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A Review on Systemic Lupus Erythematosus and Management of its Complications

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A B S T R A C T

It is a nonspecific autoimmune inflammatory disease that typically affects multiple organs and systems. It can affect the skin, joints, kidneys, brain, and other organs in the body. The genes plays a major role in the affecting the disease; the genes like *IRF5*, *PTPN22*, *STAT4*, *CDKN1A*. The abnormal activation of B-cells, T-cells, tends to form the auto antibody complex and results in organ damage. The symptoms includes Butterfly rash, Photosensitivity, Raynaud's phenomenon Discoid lesions, Chest pain, Fatigue, Fever, General discomfort, malaise, Hair loss, Mouth sores, Sensitivity to sunlight. The diagnosis of the disease based on various tests includes Antinuclear antibody (ANA),CBC with differential, Chest x-ray, Urinalysis, ESR, Kidney blood tests, Liver function blood tests Rheumatoid factor, Antiphospholipid antibodies test. The DMARDs Non steroidal anti-inflammatory drugs, Corticosteroids and Antimalarials used to manage the disease.

Keywords: Butterfly rash, Photosensitivity, inflammation, disease.

A R T I C L E I N F O

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, nonspecific autoimmune inflammatory disease that typically affects multiple organs and systems, including the skin, joints, muscles, lungs, heart, kidneys, and the central nervous and circulatory systems. Individuals with SLE include production of antibodies and inflammatory

responses that are directed at their own tissues. This abnormal reaction can occur in any organ system [1].

Historical milestones in systemic lupus erythematosus

- In the early 1900s, the first clinical description of lupus was presented and, lupus wasn't yet on the "radar screen,"
- There was, however, a mid-20th century discovery that determined that the presence of the LE (lupus erythematosus) cell in the body was a positive indication of lupus.
- It became a diagnostic test (eventually replaced with the more sensitive ANA [anti-nuclear antibody] test) that added important knowledge of the inner immune workings of the disease.
- In 1951, a Nobel Prize was awarded for the use of anti-inflammatory steroids in lupus,
- In the 1960s, the medical community began to understand the concept of autoimmunity, or the ways in which the body's immune system attacks itself.
- In the 1970s, the natural history of lupus, both in individuals and populations of patients, became more clearly understood. It means that if an individual happens to have the genes for lupus, a trigger in the environment is apparently necessary for the disease to become active.
- In the 1980s, the effects of drugs, both positive and negative, became evident.
- Certainly, from the 1990s through the present day, the emphasis on more focused medications and treatments has allowed patients to suffer a significantly reduced set of side effects [3].

2. Stages of Systemic Lupus Erythematosus

Mild SLE: Peoples with SLE just have joint and/or skin symptoms with tiredness. These are unpleasant but are not serious or life-threatening.

- **Moderate SLE**:
- This includes some inflammation of other parts of the body apart from joints and skin. This may include pleurisy, pericarditis or mild kidney inflammation [2].
- **Severe SLE**:
- In some cases, severe inflammation develops which can cause damage to organs such as the heart, lung, brain or kidneys. This can even be life-threatening.
- It is an episodic, multisystem disease characterized by wide spreading inflammation of the blood vessels and connective tissues. It can be mild to severe, and affects mostly women.
- Systemic is used because the disease can affect organs and tissue throughout the body.
- Lupus is Latin for wolf. It refers to the rash that extends across the bridge of the nose and upper cheekbones and was thought to resemble a wolf bite. Erythematosus is from the Greek word for red and refers to the color of the rash.

Complications of systemic lupus erythematus

It includes

- Cutaneous lupus erythematosus refers to lupus that is confined to the skin and does not affect other parts of the body [3].
- Discoid lupus erythematosus is a type of cutaneous lupus that produces scarring disc-shaped rash on the face, scalp, or ears.
- Drug-induced lupus is a temporary and mild form of lupus caused by certain prescription medications. They include some types of high blood pressure drugs (hydralazine, ACE inhibitors, calcium channel blockers) and diuretics.
- Neonatal lupus is a rare condition that sometimes affects infants born to mothers who have SLE. Babies with neonatal lupus are born with skin rash, liver problems, low blood counts and may develop heart problems.

Etiology

Genetics, Environmental agents such as drugs, chemicals such as hydrazine (found in tobacco) and aromatic amines (found in hair dyes), diet, environmental estrogens infection with viruses or bacteria [4].

Epidemiology

The incidence of SLE in the United States is estimated to be 5.6 to 7.3 per 100,000 persons per year, with a prevalence of between 124 and 130 cases per 100,000 persons. The disease occurs predominantly in women, with a reported female-to-male ratio approaching those afflicted with SLE are usually diagnosed between the ages of 15 and 45. SLE is less prevalent in whites than in other ethnic groups, including blacks, Hispanics, Native Americans, and Asians. Although the most typical SLE patient is a young adult woman, the disease can occur in people of any age or race and either gender.

3. Pathophysiology

- Environmental factors, such as infectious organisms, drugs, and chemicals, genetically and hormonally that makes the immune system dysregulation [5].
- These abnormal immune responses leads to hyper activation of T-helper-2 lymphocyte and B-lymphocyte function. Suppressor T-lymphocyte function, cytokine production, other immune regulatory mechanisms are abnormal and fail to down regulate auto antibody formation.
- The auto-antibodies formed from this immune dysregulation become pathogenic, form immune complexes, and activates the complement that leads to damage the host tissue. The B-cell hyperactivity and the production of pathogenic auto-antibodies caused to 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. Excess activation and production of interleukin (IL)-10 involves an imbalance of IL-10 and IL-12.
- The cytokines such as tumor necrosis factor α (TNF-α), interferon γ (INF-γ), transforming growth factor β (TGF-β), IL-1, IL-2, IL-4, IL-6,

IL-16, IL-17, and IL-18 may be also be implicated. They exert their proinflammatory and anti-inflammatory effects on the immune cells helper or CD4+ lymphocytes. The synthesis and secretion of pathogenic auto-antibodies in SLE is driven by the interaction of CD4+ and CD8+ helper T cells, and double negative T cells (CD4–CD8-) with B cells [6].

- This action may result from the inhibition of Th1 response and the enhancement of CD40L expression on lupus T cells may indirectly promote the Th2 response and lead to further B-cell hyperactivity [7]. The defectives in immune regulatory mechanisms such as the clearance of immune complexes by Phagocytic cells also contribute to the development of SLE.

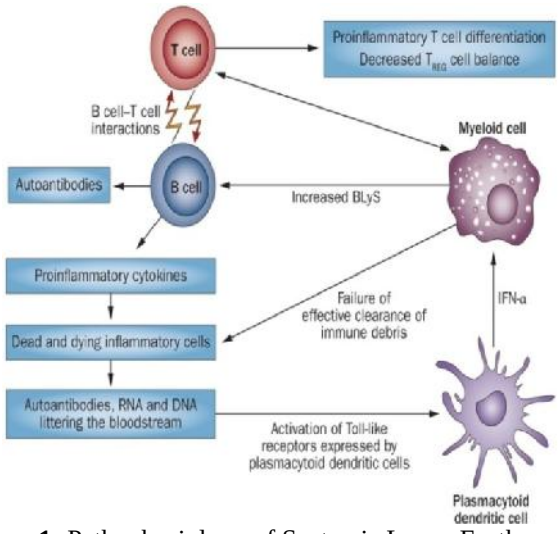

Figure 1: Pathophysiology of Systemic Lupus Erythematus

Clinical manifestations

- Constitutional (e.g., fatigue, fever, arthralgia, weight loss
- Musculoskeletal (e.g. arthralgia, arthropathy, myalgia, arthritis, necrosis)
- Dermatologic (e.g., malar rash, photosensitivity, discoid lupus)
- Renal (e.g., acute or chronic renal failure, acute nephritic disease)
- Neuropsychiatric (e.g., seizure, psychosis)
- Pulmonary (e.g., pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, interstitial lung disease)
- Gastrointestinal (e.g., nausea, dyspepsia, abdominal pain)
- Cardiac (e.g., pericarditis, myocarditis)
- Hematologic (e.g., cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia).

Diagnosis

According to the guidelines of ACR

SLE diagnostic criteria

Serositis, Oral ulcers, Arthritis, Photosensitivity, Blood disorders, renal involvement, antinuclear antibodies, Immunological phenomena, Neurologic disorder, Malar rash, Discoid rash [8].

Testing tools:

- CBC with differential
- Serum creatinine
- Urinalysis with microscopy
- ESR or CRP results
- Complement levels
- Liver function tests
- Kidney disease
- Autoantibody tests
- Chest radiography and chest CT scanning
- Echocardiography
- Brain MRI/ MRA
- Cardiac MRI

Treatment

- Antimalarial Hydroxychloroquine, 200–400 mg PO daily
- Chloroquine, 250–500 mg PO daily
- Mild disease: arthritis, skin rash, serositis
- Corticosteroid Prednisone, 1–2 mg/kg/d PO (or equivalent)<1 mg/kg/d (or equivalent)
- Methylprednisolone, 500–1000 mg IV daily × 3–6 d Life-threatening disease
- Cytotoxic Cyclophosphamide, 0.5–1.0 g/m2 IV monthly for 6 months; then, every 3 months for 2 years or for 1 year after remission
- Azathioprine, 1–3 mg/kg PO daily
- Cyclophosphamide, 1–3 mg/kg PO daily
- Mycophenolate mofetil, 1–3 g PO daily

Adverse drug reactions of drugs

Salicylates: NSAIDs gastrointestinal bleeding, hepatic toxicity, renal toxicity, hypertension.

Corticosteroids:

Hypertension, hyperglycemia, hypokalemia, osteoporosis, avascular necrosis, cataract, weight gain, infections, fluid retention

Hydroxychloroquine: Macular damage.

Azathioprine: Myelosuppression, hepatoxicity, lympho-proliferative disorders

Cyclophosphamide: Myelosuppression, myeloproliferative disorders, malignancy, immunosuppression, hemorrhagic cystitis, secondary infertility

Mycophenolatemofetil: Myelosuppression, hepatotoxicity, lymphoproliferative disorders, malignancy.

Nonselective Nonsteroidal Anti-Inflammatory Drugs and Selective Cyclooxygenase-2 Inhibitors: Naproxen (500 mg twice daily) and Ibuprofen (600 mg four times daily)

4. Treatment for Systemic Lupus Erythematosus

Nonsteroidal anti-inflammatory drugs (NSAIDs): Anti-inflammatory medications reducing the inflammation

Antimalarial drugs-Plaquenil (hydroxyl chloroquine): Medications commonly used to treat malaria can help control lupus.

Corticosteroids: Prednisone and other types of corticosteroids can counter the inflammation of lupus

Immunesuppressants:

mycophenolatemofetil, Cyclosporine, cyclophosphamide, azathioprine, Methotrexate [9].

Combination therapy with an NSAID and hydroxyl chloroquine

In SLE, the usual oral hydroxyl chloroquine dose is 400 mg administered daily for 4 to 12 weeks. Low-dose oral prednisone (10 mg/day) may be used for mild disease activity and limited to a duration of 4 to 6 weeks. NSAIDs or COX-2 inhibitors may be combined with prednisone to lower the dose and minimize side effects or given on the off day of the alternate day therapy. Prednisone initial adult doses of 1 mg/kg/day, up to 60 mg per day, and tapered over 8 weeks. Methotrexate (MTX). Weekly doses of 7.5 to 15 mg (maximum 25 mg). It can be given orally or by subcutaneous injection.

Corticosteroids and Cytotoxic Agents in Severe Disease

combination therapy with high-dose corticosteroid (e.g., oral prednisone 40–60 mg/day or IV methyl prednisolone 0.5–1.0 g/day) and pulse IV cyclophosphamide is recommended.

Lupus Nephritis Treatment

In patients diagnosed with diffuse proliferative glomerulonephritis (Class IV), the cytotoxic agent of choice, cyclophosphamide in combo with methyl prednisolone, has been shown to slow down disease progression, the most studied regimens involve treatment of lupus nephritis. An induction phase consisting of “pulse” IV methyl prednisolone (0.5–1.0 g/day) for 3 days followed by oral prednisone (40–60 mg/day) for the first month only plus pulse IV cyclophosphamide (0.5–1.0 g/m2) and continued for 6 months is given during active disease in patients with biopsy proven WHO Classes III and IV lesions[10]. The combination of cyclophosphamide and steroids is superior to steroids or cyclophosphamide alone. After the first month, oral prednisone 0.5 mg/kg/day is given between monthly pulses of methyl prednisolone and cyclophosphamide to avoid the cumulative effect of long-term daily prednisone.

Adverse Reactions: leukopenia, thrombocytopenia, and amenorrhea in premenopausal women.

Non Pharmacologic Therapy

- Patient education and counseling is an important element of non pharmacologic management of SLE and minimizing complications related to therapy.
- Dietary and lifestyle modifications should include a good balance of rest and moderate exercise, smoking cessation, appropriate nutritional food intake diet, and adherence to a diet low in saturated fat.
- Weight-bearing exercises, oral calcium, and vitamin D supplementation are the first steps in the prevention of osteoporosis.

5. Conclusion

An appreciation of the many facets of SLE is essential, including recognition of the current limit of our knowledge about the disease and its management. It is a chronic autoimmune disorder and it affects almost every system in the body with varying degrees of severity [10]. That can affect several organ systems, including the skin, kidneys, and CNS. Better and earlier recognition of the disease and more effective treatments have significantly improved survival rates it leads to minimize the disease complications.

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