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Original Article

Molecular Insights into Oral Carcinogenesis: Expression of p53, Bcl-2, and Ki-67 in Oral Lichen Planus and Oral Squamous Cell Carcinoma – A original study

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ABSTRACT

Introduction: Oral carcinogenesis is a multistep process involving molecular alterations in genes regulating apoptosis, proliferation, and DNA repair. Oral lichen planus (OLP), a chronic inflammatory disorder, has been considered a potential precursor to oral squamous cell carcinoma (OSCC). Biomarkers such as p53, Bcl-2, and Ki-67 may help identify early molecular changes associated with malignant transformation. This study assessed and compared the expression of these markers in normal oral mucosa (NOM), OLP, and OSCC to understand their role in oral carcinogenesis.

Materials and Methods: A total of 90 formalin-fixed, paraffin-embedded tissue specimens were analyzed, including 10 NOM, 40 OLP, and 40 OSCC samples. Sections were stained using hematoxylin and eosin for diagnosis and subjected to immunohistochemistry using antibodies against p53, Bcl-2, and Ki-67. Immunopositivity was assessed based on the percentage of positively stained cells using the Nakagawa scoring system. Statistical analysis was performed to compare marker expression among the three groups.

Results: Bcl-2 positivity was observed in 30% of NOM, 62.5% of OLP, and 87.5% of OSCC samples, showing a significant increasing trend ($p < 0.0001$). Ki-67 expression increased from 30% in NOM to 50% in OLP and 87.5% in OSCC ($p < 0.0001$). p53 positivity was lowest in NOM (10%), higher in OLP (62.5%), and highest in OSCC (72.5%) ($p < 0.0001$). All three markers demonstrated significant pairwise differences between NOM, OLP, and OSCC.

Conclusion: The progressive increase in p53, Bcl-2, and Ki-67 expression across NOM, OLP, and OSCC highlights their involvement in early and late events of oral carcinogenesis. Their combined evaluation may help identify OLP cases at higher risk for malignant transformation and support early detection of oral cancer.

Keywords*: Apoptosis, Immunohistochemistry, Ki-67, Oral Lichen Planus, p53.*

INTRODUCTION:

Carcinogenesis is a complex multistep process involving a series of genetic and molecular alterations. Both oncogenes (positive regulators) and tumor suppressor genes (negative regulators) play crucial roles in this pathway, and their susceptibility to environmental carcinogens and mutagens significantly contributes to malignant transformation [1]. Identifying reliable molecular markers has therefore been a focus of cancer research, as such biomarkers can improve early diagnosis and guide prognosis in human cancers.

Oral squamous cell carcinoma (OSCC) is frequently preceded by oral potentially malignant disorders (OPMDs), among which oral lichen planus (OLP) has received considerable attention. The malignant transformation potential of OLP remains a controversial topic in the literature, with transformation rates ranging between 0.4% and 2.0% over five years [2]. The most extensive studies to date report an average transformation rate of approximately 1.5% [3,4]. Notably, the presence of epithelial dysplasia in OLP is associated with an increased risk of malignant progression.

At the molecular level, alterations in specific proteins associated with cell proliferation, apoptosis, and DNA repair are recognized as early events in carcinogenesis. The p53 tumor suppressor gene plays a central role in maintaining genomic integrity by inducing cell cycle arrest or apoptosis in response to DNA damage. Loss of wild-type p53 function or altered expression is one of the most frequent events in human cancers, including OSCC [10]. Similarly, Ki-67, a nuclear protein expressed in proliferating cells, serves as a reliable marker of cellular proliferation and tumor aggressiveness [5,6.] Another critical regulator is Bcl-2, an anti-apoptotic protein that prolongs the survival of genetically altered cells, thereby facilitating accumulation of mutations and tumor progression [7,8.]

Previous studies have demonstrated the expression of p53, Bcl-2, and Ki-67 in OLP and OSCC, suggesting their potential as biomarkers of malignant transformation [9,10,11,12.] .These alterations in apoptotic and proliferative pathways may create a permissive microenvironment for neoplastic development.

Given this background, the present study was undertaken to examine the histopathological features of OLP and OSCC and to compare the immunopositivity of p53, Bcl-2, and Ki-67 in these lesions. Correlating these molecular markers with disease progression may provide important evidence regarding the malignant transformation potential of OLP.

MATERIAL AND METHOD

Study Samples

A total of 50 formalin-fixed, paraffin-embedded tissue samples were retrieved from the archival files of the private lab. The study included:

- 10 samples of normal oral mucosa (controls),
- 40 specimens comprising cases of oral lichen planus (OLP) and oral squamous cell carcinoma (OSCC).

Inclusion Criteria

- Bilateral lesions with clinical features consistent with OLP.
- Histopathological evidence of liquefaction degeneration of the basal epithelial layer and presence of a subepithelial band-like inflammatory infiltrate.

Exclusion Criteria

- Presence of epithelial dysplasia in the lesion.
- Prior drug therapy, including specific OLP treatment.
- Lesions adjacent to amalgam restorations.

Controls were obtained from patients undergoing gingivectomy or third molar extraction, after informed consent.

Tissue Processing and Histopathology

All tissues were fixed in 10% neutral buffered formalin for 24 hours, processed routinely, and embedded in paraffin. Serial sections of 5 µm thickness were cut using a rotary microtome (Leica semi-automatic) and mounted on poly-L-lysine–coated slides.

- One section from each block was stained with hematoxylin and eosin (H&E) for histopathological confirmation.
- OLP was diagnosed according to Eisenberg and Krutchkoff's criteria, and OSCC was confirmed based on WHO classification.

Immunohistochemistry (IHC)

Primary Antibodies

- p53: clone DO-7 (Biogenix, USA)
- Ki-67: clone BGX-297 (Biogenix, USA)
- Bcl-2: clone Bcl-2/100 (Biogenix, USA)

Detection System

- Biotinylated secondary antibody: Goat anti-mouse IgG (Biogenex)
- Conjugate: Streptavidin–peroxidase polymer (Biogenex)
- Chromogen: Diaminobenzidine (DAB) (Dako Cytomation, Denmark)
- Counterstaining: Hematoxylin

Protocol

1. Sections were deparaffinized in xylene and rehydrated through graded alcohols to water.
2. Antigen retrieval was performed in citrate buffer (pH 6.0) using a microwave oven (5 cycles of 3 minutes at 450 W).

3. Endogenous peroxidase activity was blocked with hydrogen peroxide.
4. Sections were incubated with a power block for 15 minutes, followed by incubation with the respective primary antibody for 1 hour at room temperature.
5. After washing with PBS, sections were treated sequentially with super enhancer, secondary antibody, and streptavidin-peroxidase conjugate.
6. Visualization was achieved using DAB chromogen, followed by counterstaining with hematoxylin.
7. Slides were dehydrated, cleared, and mounted in DPX.

Controls

- **Positive controls**
  - Lymph node for Bcl-2
  - Papilloma for Ki-67
  - Breast carcinoma for p53
- **Negative controls**
  - Omission of primary antibody (not used in this study).

Evaluation of Immunostaining

Immunoreactivity was assessed using a Labomed research microscope with DigiPro 4.0 image analysis software. Staining was considered positive when distinct brown nuclear or cytoplasmic staining was observed.

- For OSCC: 1000 cells were evaluated in 5 randomly selected high-power fields (40×).
- For OLP: 500 cells were counted in 5 high-power fields (40×).

The scoring system proposed by Nakagawa et al. was applied:

- 0 = Negative (<5% positive cells)
- 1+ = Weak (5–25% positive cells)
- 2+ = Moderate (25–50% positive cells)
- 3+ = Strong (>50% positive cells)

RESULTS

A total of 90 tissue specimens were analyzed, comprising 40 cases of oral lichen planus (OLP), 40 cases of oral squamous cell carcinoma (OSCC), and 10 cases of normal oral mucosa (NOM). Immunohistochemical expression of Bcl-2, Ki-67, and p53 was assessed and compared among these groups.

Bcl-2 Expression

Bcl-2 positivity was observed in 3 (30%) cases of NOM, 25 (62.5%) cases of OLP, and 35 (87.5%) cases of OSCC. The difference among the three groups was statistically significant (χ^2=90.27, df=2, p<0.0001). Pairwise comparisons demonstrated significantly higher Bcl-2 expression in OLP compared with NOM (p<0.00001, χ^2=57.73) and in OSCC compared with OLP (p<0.00001, χ^2=30.05). Thus, a progressive increase in Bcl-2 immunoreactivity was evident from NOM through OLP to OSCC.

Ki-67 Expression

Ki-67 nuclear staining was detected in 3 (30%) cases of NOM, 20 (50%) cases of OLP, and 35 (87.5%) cases of OSCC. The difference among the groups was statistically significant (χ^2=48.62, df=2, p<0.0001). On comparison, OLP showed significantly higher Ki-67 expression than NOM (p=0.0023, χ^2=9.3), while OSCC demonstrated significantly greater expression than OLP (p<0.0001, χ^2=15.36). These results confirm an increased proliferative activity in OSCC relative to premalignant lesions and normal mucosa.

p53 Expression

p53 positivity was found in 1 (10%) case of NOM, 25 (62.5%) cases of OLP, and 29 (72.5%) cases of OSCC. The overall difference was statistically significant (χ^2=69.11, df=2, p<0.0001). OLP showed significantly higher p53 expression compared with NOM (p=0.006, χ^2=7.52). Similarly, OSCC demonstrated significantly greater positivity compared with OLP (p<0.0001, χ^2=31.22).

Overall Findings

When all markers were considered, OSCC showed the highest immunoreactivity for Bcl-2 (87.5%), Ki-67 (87.5%), and p53 (72.5%). In OLP, Bcl-2 and p53 positivity (62.5% each) were higher than Ki-67 (50%). NOM exhibited low expression for all markers (30% for Bcl-2, 30% for Ki-67, and 10% for p53).

Histological and Immunohistochemical Observations

- NOM: Minimal or weak staining confined to basal/parabasal layers.
- OLP: Moderate to strong staining in basal and parabasal epithelial cells.
- OSCC: Strong, widespread positivity in epithelial islands, indicating dysregulated proliferation and apoptotic resistance.
- Controls: Lymph node sections showed positive Bcl-2 staining; papilloma tissues were positive for Ki-67, confirming reliability of IHC procedures.
- Table: Comparative Expression of Bcl-2, Ki-67, and p53 in NOM, OLP, and OSCC

Marker	Group	Total Cases (n)	Positive Cases (n)	Negative Cases (n)	Positivity (%)	Statistical Significance
Bcl-2	NOM	10	3	7	30%	χ^2=90.27, p<0.0001
	OLP	40	25	15	62.5%	NOM vs OLP: p<0.00001 OLP vs OSCC: p<0.00001
	OSCC	40	35	5	87.5%	
Ki-67	NOM	10	3	7	30%	χ^2=48.62, p<0.0001
	OLP	40	20	20	50%	NOM vs OLP: p=0.0023 OLP vs OSCC: p<0.0001
	OSCC	40	35	5	87.5%	
p53	NOM	10	1	9	10%	χ^2=69.11, p<0.0001
	OLP	40	25	15	62.5%	NOM vs OLP: p=0.006 OLP vs OSCC: p<0.0001
	OSCC	40	29	11	72.5%	

DISCUSSION

The present study evaluated and compared the expression of Bcl-2, Ki-67, and p53 in normal oral mucosa (NOM), oral lichen planus (OLP), and oral squamous cell carcinoma (OSCC) in order to assess the malignant potential of OLP. The results demonstrated a progressive increase in the immunopositivity of all three markers from NOM to OLP and OSCC, suggesting that molecular alterations in cell proliferation and apoptosis regulation may underlie the transition from potentially malignant disorders to carcinoma.

p53 Expression

p53 is a well-characterized tumor suppressor gene, and its alteration is one of the most frequently observed events in human cancers. In this study, p53 expression was significantly higher in OLP compared with NOM, but lower than in OSCC. These findings are consistent with earlier reports by Girod et al.[16] and Warnakulasuriya and Johnson, which highlighted the role of p53 overexpression as an early molecular event in oral carcinogenesis.[17]

The controversy regarding p53 in OLP is reflected in previous studies: some authors reported no expression in OLP, while others demonstrated strong positivity181. This inconsistency may be attributed to the stabilization of p53 protein either by mutations or by binding to other cellular proteins, which prolongs its half-life, thereby enabling immunohistochemical detection. The results of this study support the hypothesis that p53 overexpression in OLP could

be a protective response to increased proliferative activity rather than a definitive sign of malignant transformation. Nevertheless, its stepwise increase from NOM → OLP → OSCC emphasizes its role in carcinogenesis.[19]

Bcl-2 Expression

Bcl-2 is an anti-apoptotic protein that promotes survival of genetically altered cells, thereby favouring accumulation of mutations. In this study, Bcl-2 expression was weak or absent in NOM, weak-to-moderate in OLP, and moderate-to-strong in OSCC. These results agree with the findings of Hadzi-Mihailovic (2010)[13] and Sulkowska et al., who suggested that increased Bcl-2 expression may be an important early event in carcinogenesis.

Interestingly, a correlation was observed between Bcl-2 and p53 expression, suggesting that the inhibition of apoptosis (by Bcl-2) along with loss of tumor-suppressive function (by p53) may synergistically promote carcinogenesis. Such a dual mechanism could explain the enhanced survival of genetically altered epithelial cells in OLP, thereby facilitating malignant transformation.

Ki-67 Expression

Ki-67 is a marker of cellular proliferation and was found to be expressed at low levels in NOM, moderately in OLP, and strongly in OSCC. This progressive increase correlates with enhanced proliferative activity during carcinogenesis. The findings are consistent with the work of Sassi et al. (2011) and Ashraf et al. (2010)[15] , who observed significantly higher Ki-67 labelling indices in OSCC compared with premalignant lesions and normal epithelium.

Of note, a positive association between Ki-67 and p53 was observed in OLP cases. While this may appear contradictory—since Ki-67 marks proliferation and p53 is a tumor suppressor—it has been suggested that these proteins may reflect different cellular populations or may be linked through the action of cell cycle regulators such as cyclin D1. This supports the idea that OLP exhibits both proliferative activity and genetic stress responses, highlighting its borderline biological behaviour. [20,21,22]

Malignant Potential of OLP

The combined results of this study support the hypothesis that OLP has a potential for malignant transformation. The stepwise increase in expression of all three markers—p53, Bcl-2, and Ki-67—from NOM through OLP to OSCC indicates that OLP shares intermediate molecular features between normal mucosa and carcinoma. These findings are in agreement with Gonzalez-Moles et al., who reported a malignant transformation rate of 0–12.5% for OLP, and with WHO's recognition of OLP as a potentially malignant disorder[23.]

However, it is important to note that p53 overexpression in OLP may also represent a physiological protective response to epithelial stress rather than an outright indicator of malignant transformation. Similarly, Ki-67 expression may reflect increased epithelial turnover caused by lymphocytic infiltration rather than intrinsic neoplastic activity. Therefore, interpretation of these markers in isolation should be done with caution.

Figures

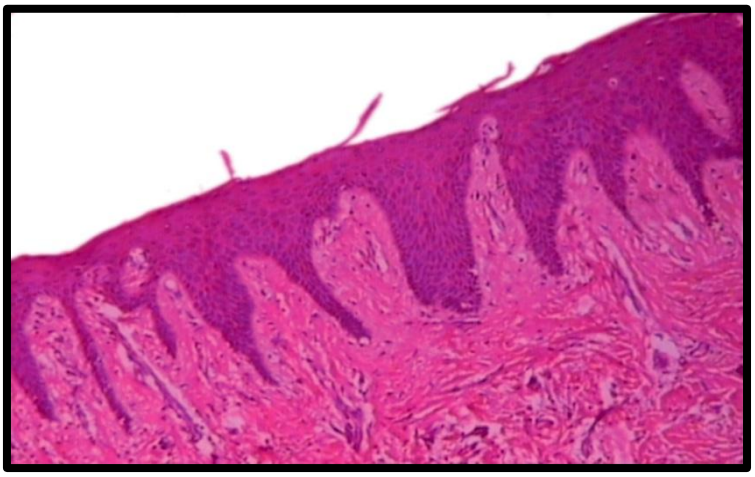

Fig. 1: Histological sections of normal oral mucosa
(hematoxylin-eosin, original magnification 10X)

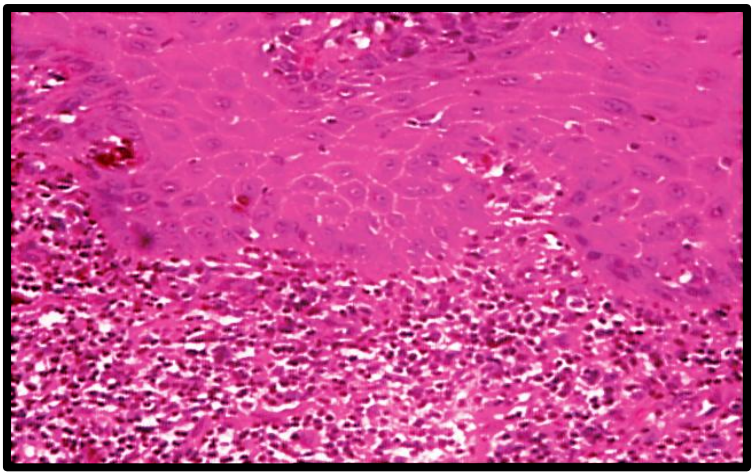

Fig. 2: Histological sections of Oral lichen planus showing subepithelial band of chronic inflammatory cells (hematoxylin-eosin, original magnification 40X)

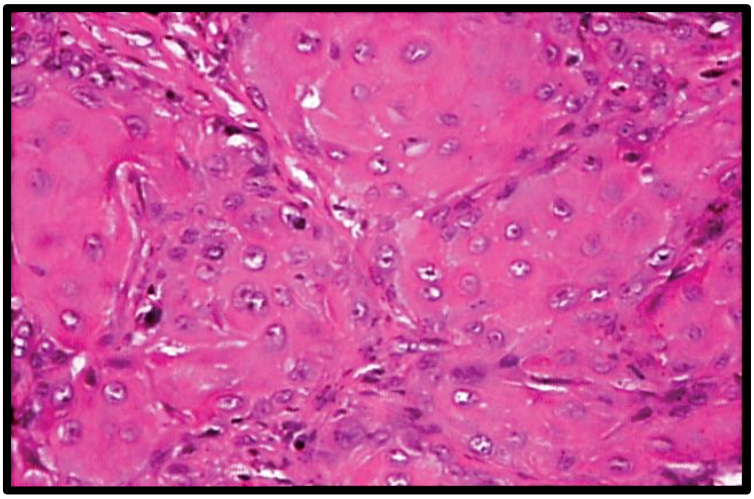

Fig. 3: Histological sections of Oral squamous cell carcinoma showing epithelial islands (hematoxylin-eosin, original magnification 40X)

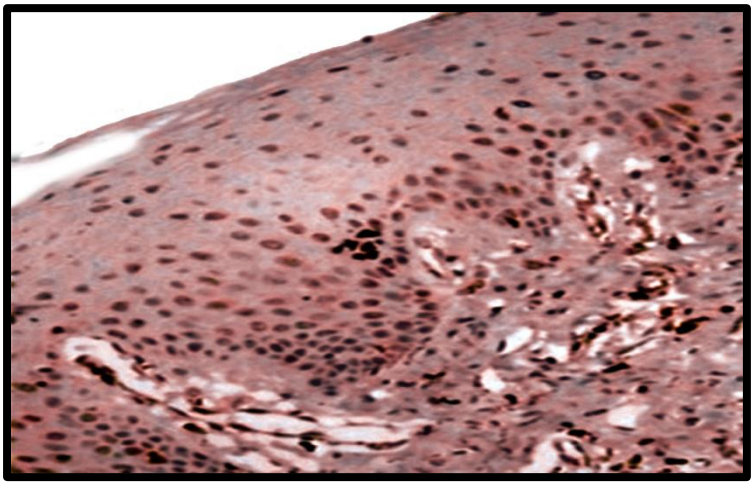

Fig. 4: Immunohistochemical staining of normal oral mucosa with Bcl-2 showing slight positive expression at basal / parabasal layer of epithelium, original magnification 20X

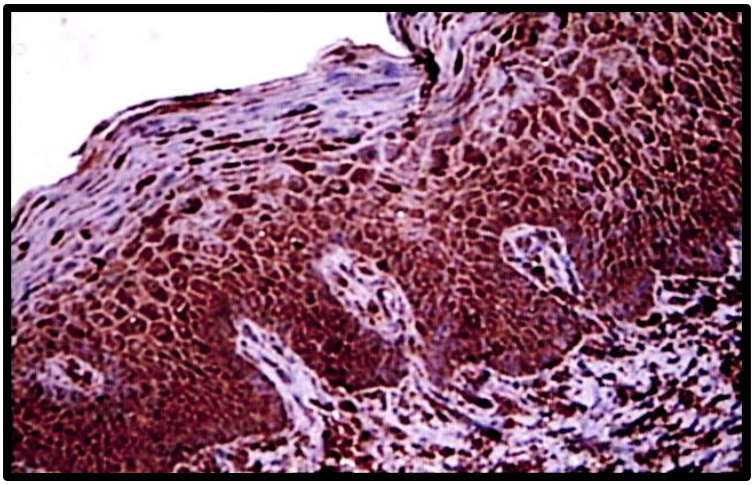

Fig. 5: Immunohistochemical staining of oral lichen planus with Bcl-2 showing strong positive expression at basal / parabasal layer of epithelium, original magnification 20X

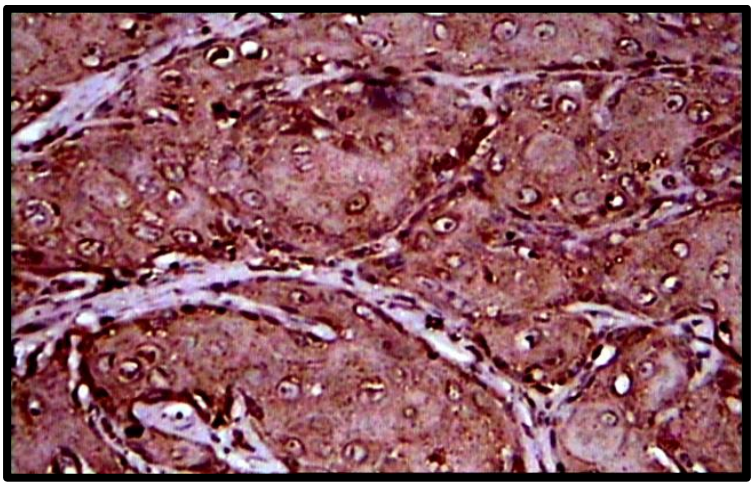

Fig. 6: Immunohistochemical staining of oral squamous cell carcinoma with Bcl-2 showing strong positive expression in epithelium islands, original magnification 40X

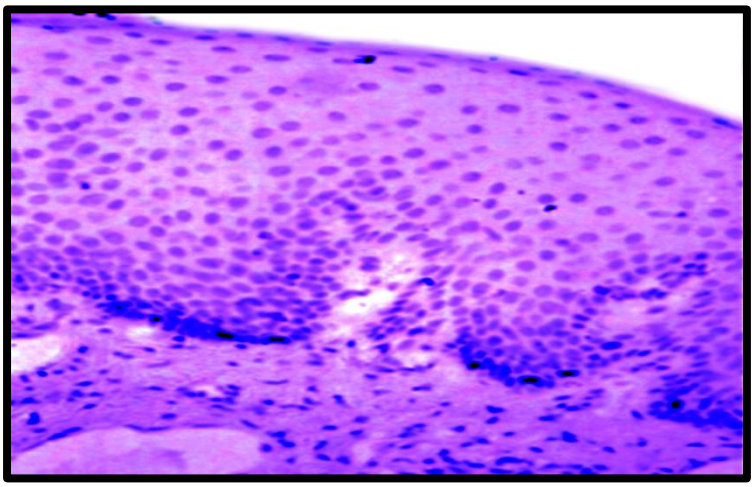

Fig. 7: Immunohistochemical staining of normal oral mucosa with Ki-67 showing slight positive expression at basal / parabasal layer of epithelium, original magnification 20X

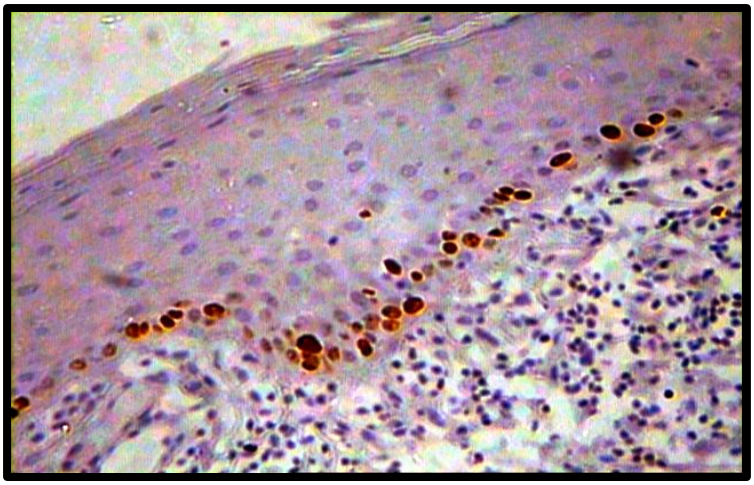

Fig. 8: Immunohistochemical staining of oral lichen planus with Ki-67 showing strong positive expression at basal layer of epithelium, original magnification 20X

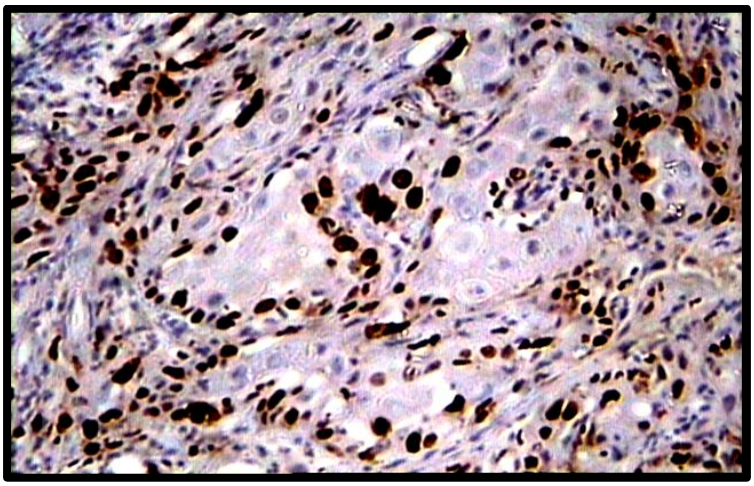

Fig. 9: Immunohistochemical staining of oral squamous cell carcinoma with Ki-67 showing strong positive expression in epithelium islands, original magnification 40X

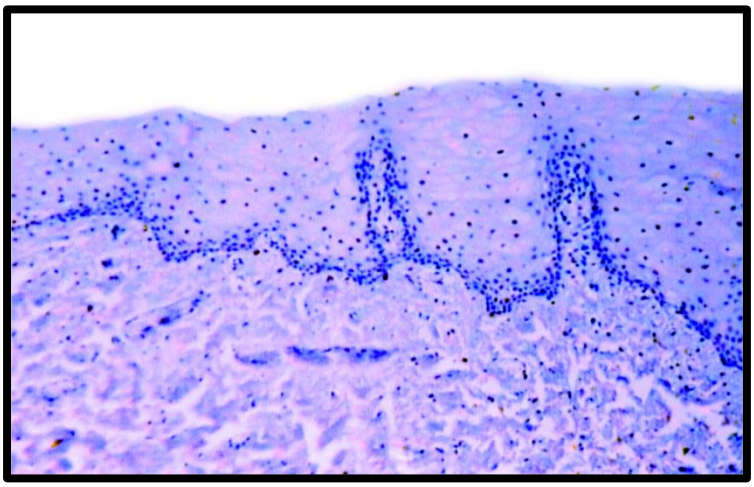

Fig. 10: Immunohistochemical staining of normal oral mucosa with p-53 showing slight positive expression at basal layer of epithelium, original magnification 20X

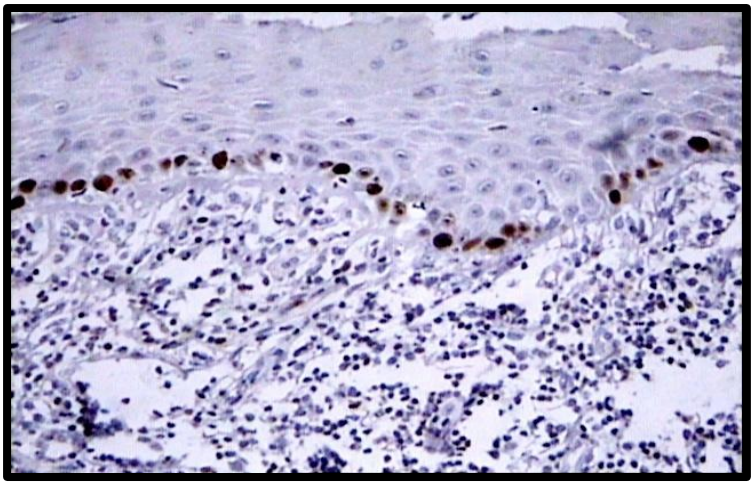

Fig. 11: Immunohistochemical staining of oral lichen planus with p-53 showing strong positive expression at basal layer of epithelium, original magnification 20X

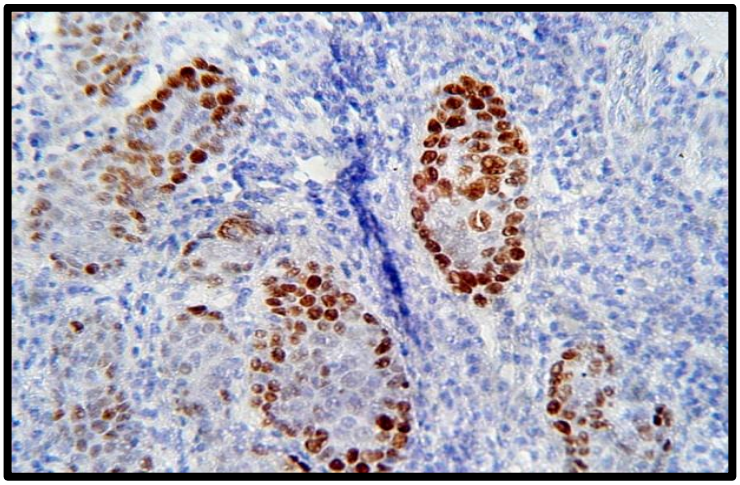

Fig. 12: Immunohistochemical staining of oral squamous cell carcinoma with p-53 showing strong positive expression in epithelium islands, original magnification 20X

Lymph nodes

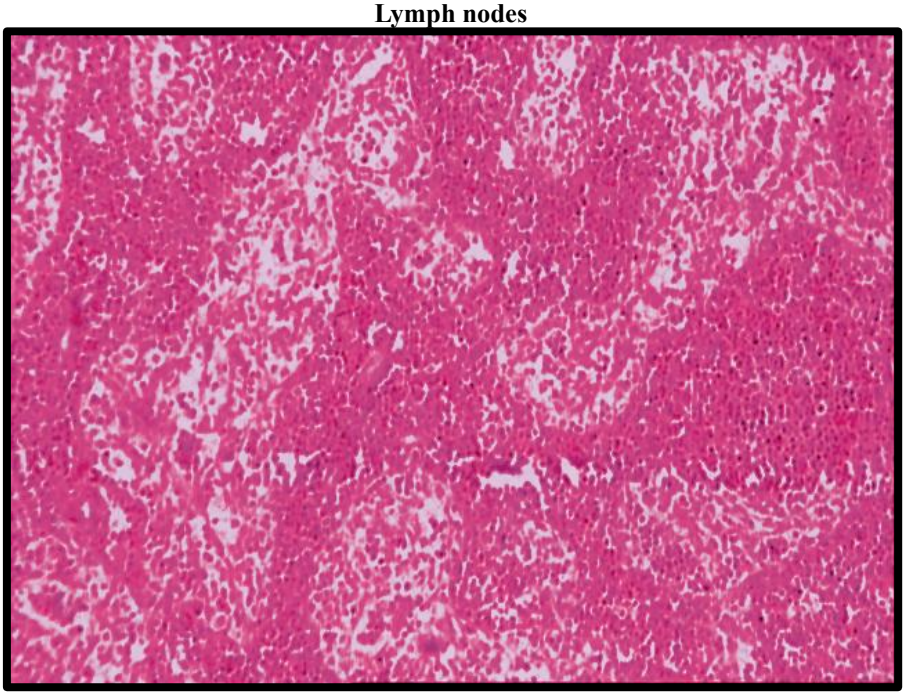

Fig. 13: Histological sections of lymph node showing lymphocytes
(hematoxylin-eosin, original magnification 4X)

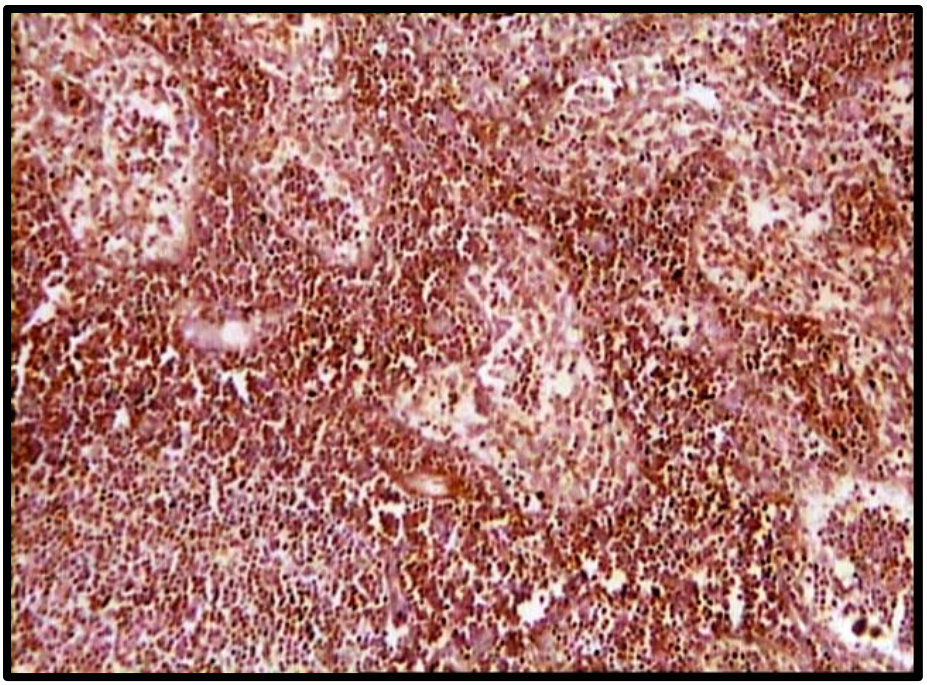

Fig. 14: Immunohistochemical section of lymph node showing positive expression of Bcl-2 in lymphatic nodules taken as positive control, original magnification 4X)

Papilloma

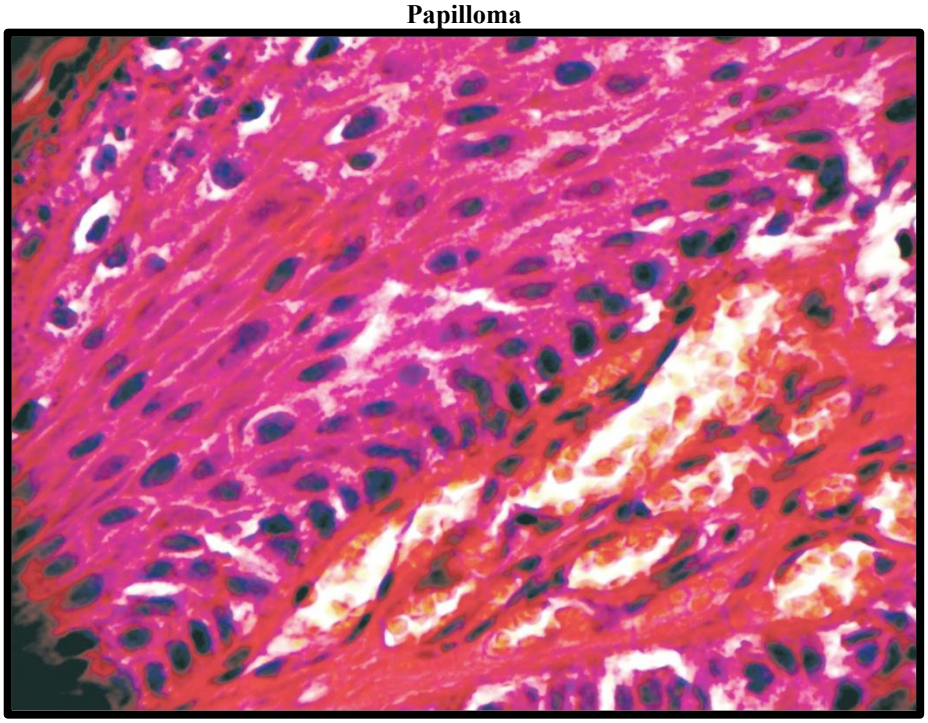

Fig. 15: Histological sections of papilloma
(hematoxylin-eosin, original magnification 4X)

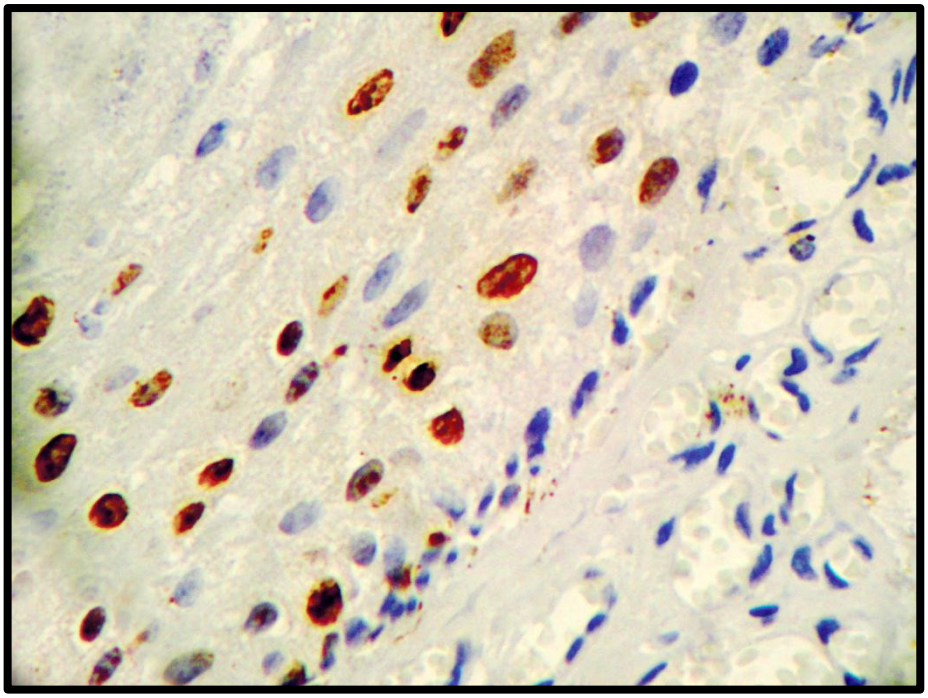

Fig. 16: Immunohistochemical staining of papilloma showing positive expression of Ki-67 at epithelial cells taken as positive control, original magnification 40X

CONCLUSION

The present study evaluated the immunohistochemical expression of p53, Bcl-2, and Ki-67 in normal oral mucosa (NOM), oral lichen planus (OLP), and oral squamous cell carcinoma (OSCC) with the objective of understanding their role in oral carcinogenesis. The findings demonstrated a clear and progressive increase in the positivity of all three markers from normal tissue to premalignant lesions and finally to malignant lesions. This pattern reflects the stepwise molecular changes that accompany the transition from chronic inflammation to dysregulated cell survival and ultimately to neoplastic transformation.

Bcl-2 expression increased significantly from NOM to OLP and from OLP to OSCC, indicating that resistance to apoptosis is an early and sustained event in oral carcinogenesis. Ki-67 expression showed a similar upward trend, suggesting that proliferative activity rises as lesions progress to malignancy. The high Ki-67 index in OSCC highlights the aggressive growth potential of these tumors. p53 positivity was also markedly higher in OLP and OSCC compared with NOM, supporting the concept that alterations in p53 function occur early and accumulate further in malignant transformation.

Together, these results suggest that OLP, although clinically benign, shows significant molecular alterations involving apoptosis and proliferation pathways. These changes may predispose a subset of cases to progress toward malignancy. The strong expression of p53, Bcl-2, and Ki-67 in OSCC further emphasizes their importance in tumor development and progression. We concluded that p53, Bcl-2, and Ki-67 can serve as valuable biomarkers for assessing malignant potential in oral lesions. Their combined evaluation may help identify high-risk OLP cases and improve early detection of oral cancer. Further studies with larger sample sizes, long-term follow-up, and molecular correlation are recommended to strengthen these observations and enhance their clinical applicability.The findings of this study emphasize the need for long-term follow-up of patients with OLP, especially those with high expression of p53, Bcl-2, and Ki-67. Immunohistochemical evaluation of these markers could aid in identifying OLP cases with a higher risk of malignant transformation, thereby guiding closer surveillance and early intervention.

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