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Systemic Lupus Erythematosus: Clinical Features and Management

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Abstract:

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of autoantibodies and the formation of immune complexes, which can lead to widespread inflammation and tissue damage. SLE predominantly affects women of childbearing age, with a female-to-male ratio of approximately 9:1, and tends to be more prevalent and severe among individuals of African, Hispanic, and Asian descent. Close monitoring and a multidisciplinary approach are essential to reduce disease activity, prevent flares, and improve long-term outcomes. Early diagnosis and individualized treatment plans contribute significantly to reducing morbidity and improving quality of life for patients with SLE.

Keywords: Systemic Lupus Erythematosus, Diagnosis, Management.

Introduction:

Childhood-onset SLE is a lifelong autoimmune disease that may be difficult to diagnose due to its multisystem involvement, and heterogeneity of clinical manifestations. It follows a more aggressive disease course than adult-onset SLE, with greater disease activity at presentation and over time, and consequently leads to greater morbidity and mortality than adult-onset SLE. Moreover children with SLE have to deal with this unpredictable, relapsing-remitting disease during puberty, an already challenging time of life when physical appearance is important, self-esteem and identity are yet to be developed, and overestimation of personal skills regarding decision making and responsibility for their disease are frequent **(1)**.

Early diagnosis is crucial in ensuring prompt treatment to minimize life-threatening complications. Diagnosing SLE in children is not always easy. Most children present with fever, arthralgia, arthritis, rashes, myalgia, and fatigue and weight loss. These symptoms are fairly non-specific. So, a high level of suspicion for the diagnosis is required and appropriate laboratory tests performed to confirm or refute the diagnosis **(2)**.

Despite relatively little new understanding of the pathogenesis and no 'cure', the long term outcome for children with SLE is fairly good if they are followed closely by a medical team with suitable expertise **(3)**.

Although a life-long and serious disease with a high morbidity and substantial mortality, the prognosis has dramatically improved largely because of the aggressive use of high-dose corticosteroids at onset and with disease fares, combined with other potent anti- inflammatory agents. The early empirical use of antibiotics for possible sepsis is essential. Early referral and frequent follow-up by a team specialized in the management of the condition has probably been critical in improving outcome **(4)**.

Clinical Features:

SLE is a multisystem disorder which can involve the skin, mucous membranes, joints, lungs, kidneys, central and/or peripheral nervous system, heart, and the gastrointestinal system **(5).**

Not all patients with SLE have the same symptoms. The symptoms may range from mild to severe

which may depend upon both genetic and environmental factors **(5).**

Constitutional symptoms

Constitutional symptoms such as fatigue, weight loss and fever are not life threatening, but have a significant impact on quality of life **(6).**

Mucocutaneous manifestations

The skin which is one of the target organs most variably affected by the disease can provide valuable diagnostic & prognostic information (**7).**

Approximately 80 percent of patients with systemic lupus erythematosus have skin manifestations. The skin lesions that are represented by lupus patients include discoid lupus erythematosus, subacute cutaneous lupus erythematosus and acute cutaneous lupus erythematosus **(8).**

Mucosal ulcers occurred in 30% of patients. The oral ulcers in SLE are usually painless, and sometimes there is no apparent association between their presence and systemic disease activity **(9).**

Hair loss occurs in most patients with lupus and in some cases can precede other manifestations of SLE. It is associated with disease activity, and grows back normally as the disease subsides **(10).**

Musculoskeletal symptoms:

The musculoskeletal system is the most commonly involved system in SLE, affecting 53% to 95% of patients **(11).**

1. **Arthritis and Arthropathy**

Joint involvement in SLE is classically described as non erosive, non-deforming arthritis primarily affecting the small joints of the hands, wrists, and knees **(12).**

2. **Myositis**

Generalized myalgia and muscle tenderness are common, especially during disease exacerbations. Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of patients **(13).**

3. **Avascular Bone Necrosis**

Avascular necrosis of bone is a major cause of significant morbidity and disability in patients with SLE. Acute joint pain manifesting late in the course of SLE and localized to a very few areas, especially shoulders, hips, and knees, may indicate the development of avascular necrosis **(14).**

Central nervous system (lupus cerebritis)

The overall prevalence of neurospsychiatric systemic lupus erythematosus (NPSLE) syndromes ranges from 14% to 75%. Neuropsychiatric events in SLE may be caused by a primary manifestation of the disease; secondary complications of the disease such as hypertension, infection, or therapy, such as drug-induced aseptic meningitis, with NSAIDs, particulary ibuprofen or a coincidental problem unrelated to SLE **(15).**

The immunopathogenic mechanisms involved in lupus cerebritis include intracranial microangiopathy, autoantibodies to neuronal and non-neuronal antigens, and the generation of proinflammatory cytokines and mediators (**16)**.

Renal (lupus nephritis) (LN)

Renal damage is one of the most serious complications of SLE. The majority of people with lupus have some degree of asymptomatic microscopic kidney damage. Renal involvement occurs in 40% to 70% of all patients**.** Almost half of patients present with asymptomatic urine abnormalities, such as hematuria and proteinuria **(11).**

The dominant feature of renal lupus is proteinuria and commonly leads to nephritic syndrome **(17).** Hematuria- proteinuria and active urinary sediment can be intermittent initially. Edema is common manifestation of lupus nephritis usually due to nephrotic syndrome as well as concomitant hypertension **(18).**

Several studies have illustrated the poor reliability of diagnoses rendered on the basis of clinical features of lupus nephritis alone **(19).** Thus, renal biopsy is an important tool in assessing patients with LN and is helpful in making decisions about drug treatments and determining prognosis by assessing the presence of active renal disease versus scarring **(20)**.

Cardiovascular Manifestations

Epidemiological studies have shown that SLE women aged 35-44 years were over 50 times more likely to have myocardial infarction than women of similar age from a population based study **(21).**

Pericarditis is the most common and found in approximately one quarter of the patients. Pericardial effusions may be asymptomatic and are usually mild to moderate **(22).**

Valvular involvement is seen in 18%–74% of SLE patients. The most common abnormality was diffuse thickening of the mitral and aortic valves followed by vegetations, valvular regurgitation, and stenosis in decreasing order of frequency (**23):**

Patients with SLE may present with acute coronary syndrome due to coronary vasculitis or premature atherosclerosis **(24).**

Pleuropulmonary manifestations of SLE

The most common pleuropulmonary manifestation of SLE is pleuritis**.** Pleuritic pain is present in 45% to 60% of patients **(25).**

Effusions are usually bilateral, but may be unilateral. Pleural effusions in SLE contain higher glucose and lower lactate dehydrogenase levels than those found in rheumatoid arthritis (**26).**

Acute pneumonitis, which occurs in 1 to 4 % of patients, manifests as unilateral or bilateral patchy consolidation, typically in the lung bases. An accompanying pleural effusion is often present **(26).**

Pulmonary alveolar hemorrhage is a rare complication of SLE and is either immune mediated or secondary to infection or uremia. Patients are typically acutely ill with hemoptysis, fever, cough, and hypoxemia, and blood loss can be extensive **(27).**

The presentation of interstitial lung disease (ILD) in the setting of SLE is consistent with ILD in other settings. Dyspnea, cough, and/or exercise intolerance are common symptoms. Auscultatory crackles and physiologic restriction with a gas exchange abnormality are often present. High resolution CT defines the presence and pattern of the disease **(28).**

Pulmonary arterial hypertension is an increasingly recognized complication of SLE and is more common in patients with antiphospholipid antibody syndrome **(28).**

Gastrointestinal

Gastrointestinal problems are common and range from vague complaints of anorexia to life-threatening bowel perforation secondary to mesenteric arteritis **(29).**

Mesenteric vasculitis with infarction is a serious and potentially life-threatening manifestation. Risk factors for the development of mesenteric vasculitis include peripheral vasculitis and CNS lupus. The clinical presentation is usually with insidious symptoms that may be intermittent for months before the development of an acute abdomen with nausea, vomiting, diarrhea, gastrointestinal bleeding, and fever. Patients with mesenteric vasculitis occasionally have an acute abdomen **(30).**

Hepatomegaly

Lupus can cause an enlarged liver. It is found in 10% of patients with SLE. Excessive fatty infiltration (steatosis) is a common finding **(31).**

Hematological abnormalities

Hematologic abnormalities (hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia) are common manifestations in patients with SLE **(32).**

1. **Anemia**

Anemia is a frequent occurrence in SLE. Multiple mechanisms contribute, including: inflammation, renal insufficiency, blood loss, dietary insufficiency, medications, hemolysis (immune or microangiopathic), infection, hypersplenism, myelofibrosis, myelodysplasia, and aplastic anemia that is suspected to have an autoimmune pathogenesis **(33).**

2. **Leukopenia**

Leukopenia (<4,000/mL) with lymphopenia (<1,500/mL) is a characteristic feature of SLE. White Blood Cell count abnormalities may result from disease activity or from drug toxicity **(34).**

3. **Thrombocytopenia**

Autoimmune thrombocytopenia purpura can be a presenting feature of SLE or occur at any time in the course of the illness. Thrombocytopenia as a consequence of the antiphopholipid antibody syndrome has also been described in SLE **(35).**

Ocular manifestations

Ocular manifestations of lupus are fairly common. Almost any part of the eye and visual pathway can be affected by inflammatory or thrombotic processes. Ocular pain and visual impairment require urgent assessment by an ophthalmologist (**36).**

Scleritis and severe retinopathy require systemic immunosuppression but episcleritis, anterior uveitis and dry eyes can usually be managed with local eye drops. Vaso-occlusive disease, particularly in the presence of antiphospholipid antibodies, requires treatment with anticoagulation and proliferative retinopathy is treated with laser therapy (**36).**

Classification and diagnosis

(Systemic Lupus Erythematosus International Collaborating clinics)

(SLICC) classification criteria for systemic lupus erythematosus

The SLICC criteria of SLE classification requires **:** Fulfillment of at Least Four criteria with at least one clinical criterion and one Immunologic criterion.**&** Lupus nephritis is the sole clinical criterion in the presence of ANA or Anti-dsDNA antibodies

Clinical Criteria :

1: Acute cutanous lupus

2: Chronic cutanous lupus

3:Oral ulcers ;palate

4: Nonscarring alopecia (diffuse thinning or hair fragility with visible broken Hairs)

5:Synovitis involving two or more joints, characterized by swelling or effusionOR tenderness in two or more joints and thity minutes of morning stiffness

6: Serositis

7: Renal involvement

8: Neurological manifestations

9: Hemolytic anemia

10: Leukopenia(lower than 4000/mm3)

11: Thrombocytopenia (lower than 100.000mm3)

Immunological criteria :

1: ANA above lab refernce range

2: Anti- dsDNA above lab refernce range

3: Anti-Sm

4: Antiphospholipid antibody

5: low complement

6: Direct Coombs test in absence of hemolytisc anemia

(SLICC) classification criteria for systemic lupus erythematosus. 2012

(Systemic Lupus Erythematosus International Collaborating clinics)

SLE criteria (37):

Clinical Criteria
1. Acute or subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral/Nasal ulcers
4. Nonscarring alopecia
5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness
6. Serositis
7. Renal: Urine protein/creatinine (or 24 hr urine protein) representing at least 500 mg of protein/24 hr or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once) OR Lymphopenia (<1000/mm3 at least once).
11. Thrombocytopenia (<100,000/mm3) at least once
Immunologic Criteria

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
3. Anti-Sm
4. Antiphospholipid antibody lupus anticoagulant false-positive test for syphilis anticardiolipin – at least twice normal or medium-high titer anti-b2 glycoprotein 1
5. Low complement low C3 low C4 low CH50
6. Direct Coombs test in absence of hemolytic anemia

Treatment of Systemic Lupus Erythematosus

There is no cure for SLE, so early diagnosis and treatment to control dysfunction and complications are important. Management is individualized, depends on symptoms, and is directed at reducing the likelihood of permanent damage to organs and tissues **(38).**

As most of therapeutic interventions in patients with SLE are associated with significant undesirable side effects, the key to select appropriate therapies relies on the careful assessment of the organ involvement and the severity of lupus disease activity (**38).**

Glucocorticoid use in SLE: Glucocorticoids are the mainstay of pharmacological treatment in patients with pSLE with or without major organ involvement. Glucocorticoids are given mainly as oral prednisone, prednisolone, or intravenous high-dose methylprednisolone **(39).**

Daily doses of glucocorticoids can vary among providers, and can range from 0.5 to 2 mg/kg/day. The initial dose is decided by the extent of disease severity and organ involvement. Taper of glucocorticoid doses is usually based on improvement in disease activity, including improving physical exam and symptoms, and response to treatment, with respect to improvement in laboratory parameters. In general, laboratory parameters that help decide whether a decrease in glucocorticoids is warranted include improvements in complement levels (usually to normal), improvement in anti-dsDNA levels, improvement of cytopenias, or other specific laboratory abnormalities such as a decrease in creatinine kinase and decrease in urine protein-to-creatinine ratios **(40).**

Intravenous methylprednisolone (IVMP) at a dose of 30 mg/kg to a max of 1 g (for 1–5 consecutive days) is usually initiated at diagnosis. IVMP helps decrease the IFN signature of disease activity in lupus. Increased expression of IFN-regulated genes, termed the IFN signature, correlates with autoantibodies in lupus **(41).**

These signatures are not decreased with oral glucocorticoids. The dosing of glucocorticoids is highly variable among pediatric rheumatologists. There have been initiatives to attempt to standardize steroid treatment, particularly for lupus nephritis (LN). In 2012, the Childhood Arthritis Rheumatology Research Alliance published consensus treatment plans for induction therapy of LN **(42)**.

Cyclophosphamide and mycophenolate mofetil are a part of these guidelines. Early side effects of

steroids include endocrine manifestations such as hyperglycemia and weight gain, which are reversible with tapering but may lead to diabetes mellitus, obesity, hypertension, hyperlipidemia, and atherosclerosis. **(39)**.

While on steroids, it is important to track height and weight which should improve as steroid therapy is tapered or discontinued. Physical body changes, including cushingoid features and striae, should be discussed often with patients. A healthy diet low in salt should be reiterated to prevent fluid retention and hypertension. Long- term glucocorticoids can also cause osteoporosis, so along with adequate calcium and vitamin D intake, a bone mineral density scan is performed annually **(40).** Glucocorticoids can also cause cataracts and increased risk of glaucoma, which may lead to visual field loss and even blindness **(43).**

Hydroxychloroquine :

Hydroxychloroquine is an antimalarial agent given to almost all patients with adult or pediatric SLE. Hydroxychloroquine inhibits Toll-like receptor pathways and minimizes flare, treats skin disease, and decreases the rate of autoantibody production **(44**). The usual prescribed dose of hydroxychloroquine is 4–6/mg/kg/day. Additionally, hydroxychloroquine has an important role in cardiovascular protection, such as anti-platelet, anti-thrombotic, lipid- regulating, anti-hypertensive, hypoglycemic properties, which are important to consider in SLE patients **(45).**

This adjunctive treatment is usually continued for a prolonged period of time. Patients require ophthalmological screening for hydroxychloroquine induced retinopathy, which can present insidiously with subtle color vision changes and paracentral scotoma, making early detection difficult **(46)**. Early screening is important to possibly arrest its progression, thereby averting or lessening visual loss **(47).**

Mycophenolate Mofetil :

Mycophenolate mofetil has been a heavily studied drug, particularly in the treatment of lupus nephritis. Trials in adults have demonstrated that mycophenolate mofetil has equivalent or better results than cyclophosphamide **(48)**. Studies have also shown that mycophenolate mofetil has lower rates of adverse effects, particularly infections, for the 6-month induction phase and long-term maintenance in comparison to cyclophosphamide (**49)**.

The usual dosage of mycophenolate mofetil is 600 mg/m^2/dose twice daily with a maximum dosage of 1500 mg taken two times per day **(42)**. MMF can also be used as a steroid sparing agent in dermatological manifestations of SLE. Side effects of mycophenolate mofetil include mild gastrointestinal symptoms, cytopenias, and teratogenicity. It is important to note that African Americans may require higher doses of mycophenolate mofetil due to increased clearance of the drug **(50)**.

Urine pregnancy tests are done while on MMF and patients should be appropriately counseled on fetal toxicity and teratogenicity. With evidence of increased risk of miscarriage and birth defects associated with MMF use, the FDA instituted a REMS program that contains both a medication guide and elements to assure safe use **(51).**

Cyclophosphamide :

Cyclophosphamide is primarily used for the management of severe SLE, including lupus nephritis, life-threatening organ involvement, and neuropsychiatric manifestations. Cyclophosphamide has been a well-established treatment for lupus nephritis for many years **(52)**. In lupus nephritis induction therapy, intravenous cyclophosphamide is given every 4 weeks for 6 months (**41**). The European protocol for treating lupus nephritis, which consists of low-dose IV cyclophosphamide (500 mg) every4 weeks for six doses, has also proven to be an effective initial treatment regimen **(53)**.

It is important to counsel female patients about fertility issues. SLE patients exposed to cyclophosphamide have a much higher risk of developing infertility and premature ovarian failure than do the counterparts who are treated with other less-toxic treatments **(54)**.

Cyclophosphamide can permanently alter the ovarian reserve in a manner that is dose-, duration-, and age-dependent, and patients should be counseled to use effective contraception until the end of treatment, and a minimum of one ovulation cycle after the end of treatment is recommended before considering conception (**55**).

Patients can consider GnRH agonists to prevent cycles. It was initially thought that cyclophosphamide led to increased infections. These infections, when thought to be related to cyclophosphamide therapy, have been in the setting of cyclophosphamide-induced reductions in total WBC count **(56)**. However, literature supports that the recommended regimens significantly lower adverse effects like infections whilst not affecting efficacy **(57)**. It is important to counsel patients of an increased risk of bladder cancer with the use of cyclophosphamide, which has been found to be dose-dependent.

Azathioprine :

Azathioprine is used to help treat lupus nephritis, as well as dermatologic and hematologic manifestations of pSLE (**58)**. Thiopurine methyltransferase (TPMT), an enzyme that metabolizes azathioprine, can be tested in order to titrate dosing to prevent azathioprine toxicity. Azathioprine is a category D drug, so there is positive evidence of risk during pregnancy. It should be continued during pregnancy if the benefits outweigh the risks. There is also an increased risk of cancers, particularly skin cancers and lymphomas, with use of azathioprine. Blood test monitoring is important in detecting azathioprine-related toxicity. Neutropenia, lymphopenia, and deranged liver function may be relevant and indicate myelotoxicity, susceptibility to infection, and hepatotoxicity, respectively (**59).**

Rituximab :

An anti-CD20 monoclonal antibody, rituximab, targets B-cells and their ability for antibody production. Studies have shown that that rituximab is particularly effective in treating SLE-associated cytopenias **(60**). In patients with severe SLE organ involvement, benefit has been shown in using rituximab and cyclophosphamide together (**61).** Prior to initiating therapy with rituximab, CBC with flow cytometry, quantitative immunoglobulins, and vaccine titers are usually obtained. Patients should be carefully monitored due to increased risk of infections. Serum immunoglobulin levels and flow cytometry are important labs to monitor after B cell depletion and can help decide whether to continue anti-CD20 monoclonal antibody therapy **(62, 63)**. Patients may require IVIG replacement therapy for hypogammaglobulinemia.

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