SLE

435 medicine teamwork

[Important | Notes | Extra | Editing file]

Lecture objectives:

- What is SLE?
- What are the Clinical features of SLE?
- How to diagnose SLE?
- How to treat SLE?
- Prognosis of SLE

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Systemic Lupus Erythematosus

Definition

What is SLE?

Chronic, multisystem inflammatory disease characterized by autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.
A Collection of signs, symptoms and lab data made into a criteria for the purpose of diagnosis and studies.

Background:

- **Etymology:** (lupus: latin for wolf), (erythro-: greek for red)
- The first written description was in the 13th century by the italian physician Rogerius.
- Osler recognized systemic features and linked rashes to organ involvement.
- Diagnosis with lupus erythematosus (LE) cells in 1948.
- Anti-DNA was described in 1959

Types:

(1) Spontaneous SLE - (2) Discoid lupus [skin lesions without systemic disease] - (3) drug induced lupus
(4) ANA-negative lupus [Findings: arthritis, Raynaud's phenomenon, subacute cutaneous lupus + Serology: anti-SS-A positive, ANA negative + risk of neonatal lupus in infants of affected women]

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**: (12/100,000) | **India**: (3.2/100,000) | **Sweden**: (39/100,000)
Generally speaking SLE is higher in **(1)** women **(2)** between 20-40 years **(3)** African descent

Pathophysiology

Disturbance in the immune system:

- High ratio of CD4+ (T-helper cell) to CD8+ (T-cytotoxic cell)
- Defects in immune system leading to production of autoantibodies targeting antigens located in nuclei, cytoplasm, on cell surfaces, and in plasma proteins.
- Autoantibodies leads to mostly immune complex formation (e.g kidney) and direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).
- Cell-mediated autoimmunity also play part.
- Tissue damage follows.

Usually your white cells do not produce autoantibodies against yourself, so with SLE there is a defect and you cannot tolerate yourself, hence your body produces auto-antibodies against your body.

Long story short *not really*:

SLE is incompletely understood, however there are several theories explaining the most likely pathophysiology. One striking theory is that SLE may occur because of defects in apoptosis or in the clearance of apoptotic cells (due to multifactorial causes mentioned in the next page). This will lead to inappropriate exposure of intracellular antigens on the cell surface by antigen presenting cells, leading to polyclonal B- and T-cell activation and autoantibodies production. The clinical manifestations are mediated by [antibodies + development and deposition of immune complexes + complement activation + neutrophils influx + abnormal cytokine production]

Aetiology

Specific cause(s) of SLE is unknown but there are multiple factors associated with SLE:

Factor	Details
Age & Gender	-**Age at onset**: 65% (16 and 55), 20% (before age 16) ,15% (after age 55) -**F:M ratio** of prevalence in different age groups: Children (F:M ratio is 3:1), adults (F:M ratio is 10-15:1), elderly (approximately 8:1) -Males do not have an age-related peak in incidence. -Men at all ages have the same risk as women who are prepubertal or postmenopausal SLE mainly occurs in females in their 20s up until menopause.
Genetic	***Genetic predisposition:** multitude of genetic associations Genes linked to the development of SLE include: **HLA-DR2**, **HLA-DR3** and deficiencies in the complement genes (C4, C2, and other early components) ***Heredity:** -Concordance rate in monozygotic (identical) twins is 25-70%. -If a mother has SLE: daughter's risk is 1:40, son's risk is 1:250. -Relatives have a high prevalence of other autoimmune diseases.
Hormonal	* **Estrogen effect** -Higher prevalence in premenopausal women -Exogenous estrogen and exacerbations of SLE. -Higher prevalence in men with Klinefelter disease. Because of an extra X, there is some faulty inhibition of X factor, so you get higher chances of autoimmunity.
Racial	* **Higher among:** - African American women than in white women, but infrequent in africans. - Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians. -In New Zealand, (50/100,000) Polynesians, but only (14.6/100,000) in whites. -In France, common among immigrants from Spain, Portugal, North Africa, and Italy. It's more common in our society than the west. * More common in urban than rural areas.
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** (can trigger flares of SLE, especially in the skin), viruses, drugs (cause or exacerbate), silica dust, cigarette smoking, alfalfa sprouts البرسيم الحجازي

Clinical Features

The diagnosis is based on a combination of clinical features and laboratory abnormalities. To fulfil the classification criteria of SLE, at least 4 of the following factors must be present or have occured in the past

American College of Rheumatology (ACR) Revised Criteria for the Classification of SLE	
Criteria	**Definition**
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds."butterfly rash"
2. Discoid rash Chronic rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3.Photosensitivity	Skin rash as a result of unusual reaction to sunlight; by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration, **usually painless**, observed by physician.
5. Arthritis	In 90% of those with SLE and is often the **first symptom** that brings patient to seek medical attention. SLE gives joint pain without deformity (normal x-ray). Nonerosive arthritis involving 2 ≥ peripheral joints, may or may not be associated with tenderness, swelling, or effusion
6. Serositis	a) Pleuritis: history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion. **OR** b) Pericarditis: documented by ECG or rub or evidence of pericardial effusion.
7. Renal disorder	a) Persistent proteinuria: > 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. mainly glomerulonephritis
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	a) Hemolytic anemia - with reticulocytosis **OR** b) Leukopenia <4,000/mm^3 total on 2 or more occasions **OR** c) Lymphopenia <1,500/mm^3 on 2 or more occasions Specially this one. Leukopenia is usually due to lymphopenia. Usually those occur more than once (suggestive for SLE), but if it comes once suspect a lab error or viral infection. The degree of lymphopenia is a good guide to for disease activity. **OR** d) Thrombocytopenia <100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) **Anti-DNA:** antibody to native DNA in abnormal titer *know this one it's important. **OR** b) Anti-Smith (Sm): presence of antibody to Sm nuclear antigen **OR** c) Positive finding of antiphospholipid antibodies on: 1. Abnormal serum level of IgG or IgM anticardiolipin antibodies (ACA). 2. Positive 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. Standard methods should be used in testing for the presence of antiphospholipid.
11. Antinuclear antibodies (ANA)	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. It has to be there, let's say the patient has -ve ANA but she/he has consistent pathology in the kidney then you should do kidney biopsy if you find Glomerulonephritis > highly suggestive of SLE > then you may call it seronegative lupus. **ANA IS THE MOST IMPORTANT MARKER IN SLE**

Organ Involvement in SLE:

Joints (90%)	
Skin: rashes(70%) - discoid lesions(30%) - alopecia(40%)	**Raynaud's phenomenon** (20%) (leading to pain, numbness and change in color (white, blue, red "the classic 3 changes")
Pleuropericardium (60%)	**Mucous membranes** (15%)
Kidney (50%)	**CNS** -psychosis/convulsions- (15%)

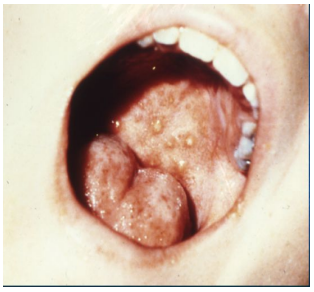
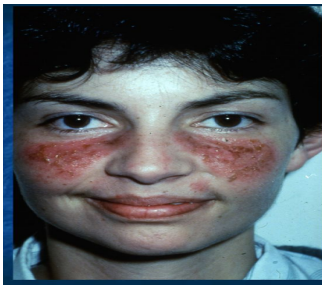
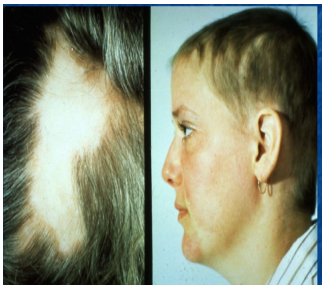
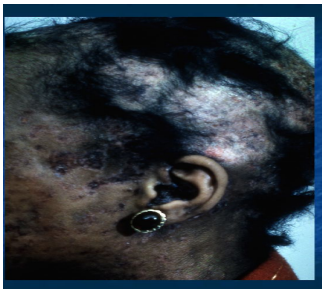
SLE prevalent symptoms: (most important one is ANA)

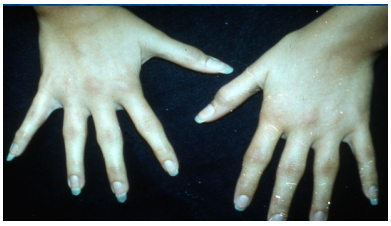
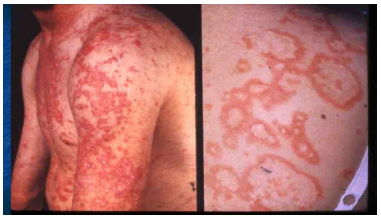
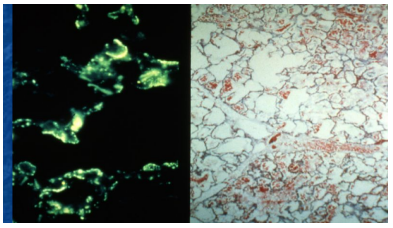
ARA criteria	+ve at presentation (n%)	+ve on follow-up (n%)	Total prevalence (n%)
Malar rash	265 (42.5)	34(5.4)	299(47.9)
Discoid rash	99 (15.9)	11(1.8)	110(17.6)
Photosensitivity	165 (26.4)	26(4.2)	191(30.6)
Oral ulcer	223 (35.7)	21(3.4)	244(39.1)
Arthritis	(72.8) 454	7(1.1)	461(73.9)
Serositis	82(13.1)	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)	0	622(**99.7**)

+ Constitutional symptoms may occur; such as fever of unknown origin (FUO)

Primary central nervous system lupus:

- 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, Psychosis,early dementia especially when associated with Anti-phospholipids.

			
Oral ulcers: rounded lesions, sometimes could be very severe	Malar rash: not uniform, some areas of redness and some are brownish & heaped up. With acute erythematous butterfly rash sometimes you get areas with discoid rash	Classical erythema (profile picture, just redness of cheeks and nose sparing nasolabial fold) Alopecia ثعلبة (either diffuse or areata), usually non scarring, this one goes back to normal once you treat the patient, the secret is that you treat early	Discoid type, initially it starts reddish then brownish then it's either brown due to postinflammatory hyperpigmentation or whitish due to post inflammatory hypopigmentation why? because the inflammation is deep it touches the melanin area and alters it. It also hits the hair follicle and leads to permanent alopecia which doesn't respond to treatment. **External meatus** is the classical site for SLE.

		
externally not distinguishable from RA, but X-ray shows non erosive correctable deformity	Upper to the right subacute cutaneous erythematosus lupus look at the annular lesions, rounded with central clearing, associated with Anti-SSA	Alveolar hemorrhage of SLE (predicts high mortality)

A common scenario: 1st three months usually only rashes occur: Three rashes occur, 1) acute, 2) chronic more disfiguring rash, and 3) abnormal sensitivity to light. Then you get the oral ulcers, arthritis, serositis and so on.

Diagnosis

After taking a good history and performing physical examination start your investigations with simple tests:

*** Blood tests:**

- CBC: shows normocytic normochromic anemia often with neutropenia/lymphopenia/thrombocytopenia
- ESR and CRP: ESR is usually raised but CRP is usually normal unless there is a coexistent infection.

*** Renal function test:**

- Urea & creatinine only rise in advanced renal disease.
- Low serum albumin OR high urine protein/creatinine ratio are early indicators of lupus nephritis.

Then you move on to advanced tests:

*** Serology:**

- **Positive ANA test:** sensitive but not specific; almost all patients with SLE have elevated serum ANA levels.
- **Anti-dsDNA (40%) & anti-Sm Ab (30%):** very specific but not sensitive; presence of either is diagnostic.
- **Anti-SSA and anti-SSB** are found in 15% to 35%. Associated with:

a. Sjögren's syndrome | b. Subacute cutaneous Lupus | c. Neonatal lupus (with congenital heart block)

Anti-SSA is associated with infants, when a women with SLE gets pregnants she might pass the antibodies to the child and cause neonatal lupus with congenital complete heart block

- **Antihistone Abs (70%):** in **drug-induced lupus** (100%). If negative, drug-induced lupus can be excluded.
- **Decreased complement levels.** (C2 and C4)

*** Histology:**

Histological and immunofluorescent abnormalities are seen in biopsies from the kidney or skin.

*** Diagnostic imaging:**

- Brain CT: shows infarct or hemorrhage with evidence of cerebral atrophy.
- Brain MRI: can detect lesions which are not seen on CT

Other modalities can be used according to the presentation.

Considerations

Drug-induced lupus:

Should be considered before diagnosing native lupus

(genetic predisposition is a must for drug induced lupus to occur)

- Sex ratios are nearly equal.
- Nephritis and CNS are not common.
- No anti-native DNA or hypocomplementemia.
- Resolution on discontinuation of drug (after about 4-5 months).

Drugs associated with lupus erythematosus:

*** Definite association:**

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

*** Possible association**

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

*** Unlikely Association**

Allopurinol, Penicillin, Oral contraceptives, Tetracyclines, Chlorthalidone, Gold salts.

Do not memorize the drugs, only hydralazine, methyldopa (because they're used in obstetrics) and isoniazid because (it's widely known for its side effects)

Treatment

Goal of therapy:

To ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, improve quality of life, and educate patients about their role in disease management.

Treatment is based on the symptoms and the severity of the disease:

1. Mild to moderate disease: disease is restricted to skin and joints, managed with Analgesics:

- NSAIDs & hydroxychloroquine.
- Frequently, however, corticosteroids may be necessary along with immunosuppressants.

If MSK: Non steroidal agents, but if they don't work → steroids & hydroxychloroquine (always oral).
if it was skin affected by SLE we treat it by Steroids (systemic or local) and Hydroxychloroquine
Serositis responds well to NSAIDS

2. Life-threatening disease: for the treatment of renal, CNS, and cardiac involvement.

- High-dose corticosteroids and immunosuppressants

Immunosuppression with high-dose steroids, AZA and/or cyclophosphamide, mycophenolate, Tacrolimus.
Targeted therapy (biological):rituximab and belimumab.
Methotrexate is always a WRONG answer for SLE!!!

3. Maintenance therapy: following the control of acute episode the patient should be switched to **oral immunosuppressant** medication.

Hydroxychloroquine is the 1st line (always a baseline treatment) for long term disease control, BUT **glucocorticoids** are the best initial therapy in acute flares.

Prevention:

- Avoid UV light and sun exposure.
- Antimalarial to prevent relapses. (Hydroxychloroquine; treatment and prevention of flare)
- Treatment of comorbidities like hypertension and dyslipidemia.
- Proper education (especially for women in the childbearing age as SLE is one of the most common causes of spontaneous abortions + the possibility of neonatal lupus)

Preventing flares is possible, however you cannot prevent the occurence of the disease itself.

Prognosis & Remission

Poor prognostic factors for survival in SLE include:

- **Renal disease** (especially diffuse proliferative glomerulonephritis).
- **Hypertension**
- **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:** similar freq of renal/skin/arthritis/CNS as women, but less photosensitivity, more serositis, an older age at diagnosis, and a higher one year mortality.
  Males get it less but if they do, it's more severe.
- **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 history of SLE or the presence of renal or neuropsychiatric disease did not preclude remission
Survival rate is very high, except for people who have anti-phospholipids or refuse or take treatment.

MCQs

A) A 34-year-old Afro-Caribbean woman has been admitted for management and investigation of increasing shortness of breath. On further questioning, she mentions that her hands have been painful and stiff over the past few months and she has been having recurrent mouth ulcers. Chest x-ray confirms bilateral pleural effusions and blood tests reveal a raised ESR and a normal CRP. A diagnosis of systemic lupus erythematosus (SLE) is suspected and a full autoantibody screen is sent to the laboratory. Which of the following auto-antibodies is most specific to the suspected diagnosis?

1) Anti-nuclear antibody
2) Rheumatoid factor
3) Anti-double stranded DNA antibody
4) Anti-centromere antibody
5) Anti-mitochondrial antibody

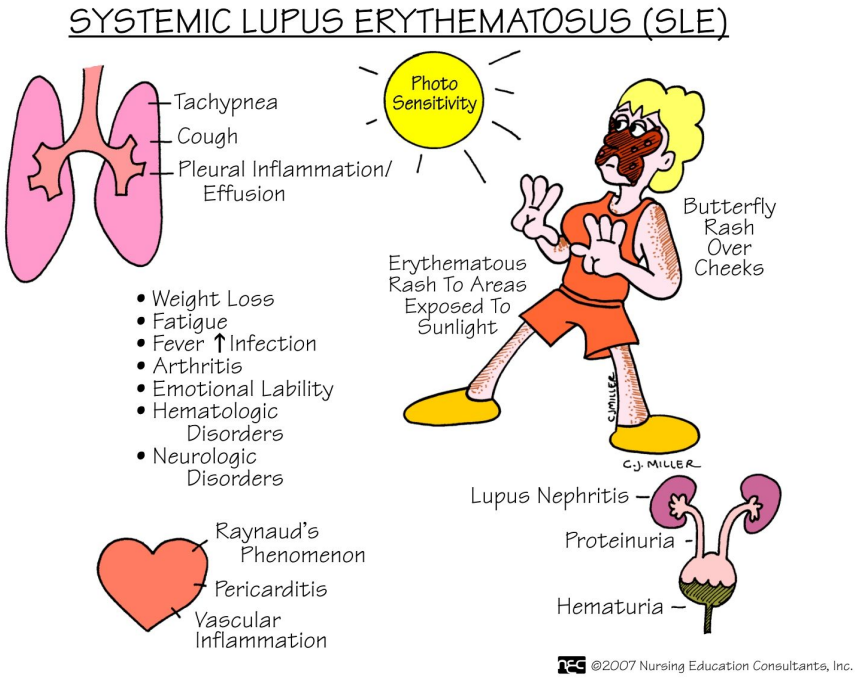
B) A 25-year-old female gives birth to a baby with complete heart block who subsequently requires pacemaker insertion. Which of the following antibodies is most likely to be detected in the maternal serum?

1) Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies
2) Anti-endomysial antibodies
3) Anti-Ro/SSA antibodies
4) Anti-SCL70 antibodies

C) Sjögren's syndrome is associated with other autoimmune diseases (CREST). Which one of the following is not involved in the CREST Syndrome?

1) Calcinosis
2) Rheumatic fever
3) Raynaud's phenomenon
4) Esophageal dysmotility
5) Telangiectasia

A → 3 , **B** → 3 , **C** → 2



D) A 24-year-old woman with recently diagnosed SLE is admitted for atypical chest pain. She has pericarditis and had a pericardial window placed several months ago. Her EKG is equivocal. Which of the following would be most useful in determining the etiology of her chest pain?

1) Complement levels
2) ESR
3) Rheumatoid factor
4) Urinalysis
5) CBC
6) SS-A and SS-B antibodies

E) Your patient with lupus becomes pregnant. Which of the following is the most accurate way to determine the risk of S LE in her child?

1) Titer of anti-DS DNA
2) Complement levels
3) Anti-SS-A (Ro)
4) Anti-Sm
5) Ultrasound

F) A woman with a history of lupus comes in because of headache, fever, and neck stiffness. She has recently had worsening of her joint pain and was placed on high-dose NSAIDs and prednisone. Her CSF shows 1 85 white blood cells that are 92% lymphocytes. C3 and C4 levels are normal. Her anti-DS DNA titer is unchanged.
What is the best step in management of this patient?

1) Start ceftriaxone and vancomycin
2) Stop NSAIDs
3) Increase the dose of steroids
4) Add cyclophosphamide
5) Add hydroxychloroquine

D → 1 , **E** → 3 , **F** → 2