433 Teams

# MEDICINE

## 27|SLE and Scleroderma

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# Objectives not given

# Systemic lupus erythematosus (SLE)

## 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.
- An autoimmune disorder leading to inflammation and tissue damage involving multiple organ systems.

## ETIOLOGY:

- The pathogenesis is not completely understood. SLE is an idiopathic chronic inflammatory disease with **genetic, environmental,** and **hormonal** factors involved in its pathogenesis.
- **Multiple factors are associated include :**
  - **Genetic**
  - **Hormonal**
  - **Racial**
  - **Environmental factors**

• **Women** of child bearing age account for 90% of cases.

• **African-American patients** are more frequently affected than Caucasian patients.

1-Very mild in elderly patients; more severe in children.

2-Usually appears in late childhood or adolescence.

**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:**

- Higher prevalence in men with Klinefelter disease.
- Estrogen-containing contraceptive pills increase the risk of developing SLE by 50%.
- Breastfeeding may decrease risk of developing SLE
- Early menarche & postmenopausal estrogen administration doubles the risk.

**Age at onset**:

- **65% have onset between 16 and 55.**
- **20% before age 16 , and 15%t after age 55 .**
  - Men at all ages have the same risk of disease as women who are prepubertal or postmenopausal
  - Males do not have an age-related peak in incidence.

**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
  - drugs cause or exacerbate
  - silica dust.
  - cigarette smoking.
  - alfasprouts.

## Pathophysiology:

- The pathophysiology involves autoantibody production, deposition of immune complexes, complement activation, and accompanying tissue destruction/vasculitis.
- Disturbances in the immune system:
  - High ratio of CD4+ to CD8+ T cells.
  - Defects in immune cell tolerance →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).
  - Serum antinuclear antibodies (ANAs) are found in nearly all individuals with active SLE.
  - Cell-mediated autoimmunity also play part.
  - Tissue damage follows

## Clinical features :

**clinical course of SLE**

• A chronic disease characterized by exacerbations and remissions

• Malar rash, joint pain, and fatigue are the most common initial findings. With more advanced disease, renal, pulmonary, cardiovascular, and nervous systems are affected.

1. **Butterfly "malar" rash:**
   erythromatous, raised and painful or itchy, occur over the cheeks with sparing of nasolabial folds.
2. **Discoid rash**:
   erythromatous raised patches with adherent keratotic scaling and follicular plugging.
3. **Photosensitivity**
4. **Oral ulcers**: (The ulcer in SLE is painless)
5. **Arthritis:**
   nonerosive arthritis involving 2 or more peripheral joints characterized by tenderness, swelling, or effusion.
6. Renal, gastrointestinal, and neurologic disorders.
7. Fever, weight loss, and mild lymphadenopathy may occur during flares of disease activity
8. **Arthralgia**:
   common symptom associated with morning stiffness.
9. **The Raynaud phenomenon**:Cold- or emotion-induced color changes of the digits of the hands and/or feet are frequent problems and may antedate other features of the disease.
10. **Keratoconjunctivitis**

Malar rash is more acute than discoid rash, and the discoid is deeper which may leave a scar if untreated

## 11. Immunologic disorder :

a) "Positive finding of antiphospholipid antibodies

b) Anti-DNA: antibody to native DNA in abnormal titer

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

d) False positive serologic test for syphilis known to be positive for at least 6 months

12. Cardiac: Pericarditis, endocarditis (Libman–Sacks endocarditis is a serious complication), myocarditis

13. Pulmonary:Pleuritis (most common pulmonary finding), pleural effusion, pneumonitis (may lead to fibrosis), pulmonary HTN (rare)

14. Immunologic: Impaired immune response due to many factors, including auto- antibodies to lymphocytes, abnormal T cell function, and immunosuppressive medications

Janeway lesions and splinter hemorrhage is seen in SLE

## Organ involvement in SLE

1. Joints = 90%
2. Skin:
   - Rashes = 70%
   - Discoid lesions = 30%
   - Alopecia = 40%
3. Pleuropericardium = 60%
4. Kidney = 50%
5. Raynaud's = 20%
6. Mucous membranes = 15%
7. CNS (psychosis/convulsions) = 15%

Kaplan

Alopecia is common in SLE but is not one of the "official" diagnostic criteria.

Pneumonia, alveolar hemorrhage, and restrictive lung disease happen in SLE but are not criteria for the diagnosis of the disease.

**Ocular findings are not part of formal diagnostic criteria:**

- Photophobia
- Retinal lesions (cotton wool spots)
- Blindness

## Primary Central Nervous System Lupus: Signs and 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 & GBS

## Drug-induced lupus

Should be considered before diagnosing native lupus. It is a special consideration **because sex ratios are nearly equal**, kidney and CNS involvement are not common, no anti-native DNA or hypocomplementemia, and there is resolution on discontinuation of the drug.

| Drugs associated with lupus erythematosus | | |
|---|---|---|
| Definite association | Possible association | Unlikely association |
| **Chlorpromazine** | **Beta blockers** | **Allopurinol** |
| Methyldopa | Phenytoin | Penicillin |
| **Hydralazine** | **Levodopa** | **Oral contraceptives** |
| Procainamide | Lithium | Tetracyclines |
| **Isoniazid** | **Captopril** | **Chlorthalidone** |
| Quinidine | Cimetidine | Gold salts |

**CLINICAL PEARL 6-2**

**Drug-induced Lupus**

- Certain drugs may produce a lupus-like syndrome that is similar to SLE except that it does not affect the CNS or kidneys.
- If renal or CNS involvement is present, it is **not** drug-induced lupus. In addition, the classic butterfly rash, alopecia, and ulcers are typically not seen in drug-induced lupus.
- Most patients improve after withdrawal of the offending drug. Therefore, the prognosis is obviously more favorable.
- Commonly implicated agents include hydralazine, procainamide, isoniazid, chlorpromazine, methyldopa, and quinidine.
- Laboratory findings in drug-induced lupus: Antihistone antibodies are always present; there is an absence of anti-ds DNA and anti-Sm Ab.

## Diagnostic Tests:

ANA antibody is the most important immunological test in the diagnosis of SLE

- **ANA:** found in 95% to 99% of cases. A negative ANA is extremely sensitive for lupus, but a positive ANA has little specificity. Many rheumatologic diseases are associated with a positive ANA.
- **Anti-double-stranded (DS) DNA (60%) and anti-Sm (30%):** These are found only in SLE. They are extremely specific for SLE.
- **Decreased complement levels:** They can correlate with disease activity. They can **drop further with acute disease exacerbations**.
- **Anti-SSA and anti-SSB:** Found in 10% to 20% of cases. They add little to the diagnosis. These tests are most often found in Sjögren syndrome (65% of cases).

(432 team)

Patients should be screened for ANA and antibodies to extractable nuclear antigens, and have complement levels checked along with routine hematology and biochemistry. Patients with active SLE almost test positive for ANA. Anti-dsDNA antibodies are characteristic of severe active SLE.

The diagnosis of SLE is based on combination of clinical features and laboratory abnormalities.

criteria to classify patients with systemic lupus erythematosus; at least 4 of the 11 must be present or have occurred in the past.

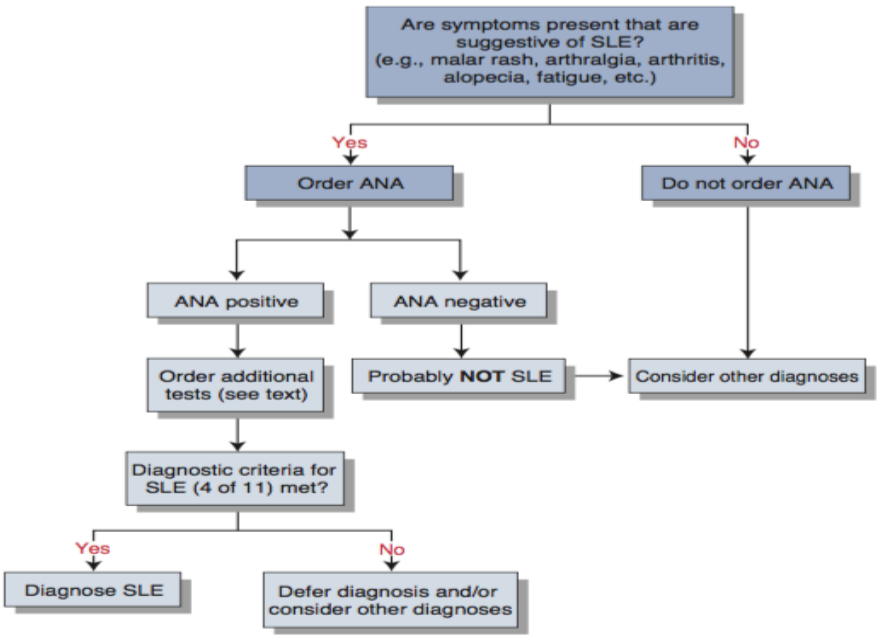
**CLINICAL PEARL 6-1**

**Useful Criteria for Diagnosing SLE**

A patient has SLE if 4 or more of these 11 criteria are present at any time.

1. Mucocutaneous signs (each counts as one)
   - Butterfly rash
   - Photosensitivity
   - Oral or nasopharyngeal ulcers
   - Discoid rash
2. Arthritis
3. Pericarditis, pleuritis
4. Hematologic disease—hemolytic anemia with reticulocytosis, leukopenia, lymphopenia, thrombocytopenia
5. Renal disease: Proteinuria >0.5 g/day, cellular casts
6. CNS—seizures, psychosis
7. Immunologic manifestations—positive LE preparation, false-positive test result for syphilis, anti-ds DNA, anti-Sm Ab
8. ANAs

FI 6-2 **Diagnosis of SLE.**



## Treatment:

- Acute lupus **flare** is treated with high-dose **boluses of steroids**.
- Hydroxy- chloroquine can control mildly chronic disease limited to skin and joint manifestations.
- Belimumab controls progression of the disease.
- Lupus nephritis may need steroids either alone or in combination with cyclophosphamide or mycophenolate. The only way to determine the severity of lupus nephritis is with a kidney biopsy. The urinalysis is insufficient to tell the severity of lupus nephritis. Biopsy is the only way to tell if there is simple **glomerulosclerosis**, or scarring of the kidney, which will not respond to therapy.

Cont. Treatment: (432):The goals of therapy for patients with systemic lupus erythematosus (SLE) are 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.

**Mild to moderate disease**: Patients with mild disease restricted to skin and joints could be managed with analgesics, NSAIDs and hydroxychloroquine. Frequently, however, corticosteroids may be necessary along with immunosuppressants.

**Life-threatening disease**:High-dose corticosteroids and immunosuppressants are required for the treatment of renal, CNS, and cardiac involvement.

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

## Prevention

- Avoid UV light and sun (sun screening).
- Antimalarial to prevent relapses.
- Treat hypertension and dyslipidemias.

## PROGNOSIS

❖ Poor prognostic factors for survival in SLE include :

- **Renal disease** (especially diffuse proliferative glomerulonephritis).
- **Hypertension**
- **renal and central nervous system (CNS) disease**
- poor compliance
- Presence of antiphospholipid antibodies
- High overall disease activity
- Male sex
- Young age

## Scleroderma(432)

- **Systemic sclerosis or scleroderma**is a generalized disorder of connective tissue affecting the skin, internal organs and vasculature.
- The peak age of onset is in the fourth or fifth decades, with a 4:1 female preponderance.
- Two distinct clinical subsets are traditionally recognized based on the extent of skin involvement:

**a.** limited cutaneous systemic sclerosis (LCSS: 70% of cases)
**b.** diffuse cutaneous systemic sclerosis (DCSS: 30% of cases).

Note:

Sclerodactyly: Localized thickening and tightness of the skin of the fingers or toes. **

Telangiectasias: are small, widened blood vessels on the skin. ***

- Patients with LCSS typically have skin involvement **distal to the elbows and knees**
- may display features of the CREST syndrome (Calcinosis cutis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia). Patients with DCSS generally have skin involvement extending to **the proximal limbs and/or trunk.**

### Classification:

- Localized: Morphea: plaque-like, linear scleroderma,'en coup de sabre' (± facial hemiatrophy)
- Generalized: diffused visceral inclocement, CREST symptoms
- Chemical induced scleroderma-like disease: vinyl chloride disease
- Diseases mimicking scleroderma: scleredema
- Eosinophilicfasciitis

**TABLE 6-4 Diffuse Versus Limited Scleroderma**

| Diffuse | Limited |
|---|---|
| Widespread skin involvement | Skin involvement limited to distal extremities (and face, neck)—sparing of the trunk |
| Rapid onset of symptoms (skin and other complications occur rapidly after onset of Raynaud's phenomenon) | Delayed onset: Skin involvement occurs slowly after the onset of Raynaud's phenomenon. Therefore, the patient has a long history or Raynaud's phenomenon before other symptoms begin |
| Significant visceral involvement (i.e., fibrosis of internal organs)—lung, heart, GI tract, kidneys | Visceral involvement occurs late—pulmonary HTN and ischemic vascular disease; minimal constitutional symptoms |
| Associated with ANAs but absence of anticentromere antibody | Anticentromere antibody is found in most patients |
| Poorer prognosis—10 year survival is 40%–65% | Better prognosis than diffuse form. Normal life span is expected in most cases, unless severe pulmonary HTN develops |
| • Peripheral edema (of hands and legs), polyarthritis, fatigue and weakness (muscle involvement), carpal tunnel syndrome<br>• Renal failure can occur, but now rare<br>• Interstitial lung disease more common | CREST syndrome is a variant<br>**C**alcinosis of the digits<br>**R**aynaud's phenomenon<br>**E**sophageal motility dysfunction<br>**S**clerodactyly of the fingers<br>**T**elangiectases (over the digits and under the nails) |

## Etiology and pathophysiology(432)

The etiology of scleroderma is unknown. The remarkable complexity of its pathogenesis suggests that no single gene or environmental trigger is, by itself, likely to be responsible for the developments of scleroderma. Genetic factors clearly influence disease susceptibility as well as patterns of disease expression

### Pathophysiology

Cytokines stimulate fibroblasts, causing an abnormal amount of collagen deposition. **It is the high quantity of collagen that causes the problems associated with this disease (composition of the collagen is normal)**.

### Cont. pathophysiology (432 team)

The pathogenesis of systemic sclerosis is complex and remains incompletely understood. Immune activation, vascular damage, and excessive synthesis of extracellular matrix with deposition of increased amounts of structurally normal collagen are all known to be important in the development of this illness. These mechanisms result from cell-cell, cell-cytokine, and cell-matrix interactions. The heterogeneity in the clinical features of patients with scleroderma is most likely a reflection of the variable contributions from each of these pathogenic factors.

Excessive collagen deposition causes skin and internal organ changes. Many factors, including environmental factors, can lead to immunologic system disturbances and vascular changes. Endothelial alterations may lead to a cascade of stimulatory changes that involve many cells, including fibroblasts, T lymphocytes, macrophages, and mast cells. In turn, the activated cells secrete a variety of substances, including cytokines and their soluble receptors and enzymes and their inhibitors. These substances lead to changes in the extracellular matrix compounds, including fibronectin; proteoglycans; and collagen types I, III, V, and VII. Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues

## clinical manifestations of scleroderma

1. **Fatigue, myalgias, and arthralgias.**
2. **Skin thickening and hardening involving the hands, fingers, and face.**3. Edematous swelling and erythema.
4. D**ifficulty in swallowing solid foods** can be followed by difficulty with swallowing liquids and subsequent nausea, vomiting, weight loss, abdominal cramps, blotting diarrhea, and fecal incontinence.
5. Cutaneous pruritus
6. **Weakness**is present in 80% of patients.
7. Palpitations may occur without characteristic pain in thoracic cavity.
8. **Raynaud phenomenon**, defined as sequential color changes in the digits precipitated by cold, stress, or even change in temperatures. Raynaud phenomenon is due to arterial vasoconstriction in the digits. 9.**Interstitial lung disease**(also called fibrosingalveolitis or pulmonary fibrosis) and pulmonary vascular disease, leading to pulmonary arterial hypertension (PAH).
10. **Microalbuminuria**, a mild elevation in the plasma creatinine concentration, and/or hypertension.

## Diagnosis:

**Progressive Systemic Sclerosis: Preliminary Diagnostic Criteria**

**Patient must have major criterion or 2 minor criteria.**

- **Major criterion:** Proximal scleroderma
- **Minor criteria:** Sclerodactyly

Digital pitting or scars or loss of substance from finger pads
Bibasilar paulmonary fibrosis

### Diagnostic Tests:

**ANA:** positive in 85% to 90%, but nonspecific

**ESR:** usually normal

**SCL-70:** the **most specific test is the SCL-70** (anti-topoisomerase), but present in only 30% of those with diffuse disease and 20% of those with limited disease

**Anticentromere:** present in half of those with CREST syndrome

**Anticentromere:** antibodies are extremely specific for CREST syndrome.

## Treatment

**Methotrexate**slows the underlying disease process of limited scleroderma. **Penicillamine is not effective**.

**Renal crisis:** ACE inhibitors (use even if the creatinine is elevated) **Esophageal dysmotility:** PPIs for GERD

**Raynaud:** calcium channel blockers and avoidance of cold exposure

**Pulmonary fibrosis: Cyclophosphamide** improves dyspnea and PFTs.

Pulmonary hypertension:

· Bosentanambrisentan(endothelinantagonist)

· Sildenafil

· Prostacyclinanalogs:iloprost,treprostinil,epoprostenol

## Prognosis(432)

Survival in patients with diffuse cutaneous disease has improved significantly; currently, the 5-year survival is estimated to be about 80%. Five-year survival in patients with limited cutaneous disease is approximately 90%.

Factors associated with a more severe prognosis are as follows: • Younger age
- African descent
- Rapid progression of skin symptoms

- Greater extent of skin involvement
- Anemia
- Elevated erythrocyte sedimentation rate (ESR)

- Pulmonary, renal, and cardiac involvement

Note :Major cause of death in scleroderma is hypertensive crisis of scleroderma.
- There is thinning of the epidermis and thickening of the dermis

## Mixed Connective tissue Disease

• Mixed connective tissue disease is an "overlap" syndrome with clinical features similar to those of SLE, RA, systemic sclerosis, and polymyositis. Findings con- sistent with each of these diseases do not necessarily occur simultaneously. It usually takes some time for a pattern to be identified and a diagnosis of mixed connective tissue disease to be made.

• Clinical findings include pulmonary involvement, esophageal dysfunction, poly- arthritis, sclerodactyly, cutaneous manifestations, myopathy, and Raynaud's phe- nomenon.

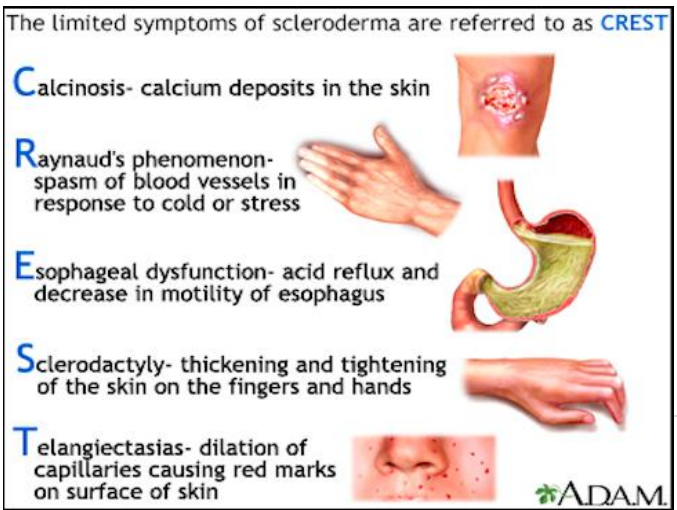
• The presence of anti-U1-RNP Abs is a key laboratory finding. High ANA and RF may be present.

• Treatment varies according to which specific disease predominates

Other signs:

- Polyarthritis

- sclerodactyly
- Abnormal esophageal motility
- Myositis
- Low incidence of lupus nephritis
- Hyperglobulinemia

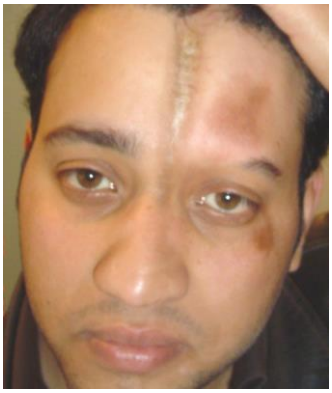



- Positive ANA (often speckled pattern)
- Antibody to nRNP

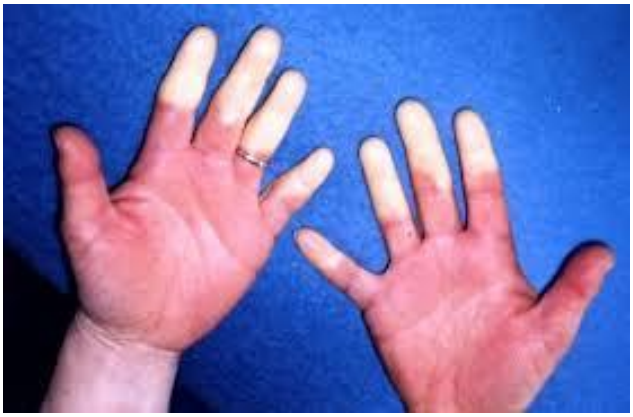
CREST

Telangiectasis is dilation of vessels and it is a feature of CREST syndrome

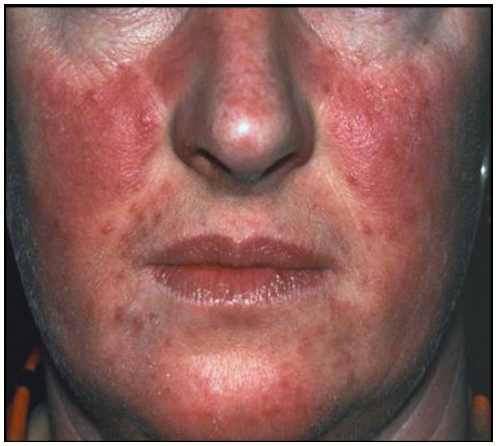
en coup de sabre



Raynaud's phenomenon



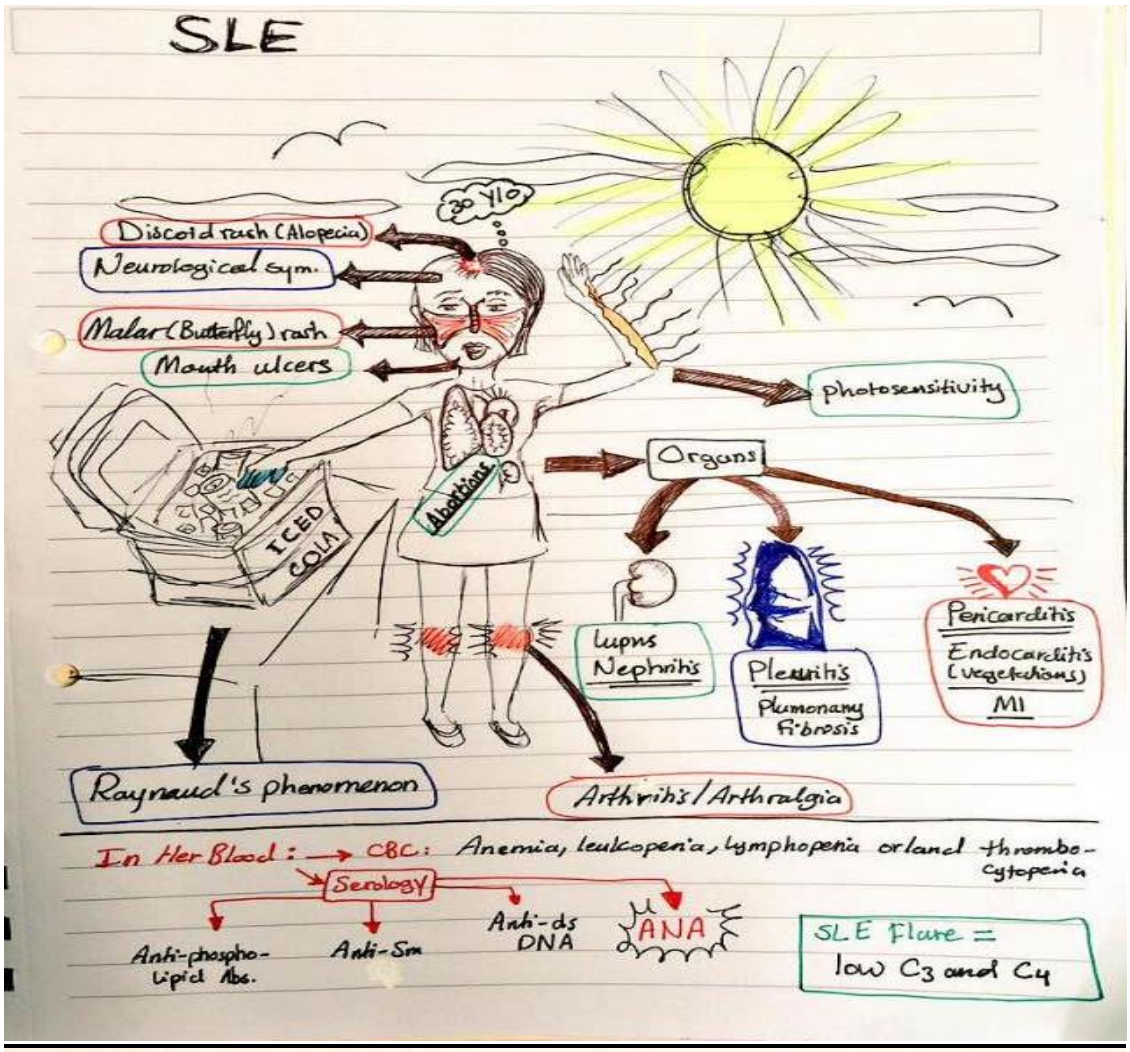
Malar rash (butterfly)

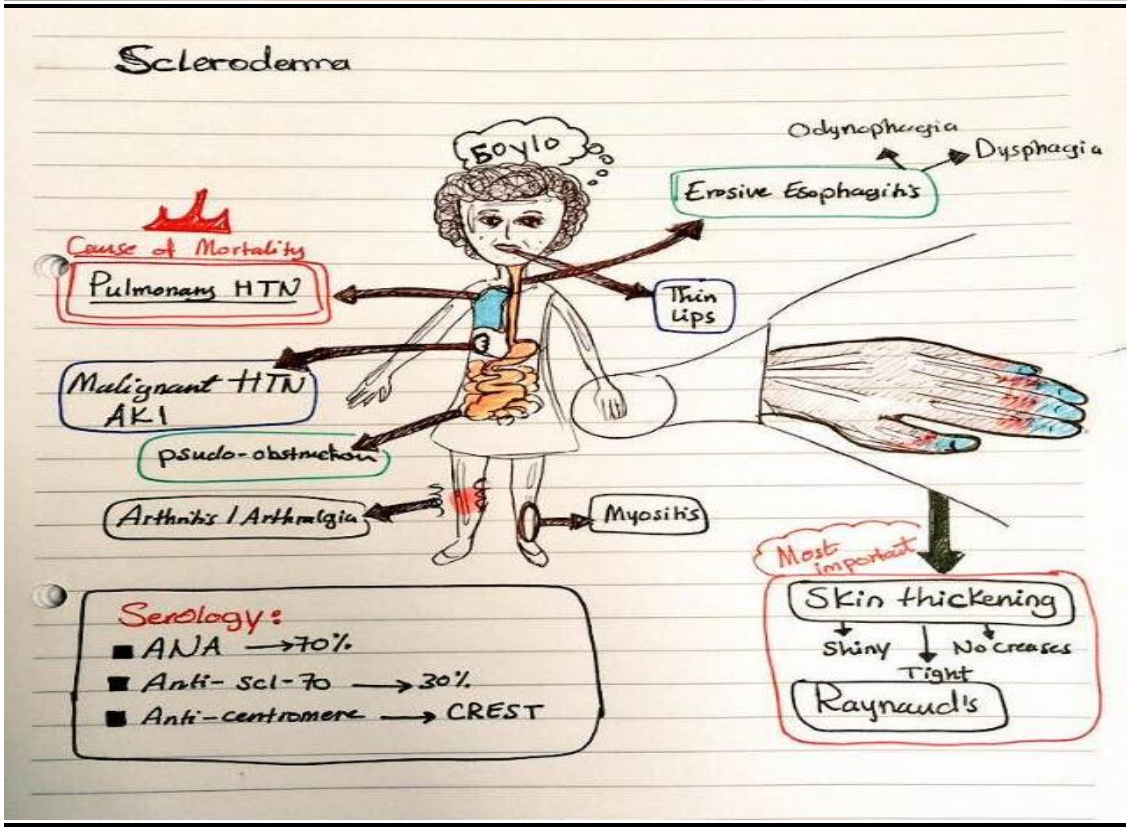


alopecia


- Nowadays the major leading cause of death in SLE is athermanous vascular disease.
- The major leading cause of death in scleroderma is pulmonary and cardiovascular complication (arrhythmias)
- Raynaud phenomenon is one of the most important sign of scleroderma.
- Linear scleroderma takes with it skin, muscle and bone, so if it happen in face it will lead to face asymmetry

## Summary


SLE
30 y/o
Discoid rash (Alopecia)
Neurological sym.
Malar (Butterfly) rash
Mouth ulcers
photosensitivity
Organs
Abortions
ICED COLA
Lupus Nephritis
Pleuritis
Pulmonary Fibrosis
Pericarditis
Endocarditis (vegetations)
MI
Raynaud's phenomenon
Arthritis / Arthralgia
In Her Blood: → CBC: Anemia, leukopenia, lymphopenia or/and thrombocytopenia
Serology
Anti-phospholipid Abs.
Anti-Sm
Anti-ds DNA
ANA
SLE Flare = low C3 and C4


Scleroderma
Boy/o
Odynophagia
Dysphagia
Erosive Esophagitis
Cause of Mortality
Pulmonary HTN
Thin Lips
Malignant HTN
AKI
psudo-obstruction
Arthritis / Arthralgia
Myositis
Most important
Skin thickening
Shiny
No creases
Tight
Raynaud's
Serology:
ANA → 70%
Anti-scl-70 → 30%
Anti-centromere → CREST

# MCQs

1. A 26 yr old Afro Caribbean married teacher with SLE presents with one week history of worsening joint symptoms, mouth ulcers, fatigue, and pleurisy. Laboratory investigations indicate active SLE, with worsening renal function, anemia, leucopenia, raised anti double stranded DNA, and low complement levels. A decision is made to treat with rituximab.

   Which of the following vaccination should be prioritized prior to treatment with rituximab?

   a) Tetanus vaccine
   b) Pneumococcal vaccine
   c) Diphtheria vaccine
   d) BCG vaccine
   e) Hepatitis B vaccine

2. All the following are features of scleroderma expect

   A. Dysphagia
   B. Raynaud's phenomenon
   C. Skin contracture
   D. Calcification in all long bones

3. A 14 year old girl on exposure to cold has pallor of extremities followed by pain and cynosis. In later stages of life she is most prone to develop

   A. SLE
   B. Scleroderma
   C. Rheumatoid arthritis
   D. Dermatomycosis

4. A 29 year old female patient diagnosed with TB have been treated with isoniazid, rifampicin and pyrazinamide since three months ago. Last week she started having joint pain on her hand, fever and swollen red circular lesions on the face. What do you think is the appropriate next step that the physician should take?

   a) Stop isoniazid
   b) Add streptomycin to treat aggressive TB
   c) Do an x-ray of the joints
   d) Order a ANA blood test

ANSWERS: 1.B - 2.D - 3.B - 4.A

5. What do you expect to be most likely present in the urine of a SLE patient?

a) Red blood cells casts
b) High glucose
c) Proteinuria
d) Hyaline casts

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

a) Calcinosis
b) Raynaud's phenomenon
c) Rheumatic fever
d) Oesophagealdysmotility
e) Telangiectasia

7. You see a 53 year old man in a follow up rheumatology clinic. He has limited cutaneous systemic sclerosis diagnosed 12 years ago. You notice elevated blood pressure, and are concerned regarding the possibility of scleroderma renal crisis.

Which one of the following is a risk factor for scleroderma renal crisis?

a) Early limited cutaneous systemic sclerosis
b) Female gender
c) Corticosteroid therapy
d) Presence of anti-GBM antibodies
e) Slowly progressive skin involvement
f) Corticosteroid therapy

8. 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?

a) Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies
b) Anti-endomysial antibodies
c) Anti-Ro/SSA antibodies
d) Anti-SCL70 antibodies
e) Rheumatoid factor

9. A 69-year-old woman taking hydralazine for hypertension presents with joint pain and chest pain. On cardiac examination, the patient has a pericardial rub. What is the diagnosis?

a) Dermatomyositis
b) Drug induced lupus erythematosus
c) Polymyalgia rheumatic
d) Felty syndrome

Answers: - 5.A - 6.C - 7.C - 8.C - 9.B -

10. A 28 year old previously healthy lady presents to the rheumatology clinic with a 6 month history of Raynaud's phenomenon and progressive shortness of breath. She has developed a few digital ulcers. Her hands are puffy and the skin feels tight. She denies sicca symptoms.

On examination she has puffy hands with nail fold vasculopathy, fine bibasal crackles, loud second heart sound, and a pansystolic murmur. She had 4/5 proximal weakness of her upper and lower limbs. She is ANA, RNP positive. FBC, UE and LFTs are normal. Her CRP is elevated at 17 mg/l. Her CK is 600 iu/l. Chest X-ray reveals interstitial changes.

Which of the following is the most likely diagnosis?

a) Dermatomyositis
b) Diffuse cutaneous systemic sclerosis.
c) Mixed connective tissue disease
d) Sjogren's syndrome
e) SLE

Answer: - 10.C -

Explanation for Q.7:

An estimated 65-86% of scleroderma renal crisis (SRC) occurs in patients with diffuse SSc, and patients with early dcSSc are at greatest risk. Rapidly progressive skin disease (found in the early phase of dcSSc) represents another risk factor; the estimated median duration of SSc at SRC diagnosis is 8 months.An estimated 66% of patients with SSc develop SRC within a year of diagnosis, rising to 86% at 4 years.Patients with limited SSc typically develop SRC later in SSc disease course, and sex appears not to influence the risk. Corticosteroid therapy increases the risk of SRC.

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