## SYSTEMIC LUPUS ERYTHROMATOSUS

**Definition**

-An autoimmune disease involving multiple organ systems that is defined clinically and associated with antibodies directed against cell nuclei.

-Its multisystem manifestations and attendant complications from use of immunosuppressive agents make the diagnosis and management of this entity challenging.

**Pathophysiology:**

-Auto antibodies, circulating immune complexes and T lymphocytes all contribute to the expression of disease.

-Organ systems affected include dermatologic, renal, central nervous system (CNS), hematologic, musculoskeletal, cardiovascular, pulmonary, the vascular endothelium, and gastrointestinal.

**The American College of Rheumatology (ACR) criteria for SLE -** “SOAP BRAIN MD” acronym:

Must include 4 of the following at any time during a patient's history (specificity 95% and sensitivity 75%):

**Serositis** - Pleurisy, pericarditis

**Oral ulcers** - Oral or nasopharyngeal, usually painless; palate is most specific

**Arthritis** - Nonerosive Jaccoud type

**Photosensitivity** - Unusual skin reaction to light exposure

**Blood disorders** - Leukopenia, lymphopenia, thrombocytopenia, Coombs test–positive anemia

**Renal involvement** - Proteinuria (>0.5 g/d or positive on dipstick testing; cellular casts)

**Antinuclear antibodies** (ANAs) - Higher titers generally more specific (>1:160)

**Immunologic phenomena** - Lupus erythematosus (LE) cells; anti–double-stranded DNA (dsDNA); anti-Smith (Sm) antibodies; antiphospholipid antibodies (anticardiolipin immunoglobulin G [IgG] or immunoglobulin M [IgM] or lupus anticoagulant); biologic false-positive serologic test results for syphilis

**Neurologic disorder** - Seizures or psychosis

**Malar rash** - Fixed erythema over the cheeks and nasal bridge

**Discoid rash** - Raised rimmed lesions with keratotic scaling and follicular plugging

**Incidence**

**Internationally:**

Incidence varies worldwide. In Northern Europe, it has been reported to be 40 cases per 100,000.

 **Mortality/Morbidity:**

-Early deaths usually are caused by active disease.

-Atherosclerosis is a leading cause in late deaths.

- Infection and nephritis are major causes of mortality in all stages of SLE.

-After dialysis or transplantation, a reduction in disease activity and flares has been reported.

-Thrombosis, often secondary to antiphospholipid syndrome, carditis, pneumonitis, pulmonary hypertension, stroke, myocardial infarction, and cerebritis cause severe morbidity and mortality.

**Race:**

SLE is more common in blacks (1:250) than in whites (1:1000). However, all ethnic groups are susceptible.

**Sex:**

-Ninety percent of cases are in women.

-Also, women who are exposed to estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE.

-The sex distribution is more equal in those who develop SLE during childhood or when older than 50 years.

**Age:**

Most (80%) cases have been reported to occur in women in their childbearing years.

**Clinical presentation**

**History:**

-The mean length of time between onset of symptoms and diagnosis is 5 years.

-The disease is characterized by exacerbations and remissions.

-Many women relate flares of their lupus to the postovulatory phase of the menstrual cycle, with resolution of symptoms at the time of menses.

a)-**Systemic symptoms** include a low-grade fever, fatigue, malaise, anorexia, nausea, and weight loss.

Initial presentation may involve one or more organ systems.

b) **Arthralgias** (53-95%)

- are the initial complaint in many patients. Often, the pain is out of proportion to physical findings.

c) **Malar, butterfly rash over the cheeks and bridge of the nose** (55-90%)

- with photosensitivity to ultraviolet (UV) light has been reported (mostly in whites). It also often involves the chin and ears.

d) **Painful or painless ulcers** in the nose and mouth are frequent complaints.

e) **CNS symptoms**

-may range from mild cognitive dysfunction to a history of seizures (12-59%).

- Any region of the brain, meninges, spinal cord, and cranial and peripheral nerves can be involved.

-CNS events often occur when SLE is active in other organ systems.

- Intractable headaches and difficulties with memory and reasoning are the most common features of neurologic disease in patients with lupus.

-Psychiatric symptoms (high-dose steroids also can cause psychosis [5-37%]) - If the psychosis gets worse after stopping the steroid, it is most likely related to the disease process.

f) **Serositis**

-Pleuritic pain (31-57%), dyspnea, cough, fever, and chest pain are important cardiopulmonary complaints.

g) **GIT**

Patients may present with abdominal pain, diarrhea, and vomiting.

- Intestinal perforation and vasculitis are important diagnoses to exclude.

A number of other symptoms can be elicited by history which can help identify other pathology, including the following:

Stroke, Pulmonary embolus, Deep venous thrombosis (DVT), Acute ischemia, Retinal vasculitis

**Physical:**

**a)-Fever** is a challenging problem in SLE.

-It can be a manifestation of active lupus or a representation of infection, malignancy, or a drug reaction.

b)-**Malar rash** is a fixed erythema sparing the nasolabial folds. It is a butterfly rash that can be flat or raised over the cheeks and bridge of the nose. It also often involves the chin and ears.

c) **Discoid rash** occurs in 20% of patients with SLE and can be disfiguring secondary to scarring.

-It presents as erythematous patches with keratotic scaling over sun-exposed areas of the skin and may occur in the absence of any systemic manifestations.

d) All patients **experience painless or painful oral or vaginal ulcers** at some time in their illness, which are helpful in making the diagnosis.

e) **GIT**- vague abdominal discomfort, nausea, and diarrhea. Acute crampy abdominal pain, vomiting, and diarrhea may signify vasculitis of the intestine.

f) **Joint findings**

-Tenderness, edema, and effusions accompany polyarthritis that is symmetric, nonerosive, and usually nondeforming.

-It frequently involves the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands, as well as the wrists and knees.

-Consider avascular necrosis, which is common in patients receiving glucocorticoids.

-Also consider septic arthritis when one joint is inflamed out of proportion to all other joints.

g) **CNS**

-All types of seizures have been reported, with grand mal being the most common.

-Sensory or sensorimotor neuropathies are also common.

-Incidence of stroke is high in the first 5 years of disease. Patients with antiphospholipid antibodies are at higher risk for such events.

h**) Eye-Funduscopic** examination is important in patients with visual complaints.

-Retinal vasculitis can lead to blindness and are demonstrated by sheathed narrow retinal arterioles with white exudates adjacent to the vessels.

i) **Renal system**

 Specific signs and symptoms of renal disease may not be apparent until advanced nephrotic syndrome or renal failure is present; therefore, obtaining a urine analysis and serum BUN and creatinine levels on a regular basis is important.

j) **CVS**

-Atherosclerosis occurs prematurely in patients with SLE and is an independent risk factor for cardiovascular disease]

-Pulmonary HTN, vasculitis with digital infarcts, and splinter hemorrhages may be observed.

-Systolic murmurs are reported in up to 70% of cases. They may be secondary to fever, hypoxia, anemia, or Libman-Sacks endocarditis (associated with antiphospholipid antibodies).

-Pericarditis has an incidence of 20-30% and is the most common presentation of heart involvement. It is usually associated with small effusions, but it may involve larger effusions when uremia is concomitant. Myocarditis can cause heart failure, arrhythmias, and sudden death

k) **Pulmonary findings**

-Tachypnea, cough, and fever are common manifestations of lupus pneumonitis.

-Hemoptysis may signify pulmonary hemorrhage. However, infection is the most common cause of infiltrates seen on radiographs

**Lab Studies:**

1. **Complete blood count (CBC)**

-Leukopenia, which generally is a good index for disease activity

-Lymphopenia

-Anemia of chronic disease (60-80%)

-Evidence of a hemolytic anemia (10%

-Thrombocytopenia (30-50% of cases), which may be profound secondary to antiplatelet antibodies or to antiphospholipid antibodies

 (**ESR) or C-reactive protein (CRP**)-Inflammatory response

2-**The partial thromboplastin time (PTT**) may be elevated secondary to lupus anticoagulant (antiphospholipid antibody), which is associated with thrombosis.

3-**Urinalysis**-Pyuria, Hematuria, Granular cast, Proteinuria

4-**Blood urea nitrogen (BUN) and creatinine**

Usually not elevated at the onset of disease

Can be useful for the determination of any progression of renal disease

5. **LFTs**: These may be mildly elevated in acute SLE or in response to therapies such as azathioprine or nonsteroidal anti-inflammatory drugs (NSAIDS).

6. **Creatinine kinase**: Creatinine kinase levels may be elevated in myositis or overlap syndrome

5-**Immunological**

**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

**Anti-SSA (Ro) or Anti-SSB** (La) - Present in 15% of patients with SLE and other connective tissue diseases such as Sjögren syndrome; associated with neonatal lupus

**Anti-ribosomal P** - Uncommon antibodies that may correlate with lupus cerebritis

**Anti-RNP** - Included with anti-Sm, SSA, and SSB in the ENA profile; may indicate mixed connective tissue disease with overlap SLE, scleroderma, and myositis Anticardiolipin - IgG/IgM variants measured with enzyme-linked immunoassay (ELISA) among the antiphospholipid antibodies used to screen for antiphospholipid antibody syndrome

**Lupus anticoagulant** - Multiple tests (eg, Direct Russell Viper Venom test) to screen for inhibitors in the clotting cascade in antiphospholipid antibody syndrome

**Coombs test** - Coombs test–positive anemia to denote antibodies on RBCs

**Anti-histone** - Drug-induced lupus (DIL) ANA antibodies often this type (eg, with procainamide or hydralazine; perinuclear antineutrophil cytoplasmic antibody [p-ANCA]–positive in minocycline-induced DIL)

**Imaging Studies:**

**CXR**-Effusion, Infiltrates, Cardiomegaly

**Echocardiogram** -may be indicated to evaluate any effusion causing pericardial pain or any valvular pathology and to confirm any signs of pulmonary hypertension.

(MRI) is most useful for assessing brain pathology.

 (CT) is useful to rule out bleeding or mass lesions.

**Other Tests:**

Cerebrospinal fluid (CSF) analysis is recommended when the diagnosis of CSF lupus is in question or infection is a possible cause of symptoms.

-High protein levels in 50% of patients and pleocytosis may be found.

May indicate cerebritis but is not specific for it.

**Causes:**

-Many of the clinical manifestations of SLE are caused by the effects of circulating immune complexes on various tissues or to the direct effects of antibodies to cell surface components.

-A genetic predisposition to the development of SLE exists. The concordance rate in monozygotic twins is 25-70%. Each patient manifests his or her disease differently

-If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250

-Photosensitivity is clearly a precipitant of skin disease.

- The presence of antiphospholipid antibodies in patients dictates a constellation of signs caused by thrombosis.

DDX**:**

1. Metastatic malignancy
2. Fever of unknown origin (FUO)
3. Mixed connective tissue disease
4. Psychogenic rheumatism
5. Scleroderma
6. Discoid lupus
7. Hemoptysis

**Drug-induced lupus**
Before making a diagnosis of SLE, ruling out drugs as the cause of the condition is important.

 Procainamide

 Hydralazine

 Isoniazid

 Methyl dopa

 Chlorpromazine

 Quinine

Many patients receiving these medications have positive antinuclear antibody test results and other serologic findings. Only a few have the clinical manifestations.
Drug-induced lupus differs from SLE by the following features:

-Sex ratios are nearly equal.

-Nephritis and central nervous system features are not commonly present.

-No antibodies to native DNA or hypocomplementemia are present.

-When the drug is discontinued, the patient has resolution of clinical manifestations and reverting of abnormal laboratory values to normal

**Management**

-Conservative management with nonsteroidal anti-inflammatory drugs including salicylates is recommended for arthritis, arthralgias, and myalgias not requiring immunosuppression.

-Only initiate high-dose glucocorticoids and cytotoxic agents by, or in consultation with, a rheumatologist.

-Patients with thrombosis require anticoagulation with warfarin for a (INR) of 2-3.

Antibiotics may be appropriate in the treatment of ordinary and opportunistic infections.

Management of individual emergencies that may be complications of SLE in the individual patient

-These can include strokes, acute myocardial infarctions, hemoptysis, respiratory distress, and pulmonary emboli

-In patients presenting with fever, treating for an infection empirically may be necessary until culture results have been received.

**Complications:**

1) Vasculitis and its various complications (eg, intestinal perforations)

2) Pericarditis

3) Myocarditis

4) Lupus pneumonitis

5) Pulmonary hemorrhage, pulmonary hypertension

6) Proliferative glomerulonephritis

7) Hemolytic anemia, thrombocytopenia

8) Intravascular thrombosis (eg, stroke and myocardial infarctions)

9) Complications of high dose glucocorticoid therapy viz; osteoporosis, poor wound healing, truncal obesity, moon facies, buffalo hump.

10) Complications of cytotoxic agents

**Prognosis:**

-Prognosis has improved over the last few years.

-Mortality typically is due to renal failure or infection.

**Patient Education:**

-Protection from the sun

-Compliance with medications and follow-up appointments