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Exploring The Pathological Role Of Cd8/ Bcl2 Axis In Lichen Planus- A Cross- Sectional Study

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ABSTRACT:-

INTRODUCTION:-

Lichen planus (LP) is a chronic inflammatory autoimmune disorder that affects the skin, mucous membranes, nails, and hair. It is characterized by immune system dysfunction, where CD8+ T cells attack basal keratinocytes, leading to inflammation and tissue damage. LP presents in various forms, including classic skin lesions, oral ulcers, genital lesions, nail changes, and, in some cases, esophageal and ocular involvement. While the exact etiology is unclear, genetic predisposition, stress, and immune dysregulation are significant contributing factors. The Bcl2/CD8+ axis plays a crucial role in the survival of CD8+ T cells during inflammation, and dysregulation of this axis may contribute to the chronicity of LP. This study investigates the expression of the CD8/Bcl2 axis in LP's pathological process, with the goal of identifying potential therapeutic targets for more effective management of the condition.

AIMS AND OBJECTIVES:

To evaluate the histopathological features and immunohistochemical expression of CD8+ T cells and Bcl-2 in lichen planus and lichenoid dermatitis.

To assess cytotoxic lymphocytes and apoptosis in tissue samples.

To explore the role of CD8+ T cells and Bcl-2 in the pathogenesis and chronicity of these conditions.

MATERIALS AND METHODS:

This cross-sectional study was conducted at the Central Laboratory, Department of Pathology, Sree Balaji Medical College, Chennai, from February to July 2024. A total of 23 lichen planus and 24 lichenoid dermatitis samples were analyzed for CD8+ T cells and Bcl-2 expression. Data were analyzed using SPSS v25, with descriptive statistics, Spearman's rank correlation, and the Chi-square test. A p-value of < 0.05 was considered statistically significant.

RESULTS:
Our study revealed an equal gender distribution in patients with lichen planus (LP), consistent with previous studies. Lesions were most commonly found on the legs, thighs, and ankles. Histopathologically, we observed characteristic lymphocytic infiltration in the subepidermal dermis, along with weak or absent expression of Bcl-2 in basal keratinocytes. Additionally, corticosteroid and UVB treatments led to reduced Bcl-2 and CD8 expression in skin biopsies. Notably, five patients developed LP lesions following COVID-19 vaccination, aligning with prior reports of vaccines potentially triggering LP.

DISCUSSION:
Our findings support the idea that immune dysregulation, specifically involving CD8+ T cells and Bcl-2, plays a key role in the pathogenesis and chronicity of LP. The presence of high levels of IL-12, IL-6, IL-21, and other cytokines suggests

that targeting the JAK1 receptor could offer therapeutic potential. The link between vaccinations and LP flare-ups warrants further investigation, as the Th1 immune response may contribute to the development of skin lesions.

CONCLUSION:
Lichen planus is an immune-mediated disorder driven by CD8+ T cell activity and apoptosis of basal keratinocytes. The reduced expression of Bcl-2 and the role of cytokines such as IL-12, IL-6, and IL-21 contribute to the disease's persistence. Vaccinations, including the COVID-19 vaccine, may trigger LP in some individuals. Further research is needed to better understand the pathogenesis and explore targeted therapies for managing LP more effectively.

KEY WORDS:

Lichen Planus, Autoimmune Disorder, CD8+ T Cells, Bcl-2, Cytotoxic Lymphocytes, Cytokines, IL-12, IL-6, IL-21, JAK1 Receptor, Therapeutic Targets, Lichenoid Dermatitis.

Introduction

Lichen planus (LP) is a chronic inflammatory disorder that primarily affects the skin, mucous membranes (such as the oral cavity, genital area, and esophagus), nails, and hair. It is characterized by an autoimmune response, where the body's immune system mistakenly targets its own cells, resulting in inflammation and tissue damage. The term "lichen planus" is derived from the Greek word lichen, meaning "tree moss," which describes the scaly, plaque-like appearance of the lesions, and the Latin word planus, which means "flat," referring to the flat nature of the skin lesions.[1]

LP is a heterogeneous condition, with a variety of clinical presentations and variable outcomes. The most common form is classic LP, which presents as purple, flat, itchy lesions on the skin, often with a shiny or silvery surface. Oral LP appears as white, lacy lesions or painful ulcerations in the mouth, while genital LP manifests as erythematous lesions and white patches, potentially causing scarring. Other forms include nail LP, which leads to nail thinning, ridging, and loss, and esophageal LP, which causes difficulty swallowing due to inflammation and strictures in the esophagus. Ocular LP can lead to inflammation and scarring of the eyes, threatening vision in severe cases.

The etiology of LP remains unclear, but several factors contribute to its development. Immune dysregulation is a key factor, as LP is considered an autoimmune disorder where CD8+ cytotoxic T cells attack basal keratinocytes in the affected tissues, leading to inflammatory responses. Genetic predisposition also plays a role, as familial clusters of LP cases have been observed, suggesting a hereditary component. [2]Additionally, psychological factors such as stress may exacerbate LP, although the exact mechanisms are still under investigation.

The immune response in LP involves complex interactions between various immune cells. Plasmacytoid dendritic cells (pdcs), mast cells, and T cells (CD4+ and CD8+) play pivotal roles in the pathogenesis. When self-antigens are exposed in the basal cell layer of the epithelium, type 1 interferons (ifns) like IFN-α are released. These cytokines activate CD8+ T cells, which then target the basal keratinocytes, causing tissue damage and perpetuating the inflammatory cycle. Additionally, RANTES (regulated on activation, normal T cell expressed and secreted) released by T cells attracts more immune cells, further exacerbating inflammation.[3]

The Bcl2/CD8+ axis is crucial in regulating the survival of CD8+ T cells during the inflammatory process. Bcl2 (B-cell lymphoma 2) is a protein that helps regulate cell apoptosis, playing a critical role in maintaining the survival of cytotoxic T cells during chronic inflammation. Dysregulation of the Bcl2 axis may result in an excessive accumulation of CD8+ T cells, contributing to the chronicity

and persistence of LP lesions. Understanding how the Bcl2/CD8+ axis modulates immune responses could offer valuable insights into the development of novel therapeutic strategies aimed at modulating immune activity in LP.

In conclusion, Lichen planus is a complex disease driven by immune dysregulation, involving interactions between CD8+ T cells, dendritic cells, cytokines, and other immune components. The dysregulation of the Bcl2/CD8+ axis is a potential mechanism that contributes to the persistence and chronicity of the disease. Further research into the molecular pathways underlying LP, particularly the role of the Bcl2/CD8+ axis, could lead to more targeted therapies and better management of this challenging condition.

The present study aims to explore the expression of CD8/ Bcl2 Axis in the pathological process of lichen planus

AIMS AND OBJECTIVES:-

Aim

To evaluate the histopathological characteristics and immunohistochemical expression of CD8+ T cells and Bcl-2 in patients with lichen planus and lichenoid dermatitis.

Objectives

To assess the presence of cytotoxic lymphocytes and the occurrence of apoptosis in tissue samples.

To investigate the potential role of CD8+ T cells and Bcl-2 in the pathogenesis and chronicity of lichen planus and lichenoid dermatitis.

MATERIALS AND METHODS:-

This cross-sectional study was conducted at the Central Laboratory, Department of Pathology, Sree Balaji Medical College, Chennai, from February 2024 to July 2024. A total of 23 lichen planus samples and 24 lichenoid dermatitis samples were collected to investigate the expression of CD8+ T cells and Bcl-2, and their correlation with factors such as age, gender, and site/location in the pathogenesis of these conditions. Data were entered into MS-Excel and analyzed using SPSS v25. The Kolmogorov-Smirnov test was employed to assess the normality of the data. Descriptive statistics were presented as percentages, and Spearman's rank correlation and the Chi-square test were used for statistical analysis due to the nature of the data distribution. A p-value of < 0.05 was considered statistically significant.

RESULTS:-

TABLE 1:- DISTRIBUTION BASED ON AGE:-

AGE RANGE (YEARS)	FREQUENCY OF CASES	PERCENTAGE (%)
0-10	1	4.4
10-20	1	4.4
20-30	6	26
30-40	4	17.4

40-50	10	43.4
50-60	0	0
60-70	0	0
70-80	1	4.4
Total	23	100
P value = 0.027		

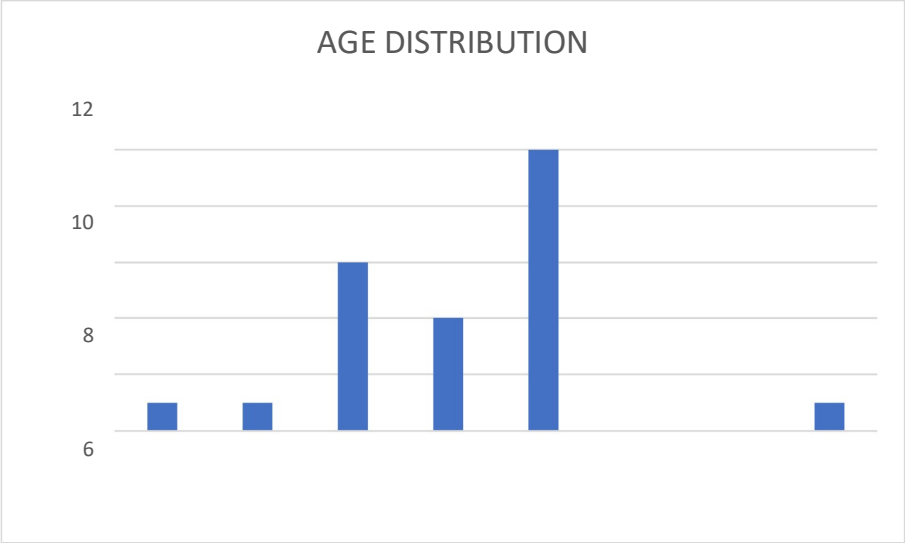


CHART 1: DISTRIBUTION OF LICHEN PLANUS BASED ON AGE

In our study, we noted that patients with Lichen planus presented with increased frequency between the age group of 30-50y with the highest frequency of patients being in their 40's.

TABLE 2:-GENDER DISTRIBUTION OF LICHEN PLANUS:

GENDER DISTRIBUTION	FREQUENCY OF CASES	PERCENTAGE (%)
Male	12	52
Female	11	48
Total	23	100
P VALUE = 0.012		

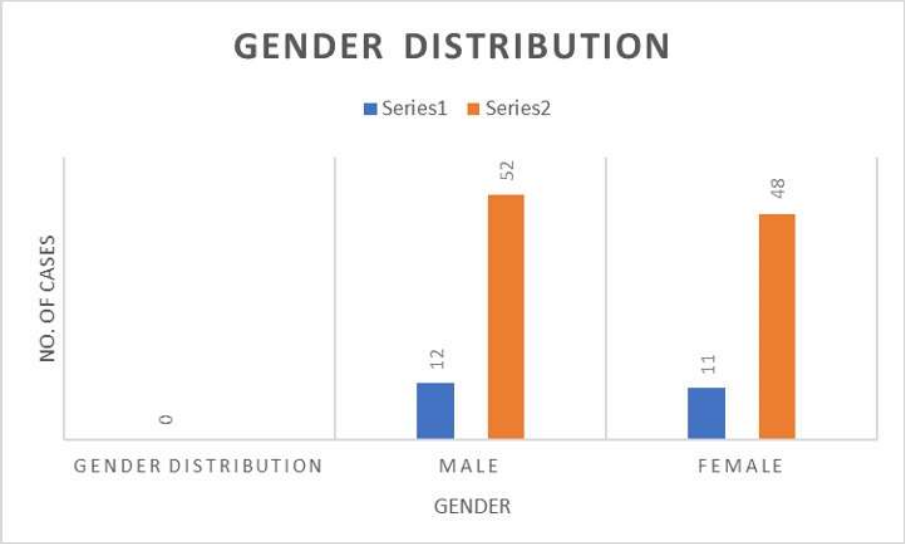


CHART 2: GENDER DISTRIBUTION OF LICHEN PLANUS

We found the number of patients with lichen planus based on gender to have a small predominance of males with a male to female ratio of 1.2:1 in our study.

TABLE 3:-SITE OF LESION IN LICHEN PLANUS

SITE OF LESION	FREQUENCY OF CASES	PERCENTAGE (%)
Upper Limb	6	26.1
Lower Limb	14	60
Chest	1	4.4
Abdomen	1	4.4
Scalp	1	4.4
Genitalia	0	0
Total	23	100
P VALUE = 0.07		

CHART 3: DISTRIBUTION OF SITES OF LESION IN LICHEN PLANUS

The parts of the body involved as studied by us from most common to least is as follows;

- Legs, thighs, ankles, dorsum of feet - 60%
- arm, forearm, hands - 26.1%
- Abdomen, chest and scalp in equal number - 4.4%

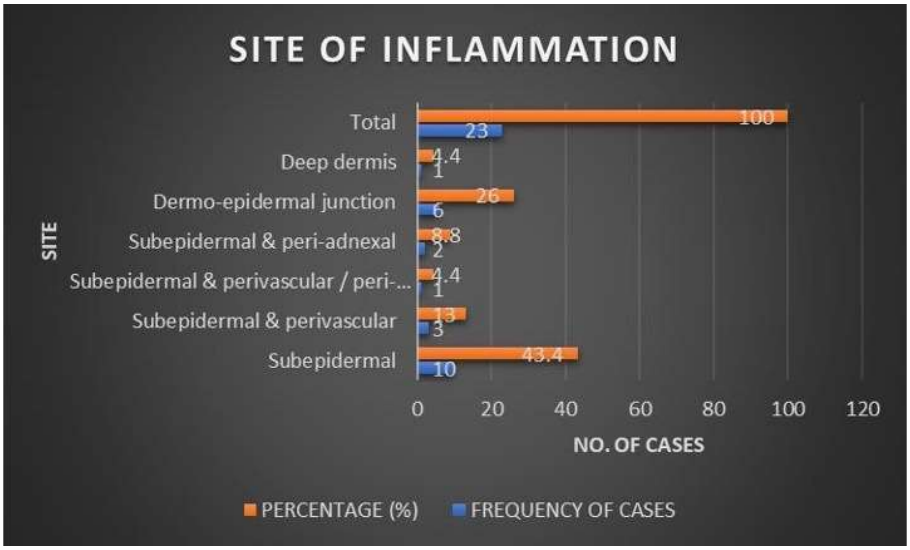
We have listed the parts of the body with the skin lesions in the table with its frequency of presentation.

IMMUNOSTAINING BY LOCATION:-

TABLE 4: IMMUNOSTAINING BY LOCATION IN SKIN IN LICHEN PLANUS

SITE OF INFLAMMATION	FREQUENCY OF CASES	PERCENTAGE (%)
Subepidermal	10	43.4
Subepidermal & perivascular	3	13
Subepidermal & perivascular / peri-adnexal	1	4.4
Subepidermal & peri-adnexal	2	8.8
Dermo-epidermal junction	6	26
Deep dermis	1	4.4
Total	23	100
P VALUE = 0.023		

CHART 4: IMMUNOSTAINING BY LOCATION IN SKIN IN LICHEN PLANUS



It was noted that increased lymphocytic inflammation was noted in the subepidermal region of the skin biopsies with a percentage of 43.4%, followed by the dermo-epidermal junction with a percentage of 26%

IMMUNOREACTIVITY:-

TABLE 5: IMMUNOREACTIVITY OF CD8 & BCl2 IN LICHEN PLANUS

LICHEN PLANUS	FREQUENCY	LICHEN PLANUS	FREQUENCY
CD8 immuno-reactivity		Bcl2 immuno-reactivity	
1+	6 (26%)	1+	2 (9%)
2+	11 (48%)	2+	4 (17%)
3+	6 (26%)	3+	17 (74%)
Total	23		23
P VALUE = 0.0012			

We found that the lymphocytic infiltrate expressed CD 8 expression ranging between 30% - 70% with Bcl2 expression ranging between 70%-100% in the lichen planus samples.

MICROSCOPIC IMAGES :-

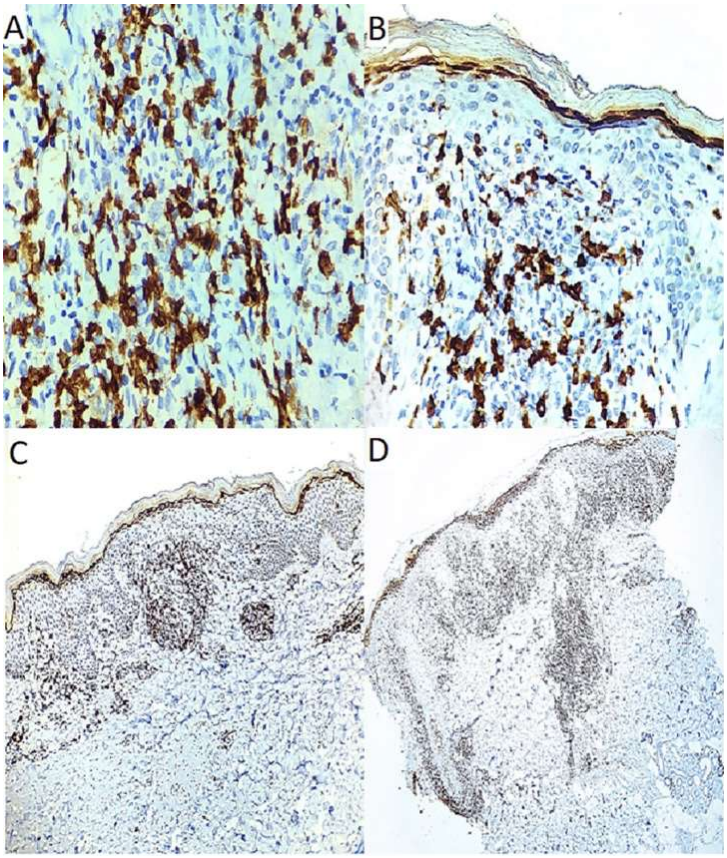


FIGURE 6: CD8 immunohistochemical expression in Lichen planus skin biopsies

CD8 stain showing membranous positivity in lymphocytes (A,40x); CD 8 stain shows weak 1+ (0 – 30%) membranous positivity in lymphocytes (B,40x); CD 8 stain shows moderate staining 2+ (30 – 70%) membranous positivity in lymphocytes (C,10x); CD 8 stain shows strong 3+ (70 – 100%) membranous positivity in lymphocytes (D,10x).

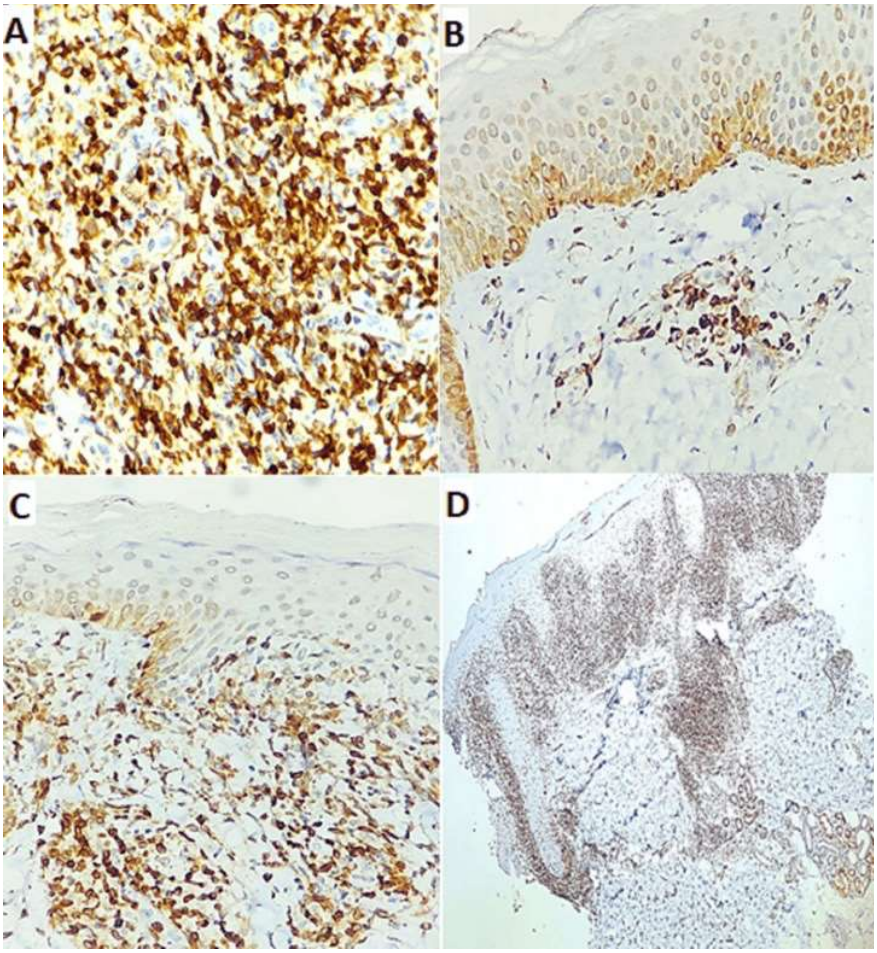


FIGURE 7: Bcl2 immunohistochemical expression in Lichen planus skin biopsies

Bcl2 stain showing cytoplasmic positivity (A,40x); Bcl2 stain shows weak 1+ (0 – 30%) cytoplasmic positivity (B,40x); Bcl2 stain shows moderate staining 2+ (30 – 70%) cytoplasmic positivity (C,40x); Bcl2 stain shows strong 3+ (70 – 100%) cytoplasmic positivity (D,10x).

DISCUSSION:-

Lichen planus (LP) is a chronic, inflammatory autoimmune condition characterized by the presence of distinctive, itchy, purple lesions on the skin and mucous membranes, including the oral cavity, genital areas, and sometimes the nails and hair. The pathogenesis of LP is primarily driven by an immune-mediated response, where activated CD8+ cytotoxic T cells target and damage the basal keratinocytes of the affected tissues. This autoimmune attack is often triggered by various environmental factors, such as stress, infections, or medications, and is exacerbated by a genetic predisposition. Histologically, LP presents with a band-like infiltrate of lymphocytes at the dermoepidermal junction, often accompanied by apoptosis of basal keratinocytes. The role of immune regulators like CD8+ T cells and Bcl-2 is significant in the disease's chronicity, as these cells and apoptotic processes contribute to the persistence of inflammation and tissue damage. Understanding these mechanisms can aid in developing targeted therapeutic strategies to manage the condition effectively.

Our study revealed an almost equal distribution of gender among those affected by lichen planus (LP), which aligns with previous research conducted by Boch et al. [4] and Le Cleach et al. [5], who also observed no significant gender predisposition in LP cases. Similarly, in a comprehensive review by Usatine et al. [6], it was noted that cutaneous LP was commonly observed in the wrists and lower limbs. Our institution's findings mirrored this observation, with lesions frequently appearing on the legs, thighs, and ankles of patients.

A comparison study by Pietschke et al. [7], which analyzed psoriasis and lichen planus as two chronic inflammatory skin diseases, pointed out certain overlapping features between them. Both conditions share characteristics such as the Koebner phenomenon, where new lesions form at sites of trauma, and a potential role of drugs as triggers. However, there are significant differences between the two. Lichen planus often affects mucosal surfaces and can cause scarring, particularly on the scalp, which is not observed in psoriasis. To better understand these diseases, Pietschke et al. delved into the immunopathogenesis of LP and psoriasis, finding that distinct cytokines play a role in each condition. In lichen planus, the inflammatory infiltrate was primarily located in the dermis, a finding consistent with our study, where we observed the majority of inflammatory cells in the subepidermal region of the dermis.

Historically, it has been suggested that Th1 cells and interferon-gamma (IFN-γ) are central to the development of lichen planus, but emerging studies are now indicating that the Th17 pathway may also be involved, although its exact role remains unclear. The cytokines IL-12, IL-6, IL-21, and the signaling molecule STAT have been identified as potentially significant in LP. These cytokines are expressed in high amounts by dermal lymphocytes in LP. Recent literature suggests that LP is associated with type-1 inflammation, with IL-21 being particularly prominent in its pathogenesis. Given the involvement of these cytokines, there is the potential for developing therapeutic inhibitors targeting the JAK1 receptor, a receptor through which IL-12, IL-6, IL-21, and STAT exert their effects. A study conducted by Vijaitu et al has established the correlation between these markers and the pathogenesis of lichen planus which has been further explored in our present study.

In terms of histopathological findings, we noted a weak or absent expression of Bcl-2 in the basal cells of LP lesions, while there was an increased expression of Bcl-2 in the subepidermal region where lymphocytic infiltration occurred. This suggests that the reduced expression of Bcl-2 in basal keratinocytes may contribute to their increased apoptosis, whereas the heightened Bcl-2 expression in the subepidermal region could be linked to the increased lymphocytic infiltration. These findings align with the observations of Kaur et al. [8] and Abdel-Latif [9], who reported similar patterns in their studies of lichen planus.

Throughout our study, we also observed that patients treated with oral or topical corticosteroids, as well as those undergoing UVB light therapy, exhibited decreased levels of Bcl-2 and CD8 expression in their skin biopsies. This mirrors the findings of Ozturk et al. [10], who concluded that treatment with prednisolone and acitretin resulted in a significant reduction of Bcl-2 and Ki-67 expression. This reduction in the markers of apoptosis likely explains the chronic nature of lichen planus, as it suggests that a lack of apoptosis may contribute to the persistence of the disease.

Additionally, we gathered detailed clinical histories of our patients, and interestingly, we found that five individuals developed skin lesions after receiving the COVID-19 vaccine. This observation is consistent with prior research that has noted a link between vaccinations and the onset of lichen planus. For instance, the hepatitis B vaccine has been well-documented as a trigger for lichen planus in some individuals. Other vaccines, including those for influenza, rabies, diphtheria, tetanus, pertussis (DTaP), and measles, mumps, and rubella (MMR), have also been associated with the development of LP to varying degrees, with the hepatitis B vaccine being the most frequently reported trigger.

Furthermore, Hiltun et al. [11] observed an increase in various skin conditions, including lichen planus, psoriasis, atopic dermatitis, vitiligo, acne vulgaris, pemphigus vulgaris, neutrophilic dermatoses, and certain connective tissue diseases following COVID-19 vaccination. They proposed that the vaccines might stimulate a Th1 immune response, leading to increased levels of cytokines such as IL-2, TNF-α, and IFN-γ. These cytokines and the activation of the Th1 pathway are involved in the destruction of basal keratinocytes in lichen planus, which may explain the observed correlation between the COVID-19 vaccine and the development of LP in some patients. However, further research is needed to establish a definitive connection between COVID-19 vaccination and the onset of skin conditions like lichen planus.

CONCLUSION:-

In conclusion, lichen planus (LP) is a multifaceted chronic autoimmune disorder with a complex etiology, driven by immune-mediated damage to basal keratinocytes. This condition is often triggered by environmental factors and influenced by genetic predisposition. Our findings, which align with previous research, reveal no significant gender preference and highlight common lesion sites, particularly on the lower limbs and legs. The immunopathogenesis of LP involves both Th1 and Th17 pathways, with cytokines like IL-12, IL-6, IL-21, and STAT playing key roles. Histologically, we observed typical features, including lymphocytic infiltration and altered Bcl-2 expression, which contribute to the disease's persistence. Treatment with corticosteroids and UVB light therapy appears to reduce apoptosis markers, offering insights for future therapeutic approaches. Furthermore, our study suggests a potential link between LP flare-ups and COVID-19 vaccination, consistent with recent literature that indicates vaccines may trigger LP through Th1-mediated immune responses. While further studies are needed, these findings improve our understanding of LP's pathogenesis and potential therapeutic targets, paving the way for more effective treatment strategies in the future.

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