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Review Article

SYSTEMIC LUPUS ERYTHEMATOSUS: DAIGNOSTIC AND TREATMENT CHALLENGES

*Ramkala Khatri Chhetri and Prof. DanQi Deng

Department of Dermatology and Venerology, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, 650032, P.R. China

ABSTRACT

The immune system normally fights off dangerous infection and bacteria to keep the body healthy and protect an individual from both outside invaders and its own altered internal cells. An autoimmune disease occurs when the immune system attack the body because it confuses it for something foreign. There are many autoimmune diseases; including systemic lupus erythematosus (SLE). SLE is a serious, potentially fatal, auto-immune disease which produces fatigue, blood disorders, frequent headache, memory impairment, psychological issues and damage to internal organs such as kidneys. It is a chronic occasionally life-threating, multisystem disorder. The rate of SLE varies between countries, ethnicity, sex, and changes over time. It is more common in women than males at any age, more often between 15 and 44. Prevalence varies with ethnicity, but is estimated to be about 1 per 100 overall with a female to male ratio 10:1. While the etiology of SLE is still unknown, epidemiologic research is continuously informing with new insights into environmental risk factors and gene- environment interaction that play a role in disease susceptibility. Patient may present with variable symptoms, signs and laboratory findings and have a variable prognosis that depends upon the disease severity and type of organ involved. Establishing the diagnosis of SLE is challenging and effective management requires clinical monitoring to assess disease activity, alleviate symptoms, prevent and treat relapses and monitoring side effects related to drug therapy for encouragement, coordinate and care of the patient. SLE treatment progress over the years. However, the mortality remains higher that in the general population. Many studies have been examined SLE patient's survival rate.

Key words: *immune system, SLE, multisystem disorder, diagnosis and management challenges.*

INTRODUCTION

SLE is a serious, potentially fatal, auto-immune disease which produces fatigue, blood disorders, frequent headache, memory impairment, psychological issues and damage to internal organs such as kidneys [1].The cause of SLE is still fully unknown. It may be due to hormonal, environmental and genetic factors [2].The risk factors such as smoking, sunlight, vitamin D deficiency, female sex hormones and certain infection may also develop SLE [2]. It is more common in women than males at any age, more often between 15 and 44[3]. Prevalence varies with ethnicity, but is estimated to be about 1 per 100 overall with a female to male ratio 10:1[1] .This disease affects Africans-Americans than in Caucasians, typically more often than people from other races [3]. Thus the rate of SLE varies between countries, ethnicity, sex, and changes over time [4].

Pathogenesis:

The exact patho-etiology of SLE remains exclusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved. It is estimated that at least for susceptibility genes are needed for the development of the disease [5]. The genes of the Major Histocompatibility Complex (MHC) have been most extensively studied for their contribution to human SLE [4].Population studies reveal that the susceptibility to SLE involves human leukocyte antigen (HLA) Class II gene polymorphisms. An association of HLA , DR2, DR3 with SLE is a common findings in patient with the relative risk of development of disease of approximately two to five [6].The HLA Class II gene have also been associated with the presence of certain auto antibodies such as anti-SM(small nuclear ribo nuclear protein),anti-Ro,anti-La, anti-nRNP (nuclear ribonuclear protein) and anti-DNA anti bodies[5].The primary pathological findings in patient with SLE are those of inflammation ,vasculitis, immune complex deposition and vasculopathy. The interaction of sex, hormonal milieu and the hypothalamo- pituitary-adrenal axis modifies this susceptibility and the clinical expression of the diseases [7].Defective immune regulatory mechanism, such as the clearance of apoptotic cells and immune complexes are important contributors to the development of SLE [8].The loss of immune tolerance, increased antigenic load ,excess Tcell help ,defective Bcell suppression and the shifting of Thelper1(Th1) to Th2 immune response leads to B cell hyperactivity and the production of pathogenic auto antibodies[9].

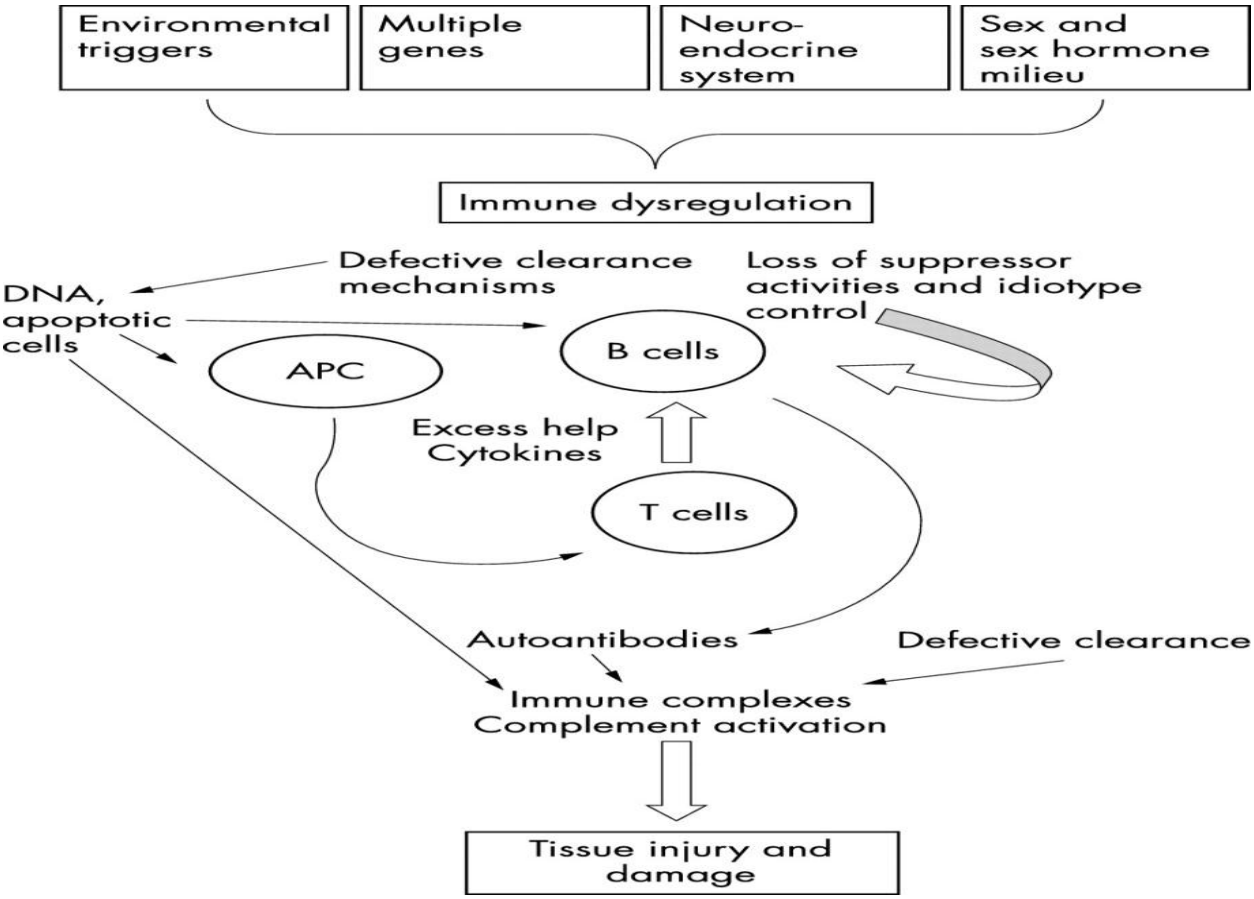

Figure [6]: The pathogenesis of systemic lupus erythematosus, APC, antigen presenting cell.

Diagnostic Challenges:

SLE is a chronic, recurrent, potentially fatal multisystem inflammatory disorder that can be difficulty in diagnosis [10, 11].Since individual with SLE can have a variety of symptoms and different combinations of organ involvement the diseases has no single diagnostic marker. It is identified through a combination of clinical and laboratory criteria including symptoms, history and the results of blood test for antinuclear antibodies[12], so accurate diagnosis is very important because treatment can reduce morbidity and mortality particularly from lupus nephrites[13,14]. Since the diagnosis of SLE is based on clinical and laboratory criteria, the 11 criteria were established by the American Rheumatism Association [15, 16]. According to these criteria, if a person has four or more of these criteria than the diagnosis of SLE is strongly suggested and these criteria are closely related to the symptoms but some people may not develop enough criteria for a definite diagnosis and they may develop after month or years of observation [16].

Classification criteria:

According to ACR at least 4 of these 11 criteria should be present for a diagnosis of SLE and presence of 4 of 11 ACR criteria yields a sensitivity of 85% and specificity of 95% of SLE [16, 17].

ACR Criteria for Diagnosing Systemic Lupus Erythematosus
1. Butterfly (malar) rash across cheeks and nose
2. Discoid (skin) rash, which appears as scaly raised red patches
3. Photosensitivity
4. Oral (mouth) ulcers
5. Arthritis in two or more joints; joints will have tenderness and swelling but will not have become deformed
6. Inflammation of the lining around the lungs (pleuritis) or the heart (endocarditis)
7. Evidence of kidney disease
8. Evidence of severe neurologic disease, such as seizures or psychosis
9. Blood disorders, including low red and white blood cell and platelet counts
10. Immunologic abnormalities as evidenced by positive tests for anti-double stranded DNA (anti-dsDNA), anti-SM, anti-Ro, and anti-LA antibodies
11. Positive antinuclear antibody (ANA) test
Note: A patient must experienced four of the criteria before a doctor can classify the condition as SLE. These criteria, proposed by the American College of Rheumatology, are not exclusive criteria for diagnosis, however.[15,16]

Laboratory Test:

No single test is available to determine whether the person has SLE or not but several laboratory test is there to confirm a diagnosis of SLE.The screenings that can help to confirm a diagnosis include blood tests such as antibody tests and complete blood count, urinalysis, chest x-ray, high levels of ANA (antinuclear antibody) that are found in more than 98% of SLE [15].ANA test is the most commonly used screening test for SLE [18].Although almost all people with lupus have the antibody a positive result does not necessarily indicate lupus. A positive result are often seen with some other diseases and in a smaller percentage of people without lupus or other autoimmune disorder so, a positive ANA by itself is not enough for a lupus diagnosis. Therefore for accurate diagnosis of lupus along with this ANA test there must be other criteria too.ANA subtypes such as Anti-double standard DNA(Anti-dsDNA) and anti-Smith (Anti-sm) antibodies are more likely to be found in SLE patient[18,19].Anti-dsDNA may play a important role in injury to blood vessels found in SLE and high levels often indicate kidney involvement. Its levels tend to fluctuate overtime and may even disappear [20].Anti-sm antibody presence almost always indicates SLE although many lupus patients may not have this antibody [19].Anti-phospholipids antibodies are a type of antibody directed against phospholipids and are a present in up to 60% of people with lupus which increase the risk for blood clots, strokes and pregnancy complications [20].

Other Blood Test:

White and Red blood cell and platelets counts are usually lower than normal depending on severity that use to determine complications such as anemia or infection[21].Erythrocyte sedimentation rate(ESR) means hoe fast red blood cell fall to the bottom of a fine glass tube that is filed with the patient's blood. A high level ESR indicates inflammation. Blood tests of patients with SLE often show low levels of serum complement which help antibodies fight invaders. Common complement test measures C3, C4, C1q and CH5o [22].A low level of complement could mean the substance is being used up because of an immune response in the body if there is kidney involvement or other disease activity[23].

Treatment Challenge:

SLE treatment progress over the years. However, the mortality remains higher in the general population. Few studies have been examined SLE patient's survival by identifying the main characteristics and risk factors to predict mortality and recognize the main cause of death in patient with SLE[24].There is no cure for SLE.The goal of treatment is to control symptoms. The range and effectiveness of treatments for SLE have increased dramatically in recent decades [1].

Non steroidal anti-inflammatory drugs(NSAIDs) that decrease inflammation are used for patient with joint ,chest pain, or fever[25].Disease modifying anti-rheumatic drugs(DMARDs) are used preventively to

reduce the incidence of flares, the process of the disease and lower the need of steroids use[26].DMARDs commonly in use are antimalarials such as plaquenil and immunosuppressant's such as methotraxate and azathioprine.A common antimalarial used to treat lupus is hydrochloroquine[1].Hydrochloroquine is an FDA-approved antimalarial use for constitutional cutaneous and articular manifestation which has relatively few side effects[26].clinical studies have found the continuous treatment with antimalarials may present flares from recurring one .Cyclophosphamide is use for glomularneprities or other organ –damaging complication[27].

Glucocorticoides are the topical treatment of choice for skin lesion in SLE[28].Due to adverse effects glucocorticoides should be administered only intermittently and not long-term ,an alternative tropical use such as calcineurin inhibitors(tacrolimus ointment, pimecrolimus cream) can be applied as long treatment [29].

In more severe cases ,patient who kidney or central nervous system are affected by lupus a type of drug called immunosuppressive may be use.Immunosupressive such as cyclosphosphamaide and mycophenolate mofetil,restrain the overactive immune system by blocking the production of the immune cells. The risk of side effects increases with the length of treatment[30]. Depending upon the doses, people who required steroids may develop chusing syndrome. New immunosuppressant drug are being actively tested for SLE [31].

Intravenous immunoglobulin may be use to control of SLE with organ involvement as vasculitis.It is believed that they reduce antibody production or promote the clearance of immune complexes from the body ,even though their mechanism of action is not well understood [32].

It is also important for people with lupus to receive regular health care, instead of seeking help only when symptoms worsen. Healthy lifestyle such as eating well, regular exercise, and not smoking particularly important for people with lupus. Protective clothing, sunglasses and sunscreen when in the sun can also somehow reduce in worsening the diseases. Occupational exposure to silica, pesticide and mercury can also can make the disease worsen [33]. Kidney transplant are the treatment of choice for end-stage in renal disease which is the complication of lupus nephritis but the recurrence of the full disease is common in up to 30%of patient [34].

Stem cell transplant (SCT):

SCT has emerged as a therapy for refractory autoimmune rheumatologic diseases, which may arrest the autoimmune disease and lead to remission. In recent decades, SCT has emerged as a new treatment modality for refactory and severe SLE, mainly hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell transplantation (MSCT) [35].HSCT especially its autologus form, has become a

significant treatment modality for severe autoimmune disease and more especially from SLE [36].Researches have reported that MSCT has promised treatment for refractory SLE.

The maintenance and repair of adult tissues and organ are guaranteed by the adult stem cell pool. Among adult stem cells, mesenchymal cells (MSCs) are emerging as hopeful candidates for cell-based therapy of numerous diseases [37]. As a class of multi-potent adult stromal cell, MSCs are capable of self –renewal and multi-lineage differentiation into various tissues of mesodermal origin [38, 39]. MSCs posses a multiple differentiation potential which permits these cells to differentiate into a variety of mesodermal cell lineages, including bone, cartilage, adipose, tendon and muscle [40]. Therefore they are considered to contribute to endogenous and organ and tissue repair [41]. At present, MSCs have been becoming hotspots in the treatment of SLE. The current application of MSCs transplantation of immune system diseases are mainly systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma, dermatomyositis and so on. In recent years[42] reported that allogenic bone marrow and umbilical cord mesenchymal stem cell transplantation can improve the condition of patients with lupus and SLE.

Stem cells (SC) can differentiate into various types of tissue and organ cells including renal tubules and glomerular cells. This is the current mechanism that stem cells can treat certain kidney damaged diseases. In recent years, studies of renal injury also showed that MSCs infusion can also promote structural repair and functional recovery of renal injury. MSCs can migrate to damage kidneys and differentiate into renal tubular epithelial cells to accelerate renal tubular cell proliferation [43]. Therefore, MSCs are multipotent, nonhematopoetic progenitor cells that are being explored as a promising new treatment for SLE.

SUMMARY

Since lupus is considered to be currently incurable, current research is being trying to find a possible cause, a cure and more effective management to extend and increase the quality of life for SLE patient. The rate of SLE varies between countries, ethnicity, sex, and changes over time. It is more common in women than males at any age, more often between 15 and 44.Prevalence varies with ethnicity, but is estimated to be about 1 per 100 overall with a female to male ratio 10:1.While the etiology of SLE is still unknown, epidemiologic research is continuously informing with new insights into environmental risk factors and gene- environment interaction that play a role in disease susceptibility. Patient may present with variable symptoms, signs and laboratory findings and have a variable prognosis that depend upon the disease severity and type of organ involved .Advances in diagnostic, optimized treatment and regular monitoring of diseases activity and damage have clearly improved the prognosis of SLE. The goal of treatment is remission or at least minimization of disease activity and prevention of flares. Now a day's anti- malarial are the basic treatment for every patient unless contraindicated in all patient with SLE whereas glucocorticoid should only be used when acutely indicated but if reduction of glucocorticoids proves impossible further extended

immunosuppressant with methotraxate, mycophenolate mofetil, azothioprine is recommended inspite intravenous cyclosphosphamide is an alternative drug to short term administration of low dose in the induction therapy for proliferative lupus.

The efficacy of SCT in SLE has been activated to resetting on aberrant immune system either through direct immune replacement with HSCT or through immunomodulation with MSCT, shifting the immune system from a highly pro-inflammatory disease environment to a less inflammatory but allogenic MSCT will be superior and more attractive than allogenic HSCT in lupus treatment with its efficacy and safety in the future. It will give a new platform in the treatment of refractory and severe SLE patient.

Abbreviations:

1. SLE: Systemic Lupus Erythematosus
2. MHC: Major Histocompatibility Complex
3. HLA:Human Leukocyte Antigen
4. ANA: Antinuclear Antibody
5. ANTI-SM: Anti-Smith
6. Anti-nRNP :Anti-Nuclear Ribonuclear Protein
7. ACR: American College of Rheumatology
8. ANTI-dsDNA: Anti-Double Standard DNA
9. ESR: Erythrocyte Sedimentation Rate
10. NSAIDs: Non Steroidal Anti-Inflammatory Drugs
11. DMARDs: Disease Modifying Anti-Rheumatic Drugs
12. SCT: Stem Cell Transplant
13. HSCT: Hematopoietic Stem Cell Transplantation
14. MSCT: Mesenchymal Stem Cell Transplantation

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