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الملخص العربى

Systemic lupus erythematosus

Acknowledgment

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple tissues and systems and is characterized by significant inter-individual variability in clinical manifestations and organ involvement ***(Cava, 2010).***

While the etiology of SLE is thought to be multi-factorial, the disease is characterized by the production of auto-antibodies which leads to immune complex deposition, inflammation and eventually, permanent organ damage ***(Lam and Petri, 2005).*** Genetic factors also are known to play an important role in the disease; there are also population differences for the disease both in terms of genetic susceptibility and disease manifestations***(Yang et al., 2010).***

Epidemiology of systemic lupus erythematosus:

SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors ***(Rahman and Isenberg, 2008).***

Race-, sex-, and age-related demographics

Worldwide, the prevalence of SLE appears to vary by race. However, there are different prevalence rates for people of the same race in different areas of the world. The contrast between low reported rates of SLE in black women in Africa and high rates in black women in the United Kingdom suggests that there are environmental influences. In general, black women have a higher rate of SLE than women of any other race, followed by Asian women and then white women ***(Danchenko et al.,2006).***

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More than 90% of cases of SLE occur in women, frequently starting at childbearing age ***(Ginzler and Tayar , 2012).*** The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease ***(Costenbader et al., 2007).***The risk of SLE development in men is similar to that in prepubertal or postmenopausal women. Interestingly, in men, SLE is more common in those with Klinefelter syndrome (ie, genotype XXY), further supporting a hormonal hypothesis. In fact, a study by Dillon et al found that men with Klinefelter syndrome had a more severe course of SLE than women but a less severe course than other men ***(Dillon et al., 2011)***.

The female-to-male ratio peaks at 11:1 during the childbearing years ***(Manzi, 2001).*** A correlation between age and incidence of SLE mirrors peak years of female sex hormone production. Onset of SLE is usually after puberty, typically in the 20s and 30s, with 20% of all cases diagnosed during the first 2 decades of life ***(Klein- Gitelman et al., 2002).***

A review of the worldwide literature (predominantly North America, Europe, and Asia) found that the incidence of pediatric-onset SLE ranged from 0.36 to 2.5 per 100,000 per year and the prevalence ranged from 1.89 to 25.7 per 100,000 ***(Pineles et al.,2011).***

Pathogenesis

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Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by multisystem inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immunoregulatory, hormonal and environmental factors (***Rahman and Isenberg, 2008 and D'Cruz and David, 2007)***.

- **Genetic susceptibility:**

There is a clear genetic component in SLE, with a sibling risk ratio 8-fold to 29-fold higher than that in the general population and a 10-fold increase in disease concordance in identical twins. In addition, there is a 24-56% concordance rate in monozygotic twins, compared with a 2-5% risk in dizygotic twins ***(Deng and Tsao, 2010).*** Although some single genes have been implicated to play a causative role in SLE, current knowledge points toward a large number of genes being involved in a multifactorial-type inheritance pattern in most patients ***(Moser et al., 2009).***

Of the genetic elements, the genes of the major histocompatibility complex (MHC) have been most extensively studied for their contribution to human SLE. Studies of human leukocyte antigens (HLA) reveal that HLA-A1, B8, and DR3 are more common in persons with SLE than in the general population. The presence of the null complement alleles and congenital deficiencies of complement (especially one of the early complement components: C1q, C2, C4) are also associated with an increased risk of SLE ***(Bartels et al., 2012).*** Genetic studies also point to disruptions in lymphocyte signaling, interferon response, clearance of

complement and immune complexes, apoptosis, and DNA methylation ***(Sestak et al., 2011).***

- **Immune dysfunction in SLE:**

SLE is characterized by multisystem microvascular inflammation with the generation of autoantibodies. Many immune disturbances, both innate and acquired, occur in SLE ***(Bartels et al., 2012).***

One longstanding proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance ***(Rahman & Isenberg, 2008).*** The redistribution of cellular antigens during necrosis/apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Subsequently, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens. Recent genetic studies point to disruptions in lymphocyte signalling, interferon response, clearance of complement and immune complexes, apoptosis, and DNA methylation ***(Sestak et al., 2011).***

- **Auto-antibodies in Lupus:**

The affected organs in lupus that have been studied most intensively are the kidneys and the skin. In both cases, there is inflammation and the deposition of antibodies and complement. In 1967, kidneys from patients with lupus nephritis were shown to contain antibodies that bound native, double-stranded DNA ***(Koffler et al., 1976).***

These antibodies are auto-antibodies; that is, they bind a normal constituent - in this case, double-stranded DNA - of the patient's cells and tissues. The importance of anti–double-stranded DNA antibodies in the pathogenesis of lupus has been confirmed ***(Isenberg et al., 2007).***

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Anti– double-stranded DNA antibodies are highly specific for lupus; they are present in 70% of patients with lupus. Levels of anti–double-stranded DNA antibodies in serum tend to reflect disease activity, but not in all patients ***(Rahman and Isenberg, 2008).***

The presence of antinuclear antibodies (ANA) is the immunological hallmark of SLE, in clinical practice; ANA testing is often used as a part of an initial investigative screen. A positive ANA is a sensitive test, found in 98% SLE patients ***(Lyons et al., 2005).***

In a study of renal-biopsy specimens obtained from patients with lupus at autopsy, Mannik et al. detected IgG that bound to a number of non- DNA antigens, including Ro (a ribonucleoprotein complex), La (an RNA-binding protein), C1q (a subunit of the C1 complement component), and Sm (nuclear particles consisting of several different polypeptides). The detection of antibodies to these antigens in autopsy specimens does not prove that they play a role in the development of lupus nephritis. Rather than cause the inflammation, these auto-antibodies may establish themselves in tissue only after the apoptosis of cells in inflamed kidney tissue exposes nuclear antigens ***(Mannik et al., 2003).***

Although anti–double-stranded DNA antibodies are the most extensively studied auto-antibodies in lupus, others play a role in clinical manifestations particularly in autoimmune hemolytic anemia, thrombocytopenia, skin disease, and neonatal lupus ***(Rahman and Isenberg, 2008).***

The presence of anti-Ro antibodies, anti-La antibodies, or both in pregnancy confers a 1 to 2% risk of fetal heart block ***(Askanase and Buyon, 2004).***

Both anti-Ro and anti-nucleosome antibodies may play a role in cutaneous lupus. Anti-Ro antibodies are associated with an increased risk of the development of a photosensitive rash ***(Rahman and Isenberg, 2008).***

Antinucleosome antibodies have been detected in skin biopsy specimens obtained from a minority of patients with active renal lupus, and these patients had no rash ***(Grootscholten et al., 2003).***

Antibodies against the N-methyl-d-aspartate (NMDA) receptor may be important in central nervous system lupus. NMDA is an excitatory amino acid released by neurons. Kowal and colleagues showed that anti–NMDA-receptor antibodies are present in the brain tissue of patients with cerebral lupus ***(Kowal et al., 2006).***

Although anti–α-actinin antibodies are not specific for lupus, these antibodies, when present in the serum of patients with lupus, can serve as a marker of renal involvement ***(Rahman and Isenberg, 2008).***

- **The Role of T and B lymphocytes:**

Auto-antibodies can occur in healthy people without causing harm, and they may play a protective role ***(Rahman and Isenberg, 2008).***

Pathogenic auto-antibodies in patients with lupus have particular properties that enable them to cause disease. Clinical investigations and studies in laboratory mice have shown that IgG antibodies with high-affinity binding to double-stranded DNA tend to be more strongly associated with tissue damage than IgM or lower affinity IgG antibodies ***(Rahman and Isenberg, 2008).***

T-cell cytokines affect B cells by stimulating cell division, switching antibody production from IgM to IgG ***(Rahman and Isenberg, 2008)***,

and promoting a change in the molecular sequence of the secreted antibody so that it binds more strongly to the driving antigen. These kinds of antibodies are closely linked to tissue damage in lupus ***(Rahman, 2004).***

Regulatory T cells from patients with active lupus have a reduced ability to suppress the proliferation of helper T cells, as compared with regulatory T cells from patients with inactive lupus or healthy controls ***(Valencia et al., 2007).***

- **BLyS and APRIL**

B lymphocyte stimulator (BlyS) also called (B cell activating factor, BAFF) is a B-cell survival factor that inhibits B cell apoptosis and favors B-cell proliferation and maturation, antibody production and IgG class switching ***(Batten et al., 2000 and Gross et al.,2000).*** A PRoliferation-Inducing Ligand (APRIL) mediates effects that are similar to those of BLyS. BLyS and APRIL are produced by monocytes/macrophages, dendritic cells, neutrophils, activated T cells, some B cells and non-hematopoietic cells ***(Scapini et al., 2008)***. Blys is synthesized as a homotrimeric transmembrane protein and APRIL is synthesized as a soluble protein.

BLyS can bind to three different receptors that are expressed on B cells. One receptor is the BAFF receptor (BAFF-R or BR3) and is highly specific for BLyS. BAFF-R in humans is expressed by all B cells except bone marrow plasma cells. BAFF-R is the predominant receptor on naïve and memory B cells.

Another receptor is called TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) and is expressed on CD27 memory B cells and bone marrow plasma cells, acts as a negative

regulator during B cell maturation. TACI deficiency in mice leads to defective B cell responses to T-independent antigens ***(Von Bulow et al., 2001)***.The third receptor is called BCMA (B lymphocyte maturation antigen), is expressed by some memory B cells and germinal center B cells and plasma cells, and influences the survival of long-lived bone marrow plasma cells ***(O'Connor et al.,2004).*** BCMA is the predominant receptor on long-lived plasma cells, where it has an important role in cell survival, also in plasma blasts ***(Avery et al., 2003)***. Interestingly, TACI and BCMA can bind to both BLyS and APRIL ***(Mackay and Schneider, 2009)***. In humans, increased serum concentrations of BLyS and APRIL are found in rheumatoid arthritis, systemic sclerosis and SLE, where they correlate with anti-dsDNA autoantibody levels and disease activity ***(Becker-Merok et al., 2006)***. Particularly, BLyS is elevated in the serum of 20–67% lupus patients, and APRIL is increased in 38–53% lupus patients ***(Zhang et al.,2001).***

The targeting of B lymphocytes has always been envisioned as a possibly valuable therapeutic opportunity in SLE because of the major role of these cells in the pathogenesis of the disease as producers of pathogenic autoantibodies

- **Cytokines:**

****Interleukin 6 (IL-6):***

IL-6 is a pleiotropic cytokine synthesized predominantly by monocytes, fibroblasts, and endothelial cells, although its secretion may also be found in T- and B-lymphocytes ***(Yap and Lai, 2010).*** One of the most important effects of IL-6 is to induce the maturation of B lymphocytes into plasma cells and augment the immunoglobulin secretion ***(Tackey et al., 2004).*** In

human lupus patients, accentuated IL-6 levels correlated with the disease activity and anti-DNA levels ***(Yap and Lai, 2010).***

****Interleukin 10 (IL-10):***

It is an important regulatory cytokine capable of downregulating immune responses. IL-10 is also known to promote B-cell functions through facilitating proliferation, differentiation and antibody production. Increased production of IL-10 by peripheral B cells and monocytes has been shown to correlate with disease activity in SLE patients. The polymorphisms in IL-10 were reported to be associated with SLE in several studies involving small cohorts of European, Hispanic American and Asian populations ***(Deng and Tsao, 2010).***

****Interleukin 17 (IL-17):***

It is a potent pro-inflammatory cytokine produced by activated T lymphocytes, with the "Th17 cells" being the most vibrant producer ***(Weaver et al., 2007).***

IL-17 has great potency to recruit monocytes and neutrophils, facilitate T cell infiltration, and up-regulate adhesion molecule expressions ***(Agarwal et al., 2008).*** In human subjects, SLE patients have raised serum levels of IL-17 and the plasma level of IL-17 correlates with disease activity ***(Yap and Lai, 2010).***

****Tumor Necrosis Factor-α (TNF-α):***

Tumor necrosis factor-alpha (TNF-α) is expressed as a trimer on cell surface and in soluble form after the activation of macrophages and dendritic cells ***(Yap and Lai, 2010).***

There is substantial evidence to show that TNF-α may play a similar pro-inflammatory role in human SLE. Serum levels of TNF-α in active SLE patients closely correlated with disease activity ***(Yap and Lai, 2010)*** and abundant TNF-α expression was demonstrated in lupus nephritis kidneys ***(Esposito et al., 2009).***

****Transforming growth factor β (TGF β):***

It is involved in the differentiation of CD8+ T cells into cells that down regulate the production of antibodies. Initial studies revealed that constitutive and active levels of TGFβ were decreased in these patients, when compared with controls. Therefore, that impaired secretion of TGFβ may in part account for the overproduction of antibody seen in lupus ***(Caserta et al., 2004).***

- ***Sex-hormones and the hypothalamo-pituitary-adrenal axis:***

SLE is predominantly a female disease ***(Cervera et al., 1993)***. First onset of SLE before puberty and after menopause is uncommon ***(Formiga et al., 1999).*** The female predilection becomes less pronounced outside the reproductive age range. In addition, patients with Klinefelter's syndrome, characterised by hypergonadotrophic hypogonadism, are prone to the development of SLE ***(French and Hughes, 1983).*** These observations suggest a role for endogenous sex hormones in disease predisposition.

Abnormal oestrogen metabolism has been demonstrated in patients with SLE of both sexes, with an increase in 16α hydroxylation of oestrone, resulting in significantly raised 16α hydroxyestrone concentrations. Women with SLE also have low plasma androgens, including testosterone, dihydrotestosterone, dehydroepiandrosterone (DHEA), and

dehydroepiandrosterone sulfate ***(Lahita et al., 1987).*** This abnormality might be explained by increased testosterone oxidation at C-17 or increased tissue aromatase activity ***(Folomeev et al., 1992).*** The concentrations of androgens correlate inversely with disease activity ***(Lahita et al., 1987).***

Estrogens may aggravate SLE by prolonging the survival of autoimmune cells, increasing T helper type 2 (Th2) cytokine production, and stimulating B cells to produce autoantibodies. The inhibition of the Th1 response and the enhancement of CD40L expression on lupus T cells ***(Rider et al., 2001)*** may indirectly promote the Th2 response and lead to further B cell hyperactivity.

Testosterone reduces immunoglobulin production from peripheral blood mononuclear cells of both normal subjects and patients with SLE ***(Kanda et al., 1997).***Dehydroepiandrosterone (DHEA) has been shown to be associated with enhancement of Th1 and inhibition of Th2 immune responses in both humans and mice**,** thus, excessive oestrogenic but inadequate androgenic hormonal activity in both men and women with SLE might be responsible for the alteration of the immune responses. ***(Suzuki et al., 1995)***

Flares of SLE are well known to occur during periods of rapid hormonal changes. These include pregnancy, puerperium, ovulation stimulation during in vitro fertilisation, and exogenous oestrogen administration ***(Mok et al., 2001)***, lupus activity tends to be reduced when patients undergo menopause It has also been noted that in many women disease flares are more common during the second half of the menstrual cycle, after the midcycle surge of oestrogen. ***(Mok et al., 1999).***

The administration of exogenous oestrogens in the form of OC pills and HRT may exacerbate the disease in patients with existing lupus ***(Petri, 2001).***

Epidemiological studies reveal an association between the use of exogenous oestrogens and the onset of SLE. In a large cohort of nurses as part of the Nurses' Health Study, it was shown that both the past use of oral contraceptive (OC) pills and hormonal replacement therapy (HRT) was associated with a slightly increased risk of SLE development ***(Sanchez-Guerrero et al., 1997).***

Studies on the function of the hypothalamo–pituitary–adrenal (HPA) axis in patients with SLE are limited and often confounded by the effect of concomitant glucocorticoid treatment. A study on a group of active untreated female patients with SLE reports that the cortisol response to induced hypoglycaemia is significantly lower in patients than in healthy controls, indicating that some degree of HPA axis dysfunction does exist ***(Gutierrez et al., 1998).***The dysregulated HPA axis in SLE may be responsible for disease susceptibility and progression.

- **<u>Environmental factors:</u>**

The contribution of the environment to the expression of SLE is unquestionable, as exemplified by the fact that clinical concordance of SLE in identical twins is limited to less than half of the pairs. Epigenetic changes such as DNA methylation have also been attributed to environmental factors associated with SLE ***(Selmi et al., 2012).*** For example, hydralazine and procainamide can induce lupus-like syndromes and are known to inhibit T-cell DNA methylation ***(Kaiser and Criswell, 2010).*** Recent animal and preliminary human studies have shown that T-

cell functions affected by DNA hypomethylation may contribute to the risk of idiopathic and drug-induced SLE ***(Zhou et al., 2008).***

Exposure to ultraviolet light is a known risk factor in clinical disease, and various environmental toxins, including smoking, have been implicated in epidemiological studies ***(Rahman and Isenberg, 2008).***

Viral infections, including parvovirus B19 and cytomegalovirus (CMV), are common in patients with SLE. Notably, much discussion has centered around the idea that a viral infection may trigger SLE ***(Aslanidis et al., 2008).***

Also EBV is implicated to play a role in the development of SLE as a high EBV viral titer is found in adult SLE patients, likely due to a T cell defect ***(Crispin et al., 2010).***

While chronic viral infection can lead to T cell exhaustion, viruses have also been implicated in contributing to autoimmunity through molecular mimicry. Some viral proteins are similar to self-antigens and therefore illicit specific immune responses that can cross-react with self-antigens. For instance, the EBV protein EBNA-1 cross reacts with the self-antigen Ro, a common target of auto antibodies. Molecular mimicry is also observed with bacterial and parasitic epitopes ***(Crispin et al., 2010).***

Diagnostic Criteria for SLE

The 1982 American College of Rheumatology (ACR) criteria summarized features necessary to diagnose SLE ***(Tan et al.,1982).***These criteria were updated in 1997***(Hochberg ,1997).***

The presence of 4 of the 11 criteria yields a sensitivity of 85% and a specificity of **95% for SLE.**