Original Article

Evaluation of the Immunohistochemical Expression of iNOS in Oral Lichen Planus

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Abstract

Background: Oral lichen planus (OLP) is a chronic inflammatory disease with an unknown etiology. Because the evolution of OLP was influenced by a wide range of external and internal stimuli, it was crucial to study the expression of inducible nitric oxide synthase (iNOS) in OLP because of the known role of a wide variety of exogenous agents in exacerbating OLP's onset. **Objectives:** To evaluate the immunohistochemical expression of iNOS and study its association with clinicopathological findings in OLP patients. **Materials and Methods:** This study was a retrospective analysis of 40 formalin-fixed paraffin-embedded tissue blocks of OLP that were detected and categorized as either reticular or erosive. For immunohistochemistry staining, a monoclonal antibody iNOS was utilized. Semiquantitative techniques were used to analyze the patterns of positively stained cells. **Results:** Forty biopsies from 24 female and 16 male OLP patients were included. The mean age was 49.15 ± 11.39 years. Using an immunohistochemical method, the results of the iNOS marker in this study showed that 18 (45%) cases had no staining, whereas 22 (55%) cases were positive. Regarding the density of iNOS marker expression, 50% of the cases had a score of 0, and 50% of the cases were positive, with a median final score index of 2, ranging between 0 and 5. **Conclusions:** Inducible nitric oxide is expressed in about 55% of OLP samples, which may, in turn, provide insight into the OLP's pathogenesis.

Keywords: Inducible nitric oxide, nitric oxide, oral lichen planus

Introduction

Oral lichen planus (OLP) is the most widespread noninfectious oral mucosal disease, affecting 1%–2% of the whole adult people. It often affects women at a ratio of about 1.4:1 more often than men. It predominantly affects adults over 40 years old; however, young adults and children can also be affected.[1] It is considered a chronic disease and necessitates long-term treatment and clinical monitoring. The etiology of OLP is not fully clear. According to most scientists, OLP disease was induced by a complicated mix of external and internal factors, and T-cells were activated to generate a characteristic lymphocyte-rich band. Following that, colonization lymphocytes may stimulate keratinocyte differentiation and apoptosis, influencing the clinical presentation of OLP patients.[2] Oral lesions have been reported to have distinct clinical and histological features and characteristic distributions.[3,4] OLP histopathological features include basal cell layer liquefaction with keratinocyte apoptosis, dense band-like lymphatic infiltration between epithelium and connective tissue, and focal areas of hyperkeratinized epithelium (that causes the clinically apparent Wickham's striae); disparate regions of the atrophic epithelium with shortened and pointed rete pegs.[5,6]

Emphasis has been placed on the importance of autoimmunity in the pathogenesis of OLP. The onset of this autoimmune-mediated response may be affected by various factors, both external and internal stimuli. Therefore, it was necessary to study the probable function of inducible nitric oxide (NO) synthase (iNOS) expression and activity as a contributor, because increased oxidative

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stress may play a role in the incidence and progression of OLP lesions.[7]

NO is a reactive nitrogen-free radical and signaling molecule created by NO synthase (NOS) isoenzymes. The neural NOS and endothelial NOS are expressed constitutively. In contrast, the inducible isoform or iNOS is expressed in response to cytokines such as interleukin-1, interferon-g (IFN-g), and tumor necrosis factor-alpha (TNF-α). It is activated by lipopolysaccharide and represented by various cell types, including macrophages, T-cells (excluding T-helper-2 cells), and natural killer cells.[8]

The iNOS generates a continuing elevated NO level in tissues, which persists for an extended duration. NO has both protective and destructive properties. Low (physiological) concentrations of NO influence blood flow, immune functions, and platelet aggregation, whereas excessive concentrations are linked to pain, atherosclerosis, cancer, and inflammatory and immunological conditions. NO, which the isoenzyme NOS2 or iNOS generates, has been related to the etiology and pathophysiology of several disorders due to its oxidative, inflammatory, and immunological characteristics.[7]

OLP is a relatively common disorder with suspected multifactorial etiology and immunopathogenesis involving various cells, including T-cells.[8,9] It is yet unclear how the NOS enzyme contributes to pathogenic processes in the oral cavity. The purpose of this study was to investigate how the development of OLP affected the expression of the iNOS isoforms.

Materials and Methods

Study design

Paraffin-embedded tissue blocks were used for this retrospective study with related histopathological information for 40 confirmed OLP cases between 2012 and 2020.

Study samples

The study samples were obtained from the Oral Pathology Laboratory, College of Dentistry, University of Baghdad. Age, gender, and sites were extracted from the related case reports.

Sample processing

Two sections of 4-µm thickness were cut from each block and loaded onto microscopic charge slides. To reassess the OLP histopathological profile and ensure adequate tissue is available, hematoxylin and eosin were used to stain one slide from each case. The immunohistochemistry (IHC) analysis was performed on the remaining slide.

Histopathologic evaluation of inflammation

Two pathologists examined the OLP cases' microscopic slides subjectively to assess the degree of inflammation according to the amount of lymphocytic infiltration. For semiquantitative analysis of inflammation, cases were divided into one of three categories:

Score (+), mild inflammation

Score (+++), moderate inflammation

Score (+++), intense inflammation.[10,11]

Immunohistochemically, deparaffinization, rehydration, antigen retrieval, endogenous peroxidase blocking, and the addition of primary and secondary antibodies to the slides were all steps in the IHC procedure. The primary antibody used in this study was the monoclonal antibody iNOS (E-AB-70051, diluted 1:50), which was bought from Elabscience Biotechnology, Wuhan, China. A detection kit from Cambridge, UK, with the catalog number ab80436 was used.

The scoring system

Using a light microscope at 400× magnification, two pathologists independently examined five random fields from each section to determine IHC expression. The scoring system for iNOS was based on the intensity of staining and the percentage of positive epithelial cells. Thus, protein expression was scored semiquantitatively. Each case was scored by adding staining intensity (viewed at 20×) to the stained area (at a magnification of 4×). The scale of staining was as follows: 0, no staining; 1+, mild staining; 2+, moderate staining; and 3+, intense staining, and the mean positive epithelial cells percentage was classified as follows: 0 (negative), when positive cells <10%; score 1+, when positive cells were >10% but <20%; score 2+, positive cells were >20% but <50%; and score 3+, when positive cells >50% of total cells.[8,9]

Ethical approval

The Ethics Committee, College of Dentistry, University of Baghdad, gave ethical approval for this study. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number (Ref # 272, date: March 25, 2021) to get this approval.

Results

The results showed that the mean age ± standard deviation of the 40 cases of patients with OLP was 49.15 ± 11.39 years, ranging from 28 to 69 years, and the ratio of males to females was 1:1.5 [Table 1]. The clinical manifestation of the patients evaluated revealed that 21 (52.5%) had the erosive type of OLP and 19 (47.5%) had the reticular type, as shown in Table 1.

Regarding the observed distribution of sites, about two-thirds of the analyzed cases with OLP were present in the buccal mucosa site, accounting for 30 (75%) cases. In contrast, the other cases were scattered in modest numbers, as depicted in Figure 1.

When categorizing OLP cases, the histological evaluation of inflammation was considered. The inflammatory score in this study was score + in 11 (27.5%) cases, score ++ in 14 (35.0%) cases, and score +++ in 15 (37.5%) cases, as shown in Figures 2 and 3.

Evaluation of IHC expression of iNOS

When the expression of the iNOS intensity in the OLP was assessed by IHC, the results showed that 18 (45%) cases had no staining, whereas 22 (55%) cases were positive. The positive stains were distributed as follows: mild staining (1+) was shown in 11 (27.5%) cases and moderate staining (2+) appeared in 11 (27.5%) cases.

Regarding the density of iNOS marker expression, 20 (50%) cases had a score of 0, 8 (20%) cases had a score of 1+, and 6 (15%) cases had a score of 2+, with the same percentage for score 3+, with a median final score index of 2, ranging between 0 and 5 [Table 2 and Figures 4–7].

Table 1: Demographic findings of studied cases

Demographic character		Number (%)
Age (years)		
<40		7 (17.5)
40–49		13 (32.5)
50–59		10 (25.0)
≥60		10 (25.0)
Mean ± SD		49.15 ± 11.39
Range		(28–69)
Gender		
Male	16 (40.0)	Mean ± SD (45.81 ± 10.41)
Female	24 (60.0)	Mean ± SD (51.37 ± 11.68)
Total	40	(100.0)
Male-to-female ratio		1:1.5
Clinical presentation		
Clinical type		
Erosive		21 (52.5)
Reticular		19 (47.5)
Total		40 (100)

SD: standard deviation

The relation of the iNOS marker expression with clinicopathological findings

Although the mean rank of the total iNOS marker was greater among the samples of males and with an erosive type and a histopathology assessment score of +++ than among the samples of females with a reticular type and a score of + and++, the mean rank for the final score index did not reveal any statistically significant differences with demographic, histopathology assessment and clinical presentation of disease ($P > 0.05$) [Table 3].

Discussion

The patients in this research with OLP ranged from 28 to 69 years old. A wide variety of median ages have been found in prior epidemiological investigations. In general, age, gender, and clinical presentation are all elements to consider when it comes to epidemiological characteristics. As a result of the limited quantity and type of research, conflicting findings between studies may be held responsible for the current study and some of the others that are not epidemiological.

Assessment of iNOS immunohistochemical expression

Earlier studies acknowledged the possible role of NO production by iNOS in OLP's etiology and pathophysiology.[8,10,12-14]

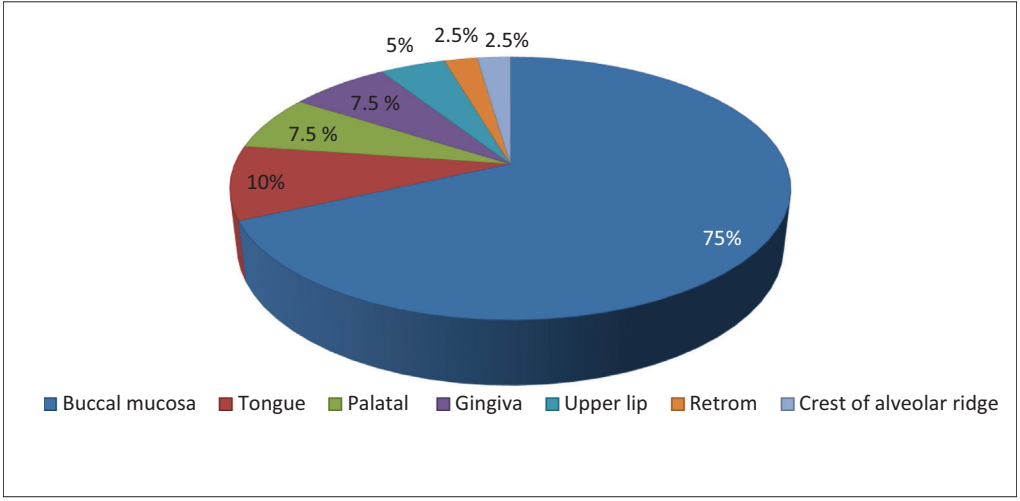

Figure 1: Sites of lichen planus in the oral cavity

The current study's findings are comparable to prior investigations that analyzed iNOS in cutaneous or OLP biopsies or salivary samples to measure NO byproduct.

Free radicals may influence the incidence and progression of OLP disease and increase oxidative stress, which exacerbates inflammatory responses with the entry of T-cells and degrades the lipid membrane of keratinocytes.[15-18] NO is a highly reactive free radical.[19]

Once evaluating positive iNOS in the included studied cases, the results demonstrated that this study's positive IHC expression was recorded in 22 of 40 cases (55%), consistent with the earlier findings,[9] which showed iNOS expression in 26 of 30 (86.5%) cases in basal and parabasal cells of the epithelium in OLP and subepithelial inflammatory cells.

Mastrangelo *et al*.[20] showed a significant rise of iNOS in OLP samples and suggested that NO generated by enhanced iNOS expression may contribute to the pathophysiology of OLP immunologically.

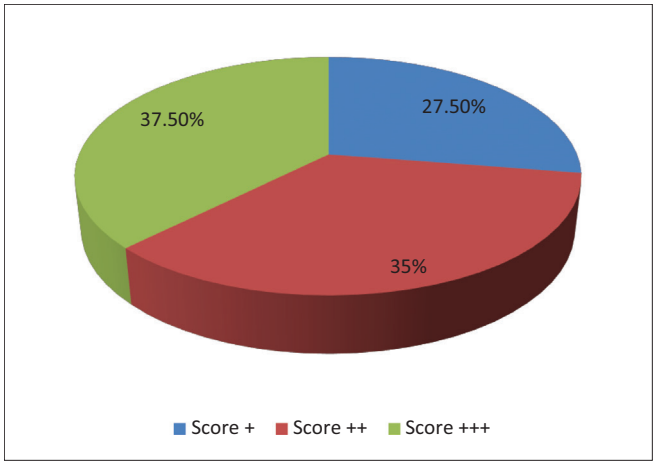

Figure 2: The score of histopathologic evaluation of inflammation

The results of this study, in comparison with the results based on the majority of prior research that estimated the NO byproduct in the saliva of individuals with cutaneous or OLP using ELISA, in an attempt to discover a possible association between NO and OLP rather than IHC. The increased NO in saliva may cause oxidative stress on reactive nitrogen species by boosting oxidant production and lowering antioxidant defense, therefore indirectly relating to OLP.[21-23] Salivary NO byproducts were measured in patients with OLP, and researchers Ohashi *et al*.[13] found that NO levels were considerably elevated in these individuals.

Mehdipour *et al*.[23] supported the presumption that elevated serum levels of NO in patients with OLP could stimulate the processes of lymphocytes and the cellular immune system, confirming the role of serum NO in the genesis of *Lichen planus*. Sezer *et al*.[24] and Aly and Shahin[25] found a considerable rise in NO in cutaneous lichen planus.

The current study's conclusions differ from those of a previous study by Brennan *et al*.,[9] in which the iNOS was investigated in 30 patients with oral reticular lichen planus using immunohistochemistry.

Table 2: Expression of iNOS marker among studied cases

Expression of iNOS	Number (%)
Intensity	
0, no staining	18 (45.0)
1+, mild staining	11 (27.5)
2+, moderate staining	11 (27.5)
Density	
Score 0	20 (50.0)
Score 1+	8 (20.0)
Score 2+	6 (15.0)
Score 3 +	6 (15.0)
Final score index	Median = 2
	Ranging between 0 and 5

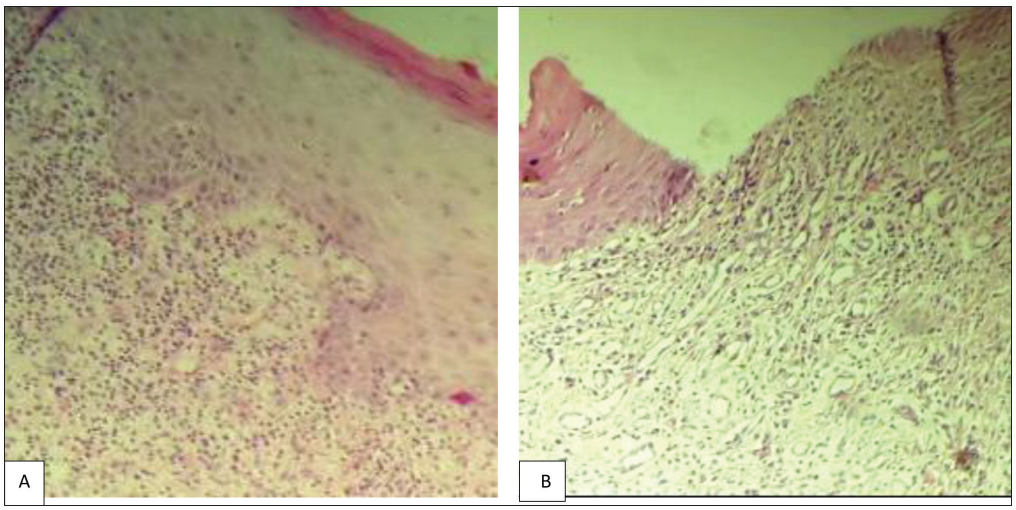

Figure 3: Histopathology of OLP. (A) Reticular oral lichen planus with intense inflammation score (+++) (parakeratinization) (200×). (B) Ulcerative erosive lichen planus with moderate inflammation (++) (200×)

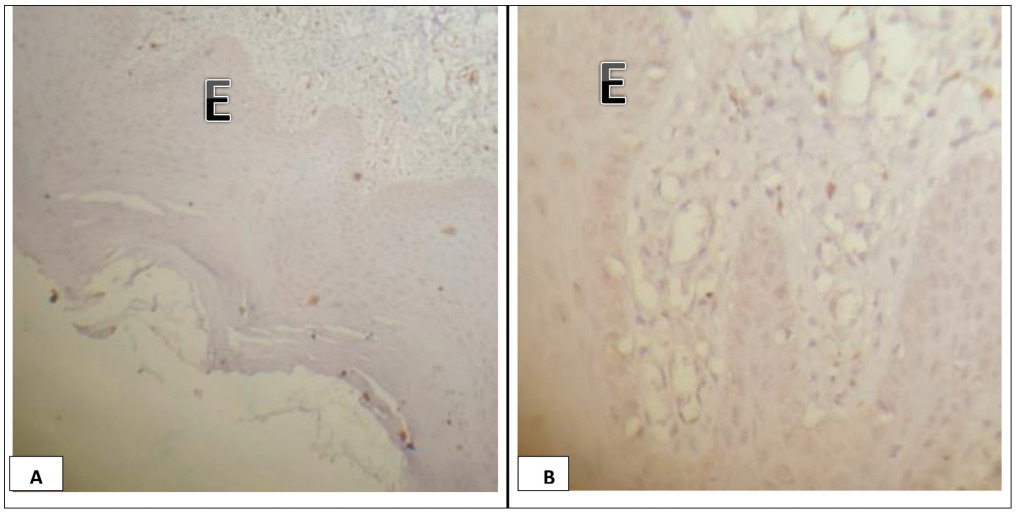

Figure 4: Immunohistochemical expression of the iNOS marker in OLP cases. (A) iNOS was demonstrated in epithelial cells (E) (with mild staining) (100×). (B) High-power view of the previous section (400×)

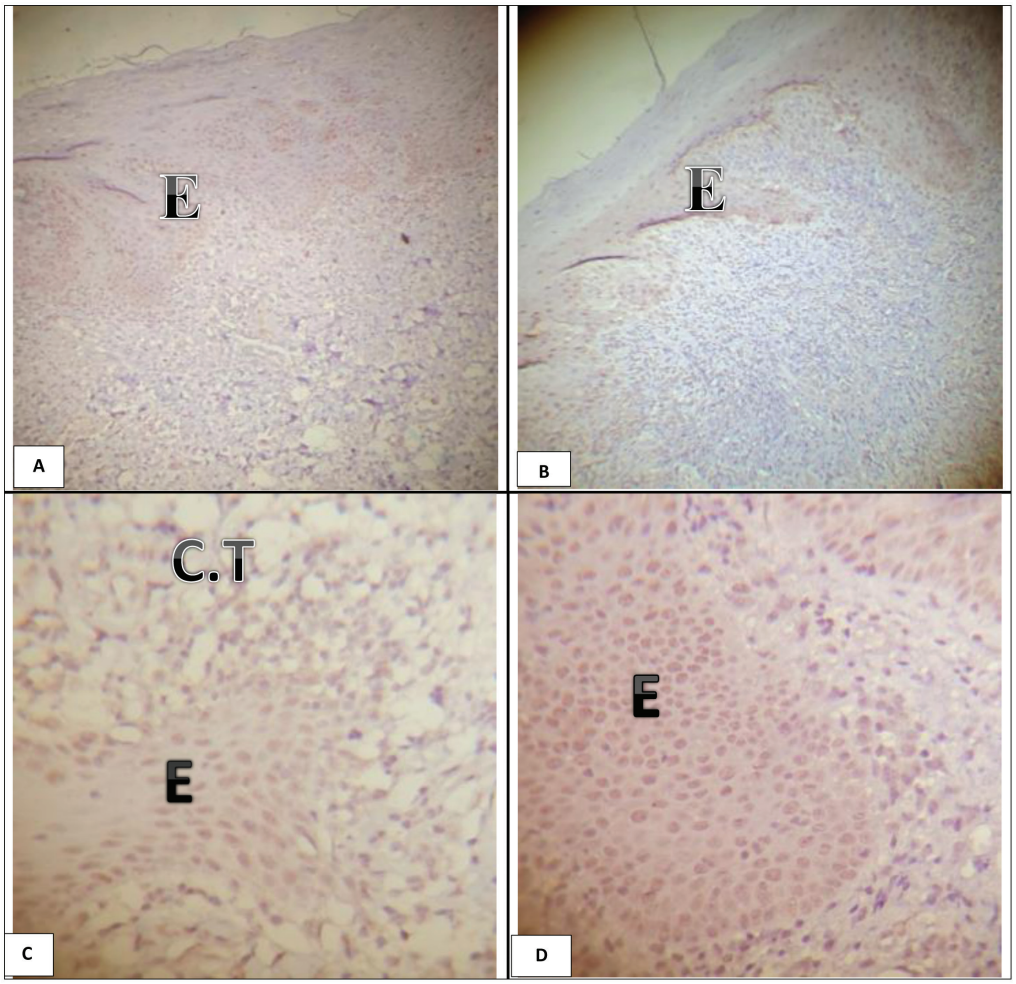

Figure 5: Immunohistochemical expression of the iNOS marker in OLP cases. (A and B) iNOS was demonstrated in epithelial cells (E) (with moderate staining) (100×). (C and D) High-power view of the previous section (400×)

Brennan *et al.*[9] stated that most OLP cases in their study do not express iNOS, and only 9 cases of 30 (5%) of cells with mild intensity were observed. The dissimilarity in the results is because, in this study and Metwaly *et al.*'s[10] study, examples of reticular and erosive lichen planus were analyzed. Still, in Brennan *et al.*'s[8] research, only reticular

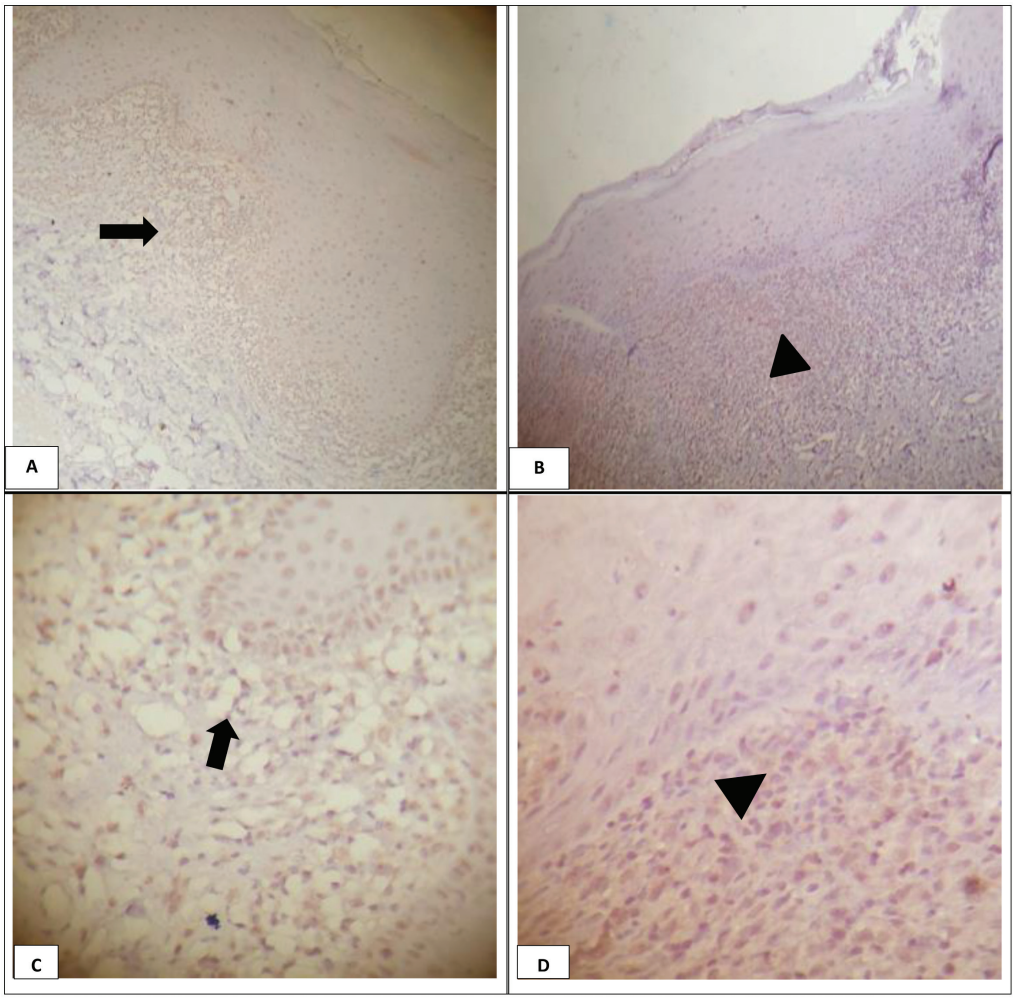

Figure 6: Immunohistochemical expression of the iNOS marker in OLP cases. (A and B) The iNOS was established in endothelial cells (arrow) and inflammatory cells (head arrow) of the subepithelial stromal space at (100×) (with moderate staining). (C and D) High-power view of the previous section (400×)

lichen planus cases were evaluated. Differences in the examined populations may have caused these different results. Differences in the examined populations may have caused these different results.

This study found negative IHC expression in 18 of 40 cases (45%), a percentage that cannot be ignored. The reason may be attributed to anti-inflammatory cytokines (IL-4 and IL-10) released by T-helper 2 cells and which diminish iNOS activation,[26,27] so more research is needed to investigate the role of T-helper 2 cells in OLP. Specific cytokine receptors such as TNF-α act as proinflammatory cytokine inhibitors,[26-28] and the small percentage of IFN-g-positive cells (about 1%) seen in OLP may reduce the expression of iNOS.[9] Administering exogenous anti-inflammatory cytokines, such as IL-10, may weaken NO production.[29]

This study also acknowledged the expression of iNOS in subepithelial inflammatory cells and endothelial cells of blood vessels, which is in agreement with the prior reports[10,30-33] detailed that endothelial cells, fibroblasts, and keratinocytes are nonimmune cells that can produce iNOS, in addition to numerous types of immune cells.

The relation of the iNOS marker (concerning the final score index) with clinicopathological findings

Despite the iNOS marker not being gender-associated, the mean rank for the total iNOS marker was lower in OLP cases, with a female ranking at 18.66, whereas in a male, the mean rank for the total iNOS marker was 21.73.

Ide *et al.*[34] established that men were subject to more oxidative stress than women.

Kander *et al.*[35] suggested that females are more resistant to oxidative damage. This may result from the antioxidant effects of estrogen and gender variations in nicotinamide adenine dinucleotide phosphate oxidase activity, whereas Wiener *et al.*[36] found that women are more susceptible to oxidative stress than men.

Regarding clinical categories, comparisons were made between OLP samples with erosive and reticular OLP.

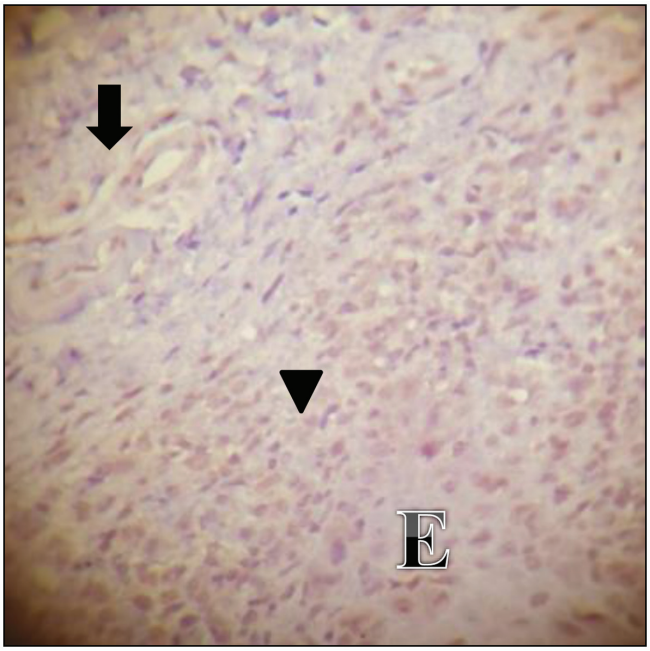

Figure 7: Immunohistochemical expression of the iNOS marker in OLP cases was recognized in epithelial cells (E), endothelial cells (arrow), and inflammatory cells (head arrow) of the subepithelial stromal space at (400×) (with moderate staining)

Table 3: Relation of iNOS expression with demographic, clinical presentation, and inflammatory score

Variable	Final score index for iNOS[a]	*P* value
	Mean rank	
Age in years		
<50	18.7	0.305
≥50	22.2	
Gender		
Male	21.73	0.385
Female	18.66	
Clinical type		
Erosive	22.32	0.31
Reticular	18.8	
Inflammatory score		
Score +	19.2	0.28
Score ++	18.3	
Score +++	24.9	

[a]Mann–Whitney U test.
Significant, $P \leq 0.05$

Despite this study not finding any significant difference in the expression of iNOS between OLP groups, the mean rank for the total iNOS marker was lower in samples with the reticular type of OLP than the erosive OLP type; this was in agreement with Jana *et al.*,[37] who demonstrated that the OLP-reticular form of OLP is less severe in terms of oxidative stress, inflammation, and DNA damage than the erosive form.

An evaluation of the inflammation using histopathology did not reveal any significant differences in the mean rank of the final score of the iNOS index. However, it is more frequent when the inflammatory score is +++.

This result is consistent with that reported by Zamora *et al.*,[30] who established that the iNOS enzyme is principally responsible for the functions of NO in inflammatory processes. NO has emerged as a significant modulator of inflammation. Therefore, antioxidant therapies may be an option in managing OLP patients.

Conclusion

The present study confirms previous findings and contributes additional evidence and highlights the significance of the current study that revealed that inducible NO is present in about 55% of OLP samples, which may provide insight into the OLP's pathogenesis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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