Systemic lupus erythematosus

General characteristics

- Unknown etiology, multifactorial disease
- Involve joints, kidneys, mucous membranes, the central nervous system
- Variety of antibodies
- Symptoms vary greatly from person to person
- Lupus tends to be chronic
- Alternation between remission and relapse

Epidemiology

- Prevalence: 50-100 /100.000
- Incidence: 2-7 /100.000/year
- age at onset: 20-30
- Female vs. male ratio: 9-10:1

Etiology

- Family history (1st degree relatives 1%)
- Genetic predisposition

  MHC genes: HLA DR2,DR3

  DR4-DIL, DR5-APS

  non-MHC genes: complement component, complement receptor, Fc receptors, CRP, cytokines, apoptotic genes (e.g., FAS)

Etiology

- Provoking factors
  - Sunlight, UV light
  - Infections
  - Hormonal status:estrogen, prolactin
  - Drugs
    - Isoniacid
    - Hidantoin
    - Hydralazin
    - Procainamid
    - D penicillinamin
    - Penicillins
    - Sulphonamids
    - TNF alpha blockers

PATHOGENESIS

Disturbed immune regulation:

- **Pathologic antigen presentation**
- **Increased MHC expression**
- **Enhanced co-stimulation**
- **Cytokine imbalance (Th1/Th2)**
- **Decrease of regulatory T cells**
- **Distrubed apoptosis**

1. **Polyclonal B cell activation**
2. **Pathologic autoantibody production**
3. **Impaired clearance of immune complexes**
4. **Accumulation of IC**
5. **Complement activation**

Pathogenesis of SLE

Provoking factors: Genetics predisposition (MHC and non-MHC genes
Triggering factors (UV, drugs, infections)
Hormonal status

Immune disregulation

Defect of clearance

Decreased Regulatory T cells activity

DNA,
Apoptotic cells

APCs

T cells
increased CD4+
actitivity

Increased help:
citokines,
co-stimulation

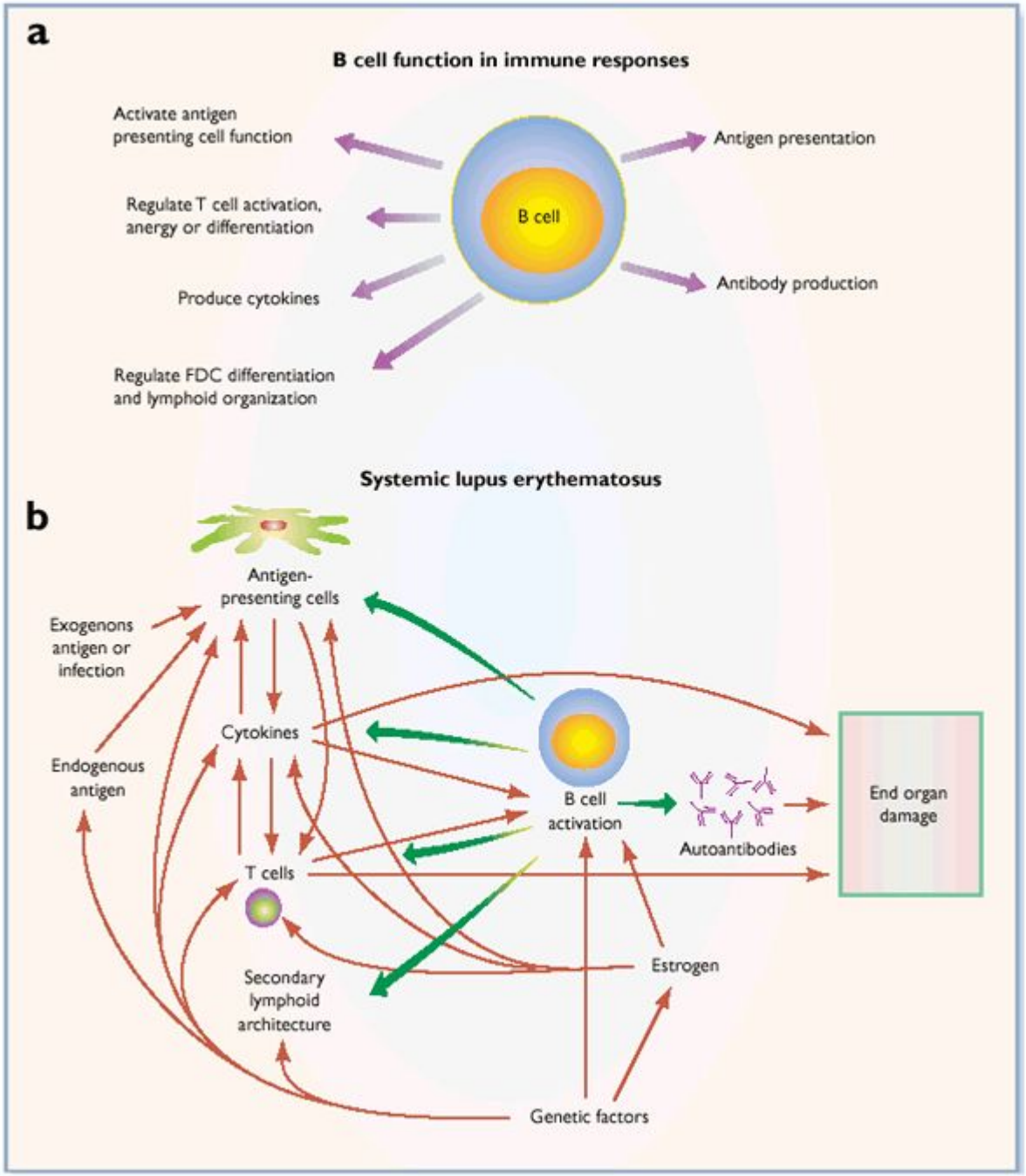
Autoreactive B cells

Production of Auto-AB

ADCC

aPL

Increased IC
C' activation
Organ damages


a
B cell function in immune responses
Activate antigen presenting cell function
Regulate T cell activation, anergy or differentiation
Produce cytokines
Regulate FDC differentiation and lymphoid organization
B cell
Antigen presentation
Antibody production
b
Systemic lupus erythematosus
Antigen-presenting cells
Exogenons antigen or infection
Endogenous antigen
Cytokines
T cells
B cell activation
Autoantibodies
End organ damage
Secondary lymphoid architecture
Estrogen
Genetic factors

Antigen targets for autoantibodies in SLE

- Nuclear antigens: ssDNA, dsDNA, histon, Sm, RNP
- Cytoplasmic antigens: SS-A, SS-B, ribosoma p protein, ANCA
- Cells surface antigens: on endothel cells, erythrocytes, neutrophils, lymphocytes, platlets
- Other antigens, plasma factors: Beta-2 glycoprotein I, phospholipids, immune globulins

General symptoms

- Weakness
- Fatigue
- Tiredness
- Fever
- Weight loss
- Hair loss
- Lymphadenopathy

CLASSIFICATION OF SKIN SYMPTOMS IN SLE (Sontheimer RD.Lupus 6:84-95, 1997)

Lupus specific

A. Acute cutan LE /ACLE/
- Butterfly rush
- Generalised ACLE
- photosensitivity.

B. Subacute cutan LE /SCLE/
- Annular
- Psoriasiform

C. Chronic cutan LE /CCLE/
- Classical discoid lesions
- Hypertrophic DLE
- Lupus panniculitis
- Mucosal ulceration
- Others (L.tumidus, Lichenoid)

non-specific for Lupus

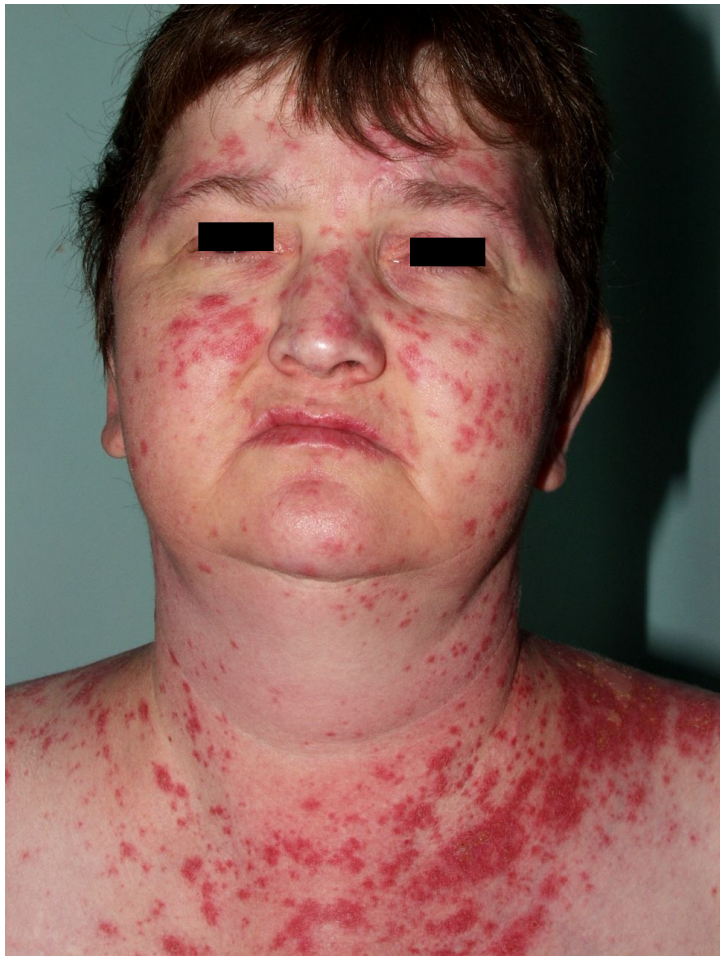
A. Cutan vascular symptoms
- Vasculitis
- Vasculopathy
- Raynaud's syndrome
- Livedo reticularis

B. Non-scarring diffuse alopecia

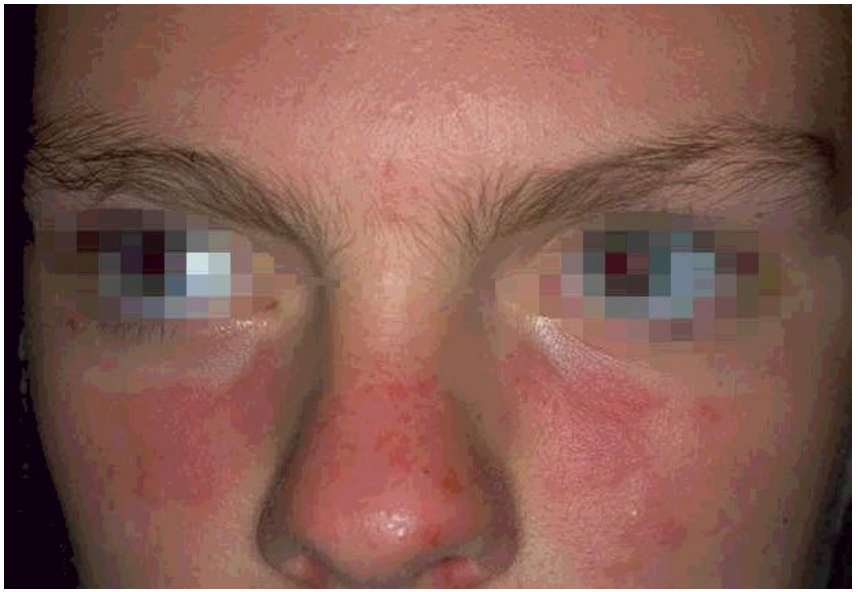
C. Urticaria

D. Erythema exsudativum multiforme

Lupus specific skin symptoms

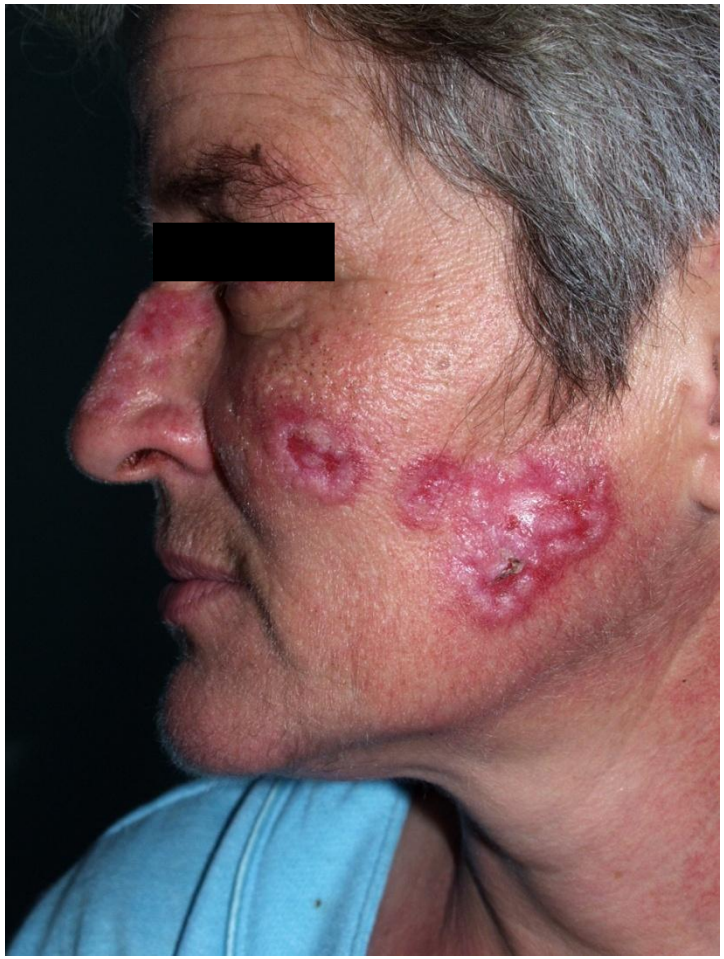


Acute cutan LE

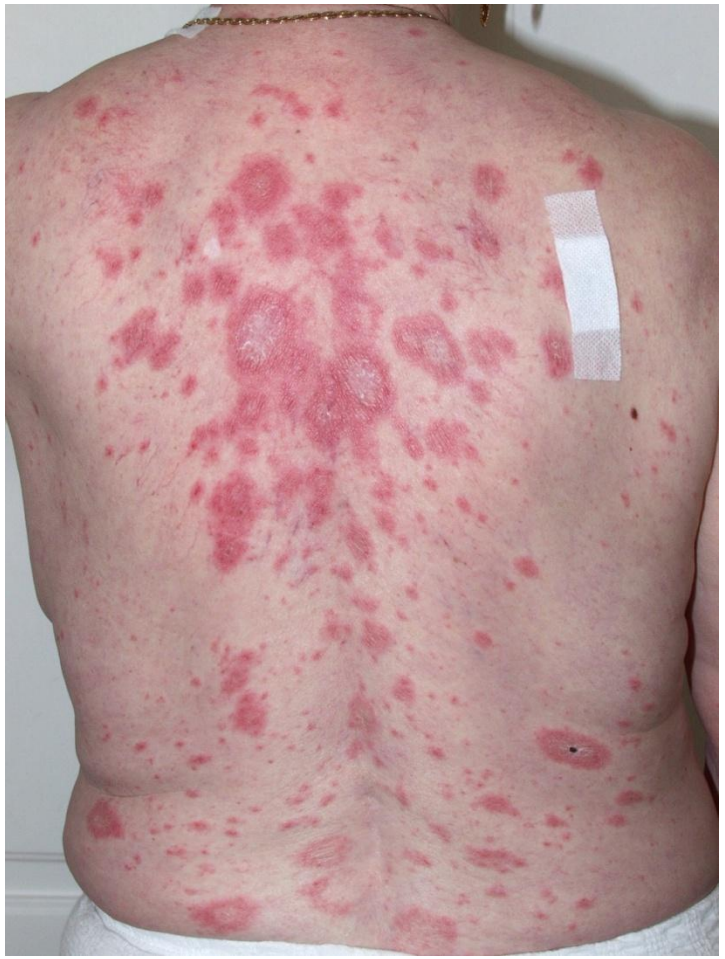


Vespertilio=butterfly rash

Lupus specific skin symptoms

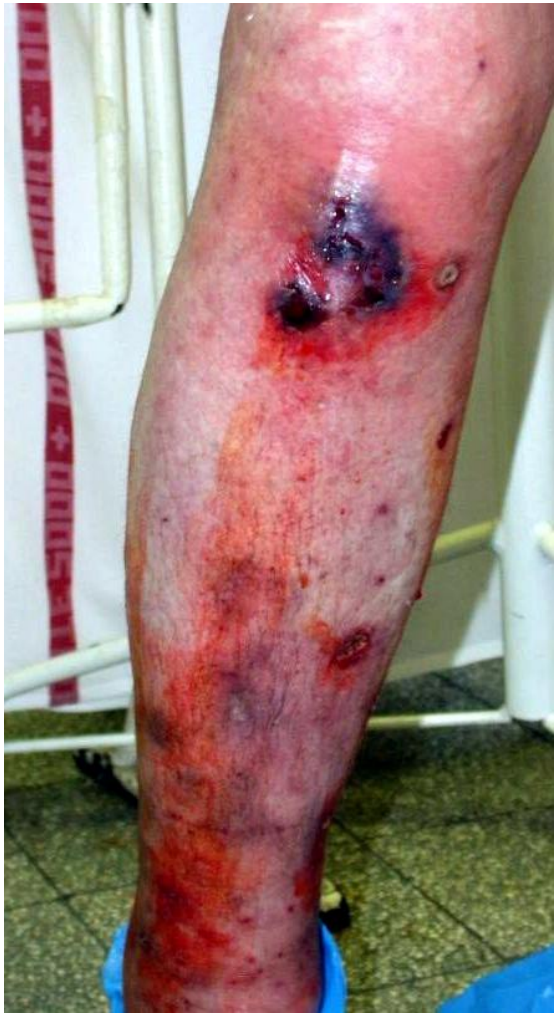


DLE

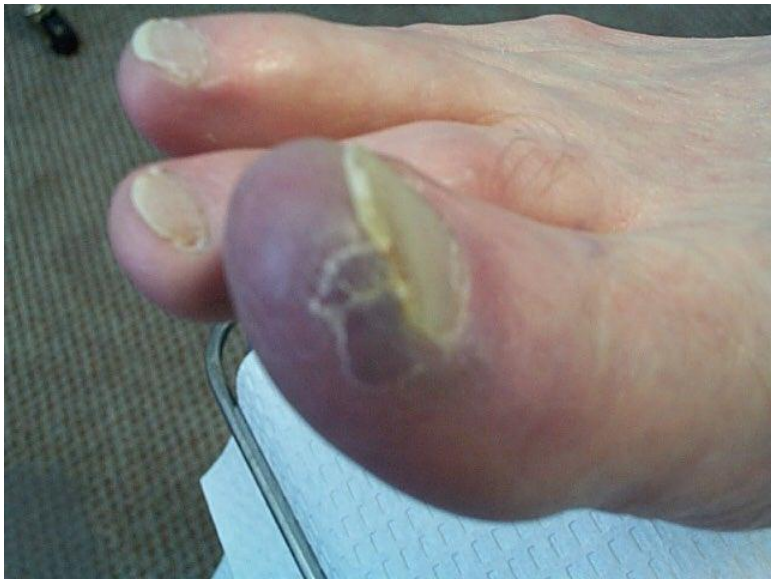


SCLE

Non-lupus specific skin symptoms



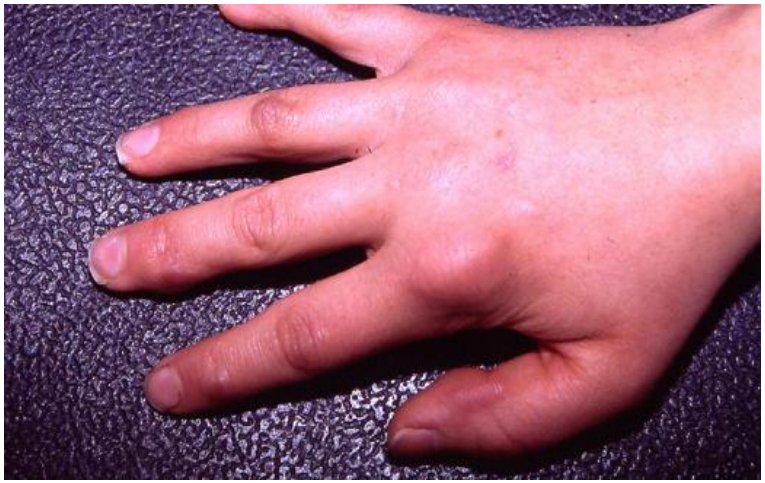
vasculitis



Raynaud phenomenon

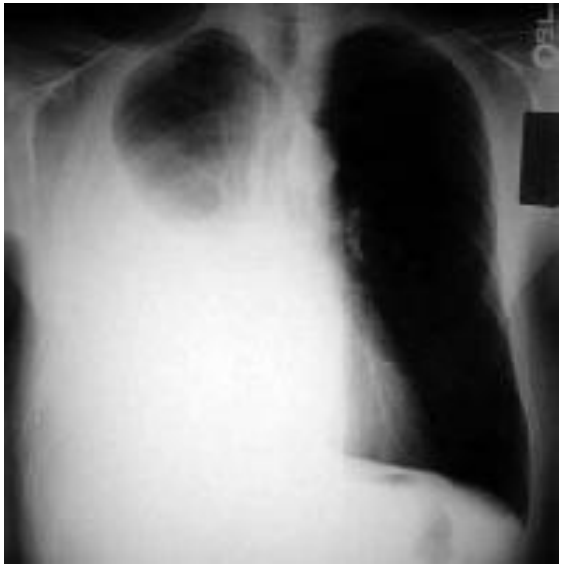
Musculosceletal involvment of lupus

- Small joint symmetric non erosive polyarthritis
- Aseptic femur neck necrosis
- Osteoporosis
- Myositis

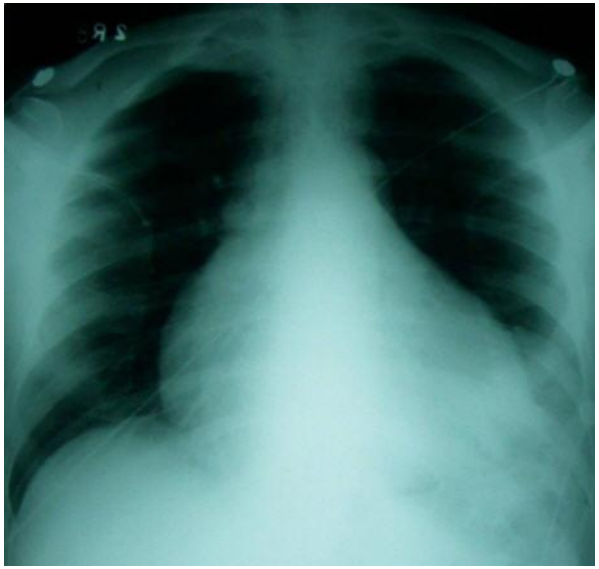


Polyserositis

- Pleuritis
- Pericarditis
- Peritonitis



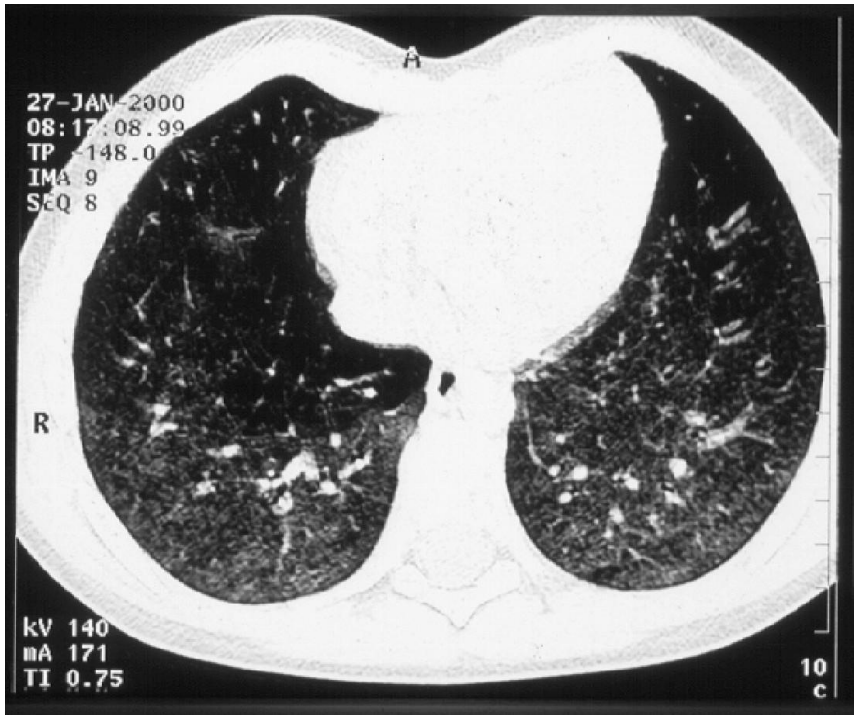
pleuritis



pericarditis

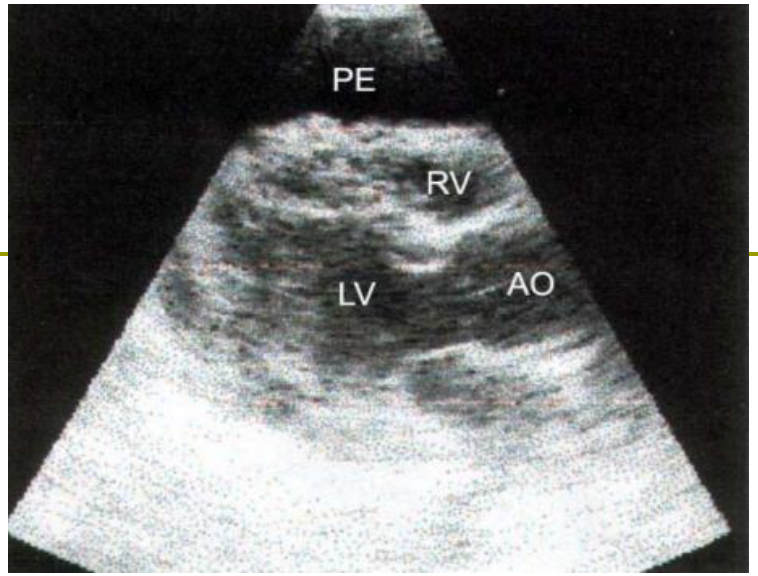
Respiratory involvment

- Pleuritis
- Alveolitis obliterans
- Pulmonal fibrosis
- Pulmonal hypertension
- ARDS
- Pulmonal embolism

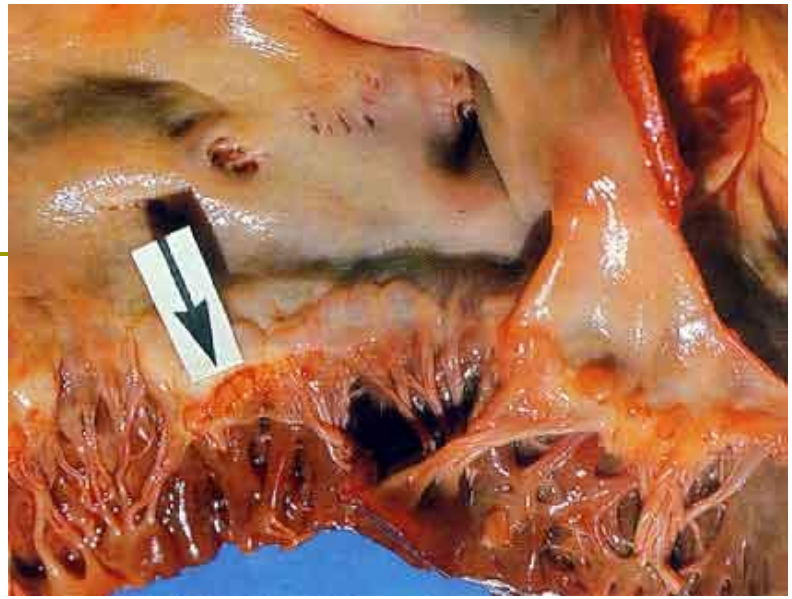


Cardiovascular involvments

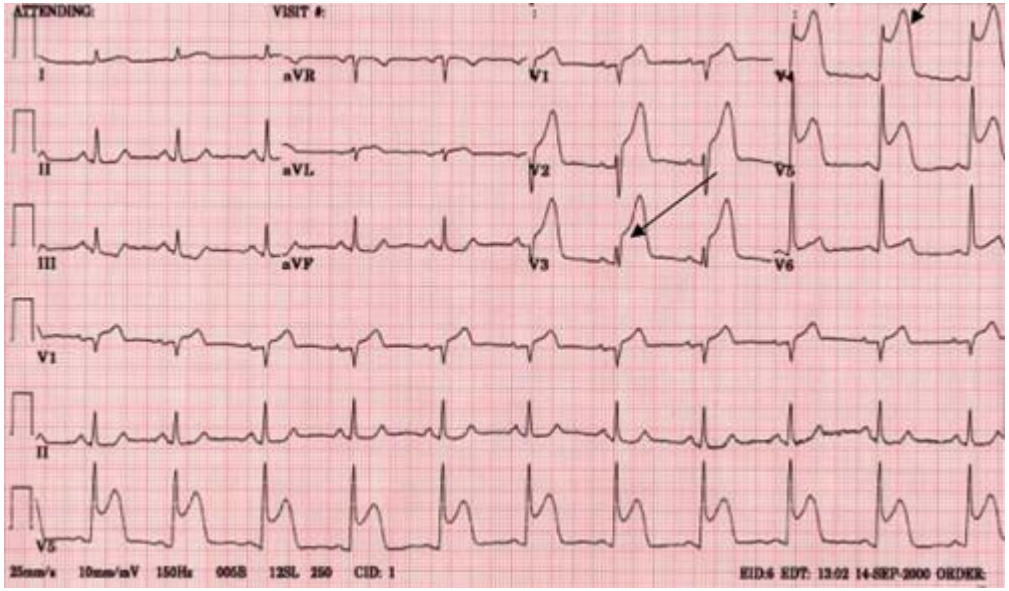
- Pericarditis
- Myocarditis
- Cardiomyopathy
- Endocarditis
  non-infectious verrucosus endocarditis
  (Libman-Sacks endocarditis)
  subacute infectious endocarditis
- Valvulopathy
- Atherosclerosis of coronary



Pericarditis



Non-infectious endocarditis



AMI

Nomenclature of neuro-psychiatric symptoms of SLE

(ACR ad hoc Committee, Arthritis Rheum. 42:599-608, 1999.)

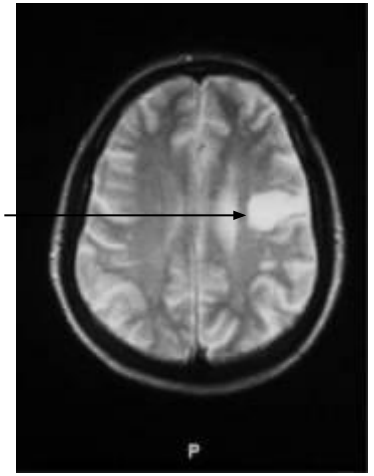
CNS

- Aseptic meningitis
- Cerebrovascular lesion
- Demyelinating syndrome
- Headache (migraine)
- Chorea
- Myelopathy
- Convulsion
- Psychosis
- Acute confusing state
- Cognitive dysfunction

PNS

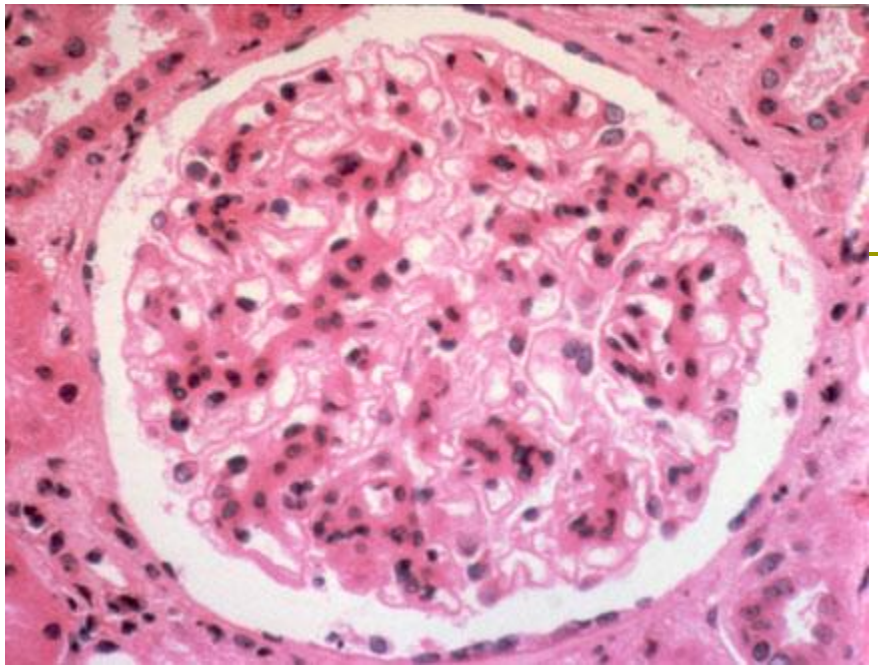
- Acute Guillain-Barré sy.
- Disturbance in autonomic nervous system
- Mononeuritis simplex/multiplex
- Myasthenia gravis like
- Cranial nerve lesion
- Polyneuropathy

Brain infarct

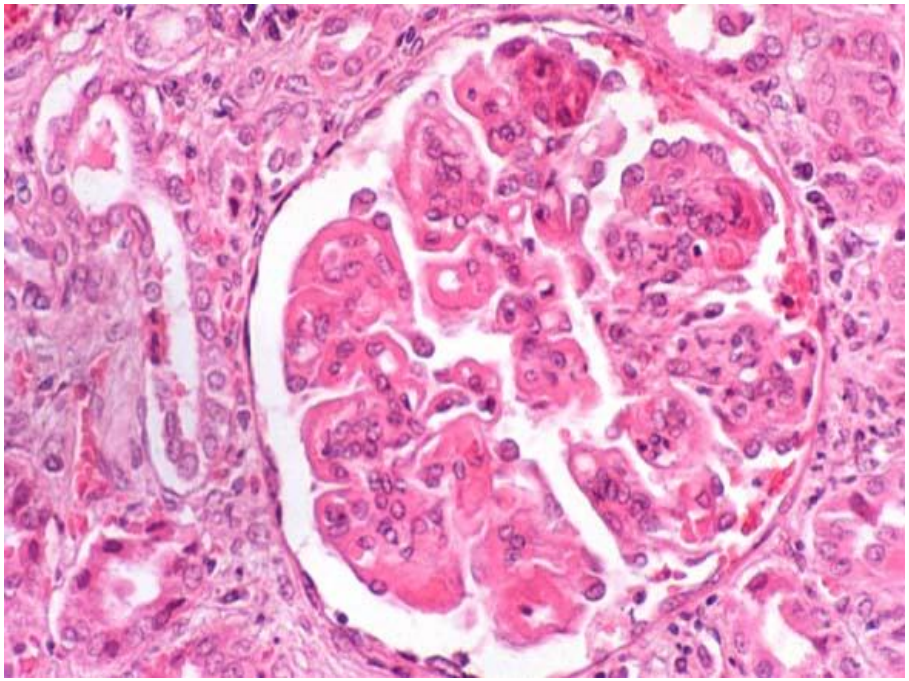


Weening JJ et al. J Am Soc Nephrol 15: 241-50, 2004

Class I. **Minimal mesangial nephritis**
Class II. **Mesangial proliferative nephritis**
Class III. **Focalis lupus nephritis** (<50% of glomeruli are involved)
A. Active lesions: focal proliferative GN
A/C. Active and chronic lesions: focal proliferativ and sclerosing GN
C. Chronic inactive lesions with glomerular scarring: focal sclerosing GN.
Class IV. **Diffuse lupus nephritis** (>50% of glomeruli are involved)
diffuse segmental (IV-s) type, when only a part of the involved glomeruli are affected
diffuse global GN (IV-G), when the entire glomeruli are affected
IV-S (A),IV-G (A),
IV-S (A/C), IV-G (C),
IV-S (C),
Class V. **Membranous lupus nephritis**
May associate with findings characterised in class III/IV.
Class VI. **Sclerosing glomerulonephritis**
>90% of glomeruli are sclerotic



Mesangial LN



Diffuse LN

Other manifestations

Haematology

- Leukopenia, lymphopenia
- AIHA/ Thrombocytopenia/Evans sy.
- Pancytopenia
- TTP, CAPS
- Lymphadenopathy/Splenomegaly

Othe

- Vasculitis
- Pancreatitis, lupus hepatitis
- Pepeticus ulcus/GI-bleeding
- Mesenterial thrombosis/vasculitis
- A./v. central retinae thrombosis
- Opticus neuritis
- Chorioretinitis
- Sicca sy.

Laboratory tests and findings in SLE

- General inflammatory findings: ESR↑, normal CRP
- Haematology: pancytopenia,
- Kidney tests: sodium, potassium, carbamide, creatinine
- enzymes: CK, AST/GOT, ALT/GPT, LDH (haemolysis, myositis, hepatitis)
- Haemostasis: Lupus anticoagulant
- Immunserology: IgG, C3, C4, CH50, ANA, aDNA, nukleosoma, histon, anti-Sm, anti-cardiolipin, anti-beta2-glikoprotein I.
- Urine (protein!) and urine sediment (WBC, RBC, count)
- 24 hours urine collection: detection of protein

Radiology and other examinations in SLE

- Chest X ray, CT (HRCT), breath test, scan
- Abdominal ultrasonograph
- ECG, echocardiography
- Neurology examination: EEG, ENG, EMG, CT, MRI, test of cerebrospinal fluid
- Biopsies: skin (vagy lupus band teszt)
  kidney
  muscles
  n. suralis

Classification criteria for the diagnosis of lupus according to the American College of Rheumatology (ACR)

1. Butterfly rush
2. Discoid lupus
3. Photosensitivity
4. Oral ulceration
5. Polyarthritis
6. Nephritis
    a. proteinuria over 0.5g/day
    b. cellular casts
7. Pleuritis/pericarditis
8. Neuropsychiatric symptoms
    a. convulsions
    b. psychosis
9. Haematological alterations
    a. haemolytic anaemia
    b. leucopenia (4.0 G/l)
    c. lymphopenia (1.5G/l)
    d. thrombocytopenia (100G/l)
10. Immunologic alterations
    a. anti-dsDNA
    b. anti-Sm
    c. anti-CL and/or LA
11. ANA

4 or more symptoms are required for the diagnosis

M Hochberg, 1997

Differential diagnosis of SLE

1. Other polysystemic autoimmune disorders

polyarthritis
myositis, muscle weakness
Raynaud's sy.
Sjögren's sy.

2. Haematologic malignancies

spleen and liver enlargement
lymphadenopathy
weight loss, fever
anaemia, thrombocytopenia

3. Infections

Fever, ESR and CRP↑
Subacute inf. endocarditis, valvulopathy
Rheumatic fever
Tuberculosis, relapsing serositis
Septicaemia, hepato-splenomegaly
Other infections, lymphadenomegaly, rushes

4. Malignant disorders

weight loss, subfebrility, fatigue, anemia, ESR ↑, recurrent thrombosis

5. Other diseases

TTP AIHA
ITP
AIDS

Monitoring of activity in SLE disease activity index: DAI

- Convulsion 8
- Psychosis 8
- Organic brain syndrome 8
- Visual field defects (retinopathy) 8
- Cranial nerve lesion 8
- Lupus headache 8
- Stroke 8
- Arthritis 4
- Myositis 4
- Casts in urine 4
- Haematuria 4
- Proteinuria 4
- Pyuria 4
- New rushes 2
- Alopecia 2
- Oral ulcer 2
- Pleuritis 2
- Pericarditis 2
- Low complement 2
- Elevated aDNA 2
- Fever 1
- Thrombopenia 1
- Leucopenia 1

Subgroups in SLE

- Subacute cutan lupus erythematosus
- Neonatal lupus erythematosus
- Drug-induced lupus
- SLE in elderly
- SLE with APS

SUBGROUPS IN SLE
1. SUBACUTE CUTAN LUPUS (SCLE)

Clinical characteristics:

- annular/psoriasiform skin eruptions
- photosensitivity (60-70%)
- less frequent kidney involvement (10%)
- less common CNS symptoms (20%)

Laboratory signs: aSSA/aSSB antibodies (60-70%)

Therapeutical considerations:

- sun screens
- topical steroids
- systemic low dose steroid
- antimalarial drugs

SLE SUBGROUPS
2. NEONATAL LUPUS (NLE)

Frequency: rare

Cause: maternal autoantibodies passing through the placenta

Clinical characteristics: generalised skin eruptions
hepato-splenomegaly
transient thrombocytopenia
autoimmun haemolytic anaemia
congenital heart block

Laboratory signs: aSSA/aSSB antibodies
ANA positivity
high a-dsDNA concentration
LE cell phenomenon

Special aspects of therapy: Corticosteroids
HIVIG
pace maker

SUBGROUPS IN SLE
3. SLE IN ELDERLY

Onset: over the age of 60

Frequency: around 10%

Clinical characteristics: musculo-skeletal symptoms
serositis
pulmonal involvement: pulm. fibrosis
skin rushes
decreased female:male ratio
sicca sy.
milder

Diff. dg.: exclusion of cancer is required!

Therapeutic considerations: low dose corticosteroids
NSAID

SLE SUBGOUPS

4. DRUG-INDUCED LUPUS (DIL)

Clinical characteristics: more frequent in elderly
reversible
milder
kidney and CNS involvement are rare
DLE is rare
more frequent pulmonal symptoms

Laboratory signs: slow acetylators
associated with HLA DR4
H2A, H2B histone antigens
are the major epitops

Therapy: cessation of provoking drug
corticosteroids

Negative prognostic factors in SLE

- Sex:male
- Age under 20 or above 50
- Diffuse proliferative lupus nephritis
- CNS manifestations
- Anti-phospholipid antibodies
- Endocarditis

Causes of death

- In the early phase of the disease process
  - Kidney failer
  - Neurology involvement
  - SLE Activity
- In the later phase of the disease process
  - Cardiovascular event
  - Thromboembolism
  - Malignant disorders
- In both:
  - infections

Therapy of lupus

- General procedures
  - Avoidance of UV lights
  - Sunscreens
  - Termination of the use of provoking drugs
  - Avoidance of contraceptive pills
  - Adequate antibiotics therapy

Therapy of SLE

- Antimalarial drugs: hydroxichlorouin, chloroquin (Delagil)

In the cases of arthralgia, arthritis, skin symptoms, serositis

Dosis: 200-400 mg/die

Side effect: ocular complications

Therapy of SLE

- Steroids: methylpednisolon (Solu-Medrol, Medrol, Methypred)

In acute flares and relapses

in neonatal lupus: dexamethason 4 mg/die

Dosis: start with 0.5-1 mg/bwkg, then slowly decreased dosis

Pulse steroid: 1 g/3 days

Side effects!

Immunosupressives

- Methotrexat (Trexan)
  7.5-20 mg/week, treatment of polyarthritis, vasculitis
  CAVE: bonemarrow and liver toxicity
- Azathiorpin (Imuran)
  1-2 mg/bwkg/day, multiorgan involvement
  CAVE: bonemarrow and liver toxicity
- Cyclophosphamid (Cytoxan)
  500-1000 mg/m2/month for 6 months, then same amount/3 months for 1.5 years (NIH protocol)
  In the cases of lupus nephritis, alveolitis, vasculitis, CNS involvement
  CAVE:bonemarrow and liver toxicity

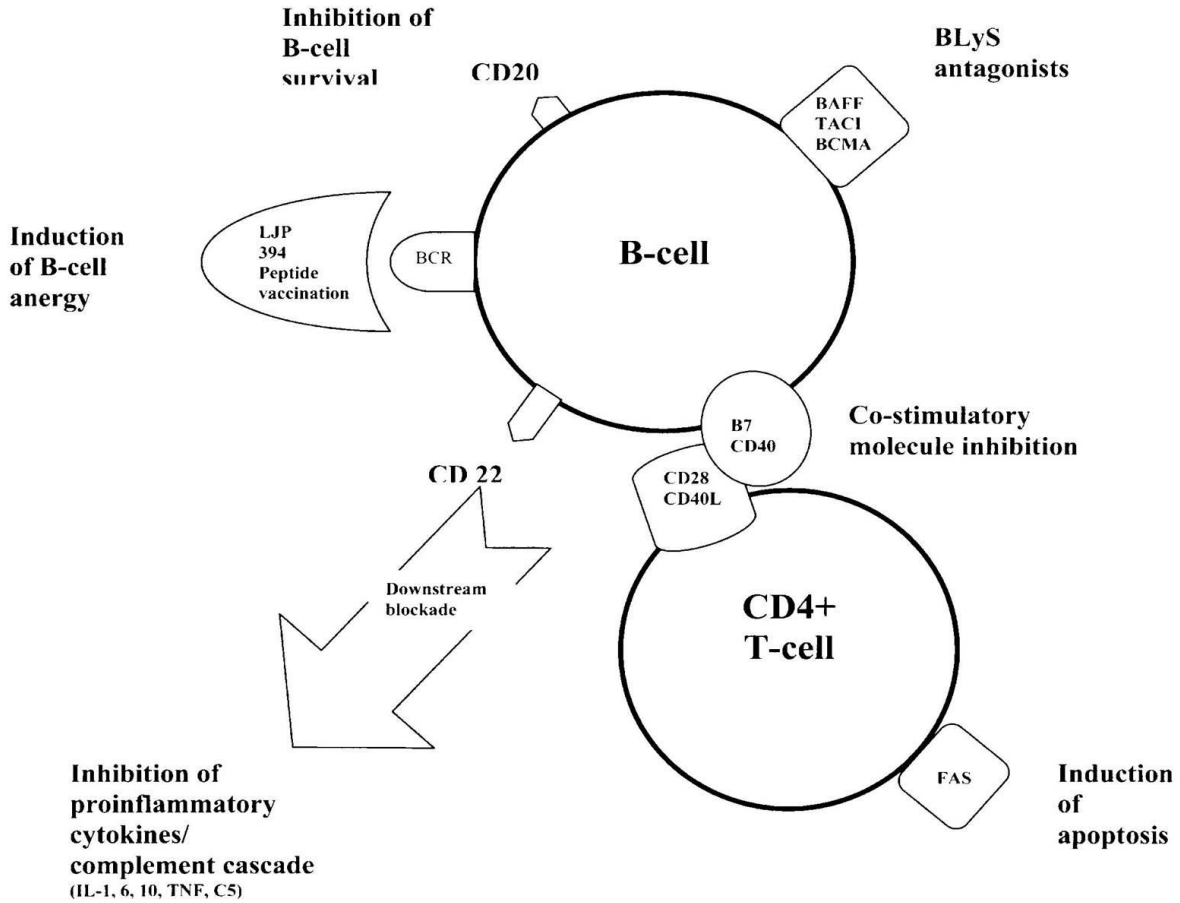
Immunmodulation

- Cyclosporin A (Sandimmun Neoral)
  In the cases of haematology involvement, membranous lupus nephritis
  dosis: 3 mg/bwkg/day

- Mycophanolat mophetil/Mycofenol acid (Cellcept/Myfortic)
  In the case of lupus nephritis max. 3 gr/day

- Diamino diphenylsulphon (Dapson)

Potential targets in the therapy of SLE



Other

- HIVIG 0.4 g/bwkg/day for 5 days
- Plasmapheresis 100 ml/bwkg plasma exchange synchronized with ISU
- Stem cell transplantation