INTRODUCTION

Lichen planus (LP) is a pruritic, papular eruption characterized by its violaceous color; polygonal shape; and, sometimes, fine scale. Lichen planus is a fairly common skin disorder that lasts for months to years. Lichen planus affects about 1 to 2% of the U.S. population and usually affects people between the ages of 20 and 70 years old and is slightly more prevalent in women than in men. The exact cause of lichen planus is unknown, but it seems to be triggered by stress, genetics, allergic reactions to medicines, and by viral infections such as hepatitis C ***(Crincoli et al., 2011).***

Lichen planus is a cell-mediated immune response of unknown origin. Lichen planus may be found with other diseases of altered immunity; these conditions include ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis ***(Shengyuan et al., 2009).***

The initial lichen planus lesion is usually located on the flexor surface of the limbs, such as the wrists. After a week or more, a generalized eruption develops with maximal spreading within 2-16 weeks. Pruritus is common in lichen planus but varies in severity depending on the type of lesion and the extent of involvement. Hypertrophic lesions are extremely pruritic ***(Raslan et al., 2009).***

Mucous membrane involvement is common and may be found without skin involvement. Lesions are most commonly found on the tongue and the buccal mucosa, oral lesions are classified as reticular, plaquelike, atrophic, papular, erosive, and bullous.. Lesions may also be found on the conjunctivae, the larynx, the esophagus, the tonsils, the bladder, the vulva, and the vaginal vault; throughout the gastrointestinal tract ***(Belfiore et al., 2011).***

Variations in lichen planus include:hypertrophic lichen planus, atrophic lichen planus,erosive/ulcerative lichen planus, follicular lichen planus,lichen planopilaris, annular lichen planus, linear lichen planus,Vesicular and bullous lichen planus, actinic lichen planus, lichen planus pigmentosus and lichen planus pemphigoides ***(Di Fede et al., 2010).***

Langerhans cells process antigens, which are then presented to T lymphocytes. This stimulated lymphocytic infiltrate is epidermotropic and attacks keratinocytes. During this lymphocytotoxic process, the keratinocytes release cytokines that attract more lymphocytes. This process has been referred to as the lichenoid tissue reaction. In addition, recent studies reveal a disruption in the epithelial anchoring system ***(Manolache et al., 2008).***

A pathogenetic link may exist between dyslipidemia and LP. Inflammation is frequently discussed as a potential major

mechanistic contributor to atherothrombosis and measurement of inflammatory markers could have the potential of improving risk stratification beyond the scope of current global risk assessment. It has been hypothesized that the association between OLP and cardiovascular (CV) risk is due to chronic systemic inflammation. Dyslipidemia constitutes a risk factor for atherosclerosis ***(Fedele et al., 2011).***

A case–control study found that lichen planus (LP) was associated with dyslipidaemia in a large series of patients. This study concluded that patients with LP presented higher significant triglycerides value, total cholesterol values, LDL-C values and lower HDL-C values than the normal subjects ***(Santiago et al., 2011).***

Lipid levels screening in men or women with LP may be useful to detect individuals at risk and start preventive treatment against the development of cardiovascular disease ***(Lopez et al., 2012).***

AIM OF THE WORK

To evaluate lipid levels in patients with lichen planus and compare them with control group, aiming to detect patients at risk of cardiovascular diseases and initiation of appropriate treatment.

Chapter (1)

LICHEN PLANUS

Lichen planus (LP) is a relatively common, inflammatory papulosquamous disorder that is characterized by polygonal, pruritic papules and erosive lesions of the oral mucosa ***(Rose et al., 2011),*** that was first described clinically by ***Wilson in 1869*** and histologically by ***Dubreuilh in 1906 (Mignogna et al., 2000).***

Natural history

Although a few cases evolve rapidly and clear within a few weeks, the onset in most cases is insidious. The skin lesions subside within nine months in 50% of cases, and in 85% of the cases, lesions clear within 18 months. Chronicity is usually attributable to the development of hypertrophic lesions or to mucous membrane involvement ***(Black, 1998).***

Incidence and Prevalence

The prevalence of lichen planus is unknown, but it is estimated to occur in less than 1 percent of the population. Estimates of the prevalence vary among different populations, but the condition does not appear to exhibit a racial predilection. LP is rare in children under the age of 5 years and more common in middle aged women ***(Bethanee, 2010),*** although equal sex incidence has been reported ***(Bhattacharya et al., 2000).***

Occasionally LP can develop within the same family. It has also been reported in monozygotic twins, suggesting a genetic predisposition nature of the disorder ***(Black, 1992).***

Etiology

The etiology of lichen planus is not known. An immune-mediated mechanism involving activated T cells, particularly CD8+ T cells, directed against basal keratinocytes has been proposed ***(Lehman et al., 2009).*** The triggering antigen is not known. The existence of rare cases of familial lichen planus and the overrepresentation of certain HLA haplotypes (e.g., HLA-DR1 in cutaneous lichen planus) suggest that genetic factors have a role in susceptibility to this disease. Several autoimmune disorders, particularly alopecia areata and ulcerative colitis, have been reported to occur more frequently in patients with lichen planus ***(Pittelkow et al., 2008).***

Other factors include antigen-presenting cells, adhesion molecules and inflammatory cytokines. While most cases of lichen planus are idiopathic, some are linked to medication use or hepatitis C virus (HCV) infection. Lichenoid drug eruptions are reactions that may occur after exposure to various medications. These eruptions may exhibit a cutaneous and histologic appearance identical to that of idiopathic lichen planus and, thus, must be considered in every patient with lichen planus**.** While an exhaustive list of possible offending agents is quite long, the most common

include gold, antimalarial agents, penicillamine, thiazide diuretics, beta blockers nonsteroidal anti-inflammatory drugs, quinidine and angiotensin-converting enzyme inhibitors ***(Rajani, 2000).***

Pathogenesis:

Lichen planus is a T-cell mediated disease, an immune reaction against basal keratinocytes seems to be the major event in the development of LP ***(Sugerman et al., 2002).***

The skin and mucous lesions are strongly infiltrated with T lymphocyte and there are conflicting opinions about the T cell population, whether the predominate cell is the CD4+ or CD8+. It has been proposed that CD8+ cytotoxic T cell recognize an antigen (currently unknown) associated with MHC Class 1 on lesional keratinocyte and lyse them. T cell and keratinocyte express IFN- γ, IL-6, lymphocyte function associated antigen-1 (LFA-1), TNF-α and TNF-R1. The primary event is antigen processing by the epidermal LCs, which are increased in number. The lichen planus antigen is unknown, although it may be a drug, virus or keratinocyte cell markers of the host may have been altered by an antigen in such a way that they are recognized as foreign and attacked by T cell. This is followed by presentation of an antigen to T cells, with subsequent keratinocyte death, colloid body formation and apoptosis. Activated CD8+ T cell may release cytokines that attract additional lymphocyte into the developing lesion ***(El-Ghamriny, 2011).***

Upregulation of intercellular adhesion molecule-1 (ICAM-1) and cytokines associated with a Th1 immune response, such as interleukin (IL)-1 alpha,, and IL-8, may also play a role in the pathogenesis of lichen planus ***(Chen et al., 2007, Hussien, 2007 and Rhodus et al., 2007).***

Role of cytotoxic T cells:

In lichen planus, dermal infiltrate of T lymphocytes usually precedes histological epidermal damage. In slightly more advanced lesions, lymphocytes are seen within the lower epidermis, and at this stage, there was evidence of epidermal damage, including vacuolar alteration of basal keratinocytes and slight spongiosis in the spinous zone ***(Ragaz and Ackerman, 1981).***

The apoptotic process is known to be mediated by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. In LP lesions, there is infiltration of T cells (both CD4+ and CD8+) in the dermis while only CD8+ T cells infiltrate the epidermis. No significant increase in NK cells was detected in LP lesions compared to biopsies taken from normal skin ***(Kastelan et al., 2004).***

Most cytotoxic clones from LP lesions were CD8+ and most noncytotoxic clones were CD4+ ***(Sugerman et al., 2000).***

These data support the hypothesis that CD8+ lesional T cells recognize an antigen associated with major histocompatibility complex (MHC) class I on lesional keratinocytes and that CD8+

cytotoxic T cells induce keratinocytes apoptosis in LP lesions ***(Kawamora et al., 2003).***

Currently, the mechanisms used by CD8+ cytotoxic T cells to trigger keratinocyte apoptosis in LP are unknown. Possible mechanisms include:

(i) T-cell-secreted tumor necrosis alpha (TNF-α) binds to TNFreceptor 1 (TNF-R1) on the keratinocyte surface ***(Erdem et al., 2003).***

(ii) T cell surface CD95L (Fas ligand) binding CD95 (Fas) on the keratinocyte surface ***(Shen et al., 2004).***

(iii) T-cell-secreted granzyme B entering the keratinocyte via perforin induced membrane pores ***(Kastelan et al., 2004).***

All of these mechanisms may activate the keratinocyte caspase cascade, resulting in DNA fragmentation and keratinocyte apoptosis (figure 2) ***(Sugerman et al., 2000).***

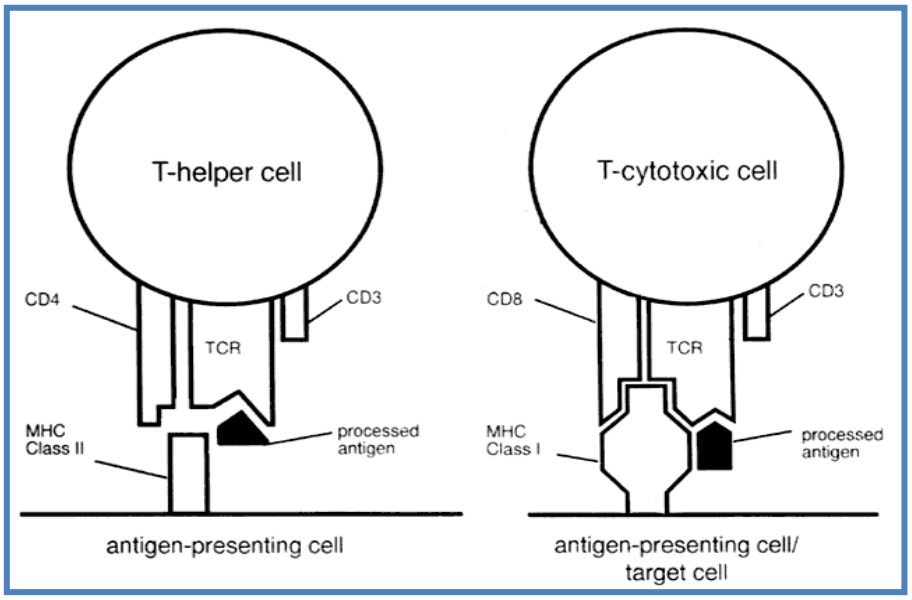

Fig. (1): Role of T cells in LP patients ***(Kawamora et al., 2003).***

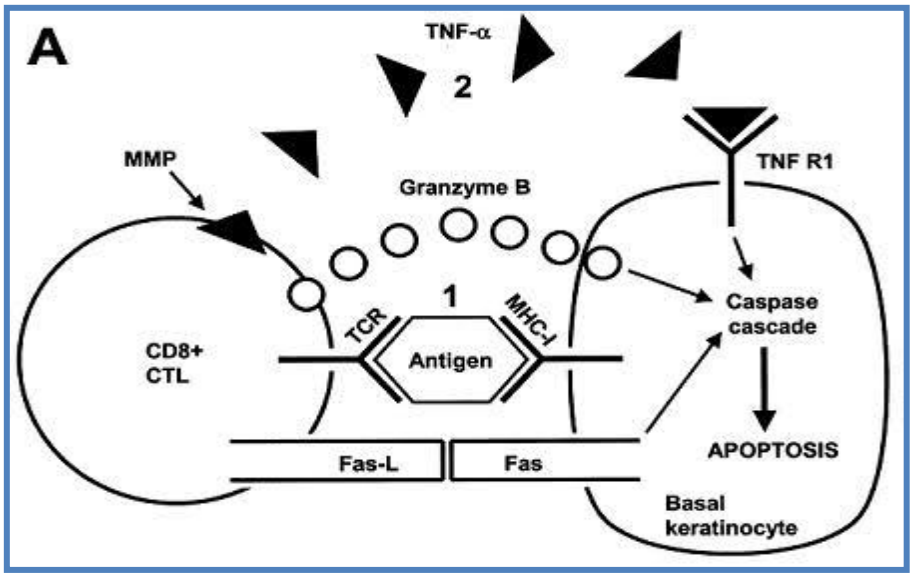

Fig. (2): Mechanism of triggering keratinocyte apoptosis in LP ***(Aggarwal et al., 2001).***

Role of dendritic cells:

Studies devoted to the analysis of dendritic cells (DCs) in LP found that they are altered in number suggesting that they may play a role in the pathogenesis of lichen planus ***(Hasseus et al., 2001).***

Before T-cells become activated, DCs must process antigen derived peptides and present them together with MHC class II molecules to T-cells.DCs receive additional activating signals, which induce a maturation process characterized by several aligned changes in DC morphology, phenotype and function. DC maturation is ultimately linked with the expression of chemokine receptor CCR7, which allows DC migration from the peripheral tissues to lymphoid organs ***(Branchereau et al., 2000).***

Role of keratinocytes:

The proinflammatory cytokines IFN-γ and IL-6 are produced not only by activated T lymphocytes but also by altered keratinocytes suggesting that stimulated keratinocytes may amplify the course of LP ***(Fayyazi et al., 1999).***

DCs or keratinocytes may present antigen associated with MHC class II to CD4+ helper T-cells that are stimulated to secrete the Th1 cytokines IL- 2 and IFN- γ ***(Albanesi et al., 1998).***

Role of the cytokines:

Based on cytokine production, CD4+T helper cells (Th cells) are divided into Th1 cells which are involved into cytotoxic T

cell response and produce IL-2 and IFN- γ & Th2 cells which are involved into antibody mediated response and produce IL-4, IL-5, IL-6, IL-9, IL-10, IL-13. CD8+cytotoxic T cells (Tc cells) are divided into Tc1 cells which produce IFN-γ & Tc2 cells which produce IL-4 and IL-5 ***(Spickett and Scwarz, 2004).***

Elevated serum level of TNF-α was found in LP patients and the TNF-α receptor was found to be expressed on the surface of skin infiltrating lymphocytes and lesional keratinocytes indicating that TNF- α plays a major role in induction of the pathogenic and apoptotic events of LP ***(Erdam et al., 2003).***

In oral lichen planus***, Kahn et al. in 2003*** reported that mononuclear cells infiltrating OLP lesions express IFN- γ and TNF-α while IL-4, IL-10.

Local production of IFN- γ may maintain keratinocyte MHC class II expression, thereby contributing to disease chronicity ***(Sugerman et al., 2002).***

Rhodus et al. in 2007 reported that there is elevation of TNF- α, IL-1α, IL-6, IL-8 in tissue transudate of OLP lesions. They concluded that a Th2 dominant immune response does occur in a subgroup of OLP patients and that Th1 or Th2 overactivation or mixed Th1/ Th2 condition may occur in the pathogenesis of OLP.

Role of the chemokines:

Th-1 cytokines induce or up regulate E-selectin and subsequently ICAM-1 and skin associated chemokines such as

CCL27 on the endothelium and this expression of adhesion molecules help in migration of lymphocytes from blood vessels to the interspace of dermis. The keratinocytes secrete a variety of lymphocyte- attractant chemokines such as IP-10, monokine induced by IFN γ (MIG), RANTES which help to attract T cells to dermo-epidermal junction ***(Spandu et al., 1998).*** Mast cell degranulation and matrix metalloprotein 9 secretion by T cells contribute to basement membrane disruption enabling migration of CD8+ T cells to the epidermis ***(Zhou et al., 2002).***

It is now known that type I T cells selectively express CCR5/CXCR3, and type 2 T cells express CCR3, CCR4, and CCR8 ***(Yoshie et al., 2001),*** and type I IFNs (α/ β) induce the production of several cytokines including IP-10/CXCL10 and Mig/CXCL9 ***(Wenzel et al., 2005).***

In LP, cytotoxic CD8+ T cells infiltrating the lesions express CXCR3 and carry respective chemokine ligand IP-10/CXCL10 in their cytotoxic granules indicating that a type 1 T cell mediated immune response is involved in the pathogenesis of LP and that interaction between CXCR3 and IP-10 represents an important self recruitment mechanism sharing in cytotoxic inflamation of LP ***(Wenzel et al., 2006).***

Role of type I interferons in cytotoxic inflammation in LP:

The role of type I IFNs in the pathogenesis of LP was suggested by many authors as they noticed exacerbation or

appearance of LP lesions during the treatment of chronic hepatitis C, lymphoproliferative diseases and melanoma with alpha-interferon (IFN-α) and improvement of these diseases after discontinuation of this drug ***(Pinto et al., 2003).***

Type I IFNs are able to induce upregulation of MHC, adhesion molecules and chemokines. They may initiate and amplify a vicious cycle leading to a chronic cytotoxic inflamation in LP ***(Wenzel et al., 2006).***

Lichen planus specific antigen:

CD8+ infiltrates in the lesional skin recognize a MHC Class I antigen called lichen planus specific antigen (LPSA). The exact nature of this antigen is unknown. It may be an auto-reactive peptide or exogenous antigen such as altered protein, drug, contact allergen and viral or other infectious agents ***(Daoud and Pittelkow, 2003).***

LPSA was demonstrated by direct immunofluorescence and It was present only in the stratum granulosum and stratum spinosum ***(Olsen et al., 1984 and El-Ghamriny, 2011).*** Detection of LPSA helps to differentiate atypical cases of LP from other dermatoses ***(Rao and Shenoi, 2006).***

Bacterial antigens:

- T lymphocytes specific for group-A streptococcal antigens were isolated from LP lesions ***(Baker et al., 1993).***

- Some authors suggested that Helicobacter pylori may be a possible antigen for LP, however the prevalence of Helicobacter pylori infection in patients with LP was not significantly different from that in patients with other skin diseases ***(Vainio et al., 2000).***

Viral antigens:

- Hepatitis C virus-RNA was isolated from lesional skin in patients with LP and chronic hepatitis C virus, and hepatitis C virus has been postulated as a possible antigen in LP ***(Kurokawa et al., 2003).***
- It has been reported that LP could be triggered or induced by hepatitis B vaccination ***(Calista and Morri, 2004),*** and HBs-Ag positivity may induce or cause proneness to oral lichen planus ***(Dogan, 2005).***
- Epstein-Barr virus DNA and human papilloma virus DNA were isolated from oral mucosa in patients with OLP ***(Sand et al., 2002 and Campisi et al., 2004).***
- Human herpes virus type 7(HHV-7) replicates were found in LP lesions suggesting that HHV-7 is possibly involved in the pathogenesis of LP ***(De Vries et al., 2006).***

Fungal antigens:

Some Candida albicans isolates with special genotypic profiles may contribute to the development and progression of OLP ***(Zeng et al., 2005).***