SYSTEMIC LUPUS ERYTHEMATOSUS

Krzysztof Wróblewski
Dept. of Internal Medicine and Nephrodiabetology,
Medical University of Lodz

UNIWERSYTET MEDYCZNY W ŁODZI

DEFINITION AND PREVALENCE

- **Systemic lupus erythematosus (SLE)** is an autoimmune disease in which organs, tissues, and cells undergo damage mediated by tissue-binding **autoantibodies** and **immune complexes.**
- 90% of patients are **women** of child-bearing years;
- However, people of both genders, all ages, and all ethnic groups are susceptible.
- highest prevalence among African Americans.

- 40 cases per 100,000 persons among Northern Europeans
- 200 per 100,000 persons among blacks.
- The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s 2 to a **15-year survival rate of 80%** today.

- The patho-aetiology of SLE probably involves complicated and multifactorial interactions among various genetic and environmental factors

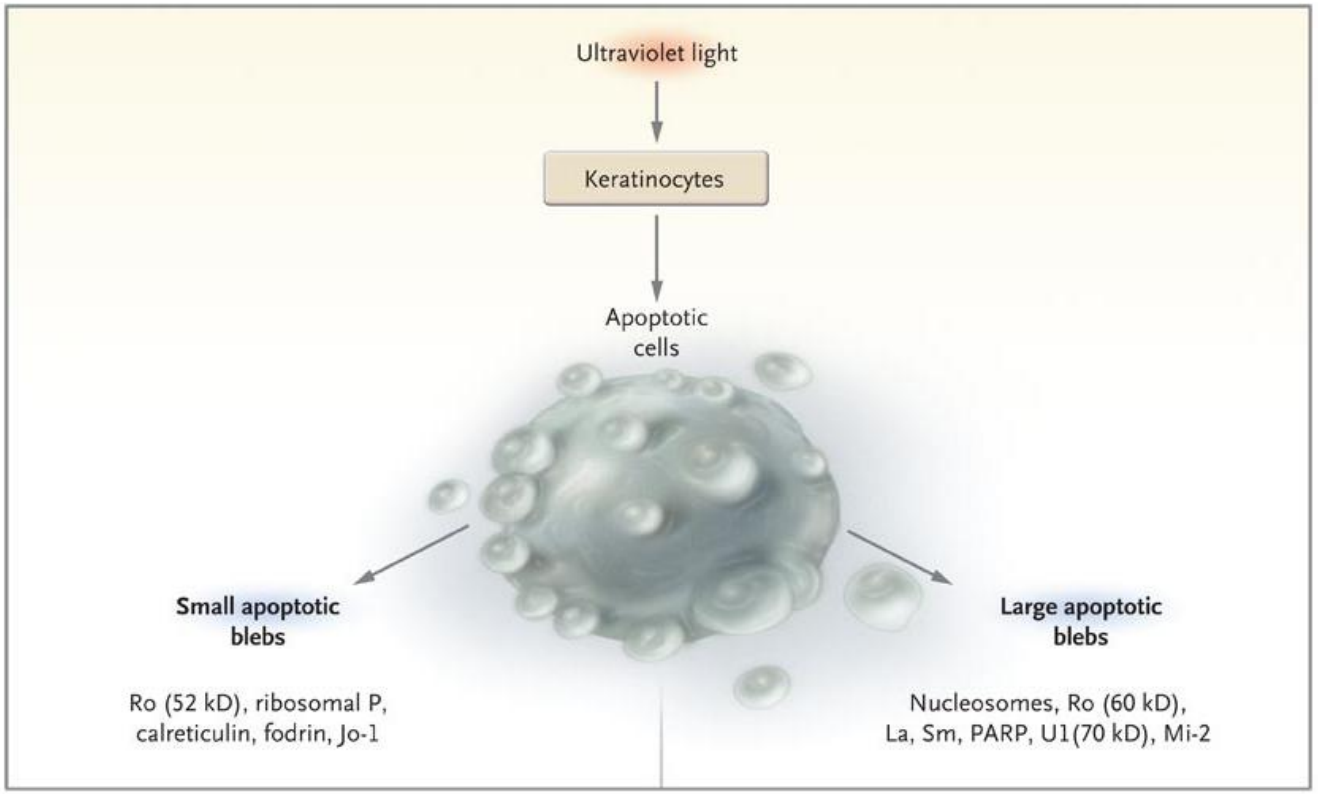
- **Multiple genes** contribute to disease susceptibility, including genes encoding complement and other components of the immune response, in addition to major histocompatibility complex class I and II genes

- **The interaction of sex, hormonal milieu** (particularly oestrogenic versus androgenic activity), and the **hypothalamo-pituitary-adrenal axis** modifies this susceptibility and the clinical expression of the disease

- **Defective immune regulatory mechanisms**, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE

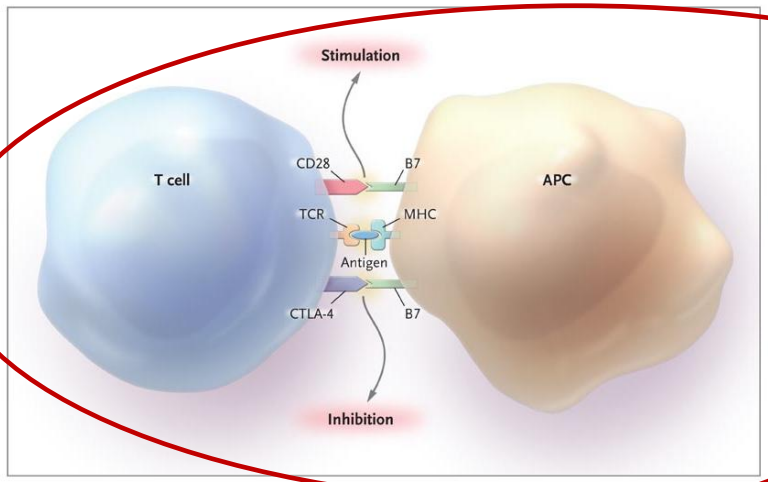
- The **loss of immune tolerance**, increased antigenic load, excess T cell help, defective B cell suppression, and the shifting of T helper 1 (Th1) to Th2 immune responses leads to B cell hyperactivity and the production of pathogenic autoantibodies

- In addition, **environmental factors**, such as chemicals and drugs, ultraviolet light, dietary factors, viruses, and environmental oestrogen are probably required to precipitate the onset of the disease

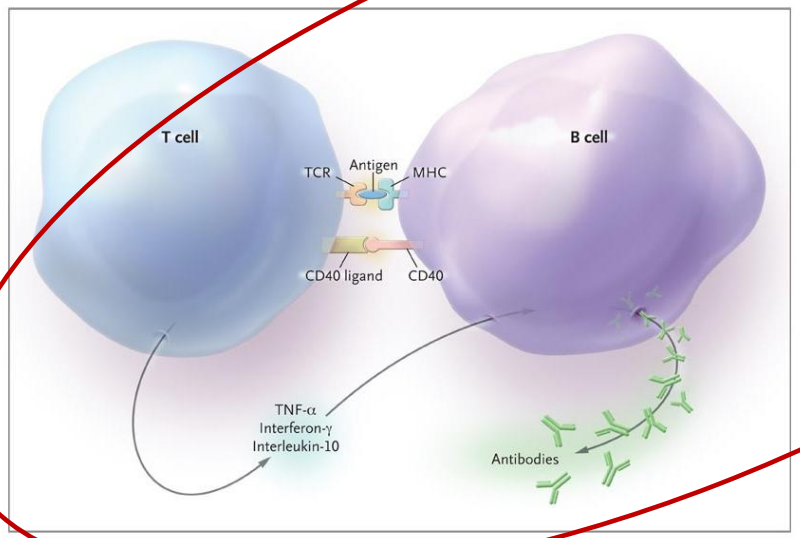


Rahman A. NEJM, 2008

pathogenesis



Rahman A. NEJM, 2008



Environmental triggers | Multiple genes | Neuro-endocrine system | Sex and sex hormone milieu

Immune dysregulation

Defective clearance mechanisms

Loss of suppressor activities and idiotype control

DNA, apoptotic cells

APC

B cells

Excess help Cytokines

T cells

Autoantibodies

Defective clearance

Immune complexes Complement activation

Tissue injury and damage

Table 2. Pathogenic Autoantibodies in Systemic Lupus Erythematosus.*

Antigen Specificity	Prevalence†	Main Clinical Effects	Source of Evidence		
			Clinical Studies	Studies of Tissues from Patients with Lupus	Animal Models
	%				
Anti–double-stranded DNA	70–80	Kidney disease, skin disease	ter Borg et al.,[23] Bootsma et al.,[31] Tseng et al.[32]	Koffler et al.[20]	Ravirajan et al.,[33] Ehrenstein et al.,[34] Madaio et al.[35]
Nucleosomes	60–90	Kidney disease, skin disease	Amoura et al.[26]	Grootscholten et al.,[36] Kalaaji et al.,[37] Kalaaji et al.[38]	Kramers et al.,[39] van Bruggen et al.[40]
Ro	30–40	Skin disease, kidney disease, fetal heart problems	Buyon and Clancy,[41] Sontheimer et al.[42]	Mannik et al.,[25] Clancy et al.,[43] Maddison and Reichlin[44]	
La	15–20	Fetal heart problems	Buyon and Clancy[41]	Mannik et al.[25]	
Sm	10–30	Kidney disease	McCarty et al.[45]	Mannik et al.[25]	
NMDA receptor	33–50	Brain disease	Yoshio et al.,[46] Lapteva et al.[47]	Kowal et al.[27]	Kowal et al.[27]
Phospholipids	20–30	Thrombosis, pregnancy loss	Alarcón-Segovia et al.[48]		Girardi et al.,[49] Pierangeli et al.[50]
α-Actinin	20	Kidney disease	Mason et al.,[51] Becker-Merok et al.[28]		Mostoslavsky et al.,[52] Deocharan et al.[53]
C1q	40–50	Kidney disease	Siegert et al.[29]	Mannik et al.[25]	

* NMDA denotes *N*-methyl-D-aspartate.

† Prevalence data were obtained from a number of sources, including Amoura et al.,[26] Kowal et al.,[27] Becker-Merok et al.,[28] Siegert et al.,[29] and Ehrenstein and Isenberg.[30]

SLE Criteria

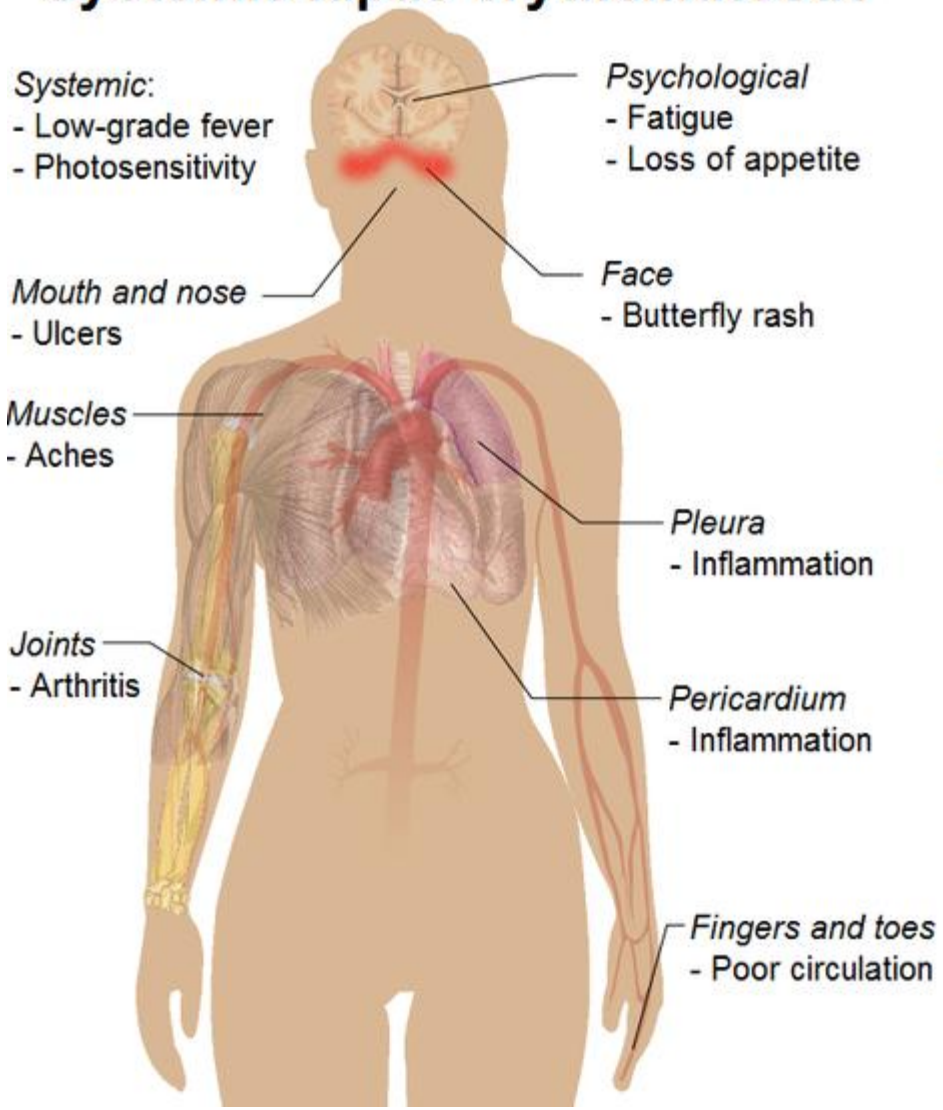
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Exposure to ultraviolet light causes rash
Oral ulcers	Includes oral and nasopharyngeal ulcers, observed by physician
Arthritis	Nonerosive arthritis of two or more peripheral joints, with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis documented by ECG or rub or evidence of effusion
Renal disorder	Proteinuria >0.5 g/d or ≥3+, or cellular casts
Neurologic disorder	Seizures or psychosis without other causes
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/μL) or lymphopenia (<1500/μL) or thrombocytopenia (<100,000/μL) in the absence of offending drugs
Immunologic disorder	Anti-dsDNA, anti-Sm, and/or anti-phospholipid
Antinuclear antibodies	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs

[a] If ≥4 of these criteria, well documented, are present at any time in a patient's history, the diagnosis is likely to be SLE. Specificity is ~95%: sensitivity is ~75%.

SOAP BRAIN MD

Most common symptoms of

Systemic lupus erythematosus



Clinical Manifestations of SLE

Systemic: Fatigue, malaise, fever, anorexia, weight loss	95
Musculoskeletal	95
Arthralgias/myalgias	95
Nonerosive polyarthritis	60
Hand deformities	10
Myopathy/myositis	25/5
Ischemic necrosis of bone	15
Cutaneous	80
Photosensitivity	70
Malar rash	50
Oral ulcers	40
Alopecia	40
Discoid rash	20
Vasculitis rash	20
Other (e.g., urticaria, subacute cutaneous lupus)	15
Hematologic	85
Anemia (chronic disease)	70
Leukopenia (<4000/μL)	65
Lymphopenia (<1500/μL)	50
Thrombocytopenia (<100,000/μL)	15
Lymphadenopathy	15
Splenomegaly	15
Hemolytic anemia	10

Neurologic	60
Cognitive disorder	50
Mood disorder	40
Headache	25
Seizures	20
Mono-, polyneuropathy	15
Stroke, TIA	10
Acute confusional state or movement disorder	2–5
Aseptic meningitis, myelopathy	<1
Cardiopulmonary	60
Pleurisy, pericarditis, effusions	30–50
Myocarditis, endocarditis	10
Lupus pneumonitis	10
Coronary artery disease	10
Interstitial fibrosis	5
Pulmonary hypertension, ARDS, hemorrhage	<5
Renal	30–50
Proteinuria >500 mg/24 h, cellular casts	30–50
Nephrotic syndrome	25
End-stage renal disease	5–10
Gastrointestinal	40
Nonspecific (nausea, mild pain, diarrhea)	30
Abnormal liver enzymes	40
Vasculitis	5
Thrombosis	15
Venous	10
Arterial	5
Ocular	15
Sicca syndrome	15
Conjunctivitis, episcleritis	10
Vasculitis	5

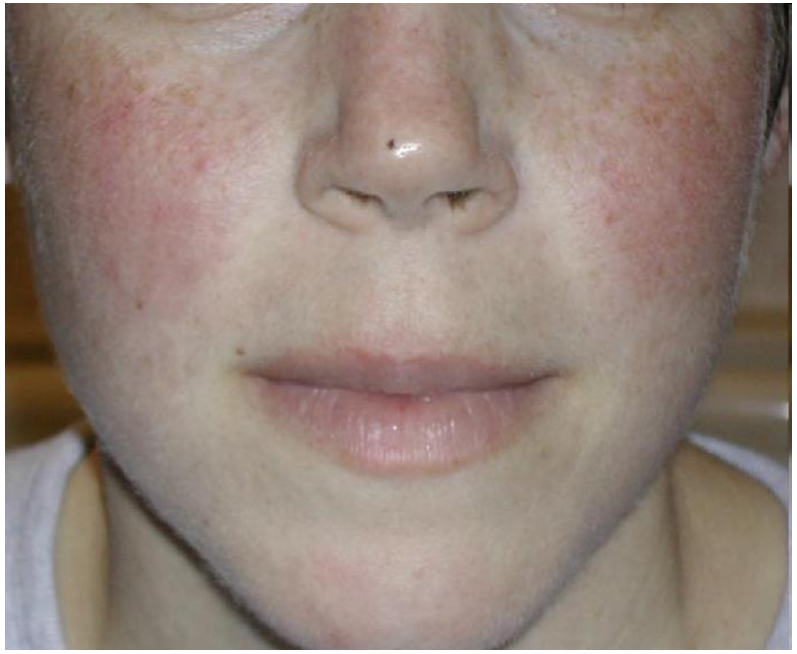
Constitutional symptoms:

- Nonspecific fatigue, fever, arthralgia, and weight changes are the most common symptoms (new cases or recurrent active SLE flares
- Fatigue, **the most common** due to active SLE, medications, lifestyle habits, or concomitant fibromyalgia or affective disorders.
- Fever,
- Weight loss active SLE or weight gain due to corticosteroid treatment or active disease such as nephrotic syndrome anasarca.

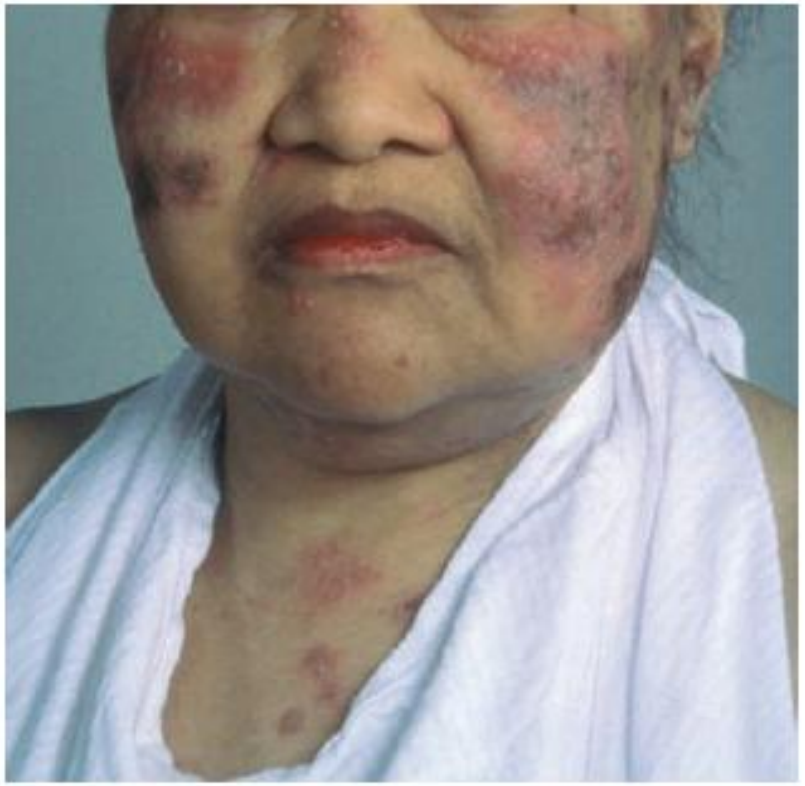
Musculoskeletal symptoms:

- Arthralgia, myalgia, and arthritis may involve the small joints of the hands, wrists, and knees.
- In contrast to rheumatoid arthritis, SLE arthritis or arthralgia may be **asymmetrical**, with pain that is disproportionate to swelling.

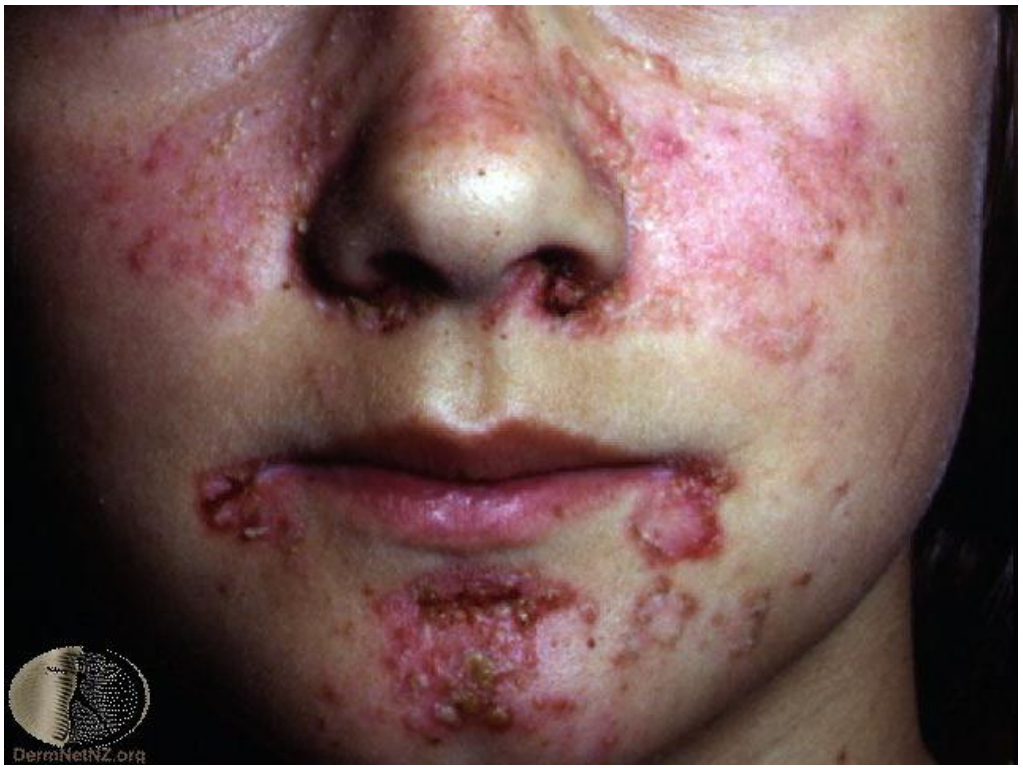
Dermatological manifestations



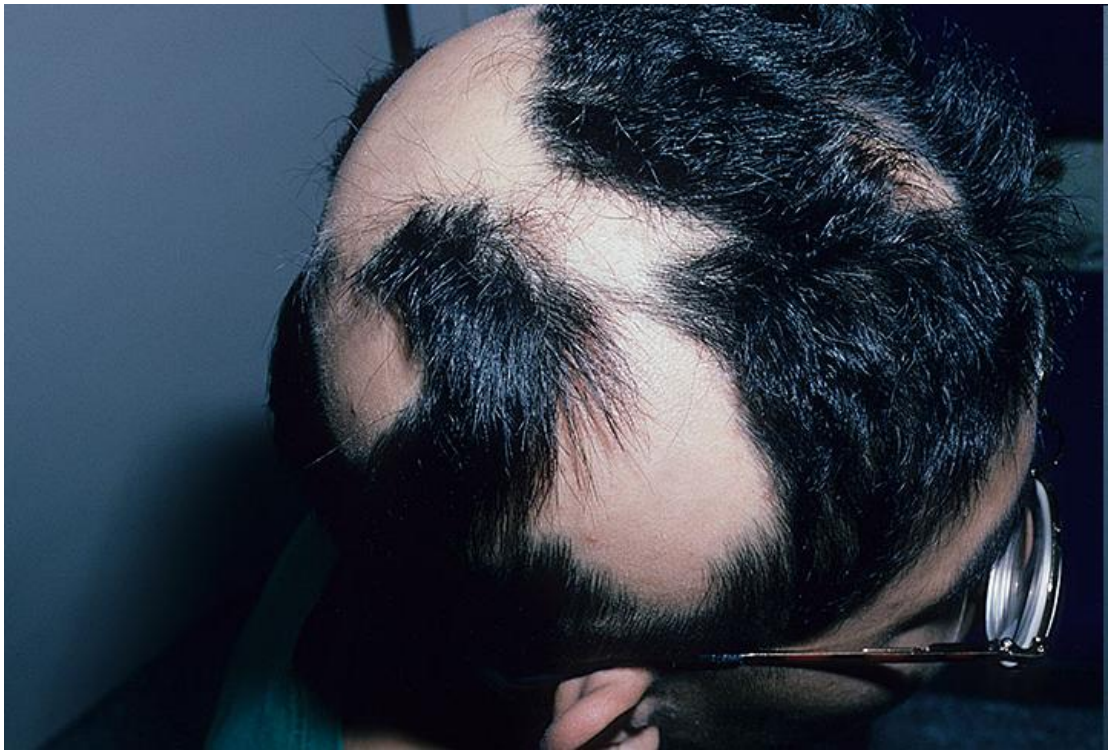
malar rash – characterized by an erythematous rash over the cheeks and nasal bridge, lasting from days to weeks, occasionally painful or pruritic.



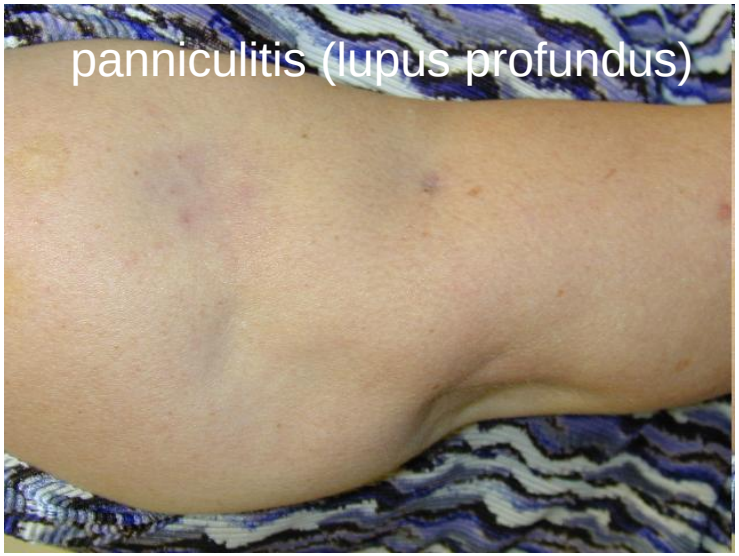
- Discoid rash – without organ involvement, as a separate diagnostic entity – **DLE – dyscoid lupus erythematosus**

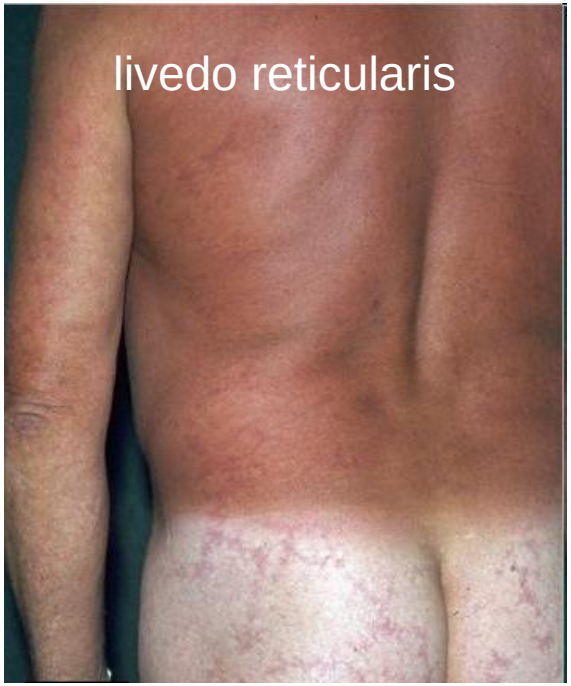


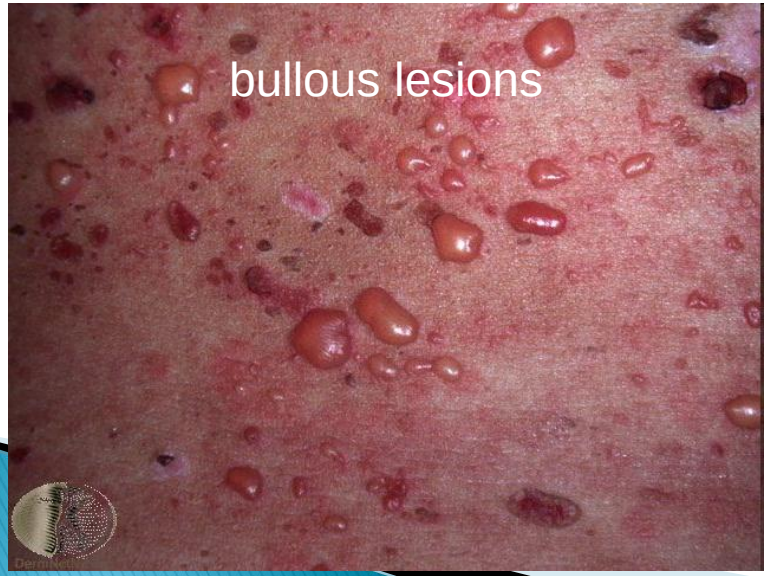
- Alopecia – often affects the temporal regions or a patchlike pattern of hair loss.

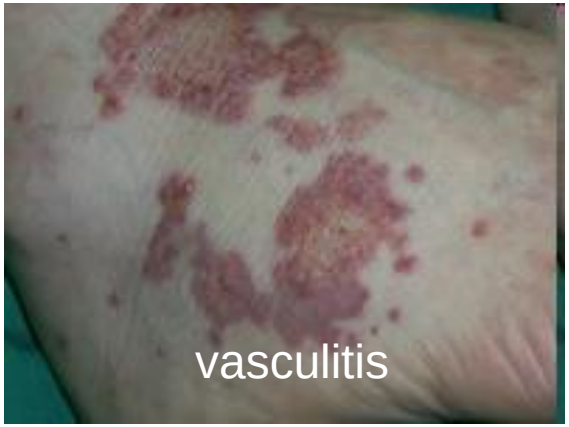


- Non-specific: Raynaud phenomenon, telangiectasias, and urticaria.



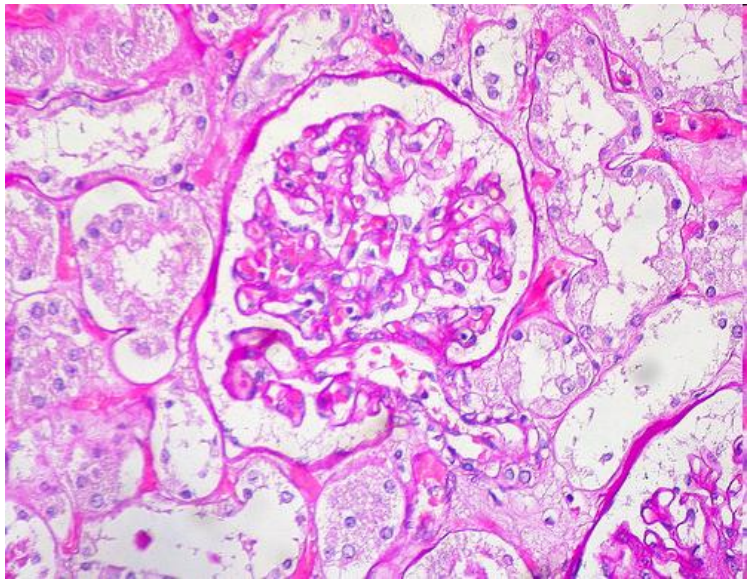


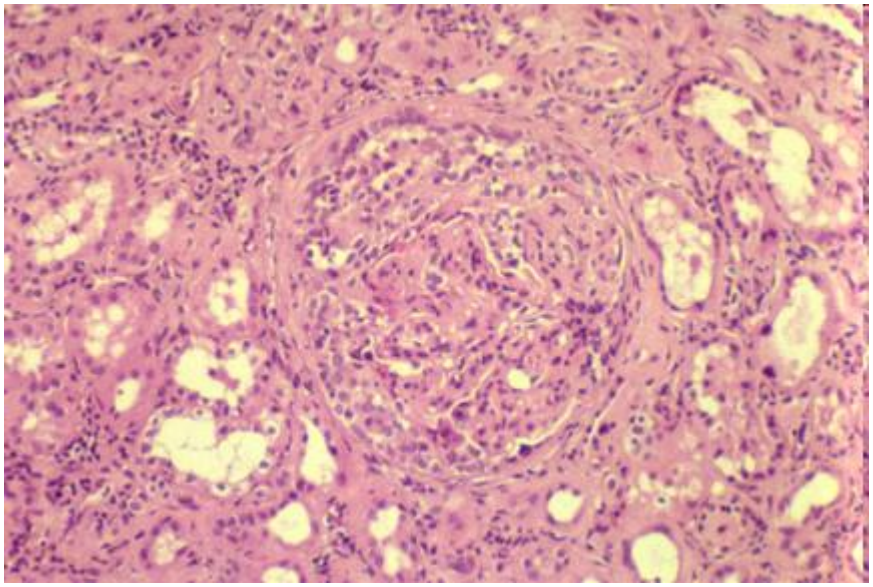


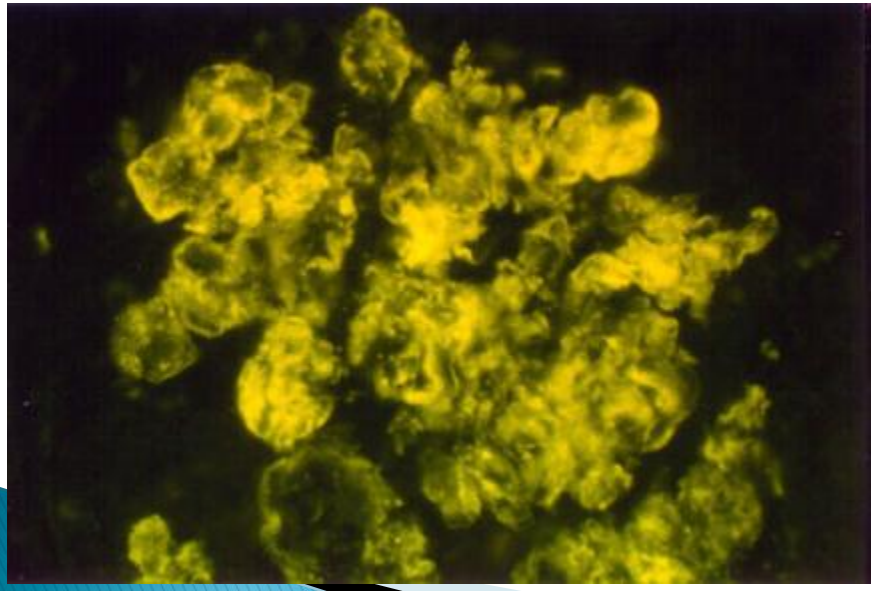


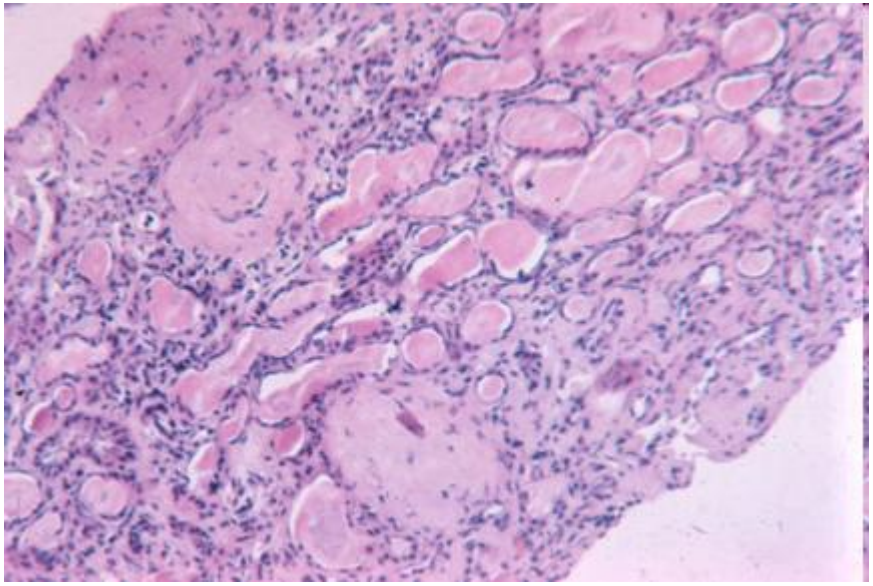
Renal manifestation

- kidneys commonly involved visceral organs in SLE. only 50% of patients with SLE develop clinically evident renal disease, **lupus nephritis is usually asymptomatic**,
- **Renal biopsy.**
- Acute or chronic renal failure may cause symptoms related to uremia and fluid overload.
- Acute nephritic disease may manifest as hypertension and hematuria.
- Nephrotic syndrome









Neuropsychiatric symptoms

- difficulty in distinguishing causal SLE associations from certain neurological features of the disease, **only seizure and psychosis** are among the diagnostic criteria.
- Psychosis may manifest as **paranoia** or **hallucinations**.
- Delirium – altered consciousness characteristic of SLE – may be caused by CNS vasculitis, encephalopathy,
- Seizures related to SLE may be generalized or partial and may precipitate status epilepticus.
- Aseptic meningitis, myelopathy, optic neuropathy, or other demyelinating disorders may also require urgent evaluation.

- Brain stroke and transient ischemic attack (TIA) may be related to antiphospholipid antibody syndrome or vasculitis.
- Migraine headaches may also be linked to antiphospholipid syndrome, although this is less clear.
- Headache and mood disorders may be the most commonly reported neurologic manifestation of SLE, but difficult to distinguish.

Cardiac manifestations

- Heart failure or chest pain must be carefully examined in patients with SLE.
- Pericarditis that manifests as chest pain is the most common cardiac manifestation of SLE
- Myocarditis may occur in SLE with heart failure symptomatology.
- Coronary vasculitis is rare, but accelerated ischemic CAD and may present as atypical anginal equivalents due to accelerated atherosclerosis.
- Libman–Sacks endocarditis is noninfectious but may manifest as symptoms similar to those of infectious endocarditis.

Pulmonary manifestations

- Pleurisy with pleuritic chest pain with or without pleural effusions is the **most common**
- Shortness of breath or dyspnea
- Serositis due to pericardial or pulmonary effusions, pulmonary embolism, lupus pneumonitis, chronic lupus interstitial lung disease, complement-mediated pulmonary leukoaggregation,
- hemoptysis due to intraalveolar hemorrhage interstitial fibrosis - life-threatening

Gastrointestinal manifestations

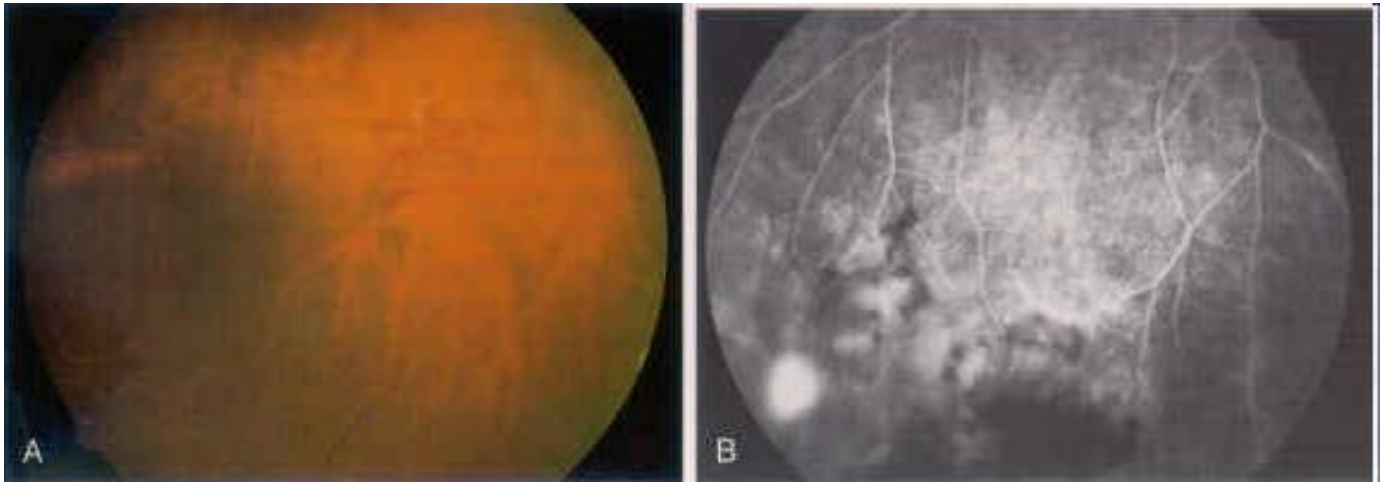
- secondary to primary SLE ora as an adverse effects of treatment
- Abdominal pain – related to active lupus, including peritonitis, pancreatitis, mesenteric vasculitis, and bowel infarction.
- Nausea and dyspepsia
- Jaundice due to autoimmune hepatitis, elevated AST, ALT

Hematologic manifestations

- Cytopenias – leukopenia (lymphopenia),
- Anemia usually normochromic,normocytic
- Hemolysis
- hypocomplementemia
- Do not overlook Anemia in young menstruating women
- Thrombocytopenia may be mild or part of a thrombotic thrombocytopenic purpura (TTP)–like syndrome or antiphospholipid antibody syndrome. (History of recurrent early miscarriages or a single late pregnancy loss)

Ocular manifestations

- Sjogren's syndrome
- Retinal vasculitis, optic neuritis

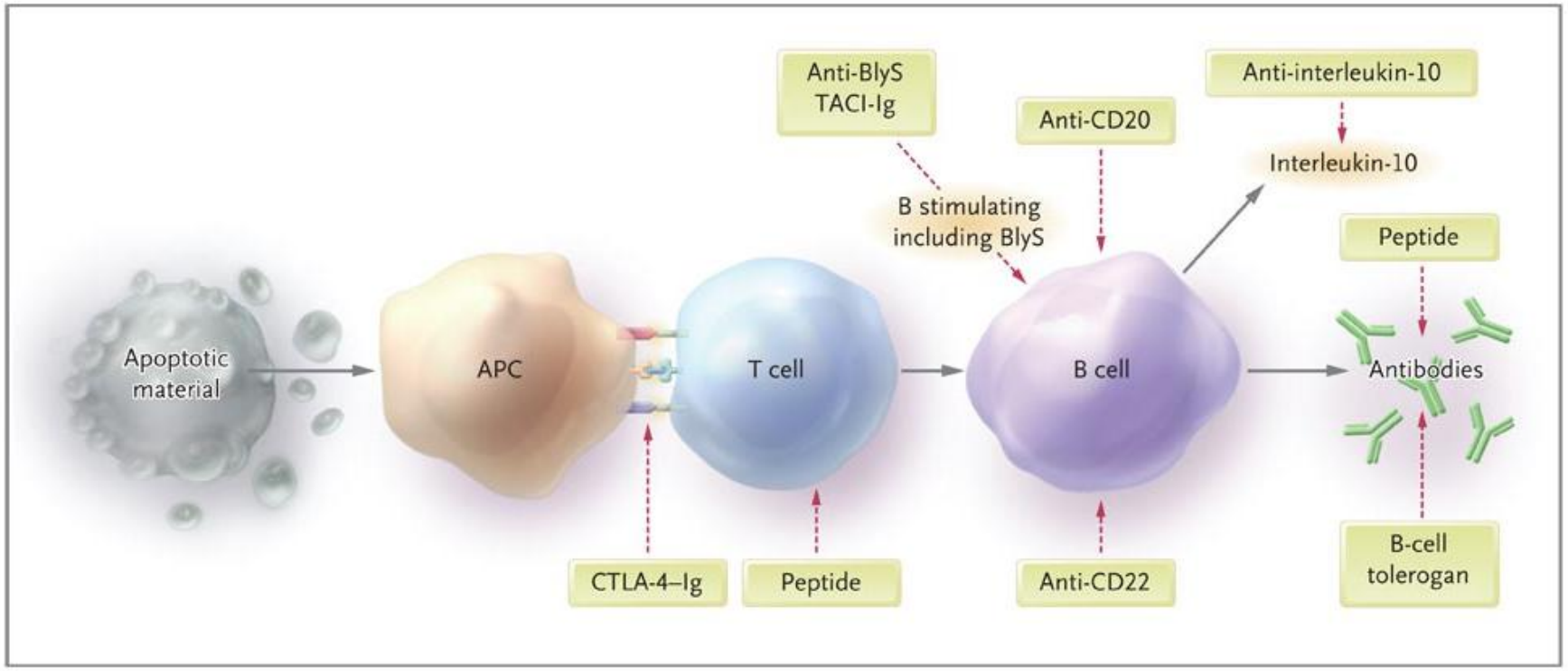


Peripheral retinal vasculitis in a patient with systemic lupus erythematosis with areas of intraretinal hemorrhage, retinal non-perfusion, and neovascularization on fluorescein angiography

treatment

- NSAIDs – symptomatic relief for arthralgias, fever, and mild serositis.
- Sunscreens
- Antimalarials (Hydroxychloroquine) – immunomodulation without overt immunosuppression for skin rashes, constitutional symptoms, arthralgias, and arthritis, reduce SLE flares

- Glucocorticoids:
  - Life-threatening SLE – methyloprednisolone 3 x 1000mg (3 days), then prednisone 0,5 – 2 mg/kg/day
- Cytotoxic drugs:
  - Methotrexate (a folic acid antagonist) – for dermatitis, arthritis,
  - Cyclophosphamide (alkylating agent) – 6 monthly dose of 500mg/m2
  - Azathioprine (a purine antagonist) – usually with clucocorticoids
  - Mycophenolate mofetil – (lymphocyte-specific inhibitor) – for lupus nephritis



Rahman A. NEJM, 2008