REVIEW ON SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Abstract:
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is potentially debilitating and sometimes fatal as the immune system attacks the body's cells and tissues, resulting in inflammation and tissue damage. SLE can affect any part of the body, the heart, joints, skin, lungs, blood vessels, kidneys and nervous system. It is characterized by the production of multiple autoantibodies, typically antinuclear and anti-DNA antibodies. In some patients, autoantibodies are also produced against platelets, lymphocytes and other cellular antigens. SLE is characterized by the total picture of clinical, immunological and pathological features and many of the pathological changes are non-specific and sometimes may appear exceptionally small in comparison with the extent of clinical manifestations. The principal pathological changes are seen in skin, joints, non erosive synovitis, kidneys, serous membranes pleuritis, and heart.

Key Words:

Introduction
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is potentially debilitating and sometimes fatal as the immune system attacks the body's cells and tissues, resulting in inflammation and tissue damage. SLE can affect any part of the body, the heart, joints, skin, lungs, blood vessels, kidneys and nervous system. Lupus can occur at any age, but is more common in women and particularly non-caucasians in their reproductive years (Ruiz et al., 2001).

It is characterized by the production of multiple autoantibodies, typically antinuclear and anti-DNA antibodies. In some patients, autoantibodies are also produced against platelets, lymphocytes and other cellular antigens. The source of the name "lupus" is unclear. All explanations originated with the characteristic butterfly shaped malar rash that the disease classically exhibits across the nose and cheeks in various accounts. Some physicians thought that the course of the disease is unpredictable with periods of illness called flares alternating with remission. In other accounts, some thought that the rash, which was often more severe in early centuries, created lesions that resemble wolf bites or scratches.

The history of (SLE) can therefore be divided into three periods: the classical, neoclassical and modern. The classical period began when the disease was first recognized in the Middle Ages and saw the description of the dermatological manifestation of the disorder (Braunwald et al., 2005). The term lupus is attributed to the 12th century physician Rogerius, who used it to describe the classic malar rash. The neoclassical period was heralded by moric kaposi recognition in 1872 of the systemic manifestations of the disease. The modern period began in 1948 with the discovery of the LE cells (the lupus erythematosus cell, a misnomer as it occurs with other diseases as well) and is characterized by advances in the knowledge of the pathophysiology and clinical laboratory features of the disease as well as advances in the treatment, useful medication for the disease was found in 1894, when quinine was first reported as an effective therapy, four years later, the use of salicylates in conjunction with quinine noted to be of greater benefit. This was the best available
treatment of patients until the middle of the twentieth century, when Hench discovered the efficacy of corticosteroids in the treatment of SLE (Tierney, 2001).

**CLASSIFICATION OF SLE**

Systemic lupus erythematosus has been classified according to types depending on where they are found. Generally, when the word lupus alone is used, it refers to the systemic lupus erythematosus. Other types have been reported namely: Neonatal lupus which is very rare but occurs in one third of mothers with systemic lupus erythematosus who carry the anti SS A (Ro) antibody. It was reported that this maternal antibody attack the fetus causing skin rash, liver problems and low blood counts. This type resolves by the age of 3 to 6 months (Greenberg and Michalska, 2005).

**Drug Induced**

In 1945, a drug induced kind of lupus was reported following lupus-like reaction to a medication of sulfasalazine. Since then, about seventy drugs have been implicated as causing exacerbating systemic lupus erythematosus. This type is most frequent in older patients with men and women at equal risk. The most common symptoms are fever, fatigue, arthralgia and sereitis. Discoid lupus erythematous, a skin disorder which causes a red, raised rash on the face scalp or rest of the body which can develop into subacut cutaneous lupus erythematosus, which causes non scanning skin lesions on patches of skin exposed to sunlight.

**SIGNS AND SYMPTOMS OF SLE**

Previous researchers reported common initial and chronic complaints as fever, malaise, myalgias and weight loss, which may equally be seen in other diseases. Other symptom reported was arthralgia musculoskeletal. This has been reported as the most common reason patients with SLE seek medical attention. It affects small joints of the hand and wrist.

**Dermatological manifestations**

Past researchers reported that as many as 20% of patients present with dermatological symptoms such as malar rash which develops after sunlight exposure (Schur, 2001). Vasculopathy: Artherial and venous thrombosis is a sequel to chronic inflammatory events triggered by autoantibodies. This has been documented to occur in the form of petechiae, purpura or ecchymoses in the skin or swollen medium sized vessels causing tender nodules, seizures, stroke or behavioural changes.

Renal: There could be renal involvement, nephritic syndrome or renal failure. Painless haematuria or proteinuria may be the only presenting symptoms. This may take place in about 35% of the patients.

**CARDIAC**

Pericarditis, myocarditis and endocarditis can occur from nonspecific inflammation. However, these lesions can manifest as immune complexes on the mitral valve, where bacteria can accumulate lesions, even when clinically silent, are found in more than half of autopsies. Atherosclerosis tends to occur more often and to advance more rapidly in patients with SLE than in the general population. SLE patients therefore are at higher risk for myocardial infarction (Bevra and Hahn, 2003).

**SEROLOGIC FEATURES**

Pluritis, pericarditis, and peritonitis are common features of SLE. Pleural effusions are usually small but can be large. The fluid often contains antinuclear antibodies (ANAS), low complement, and immune complexes.

**HAEMATOLOGIC FEATURES**

Anaemia secondary to chronic inflammation, iron deficiency and hemolysis may develop in as many as half of SLE patients. Thrombocytopenia and leucopenia may be due to SLE or side effects of pharmacologic treatment. Patients may have an association with antiphospholipid antibody syndrome (a thrombotic disorder) where autoantibodies to phospholipids are present in the patients serum. Abnormalities associated with antiphospholipid antibody syndrome include a paradoxical prolonged prothrombin time (which usually occurs in hemorrhagic disorders) and a positive test for antiphospholipid antibodies, the combination of such finding have earned the term" Lupus" "anticoagulant positive". Another autoantibody finding in lupus is the anticardiolipin antibody which can cause a false positive test for syphilis (Braunwald et al., 2005).
NEUROLOGIC MANIFESTATIONS
About 10% of patients may present with a neuro psychiatric manifestation, a third may test positive for abnormalities in the cerebrospinal fluid. Magnetic resonance imaging may show focal areas of increased signal intensity. Electro encephalography and gallium scans have not shown any diagnostic value; computed tomography may be useful for viewing infarcts (Ruiz et al., 2001).

T-CELL ABNORMALITIES
Abnormalities in T-cell signaling are associated with SLE, including deficiency in CD45 phosphatase and increased expression of CD40 ligand. Other rare manifestations include: Lupus gastroenteritis, lupus pancreatitis, lupus cystitis, autoimmune inner ear disease, sympathetic dysfunction, retinal vasculitis and systemic vasculitis.

AETIOLOGY OF SLE:
Research into the cause of SLE has dramatically increased in recent years but, the exact cause of the disease is unknown and there is still no consensus on whether it is a single condition or a group of related diseases. SLE being a chronic inflammatory disease is believed to be a type III hypersensitivity response with potential type I involvement, characterized by the body's production of antibodies against the nuclear components of its own cells. The presence of multiple autoantibodies and other immunologic abnormalities point to basic defects in immunoregulatory controls that normally maintain the immune tolerance to self antigens. Intra cellular molecular components are released from tissue cells during the programmed cell death.

B cell activation generally requires T cell help. Obligatory and enhanced T cell help for B cells is shown in SLE lymphocytes by prolonged expression and consimutatory interaction of the helper T cell surface ligand CD40L with the B-cell receptor CD40 (Desai, 2005). There are three mechanisms which lupus is thought to develop: genetic predisposition, environmental triggers and drug reaction.

Genetics
The first mechanism may arise genetically, researches indicate that SLE may have a genetic link. Lupus run in families end there is 20% concordance of SLE in homozygous twins a estimated 3 to 10 different gene loci may contribute to the risk for SLE. Studies of the human major histocompatibility complex antigens, known as the human leukocyte antigens (HLA), reveal that HLA - DR2 and HLA DR3 occur more often in people with SLE than in the general population. The involvement of HLA alleles may help explain the abnormalities of immune regulation in SLE. The presence of the null complement alleles and congenital deficiencies of complement especially C4, C2 and other early components also are associated with an increased risk of developing SLE. Links between several other HLA genes and SLE lend additional support to the idea that a genetic predisposition to SLE exists.

No single "lupus gene" has yet been identified, instead, multiple genes appear to influence a person's chance of lupus developing when triggered by environmental factors. The most important genes are located on chromosome 6, where mutations may occur randomly (de novo) or be inherited.

Environmental
The second mechanism may be due to environmental factors. These factors not only exacerbate existing lupus conditions, but can trigger the initial onset. They include certain medications such as some antidepressants and antibiotics, extreme stress, exposure to sunlight, and infections. Some researchers have sought to find a connection between certain infectious agents, viruses and bacteria, but no pathogen can be consistently linked to the disease. Ultra violet radiation has been shown to trigger the photosensitive lupus rash, but some evidence also suggests that UV light is capable of altering the structure of the DNA, leading to the creation of autoantibodies. Some researchers have found that women with silicon gel filled breast implant can produce antibodies to their own collagen, but it is not known how often these antibodies occur in the general population and there are no data that show that these antibodies cause connective tissue disease such as SLE. Drug could induce lupus, but drug induced lupus is a reversible condition that usually occurs in patients being treated for a long term illness. Symptoms usually disappear once a patient is taken off the medication which triggered the episode. There are about 400 medications currently used that can cause SLE, I though the most common drugs are procainamide, hydralazine and quinine (Cooper et al., 1998).

Hormonal influence is suggested by the 9: 1 female: male ratio of SLE, the predilection for females during the reproductive years, and the frequency of onset in the early postpartum period.

PATHOLOGY OF SLE:
SLE is characterized by the total picture of clinical, immunological and pathological features and many of the pathological changes are non-specific and sometimes may appear exceptionally small in comparison with the extent of clinical manifestations.

The principal pathological changes are seen in skin, joints, non erosive synovitis, kidneys (lupus nephritis), serous membranes pleuritis, (pericarditis), and heart (endocarditis).

The most typical histopathological lesions occur in the blood vessels, kidney and skin. In active SLE, vasculitis with subendothelial fibrinoid deposits may involve small arteries, arterioles, and capillaries of affected organs, kidneys, spleen, heart, lungs and rarely in the severest cases, acute necrotizing vasculitis may involve the entire vessel wall. Granular deposits of Igs and C are seen in the acute vascular lesions by fluorescence microscopy (Schur, 2001). In later stages, Derivascular fibrosis occurs. The small penicillar arteries of splenic pulp typically develop concentric pervascular laminations of fibrous tissue to reproduce typical "onion skin" which is characteristic but no longer regarded as specific for SLE. The renal glomerular are major targets of immune injury in SLE. Some 50% of SLE patients have glomerular disease shown by urinalysis, haematuria, proteinuria, cast or expressed clinically.

About 50% of patients have glomerular disease indicated by light microscopy and nearly all have glomerular abnormalities shown by immunofluorescence and electron microscopy. In general, the basic histopathological changes in glomerular disease include one or more of the following: cellular proliferations, glomerular basement membrane thickening, leukocyte exudation, hyalinization and sclerosis. These changes may involve virtually all glomeruli (diffuse), a minority of a part of each glomerulus segmental, (mesangial).

Skin lesion involving the face, trunk and extremities occur frequently in SLE and take many forms: facial erythema, such as the classical "butterfly" rash distributed over the cheek and base of the nose, urticaria, maculopapular lesions, ulceration and alopecia. The presence of liquefaction degeneration of the basal layer of the epidermis and fibrinoid change at the epidermal dermal junction is a microscopic change at the epidermal dermal junction of acute lesions and also of uninvolved" normal” skin (lupus band test).

The presence of these deposits in both involved and normal skin distinguishes SLE from other connective tissue diseases such as scleroderma and dermatomyositis and chronic discoid lupus. Apoptosis is increased in monocytes and keratinocytes. Expression of fas by B cells and T cells is increased. There are correlations between the apoptolic rates of lymphocytes and disease activity (Andrade et al., 2000).

Tingible body macrophages (TBMs) are large phagocytic cells in the germal centres of secondary lymph nodes. They express CD68 protein. These cells normally engulf B cell which have undergone apoptosis after somatic hypermutation. In some patients with SLE, significantly few TBMS can be found, and these cells rarely contain materials from apoptotic B cell. Also undigested apoptotic nuclei can be found outside of TBMS. This material may present a threat to the tolerization of B cells and T cells. Dendritic cells in the germal centre may endocytse such antigenic material and present it to T cells, activating them. Also apoptotic chromaton and nuclei may attach to the surfaces of follicular dendritic cells and make this aterials available for activating other B cells which may have randomly acquired self specificity through somatic hypermutation (Gaipl et al., 2006).

EPIDEMIOLOGY OF SLE

The prevalence of SLE varies in different countries. In France, the disease appears to be more common among immigrants from Portugal, Spain, North African and Italy than among natives. In Hawaii, the disease is more common in orientals or Polynesians than among whites. The disease has only recently been described in black Africans and appears to be more prevalent in China than in the united state. The average annual incidence in the United States has been estimated to be 27.5 per million population for white females and 75.4 per million populations for black female. The incidence of SLE among hospitalized patients was 4.6 per 100fOO per year in Baltimore and Maryland study and 1.8 per patients living in Rochester, Minnesota. The annual incidence rate is similar to that observed in Sweden, in New York and in Jefferson county, Albama between 1955 and 1965. Incidence rate showed a steady increase beginning in early 1960, but has stabilized since then. Probably because of a greater appreciation of milder cases and improvement of diagnostic tests during the 1960s. The prevalence of SLE in a prepared health plan for 125,000 patients indicates that SLE affects approximately 1 in 1000 women in Rochester; Mtnnesota study which included all patients in a white population. The prevalence of definite SLE per
100,000 population in 1980 was 40.0-53.8 for women and 19.0 for men. This figure is somewhat lower than 51 per 100,000 reported for prepared health group in San Francisco from 1965-1973. SLE occurs in children and elderly but the peak age of onset of the first symptoms is between 15 and 25 years. The mean age of diagnosis is 30 years. Higher percentage is affected among males in children and elderly. Females particularly young woman have a striking susceptibility to SLE as observed in virtually all epidemiologic studies. The incidence increases early in the second decade, peaks in the third, remains high during the 45 to 64 years period and declines further thereafter. Females exceed males in clinical series in a ratio of 5:1 and to a greater extent during the child bearing years. SLE was previously believed to be a rare disease but has now possible to estimate the number of people with lupus. In the United States alone, an estimated 270,000 to 1.5 million people have lupus. The disease affects both females and males, though young women are diagnosed nine times more often than men. SLE occurs, with much greater severity among African American women, who suffer more severe symptoms as well as higher mortality rate. The prevalence of SLE in whites and Indian Asian immigrants in Leicester City United Kingdom, it was observed that the overall prevalence of SLE in whites of population of 152,785 was 20.2 percent. Asian had high prevalence of 69.7% for females and 31.7% for males in a population of 37,684. The overall lupus was 3.0 times more common in Asians than whites, according to the study. Studies in blacks have shown a high prevalence of the disease in the USA and Jamaica but not in East Africa. In the Chinese, the reverse pattern holds, with the disease being less common in Chinese who have emigrated than in those who remained in their native land. LE cells was also observed to be greater in females 73% than males 5.2% and occurred more in the second and third decades of life (Schur, 2001).

**DIAGNOSIS OF SLE:**

Diagnosis is made by some physicians, on the basis of the American College of Rheumatology (ACR) classification criteria. American College of Rheumatology ACR diagnostic criteria for SLE which was established in 1982, revised in 1997 as a classificatory instrument to operationalise the definition of SLE in clinical trials. SLE patient must present with four of the below eleven symptoms either simultaneously or serially during a given period of observation. The ACR criteria are malar rash (rash on cheeks), discord lupus (red scaly patches on skin which cause scarring), Photo sensitivity (adverse reaction to sunlight (mouth or nose ulcers. More than 0.5g per day protein in urine, or cellular cast seen in urine under a microscope, seizures or sycosis pleuritis (inflammation of the membrane around the lungs or pericarditis (inflammation of the membrane around the heart). Haemolytic anaemia, leucopenia, lymphopenia or thrombocytopenia. Laboratory Test: The lupus erythematosus cell preparation (LE) cell test was designed as the first laboratory test for diagnosis of SLE. Since its inception, this test has been found to have sensitivity of only 50% and is used today as an adjunct. This test prompted research into proteins that act like antibodies but respond to normal cells. The anti-nuclear antibody test (ANA) is the main stay in diagnosis of SLE. This test has high sensitivity but poor specificity. A test using fixed and permeabilized human HEP 2 cells measures binding of the patients serum antibodies to the cell nuclei. Antibodies against the nucleus are found in more than 90% of patients at some time (Tierney, 2001). The immunofluorescent patterns of antibody distribution correlate with certain autoimmune disease stakes. Nucleolar, homogenous, and specked patterns are seen in various diseases including SLE. However the peripheral, or rim pattern is most specific to SLE, although less commonly seen. Urinalysis demonstrating hematuria (> 5 red cells per high -power field), presence of any casts, pyuria > 5 white cells per high field) in the presence of infection and proteinuria. The erythrocyte sedimentation rate could be high.

**MANAGEMENT:**

SLE is a chronic disease with no cure, some medications that modulate the immune system (primarily corticosteroids and immunosuppressants) are used to control the disease and prevent re-occurrence of symptoms (known as flares). Disease modifying antirheumatic drugs (DMARDs) are used preventively to reduce incidence of flares, the process of the disease and lower the need for steroid use. When flares occur, they are treated with corticosteroids. DMARDs commonly in use are the antimalarials (e.g. hydroxychloroquine, methotrexate and azathioprine). Hydroxychloroquine is an approved anti-malarial used for constitutional, cutaneous, and articular manifestations, while cyclophosphamide is used for severe glomerulonephritis or other organ damaging complications, and in 2005, CellCept became accepted for treatment of lupus nephritis.
Patients who require steroids frequently may develop obesity, diabetes and osteoporosis. Depending on the dosage, corticosteroids can cause other side effects such as a puffy face, an unusually large appetite and difficulty in sleeping.

**Conclusion**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is potentially debilitating and sometimes fatal as the immune system attacks the body's cells and tissues, resulting in inflammation and tissue damage. SLE can affect any part of the body, the heart, joints, skin, lungs, blood vessels, kidneys and nervous system. It is characterized by the production of multiple autoantibodies, typically antinuclear and anti-DNA antibodies. In some patients, autoantibodies are also produced against platelets, lymphocytes and other cellular antigens. Abnormalities in T-cell signaling are associated with SLE, including deficiency in CD45 phosphatase and increased expression of CD40 ligand. Other rare manifestations include: Lupus gastroenteritis, lupus pancreatitis, lupus cystitis, autoimmune inner ear disease, sympathetic dysfunction, retinal vasculitis and systemic vasculitides.

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**References**


