ORIGINAL RESEARCH

Differential COX-2 Expression in Erosive and Reticular Oral Lichen Planus Compared to Normal Oral Mucosa. An Analytical Study

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Abstract

Background: Oral Lichen Planus (OLP) is a chronic, T-cell–mediated inflammatory disease with recognized malignant potential. Cyclooxygenase-2 (COX-2), a key pro-inflammatory enzyme, has been implicated in the immunopathogenesis of several oral lesions. This study aimed to evaluate and compare COX-2 expression in erosive and reticular subtypes of OLP versus normal oral mucosa using immunohistochemistry.

Methods: A total of 60 formalin-fixed, paraffin-embedded tissue samples (20 per group: erosive OLP, reticular OLP, and normal mucosa) were subjected to immunohistochemical staining with anti–COX-2 antibody. Expression was assessed using a semi-quantitative scoring system based on staining intensity and percentage of positive cells. Statistical analysis was performed using Chi-square test (SPSS v22).

Results: The majority of OLP lesions were located on the buccal mucosa (95%), predominantly affecting females aged 50–59 years. Erosive OLP exhibited significantly higher COX-2 expression (moderate to strong) compared to reticular OLP, which showed predominantly mild expression ($p = 0.016$). Although inflammatory cell staining was more prominent in erosive OLP, the difference was not statistically significant. In contrast, 90% of normal oral mucosa samples were COX-2 negative, showing a highly significant difference compared to OLP groups ($p < 0.001$).

Conclusions: COX-2 expression is markedly upregulated in OLP, particularly in the erosive subtype, while absent in normal oral mucosa. Immunohistochemical evaluation of COX-2 may serve as a valuable prognostic tool and assist in identifying OLP patients at greater risk for malignant transformation, supporting more rigorous clinical surveillance.

Key Words: Oral Lichen Planus, Cyclooxygenase 2, Tumor Biomarker, Risk Assessment

Introduction

Oral Lichen Planus (OLP) is a chronic, immunologically-mediated inflammatory disorder, characterized by T cell–mediated autoimmune mechanisms.[1] In this condition, cytotoxic $CD8^+$ T lymphocytes induce apoptosis of basal keratinocytes, leading to the characteristic clinical manifestations.[1] A recent systematic review and meta-analysis reported a global pooled prevalence of OLP at 1.01%, with significant regional variations.[2] Europe exhibited the highest prevalence at 1.43%, while India reported the lowest at 0.49%. The reduced prevalence in India may be attributed to the masking effect of tobacco-associated keratosis, which complicates the clinical diagnosis of OLP.[2]

OLP predominantly affects middle-aged adults, with a significant increase in prevalence observed from the age of 40 years. The condition exhibits a female predominance, with a female-to-male ratio of 2:1.[2] Clinically, OLP manifests with a range of white and red lesions, typically in a bilaterally symmetrical distribution. White lesions may present as reticular, papular, or plaque-like patterns, whereas red lesions may appear atrophic (erythematous), erosive (ulcerated), or, less commonly, bullous. Mixed clinical subtypes are commonly observed.[2,3]

Given its chronic nature and potential for malignant transformation, OLP is classified by the World Health Organization (WHO) as a potentially malignant disorder.[4]

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This classification underscores the necessity for vigilant clinical monitoring and appropriate management.[5] Biomarker validation is a pivotal step in advancing newly discovered biomarkers toward clinical implementation.

Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in inflammation and immunopathology. Overexpression of COX-2 has been observed in OLP lesions, suggesting a role in the disease's pathogenesis and its potential utility as a biomarker for malignant transformation.[5,6] Moreover, increased COX-2 expression has already been established in other oral potentially malignant and malignant disorders, further supporting its relevance in oral carcinogenesis.[7,8]

Although prior studies have investigated COX-2 expression in OLP, inconsistencies remain in its expression patterns among clinical subtypes of oral lichen planus (OLP), such as reticular, erosive, and atrophic forms—each showing varying degrees of dysplasia and malignant potential. Erosive OLP, in particular, is associated with a higher risk of malignant transformation, underscoring the need to explore COX-2 expression across subtypes.

The limited understanding of COX-2 expression across clinical subtypes of OLP highlights the need for further research into its diagnostic and prognostic relevance within this condition. To address this gap, the present study evaluates and compares COX-2 expression and staining intensity in epithelial and inflammatory cells among clinically normal oral mucosa, erosive OLP, and reticular OLP. By identifying subtype-specific patterns, the study aims to clarify COX-2's role in OLP immunopathology and assess its potential as a biomarker for early malignant transformation, thereby contributing improved prognostication and targeted clinical surveillance.

Materials and Methods

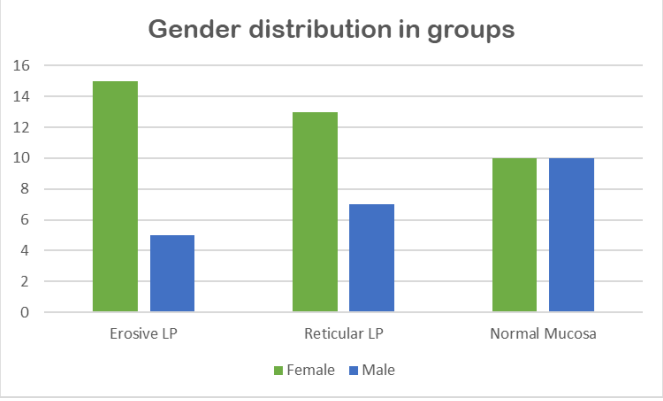
A retrospective study was conducted at Mar Baselios Dental College, Kothamangalam, Kerala, focusing on the clinicopathological evaluation of OLP. Institutional ethical clearance and a waiver of informed consent were obtained for this study. The study utilized 60 formalin-fixed, paraffin-embedded tissue blocks comprising clinicopathologically diagnosed cases of erosive lichen planus (Group I, n = 20), reticular lichen planus (Group II, n = 20), and 20 cases of clinically normal appearing mucosa as the control group.

Group I comprised cases with white striations and erythematous areas featuring ulceration and atrophy, all histologically confirmed as lichen planus. Group II included cases with white striations only—no red areas, ulceration, or atrophy—but also confirmed histologically as lichen planus. Ten tissue blocks of clinically normal oral mucosa (NOM) were obtained from gingival and vestibular sites following impacted tooth extractions; these were evaluated and deemed normal with only minimal inflammation. Exclusion criteria included prior OLP treatment, amalgam restorations, tobacco use, medications associated with lichenoid reactions, systemic disease or medically compromised status, and harmful oral habits.

All paraffin-embedded tissue blocks were sectioned at 3 µm and underwent heat-induced epitope retrieval using a domestic stainless-steel pressure cooker with citrate buffer (pH 6.0). Sections were then incubated for 1 hour at room temperature with monoclonal anti–COX-2 (clone SP21; 10–15 µg/mL) and stained using the Super Sensitive Polymer HRP Detection Kit. Color development was achieved with 3,3′-diaminobenzidine (DAB), producing a brown precipitate at antigen sites.

All slides were examined under 40× magnification. COX-2 immunoreactivity was indicated by any granular or diffuse brown cytoplasmic staining, regardless of intensity. Three random high-power fields in the lesional tissue were selected. Cell positivity was scored as: 0 = none; 1 = 20–40%; 2 = 40–60%; 3 = > 60%. Staining intensity was graded: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The sum of percentage and intensity scores in both epithelium and connective tissue yielded totals categorized as mild (1–3), moderate (4–7), or severe (8–12)

Statistical analysis was performed using SPSS version 22 to evaluate the association between erosive lichen planus, reticular lichen planus, and normal oral mucosa in terms of epithelial and inflammatory cell expression and staining intensity. The Chi-square test was employed for this analysis.

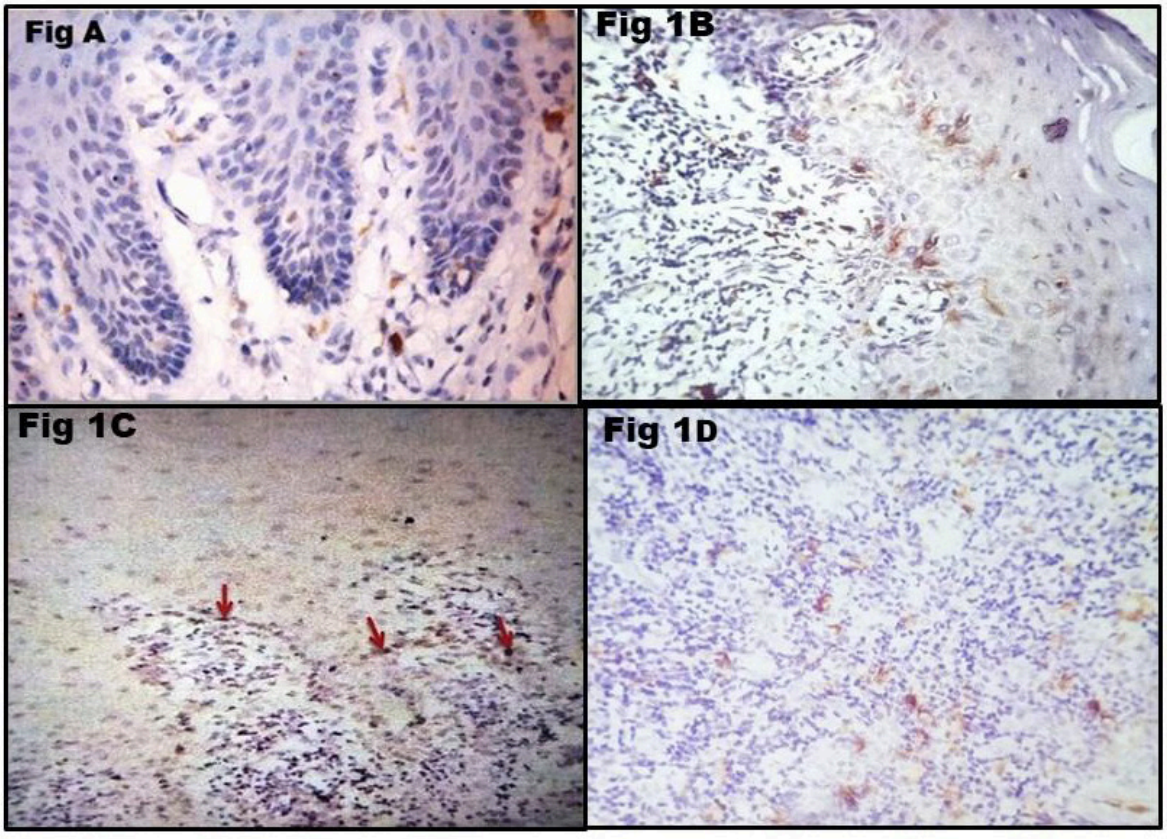


Graph shows gender distribution of study groups

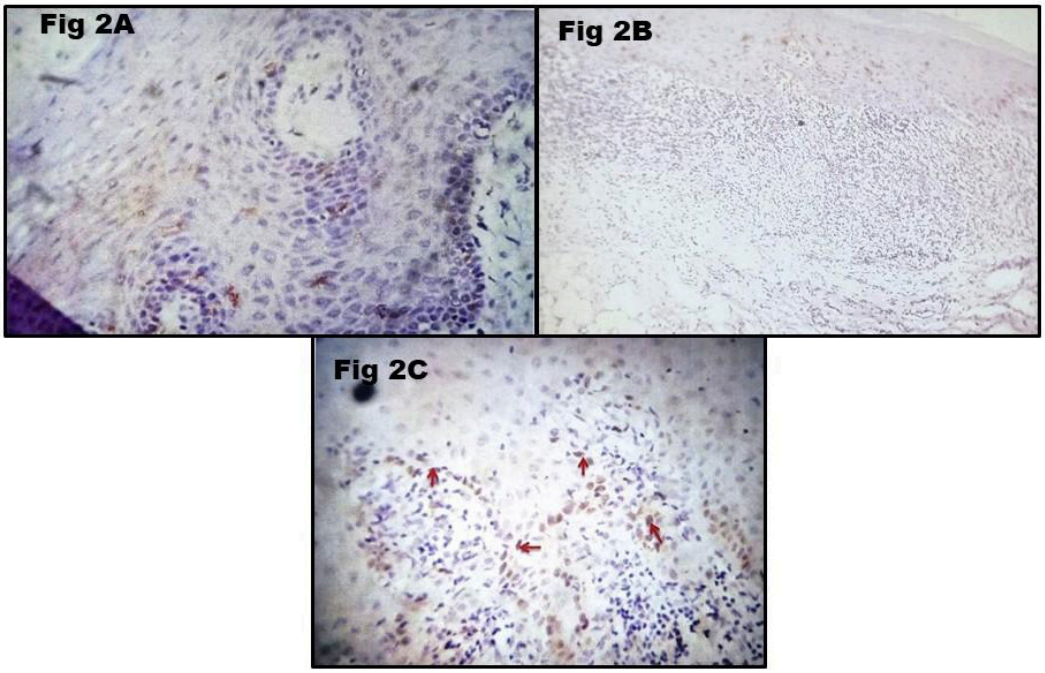
Results

Approximately 95% of lesions in all study groups were localized to the buccal mucosa, the most commonly affected intraoral site. The majority of cases—both reticular and erosive lichen planus—occurred in elderly females, predominantly aged between 50 and 59 years. (Graph I) Clinically, a burning sensation was the primary symptom in 68% of patients with erosive oral lichen planus, compared to just 32% of those with the reticular subtype.

COX-2 immunoreactivity appeared as granular to diffuse brown cytoplasmic staining in both epithelial and inflammatory cells in erosive and reticular OLP specimens (Fig. A–D and Fig. 2A–C, respectively). In erosive OLP, mild, moderate, and severe COX-2 expression patterns were observed in the epithelium and inflammatory infiltrate (Fig. A–D). Similarly, reticular OLP demonstrated varying degrees



Photomicrograph showing COX 2 expressions in Erosive OLP **Fig A:** Mild Expression IHC X 400; **Fig B:** Moderate Expression IHC x 400; **Fig C:** Severe Expression IHC x 400; **Fig D:** Inflammatory Cells expression in Erosive OLP IHC x 100.



Photomicrograph showing COX 2 expressions in Reticular OLP **Fig 2A** Mild Expression IHC x 400 **Fig 2B** Moderate Expression IHC X 100; **Fig 2C** Severe Expression IHC x 400

of COX-2 immunoreactivity ranging from mild to severe staining (Fig. 2A–C). Erosive lesions exhibited a significantly higher prevalence of moderate-to-severe COX-2 expression compared to the predominantly mild staining observed in reticular lesions. Epithelial COX-2 expression differed significantly across study groups ($p = 0.016$). In contrast, 90% of control tissues demonstrated no detectable COX-2 expression, representing a statistically significant difference from OLP groups ($p < 0.001$).

Although no statistically significant difference was observed, erosive OLP showed a trend toward higher COX-2 expression in inflammatory cells compared to reticular OLP. This suggests a potential role of COX-2 in the inflammatory milieu of erosive lesions. However, the lack of statistical significance warrants further investigation with larger sample sizes to conclusively determine the relationship between COX-2 expression in inflammatory cells and the clinical subtypes of OLP.

Discussion

Oral lichen planus (OLP) is a chronic inflammatory autoimmune condition characterized by T lymphocyte-mediated cytotoxicity against basal keratinocytes of the oral epithelium. This immune-driven epithelial damage underpins the clinical manifestations of OLP and is central to its pathogenesis.[1] Epidemiological studies have consistently reported a higher prevalence of OLP in females, a trend mirrored in our study also.

Clinically, OLP presents in several forms, ranging from asymptomatic reticular white striations to symptomatic erosive or ulcerative lesions.[3] Even in the absence of overt ulceration, patients often report discomfort, particularly a burning sensation exacerbated by spicy or acidic foods. In our study, this symptom was reported by 62% of patients with erosive OLP and 38% with the reticular subtype, highlighting a correlation between clinical severity and patient-reported symptoms.

Of particular concern is the erosive variant of Oral Lichen Planus (OLP), which has been increasingly recognized as a potentially premalignant condition.[9] Chronic inflammation, repeated epithelial injury, and an altered local immune microenvironment contribute to a milieu that favors dysplastic changes and eventual malignant transformation.[10] In our study, inflammatory cells in the erosive subtype demonstrated higher COX-2 expression, although this finding did not reach statistical significance. Notably, a large-scale cohort study reported a malignant transformation rate of approximately 6% for erosive OLP—substantially higher than that of other subtypes—emphasizing the importance of vigilant long-term monitoring and risk stratification in these patients.

Literature review has shown that band-like lymphocytic infiltrate seen in OLP, OLR, and related autoimmune diseases may result from bcl-2 overexpression, which prolongs immune cell survival by inhibiting apoptosis. This sustained inflammation is amplified by COX-2 expression and its arachidonic acid–derived metabolites, affecting not only the infiltrate but also the basal and suprabasal epithelial layers, indicating a broad epithelial involvement.[11] Moreover, COX-2 overexpression is an early event in epithelial carcinogenesis, postulating that the increased levels of COX-2 and EGFR (epidermal growth factor) in premalignant lesions constitute a mechanism for `field carcinogenesis.[12]

At the molecular level, cyclooxygenase-2 (COX-2), an inducible enzyme involved in the inflammatory cascade, plays a critical role in the pathophysiology of both chronic

Table shows COX-2 Expression in the epithelium of study and control groups

Staining Status for Epithelial Tissue Type Crosstabulation						
		Tissue Type			Total	Chi-Square Value
		Erosive	Normal	Reticular		
	Count	1	5	18	24	43.79
Nil	% within tissue type	5 %	25%	90%	40%	
Mild	Count	3	9	2	14	
	% within tissue type	15%	45%	10 %	23.30%	
Moderate	Count	9	3	0	12	
	% within tissue type	45%	15%	0%	20%	
Severe	Count	7	3	0	10	
	% within tissue type	35%	15%	0%	16.70%	
Total		100%	100%	100%	100%	

inflammation and carcinogenesis.[13] COX-2 overexpression has been implicated in tumor initiation and progression through mechanisms such as enhanced cell proliferation, inhibition of apoptosis, promotion of angiogenesis, and facilitation of invasion and metastasis.[13] Elevated COX-2 expression has been documented not only in various malignancies, including squamous cell carcinoma, but also in precancerous lesions and OLP.[4]

In our study, a statistically significant difference ($p < 0.001$) in COX-2 expression was observed between the OLP and control groups. While 90% of control samples showed no detectable COX-2 expression, the erosive OLP subtype demonstrated a notably higher prevalence of moderate to severe COX-2 expression. In contrast, the reticular form predominantly exhibited mild COX-2 expression. These findings suggest a link between the severity of the clinical phenotype and molecular dysregulation.

Our observations are consistent with the findings of Chankong et al., who reported elevated COX-2 mRNA levels in OLP lesions compared to normal oral mucosa. They proposed COX-2 as a potential biomarker for identifying OLP cases with a higher risk of malignant transformation.[14] Similarly, our study supports the hypothesis that increased COX-2 expression may serve not only as an indicator of disease severity but also as a predictor of progression from OLP to oral squamous cell carcinoma.

Conclusion

This study corroborates that COX-2 expression is markedly elevated in OLP, particularly within the erosive subtype, compared to normal mucosa where COX-2 is virtually absent. The differential staining intensity highlights a clear association between COX-2 upregulation and lesion severity. These findings align with broader research indicating COX-2's role in inflammation-driven carcinogenesis. As such, COX-2 immunohistochemistry may inform risk stratification and aid in identifying OLP patients—especially those with erosive lesions—who could benefit from enhanced surveillance and potential chemopreventive strategies.

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