SLE,SCLERODERMAM CTD

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Systemic lupus erythematosus (SLE)

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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.

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.
- In 1959, anti-DNA.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid 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	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing 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 greater than 0.5 grams per day or grater 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	**a) Hemolytic anemia--with reticulocytosis** ***OR*** **b) Leukopenia--less than 4,000/mm<>3<> total on 2 or more occasions** ***OR*** **c) Lyphopenia--less than 1,500/mm<>3<> on 2 or more occasions** ***OR*** **d) Thrombocytopenia--less than 100,000/mm<>3<> in the absence of offending drugs**
10. Immunologic disorder	**a) "Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a 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** **b) Anti-DNA: antibody to native DNA in abnormal titer** ***OR*** **c) Anti-Sm: presence of antibody to Sm nuclear antigen** ***OR*** **d) 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**
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**

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.

AETIOLOGY:

- Specific cause(s) of SLE is unknown.
- multiple factors are associated include :
  - Genetic
  - Hormonal
  - Racial
  - Environmental factors

• AETIOLOGY(cont.):

– **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.

AETIOLOGY(cont.):

- Hormonal factors:
  - 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.
  - Exogenous estrogen and exacerbations of SLE.
  - 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.

Sle in saudi arabia kkuh.

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sex	number	percent
male	58	9.3
female	566	90.7
total	624	100

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 .

AETIOLOGY(cont.):

- 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.
    - alfa alfa sprouts.

Pathophysiology:

- 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).
  - Cell-mediated autoimmunity also play part.
  - Tissue damage follows

ORGAN INVOLVEMENT IN SLE

Joints		90%
Skin		
-Rashes	70%	
-Discoid lesions		30%
-Alopecia		40%
Pleuropericardium		60%
Kidney		50%
Raynaud's	20%	
Mucous membranes		15%
CNS (psychosis/convulsions)	15%	

SLE – Presenting and Prevalent Symptoms

ARA Criteria [n = 624] SAUDI ARABIA

ARA Criteria	+ve at presentation n(%)	+ve on * followup 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)
Photo sensitivity	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)	0	622 (99.7)

* In addition to those +ve at presentation

Other presenting symptoms (n = 624).

Fever	(30.6)
Weight loss	(23.1)
Fatigue	(42.5)
Arthralgia	(86.9)
Raynaud's phenomenon	(8.7)
Alopecia	(47.6)
Lymphadenopathy	(20.0)
DVT	(7.4)
Ascites	(8.9)
Hepatomegaly	(3.2)
Splenomegaly	(2.6)
Hepatosplenomegaly	(6.1)
Genital ulcers	(1.4)
HTN	(28.4)
Myalogia	(6.6)
Pancytopenia	(12.2)
Pleuritis	(15.8)
Pericarditis	(20.7)
Pulmonary symptoms	(28.0)
Gastrointestinal symptoms	(38.6)

Primary Central Nervous System Lupus: Neurologic Signs or Symptoms

Meninges

Headache

Meningismus

Cerebrum

Dementia

Strokes

Subarachnoid hemorrhage

Migraine

Other headaches

Seizures

Chorea

Rigidity, tremor

SIADH

Cerebellum

Ataxia

Spine

Paraparesis

Multiple sclerosis-like disorder

Cranial and peripheral nerves

Cranial and peripheral sensory,motor neuropathies

Mononeuritis multiplex

Myasthenia gravis

Guillain-Barre syndrome

Special considerations:

- **Drug-induced lupus**
  (consider before diagnosing native lupus)
  - Sex ratios are nearly equal.
  - Nephritis and CNS not common.
  - No anti- native DNA or hypocomplementemia.
  - resolution on discontinuation of drug.

Drugs associated with lupus erythematosus

- **Definite association**
  - Chlorpromazine
  - Methyldopa
  - Hydralazine
  - Procainamide
  - Isoniazid
  - Quinidine

- **Unlikely Association:**
  - Allopurinol,
  - Penicillin, Chlorthalidone, Phenylbutazone, Gold salts, Reserpine,Griseofulvin,Streptomycin,Methysergide,Tetracyclines,Oral contraceptives

- **Possible Association**
  - **Betablockers**
  - **Methimazole**
  - **Captopril**
  - **Nitrofurantoin**
  - **Carbamazepine**
  - **Penicillamine**
  - **Cimetidine**
  - **Phenytoin**
  - **Ethosuximide**
  - **Propylthiouracil**
  - **Hydrazines**
  - **Sulfasalazine**
  - **Levodopa**
  - **Sulfonamides**
  - **Lithium**
  - **Trimethadione**

TREATMENT (cont.):

- **GENERAL CONSIDERATIONS :**
  - **Prevention:**
    - Avoid uv light and sun (sunsceening).
    - Antimalarial to prevent relapses.
    - Treat hypertension and dyslipidemias .
  - Treat depending on the organ system(s) involved:
    - Skin, musculoskeletal, and serositis.
      - NSAIDs,HCC,local cs.
    - More serious organ involvement(CNS,renal)

⊙ Immunosuppression with high-dose steroids,AZA and/or cyclophosphamide,mycophenolate , Tacrolimus

– Targeted therapy(biological) ,rituximab

- Other treatments
  - plasma exchange for TTP or diffuse alveolar hemorrhage
  - and intravenous immunoglobulin for severe steroid-nonresponsive thrombocytopenia.

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

SCLERODERMA

CLASSIFICATION OF SCLERODERMA

1. Localized:
   Morphea: plaque like, guttate, generalized linear scleroderma
   Scleroderma 'en coup de sabre' (± facial hemiatrophy)
2. Generalized:
   With diffuse visceral involvement
   CREST syndrome
   Overlap with other connective tissue disease.
3. Chemical-induced scleroderma-like conditions
   e.g: vinyl chloride disease
4. Diseases with skin changes mimicking scleroderma
   e.g.: scleredema
5. Eosinophilic fasciitis

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

SYSTEMIC MANIFESTATIONS OF SCLERO-DERMA

Pulmonary

Dyspnea
Cough
Hemoptysis
Pleuritic pain
Clubbing of nails

Gastrointestinal

Dysphagia
Dyspepsia
Constipation
Diarrhea
Malabsorption

Renal

Proteinuria
Azotemia
Hypertension
Renal failure

Musculoskeletal

Polyarthralgia
Swelling of joints
Contractures

Cardiovascular

Arrhythmias
Myocardial failure

Raynaud's Phenomenon: Classification and Causes (continued)

Secondary Raynaud's phenomenon

Connective tissue diseases
- Systemic sclerosis, CREST
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Rheumatoid arthritis
- Dermatomyositis/polymyositis

Miscellaneous
- Reflex sympathetic dystrophy
- Hypothyroidism
- Pheochromocytoma
- Neoplasm
- Primary pulmonary hypertension
- Variant angina

MIXED CONNECTIVE TISSUE DISEASE

(MCTD)

CLINICAL AND LABORATORY FEATURES OF MCTD

- Polyarthritis
- Raynaud's phenomenon
- Swollen hands or sclerodactyly
- Abnormal esophageal motility
- Myositis
- Low incidence of lupus nephritis
- Hyperglobulinemia
- Positive ANA (often speckled pattern)
- Antibody to nRNP

Criteria for the Diagnosis of MCTD

Positive Criterion	Algorithm of	
	Alarcon-Segovia and Villareal	Kahn and Appelboom
Serological test	Anti-(U1-RNP) titer ≥ 1:1600	Anti-(U1-RNP) titer ≥ 1:1200 in a patient with an ANA titer ≥ 1:2560 and a speckled ANA pattern
Clinical features	≥3; one of which must be synovitis or myositis, with others	≥3; one of which must be Raynaud's phenomenon, with others
	To include: •Swollen hands •Raynaud's phenomenon •Acrosclerosis	To include: •Swollen fingers •Synovitis •Myositis

Antibodies Associated with Rheumatic Diseases: Percentages of Patients Affected

Antibodies to…..	Percentages of patients
Native DNA	SLE: 50% - 60%
Sm antigen	SLE: 30%
Histones	Drug-induced SLE: 95% SLE: ≤ 60% Rheumatoid arthritis: 20%
SS-A	Sjogren's syndrome: 70% SLE: 30% - 40% Scleroderma and mixed connective tissue disease: frequency and titers low
SS-B	Sjogren's syndrome: 60% SLE: 15%

Antibodies Associated with Rheumatic Diseases: (continued)

Antibodies to…	Percentages of patients
RNP	Mixed connective tissue disease: 95% - 100% SLE: 30% at low titers Scleroderma: 10% - 20%
Scl-70	Scleroderma: 10% - 20%
Nucleolar antigens	Scleroderma: 40% - 50%
Centromere antigens	CREST: 80% - 90%
PM-1	Polymyositis: 50% Dermatomyositis: 10%