SYSTEMIC LUPUS ERYTHEMATOSUS

DEFINITION

- **Systemic lupus erythematosus (SLE)** - is a chronic, autoimmune inflammatory disease with unknown etiology, disorder characterized by an autoantibody response to nuclear and cytoplasmic antigens,in presence of genetic predisposition, and can affect any organ and system.

- SLE can affect any organ or system - joints, skin, vessels, and various types of organ-related disorders.

Epidemiology

SLE is spread worldwide,

Incidence rate - 1 case per 10,000 population (variations as 1.8-7.6 per 100 thousand) per year

Morbidity / prevalence rate is about 500 patients per 1,000,000 population (variations as 12 -50 cases / 100 000 population

Disease morbidity vary among various geographic areas

The incidence rate varies between 12-50 to 100,000 people, the highest being among African Americans, Asians, African-Caribbean's and Hispanics

The female/male ratio is 3: 1 in children, which is increasing to 7-15: 1 in adults.

MORTALITY

- The survival rate of patients whit 10-years SLE now exceeds 90%. Prior to 1955, the 5-year survival rate was less than 50%.

Race and ethnicity

The frequency of SLE rate varies between 12-50 to 100,000 people, the highest being among African Americans, Asians, African-Caribbean's and Hispanics.

The incidence of SLE in black women is approximately 4 times higher than in caucazian women.

SLE is more frequent in Asian women than in white women.

The disease is rarely reported among blacks who live in Africa.

SEX-RELATED DEMOGRAPHICS

- The prevalence of SLE is highest among women in reproductive period, bat the age limits varied from 14 to 64 years.
- For all ages, the female-to-male ratio is 8:1 and 10:1 during the childbearing years.
- The risk of SLE development in men is similar to that in prepubertal or postmenopausal women.
- SLE does not have an age predilection in males.
-

ETIOLOGY

- Although the specific cause of SLE is unknown, multiple genetic predispositions and gene-environment interactions have been identified. This complex situation perhaps explains the variable clinical manifestations in persons with SLE

- Multiple factors are associated with the development of the disease, including -
- **genetic,**
- **racial,**
- **hormonal,**
- **and environmental factors.**
- Many immune disturbances, both innate and acquired, occur in SLE.

ROLE OF INFECTIOUS ETIOLOGIES

- ***Numerous studies have investigated the role of infectious etiologies.***
- **Viruses** ***may stimulate specific cells in the immune network.***
- Different viruses are suspected, due to the presence of antiviral antibodies **(anti-ARN şi anti-ADN)** including to protein regions homologous to nuclear antigens.
- **Epstein-Barr virus (EBV)** – may perpetuate autoimmunity. Patients with SLE have higher titers of antibodies to EBV, have increased circulating EBV viral loads.
- **Anothers viruses are suspected: rubella, rubeola, citomegalovirus, retroviruses**, but the attempts to isolate the virus from the tissues of patients with SLE fails.

Bacterial infection

Certains bacterias (ex. Mycobacterial infections) may induce anti-DNA antibodies (or another antibodies) even lupuslike symptoms, and lupus flares may follow bacterial infections.

GENETIC-SUSCEPTIBILITY FACTORS

- A genetic predisposition is supported by the 25% concordance among monozygotic twins versus 2% in dizygotic twins. In monozygotic twins the Morbidity is approximately 10 times higher than in dizygotic.

The immune damages in family of patients with SLE are frequent.

Detection of antinuclear, antilimfocitary antibody and false positive test for lues at the I degree relatives.

It also proven that in the SLE patients families the incidence of other systemic connective tissue diseases is higher.

- Studies of the human leukocyte antigens (HLA) reveal that **HLA-A1, B8, HLA-DR2 and DR3** are more common in persons with SLE than in the general population.
- **the presence of antinuclear antibody Is in correlation whit HLA A2, B7 şi DR3**

  More than 10 gene loci are known to increase the risk of SLE.

Congenital deficiencies of complement - **C1,C2,C4,C5,C8** (especially C4, C2) are also associated with an increased risk of SLE.

Complement deficiency – C2, C3 şi C4 at the I degree relatives.

Endocrine – related factors

1. The negative influence of estrogens in the evolution of SLE (change for the worse during the pregnancy and in the post-partum period).
2. Breastfeeding is associated with a decreased risk of developing SLE.
3. SLE frequently starts at women of childbearing age, and the use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease.
4. The protective role of androgens in SLE.

- **UV rays**

Photosensitivity is clearly a precipitant of skin disease. UV stimulate cells apoptosis and production of autoantigens **, induce autoimune process in persones with genetics predispozition.**

UV radiation stimulate production of IL-1, favorize the immune reaction

- **vitamin D levels**
  - The results of some study suggest that low vitamin D levels increase autoantibody production in healthy individuals;

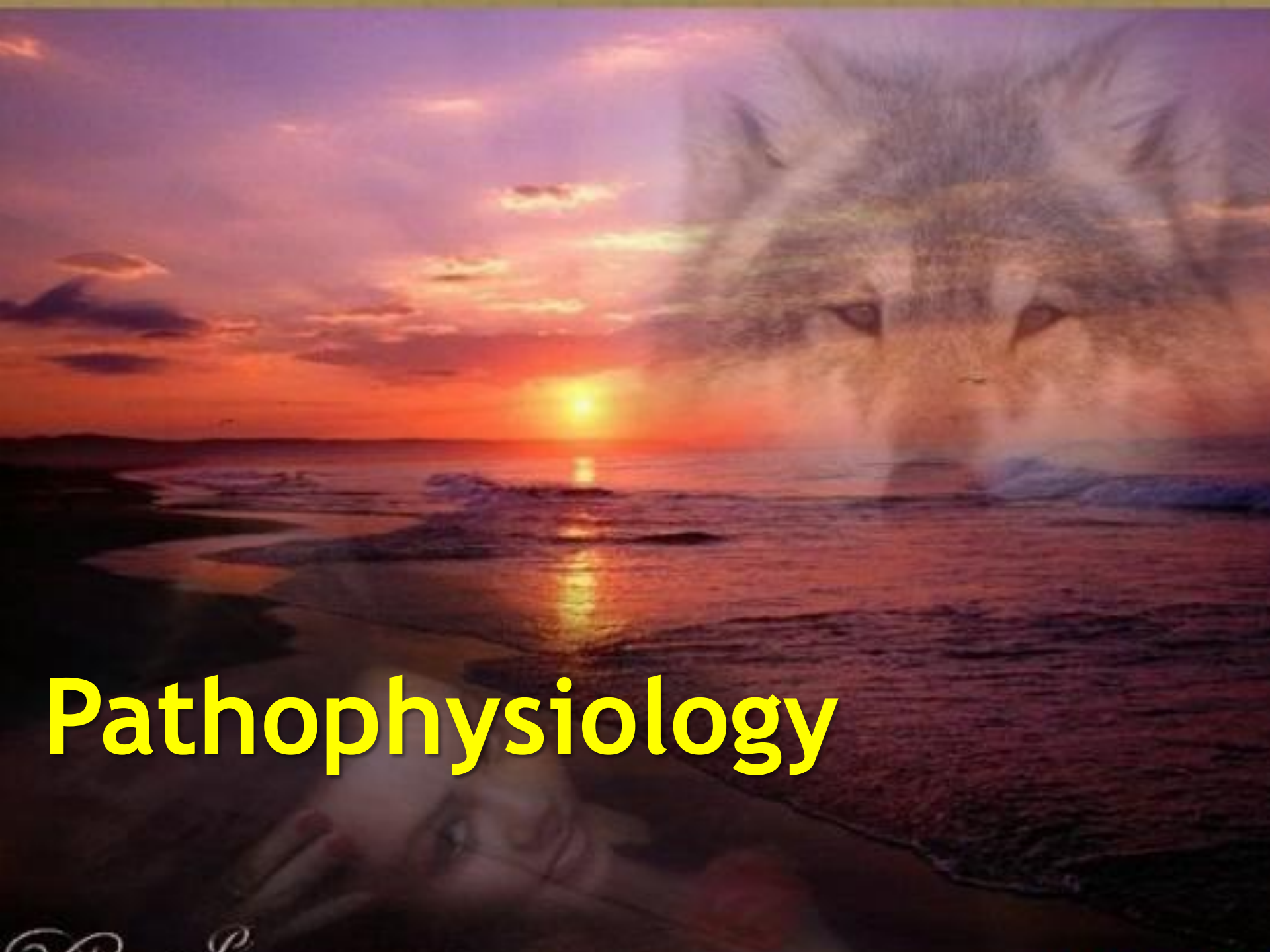
DRUG INDUCED SLE:

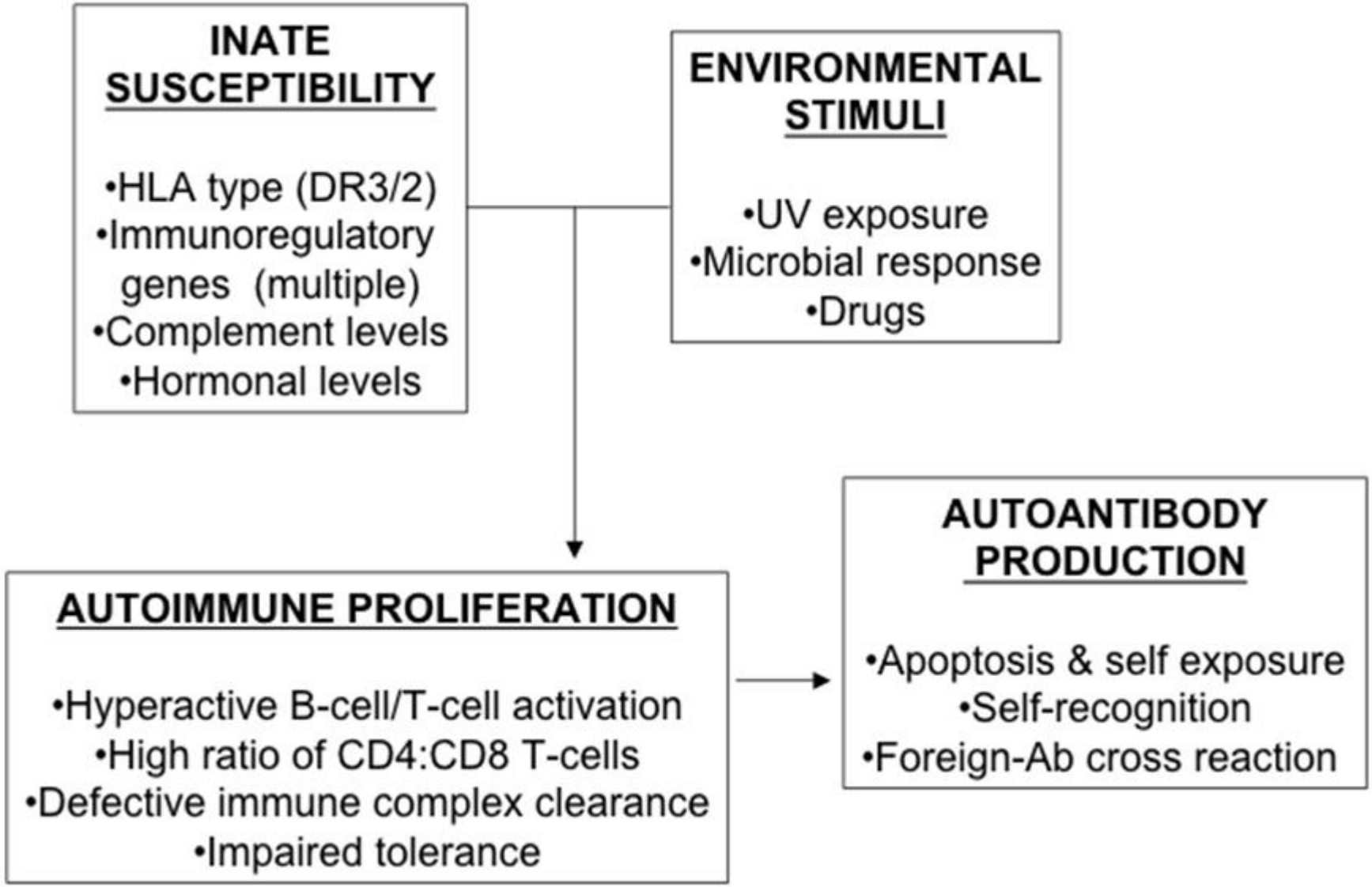
- Antibacterial- Izoniazid, certain antibiotics;
- Cardiovascular drugs - Procainamid, Hidralazin, Metildopa;

Antitiroid drugs- Metiltiouracil;

Contraceptives

The drugs are more likely to aggravate the evolution of pre - existent SLE


Pathophysiology



In systemic lupus erythematosus (SLE), many genetic-susceptibility factors, environmental triggers, antigen-antibody responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity.

LUPUS PATHOGENESIS IS CAUSED BY TWO CLOSELY RELATED PROCESSES:

I.Immunological factor

At an early stage the polyclonal (B - cell) immune activation dominates, later on - an antigen-specific T-cell immune reaction prevails.

II. Imparied apoptosis

Fundamental immune disorder underlying lupus erythematosus - congenital or induced defects programmed cell death (apoptosis)

I. SLE – IMUNOCOMPLEXE DISEASE, DEFINED:

- **The specific cause of SLE is unknown, immune-system disorders and immune-complex tissue damage are suspected. Multiple immune disturbances may predispose to SLE :**
- Dysfunction of T- and B – lymphocytes (depression of T- suppressors, hiperreactivity of B lymphocytes , amplification of B lymphocytes function and in consequence - antibodies hyper production against intracellular components (ADN, nucleoproteins ribonucleoproteins) and CIC formation .

IMMUNOLOGICAL FACTOR

- Th lymphocytes increases, they become more active,
- Thereupon occurs Th / Ts imbalance for Th,
- Th cooperates with B-lymphocytes,
- B-cell activation results in excessive auto - antibody production to a variety of antigens (antinuclear, anti-cytoplasmic, anti-DNA double stranded and single-stranded,

  anti-RNA anti-plasma membrane) and hypergammaglobulinaemia .

MORE CHARACTERISTIC FOR SLE ARE:

- anti-double-stranded DNA,
- anti-Sm,
- antiRNP (anti riboproteinic)
- anti-nucleoproteins,
- anti-Ro.

Antibodies are immunoglobulins IgG and IgM class

SERUM ANTINUCLEAR ANTIBODIES

- Serum antinuclear antibodies (ANAs) are found in virtually all individuals with active SLE, and a*ntibodies to native double-stranded DNA (dsDNA)* are relatively specific for the diagnosis of SLE.

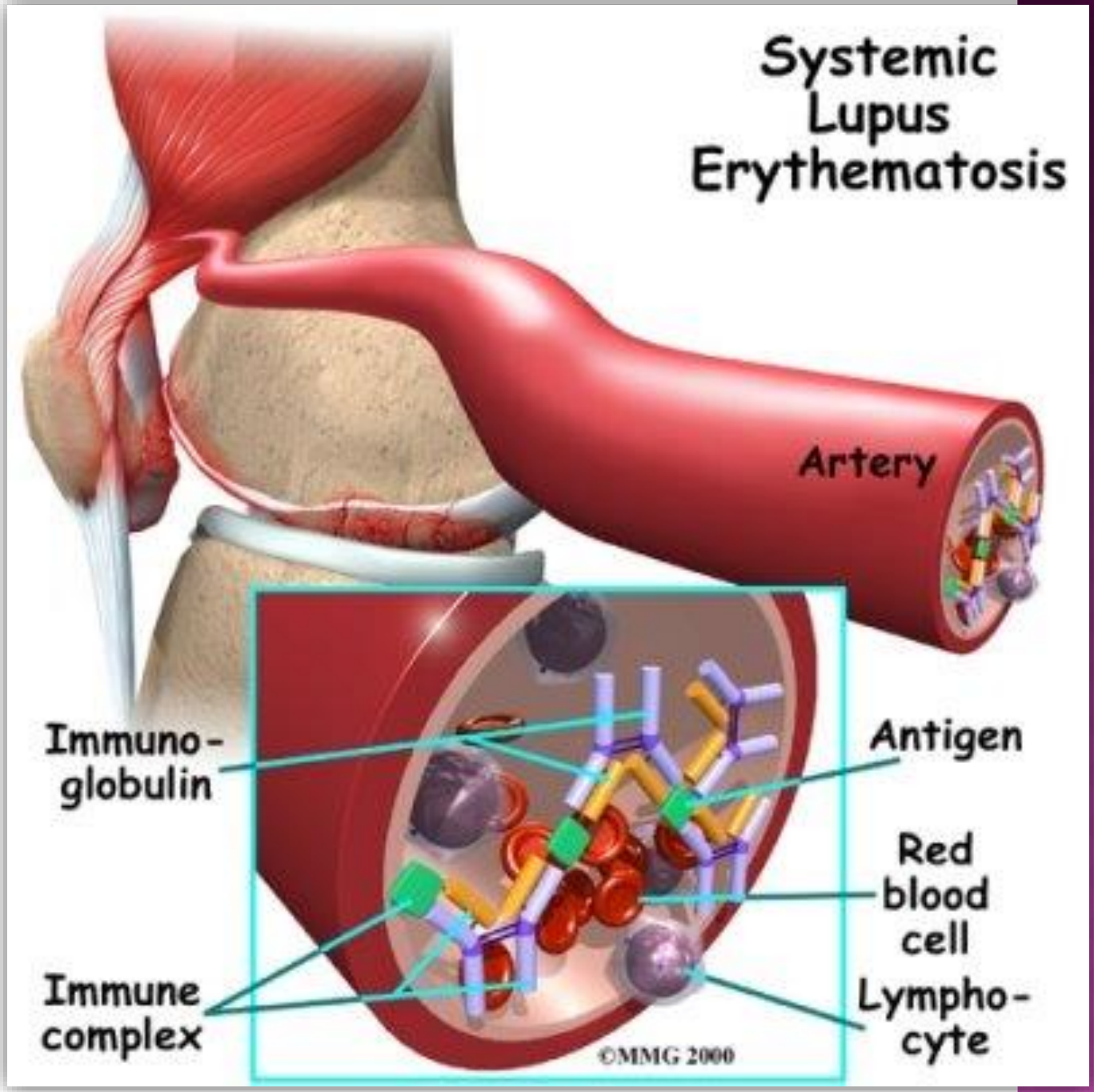
- Many of the clinical manifestations of SLE are caused by the effects of **circulating immune complexes.**
- Antibodies are linked to antigens, forming **circulating immune complexes** (CIC) -(DNA + anti-DNA), with complement activation and inflammation.

- *Antibody-antigen complexes deposit on the different tissues (ex. basement membranes of skin and kidneys, serous membranes, visceral organs) cause vaculities and various clinical manifestations.*

- *The effects of circulating immune complexes on various tissues or the direct effects of antibodies to cell surface components determine:*

1. complement activation
2.Inflammatory reaction development,
3. neutrophyls migration
4. cytokines and other lesion substances release.

In active SLE, this process has been confirmed by demonstration of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites.

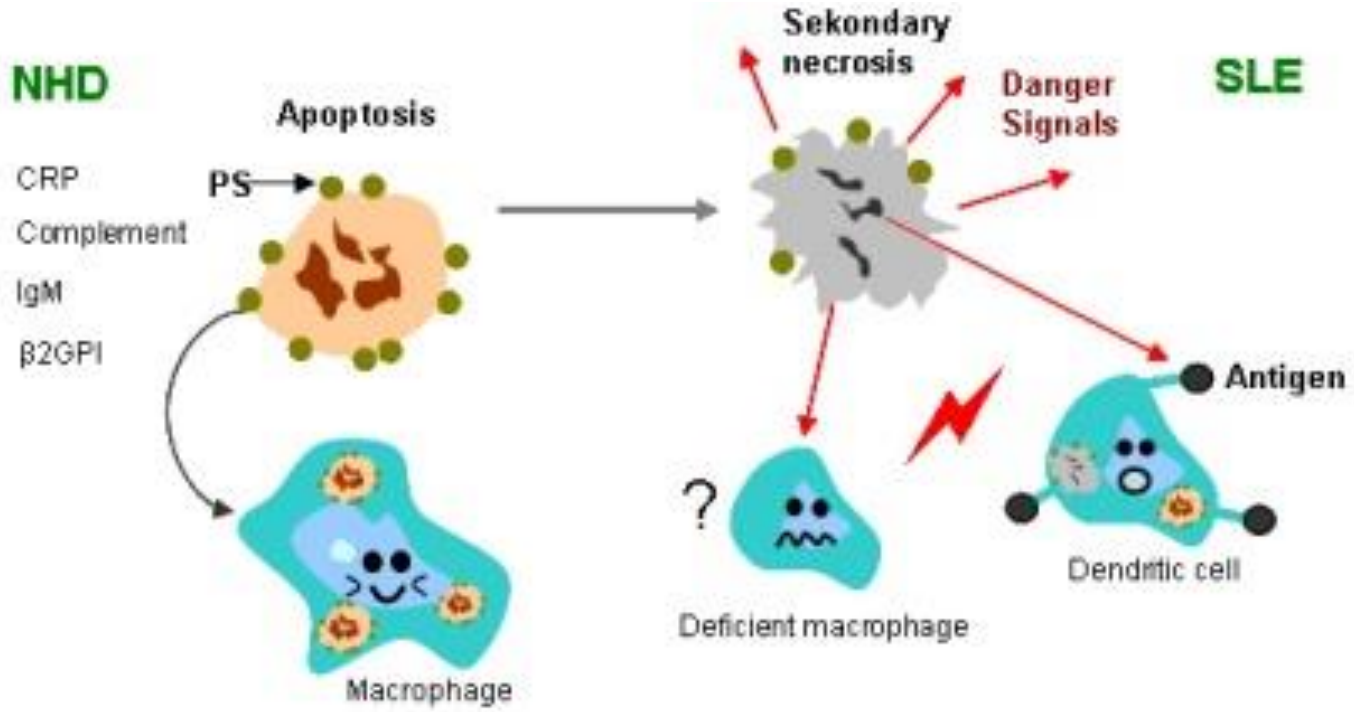


INFLAMMATORY REACTION

- The inflammatory reaction are associated with producing proinflammatory cytokines (Il - 1, Il -2) - with chemotactic and vasoactive action for neutrophyls and proinflammatory lizozomale enzymes.

II. IMPARIED APOPTOSIS

- One proposed mechanism for the development of autoantibodies involves a **defect in apoptosis** that causes increased cell death and a disturbance in immune tolerance.
- Recent evidence suggests that initially there is increased apoptosis of lymphoid cells. Nucleosomes (i.e. the DNA histone chromatin constituents) are released from these cells and are taken up by antigen-presenting cells via nucleosome receptors. They are presented to T cells that stimulate B cells to produce autoantibodies directed against these nucleosomes and their constituents (e.g. DNA).Different subsets of autoantibodies may be responsible for the various clinical patterns.



→ Clearance of apoptotic cells by macrophages is efficient

→ Cells don't become secondary necrotic and danger signals are not released

→ No establishing of autoantigens and no inflammation

Tolerance

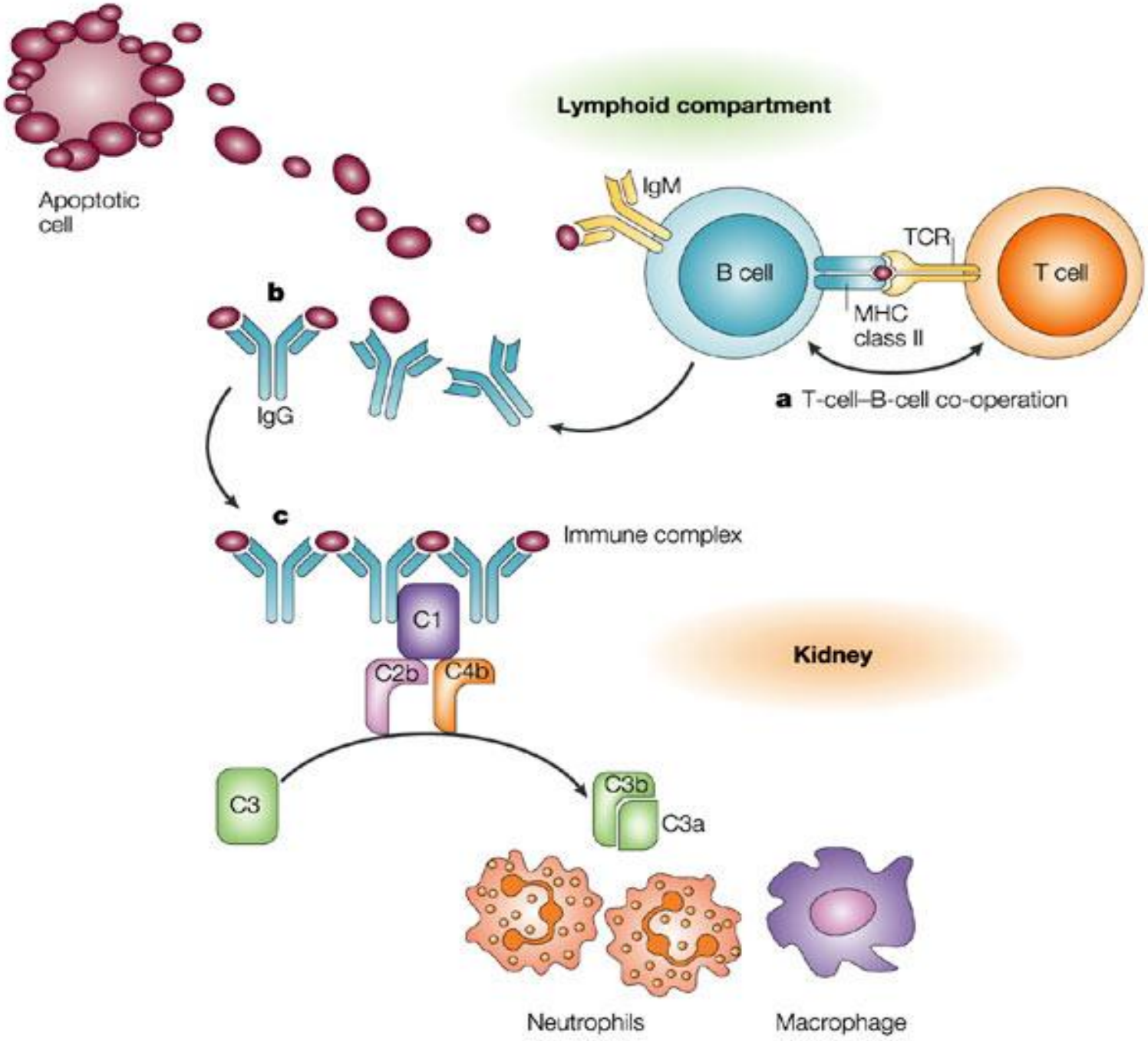
→ Clearance of apoptotic cells by Macrophages is impaired

→ Danger signals released by secondary necrotic cells

→ Accessibility of autoantigens and inflammation

Chronic Autoimmunity

Fig. *"Defects in the clearance of apoptotic cells is a possible pathway to autoimmune disease"*
CRP → C-reactive protein, PS → phosphatidylserine, IgM → immunoglobulin M, ß2GPI → ß2 glycoprotein I, SLE → systemic lupus erythematosus, NHD → normal healthy donor


Lymphoid compartment
Apoptotic cell
IgM
B cell
TCR
T cell
MHC class II
a T-cell–B-cell co-operation
b
IgG
c
Immune complex
C1
C2b
C4b
Kidney
C3
C3b
C3a
Neutrophils
Macrophage

- The redistribution of cellular antigens during apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Thus, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens.

CLASSIFICATION

(Nasonova V.A.,1986.)

I. **Depending on the evolution:**
   1. **Acute,**
   2. **Subacute,**
   3. **Cronic.**

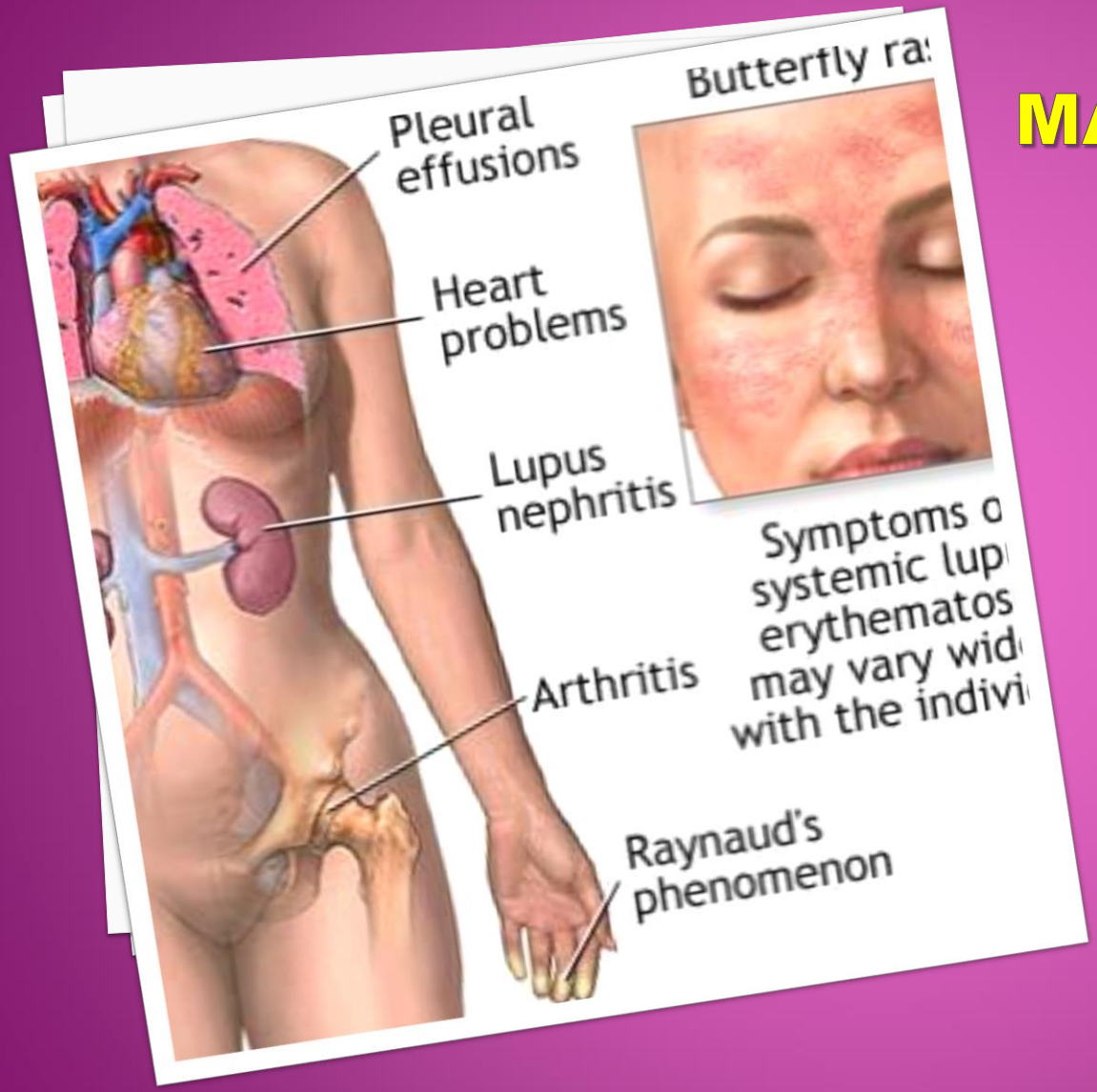
II. Depending on the disease activity :
   1. **Minimal.**
   2. **Moderate.**
   3. **Maximal.**

HISTORY (CLINICAL MANIFESTATIONS)

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system.
- SLE is characterized by: exacerbations and remissions (sometimes spontaneous).
- Its onset, presentation and course are highly variable, ranging from indolent to fulminant.

- **The triad of fever, joint pain, and rash in a woman of childbearing age should suggest the diagnosis of SLE. This is one of the most common presentations of SLE. However, patients may present with any of the following types of manifestations:**
- **Constitutional**
- **Dermatologic**
- **Musculoskeletal**
- **Pulmonary**
- **Cardiac**
- **Renal**
- **Neuropsychiatric**
- **Gastrointestinal**
- **Hematologic**
- **In patients with suggestive clinical findings, a family history of autoimmune disease should raise further suspicion of SLE.**

CLINICAL MANIFESTATIONS



CONSTITUTIONAL SYMPTOMS (GENERAL FEATURES)

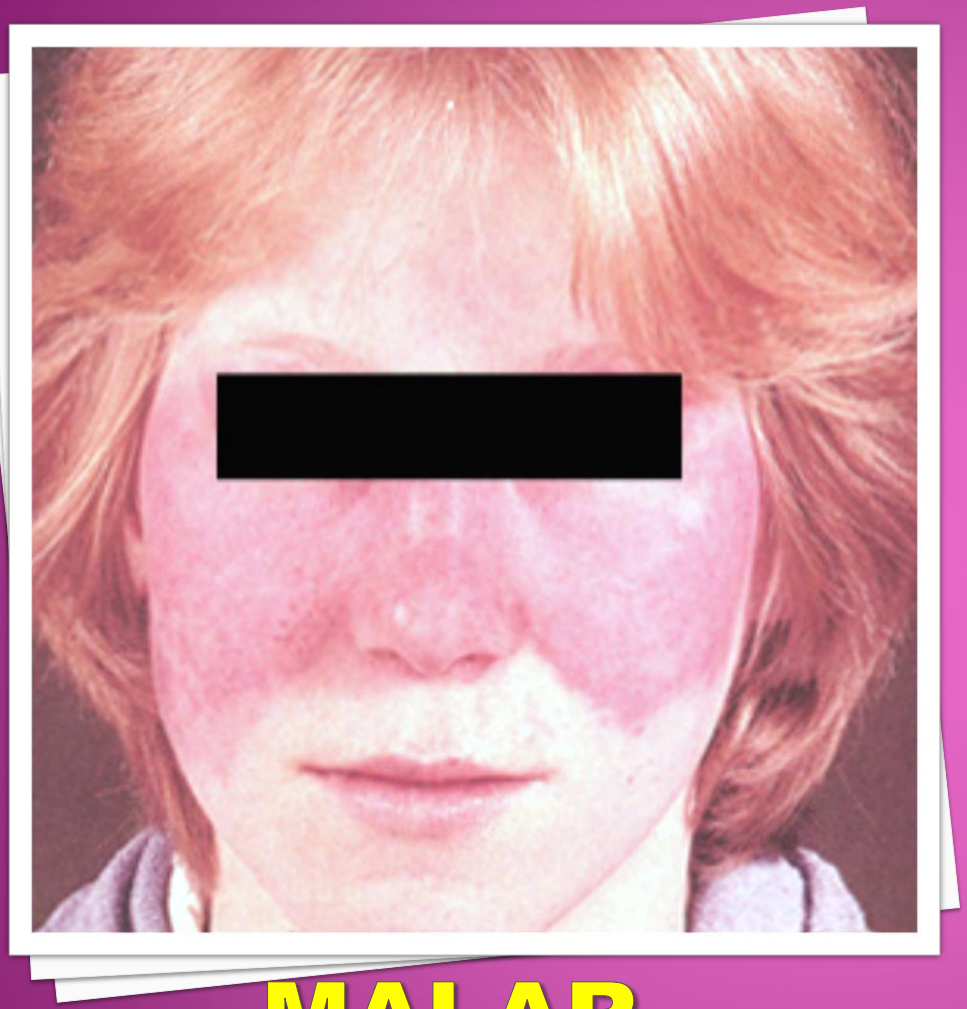
- Nonspecific fatigue,
- fever,
- weight changes
- arthralgia,

are the most common symptoms in new cases or recurrent active SLE flares.

Constitutional symptoms associated with SLE, generally occurs in concert with other clinical and laboratory markers.

CUTANEOUS MANIFESTATIONS

- **20-25% of patients with lupus have skin damage already disease onset, 60-70% - in different evolution stage, in 10-15% - cutaneous manifestations are missing**
- Cutaneous manifestations of SLE are very variable, comprise **4 diagnostic** criteria and multiple other clues to a potential diagnosis of lupus.

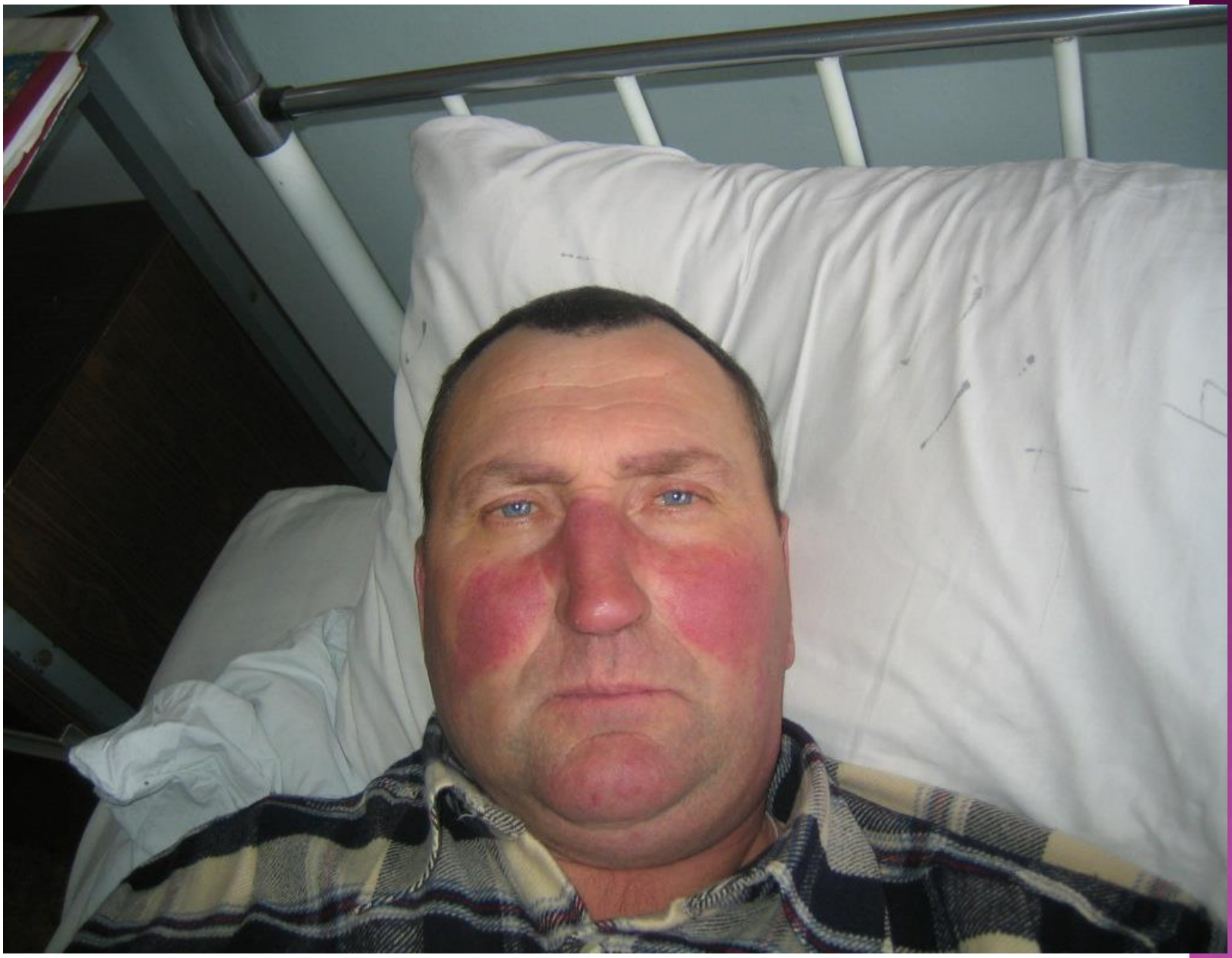


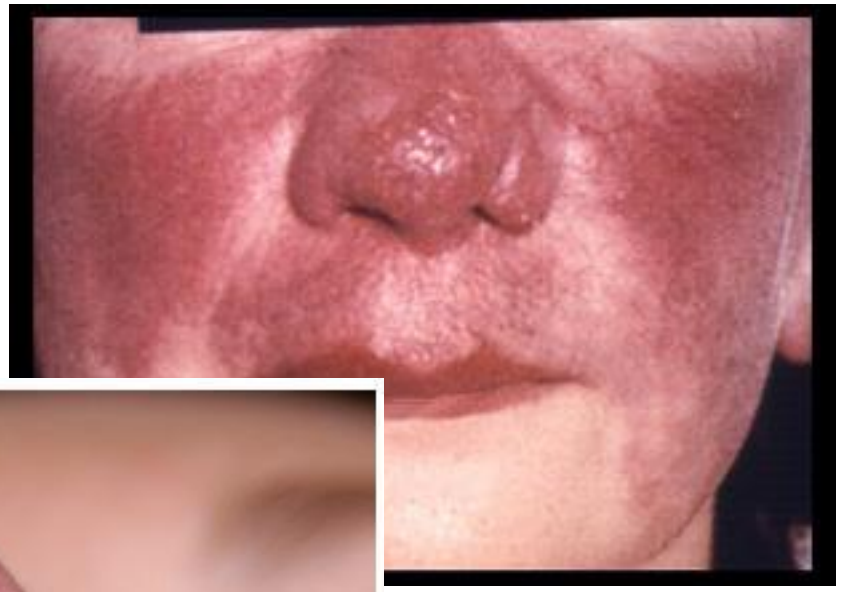
MALAR RASH

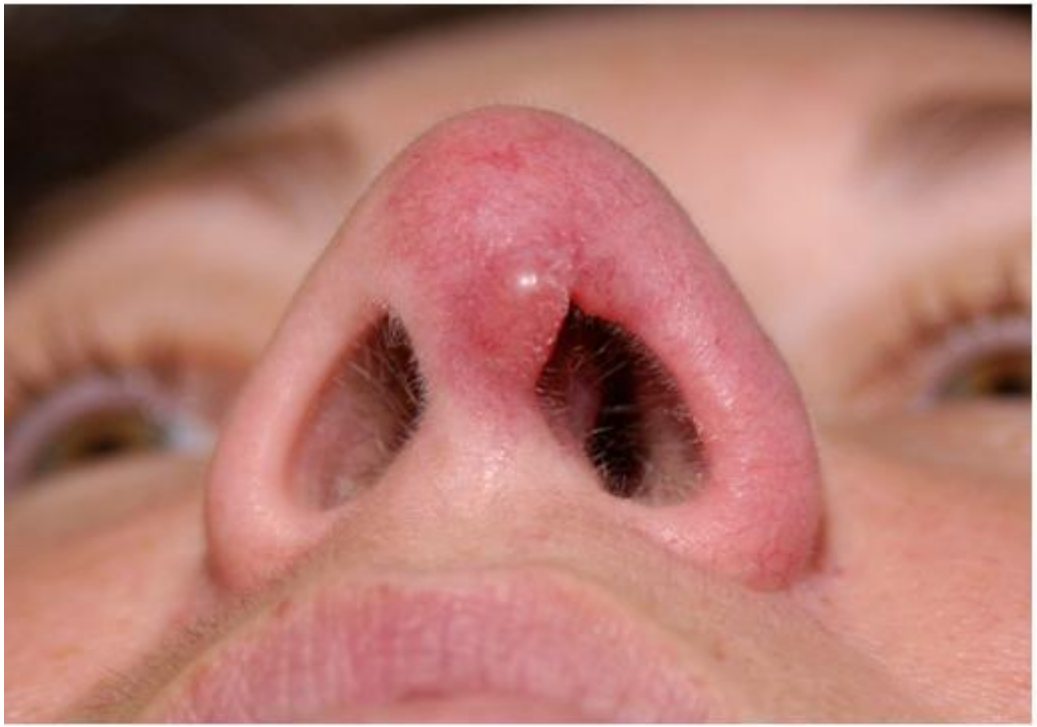
Malar rash

which is characterized by an erythematous rash (dermatitis) over the cheeks and nasal bridge who remember a butterfly.

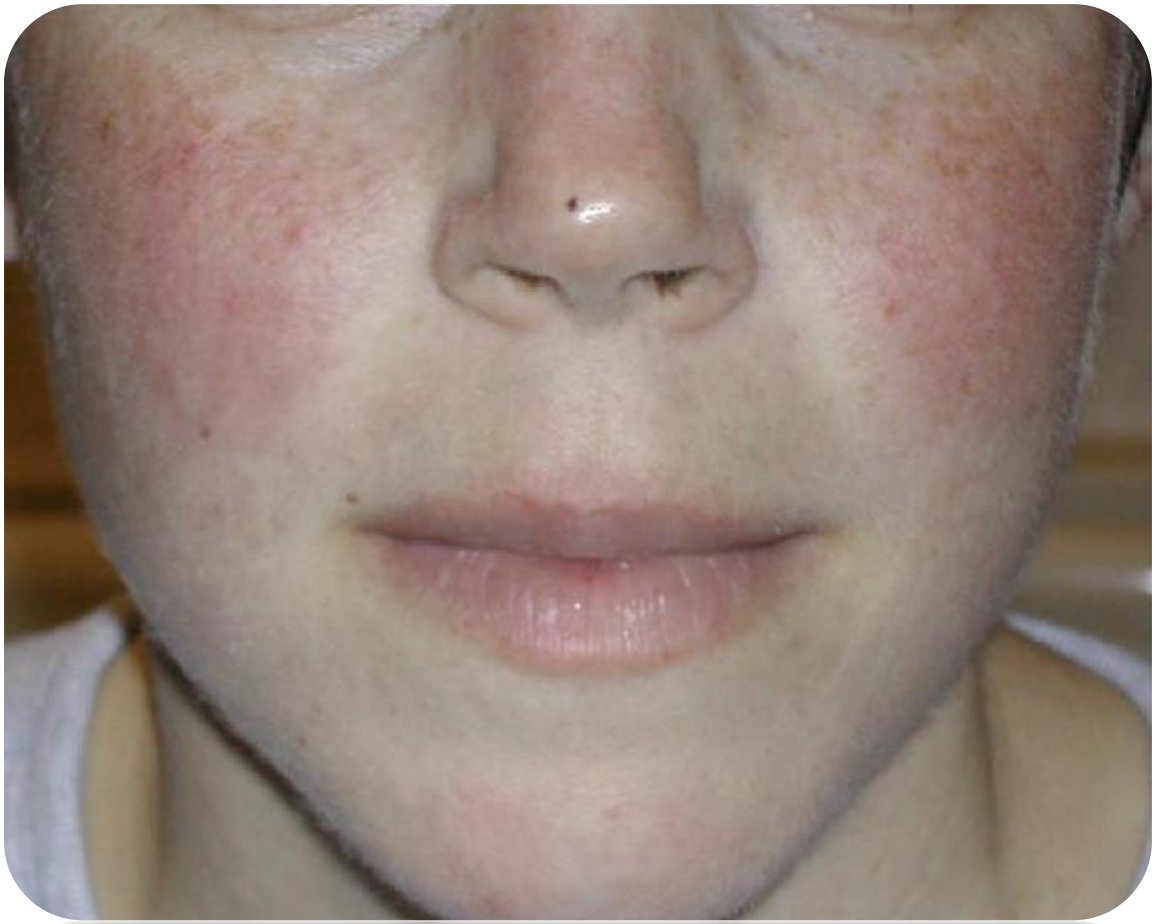
It lasts from days to weeks and is occasionally painful or pruritic.

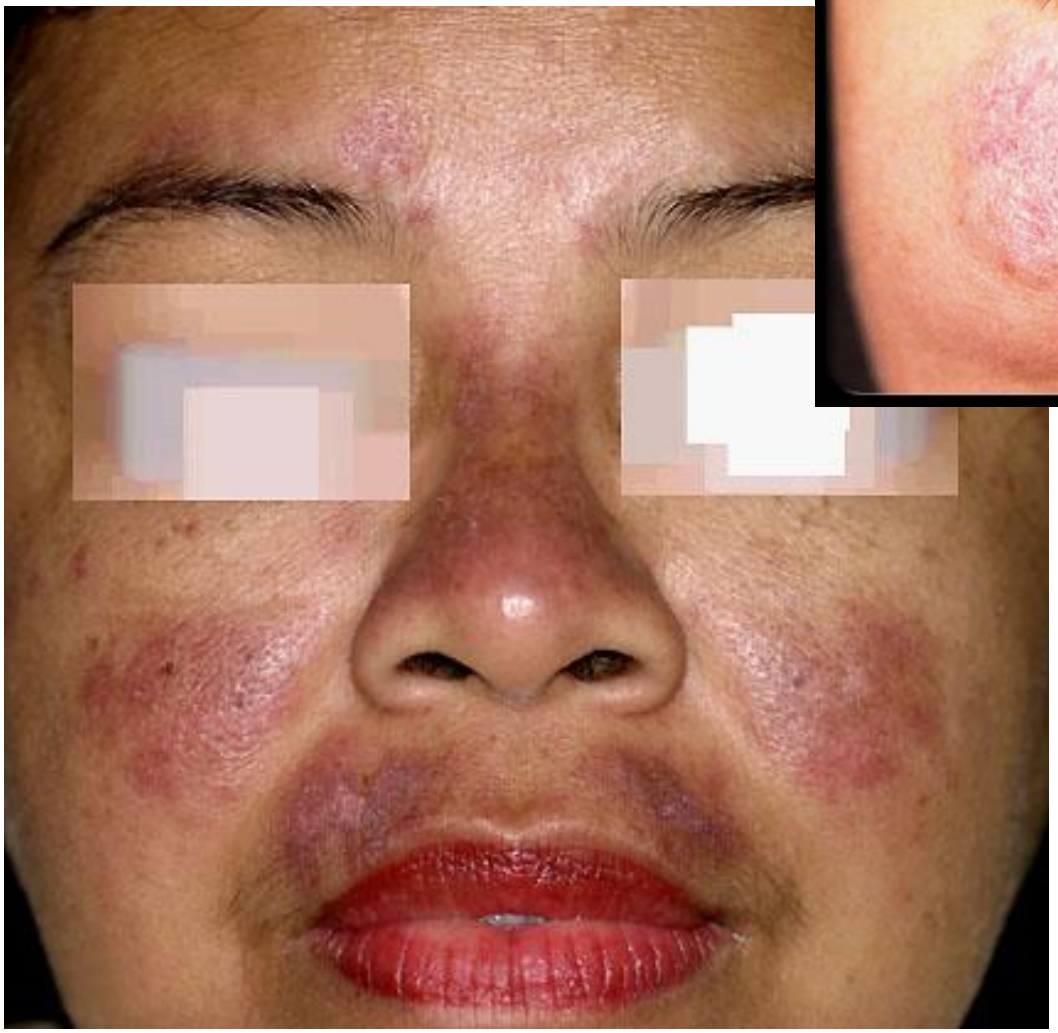


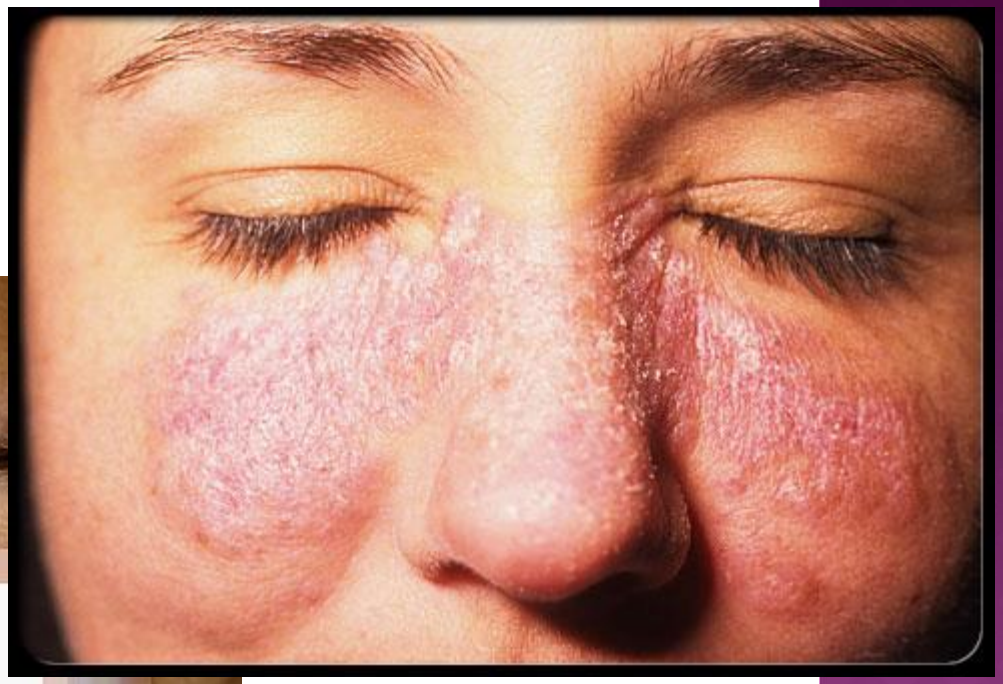


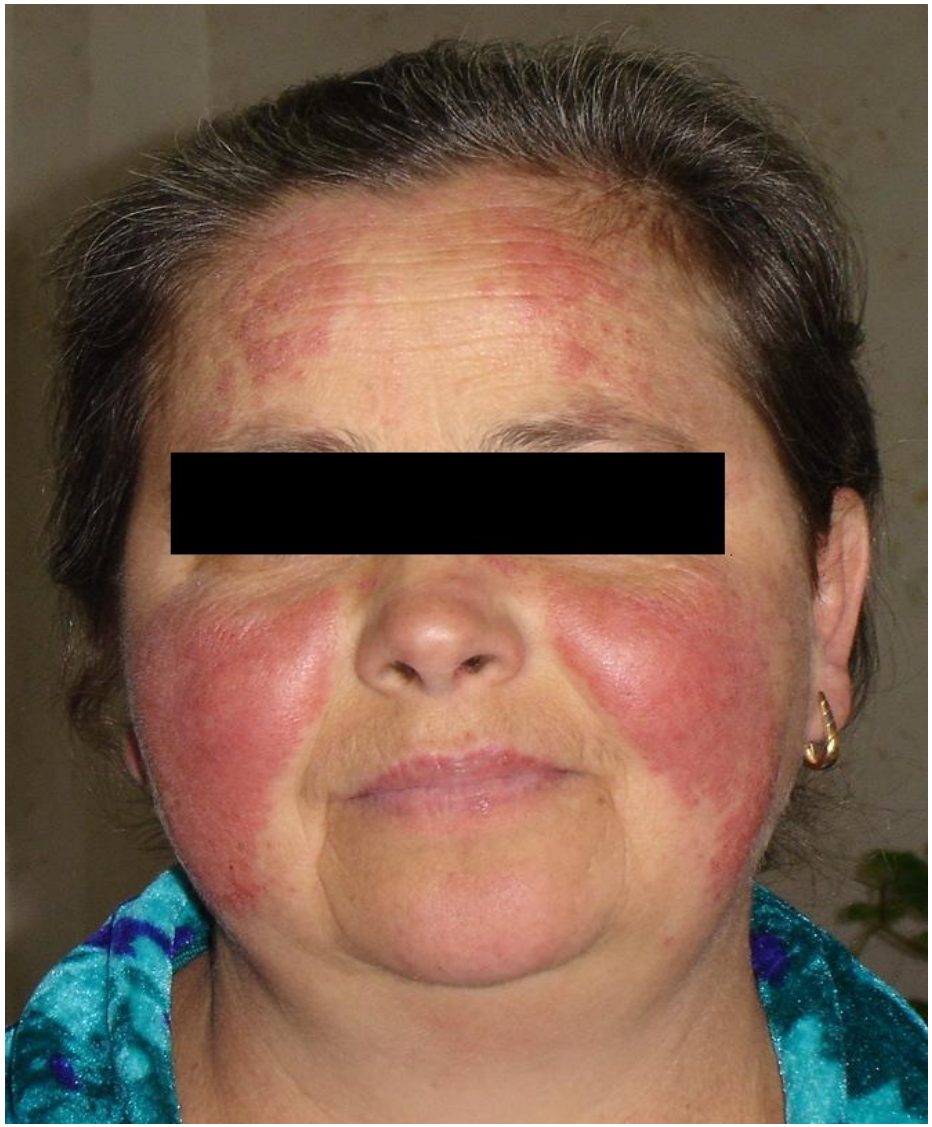


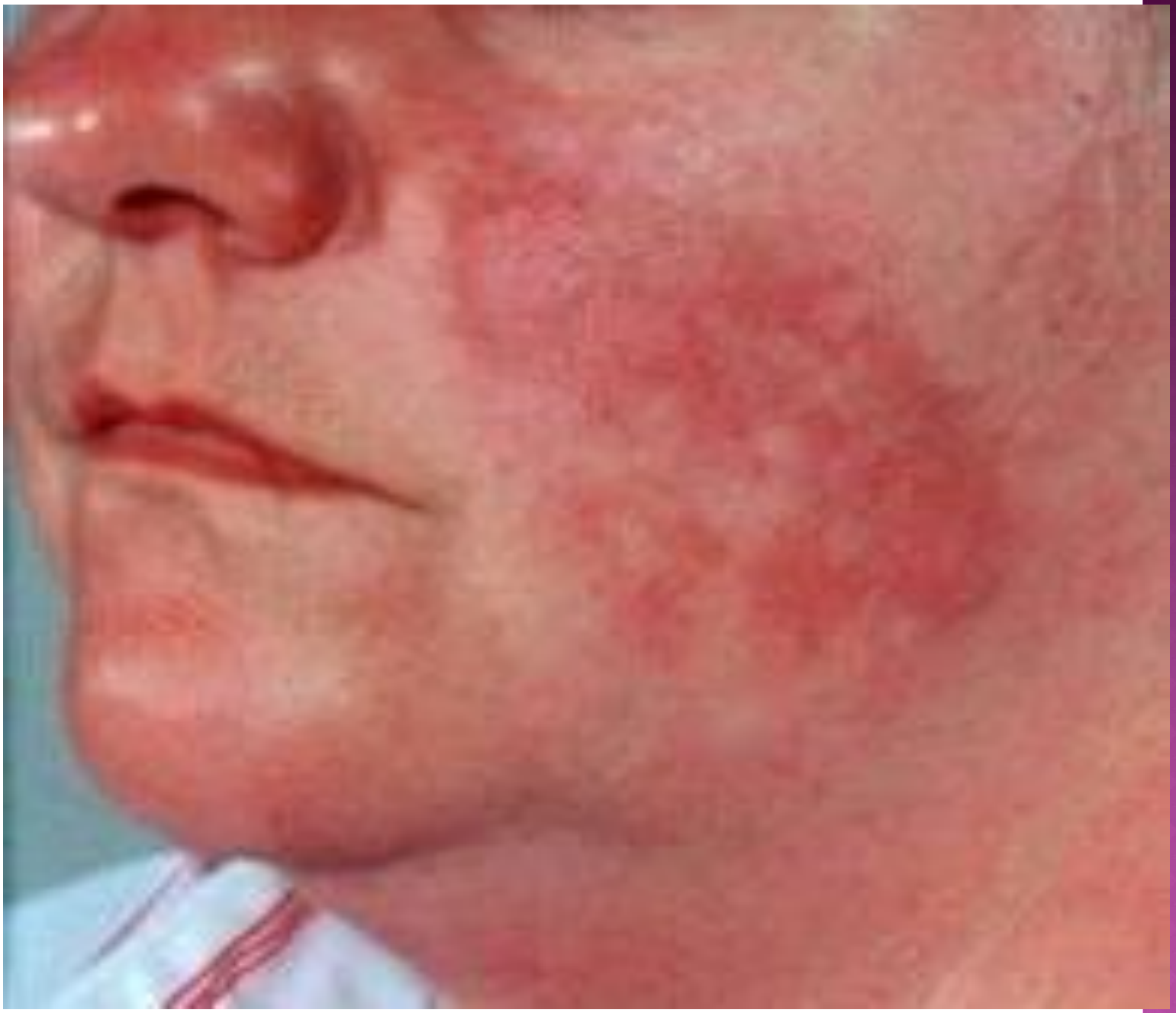
- **The classic malar rash, also known as a butterfly rash, with distribution over the cheeks and nasal bridge. Note that the fixed erythema, sometimes with mild induration as seen here, characteristically spares the nasolabial folds.**

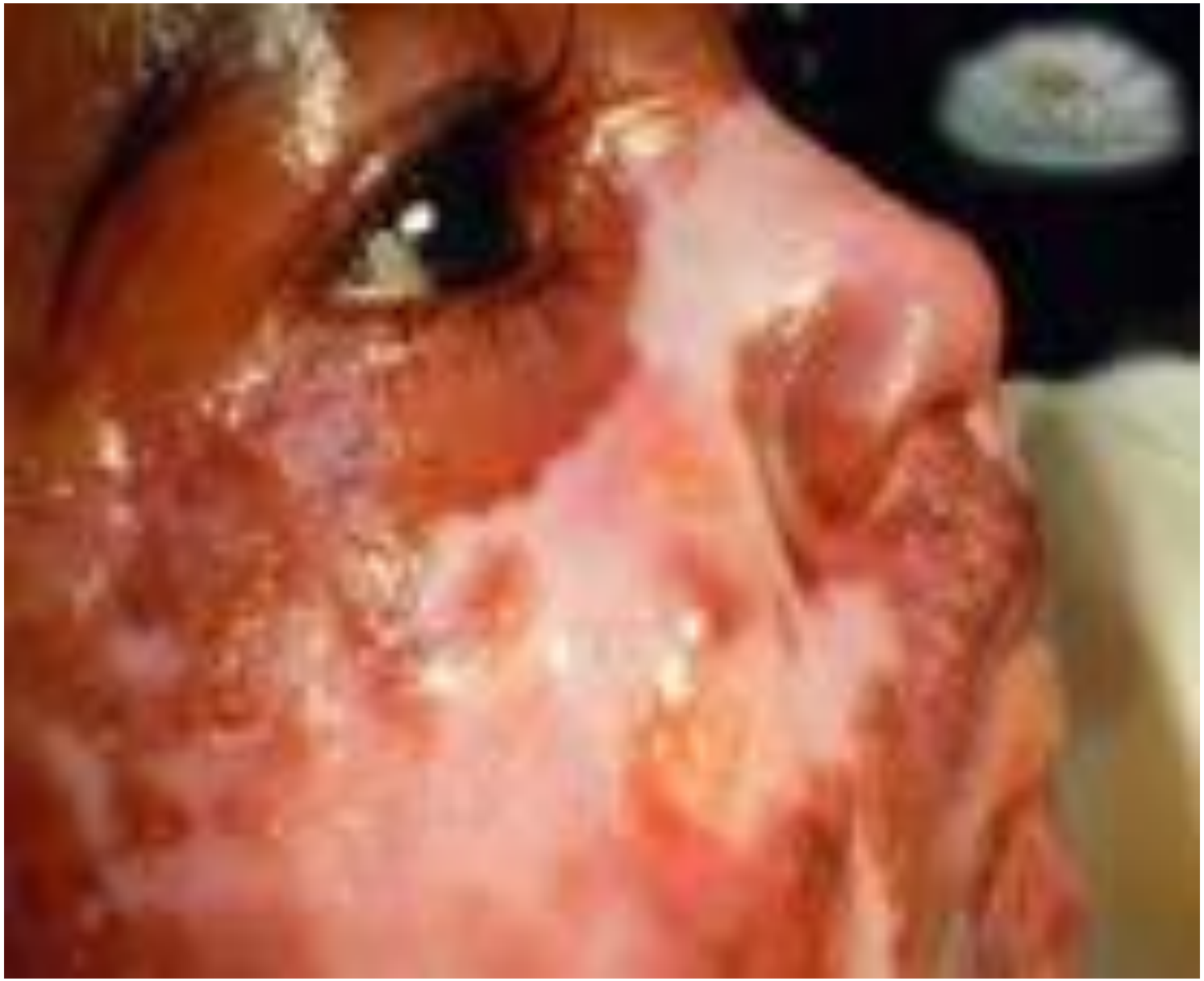




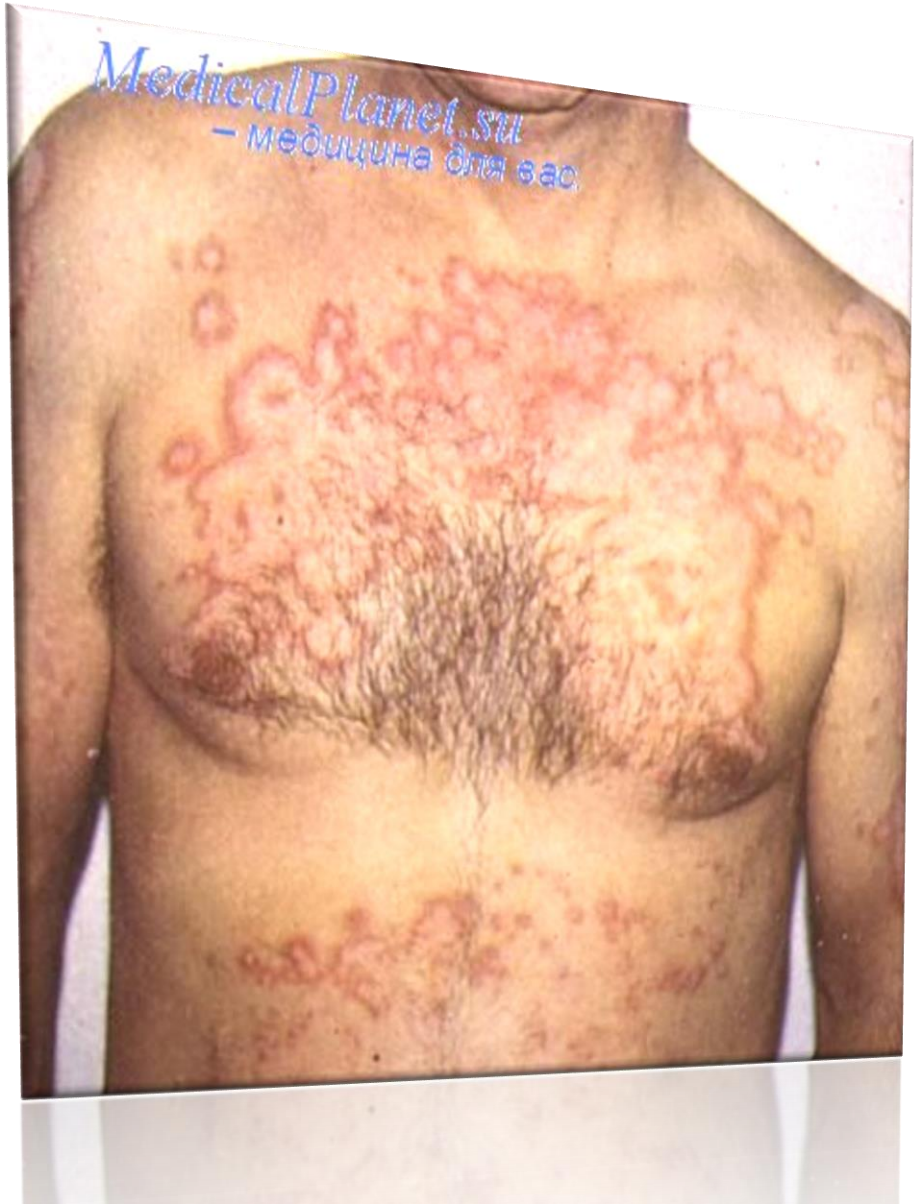


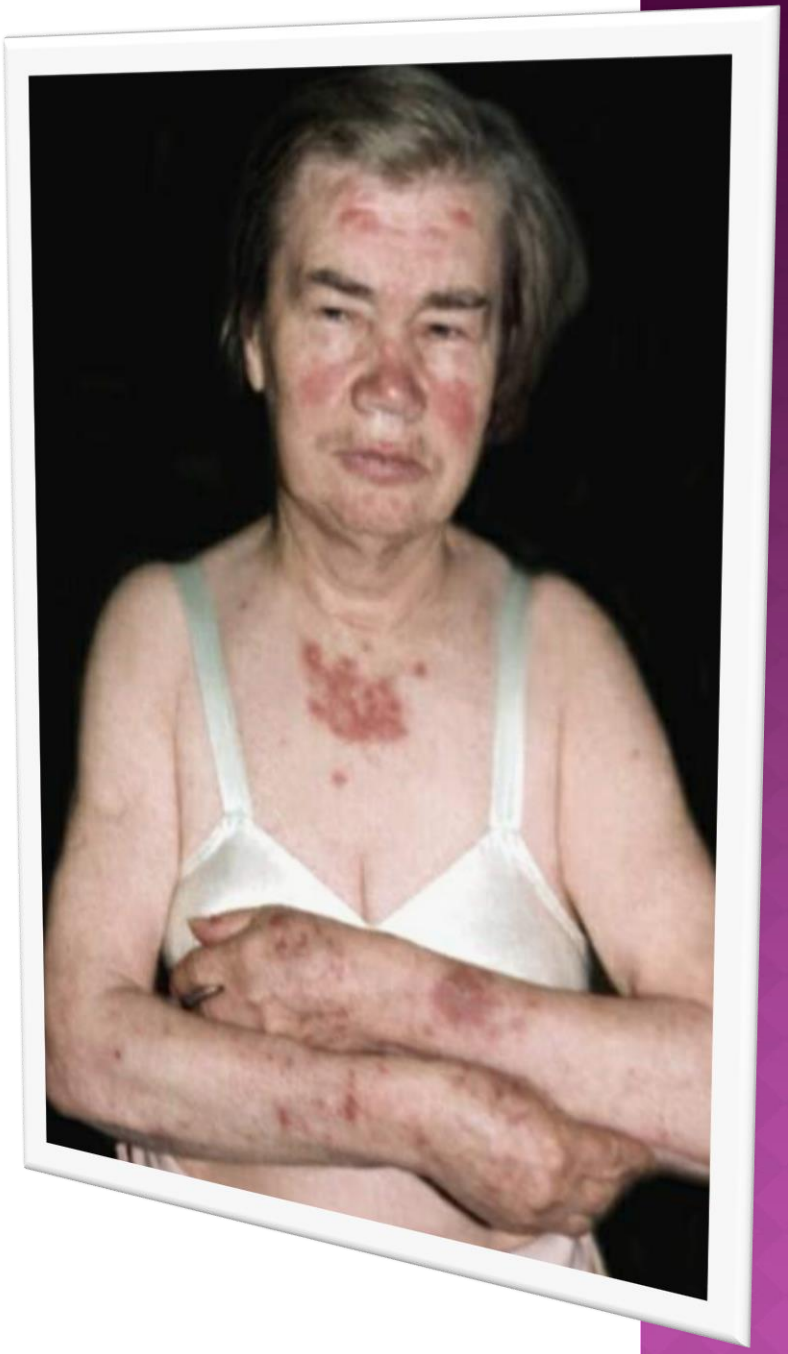


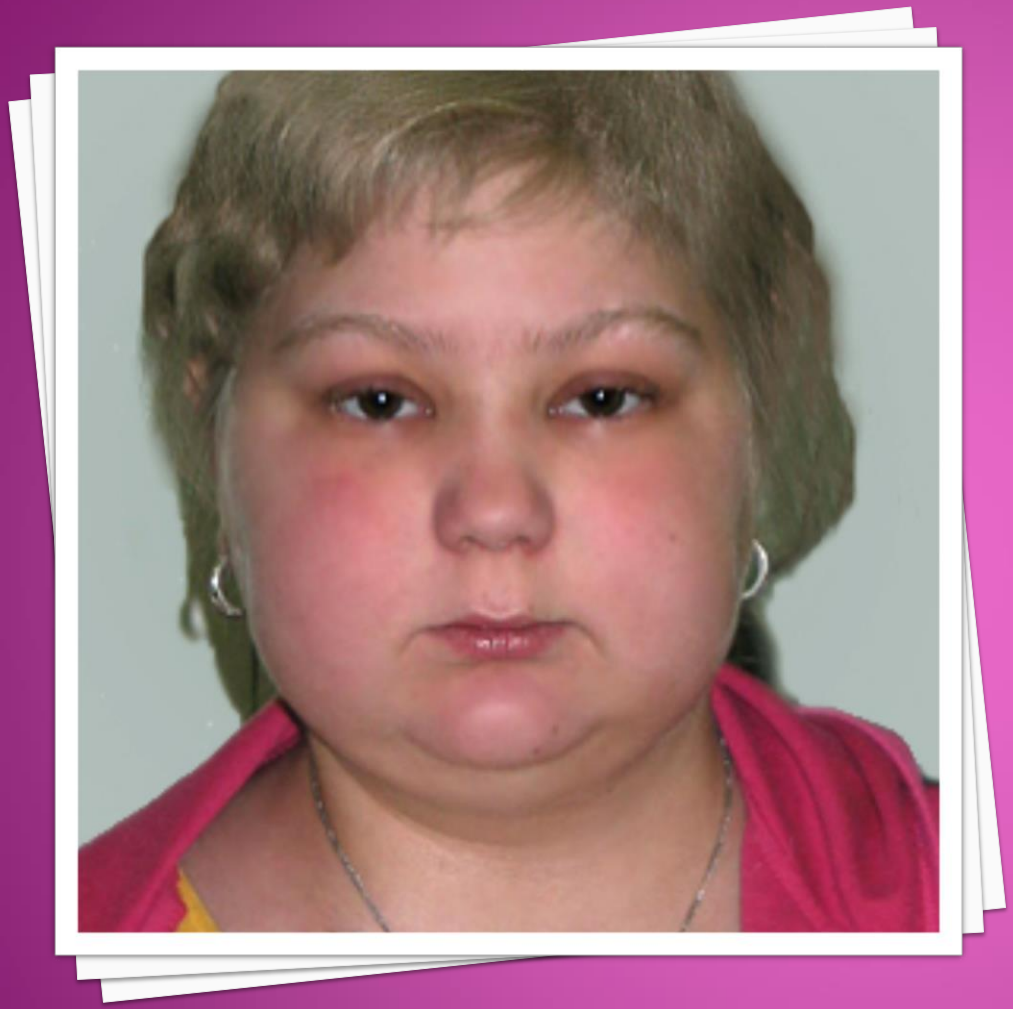




- SLE is characterized by annular erythematous and infiltrated formations with moderate atrophy and teleangiectasia elements, with subsequent formation of hypo pigmented or hyper pigmented scars.


MedicalPlanet.su
– медицина для вас

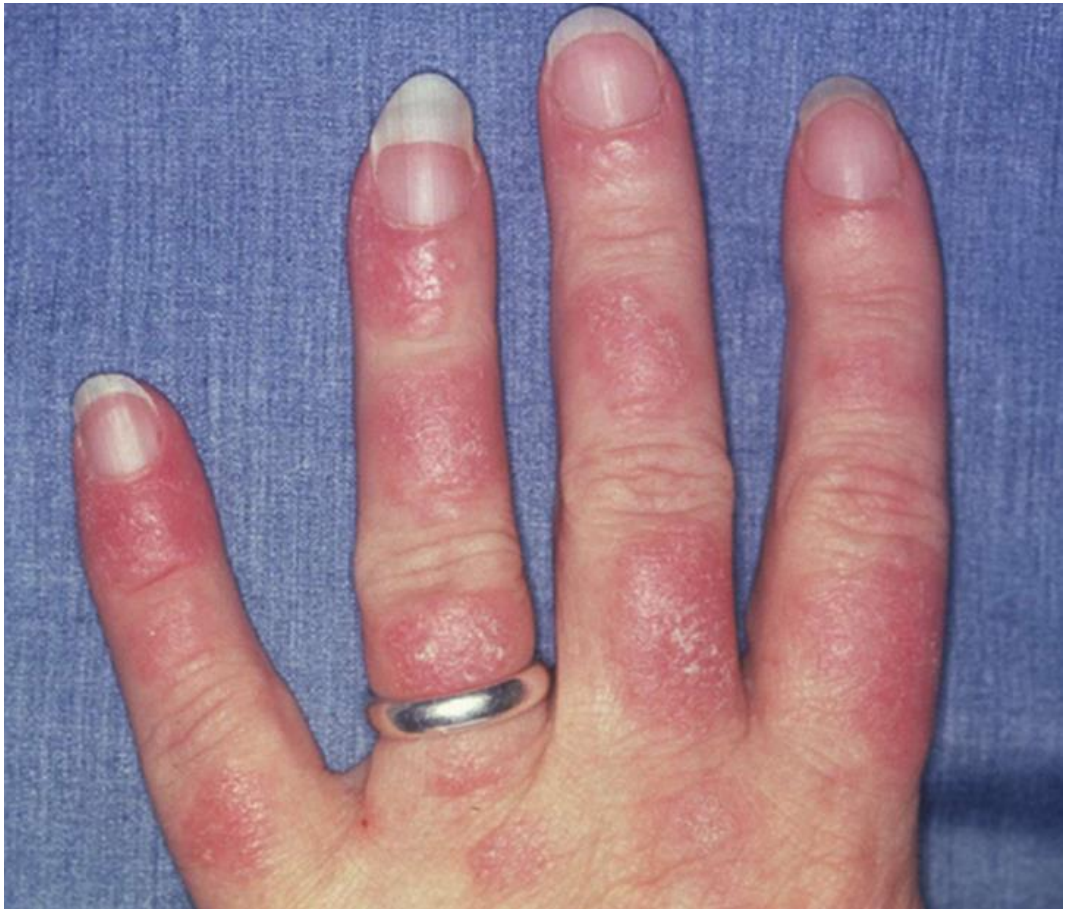


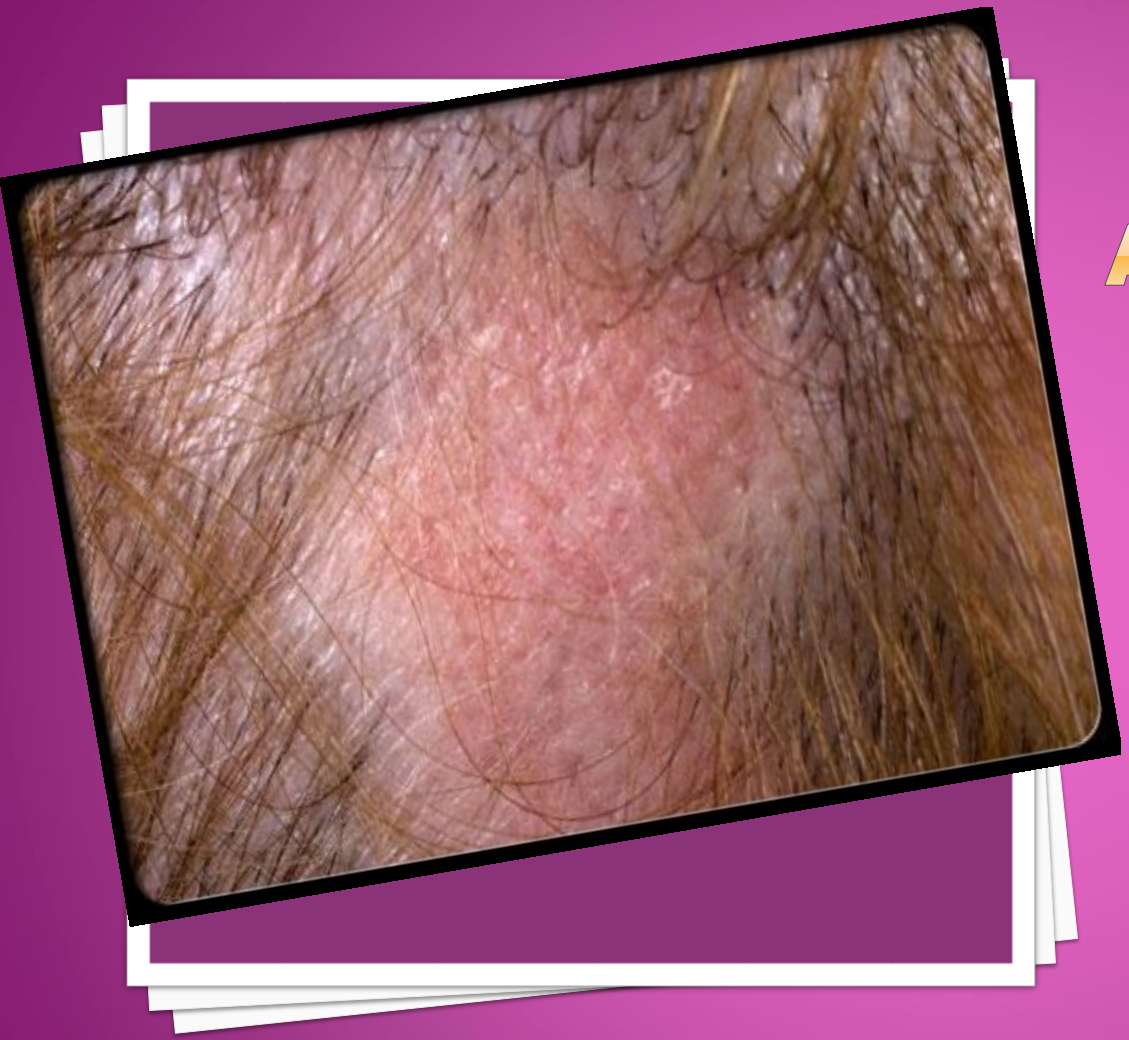


Photosensitivity which may be elicited from patients who are asked if they have any unusual rash or symptom exacerbation after sun exposure.

PHOTOSENSITIVITY

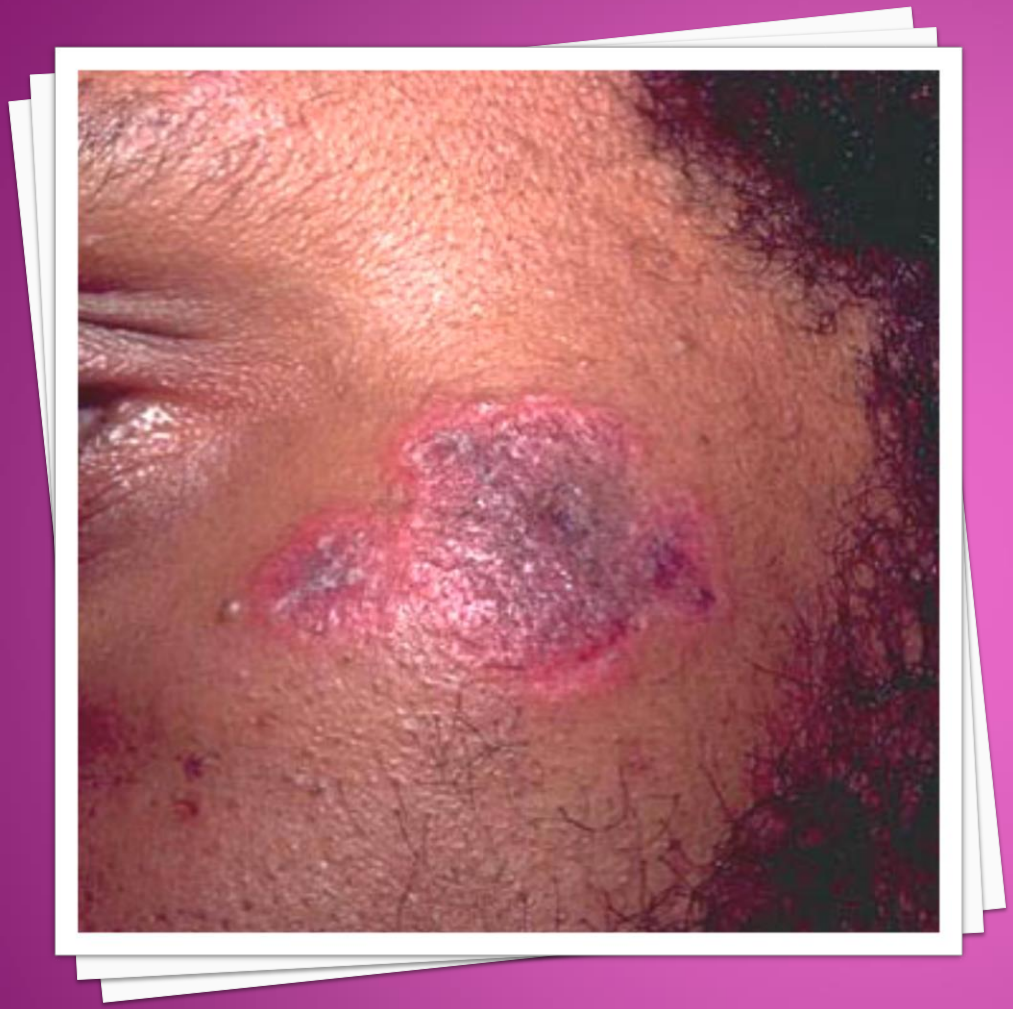
- **Photosensitive rash is often macular or diffusely erythematous in sun-exposed areas of the face, arms, or hands, as in the image below.**





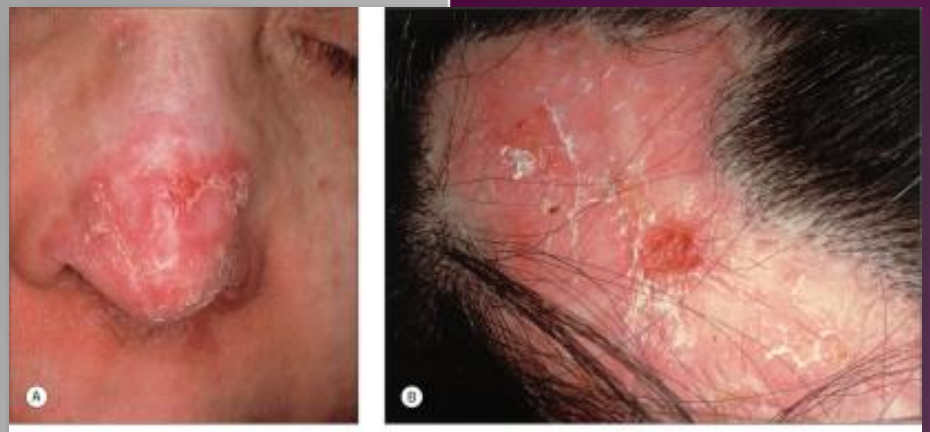
ALOPECIA

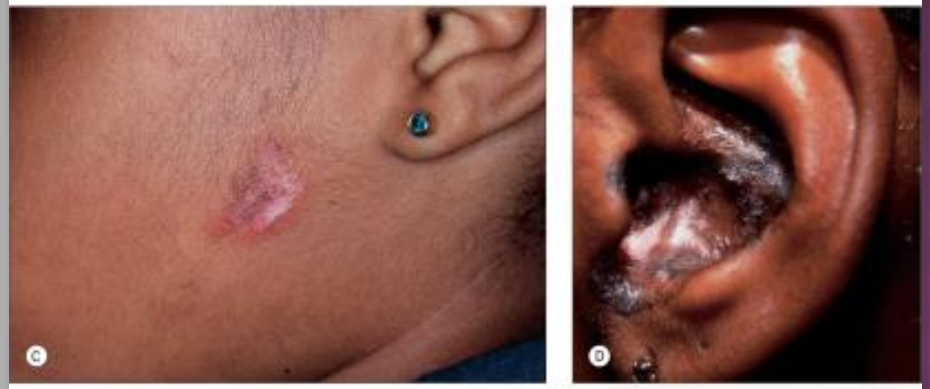
less-specific cutaneous feature of SLE. It often affects the temporal regions diffuse or creates a patchlike pattern of hair loss.

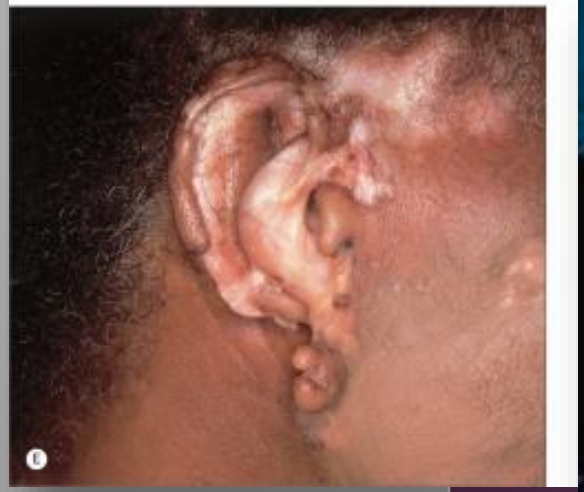


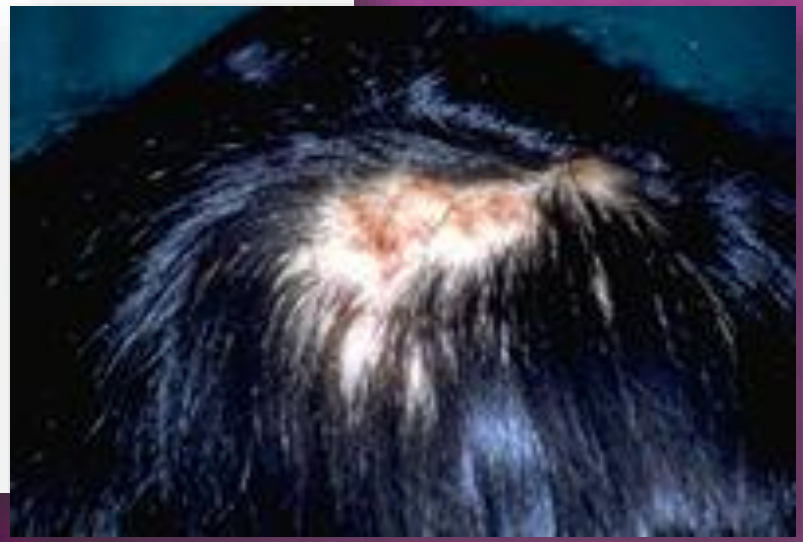
Discoid lesions often also develop in sun-exposed areas but are plaquelike in character, with follicular plugging and scarring. They may be part of systemic lupus or may represent discoid lupus without organ involvement, which is a separate diagnostic entity.

DISCOID RASH.







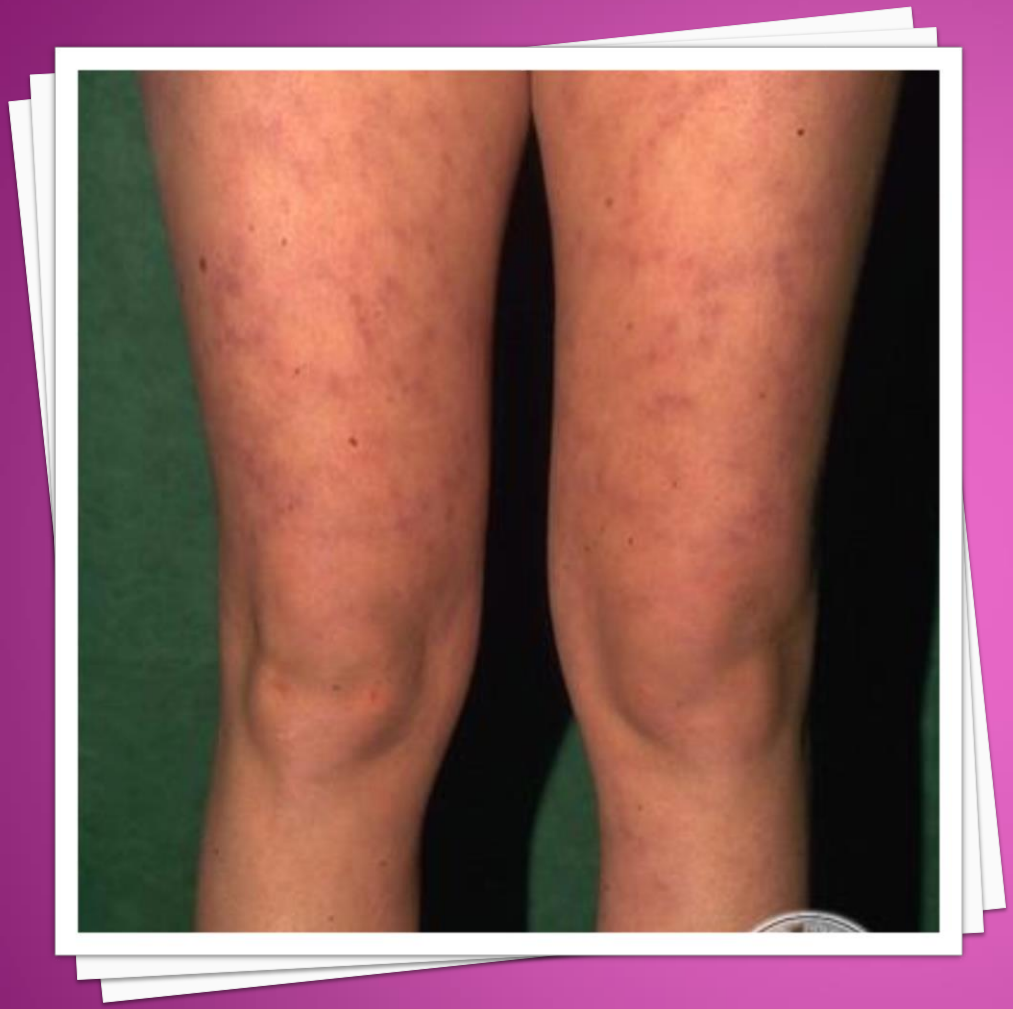


DISCOID LESIONS ALOPECIA

Discoid lesions occurs on sun-exposed body parts: face, arms, neck, associated themselves in systemic lupus erythematosus or discoid lupus may be as a separate entity.

OTHER CUTANEOUS MANIFESTATIONS

- related to but not specific to SLE include Raynaud phenomenon, livedo reticularis, panniculitis (lupus profundus), bullous lesions, vasculitic purpura, telangiectasias, and urticaria



LIVEDO RETICULARIS

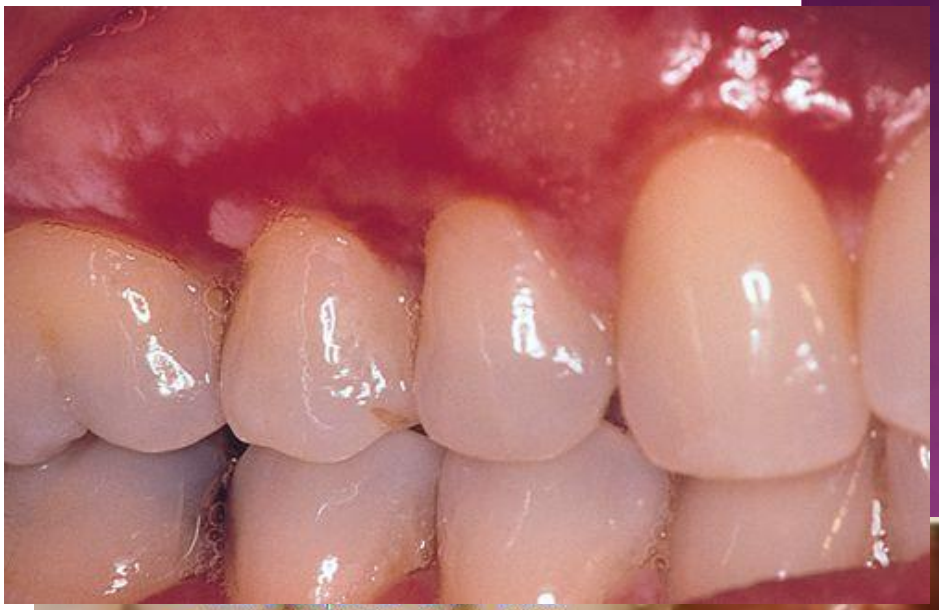
Livedo reticularis is characterized by a lacy, mottled, erythematous skin pattern

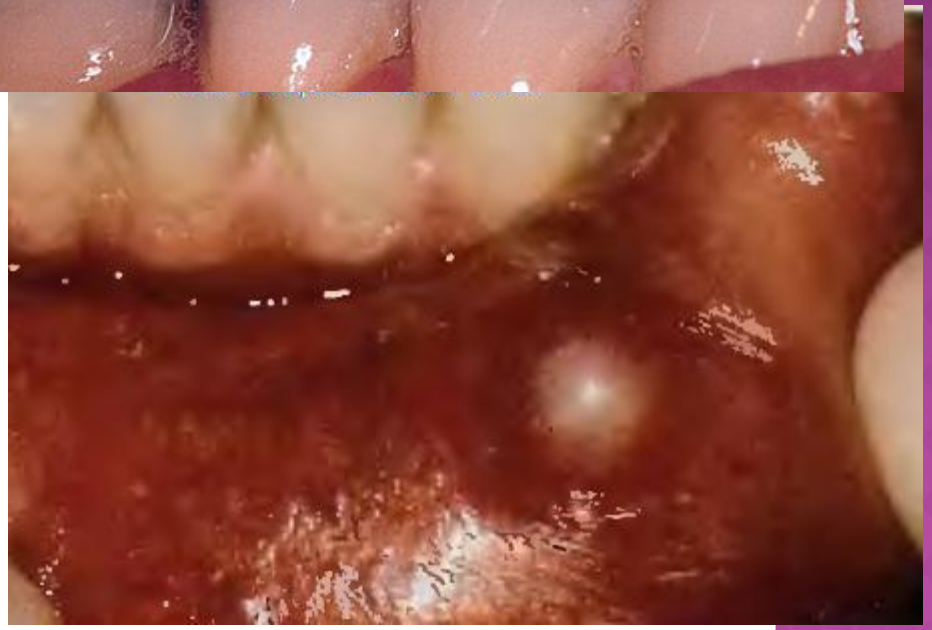
RAYNAUD PHENOMENON

may be observed with blue, white, and red color change at the distal digital tips.

MUCOSAL LESIONS

It is characterized by erythema and discoid changes, atrophy and depigmentation on the lips (cheilitis), petechiae and mouth ulcers.





MUSCULOSKELETAL SYMPTOMS

- **Joint pain** is one of the most common reasons for the initial clinical presentation in patients with SLE (90%). Arthralgia, myalgia, and frank arthritis may involve the small joints of the hands, wrists, and knees.
- In contrast to rheumatoid arthritis, SLE arthritis are non-erosive, nondeformant, with small effusion, may be asymmetrical, with pain that is disproportionate to swelling.

Most frequently are affected interphalangeal joints of hands,in decreasing:

- **metacarpophalangeal,**
- **Radiocarpal**
- **knees and joints of the foot**
- **rare plants.**
- *Femural joint necrosis may occurs in patients with antiphospholipid syndrome or after prolonged treatment with corticosteroids. Osteoporosis is a common complication of treat-ment with GCS*

- Myalgia are common (15-64%), rarely meet myiositis (5-11%), manifested by proximal muscle fatigue and increased concentration of enzymes (creatine fosfokinaze).
- In 5-10% of patients treated with steroid develops GCS myopathy.

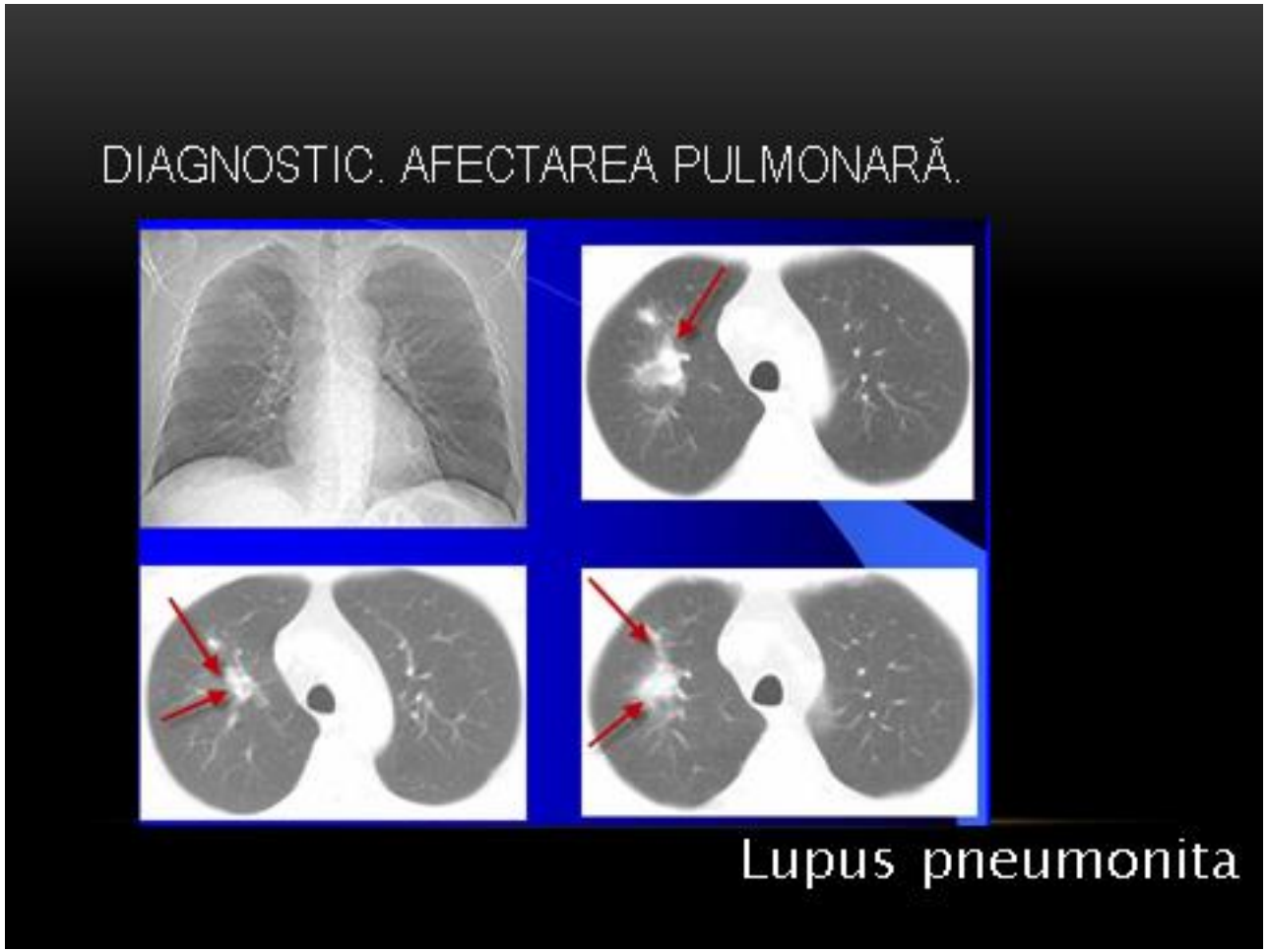
PULMONARY FEATURES (up to 50%)

- Pulmonary manifestations of SLE may manifest acutely or indolently, representing many complications.
-
- **Pleurisy** with pleuritic chest pain with or without pleural effusion is the most common feature of acute pulmonary involvement in SLE, often are bilateral.
- Shortness of breath or dyspnea may be due to many causes : pleural or pericardial effusions, pulmonary embolism, lupus pneumonitis, interstitial lesions.
-

- **Serositis** due to pericardial or pulmonary effusions, pulmonary embolism, lupus pneumonitis, chronic lupus interstitial lung disease, or infection may be related to lupus disease.
- Most seriously, hemoptysis may herald diffuse alveolar hemorrhage, a rare, acute, life-threatening pulmonary complication of SLE.
- Lung damage in SLE is a manifestation of pulmonary vasculitis.

LUPUS PNEUMONITIS

- **is characterized by dyspnea and cough with haemoptysis. X-ray detects increased pulmonary draw, infiltrates, vital capacity of lungs is reduced .**



CARDIAC FEATURES

- Heart failure or chest pain must be carefully examined in patients with SLE.
- All heart compartments may be involved - pericardium, myocardium, endocardium, valves and coronary arteries.(in 25%).

PERICARDITIS

- Pericarditis , the most frequent cardiovascular involvement, that manifests as chest pain, manifesting as positional chest pain that is often relieved when the patient leans forward. Is presented by small pericardial effusion detected during EcoCG. After resorption of effusion between pericardium surfaces light fibrous adhesions is formed.

MYOCARDITIS

- A maild myocarditis also may occurs in SLE, giving rise to arrhythmias, with heart failure symptomatology.

- Coronary vasculitis manifesting as angina or infarction is rarely reported. **The Framingham Offspring Study demonstrated that women aged 35-44 years with SLE were 50 times more likely to develop myocardial ischemia than healthy women.**

- **Libman – Sacks endocarditis** is noninfectious but may manifest as symptoms similar to those of infectious endocarditis .
- Very rare involvement of MV and AoV.
- Raynaud ‘s vasculitis arterial and venous thromboses can occur.

- The exudate in the pericardium is pale-yellow, sometimes contains streaks of blood, more than 20,000 leukocytes / mm 3 (mainly polynuclear), antinuclear antibodies (ANA), circulating immune complexes (CIC), LE-cells, the is low-complement level .

- Impairment of the peripheral vessels occurs by livedo reticularis, Lupus-panniculitis and thrombosis of arteries or veins of the limbs or internal organs, which are usually found in patients with antifisfolipidic syndrome

RENAL FEATURES

- The kidney is the most commonly involved visceral organ in SLE. Although only approximately 50% of patients with SLE develop clinically evident renal disease, biopsy studies demonstrate some degree of renal involvement in almost all patients.

RENAL FEATURES

- Glomerular disease usually develops within the first few years of SLE onset and is usually asymptomatic.
- Most type of glomerulonephritis occur, including mesangial, focal, diffuse and membranous.

RENAL FEATURES

- The most common symptom is proteinuria (1g.per 24 h), associated with hematuria and cilindruria. Proliferative glomerulonephritis is detected (the focal or diffuse) or membrouse, which is manifested by nephrotic syndrome.
- **Acute or chronic renal failure** may cause symptoms related to uremia and fluid overload.
- **Acute nephritic disease** may manifest as hypertension and hematuria.
- **Nefrotic syndrome** may cause edema, weight gain, or hyperlipidemia.
-

RENAL FEATURES - IMMUNOHISTOLOGY

- In glomeruli are detected deposits of IgG, C3 complement fraction, fibrin, IgM and less - IgA.
- The electronic microscopy is proving subendotelial, subepitelial and intramembranouse immune complex deposits, these deposits are markers of lupus nephritis.

GASTROINTESTINAL FEATURES

- Gastrointestinal symptoms secondary to primary SLE and adverse effects of medication are common among persons with SLE, bat not major presenting feature.
- Abdominal pain in SLE is significant because it may be directly related to active lupus, including peritonitis, pancreatitis, mesenteric vasculitis, and bowel infarction.

- Nausea and dyspepsia are common symptoms in patients with active SLE and are sometimes difficult to correlate with objective evidence of gastrointestinal involvement.
- Esophagus damage- dysphagia, reducing peristalsis, dilation of the esophagus (5%).
- Duodenum and stomach ulcers - caused both by the basic disease and the adverse effects of treatment
- Jaundice due to autoimmune hepatitis may also occur.
- Pancreatitis is uncommon.
- Lymphadenopaty and splenomegalia.

NEUROPSYCHIATRIC FEATURES

- Involvement of the nervous system occurs in up to 60% of cases and symptoms may fluctuate.
- There may be a mild depression but occasionally more severe psychiatric disturbances occur. Epilepsy, cerebral ataxia, aseptic meningitis , cranial nerve lesion, cerebrovascular accidents or a polyneuropathy may be seen.

- Only seizure and psychosis are included among the diagnostic criteria.

- Central nervous system is the result of cerebral vasculitis and CIC deposition (10-15% of cases) – Antineuronal, antilimphocytic, antiglial antibodies are detected.

- **Psychosis** may manifest as ***paranoia or hallucinations***.
- **Delirium** represents a spectrum of fluctuating altered consciousness characteristic of SLE. Delirium may be caused by CNS vasculitis, encephalopathy, or the manifestations previously called organic brain syndrome.

- **Seizures** related to SLE may be generalized or partial and may precipitate status epilepticus.
- **Coreea,**aseptic meningitis, myelopathy, optic neuropathy, or other demyelinating disorders may also require urgent evaluation.
- **Transverse myelitis** with spastic paraparesis is a rare but serious complication of SLE.

- **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 cause and effect may be difficult to distinguish.

Cognitive disorders

- may be variably apparent in patients with SLE. Formal neuropsychiatric testing reveals deficits in 21-67% of patients with SLE.
- Whether this represents true encephalopathy, neurological damage, medication effects, depression, or some other process is unclear.
-

- *Stroke and transient ischemic attack (TIA) may be related to antiphospholipid antibody syndrome* ***or vasculitis.***

- It can diagnose polineurite and mononeurite, peripheral sensory neuropathy, aseptic meningitis

HEMATOLOGIC FEATURES

- A history of multiple cytopenias such as **anemia,leukopenia, lymphopenia,, or thrombocytopenia** may suggest SLE, among other etiologies.
- **Leukopenia** and, more specifically, lymphopenia are common in SLE; this and hypocomplementemia may predispose persons with SLE to frequent infections.

ANEMIA

- **Anemia** is occasionally overlooked in young menstruating women. Hypochromic anemia **(50%) -** its strongly correlated with SLE activity.
- Hemolytic anemia with positive Coombs test is rarely encountered in patients with antiphospholipid syndrome.

- **Leukopenia** - autoimmune origin . **Lymphopenia** correlates with SLE activity and antilymphocitic antibody.
- **Thrombocytopenia** may be mild or part of a thrombotic thrombocytopenic purpura (TTP)–like syndrome or **antiphospholipid antibody syndrome.**

- **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 may be clues to lupus or isolated **antiphospholipid antibody syndrome.**
- A family history of autoimmune disease should also raise further suspicion of SLE.

CLASSIFICATION CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

(ACR, 1997).

Classification Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE) (1)

1. Malar rash: Fixed erythema, flat or raised, over the malar eminences
2. Discoid rash: Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity: Exposure to ultraviolet light causes rash
4. Oral ulcers: Includes oral and nasopharyngeal ulcers, observed by physician
5. Arthritis: Nonerosive arthritis of two or more peripheral joints, with tenderness, swelling, or effusion
6. Serositis: Pleuritis or pericarditis documented by ECG or rub or evidence of effusion
7. Renal disorder: Proteinuria >0.5 g/d or 3+, or cellular casts
8. Neurologic disorder: Seizures or psychosis without other causes

CLASSIFICATION CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) (2)

9. Hematologic disorder: Hemolytic anemia or leukopenia (<4000/L) or lymphopenia (<1500/L) or thrombocytopenia (<100,000/L) in the absence of offending drugs
10. Immunologic disorder: Anti-dsDNA, anti-Sm, and/or anti-phospholipid
11. 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

- Any combination of 4 or more of 11 criteria, well-documented at any time during a patient's history, makes it likely that the patient has SLE (specificity and sensitivity are 95% and 75%, respectively).

- Note: ECG, electrocardiography; dsDNA, double-stranded DNA; ANA, antinuclear antibodies.

SLEDAI - 2K (SLE DISEASE ACTIVITY INDEX)

SLEDAI SCORE

- The SLEDAI (Systemic Lupus Erythematosus Activity Index) was developed in 1985 through a nominal group process and is based on the **presence of 24 features in 9 organ systems over the patient's past 10 days. The maximal score -105 points.**
-

SLEDAI DISEASE ACTIVITY INDIEX-2K

Wt	SLEDAI score	Descriptor	Definition
8		Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8		Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8		Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.

Wt	SLEDAI score	Descriptor	Definition
8		Visual Distur - bance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8		Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8		Headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8		CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis

Wt	SLEDAI score	Descriptor	Definition
8		Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction,splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4		Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness,swelling, or effusion).
4		Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4		Urinary Casts	Heme-granular or red blood cell casts

Wt	SLEDAI score	Descriptor	Definition
4		Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4		Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4		Pyuria	>5 white blood cells/high power field. Exclude infection.
2		New Rash	New onset or recurrence of inflammatory type rash.

Wt	SLEDAI score	Descriptor	Definition
2		Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2		Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations
2		Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2		Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2		Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory

Wt	SLEDAI score	Descriptor	Definition
2		Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory
1		Fever	>38˚C. Exclude infectious cause
1		Thrombocytopenia	<100,000 platelets/mm3
1		Leukopenia	<3,000 White blood cell/mm3. Exclude drug causes

TOTAL SCORE (Sum of weights next to descriptors marked present)

Check box: If descriptor is present at the time of visit or in the proceeding 30 days

Mild or Moderate Flare □	Severe Flare □
□ **Change in SLEDAI > 3 points**	□ Change in SLEDAI > 12
□ **New/worse** **discoid,photoscnsitive,** profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ **New/worse CNS-SLE** Vasculius Nephritis Myositis Pk < 60.000 Home anemia: Hb <7% or decrease in Hb > 3% **Requiring: double prednisone** Prednisone>0.5 mg/kg/day hospitalization
Increase in Prednisone, but not to >0.5 mg/kg/day	Prednisone >0.5 mg/kg/day
Added NSAID or Plaquenil	New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)
≥1.0 Increase in PGA, but not to more than 2.5 □	Increase in PGA to > 2.5

MUSCULOSKELETAL FINDINGS

- Small-joint arthritis of the hands and wrists is the most common musculoskeletal finding in SLE, followed by arthritis of the knees. Pain reports may be out of proportion to synovitis or swelling upon examination.

- Myositis that may manifest as weakness rarely occurs and is more commonly related to overlap syndromes or corticosteroid-induced myopathy.
- Fibromyalgia, which should be distinguished by myofascial tenderness without weakness, is commonly concomitant with SLE.

CARDIOPULMONARY FINDINGS

- Pleuropericardial friction rubs and signs of effusions may be found.
- Hypoxia, tachypnea, crackles, or gross hemoptysis may be signs of pneumonitis.
- Heart failure signs or arrhythmias may point to ischemia or inflammatory myocarditis.
- Murmurs may represent Libman-Sacks endocarditis, superimposed infectious endocarditis, or thromboembolic disease.

- **Renal findings**
- Hypertension.
- Edema of periorbital or peripheral regions and anasarca are common physical findings related to nephrotic syndrome or volume overload with renal failure.

- **Gastrointestinal findings**
- Abdominal tenderness and pain may be observed in peritonitis, pancreatitis, mesenteric vasculitis, or non–lupus-related processes. Lupus peritonitis is a less-common serositis that may be present, even in the absence of ascites.

- **Neuropsychiatric findings**

  Focal neurological deficits may represent **stroke**, or **mononeuritis.**

- **Mononeuritis** may manifest as the functional loss of one or a few isolated peripheral nerves and is observed in some patients with SLE vasculitis or antiphospholipid disease.


Laboratory
Studies

ROUTINE ANALYSIS

- **Inflammatory markers:**
- Levels of inflammatory markers, including the ***erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)***, may be elevated in any inflammatory condition, including SLE.
- CRP levels change more acutely, and the ESR lags behind disease changes.

A CBC count may help to screen for

- ***anemia***,
- ***leukopenia***,
- ***lymphopenia***,
- ***and thrombocytopenia***,
- U**rinalysis (proteinuria, haematuria, leucocyturia)** and **creatinine studies** may be useful to screen for kidney lupus disease.
- **Liver test results** may be mildly elevated in acute SLE or in response to therapies such as azathioprine or nonsteroidal anti-inflammatory drugs (NSAIDS).
- **Creatinine kinase** levels may be elevated in myositis or overlap syndromes.

IMMUNOLOGICAL FINDINGS

Elevation of the antinuclear antibody (ANA)

titer 1:100 (dilution) or higher is the most sensitive of the ACR diagnostic criteria.

More than 95% of patients with systemic lupus erythematosus have an elevated ANA titer.

Although a significant proportion of patients may have a negative ANA titer early in the disease.

However, the ANA test is not specific for systemic lupus

erythematosus. Diagnostic importance is only to detect him in high titre> 1:100.

Lupus cells (LE) is detected în70-80% of cases.

PS ***A study41 involving 15 international laboratories found that ANA tests in the general population were positive in 32 percent of persons at a 1:40 and in 5 percent of persons at a 1:160 dilution.***

Rates of positive ANA tests were not affected by age up to 60 years (the upper age limit of the study)

- In patients with high clinical suspicion or high ANA titers, additional testing is indicated. This commonly includes evaluation of ***antibodies to dsDNA, complement, and ANA subtypes such as Sm, SSA, SSB, and ribonucleoprotein (RNP) (often called the ENA panel).***
-

The following are autoantibody tests used in the diagnosis of SLE: (1)

- ANA - Screening test; sensitivity 95%; not diagnostic without clinical features
- Anti-dsDNA - High specificity; sensitivity only 70%; level variable based on disease activity
- Anti-Sm - Most specific antibody for SLE; only 30-40% sensitivity
- Lupus anticoagulant is detected in 25% patients.
- Anti-SSA (Ro) or Anti-SSB (La) - Present in 15% of patients with SLE and other connective-tissue diseases such as Sjogren syndrome;
- Anti-ribosomal P - Uncommon antibodies that may correlate with lupus cerebritis

THE FOLLOWING ARE AUTOANTIBODY TESTS USED IN THE DIAGNOSIS OF SLE: (2)

- Anticardiolipin - IgG/IgM variants (ELISA) - used to screen for antiphospholipid antibody syndrome
- Lupus anticoagulant - is detected in 25% patients - (SLE=antiphospholipid syndrome)
- Coombs test - Coombs test–positive anemia to denote antibodies on RBCs
- Anti-histone - Drug-induced lupus ANA antibodies often this type (eg, with procainamide or hydralazine; perinuclear antineutrophil cytoplasmic antibody [p-ANCA]–positive in minocycline-induced drug-induced lupus)

In most patients are detected:

- circulating immune complexes,
- rheumatoid factor in low titre
- antibodies antiplateletes,
- Cryoglobulins,
- hipergamaglobulinaemia,
- higher levels of IgG, IgM,
- reduction of CH50 and of the complementfractions of C3 and C4.

- Complement levels: C3 and C4 levels are often depressed in patients with active SLE because of consumption by immune complex–induced inflammation. In addition, some patients have congenital complement deficiency that predisposes them to SLE.

- Changes in coagulation system is explained by the presence of lupus anticoagulant that inhibits the release of prostacyclin from endothelium.
- The deficit of prostacyclin, as the main inhibitor of platelet aggregation, leads to thrombus formation, and to intrauterine fetal death.

IMAGING STUDIES

- **X-ray**
- **Joint radiography** often provides little evidence of SLE given the absence of erosions, even in the presence of Jaccoud arthropathy with deformity or subluxations. The most common radiographic changes in SLE include periarticular osteopenia and soft-tissue swelling.
- **Chest radiography and chest CT** scanning can be used to monitor interstitial lung disease and to assess for pneumonitis, pulmonary emboli, and alveolar hemorrhage.

- **Brain MRI/magnetic resonance angiography** (MRA) is used to evaluate CNS lupus for white-matter changes, vasculitis, or stroke, although findings are often nonspecific and may be absent in as many as 42% of cases with neuropsychiatric symptoms.[25]
- **Echocardiography** is used to assess for pericardial effusion, pulmonary hypertension, or verrucous Libman-Sacks endocarditis.
- **Angiography** assesses signs of vasculitis, cerebral stroke and other nonspecific changes.

PROCEDURES

- Lumbar puncture may be performed to exclude infection with fever or neurologic symptoms. Nonspecific elevations in cell count and protein level and decrease in glucose level may be found in the cerebrospinal fluid of patients with CNS lupus.
- Renal biopsy is used to identify the specific type of glomerulonephritis, to aid in prognosis, and to guide treatment. Another benefit of renal biopsy is in distinguishing renal lupus from renal thrombosis, which may complicate antiphospholipid antibody syndrome and require anticoagulation rather than immunomodulatory therapy.
- Skin biopsy can help to diagnose SLE or unusual rashes in patients with SLE. Many different rashes may herald SLE, making review by a dermatopathologist important.

HISTOLOGIC FINDINGS

- Renal biopsy is used to confirm the presence of lupus nephritis, to aid in classification of SLE nephritis, and to guide therapeutic decisions. The World Health Organization classification for lupus nephritis is based on light microscopy, electron microscopy, and immunofluorescence findings.
-
- Lupus skin rash often demonstrates inflammatory infiltrates at the dermoepidermal junction and vacuolar change in the basal columnar cells. Discoid lesions demonstrate more-significant skin inflammation, with hyperkeratosis, follicular plugging, edema, and mononuclear cell infiltration at the dermoepidermal junction. In many SLE rashes, immunofluorescent stains demonstrate immunoglobulin and complement deposits at the dermoepidermal basement membrane.
-

- **Procedures**
- Lumbar puncture may be performed to exclude infection with fever or neurologic symptoms. Nonspecific elevations in cell count and protein level and decrease in glucose level may be found in the cerebrospinal fluid of patients with CNS lupus.
- Renal biopsy is used to identify the specific type of glomerulonephritis, to aid in prognosis, and to guide treatment. Another benefit of renal biopsy is in distinguishing renal lupus from renal thrombosis, which may complicate antiphospholipid antibody syndrome and require anticoagulation rather than immunomodulatory therapy.
- Skin biopsy can help to diagnose SLE or unusual rashes in patients with SLE. Many different rashes may herald SLE, making review by a dermatopathologist important.

DIFFERENTIAL DIAGNOSIS

- Antiphospholipid Syndrome
  Fibromyalgia
  Hepatitis C
  Infectious mononucleosis
  infective endocarditis
  Lyme Disease
  Lymphoma, B-Cell
  Connect-Tissue Disease Mixed
  Polyarteritis nodosumpreeclampsia
  rheumatic Fever
  Rheumatoid Arthritis
  scleroderma
  serum Sickness
  Thrombotic thrombocytopenic purpura
  Connect-Tissue Disease Undifferentiated

TREATEMENT

CORTICOSTEROIDS

- First-line medication in the treatment of SLE are corticosteroids.
- **In s**erious organic pathology, the dose of GCS should be 0.5 to 1 mg / kg, with reduction to maintenance dose (5-10 mg / day).

PULS THERAPY

- The intravenous methylprednisolone high doses administration:
- pulstherapya (500-1000 mg/24 hours) for 3-5 days.
- Pathophysiological reasoning of high doses GCS – immunosuppression and inflammation ihibition.

- Indications for pulse therapy at the onset of the disease are :
- young age,
- lupus nephritis fulminant, progressive high immunological activity and affection of nervous system.
- The combined intravenous puls therapy Recommended:
- **1000mg methyilprednisolone** for 3 days **+1000mg ciclofosfan i/v** on the first day.

CYTOSTATICS.

- Indications for complex Treatment of SLE with chemotherapy are:
- Acute lupus nephritis,
- vasculitis,
- resistant forms to GCS,
- the need for reducing the dose of GCS,
- high activity of lupus, progressive or fulminant.

It is used:

- **Cyclophosphamide** in puls therapy 1000 mg i / v per day, then 200 mg / day (5000 mg dose summary).
- **Azathioprine** - 2-2.5 mg / kg / day,
- **Methotrexate** 7.5 to **-10-15-20mg** 10 mg each / week per os,

- **Mycophenolate (CellCept) 250 mg / day** is useful for maintenance in lupus nephritis and other serious lupus cases. This agent inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby inhibiting their proliferation. It inhibits antibody production.

- **Mycophenolate (CellCept) 250 mg / day** is useful for maintenance in lupus nephritis and other serious lupus cases. This agent inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby inhibiting their proliferation. It inhibits antibody production.
- Another scheme:
  500mg per day the first week,
  500mg x 2 time the 2nd week
  750mg x2 the 3rd week
  1000mg x 2 the 4th week.

ANTIMALARIALS

Antimalarials may work through numerous proposed mechanisms in SLE,

- mediating subtle immunomodulation without causing overt immunosuppression.
- They are useful in preventing and treating lupus skin rashes, constitutional symptoms, arthralgias, and arthritis.
- They also help to prevent lupus flares and have been associated with reduced morbidity and mortality in SLE.
- Is prescribed in cases of photosensitivity and skin damage.

Dose - 200 mg per dsy.

HYDROXYCHLOROQUINE (PLAQUENIL)

- This agent inhibits chemotaxis of eosinophils and locomotion of neutrophils and impairs complement-dependent antigen-antibody reactions.
- **Dose -** 200 mg per day.

OTHER REMEDIES:

- **NonSteroidal anti-inflammatory** These agents provide symptomatic relief for arthralgias, fever, and mild serositis. NSAIDs may cause elevated liver function test results in patients with active SLE. Additionally, concomitant administration with prednisone may increase risk of GI ulceration.

Ibuprofen

Diclofenac ..

BIOLOGICAL MEDICATION

monoclonal anti-TNF a
antibody type human IgG1: **Influximab (Remicade)- 3mg/kg (maxim-10mg/kg) 1-2-6 weeks,** then every 8 weeks.

Adalimumab(Humira)-40mg,

s.c., every 2 weeks.

- **Belimumab (Benlysta)** inhibits the biological activity of B-lymphocyte stimulator (BLyS);
- **etanercept** (Enbrel);Receptors for TNFa, 25mg s.c. 2 times a week.

- Belimumab inhibits the biological activity of B-lymphocyte stimulator (BLyS); BLyS is a naturally occurring protein required for survival and for development of B-lymphocyte cells into mature plasma B cells that produce antibodies. In autoimmune diseases, elevated BLyS levels are thought to contribute to production of autoantibodies.
- This agent is indicated for active, autoantibody-positive SLE in patients who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and nonsteroidal anti-inflammatory drugs.

OTHER REMEDIES:

- **anticoagulants,**
- **antiagregan**
- **diuretics,**
- **preparations of Ca and K.**

Extracorporeal treatment methods:
plasmapheresis, hemosorbtion.

Tratamentul lupusului ce evoluează cu unele semne specifice

Tromboze	**-Aspirina, anticoagulante**
-Avorturi, moartea intrauterină a fătului	**-Aspirina şi alte remedii**
-Citopenie	**-GCS intravenos**
-Glomerulonefrită	**-GCS, citostatice**
-Tromboze ale vaselor	**-Anticoagulante**
-Vasculite	**-GCS, citostatice**
-Infarcte (secundare pe fond de vasculită)	**-GCS, citostatice, prostaciclina**
-Trombocitopenie	**-gamaglobulinăin i/v**

PROGNOSIS

- SLE carries a highly variable prognosis. The natural history of SLE ranges from relatively benign disease to rapidly progressive and even fatal disease.
- The disease course is milder and survival rate higher among persons with isolated skin and musculoskeletal involvement than in those with renal and CNS disease.
- Mortality in patients with SLE has decreased over the past 20 years. Prior to 1955, the 5-year survival rate in SLE was less than 50%; currently, the average 10-year survival rate exceeds 90%, and the 15-year survival rate is approximately 80%.

- Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE, and accelerated arteriosclerosis is a key cause of late mortality.


© SWNS