A Review: Systemic Lupus Erythematosus(SLE)

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Abstract- *Systemic lupus erythematosus (SLE) is a chronic, complicated and challenging disease to diagnose and treat. The etiology of SLE is unknown and various criteria were created to aide in the diagnosis, focusing on clinical manifestations and antibody profilespecific to SLE. Treatment options are limited to a few medications to control the inflammation and decrease organ damage. Treatment strategies vary according to the specific organ complication. Systemic lupus erythematosus (SLE) is a chronic, multifaceted autoimmune inflammatory disease that can affect any part of the body. SLE is a disease of unknown etiology with a variety of presenting features and manifestations. Interest in the disease has been stimulated in recent years, and improved methods of diagnosis have resulted in a significant increase in the number of cases recognized. It is apparent that it can no longer be regarded as a rare disease. The majority of the pathology in SLE is related to deposits of immune complexes in various organs, which triggers complement and other mediators of inflammation. Symptoms vary from person to person, and may come and go, depend on what part of the body is affected, can be mild, moderate, or severe. Diagnosis can be difficult because lupus mimics many other diseases; it requires clinical and serologic criteria.*

Keywords- Lupus, Autoimmune disorder, Antibodies, Hyper action.

I. INTRODUCTION

Immune system plays a vital role in the defence mechanism of our body. Immunity is the ability of body to fight with infectious or viral materials which causes infection. Our immunity protects us from disease and infection by controlling or killing germs that get into your body. These germs are like viruses, bacteria or sometimes fungi also. Our immunity tells to our body “that the germ detected are not the part of you”, so body destroys them. But if by any reason the normal function of this immune system changes then it causes unpredictable severe problems to our body. If the immune system show more action than the normal then it known as the autoimmune disease, in these disease our immune system attacks the healthy cells of your organs and tissues by mistake. There are more than 86 types of autoimmune diseases. They can affect any part of our body. For example, alopecia areata is an autoimmune disease that causes hair loss. Autoimmune hepatitis can affects the liver. In type 1 diabetes, the pancreas is affected by immune system.

Lupus is an autoimmune disease, which is a chronic disease in which the immune system erroneously acts against its own healthy tissues. The autiology of this disease is unclear but it considered as multifactorial disease. This disease is genetically complex and all clinical pictures of these disease are heterogeneous, so it makes it difficult for the identification of exact mechanism.[Bertsias GK, et.al., 2010]

Systemic lupus erythromatosus (SLE) is the chronic autoimmune disease that characterized by the production of the antibodies against the components of cell nucleus and that damage the body tissues. The main goal for systemic lupus erythromatosus (SLE) is in the analysis of genetic polymorphism occurred in gene which are involved in immune functions.

The pathogenesis of SLE is still unclear, with the genetic studies and environmental factors. Our body naturally forms new cells and correspondingly destroys old cells, these cell destroy phenomenon can called as cell necrosis. At critical stage the cell necrosis can develop SLE, in which the undegraded chromatin molecule and the nucleoprotein are both released into the blood, this may result in circulating the free DNA (DNA without cell) and serum nucleoprotein that responsible for the anti-dsDNA autoantibody production. These antibodies may further responsible for the breakdown of the normal healthy red blood cells or DNA fragments in the body.

The correct diagnosis of lupus is the major challenge in front of medical professionals, because in SLE the various complications and multiple clinical presentations are observed. The lupus disease can affects the lungs, kidneys, skin, musculoskeletal system, nervous system and blood circulating system as well as some other organs of our body. In recent two decades, the death rate due to SLE have declined due to a result of earlier or fast disease detection and advancement in treatment. As compaired to past 10 years the survival rate now increased by 90%; while three decades ago the 10 year average survival rate was 76%. Immunosuppressants are plays important role in increasing the survival rate. A common cause of late mortality related to SLE is an accelerated

atherosclerosis that is associated with either the disease or the treatment.[Mallavarapu RK, et.al., 2007]

Lupus is the disease associated with the multi systemic inflammation which is result of abnormal immunological function. There are four main types of Lupus are as follows:

- Neonatal and pediatric lupus erythematosus (NLE)
- Discoid lupus erythematosus (DLE)
- Drug induced lupus (DIL)
- Systemic lupus erythematosus (SLE)

- **Neonatal and pediatric lupus erythematosus (NLE)**

As a rare form of lupus observed in new born, NLE is thought to result from maternal autoantibodies passing through the placenta. However, of those pediatric patients who have positive maternal autoantibodies, only about 1% develop NLE. Common clinical presentations involve the heart, liver, and skin. Significant morbidity and mortality, along with cardiac manifestations, have been noted; however, in most NLE patients with other organ involvement (e.g. skin, liver, and blood), signs and symptoms sometimes resolve spontaneously within 4 to 6 months.

- **Discoid lupus erythematosus (DLE)**

DLE is manifested as a chronic scarring and symptom light-sensitive skin condition, might, which can achieve lupus or may occur in patients with lupus. The cause is assumed to be genetic, with the very best prevalence in ladies, African-Americans, and persons between twenty and forty years elderly. The designation is usually created by diagnostic assay of a rash on the scalp, face, neck, or arms. Chemical and physical sunblocks, topical corticosteroids, or antiprotozoal drug agents square measure unremarkably wont to forestall malady flares and to manage the clinical manifestations related to lupus.

3.Drug iatrogenic lupus (DIL)

DIL happens when exposure to a medicine, inflicting Associate in Nursing response response. numerous organ systems could also be affected, however clinical manifestations sometimes subside upon ending of the accountable agent.

4. general autoimmune disease (SLE)

systemic lupus erythematosus is that the most typical kind of lupus and is thus the main target of this review. systemic lupus erythematosus is often observed merely as "lupus," however it's differentiated from different varieties by its multi organ system effects. systemic lupus erythematosus is diagnosed in roughly twenty to one hundred fifty persons per one hundred,000 and is often seen in females of kid bearing age; but, it's going to have an effect on male or feminine patients at any age.4–6 systemic lupus erythematosus is a lot of unremarkably ascertained in African-Americans, Asians, Hispanics, and Native Americans.

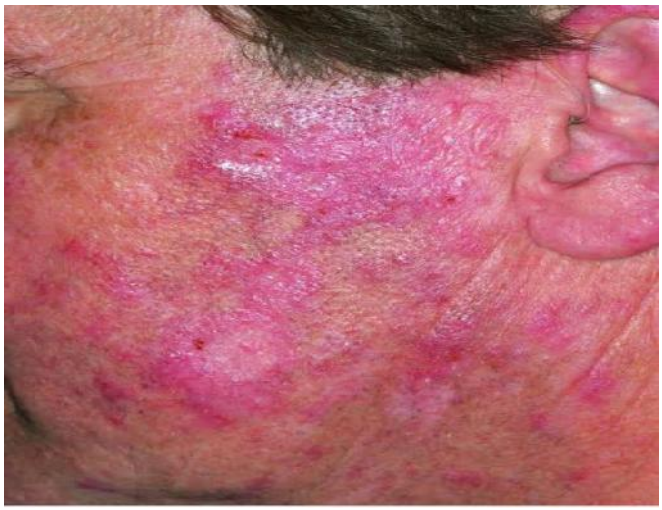


Fig.1: Systemic lupus erythematosus (SLE)

For people with lupus, some treatments can increase the risk of developing potentially fatal infections. However, the majority of people with lupus can expect a normal or near-normal life expectancy. Research has shown that many people with a lupus diagnosis have been living with the disease for up to 40 years.[Norman RA.,et. al, 2016]

Systemic lupus erythematosus (SLE), a chronic systemic inflammatory disease, is considered to be the prototypic example of systemic autoimmune disease. The incidence of SLE in Caucasians is approximately 2-8 cases per 100,000 individuals per year with a prevalence of between 15 and 50 cases per 100,000 individuals. The incidence rate of SLE in northern Sweden is 3.7 cases per 100,000 persons per year in women and 0.6 cases per 100,000 persons per year in men and the prevalence is 67.4/100,000 and 12.9/100,000, respectively, which is in line with the published values from southern Sweden. SLE predominately affects women (female: male ratio = 5-9:1) and in particular women of childbearing age. One of the female sex-hormones, estrogen, which has pro-inflammatory properties, is thought to be one of the factors responsible for the female predominance. It has been shown that some estrogen containing oral contraceptives and

pregnancy may cause the disease to flare and that disease activity may fluctuate with the menstrual cycle. However, the role of estrogen in SLE pathogenesis is controversial. SLE can occur in children, with an almost equal sex ratio, in post-menopausal women after menopause and also in men.

The explanation for the gender bias of SLE probably lies within the interaction of multiple sex hormones, including estrogen, testosterone, dehydroepiandrosterone (DHEA) and prolactin. The female predominance could also be partly explained by an X chromosome gene dosage effect. The frequency of Klinefelter's syndrome (47, XXY) has been shown to be increased approximately 14-fold in men compared with those without SLE. SLE is a disease characterized by inflammation resulting in organ damage. The immunological processes in patients with SLE produce a wide range of auto-antibodies against components of the cell nucleus resulting in a diversity of clinical manifestations. Anti double stranded DNA (dsDNA) antibodies are highly specific for SLE and belong to the group of auto-antibodies called anti-nuclear antibodies (ANAs). ANAs are present in more than 95% of the patients.14 Other ANAs are anti-single-stranded DNA (anti-ssDNA) antibodies, anti-ribonuclear protein (anti-RNP) antibodies, anti-SSA (Ro) antibodies, anti-SSB (La) antibodies, anti-histone antibodies, and anti-Sm antibodies. Another group of auto-antibodies are anti-phospholipid (aPL) antibodies, which are present in approximately 25-30% of patients with SLE. A positive test for lupus anticoagulant / anticardiolipin (aCL)/aPL antibodies indicate the presence of secondary anti-phospholipid syndrome (APS) if associated with thrombosis and/or recurrent miscarriage. Auto-antibodies have been detected up to 9 years before the onset of symptoms. ANA, anti-Ro, anti-LA and aPL are the first auto-antibodies to present and usually precede the onset of SLE by many years. Anti-Sm and anti-RNP antibodies appear only months before diagnosis and concurrently with the appearance of clinical manifestations. [Carter EE, et.al., 2016]

A common hypothesis on the pathogenesis of SLE is that cell death is responsible for the release of the extra-cellular DNA that is recognised by anti-DNA antibodies. Increasing levels of extra-cellular DNA could occur either by an increase in cell death or by an impaired clearance of dying cells. Apoptosis is a programmed cell death induced either extrinsically by signalling through the Fas ligand, or intrinsically following DNA damage. During apoptosis, proteins, DNA, and RNA are cleaved by caspases, proteases, and endonucleases. There are also post-translational modifications of autoantigens like ubiquitination, methylation and citrullination, which could contribute to the development of auto-antibodies. The plasma membrane of the cell is altered, the chromatin degraded and nucleosomes cleaved, leading to the formation of apoptotic blebs. The apoptotic blebs contain nucleosomal DNA along with other auto-antigens such as Ro, La and RNPs. The complement system plays an important role in the elimination of apoptotic cells and immune complexes. Complement is activated through three different pathways: the classical, the mannan-binding lectin (MBL) and the alternative pathway. The classical pathway is responsible for the removal of immune complexes. Deficiencies of components belonging to the classical pathway (C1q, C1r, C1s, C2, and C4) are associated with an increased risk of developing SLE with the strongest associations being found with C1q.

Classical pathway deficiencies are associated with an impaired clearance of apoptotic cells. Furthermore, it has been suggested that classical pathway deficiencies result in impaired handling of immune complexes, B-cell tolerance, and cytokine production by dendritic cells (DC), all of which may contribute to the pathogenesis of SLE.

An impaired clearance of apoptotic cells could result in increased amounts of extra-cellular DNA, in the form of nucleosomes, which in turn can form immune complexes and trigger the production of type I interferon (IFN). The type I IFN system has been shown to play an important role in the aetiopathogenesis of SLE. Increased serum levels of IFN-α have been detected in patients with SLE. The major IFN-α producing cells among human blood leucocytes were initially called natural IFN producing cells (NIPC).

The NIPC had the properties of a dendritic cell (DC) precursor and were later characterized as plasmacytoid DC (PDC) or precursor of type 2 DC (pDC2). IFN-α production by PDC is generally considered to be induced by viruses. However, in SLE, IFN-α production can be triggered by immune complexes of antibodies and either DNA or RNA. The formation of these IFN-α activating immune complexes is thought to be a consequence of apoptotic or necrotic cells. Elevated IFN-α production could result in maturation of DCs, activation of T-cells and stimulation of auto-antibody production by B-cells. These auto-antibodies in turn form new immune complexes and trigger the next cycle of IFN-α production. Clinically, SLE can manifest in multiple organ systems, e.g., heart, lungs, kidneys, joints, skin and nervous system. To be diagnosed with SLE, the patient must fulfil at least four out of the 11 criteria for SLE (Table 1). There are different measurements used to assess disease activity.

The most widely used, and validated, are the British Isles lupus assessment group (BILAG) index, the European consensus lupus activity measurement (ECLAM), the systemic lupus activity measure (SLAM), the SLE disease activity

index (SLEDAI), and the lupus activity index (LAI).54 The SLEDAI measures the disease activity within the previous 10 days and includes 24 weighted objective clinical and laboratory variables. This index scores the organ damage occurring since the onset of lupus, as ascertained by clinical assessment and present for at least 6 months.[Barbhaiya M, et.al., 2018]

Pathophysiology:

SLE is a chronic disease that affects various organ systems, primarily as a consequence of the formation and deposition of Autoantibodies and immune complexes, leading to eventual Organ damage. Hyperactive B cells, resulting from T-cell and Antigen stimulation, increase the production of these anti Bodies against antigens that are exposed on the surface of Apoptotic cells. The antigens causing T-cell and B-cell stimulation in patients With SLE can be attributed to the inappropriate disposal of Apoptotic cells. During the process of cellular death, pieces of Cellular material form on the surface of the dying cell. Antigens that are normally absent on the surface of the cellular material But instead are embedded within, are now present on the cell Surface. Nucleosomes and anionic phospholipids are examples of antigens that have been identified in patients with SLE, and they have the potential to trigger an immune response.

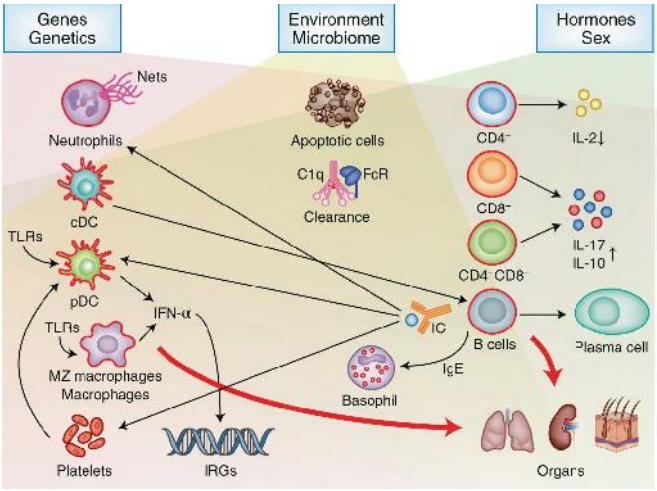


Fig. 2: Pathophysiology of systemic lupus erythematosus

It is believed that the removal of these apoptotic cells is compromised because of the impaired functioning of phagocytic Cells, resulting in suboptimal disposal of dying cells and antigen recognition in patients with SLE.14 SLE is thought to develop when a T-lymphocyte to an anti-Gen-presenting cell (APC) is introduced. The T-cell receptor binds to the major histocompatibility complex (MHC) portion Of the APC, which may lead to cytokine release, inflammation, And B-cell stimulation. Stimulation of B-cell division and the Production of immunoglobulin G (IgG) autoantibodies that can cause tissue damage also occur in SLE. Unlike the situation in healthy adults, auto antigen-specific T cells and B Cells may also interact and produce harmful autoantibodies. Many of the autoantibodies identified in SLE—the anti – Nuclear antibodies (ANAs)—target nuclear components of Cells.

The detection of ANAs in patients with SLE is essential to the diagnosis. Patients may have positive results for more Than one ANA. The ANAs that have been tested most extensively, with involvement confirmed in SLE, are the Anti double-stranded (ds) DNA antibodies. These antibodies, which are linked to SLE-induced kidney and skin disease, are highly specific for SLE and are present in a significant number of patients. ANAs also interact with single-stranded (ss) DNA As well as with RNA. Other examples of ANAs are the anti-Ro And anti-La antibodies that, when detected during pregnancy, Have been linked to fetal heart damage as well as the anti-Smith (Sm) antibodies, which are a marker of kidney disease. [Block SR, et.al., 1976]

A second grouping of autoantibodies targets the phospho-Lipid moiety of the prothrombin activator complex as well as Cardiolipin. These antiphospholipid antibodies can lead to Abnormal clotting as well as loss of pregnancy. In summary, the presence of hyperactive B cells leading to the production of autoantibodies, in conjunction with the impaired removal of apoptotic cellular material, results in the Formation of immune complexes. In the microvasculature, these complexes induce inflammatory reactions, causing the Tissue inflammation and damage associated with SLE.

The basic pathological features of SLE are that of inflammation and blood vessel abnormalities, which include band or occlusive vasculopathy, vasculitis, and immune complex deposition. The best characterised organ pathology is in the kidney.

Etiology:

The etiologic mechanism of SLE remains unknown, but multiple associations have been identified as a result of decades of research. Genetic, hormonal, immunological, and environmental factors all play a role in the development of SLE. Studies focusing on a potential connection between genetics and SLE have shown a genetic predisposition within families. First-degree relatives of patients with SLE are significantly more likely to have the disease compared with the rest of the population. A study focusing on children of mothers with SLE documented that 27% of 195 children tested positive for ANAs. Multiple studies addressing the incidence

of SLE in identical and fraternal twins have demonstrated a strong relationship, especially with identical twins. One study revealed concordance rates of 14% to 57% in identical twins sharing the same trait; a second study showed an incidence rate of 24% to 58%. In another study of non-identical twins, concordance rates of 3% to 10% were documented.

The investigation of a genetic influence on SLE has led to the discovery of a number of gene variants linked to SLE expression. Typically, a combination of these genetic variants leads to the clinical manifestations of SLE. For example, the complement component C1q eliminates necrotic cellular waste (apoptotic material) in healthy individuals. In patients with SLE, a possible deficiency of the C1q component can lead to disease expression. A second example of genetic variance is a possible deficiency of the C4 complement, a component identified in the elimination of self-reactive B cells. When the overall genetic picture of a patient with SLE is taken into account, the additive effects of these genetic variances significantly increase the risk of SLE progression. The effect of hormones on the rate of occurrence and the severity of SLE has been of particular interest to researchers.

The mechanism by which hormones affect SLE prevalence remains unknown. One hypothesis focuses on the roles of estrogens, progesterone, testosterone, dehydroepiandrosterone (DHEA), and prolactin in immune system responsiveness. Estrogen has been linked to the stimulation of T and B cells, macrophages, and cytokines. Estradiol in mice has an inhibitory effect on apoptosis, allowing the survival of B cells that produce high-affinity anti-DNA antibodies. DHEA, an androgen that is a precursor to testosterone, has immunosuppressive properties. In patients with SLE, DHEA levels may be suboptimal. Progesterone also affects autoantibody production, and elevated prolactin levels have been associated with SLE flares. Immunological involvement in SLE focuses on a patient's loss of "self-tolerance." The process of phagocytosis is compromised in SLE patients, leading to the inappropriate removal of apoptotic cells and immune complexes. [Deapen D, et.al., 2018]

The hallmark of SLE is the formation of autoantibodies that go on to form immune complexes (in combination with antigens), leading to inflammation and tissue damage. Environmental factors include certain viruses and ultra-violet (UV) light. UV light stimulates keratinocytes, leading to B-cell stimulation and antibody production; it may also stimulate T-cell activity, resulting in additional autoantibody production. Epstein–Barr virus (EBV) has also been linked to the onset of SLE in children. Patients with SLE have higher titers of antibodies to EBV. Smoking, silica, and some hair products (e.g., dyes) may also be possible triggers of lupus.

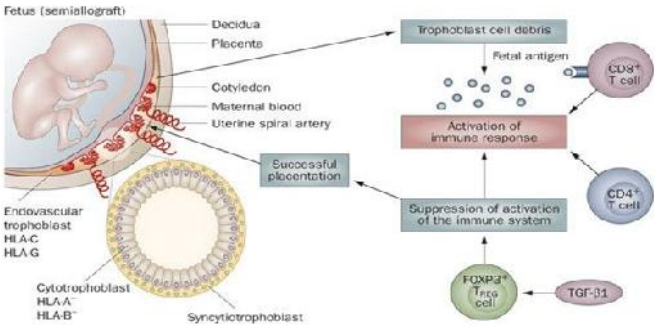
Symptoms of SLE:

- Muscle pain and weakness
- Sharp chest pain during inhaling deeply
- Anaemia or clotting problems
- Hair loss or loss of scalp hair
- Dryness of mouth
- Red rashes on face and skin
- Butterfly shaped rashes on chick and nose
- Anxiety
- Swelling in hands, feet, or around the eyes
- Blood in urine
- Weight loss
- Clinical depression
- Headache
- Joint pain or swelling
- Sensitivity to light
- Discomfort feeling
- Loss of apetite

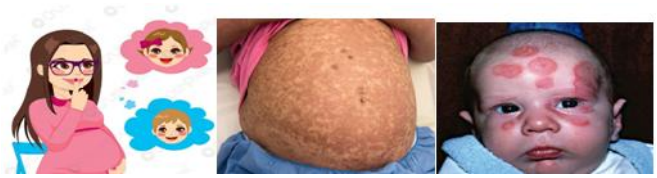
SLE in pregnancy:

Women with lupus area unit at enhanced risk for serious medical and physiological condition complications, like occlusion, infection, blood disease, transfusion, pre-eclampsia, and death. As a result of the high risk of miscarriage, stillbirths, premature delivery, and exacerbation of lupus, it's suggested that girls not become pregnant if they need active unwellness or important organ involvement. Oral contraceptives should run cautiously as a result of high doses of sex hormone will cause lupus exacerbations. Physiological condition outcomes area unit improved if conception is delayed till lupus has been inactive for a minimum of half dozen months and if the patient's medications area unit adjusted beforehand. Baseline and monthly observation (e.g., laboratory tests, prenatal diagnosis, foetal police work tests, maternal diagnostic technique, and protein testing) ought to be performed for all pregnant lupus patients, as a result of signs and symptoms of lupus flares could also be kind of like those typical of physiological condition. Neonates ought to be rigorously evaluated for placental transfer of maternal antibodies, that could lead on to cutaneal or viscus complications (e.g., inborn cardiac arrhythmia and cardiomyopathy). If a lady is pregnant and has active lupus, corticosteroids could also be prescribed with caution to manage the unwellness. Most steroids area unit physiological condition class C medicine. NSAIDs (Pregnancy class C and

D) have conjointly been used, however to a lesser extent, and that they ought to be avoided throughout early physiological condition and therefore the last trimester. If necessary, Plaquenil could also be used, however it's conjointly a physiological condition pregnancy and the last trimester. If necessary, hydroxychloroquine may be used, but it is also a Pregnancy Category C drug. Therefore, therapy must be individualized and the drug's benefits and risks must be carefully considered. Immunosuppressive agents are contraindicated in pregnancy, except for azathioprine, a Pregnancy Category C drug.



In women with SLE and antiphospholipid antibodies, prophylaxis with aspirin, low-molecular-weight heparin, or both, is indicated for the prevention of fetal loss and pregnancy defects. There is no significant difference in fertility between patients with SLE and unaffected individuals. Pregnancy may increase lupus activity but flares are usually mild. Pregnancy outcome is optimal when the disease is in clinical remission for 6–12 months and the patient's renal function is stable and normal or near normal. Patients with LN and anti-phospholipid antibodies are at risk of developing pre-eclampsia and should be monitored closely. Proteinuria may increase during pregnancy in women with underlying kidney disease. Diff erentiation of pre-eclampsia from lupus renal activity is not difficult in most cases. Very low serum complement, active urine sediment, and evidence of generalised lupus activity favour the latter. Other features such as hypertension, thrombocytopenia, rise in serum uric acid levels, and proteinuria may be observed in both conditions. Low grade activation of the classic complement pathway may be attributable to pregnancy alone.



Ovarian induction and fertilisation can be successful in SLE patients, but rates of fetal and maternal complication may be higher. SLE may affect the fetus in several ways, especially if the mother has a history of LN, antiphospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with increased risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal heart block. Neonatal lupus is a passively transferred autoimmune disease that occurs in some babies born to mothers with anti-SS-A/Ro and/or anti-SS-B/La antibodies.

The most serious complication in the neonate is complete heart block, which occurs in up to 2% of such pregnancies. Isolated skin rash occurs in a similar percentage. Once a woman has given birth to an infant with congenital heart block, the recurrence rate is about 15%.

Diagnosis

SLE represents a challenge for the treating physician in terms of diagnosis and treatment. Its protean manifestations, often multisystem but occasionally limited to a few or single organ, have led some physicians to focus exclusively on evidence of serological autoimmunity (antinuclear and more specific auto antibodies), for a disease where diagnosis is clinical after excluding competing diagnoses. Monitoring of SLE through validated disease activity and chronicity indices, including physician global assessment (PGA), is recommended. For patients with severe disease, multidisciplinary care in dedicated lupus centers is desirable. Immunosuppressive (IS) therapy (for induction and maintenance of remission) is indicated in organ-threatening lupus.

There are various diagnostic tests for SLE these are as follows:

1. Serologic tests

Antinuclear antibodies. The ANA assay is an ideal screening test because of its sensitivity (95% when using human cultured cells as the substrate) and simplicity. The entity of 'ANA-negative lupus' described in previous years is usually associated with the presence of other cytoplasmic autoantibodies such as anti-Ro (SS-A) and anti-ribosomal P protein. The specificity of ANAs for SLE is low, since they are found in many other conditions such asscleroderma, polymyositis, dermatomyositis, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, infections, neoplasms, and in association with many drugs. Also, some healthy individuals test positive for ANAs. The formation of ANAs is age-dependent; it is estimated that 10–35% of individuals older than 65 years have ANAs. However, the titres are generally lower (<1:40) than those in systemic autoimmune diseases. In contrast to the low positive predictive

value of ANA testing, a patient with a negative test has less than a 3% chance of having SLE; thus, a negative ANA test is useful for excluding the diagnosis of SLE. However, in the presence of typical features of lupus, a negative ANA test does not exclude the diagnosis.

This is especially true for laboratories that employ enzyme immunoassays or other automated assays which display marked inter-manufacturer variation in performance. In such cases, reported sensitivity against positive immunofluorescence ANA with titre at 1:160 ranges from 70–98%. Antibodies to extractable nuclear antigens (ENAs). The nucleosome a complex of DNA and histones was the first identified lupus autoantigen. Autoantibodies to single stranded DNA (ssDNA) and individual histones are common in SLE as well as in drug-induced lupus. Antibodies to double stranded (ds) DNA are found in up to 70% of SLE patients at some point during the course of their disease, and are 95% specific for SLE, making them a valuable disease marker. Anti-Sm (Smith) antibodies are detected in 10–30% and their presence is pathognomonic for SLE. Anti-nRNP antibodies are associated with anti-Sm but are not disease specific. Anti-ribosomal antibodies are specific for SLE but less sensitive than anti-dsDNA or anti-Sm antibodies.

2. Prognostic markers and the role of autoantibodies

Analysis of large cohorts has defined clusters of autoantibodies associated with distinct SLE features.
Serum anti-dsDNA titres have been correlated with LN, progression to end-stage renal disease, and increased disease severity, damage or poor survival. Antiphospholipid antibodies are strongly associated with features of the antiphospholipid syndrome (APS) (arterial/ venous thrombosis, fetal loss, thrombocytopenia), CNS involvement (especially cerebrovascular disease), severe LN, damage accrual, and death. Anti-Ro (SS-A) and anti-La (SS-B) antibodies have been associated with neonatal lupus, and congenital heart block in the children of seropositive mothers. Antibodies to other extractable nuclear antigens (anti-Ro/La/Sm/RNP) have been associated with mucocutaneous involvement and less severe nephropathy in most studies.

3. Diagnosis by typical and atypical presentations

The diagnosis of lupus requires integration of patient's symptoms, physical examination findings, and the results of diagnostic tests. Table 9 shows the frequency of various manifestations both at disease onset and at any time during the disease course. Presence of one or more of these features or the involvement of at least two different organs in young women should always raise the possibility of lupus. However, many of these features are not unique to lupus but could be seen in other infectious, metabolic, malignant, and other systemic rheumatic diseases [Petri, M. et al., 2012].

4. Differential diagnosis

Differential diagnosis from other polyarticular diseases affecting young women, such as rheumatoid arthritis or Still's disease, may not be easy at the initial stages. Other diseases to be considered include undifferentiated connective tissue disease, primary Sjögren's syndrome, primary antiphospholipid syndrome, fibromyalgia with positive ANA, idiopathic thrombocytopenic purpura, drug induced lupus, and autoimmune thyroid disease. Patients presenting with fever or splenomegaly/ lymphadenopathy must be differentiated from infectious diseases or lymphoma. In febrile patients with known SLE, leucocytosis, neutrophilia, shaking chills, and normal levels of anti-DNA antibodies favour infection. Lupus may present with localised or generalised lymphadenopathy or splenomegaly, but the size of lymph nodes is rarely >2 cm while splenomegaly is mild-to-moderate. Patients with known or suspected SLE with prominent lymphadenopathy, massive splenomegaly or expansion of a monoclonal CD19+/CD22+ B cell population should raise the suspicion of non-Hodgkin lymphoma. In patients presenting with neurological symptoms, infections, cerebrovascular accidents or immune mediated neurologic diseases such as multiple sclerosis or Guillain-Barré disease must be considered. Finally, in patients presenting with pulmonary–renal syndrome, the disease must be differentiated from Goodpasture's syndrome, or antineutrophil cytoplasmic antibody (ANCA) associated vasculitis.

Drugs used in SLE

1. Hydroxychloroquine

Hydroxychloroquine (HCQ) is recommended for all patients with SLE. There is evidence for multiple beneficial effects of HCQ in SLE,yet poor adherence to treatment is not uncommon. Concerns for retinal toxicity with long-term HCQ therapy led to the use of more sensitive screening techniques, with a prevalence of retinal abnormalities exceeding 10% after 20 years of continuous use. Major risk factors for retinopathy include duration of treatment (OR 4.71 for every 5 years of use), dose (OR 3.34 for every 100 mg daily dose), chronic kidney disease (adjusted OR 8.56) and pre-existing retinal or macular disease. Based on existing evidence suggesting that the risk of toxicity is very low for doses below 5 mg/kg real body weight, the daily dose should not exceed this threshold. Patients in long-standing remission may have their dose lowered, although no studies have formally addressed this

strategy. The choice of quinacrine, an alternative antimalarial, can be considered in patients with cutaneous manifestations and HCQ- induced retinal toxicity. [Perdriger A, et.al., 2003]

2. Glucocorticoids

GC can provide rapid symptom relief, but the medium to long-term aim should be to minimize daily dose to ≤7.5 mg/day prednisone equivalent or to discontinue them, because long-term GC therapy can have various detrimental effects including irreversible organ damage. Risks are substantially increased at continuous GC doses above 7.5 mg/day, with some studies suggesting that also lower doses might be harmful. To this end, two approaches can be considered: (1) use of pulses of intravenous methylprednisolone (MP) of various doses (depending on severity and body weight), which take advantage of the rapid non-genomic effects of GC and may allow for a lower starting dose and faster tapering of POGC, and early initiation of IS agents, to facilitate tapering and eventual discontinuation of oral GC. High-dose intravenous MP (usually 250–1000 mg/day for 3 days) is often used in acute, organ-threatening disease (renal, neuropsychiatric) after excluding infections.

3. Immunosuppressive (IS) drugs

Consequent initiation of IS drugs facilitates a more rapid GC tapering and may prevent disease flares. The choice of agent depends on prevailing disease manifestation(s), patient age and childbearing potential, safety concerns and cost.

4. Methotrexate (MTX) and azathioprine (AZA)

Should be considered in patients with poor symptom control after a trial with GC and HCQ or when HCQ alone is unlikely to be sufficient, due to the large experience gained with their use and their relatively safe profile. Mycophenolatemofetil (MMF) is a potent immunosuppressant with efficacy in renal and non-renal lupus (although not in neuropsychiatric disease). In a recent randomized, open-label trial in extra renal SLE, enteric-coated mycophenolate sodium (EC-MPS) was superior to AZA in achieving remission and reducing flares.

5. Cyclophosphamide

Cyclophosphamide (CYC) can be considered in organ-threatening disease (especially renal, cardiopulmonary or neuropsychiatric) and only as rescue therapy in refractory non-major organ manifestations; due to its gonado-toxic effects, it should be used with caution in women and men of fertile age.

6. Biological agents

There is evidence to support beneficial effects of B-cell targeting agents in SL. Belimumab should be considered in extra renal disease with inadequate control (ongoing disease activity or frequent flares) to first-line treatments (typically including combination of HCQ and prednisone with or without IS agents), and inability to taper GC daily dose to acceptable levels (ie, maximum 7.5 mg/day). (14) Patients with persistent disease may benefit from belimumab; more likely to respond are patients with high disease activity (eg, SLEDAI >10), prednisone dose >7.5 mg/day and serological activity (low C3/C4, high anti-dsDNA titres), with cutaneous, musculoskeletal and serological manifestations responding the most. Due to the negative results of randomized controlled trials (RCTs), RTX is currently only used off-label, in patients with severe renal or extra renal (mainly haematological and neuropsychiatric) disease refractory to other IS agents and/or belimumab, or in patients with contraindications to these drugs.

Additional Treatment Options

Researchers have been particularly interested in the use of stem-cell transplantation to introduce healthy cells into the body in order to help rebuild the immune system. Both DHEA and rituximab have been studied in clinical trials and have provided improvements in patients' quality of life. DHEA is believed to help in the regulation of sex hormones, whereas rituximab decreases the number of B cells and may be most beneficial in patients who do not respond to the other traditionally used immunusuppressants.

Management of SLE

The approach to the treatment of signs and symptoms of lupus depends on the type and the severity of disease. General recommendations for all patients include sun protection, proper diet and nutrition, exercise, smoking cessation, appropriate immunizations, and management of comorbid conditions. In patients with mild-to-moderate lupus, NSAIDs, antimalarial agents, and corticosteroids are commonly used to treat signs and symptoms. As the disease progresses and clinical manifestations worsen, high dose corticosteroids and immunosuppressive agents are used to help control disease progression.

NSAIDs

NSAIDs may be used to alleviate musculoskeletal pain, swelling, and aches. These drugs possess pain-reducing, anti-inflammatory, and anticoagulant properties, which are beneficial in treating common lupus-associated manifestations; however, the potential for side effects (see Table 1) must be considered before clinicians prescribe NSAIDs for a patient with lupus.

Antimalarial Medications

Some antimalarial agents have proved effective in treating the various signs and symptoms of lupus and preventing sub-sequent flares. Although the exact mechanism is unclear, antimalarials may interfere with T-cell activation and inhibit cytokine activity. These agents may also inhibit intracellular toll-like receptors, which recognize and bind foreign materials, thereby contributing to activation of the immune system. Hydroxychloroquine (e.g., Plaquenil, Sanofi) is the most commonly studied and used drug in its class, but it has the potential to cause serious visual and muscle disturbances.

Steroids

Corticosteroids mimic naturally occurring hormones excreted by the adrenal gland and help regulate blood pressure and immune function. These agents decrease the swelling and pain associated with inflammation, which can occur in a lupus flare. Because of their serious long-term side effects, corticosteroids should be used at the lowest possible dose and only for periods necessary to control an active exacerbation of lupus.

Immunosuppressive Agents

Immunosuppressants are primarily used in more severe cases of lupus when high-dose corticosteroids or antimalarial treatments have failed to control the signs and symptoms of disease. They are also used when it is necessary to induce and maintain remission and to reduce flares or relapses. Immunosuppressants may be given with high dose corticosteroids to control flares, to achieve a lower dose of each medication, or to reduce the occurrence of adverse events. The most commonly used agents in this class are cyclophosphamide (Cytoxan, Bristol-Myers Squibb) and azathioprine (Azasan, Salix; Imuran, GlaxoSmithKline). Mycophenolate (CellCept, Genen-tech/Roche) has also been used for lupus-related kidney problems.

Monoclonal Antibodies

Belimumab

In March 2011, the FDA approved the first human mono- clonal antibody for the treatment of lupus. Belimumab (Benlysta, Human Genome Sciences/GlaxoSmithKline) is the first agent in more than 50 years to be approved for patients with lupus. Belimumab inhibits the activation of B lymphocytes by interfering with a protein necessary for B-cell activity (BLyS). Previously known as LymphoStat-B, Belimumab is recommended for patients with active SLE who are receiving standard therapy with NSAIDs, antimalarials, corticosteroids, and/or immune suppressants.

Rituximab

As a genetically engineered chimeric monoclonal antibody directed against the CD20 antigen, rituximab (Rituxan, Genentech/Roche) has also shown potential in the treatment of SLE. It is believed that B cells responsible for the production of pathogenic autoantibodies, and other immune-mediated substances associated with lupus, are depleted by rituximab. During the past few years, a number of open-label and retrospective studies have reported promising results with rituximab (when taken with corticosteroids and other immune suppressants in the management of both pediatric-onset and adult-onset lupus). Benefits of rituximab have also been noted in patients with lupus nephritis, arthralgia, arthritis, serositis, cutaneous vasculitis, mucositis, rashes, fatigue, and neurological and refractory symptoms.

Adverse events were generally mild. Mild to moderate infusion reactions were reported most often. A few randomized controlled studies have provided mixed results regarding the efficacy and role of rituximab in the treatment of SLE. In a study by Terrier et al., clinical responses were reported in 71% of patients who received rituximab, demonstrating a significant benefit in refractory lupus (with or without concomitant immunosuppressive therapy). Cutaneous, articular, renal, and hematological improvements were noted most often, along with an acceptable tolerance profile. In a systematic review of 188 SLE patients treated with various regimens of rituximab, 91% showed a significant improvement in one or more systemic manifestations, particularly in patients with renal involvement (e.g., lupus nephritis). Adverse events were experienced by 23% of patients, and infections were reported most often. However, two additional randomized, placebo-controlled studies, conducted since 2010, failed to demonstrate significant clinical improvements with rituximab in patients receiving concomitant steroid therapy. Despite the favorable tolerability and safety profile of rituximab, further evaluation of this drug is required for patients with SLE.[Bertsias G, et.el.,2016]

Recommendations/Goals of treatment

To improve semipermanent patient outcomes, management ought to aim at remission of unwellness symptoms and signs, bar of harm step-up and minimisation of drug side-effects, yet as improvement of quality of life. Complete remission (absence of clinical activity with no use of Gc and IS drugs) is infrequeflar, to the current finish, new outlined low unwellness activity states (based on a SLEDAI score ≤3 on antiprotozoal drug, or instead SLEDAI ≤4, PGA≤1 with Gc Gc.5 mg of Liquid Pred and well tolerated IS agents) have shown comparable rates with remission, concerning halting of harm step-up (OR zero.5–0.7 for increase in injury index) and bar of flares. Consequently, treatment in lupus ought to aim at remission or, if this state can't be achieved, at low unwellness activity all told organ systems. In LN, medical aid ought to aim a minimum of partial remission (defined as ≥50% reduction in symptom [UPr] to subnephrotic levels and humour creatinine at intervals 100% from baseline) by 6–12 months; complete nephritic remission (proteinuria<500 mg/24 hours and SCr within 10% from baseline), however, may require longer treatment duration, often more than 12 and until 24 months. In monitoring renal response, reduction of UPr (to less than 0.8 g/day) following treatment is more important than residual haematuria. Patients with more severe proteinuria and longer-standing disease are less likely to respond or show more delayed responses.

Prevention of disease flares is an additional milestone of SLE treatment. Flares are common in the disease course and contribute significantly to organ damage accrual and worse outcome. Consistently reported risk factors for a higher disease flare rate include younger age at disease onset, no use of antimalarial drugs, persistent generalized disease activity and serological activity (anti-ds DNA, low complement).Assessment of adherence to drug treatment, close monitoring and optimization of disease control in these patients may reduce the risk for a flare.

II. CONCLUSION

1. SLE is a chronic autoimmune disorder.
2. It predominantly affects younger women, but can occur in up to 20% of patients 50 years of age or older.
3. SLE affects almost every systemic part in the body, with varying degrees of severity. Management is individualized and depends on presenting symptoms.

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