SLE

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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

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.

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**

- SLICC PI: DR. MICHELLE PETRI
- SLICC classification criteria for Systemic Lupus Erythematosus
- New Investigator: Dr. Ana-Maria Orbai Funding Source: National Institutes of Health
- View Bio

- 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 portioning 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.

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

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.

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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

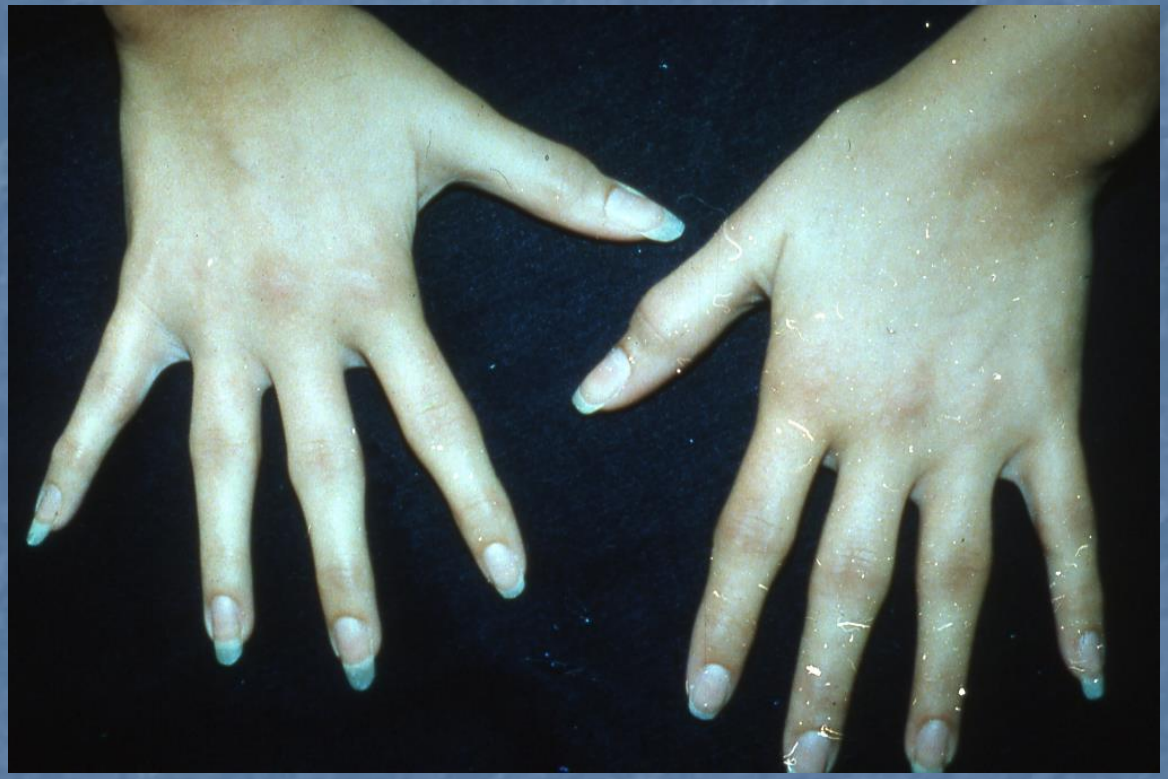
Cranial and peripheral nerves

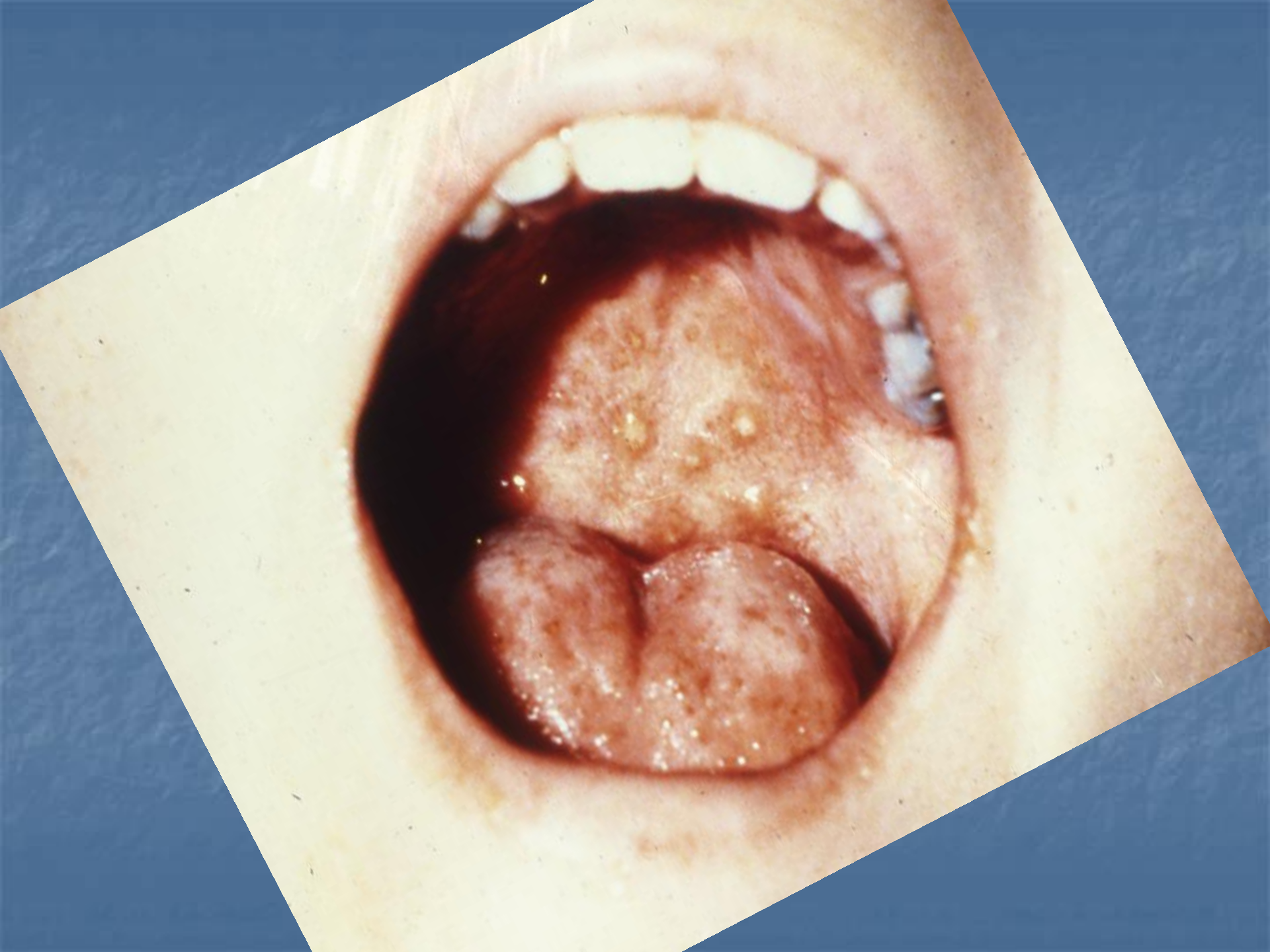
Cranial and peripheral sensory,motor neuropathies

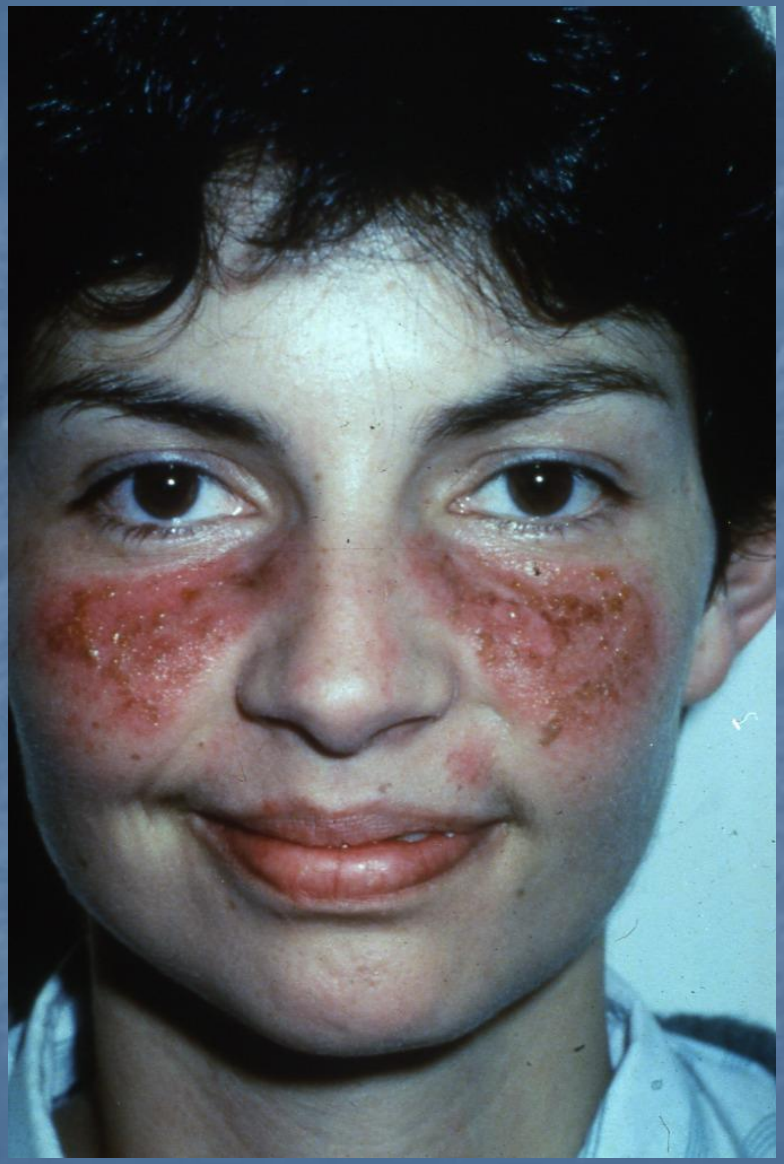
Mononeuritis multiplex

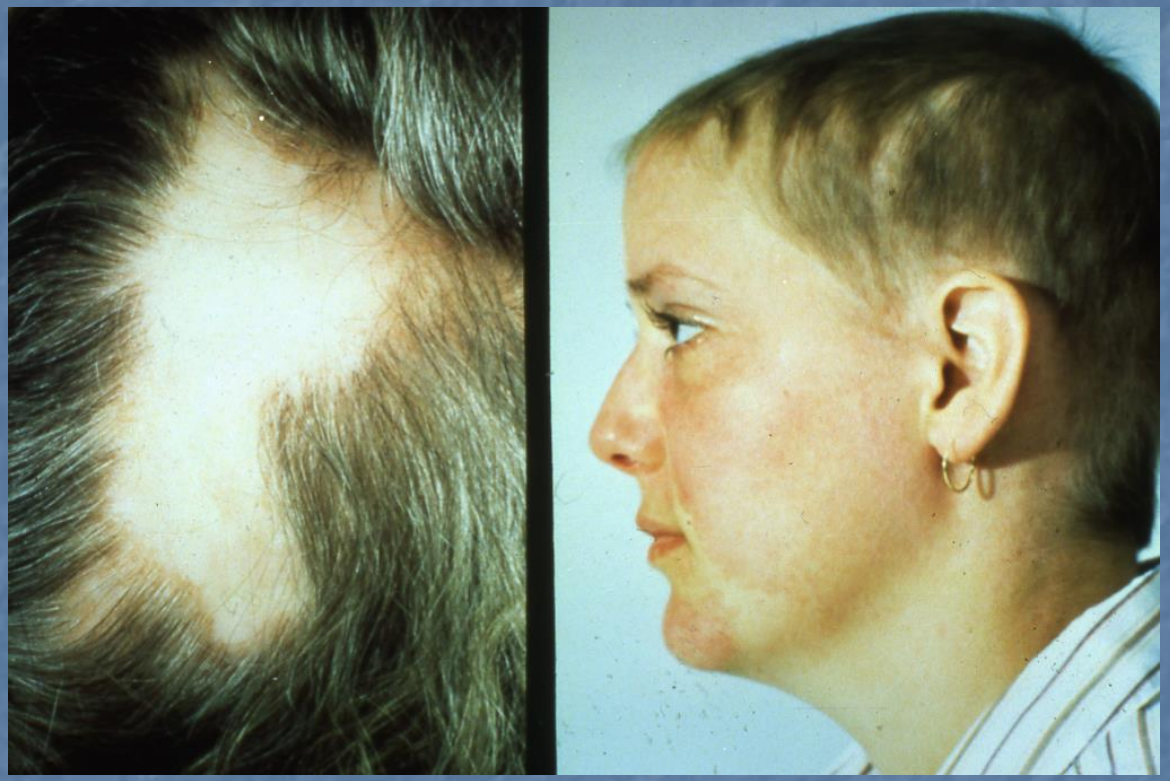
Myasthenia gravis

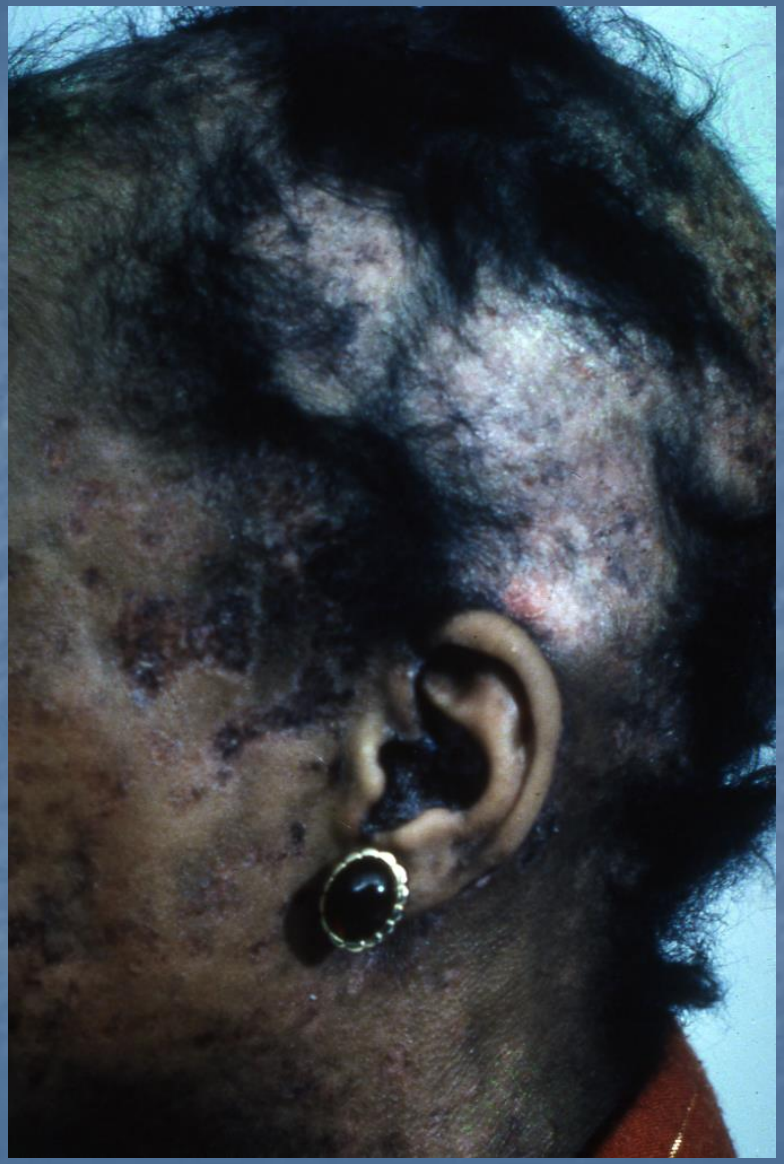
Guillain-Barre syndrome

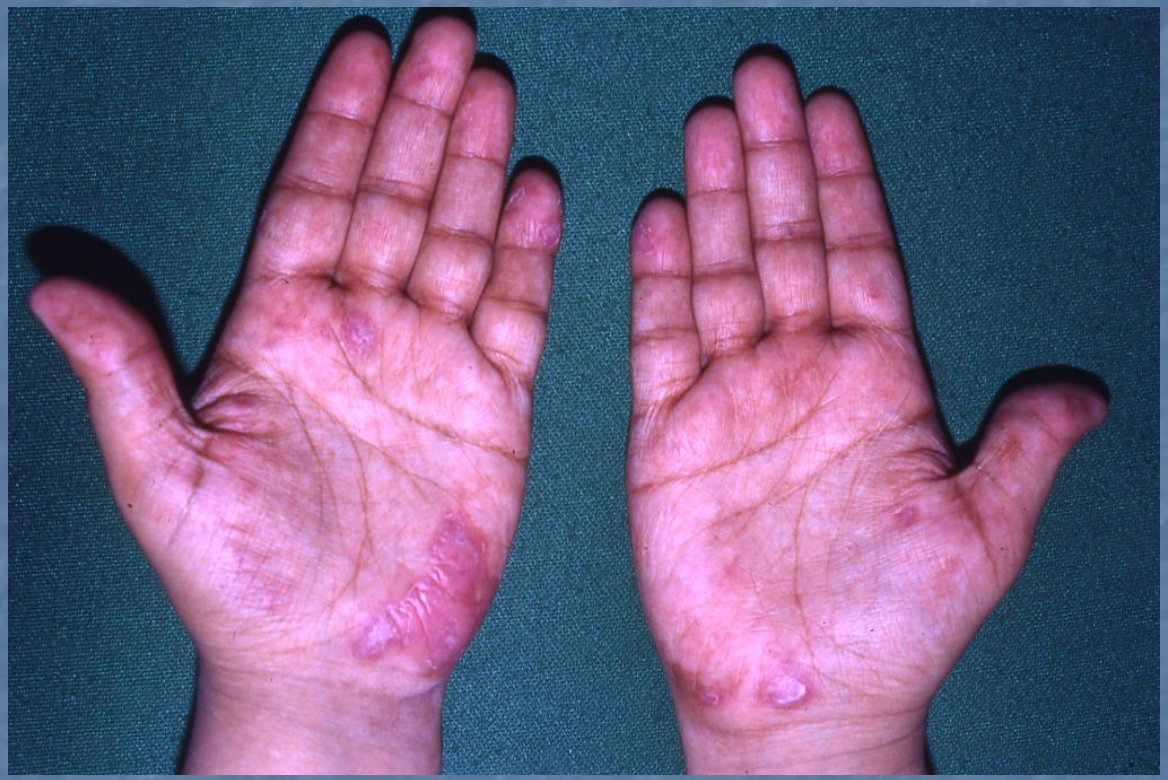


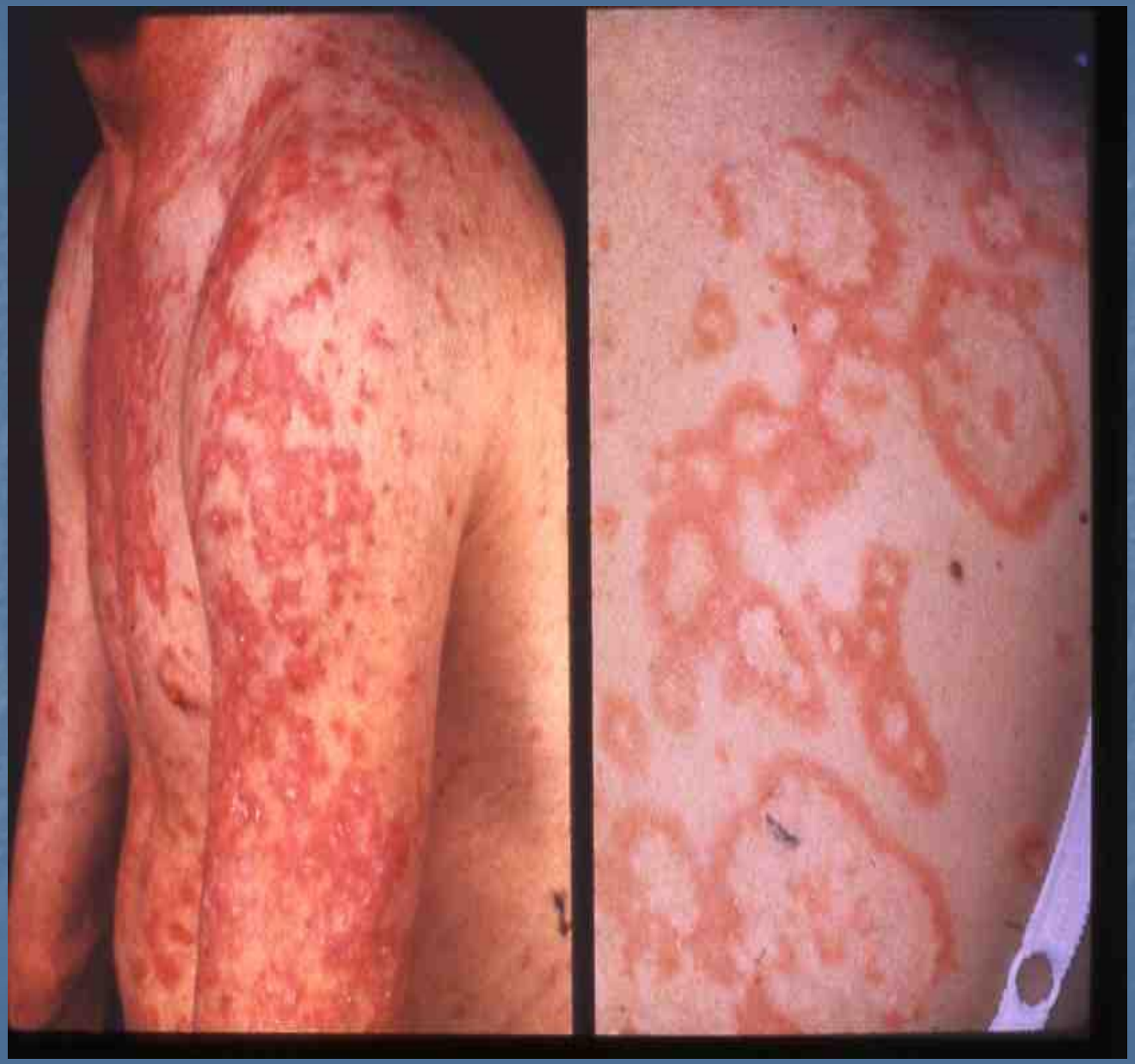


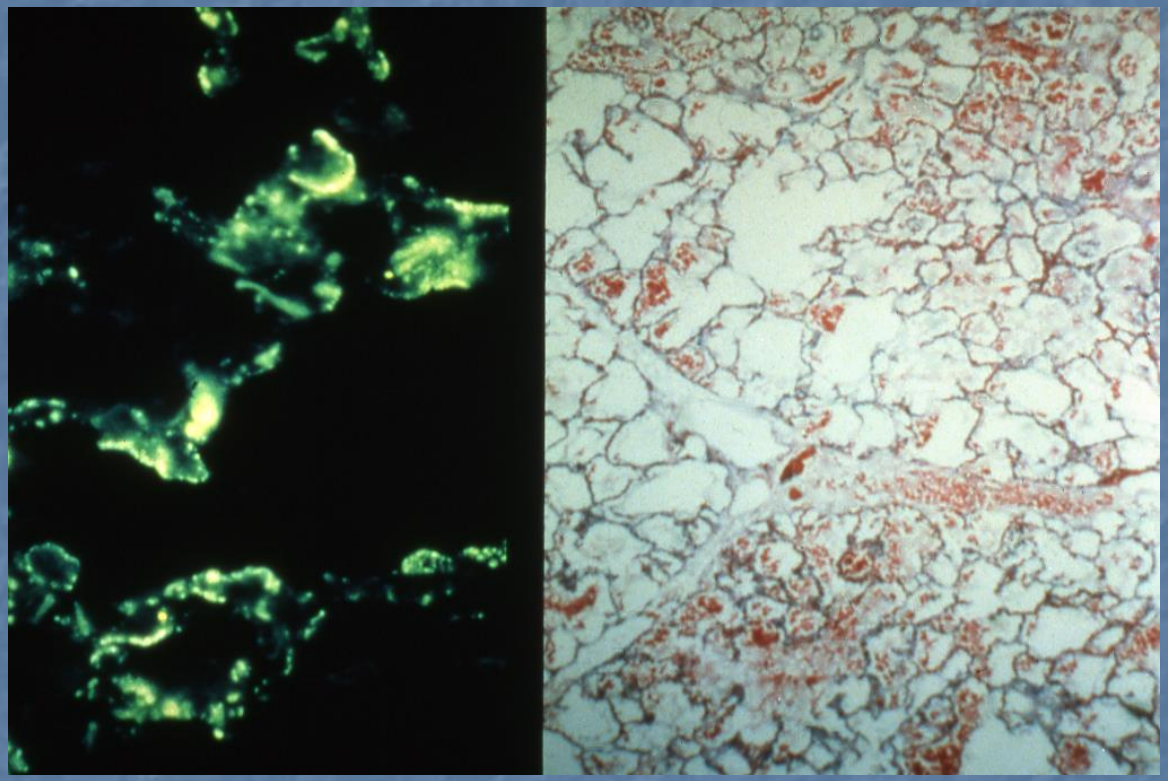












Special considerations:

- **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 :

- **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, belimumab
    - 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