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IMMUNOHISTOCHEMICAL ASSESSMENT OF CD1A AND Ki-67 IN ORAL LICHEN PLANUS

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ABSTRACT

Objective: The purpose of the current study was to assess the expression of CD1a by Langerhans cells (LCs) and cell proliferation by analyzing the expression of Ki-67 in 30 cases of oral lichen planus (OLP).

Material and methods: Immunohistochemical staining was used to analyze the expression of CD1a and Ki-67 in 30 archival paraffin blocks containing OLP specimens including 19 erosive, 6 reticular, 3 atrophic, and 2 plaque types of OLP. Normal oral mucosa served as a control. The tissue samples were thoroughly examined, and the expression pattern was analyzed quantitatively by counting the number of positive cells. A score from 1 to 3 was used to grade the intensity of CD1a immunostaining: 1) Weak staining; 2) Moderate staining; and 3) Intense staining. Scores ranging from 1 to 3 were assigned to nuclear immunostaining for Ki-67 proliferation: 1) "+" denoted low proliferation; 2) "++" denoted moderate proliferation; and 3) "+++" denoted high proliferation. SPSS-13 program was used for the statistical analysis, and $p<0.05$.

Results: All the studied cases revealed positive reactions to both CD1a and Ki-67. CD1a was weakly expressed in 43.3% of the studied OLPs, distributed within the existing epithelium. Meanwhile, intense expression of CD1a was 26.7% of the studied OLPs, shown among both epithelium and connective tissue stroma**, 75%** of them were erosive (37.5%) and reticular OLP (37.5%)**.** For Ki-67, the basal and suprabasal epithelial cells as well as the inflammatory cells of 26.7% of the OLPs under study exhibited a low nuclear response. Meanwhile, 53.3% of the studied OLPs had high nuclear expression to Ki-67 in the inflammatory cells and the basal and suprabasal cell layers of the epithelium. Interestingly, a statistically significant correlation between CD1a and Ki-67 marker expression was observed among the studied OLPs.

Conclusions: The increase density of Langerhans cells in the studied OLPs suggests its possible significant role in the adaptive immune response in OLP pathogenesis. Elevated ki-67 expression in erosive OLP with severe oral epithelial dysplasia (OED) may indicate that this type is more susceptible to premalignancy and uncontrollable proliferation.

KEYWORD: ??

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INTRODUCTION

Oral lichen planus (OLP) is a frequent chronic mucocutaneous condition with a debatable etiology [1]. The condition can affect either the skin, mucosa, or both. It can cause bilateral white striations, papules, or plaques on the buccal mucosa, tongue, and gingiva. Erythema, erosions, and blisters may or may not be present [2]. The white and red components of the lesion can be a part of several clinical phenotypes [3], reticular (most common variant), plaque-like, erythematous (also referred to as atrophic), ulcerative (also referred to as erosive), bullous (very uncommon and usually associated with one of the other phenotypes), and mixed OLP. Clinical features of OLP range from asymptomatic reticular white lesions in atrophic mucosa, to erosive-ulcerative areas accompanied by pain and discomfort, while the most characteristic feature is the presence of a lace-like network of fine white lines. The exact incidence and prevalence are still unknown [3]. OLP is a disease of middle age that affects women more frequently, with children rarely affected [4]. Although its precise etiology is still up for debate, its pathophysiology is recognized. It is currently thought to be an autoimmune cell-mediated disease that targets epithelial cells, primarily in the basal layer [1, 5]. Damage to epithelial basal cells is largely caused by T lymphocytes (cytotoxic CD8 + T cells) [6]. LP is characterized by an intense T-cell infiltrate (CD4 and especially CD8 cells) localized along the epithelial-connective tissue interface. Over time, there have been notable advancements in the diagnosis of OLP. The diagnosis of OLP is supported by the clinical (history and presentation), histopathologic, immunofluorescence, and biomarkers. The nature of antigen in OLP has not yet been established. Specific markers for LCs have been identified and are widely used to define the role of these cells in the pathogenesis of OLP. CD1a, a membrane protein expressed by dendritic cells like LCs, is a marker for immature LCs in the normal oral epithelium. Its expression in OLP was studied and compared with normal oral mucosa [7]. The process of antigen presentation to T-cells in OLP by LCs involves both immature and mature LCs whereas the immature LCs undergo a process of maturation by activation of numerous co-stimulatory pathways. The mature LCs then migrate into the connective tissue to reach the lymph nodes to present antigens to the T-cells [8]. According to the WHO, OLP is categorized into the group of orally potential malignant disorders (OPMD) [9]. More recent investigations reported a low overall frequency of malignant transformation, varying between 0.3% and 3%, commonly among the erosive and atrophic OLP forms [10]. OLP without OED is considered a lower-risk lesion for malignant transformation. However, there should be a periodic review of the lesion, especially in smokers, to assess the malignant transformation. Research studies using microsatellite analysis hypothesized that dysplastic changes are seen more often in lichenoid lesions than in LP [2]. In OLP, epithelial proliferation results from severe cellular injury. The lesion may proceed toward malignancy as a result of this transition that takes place during the cell cycle in OLP. Ki-67 is a nuclear, non-histone protein found in two isoforms with molecular weights of 356 KDa and 320 KDa. The gene is located on chromosome 10 [11]. The marker indicates the percentage of the nucleus occupied by the protein. We can also accurately assess the rate of proliferation by using this marker. Therefore, the purpose of this study was to assess Ki-67 expression in OLP.

The current study aimed to evaluate cell proliferation in OLP and its relation with the presence of OED in the studied cases.

MATERIAL AND METHODS

MATERIAL

Tissues:

This study was carried out on 30 paraffin blocks containing OLP specimens (19 erosive, 6 reticular, 3 atrophic, and 2 plaque types of OLP), and a normal

oral mucosa served as control**.** They were obtained from the archives of the Oral and Maxillofacial Pathology Departments, Faculty of Dentistry, Mansoura University, and Alexandria University.

Clinical data:

The patient's registered medical records were searched for any clinical information relevant to the OLPs under study, with a focus on age, sex, and lesion location.

Histopathological examination

For routine hematoxylin and eosin staining, the retrieved paraffin blocks of the studied cases were serially cut into 4μ thickness sections.

Immunohistochemical examination

The CD1a (Cluster of Differentiation 1a antibody), has been used to identify Langerhans' cell histiocytosis and precursor T lymphoblastic lymphoma/leukemia). For cell proliferation, a Ki-67 monoclonal antibody was employed. Tonsils were a positive control.

METHODS

In order to perform regular hematoxylin and eosin staining to inspect and confirm the diagnosis of the examined cases of OLP and normal mucosa, the retrieved paraffin blocks of the cases under study were serially cut into sections of 4μ thickness. The tissue samples stained with H&E were examined by two separate researchers. Histological evaluation of ED was performed among studied sections of OLP, according to the WHO (2017) into a three-tier grading system (mild, moderate, and severe dysplasia). Another 4-micron thickness sections were cut from the paraffin blocks of OLPs and normal oral mucosa cases and then mounted on optiplus™ slides obtained from the GEMEX laboratory. Those slides are positively charged to allow strong adhesion between tissues and slides. Positive control cases (Tonsils) for immunostaining which was performed using the Streptavidin/Peroxidase technique according to the manufacturer's instructions. CD1a and Ki-67 are ready to use.

Immunohistochemical evaluation:

The stained slides were examined under a light microscope at 100× magnification (Leitz Wetzlar; Leica Microsystems GmbH, Wetzlar, Germany). The number of positive cells and negative epithelial cells was counted manually for the percentage in randomly selected six High-Power Fields (HPF). The slide was moved in a single direction (from right to left) to avoid repeating already-examined fields. Specimens were considered to be positive for staining when cells had a brown cytoplasm/membrane or nuclei, and specimens were considered to be negative for staining when cells showed only blue nuclei or cytoplasm/membrane. Sections of the studied cases were assessed based on the percentage of positive cells stained in a nuclear pattern for Ki67 and/or cytoplasmic pattern for CD1a.

Evaluation (Interpretation) of reactivity of CD1a marker

The criteria followed for the identification of LCs were as follows: 1) Positive (brown) staining by chromogen; 2) Cell body with at least two well-visualized dendrites [12]. The number of CD1a-labelled LCs was calculated as a mean number of positive cells/HPF and presented as the percentage of positive cells [13]. The immunostaining density was established by determining the intensity of staining of CD1a-positive cells in representative fields of all specimens. Specimens showing the largest and smallest number of CD1a-positive cells were used as reference and classified as presenting intense (3) and discrete (1) immunostaining, respectively. The other specimens were classified as presenting moderate (2) [14]. A score from 1 to 3 was used to grade the intensity of CD1a immunostaining. The scale corresponds to the percentage of stained cells compared to the total cellular infiltration; counting

was scored from 1 to 3: 1) Weak staining or a few cells stained (11-25%); 2) Moderate staining or some cells stained (26-75%); 3) Intense staining or many cells stained (more than 76%) [15].

Evaluation of Ki-67 marker:

When cells showed brown nuclei, the specimen was deemed to be positive for staining. Every cell in the sample, including the positive cells, was enumerated, computed, and displayed as the proportion of positive cells. Scores ranging from 1 to 3 were used to grade Ki-67 expression sections stained for Ki-67 proliferation (observed as nuclear staining): 1)"+" denoted low-proliferation, with 10–30% positive cells; 2)"++" denoted moderate proliferation, with 30–50% positive cells; 3)"+++" denoted high proliferation, with more than 50% positive cells [16].

Statistical analysis and data interpretation:

For data analysis, SPSS software (version 26.0) for Windows was used. Analysis of variation in one direction was applied. Only when the P value was less than 0.05 was it considered statistically significant.

RESULTS

Clinical and histopathological findings:

The mean age and standard deviation of studied OLP cases was 51.87±10.08. Most of the studied OLPs (80%) were presented between 40 and 60 years (fourth and fifth decades) and the least were presented below 40 years (6.7%). There was a statistically significant difference between the ages of studied OLPs. There was a male predilection of 60% with no statistically significant difference between the genders of the studied OLPs. The buccal mucosa (bilaterally) had the highest frequency of occurrence of studied OLP (53.3%), while lip and tongue were the least common sites of distribution. There was a statistically significant difference between the sites of studied OLPs. Among the OLP under study, the erosive form was most prevalent (63.3%) with a statistically significant difference among the types of OLPs.

Examining slides stained by hematoxylin and eosin using a light microscope showed features of different types of OLP. **(Figure 1).** The WHO (2017) criteria for OED were used, and it was observed that

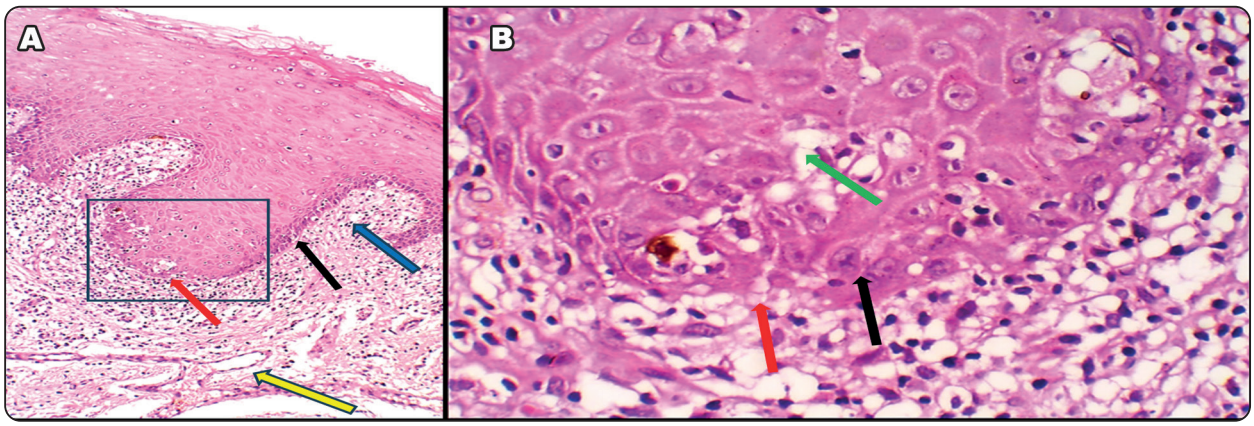

Fig. (1) Photomicrograph showing reticular OLP in gingiva. A) Revealed hyperplastic stratified epithelium with irregular rete process (black arrow) and mild OED. The basement membrane is indistinct in some areas (red arrow). The stroma shows moderate lymphocytic band infiltration and increased vascularity (thin and narrow blood vessels near the basement membrane (blue arrow) and large blood vessels deeper (yellow arrow) (H and E section X 200). B) High power showing an area of liquefication degeneration (apoptosis) of basal cells (red arrow) and mild OED as an increased nuclear-cytoplasmic ratio, nuclear and cellular pleomorphism, mitotic figures (black arrow), drop-shaped rete process, and loss of cohesion (green arrow). (H and E section X 400).

all studied OLP cases have had criteria for dysplasia. They were demonstrated as 63.3% erosive OLP, 20% reticular OLP, 10% **atrophic OLP**, and 6.7% plaque OLP with a statistically significant difference. Interestingly, among the studied OLP, 50% of all OLP were revealed as mild OED (dysplastic changes limited to the lower third of the surface epithelium). They were mostly distributed as 83.3% of reticular OLP. Meanwhile, 43.3% of all OLP were revealed to moderate OED (dysplastic changes up to two-thirds of the epithelium). They were distributed as 52.6% of erosive OLP and 50% of plaque OLP. The least was noticed as severe OED (dysplastic changes more than two-thirds of the epithelium) in 6.7% of all OLP, which was only observed among the erosive OLP **(Table 1).**

Immunohistochemical findings:

CD1a expression among the studied normal oral mucosa and OLP:

All the studied cases (normal mucosa and OLP) revealed positive cytoplasmic and/or nuclear expression for CD1a microscopically. The normal oral mucosa served as a control and revealed weak CD1a expression presented as LCs with dendritic processes distributed at the epithelium's basal, suprabasal, and mid-spinous layers. **(Figure 2).** In studied OLPs, it was weakly expressed in most cases (43.3%) of the existing epithelium. Meanwhile, intense expression (26.7%) of CD1a for OLP was shown among both epithelium and connective tissue stroma, 75% of them were erosive

TABLE (1) Degree of OED in studied OLP.

Degree of OED among OLP	Erosive LP(n=19) %	Reticular LP(n=6) %	Atrophic LP(n=3) %	Plaque LP (n=2) %	Total (n=30) %	**P-value**
Mild	7(36.8%)	**5(83.3%)**	2(66.7%)	1(50%)	**15(50%)**	
Moderate	**10(52.6%)**	1(16.7%)	1(33.3%)	1(50%)	**13(43.3%)**	**0.573**
Severe	**2(10.5%)**	0	0	0	**2(6.7%)**	
Total (n=30) %	19(63.3%)	6(20%)	3(10%)	2(6.7%)	30(100%)	**<0.001****

Data expressed as mean ±SD & frequency (N, %) SD: standard deviation, P: Probability, *: significance <0.05. The test used: One-way ANOVA for data expressed as mean ±SD & Monte-Carlo for data expressed as frequency (N, %).

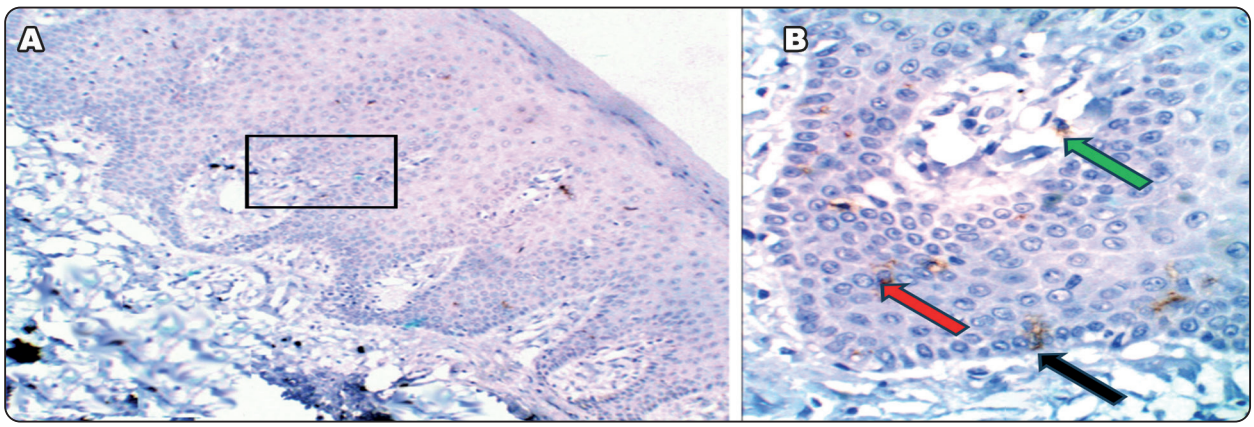

Fig. (2) Photomicrograph showing normal oral epithelium exhibits very few CD1a-positive LCS at basal (black arrow), suprabasal (red arrow), and mid-spinous layers (green arrow) of the epithelium. (A-Immunohistochemistry, ×100)(B-Immunohistochemistry, ×400)

TABLE (2) Association between CD1a expression and Clinical types of the studied OLP cases.

Clinical type	CD1a			Total N=30(%)	P-value
	Weak staining	Moderate staining	Intense staining		
Erosive OLP	9(69.2%)	7(77.8%)	**3(37.5%)**	19(63.3%)	**0.446**
Reticular OLP	1(7.7%)	2(22.2%)	**3(37.5%)**	6(20%)	
Atrophic OLP	2(15.4%)	0(0%)	1(12.5%)	3(10%)	
Plaque OLP	1(7.7%)	0(0%)	1(12.5%)	2(6.7%)	
Total N=30(%)	**13(43.3%)**	9(30%)	**8(26.7)**	30(100%)	**0.496**

Data expressed as frequency (N, %) P: Probability, *: significance <0.05 Test used: Monte-Carlo

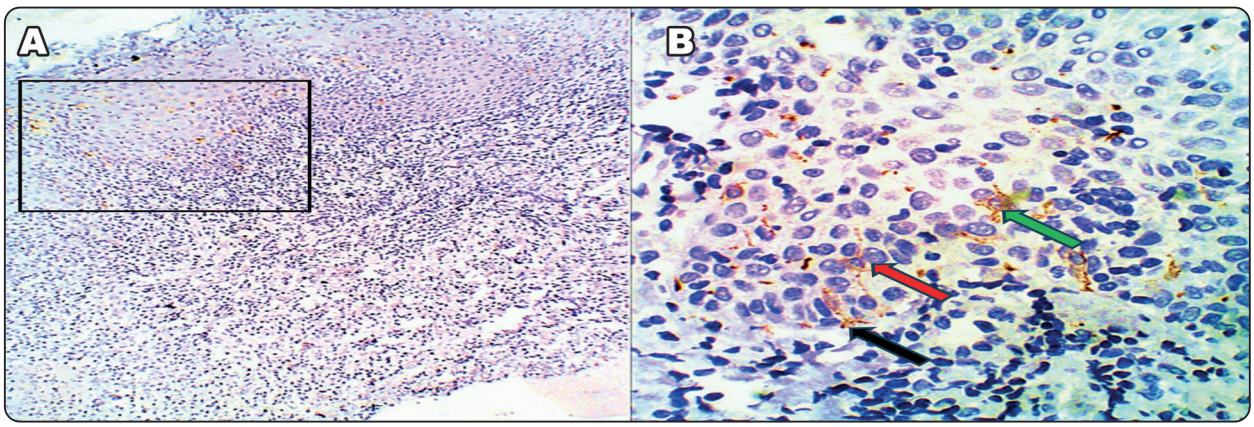

Fig. (3): Photomicrograph of erosive OLP with moderate OED revealed a weak expression of CD1a in LCs within the basal (black arrow) and suprabasal layers of the epithelium (red arrow) (note the dendritcs of LCs) (green arrow). A-(SAP-DAB X-200) B-(SAP-DAB X-400).

(37.5%) and reticular OLP (37.5%)**.** while 25% of them were plaque (12.5%) and atrophic OLP (12.5%) **(Table 2).** Interestingly, it was obvious that the epithelium positivity was more prominent than that of connective tissue stroma. Most of the stromal positivity of CD1a was presented as an intense expression for OLP among the DCs, where their dendritic processes were seen. There was no statistically significant difference between CD1a marker expression and clinical types of OLP in the studied OLP cases **(Figure 3).** Half of the CD1a intense expression was observed in OLP with mild OED in all studied OLPs. Meanwhile, OLP with severe OED was the least (12.5%). Interestingly, 53.8% of weak CD1a expression of OLP was observed with mild OED, while weak expression was absent among OLP with severe OED**.** There was no statistically significant difference between CD1a expression among the degrees of OED of the studied OLPs with weak correlation **(Table 3) and (Figure 4).**

Ki-67 expression in the studied normal oral mucosa and OLP cases

All the studied normal oral mucosa and OLPs revealed a brownish positive reaction for Ki-67. It had a nuclear reaction in basal cells of the covering epithelium and inflammatory cells in a lymphocytic band. Normal oral mucosa revealed nuclear reaction in the surface epithelium only in basal and suprabasal layers. **(Figure 5).** Low nuclear reaction in epithelial basal and suprabasal cell layers only was observed in 26.7% of studied OLPs and a few cases of them revealed very low nuclear reaction in connective tissue. Meanwhile, high nuclear expression was observed in epithelial basal and

suprabasal cell layers and inflammatory cells in 53.3% of studied OLP cases, and 62.5% of them were erosive OLP **(Table 4).** Moreover, all OLP with severe OED revealed a high Ki-67 expression of 12.5% at the basal, parabasal, and spinous layers of the epithelium, and sub-epithelial lymphocytes. There was no statistically significant difference between Ki-67 marker expression and clinical types of OLP in the studied OLP cases (**Figure 6**).

TABLE (3) Association between CD1a expression and degree of OED of the studied OLP.

Degree of OED among OLP	**CD1a**			Total N=30(%)	**P-value**
	Weak staining	Moderate staining	Intense staining		
Mild OED	**7(53.8%)**	4(44.4%)	**4(50%)**	**15(50%)**	**0.786**
Moderate OED	6(46.2%)	4(44.4%)	3(37.5%)	13(43.3%)	
Severe OED	**0**	1(11.1%)	**1(12.5%)**	2(6.7%)	
Total N=30(%)	13(43.3%)	9(30%)	8(26.7%)	30(100%)	

Data expressed as mean ±SD & frequency (N, %) SD: standard deviation, P: Probability, *: significance <0.05. The test used: One-way ANOVA for data expressed as mean ±SD & Monte-Carlo for data expressed as frequency (N, %).

TABLE (4) Association between Ki-67 expression and clinical types of studied OLP cases.

Clinical type	Ki-67			Total N=30 (%)	P
	Low-proliferation	Moderate proliferation	High-proliferation		
Erosive LP	5(62.5%)	4(66.7%)	**10(62.5%)**	19(63.3%)	0.3
Reticular LP	1(12.5%)	0(0%)	**5(31.3%)**	6(20%)	
Atrophic LP	2(25.0%)	1(16.7%)	0(0%)	3(10%)	
Plaque LP	0(0%)	1(16.7%)	1(6.3%)	2(6.7%)	
Total N=30 (%)	**8(26.7%)**	6(20%)	**16(53.3%)**	30(100%)	**0.0607**

Data expressed as frequency (N, %) P: Probability, *: significance <0.05 Test used: Monte-Carlo.

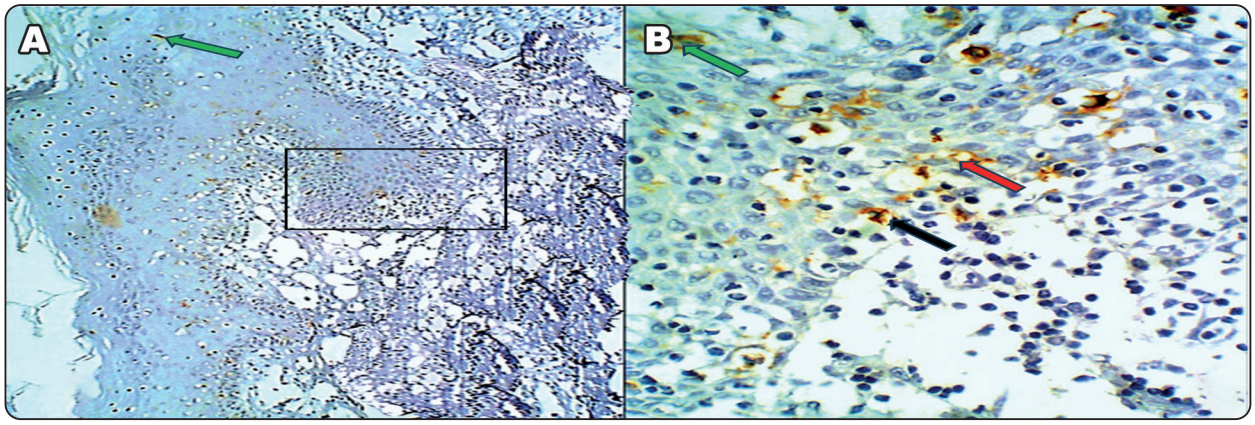

Fig. (4) Photomicrograph of reticular OLP with mild OED. A) Revealed moderate reaction of CD1a in LCs within the surface epithelium (within basal, (black arrow) suprabasal (red arrow) and mid-spinous layers of the epithelium (green arrow) (SAP-DAB X-200). B) Higher magnification showing CD1a positive LCs with dendritic processes within the basal layer (black arrow) suprabasal (red arrow) and mid-spinous layers of the epithelium (green arrow), while they were absent in the stroma (SAP-DAB X-400).

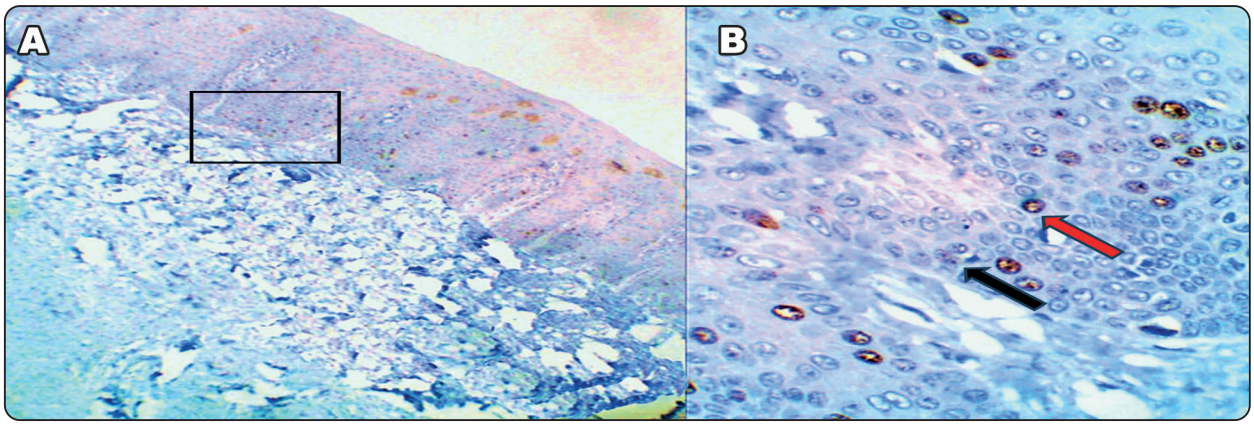

Fig. (5) Photomicrograph showing Ki-67 expression in normal oral mucosa seen in basal (black arrow) and parabasal layer (red arrow) A: (IHC stain, ×400), B: (IHC stain, ×400).

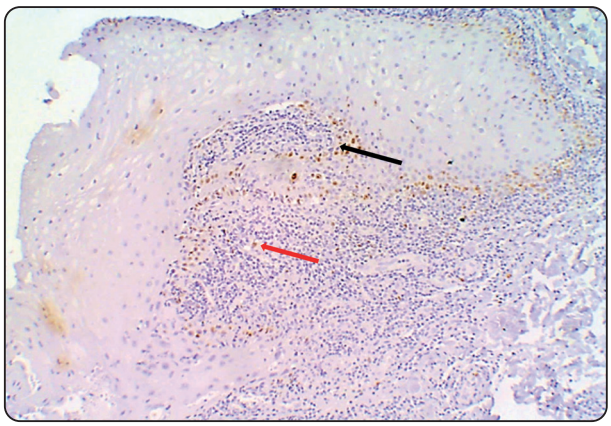

Fig. (6) Photomicrograph of erosive OLP with moderate OED showing high nuclear expression of Ki67 in basal cells of the surface epithelium of OLP (black arrow) and low expression in connective tissue (red arrow) (SAP-DAB X-100).

DISCUSSION

In the present study, the majority of the studied cases were adults (fourth and fifth decades of life) which was in agreement with ***Li, Changchang, et al.*** [17]. This could be attributed to long-standing oral habits and the oral mucosa undergoes age-related changes, [18] increasing the risk of OLP. Lastly, OLP may also be linked to denture wear, pharmaceutical use, dietary deficits, or weakened immunity. Regarding gender, contrary to many previous studies that documented that the prevalence of OLP was higher among women than among men, our results showed that there was a high propensity for males, and this is in contradiction with ***Munde et al.*** [19] who observed that the men outnumbered the women (ratio M: F = 1.61:1). Both the clinical appearance and lesion location results support findings that have already been published. Buccal mucosa had the highest frequency of occurrence at 53.3% which was in line with other studies by ***Parvini et al***. [20], and ***Mirmohammadi et al.*** [21]. OLP consists of various clinical forms. It has been believed that the atrophic, erosive, and ulcerative forms have a poor prognosis and predispose the mucosa to damage from carcinogenic agents [22-23]. In our study, the erosive type had the most common frequency (63.3%) among the studied OLPs, these findings were consistent with ***Agha-Hosseini et al.*** [24] and ***Kakar, et al.*** [25]. Oral epithelial dysplasia (OED) is a term used to describe a change in the appearance of the oral epithelium. It is characterized by abnormal epithelial maturation and increased cell proliferation. Concerning the degree of epithelial dysplasia, in this study, according to WHO criteria, it was observed that all studied cases had criteria of dysplasia. They were classified as 50% were mild OED, 43.3% were moderate OED, and 6.7% of all OLP were severe OED, which was in harmony with ***Marques et al.*** [26]. Interestingly, in all studies OLPs, mitotic figures, and nuclear and cellular pleomorphism,

were the most common signs of OED. This result came also in agreement with ***Odukoya et al.*** [27] who studied epithelial dysplasia in OLP and reported nuclear hyperchromatism in 15% and an increased number of mitotic figures in 11%. However, some studies have reported a lack of dysplastic features but report the presence of other features such as hyperplasia, hyperkeratosis, acanthosis, and the presence of necrotic keratinocytes[28]. Epstein et al stated that the presence of dysplasia in OLP increases the risk of malignant transformation, mandating management and close follow-up[29]. The presence of LCs both immature and mature forms and their expression in the epithelium of OLP has been widely investigated after the advent of immunohistochemistry. The immature LCs in oral mucosa express CD1a molecules more than any other CD1 isoforms, which are highly capable of presenting various types of microbial lipids and self-antigens to T-cells. Hence the dysregulation of LC activity can be an impact factor in the pathogenic mechanism of OLP [30]. The present study showed that in normal oral mucosa the CD1a stained LCs were abundantly seen in the epithelium just above the basal cell layer while in connective tissue the cells were sparse. Our results are in accordance with a study which reported the same results [31]. This highlights the known fact that the LCs are immune sentinels present more in normal epithelium and are always ready for antigen capture. Our study revealed, intense expression (26.7%) of, CD1a for OLP among both epithelium and connective tissue stroma compared to control normal mucosa which revealed a very weak CD1a expression presented as LCs with dendritic processes distributed only at the epithelium's basal, suprabasal, and mid-spinous layers. These results were in a line with another author who identified an increased number of CD1a+ LCs in the epithelium and submucosa of patients with OLP compared to LPL and the previously reported numbers for healthy oral mucosa [32]. It has been suggested that the increased number of LCs in the epithelium of OLP lesions is due to the capture of an unidentified antigen, leading to the mobilization of numerous LCs to the site, which in turn prevents, to some extent, the destruction of the epithelium in OLP[31]. Meanwhile, the presence of CD1a+ LCs in the connective tissue may be explained by the fact that after antigen capture, the activated LCs, in an intermediate stage of maturation, migrate to the regional lymph nodes and present captured antigens to T cells[33]. Currently, there was no statistically significant difference between CD1a expression among studied OLPs and it was obvious that the epithelium positivity was more prominent than that of connective tissue stroma. Most of the stromal positivity of CD1a was presented as an intense expression for OLP among the DCs, where their dendritic processes were seen. Similar findings have been reported by many other authors also who reported a higher number of Langerhans cells on the intraepithelial areas than to subepithelial areas[34]. Overexpression of Ki-67 indicates active cell proliferation [35]. In our study, higher expression of Ki-67 was found in erosive OLP at 62.5%, which was in line with other studies by ***Gholizadeh et al.***[36]. Moreover, all OLP with severe OED revealed a high Ki-67 expression of 12.5% at the basal, parabasal, and spinous layers of the epithelium, and sub-epithelial lymphocytes. This was consistent with the results of ***Kitayoshi et al.*** [37] and ***Takkem et al.*** [38] who found that Ki-67 expression increases significantly with an increasing dysplasia grade.

CONCLUSION

The increase in Langerhans cells in OLP suggests a possible significant role of the adaptive immune response in OLP pathogenesis. Elevated ki-67 expression in erosive OLP with severe OED may indicate more uncontrollable proliferation of this type, and it may also be used as a marker for the degree of epithelial dysplasia and increased premalignancy risk.

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