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Systemic Lupus Erythematosus (SLE): A 360 Degree Review

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Abstract In this paper we review the most important updated aspects of SLE, which is an autoimmune disorder of unknown etiology, where genetic, environmental and immunological factors are believed to play an important role in its immunopathogenesis. Aspects related to SLE causes, pathophysiology, signs and symptoms, diagnosis and treatment are discussed.

Keywords: *systemic lupus erythematosus, autoimmune disease, immunoglobulin, immunology, rheumatology*

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1. Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a disorder that is autoimmune in nature. It comprises an inflammatory response that occurs due to the immune system attacking cells and tissues leading to damage. In most cases of SLE there is damage to the renal system, skin and musculoskeletal system, cardiovascular system, nervous system and respiratory system; in fact SLE can affect any tissue in the body. It is known to have multiple differential diagnoses and present similar to other autoimmune diseases. According to an article by Rahman et al, 2008 it is a frequent item in differential diagnosis [1] and shows remissions and exacerbations.

2. SLE Causes

The cause of SLE is widely unknown but several studies have presumed that it affects persons with a genetic disposition or susceptibility affected by unknown environmental triggers with defects in their immune system. The main theory that is thought to explain SLE by Lisnevskaia et al, 2014 is defects in apoptotic destruction of cells. Phosphatidylserine is used by early apoptotic cells as express signals, which stimulate cells such as dendritic cells and macrophages to digest them. Undigested apoptotic cell materials not removed are taken up by antigen-presenting cells, which lead to an increase in antinuclear antibodies [2]. During an immune reaction to a stimulus, cells of the immune system are normally inactive because they recognize self antigens are stimulated by these antigen presenting cells. Triggers can be activated by environmental factors e.g. drugs or UV light and other factors that may include bacteria, allergens or viruses. Histones, DNA and other proteins are exposed due to these stimuli leading to destruction of cells [3]. Exposed nuclear proteins cause sensitization of B-cells which produce antibodies against the self antigens. Antibody-protein complexes are formed from these antibodies which stick to surfaces and harm blood vessels [3].

3. Pathophysiology

There are many theories as to the pathophysiology of SLE. The first suggests increased rate of apoptosis of keratinocytes and monocytes and a relationship between disease activity and the apoptotic rates of lymphocytes.

Germinal center dendritic cells may endocytose such undigested apoptotic cell material leading to presentation and activation of T cells. Also, these antigens may bind to follicular dendritic cells and activate more B cells as found by Gaipl et al, 2006 [4]. Oxidative stress, mitochondrial dysfunction, and depletion of ATP can lead to necrosis in T lymphocytes as stated in an article by Gergely et al [5].

Monocytes of people with SLE show reduced expression of CD44 surface molecules which are needed to take up apoptotic cells, smaller, few in number or die earlier. CRP, factors and some glycoproteins are, in SLE diminished, inefficient or missing which are important for phagocytosis. If the immune system undergoes extensive exposure to autoantigens it results in autoimmunity. Apoptotic cell tolerance is decreased in B and T cells and lymphocytes are activated by these autoantigens; leading to the production of antibodies triggering an inflammatory response. Polyclonal B-cell activation occurs in SLE and a shift towards immature B cells. There is decreased suppression of memory B cells with increased CD27+/IgD- which is related to increased disease activity and renal lupus [6,7,8].

SLE has a familial association and multiple genes such as class I, class II, and class III HLA genes appear to be responsible for a person developing lupus, this according to Martens et al, 2009 [25]. Additional genes, which contain risks for disease development are *PTPN22*, *IRF5*, *STAT4*, *CDKN1A*, *ITGAM*, *TNFSF4*, *BLK*, and *BANK1* [9,10]. Yang et al in 2009 looked at these genes in different populations and suggested that some they may be population specific [11].

People being treated with drugs such as procainamide, hydralazine, isoniazid, phenytoin and quinidine [1] can develop a condition called drug induced lupus that present with symptoms similar to SLE and can regress once the medication is stopped.

4. Signs and Symptoms

Wasef et al , 2004 studied gender differences among patients with SLE and they found that in the SLE population females are inclined to having Raynaud phenomenon, greater incidences of relapses, arthritis, low blood cell counts and psychiatric symptoms as opposed to males that have more renal disease, seizures, skin problems, serositis and peripheral neuropathy [12]. People with SLE during active episodes who may be pregnant tend to have a more negative result, this according to a study by Cortes – Hernandez et al, 2001 foetal death in utero and spontaneous miscarriage rates are also increased [13]. From a study done by Smyth et al, 2010 72% has been estimated to be the live-birth rate in people in these incidences with SLE [14].

Many SLE patients develop skin manifestations of the disease. The three main lesions are acute, subacute and chronic cutaneous lupus. According to the book *Head and neck manifestations of systemic disease* by Weisman and Michael 2007, up to 30-60% of patients develop a characteristic malar rash on the cheek area [15]. According to the Lupus Foundation of America, the number of patients that experience joint and/or muscle pain has been found to be more than 90% and less than 10% of these people will develop peripheral deformities [16]. A relationship between rheumatoid arthritis and SLE has been proposed in a study done by Heminki et al, 2009 [17].

In a study done by Lam et al, 1990, looking at anaemia and SLE they reported that anaemia is frequent in children with SLE [18] and another study by Giannouli et al, 2006 stated that it develops in about 50% of cases [19]. Antiphospholipid antibody syndrome [20] may be associated with SLE according to Syuto et al, 2009 who studied the antiphospholipid syndrome. This disorder is characterized by autoantibodies to phospholipids and is thrombotic in nature. A prolonged partial thromboplastin time and the presence of antiphospholipid antibodies are characteristic for antiphospholipid syndrome. A false positive test for syphilis is also obtained as anticardiolipin antibody is also elevated in SLE patients [21].

SLE can cause inflammation of the heart called endocarditis which involves the mitral or tricuspid valves and is characteristically non infective also called Libman-Sacks endocarditis. In these patients the incidence of atherosclerosis is greater and progresses faster than in the non SLE population according to many studies such as that done by Asanuma et al, 2003 [22]. In a study by Alamoudi et al, 2015, pulmonary emboli, pleuritis, lupus pneumonitis, pleural effusion, interstitial pulmonary disease, pulmonary haemorrhage or pulmonary hypertension are some of the manifestations of lung inflammation. [23]. Kidneys maybe affected in a condition called lupus nephritis that can present with haematuria or proteinuria in the urine and chronic renal impairment. Acute or end-stage renal failure can eventually be the end result [24]. Deposition of immune complexes along the glomerular basement membrane, and so when immunofluorescence testing is done on renal samples they show a characteristic granular appearance called membraneous glomerulonephritis; which is a typical renal involvement seen in patients with SLE [24].

According to Honczarenko et al, 2008 headache is the main neuropsychiatric disorder displayed by patients[25] in this same study they found that other common manifestations of SLE include polyneuropathy, mood disorder, seizures, cognitive dysfunction, anxiety disorder, and psychosis, cerebrovascular disease [25]. In another report by Xue et al, 2009 it can present with intracranial hypertension syndrome, which presents with headache, papilledema and raised intracranial pressure accompanied with abducens nerve palsy and normal cerebrospinal fluid [26]. Additional symptoms include demyelinating syndrome, movement disorders, a confusional state, aseptic meningitis, Guillain-Barré syndrome, plexopathy, myelopathy, cranial neuropathy and myasthenia gravis.

The neural manifestation of lupus is characterized by injury to the blood–brain barrier epithelium. Other symptoms include headaches [25], depression (which can affect up to 60% of women with SLE found by Zakeri et al, 2011[27], cognitive dysfunction, psychosis, seizures, cerebrovascular disease, mood disorders, anxiety disorders, personality disorders and polyneuropathy [25]. Neonatal lupus occurs when an infant is born from a patient with SLE, they experience a benign and self limiting rash resembling discoid lupus, enlargement of the liver or spleen or heart block [28].

5. Diagnosis

Due to the wide variety of presenting symptoms the diagnosis of SLE is very difficult and the gold standard is a rheumatologist's diagnosis. The American College of Rheumatology (ACR) for research purposes uses a criteria that requires 4 of 11 signs or symptoms to be present for a positive diagnosis but this can still under diagnose mild cases.

In serology the main tests used are testing for antinuclear antibodies (ANA) and anti-extractable nuclear antigens (anti-ENA). These are detected using indirect immunofluorescence (IF). Typical fluorescence patterns can lead to differentiation of these antibodies [29]. Anti-double stranded DNA (dsDNA), anti – smith antibodies and anti-histone antibodies are three types of anti – nuclear antibodies and tests can be positive in autoimmune diseases or normal individuals. Others include anti-U1 RNP, SS-A and SS-B. In a study done by Rahman et al they stated that anti-dsDNA antibodies are present in 70% of cases of SLE and in only 0.5% of normal patients [1]. These antibodies can even correlate with disease activity [1].

6. Treatment

SLE has no cure but symptoms can be controlled. Treatment of SLE consists of Biologic disease-modifying anti-rheumatic drugs (DMARDs) eg. Belimumab or rituximab, non-biologic DMARDs e.g. cyclophosphamide or methotrexate, NSAIDs e.g. acetaminophen, corticosteroids for example prednisolone or anti-malarial drugs such as Hydroxychloroquine. The European League against Rheumatism (EULAR) in 2007 released recommendations for the treatment [30]. NSAIDs may be used for short periods of time in patients who are not predisposed to developing complications. When disease is refractory or steroids cannot be used in the long term immunosuppressive agents e.g. azathioprine, mycophenolate mofetil, and methotrexate, may be used. Treatment and evaluation of SLE with neuropsychiatric symptoms are done in the same way as they would be in patients without SLE [31]. Belimumab (Benlysta) is a monoclonal antibody, which when used with standard therapy reduces disease activity in patients with SLE [32].

Rituximab has been used to deplete B-cells and an open study done by Lu et al, 2009 using rituximab showed excellent results as rescue therapy for active patients unresponsive to standard immunosuppressant therapy [33]. Studies such as those done by Huges et al, 2009 or Murray et al, 2010 have reported cases of patients with severe refractory SLE in which off-label use of rituximab showed benefits [34,35].

Cyclophosphamide is used to treat severe life threatening cases of SLE. It suppresses the immune response but can however be toxic. It still remains an option when disease-modifying anti rheumatic drugs (DMARDs) have been ineffective eg. In cases of severe lupus nephritis it may respond to pulsed cyclophosphamide [36]. In low doses methotrexate is well tolerated and safe for use in autoimmune disorders. It was originally used as a chemotherapeutic drug. Main side effects including hair loss, nausea, headaches, and skin pigmentation [37].

Antimalarial drugs or even nonsteroidal anti-inflammatory drugs can be used to treat mild or intermittent disease. Hydroxychloroquine is a malarial drug also used to treat systemic lupus erythematosus. Hydroxychloroquine increases lysosomal pH in antigen presenting cells [38]. Hydroxychloroquine, by decreasing Toll Like Receptors signalling, reduces the inflammatory process by decreasing the activation of dendritic cells.

Disease-modifying antirheumatic drugs (DMARDs) reduce the incidence of flares but flares are treated primarily with corticosteroids. There is evidence that hydroxychloroquine can improve survival. In severe glomerulonephritis cyclophosphamide or mycophenolic acid can be used but mycophenolic acid can be teratogenic [39].

Intravenous immunoglobulins are used to alleviate vasculitis or reduce organ involvement and are thought to decrease circulating antibodies or remove immune complexes from the body [40].The mortality is five times as high in SLE as the normal population due to accelerated atherosclerosis [41].

Monitoring of treatment response or flares are done using dsDNA titres. Poor prognosis is associated with high blood pressure, poor real function, low blood counts and low serum protein. According to Danchenko et al, 2006 the rate of SLE differs between gender, different geographical areas and ethnicities [42]; race has been found to be as higher as those of Afro-Caribbean descent than other ethnicities [12]. There are some studies that suggest that there is an association between race and SLE. However, in an evaluation of other research by Pons-Estel et al, 2010 which looked at the correlation between race and SLE, they found systematic and methodological errors, which did not support the connection [43], however, they found that other factors like the level of social support, health insurance and socioeconomic status can contribute to disease progression [44,45].

7. Conclusion

The advancement in the field of immunology and rheumatology has made possible the control of signs and symptoms of this disease in many patients, but still we have to walk a long way before SLE can be considered a disease easy to manage. In this respect we need to discover new mechanisms of the disease process that will be targets for new drug developments.

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