MEDICINE

432 Team

59 SLE and Scleroderma

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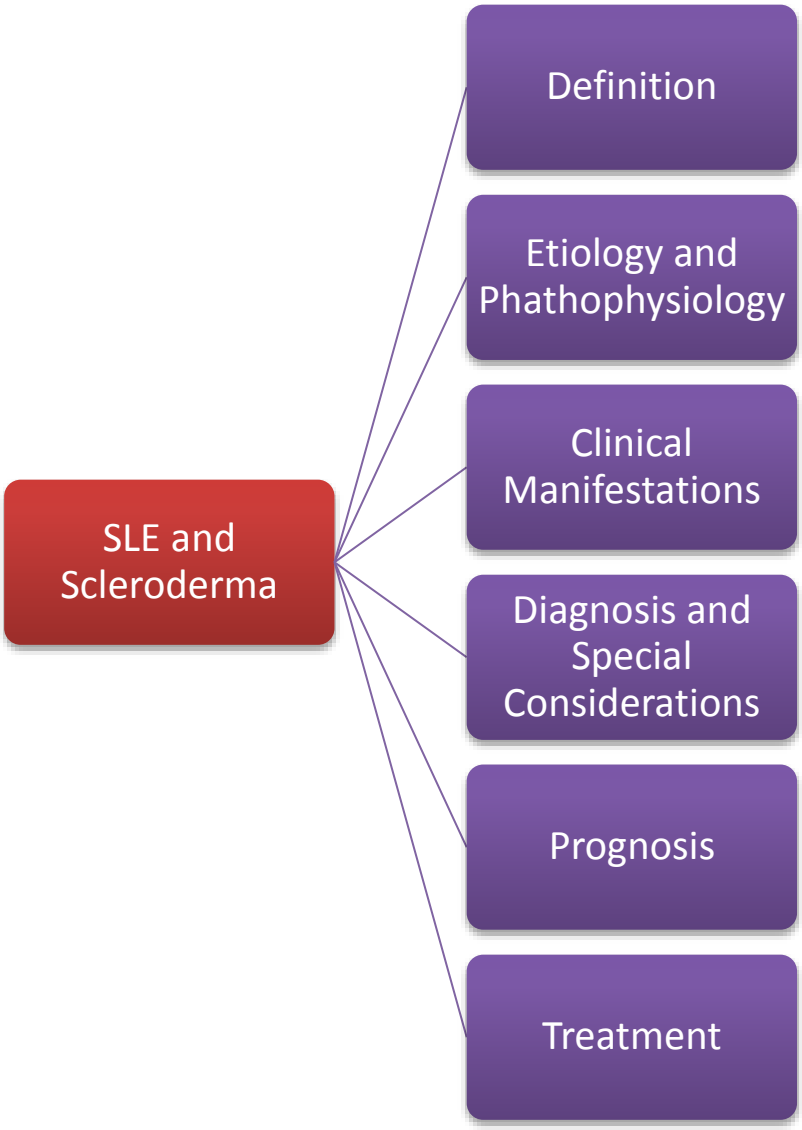
COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives


SLE and Scleroderma
Definition
Etiology and Phathophysiology
Clinical Manifestations
Diagnosis and Special Considerations
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Treatment

SLE Definition

Systemic lupus erythematosus "SLE" is a chronic, multisystem inflammatory disease characterized by **autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation** resulting in damage to the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body [1].

Etiology and Pathophysiology of SLE

Etiology: no specific symptoms are known, but multiple factors might be associated like: **genetic, hormonal, racial & environmental factors.**

> ***Note(s):***
>
> *SLE might be induced by viral infections or environmental factors.*

- **Genetic:**

Multitude of genetic associations suggests a **complex genetic predisposition.** If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250. **HLA-DR2** and **HLA-DR3** and other HLA genes occur more often in SLE than in the general population. SLE has a modest recurrence rate in families: 8% of affected patients have at least one first-degree family member (parents, siblings, and children) with SLE; this is in contrast to 0.08% of the general population. In addition, SLE occurs in both twins in **24% of identical twins** and 2% of nonidentical twins, which may be due to a combination of **genetic and environmental factors [2].**

- **Hormonal factors:**
  - The use of **estrogen-containing contraceptive agents** is associated with a **50% increase in risk of developing SLE.**
  - **Early menarche & postmenopausal estrogen administration doubles the risk.**

- Altered sex hormone levels may predispose to the development of SLE or result from the autoimmune process.
- **Breastfeeding** may decrease risk of developing SLE [3].

- There is higher prevalence in men with Klinefelter disease.

- Age:
  - 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. Female: Male ratio of prevalence in different age groups: in children the ratio is 3:1, an adults is 10-15:1, and in older is 8:1

  - Age at onset: 65% have onset between 16 and 55, 20% before age 16, and 15% after age 55.

- **Environmental factors [3]:**
  - **Viruses** may stimulate specific cells in the immune network. Patients with SLE also have **higher titers of antibodies to Epstein-Barr virus (EBV)**, have increased circulating EBV viral loads, and make antibodies to retroviruses, including to protein regions homologous to nuclear antigens.
  - **Ultraviolet light**
  - **Silica dust**, found in cleaning powders, soil, pottery materials, cement, and cigarette smoke may increase the risk of developing SLE, especially in African American women.

Pathophysiology [2][4]:

- **Autoantibody production** against cell surface, cytoplasm & nuclei and plasma proteins.
- May occur because of defects in apoptosis or in the clearance of apoptotic cells.
- High CD4:CD8 ratio.

- **Immune complex formation** causes tissue damage, leading to vasculitis and organ damage.
- **Serum antinuclear antibodies (ANAs) are found in nearly all individuals with active SLE.**
- Antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE.

Note(s):

SLE may occur because of defects in apoptosis or in the clearance of apoptotic cells, which causes inappropriate exposure of intracellular antigens on the cell surface, leading to polyclonal B- and T- cell activation and autoantibody production.

Clinical Manifestations of SLE

1. **Butterfly "malar" rash:** erythromatous, raised and painful or itchy, occur over the cheeks with sparing of nasolabial folds (4). "Leaves marks if treated late"
2. **Discoid rash:** erythromatous raised patches with adherent keratotic scaling and follicular plugging.
3. Photosensitivity
4. Oral ulcers
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 (4).
8. **Arthralgia:** common symptom associated with morning stiffness (4).
9. **Raynaud phenomenon:** Cold- or emotion-induced color changes of the digits of the hands and/or feet (the Raynaud phenomenon) are frequent problems and may antedate other features of the disease (1).
10. **Keratoconjunctivitis (1)**

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%

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

Diagnosis of SLE

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

Investigations:

The diagnosis of SLE is based on combination of clinical features and laboratory abnormalities [(4)]. The American College of Rheumatology has created criteria to classify patients with systemic lupus erythematosus; at least 4 of the 11 must be present or have occurred in the past [(4)(5)].

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion **OR**
	Pericarditis - documented by EKG, rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed **OR**
	Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures **OR** psychosis - in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia - with reticulocytosis **OR**
	Leukopenia - less than 4000/mm^3 total on two or more occasions **OR**
	Lymphopenia - less than 1500/mm^3 on two or more occasions **OR**
	Thrombocytopenia - less than 100,000/mm^3 in the absence of offending drugs
Immunologic disorders	Positive antiphospholipid antibody **OR**
	Anti-DNA - antibody to native DNA in abnormal titer **OR**
	Anti-Sm - presence of antibody to Sm nuclear antigen **OR**
	False-positive serologic test for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
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

http://www.uptodate.com/contents/image?imageKey=PI%2F71430&topicKey=EM%2F295&source=see_link&utdPopup=true

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 [(4)].**

Prognosis:

Poor prognostic factors for survival in SLE include:

1. **Renal and CNS disease**
2. Hypertension
3. Poor education
4. Black race
5. **Presence of antiphospholipid antibodies**
6. High overall disease activity
7. **Male sex**
8. **Young age**

Treatment of SLE (4)(6)

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 exposure.
- ✓ Antimalarial to prevent relapses.
- ✓ Treatment of comorbidities like hypertension and dyslipidemia.
- ✓ Proper education.

Progressive systemic sclerosis diagnostic criteria:

A major or two minor criteria
Major: Proximal scleroderma
Minor: bibasilar pulmonary fibrosis, sclerodactyly or digital pitting/scars/loss of substance from finger pads

Note(s):

Sclerodactyly: *Localized thickening and tightness of the skin of the fingers or toes. ***
Telangiectasias*: are small, widened blood vessels on the skin. ****

Scleroderma

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 [(4)]. Two distinct clinical subsets are traditionally recognized based on **the extent of skin involvement: limited cutaneous systemic sclerosis (LCSS: 70% of cases)** and **diffuse cutaneous systemic sclerosis (DCSS: 30% of cases).** Patients with LCSS typically have skin involvement **distal to the elbows and knees,** and may display features of the **CREST syndrome** (**C**alcinosis cutis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia). Patients with DCSS generally have skin involvement extending to **the proximal limbs and/or trunk [(4)(7)].**

Classification:

- **Localized:** Morphea: plaque-like, linear scleroderma
- **Generalized:** diffused visceral inclocement, CREST symptoms

- **Chemical induced scleroderma-like disease:** vinyl chloride disease
- **Diseases mimicking scleroderma:** scleredema
- **Eosinophilic fasciitis**

Etiology and Pathophysiology of Scleroderma

Etiology:

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 [8].

Pathophysiology: (I will write two similar paragraphs from different sources)

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 [9].

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 deposition in tissues is a characteristic feature of systemic sclerosis.** Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues [10].

Clinical manifestations of Scleroderma (10)(11)

1. **Fatigue, myalgias, and arthralgias.**
2. **Skin thickening and hardening involving the hands, fingers, and face.**
3. Edematous swelling and erythema.
4. **Difficulty 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 fibrosing alveolitis 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 of Scleroderma (4)

Scleroderma is primarily a **clinical diagnosis** but various laboratory abnormalities are characteristics.

1. **Elevated level of ESR with raised levels of IgG.**
2. CRP levels are normal.
3. **ANA is positive in about 70%, and approximately 30% of patients with DCSS have antibodies to topoisomerase 1.**
4. 60% of patient with CREST syndrome have anticentromere antibodies.

Prognosis (12):

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(s):

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

Treatment of Scleroderma [4]

No treatments are available that halt or reverse the fibrotic changes that underline the disease. The focus of management, therefore, is to ameliorate the effects of the disease on target organs.

1. **Raynaud's syndrome and digital ulcers:** treated by **avoidance of cold exposure** and supplemented if necessary with **calcium antagonists.**
2. **Esophageal reflux:** should be treated with proton pump inhibitors and anti-reflux agents. Antibiotics may be required for bacterial overgrowth.
3. **Hypertension:** should be treated aggressively with ACE inhibitors, even if renal impairment is present.
4. **Joint involvement:** may be treated with analgesics and/or NSAID. If synovitis is present, immunosuppressants such as Methotrexate can also be of value.
5. **Pulmonary hypertension:** may be treated with Bosentan.

Mixed connective tissue disease [4]:

Mixed connective tissue disease (MCTD) is a condition in which the clinical **features of SLE, systemic sclerosis and myositis may all occur in the same patient.** It most commonly presents with **synovitis and edema of the hands, in combination with Raynaud's phenomenon and muscle pain or weakness. Other signs:**

- Polyarthritis
- sclerodactyly
- Abnormal esophageal motility
- Myositis
- Low incidence of lupus nephritis
- Hyperglobulinemia
- Positive ANA (often speckled pattern)
- Antibody to nRNP

SUMMARY

1. SLE is an autoimmune multisystem chronic inflammatory disease
2. HLA-DR2 & HLA-DR3 genes and EBV have been associated with SLE
3. Tissue damage is a result of immune complex formation
4. Clinical manifestations:
    a. Butterfly rash, Discoid rash, photosensitivity, ulcers, arthritis, fever, weight loss, Raynaud phenomenon & keratoconjunctivitis
5. 4/11 criteria must be met to clinically diagnose SLE
6. Treatment depends on the severity of symptoms:
    a. Mild-moderate: NSAIDS & hydroxychloroquine
    b. Life threatening: high dose corticosteroids
    c. Maintenance: oral immunosuppressant
7. Scleroderma: generalized connective tissue disorder
8. Pathophysiology: Immune activation, vascular damage, and excessive synthesis of extracellular matrix with deposition of increased amounts of structurally normal collagen
9. Important Clinical manifestations:
    a. Skin thickening in the fingers, hands and face
    b. Raynaud phenomenon
    c. Interstitial lung disease
    d. Myalgia and arthralgia
    e. CREST symptoms
10. Managemed by treating the symptoms
11. Mixed connective tissue disease: features of SLE, systemic sclerosis and myositis may all occur in the same patient. It most commonly presents with synovitis and edema of the hands, in combination with Raynaud's phenomenon and muscle pain or weakness

IMPORTANT NOTES FROM EXTERNAL RESOURCES

	Notes
(1)	http://www.uptodate.com/contents/overview-of-the-clinical-manifestations-of-systemic-lupus-erythematosus-in-adults
(2)	http://emedicine.medscape.com/article/332244-overview#aw2aab6b2b4
(3)	http://www.uptodate.com/contents/epidemiology-and-pathogenesis-of-systemic-lupus-erythematosus#H6
(4)	Davidson's Principles and Practice of Medicine, 22nd Edition, Rheumatology and Bone Disease Chapter
(5)	http://www.uptodate.com/contents/systemic-lupus-erythematosus-sle-beyond-the-basics#H17
(6)	http://www.uptodate.com/contents/overview-of-the-management-and-prognosis-of-systemic-lupus-erythematosus-in-adults#H925551
(7)	http://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-systemic-sclerosis-scleroderma-in-adults
(8)	http://www.uptodate.com/contents/risk-factors-for-and-possible-causes-of-systemic-sclerosis-scleroderma
(9)	http://www.uptodate.com/contents/pathogenesis-of-systemic-sclerosis-scleroderma
(10)	http://emedicine.medscape.com/article/1066280-overview#a0104
(11)	http://www.uptodate.com/contents/overview-of-the-clinical-manifestations-of-systemic-sclerosis-scleroderma-in-adults#H2
(12)	http://emedicine.medscape.com/article/331864-overview#aw2aab6b2b5
**	http://www.medicinenet.com/script/main/art.asp?articlekey=13572
***	http://www.nlm.nih.gov/medlineplus/ency/article/003284.htm

Questions

1) Which one of the following genes are affected in SLE?
   a. HLA-DR3
   b. HLA-DR4
   c. HLA-DR5
   d. HLA-DR2

2) Which of the following drugs is associated with SLE development?
   a. Phenylbutazone
   b. Alluprinolol
   c. Quinidine
   d. Tetracyclines

432 Medicine Team Leaders

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Answers:

1st Questions: a&d

2nd Questions: c