one year.
    - The mean duration of remission was 4.6 years
      - (?underestimate since one-half of the patients were still in remission at the end of follow-up).
    - A long history of SLE or the presence of renal or neuropsychiatric disease did not preclude remission

Summary

Systemic Lupus Erythematosus

Etiology	- age (65% are between 15 - 65 years) & gender (F>M) - genetic **(HLA-DR2, HLA-DR3)** - hormonal → **estrogen** (↑↑ in perimenopausal women) - racial (↑ in **african** americans) - environmental (**ultraviolet rays**, silica dust, viruses, drug, etc..)
Clinical features	1. Malar rash (butterfly rash) 2. Discoid rash 3. Photosensitivity (unusual reaction to sunlight) 4. Oral ulcer (painless) 5. Arthritis (it is often the first symptom that brings the patient) 6. Serositis (pleuritis or pericarditis) Clinical features 7. Renal disorder (persistent proteinuria or cellular casts) 8. Neurological disorder (seizures or psychosis) 9. Hematological disorder (hemolytic anemia or leukopenia or thrombocytopenia) 10. Immunological disorder (Anti-DNA or Anti-Sm Ab or Antiphospholipid Ab) 11. Antinuclear antibodies (ANA) → most important marker! Other symptoms: fever, fatigue, alopecia,weight loss, lymphadenopathy, GI symptoms, etc.
Investigations	Serology - **ANA (elevated in almost all SLE** pts) → **sensitive but not specific** - Anti-dsDNA (40%) & anti-Sm Ab (30%) → very specific (presence is diagnostic!) but not sensitive - Anti-SSA & Anti-SSB - Antihistone Antibodies → in drug induced lupus* (100%)
Management	- Mild to moderate disease (restricted to skin and joints) → **NSAIDs** & **hydroxychloroquine** +/- steroids. - Life threatening disease (renal, CNS, cardiac involvement) → **High-dose** corticosteroids and immunosuppressants (AZA, cyclophosphamide, rituximab) - **Maintenance → hydroxychloroquine** is first line for long term disease control & glucocorticoids are best initial therapy in acute flares

Question:

1- A 22-year old woman presents to her primary care provider complaining of a facial rash. She says the rash began 3 weeks ago after hiking in the white mountains of new hampshire this summer. Since that time she has also experienced pain in her hands and wrists that is worse in the morning and accompanied by subjective fever. She denies any chest pain, shortness of breath, Nausea,Vomiting. Vital signs are (37.6 C)(BP 134/82)(RR 18/min). Examination demonstrates a rash on the patients face that spares the nasolabial folds along with painless oral ulcers. the metacarpophalangeal joints are tender to palpation and range of motion is limited by pain. CBC demonstrates normocytic anemia with thrombocytopenia, Which of the following is the best next step in diagnosis?

A) Anti-cardiolipin antibodies
B) Anti-DsDNA antibodies
C) Anti-histone antibodies
D) Anti-nuclear antibodies

2- Which of the following genes are linked to SLE?
A) HLA-B27
B) HLA-DR4
C) HLA-DR2
D) HLA-B51

3- Which of the following is the most common first manifestation in SLE patients?
A) Arthritis
B) Malar rash
C) Glomerulonephritis
D) Discoid rash

4- Which of the following antibodies is used to diagnose drug induced lupus?
A) Anti-DsDNA
B) Anti-SSA
C) Anti-nuclear
D) Anti-histones

Answers: 1)D, 2)C, 3)A, 4)D