



# Evaluation of the Potential of Malignant Transformation in Oral Lichen Planus by Immunohistochemistry

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## OBJECTIVE

Malignant transformation is suggested to be a consequence of alterations in cell cycle control, and this potential of oral lichen planus (OLP) is still controversial. The aim of this study was to evaluate the malignant transformation of OLP comparing with normal oral mucosa (NOM) and oral squamous cell carcinoma (OSCC) by immunohistochemistry.

## METHODS

Bcl-2 and p53 expressions were determined by immunohistochemistry in 100 oral mucosal biopsies including NOM (n=20), OLP (n=40) and OSCC (n=40).

## RESULTS

There were no significant differences in p53 and bcl-2 expressions between OLP and OSCC cases. However, p53 expression was higher in OLP and OSCC compared to normal epithelium ( $p<0.05$ ).

## CONCLUSION

The results of this study suggest that changes in proteins responsible for cell proliferation and apoptosis may play a role in the possible malignant transformation of OLP, but other molecular mechanisms involved in the cell cycle may also have an impact on the development of oral carcinogenesis. Therefore, long-term follow-up of patients with OLP with an accurate final diagnosis to be made by clinicopathological correlation, further research is needed to identify markers and independent risk factors that predict malignant transformation of OLP.

**Keywords:** bcl-2; malignant transformation; p53; oral lichen planus; oral squamous cell carcinoma.

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## Introduction

Lichen planus (LP) is a chronic disorder affecting stratified squamous epithelia that involve the skin, oral and genital mucous membranes, scalp, and nails.[1,2] In 40-65% of patients with LP, there is an involvement of the oral mucosa along with the skin. Oral lesions usually develop months after skin lesions. In 15-30% of cases, lesions may occur in the oral mucosa without skin involvement.[3,4]

The incidence of oral LP (OLP) differs from country to country; the rates reported in studies are 0.3% in Malaysia, 0.5% in Japan, 1.15% in Turkey, 1.9% in Sweden, and 2.6% in India.[2,5] OLP is clinically most common in the middle age group. The mean age of patients is 40 years (range 30-60 years). The average age of OLP patients in Turkey is 50 years (range 16-83 years). [6] OLP is very rare in children and young adults. In most case series, it is more common in women than men, usually at a ratio of 3:2. Similarly in Turkey, it is

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more dominant among women with a ratio of 2.36:1. [6] Intraoral incidence is 88% in the buccal mucosa, 27.6% in the tongue, 25.9% in the gingiva, 8.1% in the lip mucosa, 7.8% in the hard palate, 5.4% in the alveolar crest, 3% in the floor of the mouth, and 1.4% in the soft palate. [6] Different clinical subtypes have been described by many authors. Some have defined six subtypes that are reticular, erosive, plaque-like, papular, atrophic, and bullous, [2,7] while it is classified into three types such as reticular, erosive, and erythematous, [8] and, has been divided only into two clinical types, reticular, and erosive. [9] The most common clinical image is sharply demarcated, snow-white, lacy, stellar, or circular fine lines (striae), which are called Wickham's Striae. These white lines, characteristic of the reticular type, are an important clinical feature of OLP. These lines can sometimes turn into white papules within minutes and maybe non-palpable and firm from the surrounding mucosa. Lesions are usually bilateral and often symmetrical, which is another important clinical feature. Multiple or multifocal lesions sometimes are very strikingly symmetrical. [10-12] The reticular type is usually asymptomatic, so patients often do not notice, only the mucosa is rough and slightly firm. Patients with atrophic lesions complain of pain, while patients with erosive/ulcerative lesions have more severe symptoms such as pain and difficulty in eating.

The exact etiology of LP is unknown. Studies support its etiopathogenesis that it is a T cell-mediated autoimmune disease in which autocytotoxic CD8+ T cells cause apoptosis in cells in the basal layer of the oral mucosa. The response of T cells causes local inflammation. [2,13] The basis of the autoimmune nature of OLP is the loss of self-tolerance in basal keratinocytes. Immune suppression is impaired in OLP due to transforming growth factor- $\beta$ 1 deficiency, and, loss of "immune privilege" in OLP has been suggested. [14] Autoantigen of LP is uncertain. Many exogenous antigens (systemic drugs, viral infections, and bacterial products) are held responsible as the causative agent of the disease. In the studies, autoantibodies against Desmoglein 1-3 were detected in the serum. [15] Overexpression of heat shock proteins was detected in keratinocytes; therefore, it was suggested that heat shock protein may be autoantigen. [2] It has been thought that there are genetic reasons for the occurrence of OLP in some populations. [9] In one study, [16] it was reported that HLA-3 was detected in patients with cutaneous LP in England, but Porter et al. [17] reported that they did not find a significant relationship between familial LP cases and HLA in their study.

The histopathological examination of OLP reveals band-like lymphocytic infiltration in contact with the epithelium in the lamina propria and liquefaction degeneration in the keratinocytes in the basal layer. There is no dysplasia of the epithelium. [18]

Diagnosis of OLP is based on a combination of clinical and histopathological criteria. [19,20] Cases that do not meet the clinical and the histological diagnostic criteria set should be diagnosed as oral lichenoid lesions (OLL). OLL symptoms include contact hypersensitivity reactions to dental restorative or prosthetic materials, hypersensitivity reactions to cinnamon and some drugs, and oral findings in graft versus host disease. It should be kept in mind that OLL has a single lesion and is in atypical localizations for OLP. Microscopically, inflammatory infiltration with eosinophils extending much deeper than the band-like lymphocytic infiltration in the lamina propria is typical. [21,22]

It has been reported by various authors that oral squamous cell carcinoma (OSCC) can develop from OLP. The World Health Organization (WHO) has also defined OLP among precancerous lesions since 2005. According to this classification, OLP is one of the clinical conditions associated with a significantly increased risk for OSCC. [23]

OSCC is a malignant neoplasm of stratified squamous epithelium originating from the mucosal epithelium. It is most common in the fifth and sixth decades of life. Risk factors such as smoking, smokeless tobacco use, and alcohol consumption play a role in the occurrence of OSCC in various geographies related to daily life habits. Worldwide, OSCC is more common in men than women. However, concerning the daily usage habits of risk factors, it is more common among women in some geographical regions such as India and Thailand. In general, OSCC occurs during advanced age, with most patients aged 50-70 years. Depending on the tobacco use habits that vary from country to country, the incidence or age of occurrence has lowered. [24]

The growth of keratinocytes is regulated by the balance between molecules such as bcl-2, which controls cell survival, and p53, which controls cell death. [25] The bcl-2 protein is an antiapoptotic molecule that resides in the nucleus and mitochondria membrane. The bcl-2 protein is conversely related to p53 function, and its expression inhibits apoptotic cell death. [26] The p53 protein, a product of TP53, a tumor suppressor gene, is responsible for repairing damaged DNA and eliminating cells with irreparable DNA by apoptosis. It is also called the protector of the genome. [27]

Among many proteins involved in cell proliferation and apoptosis processes, p53 and bcl-2 are also involved in the carcinogenesis process as well as these functions.[28]

This study aimed to evaluate the expression of p53 and bcl-2 proteins in OLP and compare it with normal oral mucosa (NOM) and OSCC to obtain information about the malignant transformation potential of OLP.

## Materials and Methods

The formalin-fixed, paraffin-embedded tissues were obtained from the Department of Tumor Pathology, Institute of Oncology, Istanbul University. 40 cases of OLP cases and 40 cases of OSCC were included in the study (48 females, 32 males, mean age 49.2). 20 cases with NOM were also included in the study (11 females, 9 males, mean age 28.4). The study was approved by the Research Ethics Committee of Istanbul University (Number: 751/14).

## Immunohistochemistry

Immunohistochemical reactions against bcl-2 ready to use (Thermo Scientific, Mouse, Monoclonal MS-123-R7) and p53 (ScyTek Lab., A00009, ready to use, Logan, Utah, USA) were performed in 5 µm thick sections on charged slides. They were deparaffinized with xylene for 30 min and washed with 99% alcohol for 15 min, then 96% alcohol and distilled water. For antigen retrieval, the sections were microwaved 4 times for 5 min in citrate buffer (Ph 6.0), cooled to room temperature and then washed in phosphate-buffered saline (PBS) for 5 min. Endogenous peroxidase activity was blocked by incubating the sections with 3% H<sub>2</sub>O<sub>2</sub> and they are washed in distilled water and waited in PBS for 5 min. To prevent non-specific reactions, sections were incubated with block solution. Slides were incubated for 120 min with bcl-2 and p53. Negative control sections treated with phosphate-buffered antibodies were confirmed to be unstained. The secondary antibody was reacted for 25 min, followed by a streptavidin peroxidase reagent for 25 min. AEC (ScyTek Lab., ACJ125, Logan, Utah, USA) chromogen was used to visualize the reaction. Finally, the sections were counterstained with Mayer's hematoxylin, cover-slipped, and evaluated by a light microscope.

## Evaluation Methods

Samples were examined at 400× in Olympus BX60 microscope attached to a color video camera (Olympus Analysis Five) which was connected to a computer.

Images were captured using the camera and displayed on a computer monitor for evaluation. The expression index was determined based on the percentage of positive-stained cells in basal and parabasal layers in five high power fields. Samples were scored semi-quantitatively by developing the grading system applied by Tronstad et al.[29]

Cases were assigned to one of the following categories: 0% positive cells (-), <10% positive cells (+), 10-25% positive cells (++) , 26-50% positive cells (+++), or >50% positive cells (++++).

All calculations were performed by the SPSS 11.0 (Statistical Package for the Social Science). The student's t-test was performed, and  $p < 0.05$  was considered to be statistically significant.

## Results

The study groups of OLP and OSCC consisted of 48 females and 32 males with a mean age of 49.2. Eleven females and nine males with a mean age of 28.4 were included study as NOM.

Bcl-2 expression was observed especially in the basal layer of epithelium in OLP and normal oral mucosa groups and peripheral areas of islands of OSCC cases. No statistically difference was observed among groups in terms of bcl-2 expression ( $p > 0.05$ ).

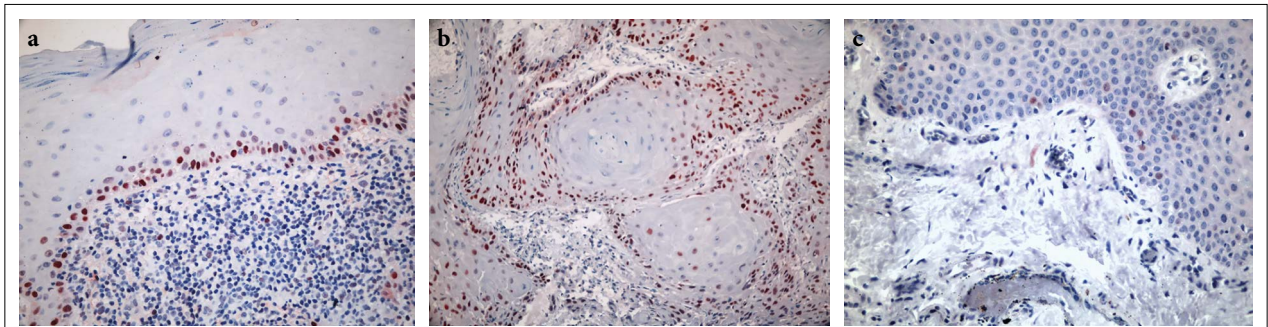
Regarding p53 expression, there were no significant differences between OLP and OSCC groups ( $p > 0.05$ ). However, p53 expression was higher in OLP and OSCC when compared to the normal oral epithelium ( $p < 0.05$ ).

Figures 1 and 2 show the representative pictures of p53 and bcl-2 expression in all groups, respectively.

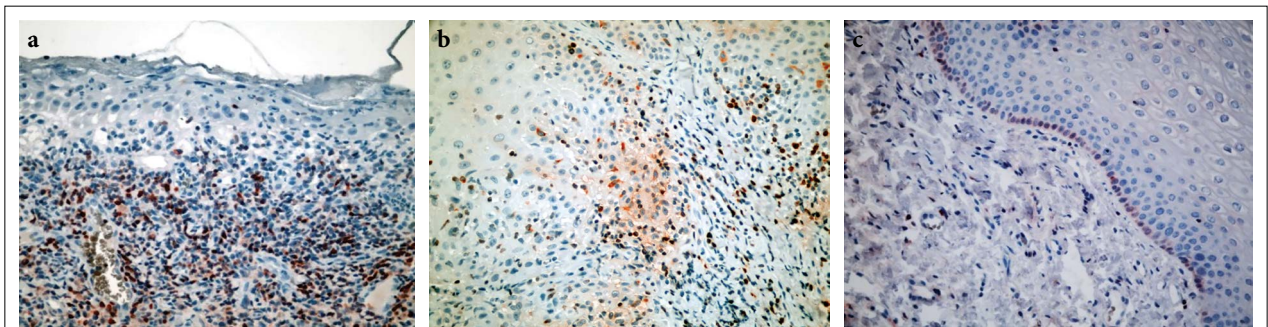
## Discussion

OLP as a lesion was first described as Oral Ruber Planus by dermatologist von Hebra in 1860 and named LP by dermatologist Wilson in 1869. OLP related carcinoma was first described by Hallopeau in 1910.[18] OLP was first included in the WHO's Classification of Head and Neck Tumors among precancerous conditions [i.e., oral premalignant disorders (OPMD)] in 2005.[23] It is also included in the latest classification in 2022.[30] Despite this, the development of OSCC from OLP is still controversial. OLP is a chronic disease, the disease is monitored periodically, and the patient is educated about the clinical course. In several series, the rate of oral cancer developing from OLP was reported as 0.04-1.74%.[8] According to some authors,[7] the rate of OSCC development from OLP is about 1% in 5 years.





**Fig. 1.** Representative pictures of immunohistochemical staining of p53. Intensive p53 positivity in OLP (a) and OSCC (b), however NOM (c) showing weak immunoreactivity to p53 (a, b, c, p53 antibody x400).  
OLP: Oral Lichen Planus; OSCC: Oral Squamous Cell Carcinoma; NOM: Normal Oral Mucosa.



**Fig. 2.** Selective immunohistochemical staining of bcl-2 in OLP (a), OSCC (b) and NOM (c). Similar immunopathologic reaction was observed in all of the groups (a, b, c, bcl-2 antibody x400).  
OLP: Oral Lichen Planus; OSCC: Oral Squamous Cell Carcinoma; NOM: Normal Oral Mucosa.

In a meta-analysis and systemic review of the malignant transformation rates of OLP that evaluated 16 studies involving 7806 patients, the overall mean rate was 1.09%.[31] As can be seen, these rates are quite low. Some patients may have clinically unrelated OLP and OSCC lesions simultaneously. Some lesions showing lichenoid features may have been histomorphologically diagnosed with OLP despite the presence of epithelial dysplasia. The malignant potential of OLP may appear higher than the correct incidence due to both synchronizations of the two separate lesions and misdiagnosis.[7,9] The potential for malignant transformation in OLP is limited to the erosive, atrophic subtypes that are difficult to control.[7-9]

At present, there is no single marker that can predict the malignant transformation of OLP. As is known, progression from this specific OPMD to OSCC requires a multistep process in which several genetic events occur that trigger DNA modifications along with epigenetic events. OLP is more likely than normal epithelium to undergo malignant transformation because of chronic T-cell-mediated damage to the epithelium.[13] One

of the most important histomorphological characteristics of OLP is the band-like lymphocytic infiltration in the lamina propria that contacts the epithelium. A small number of lymphocyte infiltration consisting of CD4+ and CD8+ cells is also seen in the epithelium. Chronic persistent inflammation in OLP is a risk factor for oral carcinogenesis.[32-34] reported that the epithelium lost its ability to regenerate due to the attack of T lymphocytes in contact with the epithelium. Bascones-Ilundain et al.[35] argued in their study that this type of epithelial response to sustained lymphocyte aggression in OLP may create a favorable environment for malignant transformation by allowing cells with damaged DNA to survive.

The lymphocytic infiltrate in OLP consists almost entirely of T cells. This infiltrate is consisting of predominant in CD4+ helper cells and fewer cytotoxic CD8+ T cells.[12,13] Th1 cells, a subtype of CD4+ T cells activate cytotoxic T cells, while other subtype regulatory T cells (Treg) are responsible for suppressive control.[33] CD8+ cytotoxic T cells can trigger keratinocyte apoptosis through activation of cells on basal keratinocytes

by a major tissue compatibility (MHC) Class I-associated antigen.[2] It has been suggested that apoptosis of basal keratinocytes causes damage to the regeneration capacity of the epithelium and creates a cyclical mechanism responsible for the chronicity of the lesion.[13] On the other hand, CD8+ lymphocytes represent immune cells that confront and resist sporadic cancer.[33]

Some of the studies[25,35-39] have revealed that p53 mutation and overexpression of bcl-2 are responsible for the onset of oral carcinogenesis.

In this study, p53 and bcl-2 expression was found to be higher in the OLP group and OSCC group than in the NOM group. No statistically significant difference was observed between OLP and OSCC of p53 and bcl-2 expression.

Similarly, de Sousa et al.[28] reported that no statistically significant difference was observed between OLP and OSCC of p53, bax, and bcl-2 expression in their study. The results of this study show that there was a change in the expression of important proteins related to apoptosis regulatory mechanisms, creating a suitable environment for malignant transformation. Therefore, they suggested that the findings may be evidence of the malignant transformation potential of OLP.

According to de Sousa et al.[28] increased p53 expression in OLP cases is associated with changes in p53 function. In their study, they concluded that there was a possibility of malignant transformation of OLP in cases with higher expression of p53 and bcl-2.

p53 overexpression in OLP is mostly associated with the wild-type form, which arrests the cell cycle for DNA repair or induction of apoptosis.[40] Mutant and wild-type forms of p53 cannot be clearly distinguished by immunohistochemistry techniques.[40] The half-life of the native form of p53 is shorter than that of the mutant type. Therefore, mutant type p53 is more easily labeled than the native form of p53 by immunohistochemical technique.

Unlike de Sousa et al.,[28] and González-Moles et al.[40] reported that they found higher p53 expression in OLP and OSCC than in normal mucosa, but mutant and wild-type p53 could not be distinguished by immunohistochemical technique. Therefore, they emphasized that p53 stains in both proliferating and quiescent cells.

Malignant transformation occurs less frequently than expected and when there is a defect in the TP53 system, as p53, which is highly activated in epithelial cells, directs the repair or apoptosis of damaged DNA by arresting the cell cycle for DNA repair. In heavily attacked, proliferating cells that do not undergo apoptosis and are not controlled by p53, the accumulation

of mutagenic events can lead to the development of a malignant phenotype.[40]

p53 expression results of this study indicate that the escape mechanism of tumorigenesis is reduced in these lesions, thus increasing the risk of developing OSCC. On the other hand, it has been suggested that malignant transformation may occur with the malfunction of the p53 system, which is activated in epithelial cells and stops the cell cycle for DNA repair. In clinically riskier (erosive/atrophic) cases, a cut-off value for p53 expression should be established, and cases with a strong possibility of malignant transformation should be determined and followed more closely.

Apoptosis is a programmed cell death induced by cell damage. It is not known who initiated the apoptosis in OLP, but the damage caused by T cells in basal layer cells is thought to be the factor that initiated the apoptosis. Research has shown that the rate of proliferation in epithelial cells increases due to the damage of T cells in OLP.[41]

In this study, a similar immunoreaction with bcl-2 was observed in NOM, OLP and OSCC groups, and there was no statistical significance between them. Likewise, Bloor et al.[42] reported in their study that there was bcl 2 expression in normal mucosa and OLP, but there was no significant difference between them. They suggested that their results showed that there was no correlation between the frequency of apoptosis induced by keratinocyte damage by T lymphocytes and the rate of cell proliferation in OLP. de Sousa et al.[28] alike did not find a significant difference between OLP and OSCC in terms of bcl-2 expression. They argued that since these results show changes in the expression of apoptosis-related proteins, it will create a favorable environment for malignant transformation. Tanda et al.[43] also reported in their study that bcl-2 expression was the same as normal control, OLP group and Lekoplakia group. They emphasized that none of the OLP cases they followed developed OSCC. Thus, they stated that the absence of apoptosis may be an indicator of premalignancy, but there is insufficient evidence for tumor development.

Some studies[44,45] have shown that apoptotic events are of little importance in OLP and are associated with sustained and intense lymphocytic infiltration of epithelial cells. They reported that they interpreted the absence of apoptosis as a mechanism to protect the epithelium, as massive apoptotic death would eliminate basal cells responsible for epithelial regeneration.

Accumulation of mutagenic events can lead to the development of a malignant phenotype unless lym-

phocytic intensely attacked proliferating cells undergo apoptosis and are controlled by p53.[40] At the same time, bcl-2 overexpression causes infiltrating lymphocytes to escape apoptosis and thus survive longer, which may be a facilitator for OSCC initiation.[13] It has been suggested by some authors[25] that OLP as a chronic disease in malignant transformation is a factor which facilitates the long-term lymphocytic exposure of the oral epithelium, especially in the erosive type whereas this risk exists for more than 5 years.

The bcl-2 findings of this study suggested that the absence of apoptosis in OLP may be related to a mechanism that protects the epithelium, or that the expression of bcl-2 is not an indicator of malignant transformation of OLP.

The findings of this study suggest that other molecules involved in cell cycle arrest, DNA repair and apoptosis processes may play a role in the possible transformation of OLP to OSCC.

Although numerous studies have been conducted on various proteins involved in cell proliferation and apoptosis processes in OLP, it is unclear whether there is an independent risk factor for malignant transformation. In many studies on malignant transformation of OLP, secondary risk factors such as tobacco and alcohol use, which are important etiological factors for OSCC, have not been evaluated. Data from most studies on the premalignant potential of OLP are different and inconsistent.[11] Therefore, the results of studies on this subject should be approached with caution.

Fitzpatrick et al.[46] detected lichenoid features in 352 cases of oral epithelial dysplasia, carcinoma in situ, or squamous cell carcinoma. They observed band-like infiltration and basal cell degeneration in these lesions, 74% and 30%, respectively.

Therefore, diagnosing OLP should be cautious. The malignant potential of OLP is still controversial due to the lack of consensus on the correct diagnostic criteria. The diagnosis of OLP is made by clinicopathological correlation. It is known that in some cases, the diagnosis of OLP is made only by clinical findings.[31] The diagnosis may be difficult if there is no classical OLP involvement anywhere in the oral mucosa and clinical subtypes other than reticular types are present, and OLP cannot be decided by histological features alone. van der Meij and van der Waal,[21] van der Waal[47] reported in their article that pathologists did not participate in 42% of all lesions clinically diagnosed as OLP, and clinicians did not participate in 50% of all lesions histologically diagnosed as OLP. For the correct diagnosis of OLP, cases should be evaluated according to the modified WHO (1978) diagnostic criteria recom-

mended by van der Meij and van der Waal in 2003[21] or the diagnostic criteria published by the American Academy of Oral and Maxillofacial Pathology in 2016. [22] The final diagnosis should be made by evaluating both clinical and histological diagnostic criteria. It should not be forgotten that clinically the lesions are bilateral or multifocal, symmetrical, and a reticular pattern must be present. The localization of the lesions should be typical for OLP. Histologically, there should be the absence of epithelial dysplasia and the absence of verrucous epithelial architectural change. The presence of epithelial dysplasia is an exclusion criterion for the histological diagnosis of OLP. In cases with a higher clinical risk (erosive/atrophic subtype), a cut-off value for p53 expression should be established and cases with a strong possibility of malignant transformation should be determined and followed more closely.

Diagnostic criteria standard, risks, predictive markers, and cut-off values for these markers should be defined for malignant transformation of OLP.

## Conclusion

It is important to mention the necessity of long-term follow-up of patients with this disease because these patients present a higher risk of developing oral cancer throughout the years, especially if exposed to risk factors, such as tobacco abuse and alcoholism; once OLP is exposed, the natural mechanisms of cell protection against carcinogens may be seriously altered due to chronic persistent lymphocytic infiltration exposure of the epithelium. The results of this study suggest that the expression of these cell survival and death proteins might be evidence of the potential of the malignant transformation process in OLP. Therefore, there is a need for an accurate final diagnosis with a clinical and histopathological correlation of OLP, for long-term follow-up of patients with OLP to detect any malignant alteration. Further research is needed to find markers and independent risk factors that predict the malignant transformation of OLP.

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