INTRODUCTION

Tuberculosis (TB) has existed for long time and remains a major global health problem. It causes ill-health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death due to infectious disease. There were 1.4 million TB deaths in 2015 and 10.4 million new TB cases ***(WHO, 2016).***

About 90% of those infected with *Mycobacterium tuberculosis* (*MTB*) are asymptomatic, sometimes called latent TB infection (LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease ***(Kumar et al., 2007)***. Immunosuppressed subjects are important targets for the screening of LTBI because of the high risk of progression to active TB ***(Bartalesi et al., 2009)***. Tuberculin skin test (TST) has been used worldwide as an aid in diagnosing both LTBI and active TB. A positive TST result is associated with an increased risk for current or future active TB. However, certain limitations are associated with its use ***(Mazurek et al., 2010).***

Many TB diagnostic techniques are used in clinical practice, but their role in the various risk groups is yet to be determined. They are based on the detection of gamma interferon in the blood (interferon gamma release assay),

which is released in response to in vitro stimulation of primed T-cells with specific antigens of *MTB* ***(Arenas Miras et al., 2012).***

A high incidence of TB has been reported in systemic lupus erythematosus (SLE) patients, with an increased frequency of extra-pulmonary forms and high mortality rates, especially in developing countries, where TB is endemic ***(Erdozain et al., 2006)***. In SLE patients, TB infection thrives under conditions of immunosuppression which may either be secondary to the disease itself or to its treatment ***(Prabu and Agrawal, 2010)***.

Aim of the Work

To estimate frequency of mycobacterium tuberculosis infection in adult SLE patients & its relation to disease duration, activity, damage and treatment.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple tissues and systems and with significant variable clinical features and organ involvement ***(Cava, 2010)***. It is characterized by a chronic, relapsing, inflammatory and often febrile multisystemic disorder of connective tissue with wide spectrum of involvement of skin, joints, kidneys and serosal membranes. The exact etiology is not known, but it represents failure of the regulatory mechanisms of immune system in which body's own defenses are turned against themselves ***(Edworthy, 2005)***.

It has a worldwide distribution with unpredictable course of flares and remissions, where a cumulative damage over time significantly interferes with organ function and quality of life ***(Putterman et al., 2012)***.

A. Epidemiology:

1- Sex:

SLE is a disease of young women, with female to male ratio 9 to 1. This is due to the presence of double X chromosomes in the female which carries immunological related genes that can mutate and contribute to the SLE

onset since Y chromosome has no identified mutations associated with autoimmune disease ***(Tsokos, 2011).***

The risk of SLE development in men is similar to that in prepubertal and postmenopausal women ***(Dillon et al., 2011).***

2- Age:

SLE occurs at any age, but more common in the child bearing age. Sixty-five percent of patients with SLE have a disease onset between the ages of 16 and 55, 20% present before age 16 and 15% after age 55 ***(Lam and Petri, 2005).***

3- Race:

The prevalence of SLE appears to vary by race around the World. Black women have a higher rate of SLE than any other race, then Asians and white women follow ***(Danchenko et al., 2006).***

4- Morbidity and Mortality:

SLE may be a relatively benign disease and may have a rapidly progressive course and even fatal disease. The disease is milder and survival is higher among persons with isolated cutaneous and musculoskeletal disease than in those with renal and CNS involvement. The most frequent

causes of death in SLE patients are Infections and diseases of the cardiovascular, renal, pulmonary, and CNS ***(Bartels et al., 2016).***

In spite of the improvement of the survival rate, patients with SLE still have a higher death rate (3-5 times) than that of general population ***(Schur, 2001).***

B. Etiology:

The definite pathologic mechanisms of SLE remain elusive, and the etiology of SLE is known to be multi-factorial, involving genetic, hormonal, and environmental factors. Environmental triggers with susceptible genetic background, act on the immune system to initiate autoimmunity ***(Tiffin et al., 2013).***

1- Genetic factors:

Many genes that may contribute to lupus have been identified by means of whole-genome scans from families in whom multiple members have SLE ***(Namjou et al., 2007).*** The genes associated with SLE are located on chromosome 6, in the region that encodes human leukocyte antigens (HLA) genes, particularly class II (DR, DQ, DP) and class III (C2, C4), two regions on chromosome 1 and chromosome 2, 4 and 16 ***(Sanchez et al., 2011).***

Studies of HLA show that HLA-A1, B8, and DR3 are commoner in individuals with SLE than in the general population ***(Bartels et al., 2016)***.

2- Epigenetic effects:

Epigenetic refers to inherited changes in gene expression not due to changes in the DNA sequence. It is an interesting field that links between genetic susceptibility and the environment in predisposing to SLE. Among lupus patients, DNA methylation, histone modifications and micro-RNA are the major epigenetic alterations ***(Altorok and Sawalha, 2013).***

3- Hormonal factors:

Sex hormones have an immunomodulatory role in the development of autoimmune disease. SLE mainly affects females more than males ***(Tan et al., 2012).*** Estrogen is implicated in the pathogenesis of lupus as it acts as a potent disease stimulator ***(Cutolo et al., 2004).*** Conversely, androgens may protect against the development of autoimmunity ***(Chen and Parker, 2004).***

SLE disease flare is expected during pregnancy due to increased levels of estrogen and prolactin. The incidence of flare-ups is higher during the second trimester of gestation and lower in the third trimester. This may be

attributed to the fact that, in SLE pregnant women, serum levels of estrogen, progesterone, testosterone and DHEAS do not show a peak in the third trimester as expected in healthy women ***(Doria et al., 2008a)*.**

4- Environmental factors:

a) Infection:

Infectious agents play a major role among environmental factors contributing to susceptibility to SLE disease ***(Sebastiani and Galeazzi, 2009).***

In the disease theory that proposes SLE pathogenesis to be a combination of genetic susceptibility with exposure to an environmental trigger, viral infection provides a convenient putative target, Epstein-Barr virus (EBV), parvovirus B19 and retroviruses can activate the innate immune system ***(James et al., 2001).***

A viral-like illness may occur at the onset of lupus or immediately before a flare. A temporal association between the onset of lupus and EBV infection has been reported**.** In a case–control study involving children and young adults, anti-EBV antibodies were present in 99% and EBV DNA was present in 100% of SLE patients ***(Draborg et al., 2012).***

b) Ultraviolet (UV) light:

Photosensitivity is a common presenting symptom of lupus. Exposure to UV light causes rash and even flare in susceptible individuals which is associated with anti-Ro antibodies and leads to the release of proinflammatory cytokines that increase the rate of apoptosis of keratinocyte ***(Kuechle & Elkon, 2007).***

c) Smoking:

Cigarette smoke contains innumerable toxic agents that could cause gene mutation and affect both humoral and cell mediated immune responses harmfully. Current smokers and past exposure had a higher prevalence of SLE than nonsmokers ***(Ekblom-Kullberg et al., 2013).***

d) Drug-induced Lupus:

Various medications have been associated with drug induced lupus. procainamide, hydralazine, isoniazid, antifungals, and some anticonvulsant are The most common drugs. Drug induced lupus is often reversible on withdrawal of the offending agent. Sometimes irreversible SLE and cutaneous lupus have been associated with anti-tumor necrosis factor medications and interferons ***(Katz and Zandman-Goddard, 2010).***

C. Pathogenesis and pathophysiology:

1- Apoptosis

One of the proposed mechanisms for the development of autoantibodies involves a defect in apoptosis that leads to increased cell death and a disturbance in immune tolerance ***(Rahman and Isenberg, 2008).*** During necrosis/apoptosis the redistribution of cellular antigens occurs that leads to a display of plasma and nuclear antigens on the cell-surface in the form of nucleosomes that are targeted by lymphocytes ***(Sestak et al., 2011).***

Attacking endogenous nuclear antigens by Immune system are characteristic of SLE. Dendritic cells present auto-antigens released by apoptotic cells to T cells leading to their activation. Activated T cells then help B cells to produce auto-antibodies to these self-antigens. The pathogenesis of SLE involves a large number of cells and molecules that participate in apoptosis, innate and adaptive immune responses ***(Bertsias et al., 2012)*** [figure 1].

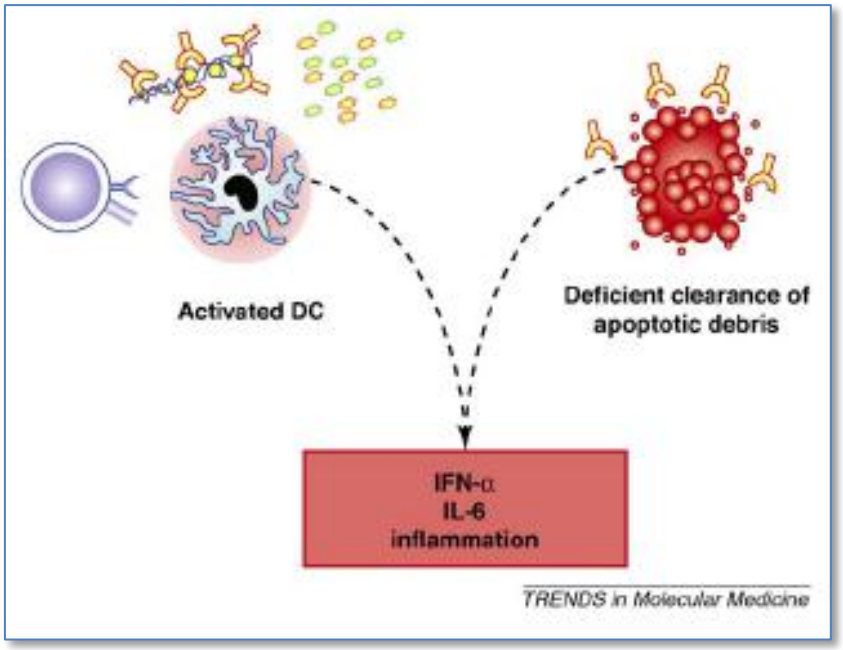

Figure (1): Activated dendritic cells (DC) induce inflammation after exposure to apoptotic and necrotic debris ***(Crispín et al., 2010).***

2- Innate immunity:

a) Dendritic cells:

Dendritic cells (DC) have an important role in regulating both innate and adaptive immune cells, and are necessary in maintaining the balance between immune response and tolerance. There are at least two different subsets of human DCs; plasmacytoid dendritic cells (pDCs) and myeloid DC (mDCs). pDCs are considered the primary source of IFN-α. Immune complex binds to surface FcγRII on the pDC, the nucleic acid component of the complex activates TLR7 or TLR9, resulting in expression of IFNα ***(Monrad et al., 2008)*** [figure 2]**.**

b) Toll-like receptors (TLRs):

TLR 7 and 9 has been thought to be of particular importance in the pathogenesis of SLE. Their distribution appears to be confined to B cells and pDCs in humans; self-nucleic acid-containing immune complexes, produced through disturbed apoptosis and internalized via FcγRIIa, engage TLR7 and/or 9 to stimulate IFN-α production and thereby promote and perpetuate SLE ***(Baccala et al., 2007)*** [figure 2]**.**

c) Complement:

Complement possesses both beneficial and harmful roles in the pathogenesis of SLE. C1q has a protective role against the development and augmentation of autoimmune responses by sharing in the clearance of apoptotic cells and immune complexes and may be by regulating DC activation ***(Crispín et al., 2010).***

Mechanisms of complement deficiency in SLE include impaired clearance of immune complexes and impaired handling of apoptotic cells, aberrant tolerance induction or changes in cytokine regulation. Also during SLE disease flares, the complement system is activated giving rise to partial deficiency or dysfunction due to consumption ***(Horák et al., 2009).***

3- Adaptive immunity:

a) B cells and T cells dysfunction:

Central to the immune dysfunction seen in SLE is the existence of overactive **B cells**, which produce autoantibodies ***(Nagy et al., 2005).*** Hyperactive or B cells activation in the peripheral blood play an important role in the pathogenesis of SLE. With the production of auto-antibodies and prolonged cell life, B-cell regulation is important in the maintenance of immune balance. B cells of patients with SLE have been shown to present auto-antigens, induce CD4+ T helper cells (Th1/Th2), inhibit T regulatory cells, and secrete pro-inflammatory cytokines ***(Sanz and Lee, 2010).*** These B cell abnormalities can precede the development of SLE ***(Nagy et al., 2005).***B cell activators, such as protein B-lymphocyte stimulator (BLyS), appear to be unregulated in lupus, further encouraging B-cell survival ***(Gerl et al., 2009)*** [figure 2].

T cells are critical players in SLE pathophysiology as they regulate B cell responses and also infiltrate target tissues, leading to tissue damage. T lymphocytes from SLE patients are unique in that they resemble naïve or somewhat anergic T cells in certain ways, such as their reduced ability to produce cytokines like interferon-γ and IL2, but simultaneously bear characteristic reminiscent of activated/ memory T cells, such as the overall increased tyrosine

phosphorylation of signaling intermediates, accelerated calcium flux responses, altered expression of signaling subunits such as the T cell receptor zeta and FcRγ, and expression of adhesion or co-stimulatory molecules such as CD44 and CD40L ***(Moulton and Tsokos, 2011)*** [figure 2]**.**

B cell and T cell are interacting and stimulating each other. T-cell cytokines affect B cells by stimulating cell division, switching antibody production from IgM to IgG, and promoting a change in the molecular sequence of the secreted antibody so that it binds more strongly to the driving antigen. Thus, T-cell helps in the production of high-affinity IgG autoantibodies. These kinds of antibodies are closely linked to tissue damage in lupus ***(Rahman, 2004).***

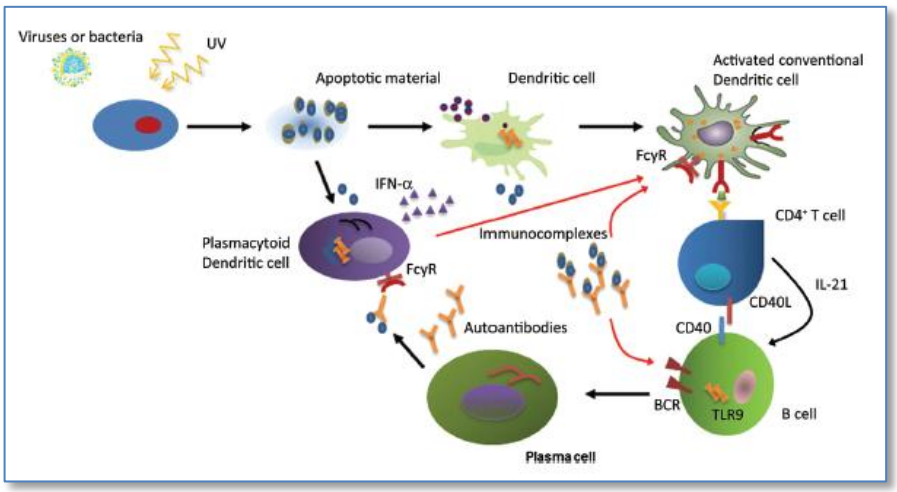

Figure (2): Role of T cell, B cell and co-stimulatory molecules in SLE *pathogenesis (Bertsias et al., 2010).*

b) 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).*** 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 secreted by T-helper cells, and stimulates B-cell proliferation and antibodies production in SLE ***(Beebe et al., 2002).*** And its elevated level may have a genetic basis ***(Gibson et al., 2001).***

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